Investigations into the Antitumour Activity of Organotin Compounds. 2.* Diorganotin Dihalide and Dipseudohalide Complexes

ALAN J. CROWE**, PETER J. SMITH

International Tin Research Institute, Fraser Road, Perivale, UB6 7AQ, U.K.

and GHANEM ATASSI

Screening Laboratory, Institut Jules Bordet, Rue Héger-Bordet, 1000 Brussels, Belgium

Received July 23, 1984

Abstract

The results of screening tests on 115 of the titled compounds against P388 lymphocytic leukaemia are reported and structure/activity relationships discussed.

Introduction

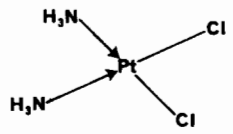
In our earlier paper [1], in which we reported the antitumour activity of a series of diorganotin dihalide complexes, modelled on active platinum compounds (*e.g.* **I–IV**), we suggested that the activity of a tin complex may be related to its stability, in that a moderately stable adduct would be expected to exhibit antitumour activity. To enable us to further study this structure/activity relationship, we have extended our original series of compounds to 115 and report here the results of testing these against the P388 lymphocytic leukaemia in mice.

Since the publication of our earlier paper [1] a number of other diorganotin compounds (Table I) have been found [2–6] to exhibit antitumour activity towards the same tumour system.

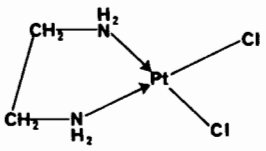
Cardarelli and his co-workers have recently studied the effects of Bu_3SnF [7], Bu_2SnCl_2·phen, Bu_2SnCl_2·bipy and Bu_2Sn(histidine)$_2$ [8], which were administered continuously, at low levels in drinking water, on cancerous mice, and, in each case, it was claimed that a significant reduction in tumour growth was observed. These and further studies [9] have led Cardarelli to propose that, "one or more tin-bearing biochemicals are produced naturally and play an active role in anticarcinogenesis".

*For Part 1, see reference [1].

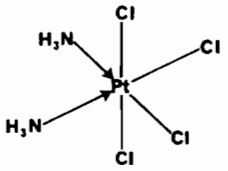
**Author to whom correspondence should be addressed.



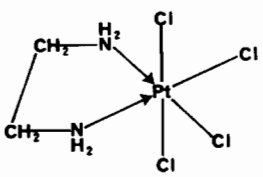
I



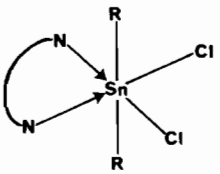
II



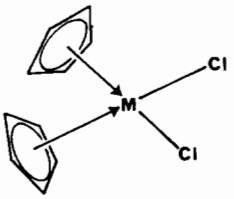
III



IV



V



VI

M = Ti, V, Nb, Mo.

0020-1693/84/$3.00

TABLE I. Organotin Compounds which Show Activity towards P388 Lymphocytic Leukaemia in Mice.

Compound	T/C (%)[a]/Dose (mg/kg)	Reference
$(ClMe_2Sn)O$[b]	141/12.5 – 123/6.25	2
Et_2SnO[b]	125/50 – 154/25 – 137/12.5 – 127/6.25	2
$ClPh_2SnOH$[b]	198/25 – 163/12.5 – 135/6.25	2
$Bu_2Sn(adenine)_2$	131/12.5 – 123/6.25	3
$Ph_2Sn(adenine)_2$	169/100 – 135/50 – 145/25 – 123/12.5	3
$Me_2Sn(glycylglycine)$	139/125 – 126/12.5	3
$Bu_2Sn(glycylglycine)$	150/3.12	3
$Ph_2Sn(glycylglycine)$	141/3.12 – 128/1.56	3
$Me_2Sn(penicillamine)$	148/400	4
$Bu_2Sn(penicillamine)$	120/3.12	4
$Ph_2Sn(cysteine)$	181/50	4
$Ph_2Sn[Ph_2P(S)S]_2$	142/12.5 – 130/6.25	5
$Bu_2Sn(OC_6H_4CHNNCSSMe)$	124/6.25	6
$Bu_2Sn(OC_6H_4CHNC_6H_4F)_2$	122/12.5	6

[a]T/C is the ratio of survival times (in days) of treated and untreated mice. A compound is considered to be active at T/C ≥ 120%. [b]Fourteen other structural analogues are reported in reference [2].

Experimental

The preparation and ^{119m}Sn Mössbauer spectral studies of the complexes have been published elsewhere [10].

