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Mononuclear diorganotin(IV) complexes with arylhydroxamates: syntheses, structures and assessment of *in vitro* cytotoxicity†

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Two series of diorganotin(IV) complexes with dihalogenobenzohydroxamate ligands (substituents = 2,4-Cl_2, 2,4-F_2, 3,4-F_2, 2,5-F_2, 2,6-F_2), formulated as [$R_2Sn(HL)_2$] (a), and the arylhydroxamato/arylcarboxylato mixed-ligand complexes [$R_2Sn(HL)(L')$] (b), were prepared and characterized by FT-IR, ^1H, ^{13}C and ^{119}Sn NMR spectroscopies, elemental analyses and melting point measurements. X-ray diffraction analysis was also carried out for the complex [$Me_2Sn\{3,4\text{-}F_2C_6H_3C(O)NHO\}_2$], 1a. These compounds exhibit *in vitro* cytotoxic activities towards human leukemic promyelocites HL-60, BGC-823, BEL-7402 and KB cell lines which, in some cases, are identical to, or even higher than, that of cisplatin. The type, position and number of the X substituents in the phenyl ring play a role in the cytotoxic activity, and complex 8a, with its 2,6-difluorobenzohydroxamato ligand, is highly active against all tumor cells. A tentative structure–activity relationship is also described. Copyright © 2007 John Wiley & Sons, Ltd.

KEYWORDS: mononuclear, organotin; hydroxamato ligand; crystal structure; cytotoxic activity

INTRODUCTION

The anticancer properties of organotin compounds are well documented. Among the many organotin compounds that have been synthesized as potential anticancer agents,[1–12] those with biologically active ligands have attracted a particular attention. Hydroxamic acids, as inhibitors of 5-lipoxygenase, can behave as strong bidentate O-donors with bioactivity.[13–16] As part of our interest in diorganotin(IV) complexes with arylhydroxamato ligands, we have recently reported the synthesis and activity of the chloro-benzohydroxamato compound [*n*-$Bu_2Sn\{4\text{-}ClC_6H_4C(O)NHO\}_2$] (DBDCT),[17] and shown that it can act as an anticancer agent with a considerable activity against gastric and liver carcinomas. However, the agent is difficult to formulate due to its low aqueous solubility. Subsequently, the fluoro-analog [*n*-$Bu_2Sn\{4\text{-}FC_6H_4C(O)NHO\}_2$] (DBDFT) was synthesized and was found[18,19] to have superior anti-hepatocellular and nasopharyngeal activity and a broad spectrum of cytotoxicity since its IC_{50} values against two human tumor cell lines, HCT-8 and Bel-7402, are 59 and 60 ng/ml, respectively. These results are significantly better than those achieved by cisplatin, and reveal a marked effect of the halo-substituent in the *para*-position of the benzohydroxamato group. To further explore the influence of the number and position of the F or Cl atom,

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and obtain an insight into possible structure–activity relationships, we have prepared series of diorganotin difluoro- and dichlorobenzohydroxamates. We could thus investigate whether the presence of a second fluoride or chloride atom on the phenyl ring of the benzohydroxamato ligand could enhance the *in vitro* cytotoxic activity of the diorganotin derivatives.

On the other hand, the activity of diorganotin compounds is greatly influenced by the molecular structure and the coordination number of the tin atom, and therefore the synthesis of compounds with a diversity of structures is of relevance for cytotoxicity screening. In this paper, following preliminary reports,[20,21] the syntheses of diorganotin(IV) hydroxamato complexes with two different coordination numbers were carried out. Diorganotin(IV) dihalogenobenzohydroxamate (substituents = 2,4-Cl_2, 2,4-F_2, 3,4-F_2, 2,5-F_2, 2,6-F_2) complexes with different Sn : arylhydroxamate ratios and structures, formulated as $[R_2Sn(HL)_2]$ (1 : 2, **a**) (HL = singly deprotonated form of the arylhydroxamic acid H_2L), and the arylhydroxamate/arylcarboxylate mixed-ligand species $[R_2Sn(HL)(L')]$ (1 : 1, **b**) (Fig. 1), were obtained and fully characterized.

To our knowledge, for the latter type of diorganotin(IV) arylhydroxamates, already obtained,[20,21] no information has been given on their biological activities. In this paper, the *in vitro* cytotoxicity of these two classes of complexes has been investigated in human immature granulocyte leukemia (HL-60), nasopharyngeal carcinoma (KB), hepatocellular carcinoma (Bel-7402) and gastric carcinoma (BGC-823) cell lines.

RESULTS AND DISCUSSION

Synthesis

The 1 : 2 alkyltin(IV) arylhydroxamates $[R_2Sn(HL)_2]$ **1a–5a** (R = Me) were prepared by reaction of dimethyltin(IV) dichloride, in an undried methanolic solution, with the appropriate arylhydroxamic acid H_2L and KOH (both in a twofold molar amount relatively to the tin complex), while the compounds **6a–14a** (R = *n*-Bu, Ph) were synthesized by reaction of the corresponding H_2L with di-*n*-butyltin (or diphenyltin) oxide in dry methanol–toluene (1 : 4 v/v). The mixed-ligand alkyltin arylhydroxamates $[R_2Sn(HL)(L')]$ **1b–2b** (R = *n*-Bu)[20,21] were produced by reaction of di-*n*-butyltin dichloride with H_2L and HL′ in the 1 : 1 : 1 stoichiometry, in undried methanol at room temperature.

