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SYNTHESIS, CHARACTERIZATION AND BINDING PROPERTIES TOWARDS CT-DNA OF MIXED-LIGAND Cu(II) COMPLEX WITH 2-AMINOBENZONITRLE AND OCTANOATE ION

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Keywords:

ABN, Cu(II) complex, Antimicrobial, Antioxidant, DNA-binding property

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ABSTRACT: A novel coordination complex of 2-aminobenzonitrile (ABN) and octanoate ion (OC) with Cu(II) metal ion has been prepared by using microwave irradiation. The molecular formula and the geometry of the complex have been deduced from elemental analysis, molar conductance, magnetic moment, electronic spectra, FT- IR spectra, cyclic voltammetry, thermal analysis and EPR spectra. The molar conductance value indicates that the complex is non-electrolyte (1:0) type. The electronic spectrum and the magnetic moment indicate the geometry of the complex is octahedral. FT-IR spectra show that 2-aminobenzonitrile is coordinated to the metal ion in a bidentate and octanoate ion in a monodentate manner. The metal-ligand covalency of Cu(II) complex has been arrived at from EPR spectrum. The antimicrobial activities of ligands and their Cu(II) complex were studied against the microorganisms, *viz.*, *staphylococcus aureus, streptococcus, Klebsiella, pseudomonas aeruginosa, salmonella typhi, Enterobacter, E. coli, C. albicans, Aspergillus flavus* and *Aspergillus niger* by agar - well diffusion method. The complex shows potential activity against the bacteria and fungi as compared to the free ligands. The free radical scavenging activity of the complex and the ligands have been determined by measuring their interaction with the stable free radical DPPH. The complex has larger antioxidant activity as compared to the ligands. The DNA-binding properties of the free ligand ABN and its Cu(II) complex have been investigated by fluorescence measurements. The results suggest that ABN and its Cu(II) complex both bind to DNA *via* an intercalative binding mode and the affinity for DNA is more strong in case of Cu(II) complex when compared with ABN.

INTRODUCTION: In the designing of coordination complexes with unique properties for an extensive variety of potential applications including gas storage [1], antimicrobial [2], conductive material [3], luminescent [4], and magnetic materials [5].

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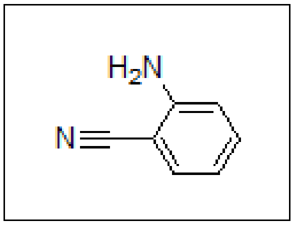
Among the aminobenzonitriles, 2-aminobenzonitrile (ABN) is used for the induction of nitrilase activity in arthrobacter, radioprotective agent and starting materials for the synthesis of biologically active compounds [6, 7]. 2-aminobenzonitrile is one of the organic ligands in coordination chemistry which can coordinate to the metal ion through different modes *viz.*, monodentate, bidentate or bridging. 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 [8].

On the other hand, the synthesis of inorganic/organic compounds using microwave irradiation has been a very rapidly developing technique in research areas [9, 10]. 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.

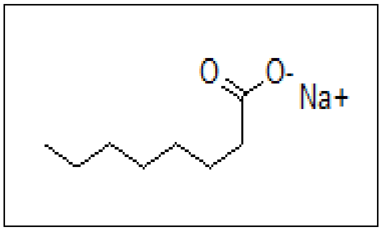
The present study aims at synthesis and spectral characterization of Cu(II) complex with neutral bidentate 2-aminobenzonitrile and anionic monodentate octanoate ion as ligands. The biological activities (antibacterial, antifungal, anti-oxidant, and DNA binding property) of the ligands and their complex have also been focused in this study.

MATERIALS AND METHOD:

Materials: The organic solvents DMSO, DMF, methanol, ethanol were purchased from Alfa Aaser Company and used as such. The 2-aminobenzonitrile, sodium octanoate, and copper nitrate were of AnalaR grade and used as such without further purification.



2-aminobenzonitrile



Sodium octanoate

Synthesis of Cu(II) Complex: 2-aminobenzonitrile 0.55g (4.32 mmol) in~ 10 ml methanol and sodium octanoate 1.22g (7.36 mmol) in ~ 10 ml ethanol were added to the copper nitrate 1.00g (2.62 mmol) in~ 10 ml methanol 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 blue colored complex was obtained with 78.35% yield.

