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Structure, properties and cytostatic activity of tributyltin aminoarylcarboxylates

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This article is dedicated to Professor J.J.R. Fraústo de Silva

Abstract

Properties of butyltin complexes $[Sn(C_4H_9\text{-}n)_3\{OOCC_6H_3(NH_2)_2\text{-}3,4\}]_n$ (**1**), $[Sn(C_4H_9\text{-}n)_3\{OOCC_6H_3(NH_2)_2\text{-}3,5\}]$ (**2**), $[Sn(C_4H_9\text{-}n)_3\{OOCC_6H_4N{=}NC_6H_4N(CH_3)_2\text{-}4\}]$ (**3**) and $[Sn(C_6H_5)_3\{OOCC_6H_3(NH_2)_2\text{-}3,5\}]_n$ (**4**) have been investigated. ^1H, ^{13}C and ^{119}Sn NMR spectra indicate that the compounds in chloroform are distorted tetrahedral and in strongly coordinating solvents trigonal-bipyramidal complexes. Structure of complex **3** has been determined by X-ray crystallography. This compound adopts trigonal bipyramidal structure with bridging carboxylato ligand bound asymmetrically with tin atoms in axial positions. The complexes are effective cytostatic agents.

Keywords: Organotin complexes; Cytostatic agents; Antitumor activity; Crystal structures

1. Introduction

Coordination and organometallic compounds are among the very important antitumor agents [1,2]. Platinum and platinum metals complexes and other transition metal compounds reveal promising antitumor activity. However, many of them show severe toxicity. This prompted a search for new drugs with high activity and decreased side-effects. A number of organotin compounds have been shown to be active against various types of cancers. A series of organotin dipeptide compounds and a number of diorganotin halides and pseudohalides $[SnR_2X_2L_2]$ (L = amino ligand, e.g. py, bpy, phen, en) have displayed modest antitumor activity [3,4]. Many di-n-butyl, tri-n-butyl and triphenyltin complexes with hydroxyarylcarboxylic, ketocarboxylic, fluoroarylcarboxylic acids and many other oxygen and nitrogen containing derivatives of carboxylic acids display high antitumor activities [5–14]. However, only few tin carboxylates with amino groups have been investigated. These complexes comprise pyridinocarboxylato and aminosalicylato organotin compounds [5,6] and [(2-dimethylaminomethyl)phenyl]diphenyltin(IV) 4-[4′-(dimethylamino)phenyl]azobenzene-sulfonate and [(2-dimethylaminomethyl)phenyl]diphenyltin(IV) 4-[4′-(dimethylamino)phenyl]azobenzoate complexes [15]. Recently we have described 3,4-diaminobenzoato and 3,5-diaminobenzoato $[Sn_4O_2Bu_8(OOCR)_4]$ and $[Sn(CH=CH_2)_3)OOCR)]$ compounds and $[SnPh_3\{OOCC_6H_3(NH_2)_2\text{-}3,4\}]$ complex and their cytostatic activity [16,17]. However, tributyltin complexes with these ligands and triphenyltin 3,5-diaminobenzoate were not investigated. These compounds should show high cytostatic activity and therefore it seemed interesting to examine their properties. Thus, here we report the synthesis, properties, structure and in vitro cytostatic activity of tributyltin complexes with 3,4-diaminobenzoate, 3,5-diaminobenzoate and 2-[4-(dimethylamino)phenylazo]benzoate as well as triphenyltin 3,5-diaminobenzoate.

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2. Experimental

2.1. Materials and methods

2.1.1. Compounds

3,4-Diaminobenzoic acid and 3,5-diaminobenzoic acid were obtained from Aldrich, 2-[4-(dimethylamino)phenylazo]benzoic acid from POCH (Poland), diphenyltin dichloride, triphenyltin chloride and tributyltin chloride from Strem and used without further purification. Diphenyltin oxide, triphenyltin oxide and tributyltin oxide were prepared from diphenyltin dichloride, triphenyltin chloride and tributyltin chloride in reaction with sodium hydroxide in aqueous ethanol solution. Syntheses were carried out in nitrogen atmosphere. Infrared spectra (KBr pellets) were recorded on a Bruker IFS 113v and ^{1}H, ^{13}C and ^{119}Sn NMR spectra were taken on a Bruker AMX 300 and a Bruker Avance 500. Carbon, hydrogen and nitrogen analyses were performed on a Perkin–Elmer 2400 CHN analyzer, and tin was determined using ICP-AES method on a ARL 3410.

