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Cyclopentadienyltin(IV) derivatives: synthesis, characterization and study of their cytotoxic activities

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ABSTRACT

The organotin compounds, $[SnPh_3(C_5H_4R)]$ (R = Bu^t (**1**), $CMe_2(CH_2CH_2CH{=}CH_2)$ (**2**)) and $[SnPh_3(C_5Me_4R)]$ (R = H (**3**), $SiMe_3$ (**4**)), were prepared by the reaction of $SnPh_3Cl$ with the lithium derivative of the corresponding cyclopentadiene. **1**–**4** have been characterized by multinuclear NMR spectroscopy (^1H, $^{13}C\{^1H\}$ and $^{119}Sn\{^1H\}$). In addition, the molecular structures of **1**, **2** and **4** were determined by single-crystal X-ray diffraction studies. The cytotoxic activity of the organotin(IV) complexes (**1**–**4**) was tested against human tumour cell lines 8505C anaplastic thyroid cancer, A253 head and neck tumour, A549 lung carcinoma, A2780 ovarian cancer, DLD-1 colon carcinoma. Compounds **1**–**4** present higher activities than cisplatin in all the studied cells. The highest sensitivity of the synthesized tin(IV) complexes was observed against A2780 ovarian cancer and DLD-1 colon carcinoma. Complex **3** presents the highest cytotoxic activity of all the studied complexes in all the cancer cells, with IC_{50} values from 0.037 to 0.085 μM, however, its trimethylsilyl-substituted analogue (**4**), showed the lowest activity against all the studied cells with IC_{50} values from 0.163 to 0.351 μM. Complexes **1** and **2** presented very similar activities on all the cancer cells (IC_{50} values from 0.044 to 0.119 μM).

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1. Introduction

Research on the synthesis and applications of metal-based drugs are currently considered as one of the most expanding areas in biomedical and inorganic chemistry [1–3]. Recent studies have shown very promising *in vitro* antitumour properties of organotin compounds against a wide panel of tumour cell lines of human origin [4–10]. In some cases, organotin(IV) derivatives have also shown acceptable antiproliferative *in vivo* activity as new chemotherapy agents [11–16]. From all the studied tin(IV) derivatives, di and triorganotin(IV) carboxylate [17–23], thiolate [24–30] and dithiocarbamate [31] complexes have been studied extensively, while cyclopentadienyltin(IV) derivatives have only recently been studied very briefly [32].

In this context, and taking into account that the modification of the cyclopentadienyl ligands has a notable effect on the antiproliferative effect of metallocene complexes in anticancer tests [33–39], we decided to study the cytotoxic activity of cyclopentadienyltin(IV) derivatives, in order to observe the influence of the substituents attached to the cyclopentadienyl ring on the final anticancer activity of the organotin(IV) complexes. Thus, as a continuation of our work in the synthesis of cyclopentadienyltin(IV) derivatives [40], we report the synthesis, structural characterization and evaluation of the cytotoxic activity on human cancer cells of four triphenyltin(IV) complexes with different cyclopentadienyl ligands (Fig. 1). One of the studied complexes is $[SnPh_3\{C_5H_4CMe_2(CH_2CH_2CH{=}CH_2)\}]$, which contains the alkenyl-substituted cyclopentadienyl ligand C_5H_4-$CMe_2(CH_2CH_2CH{=}CH_2)$ that has proven to induce an increase in the cytotoxic activity of titanocene complexes [36–38], however, in this study with cyclopentadienyltin(IV) derivatives, this positive effect of the alkenyl substituent is not observed and, in contrast to the results obtained for titanocene complexes [36–38], the compound $[SnPh_3(C_5Me_4H)]$ containing a tetramethylcyclopentadienyl moiety is the most active of the studied compounds.

2. Experimental

2.1. General manipulations

All reactions were performed using standard Schlenk tube techniques in an atmosphere of dry nitrogen. Solvents were distilled

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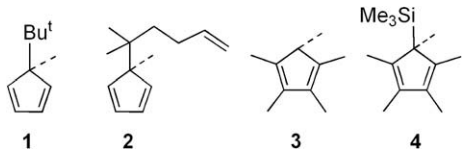


Fig. 1. Cyclopentadienyl derivatives used in this study.

from the appropriate drying agents and degassed before use. $SnPh_3Cl$ and $Li(C_5H_4Bu^t)$ were purchased from Aldrich and used without further purification. $Li\{C_5H_4CMe_2(CH_2CH_2CH{=}CH_2)\}$ [41], $Li(C_5Me_4H)$ [42] and $Li(C_5Me_4SiMe_3)$ [43] were prepared as previously reported. ^1H, $^{13}C\{^1H\}$ and $^{119}Sn\{^1H\}$ NMR spectra were recorded on a Varian Mercury FT-400 spectrometer and referenced to the residual deuterated solvent or to $SnMe_4$ in the case of $^{119}Sn\{^1H\}$ NMR. Microanalyses were carried out with a Perkin–Elmer 2400 microanalyzer. IR spectra (KBr pellets were prepared in a nitrogen-filled glove box) were recorded on a Nicolet Avatar 380 FTIR spectrometer in the range 350–4000 cm^{-1}. FAB-MS spectra were recorded on a MASPEC II spectrometer with 3-nitrobenzylalcohol as matrix.

