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SYNTHESIS, CHARACTERIZATION AND DNA BINDING ACTIVITY MACROCYCLIC SCHIFF BASE MIXED COMPLEXES BEARING THENIL AND CURCUMIN.

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Abstract:
The macrocyclic complexes of pharmaceutical importance with transition metals have been synthesized by condensation of condensation of the 1,2-Di(2-thienyl)-1,2-ethanedione (Thenil), ethane-1,2-diamine and curcumin. The structure of the synthesized ligand and complexes was characterized by, elemental analyses, Mass, IR, UV–Vis., measurements. The binding properties of these complexes towards DNA have been investigated using electronic absorption, competitive fluorescence titration, viscosity measurements and circular dichroic analyses. The results obtained indicated that the complexes get bonded with DNA via an intercalation binding mode with an intrinsic binding constant, K_b 6.76 x 10^4 M^{-1}, 5.13 x 10^4 M^{-1} and 4.18 x 10^4 M^{-1} respectively and K_{app} of 5.33 x 10^5 M^{-1}, 4.04 x 10^5 M^{-1} and 3.29 x 10^5 M^{-1}.

Keywords: *Thenil, DNA binding, Curcumin, Intercalation, hydrazine hydrate.*

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INTRODUCTION:

Cancer is becoming an increasingly important cause of death. Many different kinds of compounds have been found to be active in restraining the reproduction of cancer cells, and some of them have been used in clinical treatments [1]. The metal-based antitumor drugs like cisplatin, fulvestrant, goserelin, stilboestro, carboplatin and oxaliplatin have widely been used in clinics [2], but there are limitations due to the drug resistance over a period of time and adverse side effects [3]. These limitations have stimulated the investigations for improvement of existing platinum antitumor drugs and development of new derivatives that display better therapeutic properties [4]. In this field, copper, nickel and zinc based complexes showed promising perspectives. Copper-based complexes have been considered on the assumption that endogenous metals may be less toxic for normal cells with respect to cancer cells. Copper is also an essential element for most aerobic organisms, laboring as a structural and catalytic cofactor, and subsequently it is involved in many biological pathways. The bioinorganic chemistry of nickel has also been rapidly expanded due to the increasing interest in nickel complexes that have been shown to act as antiepileptic and anticonvulsant agents or vitamins or have shown antifungal, antimicrobial and anticancer/antiproliferative activity [5]. Zinc compounds is gaining a great attention due to their interesting structural features, catechol oxidase, schizonticidal, antimalarial, antimicrobial, tumor photosensitizers and their potential as agricultural biocides. The interaction of metal complexes with DNA has recently gained much attention because it indicates that the complexes may have potential biological activity and their activity depends on the mode and the affinity of the binding with DNA [6].

Chemotherapeutic anti-cancerous treatment involves the inhibition of the rapid cell division by targeting deoxyribonucleic acid (DNA) through covalent or non-covalent interactional modes. In recent years, there is a growing interest in the electrochemical and spectroscopic investigations of interactions of DNA with small molecules due to their relevance to physiological processes [7]. Drugs bind to DNA both covalently as well as non-covalently. Covalent binding is irreversible and the high binding strength of covalent binders is a major advantage but toxic side effects are one of the major disadvantage. Non-covalent binding (intercalation or minor groove binding) is reversible and is typically preferred over covalent adduct formation. There is a specific hydrophilic coat and hydrophobic core structure in DNA, thus an aromatic ring stacking between the base pairs of DNA, is the main driving force for the binding of a compound into double stranded DNA (ds.DNA) via intercalation. Small molecules that have a planar aromatic system (intercalators) can insert between two adjacent base pairs, resulting in widening and lengthening of the DNA helix, while crescent shaped molecules bind in the minor groove through H-bonding [8].

Curcumin [1,7-bis(4-hydroxy-3methoxyphenyl)-1,6-heptadiene- 3,5-dione], which is a naturally occurring yellow pigment obtainable from the rhizomes of turmeric (Curcuma longa Linn.), is a common ingredient used in spices, cosmetics and traditional Chinese medicine. The medicinal activity of curcumin has been known since ancient times and this molecule has been the object of several investigations in the field of biology, medicine and pharmacology [9], over the last decades, such as antioxygenation, antibiosis and antitumor activities. Curcumin has a highly conjugated β-diketone moiety. B-Diketones are long known to form complexes with almost every metal and metalloid [10]. Thenil is a versatile chelating agent having two reactive carbonyl groups capable of undergoing Schiff-base condensation with a variety of di - and polyamines. Thus, thenil has played an important role in the development of macrocyclic complexes. Such complexes show unusual structure and stability and are known to have relevance to biological system. This provides an opportunity to design and study the model biological systems to understand the chemical changes taking place in such cases [11].

Aligned with the above cited scope, we have synthesized a Schiff base ligand and their respective Cu(II), Ni(II) and Zn(II) metal complexes bearing biologically active functionalities and studied their biological activity in detail and reported in this paper. The obtained results are valuable for DNA probes so as to meet the demands of the researchers in search of an effective drug. The results were indicative of better binding efficiencies of the copper bound ligand compared to the nickel and zinc complexes themselves.

EXPERIMENTAL PROTOCOLS

Reagents and instruments

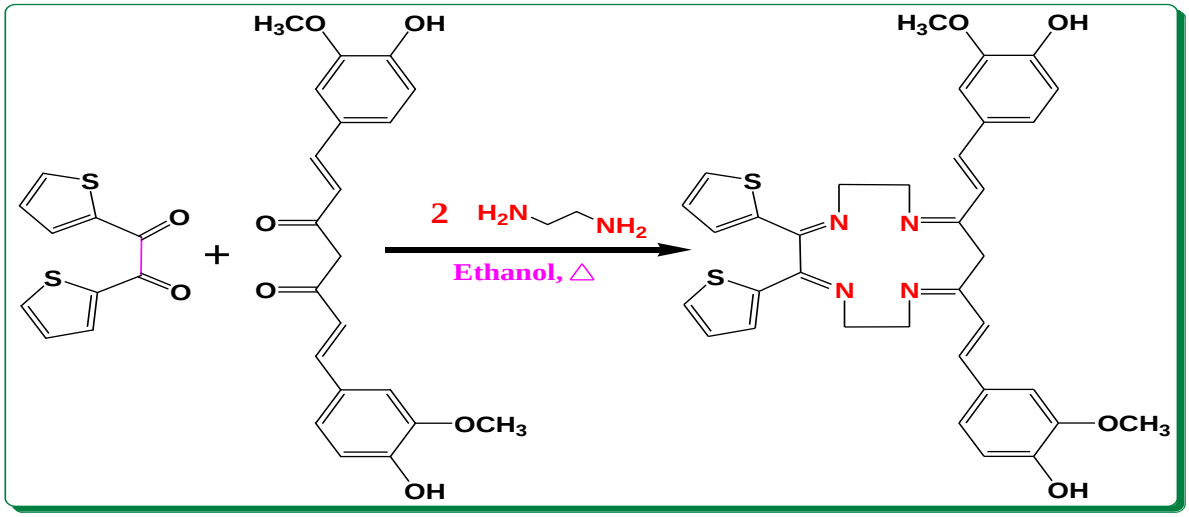
All the chemicals used in the current work *viz*, 1,2-Di(2-thienyl)-1,2-ethanedione (Thenil), ethane-1,2-diamine, curcumin and metal(II) acetates were of analytical reagent grade (produced by Merck, Germany). Commercial solvents were distilled and then used for the preparation of ligands and their complexes. DNA was purchased from Bangalore Genie (India). Tris (hydroxymethyl) aminomethane–

HCl (Tris–HCl) buffer solution was prepared by means of deionized and sonicated triple distilled water. C, H and N contents were determined by Perkin Elmer CHN 2400 elemental analyzer and IR Spectra were recorded in Perkin-Elmer FT-IR spectrophotometer in the range of 400-4000 cm^{-1} using KBr pellet. UV–visible spectra were recorded in DMF with Perkin Elmer Lambda 35 spectrophotometer operating in the range of 200-600 nm with quartz cells and ε are given in $M^{-1}cm^{-1}$. The emission spectra were recorded on Perkin Elmer LS-45 fluorescence spectrometer. Viscosity measurements were recorded using a Brookfield Programmable LV DVII+ viscometer. The electro spray mass spectra were recorded on a Q-TOF micro mass spectrometer. Circular dichroic spectra of CT-DNA were obtained using a JASCO J-715 spectro polarimeter equipped with a Peltier temperature control device at 25 ± 0.1°C with 0.1 cm path length cuvette.

