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Review

Chemical and biotechnological developments in organotin cancer chemotherapy

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Abstract

This review provides a substantial knowledge on the action mode of organotins in cancer chemotherapy. The coordinating ability of organotin compounds towards DNA and cancer cells is discussed. Most of the organotins tested are DNA-targeted and mitotic, the action mode occurring via a gene-mediated pathway. These potential anti-cancer drugs are actually being studied widely, and whilst they are efficacious and perhaps curative against a select number of neoplasias, suffer from a variety of deficiencies, notably severe systemic toxicity and a tendency to elicit drug resistance.
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Keywords: Tin; Anti-tumor compounds; Carboxylate

Contents

1. Introduction

Malignancy is the result from a multiple process by accumulation of mutations and other genetic alterations [1]. The interaction of organometallic compounds with DNA is of interest for therapeutic treatment as these molecules recognize specific DNA sequences, alter the local DNA structure, inhibit access to the activator or repressor protein and ultimately affect the gene-expression process

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[2,3]. Most of the chemotherapeutic drugs are DNA-targeted. In the present review results about the in vivo and in vitro anti-cancer activities of organotin compounds are summarized.

Organotin compounds are involved in cancer treatment via different mechanisms at the molecular level. The binding ability of organotin compounds towards DNA depends on the coordination number and nature of groups bonded to the central tin atom. The phosphate group of DNA sugar backbones usually acts as an anchoring site and nitrogen of DNA base binding is extremely effective, this often resulting in the stabilization of the tin center as an octahedral stable species.

Recent studies [4–9] have showed that low doses of organotins can exhibit anti-tumoral activity and have suggested an action mode via gene-mediated pathway in the cancer cells, opening a new research sub-area on organotin compounds. A number of metal compounds able to activate apoptosis directly involved in the apoptotic pathway, such as p53 tumor suppressor, TRAIL receptor, caspases and the Bcl-2 family of proteins have been recently developed. Since there are two primary modes of apoptosis, i.e. extrinsic and intrinsic, metal-induced apoptosis is thought to be initiated intracellularly, the mitochondria being most pertinent in mediating apoptosis via metal-induced reactive oxygen species [10].

The di-*n*-butyltin and tri-*n*-butyltin chloride are known to induce apoptosis in vitro in rat thymocytes, these organotins inhibiting DNA synthesis and increasing RNA synthesis [11]. The apoptotic pathway induced by di-*n*-butyltin and tri-*n*-butyltin chloride starts with an increase of Ca^{2+} ions and is followed by the release of the cytochrome *c* from mitocondria, activation of caspases and finally DNA fragmentation [12]. Diethyltindichloro(1,10-phenanthroline) inhibits cancer cell growth and also change the surface of the cancer cell membrane [13].

It has well established that organotin(IV) compounds are very important in cancer chemotherapy because of their apoptotic inducing character [14,15]. During last few year it is noticeable that organotin compounds occupy an important place in cancer chemotherapy reports [16–19]. Recently, Blower described thirty interesting inorganic pharmaceuticals, four of which are tin compounds [20].

2. Results and discussion

2.1. Chemical and biochemical aspects of DNA inhibition

Many studies have been performed on organotin compounds cancer chemotherapeutic agents and important observations have already been reviewed [21–25]. For example Appel [23] described various toxico-kinetic aspects of organotins pointing out that most of the studies carried out on organotin anti-tumor compounds investigated their metabolism by the monooxygenase systems, using in vitro systems. However the details of the mechanism of DNA-organotin interaction has not yet been clearly defined.

A series of organotin compounds containing salicylaldoxime-type ligands coordinated to di-*n*-butyltin moieties have been synthesized by Gielen et al. Very promising results by in vitro tests on MCF-7 a mammary tumour were indicated [26,27].

Chirality is a very important aspect in the chemistry of pharmaceuticals. Kinetics, stereochemistry and mechanism of reactions have their own significance: structural relationships and kinetic parameters of new chiral organotin clusters, anti-tumour activity and ID_{50} (μg/ml) values of potent poly-oxaalkyltin compounds against seven human tumour cell lines have been also recently reported [28].

Some steroidal organotin compounds have been synthesized and tested. These compounds have been compared in vitro with a parent steroid and two model compounds. A series of human tumor cell lines has been used to compare the results and it has been observed that the organotin steroids **I–III** depicted in Fig. 1 exhibit promising in vitro activity. In particular, **III** is highly effective towards cancer cells and may be employed as model for further investigation on the structure–activity relationship in anti-tumor organotin compounds [29].

