Research Article

Synthesis, Spectral Characterization and *in- vitro* Drug Actions of Co(II) and Ni(II) Complexes with 2-aminobenzonitrile and Benzoate Ion Ligands

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ABSTRACT

New Co(II) and Ni(II) complexes of 2-aminobenzonitrile (2-ABN) and benzoate ion (BEN) ligands have been prepared. The structure of these compounds has been investigated by using elemental analysis, molar conductance, magnetic susceptibility, spectral (Infra Red, UV-Visible, Cyclic Voltammetry, Powder X-rd) and thermal measurements. IR spectra indicate that the ligand behaves as uninegative monodentate/ bidentate with O/N,N donor sequence towards the metal ions. Bacterial and fungal activities of the ligands and their Co(II) and Ni(II) complexes were studied against *staphylococcus aureus, streptococcus, Escherichia coli, Klebsiella pneumonia, P. aeruginosa, salmonella typhi, Enterobacter, C.albicans, Aspergillus Niger* and *Aspergillus Flavus* by using well-diffusion method. The free radical scavenging activity of the metal complexes and the ligands has been determined by measuring their interaction with the stable free radical, DPPH. The complexes have superior antioxidant activity as compared to the ligands. DNA-binding properties have been studied by fluorescence-emissions method. The results suggest that the complexes strongly bind to DNA because of metal complexes are well known to speed up the drug action and the ability of a healing agent which can frequently be superior upon coordination with a metal ion.

Keywords: 2- aminobenzonitrile, benzoate ion, antifungal, antioxidant, DNA-binding ability.

INTRODUCTION

Metallo-organic compound is far above the view interest in crystal engineering which aims to predict and control the fashion molecules assemble in the solid state[1–4]. In the designing of metal complexes with unique properties for a wide range of prospective applications including antimicrobial drugs[5,6], conductive material[7], luminous[8] and magnetic materials[9]. Among the aminobenzonitriles, 2-aminobenzonitrile (2-ABN) is a second-hand for the induction of nitrilase activity in arthrobacter, radio protective agent and starting materials for the synthesis of bio-active compounds[10-12]. The 2-aminobenzonitrile is one of the organic ligands in coordination chemistry which can synchronize to the metal ion through different modes *viz.,* monodentate/bidentate or bridging manner. In general, the biological activities of the metal complexes differ from those of either the ligand or the metal ion itself, and increased and/or decreased biological activities are reported for various metal complexes[13].

Alternatively, synthesis of inorganic/organic compounds using microwave irradiation has been a very rapidly developing technique in research area[14-20]. Compared with the conventional method, microwave technique is promising due to its unique effects, such as rapid volumetric heating, higher reaction rates, higher reaction selectivity, higher yields of products and energy saving. Literature search reveals that no work has been done on the mixed ligand complexes 2-aminobenzonitrile and benzoate ion.

In this paper, we report the synthesis, characterization, antimicrobial and DNA binding studies of Co(II) and Ni(II) complexes containing 2-aminothiazole and benzoate ion as ligands. This research mainly focused on the DNA binding properties of metal complexes. Since, in recent years, DNA binding studies of transition metal complexes have become very important in the expansion of DNA molecule probes and chemotherapeutics.

MATERIALS AND METHODS

Materials

2-aminobenzonitrile, sodium benzoate, cobalt nitrate and nickel nitrate were purchased from Alfa Aaser Company and used as such. The organic solvents used, were DMSO, DMF, CH_3OH, EtOH which were of AnalaR grade, and used as such without further purification.

Synthesis of Metal Complexes

Synthesis of Co(II) complex

The ethanolic solution of 1.12 g (10.7 mmol) of 2-ABN and the ethanolic solution of 1.20 g (7.4 mmol) of sodium benzoate were added to the methanolic solution of cobalt nitrate 1.00 g (3.4 mmol) followed by microwave irradiation for a few seconds after each addition by using

IFB 25 BG-1S model microwave oven. The consequential precipitate was filtered off, washed with 1:1 ethanol: water mixture and desiccated under vacuum. A pink colored complex was obtained with 64.65 % yield.

