Diorganotin(IV) derivatives of arylhydroxamic acids: synthesis, properties and antitumor activity

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Abstract

Series of diorganotin(IV) complexes of 4-X-benzohydroxamic acid [X = NH$_2$ (HL$_1$), NO$_2$ (HL$_2$) or F (HL$_3$)] formulated as [R$_2$SnL$_2$] and [R$_2$Sn(L)]$_2$O (R = Me, Et, nBu or Ph) have been prepared and characterized by FT-IR, ^{1}H, ^{13}C and ^{119}Sn NMR spectroscopies, elemental analyses, FAB$^+$-MS and melting point determination. They are stable in air, soluble in alcohols and in hydroalcoholic solution and, in some cases, in water. Their in vitro antitumor activity against a series of human tumor cell lines was tested and, in a few of them, is identical to, or even higher than, that of cisplatin. For the mononuclear dialkyltin compounds, the activity generally increases with the length of the carbon chain of the alkyl ligand, being higher for the complexes with benzohydroxamato ligands bearing an electron-acceptor substituent (X = NO$_2$ or F). No structure-activity relationship based on the Hammett's σ_p constant, or related ones, has been recognized.
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Keywords: Diorganotin; Hydroxamate ligands; Antitumor activity

1. Introduction

Hydroxamic acids constitute a very important class of chelating agents with versatile biological activity [1,2]. The research on their coordination properties is mostly oriented towards modeling the biological function such as microbial transportation of iron [2] and inhibition of urease activity [3], although they also have been extensively used as detectors for many metal ions in analytical chemistry [4]. In particular, arylhydroxamic acids are nucleoside reductase inhibitors [5] and thus exhibit some antitumor activity [6].

Organotin(IV) complexes with bidentate O-donor ligands [7–15], including *N*-substituted hydroxamic acids, are well known and some of them exhibit antitumor activity against the MCF-7 mammary tumor and the WiDr colon tumor [16–18] but they are inactive against most of other tumors.

In previous studies of the interactions between diorganotin(IV) acceptors and benzohydroxamic acid and its derivatives [19,20], a synergic effect was recognized and most of this type of compounds showed promising in vitro activity against a series of human tumor cell lines and, in some cases, they even exhibited in vivo

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activity against gastrointestinal tumors, with the dibutyltin(IV) benzohydroxamate monomeric complexes being the lead compounds [20].

In this paper, we extend the study of diorganotin(IV) complexes to those with different substituted 4-X-benzohydroxamic acids, $HL = HL_1$ ($X = NH_2$), HL_2 ($X = NO_2$) or HL_3 ($X = F$), presenting X substituents with electron donor/acceptor properties span over quite a wide range, thus investigating their influence on the antitumor activity of the complexes, and searching for a better solubility in organic solvents, in alcohols and/or even in water, an important property in view of their possible biological application. The preparation of the mononuclear $[R_2SnL_2]$ ($R = Me$, Et, nBu, Ph; $L = L_1$, L_2 or L_3) and the dinuclear $[R_2SnL]_2O$ compounds and a study of their spectroscopic features are thus reported, as well as their antitumor in vitro activity.
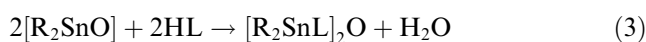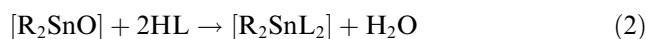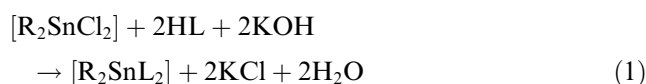
The in vitro activity, against various tumors, was also detected in some other dialkyltin(IV) complexes with diacyl or monoacyl heterocyclic derivatives of hydroxamic acids [21,22], and in some triorganotin(IV) compounds with basic forms of terebic, benzoic or salicylic acids [23].

HL
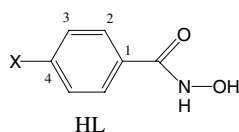
X = NH₂ (HL₁), NO₂ (HL₂) or F (HL₃)

2. Results and discussion

Complexes $[R_2SnL_2]$ were synthesized by reaction (Eq. (1)) of $[R_2SnCl_2]$ with HL and KOH (both in a twofold molar amount relatively to the tin complex) in undried methanol at room temperature [$L = L_1$, $R = Me$ (**1a1**), Et (**1b1**); $L = L_2$, $R = Me$ (**1a2**), Et (**1b2**), nBu (**1c2**)] or by reaction (Eq. (2)) of $[R_2SnO]$ with HL (twofold molar ratio) in a refluxing 1:3 mixture of benzene/methanol [$L = L_1$, $R = nBu$ (**1c1**), Ph (**1d1**); $L = L_2$, $R = Ph$ (**1d2**); $L = L_3$, $R = Me$ (**1a3**), nBu (**1c3**), Ph (**1d3**)]. The dinuclear complexes $[R_2SnL]_2O$ [$L = L_1$, $R = Me$ (**2a1**), nBu (**2c1**), Ph (**2d1**); $L = L_3$, $R = Me$ (**2a3**), nBu (**2c3**), Ph (**2d3**)] were obtained similarly from $[R_2SnO]$ but by using a stoichiometric amount of HL (Eq. (3)).

$$[R_2SnCl_2] + 2HL + 2KOH$$
$$\rightarrow [R_2SnL_2] + 2KCl + 2H_2O \quad (1)$$

$$[R_2SnO] + 2HL \rightarrow [R_2SnL_2] + H_2O \quad (2)$$

$$2[R_2SnO] + 2HL \rightarrow [R_2SnL]_2O + H_2O \quad (3)$$

The first synthetic method for the mononuclear compounds is more convenient than the second one which uses diorganotin oxide compounds as starting materials in solvent refluxing conditions and which was applied [21,22] to the preparation of other dialkyltin(IV) complexes. Complexes **1c1** and **1c2**, prepared from the corresponding diorganotin oxide, were published elsewhere [22a], but their synthesis (in the latter case by the advantageous procedure we indicate herein that starts from $[(nBu)_2SnCl_2]$) and characterization are also included for comparative purposes.

