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ORGANOTIN COMPOUNDS AND CANCER CHEMOTHERAPY

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CONTENTS

ABBREVIATIONS

acgly	*N*-acetylglycinate
acmdtcz	*o*-hydroxyacetophenone-*S*-methyl dithiocarbazate
ad	adeninate
amp	2-aminomethylpyridine
and	5-androsten-3-ol-17-one
benzbdtcz	benzaldehyde-*S*-benzyl dithiocarbazate
bipy	2,2′-bipyridyl
bipybim	2,2′-bipyridyl-4-benzimidazole
bzgly	*N*-benzoylglycinate
cphen	5-chloro-1,10-phenanthroline
cys	*O*,*S*-cysteinate
dedtp	diethyl dithiophosphate
dmdpphen	2,9-dimethyl-4,7-diphenyl-1,10-phenanthroline
dmdtp	dimethyl dithiophosphate

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dmphen	5,6-dimethyl-1,10-phenanthroline
dmso	dimethyl sulphoxide
dnpgly	*N*-(2,4-dinitrophenyl)glycinate
dpdtp	diphenyl dithiophosphate
dpphen	4,7-diphenyl-1,10-phenanthroline
fbenzbdtcz	*o*-fluorobenzaldehyde-*S*-benzyl dithiocarbazate
glygly	glycylglycinate
gmes	guanidium-2-mercaptoethane sulphonate
H_4cholate	3,7,12-trihydroxy-5β-cholan-24-oic acid
H_2acacen	bis(acetylacetone)ethylenediimine
Hcholest	cholest-5-en-3β-ol
merpy	2-mercaptopyridine
mtest	4-androsten-17β-methyl-17α-ol-3-one
napmdtcz	*o*-hydroxynaphthaldehyde-*S*-methyl dithiocarbazate
nphen	5-nitro-1,10-phenanthroline
pbi	2-(2-pyridyl)benzimidazole
pen	DL-penicillaminate
phen	1,10-phenanthroline
pphen	5-phenyl-1,10-phenanthroline
put	6-purinethiolate
py	pyridine
pypy	pyrido[2,3-*b*]pyrazine
salbdtcz	salicylaldehyde-*S*-benzyl dithiocarbazate
salfanil	*p*-fluorosalicylaldehyde iminate
salmdtcz	salicylaldehyde-*S*-methyl dithiocarbazate
smes	sodium 2-mercaptoethane sulphonate
tmphen	3,4,7,8-tetramethyl-1,10-phenanthroline

A. INTRODUCTION

Since its discovery by Furst in 1963 [1], metal chelation continues to play an important role in the cure and cause of malignancy. The finding of Rosenberg et al. [2] that platinum compounds can be safely used to treat certain types of cancer (Neoplatin is still the largest selling drug for the treatment of cancer in the U.S.A.) placed the coordination chemists on the front line in the fight against cancer. Organotin compounds show a spectrum of biological effects and have been extensively studied as fungicides, bactericides, acaricides and wood preservatives [3,4]. However, only scanty and scattered information is available on their activity against cancer.

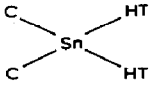
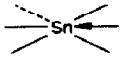
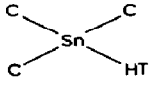
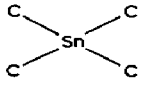
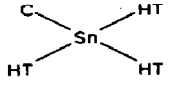
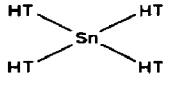
This article collects the scattered information in the literature and gives an insight into the present state of the field.

B. VARIOUS ORGANOTIN COMPOUNDS AND THEIR ACTIVITIES

In 1973 Atsushi et al. [5], in a very important piece of work, reported the very high affinity of tin for tumors (highest among the group 14 elements). This finding was further confirmed by various workers who prepared tin-labelled technetium complexes and used them as imaging agents for tumor localization [6]. Although the first organotin(IV) compound was tested for its antitumor activity in 1929, no systematic study was undertaken afterwards and as a result only 1509 organotin compounds had been tested in various tumor systems by the end of 1981 [7]. As shown in Table 1, 25% of all the compounds tested against the P388 Lymphocyte Leukaemia were active while only 1% showed activity against L1210 Lymphocyte Leukaemia. In both the systems, the most profound activity was shown by diorganotin compounds.

