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Synthesis and biological activity of trinuclear seven-coordinated tin(IV) complexes derived from tridentate ligands and trimesic acid

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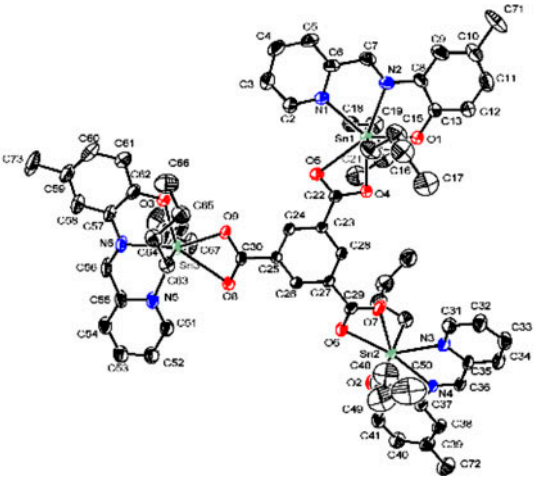

The synthesis of trinuclear Sn(IV) complexes **5a**–**h** – prepared in a one-pot reaction of 2-amino-4-R-phenol (R=H, Me, Cl, NO_2), 2-pyridine-carboxaldehyde, 1,3,5-benzenetricarboxylic acid (trimesic acid, H_3BTC), and dibutyl and dioctyltin oxides – is described. These compounds were characterized by elemental analysis, mass spectrometry, IR, and multinuclear NMR spectroscopy. The structures of **5a** and **5b** were also determined by single-crystal X-ray analysis. The trinuclear tin system is formed by bridges through the carboxylate moieties. The metal centers are seven-coordinate and the coordination polyhedron of tin can be depicted as distorted pentagonal-bipyramidal (PBP), where the equatorial plane consists of three oxygens and two nitrogens and the organic groups occupy the axial positions. The work presented here combines the useful properties of Schiff bases and H_3BTC ligands in the formation of organotin(IV) complexes, and investigates the likely antioxidant (DPPH and TBARS) and anti-inflammatory activity (TPA) of the new substances.

Keywords: Trinuclear diorganotin(IV); Carboxylate; ^{119}Sn NMR; X-ray diffraction; Seven-coordinate; Biological activity

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1. Introduction

The chemistry of polynuclear complexes containing tin has been the subject of much interest in chelate systems [1–7]. Recently, organotin(IV) complexes have emerged as a result of their potential industrial and remarkable biological applications [8–13]. These complexes play an important role either for assessing their performance as PVC stabilizers [14], biocides [15], antitumor agents [10, 16, 17], and anion-recognition agents [18], or for investigating different reactions, such as transesterification [19], acetylation of alcohols [20], and dehydration of alcohols [21]. In particular, diorganotin(IV) complexes derived from ligands containing nitrogen and oxygen donors have attracted much attention [4, 22–29]. In general, their biological activity is determined by the structures of the resulting molecules and, consequently, by the coordination number around the central tin [30–33].

Complexes containing the carboxylic R–COO–Sn (IV) bond have displayed potential in polymer chemistry, biological applications, and as antifouling agents [34–39]. Less consideration has been devoted to mixed-ligand complexes [40, 41]. There have been constant efforts to develop new strategies for the synthesis of polynuclear organotin complexes [27, 42–46], which occupy a pivotal position in understanding organotin chemistry [47–55], since the structure (in their solid state or solution) and mechanisms of action of these compounds remain a matter of research [31, 56–61]. The correlation of metal complexes with the coordinating behavior of ligand moieties, especially those containing functionalized carboxylate analogs such as trimesic acid, is scarce [62].

Specifically, 1,3,5-benzenetricarboxylic acid (H_3BTC), also known as trimesic acid, is a rigid planar molecule containing three exo-carboxylic acid groups arranged symmetrically around a benzene ring, thus forming a flat trigonal ligand that can be used as a building block [63–65]. In spite of the rich coordination chemistry exhibited by the transition metals with these ligands [63, 66–69], relatively little is known with respect to the synthesis and formal coordination of discrete organotin(IV) complexes with them; to the best of our knowledge, only a few examples of five-coordinate compounds obtained from trimesic acid with triorganotin(IV) derivatives have been reported [62, 70, 71].

In this work, we selected H_3BTC on the basis of the following considerations: (a) it has three carboxylic acid groups that may be completely or partially deprotonated, inducing rich coordination modes and allowing interesting structures with higher dimensions; (b) some of the carboxyl groups may not lie in the phenyl ring plane upon complexation to metal ions owing to hindrance, thus it may connect metal ions in different directions; and (c) it possesses high symmetry that may be helpful for the crystal growth of the product formed. There is no report about synthesis of trinuclear organotin carboxylates derived from Schiff bases. Furthermore, the driving force behind this work lies in the interesting architectures and potential applications of the products. In view of all these statements, the aim of the present contribution was to synthesize and characterize a series of trinuclear complexes, derived from Schiff bases in combination with H_3BTC ligands, and evaluate the antioxidant and anti-inflammatory properties of the compounds.

2. Experimental

2.1. *Materials and methods*

2-aminophenol, 2-amino-4-methylphenol, 2-amino-4-chlorophenol, 2-amino-4-nitrophenol, 2-pyridinecarboxaldehyde, 1,3,5-benzentricarboxylic acid, and dibutyl and dioctyltin oxides

were obtained from Aldrich Chemical Co. The ^{1}H, ^{13}C, and ^{119}Sn NMR spectra were recorded on a Bruker Avance 300. Chemical shifts are reported in ppm with respect to the references and are stated relative to the internal reference $(CH_3)_4Si$, and coupling constants are quoted in Hertz (Hz). COSY, HSQC, and HMBC experiments were carried out to assign the ^{1}H and ^{13}C spectra completely. Melting points were measured on a Fisher Johns Apparatus and were uncorrected. Mass spectra were obtained with a JEOL JMS-AX505 HA mass spectrometer in positive mode. Elemental analyses were obtained on an Exeter Analytical CE-440 instrument. IR spectra were recorded on a Bruker Tensor 27. Single-crystal X-ray diffraction measurements were done on a Bruker Smart Apex CCD diffractometer with a $\lambda_{(Mo\text{-}K\alpha)} = 0.71073$ Å, with a graphite monochromator at $T = 298$ K. All structures were solved by direct methods; all non-hydrogen atoms were refined anisotropically using full-matrix least-squares techniques. All hydrogens were placed at idealized positions based on the hybridization with thermal parameters fixed at 1.2 times (for –CH) and 1.5 times (for $–CH_3$) the value of the attached carbon. Structure solutions and refinements were performed using SHELXS-2014 and SHELXL-2014. Crystallographic data for the structural analysis have been deposited with the cambridge crystallographic data center, CCDC No. 1022654 and 1022655 for **5a** and **5b**, respectively. Both complexes possess disordered butyl groups, and in the case of **5b**, also a pyridine ring fragment and a DMSO, which were modeled in two major contributors. The ratio of the site occupational factor (SOF) for butyl groups was 0.67/0.33 for C(15)–C(17), 0.58/0.42 for C(16)–C(19), 0.62/0.38 for C(44)–C(46), 0.52/0.48 for C(48)–C(50), 0.56/0.44 for C(64)–C(66), and 0.63/0.37 for C(68)–C(70) for **5a**, where 586 restrictions were applied on the last refinement as follows: 70 parameters for SAME/SADI, 60 for DELU, and 456 for SIMU instructions. The ratio of the SOF for butyl groups was 0.83/0.17 for N(5)–C(55), 0.63/0.37 for C(15)–C(17), 0.72/0.28 for C(19)–C(21), 0.51/0.49 for C(44)–C(46), 0.55/0.45 for C(48)–C(50), 0.87/0.13 for C(64)–C(66), 0.87/0.13 for C(68)–C(70) for **5b**, and 0.72/0.28 for the DMSO solvent, where 925 restrictions were applied on the last refinement as follows: 10 parameters for DFIX, 103 for SAME/SADI, 104 for DELU, and 708 for SIMU instructions. The hydrogens on methanol were not located on the Fourier map. Reflections were merged by SHELXL, according to the crystal class for the calculation of statistics and refinement. Molar conductivity measurements were recorded in a MicroLab Conductivity Probe, Model 160, using methanol.