2.2. Synthesis of complexes

2.2.1. $[Sn(C_4H_9\text{-}n)_3\{OOCC_6H_3(NH_2)_2\text{-}3,4\}]$ (1)

A suspension of $\{Sn(C_4H_9\text{-}n)_3\}_2O$ (1,673 g, 2.81×10^{-3} mol) and $HOOCC_6H_3(NH_2)_2$-3,4 (0.854 g, 5.62 mmol) in ethanol (20 cm^3) was refluxed with stirring for 0.25 h. The pale-yellow solution was evaporated and dried in vacuo. The product $[Sn(C_4H_9\text{-}n)_3\{OOCC_6H_3(NH_2)_2\text{-}3,4\}]$ (**1**) was obtained in the form of a yellow oil. Yield 1.928 g, 77.9%. *Anal.* Calc. for $C_{19}H_{34}N_2O_2Sn$: C, 51.72; H, 7.77; N, 6.35. Found: C, 51.97; H, 8.01; N, 6.11%. IR (cm^{-1}) (film on KBr): 3420sh $\nu(NH_2)$, 3356s $\nu(NH_2)$, 3260sh $\nu(NH_2)$, 2956vs ν(CH), 2928vs ν(CH), 2872s ν(CH), 2852s ν(CH), 1615vs ν_{as}(COO), 1580vs ν_{as}(COO), 1516s, 1461ms, 1441s, 1416w, 1378s, 1357vs ν_s(COO), 1328vs ν_s(COO), 1244vs, 1180w, 1150s, 1110w, 1070m, 1045vw, 1018vw, 997vw,955w, 947m, 870m, 860m, 812m, 775s, 690m, 650s, 600m ν(SnC), 560vw, 507vw, 485m, 445m.

2.2.2. $[Sn(C_4H_9\text{-}n)_3\{OOCC_6H_3(NH_2)_2\text{-}3,5\}]$ (2)

A suspension of $\{Sn(C_4H_9\text{-}n)_3\}_2O$ (1,673 g, 2.81×10^{-3} mol) and $HOOCC_6H_3(NH_2)_2$-3,4 (0.854 g, 5.62 mmol) in ethanol (15 cm^3) was refluxed with stirring for 0.25 h. The brown solution was evaporated and dried in vacuo. The product $[Sn(C_4H_9\text{-}n)_3\{OOCC_6H_3(NH_2)_2\text{-}3,4\}]$ (**2**) was obtained in the form of a light-brown oil. Yield 2.03 g, 82.2. *Anal.* Calc. for $C_{19}H_{34}N_2O_2Sn$: C, 51.72; H, 7.77; N, 6.35. Found: C, 51.64; H, 8.02; N, 6.23%. IR (cm^{-1}) (film on KBr): 3460m $\nu(NH_2)$, 3360s $\nu(NH_2)$, 3228mw $\nu(NH_2)$, 2956vs ν(CH), 2924vs ν(CH), 2872s ν(CH), 2856s ν(CH), 1620vs ν_{as}(COO), 1594vs ν_{as}(COO), 1484w, 1464s, 1414w, 1374vs ν_s(COO), 1338mw, 1300s ν_s(COO), 1280m, 1190s, 1150s, 1150w, 1075m, 1045vw, 1018vw, 997w, 990mw, 955w, 947m, 870m, 860m, 847m, 780s, 690m, 670s, 600m ν(SnC), 508m, 492mw.

2.2.3. $[Sn(C_4H_9\text{-}n)_3\{OOCC_6H_4N{=}NC_6H_4N(CH_3)_2\text{-}4\}]$ (3)

A mixture of $\{Sn(C_4H_9)_3\}_2O$ (4.000 g, 6.71 mmol) and $HOOCC_6H_4N{=}NC_6H_4N(CH_3)_2$-4 (3.614 g, 13.42 mmol) in ethanol (10 cm^3) was refluxed with stirring for 1 h. The dark-red solution was concentrated in vacuo. Red solid complex **3** was filtered off, washed with cold ethanol and dried in vacuo. Yield 6.158 g (82.2%). *Anal.* Calc. for $C_{27}H_{41}N_3O_2Sn$: C, 58.08; H, 7.40; N, 7.53; Sn, 21.26. Found: C, 58.34; H, 7.53; N, 7.64; Sn, 21.41%. Single crystals for X-ray investigations were prepared by slow evaporation of toluene–ethanol solution of complex. IR (cm^{-1}) (KBr pellet): 3100vw ν(CH), 3060vw ν(CH), 2956s ν(CH), 2920s ν(CH), 2877m ν(CH), 2855m ν(CH), 1600vs ν_{as}(COO), 1580m, 1565s, 1555s, 1520s, 1478w, 1464mw, 1455mw, 1440w, 1415m, 1404s, 1393s, 1370vs ν_s(COO), 1310m 1260mw, 1250m, 1237mw, 1144vs, 1090m, 1030vw, 117vw, 990vw, 945m, 878w, 865mw, 850w, 812s, 760s, 730vw, 696vw, 678mw, 665ms,632vw, 610mw ν(SnC), 585w, 537m,515mw490w, 407m.

