Organotin(IV) complexes of 2-hydroxyacetophenone-N(4)-cyclohexylthiosemicarbazone (H$_2$dact): Synthesis, spectral characterization, crystal structure and biological studies

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ABSTRACT

Four new organotin(IV) complexes of the type [MeSnCl(dact)] (**2**), [BuSnCl(dact)] (**3**), [PhSnCl(dact)] (**4**) and [Ph$_2$Sn(dact)] (**5**) were synthesized by the direct reaction of 2-hydroxyacetophenone-N(4)-cyclohexylthiosemicarbazone [H$_2$dact, (**1**)] and organotin(IV) chloride(s) in absolute methanol. The ligand [H$_2$dact, (**1**)] and its organotin(IV) complexes (**2–5**) have been characterized by CHN analyses, molar conductivity, UV–Vis, FT-IR, ^{1}H, ^{13}C and ^{119}Sn NMR spectral studies. The molecular structure of complex (**5**) has also been determined by single-crystal X-ray diffraction. The crystal structure of complex (**5**) showed that the ligand is doubly deprotonated at the oxygen and sulfur atoms and is coordinated to the tin(IV) atom through thiolate-S, azomethine-N and phenoxide-O atoms. X-ray diffraction studies indicated that complex (**5**) is a monomer and the central tin(IV) atom is five coordinated in a distorted trigonal bipyramidal geometry. The cytotoxicity of the ligand (**1**) as well as its organotin(IV) complexes (**2–5**) was studied against *Artemia salina*. The *in vitro* antibacterial activities of these compounds were also evaluated. The screening results have shown that the organotin(IV) complexes (**2–5**) have better antibacterial activity than the free ligand. Furthermore, it has been shown that diphenyltin(IV) derivative (**5**) exhibits significantly better activity than the monoorganotin(IV) derivatives (**2–4**).

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1. Introduction

Thiosemicarbazones form an interesting class of compounds with a wide range of pharmacological applications [1,2]. Thiosemicarbazone usually act as chelating ligand with certain metal ions, bonding through the sulfur and hydrazine nitrogen atoms [3]. The heterocyclic thiosemicarbazones are of high interest because of their great versatility as ligands. This is due to the presence of several potential donor atoms, their flexibility and ability to coordinate either neutral or deprotonated forms. Seena and Kurup have synthesized and characterized dioxomolybdenum(IV) complexes with 2-hydroxyacetophenone-N(4)-cyclohexyl and N(4)-phenyl thiosemicarbazone which suggested that the Mo(IV) complex is penta-coordinated [4]. Rebolledo et al. have reported that Pd(II) complexes of 2-benzoylpyridine-N(4)-methyl/phenyl thiosemicarbazone ligands are active against the MCF-7, TK-10 and UACC-62 human tumor cell line [5]. For the past few years, studies of the coordination chemistry of thiosemicarbazone involved complexes

with transition metal ions [6–9]. The synthesis and characterization of organotin(IV) complexes of Schiff base ligands have always attracted the attention of inorganic chemists and is well established in the literature [10–14]. Organotin(IV) complexes have been extensively studied due to their beneficial biological activities as well as their wide industrial and agricultural applications [15–21]. de Sousa et al. have reported organotin(IV) derivatives of 2-hydroxyacetophenone-N(4)-phenylthiosemicarbazone and found that the Sn(IV) atom adopts a strongly distorted trigonal bipyramidal configuration [22]. Although the organotin(IV) complexes exhibit important cytotoxic effects, but based on the literature review there is still very limited information available regarding the X-ray and biological studies of novel organotin(IV) complexes with substituted thiosemicarbazone ligands [23]. Previous works described the synthesis and structural studies of tin(IV)/organotin(IV) complexes with N(4)-substituted thiosemicarbazone ligand [24,25]. The particular interest of this work is a better understanding of the structural diversity of organotin(IV) complexes to delineate their biological properties. This paper reports the synthesis, spectral characterization and *in vitro* biological activity of organotin(IV) complexes (**2–5**). X-ray crystal structure of diphenyltin(IV) complex (**5**) is also described.

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2. Experimental

2.1. Materials and methods

All reagents were purchased from Fluka, Aldrich and JT Baker. All solvents were purified according to standard procedures [26]. The UV–Vis spectra were recorded with $CHCl_3$ solvent on a Perkin–Elmer Lambda 25 UV–Vis spectrophotometer. Infrared spectra (IR) were recorded on KBr discs using a Perkin–Elmer Spectrum GX Fourier-Transform spectrometer (4000–375 cm^{-1}). ^1H, ^{13}C and ^{119}Sn NMR spectra were recorded on a JEOL 500 MHz-NMR spectrometer; chemical shifts were given in ppm relative to $SiMe_4$ and Me_4Sn in $CDCl_3$ solvent. Elemental analyses were recorded with a Flash EA 1112 series CHN elemental analyzer. Molar conductance values were measured with DMF solvent using a Jenway 4510 conductivity meter. A colorless block crystal of compound **5** was measured at 150 K on a CrysAlispro CCD diffractometer with graphite monochromated MoKα radiation ($\lambda = 0.7107$). The structure was solved by direct methods using SHELXL-97 and refined by full-matrix least-squares refinement on F^2 using SHELXL-97. Positional and anisotropic atomic displacement parameters were refined for all non-hydrogen atoms. Hydrogen atoms were placed in calculated positions.

