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Cyclic Trinuclear Diorganotin(IV) Complexes – The First Tin Compounds Bearing Oximehydroxamate Ligands: Synthesis, Structural Characterization and High In Vitro Cytotoxicity

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The reactions between equimolar amounts of R_2SnO (R = Me **1**, *n*Bu **2**) and *N*,2-dihydroxy-5-[*N*-hydroxyethanimidoyl]-benzamide (H_2L) under solvent reflux conditions (in toluene for **1** and methanol for **2**) for ca. 4 h led to the formation of the trinuclear tin complexes $[R_2Sn(L)]_3$ (R = Me **3**, *n*Bu **4**) isolated as colourless crystalline solids in ca. 85 % yield, which were characterized by IR, ^1H, ^{13}C and ^{119}Sn NMR spectroscopy, elemental analysis and (for **4**) by X-ray diffraction. The trinuclear Sn core is stabilized by multiple intramolecular hydrogen bonding interactions involving the hydroxamate ligands, whereas the uncoordinated oxime functions interact through intermolecular H-bonds leading to cyclic hexameric assemblies. These complexes are stable in air, soluble in common solvents and moderately in water and represent the first examples of tin species containing ligated oximehydroxamic acids. Complex **4** exhibits high in vitro tumour-inhibiting activity against the following human cell lines: promyelocyticfina leukemia (HL-60), hepatocellular carcinoma (Bel-7402), gastric carcinoma (BGC-823) and nasopharyngeal carcinoma (KB).

Introduction

Organotin(IV) complexes have drawn much attention owing to their bioactivities, in particular as potential biocidal (e.g., antimicrobial, antifungal)[1] and anticancer agents.[2] Among main-group metal compounds, they appear to exhibit the most potent antitumour activities, in some cases being more effective than cisplatin in in vitro tests.[3] Within the known cytotoxic organotin(IV) complexes, those with biologically active ligands, for example, carboxylates[4,5] or hydroxamic acids,[6,7] have attracted particular interest.

In general, the biological activity of organotin compounds is greatly influenced by the structure of the molecule and conceivably by the nuclearity of the complexes.[8] Hydroxamic acids constitute an important class of polydentate ligands with a versatile biological activity and various known binding modes.[9] In contrast, the properties of the tin(IV) centre allow stabilization of a variety of structural motifs depending on the nature of the hydroxamate ligand and the tin/hydroxamate ratio.[10]

Synthesis, structural elucidation and cytotoxicity studies of various organotin(IV) derivatives bearing hydroxamic acids were studied in recent years by us[6,7] and others.[11] Within these studies, the hydroxamic acids typically furnished metal complexes with low solubility in water, and no examples of complexation to Sn^{IV} of polyfunctional species of the oximehydroxamate-type were reported up to date, although complexes of the latter with other metals are known to possess water affinity.[12] Moreover, the vast majority of the studied Sn complexes are mononuclear, although tetranuclear or polymeric species have also been investigated, but no examples of the trinuclear organotin–hydroxamates have been reported. Polynuclear organotin(IV) species may exhibit higher antitumour activity than related mononuclear compounds.[7] Hence, the synthesis of polynuclear Sn^{IV} complexes, preferably with a different nuclearity from those previously studied, bearing oximehydroxamate ligands and with potential anticancer activity, constitutes a main objective of the current work.

For this purpose, we focused our attention on the first aromatic oximehydroxamic acid (H_2L, Figure 1), containing an incorporated HO moiety in the aromatic ring, which we recently prepared and employed as a nucleophile towards metal-bound organonitriles, leading to a novel type of imine complexes.[13] H_2L displays particularly promising coordinating properties (which have not yet been explored),

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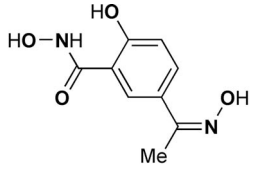
in view of its various potential binding sites (shown in bold at Figure 1), opening a possibility for the formation of metal complexes with different structural motifs and nuclearities. Moreover, the presence of the hydrophilic HON and HO moieties within the molecule may increase the water solubility for the derived complexes. Thus, following our ongoing studies on organotin(IV) species with hydroxamate ligands,[6,7] we decided to explore the coordination properties of this compound and report herein on the preparation, structural characterization and cytotoxicity studies of the first tin complexes containing a ligated oximehydroxamic acid.

