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Organotin(IV) Complexes as Chemotherapeutic Drugs Against Different Types of Cancer Cell Lines: A Review

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Abstract

Recently, organotin(IV) complexes have shown high anticancer activity against various cancer cell lines. They are promising anticancer drugs since they selectively target cancer cells. Complexes' apoptosis and caspase activities are based on alkyl or aryl groups and the anionic groups in ligands that bind to the metal. Many types of research concentrated on synthesizing different di and tri-organotin complexes using a non-aqueous medium because of its ability to hydrolyze in aqueous solutions. This current work highlights the continuing attempts to synthesize novel organotin complexes using different ligands and evaluate the cytotoxicity against the different cell lines.

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1. Introduction

Usually, cells divide and grow until they undergo apoptosis. When this process is affected, cells age and grow uncontrollably. As a result, a tumor forms and may be solid or fluid-filled. These masses are called tumors and are classified into two types: benign, localized, and malignant tumors, which can spread to other parts of the body [1]. Unlike malignant tumors, benign tumors are characterized by slow growth, but they are benign and remain dangerous when they become more significant and affect other nearby parts of the body [2]. Malignant tumors multiply, spread throughout various body parts, and are treated in several ways; they may need vast excision and radiotherapy [3]. Organotin compounds contain one or more organic substituents attached to the tin atom. There are two oxidation states (+2 and +4), but +4 is the most stable because Sn (+2) uses 5p orbitals, leaves unpaired electrons in the 5s orbital, and tends to polymerize rapidly. It thus loses all four electrons and gains the electronic configuration of xenon. A well-known stable derivative of organotin(IV) compound is bis(cyclopentadienyl)tin(II), which has sp^2 hybridization of the tin atom and two hybrid orbitals attached to the cyclopentadienyl bonds with two unpaired electrons [4, 5]. The geometry of tin is tetrahedral with sp3 hybridization with four electrons in the valence shell (5s2 5p2). Tin bonds are almost covalent, especially in solids, nonpolar solvents, and vapor phases [6]. Recently, many researchers have synthesized different organotin complexes using non-aqueous media due to their ability to decompose in aqueous solutions [7]. Organotin carboxylates are the most important due to the presence of an O=C-OR group that attaches to the central metal atom, producing the organotin ester complexes [8]. Organotin compounds ($RnSnX_{4-n}$) are classified into mono ($RSnX_3$), di (R_2SnX_2), tri (R_3SnX), and tetra-organotin (R_4Sn), where R is a substituent, and X refers to the donor group [5, 9]. Figure 1 shows the structures of some organotin compounds that have anticancer activity [10].

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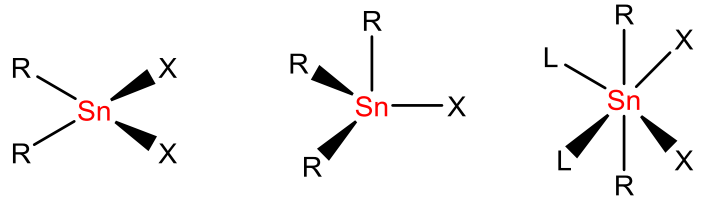


Figure 1: The structures of some organotin complexes that exhibit anticancer activity.

Organotin compounds have various physical and chemical properties based on the contents of Sn-C bonds and long hydrocarbon chains. Sn-C has high-temperature resistance above 200°C. It also exhibits good stability in water and O_2 [11]. Also, the length and numbers of organic groups and anionic species (X) in organotin compounds are reversibly proportional to their solubility in water [12].