Diorganotin 5-coordinate complexes with oxobridges are known namely diorganodicarboxylatodistannoxanes $\{[XC_6H_3(OH-2)COOSn(nBu)_2]_2O\}_2$ ($X = Me-3$, OMe-3, OMe-4, OMe-5, NH_2-4) [24] which are dimeric with the oxo ligand bridging three metals. However, a related dimeric structure for our complexes is ruled out by the detection of a single ^{119}Sn resonance (see below).

The dinuclear hydroxamate $[R_2Sn\{ONHC(O)C_6H_4-X\}]_2O$ ($R = Et$, nBu; $X = H$, OH-2, OH-4) complexes related to those of this study have been prepared by a distinct and more complex route, involving the reaction of $[R_2SnCl_2(1,10\text{-phenanthroline})]$ with hydroxamic acids [25].

All the complexes are stable in air and sparingly soluble in common organic solvents and in hydroalcoholic solutions. The fluoro- and the amino-substituted complexes tend to exhibit a higher solubility in water than the other ones.

2.1. Spectroscopic data

By comparing the IR spectra of the free HL_1, HL_2 and HL_3 with those of the corresponding complexes, one notes the disappearance of the strong and broad band centered at 2700 cm^{-1} in the former, what is indicative of the loss of the proton in the CO–NHO**H** group upon coordination, thus resulting in the elimination of the O–H$\cdots$O intramolecular stretch. The IR spectra of all the compounds show evidence for the coordination of the hydroxamate ligand via both oxygen atoms of the CONHO$^-$ group. In fact, ligation through the carbonyl oxygen is indicated by the $v(C=O)$ shift to a lower frequency, i.e. from ca. 1650 cm^{-1} in the free species to 1620 cm^{-1} in the chelated one. Moreover, the shift towards higher frequency of the N–O stretching vibration (from 849–897 to 910–1060 cm^{-1}) excludes the coordination via the nitrogen atom [26,27]. The observed strong absorptions of complexes $[R_2SnL]_2O$ in the 535–400 cm^{-1} region are due to $v(Sn–O)$ [28] and the presence of more than one stretching vibration probably reflects different Sn–O bond distances in the solid state [29–31]. Strong bands in the 611–635 cm^{-1} region are assigned to Sn–O–Sn bond vibrations [25,32].

In the ^{1}H and ^{13}C–{^{1}H} NMR spectra the assignment of phenyl protons and carbons were based on theoretical predictions [33]. The measured $^2J_{Sn–H}$ coupling constant for **1a3** and **2a3** (83.0 and 78.6 Hz, respectively) enabled the estimate, based on the equation of Lockhart and Manders (Eq. (4)) [34], of the values of the θ(C–Sn–C) angles for these compounds: 135° (**1a3**) and 129° (**2a3**) (the lower solubility of the other organotin complexes precluded the measurement of $^2J_{Sn–H}$). These θ values are compatible [20,34–37] with a distorted octahedral structure and a distorted trigonal–bipyramidal structure [θ commonly in the 115–130° range for pentacoordinate dimethyltin(IV) complexes] [34] for the monomer and the dinuclear complexes, respectively. Such deformations, which occur frequently in diorganotin(IV) compounds, are known [35,37] to be determined not only by the tin coordination number but also by electronic and stereochemical factors.

$$\theta(C–Sn–C) = 0.0161(^2J_{Sn–H})^2 − 1.32(^2J_{Sn–H}) + 133.4. \quad (4)$$

The ^{119}Sn NMR resonances of the mononuclear complexes occur at chemical shifts (from −287 to −489 ppm) that fall within the range of hexacoordinate tin(IV) complexes whereas the lower field chemical shift (−196.36 ppm) of **2a1** is in accord with the pentacoordination of this dinuclear complex. However, the other dinuclear compounds reveal δ(^{119}Sn) outside the values characteristic of pentacoordinated Sn complexes falling in the common range of 6-coordinate compounds [35,38,39]. Hence, we cannot rule out the possibility of a pseudo-octahedral environment around the tin atoms in solutions of the dinuclear complexes in a coordinating solvent such as DMSO, methanol or acetone.

The FAB$^+$ mass spectra of most of the compounds show the respective molecular ions $[M]^+$ and/or fragments formed upon sequential loss of ligands.

2.2. Antitumor activity in vitro

The antitumor activity in vitro was tested on various human tumor cell lines [immature granulocyte leukemia (HL-60) as well as nasopharyngeal (KB), hepatocellular (Bel-7402), ovarian (Hela) and colon (HCT-8) carcinomas] and mouse tumor cell lines (lymphocyte carcinomas B and T). The results are summarized in Tables 1 and 2. As observed in a previous study [20], both the organoligand R and the *para*-phenyl (X) substituent of the hydroxamate ligand appear to play an important role. Indeed, the dibutyltin(IV) complexes, with the longest alkyl chain, exhibit the strongest antitumor activity in each series of complexes, which is identical or even more potent than that of cisplatin, the clinically widely used drug. In contrast, the dimethyltin(IV) derivatives usually exhibit the weakest activity. The other organo-derivatives follow an order that is also dependent on the type of tumor and on the arylhydroxamate ligand. Hence, for [R$_2$Sn(L$_2$)$_2$], the activity follows the order *n*Bu > Ph, Et > Me for nearly all the tumor cells, with the diphenyl complex (**1d2**) being more active than the diethyl one (**1b2**) for the Bel-7402 and Hela tumors. Similar trends were also found in diorganotin(IV) carboxylates [24]. However, in our study the reverse is observed for the KB and T cases (for the HL-60 and B tumors, both complexes have comparable activities).

