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Self-assembly of extended Schiff base amino acetate skeletons, 2-{[(2*Z*)-(3-hydroxy-1-methyl-2-butenylidene)]amino}phenylpropionate and 2-{[(*E*)-1-(2-hydroxyaryl)alkylidene]amino}phenylpropionate skeletons incorporating organotin(IV) moieties: Synthesis, spectroscopic characterization, crystal structures, and *in vitro* cytotoxic activity

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Abstract

The organotin(IV) compounds, $[Ph_3SnL^1H]_n \cdot nCCl_4$ (**1**), $[Me_2SnL^2(OH_2)]$ (**2**), $[^nBu_2SnL^2]$ (**3**), $[Ph_2SnL^2]_n$ (**4**), $[Ph_3SnL^2H]_n$ (**5**) and $[Ph_3SnL^3H]_n$ (**7**) (L^1 = 2-{[(2*Z*)-(3-hydroxy-1-methyl-2-butenylidene)]amino}phenylpropionate and L^{2-3} = 2-{[(*E*)-1-(2-hydroxyaryl)alkylidene]amino}phenylpropionate), were synthesized by treating the appropriate organotin(IV) chloride(s) with the potassium salt of the ligand in a suitable solvent, while $[^nBu_2SnL^3(OH_2)]$ (**6**) was obtained by reacting the acid form of L^3 (generated in situ) with $^nBu_2SnO$. These complexes have been characterized by ^1H, ^{13}C, ^{119}Sn NMR, ESI-MS, IR and ^{119m}Sn Mössbauer spectroscopic techniques in combination with elemental analyses. The crystal structures of **1** and **4**–**7** were determined. The crystal structures of complexes **1**, **5** and **7** reveal that the complexes exist as polymeric chains in which the L-bridged Sn-atoms adopt a *trans*-R_3SnO_2 trigonal bipyramidal configuration with R groups in the equatorial positions and the axial locations occupied by a carboxylate oxygen from the carboxylate ligand and the alcoholic or phenolic oxygen of the next carboxylate ligand in the chain. The carboxylate ligands coordinate in the zwitterionic form with the alcoholic/phenolic proton moved to the nearby nitrogen atom. A polymeric zig-zag *cis*-bridged chain structure is observed for **4**, without considering the weak Sn···O interaction, the Sn-atom having a slightly distorted trigonal bipyramidal coordination geometry with the two O atoms of the tridentate amino propionate ligand in axial positions. On the other hand, the structure of **6** reveals a monomeric molecule in which the Sn-atom has a distorted octahedral coordination geometry involving the tridentate carboxylate ligand, two *n*-butyl ligands occupying *trans*-positions and one water ligand. The *in vitro* cytotoxic activity of triphenyltin(IV) compounds, viz., **1**, **5** and **7** against WIDR, M19 MEL, A498, IGROV, H226, MCF7 and EVSA-T human tumor cell lines are also reported.

Keywords: Organotin carboxylate; 2-{[(2*Z*)-(3-hydroxy-1-methyl-2-butenylidene)]amino}phenylpropionate; 2-{[(*E*)-1-(2-hydroxyaryl)alkylidene]amino}-phenylpropionate; NMR; ESI-MS; Mössbauer; Crystal structure; Cytotoxic activity

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1. Introduction

Organotin(IV) carboxylates have been found to show a variety of interesting molecular architectures [1]. The construction of multidimensional architectures depends on the combination of several factors including the type of organic ligands, tin-R groups, tin coordination geometry preferences and metal-to-ligand molar ratio. In addition, the hydrogen bonding interactions are important non-coordination and non-covalent intermolecular forces. Their unique strength and direction play key roles in the generation of a variety of supramolecular structures. The self-assembly of organotin(IV) complexed Schiff bases containing the amino acetate moiety is particularly attractive, since it can be accomplished in one-pot reactions and allows for easy fine-tuning of structural and functional features [2–9]. Thus, such Schiff bases are important building-blocks in the design of extended structures because of the type and position of the donor atoms that allow tin atoms to be linked together in diverse coordination modes (Scheme 1).

Our synthetic efforts are currently aimed towards the synthesis of supramolecular architectures based on Schiff bases with an extended amino acetate moiety, which is slightly bulkier and contains a *pro*-chiral carbon atom i.e. 2-{[(2*Z*)-(3-hydroxy-1-methyl-2-butenylidene)]amino}phenylpropionate and 2-{[(*E*)-1-(2-hydroxyaryl)alkylidene]amino}phenylpropionate, which were mainly isolated as potassium salts (Fig. 1). In this paper, we report on the synthesis, spectroscopic and structural characterization of some new organotin(IV) complexes involving these ligands. The solid-state structures of a few complexes, e.g., $[Ph_3SnL^1H]_n \cdot nCCl_4$ (**1**), $[Ph_2SnL^2H]_n$ (**4**), $[Ph_3SnL^2H)]_n$ (**5**), $[^nBu_2SnL^3H(OH_2)]$ (**6**) and $[Ph_3SnL^3H]_n$ (**7**) have been determined using single crystal X-ray crystallography in order to bestow deeper insight into their coordination geometry and supramolecular structure. The tin coordination of these complexes in solution has been deduced from ^{119}Sn NMR data in non-coordinating solvent, while the cleavage of the most labile bond in each molecule has been studied using ESI mass spectroscopy.

2. Experimental

2.1. Materials

Ph_3SnCl (Fluka AG), Ph_2SnCl_2, $^nBu_2SnCl_2$ (Merck), Me_2SnCl_2 (Aldrich), L-phenylalanine, 2-hydroxybenzaldehyde, acetylacetone (Sisco) and 2-hydroxyacetophenone (Aldrich) were used without further purification. The solvents used in the reactions were of AR grade and were dried using standard procedures. Benzene was distilled from sodium benzophenone ketyl.

2.2. Physical measurements

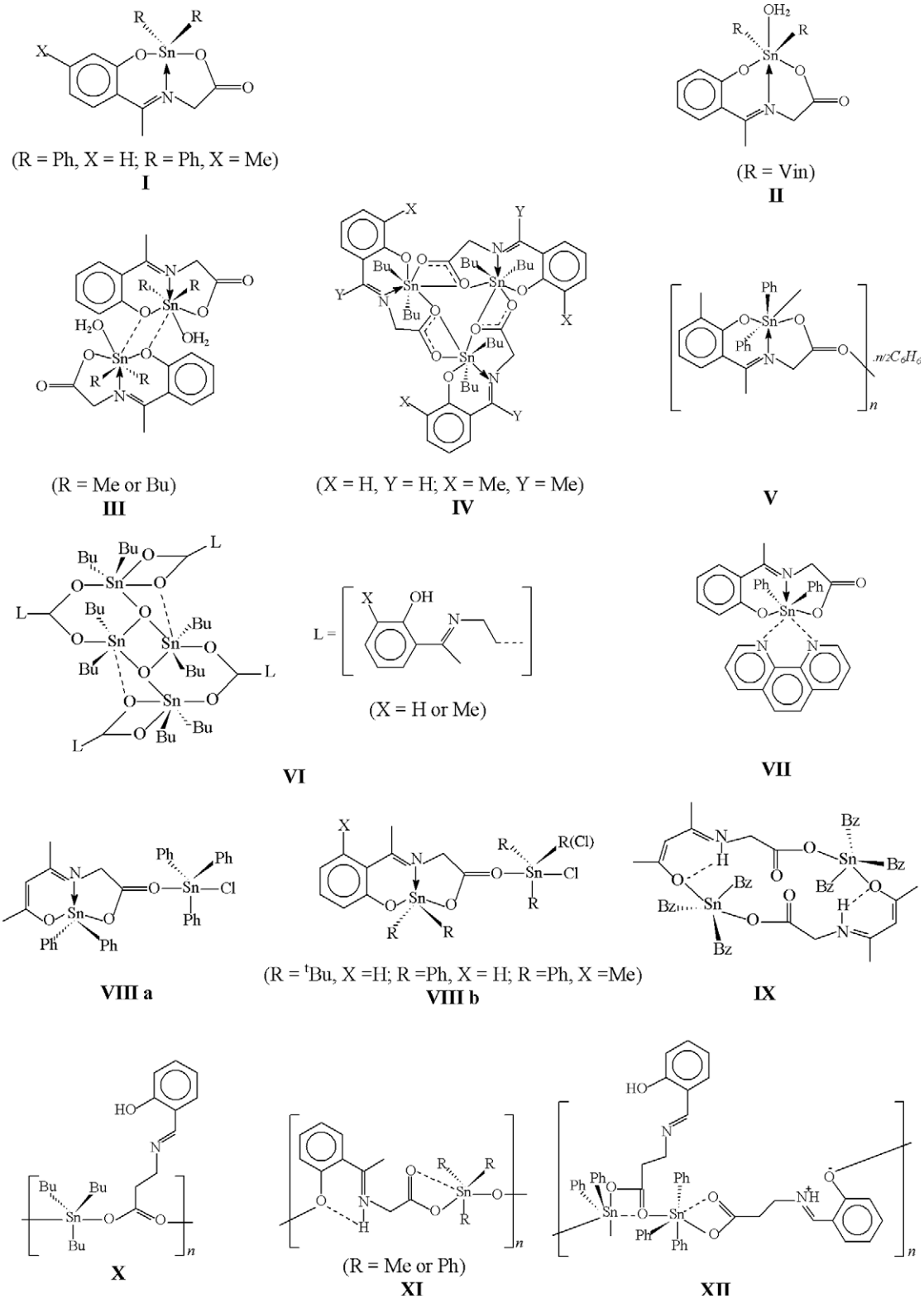
Carbon, hydrogen and nitrogen analyses were performed with a Perkin Elmer 2400 series II instrument. IR spectra in the range 4000–400 cm^{-1} were obtained on a BOMEM DA-8 FT-IR spectrophotometer with samples investigated as KBr discs. The ^{1}H, ^{13}C and ^{119}Sn NMR spectra were recorded on a Bruker AMX 400 spectrometer and measured at 400.13, 100.62 and 149.18 MHz. The ^{1}H, ^{13}C and ^{119}Sn chemical shifts were referred to Me_4Si set at 0.00 ppm, $CDCl_3$ set at 77.0 ppm and Me_4Sn set at 0.00 ppm, respectively. The Mössbauer spectra were recorded with a conventional spectrometer operating in the transmission mode. The source was $Ca^{119}SnO_3$ (Ritverc GmbH, St. Petersburg, Russia; 10 mCi), moving at room temperature with constant acceleration in a triangular waveform. The driving system was from Halder (Seehausen, Germany), and the NaI (Tl) detector from Harshaw (De Meern, The Netherlands). The multichannel analyser and the related electronics were from Takes (Bergamo, Italy). The solid absorber samples, containing ca. 0.5 mg ^{119}Sn cm^{-2}, were held at 77.3 K in a MNC 200 liquid-nitrogen cryostat (AERE, Harwell, UK). The velocity calibration was made using a ^{57}Co Mössbauer source (Ritverc GmbH, St. Petersburg, Russia, 10 mCi), and an iron foil as absorber. The isomer shifts are relative to room temperature $Ca^{119}SnO_3$. Positive-ion and negative-ion electrospray ionization (ESI) mass spectra were measured on an ion trap analyzer Esquire 3000 (Bruker Daltonics, Bremen, Germany) in the range m/z 50–2000. The complexes were dissolved in acetonitrile or methanol and analyzed by direct infusion at a flow rate of 5 μl/min. The selected precursor ions were further analyzed by MS/MS analyses under the following conditions: an isolation width of $m/z = 8$ for ions containing one tin atom and $m/z = 12$ for ions containing more tin atoms, an ion source temperature of 300 °C, a tuning parameter of compound stability 100%, a flow rate and pressure of nitrogen of 4 l/min and 10 psi, respectively. The software IsoPro 3.0 (freeware, http://members.aol.com/msmssoft/) was used for the theoretical calculation of relative isotopic abundances.

