

Biological screening, DNA interaction studies, and catalytic activity of organotin(IV) 2-(4-ethylbenzylidene) butanoic acid derivatives: synthesis, spectroscopic characterization, and X-ray structure

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The synthesized compounds interact with SS-DNA via intercalative binding mode of interaction in which the compound insert itself into the base pair of DNA resulting in hypochromic and bathochromic shift.

A series of organotin(IV) carboxylates, $[Me_2SnL_2]$ (1), $[Bu_2SnL_2]$ (2), $[Oct_2SnL_2]$ (3), $[Me_3SnL]$ (4), and $[Ph_3SnL]$ (5), where L = 2-(4-ethylbenzylidene) butanoic acid, have been synthesized and characterized by elemental analysis, FT-IR, and NMR (¹H, ¹³C, and ¹¹⁹Sn). $[Me_3SnL]$ (4) was

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analyzed by single crystal X-ray analysis which showed polymeric structure with distorted trigonal bipyramidal geometry. The complexes were screened for biological activities including antibacterial, antifungal, and cytotoxic activities. UV-vis absorption studies of **HL**, **1** and **4** with SS-DNA revealed groove binding as well as intercalation, which may be due to the presence of planar phenyl groups that facilitate interaction with DNA. The determined intrinsic binding constants, $6.04 \times 10^3 \text{ M}^{-1}$ (**HL**), $9.6 \times 10^3 \text{ M}^{-1}$ (**1**), and $1.7 \times 10^4 \text{ M}^{-1}$ (**4**), showed that **HL** and **1** have less binding strength than **4**. The catalytic activities of di- and tri-organotin(IV) complexes were assessed in transesterification of triglycerides (linseed oil) into fatty acid methyl esters (biodiesel). The tri-organotin(IV) complexes have better catalytic activity than their di-analogs.

Keywords: Organotin(IV) carboxylate; Antibacterial activity; Antifungal activity; Cytotoxicity; Transesterification

1. Introduction

Organotin(IV) carboxylates have a variety of applications as antifungal, antibacterial, anticancer agents [1, 2], agricultural fungicides, and insecticides [3, 4]. Crystallographic studies revealed that organotin(IV) carboxylates adopt structures which are dependent on both the nature of the substituent bonded to tin and on the type of carboxylate [5, 6]. Studies of organotin compounds containing carboxylates with oxygen donors indicate that new structural types may lead to different activities [7–9].

Organotin(IV) carboxylates have also been used as catalysts in the synthesis of polyesters, polyurethanes [10], in cross-linking of silicones [11], and in esterification and transesterification [12]. No extensive studies have been reported with the use of organotin(IV) carboxylates as catalysts in transesterification of triglycerides (vegetable oil) into fatty acid methyl esters (biodiesel). Biodiesel is the monoalkyl ester of long-chain fatty acids derived from renewable feed stocks, such as vegetable oil or animal fats, for use in compression ignition engines [13, 14]. It is a possible substitute of conventional diesel fuel [15]. The use of biodiesel is environmentally friendly due to reduced emission of carbon monoxide, hydrocarbons, particulate matter, sulfur dioxide, and volatile organic compounds [16].

The present study deals with the synthesis of di- and tri-organotin(IV) carboxylates of the type $R_{4-n}SnL_n$ (R = Me, *n*-Bu, Ph), L = 2-(4-ethylbenzylidene) butanoic acid and *n* = 1 or 2. These compounds were characterized by elemental analysis, FT-IR, NMR (¹H, ¹³C, and ¹¹⁹Sn), and single crystal X-ray analysis. The synthesized compounds were tested for their antibacterial, antifungal, and cytotoxic activities. DNA interaction studies of the synthesized compounds were also performed using UV–vis spectrophotometric technique. The di- and tri-organotin(IV) carboxylates have been assessed as catalysts in transesterification of triglycerides (linseed oil) into fatty acid methyl esters (biodiesel).

2. Experimental

2.1. Materials and methods

All di- and tri-organotin(IV) precursors were purchased from Sigma–Aldrich and used without purification. Solvents used were of analytical grade and dried according to reported procedures before use [17]. The melting points were recorded on a Gallenkamp (UK) electrothermal m.p. apparatus. Elemental analyses were done using a Leo CHNS 932 apparatus. FT-IR spectra were recorded from 4000 to 400 cm⁻¹ using a Thermo Nicolet-6700 FT-IR spectrophotometer using KBr pellets. ¹H and ¹³C NMR spectra were recorded at room temperature in CDCl₃ and DMSO on a Bruker Avance Digital 300 MHz NMR spectrometer (Switzerland). ¹¹⁹Sn NMR spectra were recorded on a 400 MHz JEOL ECS instrument at a working frequency of 149.4 MHz and the chemical shift was referenced to Me₄Sn

Organotin(IV)

as an external standard. The X-ray diffraction data were collected on a Bruker SMART APEX CCD diffractometer equipped with a 4 K CCD detector set 60.0 mm from the crystal. The crystals were cooled to 100 ± 1 K using the Bruker KRYOFLEX low-temperature device and intensity measurements were performed using graphite-monochromated Mo-K α radiation from a sealed ceramic diffraction tube (SIEMENS). Generator settings were 50 kV/40 mA. The structure was solved by Patterson method and extension of the model was accomplished by direct method using DIRDIF or SIR2004. Final refinement on F^2 was made by full-matrix least-squares techniques using SHELXL-97, a modified version of PLUTO (preparation of illustrations) and PLATON. Absorption spectra were recorded on a Shimadzu 1800 UV–vis spectrophotometer. The linseeds were purchased from a local market. The seeds were washed with distilled water to remove dirt and were oven-dried at 60 °C till constant weight. The oil was extracted by using an electric oil expeller (KEK P0015–10127 Germany, KEK, EGON KELLER GMBH & Co. KG).