Solubility of the organotin anti-tumour agents in non-toxic solvent such as water is very important factor in reducing the toxicity in the cell. Some organotin carboxylates and steroidcarboxylates (Figs. 2 and 3) were described and their anti-tumour activity has been checked in aqueous media [30a]. ID_{50} values (in micromolar) in ethanol against A549 cancer cells have been reported for various aminoaryl carboxylates-organotin compounds [30].

The anti-tumour activity of 3-C-[(triphenylstannyl)methyl]-1,2:5,6-di-*O*-isopropylidene-D-allofuranose (Ph_3SnCH_2carbohydrate) and 3-C-(triphenylstannyl)-1,2:5,6-di-*O*-isopyropylidene-D-allofuranose (Ph_3Sn–carbohydrate) has been reported by Caruso et al. [31]. These compounds show the following activity: (a) the triphenyltin carbohydrates are less active than Ph_3SnCl with respect to their capacity to interfere with DNA, RNA, and protein synthesis of isolated fastly proliferating thymocytes: protein synthesis was found to be most sensitive with an IC50 value of

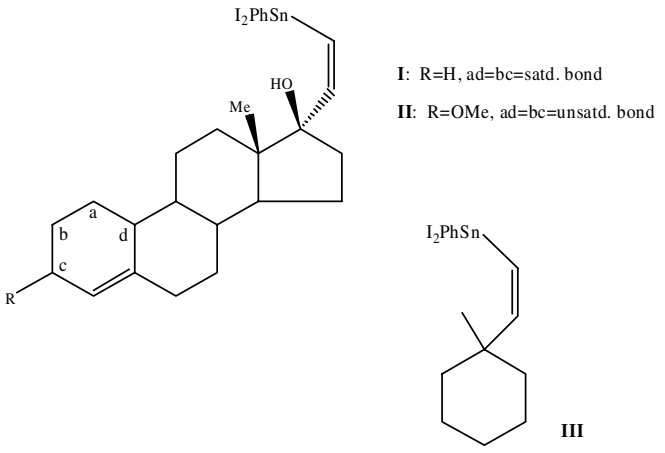


Fig. 1. Structure of organotin steroids **I–III**.

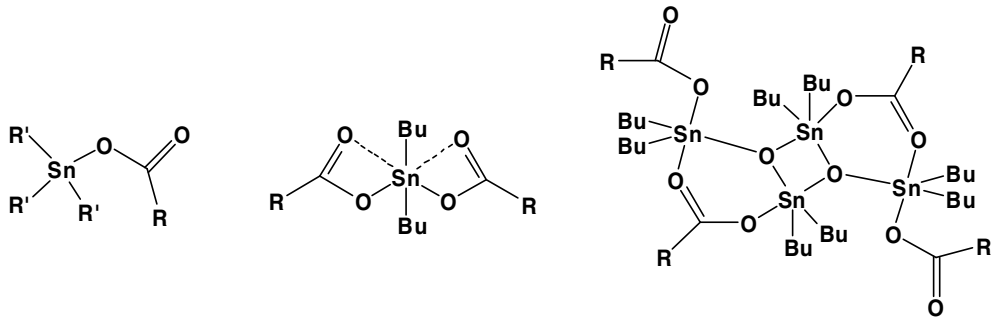


Fig. 2. Structures of diorganotin carboxylates.

