



Diorganotin(IV) complexes of biologically potent 4(3H)-quinazolinone derived Schiff bases: Synthesis, spectroscopic characterization, DNA interaction studies and antimicrobial activity

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ABSTRACT

Four Schiff base ligands and their corresponding organotin(IV) complexes have been synthesized and characterized by elemental analyses, IR, ¹H NMR, MS and thermal studies. The Schiff bases are obtained by the condensation of 3-amino-2-methyl-4(3H)-quinazolinone with different substituted aldehydes. The elemental analysis data suggest the stoichiometry to be 1:1 ratio formation. Infrared spectral data agreed with the coordination to the central metal ion through imine nitrogen, lactam oxygen and deprotonated phenolic oxygen atoms. All the synthesized compounds have been evaluated for antimicrobial activity against selected species of microorganisms. In addition, DNA binding/cleavage capacity of the compounds was analyzed by absorption spectroscopy, viscosity measurements and gel electrophoresis methods.

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1. Introduction

The Schiff bases are among the most widely used ligands due to their facile synthesis, remarkable versatility and good solubility in common solvents. Thus, they have played an important role in the development of coordination chemistry as they readily form stable complexes with most metals in different oxidation states. In the area of bioinorganic chemistry, the interest in the Schiff base complexes lies in that they provide synthetic models for the metal containing sites in metalloproteins and enzymes [1]. Quinazolinone-4(3H)-ones and its derivatives are versatile nitrogen heterocyclic compounds which have long been known as a promising class of biologically active compounds [2]. Compounds containing 4(3H)-quinazolinone ring system have been reported to possess different biological activities such as antibacterial [3], antifungal [4], anti-tubercular [5], antiviral, anticancer [6] and anticonvulsant activity depending on the substituent's in the ring system.

Over the recent decades, studies on the organotin(IV) complexes with Schiff base ligands have received considerable attention. Organotin(IV) complexes have played an important role in medicine, agriculture and industry. Up to now, considerable efforts

have been made to synthesize and characterize organotin compounds of ligands having hetero donor atoms (O, N, S), and many studies have been focused on their structure–activity correlations [7,8]. Several organotin(IV) compounds have been synthesized and tested for their antitumor activity and found to be as effective as, or even better than, traditional heavy anticancer drugs [9]. An interesting work in the field of bioinorganic chemistry is the introduction ligands which are bioactive [10]. Schiff bases are potential anticancer drugs and when administered as their metal complexes, the anticancer activity of these complexes is enhanced in comparison to the free ligand [11]. Therefore, organotin(IV) complexes of Schiff bases have received considerable attention with respect to their potential applications in medicinal chemistry and biotechnology [12]. Furthermore, organotin(IV) complexes with Schiff bases present an interesting variety of structural possibilities. This aspect has been attracting the attention of a number of researchers and a multitude of structural types have been discovered. Both aliphatic and aromatic Schiff bases in their neutral and deprotonated forms have been used to react with organotin(IV) halides; the complexes formed exhibit variable stoichiometry in the metal to ligand ratio and different modes of coordination [13]. Still, there is a lot of scope to synthesize and characterize organotin complexes with variety of ligands. Thus, the present paper reports synthesis of four ligands and their organotin(IV) complexes, and the prepared organotin complexes have been characterized

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and subjected them for biological studies. Besides, the DNA binding/cleavage activities of the complexes are also reported.

2. Experimental

2.1. Materials and methods

All the chemicals and solvents were of analytical grade and used as received. CT-DNA and pUC19 plasmid DNA were purchased from Genei laboratory, Bangalore. Elemental analysis (CHNS) was performed using a Perkin-Elmer 240 elemental analyzer. IR spectra of the Schiff base ligands and their complexes were recorded on a Shimadzu FT-IR-8300 instrument using nujol mulls method in the range of 4000–200 cm^{-1} . ^1H NMR spectra of the synthesized compounds were recorded on Bruker DRX-300 spectrometer using $\text{DMSO}-d_6$ as solvent and TMS as the internal standard. Molar conductivity measurements were recorded on a CM-82T Elico conductivity bridge in DMSO. Thermogravimetric analyses data were measured from room temperature to 700 °C at a heating rate of 20 °C/min on a Shimadzu TG-50 Thermo Balance. Absorption spectra were recorded using a HITACHI-3900 model spectrophotometer.

