Section-A [Synthetic Aspects]

The first organotin compound, diethyltindichloride, was synthesized by Frankland in 1849 [1]. The second attempt was made by some workers when they established that ethyl iodide when react with tin/sodium alloy, gave oligomeric diethyltin oxide and with halogens, gave diethyltindihalides [2, 3]. Structural aspects of organotin chemistry have been reviewed [4] and a comprehensive bibliography of X-ray diffraction studies available from the International Tin Research Institute [5]. A monograph on organotin chemistry was published by Omae [6] in 1989 and Harrison has edited a book on tin which covers particularly organotin chemistry [7] and include [8] a survey of general trends. A book on the use of organotin compounds in organic synthesis [9] was published by some workers. Yamamoto edited Tetrahedron Symposia-in-Print, Number 36, which comprises 27 papers on organotin compounds in organic synthesis [10]. Twenty volumes of Gmelin have appeared giving comprehensive survey of the specified compounds [11]. A useful reference for the synthesis, properties, reactions and application of about 1000 selected organotin compounds is available in the Dictionary of Organometallic Compounds [12]. Annual developments are reviewed in Royal Society of Chemistry's special periodical reports of organometallic chemistry [13]. Structural aspects of organotin carboxylates

in solid state were reviewed by Tiekink [14]. A review on the structural chemistry of organotin compounds was presented by Holloway and Melnik which comprises 400 references on the subject matter [15]. Mazhar *et. al.* [16] presented a review on organotin carboxylates.

Over the last 30 years, research in the chemistry of organometallic compounds of tin in +4 oxidation state has represented one of the most prominent areas of chemical activity. However, in the last 10 years there has been a steady growth in the number of investigations in the chemistry of organotin species along with their biomedicinal importance [17].

Originally, organotin compounds were developed as thermal stabilizers for chlorinated hydrocarbons which would be used in those applications for which there was a strong possibility of thermal degradation. However, as the chemistry of organotin compounds became better understood, their application expanded to catalytic and biologically active agents and most of the organotin have important industrial [18], agricultural [19-21] and biocidal [22-24] applications.

There is considerable industrial importance of organotin compounds because of their large-scale applications in the fields of polymer stabilization, organic synthesis and homogenous catalysts. Some of the most striking biological applications are given as under:-

Homogenous Catalysts

A large number of tin chemicals especially organotin carboxylates are routinely used as homogeneous catalysts in the plastic and polymer industry. A homogeneous catalyst is one, which is in the same phase as the reactants and is usually a liquid. Di-*n*-butyltindilaurate and to some extent di-*n*-butyltindiacetate and di-*n*-butyltindi(2-ethylhexoate), also called stannous octoate, are used as homogeneous catalysts in the manufacture of polyurethane foams, in the production of polyesters and in the curing of certain types of silicone resins [25]. Stannous octoate is used in flexible polyurethane foams and di-*n*-butyltindilaurate is employed in specialized flexible foams and also in certain rigid foams, elastomers and coatings [26]. Di-*n*-butyltindilaurate and tin(II) acetate have been used as catalyst in vulcanizing silicon rubbers used for the production of dental prosthetic devices [27].

Heat Stabilizers

Organotin stabilizers prevent the thermal degradation of many chlorinated compounds such as certain types of transformer oils, polyvinylchloride (PVC), chlorinated rubbers, paraffin's, and modified plastics. The organotin have also been used to stabilize other non-halogenated compounds of industrial and commercial importance such as some lubricating oils, hydrogen peroxide, cellulose acetate, polyamides

(nylon), polycarbonates, polyethylene, and polypropylene [28].

By far, the largest proportion of organotin stabilizer production is for the stabilization of PVC. The PVC resin is a white powder produced by free-radical, ionic and emulsion polymerization. In order to mold the resin into finished products, the resin is softened by heating. For unplasticized PVC, this softening temperature approaches the thermal decomposition temperature of the resin. PVC polymers are particularly susceptible to thermal degradation during processing and use. Thermal stabilizers are therefore an essential additive for both rigid and flexible PVC products [29].

The organotin compounds, especially the R_2SnX_2 and $RSnX_3$ type, are excellent stabilizers for PVC, neoprene and other polymers against degradation by light, oxygen and decomposition during hot fabrication [30]. While dialkyltinbis(carboxylates) are usually employed when good light stability is required.

