TIN-BASED ANTITUMOUR DRUGS

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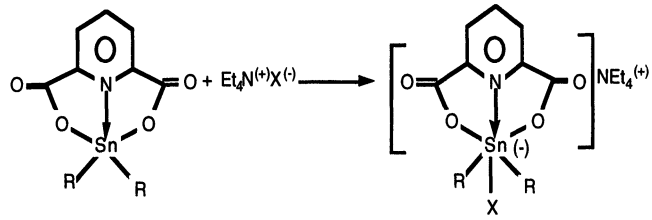
We have been active in the synthesis and characterization of tin-based antitumour compounds for several years and we would like to summarize here the results that have already been patented[1] and that may therefore be disclosed[2].

We synthesized some diorganotin 2,6-pyridinedicarboxylates.The dimethyltin compound has been found inactive *in vitro* , whereas the di-n-butyltin, di-t-butyltin and diphenyltin compounds were found more active than cisplatin[2].

In order to increase the water-solubility of these diorganotin derivatives, which might be a way to increase the antitumour activity following Atassi[4], we converted them[5] into their tetraethylammonium halide adducts.



The *in vitro* antitumour activity of the tetraethylammonium halide adducts of these diorganotin 2,6-pyridine dicarboxylates (see table 11)[5] is not better than that of the parent molecules, even if their solubility in protic and also in less polar solvents is considerably enhanced.

We synthesized a series of di-n-butyltin derivatives of substituted salicylic acids and tested them against human tumour cell lines (see table 1)[2].

	ID_{50} values in ng/mL against			ID_{50} values in ng/mL against	
Y	MCF-7	WiDr	Y	MCF-7	WiDr
3-CH_3	44	330	4-NH_2	42	330
4-CH_3	51	316	5-NH_2	38	316
5-CH_3	90	337	5-COOH	41	190
3-CH_3O	45	323	5-F	46	256
4-CH_3O	190	1 794	5-Cl	31	280
5-CH_3O	29	122	5-SO_3H	47	107
Cisplatin	850	624	Mitomycin C	3	17

Table 1: ID_{50} values (in ng/mL) of di-n-butyltin(IV) derivatives of substituted salicylic acids $[YC_6H_3(OH)COOSnBu_2]_2O\}_2$, and of cisplatin against MCF-7 and WiDr