2. Anticancer Activity:

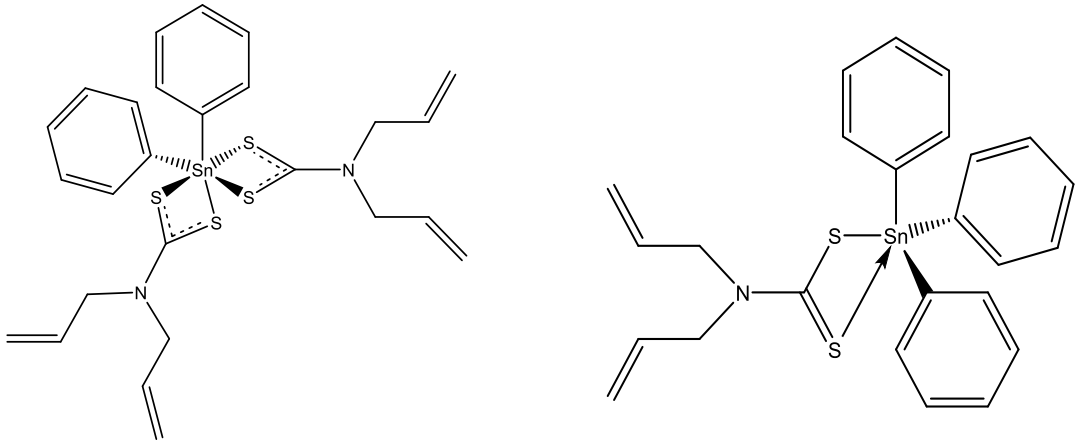
Organotin compounds exhibit high cytotoxicity targeting cancer cells, higher antiproliferative activity, and good excretion properties. It also showed fewer side effects than cisplatin, even at low concentrations [13]. The cytotoxicity effect of organotin complexes is explained by interaction with the sequences of DNA, which changes and inhibits structure, proteins, activators, and gene expression [14]. Despite the high efficiency of organotin (IV) complexes against cancer cells, they have sometimes shown cytotoxicity against normal cells, and this causes their uses in clinical therapy to be restricted. As a result, recent studies have focused on novel organotin compounds with high cytotoxicity against cancer cells and low against normal cells [31]. The nature of the R-groups that attach to the central atom (tin) and the anionic groups in the ligand that affect the activity of the organotin(IV) complexes as anticancer, whether these groups are hydrophilic or lipophilic, which promotes the movement of these complexes across cells membranes [32].

Recently, organotin has shown extensive reports for cancer chemotherapy due to its cytotoxicity and apoptosis activation, especially with Schiff base ligands that promote the efficiency of organotin complexes [15]. The cationic nature of metalloorganic complexes allows them to interact with particular amino acids and nucleotides and target both proteins and DNA, especially the aromatic parts of organic compounds that accelerate the intercalation and production of reactive oxygen species (ROS), so organotin complexes show important biological activity [16]. ROS are produced in small, balanced amounts and are effective in normal cell growth, but if a large amount of them is produced, they damage nucleic acids, proteins, and lipids [17].

Apoptosis is a morphological serial process suggested by (Kerr et al.) in 1972 that refers to the programmed cell death without any external factors, the term apoptosis (from a Greek word meaning dropping) [18]. Depending on the drugs used, it can distinguished whether cells die by apoptosis or necrosis. Several factors, such as heat, oxygen, anticancer drugs, and radiation, which cause necrosis, affect cell death [19]. Apoptosis occurs when damage in DNA or accumulation of cell proteins occurs, leading to chromatin and cell shrinkage condensation. Necrosis occurs when cells swell and become larger and membrane, and intracellular content is lost [20]. Caspases induce programmed cell death where cleavage of the substrates activates the mediators of the cell death and helps facilitate changes in cell morphology. The main caspases that activate apoptotic pathways are Caspase-8 and caspase-9 [21]. Organotin complexes have high cytotoxicity against cancer cells because they cause DNA damage, increase the cytosolic Ca^{2+}, cause apoptosis activation, inhibit the synthesis of essential macromolecules, and lead to mitochondrial dysfunction [22]. Several studies have evaluated the cytotoxicity of different organotin (IV) complexes synthesized using various ligands against cancer cell lines and showed acceptable results with different toxicity ratios.

