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Research Article

Synthesis, Spectral Characterization and Biopotential Significance of Co(II) and Ni(II) Complexes With Biologically Active Ligands

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ABSTRACT

New Cobalt(II) and Nickel(II) metal complexes of 2-aminothiazole (ATZ) and benzoate ion (BEN) ligands were synthesized under microwave irradiation. The empirical formulae and the structure of the complexes have been deduced from carbon hydrogen and nitrogen (CHN) analysis, electrical conductance, magnetic moment, electronic (DRS method), infra-red spectra, thermal gravimetric analysis, cyclic voltammetry, and powder-XRD techniques. The low electrical conductance values indicate that the complexes are non-electrolyte (1:0) type. The electronic spectra and the magnetic moment indicate the structures of the complexes are found to be octahedral geometry. Infra-red spectra illustrate that 2-aminothiazole and benzoate ion is bonded to the metal ion in a monodentate approach. The antifungal activities of ligands and their cobalt(II) and nickel(II) metal complexes were studied aligned with the few microorganisms by agar - well diffusion method at 100, 200 and 400 µg/mL concentration. The prepared cobalt(II) and nickel(II) metal complexes show prospective action against the tested fungi as compared to a free 2-aminothiazole ligand. The free radical scavenging action of the prepared complexes and the ligand has been resolved by measuring their interface with the stable free radical 2,2-diphenyl-1-picrylhydrazyl (DPPH). The complexes have larger antioxidant activity as compared to the free ligand. DNA-binding properties have been calculated by the fluorescence-emissions method. The obtained results suggest that the complexes powerfully bind to DNA because of metal complexes are well-known to speed up the drug action and the capability of healing agents, which can repeatedly be enhanced leading coordination with a metal ion.

INTRODUCTION

The monoazo heterocyclic compounds containing sulfur and/or nitrogen atoms are of extensive use as building blocks in chemistry, wherever they are acknowledged as biologically active compounds with a wide range of action and textile dyes as well.^[1-3] As a distinctive heterocyclic amine, 2-aminothiazole is the starting point for the synthesis of numerous compounds, together with sulfur drugs, biocides, fungicides dyes, and chemical reaction accelerators and as intermediates in the

synthesis of antibiotics, somewhere a huge number of 2-aminothiazoles have been substituted with different groups for pharmaceutical purposes^[4-6] and are also second-hand in the syntheses of various types of dyes for synthetic fibers^[7-15] next to their activity as corrosion inhibitors for mild steel protection^[16,17] corrosion inhibitors for copper^[18] and as an ionophore in the structure of a lutetium(III)-selective membrane sensor.^[19] These derivatives keep on attracting the awareness of biologists because of their prevalent use in the behavior of the biological systems.

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Furthermore, thiazole is classified under a five-membered heterocyclic class of compounds and is established in a lot of natural and synthetic agents. Thiazole is accessible in a large number of terrestrial and marine compounds with different pharmacological activities. Thiazole is also present in vitamin B1 (Thiamine). In synthetic substituted thiazole derivatives, 2-aminothiazoles^[20] have shown a variety of biological behavior such as anti-HIV, antitubercular, antifungal, antibacterial, anti-inflammatory, anticonvulsant, antidiabetic, anti-hypertensive, antiprotozoal, anticancer, dopaminergic, plasminogen activator inhibitor-1, neuroprotective and antioxidant. This broad spectrum of activities makes 2-aminothiazole as a beautiful moiety in therapeutic chemistry.^[21]

A literature search reveals that no work has been completed on the mixed ligand complexes 2-aminothiazole and benzoate ion. In this research paper, we report the synthesis, spectral characterization, antifungal, and DNA binding studies of cobalt(II) and nickel(II) complexes containing 2-aminothiazole and benzoate ion as ligands.

EXPERIMENTAL

Materials and Methods

2-aminothiazole, sodium benzoate, cobalt nitrate, and nickel nitrate were purchased from Alfa Aaser Company and used as such. The organic solvents used were $(\text{CH}_3)_2\text{SO}$, $(\text{CH}_3)_2\text{NC(O)H}$, CH_3OH , $\text{CH}_3\text{CH}_2\text{OH}$, which were of AnalaR grade, and used as such without more purification.