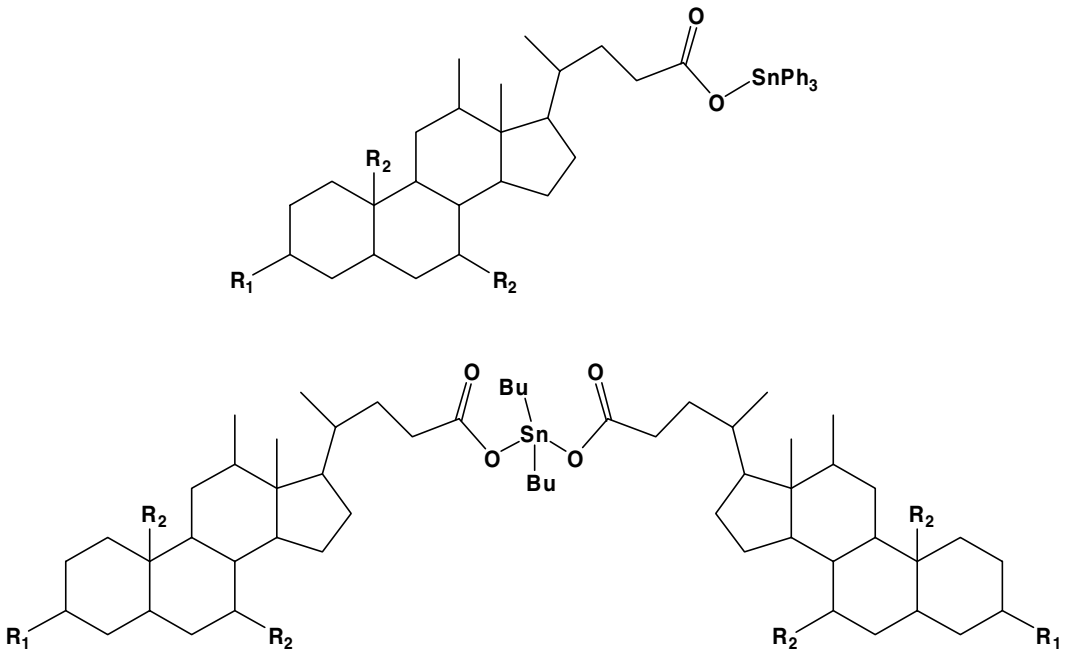


Fig. 3. Structures of organotin steroidcarboxylates.

approx. 0.3 μM for Ph_3SnCl, 3 μM for Ph_3Sn–carbohydrate, and greater than 5 μM for Ph_3SnCH_2–carbohydrate; (b) the in vitro tests toward the mouse tumor cell lines MOPC315, P815,SL2, and L1210 showed that the two triphenyltin carbohydrates were less effective than Ph_3SnCl. It was further concluded that Sn–C bonded triphenyltin carbohydrates are less active than Ph_3SnCl in vitro; Ph_3Sn–carbohydrate is more active than Ph_3SnCH_2–carbohydrate, and this may be related to the long $Sn–C_{carbohydrate}$ bond distance (2.225 Å) in the former compound that shows a striking biological activity in contrast to the normal inactivity of tetraorganotins.

It has been recently reported that dimethytin dichloride interacts with DNA and RNA with a different binding modes and mechanistic pathway with respect to those reported for other anti-cancer agent such as *cis*-$Pt(NH_3)_2Cl_2$. These binding studies, carried out a different pH values, reported binding constants values for $Sn(CH_3)_2Cl_2$–DNA ($1.47 \times 10^5\ M^{-1}$) and $Sn(CH_3)_2Cl_2$–RNA ($7.33 \times 10^5\ M^{-1}$) [32].

A new class of organotin compounds containing transition and Sn metal ions have been synthesized and spectroscopically characterized and their in vivo anti-tumour activity has been reported. The interaction of the organotin (IV) porphinate complexes (Fig. 4) towards DNA has been investigated, cytotoxicity against P388 and A-549 tumour

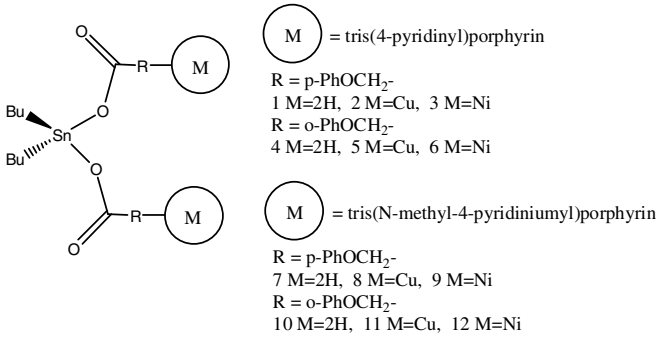


Fig. 4. Structure of dibutyltin porphinate.

cells and % inhibitory effect of these family of compounds being also described [33].

Messori et al. [34] have isolated two new anti-tumour organotin compounds: bis[(di-*n*-butyl-3,6-dioxaheptaneato)tin] (**IV**) and tri-*n*-butyltin 3,6,9-trioxodecanoate (**V**) (Fig. 5). The interaction of these compounds with DNA was investigated by using circular dichroism spectroscopy, DNA melting experiments and gel mobility shift assays. On the basis of experimental results, it has been concluded that both compounds **IV** and **V** bind to phosphate group of DNA.

