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Synthesis, Characterization, and Biological Activity of Organotin(IV) Complexes with 4-Oxo-4-[3-(trifluoromethyl)phenylamino]butanoic Acid[1]

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Abstract—Metal complexes display functional interfaces for association with and stimulation of certain enzymes, that are liable to transfer genetic information in DNA for synthesis of specific proteins. Biological activity of five organotin carboxylates based on the ligand, 4-oxo-4-[3-(trifluoromethyl)phenylamino]butanoic acid, such as [Bu_3SnL] (**1**), [Ph_3SnL] (**2**), [Me_2SnL_2] (**3**), [Bu_2SnL_2] (**4**), and [Ph_2SnL_2] (**5**) have been synthesized and their biological activity as a function of substitution on the ligand was tested. Structure of the complexes was evaluated by elemental analysis, FT-IR and ^{1}H, and ^{13}C NMR spectra. FT-IR data and theoretical calculations revieled that the ligand acted as bidentate in complexes **1–5**. NMR data revealed four and six coordinated geometry of tin in solutions. The HOMO–LUMO study indicated thermodynamic stability of the complexes. AFM confirmed catalytic potential of the synthesized complexes. Biological screening showed that, with few exceptions, all the complexes exhibited significant activity against various bacterial and fungal strains. UV-Vis study confirmed that the ligand and its complexes binded to DNA via intercalative interactions.

Keywords: organotin(IV) carboxylates, 4-oxo-4-[3-(trifluoromethyl)phenyldamino]butanoic acid, FT-IR, NMR, theoretical study, biological activity, DNA interaction study, AFM study

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According to recent studies [1], some bio-inorganic compounds demonstrate significant biological potential in cases when many clinically relevant pathogens become resistant against familiar classes of antimicrobial agents.

Organotin carboxylates exhibit a wide variety of structural types [2–7] due to presence of electro-negative groups and increase of the effective nuclear charge on tin. Organotin(IV) carboxylates have been characterized by various spectroscopic methods [8–13] that confirmed their different structures in solutions and solid state due to tin bounding to a nucleophilic group or Sn–C bonding attached with an organic group posessing donor character [14]. In that case breaking ability of Sn–C makes reactivity of the compouds different from similar organotin compounds without such functionality [15, 16].

Organotin based compounds demonstrate such valuable activities as anti-tumor and anti-cancer, and can be used in surface catalysis [17]. Coordinated sphere [17] of organotin compounds influences their bioactivity [18]. Available positions at carboxylates with four and five coordinated tin support higher activity of compounds than those with six coordinated

[1] The text was submitted by the authors in English.

tin [19]. Generally the bio-related activities are determined by the nature of organic ligands that influences transport across cell membranes [20–22].

Based on the above information and in continuation of our previous studies [23–28], we have synthesized organotin(IV) complexes with 4-oxo-4-[3-(trifluoromethyl)phenylamino]butanoic acid. The complexes have been characterized by elemental analysis, FT-IR, ^{1}H and ^{13}C NMR spectra, and molecular modelling. Antibacterial, antifungal, antileishminial, toxicity, protein kinase inhibition, and DNA binding studies have been carried out.

EXPERIMENTAL

All reagents were purchased from Aldrich (USA). According to literature procedures [29], the solvents (Merck) were dried prior to use. Melting points were measured (uncorrected) on a MP-D Mitamura Rieken Kogyo (Japan) apparatus. FT-IR spectra were recorded on a Nicolet-6700 FTIR spectrophotometer. NMR spectra were measured on a Bruker Avance 300 MHz spectrometer. UV-Vis spectra were recorded on a Shimadzu 1800 spectrophotometer at 25±1°C. For thermal degradation studies and kinetic parameters determination a Perkin Elmer TGA-7 Thermal Analyzer was used. A complex (20–30 mg) was loaded in a platinum pan and the degradation studies were carried out in the temperature range of 50–1000°C with heating rate of 20°C/min. Sodium salt of DNA (Acros) was used as received. Solution of DNA in 10 mmol/L of phosphate buffer (pH = 7.0) gave a ratio of UV absorbance at 260 and 280 nm. A_{260}/A_{280}, of 1.8–1.9 indicated the purity of DNA. Concentrated stock solution of DNA was prepared in 10 mmol/L of phosphate buffer (pH = 7.0) and the concentration was determined by UV absorbance at 260 nm upon 1 : 100 dilution. The molar absorption coefficient has been taken as 6600 mol^{-1}/cm. Stock solutions were stored below 4°C and used within 4 days. CHN analysis was carried out on a LECO CHNS-932 analyzer.

Synthesis of ligand (HL). Solution of succinic anhydride (1 mmol) in glacial acetic acid (100 mL) was mixed with a solution of 3-(triflouromethyl) benzeneamine (1 mmol) in glacial acetic acid (80 mL). The reaction mixture was magnetically stirred at room temperature for 6-8 h. The precipitates formed were filtered off and washed with distilled water (400 mL).

Synthesis of sodium salt of ligand (NaL). A mixture of equimolar aqueous solutions (5 mmol) of sodium hydrogencarbonate with ligand (HL) were stirred at room temperature for 0.5 h. The solvent was evaporated under reduced pressure to yield sodium salt of the ligand.