The electronic influence of the X substituent also affects the antitumor activity of the complexes as expected in view of its influence on the electron-donor character of the ligand. Thus, the complexes with L$_2$ and L$_3$ which have the electron-withdrawing NO$_2$ and F substituents tend to show better activities than those with L$_1$ with the electron-releasing NH$_2$ group. The strongest activity, however, in the cases of the Bel-7402 and KB carcinomas, is shown by a fluorobenzohydroxamato complex, **1c3**, although the F-substituent is a much

Table 1
Inhibition (%) of diorganotin(IV) complexes[a] against human and mouse tumor cell lines

Compound			HL-60	KB	Bel-7402	Hela	HCT-8	B	T
No.	X	R							
1a1	NH$_2$	Me	19.0	9.6	20.6	–		34.5	10.0
1b1		Et	13.0	16.5	24.2	1.3		20.8	35.8
1c1		*n*Bu	70.4	88.2	71.2	70.9		39.4	70.6
1d1		Ph	19.9	19.5	15.9	3.2		9.7	23.5
1a2	NO$_2$	Me	16.0	8.5	4.2	–		27.5	31.1
1b2		Et	64.9	86.5	42.0	43.8		71.3	66.0
1c2		*n*Bu	83.3	98.6	98.2	97.5		67.1	68.9
1d2		Ph	66.5	63.4	80.8	73.6		69.0	53.2
1c3	F	*n*Bu		79.8	95.5		91.7		
1d3		Ph		71.8	66.5		81.2		
2c3		*n*Bu		71.4	86.8		75.8		
2d3		Ph		68.3	69.1		83.7		

[a] Dose level of 10 μM (X = NH$_2$, NO$_2$) or 5 μg/mL (X = F).

Table 2
Summary of the screening data for the in vitro antitumor activity[a]

Compound	HL-60	KB	Bel-7420	Hela	HCT-8	B	T
1a1	–	–	–	–		–	–
1b1	–	–	–	–		–	+
1c1	++	++	++	++		+	++
1d1	–	–	–	–		–	–
1a2	–	–	–	–		–	–
1b2	++	++	+	+		++	++
1c2	++	+++	++	++		++	++
1d2	++	++	++	++		++	++
1c3		+++	+++		+++		
Cisplatin	++	++	++	++	++	++	++

[a] $IC_{50} > 1 \times 10^{-4}$ mol/L (–, inactivity); $IC_{50} \leqslant 1 \times 10^{-4}$ mol/L (+, weak activity); $IC_{50} \leqslant 1 \times 10^{-5}$ mol/L (++, medium activity); $IC_{50} \leqslant 1 \times 10^{-6}$ mol/L (+++, strong activity).

weaker electron-acceptor than NO_2, conceivably on account of the higher solubility in aqueous medium of the former complex. The higher water-solubility of fluorine-substituted organotin complexes with antitumor activity, relatively to related non-fluorinated compounds, has already been reported [24]. Other strategies to increase the solubility in water of bioactive organotin complexes have been applied and in particular some water-soluble polyoxaalkylcarboxylate tin complexes display rather promising anti-tumor activity [24,40–42].

3. Experimental section

3.1. General

The diorganotin(IV) chloride and oxide and the methylbenzoate derivatives were purchased from Alfa or Aldrich and used as received. All the other chemicals were of analytical grade. The substituted benzohydroxamic acids HL_1, HL_2 and HL_3, were prepared according to a known [43] general procedure.

The samples for microanalyses were dried in vacuo to constant weight (20 °C, ca. 0.1 Torr) and the analyses were carried out either by the Microanalytical Service of the Instituto Superior Técnico in Lisbon or by the Analytical Laboratory of Shanxi University, China. Infrared spectra were recorded on a Bio-Rad FTS 3000MX FT-IR spectrometer in KBr pellets (4000–400 cm^{-1}). ^{1}H, ^{13}C, ^{19}F and ^{119}Sn NMR spectra were recorded on a Varian Unity 300 spectrometer (300.0 MHz for ^{1}H, 75.5 MHz for ^{13}C, 282.2 MHz for ^{19}F and 111.9 MHz for ^{119}Sn) at ambient temperature [δ values in ppm relative to $SiMe_4$ (^{1}H, ^{13}C), $CFCl_3$ (^{19}F) or $SnMe_4$ (^{119}Sn)]. The fast-atom bombardment (FAB) mass spectrometric measurements were performed on a Trio 2000 instrument and the positive-ion FAB spectra were obtained by bombarding 3-nitrobenzyl alcohol (NOBA) matrixes of the samples with 8 keV xenon atoms. Mass calibration for the data acquisition system

was achieved using CsI. Melting points were measured on a Kofler-table (Leica Galen III).

$HONHC(O)C_6H_4NH_2$-4 (HL_1). White powder. Elemental Analysis Calcd. (%) for $H_8C_7N_2O_2$: C, 55.25; H, 5.31; N, 18.41; Found: C, 55.30; H, 5.37; N, 18.50%. IR: 3334s, 3279s v(N–H); 2700s, br v(O–H); 1648s, 1599s, 1537s and 1507s v(C⚌O)/v(N⚌C); 897s v(N–O). ^{1}H NMR [$(CD_3)_2CO$]: δ 10.55 [s, br, 1H, NH]; 8.18 [s, br, 1H, OH]; 7.74 [d, ^3J = 9.0, 2H, H(2)]; 6.81 [d, ^3J = 9.0, 2H, H(3)]; 5.35 [s, br, 2H, NH_2]. ^{13}C{^{1}H} [$(CD_3)_2CO$] δ 166.10 (CO); 152.67 [C(4)], 131.83 [C(1)], 137.00 [C(2)], 124.51 [C(3)]. Yield 54%.

