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Synthesis, Characterization, and Antibacterial Activities of Organotin(IV) Complexes with 2-Acetylpyridine-*N*(4)-cyclohexylthiosemicarbazone (HAPCT)

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ABSTRACT: *The reaction of 2-acetylpyridine-N(4)-cyclohexylthiosemicarbazone [(HAPCT), (**1**)] ligand with organotin(IV) chloride(s) afforded the five new organotin(IV) complexes: [$MeSnCl_2$(APCT)] (**2**), [$BuSnCl_2$(APCT)] (**3**), [$PhSnCl_2$(APCT)] (**4**), [Me_2SnCl(APCT)] (**5**), and [Ph_2SnCl(APCT)] (**6**). The ligand (**1**) and its organotin(IV) complexes (**2–6**) have been synthesized and characterized by CHN analyses, molar conductivity, UV–vis, FT IR, ^1H, ^{13}C, and ^{119}Sn NMR spectral studies. The single crystal X-ray diffraction studies indicated that [$PhSnCl_2$(APCT)] (**4**) is six coordinated and strongly adopts a distorted octahedral configuration with the coordination through pyridine-N, azomethine-N, and thiolato-S atoms of the ligand. The compound crystallizes into a monoclinic lattice with the space group* P*21/*n*. The ligand (**1**) and its organotin(IV) complexes (**2–6**) were assayed for in vitro antibacterial activity against* Staphylococcus aureus, Escherichia coli, Enterobacter aerogenes, *and* Salmonella typhi. *The screening results have shown that the organotin(IV) complexes (**2–6**) have better antibacterial activity than the free ligand. Furthermore, it has been shown that the diphenyltin(IV) derivative (**6**) exhibits significantly better activities than the other organotin(IV) derivatives (**2–5**).* © 2012 Wiley Periodicals, Inc. Heteroatom Chem. 24:43–52, 2013; View this article online at wileyonlinelibrary.com. DOI 10.1002/hc.21061

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INTRODUCTION

Thiosemicarbazone derivatives have attracted considerable attention in the past few decades, because of their potential biological (viz., antibacterial and antitumor) activities [1–3]. The heterocyclic NNS donor ligands play an important role in the development of coordination chemistry as they readily form complexes with most of metal ions [4–6]. Thiosemicarbazones and their organotin(IV) complexes are of considerable interest due to their

potential biological (namely, antiviral and antitumor) activities as well as their industrial and agricultural applications [7–10]. Beraldo and Gambino have investigated the pharmacological profiles of 2-formyl, 2-acetyl, and 2-benzoylpyridine thiosemicarbazones [11]. The organotin compound has antiproliferative ability and antitumor activity on mammalian cells both in vitro and in vivo [12, 13]. Roberto et al. have reported the synthesis and the coordination mode of interaction of the tin(IV) tetrahalide with 2-formylpyridine thiosemicarbazone, in which the geometry about tin(IV) is best described as roughly octahedral [14]. Among main-group organometallic compounds, organotin has been receiving considerable attention in recent years [15], for some of them are biologically active or have been used as reagents or catalysts in organic reactions [16]. Our group recently reported the structural and biological properties of organotin(IV) complexes with substituted thiosemicarbazones [17–19]. The results reveal that *N*(4)-cyclohexylthiosemicarbazones derived from 2-benzoylpyridine and pyruvic acid and their organotin(IV) complexes show significant antibacterial activities. To fortify this idea and keeping in view the biological potential of organotins, we synthesized five new organotin(IV) complexes (**2–6**) with 2-acetylpyridine-*N*(4)-cyclohexylthiosemicarbazone [HAPCT, (**1**)]. Here we report the synthesis, characterization, and antibacterial activities of organotin(IV) complexes (**2–6**). Single-crystal X-ray crystal structures of complex **4** also described here. These compounds proved to be effective antibacterial agents. This study will be helpful in designing new organotins of pharmaceutical value.

TABLE 1 Crystal Data and Refinement Parameters for $[PhSnCl_2(APCT)]$ (**4**)

Compound	*[PhSnCl$_2$(APCT)] (4)*
Empirical formula	C_{20} H_{24} Cl_2N_4SSn
Formula weight	542.10
Temperature (K)	150
Crystal system	Monoclinic
Space group	*P*21/*n*
Unit cell dimensions	
a (Å)	11.52126(19)
b (Å)	13.37948(16)
c (Å)	15.2648(2)
α (°)	90.00
β (°)	109.6302(17)
γ (°)	90.00
Volume (Å^3)	2216.29(6)
Z	4
Calculated density (mg/m^3)	1.625
Wavelength (Å)	0.71073
Radiation type λ(Å)	Mo Kα
F(000)	1088
Crystal size (mm)	0..37 × 0.21 × 0.15
Crystal color	Orange
Scan range θ (°)	2.417–28.986
Absorption coefficient (μ) (mm^{-1})	1.502
Maximum and minimum transmission	0.7983 and 0.7295
Goodness-of-fit on F^2	0.9906
Data/restrains/ parameters	5354/0/253
Final *R* indices [$I > 2\sigma(I)$]	$R_1 = 0.0207$, $wR_2 = 0.0456$
R indices (all data)	$R_1 = 0.0246$, $wR_2 = 0.0479$

