

RESEARCH ARTICLE

EVALUATION OF THE PHARMACOLOGICAL PROPERTIES OF SCHIFF BASE MIXED LIGAND CU (II), CO (II), NI (II) AND ZN (II) COMPLEXES DERIVED FROM 2-((E)-(4 NITROPHENYLIMINO) METHYL) PHENOL

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ARTICLE INFO

Article History:

Received 10th, August, 2013
Received in revised form 25th, August, 2013
Accepted 18th, September, 2013
Published online 30th September, 2013

Key words:

Biological screening, Disc diffusion, Inhibition, DNA binding, mononuclear complexes.

ABSTRACT

The coordination chemistry of 2-((E)-(4-nitrophenylimino)methyl)phenol (L^1) and 1-(4-chloro-phenylazo)-naphthalen-2-ol (L^2) has been investigated with the Cu(II), Co(II), Ni(II) and Zn(II) ions. These two ligands offer two coordination modes through phenolic oxygen and azomethine nitrogen. The effective magnetic moment, ESR and electronic spectral data supported the square planar environment of the metal ions. Spectroscopic methods like infrared spectroscopy and ^1H NMR were used for structure elucidation of the complexes. The pharmacological properties of the synthesized ligands and their mixed ligand complexes were evaluated against microbial (against the bacteria such as *Escherichia coli*, *Staphylococcus aureus*, *Klebsilla pneumonia* and *Bacillus subtilis*, and the fungi such as *Aspergillus flavu* and fungi *Fusarium oxysporum*) and CT DNA to assess their inhibitions and interactions potential.

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INTRODUCTION

The 3d transition metals bound organic compounds to possess considerable potential in many applications including clinical, analytical, catalytic, microbial, insecticidal, antibiotics, growth factors, food additive, tumor inhibitors and cell division (Abu-Hussen, 2005; Sithambaram et al., 2006; Singh et al., 2006). This is due to the unused coordination sites of the metal and ligand systems, or due to the selective oxidation state of the complexed metal ions in the coordination sphere. A large number of Schiff bases with their binding ability forms stable and active Schiff base metal complexes. These Schiff bases complexes form significant applications in medicinal and pharmaceutical chemistry with several biological applications that include antibacterial, anti-inflammatory and antipyretic antifungal and antitumor activity (Walsh et al., 1996; Belayet Hossain et al 2008). Due to their multiple implications, the transition metal complexes with Schiff bases as ligands, are of paramount scientific interest. Over the past few decades much interest has been shown in the Schiff base mixed ligand complexes of dibasic acids and amine bases considering that most of them are potentially biologically active (Shahriar Ghammamy et al., 2013). The variety of possible Schiff base metal complexes with wide choice of ligands and coordination environments has prompted us to synthesis a new potentially active Schiff base mixed lig and complexes from phenylazo)-naphthalen-2-ol.

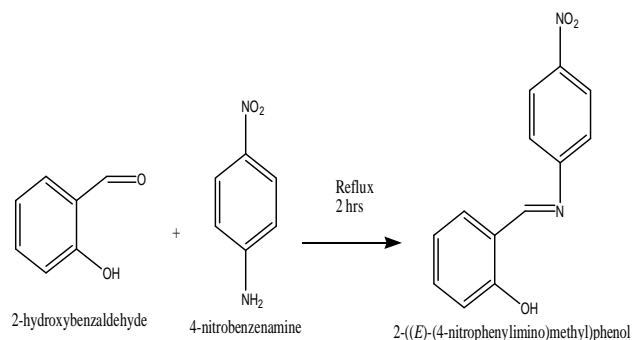
PHYSICAL MEASUREMENTS

Elemental analysis (C, H and N) was obtained using Perkin Elmer elemental analyzer. The molar conductance of the complexes in DMF (10^{-3}) solution was measured at 27 ± 3 °C with an Elico model conductivity meter. Electronic spectra were recorded on Perkin-Elmer Lambda 40 (UV-Vis) spectrophotometer. Magnetic

susceptibility measurements were carried out on a Gouy balance at room temperature using $\text{Hg}[\text{Co}(\text{SCN})_4]$ as the calibrant. FT-IR spectra were recorded in KBr disc on a Nicolet, Avatar 370 spectrophotometer in wave number region $4000-400\text{ cm}^{-1}$. ^1H -NMR spectra were recorded on a Bruker Avance III, 400 MHz model spectrometer employing TMS as internal reference and $\text{DMSO}-d_6$ as solvent. EPR spectra of compounds were recorded on E-112 ESR Spectrometer with X-band microwave frequency (9.5 GHz).