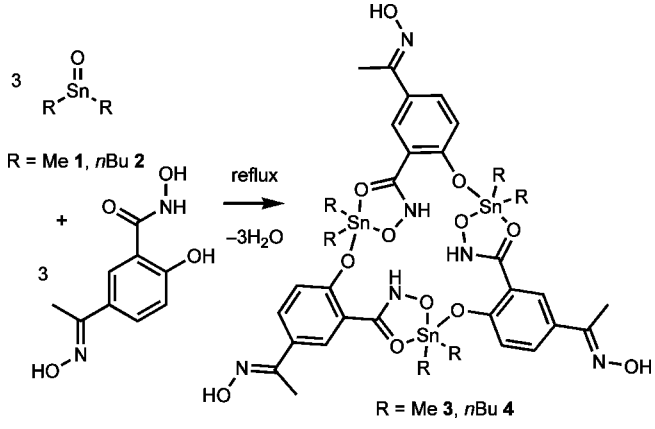


N,2-dihydroxy-5-[*N*-hydroxyethanimidoyl]benzamide

Figure 1. Aromatic oximehydroxamic acid (H_2L); potential binding atoms are indicated in bold.

Results and Discussion

The reactions between equimolar amounts of R_2SnO (R = Me **1**, *n*Bu **2**) and *N*,2-dihydroxy-5-[*N*-hydroxyethanimidoyl]benzamide (H_2L), under solvent reflux conditions (in toluene for **1** or methanol for **2**) for ca. 4 h (Scheme 1), led to the formation of colourless crystalline solids that were formulated as the trinuclear tin complexes $[R_2Sn(L)]_3$ (R = Me **3**, *n*Bu **4**) on the basis of single-crystal X-ray diffraction analysis (for **4**), IR, ^1H, ^{13}C and ^{119}Sn NMR spectroscopic data, and elemental analyses. They were isolated by filtration in ca. 80% yield.



Scheme 1.

Complexes **3** and **4** are stable in air, soluble in chloroform, dichloromethane, alcohols and Me_2SO and slightly in water. Their IR spectra show evidence for the coordination of the ligand through both oxygen atoms of the $CONHO^-$ moiety and for the deprotonation (and thus eventual ligation to Sn) of the hydroxy substituent of the phenyl ring. In fact, ligation through the carbonyl oxygen atom is indicated by the ν(C=O) shift to a lower frequency, that is, from 1676 cm^{-1} in the free species to ca. 1610 cm^{-1} in the chelated one, and there is no evidence for the ν(O–H) bands, which appeared in the 3340–3079 cm^{-1} range in free H_2L. The ^1H NMR spectra for complexes **3** and **4** display the expected two sets of peaks, one including the signals of all the aliphatic protons [C=N*Me* moieties as well as the methyl (in **3**) or butyl (in **4**) groups] and another one, in the 6.50–8.12 ppm range, involving the aromatic protons. For both complexes, $|^3J(^{119}Sn,^1H)|$ tin–proton coupling interactions were observed [60.6 Hz (**3**) and 53.7 (**4**)]. Additionally, the values of $|^2J(^{119}Sn,^1H)|$ [75.0 Hz in CD_2Cl_2] for complex **3** and $|^1J(^{119}Sn,^{13}C)|$ [586.0 Hz in CD_2Cl_2] for complex **4** enabled the estimate of the values of the θ(C–Sn–C) angles for these compounds on eth basis of Equations (1)[14] and (2), respectively.[15] The obtained values (125° for **3** and 128° for **4** in the noncoordinating CD_2Cl_2 solvent) are compatible with a distorted trigonal-bipyramidal structure [θ commonly in the 115–130° range for pentacoordinate dimethyltin(IV) complexes].[15,16]

$$\theta(\text{C–Sn–C}) = 0.0161(|^2J(^{119}Sn,^1H)|)^2 - 1.32(|^2J(^{119}Sn,^1H)|) + 133.4 \quad (1)$$