Synthesis of Metal Complexes

Synthesis of Cobalt(II) Complex

1.38 g (13.8 mmol) of anal transition zone (ATZ) in ethanol and 1.0 g (6.9 mmol) of sodium benzoate in ethanol were added to the cobalt nitrate 1.00 g (3.4 mmol) in methanol followed by microwave irradiation for 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 a 70.34% yield.

Synthesis of Nickel(II) Complex

Nickel nitrate 1.00 g (3.3 mmol) in methanol, 1.24 g (1.87 mmol) of ATZ in ethanol were added to 1.2 g (7.2 mmol) of sodium benzoate in ethanol the followed by microwave irradiation for few seconds after each addition by using IFB 25 BG-1S model microwave oven. The resulting impulsive was filtered off, washed with 1:1 ethanol: water mixture and dried under vacuum. The obtained complex is 68.85% yield and pale green colored.

Instrumentations

C, H, N, S elemental analyses were performed using Thermo Finnegan make, Flash EA1112 Series CHNS(O) analyzer. The electrical conductivity measurements were conducted using 10^{-3}M solutions of the metal complex in acetonitrile with the systronic conductivity bridge (model number-304) at 30°C . The electronic spectrum (DRS method) of the Co(II) and Ni(II) complexes were recorded on Varian, Cary 5000 model UV Spectrophotometer. Infrared spectra for the complexes and the free ligands were recorded on a Perkin Elmer, Spectrum RX-I, fourier-transform infrared spectroscopy (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. Tetrabutylammoniumtetrafluoroborates was used as the supporting electrolyte. The thermogravimetric analyses of the complexes were carried out using a Perkin Elmer Diamond TGA/DTA Instrument. The powder X-ray diffraction analysis of Co(II) and Ni(II) complexes was recorded on a Rigaku model X-ray Diffractometer.

BIOLOGICAL ACTIVITIES

Antifungal Activity

The cobalt(II) and nickel(II) complexes and the free ligands were tested for *in-vitro* antifungal activity by well diffusion method using agar nutrient as a medium. The antifungal activities of the ligands and the complexes were evaluated against the strains, cultured on potato dextrose agar as a medium. The stock solution (10^{-2}M) was prepared by dissolving the compounds in DMSO, and the solutions were sequentially diluted to find a zone of inhibition (mm) values. 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 72 hours for fungi at 35°C . At the end of the period, inhibition zones formed on the medium were evaluated in millimeters diameter (mm).^[22,23]

Antioxidant Activity

In the assessment of antioxidant activity, the stock solution was diluted to final concentrations of 10–500 $\mu\text{g/mL}$. Ethanolic and 2,2-diphenyl-1-picrylhydrazyl solutions (EtOH 1 mL, DPPH 0.3 mmol) were added to sample solutions in DMSO (3 mL) at different concentrations (10–500 $\mu\text{g/mL}$).^[24] The mixture was shaken vigorously and adequate to stand at room temperature for 30 minutes. The absorbance was then measured at 517 nm in an ultra-violet spectrophotometer. The lower absorbance of the reaction mixture indicates superior free radical scavenging activity. EtOH was used as the solvent and ascorbic acid (vitamin C) as the standard. The DPPH

radical scavenging activity was designed by the following equation:

$$\text{Scavenging effect (\%)} = \frac{A_0 - A_1}{A_0}$$

Where A1 is the absorbance in the presence of the samples or standards and A0 is the absorbance of the control reaction

Deoxyribonucleic Acid (DNA) Binding Studies

The DNA binding experiments involving the interaction of the complexes with Ct-DNA were conducted in Tris buffer containing HCl (0.01 M) adjusted to pH 7.2 with HCl 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, representing that the DNA was adequately free of protein. DNA concentration per nucleotide was determined by absorption spectroscopy using the molar absorption coefficient $6600 \text{ dm}^3 \text{ mol}^{-1} \text{ cm}^{-1}$ at 260 nm. The stock solutions were stored at 4°C and used within 4 days.^[25]

For fluorescence-quenching experiments, DNA was pre-treated EtBr for 30 minutes. The ligand/complexes 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 and metal estimation of the prepared complexes led to the empirical formulae. The percentages of C, H, N in the complexes were found to be a good agreement with the theoretical values (Table 1).