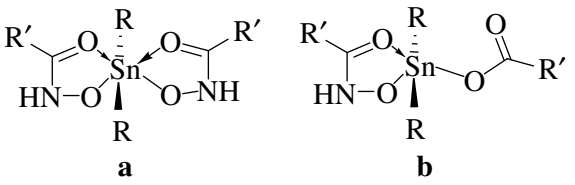

Figure 1. Two classes of mononuclear diorganotin(IV) arylhydroxamates: **a**, (1 : 2) $[R_2Sn(HL)_2]$. [HL (monodeprotonated form of arylhydroxamic acid) = R′C(O)NHO; R = Me; R′ = 3, 4-$F_2C_6H_3$ (**1a**), 2, 4-$F_2C_6H_3$ (**2a**), 2, 5-$F_2C_6H_3$ (**3a**), 2, 6-$F_2C_6H_3$ (**4a**), 2, 4-$Cl_2C_6H_3$ (**5a**). R = *n*-Bu; R′ = 3, 4-$F_2C_6H_3$ (**6a**), 2, 5-$F_2C_6H_3$ (**7a**), 2, 6-$F_2C_6H_3$ (**8a**), 2, 4-$Cl_2C_6H_3$ (**9a**). R = Ph; R′ = 3, 4-$F_2C_6H_3$ (**10a**), 2, 4-$F_2C_6H_3$ (**11a**), 2, 5-$F_2C_6H_3$ (**12a**), 2, 6-$F_2C_6H_3$ (**13a**), 2, 4-$Cl_2C_6H_3$ (**14a**).] **b**, $[R_2Sn(HL)(R'COO)]$. [HL (monodeprotonated form of arylhydroxamic acid) = R′C(O)NHO. R = *n*-Bu; R′ = 3, 4-$F_2C_6H_3$ (**1b**), 4-ClC_6H_4 (**2b**)].

The complexes were isolated as white solids in different yields. All compounds are stable in air, insoluble in water, and soluble in chloroform, acetone and DMSO. The complexes were characterized by FT-IR, ^1H, ^{13}C, ^{119}Sn NMR spectroscopies, elemental analysis and melting point determination, as well as by single-crystal X-ray diffraction analysis for $[Me_2Sn\{3,4\text{-}F_2C_6H_3C(O)NHO\}_2]$ (**1a**). The molecular structure of **1b** has previously been reported.[21]

Spectroscopic data

In the IR spectra, the bands observed in the 1621–1563, 935–893 and 549–448 cm^{-1} ranges are assigned to ν(CO/CN), ν(N–O) and ν(Sn–O), respectively.

The ^{119}Sn NMR resonances of type **a** complexes occur at chemical shifts (−261 to −465 ppm) that fall within the range of hexa-coordinate tin(IV) complexes,[22–24] but for **1a** and **5a** tin chemical shifts cannot be obtained due to inadequate low solubility in $CDCl_3$ or DMSO-d_6 solution.

On the basis of calculations with equation (1),[25] or a related one,[26] the C–Sn–C angle is usually open (132–157° range) for the hexa-coordinate complexes **a** ($^1J_{Sn-C}$ in the 633–825 Hz range). For the dimethyltin derivatives (**1a–5a**), the Me–Sn–Me angle lies within the 130–155° range, as estimated from the observed $^2J_{Sn-H}$ values (79–96 Hz) using the known[25,27] expression (2).

$$\theta(\text{C–Sn–C}) = [^1J_{Sn-C} + 875]/11.4 \quad (1)$$

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

X-ray diffraction analysis

The molecular structure of complex **1a** was authenticated by single-crystal X-ray diffraction analysis. The structure with its numbering scheme and selected bond distances and angles is shown in Fig. 2.

The coordination polyhedron consists of three O atoms derived from two hydroxamates and two C atoms of the methyl groups. The C–Sn–C angle of 142.4(3)° is much smaller than the value expected for a regular octahedron, so the coordination geometry is best described as distorted skew-trapezoidal bipyramidal. In this description, the trapezoidal plane is defined by the asymmetric Sn–O bond lengths, since the two covalent bonds are shorter [2.086(4) and 2.106(4) Å], defining a small O–Sn–O angle [78.35(15)°], while the other two oxygen–tin distances are longer [2.321(4) and 2.611(4) Å], defining an angle of 141.02(14)°. Asymmetric

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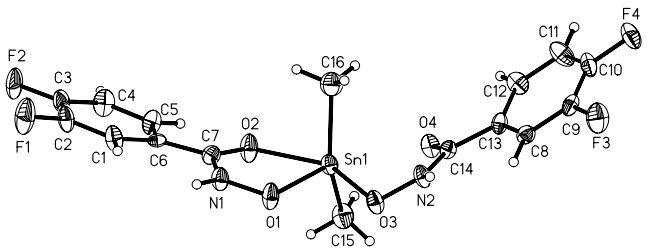

