ISSN 1070-3632, Russian Journal of General Chemistry, 2016, Vol. 86, No. 12, pp. 2768–2776. © Pleiades Publishing, Ltd., 2016.

Organotin(IV) *O*-Butyl Carbonodithioates: Synthesis, Characterization, *in vitro* Bioactivities, and Interaction with SS-DNA[1]

F. Javed[a], S. Ali[a]*, S. Shahzadi[a], M. N. Tahir[b], S. Tabassum[c], and N. Khalid[d]**

[a] *Department of Chemistry, Quaid-i-Azam University, Islamabad, 45320 Pakistan*
**e-mail: drsa54@hotmail.com; **sairashahzadi@hotmail.com*

[b] *Department of Physics, University of Sargodha, Sargodha, Pakistan*

[c] *Department of Biotechnology, Quaid-i-Azam University, Islamabad, 45320 Pakistan*

[d] *Chemistry Division, Pakistan Institute of Nuclear Science and Technology, Nilore, Islamabad, Pakistan*

Received February 28, 2016

Abstract—Organotin(IV) *O*-butyl carbonodithioates [Me_2SnL_2], [Bu_2SnL_2], [Ph_2SnL_2], [Bu_3SnL], and [Ph_3SnL], where L = $C_4H_9OCS_2^-$, have been successfully synthesized and characterized by FT-IR, ^1H and ^{13}C NMR, and single crystal X-ray analysis. The ligand coordinates to the tin atom via the carbonodithioate group. According to the X-ray diffraction data, the tin atom in [Me_2SnL_2] has distorted tetrahedral geometry. The synthesized compounds were screened in vitro for antibacterial, antifungal, antileishmanial, cytotoxic, and protein kinase inhibitory activities. The complexes [Bu_3SnL] and [Ph_3SnL] exhibited the highest anti-leishmanial activity that exceeded the activity of the reference drug amphotericin B, probably by blocking the function of parasitic mitochondria due to which it restricts further growth of the organisms. The ligand and the complexes have been shown to bind to DNA via intercalative interactions resulting in hypochromic effect with a minor red shift as confirmed by UV-Vis spectroscopic studies.

Keywords: organotin(IV) complexes, IR, NMR, single crystal X-ray analysis, DNA interaction, antibacterial, antifungal, antileishmanial, cytotoxicity, protein kinase inhibition

DOI: 10.1134/S1070363216120380

INTRODUCTION

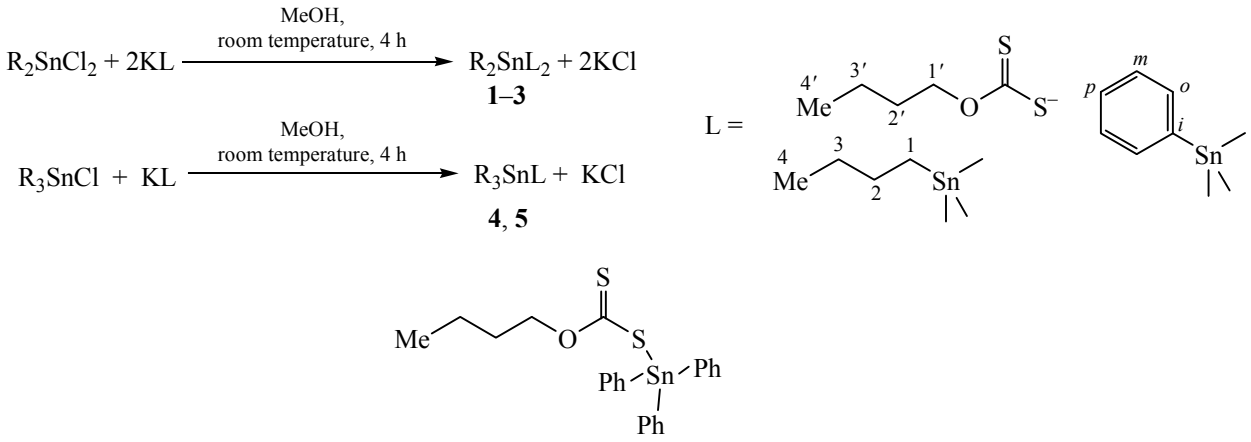
Sulfur donor ligands such as dithiophosphates, xanthates, and dithiocarboxylates have been reported to be more potent than biological ligands (peptides or amino acids) in the initiation of active sites of some metalloenzymes [1–3]. Apart from biological activity (fungicidal, bactericidal, insecticidal, and antitumor) [4, 5], organotin(IV) dithiocarboxylates have been widely studied for their structural diversity related to Sn–S bonding [6–8]. Menezes et al. [9] recently reported a series of organotin dithiocarboxylates whose antifungal activity was shown to be determined by inhibition of ergosterol biosynthesis. Furthermore, all the organotin compounds studied were more active than the uncoordinated dithiocarboxylate ligand. The coordination mode depends on the structure of the organic ligand which can exhibit mono- or bidentate behavior. Dithiocarboxylate ligands are capable of being involved in secondary intermolecular interactions that can give rise to dimeric, trimeric, and supramolecular structures [10]. In continuation of our studies related to organotin(IV) dithiocarboxylate complexes [11], we have synthesized organotin(IV) *O*-butyl carbonodithioate complexes which were characterized by elemental analyses, FT-IR, ^1H and ^{13}C NMR, and single crystal X-ray analysis. The synthesized compounds were tested for antibacterial, antifungal, antileishmanial, cytotoxic, and protein kinase inhibitory activities. DNA binding studies of the synthesized compounds were also performed using UV-Vis spectrophotometric technique.

