Diorganotin(IV) Derivatives of Substituted Benzohydroxamic Acids with High Antitumor Activity

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Abstract: A series of diorganotin(IV) and dichlorotin(IV) derivatives of 4-X-benzohydroxamic acids, [HL_1 (X = Cl) or HL_2 (X = OCH_3)] formulated as [R_2SnL_2] (R = Me, Et, *n*Bu, Ph or Cl; L = L_1 or L_2), along with their corresponding mixed-ligand complexes [$R_2Sn(L_1)(L_2)$] have been prepared and characterized by FT-IR, ^1H, ^{13}C, and ^{119}Sn NMR spectroscopy, mass spectrometry, elemental analysis, and melting points. In addition, single-crystal X-ray diffraction analyses were carried out for [Me_2SnL_2] (L = L_1 or L_2), which show coordination structures intermediate between distorted octahedra and bicapped tetrahedra. The hydroxamate ligands are asymmetrically coordinated by the oxygen atoms, the carbonyl oxygen atom is further away from the metal center than the other oxygen atom. The complexes are stable monomeric species; most of them are soluble not only in chlorohydrocarbon solvents, but also in alcohols and hydroalcoholic solutions. In polar solvents, the mixed-ligand complexes gradually decompose into the corresponding single-ligand complex couples. The complexes exhibit in vitro antitumor activities (against a series of human tumor cell lines) which, in some cases, are identical to, or even higher than, that of cisplatin. For the dialkyltin complexes, the activity increases with the length of the carbon chain of the alkyl ligand and is higher in the case of the chloro-substituted benzohydroxamato ligand. The [$nBu_2Sn(L_1)_2$] complex displays a high in vivo activity against H22 liver and BGC-823 gastric tumors, and has a relatively low toxicity.

Keywords: antitumor agents · hydroxamate ligands · organotin complexes · structure–activity relationships · tin · X-ray diffraction

Introduction

Diorganotin(IV) complexes are potential antitumor agents mainly active against P_{388} lymphocytic leukemia and other tumors[1–3] and the NCI has tested about 2000 tin-based compounds, the largest number ever tested among metal complexes.[4] The first active complexes were designed to emulate the cisplatin framework[1–5] and their disadvantages are well recognized.[2,5,6] A large number of organotin(IV) derivatives with bidentate *O*-donor ligands,[7–15] including *N*-substituted hydroxamic acids, has been prepared and some of them possess strong antitumor activity against the MCF-7 mammary tumors and WiDr colon tumors.[1,6,16] However, they are inactive against most other tumors.

Hydroxamic acids are strong bidentate *O*-donors with bioactivity.[17,18] Benzohydroxamic acid is a typical case, being a nucleoside reductase inhibitor and thus exhibiting antitumor activity to some extent.[18] One of us initiated a study of the interactions between diorganotin(IV) acceptors and benzohydroxamic acid and its derivatives[19,20] with the hope that a synergic effect would occur. It was found that most of these complexes showed promising in vitro activity against a series of human tumor cell lines, a few of them exhibited modest in vivo activity against gastrointestinal tumors,[21] and the diethyltin(IV) and dibutyltin(IV) complexes of benzohydroxamic acid are the lead compounds.[19,21] Herein, we use two arylhydroxamic acids, HL_1 (X = Cl) and HL_2 (X = OCH_3), as ligands in tin(IV) complexes to investigate the electronic influence of the X substituent on their antitumor activities. The preparation of [R_2SnL_2] (R = Me, Et, *n*Bu, Ph; L = L_1 or L_2), [$R_2Sn(L_1)(L_2)$] and [Cl_2SnL_2], and a

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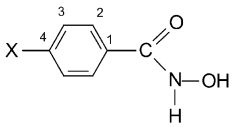
study of the spectroscopic and crystal structural features are reported, as well as their in vitro and in vivo antitumor activities and preliminary structure–activity relationships.



X = Cl (HL_1) ; OCH_3 (HL_2)

The in vitro activity against various tumors was recognized for some other dialkyltin(IV) complexes with diacyl or monoacyl heterocyclic derivatives of hydroxamic acids,[22] and for some triorganotin(IV) compounds with coordinated basic forms of terebic, benzoic, or salicylic acids.[23] However, these dialkyltin complexes were not fully structurally characterized, no X-ray analysis was performed, and no in vivo activity was reported.

Results and Discussion

Syntheses: The compounds $[R_2Sn(L_1)_2]$ (R = Me (**1**), Et (**2**), *n*Bu (**3**), or Ph (**4**)) and $[R_2Sn(L_2)_2]$ (R = Me (**5**), Et (**6**), *n*Bu (**7**), or Ph (**8**)) have been prepared by reaction of the appropriate $[R_2SnCl_2]$ with HL_1 or HL_2, in the presence of a base (KOH) and in undried methanol, at room temperature [Eq. (1)]. $[R_2Sn(L_1)(L_2)]$ (R = Me (**9**), Et (**10**), *n*Bu (**11**) or Ph (**12**)) were obtained similarly from stoichiometric amounts of both HL_1 and HL_2. This synthetic method is more convenient then that applied[10,22] to the preparation of other dialkyltin(IV) complexes which uses tin oxide compounds as starting materials in solvent-refluxing conditions. The chloro derivatives $[Cl_2SnL_2]$ (L = L_1 (**13**) and L_2 (**14**)) have been synthesized by refluxing a CH_2Cl_2 solution of $[SnCl_4]$ and the appropriate HL. Related dichloro complexes with other hydroxamates have been reported by others.[24]

$$[R_2SnCl_2] + 2\,HL + 2\,KOH \xrightarrow{MeOH} [R_2SnL_2] + 2\,KCl + 2\,H_2O$$
$$(HL = HL_1 \text{ or } HL_2;\ R = Me,\ Et,\ n\text{Bu or Ph}) \qquad (1)$$

The complexes were isolated as white solids (40–70 % yields). With the exception of **13** and **14**, which are not stable to moisture, all the complexes are stable in air, insoluble in water, and soluble in chloroform, acetone, DMSO and hydroalcoholic solutions. In polar solvents, the mixed-ligand complexes $[R_2Sn(L_1)(L_2)]$ **9**–**12** gradually decompose, as inferred from IR and NMR spectroscopy, to their corresponding single-ligand complexes $[R_2Sn(L_1)_2]$ and $[R_2Sn(L_2)_2]$, which, in some cases, were separated in the pure form by slow evaporation of chloroform solutions of the mixed-ligand compounds. All the complexes were characterized by IR, ^1H, ^{13}C, and ^{119}Sn NMR spectroscopy, mass spectrometry, elemental analysis, and melting point determination, as well as single-crystal X-ray diffraction analysis in the case of $[Me_2SnL_2]$ (L = L_1 (**1**) and L_2 (**5**)).