2.2. Synthesis

2.2.1. Synthesis of 2-(4-ethylbenzylidene) butanoic acid. Mixture of 4-ethylbenzaldehyde (3.75 g, 28 mM), ethylmalonic acid (7.39 g, 56 mM), and piperidine (4.76 g, 56 mM) in molar ratios of 1:2:2 (scheme 1) was refluxed in a two-necked round-bottom flask in pyridine as solvent for 24 h on a steam bath. After cooling, the reaction mixture was poured into ice water and acidified with conc. HCl until pH 3. The precipitates were filtered, washed with water, recrystallized in ethanol, and dried. Yield: 3.92 g, 69.6%. m.p. 109–110 °C. Anal. Calcd for $C_{13}H_{16}O_2$ (%): C, 76.44; H, 7.90. Found (%): C, 76.28; H, 7.92. FT-IR (KBr, cm⁻¹): 3329 v(OH), 1672 v(OCO)_{asym}, 1421 v(OCO)_{sym}, ($\Delta v = 251$ cm⁻¹). ¹H NMR (CDCl₃, ppm): 11.90 (s, H₁, 1H), 7.81 (s, H₃, 1H), 7.40 (d, H_{5,5'}, 2H), 7.26 (d, H_{6,6'}, 2H), 2.78 (q, H₈, 2H), 1.28 (t, H₉, 3H), 2.58 (q, H₁₀, 2H), 1.23 (t, H₁₁, 3H). ¹³C NMR (CDCl₃, ppm): 173.7 (C-1), 131.4 (C-2), 142.2 (C-3), 132.2 (C-4), 128.6 (C-5), 129.7 (C-6), 138.5 (C-7), 29.3 (C-8), 14.1 (C-9), 21.4 (C-10), 15.2 (C-11).

2.2.2. Synthesis of Na-salt of 2-(4-ethylbenzylidene) butanoic acid. The sodium salt of ligand, R'COONa, was prepared by dropwise addition of an equimolar amount of sodium hydrogen carbonate solution to a methanolic solution of R'COOH. The solution was stirred for 2 h at room temperature, evaporated under reduced pressure to give a white solid, and vacuum dried.

Scheme 2 represents numbering in ligand and R groups attached to Sn for ¹H and ¹³C NMR interpretation.

2.2.3. Dimethyltin(IV) [bis(2-(4-ethylbenzylidene) butanoate)] (1). R⁷COONa (0.4 g, 1.76 mM) was refluxed for 10 h with dimethyltin(IV) dichloride (0.194 g, 0.88 mM) in 2 : 1 M ratio in dry toluene (100 mL) contained in a 250 mL two-necked round-bottom flask. A turbid solution obtained was left overnight at room temperature. The sodium chloride formed was filtered off and the filtrate was rotary evaporated. The resultant solid mass was recrystallized from chloroform and *n*-hexane (4 : 1) mixture. Yield: 0.44 g, 89.7%. m.p. 123–125 °C. Anal. Calcd for C₂₈H₃₆O₄Sn (%): C, 60.56; H, 6.53. Found (%): C, 60.02; H, 6.48. FT-IR (KBr, cm⁻¹): 1537 ν (OCO)_{asym}, 1400 ν (OCO)_{sym}, ($\Delta \nu = 137$ cm⁻¹), 574.7 ν (Sn–C), 494 ν (Sn–O). ¹H NMR (CDCl₃ and \langle DMSO \rangle ppm): 7.81 \langle 7.85 \rangle (s, H₃, 2H), 7.36

 $\langle 7.32 \rangle$ (d, H_{5,5'}, 4H), 7.24 $\langle 7.28 \rangle$ (d, H_{6,6'}, 4H), 2.66 $\langle 2.60 \rangle$ (q, H₈, 4H), 1.25 $\langle 1.27 \rangle$ (t, H₉, 6H), 2.57 $\langle 2.53 \rangle$ (q, H₁₀, 4H), 1.20 $\langle 1.16 \rangle$ (t, H₁₁, 6H), 1.09 $\langle 1.01 \rangle$ (s, H α , 6H, ²*J*(^{119/117}Sn⁻¹H) = 82/79, C–Sn–C = 134.06°). ¹³C NMR (CDCl₃ and \langle DMSO \rangle ppm): 178.2 $\langle 177.3 \rangle$ (C-1), 133.0 $\langle 128.5 \rangle$ (C-2), 144.9 $\langle 140.7 \rangle$ (C-3), 133.3 $\langle 130.1 \rangle$ (C-4), 129.5 $\langle 127.9 \rangle$ (C-5), 128.0 $\langle 127.5 \rangle$ (C-6), 140.3 $\langle 139.2 \rangle$ (C-7), 28.7 $\langle 28.1 \rangle$ (C-8), 13.8 $\langle 14.3 \rangle$ (C-9), 21.1 $\langle 22.6 \rangle$ (C-10), 15.3 $\langle 14.8 \rangle$ (C-11), 1.0 $\langle 1.05 \rangle$ (C- α , ¹*J*(¹¹⁹Sn–¹³C) = 704/670 Hz, C–Sn–C = 138.5°). ¹¹⁹Sn NMR (CDCl₃, ppm): –136.9.

