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Review

Organotin compounds and their therapeutic potential: a report from the Organometallic Chemistry Department of the Free University of Brussels†

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An overview of the development of antitumour organotin derivatives is presented and discussed for selected classes of compounds, such as tetraorganodicarboxylatodistannoxanes and related diorganotin dicarboxylates, and for triorganotin carboxylates. Among the carboxylate groups used are steroidcarboxylates and other biologically relevant carboxylates. High to very high *in vitro* activities have been found, sometimes equalling that of doxorubicin. Solubility in water is an important issue, dominating the *in vivo* testing of compounds. Polar substituents, like fluorine or polyoxaalkyl moieties, improve the water solubility. Although organotin derivatives constitute a separate class of compounds, the comparison with cisplatin is inevitable. Among the observed toxicities, neurotoxicity, known from platinum cytostatics, and gastrointestinal toxicity, typical for many oncology drugs, have been detected, but to a lower extent. Further research to develop novel useful organotin antitumour compounds needs to be carried out.

KEYWORDS: diorganotin; triorganotin; antitumour activity; cytotoxic activity; *in vitro* screening; human tumour cells, *in vivo* screening; water solubility

INTRODUCTION

Since the discovery of the antiproliferative properties of cisplatin (see Fig. 1),[1] many platinum compounds have been synthesized, characterized, and screened as anticancer agents.

Cisplatin[1–3] and carboplatin[5,6] have found wide application in cancer chemotherapy. Testicular, ovarian, and bladder cancer have been treated successfully by combinations containing these drugs. Also, small-cell lung cancer has been shown responsive to platinum chemotherapy. Other platinum compounds, like iproplatin or lobaplatin, are under investigation for anti-cancer treatment (Fig. 1).

In 1986, our group published a series of patents[7–9] that initiated the search for antitumour-active organotin compounds. This paper presents an overview of this research

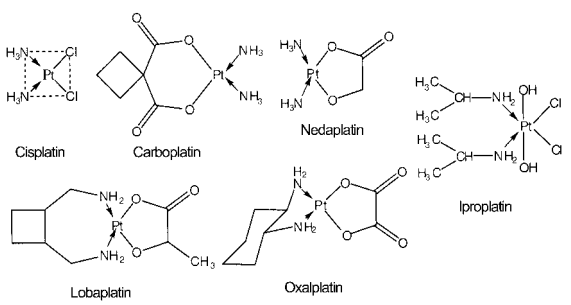

Figure 1. The clinically used antitumour drugs cisplatin and carboplatin and some other antitumour—active platinum compounds.

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Table 1. ID_{50} values of doxorubicin (DOX), cisplatin (CPT), 5-fluorouracil (5-FU), methotrexate (MTX) and etoposide (ETO)

Cell line	ID_{50} (ng ml)$^{-1}$)				
	DOX	CPT	5-FU	MTX	ETO
MCF7	10	699	750	18	2594
EVSA-T	8	422	475	5	317
WIDR	11	967	225	<3	150
IGROV	60	169	297	7	580
M19 MEL	16	558	442	23	505
A498	90	2253	143	37	1314
H226	199	3269	340	2287	3934

during the last 15 years. Some of these results have been reviewed before,[9–14] and much of this work has been patented.[15–22]

The di-*n*-butyltin analogue of carboplatin was synthesized and screened against MCF-7 and WiDr, two tumour cell lines of human origin.[23] It was characterized by ID_{50} values of 63 and 121 ng ml^{-1}, whereas the values of 600 and 967 ng ml^{-1} were obtained for cisplatin. It may be unfair to compare these two compounds because, unlike the platinum derivative, the tin compound is not a monomer. Rather, it is a polymer in which one carboxylate group of the cyclobutyl dicarboxylate moiety coordinates as a bidentate ligand to a single tin atom, whereas the other carboxylate is linked, also as a bidentate ligand, to one and to the next tin atom of an infinite polymer chain.[24]

The first antitumour tests performed by the National Cancer Institute (NCI), USA, were *in vivo* tests on leukaemias (P388, L1210). These are nowadays replaced by an *in vitro* pre-screening against a panel of cancer cell lines.[9–14,25–31]

In Table 1, ID_{50} values of some well-known oncology drugs are presented. ID_{50} values may show some variation due to the biological nature of the test. Slight changes in the system during the years of testing may also cause changes in the ID_{50} values. The actual reference values can be found in the papers pertaining to the compounds. The reference (and test) compounds were dissolved to a concentration of 238 095 ng ml^{-1} in full medium, by dilution of an ethanol solution that contained 1 mg of compound in 200 µl. Compounds that were found to be insoluble in ethanol were dissolved in dimethylsulfoxide (DMSO). The *in vitro* tests were carried out in the Laboratory for Tumor Biology and Pharmacology of the Academic Hospital Rotterdam, the Netherlands. The cell lines used were two mammary cancers, (MCF-7, EVSA-T), a colon carcinoma (WiDr), an ovarian cancer (IGROV), a melanoma (M19 MEL), a renal cancer (A 498), and a lung cancer (H226).

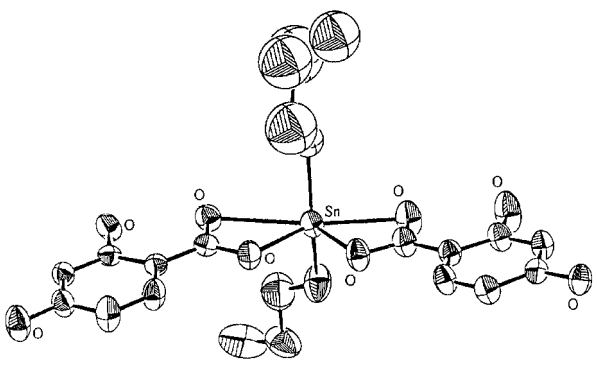


Figure 2. Di-*n*-butyltin bis (2, 4-dihydroxybenzoate).