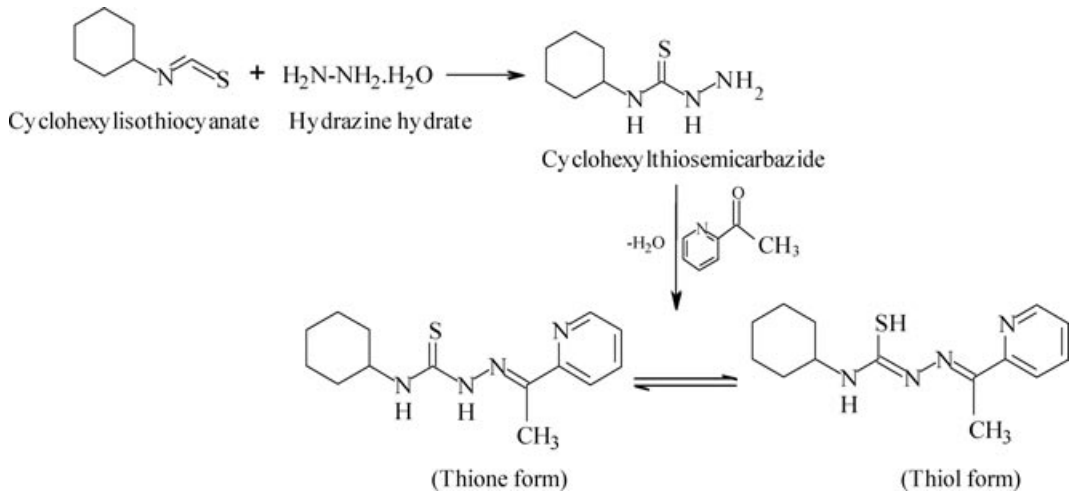
EXPERIMENTAL

General Procedure

All reagents were purchased from Fluka, Aldrich, and JT Baker. All solvents were purified according to standard procedures [20]. UV–vis spectra were recorded in DMSO solution with a Perkin Elmer Lambda 25 UV–vis spectrophotometer. Infrared spectra were recorded on KBr disks using a Perkin Elmer Spectrum GX Fourier Transform spectrometer in the range of 4000–370 cm^{-1} at room temperature. ^{1}H, ^{13}C NMR, and ^{119}Sn NMR spectra were recorded on a Jeol 500 MHz NMR spectrophotometer relative to $SiMe_4$ and Me_4Sn using $CDCl_3$ as the solvent. CHN analyses were obtained with a Flash EA 1112 series CHN elemental analyzer. Molar conductivity measurements were carried out with a Jenway 4510 conductivity meter using a DMSO solvent mode. The crystallographic data and structure refinement parameters for complex 4 are given in Table 1. An orange prismatic crystal of compound **4** was measured at 150 K on a CrysAlis CCD (Oxford diffraction, 2002) diffractometer with graphite monochromated Mo Kα radiation ($\lambda = 0.71073$ Å). CrysAlis RED; program(s) was used to solve the structure, and SHELXS97 (Sheldrick, 2008) program(s) was used to refine structure: Positional and anisotropic atomic displacement parameters were refined for all non-hydrogen atoms. Hydrogen atoms were placed in calculated positions.

Synthesis of N(4)-Cyclohexylthiosemicarbazide

N(4)-Cyclohexylthiosemicarbazide has been reported earlier in the literature [17, 18]. *N*(4)-Cyclohexylthiosemicarbazide was synthesized as follows: Cyclohexylisothiocyanate (1.41 g, 10 mmol) in 4 mL of ether was added dropwise into 4 mL of ether solution of hydrazine hydrate (2 g, 40 mmol). The



SCHEME 1 Synthesis of 2-acetylpyridine-*N*(4)-cyclohexylthiosemicarbazone [HAPCT] (**1**).

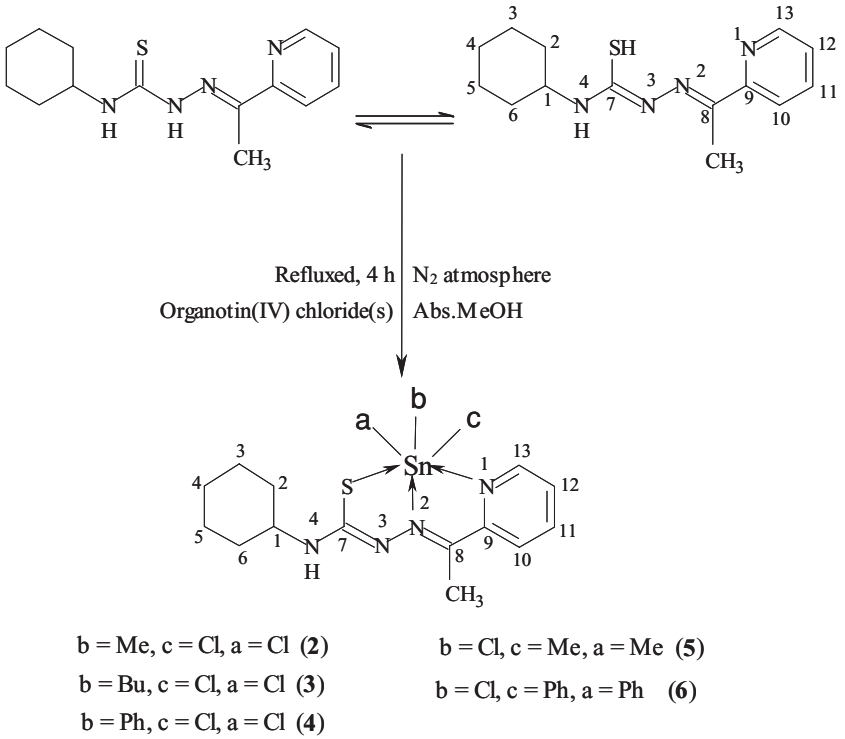
mixture was stirred vigorously for 5 h. Then, 5 mL of petroleum ether was added into the resulting solution and stirred for another 1 h and white precipitate was formed. The white precipitate was filtered, washed with a small amount of cool diethyl ether, and dried in vacuo over silica gel. Yield: 2.12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