2.2. Synthesis of Schiff base Ligands

The Schiff base ligands were synthesized according to the known condensation method [14]. The methanolic solution of 3-amino-2-methyl-4(3H)-quinazolinone (1) (2.0 mmol, 25 ml) was mixed with a methanol solution of salicylaldehyde (to obtain L_1) or 2-pyridine carboxaldehyde (to obtain L_2) or 4-hydroxy-3-methoxybenzaldehyde (to obtain L_3) or 5-ethyl-2-thiophenecarboxaldehyde (to obtain L_4) (2.0 mmol, 15 ml). The mixture was stirred magnetically for 30 min and then refluxed for 4 h. After cooling, the solution of Schiff base was filtered, washed with hot methanol, dried in air and recrystallized from ethanol. The purity of ligand was checked by thin layer chromatography. The general structure of 4(3H)-quinazolinone derived Schiff base ligands are shown in Scheme 1.

2.3. Synthesis of organotin(IV) complexes

All the complexes were synthesized by adding a methanolic solution of appropriate ligand (1 mmol, 25 ml) to a hot methanolic solution of dimethyltin chloride salt (1 mmol, 25 ml). The resulting solutions were stirred and heated to reflux for 4 h. The volume of the obtained solutions was reduced to one-half by evaporation. After one day, the colored solid of the complexes formed was filtered, washed with hot methanol and diethyl ether and finally dried in air. The synthesized complexes were recrystallized from ethanol. The purity of all the complexes was evaluated by thin layer chromatography. Development of single crystals of these complexes was unsuccessful.

2.4. Biology

2.4.1. DNA binding studies

Electronic absorption spectroscopy is an effective method to examine the binding mode of DNA with metal complexes [15]. The DNA concentration per nucleotide was determined adopting absorption spectroscopy using the known molar extinction coefficient value of $6600 \text{ M}^{-1} \text{ cm}^{-1}$ at 260 nm [16]. Absorption titrations were performed by using a fixed DNA concentration to which increments of the complex solution were added. Metal complex–DNA solutions were incubated for 10 min before the absorption spectra were recorded.

2.4.2. Viscosity measurements

Viscosity measurements were carried out in an Ostwald viscometer maintained at 30.0 ± 0.1 °C in a thermostatic water-bath. The viscometric studies were carried out in buffer solution (pH 7.2). Flow time was measured by hand with digital stopwatch, each sample was measured three times and the average flow time was calculated. Data obtained were presented as $(\eta/\eta_0)^{1/3}$ vs the concentration of complexes, where η is the viscosity of DNA in presence of complexes and η_0 is the viscosity of DNA alone. Viscosity values were calculated from the observed flow time of DNA-containing solution ($t > 100$ s) corrected for flow time of buffer alone (t_0), $\eta = t - t_0/t_0$ [17].

2.4.3. Nuclease activity

The DNA cleavage experiment was conducted using supercoiled pUC19 plasmid DNA by gel electrophoresis method. Cleavage reactions were run between the metal complexes and the supercoiled plasmid DNA, and the solutions were diluted with loading dye using 1% agarose gel. Buffer solution of 50 mmol Tris–HCl/18.2 mmol NaCl in water (pH 7.2) was used, followed by the addition of 0.5 g of powdered agarose and mixed well. The solution was heated to boiling to dissolve agarose completely. The completely dissolved agarose gel solution was kept in the water bath at 65 °C. Then, 3 μl of ethidium bromide (0.5 $\mu\text{g}/\text{ml}$) was added to the above solution and mixed well. The warmed agarose was poured and clamped immediately with comb to form sample wells. After setting (30–45 min, at room temperature) comb was removed and taped. The gel was mounted into electrophoretic tank. Enough electrophoretic buffers were added to cover the gel to a depth of about 1 mmol. The plasmid DNA (10 μmol) and different concentrations of metal complexes (10, 15 and 20 μl) in Tris–HCl/50 mmol NaCl buffer (pH 7.1) were mixed with loading dye and loaded into the well of the submerged gel using a micropipette. The electric current (70V) was passed into running buffer. The sample was running from negative to positive pole [18]. After 1 h the gel was taken out from the buffer. After electrophoresis, the extent of cleavage was measured from the intensities of the bands using the Alpha Innotech Gel documentation system (AlphaImager 2200).

2.4.4. Antimicrobial activity

The *in vitro* antimicrobial screening effects of the synthesized ligands and their corresponding organotin(IV) complexes were evaluated against four species of bacteria; *E. coli*, *Staphylococcus aureus*, *Ralstonia solanacearum* and *Xanthomonas vesicatoria* as well as fungi; *Aspergillus niger*, *Aspergillus flavus*, *Fusarium oxysporum* and *Alternaria solani* by disk-agar diffusion method [19,20]. All the tests were performed in triplicate and average is reported. The minimum inhibitory concentration values of studied compounds against tested microorganisms are also reported.