Haezam et al. synthesized two organotin complexes, diphenyltin(IV) (complex 1) and triphenyltin(IV) (complex 2), as shown in Figure 2 using diallyldithiocarbamate as a ligand. The two complexes were characterized by FTIR and NMR spectra. The cytotoxicity of these complexes was assessed via the MTT on HT-29 cell lines. The complexes showed high efficiency of these complexes as anticancer drugs depending on the structures that promote apoptosis and inhibit cell growth. The organotin(IV) compound can be influenced by the

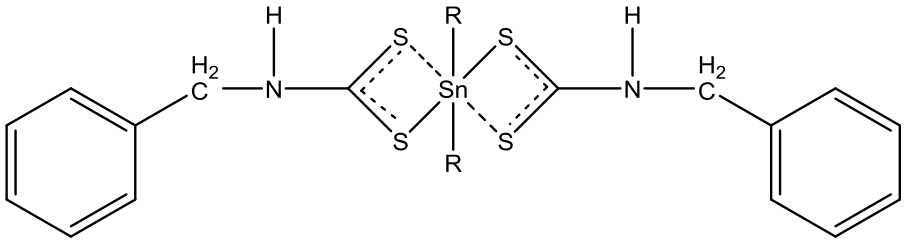
properties of the compound and the number of alkyl groups attached to the stanum atom [23].



Complex (1) Complex (2)

Figure 2: The structures of the two organotin complexes, Ph_2SnL_2 (1) and Ph_3SnL (2), by using diallyldithiocarbamate as a ligand.

Adeyemi et al. prepared three organotin complexes $[(R^1)_2SnL_2]$ (1), $[(R^2)_2SnL_2]$ (2), and $[(R^3)_2SnL_2]$ (3) as shown in Figure 3 where (R = CH_3, C_4H_9, and C_6H_5) and Ammonium benzyldithiocarbamate as ligand. The synthesized three di-organotin complexes were characterized by FT-IR and NMR and measured their cytotoxicity on two cell lines: HeLa and MCF-7. The results showed anticancer activity for the two types of cell lines, especially complex 2 and 3. The moieties in the organotin and dithiocarbamate have an essential role in anticancer activity, which increases lipophilicity and promotes the movement of the tin central atom [24].



R= CH_3, C_4H_9, C_6H_5

Figure 3: The structures of the three organotin complexes: $[(CH_3)_2SnL_2]$ (1), $[(C_6H_5)_2SnL_2]$ (2), and $[(C_6H_5)_2$-$SnL_2]$ (3) and Ammonium benzyldithiocarbamate as ligand.

Bhaskara et al. synthesized a novel di-organotin (IV) complex, as shown in figure 4, characterized by FT-IR and NMR, and measured their cytotoxicity on Vero and Hela cell lines. Results showed high cytotoxicity against the two cell lines compared to the results obtained from cisplatin [25].

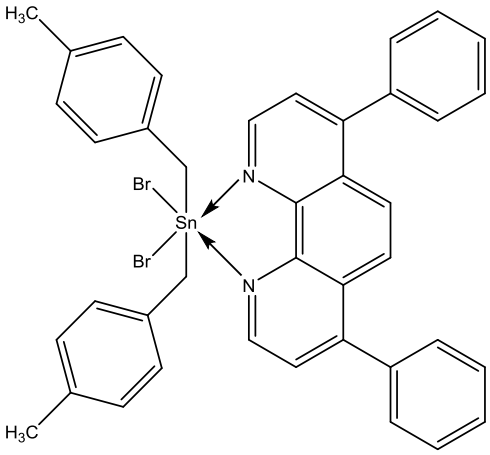


Figure 4: Structure of di-p-methylbenzyldibromo,4,7-diphenyl-1,10-phenanthrolinetin (IV) complex.

Other novel organotin(IV) complexes (Ph_2SnL_2 and Bu_2SnL_2), as shown in Figure 5, were synthesized using valsartan as a ligand. The complexes were characterized by FT-IR and NMR spectra. The complexes were evaluated using MTT assay against the A549 cell line. The results explained that the butyl complex shows higher anticancer activity than the phenyl complex based on the effect of lipophilic, van der Waals volume, and size of groups that bind with the central atom. The nature of the substituent ligand (valsartan) helps transport the organotin moiety across the cellular membrane and hydrolysis [26].