$HONHC(O)C_6H_4NO_2$-4 (HL_2). White powder. Elemental Analysis Calcd. (%) for $H_6C_7N_2O_4$: C, 46.15; H, 3.31; N, 15.38; Found: C, 46.07; H, 3.40; N, 15.49%. IR: 3249s, v(N–H); 2700s, br v(O–H); 1652s, 1599s, 1561w and 1515s v(C⚌O)/v(N⚌C); 898s v(N–O). ^{1}H NMR [$(CD_3)_2CO$]: δ 9.94 [s, br, 2H, NH and OH]; 8.23 [d, ^3J = 9.0, 2H, H(2)]; 8.48 [d, ^3J = 9.0, 2H, H(3)]. ^{13}C{^{1}H} [$(CD_3)_2CO$]: δ 166.29 (CO); 150.44 [C(4)], 138.95 [C(1)], 129.13 [C(2)], 124.41 [C(3)]. Yield 49%.

$HONHC(O)C_6H_4F$-4 (HL_3). White powder. Elemental Analysis Calcd. (%) for $H_6C_7N_1O_2$ F_1: C, 54.19; H, 3.87; N, 9.03; Found: C, 54.23; H, 3.83; N, 8.98%. IR: 3297m v(N–H); 2700s, br v(O–H); 1642s v(C⚌O)/v(N⚌C); 849s v(N–O). ^{1}H NMR [CD_3OD]: δ 7.07 [t, $^3J_{HH}$ = $^3J_{FH}$ = 9.0, 2H, H(3)]; 7.69 [dd, $^3J_{HH}$ = 9.0, $^4J_{FH}$ = 5.4, 2H, H(2)]. ^{13}C{^{1}H} [CD_3OD]: δ 166.19 [$^1J_{CF}$ = 250.6, C(4)], 116.51 [$^2J_{CF}$ = 22.3, C(3)], 130.66 [$^3J_{CF}$ = 8.7, C(2)], 129.88 [C(1)]. ^{19}F [CD_3OD]: −110.10. Yield 65%.

3.2. Syntheses of the complexes

3.2.1. Mononuclear bis(4-X-benzohydroxamato)dialkyltin(IV), [R_2SnL_2] [L = L_1, R = Me (**1a1**), Et (**1b1**); L = L_2, R = Me (**1a2**), Et (**1b2**), nBu (**1c2**)]

Dialkyltin(IV) dichloride (0.220 g, 1 mmol) was added to a methanolic solution (20 mL) of HL (2 mmol) and KOH (0.112 g, 2 mmol). A precipitate formed

gradually and the mixture was stirred for 48 h at room temperature under N_2. The precipitate was then filtered off, washed with cold methanol, recrystallized from chloroform/light petroleum (or methanol/diethylether for **1a1**) and dried to constant weight.

3.2.2. Mononuclear bis(4-X-benzohydroxamato)dialkyltin(IV), [R$_2$SnL$_2$] [L = L$_1$, R = nBu (1c1), Ph (1d1); L = L$_2$, R = Ph (1d2); L = L$_3$, R = Me, (1a3), nBu (1c3), Ph (1d3)]

Dialkyltin oxide (1 mmol) was added to a dry methanol:benzene (1:3 v/v) solution of HL (2 mmol) which was refluxed for 6 h under N_2. The solvent was then evaporated to dryness. The precipitate thus formed was recrystallized from methanol/light petroleum, chloroform (**1a3**), n-hexane (**1c3**) or ethanol (**1d3**) and dried to constant weight.

3.2.3. Dinuclear bis(4-X-benzohydroxamato)dialkyltin(IV) [R$_2$SnL]$_2$O [L = L$_1$, R = Me (2a1), nBu (2c1), Ph (2d1); L = L$_3$, R = Me (2a3), nBu (2c3), Ph (2d3)]

Dialkyltin oxide (1 mmol) was added to a methanol:benzene (1:3 v/v) solution of HL (1 mmol) and the mixture was refluxed for 6 h under N_2 whereafter the solvent was evaporated to dryness. The precipitate thus formed was filtered off, recrystallized from dry ethanol (L = L$_1$), methanol (**2a3**), cyclohexane (**2c3**) or benzene (**2d3**) and dried to constant weight.

[Me$_2$Sn{ONHC(O)C$_6$H$_4$NH$_2$-4}$_2$] (**1a1**). White; m.p.: 252 °C (dec.). Elemental Analysis Calcd. (%) for H$_{20}$C$_{16}$O$_4$N$_4$Sn: C, 42.60; H, 4.48; N, 12.42; Found: C, 42.35; H, 4.70; N, 12.34%. IR: 3360s, 3230s v(N–H); 1610s, 1561w and 1538w v(C=O)/v(N=C); 916s v(N–O); 521m v(Sn–O); 598s v(Sn–C). ^{1}H NMR [(CD$_3$)$_2$CO]: δ 7.73 [s, br, 4H, H(2)]; 6.84 [br, 4H, H(3)]; 5.43 [br, 4H, NH$_2$]; 0.96 [s, br, 6H, CH$_3$, R-Sn]. ^{13}C{^{1}H} [(CD$_3$)$_2$SO]: δ 164.13 (CO); 152.73 [C(4)], 129.69 [C(1)], 127.58 [C(2)], 115.23 [C(3)]; 5.54 (CH$_3$, R-Sn). ^{119}Sn [(CD$_3$)$_2$CO]: δ −448.69. FAB$^+$-MS: m/z 452 [M]$^+$, 437 [M − R]$^+$, 301 [M − L]$^+$, 286 [M − R − L]$^+$, 150 [M − 2L]$^+$, 135 [M − R − 2L]$^+$, 120 (Sn$^+$). Yield 38%.

