APPLIED ORGANOMETALLIC CHEMISTRY
Appl. Organometal. Chem. 2005; **19**: 132–139

In vivo toxicological effects and spectral studies of organotin(IV) *N*-maleoylglycinates

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On initial publication GJ Peters was included as an author in error. His details have been removed from this PDF file. See Erratum in Appl. Organometal. Chem. 2007; 21(8) DOI: 10.1002/aoc.1208

Received 4 July 2004; Revised 15 July 2004; Accepted 29 August 2004

Synthesis, characterization and *in vivo* anti-tumour effects of a series of organotin(IV) derivatives of *N*-maleoylglycine are reported. The ligand molecule appear to be bound to the tin atoms through the carboxyl oxygen atom. Since the compounds were not obtained as single crystals, various experimental techniques were used to characterize them and determine their structures. The results obtained by multinuclear magnetic resonance (^{1}H, ^{13}C and ^{119}Sn), fourier transform IR and ^{119m}Sn Mössbauer spectroscopy and mass spectrometric analyses suggest a hexacoordination for the diorganotin(IV) carboxylates. The triorganotin(IV) carboxylates exist as pentacoordinated trigonal bipyramidal complexes in the solid state and tetrahedral ones in solution. *In vivo* toxicity profiles in mice and antitumour activities in tumour-bearing (colon 26A) mice were obtained for the title organotin(IV) carboxylates synthesized. At their maximum tolerated doses, no antitumour effect was observed for compounds 1, 2, 5 and 6; however, compounds 3 and 4 showed antitumour activity after single dose administration. Copyright © 2004 John Wiley & Sons, Ltd.

KEYWORDS: organotin(IV) carboxylates; *in vivo* cytotoxicity

INTRODUCTION

In the last two decades, bioorganotin chemistry has developed a great deal due to the fact that certain organotin(IV) compounds in general, and organotin(IV) carboxylates in particular, play an important role in anticarcinogenesis.[1–5] In addition, organotins have been extensively investigated as wood preservatives, fungicides, agrochemical miticides and fungicides, biocides and environmental disinfectants and as additives in the production of ship hulls (antifouling paints).[6–10] Owing to their high biological activity, there is relatively little information available on organotin compounds as anticancer agents *in vivo*. The diorganotins represent the largest group of tin compounds to have been extensively examined for cytotoxicity *in vitro*; however, they are, in general, less toxic than platinum complexes.[11,12] Literature reveals that hydrolysable organotin(IV) carboxylates significantly retard tumour growth and the non-hydrolysable forms show no activity.[13] It has also been proposed that their mode of action might involve the initial transportation of the complex [$R'_2SnCl_2 \cdot 2L$] into the tumourigenic cells followed by the reaction of [R'_2SnCl_2] or one of its hydrolysed products. A moderately stable complex is required for the antitumour activity of [R'_2SnR_2] and [$R'_2Sn(OOCR)_2$] complexes and lastly transportation of the complex into the tumour cells, followed by the attack of (hydrolysed) R'_2Sn moieties.[14,15]

The choice of such a ligand was made first because it is a bioactive molecule and second in order to increase the hydrolysability of the organotin(IV) precursors due to formation of the Sn–O bonds, thus permitting the attack of the hydrolysed R'_2Sn/R'_3Sn moieties on the tumour cells, leading to an antitumour activity perhaps comparable to that of platinum compounds. On these bases, this work reports the interaction of organometallic derivatives of tin(IV) with *N*-maleoylglycine. The characterization of the compounds synthesized has been carried out by means of ^{1}H, ^{13}C, ^{119}Sn NMR, fourier transform IR (FT IR) and Mössbauer spectroscopy, as well as the elemental analysis and mass spectrometry (MS) analysis. These complexes have been tested for *in vivo* antitumour activity.