EXPERIMENTAL

All organotin(IV) halides, butanol, potassium hydroxide, carbon disulfide, and other reagents were obtained from Aldrich (USA) and used without further purification. Deoxyribonucleic acid sodium salt (Acros) was used as received. All the solvents were

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

Scheme 1.



1, R = Me; **2**, **4**, R = Bu; **3**, **5**, R = Ph.

purchased from Merck (Germany) and were dried before use according to literature procedures [12]. The melting points were measured with a Bio-Cote Model SMP10 melting point apparatus and are uncorrected. The FT-IR spectra were recorded in the range 4000–250 cm^{-1} with a Thermo Scientific Nicolet 6700 FTIR spectrometer. The ^1H and ^{13}C NMR spectra were obtained with a Bruker Avance spectrometer at 300 and 75 MHz, respectively, using DMSO-d_6 as solvent. The electronic absorption spectra were measured at 25 ± 1°C on a Shimadzu 1601 double beam UV-visible spectrometer. The elemental analyses (C, H, S) were obtained using a LECO CHNS-932 analyzer.

The X-ray diffraction data for a single crystal of **1** were collected on a Bruker SMART APEX CCD diffractometer equipped with a 4 K CCD detector set at a distance of 60.0 mm from the crystal. The crystal was cooled to 100 ± 1 K using a Bruker KRYOFLEX low temperature device, and reflection intensities were measured with graphite-monochromatized MoK_α radiation from a Siemens sealed ceramic diffraction tube (generator settings 50 kV/40 mA). The structure was solved by the Patterson method, and extension of the model was accomplished by the direct method using DIRDIF or SIR2004. The final refinement on F^2 was made by the full-matrix least-squares technique using SHELXL-97, a modified PLUTO version of (preparation of illustrations), and PLATON package.

Potassium *O*-butyl carbonodithioate was prepared by continuous stirring of butanol (1 mmol) with a mixture of potassium hydroxide (1 mmol) and carbon disulfide (1 mmol) for 4 h at room temperature. The precipitate was filtered off and dried in air. Yield 90%, mp 210–212°C [11]. IR spectrum, ν, cm^{-1}: 961 (C–O), 1459 (CSS, asym.), 1102 (CSS, sym.). ^1H NMR spectrum, δ, ppm: 0.97 t (3H, 4′-H, $^3J_{HH}$ = 7.4 Hz; 1.45 m (2H, 3′-H), 1.73 q (2H, 2′-H, $^3J_{HH}$ = 7.4 Hz), 4.40 t (2H, 1′-H, $^3J_{HH}$ = 6.6 Hz). ^{13}C NMR spectrum, δ_C, ppm: 12.8 ($C^{4'}$), 18.9 ($C^{3'}$), 30.7 ($C^{2'}$), 72.3 ($C^{1'}$), 232.4 (C=S). Found, %: C 31.85; H 4.79; S 34.03. $C_5H_9KOS_2$. Calculated, %: C 31.88; H 4.82; S 34.09.

General procedure for the synthesis of organotin (IV) *O*-butyl carbonodithioates. Potassium *O*-butyl carbonodithioate (2 mmol) was dissolved in 20 mL of methanol in a 100-mL round bottom two-necked flask with continuous stirring at room temperature. Organotin(IV) chloride R_2SnCl_2 or R_3SnCl (1 or 2 mmol, respectively) was added in portions, and the mixture was stirred for 4 h at room temperature. The solvent was slowly evaporated at room temperature, and the solid residue was dried in air and recrystallized from acetone–diethyl ether (1 : 1). The general reactions are shown in Scheme 1.

Dimethylstannanediyl bis(*O*-butyl carbonodithioate) (1). Yield: 85%, mp 107–108°C. IR spectrum, ν, cm^{-1}: 958 (C–O), 1254 (CSS, asym.), 1001 (CSS, sym.), 383 (Sn–S), 548 (Sn–C). ^1H NMR spectrum, δ, ppm: 0.98 t (6H, 4′-H, $^3J_{HH}$ = 7.4 Hz), 1.45 m (4H, 3′-H), 1.80 q (4H, 2′-H, $^3J_{HH}$ = 7.4 Hz), 4.46 t (4H, 1′-H, $^3J_{HH}$ = 6.6 Hz), 1.48 s (6H, $SnCH_3$, $^2J_{SnH}$ = 79–76 Hz). ^{13}C NMR spectrum, δ_C, ppm: 10.4 ($C^{4'}$), 19.1 ($C^{3'}$), 30.2 ($C^{2'}$), 76.2 ($C^{1'}$), 222.0 (C=S), 10.4 ($SnCH_3$, $^1J_{SnC}$ = 597–569 Hz). Found, %: C 32.19; H 5.38; S 25.65. $C_{12}H_{24}O_2S_4Sn$. Calculated, %: C 32.22; H 5.41; S 28.68.

Dibutylstannanediyl bis(*O*-butyl carbonodithioate) (2). Yield 82%, oily material. IR spectrum, ν,

cm^{-1}: 955 (C–O), 1239 (CSS, asym.), 1082 (CSS, sym.), 345 (Sn–S), 551 (Sn–C). ^{1}H NMR spectrum, δ, ppm: 0.95 m (6H, 4′-H), 1.43 m (4H, 3′-H), 1.74 m (4H, 2′-H), 4.46 t (4H, 1′-H, $^3J_{HH}$ = 6.6 Hz), 1.88 m (4H, 1-H), 1.49 m (4H, 2-H), 1.46 m (4H, 3-H), 0.92 m (6H, 4-H). ^{13}C NMR spectrum, δ_C, ppm: 13.7 ($C^{4'}$), 19.1 ($C^{3'}$), 30.3 ($C^{2'}$), 76.1 ($C^{1'}$), 223.1 (C=S); 30.5 (C^1, $^1J_{SnC}$ = 540–516 Hz), 28.8 (C^2, $^2J_{SnC}$ = 40 Hz), 26.4 (C^3, $^3J_{SnC}$ = 119–115 Hz), 13.7 (C^4). Found, %: C 40.65; H 6.80; S 24.10. $C_{18}H_{36}O_2S_4Sn$. Calculated, %: C 40.68; H 6.83; S 24.13.

