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QSAR approach to understand the antitumour activity of organotins

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Abstract

The activity of a series of diorganotin(IV) salts and complexes against murine leukaemia P388 (log(*T/C*)) is correlated to the lipophilicity (log *P*) of the organic radicals bound to the metal, as well as of radicals plus ligands in thiolato complexes. Compounds R_2Snhal_2, the related oxo and hydroxo derivatives, complexes $R_2SnX_2 \cdot L_2$ and $R_2SnL_{3,4}$ (L being ligands with N and O donor atoms), and compounds with S–Sn bonds, $R_2Sn(SR')$ and $R_2Sn(SR')_2$, seem to originate three congeneric series, described by parabolic functions log(*T/C*) versus log *P*, the latter estimated for the organic radicals in R_2Sn^{IV}. Compounds $R_2Sn(SR')$ yield an additional parabolic function, where log *P* concerns both R and SR'.

Introduction

The first systematic researches on the antitumour properties of organotins were carried out by Bulten and by Smith [1], following the very early, and apparently unique, reports by Collier [2a] and Krause [2b] in 1929. The first data were published in 1980 [3], and consequently a series of investigations has been carried out in the field; in fact, organotins tested *in vivo* against P-388 leukaemia by the protocol of the National Cancer Institute (NCI) were 2008 in 1989 [4]. Only part of these data have been published (see for example refs. 1, 5–7). Diethyltin(IV) and diphenyltin(IV) derivatives are the active species; the antitumour action has been ascribed to these diorganotin(IV) moieties, based on the role of the ligands bound to tin, as well as on the molecular structure of the complexes, in relation to the activity [1, 5–7].

The *in vivo* pre-screening on murine leukaemia P-388 has been recently dismissed by the NCI; an attempt to rationalize the structure–activity relationship for these organotin–tumour systems then seemed to be opportune, in order to possibly advance a conclusive interpretation. To this purpose, an approach through QSAR (quantitative structure–activity relationship) concepts and procedures has been effected, and the results obtained are reported in the present paper. QSAR has been widely employed in the rationalization of biological and pharmacological activities, including antitumour action, of drugs through correlation with physicochemical properties [8–11]. In view of the large biological activity of organotins [12, 13], it is not surprising that the related effects have been amply treated by QSAR approaches [11, 14].

Selection of anti-leukaemia P-388 activity data and method of treatment

Data from more than 100 diorganotin(IV) compounds are taken into account in this paper; they are reported in Table 1. These compounds describe four classes (Table 1): (A), R_2Snhal_2 and hydrolysis products of R_2Sn^{IV} moieties; (B), adducts of R_2SnCl_2 with ligands containing N and O donors, and complexes of R_2Sn^{IV} moieties; (C), (D), complexes of R_2Sn^{IV} with one and two Sn–S bonds. Compounds under (A)–(D) constitute the majority of organotins whose (*T/C*) data on *in vivo* P-388 pre-screening have already been published (see refs. 1, 3, 5–7; and refs. in Table 1).

The biological response, *BR*, to organotins in these tests is expressed in terms of the median survival time of a treated mice group (*T*) divided by that of a control group (*C*); $(T/C) \geqslant 120\%$ is necessary in order to pass activity criteria [26]. For compounds under (A) and (B), data $(T/C) \geqslant 120\%$ have been considered and are reported in Table 1, being often the only data points in the literature (lower values, even when the largest for a given compound, often are not reported, and the compound is labelled as 'inactive'). The latter is not the case for compounds (C) and (D), Table 1, for which best values of (*T/C*) are reported even when lower than 120%, and these data are taken into account here.

The compounds (A)–(D) have been selected according to the following expectations and assumptions.