PRELIMINARY ANTITUMOUR SCREENING OF DIORGANOTIN CARBOXYLATES

Because platinum and tin have common properties, for instance their possible oxidation states, tin compounds were screened as early as in 1980.[32] The first organotin compounds, for which the antitumour properties were examined, were formally similar to cisplatin,[33–41] or to its analogues carboplatin or paraplatin.[24,25,42] They exhibit borderline activities against P388 and L1210 leukaemias *in vivo*.[43–47] Arakawa[48] studied the *in vivo* activity of di-*n*-butyltin dichloride towards Ehrlich ascites tumour, IMC carcinoma, P-388 lymphocytic leukaemia, and Sarcoma 180 systems, and also showed that this compound influences the DNA synthesis of proliferating cells. Many diorganotin compounds, R_2SnX_2, were investigated in the context of their antitumour potential. The influence of the R groups and of the X ligands on the activity were examined.[49–51]

Many series of organotin derivatives of carboxylic and dicarboxylic acids were synthesized.[52–54] They are easily prepared by mixing, for example, an insoluble polymeric diorganotin oxide and a carboxylic acid in a solvent like

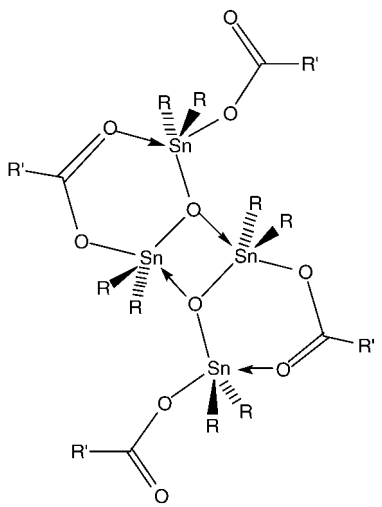


Figure 3. Structure of tetraorganodicarboxylatodistannoxanes generally observed.

Table 2. Influence of the diorganotin moiety on the ID_{50} value of selected di-organotin(IV) carboxylates

Carboxylate	RR′Sn	ID_{50} (ng ml^{-1}) against	
		MCF-7	WiDr
Pyridine-2,6-dicarboxylate	*n*-Bu_2Sn	60	106
Pyridine-2,6-dicarboxylate	Me-*n*-BuSn	1572	6780
Pyridine-2,6-dicarboxylate	Et_2Sn	822	1290
Pyridine-2,6-dicarboxylate	Ph_2Sn	170	372
Pyridine-2,6-dicarboxylate	PhMeSn	2187	3283
Pyridine-2,6-dicarboxylate	PhEtSn	918	4046
Pyridine-2,6-dicarboxylate	Ph-*n*-PrSn	223	1094
Pyridine-2,6-dicarboxylate	Ph-i-PrSn	402	1169
Pyridine-2,6-dicarboxylate	Ph-*n*-BuSn	761	3705
Pyridine-2,6-dicarboxylate	Ph-i-BuSn	121	831
Pyridine-2,6-dicarboxylate	$Ph[PhCH_2]Sn$	2910	10995
Pyridine-2,6-dicarboxylate	$Ph\text{-}[t\text{-}BuCH_2CH_2]Sn$	50	161
Pyridine-2,6-dicarboxylate	$Ph[PhMe_2CCH_2]Sn$	40	106
Pyridine-2,6-dicarboxylate	$[p\text{-}MeO-Ph]_2Sn$	4930	15800
3-Aza-2-thiosalicylate	*n*-Bu_2Sn	23	430
3-Aza-2-thiosalicylate	EtPhSn	959	3469
3-Aza-2-thiosalicylate	Ph_2Sn	353	2964
3-Aza-2-thiosalicylate	$(p\text{-}MeO-C_6H_4)_2Sn$	2754	8173
3-Aza-2-thiosalicylate	*n*-Oct_2Sn	761	1221
6-Azasalicylate	*n*-Bu_2Sn	96	337
6-Azasalicylate	Me_2Sn	>20000	>20000
6-Azasalicylate	Et_2Sn	611	1607
6-Azasalicylate	EtPhSn	319	653
Cis-platin		850	624

toluene, with the water formed being eliminated by azeotropic distillation.

The derivatives obtained are dependent upon the tin/RCOOH ratio. When a 1:2 ratio is used, a diorganotin dicarboxylate is formed (see Fig. 2):[54–68]

$$(R_2SnO)_n + 2nR'COOH \rightarrow nR_2Sn(OOCR')_2 + nH_2O \quad (1)$$

Table 3. Influence of the phenyl substituent on the ID_{50} value of $\{[Y\text{-}C_6H_3(2\text{-}OH)COOSnBu_2]_2O\}_2$ compounds against some cell lines

Y	ID_{50} (ng ml^{-1})				
	MCF-7	WiDr	A204	T24	IGR37
3-CH_3	44	330	97	86	675
3-MeO	105	474			
4-MeO	131	1182			
5-CH_3O	29	122	69	46	547
4-NH_2	42	330	105	70	642
Cis-platin	850	624	817	268	878
Doxorubicin	63	1	10	25	63
Mitomycin C	3	17	18	15	4

In contrast, the 1:1 ratio yields tetraorganodicarboxylatodistannoxane dimers (Fig. 3):[69–73]

$$(R_2SnO)_n + 2nR'COOH \rightarrow n[R_2Sn(R'COO)]SnOSn(OOCOR')R_2]_2 + nH_2O \quad (2)$$

The influence of the organotin moiety on the antitumour activity has been evaluated for several classes of diorganotin carboxylates (see Table 2).

The most active compounds of the different series examined are the di-*n*-butyltin ones, which strongly suggests that this is a general trend, even if $Ph[t\text{-}BuCH_2CH_2]Sn$ and $Ph[PhMe_2CCH_2]Sn$ compounds score as well in the pyridine-2,6-dicarboxylate series. The di-*n*-butyltin derivatives are commercially available and not expensive, being used, for instance, as PVC stabilizers. As already found in the literature, the dimethyltin compound tested is inactive.

The influence of the Y substituent on the antitumour activity of $\{[Y-C_6H_3(2\text{-}OH)COOSnBu_2]_2O\}_2$ compounds is not straightforward (see Table 3), i.e. the structure–activity relationship described by the Hammett equation is not followed.

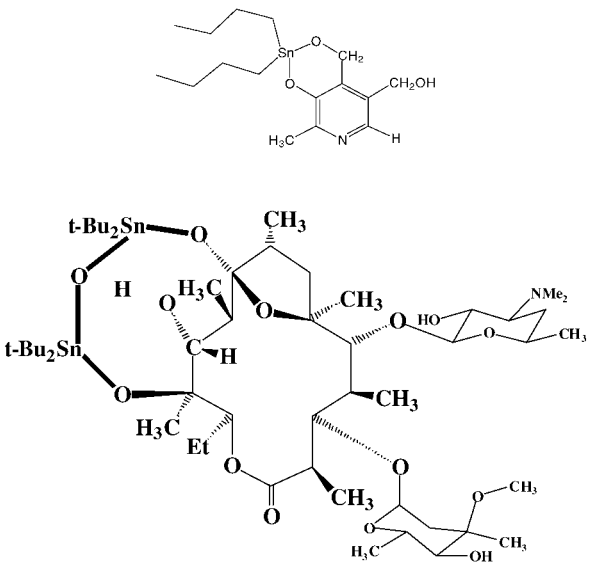


Figure 4. Structures of the organotin derivatives of pyridoxine and erythromycin.

