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Synthesis, Characterization, and In Vitro Antitumor Activity of Some Tin(IV)–Oxygen and Tin(IV)–Sulfur Heterocycles

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ABSTRACT

The synthesis of diorganotin(IV) derivatives of thiosalicylic acid, of 3-aza-2-thiosalicylic acid, and of several related compounds is reported. Their characterization by ^{1}H, ^{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 is discussed.

INTRODUCTION

We recently reported the synthesis and characterization of a series of substituted 2,2-di-butyl-4-oxo-benzo-1,3,2-dioxastannines [1]. These compounds exhibit promising in vitro antitumor activities against P388 and L1210 leukemia [2] or against human tumors [1]. Therefore we prepared a series of similar compounds in which the aromatic ligand is a pyridine instead of a benzene ring and/or the functional group is thiophenol instead of phenol. Our goal is to determine the effect of such structural and functional modifications on the anti-tumor activity of these types of compounds. We present new diorganotin(IV) derivatives of thiosalicylic acid and 3-aza-2-thiosalicylic acid, prepared, as described [1], by the reaction of thiosalicylic acid and 3-aza-2-thiosalicylic acid, respectively, with the suitable diorganotin oxide in the molar ratio 1:1. Some other related compounds were synthesized in an analogous way. Their characterization by ^{1}H, ^{13}C, and ^{119}Sn NMR, Mössbauer, and mass spectroscopy is presented, together with the results of in vitro antitumor tests.

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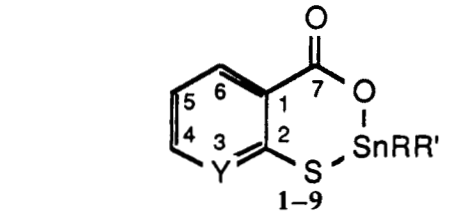
RESULTS AND DISCUSSION

Synthesis and Mössbauer Spectroscopic Data

Table 1 gives an overview of the synthesized derivatives of 3-aza-2-thiosalicylic acid (compounds **1** to **6**), of thiosalicylic acid (compounds **7** to **9**), and of two related compounds, **10** and **11**.



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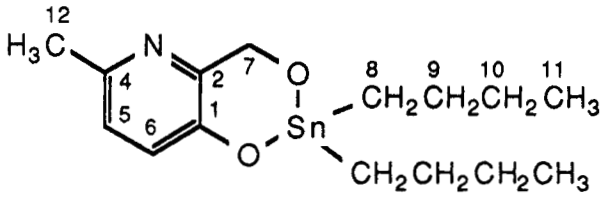

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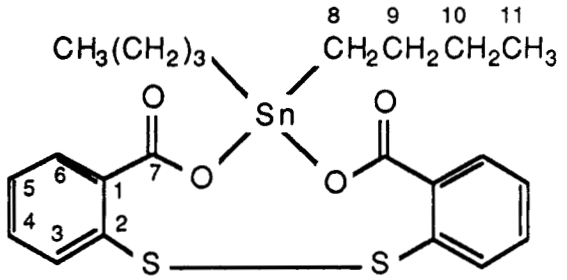

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CHART 1

Table 1 shows that the IS values are almost insensitive to the replacement of –N= by –CH= in the aromatic ring; as expected, the two diphenyltin compounds, **3** to **8**, exhibit lower IS and QS values than their dialkyltin homologs, in good correlation with their much more negative ^{119}Sn NMR chemical shifts [4]. QS values of compounds **1** to **4** are in general smaller than those of the diorganotin derivatives of salicylic acid (3.23 mm/s) [2] and of substituted salicylic acids (3.09–3.79) [1], and comparable to those of 2-thiosalicylic acid (compounds **7** to **9**). An important difference is, however, visible at the level of the preparation of salicylic vs. thiosalicylic compounds: 1:2 tin/substrate [$R_2Sn(OOCC_6H_3(OH)Y)_2$] and 2:2 tin/substrate [R_2-$(Y(OH)C_6H_3-COO)SnOSn(OOC-C_6H_3(OH)Y)R_2]_2$ condensation compounds [1] can easily be obtained when (substituted) salicylic acids $Y(OH)C_6H_3$–COOH react with diorganotin(IV) oxides R_2SnO. In contrast, the reaction of (3-aza)-2-thiosalicylic acids only yield 1:1 condensation derivatives [$R_2Sn(OOC-C_5NH_3(S)$], even in reactions with molar ratio acid:diorganotin oxide higher than 1:1. This is interpreted by the fact that the thiol is condensed to tin whereas the phenol is not.