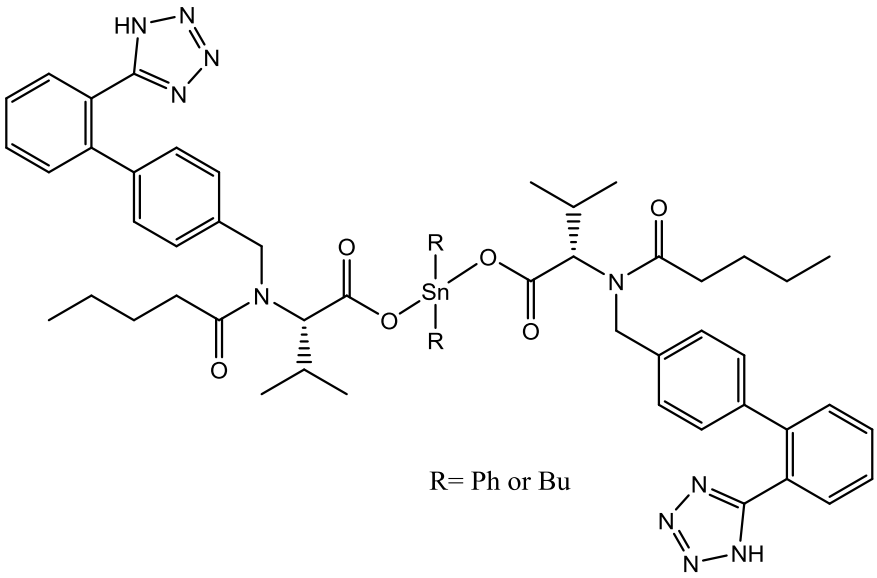
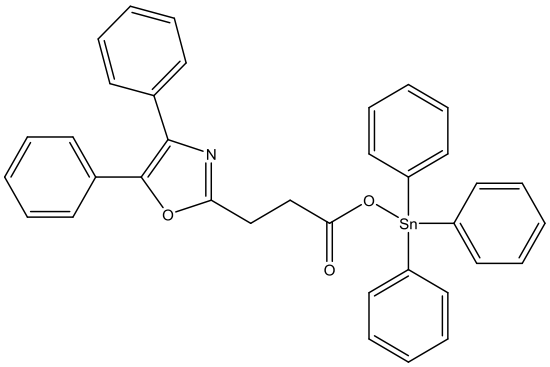


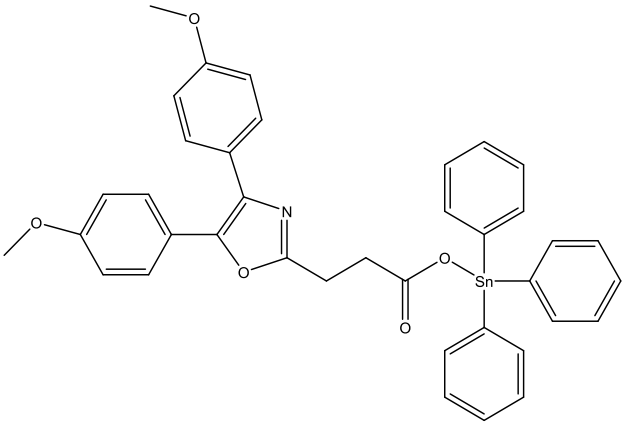
Figure 5: Using valsartan as a ligand, the structures of novel organotin complexes (Ph_2SnL_2 and Bu_2SnL_2).

Panteli et al. prepared three organotin complexes $Ph_3SnL_{(1-3)}$ (see Figure 6) using three different ligands; the first with three different ligands characterized by FT-IR and NMR. Then, they evaluated anticancer activity on different cell lines: PC-3, HT-29, MCF-7, HepG2, and the regular NIH3T3 cell line. The results obtained from the MTT assay showed that all organotin complexes exhibit anticancer activity but in different percentages and promote apoptosis and caspases. Different biological assays for investigating its mechanism of action suggest that Ph3SnL1 induces caspase-independent apoptosis in MCF-7 cells. Moreover, ICP-MS analysis indicates that this is

