ISSN 1070-3632, Russian Journal of General Chemistry, 2017, Vol. 87, No. 3, pp. 515–522. © Pleiades Publishing, Ltd., 2017.

Homobimetallic Organotin(IV) Complexes with Succinohydrazide Schiff Base: Synthesis, Spectroscopic Characterization, and Biological Screening[1]

S. Shujah[a,c]*, N. Khalid[b], and S. Ali[c]

[a] *Department of Chemistry, Kohat University of Science and Technology, Kohat, 26000 Pakistan*
**e-mail: shaukat.shujah@yahoo.com*

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

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

Received December 17, 2015

Abstract—Six new bis-diorganotin(IV) complexes, $[(Me_2Sn)_2L]$ (**1**), $[(Et_2Sn)_2L]$ (**2**), $[(n\text{-}Bu_2Sn)_2L]$ (**3**), $[(Ph_2Sn)_2L]$ (**4**), $[(n\text{-}Oct_2Sn)_2L]$ (**5**), and $[(tert\text{-}C_4H_9)_2Sn)_2L]$ (**6**), where L = $N^{1'}$,$N^{4'}$-bis(2-oxidobenzylidene)-succinohydrazide, were synthesized and characterized by elemental analysis, FT-IR, NMR (^{1}H, ^{13}C, and ^{119}Sn) and Mass spectra. Spectroscopic data authenticated the existence of two pentacoordinated tin centers in all complexes, formed via coordination of bis-ONO donor sites with dialkyltin(IV) moieties. Biological screening against selected pathogenic strains of bacteria and fungi revealed high activity of compound **3** against *Bacillus subtilis* and *Aspergillus flavis*, it also exhibited highest cytotoxicity against *Artemia salina*.

Keywords: homobimetallic, bis-diorganotin(IV), Schiff base, antimicrobial, cytotoxicity

DOI: 10.1134/S1070363217030227

INTRODUCTION

Organotin(IV) Schiff bases constitute an important class of compounds characterized by broad spectrum of applications, ranging from antitumor activity to catalytic and ion sensitive properties [1–7]. In particular, substantial interest has been displayed in metal complexes of diacylhydrazones, due to their specific structural features and various biological and pharmaceutical activities including antituberculosis, antimalarial and antimicrobial [8–10]. The presence of nitrogen and oxygen donor atoms in aroyl dihydrazones and their ability to act as monobasic bis-bidentate or tridentate, dibasic bis-tridentate or tetrabasic bis-tridentate chelators can lead to supramolecular structures [11–13]. Recently some homobimetallic organotin(IV) dithiocarbamates were studied for their promising antileishmanial activity [14]. However, few studies have been reported for the synthesis of diorganotin(IV) complexes of bis-ONO donor diacylhydrazones [15]. Presence of more than one metal center can impart special pharmacological properties to those compounds. Inspired by our previous studies on bis-diorganotin(IV) complexes derived from ONO–ONO donor ligands [16] and the mounting need for developing more potent and efficient metal based compounds that can inhibit growth of multidrug resistant infection causing pathogens, we have carried out synthesis, spectroscopic characterization and biological screening of six new homobimetallic diorganotin(IV) derivatives of $N^{1'}$,$N^{4'}$-bis(2-hydroxybenzylidene)succinohydrazide. All synthesized compounds were characterized by elemental analysis, FT–IR, multinuclear NMR (^{1}H, ^{13}C and ^{119}Sn) and Mass spectra, and screened against selected pathogenic bacterial and fungal strains. Cytotoxicity assessed by *in vivo* lethality to brine shrimp nauplii is also reported.

EXPERIMENTAL

Diorganotin(IV) dichlorides, dioctyltin(IV) oxide, butyltin(IV) chloride dihydroxide, succinic dihydrazide, and 2-hydroxybenzaldehyde were purchased from Aldrich. Analytical grade solvents were freshly dried before use adopting standard procedures [17]. The melting points were recorded on an electrothermal melting point apparatus, model MP-D Mitamura Rieken Kogyo (Japan). Element analyses were carried

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

out on a Leco CHNS 932 apparatus. IR spectra were recorded on a Bio-Rad Excaliber FT–IR, model FTS 300 MX spectrophotometer (USA) in the frequency range of 4000–400 cm^{-1} using KBr discs. Multinuclear NMR (^1H, ^{13}C, and ^{119}Sn) spectra were measured in $CDCl_3$ on a Bruker ARX 300 MHz FT–NMR and a Bruker 400 MHz FT-NMR spectrometers. Mass spectra were measured on a MAT-311A Finnigan (Germany).

***N*$^{1'}$,*N*$^{4'}$-Bis(2-hydroxybenzylidene)succinohydrazide (H_4L).** 2-Hydroxybenzaldehyde 1.66 g (13.68 mmol) and succinic dihydrazide 1.0 g (6.84 mmol) were mixed in ethanol and refluxed upon stirring for 2 h. The product was obtained as white solid, yield 78%, mp 214–216°C. FT–IR spectrum, ν, cm^{-1}: 3455 ($OH_{phenolic}$), 3178 (NH), 1669 (C=O), 1618 (C=N). ^1H NMR spectrum, δ, ppm: 2.58 s (4H, $2CH_2$), 6.89 t (2H, Ar-H, $^3J_{H–H}$ = 7.1 Hz), 6.90 d (2H, Ar-H, $^3J_{H–H}$ = 7.1 Hz), 7.27 t (2H, Ar-H, $^3J_{H–H}$ = 7.8 Hz), 7.49 d (2H, Ar-H, $^3J_{H–H}$ = 8.1 Hz), 8.28 s (2H, CH=N). ^{13}C NMR spectrum, δ, ppm: 29.4 [$(CH_2)_2$], 116.6 (Ar-C), 147.0 (CH=N), 168.2 (NCO). Found, %: C 61.06; H 5.14; N 15.79. $C_{18}H_{18}N_4O_4$. Calculated, %: C 61.01; H 5.12; N 15.81. EI-MS, *m/z*: 354 $[C_{18}H_{18}N_4O_4]^+$.