2.2.4. $[Sn(C_6H_5)_3\{OOCC_6H_3(NH_2)_2\text{-}3,5\}]$ (4)

Method a: a mixture of $Sn(C_6H_5)_2O$ (0.610 g, 2.11 mmol) and $HOOCC_6H_3(NH_2)_2$-3,5 (0.321 g, 2.11 mmol) in toluene–ethanol (3/1) (10 cm^3) was refluxed with stirring for 4 h. The light-brown solid was filtered off. The yellow filtrate was slowly concentrated giving colorless crystals of complex **4**. The solid was washed with cold ethanol and dried in vacuo. Yield 0.52 g. *Anal.* Calc. for $C_{25}H_{22}N_2O_2Sn$: C, 59.92; H, 4.42; N, 5.59; Sn, 23.69. Found: C, 60.24; H, 4.78; N, 5.32; Sn, 23.28%.

Method b: a mixture of $\{Sn(C_6H_5)_3\}_2O$ (0.501 g, 0.70 mmol) and $HOOCC_6H_3(NH_2)_2$-3,5 (0.216 g, 1.42 mmol) in ethanol (20 cm^3) was refluxed with stirring for 0.5 h. The pale-yellow solution was evaporated in vacuo. The crude complex **4** was recrystallized from toluene (10 cm^3) and washed with cold ethanol and dried in vacuo. Yield 0.436 g (62%). *Anal.* Calc. for $C_{25}H_{22}N_2O_2Sn$: C, 59.92; H, 4.42; N, 5.59; Sn, 23.69. Found: C, 59.64; H, 4.50; N, 5.64; Sn, 24.11%. IR (cm^{-1}) (KBr pellet): 3452vs $\nu(NH_2)$, 3432vs $\nu(NH_2)$, 3352vs $\nu(NH_2)$, 3064 mw $\nu(CH^{Ar})$, 3048 w $\nu(CH^{Ar})$, 3020 vw $\nu(CH^{Ar})$, 2920vw $\nu(CH^{Ar})$, 1630sh vs ν_{as}(COO), 1590vs ν_{as}(COO), 1480 ms, 1420m, 1428s, 1372vs ν_s(COO), 1340m, 1294vs ν_s(COO), 1270s, 1190s, 1076s, 996m, 948w, 870mw, 852mw, 788s, 780s, 730vs, 698vs, 660w, 550w, 540w, 518m, 500mw, 446ms.

2.3. X-ray crystallographic study

All measurements of crystal were performed on a Kuma KM4CCD κ-axis diffractometer with graphite-monochromated Mo Kα radiation. The crystal was positioned at 65 mm from the KM4CCD camera. 612 Frames were measured at 0.75° intervals with a counting time of 15 s. The data were corrected for Lorentz and polarization effects. Absorption correction were omitted. Data reduction and analysis were carried out with the Oxford Diffraction (Poland) (formerly Kuma Diffraction Wroclaw, Poland) programs. The structure was solved by the heavy atom method (program SHELXS-97 [18]) and refined by the full-matrix least-squares method on all F^2 data using the SHELXL-97 [19] programs. Non-hydrogen atoms were refined with anisotropic thermal parameters; hydrogen atoms were included from geometry of molecules and $\Delta\rho$ maps but were not refined. In studied crystals one butyl is disorderd in 2:3 ratio.

2.4. Cytostatic activity in vitro.

Human cell line A549 (lung adenocarcinoma) was used for the proliferation assay. The experiments were repeated in triplicate for each tested Sn compound concentration. Statistical significance was tested using Student's t-test ($p < 0.05$ was considered statistically significant). The in vitro tests against all cell lines were performed as described previously [17,20–22]. The stock solutions of the organotin compounds at a concentration of 10^{-4} M were prepared in 70% ethanol. The control cells culture was performed in standard media enriched with adequate dilution of 70% ethanol. The results of cytotoxic activity in vitro were expressed as ID_{50}—the dose of compound that inhibits proliferation rate of the tumor cells by 50% as compared to control untreated cells.