3. Results and discussion

Organotin(IV) complexes were obtained upon reaction between organotin and a ligand at 1:1 molar ratio. The synthesized Schiff base ligands and their tin complexes are very stable at room temperature in the solid state. The ligands and their tin complexes are generally soluble in DMF and DMSO. The analytical and physical data of ligands and their organotin complexes are presented in Table 1. The analytical data are in a good agreement with the proposed stoichiometry of the complexes.

3.1. Molar conductivity of metal chelates

The tin complexes discussed herein were dissolved in DMF and the molar conductivities of their 10^{-3} M solutions at room temperature were measured to establish the charge of the metal complexes.

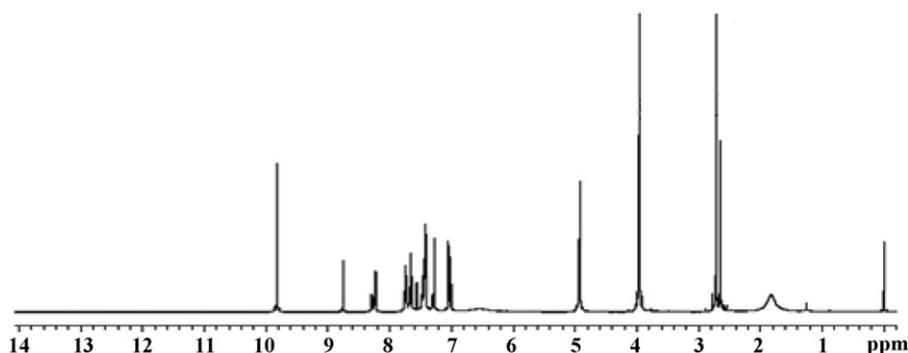


Fig. 1. ¹H NMR spectrum of L₃.

The range of conductance values (11–18 ohm⁻¹ cm² mol⁻¹) listed in Table 1 indicates that all the metal complexes have non-electrolyte nature [21].

3.2. IR spectra

The main vibrational bands of ligands and their organotin(IV) complexes are shown in Table 2. Several significant changes with respect to the ligands are observed in the corresponding tin(IV) complexes. The spectra of the ligands show characteristic bands due to $\nu(\text{C}=\text{O})$ and $\nu(\text{C}=\text{N})$ at 1682–1655 and 1655–1571 cm⁻¹ region, respectively. In L₁ and L₃, $\nu(\text{OH})$ band appears at 3441 and 3434 cm⁻¹, respectively. The $\nu(\text{C}=\text{N})$ band has been shifted to lower frequency (ca. 1602–1567 cm⁻¹) in the complexes indicating the coordination of the ligands through nitrogen atom of the azomethine group. Upon complexation, the band at 1682–1655 cm⁻¹ region in ligands due to $\nu(\text{C}=\text{O})$ has been shifted to lower frequency (ca. 1677–1641 cm⁻¹) indicating the involvement of lactam group in the coordination [22]. The $\nu(\text{OH})$ band in case of L₁ and L₃ at 3441 and 3434 cm⁻¹ has been disappeared in complexes 1 and 3. This suggests the deprotonation and involvement of the phenolic oxygen in chelation. Two medium to sharp intensity bands observed in the far IR region of the tin(IV) complexes at 411–403 cm⁻¹ and 417–413 cm⁻¹ are assigned to $\nu(\text{Sn}-\text{N})$ and $\nu(\text{Sn}-\text{O})$ modes, respectively, which are not observed in the spectra of ligands [23,24]. One strong to medium intensity band appeared in the spectra of the complexes in the region 513–506 cm⁻¹ which can be attributed to (Sn–CH₃) stretching vibrations.