Instrumentations: CHN elemental analyses were performed using Thermo Finnegan make, Flash EA1112 Series CHNS(O) analyzer. The molar conductivity measurement was 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 of the Cu(II) complex was recorded on Varian, Cary 5000 model UV Spectrophotometer. Infrared spectra for the complex and the ligands were recorded on a Perkin Elmer, Spectrum RX-I, FT IR spectrometer in KBr discs at room temperature. The cyclic voltammogram of the complex was taken in acetonitrile medium using Princeton make (MC-Tech, Applied Research) equipment. Tetra-ethylammoniumbromide was used as the supporting electrolyte. The thermogravimetric analysis of the complex was carried out using Perkin Elmer Diamond TGA/DTA Instrument. The electron paramagnetic resonance spectrum of the copper complex was recorded at room temperature using JES FA 200 EPR Spectrometer.

Biological Activities:

Antimicrobial Activity: The antibacterial and the antifungal activities of the ligands and the Cu(II) complex was evaluated by well diffusion method 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 successively diluted at different concentrations (µg/ml). According to the typical procedure [11] 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 h for bacteria and 72 h for fungi at 35 ºC. At the end of the period, inhibition zones formed on the medium were evaluated in millimeters (mm) and diameter.

Antioxidant Activity: Evaluation of antioxidant activity stock solution (1 mg/ml) was diluted to final concentrations of 10-500 µg/ml. Ethanolic DPPH solution (1 ml, 0.3 mmol) was added to the sample solutions in DMSO (3 ml) at different concentrations (10-500 µg/ml) [12]. 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 is designed by the following equation:

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

Where Ao is the absorbance of the control reaction and A_1 is the absorbance in the presence of the samples or standard.

DNA Binding Studies: The DNA binding experiments involving the interaction of the free ligand (ABN) and its Cu(II) complex with 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 $dm^3mol^{-1}cm^{-1}$ at 260 nm. The stock solutions were stored at 4°C and used within 4 days [13].

For fluorescence-quenching experiments, DNA was pre-treated with ethidium bromide (EtBr) for 30 min. The ligand and Cu(II) complex then added to this mixture respectively and their effect on the emission intensity was measured. The 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 complex led to the formula $[Cu(OC)_2(ABN)_2]$. The percentages of carbon, hydrogen, and nitrogen in the complex were found to be 47.12 (49.01), 12.55 (11.42), and 9.86 (8.98) respectively. The experimental values are in good agreement with the theoretical values (given in the parentheses).

Molar Conductance: The molar conductance value of the Cu(II) complex (10^{-3}M) in acetonitrile medium was found to be 48.66 $\Omega^{-1}cm^2\ mol^{-1}$. The low molar conductance value indicates that the copper complex is non-electrolyte [14], confirming its molecular formula $[Cu(OC)_2(ABN)_2]$.

Electronic Spectrum and Magnetic Moment of Cu(II) Complex: The electronic spectrum of Cu(II) complex exhibits three absorption bands at 14705 cm^{-1}, 17241 cm^{-1} and 23474 cm^{-1} corresponding to $^2B_{1g} \rightarrow {}^2A_{1g}$ (ν_1), $^2B_{1g} \rightarrow {}^2B_{2g}$ (ν_2) and $^2B_{1g} \rightarrow {}^2E_{2g}$ (ν_3) transitions which indicates the octahedral geometry [15, 16]. The structure is also further confirmed by the ratio ν_2/ν_1= 1.68, which is close to the value expected for octahedral structure [17]. The moderately intense band for the complex in the region 27027 cm^{-1} is assigned to the L → Cu(II) charge transfer transition. The observed magnetic moment μeff value of the Cu(II) complex is 1.78 B.M. indicates octahedral geometry [18] around Cu(II) metal ion and involving sp^3d^2 hybridisation.