ANTITUMOUR SCREENING OF ORGANOTIN DERIVATIVES OF BIOLOGICALLY RELEVANT SUBSTRATES

The organotin derivatives of pyridoxine and erythromycin (Fig. 4) were synthesized and tested several years ago, and were recently fully characterized by NMR techniques.[74,75] Against P388, L1210, and P815 leukaemias, the organotin derivative of pyridoxine gave ID_{50} values of 15 ng ml^{-1}, 19 ng ml^{-1}, and 17 ng ml^{-1}, respectively; for the organotin derivative of erythromycin the respective ID_{50} values are 38 ng ml^{-1}, 78 ng ml^{-1}, and 69 ng ml^{-1}; these values are quite similar to those obtained for organotin derivatives of cortexolone (ID_{50} = 6 ng ml^{-1}, 36 ng ml^{-1}, and 44 ng ml^{-1} respectively).

Triorganotin compounds are quite well known bactericides and fungicides.[76,77] Such compounds were sometimes prepared for that purpose, and consequently screened for their antitumour activity. Several of these were found to be quite active *in vitro*.[78,79] Examples of such high activities are shown in Tables 4 and 5.

The steroidcarboxylate series (Fig. 5) is clearly one of the major early developments in this area[7,8,80,81] (Table 4). Both di- and tri-organotin compounds were examined. Compound **1** showed some activity in the Colon 26 tumour in mice.

They appear to possess pronounced *in vitro* antitumour activity,[7,8] but the solubility still remains a drawback,[82] thus affecting their *in vivo* properties. In order to make this type of compound more soluble, a less complicated structure was designed, again containing a five-ring moiety, and also polar substituents. This led, for instance, to the synthesis of organotin terebates.[83] The *in vitro* test results of three compounds of this type are given in Table 5. The organotin

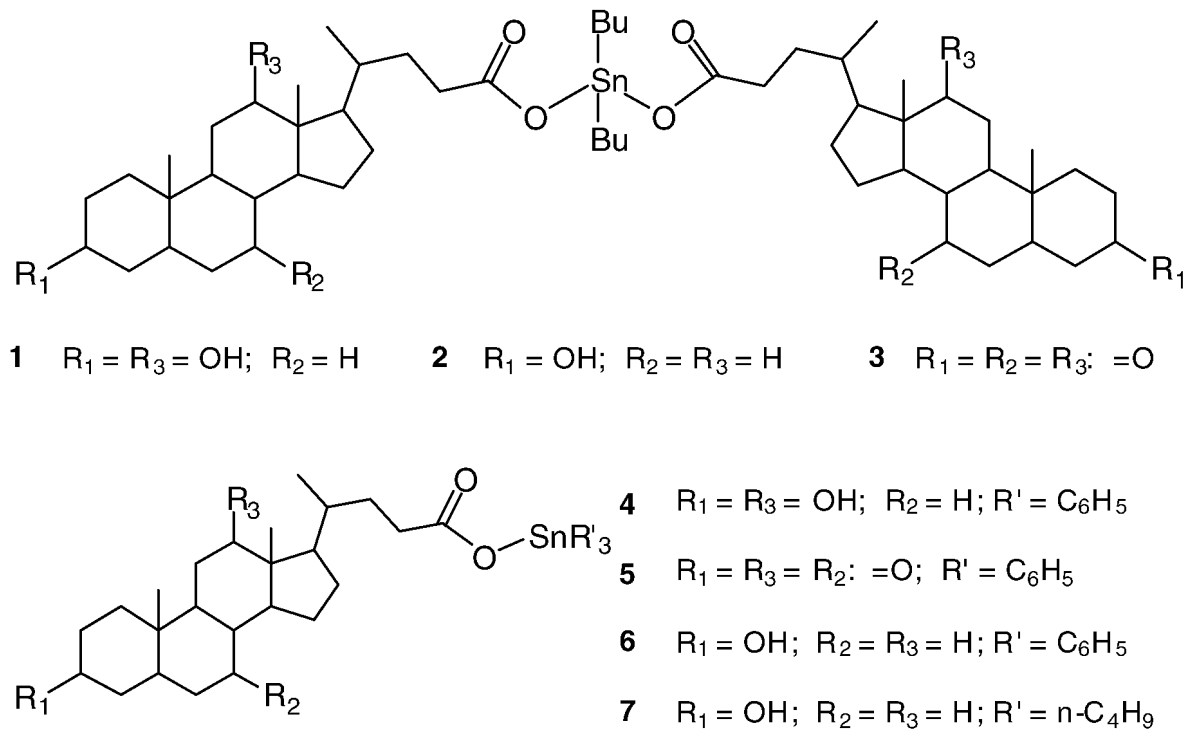


Figure 5. Structures of the organotin steroidcarboxylates screened.

Table 4. ID_{50} values of some organotin steroidcarboxylates against some cell lines (see Fig. 5)

Compound	ID_{50} (ng ml^{-1})						
	MCF7	EVSA-T	WIDR	IGROV	M19 MEL	A498	H226
1	18	<3	36	18	51	42	61
2	160	60	390	160	120	220	420
3	409	171	629	150	481	972	1229
4	18	<3	15	17	32	53	53
5	11	<3	22	16	22	11	50
6	16	<3	19	18	51	65	61
7	16	<3	15	<3	51	138	76

Table 5. ID_{50} values of some organotin terebates against some cell lines (see Fig. 6)

Compound	ID_{50} (ng ml^{-1})						
	MCF7	EVSA-T	WIDR	IGROV	M19 MEL	A498	H226
Di-*n*-butyltin terebate	27	25	134	18	61	61	104
Tri-*n*-butyltin terebate	3	<3	11	4	11	15	8
Triphenyltin terebate	17	<3	17	19	42	42	39