Diphenylstannanediyl bis(*O*-butyl carbonodithioate) (3). Yield: 79%, mp 82–83°C. IR spectrum, ν, cm^{-1}: 938 (C–O), 1254 (CSS, asym.), 1038 (CSS, sym.), 372 (Sn–S), 284 (Sn–C). ^{1}H NMR spectrum, δ, ppm: 0.88 t 6H, (4′-H, $^3J_{HH}$ = 7.4 Hz), 1.30 m (4H, 3′-H, $^3J_{HH}$ = 7.4 Hz), 1.60 m (4H, 2′-H), 4.29 t (4H, 1′-H, $^3J_{HH}$ = 6.6 Hz), 8.0 m (4H, *o*-H), 7.50 m (4H, *m*-H), 7.47 m (2H, *p*-H). ^{13}C NMR spectrum, δ_C, ppm: 13.6 ($C^{4'}$), 18.9 ($C^{3'}$), 30.0 ($C^{2'}$), 76.6 ($C^{1'}$), 218.8 (C=S), 141.5 (C^i, $^1J_{SnC}$ = 830–796 Hz), 129.0 (C^o, $^2J_{SnC}$ = 88–84 Hz), 135.4 (C^m, $^3J_{SnC}$ = 64–57 Hz), 130.1 (C^p, $^4J_{SnC}$ = 18 Hz). Found, %: C 46.20; H 4.91; S 22.42. $C_{22}H_{28}O_2S_4Sn$. Calculated, %: C 46.24; H 4.94; S 22.45.

***O*-Butyl *S*-tributylstannyl carbonodithioate (4).** Yield 75%, oily material. IR spectrum, ν, cm^{-1}: 960 (C–O), 1249 (CSS, asym.), 1000 (CSS, sym), 365 (Sn–S), 541 (Sn–C). ^{1}H NMR spectrum, δ, ppm: 0.88 t (3H, 4′-H), 1.30 m (2H, 3′-H), 1.60 m (2H, 2′-H), 4.44 t (2H, 1′-H, $^3J_{HH}$ = 6.6 Hz), 1.73 m (6H, 1-H), 1.39 m (6H, 2-H, 1.33 m (6H, 3-H), 0.93 m (9H, 4-H). ^{13}C NMR spectrum, δ_C, ppm: 13.8 ($C^{4'}$), 15.6 ($C^{3'}$), 30.3 ($C^{2'}$), 74.9 ($C^{1'}$), 217.7 (C=S), 19.4 (C^1, $^1J_{SnC}$ = 335–314 Hz), 28.6 (C^2, $^2J_{SnC}$ = 21 Hz), 27.0 (C^3, $^3J_{SnC}$ = 65–63 Hz), 13.6 (C^4). Found, %: C 46.45; H 8.22; S 14.57. $C_{17}H_{36}OS_2Sn$. Calculated, %: C 46.48; H 8.26; S 14.60:

***O*-Butyl *S*-triphenylstannyl carbonodithioate (5).** Yield 92%, mp 66–68°C. IR spectrum, ν, cm^{-1}: 942 (C–O), 1228 (CSS, asym.), 1073 (CSS, sym.), 375 (Sn–S), 272 (Sn–C). ^{1}H NMR spectrum, δ, ppm: 0.98 t (3H, 4′-H, $^3J_{HH}$ = 7.4 Hz), 1.15 m (2H, 3′-H, $^3J_{HH}$ = 7.4 Hz), 1.41 m (2H, 2′-H), 4.31 t (2H, 1′-H, $^3J_{HH}$ = 6.6 Hz), 7.69 m (6H, *o*-H), 7.46 m (6H, *m*-H), 7.42 m (3H, *p*-H). ^{13}C NMR spectrum, δ_C, ppm: 13.6 ($C^{4'}$), 18.8 ($C^{3'}$), 29.8 ($C^{2'}$), 75.7 ($C^{1'}$), 214.8 (C=S), 138.1 (C^i, $^1J_{SnC}$ = 588–562 Hz), 129.0 (C^o, $^2J_{SnC}$ = 61–59 Hz), 136.6 (C^m, $^3J_{SnC}$ = 45–43 Hz), 130.0 (C^p, $^4J_{SnC}$ = 13 Hz). Found, %: C 55.30; H 4.81; S 12.80. $C_{23}H_{24}OS_2Sn$. Calculated, %: C 55.33; H 4.85; S 12.84.

Biological Screening. UV-Vis spectrophotometric study of DNA binding and tests for antibacterial, antifungal, and antileishmanial activities, cytotoxicity, and protein kinase inhibition were performed according to the procedures reported elsewhere [11, 13].