FT-IR Spectra: In order to determine the binding modes of the ligands, 2-aminobenzonitrile and octanoate ion to copper(II) in the complex, FT-IR spectra of free ligands were compared with copper(II) complex. The 2- aminobenzonitrile shows in characteristic absorption bands in the 3433 cm^{-1}, 3388 cm^{-1}, and 2206 cm^{-1} region, assignable to asymmetric, symmetric stretching frequencies of $\nu(NH_2)$ and $\nu(C\equiv N)$ respectively [19, 20]. A small band noticed at 3040 cm^{-1} is due to aryl ν(CH). Aromatic ν(C=C) stretching vibration is seen as a sharp peak at 1568 cm^{-1} [21]. The octanoate ion shows ν(C–O) at 1207 cm^{-1}. A strong band with a shoulder noticed at 1605 cm^{-1} can be attributed to ν(C=O) of the carbonyl group [22]. The band(s) are broadened at 3390 cm^{-1} and the nitrile group of the ABN underwent higher frequency at 2223 cm^{-1} after complexation, indicating the coordination of the amino group and nitrile group to the metal atom.

In free octanoate ion the ν(C-O) stretching at 1207 cm^{-1} gets shifted to the frequencies of 1235 cm^{-1} in complex, which indicates the monodentate coordination of the octanoate ion through an oxygen atom. The low frequency region of the spectra revealed the presence of medium intensity bands in the region of 600-300 cm^{-1} due to ν(M-N) and ν(M-O) [23] respectively in the complex which supports the involvement of N, O [24] vibrations in Cu(II) complex which again supports complexation with the metal ion under investigation. Thus, the FT-IR spectral data suggest that the ABN is bound to the metal ion through the amino nitrogen & cyano nitrogen, and OC is bound through the oxygen donor atom.

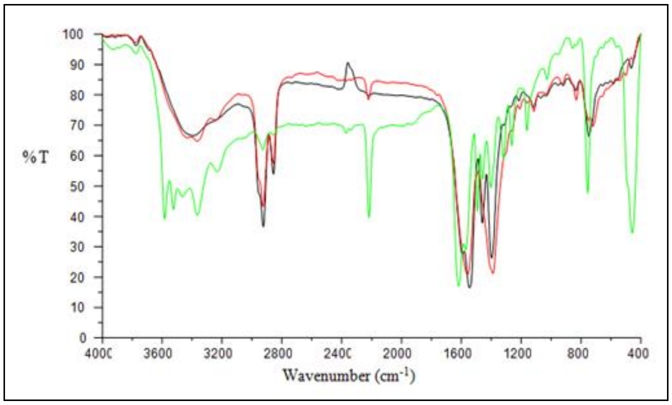


FIG. 1: FT IR SPECTRA OF FREE LIGANDS ABN, NaOC AND THEIR Cu(II) COMPLEX

Cyclic Voltammetry of Cu(II) Complex: The cyclic voltammogram of the Cu(II) complex in DMF solution shows +1.3 to -1.3V potential range, indicating quasi-reversible one-electron process [25]. A notable characteristic has been observed in the cyclic voltammogram of Cu(II) complex which is shown in **Fig. 2**.

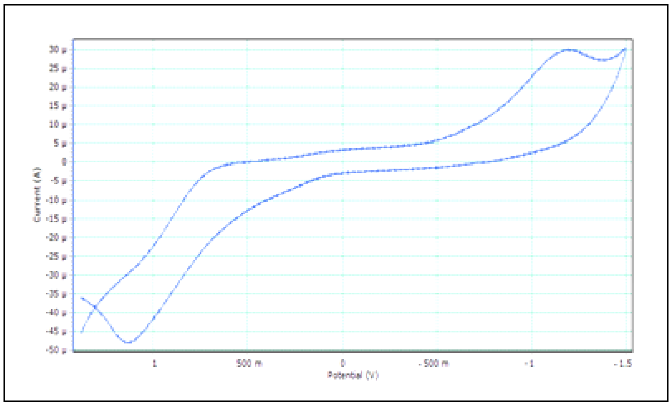


FIG. 2: CYCLIC VOLTAMMOGRAM OF Cu(II) COMPLEX

During the forward scan, it shows two cathodic reduction peaks, one at +0.6V and the other at -1.3V which are attributed to the reduction of Cu(II)→Cu(I) and Cu(I)→Cu(0), respectively. During the reverse scan, it shows two anodic peaks, one at 0.8V and the other at -1.0V which are attributed to oxidation of Cu(0)→Cu(I) and Cu(I)→Cu(II), respectively.