2.2. Synthesis of $[SnPh_3(C_5H_4Bu^t)]$ (**1**)

$Li(C_5H_4Bu^t)$ (0.75 g, 5.85 mmol) was added to a solution of $SnPh_3Cl$ (2.25 g, 5.85 mmol) in THF (50 ml) at −78 °C. The reaction mixture was allowed to reach room temperature and stirred for 16 h. Solvent was removed by applying reduced pressure and hexane (40 ml) added. The suspension was filtered and the filtrate concentrated (5 ml). Cooling to −30 °C yielded the title compound as a yellow crystalline solid. Yield: 2.34 g, 85%. FT-IR (KBr): 3139 (m), 3065 (s), 2972 (s), 2912 (s), 2845 (s), 2723 (w), 1946 (m), 1887 (m), 1813 (m), 1615 (w), 1476 (s), 1432 (s), 1372 (m), 1301 (m), 1263 (w), 1190 (w), 1074 (s), 1022 (s), 997 (m), 975 (m), 890 (s), 850 (m), 829 (m), 805 (m), 725 (s), 697 (s), 669 (s), 658 (s), 643 (m), 447 (s); ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ 1.03 (s, 9H, *Bu^t*), 5.65 (m, 2H, $^3J(^1H–Sn) = 61.2$ Hz, C_5H_4), 6.57 (m, 2H, C_5H_4) 7.42 (br m, 9H, *m*- and *p*-protons in $SnPh_3$), 7.56 (br m, 6H, $^3J(^1H–Sn) = 50.2$ Hz, *o*-protons in $SnPh_3$); $^{13}C\{^1H\}$ NMR (100.6 MHz, $CDCl_3$, 25 °C): δ 30.8 (Me of *Bu^t*, $^3J(^{13}C–Sn) = 9.2$ Hz), 32.2 (C-ipso of *Bu^t* $^2J(^{13}C–Sn)$ not observed), 90.7 (C-1 of Cp, $^1J(^{13}C–Sn)$ not observed) 125.0, 154.5 (C-2 and C-3 of Cp), 128.7 (C-3 and C-5 of $SnPh_3$, $^3J(^{13}C–Sn) = 52.3$ Hz), 129.5 (C-4 of $SnPh_3$, $^4J(^{13}C–Sn) = 9.2$ Hz), 137.2 (C-2 and C-6 of $SnPh_3$, $^2J(^{13}C–Sn) = 38.4$ Hz), 138.4 (C-1 of $SnPh_3$ $^1J(^{13}C–Sn)$ not observed); $^{119}Sn\{^1H\}$ NMR (149.2 MHz, $CDCl_3$, 25 °C): δ −101.7; MS FAB (*m/e* (relative intensity)): 472 (1) [M^++H], 395 (10) [M^+−Ph], 351 (100) [M^+−$C_5H_4Bu^t$], 241 (13) [M^+−3 × Ph]. *Anal.* Calc. for $C_{27}H_{28}Sn$: C, 68.82; H, 5.99. Found: C, 68.77; H, 5.81%.

2.3. Synthesis of $[SnPh_3\{C_5H_4CMe_2(CH_2CH_2CH{=}CH_2)\}]$ (**2**)

The preparation of **2** was carried out in an identical manner to **1**. $Li\{C_5H_4CMe_2(CH_2CH_2CH{=}CH_2)\}$ (0.75 g, 4.46 mmol) and $SnPh_3Cl$ (1.72 g, 4.46 mmol). Yield: 1.64 g, 72%. FT-IR (KBr): 3138 (m), 3065 (s), 3049 (s), 3018 (s), 2922 (s), 1946 (m), 1887 (m), 1871 (m), 1813 (m), 1756 (w), 1640 (s), 1579 (s), 1480 (s), 1430 (s), 1377 (m), 1300 (s), 1260 (m), 1190 (m), 1156 (m), 1075 (s), 1022 (m), 997 (m), 977 (m), 906 (m), 806 (s), 725 (s), 698 (m), 675 (m), 658 (m), 644 (w), 567 (m), 525 (m), 447 (s); ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ 1.00 (s, 6H, CMe_2), 1.45, 1.78 (m, 2H each, CH_2CH_2), 4.89 (*cis*), 4.95 (*trans*) (dd, 1H each, $^3J(^1H–^1H)_{cis} = 11.7$ Hz, $^3J(^1H–^1H)_{trans} = 16.9$ Hz, $CH_2–CH{=}CH_2$), 5.64 (m, 2H, $^3J(^1H–Sn) = 53.1$ Hz, C_5H_4), 5.73 (m, 1H, $CH_2–CH{=}CH_2$), 6.55 (m, 2H, C_5H_4) 7.42 (br m, 9H, *m*- and *p*-protons in $SnPh_3$), 7.56 (br m, 6H, $^3J(^1H–Sn) = 45.0$ Hz, *o*-protons in $SnPh_3$); $^{13}C\{^1H\}$ NMR (100.6 MHz, $CDCl_3$, 25 °C): δ 28.4, 29.4 (CH_2CH_2), 35.2 (CMe_2), 42.5 (Cp*C*), 113.7 ($CH_2–CH{=}CH_2$), 90.7 (C-1 of *Cp*, $^1J(^{13}C–Sn)$ not observed), 125.7, 153.0 (C-2 and C-3 of *Cp*), 128.8 (C-3 and C-5 of $SnPh_3$, $^3J(^{13}C–Sn) = 52.5$ Hz), 129.5 (C-4 of $SnPh_3$, $^4J(^{13}C–Sn) = 12.1$ Hz), 137.2 (C-2 and C-6 of $SnPh_3$, $^2J(^{13}C–Sn) = 38.3$ Hz), 138.4 (C-1 of $SnPh_3$, $^1J(^{13}C–Sn)$ not observed), 140.1 ($CH_2–CH{=}CH_2$); $^{119}Sn\{^1H\}$ NMR (149.2 MHz, $CDCl_3$, 25 °C): δ −101.2; MS FAB (*m/e* (relative intensity)): 511 (2) [M^+], 433 (7) [M^+−H−Ph], 380 (6) [M^+−Ph−$CH_2CH_2CH{=}CH_2$], 351 (100) [M^+−$C_5H_4(CMe_2(CH_2CH_2CH{=}CH_2))$]. *Anal.* Calc. for $C_{30}H_{32}Sn$: C, 70.47; H, 6.31. Found: C, 70.10; H, 6.20%.

