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Review

Antiproliferative and anti-tumor activity of organotin compounds

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Contents

Abstract

Tin compounds and their therapeutic potentials are under consideration from many research groups, while a number of early reviews recording advances in the screening for antiproliferative potential of organotins are also available. This review focuses upon results obtained on the antiproliferative activity of tin compounds in the past 5 years.

Keywords: Bioinorganic chemistry; Metallotherapeutics; Organotin(IV) compounds; Antiproliferative activity

1. Introduction

Prompted by the initial success of platinum chemotherapeutic metallopharmaceuticals, attention was first shifted to non-platinum chemotherapeutics starting from the basic cisplatin framework, with the aim to optimize the efficiency of such drugs and to avoid serious side-effects caused by platinum chemotherapeutics. Among these, organotins have emerged as potential biologically active metallopharmaceuticals. During the 1980s and later, Gielen published a series of papers on the subject [1], the anti-tumor properties of tin complexes having been established in 1929 [2]. Since then, more research groups have worked in the field [3–13]. It has well been established that organotin(IV) compounds are very important in cancer chemotherapy because of their apoptotic inducing character [14–16], while during the last few year it is noticeable that organotin compounds occupy an important place in cancer chemotherapy reports [14]. Recently, Blower described thirty interesting inorganic pharmaceuticals, four of which are tin compounds [17]. Despite this, the exact mechanism of anti-tumor action of organotin compounds remains unknown.

Tin compounds and their therapeutic potentials have been reviewed [13,14,18,19], while a number of early reviews recording advances in the screening for anti-tumor potential of

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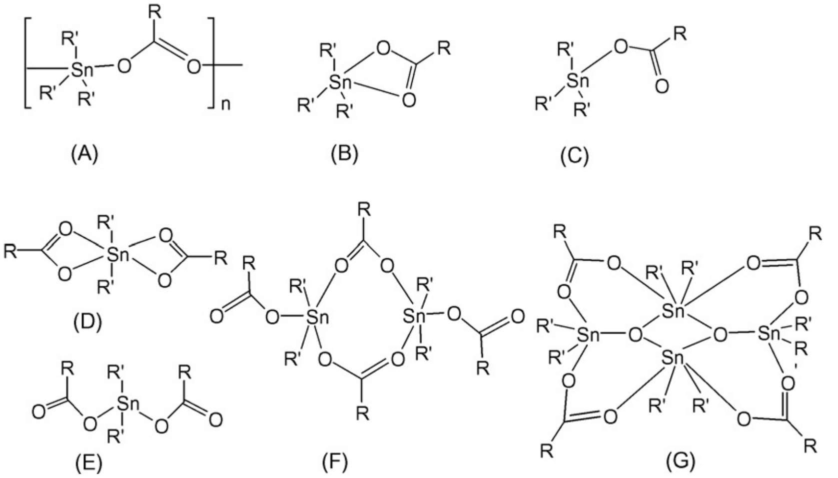


Scheme 1. Common structural motifs found for tri-organotin(IV) (A–C) and diorganotin(IV) (D–G) complexes with carboxylic acids.

organotins are also available [8–12]. This review focuses upon results obtained on the antiproliferative activity of tin compounds in the past 5 years.

2. Organotin(IV) complexes tested for their antiproliferative activity

2.1. Organotin(IV) complexes with oxygen donor ligands

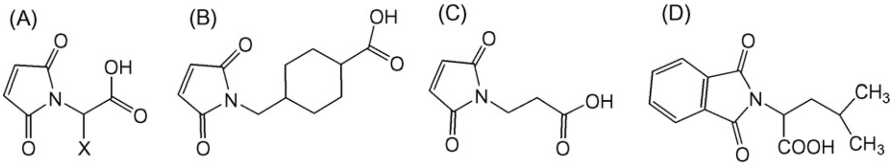
2.1.1. Carboxylates

Organotin(IV) compounds with carboxylates as ligands have been widely tested for their antiproliferative properties and these data have been included in review articles [8,9,11] and book chapters [13]. Recent results are given here. The most common structures found for organotin(IV) carboxylic acid complexes are shown in Scheme 1.

The *in vitro* properties of vinyltin and phenyltin complexes $[Sn(CH{=}CH_2)_3\{\mu\text{-}OOCC_6H_3\text{-}3,4\text{-}(NH_2)_2\}]_n$ (**1**), $[Sn(C_6H_5)_3\{OOCC_6H_3\text{-}3,4\text{-}(NH_2)_2\}]$ (**2**), $[Sn(C_6H_5)_3\{OOC\text{-}2\text{-}C_6H_4N{=}NC_6H_4N\text{-}4\text{-}(CH_3)_2\}]$ (**3**) and $[Sn(CH{=}CH_2)_3\{OOC\text{-}2\text{-}C_6H_4N{=}NC_6H_4N\text{-}4\text{-}(CH_3)_2\}]$ (**4**) have been investigated [20]. The structures of complexes **1**, **2**, and **3**, studied by X-ray crystallography, showed that compound **1** is a distorted trigonal bipyramidal complex (Scheme 1A) and compounds **2** and **3** adopt a distorted tetrahedral structure (Scheme 1B). Complexes **1**, **2**, **3**, and **4** belong to the efficient cytostatic agents against human cell lines (Table 1). The inhibition dose (ID_{50}) of the complexes against various cell lines is included in Table 1. Compound **2** is very active against HCV29T cells. The activity of compounds **1**–**4** against the HCV29T cell line decreases in the order **2** > **1** > **3** > **4**. The complexes are also very active in ethanol solution. The cytostatic activity of complexes **1** and **2** against the A549 and CACO-2 lines are relatively high, although lower than that against HCV29T cells. Thus, these compounds are promising cytostatic agents against some tumor lines *in vitro* (see Table 1).

The *in vitro* cytotoxic behavior of five new diorganotin(IV) complexes having general composition R'_2SnR_2 [R′ = 2-maleimidopropanoate (Scheme 2A; X = Me) and R = Me (**5**), Et (**6**), *n*-Bu (**7**), Ph (**8**), Bn (**9**)] have been investigated [21]. Various spectroscopic methods showed that these complexes **5**–**9** adopt an octahedral arrangement around the metal center in the solid state. In solution **5**–**7** showed hyper-coordinated arrangements around the metal center (Scheme 1D and F) and complexes **8** and **9** were tetra-coordinated (Scheme 1E). Complexes **5**–**9** and the corresponding acid (2-maleimidopropanoic acid) were tested for *in vitro* antiproliferative activity against several human tumor cell lines and the results are summarized in Table 1 and compared with the drugs; doxorubicin, cisplatin, 5-fluorouracil, methotrexate and etoposide. Complexes **8** and **9** were more potent powerful (see Table 1).

Five triorganotin(IV) derivatives of *N*-maleoyl-protected tranexamic acid (HOCOR) (Scheme 2B) with formulae $[(CH_3)_3SnOCOR]$ (**10**), $[(Et)_3SnOCOR]$ (**11**), $[(n\text{-}Bu)_3SnOCOR]$ (**12**), $[(Ph)_3SnOCOR]$ (**13**) and $[(Bn)_3SnOCOR]$ (**14**) [22] have been tested *in vitro* for their bioactivity, against several tumor cell lines of human origin. As per spectroscopic outcome, these compounds **10**–**14** are polymers with Sn(IV) five-coordinated and bridging carboxylate groups in the solid state (Scheme 1A), while



Scheme 2. Ligands used: (A) in complexes **5**–**9** (2-maleimidopropanoic acid, X = Me) and **78**–**83** (*N*-maleoylglycine X = H); (B) in complexes **10**–**14** (*N*-maleoyl-protected tranexamic acid); (C) in complexes **15**–**18** (3-maleimidopropionic acid); (D) in complexes **19**–**22** (phthalimido-4-methyl pentanoic acid).

