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Review article

Anti-proliferative and antitumor activity of organotin(IV) compounds. An overview of the last decade and future perspectives

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ABSTRACT

Organotins(IV) exhibit significant *in vitro* anti-proliferative activity, while the *in vivo* tests are encouraging. The recent reports on the anti-proliferative activity of organotin(IV) compounds are summarized in this review. The period covered by this work goes back to 2009 until late 2018, while the earlier ones, are included over the previous review of our group published by S.K. Hadjikakou, N. Hadjiliadis, in Coord Chem Rev, 253 (2009) 235–249. During the last decade (2009–2018), > 300 organotin(IV) derivatives with oxygen-donor ligands, such as carboxylic acids, amino-acids, Non Steroidal Anti-inflammatory Drugs (NSAIDs), biological active derivatives or natural products, organotins(IV) with sulfur containing ligands such as thiones, thiosemicarbazones, dithiocarbamates, organotin(IV) compounds of oximes and organotins(IV) with amines or semicarbazones were screened for their anti-proliferative effect against various cancer cell lines and their results are included in numerous reports over this period. Although much work has been carried out on organotin(IV) derivatives with O-donor ligands, however significant fewer reports are found on organotins(IV) with oximes as ligands.

1. Introduction

The application of the platinum metallodrugs, such as cisplatin, in cancer chemotherapy, stimulated the investigation of the biological activity of others active non-platinum compounds [1]. Compounds of non platinum metals, *e.g.* organotins(IV), may possess lower toxicity, better excretion from body and fewer side-effects than platinum drugs [1]. The most important feature of organotin(IV) compounds is that cells do not develop resistance against them, and may show lower toxicity compared to cisplatin analogues [1,2].

Marcel Gielen initiated the search with the anticancer activity of organotin(IV) compounds at the '80s, and his research results have been reviewed earlier [3–5]. Much of his work was also patented [6–10]. The antitumor activity of the organotin(IV) metallodrugs was, initially, tested against murine leukemia cell lines [1].

Since then, many research groups were involved in the development of organotin(IV) metallotherapeutics. These works were reviewed later in the decade of 2000 [11]. Meta-analysis of these researches shows that the biological activity of organotin(IV) compounds depends on the type and the number of R group (R = Bu, Ph, Et, Me), decreasing according to the following order: n-Bu > Ph and Et > Me, while di-n-butyltin > diphenyltin > diethyltin > dinoctyltin > dicyclohexyltin > acyclovir [11,12]. This might be due to the relative lipophilicity among organotin(IV) moieties. Gielen has also shown that the R groups play more important role on the anti-cancer activity of several organotin(IV) compounds against WiDr (colon carcinoma) and MCF-7 (breast carcinoma) cells, than their ligands [13,14].

Moreover, tri-organotins(IV) exhibit better cytotoxic activity than di-organotins(IV) [11]. This may be attributed in the free coordination position in case of tri-organotin(IV) compounds [15]. The low activity of tri-organotins(IV) is attributed to their disproportionation reaction in solution to afford R_4Sn and $R_2Sn(IV)^{2+}$ species [15]. This may also occur through the intervention of enzymes such as aromatase an enzyme which is involved in the biosynthesis of estrogens [16]. The latter could explain the selectivity exhibited by tri-organotins(IV) against MCF-7 cells (hormone depended) than MDA-MB 231 (hormone independent) [17,18].

Organotin(IV) carboxylates usually present the highest cytotoxic activity against human tumor cell lines in contrast to organotin(IV) compounds with thiolato or dithiocarbamato ligands [11].

Structure Activity Relationship (SAR) of organotin(IV) compounds has demonstrated that all active compounds are characterized by: (i) the availability of coordination positions on Sn, (ii) the occurrence of relatively stable ligand–Sn bonds, *e.g.* Sn—N and Sn—S thione and (iii) their slow hydrolytic decomposition [19]. Other studies show that organotin(IV) compounds inhibit the cells macromolecules (DNA or

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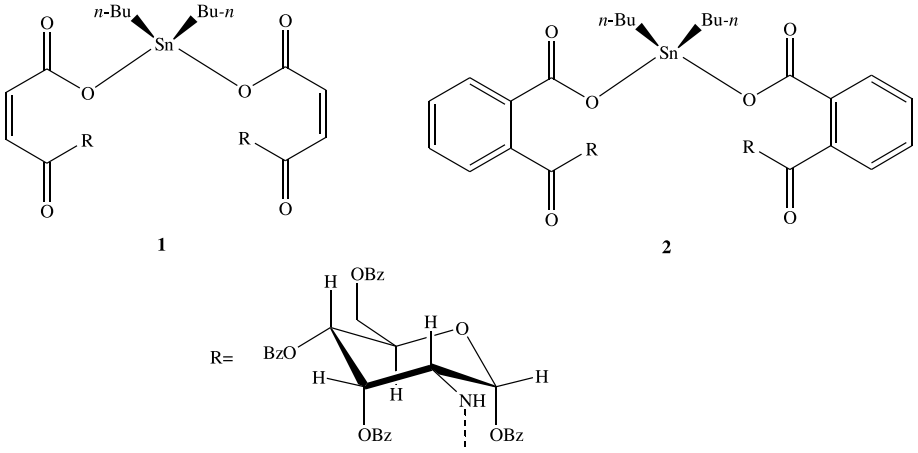


Scheme 1. The formulae of compounds **1–2** [20].

proteins) and the energy metabolism in mitochondria, while they interact with cell membranes increasing the Ca^{2+} concentration in cytoplasm [16]. Organotins(IV) cause cell death by apoptosis [1,2,12].

Within this review, the advances in the study of the anticancer activity of organotin(IV) compounds during the last ten years are being documented. The antiproliferative activity of organotins(IV) is also compared with the corresponding cisplatin: a clinically used anticancer drug. The needs for the development of new organotin(IV) metallotherapeutics which overcome cisplatin-resistant cancer cells, is emphasized in this review article.

2. Organotin(IV) compounds of oxygen donor ligands

2.1. Organotin(IV) compounds of carboxylates ligands

Two di-*n*-butyltin(IV) oxide derivatives (**1–2**) with the ligands L^1 = cis-4-[N-(1′,3′,4′,6′-tetra-O-benzoyl-2-deoxy-glucopyranosyl) imido]-4-oxo-2-butenoic acid and L^2 = o-[N-(1′,3′,4′,6′-tetra-O-benzoyl-2-deoxy-glucopyranosyl)carbamoyl]benzoic acid (Scheme 1 [20]) were characterized by IR, NMR and MS. The tumor inhibition activity of these compounds was tested against murine leukemia (P388), human leukemia (HL-60), human lung epithelial (A-549) and human hepatocellular carcinoma (BEL-7402) cell lines (Table 1). Since the major side-effect of the anticancer drugs is the damage of the hematopoietic system, the ability of the compounds to posse' toxicity against hematopoietic cell was also tested [20]. Both compounds **1** and **2** have hematopoietic cell toxicity at 10^{-6} M [20].

Organotin(IV) compounds of 2,6-dimethoxynicotinic acid (DMNIH), 1,4-benzodioxane-6-carboxylic acid (BZDOH) and 2,5-dimethyl-3-furoic acid (DMFUH) (**3–6**) with formulae [$SnCy_3$(DMNI)] (**3**), [$SnCy_3$(BZDO)] (**4**), [$SnCy_3$(DMFU)] (**5**), which have trigonal bi-pyramidal (TBP) geometry around metal centre (Scheme 1), and [$SnPh_2$(BZDO)$_2$] (**6**) which has octahedral arrangement (Scheme 2 [21]), were characterized. Compounds **3–5**, exhibit high anti-proliferative activity against pancreatic carcinoma (PANC-1), erythroleukemia (K562) and two glioblastoma multiform (U87 and LN-229) human cell lines. The IC_{50} values lie in the range of 150–475 nM (Table 1). The compounds **3–5** induced apoptosis. Also, **3–5** do not induce multidrug resistance since they are not substrates of the protein efflux pump (P-glycoprotein) [21].

Novel organotin(IV) compounds of the ligand (2E)-2-cyano-3-[4-(diphenylamino)phenyl]prop-2-enoic acid (**7–9**) with either **Sn_4O_2** core or **TBP** geometry (Scheme 3 [22]) around the metal centre were prepared. The compounds were characterized by single-crystal X-ray diffraction analysis. Compound **8** is the most efficient antitumor complex against human lung carcinoma (A549) and human breast adenocarcinoma (MDA-MB-231) cell lines. The IC_{50} values of **8** are at nano molar range and it exhibits 746-fold lower IC_{50} values than the corresponding one of cisplatin (Table 1) [22].

Compounds of 2-thienylselenoacetic acid (Scheme 4 [23]) and formula [$Me_3Sn(O_2CCH_2SeC_4H_3S\text{-}o)]_n$, (**10**) (polymeric trigonal bi-pyramidal) [$(Ph_3Sn)_6(O_2CCH_2SeC_4H_3S\text{-}o)_6$] (**11**) (in 24-angle ring ($Sn_6(OCO)_6$) arrangement) and [$(Me_2Sn)_4(\mu_3\text{-}O)_2(O_2CCH_2SeC_4H_3S\text{-}o)_4$] (**12**) (with Sn_4O_2 core architecture) adopt different structures (Scheme 4 [23]). The highest antiproliferative activity was determined for **11** (3300-fold lower IC_{50} than that of cisplatin (Table 1)), against human cervix (HeLa) and breast cancer (MDA-MB-231) cell lines (Table 1). The result demonstrates that **11** could induce apoptosis in cells *via* accumulation of ROS and collapse of the mitochondrial membrane permeabilization (MMP) [23].

Twenty one novel mixed ligand di-*n*-butyltin(IV) compounds of formula [$(n\text{-}Bu)_2$SnAL] (**13–33**) (A = substituted 4-acyl-5-pyrazolone, and L = fluorinated benzoic acid) (Scheme 5 [24]) were characterized by elemental analyses, IR, NMR (^{1}H, ^{13}C, ^{119}Sn) and X-ray crystallography. The arrangement around the metal centre resulted distorted octahedral (Scheme 5 [24]) The cytotoxicity of the compounds was studied against human nasopharyngeal carcinoma (KB) and human cervical carcinoma (HeLa) cell lines. The IC_{50} values of the compounds lie in the nanomolar range and they are more active than cisplatin (up to 100-fold (Table 1)). Between the two human tumor cell lines, HeLa cells appeared to be more sensitive than KB to **13–33**. The antitumor mechanism of 14 is correlated to the apoptosis mechanism. The toxicity of **14** was checked in normal human cervical epithelial cells (HCvEpCs) with IC_{50} = 0.26 μM which in respect to the corresponding one against the HeLa cells (IC_{50} = 0.05 μM), demonstrating a slight specificity for this tumor cells than normal ones [24].

The tributyl and triphenyl-tin compounds of 3- and 4-aminobenzoic acids **34–37** (Scheme 6 [25]) are monomers in solution, which according to NMR spectra adopt a tetrahedral tin coordination environment in chloroform and trigonal bipyramidal in DMSO (Scheme 6 [25]) due to coordination of the solvent. The 4-aminobenzoic acid is an intermediate in the synthesis of folate by bacteria, plants, and fungi. The compounds exhibit variable cytotoxic activity (IC_{50} values are in nano molar concentration) against myelogenous leukemia (K562), cervical carcinoma (HeLa) and hepatocellular carcinoma (HepG2) cell lines. The butyl derivatives are the more effective and the methyl ones the less active [25].

A series of tributyltin(IV) compounds based on 2/4-[(E)-2-(aryl)-1-diazenyl]benzoate ligands **38–41** (Scheme 7 [26]) have been structurally characterized by elemental analysis and IR, NMR (^{1}H, ^{13}C, and ^{119}Sn) and ^{119}Sn Mössbauer spectroscopy. The geometry around the metal centre is tetrahedral in solution and trigonal bipyramidal or tetrahedral one in the solid-state (Scheme 7 [26]). Cytotoxicity studies were carried out on human renal carcinoma (A498), breast

Table 1
In vitro inhibitory dose for the 50% of various cancer cell lines (IC_{50}) in μM of the organotin(IV) compounds with O-donor ligands.

Compound (scheme)	Reference	IC_{50} [cell line]
Cisplatin	[12,24,26–27,31–32,37,40,42,49,52,57–62,64–66,69–72,77,80,83,85,88–89,104,106–110,112,114]	24.00 [4T1][40], 7.50 [A498][27,58,59,64,106], 5.00 [A498][26], 2.60 [A549][12], 9.46 [A549][42], 213.30 [A549][52], 2.90 [A549][57], 1.50 [A549][60,77], 0.69 [A549][61], 0.53 [A549][65], 9.06 [A549][71], 16.40 [A549][80], 7.00 [A549][109], > 200 [A549][110,112], 4.90 [B16-F10][57], 8.10 [Bel-7402][32], 6.50 [BGC-823][32], > 200 [Caco-2][114], 12.50 [Caki-1][80], 13.74 [CoLo205][65], 13.70 [CoLo205][31], 1.40 [EVSA-T][27,58,59,64,106], 1.60 [EVSA-T][26], 4.70 [Fem-x][62], 10.90 [H226][27,58,59,64,106], 2.10 [H226][26], 46.50 [HCT116][66], 176.7 [HCT116][114], 12.30 [HCT-15][69,70], 16.80 [HCT-15][72], 3.00 [HCT-8][109], 22.40 [HEK-293][69,70], 51.50 [HEK-293][72], > 50 [HeLa][24], 6.50 [HeLa][31], 9.89 [HeLa][71], 4.40 [HeLa][85,89], 5.00 [HeLa][80], 10.50 [HeLa][83], 12.40 [HeLa][104], 4.50 [HeLa][108], > 200 [HeLa][110.112], 12.47 [HELF][71], 56.50 [HEP 3B][88], 19.90 [HepG2][69,70], 64.30 [HepG2][66], 14.62 [HepG2][71], 224.00 [HepG2][49], 1.60 [HepG2][72], 2.50 [HepG2][57], 8.30 [HepG2][108], 2.30 [HL-60][109], > 200 [HL-60][114], > 200 [HT-29][114], 0.60 [IGROV][27,58,59,64,106], 0.80 [IGROV][26], 61.90 [IMR 32][88], 5.70 [K562][62,85,89], 2.65 [KB][24], 0.37 [KB][107], 2.70 [KB][108], 0.69 [L-929][60,77], 1.53 [L-929][65], 1.90 [M19 MEL][27,58,59,64,106], 2.40 [M19 MEL][26], 41.80 [MCF-10A][40], 29.90 [MCF-7][69,70], 2.30 [MCF-7][27,58,59,64,106], 8.00 [MCF-7][60,77], 41.70 [MCF-7][61], 18.70 [MCF-7][31], 11.20 [MCF-7][66], 45.30 [MCF-7][37], 18.33 [MCF-7][40], 65.00 [MCF-7][49], 2.30 [MCF-7][52], 46.60 [MCF-7][72], 18.50 [MCF-7][80,104], > 200 [MCF-7][110,112], 50.00 [MDA-MB-231][12,80], 33.03 [MDA-MB-231][40], 6.30 [MRC-5][80], 19.60 [MRC-5][83], 24.70 [MTSV17][80], 3.10 [OAW-42][80], 33.60 [PBMC][62] 26.00 [PBMC + PHA][85,89], 19.90 [PC-3][69,70], 62.20 [PC-3][72], 45.70 [SMMC-7721][52], 41.7 [T-24][60,77], 7.99 [T-24][65], 3.20 [WIDR][27,58,59,64,106], 1.90 [WIDR][26]
1 (1)	[20]	2.4 [P388], 0.29 [HL-60], 4.5 [A-549], 1.09 [BEL-7402]
2 (1)	[20]	0.06 [P388], 0.06 [HL-60], 0.15 [A-549]
3 (2)	[21]	0.31 [K562], 0.31 [K562/R], 0.21 [LN-229], 0.29 [U87], 0.27 [PANC-1]
4 (2)	[21]	0.27 [K562], 0.32 [K562/R], 0.19 [LN-229], 0.25 [U87], 0.21 [PANC-1]
5 (2)	[21]	0.35 [K562], 0.47 [K562/R], 0.21 [LN-229], 0.27 [U87], 0.15 [PANC-1]
6 (2)	[21]	0.73 [K562], 1.41 [K562/R], 0.33 [LN-229], 0.51 [U87], 3.16 [PANC-1]
7 (3)	[22]	2.73 [A-549], 0.2 [MDA-MB-231]
8 (3)	[22]	0.1 [A-549], 0.06 [MDA-MB-231]
9 (3)	[22]	0.24 [A-549], 0.07 [MDA-MB-231]
10 (4)	[23]	5.9 [MDA-MB-231], 6.8 [HeLa]
11 (4)	[23]	0.02 [MDA-MB-231], 0.03 [HeLa]
12 (4)	[23]	8.5 [MDA-MB-231], > 10 [HeLa]
13 (5)	[24]	0.14 [HeLa], 0.31 [KB]
14 (5)	[24]	0.05 [HeLa], 0.35 [KB]
15 (5)	[24]	0.26 [HeLa], 0.36 [KB]
16 (5)	[24]	0.13 [HeLa], 0.32 [KB]
17 (5)	[24]	0.28 [HeLa], 0.34 [KB]
18 (5)	[24]	0.18 [HeLa], 0.38 [KB]
19 (5)	[24]	0.16 [HeLa], 0.54 [KB]
20 (5)	[24]	0.23 [HeLa], 0.31 [KB]
21 (5)	[24]	0.23 [HeLa], 0.29 [KB]
22 (5)	[24]	0.31 [HeLa], 0.44 [KB]
23 (5)	[24]	0.24 [HeLa], 0.51 [KB]
24 (5)	[24]	0.20 [HeLa], 0.39 [KB]
25 (5)	[24]	0.21 [HeLa], 0.37 [KB]
26 (5)	[24]	0.25 [HeLa], 0.49 [KB]
27 (5)	[24]	0.08 [HeLa], 0.54 [KB]
28 (5)	[24]	0.15 [HeLa], 0.49 [KB]
29 (5)	[24]	0.28 [HeLa], 0.46 [KB]
30 (5)	[24]	0.15 [HeLa], 0.34 [KB]
31 (5)	[24]	0.18 [HeLa], 0.35 [KB]
32 (5)	[24]	0.18 [HeLa], 0.32 [KB]
33 (5)	[24]	0.14 [HeLa], 0.45 [KB]
34 (6)	[25]	0.6 [K562], 0.3 [HeLa], 0.4 [HepG2]
35 (6)	[25]	0.3 [K562], 0.3 [HeLa], 0.4 [HepG2]
36 (6)	[25]	0.5 [K562], 0.6 [HeLa], 0.5 [HepG2]
37 (6)	[25]	0.3 [K562], 0.4 [HeLa], 0.6 [HepG2]
38 (7)	[26]	0.21 [MCF-7], 0.30 [A498], 0.18 [EVSAT], 0.27 [H226], 0.39 [IGROV], 0.22 [M19MEL], 0.19 [WIDR]
39 (7)	[26]	0.20 [MCF-7], 0.30 [A498], 0.17 [EVSAT], 0.28 [H226], 0.43 [IGROV], 0.21 [M19MEL], 0.18 [WIDR]
40 (7)	[26]	0.19 [MCF-7], 0.30 [A498], 0.05 [EVSAT], 0.28 [H226], 0.46 [IGROV], 0.22 [M19MEL], 0.18 [WIDR]
41 (7)	[26]	0.22 [MCF-7], 0.33 [A498], 0.19 [EVSAT], 0.30 [H226], 0.44 [IGROV], 0.23 [M19MEL], 0.19 [WIDR]
42 (8)	[27]	0.09 [MCF-7], 0.17 [A498], 0.07 [EVSAT], 0.17 [H226], 0.18 [IGROV], 0.17 [M19MEL], 0.17 [WIDR]
43 (8)	[27]	0.07 [MCF-7], 0.17 [A498], 0.07 [EVSAT], 0.17 [H226], 0.18 [IGROV], 0.16 [M19MEL], 0.17 [WIDR]
44 (8)	[27]	0.06 [MCF-7], 0.16 [A498], 0.05 [EVSAT], 0.16 [H226], 0.17 [IGROV], 0.16 [M19MEL], 0.16 [WIDR]
45 (8)	[27]	0.12 [MCF-7], 0.16 [A498], 0.07 [EVSAT], 0.16 [H226], 0.17 [IGROV], 0.16 [M19MEL], 0.16 [WIDR]
50 (10)	[29]	0.29 [MCF-7], 1.04 [HT29]
51 (10)	[29]	0.16 [MCF-7], 0.53 [HT29]
52 (10)	[29]	0.24 [MCF-7], 0.25 [HT29]
53 (10)	[29]	0.17 [MCF-7], 0.28 [HT29]
54 (10)	[29]	0.13 [MCF-7], 0.97 [HT29]
55 (10)	[29]	0.17 [MCF-7], 1.72 [HT29]
56 (10)	[29]	0.32 [MCF-7], 1.04 [HT29]
57 (10)	[29]	0.38 [MCF-7], 1.58 [HT29]
58 (10)	[29]	0.35 [MCF-7], 0.46 [HT29]
59 (10)	[29]	0.41 [MCF-7], 1.44 [HT29]
60 (10)	[29]	1.30 [MCF-7], 0.92 [HT29]

(*continued on next page*)

Table 1 (*continued*)

Compound (scheme)	Reference	IC_{50} [cell line]
61 (10)	[29]	0.83 [MCF-7], 1.19 [HT29]
62 (10)	[29]	0.60 [MCF-7], 1.21 [HT29]
63 (10)	[29]	0.74 [MCF-7], 1.06 [HT29]
64 (10)	[29]	0.60 [MCF-7], 0.93 [HT29]
65 (10)	[29]	1.24 [MCF-7], 1.64 [HT29]
67 (12)	[31]	0.04 [HeLa], 0.08 [MCF-7], 0.41 [CoLo205]
68 (12)	[31]	0.04 [HeLa], 0.09 [MCF-7], 0.53 [CoLo205]
69 (13)	[32]	> 10 [BGC-823], > 10 [BEL-7402]
70 (13)	[32]	> 10 [BGC-823], > 10 [BEL-7402]
71 (13)	[32]	4.90 [BGC-823], 5.20 [BEL-7402]
72 (13)	[32]	> 10 [BGC-823], > 10 [BEL-7402]
73 (13)	[32]	> 10 [BGC-823], > 10 [BEL-7402]
74 (13)	[32]	> 10 [BGC-823], > 10 [BEL-7402]
75 (14)	[33]	1.76 [HeLa]
76 (14)	[33]	0.66 [HeLa]
77 (15)	[34]	4.49 [PC-3]
78 (15)	[34]	10.4 [PC-3]
79 (15)	[34]	68.72 [PC-3]
80 (15)	[34]	6.40 [PC-3]
81 (15)	[34]	> 148 [PC-3]
82 (16)	[35]	0.32 [BEL-7402], 1.04 [HepG2]
83 (16)	[35]	3.31 [BEL-7402], 3.93 [HepG2]
84 (16)	[35]	1.20 [BEL-7402], 1.37 [HepG2]
87 (18)	[37]	0.19 [MCF-7]
88 (19)	[38]	4.12 [P388], 3.56 [HeLa]
89 (19)	[38]	3.20 [P388], 2.28 [HeLa]
90 (19)	[38]	2.44 [P388], 0.79 [HeLa]
91 (19)	[38]	2.54 [P388], 0.65 [HeLa]
92 (20)	[39]	0.03 [MCF-7]
93 (21)	[40]	2.03 [MDA-MB-231], 1.91 [MCF-7], 1.93 [4T1], 37.26 [MCF-10A]
94 (21)	[40]	2.14 [MDA-MB-231], 1.88 [MCF-7], 2.99 [4T1], 35.08 [MCF-10A]
95 (21)	[40]	2.22 [MDA-MB-231], 1.89 [MCF-7], 4.69 [4T1], 33.67 [MCF-10A]
96 (21)	[40]	6.50 [MDA-MB-231], 3.85 [MCF-7], 15.80 [4T1], 31.21 [MCF-10A]
97 (21)	[40]	16.74 [MDA-MB-231], 19.64 [MCF-7], 24.88 [4T1], 67.51 [MCF-10A]
98 (21)	[40]	5.67 [MDA-MB-231], 4.47 [MCF-7], 7.44 [4T1], 44.11 [MCF-10A]
99 (21)	[40]	12.61 [MDA-MB-231], 5.96 [MCF-7], 16.48 [4T1], 40.39 [MCF-10A]
100 (21)	[40]	11.51 [MDA-MB-231], 9.23 [MCF-7], 15.69 [4T1], 20.46 [MCF-10A]
101 (21)	[40]	1.19 [MDA-MB-231], 0.76 [MCF-7], 1.44 [4T1], 51.71 [MCF-10A]
102 (21)	[40]	25.39 [MDA-MB-231], 16.74 [MCF-7], 35.94 [4T1], 54.46 [MCF-10A]
103 (22)	[41]	0.70 [MCF-7], 1.00 [HT29]
104 (22)	[41]	0.30 [MCF-7], 1.20 [HT29]
105 (22)	[41]	0.40 [MCF-7], 0.90 [HT29]
106 (22)	[41]	0.50 [MCF-7], 0.90 [HT29]
107 (22)	[41]	0.70 [MCF-7], 0.70 [HT29]
108 (22)	[41]	0.70 [MCF-7], 0.90 [HT29]
109 (22)	[41]	0.40 [MCF-7], 1.50 [HT29]
110 (22)	[41]	0.20 [MCF-7], 0.10 [HT29]
111 (22)	[41]	1.60 [MCF-7], 1.70 [HT29]
112 (23)	[42]	0.22 [A-549]
113 (23)	[42]	0.08 [A-549]
114 (23)	[42]	0.46 [A-549]
115 (23)	[42]	3.24 [A-549]
116 (24)	[43]	25.72 [HeLa], 5.00 [HT1080], 0.06 [U87] * no units of IC_{50} value as are given in Ref. [43]
117 (24)	[43]	31.74 [HeLa], 6.40 [HT1080], 0.60 [U87] * no units of IC_{50} value as are given in Ref. [43]
118 (24)	[43]	2.68 [HeLa], 6.13 [HT1080], 74.04 [U87] * no units of IC_{50} value as are given in Ref. [43]
119 (24)	[43]	29.77 [HeLa], 10.69 [HT1080], 0.09 [U87] * no units of IC_{50} value as are given in Ref. [43]
120 (24)	[43]	4.89 [HeLa], 279.03 [HT1080], 28.96 [U87] * no units of IC_{50} value as are given in Ref. [43]
121 (24)	[43]	29.70 [HeLa], 33.38 [HT1080], 5.32 [U87] * no units of IC_{50} value as are given in Ref. [43]
122 (25)	[44]	6.56 [HeLa], 177.26 [HT1080], 82.73 [U87] * no units of IC_{50} value as are given in Ref. [44]
125 (27)	[46]	0.09 [A-549], 0.13 [85050C], 0.08 [A253], 0.06 [DLD-1]
126 (27)	[46]	0.13 [A-549], 0.17 [85050C], 0.10 [A253], 0.18 [DLD-1]
127 (28)	[47]	1.20 [HeLa]
128 (29)	[48]	5.61 [MDA-MB-231]
129 (29)	[48]	> 10 [MDA-MB-231]
130 (29)	[48]	0.48 [MDA-MB-231]
131 (29)	[48]	0.40 [MDA-MB-231]
132 (29)	[48]	8.61 [MDA-MB-231]
133 (29)	[48]	> 10 [MDA-MB-231]
134 (29)	[48]	0.62 [MDA-MB-231]
135 (29)	[48]	0.57 [MDA-MB-231]
136 (30)	[49]	0.55 [MCF-7], 0.49 [HepG2]
137 (30)	[49]	1.08 [MCF-7], 1.45 [HepG2]
138 (30)	[49]	0.84 [MCF-7], 0.96 [HepG2]
139 (31)	[50]	5.00 [HepG2]

(*continued on next page*)

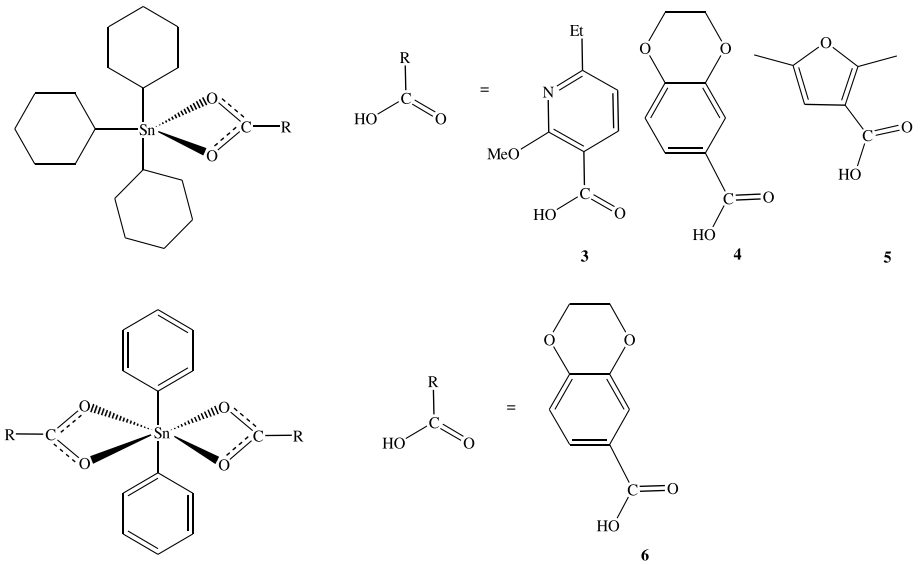
Table 1 (*continued*)