2.2. Synthesis of N(4)-cyclohexylthiosemicarbazide

Cyclohexylisothiocyanate (1.41 g, 10 mmol) in 4 mL of ether was added drop-wise into 4 mL of ether solution of hydrazine hydrate (2 g, 40 mmol). The mixture was stirred vigorously for 5 h. Then, 5 mL petroleum ether was added into the resulting solution and stirred for another 1 h and white precipitate was formed. The white precipitate was filtered, washed with a small amount of cool diethyl ether and dried *in vacuo* over silica gel. Yield: 2.12 g, 62%: Mp.: 146–148 °C: FT-IR (KBr disc, cm^{-1}) v_{max}: 3334 (s, NH_2), 3297 (s, NH), 2929, 2853 (s, cyclohexyl), 1349, 849 (w, C=S).

2.3. Synthesis of 2-hydroxyacetophenone-N(4)-cyclohexylthiosemicarbazone (H₂dact) (1)

A solution of N(4)-cyclohexylthiosemicarbazide (0.51 g, 3 mmol) in 10 mL absolute methanol was treated with 10 mL absolute methanolic solution of 2-hydroxyacetophenone (0.408 g, 3 mmol). The resulting reaction mixture was stirred and refluxed for 4 h (Scheme 1). On cooling the solution to room temperature light brown

microcrystals formed, filtered off and washed several times with methanol. The light brown microcrystals were recrystallised from methanol and dried *in vacuo* over silica gel. Yield: 0.76 g, 82%: Mp.: 173–175 °C: UV–Vis ($CHCl_3$) $\lambda_{max/nm}$: 262, 328, 361: FT-IR (KBr disc, cm^{-1}) v_{max}: 3315 (s, OH), 3102 (s, NH), 2923, 2851 (s, cyclohexyl), 1620 (m, C=N), 1296 (m, C—O), 987 (m, N—N), 1365, 840 (w, C=S). ^1H NMR ($CDCl_3$) δ: 10.87 (s, 1H, OH), 8.79 (s, 1H, N2–H), 8.35 (s, 1H, CyC1–H), 7.44–7.29 (m, 4H, phenyl ring), 2.35 (s, 3H, N=C—CH_3), 2.07–1.31 (m, 10H, CyC—H), 1.8 (s, 1H, SH). ^{13}C NMR ($CDCl_3$) δ: 184.99 (NH—C=S), 164.11 (C=N), 142.36–137.10 (aromatic ring), 48.83–32.61 (cyclohexyl ring), 8.99 (CH_3). *Anal.* Calc. for $C_{15}H_{21}N_3O_1S_1$: C, 61.82; H, 7.26; N, 14.42. Found: C, 61.77; H, 7.21; N, 14.38%.

2.4. Synthesis of [MeSnCl(dact)] (2)

H_2dact (0.291 g, 1.0 mmol) was dissolved in absolute methanol (10 mL) in a Schlenk round bottom flask under a nitrogen atmosphere. Then, a methanolic solution of methyltin(IV) trichloride (0.240 g, 1.0 mmol) was added drop wise. The resulting reaction mixture was refluxed for 4 h (Scheme 2) and cooled to room temperature. The microcrystals were filtered off, washed with a small amount of cold methanol and dried *in vacuo* over silica gel. Yield: 0.43 g, 80%: Mp.: 206–208 °C: Molar conductance (DMF) Ω^{-1} cm^2 mol^{-1}: 11.6: UV–Vis ($CHCl_3$) $\lambda_{max/nm}$: 269, 335, 385, 416: FT-IR (KBr, cm^{-1}) v_{max}: 3103 (s, NH), 2920, 2850 (s, cyclohexyl), 1598 (m, C=N—N=C), 1266 (m, C—O), 1028 (w, N—N), 1322, 825 (m, C—S), 578 (w, Sn—C), 543 (w, Sn—O), 420 (w, Sn—N). ^1H NMR ($CDCl_3$, $^2J[^{119}Sn, ^1H]$) δ: 8.78 (s, 1H, N2–H), 8.37 (s, 1H, CyC1–H), 7.43–7.26 (m, 4H, phenyl ring), 2.47 (s, 3H, N=C—CH_3), 2.09–1.28 (m, 10H, CyC—H), 1.07 (s, 3H, Sn—CH_3), [79.1 Hz]. ^{13}C NMR ($CDCl_3$) δ: 181.65 (N=C—S), 170.22 (C=N), 140.38–136.50 (aromatic ring), 48.10–35.30 (cyclohexyl ring), 18.10 (CH_3), 12.59 (Sn—CH_3). ^{119}Sn NMR ($CDCl_3$) δ: –175.80. *Anal.* Calc. for $C_{16}H_{22}N_3SOSnCl$: C, 41.90; H, 4.83; N, 9.16. Found: C, 41.88; H, 4.75; N, 9.09%.

The other complexes (**3–5**) were synthesized using a similar procedure to the organotin(IV) complex (**2**) using appropriate organotin(IV) chloride(s) (Scheme 2).

