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Synthesis, characterization and *in vitro* antitumour activity of di- and tri-organotin derivatives of fenbufen

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The di- and tri-organotin derivatives of fenbufen (4-(4-biphenyl)-4-oxobutyric acid), [{(*n*-C_4H_9)$_2$Sn(OCOCH$_2$CH$_2$COC$_6$H$_4$C$_6$H$_5$-4)}$_2$O]$_2$ (1) and R$_3$SnOCOCH$_2$CH$_2$COC$_6$H$_4$C$_6$H$_5$-4 (R=C$_6$H$_5$, 2; *c*-C$_6$H$_{11}$, 3; C$_6$H$_5$C(CH$_3$)$_2$CH$_2$, 4), have been prepared and characterized by means of elemental analysis, IR and NMR (^{1}H, ^{13}C and ^{119}Sn) spectroscopies. The crystal structure of 1, bis[4-(4-biphenyl)-4-oxobutyrato]tetra-*n*-butyldistannoxane, has been determined and it is a centrosymmetric dimer with two distinct types of carboxylate moieties and tin atoms with distorted trigonal bipyramidal geometries. The *in vitro* antitumour activity of 1 and 2 against two human tumour cell lines was found to be higher than that for *cis*-platin used clinically. Copyright © 2005 John Wiley & Sons, Ltd.

KEYWORDS: organotin; 4-(4-biphenyl)-4-oxobutyric acid; antitumour activity, crystal structure

INTRODUCTION

Organotin(IV) carboxylates form an important class of compounds that have been receiving increasing attention in recent years, not only because of their intrinsic interest but also owing to their varied applications. Some examples find wide use as catalysts and stabilizers, and certain derivatives are used as biocides, as antifouling agents and as wood preservatives.[1] In recent years, investigations have been carried out to test their antitumour activity and it has been observed that indeed several diorganotin species, as well as triorganotin species, show potential as antineoplastic agents.[2–8] Fenbufen (i.e. 4-(4-biphenyl)-4-oxobutyric acid) (Scheme 1) is a non-steroidal anti-inflammatory drug and used as analgesics, anti-inflammatories and antipyretics in clinic.[9–11] The therapeutic activity of fenbufen is believed to be due to the ability of its metabolite, 4-biphenylacetic acid, to inhibit the biosynthesis of prostaglandins.[9–11] The X-ray crystal structure and the coordination chemistry with transition metal ions of fenbufen have been studied.[12,13] The organotin complexes with anti-inflammatory drugs, such as lornoxicam,[14] mefenamic acid[15,16] and tolfenamic acid,[17] have been synthesized and characterized, but organotin esters of fenbufen have not been reported in the literature, to our knowledge. In order to explore the chemistry and biological activity of organotin/fenbufen compounds, we synthesized and characterized some di- and tri-organotin esters of fenbufen.

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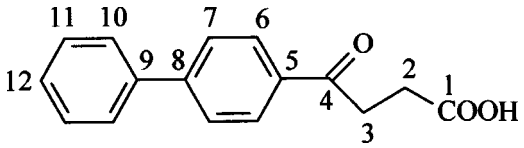
EXPERIMENTAL

Materials and physical measurements

Tri(2-phenyl-2-methylpropyl)tin hydroxide and fenbufen were prepared according to literature procedures.[18,19] All other chemicals were of reagent grade and were used without further purification. Carbon and hydrogen analyses were determined using a Perkin Elmer 2400 Series II elemental analyser. Melting points were measured on an X-4 microscopic melting-point apparatus. IR spectra were recorded on a Nicolet 470 FT-IR spectrophotometer using KBr discs in the range 4000–400 cm^{-1}. ^{1}H and ^{13}C NMR spectral data were collected using a Bruker Avance DMX500 FT-NMR



Scheme 1.

spectrometer with $CDCl_3$ as solvent and tetramethylsilane as internal standard. ^{119}Sn NMR spectra were recorded in $CDCl_3$ on a Varian Mercury Vx300 spectrometer using Me_4Sn as an internal reference.