Molar Conductance

The molar conductance (ΛM) values of the prepared complexes (10^{-3} M) in acetonitrile medium were found to be $55.08\text{--}63.98 \text{ } \Omega^{-1} \text{ cm}^2 \text{ mol}^{-1}$. The low molar conductivity value indicates that the Co(II) and Ni(II) complexes are non-electrolytic 1:0 type,^[26] confirming their molecular formulae $[\text{Co}(\text{BEN})_2(\text{ATZ})_4]$ and $[\text{Ni}(\text{BEN})_2(\text{ATZ})_4]$.

UV-Visible Spectra and Magnetic moment

Co(II) Complex

The UV-Visible spectrum of Cobalt(II) complex exhibits three absorption bands at 14390 cm^{-1} , 22850 cm^{-1} , and 24730 cm^{-1} and their corresponding transitions^[27] may

be assigned as ${}^4\text{T}_{1g}(\text{F}) \rightarrow {}^4\text{T}_{2g}(\text{F})$ (ν_1), ${}^4\text{T}_{1g}(\text{F}) \rightarrow {}^4\text{A}_{2g}(\text{F})$ (ν_2) and ${}^4\text{T}_{1g}(\text{F}) \rightarrow {}^4\text{T}_{1g}(\text{P})$ (ν_3) which are characteristic of six-coordinate octahedral geometry of Co(II) complex. A moderately intense band seen at 31250 cm^{-1} can be confined to the ligand to metal charge transfer (LMCT) transition. The observed magnetic moment, 3.75 B.M., is close to hexa-coordination around the Co(II) metal ion. The structure is also further confirmed by the ratio $\nu_2/\nu_1 = 1.58$, which is close to the expected octahedral structure.^[28,29]

Ni(II) complex

In the electronic spectrum of Ni(II) complex shows absorption bands at 14870 cm^{-1} , 21600 cm^{-1} and 23255 cm^{-1} and their corresponding transitions, which are tentatively assigned as ${}^3\text{A}_{2g}(\text{F}) \rightarrow {}^3\text{T}_{2g}(\text{F})$ (ν_1), ${}^3\text{A}_{2g}(\text{F}) \rightarrow {}^3\text{T}_{1g}(\text{F})$ (ν_2), and ${}^3\text{A}_{2g}(\text{F}) \rightarrow {}^3\text{T}_{1g}(\text{P})$ (ν_3) respectively.^[30-32] The magnetic moment of Ni(II) complex is 2.88 B.M suggests the octahedral arrangement around Ni(II) metal ion and d^2sp^3 hybridization.^[33]

FT-IR spectra

To study the stretching mode of free ligands to their metal complex, the FT-IR spectra of the free ligands are compared with the metal complexes. The free ligand 2-aminothiazole exhibited a strong band at 3332 cm^{-1} , which could be assigned as $\nu(\text{NH}_2)$. The benzoate ion show frequencies 1555 cm^{-1} and 1601 cm^{-1} which may be assigned to aromatic $\nu(\text{C}=\text{C})$ and the stretching frequency $\nu(\text{C}=\text{O})$ was revealed at 1601 cm^{-1} .^[34,35] The aromatic $\nu(\text{C}-\text{H})$ appeared at 3010 cm^{-1} .^[36,37]

The FTIR spectra of the complexes were compared to those free ligands 2-aminothiazole and the sodium benzoate. The stretching frequency of the $\nu(\text{NH}_2)$ group was observed near 3320 cm^{-1} in Co(II) and Ni(II) complexes, and they were shifted lower than those of resultant free ligand 2-aminothiazole. This shift refers to the coordination through a nitrogen atom of 2-aminothiazole, and it is in good agreement with earlier examples of reported complexes. After that, in the sodium benzoate ion $\nu(\text{C}-\text{O})$, which occurred at 1205 cm^{-1} was moved to higher frequencies after complexation, this shift confirmed the participation of COO^- of the ligand in $\text{C}-\text{O}-\text{M}$ bond formation.^[38]

Cyclic Voltammetry

Co(II) Complex

The Co(II) complex exhibits a one-electron quasi-reversible transfer process with a reduction peak at