3. Results and discussion

Complexes **1**, **2**, **3** and **4** are soluble in ethanol, methanol, acetone, chloroform, dichloromethane and in other polar organic solvents and slightly soluble in aqueous ethanol (50%). The complexes **1**–**3** have been obtained in reactions between $\{Sn(C_4H_9)_3\}_2O$ and appropriate acid in ethanol while the complex **4** has been prepared in reactions of $SnO(C_6H_5)_2$ or $\{Sn(C_6H_5)_3\}_2O$ with 3,5-diaminobenzoic acid. The structure of complex **3** is shown in Fig. 1. The crystallographic data, selected bond distances and angles are given in Tables 1 and 2. The compound $[Sn(C_4H_9\text{-}n)_3\{OOCC_6H_4N{=}NC_6H_4N(CH_3)_2\text{-}4\}]$ (**3**) is a zigzag chain polymer associating via bridging carboxylate ligands with *anti–syn* configuration. The Sn atoms in this polymeric structure exist in distorted trigonal bipyramidal environment. The three n-butyl groups define the trigonal planes with the very nearly planar SnC_3 groups. The C–Sn–C angles lie in the range 119.54(16)–120.47(16)°. The axial positions are occupied by bridging carboxylate ligands forming different

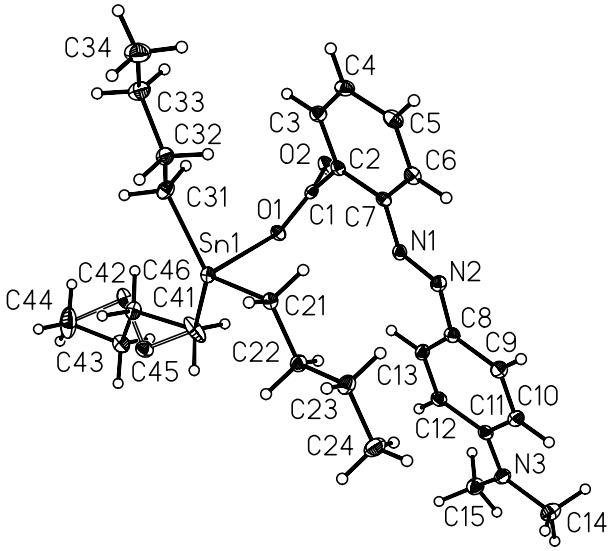


Fig. 1. Molecular structure of complex **3**, $[Sn(C_4H_9)_3\{OOC\text{-}2\text{-}C_6H_4N{=}NC6H4N(CH_3)_2\text{-}4\}]$ with crystallographic numbering. The open lines indicate a minor component of disorderd butyl group.

Table 1
Crystal data and structure refinement for complex $[Sn(C_4H_9)_3\{OOC\text{-}2\text{-}C_6H_4N{=}NC_6H_4N(CH3)_2\text{-}4\}]$ (**3**)

Empirical formula	$C_{27}H_{41}N_3O_2Sn$
Formula weight	558.32
Temperature (K)	100(2)
Wavelength (Å)	0.71073
Crystal system	monoclinic
Space group	$P2_1/n$
Unit cell dimensions	
a (Å)	10.1993(6)
b (Å)	10.9261(7)
c (Å)	25.4534(16)
β (°)	97.498(5)
V (Å^3)	2812.2(3)
Z	4
D_{calc} (Mg m^{-3})	1.319
Absorption coefficient (mm^{-1})	0.934
$F(000)$	1160
Crystal size (mm^3)	$0.16 \times 0.12 \times 0.12$
Diffractometer	Kuma KM4CCD
θ Range (°)	3.48–28.47
Ranges of h,k,l	$-13 \geq 13$, $-14 \geq 9$, $-33 \geq 33$
Reflections collected	17871
Independent reflections (R_{int})	6538 (0.0367)
Data/parameters	6538/322
Goodness-of-fit (F^2)	1.228
Final R_1/wR_2 indices ($I > 2\sigma(I)$)	0.0434/0.0841
Largest difference peak and hole (e A^{-3})	1.447/−0.925

Table 2
Bond lengths (Å) and bond angles (°) for complex $[Sn(C_4H_9)_3\{OOC\text{-}2\text{-}C_6H_4N{=}NC_6H_4N(CH3)_2\text{-}4\}]$ (**3**)