Bis[dimethyltin(IV)] [*N*$^{1'}$,*N*$^{4'}$-bis(2-oxidobenzylidene)succinohydrazide] (1). *N*$^{1'}$,*N*$^{4'}$-bis(2-Hydroxybenzylidene)succinohydrazide H_4L (0.53 g, 1.5 mmol) and TEA (0.84 mL, 6.0 mmol) were mixed and stirred for 15 min in dry toluene. Dimethyltin(IV) dichloride (0.66 g, 3.0 mmol) was added and the mixture was stirred for 5 h at room temperature. White precipitate of Et_3NHCl formed was filtered off. Upon evaporation under reduced pressure the filtrate gave yellow solid. The product was recrystallized from chloroform : *n*-hexane (4 : 1) (Scheme 1b). Yield 75 %, mp 233–235°C. FT–IR spectrum, ν, cm^{-1}: 1609 (C=N), 1077 (N–N), 563 (Sn–O), 457 (Sn–N). ^1H NMR spectrum, δ, ppm: 0.88 s [12H, H_α-SnMe, $^2J(^{119/117}Sn–^1H)$ = 78, 76 Hz], 2.58 s (4H, $2CH_2$), 6.74 d (2H, Ar-H, $^3J_{H–H}$ = 8.0 Hz), 6.72 t (2H, Ar-H, $^3J_{H–H}$ = 8.1 Hz), 7.14 d (2H, Ar-H, $^3J_{H–H}$ = 7.5 Hz), 7.32 t (2H, Ar-H, $^3J_{H–H}$ = 7.6), 8.58 s [2H, CH=N, $^3J(^{119}Sn–^1H)$ = 46 Hz]. ^{13}C NMR spectrum, δ, ppm: 30.6 $(CH_2)_2$, 116.2 (Ar-C), 156.2 (CH=N), 174.1 (NCO). ^{119}Sn NMR spectrum, δ, ppm: –158.1. Found, %: C 40.81; H 4.01; N 8.68. $C_{22}H_{26}N_4O_4Sn_2$. Calculated, %: C 40.78; H 4.04; N 8.65 EI-MS, *m/z*: 650 $[(C_8H_5N_2O_2)_2C_2H_4Sn_2(CH_3)_4]^+$.

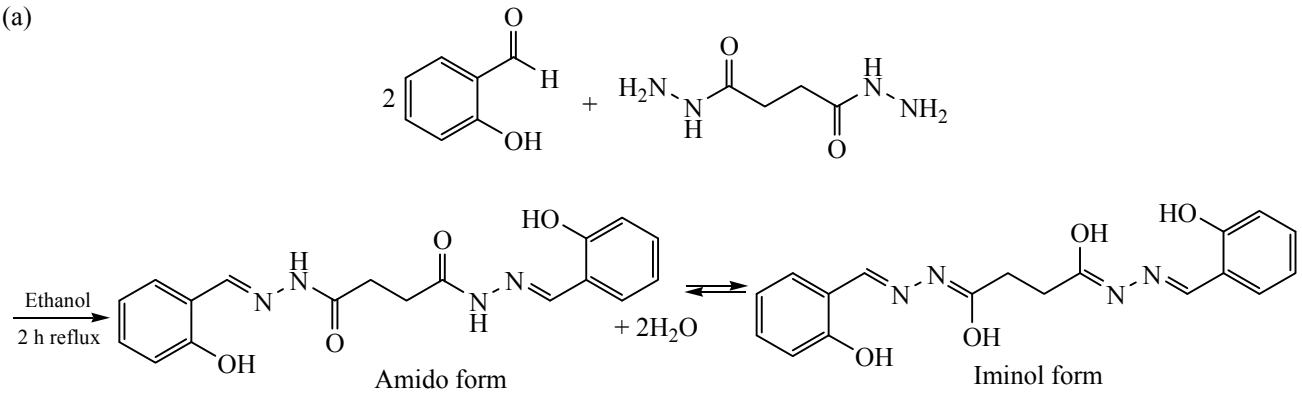
Bis[diethyltin(IV)] [*N*$^{1'}$,*N*$^{4'}$-bis(2-oxidobenzylidene)succinohydrazide] (2) was prepared similarly to **1**, using *N*$^{1'}$,*N*$^{4'}$-bis(2-hydroxybenzylidene)succinohydrazide (0.53 g, 1.5 mmol), diethyltin(IV) dichloride (0.74 g, 3.0 mmol) and triethylamine (0.84 mL, 6.0 mmol) in a molar ratio 1 : 2 : 4. Yield 72 %, mp 104–108°C. FT–IR spectrum, ν, cm^{-1}: 1612 (C=N), 1080 (N–N), 568 (Sn–O), 452 (Sn–N). ^1H NMR spectrum, δ, ppm: 1.26 t (12H, H_β-SnEt, $^3J_{H–H}$ = 7.5 Hz), 1.41–1.51 m (8H, H_α-SnEt), 2.69 s (4H, $2CH_2$), 6.70 t (2H, Ar-H, $^3J_{H–H}$ = 7.2 Hz), 6. 76 d (2H, Ar-H, $^3J_{H–H}$ = 8.4 Hz), 7.12 d (2H, Ar-H, $^3J_{H–H}$ = 7.8 Hz), 7.31 t (2H, Ar-H, $^3J_{H–H}$ = 7.0 Hz), 8.60 s [2H, CH=N, $^3J(^{119}Sn–^1H)$ = 43 Hz]. ^{13}C NMR spectrum, δ, ppm: 9.3 [C_β-SnEt, $^2J(^{119}Sn–^{13}C)$ = 44 Hz], 14.1 [C_α-SnEt, $^1J(^{119/117}Sn–^{13}C)$ = 618, 592 Hz], 30.7 $(CH_2)_2$, 116.5 (Ar-C), 160.9 (CH=N), 175.0 (NCO). Found, %: C 44.39; H 4.90; N 7.91. $C_{26}H_{34}N_4O_4Sn_2$. Calculated, %: C 44.36; H 4.87; N 7.96. EI-MS, *m/z*: 706 $[(C_8H_5N_2O_2)_2C_2H_4Sn_2(C_2H_5)_4]^+$.

