SYNTHESIS, CHARACTERIZATION AND ANTITUMOUR ACTIVITY OF DI-n-BUTYLTIN SALICYLOXAMATE

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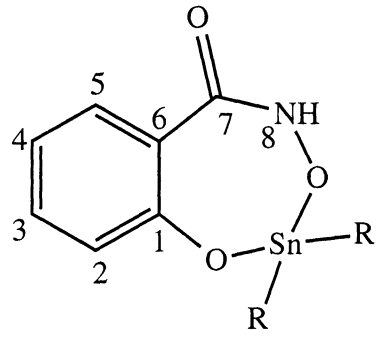
Abstract
The synthesis and characterization of di-n-butyltin and dimethyltin salicyloxamate, respectively compounds **1** and **2**, are reported. Compound **1** is more active than cisplatin, 5-fluorouracil and etoposide against seven tumoural cell lines of human origin, but less active than methotrexate and doxorubucin.

Diorganotin derivatives of salicylic acid and its substituted analogs exhibit antitumour activities *in vitro* against human tumoural cell lines[1,2]. The phenolic hydroxy group of salicylic acid is not involved in its reaction with diorganotin oxides[3,4]. In fact, salicylic acid behaves in this respect as benzoic acid, giving rise to diorganotin disalicylates with free hydroxy groups.
This report presents the synthesis and characterization of di-n-butyltin and dimethyltin salicyloxamate, respectively compounds **1** and **2**, in order to find out whether the phenolic hydroxy group of salicyloxamic acid is involved when reacting with diorganotin oxides. The antitumour activity of compound **1** was determined for comparison with that of the corresponding di-n-butyltin salicylate[5].



	α	β	γ	δ	
R =	CH_2-	CH_2-	CH_2-	CH_3	**1**
	α				
	CH_3				**2**

Compound **1**, a viscous oil, and compound **2**, a solid (m.p. 195-197°) were synthesized with 94% and 85% yield, respectively, by condensing the appropriate diorganotin oxide with salicyloxamic acid in a toluene/ethanol 4/1 mixture[3,6,7]. They were purified by chromatography on Sephadex LH-20 with chloroform/ethanol 99/1 as eluent (compound **1**) or crystallization from dichloromethane/hexane 50/50 (compound **2**). ^1H and ^{13}C NMR data ($CDCl_3$) are given in Table 1. The ^{117}Sn NMR chemical shifts of compounds **1** and **2** are respectively -140.0 and -100.2 ppm. The cationic mode electrospray mass spectra of compounds **1** and **2** exhibit the fragment corresponding to (M + H^+) (100%) at resp. m/z = 386 ($C_{15}H_{24}NO_3Sn$) and 302 ($C_9H_{12}NO_3Sn$) with the expected isotopic distribution.
Compound **1** was tested *in vitro* against seven tumoural cell lines of human origin: MCF-7 et EVSA-T, two mammary tumours, WiDr, a colon carcinoma, IGROV, an ovarian cancer, M19 MEL, a melanoma, A498, a renal cancer, and H226, a non-small cell lung cancer, as water/ethanol 99/1 solutions.
The results of the antitumoural tests are summarized in Table 2 and compared with the inhibition doses ID_{50} found against MCF-7 and WiDr for di-n-butyltin disalicylate and bis(acetylsalicylate), as well as those obtained for some clinically used reference compounds[8,9], cis-platin, 5-fluorouracil, etoposide, methotrexate and doxorubicin. Compound **1** has, especially against WiDr, a markedly higher *in vitro* activity than di-n-butyltin disalicylate and bis(acetylsalicylate) as well as cisplatin, 5-fluorouracil and etoposide. Its activity is lower than that of methotrexate and doxorubicin, except for H-226 against which compound **1** exhibits a very low inhibition dose as compared to all other compounds.

	^{1}H			^{13}C	
	1	**2**		**1**	**2**
			C_1	162.7	162.1
H_2	d: 6.54 [8]	d: 6.55 [8]	C_2	119.5	119.6
H_3	dd: 6.79 [8,8]	dd: 6.80 [8,8]	C_3	116.8	116.2
H_4	dd: 7.28 [8,8]	dd: 7.30 [8,8]	C_4	133.0	133.1
H_5	d: 7.88 [8]	d: 7.90 [8]	C_5	129.6	129.6
			C_6	116.3	116.2
			C_7	163.3	163.4
H_8	s: 13.62 (**55**)	s: 13.60 (**55**)			
H_α	-	s: 0.84 (**76/73**)	C_α	22.7 (**590/564**)	2.1 (**639/611**)
$H_{\alpha\text{-}\beta}$	m: 1.75-1.52	-	C_β	26.8 (**31**)	-
H_γ	tq: 1.37 [7,7]	-	C_γ	26.6 (**88**)	-
H_δ	t: 0.87 [7]	-	C_δ	13.6	-

Table 1: ^{1}H and ^{13}C NMR data of compounds **1** and **2** ($CDCl_3$). Chemical shifts in ppm vs. TMS; $^nJ(^1H,^1H)$ (between brackets), $^nJ(^1H,^{119/117}Sn)$ and $^nJ(^{13}C,^{119/117}Sn)$ (bold in parentheses) coupling constants in Hz. d: doublet; t: triplet; tq: triplet of quartets; s: singlet; m: complex pattern.

	MCF-7	EVSA-T	WiDr	IGROV	M19 MEL	A498	H226
1	67	59	316	103	90	140	109
Di-n-butyltin disalicylate	540	-	2974	-	-	-	-
Di-n-butyltin bis(acetylsalicylate)	283	-	2495	-	-	-	-
Cisplatin	699	422	967	169	558	2253	3269
5-Fluorouracil	750	475	225	297	442	143	340
Etoposide	2594	317	150	580	505	1314	3934
Methotrexate	18	5	<3	7	23	37	2287
Doxorubicin	10	8	11	60	16	90	199

Table 2. Inhibition doses ID_{50} of compound **1** as compared to di-n-butyltin disalicylate and bis(acetylsalicylate)[5] and of some reference compounds[8,9] against tumoural cell lines of human origin.

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