Water Repellents:

The monoalkyltin compounds have excellent water repellent properties, particularly mono-*n*-octyltin and mono-*n*-butyl-compounds are used as water repellent for cellulose-based materials such as paper, wood and cotton textiles [31].The *n*-Octyltintrilaurate has also been shown to impart water repellency to limestone more than silicone treatment [32].

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The metals have an enormous potential in medicines and their selection may offer the possibility for the discovery of new metal based drugs with novel mechanism of action. The importance of metal based drugs lies in the fact that they are essential components for various physico-chemical processes occurring in living system. The chemotherapeutic values of organotin compounds has been expanded as they have found their place among a class of potential biologically active compounds exhibiting antimicrobial activity against different kinds of microbial strains along with anti-inflammatory, cardiovascular, trypanosomal, anti-herpes and anti-tubercular activity.

Organometallics as Drugs:

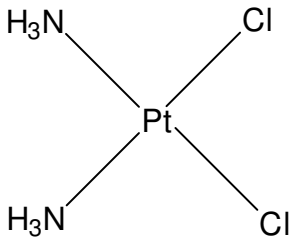
It is recently observed that metals are able to do the best and the worst; i.e. metal are able to induce cancer and other diseases and also to treat them, some are able to perform both. It is known that almost all metals are able to generate reactive oxygen species, which explains the great part of treatment of cancer. Domingo [1] categories metals into four categories. Metals with greatest toxicity that are widespread in the environment (As, Ca, Pb, Hg); essential trace metals (Cr, Co, Mn, Se, Zn), metals with biological importance (Ni, Mo) and metals with pharmacological interest (Al, Ga, Li). Basically both, transition and non-transition metals plays important role in the treatment of tumors.

Transition Metals organometallics as antitumor:

The transition metal organoplatinum compounds were the first, which were used in the treatment of cancer. The common organoplatinum compounds to be used are cisplatin, carboplatin, oxaliplatin, and nedaplatin. The last three compounds of platinum are analogs of cisplatin [2, 3].

Cisplatin:

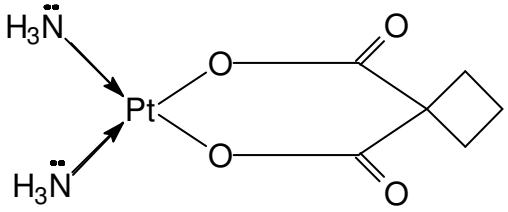
The cisplatin [Cis-dichlorodiammine platinum (II)] was found active against testicular and ovary cancer and also in lungs, gall bladder, cervix, head and neck, esophageal cancer cell line [4-7].



[Cis-platin]

Carboplatin:

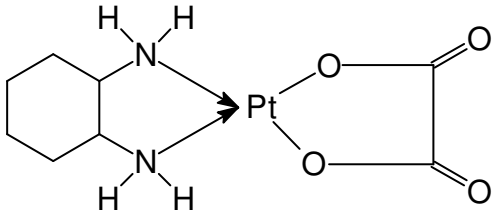
The carboplatin has low hematological toxicity in comparison with the cisplatin, so it is widely tested in a large number of tumor cell lines. It is found active against ovarian, head and neck, gall bladder, and in small cell lungs cancers [4-7].



(Carboplatin)

Oxaliplatin:

The oxaliplatin has low toxicity and high efficacy than cisplatin, so it gave



(Oxaliplatin)

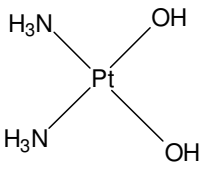
interesting results in ovarian, breast, head and neck and in acute blood cancer treatment [4-13].

Nedaplatin

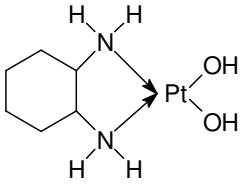
The nedaplatin was used for the cancer treatment because it produced better results than cisplatin in preclinical studies. It was generally used in the treatment of head and necks, testis, ovaries, lungs, esophageal, and cervical cancer [14, 15].

Mechanism of action:

These four platinum drugs could be considered as pro-drugs and their hydrolysis is a key step in mechanisms of action. The product of double aquation forms the active metabolites.