Synthesis of organotin(IV) complexes. Organotin(IV) complexes were synthesized by refluxing a mixture of sodium salt of a ligand NaL (5 mmol) with R_3SnCl (5 mmol)/R_2SnCl_2 (2.5 mmol) in dry toluene for 8 h (Scheme 1) and NaCl formed was filtered off. The solvent was evaporated under reduced pressure. The solid product obtained was dried in the air and recrystallized from chloroform : *n*-hexane (1 : 1). Numbering of atoms of HL and other organic moieties attached to tin atom for NMR interpretation is given in Scheme 2.

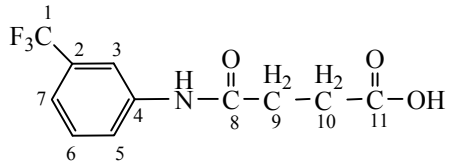
$$\mathrm{NaL} + \mathrm{R_3SnCl} \xrightarrow[\text{reflux, 8 h}]{\text{toluene}} \mathrm{R_3SnL} + \mathrm{NaCl},$$

$$\mathrm{R} = \mathrm{C_4H_9}\ (\mathbf{1}),\ \mathrm{C_6H_5}\ (\mathbf{2}),$$

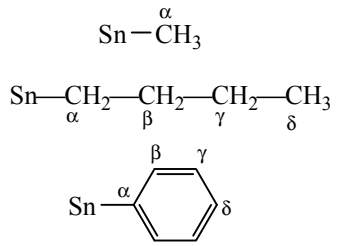
$$2\mathrm{NaL} + \mathrm{R_2SnCl_2} \xrightarrow[\text{reflux, 8 h}]{\text{toluene}} \mathrm{R_2SnL_2} + 2\mathrm{NaCl},$$

$$\mathrm{R} = \mathrm{CH_3}\ (\mathbf{3}),\ \mathrm{C_4H_9}\ (\mathbf{4}),\ \mathrm{C_6H_5}\ (\mathbf{5}).$$

Scheme 1. Synthesis of organotin(IV) compounds.



Scheme 2. NMR numbering scheme.



DNA interaction assay, antibacterial, antifungal, antileishmanial, cytotoxicity, and protein kinase inhibition studies were performed using the reported earlier procedures [30–32].

All calculations were performed by the MOPAC 2007 [33] program in gas phase using PM3 method [34]. Selected parts of the complexes not containing the metal ion were pre-optimized using molecular mechanics method. Several cycles of energy minimization were carried out for all the complexes. Geometry was optimized using Eigen Vector. All Root

Table 1. Physical data for organotin(IV) complexes with 4-oxo-4-(3-(trifluoromethyl)phenylamino)butanoic acid

Comp. no.	Formula	M_w	Yield, %	mp, °C	Found, %			Calculated, %		
					C	H	N	C	H	N
HL	$C_{11}H_{10}F_3NO_3$	261.06	85	99–101	50.54	3.82	5.39	50.58	3.86	5.36
1	$C_{23}H_{36}F_3NO_3Sn$	551.17	72	111–113	50.24	6.56	2.51	50.20	6.59	2.55
2	$C_{29}H_{24}F_3NO_3Sn$	611.07	78	108–110	57.05	3.94	2.34	57.08	3.96	2.30
3	$C_{24}H_{24}F_6N_2O_6Sn$	670.06	80	134–136	43.12	3.66	4.23	43.08	3.62	4.19
4	$C_{30}H_{36}F_6N_2O_6Sn$	754.15	65	98–100	47.80	4.79	3.76	47.83	4.82	3.72
5	$C_{34}H_{28}F_6N_2O_6Sn$	794.09	75	101–103	51.52	3.53	3.57	51.48	3.56	3.53

Table 2. IR spectral data for organotin complexes with 4-oxo-4-[3-(trifluoromethyl)phenylamino]butanoic acid

Comp. no.	IR bands, cm^{-1}							
	ν(OH)	ν(NH)	ν(C=O)	$ν(COO)_{as}$	$ν(COO)_s$	Δν	ν(Sn–C)	ν(Sn–O)
HL	3200	3352	1727	1573	1325	248	–	–
NaL	–	3345	1724	1559	1330	229	–	–
1	–	3352	1722	1558	1378	180	558	486
2	–	3355	1690	1548	1352	196	284	452
3	–	3353	1720	1557	1381	176	518	472
4	–	3351	1732	1551	1360	191	519	429
5	–	3357	1721	1559	1360	199	271	445

Mean Square Gradients for molecules were lower than one. Self-Consistent Field was achieved in each case. Absence of imaginary frequencies were checked consistently.

Deposition of films by aerosol-assisted chemical vapor deposition (AACVD). Organotin(IV) complex (0.30 g) was dissolved in toluene (20 mL) in a two-neck 100 mL round-bottom flask. The solution was purged with Ar gas for transport of the aerosol. By a reinforced tubing, flask was connected to the reactor tube. In a Carbolite furnace, the reactor tube was placed having three borosilicate glass substrates (~1 cm × 3 cm and 1 mm thick). The precursor solution in a round-bottom flask was kept in a water bath above the piezoelectric modulator of a PIFCO ultrasonic humidifier (Model no. 1077). The generated aerosol droplets of the precursor were transferred into the reactor tube by the carrier gas. The precursor vapor reached the heated substrate surface where film deposition took place via thermally induced reactions.