The activity of the complexes *in vivo* towards P388 lymphocyctic leukaemia tumour in mice was determined in accordance with the U.S. National Cancer Institute standard protocols for primary screening [11]. The evaluation of this activity was established by computing the T/C value, which is the median survival time of the treated group of animals (T), divided by that of the control group (C), expressed as a percentage. A compound is termed active if it has a T/C ≥ 120%.

The complexes were generally of a low solubility and were administered in saline; saline and Tween 80; or as a suspension in saline.

Results and Discussion

Our results are presented in Table II.

Many of the complexes which were found to possess reproducible activity towards P388 were subsequently screened against other tumour systems, *e.g.* B16 melanocarcinoma, $CD8F_1$ mammary tumour, CX-1 colon xenograph, colon 38, L1210 lymphoid leukaemia, LX-1 lung xenograph, Lewis lung carcinoma and MX-1 breast xenograph. However, in each case, the compounds were found to be inactive.

The observed activity against P388 lymphocytic leukaemia is likely to be a function of the complex, since the organic ligands are inactive, as are most of the parent diorganotin dihalides and dipseudohalides (some exceptions are shown in Table III).

TABLE II. The Activity of $R_2SnX_2 \cdot L_2$ towards P388 Lymphocytic Leukaemia.

Complex		Two best test results (T/C %)/(Dose mg/kg)	
$Me_2SnX_2 \cdot L_2$			
X = Cl,	L = DMSO	inactive[a]	
	L = merpy	inactive	
	L = py	128/25	121/50
	L_2 = AMP	inactive	
	L_2 = bipy	126/50	120/50
	L_2 = Nisalen	inactive	
	L_2 = PBI	inactive	
	L_2 = phen	inactive	
	L_2 = DPphen	inactive	
	L_2 = TMphen	inactive	
	L_2 = pypy*	137/100	135/50
X = Br,	L_2 = bipy*	135/200	131/100
	L_2 = PBI*	130/50	130/12.50
	L_2 = phen*	132/50	129/50
	L_2 = DPphen	inactive	
	L_2 = TMphen*	128/100	123/100

(continued on facing page)

TABLE II. *(continued)*

Complex		Two best test results (T/C %)/(Dose mg/kg)	
X = I,	L_2 = bipy*	131/100	127/100
	L_2 = phen*	135/200	129/100
X = NCS,	L_2 = bipy	inactive	
	L_2 = phen	inactive	
$Et_2SnX_2 \cdot L_2$			
X = F,	L_2 = phen*	138/6.25	133/12.50
	L_2 = TMphen*	138/50	123/25
X = Cl,	L = DMSO*	153/25	123/6.25
	L = py	inactive	
	L_2 = AMP	inactive	
	L_2 = bipy	inactive	
	L_2 = H_2acacen*	150/100	142/200
	L_2 = PBI*	171/100	171/100
	L_2 = phen*	177/50	176/100
	L_2 = Cphen	inactive	
	L_2 = DMphen*	128/100	123/100
	L_2 = DPphen	inactive	
	L_2 = Nphen	inactive	
	L_2 = Pphen*	142/50	125/25
	L_2 = TMphen	126/200	122/200
X = Br,	L_2 = bipy	inactive	
	L_2 = PBI*	175/12.50	161/25
	L_2 = phen*	176/25	166/50
	L_2 = DPphen*	168/25	138/50
	L_2 = TMphen*	145/50	145/25
X = I,	L_2 = bipy	inactive	
	L_2 = phen*	184/200	166/100
	L_2 = DPphen*	137/100	130/50
	L_2 = TMphen*	145/50	133/12.50
X = NCS,	L_2 = bipy*	179/12.50	166/25
	L_2 = phen*	164/100	149/100
$Pr_2SnX_2 \cdot L_2$			
X = F,	L_2 = phen	140/6.25	115/3.12
	L_2 = TMphen	127/12.50	120/6.25

