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NATURAL PRODUCTS: FROM CHEMISTRY TO PHARMACOLOGY (C HO, SECTION EDITOR)

Organotin Complexes with Promising Therapeutic Potential

Manoj Kumar[1] · Zahoor Abbas[1] · Hardeep Singh Tuli[2] · Anita Rani[1]

Abstract

Purpose of Review The diversity in co-ordination number, geometries, redox states, thermodynamics, and kinetic and intrinsic properties of the metal ion are some special characteristic of organometallic complexes. Organotin (IV) complexes have been the subject of interest because of their biomedical and commercial applications. Nowadays, the need of novel biological active compounds is growing as there is tremendous increase in antibiotic resistance.

Recent Findings Metals are known as essential cellular components to function in a number of vital enzymatic and biochemical activities of the cells. Ongoing recent investigations have reported that metal complexes with organic compounds can not only increase the potency of organic compounds but can also lower down the required dosages of action as complexation increases the lipophilic character.

Summary This review summarizes the synthesis, and structural and biological application of organotin compounds. Furthermore, the crossing points between organic compounds and their metal ion interactions can help the scientific community to design novel therapeutic molecules.

Keywords Organotin complexes · Synthesis · Characterization · Biological activities and methodology

Introduction

Organotin complexes are the most diverse segment of chemical compounds with applications ranging from material science and catalytic activities to therapeutic agent for various diseases due to its wide variety of interesting structural possibilities [1]. During the last few years, it is noticeable that organotin compounds occupied an important place in cancer chemotherapy reports [2–5], because of their cytotoxic effects, ability to bind with DNA, anti-proliferating nature, and apoptotic-inducing nature. Organotin complexes especially with Schiff base ligands have been screened for their role in anti-microbial and anti-inflammatory activities [6–8]. Research on the synthesis and applications of organotin complexes is currently considered one of the most expanding area in biomedical and inorganic chemistry because during last few years, efforts in the evaluation of platinum based anti-cancer drugs have been shifted to non-platinum metal-based drugs. Thus, an intensive study of other metals (Sn, Ti, Ga, etc.) is being carried out in order to improve the problems such as nephrotoxicity, neurotoxicity, nausea, and vomiting [9, 10]. As far as limitations of organotin complexes are concerned, the efficiency and application of various organotin derivatives seem to be limited by their poor water solubility. Therefore, in view of the applicable limitations, new organotin complexes with higher water solubility and anti-proliferative properties have received particular attention.

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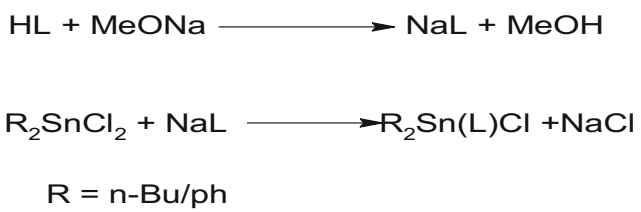
Synthesis and Characterization

The increasing interest in the chemistry of organotin (IV) compounds has led to the extended studies of their synthesis. Shabir et al. reported organotin carboxylates by reacting 4-piperidinecarboxylic acid with KOH and methanol and verified metal ligand interaction by FT-IR, ^{1}HNMR, and

semiemperical methods [11]. They also gave information about the mass of complex obtained by mass spectrometric study; however, they have not reported X-ray crystallographic data consequently crystal structure has not been reported. Similarly in another study, Schiff base (E)-4-amino-3-(2(2-hydroxybenzylidene) hydrazinyle)-1H-1, 2, 4-triazole-5(4H)-thione (HL)-derived organotin complexes with the general formula $R_2Sn(L)Cl$ is presented in Scheme 1 and Fig. 1. Investigating methods suggests that there is bidentate coordination of ligand through $O_{phenolic}$ and $N_{azomethine}$ [12].