RESULTS AND DISCUSSION

The synthesized organotin(IV) complexes were solid compounds soluble in common organic solvents (Table 1).

FT-IR spectra. In FT-IR spectra of organotin(IV) complexes (Table 2) the characteristic band of the new Sn–O bond at 429–486 cm^{-1} was recorded and it indicated deprotonation of the ligand upon coordination with di- and triorganotin(IV) moieties via oxygen atoms of the COO^- group [35]. The band in the range of 518–558 cm^{-1} indicated the presence of Sn–C bonds in the complexes **1**, **3**, and **4**. In the spectra of tri- and diphenyltin(IV) complexes **2** and **5** it appeared at 271 and 284 cm^{-1}, respectively. The value of Δν for $ν_{as}(COO^-)$ and $ν_{sym}(COO^-)$ above 250 cm^{-1} displayed a monodentate character whereas below 250 cm^{-1} showed bidentate binding mode of COO^- moiety through Sn atom [36]. The value of Δν lower than 150 cm^{-1} revealed a chelate structure [37]. In the present study,

Table 3. ^{1}H NMR data[a,b] for organotin complexes with 4-oxo-4-[3-(trifluoromethyl)phenylamino]butanoic acid

Comp. no.	HL	NaL	**1**	**2**	**3**	**4**	**5**
H^3	8.11 t (3.9)	8.10 t (3.9)	8.11 m	8.15 m	7.84 m	8.10 m	8.11 m
H^5	7.74 d (8.4)	7.73 d (8.3)	7.74 d (8.3)	7.77 m	7.63 m	7.74 d (7.8)	7.73 d (7.7)
H^6	7.53 m	7.49 m	7.53 m	7.53 m	7.39 m	7.53 m	7.53 m
H^7	7.36 d (7.7)	7.32 d (7.7)	7.35 d (7.7)	7.37 m	7.29 m	7.36 d (7.5)	7.36 m
NH	10.31 br.s	11.37 br.s	10.37 br.s	10.24 br.s	8.60 br.s	10.37 br.s	10.38 br.s
H^9	2.54 m	2.32 m	2.52 m	2.43 m	2.64 m	2.56 m	2.62 m
H^{10}	2.60 m	2.46 m	2.56 m	2.47 m	2.73 m	2.62 m	2.66 m
H^{11}	12.16 br.s	–	–	–	–	–	–
α	–	–	1.57 m	7.73 m	1.19 [74, 71]	1.65 m	7.91 m
β	–	–	1.30 m (7.4)	7.31 m	–	1.56 m	7.75 m
γ	–	–	1.11 m	7.29 m	–	1.32 q (7.4)	7.29 m
δ	–	–	0.83 t (7.2)	–	–	0.87 t (7.2)	–

[a] For numbering and α, β, γ, δ see Scheme 2.
[b] Chemical shifts (δ) in ppm. $^{n}J[^{117/119}Sn, ^{1}H]$, $^{3}J(^{1}H, ^{1}H)$ in Hz are listed in square brackets and paraenthesis, respectively.

the complexes **1–5** exhibited Δν value in the range 199–176 cm^{-1}, which revealed bidentate binding mode of COO^{-} moiety through Sn atom.

NMR spectra. According to ^{1}H NMR spectra of the ligand HL and the complexes **1–5** (Table 3) nitrogen did not participate in coordination with tin as indicated by no shift of the NH signal of the peptide linkage. The $^{2}J[^{119/117}Sn,^{1}H]$ coupling constant value of 74/71 Hz for complex **3** was expected for six-coordinate Sn being consistent with CSnC angle of 121° in solution [38]. In complexes **1** and **4** the terminal methyl protons of butyl groups attached to tin atom were recorded as a clear triplet at 0.83–0.87 ppm and a complex multiplicity for other protons made the coupling constant value $^{2}J[^{119/117}Sn, ^{1}H]$ impossible to be observed. A complex arrangement in the range of 7.29–7.91 ppm attributed to phenyl correlated well with bidentate bonding of the ligand [39–41].

In Tables 4 and 5 the chemical shifts of ^{13}C, tin–carbon coupling constants and C–Sn–C angles (deg), respectively for complexes **1–5** are listed. Values of $^{1}J[^{119}Sn,^{13}C]$ and C–Sn–C angles (Table 5) allowed to clarify the coordination of Sn(IV) atom in the solution and were calculated with the Lockhart's equation [42]. Spectra of complexes **2–5** exhibited $^{1}J[^{119}Sn,^{13}C]$, 754 Hz (123°), 572 Hz (127°), 809 Hz (156°), and 760 Hz (123°), respectively, that matched well penta and hexa coordinated Sn(IV) in solutions [43, 44]. The differences between five and six coordinated complexes **3–5** could be due to their fluxional behavior [45]. The coupling constant $^{1}J[^{119}Sn,^{13}C]$ = 462 Hz and C–Sn–C angle (121°) for the complex **1**, corresponded to four coordinated Sn(IV) in solution that was in accord with literature [46].