Synthesis of Ni(II) complex

The methanolic solution of nickel nitrate 1.00 g (3.4 mmol) is added to the ethanolic solution of 1.18 g (1.21 mmol) of 2-ABN and 1.02 g (5.7 mmol) of sodium benzoate under by microwave irradiation for a few seconds after each addition by using IFB 25 BG-1S model microwave oven. The major precipitate was filtered off, washed with 1:1 ethanol: water mixture and desiccated under vacuum. A pink colored complex was obtained with 55.70 % yield.

Instrumentations

The elemental analyses C,H,N were performed using Thermo Finnegan make, Flash EA1112 Series CHNS(O) analyzer. The molar conductivity measurements were conducted using 10^{-3} M solutions of the metal complexes in acetonitrile with Systronic Conductivity Bridge (model number-304) at 30°C. The UV-Visible spectrum of the Co(II) and Ni(II) complexes were recorded on Varian, Cary 5000 model UV Spectrophotometer. IR spectra for the complexes and the free ligands were recorded on a Perkin Elmer, Spectrum RX-I, FT IR spectrometer in KBr discs at room temperature. The cyclic voltammograms of the complexes were taken in acetonitrile medium using Princeton make (MC-Tech, Applied Research) equipment. Tetrabutylammonium tetrafluoroborates (TBATFB) was used as the supporting electrolyte. The thermogravimetric analyses of the complexes were carried out using Perkin Elmer Diamond TGA/DTA Instrument. The powder X-ray diffractogram of Co(II) and Ni(II) complexes were recorded using Rigaku model X-ray Diffractometer.

Biological Activities

Antibacterial and antifungal activity

The Co(II) and Ni(II) complexes and the free ligands were tested against *in-vitro* bacterial and fungal activity by well diffusion method. The microbial activities of the free ligands and their complexes were evaluated against the strains cultured on potato dextrose agar as medium. The stock solution was prepared by dissolving the compounds in DMSO and the solutions were successively diluted to different concentrations. According to the typical procedure a well was made on the agar medium inoculated with the microorganisms. The well was filled with the test solution using a micropipette and the plate was incubated for 24 hours for bacteria and 72 hours for fungi at 35°C. At the end of the period, zone of inhibitions formed on the medium were evaluated in millimeter (mm) diameter[21, 22].

Antioxidant activity

Evaluation of antioxidant activity stock solution (1mg/ml) was diluted to final concentrations of 10–500 µg/ml. Ethanolic DPPH solution (1 ml, 0.3 mmol) was added to sample solutions in DMSO (3 ml) at different concentrations[23] (10–500 µg/ml). The mixture was shaken energetically and acceptable to stand at room temperature for 30 min. The absorbance was then measured at 517 nm in a UV-Vis Spectrophotometer. The lower absorbance of the reaction mixture indicates higher free radical scavenging activity. Ethanol was used as the solvent and ascorbic acid as the standard. The DPPH radical scavenging activity was designed by the following equation:

$$\text{DPPH Scavenging effect (\%)} = A_o - A_1 / A_o \times 100$$

where Ao is the absorbance of the control reaction and A_1 is the absorbance in the presence of the samples or standards.

DNA binding properties

The DNA binding experiments involving interaction of the prepared Co(II), Ni(II) complexes and the free ligands with calf thymus (CT)-DNA were conducted in Tris buffer containing HCl (0.01 M) adjusted to pH 7.2 with hydrochloric acid. The CT-DNA was dissolved in Tris-HCl buffer and was dialyzed against the same buffer overnight. Solutions of CT-DNA gave the ratios of UV absorbance at 260 and 280 nm above 1.8, demonstrating that the DNA was adequately free of protein. DNA concentration per nucleotide was determined by absorption spectroscopy using the molar absorption coefficient 6600 dm^{3}mol^{-1}cm^{-1} at 260 nm. The stock solutions were stored at 4°C and used within 4 days[24].

For fluorescence-quenching experiments, DNA was pre-treated with ethidium bromide (EtBr) for 30 minutes. The ligand/ complex samples were then added to this mixture and their effect on the emission intensity was measured. Samples were excited at 450 nm and emission was observed between 500 nm and 800 nm.