TABLE 1

Evaluation of tin compounds in two tumor systems

Structure [a]	Total tested	P388		L1210	
		Tested	Active (%)	Tested	Active (%)
Compounds	1554	680	25	696	1.0
	327	129	48	136	1.0
	160	143	50	35	0.0
	358	132	9	203	0.0
	339	166	2	144	0.4
	33	11	9	11	0.0
	45	15	7	10	0.0

[a] HT, any atom except C or H (mainly N, S or halogen); - - - - -, another bond may or may not exist.

TABLE 2

The activity of diorganotin chloride adducts against P388 Lymphocyte Leukaemia

$R_2SnCl_2 \cdot nL$			Dose (mg kg^{-1})	T/C (%)	Ref.
R	*n*	L			
Et	1	phen	100	152	11
Pr	1	phen	100	127	11
Bu	1	amp	50	139	11
	1	phen	100	121	11
	1	bipy	400	130	11
Ph	1	amp	25	153	11
Me	2	dmso	–	Inactive [a]	18
	2	merpy	–	Inactive	18
	2	py	50	128	18
	1	amp	–	Inactive	18
	1	bipy	50	126	18
	1	Nisalen	–	Inactive	18
	1	pbi	–	Inactive	18
	1	phen	–	Inactive	18
	1	dpphen	–	Inactive	18
	1	tmphen	–	Inactive	18
	1	pypy	100	137	18
Et	2	dmso	25	153	18
	2	py	–	Inactive	18
	1	amp	–	Inactive	18
	1	bipy	–	Inactive	18
	1	H_2acacen	100	150	18
	1	pbi	100	171	18
	1	phen	100	177	18
	1	cphen	–	Inactive	18
	1	dmphen	100	128	18
	1	dpphen	–	Inactive	18
	1	nphen	–	Inactive	18
	1	pphen	50	142	18
	1	tmphen	200	126	18
Pr	2	py	–	Inactive	18
	1	bipy	–	Inactive	18
	1	pbi	–	Inactive	18
	1	phen	50	125	18
	1	dpphen	–	Inactive	18
	1	tmphen	–	Inactive	18
Bu	1	pbi	–	Inactive	18
	1	phen	100	141	18
	1	dpphen	25	126	18
	1	tmphen	–	Inactive	18
Ph	2	dmso	–	Inactive	18
	2	py	–	180	[b]
	1	bipy	–	Inactive [a]	18
	1	pbi	100	164	18

TABLE 2 (continued)

$R_2SnCl_2 \cdot nL$			Dose (mg kg^{-1})	T/C (%)	Ref.
R	*n*	L			
	1	phen	–	Inactive	18
	1	cphen	6.25	132	18
	1	dmdpphen	6.25	127	18
	1	dmphen	6.25	165	18
	1	dpphen	–	Inactive	18
	1	nphen	200	160	18
	1	pphen	25	130	18
	1	tmphen	12.5	158	18
Bz	1	phen	–	Inactive	18
Oct	1	bipy	–	Inactive [a]	18
	1	pbi	–	Inactive	18
	1	phen	–	Inactive [a]	18
	1	dpphen	–	Inactive	18
	1	tmphen	–	Inactive	18

[a] Adducts tested against L1210 Lymphocyte Leukaemia. [b] Data supplied by National Cancer Institute, U.S.A.