2.4. Synthesis of $[SnPh_3(C_5Me_4H)]$ (**3**)

The preparation of **3** was carried out in an identical manner to **1**. $Li(C_5Me_4H)$ (0.75 g, 5.85 mmol) and $SnPh_3Cl$ (2.25 g, 5.85 mmol). Yield: 1.82 g, 67%. FT-IR (KBr): 3135 (m), 3063 (s), 3016 (s), 2960 (s), 2910 (s), 2854 (s), 2730 (w), 1952 (m), 1877 (m), 1817 (m), 1773 (w), 1619 (m), 1578 (m), 1480 (s), 1428 (s), 1384 (m), 1332 (m), 1258 (w), 1225 (w), 1109 (s), 1040 (m), 1022 (m), 997 (m), 908 (m), 727 (m), 670 (m), 658 (m), 555 (m), 453 (s); ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ 1.75 (s, 6H, $^4J(^1H–Sn) = 19.2$ Hz, C_5Me_4), 1.82 (s, 6H, C_5Me_4), 4.09 (s, 1H, $^1J(^1H–Sn) = 100.1$ Hz, C_5Me_4H), 7.39 (br m, 9H, *m*- and *p*-protons in $SnPh_3$), 7.50 (br m, 6H, $^3J(^1H–Sn) = 51.5$ Hz, *o*-protons in $SnPh_3$); $^{13}C\{^1H\}$ NMR (100.6 MHz, $CDCl_3$, 25 °C): δ 11.8 (C_5Me_4, $^3J(^{13}C–Sn) = 9.0$ Hz), 14.0 (C_5Me_4), 57.7 (C-1 of *Cp*, $^1J(^{13}C–Sn)$ not observed), 128.3 (C-3 and C-5 of $SnPh_3$, $^3J(^{13}C–Sn) = 50.4$ Hz), 128.9 (C-4 of $SnPh_3$, $^4J(^{13}C–Sn) = 11.6$ Hz), 130.3, 134.2 (C-2 and C-3 of *Cp*), 137.0 (C-2 and C-6 of $SnPh_3$, $^2J(^{13}C–Sn) = 38.7$ Hz), 138.7 (C-1 of $SnPh_3$, $^1J(^{13}C–Sn)$ not observed); $^{119}Sn\{^1H\}$ NMR (149.2 MHz, $CDCl_3$, 25 °C): δ −113.8; MS FAB (*m/e* (relative intensity)): 472 (6) [M^++H], 395 (9) [M^+−Ph], 351 (100) [M^+−C_5Me_4H], 241 (22) [M^+−3 × Ph]. *Anal.* Calc. for $C_{27}H_{28}Sn$: C, 68.82; H, 5.99. Found: C, 68.69; H, 5.90%.

2.5. Synthesis of $[SnPh_3(C_5Me_4SiMe_3)]$ (**4**)

The preparation of **4** was carried out in an identical manner to **1**. $Li(C_5Me_4SiMe_3)$ (0.75 g, 3.74 mmol) and $SnPh_3Cl$ (1.44 g, 3.74 mmol). Yield: 1.56 g, 77%. FT-IR (KBr): 3133 (m), 3065 (s), 3020 (s), 2960 (s), 2920 (s), 2870 (s), 2725 (w), 1949 (m), 1877 (m), 1814 (m), 1772 (w), 1623 (m), 1603 (s), 1578 (m), 1481 (s), 1429 (s), 1376 (m), 1302 (s), 1247 (m), 1205 (m), 1155 (m), 1109 (w), 1073 (m), 1022 (m), 997 (m), 960 (s), 891 (w), 836 (m), 727 (s), 698 (s), 656 (m), 628 (m), 556 (m), 452 (s); ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ −0.04 (s, 9H, $SiMe_3$), 1.86 (s, 6H, $^4J(^1H–Sn) = 17.4$ Hz, C_5Me_4), 1.90 (s, 6H, C_5Me_4), 7.37 (br m, 9H, *m*- and *p*-protons in $SnPh_3$), 7.51 (br m, 6H, $^3J(^1H–Sn) = 49.5$ Hz, *o*-protons in $SnPh_3$); $^{13}C\{^1H\}$ NMR (100.6 MHz, $CDCl_3$, 25 °C): δ −0.2 ($SiMe_3$), 11.4 (C_5Me_4, $^3J(^{13}C–Sn)$ not observed), 15.6 (C_5Me_4), 61.2 (C-1 of *Cp*, $^1J(^{13}C–Sn)$ not observed), 128.1 (C-3 and C-5 of $SnPh_3$, $^1J(^{13}C–Sn) = 48.9$ Hz), 128.7 (C-4 of $SnPh_3$, $^4J(^{13}C–Sn) = 10.6$ Hz), 129.0, 136.2 (C-2 and C-3 of *Cp*), 137.4 (C-2 and C-6 in $SnPh_3$, $^2J(^{13}C–Sn) = 35.8$ Hz), 139.9 (C-1 of $SnPh_3$ $^1J(^{13}C–Sn)$ not observed); $^{119}Sn\{^1H\}$ NMR (149.2 MHz, $CDCl_3$, 25 °C): δ −135.2; MS FAB (*m/e* (relative intensity)): 544 (5) [M^+], 467 (8) [M^+−Ph], 351 (100) [M^+−$C_5Me_4SiMe_3$], 313 (9) [M^+−3 × Ph]. *Anal.* Calc. for $C_{30}H_{36}SiSn$: C, 66.31; H, 6.68. Found: C, 65.97; H, 6.52%.

2.6. Data collection and structural refinement of **1**, **2** and **4**

The data of **1**, **2** and **4** were collected with a CCD Oxford Xcalibur S (λ(Mo Kα) = 0.71073 Å) using ω and φ scans mode. Semi-empir-

ical from equivalents absorption corrections were carried out with SCALE3 ABSPACK [44]. All the structures were solved by direct methods [45]. Structure refinement was carried out with SHELXL-97 [46]. All non-hydrogen atoms were refined anisotropically, and hydrogen atoms were calculated with the riding model and refined isotropically. Crystallographic details are listed in Table 1.