Spectroscopic and mass spectra data: Comparison of the IR spectra of the complexes with those of the free ligands shows the disappearance of the broad band (intramolecular O–H···O stretch) at about 2700 cm^{-1}, as a result of the loss of the OH proton in the CO–NHO*H* group upon coordination. The shift towards lower frequencies of the highest ν(C=O) from about 1680 cm^{-1} in the free ligand to about 1600 cm^{-1} in the complexes indicates that the ligand coordinates through this oxygen. ν(N–H) bands at about 3200 cm^{-1} and the shift towards higher frequencies of ν(N–O) exclude coordination through the N atom.[25] Therefore, the IR spectra indicate coordination via both O atoms of the $CONHO^-$ group.

In the 535–400 cm^{-1} region, the two (or more) strong absorptions of the diorganotin(IV) complexes are assigned to ν(Sn–O).[26–29] The presence of more than one Sn–O band, which is more obvious for the mixed-ligand complexes, reflects different Sn–O bond lengths, as proved by the X-ray analysis. The dichlorotin derivatives **13** and **14** exhibit ν(Sn–O) bands (≈550–490 cm^{-1}) shifted to higher frequencies, reflecting the different effects of the chloro and the organo ligands.[29] Generally, a powerful electron-withdrawing group, such as Cl, increases the strength of the Sn–O bonds.[30,31] ν(Sn–Cl) for **13** and **14** are at about 310–370 cm^{-1} and their multiplicity can arise from *cis* and *trans* isomers.[29]

The mass spectra clearly show the respective molecular ions $[M]^+$ and fragments formed upon sequential loss of ligands. For the dichloro complexes, $[SnL_3]^+$ peaks were also detected under FAB conditions. The ^1H, ^{13}C, and ^{119}Sn NMR spectra show all the expected signals, with some evident coordination shifts. The ^2J(Sn,H) and ^1J(Sn,C) values, 72.3 and 686 Hz, respectively, which could be measured for complex **5** (the lower stability or solubility of the other organotin complexes precluded their measurement) are adequate for hexacoordinated tin(IV) compounds[32] and the value of the θ(C–Sn–C) angle estimated from the Lockhart and Manders Equation (2)[33] (137°) indicates quite a distorted *trans* configuration that has been confirmed by X-ray diffraction (see below). In the ^{119}Sn NMR spectra, the $\delta(^{119}Sn)$ values also fall in the range typical for hexacoordinated tin(IV) complexes.[34] There is only a single resonance for the $[R_2SnL_2]$ complexes, thus excluding the presence of isomers; however, solutions of the mixed-ligand complexes **11** and **12** exhibit two resonances as a consequence of decomposition and/or the presence of isomers.

$$\theta(C{-}Sn{-}C) = [^1J(Sn,C) + 875]/11.4 \qquad (2)$$

X-ray diffraction analyses: The molecular structures of the complexes $[Me_2SnL_2]$ (L = L_1 (**1**) and L_2 = (**5**)] were authenticated by single-crystal X-ray diffraction analyses. Crystallographic data are given as Supporting Information. Molecular structures with their respective numbering schemes are shown in Figure 1 and Figure 2, and selected bond lengths and angles are given in Table 1. The coordination polyhedron consists of four O atoms from two chelating

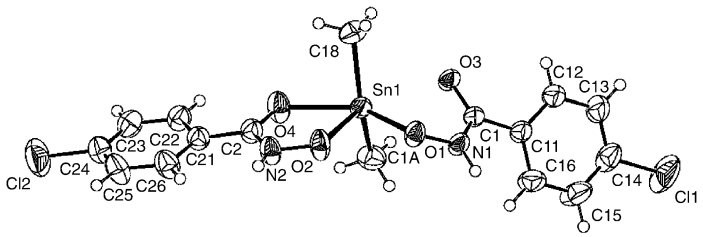


Figure 1. Molecular structure of $[(CH_3)_2Sn\{ONC(O)C_6H_4Cl\text{-}4\}_2]$ (**1**).

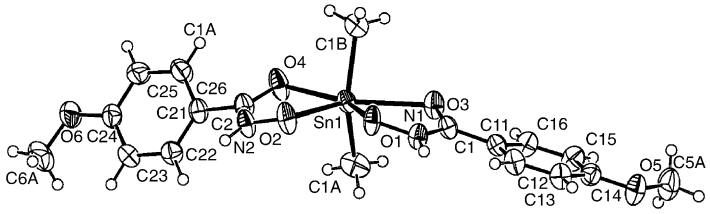


Figure 2. Molecular structure of $[(CH_3)_2Sn\{ONC(O)C_6H_4OCH_3\text{–}4\}_2]$ (**5**).

Table 1. Selected bond lengths [Å] and angles [°] for **1** and **5**.