In a separate study, Vinyak et al. synthesized organotin carboxylate complexes containing 1–4 tin centers. They established the structure of these compounds by FTIR, NMR, and single-crystal X-ray diffraction analysis; however, they have not reported mass spectrometric result of synthesized compounds. Sensing abilities of these complexes were investigated towards Cu, Fe, Zn, Cr, Co, and Mn ions [13]. Recently, novel, porous, aromatic organotin (IV) complexes were reported by a condensation reaction of telmisartan and tin chloride (Scheme 2).The structural aspects were elucidated by elemental analysis; FTIR spectra of the complexes was observed within 526–536 and 445–447 cm^{-1} that corresponds to the vibrations of Sn-C to Sn-O groups respectively; they investigated the morphology of synthesized compound by field emission scanning electron microscopy in which they found the presence of tiny particle agglomerates. However, X-ray diffraction study and mass spectral data have not been reported in this report [14].

In another study by Laijin et al. [15], triorganotin complexes of 2-phenyl-1, 2, 3-triazole was reported. Synthesis of complex involved coordination of N atom of triazole ring with tin atom which was established by providing IR and NMR (^1H,^{13}C and ^{119}Sn) data and revealed the structure by single-crystal X-ray diffraction. Similarly, in another comparative study, Shiva et al. reported four complexes with Schiff base 2,(2-hydroxybenzylideneamino)isoindoline-1,3-dione and 4-(4-hydroxy-3-methoxybenzylidene amino N-(4-pyrimidine 2-yl) benzene sulfonamide involving not only the coordination of ligand via nitrogen atom but also via oxygen atom. Molar conductivity information suggested the non-electrolytic nature for the complexes while thermal study lightened the crystal structure [16]. However, both the above reports [15, 16] lack the mass spectral study of synthesized compounds. A separate study showed dibutyltin (IV) oxide



Scheme 1 Schiff base (E)-4-amino-3-(2(2-hydroxybenzylidene) hydrazinyle)-1H-1, 2, 4-triazole-5(4H)-thione (HL)-derived organotin complexes

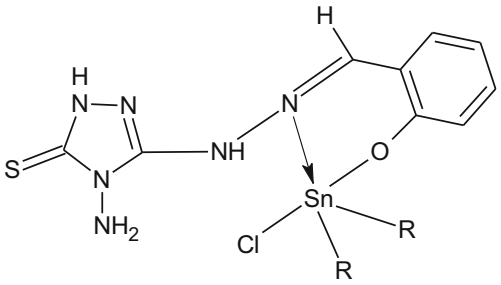
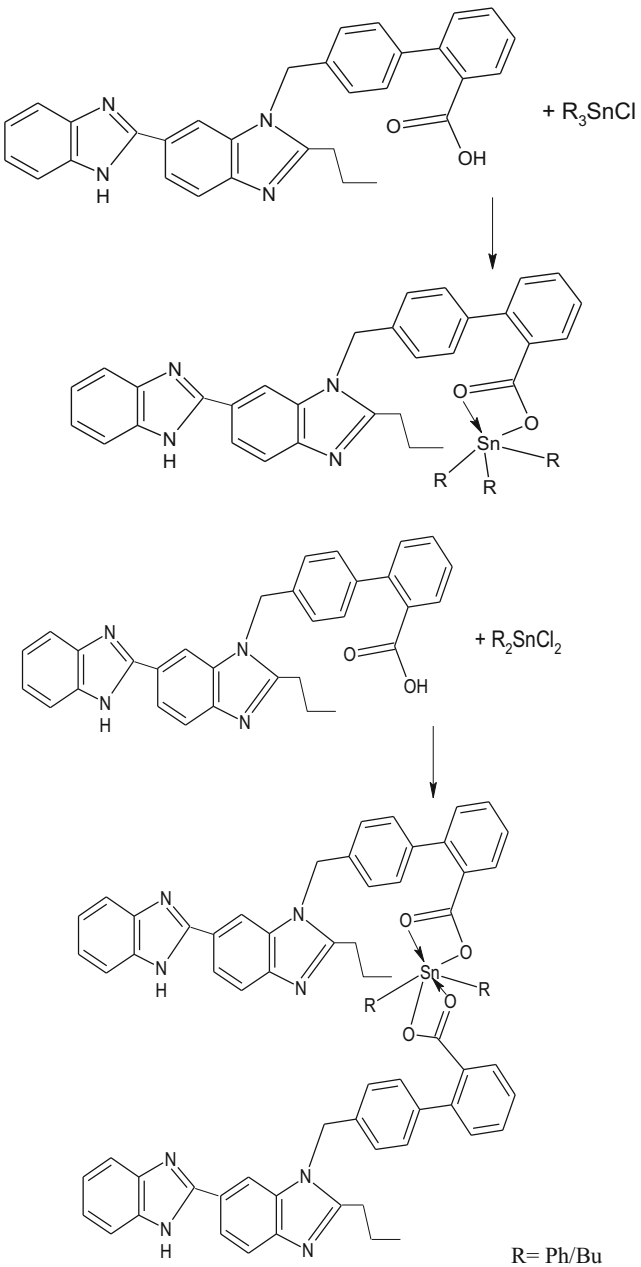