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RESULTS AND DISCUSSION

FT IR spectra

The FT IR data (Table 1) are consistent with the formation of well-defined compounds by means of compositions R'_2SnL_2 and R'_3SnL. The carboxylate group is able to coordinate to the metal in both the solid and in solution for diorganotin(IV) compounds **1**–**3**, whereas coordination is observed only in the solid state for triorganotin(IV) compounds **4**–**6**, as shown in Scheme 1.[16]

(1) When the carboxylic group of the ligand coordinates to the metal in the monodentate mode (Scheme 1(a)), the difference between the asymmetric and symmetric carboxylate stretching bands, $\Delta\nu$ ($= \nu_{as}(COO^-) - \nu_s(COO^-)$) for compounds **4** and **5** is larger than that observed for ionic compounds in non-coordinating solvents.[17,18]

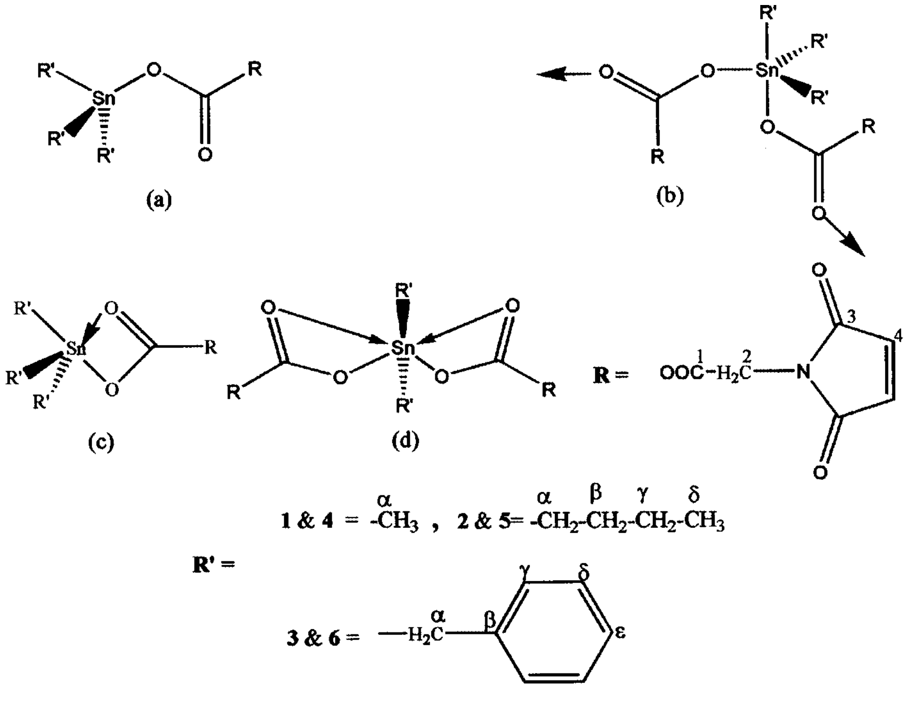
(2) Compound **6** exhibits a five-coordinated chain/polymeric structure in the solid state (Scheme 1(b)); the ligand's carboxylic group bridging two organotin(IV) moieties via oxygen–tin bonds.[19,20] When the ligand chelates (Scheme 1(c)), $\Delta\nu$ is considerably smaller than that for ionic compounds, whereas for the asymmetric bidentate coordination the value is in the range characteristic of bidentate coordination.[21]

(3) The characteristic wavenumber differences $\Delta\nu$ for compounds **1**–**3** are larger than for chelated ions and nearly the same as observed for similar compounds exhibiting octahedral geometry (Scheme 1(d)).[22]

Table 1. Selected IR frequencies (cm^{-1})

Compound	$\nu_{a/s}$(C=O)	ν(C–O)	ν(Sn–C)	ν(Sn–O)	$\Delta\nu$
1	1670/1339	1241	546	526	331
2	1725/1371	1255	548	524	354
3	1732/1365	1247	556	514	367
4	1715/1410	1240	521	513	305
5	1595/1355	1258	529	496	240
6	1600/1410	1251	536	485	210

On the basis of the above results, it was possible to determine the coordination mode of the $[-COO]^-$ group; $\Delta\nu$ values for **4** and **5** were greater than 200 cm^{-1}, characteristic of monodentate coordination, and greater than 300 cm^{-1} for **1**–**3** exhibiting bidentate coordination.[17–20] The –C–H stretching vibrations of the free acid appeared in the region 2900–2600 cm^{-1} and showed no major spectral changes when compared with the organotin compounds. In the spectra of both Bu_2Sn(IV) complexes **2** and **5**, very strong stretching vibrations of the *n*-butyl group, e.g. $\nu_a(CH_3)$ and $\nu_a(CH_2)$, appeared at 2958 and 2927 cm^{-1} wavenumbers and shifted towards high by about 10 cm^{-1}, compared with the lower wavenumber region by corresponding vibrations of free R_2SnO. A strong –C=O stretching vibration of the free ligand was observed in the 1730–1740 cm^{-1} region; after the complexation the ν(C=O) bands shifted to lower frequencies and split into two components. These absorption bands are related to the antisymmetrical and symmetrical stretching vibrations of the $-COO^-$ group. The difference between the two vibrational frequencies were in the range 330–370 cm^{-1}, indicating a bidentate coordination mode of the $-COO^-$ in