RESULTS AND DISCUSSION

Elemental analysis

The elemental analysis data, percentages of carbon, hydrogen and nitrogen for Co(II) and Ni(II) complexes are 51.28(55.03), 3.98(3.90), 12.91(11.73) and 56.44(55.53), 4.43(4.76), 11.72(10.73) respectively. The results were found to be good agreement with the theoretical values given in the parenthesis.

Molar conductance

Molar conductance value of the complexes (10^{-3} M) in acetonitrile medium was found to be 44.87-53.76 Ω^{-1}cm^{2}mol^{-1}. The low electrical conductivity value indicates that the Co(II) and Ni(II) complexes are non-electrolytic 1:0 type[25] confirming their molecular formulae [Co(BEN)$_2$(2-ABN)$_2$] and [Ni(BEN)$_2$(2-ABN)$_2$].

UV-Visible spectra and Magnetic moment

Co(II) complex

The UV-Visible spectrum of [Co(BEN)$_2$(2-ABN)$_2$] complex exhibits three absorbtion bands at 13561 cm^{-1}, 23188 cm^{-}

^{1} and 26365 cm^{-1} and their corresponding transitions [26] may be assigned as $^{4}T_{1g}(F) \rightarrow {}^{4}T_{2g}(F)$ (ν_1), $^{4}T_{1g}(F) \rightarrow {}^{4}A_{2g}(F)$ (ν_2) and $^{4}T_{1g}(F) \rightarrow {}^{4}T_{1g}(P)$ (ν_3) which are the characteristic of six coordinate octahedral geometry of Co(II) complexes. The ligand to metal charge transfer band was seen at 31250 cm^{-1}. The observed magnetic moment, 3.46 B.M is close to hexa-coordination around the Co(II) metal ion[27,28].

Ni(II) complex

The UV-Visible spectrum of [Ni(BEN)$_2$(2-ABN)$_2$] complex shows absorbtion bands at 14389 cm^{-1}, 24428 cm^{-1} and 28255 cm^{-1} and their corresponding transitions are $^{3}A_{2g}(F) \rightarrow {}^{3}T_{2g}(F)$ (ν_1), $^{3}A_{2g}(F) \rightarrow {}^{3}T_{1g}(F)$ (ν_2) and $^{3}A_{2g}(F) \rightarrow {}^{3}T_{1g}(P)$ (ν_3) respectively[29-31] suggests hexa coordination around Ni(II) metal ion in complex. The spectrum also shows a band at 27680 cm^{-1} which may be attributed to the ligand to metal charge transfer. The observed magnetic moment value of Ni(II) complex is 2.89 B.M. This suggests the presence of octahedral environnent around Ni(II) complex[32].

IR spectra

The IR spectra provide valuable information regarding the nature of functional group attached to the metal atom. In order to study the binding modes of the ligands, 2-aminobenzonitrile and benzoate ion to the complexes, the IR spectra of free ligands were compared with their Co(II) and Ni(II) complexes. The 2- ABN shows characteristic absorption bands in the 3453 cm^{-1}, 3366 cm^{-1} and 2206 cm^{-1} region, assignable to asymmetric, symmetric stretching frequencies of $\nu(NH_2)$ and ν (C≡N) respectively[33,34]. A small band noticed at 3076 cm^{-1} is due to ν(CH) aryl group. Aromatic ν(C=C) stretching vibration is seen as a sharp peak at 1563 cm^{-1} . The benzoate ion shows ν(C–O) at 1207cm^{-1}. A strong band with a shoulder noticed at 1605 cm^{-1} can be attributed to ν(C=O) of the carbonyl group[35]. The band(s) are broadened at 3417-3367 cm^{-1} and the nitrile group of the ABN underwent higher frequency at 2228 cm^{-1} after complexation, indicating the coordination of amino nitrogen and cyano nitrogen (N,N) to the metal ion. In free benzoate ion, the v(C-O) stretching at 1207 cm^{-1} get shifted to the frequencies of 1228 cm^{-1} nearly in complexes, which indicates the monodentate coordination of the benzoate ion through oxygen atom.

