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Research Article

DNA Binding and Cleavage Activities of $Na[B(Glu)(OH)_2]\cdot 2H_2O$, $Na[B(Cit)(OH)_2]\cdot 2H_2O$, $Li[B(Sal)(OH)_2]$, and $Mg[B(Sal)(OH)_2]\cdot 2H_2O$ Complexes

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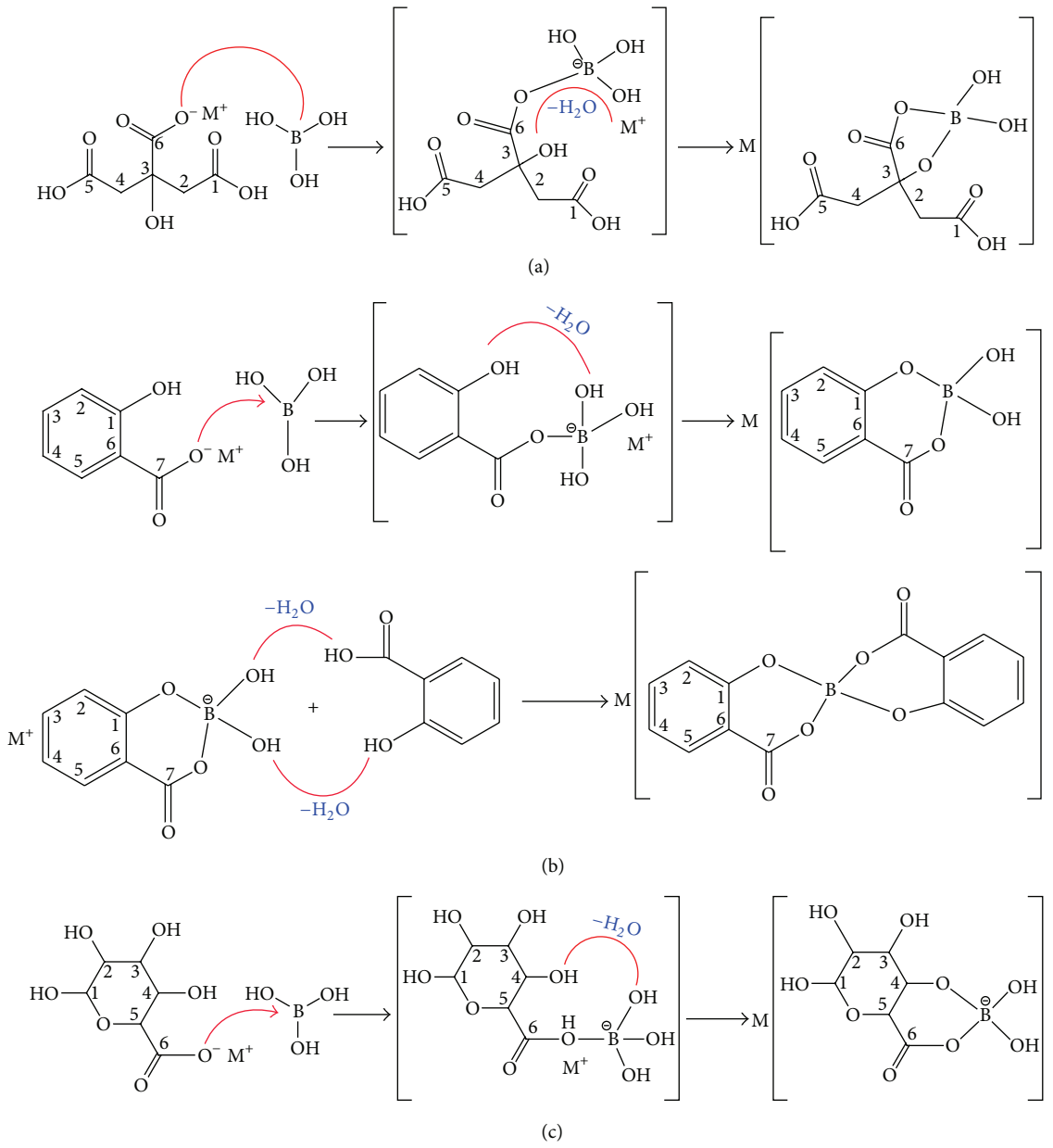
The interaction of some previously reported complexes $Na[B(Glu)(OH)_2]\cdot 2H_2O$, $Na[B(Cit)(OH)_2]\cdot 2H_2O$, $Li[B(Sal)(OH)_2]$, and $Mg[B(Sal)(OH)_2]\cdot 2H_2O$ with cattle genomic DNA (CG-DNA) was investigated using UV absorption, viscosity measurements, and fluorescence studies. These complexes interact with DNA through the intercalative mode of binding. In addition, the DNA cleavage activity of the complexes in presence of H_2O_2 was determined using agarose gel electrophoresis. All complexes exhibit moderate ability of cleavage to the DNA.