Figure 2. Molecular structure of $[Me_2Sn\{3,4\text{-}F_2C_6H_3C(O)NHO\}_2]$ (**1a**), selected bond lengths (Å) and angles (deg): Sn1–O1, 2.086(4); Sn1–O3, 2.106(4); Sn1–C16, 2.107(8); Sn1–C15, 2.107(7); Sn1–O2, 2.321(4); Sn1–O4, 2.611(4); N1–C7, 1.326(7); N1–O1, 1.380(6); N2–C14, 1.316(7); N2–O3, 1.384(6); O2–C7, 1.254(7); O4–C14, 1.261(7); C16–Sn1–C15, 142.4(3); O1–Sn1–O3, 78.35(15); O2–Sn1–O4, 141.02(14); O1–Sn1–C16, 103.5(2); O1–Sn1–O2, 73.03(15); O3–Sn1–O2, 150.98(16); O1–Sn1–O4, 145.81(14); O3–Sn1–O4, 67.91(14). The long Sn1–O4 bond is not represented.

chelation of hydroxamato ligands has been observed in other tin(IV) complexes,[17,28–31] and the structure is comparable to that reported for the mono-substituted benzohydroxamato complex $[Me_2Sn\{4\text{-}ClC_6H_4C(O)NHO\}_2]$.

In the crystal structure, molecules are stacked along the *c*-axis, and are connected by weak C–H···F, C–H···O, N–H···O hydrogen-bond interactions.

Cytotoxicity activities *in vitro*

The *in vitro* cytotoxic activity of the above complexes was tested on various human tumor cell lines [immature granulocyte leukemia (HL-60), nasopharyngeal carcinoma (KB), hepatocellular carcinoma (Bel-7402) and gastric carcinoma (BGC-823)]. The results are summarized in Table 1.

Among the 16 diorganotin(IV) complexes checked, three (**8a, 11a** and **14a**) exhibit a strong activity against all the four tumor cells, being even more active than cisplatin, which is clinically widely used. Based on the data analysis, possible structure–activity relationships could be outlined as follows: (i) as observed in previous studies,[5–7,17–19,32] the organo-ligand R appears to play an important role. Indeed, the di-*n*-butyltin complexes exhibit the strongest antitumor activity, while the methyltin derivatives usually exhibit the weakest one, and the activity of diphenyltin complexes largely depends on the arylhydroxamato ligand. Hence, for the two classes of diorganotin complexes, the activity follows the order *n*-Bu ≥ Ph > Me for nearly all the tumor cells; some diphenyltin complexes, in particular $[Ph_2Sn\{2,4\text{-}F_2C_6H_3C(O)NHO\}_2]$ (**11a**) and $[Ph_2Sn\{2,4\text{-}Cl_2C_6H_3C(O)NHO\}_2]$ (**14a**), are among the most active, which suggests that diaryltin(IV) complexes deserve further attention. (ii) The number, position and/or type of halo-substituents can have a marked influence on the activity,[17–19,33,34] for example, (a) **8a**, with the 2,6-difluorobenzohydroxamato ligand, is among the most active of all the tumor cells, and (b) the mixed-ligand complexes **b** are shown (for the first time) to exhibit marked *in vitro* cytotoxicity towards various tumor cell lines, which is ligand-dependent—the replacement of two fluoro- by one chloro-substituent (**1b** to **2b**) leads to a high activity enhancement. (iii) However, the observations in (ii) were not proved; for example, the replacement of chloro- by fluoro-substituents usually does not lead to a marked effect on the activity, further studies being required to established clear relationships with the activity. (iv) The highest activity is usually observed for the KB tumor cells and the lowest for the HL-60 tumor cells.

Table 1. Inhibition (%) of mononuclear diorganotin(IV) complexes (dose level of 10.00 μM) against human tumor cells

No.	Leukemic HL-60	Gastric carcinoma BGC-823	Hepato-cellular carcinoma Bel-7402	Naso-pharyngeal carcinoma KB
1a	—	24.65	4.33	14.55
2a	7.14	38.61	0.13	12.56
3a	2.98	44.17	6.84	11.91
4a	11.65	13.96	2.96	9.15
5a	9.57	21.48	4.56	15.62
6a	9.22	24.23	6.04	13.61
7a	38.39	53.03	90.59	95.17
8a	88.93	88.22	94.64	95.57
9a	38.77	60.59	93.23	94.86
10a	15.53	41.33	12.45	24.11
11a	82.55	89.01	90.91	95.17
12a	35.75	11.62	89.62	92.75
13a	6.07	31.06	—	9.15
14a	85.86	88.18	93.56	94.41
1b	8.09	32.76	69.53	64.33
2b	51.26	69.90	91.18	94.49
Cisplatin		90.82	79.10	