Cyclic voltammetry

Co(II) Complex

The [Co(BEN)$_2$(2-ABN)$_2$] complex exhibits one-electron quasi-reversible transfer process with a reduction peak at Epc = 0.7V, and a corresponding oxidation peak at Epa= 1.3V at the scan rate of 50mV/s. The peak separation (ΔEp) of this couple is 0.6V. With the increasing scan rates, ΔEp value also increases giving further evidence of quasi-reversible Co(II)/Co(I) couple[36].

Ni(II) complex

A significant feature is observed in the cyclic voltammogram of [Ni(BEN)$_2$(2-ABN)$_2$] complex. During the forward scan it shows two cathodic reduction peaks, one at +0.4V and the other at -1.1V which are attributed to the reduction of Ni(II)→Ni(I) and Ni(I)→Ni(0) respectively. During the reverse scan, it shows two anodic peaks, one at +0.8V and the other at -0.6V which are attributed to the oxidation of Ni(0)→Ni(I) and Ni(I)→Ni(II) respectively [37].

Thermogravimetric analysis

Thermogravimetric analysis of [Co(BEN)$_2$(2-ABN)$_2$] and [Ni(BEN)$_2$(2-ABN)$_2$] complexes of 2-ABN and benzoate ion shows two important temperature transitions of weight loss with frequent and definite stages, termed as two stages of thermal degradation. The weight loss at the range of 200-260 °C in TGA curves of complexes is termed as the first stage of thermal degradation shown in Fig.1 & 2. In these complexes, the present weight loss is in the range of (22.48- 30.50%), which may be attributed to the decomposition of benzoate ion. The beginning of second step decomposition occurs in the range of 220-300 °C, which gives the loss of 2- aminobenzonitrile (45.55 – 58.33%) bonding with the metal complexes. The experimental values are in full agreement with the percent weight calculated on the basis of stoichiometry proposed for the complexes[38].

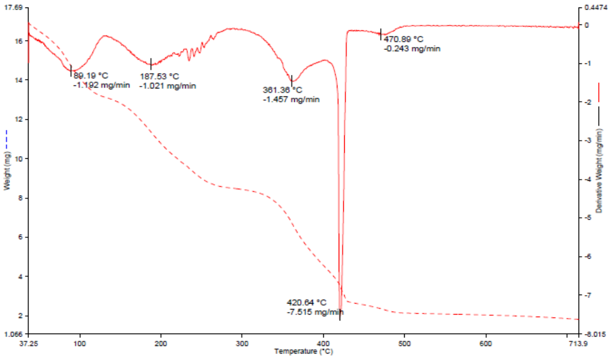

Figure 1: Thermogram of [Co(BEN)$_2$(2-ABN)$_2$]

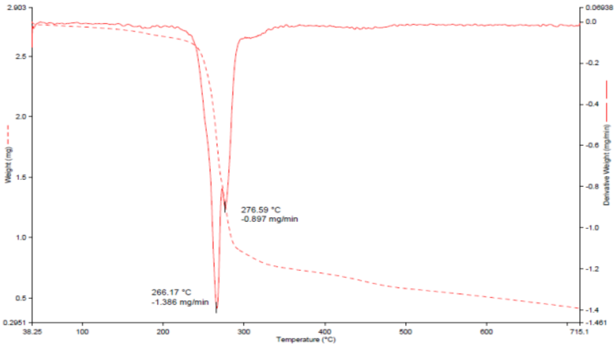

Figure 2: Thermogram of [Ni(BEN)$_2$(2-ABN)$_2$]

Powder X-ray diffraction technique

The X-rd pattern indicates that the prepared [Co(BEN)$_2$(2-ABN)$_2$] and [Ni(BEN)$_2$(2-ABN)$_2$] complexes have well defined crystalline patterns, with various degrees of crystallinity. In these complexes, the trend of the curves decreases from maximum to minimum intensity indicating amorphous nature of the complexes[39]. The powder X-rd patterns of the synthesized Co(II) and Ni(II) complexes show sharp crystalline peaks indicating their crystalline phase. The average crystallite size (d_{xrd}) of the complexes was calculated using Scherer's formula[40, 41]. The prepared complexes had an average crystallite size of around 28 nm indicating its nanocrystalline nature.