$$\theta(\text{C–Sn–C}) = [|^1J(^{119}Sn,^{13}C)| + 875]/11.4 \quad (2)$$

The ^{13}C NMR resonances appear at their usual positions and agree with the proposed structures of **3** and **4**. The single resonance in the $^{119}Sn\{^1H\}$ NMR spectra indicates the presence of tin atoms with similar coordination environments. The ^{119}Sn chemical shifts [–98 ppm for **3** and –137 ppm for **4** in CD_2Cl_2] fall well within the range reported for five-coordinate tin compounds.[14,15] The molecular structure of the complex $[nBu_2Sn(L)]_3$ (**4**) was authenticated by single-crystal diffraction analysis and is given in Figure 2. Selected bond lengths and angles (for the Sn1 metal centre) are listed in Table 1 and relevant hydrogen bond lengths are provided in Table 2.

In the crystal structure of **4**, the coordination sphere of each tin atom is formed by two butyl groups and three oxygen atoms from two chelated oximehydroxamate ligands, therefore adopting a highly distorted trigonal-bipyramidal environment. The C–Sn–C angles of 128.9(3), 131.1(3) and 135.4(3)° are comparable with the values estimated above. An important distortion of this structure is evidenced by the asymmetry in the Sn–O bonds distances: in each metallacycle, one of the Sn–O bonds [2.050(4)–2.060(4) Å] is shorter than the other one [2.172(3)–2.197(3) Å] and both define a small O–Sn–O angle of ca. 75°, which is close to those reported in other cases;[14,15] the remaining Sn–O distance (involving the deprotonated hydroxy group from a vicinal oximehydroxamate moiety) has an intermediate value [2.093(3)–2.104(3) Å]. Each metal chelate ring is described by a plane containing the tin atom and the O–N–C–O moiety; in each case this group of atoms does not deviate significantly from planarity. However, the planes are twisted relative to one another as indicated by the dihedral angles of 33.02(22), 16.18(17) and 45.47(23)° formed by the Sn1/

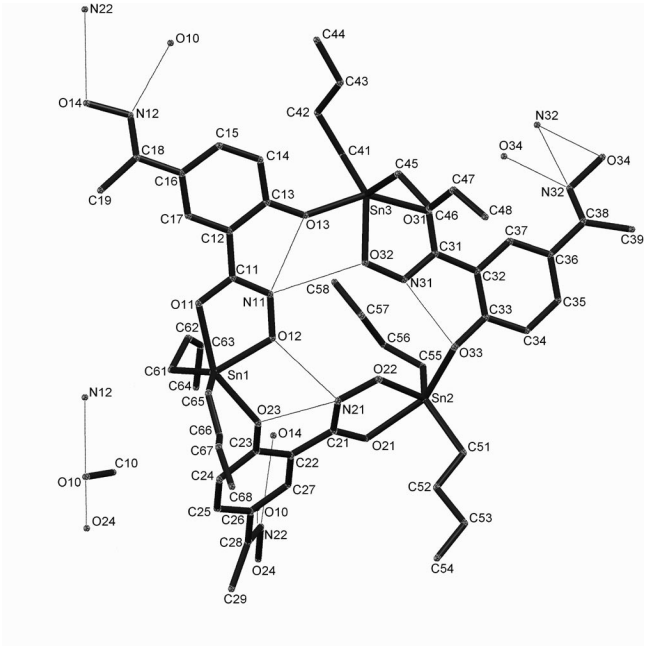


Figure 2. Molecular structure of $[n\text{Bu}_2\text{Sn(L)}]_3$ (**4**) with crystallographic numbering.

Table 1. Selected bond lengths [Å] and angles [°] for compound **4**.