Thermogravimetric Analysis: Thermogravimetric analysis of Cu(II) complex of 2-aminobenzonitrile and octanoate ion show two significant temperature transitions of weight loss with common and specific stages, termed as two stages of thermal degradation. The TGA plateau of the complex shows that these complex exhibits no mass loss up to 100 ºC, indicating the absence of coordinated water [26] and high thermal stability of the complexes. The weight loss at the range of 190 ºC in TGA curves of complex is termed the first stage of thermal degradation. In this case, the present weight loss is in the range of 46.55%, which may be attributed to the decomposition of less stable 2-aminobenzonitrile [27]. The onset of second step decomposition occurs in the range of 280 ºC, which gives the loss of octanoate ion 25.35% 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.

EPR Spectrum of Copper Complex: The spectrum of DMSO solution of Cu(II) complex of 2-aminobenzonitrile and octanoate ion measured at X-band frequency at 77 K (LNT) **Fig. 3** provides helpful information which is significant in studying metal ion environment. The spin Hamiltonian parameters of the complex calculated and Summarized as follows. The Cu(II) complex in the frozen state at 77 K shows four well-resolved peaks in the low field region and one intense peak in the high field region.

The g-tensor value of the copper complex can be used to derive the ground state. In octahedral complexes, the unpaired electron lies in the $d_{x^2-y^2}$ orbital [28]. For this Cu(II) complex, the observed g-tensor values are $g_{\parallel} = 2.17 > g_{\perp} = 2.08 > g = 2.0023$ which suggest that this complex has an octahedral geometry and the ground state is $^2B_{1g}$. The EPR parameters of the complex coincide well with the related systems and this confirms that the complex has an octahedral geometry and it is axially symmetric. In the axial spectra, the g-values are related to the exchange interaction coupling constant G by the expression [29]

$$G = g_{\parallel} - 2.0023 / g_{\perp} - 2.0023 \text{-----------} (1)$$

According to Hathaway [30], if G value is larger than four, the exchange interaction is negligible because the local tetragonal axes are aligned parallel or only slightly misaligned. If its value is less than four, the exchange interaction is considerable, and the local tetragonal axes are misaligned. For the present Cu(II) complex, the G value is 2.15, which indicates a considerable exchange interaction in the solid complex.

It is usual to determine the covalent parameters of the Cu(II) ion in various ligand field environments. The in-plane σ-bonding (α^2) and in-plane π-bonding (β^2) covalancy parameters are calculated according to the following equation (3, 4) and the out of-plane pi-bonding (γ^2) parameter is also calculated [31] using the equations (5)

$$\alpha^2 = (A_{\|}/0.036) + g_{\|} - 2.0023 + 3/7(g_{\perp} - 2.0023) + 0.04 \text{ ----- } (2)$$

$$\beta^2 = (g_{\|} - 2.0023)\, E/8\lambda\, \alpha^2 \text{ ----------- } (3)$$

$$\gamma^2 = (g_{\perp} - 2.0023)\, E/2\lambda\, \alpha^2 \text{ ----------- } (4)$$

Where λ = 259 cm^{-1} for free Cu(II) ion and E is the electronic energy for ${}^2B_{1g} \rightarrow {}^2A_{1g}$ transition, which is 14,705 cm^{-1}

The λ value is calculated using the equation

$$g_{av} = 1/3[\, g_{\|} + 2g_{\perp}] \text{ and } g_{av} = 2(1-2\,\lambda/10Dq) \text{ ------------ } (5)$$

Which is observed to be less than that of the free Cu(II) ion (828cm^{-1}). This reduction in λ from the free ion value is an evidence of covalence in M-L bond [32].

The lower value of λ indicates that there is considerable mixing of ground and excited state terms. If the α^2 value is 0.6132, it indicates a complete covalent bonding and if the value is 1.0, it suggests a complete ionic bonding. From the results, it is clear that the in-plane σ-bonding parameter α^2 (0.6132) [33] is more covalent than the in-plane π –bonding β^2 (1.94) [34]. These data are well in accordance with the other reported values.