Much of the current interest dates back to the work of Brown in the early eighties. In her fundamental work, Brown noted that triphenyltin acetate exhibited antitumor activity in mice, whereas triphenyltin chloride was inactive [8]. She hypothesized that the degree of water solubility was an important factor in organotin anticarcinogenecity. In 1975 Ozaki et al. [9] patented some 2′,3′-*O*-dialkylstannyl derivatives of 5-fluorouridine (Fig. 1) as anticarcinogenic agents. The compound caused the shrinkage of the solid tumor when injected directly.

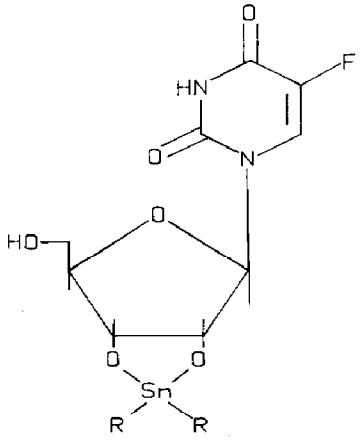


Fig. 1. 2′,3′-*O*-Dialkylstannyl derivatives of 5-fluorouridine.

Bulten and Budding [10] also reported on the antitumor activity of $(ClMe_2Sn)_2O$, $(Et_2SnO)_n$, $Ph_2Sn(OH)Cl$ and 14 other structural analogues.

In 1980, Crowe et al. [11] published the first detailed report on the antitumor activity of a series of diorganotin dihalide and pseudohalide complexes $R_2SnX_2 \cdot 2L$ (R = Me, Et, Pr, *n*-Bu or Ph; X = F, Cl, Br, I; 2L = bipyridyl, phenanthroline, 2-aminomethylpyridine; L = dimethyl sulphoxide, pyridine etc.) (Table 2).

A special feature of these complexes was that they were modelled on the active square-planar Pt(II) complexes which have *cis* halogen groups. On the basis of the high activity of $Et_2SnCl_2 \cdot 2L$ complexes, they suggested that since Et_2SnCl_2 is active (T/C = 125 [11]) and the ligands are inactive, the mode of action may involve the initial transportation of the complexed Et_2SnCl_2 compound into the tumor cells, followed by reaction of Et_2SnCl_2 (or one of its hydrolysis products) at the active sites. This suggestion is further supported by the fact that $(Et_2SnO)_n$, the hydrolysis product of Et_2SnCl_2, is also active in the same system (T/C = 137 [10]). A comparison of the Lewis acidity of R_2SnX_2 compounds and the electronegativity of the halide with the activity of these complexes stimulated them to hypothesize that moderately stable complexes are required for activity.

Barbieri et al. [12] prepared some diorganotin(IV) (R = Me, *n*-Bu, *n*-Oct and Ph) complexes of adenine and glycylglycine and screened them against P388 Lymphocyte Leukaemia in mice. These complexes showed high T/C values (Table 7) and they were interpreted in relation to the corresponding values for $R_2SnX_2 \cdot 2L$ complexes.

It was suggested that the action of water on the complex $R_2Sn(ad)_2$ (Fig. 2) and adduct $R_2SnX_2 \cdot 2L$ could yield the analogous species, owing to possible coordination of H_2O to the metal center followed by hydrolysis and to gradual dissociation of Sn–N bonds. As a consequence, the complexed species is transported into the tumor cells which are then attacked by hydrolyzed R_2Sn^{IV} moieties.

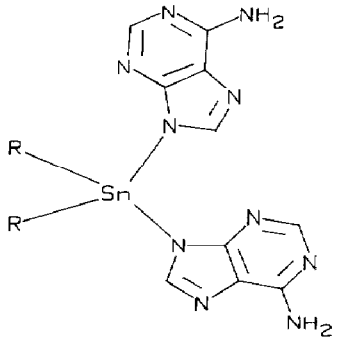


Fig. 2. $R_2Sn(ad)_2$.