2.3. Synthesis of ligands

A typical procedure is described below.

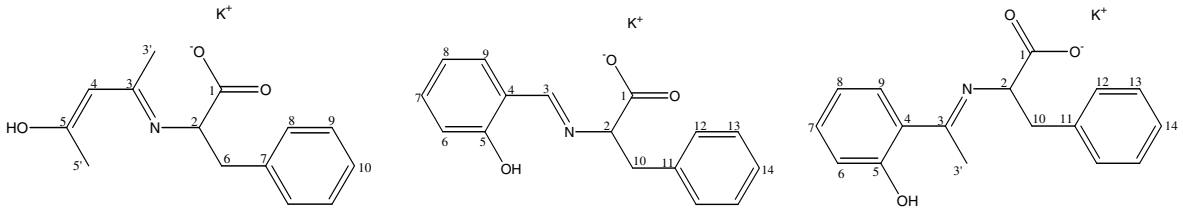
2.3.1. Synthesis of potassium 2-{[(E)-1-(2-hydroxyphenyl)methylidene]amino}phenylpropionate (L^2HK)

A cold aqueous solution (3 ml) of KOH (0.83 g, 14.8 mmol) was mixed with a cold aqueous solution (10 ml) containing L-phenylalanine (2.44 g, 14.8 mmol) and was held at 15–20 °C in an ice bath with continuous stirring. A methanolic solution (15 ml) of 2-hydroxybenzaldehyde (1.81 g, 14.8 mmol) was added drop-wise. A deep-yellow colour developed almost immediately and stirring was continued for 1 h, followed by 5 h stirring at room temperature. The volatiles were removed carefully; the yellow mass was stirred in diethylether and filtered. The residue was dissolved in a minimum amount



Scheme 1. An overview showing the coordination behaviour of Schiff bases with amino acids towards organotin(IV).

of anhydrous methanol and filtered. The filtrate was precipitated with diethylether which afforded the crude product. Repeated precipitations from a methanol–diethylether mixture yielded L^2HK in 85% (3.86 g) yield. M.p.: 178–179 °C. Anal. Calc. for $C_{16}H_{14}NKO_3$: C, 62.52; H 4.59; N; 4.55. Found: C, 63.01; H, 5.23; N, 4.25%. IR (cm^{-1}): 1628 $\nu(OCO)_{asym}$, 1605 $\nu(C{=}N)$, 1275 $\nu(Ph(C{-}O))$.



(L^1HK) (L^2HK) (L^3HK)

Fig. 1. The generic structures of the ligands, their abbreviations and numbering scheme.

2.3.2. Potassium 2-{[(2Z)-(3-hydroxy-1-methyl-2-butenylidene)]amino}phenylpropionate (L^1HK)

The same procedure was followed as for L^2HK, except that the reaction mixture was refluxed. Recrystallization from a methanol–diethylether mixture gave a yellow precipitate in 80% yield. M.p.: 200–201 °C. Anal. Calc. for $C_{14}H_{16}NKO_3$: C, 58.94; H 5.65; N; 4.90. Found: C, 59.36; H, 5.71; N, 4.90%. IR (cm^{-1}): 1613 $\nu(OCO)_{asym}$, 1613 ν(C=N), 1314 ν(Ph(C–O)).

2.3.3. Potassium 2-{[(E)-1-(2-hydroxyphenyl) ethylidene]amino}phenylpropionate (L^3HK)

The same procedure was followed as for L^2HK and the work-up of the reaction mixture yielded a yellow pasty mass which could not be isolated in powder form. So, the potassium salt was generated in situ prior to the reaction with the organotin reactant.

2.4. Synthesis of the organotin(IV) complexes

*2.4.1. Synthesis of $[Ph_3SnL^1H]_n \cdot nCCl_4$ (**1**)*

A warm solution of Ph_3SnCl (0.5 g, 1.30 mmol) in anhydrous methanol (ca. 10 ml) was added drop-wise to a warm solution of L^1HK (0.37 g, 1.30 mmol) in anhydrous methanol (ca. 20 ml) under stirring conditions. The reaction mixture was refluxed for 5 h, then filtered and the filtrate was then evaporated to dryness and the residue was dried *in vacuo*. The dried mass was washed thoroughly with hexane, dried *in vacuo*, extracted in carbon tetrachloride (ca. 20 ml) and filtered while hot. The filtrate was left to evaporate slowly at room temperature to afford light-yellow crystals of **1** in 77% (0.59 g) yield. M.p.: 138–139 °C. Anal. Calc. for $C_{33}H_{31}Cl_4NO_3Sn$: C, 52.85; H, 4.16; N, 1.87. Found: C, 52.64; H, 4.25; N, 2.17%. IR (cm^{-1}): 1657 $\nu(OCO)_{asym}$, 1600 ν(C=N), 1310 ν(Ph(CO)). ^1H NMR ($CDCl_3$): ligand skeleton: 10.70 (brs, 1H, OH), 7.01 (m, 5H, H-8, H-9 and H-10), 4.66 (s, 1H, H-4), 4.09 (q, 1H, H-2), 2.70 and 3.0 (dd, 2H, H-6), 1.74 and 1.40 (s, 6H, H-3′ and H-5′); Sn–Ph skeleton: 7.62 (m, 6H, H-2*), 7.29 (m, 9H, H-3* and H-4*), ppm. ^{13}C NMR ($CDCl_3$): ligand skeleton: 193.8 (C-1), 174.7 (C-3), 162.2 (C-5), 137.2 (C-7), 129.3 (C-8), 128.3 (C-9), 126.5 (C-10), 95.6 (C-4), 59.2 (C-2), 39.3 (C-6), 28.3 and 18.9 (C-3′ and C-5′); Sn–Ph skeleton [$^nJ(^{13}C–^{119}Sn$, Hz)]: 140.0 (C-1*) [600], 136.8 (C-2*) [54], 129.6 (C-4*) [16], 128.7 (C-3*) [60], ppm. ^{119}Sn NMR ($CDCl_3$): −99.3 ppm. ^{119}Sn Mössbauer: $\delta = 1.21$, $\Delta = 3.14$, $\Gamma\pm = 0.80$ mm s^{-1}, $\rho = 2.59$. ESI-MS: MW = $M_{mono} = 597 = L^1HSnPh_3$. Positive-ion MS: *m/z* 948 $[M_{mono}+SnPh_3]^+$; *m/z* 636 $[M_{mono}+K]^+$; *m/z* 620 $[M_{mono}+Na]^+$, 100%; *m/z* 351 $[SnPh_3]^+$. Negative-ion MS: *m/z* 843 $[M_{mono}+L^1H]^-$, 100%; *m/z* 439 $[ClSnPh_3+Cl+H_2O]^-$; *m/z* 246 $[L^1H]^-$; *m/z* 202 $[L^1H-CO_2]^-$.

*2.4.2. Synthesis of $[Me_2SnL^2(OH_2)]$ (**2**)*

A solution of Me_2SnCl_2 (0.35 g, 1.59 mmol) in CCl_4 (5 ml) was added drop-wise to a suspension of L^2HK (0.49 g, 1.59 mmol) in CCl_4 (20 ml) under stirring conditions at room temperature. The stirring was continued for 5 h. The reaction mixture was filtered; the filtrate was reduced to one-fourth of its initial solvent volume and then precipitated with hexane to give a yellow coloured product. The crude product was washed thoroughly with hexane, dried *in vacuo* and re-crystallized from CCl_4/hexane (2:1 v/v) which afforded a yellow crystalline product of **2** in 63% (0.49 g) yield. m.p.: 82–84 °C. Anal. Calc. for $C_{18}H_{21}NO_4Sn$: C, 49.75; H, 4.98; N, 3.22. Found: C, 50.01; H, 4.80; N, 3.33%. IR (cm^{-1}): 1669 $\nu(OCO)_{asym}$, 1613 ν(C=N), 1302 ν(Ph(CO)). ^1H NMR ($CDCl_3$): ligand skeleton: 7.58 (s, 1H, H-3), 7.41 (t, 1H, H-7), 7.27 (m, 4H, H-12 and H-13), 7.13 (m, 1H, H-14), 6.85 (dd, 1H, H-9), 6.76 (dd, 1H, H-6), 6.68 (t, 1H, H-8), 4.20 (q, 1H, H-2), 3.49 and 3.12 (dd, 2H, H-10); Sn-Me skeleton: 0.63 and 0.65 (s, 6H), ppm. ^{13}C NMR ($CDCl_3$): ligand skeleton: 172.5 (C-1 and C-3), 168.9 (C-5), 137.7 (C-7), 135.2 (C-9), 135.0 (C-11), 130.2 (C-12), 128.9 (C-13), 127.5 (C-14), 122.5 (C-6), 117.2 (C-8), 116.7 (C-4), 69.8 (C-2), 41.9 (C-10); Sn–Me skeleton: 0.22 and 0.55, ppm. ^{119}Sn NMR ($CDCl_3$): −157.5 ppm. ^{119}Sn Mössbauer: $\delta = 1.25$, $\Delta = 3.69$, $\Gamma\pm = 0.95$ mm s^{-1}, $\rho = 2.95$. ESI-MS: MW = $M_{mono} = 417$. Positive-ion MS: *m/z* 873 $[2^*M_{mono}+K]^+$; *m/z* 857 $[2^*M_{mono}+Na]^+$; *m/z* 456 $[M_{mono}+K]^+$; *m/z* 440 $[M_{mono}+Na]^+$, 100%; *m/z* 418 $[M_{mono}+H]^+$. Negative-ion MS: *m/z* 416 $[M_{mono}\text{-}H]^-$, 100%.