2.2.4. Dibutyltin(IV) [bis (2-(4-ethylbenzylidene) butanoate)] (2). Compound 2 was prepared in the same way as 1 using R[/]COONa (0.4 g, 1.76 mM) and dibutyltin(IV) dichloride (0.27 g, 0.88 mM) in 2 : 1 M ratio. The product was recrystallized from chloroform and *n*-hexane (4 : 1) mixture. Yield: 0.46 g, 82%. m.p. 93–95 °C. Anal. Calcd for C₃₄H₄₈O₄Sn (%): C, 63.86; H, 7.57. Found (%): C, 64.04; H, 7.61. FT-IR (KBr, cm⁻¹): 1508 ν (OCO)_{asym}, 1367 ν (OCO)_{sym}, ($\Delta \nu = 141 \text{ cm}^{-1}$), 503 ν (Sn–C), 459 ν (Sn–O). ¹H NMR (CDCl₃ and \langle DMSO \rangle ppm): 7.81 \langle 7.84 \rangle (s, H₃, 2H), 7.37 \langle 7.41 \rangle (d, H_{5.5}, 4H), 7.27 \langle 7.25 \rangle (d, H_{6.6}, 4H), 2.67 \langle 2.61 \rangle (q, H₈, 4H), 1.26 \langle 1.29 \rangle (t, H₉, 6H), 2.60 \langle 2.55 \rangle (q, H₁₀, 4H), 1.21 \langle 1.25 \rangle (t, H₁₁, 6H), 1.75 \langle 1.69 \rangle (t, H_a, 4H), 1.39–1.45 \langle 1.30–1.37 \rangle (m, H_β, 4H), 1.45–1.51 \langle 1.39–1.48 \rangle (m, H_γ, 4H), 0.92 \langle 0.90 \rangle (t, H_δ, 6H). ¹³C NMR (CDCl₃ and \langle DMSO \rangle ppm): 178.2 \langle 180.1 \rangle (C-1), 133.2 \langle 134.2 \rangle (C-2), 144.8 \langle 140.4 \rangle (C-3), 133.6 \langle 132.8 \rangle (C-4), 128.0 \langle 127.6 \rangle (C-5), 129.5 \langle 128.2 \rangle (C-6), 139.9 \langle 140.1 \rangle (C-7), 28.7 \langle 28.1 \rangle (C-8), 13.8 \langle 14.2 \rangle (C-9), 21.1 \langle 21.5 \rangle (C-10), 15.3 \langle 14.9 \rangle (C-11), 25.2 \langle 25.6 \rangle (C-*a*, ⁻¹*J*(¹¹⁹Sn–¹³C) = 785 Hz, C–Sn–C = 152.1°), 26.3 \langle 25.9 \rangle (C- β , ²*J*(¹¹⁹Sn–¹³C) = 42 Hz), 26.8 \langle 26.1 \rangle (C- γ , ³*J*(¹¹⁹Sn–¹³C) = 131 Hz), 13.6 \langle 14.0 \rangle (C- δ). ¹¹⁹Sn NMR (CDCl₃, ppm): -147.9.

2.2.5. Dioctyltin(IV) [bis (2-(4-ethylbenzylidene) butanoate)] (3). Compound 3 was prepared from R[/]COOH (0.32 g, 1.56 mM) and dioctyltin(IV) oxide (0.28 g, 0.78 mM). The reactant mixture was suspended in 100 mL dry toluene in a single-necked round-bottom flask (250 mL), equipped with a Dean-Stark apparatus. The mixture was refluxed for 10 h and water formed during the condensation was removed at regular intervals. A clear solution thus obtained was cooled to room temperature and solvent was removed under reduced pressure. The solid obtained was recrystallized from chloroform and *n*-hexane (4:1) mixture. Yield: 0.44 g, 76%. m.p. semi-solid. Anal. Calcd for C42H64O4Sn (%): C, 67.11; H, 8.58. Found (%): C, 66.34; H, 8.13. FT-IR (KBr, cm⁻¹): 1509 ν (OCO)_{asym}, 1365 ν (OCO)_{sym}, ($\Delta \nu = 144$ cm⁻¹), 560 v(Sn–C), 420 v(Sn–O). ¹H NMR (CDCl₃ and (DMSO) ppm): 7.80 (7.86) (s, H₃, 2H), 7.37 $\langle 7.40 \rangle$ (d, H_{5,5'}, 4H), 7.26 $\langle 7.31 \rangle$ (d, H_{6,6'}, 4H), 2.66 $\langle 2.59 \rangle$ (q, H₈, 4H), 1.75 (1.68) (t, H₉, 6H), 2.59 (2.49) (q, H₁₀, 4H), 1.41 (1.43) (t, H₁₁, 6H), 1.30–1.21 (1.25–1.19) (bs, H_{$\alpha,\beta,\gamma,\delta,\alpha',\beta',\gamma'$}, 28H), 0.84 (0.89) (t, H_{$\delta'}, 6H). ¹³C NMR (CDCl₃ and <math>(DMSO)$ ppm):</sub> 178.1 (180.2) (C-1), 133.2 (131.5) (C-2), 144.8 (141.1) (C-3), 133.6 (132.4) (C-4), 128.0 (127.6) (C-5), 129.5 (128.7) (C-6), 130.8 (130.1) (C-7), 33.4 (32.1) (C-8), 14.0 (14.2) (C-9), 21.1 (22.4) (C-10), 15.3 (14.8) (C-11), 22.6 (21.7) (C- α , ¹J(¹¹⁹Sn–¹³C) = 575 Hz, C– Sn-C = 127.1°), 31.8 (30.9) (C- β), 29.2 (29.5) (C- γ), 29.1 (29.3) (C- δ), 28.7 (28.4) (C- α '), 25.5 (25.0) (C- β'), 24.6 (24.9) (C- γ'), 13.8 (14.1) (C- δ'). ¹¹⁹Sn NMR (CDCl₃, ppm): -162.7.

2.2.6. Trimethyltin(IV) 2-(4-ethylbenzylidene) butanoate (4). Compound 4 was prepared in the same way as 1 using R[/]COONa (0.4 g, 1.76 mM) and trimethyltin(IV) chloride (0.35 g, 1.76 mM) in 1:1 M ratio. The product was recrystallized from chloroform and *n*-hexane

(4 : 1) mixture. Yield: 0.44 g, 89%. m.p. 80–81 °C. Anal. Calcd for $C_{16}H_{24}O_2Sn$ (%): C, 52.35; H, 6.59. Found (%): C, 52.16; H, 6.41. FT-IR (KBr, cm⁻¹): 1539 ν (OCO)_{asym}, 1376 ν (OCO)_{sym}, ($\Delta \nu = 163 \text{ cm}^{-1}$), 547 ν (Sn–C), 435 ν (Sn–O). ¹H NMR (CDCl₃ and \langle DMSO \rangle ppm): 7.65 \langle 7.77 \rangle (s, H₃, 1H), 7.32 \langle 7.38 \rangle (d, H_{5,5'}, 2H), 7.21 \langle 7.25 \rangle (d, H_{6,6'}, 2H), 2.64 \langle 2.55 \rangle (q, H₈, 2H), 1.24 \langle 1.25 \rangle (t, H₉, 3H), 2.53 \langle 2.45 \rangle (q, H₁₀, 2H), 1.16 \langle 1.08 \rangle (t, H₁₁, 3H), 0.52 \langle 0.53 \rangle (s, H_a, 9H) ²J(^{119/117}Sn–¹H) = 58/56 Hz, C–Sn–C = 110.66°). ¹³C NMR (CDCl₃ and \langle DMSO \rangle ppm): 173.8 \langle 175.2 \rangle (C-1), 133.7 \langle 134.5 \rangle (C-2), 144.3 \langle 141.5 \rangle (C-3), 135.4 \langle 136.2 \rangle (C-4), 127.9 \langle 126.8 \rangle (C-5), 129.3 \langle 128.6 \rangle (C-6), 137.9 \langle 137.1 \rangle (C-7), 28.6 \langle 29.3 \rangle (C-8), 13.9 \langle 14.3 \rangle (C-9), 21.4 \langle 22.3 \rangle (C-10), 15.3 \langle 16.1 \rangle (C-11) –2.2 \langle 2.4 \rangle (C- α), ¹J(¹¹⁹Sn–C) = 388 Hz, C–Sn–C = 110.78°). ¹¹⁹Sn NMR (CDCl₃, ppm): +127.8.