Bond lengths			
Sn(1)–C(41)	2.124(4)	C(2)–C(3)	1.392(4)
Sn(1)–C(21)	2.134(3)	C(2)–C(7)	1.392(4)
Sn(1)–C(31)	2.142(3)	C(5)–C(6)	1.383(5)
Sn(1)–O(2i)	2.226(2)	C(6)–C(7)	1.401(4)
Sn(1)–O(1)	2.365(2)	N(1)–C(7)	1.427(4)
O(1)–C(1)	1.244(4)	N(2)–C(8)	1.410(4)
O(2)–C(1)	1.275(4)	N(3)–C(11)	1.368(4)
O(2)–Sn(1ii)	2.226(2)	N(3)–C(14)	1.444(4)
C(1)–C(2)	1.508(4)	N(3)–C(15)	1.451(4)
Bond angles			
C(41)–Sn(1)–C(21)	119.54(16)	C(21)–Sn(1)–O(1)	94.99(10)
C(41)–Sn(1)–C(31)	119.86(16)	C(31)–Sn(1)–O(1)	87.20(11)
C(21)–Sn(1)–C(31)	120.47(12)	O(2)#1–Sn(1)–O(1)	168.97(8)
C(41)–Sn(1)–O(2i)	85.68(11)	C(1)–O(1)–Sn(1)	136.6(2)
C(21)–Sn(1)–O(2i)	93.99(10)	C(1)–O(2)–Sn(1ii)	130.2(2)
C(31)–Sn(1)–O(2i)	93.75(11)	O(1)–C(1)–O(2)	124.9(3)
C(41)–Sn(1)–O(1)	84.33(11)		

Symmetry transformations used to generate equivalent atoms: i: $-x+1/2, y+1/2, -z+1/2$; ii: $-x+1/2, y-1/2, -z+1/2$.

Sn–O distances. The shorter Sn(1)–O(2A) bond is equal to 2.226(2) Å and the longer Sn(1)–O(1) distance is 2.365(2) Å. The difference between these bonds (0.139 Å) is relatively small. In the case of many analogous compounds this difference is 0.2–0.5 Å [23,24]. It is equal to 0.325 Å in the complex $[SnBu_3(OOCC_9H_8N)]$ [24]. The O(1)–Sn(1)–O(2A) angle is 168.97(8)° and belongs to the lowest values found in the single strand $[SnR_3(OOCR')]_n$ polymers [23,24]. The polymeric zigzag chains are located along the [001] direction. The crystal structure of compound **3** is stabilized by intermolecular stacking interaction between parallel C(8)–C(13) phenyl rings of the two neighbor molecules. The distance between these rings and offset are 3.50 Å and 1.43 Å, respectively (Fig. 2). This distinctive and recurring zipperlike motif is observed only in the *bc* planes. The consecutive chains along the [100] direction form a weak attractive interactions between the C2–C7 aromatic ring of the first chain and the methyl group (C15) of the second one (Fig. 3). The C···Ph(centroid) distance of 3.53 Å suggests the presence of the C–H···Ph weak interaction between both groups. It was found that the weak hydrogen bonding can be important for crystallization of compounds [25,26].

Infrared spectra of all investigated complexes are consistent with X-ray data for compound **3**. The presence of ν_{as}(COO) and ν_s(COO) in the range 1580–1630 and 1330–1374 cm^{-1}, respectively, and therefore large $\Delta\nu = \nu^{as}_{COO} - \nu^{s}_{COO}$ values are consistent with the presence in the complexes **1**, **2**, **3** and **4** asymmetrically coordinated carboxylato group. These differences are larger for complexes **1**, **2** and **4** in comparison with compound **3**. This suggests that corboxylato groups in the former complexes are coordinated more asymmetrically than in the latter. This is consistent with relatively small difference between Sn(1)–O(1) and Sn(1)–O(2i) distances. The intense $\nu_s(NH_2)$ vibrations are observed at relatively low frequencies and are broadened, suggesting that strong hydrogen bonding is pronounced in the **1**, **2** and **4** compounds, while in compound **3** crystal structure is controlled by weak hydrogen bonding and stacking of phenyl rings of the ligands. The ν(SnC) bands for butyl compounds (**1**–**3**) are observed in the range 600–610 cm^{-1}, thus at values similar to other bytyl Sn(IV) compounds.[27].

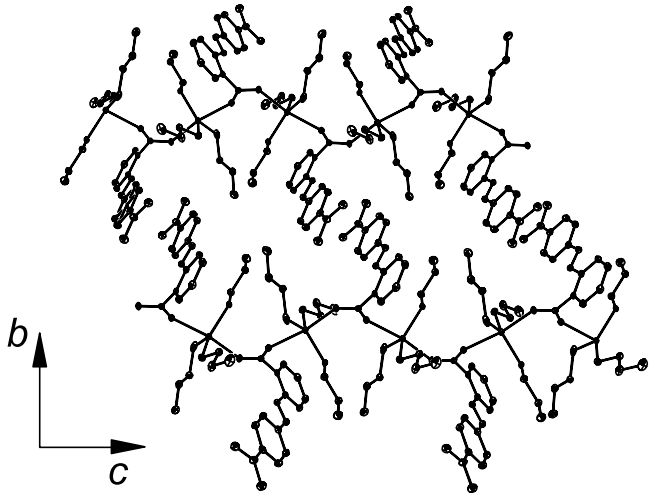


Fig. 2. Molecular packing along the [100] direction showing the stacking of the OOC-$C_6H_4N{=}NC_6H_4N(CH_3)_2$ ligand domains of **3** within the lattice. The hydrogen atoms are omitted for clarity.