Bis[di-*n*-butyltin(IV)] [*N*$^{1'}$,*N*$^{4'}$-bis(2-oxidobenzylidene)succinohydrazide] (3) was prepared similarly to **1**, using *N*$^{1'}$,*N*$^{4'}$-bis(2-hydroxy-benzylidene)succinodihydrazide (0.53 g, 1.5 mmol), dibutyltin(IV) dichloride (0.91 g, 3.0 mmol) and TEA (0.84 mL, 6.0 mmol) in a molar ratio 1 : 2 : 4. Yield 78 %, paste. FT–IR spectrum, ν, cm^{-1}: 1610 (C=N), 1075 (N–N), 570 (Sn–O), 458 (Sn–N). ^1H NMR spectrum, δ, ppm: 0.87 t (12H, H_δ-SnBu, $^3J_{H–H}$ = 7.2 Hz), 1.30–1.41 m (8H, H_γ-SnBu), 1.46–1.54 m (8H, H_β-SnBu), 1.60–1.67 m (8H, H_α-SnBu), 2.67 s (4H, $2CH_2$), 6.70 t (2H, Ar-H, $^3J_{H–H}$ = 7.8 Hz), 6. 76 d (2H, Ar-H, $^3J_{H–H}$ = 8.4 Hz), 7.12 d (2H, Ar-H, $^3J_{H–H}$ = 7.8 Hz), 7.31 t (2H, Ar-H, $^3J_{H–H}$ = 7.0 Hz), 8.58 s [2H, CH=N, $^3J(^{119}Sn–^1H)$ = 43 Hz]. ^{13}C NMR spectrum, δ, ppm: 13.6 (C_δ-SnBu), 22.0 (C_α-SnBu), 26.4 [C_γ-SnBu, $^3J(^{119/117}Sn–^{13}C)$ = 89 Hz], 26.8 [C_β-SnBu, $^2J(^{119/117}Sn–^{13}C)$ = 18 Hz], 30.8 $(CH_2)_2$, 116.5 (Ar-C), 160.8 (CH=N), 174.9 (NCO). ^{119}Sn NMR spectrum, δ, ppm: –194.0. Found, %: C 49.98; H 6.20; N 6.84. $C_{34}H_{50}N_4O_4Sn_2$. Calculated, %: C 50.03; H 6.17; N 6.86. EI-MS, *m/z*: 761 $[(C_8H_5N_2O_2)_2C_2H_4Sn_2(C_4H_9)_3]^+$.

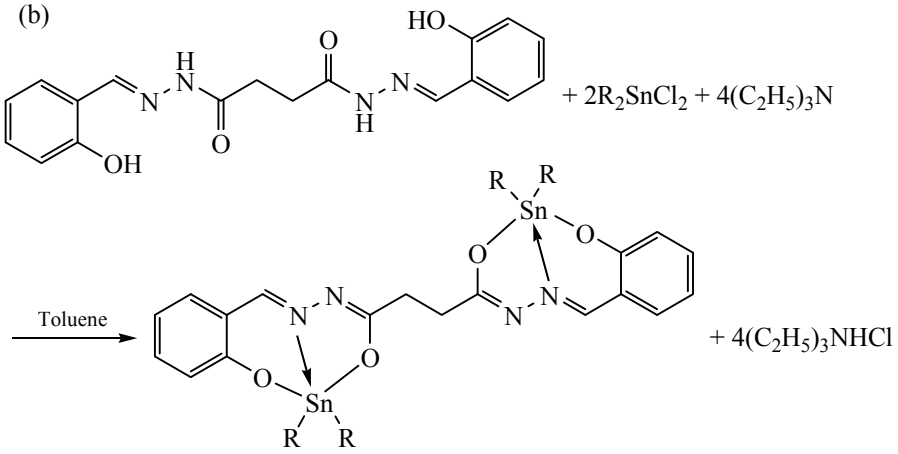
Bis(diphenyltin(IV)) [*N*$^{1'}$,*N*$^{4'}$-bis(2-oxidobenzylidene)succinohydrazide] (4) was prepared similarly to **1**, using *N*$^{1'}$,*N*$^{4'}$-bis(2-hydroxybenzylidene)succinohydrazide (0.53 g, 1.5 mmol), diphenyltin(IV) dichloride (1.03 g, 3.0 mmol) and TEA (0.84 mL, 6.0 mmol) in a molar ratio 1 : 2 : 4. Yield 78 %, mp 236–238°C. IR spectrum, ν, cm^{-1}: 1608 (C=N), 1070 (N–N), 568 (Sn–O), 451 (Sn–N). ^1H NMR spectrum, δ, ppm: 2.97 s (4H, $2CH_2$), 6.78 t (2H, Ar-H, $^3J_{H–H}$ = 7.5 Hz), 7.10 d (2H, Ar-H, $^3J_{H–H}$ = 8.4 Hz), 7.15 d (2H, Ar-H, $^3J_{H–H}$ = 7.8 Hz), 7.37–7.42 m (2H, Ar-H), 7.81–7.87 m (4H, H_β-SnPh), 8.55 s[(2H, CH=N, $^3J(^{119}Sn–^1H)$ = 52 Hz]. ^{13}C NMR spectrum, δ, ppm: 30.7 $(CH_2)_2$, 116.6 (Ar-C), 136.2 [C_b-SnBu, $^2J(^{119/117}Sn–^{13}C)$ = 54 Hz], 128.8

Scheme 1. Synthesis of $N^{1'}$,$N^{4'}$-bis(2-hydroxybenzylidene)succinohydrazide (a) and bis[diorganotin(IV)] derivatives (b–c). Numbering scheme of alkyl groups bonded to tin atom in bis[dialkyltin(IV)] derivatives (d).