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TABLE 1. The effect of R_2Sn^{IV} derivatives on murine leukaemia P-388[a]

Code nos.	Compound, or class of compounds	Nos. tested (with *T/C* (%) ⩾120)	Reference	Optimal dose[b] or range of optimal doses (mg/kg/inj)	*T/C* (%)[c] or average values of *T/C* (%) ⩾120 (standard error)
(A) R_2Snhal_2 and hydrolyzed species					
1	$(Me_2SnCl)_2O$	1	15	12.5	133
2	Et_2SnCl_2; $(Et_2SnX)_2O$[d]; Et_2SnO	4	15–17	6.25–25	139.4 (8.9)
3	$Pr^n_2Snhal_2$[e]	3	17	6.25–25	135.7 (3.7)
4	$Bu^n_2SnCl_2$	1	1	3	120
5	Ph_2SnF_2[f]; $Ph_2Sn(OH)Cl$; $(Ph_2SnNO_3)_2O$; Ph_2SnO	4	15–17	4–25	154.1 (15.6)
6	$BzPhSnCl_2$	1	6	12.5	129
7	EtPhSnO	1	15	50	135
8	$(EtBu^nSnCl)_2O$	1	15	6.25	137
9	Bu^nPhSnO	1	15, 16	100	131.5
10	Bu^sPhSnO	1	16	3.12	153
11	Pr^nBzSnO	1	16	3.12	143
12	$[(o\text{-Tolyl})_2SnCl]_2O$	1	15	1.56	129
13	$[(p\text{-Tolyl})_2SnCl]_2O$	1	15	12.5	141
14	$(CyPhSnCl)_2O$	1	15	1.56	137
15	$[(p\text{-Cl-Phenyl})_2SnCl]_2O$	1	15	12.5	146
(B) $R_2SnX_2L_2$, R_2SnL_3 and R_2SnL_4[g]					
16	$Me_2SnX_2L_2$[h]; $Me_2SnGlyGly$	10	17, 18	25–200	132.1 (1.3)
17	$Et_2SnX_2L_2$[i]	18	17	6.25–200	155.3 (4.5)
18	$Pr^n_2SnX_2L_2$[j]	7	17	6.25–100	139.4 (4.2)
19	$Bu^n_2SnX_2L_2$[m]; $Bu^n_2SnAd_2$; $Bu^n_2SnGlyGly$; $Bu^n_2SnPydicarb$; Bu^n_2SnFa	10	6, 17–19	3.12–400	134.4 (3.0)
20	$Ph_2SnX_2L_2$[n]; Ph_2SnAd_2; $Ph_2SnGlyGly$	16	17, 18	3.12–200	153.4 (4.2)
21	$(p\text{-OMe-Phenyl})_2SnCl_2L_2$[o]	3	20	7.5–15	156 (2.0)
22	$(p\text{-Tolyl})_2SnCl_2 \cdot amp$	1	20	3.75	138
23	$(p\text{-Cl-Phenyl})_2SnCl_2 \cdot amp$	1	20	240	146
24	$(p\text{-CF}_3\text{-Phenyl})_2SnCl_2 \cdot L_2$[p]	2	20	120; 240	140.5
		Nos. tested (total)	Reference	Optimal dose[b] or range of optimal doses (mg/kg/inj)	*T/C* (%)[c] average values, total (standard error)
(C) R_2SnSR'[q]					
25	$Me_2SnL\text{-Cys}$; Me_2SnD-, L-, and -DL-Pen; Me_2SnMpr	5	21–23	25–400	124.4 (7.6)
26	$Et_2SnL\text{-Cys}$; Et_2SnCys; Et_2SnMpr	3	7, 21, 22	12.5–25	153.3 (15.9)
27	$Bu^n_2SnL\text{-Cys}$; $Bu^n_2Sn\text{-DL-Pen}$; Bu^n_2SnDtc	3	21, 23, 24	0.23–6.25	119 (5.5)
28	$Ph_2SnL\text{-Cys}$; Ph_2SnCys; $Ph_2SnDL\text{-Pen}$; Ph_2SnMpr	4	7, 22, 23	6.25–50	138 (16.5)
(D) $R_2Sn(SR')_2$[q,r]					
29	$Me_2Sn[R_2''P(S)S]_2$[s]; $Me_2Sn(D\text{- and L-PenH})_2$; $Na_2[Me_2Sn(Mes)_2] \cdot 2H_2O$	6	22, 23, 25	15–50	114.8 (2.7)
30	$Na_2[Et_2Sn(Mes)_2] \cdot 2H_2O$; $Gu_2[Et_2Sn(Mes)_2]$	2	23	7.5	130

(*continued*)

TABLE 1. (*continued*)