Compound **10** gives broad absorption lines that could not unambiguously be deconvoluted in an additional doublet splitting. The coexistence of several tin configurations or coordinations in the analyzed solid is probably the reason for this broadening. The rather high QS value observed for compound **11** (3.39 mm/s) should be attributed to the carboxylate groups acting as bidentate ligands and sulfur being not coordinated to tin. This results in a trans-hexacoordinated structure with two apical butyl groups and four equatorial oxygen atoms.

NMR Data

The ^{1}H NMR data of compounds **1** to **4** are summarized in Table 2a. Those of compounds **7** to **11** are compiled in Table 2b. We have numbered the

TABLE 1 Melting Points, Recrystallization Solvents, Yields, and Mössbauer Parameters (isomer shift IS, quadrupole splitting QS, and line widths Γ) of Compounds **1** to **11**

Cpd	Y	R	R'	mp °C	solv.	yield %	IS mm/s	QS mm/s	Γ_1 mm/s	Γ_2 mm/s
1	N	Bu	Bu	275–277	$CHCl_3$	90	1.39	2.96	0.94	0.94
2	N	Oct	Oct	241–243	$CHCl_3$	89	1.37	2.91	1.05	0.97
3	N	Ph	Ph	>350	$CHCl_3$	70	1.19	2.55	0.85	0.83
4	N	Et	Ph	>350	$CHCl_3$	64	1.33	2.80	0.86	0.85
5	N	Me	Me	325–326	[c]	76	1.37	3.10	0.90	0.88
6	N	Et	Et	>350	[c]	48	1.35	3.08	0.85	0.85
7	CH	Bu	Bu	205–206[a]	$CHCl_3$/hexane	75	1.37	3.13	1.02	0.96
8	CH	Ph	Ph	>350[b]	[d]	82	1.19	2.75	0.85	1.02
9	CH	Et	Ph	240–241	[d]	77	1.39	3.20	1.06	1.06
10				220 (dec)	$CHCl_3$	86	1.34	3.73	1.45	1.17
11				113–115	$CHCl_3$	89	1.37	3.39	1.04	0.92

[a] Lit. [3]: 185–186.
[b] Lit. [3]: 295–296.
[c] Insoluble.
[d] Only soluble in DMSO.

TABLE 2a ^{1}H NMR Chemical Shift in ppm (multiplicity, coupling constant in Hz) of Compounds **1** to **4** (solvent: $CDCl_3$)

	1	**2**	**3**	**4**
CH_3	0.88 (t, 7) ^1J(H–C): 127	0.84 (t, 7) ^1J(H–C): 133	—	1.45 (t, 8) ^3J(H–Sn) = 141
$(CH_2)_n$	1.41 (tq, 7, 7)	1.22 (m) 1.38 (m)	— —	— —
$SnCH_2$	1.63–1.89 (m)	1.73 (m)	—	1.98 (q, 8)[a] ^2J(H–Sn) = 70
C_6H_5-*o*	—	—	7.8–7.9 (m) ^3J(H–Sn): 78	7.72–7.74 (m) ^3J(H–Sn): 70
C_6H_5-*m,p*	—	—	7.3–7.5 (m)	7.2–7.4 (m)
4H	7.96 (dd, 5, 2)	7.94 (dd, 5, 2)	7.79 (dd, 5, 2)	7.93 (d, 5)
5H	7.12 (dd, 7, 5)	7.10 (dd, 7, 5)	7.04 (dd, 7, 5)	7.11 (dd, 7, 5)
6H	8.46 (dd, 7, 2)	8.45 (dd, 7, 2)	8.45 (dd, 7, 2)	8.49 (d, 7)

d: doublet; q: quartet; m: unresolved pattern; t: triplet.
[a] Overlapping signals of two diastereotopic protons.