Thermogravimetric analysis. The thermogravimetric (TG) studies defined thermal behavior, degradation and the percentage purity of the complexes **1–5**. Analysis was performed in the range of 25–1000°C, with a heating frequency of 20°C/min and 60 s gap at 100°C in N_2 (50 mL/min supply). The theoretically calculated weight loss was compared with experimental results. The minor variations in the values showed the errors, that were within the acceptable range of ±3% [47]. Summary of decomposed fragments against various temperature ranges is given in Table 6. The organotin(IV) complexes exhibited different patterns with respect to stability and bulkiness of ligands. The first step of decomposition for the complex **2** corresponded to loss of the ligand moiety and one phenyl group attached to tin in the range of 158–281°C and the second step of degradation was refered to loss of two phenyl groups along with formation of SnO_2 as the final residue in the temperature range of 282–400°C. Complexes **1**, **4**, and **5** displayed one step degradation within temperature

Table 4. ^{13}C NMR data[a,b] for organotin(IV) complexes with 4-oxo-4-[3-(trifluoromethyl)phenylamino]butanoic acid

Comp. no.	HL	NaL	**1**	**2**	**3**	**4**	**5**
C^1	115.3 [12]	115.2 [12]	115.3 [12]	115.3 [12]	116.7 [12]	115.32 [12]	115.3 [12]
C^2	119.7 [12]	119.2 [12]	119.6 [12]	119.5 [12]	120.7 [12]	119.7 [12]	119.7 [12]
C^3	122.8	122.7	122.7	122.7	123.6	122.8	122.8
C^4	140.4	140.9	140.4	143.6	138.3	140.3	140.3
C^5	129.6	129.5	129.6	129.6	130.7	129.6	129.2
C^6	130.0	130.0	130.0	130.0	132.3	130.0	129.6
C^7	126.3	126.4	126.3	126.4	125.6	126.3	126.3
C^8	171.2	172.9	171.2	171.7	171.0	170.9	170.9
C^9	29.0	33.0	29.0	31.2	29.0	28.7	28.7
C^{10}	31.5	34.2	31.4	32.8	31.5	31.3	31.3
C^{11}	174.2	176.2	174.2	176.0	174.0	173.2	173.2
α	–	–	21.4 [458, 437]	140.6 [754, 716]	9.1 [572, 546]	38.3 [809, 767]	139.0 [760, 730]
β	–	–	28.2 [28]	128.5 [69]	–	27.8 [45]	128.0 [80]
γ	–	–	26.7 [74,70]	136.6 [46]	–	26.0 [159,153]	135.1
δ	–	–	14.0	129.1 [10]	–	14.2	127.7

[a] For numbering and α, β, γ, δ see Scheme 2.
[b] Chemical shifts (δ) in ppm. $^nJ[^{119/117}Sn, ^{13}C]$, $^nJ[^{119}Sn, ^{13}C]$ in Hz are listed in square brackets, respectively.

range of 108–279, 129–296, and 88–291°C, respectively. Complex **3** demonstrated a two step degradation with the first step related to loss of one methyl and CF_3 groups within 118–186°C, and second step within 204–320°C reflected loss of the ligand moiety with formation of SnO. The first order reaction was established for thermal degradation of the tested compounds. The apparent activation enthalpy, Gibb's free energy and entropy values indicated spontaneous processes for all the complexes (Table 7).

Atomic force microscopic analysis (AFM). Thin films of tin sulfides were deposited on glass substrates using toluene solution of complex **2** by chemical vapour deposition method (CVD). The complex **2** was chosen as the precursor for CVD trials because of its superior volatility. The film deposition temperature was varied over the range of 400−530°C in the atmosphere of Ar. Substrate temperature below 400°C was not high enough to initiate deposition. The complex **2** deposited as a dense, brownish yellow adherent film at 400°C, whereas at 450 and 500°C, dark black films were deposited. Formation of SnO films in the CVD experiment indicated the facile reduction of metal center, Sn(IV) to Sn(II), in the atmosphere of Ar [48, 49]. Morphology of films deposited from toluene solution of precursor **2** was characterized by atomic force microscopy. AFM scans demonstrated grains as highly symmetric and triangular in shape. Two types of grains were observed with the measured width of 370 nm and length 875 nm for one type and width of 560 nm and length 980 nm for another type. The root

Table 5. C–Sn–C angles based on NMR data for organotin(IV) derivatives

Comp. no.	$^1J[^{119}Sn, ^{13}C]$, Hz	$^2J[^{119}Sn, ^1H]$, Hz	Angles, deg	
			^1J	^2J
1	462	–	121	–
2	754	–	123	–
3	572	74	127	121
4	809	–	156	–
5	760	–	123	–

Table 6. Proposed degradation pattern for organotin(IV) carboxylates

Comp. no.	Formula	Temperature, °C	Fragment evolved	Fragment residue	Residue, %	
					found	calculated
1	$C_{23}H_{36}F_3NO_3Sn$	108–279	$C_{20}H_{31}F_3NO_3Sn$	C_3H_5	7.98	7.16
2	$C_{29}H_{24}F_3NO_3Sn$	158–281	$C_{16}H_{16}F_3NO$			
		282–400	$C_{13}H_{12}$	SnO_2	21.30	22.57
3	$C_{24}H_{24}F_6N_2O_6Sn$	118–186	$C_4H_5F_3$			
		204–320	$C_{20}H_{25}F_3N_2O_5$	SnO	9.78	10.10
4	$C_{30}H_{36}F_6N_2O_6Sn$	129–296	$C_{29}H_{33}F_6N_2O_6Sn$	CH_3	2.15	1.98
5	$C_{34}H_{28}F_6N_2O_6Sn$	88–290	$C_{33}H_{28}F_6N_2O_2$	$CSnO_4$	25.20	24.46