3.3. ¹H NMR spectra

The proton NMR spectra of the ligands and their corresponding complexes were recorded in DMSO-*d*₆ using TMS as the internal standard. The ¹H NMR spectrum of L₃ is shown in Fig. 1. The ligands exhibit peaks in the region 2.72–2.61, 8.9–7.7, 7.9–7.2 and 10.8–9.8 ppm corresponds to CH₃, N=CH, Ar–H and OH protons, respectively [25]. Upon comparison of ¹H NMR spectra of ligands with their corresponding tin(IV) complexes, the N=CH signal has been shifted downfield at around 9.21–9.06 ppm indicating the involvement of azomethine nitrogen in the complexation. The methyl groups in complexes attached to the central tin atom gives a single band at a very upfield region (ca. 1.70–1.40). The ¹H NMR data concludes that the deshielding of protons is observed in all the complexes, which is probably due to electrophilic character of tin atom and coordination of the carbonyl oxygen atom in all the complexes [26,27]. A comparison of ¹H NMR spectra of complex 1 and 3 with the L₁ and L₃ have shown disappearance of signal of OH (10.8–9.8 ppm) proton on the formation of Sn–O band [28].

3.4. Mass spectra

The mass spectrum of the L₄ is given in Fig. 2. Fragments at $m/z = 280$ (base peak) are attributed to C₁₆H₁₃N₃O₂⁺ ion. The other molecular ion peaks appeared in the mass spectra is attributed to the fragmentation of the ligand molecule obtained from the rupture of different bonds inside the molecule. The mass spectra of tin(IV)

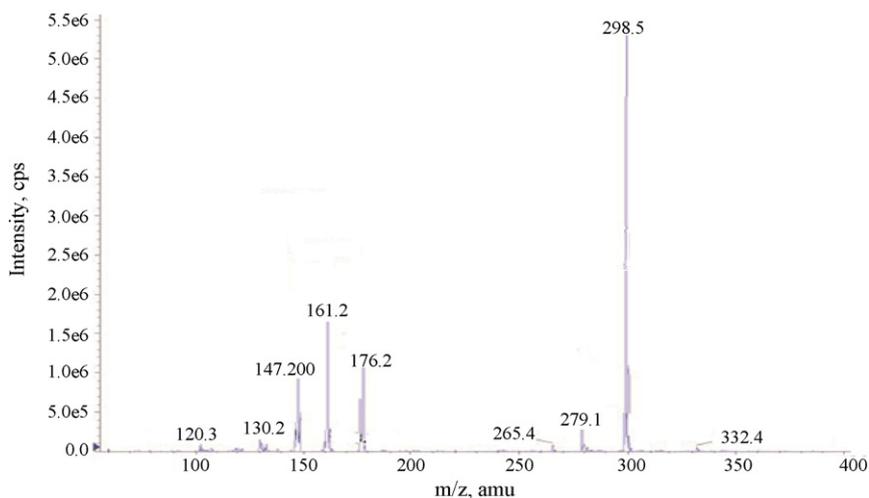


Fig. 2. Mass spectrum of L₄.

Table 1
Analytical data and physical properties of the Schiff base ligands and their organotin(IV) complexes.

Compound	Mol. formula	Yield, %	Calculated (Found), %				Molar conductivity, S cm ² mol ⁻¹
			C	H	N	S	
L ₁	C ₁₆ H ₁₃ N ₃ O ₂	77	68.43(68.69)	4.58(4.67)	14.9 (15.03)	–	–
L ₂	C ₁₅ H ₁₂ N ₄ O	69	68.18(68.56)	4.28(4.39)	21.22(21.35)	–	–
L ₃	C ₁₇ H ₁₅ N ₃ O ₃	81	66.01(66.45)	4.93(5.03)	13.58(13.72)	–	–
L ₄	C ₁₆ H ₁₅ N ₃ OS	73	64.8 (64.82)	5.0 (5.11)	14.6 (14.82)	10.8(10.97)	–
1	C ₁₈ H ₁₈ N ₃ O ₂ Sn	58	50.58(50.86)	4.21(4.63)	9.83 (10.23)	–	13.7
2	C ₁₇ H ₁₈ N ₄ OSn	62	49.39(49.87)	4.35(4.51)	13.55(13.81)	–	11.1
3	C ₁₉ H ₂₀ N ₃ O ₃ Sn	49	49.89(50.22)	4.37(4.82)	9.19 (9.49)	–	14.9
4	C ₁₈ H ₂₁ N ₃ OSSn	53	48.43(48.77)	4.7 (4.92)	9.41 (9.68)	7.17 (7.73)	17.8

Table 2
Infrared spectral data of the ligands and their organotin(IV) complexes.

