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Synthesis and Characterization of Schiff Base Co^{II}, Ni^{II} and Cu^{II} Complexes Derived from 2-Hydroxy-1-naphthaldehyde and 2-Picolylamine

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Abstract

New Co^{II}, Ni^{II} and Cu^{II} complex has been synthesized and characterized by elemental analysis, UV-Vis, FT-IR and thermal analysis. binding of this Co^{II}, Ni^{II} and Cu^{II} complex with calf thymus DNA was investigated by UV-Visible absorption, fluorescence spectroscopy techniques. The intrinsic binding constants K_b of complex with CT-DNA obtained from UV-Vis absorption studies were 4.43 × 10^5 M^{-1}. Further, the *in vitro* cytotoxic effect of the complexes examined on cancerous cell line, such as human breast cancer cells (MCF-7).

Keywords: Co^{II}; Ni^{II} and Cu^{II} complex; DNA interaction; Electrochemical studies; Cytotoxicity activity

Introduction

There has been enormous report directed towards the development of novel chemical compounds able to arrest or reverse the development of cancer [1,2]. Biological activities of transition metal complexes derived from Schiff base ligands are one of the most exhaustively studied topic in coordination chemistry, due to their enhanced activities compared to non - Schiff base complexes [3-7]. Schiff base complexes show important physiological and pharmacological activities due to their favorable cell membrane permeability [8-12]. For example, amino acid Schiff base metal complexes have a wide variety of applications including biological, clinical [13] analytical and industrial area in addition to their important role in catalysis and organic synthesis [14,15]. It was found the Schiff base products containing short chain amino acid are not stable. One effective method to make it stable is to reduce the double bond to form reduced Schiff base ligands (also called Mannich base), which is also a biological intermediate [16]. The ligands is now more flexible and not constrained to remain planar. This investigation of the packing model will give useful information to biological reactions and will help to investigated the hidden characters of the ligands [17-24]. Furthermore, nickel is an important transition metal and its coordination compounds display interesting binding properties with proteins and nucleic acids [25]. The N – and O – containing Schiff base ligands and their nickel (II) complexes have become important due to their wide biological activity [26-28].

ESI-Mass spectrum studies

Electron spray ionization (ESI) mass spectral data (Figure 1A-1C) of complex **4** shows peak at *m/z* 378 assignable to [M+]. The loss of NSC molecule leads to formation of peak at *m/z* 320 [M+-NSC].

The complex **5** shows the peak at *m/z* 378 which is assignable to [M+]. The loss of -NSC molecule leads to formation of peak at *m/z* 320 [M-NSC]. The complex 6 shows the peak at *m/z 382* which is assignable to [M+]. The loss of -NSC ion leads of peak at *m/z 324* due to formation of [M+NSC)]. Few other intense peaks are also obtained for complexes 4-6.

FT-IR and UV-Vis spectroscopy

The IR spectra of complexes 4-6 were recorded in the region of 4000–400 cm^{-1} (Figure 2A and 2B). However, a relative decrease of ν(C=N) frequency to 1501–1597 cm^{-1} supports the coordination of amine nitrogen atom with metal ion in complexes. The ligands as well as its corresponding complexes show absorption in the region 3000–2900 cm^{-1}, which may be due to ν C–H. All complexes have bands in the region of 3070–3095 cm^{-1} and 2081–2994 cm^{-1}, which can be assigned to C–H stretching vibrations. This band disappeared on complexation and a new νC–O band at 1472–1492 cm^{-1} appeared [29]. Provided by the existence of medium intensity bands in the region 585–510 cm to ν(M-O) [30,31]. The absorption spectral data were obtained experimentally for all the complexes in DMF solution (Figure 3) In the UV region, complexes 4-6 show peaks near 227 -270 nm due to π → π* transition of Schiff's base ligands. In the UV region of complexes 4-6, intense peaks or a shoulder is observed in the region of 312–398 nm which could be assigned for ligand to metal charge-transfer transitions [32]. The spectrum of complex 4 shows absorption band at 638-658 cm^{-1} for complexes 4-6 which can be attributed to the $^4T_{1g} \rightarrow {}^4A_{2g}$, $^4T_{1g} \rightarrow {}^4T_{2g}$ (F) d-d transitions, for cobalt complex [33,34]. These d–d transition may be assigned to the transitions $dx^2–y^2 \rightarrow$ d xz yz; dz^2; dxy [35] for copper complexes and $^3T_{2g} \leftarrow {}^3A_{2g}$ and $^3T_{1g}(F) \leftarrow {}^3A_{2g}$ [36] for nickel complexes. The molar conductivity measurement for the complexes 1-3 in DMF solution (ca. 10^{-3} M) are in the range of 11–15 Λ_M/Scm^2mol^{-1} at 25°C, indicating neutral electrolytic behaviour.