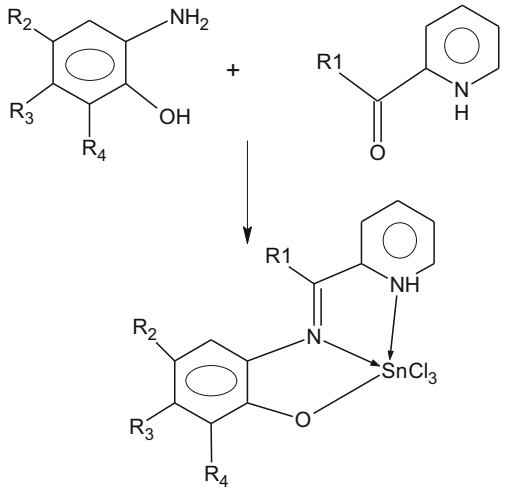
Fig. 1 Schiff base (E)-4-amino-3-(2(2-hydroxybenzylidene) hydrazinyle)-1H-1, 2, 4-triazole-5(4H)-thione (HL)-derived organotin complexes



Scheme 2 Novel, porous, aromatic organotin (IV) complexes reported by a condensation reaction of telmisartan and tin chloride

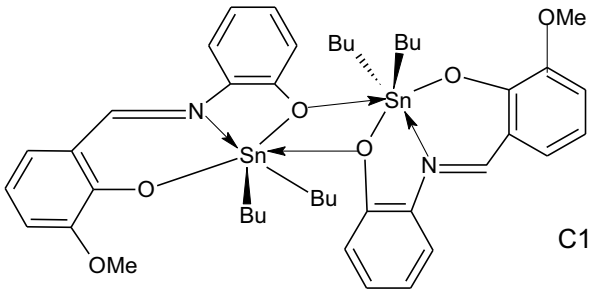
complexes containing substituted salicylaldehyde *O*-aminophenol Schiff (Fig. 2). Authors explained that the coordination of nitrogen atom with tin not only provided IR absorptions but also informed the difference in UV absorptions of ligand and complex after coordination. The crystal structure of the complexes has been determined by X-ray diffraction with graphite monochromated Mo-K_α radiation (λ = 0.71073 Å) [17].

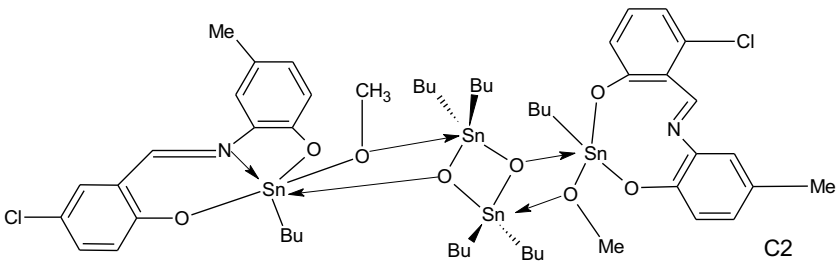
Recently, in a breakthrough, six coordinated tin (IV) complexes were prepared (Scheme 3) by template synthesis from tin tetrachloride, O-amino-phenols, and α-carbonyl-substituted pyridines. The report discloses that the geometry of obtained tin coordination polyhedron, on the basis of X-ray diffraction study and electronic spectra elucidation, was distorted octahedron [18]. They calculate the difference in UV band of different complexes on the basis of quantum chemical calculations of complexes which indicated that LUMO, and the HOMO orbitals were almost completely concentrated on the organic ligand and thus concluded the coordination as N → Sn. However, the cause of distortion in the geometry of metal complexes has not been explained in this report.