TABLE 2b ^{1}H NMR Chemical Shift in ppm (multiplicity, coupling constant in Hz) of Compounds **7** to **11** (**7**, **10**, and **11** in $CDCl_3$; **8** and **9** in d_6-DMSO); The Positions in the Alkyl Substituents Are Numbered with 8 for the α-Position with Respect to Tin and Onward

Proton	**7**	**8**	**9**	**10**	**11**
CH_3	0.80 [t, 7][a] 0.83 [t, 7] 0.85 [t, 7]	—	1.19 [t, 8] ^3J(H–Sn): 142	0.88 [t, 7]	0.91 [t, 7] ^1J(C–H) = 116
CH_2[c]	8, 10H: 1.1–1.8 (m) ^2J(Sn–H): 83	—	1.53 [q, 8] ^2J(Sn–H): 79	10H: 1.36 [tq, 7, 7]	10H: 1.45 [tq, 7, 7]
	9H: 1.34 [q, 7]			8, 9H { 1.4–1.6 (m); 1.6–1.7 (m) }	9H: 1.8–1.9 (m) 8H: 1.9–2.0 (m) ^2J(Sn–H) = 60
C_6H_5-*o*	—	7.7 (m)	7.57–7.62 (m)		
C_6H_5-*m,p*	—	7.4 (m)	7.34–7.43 (m)		
12H				2.40	
7H				4.89 [^3J(Sn–H): 43]	
6H	7.95–7.99 (m)	7.85 [d, 7]	7.76 [dd, 2, 8]	6.97[b] [8]	8.21 [dd, 2, 8]
5H	7.26–7.32 (m)	7.29 [t, 7]	7.15 [dt, 2, 8]	6.94[b] [8]	7.25 [t, 8]
4H	7.16–7.22 (m)	7.20 [t, 7]	7.24 [dt, 2, 8]	—	7.43 [dt, 2; 8]
3H	7.60–7.70 (m)	7.53 [d, 7]	7.48 [dd, 2; 8]	—	7.77 [d, 8]

[a] Intensities: 1:2:2.
[b] AB spectrum.

carbons of compounds **1** to **4** as in salicylic acid so as to allow an easier comparison between the NMR data of these compounds and of compounds **7**, **8**, **9**, and **11**.

Proton 6 in compound **1** is the most deshielded among the aromatic protons. Indeed, it undergoes cumulative deshielding from the ring nitrogen in para and from the C=O double bond in ortho. This is confirmed by the coupling constant of 7 Hz to its neighbor, a value typical for $^3J_{meta,\ para}$ couplings in pyridine. The other proton, 4, coupled with only one ortho proton therefore corresponds to the resonance at δ = 7.96. The assignment of proton 5 is straightforward because it is coupled to two ortho protons and therefore displays a different multiplet pattern.

The assignments for compounds **2**, **3**, and **4** are performed as for **1**, thanks to strong chemical shift analogies. For compounds **7**, **8**, and **9**, proton 6 is also the most deshielded one and the other signals can be assigned using similar arguments.

The methyl protons of compound **7** exhibit three triplets of different intensities. The reason for this is not yet clear. A mixture of monomer and oligomers could explain this result, in analogy to Lockhart's proposal [5].

For compound **10** the ^{1}H NMR data are compatible with a 1:1 or 2:2 composition. There is no evidence of any dimer formation as in bis(carboxylatodiorganotin) oxide.

The proton NMR spectrum of compound **11** is very similar to those of 2:1 condensation products

of salicylic acids with dibutyltin oxide. These data are compatible with the trans-hexacoordinated structure containing two apical butyl groups and two equatorial bidentate carboxylates as proposed from the Mössbauer parameters.

