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Synthesis, characterization and *in vitro* antitumor activity of dimethyl-, diethyl, and di-t-butyl-tin(IV) derivatives of substituted salicylic acids

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The synthesis of dimethyl-, diethyl- and/or di-t-butyl-tin(IV) derivatives of substituted salicylic acids of the type a, $(X\text{-}Y\text{-}2\text{-}OH\text{-}C_6H_2COO)_2SnR_2$ (X, Y = H, H; H, 5-CH_3; H, 5-Cl; H, 5-F; H, 3-CH_3O; H, 5-CH_3O; 3-CH_3, 6-$(CH_3)_2CH$; 3,5-$[(CH_3)_2CH]_2$ and 4,5-benzo) and b $\{[R_2(X\text{-}Y\text{-}2\text{-}OH\text{-}C_6H_2COO)Sn]_2O\}_2$ (X, Y = H, 3-CH_3O; H, 5-CH_3O: 3-CH_3, 6-$(CH_3)_2CH$; 3,5-$[(CH_3)_2CH]_2$ and 4,5-benzo) is reported. Their characterization by ^1H, ^{13}C and ^{119}Sn NMR, Mössbauer and mass spectrometry is described. The *in vitro* antitumor activity of selected derivatives against two human tumoral cell lines, MCF-7 and WiDr, is presented.

Keywords: Diorganotin, salicylic acid, NMR, Mössbauer, antitumor

INTRODUCTION

Di-n-butyltin(IV) derivatives of substituted salicylic acids have already been reported.[1] They showed *in vitro* antitumor activities on five human cell lines to an extent justifying them being patented.[2] Some diorganotin(IV) derivatives of aza-, thio- and azathio-salicylic acids were also prepared and tested.[3] Again some of them exhibited interesting *in vitro* antitumor properties. A literature review reveals that diethyltin(IV) compounds are often the most active, whereas dimethyltin(IV) compounds are not[4,5] amongst the diorganotin compounds tested *in vivo*. Therefore, we prepared some diethyltin(IV) analogs of the di-n-butyltin compounds previously synthesized in order to compare their antitumor activities *in vitro* against the two human tumoral cell lines MCF-7 and WiDr. Diethyltin compounds have the advantage that their proton NMR spectra reveal easily measurable ^2J and ^3J coupling constants, in contrast to di-n-butyltin compounds. Because such couplings contain useful information with regard to the coordination at tin[6] and because the dimethyl- and di-t-butyltin compounds also exhibit these analogous couplings, we prepared and characterized for comparison three series of these analogs, compounds **1a** and **1b** (dimethyltin compounds) and **11b** (di-t-butyltin compound).

RESULTS AND DISCUSSION

Synthesis, purification and Mössbauer spectral data

The compounds, prepared following Refs 1 and 2 from the diorganotin oxide and a substituted salicylic acid, are given in Fig. 1. The diorganotin disalicylates prepared are represented with a label **a**. They were obtained from the condensation of the appropriate diorganotin oxide and substituted salicylic acid in the molar ratio 1:2, as follows: 0.02 mmol of the diorganotin oxide and 0.04 mmol (compounds of type **a**) or 0.02 mmol (compounds of type **b**) of the substituted salicylic acid were refluxed in 100 cm^3 ethanol and 400 cm^3

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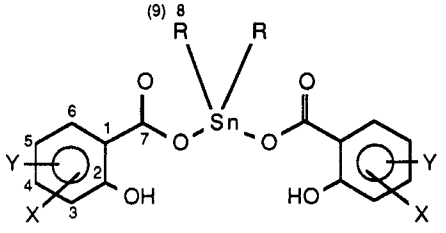
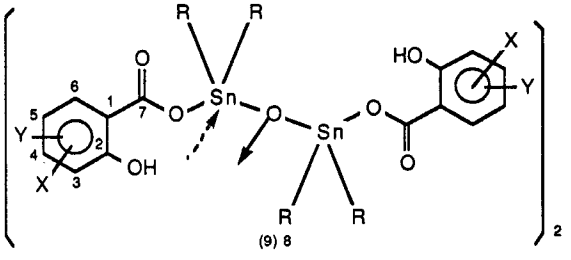
Compounds of type **a**



Compd	R	X	Y
1a	Me	3-i-Pr	5-i-Pr
2a	Et	H	H
3a	Et	H	3-MeO
4a	Et	H	5-MeO
5a	Et	3-Me	6-i-Pr
6a	Et	3-i-Pr	5-i-Pr
7a	Et	H	5-Me
8a	Et	H	5-F
9a	Et	H	5-Cl
10a	Et	[Benzo*]	

* Naphthalene compounds.