Table 1: Elemental analysis and molar conductance

S. No.	Complex	Elements found (Calc) %				Λm ($\Omega^{-1} \text{ cm}^2 \text{ mol}^{-1}$)
		C	H	N	M	
1	$[\text{Co}(\text{BEN})_2(\text{ATZ})_4]$	56.08 (57.03)	3.87 (3.90)	11.71 (11.73)	8.12 (8.18)	55.08
2	$[\text{Ni}(\text{BEN})_2(\text{ATZ})_4]$	62.50 (62.53)	4.41 (4.43)	8.72 (8.73)	4.20 (4.23)	63.98

BEN-Benzoate ion; ATZ-2-aminothiazole



Epc = 0.6 V, and a corresponding oxidation peak at Epa = 1.2 V at the scan rate of 50 mV/s. The peak separation (ΔE_p) of this couple is 0.6 V. With the increasing scan rates, ΔE_p value also increases, giving further evidence of quasi-reversible Co(II)/Co(I) couple.^[39]

Ni(II) Complex

A significant feature is observed in the cyclic voltammogram of Ni(II) complex. During the forward scan it shows two cathodic reduction peaks, one at +0.4 V and the other at -1.1 V, 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 +0.8 V and the other at -0.6 V, which are attributed to the oxidation of Ni(0)→Ni(I) and Ni(I)→Ni(II) respectively.^[40]

Thermogravimetric Analysis

The thermogravimetric analysis (TGA) of [Co(BEN)₂(ATZ)₄] and [Co(BEN)₂(ATZ)₄] complexes (ATZ: 2-aminothiazole, BEN: benzoate ion) show two significant weight loss with common and specific stages, termed as two stages of thermal degradation. The weight loss at the range of 190–280°C in TGA curves of complexes is termed the first stage of thermal degradation. In this case, the present weight loss is in the range of 18.22–30.46%, which may be attributed to the decomposition of benzoate ion. The onset of second step decomposition occurs in the range of 280–340°C, which gives the loss of 2-aminothiazole (38.65–52.42%) 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 (Table 2).^[41]

Powder X-ray Diffraction Technique

The XRD pattern indicates that the prepared [Co(BEN)₂(ATZ)₄] and [Co(BEN)₂(ATZ)₄] complexes have well defined crystalline patterns, with various degrees of crystallinity. In the complexes, the trend of the curves decreases from maximum to minimum intensity indicating amorphous

nature and crystalline phase of the complexes.^[42] The crystallite size (d_{XRD}) of the complexes was calculated using Scherer's formula.^[43,44] The prepared complexes had an average crystallite size of 33–55 nm, indicating their nanocrystalline (Fig. 1 and 2).

Biological Activity

Antifungal Activity

The synthesized [Co(BEN)₂(ATZ)₄], and [Co(BEN)₂(ATZ)₄] complexes and the ligands ATZ and BEN were evaluated

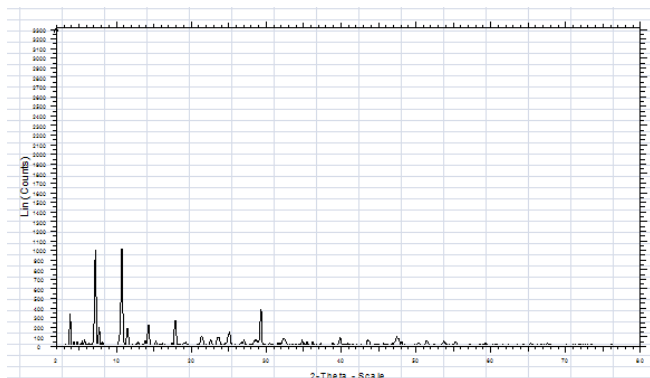


Fig. 1: X-Ray diffractogram of Co(II) complex

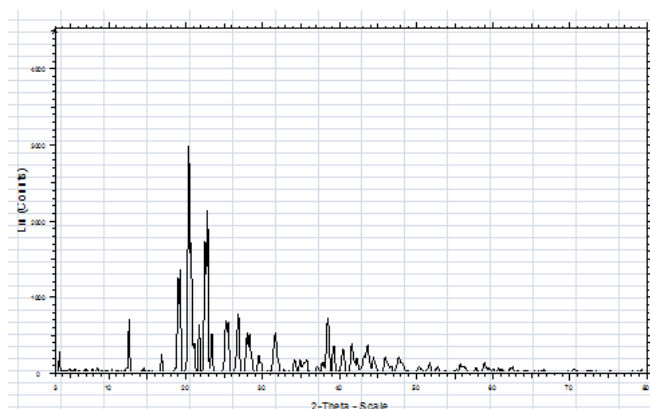


Fig. 2: X-Ray diffractogram of Ni(II) complex

Table 2: Antifungal activities free ligand ATZ, BEN and their [Co(BEN)₂(ATZ)₄] and [Co(BEN)₂(ATZ)₄] complexes of Ketoconazole (standard) (Diameter of zone of inhibition in mm)

