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Tin-based antitumour drugs[1]

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Contents

Abstract

An overview is given of the results of the in vitro screening against MCF-7, a mammary tumour, and WiDr, a colon carcinoma, of several series of organotin compounds synthesized in the Free University of Brussels. Many di- and triorganotin compounds exhibit very promising in vitro antitumour activities. Di-*n*-butyltin bis(2,5-dihydroxybenzoate) is as active as cisplatin in vivo against murine Colon 26 carcinoma.

Keywords: Antitumour drug; Carcinoma; Organotin compound; Tin compound

1. Introduction

Cisplatin is unfortunately very nephrotoxic but is effective against testicular carcinomas, which had almost invariably caused death before cisplatin was discovered

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but have become curable nowadays thanks to its use. However, cisplatin does not show any, or only little, effect on more common tumours such as lung tumours or gastrointestinal adenotumours. The excellent activity of cisplatin against testicular carcinomas shows that it should be possible to find new metal-based drugs capable of curing specific types of tumours.

This has been a considerable impetus for inorganic and organometallic chemists to search for new metal compounds with similar good activities, preferably against tumour types that are responsible for the major share of cancer mortality today.

2. Early studies on diorganotin pyridinedicarboxylates

We have synthesized several series of organotin compounds that exhibit interesting in vitro antitumour activities [1–3]. For instance, di-*n*-butyltin, di-*t*-butyltin and diphenyltin 2,6-pyridinedicarboxylates [4,5] were found to be more active than cisplatin against MCF-7, a mammary tumour, and WiDr, a colon carcinoma.

Because Crowe has proposed that, among the factors responsible for the mode of action of diorganotin compounds R_2SnX_2, the organic groups **R** determine the potential activity [6], we prepared some more diorganotin 2,6-pyridinedicarboxylates $C_5H_3N(COO)_2SnRR'$ by varying the groups **R** and **R'** bound to tin and found that almost all the compounds synthesized were less active than the di-*n*-butyltin derivative (Table 1) [7].

The structure of one of these compounds, bis[aquaethyl(phenyl)(2,6-pyridinedicarboxylato)tin(IV)] [8(a)], is shown in Fig. 1.

Table 1
ID_{50} values of selected 2,6-pyridinedicarboxylatodiorganotin(IV) derivatives $C_5H_3N(COO)_2SnRR'(H_2O)$ against MCF-7 and WiDr

RR'	ID_{50} (ng ml^{-1}) against	
	MCF-7	WiDr
***n*-Bu$_2$**	**60**	**106**
(*p*-MeO-Ph)$_2$	4930	15800
Ph$_2$	170	372
PhMe	2187	3283
PhEt	918	4046
Ph^{n}Pr	223	1094
Ph^{i}Pr	402	1169
Ph^{n}Bu	761	3705
Ph^{i}Bu	121	831
Ph(PhCH$_2$)	2910	10995
Ph(^{t}BuCH$_2$CH$_2$)	50	161
Ph(PhMe$_2$CCH$_2$)	40	106

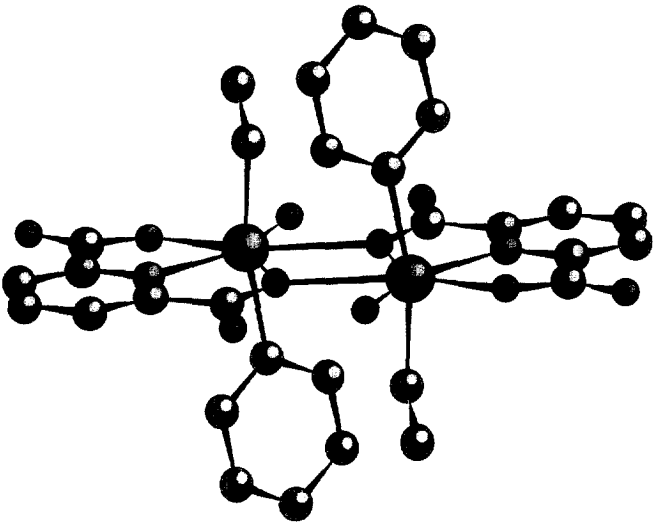

Fig. 1. Molecular structure of bis[aquaethyl(phenyl)(2,6-pyridinedicarboxylato)tin(IV)] [8(a)].