Compounds of type **b**



Compd	R	X	Y
1b	Me	3-i-Pr	5-i-Pr
3b	Et	H	3-MeO
4b	Et	H	5-MeO
5b	Et	3-Me	6-i-Pr
6b	Et	3-i-Pr	5-i-Pr
10b	Et	[Benzo*]	
11b	t-Bu	H	5-MeO

* Naphthalene compounds.

Figure 1 Dimethyl-, diethyl- and di-t-butyl-tin derivatives of the substituted salicylic acids studied.

toluene. After 20 min a clear solution was obtained. The mixture was refluxed for a further 4 h. The ternary azeotrope water/ethanol/toluene was distilled off with a Dean–Stark funnel until reduction of the total volume to one-half. The resulting solution was then evaporated under vacuum. The compound obtained was recrystallyzed from the solvent mixture given in Table 1.

In contrast, the bis(salicylatodiorganotin) oxides, labeled **b**, were obtained from a condensation in the molar ratio 1:1. As shown previously,[7] they exist as dimers with a dioxadistannetane ring. The yields, melting points and recrystallization solvents of compounds **1a–10a**, **1b**, **3b–6b**, **10b** and **11b**, together with their Mössbauer parameters, are given in Table 1.

NMR spectral data

^{1}H NMR

The ^{1}H NMR spectra of compounds **1a–10a** are given in Tables 2a and 2b; those of **1b**, **3b–6b**, **10b** and **11b** are described in Tables 2c and 2d.

The ^{1}H NMR spectrum has also been recorded for a DMSO solution of compound **3a**. The signals appear at 1.19 (9-H, t, 8, ^3J(Sn–H) = 157), 1.54 (8-H, q, 8, ^2J(Sn–H) = 90), 3.75 (3-CH_3O, s), 7.04 (4-H, d, 8), 6.73 (5-H, dd, 8, 8) and 7.39 (6-H, dd, 8, 1.5).

The ethyl groups exhibit the expected triplet and quartet with tin coupling satellites, ^3J being larger than ^2J, as usual. Fluorine–proton couplings are also observed in compound **8a**. The isopropyl septets of compound **1a** were assigned by nuclear Overhauser enhancement generated by irradiation of the appropriate aromatic neighbor protons. In compounds **6a** and **1b**, the assignment was done by analogy with **1a**. In compounds **1a** and **6a**, the isochrony of the isopropyl methyl doublets is too strong for their assignment to be possible. In compound **1b**, however, this could be achieved by selective irradiation of the isopropyl septet.

For compound **1b**, two methyl–tin signals are observed, in agreement with the dimeric structure observed for analogous distannoxanes in the solid state as well as in chloroform solution. Indeed, this dimer contains two inequivalent pairs of organotin moieties, one involved in a dioxadistannetane four-membered ring, the other being a substituent of this ring.

Likewise, two triplets and two quartets characterize the diethyltin moieties of compounds **3b**, **5b** and **6b**, for the same reason. Exceptionally, the inequivalence is even reflected in the resonances of the substituted salicylate in compound **3b**. All

Table 1 Yields, melting points, recrystallization solvents and Mössbauer parameters (isomer shift IS, quadrupole splitting QS and line widths Γ_1 and Γ_2) of compounds **1a–10a**, **1b**, **3b–6b**, **10b** and **11b**

Compd	Yield (%)	M.p. (°c)	Recrystallization solvent	IS ($mm\ s^{-1}$)	QS ($mm\ s^{-1}$)	Γ_1 ($mm\ s^{-1}$)	Γ_2 ($mm\ s^{-1}$)
1a	85	149–150	Petrol. ether	1.31	3.43	0.90	0.88
2a	84	124–125	$CHCl_3$/hexane	1.47	3.60	0.84	0.86
3a	80	196–197	$CHCl_3$/hexane	1.56	3.88	0.88	0.93
4a	91	133–134	$CHCl_3$/EtOH	1.50	3.63	0.87	0.87
5a	76	100–101	Petrol. ether	1.33	3.41	1.08	0.94
6a	74	135–136	Petrol. ether	1.36	3.51	0.92	0.92
7a	82	170–171	$CHCl_3$/petrol. ether	1.51	3.73	0.90	0.90
8a	89	145–146	$CHCl_3$/hexane	1.52	3.68	0.82	0.76
9a	85	157–158	$CHCl_3$/hexane	1.47	3.58	0.88	0.88
10a	88	162–163	$CHCl_3$/petrol. ether	1.51	3.78	0.83	0.83
1b	78	256–257	Petrol. ether	1.21	3.27	0.81	0.81
3b	77	164–166	$CHCl_3$/hexane	1.39	3.71	1.12	1.03
4b	76	192–194	$CHCl_3$/EtOH	1.19	3.40	1.38	1.22
5b	83	250–251	$CHCl_3$/hexane	1.33	3.41	1.08	0.94
6b	72	178–180	Petrol. ether	1.36	3.51	0.91	0.92
10b	67	>350	$CHCl_3$/hexane	1.39	3.60	0.99	1.01
11b	72	>350	Toluene	1.46	3.27	0.81	0.88