2.5. Synthesis of [BuSnCl(dact)] (3)

Yield: 0.45 g, 78%: molar conductance (DMF) Ω^{-1} cm^2 mol^{-1}: 9.72: UV–Vis ($CHCl_3$) $\lambda_{max/nm}$: 265, 332, 385, 412: FT-IR (KBr, cm^{-1}) v_{max}: 3105 (s, NH), 2925, 2853 (s, cyclohexyl),
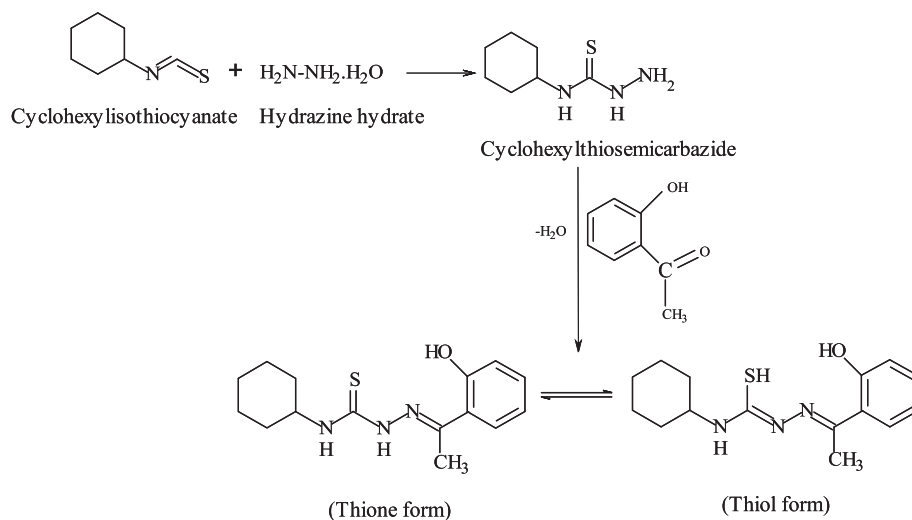
Scheme 1. Synthesis of 2-hydroxyacetophenone-N(4)-cyclohexylthiosemicarbazone (H₂dact) ligand (**1**).
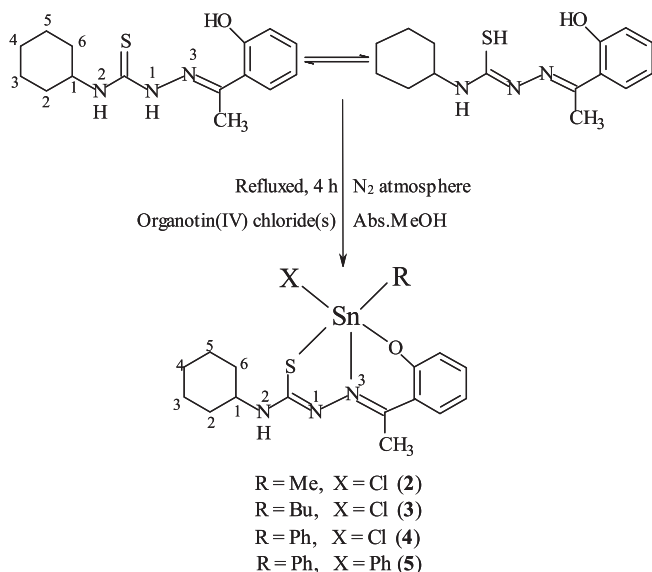
Scheme 2. The reaction scheme for the synthesis of organotin(IV) complexes (**2–5**).

R = Me, X = Cl (**2**)
R = Bu, X = Cl (**3**)
R = Ph, X = Cl (**4**)
R = Ph, X = Ph (**5**)

1596 (m, C=N—N=C), 1268 (m, C—O), 1027 (w, N—N), 1325, 827 (m, C—S), 580 (w, Sn—C), 538 (w, Sn—O), 422 (w, Sn—N). ^{1}H NMR (CDCl$_3$) δ: 8.77 (s, 1H, N2—H), 8.35 (s, 1H, CyC1—H), 7.43–7.25 (m, 4H, phenyl ring), 2.46 (s, 3H, N=C—CH$_3$), 2.07–1.79 (m, 10H, CyC—H), 1.73–1.70 (t, 2H, Sn—CH$_2$—CH$_2$—CH$_2$—CH$_3$), 1.63–1.60 (m, 2H, Sn—CH$_2$—CH$_2$—CH$_2$—CH$_3$), 1.44–1.39 (m, 2H, Sn—CH$_2$—CH$_2$—CH$_2$—CH$_3$), 0.93–0.90 (t, 3H, Sn—CH$_2$—CH$_2$—CH$_2$—CH$_3$). ^{13}C NMR (CDCl$_3$) δ: 179.22 (N=C—S), 168.55 (C=N), 141.87–136.43 (aromatic ring), 47.99–32.60 (cyclohexyl ring), 32.88, 26.32, 24.88, 20.73 (Sn—CH$_2$—CH$_2$—CH$_2$—CH$_3$), 16.50 (CH$_3$). ^{119}Sn NMR (CDCl$_3$) δ: −183.05. *Anal.* Calc. for C$_{19}$H$_{28}$N$_3$SOSnCl: C, 45.58; H, 5.63; N, 8.39. Found: C, 45.53; H, 5.59; N, 8.36%.