2.2.7. Triphenyltin(IV) 2-(4-ethylbenzylidene) butanoate (5). Compound 5 was prepared in the same way as 1 using R/COONa (0.4 g, 1.76 mM) triphenyltin(IV) chloride (0.68 g, 1.76 mM) in 1 : 1 M ratio. The product was recrystallized from chloroform and *n*-hexane (4 : 1) mixture. Yield: 0.73 g, 74%. m.p. 145–146 °C. Anal. Calcd for $C_{31}H_{30}O_2Sn$ (%): C, 67.30; H, 5.47. Found (%): C, 66.23; H, 5.06. FT-IR (KBr, cm⁻¹): 1537 v(OCO)_{asym}, 1393 v(OCO)_{sym}, ($\Delta v = 144$ cm⁻¹), 537 v(Sn–C), 442 v(Sn–O). ¹H NMR (CDCl₃ and $\langle DMSO \rangle$ ppm): 7.34 $\langle 7.46 \rangle$ (s, H₃, 1H), 7.32 $\langle 7.38 \rangle$ (d, H_{5.5}', 2H), 7.10 $\langle 7.0 \rangle$ (d, H_{6.6}', 2H), 2.62 $\langle 2.69 \rangle$ (q, H₈, 2H), 1.21 $\langle 1.29 \rangle$ (t, H₉, 3H), 2.54 $\langle 2.47 \rangle$ (q, H₁₀, 2H), 1.17 $\langle 1.11 \rangle$ (t, H₁₁, 3H), 7.35–7.30 $\langle 7.29–7.21 \rangle$ (H_{β}, H_{γ}, H_{δ}, 15H). ¹³C NMR (CDCl₃ and $\langle DMSO \rangle$ ppm): 173.6 $\langle 176.2 \rangle$ (C-1), 133.2 $\langle 135.1 \rangle$ (C-2), 145.3 $\langle 142.3 \rangle$ (C-3), 135.8 $\langle 134.2 \rangle$ (C-4), 129.1 $\langle 130.6 \rangle$ (C-5), 130.3 $\langle 130.2 \rangle$ (C-6), 137.2 $\langle 138.7 \rangle$ (C-7), 28.2 $\langle 29.5 \rangle$ (C-8), 14.3 $\langle 14.6 \rangle$ (C-9), 22.4 $\langle 21.7 \rangle$ (C-10), 15.7 $\langle 16.1 \rangle$ (C-1), 131.0 $\langle 132.2 \rangle$ (C- α , $J(^{119}Sn-^{13}C) = 648$ Hz, C-Sn–C = 116.4°), 139.5 $\langle 140.4 \rangle$ (C- β , $^2J(^{119}Sn-^{13}C) = 49$ Hz), 130.5 $\langle 129.6 \rangle$ (C- γ , $^3J(^{119}Sn-^{13}C) = 65$ Hz), 130.7 $\langle 129.8 \rangle$ (C- δ). ¹¹⁹Sn NMR (CDCl₃, ppm): +101.8.

2.3. Antibacterial studies

HL and its organotin(IV) complexes were tested against five bacterial strains; two Gram-positive (*Micrococcus luteus* and *Staphylococcus aureus*) and three Gram-negative (*Escherichia coli, Bordetella bronchiseptica,* and *Pseudomonas aeruginosa*). The agar-well diffusion method was used for the determination of antibacterial activities [18]. Broth culture (0.75 mL) containing ca. 10^6 colony-forming units per mL of the test strain was added to 75 mL of nutrient agar medium at 45 °C, mixed well, and then poured into a 14 cm sterile Petri plate. The media were allowed to solidify and 8 mm wells were dug with a sterile metallic borer. Then a DMSO solution of test sample ($100 \,\mu$ L) at 1 mg/mL was added to the respective wells. DMSO served as negative control, and the standard antibacterial drugs *Roxyithromycin* (1 mg/mL) and *Cefixime* (1 mg/mL) were used as positive control. Triplicate plates of each bacterial strain were prepared and incubated aerobically at 37 °C for 24 h. The activity was determined by measuring the diameter of zone showing complete inhibition (mm).

2.4. Antifungal studies

Antifungal activities against five fungal strains (Aspergillus flavus, Aspergillus niger, Fusarium solani, Mucor spp., and Aspergillus fumigatus) were determined by using the

agar tube dilution method [19]. Screw-capped test tubes containing Sabouraud dextrose agar (SDA) medium (4 mL) were autoclaved at 121 °C for 15 min. Tubes were allowed to cool at 50 °C and non-solidified SDA was loaded with 66.6 μ L of compound from the stock solution (12 mg/mL in DMSO) to make 200 μ g/mL final concentration. Tubes were then allowed to solidify in slanting position at room temperature. Each tube was inoculated with 4 mm diameter piece of inoculum from seven-day-old fungal culture. The media supplemented with DMSO and *Terbinafine* (200 μ g/mL) were used as negative and positive control, respectively. The tubes were incubated at 28 °C for seven days and growth was determined by measuring linear growth (mm). The growth inhibition was calculated with reference to growth in vehicle control,

% Growth inhibition =
$$100 - \left(\frac{\text{Linear growth in test sample (mm)}}{\text{Linear growth in control (mm)}} \times 100\right)$$

2.5. Cytotoxic studies

Cytotoxicity was studied by the brine-shrimp lethality assay method [18]. Brine-shrimp (*Artemia salina*) eggs were hatched in artificial sea water (3.8 g sea salt/L) at 23 ± 1 °C. After two days, these shrimps were transferred to vials containing 5 mL of artificial sea water (10 shrimps per vial) with 10, 100, and 1000 µg/mL final concentrations of each compound taken from their stock solutions of 12 mg/mL in DMSO. After 24 h, the number of surviving shrimps was counted. Data were analyzed with a Biostat 2009 computer program (Probit analysis) to determine LD₅₀ values.