2.2. *Syntheses*

HL1-4 were synthesized as described previously [72] and used to compare the antioxidant and anti-inflammatory activities with the corresponding complexes.

2.2.1. General procedure for the synthesis of 5a–h. All complexes were obtained in a one-step reaction using 2.254 mmol (3 equiv) of 2-pyridinecarboxaldehyde in 50 mL of methanol and 2.254 mmol (3 equiv) of the corresponding 2-amino-4-R-phenol (X=H, Me, Cl, NO_2), stirred for 10 min. Then, 2.254 mmol of diorganotin oxide(IV) was added, the reaction mixture was stirred for 30 min, and 0.751 mmol (1 equiv) of 1,3,5-benzenetricarboxylic acid was added. The reaction mixture was stirred at room temperature or refluxed for the time indicated for each compound using standard Schlenk technique. Then, 15 mL of solvent was removed under reduced pressure giving a precipitate, which was filtered off.

2.2.1.1. *Synthesis of* ***5a***. After 2 h at room temperature, a precipitate was observed which was filtered off to give 0.938 g (0.626 mmol, 83% yield) of a red solid, m.p. 195 °C (dec.). IR (KBr) *v*: 2953, 2922, 2856, 1610, 1589 (C=N), 1545 (ν_{as} COO^-), 1482, 1449, 1365 (ν_s COO^-), 1321, 1273, 1248, 1143, 771, 733, 678, 584, 539 (Sn–O), 513 (Sn–C), 414 (Sn–N) cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz) δ: 9.47 (3H, d, $J = 4.7$ Hz, H-12), 9.28 (3H, s, H-15, H-17, H-19), 8.79 (3H, s, H-7), 8.10 (3H, ddd, $J = 7.6$, 7.5, 1.0 Hz, H-10), 7.81 (3H, d, $J = 7.6$ Hz, H-9), 7.74 (3H, ddd, $J = 7.1$, 5.2, 1.7 Hz, H-11), 7.56 (3H, d, $J = 7.7$ Hz, H-4), 7.31 (3H, dd, $J = 7.5$, 7.3 Hz, H-2), 7.20 (3H, d, $J = 7.6$ Hz, H-1), 6.66 (3H, ddd, $J = 7.7$, 7.1, 1.0 Hz, H-3), 0.98–1.40 (36 H, m, Sn–($\underline{CH_2}$)$_3$–CH_3), 0.58 (18 H, t, $J = 7.1$ Hz, Sn–$(CH_2)_3$–$\underline{CH_3}$) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 175.6 (C-13), 164.8 (C-6), 150.3 (C-12), 148.3 (C-5), 141.7 (C-7), 139.2 (C-10), 135.0 (C-15, C-17, C-19), 133.5 (C-14, C-16, C-18), 133.3 (C-2), 130.2 (C-8), 126.3 (C-9), 126.3 (C-11), 122.4 (C-1), 116.0 (C-4), 115.5 (C-3), 32.1 (C-α), 27.6 (C-γ), 26.3 (C-β), 13.5 (C-δ) ppm. ^{119}Sn NMR ($CDCl_3$, 112 MHz) δ: −370.8, (DMSO-d_6) −363.7 ppm. MS (FAB^+) [*m/z*] 9 (%): [M^+, 1497] (1); [M^+ – Bu, 1442] (3); [$M^+ - C_{49}H_{57}N_4O_8Sn_2$, 431] (100); [$C_{12}H_9N_2OSn^+$, 317] (75). Anal. Calcd for $C_{69}H_{84}N_6O_9Sn_3$ (%): C, 55.34; H, 5.65; N, 5.61. Found: C, 53.69; H, 5.74; N, 5.39. Molar conductivity (1×10^{-3} M, MeOH): 12.0 Ω^{-1} cm^2 mol^{-1}.

2.2.1.2. *Synthesis of* ***5b***. The reaction mixture was stirred at room temperature for 1 h. The precipitate was filtered off to give 0.973 g (0.630 mmol, 84% yield) of a red solid, m.p. 232 °C (dec.). IR (KBr) *v*: 2951, 2920, 2851, 1605 (C=N), 1545 (ν_{as} COO^-), 1490, 1463, 1438, 1367 (ν_s COO^-), 1303, 1246, 1140, 815, 771, 731, 552 (Sn–O), 513 (Sn–C), 414 (Sn–N) cm^{-1}. ^1H NMR (DMSO-d_6, 300 MHz) δ: 9.41 (3H, s, H-15, H-17, H-19), 9.20 (3H, d, $J = 4.5$ Hz, H-12), 8.87 (3H, s, H-7), 8.34 (3H, dd, 7.6, 7.5 Hz, H-10), 8.13 (3H, d, $J = 7.7$ Hz, H-9), 7.91 (3H, dd, $J = 7.1$, 5.1 Hz, H-11), 7.63 (3H, s, H-4), 7.13 (3H, d, $J = 8.4$ Hz, H-2), 6.89 (3H, d, $J = 8.4$ Hz, H-1), 2.28 (9H, s, CH_3), 0.93–1.27 (36H, m, Sn–($\underline{CH_2}$)$_3$–CH_3), 0.54 (18H, t, $J = 7.2$ Hz, Sn–$(CH_2)_3$–$\underline{CH_3}$) ppm. ^{13}C NMR (DMSO-d_6, 75 MHz) δ: 173.7 (C-8), 161.6 (C-5), 161.6 (C-6), 149.2 (C-12), 148.3 (C-13), 146.9 (C-15, C-17, C-19), 140.8 (C-10), 134.6 (C-2), 133.6 (C-7), 130.3 (C-14, C-16, C-18), 128.5 (C-9), 127.8 (C-11), 124.8 (C-3), 120.6 (C-1), 117.6 (C-4), 31.6 (C-α), 27.6 (C-γ), 26.0 (C-β), 20.7 (CH_3), 13.9 (C-δ) ppm. ^{119}Sn NMR (DMSO-d_6, 112 MHz) δ: −360.0 ppm. MS (FAB^+) [*m/z*] (%): [M^+, 1539] (1); [M^+ – Bu, 1482] (2); [$M^+ - C_{51}H_{61}N_4O_8Sn_2$, 445] (100); [$C_{13}H_{11}N_2OSn^+$, 331] (57). Anal. Calcd for $C_{72}H_{90}N_6O_9Sn_3$ (%): C, 56.17; H, 5.89; N, 5.46. Found: C, 55.02; H, 5.90; N, 5.17. Molar conductivity (1×10^{-3} M, MeOH): 6.2 Ω^{-1} cm^2 mol^{-1}.