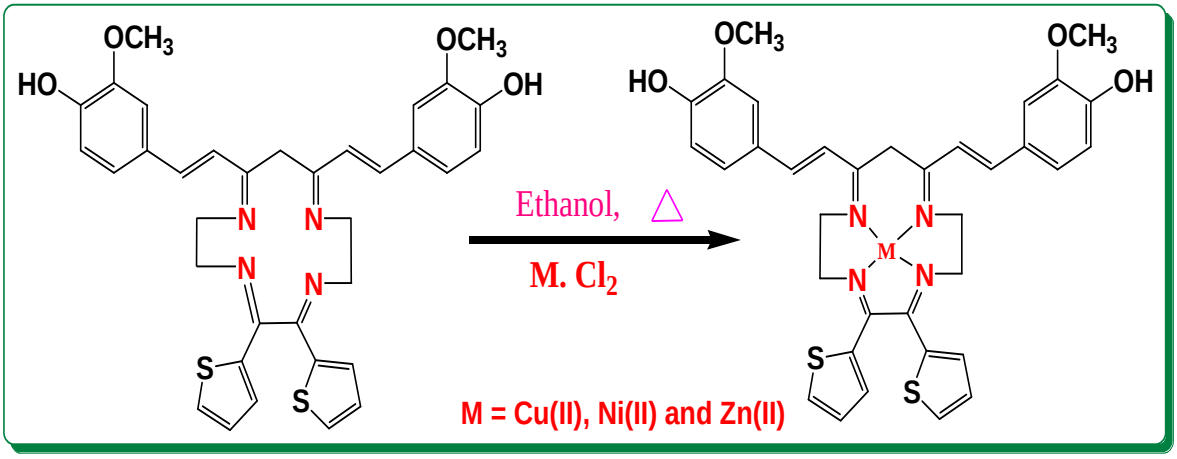
Synthesis of Schiff base ligand L

The design of the synthesis of the ligand is publicized in Scheme 1. 1,2-Di(2-thienyl)-1,2-ethanedione (0.005 mmol, 1.2 gm) and Curcumin (0.005 mol, 1.9 gm) were dissolved in ethanol (40 mL) and stirred magnetically till the appearance of clear solution. To the clear solution, 20 mL of ethanol containing (0.010 mol, 0.75 ml) ethane-1,2-diamine is added. The solution was refluxed on an oil bath for 24 h with stirring and a yellow precipitate formed. The yellow precipitate was filtered, washed several times with ethanol and recrystallized from DMF and water to give the ligand.

Scheme 1: Synthesis of macrocyclic Schiff base ligand L.



Scheme 2: Synthesis of macrocyclic Schiff base complexes using ligand L.



Synthesis of Schiff base metal complexes.
All complexes were synthesized using the same procedure as given below:

To the vigorous stirred solution of ligand L (0.010 mol) in 25 mL ethanol, the corresponding equimolar amount of appropriate metal chloride salts (0.010 mol) [M = Cu(II), Ni(II) and Zn(II)] in ethanol (20 mL) was added. The solution is heated to 80^0C for about 8 hours under continuous stirring over oil bath. At the end of the reaction, determined through thin layer chromatography, the precipitate was filtered off, washed with ethanol and diethyl ether, and dried in vacuo. The synthetic route of the planned complexes is depicted as in scheme 2.

DNA binding experiments

Absorption spectral studies

Electronic absorption titrations were performed in Tris–HCl/NaCl buffer (5 mmol L^{-1} Tris–HCl/50 mmol L^{-1} NaCl buffer pH 7.2) using DMF (10%) solution of metal complexes at room temperature. The concentration of CT-DNA was determined from the absorption intensity at 260 nm with e value of 6600 $(mol\ L^{-1})^{-1}$ – cm^{-1}. Absorption titration experiments were made using different concentrations of CT-DNA, keeping the complex concentration constant. Correction was made for absorbance of the CT-DNA itself. Metal-DNA solutions were allowed to incubate for 5 min before the absorption spectra were recorded. For metal(II) complexes, the intrinsic binding constant (Kb) was determined by monitoring the changes of absorption in the MLCT band with increasing concentration of DNA using the following equation [12] (1)

$$[DNA]/(\varepsilon_a - \varepsilon_f) = [DNA]/(\varepsilon_b - \varepsilon_f) + 1/K_b(\varepsilon_b - \varepsilon_f) \quad \text{--- (1)}$$

Where [DNA] is the concentration of DNA in base pairs. The apparent absorption coefficients ε_a, ε_f and ε_b correspond to A_{obsd}/ [complex], the extinction coefficient of the complex when fully bound to equilibrium binding constant in $(mol\ L^{-1})^{-1}$ respectively. Each sample solution was scanned from 200 to 500 nm. The non-linear least square analysis was performed using Origin lab, version 6.1.

Fluorescence emission spectral studies

Competitive binding of metal complexes with CT DNA in a solution of Na phosphate buffer (pH ~ 7.2) was studied using fluorescence spectral technique. The extent of fluorescence quenching of EB bound to DNA can be used to determine the extent of binding between the second molecule and DNA. The competitive binding experiments were carried out in the buffer by keeping [DNA]/[EB] and varying the concentrations of the compounds. The fluorescence spectra of EB were measured using an excitation wavelength of 520 nm and the emission range was set between 550 and 700 nm. Quenching of the fluorescence of Eth-Br bound to DNA were measured with increasing amount of metal complexes as a second molecule and Stern–Volmer quenching constant K_{sv} was obtained from the following equation [13].

$$I_o/I = 1 + K_{svr}. \quad \text{----------} \quad (2)$$

Where I_0, is the ratio of fluorescence intensities of the complex alone, I is the ratio of fluorescence intensities of the complex in the presence of CT-DNA. Ksv is a linear Stern – Volmer quenching constant and r is the ratio of the total concentration of quencher to that of DNA, [M] / [DNA]. A plot of I_0 / I vs. [complex]/ [DNA], Ksv is given by the ratio of the slope to the intercept. The apparent binding constant (K_{app}) was calculated using the equation K_{EB}[EB] / K_{app}[complex], where the complex concentration was the value at a 50% reduction of the fluorescence intensity of EB and K_{EB} = 1.0 x 10^7 M^{-1} ([EB] = 3.3 μM).

Viscosity measurements

Viscosity measurements were carried out using a capillary viscometer at a constant temperature (25.0 ± 0.1 ºC). Flow times were measured with a digital stopwatch, and each sample was measured three times, and then an average flow time was calculated. To find the binding mode of the complexes towards CT-DNA, viscosity measurements were carried out on CT-DNA (0.5 mM) by varying the concentration of the complexes (0.01 mM, 0.02 mM, 0.03 mM, 0.04 mM, 0.05 mM). Data were presented as (η/η_o) versus binding ratio of concentration of complex to that of concentration of CT-DNA , where η is the viscosity of DNA in the presence of complex and η_o is the viscosity of DNA alone.