Table 2a ^1H NMR chemical shift in ppm (multiplicity, coupling constant in Hz) of compounds **1a–5a** (solvent: $CDCl_3$)

	1a	**2a**	**3a**	**4a**	**5a**
R	Me	Et	Et	Et	Et
X	3-i-Pr	H	H	H	3-Me
Y	5-i-Pr	H	3-MeO	5-MeO	6-i-Pr
9-H	—	1.377 (t, 8)	1.366 (t, 8)	1.376 (t, 8)	1.391 (t, 8)
$^3J(^1H-^{117/119}Sn)$	—	139/146	140/146	141/147	137/143
8-H	1.999 (s)	1.853 (q, 8)	1.869 (q, 8)	1.859 (q, 8)	1.864 (q, 8)
$^2J(^1H-^{117/119}Sn)$	79/82	66/69	68	66/69	64/67
3-H	—	7.000 (dd, 8, 1)	—	6.931 (d, 9)	—
4-H	7.320 (d, 2)	7.492 (ddd, 8, 8, 2)	7.077 (dd, 8, 2)	7.114 (dd, 9, 3)	7.274 (d, 8)
5-H	—	6.929 (ddd, 8, 8, 1)	6.867 (dd, 8, 8)	—	6.863 (d, 8)
6-H	7.736 (d, 2)	8.020 (dd, 8, 2)	7.615 (dd, 8, 2)	7.448 (d, 3)	—
3-CH	2.904 (se, 7)	—	—	—	—
$3\text{-}CH_3$	1.283 (d, 7)	—	3.92 (bs)	—	2.251 (s)
5- or 6-CH	3.384 (se, 7)	—	—	—	4.143 (se, 7)
5- or $6\text{-}CH_3$	1.283 (d, 7)	—	—	3.820 (s)	1.263 (d, 7)
2-OH	10.7 (bs)	10.6 (bs)	10.8 (bs)	10.2 (bs)	11.5 (bs)

Abbreviations: b, broad; d, doublet; q, quartet; s, singlet; se, septet; t, triplet.

Table 2b ^{1}H NMR chemical shift in ppm (multiplicity, coupling constant in Hz) of compounds **6a–10a** (solvent: $CDCl_3$)

	6a	**7a**	**8a**	**9a**	**10a**
R	Et	Et	Et	Et	Et
X	3-i-Pr	H	H	H	4,5-Benzo
Y	5-i-Pr	5-Me	5-F	5-Cl	
9-H	1.398 (t, 8)	1.366 (t, 8)	1,374 (t, 8)	1.372 (t, 8)	1.426 (t, 8)
$^3J(^1H-^{117/119}Sn)$	140/146	139/146	140/146	140/147	140/146
8-H	1.854 (q, 8)	1.835 (q, 8)	1.866 (q, 8)	1.857 (q, 8)	1.938 (q, 8)
$^2J(^1H-^{117/119}Sn)$	69	69	68/72	59	66
3-H	—	6.895 (d, 8)	6.956 (dd, 9, 4[a])	6.949 (d, 9)	7.344 (s)
4-H	7.322 (d, 2)	7.290 (dd, 8, 2)	7.221 (ddd, 9, 9[b], 3)	7.427 (dd, 9, 3)	—
6-H	7.754 (d, 2)	7.820 (d, 2)	7.677 (dd, 9[b], 3)	7.985 (d, 3)	8.744 (s)
3-CH	2.910 (se, 7)	—	—	—	—
$3-CH_3$	1.288 (d, 7)[c]	—	—	—	—
5-CH	3.393 (se, 7)	—	—	—	—
$5-CH_3$	1.290 (d, 7)[c]	2.304 (s)	—	—	—
Benzo	—	—	—	—	7.705 (d, 8)
	—	—	—	—	7.871 (d, 8)
	—	—	—	—	7.340 (dd, 8, 8)
	—	—	—	—	7.314 (ddd, 8, 8, 1)
2-OH	10.82 (bs)	10.38 (bs)	10.35 (bs)	10.54 (bs)	10.37 (bs)

[a] $^4J(^1H-^{19}F)$. [b] $^3J(^1H-^{19}F)$. [c] Assignment permutable.

