Chapter 3

3.1 Introduction

Organotin compounds have many sustainable chemistry applications, from wood preservation to organic syntheses, and more recently antitumor drugs [1-4] and carbon dioxide capture [5]. Organotin(IV) carboxylates in particular have found use as homogenous catalysts in PVC stabilisation, polyurethane formation and transesterification [6]. The structural chemistry of organotin(IV) carboxylates display a rich diversity including monomers, dimers, tetrameric ladders, hexameric drums and polymers [7-9]. Organotin(IV) compounds have also displayed diverse medicinal applications such as anti-viral, anti-microbial, anti-parasitic, anti-hypertensive, anti-hyperbilirubinemia and anti-cancer activities, apart from their standard uses as biocides, catalyzers and stabilizers [1,3,4,10-12].

3.2 Organotin carboxylates and its cytotoxic potentials

Early accomplishment of platinum chemotherapeutic metallopharmaceuticals has shifted to non-platinum compounds with the objective of minimizing side effects. This has motivated inorganic and organometallic chemists to search for other platinum and nonplatinum metallodrugs (e.g., Sn, Ti, Au, Cu, Ru, Pd) that might exhibit similar cytotoxic properties accompanied by a different pattern of antitumor specificities and by a more promising pharmacological and toxicological profile, preferably against tumors that are responsible for high cancer mortality [13-23]. Several organotin(IV) compounds, particularly the carboxylate derivatives, have demonstrated interesting anticancer activities [4,14,10,24-26]. In line with other metal compounds, organotin(IV) compounds have also been investigated for cytotoxic potentials. The key organotin(IV) carboxylate architectures [27] that are responsible for anticancer activities are shown in Chart 3.1 (I-III).
Chart 3.1 Important building blocks of some biologically active organotin(IV) compounds.

Several di- and tri-organotin(IV) derivatives of polyoxaalkane- and steroid-carboxylic acids, terebic acid, and gibberellic acid (Chart 3.2) were investigated for their antitumor potential and have shown better activity than clinically used standard drugs [27].

Chart 3.2 Structure of some biologically active organotin(IV) compounds of steroidcarboxylates, terebates and gibberellates.
Accordingly, a large number of organotin(IV) carboxylates have been studied in great detail [1,2,10,28]. The presence of the carboxylate group is vital for aqueous solubility and results increased cellular accumulation [29,30]. Dibutyltin(IV) compounds of composition \([\{\text{Bu}_2\text{Sn}(L)\}_2\text{O}\}_2\), where \(L = 4\prime-(7\text{-oxabicyclo[2,2,1]5-heptane-2,3-dicarboximide})\text{benzoate}\) [31] and \(L = p-[N,N\prime\text{-bis}(2\text{-chloroethyl})\text{amino}]\text{benzoate}\) [32], were also exhibited high cytotoxicity against P388 (murine leukemia), HL-60 (human leukemia) and A-549 (human lung epithelial) cell lines. The dibutyltin(IV) compounds of Schiff base and azo compounds of composition \([\{\text{Bu}_2\text{Sn}(L)\}_2\text{O}\}_2\), where \(L\) is \([\beta\prime\{((E)\text{-1-(2-hydroxyphenyl})\text{ethylidene}}\text{amino}]\text{propionate}\) [33] or \([5\prime-((E)\text{-2-phenyl-1-diazenyl})\text{-2-hydroxybenzoate and 5-[(E)\text{-2-(4-methylphenyl)-1-diazenyl}]2-hydroxybenzoate}\) [34], have also demonstrated encouraging antitumor activity against WIDR (colon cancer), M19 MEL (melanoma), A498 (renal cancer), IGROV (ovarian cancer) and H226 (non-small cell lung cancer), MCF7 (breast cancer) and EVSA-T (breast cancer) cell lines. Recently, in vitro cytotoxic studies of di- and triorganotin(IV) carboxylates derived from aryltelluronic acids showed promising results against human lung cancer cells (A549) and hepatocellular carcinoma cells (HepG2) [35].