1. Introduction

There is a significant literature supporting the application of artificial DNA binding and cleaving agents in biotechnology. Compounds showing the properties of effective binding as well as cleaving double-stranded DNA under physiological conditions are of great importance since these could be used as diagnostic agents in medical and genomic research. Therefore, it is obvious that the nature of the ligands plays significant roles in their interaction with DNA molecule [1–5].

Boron complexes of inorganic and organic molecules have amazing pharmacological properties such as for instance hypolipidemic, anti-inflammatory, antiosteoporosis, and antineoplastic activities [6–8]. Nowadays, there has been interest in the synthesis of boron complexes with potential use for the treatment of some types of malignant cancers such as melanoma and glioblastoma multiforme brain tumors [9]. The study of boron complexes of biomolecules like amino acids, peptides, nucleosides, and porphyrins is the main field of research [10]. There is increasing indication from a sort of experimental patterns that indicates boron is a bioactive and useful element for humans. Bis-chelate complexes of boron based on aromatic or aliphatic diols and carboxylic acids are generally nontoxic, inexpensive, and thermally and electrochemically stable. Therefore, in the literatures, the boron complexes of such ligands are usually based on 1 : 2 complexes. Citric acid molecule possesses different coordination sites for complex formation with metals. In the literature, several studies defined the bis-chelate boron complexes with citrate ligand [11] (Scheme 1(a)). There are efforts to put together boron into various biologically active molecules for nutritional and medicinal applications. Salicylic acid is a well-known complexing ligand with boric acid (Scheme 1(b)) [12, 13]. Several bis-salicylatoborate complexes have been reported in the literature [14–22]. In a similar way, the glucuronic acid (Scheme 1(c)) has a carboxylic acid function and a number of cis-OH groups on the pyran ring available for complex formation with boron.

In this research, alkaline and alkaline earth metal ions such as Na(I), Li(I), and Mg(II) were chosen because of their potential to increase the biological activities of the ligands.



Scheme 1: (a) Proposed complexation mechanism of boric acid with citric acid, M = Na. (b) Proposed mechanism for the complexation of boric acid with salicylic acid, M = Mg, Li. (c) Proposed mechanism for the complexation of boric acid with glucuronic acid, M = Na, [23].

DNA binding abilities and CG-DNA cleavage activities of synthesized $Na[B(Glu)(OH)_2]\cdot 2H_2O$ (1), $Na[B(Cit)(OH)_2]\cdot 2H_2O$ (2), $Li[B(Sal)(OH)_2]$ (3), and $Mg[B(Sal)(OH)_2]_2\cdot H_2O$ complexes (4) [23] were studied with cattle genomic DNA to prove their abilities of binding and cleavage of the DNA using UV absorption, agarose gel electrophoresis, and viscosity experiments [19, 24, 25].