RESULTS AND DISCUSSION

FT-IR spectra. The binding mode of the dithiocarbonate ligand to tin(IV) was determined by comparing the IR spectrum of the ligand with the spectra of organotin(IV) complexes **1**–**5**. A new peak in the region 345–383 cm^{-1} indicated formation of Sn–S bond in **1**–**5**. The spectra of **1**, **2**, and **4** displayed a sharp Sn–C stretching band at 541–551 cm^{-1}, while di- and triphenyltin(IV) derivatives **3** and **5** showed a weak band at 284 and 272 cm^{-1}, respectively, due to $Sn–C_{arom}$ stretchings. These data are in close agreement with those reported previously for organotin(IV) derivatives [14]. The C–S stretching frequencies give valuable information regarding the mode of ligand coordination to the Sn atom and structure of the complexes. Complexes **1**–**5** gave strong peaks at 1204–1254 and 1000–1082 cm^{-1} due to asymmetric and symmetric stretching vibrations of the CS_2 group, respectively. The difference Δν between the asymmetric and symmetric stretching frequencies ranged from 155 to 253 cm^{-1}, indicating bidentate coordination of the ligand to the central tin atom in **2**, **3**, and **5** and monodentate coordination mode in **1** and **4** [14]. The FT-IR data for compound **1** were consistent with the X-ray crystallographic data.

NMR spectra. Signals in the ^{1}H NMR spectra of **1**–**5** (in DMSO-d_6) were assigned on the basis of their position, multiplicity, and intensity patterns. Protons of the butyl group of the ligand resonated in the range δ 0.97–4.40 ppm, and the corresponding signals of **1**–**5** were observed in the region (δ 0.98–4.46 ppm). These observations are in agreement with the previously reported data for metal dithiocarbamates [15]. The configuration of the Sn atom was deduced from the $^2J(^{119–117}Sn–^1H)$ coupling constant for **1**; the observed value (76–79 Hz) indicated six-coordinate Sn atom in solution. However, a multiplet was observed for the terminal methyl group in **2** and **4** at δ 0.97 and 0.88 ppm, respectively. A shielding effect is experienced through the carbon chain in compound **4** due to the presence of *n*-butyl groups on the electropositive Sn atom [16]. The *ortho*-protons of the phenyl groups attached to Sn in complexes **3** and **5** were observed as

Table 1. Coupling constants $^{1}J(^{119}Sn–^{13}C)$ and calculated C–Sn–C angles (deg) in compounds **1**–**5**

Comp. no.	$^{1}J(^{119}Sn–^{13}C)$, Hz	$^{2}J(^{119}Sn–^{1}H)$, Hz	Angle, deg	
			^{1}J	^{2}J
1	597	79	129	125
2	540	–	129	–
3	830	–	129	–
4	335	–	108	–
5	588	–	112	–

multiplets at δ 8.0 and 7.69 ppm (*o*-H), respectively, and the *meta*- and *para*-protons therein resonated in the region δ 7.42–7.50 ppm.

The ^{13}C chemical shifts due to butyl and phenyl groups attached to Sn were consistent with those reported for other similar compounds [17, 18]. The CS_2 carbon signal appeared in the range δ_C 214.8–223.1 ppm, indicating ligand coordination to the metal center via the CSS moiety [16]. The configuration of the Sn atom in the di- and triorganyltin(IV) compounds was determined from the $^{1}J(^{119}Sn–^{13}C)$ coupling constants and C–Sn–C bond angles (108°–129°) calculated by Lockhart's equation [19] (Table 1). The observed $^{1}J(^{119}Sn–^{13}C)$ coupling constants and calculated C–Sn–C angles are, respectively, 597 Hz and 129.0° for **1**, 540 Hz and 129.0° for **2**, 830 Hz and 129.0° for **3**, and 588 Hz and 112.0° for **5**, which correspond to six-coordinate tin atom in **1**–**3** and five-coordinate tin atom in **5**. The $^{1}J(^{119}Sn–^{13}C)$ value (335 Hz) and C–Sn–C angle (108°) for **4** indicate four-coordinate tin(IV) atom, which is in accordance with published data [20].

X-Ray analysis of compound 1. The ORTEP view of molecule **1** is shown in Fig 1, and the structure refinement parameters are given in Table 2. Selected bond lengths and bond angles in molecule **1** are given in Table 3. The tin atom in complex **1** has distorted tetrahedral geometry defined by two methyl groups and two sulfur atom of the carbonodithioate ligand. The ligand coordinates to the tin atom in monodentate mode. The CSnC and SSnC angles are within the expected range of four-coordinate tetrahedral geometry (C^7SnC^6 128.9°, S^1SnC^6 108.4°, S^1SnC^7 109.5°) [21]. No weak interactions were found between molecules **1** in crystal, and the Me_2SnL_2 molecule exists as an independent unit. The ligands are coordinated symmetrically through shorter Sn–S^1 bonds [2.4942(7) Å]. The other Sn–S distances are significantly shorter than the sum of the corresponding van der Waals radii (4.0 Å), and the coordination number of Sn is assigned as four. Furthermore, the degree of symmetry in the Sn –S^1 bond distances is the same in the two ligands. The S^1SnC^6 and S^1SnC^7 bond angles demonstrate inclination of the Sn–C bonds toward the longer Sn–S bonds due to repulsion between the bonding electron pairs around the central Sn atom. Electronic and steric factors have also been involved to explain distortion of similar structures from the regular tetrahedral geometry [22].

The crystallographic data for compound **1** were deposited to the Cambridge Crystallographic Data Centre (CCDC entry no. 1 062 079).