Compound	$\nu(\text{C}=\text{O})$	$\nu(\text{C}=\text{N})$	$\nu(\text{O}-\text{H})$	$\nu(\text{M}-\text{N})$	$\nu(\text{M}-\text{O})$	$\nu(\text{Sn}-\text{CH}_3)$
L ₁	1656	1603	3123	–	–	–
L ₂	1684	1597	–	–	–	–
L ₃	1650	1586	3117	–	–	–
L ₄	1702	1609	–	–	–	–
1	1596	1582	–	407	414	511
2	1643	1602	–	403	417	513
3	1697	1581	–	411	415	507
4	1581	1593	–	409	413	509

complexes give a well defined parent peak at $m/z = 427$ (MH⁺), 413 (MH⁺), 457 (MH⁺) and 446 (MH⁺) for complexes 1, 2, 3 and 4, respectively.

3.5. Thermal studies

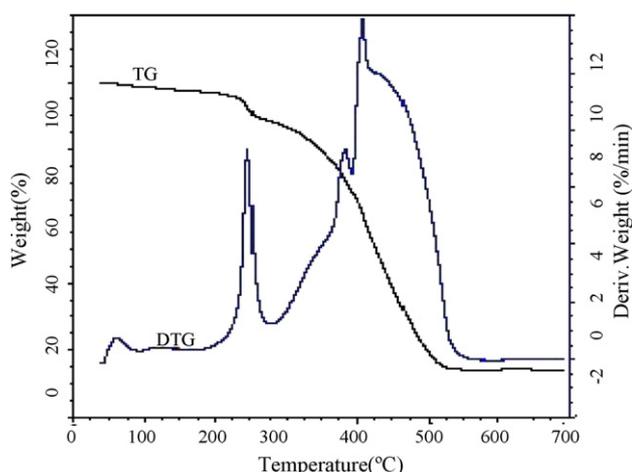
The thermal property of complex 1 was investigated by TGA and DTG studies. Fig. 3 presents the recorded TGA/DTG curves of complex 1 in nitrogen atmosphere. The complex undergoes two-step decomposition. The first-step is endothermic decomposition at 240 °C, corresponds to the loss of methyl groups. The ligand moiety then decomposes exothermically at 380–430 °C and finally leaving SnO as the residual product [29].

Based on the above analytical and spectral studies, following structures are assigned for the complexes (Fig. 4).

3.6. Biology

3.6.1. DNA binding studies

The absorption spectra of the interaction of CT-DNA with the complexes 1 and 2, have been recorded for a constant DNA by

**Fig. 3.** TG and DTG curves of complex 1.

varying metal complex concentration and they are shown in Fig. 5. The changes observed in the absorption spectra of CT-DNA in the presence of complex, that is, the decrease in the intensities in the range $\lambda_{\text{max}} = 258\text{--}253$ nm. This indicate that the interaction with CT-DNA [30]. This interaction results the direct formation of a new complex with double stranded CT-DNA [31] which simultaneously may cause the slight change of the conformation of DNA [32] in case of complexes. The observed hypsochromism is due to the intercalative binding mode [33] between the chromophores of the complexes and DNA base pairs. Additionally, the observed blue shift of 6 nm is an evidence of the stabilization of the CT-DNA duplex [34]. From the observed spectral changes the value of the intrinsic binding constant K_b were found to be $1.83 \times 10^4 \text{ M}^{-1}$ and $2.38 \times 10^4 \text{ M}^{-1}$ for the complexes 1 and 2, respectively. As we know that the extent of hypsochromism is commonly consistent with the strength of the DNA binding interaction [35], we can rationalize the DNA binding affinity of the complexes by studying the rate of hypsochromism as shown in the UV–vis spectra of the complexes.

3.6.2. Viscometric studies

The viscosity measurements of CT-DNA are regarded as the least ambiguous and the most critical tests of a binding model in solution in the absence of crystallographic structural data. A classical intercalation model demands that the DNA helix lengthens as base pairs are separated to accommodate the bound complex, leading to the increase of DNA viscosity [36]. Fig. 6 shows the increase in the viscosity of CT-DNA up on addition of complexes 1 and 2. This result further suggested an intercalative binding mode of the complex with DNA.

3.6.3. Nuclease activity

The cleavage reaction on plasmid DNA was monitored by agarose gel electrophoresis. When circular plasmid DNA was subjected to electrophoresis, relatively fast migration was observed for the intact supercoiled DNA (Form I). If scission occurs on one strand, the supercoiled DNA will relax to generate a slower moving open circular/nicked type (Form II). If both the strands are cleaved, a linear form (Form III) that migrates between Form I and Form II will be generated [37].