3. Substituted bis(salicylato)tetraorganodistannoxanes

A series of 1:1 condensation compounds of substituted salicylic acids with diorganotin oxides was synthesized (see Fig. 2 [8(b)]). They were tested against the same two human tumour cell lines. Typical ID_{50} values obtained are 50 ng ml^{-1} against MCF-7 and 300 ng ml^{-1} against WiDr [2,3] (Table 2). The 5-methoxysalicylate was one of the most active compounds of this series.

Several 1:1 condensation compounds of substituted salicylic acids with diorganotin oxides having various organic groups R linked to tin were also synthesized. Again all compounds prepared were less active than the corresponding di-*n*-butyltin ones [2,3] (Table 3).

4. Substituted di-*n*-butyltin dibenzoates

Di-*n*-butyltin dibenzoates, including some disalicylates (where X means 2-OH), were prepared from diorganotin oxides and carboxylic acids in a 1:2 molar ratio [2,3] (Fig. 3).

The 4-hydroxy-3-methoxybenzoate exhibits quite high in vitro activities (Table 4).

5. Di-*n*-butyltin derivatives of mono-, di-, tri-, tetra- and perfluorobenzoic acids

Several 1:1 and 1:2 condensation compounds of di-*n*-butyltin oxide with mono- [10], di- [11], tri-, tetra- [12] and pentafluorobenzoic [13] acids were prepared recently (Fig. 4).

Table 2
ID_{50} values of di-*n*-butyltin(IV) derivatives of substituted salicylic acids $\{[YC_6H_3(OH)COOSnBu_2]_2O\}_2$, and of cisplatin and mitomycin C against MCF-7 and WiDr

Y	ID_{50} (ng ml^{-1}) against	
	MCF-7	WiDr
3-CH_3	44	330
4-CH_3	51	316
5-CH_3	90	337
3-CH_3O	45	323
4-CH_3O	190	1794
5-CH_3O	**29**	**122**
4-NH_2	42	330
5-NH_2	38	316
5-COOH	41	190
5-F	46	256
5-Cl	31	280
5-SO_3H	47	107
Cisplatin	850	624
Mitomycin C	3	17

Table 3
ID_{50} values of selected 1:1 condensation compounds of diorganotin(IV) oxides with 5-methoxysalicylic acid against MCF-7 and WiDr

RR′	ID_{50} (ng ml^{-1}) against	
	MCF-7	WiDr
^{n}Bu$_2$	29	122
Me^{n}Bu	1488	2784
Et_2	2236	4806
^{n}Oct$_2$	4677	10639

They do exhibit very promising in vitro antitumour activities (Table 5).

Against MCF-7 the difluorobenzoates are more active than the monofluorobenzoates, which shows that the activity is enhanced when the number of fluorine atoms on the benzoate moiety is increased. They indeed provide ID_{50} values comparable with that of mitomycin C. The ID_{50} value of the corresponding 2,3,6-trifluorobenzoate is of the same order of magnitude, while those of the 2,3,4,5-tetra- and pentafluorobenzoates are lower. Against WiDr all fluorobenzoates exhibit comparable activities, except the 2,3-difluoro compound which is slightly more active.