Table 1

In vitro inhibitory dose for the 50% of various cancer cell lines (ID_{50}) in μg/ml of the organotin(IV) compounds with carboxylic acids **1–70**

Compound	Coordination mode	ID_{50} (μg/ml) against cancer cell line															Refs.
		HCV29T	A549	CACO	A498	EVSA-T	H226	IGROV	M19	MCF7	WiDr	Lemna aequinoctialis Welv	HeLa	CoLo 205	KB	P388	
Cisplatin	Four				2.253	0.422	3.269	0.169	0.558	0.699	0.697		0.433	1.384	0.111		[29,31,32]
1	Five	0.48	7.02	4.21													[20]
2	Four	0.0039	0.49														[20]
3	Four	0.32															[20]
4		0.6															[20]
5	Six				0.141	0.265	0.36	0.202	0.107	0.234	0.147						[21]
6	Six				0.156	0.137	0.133	0.12	0.143	0.089	0.211						[21]
7	Six				0.178	0.161	0.256	0.087	0.044	0.104	0.111						[21]
8	Six				0.043	0.062	0.047	0.231	0.038	0.04	0.214						[21]
9	Six				0.066	0.89	0.14	0.084	0.17	0.036	0.071						[21]
10	Five				0.093	0.082	0.066	0.112	0.105	0.096	0.101						[22]
11	Five				0.086	0.08	0.077	0.101	0.1	0.03	0.068						[22]
12	Five				0.077	0.081	0.03	0.083	0.101	0.024	0.052						[22]
13	Five				0.07	0.042	0.021	0.8	0.093	0.017	0.023						[22]
14	Five				0.05	0.033	0.005	0.12	0.89	0.006	0.017						[22]
15	Six					0.023	0.034	0.025		0.031	0.015						[23]
16	Five					0.355	0.036	0.024		0.025	0.055						[23]
17	Five					0.101	>300	0.155		0.124	0.232						[23]
18	Five						0.084	0.182		0.115	0.122						[23]
19	Six											0.125					[24]
20	Five, six											0.125					[24]
21	Four											0.125					[24]
22	Five											0.125					[24]
23	Five				0.135	0.014	0.205	0.149	0.052	0.027	0.116						[25]
26	Five, six				0.14	0.014	0.217	0.155	0.054	0.029	0.115						[25]
29	Six				0.387	0.063	0.337	0.179	0.122	0.124	0.359						[26]
30	Five		0.11														[27]
31	Five		0.252														[27]
32	Five		1.007														[27]
33	Five		0.192														[27]
34	Five, six				0.376	0.034	0.237	0.174	0.225	0.147	0.895						[28]
35	Five									0.085			0.0046	0.039			[29]
36										0.238			0.187	0.424			[29]
37	Four									0.532			1.39	1.138			[29]
38	Five									0.289			0.132	0.399			[30]
39	Five, six				0.301	0.164	0.338	0.169	0.22	0.138	0.514						[31]
40	Six				0.195	0.142	0.291	0.139	0.174	0.146	0.439						[31]
41	Five, six				0.182	0.14	0.246	0.102	0.172	0.074	0.283						[31]
42	Six														0.22		[32]
43	Six														3.32		[32]
44	Six														0.15		[32]
45	Six														0.34		[32]
46	Six														0.18		[32]
47	Five														0.39		[32]

Table 1 (*Continued*)

Compound	Coordination mode	ID$_{50}$ (μg/ml) against cancer cell line															Refs.
		HCV29T	A549	CACO	A498	EVSA-T	H226	IGROV	M19	MCF7	WiDr	Lemna aequinoctialis Welv	HeLa	CoLo 205	KB	P388	
48	Five														0.16		[32]
49	Five														0.35		[32]
50	Five														0.18		[32]
51			N.E.													N.E.	[33]
52			S.E.													S.E.	[33]
53			S.E.													S.E.	[33]
54			N.E.													N.E.	[33]
55			W.E.													S.E.	[33]
56			W.E.													S.E.	[33]
57			W.E.													S.E.	[33]
58			S.E.													S.E.	[33]
59			S.E.													S.E.	[33]
60			S.E.													S.E.	[33]
61			S.E.													S.E.	[33]
62			S.E.													S.E.	[33]
63	Six														0.21		[34]
64	Six														3.3		[34]
65	Six														0.14		[34]
66	Six														0.36		[34]
67	Six														0.2		[34]
68	Five		251.7–25.1												25.17–2.517		[35]
69	Six		0.52												0.520–0.052		[35]
70	Five		0.20–0.020												2–0.2		[36]

N.E.: non-effective, W.E.: weak effective and S.W.: strong effective; the *in vitro* cytotoxicity of complexes **24**, **25**, **27** and **28** is not reported in [25].

five-coordinated with trigonal bipyramidal geometries in solution (Scheme 1B). The complexes **10–14** displayed significant *in vitro* activities in comparison to *N*-maleoyl-protected tranexamic acid and the reference drugs (doxorubicin, cisplatin, 5-fluorouracil, methotrexate and etoposide) (Table 1). The nature (alkyl/phenyl/aryl) and size of covalently attached R′ groups of Sn(IV) atom and partition coefficients played a key role in the toxicities of the reported complexes. In complexes **10–14** the *in vitro* toxicity is enhanced by the bulkiness of the functional groups R′ attached to Sn(IV), against the tumor cell lines used. In case of complexes **10–14**, hydrophillicity increases with the bulkiness of R′ groups and boost up the bioactivity of these complexes. The increase in hydrophilicity of these complexes **10–14** is in the same order with their bioactivity. Furthermore, complexes **13** and **14** showed higher toxicity as compared to complexes **10–12** and the acid.

Four organotin(IV) compounds of the mono carboxylic acid 3-maleimidopropionic acid (LH) Scheme 2C; with formulae $(n\text{-Bu})_2Sn(L)_2$ (**15**), $\{[(n\text{-Bu})_2Sn(L)]_2O]\}_2$ (**16**), $Ph_3Sn(L)$ (**17**) and $CyHex_3Sn(L)$ (**18**) were prepared and studied for their biological activity [23]. The *in vitro* antiproliferative activity tests of complexes **15–18**, against five human tumor cell lines were measured (Table 1). Triorganotin(IV) compounds **17** and **18** were less toxic in comparison with diorganotin(IV) compounds **15** and **16** in the antiproliferative biological activity screenings. Whereas literature reveals that triorganotin R'_3SnX complexes show a higher activity than other classes like R'_2SnX_2 or $R'SnX_3$, while the tetraalkyltins R'_4Sn are very toxic to many species including humans, the higher activity of di-organotin compared to tri-organotin compounds **15–18** can be explained in terms of ligands toxicity and the degree of hydrophilicity of the complexes [23a]. In addition, diorganotin(IV) compounds can affect the cellular metabolism, while the triorganotin(IV) compounds mediate an exchange of hydroxyl ions across the mitochondrial membranes [23b–e].

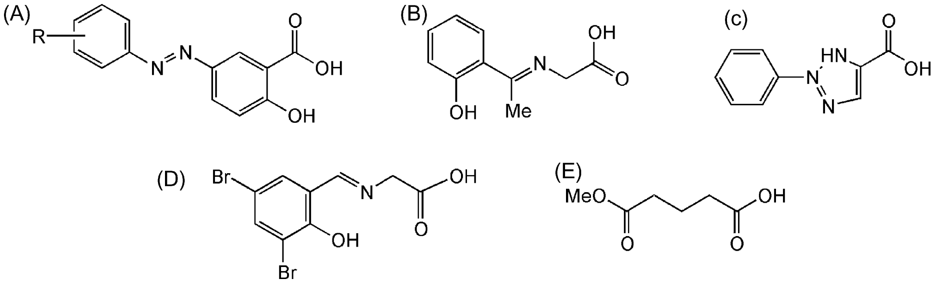
The di-*n*-butyl-, tricyclohexyl- and triphenyl-tin(IV) complexes with phthalimido-4-methylpentanoic acid (HPMPA) (Scheme 2D) of formulae $(PMPA)_2Sn(n\text{-Bu})_2$ (**19**), $[\{(PMPA)Sn(n\text{-Bu})_2\}_2O]_2$ (**20**), $[(C_6H_5)_3Sn(PMPA)]$ (**21**) and $[(c\text{-Hex})_3Sn(PMPA)]$ (**22**) (Scheme 1D, E, and G) [24] have been studied for their *in vitro*, antiproliferative activity ID_{50}. The triorganotin(IV) complexes **21** and **22** exhibit excellent antiproliferative behavior against *Lemna aequinoctialis Welv* and show the highest such activity towards the corresponding diorganotin complexes **19** and **20** (Table 1).

Reactions of 5-[(*E*)-2-aryl-1-diazenyl]-2-hydroxybenzoic acids (Scheme 3A) (LHH′, where the aryl group is an R-substituted phenyl ring such that for L^1HH': R = H; L^2HH': R = 2′-CH_3; L^3HH': R = 3′-CH_3; L^4HH': R = 4′-CH_3; L^5HH': R = 4-Cl; L^6HH': R = 4′-Br) with $(n\text{-Bu})_2SnO$ in a 1:1 molar ratio yielded complexes of composition $\{[n\text{-Bu}_2Sn(LH)]_2O\}_2$ (**23–28**) (Scheme 1G) [25]. The *in vitro* cytotoxicity tests on compounds **23** and **26** were performed (Table 1). The results clearly show that compounds **23** and **26** are more active *in vitro* than $n\text{-Bu}_2Sn(L^2H)_2$ (**29**). This encouraging cytotoxic effect may be predictive of *in vivo* anti-tumor activity of compounds **23** and **26** [25].