2.6. DNA interaction studies by UV-vis spectroscopy

0.2 g of SS-DNA (salmon sperm) was dissolved in 100 mL of double-deionized water and kept at 4 °C. Solutions of DNA in 20 mM Tris-HCl (pH 7.4) gave the ratio of UV absorbance at 260 and 280 nm, A_{260}/A_{280} , of 1.86 indicating that the DNA is sufficiently free from protein [20]. The DNA concentration was determined via absorption spectroscopy using the molar absorption coefficient of 6600 M⁻¹ cm⁻¹ at 260 nm [21], and was found as 7.45×10^{-5} M. From this stock solution, 3, 6, 9, 12, 15, 18, 21, 24, and 27 µM of working solutions were prepared by dilution. The complexes were dissolved in 10% DMSO at a concentration of 1×10^{-3} M of **HL** and **4** while 5×10^{-5} M of **1**. The UV absorption titrations were performed by keeping the complex concentration fixed while varying the concentration of DNA. Equivalent solutions of DNA were added to the complex and reference solutions to eliminate the absorbance of DNA itself. Compound–DNA solutions were kept for 30 min at ambient temperature before absorption measurements were recorded using cuvettes of 1 cm path length.

2.7. Catalytic experiment

Transesterification of linseed oil was carried out using organotin(IV) carboxylates as catalysts in molar ratio of 400:100:1 (methanol, oil, and catalyst). Linseed oil (0.01 M) was transesterified using 0.04 M methanol and 0.1 mM catalyst in a 100 mL three-necked round-bottom flask equipped with a reflux condenser, magnetic stirrer, thermometer, and sampling

outlet. Before the reaction, the organotin catalyst was solubilized in 0.5 mL chloroform. The reaction mixture was refluxed and stirred with a constant speed of 600 rpm. The sample was taken after 1, 8, 12, and 24 h and analyzed by ¹H NMR to check the % conversion of triglycerides in linseed oil into fatty acid methyl esters (biodiesel).

3. Results and discussion

3.1. Syntheses of 1–5

Di- and tri-organotin chlorides react with NaL in 1:2 and 1:1, respectively, while R₂SnO with **HL** in 1:2 M ratios gave complexes according to the following equations:

$$\begin{array}{rcl} R_2 SnCl_2 + \ 2NaL & \to & R_2 SnL_2 + \ 2NaCl & (1) & R = & CH_3(1), n - C_4 H_9(2), \\ R_2 SnO & + & 2HL & \to & R_2 SnL_2 + & H_2 O & (2) & R = n - C_8 H_{17}(3) \\ R_3 SnCl & + & NaL & \to & R_3 SnL & + & NaCl & (3) & R = CH_3(4), & C_6 H_5(5) \end{array}$$

3.2. FT-IR analysis

FT-IR spectra of complexes were recorded from 4000 to 400 cm⁻¹ to determine the mode of carboxylate coordination to tin. The difference between the asymmetric and symmetric carboxylate stretch [$\Delta v = v_{asym}(COO^-) - v_{sym}(COO^-)$] gives the mode of binding of COO⁻ to tin [22]. Difference (Δv) between asymmetric (COO⁻) and symmetric (COO⁻) absorption frequencies below 200 cm⁻¹ represents bidentate carboxylate, and greater than 200 cm⁻¹ represents unidentate carboxylate [23]. The magnitudes of Δv [($v_{asym}(COO^-) - v_{sym}(COO^-)$] for 1–5 are in the range 141–163 cm⁻¹, indicating bidentate carboxylates in these complexes [24]; Δv value between 150 and 250 cm⁻¹ indicates bridging while a value less than 150 cm⁻¹ exhibits a chelate structure [1]. The carboxylates are chelated bidentate in 1–3 and 5 in solid state. The Δv for 4 is compatible with bridging bidentate giving five-coordinate Sn(IV) in the solid state and is matched with X-ray structure of 4. The structures proposed by IR data are consistent with reported data [1, 9, 25, 26]. Absorption bands at 420–494 cm⁻¹ for 1–5 are assigned to Sn–O stretch which indicates the formation of complexes [27].

3.3. NMR studies

All the protons in 1–5 were identified by the position and number with the protons calculated from the incremental method [28]. The methyl protons of dimethyltin(IV) (1) and trimethyltin(IV) (4) are sharp singlets with well-defined satellites at 1.09–1.28 and 0.52–0.71 ppm having coupling constants of 82/79 and 58/56 Hz [${}^{2}J$ (${}^{119/117}$ Sn, ${}^{1}H$)], respectively. The determined ${}^{2}J$ values indicate five or six coordination for 1 and four coordination for 4 in solution, consistent with our earlier reports [25, 26]. The protons of *n*-butyltin (IV) derivative showed a complex pattern and were assigned according to the literature [29, 30]. Despite the complex pattern of ${}^{1}H$ NMR spectra of di-*n*-butyltin(IV) (2) derivative, a clear triplet due to terminal methyl appears at 0.92–0.97 ppm. The methylene protons (CH₂) of *n*-octyltin(IV) 3 exhibited different behavior compared with the *n*-butyl groups of the respective complexes and gave broad/multiplets at 0.84–1.30 ppm, which are consistent with the values calculated by the incremental method [28].

The carbons attached to Sn atom have satellites due to ${}^{1}J$ [119 Sn, 13 C] coupling. The values of the coupling constant ${}^{1}J$ [119 Sn, 13 C] are helpful to find coordination behavior of tin(IV) in solution. Complexes 1–3 exhibit ${}^{1}J$ [119 Sn, 13 C], 704 Hz, 705 Hz, and 575 Hz, respectively, which correspond to five-coordinate tin(IV) in solution [31]. Complexes 4 and 5 exhibit ${}^{1}J$ [119 Sn, 13 C], 388 Hz, and 648 Hz which correspond to four-coordinate tin(IV) in solution [32]. The C–Sn–C angles, calculated by Lockhart's equation [33], also support five-coordinate di-organotin(IV) complexes 1–3 and four coordinate for tri-organotin(IV) complexes 4 and 5 in solution.