Synthesis of 2-((E)-(4-nitrophenylimino)methyl)phenol

The Schiff base ligand was prepared by mixing an ethanolic solution of 4-nitrobenzenamine (1 mmole) and ethanolic solution of 2-hydroxybenzaldehyde (1 mmole) with constant stirring. On adding solution of 4-nitrobenzenamine to the solution of 2-hydroxybenzaldehyde, the colourless solution turns reddish orange solution. This mixture was then refluxed for 2 hrs on waterbath. Then the resulting solution was then allowed to cool at room temperature. As the volume of the solvent is reduced the reddish orange crystal separates out and is then dried and cooled.

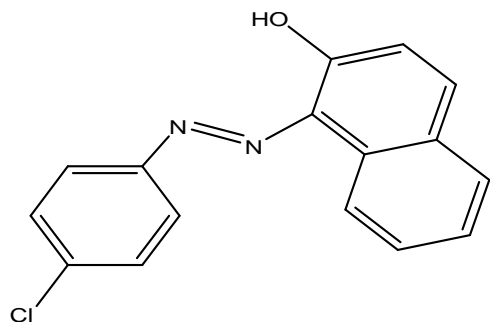

Figure 1 Structure of Schiff base Ligand (L^1)

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Synthesis of 1-(4-chloro-phenylazo)-naphthalen-2-ol (L^2)

A (0.054 mol) of 4-chloroaniline was dissolved in 16 ml of conc. HCl and 16 ml of water; it is then cooled in ice bath. Then 20 ml of (0.058 mol) sodium nitrite solution was added to the above solution with constant stirring. A cooled solution (45 ml) 10 % NaOH solution of 2-naphthol (0.054 mol) was added drop wise to the resulting solution with stirring and the mixture was left for 1 hr at 0 °C. Red precipitate was filtered and recrystallized from acetic acid, then washed with ethanol.



1-(4-Chloro-phenylazo)-naphthalen-2-ol
Figure 2 Structure of Azo dye Ligand (L^2)

Synthesis of Schiff base mixed ligand Metal (II) Complexes

1 mmole of metal salt in ethanol (20 ml) were mixed and stirred with 1 mmole Schiff base ligand (L^1) in warm alcoholic solution (20 ml) in round bottom flask. It is then followed by the addition of azo dye ligand (L^2). Resulting reaction mixture was refluxed for 4 hours on water bath. Dark coloured complexes were allowed to digest and collected by filtration through whatmann filter paper. Then washed with sufficient quantity of hot ethanol to apparent to dryness and dried in vacuum desiccators. Obtained product is dried and stored in a sample glass bottle.