CD spectral studies

CD spectra of DNA were recorded on a JASCO J-715 spectro polarimeter equipped with a Peltier temperature control device at 25 ± 0.1 °C with a 0.1 cm path length cuvette scanning speed of 100 nm/min with scope of 200– 400 nm at room temperature in the absence or presence of 1.0 x 10^{-4} M compound. The concentration of DNA was 1.0 x 10^{-4} M and the buffer solution was 1% CH_3CN/50 mM NaCl/5 mM Tris–HCl. The sample was completely mixed and stands 5 min before scanning. The buffer background was subtracted automatically. Each CD spectrum has been subtracted with that of buffer solution and the compounds, thus the spectrum

purely reflect the changes of DNA structure upon binding with the compounds.

RESULTS:

Structural characterization of the Schiff base ligand and metal complexes.

FT-IR spectral analysis

The IR spectra of ligand show bands at 1658 cm^{-1} which is assignable to ν(C=N) as represented in figure 1. The azomethine (C=N) stretching frequency of free ligand appeared around 1658 cm^{-1} which has been shifted to a lower wave number in the range 1622 cm^{-1} for Cu(II),1625 cm^{-1} for Ni(II) and 1628 cm-1 for Zn(II) complexes respectively in accordance with the coordination of the azomethine function to the metal ion for all the complexes. This is due to the decrease in electron density around the nitrogen atom of the azomethine group [14]. In the spectra of complexes, these bands were shifted to. In addition, the complexes showing new bands at 410–445 cm^{-1} are assigned to ν (M-N) bands as shown in figure 2-4.

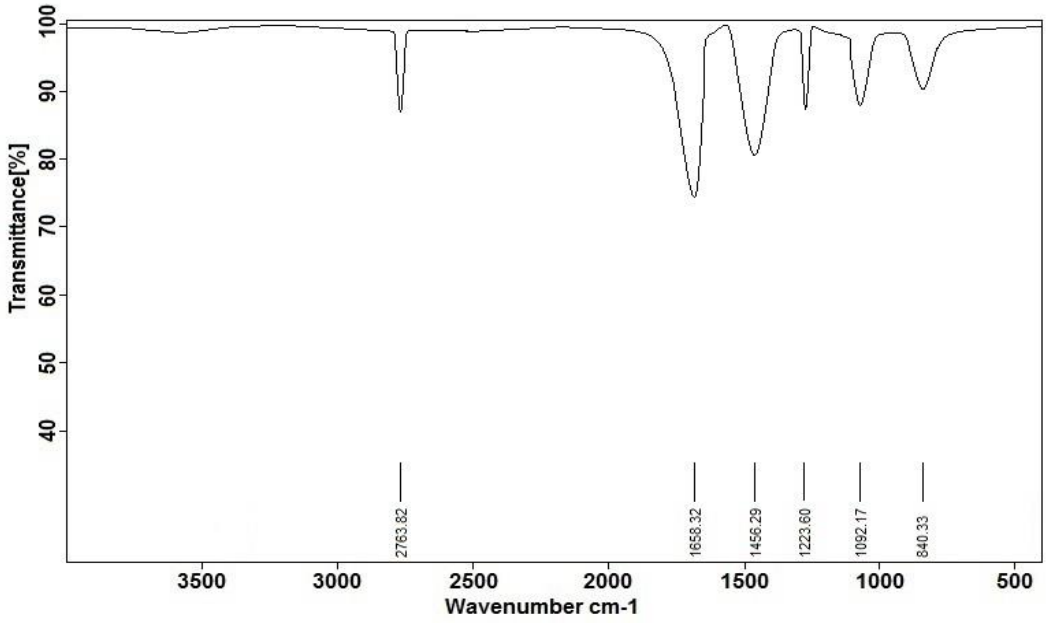


Fig 1: FT-IR spectrum of the Schiff base ligand (L).

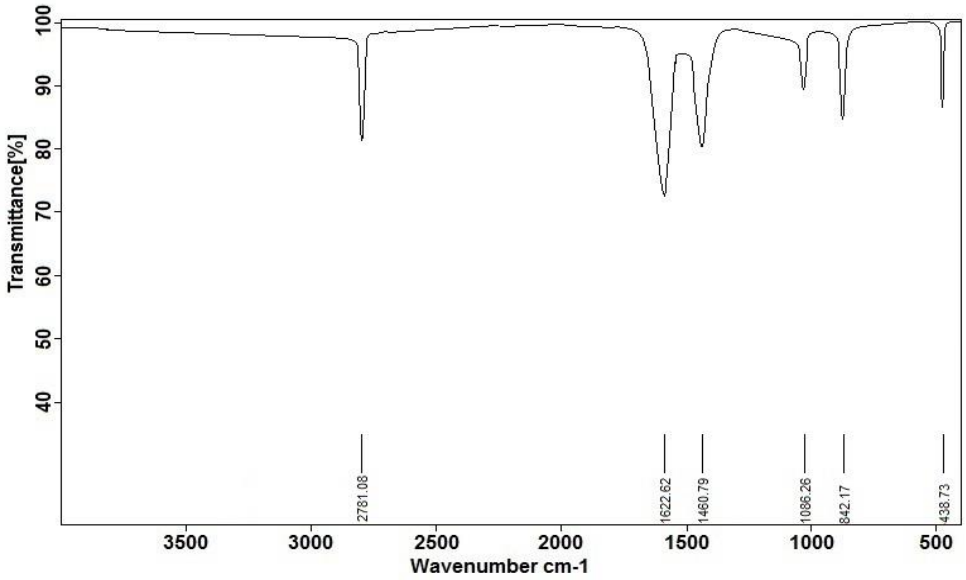


Fig 2: FT-IR spectrum of Cu(II) complex.

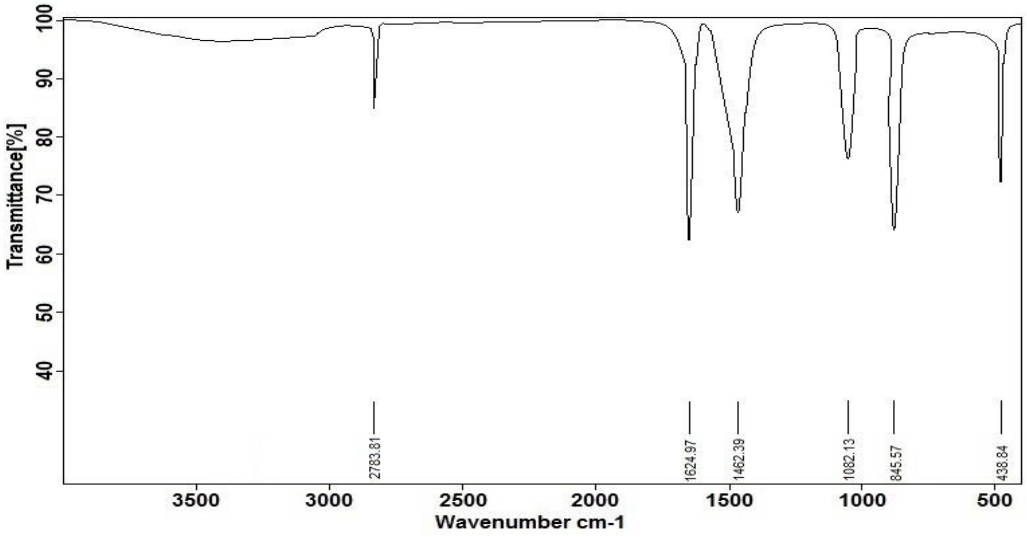


Fig 3: FT-IR spectrum of Ni(II) complex.