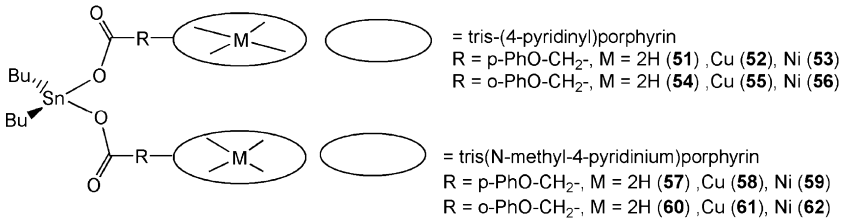
The *in vitro* biological activity against the human cell line A549 (lung adenocarcinoma) of *n*-butyltin complexes $[Sn(n\text{-}C_4H_9)_3\{OOCC_6H_3(NH_2)_2\text{-}3,4\}]_n$ (**30**), $[Sn(n\text{-}C_4H_9)_3\{OOCC_6H_3(NH_2)_2\text{-}3,4\}]$ (**31**), $[Sn(n\text{-}C_4H_9)_3\{OOCC_6H_4Nx{=}NC_6H_4N(CH_3)_2\text{-}4\}]$ (**32**) and $[Sn(C_6H_5)_3\{OOCC_6H_3(NH_2)_2\text{-}3,4\}]_n$ (**33**) have been investigated [27]. The complexes **30–33** are very active against A549 cells (Table 1) while their activity against this cell line decreases in the series **30** > **33** > **31** > **32**.

The *in vitro* cytotoxic activity of the compound derived from the reaction of potassium β-{[(*E*)-1-(2-hydroxypheny)ethylidene]amino}propionate (Scheme 3B) with $(n\text{-Bu})_2SnCl_2$ with formula $\{[n\text{-Bu}_2Sn(L^2H)]_2O\}_2$ (**34**) [28], against various cell lines has shown quite promising antiproliferative activity especially when compared with CDDP (cisplatin). The di-*n*-butyltin compound **34** is a centrosymmetric tetranuclear complex containing a planar Sn_4O_2 core in which two μ_3-oxo O-atoms connect an Sn_2O_2 ring to two exocyclic Sn-atoms. *In vitro* ID_{50} values of compound **34** were satisfactory. Compound **34** may be a suitable candidate for modifications in order to improve better cytotoxic and dissolution properties.

The cytotoxic activity against three human tumor cell lines HeLa (cervix tumor cell), CoLo 205 (colon carcinoma cell) and MCF-7 (mammary tumor cell) of the triorganotin 2-phenyl-1,2,3-triazole-4-carboxylates, with formulae $2\text{-PhC}_2N_3CO_2SnR_3$ (R = C_6H_5, **35**; *c*-C_6H_{11}, **36**; $C_6H_5C(CH_3)_2CH_2$, **37**) (Scheme 3C), have shown that these compounds displayed high *in vitro* cytotoxicities compared to



Scheme 3. Ligands used: (A) in complexes **23–29** (5-[(*E*)-2-(aryl)-1-diazenyl]-2-hydroxybenzoic acids (R = H, L^1HH'; 2′-CH_3, L^2HH'; 3′-CH_3 L^3HH'; 4′-CH_3, L^4HH'; 4-Cl, L^5HH'; 4′-Br, L^6HH'); (B) in complex **34** (β-{[(*E*)-1-(2-hydroxypheny)ethylidene]amino}propionatic acid); (C) in complexes **35–37** (2-phenyl-1,2,3-triazole-4-carboxylic acid); (D) in complex **38** (*N*-[(3,5-dibromo-2 hydroxyphenyl)methylene] valinic acid); (E) in complexes **39–41** (monomethyl glutaric acid).



Scheme 4. Molecular structure of complexes **51**–**62**.

cisplatin [29]. Compound **35** is polymeric with a trigonal bipyramidal configuration, and compound **37** shows a tetrahedral geometry. The activity of the compounds against the three human tumor cell lines decreased in the order **35** > **36** > **37** (Table 1).

The mixed organotin binuclear complex $Ph_3Sn(HL)\cdot Ph_2SnL$ (**38**) [L = *N*-[(3,5-dibromo-2 hydroxyphenyl)methylene]valinate (Scheme 3D)] [30] having two distinct types of carboxylate coordination mode (*trans*-O_2SnC_2N and *trans*-O_2SnC_3) in distorted trigonal bipyramidal geometries, has been tested *in vitro* for its cytotoxicity. The activity of complex **38** against three human tumor cell lines (see Table 1) shows that it is a very efficient cytostatic agent and its *in vitro* antiproliferative activities were higher than the ones of the clinically used cisplatin.

The antiproliferative activity of $\{[n\text{-}Bu_2(2\text{-}Ph\text{-}m\text{-}C_2B_{10}H_{11}\text{-}1\text{-}COO)Sn]_2O\}_2$ (**39**), $(1,2\text{-}C_2B_{10}H_{11}\text{-}9\text{-}COO)_2Sn\text{-}n\text{-}Bu_2$ (**40**), $\{[(2\text{-}CH_3\text{-}1,2\text{-}C_2B_{10}H_{10}\text{-}1\text{-}CH_2\text{-}COO)Bu_2Sn]_2O\}_2$ (**41**) complexes was experimentally investigated and reported [31]. All compounds tested exhibited stronger *in vitro* cytotoxic activity than that of cisplatin (Table 1).

The *in vitro* antiproliferative activity of a series of di- and tri-organotin(IV) complexes of monomethyl glutarate (Scheme 3E) of formulae R_2SnL_2 (**42**–**46**) and R_3SnL (**47**–**50**) (R = methyl, ethyl, phenyl and benzyl) have also been studied [32]. The ethyltin derivative **43** was less active against KB cell lines derived from epidermoid carcinoma than the other tin(IV) derivatives (**42**, **44**–**50**) (see Table 1).

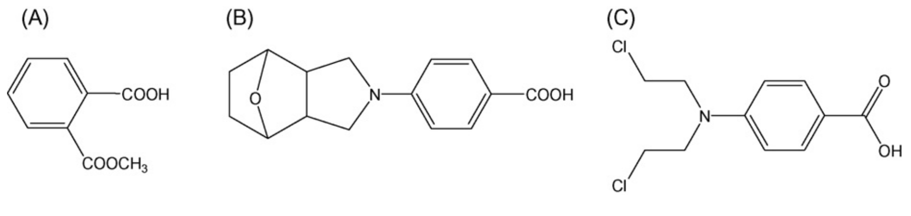
The water-insoluble and water-soluble organotin(IV) porphinate complexes **51**–**62** (Scheme 4) based on the tris-(4-pyridinyl)porphyrin and tris(*N*-methyl-1,4-pyridiniumyl)porphyrin moieties [33] were tested *in vitro* for their cytostatic activity. The antiproliferative activities of organotin(IV) porphinates is related to the water solubility of the compounds and the central ion in the porphyrin ring. The interaction between the water-soluble di-*n*-butyltin(IV) porphinate (**57** and **60**, Scheme 4) complexes and DNA has been investigated. The result shows that compounds **57** and **60** cause DNA hypochromism measured by A_{260}, a slight increase in the viscosity of the DNA, and an increase in the melting point of DNA by 2.9 and 1.6 °C, respectively, at $DNA_{base}/Drug_{Por}$ ratios of 60. Electrophoresis tests showed that the compounds cannot cleave the DNA. According to the electrophoresis test results and all the above results, the cytotoxic activity against P388 and A-549 tumor cells appears not to derive from the cleavage of DNA caused by the compounds but from the high affinity of compounds to DNA (Table 1).

Complexes of general formula R_2SnL_2 (R = methyl, ethyl, *n*-butyl, phenyl and benzyl groups) (Scheme 5A) (**63**–**67**) have also been tested against cell lines KB [34]. All complexes show significant cytostatic activities. In particular, the di-*n*-butyltin complex **65** is more active than the cisplatin. The complexes $[(p\text{-}C_8H_8NO_3\text{-}C_6H_4\text{-}COOSnBu_2)_2O]_2$ (**68**) [35], $(p\text{-}C_8H_8NO_3\text{-}C_6H_4\text{-}COOSnBu_2)$ (**69**) [35] and $\{\{4\text{-}[(ClCH_2CH_2)_2N]C_6H_4COOSnBu_2\}_2O\}_2$ (**70**) [36] derived from the reaction of di-*n*-butyltin(IV) oxide with the cantharidin analogue 4′-(7-oxabicyclo[2,2,1]-5-heptane-2,3-dicarboximide benzoic acid (Scheme 5B) and *p*-[*N*,*N*-bis(2-chloroethyl)amino]benzoic acid (Scheme 5C) were tested for cytotoxicity *in vitro* (Table 1). Compounds **68** and **69** exhibit high cytotoxicity again against P388, 91.8 and 28.3%, respectively, against HL-60 and 38.1 and 27.9% against A-549. The inhibitory rates of **70** are also included in Table 1.