From foregoing discussion, it is clear that organotin(IV) compounds display promising in vitro anticancer activity, but the poor water solubility remains the drawback for in vivo test. Nevertheless, the limited solubility needs to be further enhanced in a way comparable to cisplatin, which shows limited water solubility too. It is therefore important to find more effective and safer organotin(IV) compounds for therapeutic use by designing and synthesizing new compounds and to find suitable means of their delivery to the biotargets. In line with these findings, the new generations of nano-medicine incorporating organotin(IV) compounds (nano-formulations) were developed which can cross the biological, biophysical and biomedical barricades that the human body enforces against conventional anticancer agents [36]. In this perspective, organotin(IV)-loaded mesoporous silica has been used as a biocompatible strategy for cancer treatment. Organotin(IV) loaded in nano-structured silica (SBA-15pSn) demonstrated a complete eradication of tumor growth in syngeneic C57BL/6 mice. This functionalized nano-material was able to differentiate between cancer and
non-invasive cells. The nano material displayed a non-aggressive mode of action, being highly efficient against cancer cells and found to be non-toxic towards normal tissues. JNK-independent apoptosis (jun-amino-terminal kinase), which was accompanied by the development of the melanocyte-like non-proliferative phenotype of survived cells, indicated the potential of SBA-15pSn for the suppression of tumor growth without undesirable compensatory proliferation of malignant cells in response to neighboring cell death [36,37]. It is well known that organotin(IV) compounds can bind membrane proteins or glycoproteins, or to cellular proteins such as, hexokinase, ATPase, acetyl cholinesterase of the human erythrocyte membrane, and skeletal muscle membranes [38]; they may also interact directly with DNA [39], causing cell death either by apoptotic or necrotic mechanisms.

Compared to standard drugs, the majority of organotin(IV) carboxylates discussed in the literature have shown superior anticancer activity against various cell lines. Additionally, some of them have demonstrated distinct anticancer activity even against CDDP-resistive cancer cells. Organotin(IV) compounds with pronounced medicinal properties also exhibit drawbacks such as reproductive toxicity, neurotoxicity and other toxic effects apart from poor water solubility; however, these can be circumvented by a rational design of the structures of the compounds, but the vital point still remains the activity. In practice, organotin(IV) compounds are dissolved in DMSO and diluted with test medium prior to in vitro testing. Nevertheless, the limited solubility needs to be further enhanced in a way comparable to CDDP, which also shows limited water solubility. It is therefore important to find more effective and safer organotin(IV) compounds for therapeutic use by designing and synthesizing new compounds. In this pursuit, recently a novel biocompatible strategy of drug delivery employing nano-structured silica-based material loaded with triphenyltin(IV) compound was used. This resulted in an increase in efficacy of the drug and the pattern of action leads to the non-aggressive suppression of melanoma tumor growth with non-recognizable toxicity toward normal tissue [40]. While the potency of a drug is a very important consideration, drug selectivity towards cancer cells is key to ensuring both safety and effectiveness [41]. Additionally, the mechanism of action of organotin(IV)
compounds in achieving cell death remains uncertain, and hence additional work is essential to identify the actual apoptotic or necrotic pathways.

3.3 Organotin carboxylates derived from Schiff bases

Schiff bases are generally obtained by condensing amino and keto-/formyl precursors. A careful selection of the precursor allows for the variation of the number and nature of the donor groups and, consequently, a large number of Schiff bases are available. Furthermore, the stereochemistry of the metal ions in Schiff base compounds can be tuned by introducing bulky groups into the ligand precursors. The basic imine nitrogen atom in Schiff bases exhibits \( \pi \)-acceptor properties and the presence of donor groups in the proximity influences the chelating ability. The reversible nature of imine bonds provides access to dynamic covalent chemistry, which today is employed for the construction of compound metal-organic materials and/or self-assembled architectures that are promising for sustainable energy, environmental, and biological applications [42-49]. Organotin(IV) compounds of Schiff bases present a wide variety of interesting structural possibilities. Both aliphatic and aromatic Schiff bases in their neutral and deprotonated forms yielded adducts and chelates with variable stoichiometry and different mode of coordination and their biological application have also been documented [25] and hence these were not discussed in details.