Table 7. Kinetic parameters for organotin(IV) carboxylates

Comp. no.	Formula	Temperature, °C	Order *n*	*E**, kJ/mol	Δ*H**, kJ/mol	Δ*S** J mol^{-1} K^{-1}
1	$C_{23}H_{36}F_3NO_3Sn$	108–279	0.9	16.25	14.3	–128.66
2	$C_{29}H_{24}F_3NO_3Sn$	158–281	1.21	17.21	14.8	–147.67
		282–400				
3	$C_{24}H_{24}F_6N_2O_6Sn$	118–186	1.28	18.46	16.38	–120.77
		204–320				
4	$C_{30}H_{36}F_6N_2O_6Sn$	129–296	1.16	17.25	15.13	–136.62
5	$C_{34}H_{28}F_6N_2O_6Sn$	88–290	1.15	15.55	13.64	–136.68

Table 8. Selected geometric parameters of the optimized structures of complexes **3** and **5**

Comp. no.	C–Sn–C	O–Sn–O	C–Sn–O	
Selected bond angles, deg				
HL	–	–	–	
3	114.9	97.4	98.4, 108.6, 112.9, 121.0	
5	112.7	98.0	111.3, 123.2, 98.8, 109.2	
Selected bond lengths, Å				
	C–Sn	O–Sn	C–O	C–F
HL	–	–	1.35, 1.22, 1.22	1.35 (all)
3	2.08, 2.08	2.00, 2.02	1.32, 1.32, 1.24, 1.24	1.35 (all)
5	2.05, 2.05	2.00, 2.00	1.32, 1.32, 1.24, 1.24	1.35 (all)

mean square (RMS) roughness was observed in 300–750 nm range, which indicated that the desired material could be efficient for both homogenous and heterogenous catalysis.

Theoretical study. Geometry of organotin(IV) complexes **3** and **5** were optimized by means of the PM3 method to support the IR and NMR data. The optimized structures are presented in Fig. 1. The ligand

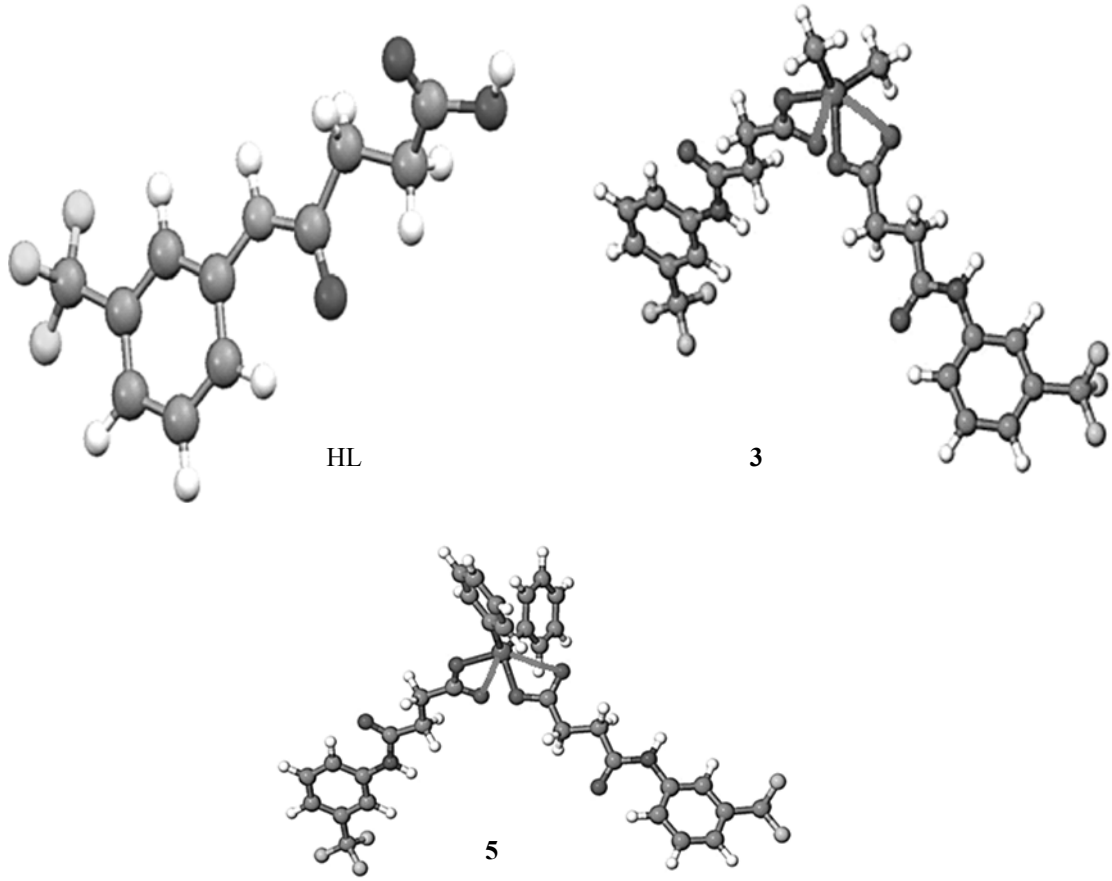


Fig. 1. Optimized structures of the ligand (HL) and complexes **3** and **5**.