1		**5**	
Sn1–O1	2.090(2)	Sn1–O1	2.108(4)
Sn1–O2	2.088(2)	Sn1–O2	2.067(4)
Sn1–O3	2.597(2)	Sn1–O3	2.491(4)
Sn1–O4	2.330(2)	Sn1–O4	2.407(4)
Sn1–C1A	2.101(4)	Sn1–C1A	2.114(6)
Sn1–C1B	2.098(4)	Sn1–C1B	2.095(5)
O1–N1	1.381(5)	O1–N1	1.369(5)
O2–N2	1.384(4)	O2–N2	1.383(5)
O3–C1	1.254(4)	O3–C1	1.266(6)
O4–C2	1.254(4)	O4–C2	1.251(6)
N1–C1	1.312(4)	N1–C1	1.322(6)
N2–C2	1.304(5)	N2–C2	1.315(6)
O1-Sn1-O2	76.43(9)	O1-Sn1-O2	75.56(13)
O1-Sn1-O3	67.64(8)	O1-Sn1-O3	69.99(12)
O1-Sn1-O4	148.78(8)	O1-Sn1-O4	147.02(12)
O2-Sn1-O3	143.99(8)	O2-Sn1-O3	144.86(13)
O2-Sn1-O4	72.82 (9)	O2-Sn1-O4	71.82(13)
O3-Sn1-O4	143.17(8)	O3-Sn1-O4	142.96(11)
C1A-Sn1-C1B	142.7(2)	C1A-Sn1-C1B	140.8(2)

groups are accommodated towards the side of the latter Sn–O bonds. Asymmetric chelation of hydroxamate-type ligands has been observed in other tin(IV) complexes.[4b,7,8,14,15,29,34,35] The endocyclic C–O and N–C bond lengths are indicative of a significant electronic delocalization. The least-square plane of the four oxygen atoms in each molecule is such that all of the O atoms are within a standard deviation of 0.053 (**1**) or 0.083 Å (**5**). The tin atoms lie in each of these planes. Both hydroxamate ligands in each molecule are planar, the chelate rings are described by the planes containing the O-N-C-O moieties (all atoms within a standard deviation of 0.0010 or 0.0039 (**1**) and 0.0016 and 0.0057 Å (**5**)); the tin atoms are slightly outside these planes (by 0.1104(66) or 1.1632(51) (**1**) and 0.5830(79) or 0.5451(73) Å (**5**), respectively). In each molecule, the two planes define angles of 44.47 (15)° (**1**) and 35.45(26)° (**5**).

Antitumor activities in vitro and in vivo: The in vitro antitumor activity has been tested on various human tumor cell lines [immature granulocyte leukemia (HL-60), nasopharyngeal carcinoma (KB), hepatocellular carcinoma (Bel-7402) and ovarian carcinoma (Hela)] and on mouse tumor cell lines (lymphocyte carcinomas (B and T)). The selected results obtained for the dose level of 10.0 μM are given in Table 2, whereas the complete listing for the three tested levels (0.1, 1.0, and 10.0 μM) are given in the Supporting Information, together with a summary of the screening data for the antitumor activity of all the complexes. The following structure–activity relationships could be recognized: 1) with regard to the R group: the activity decreases in the order *n*Bu > Ph, Et > Me; 2) with regard to the X substituent of the hydroxamate aromatic ring: for the dibutyl and diethyl tin(IV) derivatives, the activity tends to decrease as the electron-acceptor character of X decreases, that is, from the electron-withdrawing Cl substituent to the electron-donating OCH_3 group, whereas the opposite is observed for the diphenyl tin(IV) complexes. Hence, the antitumor activity can be determined by a delicate balance of electronic effects of the ligands; however, the best combination is provided by the dibutyltin(IV) (R = *n*Bu) complex with the chloro-substituted (X = Cl) hydroxamate ligand, namely $[n\mathrm{Bu}_2\mathrm{Sn}(\mathrm{L}_1)_2]$ (**3**), which is more active than "cisplatin", the clinically widely used drug. Complex **3** was then selected for in vivo tests (administered orally) against the mouse H22 liver tumor and BGC-823 gastric tumor (Table 3). The ob-

Table 2. Inhibition [%] of diorganotin(IV) complexes [dose level of 10.00 μM] against human and mouse tumor cell lines.

Complex	Leukem. HL-60	Nasophar. carcinoma KB	Hepatocel. carcinoma Bel-7402	Ovarian carcinoma Hela	Lymph. carcinoma B	Lymph. carcinoma T
1	27.6	16.8	11.9	–	25.4	38.6
2	69.2	88.6	63.4	66.8	73.9	69.9
3	85.1	98.5	97.2	96.2	84.8	72.2
4	27.5	39.9	14.6	16.2	6.4	–
6	55.0	78.3	22.2	45.4	70.4	67.0
7	80.7	100.0	70.5	77.5	48.7	–
8	67.0	86.7	84.2	84.3	68.5	–

hydroxamates and two C atoms of the methyl groups. The C-Sn-C angles of 142.7(2) (**1**) and 140.8(2)° (**5**) are much smaller than the value expected for a regular octahedron. The structures are intermediate between a distorted octahedron and a bicapped tetrahedron. Another important distortion is caused by the asymmetric Sn–O bond lengths, since two of the Sn–O bonds are short (2.090(3) and 2.088(2) (**1**) or 2.108(4) and 2.067(4) (**5**) Å), defining a small O-Sn-O angle (76.43(9) (**1**) or 75.56(13)° (**5**)), while the other two are longer (2.330(2) and 2.597(2) (**1**) or 2.491(4) and 2.407(4) Å (**5**)), defining an angle of about 143° (average). The methyl

Table 3. In vivo antitumor activity.[a]

Compound or group	Dosage [mg kg^{-1}]	Mouse weight [g] initial	Mouse weight [g] final	Tumor weight [g]	Inhibition[b] [%]	P
against mouse H22 liver tumor						
3	20	19.2±0.7	23.8±4.8	0.50±0.14	63.5	<0.001
	10	19.3±1.2	22.6±1.6	0.77±0.11	43.8	<0.01
	5	19.2±1.0	26.7±3.0	1.23±0.12	10.2	>0.05
carboplatin[c]	20	19.4±1.0	23.0±2.4	0.34±0.15	75.2	<0.001
control group[d]	–	19.3±0.9	28.5±4.3	1.37±0.25	–	–
against mouse BGC-823 gastric tumor						
3	15	20.4±2.2	23.9±4.5	0.38±0.09	61.6	<0.001
	10	19.9±1.1	24.5±1.5	0.59±0.25	40.4	<0.01
	5	20.1±1.0	27.6±2.8	0.95±2.60	10.2	0.05
cyclophosphamide[c]	80	20.2±1.2	24.5±2.2	0.29±0.14	70.2	<0.001
control group[d]	–	20.4±1.6	28.7±2.0	0.99±0.19	–	–

[a] Starting number = final number of mice = 10, except for the control group with 20 mice. All the compounds were administered orally, with the exception of "carboplatin" which was injected subcutaneously. [b] (Inhibited tumor weight)/(tumor weight) [%]. [c] Included for comparative purposes. [d] Without any drug administration.

served in vivo activities are close to those of "carboplatin" in the case of the liver tumor, whereas the gastric tumor complex **3** exhibits an activity close to that of cyclophosphamide.