*Synthesis of 2-Acetylpyridine-N(4)-cyclohexylthiosemicarbazone [HAPCT] (**1**)*

N(4)-Cyclohexylthiosemicarbazide (0.51 g, 3 mmol) was dissolved in 10 mL of dry methanol before mixing it with 10 mL of dry methanolic solution of 2-acetylpyridine (0.363 g, 3 mmol). The resulting mixture was refluxed for 4 h (Scheme 1) and cooled to room temperature. White microcrystals were formed and filtered off. The microcrystals were washed several times with a small amount of cool methanol subsequent with cool hexane. The microcrystals were recrystallized from methanol and dried in vacuo over silica gel. Yield: 0.643 g, 72%: mp.: 180–182°C: UV–visible (DMSO) $\lambda_{max/nm}$: 325, 327, 382: FT-IR (KBr, cm^{-1}) ν_{max}: 3335 (s, NH), 2938, 2845 (s, cyclohexyl), 1583 (w, C=N), 984 (m, N—N), 1358, 865 (w, C=S), 608 (m, pyridine in plane). ^{1}H NMR ($CDCl_3$, ppm) δ: 10.30 (*s*, 1H, N4-H), 8.57 (d, J = 5.20 Hz, 1H, pyridine ring C13-H), 8.25 (t, J = 5.24 Hz, 1H, pyridine ring C11-H), 8.13 (d, J = 5.19 Hz, 1H, pyridine ring C10-H), 7.81 (t, J = 5.27 Hz, 1H, pyridine ring C12-H), 7.39 (s, 1H, CyC1-H), 2.37 (s, 3H, CH_3—C=N), 2.24–1.71 (m, 10H, Cy-H), 1.8 (SH). ^{13}C NMR ($CDCl_3$, ppm) δ: 190.07 (NH—C=S), 160.03 (C=N), 147.32–136.29 (pyridine ring), 53.11–26.49 (cyclohexyl), 10.01 (CH_3). Anal. Calcd for $C_{14}H_{20}N_4S$: C, 60.83; H, 7.29; N, 20.26%. Found: C, 60.53; H, 7.11; N, 20.01%.

*Synthesis of [$MeSnCl_2$(APCT)] (**2**)*

HAPCT (**1**) (0.28 g, 1.0 mmol) was dissolved in absolute methanol (10 mL) under a nitrogen atmosphere in an Schlenk round-bottomed flask. Then, a methanolic solution of methyltin(IV) trichloride (0.24 g, 1.0 mmol) was added dropwise and resulted in a yellow solution. The resulting reaction mixture was refluxed for 4 h (Scheme 2) and cooled to room temperature. The yellow microcrystals were obtained from slow evaporation of the resulting solution at room temperature. The microcrystals were filtered off, washed with a small amount of cold methanol, and dried in vacuo over silica gel. Yield: 0.447 g, 83%: mp.: 278–280°C: molar conductance (DMSO) Ω^{-1} cm^2 mol^{-1}: 9.28: UV–visible (DMSO) $\lambda_{max/nm}$: 325, 327, 382, 465: FT-IR (KBr, cm^{-1}) ν_{max}: 3256 (s, NH), 2928, 2854 (s, cyclohexyl), 1596 (m, C=N—N=C), 1025 (w, N—N), 1347, 830 (m, C—S), 649 (w, pyridine in plane), 567 (w, Sn—C), 477 (w, Sn—N). ^{1}H NMR ($CDCl_3$, ppm) δ: 10.29 (*s*, 1H, N4-H), 8.86 (d, J = 5.18 Hz, 1H, pyridine ring C13-H), 8.80 (t, J = 5.22 Hz, 1H, pyridine ring C11-H), 8.77 (d, J = 5.20 Hz, 1H, pyridine ring C10-H), 8.14 (t, J = 5.25 Hz, 1H, pyridine ring C12-H), 7.39 (s, 1H, CyC1-H), 2.45 (s, 3H, CH_3—C=N), 2.19–1.71 (m, 10H, Cy-H), 1.26 (s, 3H, Sn—CH_3), ^{2}J[(^{119}Sn, ^{1}H) = 93.4 Hz]. ^{13}C NMR ($CDCl_3$, ppm,) δ: 180.88 (N=C—S), 172.619 (C=N), 144.11–140.21 (pyridine ring), 53.35–26.33 (cyclohexyl), 14.28 (CH_3), 17.88 (Sn-CH_3), [J(^{13}C–^{119}Sn) = 812 Hz)]. ^{119}Sn NMR ($CDCl_3$, ppm) δ: –328,



SCHEME 2 Reaction scheme for the synthesis of organotin(IV) complexes (**2–6**).

Anal. Calcd for $C_{15}H_{22}N_4SSnCl_2$: C, 37.53; H, 4.62; N, 11.67. Found: C, 37.23; H, 4.39; N, 11.55.

The other complexes (**3–6**) were synthesized using a similar procedure of organotin(IV) complex (**2**) using appropriate organotin(IV) chloride(s) (Scheme 2).