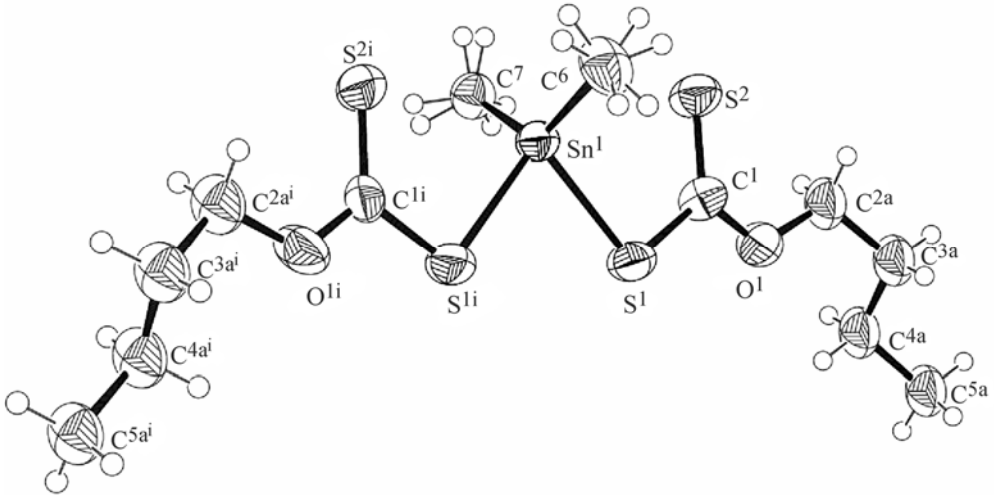


Fig. 1. Crystal structure of compound **1**.

Table 2. Crystallographic data and structure refinement parameters for compound **1**

Parameter	Value	Parameter	Value
Formula	$C_{12}H_{24}O_2S_4Sn$	Crystal size, mm	0.28×0.22×0.18
Molecular weight	447.24	Radiation	MoK_α (λ = 0.71073 Å)
Temperature, K	296(2)	2θ range	5.6° to 52°
Crystal system	Orthorhombic	Index ranges	$-17 \le h \le 25$, $-7 \le k \le 7$, $-9 \le l \le 7$
Space group	$Pmn2_1$	Reflections collected	7166
a, Å	20.3843(16)	Independent reflections	1633 [R_{int} = 0.0181, R_σ = 0.0215]
b, Å	6.0425(4)	Data/restraints/parameters	1633/7/91
c, Å	7.8015(6)	Goodness of fit on F^2	1.055
Volume, Å^3	960.93(12)	Final *R* indexes [$I \ge 2\sigma(I)$]	R_1 = 0.0218, wR_2 = 0.0491
Z	2	Final *R* indexes (all data)	R_1 = 0.0269, wR_2 = 0.0522
d_{calc}, mg/mm^3	1.546	Largest diff. peak/hole, ē Å^{-3}	0.38/–0.23
μ, mm^{-1}	1.760	Flack parameter	0.40(8)
F(000)	452.0		

Table 3. Selected bond lengths and bond angles in molecule **1**

Bond	*d*, Å	Bond	*d*, Å	Angle	ω, deg	Angle	ω, deg
Sn^1–S^1	2.4942(7)	C^6–Sn^1	2.174(14)	$C^7Sn^1C^6$	128.9(2)	$C^6Sn^1S^1$	108.4(4)
Sn^1–C^7	2.066(14)	S^1–C^1	1.732(3)	$C^1S^1Sn^1$	96.25(9)	$C^7Sn^1S^1$	109.5(3)
S^2–C^1	1.643(3)	O^1–C^1	1.314(3)	$C^1O^1C^{2A}$	118.9(4)	$S^2C^1S^1$	123.87(17)
O^1–C^{2A}	1.490(7)	O^1–C^2	1.484(17)	$O^1C^1S^1$	110.4(2)	$S^2C^1S^1$	125.8(2)
				$O^1C^{2A}C^{3A}$	111.2(7)	$C^{3A}C^{4A}C^{5A}$	111.8(7)

DNA binding study. The interaction of compounds **1**–**5** with DNA was studied by UV-visible spectroscopy [23]. The spectra of the ligand and compounds **1**–**5** were recorded in the absence and in the presence of DNA at different concentrations [24–26]. The UV spectra of the ligand (KL) and its complexes showed a strong absorption peak at λ 309–310 nm due to *n*–π* transition of the C=S bond. As the concentration of DNA increased, a hypochromic effect was observed along with a minor red shift (1–2 nm), as illustrated by Fig. 2 for compounds **3** and **5**. Hypochromic effect and red shift are the signs of intercalative binding mode involving stacking interaction between the chromophore and DNA base pair. After intercalating the base pairs of DNA, the π* orbital of the intercalated ligand could couple with the π orbital of DNA base pair, thus decreasing the π–π* transition energy, which results in bathochromic shift. On the other hand, coupling of the π orbital with partially filled electron shell decreases the transition probability, which leads to hypochromic effect. Hypochromism in the case of intercalative binding mode originates from π–π* stacking interactions, while bathochromic (red) shift is observed when the DNA duplex is stabilized [27, 28]. The intrinsic binding constants *K* of the ligand and organotin(IV) carbondithioates **1**–**5** were calculated by the Benesi–Hildebrand equation [29] (Table 4) in order to compare the respective binding strengths.