(a)

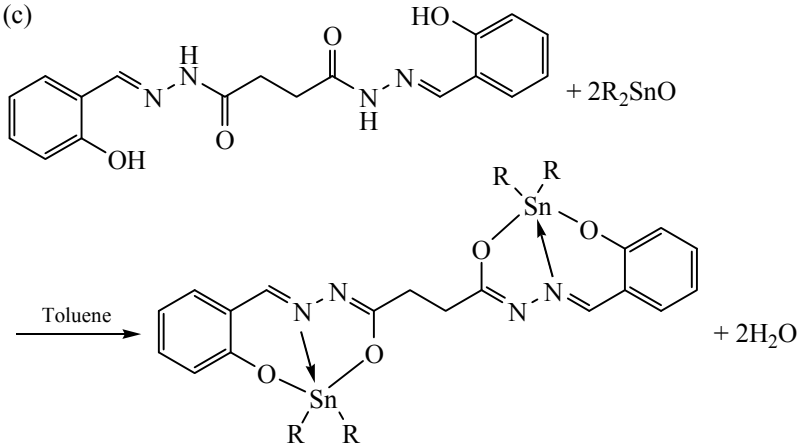


(b)



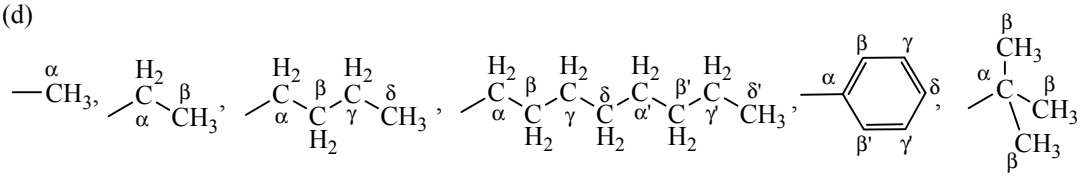
R = CH_3 (**1**), C_2H_5 (**2**), C_4H_9 (**3**), C_6H_5 (**4**), *tert*-C_4H_9 (**6**).

(c)



R = C_8H_{17} (**5**).

(d)



[C_γ-SnBu, $^3J(^{119/117}Sn–^{13}C)$ = 88], 130.5 [C_δ-SnBu, $^4J(^{119/117}Sn–^{13}C)$ = 17 Hz], 139.0 [C_α-SnBu, $^1J(^{119/117}Sn–^{13}C)$ = 592 Hz], 161.2 (CH=N), 174.6 (NCO). ^{119}Sn NMR spectrum, δ, ppm: –342.0. Found, %: C 56.31; H 3.79; N 6.21. $C_{42}H_{34}N_4O_4Sn_2$. Calculated, %: C 56.29; H 3.82; N 6.25. EI-MS, *m/z*: 463 $[(C_8H_5N_2O_2)C_2H_4Sn(C_6H_5)_2]^+$.

Bis[di-*n*-octyltin(IV)][*N*$^{1'}$,*N*$^{4'}$-bis(2-oxidobenzylidene)succinohydrazide] (5) was prepared by refluxing *N*$^{1'}$,*N*$^{4'}$-bis(2-hydroxybenzylidene)succinohydrazide (0.53 g, 1.5 mmol) and dioctyltin(IV) oxide (1.09 g, 3.0 mmol) in 100 mL of dry toluene, molar ratio 1 : 2. The accumulated water was removed by a Dean-Stark apparatus. The yellow solution obtained was evaporated under reduced pressure. The solid product was recrystallized from chloroform *n*-hexane (4 : 1) (Scheme 1c). Yield 72%, paste. FT–IR spectrum, ν, cm^{-1}: 1612 (C=N), 1070 (N–N), 564 (Sn–O), 458 (Sn–N). ^{1}H NMR spectrum, δ, ppm: 0.87 t (12H, $H_{\delta'}$-SnOct, $^3J_{H–H}$ = 6.9 Hz), 1.22–1.36 br.s (32H, $H_{\gamma\text{-}\gamma'}$-SnOct), 1.44–1.48 m (8H, H_β-SnOct), 1.63–1.67 m (8H, H_α-SnOct), 2.66 s (4H, $2CH_2$), 6.70 t (2H, Ar-H, $^3J_{H–H}$ = 7.2 Hz), 6.75 d (2H, Ar-H, $^3J_{H–H}$ = 8.4 Hz), 7.11 d (2H, Ar-H, $^3J_{H–H}$ = 7.2 Hz), 7.30 t (2H, Ar-H, $^3J_{H–H}$ = 7.2 Hz), 8.57 s [2H, CH=N, $^3J(^{119}Sn–^1H)$ = 43 Hz]. ^{13}C NMR spectrum, δ, ppm: 14.1 (C_δ-SnOct), 22.4 [C_α-SnOct, $^1J(^{119/117}Sn–^{13}C)$ = 602 Hz], 22.7 ($C_{\delta\text{-}\gamma'}$-SnOct), 24.7 [$C_b$-SnOct, $^2J(^{119/117}Sn–^{13}C)$ = 35 Hz], 30.8 $(CH_2)_2$, 33.4 [C_γ-SnOct, $^3J(^{119/117}Sn–^{13}C)$ = 79 Hz], 116.6 (Ar-C), 160.7 (CH=N), 174.9 (NCO). ^{119}Sn NMR spectrum, δ, ppm: –198. Found, %: C 57.68; H 7.97; N 5.40. $C_{50}H_{82}N_4O_4Sn_2$. Calculated, %: C 57.71; H 7.94; N 5.38. EI-MS, *m/z*: 929 $[(C_8H_5N_2O_2)_2C_2H_4Sn_2(C_8H_{17})_3]^+$.