Synthesis

To a suspension of dibutyltin oxide or triorganotin hydroxide (2 mmol) in 50 ml of benzene was added fenbufen (0.51 g, 2 mmol). The reaction mixtures were heated under reflux for 8 h with a Dean–Stark separator, and then allowed to cool to room temperature. The solution was filtered and the solvent was removed under reduced pressure. The resulting white solid was recrystallized from ethanol. The yield, m.p., and spectral data for compounds **1**–**4** are as follows.

*[(n-C_4H_9)$_2$Sn(OCOCH$_2$CH$_2$COC$_6$H$_4$C$_6$H$_5$)]$_2$O (**1**)*

Yield 84.5%, m.p. 143–144 °C. Anal. Found: C, 59.37; H, 6.16. Calc. for $C_{48}H_{62}O_7Sn_2$: C, 58.33; H, 6.32%. IR (KBr), cm^{-1}: 1684 [ν(C=O)], 1645, 1572 [$\nu_{as}(COO^-)$], 1404, 1382 [$\nu_s(COO^-)$], 640 [ν(Sn–O–Sn)]. ^1H NMR (500 MHz, $CDCl_3$) δ, ppm: 8.04 (2H, d, $J = 8.1$ Hz, H-6), 7.66 (2H, d, $J = 8.1$ Hz, H-7), 7.61 (2H,d, $J = 7.3$ Hz, H-10), 7.45 (2H, dd, $J = 7.3$, 7.3 Hz, H-11), 7.38 (1H, t, $J = 7.3$ Hz, H-12), 3.25 (2H, t, $J = 5.9$ Hz, H-3), 2.64 (2H, t, $J = 5.9$ Hz, H-2), 1.68–1.61 (4H, m, $2CH_2$-α), 1.47–1.40 (4H, m, $2CH_2$-β), 1.39–1.33 (4H, m, $2CH_2$-γ), 0.94 (3H, t, $J = 7.2$ Hz, CH_3), 0.88 (3H, t, $J = 7.2$ Hz, CH_3). ^{13}C NMR (125 MHz, $CDCl_3$) δ, ppm: 198.13 (C-4), 178.55 (C-1), 145.80, 140.17, 135.81, 129.15, 128.81, 128.38, 127.48, 127.40 (C-5–C-12), 34.50 (C-3), 30.44 (C-2), 29.05 ($^1J(^{119}Sn-^{13}C)$ = 606.9 Hz, C-α), 27.86 ($^1J(^{119}Sn-^{13}C) = 615.4$ Hz, C-α), 27.57 ($^2J(^{119}Sn-^{13}C) = 37.6$ Hz, C-β), 27.21 ($^2J(^{119}Sn-^{13}C)$ non-visible, C-β), 27.06 ($^3J(^{119}Sn-^{13}C)$ non-visible, C-γ), 26.96 ($^3J(^{119}Sn-^{13}C) = 122.6$ Hz, C-γ), 13.97(C-δ), 13.92 (C-δ). ^{119}Sn NMR (111.9 MHz, $CDCl_3$) δ, ppm: −205.01, −216.15.