Saxena and Tandon [13] screened a series of di-*n*-butyltin complexes of Schiff bases derived from *S*-substituted dithiocarbazates and *p*-fluoroaniline for their activity against P388 Lymphocyte Leukaemia and suggested that the presence of highly electronegative groups can greatly enhance the activity. At about the same time, Takahashi et al. [14] studied the effects of timing a single intragastric application of dibutyltin dichloride on pancreatic carcinoma induced with *N*-nitroso bis(2-oxopropyl)amine (BOP) in female Syrian golden hamsters.

Haiduc et al. [15] have studied the activity of a series of organotin compounds of the type $[R_2P(S)S]_2SnR'_2$ ($R' = Me$ or Ph) in vitro against P388 Lymphocyte Leukaemia in mice. They also studied the complexed and uncomplexed diorganotin dihalides, e.g. $PhMeSnBr_2$ and $(PhCH_2)PhSnCl_2$, and found that uncomplexed halides are not only more toxic but also more active. Clercq et al. [16] screened six organotin compounds of the type $[CF_3(CF_2)_5CH_2CH_2]_2SnX_2$ and $[CF_3(CF_2)_5CH_2CH_2]_2SnX_2 \cdot o$-phen against murine P388 Lymphocyte Leukaemia. It is speculated that the poor activity of these compounds may be due to low water solubility.

Recently, Crowe et al. [17,18] screened a number of diorganotin halide and pseudohalide adducts against P388 Lymphocyte Leukaemia. These complexes were modelled on active platinum complexes and the results were explained by comparing them with platinum and metallocene derivatives. The T/C values are given in Tables 2–6. It is suggested that diethyltin and/or diphenyltin complexes usually possess the highest activity, and most of the ligands in active complexes contain strong nitrogen donor atoms. Köpf and Köpf-Maier [19] have recently shown that the antitumor activity of metallocene dichlorides (Cp_2MCl_2, where M = Ti, Zr, V, Nb or Mo) and *cis*-platin may be dependent on the Cl–M–Cl bond angle and hence on the corresponding non-bonding Cl · · · Cl distance. Only those compounds in which the Cl–M–Cl angle is less than 95°C are active. By analyzing the X-ray crystallographic data of these organotin adducts it was found that the Cl–M–Cl angles of both active and inactive adducts are of similar magnitude (ca. 103–105°) and well above the limiting value proposed by Köpf. It was an important observation that, although these adducts were modelled on platinum complexes, the mode of action for the formation of metal–base cross-links for organotin adducts takes place via a different route. They observed that the active complexes have an average Sn–N bond length equal to or greater than 2.39 Å whereas the inactive ones have a bond length of less than 2.39 Å and suggested that more stable complexes have lower activities.

In 1984 Cardarelli gave a new impetus to the field of organotin compounds in anticarcinogenesis. A number of organotin compounds, i.e. tributyltin fluoride, dibutyltin dichloride · 2,2′-bipyridyl, 1,10-phenanthroline

TABLE 3

The activity of diorganotin bromide adducts against P388 Lymphocyte Leukaemia (data from ref. 18 unless otherwise stated)

$R_2SnBr_2 \cdot 2L$		Dose (mg kg^{-1})	T/C (%)
R	2L		
Me	bipy	200	135 [a]
	phen	50	131 [a]
	pbi	12.5	130
	dpphen	–	Inactive
	tmphen	100	128
Et	bipy	–	Inactive
	pbi	12.5	175
	phen	25	176
	dpphen	25	168
	tmphen	25	145
Pr	bipy	–	Inactive
	pbi	6.25	148
	phen	50	140
	dpphen	–	Inactive
	tmphen	12.5	158
Bu	bipy	–	Inactive
	pbi	–	Inactive
	phen	–	Inactive
	dpphen	–	Inactive
	tmphen	–	Inactive
Ph	bipy	–	Inactive
	pbi	12.5	144
	phen	12.5	134
	dpphen	25	154
	tmphen	6.25	177

[a] Data from ref. 11.