2.7. In vitro studies

2.7.1. Preparation of drug solutions

Stock solutions of the studied tin compounds were prepared in dimethyl sulfoxide (**1** and **2**; DMSO, Sigma Aldrich) and dimethyl formamide (**3** and **4**; DMF, Sigma Aldrich) at a concentration of 20 mM, filtered through Millipore filter, 0.22 μm, before use, and diluted by nutrient medium to various working concentrations. Nutrient medium was RPMI-1640 (PAA Laboratories) supplemented with 10% fetal bovine serum (Biochrom AG) and penicillin/streptomycin (PAA Laboratories).

2.7.2. Cell lines and culture conditions

The cell lines 8505C, A253, A549, A2780 and DLD-1 that were included in this study, were kindly provided by Dr. Thomas Mueller, Department of Hematology/Oncology, Martin Luther University of Halle-Wittenberg, Halle (Saale), Germany. Cultures were maintained as monolayer in RPMI 1640 (PAA Laboratories, Pasching, Germany) supplemented with 10% heat inactivated fetal bovine serum (Biochrom AG, Berlin, Germany) and penicillin/streptomycin (PAA Laboratories) at 37 °C in a humidified atmosphere of 5% (*v*/*v*) CO_2.

2.7.3. Cytotoxicity assay

The cytotoxic activities of the tin complexes were evaluated using the sulforhodamine-B (SRB, Sigma Aldrich) microculture colorimetric assay [47]. In short, exponentially growing cells were seeded into 96-well plates on day zero at the appropriate cell densities to prevent confluence of the cells during the period of the experiment. After 24 h, the cells were treated with serial dilutions of the studied compounds for 96 h. Final concentrations achieved in treated wells were 0.01, 0.03, 0.1, 0.3, 1, 3, 10, 30 and 100 μmol/l. Each concentration was tested in triple quadruplicate on each cell line. The final concentrations (<0.1%) of DMSO and DMF, were non-toxic to the cells. The percentages of surviving cells relative to untreated controls were determined 96 h after the beginning of drug exposure. After 96 h treatment, the supernatant medium from the 96-well plates was thrown away and the cells were fixed with 10% TCA. For a thorough fixation, plates were now allowed to stand at 4 °C. After fixation the cells were washed in a strip washer. The washing was carried out four times with water using alternate dispensing and aspiration procedures. The plates were then dyed with 100 μl of 0.4% SRB for about 45 min. After dyeing the plates were again washed to remove the dye with 1% acetic acid and allowed to air dry overnight. 100 μl of 10 mM Tris base solutions was added to each well of the plate and absorbance was measured at 570 nm using a 96-well plate reader (Tecan Spectra, Crailsheim, Germany). The IC_{50} values, defined as the concentrations of the compound at which 50% cell inhibition was observed, was estimated from the dose–response curves.

3. Results and discussion

3.1. Synthesis and characterization of the cyclopentadienyltin(IV) complexes *1–4*

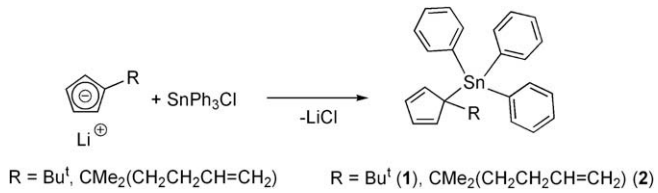
The preparation of tin complexes was achieved via the reaction of one equivalent of the lithium cyclopentadienyl derivative with $SnPh_3Cl$ (Schemes 1 and 2).

Complexes **1–4** have been characterized by ^1H, $^{13}C\{^1H\}$ and $^{119}Sn\{^1H\}$ NMR spectroscopy, mass spectrometry and elemental analysis (see Sections 2.2–2.5). NMR spectral data for **1–4** indicated that, in solution, only one of the possible double bond positional isomers was present. This phenomenon differs from the observation of multiple isomers in analogous silicon and germanium bridged cyclopentadiene ligands [48–52].

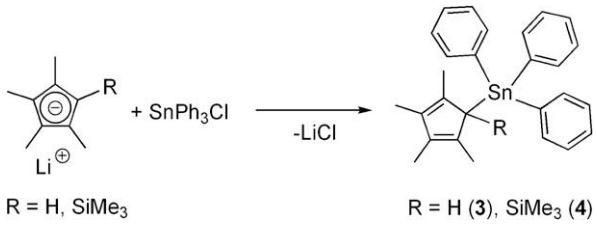
In the ^1H NMR spectra of **1–4**, two different multiplets, at ca. 7.2 corresponding to the *m*- and *p*-protons and at 7.5 ppm assigned to

Table 1
Crystallographic data for **1**, **2** and **4**.

	1	**2**	**4**
Formula	$C_{27}H_{28}Sn$	$C_{30}H_{32}Sn$	$C_{30}H_{36}SiSn$
Fw	471.18	511.25	543.37
T (K)	130(2)	130(2)	130(2)
Crystal system	triclinic	triclinic	triclinic
Space group	$P\bar{1}$	$P\bar{1}$	$P\bar{1}$
a (Å)	11.0569(7)	9.394(1)	8.4654(5)
b (Å)	13.7460(8)	11.682(1)	9.8404(8)
c (Å)	16.5966(9)	12.396(2)	17.866(1)
α (°)	80.945(5)	71.007(9)	93.486(6)
β (°)	88.554(5)	86.457(9)	101.221(6)
γ (°)	66.918(6)	78.040(8)	111.870(7)
V (nm^3)	2.2898(3)	1.2584(3)	1.3402(2)
Z	4	2	2
Dc ($Mg\ m^{-3}$)	1.367	1.349	1.346
μ (mm^{-1})	1.125	1.029	1.013
F(0 0 0)	960	524	560
Crystal dimension (mm)	0.3 × 0.15 × 0.04	0.3 × 0.1 × 0.1	0.4 × 0.2 × 0.04
θ Range (°)	2.75–25.68	2.61–26.37	2.65–30.51
hkl Ranges	$-12 \leqslant h \leqslant 12$	$-11 \leqslant h \leqslant 11$	$-12 \leqslant h \leqslant 11$
	$-16 \leqslant k \leqslant 16$	$-14 \leqslant k \leqslant 14$	$-14 \leqslant k \leqslant 13$
	$-20 \leqslant l \leqslant 17$	$-15 \leqslant l \leqslant 15$	$-25 \leqslant l \leqslant 17$
Data/parameters/restraints	8645/511/0	5152/282/0	8165/296/0
Goodness-of-fit (GOF) on F^2	0.940	0.916	0.885
Final R indices [$I > 2\sigma(I)$]	$R_1 = 0.0530$, $wR_2 = 0.1045$	$R_1 = 0.0344$, $wR_2 = 0.0562$	$R_1 = 0.0324$, $wR_2 = 0.0544$
R indices (all data)	$R_1 = 0.1130$, $wR_2 = 0.1114$	$R_1 = 0.0538$, $wR_2 = 0.0588$	$R_1 = 0.0456$, $wR_2 = 0.0558$
Largest difference in peak and hole ($e\ Å^{-3}$)	1.545 and −0.542	1.196 and −0.583	0.885 and −0.353