Compound (scheme)	Reference	IC_{50} [cell line]
140 (31)	[50]	21.70 [HepG2]
141 (31)	[50]	9.10 [HepG2]
144 (33)	[52]	26.22 [A-549], 13.11 [MCF-7], 10.93 [SMMC-7721]
145 (33)	[52]	31.69 [A-549], 5.63 [MCF-7], 0.04 [SMMC-7721]
146 (33)	[52]	42.40 [A-549], 25.44 [MCF-7], 89.04 [SMMC-7721]
147 (33)	[52]	40.05 [A-549], 0.05 [MCF-7], 45.56 [SMMC-7721]
148 (33)	[52]	69.63 [A-549], 21.76 [MCF-7], 56.57 [SMMC-7721]
149 (33)	[52]	21.06 [A-549], 12.64 [MCF-7], 30.90 [SMMC-7721]
150 (34)	[53]	0.06 [K562], 0.06 [HeLa], 0.06 [PBMC]
151 (35)	[54]	0.53 [BEL-7402], 0.40 [HepG2]
152 (36)	[55]	3.49 [MCF-7], 1.50 [HepG2], 3.02 [NCI-H460], 7.06 [HL7702]
153 (36)	[55]	11.95 [MCF-7], 10.80 [HepG2], 17.78 [NCI-H460], 35. 00 [HL7702]
154 (37)	[56]	41.25 [L210]
155 (37)	[56]	17.86 [L210]
156 (37)	[56]	11.30 [L210]
157 (38)	[57]	0.19 [A-549], 0.28 [HepG2], 0.04 [B16-F10]
158 (38)	[57]	0.73 [A-549], 0.86 [HepG2], 0.56 [B16-F10]
159 (38)	[57]	0.21 [A-549], 0.36 [HepG2], 0.38 [B16-F10]
160 (39)	[58]	0.28 [MCF-7], 0.51 [A498], 0.16 [EVSAT], 0.97 [H226], 0.73 [IGROV], 0.44 [M19MEL], 1.06 [WIDR]
161 (39)	[58]	0.50 [MCF-7], 1.41 [A498], 0.45 [EVSAT], 1.38 [H226], 1.80 [IGROV], 1.09 [M19MEL], 2.57 [WIDR]
162 (39)	[58]	0.22 [MCF-7], 0.51 [A498], 0.18 [EVSAT], 0.67 [H226], 0.60 [IGROV], 0.40 [M19MEL], 0.74 [WIDR]
163 (40)	[59]	0.13 [MCF-7], 0.17 [A498], 0.08 [EVSAT], 0.16 [H226], 0.16 [IGROV], 0.17 [M19MEL], 0.15 [WIDR]
164 (40)	[59]	0.15 [MCF-7], 0.17 [A498], 0.07 [EVSAT], 0.17 [H226], 0.18 [IGROV], 0.17 [M19MEL], 0.17 [WIDR]
165 (41)	[60]	0.43 [A-549], 3.23 [MCF-7], 0.18 [T24], 0.42 [L929]
166 (42)	[61]	60.44 [A-549], 1.26 [MCF-7], 4.78 [T24], 5.85 [L929]
167 (42)	[61]	10.28 [A-549], 2.01 [MCF-7], 3.49 [T24], 5.40 [L929]
168 (42)	[61]	0.22 [A-549], 0.17 [MCF-7], 3.27 [T24], 1.15 [L929]
169 (42)	[61]	7.21 [A-549], 0.68 [MCF-7], 0.29 [T24], 7.23 [L929]
170 (43)	[62]	0.08 [K562], 0.17 [HeLa], > 0.20 [PBMC], 0.08 [Fem-x]
171 (43)	[62]	0.05 [K562], 0.15 [HeLa], 0.20 [PBMC], 0.07 [Fem-x]
172 (43)	[62]	0.17 [K562], 0.22 [HeLa], 0.24 [PBMC], 0.16 [Fem-x]
173 (43)	[62]	0.90 [K562], 1.18 [HeLa], > 20.00 [PBMC], 0.93 [Fem-x]
174 (43)	[62]	0.53 [K562], 1.04 [HeLa], 1.27 [PBMC], 0.63 [Fem-x]
175 (43)	[62]	0.85 [K562], 1.57 [HeLa], > 20.00 [PBMC], 0.80 [Fem-x]
176 (43)	[62]	0.96 [K562], 1.23 [HeLa], > 20.00 [PBMC], 0.82 [Fem-x]
177 (44)	[63]	85.04 [MCF-7], 100.28 [HEK-293], 80.44 [PC-3], 49.757 [HCT-15], 49.54 [HepG2]
178 (44)	[63]	999.83 [MCF-7], 543.73 HEK-293, 898.72 [PC-3], 220.28 [HCT-15], 534.74 [HepG2]
179 (44)	[63]	809.16 [MCF-7], 994.19 HEK-293, 49.33 [PC-3], 79.66 [HCT-15], 170.49 [HepG2]
180 (44)	[63]	212.68 [MCF-7], 403.07 [HEK-293], 559.15 [PC-3], 807.86 [HCT-15], 854.17 [HepG2]
181 (44)	[63]	72.04 [MCF-7], 107.26 [HEK-293], 84.88 [PC-3], 19.92 [HCT-15], 54.57 [HepG2]
182 (44)	[63]	280.82 [MCF-7], 669.99 [HEK-293], 62.18 [PC-3], 31.23 [HCT-15], 38.47 [HepG2]
183 (44)	[63]	> 1000 [MCF-7], > 1000 [HEK-293], > 2000 [PC-3], > 4000 [HCT-15], > 1000 [HepG2]
184 (45)	[63]	> 1000 [MCF-7], > 1000 [HEK-293], > 2000 [PC-3], > 1000 [HCT-15], > 2000 [HepG2]
185 (45)	[64]	55.15 [MCF-7], 55.11 [HEK-293], 49.09 [PC-3], 51.48 [HCT-15], 52.40 [HepG2]
186 (45)	[64]	47.13 [MCF-7], 43.92 [HEK-293], 43.01 [PC-3], 49.66 [HCT-15], 42.93 [HepG2]
187 (45)	[64]	65.18 [MCF-7], 71.60 [HEK-293], 60.25 [PC-3], 70.64 [HCT-15], 71.54 [HepG2]
188 (45)	[64]	27.10 [MCF-7], 32.13 [HEK-293], 35.12 [PC-3], 33.96 [HCT-15], 47.55 [HepG2]
189 (45)	[64]	23.08 [MCF-7], 23.00 [HEK-293], 25.80 [PC-3], 28.79 [HCT-15], 47.58 [HepG2]
190 (45)	[64]	40.08 [MCF-7], 36.07 [HEK-293], 50.81 [PC-3], 56.40 [HCT-15], 67.29 [HepG2]
191 (45)	[64]	17.40 [MCF-7], 11.54 [HEK-293], 12.43 [PC-3], 25.03 [HCT-15], 35.14 [HepG2]
192 (45)	[64]	4.44 [MCF-7], 11.24 [HEK-293], 11.54 [PC-3], 6.88 [HCT-15], 8.67 [HepG2]
193 (45)	[64]	20.46 [MCF-7], 18.87 [HEK-293], 17.57 [PC-3], 35.15 [HCT-15], 47.59 [HepG2]
194 (46)	[65]	1.10 [A-549], 1.24 [HeLa], 4.42 [HepG2], 18.39 [HELF]
195 (46)	[65]	4.36 [A-549], 0.94 [HeLa], 2.33 [HepG2], 47.29 [HELF]
196 (47)	[66]	31.82 [MCF-7], 30.96 [HEK-293], 40.27 [PC-3], 40.57 [HCT-15], 48.46 [HepG2]
197 (47)	[66]	16.24 [MCF-7], 11.67 [HEK-293], 12.92 [PC-3], 15.75 [HCT-15], 15.03 [HepG2]
198 (47)	[66]	150.14 [MCF-7], 120.11 [HEK-293], 100.10 [PC-3], 120.11 [HCT-15], 150.14 [HepG2]
199 (47)	[66]	21.54 [MCF-7], 23.29 [HEK-293], 27.31 [PC-3], 22.46 [HCT-15], 23.47 [HepG2]
200 (47)	[66]	34.00 [MCF-7], 34.89 [HEK-293], 25.18 [PC-3], 21.71 [HCT-15], 37.92 [HepG2]
201 (47)	[66]	60.00 [MCF-7], 69.37 [HEK-293], 63.54 [PC-3], 50.00 [HCT-15], 55.12 [HepG2]
202 (47)	[66]	33.92 [MCF-7], 50.29 [HEK-293], 35.43 [PC-3], 31.80 [HCT-15], 32.09 [HepG2]
203 (47)	[66]	18.38 [MCF-7], 17.22 [HEK-293], 19.54 [PC-3], 15.78 [HCT-15], 26.29 [HepG2]
204 (47)	[66]	950.00 [MCF-7], 1893.94 [HEK-293], 946.97 [PC-3], 4734.85 [HCT-15], 12.31 [HepG2]
205 (47)	[66]	44.51 [MCF-7], 46.93 [HEK-293], 49.35 [PC-3], 49.93 [HCT-15], 46.63 [HepG2]
206 (47)	[66]	22.24 [MCF-7], 16.65 [HEK-293], 22.86 [PC-3], 14.22 [HCT-15], 23.91 [HepG2]
207 (47)	[66]	34.06 [MCF-7], 31.80 [HEK-293], 28.16 [PC-3], 39.66 [HCT-15], 51.47 [HepG2]
208 (47)	[66]	0.19 [MCF-7], 0.31 [HEK-293], 0.17 [PC-3], 2.00 [HCT-15], 2.82 [HepG2]
209 (47)	[66]	0.26 [MCF-7], 0.46 [HEK-293], 0.15 [PC-3], 3.08 [HCT-15], 4.11 [HepG2]
210 (47)	[66]	18.00 [MCF-7], 12.57 [HEK-293], 20.81 [PC-3], 14.54 [HCT-15], 25.20 [HepG2]
211 (47)	[66]	35.49 [MCF-7], 34.17 [HEK-293], 33.52 [PC-3], 33.05 [HCT-15], 38.74 [HepG2]
212 (48)	[67]	0.25 [MCF-7], 0.20 [MDA-MB-231], 0.22 [MRC-5]
213 (48)	[67]	0.21 [MCF-7], 0.12 [MDA-MB-231], 0.11 [MRC-5]
214 (49)	[68]	1.51 [HepG2], 1.8 [SGC-7901], 2.48 [LS174T]
215 (49)	[68]	> 100 [HepG2], > 100 [SGC-7901], > 100 [LS174T]

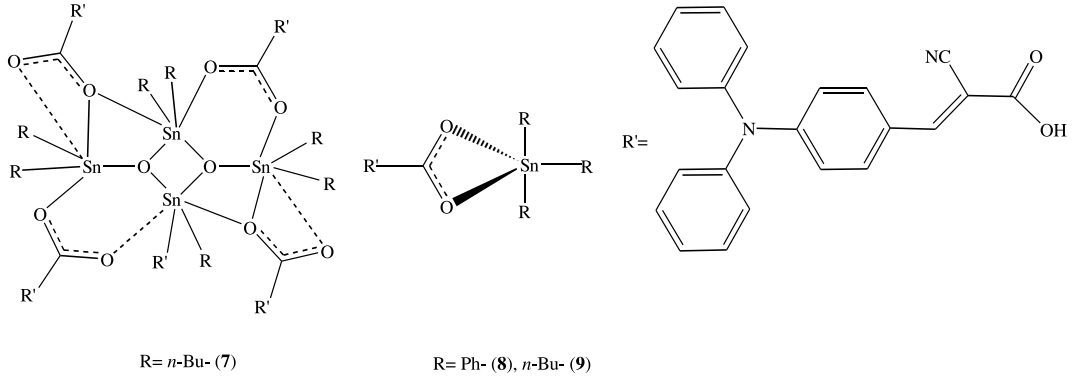
(*continued on next page*)

Table 1 (*continued*)

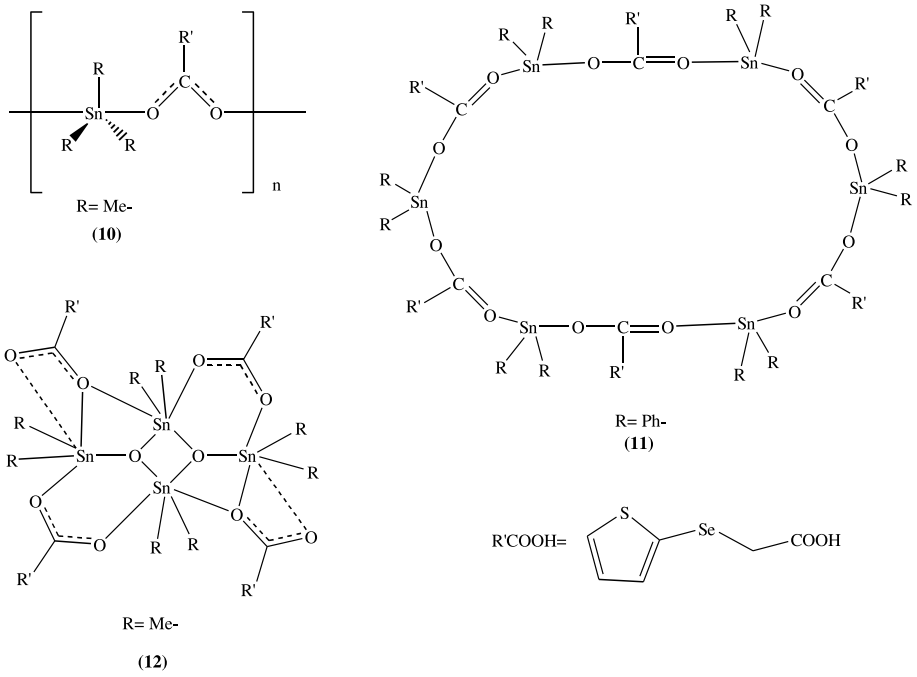
Compound (scheme)	Reference	IC_{50} [cell line]
216 (50)	[69]	0.06 [MCF-7], 0.17 [A498], 0.06 [EVSAT], 0.10 [H226], 0.16 [IGROV], 0.07 [M19MEL], 0.06 [WIDR]
217 (50)	[69]	0.13 [MCF-7], 0.18 [A498], 0.08 [EVSAT], 0.19 [H226], 0.17 [IGROV], 0.13 [M19MEL], 0.07 [WIDR]
218 (50)	[69]	0.05 [MCF-7], 0.07 [A498], 0.05 [EVSAT], 0.06 [H226], 0.08 [IGROV], 0.06 [M19MEL], 0.05 [WIDR]
219 (50)	[69]	0.89 [MCF-7], 1.95 [A498], 0.55 [EVSAT], 1.68 [H226], 0.39 [IGROV], 0.81 [M19MEL], 0.80 [WIDR]
220 (51)	[70]	36.82 [A-549], 58.68 [CoLo205]
221 (51)	[70]	35.37 [A-549], 49.88 [CoLo205]
222 (51)	[70]	21.65 [A-549], 38.02 [CoLo205]
223 (51)	[70]	39.98 [A-549], 59.4 [CoLo205]
224 (52)	[71]	0.52 [MCF-7], 1.08 [HepG2], 2.24 [HCT116]
225 (53)	[72]	0.65 [KB]
226 (53)	[72]	0.39 [KB]
227 (53)	[72]	1.55 [KB]
228 (53)	[72]	0.30 [KB]
229 (53)	[72]	0.60 [KB]
230 (54)	[73]	0.10 [A-549], 0.09 [A253], 0.13 [8505C], 0.12 [A2780], 0.10 [DLD-1]
231 (54)	[73]	0.15 [A-549], 0.14 [A253], 0.18 [8505C], 0.17 [A2780], 0.17 [DLD-1]
232 (54)	[73]	0.24 [A-549], 0.24 [A253], 0.24 [8505C], 0.13 [A2780], 0.21 [DLD-1]
234 (55)	[74]	0.2 [HCT-116], 0.8 [MCF-7]
235 (55)	[74]	0.8 [HCT-116], 0.4 [MCF-7]
236 (55)	[74]	0.3 [HCT-116], 0.2 [MCF-7]



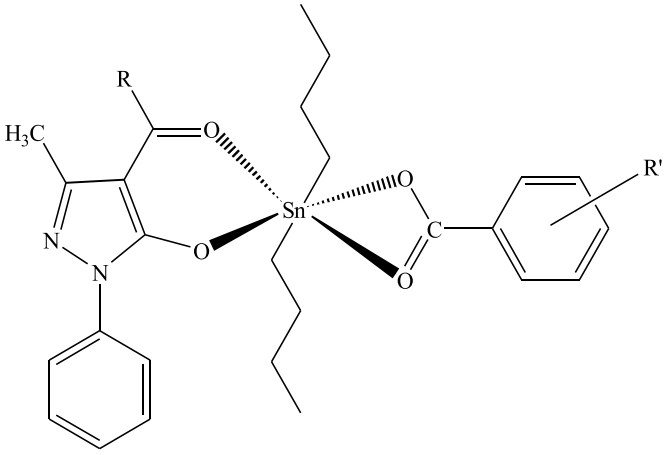
Scheme 2. The formulae of compounds **3–6** [21].



Scheme 3. The formulae of **7–9** [22].



Scheme 4. The formulae of **10–12** [23].

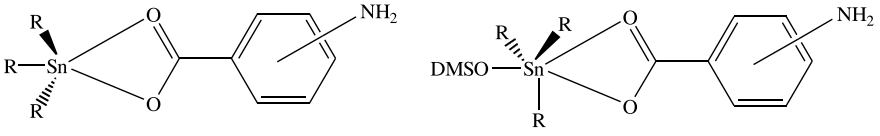


R
C_6H_5-, (HA1)
CH_3-, (HA2)
4-$CH_3C_6H_4$-, (HA3)
4-$CF_3C_6H_4$-, (HA4)
4-FC_6H_4-, (HA5)
4-ClC_6H_4-, (HA6)
4-BrC_6H_4-, (HA7)
4-IC_6H_4- (HA8)

R'
4-F-, (HL1)
2,4-F, (HL2)
3,4-F (HL3)

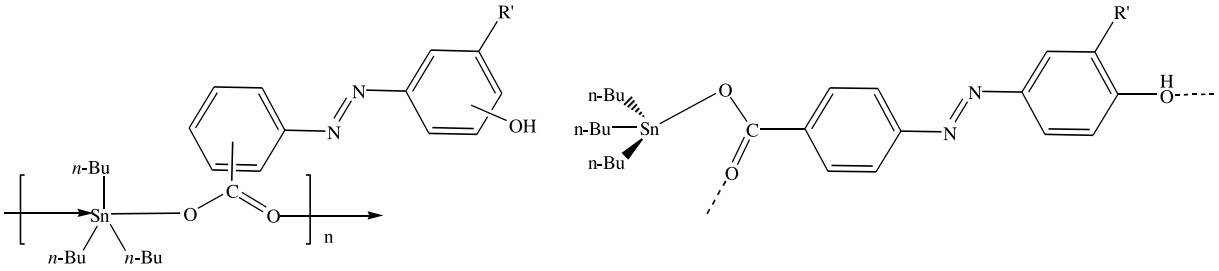
$Bu_2SnA1L1$ (**13**),
$Bu_2SnA2L1$ (**14**),
$Bu_2SnA3L1$ (**15**),
$Bu_2SnA4L1$ (**16**),
$Bu_2SnA5L1$ (**17**),
$Bu_2SnA6L1$ (**18**),
$Bu_2SnA7L1$ (**19**),
$Bu_2SnA8L1$ (**20**),
$Bu_2SnA1L2$ (**21**),
$Bu_2SnA3L2$ (**22**),
$Bu_2SnA4L2$ (**23**),
$Bu_2SnA5L2$ (**24**),
$Bu_2SnA6L2$ (**25**),
$Bu_2SnA7L2$ (**26**),
$Bu_2SnA1L3$ (**27**),
$Bu_2SnA2L3$ (**28**),
$Bu_2SnA3L3$ (**29**),
$Bu_2SnA4L3$ (**30**),
$Bu_2SnA5L3$ (**31**),
$Bu_2SnA6L3$ (**32**),
$Bu_2SnA7L3$ (**33**).

Scheme 5. The formulae of **13–33** [24].



R= *n*-Bu- and m-NH_2-, (**34**)
R= *n*-Bu- and p-NH_2-, (**35**)
R= Ph- and m-NH_2-, (**36**)
R= Ph- and p-NH_2-, (**37**)

Scheme 6. The formulae of **34–37** [25].



L^1HH'= 2-COOH, 2'-OH, R'= CH_3- **(38)**
L^2HH'= 2-COOH, 2'-OH, R'= $C(CH_3)_3$- **(39)**
L^3HH'= 4-COOH, 2'-OH, R'= $C(CH_3)_3$- **(40)**
L^4HH'= 4-COOH, 4'-OH, R'= CH_3- **(41)**

Scheme 7. The formulae of **38–41** [26].

adenocarcinoma (EVSA-T), non-small-cell lung carcinoma (H226), ovarian carcinoma (IGROV), melanoma (M19 MEL), breast adenocarcinoma (MCF-7) and colon carcinoma (WIDR) cell lines. Despite the presence of substantial steric bulk due to Sn–Bu ligands the tested compounds had remarkably good activity at nano molar concentrations as compared to that of cisplatin (Table 1). The cytotoxic activity may be associated with the tetrahedral geometry of the compounds in solution and the presence of an azo functionality in the ligand framework [26].

Four triphenyltin(IV) compounds of the 2-/4-[(E)-2-(aryl)-1-diazenyl]benzoate **42–45** (Scheme 8 [27]) were synthesized and characterized by ^1H, ^{13}C and ^{119}Sn NMR, IR, ^{119}Sn Mössbauer spectroscopies. The geometry of the compounds in the solid state and in solution is trigonal bi-pyramidal or tetrahedral (Scheme 8 [27]). The antiproliferative studies were performed against human renal carcinoma (A498), breast adenocarcinoma (EVSA-T), non-small-cell lung carcinoma (H226), ovarian carcinoma (IGROV), melanoma (M19 MEL), breast adenocarcinoma (MCF-7) and colon carcinoma (WIDR) cell lines. Compounds appear to display similar cytotoxicity each other, irrespective of their nuclear substituent in the coupling moiety. The compounds are more active than cisplatin up to 32.3-fold (Table 1) [27].

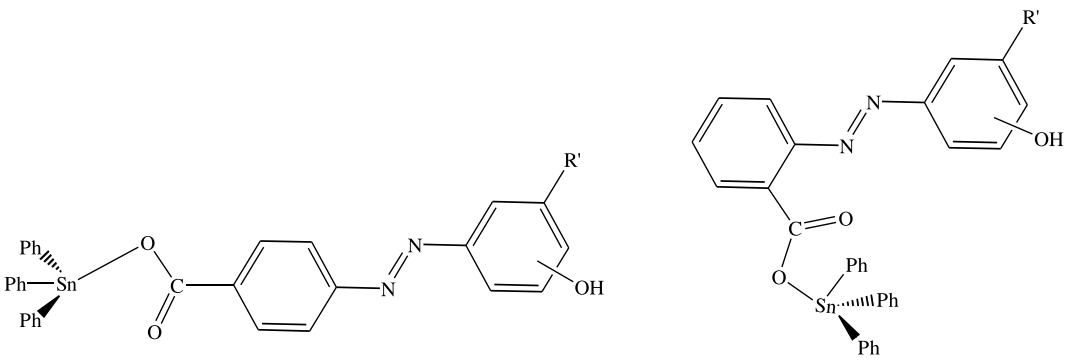
The dibutyltin(IV) compounds of 2-{(E)-4-hydroxy-3-[(E)-4-(aryl) iminomethyl] phenyldiazenyl}benzoic acid which contain the Sn_4O_2 core **46–49** (Scheme 9 [28]) were examined for their *in vitro* cytotoxic potency towards melanoma (A375) and colon carcinoma (HCT116) cell lines. Dibutyltin(IV) compounds induce cell death without cytolysis or necrosis and decrease the membrane fluidity, without interfering with p53 [28].

The antitumor activity of di-n-butyltin(IV) carboxylates **50–65** (Scheme 10 [29]) has been tested against colon carcinoma (HT-29) and breast adenocarcinoma (MCF-7) cell lines. The geometry around tin centre is tetrahedral (Scheme 10 [29]). Their IC_{50} values lie between 0.1 and 1.6 μM (Table 1). The **50–65** induce apoptosis in the lymphoma (BJAB) cell line [29].

Cell viability assay and cytometric analysis showed that the dibutyltin(IV) complex of caffeic acid (HCAF) (**66**) with tetrahedral arrangement (Scheme 11 [30]) induce cytotoxic effect on adenocarcinoma breast cells negative to estrogen receptors (MDA-MB 231) and colon carcinoma (HCT 116) cells, with an increase in the percentage of cells in G_2/M phase. The induction of apoptotic pathway was confirmed by the appearance of sub-G_0 peak in cell cycle [30].

The organotin(IV) compounds of bis(tricyclohexyltin)benzenedioxyacetates **67–68** with tetrahedral arrangement around tin (Scheme 12 [31]) exhibit stronger *in vitro* cytotoxic activity than cisplatin (up to 66-fold (Table 1)), against HeLa, MCF-7 and CoLo205 (colon carcinoma) cells. The compounds show also selectivity against HeLa cells (Table 1). It seems that both organotin(IV) moiety and the ligand, play an important role in the activity of the compounds [31].

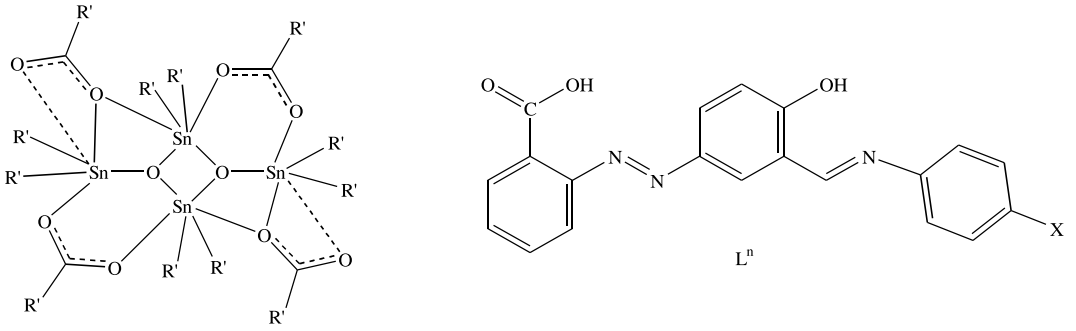
The organotin(IV) compounds of 1-(4-chlorophenyl)-1-cyclopentanecarboxylic acid (**69–74**) which contain the $[(Sn_3O_3)_2]$ core and distorted octahedral conformation (Scheme 13 [32]), were screened for their *in vitro* antitumor activities towards promyelocytic leukemic (HL-60), hepatocellular carcinoma (BEL-7402), gastric carcinoma (BGC-823) and nasopharyngeal carcinoma (KB) cell lines. The IC_{50} values were evaluated only for **71**, since the corresponding values for the rest of the compounds were > 10 μM (Table 1). The antitumor activity of **71** is slightly higher than the corresponding one of cisplatin (Table 1),



L^1H= 4-COOH, 2'-OH, R'= Me- **(42)**
L^2H= 4-COOH, 4'-OH, R'= Me- **(43)**
L^3H= 4-COOH, 2'-OH, R'= t-Bu- **(44)**

L^4H= 2-COOH, 2'-OH, R= t-Bu- **(45)**

Scheme 8. The formulae of **42–45** [27].



R= Bu-, R'= L^n; X= Et (**46**), OMe (**47**), OEt (**48**), Cl (**49**)

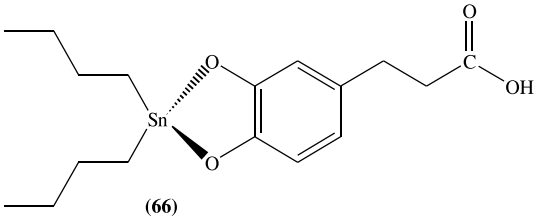
Scheme 9. The formulae of **46–49** [28].

indicating that the type and the number of alkyl- or aryl-groups play an important role, while the nuclearity, does not cause variations in the biological activity [32].

The organotin(IV) carboxylates of (2E)-3-(3-nitrophenyl)prop-2-enoic acid (HL), (**75–76**) (Scheme 14 [32]) adopt either 1D polymeric chain conformation, which is generated by the bridging ligands, with trigonal bi-pyramidal geometry around the five-coordinated tin centre, or centro-symmetric one which feature a central rhombus Sn_2O_2 core (Scheme 14 [33]). The compounds showed a dose dependent antitumor effect towards the cervix adenocarcinoma (HeLa) cells line. Tri-organotin(IV) compounds show better antitumor activity than di-organotin (IV) derivatives (Table 1) [33].