Considering the importance and properties of Schiff bases, prompted by broad therapeutic activity of organotin(IV) carboxylates (as discussed above) combining with their structural diversity [8], organotin(IV) Schiff bases derived from amino acetates have been investigated. Both di- and tri-organotin(IV) compounds can be active as far as cytotoxicity is concern [50], but the most effective groups are normally diorganotin(IV) compounds with butyl moiety and less so the phenyl moiety, and moreover diphenyltin(IV) compounds also lack solubility [51]. Active organotin(IV) compounds do appear to share certain characteristics, including available coordination positions on the tin and low hydrolytic cleavage of the Sn-R (R = alkyl or aryl) bonds. There also appears to be a necessary balance between lipophilic properties needed for crossing the cell membrane and hydrophilic character required to display activity in an
aqueous environment [52]. Considering all these points, organotin(IV) derivatives of Schiff bases prepared from amino acids and aminoalohols have also exhibited various structural possibilities and cytotoxic potential. Among these, series of organotin(IV) compounds derived from Schiff bases of amino acids, such as 2-aminoacetic-, 3-aminopropanoic-, (S)-2-amino-3-phenylpropanoic-, 2-amino-3-methylbutanoic-, 2-amino-4-methylpentanoic- and 2-amino-3-hydroxypropanoic acids have been prepared and structurally characterized [33,53-70]. The molecular structures of these compounds displayed varying structural features comprising both the ligand coordination modes and the metal coordination geometry, which are mainly influenced by the nature of the ligand and the Sn-R groups. Single-crystal X-ray diffraction analysis of several such organotin(IV) compounds revealed that Schiff bases derived from amino acids are versatile ligands with conformational flexibility, thereby creating mono-, di-, tri-, tetra- or polymeric assemblies with a variety of coordination modes. The molecular structures of the compounds are strongly influenced by the nature of the ligand, although in some cases, the structure can be modulated by varying the reaction conditions. An overview of the structural versatility resulting by the coordination of such Schiff bases towards organotin(IV) is given in Chart 3.3.
Chart 3.3 An overview showing the coordination behavior of Schiff bases derived from 2-aminoacetic-, 3-aminopropanoic-, (S)-2-amino-3-phenylpropanoic-, 2-amino-3-methylbutanoic-, 2-amino-4-methylpentanoic- and 2-amino-3-hydroxypropanoic acids towards organotin(IV) moieties.
In line with these development, five new organotin(IV) compounds of compositions [Bz\(_2\)Sn(L\(_a\))^n], [Bz\(_3\)Sn(L\(_a\)H)(H\(_2\)O)], [Me\(_2\)Sn(L\(_b\)H)(H\(_2\)O)], [Me\(_2\)Sn(L\(_c\))] and [Bz\(_3\)Sn(L\(_c\)H)]\(_n\) where L\(_a\) = (2S)-2-[[[(E)-2-(4-hydroxypentan-2-ylidene)]amino]-4-methylpentanoate, L\(_b\) = (rac)-2-[[[(E)-1-(2-hydroxyphenyl)methylidene]amino]-4-methylpentanoate and L\(_c\) = (2S)- (for 5) or (rac)- (for 4) 2-[[[(E)-1-(2-hydroxyphenyl)ethylidene]amino]-4-methylpentanoate) (Chart 3.4) were synthesized and structurally characterized [71]. Of interest was the dependence of the coordination mode of the Schiff base ligand, L, on the number and bulk of the R ligands at the Sn-atom, as well as the influence of variations in L itself.

**Chart 3.4** The general representation of potassium salts (L\(_a\)HK-L\(_c\)HK) and bonding interactions in the organotin(IV) compounds [Bz\(_2\)Sn(L\(_a\))^n], [Bz\(_3\)Sn(L\(_a\)H)(H\(_2\)O)], [Me\(_2\)Sn(L\(_b\)H)(H\(_2\)O)], [Me\(_2\)Sn(L\(_c\))] and [Bz\(_3\)Sn(L\(_c\)H)]\(_n\) illustrating chirality as observed in structural models.