S. No	Ligands/Complexes	Conc. µg/mL	Zone of Inhibition in diameter (mm)				
			<i>C. albicans</i>	<i>Aspergillus niger</i>	<i>Aspergillus flavus</i>	<i>Aspergillus oryzae</i>	<i>Aspergillus sojae</i>
1	2-aminothiazole	100	08	05	07	03	05
		200	14	09	15	06	11
		400	20	13	20	12	18
2	Sodium benzoate	100	06	15	10	15	02
		200	14	09	15	06	11
		400	21	16	21	12	15
3	[Co(BEN) ₂ (ATZ) ₄]	100	25	23	20	18	21
		200	33	28	32	24	35
		400	42	38	44	36	48
4	[Ni(BEN) ₂ (ATZ) ₄]	100	20	18	21	20	13
		200	28	32	24	35	28
		400	38	44	42	52	35

00–15 Resistant; 16–30 Moderate; 31–46 High activity; 46–60 Enhanced activity

against the fungal strain, viz., *C. albicans*, *Aspergillus Niger*, *Aspergillus Flavus*, *Aspergillus oryzae*, and *Aspergillus sojae* at 100, 200, and 400 µg/mL concentrations by agar-well diffusion method. The complexes $[\text{Co}(\text{BEN})_2(\text{ATZ})_4]$ and $[\text{Co}(\text{BEN})_2(\text{ATZ})_4]$ shows superior fungicidal activity than the free ligands because of the metal complexes have a more significant lipophilic nature and the metal chelation.^[45]

Antioxidant Activity (Radical Scavenging Activity)

The DPPH (2,2''-diphenyl-1-picrylhydrazyl) radical assay provides an easy and rapid way to evaluate the antiradical activities of antioxidants. The fortitude of the reaction kinetic types DPPH is a product of the reaction between $\text{DPPH}^\bullet$ and an antioxidant.



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

The 2,2''-diphenyl-1-picrylhydrazyl radical was used as a stable free radical electron accepts or hydrogen radical to become a stable diamagnetic molecule.^[46] It is a stable free radical containing an odd electron in its structure and usually used for the detection of the radical scavenging activity in the chemical analysis.^[47] The reduction capability of DPPH radical was determined by the decrease in its absorbance at 517 nm induced by antioxidants.^[48] 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 $[\text{Co}(\text{BEN})_2(\text{ATZ})_4]$

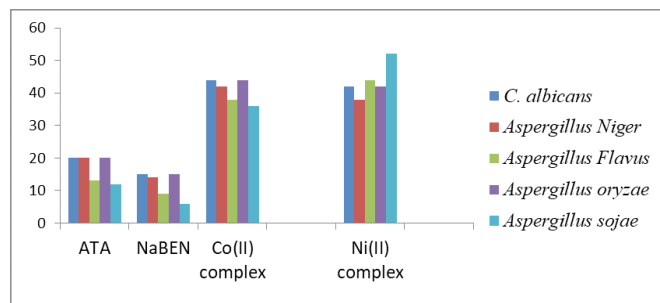


Fig. 3: Antifungal activities of free ligands and their complexes

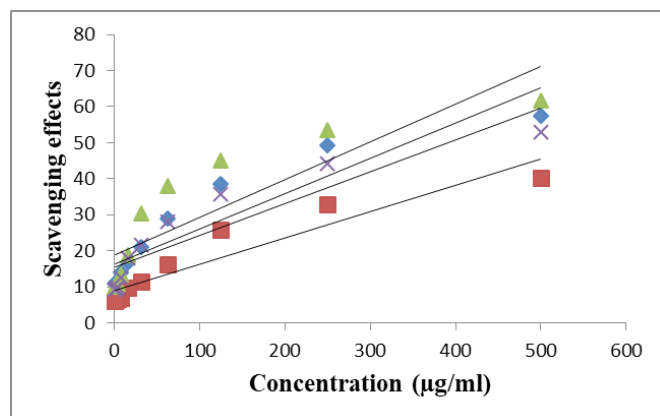


Fig. 4: Antioxidant activities of free ligands and their complexes

and $[\text{Co}(\text{BEN})_2(\text{ATZ})_4]$ complexes were compared with Vitamin C as a standard and showed enhanced activity; 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 (Fig. 4).^[49-51]