2.2.1.3. *Synthesis of* ***5c***. The reaction mixture was stirred at reflux for 2 h. The precipitate was filtered off and washed with hexane: AcOEt [70 : 30] mixture to give 0.105 g (0.066 mmol, 9% yield) of a dark red solid, m.p. 213 °C (dec.). IR (KBr) *v*: 2953, 2923, 2857, 1610, 1587 (C=N), 1555 (ν_{as} COO^-), 1480, 1456, 1366 (ν_s COO^-), 1304, 1273, 1240, 1157, 930, 816, 770, 732, 681, 654, 632, 544, 544 (Sn–O), 510 (Sn–C), 413 (Sn–N) cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz) δ: 9.46 (3H, d, $J = 4.7$ Hz, H-12) ppm, 9.27 (3H, s, H-15, H-17, H-19), 8.74 (3H, s, H-7), 8.12 (3H, dd, $J = 7.0$, 6.9 Hz, H-10), 7.81 (3H, d, $J = 7.8$ Hz, H-9), 7.74 (3H, ddd, $J = 7.0$, 5.2, 1.7 Hz, H-11), 7.53 (3H, d, $J = 1.7$ Hz, H-4), 7.27 (3H, d, $J = 8.7$ Hz, H-2), 7.13 (3H, d, $J = 8.9$ Hz, H-1), 0.98–1.40 (36H, m, Sn–($\underline{CH_2}$)$_3$–CH_3), 0.61 (18H, t, $J = 7.1$ Hz, Sn–$(CH_2)_3$–$\underline{CH_3}$) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 175.7 (C-13), 163.4 (C-6), 150.4 (C-12), 148.0 (C-8), 142.7 (C-7), 139.4 (C-10), 135.1 (C-15, C-17, C-19), 133.4 (C-2), 133.1 (C-14, C-16, C-18), 130.4 (C-5),

126.7 (C-9), 126.7 (C-11), 123.4 (C-1), 120.2 (C-3), 115.8 (C-4), 30.9 (C-α), 27.6 (C-γ), 26.3 (C-β), 13.5 (C-δ) ppm. ^{119}Sn NMR ($CDCl_3$, 112 MHz) δ: −368.9 ppm. MS (FAB^+) [*m/z*] (%): [M^+ – Bu, 1543] (1); [$M^+ - C_{49}H_{55}Cl_2N_4O_8Sn_2$, 465] (100); [$C_{12}H_8ClN_2OSn^+$, 351] (65). Anal. Calcd for $C_{69}H_{81}Cl_3N_6O_9Sn_3$ (%): C, 51.77; H, 5.10; N, 5.25. Found: C, 49.82; H, 5.16; N, 4.82. Molar conductivity (1×10^{-3} M, MeOH): 11.0 Ω^{-1} cm^2 mol^{-1}.

2.2.1.4. *Synthesis of* ***5d***. The reaction mixture was stirred at reflux for 2 h. The precipitate was filtered off and washed with hexane : AcOEt [70 : 30] mixture to give 0.960 g (0.588 mmol, 78% yield) of an orange solid, m.p. 217 °C (dec). IR (KBr) *v*: 2954, 2923, 2856, 1636, 1589 (C=N), 1560 (v_{as} COO^-), 1486, 1439, 1343 (v_s COO^-), 1294, 1162, 1083, 887, 734, 678, 620, 543 (Sn–O), 511 (Sn–C), 467 (Sn–N) cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 9.53 (3H, d, J = 4.5 Hz, H-12), 9.31 (3H, s, H-15, H-17, H-19), 9.04 (3H, s, H-7), 8.62 (3H, d, J = 1.7 Hz, H-4), 8.20–8.29 (6H, m, H-2, H-10), 7.99 (3H, d, J = 7.6 Hz, H-9), 7.89 (3H, dd, J = 7.1, 5.1 Hz, H-11), 7.17 (3H, d, J = 9.1 Hz, H-1), 0.98–1.45 (36H, m, Sn–($\underline{CH_2}$)$_3$–CH_3), 0.62 (18H, t, J = 6.9 Hz, Sn–$(CH_2)_3$–$\underline{CH_3}$) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 176.0 (C-13), 170.1 (C-6), 150.6 (C-12), 147.5 (C-5), 145.6 (C-7), 140.0 (C-10), 136.2 (C-14, C-16, C-18), 135.4 (C-15, C-17, C-19), 132.9 (C-3), 129.2 (C-8), 128.6 (C-2), 127.7 (C-9), 127.6 (C-11), 121.8 (C-1), 113.6 (C-4), 32.5 (C-α), 27.6 (C-γ), 26.2 (C-β), 13.5 (C-δ) ppm. ^{119}Sn NMR ($CDCl_3$, 112 MHz) δ: −377.5 ppm. MS (FAB^+) [*m/z*] (%): [M^+ – Bu, 1575] (1); [$M^+ - C_{49}H_{55}N_6O_{12}Sn_2$, 475] (100); [$C_{12}H_8N_3O_3Sn^+$, 362] (30). Anal. Calcd for $C_{69}H_{81}N_9O_{15}Sn_3$ (%): C, 50.76; H, 5.00; N, 7.72. Found: C, 50.61; H, 5.01; N, 7.64. Molar conductivity (1×10^{-3} M, MeOH): 15.0 Ω^{-1} cm^2 mol^{-1}.

2.2.1.5. *Synthesis of* ***5e***. The reaction mixture was stirred at room temperature for 2 h. The precipitate was filtered off to give 1.075 g (0.482 mmol, 78% yield) of a red solid, m.p. 185 °C (dec.). IR (KBr) *v*: 2951, 2920, 2850, 1608, 1590 (C=N), 1546 (v_{as} COO^-), 1483, 1442, 1367 (v_s COO^-), 1320, 1272, 1248, 1143, 869, 772, 734, 678, 584, 538 (Sn–O), 515 (Sn–C), 415 (Sn–N) cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 9.49 (3H, d, J = 4.4 Hz, H-12), 9.29 (3H, s, H-15, H-17, H-19), 8.78 (3H, s, H-7), 8.08 (3H, dd, J = 7.7, 7.1 Hz, H-10), 7.79 (3H, d, J = 7.7 Hz, H-9), 7.74 (3H, dd, J = 6.9, 5.0 Hz, H-11), 7.54 (3H, d, J = 7.7 Hz, H-4), 7.30 (3H, d, J = 7.8 Hz, H-2), 7.20 (3H, d, J = 8.0 Hz, H-1), 6.66 (3H, ddd, J = 7.7, 7.1, 1.0 Hz, H-3), 1.04–1.41 (36H, m, Sn–($\underline{CH_2}$)$_3$–CH_3), 0.72 (18H, t, J = 6.9 Hz, Sn–$(CH_2)_3$–$\underline{CH_3}$) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 175.6 (C-13), 164.9 (C-6), 150.4 (C-12), 148.4 (C-5), 141.7 (C-7), 139.1 (C-10), 135.0 (C-15, C-17, C-19), 133.5 (C-14, C-16, C-18), 133.5 (C-2), 130.2 (C-8), 126.3 (C-9), 126.3 (C-11), 122.5 (C-1), 115.9 (C-4), 115.5 (C-3), 22.6–33.3 (Sn–($\underline{C}H_2$)$_7$–CH_3), 14.1 (Sn–$(CH_2)_7$–$\underline{C}H_3$) ppm. ^{119}Sn NMR ($CDCl_3$, 112 MHz) δ: −371.2, (DMSO-d_6) −364.5 ppm. MS (FAB^+) [*m/z*] (%): [M^+ – Bu, 1720] (1); [$M^+ - C_{65}H_{89}N_4O_8Sn_2$, 645] (88); [$C_{12}H_9N_2OSn^+$, 351] (100). Anal. Calcd for $C_{93}H_{132}N_6O_9Sn_3$ (%): C, 60.90; H, 7.25; N, 4.58. Found: C, 60.42; H, 7.07; N, 4.85. Molar conductivity (1×10^{-3} M, MeOH): 21.0 Ω^{-1} cm^2 mol^{-1}.