Cis-diamine diaquo platinum



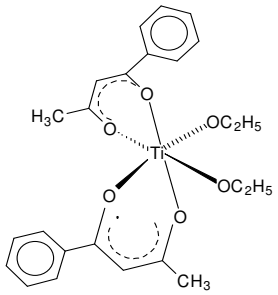
Diaminocyclohexane diaquo platinum

The diaquo-platinum species reacted with amine group of proteins, RNA and DNA, forming the respective adducts; which appears to be associated with clinical activity. They generally reacted with the N-7 position of adenine and guanine and produces cross linking between bases in the same or in opposite strand [16] and mediated cytotoxcity by inhibiting DNA replication and transcription [17]. The efficacy of platinum drugs

against cancer cells could be related to inhibition of new DNA synthesis [18].

Non platinum organometallics as antitumor:

In past twenty years new metal complexes other than platinum have been explored for this wide spread disease. The first non platinum complex tested in clinical trials was cis-[$(CH_3CH_2O)_2$ $(bzac)_2$ Ti(iv)].



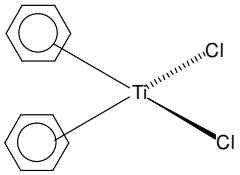
This complex of titanium was used first against a variety of ascites and solid tumors [19-21], such as Ehrlich ascites, sarcoma-180 ascites tumor. Their marginal responses were found in leukemia p 388 and L1210. The medicinal properties of transition metal organometallics compounds were not explored until 1979, when köpf-maier and köpf published the first metallocene with antitumor activity [22].

Titanocene dichloride:

It was the most effective organometallic compounds, showing its best activity against colon, lungs and breast cancer cell line [23].

In contrast to platinum complexes, titanocene dichloride showed no evidences of nephro and mylotoxicity [23-25]. Because of the low toxicity

this compound is presently in clinical trials [26-30]. It was found that titanocene dichloride showed enhanced activity over cis-platin [31] and cis-platin resistant ovarian carcinoma cell line[32-34], and higher effective against ovarian cancer cell line in comparison to 5-fluerouracil and cyclophosphamide [35,36]. A series of ionic titanocene complexes containing thiomicliobases has been synthesized and investigated [37] and have been found to be more potent antiproliferative agent [38].



Mechanism of action:

The nucleic acids have been proposed to be the target site in the cellular system [39-42]. The binding of titanium complexes with calf thymus DNA have been pursued by spectrophotometrically and fluorescence spectroscopy [43-48]. The interaction of titanocene dichloride and a mixture of 5'-AMP and 5'-TMP has shown the complex disrupts the hydrogen bonding of the A-T base pair, which suggests the part of cause of antitumor activity [47,48]. Titanocene dichloride may also inhibits the protein kinase-C, an enzyme responsible for cell proliferation [41], Human topoisomerase-II, an enzymes responsible for DNA replication [49] and stops the cell proliferation.

Vanadium compounds as antitumor:

The chemical composition and antitumor activity and toxicity of the vanadium compounds play a significant role in controlling the various kinds of tumors [50]. The peroxovanadates [50, 51] may play dynamic role in controlling the tumors growth. Vanadocene, containing vanadium (IV), belonging to the metallocene class of antitumor agent [52-56] shows both *in-vitro* and *in-vivo* antitumor activity [57-60]. The reduction of vanadium (V) to vanadium (IV) seems to regulate various cellular actions such as cytotoxic, cytostatic and some morphological effects [61-63]. The vanadium complexes are best effective against breast cancer, cell line [64-68].

Mechanism of action:

Fluorescence activated cell sorting assessments shows that peroxovanadates, blocks the G_2-M transition state of the cell cycle in cancer cell line, leading to significant reduction in growth of tumors [69]. Vanadium compounds may also play important role in controlling cell proliferation via interaction with DNA. Vanodocine complexes interact with DNA nucleotide phosphate group forming a liable outer sphere complex via a water group [70] and inhibit the cell proliferation.

Non-Transition Metal Based organometallics as antitumor

Not only transition metals but a series of non-transition metals complexes are also known to possess antiproliferative activity.