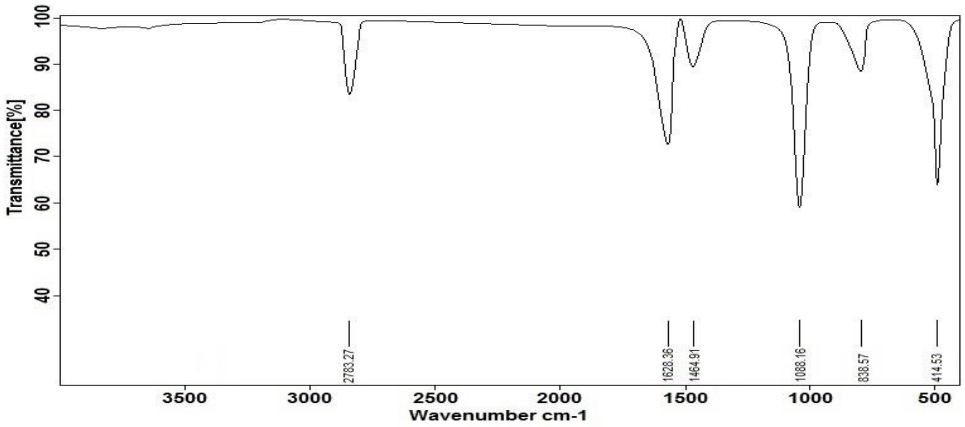


Fig 4: FT-IR spectrum of Zn(II) complex.

Mass spectral analysis

The molecular ion peak [M^+] at m/z = 638 confirms the molecular weight of the Schiff base ligand L $C_{35}H_{34}N_4O_4S_2$. The peaks at m/z = 546, 470, 394, 370, 342, 260, 248, 212, 178, 104 and 78 corresponds to the various fragments $C_{33}H_{30}N_4S_2$, $C_{27}H_{26}N_4S_2$, $C_{21}H_{26}N_4S_2$, $C_{21}H_{22}N_4S_2$, $C_{19}H_{22}N_4S_2$, $C_{17}H_{18}N_4S_2$, $C_{13}H_{16}N_4S$, $C_{12}H_{12}N_2S_2$, $C_{14}H_{16}N_2$, $C_9H_{14}N_4$, C_8H_8 and C_6H_6 respectively as shown in Figure 5.

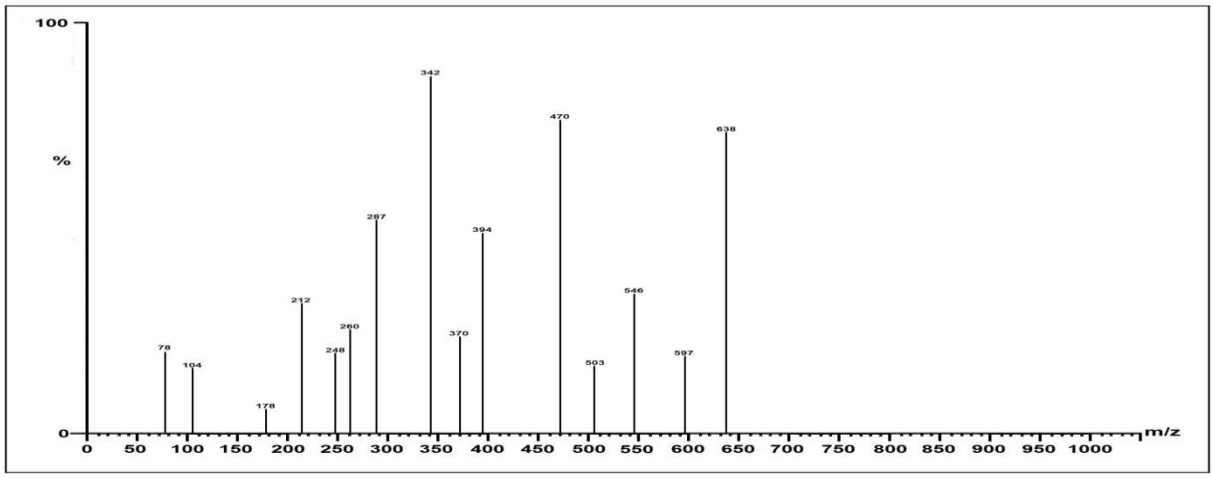


Fig 5: Mass spectrum of the Schiff base ligand (L).

The molecular ion peak [M^+] at m/z = 702 confirms the molecular weight of the Schiff base Cu(II) complex $C_{35}H_{34}N_4O_4S_2Cu$. The peaks at m/z = 656, 610, 534, 458, 406, 390, 323, 293, 241 and 179 corresponds to the various fragments $C_{34}H_{32}N_4O_2S_2$, $C_{33}H_{30}N_4S_2$, $C_{27}H_{26}N_4S_2$, $C_{21}H_{22}N_4S_2$, $C_{17}H_{18}N_4S_2$, $C_{18}H_{22}N_4S$, $C_{13}H_{16}N_4S$, $C_{13}H_{18}N_4$, $C_9H_{14}N_4$ and $C_4H_{12}N_4$ respectively as shown in Figure 6. The molecular ion peak [M^+] at m/z = 697 and 704, confirms the molecular weight of the Schiff base Ni(II) and Zn(II) complex $C_{35}H_{34}N_4O_4S_2M$ [M = Ni(II) and Zn(II)] as represented in Figure 7 and 8. The type of fragmentation observed in Ni(II) and Zn(II) complex was similar with that of the Cu(II) complex.

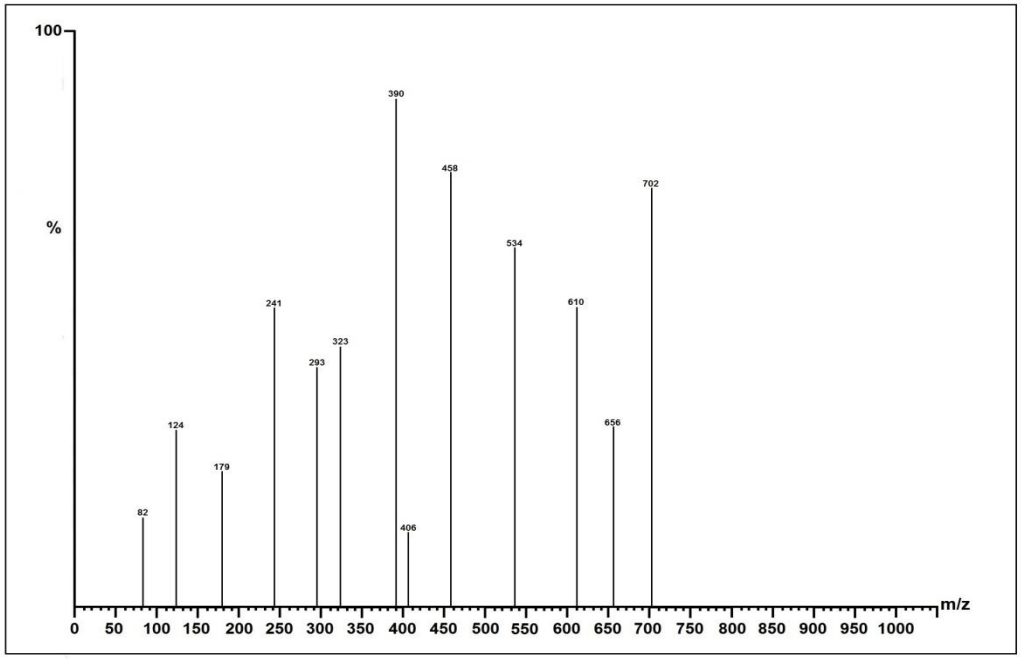


Fig 6: Mass spectrum of the Cu(II) complex.