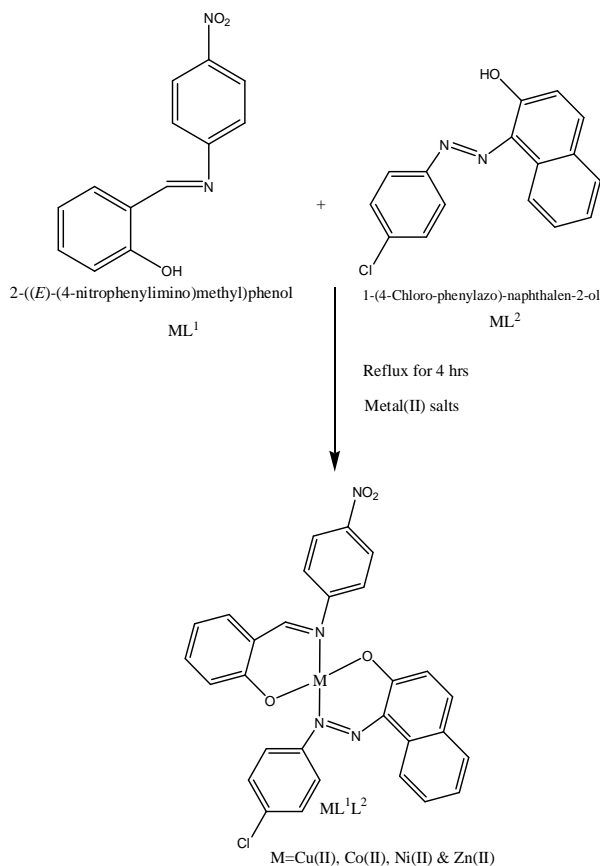


Figure 3 Synthesis of Schiff base mixed ligand complexes [ML^1L^2]

Evaluation of Pharmacological Properties**Paper disc diffusion technique**

The sterilized (autoclaved at 120 °C for 30 min) medium (40–50 °C) was inoculated (1 ml/100 ml of medium) with the suspension of the microorganism and poured into a petridish to give a depth of 3–4 mm. The paper impregnated with the test compounds (50 µg/ml in dimethylformamide) was placed on the solidified medium. The plates were pre-incubated for 1 hr at room temperature and incubated at 37 °C for 24 hrs. Streptomycin (50 µg/ml/ disc) were used as standard and the inhibition of synthesized compounds were compared with the standard zone.

Antifungal Activity

One day prior to the experiment, the fungal cultures were inoculated in nutrient broth (inoculation medium) and incubated overnight at 37 °C. Inoculation medium containing 24 h grown culture was added aseptically to the nutrient medium and mixed thoroughly to get uniform distribution. This solution was poured (25 ml in each dish) into petri dishes and then allowed to attain room temperature. Wells (6 mm in diameter) were cut in the agar plates using proper sterile tubes. Then, the wells were filled up to the surface of agar with 50 µg/ml of the test compounds dissolved in DMSO. The plates were allowed to stand for an hour in order to facilitate the diffusion of the drug solution. Then the plates were incubated at 37 °C for 48 hr for fungi and the diameter of the inhibition zones was measured. The concentration of DMSO in the medium did not affect the growth of any of the microorganisms tested.

DNA-binding experiments

Electronic absorption spectroscopy has been widely employed to determine the binding characteristics of metal complexes with DNA. The DNA binding experiments were performed in Tris-HCl/ NaCl buffer (50 mM Tris-HCl/ 1 mM NaCl buffer, pH 7.5) using DMF (dimethylformamide) solution (10 %) of the metal complexes. The concentration of calf-thymus (CT) DNA was determined from the absorption intensity at 200 nm. Absorption titration experiments were made using different concentrations of CTDNA [0–100 µM], keeping the concentration of the complexes constant, with due correction for the absorbance of the CT-DNA itself. The absorbance (A) was recorded after successive additions of CT-DNA. While measuring the absorption spectra, an equal amount of CT-DNA was added to both the compound solution and the reference solution to eliminate the absorbance of the CT-DNA itself. Samples were equilibrated before recording each spectrum. Viscosity measurements were conducted on Ostwald's viscometer at $30 \pm 0.01^\circ\text{C}$ using fixed concentration of DNA solution (100 µM) with increasing concentration of chiral Schiff base metal complexes (0–50 µM) in phosphate buffer (10 mM, pH 7.0) for flow time measurements. Each sample was measured in triplicate and the average flow time was calculated with a digital stopwatch. Data were presented as $(\eta/\eta_0)^{1/3}$ versus the ratio of the concentration of the compound and DNA, where η is the viscosity of DNA in the presence of the complex, and η_0 is the viscosity of DNA alone.