*Synthesis of [$BuSnCl_2$(APCT)] (**3**)*

Yield: 0.438 g, 78%: mp.: 248–250°C: molar conductance (DMSO) Ω^{-1} cm^2 mol^{-1}: 8.80: UV–visible (DMSO) $\lambda_{max/nm}$: 320, 376, 385, 400: FT-IR (KBr, cm^{-1}) ν_{max}: 3308 (s, NH), 2931, 2855 (s, cyclohexyl), 1602 (m, C=N—N=C), 1020 (w, N—N), 1345, 833 (m, C—S), 652 (w, pyridine in plane), 570 (w, Sn—C), 475 (w, Sn—N). ^{1}H NMR ($CDCl_3$, ppm) δ: 10.28 (*s*, 1H, N4-H), 8.81 (d, J = 5.19 Hz, 1H, pyridine ring C13-H), 8.79 (t, J = 5.21 Hz, 1H, pyridine ring C11-H), 8.75 (d, J = 5.20 Hz, 1H, pyridine ring C10-H), 8.45 (t, J = 5.24 Hz, 1H, pyridine ring C12-H), 7.25 (s, 1H, CyC1-H), 2.58 (s, 3H, CH_3—C=N), 2.38–1.76 (m, 10H, Cy-H), 1.74–1.72 (t, 2H, Sn—CH_2—CH_2—CH_2—CH_3), 1.53–1.48 (m, 2H Sn—CH_2—CH_2—CH_2—CH_3), 1.38–1.22 (m, 2H, Sn—CH_2—CH_2—CH_2—CH_3), 0.98–0.84 (t, 3H, Sn—CH_2—CH_2—CH_2—CH_3). ^{13}C NMR ($CDCl_3$, ppm) δ: 182.23 (N=C—S), 173.61 (C=N), 145.15–141.25 (pyridine ring), 53.35–36.31 (cyclohexyl), 12.24 (CH_3), 32.81, 28.15, 26.35, 17.77 (Sn-Bu). ^{119}Sn NMR ($CDCl_3$, ppm) δ: –324. Anal. Calcd for $C_{18}H_{28}N_4SSnCl_2$: C, 41.40; H, 5.40; N, 10.73. Found: C, 41.24; H, 5.17; N, 10.59.

*Synthesis of [$PhSnCl_2$(APCT)] (**4**)*

Yield: 0.45 g, 77%: mp.: 250–252°C: molar conductance (DMSO) Ω^{-1} cm^2 mol^{-1}: 8.70: UV–visible (DMSO) $\lambda_{max/nm}$: 318, 354, 382, 403: FT-IR (KBr, cm^{-1}) ν_{max}: 3414 (s, NH), 2931, 2854 (s, cyclohexyl), 1603 (m, C=N—N=C), 1019 (w, N—N), 1334, 829 (m, C—S), 695 (w, pyridine in plane), 574 (w, Sn—C), 472 (w, Sn—N). ^{1}H NMR ($CDCl_3$, ppm) δ: 10.30 (*s*, 1H, N4-H), 8.84 (d, J = 5.17 Hz, 1H, pyridine ring C13-H), 8.80 (t, J = 5.23 Hz, 1H, pyridine ring C11-H), 8.61 (d, J = 5.19 Hz, 1H, pyridine ring C10-H), 8.35 (t, J = 5.26 Hz, 1H, pyridine ring C12-H), 8.11 (s, 1H, CyC1-H), 7.52–7.35 (m, 5H, phenyl ring), 2.73 (s, 3H, CH_3—C=N), 2.13–1.29 (m, 10H, Cy-H). ^{13}C NMR ($CDCl_3$, ppm) δ: 180.80 (N=C—S), 172.28 (C=N), 143.94–141.79 (pyridine ring), 135.97–128.80 (phenyl ring), 53.35–32.03 (cyclohexyl), 16.11 (CH_3). ^{119}Sn NMR ($CDCl_3$, ppm) δ: –322. Anal. Calcd for $C_{20}H_{24}N_4SSnCl_2$: C, 44.31; H, 4.46; N, 10.33. Found: C, 44.11; H, 4.31; N, 10.16.

*Synthesis of [Me_2SnCl(APCT)] (**5**)*

Yield: 0.36 g, 72%: mp.: 215–217°C: molar conductance (DMSO) Ω^{-1} cm^2 mol^{-1}: 11.36: UV–visible (DMSO) $\lambda_{max/nm}$: 322, 329, 381, 454: FT-IR (KBr, cm^{-1}) ν_{max}: 3251 (s, NH), 2927, 2855 (s, cyclohexyl), 1596 (m, C=N—N=C), 1021 (w, N—N), 1345, 829 (m, C—S), 649 (w, pyridine in plane), 587 (w, Sn—C), 478 (w, Sn—N). ^{1}H NMR ($CDCl_3$, ppm) δ: 10.31 (*s*, 1H, N4-H), 8.83 (d, J = 5.16 Hz, 1H, pyridine ring C13-H), 8.79 (t, J = 5.20 Hz, 1H, pyridine ring C11-H), 8.58 (d, J = 5.18 Hz, 1H, pyridine ring C10-H), 8.32 (t, J = 5.28 Hz, 1H, pyridine ring C12-H), 7.73 (s, 1H, CyC1-H), 2.50 (s, 3H, CH_3—C=N), 2.33–1.71 (m, 10H, Cy-H), 1.17 (s, 6H, Sn-CH_3), ^{2}J[(^{119}Sn, ^{1}H) = 112 Hz]. ^{13}C NMR ($CDCl_3$, ppm) δ: 181.11 (N=C—S), 173.32 (C=N), 144.25–141.61 (pyridine ring), 54.35–26.33 (cyclohexyl), 15.39 (CH_3), 18.46 (Sn—CH_3), [J(^{13}C–^{119}Sn) = 865 Hz)]. ^{119}Sn NMR ($CDCl_3$, ppm) δ: –341. Anal. Calcd for $C_{16}H_{25}N_4SSnCl$: C, 41.81; H, 5.48; N, 12.18. Found: C, 41.77; H, 5.44; N, 12.16.