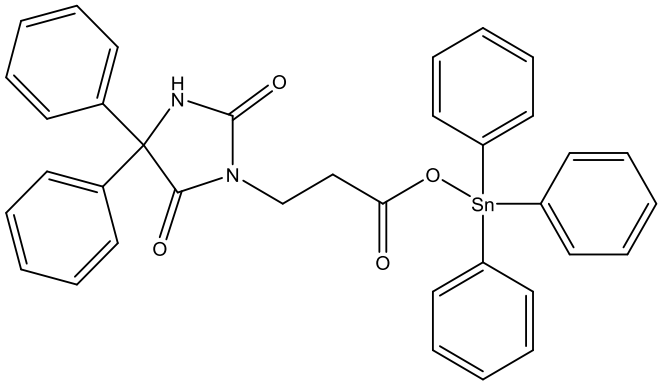
achieved with lower intracellular concentrations of tin in MCF-7 cells than platinum. Considering the required extracellular concentrations, the triphenyltin(IV) compounds show better cell bioavailability and accumulation, a common phenomenon for lipophilic (and cationic) substances [27].



Complex (1)



Complex (2)



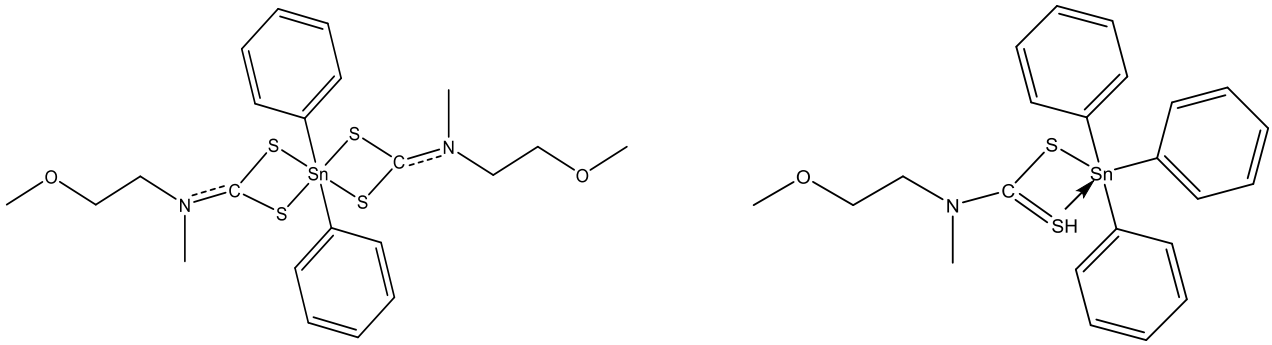
Complex (3)

Figure 6: Structures of three organotin complexes $Ph_3SnL_{(1-3)}$ by using three different propanoic acid ligands; L_1: (3-(4,5-diphenyloxazol-2-yl), L_2: 3-(4,5- bis(4-methoxylphenyl)oxazol-2-yl), L_3: 3-(2,5-dioxo-4,4-diphenylimidazolidin- 1-yl).

Adeyemi et al. prepared several organotin complexes: $MeSnClL_2$, $BuSnClL_2$, $PhSnClL_2$, Me_2SnL_2, Bu_2SnL_2, and Ph_2SnL_2 by using N-ethyl-N-phenyl dithiocarbamate as ligand. By using the MTT assay, all complexes are measured for their cytotoxicity on HeLa cells, and the complexes exhibit high anticancer, especially the PhSnClL2 and Ph2SnL2 that exhibit the highest activity because of the presence of planar phenyl that act to promote the lipophilic and penetration into cells. The organotin complexes with the disubstituted alkyl/aryltin(IV) groups induced better cytotoxic activity than their mono-substituted derivatives compared to the standard drug 5FU. Complex Ph_2SnL_2 showed the best activity among this group of organotin(IV) dithiocarbamate compounds. The reactivity has been attributed to the improved lipophilicity due to the presence of one or more phenyl groups in the complexes [28].

