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Dialkyltin Derivatives of Dicarboxylic Acids: Synthesis, Characterization and in vitro Antitumor Properties

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ABSTRACT

Diorganotin derivatives of dicarboxylic acids, including diethyltin propene-1,3-dicarboxylate, diethyltin homophthalate, and di-n-butyltin tetrafluorophthalate, were tested in vitro against two human tumor cell lines, MCF-7, a mammary tumor, and WiDr, a colon carcinoma. Most of these display lower inhibition doses ID_{50} than cis-platin. The synthesis and characterization of the last three compounds by Mössbauer spectroscopy, ^{1}H, ^{13}C and/or ^{119}Sn NMR and mass spectrometry, are also presented.

INTRODUCTION

Many diorganotin(IV) compounds have already been prepared, characterized and tested in vitro against human tumor cell lines [1]. Their prescreening activities are generally far superior to those of cis-platin [2, 3]. We have prepared, characterized and tested some dialkyltin derivatives of dicarboxylic acids, a class of compounds not extensively studied so far in the present context.

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RESULTS AND DISCUSSION

In Vitro Tests

Several classes of diorganotin compounds of dicarboxylic acids (see Figure 1), recently synthesized and characterized, compounds **1** to **10**, were tested against human tumor cell lines, MCF-7, a mammary tumor, and WiDr, a colon carcinoma [3]. All organotin compounds, except **5c, 7, 9** and **10** display inhibition doses ID_{50} significantly lower than those of *cis*-platin against both MCF-7 and WiDr cell lines. Although usually di-*n*-octyltin compounds have lower activities than their di-*n*-butyltin analogs [2, 3], the much lower activity of compound **5c** with respect to **5b** is worth outlining. Most active compounds score better than etoposide against the same tumor cell line. All compounds, except **5c, 7, 9** and **10**, are even more active than *cis*-platin and etoposide against WiDr, a usually less sensitive cell line. The very high activity of compounds **6a** and **8** against both tumor cell lines should be underlined since their activity is comparable to that of doxorubicin.

1042-7163/92/$3.50 + .25

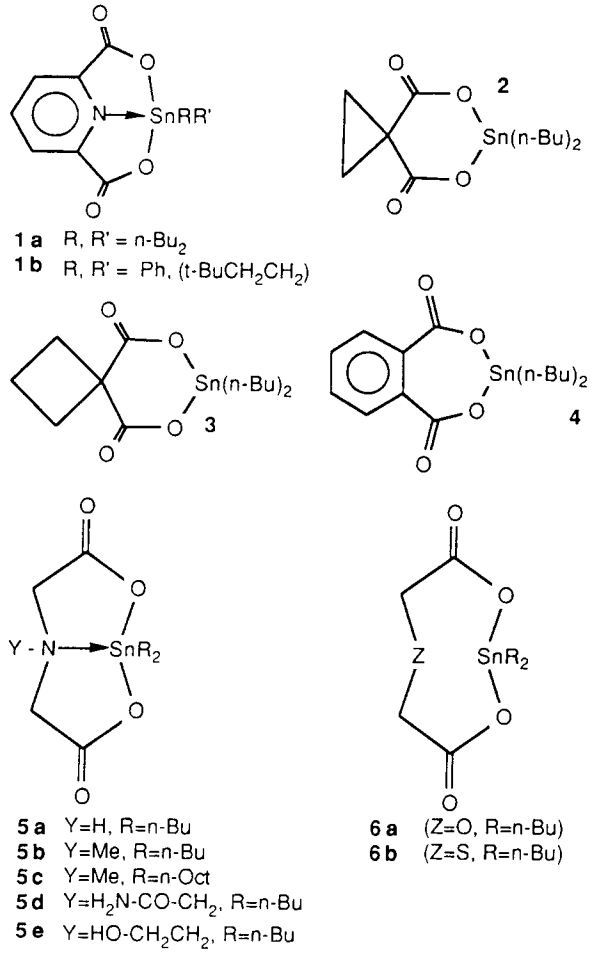


FIGURE 1

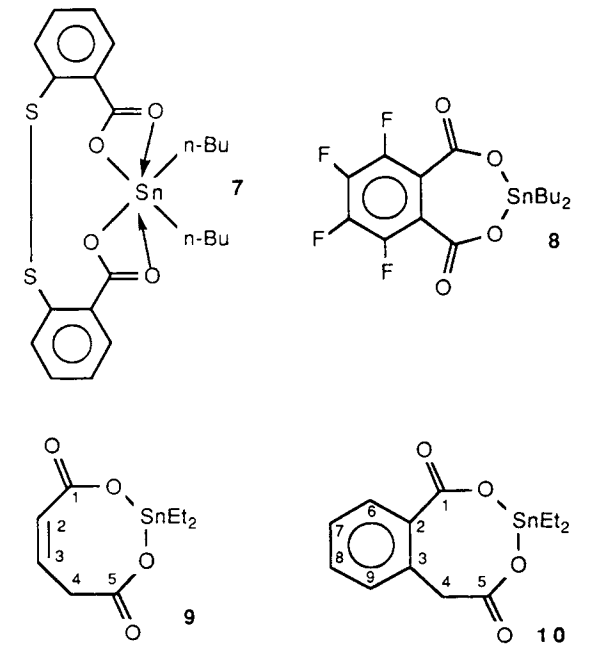


FIGURE 1 Diorganotin derivatives of dicarboxylic acids tested.