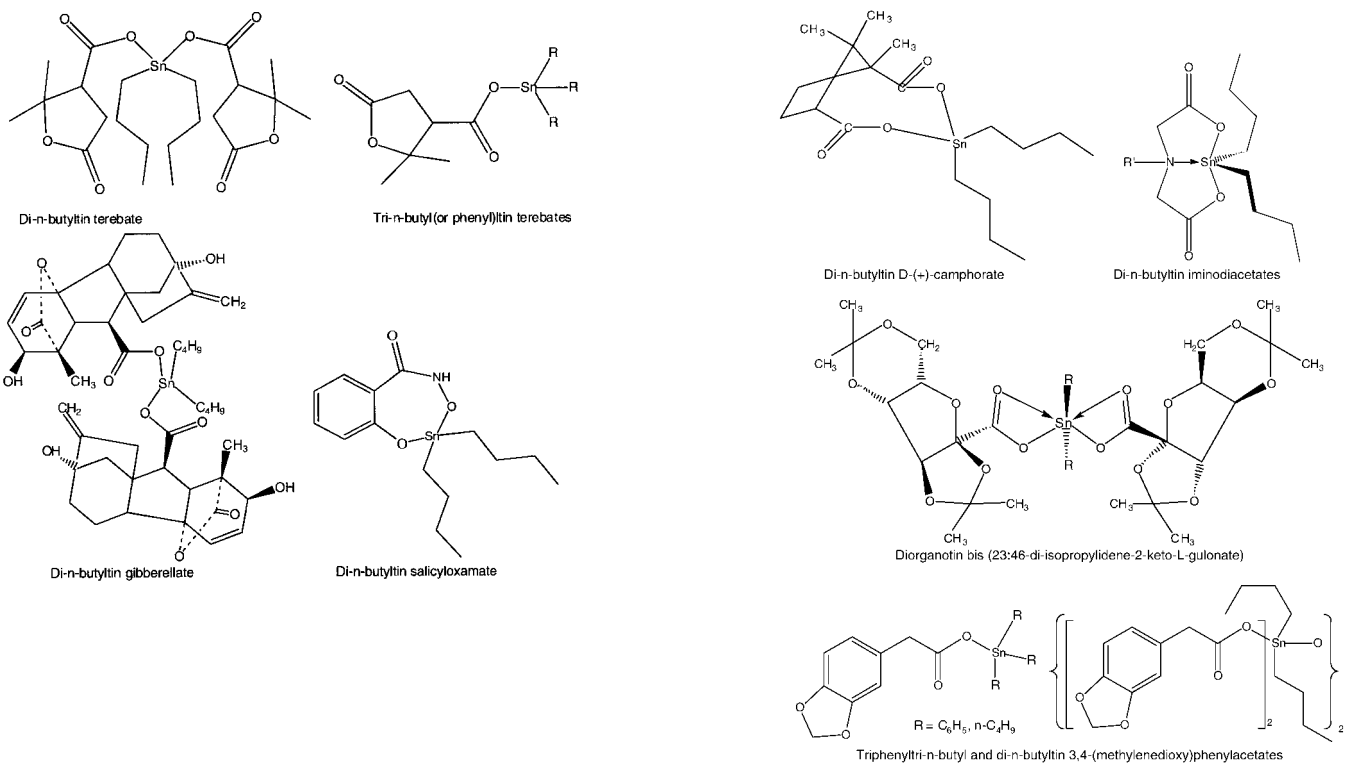


Figure 6. Examples of organotin derivatives of biologically relevant substrates of which the antitumour-activity has been determined.

Table 6. *In vivo* activity of some organotin terebates in the murine Co 26 model

Compound	Dose (mg kg^{-1})	Schedule	T/C (%)	ILS (%)
Di-*n*-butyltin terebate	5	qd7 × 2	91	100
Tri-*n*-butyltin terebate	10	qd7 × 2	121	157
Triphenyltin terebate	15	qd7 × 1	78	100

terebates were found to exhibit high *in vitro* antitumour activity.

These organotin terebates were tested *in vivo* against the mouse Colon 26 tumour. The mouse Colon 26 model is indeed expected to possess a higher predictive value than the L1210 model, and was used instead of the L1210 model formerly used by the NCl (Table 5). The solubility of triphenyltin terebate in DMSO, normally diluted by a 100 times excess of water, is poor. Therefore, the DMSO solution was further diluted with arachidis oil, resulting in a colloidal suspension. The toxicity of the compounds was unpredictable and variable, probably as the result of the limited solubility. There was considerable toxicity. Only one injection of triphenyltin terebate could be given. Two injections of tri-*n*-butyltin terebate resulted in 3–5 toxic deaths in 1 week in mice. The results of the *in vivo* tests are summarized in Table 5. Some *in vivo* activity was detected. *In vivo* tests were carried out by the Department of Medical Oncology of the Free University of Amsterdam, the Netherlands, under the supervision of Dr G.J. Peters.

Other biologically relevant molecules have also been studied[84–88] (Fig. 6). Their *in vitro* antitumour activities are gathered in Table 6.

ANTITUMOUR SCREENING OF FLUORINE-CONTAINING ORGANOTIN CARBOXYLATES

From the data available in the literature, a number of factors relating to the mode of action of diorganotin compounds R_2SnX_2 have been identified: the organic groups R determine the potential activity, the X groups control the delivery of the active R_2Sn^{2+} species, and the hydrolytic stability of the Sn—X bonds determines whether this potential activity is realized.[89,90] Other factors, like the lipophilic/hydrophilic character of the compounds, are probably very important; their lipophilic properties are essential for crossing the cell membrane, and their hydrophilic character, is required in order to be accepted by a water-rich cell.[82]

A first attempt to increase the water solubility was to

Table 7. ID_{50} values of some organotin derivatives of biologically relevant substrates

Substrate	ID_{50} (ng ml^{-1})						
	MCF-7	EVSA-T	WiDr	IGROV	M19 MEL	A 498	H 226
Bu_2Sn digibberellate	262	244	401	245	247	327	306
Ph_3Sn gibberellate	<3	<3	<3	7	5	20	>60000
Bu_3Sn gibberellate	102	53	74	116	111	170	146
Bu_2Sn salicyloxamate	67	59	316	103	90	140	109
Bu_2Sn camphorate	49	28	100	45	66	49	178
Me_2Sn camphorate	1342	903	3504	1006	1111	1548	764
Bu_2SnN-benzyliminodiacetate	56	46	207	66	80	68	71
Bu_2SnN-*o*-Me-benzyliminodiacetate	53	47	302	61	83	61	86
Bu_2SnN-*m*-Me-benzyliminodiacetate	55	48	277	75	82	71	74
Bu_2SnN-*p*-Me-benzyliminodiacetate	52	46	179	60	58	49	62
Gulonate	498	180	781	666	70	331	3279
Ph_3Sn-Methylenedioxyphenylacetate	34	22	37	32	35	36	36
Bu_3Sn-Methylenedioxyphenylacetate	82	40	41	51	64	110	70
Bu_2Sn(Methylenedioxyphenylacetate)$_2$	128	55	307	55	75	116	113
DOX	10	8	11	60	16	90	199
CPT	699	422	967	169	558	2253	3269
5-FU	750	475	225	297	442	143	340
MTX	18	5	<3	7	23	37	2287
ETO	2594	317	150	580	505	1314	3934