Table 2c ^{1}H NMR chemical shift in ppm (multiplicity, coupling constant in Hz) of compounds **1b**, **3b**, **4b** and **5b**

	1b ($CDCl_3$)	**3b** ($CDCl_3$)	**4b** (DMSO-d_6)	**5b** ($CDCl_3$)
R	Me	Et	Et	Et
X	3-i-Pr	H	H	3-Me
Y	5-i-Pr	3-MeO	5-MeO	6-i-Pr
9-H	—	1.381 (t, 8)	1.110 (t, 7)	1.349 (t, 8)
		1.397 (t, 8)		1.377 (t, 8)
$^3J(^1H-^{117/119}Sn)$	—	nv	139/146	146
8-H	1.047 (s)	1.665 (q, 8)	1.300 (q, 7)	1.47–1.83 (m)
	1.110 (s)	1.743 (q, 8)		
$^2J(^1H-^{117/119}Sn)$	89/92; 85	nv	89	nv
3-H	—	—	6.633 (d, 9)	—
4-H	7.274 (d, 2)	7.053 (d, 7)	6.815 (dd, 9, 3)	7.215 (d, 7)
5-H	—	6.87–6.89 (m)	—	6.818 (d, 7)
6-H	7.741 (d, 2)	7.388 (d, 7)	7.278 (d, 3)	—
		7.61 (bs)		
3-CH	2.910 (se, 7)	—	—	—
$3-CH_3$	1.269 (d, 7)	3.912 (s)	—	2.231 (s)
5- or 6-CH	3.374 (se, 7)	—	—	4.04–4.18 (m)
5- or $6-CH_3$	1.281 (d, 7)	—	3.643 (s)	1.231 (d, 7)
2-OH	10.7 (bs)	11.2 (bs)	11.9 (bs)	11.5 (bs)
	11.4 (bs)	11.7 (bs)		

Abbreviations: m, complex pattern; nv, non visible.

Table 2d ^{1}H NMR chemical shift in ppm (multiplicity, coupling constant in Hz) of compounds **6b**, **10b** and **11b**

	6b ($CDCl_3$)	**10b** (DMSO-d_6)	**11b** ($CDCl_3$)
R	Et	Et	t-Bu
X	3-i-Pr	4,5-Benzo	H
Y	5-i-Pr	4,5-Benzo	5-MeO
9-H	1.404 (t, 8) 1.440 (t, 8)	1.129 (t, 8)	1.442 (s)
$^{3}J(^{1}H-^{117/119}Sn)$	nv	141	110/115
8-H	1.666 (q, 8) 1.787 (q, 8)	1.360 (q, 8)	—
$^{2}J(^{1}H-^{117/119}Sn)$	nv	82	—
3-H	—	7.058 (s)	6.872 (d, 9)
4-H	7.283 (s)	—	7.006 (dd, 9, 3)
6-H	7.520 (s)	8.432 (s)	7.356 (d, 3)
3-CH	2.920 (se, 7)	—	—
$3-CH_3$	1.279 (d, 7)	—	—
5-CH	3.389 (se, 7)	—	—
$5-CH_3$	1.283 (d, 7)	—	3.754 (s)
Benzo	—	7.543 (d, 8); 7.768 (d, 8)	—
	—	7.12 (dd, 8, 8); 7.32 (dd, 8, 8)	—
2-OH	11.61 (bs)	12.42 (bs)	11.30 (bs)

Table 3a ^{13}C NMR chemical shift in ppm (calculated value) of compounds **1a–5a**

	1a ($CDCl_3$)	**2a** ($CDCl_3$)	**3a** (DMSO-d_6)	**4a** ($CDCl_3$)	**5a** ($CDCl_3$)
R	Me	Et	Et	Et	Et
X	3-i-Pr	H	H	H	3-Me
Y	5-i-Pr	H	3-MeO	5-MeO	6-i-Pr
C-9	—	9.2	9.3	9.3	9.4
$^{2}J(C-Sn)$	—	50	43	nv	nv
C-8	5.6	18.9	23.0[b]	19.1	18.6
$^{1}J(^{13}C-^{117/119}Sn)$	619/647	560/585	≈880[b]	562/588	nv
C-1	111.8 (117.4)	113.0 (117.4)	115.9 (116.4)	112.4 (118.4)	111.3 (115.3)
C-2	158.0 (157.8)	162.1 (157.3)	151.8 (142.9)	152.6 (149.6)	161.4 (158.0)
C-3	136.9 (135.5)	117.0 (115.4)	148.3 (146.8)	118.9 (116.4)	124.5 (122.1)
C-4	132.0 (130.4)	136.6 (134.4)	115.9 (120.0)	125.3 (120.0)	136.2 (135.1)
C-5	139.6 (140.9)	119.7 (120.8)	117.0 (121.8)	156.6 (152.2)	117.2 (118.7)
C-6	126.3 (127.3)	132.1 (131.5)	121.8 (124.1)	113.6 (117.4)	152.0 (148.8)
C-7	179.0	178.3	172.8	178.0	179.8
3-CH	27.2	—	—	—	—
$3-CH_3$	22.7	—	55.5	—	16.4
5- or 6-CH	33.8	—	—	—	30.7
5- or $6-CH_3$	24.4	—	—	56.4	24.7