 119 Sn NMR spectroscopy is valuable for the study of coordination number of tin(IV) with wide range of tin chemical shifts and strong dependence of tin chemical shifts upon the substituents. 119 Sn NMR spectra show only a sharp singlet, indicating the formation of a single species. A representative 119 Sn NMR spectrum is shown in figure 1. 119 Sn NMR values for 1–3 are –136.9, –147.9, and –162.7 ppm, respectively, falling in the range of five coordination and for 4 and 5 are +127.8 and +101.8 ppm, respectively, suggesting four-coordinate tin(IV) in non-coordinating solvent [33].

3.4. Crystal structure of 4

The molecular and polymeric bridging structure of 4 is shown in figures 2 and 3, respectively. The crystal data, selected bond lengths, and bond angles of 4 are listed in tables 1 and 2, respectively. Sn1 is bonded with three methyl carbons and two oxygens from the



Figure 1. 119 Sn NMR of 1.



Figure 2. Molecular structure of Me₃SnL (4).



Figure 3. Polymeric structure of 4.



Scheme 1.

Table 1. Crystal data and structure refinement parameters for Me₃SnL (4).

Chemical formula	$C_{16}H_{24}O_2Sn$
Formula mass $(g M^{-1})$	367.06
Crystal system	Monoclinic
Space group	$P_2 l/n$
Unit cell dimensions	
<i>a</i> (Å)	6.9755(2)
b(Å)	9.9214(2)
<i>c</i> (Å)	25.2694(6)
α (°)	90.00
β (°)	97.806(1)
γ(°)	90.00
Volume ($Å^3$)	1732.61(7)
Ζ	4
Temperature (K)	296(2)
Density (Calcd) $(g \text{ cm}^{-3})$	1.407
Absorption coefficient (mm^{-1})	1.472
F(000)	744
Radiation (A^0) (Mo-K α)	0.71073
Index ranges	$h: -8 \rightarrow 8; k: -10 \rightarrow 12; l: -31 \rightarrow 31$
θ (°) Min Max	2.62-26.0
Total reflections	3411
Restraints/parameters	06/206
$R_{\rm all}, R_{\rm gt}$	0.0316, 0.0241
WR _{ref} , WR _{gt}	0.0647, 0.0594
Goodness of fit	1.034

Table 2. Selected bond lengths (Å) and angles (°) of Me₃SnL (4).

Bond lengths (Å)			
Sn1-C14	2.112(3)	O1–C1	1.241(3)
Sn1-C13	2.112(3)	O2C1	1.282(3)
Sn1-C12	2.118(3)	Sn1-O1	2.457(2)
		Sn1-O2	2.1687(19)
Bond angles (°)			
C14-Sn1-C13	120.78(15)	O1–Sn–O2	172.15(7)
C14-Sn1-C12	121.87(15)	C14-Sn1-O2	98.04(11)
C13-Sn1-C12	116.23(16)	C13-Sn1-O2	88.71(11)
C14-Sn1-O1	85.41(10)	C12-Sn1-O2	93.49(11)
C13-Sn1-O1	83.48(11)	C1-O1-Sn1	143.91(19)
C12-Sn1-O1	90.63(11)		

two carboxylates. The Sn1–O1 and Sn1–O2 bond distances are 2.457(2) and 2.1687(19) Å, respectively, showing the former is coordinate covalent (shorter than the sum of the van der Waals radii of connected atoms, 3.68 Å) and the latter is a covalent bond (covalent bond length, 2.13 Å) [34]. The two oxygens bonded with Sn1 have axial positions O1–Sn1–O2



Scheme 2.

angle of 172.15(7)° and the three methyl groups are equatorial having angles C14–Sn1– C13 = 120.78(15) Å, C14–Sn1–C12 = 121.87(15) Å, and C13–Sn1–C12 = 116.23(16) Å. Therefore, Sn1 is best assigned as distorted trigonal bipyramidal, consistent with FT-IR and literature [9, 34, 35]. The geometry around Sn can also be deduced by the value of $\tau = (\beta - \alpha)/60$, where β is the largest and α is the second largest basal angles around Sn [36]. The angle values $\alpha = \beta = 180^{\circ}$ correspond to a square-pyramidal geometry and the value of $\alpha = 120^{\circ}$ corresponds to a perfect trigonal-bipyramidal geometry. Thus, $\tau = 0$ for a perfect

Table 3. Antibacterial data of HL and its organotin(IV) complexes.

Compound	Average zone of inhibition (mm) mean \pm SD				
	Staphylococcus aureus	Escherichia coli	Bordetella bronchiseptica	Pseudomonas aeruginosa	Micrococcus luteus
HL	0	17 ± 2	0	0	17 ± 1
1	0	15 ± 1	19 ± 1	20 ± 1	0
2	14 ± 1	13.3 ± 0.6	17 ± 1	19 ± 1	11 ± 1
3	13 ± 1	15 ± 1	17 ± 2	17.7 ± 0.6	13 ± 1
4	17 ± 1	17 ± 1	20 ± 1	25 ± 1	25 ± 1
5	20 ± 1	19 ± 1	19 ± 1	26 ± 1	14 ± 1
Cefixime	22.3 ± 0.6	25.7 ± 0.6	21 ± 1	24 ± 2	26 ± 1
Roxythromycin	27 ± 1	26 ± 1	24 ± 1	25 ± 1	30 ± 1

Note: Concentration: 1 mg/mL of DMSO. Reference drugs, Roxythromycin and Cefixime 1 mg/mL.