[Et$_2$Sn{ONHC(O)C$_6$H$_4$NH$_2$-4}$_2$] (**1b1**). Light yellow; m.p.: 158–159 °C. Elemental Analysis Calcd. (%) for H$_{24}$C$_{18}$O$_4$N$_4$Sn: C, 45.12; H, 5.06; N, 11.70; Found: C, 45.89; H, 5.27; N, 11.43%. IR: 3348s and 3216s v(N–H); 1605s, 1558w and 1539w v(C=O)/v(N=C); 915s v(N–O); 512m v(Sn–O); 627s and 561w v(Sn–C). ^{1}H NMR [(CD$_3$)$_2$SO:CDCl$_3$]: δ 11.40 [br, 2H, NH] 7.01 [s, br, 4H, H(2)]; 6.09 [br, 4H, H(3)]; 4.54 [br, 2H, NH$_2$], 4.32 [br, 2H, NH$_2$]; 2.79 [s, br, CH$_2$, R-Sn, partially buried under DMSO ressonance]; 0.72 [s, br, 6H, CH$_3$, R-Sn]. ^{13}C{^{1}H} [(CD$_3$)$_2$SO:CDCl$_3$]: δ 160.86 (CO); 149.90 [C(4)], 129.70 [C(1)], 126.93 [C(2)], 112.56 [C(3)]; 17.02 (CH$_2$, R-Sn); 9.03 (CH$_3$, R-Sn). ^{119}Sn [(CD$_3$)$_2$SO:CDCl$_3$): δ −355.69. Yield 40%.

[nBu$_2$Sn{ONHC(O)C$_6$H$_4$NH$_2$-4}$_2$] (**1c1**). Light yellow; m.p.: 168–169 °C. Elemental Analysis Calcd. (%) for H$_{32}$C$_{22}$O$_4$N$_4$Sn: C, 49.36; H, 6.04; N, 10.47; Found: C, 45.96; H, 6.11; N, 9.97%. IR: 3352s and 3219s v(N–H); 1607s, 1562w and 1534w v(C=O)/v(N=C); 915s v(N–O); 515m v(Sn–O); 629s and 557w v(Sn–C). ^{1}H NMR [(CD$_3$)$_2$SO]: δ 12.15 [br, 2H, NH], 7.69 [d, $^3J_{HH}$ = 8.1, 4H, H(2)]; 6.80 [d, $^3J_{HH}$ = 8.1, 4H, H(3)]; 5.46 [br, 2H, NH$_2$], 5.28 [br, 2H, NH$_2$]; 3.55–3.05, 2.16–0.96 [m, R-Sn]. ^{13}C{^{1}H} [(CD$_3$)$_2$SO]: δ 163.36 (CO); 153.25 [C(4)], 116.32 [C(1)], 128.76 [C(2)], 114.36 [C(3)]; 28.02–13.33 (m, R-Sn). ^{119}Sn [(CD$_3$)$_2$SO:CDCl$_3$]: δ −356.96. Yield 34%.

[Ph$_2$Sn{ONHC(O)C$_6$H$_4$NH$_2$-4}$_2$] (**1d1**). White; m.p.: 162–164 °C. Elemental Analysis Calcd. (%) for H$_{32}$C$_{26}$O$_4$N$_4$Sn: C, 54.28; H, 4.21; N, 9.74; Found: C, 55.08; H, 4.22; N, 9.82%. IR: 3323s and 3240s v(N–H); 1607s, 1562w and 1534w v(C=O)/v(N=C); 915s v(N–O); 515m v(Sn–O); 629s and 557w v(Sn–C). ^{1}H NMR [(CD$_3$)$_2$CO]: δ 12.03 [br, 2H, NH], 7.37[d, $^3J_{HH}$ = 6.0, 4H, H(2)]; 6.79 [d, $^3J_{HH}$ = 6.0, 4H, H(3)]; 5.37 [br, 2H, NH$_2$]; 7.85–7.50 [m, R-Sn]. ^{13}C{^{1}H} [(CD$_3$)$_2$CO]: 163.44 (CO); 152.68 [C(4)], 137.63–127.49 [m, C(1), C(2), C(3), R-Sn]. ^{119}Sn [(CD$_3$)$_2$CO]: δ −357.01. Yield 80%.

[Me$_2$Sn{ONHC(O)C$_6$H$_4$NO$_2$-4}$_2$] (**1a2**). Light yellow; m.p.: >300 °C. Elemental Analysis Calcd. (%) for H$_{16}$C$_{16}$O$_8$N$_4$Sn: C, 37.60; H, 3.16; N, 10.97; Found: C, 37.32; H, 3.61; N, 10.89%. IR: 3113s v(N–H); 1626m, 1596m, 1573s and 1225s v(C=O)/v(N=C); 1015m v(N–O); 525m and 491s v(Sn–O); 643s and 571w v(Sn–C). ^{1}H NMR [(CD$_3$)$_2$CO]: δ 8.45 [d, ^3J = 8.8, 4H, H(2)]; 8.22 [d, ^3J = 8.8, 4H, H(3)]; 0.91 [s, br, 6H, CH$_3$, R-Sn]. ^{119}Sn [(CD$_3$)$_2$CO]: δ −449.14. Yield 30%.

[Et$_2$Sn{ONHC(O)C$_6$H$_4$NO$_2$-4}$_2$] (**1b2**). Light yellow; m.p.: 212–215 °C. Elemental Analysis Calcd. (%) for H$_{20}$C$_{18}$O$_8$N$_4$Sn: C, 40.10; H, 3.75; N, 10.39; Found: C, 40.65; H, 3.69; N, 10.43%. IR: 3192s v(N–H); 1620m, 1581s and 1519s v(C=O)/v(N=C); 962m v(N–O); 520m and 498w v(Sn–O); 567w v(Sn–C). ^{1}H NMR [(CD$_3$)$_2$CO]: δ 8.40–8.20 [m, 8H, H(2), H(3)]; 1.43–1.75 [m, 10H, R-Sn]. ^{13}C{^{1}H} [(CD$_3$)$_2$CO]: δ 162.95 (CO); 151.72 [C(4)], 137.29 [C(1)], 132.18 [C(2)], 124.52 [C(3)]; 27.56–13.93 (m, R-Sn). ^{119}Sn [(CD$_3$)$_2$CO]: δ −287.09. Yield 55%.