Electrochemical studies

The electrochemical behaviour of the complexes 4-6 (10^{-3}M) have been studied using cyclic voltammetry in the potential range of 0 to -1.2 V in the DMF solution containing 10^{-1}M tetra(n-butyl) ammonium perchlorate and scan rate 50 mVs^{-1}. The voltammograms of the complexes 4-6 were displayed in Figure 4 The cyclic voltammograms of all the complexes 1-3 have almost the same shape, and exhibit one irreversible redox couple at -0.811, -0.64 V for complex 4, -1.09, -0.85 V for complex 5 and -0.97, -0.67 V for complex 6, respectively.

DNA binding studies

Absorption spectral studies: The application of electronic absorption spectroscopy in DNA binding studies is one of the most useful techniques [9]. The absorption spectra of complexes 1-3 in the

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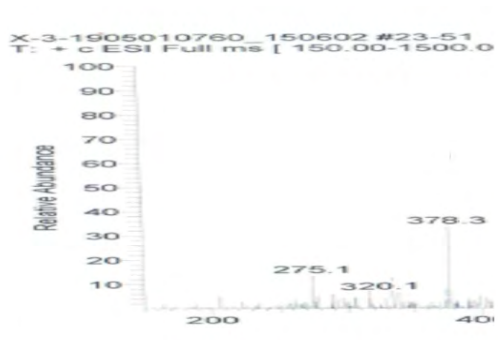

Figure 1A: Mass spectra of complex 4.

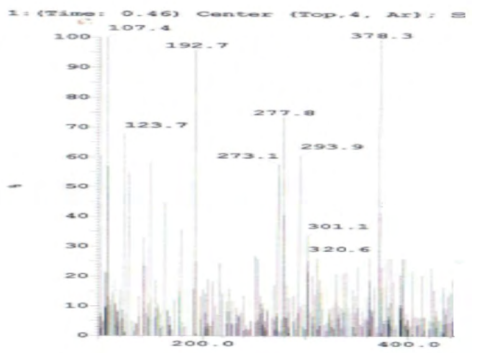

Figure 1B: ESI mass spectrum of complex 5.

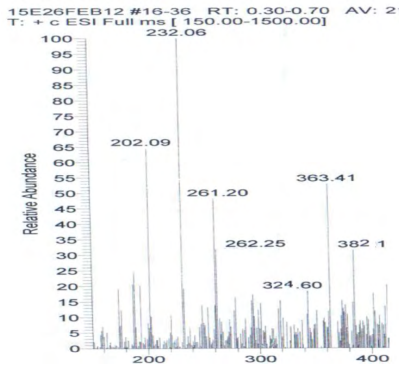

Figure 1C: ESI mass spectrum of complex 6.

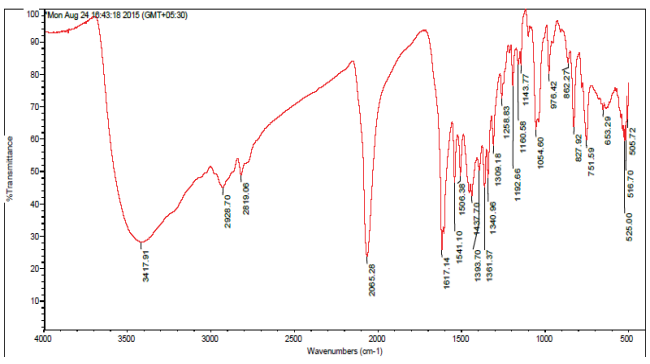

Figure 2A: FT-IR spectra of complex 4.