Diorganotin(IV) compounds [Me\(_2\)Sn(L\(_d\)H)]\(_2\)H\(_2\)O, [nBu\(_2\)Sn(L\(_d\)H)], [Ph\(_2\)Sn(L\(_d\)H)]\(_2\)C\(_6\)H\(_6\), [Me\(_2\)Sn(L\(_d\)H)]-CHCl\(_3\) and [Ph\(_2\)Sn(L\(_d\)H)] (Chart 3.5) were prepared by reacting diorganotin dichlorides, R\(_2\)SnCl\(_2\) (R = Me, nBu and Ph) with sodium salts of the
tridentate NO$_2$ ligands $(E)$-3-hydroxy-2-((2-hydroxybenzylidene)amino)propanoic acid (L$_d^4$H$_2$Na) and (E)-3-hydroxy-2-((1-(2-hydroxyphenyl)ethylidene)amino)propanoic acid (L$_e^6$H$_2$Na). Single-crystal X-ray diffraction studies revealed that the only compound [Ph$_2$Sn(L$_d^4$H)]·2C$_6$H$_6$ has a distorted trigonal-bipyramidal geometry in the solid state. For compounds [Me$_2$Sn(L$_d^4$H)]·H$_2$O, [Me$_2$Sn(L$_d^6$H)]·CHCl$_3$ and [Ph$_2$Sn(L$_e^6$H)], the coordination geometries are distorted octahedral, either due to intermolecular association through Sn···O interactions or coordination through the oxygen atom from the pendant CH$_2$OH group. At the supramolecular level, the molecular structures are linked through O-H/O hydrogen bonds to give discrete dimeric assemblies, 1D chains and 2D hydrogen bonded layers [72].

![](chart.png)

**Chart 3.5** The general representation of sodium salts L$_d^4$H$_2$Na and L$_e^6$H$_2$Na, and bonding interactions in the corresponding diorganotin(IV) compounds [Me$_2$Sn(L$_d^4$H)]·H$_2$O, [nBu$_2$Sn(L$_d^4$H)], [Ph$_2$Sn(L$_d^4$H)]·2C$_6$H$_6$, [Me$_2$Sn(L$_d^6$H)]·CHCl$_3$ and [Ph$_2$Sn(L$_e^6$H)] in solid state.

L-2-amino-3-(4-hydroxyphenyl)propanoate has been incorporated in NO$_2$-type Schiff base molecules, which were isolated as sodium 2-((E)-(Z)-4-hydroxypent-3-en-2-ylidene)amino)-3-(4-hydroxyphenyl)propanoate (L$_d^4$H$_2$Na), silver (E)-2-((2-hydroxybenzylidene)amino)-3-(4-hydroxyphenyl)propanoate (L$_d^6$H$_2$Ag) and silver (E)-3-(4-hydroxyphenyl)-2-((1-(2-hydroxyphenyl)ethylidene)amino)propanoate (L$_e^6$H$_2$Ag). These salts were subsequently reacted with four different diorganotin(IV) precursors, affording a variety of diorganotin(IV) compounds of compositions [Me$_2$Sn(L$_d^4$H)], [nBu$_2$Sn(L$_d^4$H)], [Ph$_2$Sn(L$_d^4$H)], [Bz$_2$Sn(L$_d^4$H)], [Me$_2$Sn(L$_d^6$H)(MeOH)].MeOH and
[Ph₂Sn(L³H)] (Chart 3.6). The crystal structures of the compounds revealed discrete molecular structures in all cases with distorted trigonal-bipyramidal geometries except for [Me₂Sn(L⁴H)(MeOH)].MeOH which showed a strongly distorted six-fold coordination due to association of a MeOH solvent molecule [73].

**Chart 3.6** The general representation of the sodium/silver salts L¹H₂Na, L²H₂Ag and L³H₂Ag and bonding interactions in the [Me₂Sn(L¹H)], [nBu₂Sn(L¹H)], [Ph₂Sn(L¹H)], [Bz₂Sn(L¹H)], [Me₂Sn(L³H)(MeOH)].MeOH and [Ph₂Sn(L³H)] found in the solid state.