Biological activities

Antibacterial activity

The synthesized Co(II) and Ni(II) complexes and the free ligands 2-ABN and sodium benzoate are tested against the bacteria *viz., staphylococcus aureus, streptococcus, Escherichia coli, Klebsiella pneumonia, P. aeruginosa, salmonella typhi* and *Enterobacter* at different concentrations by agar-well diffusion method *in-vitro* conditions. The complexes have potential activity against the bacteria compared to free ligands as shown in Fig. 3. This is probably due to the greater lipophilic nature of the complexes. It is evident from the data that this activity significantly increases on coordination[42].

Antifungal activity

The synthesized Co(II) and Ni(II) complexes and the free ligands 2-ABN and sodium benzoate were evaluated against the fungi, *viz., C.albicans, Aspergillus Niger, Aspergillus Flavus,* at different concentrations by agar-well diffusion method. The complex shows superior activity against the tested fungi. A proportional study of zone of inhibition diameter values of the ligands and their complexes indicate that the metal complexes have a better fungicidal activity than the free ligands as shown in Fig. 4.

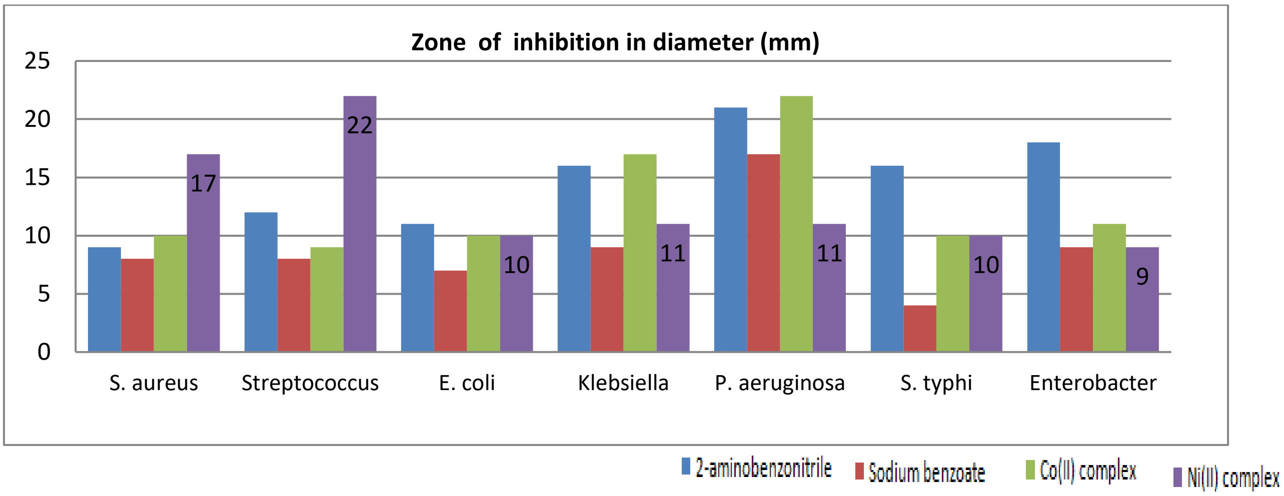

Figure 3: Antibacterial activities of free ligands and their Co(II) and Ni(II) complexes