The acute toxicity tests of those organotin complexes reveal LD_{50} values (drug dose leading to the death of 50% of the tested animals) higher than 400 mg kg^{-1}, that is, well above those of "cisplatin", which indicates a lower toxicity of the former complexes.

Conclusion

In this work we have prepared and fully characterized a series of diorgano- and dichlorotin complexes with substituted benzohydroxamic acids and found that they exhibit notable in vitro and in vivo antitumor activities (the latter against liver and gastric tumors), with a relatively low toxicity. The study also shows that the activity is dependent on the length of the carbon chain of the alkyl ligand and on the electronic properties of the substituent of the benzohydroxamato ring, increasing with the length of the carbon chain and with the electron-withdrawing ability of the substituent for the dialkyltin complexes, although for the diphenyltin complexes the reverse electronic effect appears to hold.

The X-ray analysis of two members of the series provided additional information about the structure of this type of complexes (intermediate between distorted octahedron and bicapped tetrahedron) and the coordination mode of the arylhydroxamate ligands.

Hence, the obtained results allow the recognition of preliminary structure–activity relationships (although it shows that generalizations have to be taken rather cautiously) and provide some foundation for further design and structure optimization of diorganotin(IV) complexes in the search for a suitable candidate for clinical usage.

Experimental Section

The tin(IV) and diorganotin(IV) halides were purchased from Alfa and Aldrich, and the methylbenzoate derivatives were obtained from Aldrich. They were used as received. The other chemicals are of analytical grade. The substituted benzohydroxamic acids, HL_1 and HL_2, were prepared according to a known[36] general procedure. The samples for microanalyses were dried to constant weight in a vacuum (20 °C, ≈0.1 Torr). The IR spectra were recorded with a Bio-Rad FT-IR instrument in KBr plates. ^{1}H, ^{13}C, and ^{119}Sn NMR spectra were recorded on a VXR-300 Varian spectrometer at room temperature (300.0 MHz for ^{1}H, 75.5 MHz for ^{13}C and 111.9 MHz for ^{119}Sn). Mass spectra were performed on a Trio 2000 VG spectrometer connected to a Carlo Erba GC system. The positive-ion FAB spectra were obtained by bombarding 3-nitrobenzyl alcohol (NOBA) matrices of the samples with 8 keV xenon atoms. Melting points were measured on a Leica Galen III Electrothermal instrument. Elemental analyses were performed at the Analytical Laboratory of the Institute Superior Técnico.

Syntheses of the complexes

Bis(4-X-benzohydroxamato)dimethyltin(IV), [R_2SnL_2] (L = L_1: R = Me (1), Et (2), *n*Bu (3), or Ph (4); L = L_2: R = Me (5), Et (6), *n*Bu (7) or Ph (8)): The appropriate [R_2SnCl_2] (1.0 mmol) complex was added to an undried methanolic solution (20 mL) of the aryl hydroxamic acid HL (0.344 g (HL_1) or 0.336 g (HL_2), 2.0 mmol) and KOH (0.112 g, 2.0 mmol). The solution was stirred under N_2 at room temperature overnight. Water (20 mL) was added leading to the formation of a white precipitate of [R_2SnL_2], which was separated by filtration, washed with water and cold methanol, recrystallized from ethanol (**3**, **5** or **7**), ethanol/chloroform (**1**, **4** or **8**) or chloroform/pentane (**2** or **6**), and dried in vacuo to constant weight (40–70% yield).

*[Me_2Sn{ONHC(O)C_6H_4Cl-4}$_2$] (**1**)*: White; m.p. 205–206 °C; IR (KBr): $\tilde{\nu}$ = 3205 s (N–H); 1557 s and 1601 s (CO)/(NC); 910 s (N-O); 471 m, 488 m and 534 m (Sn–O); 578 s (Sn–C) cm^{-1}; ^{1}H NMR ([D_6]DMSO): δ = 12.93 (br s, 2H, N*H*–O), 7.71 [br d, ^3J(H,H) = 7.5 Hz, 4H, H(2)], 7.50 [br, 4H, H(3)], 0.45 ppm (br s, 6H, CH_3, *R*-Sn); ^{13}C{^{1}H} NMR ([D_6]DMSO): δ = 162.95 (CO), 139.30 [C(4)], 131.31 [C(1)], 129.28 [C(3)], 128.15 [C(2)], 7.48 ppm (CH_3, *R*-Sn); ^{119}Sn NMR ([D_6]DMSO): δ = −446.4 ppm; FAB$^+$-MS: *m*/*z*: 490 [*M*]$^+$, 475 [*M*−R]$^+$, 320 [*M*−L]$^+$, 305 [*M*−R−L]$^+$, 150 [*M*−2L]$^+$, 135 [*M*−R−2L]$^+$, 120 (Sn$^+$); elemental analysis calcd (%) for $H_{16}C_{16}N_2O_4Cl_2Sn$: C 39.22, H 3.27, N 5.72; found: C 38.93, H 3.22, N 5.14.

*[Et_2Sn{ONHC(O)C_6H_4Cl-4}$_2$] (**2**)*: White; m.p. > 300 °C; IR (KBr): $\tilde{\nu}$ = 3258 s (N–H); 1535 s, 1559 m and 1605 s (CO)/(NC); 909 s (N–O); 496 m and 537 s (Sn–O); 583 w (Sn–C) cm^{-1}; ^{1}H NMR ([D_1]$CDCl_3$): δ = 7.51 [br, 4H, H(2)], 7.19 [br, 4H, H(3)], 1.54 (br, 4H, CH_2, *R*–Sn), 1.21 ppm (br, 6H, CH_3, *R*–Sn); ^{13}C{^{1}H} NMR ([D_1]$CDCl_3$): δ = 161.30 (CO), 136.18 [C(4)], 128.03 [C(3)], 127.40 [C(2)], 18.73 (CH_2, *R*–Sn), 9.02 ppm (CH_3, *R*–Sn); ^{119}Sn NMR ([D_1]$CDCl_3$): δ = −441.4 ppm; elemental analysis calcd (%) for $H_{20}C_{18}N_2O_4Cl_2Sn$: C 41.73, H 3.90, N 5.41; found: C 41.56, H 3.88, N 5.29.