In order to achieve the specificity, Schiff bases derived from amino acids figure as promising complexing agents for organotins as described above, but yet a wide variety of Schiff bases can be explored. L-tryptophan (2S)-2-amino-3-(1H-indol-3-yl)propanoic acid) is an essential α-amino acid has been integrated in the Schiff base structure, aiming to benefit from their biological properties, which is required for designing specific molecules and possibly may permit a variety in their coordination behavior. Three sodium salts, viz., sodium 2-((E)-((Z)-4-hydroxypent-3-en-2-ylidene)amino)-3-(1H-indol-3-yl)propanoate (L¹HNa), sodium (E)-2-((2-
hydroxybenzylidene)amino)-3-(1H-indol-3-yl)propanoate (L^i\text{HNa}) and sodium \((E)-2-((1-(2-hydroxyphenyl)ethylidene)amino)-3-(1H-indol-3-yl)propanoate (L^k\text{HNa})\) were subsequently reacted with organotin(IV) precursors, which afforded new organotin(IV) compounds of compositions \([\text{Me}_2\text{Sn}(L^j)]\), \([\text{Me}_2\text{Sn}(L^j)]_n\), \([\text{Me}_2\text{Sn}(L^k)]\) and \([\text{Ph}_3\text{Sn}(L^i\text{H})]_n\) [74] and their mode of coordination has been presented in Chart 3.7.

![Chart 3.7](image)

**Chart 3.7** The general representation of the sodium salts (L^i\text{HNa}-L^k\text{HNa}) and bonding interactions in the organotin(IV) compounds \([\text{Me}_2\text{Sn}(L^j)]\), \([\text{Me}_2\text{Sn}(L^j)]_n\), \([\text{Me}_2\text{Sn}(L^k)]\) and \([\text{Ph}_3\text{Sn}(L^i\text{H})]_n\) found in the solid state.

Triphenyl(2-\(((E)-((Z)-4-hydroxypent-3-en-2-ylidene)amino)-3-(1H-indol-3-yl)propanoato)\text{tin(IV)})\) i.e. compound \([\text{Ph}_3\text{Sn}(L^i\text{H})]_n\) was envisaged for its cytotoxic potential which demonstrated potent apoptotic activity in melanoma cells, compared to epithelial or breast tumor cells at reasonably low concentration (IC\textsubscript{50} value of 261 nM). Cell death potency in tumor cells was determined by several assays, like MTT assay, Live and Dead assay, and PARP cleavage. The side effect was found to be minimal as
the cell necrosis was within 10%. The bioavailability in the cellular system was about 6 h and then loses its activity, possibly by degradation posing its positive aspect as potent chemotherapeutic (Fig. 3.1).

Fig. 3.1 Fluorescence images of the cells incubated with 1 μM of [Ph₃Sn(L’H)]₅ showing the bioavailability in the cellular system (For details, see ref. 78).

Measurements of membrane fluorescence and membrane fluidity were also investigated to clinch the final discussion. As a result of promising cytotoxic activity, the mechanistic role of the interaction ability between triphenyltin(IV) compound
[Ph₃Sn(L¹H)]ₙ and cyclodextrin (CD) was also investigated since the latter can enhance the solubility in aqueous medium and can act as a drug carrier (Fig. 3.2). [74].

![Fig. 3.2 Pictorial representation of optimal model showing the inclusion/interaction of compound triphenyltin(IV) compound [Ph₃Sn(L¹H)]ₙ and γ-CD acquired with (a) visual molecular dynamics (VMD), (b) PLATON (For details, see ref. 74).](image)

Examples of organotin(IV) compounds of Schiff base amino acids incorporating bifunctional carboxylates are also available and in this context L-Aspartic acid, hereafter (S)-2-aminosuccinic acid were combined with appropriate aromatic aldehydes/ketones to obtain ditopic Schiff base ligands with two distinct coordination sites. It is anticipated that the design and construction of Schiff bases from (S)-2-aminosuccinic acid are likely to provide suitable coordination environments for two di- and triorganotin fragments, which can be bound within close proximity to form dinuclear organotin(IV) carboxylates. Several dinuclear organotin(IV) compounds, viz. [Bz₂Sn(L¹)SnBz₂Cl]ₙ·nCHCl₃, [Bz₂Sn(Lⁿ)SnBz₂Cl]ₙ, [Bz₂Sn(Lⁿ)SnBz₃],
[nBu₃Sn(L°H)SnBu₃]n, and [nBu₃Sn(L°H)SnBu₃]n were synthesized and structurally characterized [75]. The observed coordination modes are depicted in Chart 3.8.