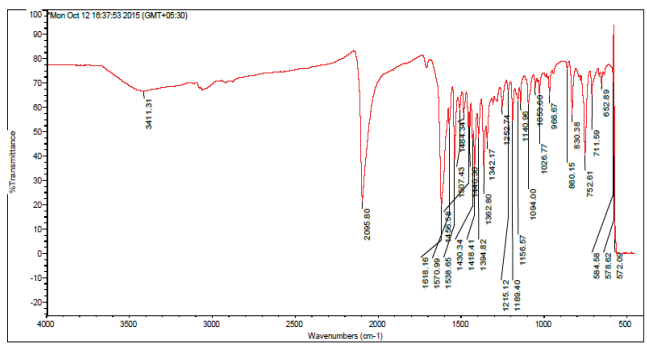

Figure 2B: FT-IR spectra of complex 5.

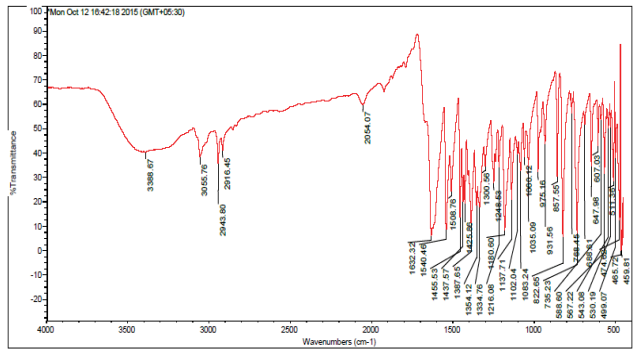

Figure 3: FT-IR spectra of complex 6.

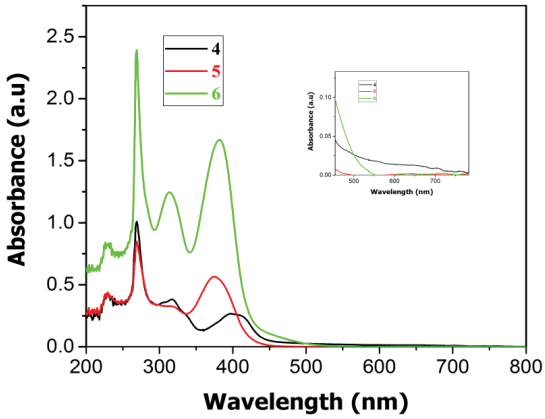

Figure 4: UV-Vis spectra of complexes 4-5.

absence and presence of CT-DNA (at a constant concentration of complex) was given in (Figure 5) In the presence of DNA, the absorption bands of the complex about 277 nm exhibited hypo chromium of about 10.12% for complex 1, 12% for complex **2** and 12.9% for complex 3. The spectroscopic changes suggest that the complex has interaction with DNA. After the complexes groove bind with the base pairs of DNA. In order to affirm quantitatively the affinity of the complex bound to DNA, the intrinsic binding constants K_b of the complex with DNA was obtained by monitoring the changes in absorbance peak for the title complexes 1-3 with increasing concentration of DNA using the following Eq. (1) [37].

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

Where ε_a is the extinction coefficient observed for the charge transfer absorption at a given DNA concentration, ε_f the extinction coefficient of the free complex in solution, ε_b the extinction coefficient of the complex when fully bound to DNA, K_b the equilibrium binding constant, and [DNA] gives K_b as the ratio of the slope to the intercept (Figure 6) The intrinsic binding constant K_b values obtained for complexes 4-6 were found to be 1.91×10^4, 2.3×10^5 and 2.98×10^4 M^{-1}, respectively, revealing higher binding propensity of complex 6 as compared to 1 and 2, which suggests that the interaction of the complex with DNA is by strong groove binding mode [38]. The complex 6 serves as better DNA binding agent with efficient activity compared with that of the other complexes, which suggests that the interaction of the complexes with DNA is strong and through groove binding. As a result, the binding interaction of the copper complexes with DNA follows the trend from high to low: 6>5>2 in 5 mM Tris-HCl/50 mM NaCl buffer upon addition of DNA. Arrow shows the absorbance changing upon increase of DNA concentration. The inner plot of [DNA/(εa-εf) vs [DNA] for the titration of DNA with complexes.