was coordinated via oxygen atoms and acted as bidentate in case of complexes **3** and **5** showing distorted octahedral geometry (Table 8). The Sn–O distance was in the range of 2.0–2.02 Å and Sn–C in the range of 2.05–2.08 Å as well as the other bond distances and angles were in good agreement with the values reported for Sn-complexes using X-ray diffraction [50–52]. Computed negative heat of formation, enthalpy, entropy, and heat capacity for the compounds **3** and **5** indicated that molecules were thermodynamically more stable than the ligand (Table 9). In case of the free ligand, LUMO orbitals were distributed on the phenyl group, while the HOMO orbitals were distributed over the phenyl group and the O–NH atoms [53]. For complexes **3** and **5** the LUMO were distributed primarily on Sn and the atoms ligating to Sn, while the HOMO orbitals were distributed on the phenyl group and the O–NH atoms of one of the carboxylate ligands. Position of HOMO orbitals was the same as that of the ligand. The calculated HOMO and LUMO energies, dipole moments and polarizability of the complexes are summarized in Table 10. In the present study, the determined band gaps (Table 10) of complexes **3** and **5** were 8.289 and 8.166 eV, respectively, indicating the complexes to be stable [54]. LUMO of the complexes is concentrated around the tin(IV) center. The observed values of η and S (Table 10) proposed that the complexes **3** and **5** resisted the charge transfer and therefore had low polarizability. Dipole moments of complexes **3** and **5**

Table 9. Computed thermodynamic parameters for compounds **3** and **5**

Parameters at 298 K	HL	**3**	**5**
Heat of formation, kcal/mol	–269.824	–545.110	-472.843
Enthalpy, kcal/mol	8195.46	17394.52	19546.11
Entropy, kcal/mol	109.16	172.04	184.10
Heat capacity (Cp), Cal mol^{-1} K^{-1}	52.04	115.45	134.69

Table 10. Computed molecular descriptors for compounds **3** and **5**

Parameter	HL	**3**	**5**
HOMO energy, eV	–9.425	–9.250	–9.240
LUMO energy, eV	–0.558	–0.958	–1.074
HOMO–LUMO, eV	8.866	8.289	8.166
Global hardness η, eV	4.433	4.144	4.083
Global softness *S*, eV^{-1}	0.112	0.120	0.122
Chemical potential μ, eV	–4.991	–5.103	–5.157
Electrophilicity ω	2.810	3.141	3.257
Dipole moment D	2.292	4.125	4.304

were determined to be 4.125 and 4.304 Debye, respectively [55].

DNA binding studies. Absorption spectra of the ligand HL, complexes **2**, **3**, and **5** were recorded with and without different concentrations of salmon sperm DNA (SS-DNA) for indicating their interaction with DNA [56–58] (Fig. 2). Upon addition of DNA to complex **2** significant hypochromism with the red shift of 5 nm was observed, while in case of complex **5** hypsochromic shift of the spectral band with significant hypochromism was recorded [59]. The observed peculiar hypochromism was attributed to intercalation of the complexes into the DNA base pairs [60]. Hypochromism and bathochromic shift were due to the combination of π electrons of the compound with π electrons of DNA bases. Therefore, the energy level of the π–π* electron transition decreased causing the red shift [61], while hypsochromic shift with hypochromism could be attributed to the strong hydrogen bonding of the ligand chromophore with the base pairs of the DNA due to the presence of electronegative nitrogen atom on the coordinated ligand. Stabilization of non-bonding orbital took place due to the hydrogen bonding with the DNA base pairs thus increasing the *n*–π* transition energy which resulted in the blue shift. To evaluate binding ability of the complexes **2**, **3**, and **5** with DNA, the intrinsic binding constant was determined in accordance with Benesi-Hildebrand equation [62]:

$$\frac{A_0}{A - A_0} = \frac{\varepsilon_G}{\varepsilon_{H-G} - \varepsilon_0} + \frac{\varepsilon_G}{\varepsilon_{H-G} - \varepsilon_G}\,\frac{1}{K[\mathrm{DNA}]},$$

Here K is the binding constant, A_0 and A are the absorbances of the drug and its complex with DNA, and ε_G and ε_{H-G} are the absorption coefficients of the drug and drug-DNA complex, respectively.

The binding constants were obtained from the intercept to slope ratios of $A_0/(A - A_0)$ vs 1/[DNA] plots. The binding constants were determined to be 3.8×10^4, 1.7×10^6, 3.8×10^5, and 2.3×10^5 M^{-1} for HL, **2**, **3**, and **5**, respectively, indicating that among the tested complexes, the binding strength of the complex **2** with DNA was the highest. The Gibb's free energy (G) of the ligand HL and organotin(IV) carboxylates **2**, **3**, and **5** were determined by using the equation: $\Delta G = -RT\ln K$.