2.2.1.6. *Synthesis of* ***5f***. The reaction mixture was stirred at room temperature for 2 h. The precipitate was filtered off to give 1.096 g (0.584 mmol, 78% yield) of a red solid, m.p. 227 °C (dec.). IR (KBr) *v*: 2951, 2920, 2850, 1605 (C=N), 1546 (v_{as} COO^-), 1490, 1464, 1438, 1368 (v_s COO^-), 1303, 1246, 1206, 1141, 1100, 815, 772, 732, 680, 552 (Sn–O), 513 (Sn–C), 477, 414 (Sn–N) cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 9.47 (3H, d, J = 4.7 Hz, H-12), 9.27 (3H, s, H-15, H-17, H-19), 8.75 (3H, s, H-7), 8.08 (3H, dd, J = 7.7,

7.5 Hz, H-10), 7.78 (3H, d, J = 7.7 Hz, H-9), 7.70 (3H, ddd, J = 7.2, 5.2, 1.7 Hz, H-11), 7.34 (3H, s, H-4), 7.16 (3H, dd, J = 8.5, 1.1 Hz, H-2), 7.10 (3H, d, J = 8.6 Hz, H-1), 2.31 (9H, s, CH_3), 0.94–1.40 (36H, m, Sn–($\underline{CH_2}$)$_3$–CH_3), 0.74 (18H, t, J = 6.9 Hz, Sn–$(CH_2)_3$–$\underline{CH_3}$) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 175.5 (C-13), 162.9 (C-6), 150.3 (C-12), 148.5 (C-5), 141.1 (C-7), 139.1 (C-10), 134.9 (C-2), 134.9 (C-15, C-17, C-19), 133.3 (C-14, C-16, C-18), 129.6 (C-8), 126.1 (C-9), 126.1 (C-11), 124.7 (C-3), 122.1 (C-1), 115.7 (C-4), 22.6–33.3 (Sn–($\underline{C}H_2$)$_7$–CH_3), 20.7 (CH_3), 14.1 (Sn–$(CH_2)_7$–$\underline{C}H_3$) ppm. ^{119}Sn NMR ($CDCl_3$, 112 MHz) δ: −368.1 ppm. MS (FAB$^+$) [m/z] (%): [M^+ – $C_{67}H_{93}N_4O_8Sn_2$, 445] (100); [$C_{13}H_{11}N_2OSn^+$, 331] (89). Anal. Calcd for $C_{96}H_{138}N_6O_9Sn_3$ (%): C, 61.45; H, 7.41; N, 4.48. Found: C, 61.40; H, 7.38; N, 4.44. Molar conductivity (1 × 10^{-3} M, MeOH): 8.3 Ω^{-1} cm^2 mol^{-1}.

2.2.1.7. *Synthesis of* ***5g***. The reaction mixture was stirred at reflux for 2 h. The precipitate was filtered off with hexane : AcOEt [70 : 30] to give 0.194 g (0.099 mmol, 13% yield) of a dark red solid, m.p. 195 °C. IR (KBr) ν: 2951, 2920, 2851, 1609, 1589 (C=N), 1548 (ν_{as} COO^-), 1479, 1456, 1415, 1367 (ν_s COO^-), 1303, 1272, 1239, 1158, 1100, 930, 816, 770, 733, 680, 654, 632, 544 (Sn–O), 511 (Sn–C), 412 (Sn–N) cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 9.44 (3H, s broad, H-12) ppm, 9.25 (3H, s, H-15, H-17, H-19), 8.77 (3H, s, H-7), 8.12 (3H, dd, J = 7.6, 7.0 Hz, H-10), 7.86 (3H, d, J = 7.5 Hz, H-9), 7.74 (3H, dd, J = 6.9, 4.9 Hz, H-11), 7.53 (3H, s, H-4), 7.24 (3H, d, J = 9.0 Hz, H-2), 7.12 (3H, d, J = 8.9 Hz, H-1), 0.92–1.45 (36H, m, Sn–($\underline{CH_2}$)$_3$–CH_3), 0.74 (18H, t, J = 6.5 Hz, Sn–$(CH_2)_3$–$\underline{CH_3}$) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 175.3 (C-13), 163.2 (C-6), 150.3 (C-12), 148.1 (C-8), 143.1 (C-7), 139.4 (C-10), 135.2 (C-15, C-17, C-19), 133.6 (C-14, C-16, C-18), 133.4 (C-2), 130.5 (C-5), 126.8 (C-9), 126.7 (C-11), 123.3 (C-1), 120.4 (C-3), 115.8 (C-4), 22.7–33.2 (Sn–($\underline{C}H_2$)$_7$–CH_3), 14.1 (Sn–$(CH_2)_7$–$\underline{C}H_3$) ppm. ^{119}Sn NMR ($CDCl_3$, 112 MHz) δ: −368.8 ppm. MS (FAB$^+$) [m/z] (%): [M^+ – Oc, 1822] (1); [M^+ – $C_{65}H_{87}Cl_2N_4O_8Sn_2$, 577] (86); [$C_{12}H_8ClN_2OSn^+$, 351] (100). Anal. Calcd for $C_{93}H_{129}Cl_3N_6O_9Sn_3$ (%): C, 57.65; H, 6.71; N, 4.34. Found: C, 57.32; H, 6.73; N, 4.28. Molar conductivity (1 × 10^{-3} M, MeOH): 9.4 Ω^{-1} cm^2 mol^{-1}.

2.2.1.8. *Synthesis of* ***5h***. The reaction mixture was stirred at reflux for 2 h. The precipitate was filtered off with hexane : AcOEt [70 : 30] to give 1.204 g (0.611 mmol, 81% yield) of a dark orange solid, m.p. 222 °C. IR (KBr) ν: 2953, 2920, 2851, 1615, 1588 (C=N), 1561 (ν_{as} COO^-), 1486, 1439, 1374 (ν_s COO^-), 1342, 1311, 1296, 1162, 1086, 890, 734, 678, 627, 545 (Sn–O), 510 (Sn–C), 411 (Sn–N) cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 9.53 (3H, d, J = 4.7 Hz, H-12), 9.32 (3H, s, H-15, H-17, H-19), 9.10 (3H, s, H-7), 8.63 (3H, d, J = 1.9 Hz, H-4), 8.21–8.26 (6H, m, H-2, H-10), 8.04 (3H, d, J = 7.5 Hz, H-9), 7.88 (3H, dd, J = 7.1, 5.0 Hz, H-11), 7.17 (3H, d, J = 9.2 Hz, H-1), 0.93–1.46 (36H, m, Sn–($\underline{CH_2}$)$_3$–CH_3), 0.74 (18H, t, J = 6.9 Hz, Sn–$(CH_2)_3$–$\underline{CH_3}$) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 176.0 (C-13), 170.1 (C-6), 150.6 (C-12), 147.5 (C-5), 145.7 (C-7), 139.9 (C-10), 136.2 (C-14, C-16, C-18), 135.4 (C-15, C-17, C-19), 133.9 (C-3), 129.2 (C-8), 128.6 (C-2), 127.7 (C-9), 127.6 (C-11), 121.8 (C-1), 113.6 (C-4), 22.5–33.4 (Sn–($\underline{C}H_2$)$_7$–CH_3), 14.1 (Sn–$(CH_2)_7$–$\underline{C}H_3$) ppm. ^{119}Sn NMR ($CDCl_3$, 112 MHz) δ: −377.8 ppm. MS (FAB$^+$) [m/z] (%): [M^+ – Oc, 1857] (1); [M^+ – $C_{65}H_{87}N_6O_{12}Sn_2$, 588] (100); [$C_{12}H_8N_3O_3Sn^+$, 362] (84). Anal. Calcd for $C_{93}H_{129}N_9O_{15}Sn_3$ (%): C, 56.72; H, 6.60; N, 6.40. Found: C, 50.45; H, 6.54; N, 3.89. Molar conductivity (1 × 10^{-3} M, MeOH): 3.1 Ω^{-1} cm^2 mol^{-1}.