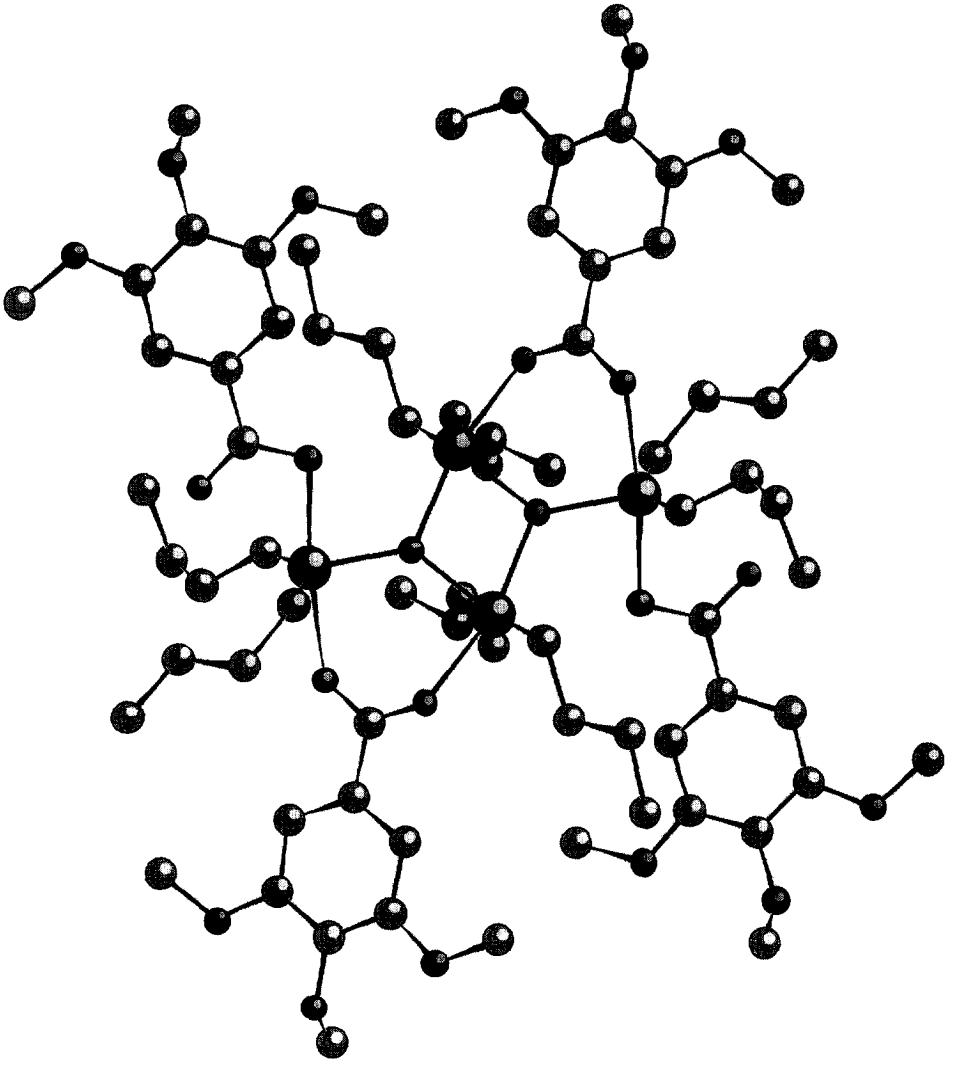

Fig. 2. X-Ray crystal structure of the bis(3,4,5-trimethoxysalicylato)tetra-*n*-butyldistannoxane dimer [8(b)].

6. Substituted triphenyltin benzoates

Substituted triphenyltin benzoates [14,15] have been found to be very active in vitro against the same two human tumour cell lines (Table 6).

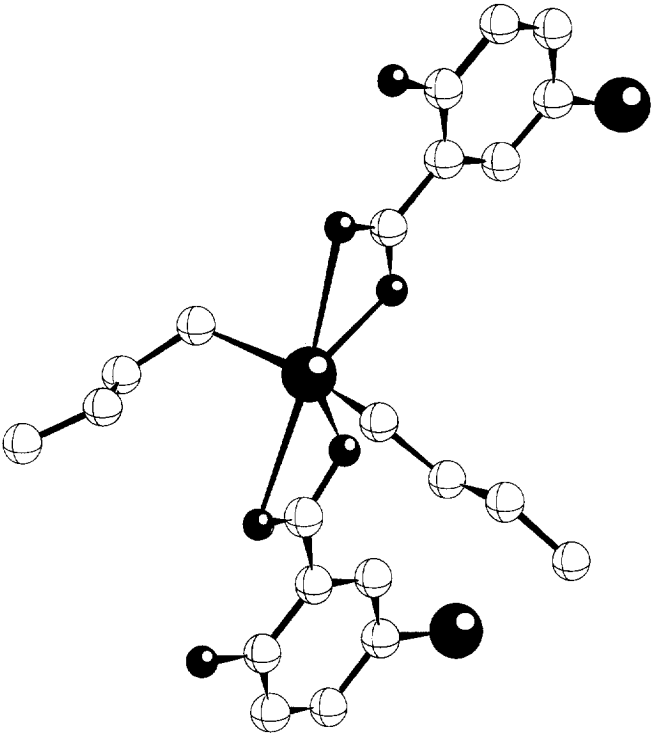

Fig. 3. X-Ray crystal structure of di-*n*-butyltin 5-chlorosalicylate [9].