A series of organotin(IV) compounds with the (4-methoxyphenyl) ethanoic acid, (**77–81**), which adopt either 1D polymeric architecture with either trigonal bi-pyramidal conformation around tin (**80**) or distorted octahedral one (**77–79**, **81**) (Scheme 15 [34]). The compounds were tested for their antiproliferative activity against prostate cancer (PC-3) cell line (Table 1). The compounds exhibit lower anticancer activity than the drug doxorubicin [34].

The organotin(IV) compounds of 2-(9H-carbazol-9-yl) acetic acid, (**82–84**) were crystallized in the solid state in to two different conformations. One which contains tetra-nuclear Sn_4O_2 core and the second two hexamers (Sn_3O_3) cores placed in parallel position (Scheme 16 [35]). The compounds were tested for their anticancer activities against human hepatocellular carcinoma (BEL-7402) and human hepatocellular liver carcinoma (HepG2) cell lines (Table 1). The di-*n*-butyltin(IV) derivative **82** with shorter Sn—O bond is more active against both cell lines than the rest of the compounds [35].

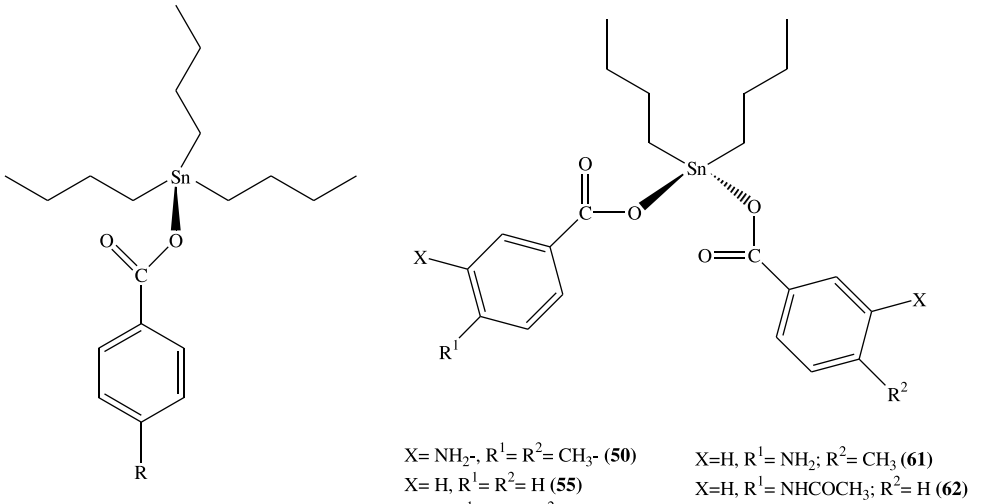


(66)

Scheme 11. The formula of **66** [30].

The organotin(IV) carboxylates **85–86** (Scheme 17 [36]) adopt octahedral geometry around tin atom and they have been screened against cervical adenocarcinoma (HeLa), fibrosarcoma (HT1080) and glioma (U87) cell lines. Overall, the complex **85** exhibits higher activity than **86** [36].

The tetranuclear triphenyltin carboxylate of 1,2,4,5-benzenetetracarboxylic acid (H_4btec), **87** (Scheme 18 [37]) with tetrahedral

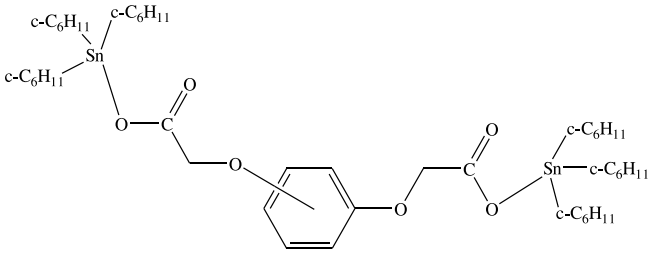


X= H, R= H (**51**)
X=H, R= CH_3 (**52**)
X=H, R= OCH_3 (**53**)
X=H, R= Cl (**54**)

X= NH_2-, R^1= R^2= CH_3- (**50**)
X= H, R^1= R^2= H (**55**)
X=H, R^1= CH_3; R^2= H (**56**)
X=H, R^1= OCH_3; R^2= H (**57**)
X=H, R^1= Cl; R^2= H (**58**)
X=H, R^1= NH_2; R^2= H (**59**)
X=H, R^1= $N(CH_3)_2$; R^2= H (**60**)

X=H, R^1= NH_2; R^2= CH_3 (**61**)
X=H, R^1= $NHCOCH_3$; R^2= H (**62**)
X=H, R^1= H; R^2= $NHCOCH_3$ (**63**)
X=H, R^1= $NHCOCH_3$; R^2= CH_3 (**64**)
X=H, R^1= CH_3; R^2= $NHCOCH_3$ (**65**)

Scheme 10. The formulae of **50–65** [29].



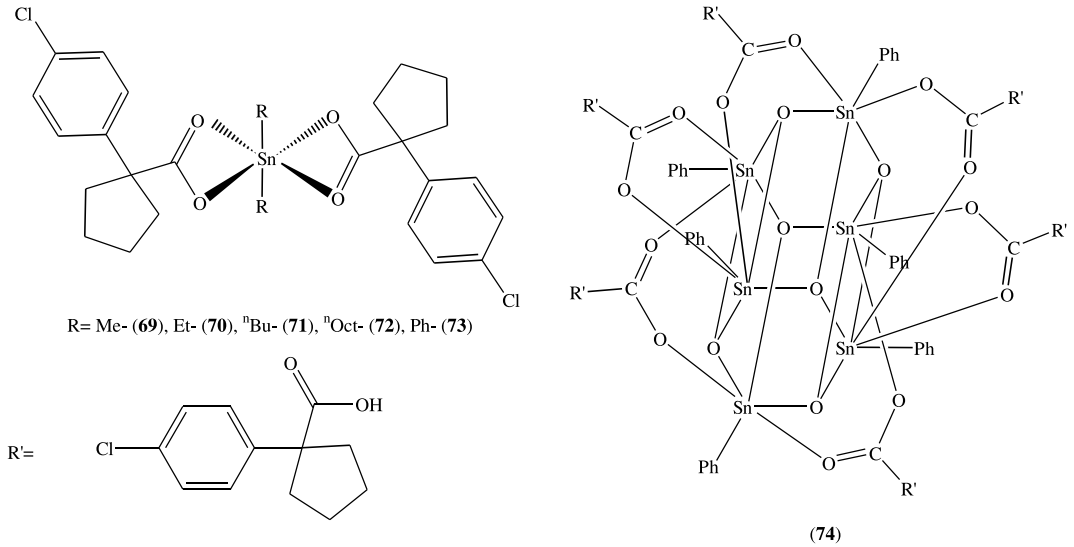
1,3-Benzodiacetic acid (**67**)
1,4-Benzodiacetic acid (**68**)

Scheme 12. The formulae of **67–68** [31].

arrangement, exhibits higher inhibition activity against human breast adenocarcinoma (MCF-7) cell line than cisplatin and its ligand (Table 1) [37].

The heteroleptic tri-organotin(IV) compounds **88–91** (Scheme 19 [38]) of (η^5-C_5H_5)Fe(η^5-C_5H_4), and 1,10-phenanthroline (phen) or 4,4′-Bipyridine (4,4′-bipy) derivatives with trigonal bipyramidal geometry, were tested for their antitumor activity against leukemia (P388) and cervix adenocarcinoma (HeLa) cell lines [38]. Organotins(IV) **88–91** exhibit medium activity towards P388 cells line, but **90–91** exhibit strong activity towards Hela cells.

The antiproliferative activity of the bi-nuclear tri-organotin(IV) compound **92**, which contains the ligand 2-mercapto-nicotinic acid, with the two tin centres to be adopted both trigonal bi-pyramidal and

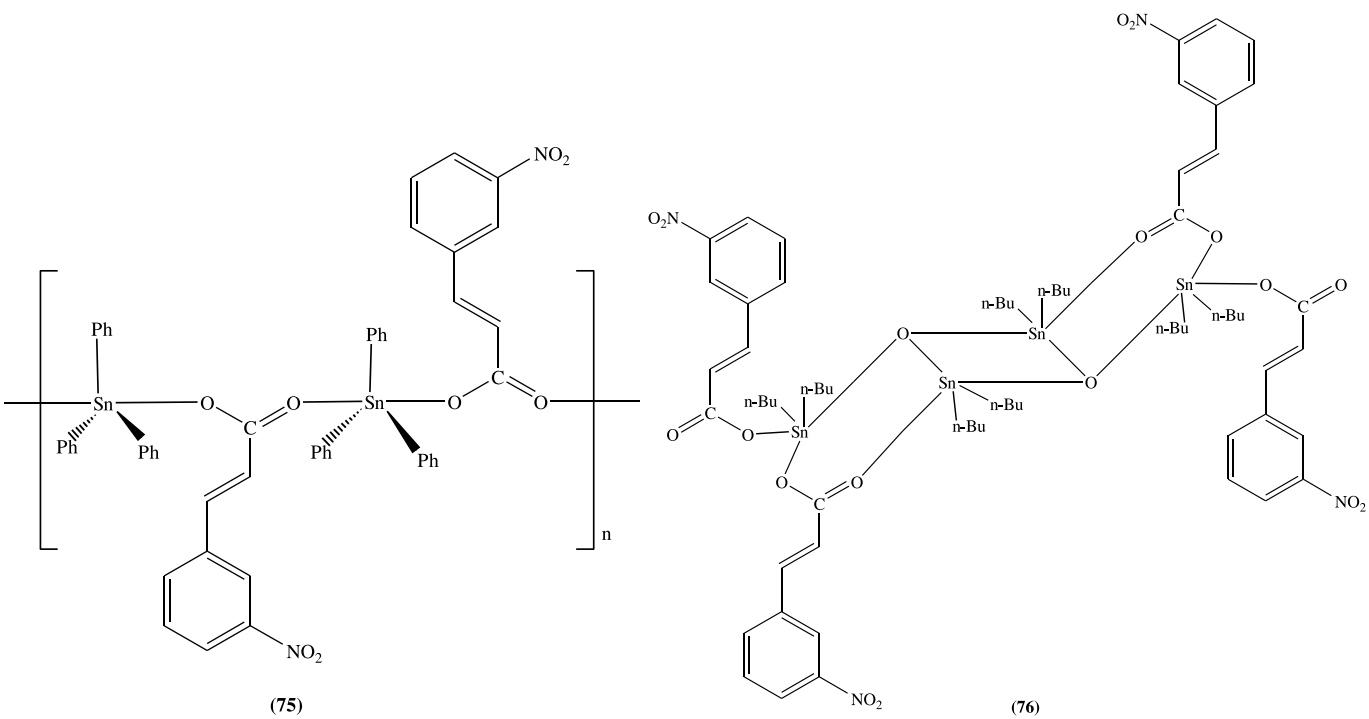


R= Me- (**69**), Et- (**70**), ^{n}Bu- (**71**), ^{n}Oct- (**72**), Ph- (**73**)

R'=

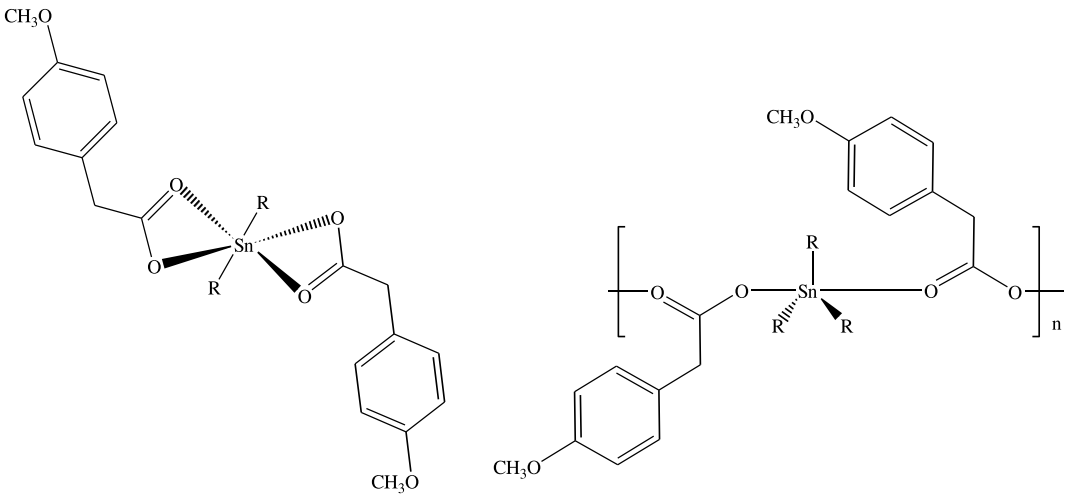
(**74**)

Scheme 13. The formulae of **69–74** [32].



(**75**) (**76**)

Scheme 14. The formulae of **75–76** [33].

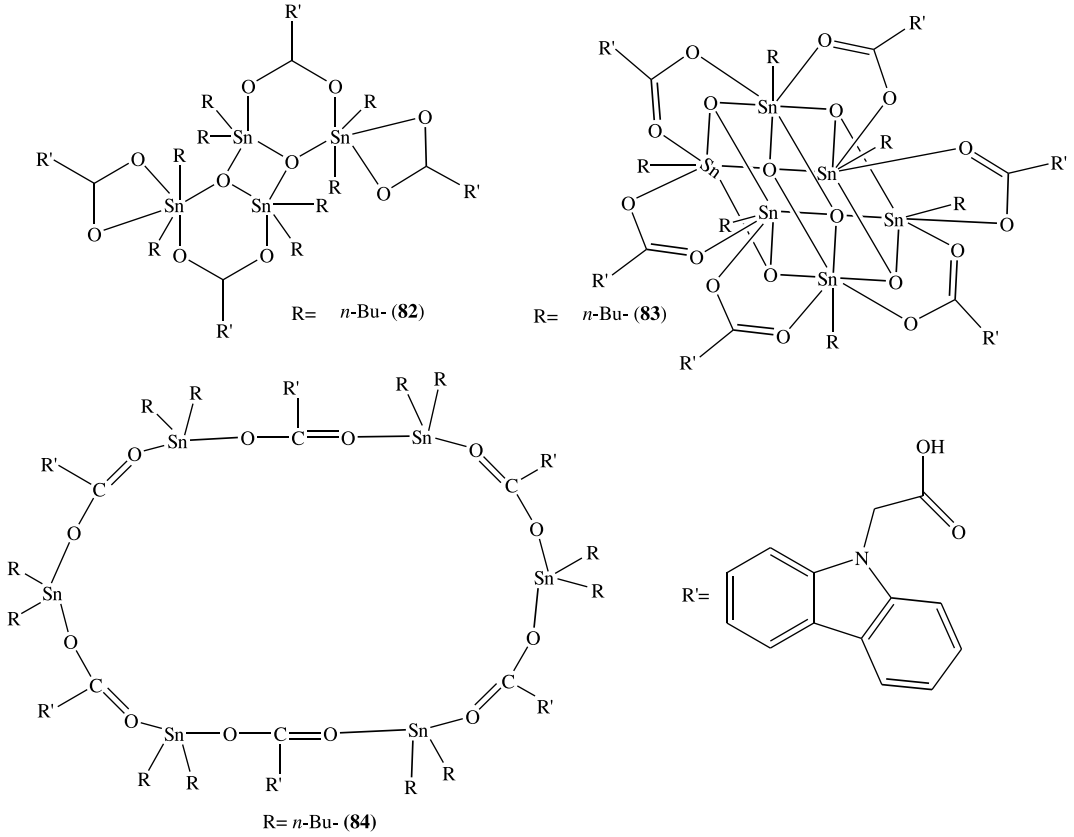


R= *n*-Bu (**77**), Et (**78**), Me (**79**), n-Octyl (**81**) R= Me (**80**)

Scheme 15. The formulae of **77–81** [34].

octahedral geometries (Scheme 20 [39]), against human breast adenocarcinoma (MCF-7) cells, is 200 times higher than cisplatin, (Table 1). The compound causes cell death through apoptosis. Its *in vivo* toxicity was tested against Wistar rats, indicating kidney and lung toxicity. The *in vivo* antitumor activity was also tested on Wistar rats [39].

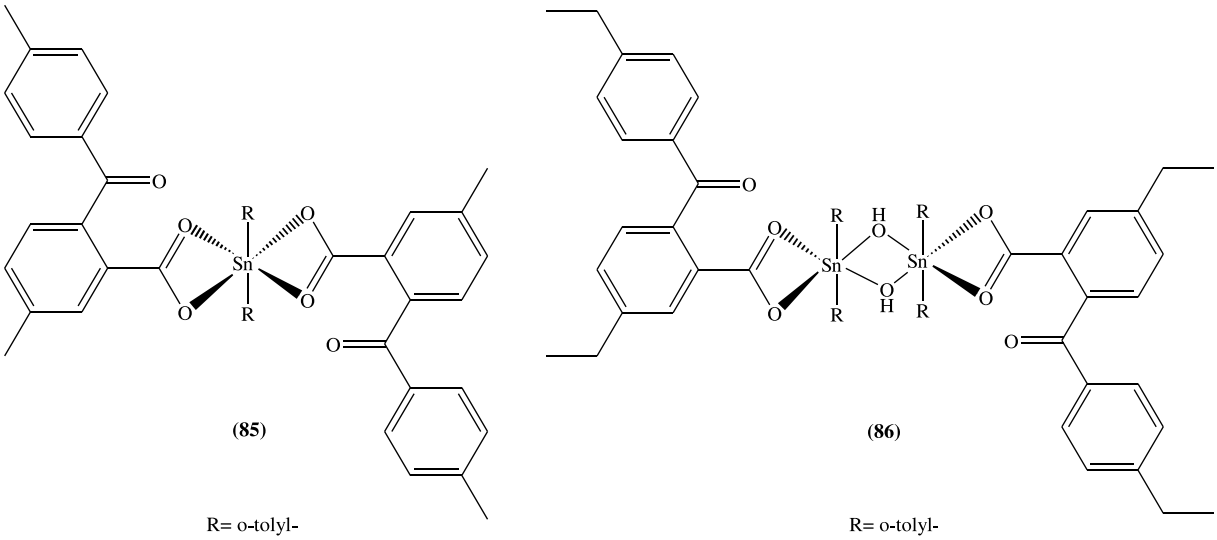
Coordination of tribenzyltin with the *N,N*-di-isopropyl-carbamothioyl-sulfanyl acetate or isonicotinate forms polymeric tri-organotin(IV) compounds (**93–102**) with trigonal bi-pyramidal geometry around tin ions (Scheme 21 [40]). The presence of tin ions in the molecules enhances the anticancer properties of the compounds against human breast adenocarcinoma, MCF-7 (positive to estrogen receptors), and MDA-MB231 (negative to estrogen receptors) and metastatic murine breast cancer nontransformed (4T1) cell lines (Table 1). The fluorine-substituted compound exhibits the highest anticancer activity, while the non-halogenated analogue exhibits the lowest activity, indicating that the fluorination improves the selectivity, reactivity and stability of the molecules. The compounds are more selective or cytotoxic towards cancer cells than normal cells (human mammary epithelial cell line, MCF-10A) and they can induce cell death *via* caspase dependent apoptosis induction and they inhibit the cell migration and invasion [40].



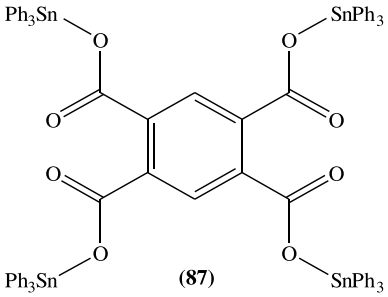
R= *n*-Bu- (**82**) R= *n*-Bu- (**83**)

R= *n*-Bu- (**84**) R'=

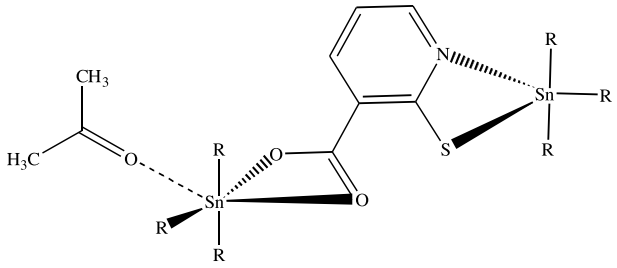
Scheme 16. The formulae of **82–84** [35].



Scheme 17. The formulae of **85–86** [36].

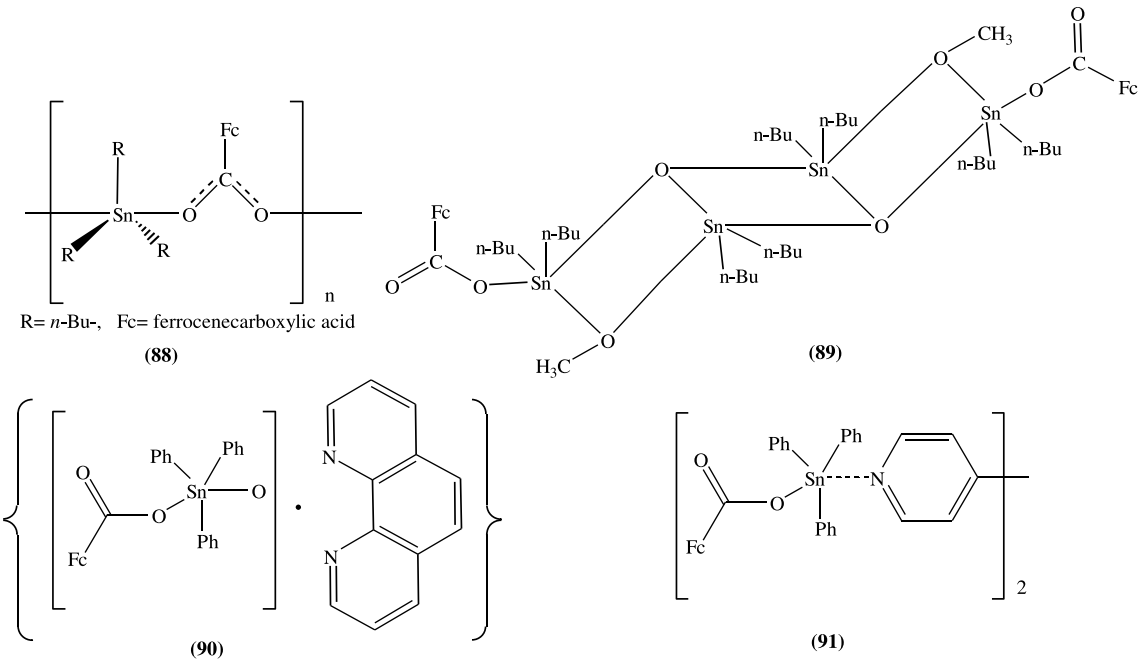


Scheme 18. The formula of **87** [37].

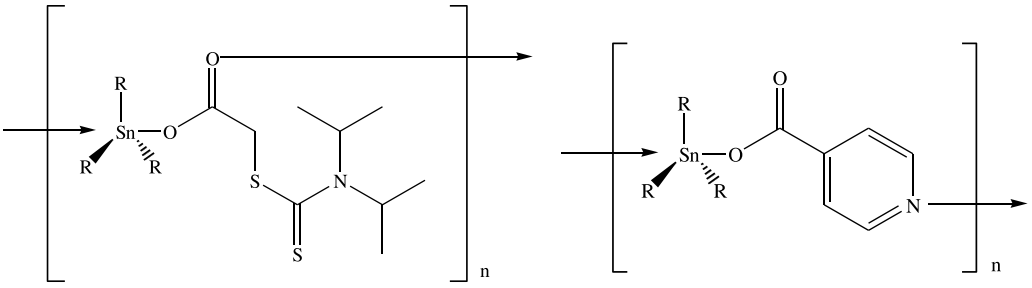


Scheme 20. The formula of **92** [39].

Organotin(IV) compounds with maleimide and naphthalimide of either octahedral or trigonal bi-pyramidal geometries (**103–111**) (Scheme 22 [41]) were investigated for their inhibitory activity towards the enzyme thioredoxin reductase and antiproliferative effect against breast adenocarcinoma (MCF-7) and colon carcinoma (HT-29) cells. The IC_{50} values are in the micromolar range (Table 1). The compounds were moderate inhibitors of thioredoxin reductase, supposed that, this enzyme is not a critical target for tin organometallics. Moreover, two of



Scheme 19. The formulae of **88–91** [38].



R= 4-FBn (**93**), 4-ClBn (**94**), 4-BrBn (**95**), Bn (**96**), Ph (**97**) R= 4-FBn (**98**), 4-ClBn (**99**), 4-BrBn (**100**), Bn (**101**), Ph (**102**)

Scheme 21. The formulae of **93–102** [40].

the tested compounds overcome the multidrug resistance in P-glycoprotein [41].

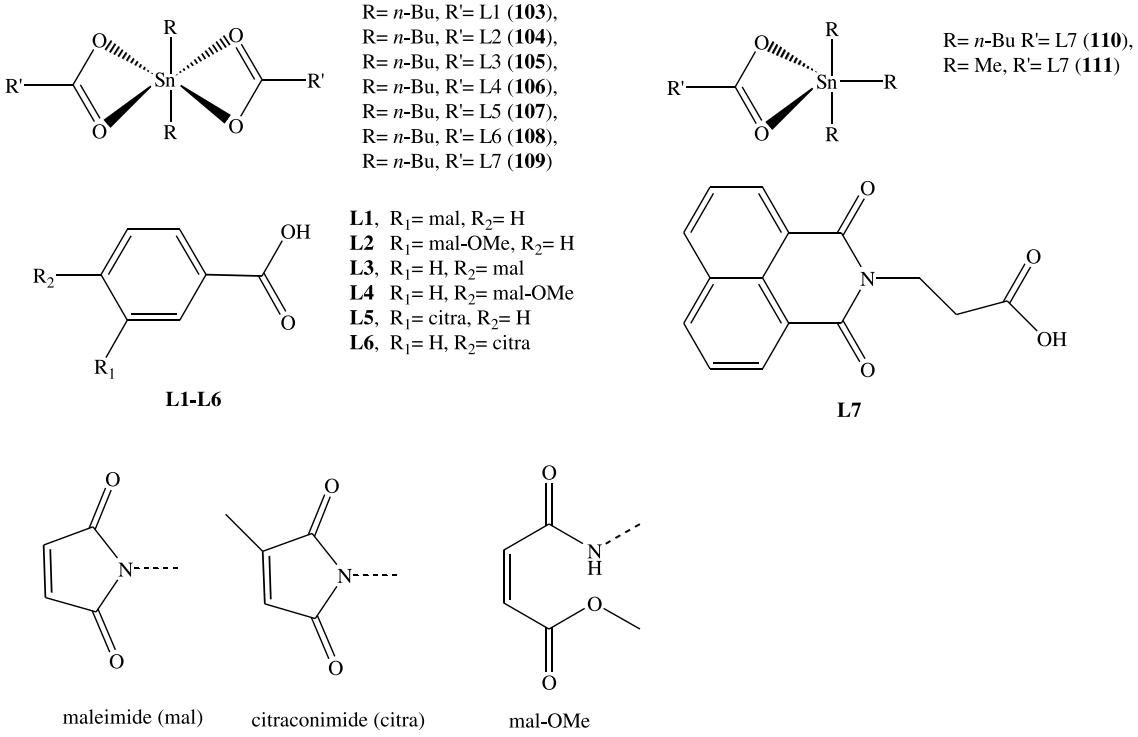
The *in vitro* cytotoxicity of the tri-organotin(IV) compounds of 3,5-di-*tert*-butyl-4-hydroxybenzoates, (**112–115**) (Scheme 23 [42]) were tested against lung carcinoma (A549) cell line. Their cytotoxic activity is higher than that of cisplatin (Table 1) [42].

Organotin(IV) carboxylates based on 1,3-benzenedicarboxylic acid and 1,4-benzenedicarboxylic acid derivatives (**116–121**) (Scheme 24 [43]) were tested for their antiproliferative activity against human cervix carcinoma (HeLa), fibrosarcoma (HT1080) and glioma (U87) cell lines [43]. The activity of the compounds **116–118** towards the cells lines used follow the order **118** > **116** > **117** (HeLa), **116** > **118** > **117** (HT1080) and **116** > **117** > **118** (U87), while the corresponding ones of **119–121** are **120** > **121** > **119** (HeLa), **119** > **121** > **120** (HT1080) and **119** > **121** > **120** (U87). The IC_{50} values, show that **118** is the most efficient antitumor agent for HeLa, while its antitumor activity is higher than that of cisplatin. Compounds **116**, **117** and **119** are most efficient antitumor agents for U87 having higher activities than cisplatin. Despite that cisplatin exhibits no cytotoxicity effect against HT1080 cancer cells, **116–118** inhibit proliferation of HT1080, with **116** to be the stronger agent for HT1080.

The tetranuclear di-organotin(IV) dicarboxylate compound (**122**) containing naphthalene-1,4-dicarboxylic acid, (Scheme 25 [44]) was checked for its cytotoxic activity against human cervix carcinoma (HeLa), fibrosarcoma (HT1080) and glioma (U87) cell lines [44]. The antitumor activity of **122** is higher than that of its ligand. From the IC_{50} values, it is concluded that the activity of **122** against HeLa cells is better than against HT1080 and U87 cell lines.