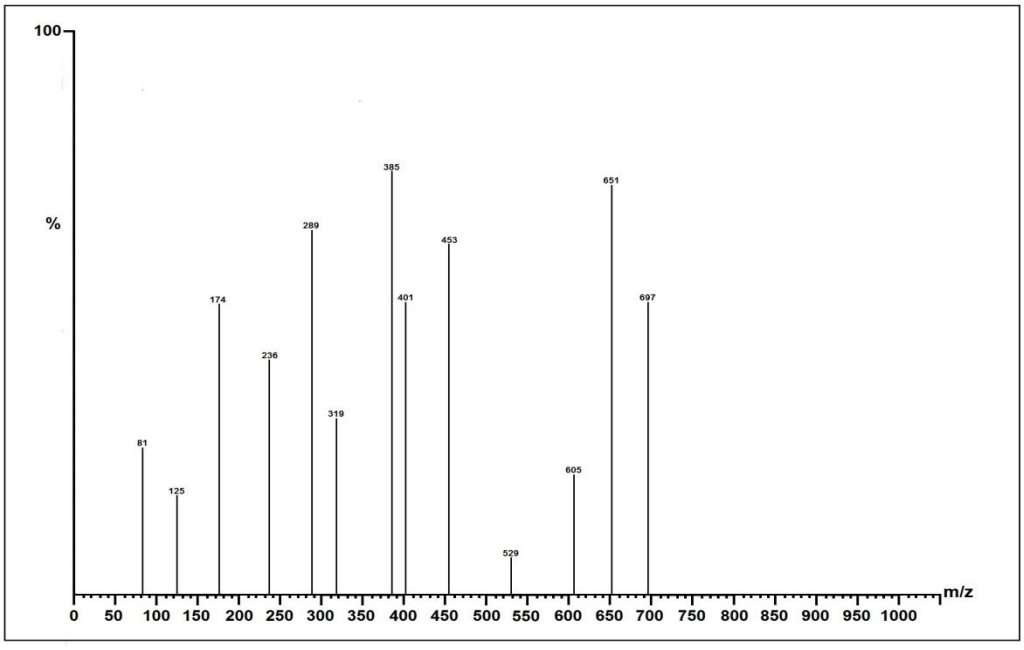


Fig 7: Mass spectrum of the Ni(II) complex.

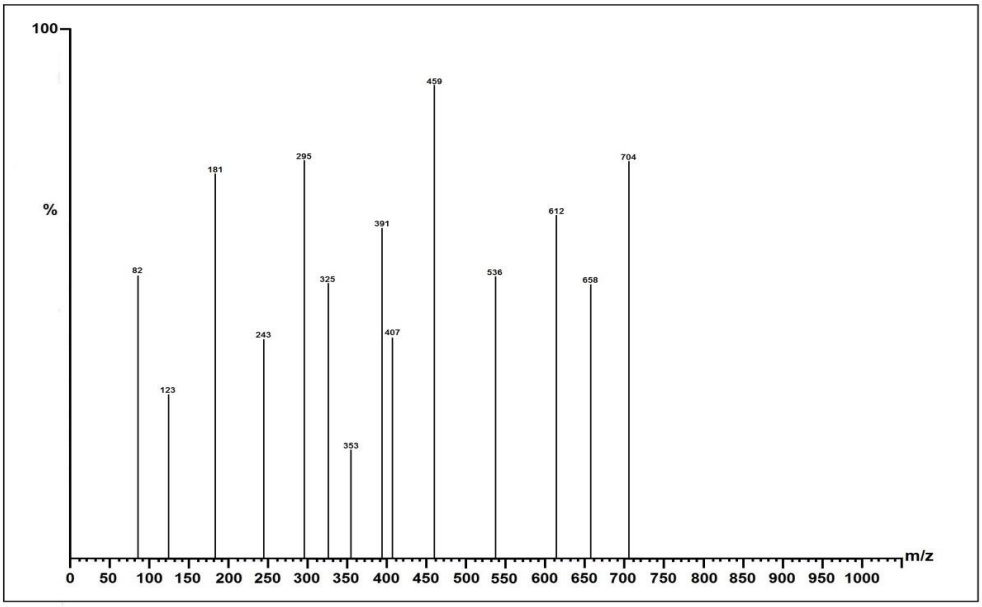


Fig 8: Mass spectrum of the Zn (II) complex.

DNA binding experiments

Absorption spectral studies

The absorption spectrum of the synthesized complex indicates two absorption bands attributed to π-π* and n-π* at 255 and 380 nm. The n-π* absorption band was chosen to determine the interaction of this complex with DNA. The representative absorption spectra of Cu (II) complex in presence and absence of CT-DNA are shown in Figure 9. The absorption spectra of other complexes are given in Figure 10 and 11. With increasing concentration of CT-DNA the absorption bands of the complexes were affected resulting in the tendency of hypochromism and a minor red shift was observed in all the complexes. The observed spectral effect was ascribed to a strong interaction between the electronic state of the intercalating chromophore and that of the DNA bases. The strength of this electronic interaction is attended to decrease as the cube of the distance between the chromophore and the DNA bases[15]. Binding of metal complex to CT-DNA induces a shift in the metal–ligand centered band of the UV spectrum. In the UV region, the intense sharp band at 255 nm for the complex is attributed to the intraligand π-π* transition. It is clear that, a slight red-shift is observed with increasing of CT-DNA concentration, indicating the existence of an intercalative mode between them.

In order to compare quantitatively the binding strength of the complexes, the intrinsic binding constants K_b of the complexes with DNA were obtained by monitoring the changes in absorbance with increasing concentration of DNA. Intrinsic binding constants K_b of Cu, Ni and Zn complexes are obtained as 6.76×10^4 M^{-1}, 5.13×10^4 M^{-1} and 4.18×10^4 M^{-1}respectively as represented in the inset of Figure 9. The significant difference in DNA-binding affinity of the three metal (II) complexes could be understood as a result of the fact that the complex with higher numbers of metal (II) chelates showed stronger binding affinity with DNA. These results suggest a close association of the compounds with CT-DNA and it is also probable that compounds bind to the helix via intercalative mode.

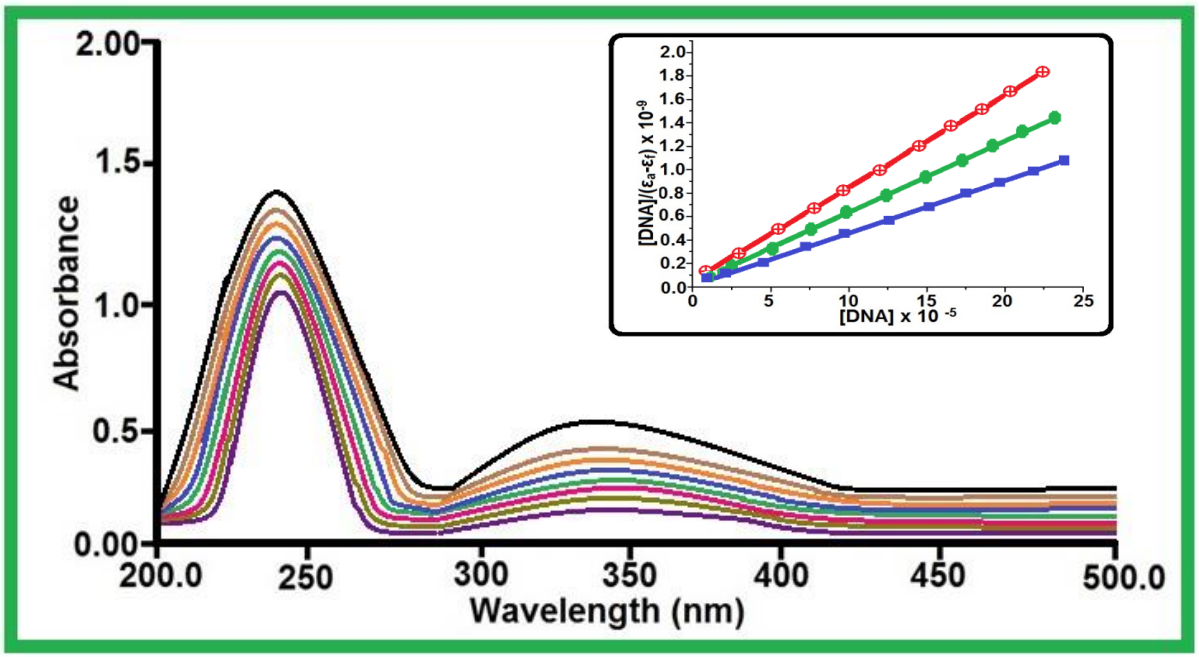


Fig 9: Absorption spectra of complex Cu(II) (1 x 10^{-5} M) in the absence and presence of increasing amounts of CT-DNA (0-2.5 x 10^{-3} M) at room temperature in 50 mM Tris-HCl / NaCl buffer (pH = 7.5). The Inset shows the plots of [DNA] / (ϵ_a-ϵ_f) versus [DNA] for the titration of DNA with Cu(II), Ni(II) and Zn(II) complexes.