Table 4
ID_{50} values of a series of diorganotin(IV) dicarboxylates (X, Y, Z-$C_6H_2COO)_2Sn^nBu_2$ and of cisplatin against MCF-7 and WiDr

X	Y	Z	ID_{50} (ng ml^{-1}) against	
			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	2974
2-OH	H	3-OCH_3	105	474
2-OH	H	5-OCH_3	54	611
2-OH	H	5-Cl	89	319
4-OH	**H**	**3-OCH_3**	**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 5
ID_{50} values of compounds of the type $\{[(F_nC_6H_{5-n}COO)(n\text{-}C_4H_9)_2Sn]_2O\}_2$ (1:1 molar ratio) and of reference compounds tested against two human tumour cell lines, MCF-7 and WiDr

Substituent	ID_{50} (ng ml^{-1}) against	
	MCF-7	WiDr
2-F	91	330
4-F	81	360
2,3-F_2	9	120
2,5-F_2	7	277
2,6-F_2	3	174
3,5-F_2	11	172
2,3,6-F_3	13	200
2,3,4,5-F_4	35	250
F_5	44	214
Cisplatin	850	624
Mitomycin C	3	17

7. Substituted tri-*n*-butyltin benzoates

Tri-*n*-butyltin difluorobenzoates [16] (see Table 7) are less active than the corresponding triphenyltin derivatives and also less active than the corresponding di-*n*-butyl compounds [11].

8. In vivo antitumour activities of organotin compounds

The antitumour activity in tumour-bearing mice was screened for four triorganotin compounds, namely triphenyltin 5-sulphosalicylate (TPSS), triphenyltin 5-aminosalicylate (TPAS), triphenyltin 4-fluorobenzoate (TPFB) and tri-*n*-butyltin 2,6-difluorobenzoate (TBDFB), and for a diorganotin compound, di-*n*-butyltin bis(2,5-dihydroxybenzoate) (DBDHB). The results [17] are presented in Table 8.

The T/C (>0.6) and GDF (<1) data of TPSS, TPAS, TPFB and TBDFB show that a single dose administration of these compounds was inactive against the tumour Colon 26 in mice. DBDHB showed the largest antitumour activity. For DBDHB the measured T/C of 0.43 was about 1.5–2 times lower than for the other compounds tested. Also, the GDF >1, above the cut-off level for sensitivity, indicated that DBDHB exerted marked antitumour activity. The treatment with TPSS, TPAS, TPFB and TBDFB resulted in a slight increase in medium life span (MLS) (111%). Furthermore, all treated mice showed a large weight loss (MWL), most for DBDHB with an MWL of 18.7% at day 4. Part of the weight loss was due to cachexia caused by the tumour.

To compare the results of the organotin derivatives with other metal-based drugs, the results of a single dose administration of cisplatin (5.5 and 9 mg kg^{-1}) are also

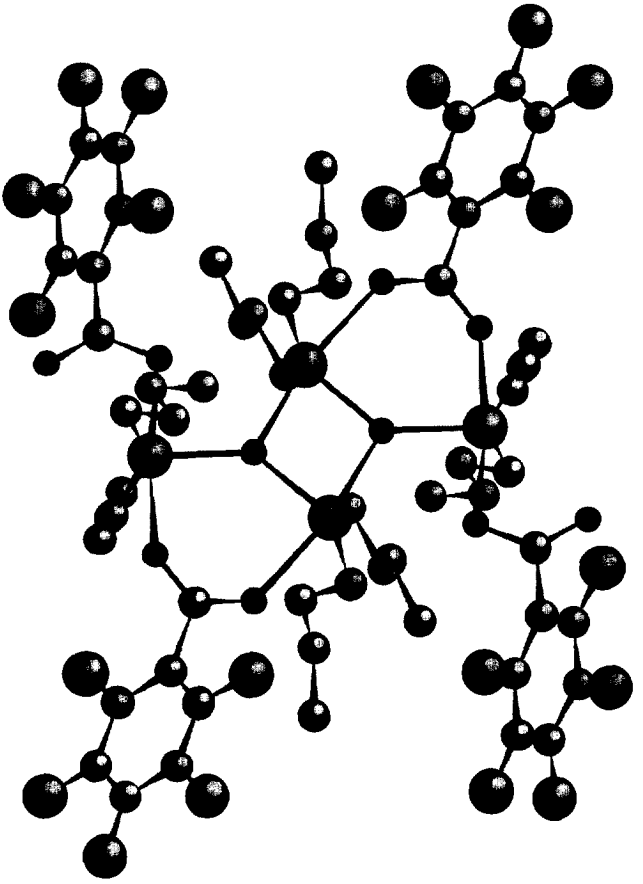

Fig. 4. X-Ray crystal structure of the bis(perfluorobenzoato)tetra-*n*-butyldistannoxane dimer [13].

depicted in Table 8. The treatment with cisplatin at a dose of 5.5 mg kg^{-1} resulted in the same T/C (0.73) as for TPSS, TPAS, TPFB and TBDFB. In the experiment with DBDHB it was attempted to give the drug again after an interval of 1 week. However, the toxicity was considered too severe to continue treatment.