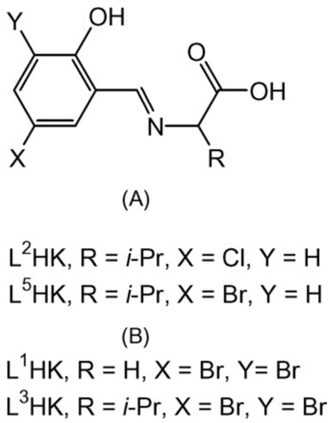
Table 1 compares the ID_{50} values against various cancer cell lines (μg/ml) of the organotin(IV) carboxylates with their coordination modes around tin(IV) atom.

2.1.2. α-Amino acids and their derivatives

Diorganotin(IV) complexes of *N*-(5-halosalicylidene)-α-amino acid (Scheme 6A), $R'_2Sn(5\text{-}X\text{-}2\text{-}OC_6H_3CH{=}NCH(i\text{-}Pr)COO)$ (where X = Cl and R′ = *n*-Bu (**71**), X = Cl and R′ = Ph (**72**), X = Cl and R′ = Cy (**73**) and X = Br and R′ = Ph (**74**), were tested in order to study the effects of the alkyl groups bound to tin on their cytotoxic activity [37]. The results of these assays and the reference drug, cisplatin, against the three human tumor cell lines HeLa, CoLo205 and MCF-7 show that these compounds are efficient cytostatic agents and their cytotoxic



Scheme 5. Ligands used: (A) in complexes **63**–**67** (monomethyl phthalic acid); (B) in complexes **68**–**69** (cantharidin analogue, 4′-(7-oxabicyclo [2,2,1]-5-heptane-2,3-dicarboximide) benzoic acid); (C) in complex **70** (*p*-[*N*,*N*-bis(2-chloroethyl)amino]benzoic acid).



Scheme 6. Ligands used: (A) in complexes **71**–**74** (*N*-(5-halosalicylidene)-α-amino acid); (B) **75**–**77** and **84** (*N*-(3,5-dibromosalicylidene)-α-amino acid).

activities were higher than those of the clinically widely used cisplatin, except compound **72** against HeLa. However, they were less active than the di-*n*-butyltin and diphenyltin complexes of (2-hydroxynaphthalidene)glycine (Table 2). As observed in previous studies, both the organotin moiety (R′) and the Ligand (L) appear to play an important role. The data reveal that dicyclohexyltin derivatives are the most active against the three cell lines and that the activity decreases in the order CyHex > *n*-Bu > Ph for the R′ group bound to tin.

The cytotoxic activity of diphenyltin(IV) complexes of *N*-(3,5-dibromosalicylidene)-α-amino acid (Scheme 6B) with formulae $Ph_2Sn(L^1)$ (**75**), $Ph_2Sn(L^3)$ (**76**), and $Ph_2Sn(L^3)\cdot Ph_2SnCl_2$ (**77**) against HeLa, CoLo205 and MCF-7 [38] shows that these compounds possess higher activity than those of the clinically widely used cisplatin. The data reveal that the binuclear adduct **77** is the more active against the three cell lines than the mononuclear complexes **75** and **76** (Table 2).

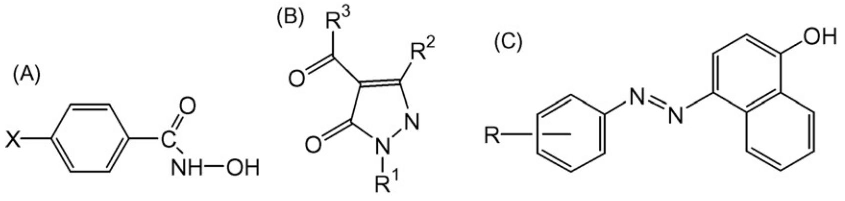
In vivo anti-tumor effects of a series of organotin(IV) derivatives of *N*-maleoylglycine (HL) (Scheme 2A, X = H) of formulae $R_2Sn(L)_2$ (**78–80**) or R_3SnL (R = methyl, *n*-butyl and benzyl group) (**81–83**) were also reported [39]. *In vivo* toxicity profiles in mice and anti-tumor activities in tumor-bearing (colon 26A) mice were obtained for the title organotin(IV) carboxylates **78–83**. At their maximum tolerated doses, no anti-tumor effect was observed for compounds Me_2SnL_2 (**78**), $(n\text{-}Bu)_2SnL_2$ (**79**), $(n\text{-}Bu)_3SnL$ (**82**) and Bz_3SnL (**83**); however, compounds Bz_2SnL_2 (**80**) and Me_3SnL (**81**) showed anti-tumor activity after a single dose administration. Compounds **80** and **81** showed *T*/*C* = 0.55 and 0.24, respectively, where *T*/*C* is the ratio of the tumour size of the treated mice to that of the control mice expressed as a percentage.

The *in vitro* antiproliferative activity of the mixed organotin binuclear complex $(HL)SnPh_3\cdot Ph_2SnL$ [L = 2-O-3,5-$Br_2C_6H_3CH{=}NCH(i\text{-}Pr)COO$ (Scheme 6B L^5HK)] (**84**) was

Table 2
In vitro inhibitory dose for the 50% of various cancer cell lines (ID_{50}) in μg/ml of the organotin(IV) compounds with amino acids **71**–**104**

Compound	Coordination mode	ID_{50} (μg/ml) against cancer cell line										Refs.
		A498	EVSA-T	H226	IGROV	M19	MCF7	WiDr	BGC 832	HeLa	CoLo 205	
71	Five						2.1			0.31	1.4	[37]
72							2.97			2.9	2.72	[37]
73							0.21			0.25	0.61	[37]
74	Five						2.68			0.77	3.15	[37]
75	Five						2.14			1.96	1.99	[38]
76							5.74			3.31	11.6	[38]
77	Five						0.28			0.16	1.1	[38]
84	Five						0.288			0.132	0.397	[40]
85									3.53–0.353	3.53–0.353		[41]
86									n.d.	3.93–0393		[41]
87									4.88–0.488	n.d.		[41]
88									n.d.	50.3–5.03		[41]
89									n.d.	n.d.		[41]
90									6.27–0.627	n.d.		[41]
91	Five									<6.73		[42]
92	Five									n.d.		[42]
93	Six									n.d.		[42]
94	Five									<6.22		[42]
95	Six									<8.14		[42]
96	Five									<5.72		[42]
97	Six									<7.64		[42]
98	Five	0.138	0.021	0.057	0.025	0.073	0.04	0.284				[43]
99	Five	0.196	0.064	0.133	0.072	0.182	0.093	0.424				[43]
100	Five	0.336	0.074	0.177	0.118	0.205	0.15	0.42				[43]
101	Five	0.155	0.056	0.108	0.09	0.15	0.096	0.295				[43]
102	Five	0.134	0.032	0.78	0.046	0.089	0.051	0.265				[43]
103	Five	0.332	0.084	0.105	0.199	0.139	0.478	0.332				[43]
104	Four	0.03	0.007	0.011	0.006	0.016	0.01	0.008				[43]

Complexes **78**–**83** have been tested only *in vivo* [39].



Scheme 7. Ligands used: (A) in complexes **105–136** (4-X-benzohydroxamic acids); (B) in complexes **137–138** (4-acylpyrazolon-5-one); (C) in complex **144** (5-[(*E*)-2-(phenyl)-1-diazenyl]quinolin-8-ol).

also investigated [40]. The IC_{50} values found were higher than cisplatin used in clinic (Table 2).

The *in vitro* antiproliferative activity of the organotin compounds $[(n\text{-}C_4H_9)_2Sn(cys)]$ (**85**), $[(C_6H_5)_2Sn(cys)]$ (**86**), $[(C_6H_5)_3Sn(Hcys)(H_2O)]$ (**87**), $\{[(CH_3)_2Sn(Kcys)_2]\cdot 2(H_2O)\}$ (**88**), $\{[(n\text{-}C_4H_9)_2Sn(Kcys)z]\cdot 2(H_2O)\}$ (**89**) and $\{[(C_6H_5)_2Sn(Kcys)_2]\cdot 2(H_2O)\}$ (**90**) (where Hcys is L-cysteine) against various human cell lines were evaluated [41]. Complexes (**85**), (**86**) and (**88**) exhibit high cell toxicity against Hela while complexes (**85**), (**87**) and (**90**) show high cell toxicity against BGC (Table 2). A further systematic investigation of the biological properties of these metal compounds was recommended focusing on their mutual significance for tumor induction of neoplastic growth [41].