2.3. *Biological activities*

To evaluate the stability of the synthesized complexes, ^{1}H and ^{119}Sn NMR spectroscopy was recorded in $CDCl_3$ and DMSO-d_6, showing non-decomposed products or changes in the coordination after 72 h, indicating that the solution structures remained without modification (^{1}H and ^{119}Sn NMR spectra of **5a** and **5e** were included as Supporting Material).

2.3.1. TPA-induced ear edema in mice. The assay of TPA-induced ear edema in mice was based on a previously described method [73, 74]. The percentage inhibition of edema was calculated by the equation: % = (edema A – edema B/edema A) × 100, where edema A = edema induced by TPA alone and edema B = edema induced by TPA plus the sample. All tested compounds were evaluated in a chloroform solution.

2.3.2. Reduction of 2,2-diphenyl-1-picrylhydrazyl radical (DPPH). The test was carried out in 96-well microplates. For this, 50 μL of the solution of the test compound was mixed with 150 μL of ethanolic solution of DPPH (final concentration 100 μM), then was incubated at 37 °C for 30 min and subsequently the absorbance was measured at 515 nm in a microplate reader ELx 808. The percent inhibition of each compound was determined by comparison with a 100 μM DPPH ethanolic blank solution. Quercetin and α-tocopherol were used as standards. The ligands and complexes tested were reacted with the stable DPPH radical in an ethanolic solution. In the case of dibutyltin oxide, a suspension in water was used due to its insolubility in organic solvents.

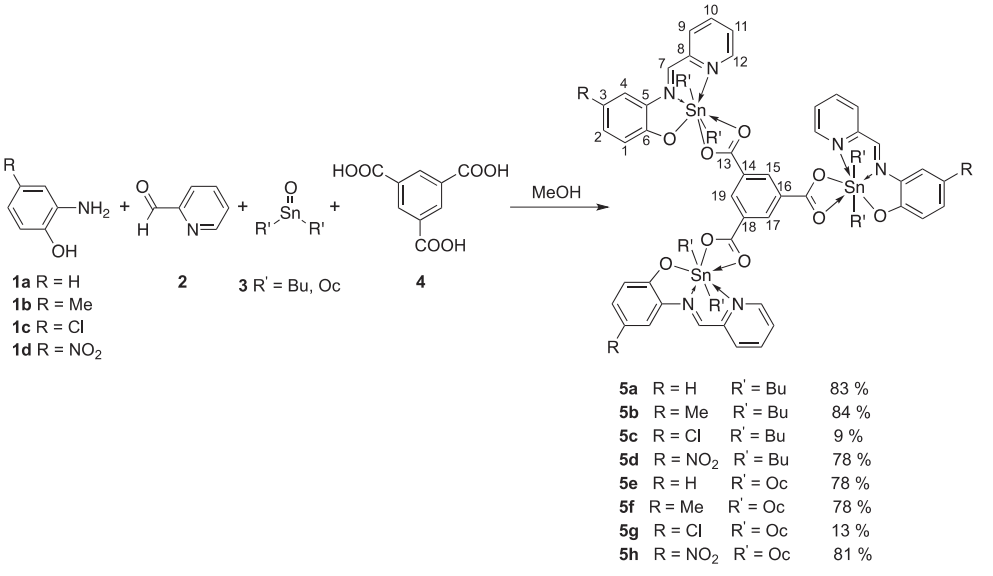
2.3.3. Antioxidant activity (TBARS) in rat brain homogenates. As an index of lipid peroxidation, TBARS levels were measured using rat brain homogenates according to the method described by Ng *et al*. [75]. All ligands were evaluated in an ethanol solution, and DMSO was used for the corresponding complexes.

The antioxidant activity was evaluated by measuring the amount of plasma concentration of thiobarbituric acid (TBA) reactive substances (TBARS) that represent lipid peroxidation. Malondialdehyde (MDA) forms complexes with TBA to produce a pink complex, spectrophotometrically measured at 540 nm. The results of the TBARS assay are expressed as the amount of free MDA equivalents per 1 mg tissue through the calibration curve generated from 1,1,3,3-tetramethoxypropane (TMP).

3. Results and discussion

3.1. *Synthesis*

The syntheses of the diorganotin(IV) derivatives of Schiff bases were performed in a one-pot reaction, as illustrated in scheme 1. Complexes **5a**–**h** were synthesized as colored solids by reaction of the 2-amino-4-R-phenol (**1a**–**d**, R=H, Me, NO_2, Cl) with 2-pyridinecarboxaldehyde (**2**), followed by addition of the corresponding diorganotin oxide (**3a**–**b**) and H_3BTC (**4**) in a 3 : 3 : 3 : 1 stoichiometry, affording air-stable complexes in good yields. The reactions were quite feasible and required 4 h of reflux.



Scheme 1. Syntheses of **5a**–**h**.

3.2. *Spectroscopic studies*

3.2.1. FT-IR analysis. In the IR spectra of **5a**–**h**, interesting stretching frequencies are those associated with C=N, COO, Sn–C, Sn–O, and Sn–N groups. The azomethine C=N band at 1590–1597 cm^{-1} in the IR spectrum of the free ligand (**HL1-4**) shifts to lower wave number in the complexes to confirm coordination of the imine nitrogen to the diorganotin (IV) moiety.

In the organotin carboxylate complexes, IR spectroscopy provides useful information concerning the coordination mode of carboxyl group, as reported [76]. The $\Delta\nu$ values, defined by Deacon and Phillips as $\nu_{as}(COO^-) - \nu_{sym}(COO^-)$ [77], give some qualitative structural information concerning the coordination modes of the carboxylate groups and are summarized in table 1. While the smaller values of $\Delta\nu$ are consistent with chelating coordination, the larger values could indicate the existence of unidentate coordinated carboxylate. After deprotonation and coordination with tin, the bands of the type C=O···H–O at 1720 cm^{-1} and a broad band in the region of 3400–2800 cm^{-1} in the uncoordinated H_3BTC were absent, indicative of reaction completion, and were replaced by strong bands at 1617–1623 and 1343–1561 cm^{-1}, which correspond to the symmetric and asymmetric vibrations, respectively, of the COO moiety. The $\Delta\nu$ values (177–217 cm^{-1}) of **5a**–**h** reveal that the coordination mode of the carboxylate is bidentate. This is consistent with X-ray diffraction study (see below). The strong absorption at 538–552 cm^{-1}, which is absent in the spectrum of the free ligand, was assigned to Sn–O stretch. In addition, new bands at 411–415 cm^{-1}, assigned to ν(Sn–N), further support the bonding of nitrogen to the tin [78, 79]. Accordingly, the weak or medium-intensity band at 510–515 cm^{-1} can be assigned to Sn–C stretches. All these values are consistent with those detected in a number of organotin (IV)–oxygen derivatives [80, 81].

Table 1. FT-IR vibrations (cm^{-1}) for **HL1-4** and **5a**–**h**.

Compound	$\nu_{as}(COO^-)$	$\nu_s(COO^-)$	$\Delta\nu$	ν(C=N)	ν(Sn–O)	ν(Sn–C)	ν(Sn–N)
HL1	–	–	–	1594	–	–	–
HL2	–	–	–	1590	–	–	–
HL3	–	–	–	1590	–	–	–
HL4	–	–	–	1597	–	–	–
5a	1545	1365	180	1589	539	513	414
5b	1545	1367	178	1605	552	513	414
5c	1555	1366	189	1588	544	510	413
5d	1560	1343	217	1589	543	511	411
5e	1545	1367	178	1590	538	515	415
5f	1545	1368	177	1605	552	513	414
5g	1548	1367	181	1589	544	511	412
5h	1561	1374	187	1588	545	510	411

3.2.2. Mass spectrometry (FAB^+). The mass spectra (FAB^+) of the synthesized compounds support the assumption that trimeric structures were obtained, since in almost all cases, the ions $[M^+ - Bu]^+$ or $[M^+ - Octyl]^+$ were observed. However, the peak corresponding to the molecular ion could not be detected in any case. Two of the most prominent fragments correspond to mononuclear species, consisting of $[LSn]^+$ and $[LSn + 2Bu]^+$ or $[LSn + 2Octyl]^+$ fragments.