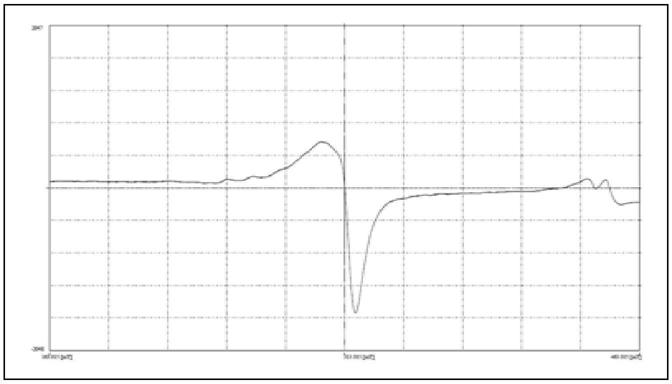


FIG. 3: EPR SPECTRUM OF [$Cu(OC)_2(ABN)_2$]

Biological Activity:

Antibacterial Activity: The free ligands and their Cu(II) complex were evaluated against the bacteria *staphylococcus aureus, streptococcus, Escherichia coli, Klebsiella pneumonia, P. aeruginosa, salmonella typhi* and *Enterobacter* at different concentration by using agar-well diffusion method. The complex shows enhanced activity than the free ligands against the tested bacterial strain. The enlarged activity of the metal complex can be explained on the basis of chelation theory [35]. It is known that chelation tends to make the ligand act as powerful and potent bactericidal agents, killing more bacteria than the ligand.

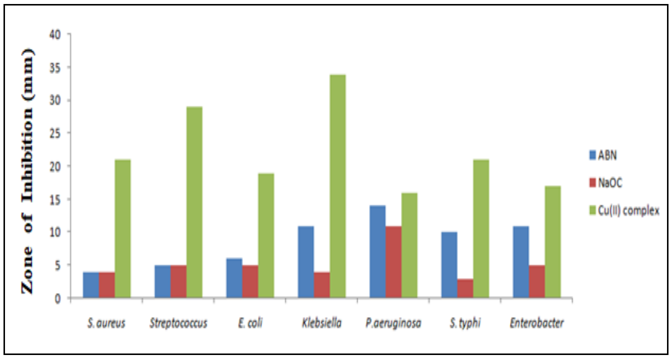


FIG. 4: ANTIBACTERIAL ACTIVITY OF THE FREE LIGANDS AND THEIR Cu(II) COMPLEX - ZONE OF INHIBITION DIAMETER (mm). 05-10 Resistant; 11-16 Moderate; 16-21 Highly activity; above 21 Enhanced activity

Antifungal Activity: The synthesized Cu(II) complex and the free ligands were evaluated against the fungi, *viz., C. albicans, Aspergillus Niger* and *Aspergillus Flavus* at different concentrations by agar-well diffusion method. The complex shows enhanced activity against the tested fungal strain. A comparative study of the zone of inhibition diameter values of the ligands and their complex indicate that the metal complex has an improved fungicidal activity than the free ligands.

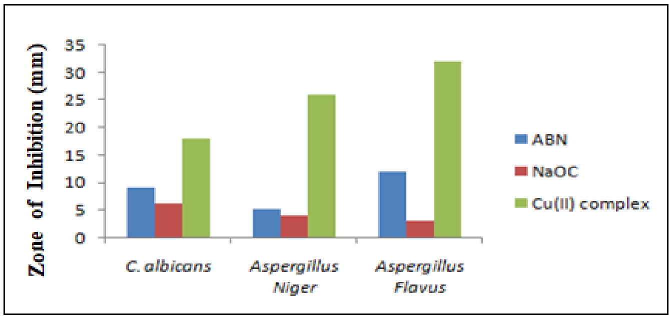


FIG. 5: ANTIFUNGAL ACTIVITY OF THE FREE LIGANDS AND THEIR Cu(II) COMPLEX - ZONE OF INHIBITION DIAMETER (mm). 05-10 Resistant; 11-16 Moderate; 16-21 Highly activity; above 21 Enhanced activity

This is probably due to the greater lipophilic nature of the complexes. It is evident from the data that this activity significantly increases coordination [36].

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.

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

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 [37]. 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 [38]. The reduction capability of DPPH radicals was determined by decrease in its absorbance at 517 nm induced by antioxidants [39]. 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 Cu(II) complex was compared with ascorbic acid as a standard. The metal complex showed enhance activity (radical scavenging) 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 [40, 41, 42].