Oganotin(IV) complexes with ethylsarcosine hydrochloride ligand (*N*-methylgycine ethyl ester hydrochloride, ES) of formulae $[Ph_3SnCl(ESH)]^+Cl^-$ (**91**), $[R_2SnCl_2(ESH)_n]^{n+}nCl^-$ (R = Me and *n* = 1, **92**; *n* = 2, **93**; R = Ph and *n* = 1, **94**; *n* = 2, **95**; R = *n*-Bu and *n* = 1, **96**; *n* = 2, **97** and ESH = protonated ethylsarcosine) [42] have been tested for their *in vitro* cytotoxicity against human adenocarcinoma (HeLa) cells and showed high antiproliferative activity, higher than that of cisplatin except of complexes **92** and **93** which are inactive.

New organotin(IV) derivatives with general formulae $(n\text{-}Bu)_2SnL$, where L is the dianion of glycyltyrosine (H_2L-1), glycyltryptophane (H_2L-2), leucyltyrosine (H_2L-3), leucylleucine (H_2L-4), valylvaline (H_2L-5) and alanylvaline (H_2L-6) and $Ph_3Sn(HL\text{-}7)$ (H_2L-7 = glycylleucinate) (**98–104**) [43] have been screened against several cancer cell lines. $Ph_3Sn(HL\text{-}7)$ displays the lowest ID_{50} values of the tin compounds tested, comparable to those of methotrexate and 5-fluorouracil. All the di-*n*-butyltin compounds exhibit lower *in vitro* antiproliferative activities than $Ph_3Sn(HL\text{-}7)$; although, they do provide significantly better activities than etoposide and cisplatin [43] (Table 2).

Table 2 compares 50% inhibitory dose (ID_{50}) against various cancer cell lines (μg/ml) of the organotin(IV) compounds of amino acids with their coordination modes around tin(IV) atom.

2.1.3. Oxamates

A series of diorganotin(IV) and dichlorotin(IV) derivatives of 4-X-benzohydroxamic acids (Scheme 7A), [HL1 (X = Cl) or HL2 (X = OCH_3)] formulated as $[R_2SnL_2]$ (R = Me, Et, *n*-Bu, Ph or Cl; L = L1 (**105–108**, **117**) or L2 (**109–112**, **118**), along with their corresponding mixed-ligand complexes $[R_2Sn(L1)(L2)]$ (**113–116**) have been tested *in vitro* for their antiproliferative

Table 3
Inhibition [%] of diorganotin(IV) complexes with oxamic acids [dose level of 10.00 μM] against human and mouse tumor cell lines

Complex	Leukemia HL-60	Nasophar carcinoma KB	Hepatocel carcinoma Bel-7402	Ovarian carcinoma Hela	Lymph carcinoma B	Lymph carcinoma T	Refs.
105	27.6	16.8	11.9		25.4	38.6	[44]
106	69.2	88.6	63.4	66.8	73.9	69.9	[44]
107	85.1	98.5	97.2	96.2	84.8	72.2	[44]
108	27.5	39.9	14.6	16.2	6.4		[44]
110	55.0	78.3	22.2	45.4	70.4	67.0	[44]
111	80.7	100.0	70.5	77.5	48.7		[44]
112	67.0	86.7	84.2	84.3	68.5		[44]
119	19.0	9.6	20.6		34.5	10.0	[45]
120	13.0	16.5	24.2	1.3	20.8	35.8	[45]
121	16.0	8.5	4.2		27.5	31.1	[45]
122	64.9	86.5	42.0	43.8	71.3	66.0	[45]
123	83.3	98.6	98.2	97.5	67.1	68.9	[45]
124	70.4	88.2	71.2	70.9	39.4	70.6	[45]
125	19.9	19.5	15.9	3.2	9.7	23.5	[45]
126	66.5	63.4	80.8	73.6	69.0	53.2	[45]
128		79.8	95.5				[45]
129		71.8	66.5				[45]
134		71.4	86.8				[45]
135		68.3	69.1				[45]

Complexes **109**, **113–118** and **130–133** have not been tested for their *in vitro* activity reports [44,45].

activities against a series of human tumor cell lines and on mouse tumor cell lines which, in some cases, are identical to, or even higher than that of cisplatin [44]. The selected results obtained are summarized in Table 3.

For the dialkyltin complexes, the activity increases with the length of the carbon chain of the alkyl ligand and is higher in the case of the chloro-substituted benzohydroxamato ligand. The following structure activity relationships could be recognized: (1) with regard to the R group: the activity decreases in the order *n*-Bu > Ph, Et > Me; (2) with regard to the X substituent of the hydroxamate aromatic ring: for the di-*n*-butyl and diethyltin(IV) derivatives, the activity tends to decrease as the electron-acceptor character of X decreases, that is, from the electron-withdrawing Cl substituent to the electron-donating OCH_3 group, whereas the opposite is observed for the diphenyltin(IV) complexes. Hence, the antiproliferative activity can be determined by a delicate balance of electronic effects of the ligands; however, the best combination is provided by the di-*n*-butyltin(IV) (R = *n*-Bu) complex with the chloro-substituted (X = Cl) hydroxamate ligand, namely $[n\text{-}Bu_2Sn(L1)_2]$ (**107**), which is more active than cisplatin [44]. Complex **107** was then selected for *in vivo* tests (administered orally) against the mouse H22 liver tumor and BGC-823 gastric tumor. The observed *in vivo* activities are close to those of carboplatin in the case of the liver tumor, whereas the gastric tumor complex **107** exhibits an activity close to that of cyclophosphamide. At 20 mg/kg dosage the inhibition range caused by compound **107** against the mouse H22 liver is 63.5% {(Inhibited tumor weight)/(tumor weight) [%]} while the corresponding value of carboplatin is 75.2%. The in vivo activity of compound **107** against BGC-823 gastric tumor is 61.6% at a dosage of 15 mg/kg while cyclophosphamide inhibit the gastric tumor by 71.6% at a dosage of 80 mg/kg. The $[n\text{-}Bu_2Sn(L1)_2]$ complex displays a high *in vivo* activity against H22 liver and BGC-823 gastric tumors, and has a relatively low toxicity. The acute toxicity tests of those organotin complexes reveal LD_{50} values higher than those of cisplatin, indicating a lower toxicity of the former complexes [44].

The *in vitro* antiproliferative activity of diorganotin(IV) complexes with 4-X-benzohydroxamic acid [X = NH_2 (HL^1), NO_2 (HL^2) or F (HL^3)] (Scheme 7A) formulated as $[R_2SnL_2]$ (L = L^1, R = Me (**119**), Et (**120**), L = L^2, R = Me (**121**), Et (**122**), *n*-Bu (**123**), L = L^1, R = *n*-Bu (**124**), Ph (**125**), L = L^2, R = Ph (**126**), L = L^3, R = Me (**127**), *n*-Bu (**128**), Ph (**129**)) and $[R_2Sn(L)]_2O$ (L = L^1, R = Me (**130**), *n*-Bu (**131**), Ph (**132**), L = L^3, R = Me (**133**), *n*-Bu (**134**), Ph (**135**)) were tested against various human and mouse tumor cell lines [45] (see Table 3). In a few of these complexes the IC_{50} values were identical to or even higher than that of cisplatin. For the mononuclear dialkyltin compounds, the activity generally increases with the length of the carbon chain of the alkyl ligand, being higher for the complexes with benzohydroxamato ligands bearing an electron-acceptor substituent (X = NO_2 or F). No structure–activity relationship based on the Hammett's σ_p constant, or related ones, has been recognized.