Bis[di-*tert*-butyltin(IV)] [*N*$^{1'}$,*N*$^{4'}$-bis(2-oxidobenzylidene)succinohydrazide] (6) was prepared similarly to **1**, using *N*$^{1'}$,*N*$^{4'}$-bis(2-hydroxybenzylidene)succinohydrazide (0.53 g, 1.5 mmol), di-*tert*-butyltin(IV) dichloride (0.91 g, 3.0 mmol) and TEA 0.84 mL (6.0 mmol) in a molar ratio 1 : 2 : 4. Yield 70 %, mp 128–133°C. FT–IR spectrum, ν, cm^{-1}: 1607 (C=N), 1071 (N–N), 559 (Sn–O), 452 (Sn–N). ^{1}H NMR spectrum, δ, ppm: 1.31 s [18H, H_β-Sn-*tert*-Bu, $^3J(^{119/117}Sn\text{-}^1H)$ = 109, 105 Hz], 2.72 s (4H, $2CH_2$), 6.67 t (2H, Ar-H, $^3J_{H–H}$ = 7.5 Hz), 6.81 d (2H, Ar-H, $^3J_{H–H}$ = 8.1 Hz), 7.10 d (2H, Ar-H, $^3J_{H–H}$ = 7.8 Hz), 7.30 t (2H, Ar-H, $^3J_{H–H}$ = 7.6), 8.58 s (2H, CH=N, $^3J(^{119}Sn–^1H)$ = 39 Hz)]. ^{13}C NMR spectrum, δ, ppm: 29.6 (C_β-Sn-*tert*-Bu), 30.4 $(CH_2)_2$, 40.4 (C_α-Sn-*tert*-Bu), 116.4 (Ar-C), 160.5 (CH=N), 175.0 (NCO). Found, %: C 49.98; H 6.21; N 6.84. $C_{34}H_{50}N_4O_4Sn_2$. Calculated, %: C 50.03; H 6.17; N 6.86. EI-MS, *m/z*: $[(C_8H_5N_2O_2)_2C_2H_4Sn_2(C_4H_9)_3]^+$ 761.

Antibacterial activity. The synthesized ligand (H_4L) and bis-diorganotin(IV) complexes were evaluated for antibacterial activity against *Escherichia coli* ATCC 11229, *Bacillus subtilis* ATCC 11774, *Shigella flexneri* ATCC 10782, *Staphylococcus aureus* ATCC 25923, *Pseudomonas aeruginosa* ATCC 10245 and *Salmonella typhi* ATCC 10749 using the agar well diffusion method [18]. Imipenum was used as epy standard drug and 6 mm diameter wells were dug in the media with the help of a sterile metallic borer. In 8 h old bacterial inoculums containing ca 10^4–10^6 colony forming units (CFU)/mL were spread on the surface of nutrient agar with the help of a sterile cotton swab. The recommended concentration of the test sample (2 mg/mL in DMSO) was introduced into the respective wells. Other wells supplemented with DMSO and reference antibacterial drug served as negative and positive controls, respectively. The plates were incubated immediately at 37 °C for 20 h. Activity was determined by measuring diameter of the inhibition zone in mm. Growth inhibition was calculated with reference to the positive control.

Antifungal activity. The *in vitro* antifungal activity of synthesized compounds was investigated against six fungal strains [*Trichophyton longifusus* ATCC 22397, *Candida albicans* ATCC 2192, *Aspergillus flavus* ATCC 1030, *Microsporum canis* ATCC 9865, *Fusarium solani* ATCC 11712, *Candida glabrata* ATCC 90030] using the agar tube dilution test [19]. Miconazole and Amphotericin B were used as the standard drugs. Stock solutions of pure compounds (200 mg/mL) were prepared in sterilized DMSO. Sabouraud dextrose agar was prepared by mixing Sabouraud (32.5 g), glucose agar (4%) and agar-agar (20 g) in 500 mL of distilled water followed by dissolution at 90–95°C. The media (4 mL) was dispensed into screw-capped tubes and autoclaved at 121 °C for 15 min. Known amounts of test compounds were added from the stock solution to non-solidified Sabouraud agar media (50 °C). The contents of the tubes were then solidified at room temperature and inoculated with 4 mm diameter portion of inoculums derived from a 7 days old respective fungal culture. For non-mycelial growth an agar surface streak was employed. The tubes were incubated at 27–29°C for 7–10 days and growth in the compound containing media was determined by measuring the linear growth in mm.

Cytotoxicity. Cytotoxicity of the compounds was studied by the Brine shrimp lethality bioassay [19]. Brine shrimps (*Artemia salina*) were hatched using brine shrimp eggs in a vessel, filled with sterile simulated seawater (prepared using sea salt 38 g/L and adjusted to pH 8.5 using 1 M NaOH) at 22–29°C with constant aeration for two days. After hatching, thirty active nauplii were drawn through a glass capillary and placed in a vial containing 4.5 mL of brine solution and a drop of yeast suspension. In each experiment, 0.5 mL of the test solution was added to the vial and maintained at ambient temperature for 24 h, the surviving larvae were counted. All experiments with different concentrations (1, 10, 100 mg/mL) of the test substances were conducted in triplicate and compared with the control. Data were analyzed with Finney's probit analysis to determine the LD_{50} [20]. Etoposide was used as the standard drug.

RESULTS AND DISCUSSION

All synthesized compounds were stable in the air. Efforts to obtain single crystal were not successful.

Mass spectra. MS data for the fragmented ions were in good agreement with structureы of the compounds. The molecular ion peaks M^+ were observed only for H_4L compounds **1** and **2**. Primary fragmentation took place by loss of the R group. Loss of the ligand in a subsequent step led to the formation of $[RSn]^+$. $[Sn]^+$ fragment was formed by elimination of R radical. The $[C_4H_9]^+$ and $[CH_3]^+$ ions were also observed with significant intensities.

FT-IR spectra. Comparison of IR spectra of complexes with that of ligand provided evidence for the binding sites involved in chelation. Absorption bands observed in the solid state IR spectrum of ligand at 3455, 3178, and 1669 cm^{-1} have been assigned to the stretching vibrations of OH, NH, and C=O groups, all bands disappearув in the IR spectra of bis-diorganotin(IV) complexes, suggesting tautomeric shift followed by deprotonation and coordination of phenolic and enolic oxygens to the diroganotin(IV) moieties. The shift of stretching vibrations of C=N to lower frequencies provided evidence for the interaction of azomethine nitrogen with Sn atom. The band assigned to N–N was shifted to higher frequencies (1070–1080 cm^{-1}) in the spectra of organotin(IV) complexes due to the decrease in repulsion of the lone pairs of electrons on nitrogen atoms. Appearance of new bands in the regions of 559–570 and 451–458 cm^{-1} indicated formation of the Sn–O and Sn–N bonds, respectively [21–23].