Scheme 1.

the solid for diorganotin compounds **1–3**.[23] In the spectra of the free acid, there is very strong ν(C–O(H)) bands at 1283 cm^{-1} and at 1250 cm^{-1}. A change in the electronic system of the COO^- group (deprotonation of the OH group, interaction with the tin atom, formation of an O–Sn bond) is confirmed by the shift of the ν(C–O(H)) and by the change into ν(C–O(Sn)). The ν(C=C) vibrations of the free ligand appeared with no major spectral changes after complexation. The O–Sn bond furnished characteristic vibrational bands in the FT IR spectra.[24, 25]

^{119m}Sn Mössbauer spectra

In the ^{119m}Sn Mössbauer spectra (Table 2) of compounds **1–6**, the isomeric shifts are typical for one tin(IV) site. A slight lowering of the isomeric shift values is observed compared with the organotin precursors owing to a reduction in the tin atom 5s orbital electronic density; this is due to expansion of the coordination sphere changing the atomic hybridization by additionally using the 5d orbital with a reduction in the s-electronic density.[22]

A comparison between the quadrupole splitting data for the organotin(IV) derivatives of *N*-maleoylglycine and those reported in the literature for analogous compounds[14,17,18,22] leads to a conclusion that, in the solid state, compounds **4** and **5** are four-coordinated (Scheme 1(a)) and compounds **1–3** are hexacoordinated (Scheme 1(d)) with organic groups (R′) occupying axial positions. These results are in full agreement with the structural hypothesis based upon the FT IR study.

Table 2. ^{119m}Sn Mössbauer data (mm s^{-1})

Compound	QS	IS	Γ_1	Γ_2	ρ = QS/IS
1	3.36	1.11	1.03	1.14	3.03
2	3.42	1.33	1.24	1.20	2.56
3	3.01	1.52	1.36	1.11	1.99
4	3.68	1.31	0.89	0.85	2.81
5	2.66	1.41	1.33	1.49	2
6	3.08	1.26	0.69	0.95	2.44

Solution studies

In order to determine the structures of the organotin(IV) carboxylates in solution, ^{1}H, ^{13}C, and ^{119}Sn NMR spectra (Tables 3–5) were recorded. The expected NMR resonances are assigned by the multiplicity, intensity and coupling constants patterns. The exhibited $^nJ(^{119}Sn–^{13}C)$ coupling constants in solution are characteristic of octahedral complexes for **1–3**, being of the order of 336, 358 and 387 Hz (Scheme 1(d)); compounds **4–6** gave clear indications of weaker coordination in the solution state (Scheme 1(c)). The *n*-butyl groups covalently attached to tin in compound **2** show the trend $[^1J] >> [^2J] < [^3J]$ and the benzyl group in compound **3** shows the trend $[^1J] >>> [^2J] > [^3J] < [^4J]$; thus, the coupling constants $^nJ(^{119}Sn–^{13}C)$ are characteristic of diorganotin(IV) carboxylates in an octahedral geometry.[26–29] The ^{119}Sn NMR chemical shift values[30] for compounds **4–6** validate the spectroscopic structural elucidation of the title complexes explained so far. The appearance of a single resonance in all the ^{119}Sn NMR spectra of the title complexes confirms the presence of only one type of tin atom and supports our discussion too. Finally, the CHN analyses and MS data corroborated the spectroscopic data discussed so far. The MS data of the compounds **1–6** are fully compatible with the structures proposed (see Experimental section for details).