*2.4.3. Synthesis of $[^nBu_2SnL^2]$ (**3**)*

This compound was prepared in the same manner as described for **2** by using $^nBu_2SnCl_2$ (0.44 g, 1.48 mmol) and L^2HK (0.40 g, 1.49 mmol). After work-up, the crude product was re-crystallized from chloroform which upon

slow evaporation afforded a yellow crystalline product of **3** in 70% (0.57 g) yield. M.p.: 123–124 °C. Anal. Calc. for $C_{24}H_{31}NO_3Sn$: C, 57.63; H, 6.24; N, 2.80. Found: C, 57.50; H, 6.50; N, 2.80%. IR (cm^{-1}): 1668 $\nu(OCO)_{asym}$, 1616 ν(C=N), 1296 ν(Ph(CO)). ^{1}H NMR ($CDCl_3$): ligand skeleton: 7.45 (s, 1H, H-3), 7.39 (t, 1H, H-7), 7.24 (m, 4H, H-12 and H-13), 7.12 (m, 1H, H-14), 6.75 (m, 2H, H-6 and H-9), 6.63 (t, 1H, H-8), 4.16 (q, 1H, H-2), 3.54 and 3.04 (dd, 2H, H-10); Sn–^{n}Bu skeleton: 1.69–1.57 (m, 4H, H-1*), 1.51–1.21 (m, 8H, H-2* and H-3*), 0.94 and 0.79 (t, 6H, H-4*), ppm. ^{13}C NMR ($CDCl_3$): ligand skeleton: 173.0 (C-1), 172.4 (C-3), 169.5 (C-5), 137.6 (C-7), 135.3 (C-9 and C-11), 130.2 (C-12), 128.9 (C-13), 127.5 (C-14), 122.4 (C-6), 117.0 (C-8), 116.8 (C-4), 69.9 (C-2), 41.9 (C-10); Sn–^{n}Bu skeleton: 27.0 and 26.8 (C-2*), 26.6 and 26.4 (C-3*), 21.7 and 21.6 (C-1*), 13.5 and 13.4 (C-4*), ppm. ^{119}Sn NMR ($CDCl_3$): −198.3 ppm. ^{119}Sn Mössbauer: $\delta = 1.19$, $\Delta = 2.70$, $\Gamma\pm = 0.84$ mm s^{-1}, $\rho = 2.27$. ESI-MS: MW = M_{mono} = 501. Positive-ion MS: *m/z* 1025 $[2^*M_{mono}+Na]^+$, 100%; *m/z* 540 $[M_{mono}+K]^+$; *m/z* 524 $[M_{mono}+Na]^+$; *m/z* 502 $[M_{mono}+H]^+$. Negative-ion MS: *m/z* 500 $[M_{mono}-H]^-$, 100%.

2.4.4. Synthesis of $[Ph_2SnL^2]_n$ (4)

An identical method to that for **2** was followed using Ph_2SnCl_2 and L^2HK. Yellow crystals of compound **4** were obtained from ethanol in 58% yield. M.p.: 168–170 °C. Anal. Calc. for $C_{28}H_{23}NO_3Sn$: C, 62.27; H, 4.29; N, 2.59. Found: C, 62.31; H, 4.05; N, 2.67%. IR (cm^{-1}): 1679 $\nu(OCO)_{asym}$, 1614 ν(C=N), 1304 ν(Ph(CO)). ^{1}H NMR ($CDCl_3$): ligand skeleton: 8.00 (t, 1H, H-7), 6.85 (dd, 1H, H-9), 7.22 (s, 1H, H-3), 7.12 (m, 5H, H-12, H-13 and H-14), 6.92 (dd, 1H, H-6), 6.68 (t, 1H, H-8), 4.18 (q, 1H, H-2), 3.50 and 2.70 (dd, 2H, H-10); Sn-Ph skeleton: 7.48 (m, 4H, H-2*), 7.38 (m, 6H, H-3* and H-4*), ppm. ^{13}C-NMR ($CDCl_3$): ligand skeleton: 173.0 (C-1), 172.1 (C-3), 169.3 (C-5), 135.4 (C-7), 135.0 (C-11), 130.0 (C-9), 129.0 (C-12), 128.9 (C-13), 127.4 (C-14), 122.7 (C-6), 117.7 (C-8), 116.8 (C-4), 70.5 (C-2), 41.5 (C-10); Sn-Ph skeleton: 138.0 and 137.9 (C-1*), 136.6 and 136.4 (C-2*), 130.8 and 130.7 (C-4*), 128.9 (C-3*), ppm. ^{119}Sn NMR ($CDCl_3$): −341.8 ppm. ^{119}Sn Mössbauer: $\delta = 1.15$, $\Delta = 3.57$, $\Gamma\pm = 0.81$ mm s^{-1}, $\rho = 3.10$. ESI-MS: MW = M_{mono} = 541. Positive-ion MS: *m/z* 1121 $[2^*M_{mono}+K]^+$; *m/z* 1105 $[2^*M_{mono}+Na]^+$; *m/z* 580 $[M_{mono}+K]^+$, 100%; *m/z* 564 $[M_{mono}+Na]^+$; *m/z* 542 $[M_{mono}+H]^+$. Negative-ion MS: *m/z* 540 $[M_{mono}-H]^-$, 100%.

2.4.5. Synthesis of $[Ph_3SnL^2H]_n$ (5)

An identical method to that for **1** was followed using Ph_3SnCl and L^2HK, except that the reaction was conducted in anhydrous benzene for 5 h. Yellow crystals of compound **5** were obtained from ethanol in 70% yield. M.p.: 157–159 °C. Anal. Calc. for $C_{34}H_{29}NO_3Sn$: C, 66.05; H, 4.72; N, 2.26. Found: C, 66.10; H, 4.70; N, 2.37%. IR (cm^{-1}): 1662 $\nu(OCO)_{asym}$, 1609 ν(C=N), 1313 ν(Ph(CO)). ^{1}H NMR ($CDCl_3$): ligand skeleton: 12.50 (brs, 1H, OH), 7.80 (s, 1H, H-3), 7.18 (m, 5H, H-12, H-13 and H-14), 6.95 (m, 2H, H-7 and H-9), 6.78 (dd, 1H, H-6), 6.59 (t, 1H and H-8), 4.06 (q, 1H and H-2), 3.18 and 3.01 (dd, 2H, H-10); Sn–Ph skeleton: 7.56 (m, 6H, H-2*), 7.28 (m, 9H, H-3* and H-4*), ppm. ^{13}C NMR ($CDCl_3$): ligand skeleton: 176.5 (C-1), 166.2 (C-3), 161.1 (C-5), 137.2 (C-11), 132.5 (C-7), 131.6 (C-9), 129.3 (C-12), 128.3 (C-13), 126.6 (C-14), 118.7 (C-4), 118.4 (C-6), 117.0 (C-8), 73.0 (C-2), 40.6 (C-10); Sn–Ph skeleton [$^nJ(^{13}C–^{119}Sn$, Hz)]: 137.7 (C-1*) [610], 136.8 (C-2*) [50], 130.3 (C-4*) [20], 129.0 (C-3*) [60], ppm. ^{119}Sn-NMR ($CDCl_3$): −99.7 ppm. ^{119}Sn Mössbauer: $\delta = 1.21$, $\Delta = 3.04$, $\Gamma\pm = 0.75$ mm s^{-1}, $\rho = 2.51$. ESI-MS: MW = $M_{mono} = 619 = L^2HSnPh_3$. Positive-ion MS: *m/z* 992 $[M_{mono}+Na-H+SnPh_3]^+$; *m/z* 970 $[M_{mono}+SnPh_3]^+$, 100%; *m/z* 658 $[M_{mono}+K]^+$; *m/z* 642 $[M_{mono}+Na]^+$; *m/z* 351 $[SnPh_3]^+$. Negative-ion MS: *m/z* 887 $[M_{mono}+ligand]^-$, 100%; *m/z* 618 $[M_{mono}-H]^-$; *m/z* 574 $[M_{mono}-H-CO_2]^-$; *m/z* 439 $[ClSnPh_3+Cl+H_2O]^-$; *m/z* 351 $[SnPh_3]^-$; *m/z* 224 $[ligand-CO_2]^-$; *m/z* 197 $[ligand-CO_2\text{-}27]^-$.