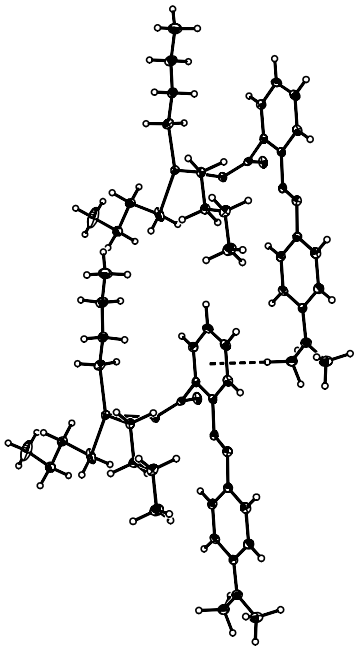
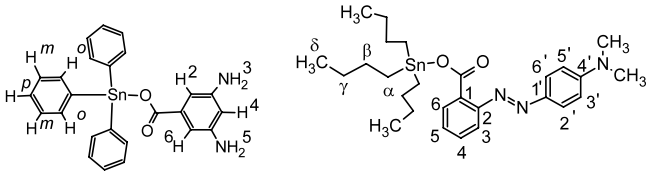


Fig. 3. Weak hydrogen bonding between consecutive polymeric chains.

Table 3
^{1}H, ^{13}C and ^{119}Sn NMR spectra of complexes $[Sn(C_4H_9\text{-}n)_3\{OOCC_6H_3(NH_2)_2\text{-}3,4\}]$ (**1**), $[Sn(C_4H_9\text{-}n)_3\{OOCC_6H_3(NH_2)_2\text{-}3,5\}]$ (**2**), $[Sn(C_4H_9\text{-}n)_3\{OOCC_6H_4N{=}NC_6H_4N(CH_3)_24\}]$ (**3**) and $[(C_6H_5)_3Sn\{OOCC_6H_3(NH_2)_2\text{-}3,5\}]$ (**4**)