[nBu$_2$Sn{ONHC(O)C$_6$H$_4$NO$_2$-4}$_2$] (**1c2**). Light yellow; m.p.: 243–245 °C. Elemental Analysis Calcd. (%) for H$_{28}$C$_{22}$O$_8$N$_4$Sn: C, 44.39; H, 4.75; N, 9.41; Found: C, 44.23; H, 4.80; N, 9.36%. IR: 3115s v(N–H); 1598m, 1585s, 1526s and 1525s v(C=O)/v(N=C); 1016m v(N–O); 530m and 501w v(Sn–O); 581s v(Sn–C). ^{1}H NMR [(CD$_3$)$_2$CO]: δ 8.40 [d, $^3J_{HH}$ = 8.8, 4H, H(2)]; 8.20 [d, $^3J_{HH}$ = 8.8, 4H, H(3)]; 0.98–1.87 [m, 18H, R-Sn]. ^{13}C{^{1}H} [(CD$_3$)$_2$CO]: δ 172.22 (CO); 151.67 [C(4)], 137.29 [C(1)], 132.18 [C(2)], 124.52

[C(3)]; 27.56–13.93 (m, R-Sn). ^{119}Sn [(CD$_3$)$_2$CO]: δ −380.44. Yield 58%.

[Ph$_2$Sn{ONHC(O)C$_6$H$_4$NO$_2$-4}$_2$] *(1d2)*. Yellow; m.p.: 250 °C (dec). Elemental Analysis Calcd. (%) for H$_{28}$C$_{26}$O$_8$N$_4$Sn: C, 49.16; H, 3.18; N, 8.82; Found: C, 49.31; H, 3.37; N, 8.52%. IR: 3202s v(N–H); 1597s and 1529s (C═O)/v(N═C); 918s v(N–O); 517m and 448m v(Sn–O); 559w v(Sn–C). ^{1}H NMR [(CD$_3$)$_2$CO]: δ 8.37–7.22 [m, 18H, H(2), H(3), R-Sn]. ^{13}C{^{1}H} [(CD$_3$)$_2$CO]: 161.36 (CO); 150.43 [C(4)], 137.49–123.59 [m, C(1), C(2), C(3), R-Sn]. ^{119}Sn [(CD$_3$)$_2$CO]: δ −344.46. Yield 44%.

[Me$_2$Sn{ONHC(O)C$_6$H$_4$F-4}$_2$] *(1a3)*. White; m.p.: >300 °C. Elemental Analysis Calcd. (%) for H$_{16}$C$_{16}$N$_2$O$_4$F$_2$Sn: C, 42.01; H, 3.50; N, 6.13; Found: C, 41.97; H, 3.58; N, 6.03%. IR: 3474w and 3222 v(N–H); 1613s (C═O)/v(N═C); 910s v(N–O); 490m (Sn–O). ^{1}H NMR [CD$_3$OD]: δ 7.18 [t, $^3J_{HH}$ = $^3J_{HF}$ = 8.8, 4H, H(3)]; 7.78 [dd, $^3J_{HH}$ = 8.8, $^4J_{HF}$ = 5.4, 4H, H(2)]; 4.95 [s, br, 2H, NH]; 0.59 [s, $^2J_{SnH}$ = 83.0]. ^{13}C{^{1}H} [CD$_3$OD]: δ 166.17 [d, $^1J_{CF}$ = 250.5, C(4)], 116.63 [d, $^2J_{CF}$ = 22.3, C(3)]; 130.36 [d, $^3J_{CF}$ = 9.3 C(2)], 130.50 [C(1)]. ^{119}Sn [CD$_3$OD]: δ −488.30. ^{19}F [CD$_3$OD]: δ −109.80. FAB$^+$-MS: m/z 443 [M − R]$^+$, 304 [M − L]$^+$, 274 [M − 2R − L]$^+$. Yield 42%.

[nBu$_2$Sn{ONHC(O)C$_6$H$_4$F-4}$_2$] *(1c3)*. White; m.p.: 140–143 °C. Elemental Analysis Calcd. (%) for H$_{28}$C$_{22}$N$_2$O$_4$F$_2$Sn: C, 48.80; H, 5.18; N, 5.18; Found: C, 48.92; H, 5.15; N, 5.12%. IR: 3211m (N–H); 1611s v(C═O)/v(N═C); 915s (N–O); 512m v(Sn–C); 467m v(Sn–O). ^{1}H NMR [CD$_3$OD]: δ 7.18 [t, $^3J_{HH}$ = $^3J_{HF}$ = 8.7, 4H, H(3)]; 7.79 [dd, $^3J_{HH}$ = 8.7, $^4J_{HF}$ = 5.4, 4H, H(2)]; 1.69–1.59, 1.43–1.30 [m, 14H, CH$_3$CH$_2$CH$_2$]; 0.85 [t, $^3J_{HH}$ = 7.2, –CH$_2$Sn]; 1.65 [s, 2H, NH]. ^{13}C{^{1}H} [CD$_3$OD]: δ 166.37 [d, $^1J_{CF}$ = 250.5, C(4)], 117.00 [d, $^2J_{CF}$ = 22.5, C(3)]; 130.42 [d, $^3J_{CF}$ = 8.7, C(2)]; 128.40 [C(1)]; 28.74 [s, $^1J_{SnC}$ = 36.7, Sn–C]; 27.92, 27.34, 14.42 [Sn-R]. ^{119}Sn [CD$_3$OD]: δ −488.30. ^{19}F [CD$_3$OD]: δ −109.94. FAB$^+$-MS: m/z 485 [M − R]$^+$, 388 [M − L]$^+$, 274 [M − 2R − L]$^+$. Yield 55%.