Scheme 3 Six coordinated tin (IV) complexes prepared by template synthesis from tin tetrachloride, O-amino-phenols, and α-carbonyl-substituted pyridines

Similarly, Handong et al. reported diorganotin complexes of diimido. Structural analysis reveals that all compounds present are dimeric and centro symmetric but the monomer





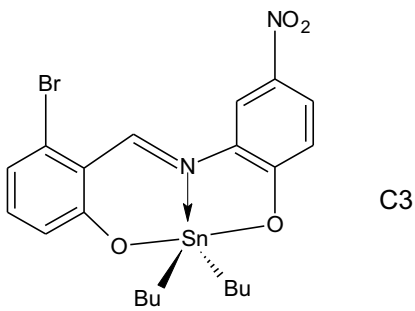


Fig. 2 Structure of C1, C2, and C3 complexes

unit has distorted trigonal bipyramidal geometry for Sn atom and the presence of intermolecular hydrogen bonding confirmed by X-ray crystallographic observations [19]. However, the report lacks explanation about the cause. Recently, Javed et al. synthesized a series of organotin derivatives of *O*-isobutyl carbonodithioate with four and six coordinated geometries. In this study statistical HOMO-LUMO approach was used to study stability of the complexes [20] while structure was confirmed with NMR and X-ray crystallography. In another study, Sheida et al. reported diorganotin complexes derived unsymmetrical Schiff ligand. The binding interaction of ligand and metal ion was identified by IR spectroscopic measurements; computational analysis was performed to study electronic and molecular structures [21]. In a separate analysis, Farukh et al. reported structural relationship of valine-derived chiral complexes of $SnCl_4$. Such complexes were characterized by elemental analysis, IR, ^{1}HNMR, and ESI mass spectroscopy [22]. Baul and co-workers in another study reported various Schiff base organotin complexes derived from amino acids, investigated by ^{1}HNMR, IR, and mass spectroscopy extensively [23]. Organotin carboxylates derived from 2-{[(2Z)-(3-hydroxy-1-methyl–butylidene)] amino}v-4-methyl pentanoate and 2-{[(E)-1-(2-hydroxyphenyl)-alkylidene] amino}-4-methyl pentanoate were synthesized and spectroscopic characterization was carried out [24]. In another investigation, a binuclear organotin complex with Sn^{+4} was connected by doubly deprotonated oxalybis[(2-oxidobenzylidene)hydrazide] ligand (Fig. 3). Spectral analysis suggested distorted trigonal bipyramidal geometry [25].

In a conclusive effort, the coordination and structural chemistry of organotin compounds bearing O– and –N donor ligands like 4-acyl-5 pyrazolonates, and bis- and tris-(pyrazolyl) alkanes were reported by Pettinari et al. [26]. Atassi et al. synthesized organotin complexes, and an attempt was made to incorporate the lipophilic/hydrophilic nature of synthesized complexes in biological systems [27]. Complexes of (R)- and (S)-N, *N*-bis [(R/S-)-1-benzyl-2-ethoxy ethane [28] were synthesized by condensation of (R/S-) 2-amino-2–phenyl-, ethanol, and dibromoethane. IR, ES-MS, ^{1}H, ^{13}C, and ^{119}Sn multinuclear ^{1}H NMR were employed for characterization. In a separate study, amino acid–based ligand organotin complexes were reported by Robina Aman [29]. Spectroscopic data suggests monodentate nature of carboxylate groups. Nath et al. reported bidentate L-glutamine, trigonal bipyramidal L-proline, hexacoordinated octahedral L-proline, and trans–hydroxy L-proline organotin derivatives [30]. Boron, sulfur, and nitrogen containing ligand dihydrobis (2-mercaptothiazolinyl) borate and its complexes were reported by Joshi et al. [31]. Coordinating abilities of para-substituted benzohydroxamates with metal center of organotin (IV) ions have been investigated using DFT. Complexes have found in between distorted octahedron and bicapped tetrahedron [32].Crystal structure of tribenzyl(chloro) (4-*N*, *N*-dimethylaminopyridine) tin (IV) was reported, and computational data using PM3 Hamiltonian suggests trigonal bipyramidal structure [33]. Andrea et al. recently reported new bis-stannylated derivatives with C_2 –symmetry, by radical addition of triorganotin hydrides and diorganotin chlorides to bis-α, β-unsaturated diesters derived from (S) BINOL [34].