TABLE II. *(continued)*

Complex		Two best test results (T/C %)/(Dose mg/kg)	
X = Cl,	L = py	inactive	
	L_2 = bipy	inactive	
	L_2 = PBI	inactive	
	L_2 = phen*	127/100	125/50
	L_2 = DPphen	inactive	
	L_2 = TMphen	inactive	
X = Br,	L_2 = bipy	inactive	
	L_2 = PBI*	148/6.25	136/12.50
	L_2 = phen*	140/50	121/25
	L_2 = DPphen	inactive	
	L_2 = TMphen*	158/12.50	142/25
X = I,	L_2 = bipy	inactive	
	L_2 = PBI	inactive	
	L_2 = phen	inactive	
	L_2 = DPphen	inactive	
	L_2 = TMphen*	136/25	125/12.50
X = NCS,	L_2 = bipy	inactive	
	L_2 = phen	inactive	
$Bu_2SnX_2 \cdot L_2$			
X = F,	L_2 = phen*	145/12.5	133/12.5
	L_2 = TMphen	inactive	
X = Cl,	L_2 = AMP*	140/50	138/50
	L_2 = bipy*	131/400	128/400
	L_2 = PBI	inactive	
	L_2 = phen*	141/100	126/200
	L_2 = DPphen*	126/25	120/25
	L_2 = TMphen	inactive	
X = Br,	L_2 = bipy	inactive	
	L_2 = PBI	inactive	
	L_2 = phen	inactive	
	L_2 = DPphen	inactive	
	L_2 = TMphen	inactive	
X = I,	L_2 = bipy	inactive	
	L_2 = phen	inactive	
X = NCS,	L_2 = bipy*	123/25	122/50
	L_2 = phen	inactive	

(continued overleaf)

TABLE II. *(continued)*

Complex		Two best test results (T/C %)/(Dose mg/kg)	
$Ph_2SnX_2 \cdot L_2$			
X = Cl,	L = DMSO	inactive[a]	
	L = py	180/–[†]	156/–[†]
	L_2 = AMP*	153/25	150/100
	L_2 = bipy	inactive[a]	
	L_2 = PBI*	164/100	141/50
	L_2 = phen	inactive	
	L_2 = Cphen*	132/6.25	123/6.25
	L_2 = DMDPphen	127/6.25	
	L_2 = DMphen*	165/6.25	151/3.12
	L_2 = DPphen	inactive	
	L_2 = Nphen*	160/200	148/100
	L_2 = Pphen*	130/25	125/12.50
	L_2 = TMphen*	158/12.50	130/6.25
X = Br,	L_2 = bipy	inactive	
	L_2 = PBI*	144/12.50	143/6.25
	L_2 = phen*	134/12.5	120/12.5
	L_2 = DPphen*	154/25	142/25
	L_2 = TMphen*	177/6.25	156/6.25
X = I	L_2 = bipy	inactive	
	L_2 = phen	inactive	
	L_2 = DPphen*	166/6.25	130/3.12
X = NCS,	L_2 = bipy	inactive	
	L_2 = phen	inactive	
$Bz_2SnCl_2 \cdot$phen		inactive	
$Oct_2SnCl_2 \cdot L_2$			
	L_2 = bipy	inactive[a]	
	L_2 = PBI	inactive	
	L_2 = phen	inactive[a]	
	L_2 = DPphen	inactive	
	L_2 = TMphen	inactive	
$SnCl_4 \cdot L_2$			
	L = py	inactive	
	L_2 = bipy*	130/400	123/200
	L_2 = phen*	123/100	123/100

*Selected for further tests. [†]Data supplied by NCI. [a]L1210 lymphoid leukaemia. AMP = 2-aminomethylpyridine; bipy = 2,2′-bipyridyl; H_2acacen = bis(acetylacetone)ethylenediimine; merpy = 2-mercaptopyridine; Nisalen = bis(salicylaldehyde)ethylenediiminato nickel(II); PBI = 2-(2-pyridyl)-benzimidazole; phen = 1,10-phenanthroline; Cphen = 5-chloro-1,10-phenanthroline; DMphen = 5,6-dimethyl-1,10-phenanthroline; DMDPphen = 2,9-dimethyl-4,7-diphenyl-1,10-phenanthroline; DPphen = 4,7-diphenyl-1,10-phenanthroline; Nphen = 5-nitro-1,10-phenanthroline; Pphen = 5-phenyl-1,10-phenanthroline; TMphen = 3,4,7,8-tetramethyl-1,10-phenanthroline; py = pyridine; pypy = pyrido[2,3-b]pyrazine.

TABLE III. Diorganotin Dihalides with Activity towards P388 Lymphocytic Leukaemia.

Compound	Two best test results (T/C %)/(Dose mg/kg)	
Et_2SnCl_2[a]	136/12.5	121/12.5
Pr_2SnF_2[a]	129/6.25	128/3.12
Pr_2SnCl_2	136/–[b]	131/–[b]
Pr_2SnBr_2[a]	142/25	131/6.25
Ph_2SnF_2	196/–[b]	144/–[b]

[a]Selected for further tests. [b]Data supplied by NCI.

TABLE IV. Summary of Antitumour Activity of $R_2SnX_2 \cdot L_2$ (where R = C_n, n = 1–6; L_2 = bipy, phen, DPphen, TMphen, PBI) in relation to X.