New 4-X-benzohydroxamic acid diorganotin (IV) derivatives (**L**, X = NH_2, NO_2 or F) [R_2SnL_2] and [$R_2SnL]_2O$ (R = Me, Et, Bu or Ph) were prepared and characterized. The in vitro anti-tumor activity against human tumor cell lines has been tested, activity generally increasing on increasing length of the carbon chain in the alkyl ligand and being higher for complexes containing a benzohydroxamato ligands bearing an electron-acceptor substituent (X = NO_2 or F) [35].

Various physical–chemical methods have been used to authenticate the DNA–organotin binding. Moosavi-Movahedi et al. [36] have reported very important thermodynamic aspects of DNA–organotin interactions. They have performed isothermal titration calorimetry (ITC), UV, fluorescence and IR spectroscopy, the binding isotherm and enthalpy curve for Me_2SnCl_2–DNA interaction being reported as a biphasic transition process. They concluded that the Me_2SnCl_2 binding to DNA at low concentration occurs through an outside interaction by an exothermic process and partial unfolding DNA caused at higher concentration of Me_2SnCl_2.

Synthesis, crystal structure and in vitro anti-tumour activity of di-*n*-butyltin{4-(7-oxo bicycle[2,2,1]-5-heptane-2,3-dicarboxamide)benzoates} has been reported by Zhou et al. [37]. These compounds are highly active at 10^{-8} mol/l concentration against P388 (inhibition of ca. 81.8%) and HL-60 (75.3%) and slightly less effective towards tumour cell of A-549 (18.1%).

A comparative study of the in vitro anti-tumour profiles of platinum and organotin complexes containing 1,2-diaminocyclohexane (L_N), drug modulation and drug resistance has been discussed. The results show that the $RSnX_3(L_N)$ are not good inhibitors, activity against human tumour cell lines (SW620, SW1116, colon carcinoma, ZR-75-1, HT1376, Skov-3 and PA-1ovarian cancer) increasing on going from diphenyltin ($IC_{50} = 7.26$ μmol ml^{-1}) to dibutyltin species ($IC_{50} = 2.58$ μmol ml^{-1}) [38].

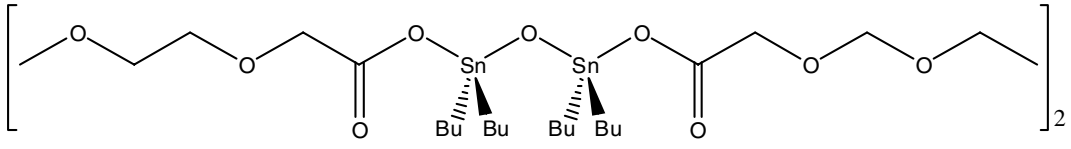
2.2. Biotechnological aspects of cancer chemotherapy

Biotechnological studies on organotin cancer chemotherapy is a new and important area of research. It is widely accepted that cellular stress can induce the activation and stabilization of the tumour suppressor p53, loss of p53 function occurring in the early stage of cancer where the restoration of p53 gene in tumour cell result in their apoptosis [39].

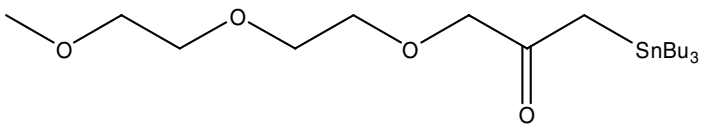
A large number of compounds have been tested against different cancer cell lines via gene mediated pathway. Organotin compounds of flufenamic acid and flufenamates (flu) were evaluated for anti-proliferative activity in vitro. [Bu_2(flu)SnOSn(flu)Bu_2] and [Bu_2Sn(flu)$_2$] (Hflu = *N*-[(3-trifluoromethyl)-phenyl]-anthranilic acid) exhibited high cytotoxic activity against the cancer cell line A549 (non-small cell lung carcinoma) [40].

The anti-cancer activity of organotin polyamines derived from 2-chloro-*p*-phenylene diamine, inhibiting an ovarian cancer cell line, has been also reported. The dibutyltin polyamine derived from 2-chloro-1,4-benzenediamine showed superior inhibition of the Caov-3 cancer cell line with respect to the most widely used anti-cancer drug, cisplatin [41].