2.4.6. Synthesis of $[^nBu_2SnL^3(OH_2)]$ (6)

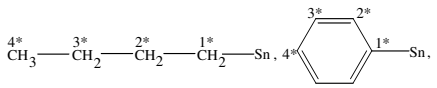
A mixture of $^nBu_2SnO$ (0.4 g, 1.60 mmol), *l*-phenylalanine (0.26 g, 1.60 mmol) and 2-hydroxyacetophenone (0.22 g, 1.60 mmol) were refluxed in ethanol (30 ml) for 8 h using a Dean and Stark apparatus. The clear yellowish green solution was evaporated using a rotary evaporator. Then anhydrous toluene (30 ml) was added to the syrupy mass and refluxed for 6 h using a Dean and Stark setup. The reaction mixture was filtered while hot and the filtrate was evaporated to give a yellow mass, which upon recrystallization from a toluene/hexane (1:1) mixture furnished a pure product of **6** in 66% (0.56 g) yield. M.p.: 94–95 °C. Anal. Calc. for $C_{25}H_{35}NO_4Sn$: C, 56.43; H, 6.63; N, 2.63. Found: C, 56.50; H, 6.70; N, 2.70%. IR (cm^{-1}): 1641 $\nu(OCO)_{asym}$, 1601 ν(C=N), 1311 ν(Ph(CO)). ^{1}H NMR ($CDCl_3$): ligand skeleton: 7.34 (m, 2H, H-7 and H-9), 7.24 (m, 5H, H-12, H-13 and H-14), 6.89 (m, 1H, H-6), 6.72 (t, 1H, H-8), 4.68 (q, 1H, H-2), 3.51 and 3.08 (dd, 2H, H-10), 2.18 (s, 3H, H-3′); Sn–^{n}Bu skeleton: 1.80–1.67 (m, 4H, H-1*), 1.51–1.11 (m, 8H, H-2* and H-3*), 0.95 and 0.74 (t, 6H, H-4*), ppm. ^{13}C NMR ($CDCl_3$): ligand skeleton: 179.8 (C-1), 173.4 (C-3), 166.9 (C-5), 135.5 (C-7), 135.4 (C-9), 130.1 (C-11), 129.8 (C-12), 129.0 (C-13), 127.4 (C-14), 123.8 (C-6), 120.8 (C-4), 117.6 (C-8), 65.1 (C-2), 41.0 (C-10), 22.1 (C-3′); Sn–^{n}Bu skeleton: 27.2 and 26.8 (C-2*), 26.6 and 26.3 (C-3*), 20.2 and 18.1 (C-1*), 13.5 and 13.3 (C-4*), ppm. ^{119}Sn NMR ($CDCl_3$): −208.8 ppm. ^{119}Sn Mössbauer: $\delta = 1.34$, $\Delta = 3.64$, $\Gamma\pm = 0.87$ mm s^{-1}, $\rho = 2.71$. ESI-MS: MW = M_{mono} = 515. Positive-ion MS: *m/z* 1053 $[2^*M_{mono}+Na]^+$, 100%; *m/z* 554 $[M_{mono}+K]^+$; *m/z* 538 $[M_{mono}+Na]^+$; *m/z* 516 $[M_{mono}+H]^+$. Negative-ion MS: *m/z* 514 $[M_{mono}-H]^-$, 100%.

2.4.7. Synthesis of $[Ph_3SnL^3H]_n$ (7)

An anhydrous methanol solution (2 ml) of KOH (0.09 g, 1.60 mmol) was added to a round bottom flask containing

l-phenylalanine (0.27 g, 1.63 mmol) in 2 ml of methanol and the reaction mixture was stirred until a clear solution was obtained. To this, a methanol solution (3 ml) of 2-hydroxyacetophenone (0.22 g, 1.61 mmol) was added drop-wise and refluxed for 2 h. Then, a solution of Ph_3SnCl (0.62 g, 1.61 mmol) in anhydrous methanol (5 ml) was added and the reaction mixture was refluxed for an additional 5 h. The volatiles were removed and the residue was washed thoroughly with petroleum ether (60–80 °C) and dried *in vacuo*. The dried residue was extracted into warm chloroform (25 ml) and filtered. The filtrate was concentrated, precipitated with petroleum ether (60–80 °C), filtered and the yellow coloured precipitate was dried *in vacuo*. The crude product was then re-crystallized from a chloroform–ethanol (1:1 v/v) mixture which afforded a lemon yellow microcrystalline product of **7** in 60% (0.53 g) yield. M.p.: 158–159 °C. Anal. Calc. for $C_{35}H_{31}NO_3Sn$: C, 66.43; H, 4.94; N, 2.21. Found: C, 66.80; H, 5.01; N, 2.30%. IR (cm^{-1}): 1658 $\nu(OCO)_{asym}$, 1605 $\nu(C{=}N)$, 1314 $\nu(Ph(CO))$. ^1H NMR ($CDCl_3$): ligand skeleton: 14.8 (brs, 1H, OH), 7.21 (m, 5H, H-12, H-13 and H-14), 6.99 (m, 2H, H-7 and H-9), 6.76 (dd, 1H, H-6), 6.54 (t, 1H, H-8), 4.46 (q, 1H, H-2), 3.32 and 3.01 (dd, 2H, H-10), 1.68 (s, 3H, H-3′); Sn-Ph skeleton: 7.61 (m, 6H, H-2*), 7.31 (m, 9H, H-3* and H-4*), ppm. ^{13}C NMR ($CDCl_3$): ligand skeleton: 177.0 (C-1), 171.5 (C-3), 163.0 (C-5), 137.3 (C-11), 131.9 (C-7), 129.5 (C-9), 128.2 (C-12), 127.8 (C-13), 126.4 (C-14), 119.6 (C-4), 118.6 (C-6), 116.7 (C-8), 64.4 (C-2), 40.8 (C-10), 14.3 (C-3′); Sn-Ph skeleton [$^nJ(^{13}C–^{119}Sn$, Hz)]: 137.7 (C-1*) [620], 136.9 (C-2*) [50], 129.9 (C-4*) [16], 128.7 (C-3*) [60], ppm. ^{119}Sn NMR ($CDCl_3$): −98.3 ppm. ^{119}Sn Mössbauer: $\delta = 1.22$, $\Delta = 3.10$, $\Gamma\pm = 0.81$ mm s^{-1}, $\rho = 2.54$. ESI-MS: $MW = M_{mono} = 633 = L^3HSnPh_3$. Positive-ion MS: *m/z* 1006 $[M_{mono}+Na-H+SnPh_3]^+$; *m/z* 984 $[M_{mono}+SnPh_3]^+$; *m/z* 672 $[M_{mono}+K]^+$; *m/z* 656 $[M_{mono}+Na]^+$, 100%; *m/z* 634 $[M_{mono}+H]^+$; *m/z* 351 $[SnPh_3]^+$. Negative-ion MS: *m/z* 915 $[M_{mono}+ligand]^-$, 100%; *m/z* 439 $[ClSnPh_3+Cl+H_2O]^-$; *m/z* 351 $[SnPh_3]^-$; *m/z* 238 $[ligand-CO_2]^-$.

For the ^1H and ^{13}C NMR assignments, refer to Fig. 1 for the numbering scheme of the ligand skeleton, while for the Sn–R skeleton, the numbering is as shown below:



2.5. X-ray crystallography

Crystals of compounds **1**, **4**–**7** suitable for an X-ray crystal-structure determination were obtained from carbon tetrachloride (**1**), ethanol (**4** and **5**), toluene/hexene (**6**) or acetone (**7**) solutions of the respective compounds. All measurements were made at 160 K on a Nonius KappaCCD diffractometer [10] with graphite-monochromated Mo Kα radiation ($\lambda = 0.71073$ Å) and an Oxford Cryosystems Cryostream 700 cooler. Data reductions were performed with HKL DENZO and SCALEPACK [11]. The intensities were corrected for *Lorentz* and polarization effects, and empirical absorption corrections based on the multi-scan method [12] were applied. Equivalent reflections were merged, other than the *Friedel* pairs for**1** and **7**. The data collection and refinement parameters are given in Table 1, and views of the molecules are shown in Figs. 2–6. The structures were solved by direct-methods using SIR92 [13] for **1**, **4**, **5** and **7**, and SHELXS97 [14] for **6**, and the non-hydrogen atoms were refined anistropically.

Compounds **1**, **4**, **5** and **7** exist as polymeric chains with the carboxylate ligands bridging between the Sn-atoms and in each case the asymmetric unit contains just one of the chemical repeat units of the polymer. In **1**, the asymmetric unit also contains one molecule of CCl_4. One of the phenyl ligands is disordered. Two sets of positions were defined for all atoms of the disordered phenyl ring, except for the *ipso* C-atom and the site occupation factor of the major conformation refined to 0.673(4). Neighbouring atoms within and between each conformation of the disordered phenyl ring were restrained to have similar atomic displacement parameters.

The carboxylate ligand in **5** is disordered from the carboxylate group through to and including the benzyl group. The disorder includes one of the carboxylate O-atoms, O(2), but not C(1). Two sets of overlapping positions were defined for the disordered atoms and the site occupation factor of the major conformation refined to 0.678(6). Similarity restraints were applied to the chemically equivalent bond lengths and angles involving all disordered atoms, while neighbouring atoms within and between each conformation were restrained to have similar atomic displacement parameters. Pesudo-isotropic restraints were also applied to the disordered position of the carboxylate carbonyl O-atom.

In **6**, there are two symmetry-independent monomeric molecules in the asymmetric unit. The terminal ethyl group of one butyl ligand of one of the symmetry-independent molecules is disordered over two conformations. Two sets of overlapping positions were defined for the disordered atoms and the site occupation factor of the major conformation refined to 0.566(8). Similarity restraints were applied to the chemically equivalent bond lengths and angles involving all disordered C-atoms, while neighbouring atoms within and between each conformation of the disordered group were restrained to have similar atomic displacement parameters. The water ligand H-atoms were placed in the positions indicated by a difference electron density map and their positions were allowed to refine together with individual isotropic displacement parameters, while lightly restraining the O–H distances to 0.84 Å.

For **7**, the ammonium H-atom was placed in the position indicated by a difference electron density map and its position was allowed to refine together with an isotropic displacement parameter. All other H atoms in all structures

Table 1
Crystallographic data and structure refinement parameters for compounds **1** and **4**–**7**

	1	**4**	**5**	**6**	**7**
Empirical formula	$C_{32}H_{31}NO_3Sn{\cdot}CCl_4$	$C_{28}H_{23}NO_3Sn$	$C_{34}H_{29}NO_3Sn$	$C_{25}H_{35}NO_4Sn$	$C_{35}H_{31}NO_3Sn$
Formula weight	750.02	540.09	618.21	532.15	632.23
Crystal size (mm)	$0.13\times0.20\times0.33$	$0.15\times0.17\times0.25$	$0.05\times0.07\times0.12$	$0.15\times0.25\times0.28$	$0.12\times0.17\times0.32$
Crystal color, habit	Colorless, prism	Pale yellow, prism	Yellow, prism	Colorless, prism	Yellow, prism
Crystal system	Orthorhombic	Monoclinic	Monoclinic	Triclinic	Orthorhombic
Space group	$P2_12_12_1$	$P2_1/c$	$P2_1/c$	$P\bar{1}$	$P2_12_12_1$
a (Å)	11.0077(2)	11.5921(2)	11.0911(2)	9.9886(2)	11.2346(1)
b (Å)	17.3960(2)	9.2157(2)	12.8357(3)	12.5048(2)	12.5781(2)
c (Å)	17.6395(2)	21.6622(4)	20.0734(4)	20.2658(3)	20.8002(3)
α (°)	90	90	90	81.703(1)	90
β (°)	90	96.7398(9)	105.180(1)	89.952(1)	90
γ (°)	90	90	90	79.9294(8)	90
V (Å^3)	3377.79(8)	2298.17(8)	2758.0(1)	2465.45(7)	2939.27(7)
Z	4	4	4	4	4
D_x (g cm^{-3})	1.475	1.561	1.489	1.434	1.429
μ (mm^{-1})	1.105	1.141	0.962	1.065	0.904
Transmission factors (min, max)	0.791; 0.895	0.745; 0.848	0.884; 0.956	0.676; 0.858	0.831; 0.900
$2\theta_{max}$ (°)	60	56	52	60	60
Reflections measured	65005	44041	46415	55207	51297
Independent reflections; R_{int}	9852; 0.065	5481; 0.061	5417; 0.078	14222; 0.053	8605; 0.058
Reflections with $I > 2\sigma(I)$	8315	4618	4516	11556	7772
Number of parameters	427	299	435	601	367
Number of restraints	102	0	236	36	0
$R(F)$ [$I > 2\sigma(I)$ reflections]	0.036	0.034	0.043	0.038	0.032
$WR(F^2)$ (all data)	0.082	0.084	0.084	0.096	0.067
GOF(F^2)	1.08	1.14	1.25	1.07	1.07
Secondary extinction coefficient	–	0.0013(3)	0.0025(5)	–	0.0015(2)
$\Delta\rho_{max,\ min}$ (e Å^{-3})	1.30; −1.03	1.46; −0.90	0.61; −0.65	2.38; −1.51	1.28; −0.85