Scheme 1. Synthesis of complexes **1** and **2**.



Scheme 2. Synthesis of complexes **3** and **4**.

the *o*-protons of $SnPh_3$ moiety respectively, were observed. In addition, satellite signals of the *o*-protons, due to coupling with the ^{117}Sn and ^{119}Sn isotopes at a three bond distance were observed, however, we were unable to resolve the independent satellite signals corresponding to the two tin nuclei. Therefore, the observed coupling constant for these protons of approximately 50 Hz is an approximate value that can be applied to either nucleus.

In the ^{1}H NMR spectra of **1** and **2**, two multiplets, at ca. 5.6 and 6.6 ppm, were assigned to the four C_5 ring protons. This indicates that the symmetry of the molecule is such that the alkyl substituent is located in the C-1 position of the cyclopentadienyl ring. For the equivalent cyclopentadienyl ring protons, C-2 and C-5, at three bond distance to the tin atom, tin satellite signals were observed with values of $^3J(^1$H–Sn) of ca. 30 Hz.

For **1**, a singlet signal at 1.03 ppm was observed in the ^{1}H NMR spectrum and assigned to the protons of the *tert*-butyl group. For **2** a singlet due to the two methyl groups substituting the carbon atom adjacent to the cyclopentadienyl ring was observed at 1.00 ppm. The alkenyl fragment exhibited five sets of signals, two corresponding to the methylene protons (two multiplets at ca. 1.5 and 1.8 ppm), one for the proton of the C-γ (a multiplet at ca. 5.6 ppm) and two for the terminal olefinic protons (multiplets at 4.89 and 4.95 ppm).

The ^{1}H NMR spectra of **3** and **4** are very similar. Both spectra show two singlets for the methyl substituents of the cyclopentadienyl rings between 1.7 and 1.9 ppm, one of which corresponds to the protons of the methyl groups in the C-2 and C-5 of the ring and shows satellites with $^4J(^1$H–Sn) of ca. 18 Hz, and the other to the protons of the C-3 and C-4 methyl groups in the cyclopentadienyl ligand. In the ^{1}H NMR spectrum of **3** a signal, at 4.09 ppm, with tin satellites (^2J ^{1}H–Sn 100.1 Hz) was recorded for the proton in the C-1 position, while in the ^{1}H NMR spectrum of **4** a singlet was observed at −0.04 ppm and assigned to the trimethylsilyl protons.

In the $^{13}C\{^1H\}$ NMR spectra of **1–4**, four signals at ca. 128, 129, 137 and 139 ppm were observed for the C-3/C-5, C-4, C-1 and C-2/C-6 carbon atoms of the phenyl groups. Tin–carbon coupling constants for these signals gave values of approximately $^2J(^{13}$C–Sn) 35 Hz, $^3J(^{13}$C–Sn) 50 Hz, and $^4J(^{13}$C–Sn) 10 Hz.

In addition to the signals assigned to the phenyl groups, three signals were recorded for the cyclopentadienyl carbon atoms. The C-1 atom gave a signal at ca. 100 ppm for **1** and **2** and 60 ppm for **3** and **4**. In all cases, the coupling constant at one bond distance, between the ^{13}C and ^{117}Sn and ^{119}Sn nuclei was not observed due to the low intensity of these signals, even when recording the spectra at very long relaxation times. Two signals assigned to the remaining carbon atoms of the cyclopentadienyl ring, were observed at ca. 125 and 154 ppm for **1** and **2**, and at ca. 130 and 135 ppm for **3** and **4**.

The expected signals corresponding to the different substituents of the cyclopentadienyl moiety were observed in the $^{13}C\{^1H\}$ NMR spectra of **1–4** (see Sections 2.2–2.5). One signal was observed in the $^{119}Sn\{^1H\}$ NMR spectra of **1–4** between −100 and −135 ppm.

The $^{119}Sn\{^1H\}$ NMR characterization of all complexes was repeated with the solutions being prepared in an air atmosphere. Spectra were recorded in DMSO/$CDCl_3$ or DMF/$CDCl_3$ at 2, 4, 12, 24 and 48 h and no evidence of decomposition or evolution to other tin-containing products was observed.

Complexes **1–4** were also characterized by FAB-MS. The mass spectra showed the molecular ion peaks. Fragments indicative of the loss of different numbers of substituents were also observed (see Sections 2.2–2.5).

3.2. Structural studies

The molecular structures of **1**, **2** and **4** were established by single-crystal X-ray diffraction studies. The molecular structures and atomic numbering schemes are shown in Figs. 2–4, respectively. Selected bond lengths and angles for **1**, **2** and **4** are given in Table 2.

For **1**, two almost identical crystallographic independent molecules were located in the asymmetric unit, of which only one will be discussed.