*$Ph_3SnO_2CCH_2CH_2COC_6H_4C_6H_5$ (**2**)*

Yield 78.5%, m.p. 65–67 °C. Anal. Found: C, 67.73; H, 4.57. Calc. for $C_{34}H_{28}O_3Sn$: C, 67.69; H, 4.68%. IR (KBr), cm^{-1}: 1685 [ν(C=O)], 1529 [ν_{as}(COO)], 1394 [ν_s(COO)]. ^1H NMR (500 MHz, $CDCl_3$) δ, ppm: 8.03 (2H, d, $J = 8.4$ Hz, H-6), 7.72–7.70 (6H, m, $^3J(^{119\,117}Sn-H) = 59.5/50.3$ Hz, *o*-H in Ph), 7.67 (2H, d, $J = 8.4$ Hz, H-7), 7.62 (2H, d, $J = 7.3$ Hz, H-10), 7.47 (2H, dd, $J = 7.3$, 7.3 Hz, H-11), 7.42–7.45 (9H, m, *m*-H and *p*-H in Ph), 7.40 (1H, t, $J = 7.3$ Hz, H-12), 3.36 (2H, t, $J = 6.9$ Hz, H-3), 2.90 (2H, t, $J = 6.9$ Hz, H-2). ^{13}C NMR (125 MHz, $CDCl_3$) δ, ppm: 197.98 (C-4), 179.01 (C-1), 145.78, 140.21, 135.89, 129.14, 128.82, 128.35, 127.49, 127.37 (C-5–C-12), 34.85 (C-3), 29.39 (C-2), 129.27 ($^3J(^{119/117}Sn-^{13}C) = 63.3$ Hz, *m*-C), 130.64 ($^4J(^{119}Sn-^{13}C) = 12.8$ Hz, *p*-C), 137.23 ($^2J(^{119}Sn-^{13}C) = 48.1$ Hz, *o*-C of Ph), 137.77 ($^1J(^{119/117}Sn-^{13}C) = 642.5/614.1$ Hz, *i*-C). ^{119}Sn NMR (111.9 MHz, $CDCl_3$) δ, ppm: −105.97.

*$Cy_3SnO_2CCH_2CH_2COC_6H_4C_6H_5$ (**3**)*

Yield 75.8%, m.p. 74.0–74.9 °C. Anal. Found: C, 65.56; H, 7.34. Calc. for $C_{34}H_{46}O_3Sn$: C, 65.71; H, 7.46%. IR (KBr), cm^{-1}: 1685 [ν(C=O)], 1650 [ν_{as}(COO)], 1385 [ν_s(COO)]. ^1H NMR (500 MHz, $CDCl_3$) δ, ppm: 8.06 (2H, d, $J = 8.4$ Hz, H-6), 7.67 (2H, d, $J = 8.4$ Hz, H-7), 7.62 (2H, d, $J = 7.3$ Hz, H-10), 7.47 (2H, dd, $J = 7.3$, 7.3 Hz, H-11), 7.40 (1H, t, $J = 7.3$ Hz, H-12), 3.32 (2H, t, $J = 6.8$ Hz, H-3), 2.79 (2H, t, $J = 6.8$ Hz, H-2), 1.94–1.84 (9H, m), 1.65–1.1.57 (15H, m), 1.35–1.24 (9H, m) (Cy). ^{13}C NMR (125 MHz, $CDCl_3$) δ, ppm: 198.57 (C-4), 178.00 (C-1), 145.79, 140.23, 135.94, 129.15, 128.86, 128.36, 127.48, 127.38 (C-5–C-12), 34.83 (C-3), 29.35 (C-2), 33.96 ($^1J(^{119/117}Sn-^{13}C) = 337.2/322.4$ Hz, C-α), 31.26 ($^2J(^{119}Sn-^{13}C) = 14.4$ Hz, C-β), 29.14 ($^3J(^{119}Sn-^{13}C) = 63.8$ Hz, C-γ), 27.14 (C-δ). ^{119}Sn NMR (111.9 MHz, $CDCl_3$) δ, ppm: 16.05.