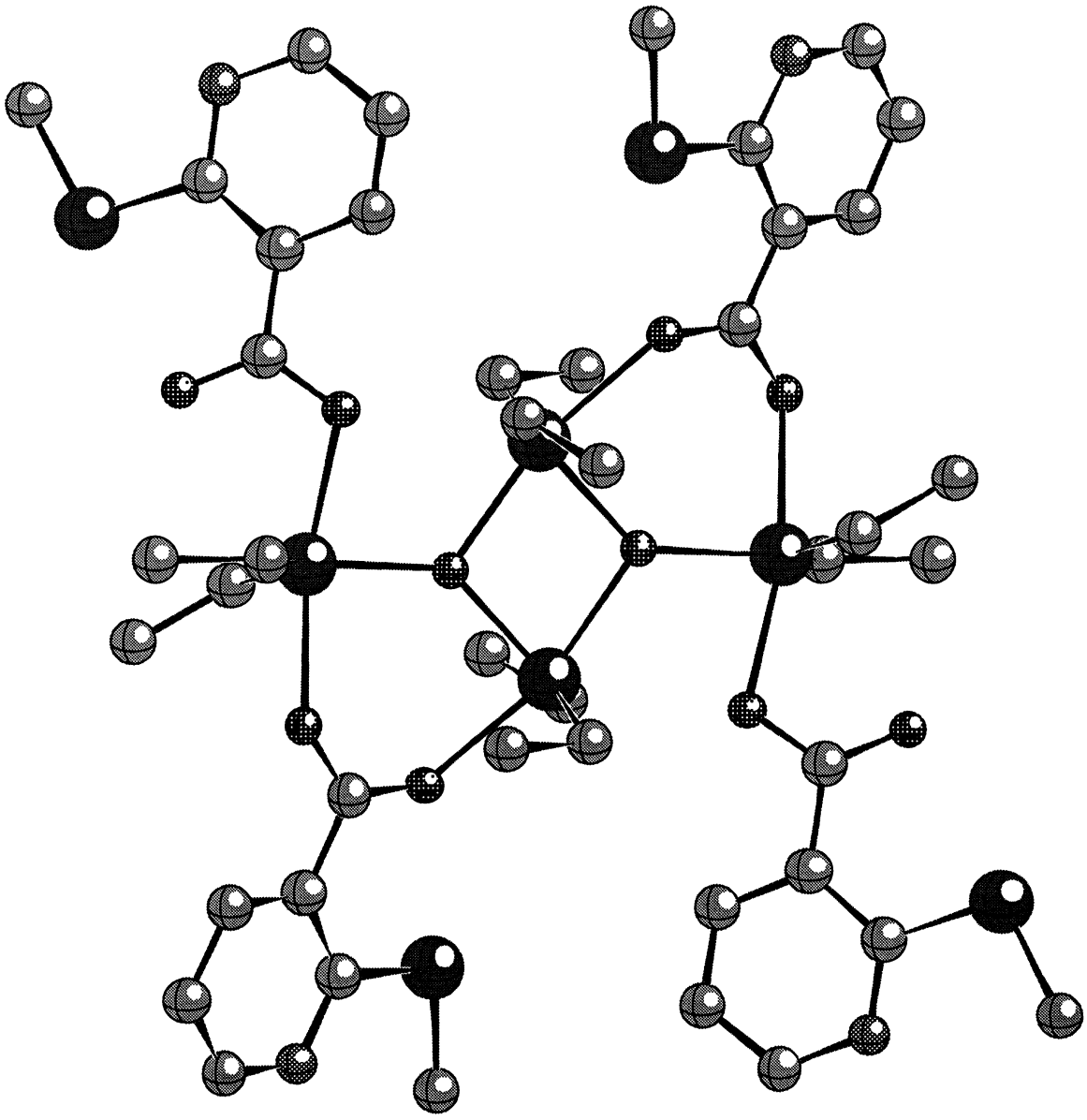


Figure 1: X-ray structure of [diethyl(2-methylthio-3-pyridinecarboxylato) tin] oxide [6]

Because Crowe has proposed that, among the factors relating the mode of action of diorganotin compounds R_2SnX_2, the organic groups R determine the potential activity[7], we prepared some diorganotin derivatives of substituted salicylic acids with various organic groups R linked to tin (see table 2)[2]. All the compounds of this type that we prepared were less active than the corresponding dibutyltin ones and than cisplatin.

RR'	Y	ID_{50} values in ng/ml against MCF-7	WiDr
Me-n-Bu	5-CH_3O	1 488	2 784
Et_2	5-CH_3O	2 236	4 806
n-Oct_2	5-CH_3O	4 677	10 639
Cisplatin		850	624

Table 2: ID_{50} values of selected di-organotin(IV) derivatives of substituted salicylic acids, $\{[Y\text{-}C_6H_3(OH)COOSnRR']_2O\}_2$ and of cisplatin

We also synthesized some other diorganotin 2,6-pyridinedicarboxylates, $C_5H_3N(COO)_2SnRR'$, varying once more the groups R and R' bound to tin (see table3). Here again, almost all the compounds prepared were less active than the di-n-butyltin derivative already described[2].

RR'	ID_{50} values in ng/ml against MCF-7	WiDr	RR'	ID_{50} values in ng/ml against MCF-7	WiDr
n-Bu_2	60	106	Ph-i-Pr	402	1 169
[p-MeO-Ph]$_2$	4 930	15 800	Ph-n-Bu	761	3 705
Ph_2	170	372	Ph-i-Bu	121	831
PhMe	2 187	3 283	Ph[$PhCH_2$]	2 910	10 995
PhEt	918	4 046	Ph-[t-$BuCH_2CH_2$]	50	161
Ph-n-Pr	223	1 094	Ph[$PhMe_2CCH_2$]	40	106
Cisplatin	850	624			

Table 3: ID_{50} values (in ng/ml) of selected 2,6-pyridinedicarboxylatodiorganotin(IV) derivatives $C_5H_3N(COO)_2SnRR'$ and of cisplatin

Di-n-butyltin **di**carboxylates were also prepared, including some disalicylates[2] (see table 4). The 4-hydroxy-3-methoxybenzoate shows very high activities.

Several di-n-butyltin difluorobenzoates that we synthesized and characterized recently [9] exhibited very promising in vitro antitumour activities that are reported in table 5 together with ID_{50} values on some compounds currently used clinically as antitumour agents are given for comparison.

From these data, it can be deduced that all the tested compounds score slightly better than cisplatin or etoposide against WiDr. Against MCF-7, they are even more active than doxorubicin, the 2,6-difluorobenzoate being as active as mitomycin C.