Alama et al. [42] performed a complete biotechnological studies on triethyltin(IV)lupinylsulfide hydrochloride (IST-FS 29) (Fig. 6). This compound exhibited potent anti-proliferative effect on different cancer cell lines, ovary (PA-1), colon carcinoma (HCT-8) and glioblastoma (A-172). Cytotoxicity by MTT, cell content assays and significant cell growth inhibition up to 95% in HCT-8 after 72 h has been reported. The cytocidal effects due to IST-FS29 seem consistent with necrosis or delayed cell death rather than apoptosis.



IV



V

Fig. 5. Structures of bis[(di-*n*-butyl-3,6-dioxaheptaneato)tin] (**IV**) and tri-*n*-butyltin 3,6,9-trioxodecanoate (**V**).

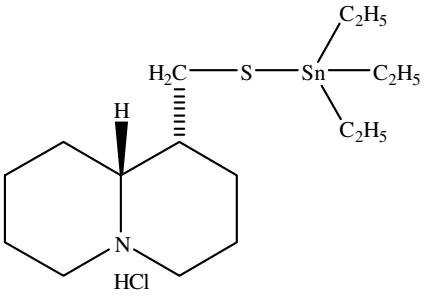


Fig. 6. Structure of triethyltin(IV)lupinylsulphide hydrochloride.

Triethyltin(IV)lupinylsulfide hydrochloride administered by the oral route, have been also evaluated against three transplantable murine tumor models: P388 lymphocytic leukemia, B16F10 melanoma and 3LL Lewis lung carcinoma. Mild and reversible signs of acute toxicity such as behavioral symptoms, weight loss and histological alterations were mainly reported at the highest single dose of 28 mg/kg. On the other hand lower concentrations of compound ranging from 7 to 21 mg/kg did not result in major toxic effects, even after repeated administration. The anti-tumor activity studies showed that fractional dosing, rather than single bolus administration, over 1 week, might prove more active and better tolerated by allowing the achievement of the highest therapeutic total dose of IST-FS 29 (42 mg/kg). Indeed, repeated administrations of IST-FS 29 resulted in marked significant improvement of anti-tumor activity against B16F10 (50% of tumor vol. inhibition, $p = 0.0003$) and, to a greater extent, 3LL (90% of tumor vol. inhibition, $p = 0.0001$) tumors. These results indicate that IST-FS 29 might be a suitable candidate as an orally administrable anti-cancer drug and support its further development in human tumor xenografts [43].

The expressions of p53, p21 and cyclin D1 involved in response to DNA damaging stress were analyzed by western blot. In response to DNA damaging agents, some tumour cells can arrest in G2/M phase in p53 independent manner. As a consequence, tumour cells that have sustained DNA damage progress through the cell cycle beyond the G2/M check point and undergo apoptosis [44]. Apoptotic induction by organotin compound was shown to mediate in a p53 dependent manner; loss of p53 impairs the release of cytochrome *c* and Smac/DAIBLO from mitochondria to cytosol.

Diethyltin-*N*-(2-pyridylmetylene)-4-toluidine dichloride was tested against P338 leukemia in mice and showed anti-neoplastic effects. This compound has induced significant delay in cell cycle in mouse bone marrow cells. The cellular glutathione (GSH) is a depleting agent: when the GSH level was low the extent of delay in cell cycle was reduced [45].

The anti-cancer activity of Norfloxacin (TM) organotin polymers against normal Babl/3T3 cells has been reported [46] the order of the activity being the following:

butyltin ≫ propyltin ≫ ethyltin > methyltin = octyltin = lauryltin

The diethyltin polymers were active at conc. ca 3 μg/mL whereas the diproplytin at ca. 0.25 μg/mL; in the case of the dibutyltin the activity was down to below 0.1 μg/mL. The activities of the dipropyltin and dibutyltin are well within the lower levels for *cis*-DDP, the most widely used cancer drug. Due to the non-toxic nature of the organotin polymers, they are prime candidates in the war against cancer. They are currently undergoing further tests against various cancer cell line.

The in vivo anti-proliferative and anti-tumour acivity of dibutyl and tributyl tin species towards Ehrlich ascites tumour IMC carcinoma, P388 and Sarcoma 180 has been reported. The cellular mechanism of the anti-proliferative activities reveals that the dibutyl- and tributyl-tin species selectively accumulate near the nucleus, golgi apparatus and endoplasmic reticulum in the cell and then destroy the structure of Golgi apparatus, endoplasmic reticulum, inhibiting the function ceramide metabolism, inositol triphosphate (IP3)-induced intracellular Ca^{2+} mobilization and finally stopping the membrane mediated signal transaction leading to DNA synthesis [47].

Acknowledgments

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