Table 8. ID_{50} values of dihydroxybenzoatotin compounds against some cell lines

Compound	ID_{50} (ng ml^{-1})					
	MCF7	EVSA-T	WIDR	IGROV	M19 MEL	A498
$[2,4\text{-}(OH)_2C_6H_3COO]_2Sn(n\text{-}Bu)_2$	16	54	120	85	58	130
$[2,6\text{-}(OH)_2C_6H_3COO]_2Sn(n\text{-}Bu)_2$	15	58	130	110	65	130
$[2,3\text{-}(OH)_2C_6H_3COO]_2Sn(n\text{-}Bu)_2$	7	43	90	51	50	50
$[3,5\text{-}(OH)_2C_6H_3COO]_2Sn(n\text{-}Bu)_2$	130	30	500	120	190	280
$[2,5\text{-}(OH)_2C_6H_3COO]_2Sn(n\text{-}Bu)_2$	4	48	115	60	65	100

substitute hydrogen atoms of phenyl rings by hydroxyl groups. The activities found for some compounds of this category are shown in Table 7. The introduction of such polar groups leads to some improvement in the solubility, and definitely to a considerable increase of the *in vitro* activity. In this respect, fluorine-substituted organotin compounds were also candidates to be tried.

Already by 1984, fluorine-containing organotin compounds were synthesized to check if the replacement of hydrogen by fluorine affected antiproliferative activity.[89,90] Fluorine is indeed a very unusual atom: it is much heavier (19 times) than hydrogen, which might imply, for instance, that the boiling points of perfluoroalkanes (freons), which are expected to increase with molecular mass, should be much higher than that of the corresponding hydrogen-substituted analogues. In fact, this is not the case: freons are often gases at atmospheric pressure when the corresponding alkanes are liquids. Another property of fluorine-substituted compounds is that they are more soluble in water than their hydrogen analogues, and still well soluble in non-polar solvents. Perfluoroalkanes have found very useful applications, for instance as blood substitutes.[91]

Fluorine-containing organotin compounds[92–96] are a possible way to solve the water-solubility problem encountered with almost all the organotin compounds described in the preceding paragraphs. The results were quite encouraging. Some of the numerous fluorine-containing organotin compounds synthesized and screened are given in Table 8. Examples are given in Figs 7 and 8.

Two of the compounds were tested *in vivo* in the murine Co 26 model. A summary of the results is given in Table 9. Toxicity was mainly gastrointestinal.

Another possible way to increase the hydrophilicity of organotin compounds is to prepare organotin salts, for instance stannates.[97–101] Here, the antitumour results were

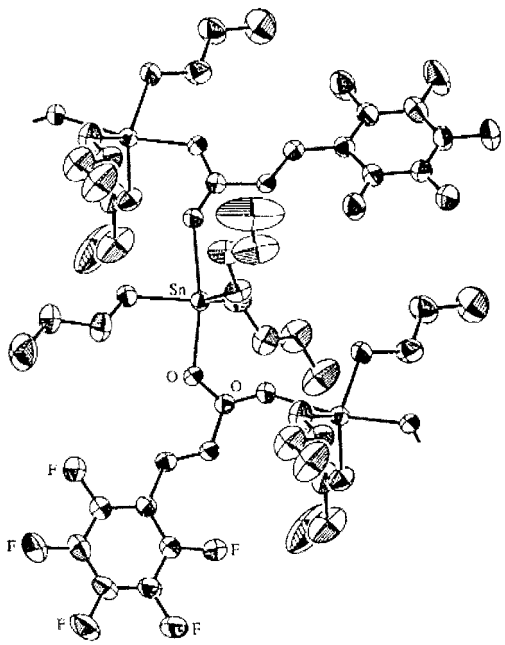


Figure 7. Part of the crystal polymeric structure of tri-*n*-butyltin pentafluorocinnamate.

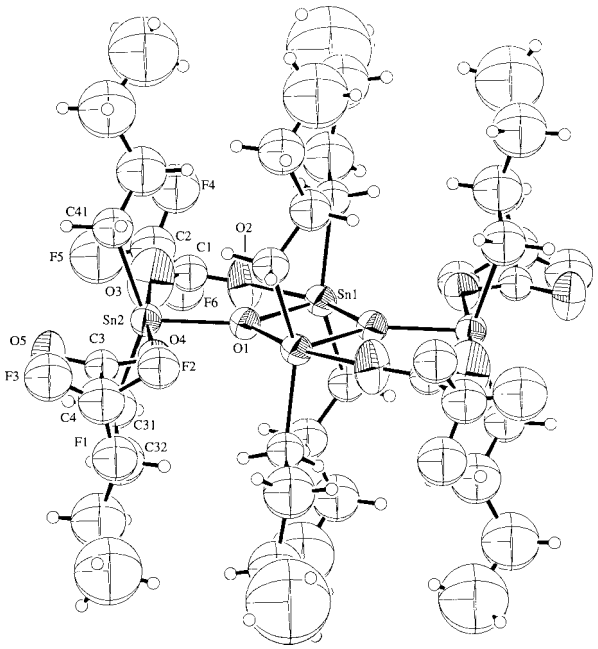


Figure 8. Structure of the dimer of tetra-*n*-butylbis(trifluoromethylacetato)distannoxane$\{[Bu_2Sn(O_2CCF_3)_2]_2O\}_2$.

Table 9. ID_{50} values of selected tin fluorine-substituted aromatic carboxylates against some cell lines