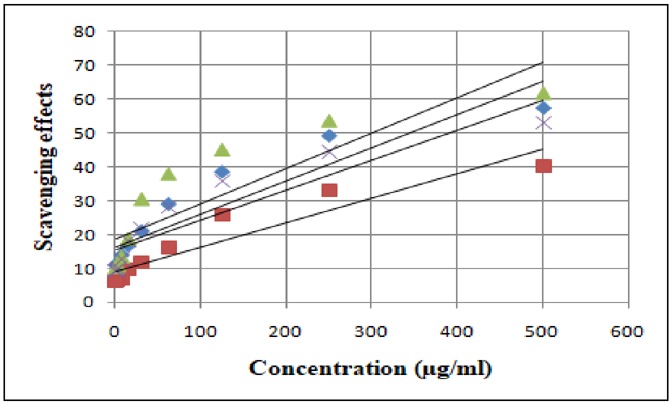


FIG. 6: ANTIOXIDANT ACTIVITY LIGANDS AND THEIR COMPLEX

DNA Binding – Emission study: The binding of free ligand and copper(II) complex 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 [43, 44]. 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 the ethidium to the DNA.

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 K values for Cu(II) complex and ABN are 3.66×10^4 M^{-1} and 1.52×10^4 M^{-1} respectively, suggest that the interaction of Cu(II) complex with DNA is strongest than the ligand ABN and also intercalative mode [45] of binding.

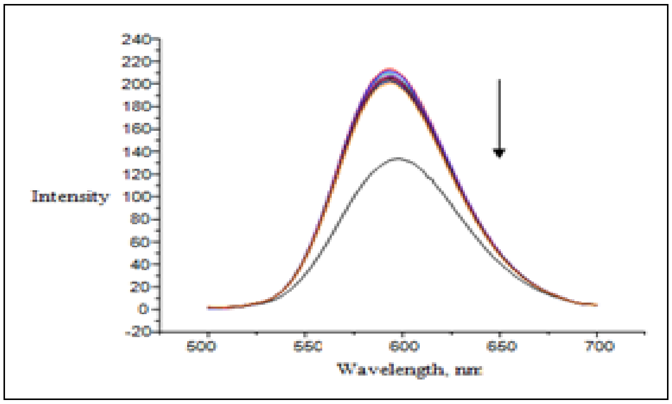


FIG. 7: EMISSION SPECTRUM OF EtBr BOUND TO DNA IN THE ABSENCE AND PRESENCE OF ABN

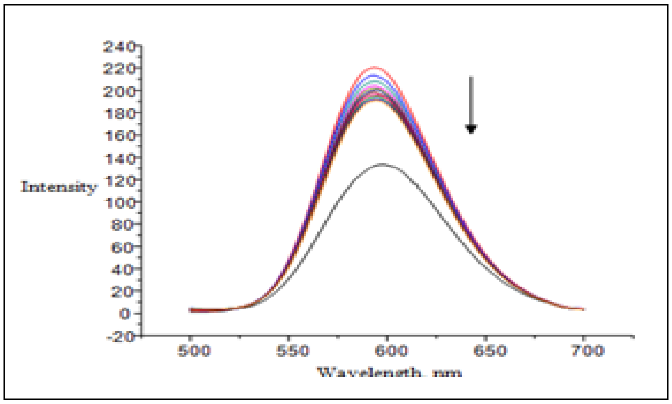


FIG. 8: EMISSION SPECTRUM OF EtBr BOUND TO DNA IN THE ABSENCE AND PRESENCE OF Cu(II) COMPLEX

CONCLUSION: In the present study, our efforts was to synthesize and characterize the copper(II) metal complex with 2-aminobenzonitrile and octanoate ion as ligands. The new complex was synthesized using microwave irradiation. The synthesized metal complex was characterized by different physico-chemical and spectral analyses. Based on the analytical, molar conductance, spectral and magnetic moment, octahedral geometry has been suggested for the Cu(II) complex. The synthesized complex was tested for antimicrobial and antioxidant activities. The metal complex has prospective antimicrobial and antioxidant activities as compared to the free ligands. The effectiveness of the DNA binding property of complex is being confirmed by means of change in intensity of emission in the case of emission spectral studies.

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CONFLICT OF INTEREST: The authors declared that there is no conflict of interest.

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