Abbreviations: b, broad; nv, non visible.

the compounds exhibit broad resonances. In contrast, in DMSO solution, compounds **4b** and **10b**, insoluble in $CDCl_3$, exhibit only one triplet and one quartet, showing that the dimer present in chloroform is decomposed into a monomeric species involving the very nucleophilic dimethylsulfoxide as a ligand.

Compound **11b** exhibits only one singlet for the di-t-butyltin moiety, which is not unexpecteed because the very bulky di-t-bultyltin is likely to hinder the formation of the dioxadistannetane ring. The ^{119}Sn NMR data confirm this proposal (see below).

^{13}C NMR

The ^{13}C NMR spectra of compounds **1a–10a** are described in Tables 3a and 3b, those of compounds **1b**, **3b–6b**, **10b** and **11b** in Tables 3c and 3d.

The ^{13}C assignments in the aromatic parts are easily achieved on the basis of DEPT spectra and incremental chemical shift rules on substituted benzene compounds.[8] In the speical case of compounds **10a** and **10b**, which are naphthalene compounds, the aromatic ^{13}C chemical shifts were assigned by comparison with those calculated for 3-hydroxy-2-naphthoic acid, as deduced from increments determined from the ^{13}C spectra of naphthalene, 2-naphthoic acid and 2-naphthol.[8] Here also, tertiary and quaternary ^{13}C nuclei were discriminated from DEPT spectra. In Tables 3b and 3d, the carbons labeled C_α, $C_{\alpha'}$, C_β and $C_{\beta'}$ correspond respectively to the C-8, C-5, C-7 and C-6 of 3-hydroxy-2-naphthoic acid in the standard labeling. For compounds **4a** and **4b**, the ^{13}C assignment of the tertiary ligand carbons was achieved by a $\{^1H-^{13}C\}$ 2D HETCOR spectrum of **4b**, confirming partially the assignment suggested by the incremental rules. A HETCOR spectrum of **1b** allowed the unambiguous assignment of the methyl ^{13}C resonances of all the compounds, **1b**, **6b**, **1a** and **6a**, containing two isopropyl groups in positions 3 and 5 of the aromatic ligand.

The ^{13}C NMR spectra of compounds of type **a** exhibit a single resonance for carbon-8, as expected from the ^1H NMR spectra. They fully confirm the structure proposal made for this type of compounds.

In contrast, the compounds of type **b** exhibit two signals for C-8 when chloroform is used as a solvent (**1b**, **3b**, **5b**; see Table 3c), confirming the dimeric structure proposed for compounds **b** from the ^1H NMR and previous literature data.

As in the ^1H NMR spectrum, some ^{13}C resonances of compound **3b** exhibit a duplication not observed in the other compounds of type **b**. The origin of this higher degree of duplication is unclear but is compatible with some exchange

Table 3b ^{13}C NMR chemical shift in ppm (calculated value) of compounds **6a–10a** (solvent: $CDCl_3$)

	6a	**7a**	**8a**	**9a**	**10a**
R	Et	Et	Et	Et	Et
X	3-i-Pr	H	H	H	4,5-Benzo
Y	5-i-Pr	5-Me	5-F	5-Cl	4,5-Benzo
C-9	9.2	9.1	9.3	9.3	9.4
^2J(C–Sn)	43	44	43	44	44
C-8	18.8	18.8	19.1	19.2	19.3
^1J(C–Sn)	575/606	577/604	546/576	554/580	556/581
C-1	111.9 (117.4)	112.5 (117.3)	113.1 (119.0)[a]	114.2 (118.8)	114.9 (120.8)
C-2	158.0 (152.8)	160.0 (154.2)	158.4 (152.9)	160.8 (155.4)	156.7 (153.8)
C-3	137.0 (135.5)	117.6 (115.3)	119.2 (117.0)[a]	119.6 (116.8)	112.1 (110.8)
C-4	131.8 (130.4)	137.6 (135.1)	124.2 (121.4)[b]	136.6 (134.8)	138.9 (137.6)
C-5	139.5 (140.9)	128.9 (130.0)	155.8 (155.6)[c]	124.7 (127.1)	127.7 (128.7)
C-6	126.5 (127.3)	131.8 (132.5)	117.2 (118.8)[b]	131.3 (132.2)	134.8 (133.9)
C-7	179.1	178.5	177.3	177.3	178.2
3-CH	27.3	—	—	C_α:	129.7 (130.1)
3-CH_3	22.7	—	—	$C_{\alpha'}$:	126.8 (127.2)
5- or 6-CH	33.8	—	—	C_β:	124.4 (125.5)
5- or 6-CH_3	24.4	—	—	$C_{\beta'}$:	129.7 (129.9)