Complex, solvent	^{1}H NMR ppm (Hz)	^{13}C NMR ppm (Hz)	^{119}Sn NMR ppm (Hz)
1, $CDCl_3$	CH_2-α, 1.57–1.65, (m); CH_2-β+CH_2-γ, 1.24–1.35 (m); CH_3-δ, 0.87 (t, ^{3}J(H–H) 7.4); H^6, 7.43 (dd, $^{3}J(H^6,H^5) = 8.1$); H^2, 7.37 (d, $^{4}J(H^2,H^6) = 1.7$); H^5, 6.57 (d); 3,4-NH_2, 3.94 (s), 3.70 (s)	C-α, 16.30 ($^{1}J(^{13}C–^{119/117}Sn) = 361.5/344.7$); C-β, 27.67 ($^{2}J(^{13}C–^{119/117}Sn) = 20.2$); C-γ, 26.81 ($^{3}J(^{13}C–^{119/117}Sn) = 63.9$); C-δ, 13.44; (COO) 171.87; C^4 139.49; C^3 132.80; C^6 123.41; C^1 122.53; C^2 118.70; C^5 114.59	104.4
1, $(CD_3)_2SO$	CH_2-α, 1.51–1.63, (m); CH_2-β 1.19–1.32, CH_2-γ, 1.00–1.35 (m); CH_3-δ, 0.81 (t, ^{3}J(H–H) 7.3); H^2, 7.11 (s); H^6, 7.05 (d, $^{3}J(H^5,H^6) = 8.2$); H^5, 6.47 (d); 3,4-NH_2, 3.94 (s), 3.70 (s)	C-α, 19.33 ($^{1}J(^{13}C–^{119/117}Sn) = 496.9/480.0$); C-β, 27.6 ($^{2}J(^{13}C–^{119/117}Sn) = 27.8$); C-γ, 26.61 ($^{3}J(^{13}C–^{119/117}Sn) = 79.6$); C-δ, 13.66; (COO) 168.04; C^4 139.45; C^3 133.65; C^6 120.40 C^1 119.05; C^2 115.35; C^5 112.66	
2, $CDCl_3$	CH_2-α, 1.57–1.65 (m); CH_2-β+CH_2-γ, 1.24–1.35 (m); CH_3-δ, 0.87 (t, $^{3}J(H,H) = 7.4$); H^2, H^6, 6.71 (s); H^4, 6.17 (s); 3,5–NH_2 3.78 (s)	C-α, 16.36 ($^{1}J(^{13}C–^{119/117}Sn) = 358.9/343.9$); C-β, 27.66 ($^{2}J(^{13}C–^{119/117}Sn) = 20.2$); C-γ, 26.83 ($^{3}J(^{13}C–^{119/117}Sn) = 64.7$); C-δ, 13.45; (COO), 171.77; C^3, C^5 147.21; C^1 133.69; C^2, C^6 107.40; C^4 105.02	110.7
2, $(CD_3)_2SO$	CH_2-α, 1.51–1.62 (m); CH_2-β 1.18–1.32; CH_2-γ, 1.00–1.08 (m); CH_3-δ, 0.81 (t, $^{3}J(H,H) = 7.3$); H^2, H^6, 6.40 (s); H^4, 5.98 (s)	C-α, 19.13 ($^{1}J(^{13}C–^{119/117}Sn) = 505.5/482.8$); C-β, 27.61; C-γ, 26.60 ($^{3}J(^{13}C–^{119/117}Sn) = 80.9$); C-δ, 13.60; (COO), 168.39; C^3, C^5 149.13; C^1 131.67; C^2, C^6 104.06; C^4 103.51	
3, CD_3COCD_3	CH_2-α, 1.63–1.71 (m); CH_2-β+CH_2-γ, 1.28–1.38 (m); CH_3-δ, 0.66 (t, $^{3}J(H,H) = 7.3$); $H^{2'}$, $H^{6'}$, 7.83 (m, $^{3}J(H^{2'},H^{3'}) = 9.4$); H^6, 7.68 (d $^{3}J(H^5,H^6) = 7.6$); H^3, 7.52 (d, $^{3}J(H^3,H^4) = 7.7$); H^4, 7.48 (dt, $^{3}J(H^4,H^5) = 7.6$, $^{4}J(H^4,H^6) = 1.5$), H^5, 7.39 (dt, $^{4}J(H^3,H^5) = 1.5$); $H^{3'}$, $H^{5'}$, 6.83 (m, $^{3}J(H^{5'},H^{6'}) = 9.4$); CH_3, 3.08 (s)	C-α, 16.5 ($^{1}J(^{13}C–^{119/117}Sn) = 390.7/373.6$); C-β, 27.55 ($^{2}J(^{13}C–^{119/117}Sn) = 24.3$); C-γ, 26.59 ($^{3}J(^{13}C–^{119/117}Sn) = 70.2$); C-δ, 12.86; (COO) 172.09; C^2 152.53; $C^{4'}$ 151.50; $C^{1'}$ 143.58; C^1 133.19; C^4 129.65; C^6 128.76; C^5 127.87; $C^{2'}$, $C^{6'}$ 124.82; C^3 116.86; $C^{3'}$, $C^{5'}$ 111.04; CH_3 39.20	77.9
4, $CDCl_3$	H^o, 7.76–7.83 (m, $^{3}J(^{1}H–^{119/117}Sn) = 62.1$); H^m, H^p, 7.40–7.50 (m); H^2, H^6 6.88 (d, $^{4}J(H^2,H^6) = 2.0$); H^4 6.09 (t); 3,5-NH_2– 3.59 (s)	C^i 140.69; C^o, 137.65, ($^{2}J(^{13}C–^{119/117}Sn = 47.5$); C^m,128.82 ($^{3}J(^{13}C–^{119/117}Sn) = 63.5$); C^p, 130.02 ($^{4}J(^{13}C–^{119/117}Sn) = 13.2$); (COO) 173.21; C^3, C^5 147.33; C^1 132.13; C^2, C^6 107.91; C^4 105.56	− 112.0