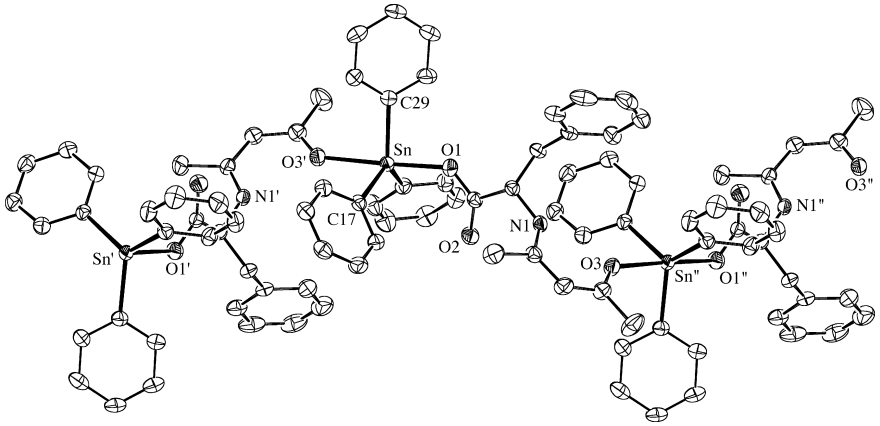


Fig. 2. Three repeats of the crystallographically and chemically unique unit in the polymeric $[Ph_3SnL^1H]_n$ chain structure of **1** (50% probability ellipsoids; only one of the conformations of the disordered phenyl ring is shown; symmetry operators: $'-x,\ -\frac{1}{2}+y,\ \frac{1}{2}-z$; $''-x,\ \frac{1}{2}+y,\ \frac{1}{2}-z$). The hydrogen atoms have been omitted for clarity.

were placed in geometrically calculated positions and refined using a riding model where each H atom was assigned a fixed isotropic displacement parameter with a value equal to 1.2 U_{eq} of its parent C atom (1.5 U_{eq} for the methyl groups). The refinement of each structure was carried out on F^2 using full-matrix least-squares procedures, which minimized the function $\Sigma w(F_o^2-F_c^2)_2$. Corrections for secondary extinction were applied for **4**, **5** and **7**. Refinement of the absolute structure parameter [15] for **1** and **7** yielded a value of −0.04(2) in each case, which confidently confirms that the refined coordinates represent the true enantiomorph. All calculations were performed using the SHELXL97 program [16].

2.6. Biological tests

The *in vitro* cytotoxicity test of compounds **1**, **5** and **7** was performed using the SRB test for the estimation of cell viability. The cell lines WIDR (colon cancer), M19 MEL (melanoma), A498 (renal cancer), IGROV (ovarian

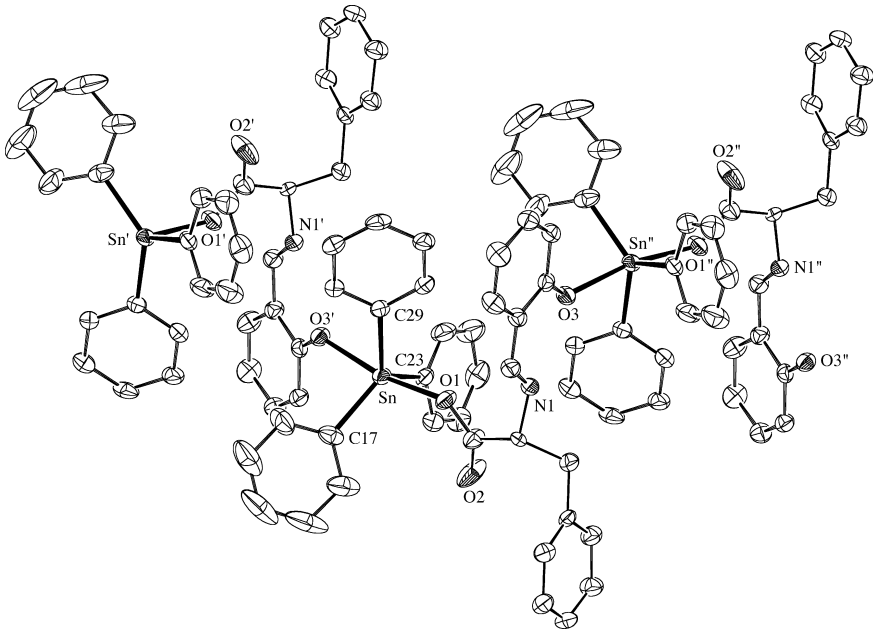


Fig. 3. Three repeats of the crystallographically and chemically unique unit in the polymeric $[Ph_3SnL^2H]_n$ chain structure of **5** (50% probability ellipsoids; only one of the conformations of the disordered carboxylate ligand is shown; symmetry operators: $'2-x,\ \frac{1}{2}+y,\ 1\frac{1}{2}-z;\ ''2-x,\ -\frac{1}{2}+y,\ 1\frac{1}{2}-z$). The hydrogen atoms have been omitted for clarity.

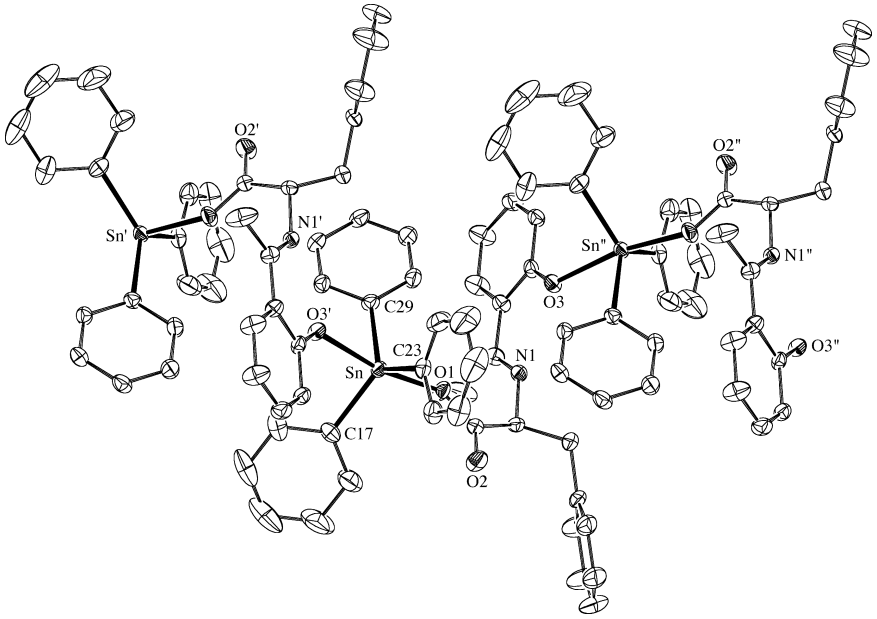


Fig. 4. Three repeats of the crystallographically and chemically unique unit in the polymeric $[Ph_3SnL^3H]_n$ chain structure of **7** (50% probability ellipsoids; symmetry operators: $'2-x,\frac{1}{2}+y,\frac{1}{2}-z;\ ''2-x,-\frac{1}{2}+y,\frac{1}{2}-z$). The hydrogen atoms have been omitted for clarity.

cancer) and H226 (non-small cell lung cancer) belong to the currently used anticancer screening panel of the National Cancer Institute, USA [17]. The MCF7 (breast cancer) cell line is estrogen receptor (ER)+/progesterone receptor (PgR)+ and the cell line EVSA-T (breast cancer) is (ER)−/(Pgr)−. Prior to the experiments, a mycoplasma test was carried out on all cell lines and found to be negative. All cell lines were maintained in a continuous logarithmic culture in RPMI 1640 medium with Hepes and phenol red. The medium was supplemented with 10% FCS, penicillin 100 μg/ml and streptomycin 100 μg/ml. The cells were mildly trypsinized for passage and for use in the experiments. RPMI and FCS were obtained from Life technologies (Paisley, Scotland). SRB, DMSO, Penicillin and streptomycin were obtained from Sigma (St. Louis MO, USA), TCA and acetic acid from Baker BV (Deventer, NL) and PBS from NPBI BV (Emmer-Compascuum, NL).

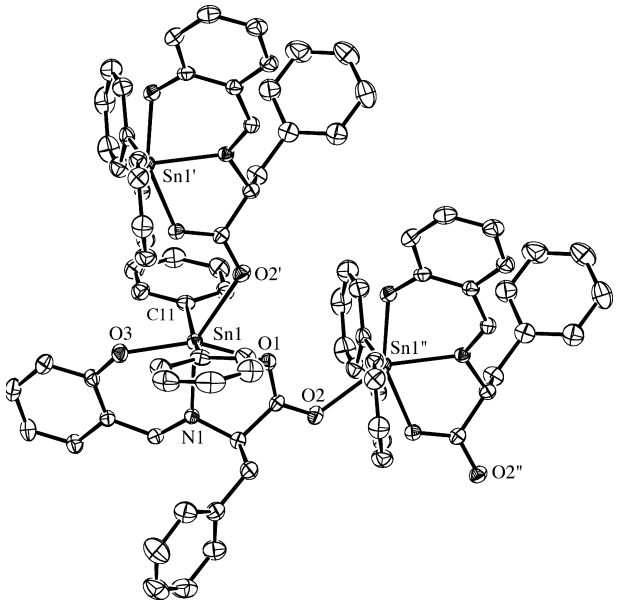


Fig. 5. Three repeats of the crystallographically and chemically unique unit in the polymeric $[Ph_2SnL^2]_n$ chain structure of **4** showing the *cis*-bridged Ph_2SnL^2 chain (50% probability ellipsoids; symmetry operators: $' -x, \frac{1}{2}+y, 1\frac{1}{2}-z$; $'' -x, -\frac{1}{2}+y, 1\frac{1}{2}-z$). s. The hydrogen atoms have been omitted for clarity.