The ^{13}C data are compiled in Tables 3a and 3b.

For compound **1**, the assignment of the carbon signals has been done from a 2D ^{13}C-{1H} HETEROCOSY spectrum. This is confirmed by the fact that ^{1}H irradiation at the frequency of the resonance at lowest field in the proton spectrum transforms the doublet at δ = 142.0 in the undecoupled

TABLE 3a ^{13}C NMR Data Chemical Shifts of Compounds **1** to **4** (solvent: $CDCl_3$); Figures *in Italics* between Parentheses are Calculated Values Obtained by Using the Aromatic Chemical Shift Increment Rules [9, 10]

	1	2	3	4	
C-15, *p*		14.1	130.2	129.8	(*128.2*)
C-14, *m*		22.6	128.9, ^{3}J(Sn–C) = 82	128.6, ^{3}J(Sn–C) = 69	(*128.3*)
C-13, *o*		31.9	136.0, ^{2}J(Sn–C) = 58	135.7, ^{2}J(Sn–C) = 44	(*135.9*)
C-12, *i*		29.1	139.7	140.6	(*141.9*)
C-11	13.5	29.2			
C-10	26.6 ^{3}J(Sn–C) = 113	33.6 ^{3}J(Sn–C) = 81			
C-9	27.9 ^{2}J(Sn–C) = 34	25.8 ^{2}J(Sn–C) = 33		10.3 ^{2}J(Sn–C) = 38	
C-8	22.2 $^{1}J(^{119/117}Sn–C)$ = 616/581	22.6 $^{1}J(^{119/117}Sn–C)$ = 475/447		14.6 $^{1}J(^{119/117}Sn–C)$ = 612/574	
7	168.30[a]	168.3[c]	167.3[b]	167.7[c]	
2	168.33[a]	168.3[c]	167.3[b]	167.6[c]	(*153.7*)
6	142.0	142.0	142.8	142.3	(*138.4*)
5	118.9	118.9	119.8	119.4	(*120.7*)
4	147.1	147.0	147.5	147.5	(*154.5*)
1	129.6	129.7	129.3	129.3	(*126.6*)

[a] Double irradiation experiment, see text.
[b] Isochronous.
[c] Nearly isochronous, not assigneable.

TABLE 3b ^{13}C NMR Chemical Shifts of Compounds **7** to **11** (solvent: $CDCl_3$); Figures *in Italics* between Parentheses are Calculated Values Obtained from the Aromatic Chemical Shift Increment Rules [9, 10]

	7	8	9	10	11
C-*p*		129.8	129.3 (*128.2*)		
C-12, *m*		128.4 ^{3}J(Sn–C) = 83	128.1 (*128.3*) ^{3}J(Sn–C) = 75	22.0	
C-11, *o*-	13.8	135.2 ^{2}J(Sn–C) = 32	135.2 (*136.0*) ^{2}J(Sn–C) = 54	13.5	13.6
C-10, *i*	26.3, 26.6	140.4	142.1 (*141.9*)	26.8 ^{3}J(Sn–C) = 103	26.3 ^{3}J(Sn–C) = 100
C-9	27.7; 27.0 ^{2}J(Sn–C) = 44		9.3 ^{2}J(Sn–C) = 55	27.1 ^{2}J(Sn–C) = 52	26.8
C-8	23.1, 23.2, 23.6		15.6 $^{1}J(^{119/117}Sn–C)$ = 707/671	23.1	26.0
C-7	175.0; 175.1; 175.3; 175.5	168.5	168.6	68.7	175.6
C-2	138.3	135.3	135.7 (*132.5*)	147.6 (*149.2*)	140.7 (*137.9*)
C-3	131.47; 131.67	130.0	129.6 (*128.9*)		125.4 (*126.9*)
C-4	132.1; 132.3; 132.4; 132.6; 132.7	133.3	133.5 (*134.0*)	155.7 (*151.7*)	132.8 (*133.8*)
C-5	125.3; 125.4	125.2	124.9 (*125.0*)	127.4 (*125.2*)	125.8 (*127.1*)
C-6	138.6	131.4	131.2 (*130.7*)	124.0 (*123.5*)	133.2 (*131.2*)
C-1	135.8	132.7	[a] (*130.9*)	145.7 (*146.8*)	127.8 (*128.9*)

[a] Probably isochronous with another signal.