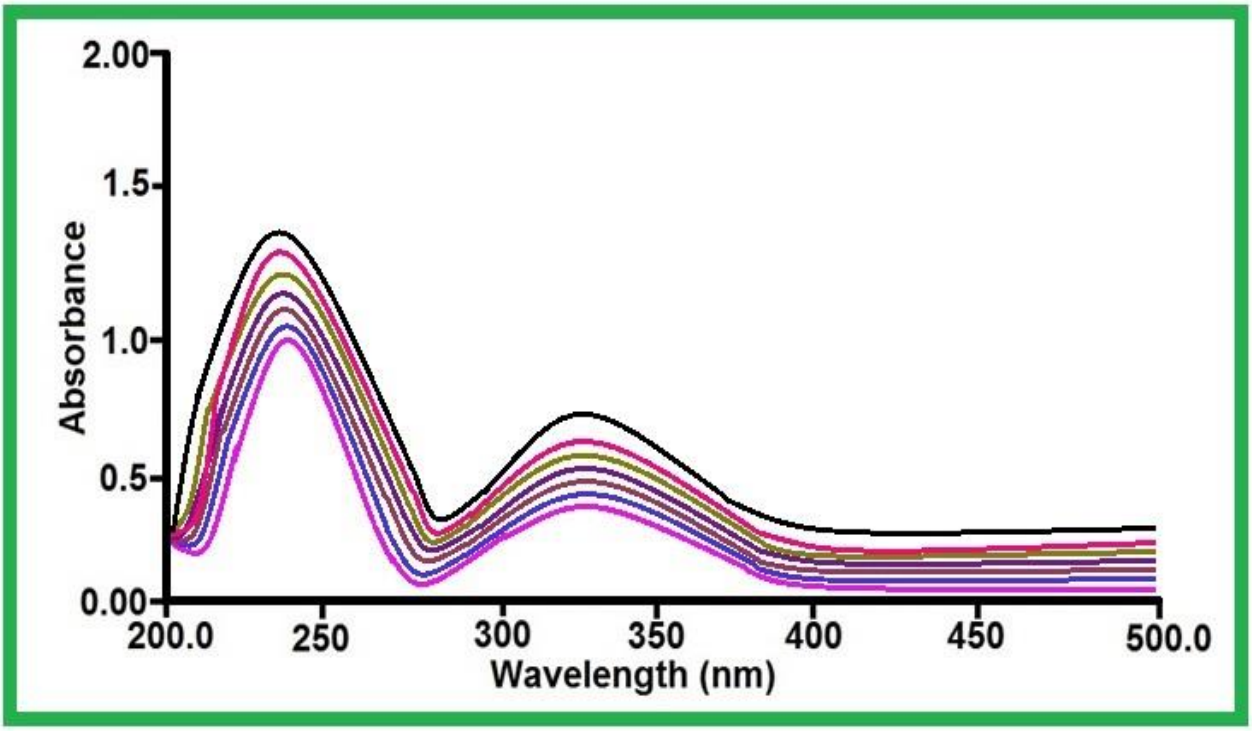


Fig 10: Absorption spectra of complex Ni(II) (1 x 10^{-5} M) in the absence and presence of increasing amounts of CT-DNA (0-2.5 x 10^{-3} M) at room temperature in 50 mM Tris-HCl / NaCl buffer (pH = 7.5).

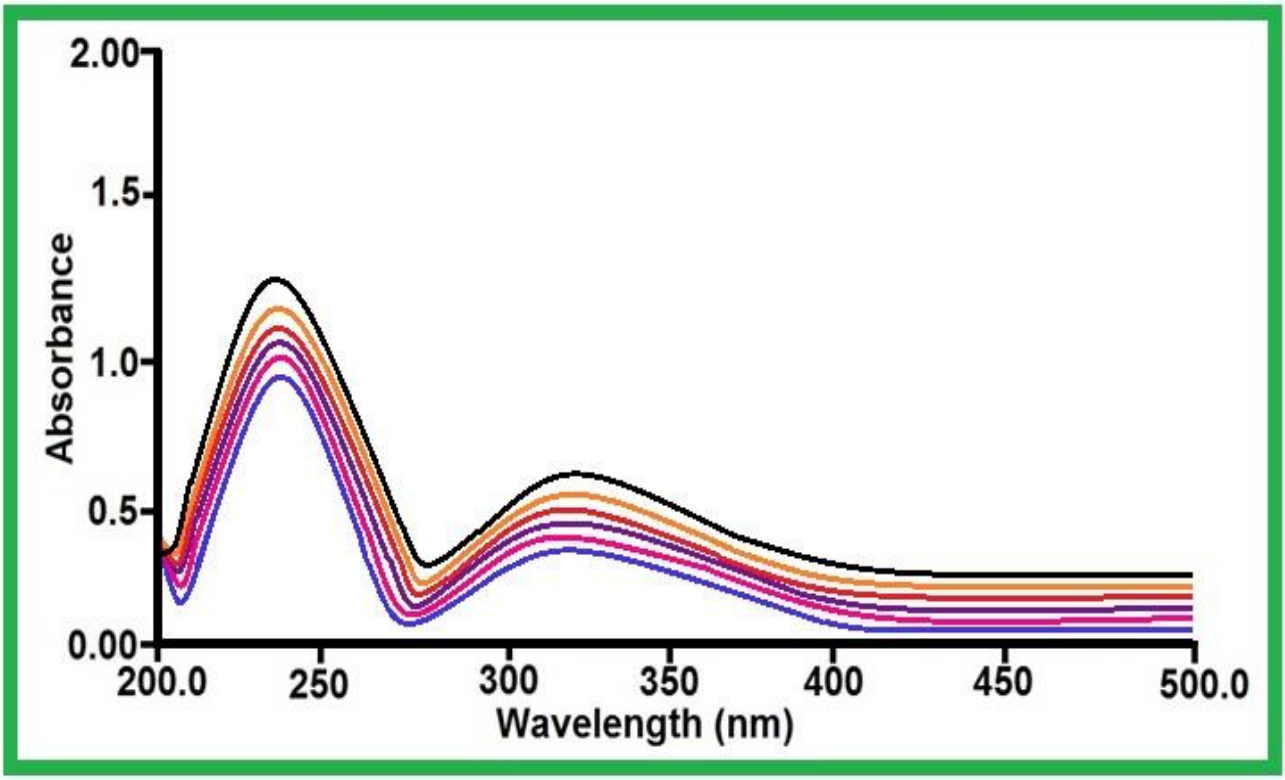


Fig 11: Absorption spectra of complex Zn(II) (1 x 10^{-5} M) in the absence and presence of increasing amounts of CT-DNA (0-2.5 x 10^{-3} M) at room temperature in 50 mM Tris-HCl / NaCl buffer (pH = 7.5).