3.2.3. ^{1}H, ^{13}C, and ^{119}Sn NMR. The ^{1}H, ^{13}C, and ^{119}Sn NMR data were recorded in $CDCl_3$, except **5b**, where DMSO-d_6 was necessary because of its low solubility in the most common organic solvents. The organic group protons were assigned from multiplicities and integration ratios. The ^{1}H and ^{13}C NMR spectra were assigned completely by 2D correlation experiments (COSY, HSQC, and HMBC). The ratio of the integrals of signals from protons of the Schiff base to those of protons of the H_3BTC confirms a 3 : 1 ratio of metal to H_3BTC ligand in the complexes. This is an evidence that the three imine nitrogens are coordinated with tin(IV) centers. The appearance of only one set of signals in ^{1}H and ^{13}C NMR of complexes shows that the three parts of the molecule are similar in solution. This was also confirmed in the solid state by the X-ray structures of **5a** and **5b** that show seven-coordinate geometries.

The ^{1}H NMR spectra show the expected integration and peak multiplicities. The pattern of the aromatic protons of all complexes shows a downfield shift compared with the free Schiff base, confirming that nitrogen is coordinated with tin, as deduced from the IR spectroscopic data. The signal for the COOH proton (11–12 ppm) of the free ligand is absent in the spectra of **5a**–**h**, which indicate that carboxylate groups coordinate with Sn [24, 82]. The chemical shifts of the signals for the phenyl group (δ = 9.25–9.41) are downfield with respect to the ligand ($\Delta\delta$ = 8.68). The ^{13}C NMR spectra of **5a**–**h** contained resonances similar to those of the free ligand, except that the iminic carbon C-7 shifted to lower frequencies ($\Delta\delta$ = 15.3–15.8) with respect to the free Schiff base, probably induced by the Sn–O bond. The carbon C-6 shifts to higher frequencies ($\Delta\delta$ = 8.5–10.8). The single resonance at 175.3–176.0 ppm was attributed to COO^-groups. For all complexes, the coupling constants $^1J(^{13}C–^{119/117}Sn)$ were not detected in the ^{13}C NMR spectra. The appearance of only a sharp singlet in the ^{119}Sn NMR spectra of all complexes indicates formation of a single species and shows similar environment for the three tin centers in the complexes. The ^{119}Sn NMR spectroscopic data allowed us to establish the coordination number of tin.

According to the information reported [41], the chemical shift values for **5a**–**h** (δ between −368 and −378 ppm) indicate that tin is seven-coordinate in solution. Figure 1 shows the ^{119}Sn NMR spectrum of **5a** in $CDCl_3$, as a representative example. The chemical shifts are similar to those observed for the mononuclear and dinuclear compounds described previously [41, 82]. This was confirmed by the X-ray crystal structures in the solid state. Despite the differences in the coordinating character of the solvent used ($CDCl_3$ or DMSO), the chemical shifts were quite similar, indicative of no solvent interaction with tin [83].

3.3. *X-ray crystal structures of 5a and 5b*

The proposed structures of **5a** and **5b** were confirmed by X-ray analysis. The molecular perspective views are shown in figure 2. Single crystals of both complexes were grown from solution in a mixture of DMSO : methanol or methanol. Crystal data, bond lengths, and angles are summarized in tables 2 and 3. A solvating water molecule is present in **5a**, and one each of methanol and DMSO in **5b**. The molecular structures of both complexes reveal that they possess a pentagonal-bipyramidal (PBP) geometry, wherein the pentagonal plane comprises two nitrogens from azomethine and pyridine, and three oxygens, one from the ligand and two from the carboxylate group. The axial positions are occupied by the organic groups, having C–Sn–C angles of 172.4(4), 173.4(4), and 167.6(5)° for **5a** and 166.2(4), 173.0(4), and 164.9(4)° for **5b**. These values indicate that the geometry around tin for **5b** shows greater distortion in the axial plane than in **5a**. The atoms in the equatorial plane N–Sn–N and N–Sn–O exhibit angles of 64.2°–73.4°. Each monomer is composed of two

Figure 1. ^{119}Sn NMR spectrum of **5a** in $CDCl_3$.

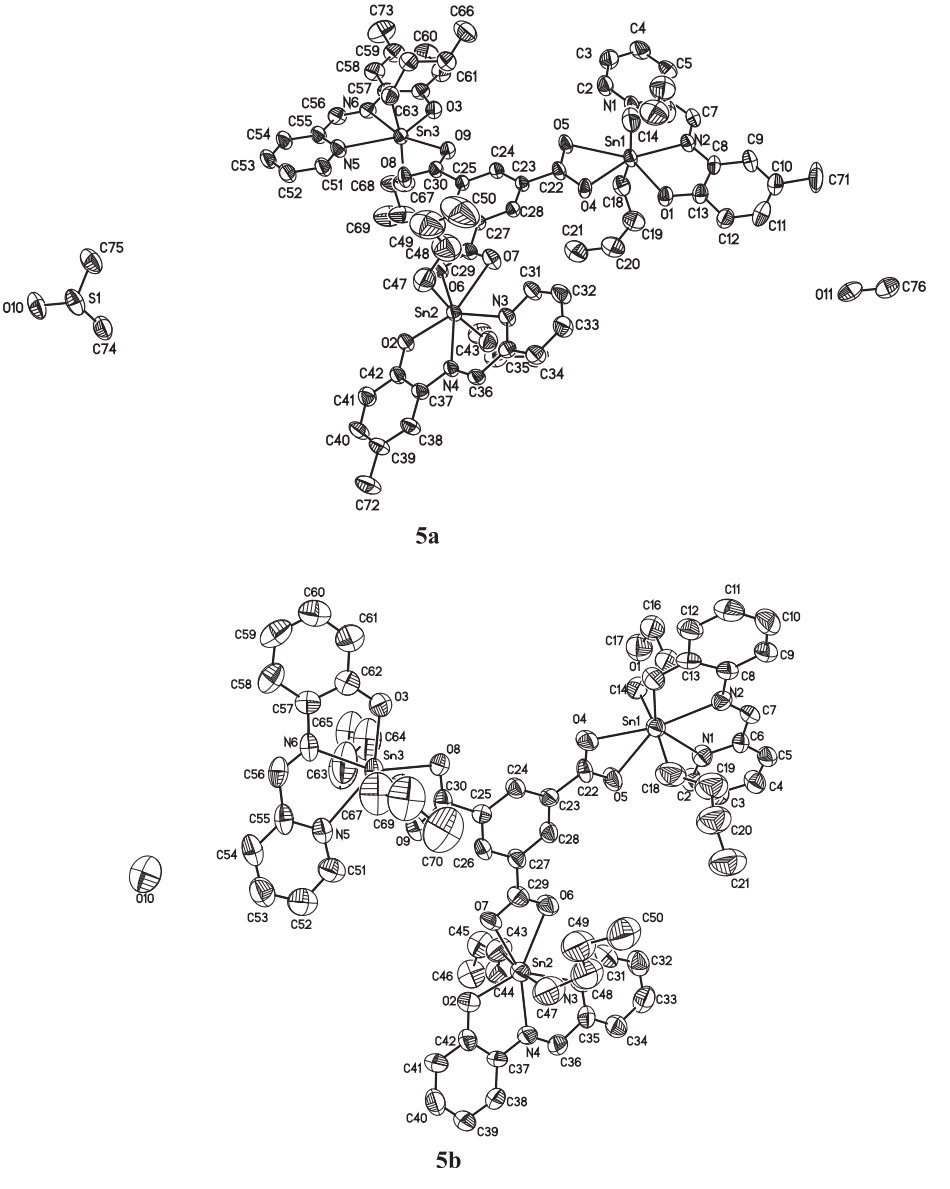


Figure 2. ORTEP view of **5a** and **5b**. Thermal ellipsoids at 30% probability level. The minor component of the disordered butyl group was omitted for clarity.

nearly planar five-membered chelate rings and one four-membered chelate ring. In each case, the five coordinating atoms are coplanar with the metal center.