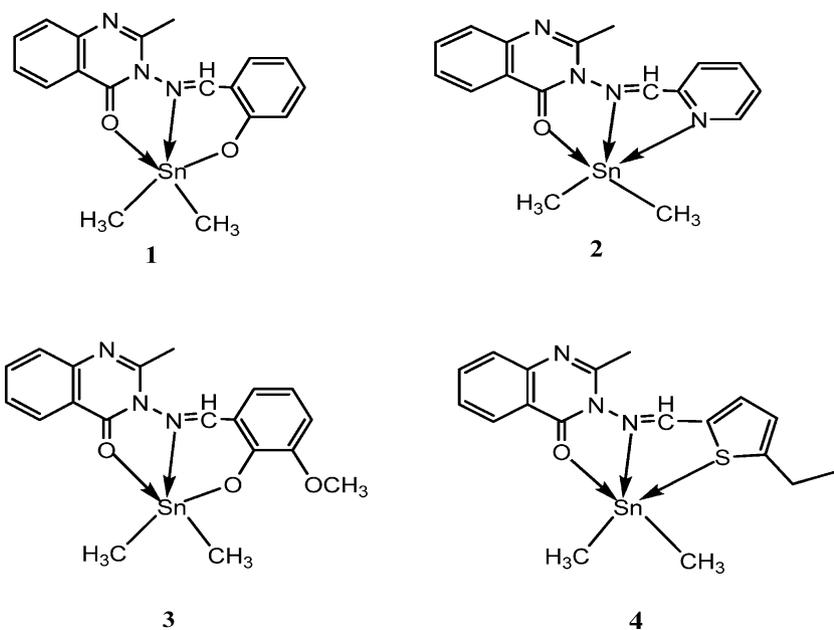


Fig. 4. Proposed structures for diorganotin(IV) complexes.