[a] $^3J(^{13}C-^{19}F) = 7$. [b] $^2J(^{13}C-^{19}F) = 24$. [c] $^1J(^{13}C-^{19}F) = 239$; ^1J(C–Sn): $^1J(^{13}C-^{117}Sn)$ and $^1J(^{13}C-^{119}Sn)$; ^2J(C–Sn): unresolved $^2J(^{13}C-^{117/119}Sn)$.

Table 3c ^{13}C NMR chemical shift in ppm (calculated value) of compounds **1b** and **3b–5b**

	1b ($CDCl_3$)	**3b** ($CDCl_3$)	**4b** (DMSO-d_6)	**5b** ($CDCl_3$)
R	Me	Et	Et	Et
X	3-i-Pr	H	H	3-Me
Y	5-i-Pr	3-MeO	5-MeO	6-i-Pr
C-9	—	9.5; 10.0; 10.5	9.1	10.2
$^2J(^{13}C-^{117/119}Sn)$	—	nv	49	nv
C-8	9.6; 8.1	21.5; 23.7	19.8	20.5; 26.3
$^1J(^{13}C-^{119}Sn)$	741; 765	nv	nv	nv
$^1J(^{13}C-^{117}Sn$	711; 732	nv	nv	nv
C-1	113.6 (117.4)	115.2; 114.8 (118.4)	118.6 (118.4)	114.5 (115.3)
C-2	158.0 (152.8)	152.7 (142.9)	149.3 (149.6)	160.0 (158.0)
C-3	136.9 (135.5)	149.2 (146.8)	120.4 (116.4)	124.1 (122.1)
C-4	130.8 (130.4)	117.7 (120)	122.3 (120.0)	135.2 (135.1)
C-5	138.9 (140.9)	118.7 (121.8)	159.0 (152.2)	117.1 (118.7)
C-6	125.3 (127.3)	122.7; 124.3 (124.1)	114.1 (117.4)	151.0 (148.8)
C-7	176.7	175.8; 177.3	169.0	178.0
3-CH	27.2	—	—	29.9
$3\text{-}CH_3$	22.7	56.6	—	24.9
5- or 6-CH	33.8	—	—	—
5- or 6-CH_3	24.6	—	55.1	16.4

Abbreviation: nv, not visible.

Table 3d ^{13}C NMR chemical shift in ppm (calculated value) of compounds **6b**, **10b** and **11b**

	6b ($CDCl_3$)	**10b** (DMSO-d_6)	**11b** ($CDCl_3$)
R	Et	Et	t-Bu
X	3-i-Pr	4,5-Benzo	H
Y	5-i-Pr	4,5-Benzo	5-MeO
C-9	9.9; 10.3	9.3	30.6
^2J(C–Sn)	nv	50	nv
C-8	21.8	20.3	42.3
^1J(C–Sn)	nv	780/840	550/580
C-1	113.8 (117.4)	124.2 (120.8)	116.5 (118.4)
C-2	158.2 (152.8)	161.2 (153.8)	156.4 (149.6)
C-3	137.0 (135.5)	113.9 (110.8)	118.4 (116.4)
C-4	130.7 (130.4)	136.5 (137.6)	122.4 (120.0)
C-5	138.9 (140.9)	125.6 (128.7)	152.3 (152.2)
C-6	125.7 (127.3)	132.7 (133.9)	114.6 (117.5)
C-7	176.9	168.5	176.5
3-CH	27.2	—	—
$3\text{-}CH_3$	22.8	—	—
5-CH	33.9	—	—
$5\text{-}CH_3$	24.6	—	56.2
C_α	—	128.4 (130.1)	—
$C_{\alpha'}$	—	124.7 (127.2)	—
C_β	—	121.5 (125.5)	—
$C_{\beta'}$	—	126.8 (129.9)	—

Abbreviation: nv, non visible.

phenomenon. This exchange should be rapid on the NMR time scale for the single averaged resonances but slow for those not yet averaged and still duplicated. The presence of other species in a $CDCl_3$ solution of **3b** is evidenced by a third broad C-9 resonance (9.50 ppm) and by the ^{119}Sn spectrum (see below).