	Number of active complexes expressed as a percentage	
	X only[a]	X *versus* all active adducts[b]
Cl	10/24 = 42%	10/32 = 31%
Br	15/25 = 60%	15/32 = 47%
I	7/16 = 43%	7/32 = 22%
Total	32/65 = 49%	32/32 = 100%

[a](Number of active complexes containing X)/(Total number of complexes containing X). [b](Number of active complexes containing X)/(Total number of active complexes).

In discussing structure/activity relationships for the complexes, $R_2SnX_2 \cdot L_2$, three primary factors are involved: the organic groups, R; the halide or pseudohalide radical, X; and the donor ligand(s), L.

The acceptor strength (Lewis acidity) of the tin halides is reported [12] to decrease in the following order:

$$SnCl_4 > SnBr_4 > SnI_4$$

$$SnCl_4 > Ph_2SnCl_2 > Me_2SnCl_2 > > Et_2SnCl_2 > Bu_2SnCl_2.$$

A consideration of the screening results for the bipy, phen, DPphen, TMphen and PBI complexes (where R = C_n, n = 1–6; X = Cl, Br, I), which form almost a complete series, reveals (Table IV) that many more of the dibromo-complexes are active than dichloro- or diiodo-compounds, whilst, for R, the diethyl- and/or diphenyl-tin complexes usually possess the highest activity. Indeed, this latter trend is seen for many of the compounds listed in Table II. However, no real link between acceptor strength of the parent organotin halide and activity can be discerned.

The majority of the ligands used were bidentate, to ensure that the resulting octahedral complex possessed *cis*-halogens, which has been shown, in the case of platinum compounds, to be an essential requirement for activity [13]. A ^{119m}Sn Mössbauer study has demonstrated [10] that the complexes do possess *cis*-halogens with a *trans*-(**V**) or distorted *trans*-R_2SnX_4 octahedral geometry about tin, although a few of the diphenyl compounds were found to possess a *cis*-R_2SnX_4 octahedral structure. However, no correlation can be made between either the geometry about the tin atom or the value of the quadrupole splitting parameter and antitumour activity (Table V). Similarly, substituents on the ligand do not appear to have a predictable effect (Table V). Most of the ligands possess strong nitrogen-donor atoms, and, of these, 1,10-phenanthroline (14/24 = 58% active), 3,4,7,8-tetramethyl-1,10-phenanthroline (10/16 = 63%) and 2-(2-pyridyl)-benzimidazole (6/12 = 50%) appear, from our results, to be the better ligands for activity.

The mode of action of *cis*-$PtCl_2(NH_3)_2$, cisplatin (**I**), and its analogues in their antitumour activity appears to be fairly well established; the complexes are believed to lose their chloride ligands and the metal subsequently coordinates with suitably orientated nitrogenous bases on DNA [14]. Since the tin complexes were structurally similar to those of platinum, we expected that their mode of action would also be similar; certainly, examples of tin derivatives of nitrogenous bases, *e.g.* $R_2Sn(adenine)_2$ [3] are known.

A recent study of metallocene dichlorides (**VI**) has shown [15] that the antitumour activity of such compounds, as well as that of cisplatin, may be dependent upon the Cl–$\hat{M}$–Cl bond angle and hence the corresponding non-bonding Cl····Cl distance (bite). Only those compounds for which the Cl–$\hat{M}$–Cl angle is <95°, giving a bite size of <3.6 Å (the upper limit for DNA–metal crosslinks), are active.

The X-ray structural parameters of six diorganotin dihalide complexes, $R_2SnX_2 \cdot L_2$, have been examined [16]. It was found (Table VI) that the Cl–$\hat{M}$–Cl bond angles of both active and inactive compounds are all of a similar magnitude (*ca.* 103–105°) and well above the limiting value proposed by Köpf and

TABLE V. Antitumour Activity, Mössbauer Quadrupole Splitting Parameters and Structure of $R_2SnCl_2 \cdot L_2$ (R = Et, Ph; L_2 = phen and substituted phen).

$Et_2SnCl_2 \cdot L_2$ L_2	Two best T/C %	Quadrupole splitting parameter ΔE_q (mm s^{-1})	Structure[a]
phen	177/176	4.11	I
Cphen	inactive	4.11	I
DMphen	128/123	4.06	I
DPphen	inactive	3.95	I
Nphen	inactive	4.11	I
Pphen	142/125	4.08	I
TMphen	126/122	4.06	I
$Ph_2SnCl_2 \cdot L_2$ L_2			
phen	inactive	3.52	III
CPphen	132/123	3.47	III
DMphen	165/151	3.35	III
DPphen	inactive	3.50	III
Nphen	160/148	2.31	II
Pphen	130/125	3.57	III
TMphen	158/130	3.63	III

[a]I = *trans*-R_2SnX_4; II = *cis*-R_2SnX_4; III = distorted *trans*-R_2SnX_4.