Chart 3.8 The general representation of the sodium salts (L¹HNa₂, L°HNa₂, L°°H² and L°°H²) and bonding interactions in the organotin(IV) compounds [Bz₂Sn(L¹)SnBz₂Cl]ₙ, nCHCl₃, [Bz₂Sn(L°)SnBz₂Cl]ₙ, [Bz₂Sn(L°°)SnBz₃]ₙ, [Bu₃Sn(L°°H)SnBu₃]ₙ, and [Bu₃Sn(L°°H)SnBu₃]ₙ, found in the solid state.

As shown in Chart 3.8, by combining hydroxyl-substituted aldehydes and ketones, and (S)-2-aminosuccinic acid provides interesting ligands with heteroditopic coordination sites for the simultaneous complexation of di- and triorganotin moieties. Of these, the diorganotin fragments are involved in a bis-chelate NO₂ coordination environment formed by the Schiff base and the α-amino acid segment of the ligand with an additional weak intramolecular secondary O/Sn interaction resulting from the β-
carboxylate group. On the contrary, the triorganotin and monochloro-diorganotin moieties are coordinated to the α- and/or β-carboxyl group without chelate ring formation. It was envisioned that these compounds might exhibit particular biological properties due to the presence of two organotin sites having different coordination numbers and geometries and, thus, different reactivity.

A series of new pentacoordinated Schiff-base diorganotin(IV) complexes derived from nonpolar side chain α-amino acids (isoleucine, leucine, methionine, phenylalanine and aminophenylacetic acid), 2,4-dihydroxybenzaldehyde, 2-hydroxy-4-methoxybenzaldehyde and either di-n-butyltin(IV) oxide or diphenyltin(IV) oxide were prepared in good yields by multicomponent reactions (MCRs) in methanol [76]. Among twenty synthesized compounds, only two diphenyltin(IV) compounds were structurally characterized where tin atom displayed a distorted trigonal bipyramidal geometry (motif I) as described in Chart 3.3. These compounds were tested in tumor cell lines, MCF-7 (breast adenocarcinoma), HCT-15 (colon adenocarcinoma) and HeLa (cervical uterine adenocarcinoma), in order to evaluate the antiproliferative activity and to obtain the medial inhibitory concentrations (IC50) values. In general, organotin(IV) compounds showed high antineoplastic activity regardless of cell line type; the IC50 concentrations were below the IC50 values for cisplatin. Although, the selectivity was observed in the activities of some compounds for particular cell lines, which is important for the future medicinal applications in order to avoid the side effects, thus synthesized compounds were found to be promising [76].

Recently, six new luminescent pentacoordinate organotin(IV) compounds were also synthesized following the MCRs derived from Schiff bases by condensation of three essential L-amino acids (tryptophan, tyrosine, or phenylalanine), 2-hydroxy-1-naphthaldehyde, and the corresponding diorganotin oxide \( (R_2SnO, R = nBu \text{ or Ph}) \) in methanol but now using a microwave [77]. Crystal structure of a representative dibutyltin(IV) compound indicated a distorted trigonal bipyramidal geometry (motif I, Chart 3.3) around the tin atom. Cytotoxicity results indicated that the compounds are practically safe towards B16F10 (Murine skin melanoma B16F10) cells. Additionally, the interactions of a truncated organotin-fibroin complex were also investigated [77]. DFT calculations revealed two major stabilizing non-covalent interactions between the
organotin(IV) compound and the fibroin model i.e. (i) intermolecular hydrogen bond between the N–H group of fibroin and the C=O group of the organotin(IV) compound (N–H···O = 2.081 Å) and (ii) a C–H···π interaction between the CH₃ group of fibroin and the phenol moiety of the organotin(IV) compound (H to phenol ring center distance 2.977 Å), as shown in Fig. 3.3.