2. Materials and Methods

2.1. Genomic DNA Isolation. All reagents and the solvents were purchased commercially and used without further purification in all the synthetic work. All the solvents and the reagents were obtained from Merck, Turkey. Genomic DNA was extracted from calf through the earlier reported methods [26]. Peripheral blood samples (6–9 mL) of calves were collected in EDTA tubes and DNA samples were isolated by Promega Wizard genomic DNA purification kit (Cat. no. A1120). Concentrations of DNA samples were measured on a microplate spectrophotometer (Epoch, BioTek) and concentrated at 250 ng/μL prior to DNA binding experiments.

The UV-visible spectra of the samples were obtained on microplate spectrophotometer (Epoch BioTech) with the Thermo Scientific Varioskan Flash spectral scanning method.

2.2. Preparation of the Metal Complexes. $Na[B(Cit)(OH)_2]\cdot 2H_2O$ (Scheme 1(a)), $Li[B(Sal)(OH)_2]$ (Scheme 1(b)), $Mg[B(Sal)(OH)_2]_2\cdot H_2O$ (Scheme 1(b)), and $Na[B(Glu)(OH)_2]\cdot 2H_2O$ (Scheme 1(c)) complexes (4) were synthesized as previously described [1]; the synthesized metal complexes and ligand were specified by chemical analysis, melting point measurements, thermal analysis, FT-IR analysis, 1H-NMR and ^{13}C-NMR analysis, ^{13}C MAS NMR analysis, ^{11}B MAS NMR, crystallographic studies, and ultraviolet-visible (UV-vis) physicochemical characterization [1].

2.3. DNA Binding Experiments. In these studies, all complexes were dissolved in sterile distilled water to have the desired pH 7.1. All experiments involving the interaction of complexes with DNA were fulfilled in buffer [27]. The spectroscopic titrations were performed by adding increasing amounts (50 and 100 μL) of DNA to a solution of the complex (100 μM) at a constant concentration; UV-vis spectra were performed after each addition of sample [28, 29].

2.4. Electronic Absorption Spectra. The experiment of electronic absorption spectra was fulfilled with constant concentration of the complexes (100 μM), whereas the concentration of DNA was gradually increased. When the absorption spectra were measured, an equivalent amount of DNA was added to all the complexes solutions and the control solution to eliminate the absorbance of DNA itself. The solutions of DNA were allowed to incubate for 3 h at 37°C before the absorption spectra were carried out.

2.5. DNA Cleavage Experiments. The extent of cleavage of DNA was observed by agarose gel electrophoresis. A solution containing 25 μL of CT-DNA (1,67 ng/μL), HCl (50 mM), pH 7.10, NaCl (50 mM), the complexes (50 mM), and H_2O_2 (60 mM) was incubated for 3 h at 37°C. The electrophoresis experiment was carried out at 75 volt for 3 h in a TBE buffer. The gel was then stained by 3xGelred(Biotium) fluorescent nucleic acid dye for 30 min by shaking 1 μg and photographed using Doc EZ gel imaging system (Bio-Rad) under ultraviolet light [30]. All experiments of the cleavage of the DNA were conducted at room temperature.

2.6. Viscosity Experiments. Viscosity measurements were conducted using an Ubbelodhe viscometer, which was submerged in a thermostatic water-bath kept at a fixed temperature at 25°C. The complexes (10–15 μM) were put in the DNA solution (15 μM) which was presented in the viscometer. The flow time of each complex was measured by a digital stopwatch. Data are displayed as $(\eta/\eta_0)^{1/3}$ versus binding ratio [31], where η and η_0 are the viscosity of DNA in the presence and absence of the complexes. Viscosity values were calculated from the observed flow time of DNA containing solutions corrected from the flow time (t_0), $\eta = t - t_0$ [31–33].