*[nBu_2Sn{ONHC(O)C_6H_4Cl-4}$_2$] (**3**)*: White; m.p. 189–191 °C; IR (KBr): $\tilde{\nu}$ = 3188 vs (N–H); 1534 m, 1557 s and 1594 vs (CO)/(NC); 913 s (N–O); 421 m and 527 s (Sn–O); 551 m and 572 w (Sn–C) cm^{-1}; ^{1}H NMR ([D_6]DMSO): δ = 13.2 (br, N–*H*), 7.33 [br d, ^3J(H,H) = 6.7 Hz, 4H, H(2)], 7.09 [br, 2H, H(3)], 6.94 [br d, ^3J(H,H) = 6.6 Hz, 2H, H(3)], 1.17 (t br, ^3J(H,H) ≈9 Hz, 4H, CH_2, *R*–Sn), 0.98–0.85 (br m,, 8H, CH_2, *R*–Sn), 0.41 ppm (q, due to two overlapping triplets at δ = 0.42 and 0.40 ppm, ^3J(H,H) = 7.5 Hz, 6H, CH_3, *R*–Sn); ^{13}C{^{1}H} NMR ([D_1]$CDCl_3$): δ = 162.93 (CO); 138.49 [C(4)], 131.36, 131.35, 129.20, 128.32 and 127.78 (C_{arom}); 26.83, 26.38, 26.10 (CH_2, *R*–Sn); 13.60 ppm

(CH_3, *R*–Sn); ^{119}Sn NMR ([D$_1$]CDCl$_3$): $\delta = -443.6$ ppm; FAB$^+$-MS: *m*/*z*: 574 $[M]^+$, 517 $[M-R]^+$, 404 $[M-L]^+$, 347 $[M-R-L]^+$, 234 $[M-2L]^+$, 177 $[M-R-2L]^+$, 120 (Sn^+); elemental analysis calcd (%) for $H_{28}C_{22}N_2O_4Cl_2Sn$: C 46.02, H 4.92, N 4.88; found: C 46.83, H 4.95, N 4.79.

*[Ph$_2$Sn{ONHC(O)C$_6$H$_4$Cl-4}$_2$] (**4**)*: White; m.p. 235–237 °C; IR (KBr): $\tilde{\nu}$ = 3189 s (N–H); 1523 m, 1561 m, 1596 w and 1647 m (CO)/(NC); 914 s (N–O); 536 m and 446 m (Sn–O); 557 w and 571 w (Sn–C) cm^{-1}; ^{1}H NMR ([D$_1$]CDCl$_3$): δ = 12.92 (br s, 2H, N*H*–O); 7.84–7.17 ppm (m, 18H, H_{arom}); ^{13}C{^{1}H} NMR ([D$_1$]CDCl$_3$): δ = 160.33 (CO); 135.08 [C(4)], 131.17–126.80 ppm (C_{arom}); ^{119}Sn NMR ([D$_1$]CDCl$_3$): δ = −442.0 ppm; elemental analysis calcd (%) for $H_{20}C_{26}N_2O_4Cl_2Sn$: C 50.85, H 3.29, N 4.55; found: C 50.65, H 3.51, N 4.38.

*[Me$_2$Sn{ONHC(O)C$_6$H$_4$OMe-4}$_2$] (**5**)*: White; m.p. 219–223 °C (decomp.); IR (KBr): $\tilde{\nu}$ = 3210 s (N–H); 1500 s, 1561 s and 1604 s (CO)/(NC); 914 s (N–O); 484 m and 511 s (Sn–O); 570 w and 617 s (Sn–C) cm^{-1}; ^{1}H NMR ([D$_6$]DMSO): δ = 12.63 (br s, 2H, NH–O); 7.64 [d, ^3J(H,H) = 8.7 Hz, 4H, H(2)]; 6.95 [d, ^3J(H,H) = 8.7 Hz, 4H, H(3)]; 3.76 (s, 3H, OCH_3); 3.34 (s, 3H, OCH_3); 0.26 ppm (s + d, ^2J(Sn,H) = 72.3 Hz, 6H, CH_3, R–Sn); ^{13}C{^{1}H} NMR ([D$_6$]DMSO): δ = 161.42 [C(4)]; 161.01 (CO); 127.78 [C(2)]; 122.02 [C(1)]; 113.88 [C(3)]; 55.32 (OCH_3); 6.23 ppm (CH_3, ^1J(Sn,C) = 686 Hz, R–Sn); ^{119}Sn NMR ([D$_1$]CDCl$_3$): δ = −488.3 ppm; FAB$^+$-MS: *m*/*z*: 482 $[M]^+$, 467 $[M-R]^+$, 315 $[M-L]^+$, 301 $[M-R-L]^+$, 150 $[M-2L]^+$, 135 $[M-R-2L]^+$, 120 (Sn^+); elemental analysis calcd (%) for $H_{22}C_{18}N_2O_6Sn$: C 44.93, H 4.62, N 5.82; found: C 44.80, H 4.86, N 5.72.