NMR spectra. Signals of OH and NH in ^1H NMR spectrum of the ligand disappeared in the spectra of bis-diorgnaotin(IV) complexes **1–6** suggesting deprotonation and enolization of the ligand in the course of complex formation [24]. Aromatic protons of the ligand and methylene protons of the alkyl linker were recorded by signals in the regions 6.90–7.49 and 2.58 ppm, respectively. These groups were not involved in bonding and their signals remained unaffected in the NMR spectra of bis-diorganotin(IV) by complexes formation. The signal at 8.28 ppm was assigned to the noncoordinated azomethine (CH=N) proton. Upon coordination its downfield shift to 8.55–8.60 ppm with $^3J(^{119}Sn–^1H)$ = 39–52 Hz indicated shifting of electrons density from azomethine nitrogen to Sn atom, thus, affirming the presence of Sn–N bond in a solution. The chemical shifts and coupling constants were consistent with reported diorganotin(IV) complexes of bis-ONO donor type ligands [25].

The CH_3 protons in complex **1** resonated as a singlet at 0.88 ppm with Sn satellites corresponding to $^2J(^{119}Sn–^1H)$ coupling constant of 78 Hz. Substitution into the Lockhart–Manders equation, $\theta = 0.016|^2J|^2 – 1.32|^2J| + 133.4$, gave C–Sn–C angle of 128.4° indicating a pentacoordinated Sn atom in a solution [26].

Complexation induced a shift of the electron density from the ligand to diorganotin(IV) moieties and, hence, a downfield shift of ^{13}C signals of the ligand. In organotin(IV) compounds, the ^1J (^{119}Sn, ^{13}C) value was an important parameter used to establish the coordination around tin in solution. The calculated coupling constants for compounds **1, 2, 4**, and **5** were in the range of 592–649 Hz indicating pentacoordination around the Sn atom in a solution [27]. The calculated C–Sn–C angles (deg) based on NMR parameters (^1J and ^2J) are presented in Table 1.

^{119}Sn NMR spectra were used to ascertain the coordination geometry of Sn atom. All complexes exhibited a single sharp resonance indicating similar coordination environment around each Sn atom. The ^{119}Sn NMR signals for dimethyl, dibutyl and dioctyl complexes were observed at –158, –194, and –198 ppm, respectively. For the diphenyl complex the anisotropic shielding effects and pi interactions caused the signal to appear at –342 ppm. The chemical shift data accumulated for complexes in $CDCl_3$ suggested that in noncoordinating solvents each Sn atom was

Table 1. C–Sn–C angles (deg) based on NMR parameters of selected bis-diorganotin(IV) complexes

Comp. no.	Angle, deg			
	$^{1}J(^{119}Sn, ^{13}C)$, Hz	$^{2}J(^{119}Sn, ^{1}H)$, Hz	^{1}J, Hz	^{2}J, Hz
1	649	78	133.7	128.4
2	618	–	131.0	–
4	592	–	134.1	–
5	602	–	135.1	–

pentacoordinated with trigonal bipyramidal geometry [28–31].

Antibacterial activity. The corresponding data (Table 2) demonstrated an increase in the antibacterial activity upon complexation with the diorganotin(IV) [32]. The synthesized bis-diorganotin(IV) complexes **1–6** exhibited elevated inhibitory activity against gram positive bacteria (*B. subtilis, S. aureus*) which had a loosely packed polyglycane outer layer making the penetration of complexes into the cell easily. On the other hand, Gram-negative bacterial cell with a bilayer phospholipid structure protected the inner cytoplasmic membrane to a greater degree against the inhibitory action of the organotin(IV) complex. All synthesized compounds were inactive against *S. typhi*. Highest activity was demonstrated by **3** against *B. subtilis*. Information about the exact mechanism was meager and is yet to be fully explored. However, the enhanced activity of complexes can be rationalized on the basis of Overtone's concept and Tweedy's chelation theory, which demands enhanced lipophilicity for antimicrobial action [33–35]. None of the synthesized compounds was more active than the standard drug.

Antifungal activity. The *in vitro* antifungal activity of ligand H_4L and bis[diorganotin(IV)] complexes **1–6** was tested against six human pathogenic fungal strains including yeasts (*Candida albicans*, *Candida glabrata*), dermatophytes (*Microsporum canis*, *Trichophyton longifusus*) and opportunistic molds (*Aspergillus flavus, Fusarium solani)* using the agar tube dilution

Table 2. Antibacterial activity of bis-diorganotin(IV) derivatives of $N^{1'},N^{4'}$-bis(2-hydroxybenzylidene)succinohydrazide[a,b]

Bacteria (ATCC no.)	Inhibition zone diameter, mm							
	H_4L	**1**	**2**	**3**	**4**	**5**	**6**	reference drug[c]
Escherichia coli (11229)	–	12	–	12	14	–	–	30
Bacillus subtilis (11774)	–	11	12	16	14	–	14	37
Shigella flexnari (10782)	–	14	–	–	–	11	12	36
Staphlococcus aureus (25923)	–	12	10	12	–	–	12	26
Pseudomonas aeruginosa (10145)	–	11	–	–	–	–	–	32
Salmonella typhi (10749)	–	-	–	–	–	–	–	30

[a] Concentration 1 mg/mL of DMSO. [b] Reference drug, imipenum. [c] (–) Insignificant activity.