The dinuclear organotin(IV) compounds of iminodiacetic acid, 2,2′-bipyridine (Bipy), iminodiacetic acid (H_2imda) and 1,10-phenanthroline (Phen), (**123–124**) (Scheme 26 [45]) were tested for their *in vitro* cytotoxicity against murine leukemia (P388), human leukemia (HL-60) and human lung epithelial (A-549) cell lines. The inhibitory effects of the compounds **123** and **124** were relatively higher than the corresponding ones of cisplatin against tumor cell lines used, at the concentrations range tested (10^{-4}–10^{-7} M) (Table 1) [45].

The cytotoxic activities of the triphenyltin(IV) carboxylate compounds (**125–126**), containing the ligands [(2,4,6-trimethylphenyl) sulfanyl]acetic acid and [(3,5-dimethylphenyl)sulfanyl]acetic acid (Scheme 27 [46]), were tested against anaplastic thyroid carcinoma (8505C), colon carcinoma (DLD-1), cisplatin sensitive head-neck carcinoma (A253) and lung carcinoma (A549) cell lines (Table 1). The



R= *n*-Bu, R'= L1 (**103**),
R= *n*-Bu, R'= L2 (**104**),
R= *n*-Bu, R'= L3 (**105**),
R= *n*-Bu, R'= L4 (**106**),
R= *n*-Bu, R'= L5 (**107**),
R= *n*-Bu, R'= L6 (**108**),
R= *n*-Bu, R'= L7 (**109**)

R= *n*-Bu R'= L7 (**110**),
R= Me, R'= L7 (**111**)

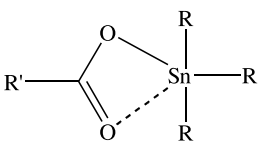
L1, R_1= mal, R_2= H
L2 R_1= mal-OMe, R_2= H
L3, R_1= H, R_2= mal
L4 R_1= H, R_2= mal-OMe
L5, R_1= citra, R_2= H
L6, R_1= H, R_2= citra

L1-L6

L7

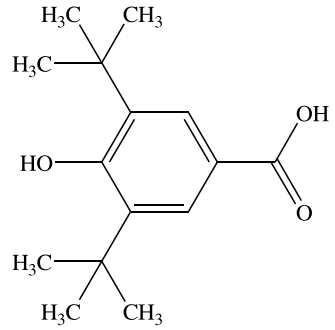
maleimide (mal) citraconimide (citra) mal-OMe

Scheme 22. The formulae of **103–111** [41].



R= c-C_6H_{11}- (**112**); C_6H_5- (**113**);
$C_6H_5CH_2$- (**114**); $C_6H_5C(CH_3)_2CH_2$- (**115**)

R'=



Scheme 23. The formulae of **112–115** [42].

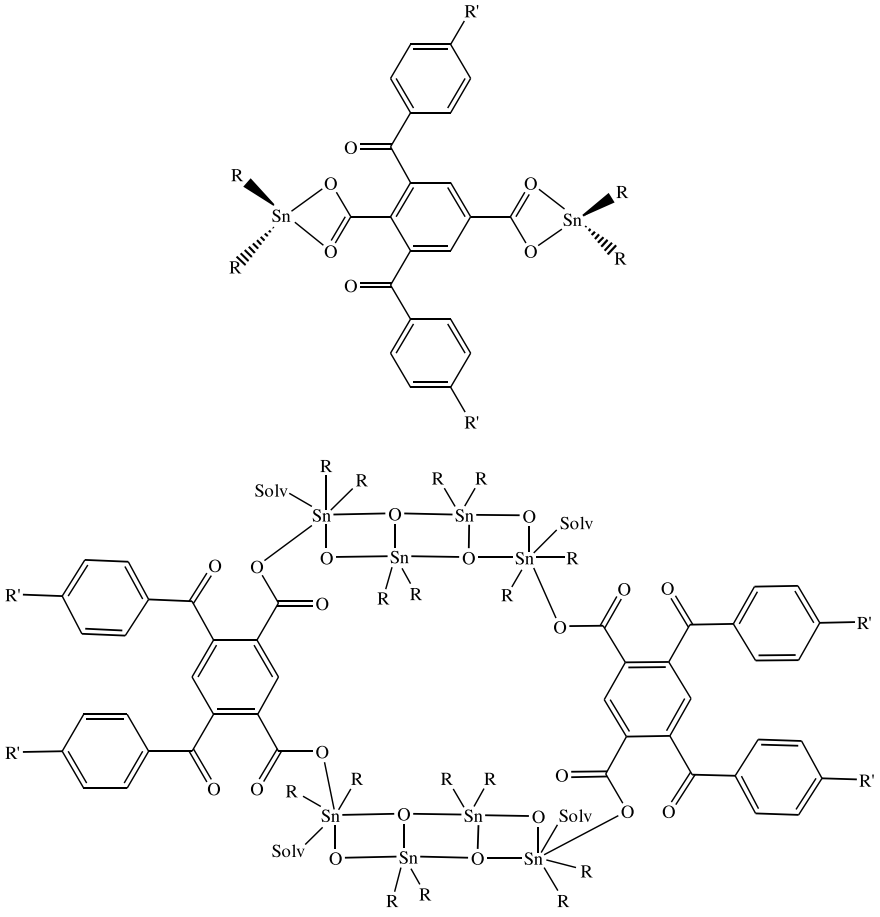
antiproliferative activity of **125–126** is higher than cisplatin up to 85 times (Table 1). Compounds **125–126** – DNA interaction tests indicate that the most cytotoxic compound show also high affinity towards DNA [46].

The antitumor activity of the 2-(4-methylbenzoyl)benzoic acid (**127**) (Scheme 28 [47]) was tested against human cervix adenocarcinoma (HeLa) cell line (Table 1) [47]. Compound **127** exhibits lower IC_{50} value than the corresponding one of cisplatin.

The organotin(IV) compounds with 4-fluorophenylsulfanylacetic acid or 4-fluorophenylselanylacetic acid (**128–135**) (Scheme 29 [48]) were evaluated for their *in vitro* cytostatic activity against human breast adenocarcinoma (MDA-MB-231) cell line (Table 1). The organoseleniumtin compounds exhibit the highest anticancer activity. The molecular mechanism of the most promising compound **131**, demonstrates its antiproliferative and apoptotic effect against MDA-MB-231 cells. The mechanism of bioactivity of **131** involves the collapsing of mitochondrial membrane potential by the ROS and releasing of cytochrome C from outer membrane of mitochondria. This activates caspase-3 consequently.

The antiproliferative activity of the organotin(IV) carboxylates (**136–138**) containing the amide carboxylic acid 2-(1,3-dioxo-1H-benzo [*de*]isoquinolin-2(3H)-yl)acetic acid, (Scheme 30 [49]) is higher than that of cisplatin against hepatocarcinoma (HepG2) and breast adenocarcinoma (MCF-7) cell lines (Table 1) [49].

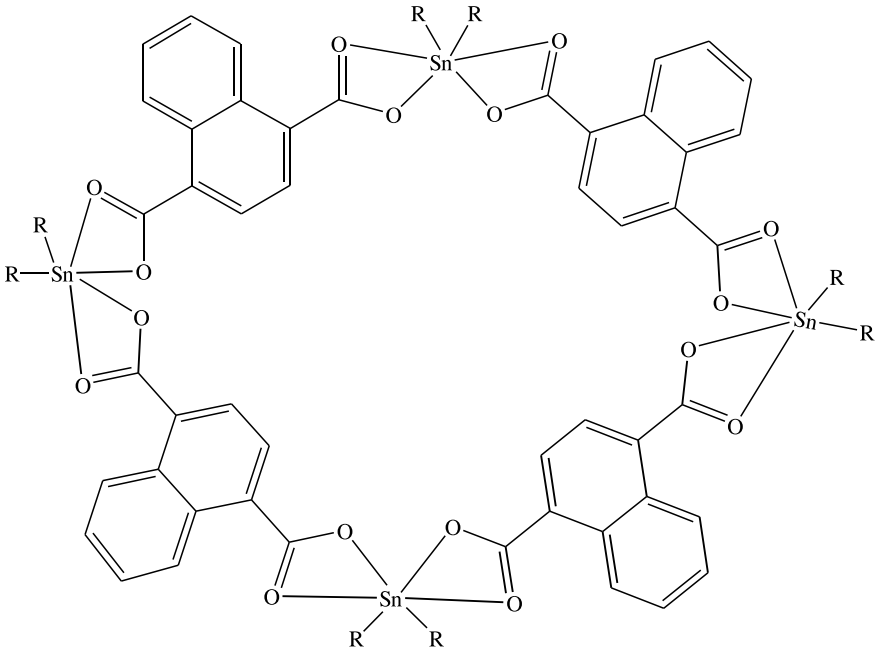
The anticancer activity of organotin(IV) carboxylates (**139–141**) (Scheme 31 [50]) of the amide carboxylic acids: 3,3′-(1,3,5,7-tetraoxo-



R= Ph, R'= H, (**116**)
R= Ph, R'= CH_3 (**117**)
R= Ph, R'= CH_2CH_3. (**118**)

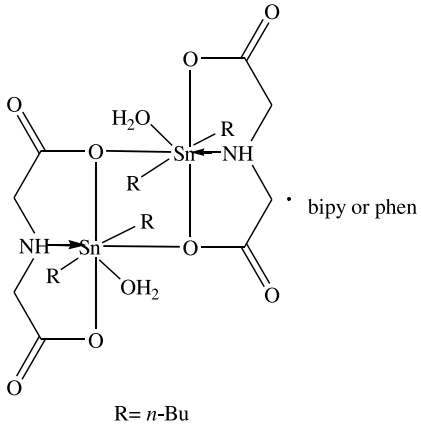
R= *n*-Bu, R'= H Solv= EtOH (**119**)
R= *n*-Bu, R'= H Solv= *n*-BuOH (**120**)
R= *n*-Bu, R'= CH_3. Solv= EtOH (**121**)

Scheme 24. The formulae of **116–121** [43].



R= *n*-Bu- (**122**)

Scheme 25. The formulae of **122** [44].



R= *n*-Bu

bipy= 2,2'-dipyridine (**123**), phen= 1,10-Phenathroline (**124**)

Scheme 26. The formulae of **123–124** [45].

5,7-dihydropyrrolo[3,4-*f*]isoindole-2,6(1H,3H)-diyl)dipropionic acid, 3,3′-(1,3,6,8-tetraoxo-1,3,6,8-tetrahydrobenzo[*lmn*][3,8]phenanthroline-2,7-diyl)dipropionic acid, 2,2′-(1,3,5,7-tetraoxo-5,7-dihydropyrrolo[3,4-*f*]isoindole-2,6(1H,3H)-diyl) dibenzoic acid, were evaluated against HepG2 cells (Table 1) [50]. The IC_{50} values illustrate that among these compounds, **139** exhibits the strongest growth inhibition against HepG2 cells.

The organotin(IV) carboxylates compounds (**142–143**) (Scheme 32 [51]) of (E)-3-(2-nitrophenyl) propenoic acid, have been screened against cervical adenocarcinoma (HeLa), fibrosarcoma (HT1080) and glioma (U87) cell lines [51]. Compound **142** exhibits the strongest activity against all cell lines used for the screening.

The chiral tri-organotin(IV) compounds (**144–149**) (Scheme 33 [52]) have been synthesized using carboxylic acids of (*R*)-(+)-methylsuccinic acid, (*S*)-(+)-methylglutaric acid and L-(−)-malic acid. The antitumor activity of **144–149** was studied against the hepatocellular carcinoma (SMMC-7721), human lung carcinoma (A549) and human breast adenocarcinoma (MCF-7) cell lines (Table 1). The most promising compounds are: **145** with IC_{50} value of 44 nM against SMMC-7721 cells, and **148** with IC_{50} value of 50 nM against MCF-7 cells. Moreover, the compounds have similar structures both in solution and solid state [52].

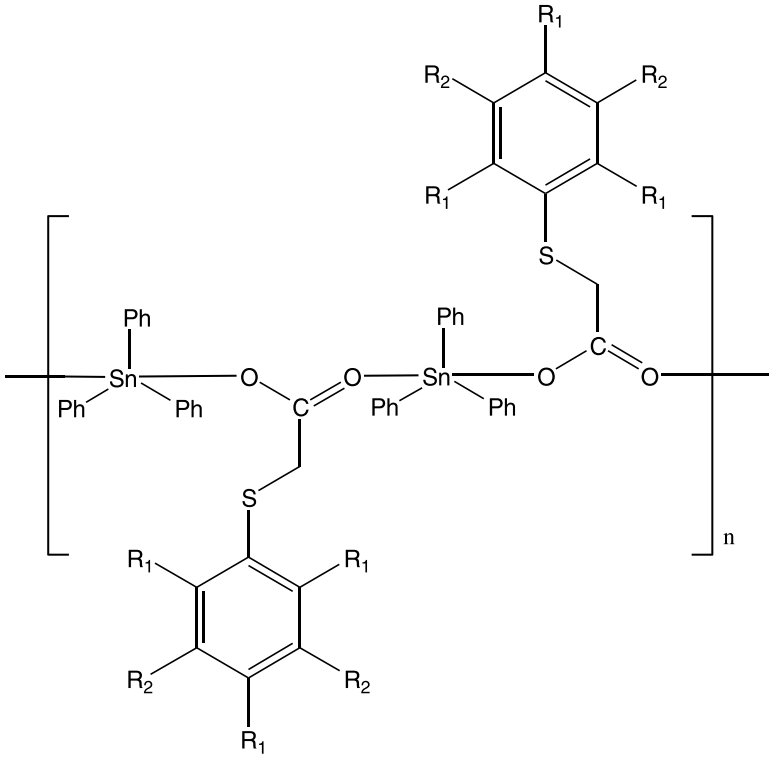
The organotin(IV) compound (**150**) (Scheme 34 [53]) exhibits strong *in vitro* antitumor activity against human cervix carcinoma (HeLa), human myelogenous leukemia (K562) and peripheral blood mononuclear cells (PBMC) (Table 1). The compound exhibits higher activity than cisplatin (up to 195 times (Table 1)). The similar IC_{50} values of the compound against cell lines, indicates that the activity of the complex may not be cell-type specific [53].

The complex (**151**) (Scheme 35 [54]) of 9-Hexyl-9H-carbazole-3-carboxylic acid, was evaluated against human hepatocellular carcinoma (BEL-7402) and human hepatocellular liver carcinoma (HepG2) cell lines (Table 1). The activity of **151** was greater than that for 5-fluorouracil, up to 74-times, for both cell lines. The high activity of **151** can be explained, by the weak Sn—O bond and the ligand replacement with DNA [54].

Two 1D chain like of benzyltin compounds (**152–153**) (Scheme 36 [55]) were evaluated for their anticancer activities against human lung cancer (NCI-H460), human hepatocellular liver carcinoma (HepG2), human breast adenocarcinoma (MCF-7) and primary human liver (HL-7702) cell lines. The compound **152** exhibits 2-fold stronger antitumor activity than that of carboplatin. The toxicity of both compounds was less towards normal cell lines than the cancerous cell lines (Table 1) [55].

Organotin(IV) benzoate compounds (**154–156**) (Scheme 37) were screened against leukemia (L1210) cell line, indicating that the triphenyltin(IV) benzoate exhibits higher antitumor activity in contrast to dibutyltin(IV) and diphenyltin(IV) analogous. The number of carbon atoms of the tin substituent seems to affect strong the anticancer activity of the tested compounds. The compound with high number of carbon atoms present the lower IC_{50} value (Table 1) [56].

Three organotin(IV) carboxylate derivatives (**157–159**) containing the ligand 3-trifluoromethyl-5-ferrocenyl-pyrazol-1-yl-acetic acid (LCOOH) (Scheme 38 [57]) have been evaluated for their anticancer



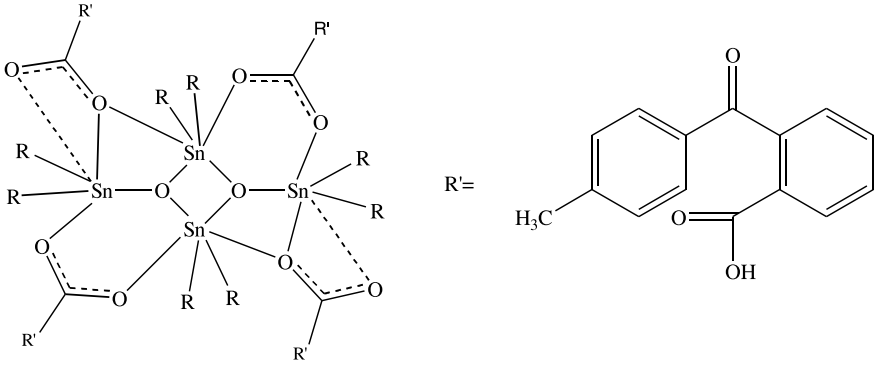
R_1= CH_3-, R_2= H, [(2,4,6-trimethylphenyl)sulfanyl]acetic acid **(125)**
R_1= H, R_2= CH_3 , [(3,5-dimethylphenyl)sulfanyl]acetic acid **(126)**

Scheme 27. The formulae of **125–126** [46].

activities towards human hepatocellular liver carcinoma (HepG2), human lung carcinoma (A549) and the melanoma (B16-F10) cell lines (Table 1). The compound **157** exhibits 18-fold higher anticancer activity than that of cisplatin, with n IC_{50} value of 41 nM (Table 1). The high activity of the compound is probably due to less number of coordination sites/bonds, which facilitates the easier formation of [$Ph_2(CH_3OH)Sn_2^+$(IV)] moiety [57].

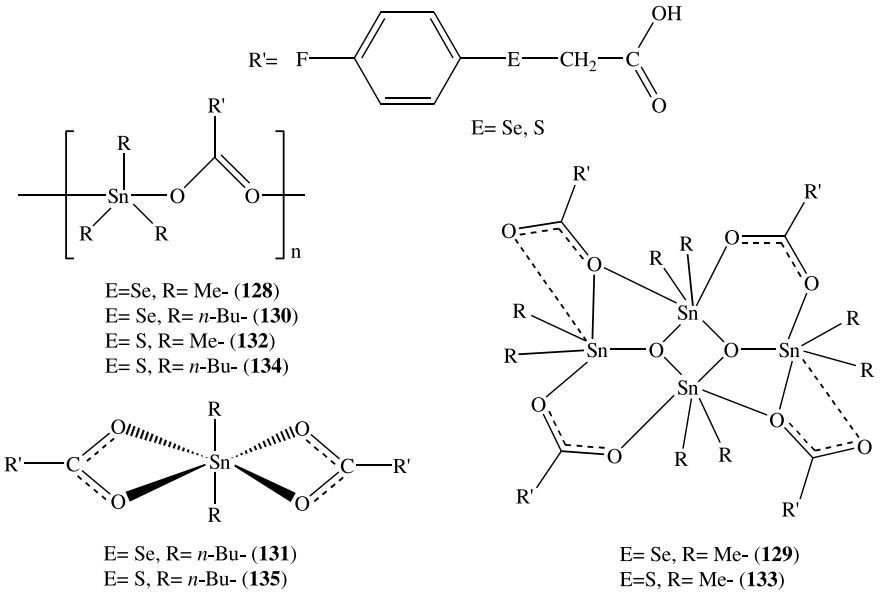
Dibutyltin(IV) compounds (**160–162**) of 2-[(*E*)-(5-tert-butyl-2-hydroxyphenyl)diazenyl] benzoate or 4-[(E)-(5-tert-butyl-2-hydroxyphenyl)diazenyl]benzoate or 4-[(E)-(4-hydroxy-5-methylphenyl)diazenyl]benzoate (Scheme 39 [58]), were tested for their antiproliferative activity against human renal carcinoma (A498), human breast adenocarcinoma (EVSA-T), human non-small-cell lung carcinoma (H226), human ovarian carcinoma (IGROV), human melanoma (M19 MEL), human breast adenocarcinoma (MCF7) and human colon carcinoma (WIDR) cell lines (Table 1). The metallodrug **162** is found to be up to 4-times superior than cisplatin (Table 1) and 16-times than the etoposide, towards MCF-7 cells. The rest of the compounds possess lower activity which it may be attributed to the steric crowding of bulky t-Bu of the ligand skeleton [58].

The tetrahedral triphenyltin(IV) compounds (**163–164**) of 2-[(E)-2-(3-formyl-4-hydroxyphenyl)-1-diazenyl]benzoate or 2-[(E)-2-(4-Hydroxy-5-methylphenyl)-1-diazenyl]benzoate (Scheme 40 [59]) were screened against human renal carcinoma (A498), human breast adenocarcinoma (EVSA-T), human non-small-cell lung carcinoma (H226), human ovarian carcinoma (IGROV), human melanoma (M19 MEL), human breast adenocarcinoma (MCF7) and human colon carcinoma (WIDR) cell lines (Table 1). Their IC_{50} values are in the range 0.07–0.17 μM. Both compounds are far superior than cisplatin. Their activity reaches up to 31 times the corresponding of cisplatin, in the

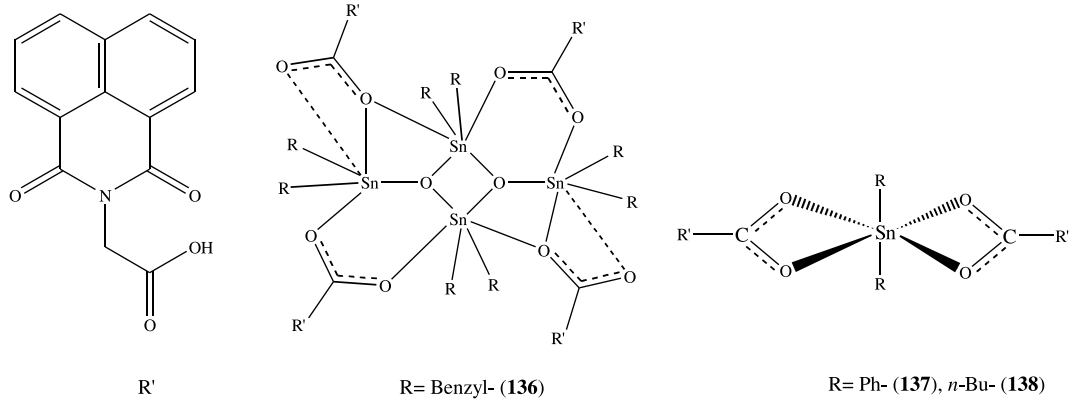


R= *n*-Bu **(127)**

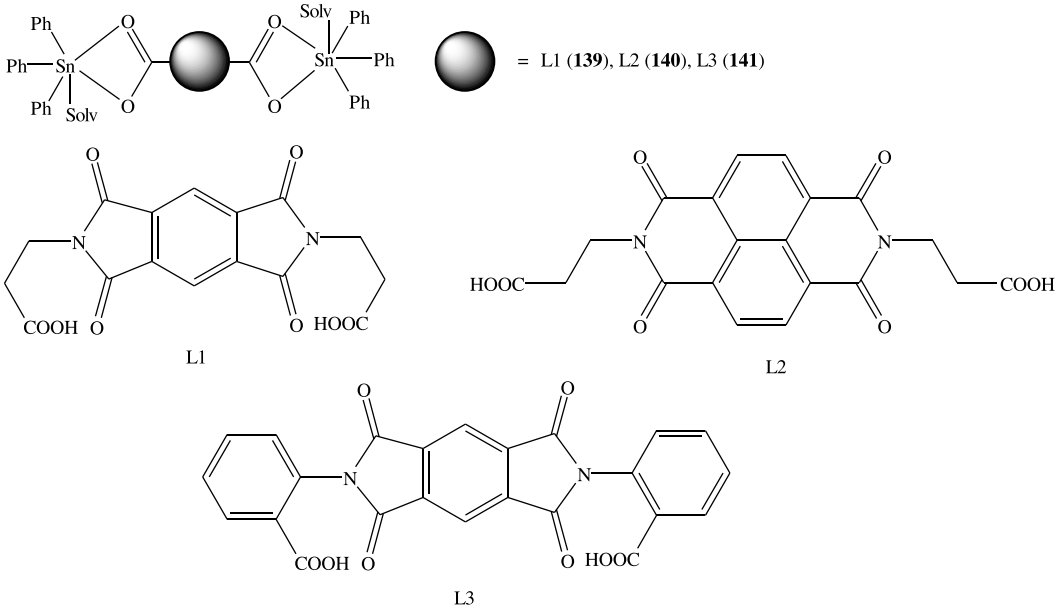
Scheme 28. The formulae of **127** [47].



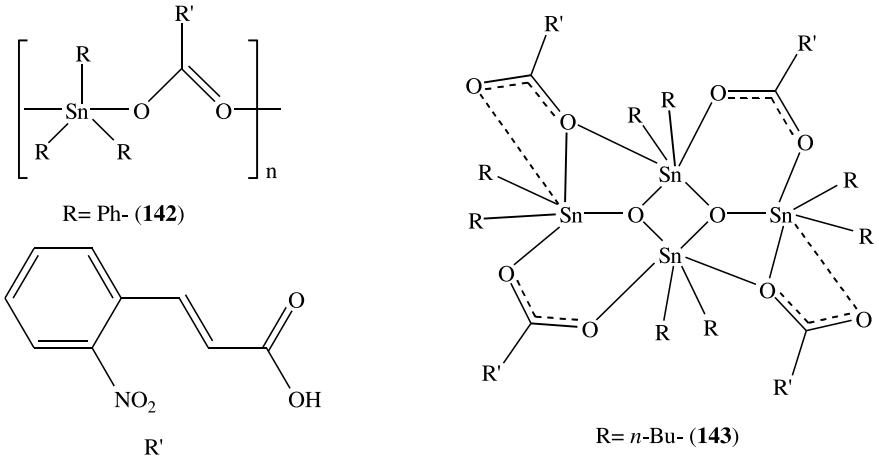
Scheme 29. The formulae of **128–135** [48].



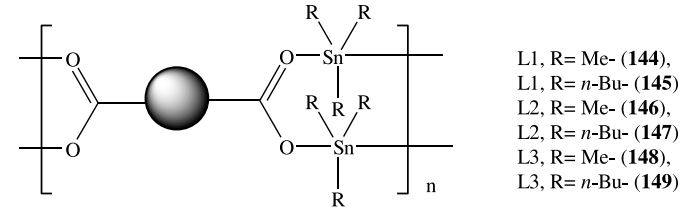
Scheme 30. The formulae of **136–138** [49].

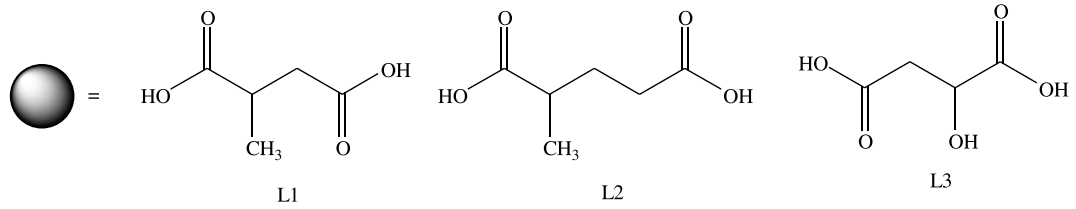


Scheme 31. The formulae of **136–138** [50].

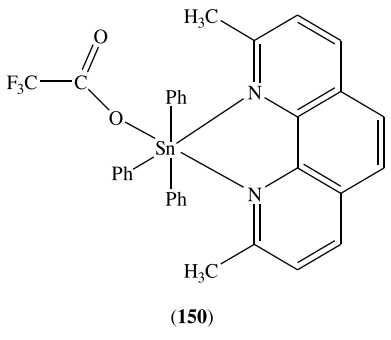


Scheme 32. The formulae of **142–143** [51].

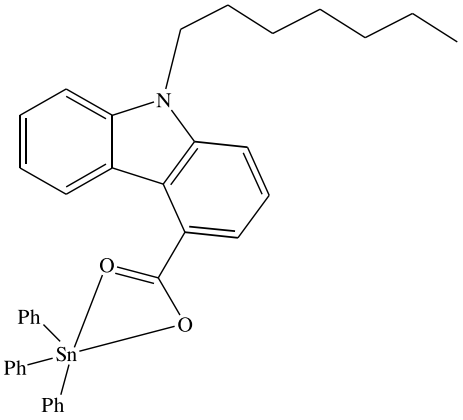




Scheme 33. The formulae of **144–149** [52].



Scheme 34. The formula of **150** [53].



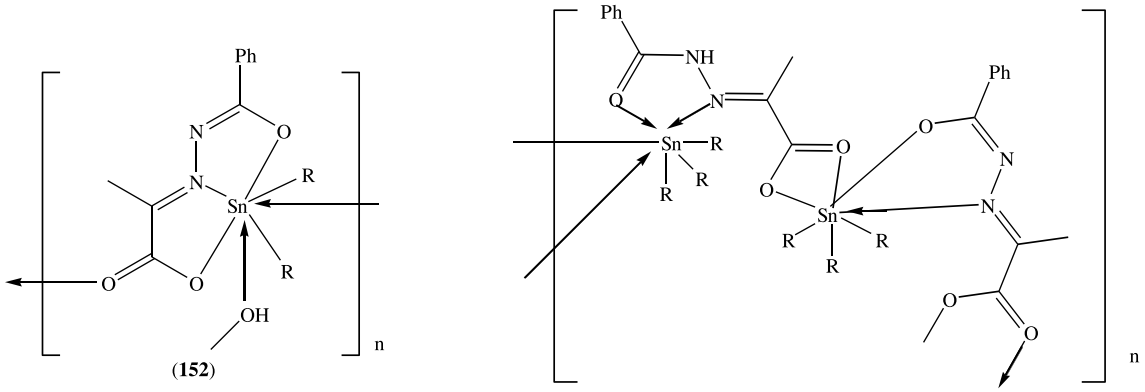
Scheme 35. The formula of **151** [54].

case of H226 cells (Table 1). The presence of the azo group affects the biological activity of the compounds towards cancerous cell lines [59].