^{13}C spectrum into a singlet, leaving the two doublets at δ = 147.1 and 118.9 unchanged. Furthermore, in the undecoupled spectrum of compound **1**, the signal at δ = 168.3 is a complex pattern with two $^3J(^{13}C-^1H)$ coupling constants equal to 6.6 and 3.5 Hz. Upon double irradiation at the frequency of the resonance at lowest field in the proton spectrum, the doublet with the 6.6 Hz splitting in this complex pattern is transformed into a singlet at δ = 168.33, the remainder of the pattern being a doublet at δ = 168.30 with a coupling constant of 3.5 Hz [11]. Because the coupling constant between proton 6 and carbon 5 should be about 1 Hz, as in pyridine, and because the coupling constant between proton 6 and carbons 2 and 4 should be about 6 Hz, the remaining doublet found upon irradiation of proton 6 cannot arise from carbon 2 and should be carbon 7. The chemical shifts calculated with the increments [9] fit reasonably well with the assigned ones. On the other hand, each type of aromatic carbon having the same chemical shift within less than δ = 1 and sometimes even less than 0.5 in compounds **1** to **4**, the assignment achieved for **1** can safely be transposed to **2**, **3**, and **4**.

Multiple resonances for most carbons of compound **7** are to be explained by several conglomerates observed in chloroform for such compounds [9]. Only single resonances are found for each carbon of compounds **8** and **9** in the very nucleophilic solvent DMSO.

Solid state CP-MAS ^{13}C NMR spectra have been recorded for the two insoluble compounds **5** and **6**. The data are given in Table 4. These assignments are to be paralleled with those of compounds **1** to **9** in solution. The presence of more than the expected number of signals for the methyl and ethyl groups is likely to be due to structural nonequivalences related to crystal packing.

The ^{119}Sn NMR data of compounds **1**, **3**, **4**, **7**, **8**, **9**, **10**, and **11** in solution are summarized in Table 5. The ^{119}Sn signals in the diphenyltin compounds (**3** and **8**) are much more shifted to high field than in the dibutyltin compounds (resp. **1** and **7**). This upfield shift in diphenyltin compounds is well known in diorganotin dichlorides [4].

In compound **4** the organic groups bound to tin are different. The presence of several chiral tin atoms in an oligomer leads to diastereomerism that is likely to explain the large number of resonances in the ^{119}Sn NMR spectrum of compound **4**.

The ^{119}Sn NMR spectrum of compound **7** exhibits three resonances, which is in agreement with the proton spectrum. The ^{119}Sn chemical shift of compound **10** corresponds to a coordination number of five or six [6]. X-ray structural studies on stannylene derivatives of sugars [7] have shown that these compounds are dimeric in the solid state and that the tin atom is pentacoordinated in some of the compounds and hexacoordinated in others.

The tin chemical shift observed for compound **11** lies in the typical range (δ = −121.7 to −150.5) of trans-hexacoordinated 2:1 condensation compounds of substituted salicylic acids with dibutyltin oxide [6], which confirms our proposal from ^1H and Mössbauer data.

Mass Spectroscopic Data

The 70 eV mass spectra of compounds **1** to **10** are described in Table 6.