In the DMSO solutions of compounds **4b** and **10b**, only one signal is observed for both C-8 and C-9 carbons, confirming the ^1H NMR observations. For compound **6b**, only one signal is found for C-8, but two are clearly visible for C-9. Again, only one signal is found for the C-8 of compound **11b**, as expected from proton NMR data.

^{119}Sn NMR

The ^{119}Sn NMR spectra of a series of selected compounds are described in Table 4.

Compounds of type **a** exhibit a single resonance, in agreement with the ^1H and ^{13}C NMR results. The same holds for compound **4b** in DMSO-d_6. Compound **3b** exhibits the expected two resonances with $^2J(^{119}Sn–O–^{117/119}Sn)$ satellites. However other minor resonances are also observed, that are attributed to other oligomeric species in equilibrium with the dimeric 2:2 condensation products. Likewise compounds **1b** and **6b** exhibit the two equally intense resonances with

Table 4 ^{119}Sn NMR chemical shift in ppm with respect to tetramethyltin as external standard of compounds **1a–11b** (solvent: $CDCl_3$ except when otherwise stated

	1a	**3a** in DMSO-d_6	**6a**	**1b**	**3b**	**4b** in DMSO-d_6	**6b**	**11b**
δ	−103	−293	−137	−156	−188	−263	−190	−266
	—	—	—	−162	−199	—	−192	—
^2J(Sn–O–Sn)	—	—	—	109	130	—	125	242[a]

Unresolved $^2J(^{119}Sn–O–^{117/119}Sn)$: error ±4 Hz. [a] $^2J(^{119}Sn–O–^{117}Sn)$ only.

Table 5a Relative intensities of fragment-ions observed in the monoisotopic mass spectra of compounds **1a–10a**

	1a	**2a**	**3a**	**4a**	**5a**	**6a**	**7a**	**8a**	**9a**	**10a**
$Sn^{\cdot+}$	—	17	13	11	—	—	6	6	—	—
HSn^+	—	—	12	9	—	—	—	8	—	—
$HOSn^+$	—	48	50	35	11	—	—	45	70	48
$EtSn^+$	—	27	—	—	—	—	—	30	—	—
Et_2SnH^+	—	18	20	37	—	—	18	47	28	17
$ArOSn^+$	—	—	—	—	15	29	—	—	—	—
$ArCOOSn^+$	—	52	54	54	—	—	22	—	77	—
$ArOH(COO)Sn^+$	44	100	84	65	—	44	89	77	76	36
$ArOH(COO)SnR_2^+$	100	69	100	100	100	100	100	100	100	100
$ArOH(COO)SnR_2O^+$	—	—	—	—	—	53	—	—	—	—
Miscellaneous	—	[a]	—	—	—	—	—	—	—	—

[a] Fragment-ions at $m/z = 241$ ($C_7H_5O_2Sn^+$, 62%) and 228 ($ArSnH^{\cdot+}$, 29%) have also been observed.

Table 5b Relative intensities of fragment-ions observed in the monoisotopic mass spectra of compounds **1b**, **3b–6b**, **10b** and **11b**

	1b	**3b**	**4b**	**5b**	**6b**	**10b**	**11b**
$Sn^{\cdot+}$	—	13	24	13	6	—	—
HSn^+	—	9	21	9	4	—	—
$HOSn^+$	—	46	90	66	16	18	12
$EtSn^+$	—	—	55	47	7	—	—
Et_2SnH^+	—	44	100	100	17	23	—
$ArOSn^+$	—	—	—	82	—	—	—
$ArCOOSn^+$	—	41	92	—	—	—	13
$ArOH(COO)Sn^+$	16	28	75	—	54	18	20
$ArOH(COO)SnR_2^+$	20	100	95	57	53	100	100
$ArOH(COO)SnR_2O^+$	100	—	—	—	—	—	—
Miscellaneous	[a]	[b]	—	[c]	[d]	—	[e]

[a] A fragment-ion at $m/z = 357$ ($ArOH(COO)MeSnH^+$, 68%) has also been observed. [b] Fragment-ions at $m/z = 193$ (Et_2MeSn^+, 43%) and 151 ($EtSnH_2^+$, 22%) have also been observed. [c] Fragment-ions at $m/z = 221$ ($i\text{-}PrEt_2Sn^+$, 38%) and 237 (3%) have also been observed. [d] Fragment-ions at $m/z = 355$ ($ArOSnEt_2^+$, 24%) and 237 (100%) have also been observed. [e] Fragment-ions at $m/z = 345$ ($ArOH(COO)t\text{-}BuSnH^+$, 24%) and 179 ($t\text{-}BuSnH_2^+$, 32%) have also been observed.