2.6. Synthesis of [PhSnCl(dact)] (**4**)

Yield: 0.47 g, 79%: Mp.: 212–214 °C: molar conductance (DMF) Ω^{-1} cm^2 mol^{-1}: 13.11: UV–Vis (CHCl$_3$) $\lambda_{max/nm}$: 265, 331, 386, 404; FT-IR (KBr, cm^{-1}) ν_{max}: 3104 (s, NH), 2924, 2851 (s, cyclohexyl), 1595 (m, C=N—N=C), 1261 (m, C—O), 1025 (w, N—N), 1328, 822 (m, C—S), 598 (w, Sn—C), 531 (w, Sn—O), 425 (w, Sn—N). ^{1}H NMR (CDCl$_3$) δ: 8.74 (s, 1H, N2—H), 8.36 (s, 1H, CyC1—H), 7.43–7.27 (m, 9H, phenyl ring), 2.49 (s, 3H, N=C—CH$_3$), 2.07–1.42 (m, 10H, CyC—H). ^{13}C NMR (CDCl$_3$) δ: 180.77 (N=C—S), 174.45 (C=N), 140.11–138.23 (aromatic ring), 48.30–32.77 (cyclohexyl ring), 17.60 (CH$_3$). ^{119}Sn NMR (CDCl$_3$) δ: −188.92. *Anal.* Calc. for C$_{21}$H$_{24}$N$_3$SOSnCl: C, 48.44; H, 4.64; N, 8.07. Found: C, 48.40; H, 4.59; N, 8.02%.

2.7. Synthesis of [Ph$_2$Sn(dact)] (**5**)

Yield: 0.48 g, 75%: Mp.: 258–260 °C: molar conductance (DMF) Ω^{-1} cm^2 mol^{-1}: 8.17: UV–Vis (CHCl$_3$) $\lambda_{max/nm}$: 264, 350, 382, 408: FT-IR (KBr, cm^{-1}) ν_{max}: 3103 (s, NH), 2923, 2850 (s, cyclohexyl), 1598 (m, C=N—N=C), 1267 (m, C—O), 1021 (w, N—N), 1347, 822 (m, C—S), 600 (w, Sn—C), 533 (w, Sn—O), 447 (w, Sn—N). ^{1}H NMR (CDCl$_3$) δ: 8.78 (s, 1H, N2—H), 8.39 (s, 1H, CyC1—H), 7.40–7.32 (m, 14H, phenyl ring), 2.51 (s, 3H, N=C—CH$_3$), 2.09–1.41 (m, 10H, CyC—H). ^{13}C NMR (CDCl$_3$) δ: 179.98 (N=C—S), 171.75 (C=N), 142.20–138.21 (aromatic ring), 50.48–32.83 (cyclohexyl ring), 15.88 (CH$_3$). ^{119}Sn NMR (CDCl$_3$) δ: −170.10. *Anal.* Calc. for

C$_{27}$H$_{29}$N$_3$SOSn: C, 57.67; H, 5.19; N, 7.47. Found: C, 57.61; H, 5.14; N, 7.43%.

2.8. Cytotoxicity

The substituted thiosemicarbazone ligand (**1**) and its organotin(IV) complexes (**2–5**) were screened for toxicity using the published method [27] with some modifications. A stock solution of 5000 ppm of the ligand [H$_2$dact, (**1**)] and its organotin(IV) complexes (**2–5**) were prepared in DMSO. Then, the stock solutions were further diluted into seven different levels of dose and later topped up to 5 mL; which were 1, 5, 10, 50, 100, 150 and 300 ppm. The hatching process was carried out at ambient temperature for 24 h, and a pinch of *Artemia salina* cysts was placed in a beaker with 100 mL treated sea water. During the hatching process, aeration and light was provided at room temperature. After 24 h, the hatched nauplii were attracted by the light source and tended to stay at the surface of the sea water, while the shells and remaining cysts were deposited at the bottom of the sea water. The shrimps were transfer to fresh sea water in a Petri dish for ease of calculation. About 20 active shrimps were added to 5 mL diluted test solution in each and every plastic testing mug. After 24 h on incubation under direct light at room temperature, the mortality of the shrimps in each mug was counted. The mortality was computed and corrected for the natural death observed in the negative control using Abbott's formula [27]. All results of the mortality were expressed in percentages and plotted in an allosteric sigmoidal graph using a Graph pad prism.

2.9. Antibacterial test

The antibacterial test of synthesized ligand (**1**) and its organotin(IV) complexes (**2–5**) was carried out using the agar well diffusion method [28]. Doxycycline was used as the standard drug. The bacteria from stock culture were lightly inoculated into the Mueller Hinton Broth (MHB) and allowed to grow overnight at 37 °C in an ambient air incubator. The culture was diluted with a new MHB in order to achieve an absorbance value of 2.0×10^6 colony forming units (CFU/mL) or 0.168 at wavelength of 550 nm in the spectrophotometer. Sterile cotton swab was dipped into the broth culture and inoculated on the Mueller Hinton Agar (MHA). Sterile paper discs with 6 mm diameter were placed on the agar in equal distance. The recommended concentration of the test sample (2 mg/mL in DMSO) was introduced individually to each of the discs. The agar plates were incubated immediately at 37 °C for 20 h. For each plate, DMSO mixture and reference antibacterial drug such as doxycycline served as negative and positive controls, respectively. The activity was determined by measuring the diameter of zones showing complete inhibition (mm). Growth inhibition was calculated with reference to the positive control.