3. Result and Discussion

3.1. Electronic Absorption Spectra. The application of electronic absorption spectroscopy in DNA binding investigations is one of the most noteworthy methods [34]. The DNA binding studies of the boron complexes were investigated by the absorption spectra via the changes observed in the absorbance and shift in the wavelength. The absorption spectra of $Na[B(Glu)(OH)_2]\cdot 2H_2O$, $Na[B(Cit)(OH)_2]\cdot 2H_2O$, $Li[B(Sal)(OH)_2]$, and $Mg[B(Sal)(OH)_2]_2\cdot H_2O$ complexes in the absence and presence of **CT**-DNA are shown in Figures 1(a), 1(b), 1(c), and 1(d), respectively. The interaction of $Na[B(Glu)(OH)_2]\cdot 2H_2O$, $Na[B(Cit)(OH)_2]\cdot 2H_2O$, $Li[B(Sal)(OH)_2]$, and $Mg[B(Sal)(OH)_2]_2\cdot H_2O$ complexes with DNA was monitored by UV-visible spectra. The observed maximum wavelength of complex 1 shifted from 245 nm to 300 nm (Figure 1(a)), and complex 2 from 265 nm to 320 nm (Figure 1(c)), and complex 3 and complex 4 showed band at around 270 nm (Figures 1(b) and 1(d)) when the complexes interacted with the DNA. The absorption bands of $Na[B(Glu)(OH)_2]\cdot 2H_2O$ (1) and $Li[B(Sal)(OH)_2]$ (3) complexes showed significant hypochromism. $Na[B(Cit)(OH)_2]\cdot 2H_2O$ (2) and $Mg[B(Sal)(OH)_2]_2\cdot H_2O$ (3) complexes also exhibited hypochromism. The hypochromic impact, which is a characteristic of intercalation binding to DNA, has been usually identified with the interaction between the electronic states of the complexes and those of the DNA bases [35]. Thereby, the spectroscopic modification suggested that all of the compounds, usually complex 1 and complex 3 had strong interaction with DNA.

3.2. DNA Cleavage Activity. The interaction of DNA with $Na[B(Glu)(OH)_2]\cdot 2H_2O$, $Na[B(Cit)(OH)_2]\cdot 2H_2O$, $Li[B(Sal)(OH)_2]$, and $Mg[B(Sal)(OH)_2]_2\cdot H_2O$ complexes was investigated in order to specify the DNA cleavage efficiencies of these complexes. The aim was reached using agarose gel electrophoresis of DNA. The cleavage of DNA was observed for all four complexes without taking into account varied incubation periods and variation of the concentrations of the test solutions. The cleavage of DNA was observed for all four complexes without taking into account varied incubation periods and variation of the concentrations of the test solutions. The results of the experiments implemented in the concentration range from 50 μM to 500 μM for complexes 1, 2, 3, and 4 after 3 hours of incubation are shown in Figure 2. The DNA cleavage of $Na[B(Glu)(OH)_2]\cdot 2H_2O$, $Na[B(Cit)(OH)_2]\cdot 2H_2O$, $Li[B(Sal)(OH)_2]$, and $Mg[B(Sal)(OH)_2]_2\cdot H_2O$ complexes was investigated in the presence of H_2O_2 and a concentration-dependent cleavage was seen. It was found that the DNA was cleaved by $Na[B(Glu)(OH)_2]\cdot 2H_2O$, $Na[B(Cit)(OH)_2]\cdot 2H_2O$, $Li[B(Sal)(OH)_2]$, and $Mg[B(Sal)(OH)_2]_2\cdot H_2O$ complexes. It was observed that all complexes have significant cleavage activity and they were investigated for DNA cleavage under certain conditions. In fact, the complexes showed a concentration-dependent cleavage. It is known that the extremely reactive $^{\bullet}OH$ radical is produced from O_2^- and H_2O_2 is a cause of DNA strand scission leading to cellular damage [36]. The high cleavage was displayed by all complexes because of the increased reaction of complexes with H_2O_2 thereby creating hydroxyl radicals or molecular oxygen, both of which have the ability to damage DNA [37, 38].