2.2. Organotin(IV) compounds of carboxylate anti-inflammatory drugs

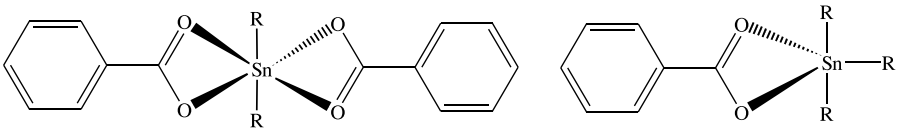
The triphenyltin(IV) complex (**165**) of the Non Steroidal Anti-inflammatory Drug meclofenamic acid (HMeclo) (Scheme 41 [60]), has been structurally characterized by IR, ^{1}H, ^{13}C NMR spectroscopies and X-ray crystallography. The geometry around the metal centre is trigonal bi-pyramidal (Scheme 41 [60]). The antiproliferative activity of **165** is higher than that of cisplatin (from 1.7 to 231 fold) against human breast adenocarcinoma (MCF-7), bladder carcinoma (T24), non-small cell lung carcinoma (A-549) and mouse fibroblast (L-929) cell lines (Table 1) [60].

The trigonal bi-pyramidal compounds of triphenyltin(IV) (**166–169**) of flufenamic acid (Hflu), 2-(2,3-dichlorophenylamino) benzoic acid (Hdcpa), 2-(2,6-dimethylphenylamino)benzoic acid (Hdmpa) and mefenamic acid (Hmef), (Scheme 42 [61]) were characterized by IR, ^{1}H, ^{13}C NMR spectroscopic and X-ray diffraction analysis. The cytotoxic activity was evaluated against human breast



(**152**) (**153**)

Scheme 36. The formula of **152–153** [55].

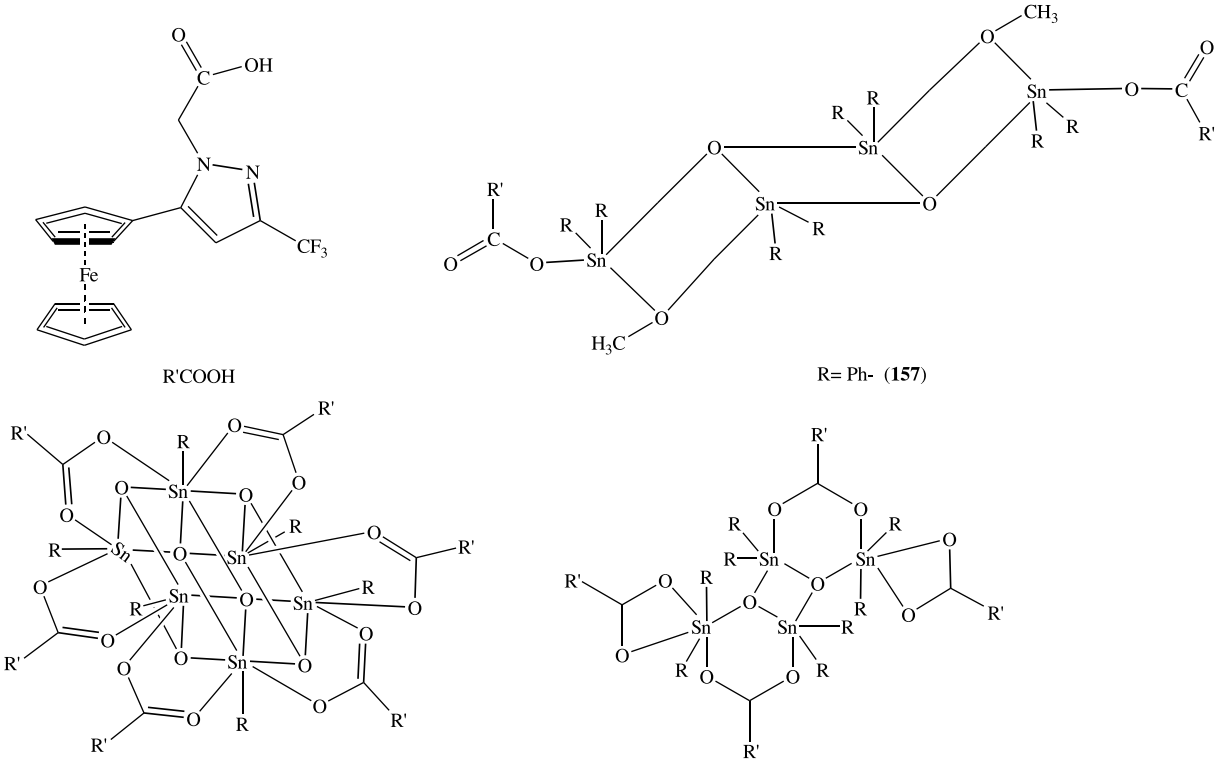


R= *n*-Bu (**154**), Ph- (**155**) R=Ph- (**156**)

Scheme 37. The formulae of **154–156** [56].

adenocarcinoma (MCF-7), bladder carcinoma (T24), non-small cell lung carcinoma (A-549) and mouse fibroblast (L-929) cell lines (Table 1). The complex **168** exhibits up to 245-fold, higher activity, than that of cisplatin (Table 1) [61].

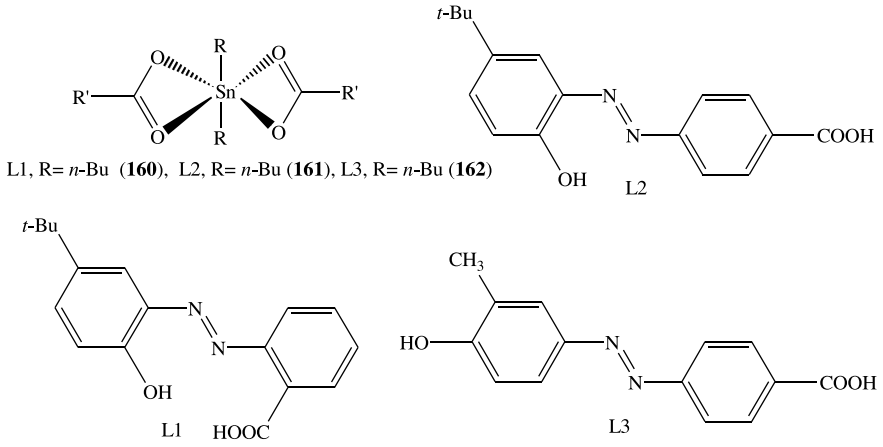
The organotin(IV) compounds (**170–176**) of 4-methoxyphenylacetic acid (4-MPAH), 2,5-dimethyl-3-furoic acid (DMFUH), BZDOH and 3-methoxyphenylacetic acid (MPAH) (Scheme 43 [62]) were tested against human adenocarcinoma (HeLa), human myelogenous leukemia (K562), human malignant melanoma (Fem-x) and peripheral blood mononuclear (PBMC) cells (Table 1). The most cytotoxic compound **171** presents IC_{50} values from 51 to 200 nM, and it is a more potent anticancer compound than cisplatin, from 30 to 112 times (Table 1). Diphenyltin(IV) derivatives show high selectivity towards tumor cell lines in contrast to normal cells but lower antitumor activity than



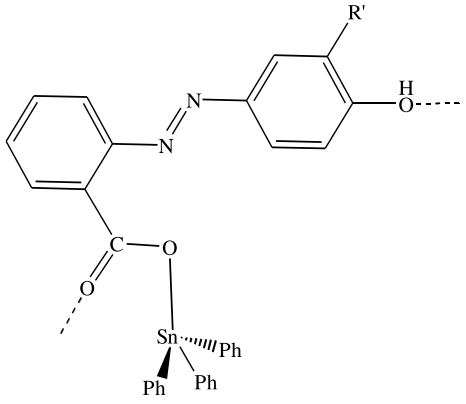
R'COOH R= Ph- (**157**)

R= *n*-Bu (**158**) R= *n*-Bu (**159**)

Scheme 38. The formulae of **157–159** [57].



Scheme 39. The formula of **160–162** [58].



Scheme 40. The formulae of **163–164** [59].

triphenyltin(IV) derivatives [62].

2.3. Organotin(IV) compounds of biological related carboxylates ligands

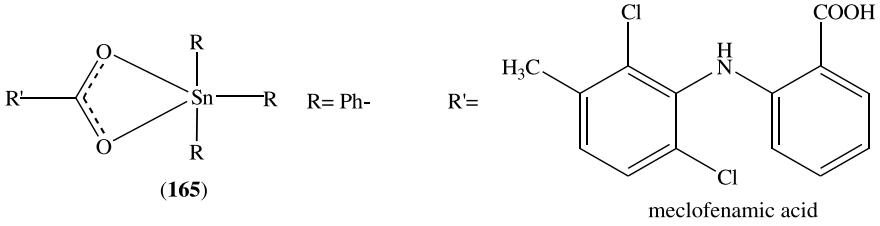
Tri- and di-organotin(IV) orotates (**177–184**) (Scheme 44 [63]) have been synthesized and characterized by X-ray diffraction. The geometry around tin atom varied between tetrahedral, trigonal bipyramidal and octahedral ones. Orotic acid, 6-uracilic acid or 1,2,3,6-tetrahydro-2,6-di-oxo-4-pyrimidine carboxylic acid, (H_3Or) is an important intermediate in the 'de nuovo' biosynthesis of pyrimidine bases. The *in vitro* anticancer activity was screened against human breast adenocarcinoma (MCF-7), human embryonic kidney (HEK-293), prostate adenocarcinoma (PC-3), colon adenocarcinoma (HCT-15) and hepatocellular carcinoma (HepG2) cell lines. All the compounds are less active than cisplatin (Table 1). DNA laddering and antioxidant enzyme assays indicate that the compounds inhibit the cancer cells growth, through apoptosis. However, marginal increase in LDH suggests that necrosis may also be occurred to a small extent. The compounds exhibit low *in vivo* toxicity (Lethal Dose values > 600 mg/kg in albino mice). The organotins(IV) exhibit similar *in vivo* anti-inflammatory activity with that of indomethacin and ibuprofen [63].

The tri-organotin(IV) hydroxycarboxylates, of glucuronic acid (HGlu), gallic acid (HGal) and mandelic acid (HMal) (**185–193**) with trigonal-bipyramidal geometry (Scheme 45 [64]) have been *in vitro* screened against human adenocarcinoma (MCF-7), kidney carcinoma (HEK-293), prostate carcinoma (PC-3), colon carcinoma (HCT-15) and hepatocellular adenocarcinoma (HepG2) cell lines. Only, the complex **192** exhibits similar or higher activity than cisplatin (Table 1). The cell death is caused through apoptosis due to the reactive oxygen species. The compounds exhibit low *in vivo* toxicity in albino mice (the lethal dose values are found in the range > 200 to 800 mg/kg) [64].

2.4. Organotins(IV) compounds of carboxylic natural products

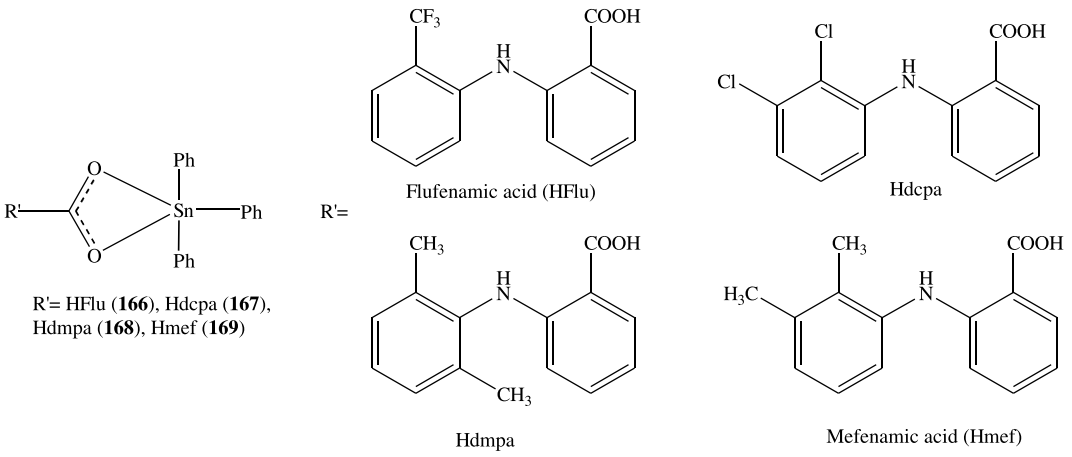
Organotin(IV) carboxylate compounds (**194–195**), containing coumarin derivatives (Scheme 46 [65]), exhibit higher cytotoxic potency than cisplatin (up to 10-times) against human cervix carcinoma (HeLa), human hepatocellular liver carcinoma (HepG2) and lung carcinoma (A549) cell lines (Table 1 [65]). The compounds show high selectivity against cancerous than non-cancerous cells (human embryonic lung fibroblast, HELF cell line). Both compounds are accumulated in the cytoplasm of HepG2 cells and induced apoptosis *via* ROS-mediated mitochondrial dysfunction pathway [65].

Organotin(IV) carboxylates of lauric (HLA), stearic (HSA) and myristic acid (HMA) (**196–211**) (Scheme 47 [66]) have been synthesized and characterized. Tri- and di-organotin(IV) carboxylates adopt trigonal bipyramidal and octahedral geometry, respectively. The compounds were evaluated for cytotoxic activity against human breast adenocarcinoma, (MCF-7), human embryonic kidney (HEK-293), prostate adenocarcinoma (PC-3), colon adenocarcinoma (HCT-15) and hepatocellular carcinoma (HepG2) cell lines (Table 1). Among the tri-organotin(IV) carboxylates, **208** exhibits the highest activity, with IC_{50} range from 0.17 to 2.8 μM against all cell lines. The antiproliferative

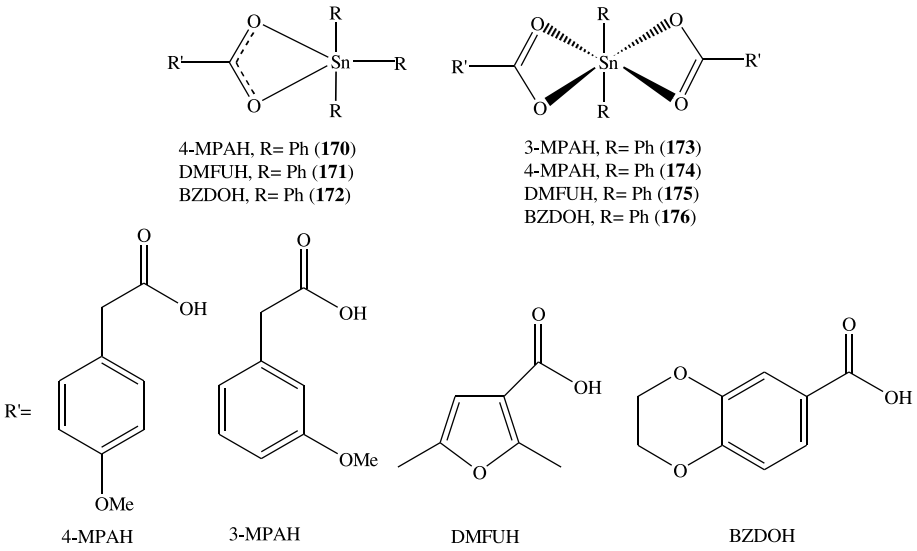


(**165**)

Scheme 41. The formula of **165** [60].



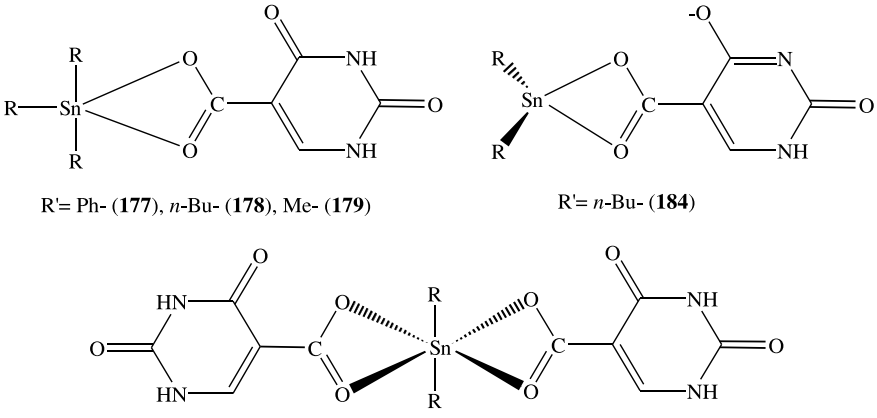
Scheme 42. The formulae of **166–169** [61].



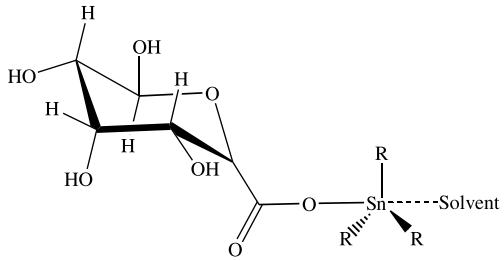
Scheme 43. The formulae of **170–176** [62].

activity of **208** is higher than that of cisplatin (up to 220 times (Table 1)). Among the di-organotin(IV) carboxylates, **210** exhibits the highest activity with IC_{50} range from 13 to 25 μM. The structure-activity correlation reveals that the tri-organotin(IV) derivatives are more active than di-organotin(IV) derivatives, the phenyl derivatives are less active than alkyl derivatives, and the order of activity of alkyl derivatives is Bu > Pr > Me ≈ Oct. Also, the increase of glutathione peroxidase activity and of lipid peroxidation shows that cancer cells undergo oxidative stress and die by apoptosis [66].

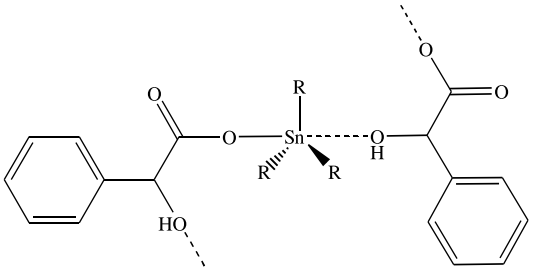
The organotin(IV) polymers of acetic acid with formula {[R_3Sn



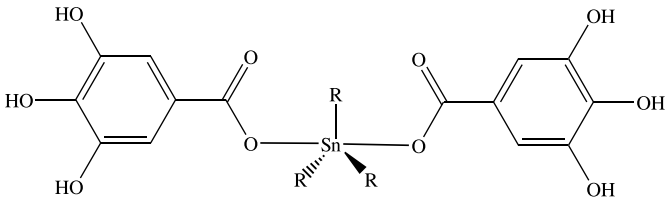
Scheme 44. The formulae of **177–184** [63].



glucuronic acid (HGlu): Ph- (**185**), *n*-Bu- (**186**), Me- (**187**)



mandelic acid (HMal): Ph- (**188**), *n*-Bu- (**189**), Me- (**190**)



gallic acid (HGal): Ph- (**191**), *n*-Bu- (**192**), Me- (**193**)

Scheme 45. The formulae of **185–193** [64].

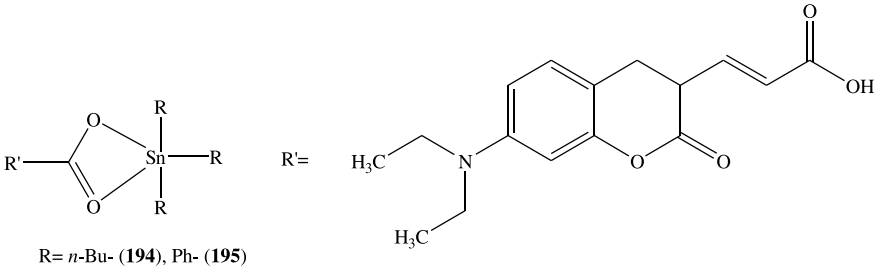
$(CH_3COO)]_n\}$ (R = *n*-Bu- (**212**) and R = Ph (**213**)) (Scheme 48 [67]), were evaluated for their *in vitro* biological properties against human breast adenocarcinoma cancer cell lines (MCF-7 (hormone depended) and MDA-MB-231 (hormone independent)). Their toxicity has been studied against MRC-5 cells. The IC_{50} values of **212** and **213** against MCF-7(HD) cells are 0.25 ± 0.02 and 0.21 ± 0.01 μM respectively, while their corresponding IC_{50} values against MDA-MB-231 cells are 0.20 ± 0.01 and 0.12 ± 0.01 μM. The lower activity of both compounds against MCF-7 than MDA-MB-231 suggests no interference of the hormone receptors to their mechanism. By taking into account the IC_{50} value of cisplatin against MCF-7 and MDA-MB-231 cells (5.5 ± 0.4 and 26.7 ± 1.1 μM respectively), both compounds exhibit extremely cytotoxic activity against these cell lines. These values indicate 22 and 26-fold higher activity of **212** and **213** against MCF-7 cells than cisplatin and 134 and 223-fold against MDA-MB-231 cells. Despite their strong activity against tumor cells, compounds also exhibit high toxic activity against MRC-5 cells with IC_{50} values of 0.22 ± 0.01 (**212**) and 0.11 ± 0.01 (**213**) μM respectively [67].

2.5. Organotin(IV) compounds of aminoacids as ligands

The di-organotin(IV) compounds **214–215** (Scheme 49 [68]) of 4-nitro-N-phthaloyl-glycine with octahedral arrangement around tin(IV) were evaluated for their *in vitro* antitumor activities against human liver carcinoma (HepG2), human gastric carcinoma (SGC-7901) and human colon carcinoma (LS174T) cancer cell lines (Table 1). Molecular mechanism studies suggested that the most potent anticancer complex **214** induces apoptosis through the mitochondrial pathway with intracellular reactive oxygen species promotion and mitochondrial membrane potential disruption by activating effector caspase-3/9. The complex **214** binds to DNA with multiple binding modes [68].

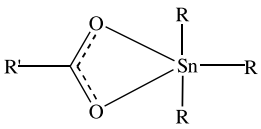
Organotin(IV) carboxylates **216–219** (Scheme 50 [69]) involving the 2-{[(2Z)-(3-hydroxy-1-methyl-2-butenylidene)]amino}-4-methyl-pentanoate and 2-{[(*E*)-1-(2-hydroxyphenyl)-alkylidene]amino}-4-methyl-pentanoate moieties have been characterized by ^{1}H, ^{13}C, ^{119}Sn NMR, IR spectroscopic techniques and X-ray analysis. Although the compounds adopt trigonal bi-pyramidal geometry around Sn(IV) ion, however the configuration of tri-organotins(IV) is 1D polymeric one while the corresponding of di-organotin(IV) is monomeric. The organotin(IV) compounds were tested against human renal carcinoma (A498), human breast adenocarcinoma (EVSA-T), human non-small-cell lung carcinoma (H226), human ovarian carcinoma (IGROV), human melanoma (M19 MEL), human breast adenocarcinoma (MCF7) and human colon carcinoma (WIDR) cell lines (Table 1). The range of IC_{50} values of **216–219** are 0.05–1.95 μM and the compounds are more cytotoxic than cisplatin, for all the cell lines studied (Table 1). The organotin(IV) compound with the ligand of potassium 2-{[(E)-1-(2-hydroxyphenyl) ethylidene]amino}-4-methyl-pentanoate is far superior to cisplatin up to 86 fold for H226 cell line. The high cytotoxicity of triphenyltin(IV) compounds is likely to be because of the non-involvement of the nitrogen atom in the complexation with the tin atom [69].

The diethyltin compounds of 2-{(E)-[(2-hydroxyphenyl)methylidene]amino}-3-phenylpropanoic acid derivatives **220–223**, have been characterized by IR, NMR (^{1}H, ^{13}C and ^{119}Sn) and X-ray. The

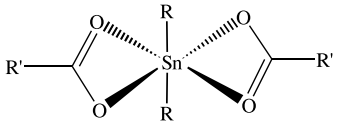


R= *n*-Bu- (**194**), Ph- (**195**)

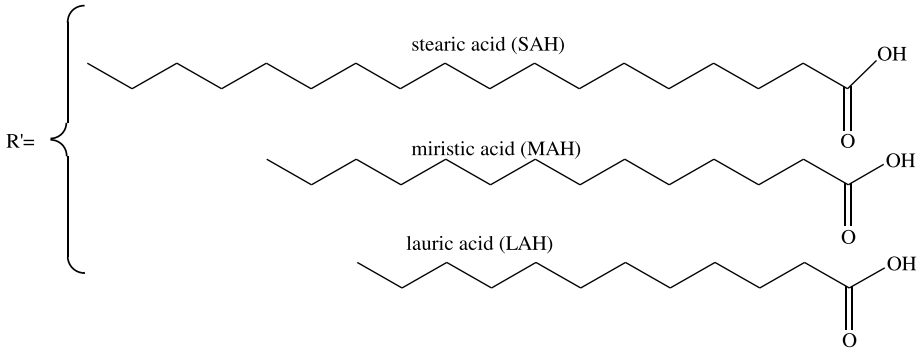
Scheme 46. The formulae of **194–195** [65].



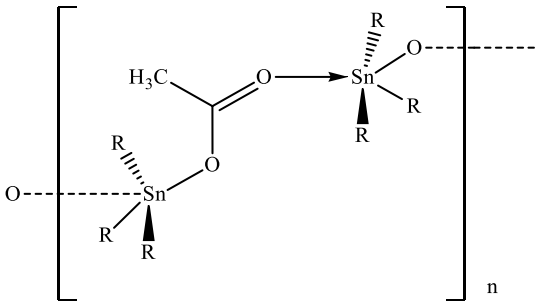
R'= SAH; R = Pr (**196**), *n*-Bu (**197**) and Ph (**198**);
R'= MAH; R = Me (**201**), Pr (**202**), *n*-Bu (**203**) and Ph (**204**);
R'= LAH; R = *n*-Bu (**208**) and Ph (**209**)



R'= SAH; R = *n*-Bu (**199**) and Oct (**200**);
R'= MAH; R = Me (**205**), *n*-Bu (**206**) and Oct (**207**);
R'= LAH; R = *n*-Bu (**210**) and Oct (**211**)



Scheme 47. The formulae of **196–211** [66].



R= *n*-Bu- (**212**) and R=Ph (**213**)

Scheme 48. The formulae of **212–213** [67].

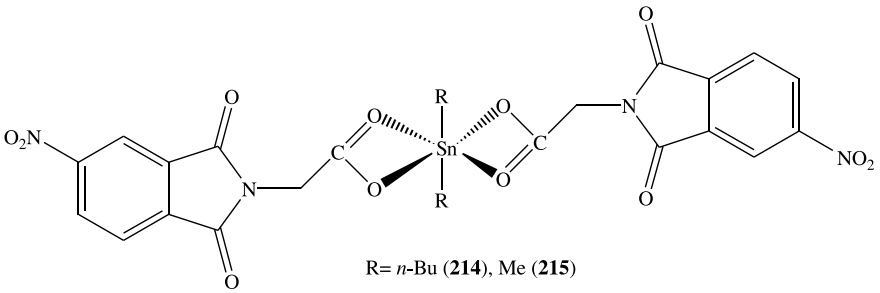
compounds assemble trigonal bipyramidal geometry around tin(IV) ions (Scheme 51 [70]). Bioassay results showed that the compounds have weaker *in vitro* activity than cisplatin (Table 1), against human lung carcinoma (A549) and colon carcinoma (CoLo205) cell lines. This indicates that the cytotoxicity depends upon the chain length and nature of the organic alkyl groups bound to tin [70].

The complex **224** of *N*-tert-butoxycarbonyl-L-ornithine (Scheme 52 [71]) exhibits 20–60 times stronger cytotoxic effect than cisplatin, against hepatocarcinoma (HepG2), breast adenocarcinoma (MCF-7) and colorectal carcinoma (HCT116) cell lines (Table 1). The mechanism of **224** against HepG2 cells, was pro-apoptotic and it is associated with externalization of plasma membrane phosphatidylserine, chromatin condensation or fragmentation and mitochondrial dysfunction, which is related to the p53-dependent activation of the mitochondrial pathway of apoptosis [71].

Octahedral di-organotin(IV) compounds **225–229** of 2-phenylmonomethylglutarate (Scheme 53 [72]), have been tested for their anticancer activity against human epidermoid carcinoma (KB) cell line. The compounds are less active against KB cell line than their ligand (Table 1) [72].