Fluorescence spectral studies: The emission spectrum is obtained by setting the excitation monochromator at the maximum excitation wavelength and scanning with emission monochromator. Often an excitation spectrum is first made in order to confirm the identity of the substance and to select the optimum excitation wavelength. Further experiments were carried out to gain support for the mode of binding of complexes with CT-DNA. Non-fluorescent or weakly fluorescent compound scan often be reacted with strong fluorophores enabling them to be determined quantitatively. On this basis, molecular fluorophore EtBr was used which emits fluorescence in presence of CT-DNA due to its strong intercalation (Figure 7) Quenching of the fluorescence of EtBr bound to DNA were measured with increasing amount of metal complexes as a second molecule and Stern–Volmer quenching constant K was obtained from the following equation [39]. $I_0/I=1+K_{sv}[Q]$, Where, I_0 and I are emission intensity in absence and presence of the complexes. K_{sv} is a linear Stern-Volmer quenching constant, [Q] is the ratio of the total concentration of complex to that of DNA. The quenching plot illustrates that the quenching of EB bound to DNA by the iridium(III) complexes is in good agreement with the linear Stern-Volmer equation, which also indicated that the complexes binds to DNA. In the plot of I_0/I vs [Complex]/[DNA], K_{sv} is given by the ratio of the slope to intercept (Figure 8) and resulting K_{sv} values for be complexes 4-6 are 2.98×10^3, 3.23×10^3, and 3.96×10^3 M^{-1}, respectively which varies in the order: 6>5>4. The results clearly suggested that **6** have greater tendency to replace EB relatively to other complexes. The quenching constant value of Ir(III) complexes 4-6 may suggest that the complexes 4-6 have intercalative mode of binding that involves a stacking between the complex and the base pairs of DNA. The data suggest that the interaction of 6 with DNA is the strongest, followed by 4, and then 5, which is consistent with the above absorption spectral results.

Binding of the complexes to serum albumins: The study of the interaction of drugs and their compounds with blood plasma proteins and especially with serum albumin, which is the most abundant protein in plasma and is involved in the transport of metal ions and metal complexes with drugs through the blood stream, is of increasing interest. Binding to these proteins may lead to loss or enhancement of the biological properties of the original drug, or provide paths for drug transportation. Bovine serum albumin (BSA) is the most extensively studied serum albumin, due to its structural homology with human serum albumin (HSA). HSA (one Trp-214) and BSA (containing two tryptophans, Trp-134 and Trp-212) solutions exhibit a strong

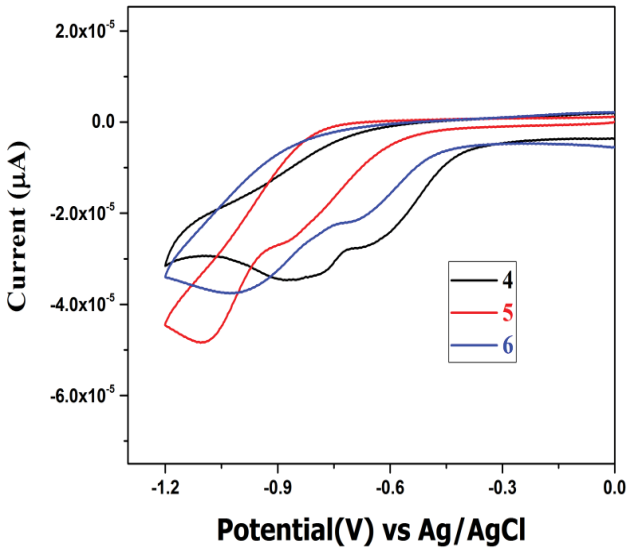

Figure 5: Cyclic voltammograms of complexes 4-6.

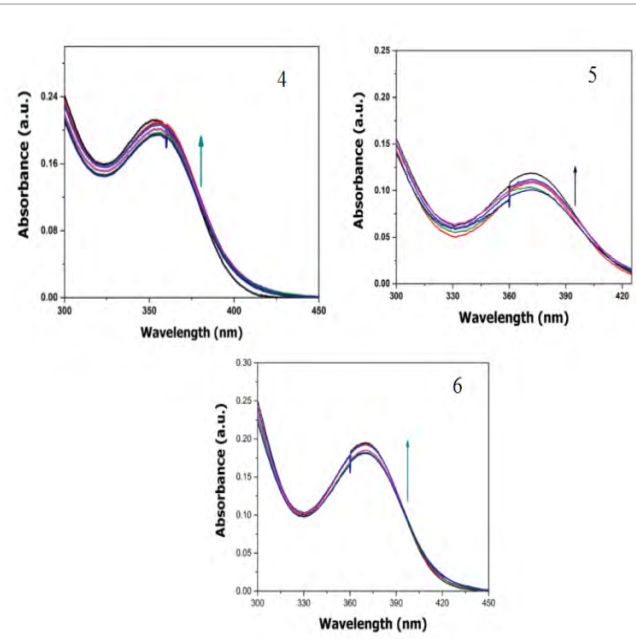

Figure 6: Absorption spectra of complexes (11-14) in 5 mM Tris-HCl/ 50 mM NaCl buffer upon addition of DNA. Arrow shows the absorbance changing upon increase of DNA concentration. The inner plot of [DNA/(εa-εf) vs [DNA] for the titration of DNA with complexes.