Code nos.	Compound, or class of compounds	Nos. tested (total)	Reference	Optimal dose[b] or range of optimal doses (mg/kg/inj)	*T/C* (%)[c] average values, total (standard error)
31	$Bu_2^nSn(Put)_2$; $Na_2[Bu_2^nSn(Mes)_2]$; $Gu_2[Bu_2^nSn(Mes)_2]$	3	23	2.0–240	114.3 (7.5)
32	$Na_2[Ph_2Sn(Mes)_2]\cdot 2H_2O$; $Gu_2[Ph_2Sn(Mes)_2]$; $Ph_2Sn[Ph_2P(S)S]_2$	3	23, 25	3.75–12.5	146 (3.0)

[a]The implantation of the tumor, and the methods and vehicles of administration of the drugs, were as described in Anon., "Instruction 14, Screening Data Summary Interpretation and Outline of Current Screen", Drug Evaluation Branch, National Cancer Institute, Bethesda, MD, USA, 1980. See text, and pertinent literature cited in this paper. [b]mg of drug per kg of body weight per injection, yielding the best *T/C* (%) value in the context of a given set of tests. [c]Median survival time of the treated mice group (*T*) divided by that of the control group (*C*). Activity criteria are passed for $T/C \geqslant 120\%$. In this Table, values of $T/C \geqslant 120\%$ are considered for compounds of classes (A) and (B), while the full set of reported *T/C* data, including values <120%, are taken into account for compounds under (C) and (D). See text. [d]X = Cl, CH_3COO. [e]hal = F, Cl, Br; the optimal dose for hal = Cl is missing [17]. [f]The optimal dose is missing. [g]Abbreviations for the ligands L: py = pyridine; bipy = 2,2′-bipyridyl; pypy = pyrido[2,3-b] pyrazine; pbi = 2-(2-pyridyl)benzimidazole; phen = 1,10-phenanthroline; tmphen = 3,4,7,8-tetramethyl-1,10-phenanthroline; dmso = dimethyl sulfoxide; H_2acacen = bis(acetylacetone)ethylenediimine; pphen = 5-phenyl-1,10-phenanthroline; dpphen = 4,7-diphenyl-1,10-phenanthroline; amp = 2-aminomethylpyridine; cphen = 5-chloro-1,10-phenanthroline; dmdpphen = 2,9-dimethyl-4,7-diphenyl-1,10-phenanthroline; dmphen = 5,6-dimethyl-1,10-phenanthroline; nphen = 5-nitro-1,10-phenanthroline; HAd = Adenine; H_2GlyGly = glycylglycine; Pydicarb = 2,6-pyridine dicarboxylate; Fa = Schiff base from fluoroaniline. [h]X = Cl, $L_2 = (py)_2$, bipy, pypy; X = Br, L_2 = bipy, pbi, phen, tmphen; X = I, L_2 = bipy, phen. [i]X = F, L_2 = phen and tmphen; X = Cl, $L_2 = (dmso)_2$, H_2acacen, pbi, phen, pphen, tmphen; X = Br, L_2 = pbi, phen, dpphen, tmphen; X = I, L_2 = phen, dpphen, tmphen; X = NCS, L_2 = bipy, phen. [l]X = F, L_2 = phen, tmphen; X = Cl, L_2 = phen; X = Br, L_2 = pbi, phen, tmphen; X = I, L_2 = tmphen. [m]X = F, L_2 = phen; X = Cl, L_2 = amp, bipy, phen, dpphen; X = NCS, L_2 = bipy. [n]X = Cl, L_2 = pbi, amp, cphen, dmdpphen, dmphen, nphen, pphen, tmphen; X = Br, L_2 = pbi, phen, dpphen, tmphen; X = I, L_2 = dpphen. [o]L = bipy, phen, amp. [p]L = phen, amp. [q]Abbreviations: H_2Cys = cysteine; H_2pen = penicillamine; H_2Mpr = 3-thiopropanoic acid; Dtc = $OC_6H_4CH{=}N{-}NCSSMe$. [r]Abbreviations: HMes (Na, Gu) = 2-mercaptoethanesulfonate, sodium or guanidinium salt; HPut = 6-mercaptopurine. [s]R″ = Me, Et, Ph.