3. Results and discussion

The ligand 2-hydroxyacetophenone-N(4)-cyclohexylthiosemicarbazone (H$_2$dact) was prepared by the condensation reaction of 2-hydroxyacetophenone and N(4)-cyclohexylthiosemicarbazide. The ligand (**1**) acts as dinegative tridentate ONS donors in this work. It has two tautomers within the structure, existing as either a thione or a thiol tautomer (Scheme 1). Four new organotin(IV) complexes (**2–5**) were obtained in good yields by the equimolar reaction of organotin(IV) salts with H$_2$dact (**1**) (Scheme 2). The physical and analytical data of **1–5** are given in the experimental section. All organotin(IV) compounds were stable in N$_2$ atmosphere and soluble in common organic solvents. The molar conductivity of the organotin(IV) complexes (**2–5**) in DMF is

13.11–8.17 Ω^{-1} cm^2 mol^{-1} showing that the complexes are non-electrolytes [29].

3.1. UV–Vis spectra

The UV–Vis spectra of ligand (**1**) and its organotin(IV) complexes (**2–5**) were carried out in CHCl$_3$ (1×10^{-4} mol L^{-1}) at room temperature. The electronic absorption spectrum of ligand (**1**) showed three absorption bands at 262, 328 and 361 nm, corresponding to the HOMO/LUMO transition of phenolic group, azomethine and thiolate function, respectively [30]. After complexation, the complexes (**2–5**) showed four absorption bands at 264–269, 331–350, 382–385 and 404–416 nm, respectively. In the electronic spectra of the complexes (**2–5**), the intraligand transition is shifted to higher wavelength as a result of coordination. The new absorption at 404–416 nm, observed in the spectra of organotin(IV) complexes (**2–5**), is assigned to ligand → metal charge transfer (LMCT) [31]. The shift of λ_{max} from the ligand to the complexes is a clear indication of coordination between tin(IV) ion and the ligand.

3.2. Infrared spectra

The free ligand (**1**) showed absorption bands at 3315 and 3202 cm^{-1}, which are due to the stretching vibrations of the OH and NH groups, respectively. The C—H stretching vibrations of cyclohexyl moiety were observed at 2923 and 2851 cm^{-1}. The other bands observed in the spectrum at 1620, 1296, 987 and 1365, 840 cm^{-1} due to v(C=N), v(C—O), v(N—N) and v(C=S), respectively. Several significant changes with respect to the free ligand (**1**) bands on complexation suggest coordination through the phenolic group, azomethine and sulfur of the thiolic form of the ligand. The strong stretching band at 3315 cm^{-1} that corresponds to the v(OH) group in the spectrum of ligand (**1**) has disappeared in the spectra of complexes (**2–5**) due to the deprotonation, indicates metal–ligand bond formation through the site. The free ligand (**1**) showed a band at 1296 cm^{-1} which is due to v(C—O). This band is shifted to lower wave numbers at 1261–1268 cm^{-1} in the complexes (**2–5**), indicating the coordination of O$^-$ to the tin(IV) atom [32]. The newly formed v(C=N—N=C) bond showed medium to strong absorption peaks within the range of 1595–1598 cm^{-1} in the spectra of the complexes (**2–5**), indicating coordination of azomethine nitrogen to tin(IV) atom [33]. The v(N—N) band of the free ligand at 987 cm^{-1} is shifted to higher frequencies at 1021–1028 cm^{-1} in the spectra of organotin(IV) complexes (**2–5**), again confirms the coordination of azomethine nitrogen to the Sn(IV) atom [34]. The stretching and bending frequency of the v(C—S)) band observed at 1365 and 840 cm^{-1} in the spectrum of the ligand (**1**) are shifted to lower frequencies at 1322–1347 and 822–827 cm^{-1} in the spectra of the complexes (**2–5**), indicating coordination of sulfur atom in the thiolate form [35,36]. Characteristically one new band was observed at 543–531 cm^{-1} in the spectra of the complexes (**2–5**), suggesting the presence of Sn—O bonding in their structure. There are two new bands at 598–600 and 420–447 cm^{-1}, respectively, tentatively assigned to v(Sn—C) and v(Sn—N). The IR observation indicated the coordination of ligand (**1**) to the tin(IV) core of the complexes (**2–5**) *via* phenoxide-O, azomethine-N and thiolato-S atoms. These observations have also been confirmed by X-ray single crystal structure analysis of complex **5**.

3.3. ^{1}H, ^{13}C and ^{119}Sn NMR spectra

The ^{1}H NMR spectral assignments of ligand (**1**) and its organotin(IV) complexes (**2–5**) were carried out and interpreted based on the atom labeling in Scheme 2. ^{1}H NMR spectrum of free ligand (**1**) showed resonance signals at 10.89, 8.79, 8.35, 7.44–7.29, 2.35 and