	Mean value of percent growth inhibition (%) mean \pm SD					
Compound	Aspergillus flavus	Aspergillus niger	Aspergillus fumigatus	Fusarium solani	Mucor spp.	
HL	11 ± 3	13 ± 1	0	0	38 ± 2	
1	13 ± 2	14.3 ± 0.6	13 ± 2	12 ± 2	60 ± 3	
2	15 ± 2	17 ± 1	14 ± 1	16 ± 1	24 ± 2	
3	15 ± 2	14 ± 3	15 ± 3	16 ± 1	22 ± 1	
4	19 ± 2	25 ± 2	17 ± 2	52 ± 2	74 ± 3	
5	22 ± 3	64 ± 3	13 ± 2	50 ± 3	86 ± 3	
Terbinafine	100	100	100	100	100	

Table 4. Antifungal activity data of HL and its organotin(IV) complexes.

Note: In vitro agar tube dilution method, concentration: 200 μ g/mL of DMSO; % inhibition of fungal growth = 100 - gt/gc × 100. gt = linear growth in test (mm) and gc = linear growth in vehicle control (mm).

	No. of shrin	er dilution		
Compound	1000 µg/mL	100 µg/mL	10 µg/mL	$LD_{50} \; (\mu g/mL)$
HL	10	06	0	729
1	20	12	06	108
2	15	8	05	137
3	12	8	06	620
4	20	15	08	19
5	20	20	15	6
Vehicle control	0	0	0	

Table 5. Cytotoxicity data of HL and its organotin(IV) complexes.

square-pyramidal and unity for perfect trigonal-bipyramidal. In 4, $\beta = 172.15^{\circ}$ and $\alpha = 121.87^{\circ}$, so the calculated τ value is 0.84 which indicates distorted trigonal-bipyramidal arrangement around Sn.

3.5. Biological studies

3.5.1. Antibacterial studies. In vitro antibacterial activities of HL and 1–5 were carried out by agar-well diffusion. *Roxyithromycin* and *Cefixime* were used as positive controls. The results are shown in table 3. Criteria for activity are based on zone of inhibition (mm) with inhibition zone more than 20 mm showing significant activity, 18–20 mm activity is good, 15–17 mm is low, and below 14 mm is non-significant [20]. The antibacterial study showed that all the complexes were active compared to HL but lower than standard reference drugs except 4 and 5 whose antibacterial activities against *P. aeruginosa* is comparable with the standard reference drugs. In general, 4 and 5 (tri-organotin(IV) derivatives) exhibited greater activity than 1–3 (di-organotin(IV) derivatives), consistent with the literature [9].

3.5.2. Antifungal studies. HL and 1–5 were also screened for antifungal activities against five fungal strains (*A. flavus, A. niger, A. fumigatus, F. solani,* and *Mucor* spp.) by using agar tube dilution method. The results are shown in table 4. *Terbinafine* was used as standard drug in this assay. Criteria for activity are based on percent growth inhibition with



Figure 4. Absorption spectra of 1 mM HL in the absence (a) and the presence of $3-27 \,\mu$ M (a–j) DNA. The arrow direction indicates increasing concentrations of DNA. Inside graph is the plot of $A_0/(A-A_0)$ vs. 1/[DNA] for the determination of binding constant and Gibb's free energy of the HL – DNA adduct.



Figure 5. Absorption spectra of 50 μ M of compound in the absence (a) and the presence of 3–27 μ M (a–j) DNA. The arrow direction indicates increasing concentrations of DNA. Inside graph is the plot of $A_0/(A - A_0)$ vs. 1/[DNA] for the determination of binding constant and Gibb's free energy of the **1** – DNA adduct.



Figure 6. Absorption spectra of 1 mM of compound in the absence (a) and the presence of $3-27 \,\mu\text{M}$ (a–j) DNA. The arrow direction indicates increasing concentrations of DNA. Inside graph is the plot of $A_0/(A - A_0)$ vs. 1/[DNA] for the determination of binding constant and Gibb's free energy of the 4 – DNA adduct.

more than 70% growth inhibition considered significant, 60-70% good, 50-60% moderate while below 50% non-significant. The data showed that the antifungal activity of 1-5 was higher than **HL** but lower than the reference drug.

3.5.3. Cytotoxic studies. Cytotoxicities of **HL** and **1–5** were studied *in vitro* using the brine-shrimp lethality method by using reference drug MS-222 (*Tricaine methanesulfonate*); the results are shown in table 5. The data are based on mean value of two replicates each of 10, 100, and 1000 μ g mL⁻¹. The LD₅₀ data exhibited that **4** and **5** are toxic while ligand **HL** and **1–3** are less toxic.

3.6. DNA binding studies

The binding interactions of **HL**, **1** and **4** with SS-DNA were investigated by comparing their absorption spectra with and without SS-DNA. Both **HL**, **1** and **4** showed minor bathochromic shift of the spectral band with significant hypochromicity, suggesting groove binding as well as intercalation of the compounds with the DNA helix (figures 4–6). This may be attributed to the presence of phenyl group that facilitates interaction with double-stranded DNA [37]. After 24 h, the spectrum was taken again and the same results were obtained which confirm the stability of the drug-DNA complex.

The intrinsic binding constant K of **HL**, **1** and **4** were calculated to compare binding strengths of ligand-DNA and complex-DNA by using the Benesi–Hildebrand equation [38]:

$$\frac{A_0}{A - A_0} = \frac{\varepsilon_{\rm G}}{\varepsilon_{\rm H-G} - \varepsilon_0} + \frac{\varepsilon_{\rm G}}{\varepsilon_{\rm H-G} - \varepsilon_{\rm G}} \times \frac{1}{K[{\rm DNA}]}$$

Organotin(IV)

where K = binding constant, A_0 = absorbance of the drug, A = absorbance of the drug and its complex with DNA, ε_G = absorption coefficient of the drug and ε_{H-G} = absorption coefficient of the drug-DNA adduct. The binding constants were obtained from the intercept to slope ratios of $A_0/(A-A_0)$ versus 1/[DNA] plots. The binding constants were $6.04 \times 10^3 \text{ M}^{-1}$ (HL), $9.6 \times 10^3 \text{ M}^{-1}$ (1), and $1.7 \times 10^4 \text{ M}^{-1}$ (4).

The Gibb's free energies (Δ G) of **HL**, 1 and 4 were determined at 298 K to be -21.57 (**HL**), -9.9 (1), and -24.14 kJ M⁻¹ (4), respectively.