Biological Activities

Previous literature reports have revealed that biological activities of organotin compounds are related to the nature of and number of R groups attached to tin atom. R groups provide attacking site to complex towards carbohydrates, nucleic acids, amino acids, etc. The presence of N, O, or S atoms in ligands plays an important role in geometry and affect the biological activities.

Anti-microbial Activity and Methodology

Farukh et al. evaluated chromone Schiff base organotin complexes against two gram-positive and -negative strains. Agar well diffusion method was adopted for measuring antibacterial and anti-fungal activity, *C. albicans* [35]. In a study, tetra-coordinated tin (IV) compounds of Schiff base derived from L-histidine show potential activity against *S. aureus* [36]. In a correlation analysis, Schiff base 4-(2-hydroxymethyl-phenylimino)-2-methyl-4H-pyran-3-ol (H_2L^1) and 4(benzothiazol-2-ylimino)-2-methyl-4H-pyran-3-ol (HL^2)-derived organotin complexes (Fig. 4) were synthesized. Anti-microbial activity on the grounds of structural characteristics of the complexes and quantitative structure activity relationship (QSAR) studies were undertaken [37].

In vitro anti-bacterial property of diorganotin (IV) complexes of *N*-methyl-4-bromobenzohydroxamic acid was

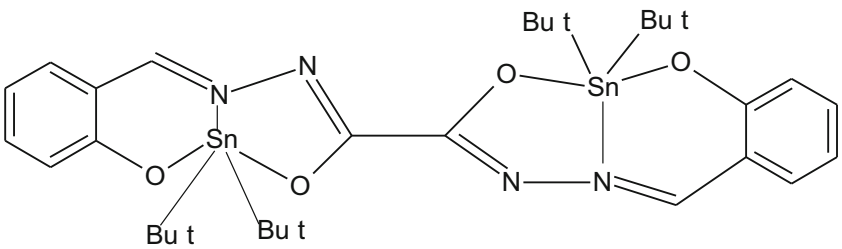


Fig. 3 A binuclear organotin complex with Sn^{+4}

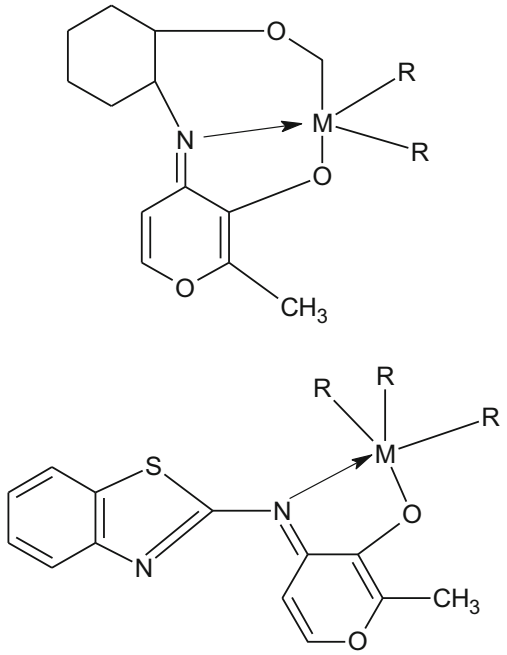


Fig. 4 R_2ML^1 and R_3ML^2 derived penta-coordinated organotin complexes

reported by Ali Irshad. Activity was assayed by agar well and disc diffusion method [38]. Triazole Schiff base complexes were screened against *Staphylococcus aureus*, *Bacillus subtillis*, *Escherichia coli*, and *Pseudomonas aeruginosa* [39]. Recently, thymol-derived complexes were thoroughly evaluated against *Staphylococcus aureus*, *B. subtilis*, *Escherichia coli*, and *Pseudomonas aeruginosa*. MIC values ranged 8–32 μg ml^{-1} and 32–128 μg ml^{-1} against gram-positive and gram-negative respectively; ciprofloxacin was used as a reference antibiotic. Anti-fungal activity against *Aspergillus niger*, *A. flavus*, *and Penicillium* species was also evaluated [40]. In a comparative study, organotin chlorides and carboxylates were evaluated as putative efflux pump inhibitors against *S. aureus* strains [41]. Azomethine-derived complexes against *S. aureus*, *M. luteus*, and *B. Bronchiseptica* were compared with roxyithronycin and cefixine as standard drugs. A total of 60–70% growth inhibition against *A. niger*, *F. solani*, and *Mucor* species were recorded [8]. In vitro anti-bacterial activity of Schiff base complexes have been evaluated against *Escherichia coli*, *Pseudomonas aeruginosa*, and gram-positive and gram-negative