RESULTS AND DISCUSSION

The Schiff base ligand (L^1) was reddish orange and azo dye ligand (L^2) was red in colour, but the prepared complexes of these ligands vary in colour depending on the metal ions used during this research. The experimental results of the elemental analyses

of the ligand and its metal complexes are good agreement with theoretical expectation. The elemental analyses of the complexes indicate that the (M: L¹:L²) ratios were (1:1:1) in the [M L¹L²] where M = Co (II), Ni (II), Cu (II) and Zn (II). The complexes were found to be stable in air and insoluble in water, but soluble in DMF, DMSO and Acetonitrile.

Table 1 Molar conductance and Infrared spectroscopic data of the synthesized ligands and its mixed ligand complexes

Complexes	ν (C=N)	ν (O-H)	ν (N=N)	ν (M-O)	ν (M-N)	$\text{scm}^2\text{mol}^{-1}$
L ¹	1621	3396	-	-	-	-
L ²	-	3431	1577	-	-	-
[CuL ¹ L ²]	1609	-	1523	541	446	5.2
[CoL ¹ L ²]	1611	-	1527	554	435	4.8
[NiL ¹ L ²]	1604	-	1531	559	431	6.3
[ZnL ¹ L ²]	1601	-	1539	544	450	3.2

Microanalysis

The elemental analysis data the complexes exhibit the formation 1:1:1 [M L¹L²] ratio. It was found that the theoretical values are in a good agreement with the found data. The purity of the Schiff base ligand was listed by TLC technique and C, H and N elemental analyses. Analytical data of the synthesized compounds are

Schiff base ligand (L¹): Yield: 70 %; M.pt. 172 °C. Colour: Reddish orange, Anal. Calcd. For C₁₃H₁₀N₂O₃ (FW 242.23): C, 64.46; H, 4.16; N, 11.56; Cu, 12.39. Found: C, 64.31; H, 4.02; N, 11.38.

Azo dye ligand (L²): Yield: 80 %. Colour: Red, Anal. Calcd. For C₁₆H₁₁ClN₂O (FW 282.06): C, 67.97; H, 3.92; N, 9.91. Found: C, 67.75; H, 3.71; N, 9.72.

[CuL¹L²]: Yield: 65 %. Colour: black, Anal. Calcd. For C₂₉H₁₉ClCuN₄O₄ (FW 586.48): C, 59.39; H, 3.27; N, 9.55; Cu, 10.84. Found: C, 59.19; H, 3.01; N, 9.23, Cu, 10.51.

[CoL¹L²]: Yield: 60 %. Colour: brown, Anal. Calcd. For C₂₉H₁₉ClCoN₄O₄ (FW 581.87): C, 59.86; H, 3.29; N, 9.63; Co, 10.13. Found: C, 59.15; H, 3.04; N, 9.13, Co, 10.01.

[NiL¹L²]: Yield: 65 %. Colour: black, Anal. Calcd. For C₂₉H₁₉ClNiN₄O₄ (FW 580.04): C, 59.89; H, 3.29; N, 9.63; Ni, 10.09. Found: C, 59.39; H, 3.09; N, 9.24, Ni, 9.98.

[ZnL¹L²]: Yield: 70 %. Colour: brownish yellow, Anal. Calcd. For C₂₉H₁₉ClZnN₄O₄ (FW 588.33): C, 59.20; H, 3.26; N, 9.52; Ni, 11.11. Found: C, 59.11; H, 3.02; N, 9.13, Ni, 10.96.

Molar conductivity

With a view of studying the electrolytic nature of the mononuclear metal complexes, their molar conductivities were measured in DMF (Dimethylformamide) at 10⁻³ M. The molar conductivities values of these metal complexes are in the range of 3.2- 6.3 $\text{scm}^2\text{mol}^{-1}$ at room temperature (Table.1). These lower values indicate that Schiff base mixed ligand complexes are non-electrolytes due to lack of counter ions in the proposed structures of the Schiff base mixed ligand metal complexes (Tasa et al., 2010).