*Synthesis of [Ph_2SnCl(APCT)] (**6**)*

Yield: 0.423 g, 68%; mp.: 190–192°C: molar conductance (DMSO) Ω^{-1} cm^2 mol^{-1}: 9.84; UV–visible (DMSO) $\lambda_{max/nm}$: 325, 334, 393, 400; FT-IR (KBr, cm^{-1}) ν_{max}: 3357 (s, NH), 2929, 2851 (s, cyclohexyl), 1604 (m, C=N—N=C), 1020 (w, N—N), 1299, 828 (m, C—S), 693 (w, pyridine in plane), 548 (w, Sn—C), 455 (w, Sn—N). ^{1}H NMR ($CDCl_3$, ppm) δ: 10.31 (*s*, 1H, N4-H), 8.84 (d, J = 5.16 Hz, 1H, pyridine ring C13-H), 8.80 (t, J = 5.21 Hz, 1H, pyridine ring C11-H), 8.63 (d, J = 5.24 Hz, 1H, pyridine ring C10-H), 8.38 (t, J = 5.26 Hz, 1H, pyridine ring C12-H), 7.52 (s, 1H, CyC1-H), 7.42–7.25 (m, 10H of phenyl ring), 2.53 (s, 3H, CH_3—C=N), 2.07–1.61 (m, Cy-H). ^{13}C NMR ($CDCl_3$, ppm) δ: 182.36 (N=C—S), 172.19 (C=N), 143.87–141.05 (pyridine ring), 134.87–127.50 (phenyl ring), 52.35–33.15 (cyclohexyl), 17.05 (Sn-Ph), [J(^{13}C–^{119}Sn) = 986 Hz)]. ^{119}Sn NMR ($CDCl_3$, ppm) δ: –335. Anal. Calcd for $C_{26}H_{29}N_4SSnCl$: C, 53.49; H, 5.00; N, 9.59. Found: C, 53.31; H, 4.82; N, 9.43.

Antibacterial Test

The antibacterial test of synthesized ligand (**1**) and its organotin(IV) complexes (**2–6**) was carried out using the agar well diffusion method [21]. 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 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. Sterile paper disks with 6 mm diameter were placed on the agar at equal distance. The recommended concentration of the test sample (2 mg/mL in DMSO) was introduced individually to each of the disks. 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.

RESULTS AND DISCUSSION

Synthesis

2-Acetylpyridine-*N*(4)-cyclohexylthiosemicarbazone [HAPCT, (**1**)] was synthesized by the condensation reaction of *N*(4)-cyclohexylthiosemicarbazide and 2-actylpyridine in absolute methanol. It has two tautomers within the structure, existing as either a thione or a thiol tautomer (Scheme 1). Five new organotin(IV) complexes (**2–6**) were obtained in good yields by the equimolar reaction of organotin(IV) chloride(s) with HAPCT (**1**) (Scheme 2). The physical and analytical data of **1–6** are given in the Experimental section. All organotin(IV) compounds were stable under N_2 atmosphere and soluble in CH_2Cl_2, $CHCl_3$, DMF, DMSO, and MeCN solvents. The molar conductivity of the organotin(IV) complexes (**2–6**) in DMSO is 11.36–8.70 Ω^{-1} cm^2 mol^{-1} showing that the complexes are nonelectrolytes [22].

UV–Visible Spectra

The UV–Vis spectra analyses of ligand (**1**) and its organotin(IV) complexes (**2–6**) were carried out in DMSO (10^{-4} M) at room temperature. The electronic spectrum of the ligand (**1**) showed three absorption bands at 325, 327, and 382 nm correspond to the n–π^* transition of the pyridine ring, azomethine, thiolate functions, and the benzene group, respectively [23]. After complexation, the complexes (**2–6**) showed four absorption bands at 318–325, 327–376, 381—393, and 400–465 nm, respectively. In the electronic spectra of complexes (**2–6**), the intraligand transition is shifted to higher wavelength as a result of coordination. The new absorption at 400–465 nm,

observed in the spectra of organotin(IV) complexes **(2–6)**, is assigned to ligand → metal charge transfer [24]. The shift of the λ_{max} band from the ligand to the complexes is a clear indication that coordination occurred between tin(IV) and ligand.