*[Et$_2$Sn{ONHC(O)C$_6$H$_4$OMe-4}$_2$] (**6**)*: White; m.p. 189–190 °C; IR (KBr): $\tilde{\nu}$ = 3206 s (N–H); 1500 s, 1555 s, 1564 s and 1608 s (CO)/(NC); 917 m (N–O); 403 m and 519 s (Sn–O)]; 554 m (Sn–C) cm^{-1}; ^{1}H NMR ([D$_6$]DMSO): 8.05 [d, ^3J(H,H) = 8.7 Hz, 2H, H(2)]; 7.79 [d, ^3J(H,H) = 8.7 Hz, 2H, H(2)]; 6.89 [d, ^3J(H,H) = 8.7 Hz, 2H, H(3)]; 6.85 [d, ^3J(H,H) = 8.7 Hz, 2H, H(3)]; 3.87 (s, 3H, OCH_3); 3.76 (s, 3H, OCH_3); 1.68 (q + dq, ^3J(H,H) = 7.9 Hz, ^2J(Sn,H) = 72.6 Hz, 4H, CH_2, *R*-Sn), 1.33 ppm (t, ^3J(H,H) = 7.9 Hz, 4H, CH_3, *R*-Sn); ^{13}C{^{1}H} NMR ([D$_1$]CDCl$_3$): δ = 162.58 [C(4)]; 162.30 (CO); 128.55 [C(2)], 120.23 [C(1)], 113.87 [C(3)]; 55.20 (OCH_3); 20.30 (CH_2, *R*–Sn); 9.68 ppm (CH_3, *R*–Sn); ^{119}Sn NMR ([D$_1$]CDCl$_3$): δ = −443.6 ppm; elemental analysis calcd (%) for $H_{26}C_{20}N_2O_6Sn$: C 47.17, H 5.16, N 5.50; found: C 47.27, H 5.30, N 5.67.

*[nBu$_2$Sn{ONHC(O)C$_6$H$_4$OMe-4}$_2$] (**7**)*: White; m.p. 110–113 °C; IR (KBr): $\tilde{\nu}$ = 3202 s (N–H); 1565 m and 1607 s (CO)/(NC); 916 s (N–O); 449 m and 524 w (Sn–O)]; 567 w (Sn–C) cm^{-1}; ^{1}H NMR ([D$_1$]CDCl$_3$): δ = 12.22 (br s, 1H, N*H*–O), 7.77 [br, 4H, H(2)]; 6.74 [br, 4H, H(3)]; 3.68 (br, 6H, OCH_3 and 2H, CH_2); 1.67 (br m, 10H, CH_2, *R*–Sn), 0.87 ppm (br, 6H, CH_3, *R*–Sn); ^{13}C{^{1}H} NMR ([D$_1$]CDCl$_3$): δ = 173.54 [C(4)], 162.31 (CO), 132.19 [C(2)], 128.51 [C(1)], 113.89 [C(3)], 55.18 (OCH_3); 27.19, 26.33, 25.96 (CH_2, *R*–Sn); 13.55 ppm (CH_3, *R*–Sn); ^{119}Sn NMR ([D$_1$]CDCl$_3$): δ = −356.7 ppm; elemental analysis calcd (%) for $H_{34}C_{24}N_2O_6Sn$: C 50.99, H 6.07, N 4.96; found: C 51.22, H 6.24, N 4.78.

*[Ph$_2$Sn{ONHC(O)C$_6$H$_4$OMe-4}$_2$] (**8**)*: White; m.p. 209–212 °C (decomp.); IR (KBr): $\tilde{\nu}$ = 3206 s (N–H); 1531 m, 1566 m and 1607 s (CO)/(NC); 917 s, (N–O); 521 m (Sn–O); 554 m (Sn–C) cm^{-1}; ^{1}H NMR ([D$_6$]DMSO): δ = 12.69 (br s, 2H, N*H*–O), 7.02–6.10 (m, 18H, H_{arom}), 2.96 and 2.94 ppm (s, 6H, OCH_3); ^{13}C{^{1}H} NMR ([D$_1$]CDCl$_3$): δ = 162.78 [C(4)]; 162.26 (CO), 135.89–128.47, 119.79–113.15 (C_{arom}), 55.21 ppm (OCH_3); ^{119}Sn NMR ([D$_1$]CDCl$_3$): δ = −488.3 ppm; elemental analysis calcd (%) for $H_{26}C_{28}N_4O_6Sn$: C 55.56, H 4.34, N 4.63; found: C 55.86, H 4.56, N 4.59.

Mixed-ligand diorganotin(IV) complexes, [R$_2$Sn(L$_1$)(L$_2$)] (R = Me (9), Et (10), *n*Bu (11) or Ph (12): The appropriate [R$_2$SnCl$_2$] complex (1 mmol) was added to an undried methanolic solution (20 mL) of HL$_1$ (0.172 g, 1 mmol) and HL$_2$ (0.168 g, 1 mmol), with KOH (0.112 g, 2 mmol). The clear reaction solution was stirred overnight at room temperature under N_2. Addition of water (15 mL) led to the immediate formation of a white precipitate of [R$_2$Sn(L$_1$)(L$_2$)], which was separated by filtration, washed with water and cold methanol, recrystallized from ethanol-dichloromethane, and dried to constant weight.

*[Me$_2$Sn{ONHC(O)C$_6$H$_4$Cl-4}{ONHC(O)C$_6$H$_4$OMe-4}] (**9**)*: White; m.p. 195–197 °C; IR (KBr): $\tilde{\nu}$ = 3208 s (N–H); 1559 s and 1599 vs (CO)/(NC); 912 s (N–O); 424 w, 485 m and 527 m (Sn–O); 575 w and 619 s (Sn–C) cm^{-1}; ^{1}H NMR ([D$_1$]CDCl$_3$): δ = 7.88–6.75 (m, 8H, H_{arom}); 3.74 (br s, 3H, OCH_3), 0.93 ppm (s + d, 6H, *R*–Sn; ^2J(Sn,H) = 86.4 Hz); ^{13}C{^{1}H} NMR ([D$_1$]CDCl$_3$): δ = 172.42 [C(4), L$_2$], 163.41 and 162.41 (CO, L$_1$ and L$_2$); 138.29 [C(4), L$_1$], 131.30, 128.86, 128.23, 127.88 (C_{arom}), 114.07 [C(3), L$_2$], 55.33 (OCH_3), 30.92 ppm (CH_3, *R*–Sn); ^{119}Sn NMR ([D$_1$]CDCl$_3$): δ = −312.4 ppm; elemental analysis calcd (%) for $H_{19}C_{17}N_2O_5ClSn$: C 42.05, H 3.95, N 5.77; found: C 42.38, H 4.02, N 5.51.