The molecular structures of **1**, **2** and **4** are of a similar nature, all of them crystallize in the triclinic space group $P\bar{1}$ with four (**1**) or two (**2** and **4**) molecules located in the unit cell. In the molecular structures of **1**, **2** and **4** the geometry around the tin atom is clearly tetrahedral. The cyclopentadienyl units are essentially planar with the C-1 atom located only 0.108 Å for **1**, 0.077 Å for **2** and 0.011 Å for **4**, out of the plane defined by the other four carbon atoms (C(2) to C(5)). Three long bond lengths of about 1.47 Å and two short bond distances of ca. 1.35 Å are observed between the carbon atoms of the C_5 ring.

The hybridization of the C-1 atom of the cyclopentadienyl moiety is sp^3 and the σ-bond lengths with the tin atom of about 2.19 Å are slightly longer than those recorded for the tin-phenyl carbon distances (ca. 2.13 Å). The tin–C-1-ring plane angles (110.90° for **1**, 111.70° for **2** and 115.86° for **4**) rule out an

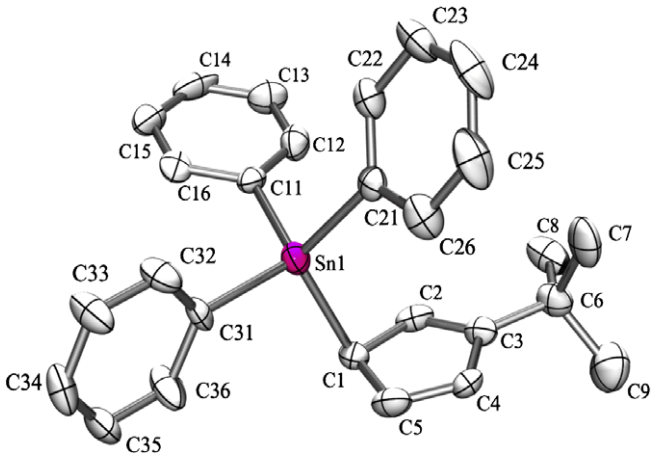


Fig. 2. Molecular structure and atom-labelling scheme for one of the two symmetry independent molecules of **1** with thermal ellipsoids at 50% probability (hydrogen atoms are omitted for clarity).

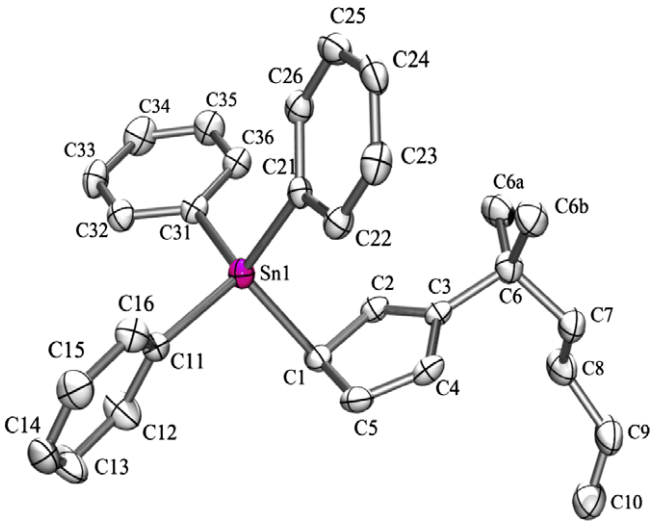


Fig. 3. Molecular structure and atom-labelling scheme for **2** with thermal ellipsoids at 50% probability (hydrogen atoms are omitted for clarity).

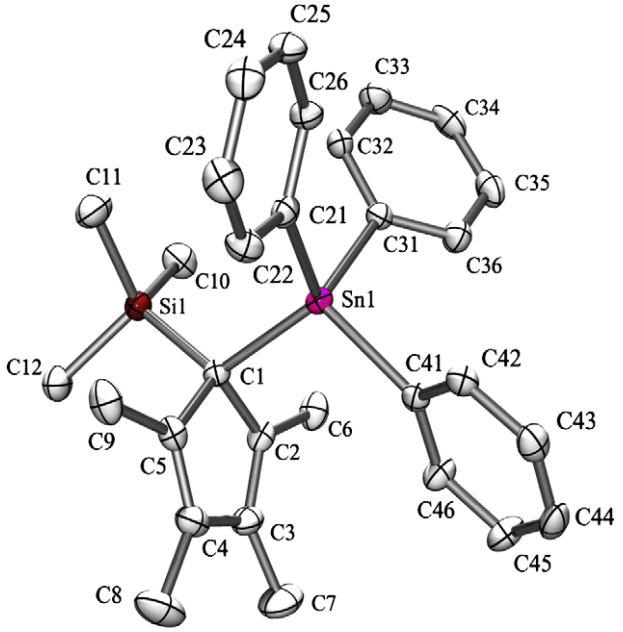


Fig. 4. Molecular structure and atom-labelling scheme for **4** with thermal ellipsoids at 50% probability (hydrogen atoms are omitted for clarity).

π-η^1 type interaction of the metal with the aromatic ring as has been previously observed in beryllium and zinc metallocene complexes [53–59].

In contrast to the observed spectroscopic data of the complexes **1** and **2** in solution, in which the obtained signals showed that the substituent at the cyclopentadienyl ligand was located in the C-1 position, due the rapid sigmatropic migration in solution of the tin atom around the cyclopentadienyl ring [60], in solid state, this substituent is located in the C-3 position, probably in order to minimize steric impediments as has been previously observed for other cyclopentadienyltin(IV) derivatives [60]. Thus, complex **1** presents the Bu^t substituent at the C-3 position and shows typical C–C bond lengths and angles. The alkenyl substituent of **2**, is also located at the C-3 atom of the C_5 ring. The distance C(9)–C(10) is typical for terminal C–C double bonds [41,61–63] and the angle C(8)–C(9)–C(10), 126.2(3)° confirms the sp^2 hybridization of C(9).

Table 2
Selected bond lengths (Å) and angles (°) for **1**, **2** and **4**.