Antitumour activity

Initial dose-finding studies were performed with groups of two mice, which were treated for 2 weeks by i.p. injection (qd7 × 2). Results are shown in Figs 1–6 for compounds **1–6**. Based on the results obtained in dose-finding studies, a dose was chosen for each compound that was somewhat lower than the maximum tolerated dose (MTD), since experience with previous compounds demonstrated more toxicity in tumour-bearing mice. The expected toxicity should be less than 10%. However, the toxicity in tumour-bearing (colon 26A) Balb/C mice was unexpectedly high, as shown in Figs 7–9. For compounds **3** and **4**, severe toxicities were observed even after one injection. Therefore, administration of a second injection of these compounds was not acceptable. However, for compounds **1**, **2**, **5**, and **6** the mice could be treated twice. To elaborate the dose impact further, the

Table 3. ^{1}H NMR data[a]

Proton	**1**	**2**	**3**	**4**	**5**	**6**
2	4.16	4.19	4.21	4.20	4.18	4.21
4	7.50	7.48	7.51	7.52	7.49	7.47
α	0.4	1.1 t(11)	2.79 s	0.13 s	0.67 t(18)	2.71 s
β	—	1.68 q(5,8)	—	—	1.21 m	—
γ	—	1.41 m	7.02 d(3)	—	2.44 m	7.23 d (3)
δ	—	0.86 t(8)	7.16 t(9)	—	0.85 t (5)	7.36 t(7)
ε	—		7.28 t(18)	—		7.39 t(9)

[a] Solvent: $CDCl_3$; standard: $SiMe_4$ and $SnMe_4$; abbreviations: s: singlet; d: doublet; t: triplet; m: complex pattern; no: not observed; coupling constants are given in hertz in parentheses for $^nJ(^{119}Sn–^{13}C)$.

Table 4. ^{13}C NMR data[a]

Carbon	1	2	3	4	5	6
1	171.3	168.7	172.2	168.5	166.3	162.9
2	46.7	43.6	46.2	45.2	44.8	46.1
3	170.1	168.4	167.4	169.4	169.6	168.5
4	135.8	134.2	133.2	134.8	133.0	136.01
α	4.36 (336)	19.5 (358)	21.2 (387)	0.47 (621)	15.8 (579)	22.52 (415)
β	—	26.9 (33)	141.0 (64)	—	26.0 (46)	139.6 (52)
γ	—	30.1 (96)	128.9 (55)	—	24.4 (89)	132.2 (98)
δ	—	13.4	131 (33)	—	12.45	130.4 (68)
ε	—		126 (39)	—	—	127.3 (101)

[a] Coupling constants in hertz in parentheses for $^{n}J(^{119}\text{Sn}-^{13}\text{C})$.

Table 5. Comparison of different (^{119}Sn) values in di- and tri-organotin compounds **1**–**6** with different coordination numbers

Six-coordinate		Four-coordinate		
Compound	δ (ppm)	Compound	δ (ppm)	Δ[a]
1	−169	**4**	121	290
2	−163.8	**5**	105.82	269.62
3	−129.3	**6**	−98.6	30.7

[a] $\Delta = \delta$ (six-coordinate) $-\delta$ (four-coordinate).

initial slopes of the plots (Figs 1–6) were calculated and scaled with the dose of the compound given. The results so obtained are plotted in Fig. 10 and extrapolated to zero dose value. Thus, we can conclude that the impact goes down with the increase in dose value, and most of the drugs work well up to 7.5 mg kg^{-1}. However, the increase in dose leads either to death of the mice or its positive impact is not up to the expected mark. For example, in the case of compounds **1**, **3** and **4** the dose impact is quite low in the case of 10 mg kg^{-1} compared with 5 or 7.5 mg kg^{-1}.

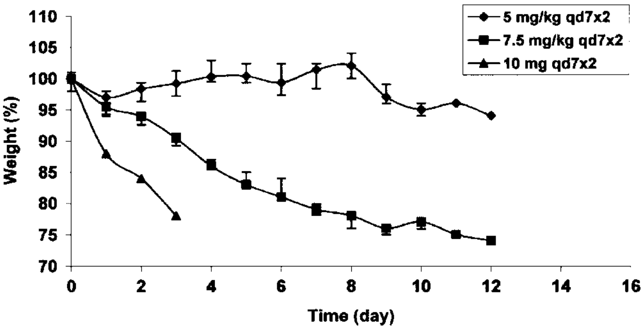


Figure 1. Dose-finding study for compound **1** in Balb/C mice.