Table 3. Antifungal activity of bis-diorganotin(IV) derivatives of $N^{1'},N^{4'}$-bis(2-hydroxybenzylidene)succinohydrazide[a,b]

Fungi (ATCC no.)	Inhibition, %							
	H_4L	**1**	**2**	**3**	**4**	**5**	**6**	standard drug[c]
Trichophyton longifusus (22397)	–	–	10	20	–	–	10	100
Candida albicans (2192)	30	–	–	–	–	–	–	100
Aspergillus flavis (1030)	40	–	–	70	–	–	30	100
Microsporum canis (9865)	–	–	–	–	–	–	–	100
Fusarium solani (11712)	45	30	35	-	70	–	–	100
Candida glaberata (90030)	–	–	–	–	–	–	–	100

[a] Concentration 400 μg/mL of DMSO. [b] Standard drug: amphotericin-B, miconazole. [c] (–) No inhibition.

Table 4. Brine Shrimp (*Artemia salina*) lethality bioassay data of bis-diorganotin(IV) derivatives of $N^{1'}$,$N^{4'}$-bis(2-hydroxybenzylidene)succinohydrazide[a]

Comp. no.	LD_{50}, μg/mL
H_4L	–
1	–
2	–
3	32.11
4	–
5	–
6	–

[a] Standard drug: etoposide, LD_{50} = 7.46 μg/mL.

protocol [19]. Amphotericin-B and miconazole were used as standard drugs (Table 3). Inclusion of organotin moieties enhanced antifungal activity of the ligand. The highest activity was exhibited by compounds **3** and **4** aganint *A. flavis* and *F. solani*, respectively. The detailed mechanism of antifungal activity is yet to be investigated, however, the activity of synthesized compounds can be attributed to their ability to interact with intracellular bioreceptors causing disruption in the movement of ribosome and blocking the synthesis of protein and DNA in the cell nucleus [36, 37].

Cytotoxicity. Cytotoxicity of the synthesized ligand H_4L and bis[diorganotin(IV)] complexes **1–6** was assessed by *in vivo* lethality to brine shrimp nauplii (Table 4). Organotin(IV) complexes can exert their biochemical effects by binding with nuclear receptors, membrane active sites, intracellular proteins and DNA. Toxicity of organotin(IV) compounds depends on the lipophilic character of alkyl group and can cause prevention of the mitochondrial oxidative phosphorylation, prompting DNA damage, apoptosis, necrosis or blockage of estrogen receptors [38, 39]. Among the synthesized compounds bis-[dibutyltin(IV)] **3** derivative displayed highest toxicity with LD_{50} = 32.11 μg/mL.

CONCLUSIONS

New six homobimetallic bis-diorganotin(IV) Schiff bases have been synthesized and characterized by elemental analysis, FT–IR and multinuclear (^{1}H, ^{13}C and ^{119}Sn) NMR spectra. The emergence of new bands for Sn–O (559–570 cm^{-1}) and Sn-N (451–458 cm^{-1}) and decrease in C=N stretching frequency supported formation of compounds **1–6**. ^{1}H and ^{13}C NMR spectra indicated five-coordinated structure of Sn (**1–6**) in a solution. The complexes exhibited high antimicrobial activity as compared to ligand indicating the role of Sn in their antimicrobial action. Compound **3** exhibited the highest activity against *Bacillus subtilis* and *Aspergillus flavis*. The highest cytotoxicity was demonstrated by compound 3 (LD_{50} 32.11 μg/mL).

ACKNOWLEDGMENTS

We thank the Higher Education Commission of Pakistan for the financial support.

REFERENCES

1. Degaonkar, M.P., Puranik, V.G., Tavale, S.S., Gopinathan, S., and Gopinathan, C., *Bull. Chem. Soc. Jpn.*, 1994, vol. 67, p. 1797. doi 10.1246/bcsj.67.1797
2. Baul, T.S.B., Singh, K.S., Lycka, A., Holcapek, M., and Linden, A., *J. Organomet. Chem.*, 2005, vol. 690, p. 1581. doi 10.1016/j.jorganchem.2004.12.030
3. Tian, L., Sun, Y., Qian, B., Yang, G., Yu, Y., Shang, Z., and Zheng, X., *Appl. Organomet. Chem.*, 2005, vol. 19, p. 1127. doi 10.1002/aoc.968
4. Singh, N., and Bhattacharya, S., *J. Coord. Chem.*, 2011, vol. 64, p. 2170. doi 10.1080/00958972.2011.590589
5. Zhang, R., Ren, Y., Wang, Q., and Ma, C., *Inorg. Chim. Acta*, 2010, vol. 363, p. 1597. doi 10.1016/j.ica.2010.01.016
6. Majumdar, K.K., Kundu, A., Das, I., and Roy, S., *Appl. Organomet. Chem*., 2000, vol. 14, p. 79. doi 10.1002/(SICI)1099-0739(200002)14:2<79::AID-AOC931>3.0.CO;2-9
7. Liu, D., Chen, W.C., Yang, R.H., Shen, G.L., and Yu, R.Q., *Anal. Chim. Acta*, 1997, vol. 338, p. 209. doi 10.1016/S0003-2670(96)00382-0
8. Cocco, M.T., Congiu, C., Lilliu, V., and Onnis, V., *Bioorg. Med. Chem.*, 2004, vol. 14, p. 5787. doi 10.1016/j.bmcl.2004.09.045
9. Vicini, P., Zani, F., Cozzini, P., and Doytchinova, I., *Eur. J. Med. Chem.*, 2002, vol. 37, p. 553. doi 10.1016/S0223-5234(02)01378-8
10. Walcourt, A., Loyevsky, M., Lovejoy, D.B., Gordeuk, V.R., and Richardson, D.R., *Int. J.Biochem. Cell Biol.*, 2004, vol. 36, p. 401. doi 10.1016/S1357-2725(03)00248-6
11. Patole, J., Sandbhor, U., Padhye, S., Deobagkar, D.N., Anson, C.E., and Powell, A., *Bioorg. Med. Chem. Lett.*, 2003, vol. 13, p. 51. doi 10.1016/S0960-894X(02)00855-7
12. Dey, D.K., Dey, S.P., Karan, N.K., Lycka, A., and Rosair, G.M., *J. Organomet. Chem.*, 2014, vol. 749, p. 320. doi : 10.1016/j.jorganchem.2013.09.011
13. Barba, V., Vega, E., Luna, R., Höpfl, H., Beltrán, H.I.,

and Zamudio-Rivera, L.S., *J. Organomet. Chem.*, 2007, vol. 692, p. 731. doi 10.1016/j.jorganchem.2006.09.064