The carboxylate oxygens of H_3BTC are coordinated with Sn in a bidentate form, as expected from the IR section. As a result of the bidentate coordination, each tin is seven-coordinate and the Sn–O bond distances are 2.219(4)–2.338(4) and 2.438(5)–2.5112(6) Å, shorter than the sum of the van der Waals radii (3.68 Å) [84]. These values are in

Table 2. Crystal data and structure refinement for **5a** and **5b**.

	5a	**5b**
Formula	$C_{69}H_{82}N_6O_9Sn_3 \cdot H_2O$	$C_{72}H_{87}N_6O_9Sn_3 \cdot 2DMSO \cdot MeOH$
Formula weight	1513.49	1631.70
Temperature (K)	298(2)	298(2)
Crystal system	Orthorhombic	Triclinic
Space group	*Pbca*	*P−1*
Unit cell dimensions		
a (Å)	18.515(1)	14.377(1)
b (Å)	17.512(1)	14.785(1)
c (Å)	44.382(3)	21.445(2)
α (°)	90	76.928(1)
β (°)	90	81.135(1)
γ (°)	90	69.597(1)
V (Å^3)	14390.1(2)	4147.5(6)
D_{calcd} (Mg m^{-3})	1.397	1.307
Z	8	1
Absorption coefficient (mm^{-1})	1.091	0.976
F(0 0 0)	6160	1670
Crystal size (mm)	0.40 × 0.18 × 0.14	0.46 × 0.26 × 0.18
θ range for data collection (°)	1.83–25.35	1.87–25.37
Reflections collected	114,663	34,434
Independent reflections (R_{int})	13,180 (0.1642)	15,138 (0.0483)
Completeness to $\theta = 25.35°$	99.9%	99.8%
Absorption correction	Empirical	Semi-empirical
Max. and min. transmission	0.8962 and 0.6847	0.8439 and 0.6624
Data/restraints/parameters	13,158/586/961	15,138/925/1143
Goodness-of-fit on F^2	0.802	1.030
Final R indices [$I > 2\sigma(I)$]	$R_1 = 0.0544$, $wR_2 = 0.1060$	$R_1 = 0.0658$, $wR_2 = 0.1628$
R indices (all data)	$R_1 = 0.1664$, $wR_2 = 0.1309$	$R_1 = 0.1097$, $wR_2 = 0.1854$
Largest diff. peak and hole (e Å^{-3})	0.558 and −0.367	1.080 and −0.504

agreement with complexes described previously [61, 72]. The Sn–O bond distances associated with non-coordinating O (phenoxyl group) are significantly shorter than the coordinating Sn–O bond distances from the carboxylate, Sn(1)–O(1) [2.118(5), 2.148(5)], Sn(2)–O(2) [2.130(5), 2.116(6)], and Sn(3)–O(3) [2.118(6), 2.110(5)] Å for **5a** and **5b**, respectively. Therefore, the non-coordinating Sn–O bond lengths approach those of covalent radii (2.13 Å). Additionally, the Sn–C bond lengths [2.125(9)–2.147(9) Å] are consistent with those reported in other triorganotin carboxylates [85]. The Sn–N bond lengths from azomethine for **5a** and **5b** range from 2.314(7) to 2.355(7), which are shorter than the Sn–N coordination bond from the pyridine nitrogen 2.468(6)–2.521(7). All these values are shorter than the sum of the van der Waals radii (3.75 Å).

Both complexes possess disordered butyl groups. In addition, **5b** also contains a ligand fragment and the DMSO molecule, which were modeled in two major contributors. The ratios of the SOF are given in the experimental section.

3.4. *Molar conductivity*

Low molar conductivity (3.1–21.0 Ω^{-1} cm^2 mol^{-1}) values of 10^{-3} M solutions of organotin (IV) complexes in methanol solution indicate their non-electrolytic nature.

Table 3. Bond lengths (Å) and angles (°) for **5a** and **5b**.

Bond lengths (Å)	**5a**	**5b**	Bond lengths (Å)	**5a**	**5b**	Bond lengths (Å)	**5a**	**5b**
Sn(1)–O(1)	2.118(5)	2.148(5)	Sn(2)–O(2)	2.130(5)	2.116(6)	Sn(3)–O(3)	2.118(6)	2.110(5)
Sn(1)–O(4)	2.286(4)	2.328(5)	Sn(2)–O(6)	2.338(4)	2.496(5)	Sn(3)–O(8)	2.286(5)	2.648(5)
Sn(1)–O(5)	2.510(5)	2.491(5)	Sn(2)–O(7)	2.438(5)	2.283(5)	Sn(3)–O(9)	2.512(6)	2.219(4)
Sn(1)–N(1)	2.507(6)	2.468(6)	Sn(2)–N(3)	2.502(6)	2.484(8)	Sn(3)–N(5)	2.521(7)	2.513(7)/2.508(10)
Sn(1)–N(2)	2.345(6)	2.314(7)	Sn(2)–N(4)	2.350(5)	2.355(7)	Sn(3)–N(6)	2.347(7)	2.349(6)
Sn(1)–C(14)	2.126(9)	2.128(8)	Sn(2)–C(43)	2.147(9)	2.147(9)	Sn(3)–C(63)	2.110(10)	2.139(8)
Sn(1)–C(18)	2.146(8)	2.115(8)	Sn(2)–C(47)	2.142(11)	2.142(11)	Sn(3)–C(67)	2.140(10)	2.125(9)
Bond angles (°)			Bond angles (°)			Bond angles (°)		
C(18)–Sn(1)–C(14)	172.4(4)	166.2(4)	C(47)–Sn(2)–C(43)	173.4(5)	173.0(4)	C(63)–Sn(3)–C(67)	167.6(5)	164.9(4)
O(1)–Sn(1)–N(2)	72.8(2)	73.1(2)	O(2)–Sn(2)–N(4)	72.8(3)	73.4(2)	O(3)–Sn(3)–N(6)	72.6(3)	73.4(2)
N(2)–Sn(1)–N(1)	67.7(3)	67.6(2)	N(4)–Sn(2)–N(3)	67.3(3)	67.3(2)	N(6)–Sn(3)–N(5)	67.7(3)	64.2(5)/67.5(2)
N(1)–Sn(1)–O(5)	79.1(2)	78.7(2)	N(3)–Sn(2)–O(7)	136.5(3)	77.2(2)	N(5)–Sn(3)–O(8)	135.6(3)	85.2(5)/81.2(2)
O(1)–Sn(1)–O(4)	87.2(2)	86.4(2)	O(2)–Sn(2)–O(6)	137.7(2)	87.9(2)	O(8)–Sn(3)–O(9)	54.4(18)	84.8(2)
C(22)–O(4)–Sn(1)	96.1(5)	97.7(4)	C(29)–O(6)–Sn(2)	88.0(5)	94.2(4)	C(30)–O(8)—Sn(3)	96.3(5)	83.0(4)
C(22)–O(5)–Sn(1)	87.9(5)	87.9(4)	C(29)–O(7)–Sn(2)	98.2(6)	90.0(4)	C(30)–O(9)–Sn(3)	85.3(6)	102.0(4)
O(4)–C(22)–O(5)	121.3(8)	119.8(6)	O(7)–C(29)–O(6)	119.1(9)	121.3(6)	O(8)–C(30)–O(9)	124.0(9)	121.8(6)