*($PhC(CH_3)_2CH_2)_3SnO_2CCH_2CH_2COC_6H_4C_6H_5$ (**4**)*

Yield 86.7%, m.p. 62–63 °C. Anal. Found: C, 72.09; H, 6.66. Calc. for $C_{46}H_{52}O_3Sn$: C, 71.60; H, 6.79%. IR (KBr), cm^{-1}: 1685 [ν(C=O)], 1665 [ν_{as}(COO)], 1375 [ν_s(COO)]. ^1H NMR (500 MHz, $CDCl_3$) δ, ppm: 8.08 (2H, d, $J = 8.4$ Hz, H-6), 7.70 (2H, d, $J = 8.4$ Hz, H-7), 7.62 (2H, d, $J = 7.3$ Hz, H-10), 7.48 (2H, dd, $J = 7.3$, 7.3 Hz, H-11), 7.40 (1H, t, $J = 7.3$ Hz, H-12), 7.29 (6H, dd, $J = 7.3$, 7.3 Hz, *m*-H in Ph), 7.19 (3H, t, $J = 7.3$ Hz, *p*-H in Ph), 7.07 (6H, d, $J = 7.3$ Hz, *o*-H in Ph), 3.23 (2H, t, $J = 6.9$ Hz, H-3), 2.70 (2H, t, $J = 6.9$ Hz, H-2), 1.18 (18H, s, $6CH_3$), 1.16 (6H, s, $^2J(^{119}Sn-H) = 51.0$ Hz, $3CH_2Sn$). ^{13}C NMR (125 MHz, $CDCl_3$) δ, ppm: 198.44 (C-4), 177.90 (C-1), 151.06, 145.77, 140.12, 135.87, 129.14, 128.89, 128.55, 128.35, 127.48, 127.36, 126.05, 125.51 (C-5–C-12 and Ph), 37.84 (Ph-*C*), 34.88 (C-3), 33.67 ($^1J(^{119/117}Sn-^{13}C) = 347.6/333.0$ Hz, CH_2Sn), 32.75 ($^3J(^{119}Sn-^{13}C) = 43.6$ Hz, CH_3), 30.23 (C-2). ^{119}Sn NMR (111.9 MHz, $CDCl_3$) δ, ppm: 107.41.

Crystal structure determination of 1

A colourless crystal of **1** having approximate dimensions of $0.46 \times 0.24 \times 0.16\ mm^3$ was mounted on a glass fibre. All measurements were made on a Rigaku RAXIS RAPID imaging-plate area detector with graphite monochromated Mo Kα radiation (0.7107 Å). The data were collected at a temperature of 25 ± 1 °C to a maximum 2θ value of 55.0° using the ω scans technique. Of the 18 288 reflections that were collected, 8286 were unique ($R_{int} = 0.026$); equivalent reflections were merged. An empirical absorption correction was applied, which resulted in transmission factors ranging from 0.637 to 0.837. The data were corrected for Lorentz and polarization effects. Crystal data: $C_{48}H_{62}O_7Sn_2$, $M = 988.36$, triclinic, space group $P\bar{1}$, $a = 12.3740(5)$, $b = 12.6346(5)$, $c = 16.0651(6)$ Å, $\alpha = 103.651(2)°$,

$\beta = 90.639(1)°$, $\gamma = 105.407(2)°$, $V = 2345.64(16)$ Å^3, $Z = 2$, $D_c = 1.399$ g cm^{-3}, μ(Mo Kα) $= 1.112$ mm^{-1}, $F(000) = 1012$.

The structure was solved by the heavy-atom Patterson method[20] and expanded using Fourier techniques.[21] The non-hydrogen atoms were refined anisotropically. Hydrogen atoms were placed at calculated positions in the riding model approximation. The refinement by the full-matrix least-squares method on F^2 converged to final $R = 0.0375$, $wR = 0.0887$ for 6661 observed reflections ($I > 2\sigma(I)$) and $R = 0.0514$, $wR = 0.0947$ for all data. The maximum and minimum peaks on the final difference Fourier map corresponded to 0.722 e$^-$ Å^{-3} and -0.457 e$^-$ Å^{-3} respectively. All calculations were performed using the SHELXL-97 programs.[22]

In vitro antitumour screening

The samples were prepared by dissolving compounds **1** and **2** in ethanol, and by diluting the solution obtained with water. In the assays, the concentration of the solvent, ethanol, was less than 0.1%. Two human tumour cell lines, HeLa, a cervix tumour, and CoLo205, a colon carcinoma, were obtained from the Tumour Institute of Zhejiang University. *In vitro* antitumour activities of the compounds were measured according to the literature methods.[23,24]