1.8 ppm due to OH, N2—H, CyC1—H, aromatic ring protons, N=C—CH$_3$ and SH, respectively. The resonance signal of SH is not found in the spectra of complexes (**2–5**) which suggested the deprotonation of the SH proton and confirming that the ligand coordinated to the Sn(IV) in the thiolate form. The OH proton signal was also absent in the spectra of the complexes (**2–5**), suggested deprotonation of the phenolic proton and supported the phenolic oxygen atom was coordinated with tin(IV) atom. The azomethine proton (N=C—CH$_3$) signal appears at 2.35 ppm in the free ligand (**1**) which is shifted to downfield at 2.51–2.46 ppm in the complexes (**2–5**). This downfield shift indicating the azomethine nitrogen atom is coordinated to tin (IV) atom [37]. The resonance signals for the protons of phenyl moiety of the ligand (**1**) were observed at 7.44–7.29 ppm, which also appeared in the up field region at 7.43–7.25 ppm in the complexes (**2–5**). This is due to the electron withdrawal tendency from the aromatic ring owing to coordination with tin(IV). The cyclohexyl moiety forms a chair conformation and hence the protons exist in axial and equatorial environments. The equatorial protons 2.09–2.07 ppm are found to resonate at a slightly higher field compared to that of the axial protons 1.79–1.28 ppm in the ligand (**1**) and its organotin(IV) complexes (**2–5**). The methyl group attached to the tin(IV) in complex (**2**) give a singlet at 1.07 ppm with ^{2}J[^{119}Sn, ^{1}H] coupling constant value equal to 79.1 Hz, supported the five-coordinate environment around tin(IV) [38]. The three butyl groups attached to the tin(IV) moiety in the organotin(IV) complex (**3**) gave four resonance signals namely, 2.03–2.02 ppm (triplet, Sn—CH$_2$—CH$_2$—CH$_2$—CH$_3$), 1.65–1.60 ppm (multiplet, Sn—CH$_2$—CH$_2$—CH$_2$—CH$_3$), 1.52–1.23 ppm (multiplet, Sn—CH$_2$—CH$_2$—CH$_2$—CH$_3$) and 0.89–0.84 ppm (triplet, Sn—CH$_2$—CH$_2$—CH$_2$—CH$_3$). ^{1}H NMR information also supported the IR data of the complexes (**2–5**).

The ^{13}C NMR signals of the free ligand (**1**) were observed at 184.99, 164.11, 142.36–137.10, 48.83–32.61 and 8.99 ppm, due to the δ(NH—C=S), δ(C=N), δ(aromatic ring), δ(cyclohexyl ring) and δ(CH$_3$), respectively. After complexation, the carbon signals of the N=C—S group shifted to up field at 181.10–179.22 ppm in the complexes (**2–5**) in compared to the ligand (**1**), indicating participation of the N=C—S group in coordination to tin(IV) atom. The chemical shifts of carbon in C=N and CH$_3$ in the free ligand (**1**) were observed at 164.11 and 8.99 ppm which were shifted to down field region at 174.45–164.11 and 18.10–15.88 ppm, respectively, in the complexes (**2–5**), indicating the azomethine-N is coordinated to the tin(IV) moiety. The δ value of carbon atoms in the cyclohexyl ring and aromatic ring did not have much change in the complexes (**2–5**) as compared to the free ligand. The butyl group attached to the organotin(IV) moiety in complex **3** gave four resonance signals at 32.88, 26.32, 24.88 and 20.73 ppm. The sharp signal attributed to the methyl group attached to the tin(IV) core appeared at 12.59 ppm in complex **2**.

^{119}Sn NMR chemical shifts of the complexes (**2–5**) were recorded in CDCl$_3$ solution. ^{119}Sn NMR spectroscopy gives significant information to determine the coordination number around the tin atom. The ^{119}Sn NMR of all the complexes (**2–5**) shows only one resonance signal in the range of −170.10 to −188.94 ppm. The occurrence of ^{119}Sn chemical shifts in these areas indicates five-coordinated environment in organotin(IV) derivatives around the central tin atoms [39,40].

3.4. X-ray crystallography diffraction analyses

Crystals suitable for X-ray diffraction studies of the diphenyltin(IV) complex (**5**) were grown by slow evaporation of chloroform/methanol (1:1) at room temperature. The compound crystallized into a monoclinic lattice with space group symmetry $P2_1/n$ with one molecule per asymmetric unit. The molecular structure of diphenyltin(IV) complex (**5**) with atom numbering scheme