For compound **4**, fragment-ions are also present at m/z = 285 (90%), 256 (94%), 211 (77%), 195 (72%), 179 (89%), and 136 (98%). Compound **5** also exhibits fragment-ions at m/z = 241 (33%), 209 (59%), 193 (50%), 179 (23%), 166 (53%), 165 (59%), and 151 (40%), while compound **6** also shows fragment-ions at m/z = 209 (31%), 193 (41%), 179 (19%), and 165 (52%). Fragment-ions are also present at m/z = 293 (80%), 255 ($C_6H_5SnBuH^+$:30%), 241 ($C_6H_5COOSn^+$:26%), and 211 ($C_6H_5CH_2Sn^+$:65%) for compound **7**, at m/z = 306 (13%) for compound **8**, at m/z = 317 ($C_6H_4SSnC_6H_5^+$:40%), 211

TABLE 4 Solid State CP-MAS^{13}C NMR Shifts of Compounds **5** and **6**

	C-9 or/and 8	*C-7*	*C-6*	*C-5*	*C-4*	*C-2*	*C-1*
5	4.1, 7.4	170.1	141.5	120.0	150.9	165.6	127.8
6	3.9, 4.9, 6.8	170.0	142.8	121.2	150.5	166.2	127.3

TABLE 5 ^{119}Sn NMR Spectra of Compounds **1**, **3**, **4**, **7**, **8**, **9**, **10**, and **11** (in $CDCl_3$ except for **8** and **9** that are recorded in d_6-DMSO); Between Parentheses for Compound **7**: Relative Integrated Areas

	1	**3**	**4**	**7**	**8**	**9**	**10**	**11**
δ	−95.2	−234.6	−163.8 −164.0 −164.1 −164.4 −164.9	−124.5 (1.4) −126.3 (5.6) −127.8 (8.9)	−207.1	−276.4	−198.4	−133.5

TABLE 6 70 eV Mass Spectra of Compounds **1** to **10**, Condensation Productions of ArYH(CXOH) and RR'SnO (X = H_2, O)

Cpd		**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
	RR'	Bu_2	Oct_2	Ph_2	PhEt	Me_2	Et_2	Bu_2	Ph_2	PhEt	Bu_2
	Ar	H_3C_5N	H_3C_5N	H_3C_5N	H_3C_5N	H_3C_5N	H_3C_5N	H_4C_6	H_4C_6	H_4C_6	H_8C_7N
	Y	S	S	S	S	S	S	S	S	S	O
	X	O	O	O	O	O	O	O	O	O	H_2
Fragment-ion											
$Sn^{\cdot+}$ (m/z = 120)		17	8	65	—	—	—	—	58	—	19
HSn^+ (m/z = 121)		9	6	—	—	—	—	—	19	—	27
$HOSn^+$ (m/z = 137)		16	9	6	—	—	—	—	6	—	21
RSn^+		—	74	—	57	—	—	13	51	—	—
$ArYSnH^+$		68	53	—	95	32	27	47	34	65	—
$ArYSnR^+$		5	—	20	—	—	—	—	100	—	—
$ArY(CXO)SnH^+$		100	100	30	100	33	27	100	21	91	81
$ArY(CXO)SnR^+$		—	20	—	—	—	—	—	5	—	9
$ArY(CXO)SnRH^{\cdot+}$		15	—	100	—	—	—	—	—	—	—
$M^{\cdot+}$		7	2	6	—	—	—	—	46	—	100
$(M + H)^+$		3	1	1	42	100	—	70	8	100	17

(Et_2SnSH^+:33%), and 199 (Et_2SnOH^+:24%) for compound **9** and at m/z = 256 (93%) and 228 (86%) for compound **10**.

The molecular ion loses one of the organic groups R or R' linked to tin yielding $ArY(CXO)SnR^+$. The latter loses the alkene (R minus H) yielding $ArY(CXO)SnH^+$ or CXO yielding $ArYSnR^+$. The fragment-ions RSn^+, $SnOH^+$, SnH^+, and $Sn^{\cdot+}$, commonly observed in the mass spectra of organotin compounds [8], are also present here. For all compounds except **6**, the $(M + H)^+$ ion is also observed. It loses an alkene (R minus H) to yield $ArY(CXO)SnRH^{\cdot+}$.