**Fig. 3.3** Non-covalent interactions showing between the diphenyltin(IV) compound and the fibroin model (For details, see ref. 77).

Thus, new application of fluorescent diorganotin(IV) compounds as colorants for staining silk fibroin, and the stained fibroin might have potential applications as a scaffold in tissue engineering owing to the biocompatibility of silk fibroin and the low cytotoxicity in vitro. It may be inferred that organotin(IV) compounds based on Schiff base amino acetate skeletons have been becoming increasingly important in the development of inorganic biochemistry as they offer ease and flexibility of the synthetic
procedure, diverse properties and biological activity.

In spite of several studies, the mechanisms of organotin(IV) induced apoptosis are still not fully comprehended and in this regard, small modular ligands with imino-scaffolds were also used for the syntheses of triphenyltin(IV) carboxylates, where the carboxylate functionality was varied from ortho-, to meta- and para-positions. It was anticipated that this variation would significantly influence the nature of interaction with enzyme amino acid residues and hence, the activity of the compounds. In this pursuit, triphenyltin(IV) esters, [Ph₃Sn(L⁰)], [Ph₃Sn(Lᵖ)] and [Ph₃Sn(L⁹)] where L⁰-L⁹ are 2/3/4-{[(E)-{[4-(dimethylamino)phenyl]methylidene}amino]benzoates (Fig. 3.4) have been synthesized and cytotoxic potency was determined [78]. The structure of [Ph₃Sn(Lᵖ)] (Fig. 3.4) was analyzed by single crystal X-ray crystallography where the tin atom is tetrahedrally coordinated within a C₃O donor set, implying a monodentate mode of coordination of the carboxylate ligand.

![Diagram](image.png)

**Fig. 3.4** The general representation of the ligands (L⁰H, LᵖH and L⁹H) and bonding interactions in the triphenyltin(IV) compound [Ph₃Sn(Lᵖ)] found in the solid state.

Biological results indicated that the location of triphenyltin ester in ortho-, meta- and para- positions of the ligand does exert a meaningful influence on the cytotoxicity. Among all the three compounds, [Ph₃Sn(Lᵖ)] demonstrated remarkable activity, exhibiting very high cytotoxic activity (31-fold) compared to CDDP, towards HeLa cells with a IC₅₀ value of 0.88 µM (Fig. 3.5), yet the series of compounds had minimal cytotoxic effect on normal HEK 293 (human embryonic kidney) cell line.
Fig. 3.5 Dose dependent cytotoxic effects of compounds [Ph₃Sn(Lο)], [Ph₃Sn(Lρ)] and [Ph₃Sn(L𝑞)] on HeLa cells by MTT assay after incubation with various concentrations of compounds for 24 h.

The underlying investigation suggested that the organotin(IV) compounds induce oxidative stress, which leads to apoptotic cell death as revealed from ROS measurement by DCFH-DA (Fig. 3.6) and Hoechst 33342/PI staining (Fig. 3.7), respectively.
**Fig. 3.6** Dose-dependent generations of ROS when treated with IC\textsubscript{50} concentrations of the respective compounds induced by [Ph\textsubscript{3}Sn(L\textsuperscript{p})] in HeLa cells detected by measuring the fluorescence intensity using DCFH-DA viewed through fluorescence microscope.

**Fig. 3.7** Fluorescence microscope images showing morphological (nuclear) changes in HeLa cells upon treatment with specified concentrations of Ph\textsubscript{3}Sn(L\textsuperscript{p}) compound, by dual staining with Hoechst 33342 and PI for 24 h. (For details, see ref. 78).
Thus, compounds exert their antitumor effect by elevating intracellular ROS generation, independent of the cell line [78] and compound Ph₃Sn(L⁰) merits further investigation as a new potential therapeutic candidate for cancer treatment.

From the foregoing description of the structural chemistry of organotin(IV) carboxylates and biological applications, it is clear that there exists a rich diversity in Sn atom geometry and coordination modes of the Schiff base ligands themselves. The advances of related work involving the Schiff bases and organotin(IV) constitute the subject matter of Chapter 4. The specific introduction section is included in the beginning of Chapter 4 and hence not discussed further.
References