The Gibb's free energies were found to be –16.24, –20.04, –20.84, and –18.04 kJ/mol for (HL), **2**, **3**, and **5**, respectively, indicating interactions of the compounds with DNA to be spontaneous.

Biological activity. Biological activity tests of the complexes were carried out against three gram-positive [*Bacillus subtillis* (ATCC 6633), *Staphylococcus aureus* (ATCC 6538), *Micrococcus luteus* (ATCC 53598)] and two gram-negative bacteria [*Escherichia coli*, (ATCC 15224), *Bordetella bronchiseptica* (ATCC 4617)] by the agar diffusion method [63] (Table 11). Cefixime was used as the positive control. Complex **2** exhibited the highest activity against *M. luteus*, followed by *E. coli* and *B. subtillis*. Complex **1** was active against all tested bacteria except *B. bronchiseptica,* while the highest activity of the compound was against *M. luteus*. Complex **3** showed low activity against all tested strains. Complexes **4** and **5** were determined to be more active against gram-positive bacteria than gram-negative.

Antifungal activity (Table 12) was recorded against five fungal strains, *Fusirum solani, Aspergillus niger, Mucor specie, Helminthosporium solani* and *Aspergillus flavus* using the agar dilution method [63]. Terbinafine was used as the standard drug. Complexes **1** and **2** showed 100 % growth inhibition against all fungal strains. Complex **5** demonstrated significant activity against all tested strains, while compounds **3** and **4** presented low activity which was in accordance with the earlier studies that had determined triorganotin compounds to be biocidally more active than their diorganotin analogues [9, 64].

Brine Shrimps (Artemia salina), a tiny crustacean, have been used for the determination of toxicity of the organotin carboxylates (Table 13). The highest toxicity was demonstrated by complexes **1**, **2**, and **4** with LD_{50} value <10 μg/mL, while the lowest toxicity was