Sn1–O11	2.197(3)	N11–C11	1.303(7)
Sn1–O12	2.050(4)	O11–Sn1–O23	152.18(13)
Sn1–O23	2.104(3)	O12–Sn1–O23	76.64(13)
Sn1–C65	2.098(7)	C61–Sn1–C65	135.4(32)
O11–C11	1.274(6)	O12–Sn1–C61	113.3(2)
O12–N11	1.378(5)	O12–Sn1–C65	110.6(3)

Table 2. Hydrogen bond geometry in **4**.[a]

Intramolecular hydrogen bonding interactions			
D–H···A	H···A	D···A	D–H···A
N11–H11···O13	1.92	2.598(5)	133
N11–H11···O32	2.23	3.044(6)	154
N21–H21···O12	2.22	2.969(6)	143
N21–H21···O23	1.96	2.635(5)	133
N31–H31···O33	1.92	2.611(6)	134
Intermolecular hydrogen bonding interactions			
O10–H10···N12^{i}	1.89	2.718(6)	171
O14–H14A···N22^{ii}	1.99	2.819(6)	171
O24–H24A···O10^{iii}	1.92	2.675(6)	149
O34–H34A···N32^{iv}	2.10	2.790(7)	139

[a] Symmetry transformation used to generate equivalent atoms: (*i*) 1 – *x*, *y*, 3/2 – *z*; (*ii*) 1 – *x*, –1 + *y*, 3/2 – *z*; (*iii*) *x*, 1 + *y*, *z*; (*iv*) 3/2 – *x*, 5/2 – *y*, 2 – *z*.

Sn2, Sn2/Sn3 and Sn1/Sn3 metal rings least-squared planes, respectively. The distance between two adjacent tin atoms in the molecule is in the 6.817–7.022 Å range, whereas the nearest Sn···Sn intermolecular separation is 12.206 Å.

Extensive intra- and intermolecular hydrogen bonds were detected. The former involve the hydroxamate and the deprotonated hydroxy substituents of the phenyl ring, whereas the latter concern the noncoordinated oxime functions and lead to hexameric ring assemblies (Figures 2 and 3; Table 2). These H-bonds provide further stabilizations of the structure.

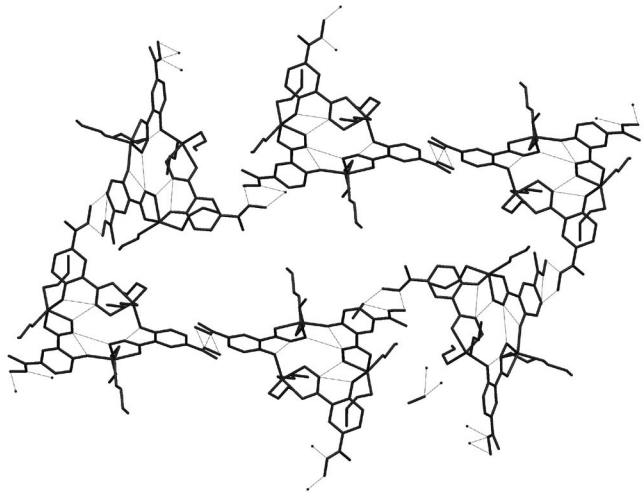


Figure 3. Intra- and intermolecular hydrogen bonding interactions for $[n\text{Bu}_2\text{Sn(L)}]_3$ (**4**).

Trinuclear compound **4** was screened (at three different concentrations) for the in vitro tumour-inhibiting activity against four different cell lines: a human promyelocyticfina leukemic cell line (HL-60), a human hepatocellular carcinoma cell line (Bel-7402), a human gastric carcinoma cell line (BGC-823) and a human nasopharyngeal carcinoma (KB). The inhibitory concentration IC_{50} has also been assayed. The results, summarized in Table 3, show that complex **4** exhibits strong in vitro activity towards all the tested tumour cells, which can be even higher than that of the clinically used bench-drug cisplatin. They are also more active than mononuclear (hydroxamato)organotin complexes.[7]

Table 3. Inhibition [%] of **4** against various human tumour cell lines.[a]

Tumour cell line	Dosage [μM]	Inhibition [%]	IC_{50}
HL-60	0.1	–10.53	+++
	1	86.23	
	10	**91.53**	
BGC-823	0.1	34.97	+++
	1	93.98	
	10	**96.68**	
BEL-7402	0.1	–0.21	+++
	1	82.38	
	10	**96.50**	
KB	0.1	28.84	+++
	1	**96.88**	
	10	96.57	