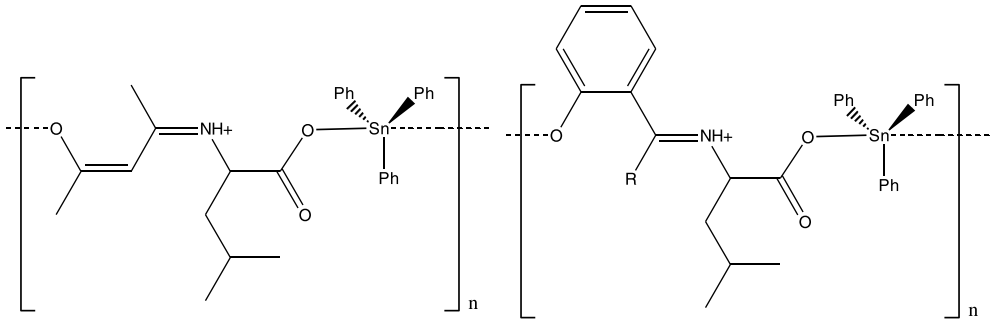
The triphenyltin(IV) chlorido compounds **230–232** (Scheme 54 [73]) of (1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)acetic acid, 2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)propanoic acid and 1,3-dioxo-1,3-dihydro-2-benzofuran-5-carboxylic acid were tested against anaplastic thyroid (8505C), head-neck carcinoma (A253), lung carcinoma (A549), ovarian carcinoma (A2780) and colon carcinoma (DLD-1) (Table 1). All the compounds are more cytotoxic than cisplatin (up to 50 times (Table 1)). The metallodrug **230** exhibits the highest IC_{50} values, 93 nM and 103 nM against A253 and DLD-1 cells, respectively. The compound induces apoptosis against DLD-1 cells *via* extrinsic pathways, probably by accumulation of caspases. It also causes cell cycle arrest in G_1 and G_2/M phases, indicating that it interacts with protein kinases and DNA. According to stability studies, the active species of the compounds are the $SnPh_3^+$ cations [73].

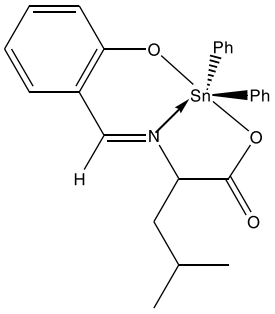
Recently, the tri- and di-organotin(IV) derivative of D-(+)-Galacturonic acid (Gala) with formulae $R_2SnGala$ [R = Me (**233**),



R= *n*-Bu (**214**), Me (**215**)

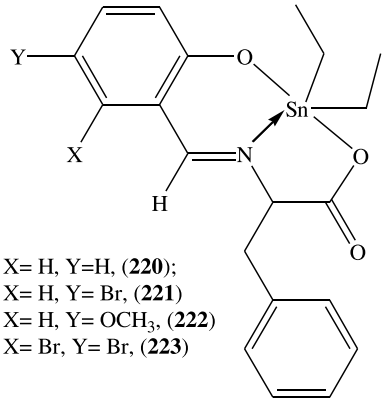
Scheme 49. The formulae of **214–215** [68].



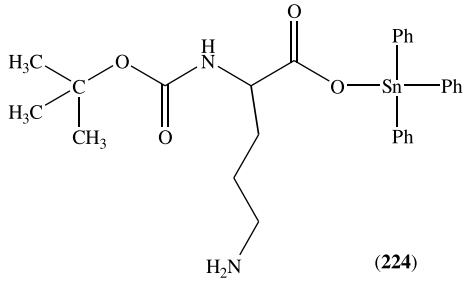


(219)

Scheme 50. The formulae of **216–219** [69].

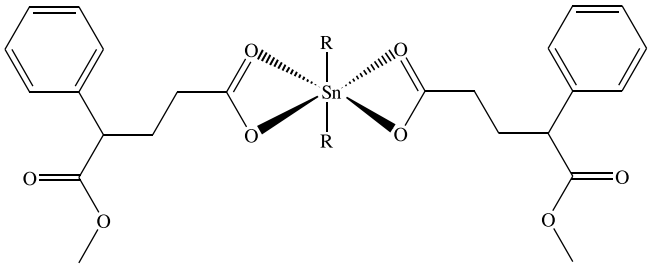


Scheme 51. The formulae of **220–223** [70].



Scheme 52. The formula of **224** [71].

n-Bu (**234**), Ph (**235**)] and $R_3SnGala$ [R = Me (**236**) *n*-Bu (**237**)] (Scheme 55 [74]) were synthesized and characterized. The acid behaves as dianion in diorganotin(IV) compounds and as mono-anion in triorganotins(IV). The compounds were tested against human tumor cell lines of intestinal carcinoma (HCT-116) and breast adenocarcinoma (MCF-7). The cytotoxicity of the compounds follows the order **237** > **235** > **234**, while **233** and **236**, are ineffective. The activity of



R= Me- (**225**), Et- (**226**), *n*-Bu (**227**), Ph- (**228**), Ph-CH_2- (**229**)

Scheme 53. The formulae of **225–229** [72].

237 is peculiar and it is stronger than cisplatin [74].

3. Organotin(IV) compounds of sulfur donor ligands

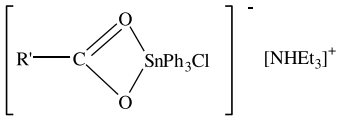
3.1. Organotin(IV) compounds of thione/thiol, thiosemicarbazones

The cytotoxic activity of *n*-butyltin(IV) compounds **238–240** of 2-pyridineformamide thiosemicarbazone (Scheme 56 [75]) has been investigated against glioblastoma cell line at the concentration of 10 μgr/ml. No IC_{50} values are given. However, the rate of the cancer cells inhibition suggests stronger activity of **240** [75].

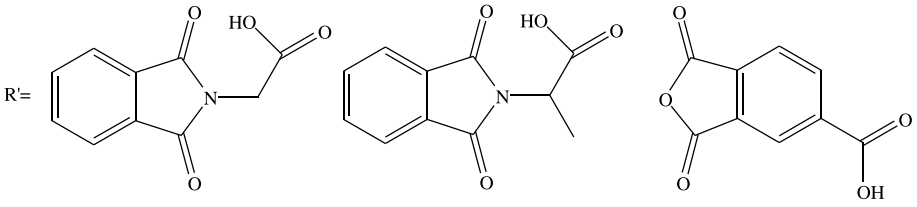
The antitumor activity of **241** (Scheme 57 [76]) of mercaptoacetic, was tested against human lung epithelial (A-549) and colon carcinoma (HCT-8) cell lines with IC_{50} values 1.9 μM and 0.7 μM, respectively (Table 2) [76].

The *in vitro* cytotoxic activity of the organotin(IV) compounds **242–243** of lupinylsulfide hydrogen fumarate (Scheme 58 [77]) was investigated in a panel of cancerous cell lines (MCF7, MDA-MB-231 (breast), A2780, OVCAR-3 (ovarian carcinoma), DBTRG-0.5MG, U87 MG, U373 MG, A-172 (glioma) and mouse glioma (GL261)), with a range of IC_{50} values between 0.16 and 1.8 μM. The *in vivo* anticancer activity of **243** was demonstrated that is able to inhibit about 96% of the tumor volume in mice [77].

The organotin(IV) compounds **244–246** (Scheme 59 [78]) of 3-

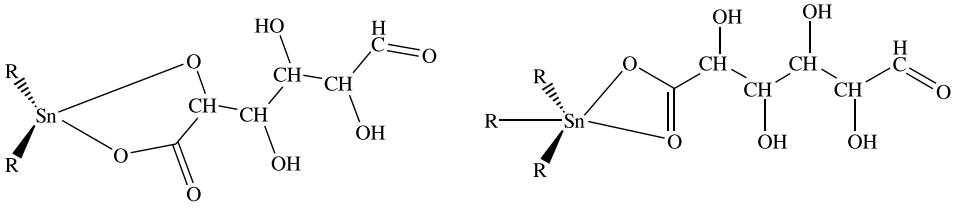


R'= P-GlyH (**230**), P-AlaH (**231**), BTCH (**232**)



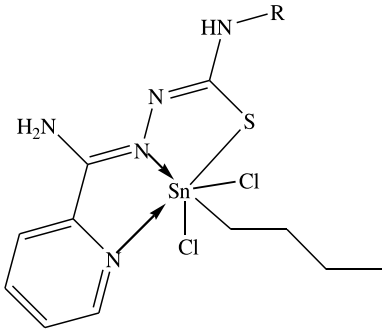
N-Phthaloyl-glycine (P-GlyH) N-Phthaloyl-L-alanine (P-AlaH) 1,2,4-Benzentricarboxylic acid 1,2-Anhydride (BTCH)

Scheme 54. The formulae of **230–232** [73].



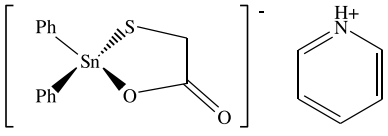
R= Me (**233**), n-Bu (**234**), Ph (**235**) R= Me (**236**), n-Bu (**237**)

Scheme 55. The formulae of **233–237** [74].



R= H- (**238**), Me- (**239**), Et- (**240**)

Scheme 56. The formulae of **238–240** [75].



(**241**)

Scheme 57. The formulae of **241** [76].

methoxysalicylaldehyde thiosemicarbazone (H_2mstsc) have been tested for their *in vitro* cytotoxicity against human acute lymphoblastic leukemia (Jurkat cells) (Table 2). The antitumor activity for the dialkyltin compounds is increased with the length of the carbon chain of the alkyl ligand, whiles the most potent compound exhibits IC_{50} value of 110 μM [78].

The compounds **247–249** (Scheme 60 [79]) of pyruvic acid thiosemicarbazone (H_2pt) were tested for their cytotoxic activity against human breast adenocarcinoma (MCF-7), bladder carcinoma (T24), non-small cell lung carcinoma (A-549) and mouse fibroblast (L-929) cell lines (Table 2). The range of IC_{50} values are 0.43 to 19.73 μM. The most potent complex is **248**, with IC_{50} value 0.43 μM against T-24 cells. **248** exhibits better activity than cisplatin, up to 96 times for the same cell line (Table 1) [79].

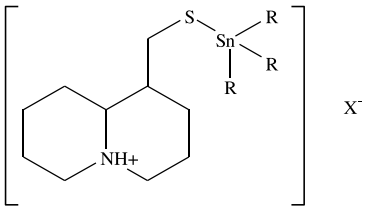
The biological activities of the organotin(IV) compounds **250–253** (Scheme 61 [80]) of 2-hydroxy-5-methoxybenzaldehyde-N(4)-methyl-thiosemicarbazone (H_2dmmt) were investigated against colorectal carcinoma (HCT116) cell line (Table 2). All compounds showed higher activity than that of 5-fluorouracil. It is also suggested that the activity of **250–253** depends on the alkyl- or aryl-groups coordinated to the tin (IV) atoms (order **253** > **252** > **250** > **251**). Compound which contains bulky phenyl group exhibits enhanced anticancer activity [80]. Since butyl organotins(IV) derivatives were more active, the difference observed in this type of compounds should be attributed to the ligand type. Therefore, the activity depends on both the alkyl, aryl substituent, and on the ligand.

R_2Sn(IV) compounds (R = Me and *n*-Bu) **254–255** of *N*-acetyl-L-cysteine (H_2NAC) (Scheme 62 [81]) were tested for their *in vitro* cytotoxic activity towards hepatocellular carcinoma (HepG2) cells and the non tumorigenic liver cells (Chang). Among them the Bu_2Sn(IV) derivative of NAC^{2-} exhibit significant selectivity to cancer than normal cells since it induces loss of viability in HCC cells and only moderates effects in non-tumor Chang liver cells. Given that H_2NAC showed lower cytotoxic activity than Bu_2SnCl_2, the binding with NAC^{2-} modulates the marked cytotoxic activity exerted by Bu_2SnCl2. Moreover compound **255** induces activation of caspase-3 [81].

The tri-organotin(IV) compounds **256–257** containing the 2-thiobarbituric acid (H_2TBA) (Scheme 63 [17,82]) with trigonal bi-pyramidal geometry were evaluated for their *in vitro* cytotoxic activity against human cancer cell lines: human cervical carcinoma (HeLa), ovarian carcinoma (OAW-42), human breast adenocarcinoma positive to estrogen receptors (MCF-7), human breast adenocarcinoma negative to estrogen receptors (MDA-MB-231), human lung carcinoma (A549)

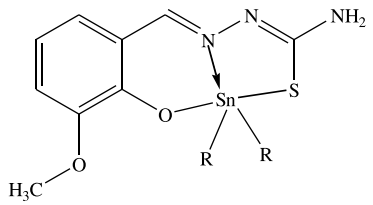
Table 2
In vitro inhibitory dose for the 50% of various cancer cell lines (IC_{50}) in μM of the organotin(IV) compounds with S-donor ligands.

Compound (scheme)	Reference	IC_{50} [cell line]
241 (57)	[76]	1.90 [A-549], 0.70 [HCT-8]
244 (59)	[78]	262.00 [Jurkat]
245 (59)	[78]	699.00 [Jurkat]
246 (59)	[78]	110.00 [Jurkat]
247 (60)	[79]	0.69 [MCF-7], 7.20 [A-549], 0.43 [T-24], 0.88 [L929]
248 (60)	[79]	1.24 [MCF-7], 0.91 [A-549], 19.73 [T-24], 1.02 [L929]
249 (60)	[79]	0.62 [MCF-7], 4.83 [A-549], 4.52 [T-24], 0.95 [L929]
250 (61)	[80]	5.45 [HCT 116]
251 (61)	[80]	6.72 [HCT 116]
252 (61)	[80]	4.38 [HCT 116]
253 (61)	[80]	3.85 [HCT 116]
256 (63)	[17,82]	0.11 [HeLa], 0.10 [MCF-7], 0.24 [A-549], 0.20 [OAW-42], 0.20 [MDA-MB-231], 0.12 [Caki-1], 0.13 [MRC-5], 0.09 [MTSV17]
257 (63)	[17,82]	0.07 [HeLa], 0.068 [MCF-7], 0.24 [A-549], 0.07 [OAW-42], 0.11 [MDA-MB-231], 0.41 [Caki-1], 0.11 [MRC-5], 0.07 [MTSV17]
264 (65)	[84]	20.64 [HeLa], 3.12 [MCF-7], > 20 [MRC-5]
265 (65)	[84]	7.86 [MCF-7]
266 (65)	[84]	0.58 [MCF-7]
267 (65)	[84]	> 30 [MCF-7]
268 (65)	[84]	> 30 [MCF-7]
269 (66)	[85]	23.90 [HeLa], 19.20 [MCF-7], 19.50 [MRC-5]
270 (66)	[85]	4.90 [HeLa], 6.20 [MCF-7], 7.30 [MRC-5]
271 (66)	[85]	0.40 [HeLa], 0.40 [MCF-7], 0.61 [MRC-5]
272 (66)	[85]	5.90 [HeLa], 6.20 [MCF-7], 12.40 [MRC-5]
273 (66)	[85]	> 30 [HeLa], > 30 [MCF-7], > 30 [MRC-5]
274 (66)	[85]	2.90 [HeLa], 4.90 [MCF-7], 3.36 [MRC-5]
275 (66)	[85]	0.16 [HeLa], 0.025 [MCF-7], 0.22 [MRC-5]
276 (67)	[86]	0.042 [CoLo205], 0.058 [Bcap37]
277 (67)	[86]	9.62 [CoLo205], 3.00 [Bcap37]
278 (68)	[87]	0.2 [HeLa], 0.36 [K562], 0.02 [PBMC-PHA]
279 (68)	[87]	0.24 [HeLa], 0.32 [K562], 0.21 [PBMC-PHA]
280 (68)	[87]	0.26 [HeLa], 0.30 [K562], 0.03 [PBMC-PHA]
281 (68)	[87]	0.28 [HeLa], 0.03 [K562], 0.03 [PBMC-PHA]
282 (69)	[88]	> 50 [K562], 32.00 [Jurkat], > 50 [HepG2], 42.30 [L929]
283 (69)	[88]	> 50 [K562], 22.00 [Jurkat], > 50 [HepG2], 40.00 [L929]
284 (69)	[88]	11.00 [K562], 1.80 [Jurkat], 10.00 [HepG2], 7.00 [L929]
285 (69)	[88]	5.80 [K562], 2.20 [Jurkat], 12.00 [HepG2], 9.00 [L929]
286 (70)	[89]	0.35 [HL-60]
287 (70)	[89]	0.40 [HL-60]
288 (71)	[90]	4.40 [HEP 3B], 4.30 [IMR 32]
289 (71)	[90]	4.50 [HEP 3B], 4.30 [IMR 32]
290 (71)	[90]	3.80 [HEP 3B], 5.70 [IMR 32]
291 (71)	[90]	2.90 [HEP 3B], 3.10 [IMR 32]
292 (71)	[90]	3.00 [HEP 3B], 3.50 [IMR 32]
293 (71)	[90]	3.80 [HEP 3B], 6.10 [IMR 32]
294 (72)	[91]	0.21 [HeLa], 0.02 [K562], 0.008 [PBMC-PHA]
295 (72)	[91]	0.40 [HeLa], 0.40 [K562], 0.63 [PBMC-PHA]



R= Et-, X= Cl^- (**242**)
R= *n*-Bu-; X= $HOOC\text{-}CH{=}CH\text{-}COO^-$ (**243**)

Scheme 58. The formulae of **242–243** [77].



R= Ph (**244**), Me (**245**), *n*-Bu (**246**)

Scheme 59. The formulae of **244–246** [78].

and renal carcinoma (Caki-1). Their toxicity was evaluated towards normal human fetal lung fibroblast cells (MRC-5) and normal immortalized human mammary gland epithelial cells (MTSV17) (Table 2). The compounds can induce apoptosis and cell cycle arrest in phase S, suggesting DNA intercalation (direct or indirect) or interaction with metalloenzymes, such as lipoxygenase (LOX) [17,82].

Organotin(IV) compounds **258–263** (Scheme 64 [83]) containing heterocyclic thioamides: 2-mercapto-benzothiazole (Hmbzt), 5-chloro-2-mercapto-benzothiazole (Hcmbzt), 2-mercapto-benzoxazole (Hmbzo) were tested for their cytotoxic activity against leiomyosarcoma cells from Wistar rat. The compounds inhibit strongly the metalloenzyme of lipoxygenase (LOX) through a free radical mechanism. It is notified that **258–263** inhibit LOX within the same manner that the cancerous cells are inhibited. Therefore, LOX inhibition could be used for pre-screening evaluation of the antiproliferative activity of this type of compounds [83].

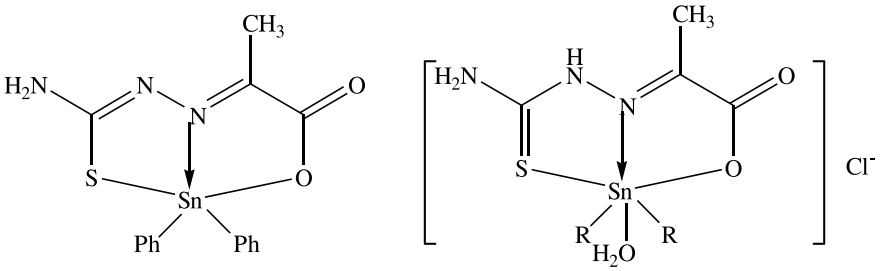
The compounds **264–268** derived from dichloridobis(3,5-di-tert-butyl-phenyl)tin(IV) (Scheme 65 [84]) with the heterocyclic thioamides: 2-mercapto-pyrimidine (PMTH), 2-mercapto-4-methyl-pyrimidine (MPMTH), 2-mercapto-pyridine (PYTH), 2-mercapto-benzothiazole (MBZTH), (Scheme 65 [84]) were tested for their *in vitro* cytotoxicity against human breast adenocarcinoma (MCF-7) cells (Table 2). The compound **265** exhibits 32 fold stronger activity than that of cisplatin (Table 1). The anticancer activity of this series of compounds is attributed to the stable free radicals formed in solution [84].

The biological activity of organotin(IV) compounds **269–275** (Scheme 66 [85]) containing dichloridobis(3,5-di-tert-butyl-phenyl)tin (IV), were tested against human breast adenocarcinoma (MCF-7) and human cervical carcinoma (HeLa) cells. The toxicity of compounds was also evaluated towards normal human fetal lung fibroblast cells (MRC-5) (Table 2). The range of IC_{50} values of the compounds is 0.16 to > 30 μM, for all tested cell lines. The highest activity against both cell lines was determined for the triphenyltin complex **275** with IC_{50} values 250 nM (MCF-7) and 160 nM (HeLa). The compound **275** is more cytotoxic than cisplatin up to 75-fold (Table 1). The high antiproliferative activity of **275** is attributed to its high lipophilicity and its ability to interact with colchicine site of tubulin which causes antimitotic activity. Also, the highly hindered phenol groups decrease the cytotoxicity of compounds against normal cells [85].

3.2. Organotin(IV) compounds of dithiocarbamates

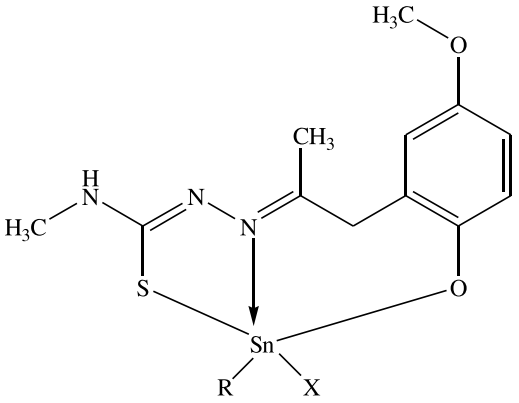
The phenyltin(IV) compounds **276–277** (Scheme 67 [86]) were tested for their *in vitro* cytotoxicity activity against colon carcinoma (CoLo205) and human breast cancer (Bcap37) cell lines (Table 1). Both compounds are more active than cisplatin up to 330-fold against CoLo205 cell line (Table 1). The chlorodiphenyltin complex displays weak cytotoxic activity in contrast to the triphenyltin ones, due to the coordination of a chloride on tin atom [86].

The cytotoxic activity of the di-organotin(IV) compounds **278–281** (Scheme 68 [87]) with the ligand morpholine-1-carbodithioate (MCDT)



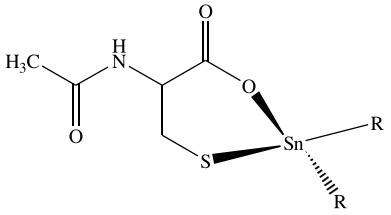
(**247**) R= Me- (**248**), Ph- (**249**)

Scheme 60. The formulae of **247–249** [79].



R= Me-, X= Cl (**250**); R= *n*-Bu, X= Cl (**251**); R= Ph-, X= Cl (**252**); R= Ph-, X= Ph- (**253**)

Scheme 61. The formulae of **250–253** [80].



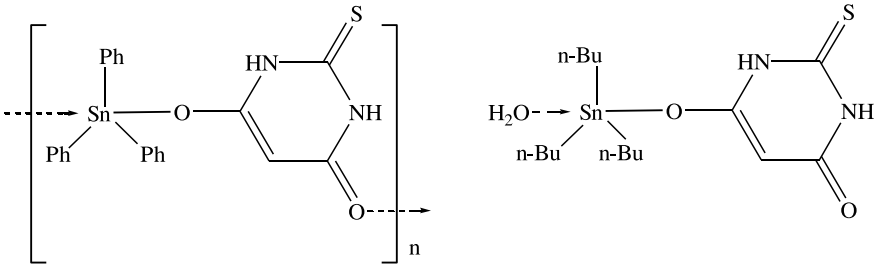
R= Me- (**254**), *n*-Bu- (**255**)

Scheme 62. The formulae of **254–255** [81].

was evaluated against human cervical carcinoma (HeLa), human myelogenous leukemia (K562) and normal immunocompetent cells: peripheral blood mononuclear cells (PBMC + PHA) (Table 2). The bioassay results indicate that the organotin(IV) compound with the benzyl moiety presents 85-fold higher activity than that of cisplatin against K562 cells. The organotin(IV) compound with the methyl moiety presents the highest activity against HeLa cells which is also 15-fold higher than that of cisplatin (Table 1). The tested compounds show also high cytotoxic activity against PBMC + PHA [87].

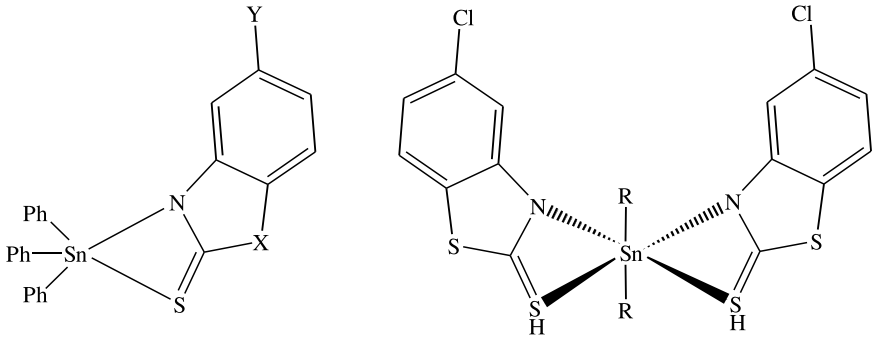
The compounds **282–285** (Scheme 69 [88]) of p-bromo-*N*-methylbenzylaminedithiocarbamate and p-fluoro-*N*-methylbenzylaminedithiocarbamate were evaluated for their *in vitro* antiproliferative activity against human leukemic lymphoblastoma Jurkat cells, human myelogenous leukemia (K562), hepatocellular carcinoma (HepG2) and mouse fibroblast (L-929) cell lines (Table 2). While the dibutyltin compounds exhibit the highest antiproliferative effect compared to the dimethyltin ones, all tested compounds are less active than doxorubicin [88].

Organotin(IV) dithiocarbamate compounds **286–287** of methoxyethyldithiocarbamate (Scheme 70 [89]) were evaluated for their *in*



(**256**) (**257**)

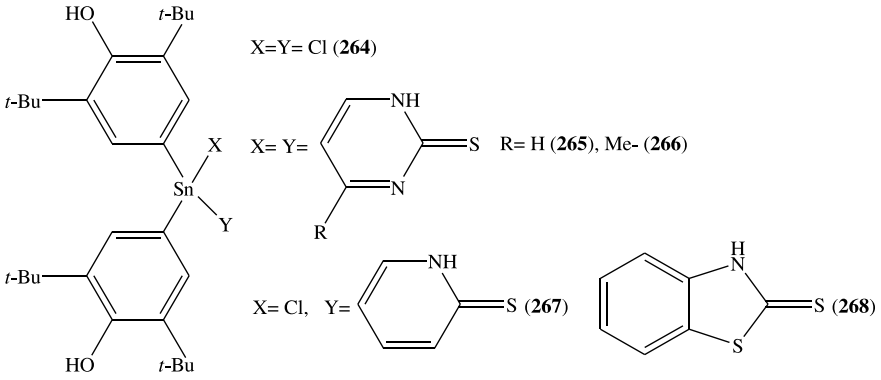
Scheme 63. The formulae of **256–257** [82].



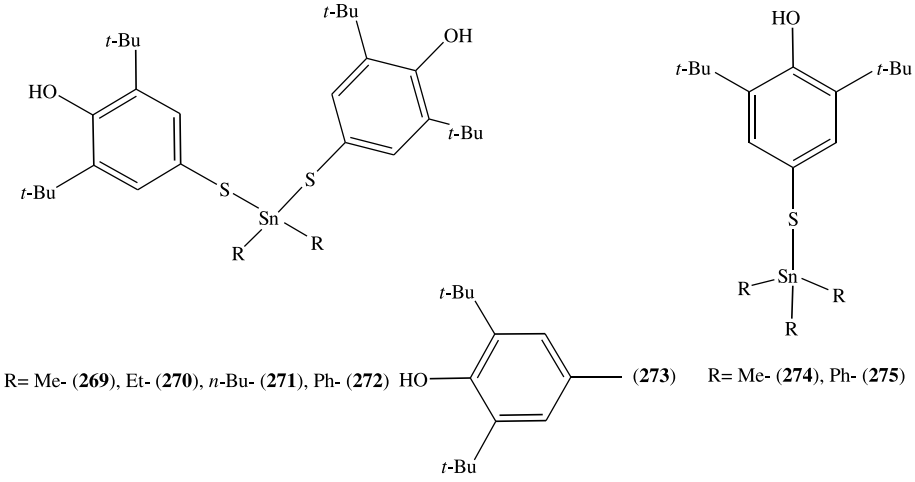
X= S, Y= H; [$Ph_3Sn(mbzt)$] (**258**),
X= O, Y= H; [$Ph_3Sn(mbzo)$] (**259**),
X= S, Y= Cl; [$Ph_3Sn(cmbzt)$] (**260**)

R=Ph-; [$Ph_2Sn(cmbzt)_2$] (**261**),
R= *n*-Bu-; [$(n\text{-}Bu)_2Sn(cmbzt)_2$] (**262**),
R= Me-; [$Me_2Sn(cmbzt)_2$] (**263**)

Scheme 64. The formulae of **258–263** [83].



Scheme 65. The formulae of **264–268** [84].

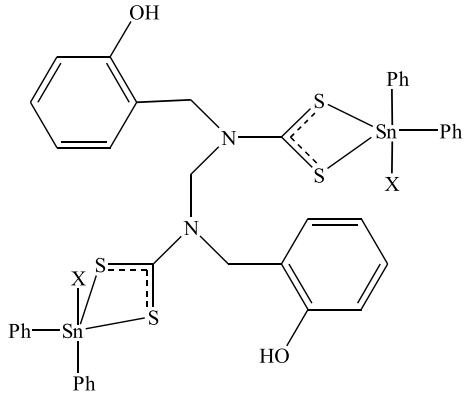


Scheme 66. The formulae of **269–275** [85].

vitro antiproliferative activity against promyelocytic leukemic (HL-60) cell line. Both compounds show lower activity than that of doxorubicin hydrochloride (Table 2) [89].