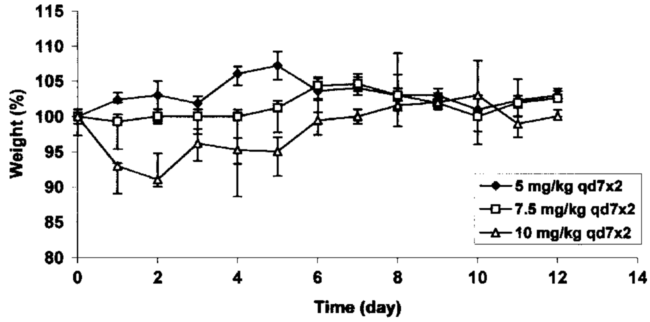


Figure 2. Dose-finding study for compound **2** in Balb/C mice.

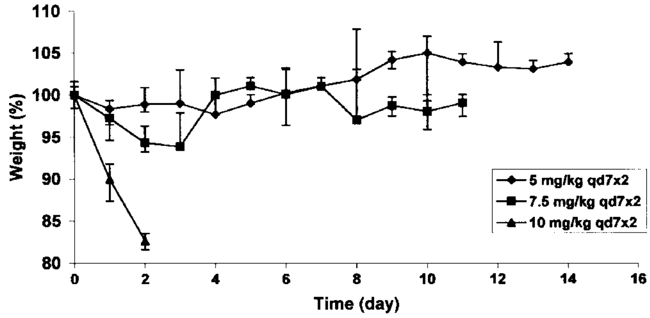


Figure 3. Dose-finding study for compound **3** in Balb/C mice.

In vivo antitumour activity

Although the compounds were too toxic to administer according to the scheduled use in the dose-finding study, conclusions can be drawn on a single dose treatment of the colon26A-bearing mice. The assumption was made that as even at this high dose there is no antitumour activity is present it would be unlikely, therefore, that lower doses at a schedule of qd7 × 2 would be able to produce an antitumour effect.

At their MTD no antitumour effects were seen for **1**, **2**, **5** or **6**, i.e. the $T/C \gtrsim 1$ (Figs 11–13). Compounds **3** and **4** displayed

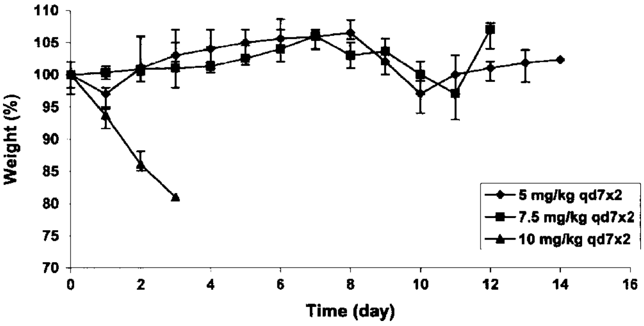


Figure 4. Dose-finding study for compound **4** in Balb/C mice.

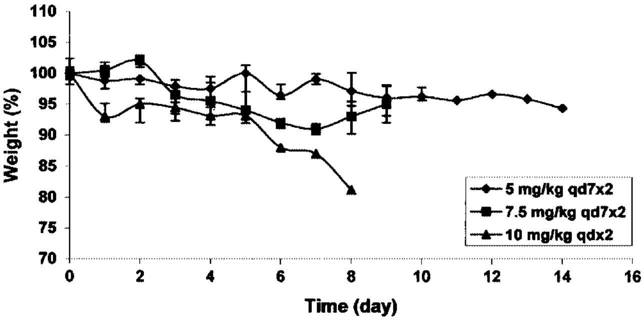


Figure 5. Dose-finding study for compound **5** in Balb/C mice.

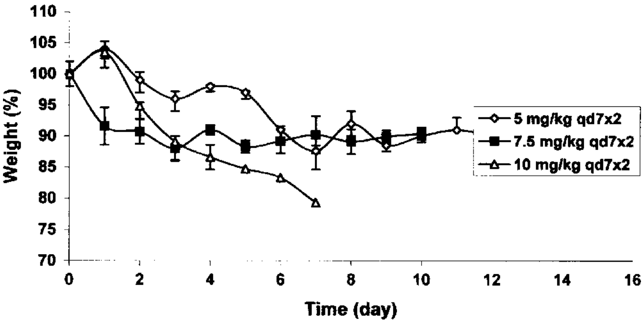


Figure 6. Dose-finding study for compound **6** in Balb/C mice.