3.7. Catalytic activities of organotin(IV) complexes

The catalytic activities of the complexes were investigated in a transesterification reaction of triglycerides in linseed oil with methanol to produce biodiesel. The general transesterification can be represented as:



Transesterification of triglyceride with methanol

The tin complexes were selected due to the Lewis acid character of tin. Tin can expand its coordination, an important factor in the catalytic activity. The tin may activate carbonyl groups in triglycerides and cause interaction by increasing the electrophilicity of carbonyl carbon.

The transesterification of triglycerides in linseed oil was carried out with molar ratio of 400:100:1 (methanol:oil:catalyst) to assess the catalytic activity of organotin(IV) carboxylates. The conditions for experiments were not optimized and no attempt was made to remove the added catalyst from the reaction mixture. However, the effect of reaction time on % conversion of triglycerides into fatty acid methyl esters (biodiesel) was studied. Samples were taken from the reaction mixture at 1, 8, 16, and 24 h and analyzed by ¹H NMR to calculate % conversion of triglycerides into fatty acid methyl esters. The equation used [39, 40] to quantify the extent of transesterification was

$$C = 100 \times \frac{2A_{\rm Me}}{3A_{\rm CH_2}}$$

where C = percentage conversion of triglycerides to corresponding methyl esters, $A_{Me} =$ integration value of the methoxy protons of the methyl esters, and $A_{CH2} =$ integration value of α -methylene protons. The results are shown in figure 7. A representative ¹H NMR spectrum showing % conversion (30.82%) of oil (triglycerides) into biodiesel (fatty acid methyl esters)

is shown in Supplementary material (see online supplemental material at http://dx.doi.org/ 10.1080/00958972.2014.884217). The characteristic peak of methoxy protons was observed as a strong singlet at 3.65 ppm and a triplet of α -CH₂ protons at 2.33 ppm. These two peaks are distinct for the confirmation of conversion of oil (triglycerides) into biodiesel [13]. The peaks at 4.11–4.32 ppm indicate glyceridic protons and incomplete conversion of oil (triglycerides) into biodiesel (fatty acid methyl esters). These glyceridic protons peaks are absent in complete conversion of oil (triglycerides) into biodiesel [13]. The tested complexes showed less to good catalytic activity in the order n-Bu₂SnL₂ \leq Me₂SnL₂ \leq Ph₃SnL \leq Me₃SnL. The proposed mechanisms for the catalytic activity of organotin(IV) carboxylates involve Lewis acid character of tin as in polyesterification [41-43]. All the tested complexes showed catalytic activity but Me₃SnL and Ph₃SnL showed better activity which may be due to the presence of methyl groups which cause less hindrance during attack on triglyceride molecules and greater Lewis acidity in Ph₃SnL. The Lewis acidities of Sn increase, Me < Bu < Ph, because methyl and butyl groups are electron-donating while phenyl is electron-withdrawing. The stronger Lewis acidity should have greater catalytic efficiency but in our studies catalytic performance is in the reverse order, due to size of groups (Me, Bu, Ph) attached to Sn. However, catalytic activity (not Lewis acidity) may be related to geometry because in R₃SnL compared to R₂SnL₂, there would be more space for attack of nucleophilic group.

3.8. Structure-activity relationship of organotin(IV) complexes

The structure–activity relationship is required to understand the relationship between the structure and biological activity of compounds. This relationship is also helpful to predict the activity of compounds even before synthesizing. The behavior of tin is exceptional, i.e. non-toxic in its inorganic forms and highly toxic in organotin form probably due to its structures. Organotin(IV) complexes display a broad spectrum biological effect and have been extensively studied as bactericides, fungicides, wood preservatives, antitumor, and anticancer agents [44–46]. The biological activities may depend on substituted aromatic rings in the ligand and organic groups attached with tin [47–50]. To correlate structure and activity of biocidal complexes, we have studied antibacterial results of 47 and antifungal results of 38 organotin(IV) complexes [1, 9, 25, 26, 51–53]. Oxygen and sulfur donor ligands having substituted aromatic rings have increased biological activities. Muhammad *et al.* [1, 9] showed that attachment of halo group, e.g. bromo derivatives [9], gave better



Figure 7. Percentage conversion of linseed oil triglycerides into biodiesel.

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biocidal results than methoxy derivatives [1]. However, fluoro- and cyano-substituted aromatic derivatives [25, 26] show interesting and better results than bromo and methoxy derivatives [1, 9]. Rehman *et al.* [51] used sulfur donor ligands with more aromatic and cyclic parts with better results than Jabbar *et al.* [52]. Electron-withdrawing groups in the aromatic moiety provided better biocidal results [9, 25, 26] than electron-donating groups [1] due to electron-withdrawing character that make the benzene ring electron deficient with delocalized positive charge promoting interaction with negatively charged outer layer of Gram-negative bacteria. For Gram-positive bacteria, complexes having substituted aromatic rings exhibit more activity [1, 25, 26]; complexes with no substituent on aromatic ring showed less activity [53].

4. Conclusion

Five organotin(IV) complexes of 2-(4-ethylbenzylidene) butanoic acid were synthesized and characterized by elemental analysis, FT-IR, and NMR (1 H, 13 C, and 119 Sn). **4** was also analyzed by single-crystal X-ray analysis; **4** has tetrahedral geometry in solution and distorted trigonal bipyramidal with polymeric bridging behavior in the solid state. The antimicrobial studies revealed that **4** and **5** have greater activity than **1–3**. Cytotoxic studies revealed that **5** shows more toxicity than **1–4**. DNA binding studies showed that **HL**, **1** and **4** bind with DNA via groove binding as well as intercalation, due to the presence of phenyl that facilitates interaction with double-stranded DNA. Me₃SnL exhibited better catalytic activity in transesterification for the synthesis of biodiesel due to small methyl groups which cause less hindrance during attack on triglyceride molecules.

Supplementary material

Crystallographic data for the structure reported in this article has been deposited with the Cambridge Crystallographic Data Center, CCDC 891311 of complex **4**. Copies of this information may be obtained free of charge from The Director, CCDC, 12 Union Road, Cambridge CB2 1EZ (Fax: +44 1223 336 033; E-mail: deposit@ccdc.cam.ac.uk or http://www.ccdc.cam.ac.uk).

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