Emission spectral studies

The mode of binding of metal complexes with DNA was further supported by their competitive displacement assay of ethidium bromide. The extent of quenching of fluorescence of DNA bound EB in the presence of complexes showed their extent of DNA binding as depicted in Figure 12 - 14. The EB molecule is a phenanthridine fluorescence dye, a typical indicator of intercalation. It forms soluble adduct with nucleic acids and emits intense fluorescence on intercalation with the base pairs of DNA[16]. The addition of complexes can quench the emission from DNA–EB system either by replacing the EB and/or by accepting the excited-state electron of the EB through a photoelectron transfer mechanism[17]. In current case, the decrease in emission intensity could be attributed to the displacement of EB from DNA-EB adduct by the complexes, suggesting their competition for the intercalative binding site of the DNA. The results show that the fluorescence intensity of DNA-EB decreases remarkably with the addition of the complex which indicate that the complex binds to DNA by intercalation or partial intercalation replacing EB from the DNA structure.

The quenching plots (insets in Figure 12) illustrate that the fluorescence quenching of EB bound to DNA by Cu(II), Ni(II) and Zn(II) complexes in linear agreement with the Stern–Volmer equation, which confirms that the complexes bound to DNA. The K_{app} values for Cu(II), Ni(II) and Zn(II) complexes are found to be 5.33 x 10^5 M^{-1}, 4.04 x 10^5 M^{-1} and 3.29 x 10^5 M^{-1} respectively. The attained results are in consistent with that of absorption spectroscopic studies. Anyway, it may be concluded that the entire complexes bound to DNA *via* the similar mode and the quenching constants of the synthesized complexes reveals that the interaction of the compound with DNA should be intercalation.

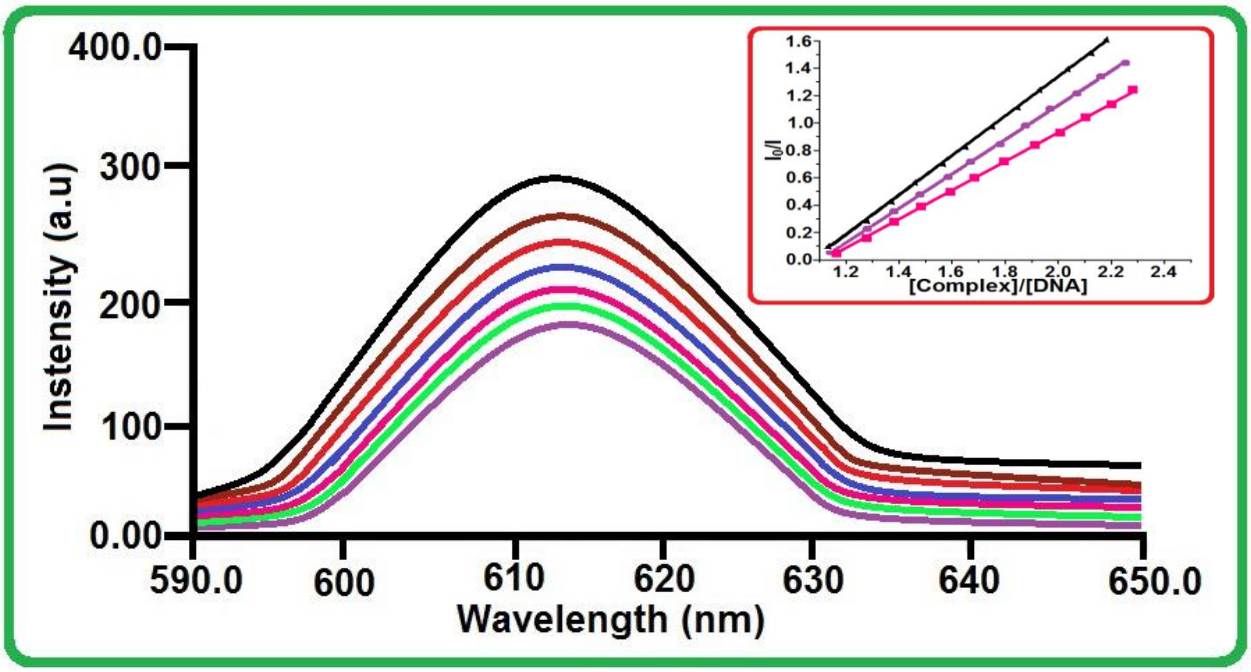


Fig 12: Emission spectrum of EB bound to DNA in the presence of Cu(II): ([EB] = 3.3 µM, [DNA] = 40 µM, [complex] = 0-25 µM, λex= 440 nm). Inset shows the plots of emission intensity I_o / I *vs* [DNA] / [complex] for the titration of DNA with Cu(II), Ni(II) and Zn(II) complexes.

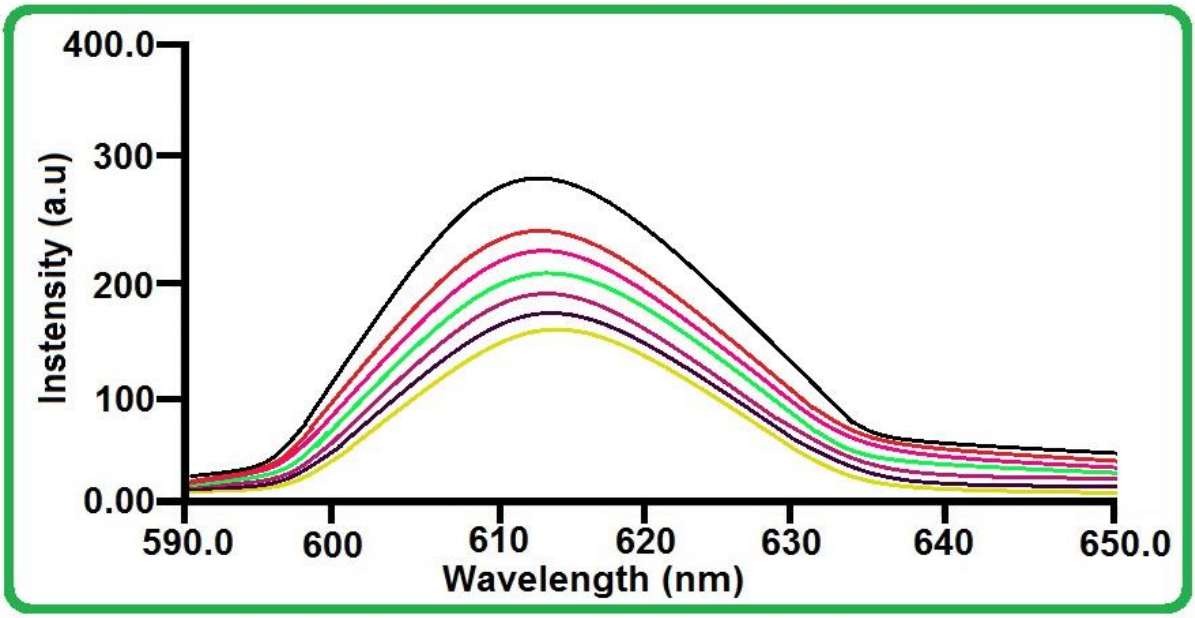


Fig 13: Emission spectrum of EB bound to DNA in the presence of Ni(II): ([EB] = 3.3 µM, [DNA] = 40 µM, [complex] = 0-25 µM, λex= 440 nm).