The test compounds **1**, **5** and **7** and reference compounds were dissolved to a concentration of 250 000 ng/ml in full medium by 20-fold dilution of a stock solution, which contained 1 mg of compounds **1**, **5** and **7**/200 μl. All the three compounds were dissolved in DMSO. Cytotoxicity was estimated by the microculture sulforhodamine B (SRB) test [18].

2.6.1. Experimental protocol and cytotoxicity tests

The experiment was started on day 0. On day 0, 150 μl of trypsinized tumor cells (1500–2000 cells/well) were plated in 96-well flat-bottomed micro-titer plates (falcon 3072, BD). The plates were pre-incubated for 48 h at 37 °C, 5.5% CO_2 to allow the cells to adhere. On day 2, a 3-fold dilution sequence of 10 steps was made in full medium, starting with the 250 000 ng/ml stock solution. Every dilution was used in quadruplicate by adding 50 μl to a column of four wells. This results in a highest concentration of 62 500 ng/ml being present in column 12. Column 2 was used for the blank. To column 1, PBS was added to diminish interfering evaporation. On day 7, washing the plate twice with PBS terminated the incubation. Subsequently, the cells were fixed with 10% trichloroacetic acid in PBS and placed at 4 °C for an hour. After three washings with tap water, the cells were stained for at least 15 min with 0.4% SRB dissolved in 1% acetic acid. After staining, the cells were washed with 1% acetic acid to remove the unbound stain. The plates were air-dried and the bound stain was dissolved in 150 μl (10 mM) Tris-base. The absorbance was read at 540 nm using an automated microplate reader (Labsystems Multiskan MS). Data were used for construction of concentration–response curves and the determination of ID_{50} values by use of Deltasoft 3 software.

The variability of the *in vitro* cytotoxicity test depends on the cell lines used and the serum applied. With the same batch of cell lines and the same batch of serum the inter-experimental CV (coefficient of variation) is 1–11% depending on the cell line and the intra-experimental CV is 2–4%. These values may be higher with other batches of cell lines and/or serum.

The *in vitro* cytotoxicity experiments were carried out by Ms. P.F. van Cuijk in the Laboratory of Translational Pharmacology, Department of Medical Oncology, Erasmus Medical Center, Rotterdam, The Netherlands, under the supervision of Dr. E. A. C. Wiemer and Prof. Dr. G. Stoter.

3. Results and discussion

3.1. Synthetic aspects

The organotin(IV) complexes (**1**–**5**) were prepared by reacting the potassium salts of the ligands ($L^{1-2}HK$; Fig. 1) with the appropriate organotin(IV) halide(s) in 1:1 molar ratios in appropriate solvents (see Section 2.4). On the other hand, the 2-{[(*E*)-1-(2-hydroxyphenyl)ethylidene]amino}phenylpropionic acid (L^3HH') or its potassium salt (L^3HK) could not be isolated as powder. However, both L^3HH' and L^3HK frameworks can be generated in situ and can be used for the reactions with appropriate organotin(IV) oxide or halide(s), respectively, which yielded rest of the organotin(IV) complexes (**6**–**7**). The details of their synthesis and characterization data are presented in Section 2.4. The complexes were obtained in good yield and purity. They are stable in air and soluble in all common organic solvents.

3.2. Crystal structures

The molecular structures of compounds **1**, and **4**–**7** are shown in Figs. 2–6 (see Scheme 2 for line diagrams), while selected geometric parameters are collected in Tables 2–5.

The crystal structures of complexes **1**, **5** and **7** are very similar and exhibit the same structural motif of a polymeric chain where a single carboxylate ligand bridges adjacent R_3Sn centres *via* its carboxylate and oxide O-atoms, as illustrated in Figs. 2–4. The asymmetric unit in each structure contains one of the chemical repeat units of the polymeric Sn-compound, while **1** includes additionally one molecule of CCl_4. The primary coordination sphere of the Sn-atom is trigonal bipyramidal with the phenyl ligands in the equatorial plane and the axial positions being occupied by one O-atom from the carboxylate group of one ligand and the oxide O-atom (formerly the hydroxy group) of the next carboxylate ligand in the chain. In each structure, the chains propagate in the crystallographic [0 1 0] direction. A polymeric structure with a similar mode of

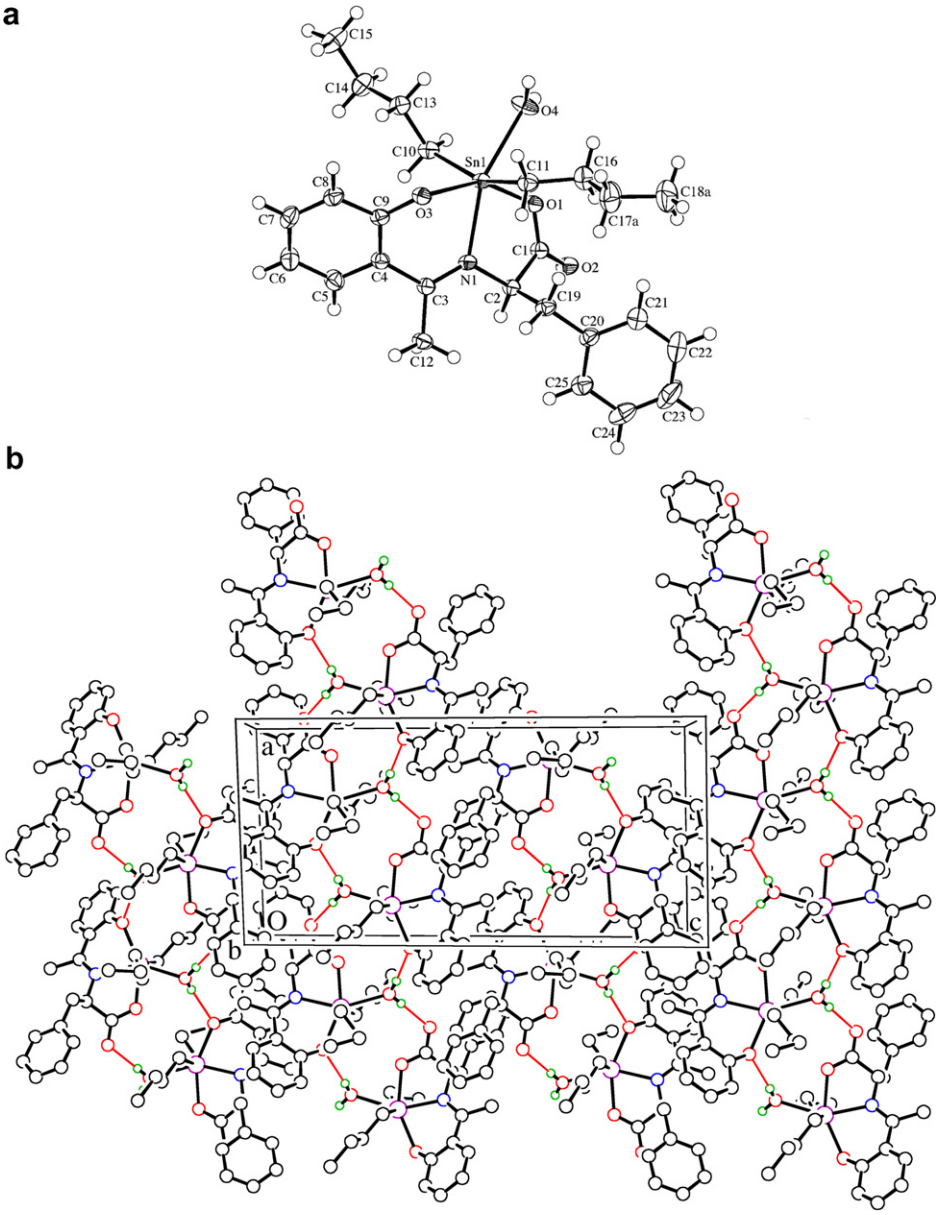
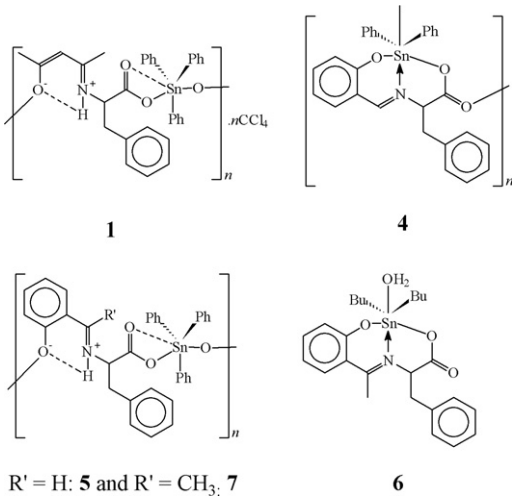


Fig. 6. (a) The molecular structure of one of the disordered conformations of one of the two symmetry-independent molecules (molecule A) of [^{n}Bu$_2$SnL^3(OH$_2$)] (**6**) (50% probability ellipsoids). (b) The molecular packing of [^{n}Bu$_2$SnL^3 (OH$_2$)] (**6**) showing the intermolecular hydrogen bonding (thin lines).

coordination and geometry about the Sn-atom was observed in [Ph$_3$Sn{2-OHC$_6$H$_4$C(H) = NCH$_2$COO}$_n$] [4]. The second O-atom of the carboxylate group is not involved in the primary coordination sphere of the Sn-atom, but coordinates very weakly to the Sn-atom *via* a long Sn···O(2) interaction of about 3.53 Å (see Table 2, although this is still within the sum of the van der Waals radii of the respective atoms (ca. 3.6 Å). There does not appear to be any major distortion of the trigonal bipyramidal Sn-coordination geometry as a result of the Sn···O(2) contact. Similar additional weak Sn···O coordination was also observed in the structures of related polymeric [Ph$_3$SnLH]$_n$ derivatives [8]. The formal hydroxy group has lost its H-atom, so it is negatively charged. Instead the N-atom of the C=N group is protonated, thus leading to a zwitterionic ligand. This N–H group forms an intramolecular hydrogen bond with the oxide O-atom. It is worth mentioning that the crystals of compounds **1** and **7** are enantiomerically pure (*S*-configuration of the zwitterionic carboxylate ligand) and their absolute configuration has been determined independently by the diffraction experiment. On the other hand, the carboxylate ligand in **5** is disordered from the carboxylate group through to the benzyl group (see Section 2.5). This disorder results from random coordination of either an *R*-configured or *S*-configured ligand at each Sn-atom. This comes about because both enantiomers of the racemic ligand apparently have similar spatial requirements. One of the phenyl



Scheme 2. Structure of the complexes **1**, **4**–**7**.