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

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

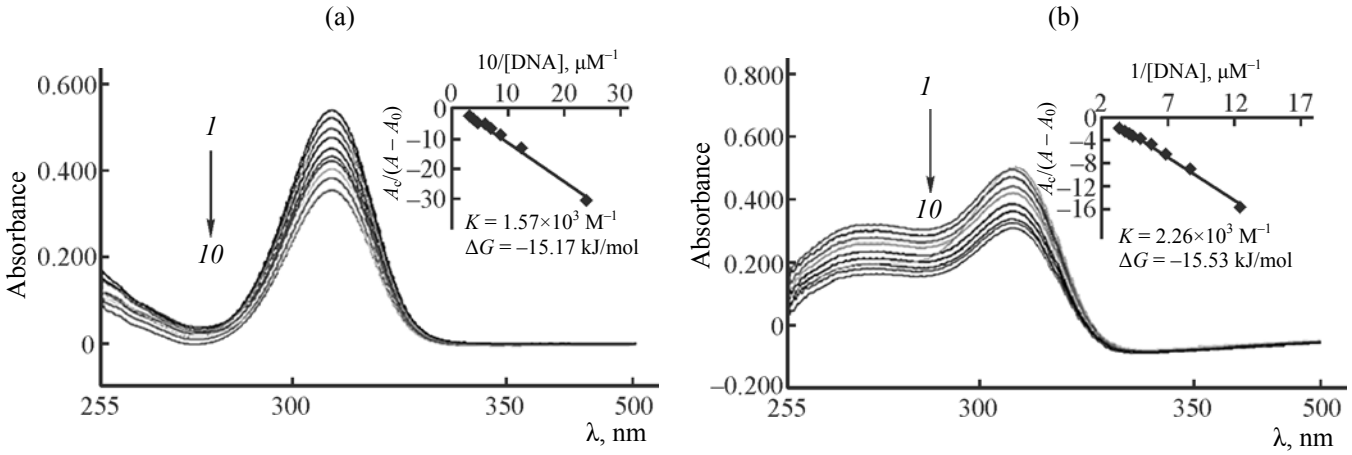


Fig. 2. UV spectra of compounds (a) **3** and (b) **5** ($c_3 = c_5 = 0.8$ mM) (*1*) in the absence and in the presence of (*2*) 20, (*3*) 40, (*4*) 62, (*5*) 83, (*6*) 104, (*7*) 125, (*8*) 150, (*9*) 170, and (*10*) 192 μM of DNA.

drug and drug–DNA complex, respectively. The calculated values of Δ*G* and binding constants are given in Table 4. As follows from the negative Δ*G* values, the interaction of KL and **1**–**5** with DNA is a spontaneous process.

Antibacterial activity. All the synthesized compounds were subjected to antibacterial activity assay against five selected bacterial strains, gram positive *Staphylococcus aureus* (ATCC 6538) and *Micrococcus luteus* (ATCC 53598) and gram negative *Bordetella bronchiseptica* (ATCC 4617), *Salmonella typhimurium* (ATCC 14028), and *Enterobacter aerogens* (ATCC 13048), using the disk diffusion method [30]. The results are presented in Table 5. All complexes **1**–**5** showed moderate activity against the selected strains, and the activity is highly strain-dependent. The activities of **4** and **5** against *M. luteus*, *S. aureus*, *B. bronchiseptica*, and *E. aerogenes* are comparable to those of the reference drug. This may be ascribed to Tweedy's theory, according to which chelation reduces the polarity of the central metal atom because of partial sharing of its positive charge with the ligand, which favors permeation of the complex through the lipid layer of cell membrane [31].

Table 4. DNA binding constants and Gibbs free energies for free ligand KL and compounds **1**–**5**

Comp. no.	*K*, L/mol	–Δ*G*, kJ/mol
KL	9.80×10^2	14.67
1	4.50×10^3	14.10
2	4.02×10^3	20.13
3	1.57×10^3	15.17
4	6.26×10^3	21.66
5	2.26×10^3	15.53

Antifungal activity. The results of *in vitro* disk diffusion assay [30] of the ligand and organotin(IV) compounds **1**–**5** against five fungal strains (*Aspergillus flavus*, *Aspergillus niger*, *Fusarium solani*, *Aspergillus fumigates*, and *Mucor species*) are summarized in Table 6. Terbinafine was used as standard drug. Compound **4** showed higher activity than that of the standard drug against *Aspergillus flavus*, *Aspergillus niger*, *and Aspergillus fumigates*. Compound **5** showed significant activity against all the tested fungal strains, while the activity of **1**–**3** was insignificant. These findings were consistent with published data according to which triorganotin derivatives are more biocidal than diorganotin analogs [32, 33]. Although the exact mechanism is not completely known, the action of antimicrobials may involve various targets in the microorganisms. Organotin compounds disturb the cell respiration process and thus block protein synthesis, which restricts further growth of the organisms. In comparison to diorganotin complexes, four- and five-coordinate triorganotins exhibit extensive biological activities due to availability of more space for incoming group (microorganisms), which results in increased liposolubility of the molecules in crossing cell membrane of microorganisms [34, 35].

Cytotoxicity. The cytotoxicities of KL and **1**–**5** were studied *in vitro* by the brine-shrimp lethality method [36] using Tricaine methanesulfonate (MS-222) as reference drug (Table 7). The mean values of duplicate readings at 10, 50, and 100 μg/mL are given. The LD_{50} values range from less than 10 to 52 μg/mL

Table 5. Antibacterial activity of KL and complexes **1**–**5** (inhibition zone, mm)

Compound no.	*M. luteus*	*S. Aureus*	*B. bronchiseptica*	*S. typhimurium*	*E. aerogenes*
KL	10	0	10	13	18
1	15	10	16	11	16
2	13	17	7	11	14
3	15	10	14	13	18
4	17	19	18	14	10
5	20	18	15	10	15
Roxithromycin[a]	20	20	20	20	20

[a] Reference drug.