Infrared spectra

The IR spectra provided valuable information regarding the nature of functional group attached to the metal atom. There are similarities in the IR spectra of the ligands and their corresponding metal complexes to each other, except for some slight variations in the shifts and intensities caused by different metal(II) ions. The

observed band in the range 1577 cm^{-1} is due to ν (N=N) group of the 1-(4-chloro-phenylazo)-naphthalen-2-ol ring moiety. The value of the ν (C=N) stretching vibration of the complexes was found at a frequency (1601-1611 cm^{-1}) than the expected value (1621 cm^{-1}). This may be explained based on a drift of the lone pair density of the azomethine nitrogen towards the metal atom (Nura Suleiman Gwaram et al., 2012; Krishnankutty et al., 2008) indicating that coordination occurred through nitrogen of the (C=N) groups. Another medium intensity band around 3396-3431 cm^{-1} in the free ligands due to phenolic -OH was absent in the complexes indicating the deprotonation of the Schiff bases prior to the coordination. This fact is further supported by the increase in the absorption frequency of the phenolic C-O from 1255-1279 cm^{-1} in the free ligands to 1286-1334 cm^{-1} in the metal(II) complexes confirming the other coordination site of Schiff base is the phenolic oxygen atom. Additionally, the presence of two new medium intensity bands at 541-559 cm^{-1} and 431-450 cm^{-1} corresponds to ν M-O and ν M-N vibrations (Navendran Padma Priya et al., 2011). Thus the IR spectra suggest that metal ion of the complexes coordinates through phenolic oxygen and nitrogen of azo group and azomethine group.

Electronic absorption spectra

The electronic absorption spectra are often very helpful in the evaluation of results furnished by other methods of structural investigation. The UV-Vis spectra of ligands show two bands: L¹ at 245 nm (40816 cm^{-1}) and 348 nm (28735 cm^{-1}), L² at 276 nm (36231 cm^{-1}) and 354 nm (28248 cm^{-1}) which is assigned to $\pi \rightarrow \pi^*$ and $n \rightarrow \pi^*$ transitions with in molecule.

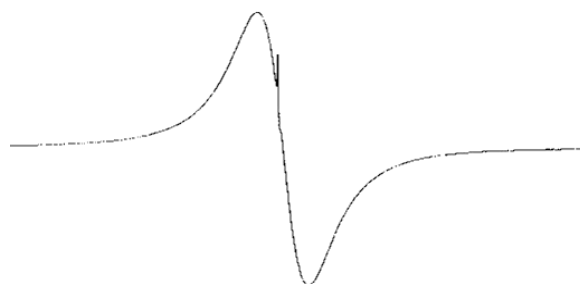


Figure 4 ESR Spectra of Cu(II) complex

Copper (II) complex

The magnetic moment value of Cu(II) complex (1.73 B.M), this value indicate within the expected for one electron, and d-d spectrum of this complex shows band at 546 nm (18315 cm^{-1}) and 462 nm (21645 cm^{-1}) which may assigned to $^2B_{1g} \rightarrow ^2A_{1g}$ transition and intra-ligand charge transfer bands, these data suggest square-planar geometry around Cu(II) (Netra Pal Singh et al., 2012).

Cobalt (II) complex

The electronic spectrum of Co(II) complex showed three broad peaks at 626 nm (15974 cm^{-1}) and 575 nm (17391 cm^{-1}) assigned to $^4A_{2g} \rightarrow ^4T_{1g}$ (F) and $^4A_{2g} \rightarrow ^4T_{1g}$ (P) transitions, respectively. The magnetic moment value of the Co(II) complex is 3.26 B.M. The spectrum resembles those reported for square planar complex (Mohammad Shakir et al., 2011).

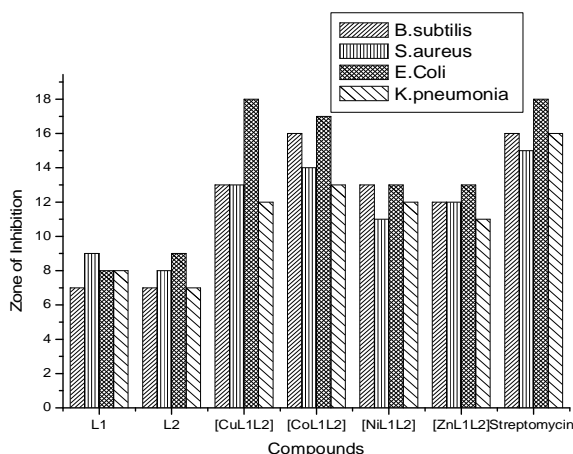


Figure 5 Inhibition zone of synthesized L^1 , L^2 and its complexes against various bacteria