Table 2
Selected bond lengths (Å) and angles (°) for compounds **1**, **5** and **7**[a]

	1	5	7
Sn–O(1)	2.152(2)	2.191(3)	2.182(2)
Sn–O(3′)	2.323(2)	2.251(3)	2.284(2)
Sn–O(2)	3.507(2)	ca. 3.55	3.539(2)
Sn–C(17)	2.129(3)	2.138(4)	2.129(3)
Sn–C(23)	2.131(3)	2.118(4)	2.123(3)
Sn–C(29)	2.126(3)	2.131(3)	2.132(2)
C(17)–Sn–C(23)	123.4(1)	123.2(2)	120.5(1)
C(17)–Sn–C(29)	114.5(1)	117.3(2)	117.3(1)
C(23)–Sn–C(29)	121.4(1)	118.9(2)	121.3(1)
O(1)–Sn–O(3′)	175.89(8)	169.13(9)	169.64(6)

[a] Primed atoms refer to atoms from the next symmetrically-related ligand in the polymeric chain (symmetry code for **1**: $-x, -\frac{1}{2}+y, \frac{1}{2}-z$; for **5**: $2-x, \frac{1}{2}+y, 1\frac{1}{2}-z$; for **7**: $2-x, \frac{1}{2}+y, \frac{1}{2}-z$).

Table 3
Selected bond lengths (Å) and angles (°) for compound **4**[a]

Sn(1)–O(1)	2.200(2)
Sn(1)–O(3)	2.135(2)
Sn(1)–O(2′)	2.402(2)
Sn(1)–O(1′)	3.313(2)
Sn(1)–N(1)	2.237(2)
Sn(1)–C(10)	2.119(3)
Sn(1)–C(11)	2.130(3)
O(1)–Sn(1)–C(10)	96.3(1)
O(1)–Sn(1)–C(11)	91.9(1)
O(1)–Sn(1)–O(3)	154.39(8)
O(1)–Sn(1)–N(1)	73.28(8)
O(3)–Sn(1)–C(10)	89.2(1)
O(3)–Sn(1)–C(11)	90.9(1)
O(3)–Sn(1)–N(1)	81.16(8)
N(1)–Sn(1)–C(10)	98.9(1)
N(1)–Sn(1)–C(11)	100.0(1)
C(10)–Sn(1)–C(11)	160.9(1)

[a] Primed atoms refer to atoms from the next symmetrically-related ligand in the polymeric chain (symmetry code: $-x, \frac{1}{2}+y, 1\frac{1}{2}-z$).

Table 4
Selected bond lengths (Å) and angles (°) for compound **6**

Molecule A		Molecule B	
Sn(1)–O(1)	2.152(2)	Sn(2)–O(5)	2.158(2)
Sn(1)–O(3)	2.201(2)	Sn(2)–O(7)	2.193(2)
Sn(1)–O(4)	2.390(2)	Sn(2)–O(8)	2.420(2)
Sn(1)–N(1)	2.259(2)	Sn(2)–N(2)	2.258(2)
Sn(1)–C(10)	2.126(3)	Sn(2)–C(40)	2.121(3)
Sn(1)–C(11)	2.122(3)	Sn(2)–C(41)	2.121(3)
O(1)–Sn(1)–C(10)	95.60(9)	O(5)–Sn(2)–C(40)	95.07(9)
O(1)–Sn(1)–C(11)	100.6(1)	O(5)–Sn(2)–C(41)	100.70(9)
O(1)–Sn(1)–O(3)	152.04(7)	O(5)–Sn(2)–O(7)	152.74(6)
O(1)–Sn(1)–O(4)	77.98(7)	O(5)–Sn(2)–O(8)	78.38(7)
O(1)–Sn(1)–N(1)	73.47(7)	O(5)–Sn(2)–N(2)	73.74(7)
O(3)–Sn(1)–C(10)	89.96(9)	O(7)–Sn(2)–C(40)	90.15(9)
O(3)–Sn(1)–C(11)	83.97(9)	O(7)–Sn(2)–C(41)	84.39(9)
O(3)–Sn(1)–O(4)	129.96(7)	O(7)–Sn(2)–O(8)	128.88(7)
O(3)–Sn(1)–N(1)	78.59(7)	O(7)–Sn(2)–N(2)	79.00(7)
O(4)–Sn(1)–C(10)	82.71(9)	O(8)–Sn(2)–C(40)	81.54(9)
O(4)–Sn(1)–C(11)	83.6(1)	O(8)–Sn(2)–C(41)	83.39(9)
O(4)–Sn(1)–N(1)	151.45(8)	O(8)–Sn(2)–N(2)	152.12(7)
N(1)–Sn(1)–C(10)	99.92(9)	N(2)–Sn(2)–C(40)	100.60(9)
N(1)–Sn(1)–C(11)	101.5(1)	N(2)–Sn(2)–C(41)	101.76(9)
C(10)–Sn(1)–C(11)	156.1(1)	C(40)–Sn(2)–C(41)	155.5(1)

Table 5
Hydrogen bonding geometry (Å, °) for **6**[a]

D–H···A	D–H	H···A	D···A	D–H···A
O(4)–H(41)···O(6′)	0.82(2)	1.87(2)	2.689(3)	178(4)
O(4)–H(42)···O(7)	0.80(2)	1.94(2)	2.741(3)	174(4)
O(8)–H(81)···O(2)	0.81(2)	1.91(2)	2.719(3)	174(4)
O(8)–H(82)···O(3″)	0.82(2)	1.94(2)	2.752(3)	176(4)

[a] Primed atoms refer to the molecule in the following symmetry related positions: $'1+x,y,z$; $''-1+x,y,z$.

ligands in **1** is disordered over two orientations which differ by a rotation of 55.8(6)° about the Sn–C bond.

In the crystal structure of **4**, the Sn-complex units are linked into a polymeric zig-zag *cis*-bridged chain by a Sn(1)–O(2)′ (symmetry operation of primed atom $= -x, \frac{1}{2}+y, 1\frac{1}{2}-z$) interaction of 2.402(2) Å (Table 3) involving the Sn-atom and the exocyclic carboxylate carbonyl O-atom of the tridentate ligand of a neighboring Sn-complex unit (Fig. 5). The chain propagates in the crystallographic [0 1 0] direction. The coordination geometry of the Sn-atom is best described as that of a rather distorted octahedron in which the Sn(1)–O(2)′ bond is almost *trans* to one of the phenyl groups. This contrasts with the trigonal bipyramidal coordination geometry observed in the related diphenyltin(IV) amino acetate [6].

In contrast to the polymeric structures encountered for complexes **1**, **4**, **5** and **7**, the crystal structure of **6** reveals a monomeric molecule in which the Sn-atom has a distorted octahedral coordination geometry involving the tridentate carboxylate ligand, two *n*-butyl ligands occupying *trans*-positions (C(10)–Sn(1)–C(11) = 156.1(1)°) and one water ligand (Fig. 6a and Table 4). An essentially similar coordination geometry was found for an aqua

divinyltin(IV) amino acetate analogue [2]. The occupation of a Sn coordination site by the water ligand in **6** presumably prevents the formation of a polymeric structure by blocking the possibility for coordination of the carboxylate carbonyl O atom of another carboxylate ligand to the Sn-atom, as occurred in **4**. In all other respects, the coordination behaviour of the tridentate carboxylate ligand in **4** and **6** is the same. It should be noted that the Sn-atom in complex **6** was found to be five-coordinate in solution (see Section 3.3).

There are two symmetry-independent molecules in the asymmetric unit in the crystal structure of **6**. Aside from variations in the conformations of the *n*-butyl ligands, the two independent molecules have very similar geometries (Table 4). The terminal ethyl group of one *n*-butyl ligand of one of the symmetry-independent molecules is disordered over two conformations. The water ligand in molecule A forms intermolecular hydrogen bonds with the phenoxy O-atom of molecule B and the carboxylate carbonyl O-atom of a different molecule B (Table 5). These interactions links the molecules into extended $\cdots$A$\cdots$B$\cdots$A$\cdots$B$\cdots$ chains, in which molecule A acts twice as a donor and molecule B acts twice as an acceptor. The chains run parallel to the [1 0 0] direction and can be described by a graph set motif [19] of $C_2^2(8)$. Within these chains, the water ligand in molecule B interacts in a similar fashion with the carboxylate carbonyl O-atom of the original molecule A and the phenoxy O-atom of a different molecule A, thereby forming a second strand of interactions within the $\cdots$A$\cdots$B$\cdots$A$\cdots$B$\cdots$ chains, in which molecule B now acts twice as a donor and molecule A acts twice as an acceptor (see Fig. 6b).

3.3. Spectroscopy

The solid-state IR spectra displayed a strong sharp band in the range 1640–1680 cm^{-1} for diorganotin(IV) complexes (**2**–**4** and **6**) and at around 1660 cm^{-1} for triorganotin(IV) complexes (**1**, **5** and **7**) which has been assigned to the carboxylate antisymmetric [ν_{asym}(OCO)] stretching vibration, in accord with our earlier reports [2,4,5,8]. The assignment of the symmetric [ν_{sym}(OCO)] stretching vibration band could not be made owing to the complex pattern of the spectra.