fluorescence emission with a peak at 351 nm and 343 nm, respectively, due to the tryptophan residues, when excited at 295 nm [40]. The interaction of complexes 4-6 with serum albumins has been studied from tryptophan emission-quenching experiments. The changes in the emission spectra of tryptophan in BSA are primarily due to change in protein conformation, subunit association, substrate binding or denaturation complexes 4-6 exhibited a maximum emission at 354 nm under the same experimental condition (Figure 9) and the SA fluorescence spectra have been corrected before the experimental data processing.

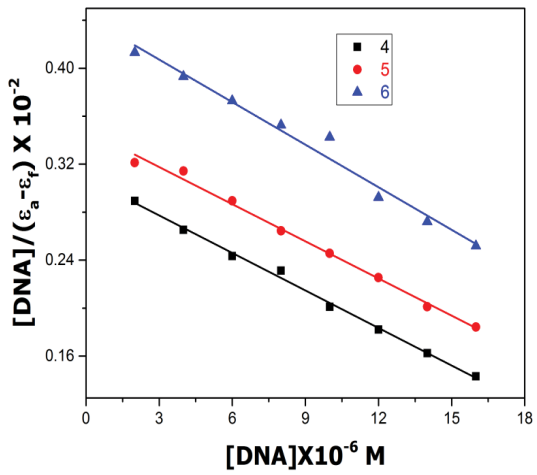

Figure 7: The plot of [DNA/(εa-εf) vs [DNA] for the titration of DNA with complexes.

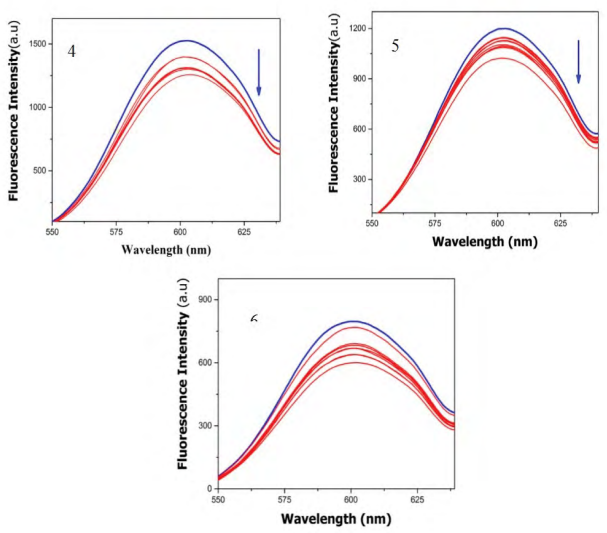

Figure 8: Fluorescence emission spectra of the EB-DNA in presence of complexes (4-6) in 5 mM Tris HCl/ 50 mM NaCl buffer (pH 7.2).

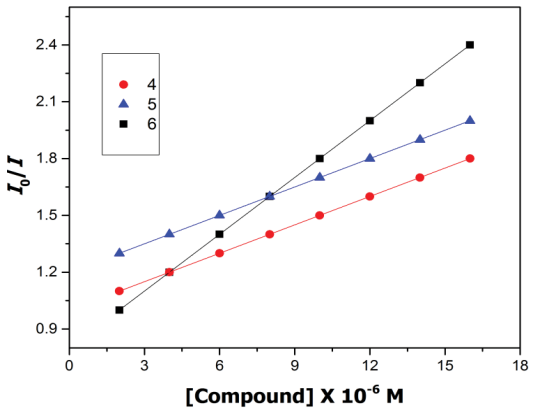

Figure 9: The Stern-Volmer plot illustrating the quenching of EB bound to DNA by complexes (4-6).