*[Et$_2$Sn{ONHC(O)C$_6$H$_4$Cl-4}{ONHC(O)C$_6$H$_4$OMe-4}] (**10**)*: White; m.p. 253–255 °C; IR (KBr): $\tilde{\nu}$ = 3246 s (N–H); 1526 m, 1568 s, 1598 s and 1607 vs (CO)/(NC); 916 vs (N–O); 415 w, 465 m and 530 s (Sn–O); 572 s (Sn–C) cm^{-1}; ^{1}H NMR ([D$_6$]DMSO): δ = 12.94 (br, N*H*); 7.31–7.28 (m, 4H, H_{arom}), 7.04–6.91 (m, 2H, H_{arom}), 6.61–6.53 (m, 2H, H_{arom}), 3.36 (s, 3H, OCH_3), 1.14 (br q, ^3J(H,H) = 7.50 Hz, 2H, CH_2, *R*–Sn), 0.92–0.85 (m, 5H, CH_2+CH_3, *R*–Sn) and 0.397 ppm (t, ^3J(H,H) = 7.50 Hz, 3H, CH_3, *R*–Sn); ^{13}C{^{1}H} NMR ([D$_1$]CDCl$_3$): δ = 173.10 (CO, L$_2$), 162.74 (CO, L$_1$), 160.77 [C(1), L$_2$], 135.61 [C(1), L$_1$], 132.41 [C(4), L$_1$], 130.19 [C(3), L$_1$], 128.32 [C(3), L$_2$], 127.63 [C(2), L$_1$], 55.40 (OCH_3), 18.54 (CH_2, *R*–Sn), 5.51 ppm (CH_3, *R*–Sn); ^{119}Sn NMR ([D$_1$]CDCl$_3$): δ = −580.5 ppm; elemental analysis calcd (%) for $H_{23}C_{19}N_2O_5ClSn$: C 44.43, H 4.52, N 5.46; found: C 44.31, H 4.69, N 5.47.

*[nBu$_2$Sn{ONHC(O)C$_6$H$_4$Cl-4}{ONHC(O)C$_6$H$_4$OMe-4}] (**11**)*: White; m.p. 196–200 °C (decomp.); IR (KBr): $\tilde{\nu}$ = 3211 s (N–H); 1528 s, 1596 vs and 1605 s (CO)/(NC), 917 s (N–O), 414 w, 460 m and 537 s (Sn–O), 570 s and 619 m (Sn–C) cm^{-1}; ^{1}H NMR ([D$_1$]CDCl$_3$): δ = 12.00 (br, N*H*-O), 7.71–6.45 (m, 8H, H_{arom}), 1.73–0.89 ppm (m, 18H, *R*-Sn); ^{13}C{^{1}H} NMR ([D$_1$]CDCl$_3$): δ = 162.63 and 161.68 [CO or C(4) L$_1$]; 138.14, 131.40, 128.49, 128.07, 113.90 (C_{arom}) 55.33 (OCH_3); 27.16–25.92 (CH_2, *R*–Sn), 13.57 ppm (CH_3, *R*–Sn); ^{119}Sn NMR ([D$_1$]CDCl$_3$): δ = −355.1 and −514.1 ppm (relative intensities, 1:1.6) (see text); elemental analysis calcd (%) for $H_{31}C_{23}N_2O_5ClSn$: C 48.49, H 5.44, N 4.92; found: C 48.13, H 5.48, N 4.76.

*[Ph$_2$Sn{ONHC(O)C$_6$H$_4$Cl-4}{ONHC(O)C$_6$H$_4$OMe-4}] (**12**)*: White; m.p. 195–197 °C; IR (KBr): $\tilde{\nu}$ = 1528 m, 1574 m, 1598 s and 1601 s (CO)/(NC); 911 m (N-O), 448 s, 500 m and 523 s (Sn–O), 557 m (Sn–C) cm^{-1}; ^{1}H NMR ([D$_1$]CDCl$_3$): δ = 8.80–6.45 (m, 18H, H_{arom}), 3.61 ppm (s, 3H, OCH_3); ^{13}C{^{1}H} NMR ([D$_1$]CDCl$_3$): δ = 167.94, 162.42 and 162.08 [CO and C(4)], 135.50, 128.37, 113.95 (C_{arom}); 55.39 ppm (OCH_3); ^{119}Sn NMR ([D$_1$]CDCl$_3$): δ = −345.0 and −578.1 ppm (relative intensities, 5:1) (see text); elemental analysis calcd (%) for $H_{23}C_{27}N_2O_5ClSn$: C 53.20, H 3.81, N 4.60; found: C 54.01, H 3.90, N 5.42.

Bis(4-X-benzohydroxamato)dichlorotin(IV), [Cl$_2$SnL$_2$], L = L$_1$ (13) or L$_2$ (14): Tin tetrachloride (2.60 g, 1 mmol) was added to a solution of HL [0.344 g (HL$_1$) or 0.336 g (HL$_2$), 2 mmol] in dichloromethane (25 mL). The reaction mixture was refluxed overnight. The hot solution was filtered and a white crystalline precipitate of [Cl$_2$SnL$_2$] was formed slowly from the filtered solution left at room temperature. The solid was separated by filtration and dried to constant weight.

*[Cl$_2$Sn{ONHC(O)C$_6$H$_4$Cl-4}$_2$] (**13**)*: White; m.p. 246 °C (decomp); IR (KBr): $\tilde{\nu}$ = 3242 s (N–H); 1517 s, 1569 m and 1599 vs (CO)/(NC); 917 s (N–O), 581 m and 615 m (Sn–C), 490 m and 546 m (Sn–O); 314 s, 340 s and 368 m (Sn-Cl) cm^{-1}; ^{1}H NMR ([D$_1$]CDCl$_3$): δ = 12.39 (br s, 2H, N*H*–O); 7.03–6.8 ppm (m, 8H, H_{arom}); ^{13}C{^{1}H} NMR ([D$_6$]DMSO): δ = 160.34 (CO); 137.83 [C(4)], 129.23 [C(1)], 128.38 [C(3)], 125.20 ppm [C(2)]; ^{119}Sn NMR ([D$_1$]CDCl$_3$): δ = −422.1 ppm; FAB$^+$-MS: *m*/*z*: 530 $[M]^+$, 290 $[M-2Cl-L]^+$, 495 $[M-Cl]^+$, 629 $[M-2Cl+L]^+$; elemental analysis calcd (%) for $H_{10}C_{14}N_2O_2Cl_3Sn$: C 31.68, H 1.90, N 5.28; found: C 31.75, H 1.85, N 5.10.