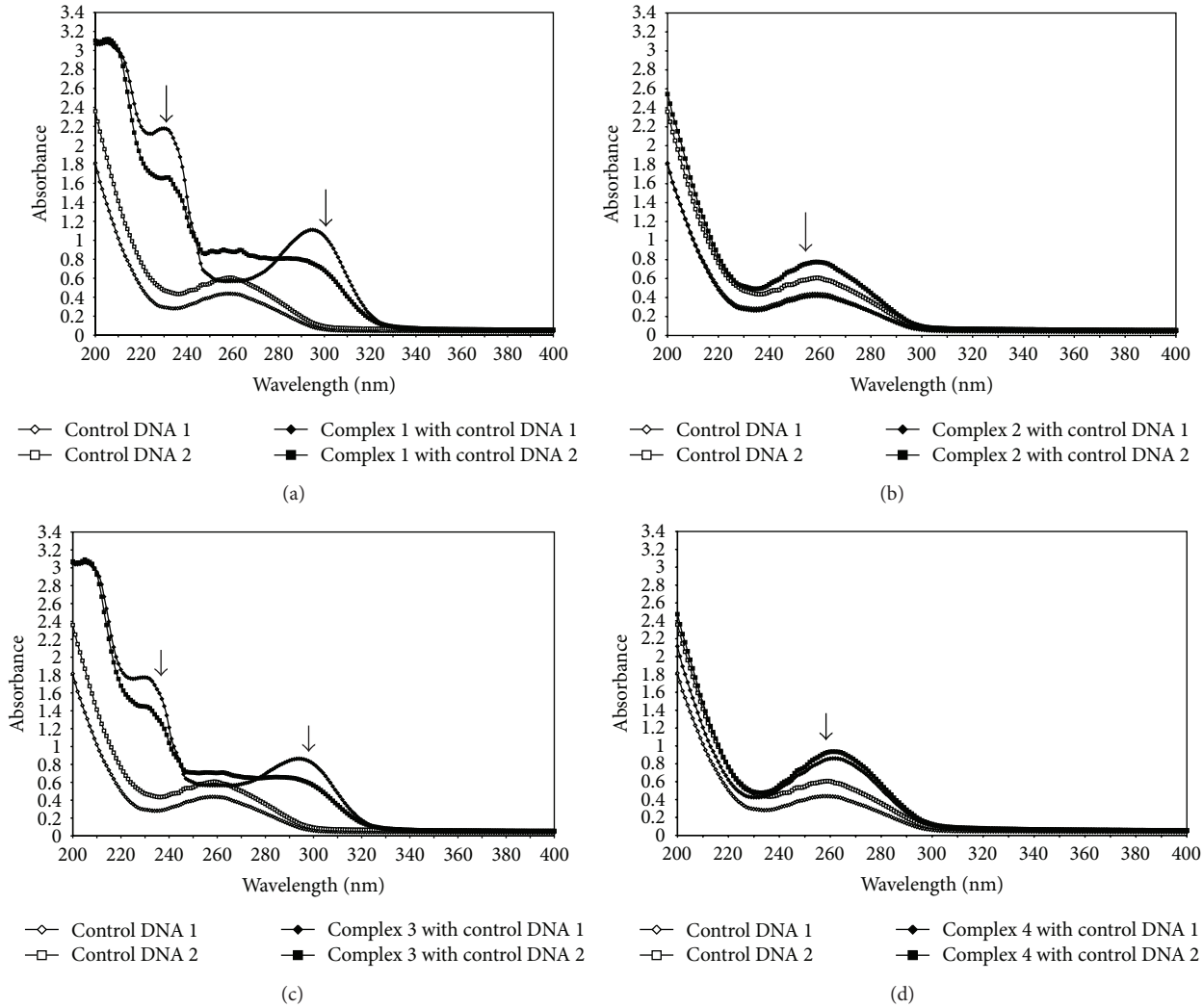


Figure 1: (a) Electronic absorption spectra of complex 1 (100 μM) with increasing amounts of DNA 1 (11.2 μg) and DNA 2 (22.5 μg). (b) Electronic absorption spectra of complex 2 (100 μM) with increasing amounts of DNA 1 (11.2 μg) and DNA 2 (22.5 μg). (c) Electronic absorption spectra of complex 3 (100 μM) with increasing amounts of DNA 1 (11.2 μg) and DNA 2 (22.5 μg). (d) Electronic absorption spectra of complex 4 (100 μM) with increasing amounts of DNA 1 (11.2 μg) and DNA 2 (22.5 μg). Arrows show the changes in absorbance with respect to an increase in DNA concentration.

3.3. Viscosity Measurements. The viscosity studies of $Na[B(Glu)(OH)_2]\cdot 2H_2O$, $Na[B(Cit)(OH)_2]\cdot 2H_2O$, $Li[B(Sal)(OH)_2]$, and $Mg[B(Sal)(OH)_2]_2\cdot H_2O$ complexes with DNA provide more information about DNA binding of the complexes. A standard intercalative style interaction with DNA leads to a significant increase in viscosity of DNA solution because of a raise in dispersion of base pairs at intercalation locations. Conversely, complexes bind particularly in the DNA grooves with partial nonclassical intercalation, under the same conditions, generally leading to negative or no shift in DNA solution viscosity [39, 40]. In order to understand the interaction nature between the complexes and DNA, viscosity measurements were performed. In order to verify the binding mode of complexes 1, 2, 3, and 4 with DNA, the viscosity measurements of the complexes with DNA were carried out by changing the concentration of complexes. The effect of $Na[B(Glu)(OH)_2]\cdot 2H_2O$, $Na[B(Cit)(OH)_2]\cdot 2H_2O$, $Li[B(Sal)(OH)_2]$, and $Mg[B(Sal)(OH)_2]_2\cdot H_2O$ complexes on the viscosity of DNA is indicated in Figure 3.