9. Conclusions

To summarize, we can state that several organotin compounds exhibit rather promising in vitro antitumour activities [18] against human tumour cell lines. However, more work has to be done on the preparation and testing of organotin molecules that might become useful antitumour drugs in the future.

Table 6
Inhibition doses ID_{50} against two human tumour cell lines, MCF-7 and WiDr, obtained for a series of substituted triphenyltin benzoates and for a clinically used antitumour drug, cisplatin

Compound	ID_{50} (ng ml^{-1}) against	
	MCF-7	WiDr
2-CH_3O-$C_6H_4CO_2SnPh_3$	16	15
4-F-$C_6H_4CO_2SnPh_3$	15	14
2,3-$F_2C_6H_3CO_2SnPh_3$	17	24
3,5-$F_2C_6H_3CO_2SnPh_3$	18	17
2,4,5-$(CH_3O)_3C_6H_2CO_2SnPh_3$	16	15
2-OH-5-Cl-$C_6H_3CO_2SnPh_3$	11	18
2-OH-5-NH_2-$C_6H_3CO_2SnPh_3$	14	17
2-OH-5-OCH_3-$C_6H_3CO_2SnPh_3$	6	15
2-OH-5-SO_3H-$C_6H_3CO_2SnPh_3$	100	131
2-OH_3-$CH(CH_3)_2$-5-$CH(CH_3)_2$-$C_6H_3CO_2SnPh_3$	8	13
Cisplatin	850	624

Table 7
Inhibition doses ID_{50} obtained in vitro against six human tumour cell lines, MCF-7 and EVSAT (breast cancers), WiDr (a colon carcinoma), IGROV (an ovarian cancer), M19 (a melanoma) and A498 (a renal cancer), for two tri-*n*-butyltin difluorobenzoates and for three clinically used antitumour drugs

Compound	MCF-7	EVSAT	WiDr	IGROV	M19	A498
2,5-$F_2C_6H_3COOSnBu_3$	38	12	58	20	58	80
2,6-$F_2C_6H_3COOSnBu_3$	480	250	800	610	710	1100
Cisplatin	800	1200	650	79	520	1200
Carboplatin	5500	1100	1500	780	5300	3500
Doxorubicin	8	6	20	28	5	5

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Table 8
Antitumour activity and toxicity of triphenyltin 5-sulphosalicylate (TPSS), triphenyltin 5-aminosalicylate (TPAS), triphenyltin 4-fluorobenzoate (TPFB), tri-*n*-butyltin 2,6-difluorobenzoate (TBDFB) and di-*n*-butyltin bis(2,5-dihydroxybenzoate) (DBDHB) on Colon 26-bearing mice

Treatment	GDF	maximum T/C (% (days))	Mean TD	ILS (%)	MWL (% (days))
Control			3.1 ± 1.2	100	11.2 (7)
TPSS, 5 mg kg^{-1}	0.43	80 (3)	4.4 ± 1.5	111	14.7 (7)
TPAS, 8 mg kg^{-1}	0.38	71 (7)	4.3 ± 2.3	100	18.5 (7)
TPFB, 6 mg kg^{-1}	0.36	67 (10)	4.2 ± 1.9	111	18.9 (7)
TBDFD, 5 mg kg^{-1}	0.02	87 (3)	3.1 ± 0.8	111	7.9 (7)
DBDHB, 6 mg kg^{-1}	1.18	43 (3)	5.9 ± 1.5	111	18.7 (4)
Cisplatin, 5.5 mg kg^{-1}	0.18	73 (3)	5.3 ± 1.3		0.9 (1)
Cisplatin, 9 mg kg^{-1}	0.66	39 (7)	5.8 ± 1.6		8.8 (7)

GDF: growth delay factor; indicates the tumour doubling time gained by treatment. $GDF = (TD_{treated} - TD_{control})/TD_{control}$.
T/C: (relative tumour volume of treated mice)/(relative tumour volume of control mice) × 100%.
TD: tumour doubling time.
ILS: increase in life span $= (MLS_{treated\ mice})/(MLS_{untreated\ mice}) \times 100\%$. MLS: median life span.
MWL: maximum weight loss compared with the weight at first day of treatment ($d = 0$).

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