Gallium complexes as antitumor:

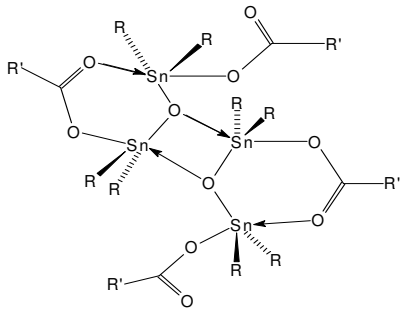
The anticancer properties of gallium compounds were first time reported in 1971 [71, 72]. The radioactive gallium^{67} and gallium^{68} shows some prominent activity against bone marrow cancer [73]. The new compounds of gallium maltolate, doxorubicin-gallium transferrin conjugate and tris (8-quinolinolato) gallium (III); all these compounds show interesting antiproliferative activity against tumor cell line [74-77]. Gallium nitrate was reported as potent antitumor agent for human leukemic cell line and breast cancer cell line [78,79]. Gallium chlorides are also active against breast cancer when taken orally [80, 81].

Mechanism of action:

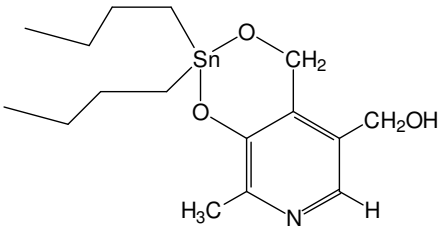
Gallium compounds generally interact in trivalent state, with the DNA molecules in aqueous solution in different pH [82]. Gallium compounds are bound to DNA phosphate forming a stable complex. Gallium may also interact with DNA by acting as a competitor with magnesium for DNA binding. It has been found that the affinity of gallium for DNA is 100 times higher than that of magnesium [83]. Gallium compound may inhibit the RNA-reductase and inhibits the replication of DNA, therefore inhibiting the growth of cells [84].

Organotin compounds as antitumor

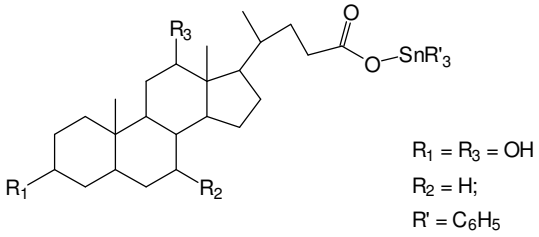
The first organotin compounds, for which the anti-tumor activities examined, were formally similar to cisplatin [85-93] or to its analogous carboplatin and paraplatin [94-96]. These compounds show borderline activities against leukemia P388 and L1210 [97-102]. Arakawa [103] studied the antitumor activity of di-n-butyl tin dichloride towards Ehrlich ascites tumor, p388 lymphocytic leukemia and sarcoma 180 cell line; showed that this compound influences the DNA synthesis of proliferating cells. Many diorganotin compounds, R_2SnX_2, were investigated in context of their antitumor activity [103-105]. The di-n-butyltin analogue of carboplatin was synthesized and screened against MCF-7 and WiDr, tumor cell line of humans [106]. Besides this, series of organotin-derivatives of carboxylic and dicarboxylic acids were synthesized [107-109]. The organotin derivatives of pyridoxine and erythromycin were synthesized and tested against tumors cell line [110,111]. Some triorganotin compounds were also found active against various tumors cell line [112,113]. The steroid carboxylate series is one of the major early developments in this area [114-117]. They appear to contain pronounced *in vitro* antitumor activity [114,115] but their solubility still remains a draw back [118], which affect the tumor activity. In order to make this kind of compounds more soluble in water, less complicated structure was designed which contains polar moieties [119].