RESULTS AND DISCUSSION

The synthesis of four organotin derivatives of fenbufen (R′COOH) may be represented by the following equations:

$$4Bu_2SnO + 4R'COOH \longrightarrow \underset{(1)}{\left[\{Bu_2Sn(OOCR')\}_2O\right]_2} + 2H_2O$$

$$R_3SnOH + R'COOH \longrightarrow \underset{(2)-(4)}{R_3SnOOCR'} + H_2O$$

where R = C_6H_5 (**2**), *c*-C_6H_{11} (**3**), $C_6H_5C(CH_3)_2CH_2$ (**4**). These compounds are white crystals, air stable and soluble in benzene and in common polar organic solvents (e.g. methanol, ethanol, dichloromethane, chloroform, acetone and nitrobenzene) but insoluble in saturated hydrocarbons (e.g. hexane and petroleum ether).

Crystal structure of 1

The molecular structure for compound **1** is shown in Fig. 1. The selected bond lengths and bond angles are given in Table 1. Compound **1** is a centrosymmetric dimer built up around the planar cyclic Sn_2O_2 unit. The two oxygen atoms (O7 and O7^i, symmetry transformation i: $-x+1$, $-y+1$, $-z+1$) of this unit are tridentate as they link three tin centres, two endocyclic and one exocyclic. Additional links between the endo- and exo-cyclic tin atoms are provided by bidentate carboxylate ligands. Each exocyclic tin atom is also coordinated by a monodentate carboxylate ligand. The coordination geometry about each of the tin atoms is best described as distorted trigonal bipyramidal with axial positions occupied by oxygen atoms. Distortions from the ideal geometry arise partly owing to the close intramolecular approach of oxygen atoms such that Sn2···O1 is 2.654(3) Å and Sn1···O2 is 3.078(3) Å. Although these separations are considered too long to represent significant bonding interactions between tin and oxygen, they do exert an important influence on the respective coordination geometries, as seen in the expansion of the C41–Sn2–C45 and C3–Sn1–C4 angles to 142.70(19)° and 134.8(2)° respectively from an ideal value of 120°. The structures of compounds with the general formula $[R_2(R'CO_2)SnOSn(O_2CR')R_2]_2$ had been classified into four major types by Ng *et al*.[25] and Tiekink.[26]

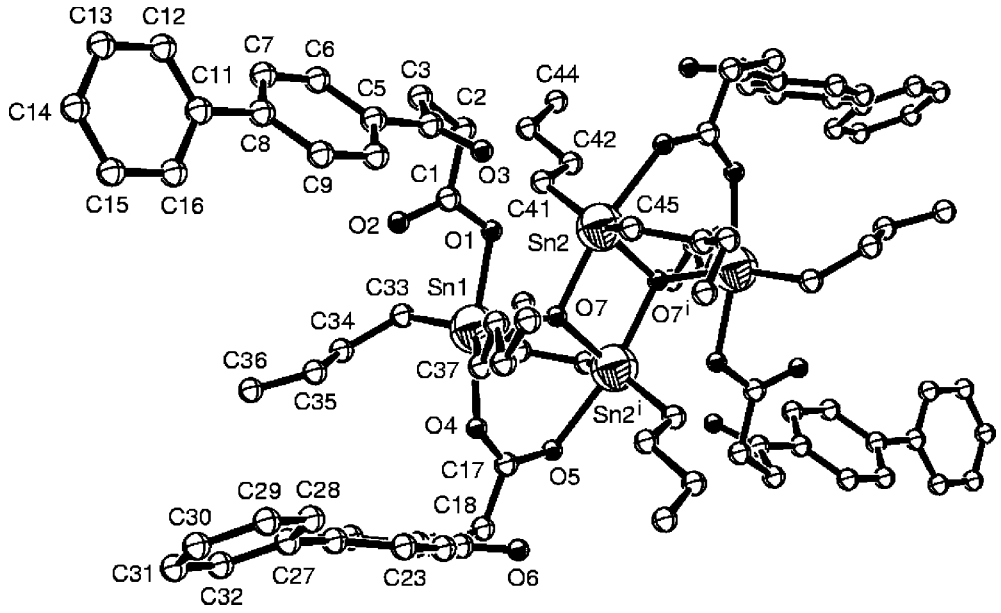


Figure 1. Molecular structure of **1**.