Compound	ID_{50} (ng ml^{-1})					
	MCF7	EVSA-T	WIDR	IGROV	M19 MEL	A498
{[(2-FC_6H_4COO)(*n*-Bu)$_2$Sn]$_2$O}$_2$	91		330			
{[(4-FC_6H_4COO)(*n*-Bu)$_2$Sn]$_2$O}$_2$	81		360			
{[(3-FC_6H_4COO)(*n*-Bu)$_2$Sn]$_2$O}$_2$	496		3431			
(3-FC_6H_4COO)$_2$Sn(*n*-Bu)$_2$	39		271			
(2,3-$F_2C_6H_3COO$)$_2$Sn(*n*-Bu)$_2$	23		283			
{[(2,3-$F_2C_6H_3COO$)(*n*-Bu)$_2$Sn]$_2$O}$_2$	9		120			
{[(2,5-$F_2C_6H_3COO$)(*n*-Bu)$_2$Sn]$_2$O}$_2$	7		277			
(3,5-$F_2C_6H_3COO$)$_2$Sn(*n*-Bu)$_2$	30		407			
{[(2,6-$F_2C_6H_3COO$)(*n*-Bu)$_2$Sn]$_2$O}$_2$	3		174			
{[(3,5-$F_2C_6H_3COO$)(*n*-Bu)$_2$Sn]$_2$O}$_2$	11		172			
{[(2-$FC_6H_4CH{=}CH-COO$)(*n*-Bu)$_2$Sn]$_2$O}$_2$	28		368			
4-$FC_6H_4COOSnPh_3$	15		14			
3-$FC_6H_4COOSnPh_3$	10		12			
3,5-$F_2C_6H_3COOSnPh_3$	18		17			
2,3-$F_2C_6H_3COOSnPh_3$	31		24			
2,6-$F_2C_6H_3COOSnPh_3$	18		<1			
{[(C_6F_5COO)(*n*-Bu)$_2$Sn]$_2$O}$_2$	44	39	214	53	86	76
{[($C_6F_5CH_2COO$)(*n*-Bu)$_2$Sn]$_2$O}$_2$	55	43	275	60	114	105
($C_6F_5CH_2COO$)$_2$Sn(*n*-Bu)$_2$	10	19	145	20	36	50
{[($C_6F_5CH{=}CHCOO$)(*n*-Bu)$_2$Sn]$_2$O}$_2$	32	37	234	41	66	135

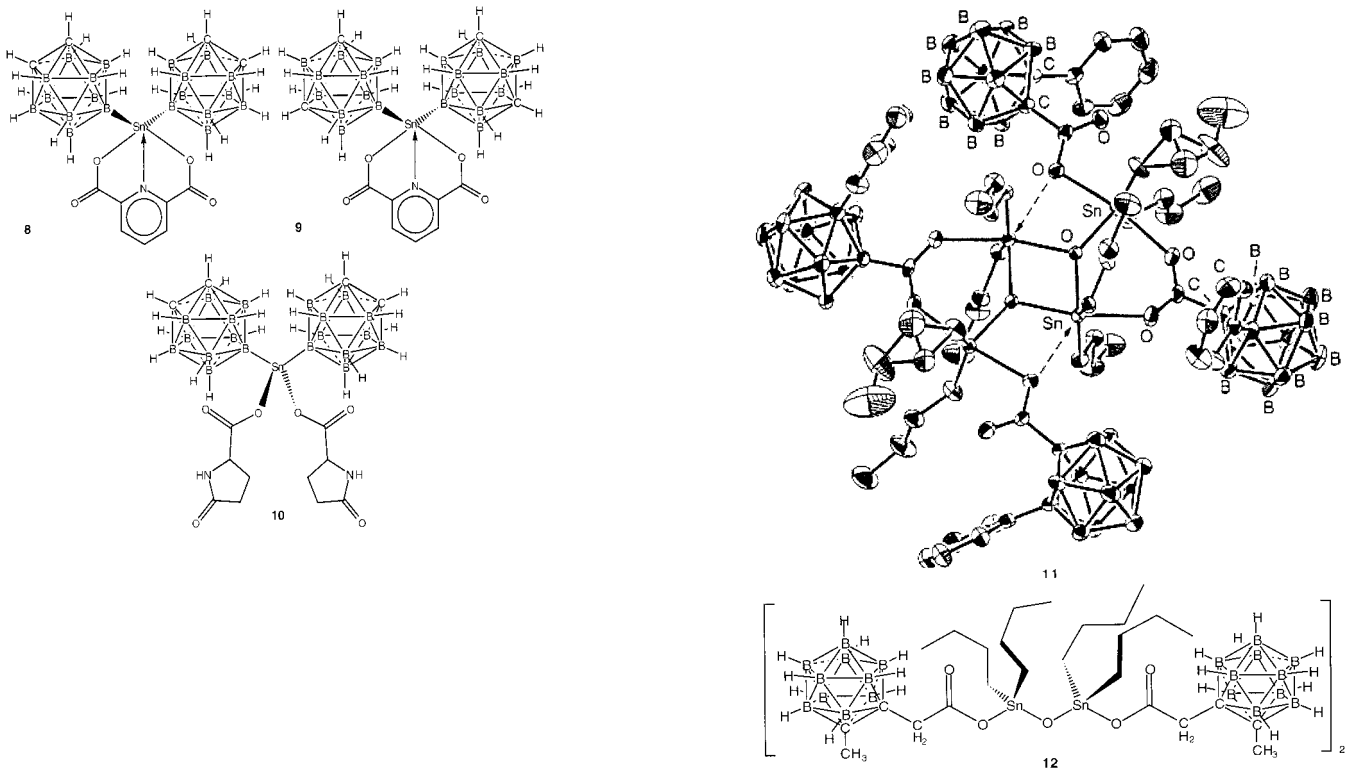


Figure 9. Structures of compounds **8**–**12**.

Table 10. *In vivo* Co 26 test results of four organotin compounds

Compound	Dose (mg kg^{-1})	Schedule	T/C (%)	ILS (%)
$\{[(C_6F_5CH_2COO)(n\text{-}Bu)_2Sn]_2O\}_2$	10	qd7 × 2	120	97
$(C_6F_5CH_2COO)_2Sn(n\text{-}Bu)_2$	16	qd7 × 2	63	126

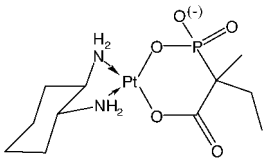


Figure 10. Water-soluble platinum compound.

not as good as expected, and so this route has been abandoned.

ANTITUMOUR SCREENING OF BORON-CONTAINING ORGANOTIN CARBOXYLATES

During the same period, carboranyltin compounds (Fig. 9) were also screened.[102,103] Boron, furthermore, is an element that can be useful for neutron capture cancer therapy, for compounds accumulating in localized tumours.

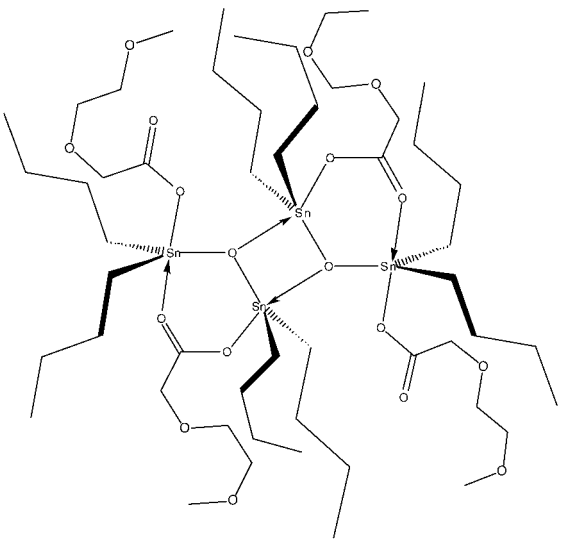
In compounds **8**, **9**, and **10** the tin atom is linked directly to one of the boron atoms of the carbonane moiety. Their activity is comparable to that of the corresponding organotin dichloride, whereas *o*-carborane itself and phenylcarborane-carboxylic acid are inactive (Table 10). Clearly, the tin atom is responsible for the activity. In compounds **11** and **12**, the carborane moiety is bound to a CO_2 or to a CH_2CO_2 that is linked to the tin atoms of a distannoxane structure. They are less active than compound **10**.