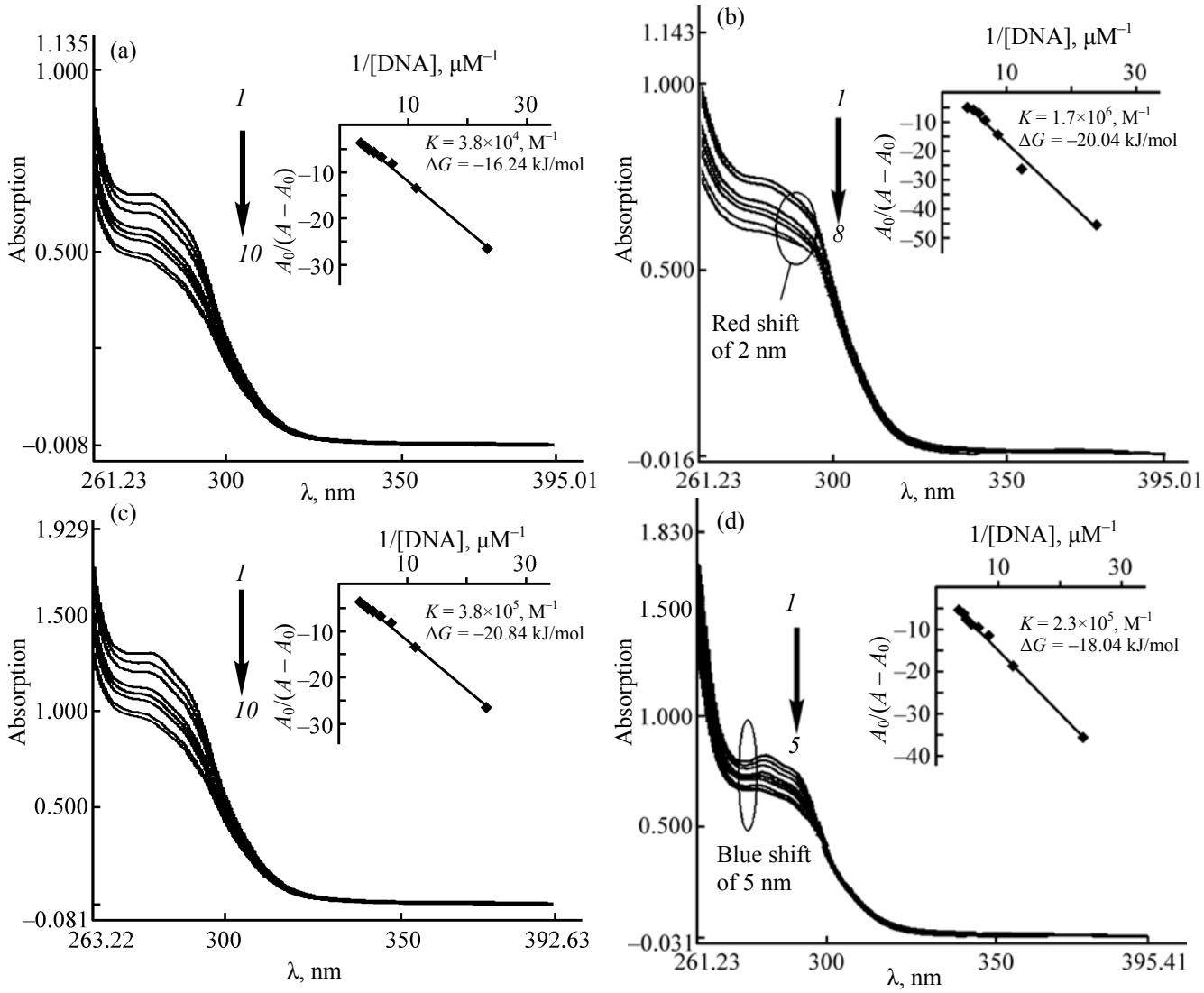


Fig. 2. UV-Vis spectroscopic response of 0.8 mmol/L (a) HL, (b) Ph_3SnL (**2**), (c) Me_2SnL_2 (**3**), and (d) Ph_2SnL_2(**5**) in the absence and presence of (*1*) 20, (*2*) 40, (*3*) 62, (*4*) 83, (*5*) 104, (*6*) 125, (*7*) 150, (*8*) 162 , (*9*) 170, and (*10*) 192 μM DNA.

observed for HL. The results showed that toxicity of organotin compounds depended upon the nature of the organic group [65, 66]. The highest toxicity was detrmined for the triorganotin complexes. It can be explained on the basis of triorganotin-ligand behavior, which showed that the function of an ionic group was to transport the active organic moiety to the site of action. The ligand was displaced from tin, when organic moiety was attached to the active sites of a biological system, otherwise the ligand could remain bonded to tin until it reached its receptor sites. Under such condition, an ionic ligand could influence the ease with which R_3SnL was transported [67].

Antiprotozoal activity of the complexes was tested against pathogenic Leishmania (Table 14). All the studied complexes showed high anti-leishminial activity confirming the important role of tin. The activity decreased in the order: Bu_3SnL (**1**) > Ph_3SnL (**2**) > Bu_2SnL_2 (**4**), Ph_2SnL_2 (**5**) > Me_2SnL_2 (**1**). According to literature [68], the antileishmanial activity depends on various factors: geometry, planarity, lipophilicity, and molecular weight. High activity of Bu_3SnL (**1**) could be explained by four-coordinated geometry around tin atom which demonstrated higher activity than five and six-coordinated complexes. Activity of complex **2** was due to the planar phenyl groups that could penetrate easily into the lipid bilayer.

According to the data of protein kinase inhibition study (Table 14), all the complexes developed the

Table 11. Antibacterial data for HL and its organotin(IV) complexes

Comp. no.	Zone of inhibition, mm				
	B.subtillis	*M.luteus*	*S.aureus*	*E.coli*	*B.bronchiseptica*
HL	–	11	–	9	–
1	21	29	27	22	17
2	21	28	18	25	13
3	10	19	–	14	14
4	14	23	18	11	16
5	18	22	–	17	10
Cefixime	29	32	35	37	30

Table 12. Antifungal data for **HL** and its organotin(IV) complexes

Comp. no.	Growth inhibition, %				
	Fusarium solani	*Aspergillus nigar*	*Mucor species*	*Helminthosporium solani*	*Aspergillus flavus*
HL	5	0	15	15	0
1	100	100	100	100	100
2	95	95	100	100	100
3	0	10	20	0	30
4	0	45	15	10	100
5	60	60	80	75	90
Turbinafine	100	100	100	100	100
DMSO	0	0	0	0	0

zones of inhibition ranging from 4.0 to 11.0 mm vs standard's value of 18 mm.

According to the presented above data, biological activity of complexes **1–5** was the function of a substituent on the ligand, stability of the Sn–O bond, availability of coordination positions at tin, and nature of organic groups attached to tin [69].

The lower activity of diorganotin complexes **1–3** could be due to stronger interactions of the ligand with tin and formation of the most stable bond upon complexation. High activity of triphenyltin(IV) complex **2** was probably due to the lower number of coordination sites/bonds, that enabled easier formation of Ph_3Sn^{2+}(IV) moiety as a part of inhibition.

Table 13. Cytotoxicity data for **HL** and its organotin(IV) complexes

Comp. no.	Number of shrimps killed out of 20 per dilution, μg/mL			
	100	50	10	LD_{50}
HL	13	9	2	59.5
1	20	20	20	<10
2	20	20	20	<10
3	8	4	0	52.8
4	20	20	20	<10
5	20	8	4	50.6

Table 14. Antileishminial data for **HL** and its organotin(IV) derivatives

Comp. no.	LC_{50}, μg/mL
HL	2.0480
1	0.0011
2	0.0012
3	0.7740
4	0.0910
5	0.8320
Amphotericin B	0.0480

CONCLUSIONS

According to FT-IR data, the ligand acted as bidentate in complexes **1–5** that was also confirmed by the semi-empirical study. NMR data revealed four and six coordinated geometry of the compounds in solutions. The synthesized compounds binded to DNA via intercalative mode of interaction as revealed by UV-Vis studies. The negative values of Gibb's free energy change indicated spontaneous character of the interactions. HOMO-LUMO calculations showed that all complexes were thermodynamically stable. Biological studies revealed substantial activity of the complexes.

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