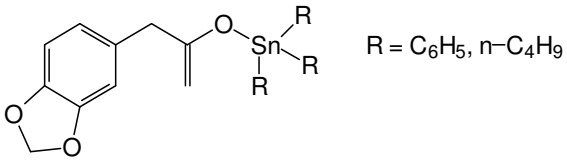
Structure of tetraorganodicarboxylatodistannoxanes



Organotin derivatives of pyridoxine



Organotin steroid carboxylate

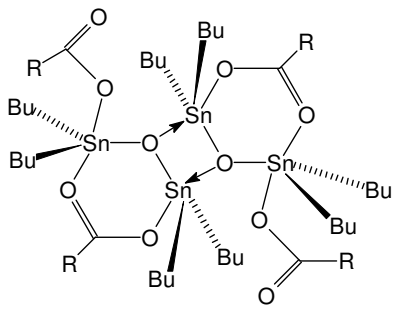


Triphenyltri-n-butyltin complex

Water-soluble organotin compounds as antitumor agents

The introduction of polar groups in the organotin molecules leads to some improvement in the solubility and *in vitro* antitumor activity. Fluorine containing organotin compounds were synthesized to check the effect of

compounds on tumor cell line [120,121]. Fluorine containing compounds are more soluble in water and still very soluble in non-polar solvents perfluoro alkanes have found very useful application in tumor activity [122-127]. The solubility can also be increases by preparing salts of organotin compounds [128-132]. The most recent development in the field of antitumor active organotin compounds has been achieved by the synthesis and screening of compounds containing polyoxaalkyl moiety [133,134] which exhibit high antitumor activity.



Organotin polyoxa-substituted carboxylates

Mechanism of action:

Study of the interaction of antitumor active organotin compounds with DNA was recently undertaken using NMR study [127]. At around pH-7, a very weak hardly detectable interaction is observed in contrast with the results found in the case of platinum [135]. The interaction of DNA and DNA fragment with dimethyltin dichloride was also studied very recently [136-145]. Interfering the DNA replication by interacting with it, they stop the growth of cell line.

Organotin compounds in Biochemical Investigations:

Organotin compounds have been frequently used in biochemical investigations. The capacity of organotin compounds to deactivate enzymes makes these compounds very useful for investigating the nature of enzyme active sites. Some workers have studied the inhibitory effects of organotin compounds on enzyme [146-150]. Organotin compounds bind to biologically important biomolecules other than enzymes and as such help in finding the binding sites. Chloromethyldi-n-butyltinchloride binds to mitochondrial adenosine tri-phosphate sites [151].

Organotin compounds in Agrochemical Applications:

About one third of the world's food production is lost due to pests and fungal diseases, despite great progress having been made in agriculture. Organometallic compounds have played a vital role in control of pests. Though the use of organotin compounds is relatively new compared to organomercury and arsenic compounds, they are the predominant organometals currently used. A number of tri-organotin compounds have been developed, possessing pronounced pesticidal activity towards pests of agricultural and horticultural crops. The main advantage of organotin agrochemicals includes low phytotoxicity, favorable environmental degradation to non-toxic mono-organotin and inorganic tin products and low toxicity to non-target organisms [152-154]. The tri-organotin

compounds introduced recently as agrochemicals in market are triphenyltin oxide, triphenyltin acetate, triphenyltin chloride, tricyclohexyltin hydroxide etc.

Organotin compounds as Agricultural Fungicides:

Triphenyltin acetate and triphenyltin hydroxide are effective against a number of fungal diseases in various crops such as potato blight, leaf spot on sugar beets and cerely, rice blast, coffee leaf rust and coffee berry disease. These triphenyltin fungicides also work as antifeedant and may also act as insect chemosterilants [155].

Organotin compounds as Pesticides and Insecticides:

Generally as pesticides and insecticides, the organotin compounds have been very effective. Trialkyltin compounds such as triphenyltin acetate and hydroxide, tributyltin chloride, and dibutyltin dilaurate when applied to foliage generally repel insects. The environmental and biological effects of organotin pesticides on orchard trees have been studied by some workers [156]. 1-Tricyclohexylstannyl-l,2,4-triazole is the organotin insecticide available in the market for use against red spider and spider mites in fruit, grapes and vegetable crops.

Organotin compounds as Medical and Pharmaceutical Applications:

There are number of studies on organotin compounds where their biocidal properties are opening new frontiers of research. Organotin

compounds have been widely used against pathogenic bacterial and fungal strains [157-159]. Another important medical use of organotin compounds is in the chemotherapy of leishmaniasis, a parasitic infection that affects the skin [160]. Mosquitoes are still a serious problem in many parts of the world and organotin compounds have been reported as safe antimosquitoes larvae repellents [161]. The Dialkyltin compounds have also been used in the control of other parasitic diseases of poultry, sheep, and swine [162-165].

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