Kamaludin et al. prepared two novel organotin complexes; the first is 2-methoxyethyl) methyldithiocarbamate, and the second is 2-methoxyethyl) methyl dithiocarbamate, as shown in Figure 7 and evaluated against the human erythroleukemia cells (K562). Dithiocarbamate derivatives are lipophilic compounds with a higher level of solubility in organic solvents than in water,

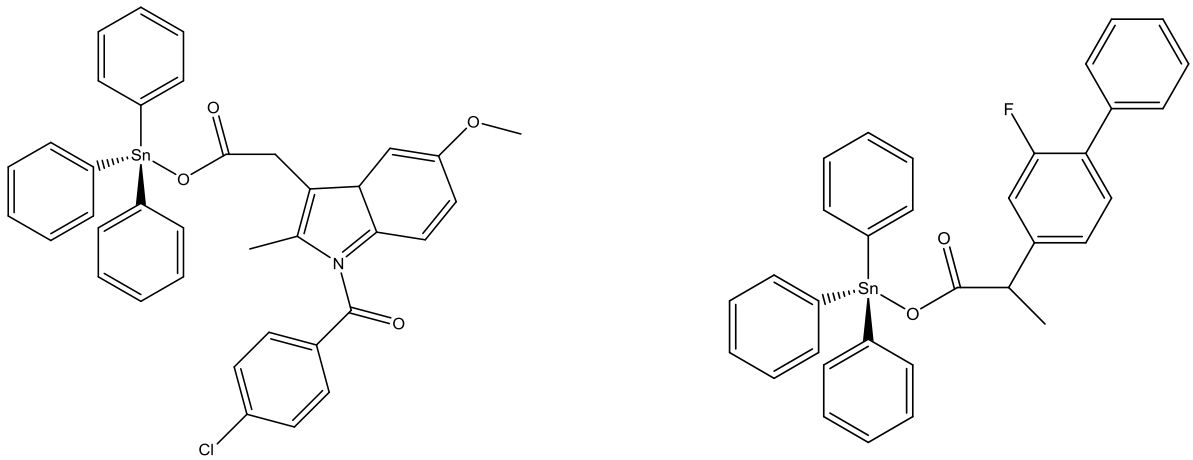
which is one of the essential factors for biological activities and facilitates the transport of compounds through the membranes in biological systems. Both complexes showed high cytotoxicity against this cell line, and they act to promote cell death and apoptosis [29].



Complex (1) Complex (2)

Figure 7: The structures of the two novel organotin complexes: complex (1): 2-methoxyethyl) methyldithiocarbamate and complex (2): 2-methoxyethyl) methyl dithiocarbamate.

Predarska et al. prepared two organotin complexes [Ph_3Sn(IND)] complex (1) and [Ph_3Sn(FBP)] complex (2) figure 8 from (indomethacin (HIND) and flurbiprofen (HFBP)). The complexes' cytotoxicity was studied on several breast cancer cell lines (BT-474, MDA-MB-468, MCF-7, and HCC1937). The ligand did not impact the examined cancer cell proliferation, but the organotin(IV) complexes demonstrated IC50 values at nanomolar concentrations. This superior cytotoxicity demonstrated against all cell lines involved, represents a significant enhancement in comparison to the effect of cisplatin. The results of IC_{50} explained that both complexes have high anticancer activity against all cell lines due to cell growth inhibition and decreases in NO production [30].



Complex (1) Complex (2)

Figure 8: The structures of the two organotin complexes [Ph_3Sn(IND)] complex (1) and [Ph_3Sn(FBP)] complex (2) from (indomethacin (HIND) and flurbiprofen (HFBP)).

3. Conclusions

The organotin has shown high anticancer activity against different cancer cell lines by different mechanisms. The applications of organotin (IV) complexes as chemotherapeutics depend on length, number of alkyl/aryl organic groups, and anionic species in the organotin compounds. They can interact with DNA sequences, change their structures, inhibit the reach of proteins and activators, and affect gene expression. These complexes showed activity to activate the caspases that increased the apoptosis, which occurs when DNA damage in cells leads to chromatin condensation and shrinkage of cells.

Conflicts of Interest: The authors confirm that there are no conflicts of interest.

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