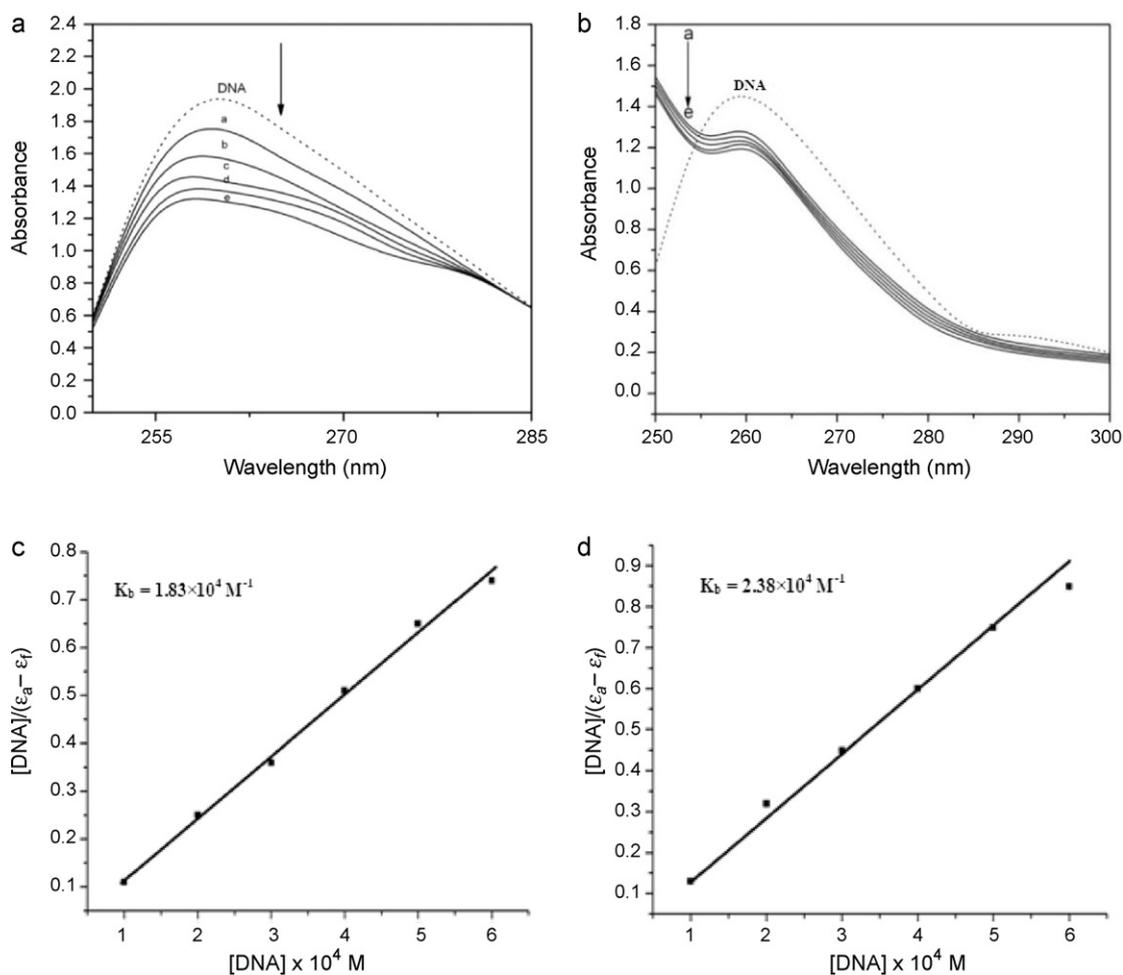


Fig. 5. UV spectra of CT DNA in buffer solution (150 mM NaCl and 15 mM trisodium citrate at pH 7.0) in the presence of (a) complex 1, ($[\text{DNA}] = 0.10 \text{ mM}$) and (b) complex 2, ($[\text{DNA}] = 0.10 \text{ mM}$), at a complex concentration of $5.0 \times 10^{-5} \text{ M}$. Dotted curve shows the absorption of DNA alone. The arrows show the intensity changes upon increasing concentration (a–e) (20, 40, 60, 80, 100 μl) of complex. Plot of $[\text{DNA}]/(\epsilon_a - \epsilon_f)$ vs. $[\text{DNA}]$ for the titration of DNA (10, 20, 30, 40, 50 and 60 μM) with (c) 1 and (d) 2 complexes.

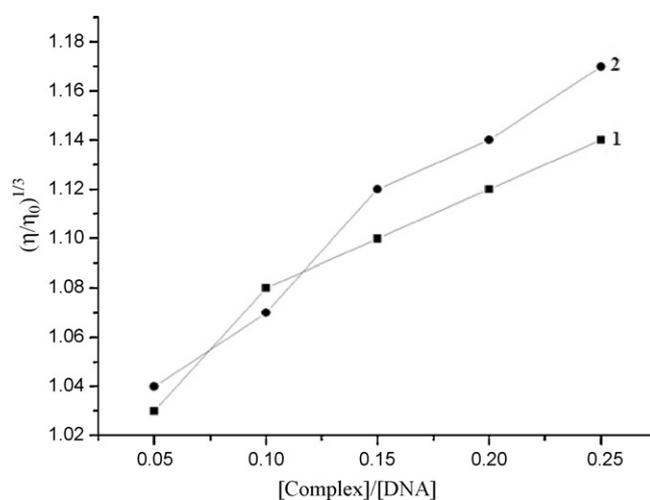


Fig. 6. Effect of increasing amount of complexes on the relative viscosity of CT-DNA.

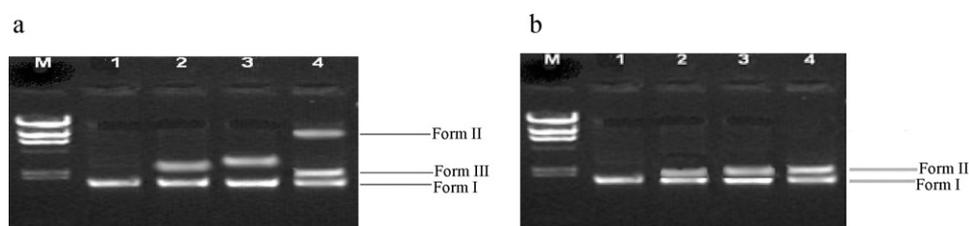


Fig. 7. Cleavage of supercoiled pUC19 DNA (0.5 μg) by complexes 1 and 2 in a buffer containing 50 mM Tris–HCl at 37 °C (30 min): (a) lane M: marker; lane 1: DNA control; lane 2: 10 μl complex 1 + DNA; lane 3: 15 μl complex 1 + DNA; lane 4: 20 μl complex 1 + DNA. (b) Lane M: marker; lane 1: DNA control; lane 2: 10 μl complex 2 + DNA; lane 3: 15 μl complex 2 + DNA; lane 4: 20 μl complex 2 + DNA.

Table 3

Minimum inhibitory concentrations (MIC) (in μg/ml) of compounds by using macrodilution method.