EXPERIMENTAL

Materials and methods

Dialkyltin(IV) dichlorides, 2,4-dichlorobenzoic acid, methyl 2,4-difluorobenzoate, methyl 2,5-difluorobenzoate, methyl 3,4-difluorobenzoate and methyl 2,6-difluorobenzoate were purchased from Aldrich and used as received. The other reagents were of analytical grade. 3,4-Difluorobenzohydroxamic acid (H_2L^1), 2,4-difluorobenzohydroxamic acid (H_2L^2), 2,5-difluorobenzohydroxamic acid (H_2L^3), 2,6-difluorobenzohydroxamic acid (H_2L^4) and 2,4-dichlorobenzohydroxamic acid (H_2L^5) were prepared according to the reported methods.[35–37] [*n*-$Bu_2Sn\{4\text{-}ClC_6H_4C(O)NHO\}$

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{4-ClC_6H_4COO}] was prepared as reported previously.[20] Elemental analyses were performed on a PE-2400-I elemental analyzer. IR spectra in the range 4000–400 cm^{-1} were recorded on a Perkin Elmer FT-IR spectrophotometer in KBr discs. ^1H, ^{13}C, ^{119}Sn NMR spectra were recorded on a Varian INOVA 600 spectrometer (600.0 MHz for ^1H, 150.8 MHz for ^{13}C and 223.6 MHz for ^{119}Sn) at ambient temperature [δ values in ppm relative to Me_4Si (^1H, ^{13}C) or Me_4Sn (^{119}Sn)].

*3,4-$F_2C_6H_3C(O)NHOH$ (**H_2L^1**)*

Yield: 34%; white plate crystals; m.p. 108–110 °C. IR: ν = 3545 s, (N–H); 3276 s br (O–H); 1634 s and 1515 s (CO/NC); 881 s (N–O) cm^{-1}. ^1H NMR ($CDCl_3$): $\delta = 8.14$ [s, 1H, H(2)]; 7.74 [d, 1H, H(5)]; 6.81 [d, 1H, H(6)]. ^{13}C NMR ($CDCl_3$) δ = 166.9 (CO); 152.6, 151.9, 131.8, 131.0, 124.5, 111.3 (C_{arom}) ppm.

*2,4-$F_2C_6H_3C(O)NHOH$ (**H_2L^2**)*

Yield: 44%; white plate crystals; m.p. 130–132 °C. IR: ν = 3337 s (N–H); 3108s, br (O–H); 1655s and 1612s (CO/NC); 890s (N–O) cm^{-1}. ^1H NMR ($CDCl_3$): $\delta = 8.18$ [d, $^3J_{FH}$ = 7.2 Hz, 1H, H(3)]; 7.03 [d, 1H, H(5)]; 6.91 [d, 1H, H(6)]. ^{13}C NMR ($CDCl_3$) δ = 165.1 (CO); 152.7, 151.8, 137.0, 127.5, 124.5, 120.5 (C_{arom}) ppm.

*2,5-$F_2C_6H_3C(O)NHOH$ (**H_2L^3**)*

Yield: 37%; white powder; m.p. 134–136 °C. IR: ν = 3239 s (N–H); 2880 s, br (O–H); 1619s and 1596 s (CO/NC); 893 s (N–O) cm^{-1}. ^1H NMR ($CDCl_3$): $\delta = 7.89$ [dd, 1H, H(6)]; 7.37 [dd, 1H, H(3)]; 7.12 [t, 1H, H(4)] ppm. ^{13}C NMR ($CDCl_3$) δ = 163.7 (CO); 162.3, 159.8, 136.5, 126.2, 122.4, 113.3 (C_{arom}) ppm.

*2,6-$F_2C_6H_3C(O)NHOH$ (**H_2L^4**)*

Yield: 26%; white needle crystals; m.p. 112–113 °C. IR: ν = 3274 s (N–H); 2899 s, br (O–H); 1652 s and 1591s (CO/NC); 899 s (N–O) cm^{-1}. ^1H NMR ($CDCl_3$): $\delta = 7.45$ (dd, 1H, C_6H_3); 7.02 (t, 2H, C_6H_3) ppm. ^{13}C NMR ($CDCl_3$) δ = 170.3 (CO); 166.8, 160.2, 132.4, 126.5, 120.6, 111.8 (C_{arom}) ppm.

*2,4-$Cl_2C_6H_3C(O)NHOH$ (**H_2L^5**)*

Yield: 48%; white needle crystals; m.p. 143–144 °C. IR: ν = 3293 s (N–H); 2749 s, br (O–H); 1651 s, 1598 s and 1562 s (CO/NC); 901s (N–O) cm^{-1}. ^1H NMR ($CDCl_3$): $\delta = 7.81$ [d, $^3J_{ClH}$ = 8.4 Hz, 1H, H(3)]; 7.47 [d, 1H, H(5)]; 7.38 [d, $^3J_{HH}$ = 7.8 Hz, 1H, H(6)] ^{13}C NMR ($CDCl_3$) δ = 159.3 (CO); 151.8, 150.2, 135.3, 126.5, 123.1, 110.7 (C_{arom}) ppm.