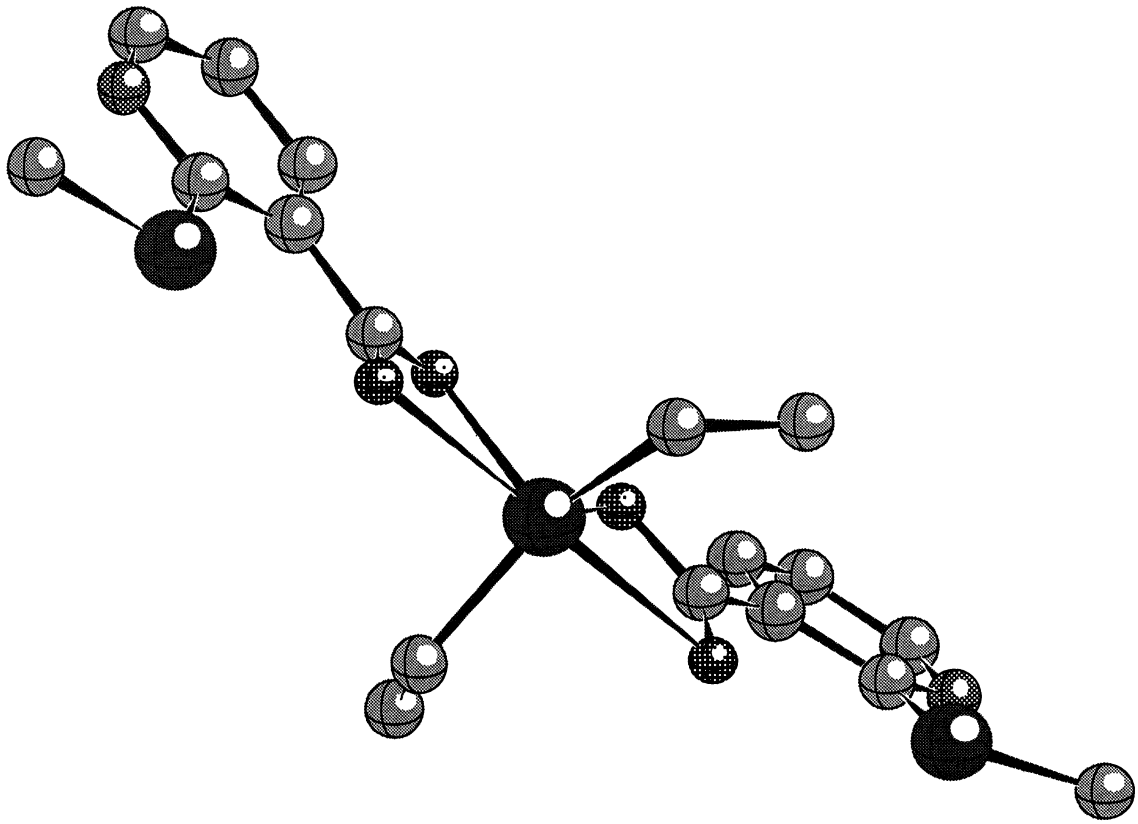


Figure 2: X-ray crystal structure of diethyltin bis(2-methylthio-3-pyridinecarboxylate) [6]

X	Y	Z	MCF-7	WiDr
H	H	2-F	74	242
H	H	3-F	63	197
H	H	4-F	90	309
2-OH	H	H	541	2 974
2-OH	H	3-CH_3O	105	474
2-OH	H	5-CH_3O	54	611
2-OH	H	5-Cl	89	319
4-OH	H	3-CH_3O	44	82
3-OCH_3	4-OCH_3	5-OCH_3	84	356
2-OCH_3	3-OCH_3	4-OCH_3	93	398
2-OCH_3	4-OCH_3	5-OCH_3	132	368
Cisplatin			850	624

Table 4: ID_{50} values (in ng/ml) of a series of diorganotin(IV) dicarboxylates $(X,Y,Z\text{-}C_6H_2COO)_2SnRR'$ and of cisplatin [9]

Molar ratio	Sunstituents	MCF-7	WiDr
1:2	2,3-F_2	23	283
1:2	3,5-F_2	30	407
1:1	2,3-F_2	9	120
1:1	2,5-F_2	7	277
1:1	2,6-F_2	3	174
1:1	3,5-F_2	11	172
Cisplatin		850	624
Etoposide		187	624
Doxorubicin		63	31
Mitomycin C		3	17

Table 5: ID_{50} values (ng/mL) of compounds of the type $(F_2C_6H_3COO)_2Sn(n\text{-}C_4H_9)_2$ (1:2 molar ratio), of the type $\{[(F_2C_6H_3COO)(n\text{-}C_4H_9)_2Sn]_2O\}_2$ (1:1 molar ratio), and of reference compounds tested against two human tumour cell lines, MCF-7 and WiDr

We prepared also several original series of organotin molecules that are as active *in vitro* as mitomycin C against MCF-7 and WiDr. The first of these, that has recently been patented[1], are triphenyltin carboxylates[8].