the unresolved $^2J(^{119}Sn–O–^{117/119}Sn)$ satellites characteristic for the proposed 2:2 distannoxanes. Compound **11b** is a monomeric 2:2 distannoxane as evidenced by the single ^{119}Sn resonance exhibiting a $^2J(^{119}Sn–O–^{117}Sn)$ satellite. Compounds **3a** and **4b**, that are only very poorly soluble in $CDCl_3$, exhibit a single resonance in DMSO-d_6 at much higher fields. This is attributed to six-coordinate monomeric species involving the nucleophilic DMSO-d_6 as ligands. According to the monomeric structure proposed for compounds of type **a**, a single resonance is observed for compound **6a**.

Mass spectral data

The mass spectra of compounds **1a–10a** are given in Table 5a, and those of compounds **1b**, **3b–6b**, **10b** and **11b** in Table 5b.

For compounds of type **a**, the fragment-ion $ArOH(COO)SnR_2^+$ is the base peak or an intense one. $ArOH(COO)Sn^+$ is also generally quite intense. For compounds of type **b**, $ArOH(COO)SnR_2^+$ is also an intense peak, but Et_2SnH^+ is sometimes the base peak.

Table 6 ID_{50} values of selected diorganotin(IV) disalicylates (X-Y-2-OH-$C_6H_2COO)_2SnR_2$, **3a**, **5a**, **8a** and **9a**, and bis)diorganosalicylatotin) oxides {[X-Y-OH-$C_6H_2COOSnR_2]_2O\}_2$, **3b** and **4b**

Compd	RR'	X	Y	ID_{50} ($ng\ cm^{-3}$) against: MCF-7	WiDr
3a	Et_2	H	3-MeO	980	2495
n-Bu_2Sn analog of **3a**[a]		H	3-MeO	105	474
5a	Et_2	3-Me	6-i-Pr	1131	4985
8a	Et_2	H	5-F	850	2361
9a	Et_2	H	5-Cl	675	1680
n-Bu_2Sn analog of **9a**[a]		H	5-Cl	89	319
3b	Et_2	H	3-MeO	524	1002
n-Bu_2Sn analog of **3b**[b]		H	3-MeO	45	323
4b	Et_2	H	5-MeO	2236	4806
n-Bu_2Sn analog of **4b**[b]		H	5-MeO	29	122
11b	t-Bu_2	H	5-MeO	38	163

The activity of some of the di-n-butyltin analogs is given for comparison.
[a] From Ref. 2. [b] From Ref. 1.

$ArOH(COO)Sn^+$ is also generally present. All the fragment-ions observed are compatible with the fragmentation rules described in the literature.[9]

In vitro antitumor screening

Some of the compounds were screened *in vitro* against MCF-7, a human mammary tumor cell line, and WiDr, a human colon carcinoma cell line.

The toxicity of the compounds against the cell lines was assessed according to the PIT method as essentially described by Van Lambalgen and Lelleveld);[12] the cells were maintained in a continuous logarithmic culture in Dulbecco's medium supplemented with 10% fetal calf serum, penicillin ($100\ i.u.\ cm^{-3}$) and streptomycin ($100\ \mu g\ cm^{-3}$); they were mildly tryptinized for passage and for use in experiments. The cells were plated in the wells of flat-bottomed microtiter plates and incubated at 37 °C. After two days the compounds were added to wells. Of each compound 12 concentrations were tested in duplicate. Serial control dilutions were made with the vehicle in the absence of drugs. After further incubation for five days, the experiments were terminated by the addition of saline containing propidium iodide (0.02%, w/w), 0.3% drawing ink and 0.5% Triton X-100. After standing overnight at 4 °C, the plates were evaluated by measuring fluorescence intensity under halogen light. For each compound the ID_{50} value (the concentration of compound inhibiting cell growth by 50%) was calculated.

Because they are much less active than the corresponding di-n-butyltin derivatives[2] (see Table 6), the other diorganotin compounds reported in this paper were not tested. The observation that diethyltin derivatives are less active than the corresponding di-n-butyl ones is in strong contrast with previous screening results reported in the literature.[4,5] We attribute this lower activity of our diethyltin derivatives to their general poorer solubility compared with the di-n-butyltin ones. It should be outlined, however, that the previous screenings were performed *in vivo* on the murine leukemiae P388 and L1210. Therefore the activity inversion observed between the diethyl- and di-n-butyl-tin compounds should be considered with caution. The only di-t-butyltin compound tested exhibits an activity as high as that of the di-n-butyltin compound. Therefore such compounds deserve further studies.

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