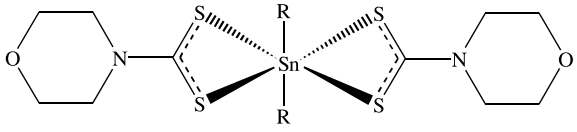
Binuclear diphenyltin(IV) dithiocabamate macrocyclic compounds **288–293** (Scheme 71 [90]) were synthesized and evaluated for their cytotoxicity against hepatoma (HEP 3B) and neuroblastoma (IMR 32) cell lines (Table 2). The range of IC_{50} values lie between 3.0 and 6.1 μM in both cell lines. The compounds found to be active against both cell lines and the cytotoxicity data showed up 20-fold better potency than cisplatin (Table 1). Moreover, the compounds cause apoptosis in the tested cell lines [90].

The cytotoxic activity of **294–295** of morpholine-1-carbodithioate (MCDT) (Scheme 72 [91]) was investigated towards human cervix carcinoma (HeLa), human myelogenous leukemia (K562) and peripheral blood mononuclear cells (PBMC) (Table 2). Both compounds present lower IC_{50} values (IC_{50} range between 0.008 and 0.63 μM) than those of cisplatin (Table 1). The replacement of the benzyl group with the phenyl one increases the cytotoxic activity [91].



X= Ph- (**276**), Cl- (**277**)

Scheme 67. The formulae of **276–277** [86].



R= Me- (**278**), *n*-Bu- (**279**), Ph- (**280**), Ph-CH_2- (**281**)

Scheme 68. The formulae of **278–281** [87].

4. Organotin(IV) compounds of oximes as ligands

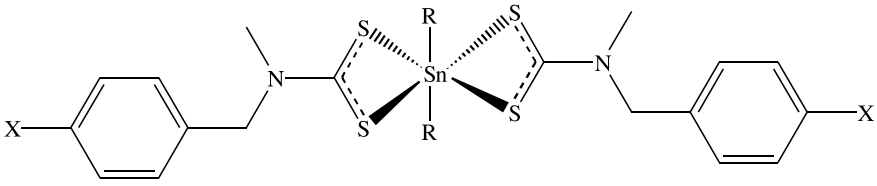
Di-organotin(IV) derivatives **296–299** (Scheme 73 [92]) were evaluated for their *in vitro* and *in vivo* antitumor activity against cancerous cells (hepatocellular carcinoma (HepG2), human neuroblastoma (SHSY5Y), human endometrial adenocarcinoma (HEC-1-B), human embryonal carcinoma (EC), bladder carcinoma (T24), human cervical carcinoma (HeLa) and human lung carcinoma (A549)) (Table 3). The di-organotin(IV) compounds caused a dose-dependent growth inhibition. The compound **296** exerted the strongest cytotoxicity but the weakest antitumor *in vivo* activity. The compound **298** show the lowest antitumor activity one *in vitro* and the highest one *in vivo*. The difference between the activities *in vivo* and *in vitro* may be due to their difference in the absorption, distribution in tissues, organs, and the metabolism of compounds due to their different lipophilicity [92].

Di-organotin(IV) cycloalkylhydroxamate compounds **300–311** with different ring sizes (cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl) (Scheme 74 [93]), were tested against human leukemia (HL-60), hepatocellular carcinoma (BEL-7402), gastric carcinoma (BGC-823) and nasopharyngeal carcinoma (KB) cell lines at the concentration of 10 μM [93]. The results showed that among **300–311**, **306** exhibits the strongest activity against HL-60 cells, compound **303** against BGC-823 cells; **302** against Bel-7402 cells and **305** against KB cells.

The di-organotin(IV) complex **312** (Scheme 75 [94–96]), of the 4-chlorobenzohydroxamic acid was examined for *in vitro* cytotoxic activity, towards human leukemia (HL-60), human gastric carcinoma (SGC-7901), cervix adenocarcinoma (HeLa) and bladder carcinoma (T24) cell lines. Its *in vitro* or *in vivo* activity was equal or higher than that of cisplatin (Table 1). The survival extending rates on mice Ehrlich's ascites tumor after injection of **312** were higher than those of cisplatin (Table 1) [94]. The mechanism of **312** was further investigated against SGC-7901 cells. The compound blocks the cell cycle in G_1 and G_2-M phase, through the induction of protein p21. It also induces ROS generation and loss of mitochondrial membrane potential, activated caspase-3 and -9, leading to apoptosis [95,96].

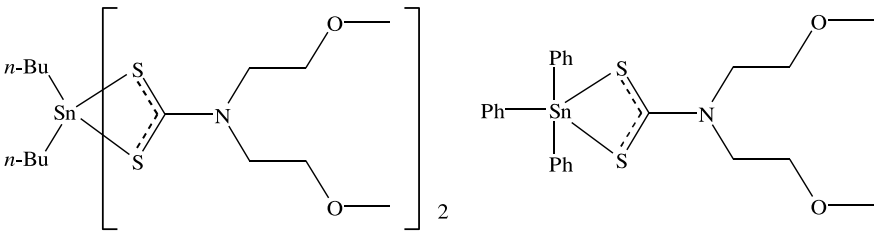
The *in vitro* cytotoxicity of the polynuclear di-organotin(IV) compounds **313–324** (Scheme 76 [97]) with di-halogenbenzohydroxamate ligands were investigated towards promyelocytic leukemic (HL-60), hepatocellular carcinoma (BEL-7402), gastric carcinoma (BGC-823) and nasopharyngeal carcinoma (KB) cell lines [97]. Their activities are identical, or even higher than that of cisplatin. Compounds containing long carbon chain such as butyltin are the most active ones.

The di-organotin(IV) derivatives **325–327** of *N*-methyl *p*-fluorobenzohydroxamic acid (Scheme 77 [98]) with six coordination



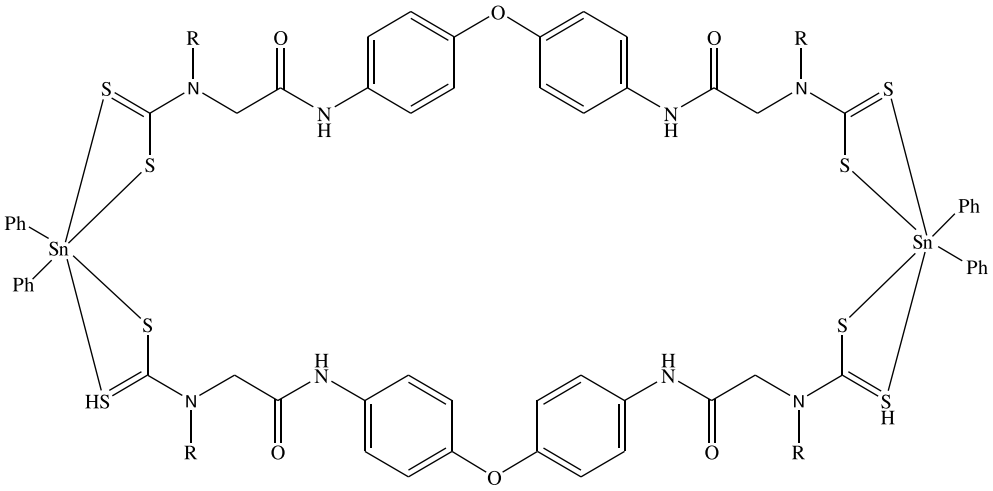
R= Me-, X= Br (**282**); R=Me, X=F (**283**); R= *n*-Bu-, X= Br (**284**); R= *n*-Bu-, X= F (**285**)

Scheme 69. The formulae of **282–285** [88].



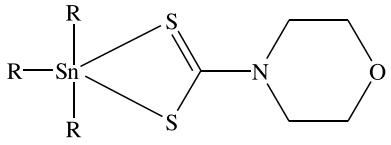
(**286**) (**287**)

Scheme 70. The formulae of **286–287** [89].



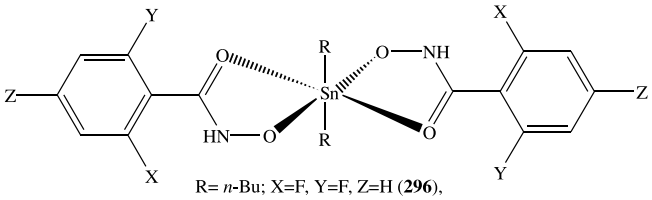
R = *i*-Pr (**288**), *s*-Bu (**289**), *n*-Bu (**290**), Cy (**291**), 2-furfuryl (**292**), benzyl (**293**)

Scheme 71. The formulae of **288–293** [90].



R= Ph- (**294**), Ph-CH_2- (**295**)

Scheme 72. The formulae of **294–295** [91].



R= *n*-Bu; X=F, Y=F, Z=H (**296**),
R= Ph; X=F, Y=H, Z=F (**297**),
R= Ph; X=Cl, Y=H, Z=Cl (**298**),
R= *n*-Bu; X=H, Y=H, Z=Cl (**299**)

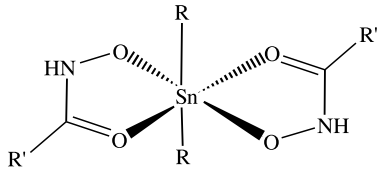
Scheme 73. The formulae of **296–299** [92].

geometry, exhibit low cytotoxic effect against colorectal carcinoma (HCT116) cell line (Table 3) [98].

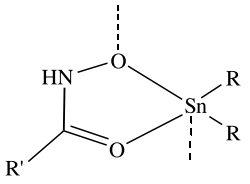
The trinuclear tin complex **328** of *N*,2-dihydroxy-5-[*N*-hydroxyethanimidoyl]-benzamide (Scheme 78 [99–102]) was tested for its tumor-inhibiting activity against human leukemia (HL-60), human hepatocellular carcinoma (BEL-7402), gastric carcinoma (BGC-823) and nasopharyngeal carcinoma (KB) cell lines [99]. Subsequently, the same compound was evaluated for its *in vitro* antiproliferative activity against colorectal carcinoma (HCT116), hepatocarcinoma (HepG2), breast adenocarcinoma (MCF-7) cell lines, human healthy fibroblasts [100] and human mammary epithelial (MCF-10A) cell line [101]. Moreover, the compound induces cell death *via* apoptosis and up-regulation of Cu/Zn superoxide dismutase correlating with increased levels of ROS in HCT116 cells [100] (Table 3). Moreover, the compound induces cell death by apoptosis with an increase of at least 1.6-fold on the effector caspases 3/7 activities and it interacts with CT-DNA by a groove-binding mechanism. The preliminary data on the *in vivo* antitumor activity of **328**, shows that it reduces the colorectal carcinoma tumor [101]. Also, the development of liposomal formulations for encapsulation of the Sn(IV)-complex was checked. The liposomal formulations allowed a considerable decrease of the IC_{50} value against HCT116 and HepG2 cells when it was compared to free complex. The cell uptake was increased after encapsulation of compound into

Table 3
In vitro inhibitory dose for the 50% of various cancer cell lines (IC_{50}) in μM of the organotin(IV) compounds with oximes ligands.

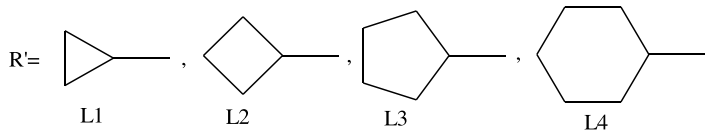
Compound (scheme)	Reference	IC_{50} [cell line]
296 (73)	[92]	2.20 [T24], 3.60 [EC], 4.50 [HepG2], 4.60 [HEC-1-B], 3.30 [SHSY5Y], 4.30 [HeLa], 2.10 [A549]
297 (73)	[92]	1.20 [T24], 1.50 [EC], 2.20 [HepG2], 2.50 [HEC-1-B], 3.10 [SHSY5Y], 3.90 [HeLa], 2.30 [A549]
298 (73)	[92]	4.60 [T24], 3.30 [EC], 4.80 [HepG2], 4.40 [HEC-1-B], 3.10 [SHSY5Y], 3.40 [HeLa], 3.10 [A549]
299 (73)	[92]	1.50 [T24], 1.40 [EC], 1.90 [HepG2], 1.60 [HEC-1-B], 3.30 [SHSY5Y], 4.00 [HeLa], 1.50 [A549]
325 (77)	[98]	> 40 [HCT116]
326 (77)	[98]	NA [HCT116]
327 (77)	[98]	2.50 [HCT116]
328 (78)	[99–102]	0.20 [HepG2], 0.24 [HCT116]
329 (79)	[103]	15.20 [HeLa], 15.38 [Bel-7402]
330 (79)	[103]	11.18 [HeLa], 12.04 [Bel-7402]
331 (80)	[104]	> 20 [HL-60], > 20 [BGC-823], 15.95 [KB]
332 (80)	[104]	14.83 [HL-60], 16.05 [BGC-823], 4.96 [KB]
333 (80)	[104]	5.13 [HL-60], 8.97 [BGC-823], 1.94 [KB]
334 (80)	[104]	0.05 [HL-60], 0.06 [BGC-823], 0.012 [KB]
335 (80)	[104]	0.21 [HL-60], 1.49 [BGC-823], 0.13 [KB]
336 (80)	[104]	4.23 [HL-60], 6.55 [BGC-823], 2.88 [KB]



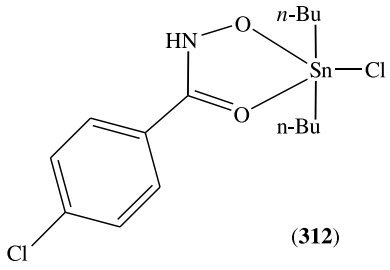
R= n-Bu, R'= L1 (**300**), R= n-Bu, R'= L2 (**301**)
R= n-Bu, R'= L3 (**302**), R= n-Bu, R'= L4 (**303**)
R= Ph, R'= L1 (**304**), R= Ph, R'= L2 (**305**)
R= Ph, R'= L1 (**306**), R= Ph, R'= L1 (**307**)



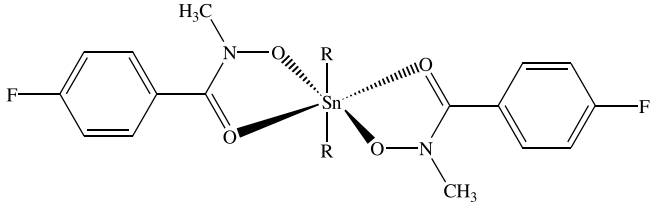
R= n-Bu, R'= L1 (**308**), R= n-Bu, R'= L2 (**309**)
R= n-Bu, R'= L3 (**310**), R= n-Bu, R'= L4 (**311**)



Scheme 74. The formulae of **300–311** [93].



Scheme 75. The formulae of **312** [94–96].



R= Me- (**325**), *n*-Bu- (**326**), Ph- (**327**)

Scheme 77. The formulae of **325–327** [98].

liposomes. The current liposomes show low toxicity towards macrophages, demonstrating an intrinsic selectivity towards cancer cells by the complex [102].

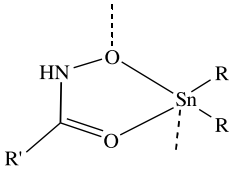
The organotin(IV) metallacrowns **329–330** of 5-chlorosalicylhydroxamic acid (Scheme 79 [103]) exhibit weak activity (IC_{50} values higher than 10 μM) towards human hepatocellular carcinoma (BEL-7402) and human cervical carcinoma (HeLa) cell lines (Table 3) [103].

The di-*n*-butyltin(IV) arylhydroxamate compounds **331–336** (Scheme 80 [104]) were investigated for their cytotoxicity against promyelocytic leukemic (HL-60), gastric carcinoma (BGC-823) and nasopharyngeal carcinoma (KB) cell lines (Table 3). Almost all compounds show selectivity against KB carcinoma cells. The compound **334**, with two fluorine atoms at C2 and C6 position of benzene ring, shows the highest activity (up to 200 times) in contrast to the rest compounds and cisplatin (Table 1). The compound **334** induces apoptosis towards KB cells [104].

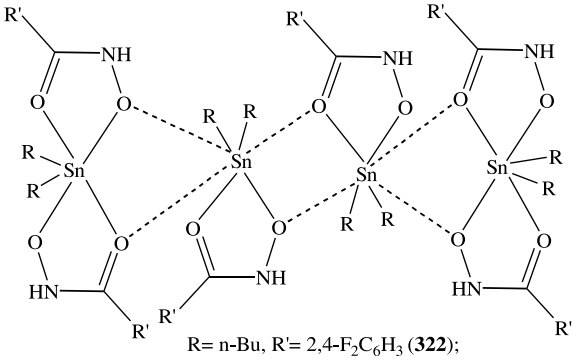
5. Organotin(IV) compounds of amines as ligands

The organotin(IV) compounds **337–345** of 5,7-di-tert-butyl-1,2,4-triazolo[1,5-*a*]pyrimidine (dbtp) and 5,7-diphenyl-1,2,4-triazolo[1,5-*a*]pyrimidine (dptp) (Scheme 81 [105]), showed a dose dependent antiproliferative effect against hepatocellular carcinoma (HepG2), cervical carcinoma (HeLa) and breast adenocarcinoma (MCF-7) cell lines (Table 4). Generally, the cytotoxicity of the compounds follows the order *n*-Bu > Ph > Et > Me, against cells. The *n*-Bu (**342–343**) and Ph compounds (**344–345**) inhibit the cell entry in S-phase, inducing apoptosis. The most potent antiproliferative compound **342**, which shows IC_{50} values between 0.3 and 1.2 μM [105].

The distorted octahedral mononuclear Sn(IV) compounds **346–350**

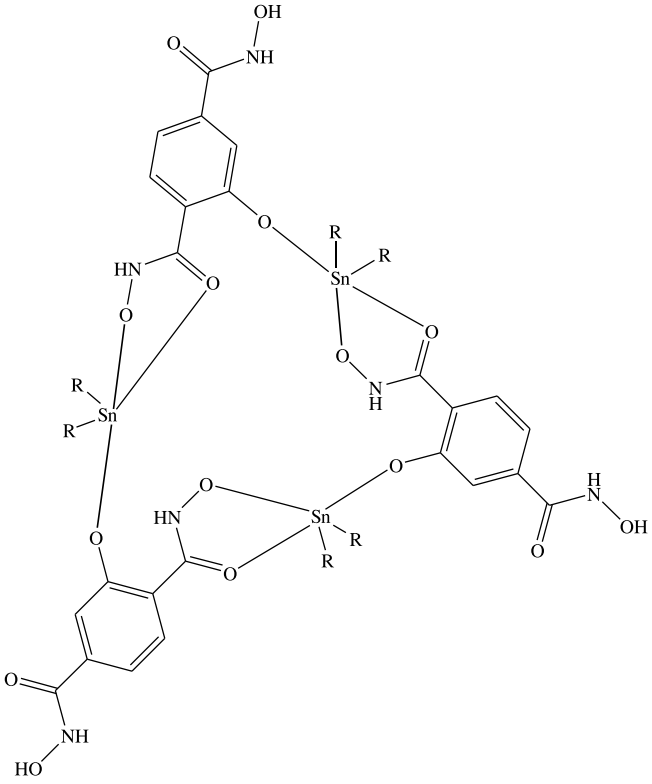


R= Me; R' = 3,4-$F_2C_6H_3$ (**313**), 2,4-$F_2C_6H_3$ (**314**), 2,5-$F_2C_6H_3$ (**315**), 2,6-$F_2C_6H_3$ (**316**), 2,4-$Cl_2C_6H_3$ (**317**).
R= n-Bu; R' = 3,4-$F_2C_6H_3$ (**318**), 2,5-$F_2C_6H_3$ (**319**), 2,6-$F_2C_6H_3$ (**320**), 2,4-$Cl_2C_6H_3$ (**321**)



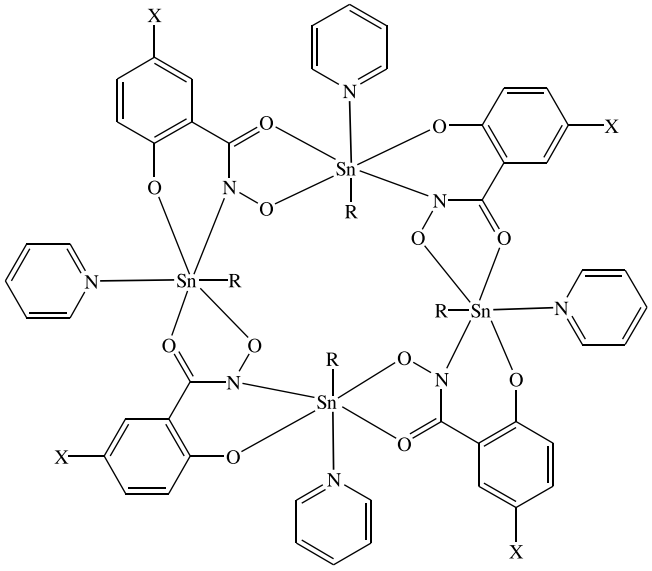
R= n-Bu, R'= 2,4-$F_2C_6H_3$ (**322**);
R= Me, R'= 2,4-$Cl_2C_6H_3$ (**323**);
R= n-Bu, R'= 4-FC_6H_4 (**324**)

Scheme 76. The formulae of **313–324** [97].



R= *n*-Bu- (**328**)

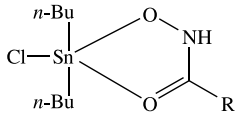
Scheme 78. The formulae of **328** [99–102].



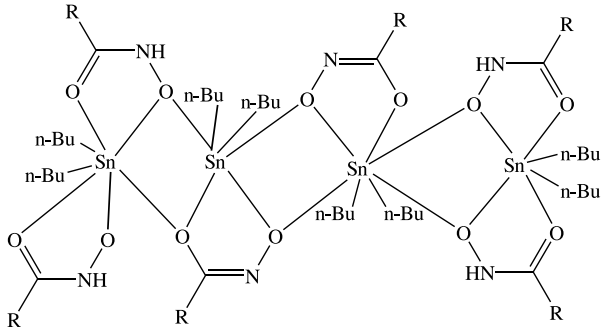
X=Cl R=Et- (**329**), *n*-Bu- (**330**)

Scheme 79. The formulae of **329–330** [103].

of 4′-p-*N*,*N*-Bis(2-hydroxyethyl)benzyl-2,2′:6,2″-terpyridine and 4′-p-9-Anthracenevinyl-2,2′:6,2″-terpyridine (Scheme 82 [106]), show higher or equal cytotoxicity against cervical carcinoma (HeLa) and breast adenocarcinoma (MCF-7) cell lines (Table 4) than cisplatin (Table 1) [106]. Among these compounds the monomethyltin(IV) one exhibit the stronger activity. Given that the monophenyltin shows similar activity with the corresponding one of the di-organotin the activity of the monomethyltin compounds should be attributed to their lower lipophilicity.



R= 3,4-$F_2C_6H_3$ (**331**), 2,4-$F_2C_6H_3$ (**332**), 2,5-$F_2C_6H_3$ (**333**), 2,6-$F_2C_6H_3$ (**334**)



R= 3-BrC_6H_4 (**335**), 4-BrC_6H_4 (**336**)

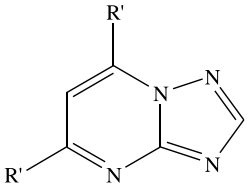
Scheme 80. The formulae of **331–336** [104].

Organotin(IV) compounds **351–354** derived from pyridine Schiff base 2,2′-{pyridine-2,6-diylbis[(E)methanylylidene(E)azanylylidene]} diphenolate (Scheme 83 [107]) were evaluated against colon adenocarcinoma (HCT-15), breast adenocarcinoma (MCF-7), myelogenous leukemia (K562), human glioblastoma (U251), prostate cancer (PC-3), and human lung adenocarcinoma (SKLU-1) cell lines (Table 4). The compounds exhibit higher activity than cisplatin (up to 52 times (Table 1)) towards K562 cell line. The range of their IC_{50} values of **351–354** is between 0.29 and 5.30 μM in the case of K562 cells line. The lowest IC_{50} value is exhibited by **354** where Cl and NO_2 are positioned at the aromatic ring [107].

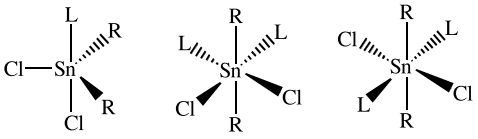
The di-organotin(IV) compounds of N-(2-pyridylmethylene)arylamine **355–357** (Scheme 84 [108]) were evaluated in a panel of cell lines, such as human renal carcinoma (A498), human breast adenocarcinoma (EVSA-T), human non-small-cell lung carcinoma (H226), human ovarian carcinoma (IGROV), human melanoma (M19 MEL), human breast adenocarcinoma (MCF7) and human colon carcinoma (WIDR) cells (Table 4). It can be concluded that the cytotoxic potential is affected by the Sn-R groups and Sn—N bond lengths (longer Sn—N bond lengths, higher activity). The range of IC_{50} values are from 0.003 to 4.82 μM [108].

The octahedral di-organotin(IV) compounds **358–362** of the Schiff base ligand derived from 7-methoxy-2-hydroxy-1-naphthaldehyde, 1,2-phenylenediamine and salicylaldehyde (Scheme 85 [109]) were screened against human nasopharyngeal carcinoma (KB) cell line (Table 4). The diethyltin(IV) complex showed the most promising cytotoxic result (IC_{50} = 0.35 μM) against KB cells which is comparable with that of cisplatin (Table 1). According to docking studies, the compounds interact with DNA [109].

The dimeric di-organotin(IV) compounds **363–372** of arylhydrazones of β-diketone (Scheme 86 [110]) were screened against human cervical carcinoma (HeLa), human nasopharyngeal carcinoma (KB) and hepatocellular carcinoma (HepG2) cell lines (Table 4). Generally, the compounds exhibit selectivity towards KB cells. The compounds affected the cell viability and induced cell apoptosis towards KB cells. It has been shown that the activity decreased according to the following order n-Bu > Ph > Et > Oct > Me. The dialkyltin(IV) derivatives with the nitro substituent are more active than the unsubstituted ones. The IC_{50} value of **368** with the nitro-substituted arylhydrazone ligand is up to 15-fold higher than that of cisplatin against HeLa cells (Table 1) [110].



R'= t-Bu-(dbtp), Ph- (dptp)



(a) (b) (c)

(a) R = Me; L= dbtp (**337**), Et; L= dbtp (**339**), *n*-Bu; L= dbtp (**341**), Ph; L= dbtp (**343**), Ph; L= dptp (**344**)
(b) R = Me; L= dbtp (**338**), Et; L= dbtp (**340**), *n*-Bu; L= dbtp (**342**)
(c) R = Ph; L= dptp (**345**)

Scheme 81. The formulae of **337–345** [105].

6. Organotin(IV) compounds of semicarbazones as ligands

The organotin(IV) compounds **373–376** of 2-hydroxy-1-naphthaldehyde 5-chloro-2-hydroxybenzoylhydrazone (Scheme 87 [111]) were evaluated for their *in vitro* antitumor activity towards human colon cancer (HCT-8), human lung epithelial (A-549) and human leukemia (HL-60) cell lines (Table 4). It is shown that the polymeric complex **376** with long carbon chain is the most active one in contrast to cisplatin (up to 23 times (Table 1)). The type of alkyl groups attached to the organotin(IV) moiety affects the antitumor activity [111].

The *in vitro* cytotoxicity of organotin(IV) hydrazone compounds **377–381** of *N′*-[(1E)-(2-hydroxyl-3-methoxyphenyl)methylidene]pyridine-3-carbohydrazone (Scheme 88 [112]), was tested towards human lung epithelial (A-549), cervical carcinoma (HeLa) and breast adenocarcinoma (MCF-7) cell lines (Table 4). The activity of **377–381** follows the order *n*-Bu > Ph > Me. The introduction of tin atom in the centre of the structure symmetry enhances the anticancer activity of the compounds. All the compounds are more active than cisplatin (Table 1). The most effective compound against the cancerous cell lines it also interacts strongly with DNA or bovine serum albumin [112].

The *in vitro* cytotoxicity of the organotin(IV) compounds 382-383 from salicylaldehyde nicotinoyl hydrazone and the dialkyltin(IV) precursor (Scheme 89 [113]) was assessed towards human cisplatin-resistant tumor cell lines (lung carcinoma (A549), cervix (HeLa) and breast adenocarcinoma (MCF-7)) (Table 4). The activity of 382-383 follows the order *n*-Bu > Ph against tumor cells, which is observed previously for other organotins(IV) compounds. The compounds exhibit better antiproliferative activity (up to 10 times higher) than that of cisplatin. The compounds can also bind to serum albumin (Table 1) [113].

The *in vitro* antitumor activity of dialkytin compounds 384-386 (Scheme 90 [114]) was evaluated against human lung cancer (NCI-H460), human hepatocellular liver carcinoma (HepG2), human breast adenocarcinoma (MCF-7) and primary human liver (HL-7702) cell lines (Table 4). The compounds are more cytotoxic than carboplatin and exhibit selectivity against normal cell lines in contrast to the cancerous ones. The range of IC_{50} values is between 1.2 and 14.5 μM. Moreover, the compounds interact with DNA by intercalation or electrostatic binding mode [114].