X	Y	Z	MCF-7	WiDr
H	H	2-OCH_3	16	15
H	H	4-F	15	14
H	3-F	5-F	18	17
H	2-OH	5-Cl	11	18
H	2-OH	5-NH_2	14	17
H	2-OH	5-OCH_3	6	15
2-OH	3-$CH(CH_3)_2$	5-$CH(CH_3)_2$	8	13
Cisplatin			850	624
Mitomycin C			3	17

Table 5: Inhibition doses ID_{50} in ng/mL against MCF-7 and WiDr obtained for a series of triphenyltin benzoates, $(C_6H_5)_3Sn\text{-}OOC\text{-}C_6H_2XYZ$ and for two reference compounds

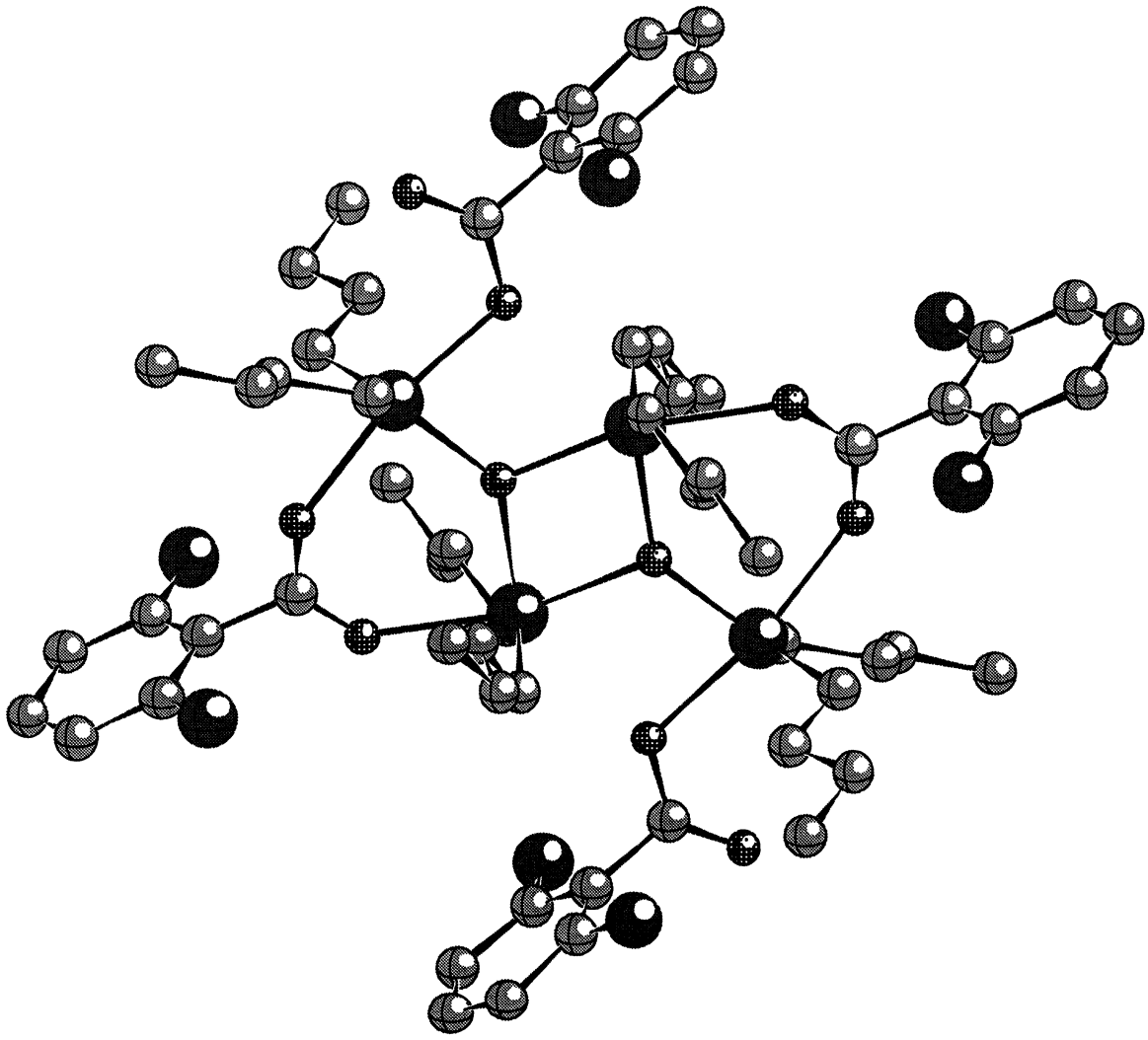


Figure 2: X-ray crystal structure of [di-n-butyl(2,6-difluorobenzoato) tin] oxide (9)

I hope that I have convinced you that several organotin compounds exhibit rather promising *in vitro* antitumour activities again human tumour cell lines. Of course we have to wait for the *in vivo* test results before claiming anything about the interest of such compounds for cancer chemotherapy. More work has to be done in the field of the preparation and testing of organotin molecules that might become useful antitumour drugs in the future.

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