The results of viscosity measurements obviously exhibit that all the complexes have an intercalative interaction with DNA base pairs. Also, it creates an extension in the DNA helix and raises the viscosity of DNA with an increasing concentration of the complexes. Entire spectroscopic studies and the viscosity measurements provide the boron complexes which can bind to CT DNA through an intercalative interaction.

3.4. Fluorescence Spectra. Competitive binding studies of the complexes were monitored by a fluorescent EB (ethidium bromide) that could provide rich information about DNA binding and relative DNA binding affinity. EB intercalates nonspecifically into the DNA which causes it to fluoresce strongly [41]. The fluorescence spectra of complexes 1, 2, 3 and 4 were performed in the buffer solution at room temperature. The emission maxima fell in the range 370–470 nm. Figures 4,

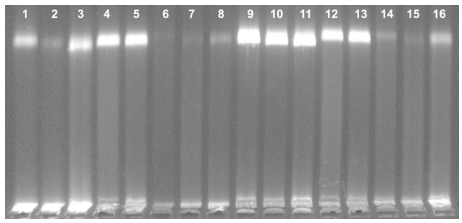


Figure 2: DNA cleavage by the complexes 1, 2, 3, and 4 obtained using agarose gel electrophoresis showing the chemical activity of the DNA incubated at 37°C for 3 h with different concentrations of complexes 1, 2, 3, and 4 in the presence of H_2O_2 as an oxidizing agent: lane 4, control (DNA); lane 5, DNA + H_2O_2 (60 μM); lanes 1, 2, and 3, DNA + H_2O_2 (60 μM) + complex 1 (5, 25, and 50 μM); lanes 6, 7, 8, DNA + H_2O_2 (60 μM) + complex 2 (5, 25, and 50 μM); lanes 9, 10, and 11, DNA + H_2O_2 (60 μM) + complex 3 (5, 25, and 50 μM); lane 12, control (DNA); lane 13, DNA + H_2O_2 (60 μM); lanes 14, 15, and 16, DNA + H_2O_2 (60 μM) + complex 4 (5, 25, and 50 μM).

