Novel Organotins as Antitumour Agents

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Abstract
Metal complexes and organo-metallic compounds have a growing importance in medicine, particularly in oncology. Cisplatin is among the most widely used anticancer agents, but other platinum (PtII) complexes are being introduced in the therapy of tumours. Cell resistance to cisplatin and its analogues is the main reason for treatment failure and clinical relapse. In order to overcome this issue, novel PtII and PtIV as well as non-platinum metal complexes have been developed, with encouraging results. Organotin derivatives have caught much attention during the last two decades for their potential biocidal activities. In recent years several organotin compounds have been synthesised, some with interesting cytotoxic properties. Little is known about the exact mechanisms by which these agents induce cell growth inhibition, although macromolecular synthesis and mitochondrial energy metabolism appear to be the targets. This article will focus on the relevance of organotin derivatives as very promising potential candidates in anticancer therapy.

Keywords
Metal-based compounds, organotins, cytotoxicity, antitumour activity, trimethyltin and tributyltin (IV) lupinylthiolates

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Metal-based Compounds in Therapy
Metal-based compounds enjoyed wide use in old therapeutic procedures, but because of their limited selectivity and heavy toxicities metal derivatives have been progressively neglected in favour of the more reliable organic compounds, either synthetic or those isolated from natural sources. Thus, the number of metal-based drugs has decreased steadily and now very few are worth mentioning. Silver sulfadiazine is still the agent of choice for the prevention of burn infections, while auranofin, once highly valuable for the treatment of rheumatoid arthritis, is being replaced by immunosuppressants and cytokine receptor antagonists. Lithium carbonate and citrate, largely used in the past as diuretics and to dissolve urate deposits, are a mainstay of the treatment of mania and prophylaxis of bipolar disorders. Bismuth citrate and subsalicylate are currently used for traveller’s diarrhoea and Helicobacter pylori eradication. Finally, melarsoprol and sodium stibogluconate are used, respectively, in the treatment of late-stage African trypanosomiasis and leishmaniosis and other protozoan infections.

The serendipitous discovery by Rosenberg in 1965 of the antiproliferative activity of a platinum complex – cis-diammine-dichloroplatinum (II) (cisplatin [CPT]) – and its successful introduction in the therapy of testicular cancer fostered a renewed interest in metal-based drugs, particularly organometallic complexes, as antitumour agents. Metal ions in anions and organic ligands (with their inherent chemical and biological properties) create a spatial distribution that enables them to more effectively attack the target cancer cell constituents.

The outstanding clinical effectiveness of CPT for particular types of cancer is greatly limited by drug resistance and significant side effects. A huge number of platinum derivatives have therefore been developed to overcome these issues. Nearly 40 complexes were found and analysed before the identification and development of carboplatin and oxaliplatin. These were approved for clinical use in 1989 and 2003, respectively.²

Despite these successful achievements, further significant improvements in metal-based cancer therapies are expected from the study of platinum (Pt) complexes of unconventional structure (sterically hindered PtII, all-trans trinuclear and PtIV complexes) and even more from the study of non-platinum metal compounds.³–⁷ Several thousand compounds derived from about 30 metals have been prepared and tested. Some of them are now in phase II and III clinical trials. Ruthenium (KP1019, NAMI-A) and gallium (gallium 8-quinolinolate and nitrate) complexes are drug candidates of high relevance. Very interesting compounds have also been derived from iron, cobalt and gold. Indeed, by being able to hit different biological targets from cisplatin, they have the potential to be active against cisplatin-resistant cancers.

Organotin Compounds
Among the non-platinum metal compounds with antitumour activity, organotin derivatives deserve particular notice. There are a large variety of organotin compounds that can be prepared, with multiple mechanisms of action that may prevent or retard the development of drug resistance. It is worth noting that, for a long time, organotin compounds have been widely used in a variety of industrial and
agricultural applications\textsuperscript{4} and wide availability has fostered further synthesis of ever more elaborate derivatives. Since a large number of organotin compound applications are related to their potent biocidal activity, they have also been extensively studied as potential environmental toxicants and found to target a variety of cellular structure and enzymatic systems.\textsuperscript{9–11}