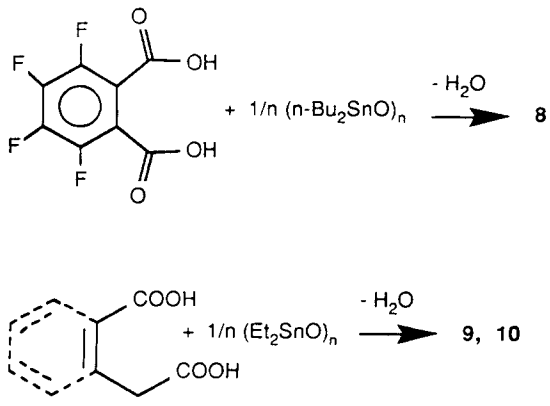
TABLE 1 Inhibition doses ID_{50} values (in ng / mL) obtained for compounds **1** to **10** and for *cis*-platin, etoposide and doxorubicin as reference compounds against MCF-7, a mammary tumor, and WiDr, and colon carcinoma

No	*MCF-7*	*WiDr*
1a	60	106
1b	50	161
2	60	302
3	63	121
4	128	464
5a	42	277
5b	38	292
5c	5 500	14 000
5d	76	349
5e	52	277
6a	28	72
6b	178	356
7	653	1 488
8	51	68
9	3 283	6 560
10	604	1 290
Cis-platin [5]	850	624
Etoposide [5]	187	624
Doxorubicin [5]	63	31

Compound **3** contains the 1,1-cyclobutanedicarboxylate ligand, the same structural organic moiety as in carboplatin. Whereas this compound meets the criteria of significant activity in vitro against the present cell lines, it displayed only borderline activity in vivo against the murine leukemia P388 [9].

Syntheses

The synthesis of compounds **1** to **7** was described earlier [4, 7–12]. Di-*n*-butyltin tetrafluorophthalate, **8**, diethyltin propene-1,3-dicarboxylate, **9**, and diethyltin homophthalate, **10**, are prepared analogously by condensing the dicarboxylic acid and diorganotin oxide in a 1 : 1 molar ratio and under elimination of water [4]:



The NMR, mass spectroscopic and Mössbauer data are consistent with the expected compound compositions. We have no explanation for the rather large value of Γ_1 in compound **8**.

EXPERIMENTAL

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 a temperature between 90 and 100 K, the source at room temperature. The digital data are treated with an iterative program and least square deconvoluted as a linear combination of Lorentzian functions [10]. The mass spectra were recorded on a AEI MS 902S instrument coupled to a NOVA computer. Samples were introduced via the direct insertion probe.

The ^1H and ^{13}C NMR spectra were recorded at 270.13 and 67.93 MHz respectively on a Bruker AM 270 instrument. The ^{19}F NMR spectra were recorded at 235.36 MHz on a Bruker AC250 instrument. The ^{119}Sn NMR spectra were recorded at 186.5 MHz on a Bruker WM 500 instrument.

The cell lines were maintained in a continuous logarithmic culture in Dulbecco's medium supplemented with 10% fetal calf serum, penicillin (100 IU/mL0 and streptomycin (100 μg/mL). The cells were mildly trypsinised for passage and for use in experiments. Stock solutions of the compounds to be tested were prepared in DMSO and full growth medium. In the assays the concentration of the solvent was less than 1% v/v. The toxicity of the compounds against the cell lines was assessed according to the PIT method described previously [5]. Briefly, the cells were plated in the wells of flatbottomed microtiter plates and incubated at 37°C. After 2 days the compounds were added to wells. The highest concentration was serially diluted 3-fold. 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 5 days, the experiments were terminated by the addition of saline containing propidium iodide (0.002% w/v), 0.3% drawing ink and 0.5% triton X-100. After having been allowed to stand overnight at 4°C, the plates were evaluated by measuring fluorescence intensity under halogen light. For each compound the IC_{50} value (the concentration of compound inhibiting cell growth by 50%) was calculated.

The synthesis and characterization of compounds **1a** [7], **1b** [8], **2** and **3** [9], **4** [4], **5a** to **5c** [10], **5d** and **5e** [11], **6a**, **6b** and **7** [12] have been described earlier. For compounds **8** to **10**, 0.01 mole of diorganotin oxide was suspended in a solution of 0.01 mole of the appropriate dicarboxylic acid in 200 ml of benzene and refluxed for 20 hr. One half of the solvent was distilled off with a Dean-Stark apparatus. The remaining homogeneous solution was then cooled and filtered. The solvent was evaporated under vacuum. The obtained solid was recrystallized.