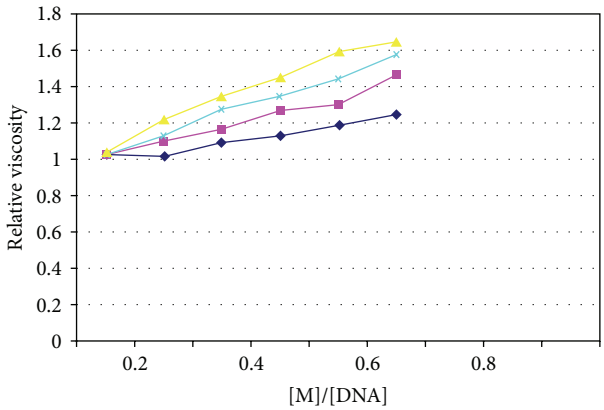


Figure 3: Effect of increasing concentrations of the complexes on the relative viscosity of CT-DNA at 25°C.

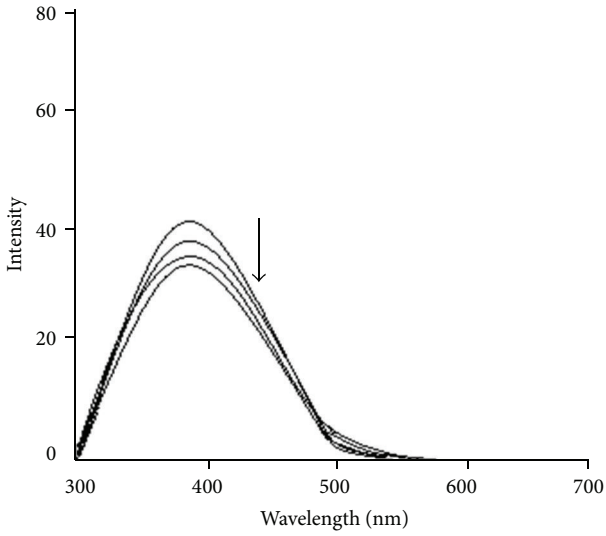


Figure 4: Fluorescence spectra of DNA-EB (10 mM), in the presence of 0, 15, 25, and 35 mM of complex 1. Arrow shows the changes in the emission intensity as a function of complex concentration.

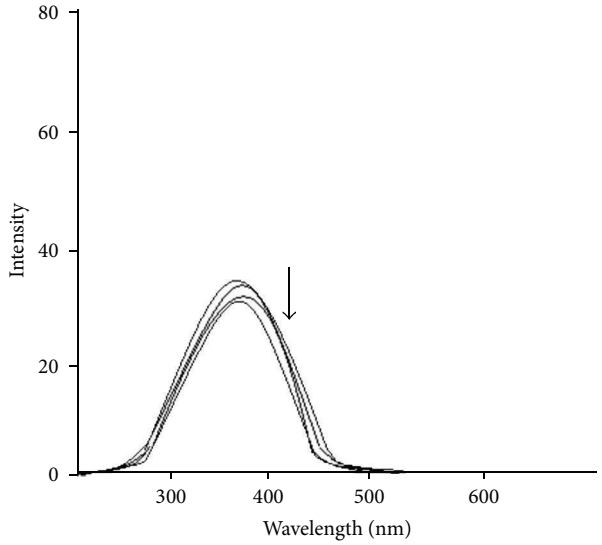


Figure 5: Fluorescence spectra of DNA-EB (10 mM) in the presence of 0, 15, 25, and 35 mM of complex 2. Arrow shows the changes in the emission intensity as a function of complex concentration.