Early studies in 1929 on the activity of organolead and organotin (IV) compounds in experimental mouse cancer produced contradictory results.\textsuperscript{12} However, in 1972 it was shown that triphenyltin acetate, but not the corresponding chloride, retarded tumour growth in mice, suggesting the particular importance of the leaving group (acetate and chloride).\textsuperscript{13} Since then, a huge number of organotin derivatives have been prepared and tested \textit{in vitro} and \textit{in vivo}, first against two murine leukemia cell lines (P388 and L1210) and later against different panels of human cell lines.\textsuperscript{13–15} In the early studies, most compounds exhibited interesting activity in specific cancer models, but they commonly lacked activity against a broad spectrum of experimental tumours, leading to the opinion that organotins were not very suitable antitumour drugs. Since then, the possibility of varying the organic moieties and donor ligands linked to the metal has resulted in several diorgano- and triorganotin (IV) compounds with high antiproliferative activity \textit{in vitro} against a variety of solid and hematological cancers.\textsuperscript{15,16}

In solution, some triorganotin compounds may undergo spontaneous disproportionation into the corresponding di- and tetraorganotin derivatives,\textsuperscript{17} while \textit{in vivo} the loss of one alkyl or aryl group may occur through the intervention of enzymes such as aromatase.\textsuperscript{18,19} Since tetraorganotins are highly toxic and generally devoid of antitumour activity, the diorganotin compounds might be considered the ultimate cytotoxic agents and the frequently observed higher activity of triorganotins may be related to pharmacokinetics. Thus, the possibility of disproportionation should be carefully investigated and ruled out in the development of useful compounds.

Besides halides (Cl-, Br-) or pseudohalides (SCN-), most organotin compounds contain carboxylate anions as exchangeable groups. These may be aliphatic (including aminoacids and peptides), cycloaliphatic, aromatic, arylaliphatic and heterocyclic, eventually bearing very diverse substituents. Biologically active acids that have also been considered include flufenamic acid, indomethacin, norfloxacin, cephalexin, etc.\textsuperscript{16} Triorganotin carboxylates may exist in monomeric or polymeric forms, whereas diorganotin derivatives, in relation to the ratio of metal:acid, may exist as true dicarboxylates \((R_2Sn(OCOR')_2)\), or contain an oxygen bridge between two tin atoms (distannoxane derivatives: \([R_2Sn(OCOR')]_2O\), which may further aggregate in manners that influence both solubility and bioavailability.

In particular, di- and triorganotin terebates and lithocholates were tested against a panel of seven human cancer cell lines and found to be highly active. They had IC\textsubscript{50} values (defined as the concentration required to inhibit cell growth by 50\% relative to the untreated control) from <3 to 134ng/ml (<4.5–245nM). Thus, they are much more potent than CPT and comparable, or even a little superior, to doxorubicin (DOX). In both cases, the IC\textsubscript{50} values of tributyl derivatives were better than those of triphenyl and dibutyl derivatives \((Bu_3Sn \geq Ph_3Sn \geq DOX \gg Bu_2Sn \gg CPT)\). Although some \textit{in vivo} activity of tributyl terebate was observed, toxicity was also reported.\textsuperscript{16,20}
An impressive cytotoxicity against the same panel of cancer cells was shown by dibutyltin polyoxaalkanoates and tributyl benzyl-(15-crown-5)carboxylates, with IC50 never higher than 3.3ng (5.5nM) and often lower than 1ng/ml (1.2nM). Despite the high cytotoxicity observed in vitro assays, the excessive lipophilicity or hydrophilicity of the above-mentioned organotin carboxylates may represent an important drawback, hampering bioavailability and therapeutic efficacy. Other carboxylates that exhibited important activity against one or more cancer cell lines were the triphenyltin 3,4-diaminobenzoate, 2-phenyl-1,2,3-triazole-4-carboxylate and glycylleucinate and the tributyltin N-maleoyltranexamate. Additional organotin derivatives containing oxygen donor ligands, other than carboxylates, were obtained from polyethyleneglycols, 4-acylpyrazolin-5-ones and different kinds of phenolic compound, such as the polymeric derivatives of some O-(dialkyltin)stilbestrols and the dibutyltin-2-[N-(hydroxyalkyl)amino]phenoxydes. Both types of compound were tested against four (colon, two breast carcinomas and prostate) and five (glioblastoma, prostate, chronic myelogenous leukaemia, colon and breast) human cancer cell lines, respectively. O-(dialkyltin)stilbestrols showed cytotoxicity comparable to or, as for dibutyltin-2-[N-(hydroxyalkyl)amino]phenoxydes, higher than that of CPT.