Nickel (II) complex

The electronic spectrum of this complex shows band at 696 nm (14367 cm^{-1}), 655 nm (15267 cm^{-1}) and 564 nm (17730 cm^{-1}) which can be assigned to $^1A_{1g} \rightarrow ^1A_{2g}$, $^1A_{1g} \rightarrow ^1B_{2g}$ and $^1A_{1g} \rightarrow ^1E_g$ respectively, characteristic of square planar geometry around Ni(II) ion. The diamagnetic nature revealed by magnetic moment studies further confirms the square planar environment around the Ni (II) ion (Cemal Senol et al., 2011).

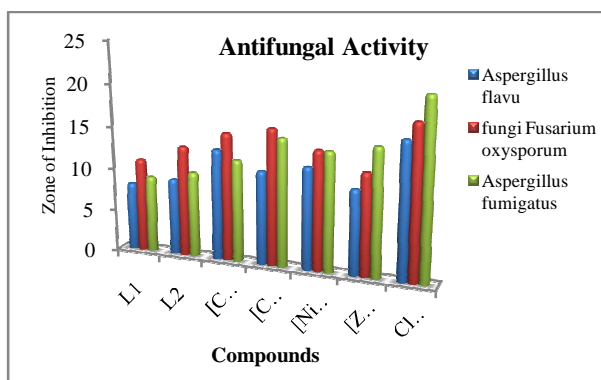


Figure 6 Inhibition zone of synthesized L^1 , L^2 and its complexes against various Fungi

Zinc(II) complex

Metal complex is diamagnetic consistent with the (d^{10}) configuration and no d-d transition is expected. The electronic spectra of these complex exhibit high intense charge transfer transition which are assigned to (INCT) (Kerim Serbest et al., 2008).

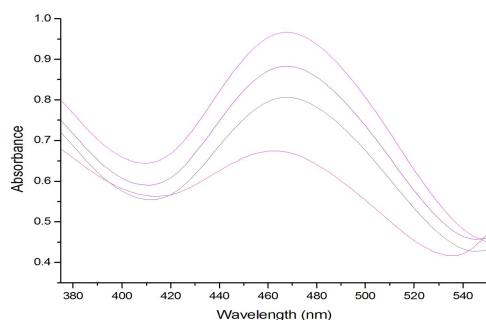


Figure 7 Absorption spectra of $[CuL^1L^2]$ in Tris-HCl buffer upon addition of DNA. $[Cu(II)] = 0.5\text{ }\mu\text{M}$, $[DNA] = 0-100\text{ }\mu\text{M}$.

1H NMR Spectra

The 1H NMR spectra of free ligand are reported along with possible assignments in the experimental section. 1H NMR spectrum of the Schiff base ligand (L^1) was recorded in $DMSO-d_6$. All the protons were found as to be in their expected region (Muneerah et al., 2013). The observed signal at 10.40 ppm was assigned to the proton of phenolic -OH group. This peak is due to hydrogen bonded phenolic protons and the integration is generally less than 2.51 ppm due to this intramolecular hydrogen bonding. Signal for the methine proton of the characteristic azomethine group for Schiff base, $-N=CH-$ were observed at 8.34 ppm. In the region of 6.98–6.42 ppm chemical shifts were assigned for hydrogen of the aromatic ring. These support the proposed structure of the Schiff base ligand (L^1).