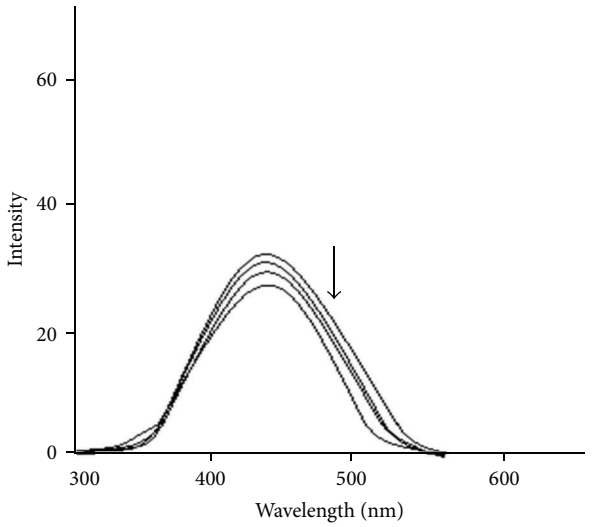


Figure 6: Fluorescence spectra of DNA-EB (10 mM) in the presence of 0, 15, 25, and 35 mM of complex 3. Arrow shows the changes in the emission intensity as a function of complex concentration.

5, 6, and 7 show the fluorescence spectra of the complexes in the absence and presence of varying amounts of the DNA. In the fluorescence spectra for the complexes, with increasing the DNA concentration, the emission intensity is decreased due to self-stacking of some free bases in the compound along the DNA surface [42]. It was found that the interaction between the complexes and the DNA in a groove binding mode causes a strong fluorescence quenching [43, 44].

4. Conclusions

The citric acid, glucuronic acid, and salicylic acid ligands and their boron (boric acid) complexes were previously prepared

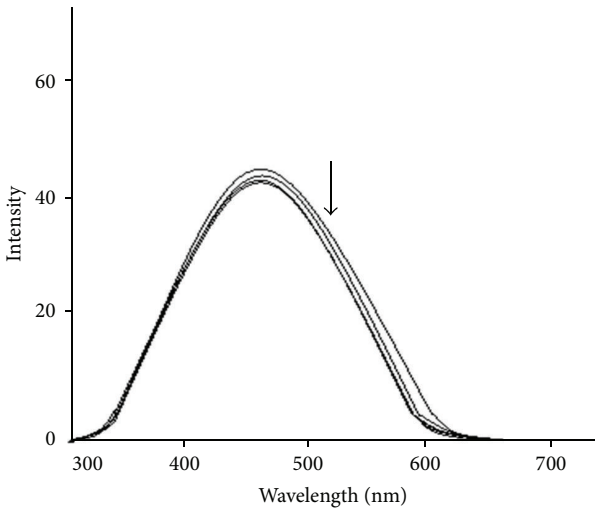


Figure 7: Fluorescence spectra of DNA-EB (10 mM) in the presence of 0, 15, 25, and 35 mM of complex 4. Arrow shows the changes in the emission intensity as a function of complex concentration.

and fully characterized. UV-vis absorption and viscosity measurements studies indicated that $Na[B(Glu)(OH)_2]\cdot 2H_2O$, $Na[B(Cit)(OH)_2]\cdot 2H_2O$, $Li[B(Sal)(OH)_2]$, and $Mg[B(Sal)(OH)_2]_2\cdot H_2O$ complexes showed intercalation binding affinity with the DNA. Furthermore, also all synthesized complexes were assessed for DNA cleavage studies. The DNA binding of the complexes investigated by absorption and viscosity measurements showed that there was an intercalative interaction between the complexes and DNA. DNA cleavage studies revealed that four of the complexes had the capability to cleave DNA. On the basis of the obtained data, these newly synthesized complexes are potential candidate for medical usage.

Abbreviations

UV-vis:	Ultraviolet-visible
Glu:	Glucuronate anion
Sal:	Salicylate anion
Cit:	Citrate monoanion
CG-DNA:	Cattle genomic DNA.

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