	1[a]	2	4
Sn(1)–C(1)	2.183(7)/2.193(6)	2.197(3)	2.189(2)
Sn(1)–C(11)	2.127(7)/2.132(7)	2.137(3)	
Sn(1)–C(21)	2.147(7)/2.126(8)	2.128(3)	2.147(2)
Sn(1)–C(31)	2.135(7)/2.135(7)	2.140(3)	2.143(2)
Sn(1)–C(41)			2.149(2)
Si(1)–C(1)			1.907(2)
C(1)–C(2)	1.454(9)/1.476(9)	1.466(4)	1.501(3)
C(1)–C(5)	1.459(9)/1.440(9)	1.470(4)	1.495(3)
C(2)–C(3)	1.363(9)/1.344(9)	1.346(4)	1.354(3)
C(3)–C(4)	1.435(9)/1.452(9)	1.442(4)	1.444(3)
C(4)–C(5)	1.352(9)/1.36(1)	1.344(4)	1.354(3)
C(3)–C(6)	1.49(2)/1.50(1)	1.522(4)	
C(6)–C(7)	1.54(1)/1.50(2)	1.541(4)	
C(7)–C(8)		1.530(4)	
C(8)–C(9)		1.496(5)	
C(9)–C(10)		1.296(5)	
C(1)–Sn(1)–C(11)	109.4(3)/105.9(3)	105.7(1)	
C(1)–Sn(1)–C(21)	113.2(3)/111.2(3)	112.2(2)	117.34(7)
C(1)–Sn(1)–C(31)	106.8(3)/111.1(3)	105.9(2)	110.10(7)
C(1)–Sn(1)–C(41)			109.79(7)
C(11)–Sn(1)–C(21)	105.9(3)/109.8(3)	111.2(1)	
C(11)–Sn(1)–C(31)	108.4(3)/112.4(3)	111.1(2)	
C(21)–Sn(1)–C(31)	113.0(3)/106.5(3)	110.5(1)	105.76(8)
C(21)–Sn(1)–C(41)			105.97(7)
C(31)–Sn(1)–C(41)			107.37(7)
C(1)–C(2)–C(3)	109.9(6)/110.1(6)	109.7(3)	109.3(2)
C(1)–C(5)–C(4)	109.0(7)/109.5(7)	108.0(3)	109.2(2)
C(2)–C(3)–C(4)	107.5(6)/107.3(7)	107.7(3)	109.1(2)
C(3)–C(4)–C(5)	109.3(6)/109.0(7)	110.3(3)	109.6(2)
C(5)–C(1)–C(2)	103.7(6)/103.8(6)	104.2(2)	102.8(2)
C(7)–C(8)–C(9)		113.3(3)	
C(8)–C(9)–C(10)		126.2(3)	

[a] Values of the two symmetry independent molecules are given.

Selected structural data of **1**, **2** and **4** can be compared with similar cyclopentadienyltin(IV) compounds using Table 3.

3.3. Cytotoxic studies

The *in vitro* cytotoxicities of complexes **1**–**4** and cisplatin against human tumour cell lines 8505C anaplastic thyroid cancer, A253 head and neck tumour, A549 lung carcinoma, A2780 ovarian cancer and DLD-1 colon carcinoma were determined by using the sulforhodamine-B microculture colorimetric assay [47]. This study has been carried out in order to understand the relationship between the different tin(IV) compounds and the cytotoxic activity. The IC_{50} values of the studied compounds and cisplatin are summarized in Table 4.

Triphenyltin(IV) complexes (**1**–**4**) showed a dose-dependent antiproliferative effect toward all cancer cell lines (Fig. 5), presenting, in all cases, lower IC_{50} values than those of cisplatin. These results indicate their high activity against the tumoural cell lines evaluated.

In contrast to the results obtained for titanocene complexes with similar cyclopentadienyl ligands [36–38], **3** (which contains the tetramethylcyclopentadienyl moiety) is the most active compound with cytotoxic activities from 17 (against A253) to 104 times (against DLD-1) better than that of cisplatin, and IC_{50} values between ca. 0.037 and 0.085 μM. Complexes **1** and **2**, which contain alkyl and alkenyl-substituted cyclopentadienyl ligands, present comparable cytotoxic activities on all the studied cells, showing IC_{50} values from 0.044 to 0.119 μM. However, their activities are, in all cases, lower than those observed for **3**, indicating the absence of the positive effect on the cytotoxic activity provided by alkenyl-substituted cyclopentadienyl ligands [36–38], in tin(IV) complexes.

Table 3
Selected structural data of cyclopentadienyltin(IV) compounds.

Compound	Sn–$C^1_{(Cp)}$ (Å)	C–$C_{(Cp)}$ (Å)	C=$C_{(Cp)}$ (Å)	Si–$C^1_{(Cp)}$ (Å)	Reference
$[SnPh_3(C_5H_4Bu^t)]$ (**1**)[a]	2.183(7)	1.435(9)	1.363(9)		This work
	2.193(6)	1.440(9)	1.344(9)		
		1.452(9)	1.352(9)		
		1.454(9)	1.36(1)		
		1.459(9)			
		1.476(9)			
$[SnPh_3\{C_5H_4CMe_2(CH_2CH_2CH{=}CH_2)\}]$ (**2**)	2.197(3)	1.442(4)	1.344(4)		This work
		1.466(4)	1.346(4)		
		1.470(4)			
$[SnPh_3(C_5Me_4SiMe_3)]$ (**3**)	2.189(2)	1.444(3)	1.354(3)	1.907(2)	This work
		1.495(3)	1.354(3)		
		1.501(3)			
$[SnMe_2(C_5Me_4H)_2]$[a]	2.195(4)	1.457(6)	1.353(6)		[40]
	2.205(4)	1.459(5)	1.353(6)		
	2.206(4)	1.475(6)	1.356(5)		
	2.202(4)	1.480(5)	1.359(5)		
		1.480(6)			
		1.497(5)			
$[SnMe_2(C_5Me_4SiMe_3)_2]$	2.190(2)	1.456(3)	1.350(3)	1.905(2)	[40]
		1.502(3)	1.358(3)		
		1.505(3)			

[a] Values for the two independent molecules found in the asymmetric unit are given.