dibutyltin complex and dibutyltin histidine were given to cancerous mice in drinking water and tumor growth rates were significantly reduced. Tributyltin fluoride applied dermally to the same mice was found to be inactive [20]. However, the difference in the tumor growth retardation may be due to the feeding effect. Studies on the tin content in various body organs led Cardarelli et al. [21] to hypothesize that soluble organotin compounds of varying types introduced into the body are concentrated in the thymus gland. The tin in the thymus is then processed into one or more biochemicals that act as anticarcinogens and/or antioncogens. The isolation and evaluation of thymic extracts reasonably pointed to the unknown tin-bearing antioncogenic biochemicals of a steroid nature. These tin steroids (Fig. 3),

TABLE 4

The activity of diorganotin iodide adducts against P388 Lymphocyte Leukaemia (data from ref. 18).

$R_2SnI_2 \cdot 2L$		Dose (mg kg^{-1})	T/C (%)
R	2L		
Me	bipy	100	131
	phen	200	135
Et	bipy	–	Inactive
	phen	200	184
	dpphen	100	137
	tmphen	50	145
Pr	bipy	–	Inactive
	pbi	–	Inactive
	phen	–	Inactive
	dpphen	–	Inactive
	tmphen	25	136
Bu	bipy	–	Inactive
	phen	–	Inactive
Ph	bipy	–	Inactive
	phen	–	Inactive
	dpphen	6.25	166

TABLE 5

The activity of miscellaneous diorganotin halide/pseudohalide adducts against P388 Lymphocyte Leukaemia (data from ref. 18)

$R_2SnX_2 \cdot 2L$			Dose (mg kg^{-1})	T/C (%)
R	X	L		
Me	NCS	bipy	–	Inactive
	NCS	phen	–	Inactive
Et	F	phen	6.25	138
	F	tmphen	50	138
	NCS	bipy	12.5	179
	NCS	phen	100	164
Pr	F	phen	6.25	140
	F	tmphen	12.5	127
	NCS	bipy	–	Inactive
	NCS	phen	–	Inactive
Bu	F	phen	12.5	145
	F	tmphen	–	Inactive
	NCS	bipy	25	123
	NCS	phen	–	Inactive
Ph	NCS	bipy	–	Inactive
	NCS	phen	–	Inactive

TABLE 6

The activity of some diorganotin halides against P388 Lymphocyte Leukaemia

Compound	Et_2SnCl_2 [a]	Pr_2SnF_2 [a]	Pr_2SnCl_2 [b]	Pr_2SnBr_2 [a]	Ph_2SnF_2 [b]	Rf_2SnCl_2 [c]
Dose (mg kg^{-1})	12.5	6.25	–	25	–	240
T/C (%)	136	129	136	142	196	125

[a] Ref. 18. [b] Data supplied by National Cancer Institute, U.S.A. [c] Ref. 16.

and probably peptides produced by thymus, are multifunctional and act as hormones in the suppression of oncogenesis.

On the basis of their hypothesis, Cardarelli et al. [22] patented several organotin compounds of steroids which show marked antitumor activity. However, no structure–activity correlations could be made as most of the samples tested contained one or more tin-bearing unit. Yamamoto et al. [23] studied the comparative antitumor activity of a number of organometallic complexes of alkylidene triphenylphosphorine in L1210 Leukaemia in mice. The organotin compounds were found to be second to organolead compounds in activity. Huber et al. [24] recently reported the antitumor activity of 20 diorganotin and triorganotin compounds of the type R_2SnL (H_2L = L-cysteinate or DL-penicillamine; R = Me, Bu or Ph), Me_2Sn complexes of *N*-benzoylglycinate and other substituted glycinates, $[RSn(SCH_2CH_2SO_3)_2]^{2-}$ and $Bu_2Sn(put)_2$ or $(Ph_3Sn)_3(put)_2$ (Hput = purine-6-thiol) and correlated the structures with the activity. The T/C values are given in Table 7. A comparison of the structures of active and inactive compounds suggests that in all active compounds there is (i) the availability of coordination positions at Sn, (ii) the occurrence of relatively stable ligand–Sn bonds, Sn–N and Sn–S, (iii) slow hydrolytic decomposition of these bonds. One important feature of the work is that none of the purine-6-thiol complexes showed any activity, though the ligand itself is an antileukaemia drug in clinical use.