(1) Organotins are administered to mice intraperitoneally (i.p.) generally in suspension in aqueous phases containing NaCl, eventually buffers (at physiological pH values), and surfactants [26], and this is the case for the compounds in Table 1, where only Me_2Sn^{IV} derivatives are eventually injected as aqueous solutions (see refs. in Table 1); upon injection, the pH of the aqueous phase is expected anyway to attain a value around 7.4.

(2) Organotins would then interact with the biological environment either as the species present in aqueous solution at pH = 7.4, as well as solids suspended in water, or water–surfactant systems.

(3) The solid particles could dissolve into lipophilic phases, such as cell membranes.

(4) In aqueous solution, compounds belonging to classes (A) and (B), Table 1, may occur as hydrolyzed species, taking into account the reported values of hydrolysis constants as well as of stability constants of, say, 1,10-phenanthroline, acetylacetone and picolinic acid complexes of dimethyltin (IV), which occur in aqueous solution at acid pH (e.g. $Me_2Sn(OH)_2$ does not interact with acetylacetone) [27–29].

(5) Instead, compounds of classes (C) and (D), Table 1, may act as aquated molecular species $R_2Sn(SR')$ and $R_2Sn(SR')_2$ in a special way for R = Me, Et and SR′ = anions of cysteine, penicillamine and 3-thiopropanoic acid (i.e. hydrophilic tails in the complexes); the occurrence of these species is proposed in view of the large stability constants of tin–thiol sulfur bonds [28], and this has been largely confirmed by spectroscopic work in aqueous phases [21, 30–33].

The biological response due to a given drug is a function of lipophilic, electronic and steric factors, as first suggested by Hansch in the context of QSAR treatments; besides, among these effects 'lipophilicity ranks first' [8–10]. This property may be expressed through the experimental determination of partition coefficients, *P*, in octanol–water systems, which in turn may be estimated, *inter alia*, by the 'hydrophobic fragmental systems' [8–10]:

$$\log P = \sum_{1}^{N} a_n f_n \qquad (1)$$

where *f* is the lipophilicity contribution of a given constituent part of the molecule under consideration, '*a*' being the proper numerical factor [8–10]. Lipophilicity is also expressed in terms of the total molecular surface area [13, 14c–e]. In the present paper, log *P* values are employed, e.g. in functions in Figs. 1–4, which have been extracted from the data in Table 2, as follows:

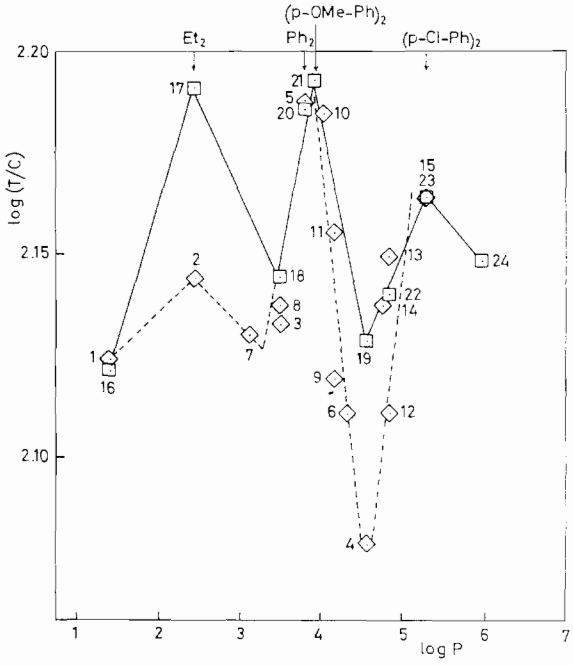

Fig. 1. The representation of the data points log (biological response) = log(T/C), nos. (1)–(24) of Table 1, as function of the lipophilicity of the two organic radicals covalently bound to tin, expressed as the summation of hydrophobic fragmental constants f (see text and Table 2). ◇: R_2Snhal_2, and hydrolyzed species, nos. (1)–(15). ⊡: $R_2SnX_2 \cdot L_2$ and related species, nos. (16)–(24).