$$\frac{I_o}{I} = 1 + k_q \tau_0 [Q] = 1 + K_{sv}[Q]$$

Addition of complexes to BSA results in relatively moderate fluorescence quenching (up to 33% of the initial fluorescence intensity of BSA for complex 4, 46% for **5** and 59% for complex 6 as calculated after the correction of the initial fluorescence spectra) (Figure 10) due to possible changes in protein secondary structure of BSA indicating the binding of the compounds to BSA. The Stern-Volmer and Scatchard graphs may be used in order to study the interaction of a quencher with serum albumins. According to Sterne Volmer quenching equation [41] Where I_0=the initial tryptophan fluorescence intensity of SA, I=the tryptophan fluorescence intensity of SA after the addition of the quencher, k_q=the quenching rate constants of SA, K_{sv}=the Stern-Volmer constant, t_0=the average lifetime of SA without the quencher, [Q]=the concentration of the quencher respectively,

$$K_{sv} = k_q \tau_0$$

and, taking as fluorescence lifetime (t_0) of tryptophan in SA at around 10^{-8} s, the Stern-Volmer quenching constant (K_{sv}, M^{-1}) can be obtained by the slope of the diagram I_0/I vs [Q] (Figure 10) and subsequently the approximate quenching constant (k_q, M^{-1} s^{-1}) may be calculated. The calculated values of K_{sv} and k_q for the interaction of the compounds with BSA are given in Table 1 and indicate a good BSA binding propensity of the complexes exhibiting the highest BSA quenching ability. The k_q values are higher than those characterizing diverse kinds of quenchers, pointing towards the existence of a static quenching mechanism [42]. Using the Scatchard equation [43]

$$\frac{\Delta I / I_0}{[Q]} = nK - K\left(\frac{\Delta I}{I_0}\right)$$

where n is the number of binding sites per albumin and K is the association binding constant, K (M^{-1}), may be calculated from the slope in plots $(\Delta I_0/I)/[Q]$ vs $(\Delta I/I_0)$ (Figure 11) and n is given by the ratio of the y intercept to the slope. It is obvious (Table 1) that the coordination of Co(III) complexes results in a decreased K value for BSA with complex 1 exhibiting the highest K value among the other complexes. The Stern-Volmer equation applied for the interaction with BSA in Figure 12 shows that the curves have fine linear relationships (r^2=0.9798-0.9921). The calculated values of K_{SV} and k_q are given in Table 1 and indicate their good BSA binding propensity with complex 1 exhibiting the highest BSA quenching ability. From the Scatchard graph (Figure 10) the associated binding constant to BSA of each compound has been calculated. The n values of complexes (4-6) are given in Table 1. Additionally, complexes exhibited higher binding affinity for BSA than other complexes, which occurs in a similar way to that observed in the DNA binding studies.

Anticancer activity studies: To investigate the proliferation-inhibitory effect of the complexes, human cervical cancer HeLa cells were treated with both the complexes dissolved in DMSO in different concentrations followed by 3- [4,5-dimethyltiazol-2-yl]-2,5-diphenyl-tetrazolium bromide (MTT) assay. Cells treated with DMSO were used as solvent control. We found that both of them potentially inhibited cellular proliferation (Figure 13). The IC_{50} value of the complex is 18.41

Compound	K_{sv}(M-1)	k_q($M^{-1}s^{-1}$)	K(M^{-1})	n	r
1	3.0×10^5	3.0×10^{13}	0.02845	0.0854	0.9898
2	3.3×10^5	3.3×10^{13}	0.03452	0.0879	0.9802
3	3.9×10^5	3.9×10^{13}	0.03651	0.0899	0.9921

Table 1. The BSA binding constant and parameters (K_{sv}, k_q, K, n and r) derived for complexes (1 and 2). 0.9798-0.9902

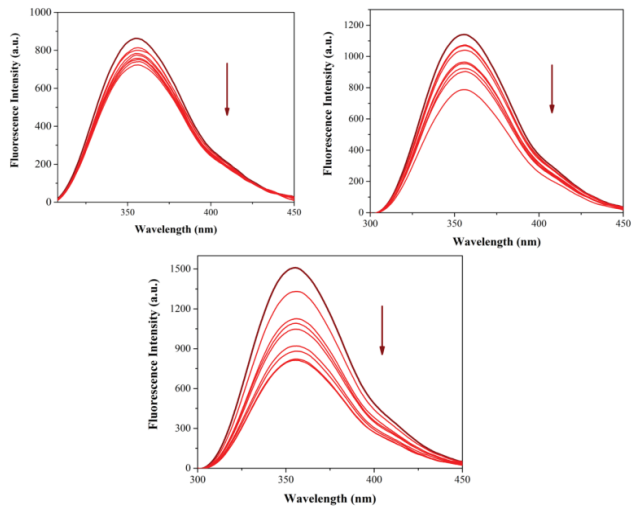

Figure 10: Fluorescence spectra of BSA in presence of various concentration of complexes (4-6).