[a] IC_{50} (half maximal inhibitory concentration); $IC_{50} > 1 \times 10^{-4}$ M (–, inactivity); $IC_{50} \leq 1 \times 10^{-4}$ M (+, weak activity); $IC_{50} \leq 1 \times 10^{-5}$ M (++, medium activity); $IC_{50} \leq 1 \times 10^{-6}$ M (+++, strong activity). For cisplatin, the IC_{50} values for the four cell lines are ++.[7]

Conclusions

The first tin complexes containing an oximehydroxamate ligand were easily prepared by reaction of the correspond-

ing dialkyltin(IV) oxides with an oximebenzohydroxamic acid containing a hydroxy substituent in the *ortho* position relative to the chelating hydroxamic functionality. Such a hydroxy group readily deprotonates and binds to another Sn atom, leading to the formation of an unusual trinuclear triangular assembly with deprotonated hydroxobenzohydroxamate bridges. The oxime functionality remains uncoordinated but allows the formation, in the solid state, of intermolecular H-bonds that lead to uncommon cyclic hexameric assemblies of the trinuclear molecules. The availability of the three oxime groups of each $[R_2Sn(L)]_3$ molecule for coordination deserves to be explored towards the synthesis of higher nuclearity frameworks.

Moreover, such multinuclear complexes, with (arylhydroxamato)Sn^{IV} centres and oxime functions, also display a high in vitro activity against various tumour cell lines, what can be favoured by their multinuclear character, thus presenting a few Sn centres available for binding to DNA.[7] Their air stability and moderate solubility in water are also favourable properties, and the compounds appear to be promising for further in vivo tests, which are being planned.

Experimental Section

General: All experiments were carried out in flame-dried glassware under a nitrogen atmosphere by using inert gas flow and high-vacuum-line techniques. All reagents were obtained from commercial sources and used as received, whereas methanol and toluene were purified by conventional distillation over magnesium powder and sodium/benzophenone, respectively. *N*,2-Dihydroxy-5-[*N*-hydroxyethanimidoyl]benzamide was prepared as previously reported.[13] C, H and N elemental analyses were carried out by the Microanalytical Service of the Instituto Superior Técnico. ESI^+ mass spectra were obtained with a Varian 500-MS LC ion trap mass spectrometer. Infrared spectra (4000–400 cm^{-1}) were recorded with a Biorad FTS 3000MX instrument in KBr pellets. 1D [^1H, $^{13}C(^1H)$, ^{119}Sn] and 2D NOESY NMR spectra were recorded with Bruker Avance II+ 400 MHz (UltraShield Magnet) and Bruker Avance II+ 500 MHz (UltraShield Plus Magnet) spectrometers at ambient temperature. ^1H and ^{13}C chemical shifts (δ) are expressed in ppm relative to Me_4Si, whereas ^{119}Sn nuclei were referenced to external Me_4Sn in $CDCl_3$; all coupling constants (J) are in Hz. Labelling of the corresponding nuclei in **3** and **4** is given in Figure 4.

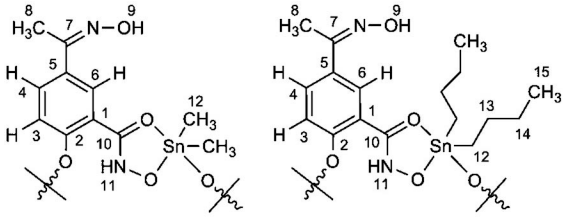


Figure 4. Labelling scheme for complexes **3** (left) and **4** (right).