[Ph$_2$Sn{ONHC(O)C$_6$H$_4$F-4}$_2$] *(1d3)*. White; m.p.: 235 °C (dec.). Elemental Analysis Calcd. (%) for H$_{20}$C$_{26}$N$_2$O$_4$F$_2$Sn: C, 53.52; H, 3.77; N, 4.80; Found: C, 53.62; H, 3.90; N, 4.78%. IR: 3200m v(N–H); 1606s v(C═O)/v(N═C); 915s v(N–O). ^{1}H NMR [CD$_3$OD]: δ 6.47–6.31 and 6.99–6.75 [m, 18H, H(3), H(2), RSn]; 10.35 [s, 2H, NH]. ^{13}C{^{1}H} [(CD$_3$)$_2$SO] (unstable in solution): δ 159.6 [CO]; 135.03, 129.0–127.3, 115.4 [C(3), C(2), C(1), Sn-R]. ^{119}Sn [(CD$_3$)$_2$SO]: δ −488.31 and −429.04. ^{19}F [(CD$_3$)$_2$SO]: δ −108.01 and −107.45. FAB$^+$-MS: m/z 581 [M]$^+$, 505 [M − L]$^+$, 737 [M + L]$^+$, 1028 [2M − 2R + O]$^+$. Yield 41%.

[Me$_2$Sn{ONHC(O)C$_6$H$_4$NH$_2$-4}$_2$]$_2$O *(2a1)*. Light yellow; m.p.: 260 °C (dec.). Elemental Analysis Calcd. (%) for H$_{26}$C$_{18}$O$_5$N$_4$Sn: C, 35.10; H, 4.22; N, 9.10; Found: C, 34.98; H, 4.03; N, 9.54%. IR: 3219s, 3340s

v(N–H); 1625s, 1587s, 1552s and 1514m v(C═O)/v(N═C); 911s v(N–O); 625s and 571s v(Sn–O–Sn) and v(Sn–C); 527m, 499w and 422m v(Sn–O);. ^{1}H NMR [(CD$_3$)$_2$CO]: δ 12.24 [s, br, 4H, NH$_2$]; 7.37 [d, $^3J_{HH}$ = 6.9, 4H, H(2)]; 6.50 [d, $^3J_{HH}$ = 6.9, 4H, H(3)]; 5.65 [br, 2H, NH$_2$], 5.24 [br, 2H, NH$_2$]; 0.63–0.18 [m, 12H, CH$_3$, R-Sn]. ^{13}C{^{1}H} [(CD$_3$)$_2$CO]: δ 161.75 (CO); 151.65 [C(4)], 116.15 [C(1)], 127.50 [C(2)], 112.91 [C(3)]; 8.71, 6.97, 5.26 (CH$_3$, R-Sn). ^{119}Sn [(CD$_3$)$_2$CO]: δ −196.36. Yield 46%.

[nBu$_2$Sn{ONHC(O)C$_6$H$_4$NH$_2$-4}$_2$]$_2$O *(2c1)*. Light yellow; m.p.: 160–161 °C. Elemental Analysis Calcd. (%) for H$_{26}$C$_{18}$O$_5$N$_4$Sn: C, 45.95; H, 6.38; N, 7.15; Found: C, 45.32; H, 6.28; N, 7.23%. IR: 3216s and 3354s v(N–H); 1607s, 1527w and 1514m v(C═O)/v(N═C); 910s v(N–O); 627s v(Sn–O–Sn) and v(Sn–C); 595s v(Sn–C); 525m and 515s v(Sn–O). ^{1}H NMR [(CD$_3$)$_2$CO]: δ 7.71 [d, $^3J_{HH}$ = 8.0, 4H, H(2)]; 6.73 [d, $^3J_{HH}$ = 8.0, 4H, H(3)]; 5.36 [br, 4H, NH$_2$]; 1.80–0.95 [m, 36H, R-Sn]. ^{13}C{^{1}H} [(CD$_3$)$_2$CO]: δ 163.21 (CO); 152.78 [C(4)], 128.86 [C(2)], 114.35 [C(3)]; 15.12, 13.46 (R-Sn). ^{119}Sn [(CD$_3$)$_2$CO]: δ −443.58. Yield 58%.

[Me$_2$Sn{ONHC(O)C$_6$H$_4$F-4}$_2$]$_2$O *(2a3)*. White; m.p.: >300 °C. Elemental Analysis Calcd. (%) for H$_{22}$C$_{18}$N$_2$O$_5$F$_2$Sn$_2$: C, 34.73; H, 3.54; N, 4.50; Found: C, 34.69; H, 3.51; N, 4.58%. IR: 3436w v(N–H); 1607s v(C═O)/v(N═C); 902s v(N–O); 634s and 625s v(Sn–O–Sn) and v(Sn–C); 521m v(Sn–C). ^{1}H NMR [(CD$_3$)$_2$SO]: δ 6.27 [d, $^3J_{HH}$ = $^3J_{HF}$ = 8.7, 4H, H(3)]; 6.90 [dd, $^3J_{HH}$ = 8.7, $^4J_{HF}$ = 6.0, 4H, H(2)]; 1.65 [s, br, 2H, NH]; −0.30 [s, $^2J_{SnH}$ = 78.6]. ^{119}Sn [(CD$_3$)$_2$SO]: δ −488.31. ^{19}F [(CD$_3$)$_2$SO]: δ −112.86. Yield 48%.

[nBu$_2$Sn{ONHC(O)C$_6$H$_4$F-4}$_2$]$_2$O *(2c3)*. White; m.p.: 180–182 °C. Elemental Analysis Calcd. (%) for H$_{46}$C$_{30}$N$_2$O$_5$F$_2$Sn$_2$: C, 45.57; H, 5.82; N, 3.54; Found: C, 45.45; H, 5.79; N, 3.66%. IR: 3500w v(N–H); 1606s v(C═O)/v(N═C); 912s and 900s v(N–O); 635s, br and 611s, br v(Sn–O–Sn) and v(Sn–C); 517m v(Sn–C); 503m v(Sn–O). ^{1}H NMR (CDCl$_3$): δ 14.44 [s, br, NH]; 7.08–7.54 [m, 4H, H(3)]; 7.86–7.54 [m, H(2)]; 1.47–1.34, 1.80–1.70, 0.95 [m, 36H, SnR]. ^{13}C{^{1}H} (CDCl$_3$): δ 164.6 and 161.8 [CO]; 164.49 [d, $^1J_{CF}$ = 242.9], 163.41 [d, $^1J_{CF}$ = 241.7] [C(4)]; 114.82 [d, $^2J_{CF}$ = 21.0], 115.60 [d, $^2J_{CF}$ = 22.0] [C(3)]; 128.59 [d, $^3J_{CF}$ = 8.2], 129.09 [d, $^3J_{CF}$ = 8.7] [C(2)]; 130.15 and 126.31 [C(1)]; 28.7–26.2 and 13.9–13.6 [m, Sn-R]. Yield 64 %.