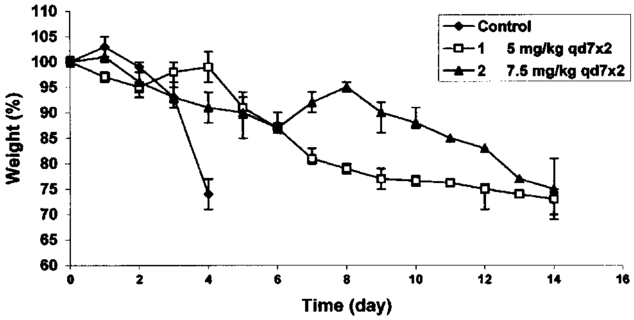


Figure 7. Weight loss for Balb/C (colon 26A) induced by compounds **1** and **2**.

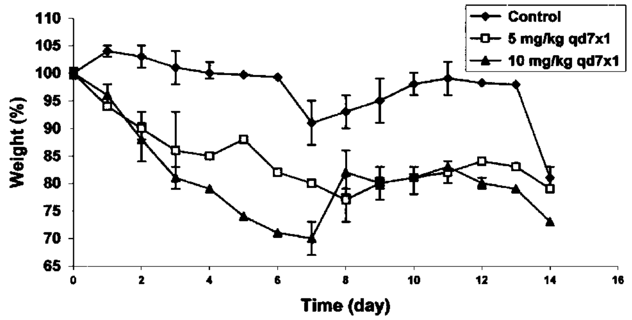


Figure 8. Weight loss for Balb/C (colon 26A) induced by compounds **3** and **4**.

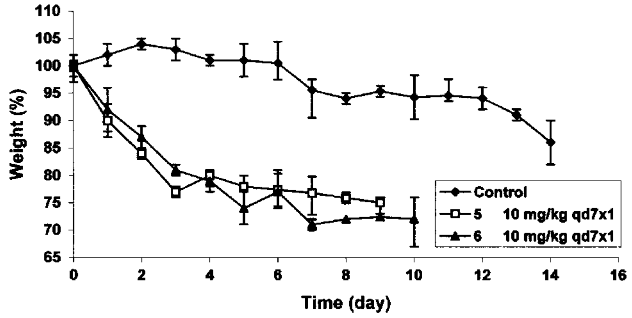


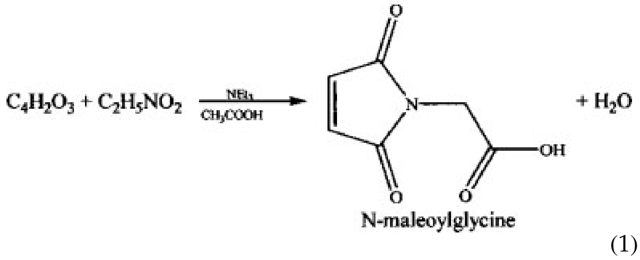
Figure 9. Weight loss for Balb/C (colon 26A) induced by compounds **5** and **6**.

clear activity after single dose administration (for **3** and **4** $T/C = 0.55$ and 0.24 respectively).

EXPERIMENTAL

Materials

Glycine, maleic anhydride, di-*n*-butyltin(IV) dichloride, dimethyltin(IV) dichloride, tri-*n*-butyltin(IV) chloride, trimethyltin(IV) chloride and triethylamine were available from commercial sources (AR Grade, Aldrich Chemicals) and used as such; dibenzyltin(IV) dichloride and tribenzyltin(IV) chloride were prepared as reported in the literature.[31,32] Standard methods[33] were adopted for drying of all the organic solvents used during the synthesis of compounds **1**–**6**. The free acid was synthesized according to a reported procedure[34] as given in Eqn (1):



(1)

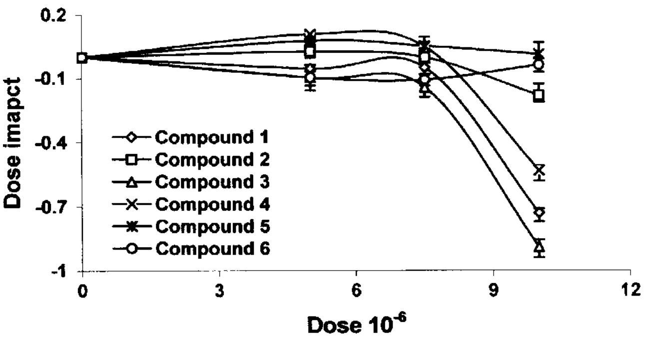


Figure 10. Dose impact of compounds **1**–**6**.