Syntheses of the complexes

*1 : 2 Alkyltin(IV) arylhydroxamates [$R_2Sn(HL)_2$] [R = Me; L = L^1 (**1a**), L^2 (**2a**), L^3 (**3a**), L^4 (**4a**), L^5 (**5a**)]*

Dimethyltin(IV) dichloride (0.220 g, 1.0 mmol) was added to an undried methanolic solution (20 ml) of the appropriate aryl hydroxamic acid 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 then added, leading to the formation of a white precipitate of [$R_2Sn(HL)_2$], which was separated by filtration, washed with water and cold methanol, recrystallized from ethanol (**1a, 3a** or **5a**) or ethanol–chloroform (**2a** or **4a**) and dried to constant weight (yield 40–65%).

*[Me_2Sn{3,4-$F_2C_6H_3C(O)NHO$}$_2$] (**1a**)*

Yield: 54%; m.p. 212 °C (dec.); elemental analysis calcd (%) for $C_{16}H_{14}F_4N_2O_4Sn$: C, 38.98; H, 2.86; N, 5.68; found: C, 38.81; H, 2.90; N, 5.55. IR: ν = 3419 s, 3214 s (N–H), 1621 s and 1578 w (CO/NC); 915 s (N–O); 568 s (Sn–C); 549 m (Sn–O) cm^{-1}. ^1H NMR ($CDCl_3$): $\delta = 7.62$ [br, 2H, H(5)], 7.56 [s, br, 2H, H(2)]; 7.35 [br, 2H, H(6)]; 0.59 [s, br, 6H, CH_3, R–Sn, ^2J(Sn–H) = 79 Hz] ppm. ^{13}C NMR (d_6-DMSO): $\delta = 161.6$ (CO); 153.4, 151.8, 127.1, 125.8, 120.6, 108.4 ($C_{arom.}$); 6.7 (CH_3, R–Sn) ppm.

*[Me_2Sn{2,4-$F_2C_6H_3C(O)NHO$}$_2$] (**2a**)*

Yield: 36%; m.p. 216 °C (dec.); elemental analysis calcd (%) for $C_{16}H_{14}F_4N_2O_4Sn$: C, 38.98; H, 2.86; N, 5.68; found: C, 38.65; H, 2.92; N, 5.37. IR: ν = 3234 s (N–H); 1611s and 1567 w (CO/NC); 918 s (N–O); 583 s (Sn–C); 524 m (Sn–O) cm^{-1}. ^1H NMR ($CDCl_3$): $\delta = 7.84$ [s, 2H, H(3)], 7.66 [d, 2H, H(5)]; 6.95 [d, 2H, H(6)]; 0.88 [s, br, 6H, CH_3, R–Sn, ^2J(Sn–H) = 79 Hz] ppm. ^{13}C NMR (d_6-DMSO): δ = 164.1 (CO); 155.7, 152.2, 129.7, 127.6, 122.4, 114.1 (C_{arom}); 6.5 (CH3, R–Sn) ppm. ^{119}Sn NMR (d_6-DMSO): $\delta = -378.5$ ppm.

*[Me_2Sn{2,5-$F_2C_6H_3C(O)NHO$}$_2$] (**3a**)*

Yield: 33%; m.p. >300 °C; elemental analysis calcd (%) for $C_{16}H_{14}F_4N_2O_4Sn$: C, 38.98; H, 2.86; N, 5.68; found: C, 38.85; H, 2.94; N, 5.35. IR: ν = 3213 s (N–H); 1617 s and 1563 w (CO/NC); 926 s (N–O); 588 s (Sn–C); 526 m (Sn–O) cm^{-1}. ^1H NMR ($CDCl_3$): δ = 12.65 (s, br, 1H, NH), 11.08 (s, br, 1H, NH), 8.31 [d, 2H, H(3)], 7.44 [d, br, 2H, H(4)]; 7.37 [br, 2H, H(6)]; 0.53 (s, br, 6H, CH_3, R–Sn) ppm. ^{13}C NMR (d_6-DMSO): δ = 158.5 (CO); 156.9, 156.0, 124.3, 117.9, 115.8 (C_{arom}); 6.2 (CH_3, R–Sn) ppm. ^{119}Sn NMR (d_6-DMSO): $\delta = -374.9$ ppm.

*[Me_2Sn{2,6-$F_2C_6H_3C(O)NHO$}$_2$] (**4a**)*

Yield: 32%; m.p. >300 °C; elemental analysis calcd (%) for $C_{16}H_{14}F_4N_2O_4Sn$: C, 38.98; H, 2.86; N, 5.68; found: C, 38.65; H, 2.92; N, 5.37. IR: ν = 3228 s (N–H); 1614 s and 1585 s (CO/NC); 921 s (N–O); 535 m (Sn–O); 574 s (Sn–C) cm^{-1}. ^1H NMR ($CDCl_3$): δ 11.20 (s, br, 1H, NH), 9.41 (s, br, 1H, NH), 7.38 [d, 4H, H(3)], 7.04 [d, br, 2H, H(4)]; 0.60 [s, br, 6H, CH_3, R–Sn, ^2J(Sn–H) = 96 Hz] ppm. ^{13}C NMR (d_6-DMSO): δ = 170.8 (CO), 160.7, 132.5, 111.3 and 104.7 (C_{arom}), 6.1 (CH_3, R–Sn) ppm. ^{119}Sn NMR (d_6-DMSO): $\delta = -261.9$ ppm.