2.1.4. Miscellaneous

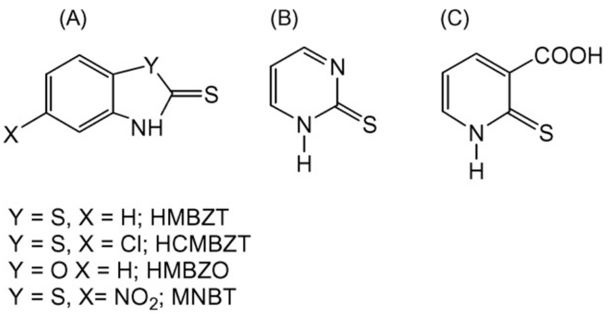
Two 4-acylpyrazolon-5-ato-dihalotin(IV) complexes, $[Q_2SnCl_2]$, (HQ^{Bn} = 1,2-dihydro-3-methyl-1-phenyl-4-(2-phenylacetyl)pyrazol-5-one (**136**) and $HQ^{CF3,py}$ = (4-(2,2,2-trifluoroacetyl)-1,2-dihydro-3-methyl-1-(pyridin-2-yl)pyrazol-5-one (**137**) (Scheme 7B), were tested for their *in vitro* antiproliferative activity against three human melanoma cell lines and two melanoma cell clones [46]. The results showed dose-dependent decrease of cell proliferation in all cell lines for both complexes **136** and **137**. The activity correlates with the nature of the substituent on position **1** of pyrazole, decreasing in the order pyridyl > phenyl ≫ methyl (Table 4).

The *in vitro* antiproliferative activity of new triorganotin compounds of formulae R_3SnL (L = 5-hydroxy-1,4-naphthoquinone and R = Ph (**138**), *n*-Bu (**139**), L = 2-hydroxy-1,4-naphthoquinone and R = Ph (**140**) and $(R_3Sn)_2L$ (L = 5,8-dihydroxy-1,4-naphthoquinone and R = Ph (**141**) or *n*-Bu (**142**) have been reported [47]. The compounds were tested for their cytotoxicity against five human tumor cell lines and one non-tumor human cell line (Table 4). Most of the compounds were toxic not only against tumor cells, but also against the non-tumor human MRC5 cells. The compounds were tested in the range of concentrations from 10^{-8} to 10^{-4} M and they were continuously present in the culture for 48 h. Regarding the profile of cytotoxicity, a dose-dependent response was found for all cell lines except PC3 (prostate carcinoma cell line), i.e., cytotoxicity of compound increased with concentration, whereas in PC3 cell line the highest response was obtained with the smallest concentration of the compounds. This is quite unusual but the same response was obtained during the second experimentation with PC3 cells. Also the triphenyl and tri-*n*-butyl derivatives

Table 4
In vitro inhibitory dose for the 50% of various cancer cell lines (ID_{50}) in μg/ml of the organotin(IV) compounds **136–143**

Compound	Coordination mode	ID_{50} (μg/ml) against cancer cell line								Refs.
		JR8	SK-MEL	MEL-501	K562	MCF-7	HeLa	Hs294T	MRC-5	
136	Six	235.19	117.6	243.3						[46]
137	Six	40.55	40.55	40.55						[46]
138					0.047	0.62	0.31	0.303	0.00062	[47]
139					0.254	9.24	2.16	10.8	0.000185	[47]
140					0.152	0.063	5.16	0.146	0.0043	[47]
141					0.337	1.3	0.036	0.524	0.0073	[47]
142					>76.8	>76.8	0.038	18.88	7.5	[47]

The ID_{50} values found against A498, EVSA-T, H226, IGROV, M19, MCF-7 and WIDR for **143** are 16.902, 8.677, 8.950, 4.774, 10.104, 7.332 and 8.441 μg/ml, respectively.



Scheme 8. Ligands used: (A) in complexes **145**–**150** and **157**–**159** (heterocyclic thioamides); (B) in complexes **151**–**154** (2-mercapto-pyrimidine); (C) in complex **156** (2-mercapto-nicotinic acid); (D) in complex **163** (lupinylsulfide hydrochloride).

of naphthazarine are approximately 100-fold more potent than doxorubicin against HeLa cells [47].

The *in vitro* cytotoxicity against seven human tumor cell lines of the complex $Ph_2Sn(L^1)_2\ (CH_3)_2CO$ (**143**), $HL^1 = \{5$-[(*E*)-2-(phenyl)-1-diazenyl]quinolin-8-ol (Scheme 7C) [48] was compared with those of $Ph_2Sn(Ox)_2$ (Ox = deprotonated quinolin-8-ol) and cisplatin (See Table 4). Compound **143** is less active than both $Ph_2Sn(Ox)_2$ and cisplatin.

Table 4 compares the 50% inhibitory dose (ID_{50}) against various cancer cell lines (μg/ml) of the organotin(IV) compounds **136**–**143** with their coordination modes around tin(IV) atom.

2.2. Organotin(IV) complexes with sulfur donor ligands

2.2.1. Thione/thiol

The influence on the peroxidation of oleic acid [3,5,49] organotin(IV) complexes with heterocyclic thioamides: 2-mercapto-benzothiazole (HMBZT), 5-chloro-2-mercapto-benzothiazole (HCMBZT) and 2-mercapto-benzoxazole (HMBZO) (Scheme 8A) of formulae $[(C_6H_5)_3Sn(MBZT)]$ (**144**), $[(C_6H_5)_3Sn(CMBZT)]$ (**146**) and $[(C_6H_5)_2Sn(CMBZT)_2]$ (**147**), together with the already known $[(C_6H_5)_3Sn(MBZO)]$ (**145**), $[(n\text{-}C_4H_9)_2Sn(CMBZT)_2]$ (**148**) and $[(CH_3)_2Sn(CMBZT)_2]$ (**149**) were studied. Compounds **144**–**149** were tested for *in vitro* cytotoxicity against leiomyosarcoma cells (Table 5). Among tri-organotin complexes **144**–**146** complex **146** shows the higher cytotoxic activity, while among diorganotin **147**–**149** derivatives complex **147** is the most active. Between tri- and di-organotin complexes, compound **147** is more cytotoxic than **146**. The influence of complexes **146**–**149** upon peroxidation of oleic acid showed that the formation of reactive radicals caused the initiation of the chain radical oxidation of the substrate. The influence of complexes **144**–**149** upon the catalytic peroxidation of linoleic acid by the enzyme Lipoxygenase (LOX) was also studied and compared to those of cisplatin. Complexes **144**–**149** are inhibit strongly the peroxidation of linoleic acid by the enzyme lipoxygenase with the same rate that these compounds promote the peroxidation of oleic acid non-enzymatically.

The organotin(IV) complexes of the heterocyclic thioamide 2-mercapto-pyrimidine (**PMTH**) (Scheme 8B), of formulae $[(CH_3)_2Sn(PMT)_2]$ (**150**), $[(n\text{-}C_4H_9)_2Sn(PMT)_2]$ (**151**), $[(C_6H_5)_2Sn(PMT)_2]$ (**152**) and $[(C_6H_5)_3Sn(PMT)]$ (**153**), were used to study their cytotoxicity against sarcoma cancer cells [50]. These results show the antiproliferative effects for complexes **150**–**153** (Table 5).

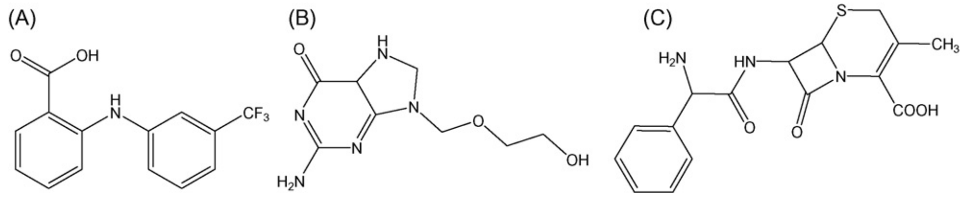
The *in vitro* cytotoxicity against the cancer cell line of sarcoma cells (mesenchymal tissue) from the Wistar rat, polycyclic aromatic hydrocarbons (PAH, benzo[*a*]pyrene) carcinogenesis of the organotin(IV) complexes with the heterocyclic thioamides; 2-mercapto-benzothiazole (Hmbzt), and 2-mercapto-nicotinic acid (H_2MNA) (Scheme 8C) of formulae $[(n\text{-}C_4H_9)_2Sn(MBZT)_2]$ (**154**) and $\{[(C_6H_5)_3Sn]_2(MNA)\cdot[(CH_3)_2CO]\}$ (**155**) have been studied [3,4]. Compound (**155**) exhibits a strong cytotoxic activity, stronger than the corresponding one of cisplatin, while complex (**154**) show less cytotoxic activity (Table 5). The very strong cytotoxic activity exhibited by complex **155** is most probably due to the availability of the free coordination positions around tin(IV) atoms since both Sn(IV) are five-coordinated with trigonal bipyramidal geometry [3,4]. One additional reason for this behavior should be the presence of two tin(IV) atoms in this compound **155**.