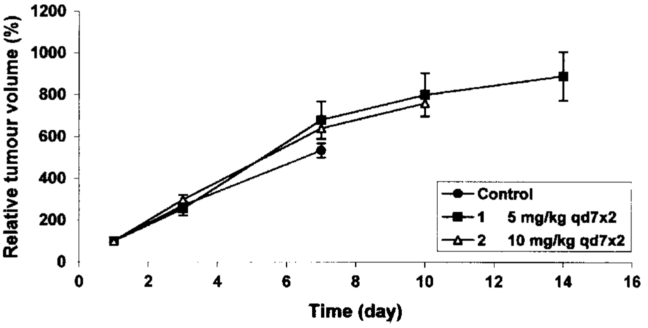


Figure 11. Antitumour activity of compounds **1** and **2** against colon 26A in Balb/C mice.

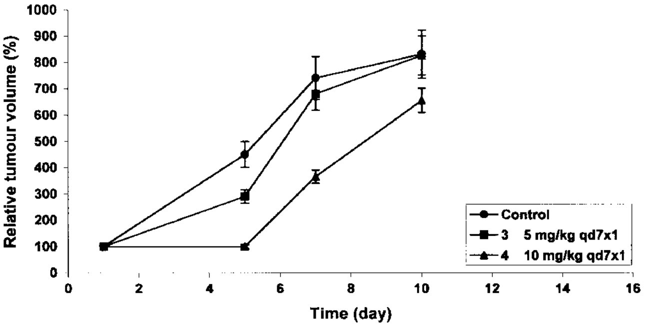


Figure 12. Antitumour activity of compounds **3** and **4** against colon 26A in Balb/C mice.

Instrumentation

Elemental analyses (C, H, N) were performed on a Yanaco high-speed CHN analyser; antipyrene was used as a reference. Melting points were obtained on Reichert Thermovar of F. G. Bode Co., Austria.

The FT IR spectra of the ligand and the complexes in the KBr pellets were measured on a Perkin Elmer FT IR spectrophotometer in the range of 4000–400 cm^{-1}. ^{1}H, ^{13}C and ^{119}Sn NMR spectra were recorded on a multinuclear FT NMR 200 MHz spectrometer (JEOL) operating at room temperature (200 MHz for ^{1}H, 50 MHz for ^{13}C and 93.28 MHz for ^{119}Sn) in deuterated chloroform ($CDCl_3$). The proton and carbon chemical shifts were measured with respect to $SiMe_4$, and tin chemical shifts were measured with respect to $SnMe_4$.

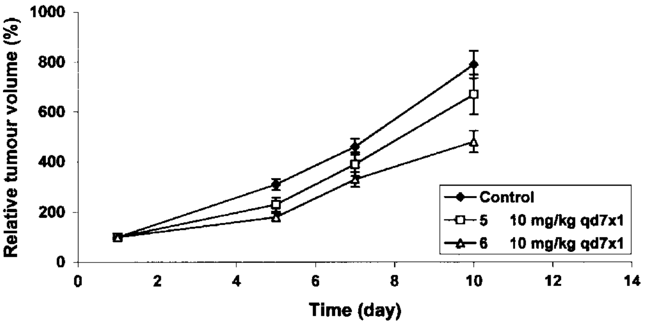


Figure 13. Antitumour activity of compounds **5** and **6** against colon 26A in Balb/C mice.

For Mössbauer measurements, the solid samples were maintained at liquid-nitrogen temperature (77.3 K; V. G. Micromass 7070 F Cryolid liquid nitrogen cryostat). The multichannel calibration was performed with an enriched iron foil using a ^{57}Co–Pd source, and the zero point of the Doppler velocity scale was determined through the absorption spectra of $CaSnO_3$ ($^{119}\text{Sn} = 0.5\ \text{mg cm}^{-2}$). The resulting 5×10^5 count spectra were refined to obtain the isomeric shift IS (mm s^{-1}), the nuclear quadrupole splitting QS, ρ (mm s^{-1}) and the width at half-height of the resonant peaks, Γ (mm s^{-1}).