Table 4
IC_{50} (μM) for the 96 h of action of the studied compounds and cisplatin on 8505C anaplastic thyroid cancer, A253 head and neck tumour, A549 lung carcinoma, A2780 ovarian cancer and DLD-1 colon carcinoma determined by sulforhodamine-B microculture colorimetric assay.

Compound	IC_{50}±SD				
	8505C	A253	A549	A2780	DLD-1
1	0.103 ± 0.015	0.077 ± 0.012	0.079 ± 0.002	0.042 ± 0.004	0.044 ± 0.007
2	0.110 ± 0.011	0.118 ± 0.028	0.108 ± 0.018	0.061 ± 0.002	0.119 ± 0.004
3	0.085 ± 0.007	0.045 ± 0.004	0.038 ± 0.003	0.037 ± 0.007	0.048 ± 0.002
4	0.343 ± 0.046	0.351 ± 0.045	0.384 ± 0.021	0.163 ± 0.002	0.309 ± 0.003
Cisplatin	5	0.8	1.5	0.55	5

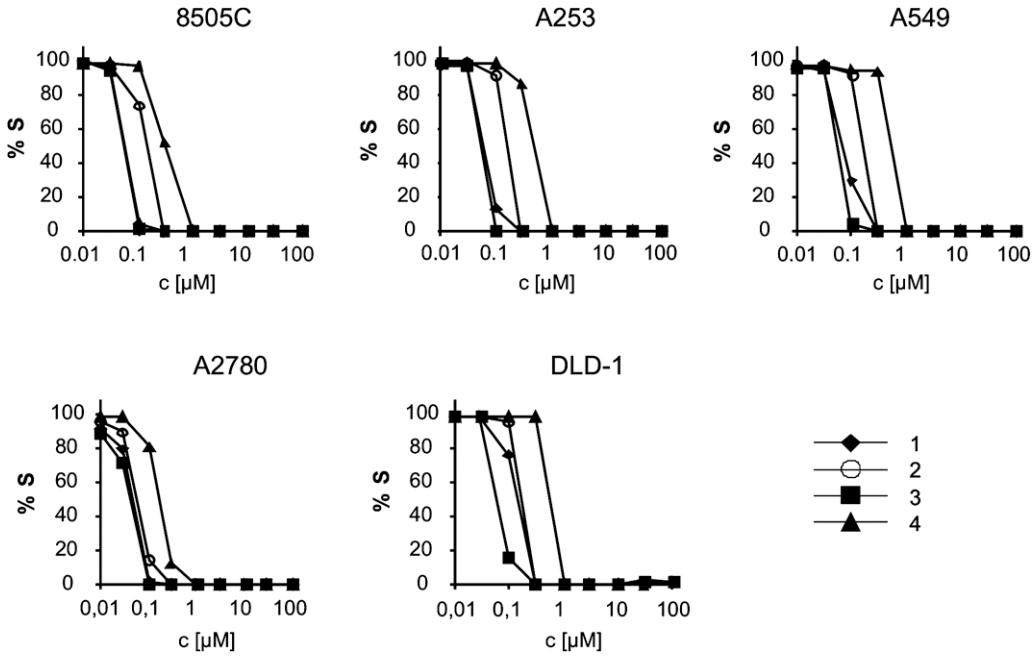


Fig. 5. Representative graphs showing survival of 8505C, A253, A549, A2780 and DLD-1 cells grown for 96 h in the presence of increasing concentrations of the studied compounds (**1–4**). Standard deviations are omitted for clarity.

Interestingly, the trimethylsilyl-substituted complex **4** showed lower *in vitro* antitumoural activity in comparison to other studied derivatives, with IC_{50} values from ca. 0.163 to 0.351 μM. Again, the enhancement of the antiproliferative activity of $SiMe_3$ groups

reported by McGowan and coworkers using trimethylsilyl-substituted titanocene complexes [64], is not observed for tin(IV) complexes. In addition, complexes **1**–**4** present substantially higher cytotoxic activity on cancer cell lines (up to 5000 times) than other reported cyclopentadienyltin(IV) derivatives [32].

With these data, one can conclude a ligand-dependent activity of the studied complexes on the different cells. Complexes bearing monosubstituted cyclopentadienyl ligands present different cytotoxic activities with respect to their tetra- and pentasubstituted analogues. In addition, one can conclude a different behaviour in the influence of the substituents of the cyclopentadienyl ligands on the final cytotoxic activity of titanocene and organotin(IV) complexes, indicating a substantial difference in the anticancer mechanism of these two class of metal-based drugs.

In addition, the cytotoxic activities of the previously reported titanocene complexes bearing similar ligands presented IC_{50} values from 24 to 175 μM [36–38] which are much lower than those found in the cyclopentadienyltin(IV) derivatives with IC_{50} values from 0.037 to 0.384 μM.

4. Conclusions

A variety of cyclopentadienyltin(IV) compounds have been synthesized and structurally characterized. Metal derivatives, were tested *in vitro* against human tumour cell lines 8505C anaplastic thyroid cancer, A253 head and neck tumour, A549 lung carcinoma, A2780 ovarian cancer and DLD-1 colon carcinoma. The studied tin(IV) compounds presented very high activity against the evaluated tumoural cell lines, up to ca. 100 times higher than that of cisplatin and up to ca. 5000 times higher than those reported for similar cyclopentadienyltin(IV) derivatives [32].

3 (which contains the tetramethylcyclopentadienyl ligand) is the most active compound against all the studied cancer cells, presenting IC_{50} values between 0.037 and 0.085 μM.

Following on from these results, intensive studies on the mechanism of action of cyclopentadienyltin(IV) derivatives against the different studied cancer cells are currently being carried out.

Supplementary data

CCDC 729606, 729607 and 729608 contain the supplementary crystallographic data for **1**, **2** and **4,** respectively. These data can be obtained free of charge via http://www.ccdc.cam.ac.uk/conts/retrieving.html, or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: (+44) 1223-336-033; or e-mail: deposit@ccdc.cam.ac.uk.

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