14. Ali, S., Zia-ur-Rehman, Muneeb-ur-Rehman, Khan, I., Shah, S.N.A., Ali, R.F., Shah, A., Badshah, A., Akbar, K., and Gariepy, F.B., *J. Coord. Chem.*, 2014, vol. 67, p. 3414. doi 10.1080/00958972.2014.960406
15. Yin, H., Cui, J., and Qiao, Y., *Polyhedron*, 2008, vol. 27, p. 2157. doi 10.1016/j.poly.2008.04.013
16. Shujah, S., Zia-ur-Rehman, Muhammad, N., Shah, A., Ali, S., Meetsma, A., and Hussain, Z., *J. Organomet. Chem.,* 2014, vol. 759, p. 19. doi 10.1016/j.jorganchem.2014.02.010
17. Perrin, D.D. and Armengo, W.L.F., *Purification of Laboratory Chemicals*, Oxford: Pergamon Press, 1988, 3rd ed.
18. Rehman, W., Baloch, M.K., and Badshah, A., *Eur. J. Med. Chem.*, 2008, vol. 43, p. 2380. doi 10.1016/j.ejmech.2008.01.019
19. Rahman, A., Choudhary, M.I., and Thomsen, W.J., *Bioassay Techniques for Drug Development*, Amsterdam: Harward Academic Press, 2001, p. 14.
20. Finney, D.J., *Probit Analysis*, Cambridge: Cambridge University Press, 1971, 3rd ed.
21. Hong, M., Yin, H.D., Cui, J.C., *Solid State Sci.*, 2011, vol. 13, p. 501. doi 10.1016/j.solidstatesciences.2010.11.010
22. Muhammad, N., Zia-ur-Rehman, Shujah, S., Shah, A., Ali, S., Meetsma, A., and Hussain, Z., *J. Coord. Chem.*, 2012, vol. 65, p. 3766. doi 10.1080/00958972.2012.718076
23. Yin, H.D., Hong, M., Li, G., Wang, D.Q., *J. Organomet. Chem.*, 2005, vol. 690, p. 3714. doi 10.1016/j.jorganchem.2005.04.049
24. Shujah, S., Zia-ur-Rehman, Muhammad, N., Ali, S., Khalid, N., and Tahir, M. N., *J. Organomet. Chem.*, 2011, vol. 696, p. 2772. doi 10.1016/j.jorganchem.2011.04.010
25. Sedaghat, T., Aminian, M., Rudbari, H.A., and Bruno, G., *J. Organomet. Chem.*, 2014, vol. 754, p. 26. doi 10.1016/j.jorganchem.2013.12.034
26. Lockhart, T.P. and Manders, W.F., *Inorg. Chem.*, 1986, vol. 25, p. 892. doi 10.1021/ic00227a002
27. Holecek, J. and Lycka, A., *Inorg. Chim. Acta*, 1986, vol. 118, p. L15. doi 10.1016/S0020-1693(00)86395-1
28. Holecek, J., Nadvornik, M., Handlir, K., and Lycka. A., *J. Organomet. Chem*., 1983, vol. 241, p. 177. doi 10.1016/S0022-328X(00)98505-X
29. Nadvornik, M., Holecek, J., Handlir, K., and Lycka, A., *J. Organomet. Chem.*, 1984, vol. 275, p. 43. doi 10.1016/0022-328X(84)80576-8
30. Lycka, A., Holecek, J., Nadvornik, M., and Handlir, K., *J. Organomet. Chem.*, 1985, vol. 280, p. 323. doi 10.1016/0022-328X(85)88109-2
31. Holecek, J., Nadvornik, M., Handlir, K., Lycka, A., *J. Organomet. Chem.*, 1986, vol. 315, p. 299. doi 10.1016/0022-328X(86)80450-8
32. Anwer, J., Ali , S., Shahzadi , S., Shahid, M., Sharma, S.K., and Qanungo, K., *J. Coord. Chem.*, 2013, vol. 66, p. 1142. doi : 10.1080/00958972.2013.776678
33. Zia-ur-Rehman, Muhammad, N., Shuja, S., Ali, S., Butler, I.S., Meetsma, A., and Khan, M., *Polyhedron*, 2009, vol. 28, p. 3439. doi 10.1016/j.poly.2009.07.025
34. Muhammad, N., Zia-ur-Rehaman, Shujah, S., Shah, A., Ali, S., Meetsma, A., and Hussain, Z., *J. Coord. Chem*., 2012, vol. 65, p. 3766. doi 10.1080/00958972.2012.718076
35. Fukushima, K., Dubey, S.K., and Suzuki, S., *J. Gen. Appl. Microbiol.*, 2012, vol. 58, p. 283.
36. Chaudhary, P., Swami, M., Sharma, D.K., and Singh, R.V., *Appl. Organomet. Chem.*, 2009, vol. 23, p. 140. doi 10.1002/aoc.1484
37. Ayoko, G.A., Bonire, J.J., Abdulkadir, S.S., Olurinola, P.F., Ehinmidu, J.O., Kokot, S., and Yiasel, S., *Appl. Organomet. Chem.*, 2003, vol. 17, p. 749. doi 10.1002/aoc.520
38. Shpakovsky, D. B., Banti, C.N., Mukhatova, E.M., Gracheva, Yu.A., Osipova, V.P., Berberova, N.T., Albov, D.V., Antonenko, T.A., Aslanov, L.A., Milaeva, E.R., and Hadjikakou, S.K., *Dalton Trans.*, 2014, vol. 43, p. 6880. doi 10.1039/C3DT53469C
39. Nath, M., *Appl. Organomet. Chem.*, 2008, vol. 22, p. 598. doi 10.1002/aoc.1436