Infrared Spectra

The free ligand (**1**) showed absorption bands at 3335, 2938, 2845, 1583, 984, 1358, 865, and 608 cm^{-1} due to ν(NH), ν(cyclohexyl), ν(C=N), ν(N—N), ν(C=S), and the pyridine ring in plane, respectively. After complexation, there are significant changes with respect to the free ligand (**1**) and its organotin complexes (**2–6**). The newly formed C=—N=C bond showed medium to strong absorption peaks within the range of 1596–1604 cm^{-1} in the spectra of the complexes (**2–6**), indicating the coordination of the azomethine nitrogen to the tin(IV) atom [25]. The ν(N—N) band of the free ligand (1) at 984 cm^{-1} is shifted to higher frequencies at 1019–1028 cm^{-1} in the organotin(IV) complexes (**2–6**), again supported the coordination of azomethine nitrogen to the Sn(IV) ion [26]. The stretching and bending frequency of the ν(CS) bands observed at 1358 and 865 cm^{-1} in the spectrum of free ligand (**1**) are shifted to lower frequencies at 1299–1347 and 828–833 cm^{-1} in the spectra of the complexes (**2–6**), indicating the coordination of the sulfur atom in the thiolate form [27]. A sharp band at 608 cm^{-1} of the pyridine ring in plane in the spectrum of the free ligand (**1**) is shifted to higher frequencies at 649–695 cm^{-1} in the complexes (**2–6**), suggesting the coordination of the pyridine ring nitrogen to tin(IV) ion [28]. Characteristically one new band was observed at 455–478 cm^{-1} in the spectra of the complexes **(2–6)**, suggesting the presence of Sn—N bonding in their structure [29]. There are IR bands observed at 548–587 cm^{-1} tentatively assigned to the ν(Sn—C) mode of the complexes (**2–6**). The IR observation indicated the coordination of ligand (**1**) to the tin(IV) core of the complexes (**2–6**) via pyridine-N, azomethine-N, and thiolato-S atoms. These observations have also been confirmed by X-ray single structures analyses of complex **4**.

^{1}H, ^{13}C, and ^{119}Sn NMR Spectra

The ^{1}H NMR spectral assignments of ligand (**1**) and its organotin(IV) complexes (**2–6**) were carried out and interpreted based on the atom labeling as shown in Scheme 2. ^{1}H NMR spectrum of free ligand (**1**) showed a singlet at 10.30 ppm, corresponding to the resonance signal of N4-H. The resonance signal at 1.8 ppm is assigned to the SH proton. The pyridine ring protons gave four resonance signals at 8.57, 8.25, 8.13, and 7.81 ppm corresponded to the C13-H, C11-H, C10-H, and C12-H, respectively. A singlet at 7.39 ppm corresponded to CyC1-H. The resonance signal at 2.37 ppm is due to CH_3—C=N. After complexation, the resonance signal of SH is absent in the spectra of the complexes (**2–6**), which suggested the deprotonation of the SH proton and confirming that the ligand coordinated to the tin(IV) in the thiolate form. The resonance signals of the C13-H in the organotin(IV) complexes (**2–6**) were observed at 8.86–8.81 ppm shifted downfield compared to the free ligand (**1**). The resonance signals of the C11-H, C10-H, and C12-H were observed at a range of between 8.80–8.79, 8.77–8.61, and 8.55–8.14 ppm, which are shifted downfield compared to the free ligand (**1**), respectively. This downfield shift also supported the observation that the pyridine ring nitrogen is coordinated to the Sn atom. The azomethine proton (CH_3—C=N) signal appears at 2.37 ppm in the free ligand (**1**), which is shifted to downfield at 2.73–2.45 ppm in the complexes (**2–6**). This downfield shift indicating the azomethine nitrogen atom is coordinated to the Sn(IV) atom [30]. The proton resonance signals for N4-H and CyC1-H are appeared at 10.31–10.27 and 8.11–7.25 ppm in the complexes (**2–6**). The multiplet signals of aromatic-H in the complexes **4** and **6** were observed at 7.52–7.25 ppm. In cyclohexyl, the equatorial protons are observed at a slightly higher chemical shift compared to that of the axial proton in the free ligand (**1**) and complexes (**2–6**). The methyl group attached to the tin(IV) core in **2** and **5** gives a singlet at 1.26 and 1.17 ppm, respectively. The ^{2}J [^{119}Sn, ^{1}H] values of the tin(IV) complex (**2**), 93.4 Hz, and tin(IV) complex (**5**), 112 Hz, supported the six-coordinated environments around the tin(IV) atom [31]. The butyl groups attached to the tin(IV) moiety in the organotin(IV) complex **3** gave four resonance signals, namely 1.75–1.65 ppm (triplet, Sn—CH_2—CH_2—CH_2—CH_3), 1.53–1.47 ppm (multiplet, Sn—CH_2—CH_2—CH_2—CH_3), 1.38–1.20 ppm (multiplet, Sn—CH_2—CH_2—CH_2—CH_3), and 0.99–0.84 ppm (triplet, Sn—CH_2—CH_2—CH_2—CH_3). ^{1}H NMR information also supported the IR data of the complexes (**2–6**).

The ^{13}C NMR signals of the free ligand (**1**) was observed at 190.07, 160.03, 147.32–136.29, 53.11–26.49, and 10.01 ppm are attributed to δ(NH—C=S), δ(C=N), δ(pyridine ring), δ(cyclohexyl ring), and δ(CH_3), respectively. After complexation, the carbon signals of the N=C—S group shifted to upfield at 182.36–180.80 ppm in the complexes (**2–6**) in

compared to the free ligand, indicating coordination of the N=C—S group with the tin(IV) atom. The chemical shifts of the C=N and CH_3 were observed at 160.03 and 10.01 ppm, respectively, in the free ligand (**1**), which were shifted to downfield at 174.60–172.19 and 17.05–12.24 ppm, respectively, in all the complexes (**2–6**). This is also supported the H_3C—C=N coordinated to the tin(IV) moiety. The resonance signals of the carbons assigned to the pyridine ring was shifted to the approximately 3.45–1.77 ppm upfield region in the complexes (**2–6**) in comparison with the free ligand (**1**), suggesting participation of the pyridine ring nitrogen in coordination to the tin(IV) atom. The coupling constant, $^1J[^{119}Sn, ^{13}C]$ is one of the key parameters in assessing the possible coordination geometries of organotin(IV) compounds in solution. The observed $[^1J(^{13}C–^{119}Sn]$ coupling constant are 812.62, 865.20, and 986.5 Hz for monomethyltin(IV) (**2**), dimethyltin(IV) (**5**), and diphenyltin(IV) (**6**) compounds, respectively. These values are in accordance with a hexa-coordinate environment about the tin atom in these compounds [31–33].