TABLE VI. Crystallographic and Antitumour Activity (P388 Lymphocytic Leukaemia) Data for Diorganotin Dihalide Complexes [16].

	$\widehat{ClSnCl}$ (°)	Cl···Cl (Å)	Average Sn–N (Å)	Best T/C[a] (%)	
Ph_2SnCl_2·bipy	103.5	3.94	2.36	103	inactive
Et_2SnCl_2·bipy	104.2	4.00	2.38	115	
Bu_2SnCl_2·phen	105	4.05	2.39	141	active
Bu_2SnCl_2·bipy	104.3	4.00	2.40	131	
Et_2SnCl_2·phen	105.2	4.02	2.41	176	
Et_2SnCl_2·pdt[b]	103.2	3.88	2.50	144	

[a]Median survival time of treated group of mice divided by that of the control group; a compound is active if it has a T/C ⩾ 120%. [b]3-(2-pyridyl)-5,6-diphenyl-1,2,4-triazine.

Köpf-Maier [15]. This suggested that the mode of action for the formation of metal-base cross-links for the organotins, takes place *via* a different route. The active compounds had average Sn–N bond lengths ⩾2.39 Å whereas those with average Sn–N bond lengths <2.39 Å were inactive. This observation led to the suggestion [16] that the more stable complexes had lower activities, which in turn implied that a predissociation of the bidentate ligand may be a crucial step in the formation of a tin–DNA complex.

X-ray structural studies of other complexes are under way, to further examine the link between Sn–N bond length and antitumour activity.

Acknowledgements

The International Tin Research Council, London and the U.S. National Cancer Institute, Bethesda, Md., are thanked for permission to publish this work.

References

1 A. J. Crowe, P. J. Smith and G. Atassi, *Chem. Biol. Interact., 32,* 171 (1980).
2 *U.K. Pat. Appl. 2 077 266 A* (1981) to E. J. Bulten and H. A. Budding.
3 R. Barbieri, L. Pellerito, G. Ruisi, M. T. LoGiudice, F. Huber and G. Atassi, *Inorg. Chim. Acta, 66,* L39 (1982).
4 F. Huber, Plenary Lecture, *4th Internat. Conf. Organomet. Coord. Chem. Ge, Sn, Pb.,* McGill University, Montreal, Canada, Aug 8–11, 1983.
5 I. Haiduc, C. Silvestru and M. Gielen, *Bull. Soc. Chim. Belg., 92,* 187 (1983).
6 A. Saxena and J. P. Tandon, *Cancer Lett., 19,* 73 (1983).
7 N. F. Cardarelli, B. M. Quitter, A. Allen, E. Dobbins, E. P. Libby, P. Hager and L. R. Sherman, *Aust. J. Exp. Biol. Med., 62,* 199 (1984).
8 N. F. Cardarelli, B. M. Cardarelli, E. P. Libby and E. Dobbins, *Aust. J. Exp. Biol. Med., 62,* 209 (1984).
9 N. F. Cardarelli and B. M. Cardarelli, paper presented at *9th Internat. Symp. Control. Rel. Bioact. Mat.,* Florida, U.S.A., July, 1982.
10 A. J. Crowe and P. J. Smith, *J. Organomet. Chem., 224,* 223 (1982).
11 Anon., 'Screening Data Summary Interpretation', U.S. Natl. Cancer Inst., Instruction 14, 1978.
12 R. C. Poller, 'The Chemistry of Organotin Compounds', Logos, London, 1970, ch. 11.
13 M. J. Cleare, *Coord. Chem. Rev., 12,* 349 (1974).
14 A. W. Prestayko, S. T. Crooke and S. K. Carter (eds.), 'Cisplatin: Current status and new developments', Academic Press, New York and London, 1980.
15 H. Köpf and P. Köpf-Maier, in S. J. Lippard (ed.), 'Platinum, Gold and Other Metal Chemotherapeutic Agents: Chemistry and Biochemistry', ACS Symposium Series 209, Washington D.C., 1983.
16 A. J. Crowe, P. J. Smith, C. J. Cardin, H. E. Parge and F. E. Smith, *Cancer Lett., 24,* 45 (1984).