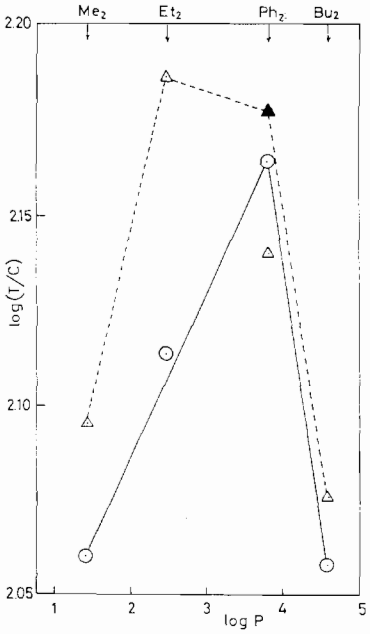

Fig. 2. Log $BR = \log(T/C)$, nos. (25)–(32) of Table 1 vs. the lipophilicity of the two organic radicals bound to tin (Table 2). △: $R_2Sn(SR')$, nos. (25)–(28). ⊙: $R_2Sn(SR')_2$, nos. (29)–(32). ▲: the data point for $Ph_2Sn(SR')$ calculated without the value $T/C = 101\%$ for Ph_2Sn(DL-Pen) [23], possibly an outlier term due to the log P value of Pen (see text and Fig. 3).

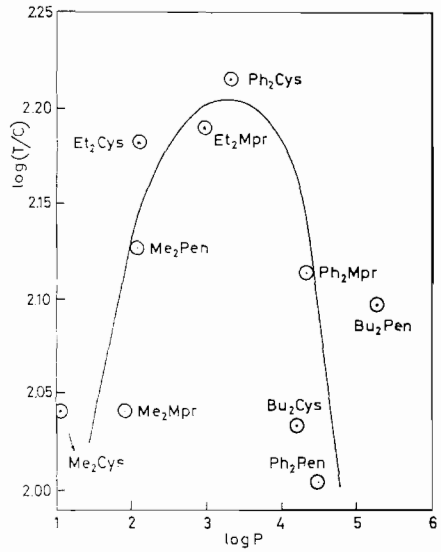

Fig. 3. Log $BR = \log(T/C)$ of $R_2Sn(SR')$ derivatives plotted vs. the lipophilicity of cysteine (Cys), penicillamine (Pen) and 3-mercaptopropionic acid (Mpr) added to two fragmental values for R of R_2Sn^{IV} (see text, Selection of data and method of treatment; see Table 2). (T/C) values are from refs. 7, 21–23.

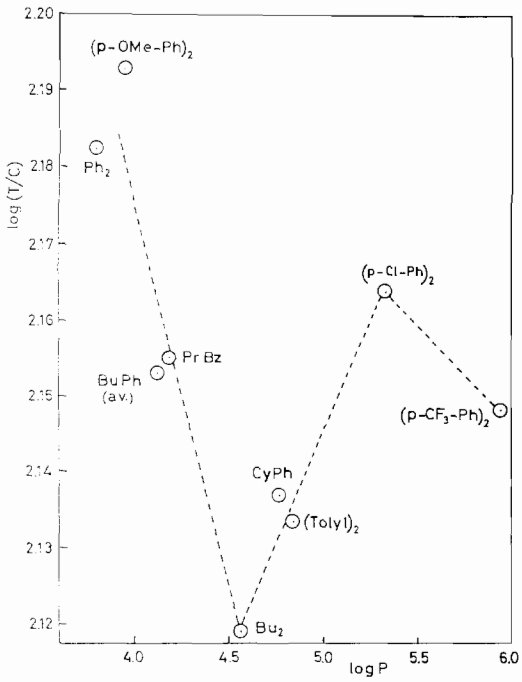

Fig. 4. The plot of functions log $BR = \log(T/C)$ vs. log P for data points in Table 1 having log $P \geqslant 3.79$, the Ph_2 value (see Table 2), and (T/C) $\geqslant 120\%$. The point for Ph_2 is the arithmetic average of 26 data T/C (%), $\geqslant 120\%$, under nos. (5), (20), (28), (32). The point for Bu_2 comes from a total of 14 data ($T/C \geqslant 120\%$) under nos. (4), (19), as well as the values $T/C = 125$, 127 and 124 related to Bu_2^nSn(DL-Pen), $Bu_2^nSn(Put)_2$ and Bu_2^nSnDtc, respectively [23, 24].