3.5. *Biological activities*

3.5.1. Anti-inflammatory activity toward 12-O-tetradecanoylphorbol-13-acetate-(TPA-) induced mouse ear edema. The TPA of organotin derivatives was evaluated *in vivo* using the TPA ear edema bioassay in mice. In this model, ear edema is induced by a phorbol ester (TPA) and the TPA of a sample can be evaluated. Indomethacin was used as the positive control. All synthesized complexes inhibited TPA-induced ear edema; however, dibutyltin derivatives **5a**–**d** showed greater effect than **5e**–**g** (dioctyl substituents attached to the metallic center). In general, all ligands showed lower activity in comparison with the corresponding complexes. A substantial improvement was evident with **5a** and **5e**, which exhibited a significant inhibitory effect compared to **HL1**.

Additionally, the substituent bonded to the aromatic ring seems to be important, as described previously [11, 72]. Chlorine derivatives **5c** and **5g** showed the highest inhibitory effect and were more active than indomethacin (table 4).

3.5.2. Antioxidant activity

3.5.2.1. *DPPH radical scavenging activity assay.* The antioxidant activities of **5a**–**g** were evaluated by assessing both the 2,2-diphenyl-1-picrylhydrazyl (DPPH) radical in rat brain homogenates and the inhibition of TBARS formation.

The DPPH assay is one of the most popular and frequently employed methods to evaluate antioxidant capacity, as it tests the ability of compounds to act as free radical scavengers or hydrogen donors. The results are summarized in table 5. The DPPH radical reducing activity of the two series of complexes showed that the butyltin derivatives were stronger DPPH radical scavengers than the dioctyltin ones (**5e**, **5g**, **5h**) which were essentially

Table 4. TPA of **5a**–**5h** TPA assay.

Compound	Edema (mg)	Inhibition (%)
HL1[a]	13.60 ± 1.25	7.48 ± 8.53
HL2[a]	5.84 ± 0.10**	60.27 ± 6.78**
HL3[a]	5.36 ± 0.99**	63.54 ± 6.77**
HL4[a]	7.54 ± 0.75**	48.71 ± 5.10**
Dibutyltin oxide	11.98 ± 1.02	18.50 ± 6.95
5a[b]	7.30 ± 1.42**	54.66**
5b[d]	3.48 ± 0.43**	71.57**
5c[d]	2.14 ± 0.30**	86.85**
5d[e]	4.66 ± 0.93**	69.19**
5e[b]	9.47 ± 1.20**	41.20**
5f[f]	8.50 ± 1.19**	47.20**
5g[d]	3.10 ± 0.40**	80.98**
5h[g]	6.27 ± 0.78**	53.81**
Indomethacin	2.88 ± 0.73**	78.76**

Controls (mg):
[a]14.70 ± 0.33,
[b]16.10 ± 0.25,
[c]12.23 ± 0.59,
[d]16.30 ± 0.19,
[e]15.11 ± 0.58,
[f]16.10 ± 0.25,
[g]13.57 ± 0.25, doses (1 μmol ear^{-1}).
Each value represents the mean of 3–7 animals. The results were analyzed using the *t* Student test. The value $p \leq 0.05$ (*) y $p \leq 0.01$ (**) were considered as significant difference with respect to the standard.

Table 5. Antioxidant activity (IC_{50}) of **5a**–**h**.

Compound	DPPH (IC_{50} μM)	TBARS (IC_{50} μM)
HL1	26.29 ± 2.89	32.79 ± 1.12
HL2	21.10 ± .37	4.00 ± 0.25
HL3	36.26 ± 2.59	6.80 ± 0.32
HL4	30.22 ± 0.72	51.26 ± 15.69
5a	10.49 ± 2.11	8.75 ± 0.53
5b	6.17 ± 0.56	2.27 ± 0.16
5c	9.96 ± 1.12	1.54 ± 0.08
5d	34.88 ± 3.86	11.11 ± 0.41
5e	43.18 ± 1.03	11.38 ± 0.83
5f	5.83 ± 0.16	2.38 ± 0.24
5g	60.86 ± 2.96	4.86 ± 0.29
5h	55.30 ± 1.76	11.66 ± 1.34
Quercetin	10.89 ± 0.47	1.49 ± 0.03
α-tocopherol	31.74 ± 1.04	6.78 ± 2.16
Dibutyltin oxide	NA	NA

Note: NA = nonactive.

inactive; nevertheless, methyl derivatives **5b** and **5f** showed the highest activity. Both exhibited similar activity to quercetin and higher activity than α-tocopherol. In general, all ligands showed comparable activity to α-tocopherol. However, it was evident that butyl derivatives were more active than the corresponding ligands. In summary, the substituent attached to tin and the electronic contribution at the aromatic ring seem to be important, since the results show that methyl might enhance DPPH radical reducing activity, whereas the nitro group may not contribute to DPPH radical scavenging. Similar behavior has been observed for seven-coordinate tin complexes [11, 72]. Compounds **5a**–**d** showed greater activity than dinuclear seven-coordinate complexes derived from terephthalic acid reported recently by our research group [72].

3.5.2.2. *Inhibition of the formation of TBARS as a measure of lipid peroxidation.* The *in vitro* antioxidant capacity of **5a**–**g** was also tested on brain homogenates by measuring the plasma concentration of TBARS, which represents lipid peroxidation (table 5). The IC_{50} values indicate that butyltin complexes were more active than the octyltin derivatives, as observed for the DPPH assay, where α-tocopherol (vitamin E) and quercetin were used as positive controls, as they are considered to be excellent antioxidants. Compounds **5b**–**c** and **5f**–**g** showed superior lipid peroxidation inhibition in comparison with α-tocopherol, whereas in the remaining complexes, the activity decreased; nevertheless, comparison of the IC_{50} values of all synthesized complexes with quercetin did not show a significant antioxidant effect. All complexes exhibited a stronger effect than the free ligands. The assays for the nitro derivatives showed considerable antioxidant activity in comparison with **HL4**. These results confirm the same trend as seen with the DPPH assay, where methyl and chlorine substituents bonded to the aromatic ring contributed to the inhibition of lipid peroxidation.

4. Conclusion

By carefully controlling the reaction conditions, we have found that H_3BTC is a versatile building block for construction of metal-organic complexes. The results presented in this

contribution have shown that the synthetic strategy previously applied to the formation of mononuclear diorganotin carboxylates could be extended to the preparation of trinuclear analogs.

These new derivatives represent an option for molecules with anti-inflammatory and antioxidant activities. Our study has demonstrated that topical application of **5a**–**d** is capable of reducing, in a dose-dependent manner, the TPA-induced skin inflammatory response. Therefore, our data showing significant edema reduction after TPA application in mouse ears caused by the topical application of **5c** and **5g** might be potentially relevant in the search for new therapeutic agents which have prostanoids as the target.

Complexes **5a**–**g** showed antioxidant activity using two assays, *i.e.* 2,2-diphenyl-1-picrylhydrazyl (DPPH) radical scavenging in rat brain homogenates and the inhibition of TBARS formation. The IC_{50} values indicated that dibutyltin complexes were more active than dioctyltin derivatives; the antioxidant effect seems to be associated with the substituent attached to the metal center and the electronic contribution at the aromatic system.

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Disclosure statement

No potential conflict of interest was reported by the authors.

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Supplemental data

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