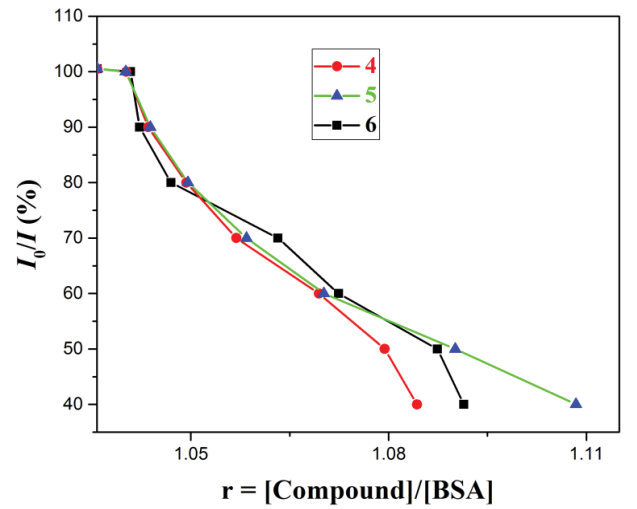

Figure 11: Plot of % EB relative fluorescence intensity at λem=353 nm (*I*0/*I* (%)) vs r (r=[complex]/[BSA]) for complexes (**4-6**) in buffer solution (150 mM NaCl and 15 mM trisodium citrate at pH 7.0).

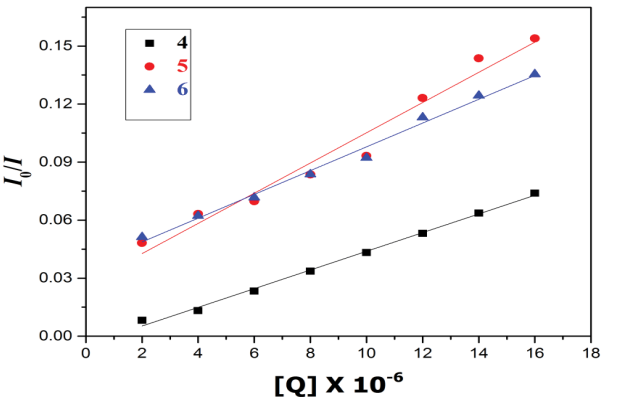

Figure 12: Fluorescence spectra of BSA in emission intensity *I*0/*I* vs [Q]. Q=complexes.

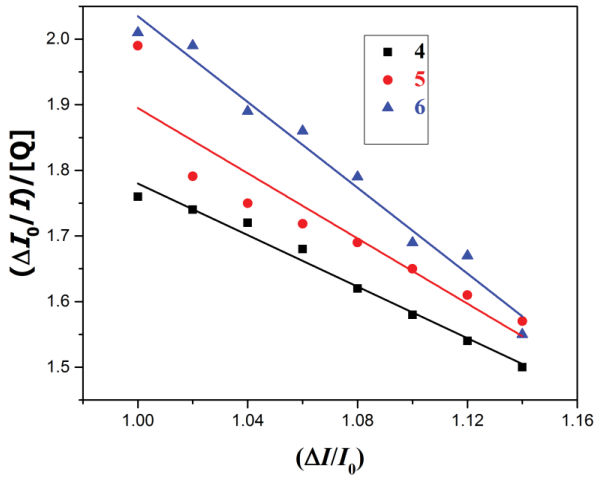

Figure 13: Determination of the complex-BSA binding constant and the number of binding of BSA.

μM for complex **1**, 15.22 μM for complex **2,** 11.21 μM. It is commonly believed that the biological activities of anticancer metal complexes are dependent on their ability to bind DNA and damage its structure resulting in the impairment of its function [44], which is followed by inhibition of replication and transcription processes and, eventually cell death, if the DNA lesions are not properly repaired. The proliferation inhibitory activity of the complex on human breast cancer HeLa cells. The finding of the *in vitro* cytotoxic activities further confirms the binding of the complex to DNA, which consequently leads to cell death [45,46].

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