*[Cl$_2$Sn{ONHC(O)C$_6$H$_4$OMe-4}$_2$] (**14**)*: White; m.p. 210 °C (decomp.); IR (KBr): $\tilde{\nu}$ = 1599 s and 1604 s (CO)/(NC), 912 s (N–O), 579 m and 625 s (Sn–C), 491 w and 552 m (Sn–O); 328 s, 334 s and 352 s (Sn–Cl) cm^{-1}; ^{1}H NMR ([D$_6$]DMSO): δ = 14.22 (br, 2H, N*H*), 7.78 [br, 4H, H(2)], 6.98 [br, 4H, H(3)], 3.79 (br, 3H, OCH_3), 3.18 ppm (br, 3H, OCH_3); ^{13}C{^{1}H} NMR ([D$_1$]CDCl$_3$): δ = 161.13 [C(4)], 159.18 (CO), 126.77 [C(2)], 116.79 [C(1)], 112.83 and 112.35 [C(3)], 53.99 and 53.49 ppm (OCH_3); ^{119}Sn NMR ([D$_1$]CDCl$_3$): δ = −530.1 ppm; FAB$^+$-MS: *m*/*z*: 522 $[M]^+$, 286 $[M-2Cl-L]^+$, 487 $[M-Cl]^+$, 618 $[M-2Cl+L]^+$; elemental analysis calcd (%) for $H_{10}C_{14}N_2O_2Cl_2Sn$: C 36.84, H 3.10, N 5.37; found: C 36.96, H 3.15, N 5.28.

X-ray crystallography of complexes 1 and 5: Diffraction measurements were carried out at room temperature on an Enraf-Nonius MACH3 dif-

fractometer, with a graphite monochromator and $Mo_{K\alpha}$ radiation (λ = 0.71073 Å). Cell dimensions were obtained from centered reflections with θ values ranging from 8 to 12°. Data were collected with θ values between 2 and 25° (**1**) or 1.8 and 25° (**5**). Range of *hkl*: $h = -11$ to 11, $k = -24$ to 24, $l = 0$ to 11 (**1**); $h = -9$ to 9, $k = -13$ to 14, $l = 0$ to 15 (**5**). The intensities of 6962 (**1**) and 4024 (**5**) reflections were observed and a total of 3335 (**1**) and 3837 (**5**) (R_{int} = 0.029 and 0.014, respectively) unique reflections were used for structure solution and refinement. Structures were solved by direct methods by with the SHELXS-97 package.[37] The structure refinements were carried out with SHELXL-97.[38] All hydrogens were inserted in calculated positions. Least-square refinements with anisotropic thermal motion parameters for all the non-hydrogen atoms and isotropic for the remaining atoms gave R_1 = 0.0294 (**1**) or 0.0311 (**5**) [$I > 2\sigma(I)$; R_1 = 0.0902 (**1**) or 0.0929 (**5**) (all data)]. The maximum and minimum peaks in the final difference electron density map are of 1.07 and −0.86 (**1**) or 1.04 and −0.83 e Å^{-3} (**5**) located in the immediate vicinity of the tin atom.

CCDC-213290 and CCDC-213291 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: (+44) 1223-336033; or deposit@ccdc.cam.uk).

Antitumor activity in vitro: The antitumor activity against tumor cell lines was assayed by the MTT method[39] in the State Key Laboratory of Natural and Mimic Drugs, Beijing Medical University (China). The cell lines, human immature granulocyte leukemia (HL-60), human hepatocellular carcinoma (Bel-7402), human nasopharyngeal carcinoma (KB), and human ovarian carcinoma (Hela) along with mouse lymphocyte carcinomas (B and T) were used for screening. Aliquots of log-phase cells were incubated for 72 h at 37 °C with three dose levels (0.1, 1.0, and 10.0 μM) of each diorganotin(IV) compounds in triplicate. 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 optical density of each well was measured at 570 nm. The antitumor activity was determined by expressing the mean optical densities for drug-treated cells at each concentration as a percentage of those for untreated cells. The dose causing 50 % inhibition of cell growth (IC_{50}) was determined from the curve of inhibiting percentage versus dose.

Antitumor activity in vivo: Compound [nBu$_2$Sn(L$_1$)$_2$] (**3**) was suspended in 0.5 % sodium carboxymethyl cellulose before use and was administered orally. For the in vivo tests against H22 liver cancer and gastric carcinoma BGC-823 (in nude mice), the positive contrast drug was cyclophosphamide (CTX, purchased from Shanghai Hualian Pharmaceutical Factory, lots: 20010328 or 200107, respectively). The ICR strain mice (grade second, 18–22 g, male and female in equal numbers) were purchased from Beijing Veilitong Experimental Animal Technology Corporation (License number: SCXK 11-00-0008) and raised in the animal center of Beijing University People's hospital (GRADE SPF) (License number: SYXK 11-00-0001). The H22 liver cancer was cultured from generation to generation in the mice's abdominal cavity in the Chinese laboratory.

1) Ninety mice were randomly divided into nine groups of ten mice each. A suspension of **3** with drug dosage of 20, 10, and 5 mg kg^{-1} weight was administered orally, once a day, to six experimental groups and the experiments lasted for four days. In the positive group, carboplatin with the 20 mg kg^{-1} dosage was injected subcutaneously, once a day, during four days. In the two negative (control) groups the same volume of water was administered orally. All mice were killed on the eighth day. The body and neoplasm weights were measured and the percentage of the inhibited cancer was estimated. All data were analyzed by the t test.
2) In the nude mice experiments, human gastric carcinoma cells (BGC-823) cultured from generation to generation in the Chinese laboratory were inoculated subcutaneously in the nude mice's right armpit (1×10^7 mL^{-1}, 0.2 mL for each mouse). When the cancer lump could be touched at the place of inoculation, all mice were divided into three groups and then a suspension of **3** in the dosage of 15, 10 and 5 mg kg^{-1} weight was administered orally.

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