In Vitro Anticancer Screening

The soluble compounds **1–4** and **7–11** were submitted to in vitro tests against two human tumor cell lines, MCF-7 (mammary tumor) and WiDr (colon carcinoma). The results are given in Table 7. For compound **10**, additional ID_{50} values of 80, 43, and 530 ng/mL have been obtained for A204 (rhabdomyosarcoma), T24 (bladder carcinoma), and IgR-37 (melanoma), respectively.

From Table 7, it is quite clear that compounds **1** and **10** exhibit interesting [12] in vitro antitumor activities especially against MCF-7. Many others are more active than or comparable to cis-platin against MCF-7, but less than the other nonmetallic reference compounds.

EXPERIMENTAL

Syntheses

The synthesis of compounds **1** to **10** is analogous to that of the substituted or unsubstituted salicylic acids [1, 2].

For compounds **1** to **4**, 0.01 mole of diorganotin oxide is suspended in a solution of 0.01 mole of the appropriate 3-aza-2-thiosalicylic acid in 200 mL of benzene and refluxed for 20 h. One half of the solvent is distilled off with a Dean-Stark apparatus. The remaining homogeneous solution is then cooled and filtered. The solvent is evaporated under vacuum. The solid obtained is recrystallized from chloroform.

For compound **7**, 0.01 mole of dibutyltin oxide is added to a solution of 0.01 mole of thiosalicylic acid in 70 mL ethanol and 280 mL toluene and refluxed for 4 h. The solvent is evaporated under reduced pressure and the light yellow oil obtained is crystallized from hexane/chloroform.

For compounds **8** to **9**, the reaction mixture remains heterogeneous even after 24 h at reflux. After filtration, the solid is washed several times with hot chloroform and dried under reduced pressure.

TABLE 7 ID_{50} Values in Vitro (in ng/mL) Against the Human Tumor Cell Lines MCF-7 and WiDr

	MCF-7	*WiDR*
1	23	430
2	761	1221
3	353	2964
4	959	3469
7	92	334
8	585	15800
9	3585	12140
10	37	212
11	653	1488
"Cis-platin" [12]	850	624
Doxorubicin [12]	63	31
Etoposide [12]	187	624
Mitomycin C [12]	3	17

For compound **10**, 0.01 mole of dibutyltin oxide is added to a solution of 0.01 mole of 2-hydroxymethyl-3-hydroxy-6-methylpyridine in 70 mL ethanol and 280 mL toluene and refluxed for 4 h. The ternary azeotrope water/ethanol/toluene is distilled off with a Dean-Stark apparatus and the volume of the solvent is then reduced to 50%. The homogeneous solution obtained is kept in the refrigerator for one night. The precipitate generated is vacuum filtered, washed several times with petroleum ether (light fraction), and recrystallized from chloroform.

For compound **11**, 0.01 mole of dibutyltin oxide is added to a solution of 0.01 mole of the corresponding diacid in 70 mL ethanol and 280 mL toluene and refluxed for 4 h. The solvent is evaporated under reduced pressure and the brownish oil obtained is precipitated by petroleum ether. The solid is dried and crystallized from chloroform.

Estimation of ID50 Values

Drug activity was determined using an automated in vitro technique described previously [13].

Equipment

The Mössbauer spectra were recorded with the constant acceleration mode on an Elscint MVT4 Promeda counting instrument, with a $Ca^{119m}SnO_3$ source from Amersham. The probe is maintained at the temperature of liquid nitrogen, whereas the source is kept at room temperature. The digital data are treated with a least squares iterative program deconvoluting the spectrum as a sum of lorentzians.

The ^1H NMR spectra were recorded on a Bruker AM 270 instrument equipped with an Aspect 2000 computer; the solution ^{13}C NMR spectra were taken on a Bruker SF 250 instrument equipped with an Aspect 3000 computer. The ^{119}Sn NMR spectra were recorded on a Bruker WM 500 instrument equipped with an Aspect 3000 computer. The CP-MAS ^{13}C solid state NMR spectra were recorded on a Varian 200 instrument. The mass spectra were recorded on a V.G. Micromass 7070 F instrument (source temperature: 200°C).

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