Since the early studies on the antiproliferative activity of organotin derivatives, a particular relevance has been ascribed to complexes with sulphur donor ligands. Indeed, if the organotin moiety is crucial for cytotoxicity, the ligand plays a key role in transporting and presenting the molecule to the target while resisting untimely exchange with biomolecules. Sulphur-containing ligands appear particularly suitable for this task, even if in some cases the leaving group might be released too slowly for activity to be seen. The sulphur-containing ligands that have been used represent widely differing chemical structures, as shown by the following examples:

- L-cysteine;
- penicillamine;
- sodium 2-mercaptoethansulphonate;
- dithiocarbamates;
- aldehyde thiosemicarbazones;
- diphenyl dithiophosphinic acid;
- 6-mercaptopurine;
- 2-mercaptopyrimidine; and
- 2-mercaptopenicotic acid, etc.

Some of these ligands may be endowed with intrinsic biological activity, which may be enhanced by metal complexation or may be due to the cytotoxicity of the metal. Besides 6-mercaptopurine, which has been approved for treatment of human leukaemia, heterocyclic aldehyde thiosemicarbazones are worth mentioning for their ability to act as enzyme inhibitors. The thiosemicarbazones of 1-formyl isouquinoline inhibits ribonucleotide reductase, while that of pyridoxal inhibits leukaemia virus reverse transcriptase. Triphenyltin (IV) pyrimidine thiolate and diphenyltin (IV) 5-chloro-2-benzothiazole...
Holloway LN, et al., 2. Kelland B, 4. Bruijnincx PCA, Sadler PJ, 7. Schatzschneider U, after a single intravenous injection. Since IST-FS 35 produced tumour growth of implanted P388 and B16-F10 cells by up to 96% in vivo against leiomyosarcoma (triphenyltinmercapto) nicotinate showed an IC_{50} as low as 0.005g/ml (5.5nM) against leiomyosarcoma.

Finally, it should be underlined how tert-aminoalkylthiols have not received much attention as ligands to address the solubility issue in vivo in murine tumour models (P388 myelomonocytic leukaemia, B16-F10 melanoma and 3LL Lewis lung carcinoma), after (5.5nM) against leiomyosarcoma.

Organotin moiety and/or in the aminothiol itself. Enhanced by increasing the number of carbon atoms in the organotin moiety and/or in the aminothiol itself.

Increased histone acetyltransferase activity and activation of retinoid X receptor and peroxisome proliferator-activated receptor may play additional roles in the antiproliferative activity of organotins. It has been suggested that most of these mechanisms of action may be triggered by the selective binding of tin to the thiol groups of appropriate proteins and enzymes while bypassing capture and inactivation by blood components. Thus, the organotins, differing from the behaviour of other organometals, particularly CPT and its analogues, whose major mode of action is direct DNA damage, may result in useful action against CPT-resistant cancers.

Conclusions
This short article clearly shows that organotin compounds have vast potential for application as antitumour agents, especially due to their low toxicity and diverse mechanisms of action. The cytotoxicity induced by the different kinds of organotins has been related to several mechanisms – inhibition of macromolecular synthesis, mitochondrial energy metabolism, reduction of DNA synthesis and direct interaction with the cell membrane with increase of cytotoxic calcium ion concentration. Promotion of oxidative and DNA damage has been detected in vivo. Both oxidative damage and increased concentration of intracellular calcium ions seem to be major factors contributing to triorganotin-induced apoptosis in many cell lines. Increased histone acetyltransferase activity and activation of retinoid X receptor and peroxisome proliferator-activated receptor may play additional roles in the antiproliferative activity of organotins. It has been suggested that most of these mechanisms of action may be triggered by the selective binding of tin to the thiol groups of appropriate proteins and enzymes while bypassing capture and inactivation by blood components. Thus, the organotins, differing from the behaviour of other organometals, particularly CPT and its analogues, whose major mode of action is direct DNA damage, may result in useful action against CPT-resistant cancers.