Table 6. Antifungal activity of KL and organotin(IV) compounds **1**–**5** (inhibition zone, mm)

Compound no.	*Aspergillus flavus*	*Aspergillus niger*	*Fusirum solani*	*Aspergillus fumigates*	*Mucor specie*
KL	–[b]	–	–	–	–
1	12	6	–	4	–
2	4	7	–	11	–
3	14	–	9	–	–
4	18	20	14	22	14
5	16	13	14	10	9
Terbinafine[a]	16	16	16	16	16

[a] Reference drug. [b] "–" stands for no activity.

Table 7. Cytotoxicity data (number of shrimps killed out of 20) of KL and organotin(IV) compounds **1**–**5**

Compound no.	c = 100 μg/mL	c = 50 μg/mL	c = 10 μg/mL	LD_{50}, μg/mL
KL	15	12	11	13.2
1	11	10	9	22
2	9	8	5	52
3	11	9	5	48.2
4	20	20	20	<10
5	20	20	20	<10

against 4.3 μg/mL for the reference drug. Compounds **4** and **5** proved to be more toxic than the other tested compounds. The high toxicity is due to high lipid solubility which allows cell penetration and association with intracellular sites, while cell wall components also play an important role [37]. Cytotoxic drugs work better in cancer disease where the cancer cells are rapidly dividing and multiplying. Hence compounds **4** and **5** may be promising as potential drugs for the treatment of cancer.

Antileishmanial activity. The synthesized compounds were tested against the promastigote forms of leishmania major. The IC_{50} values shown in Table 8 indicate moderate antileishmanial activity of **1**–**3** and strong antileishmanial activity of **4** and **5** (IC_{50} 0.001

Table 8. Antileishmanial activity of the ligand (KL) and organotin(IV) compounds **1**–**5**

Compound no.	LC_{50}, μg/mL
KL	0.651
1	0.965
2	0.012
3	0.832
4	0.003
5	0.001
Amphotericin B[a]	0.048

[a] Reference drug.

and 0.003 μg/mL, respectively, against 0.048 μg/mL for the standard drug). These compounds disturb the respiration process by blocking the function of parasitic mitochondria, which restricts further growth of the organisms.

Protein kinase inhibition. Compounds **1**, **3**, and **4** showed different degrees of inhibition estimated at 13, 5, and 7 mm, respectively, while compounds **2** and **5** displayed no activity as compared to the standard value (18 mm). Compound **1** may be considered as potential candidate to inhibit tumor initiation.

In summary, potassium *O*-butyl carbonodithioate and its organotin(IV) complexes were successfully synthesized and characterized. The ligand coordinates to the tin atom through the sulfur atom. As revealed by UV-Vis studies, the synthesized compounds bind to DNA via intercalative interaction resulting in hypochromic effect with a minor red shift. The negative values of Gibbs free energy change indicated spontaneity of these interactions. Biological studies revealed that the triorganotin(IV) complexes generally proved to be more active than the corresponding diorganotin(IV) analogs probably due to their greater liphophilicity.

ACKNOWLEDGMENTS

F. Javed thanks the Higher Education Commission (HEC), Islamabad, Pakistan for financial support (PIN 117-7469-PS7-018).

REFERENCES

1. Pellerito, L. and Nagy, L., *Coord. Chem. Rev*., 2002, vol. 224, no. 1, p. 111. doi 10.1016/S0010-8545(01)00399-X
2. Nath, M., Pokharia, S., and Yadav, R., *Coord. Chem. Rev*., 2001, vol. 215, no. 1, p. 99. doi 10.1016/S0010-8545(00)00404-5
3. Al-Najjar, A.A., Shehata, M.R., Mohamed, M., and Shoukry, M.M., *Main Group Met. Chem*., 1999, vol. 22, no. 4, p. 253. doi 10.1515/MGMC.1999.22.4.253
4. Tiekink, E.R.T., *Appl. Organomet. Chem*., 2008, vol. 22, no. 9, p. 533. doi 10.1002/aoc.1441
5. Yin, H.D. and Xue, S.C., *Appl. Organomet. Chem*., 2006, vol. 20, no. 4, p. 283. doi 10.1002/aoc.1048
6. Tiekink, E.R.T., *Main Group Met. Chem*., 1992, vol. 15, p. 161. doi 10.1002/chin.199321265
7. Hussain, H., Ahmad, V.U., Green, I.R., Krohn, K., Hussain, J., and Badshah, A., *Arkivoc*, 2007, vol. 2007, part 14, p. 289. http: 10.2298/JSC0802179H.
8. Khan, S., Nami, S.A., and Siddiqi, K.S., *J. Organomet. Chem*., 2008, vol. 693, no. 6, p. 1049. doi 10.1016/j.jorganchem.2007.12.026
9. Menezes, D.C., Vieira, F.T., De Lima, G.M., Wardell, J.L., Cortés, M.E., Ferreira, M.P., and Vilas Boas, A., *Appl. Organomet. Chem*., 2008, vol. 22, no. 4, p. 221. doi 10.1002/aoc.1375
10. Muhammad, N., Shuja, S., Ali, S., Butler, I.S., Meetsma, A., and Khan, M., *Polyhedron*, 2009, vol. 28, no. 16, p. 3439. doi 10.1016/j.poly.2009.07.025
11. Javed, F., Ali, S., Shah, M.W., Munawar, K.S., Shahzadi, S., Hameedullah, Sharma, S.K., and Qanungo, K., *J. Coord. Chem*., 2014, vol. 67, no. 16, p. 2795. doi 10.1080/00958972.2014.947967
12. Armarego, W.L. and Chai, C.L.L., *Purification of Laboratory Chemicals*, London: Butterworth Heinemann, 2003, 5th ed.
13. Sirajuddin, M., Ali, S., Shah, N.A., Khan, M.R., and Tahir, M.N., *Spectrochim. Acta, Part A*, 2012, vol. 94, p. 134. doi 10.1016/j.saa.2012.03.068
14. Shaheen, F., Ali, S., Rehman, Z.U., and Meetsma, A., *Polyhedron*, 2012, vol. 31, no. 1, p. 697. doi 10.1016/j.poly.2011.10.025
15. Domazetis, G., Magee, R.J., and James, B.D., *J. Organomet. Chem*., 1977, vol. 141, no. 1, p. 57. doi 10.1016/S0022-328X(00)90667-3
16. Gómez-Ortiz, L.A., Cea-Olivares, R., García-Montalvo, V., and Hernández-Ortega, S., *J. Organomet. Chem*., 2002, vol. 654, no. 1, p. 51. doi 10.1016/S0022-328X(02)01373-6
17. Nadvornik, M., Holeček, J., Handlíř, K., and Lyčka, A., *J. Organomet. Chem*., 1984, vol. 275, no. 1, p. 43. doi 10.1016/0022-328X(84)80576-8
18. Eng, G., Song, X., Duong, Q., Strickman, D., Glass, J., and May, L., *Appl. Organomet. Chem*., 2003, vol. 17, no. 4, p. 218. doi 10.1002/aoc.423
19. Lockhart, T.P., Manders, W.F., and Holt, E.M., *J. Am. Chem. Soc*., 1986, vol. 108, no. 21, p. 6611. doi 10.1021/ja00281a026