*[Me_2Sn{2,4-$Cl_2C_6H_3C(O)NHO$}$_2$] (**5a**)*

Yield: 55%; m.p. 202 °C (dec.); elemental analysis calcd (%) for $C_{16}H_{14}Cl_4N_2O_4Sn$: C, 34.39; H, 2.53; N, 5.01; found: C, 34.09; H, 2.65; N, 4.97. IR(KBr): ν = 3287 s (N–H), 1599 s, 1562 s (CO/NC), 914 s (N–O), 575 s (Sn–C), 544 s (Sn–O) cm^{-1}.^1H NMR ($CDCl_3$): δ = 10.21 (s, br, 2H, N–H), 7.54–7.15 (m, 6H,

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$2C_6H_3$), 0.94 [s, $2CH_3$, R–Sn, ^2J(Sn–H) = 80 Hz] ppm. ^{13}C NMR (d_6-DMSO): δ = 169.2 (CO), 157.2, 155.4, 130.6, 114.0, 112.3 and 102.1 (C_{arom}), 6.4 (CH_3, R–Sn) ppm.

*1 : 2 Alkyltin(IV) arylhydroxamates [$R_2Sn(HL)_2$] [R = n-Bu; L = L^1 (**6a**), L^3 (**7a**), L^4 (**8a**), L^5 (**9a**). R = Ph; L = L^1 (**10a**), L^2 (**11a**), L^3 (**12a**), L^4 (**13a**), L^5 (**14a**)]*

Di-*n*-butyltin (or diphenyltin) oxide (1 mmol) was added to a dry methanol-toluene (1 : 4 v/v, 150 ml) solution of HL_2 (2 mmol) which was refluxed under nitrogen atmosphere for 8 h, whereafter the solvent was evaporated to dryness. The white precipitate thus formed was recrystallized from methanol/benzene (**6a, 7a**), ethanol (**8a, 9a**) or dichloromethane (**10a–14a**) and dried to constant weight.

*[n-Bu_2Sn{3,4-$F_2C_6H_3$C(O)NHO}$_2$] (**6a**)*

Yield: 35%; m.p. 160–162 °C; elemental analysis calcd (%) for $C_{22}H_{26}N_2O_4F_4Sn$: C, 45.78; H, 4.54; N, 4.85; found: C, 45.72; H, 4.65; N, 4.82. IR: ν = 3230 s (N–H), 2959 m (Bu); 1615 s, 1567 w (CO/NC); 928 s (N–O); 523 m (Sn–C); 466 m (Sn–O) cm^{-1}. ^{1}H NMR ($CDCl_3$): 7.74–7.36 (m, 6H, $2C_6H_3$); 1.64–1.59 (m, 8H, $2CH^2{}_2CH^1{}_2$), 1.38–1.33 (m, 4H, $2C^3H_2$), 0.86 (t, J = 7.2 Hz, 6H, $2C^4H_3$) ppm. ^{13}C NMR ($CDCl_3$): δ = 158.7 (CO); 150.1, 148.4, 132.4, 129.2, 117.6, 114.3 (C_{arom}); 27.1($CH^1{}_2$, R–Sn, ^1J(^{119}Sn–^{13}C) = 633 Hz), 25.6, 24.8, 13.6 (*n*-Bu, R–Sn) ppm. ^{119}Sn NMR ($CDCl_3$): δ = −375.8 ppm.

*[n-Bu_2Sn{2,5-$F_2C_6H_3$C(O)NHO}$_2$] (**7a**)*

Yield: 43%; m.p. 166–168 °C; elemental analysis calcd (%) for $C_{22}H_{26}N_2O_4F_4Sn$: C, 45.78; H, 4.54; N, 4.85; found: C, 45.83; H, 4.58; N, 4.72. IR: ν = 3227 s (N–H), 2957 m (Bu); 1611s, 1571 w (CO/NC); 935 s (N–O); 550 m (Sn–C); 495 m (Sn–O) cm^{-1}. ^{1}H NMR ($CDCl_3$): 7.58–7.24 (m, 6H, $2C_6H_3$); 1.67–1.55 (m, 8H, $2CH^2{}_2CH^1{}_2$), 1.38–1.25(m, 4H, $2C^3H_2$), 0.90 (t, J = 14.4 Hz, 6H, $2C^4H_3$) ppm. ^{13}C NMR ($CDCl_3$): δ = 159.2 (CO); 154.7, 152.3, 132.0, 122.4, 117.3, 104.9 (C_{arom}); 27.7[$CH^1{}_2$, R–Sn, ^1J(^{119}Sn–^{13}C) = 814 Hz], 26.6, 25.6, 13.4 (*n*-Bu, R–Sn) ppm. ^{119}Sn NMR ($CDCl_3$): δ = −371.6 ppm.