DNA Binding-Emission Study

The binding of free ligands ATZ, BEN, and their $[\text{Co}(\text{BEN})_2(\text{ATZ})_4]$ and $[\text{Co}(\text{BEN})_2(\text{ATZ})_4]$ complexes to CT-DNA can be studied by competitive binding experiments. EtBr 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.^[52,53] 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 an 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

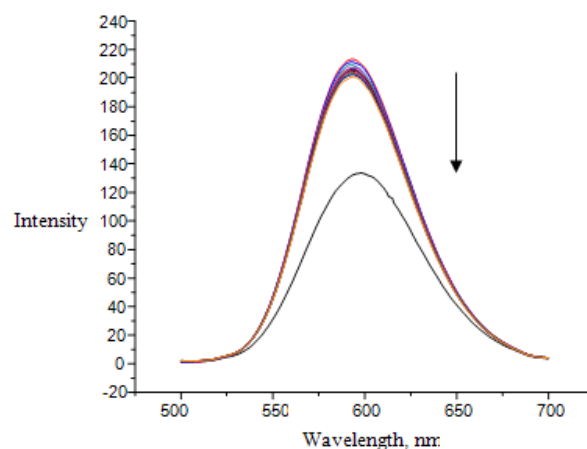


Fig. 5: Emission spectrum of EtBr bound to DNA in the absence and presence of Ni(II) complex.

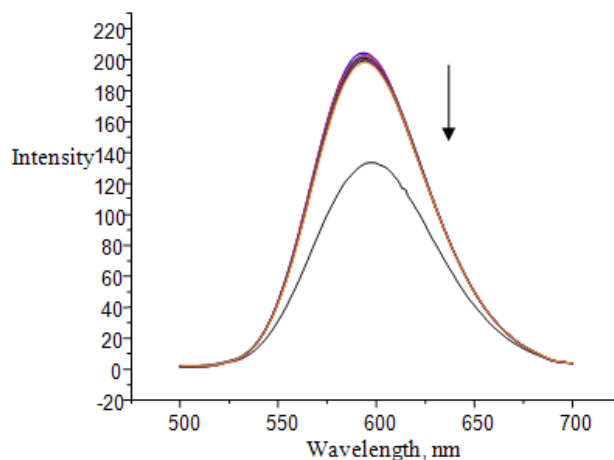


Fig. 6: Emission spectrum of EtBr bound to DNA in the absence and presence of Cu(II) complex.



the ethidium to the DNA. According to the classical Stern-Volmer equation: $I_0/I = 1 + K_{SV}r$, where I_0 and I are the fluorescence intensities in the absence and the presence of complex, respectively. K_{SV} 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 complex/ C_{DNA} , K is given by the ratio of the slope to intercept. The data suggest that the interaction of complexes with DNA is strongest, which is consistent with the above absorption spectral results. K values indicate that the interaction of the complex with DNA is an intercalative mode (Fig. 5 and 6).^[54]

CONCLUSION

In the current study, our work was to synthesize and characterize the new $[Co(BEN)_2(ATZ)_4]$ and $[Co(BEN)_2(ATZ)_4]$ complexes (ATZ: 2-aminothiazole; BEN: benzoate). The synthesized metal complexes were characterized by CHN analysis, electrical conductance, magnetic moment, electronic (DRS method), infra-red spectra, TGA analysis, cyclic voltammetry, powder-XRD techniques, and biological activities. Based on the analytical, molar conductance, spectral and magnetic moment, octahedral geometry has been suggested for the Co(II) and Ni(II) complexes. The metal complexes have significant antifungal and antioxidant activities as compared to the free ligands. The effectiveness of the DNA binding of complexes is being confirmed by the means of change in the intensity of emission in the case of emission spectral studies.

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