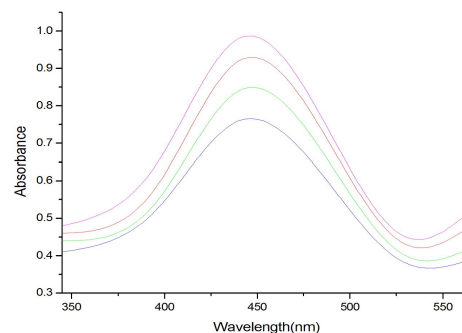


Figure 8 Absorption spectra of $[CoL^1L^2]$ in Tris-HCl buffer upon addition of DNA. $[Co(II)] = 0.5\text{ }\mu\text{M}$, $[DNA] = 0-100\text{ }\mu\text{M}$.

EPR Spectroscopy Study

The EPR spectrum pattern of the solid copper(II) complex at room temperature exhibits g values ($g_{\parallel} = 2.430$, $g_{\perp} = 2.096$ and $\Delta g = 0.334$), where $g_{\parallel} > g_{\perp} > 2.0023$, indicating $d(x^2-y^2)$ ground state for square planar copper(II) complexes. The calculated $g_{av} = (g_{\parallel} + 2g_{\perp})/3 = 2.207$, suggests the high covalence property of complex (Sulekh Chandra et al., 2005).

Antibacterial activity

The antibacterial activities of all prepared ligands and its complexes have been evaluated against two gram positive pathogenic strains such as Staphylococcus aureus, Bacillus subtilis while Escherichia coli and Klebsiella species were gram negative strains. The disc diffusion technique was followed at a concentration of 50 $\mu\text{g/mL}$ with Streptomycin taken as the standard drugs.

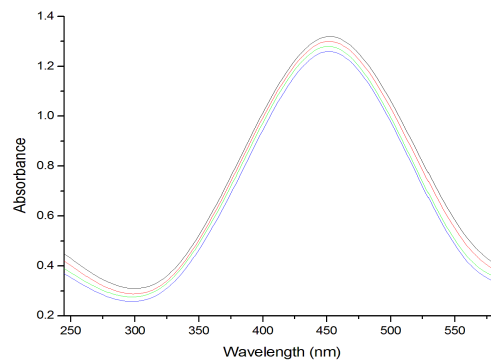


Figure 9 Absorption spectra of $[NiL^1L^2]$ in Tris-HCl buffer upon addition of DNA. $[Ni(II)] = 0.5\text{ }\mu\text{M}$, $[DNA] = 0-100\text{ }\mu\text{M}$.

The measured antibacterial activities of all the synthesized compounds are presented in figure 5. Against *Escherichia coli*, Cu(II) and Co(II) complexes showed maximum zone of inhibition greater than 15 mm. The ligands and their complexes are less effective towards other bacteria. Also, it was noted that the complexes showed greater inhibition than the ligands (Krishnakumar et al., 2013). It was evident that overall potency of the ligand was enhanced on coordination with the metal ions. This enhancement in the activity may be rationalized on the basis that ligands mainly possess C=N bond. It has been suggested that the ligands with nitrogen and oxygen donor atoms inhibit enzyme activity, since the enzymes which require these groups for their activity appear to be especially more susceptible to deactivation by metal ions on coordination.

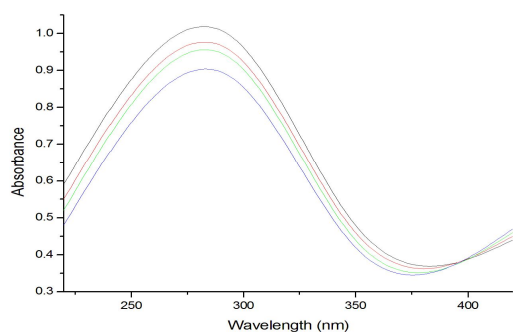


Figure 10: Absorption spectra of $[ZnL^1L^2]$ in Tris-HCl buffer upon addition of DNA. $[Zn(II)] = 0.5 \mu M$, $[DNA] = 0-100 \mu M$.

Moreover, coordination reduces the polarity of the metal ion essentially because of the partial sharing of its positive charge with the donor groups (Halli et al., 2012) within the chelate ring system formed during coordination. This process, in turn, increases the lipophilic nature of the central metal atom, which favours its permeation more effectively through the lipid layer of microorganism, thus destroying them more aggressively. In conclusion the complexes prepared with the new Schiff base could be used for the treatment of some common diseases caused by *E. coli*.