Reaction of Me_2SnO with *N*,2-Dihydroxy-5-[*N*-hydroxyethanimidoyl]benzamide: A mixture of dimethyltin(IV) oxide (0.065 g, 0.39 mmol) and *N*,2-dihydroxy-5-[*N*-hydroxyethanimidoyl]benzamide (0.082 g, 0.39 mmol) in toluene (20 mL) was heated at reflux under an atmosphere of nitrogen for 4 h. The colourless precipitate formed (complex **3**) was filtered off, washed with toluene (2 × 3 mL) and dried under vacuum. An additional amount of **3** was obtained upon evaporation of the mother solution to ca. 1/4 of its initial volume followed by slow evaporation of the resulting solution in air for ca. 2 d and was isolated and treated in the same way as above. Total yield: 107 mg (77% based on Sn). $C_{33}H_{42}N_6O_{12}Sn_3$ (1070.85): calcd. C 37.01, H 3.95, N 7.85; found C 36.91, H 3.85, N 7.72. IR (KBr): $\tilde{\nu}$ = 3484 [mw, br., ν(O–H)], 3194 [m, ν(N–H)], 2968 (w), 2921 [w, $\nu_{as+sym}(CH_3)$], 1609 (vs), 1570 (m), 1504 (s), 1312 [s, ν(C=O)/ν(C=N)], 630 (m), 587 [mw, ν(Sn–C)], 474 [mw, ν(Sn–O)] cm^{-1}. ^1H NMR (400.13 MHz, CD_2Cl_2): Sn–*Me*: δ = 0.89 [s, $^2J(^{119}Sn,^1H)$ = 75 Hz, 6 H, H^{12}] ppm; *Ligand skeleton*: δ = 2.25 (s, 3 H, H^8), 6.56 [d, $^3J(H^3H^4)$ = 8.4 Hz, 1 H, H^3], 7.45 (s, 1 H, H^9), 7.64 [dd, $^3J(H^4H^3)$ = 8.5 Hz, $^4J(H^4H^6)$ = 2.4 Hz, 1 H, H^4], 8.12 [d, $^4J(H^4H^6)$ = 2.4 Hz, 1 H, H^6], 13.52 [s, $^3J(^{119}Sn,^1H)$ = 60.6 Hz, 1 H, H^{11}] ppm. $^{13}C\{^1H\}$ NMR (100.613 MHz, CD_2Cl_2): Sn–*Me*: δ = 2.0 (C^{12}) ppm; *Ligand skeleton*: δ = 11.4 (C^8), 115.8, 119.8, 125.8, 127.4, 130.8 (C^1–C^6), 155.3 (C^7), 163.1, 163.2 (C^{10}) ppm. ^{119}Sn NMR (149.211 MHz, CD_2Cl_2): δ = –98 ppm.

Reaction of nBu_2SnO with *N*,2-Dihydroxy-5-[*N*-hydroxyethanimidoyl]benzamide: Dibutyltin(IV) oxide (0.177 g, 0.71 mmol) was added to a methanol solution (20 mL) of *N*,2-Dihydroxy-5-[*N*-hydroxyethanimidoyl]benzamide (0.149 g, 0.71 mmol), and the mixture was heated at reflux for ca. 4 h under an atmosphere of nitrogen. The solvent was evaporated to ca. 1/4 of its initial volume and left to stand in a freezer (at ca. –18 °C) for a few days. The colourless crystalline product formed (**4**) was filtered off and dried under vacuum. Yield: 260 mg (81% based on Sn). $C_{51}H_{78}N_6O_{12}Sn_3{\cdot}(CH_3OH)$ (1355.37): calcd. C 46.08, H 6.10, N 6.20; found C 46.08, H 6.44, N 6.24. IR (KBr): $\tilde{\nu}$ = 3429 [mw, br., ν(O–H)], 3204 [m, ν(N–H)], 2956, 2925 (m), 2860 [mw, $\nu_{as+sym}(CH_3, CH_2)$], 1608 (vs.), 1569 (s), 1501 (s) and 1311 [s, ν(C=O)/ν(C=N)], 688 (s), 531 [mw, ν(Sn–C)], 551 (s), 469 [w, ν(Sn–O)] cm^{-1}. ^1H NMR (400.13 MHz, CD_2Cl_2): Sn–*nBu skeleton*: δ = 0.87 [t, $^3J(H^{15}H^{14})$ = 7.0 Hz, 6 H, H^{15}], 1.36–1.51 (m, 4 H, H^{14}), 1.54–1.61 (m, 4 H, H^{13}), 1.64–1.75 (m, 4 H, H^{12}); *Ligand skeleton*: δ = 2.23 (s, 3 H, H^8), 6.59 [d, $^3J(H^3H^4)$ = 8.0 Hz, 1 H, H^3], 8.15 (s, 1 H, H^9), 7.66 [d, $^3J(H^4H^3)$ = 8.0 Hz, 1 H, H^4], 8.77 (s, 1 H, H^6), 13.52 [s, $^3J(^{119}Sn,^1H)$ = 53.7 Hz, 1 H, H^{11}] ppm. $^{13}C\{^1H\}$ NMR (100.613 MHz, CD_2Cl_2): Sn–*nBu skeleton*: δ = 13.7 (C^{15}), 23.2 [$^1J(^{119/117}Sn,^{13}C)$ = 586.0/560.3 Hz, C^{12}], 26.8 [$^3J(^{119}Sn,^{13}C)$ = 85.9 Hz, C^{14}], 27.0 [$^2J(^{119}Sn,^{13}C)$ = 35.0 Hz, C^{13}]; *Ligand skeleton*: δ = 12.0 (C^8), 116.1, 120.1, 125.7, 127.8, 130.9 (C^1–C^6), 155.3 (C^7), 163.5, 164.1 [$^3J(^{119}Sn,^{13}C)$ = 67.3 Hz, $^2J(^{119}Sn,^{13}C)$ = 24.0 Hz, C^{10}] ppm. ^{119}Sn NMR (149.211 MHz, CD_2Cl_2): δ = –137 ppm.