ANTITUMOUR SCREENING OF ORGANOTIN CARBOXYLATES CONTAINING THE POLYOXAALKYL MOIETY

Already in 1969, Atassi[82] mentioned that the lack of sufficient water solubility of organotin compounds is a serious drawback and that charges to this parameter might improve their activity considerably.

A water-soluble platinum compound (Fig. 10) was recently described as having a pronounced activity in S180a, L1210, and M5076 murine models.[104]

We decided to synthesize and test some more water-soluble organotin compounds. The most recent development in the field of antitumour-active organotin compounds has been achieved by the synthesis and screening of organotin compounds containing a polyoxaalkyl moiety linked to tin either by a carbon–tin or by a tin–oxygen bond.[105,106] Many of these compounds (Figs 11–13), of which some are water-



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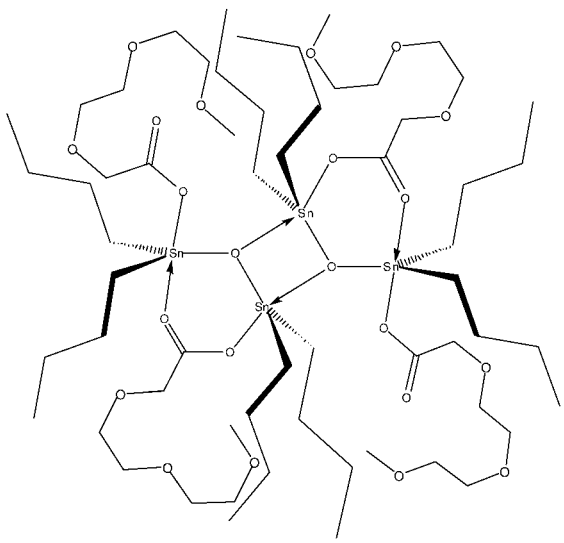

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Figure 11. Structures of tetra-*n*-butyltin-bis-3,6-dioxaheptanoato- (compound **16**) and -bis-3,6,9-trioxadecanoato-distannoxane (**20**) dimers

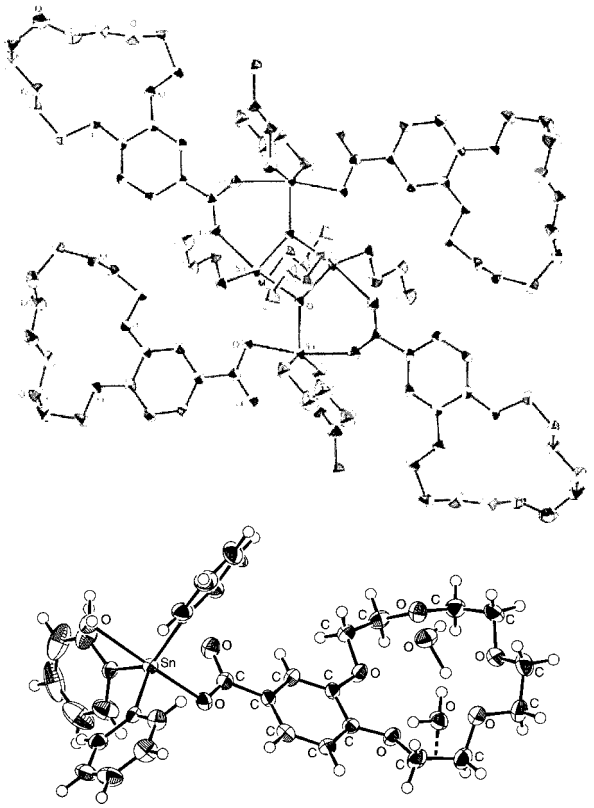

Figure 12. Structures of the di-*n*-butyl- (**24**) and triphenyltin (**25**) derivatives of 4-carboxybenzo-15-crown-5 in the crystalline state.

soluble, exhibit very high *in vitro* antitumour activities against the seven human cell lines studied (Tables 11 and 12).

Of the polyoxaalkyltin compounds tested, two distannoxanes and two triorganotin derivatives, compounds **16**, **20**, **25**, and **26**, exhibit very pronounced *in vitro* antitumour properties (Table 12).

The organotin crown ether derivatives exhibit quite interesting properties. Their tin atom is electrophilic, because tin is an element of the fifth period, in the periodic table. It can therefore become five-, six-, or seven- (and even eight-) coordinate, by adding a nucleophile; furthermore, the crown ether has a great affinity for alkali metals. Such compounds can easily react with, for instance, sodium thiocyanate, yielding the adduct shown in Fig. 14.

MODE OF ACTION OF ANTITUMOUR-ACTIVE ORGANOTIN COMPOUNDS

The platinum compounds used as antitumour drugs have been studied intensively and their probable mode of action has been elucidated: they interact with DNA and inhibit cell division.

A study of the interaction of the antitumour-active diethyltin dichloride with DNA fragments was recently undertaken using NMR techniques.[96] This showed that, at around pH 7, a very weak hardly detectable interaction, if any, is observed (Fig. 15), in contrast with the results found in the platinum case.[107] Similarly, diethyltin dichloride almost does not interact with DNA.[108] The interaction of DNA and DNA fragments with the antitumour-inactive dimethyltin dichloride was also studied very recently.[109–116]. It would therefore, be very useful to check whether antitumour-active organotin compounds do interact with proteins and whether they could be active due to this property.