Antifungal activity

Measurement of antifungal activities of all the synthesized ligands and its Schiff base mixed ligand complexes have been done using well diffusion technique. The drugs dilution was $50 \mu g/mL$ in DMF. Clotrimazole has been taken as the standard drug. The observed antifungal activities of all synthesized compounds are presented in Figure 6. From the results obtained by the antifungal activity it was found that the metal complexes are more active against all tested fungi than the ligands (Hassan et al., 2012).

DNA binding experiments

Absorption titration

The absorption spectroscopy was used to monitor the interactions of complexes with DNA. In general, complex bound to DNA through intercalation usually results in hypochromism and red shift (bathochromism), due to the strong stacking interaction between aromatic chromophore of the complex and the base pairs of DNA. The extent of the hypochromism and red shift commonly gives a measure of the strength of DNA binding (Sangeetha Gowda et al., 2013). The absorption spectra of Schiff base mixed ligand Cu (II), Ni (II), Co (II) and Zn (II) complexes

in the presence and absence of CT-DNA is shown in Figure 7-10. When an incremental concentration of CT-DNA solution was added to a fixed concentration of the metal complex solution, a decrease in absorption intensities (hypochromism) of the metal complexes was observed.

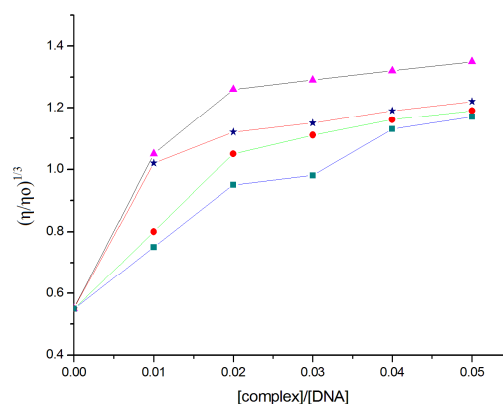


Figure 11: Plot of relative viscosity vs $[Complex]/[DNA]$. Effect of increasing amounts of $[CuL^1L^2]$ (▲), $[ZnL^1L^2]$ (*), $[CoL^1L^2]$ (●) and $[ZnL^1L^2]$ (■), on the viscosity of CT-DNA at room temperature. $R = [complex]/[DNA]$. Complex = 0–50 μM , $[DNA] = 100 \mu M$.

The interactions between the complex and DNA were investigated by viscosity measurements. Viscosity experimental results clearly show that all the complexes can intercalate between adjacent DNA base pairs, causing an extension in the helix, and thus increase the viscosity of DNA. The complexes can intercalate strongly, leading to a greater increase in viscosity of the DNA with an increasing concentration of complexes as shown in Figure 11. Moreover, the sequence of the observed increase in values of viscosity correlates the binding affinity to DNA, thus shows the highest binding affinity to DNA and the highest viscosity. The observations made during the absorption titration, viscosity measurements are reminiscent of those reported earlier for various metallo intercalators, thus suggesting that the complexes bound to DNA by intercalations (Sreekanth et al., 2011).

CONCLUSION

A series of mononuclear Cu (II), Co (II), Ni (II) and Zn (II) complexes have been synthesized from Schiff bases (L^1) and azo ligand (L^2) in 1:1:1 ratio. The stoichiometries of complexes have been confirmed by elemental analyses, IR, 1H NMR spectral data and molar conductance studies. Tetra coordinated (NNOO) square planar geometry has been suggested to complexes by ESR, UV-Visible spectroscopy and magnetic data. All the synthesized mixed ligand complexes have been comparatively active against *B. Subtilis*, *K. Pneumonia*, *E. coli* and *S. aureus*. It also shows efficient activity in DNA binding studies.

Acknowledgements

Financial support from DST INSPIRE Fellowship, New Delhi, is gratefully acknowledged. We are also thankful to our supervisor and professors of department of chemistry, Periyar University – Salem, for further support.

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