*[n-Bu_2Sn{2,6-$F_2C_6H_3$C(O)NHO}$_2$] (**8a**)*

Yield: 32%; m.p. 171–173 °C; elemental analysis calcd (%) for $C_{22}H_{26}N_2O_4F_4Sn$: C, 45.78; H, 4.54; N, 4.85; found: C, 45.75; H, 4.63; N, 4.99. IR: ν = 3212 s (N–H); 1619 s (CO/NC); 915 s (N–O); 516 m (Sn–C); 476m (Sn–O) cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 10.40 (s, br, 1H, NH), 10.12 (s, br, 1H, NH), 7.49 [d, 4H, H(3)], 7.03 [d, br, 4H, H(4)]; 1.79–1.61 (m, 8H, $2CH^2{}_2CH^1{}_2$), 1.44–1.39 (m, 4H, $2C^3H_2$), 0.93 (t, J = 7.2 Hz, 6H, $2C^4H_3$) ppm. ^{13}C NMR ($CDCl_3$): δ = 166.2 (CO); 159.7, 130.6, 115.3 (C_{arom}); 27.8[$CH^1{}_2$, R–Sn, ^1J(^{119}Sn–^{13}C) = 745 Hz], 27.0, 26.6, 13.5 (*n*-Bu, R–Sn) ppm. ^{119}Sn NMR ($CDCl_3$): δ = −457.2 ppm.

*[n-Bu_2Sn{2,4-$Cl_2C_6H_3$C(O)NHO}$_2$] (**9a**)*

Yield: 63%; m.p. 126–128 °C; elemental analysis calcd (%) for $C_{22}H_{26}N_2O_4Cl_4Sn$: C, 41.10; H, 4.08; N, 4.36; found: C, 41.01; H, 4.17; N, 4.28. IR(KBr): ν = 3257 s (N–H), 2958 m (Bu), 1615 s, 1580 s (CO/NC), 893 s (N–O), 582 w (Sn–C); 471 m, 549 s (Sn–O) cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 9.92 (s, br, 2H, NH), 7.78 [s, br, 2H, H(3)], 7.03 [d, 2H, H(5)], 6.80 [d, 2H, H(6)]; 1.71–1.65 (m, 8H, $2CH^2{}_2CH^1{}_2$), 1.39–1.37 (m, 4H, $2C^3H_2$), 0.92 (t, J = 7.2 Hz, 6H, $2C^4H_3$) ppm. ^{13}C NMR (d_6-DMSO): δ = 165.2 (CO); 157.7, 152.3, 127.7, 124.0, 120.1, 117.3 (C_{arom}); 28.3[$CH^1{}_2$, R–Sn, ^1J(^{119}Sn–^{13}C) = 825 Hz], 27.2, 26.6, 13.5 (*n*-Bu, R–Sn) ppm. ^{119}Sn NMR (d_6-DMSO): δ = −256.7 ppm.

*[Ph_2Sn{3,4-$F_2C_6H_3$C(O)NHO}$_2$] (**10a**)*

Yield: 74%; m.p. 123–125 °C; elemental analysis calcd (%) for $C_{26}H_{18}N_2O_4F_4Sn$: C, 50.57; H, 2.92; N, 4.54; found: C, 50.42; H, 3.03; N, 4.48. IR: ν = 3204 s (N–H), 1607 s and 1565 m (CO/NC); 916s (N–O), 526 w (Sn–O) cm^{-1}. ^{1}H NMR ($CDCl_3$): δ = 13.32 (s, 2H, NH), 7.78–7.34 (m, 16H, H_{arom}) ppm. ^{13}C NMR ($CDCl_3$): δ = 158.7 (CO); 151.3, 150.2, 148.6, 146.3, 136.0–127.9, 122.7.5, 117.8 (C_{arom}) ppm; ^{119}Sn NMR ($CDCl_3$): δ = −428.0 ppm.

*[Ph_2Sn{2,4-$F_2C_6H_3$C(O)NHO}$_2$] (**11a**)*

Yield: 62%; m.p. 116–118 C; elemental analysis calcd (%) for $C_{26}H_{18}N_2O_4F_4Sn$: C, 50.57; H, 2.92; N, 4.54; found: C, 50.30; H, 3.09; N, 4.33. IR: ν = 3200 s (N–H); 1606 s (CO/NC); 915 s (N–O) cm^{-1}. ^{1}H NMR ($CDCl_3$): δ = 13.23 (s, 2H, NH), 7.90–7.08 (m, 16H, H_{arom}) ppm. ^{13}C NMR ($CDCl_3$): δ = 160.5 (CO); 160.4, 158.8, 149.5, 146.2, 136.0–127.8, 112.5, 105.2 (C_{arom}) ppm; ^{119}Sn NMR ($CDCl_3$): δ = −432.3 ppm.