Meinema et al. [25] have screened a number of complexes of the type $RR'Sn(CH_2COOMe)_2$ (where R = Me, Et, Ph or Bu) and RR'SnO against P388 Lymphocyte Leukaemia in mice. The high T/C values, tabulated in

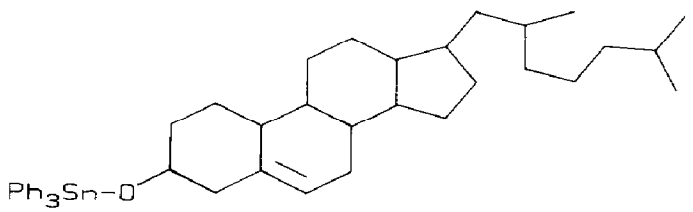


Fig. 3. Tin-bearing antioncogenic steroid postulated to be present in thymic extracts.

TABLE 7

The activity of organotin compounds against P388 Lymphocyte Leukaemia

Compound	Dose (mg kg^{-1})	T/C (%)	Ref.
n-$Bu_2Sn(ad)_2$ [a]	12.5	131	12
$Ph_2Sn(ad)_2$ [a]	100	169	12
$Me_2Sn(glygly)$ [b]	25.0	139	12
n-$Bu_2Sn(glygly)$ [b]	3.12	150	12
n-$Oct_2Sn(glygly)$ [b]	1.56	132	12
$Ph_2Sn(glygly)$ [a]	3.12	141	12
n-$Bu_2(salmdtcz)$ [c]	6.25	124	13
n-$Bu_2(salfanil)_2$ [c]	12.5	122	13
n-$Bu_2Sn(salbdtcz)$ [c]	–	Inactive	13
n-$Bu_2(acmdtcz)$ [c]	–	Inactive	13
n-$Bu_2(fbenzbdtcz)_2$ [c]	–	Inactive	13
n-$Bu_2Sn(napmdtcz)$ [c]	–	Inactive	13
n-$Bu_2Sn(benzbdtcz)_2$ [c]	–	Inactive	13
$Me_2Sn(dpdtp)_2$	–	Inactive	15
$Me_2Sn(dedtp)_2$	–	Inactive	15
$Me_2Sn(dmdtp)_2$	50	120	15
$Ph_2Sn(dpdtp)_2$	12.5	142	15
$Ph_2Sn(cys)$	50	181	24
$Me_2Sn(pen)$	400	148	24
n-$Bu_2Sn(pen)$	3.12	120, 130	24
$Ph_2Sn(pen)$	–	Inactive	24
$Et_2Sn(gmes)_2$	1.87	130	24
$Ph_2Sn(gmes)_2$	3.75	152	24
n-$Bu_2Sn(gmes)_2$	–	Inactive	24
$Me_2Sn(smes)_2 \cdot 2H_2O$	15	120	24
$Et_2Sn(smes)_2 \cdot 2H_2O$	1.5	137	24
n-$Bu_2Sn(smes)_2 \cdot 2H_2O$	–	Inactive	24
$Ph_2Sn(smes)_2 \cdot 2H_2O$	3.15	144	24
$Me_2Sn(bzgly)_2$	–	Inactive	24
$Me_3Sn(bzgly)$	–	Inactive	24
n-$Bu_3Sn(acgly)$	–	Inactive	24
$Me_3Sn(dnpgly)$	–	Inactive	24
n-$Bu_2Sn(put)_2$	1.56	123	24
$Me_3Sn(put)$	–	Inactive	24
n-$Bu_3Sn(put)$	–	Inactive	24
$Ph_3Sn(put)$	–	Inactive	24
$(Ph_3Sn)_3(put)_2$	–	Inactive	24

[a] Suspension or solution in Klucel. [b] Suspension or solution in saline with Tween-80. [c] Suspension or solution in Tween-80–distilled water–alcohol mixture.