The ^{119}Sn NMR chemical shift of the complexes (**2–6**) was 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 (**2–6**) shows only one resonance signal in the range of –322.18 to –341.42 ppm. The occurrence of ^{119}Sn chemical shifts in these areas indicates six-coordinated environment in organotin(IV) derivatives around the central tin atom [34].

X-Ray Crystallography Diffraction Analyses

Suitable single crystals of phenyltin(IV) complex (**4**) were grown from methanol at room temperature. The molecular structure of the phenyltin(IV) complex (**4**) with appropriate numbering is shown in Fig. 1. Selected bond length (Å) and bond angle (°) of the complex **(4)** are summarized in Table 1. The summary of crystal data and refinement parameters of the phenyltin(IV) complex (**4**) is listed in Table 2. In the molecular structure of complex (**4**), the tin(IV) atom adopts a distorted octahedral geometry with the *N*(4)-cyclohexylthiosemicarbazone ligand coordinated to it as a mononegative tridentate chelating agent via pyridine-N, azomethine-N, and thiolato-S atoms. The equatorial position is occupied by S4, N7, and N10, and remaining sites are occupied by the two chlorine atoms and one carbon atom of the phenyl group. The Sn1–S4 bond distance is 2.4766(4) Å, which is close to the sum of the covalent radii of tin and sulfur 2.42 Å [35], but much smaller than the Van der Waals radii 4.0 Å [36], indicating the S atom is coordinated in the thiolate form. The Sn1–N7 and Sn1–N10 bond lengths are 2.2301(13) Å and 2.2544(13) Å, respectively, which is close to the sum of the covalent radii of Sn–N (2.15 Å), indicating significant bonding of the Sn1 atom with N7 and N10, respectively [37]. In

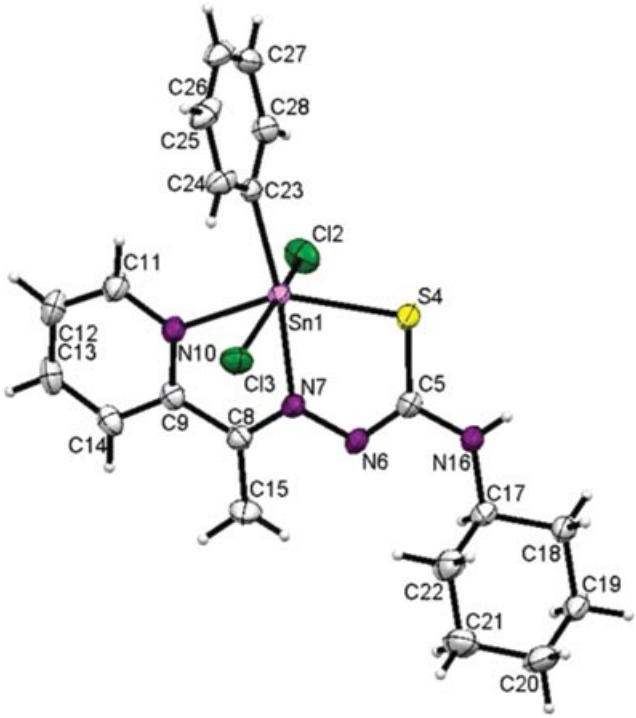


FIGURE 1 Molecular structure of $[PhSnCl_2(APCT)]$ (**4**).

TABLE 2 Selected Bond Lengths (Å) and Angles (°) of $[PhSnCl_2(APCT)]$ (**4**)

Bond Lengths (Å)			
Sn1–S4	2.4766(4)	Sn1–Cl2	2.4588(5)
Sn1–N7	2.2301(13)	Sn1–Cl3	2.5088(4)
Sn1–N10	2.2544(13)	C23–C24	1.3892(3)
N7–C8	1.298(2)	C24–C25	1.393(2)
N6–C5	1.322(2)	C25–C26	1.386(3)
C5–S4		C26–C27	1.384(3)
Sn1–C23	2.1559(16)	C27–C28	1.396(2)
Bond Angles (°)			
Cl2–Sn1–Cl3	163.986(15)	C9–N10–C11	120.21(14)
C23–Sn1–Cl2	95.97(5)	N10–C11—C12	112.09(16)
S4–Sn1–Cl2	94.162(18)	C11–C12—C13	118.43(16)
N7–Sn1–N10	151.03(4)	C12–C13—C14	119.70(16)
S4–Sn1–C23	107.95(4)	C13–C14—C9	119.39(16)
C23–Sn1–N10	101.01(5)	C14–C9–N10	120.16(15)