Table 1. Selected bond lengths (Å) and bond angles (°) of **1**

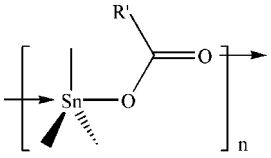
Bond lengths			
Sn1–O1	2.167(3)	Sn2–O5^{i}	2.287(3)
Sn1–O4	2.170(3)	Sn2–O7	2.168(2)
Sn1–O7	2.029(2)	Sn2–O7^{i}	2.047(2)
Sn1–C33	2.101(5)	Sn2–C41	2.108(4)
Sn1–C37	2.110(5)	Sn2–C45	2.108(5)
C1–O1	1.293(5)	C17–O4	1.247(5)
C1–O2	1.217(5)	C17–O5	1.240(5)
Bond angles			
O1–Sn1–O4	167.37(10)	O7–Sn2–C41	99.44(15)
O1–Sn1–O7	78.07(10)	O7–Sn2–C45	96.82(16)
O1–Sn1–C33	96.15(17)	O7^{i}–Sn2–O5^{i}	92.48(10)
O1–Sn1–C37	100.45(17)	O7–Sn2–O7^{i}	75.96(10)
O4–Sn1–O7	89.34(10)	O5^{i}–Sn2–O7	168.16(10)
O4–Sn1–C33	89.11(18)	C41–Sn2–O7^{i}	108.34(15)
O4–Sn1–C37	83.68(18)	C45–Sn2–O7^{i}	108.09(15)
O7–Sn1–C33	110.55(16)	C45–Sn2–O5^{i}	84.18(16)
O7–Sn1–C37	113.93(19)	C41–Sn2–C45	142.70(19)
C33–Sn1–C37	134.8(2)	C41–Sn2–O5^{i}	86.51(15)
C1–O1–Sn1	117.0(2)	C17–O4–Sn1	142.3(3)
C17–O5–Sn2^{i}	133.5(3)	Sn2^{i}–O7–Sn1	136.62(13)
Sn2–O7–Sn2^{i}	104.04(10)	Sn1–O7–Sn2	119.34(12)
O2–C1–O1	123.1(4)	O5–C17–O4	124.5(4)

Symmetry transformation i: $-x+1, -y+1, -z+1$.

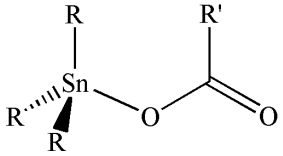
The structural type of **1** belongs to Type I, and its structural features are similar to those found in compounds $[\{Bu_2Sn(O_2CC_6H_4(NH(C_6H_3Me_2\text{-}2,3))\text{-}2)\}_2O]_2$,[16] $[\{Bu_2Sn(O_2CC_6H_4(NH(C_6H_3Me\text{-}2\text{-}Cl\text{-}3))\text{-}2)\}_2O]_2$,[17] $[\{Bu_2Sn(O_2CC_5H_3NSMe\text{-}2)\}_2O]_2$,[24] $[\{Et_2Sn(O_2C^tBu)\}_2O]_2$,[27] $[\{Bu_2Sn(O_2CCH_2C_6F_5)\}_2O]_2$,[28] $[\{Bu_2Sn(O_2CC_6H_4OMe\text{-}2)\}_2O]_2$,[29] $[\{Me_2Sn(O_2CC_6H_4Me\text{-}4)\}_2O]_2$,[30] $[\{Bu_2Sn(O_2CCF_3)\}_2O]_2$,[31] and $[\{Bu_2Sn(O_2CC_{12}H_8NO_2\text{-}4)\}_2O]_2$.[32]