Di-n-butyltin Tetrafluorophthalate (**8**)

Recrystallization solvent: methanol; yield: 85%; mp: 210–5°C; Mössbauer parameters: IS: 1.43 mm/s against $Ca^{119m}SnO_3$; QS: 3.43 mm/s; Γ_1: 1.20; Γ_2: 0.91; ^1H NMR (TMS as internal reference, DMSO-d_6): δ = 1.94 (t, 7, α-CH_2); 1.73 (tt, 7, 7, β-CH_2); 1.32 (tq, 7, 7, γ-CH_2); 0.87 (t, 7, CH_3); ^{13}C NMR (TMS as internal reference, $CDCl_3$): δ = 117.1, C-1; 145.7, dd, 260, 8, C-2; 141.9, dddd, 265, 19, 19, 7, C-3; 170.6, C=O; 26.5 [$^1J(^{13}C—^{117/119}Sn)$ = 512/536, $SnCH_2$]; 26.3 [$^2J(^{13}C—Sn)$ = 55 Hz, β-CH_2]; 26.3 [$^3J(^{13}C—Sn)$ = 102 Hz, γ-CH_2]; 13.6, CH_3; ^{19}F NMR ($CFCl_3$ as external reference): AA'XX' spectrum with δ_A = −137.57, δ_X = −149.74, $J_{AX} \approx 20 \pm 1$ Hz, $J_{AX'} \approx -6 \pm 1$ Hz, $J_{AA'} \approx 11 \pm 1$ Hz, $J_{XX'} \approx 23 \pm 1$ Hz; ^{119}Sn NMR (tetramethyltin as external reference, $CDCl_3$): δ = −116.9; FAB mass spectral data: Bu_2SnH^+ (3%); $F_4C_6(CO_2)_2SnH^+$ (100); $Bu_3Sn_2O_2$ (47); $Bu_5Sn_2O_2$ (25)

Diethyltin Propene-1,3-dicarboxylate (**9**)

Recrystallization solvent: chloroform/hexane; yield: 78%; mp: 142–143°C; Mössbauer spectroscopy: IS: 1.54; QS: 3.85; Γ_1: 0.92; Γ_2: 0.95; ^1H NMR ($CDCl_3$): δ = 1.275 (t, 8, $^3J(^1H—^{117/119}Sn)$ = 139/145 Hz, CH_3); 1.65 (q, 8, $^2J(H—Sn)$ = 71 Hz, $SnCH_2$); 6.34 (d, 1, 2-H); 5.67 (d, 1, 3-H); 3.36 (s, 4-H); ^{13}C NMR (TMS as internal reference, $CDCl_3$): δ = 8.9 [$^2J(^{13}C—Sn)$ = 41 Hz, CH_3]; 17.6 [$^1J(^{13}C—^{117/119}Sn)$ = 570/596, $SnCH_2$]; 175.5 and 180.4, C-1 and C-5; 129.2 and 134.2, C-2 and C-3; 38.0, C-4; ^{119}Sn NMR (tetramethyltin as external reference, $CDCl_3$): −150.1; FAB mass spectral data: Sn^{+}: 46%; SnH^+: 20; $SnOH^+$: 100; $EtSn^+$: 37; Et_2SnH^+: 44; tin-containing fragment-ions also appear at m/z = 163 (37%) and 211 (52%); ditin-containing fragment-ions appear at m/z = 269, 297, 327, 385, 461 and 535.

Diethyltin Homophthalate (**10**)

Recrystallization solvent: chloroform/hexane; yield: 82%; mp: 179–180°C; Mössbauer spectroscopy: IS: 1.41; QS: 3.40; Λ_1: 0.95; Λ_2: 0.92; ^1H NMR ($CDCl_3$): δ = 1.29 (t, 8, $^3J(^1H—^{117/119}Sn)$ = 137/143 Hz, CH_3); 1.66 (q, 8, $^2J(H—Sn)$ = 70 Hz, $SnCH_2$); 4.14 (s, 4-H); 8.21 (dd, 8, 1, 6-H); 7.352 (ddd, 8, 8, 1) and 7.49 (ddd, 8, 8, 1), 7-H and 8-H; 7.28 (dd, 8, 1, 9-H); ^{13}C NMR ($CDCl_3$): δ = 9.1 [$^2J(^{13}C—Sn)$ = 42 Hz, CH_3]; 17.6 [$^1J(^{13}C—^{117/119}Sn)$ = 531/554 Hz,

$SnCH_2$]; 176.8 and 181.7, C-1 and C-5; 129.5 and 137.1, C-2 and C-3; 127.1, 131.7, 132,3 and 132.5, C-6 to C-9; 40.3, C-4; FAB mass spectral data: Sn^+: 30%; SnH^+: 25; $SnCH_3^+$: 20; $SnOH^+$: 63; $EtSn^+$: 66; Et_2SnH^+: 83; $EtSn(CO_2)_2^+$: 100; ditin-containing fragment-ions appear at m/z = 269, 297, 327, 385, 461 and 535.

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