The *in vitro* antiproliferative biological activity of the diorganotin(IV) complexes with 2-mercapto-6-nitrobenzothiazole (MNBT) (Scheme 8A) of formulae $[Ph_2SnCl(MNBT)]$ (**156**), $[(PhCH_2)_2Sn(MNBT)_2]$ (**157**) and $[(n\text{-}Bu)_2Sn(MNBT)_2]$ (**158**) [51] towards culture cells of Ehrlich ascites carcinoma showed inhibition rates of 78%, 79% and 86%, respectively. The *n*-butyl derivative of **158** was the most active. Also, complexes **156**, **157** and **158** demonstrate a biological activity against Ehrlich ascites tumor comparable with that of cisplatin.

The complexes di-*n*-butyldi(2-pyridinethiolato-*N*-oxide) tin(IV) (**159**), diphenyldi(2-pyridinethiolato-*N*-oxide)tin(IV) (**160**) and dibenzyldi(2-pyridinethiolato-*N*-oxide)tin(IV) (**161**) were evaluated for their *in vitro* cytotoxicity [52] (Table 5). The screening results indicate that the activities of complexes **159**, **160** and **161** are greater than cisplatin and comparable to diorganotin(IV) pyridine-2,6-dicarboxylates, but they are all less than those of the fluorinated aromatic carboxylates and polyoxaalkyltin compounds [52]. Complex **159**, the most active among the three complexes, is comparable to or slightly better than doxorubicin against MCF-7 and tin fluorine-substituted aromatic carboxylates against WiDr [52].

Table 5
Cytostatic activity of complexes **144–195** as 50% inhibitory dose (ID_{50}) μg/ml values against various cancer cell lines

Compound	Leiomiosarcoma	MCF-7	WiDr	EVSA-T	IGROV	M266	A-172	DBTRG. 05MG	U-87MG	CAS-1	A-549	L929	143	Vero	BSC-1	K562	HeLa	Ref.
Cisplatin	1.2–1.5											2.8				4.9	0.433	[3,5,59]
Carboplatin												>50				12.2	38.7	[59]
Oxaplatin												0.3				0.3	33.2	[59]
144	0.77–1.55																	[3,5]
145	0.65–1.50																	[5,49]
146	0.28–044																	[5,49]
147	1.01–1.51																	[5,49]
148	0.38–0.51																	[5,49]
149	2.9–4,36																	[5,49]
150	7.4–22.3																	[50]
151	0.30																	[50]
152	0.5–1.0																	[50]
153	0.05																	[50]
154	79																	[3]
155	0.005																	[3]
159		0.056	0.209															[52]
160		0.296	1.185															[52]
161		0.299	0.930															[52]
162							5.0	5.0	10.5	3.0								[53]
163		0.035	0.020	0.023	0.031	0.037												[54]
164		0.033	0.019	0.022	0.029	0.036												[54]
165		0.030	0.017	0.022	0.027	0.034												[54]
166		0.040	0.025	0.031	0.036	0.045												[54]
167		0.046	0.035	0.038	0.042	0.053												[54]
168		0.028	0.032	0.041	0.035	0.030												[54]
169		0.020	0.019	0.016	0.030	0.024												[54]
170		0.008	0.034	0.014	0.011	0.016												[54]
171		0.016	0.016	0.023	0.014	0.029												[54]
172		0.013	0.021	0.026	0.012	0.018												[54]
174											0.24							[55]
175											0.35							[55]
177												40	20	50	80			[56]
178												45	10	45	20			[56]
179												40	35	50	75			[56]
180												50	30	60	80			[56]
181												40	8	55	60			[56]
187												>50				22.7	42.3	[59]
188												42.2				18.4	37.0	[59]
189												>50				22.4	38.8	[59]
190												34.0				17.1	32.5	[59]
191												33.3				17.8	34.7	[59]
192												0.6				0.2	4.7	[59]
193												0.6				0.2	3.7	[59]
194												1.0				0.3	4.3	[59]
195											2.22							[60]



Scheme 9. Ligands used: (A) in complexes **174–176** (flufenamic acid); (B) in complexes **177–182** (acyclovir); (A) in complexes **183–186** (deacetoxycephalo-sporin-antibiotic cephalexin).

Malignant gliomas are the most common primary brain tumors in humans [53]. However, poor response to conventional therapeutic approaches, including chemotherapy, leads invariably to disease recurrence and progression [53]. The organotin derivative triethyltin(IV) lupinylsulfide hydrochloride with formula Et_3SnL (**162**) (IST-FS 29) (HL = lupinylsulfide hydrochloride, shown in Scheme 7D) was identified and developed as potential antiproliferative agent in human cancer cell lines. Compound **162** also appeared an eligible candidate for the treatment of glioblastoma cells. The experiments were designed to explore the *in vitro* effects of IST-FS 29 (**162**) on four human glioblastoma cell lines (see Table 5).

2.2.2. Dithiocarbamates

Ten organotin(IV) derivatives with dithiocarbamates of formulae $(4\text{-}NCC_6H_4CH_2)_2Sn(S_2CNEt_2)_2$ (**163**), $(4\text{-}NCC_6H_4CH_2)_2Sn(S_2CNBz_2)_2$ (**164**), $(4\text{-}NCC_6H_4CH_2)_2Sn[S_2CN(CH_2CH_2)_2NCH_3]_2$ (**165**), $(2\text{-}ClC_6H_4CH_2)_2Sn(S_2CNEt_2)_2$ (**166**), $(2\text{-}ClC_6H_4CH_2)_2Sn(S_2CNBz_2)_2$ (**167**), $(4\text{-}NCC_6H_4CH_2)_2Sn(Cl)S_2CNEt_2$ (**168**), $(4\text{-}NCC_6H_4CH_2)_2Sn(Cl)S_2CNBz_2$ (**169**), $(4\text{-}NCC_6H_4CH_2)_2Sn(Cl)S_2CN(CH_2CH_2)_2NCH_3$ (**170**), $(2\text{-}ClC_6H_4CH_2)_2Sn(Cl)S_2CNEt_2$ (**171**) and $(2\text{-}ClC_6H_4CH_2)_2Sn(Cl)S_2CNBz_2$ (**172**) [54] were tested *in vitro* for cytotoxicity against five human tumor cell lines (Table 5). The inhibition rates (%) against culture cells of Ehrlich ascites carcinoma are uniformly in the range 50–70%, usually at the upper end, indicating that these complexes have a significant biological activity to Ehrlich ascites carcinoma compared with that of cisplatin (55%). Complex **170** is the most active. The *in vitro* cytotoxicity of the complexes $(ArCH_2)_2Sn(Cl)S_2CNR_2$ is stronger than that of complexes $(ArCH_2)_2Sn(S_2CNR_2)_2$. A possible reason is that $(ArCH_2)_2Sn(Cl)S_2CNR_2$ can hydrolyze more easily and release $(ArCH_2)_2Sn^{2+}$ in comparison with $(ArCH_2)_2Sn(S_2CNR_2)_2$.

2.3. Organotin(IV) complexes with ligands used as drugs

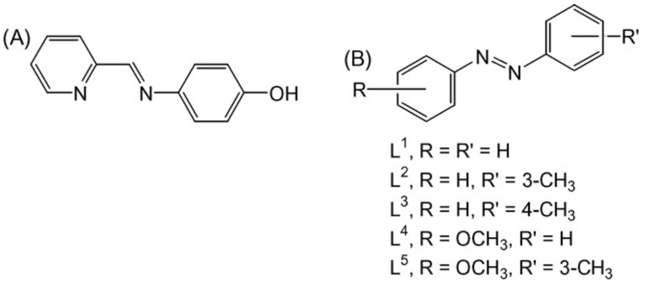
The organotin flufenamates $[Me_2(flu)SnOSn(flu)Me_2]_2$ (**173**), $[Bu_2(flu)SnOSn(flu)Bu_2]_2$ (**174**) and $[Bu_2Sn(flu)_2]$ (**175**) (Flu = flufenamic acid Scheme 9A) [55] were evaluated for antiproliferative activity *in vitro*. Among the compounds tested **174** and **175** exhibited high cytotoxic activity against the cancer cell line A549 (Table 5).

Organotin polyamine ethers containing acyclovir (Scheme 9B) in their backbone of formulae $[R_2SnL]_n$ (R = Me (**176**), Et (**177**), *n*-Bu (**178**), *n*-Oc (**179**), Ph (**180**) and Cy (**181**)) [56] were tested for their inhibition towards a number of cancer cell lines (Table 5). BSC-1 cells are African green monkey kidney epithelial cells as are vero cells but from a different strain. Both are transformed to behave as cancer cells. L929 cells are transformed mouse fibroblast cells, and 143 cells are human fibroblast bone osteosarcoma cells. There is a difference in the growth inhibition (GI) values of cancer cell lines. The order of inhibition is di-*n*-butyltin > diphenyltin > diethyltin > di-*n*-octyltin > dicyclohexyltin > acyclovir.