*[Ph_2Sn{2,5-$F_2C_6H_3$C(O)NHO}$_2$] (**12a**)*

Yield: 55%; m.p. 190–192 C; elemental analysis calcd (%) for $C_{26}H_{18}N_2O_4F_4Sn$: C, 50.57; H, 2.92; N, 4.54; found: C, 50.62; H, 2.90; N, 4.38. IR: ν = 3198 s (N–H); 1646 s and 1596 w (CO/NC); 914 s (N–O), 571 w (Sn–C), 536m (Sn–O) cm^{-1}. ^{1}H NMR ($CDCl_3$): δ = 13.23 (s, 2H, NH), 7.90–7.08 (m, 16H, H_{arom}) ppm. ^{13}C NMR ($CDCl_3$): δ = 160.3 (CO); 158.9, 156.8, 147.5, 144.2, 135.1–127.8, 111.3, 104.2 (C_{arom}) ppm; ^{119}Sn NMR ($CDCl_3$): δ = −411.5 ppm.

*[Ph_2Sn{2,6-$F_2C_6H_3$C(O)NHO}$_2$] (**13a**)*

Yield: 70%; m.p. 149–151 C; elemental analysis calcd (%) for $C_{26}H_{18}N_2O_4F_4Sn$: C, 50.57; H, 2.92; N, 4.54; found: C, 50.39; H, 3.12; N, 4.31. IR: ν = 3207 s (N–H); 1608 s and 1533 w (CO/NC); 917 s (N–O), 554 w (Sn–C), 522 m (Sn–O) cm^{-1}. ^{1}H NMR ($CDCl_3$): δ = 14.13 (s, br, 1H, NH), 11.18 (s, 1H, NH), 7.78–7.10 (m, 16H, H_{arom}) ppm. ^{13}C NMR ($CDCl_3$): δ = 166.8 (CO); 159.6, 135.1–127.8, 115.1, 104.2 (C_{arom}) ppm; ^{119}Sn NMR($CDCl_3$): δ = −431.1, −452.9 ppm.

*[Ph_2Sn{2,4-$Cl_2C_6H_3$C(O)NHO}$_2$] (**14a**)*

Yield: 82%; m.p. 133–135 C; elemental analysis calcd (%) for $C_{26}H_{18}N_2O_4Cl_4Sn$: C, 45.68; H, 2.64; N, 4.10; found: C, 45.52; H, 2.90; N, 4.01. IR: ν = 3216 s (N–H); 1601 s and 1574 w (CO/NC); 911 s (N–O), 557 m (Sn–C), 523 m and 448 s (Sn–O) cm^{-1}. ^{1}H NMR ($CDCl_3$): δ = 12.66 (s, br, 2H, NH), 7.03–6.02 (m, 16H, H_{arom}) ppm. ^{13}C NMR (d_6-DMSO):

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δ = 162.4 (CO); 159.8, 149.5, 136.3–127.3, 113.0, 104.9 (C_{arom}) ppm; ^{119}Sn NMR (d_6-DMSO): δ = −339.8, −427.1 ppm.

*Mixed-ligand alkyltin(IV) arylhydroxamates/carboxylates [$R_2Sn(HL)(L')$] [R = n-Bu; L = L^1, L′ = 3,4-$F_2C_6H_3COO$ (**1b**); L = 4-$ClC_6H_4C(O)NHO$, L′ = 4-ClC_6H_4COO (**2b**)]*

Complexes **1b** and **2b** were previously obtained[20,21] by a related procedure and the characterization data are not repeated herein.

Structural determination and refinement

A suitable single crystal of **1a** was mounted in a glass capillary for X-ray structural analysis. Diffraction data were collected on a Bruker SMART CCD diffractometer with Mo K_α (λ = 0.71073 Å) radiation at room temperature. The structure was solved by direct-methods using SHELXS-97[38] and refinement followed standard procedures with SHELXS-97.[38] For the minor orientational component, the site occupancy factor is 0.5; the phenyl rings were constrained to be planar regular hexagons.

Formula $C_{16}H_{14}F_4N_2O_4Sn$, M = 492.98, triclinic, space group, P-1, a = 7.7812(10), b = 7.9714(10), c = 14.8660(18) Å, α = 88.362(2), β = 75.075(2), γ = 80.472(2)°, V = 878.60(19) Å^3, Z = 2, D_x = 1.863 g cm^{-3}, μ = 1.520 mm^{-1}, 3789 independent reflections, θ range = 2.6–27.0°, 2840 reflections with $I \geq 2\sigma(I)$, R (obs. data) = 0.057, wR_2 (all data) = 0.121.

CCDC-624639 contains the supplementary crystallographic data for **1a**. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_ request/cif or by emailing data_request@ccdc.cam.ac.uk or by contacting The Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge, CB2 1EZ, UK; fax: +44 1223 336033.

Determination of cytotoxicity

Cell proliferation in compound-treated cultures was evaluated by using a system based on the tetrazolium compound 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 gastric carcinoma (BGC-823) were used for screening. Aliquots of log-phase cells were incubated for 72 h at 37 °C with 10.0 μM of each diorganotin(IV) compound in triplicate. A 50 μL aliquot 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 the concentration as a percentage of those for untreated cells.

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