X-ray Structure Determinations: Intensity data from very poor quality crystals of compound **4** were collected at 150 K using a Bruker AXS KAPPA APEX II diffractometer with graphite monochromated Mo-K_α radiation. ω scans of 0.5° per frame were used and a full sphere of data was obtained. Cell parameters were retrieved using Bruker SMART software and refined using Bruker SAINT[16] on all the observed reflections. Absorption corrections were applied using SADABS.[16] Structures were solved by direct methods by using the SHELXS-97 package[17] and refined with SHELXL-97.[18] Calculations were performed using the WinGX System-Version 1.80.03.[19] All hydrogen atoms were inserted in calculated positions. Least-square refinements with anisotropic thermal motion parameters for all non-hydrogen atoms and isotropic for the remaining atoms were employed. Moreover, there is disordered solvent in the structure. PLATON/SQUEEZE[20] was used to correct the data. CCDC-729868 contains the supplementary crystallographic data for this paper. These data can be obtained free

of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Antitumour Activity In Vitro: The cell lines, human promyelocyticfina leukemic cell line (HL-60), human hepatocellular carcinoma cell line (BEL-7402), human gastric carcinoma cell line (BGC-823) and human nasopharyngeal carcinoma (KB) were used for screening. All cell lines were grown and maintained in RPMI-1640 medium supplemented with 10% fetal bovine serum, penicillin (100 U mL^{-1}), and streptomycin (100 μg mL^{-1}) at 37 °C in humidified incubators in an atmosphere of 5% CO_2. Cell proliferation in compound-treated cultures was evaluated by using a system based on the tetrazolium compound (MTT)[21] and sulforhodamine B (SRB) methods[21] in the State Key Laboratory of Natural and Biomimetric Drugs, Beijing Medical University (China). All cell lines were seeded into 96 well plates at a concentration of about 50 000 cells/mL and were incubated in an atmosphere of 5% CO_2 for 24 h. Then, 20 μL of the sample (organotin complex) solution were added and further incubation was carried out at 37 °C for 48 h. The compounds were serially diluted (in four to six steps) with DMSO and added to cell incubation medium at the final concentration of 1.0% DMSO in the medium. 50 μL of 0.1% MTT or SRB (Sigma) was added to each well. After 4 h incubation, the culture medium was removed, and 150 μL of 2-propanol was added to dissolve the insoluble blue formazan precipitates produced by MTT reduction. The plate was shaken for 20 min on a plate shaker to ensure complete dissolution. The optical density of each well was measured at 570 nm (MTT) or 540 nm (SRB) wavelength. The antitumour activity was determined three times in independent experiments, using three replicate wells per toxicant concentration (10, 1, 0.1 μM) and obtained the mean optical densities for drug-treated cells at each concentration as a percentage of that of untreated cells.

Acknowledgments

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