The biological activity of dialkyltin(IV) and trialkyltin(IV) complexes of the deacetoxycephalo-sporin-antibiotic cephalexin [7-(D-2-amino-2-phenylacetamido)-3-methyl-3-cephem-4-carboxylic acid] (Hceph) (Scheme 9C) with formulae $R_2Sn(ceph)_2$ (R = Me (**182**), *n*-Bu (**183**)) and $R_3Sn(ceph)$ (R = Me (**184**), *n*-Bu (**185**)) was evaluated [57]. The cytotoxic activity of organotin(IV) cephalexinate derivatives has been tested using two different chromosome-staining techniques Giemsa and CMA_3, towards spermatocyte chromosomes of the mussel Brachidontes pharaonis (Mollusca: Bivalvia). Colchicinizedlike mitoses (c-mitoses) on slides obtained from animals exposed to organotin(IV) cephalexinate compounds, demonstrated the high mitotic spindle-inhibiting potentiality of these chemicals. Moreover, structural damages such as “chromosome achromatic lesions”, “chromosome breakages” and “chromosome fragments” have been identified through a comparative analysis of spermatocyte chromosomes from untreated specimens (negative controls) and specimens treated with the organotin(IV) complexes.

2.4. Miscellaneous

The $Et_2SnCl_2{\cdot}L$ [L = *N*-(2-pyridylmethylene)-4-toluidine (OTC) (Scheme 10A)] (**186**) has been subjected to investigation



Scheme 10. Ligands used: (A) in complex **187** (*N*-(2-pyridylmethylene)-4-toluidine); (B) in complexes **188–195** (schiff bases derived from salicylaldehyde and aminopyridines).

for its cytotoxic effect in mouse bone marrow cells (BMCs) and human peripheral blood lymphocyte cells (HPBLs) [58]. The Sn–N bond in OTC is 2.46 Å which is greater than 2.39 Å and consequently an easier formation of tin–DNA complex following the Sn–N cleavage is expected [58] in this case, according to Huber and Saxena [8]. The present data indicate that OTC induced significant delay in cell kinetics and sister chromatid exchanges (SCEs) in both BMCs and HPBLs, whereas, induction of chromosome aberrations was found only in HPBLs. The presence of buthionine sulfoximine (BSO) modulated cellular sensitivity towards OTC in both cell systems. It may be inferred that the OTC could bind on DNA more easily owing to its structural advantage and this may explain the induction of DNA damage and the delay in cell proliferation. Since the cytotoxic effect of OTC is more in glutathione depleted cells, the concentration of OTC may be reduced to get an anti-tumor effect in GSH-depleted cells and thus minimizes its toxic side-effect.

Organotin(IV) complexes with Schiff bases derived from salicylaldehyde and aminopyridines (Scheme 10B) of general formulae $Me_2SnCl_2 \cdot 2L$ ($L = L^1$ (**187**), L^2 (**188**), L^3 (**189**)) or $Me_2SnCl_2 \cdot L$ ($L = L^4$ (**190**), L^5 (**191**)) and ionic compounds $[H_2NpyN\text{–}H^+]_2\ [Ph_2SnCl_4]^{2-}$ ($H_2NpyN\text{–}H^+$ = aminopyridines used for the preparation of Schiff bases L^1–L^5) (**192–194**), respectively, were screened against the human myleogenous leukaemia K562, cervix (HeLa) and murine L929 fibrosarcoma cell lines and the results were compared with those of the anticancer drugs, cisplatin, carboplatin and oxaliplatin (Table 5) [59]. The free Schiff bases (L^1–L^5) and their Me_2SnCl_2 complexes have no cytotoxic activity against any of the three tumor cell lines used. The most cytotoxically active compounds among all the compounds studied were the ionic compounds **192–194** (Table 5) whose ID_{50} values ranged between 0.2 and 4.7 μg/ml. The cytotoxicity of the ionic compounds is stronger than those of the reference standards, cisplatin (ID_{50} ranged between 2.8 and 28.3 μg/ml) and carboplatin (ID_{50} ranged between 12.2 and >50 μg/ml) and even higher than that of oxaliplatin (ID_{50} is 33.2 μg/ml) against the HeLa cell lines. Further, the IC_{50} values of the ionic compounds **192–194** against the K562 cell line, i.e., 0.2–0.3 μg/ml, are very similar to that of oxaliplatin (ID_{50} = 0.3 μg/ml) against the same cell lines.

The tin(IV) complex $[Sn_2(CH_2CH_2CN)_6]$ (**195**), where there are two independent molecules in the crystal structure which both adopt distorted eclipsed conformation, show modest cytotoxic activity against A549 (lung adenocarcinoma) and HSMC (vascular human smooth muscle cells) isolated from human aortas, cells [60] (Table 5). The antiproliferative activity of this compound is lower than the most active organotin(IV) complexes tested.

3. Concluding remarks

Organotins exhibit significant *in vitro* antiproliferative activity which, in some cases, is higher than the corresponding activity of cisplatin or other drugs used for clinical treatment in cancer chemotherapy. Also organotin complexes have been tested *in vivo* with encouraging results. Although the mechanism of this antiproliferative activity is not well established, it has been suggested [22] that organotin(IV) compounds wield antiproliferative effects through binding to thiol groups of the proteins hence differing from the behavior of several cytotoxic complexes of other metals, e.g., Pt, which interacts with DNA [61,62]. However, the cause of enhancement in cytotoxicity and exact mechanism of action of such organotin(IV) complexes is still a question to be answered.

According to Huber and Saxena [8] the structures of all organotin antiproliferative active compounds are characterized by (i) the availability of coordination positions at Sn and (ii) the occurrence of relatively stable ligand–Sn bonds, e.g., Sn–N and Sn–S and their slow hydrolytic decomposition. Nevertheless, in case of organotin–thioamide complexes studied [5], the highest cytotoxic activity is shown by the six-coordinated $Ph_2Sn(cmbzt)_2$ complex (**147**) which has less free coordination position, while its Sn–S and Sn–N bond distances are shorter than those found in tri-organotin complexes. Organotin(IV)–thioamide complexes also inhibit strongly the peroxidation of linoleic acid by the enzyme lipoxygenase (LOX) while a direct relationship between the LOX activity inhibition and the cytotoxic activity of these complexes exists [5]. In this case the free radicals formed from the reaction between organotin complexes and the peroxyl radicals derived from the oxidation of the acid, may explain the LOX inhibition caused by these complexes. EPR studies show

Table 6
The most active organotin compound between **1** and **195** against various common cancerous cell lines

Compound	Cancerous cell line	ID_{50} (μg/ml)	Coordination mode	Ligand	Total number of compounds tested	Cisplatin ID_{50} (μg/ml)
2	HCV29T	0.004	Four	Carboxylic acid	4	0.7[a]
70	A549	0.20–0.020	Five	Carboxylic acid	24	3.3[a]
104	A498	0.03	Four	Amino acid	24	2.253
104	EVSA-T	0.007	Four	Amino acid	37	0.422
14	H226	0.005	Five	Carboxylic acid	27	3.269
104	IGROV	0.006	Four	Amino acid	28	0.169
104	M19	0.016	Four	Amino acid	17	0.558
14	MCF7	0.008	Five	Carboxylic acid	40	0.699
104	WiDr	0.008	Four	Amino acid	40	0.697
35	HeLa	0.005	Five	Carboxylic acid	41	0.433
155	Leiomiosarcoma	0.005	Five	Thioamide	12	1.2–1.5

[a] ID_{50} values reported in Ref. [63].

that the spin electron of the radicals is located onto the ligands of the complexes, and therefore R_2SnL_2 complexes are expected to exhibit stronger inhibitory activity towards LOX enzyme, thus possessing better cytotoxic activity, although they have no coordination position available than the corresponding triorganotins [5]. The strong cytotoxic activity ($IC_{50} = 0.005\ \mu g/ml$), stronger than the corresponding of cisplatin, found in case of $\{[(C_6H_5)_3Sn]_2(MNA)\cdot[(CH_3)_2CO]\}$ (**155**), on the other hand, is most probably due to the availability of the free coordination positions around tin(IV) atoms since both Sn(IV) are five-coordinated with trigonal bipyramidal geometry [3,4] and to the presence of two tin(IV) atoms as in **155**.

Therefore, the organotin moiety (R′), the ligand (L) and the number of tin atoms and the number of free coordination positions offered appear to play an important role in their antiproliferative action of the compounds.

Table 6 shows the most active organotin compound among **1–195** for each cancerous cell line studied.

All these compounds posses better antiproliferative properties than cisplatin. Finally the most active compounds were four- or five-coordinated with free coordination positions around Sn(VI), confirming the above conclusion.

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