In order to obtain further structural conclusions in the solid-state, the Mössbauer spectra of the complexes have been recorded and are listed in Section 2.4. The spectra show a characteristic doublet absorption with narrow line width, Γ, indicating the occurrence of unique tin coordination sites in all compounds. The isomer shift (δ) values found (1.15–1.34 mm s^{-1}) are typical of quadrivalent organotin derivatives [20]. The triphenyltin(IV) complexes (**1**, **5** and **7**) exhibit very similar ^{119}Sn Mössbauer spectra characterized by Δ values of ~3.10 mm s^{-1}, which are characteristic of trigonal bipyramidal structures with phenyl groups in equatorial positions and axial electronegative ligands [20,21]. Similar Δ values were found for the triphenyltin(IV) derivatives [$Ph_3Sn\{O_2CC_6H_4(N=N(C_6H_3$-4-OH-5-CHO))-*o*$\}OH_2$] [22], [$Ph_3Sn\{2$-$OC_6H_4C(H)=NCH_2CO_2\}]_n$ [4] and [$Ph_3Sn\{O_2C(CH_2)_2N=CH(C_6H_4$-2-OH)$\}]_n$ [8] which are all characterized by a *trans*-O_2 trigonal bipyramidal geometry. These results are in agreement with the structures determined by X-ray crystallography (see Section 3.2) after ignoring the long Sn$\cdots$O contact, which has no significant influence on the trigonal bipyramidal geometry.

Concerning the diorganotin(IV) derivatives, the crystallographic data show that the amino acetate moiety acts as a dianionic O,N,O tridentate ligand, the tin atom expanding the coordination number to six through carboxylate bridging (complex **4**) or coordination by a water molecule (complex **6**). The Δ values observed for these derivatives are consistent with distorted *trans*-R_2Sn octahedral structures. Simplified point-charge calculations, based on the assumption that the electric field gradient on tin nucleus is dominated by the highly covalent Sn–C bonds [23], give C–Sn–C bond angle estimates of 157° and 147° for complexes **4** and **6**, respectively, which fit reasonably well with the experimental crystallographic values (Tables 3 and 4). The quadrupole splitting value for complex **2**, [Me_2Sn-$L^2(OH_2)$], Δ = 3.69 mm s^{-1}, is typical of distorted *trans*-R_2Sn octahedral structures and fully comparable with that of complex **6**, and that of the analogous aqua di-*n*-butyltin(IV) amino acetate [$^nBu_2Sn\{2$-$OC_6H_4C(CH_3)=NCH_2CO_2\}(OH_2)]_2$, which has also been characterized crystallographically (see Ref. [24] for the Mössbauer data and Ref. [6] for the crystal structure). On this basis, and in view of the similarity of the ligands, it can be inferred that complex **2** assumes the same structure as complex **6**.

Complex **3**, [$^nBu_2SnL^2$], is characterized by a quadrupole splitting value of 2.70 mm s^{-1} which strongly suggests a *cis*-R_2Sn trigonal bypiramidal structure with ^{n}Bu groups and a nitrogen atom in the equatorial plane and oxygen atoms in axial positions. Polymerization through carboxylate bridges, as observed in complex **4**, can be ruled out. Thus, ^{119}Sn Mössbauer results provide a reliable indicator in the structural characterization of the organotin(IV) complexes, especially in the absence of crystallographic data.

The ^{1}H and ^{13}C NMR signals were assigned by the use of homonuclear correlated spectroscopy (COSY), heteronuclear single-quantum correlation (HSQC) and heteronuclear multiple-bond connectivities (HMBC) experiments. The ^{1}H and ^{13}C chemical shift assignment (Section 2.4) of the organotin moiety is straightforward from the multiplicity patterns and resonance intensities. The ^{1}H NMR integration values were completely consistent with the formulation of the products. The ^{13}C NMR spectra of the ligand and Sn–R skeletons displayed the expected carbon signals in all cases. It should be noted that the diorganotin(IV) complexes **2**–**4** and **6**, all displayed two sets of ^{1}H and ^{13}C NMR signals from the Sn–R groups indicating that the two R groups experience different environments on the NMR time scale.

The solution-state structures of complexes **1**–**7** were derived from ^{119}Sn NMR chemical shifts, which are summarized in Section 2.4. The triphenyltin(IV) complexes (**1**, **5** and **7**) in $CDCl_3$ exhibit a single sharp resonance at around −99.0 ppm, suggesting that the Sn-atoms in the complexes have the same four-coordinate environment [4,8,25,26]. These results demonstrate that the polymeric structure with five-coordinate tin atoms found in the solid state is lost upon dissolution (see Section 3.2 for the crystal structure discussion). On the other hand, the chemical shift data for complexes **2**, **3** and **6** in $CDCl_3$ suggest that in non-coordinating solvents all species are monomeric, with pentacoordinated tin atoms bound to two oxygen atoms, one nitrogen atom and two alkyl groups, since all chemical shifts appear in the typical range for a trigonal bipyramidal geometry [27]. This is further supported by our recent work on analogous dialkyltin(IV) carboxylates of cognate ligands [6,24]. The corresponding solid-state Mössbauer data of complexes **2** and **6** indicate a *trans*-R_2Sn octahedral geometry (because of an additional H_2O ligand) while complex **3** shows a trigonal bipyramidal geometry where the interaction due to the H_2O ligand is absent. This is in agreement with the results obtained from the X-ray crystal structure determination of the complex **6** (vide supra), which indicated that in the solid state the Sn-atom has a distorted octahedral coordination geometry. Thus, the ^{119}Sn NMR result specifies that the six-coordinate Sn-atom in the solid state structures of complexes **2** and **6** (as revealed by the crystal structures and the Mössbauer spectra, vide supra) is lost upon dissolution giving rise to a five-coordinate Sn-atom in solution. The diphenyltin(IV) complex **4** displayed a ^{119}Sn chemical shift at −341 ppm in solution, which closely matches the shifts reported for diphenyltin(IV) amino acetate [2,24], which has five-coordinate Sn-atoms in solution. This shift testifies that the polymeric structure of **4**, revealed in the crystal structure, is also not retained in solution.

The ESI mass spectra of the complexes **1**–**7** were recorded in order to confirm the molecular weights (from first-order mass spectra), to verify the structural features (from tandem mass spectra; MS^n) and to examine the cleavage of the most labile bond in each molecule [28–32]. The most common ions observed in the first-order positive-ion mass spectra are sodium or potassium ion adducts and in some cases also protonated molecules, which are used for the verification of molecular weights of monomeric units (M_{mono}). Moreover, the adducts of monomeric units with $SnPh_3$ are observed for triphenyltin(IV) compounds (**1**, **5** and **7**) and dimeric ions for diorganotin(IV) compounds **2**–**4** and **6**. The formation of similar adducts is known in the ESI mass spectra of complex organotin(IV) compounds [22,33]. On the other hand, the most common ions observed in the first-order negative-ion mass spectra are anionic adducts $[M_{mono}+ligand]^-$, except for compounds **2**–**4** and **6**, which have no signal in the negative-ion mode in acetonitrile solution. The mass spectra do not provide the information on the polymeric structures of compounds **1**, **4**, **5** and **7** as identified by X-ray crystallography, which can probably be explained by easy fragmentation even under the softest ionization conditions, but the masses of the monomeric units and the structures of particular ligands are confirmed based on the characteristic ions described in Section 2.4.

3.4. In vitro cytotoxicity

The results of the *in vitro* cytotoxicity tests performed with some triphenyltin(IV) compounds, (**1**, **5** and **7**) are summarized in Table 6 and the screening results are compared with the results from other related triphenyltin(IV)

Table 6
In vitro ID_{50} values (ng/ml) of test compounds **1**, **5** and **7** along with some reported triphenyltin(IV) compounds against some standard drugs used as cell viability tests in seven human tumour cell lines[a]

Test compound[b]	Cell lines						
	A498	EVSA-T	H226	IGROV	M19 MEL	MCF-7	WIDR
$[Ph_3SnL^1H]_n{\cdot}nCCl_4$ (**1**)	105	81	105	101	102	111	106
$[Ph_3SnL^2H]_n$ (**5**)	120	100	115	105	130	115	110
$[Ph_3SnL^3H]_n$ (**7**)	113	96	108	106	112	110	109
DOX	90	8	199	60	16	10	11
CDDP	2253	422	3269	169	558	699	967
5-FU	143	475	340	297	442	750	225
MTX	37	5	2287	7	23	18	<3.2
ETO	1314	317	3934	580	505	2594	150
TAX	<3.2	<3.2	<3.2	<3.2	<3.2	<3.2	<3.2
Ph_3SnR_1 [34]	42	<3	39	19	42	17	17
Ph_3SnR_2 [34]	65	<3	61	18	51	16	19
Ph_3SnR_3 [34]	<2	<2	<2	<2	<2	2.9	<2
CDDP	2253	422	3269	169	558	699	967
DOX	90	8	199	60	16	10	11

[a] *Abbreviation:* DOX = doxorubicin, CDDP = cisplatin, 5-FU = 5-fluorouracil, MTX = methotrexate, ETO = etoposide and TAX = paclitaxel; for reported triphenyltin(IV) compounds, R is a carboxylate residue where R_1 = -terebate, R_2 = -steroidcarboxylate, R_3 = -benzocrowncarboxylate.
[b] Standard drug reference values are cited immediately after the test compounds under identical conditions.

compounds with respect to the standard drugs that are in current clinical use as antitumour agents. Recently, we have reported *in vitro* cytotoxic results on a diorganotin(IV) compound $\{[^{n}Bu_2Sn(2\text{-}OHC_6H_4C(CH_3)=N(CH_2)_2COO)]_2O\}_2$ where the ligand is a Schiff base derived from β-alanine [8]. On the basis of this study, the present investigation was designed to investigate organotin(IV) compounds with improved *in vitro* antitumor activity. Indeed an improved activity was observed for the triphenyltin(IV) compounds of the present investigation (see Table 6). The activity was found to be better than that of CDDP (cisplatin). Interestingly, all the three triphenyltin(IV) compounds of the present investigation show comparable cytotoxic activity across a panel of cell lines studied. This encouraging cytotoxic effect is predictive of *in vivo* antitumour activity. Compounds **1**, **5** and **7** may be suitable candidates for modification in order to improve dissolution properties which may influence cytotoxicity. Although the triphenyltin(IV) compounds in the present investigation possess quite high *in vitro* cytotoxicity, it should be noted that the triphenyltin(IV) -terebate, -steroidcarboxylate and -benzocrowncarboxylate are even more cytotoxic *in vitro* (see Table 6) [34]. Different active organotin(IV) compound may still show slight variation in *in vitro* cytotoxicity due to different kinetic and mechanistic behaviour [8]. In conclusion, the present study reports new structures with improved *in vitro* anti-tumor activity which is of added value in determining the structure–activity relationship in the area of organotin(IV) chemistry with possible future clinical application.

4. Supplementary material

CCDC 648364, 648365, 648366, 648367 and 648368 contain the supplementary crystallographic data for **1**, **4**, **5**, **6** and **7**, respectively. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via http://www.ccdc.cam.ac.uk/data_request/cif.

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