IR spectra

In all complexes, the strong band at 1685 cm^{-1} assigned to the stretching vibration of keto-carbonyl is the same as that of the free fenbufen, indicating that keto-carbonyl is not coordinated to a tin atom. The difference between the $\nu_{as}(CO_2)$ and $\nu_s(CO_2)$ bands, $\Delta\nu(CO_2)$, is indicative of the coordination number around tin.[33] For **1**, the $\Delta\nu(CO_2)$ value (263 and 168 cm^{-1}) is close to that found for a monodentate carboxylate ligand and bridging bidentate carboxylato groups.[16,17,32,34] A strong band at 640 cm^{-1} is assigned to vibrations of associated with the Sn–O–Sn stretch.[32,35] The $\Delta\nu(CO_2)$ value for **2** is 125 cm^{-1}, indicating the penta-coordinate structure in the solid (Scheme 2).[36–38] For **3** and **4** the $\Delta\nu(CO_2)$ values are 265 cm^{-1} and 290 cm^{-1} respectively, which clearly suggests the presence of a monodentate carboxylate ligand and four-coordinated tin (Scheme 3).[34,39,40] The medium–strong absorption band at ~460 cm^{-1}, which is absent in the spectra of the ligand and parent organotins, may be assigned to the Sn–O vibration.[34,39,40]



Scheme 2.



Scheme 3.

NMR spectra

The ^1H NMR spectra of the compounds showed the expected integration and peak multiplicities. Two resonances were observed for the butyl protons and carbon atoms in compound **1**, which is consistent with the presence of a dimer in solution by analogy with related compounds.[17,28,31,41] The $^1J(^{119}Sn-^{13}C)$ values (606.9, 615.4 Hz) are also similar to those of related compounds, such as $[\{Bu_2Sn(O_2CCF_3)_2\}O]_2$[31] and $[\{Bu_2Sn(O_2CC_{12}H_8NO_2\text{-}4)_2\}O]_2$.[32] Two ^{119}Sn resonances (−216.15, −205.01 ppm) are assigned to the endocyclic and exocyclic tin atoms.[28,31] In chloroform solution, the $^1J(^{119/117}Sn-^{13}C)$ values of 642.5/614.1 H, 337.2/322.4 H, and 347.6/333.0 H found for **2, 3**, and **4** respectively are close to those for the corresponding triorganotin carboxylates, such as $Ph_3SnO_2CCH_2CH_2COPh$,[38] $Cy_3SnO_2CCH(CH_3)CH(Ph)GePh_3$,[40] $(PhC(CH_3)_2CH_2)_2SnO_2CCH_2CH(o\text{-}C_6H_4Cl)GePh_3$,[39] indicating that compounds **2, 3**, and **4** are four-coordinated, in agreement with their ^{119}Sn NMR resonances (−105.97, 16.05, and 107.41 ppm).[39,40,42]

In vitro antitumour activity

The results of the *in vitro* antitumour tests against HeLa and CoLo205 are shown in Table 2. Compounds **1** and **2** display high *in vitro* antitumour activities, with compound **1** being slightly better than *cis*-platin and compound **2** being much better than *cis*-platin. The triphenyltin derivative **2** is more active than the dibutyltin derivative **1**, which is similar to the results reported previously by Gielen.[5]

Table 2. *In vitro* antitumour results against HeLa and CoLo205 of **1** and **2**

	IC_{50} (μg ml^{-1})	
Compound	HeLa	CoLo205
1	0.34 ± 0.02	1.06 ± 0.20
2	0.01 ± 0.00	0.13 ± 0.01
cis-Platin	1.44 ± 0.33	4.42 ± 1.11

Supplementary materials

Crystallographic data for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre, CCDC No. 214 280. Copies of this information may be obtained free of charge from The Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44-1223-336-033; e-mail: deposit@ccdc.cam.ac.uk or http://www.ccdc.cam.ac.uk).

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