TABLE 2. Fragmental values, f, and lipophilicity functions $\log P = \sum_1^N a_n f_n$, of radicals and ligands bound to Sn in R_2Sn^{IV} derivatives[a]

Fragment	f or $\sum_1^N a_n f_n$	Fragment or molecule	f or $\sum_1^N a_n f_n$
C	0.157	C_6H_{11}	2.871
CH	0.236	CF_3–C_6H_4	2.969
CH_2	0.527	–O–(ar)	−0.454
CH_3	0.702	–S–[c]	0.000
CH_3–CH_2	1.230	NH_2	−1.38
CH_3–CH_2–CH_2	1.756	COOH	−1.003
CH_3–CH–CH_2–CH_3	2.167	(Sn)S–CH_2CH(NH_2)COOH[d]	−0.36
CH_3–CH_2–CH_2–CH_2	2.283	(Sn)S–C(CH_3)$_2$CH(NH_2)COOH[e]	0.674
C_6H_5	1.896	(Sn)S–CH_2CH_2COOH[f]	0.511
CH_3O–C_6H_4[b]	1.967		
F–C_6H_4	2.131		
CH_3–C_6H_4	2.421		
C_6H_5–CH_2	2.423	proximity effects[g]	
Cl–C_6H_4	2.662	at one carbon atom	0.80
		at two carbon atoms	0.46

[a]Data from ref. 9 (Tables III-2, -6, -7, -10, -11, -14, -21, -23); values estimated by eqn. (1) and data in ref. 9. [b]$f(C_6H_4)+f(-O-_{ar})+f(CH_3)$. An analogous value is obtained from $f(C_6H_5$–$OCH_3) - f(H_{ar}) = 2.11 - 0.199 = 1.911$. No proximity effects are then taken into account. [c]The value of –S–H, here employed for thiol sulfur in –S–Sn. [d]Cysteine, bound to Sn: $f(-S-)+f(CH_2)+f(CH)+f(NH_2)+f(COOH)$ + proximity effect at 1 C atom + proximity effect at 2 C atoms. [e]Penicillamine, bound to Sn: $f(-S-)+f(C)+2f(CH_3)+f(CH)+f(NH_2)+f(COOH)$ + proximity effect at 1 C atom + proximity effect at 2 C atoms. [f]3-Mercaptopropionic acid, bound to Sn: $f(-S-)+2f(CH_2)+f(COOH)$ + proximity effect at 2 C atoms. [g]Ref. 9, Table III-2, and p. 98 following. Examples of calculations, pp. 102–103.

(1) Compounds (A)–(D) of Table 1 in Figs. 1, 2 and 4: $\log P = 2f_R$ and $= f_R + f_{R'}$ for moieties R_2Sn^{IV} and $RR'Sn^{IV}$, respectively;

(2) Compounds (C) in Fig. 3: $\log P = 2f_R + f(\text{ligand})$, where R are radicals in R_2Sn^{IV} and ligand = cysteinate, penicillaminate and 3-mercaptopropionate.

In the present context, no fragmental values for tin, nor values for charged fragments such as protonated amino groups or dissociated carboxyls, are taken into account, being not reported in ref. 9, whose procedures are followed here.

Results

The functions $\log BR = \log(T/C)$ versus $\log P$ of Figs. 1–4 suggest the following comments:

(1) The compounds R_2Snhal_2 and their hydrolysis products, class (A) of Table 1, and complexes $R_2SnX_2 \cdot L_2$ and $R_2SnL_{3,4}$, class (B), seem to originate one only class of congeneric [8–10] compounds. In fact, the data points in Fig. 1 show maxima for Et_2Sn^{IV} and Ph_2Sn^{IV}-(p-OMe-$C_6H_4)_2Sn^{IV}$, and minima for Pr_2Sn^{IV} or Et-$BuSn^{IV}$, as well as for Bu_2Sn^{IV}. This behaviour would be in line with the predictions in the preceeding section, i.e. compounds (A) and (B) would yield organotin hydrolyzed species in the vehicle of drug administration or into the organism. In any case, the sensibly larger activity of, say, $Et_2SnX_2 \cdot L_2$ (17, Table 1) with respect to Et_2SnCl_2 and related species (2, Table 1), would suggest a consistent contribution by the complex species through, for example, interaction of the solid with lipophilic sites (*vide supra*).