Antitumour activity

The experimental conditions for *in vivo* cytotoxicity are described elsewhere.[35] The test compounds were dissolved in dimethylsulfoxide (DMSO) to a concentration ranging from 50 to 100 mg ml^{-1} and diluted to 10 mg ml^{-1} in arachidis oil, which was also used for further dilutions. DMSO was acidified or alkalined to obtain a clear solution. The amount of DMSO could not be increased, since mice do not tolerate more than 1%. Mice were injected intra-peritoneally. The MTD was defined as the dose resulting in 10–15% weight loss; T/C is the ratio of the tumour size of the treated mice to that of the control mice expressed as a percentage.

Spectroscopic data

CHN analyses: Calculated values (%) are given in parentheses; antipyrene was standard. Selected cationic fragments of **1**–**6** have been given (in m/z) taking $H = 1$, $C = 12$, $N = 14$, $O = 16$ and $Sn = 119$; percentage relative abundances of selected fragments are given in parentheses.

Compounds 1–3

These compounds were prepared by reacting the triethylammonium salt of the acid with the diorganotin(IV) halides in 2 : 1 molar ratios, in dry toluene (150 ml) for 3.5–4.0 h. The triethylammonium chloride formed during these reactions was removed via filtration. Compounds **1** and **3** were recrystallized from hexane, and **2** was obtained as a semi-solid that was soluble in chloroform.

1 [Me_2SnR_2]. Yield: 89%; MP: 141 °C. %CHN analyses: C: 36.79 (36.80); H: 3.07 (3.09); N: 6.10 (6.13). MS: $[Me_2Sn]^+$, $m/z = 149$ (69%); $[R - Sn]^+$: $m/z = 273$ (37%); $[CH_3 - Sn]^+$: $m/z = 134$ (68%).

2 [Bu_2SnR_2]. Yield: 86%; MP: 189 °C. %CHN analyses: C: 44.37 (44.39); H: 4.82 (4.84); N: 5.15 (5.18). MS: $[Bu_2Sn]^+$, $m/z = 233$ (85%).

3 [$Benz_2SnR_2$] (Benz = benzyl). Yield: 93%; MP: 98 °C. %CHN analyses: C: 51.25 (51.26); H: 3.62 (3.64); N: 4.58 (4.60). MS: $[Benz_2Sn]^+$, $m/z = 301$ (73%); $[COOSn]^+$, $m/z = 164$ (39%).

Compounds 4–6

These compounds were prepared by dissolving the triethylammonium salt of the acid with the triorganotin(IV) halides in equimolar ratios, in dry benzene and toluene (75 ml) for 3 h only; the precipated triethylammonium chloride formed was filtered off. Solvent was removed on a rotary evaporator; the solid mass left was recrystallized from benzene for **4** and **6**, and **5** was obtained from a mixture of hexane and benzene.

4 [Me_3SnR]. Yield: 91%; MP: 159–161 °C. %CHN analyses: C: 33.97 (34.00); H: 4.70 (4.72); N: 4.40 (4.41). MS: $[Me_3Sn]^+$, $m/z = 164$ (73%); $[(CH_3)_2Sn]^+$: $m/z = 149$ (68%).

5 [Bu_3SnR]. Yield: 91%; MP: 126 °C. %CHN analyses: C: 48.66 (48.68); H: 7.05 (7.07); N: 3.73 (3.75). MS: $[Bu_3Sn]^+$, $m/z = 248$ (73%).

6 [$Benz_3SnR$]. Yield: 91%; MP: 152 °C. %CHN analyses: C: 59.35 (59.37); H: 4.59 (4.61); N: 2.54 (2.56). MS: $[Bu_2Sn]^+$, $m/z = 233$ (73%).

CONCLUSIONS

From the data obtained during the characterization of the title complexes, compounds **1**–**3** are octahedral six-coordinate and compounds **4**–**6** are trigonal bipyramidal five-coordinate compounds. Compounds **3** and **4** might be of interest for further antitumour activity studies. The severe toxic behaviours of these compounds are difficult to interpret; moreover, an adopted formulation for administration of these compounds will be necessary to evaluate further for possible antitumour effects.

Acknowledgements

Professor Abdul Malik, HEJ Research Institute of Chemistry, University of Karachi, is gratefully acknowledged for spectroscopic studies of the title compounds.

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