The organotin(IV) compounds 387-391 of *N′*-[(1E)-(2-hydroxy-3-methoxyphenyl)methylidene]pyridine-4-carbohydrazone (Scheme 91 [115]) were tested for their *in vitro* antitumor activity against human leukemia (HL-60), human lung epithelial (A-549), colon carcinoma (HT-29, HCT116 and Caco-2). The compounds are more active than cisplatin (Table 4). The length of the organic group affects the activity of di-organotin(IV) compounds towards tumor cells. In particular, the diorganotin(IV) derivatives with short (methyl) or long (n-octyl) carbon chain tend to exhibit low antiproliferative activity. The activity follows the consistent order: *n*-Bu > Ph > *n*-Oct > Me. For these compounds, the derivatives of $R_2Sn(IV)^{2+}$ exhibit higher antitumor activity than those of corresponding mono-, tri- and tetra-organotin(IV) or the inorganic Sn(IV) derivatives. On the contrary in the case of organotin (IV) compounds with other type of ligands such as those of thioamides tri-organotins(IV) exhibit higher activity than di-organotin(IV) compounds [11]. The di-*n*-butyltin(IV) compound interacts with DNA and albumin protein [115].

7. Concluding remarks

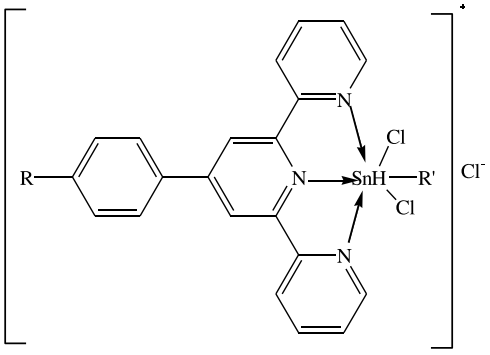
Organotins(IV) exhibit significant *in vitro* antiproliferative activity, while their *in vivo* tests are encouraging. Organotins(IV) were studied mainly against MCF-7, HeLa and HepG2 cells. Table 5 compares the data against these lines.

Organotins(IV) with O-donor ligands exhibit strong activity against HeLa cells, while those of S-donors show also high activity against MCF-7 cells. Compounds of N-donor ligands are better against HepG2 cells. Therefore the biological effect of organotins(IV) is related on the kind of the cancer cells each time. Across the organotins(IV) of the same category of ligands, the variations in the antiproliferative activity is attributed to the different tissues of their origin. Moreover, organotins(IV) exhibit higher activity than cisplatin, which rises up to 3300-fold, (Table 1). Among organotins(IV) the compound **355** [108], exhibits the strongest activity against MCF-7 cells, (IC_{50} = 0.004 μM), while the compound **11**, exhibits the highest activity (IC_{50} = 0.030 μM) against HeLa [23]. In the case of HepG2 cells, the strongest activity is observed for compound **157** [57] (IC_{50} = 0.284 μM).

Generally, tri-organotins(IV) small molecules demonstrate better antitumor activity than di-organotin(IV) derivatives, while among tri-

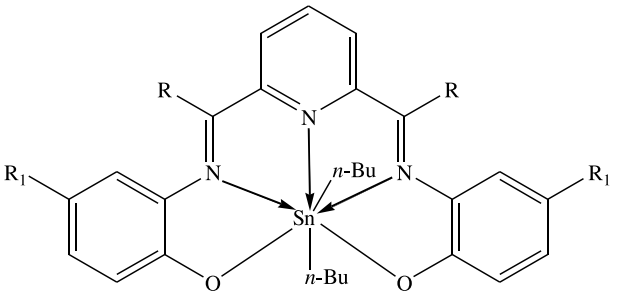
Table 4
In vitro inhibitory dose for the 50% of various cancer cell lines (IC_{50}) in μM of the organotin(IV) compounds with amines as ligands.

Compound (scheme)	Reference	IC_{50} [cell line]
337 (81)	[105]	NA [HepG2], NA [HeLa], NA [MCF-7]
338 (81)	[105]	NA [HepG2], NA [HeLa], NA [MCF-7]
339 (81)	[105]	> 50 [HepG2], 12.00 [HeLa], > 50 [MCF-7]
340 (81)	[105]	> 50 [HepG2], 15.00 [HeLa], > 50 [MCF-7]
341 (81)	[105]	20 [HepG2], 7.50 [HeLa], 20.00 [MCF-7]
342 (81)	[105]	1.00 [HepG2], 0.30 [HeLa], 1.20 [MCF-7]
343 (81)	[105]	0.60 [HepG2], 0.70 [HeLa], 1.60 [MCF-7]
344 (81)	[105]	4.00 [HepG2], 4.80 [HeLa], 7.00 [MCF-7]
345 (81)	[105]	3.00 [HepG2], 3.80 [HeLa], 7.50 [MCF-7]
346 (82)	[106]	1.67 [HeLa], 2.60 [MCF-7]
347 (82)	[106]	6.10 [HeLa], 4.50 [MCF-7]
348 (82)	[106]	6.70 [HeLa], 8.30 [MCF-7]
349 (82)	[106]	7.20 [HeLa], 11.20 [MCF-7]
350 (82)	[106]	10.10 [HeLa], 23.50 [MCF-7]
351 (83)	[107]	1.90 [MCF-7], 4.90 [PC3], 4.10 [HCT15], 0.97 [K562], 1.60 [U251], 1.80 [SKLU-1]
352 (83)	[107]	2.30 [MCF-7], 4.80 [PC3], 6.40 [HCT15], 3.70 [K562], 2.40 [U251], 2.10 [SKLU-1]
353 (83)	[107]	3.50 [MCF-7], 5.30 [PC3], 3.04 [HCT15], 2.90 [K562], 4.50 [U251], 2.10 [SKLU-1]
354 (83)	[107]	1.01 [MCF-7], 1.62 [PC3], 0.51 [HCT15], 0.29 [K562], 0.78 [U251], 0.57 [SKLU-1]
355 (84)	[108]	0.02 [MCF-7], 0.03 [A498], 0.02 [EVSTAT], 0.03 [H226], 0.05 [IGVOR], 0.02 [M19-MEL], 0.04 [WIDR]
356 (84)	[108]	0.004 [MCF-7], 0.004 [A498], 1.88 [EVSTAT], 4.82 [H226], 0.007 [IGVOR], 2.21 [M19-MEL], 0.007 [WIDR]
357 (84)	[108]	0.90 [MCF-7], 1.16 [A498], 0.56 [EVSTAT], 1.80 [H226], 0.68 [IGVOR], 0.54 [M19-MEL], 1.05 [WIDR]
358 (85)	[109]	0.95 [KB]
359 (85)	[109]	0.35 [KB]
360 (85)	[109]	2.00 [KB]
361 (85)	[109]	1.75 [KB]
362 (85)	[109]	1.55 [KB]
363 (86)	[110]	117.80 [HepG2], 93.70 [HeLa], 25.30 [KB]
364 (86)	[110]	41.40 [HepG2], 29.90 [HeLa], 23.90 [KB]
365 (86)	[110]	14.20 [HepG2], 19.70 [HeLa], 6.10 [KB]
366 (86)	[110]	5.30 [HepG2], 8.20 [HeLa], 2.60 [KB]
367 (86)	[110]	4.40 [HepG2], 2.10 [HeLa], 0.30 [KB]
368 (86)	[110]	1.70 [HepG2], 0.30 [HeLa], 0.20 [KB]
369 (86)	[110]	6.30 [HepG2], 0.50 [HeLa], 0.40 [KB]
370 (86)	[110]	4.20 [HepG2], 1.60 [HeLa], 1.20 [KB]
371 (86)	[110]	2.90 [HepG2], 1.30 [HeLa], 0.90 [KB]
372 (86)	[110]	59.90 [HepG2], 8.40 [HeLa], 5.50 [KB]
373 (87)	[111]	1.84 [A549], 1.02 [HCT-8], 19.07 [HCT60]
374 (87)	[111]	> 16 [A549], 6.70 [HCT-8], > 16.34 [HCT60]
375 (87)	[111]	> 12.52 [A549], 4.88 [HCT-8], 0.75 [HCT60]
376 (87)	[111]	0.14 [A549], 0.80 [HCT-8], 0.64 [HCT60]
377 (88)	[112]	10.38 [HeLa], 10.00 [MCF-7], 11.02 [A549]
378 (88)	[112]	0.31 [HeLa], 0.35 [MCF-7], 0.45 [A549]
379 (88)	[112]	0.56 [HeLa], 0.43 [MCF-7], 0.72 [A549]
380 (88)	[112]	1.17 [HeLa], 0.96 [MCF-7], 1.51 [A549]
381 (88)	[112]	3.19 [HeLa], 3.00 [MCF-7], 5.09 [A549]
382 (89)	[113]	1.40 [HeLa], 0.96 [MCF-7], 1.45 [A549]
383 (89)	[113]	2.27 [HeLa], 2.11 [MCF-7], 2.43 [A549]
384 (90)	[114]	1.15 [HepG2], 1.84 [MCF-7], 3.39 [NCI-H460], 3.71 [HL7702]
385 (90)	[114]	3.14 [HepG2], 4.20 [MCF-7], 6.50 [NCI-H460], 14.80 [HL7702]
386 (90)	[114]	1.75 [HepG2], 4.50 [MCF-7], 5.80 [NCI-H460], 11.40 [HL7702]
387 (91)	[115]	> 12 [HCT-116], > 12 [A549], 3.10 [HL-60], > 12 [Caco-2], 5.70 [HT-29]
388 (91)	[115]	0.28 [HCT-116], 0.60 [A549], 0.09 [HL-60], 1.10 [Caco-2], 0.21 [HT-29]
389 (91)	[115]	6.45 [HCT-116], 12.10 [A549], 1.12 [HL-60], > 16 [Caco-2], 6.17 [HT-29]
390 (91)	[115]	2.01 [HCT-116], 3.00 [A549], 0.33 [HL-60], 3.20 [Caco-2], 2.17 [HT-29]
391 (91)	[115]	9.70 [HCT-116], 2.38 [A549], 4.12 [HL-60], > 23 [Caco-2], 12.40 [HT-29]



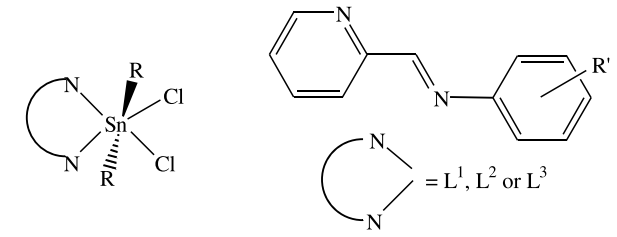
R=4'-p-N,N-Bis(2-Hydroxyethyl)benzyl-2,2':6,2"-terpyridine, R'= Me- (**346**),
R= 4'-p-N,N-Bis(2-Hydroxyethyl)benzyl-2,2':6,2"-terpyridine, R'= Me- (**347**),
R= 4'-p-N,N-Bis(2-Hydroxyethyl)benzyl-2,2':6,2"-terpyridine R'= Ph- (**348**),
R= 4'-p-N,N-Bis(2-Hydroxyethyl)benzyl-2,2':6,2"-terpyridine R'= Ph- (**349**),
R= 4'-p-9-Anthracenevinyl-2,2':6,2"-terpyridine, R'= Me- (**350**)

Scheme 82. The formulae of **346–350** [106].



R=H; R_1= H (**351**),
R=H; R_1= Me (**352**),
R=H; R_1= Cl (**353**),
R=H; R_1= NO_2 (**354**)

Scheme 83. The formulae of **351–354** [107].

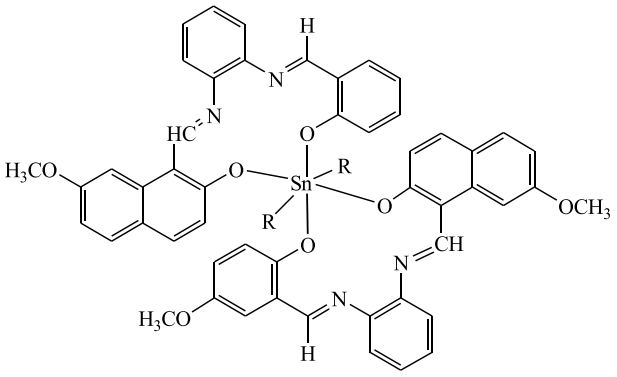


R= Me; R'= L^1 (**355**),
R= Et, R'= L^2 (**356**),
R= Ph, R'= L^3 (**357**)

R'= 3-Me (L^1), 4-Me (L^2), 4-OMe (L^3)

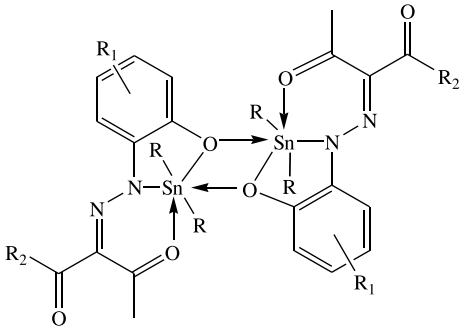
Scheme 84. The formulae of **355–357** [108].

organotins(IV), the triphenyl ones exhibits better activity. Moreover, organotins(IV) with tetrahedral arrangement of the ligands around tin (IV) ions exhibit stronger activity than those of TBP, the latter is more effective than those with octahedral geometry. This has been attributed by Huber and Saxena [19] to the availability of coordination positions at Sn which is reduced on going from tetrahedral to trigonal bi-pyramidal and octahedral geometries. However, the polymers tri-butyltin derivatives exhibit stronger activity. Thus, against MCF-7 cells, both the polymers **183** [65] and **145** [52] exhibit the higher activity with the same IC_{50} values of 0.050 μM. Polymeric anticancer agents have an advantage over small molecules since (i) the polymers overcome cellular resistance mechanisms (ii) the polymers could be used as carriers



R= Me (**358**), Et (**359**), *n*-Bu (**360**), Ph (**361**), Bz (**362**)

Scheme 85. The formulae of **358–362** [109].



R= Me, R_1= H, R_2= CH_3 (**363**)
R= Me, R_1=$_9$-NO_2, R_2= CH_3 (**364**)
R= Et, R_1= H, R_2= CH_3 (**365**)
R= Et, R_1=$_9$-NO_2, R_2= CH_3 (**366**)
R= Bu, R_1= H, R_2= CH_3 (**367**)
R= Bu, R_1=$_9$-NO_2, R_2= CH_3 (**368**)
R= Bu, R_1= H, R_2= OCH_2CH_3 (**369**)
R= Ph, R_1= H, R_2= CH_3 (**370**)
R= Ph, R_1=$_9$-NO_2, R_2= CH_3 (**371**)
R= Oct, R_1=$_9$-NO_2, R_2= CH_3 (**372**)

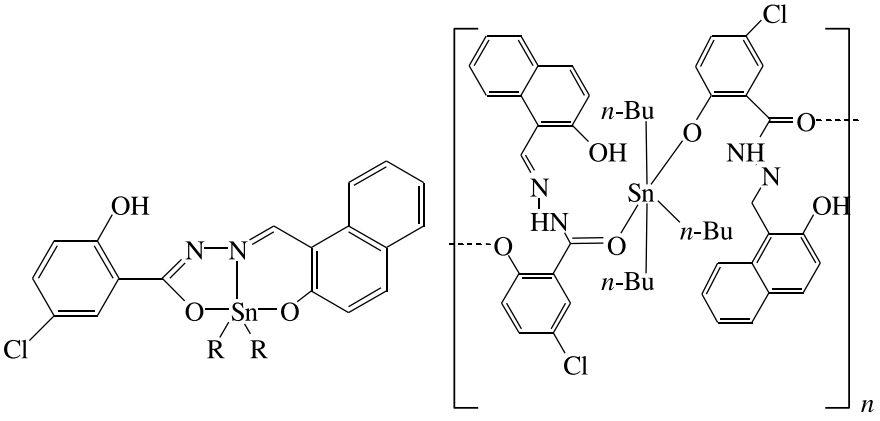
Scheme 86. The formulae of **363–372** [110].

in high-dose chemotherapy (iii) polymers are filtered out by the kidneys more slowly than small compounds increasing the body retention time (iv) the size and structure of the polymer provide more binding sites to cellular targets (v) the polymers are hybrid drugs incorporating multiple anticancer agents against cells through different mechanisms (vi) the polymers accumulate in solid tumors more than in normal tissues [67].

For the most of organotins(IV), apoptosis has been proposed as cell death aetiology. Cells apoptosis is either caused through organotins(IV) interfering in the cells redox signaling pathways (accumulation of ROS) or in the mitochondria membrane permeability dysfunction, activation of caspase apoptosis pathway and interaction with DNA [23]. Moreover, enzymes inhibition caused by organotins(IV), follows the same order with their antiproliferative activity. However, more data are needed for a safe conclusion, since the literature is poor on the matter.

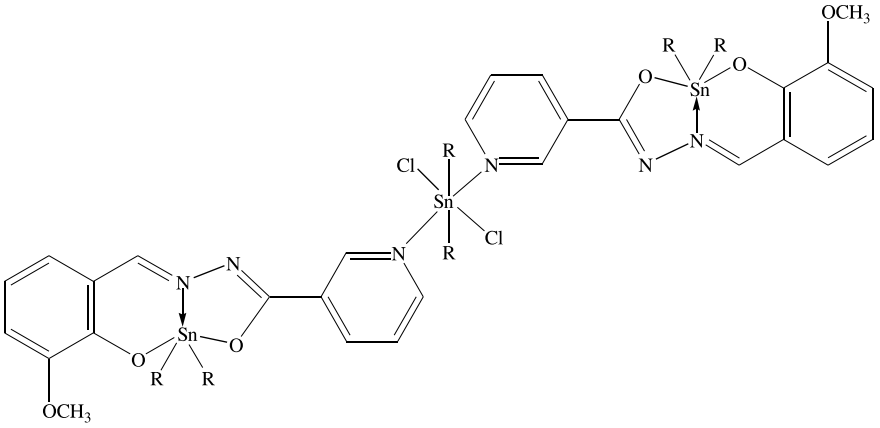
Despite the work already performed on the cytotoxicity of organotins(IV) against tumor cells, there are no much data from their *in vitro* toxicity tests, against normal cell lines. Thus, the screening of non-cancerous cell lines such as human fetal lung fibroblast (MRC-5) cells, human mammary epithelial (MCF-10A), peripheral blood mononuclear (PBMC), primary human liver (HL7702), normal human cervical epithelial cells (HCvEpCs), human embryonic lung fibroblast (HELF) and mouse fibroblast (L-929) cells, incubated with organotins lead into no secure conclusion. Moreover, the most used normal cells for the evaluation of the toxicity of organotins(IV) are MRC-5 together with MCF-10A.

In conclusion, regardless the significant strong antitumor activity of organotin(IV) compounds, which for the majority of triaryl substituted compounds lie in the nano molar region, it is inferred that, organotins (IV) discussed here have no selectivity against cancer than normal cells generally. In this context, the di- and tri-organotin(IV) compounds with D-(+)-Galacturonic acid have showed an appreciable selective activity towards HCT-116 and MCF-7 cancer cell lines than normal intestinal and liver cells [74]. This initiates a new research era in the anti-proliferative and antitumor activity of organotin(IV) compounds. Within the future perspectives of organotins(IV), their incorporation in nanoparticles efficient in hosting, protecting, carrying and releasing of the therapeutic agents at the target tissues introduce the organotins(IV) in the field of modern nanomedicine [102].

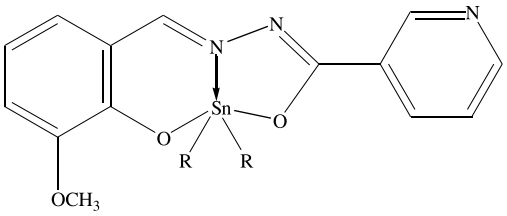


R= Me (**373**), Ph (**374**), o-ClPhCH_2 (**375**) (**376**)

Scheme 87. The formulae of **373–376** [111].

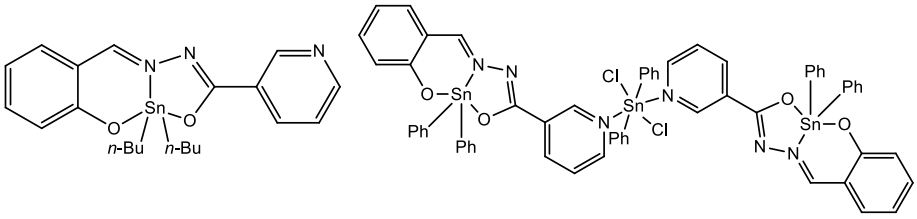


R= Me (**377**), *n*-Bu (**378**), Ph (**379**)



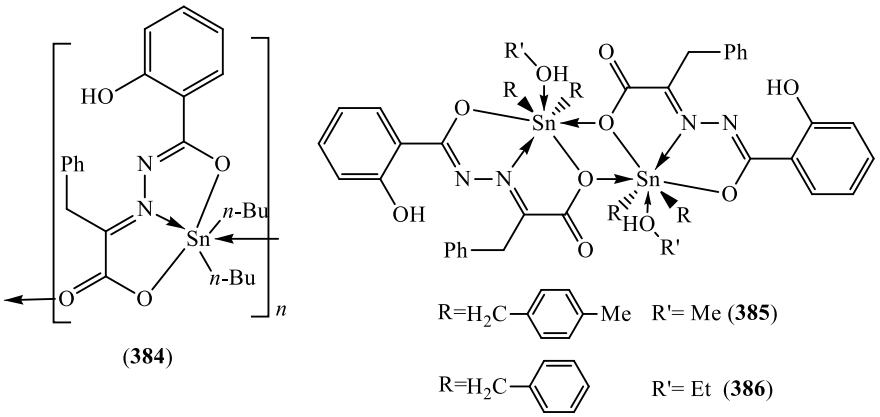
R= *n*-Bu (**380**), Ph (**381**)

Scheme 88. The formulae of **377–381** [112].



(**382**) (**383**)

Scheme 89. The formulae of 382-383 [113].

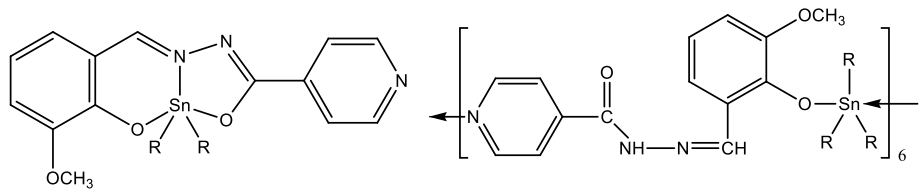


(**384**)

R=H_2C—Me R'= Me (**385**)

R=H_2C— R'= Et (**386**)

Scheme 90. The formulae of 384-386 [114].



R= Me (**387**), n-Bu (**388**), Oct (**389**), Ph (**390**) R= Me (**391**)

Scheme 91. The formulae of 387-391 [115].

Table 5
IC_{50} values against cancer (MCF-7, HeLa, HepG2) and normal cell lines.

Cell line	IC_{50} range (μM)	O-donor IC_{50} (μM) mean value ± conf. (counts)	S-donor IC_{50} (μM) mean value ± conf. (counts)	N-donor IC_{50} (μM) mean value ± conf. (counts)
MCF-7	0.004–999.83	0.03–999.83 42.46 ± 30.25 (104)	0.03–19.20 3.66 ± 2.74 (14)	0.004–23.50 4.86 ± 2.10 (29)
HeLa	0.03–93.70	0.03–6.80 0.68 ± 0.33 (46)	0.07–23.90 4.04 ± 3.880 (15)	0.30–93.70 8.66 + −6.64 (29)
HepG2	0.20–854.17	0.28–854.17 51.61 ± 36.09 (54)	10.00–12.00 11.00 ± 1.96 (2)	0.60–117.80 15.25 ± 12.48 (20)
MRC-5	–	nda	0.11–19.50 5.45 ± 4.98 (8)	nda
MCF-10A	–	20.46–67.51 41.59 ± 8.33 (10)	nda	nda

nda = no data available, conf. = confidence limit for the 95% of the values.

Abbreviations

Cell lines reported

4T1 murine breast cancer nontransformed
8505C anaplastic thyroid carcinoma
A-172 glioma
A253 cisplatin sensitive head-neck carcinoma
A2780 ovarian carcinoma
A375 melanoma
A498 human renal carcinoma
A-549 human lung epithelial
B16-F10 melanoma
Bcap37 human breast cancer
BEL-7402 human hepatocellular carcinoma
BGC-823 gastric carcinoma
BJAB lymphoma
Caco-2 colon carcinoma
Caki-1 renal carcinoma
Chang liver cells
CoLo205 colon carcinoma
DBTRG-0.5MG glioma
DLD-1 colon carcinoma
EC human embryonal carcinoma
EVSA-T breast adenocarcinoma
Fem-x human malignant melanoma
GL261 mouse glioma
H226 non-small-cell lung carcinoma
HCT116 colon carcinoma
HCT-15 colon adenocarcinoma
HCT-8 colon carcinoma
HCvEpCs human cervical epithelial cells
HEC-1-B human endometrial adenocarcinoma
HEK-293 human embryonic kidney
HeLa human cervix adenocarcinoma
HELF human embryonic lung fibroblast
HEP 3B hepatoma
HepG2 hepatocellular carcinoma
HL-60 human leukemia or promyelocytic leukemic
HL-7702 primary human liver
HT1080 fibrosarcoma
HT-29 colon carcinoma
IGROV ovarian carcinoma
IMR 32 neuroblastoma
Jurkat human acute lymphoblastic leukemia
K562 erythroleukemia or myelogenous leukemia
KB human nasopharyngeal carcinoma
L1210 leukemia
L-929 mouse fibroblast
LN-229 glioblastoma
LS174T human colon carcinoma
M19 MEL melanoma
MCF-10A human mammary epithelial
MCF-7 breast adenocarcinoma positive to estrogen receptor
MDA-MB 231 breast carcinoma negative to estrogen receptors
MRC-5 normal human fetal lung fibroblast cells
MTSV17 normal immortalized human mammary gland epithelial cells
NCI-H460 human lung cancer
OAW-42 ovarian carcinoma
OVCAR-3 ovarian carcinoma
P388 murine leukemia
PANC-1 pancreatic carcinoma
PBMC peripheral blood mononuclear cells
PC12 rat pheochromocytoma
PC-3 prostate cancer
SGC-7901 human gastric carcinoma
SHSY5Y human neuroblastoma
SKLU-1 human lung adenocarcinoma
SMMC-7721 hepatocellular carcinoma
T24 bladder carcinoma
U251 human glioblastoma
U373 MG glioma
U87 glioblastoma
U87 MG glioma
WiDr colon carcinoma

Ligands

4,4′-bipy	4,4′-Bipyridine derivatives
4-MPAH	4-methoxyphenylacetic acid
ANTPY	4′-p-9-Anthracenevinyl-2,2′:6,2″-terpyridine
Bipy	2,2′-bipyridine
BTCH	1,2,4-benzenetricarboxylic 1,2-anhydride
BZDOH	1,4-benzodioxane-6-carboxylic acid
dbtp	5,7-di-tert-butyl-1,2,4-triazolo[1,5-*a*]pyrimidine
DMFUH	2,5-dimethyl-3-furoic acid
DMNIH	2,6-dimethoxynicotinic acid
dptp	5,7-diphenyl-1,2,4-triazolo[1,5-*a*]pyrimidine
H_2dmmt	2-hydroxy-5-methoxybenzaldehyde-N(4)-methylthiosemi-carbazone
H_2imda	iminodiacetic acid
H_2mstsc	3-methoxysalicylaldehyde thiosemicarbazone
H_2pt	pyruvic acid thiosemicarbazone
H_2TBA	2-thiobarbituric acid
H_3Or	orotic acid or 6-uracilic acid or 1,2,3,6-tetrahydro-2,6-di-oxo-4-pyrimidine carboxylic acid
H_4btec	1,2,4,5-benzenetetracarboxylic acid
HCAF	caffeic acid
Hcmbzt	5-chloro-2-mercapto-benzothiazole
Hdcpa	2-(2,3-dichlorophenylamino) benzoic acid
Hdmpa	2-(2,6-dimethylphenylamino)benzoic acid
Hflu	flufenamic acid
HGal	gallic acid
HGlu	glucuronic acid
HLA	lauric acid
HMA	myristic acid
HMal	mandelic acid
Hmbzo	2-mercapto-benzoxazole
Hmbzt	2-mercapto-benzothiazole
HMeclo	meclofenamic acid
HSA	stearic acid
MBZTH	2-mercapto-benzothiazole
MCDT	morpholine-1-carbodithioate
Mes	2,4,6-$Me_3C_6H_2$
MPAH	3-methoxyphenylacetic acid
MPMTH	2-mercapto-4-methyl-pyrimidine
P-AlaH	*N*-phthaloyl-L-alanine
P-GlyH	*N*-phthaloylglycine
phen	1,10-phenanthroline
PMTH	2-mercapto-pyrimidine
PYTH	2-mercapto-pyridine
SAR	Structure Activity Relationship
TPYOH	4′-p-*N*,*N*-Bis(2-hydroxyethyl)ben-zyl-2,2′:6,2″-terpyridine
Xyl	3,5-$Me_2C_6H_3$

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