(2) The series (A) + (B) would in fact consist, according to the functions in Fig. 1, of three sub-series of congeneric compounds, originating three parabolic functions $\log BR$ versus $\log P$, consisting of alkyltins ($\log BR_{max}$ for Et_2Sn^{IV}), of aryl–alkyls and diaryls (but $\log BR_{max}$ would occur for (p-OMe-$C_6H_4)_2SnCl_2 \cdot L_2$) and of substituted diaryls ($\log BR_{max}$ for the (p-Cl-$C_6H_4)_2SnCl_2 \cdot L_2$ data point). It seems worth noting here that our systems are congeneric also with respect to the "left hand part of the QSAR equation" [10]; in fact, both tumor and drug are inoculated and injected i.p..

(3) From Figs. 1 and 2, it appears that the $\log BR$ data of R_2Sn^{IV} compounds with a given R generally decrease in the sequence (A) ≥ (B) > (C) > (D) for R = Me, Et, Ph, Bu, except Et_2SnSR' (26, Table 1) which shows an activity similar to that of $Et_2SnX_2 \cdot L_2$ (17, Table 1). The latter again suggests an analogous role of the ligand molecule (−SR' in this case) in dictating the biological response (*vide supra*) [1].

(4) The interpretation of the activity of compounds (C) and (D), with Sn–S (covalent) bonds [21, 30–33], seems to require the estimate of the lipophilicity of the whole molecular components, including the thiol-containing ligands; this is shown by the function in

Fig. 3, concerning the occurring congeneric series $R_2Sn(SR')$. In fact, the data in Fig. 3 rationalize the trend shown in Fig. 2, which is based on log P values of only the organic radicals bound to the metal.

(5) The reliability of the assumption of a congeneric series of R_2Sn^{IV} compounds having the log BR_{max} at $(p\text{-Cl-}C_6H_4)_2Sn^{IV}$ (Fig. 1; see (2) in the preceeding) is demonstrated by the function in Fig. 4, where data points with log $P \geqslant 2$xPh come from all pertinent T/C data of Table 1. It is worth noting that the data point for the (inactive) compound $(p\text{-F-}C_6H_4)_2SnCl_2 \cdot L_2$ (ref. 20; $(T/C)_{av} = 106.5$; log $P = 4.26$, see Table 2) inserts well into functions in Figs. 1 and 4, where it locates in proximity of the minima due to Bu_2Sn^{IV} derivatives.

Discussion

The functions log BR versus log P in Figs. 1–3 seem to be parabolic, in line with the expectation. In fact, a squared lipophilicity term appears in the QSAR Hansch's equation, which is in line with a large number of biological effects of a series of chemicals [8–10]. Parabolic functions have been insofar reported, and widely discussed, even for biological effects of organotins [11].

The occurrence of these functions, and the localization of the maxima, may be associated with the interaction drug–cell membrane, so that, in the present context, we would deal with congeneric series of organotins preferentially transferring through three different classes of cellular membrane systems [9–11], according to Fig. 1.

The assumption that ligand molecules play a role in increasing the antitumour activity of organotins (ref. 1, pp. 142–145) seems to hold at least for the complexes $Et_2SnX_2 \cdot L_2$ (Table 1, no. 16) and $Et_2Sn(SR')$ (Table 1, no. 26). This effect cannot be due to $Et_2SnX_2 \cdot L_2$ in aqueous solution at physiological pH, where hydrolyzed species, eventually soluble [34, 35], would be formed (*vide supra*), which could, *inter alia*, react with thiols [30]. Taking into account that both $Et_2SnX_2 \cdot L_2$ and $Et_2Sn(SR')$ species have been administered as suspensions in the antitumour tests, it would be argued that the activity of these derivatives depends upon the direct interaction of the solid state complexes with lipophilic sites into the biological environment, where the ligand coordination to tin, and the configuration of the complexes, would be maintained even in eventual 'solution' phases (such as in an organic solvent). Anyway, it seems hard to assume that the latter holds only for ethyl derivatives, and not for all other R_2Sn^{IV} complexes, which too are mainly injected as solids in suspension in aqueous phases [1, 15–25].

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