Table 8, indicate that specific complex formation is not a prerequisite for antitumor activity since these compounds either contain an Sn–O bond or generate such a bond on hydrolysis. One important observation was that

TABLE 8

The activity of some oxygen-containing organotin compounds against P388 Lymphocyte Leukaemia (data from ref. 25)

Compound	Dose (mg kg^{-1})	T/C (%)
$(Me_2ClSn)_2O$	12.5	121–141
$(Et_2ClSn)_2O$	8	120
$(Bu_2ClSn)_2O$	–	Inactive
$(EtBuClSn)_2O$	6.25	137
$(CyPhClSn)_2O$	1.56	137
$(o\text{-}Tol_2ClSn)_2O$	1.56	125–133
$(p\text{-}Tol_2ClSn)_2O$	12.5	141
$(p\text{-}Cl\text{-}Ph_2ClSn)_2O$	12.5	146
$Ph_2SnClOH$	25	138–198
$(Et_2SnO)_n$	25	154
$(Ph_2SnO)_n$	4	133
$(EtPhSnO)_n$	50	123–147
$(BuPhSnO)_n$	–	Inactive
$Me_2Sn(CH_2COOMe)_2$	16	128
$Et_2Sn(CH_2COOMe)_2$	12.5	170
$Ph_2Sn(CH_2COOMe)_2$	5	133
$EtPhSn(CH_2COOMe)_2$	50	143–181
$Me_2Sn(CH_2CH_2COOMe)_2$	–	Inactive

active organotin compounds induce filamentous growth in bacteria, indicative of DNA interaction.

So far most of the studies on antitumor activities of organotin compounds have been confined to the P388 Lymphocyte Leukaemia system in mice. Atassi [26] has very recently reported the activity of two organotin adducts (Fig. 4) in various tumor systems including a newly characterized tumor, i.e. the renal adenocarcinoma. The T/C values in Table 9 indicate the very high activity of these compounds in renal adenocarcinoma.

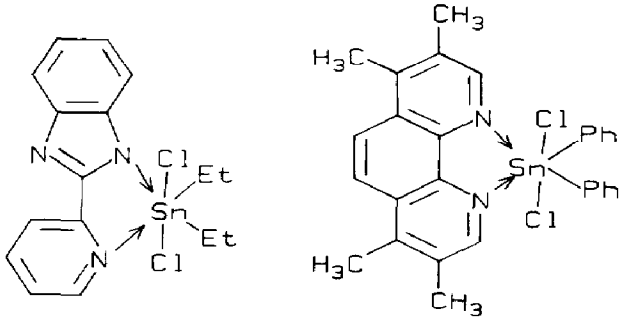


Fig. 4. Two organotin adducts studied by Atassi [26].

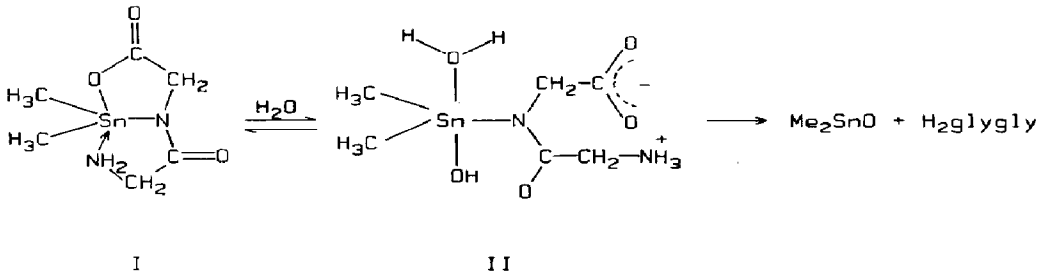
TABLE 9

The activity of two diorganotin chloride adducts against various murine transplanted tumors [26]