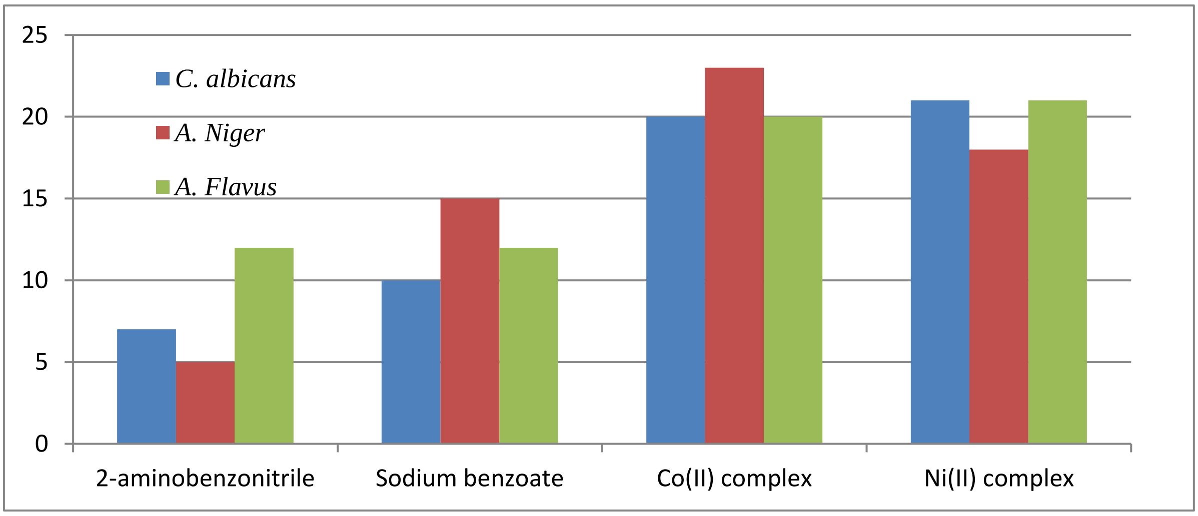

Figure 4: Fungal activities of free ligands and their Co(II) and Ni(II) complexes

Antioxidant activity (Radical Scavenging Activity)

The 2,2′′-diphenyl-1-picrylhydrazyl (DPPH) radical assay provides an easy and rapid way to evaluate the antiradical activities of antioxidants. Determination of the reaction kinetic types DPPHH is a product of the reaction between DPPH• and an antioxidant.

$$(AH): DPPH^{\bullet} + AH \rightarrow DPPHH + A^{\bullet}$$

The reversibility of the reaction is evaluated by adding DPPHH at the end of the reaction. If there is an increase in the percentage of remaining $DPPH^{\bullet}$ at the plateau, the reaction is reversible, otherwise it is a complete reaction.

DPPH was used as a stable free radical electron accepts or hydrogen radical to become a stable diamagnetic molecule[43]. DPPH is a stable free radical containing an odd electron in its structure and usually used for detection of the radical scavenging activity in chemical analysis[44]. The reduction capability of DPPH radicals was determined by decrease in its absorbance at 517 nm induced by antioxidants[45]. The graph was plotted with percentage scavenging effects on the y-axis and concentration (µg/ml.) on the x-axis. The scavenging ability of the Co(II) and Ni(II) complexes were compared with Vitamin C as a standard. In Fig.5, the metal complexes showed enhanced activity as a radical scavenger compared with ascorbic acid, these results were in good agreement with previous metal complexes studies where the ligand has the antioxidant activity and it is expected that the metal moiety will increase its activity[46-48].