CONCLUSION

It is quite clear from the paragraphs above that some promising compounds were developed that exhibit clearly

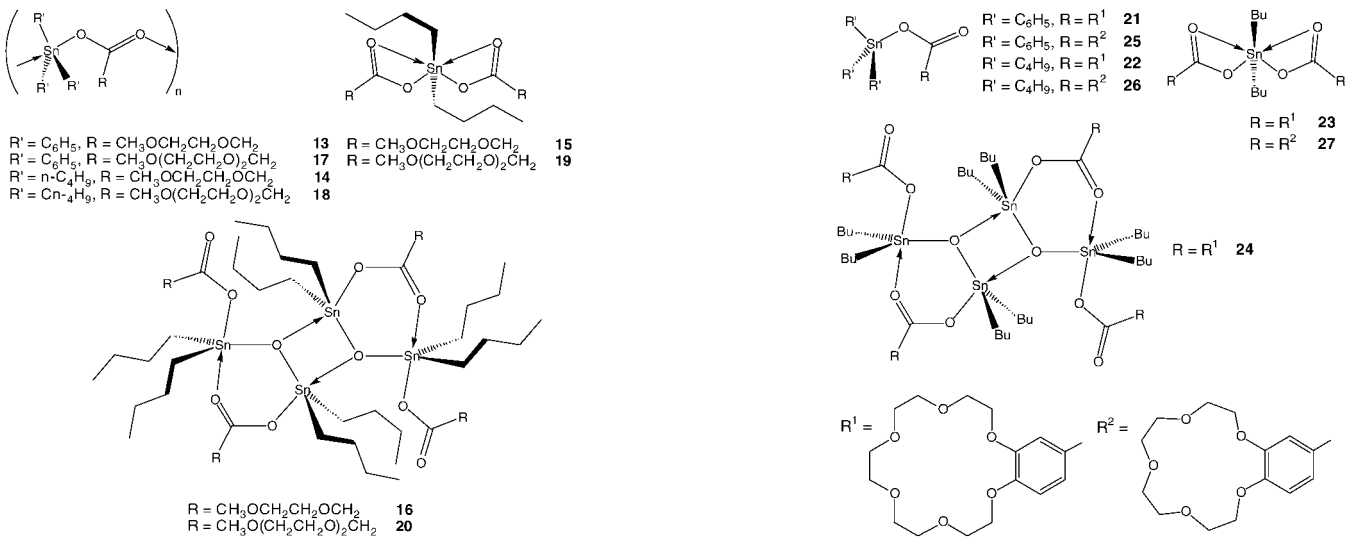

Figure 13. Organotin polyoxa-substituted carboxylates tested against human tumour cell lines.

Table 11. ID_{50} values (ng/ml) of some dicarboranyltin compounds

Compound	ID_{50} (ng ml^{-1})						
	MCF7	EVSA-T	WIDR	IGROV	M19 MEL	A498	H226
o-$C_2B_{10}H_{12}$	36817	22 456					
(*m*-$C_2B_{10}H_{11}$-9)$_2SnCl_2$	5	31					
8	14	197					
9	11	45					
10	60	48	410	3	30	110	
2-Ph-*m*-$C_2B_{10}H_{11}$-1-COOH	56527	45168	42426	58292	>60000	55032	11747
11	138	164	514	169	220	301	388
12	74	283	102	172	182	246	140

Table 12. ID_{50} values of some polyoxaalkyltin compounds tested against seven human tumour cell lines

Compound	ID_{50} (ng ml^{-1})						
	MCF-7	EVSA-T	WiDr	IGROV	M19 MEL	A 498	H 226
13	27	25	70	77	64	66	68
14	74	93	190	190	200	350	141
15	120	124	760	260	230	270	320
16	<1	<1	3.9	<1	<1	<1	3.3
17	17	17	36	63	46	40	47
18	76	53	84	187	160	200	118
19	147	112	840	300	280	250	480
20	<1	<1	<1.8	<1	<1	<1	<1
21	21	17	18	43	23	61	52
22	53	9	17	45	106	150	150
23	160	136	830	280	230	300	300
24	15	19	100	34	29	53	31
25	2.9	<2	<2	<2	<2	<2	<2
26	3.3	<2	<2	<2	<2	<2	<2
27	320	280	390	380	330	57	580

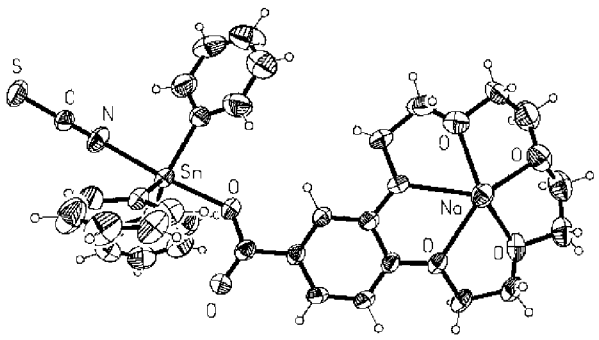

Figure 14. Structure of the sodium thiocyanate adduct to the triphenyl derivative of 4-carboxybenzo-15-crown-5 in the crystalline state.

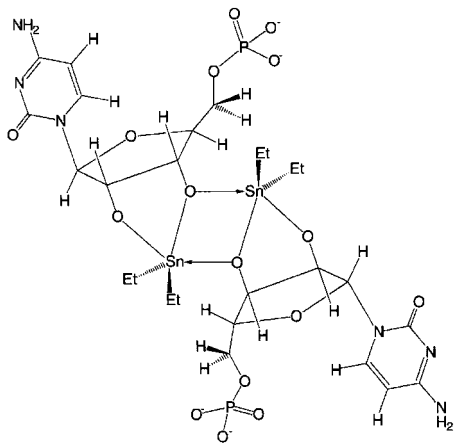

Figure 15. Organotin compounds formed when mixed with a mononucleotide at high pH.

high *in vitro* antitumour activities. The study of other series of organotin derivatives might lead to even more active compounds. The next step is the screening of promising new derivatives in human tumour xenografts on nude mice. *In vivo* testing is, in general, much more time consuming than *in vitro* testing. In particular, nude mice experiments are rather elaborate due to the nature of the animals and the test and evaluation period.

The *in vivo* testing was often affected by the limited water-solubility of the compounds. This is one of the most important factors emerging from the evaluation of the results. The lack of water solubility prevents the use of aqueous solutions in the *in vivo* tests and necessitates the use of arachidis oil for the preparation of a suspension.

Further chemical and pharmacological studies are necessary in order to unravel a structure–activity relationship from which novel organotin antitumour drugs for use in patients can be developed.

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I would like to thank very sincerely all my coworkers who allowed us to gather all this material and to obtain a better knowledge of the antitumour activity of organotin compounds. They succeeded in synthesizing, purifying, and characterizing many series of such derivatives that were tested thanks to Dr Dick de Vos, Pharmachemie, the Netherlands. We are also grateful to Professor Edward Tiekink (National University of Singapore), who determined by X-ray diffraction the structures of many of the compounds synthesized. I also wish to thank the Fonds voor Wetenschappelijk Onderzoek–Vlaanderen for financial support, as well as COST D8 and INTAS, which allowed us to develop cooperations with several other groups in Europe.

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