[Ph$_2$Sn{ONHC(O)C$_6$H$_4$F-4}$_2$]$_2$O *(2d3)*. White; m.p.: >300 °C. Elemental Analysis Calcd. (%) for H$_{30}$C$_{38}$N$_2$O$_5$F$_2$Sn$_2$: C, 52.17; H, 3.89; N, 3.20; Found: C, 51.14; H, 3.93; N, 3.18%. IR: 3364m v(N–H); 1607s v(C═O)/v(N═C); 916s v(N–O); 625s v(Sn–O–Sn) and v(Sn–C); 446m v(Sn–O). ^{1}H NMR [(CD$_3$)$_2$SO]: δ 12.55 [s, br, 2H, NH]; 6.47–6.39 and 6.99–6.67 [m, 28H, H(3), H(2), SnR]. ^{13}C{^{1}H} [(CD$_3$)$_2$SO]: δ 159.6 [CO]; 148.18 [d, $^1J_{CF}$ = 265.5, C(4)]; 115.46 [d,

$^2J_{CF}$ = 21.7, C(3)]; 135.10 [d, $^3J_{CF}$ = 6.2, C(2)]; 128.95 [C(1)]; 135.43, 128.17, 127.76 [Sn-*R*]. ^{119}Sn [(CD$_3$)$_2$SO]: δ −427.95. ^{19}F [(CD$_3$)$_2$SO]: δ −106.73. FAB$^+$-MS: *m/z* 505 [SnLR$_2$]$^+$, 425 [SnL$_2$]$^+$, 366 [SnLRO]$^+$, 347 [SnLPh]$^+$. Yield 65%.

3.3. Antitumor activity in vitro

The antitumor activity against tumor cell lines was assayed by the MTT method [44] in the State Key Laboratory of Natural and Mimic Drugs, Beijing Medical University, China. The following cell lines were used for screening: human immature granulocyte leukemia (HL-60) as well as nasopharyngeal (KB), hepatocellular (Bel-7402), ovarian (Hela) and colon (HCT-8) carcinomas, along with mouse lymphocyte carcinomas B and T. Aliquots of log-phase cells were incubated for 72 h at 37 °C with three dose levels of each diorganotin(IV) compounds in triplicate. About 50 μL of 0.1% MTT was added to each well. After 4 h incubation, the culture medium was removed, and the blue formazan in the cells was dissolved with 2-propanol by vigorous shaking. The absorbance of each well was measured at 570 nm. The antitumor activity was determined by expressing the mean absorbance for drug-treated cells at each concentration as a percentage of that for untreated cells. The dose causing 50% inhibition of cell growth (IC$_{50}$) was determined from the curve of inhibiting percentage versus dose.

4. Final comments

We have prepared series of diorganotin(IV) complexes with different organo and substituted arylhydroxamate ligands and shown that they display in vitro antitumor activity which is markedly ligand dependent.

A first conclusion is that the mononuclear dibutyltin complexes, i.e. those with the organo-ligands having the longest carbon chain, exhibit the highest activity, as known [24] to occur for other diorganotin(IV) complexes.

Concerning the X substituents, one can compare, over a wide range of electronic properties, their effects on the antitumor activities by considering the results obtained in this work and those in our previous study [20], i.e. for the series of *p*-substituted benzohydroxamate complexes of the type [R$_2$SnL$_2$] (R = Me, Et, *n*Bu, Ph; L = ONHC(O)C$_6$H$_4$X-4 with X = NO$_2$, Cl [20], F, OMe [20], NH$_2$). In fact, the electron withdrawing/donor character of X varies drastically from the very strong acceptor NO$_2$ group to the quite effective donor NH$_2$ substituent, in the following order (with the values of the Hammett's σ_p constant [45] given in parentheses): NO$_2$ (0.778) > Cl (0.227) > F (0.062) > OMe (−0.268) > NH$_2$ (−0.66).

However, no general trend could be found between the antitumor activity of the complexes and the σ_p or any other constant (like σ_p^+, σ_I, Taft polar constant, etc. [45]) that measures the electronic effects (either the inductive, the resonance or the overall one) of the X-substituent.

In other series of diorganotin(IV) complexes with carboxylate ligands [24], the most active ones were the *n*-butyl derivatives, as in our case, and similarly no relationship between the activity and the substituent Hammett's σ_p constant was recognized.

Although for the dialkyl complexes the antitumor activity tends to increase with the electron withdrawing ability of the substituent from X = NH$_2$ up to X = Cl, a further increase of the latter character does not result in an additional enhancement of that activity, i.e. the strongest acceptor, NO$_2$, does not lead to the highest activity. The solubility of the complexes also plays a role, and the upper activity of the fluoro-substituted complexes, relative to the nitro-substituted ones, may result from the higher solubility in water of the former. The use of dinuclear complexes does not improve the activity.

Hence, the antitumor activity appears to be determined by a complex combination of effects of the various ligands and the establishment of structure-activity relationships with considerable generality still requires further investigation. Nevertheless, the best combination appears to be provided by the mononuclear dibutyltin(IV) (R = *n*Bu) complexes, i.e. with the organo-ligands having the longest carbon chain, in particular those with hydroxamate ligands presenting an electron-acceptor X substituent (a halo-atom or the nitro group).

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