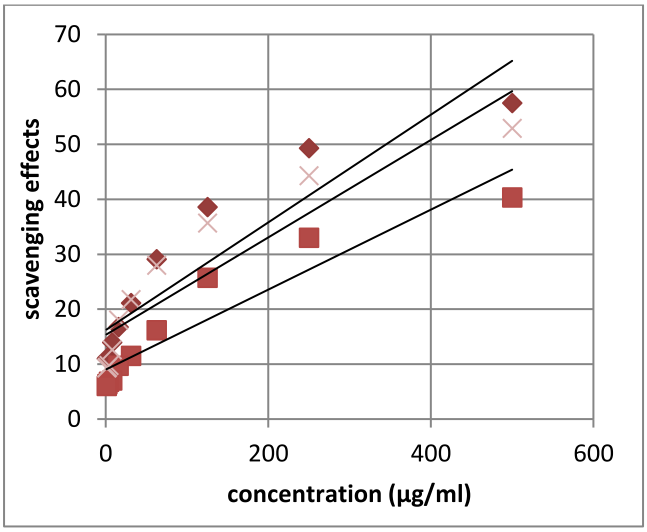

Figure 5: Antioxidant activities of free ligands and their complexes

DNA Binding – Emission study

The binding of free ligands and their Co(II) and Ni(II) complexes to *CT*-DNA can be studied by competitive binding experiments. Ethidium bromide (EB) is known to show fluorescence when bound to DNA, due to its strong intercalation between the adjacent DNA base pair. The fluorescent light is quenched by the addition of a second molecule[49,50]. The quenching extent of fluorescence of ethidium bromide binding to DNA is used to determine the extent of binding between the second molecule and DNA. The addition of the complex to DNA pretreated with ethidium bromide causes appreciable reduction in the emission intensity, indicating the replacement of the ethidium bromide fluorophore by the complex results in a decrease of the binding constant of the ethidium to the DNA as shown in Fig.6 &7. According to the classical Stern-Volmer equation: Io/I = 1 + Ksvr, where Io and I are the fluorescence intensities in the absence and the presence of complex respectively. Ksv is a linear Stern–Volmer quenching constant, r is the ratio of the total concentration of complex to that of DNA. The quenching plots illustrate that the quenching of ethidium bromide bound to DNA by the complex are in good agreement with the linear Stern-Volmer equation, which also indicates that the complex binds to DNA. In the plot of I_0/I versus $C_{Complex}/C_{DNA}$, K is given by the ratio of the slope to intercept.

The Kb values for Co(II) and Ni(II) complexes and ligand with DNA were 2.14×10^4 M^{-1}, 3.71×10^4 M^{-1} and 1.24×10^4 M^{-1}, respectively. Furthermore, Ni(II) complex is complex strongly bind to DNA compared to other complexes and the ligand. The binding constant (Kb) values indicate that interaction of the complexes with DNA is intercalative mode[51].

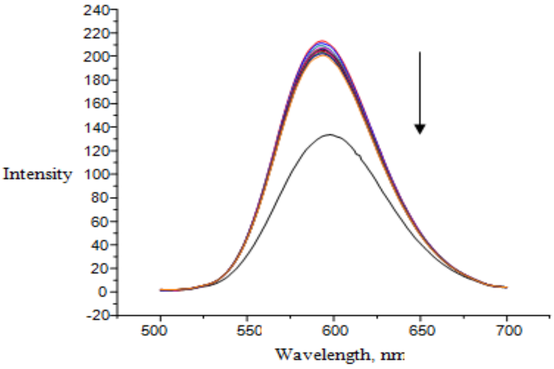

Figure 6: Emission spectrum of EtBr bound to DNA in the absence and presence of Co(II) complex. Arrows indicate the intensity changes upon increasing concentration of the complexes.

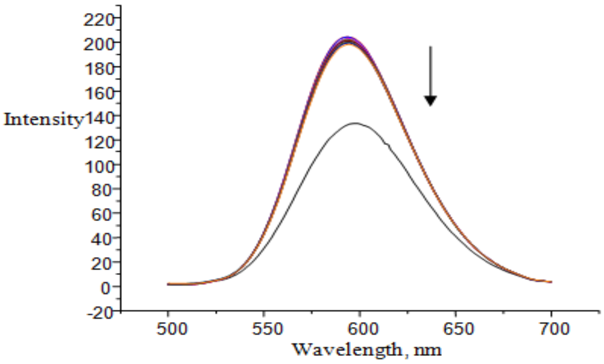

Figure 7: Emission spectrum of EtBr bound to DNA in the absence and presence of Ni(II) complex. Arrows indicate the intensity changes upon increasing concentration of the complexes.

CONCLUSION

In the present study, our efforts were to synthesize and characterize the Co(II) and Ni(II) complexes with 2-aminobenzonitrile and benzoate ion as ligands. The new complexes were prepared under microwave irradiation. The synthesized metal complexes were characterized by various physico-chemical and spectral analyses. Based on the analytical, molar conductance, spectral and magnetic moment, octahedral geometry have been suggested for the Co(II) and Ni(II) complexes. The synthesized complexes were tested for antifungal activities. The metal complex has significant antifungal and antioxidant activities as compared to the free ligands. The effectiveness of the DNA binding of the complexes is being confirmed by means of change in the intensity of emission in the case of emission spectral studies.

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