general, the Sn–N bond distances reported here can be considered within the usual range reported for other related tin(IV)–thiosemicarbazone complexes [38]. The bond distances N7–C8 and N6–C5 are 1.298(2) Å and 1.322(2) Å, respectively, which is in conformity with a formal C=N double bond (1.28 Å). Therefore, the C5–S4 bond changes from a double bond to a predominately single bond, whereas C5–N6 acquires some double bond characteristics. The remaining sites are occupied by the negative charged phenyl group [d(Sn1–C23) = 2.1559(16) Å] and by two chlorine atoms [d(Sn1–Cl2) = 2.4588(5) Å, d(Sn1–Cl3) = 2.5088(4) Å]. The bond length Sn1–C23 (2.1559(16) Å is very much longer than C23–C24 (1.3892(3) Å, C24–C25 (1.393(2) Å, C25–C26 (1.386(3) Å, C26–C27 (1.384(3) Å, and C27–C28 (1.396(2) Å in a phenyl ring; it may be due to steric hindrance of the central Sn1 atom. The two chlorines do not occupy the exact axial positions as a result the (Cl2–Sn1–Cl3) angle is 163.98°, which showed the significant distortion from the linear angle 180°. The deviation of the axial plane from linearity might be due to the steric hindrance by the phenyl group. Owing to steric effects between the phenyl group and chlorine atom, the tin(IV) atom may be viewed as distorted octahedral geometry. The angle C23–Sn1–Cl2 (95.97(5)°) is larger than S4–Sn1–Cl2 (94.162(18)°). The sum of the equatorial angles S4–Sn1–N7 (79.00(4)°), N7–Sn1–N10 (72.08(5)°), and S4–Sn1–N10 (151.03(4)°) is 302.11° showing more distortion from an ideal bond angle 360°. The sum of the angle S4–Sn1–C23 (107.95(4)°), S4–Sn1–N7 (79.00(4)°), N7–Sn1–N10 (72.08(5)°), and C23–Sn1–N10 (101.01(5)°) is 360°. So that the atoms Sn1, S4, C23, N10, and N7 are almost in the same plane. The angle C11–N10–C9 (120.24(14)°), N10–C11–C12 (122.04(16)°), C11–C12–C13 (118.43(16)°), C12–C13–C14 (119.70(16)°), C13–C14–C9 (119.39(16)°), and C14–C9–N10 (120.16(15)°) are not 120°; thus all the atoms in the pyridine ring are not in the same.

Antibacterial Activity

The synthesized ligand (**1**) and its organotin(IV) complexes (**2–6**) were tested for their antibacterial activity against *Staphylococcus aureus, Escherichia coli*, *Enterobacter aerogenes,* and *Salmonella typhi*. The results are presented in Table 3. Inhibition zone diameter over 7 mm indicates that all test compounds are active against the bacteria under investigation [39]. The free ligand (**1**) was found to be of little activity against bacteria. The screening results exhibited that complexes (**2–6**) showed high activity against various bacteria but low activity than the reference drug (doxycycline). Diphenyltin(IV) complex **6** showed the highest inhibition to growth of organisms, i.e., 27.6, 27.5, 25.9, and 24.8 mm inhibition zones against *S. aureus, E. coli*, *E. aerogenes,* and S*almonella typhi*, respectively. Dimethyltin(IV) complex **5** was second in toxicity to all bacterial strains. PhSn(IV)/BuSn(IV) complexes (**3–4**) show enhanced activity compared to the corresponding MeSn(IV) (**2**) complex. The activity might be due to the increasing of lipophilic nature of these complexes resulted from the metal chelation [40–42]. The electron delocalization in the chelate ring increases the lipophilic character of the metals chelate. Therefore, changing the organotin(IV) groups must play a significant role in these compounds growth inhibitory activity. In addition, the antimicrobial activity might due to the presence of the NH group; this group is believed to impart the transformation reaction in the biological system. It is believed that the antimicrobial activity of the organotin(IV) complexes may also be due to the inhibition of ATP production (energy production) such as inhibiting the respiration or by uncoupling of oxidative phosphorylation [43]. Antibacterial activity of compounds is due to either bactericide effects (killing the bacteria) or bacteriostatic effects (inhibiting multiplication of bacteria by blocking their active sites) [44]. The present observations corroborates previously reported tin compounds, wherein enhancement of activity has been described due to coordination of ligand to metal and efficient diffusion of the metal complexes into bacterial cell takes place [45, 46].

TABLE 3 Antibacterial Activity[a] of the Free Ligand (**1**) and Its Organotin(IV) Complexes (**2–6)** (Inhibition Zone in mm)

	Bacterium			
Samples	S. aureus	E. coli	E. aerogenes	Salmonella typhi
1	–	10	–	8
2	21.8	20.7	22.6	25.5
3	22.2	20.1	22.4	23.5
4	22.5	20.8	23.3	22.6
5	25.1	23.2	24.8	23.7
6	27.6	27.5	25.9	24.8
R	34.2	33.7	29.6	34.8

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

CONCLUSIONS

2-Acetylpyridine-*N*(4)-cyclohexylthiosemicarbazone (**1**) and its organotin(IV) complexes (**2–6**) were synthesized and completely characterized. The

ligand (**1**) exists in a 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 six-coordinated structures of the complexes (**2–6**). The X-ray crystallography diffraction has also revealed that the complex **4** is rendered a distorted octahedral geometry. Biological studies revealed that all the organotin(IV) complexes (**2–6**) are more potent antibacterial agent than their free ligand (**1**), whereas the diphenyltin(IV) complex (**6**) is more active than the other organotin(IV) derivatives (**2–5**).

SUPPLEMENTARY DATA

CCDC reference number 795016 contains the supplementary crystallographic data for [$PhSnCl_2$(APCT)] (**4**). This data can be obtained free of charge from the Cambridge Crystallographic data center via www.ccdc.ac.uk/data_request/cif or from the Cambridge Crystallographic data center, 12 Union Road, Cambridge CB2 1EZ, UK; fax: (+44) 1223-336-033; or e-mail: deposit@ccdc.cam.ac.uk.

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