is shown in Fig. 1. The main crystal parameters are reported in Table 1. Selected bond lengths and bond angles are given in Table 2. The molecular structure of diphenyltin(IV) complex (**5**) was found to be a distorted trigonal bipyramidal arrangement. The meridional plane of the tin(IV) complex (**5**) is taken up by the azomethine nitrogen (N10A) and two phenyl rings from the centre tin(IV). The sum of the bond angles N10A—Sn1A—ClC (117.32(10)°), C1C—Sn1A—C1B (116.81(11)°) and C1B—Sn1A—N10A (125.57(9)°) is 359.7° showing thiosemicarbazone moiety is in the same plane of the Sn atom. The axial plane is composed of the enolic oxygen (O1A) and the sulfur (S13A) atoms of the ligand. In diphenyltin(IV) complex (**5**), the largest bond angle involving the tin(IV) atom was O1A—Sn1A—S13A (157.76(5)°), indicating strong deviation from the ideal value of 180°. The bond angle of O1A—Sn1A—N10A is 80.77(8)° whereas the bond angle of N10A—Sn1A—S13A is 77.30(6); therefore the total of these two angles is 158.07° showing deviation from the ideal value 180°. Thus, the geometric results support the tin(IV) complex (**5**) rendered distorted trigonal bipyramidal configuration. The Sn1A—N10A bond length is 2.211(2) Å which is close to the sum of covalent radii of Sn and N (2.15 Å), but is considerably less than the sum of the Van der Waals radii (3.75 Å) [39], indicating azomethine nitrogen (N10A) was bonded very firmly with the tin (Sn1A) atom. The Sn1A—O1A bond distance is 2.08 Å which is almost similar to the covalent radii of tin and oxygen (2.10 Å) [41], indicating enolic oxygen (O1A) is strongly coordinated to the tin(IV) core. These bond lengths are comparable with the published diphenyltin(IV) complex [Ph$_2$Sn(2,6-pdc)] [42]. The Sn1A—S13A bond distance is 2.5026 (7)Å which is close to the sum of the covalent radii of tin and sulfur 2.42 Å [43], but much smaller than the Van der Waals radii 4.0 Å [44], and reveals that the S atom is coordinated to the Sn core in the thiolate form and also indicated the formation of Sn—S bond. The bond length of Sn1A—C1C (2.138(3) Å) and Sn1A—C1B (2.141(3) Å) are slightly shorter than the non-polar covalent radii of Sn—C (2.17 Å) [41], but the values are consistent with those reported in other diorganotin(IV) complexes [45,46]. The bond distances C12A—S13A (1.761(3) Å) and N10A—N11A (1.384(3) Å) were consistent with single bonds, whereas a double bond character is evident in C12A—N11A ((1.315(3) Å) and C8A—N10A (1.311(3) Å) bonds.
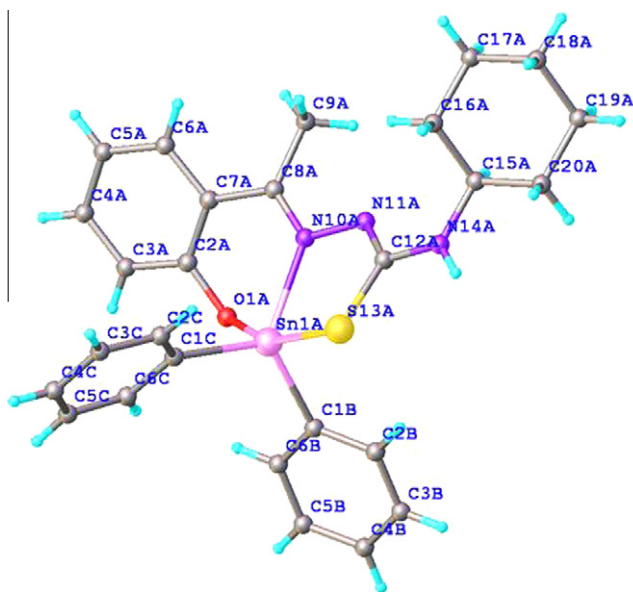
Table 1
Summary of crystal data and structure refinement parameters for complex (**5**).

Compound	[Ph$_2$Sn(dact)] (**5**)
Empirical formula	C$_{27}$H$_{29}$N$_3$OSSn
Formula weight	562.28
T (K)	150
Crystal system	monoclinic
Space group	P2$_1$/n
Unit cell dimensions	
a (Å)	9.4030(4)
b (Å)	19.0623(9)
c (Å)	14.5854(7)
α (°)	90.00
β (°)	102.032(4)
γ (°)	90.00
V (Å^3)	2556.88(19)
Z	4
D_{calc} (mg/m^3)	1.461
Wavelength (Å)	0.7107
Radiation type λ (Å)	MoKα
$F(000)$	1144
Crystal size (mm)	0.2168 × 0.0948 × 0.0723
Crystal color	colorless
Scan range θ (°)	3.5030–28.5104
Absorption coefficient (μ) (mm^{-1})	1.105
Maximum and minimum transmission	0.947 and 0.849
Goodness-of-fit (GOF) on F^2	1.034
Data/restrains/parameters	5198/0/299
Final R indices [$I > 2\sigma(I)$]	$R_1 = 0.0315$, $wR_2 = 0.0592$
R indices (all data)	$R_1 = 0.0417$, $wR_2 = 0.0645$

Table 2
Selected bond lengths (Å) and angles (°) of [Ph$_2$Sn(dact)] (**5**).

Bond lengths (Å)			
Sn1A–S13A	2.5026(7)	N10A–N11A	1.384(3)
Sn1A–N10A	2.211(2)	N10A–C8A	1.311(3)
Sn1A–O1A	2.0871(17)	N11A–C12A	1.315(3)
Sn1A–C1B	2.141(3)	N14A–C12A	1.334(3)
Sn1A–C1C	2.138(3)	N14A–C15A	1.467(3)
S13A–C12A	1.761(3)	C8A–C9A	1.500(4)
O1A–C2A	1.347(3)	C8A–C7A	1.466(4)
Bond angles (°)			
O1A–Sn1A–S13A	157.76(5)	C1B–Sn1A–N10A	125.57(9)
O1A–Sn1A–N10A	80.77(8)	C1C–Sn1A–N10A	117.32(10)
O1A–Sn1A–C1B	89.88(9)	C1C–Sn1A–C1B	116.81(11)
O1A–Sn1A–C1C	94.41(9)	C1C–Sn1A–S13A	98.87(7)
N10A–Sn1A–S13A	77.30(6)	C12A–S13A–Sn1A	94.52(9)
C1b–Sn1AS13A	99.81(8)	C2A–O1A–Sn1A	118.13(18)

