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ORIGINAL ARTICLE

Biologically active diorganotin(IV) complexes of *N*-(2-hydroxy-3-isopropyl-6-methyl benzyl) glycine

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Abstract A new series of diorganotin(IV) complexes of general formula $[Ph_2Sn(OPri)(Hhbgl)]$ (**1**), $[Ph_2Sn(Hhbgl)_2]$ (**2**), $[Bu_2Sn(OPri)(Hhbgl)]$ (**3**), $[Bu_2Sn(Hhbgl)_2]$ (**4**), $[Me_2Sn(OPri)(Hhbgl)]$ (**5**), and $[Me_2Sn(Hhbgl)_2]$ (**6**) [where H_2hbgl = *N*-(2-hydroxy-3-isopropyl-6-methyl benzyl) glycine] were synthesized by reacting diorganotin(IV) chloride with the ligand, with the aid of sodium isopropoxide in appropriate stoichiometric ratios (1:1 and 1:2). All the six complexes were tested in vitro for their antibacterial activity against Gram-positive bacteria namely, *Staphylococcus aureus* MTCC 96, *Bacillus subtilis* MTCC 121 and two Gram-negative bacteria namely, *Escherichia coli* MTCC 1652 and *Pseudomonas aeruginosa* MTCC 741 and in vitro antifungal activity against three pathogenic fungal strains namely, *Aspergillus niger*, *Aspergillus flavus* and *Penicillium* sp.

1. Introduction

The use of organotin complexes has risen over the last thirty years due to their industrial, medicinal and agricultural applications (Smith, 1997). Since years, organotin(IV) complexes and their derivatives received considerable attention due to their potential and beneficial use in a wide range of biological field (Li et al., 2011; Matela and Aman, 2012; Molter et al., 2012; Nath and Saini, 2011; Torres et al., 2011). Organotin(IV) complexes, having the carboxylate group, show interesting tin chemistry with different coordination spheres at tin atom. Generally five- and six coordination numbers are observed in diorganotin(IV) complexes (Azadmeher et al., 2008; Amini et al., 2009; Amini et al., 2007). While seven coordinated diorganotin(IV) complexes are also observed with mono- and

Abbreviations: H_2hbgl, *N*-(2-hydroxy-3-isopropyl-6-methyl benzyl) glycine; NaOPri, sodium isopropoxide; $Ph_2Sn(OPri)_2$, diphenyltin(IV) diisopropoxide; $Bu_2Sn(OPri)_2$, dibutyltin(IV) diisopropoxide; $Me_2Sn(OPri)_2$, dimethyltin(IV) diisopropoxide; Ph, phenyl; Bu, butyl; Me, methyl; DMSO, dimethylsulphoxide; MIC, minimum inhibitory concentration; SDA, Sabouraud dextrose agar

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bidentate bonding of the carboxylate group (Salam et al., 2012; Azadmeher et al., 2008).

The biological activity of organotin(IV) complexes is greatly influenced by the geometrical structure and the coordination number of the tin atom. In general, triorganotin(IV) complexes show a stronger biological activity than their di- and mono-organotin(IV) complexes (Demertzi et al., 2009; Rehman et al., 2007). Recent researches across the globe, signify the importance of organotin(IV) complexes in biological activities. A number of studies have been done on antibacterial and antifungal activities of diorganotin(IV) complexes (Saeed et al., 2010; Rehman et al., 2007). Recent years, organotin(IV) complexes also display significant antitumour activity (Alama et al., 2009; Casas et al., 2008; Sun et al., 2011). A promising pharmacological activity such as antiproliferative and antituberculosis activities is investigated by Demertzi et al. (2009). Recently, a luminescent property of organotin(IV) complexes is also observed by Torres et al. (2010). Therefore, the importance of the biological properties and the structure of organotin(IV) complexes has stimulated the study of tin chemistry. Synthesis and biological activities of tin- and triorganotin(IV) complexes of *N*-(2-hydroxy-3-isopropyl-6-methyl benzyl) glycine have been reported in the previous work (Matela et al., 2013). In the present investigation we have synthesized diorganotin(IV) complexes of *N*-(2-hydroxy-3-isopropyl-6-methyl benzyl) glycine and studied their biological activities against various bacterial and fungal strains.

2. Materials and methods

All the reagents, viz., diphenyltin(IV) dichloride (Alfa Aesar), dibutyltin(IV) dichloride (Alfa Aesar), dimethyltin(IV) dichloride (Merck) and thymol (sigma–aldrich) were used as received. All the chemicals and solvents used, were dried and purified by standard methods, and moisture was excluded from the glass apparatus using $CaCl_2$ drying tubes. The melting points were determined in open capillaries with electronic melting point apparatus. C, H and N analyses of ligand and complexes were carried on a VarioEL, CHNS elemental analyser. The tin content in the synthesized complexes was determined gravimetrically as SnO_2. Infrared spectra of the solid compounds were recorded on a Perkin–Elmer 1600 series FT-IR spectrophotometer in the range of 4000–500 cm^{-} from KBr discs and 500–200 from CsI discs. ^1H NMR spectra were recorded on a Bruker Avance II 400 NMR at the Sophisticated Analytical Instrument Facility (SAIF), Punjab University, Chandigarh, India, using DMSO or MeOD as a solvent and TMS as the internal standard. The Conductivity Measurement was performed using a conductometer EcoTestr EC Low in DMSO having 10^{-3} M at room temperature.