The ^{1}H NMR data of complexes **1**–**4** are given in Table 3. The proton chemical shifts of the $Sn(C_4H_9)_3$ moiety are similar to those of other $[Sn(C_4H_9)_3X]$ complexes [7,28–32]. All CH_2 signals of n-butyl groups are multiplets both in $CDCl_3$ and $(CD_3)_2SO$, therefore the determination of $^{n}J(^{119/117}Sn-^{1}H)$ coupling constants was not possible. The ^{1}H chemical shift of the phenyl and carboxylato ligands were deduced from resonance intensities and $^{n}J(^{1}H-^{1}H)$ and $^{n}J(^{119/117}Sn-^{1}H)$ coupling constants. Both chemical shifts and coupling constants for complexes **1**–**4** agree well with data found for $[Sn(C_4H_9)_3(OOCR)]$, $[Sn(C_6H_5)_3(OOCC_6H_5)]$ [7,28–32], $[Sn(C_6H_5)_3(OOCC_6H_4NH_2)]$ and other triphenyltin(IV) compounds [30–32] and with spectra of 3,4-diaminobenzoic and 2-(4-dimethylaminophenylazo)benzoic acids and their metal salts. The ^{119}Sn chemical shifts are higher for four-coordinate compounds than for the five-coordinate complexes. They depend strongly also on the number and nature of alkyl or aryl groups as well as on electronegativity of inorganic ligand coordinated with tin central atom. The values of the $\delta(^{119}Sn)$ for the complexes **1**, **2** and **4** in $CDCl_3$ are 104.4, 110.7 and −112.0 ppm respectively and for compound **3** in $(CD_3)_2CO$, 77.9 ppm. They are in the range found for $[Sn(C_4H_9)_3(OOCR)]$ and $Sn(C_6H_5)_3(OOCR)]$ complexes. The higher values of the $\delta(^{119}Sn)$ for complexes **1** and **2** in comparison with that for compound **3** indicate that electronegativity of 3,4-diaminobenzoate and 3,5-diaminobenzoate ligands is higher than that of 2-(4-dimethylaminophenylazo)benzoate. The assignment of the ^{13}C resonances of the tri-n-butyl part follows from the $^{n}J(^{119/117}Sn-^{3}C)$ coupling constants and the aromatic resonances of triphenyltin moiety from both the $^{n}J(^{119/117}Sn-^{13}C)$ coupling constants and signal intensities. It is known that $^{n}J(^{119/117}Sn-^{13}C)$ coupling constants depend on properties of ligands in organotin compounds and increase with increasing of coordination number of tin atom [29–32]. They decrease in the order: $^{1}J(^{119/117}Sn-^{13}C) \gg {}^{3}J(^{119/117}Sn-^{13}C) > {}^{2}J(^{119/117}Sn-^{13}$ 13C) and are considerably larger for phenyl tin compounds than for alkyltin complexes. The values of the $^{1}J(^{119/117}Sn-^{13}C)$ coupling constants for complexes **1** and **2** in chloroform (358.9 and 361.5 Hz) indicate that in chloroform these compounds are monomeric with four-coordinate tetrahedral tin atom. The $^{1}J(^{119/117}Sn-^{13}C)$ coupling constant for compound **3** in $(CD_3)_2CO$ is equal to 390.7 Hz. Thus, it is greater by about 30 Hz than the $^{1}J(^{119/117}Sn-^{13}C)$ constants for complexes **1** and **2** in chloroform. This indicates that C–Sn–C angle in complex **3** in acetone is greater by 3–4° than that in complexes **1** and **2** in $CDCl_3$. Therefore interaction of acetone with complex **3** is weak. Strong coordination of solvent molecule with tin leads to considerably larger enhancement of the $^{1}J(^{119/117}Sn-^{13}C)$. Thus the $^{1}J(^{119/117}Sn-^{13}C)$ coupling constants for complexes **1** and **2** in $(CD_3)_2SO$ (496.9 and 505.5 Hz) are typical of the five-coordinate organotin compounds with trigonal-bipyramidal structure [29–32]. The estimated C–Sn–C angles for **1** and **2** in DMSO are approximately 118 and 119°, respectively.

Table 4
Inhibition doses ID_{50} of complexes **1**–**4** against A549 cancer cells

Compound	ID_{50} (μmol dm^{-3})	Compound	ID_{50} (μmol dm^{-3})
1	0.25	$HOOCC_6H_4N{=}NC_6H_4NMe_2$-4	84.29
2	0.57	$HOOCC_6H_3(NH_2)_2$-3,4	i.
3	1.80	$HOOCC_6H_3(NH_2)_2$-3,5	i.
4	0.30		

i., inactive.

The complexes **1**, **2**, **3** and **4** belong to the very efficient cytostatic agents (Table 4). Compounds are very active against A547 cells ($ID_{50} = 0.25–1.80$ μmol dm^{-3}). Activity of the compounds against this cell line decreases in the series $\mathbf{1} \geq \mathbf{4} \geq \mathbf{2} > \mathbf{3}$. It is noteworthy that the complexes are active in ethanol solutions. Thus these compounds are promising cytostatic agents in vitro.

4. Supplementary material

Crystallographic data (excluding structure factors) for the structural analysis have been deposited with the Cambridge Crystallographic Data Centre, CCDC No. 204437. 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 www: http://www.ccdc.cam.ac.uk).

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