3.5. Artemia cytotoxicity

A brine shrimp (*A. salina*) lethality bioassay was carried out to investigate the preliminary toxicity of ligand (**1**) and its organotin(IV) complexes (**2–5**). The *A. salina* toxicity of **1–5** compounds
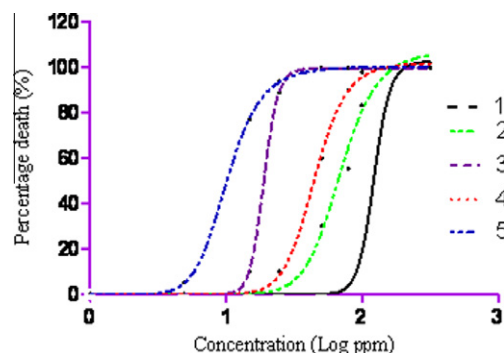
Fig. 1. Molecular structure of [Ph$_2$Sn(dact)] (**5**).

Fig. 2. Results of *Artemia* toxicity test of compounds **1–5**.

Table 3
The LC$_{50}$ of the ligand (**1**) and its organotin(IV) complexes (**2–5**).

Complexes		LC$_{50}$ (ppm)
H$_2$dact	**1**	120.89
[MeSnCl(dact)]	**2**	37.17
[BuSnCl(dact)]	**3**	61.20
[PhSnCl(dact)]	**4**	18.21
[Ph$_2$Sn(dact)]	**5**	9.87

Table 4
Antibacterial activity[a] of the free ligand (**1**) and its organotin(IV) complexes **2–5** (inhibition zone in mm).

Bacterium	1	2	3	4	5	R
Escherichia coli	–	16	14	15	19	28
Staphylococcus aureus	–	14	11	16	17	31
Enterobacter aerogenes	–	12	–	11	21	32
Salmonella typhi	–	15	10	17	23	26

[a] Concentration used: 2 mg/ml of DMSO, R = standard drug: doxycycline, dash indicate inactivity.

are presented in Fig. 2 and the LC$_{50}$ values are shown in Table 3. The ligand (**1**) has a higher LC$_{50}$ value compared to all its organotin(IV) complexes (**2–5**). From the results, it is evident that all the organotin(IV) complexes displayed potent cytotoxic activity against *A. salina*. The highest toxicity was shown by diphenyltin(IV) complex (**5**) whose LC$_{50}$ value is 9.87 ppm while the lowest toxicity is shown by compound (**3**) whose LC$_{50}$ value is 61.20 compared to the free ligand (**1**). It is evident that bulky organo groups may enhance the dissociation of the tin(IV) complex to form ionic compounds and enhance the permeation of the compound through the membrane cell [47].

3.6. Antibacterial activity

The synthesized ligand (**1**) and its organotin(IV) complexes (**2–5**) were screened against *Escherichia coli*, *Staphylococcus aureus*, *Enterobacter aerogenes* and *Salmonella typhi* to assess their antibacterial activity. The results of the antibacterial studies are given in Table 4. The free ligand (**1**) was found to be inactive against all bacteria. The screening results exhibited that complexes (**2–5**) showed higher activity against various bacteria but comparatively lower activity than the reference drug. Based on the results, diphenyltin(IV) complex (**5**) displayed higher antibacterial activity than the monoorganotin(IV) complexes (**2–4**) against tested bacteria. PhSn(IV) complex (**4**) shows enhanced activity compared to the corresponding MeSn(IV) (**2**)/BuSn(IV) (**3**) complexes. Therefore, changing the organotin(IV) groups must play a significant role in these compounds growth inhibitory activity. In addition, the increased antibacterial activity of organotin(IV) complexes (**2–5**) can be explained on the basis of chelation theory. In organotin(IV) complexes, on chelation the polarity of the tin ion will be reduced to a greater extent due to the overlap of the substituted thiosemicarbazone ligand orbital and partial sharing of the positive charge of the tin ion with donor groups. The activity might be due to the increasing lipophilic nature of these complexes resulting from the metal chelation. The electron delocalization in the chelate ring increases the lipophilic character of the metals chelate. Therefore, for the complexes studied in the present work, the results are consistent with those reported data for the biological activities in other organotin(IV) complexes [48]. It is suggested that antibacterial activity of the organotin(IV) complexes (**2–5**) are due to either killing the microbes or inhibiting their multiplication by blocking their active sites [49].

4. Conclusion

Four new organotin(IV) complexes of 2-hydroxyacetophenone-*N*(4)-cyclohexylthiosemicarbazone have been reported and fully characterized by UV–Vis, FT-IR, ^{1}H, ^{13}C and ^{119}Sn NMR spectral studies. The ligand (H$_2$dact) exists in thione form in a solid state but it takes on a thiol form when it is in solution. The results obtained from the spectroscopic characterization support the proposed five coordinated structures of the complexes (**2–5**). X-ray crystallographic diffraction has revealed that complex **5** is rendered into a distorted trigonal bipyramidal geometry. Biological studies showed that all the organotin(IV) complexes (**2–5**) are more potent antibacterial and cytotoxic agents than their free ligand (**1**), while the diphenyltin(IV) complex (**5**) is more active than the other organotin(IV) derivatives (**2–4**).

Appendix A. Supplementary material

Supplementary material CCDC 828343 contains the supplementary crystallographic data for [Ph$_2$Sn(dact)] (**5**). These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via http://www.ccdc.cam.ac.uk/data_request/cif. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.ica.2012.01.020.

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