Compound	Minimum inhibitory concentration values (in μg/ml)							
	Antibacterial activity				Antifungal activity			
	<i>E.coli</i>	<i>S. aureus</i>	<i>R. solanacearum</i>	<i>X. vesicatoria</i>	<i>A. niger</i>	<i>A. flavus</i>	<i>F. oxysporum</i>	<i>A. solani</i>
L ₁	128	128	64	128	128	128	128	128
L ₂	128	128	128	128	128	128	128	128
L ₃	64	128	128	64	128	128	128	128
L ₄	128	128	128	128	128	128	128	128
1	64	64	32	16	64	64	64	32
2	64	64	64	64	64	64	64	64
3	32	32	32	16	64	32	32	32
4	128	64	64	64	128	32	64	64
Chloramphenicol	8	8	8	2	–	–	–	–
Terbinafin	–	–	–	–	8	2	2	2

Table 4

Antimicrobial activity of Schiff bases and their corresponding organotin(IV) complexes.

Compound	Zone of inhibition (in mm) ^a							
	Antibacterial activity				Antifungal activity			
	<i>E. coli</i>	<i>S. aureus</i>	<i>R. solanacearum</i>	<i>X. vesicatoria</i>	<i>A. niger</i>	<i>A. flavus</i>	<i>F. oxysporum</i>	<i>A. solani</i>
L ₁	18	12	09	12	11	10	12	09
L ₂	13	11	03	07	02	03	06	03
L ₃	21	20	11	15	13	15	17	12
L ₄	11	13	06	09	05	08	07	06
1	15	22	12	19	13	10	13	09
2	19	21	09	13	06	07	10	05
3	23	33	21	27	19	18	26	17
4	17	24	13	18	09	11	14	10
Chloramphenicol	34	35	32	29	–	–	–	–
Terbinafin	–	–	–	–	22	24	29	25

^aAverage of three replicates.

The nuclease activity of complexes 1 and 2 has been studied under physiological pH and temperature by gel electrophoresis using supercoiled pUC19 plasmid DNA as the substrate. As shown in Fig. 7(a) and b, with increase of complex concentration, the intensity of the circular supercoiled DNA (Form I) band decreases, while that of nicked (Form II) and linear (Form III) bands increases (lanes 2–4). When the complex concentration was 20 μl (40 μM , lane 4), all the three forms are well separated with complex 1. In comparison, complex 1 acts as most effective cleaving agent than the complex 2.

3.6.4. Antimicrobial activity

All the synthesized ligands and their diorganotin(IV) complexes were evaluated for their antimicrobial activity by disk-agar diffusion method. Chloramphenicol and Terbinafin were used as standard antibacterial and antifungal agents, respectively. The compounds to be tested were dissolved in DMF at a concentration 0.25 mg/ml. The minimum inhibitory concentration (MIC), defined as the lowest concentration of each compound that totally inhibited visible microorganism growth, was recorded for each compound assayed (Table 3).

Table 4 clearly shows that the ligands and their complexes showed moderate to good antimicrobial activity. The results indicate that the complexes show more activity than ligands against same microorganisms under identical experimental conditions. This would suggest that the chelation could facilitate the ability of a complex to cross a cell membrane and can be explained by Tweedy's chelation theory [37,38]. Such a chelation could enhance the lipophilic character of the central atom, which subsequently favors its permeation through the lipid layer of the cell membrane. The variation in the effectiveness of different compounds against different organisms depends either on the impermeability of the cells of the microbes or on differences in ribosome of microbial cells.

L_1 and L_3 have greater activity than L_2 and L_4 . This higher activity of L_1 and L_3 may be due to the presence of hydroxyl group, which may play an important role in antimicrobial activity [38]. All the complexes displayed good activity than their corresponding ligands against the tested microorganism. Among the complexes, complex 3 show higher activity against three bacteria, *S. aureus*, *X. vesicatoria*, *R. solanacearum* and two fungi, *A. niger* and *F. oxysporum*. This may be due to the presence of methoxy group. Fig. 8 shows the antimicrobial activity of L_3 and its corresponding organotin(IV) complex 3 against *X. vesicatoria*.

4. Conclusions

Novel diorganotin(IV) complexes were synthesized using 4(3H)-quinazolinone derived Schiff bases. The ligands and their complexes were characterized by IR, ^1H NMR, MS, elemental analyses, molar conductance and thermal studies. The complexes are non-electrolytic in nature. Complexes bind to DNA through intercalating mode. Gel electrophoresis experiment suggests that the complexes cleave supercoiled DNA at higher concentration. The antimicrobial results indicated that the complexes are much active compared to their corresponding ligands.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.saa.2011.06.010.

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