20. Willem, R., Verbruggen, I., Gielen, M., Biesemans, M., Mahieu, B., Basu Baul, T.S., and Tiekink, E.R.T., *Organometallics*, 1998, vol. 17, no. 26, p. 5758. doi 10.1021/om980504u
21. Mohamed-Ibrahim, M.I., Chee, S.S., Buntine, M.A., Cox, M.J., and Tiekink, E.R.T., *Organometallics*, 2000, vol. 19, no. 25, p. 5410. doi 10.1021/om000717v
22. Ali, S., Muhammed, N., and Meetsma, A., *Acta Crystallogr., Sect. E*, 2007, vol. 63, p. m431. doi 10.1107/S1600536806056236
23. Sun, H., Xiang, J., Liu, Y., Li, L., Li, Q., Xu, G., and Tang, Y., *Biochimie*, 2011, vol. 93, no. 8, p. 1351. doi 10.1016/j.biochi.2011.06.007
24. Jaumot, J., and Gargallo, R., *Curr. Parm. Des*., 2012, vol. 18, no. 14, p. 1900. doi 10.2174/138161212799958486
25. Wei, C., Wang, J., and Zhang, M., *Biophys. Chem*., 2010, vol. 148, no. 1, p. 51. doi 10.1016/j.bpc.2010.02.009
26. Bhadra, K. and Kumar, G.S., *Biochim. Biophys. Acta, Gen. Subj*., 2011, vol. 1810, no. 4, p. 485. doi 10.1016/j.bbagen.2011.01.011
27. Yang, X., Shen, G.L., and Yu, R.Q., *Microchem. J*., 1999, vol. 62, no. 3, p. 394. doi 10.1006/mchj.1999.1747
28. Xu, Z., Bai, G., and Dong, C., *Bioorg. Med. Chem*., 2005, vol. 13, no. 20, p. 5694. doi 10.1016/j.bmc.2005.06.023
29. Ibrahim, M.S., Shehatta, I.S., and Al-Nayeli, A.A., *J. Pharm. Biomed. Anal*., 2002, vol. 28(2), p. 217. doi 10.1016/S0731-7085(01)00624-0
30. Fritsche, T.R., McDermott, P.F., Shryock, T.R., and Walker, R.D., *J. Clin. Microbiol*., 2007, vol. 45, no. 8, p. 2758. doi 10.1128/JCM.00569-07
31. Rehman, Z.U., Muhammad, N., Shah, A., Ali, S., and Khan, E., *Heteroatom Chem*., 2012, vol. 23, no. 6, p. 560. doi 10.1002/hc.21050
32. Ferreira, I.P., de Lima, G.M., Paniago, E.B., Rocha, W.R., Takahashi, J.A., Pinheiro, C.B., and Ardisson, J.D., *Polyhedron*, 2014, vol. 79, p. 161. doi 10.1016/j.poly.2014.05.001
33. Shi, Y., Zhang, B.Y., Zhang, R.F., Zhang, S.L., and Ma, C.L., *J. Coord. Chem*., 2012, vol. 65, no. 23, p. 4125. doi 10.1080/00958972.2012.734814
34. Neelakantan, M.A., Esakkiammal, M., Mariappan, S.S., Dharmaraja, J., and Jeyakumar, T., *Indian J. Pharm. Sci*., 2010, vol. 72, no. 2, p. 216. doi 10.4103/0250-474X.65015
35. Neelakantan, M.A., Rusalraj, F., Dharmaraja, J., Johnsonraja, S., Jeyakumar, T., and Pillai, M.S., *Spectrochim. Acta, Part A*, 2008, vol. 71, no. 4, p. 1599. doi 10.1016/j.saa.2008.06.008
36. Meyer, B.N., Ferrigni, N.R., Putnam, J.E., Jacobsen, L.B., Nichols, D.J., and McLaughlin, J.L., *Planta Med*., 1982, vol. 45, no. 5, p. 31. doi 10.1055/s-2007-971236
37. Saxena, A.K., *Appl. Organomet. Chem*., 1987, vol. 1, no. 1, p. 39. doi 10.1002/aoc.590010107