Adduct	Tumor system		Days of treatment	Route	Optimal dose [a]	T/C (%)
$Et_2SnCl_2 \cdot$ bipybim	P388 Leukaemia	IP	1, 5, 9	IP	100	171
	L1210 Leukaemia	IP	1–9	IP	25	113
	B16 Melanoma	IP	1–9	IP	12.5	102
	Lewis lungcarcinoma	IV	1–9	IP	6.25	104
	Colon 38	SC	2 and 9	IP	50	48 [b]
	Renal carcinoma	IP	1, 5, 9, 13, 17	IP	40	218
	Renal carcinoma	SC	1, 5, 9, 13, 17	IP	60	106
$Ph_2SnCl_2 \cdot$ tmphen	P388 Leukaemia	IP	1, 5, 9	IP	12.5	158
	Renal carcinoma	SC	1, 5, 9, 13, 17	IP	12.5	128
	Renal carcinoma	IP	1, 5, 9, 13, 17	IP	12.5	173

[a] Dose in milligrams per kilogram per injection; [b] T/C (%) = growth inhibition.

Ruisi et al. [27] have tried to interpret the action of $R_2Sn(IV)$glycylglycinates (R = Me, *n*-Bu, *n*-Oct or Ph) on a molecular basis. The reaction of Me_2Sn(glygly) in aqueous solution seems to consist of a hydrolytic process occurring via the mechanism given in Scheme 1. The species **I** would



I II

Scheme 1.

structurally correspond to the solid state structure or the structure in organic solvents (in some way mimicking the cell membrane phase). The species **II**

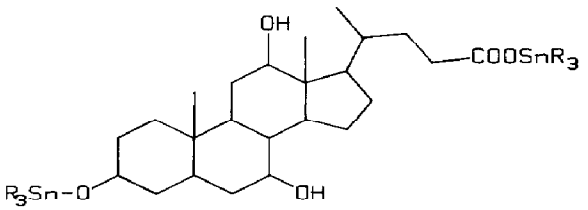


Fig. 5. Type of organotin steroid studied by Saxena et al. [28].

TABLE 10

A comparative in vitro assay data on some organotin steroids and anticancer drugs

Test substance	ED_{50} [a]	
	KB human tumor	P388 Leukaemia
$Ph_3Sn(H_3cholate)$	0.3	0.3
$(Ph_3Sn)_2(H_2cholate)$	0.2	0.4
$Ph_3Sncholest$	0.3	0.4
$Me_2SnCl_2 \cdot 2mtest$	25	11
$Me_2SnCl_2 \cdot 2and$	22	3.2
Prednisolone [b]	80	36
Tamoxifen [b]	17	3.5
Testosterone propionate [b]	24	30
6-Purine thiol	0.3	1.2

[a] The results are expressed in micrograms per millimeter of material necessary to inhibit 50% of control growth. Maximum concentration to show activity is 1 $\mu g\ ml^{-1}$. [b] Data taken from ref. 29.

slowly releases $R_2Sn(IV)$ moieties in aqueous media, which are responsible for the antitumor activity.

Very recently Saxena et al. [28] have studied the antitumor activity of a number of organotin steroids of the type shown in Fig. 5 and compared the activity with that of a number of antitumor drugs (Table 10).

The organotin steroids which have covalent bonding between Sn and O atoms are very active compared with organotin steroids which have coordinate bonds between them.

C. CONCLUDING REMARKS

These studies clearly show that organotin compounds have vast potential for use as antitumor agents, especially because of their low toxicity. However, much work is needed to explain the mechanism of their activity, and concerted efforts should be made to study the structures of tested compounds in solution (especially in aqueous media), since most of the drugs are administered in solution phase. The low solubility of most organotin compounds in water is also an obstacle to their high activity.

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