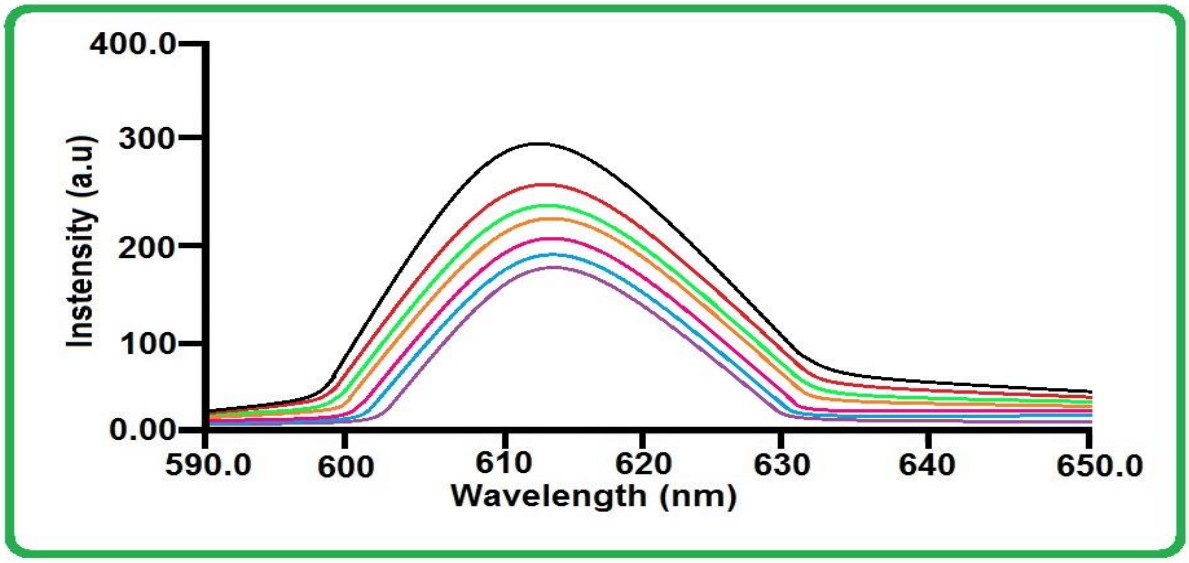


Fig 14: Emission spectrum of EB bound to DNA in the presence of Zn(II): ([EB] = 3.3 µM, [DNA] = 40 µM, [complex] = 0-25 µM, λex= 440 nm).

Viscosity studies

The experimental results clearly showed that all the complexes can intercalate between adjacent DNA base pairs as also evidenced by UV–Vis and emission spectroscopic results .The viscometric measurement is also an important tool to find the nature of binding of metal complexes to the DNA. Hydrodynamic measurements (i.e., viscosity and sedimentation) sensitive to length changes are the most critical and least ambiguous tests of binding in solution without crystallographic data[18]. A classical intercalation molecule, such as EB, results in the lengthening of the DNA helix. This leads to an increase in DNA viscosity, which is caused by an increase in the separation of base pairs at the interaction site and an increase in overall double helix length. By contrast, a partial or non classical intercalation of the complex results in bending of the DNA helix, which reduces the effective length of DNA, as well as the DNA viscosities. The relative specific viscosity of DNA is determined by varying the concentration of the added metal complexes. The effects of all the synthesized complexes on the viscosity of DNA at 30 ± 0.1 °C are shown in Figure 15. In the presence of lower concentrations of complexes, no significant changes were observed in the relative viscosity of DNA. However, at higher concentrations of complexes, the relative specific viscosity of DNA increased, but the increase is less than that observed for the typical intercalator EB, indicating that intercalative binding mode has taken place. This observation suggests that the mode of DNA binding by complexes involved base pair intercalation.

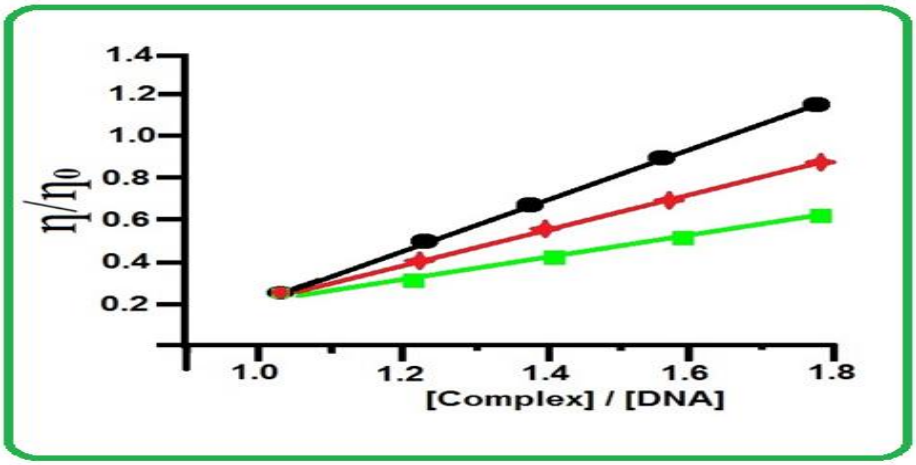


Fig 15: Viscosity measurements of the Cu(II), Ni(II) and Zn(II) complexes.

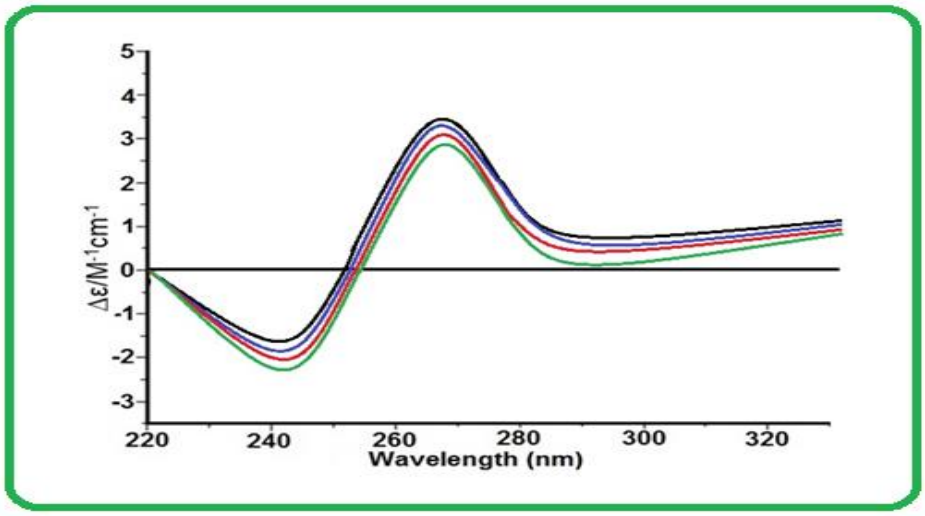


Fig 16: CD spectra recorded over the wavelength range 220-320 nm for solutions containing 2:1 ratio of CT-DNA (200 µM) and mononuclear Cu(II), Ni(II) and Zn(II) complexes (100 µM).

Circular dichroic spectral studies

The structural changes of CT-DNA due to the interactions with complexes were measured using circular dichroism (CD) spectroscopy. It is a powerful, sensitive and sophisticated tool to identify the conformational changes occurred in DNA during the interaction of small molecules. The so-called right handed B form of free helical DNA exhibits a positive band at 275 nm due to base stacking and a negative band at 245 nm due to helicity[19]. As represented in Figure 16, the CD spectrum of DNA exhibits a positive absorption at 277nm due to the base stacking and a negative band at 240nm due to the helicity of B-DNA. In the presence of the complex, both the positive and negative peak intensities of the CD spectra of DNA were increased. The changes in the CD spectra in the presence of the complex show stabilization of the right handed B form of CT-DNA. These observations clearly indicate that the binding mode of the complexes should be intercalative, the stacking of the complex molecules between the DNA base pairs leads to an enhancement in the positive band and the partial unwinding of the helix decreases intensity of the negative band. So, the main interactions of the complexes with DNA can be ascribed to the intercalative mode.

CONCLUSION:

The synthetic direction adopted for the synthesis of new complexes was very simple with good yield. The binding behavior of metal complexes with DNA was studied by electronic absorption, competitive fluorescence titration, viscosity measurements and circular dichroic assay under various conditions. All the experimental evidences indicate that all the three complexes of various ligands can strongly bind to CT DNA *via* an intercalation mode the binding constant K_b is found to be 6.76 x 10^4 M^{-1}, 5.13 x 10^4 M^{-1} and 4.18 x 10^4 M^{-1}respectively.

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