2.1. Synthesis of ligand [H_2hbgl]

An equimolar mixture of thymol (11.86 g, 0.05 mol), glycine (3.75 g, 0.05 mol), and sodium acetate crystals (6.8 g, 0.05 mol) was dissolved in glacial acetic acid (25 ml). Formalin solution (37% (w/v); 4.05 ml) was added to it drop wise with stirring and the contents were heated at 60–80 °C, till a viscous mass was obtained. The viscous mass was then poured drop wise with brisk stirring into an excess of water. The thus obtained crude product was purified by dissolving it in a requisite quantity of *ca.* 7 M sodium hydroxide solution followed by its reprecipitation by 6 M hydrochloric acid. It was further purified by recrystallization from ethanol.

Yield: 9.5 g; colour: yellow; m.p. 70 °C; Anal. Calculated for $C_{13}H_{19}NO_3$: C 65.74%, H 8.00%, N 6.04%; Found: C 65.84%, H 8.10%, N 5.80%; IR (KBr/CsI, cm^{-1}): 3390 ν(–OH), 3056 ν(C–H), 2956, 2856 ν_{as}(C–H)/ν_s(C–H), 1582 ν_{as}(COO), 1413 ν_s(COO); ^1H NMR (DMSO, ppm): δ 6.50 (d, 1H, J = 7.8 Hz, Ar–H), δ 6.90 (d, 1H, J = 8 Hz, Ar–H), δ 8.38 (s, 1H, phenolic –OH), δ 7.15 (br, 1H, –NH), δ 2.13 (s, 3H, $-CH_3$), δ 1.81 (s, 2H, Ar–C$\underline{H_2}$–), δ 3.10 (s, 2H, $-CH_2-$), δ 1.12 (d, 6H, J = 6.9 Hz, –CH(C$\mathbf{H}_3$)$_2$); ESI-MS m/z (relative abundance, %): $[C_{13}H_{19}NO_3]^+$ 237.9 (48%), $[C_{11}H_{15}O]^+$ 163.1 (30%).

2.2. Synthesis of complexes

2.2.1. [$Ph_2Sn(OPr^i)$(Hhbgl)] (**1**)

The solution of diphenyltin(IV) diisopropoxide (1.955 g, 0.005 mol) and H_2hbgl (1.067 g, 0.0045 mol) was refluxed in benzene (30 ml) for 8–10 h at 95–100°. The complex, [$Ph_2Sn(OPr^i)$(Hhbgl)], isolated as a yellow colour solid, was purified by recrystallization from alcohol at room temperature and dried under reduced pressure.

Yield: 1.746 g; colour: yellowish brown; m.p. > 300 °C; Molar conductance: 30 μS cm^{-1}; elemental analysis calculated for $C_{28}H_{35}NO_4Sn$: C 59.12%, H 6.16%, N 2.46%, Sn 20.89%; Found: C 59.16%, H 6.20%, N 2.40%, Sn 20.92%; Isopropanol in azeotrope calculated: 0.299 g; Found: 0.270 g.

IR (ν_{max}, cm^{-1}; in KBr): 3405 ν(OH), 3055 ν(C–H), 2959, 2872 ν_{as}(C–H)/ν_s(C–H), 1639 ν_{as}(COO), 1416 ν_s(COO), $\Delta\nu$: 223, 1077, 1028ν(C–O) Sn, 1220 ν(C–O), 551 ν(Sn–O), 269, 228 ν_{as}(Sn–C)/ν_s(Sn–C).

^1H NMR (DMSO, ppm): δ 7.29–7.86 (m, 12H, Ar–H and Sn–C_6H_5), δ 8.06 (s, 1H, phenolic –OH), δ 6.9 (br/s, 1H, –NH), δ 2.10 (s, 3H, $-CH_3$), δ 1.09 (d, 3H, J = 4 Hz, –CH(C$\mathbf{H}_3$)$_2$), δ 1.04 (d, 3H, J = 4.4 Hz, –CH(C$\mathbf{H}_3$)$_2$).

2.2.2. [$Ph_2Sn(Hhbgl)_2$] (**2**)

Complex 2 was prepared in the similar way as complex 1 using diphenyltin(IV) diisopropoxide (1.955 g, 0.005 mol) and H_2-hbgl (2.135 g, 0.009 mol).

Yield: 2.288 g; colour: cream; m.p. > 300 °C; Molar conductance: 22 μS cm^{-1}; elemental analysis calculated for $C_{38}H_{46}N_2O_6Sn$: C 61.17%, H 6.17%, N 3.76%, Sn 15.92%; Found: C 61.20%, H 6.21%, N 3.72%, Sn 15.98%; Isopropanol in azeotrope calculated: 0.598 g; Found: 0.540 g.

IR (ν_{max}, cm^{-1}; in KBr): 3406 ν(OH), 3056 ν(C–H), 2959, 2863 ν_{as}(C–H)/ν_s(C–H), 1639 ν_{as}(COO), 1413 ν_s(COO), $\Delta\nu$: 226, 1081, 1022 ν(C–O) Sn, 1221 ν(C–O), 570 ν(Sn–O), 281, 222 ν_{as}(Sn–C)/ν_s(Sn–C), 441 ν(Sn ← N).

^1H NMR (DMSO, ppm): δ 6.58–7.86 (m, 14H, Ar–H and Sn–C_6H_5), δ 8.11 (s, 2H, phenolic –OH), δ 6.8 (br/s, 2H, –NH), δ 2.10 (s, 6H, CH_3), δ 1.14 (d, 6H, J = 6.8 Hz, –CH(C$\mathbf{H}_3$)$_2$), δ 1.05 (d, 6H, J = 7.2 Hz, –CH(C$\mathbf{H}_3$)$_2$).

2.2.3. [$Bu_2Sn(OPr^i)$(Hhbgl)] (**3**)

Complex 3 was prepared in the similar way as complex 1 using dibutyltin(IV) diisopropoxide (1.754 g, 0.005 mol) and H_2hbgl (1.067 g, 0.0045 mol).