bacteria respectively. H_2L^x, H_2L^z ligands and its complexes show remarkable activities, thus act as potential drugs [42]. *S. aureus* possesses a wide spectrum of infectious diseases that are found to be associated with remarkable mortality rate in patients [43]. Pathogenic *staphylococci* show amazing ability to acquire resistance against antibiotics. Drug resistance as a major problem has created an immediate need to design a novel therapeutic option [44]. In the above view, in vitro anti-staphylococcal activity of organotin complexes of 5.7 diterbutyl-1,2,4-triazolo[1,5-a]pyrimidine(dbtp) and 5,7 diphenyl-1,2,4-triazolo[1,5-a] pyrimidine (dptp) was evaluated [45]. In a study, insecticidal, nematicidal, fungicidal, and bactericidal activities of N∩N donor sulfonamide imine tin complexes were reported by Jain et al. [46]. Tricyclohexytin (IV) complexes with various oxygen donor ligands were investigated against *S. aureus*, *B.subtillis*, and *E. coli* by disc diffusion method. Anti-fungal activity against *A. flavus*, *A. Niger*, *A. alternate*, and *H.* myedis has also been investigated [47]. Hexanediolic acid ligand complexes show anti-bacterial activity ranging from 24 to 27 mm with MIC 10–20 μg/ml [48].Organotin (IV) dithiocarbamate complexes show broad-spectrum activities against gram-positive and gram-negative bacteria [49]. Bioassay results of organotin 4-methoxyphenyl ethanoates show remarkable anti-bacterial and anti-fungal activities [50]. Sulfur-containing organotin compounds have been screened against *S. aureus*, *Salmonella typhimurium*, *P. aeruginosa*, and *B. subtilis*, and promising results have been found against *S. aureus and S. typhi* [51]. In a recent study, tin complexes based on azine Schiff base ligands were screened for anti-bacterial and anti-fungal activities. Metal complexes have been found to be more potent as compared with ligands; reports also suggest that activity significantly increased on coordination [52]. Another study bis-(2-[(9H-purin-6-ylimino)]-phenolate) diphenyltin exhibited excellent activity against all types of bacteria and fungi used in comparison with imipenen ($C_{12}H_{17}N_3O_4S$) as a standard drug. Anti-fungal activity of metal- ligand complexes was suggested due to metal ion on cell processes. Rate of toxicity increase was taken in view of Tweede's chelation theory [53]. Anti-viral (Hepatitis c virus) activity of triorganotin compounds was evaluated using *Gaussia* luciferase assay system by Farooq et al. [54]. In prevalence of newly emerging virulence and drug resistance, Pachna et al. explored anti-microbial activity of organotin (IV) complexes of ciprofloxacin (Fig. 5) against *E. faecalis*, *S. aureus*, *K. pneumoniae*, *E. coli*, *P. aeruginosa*, and *P. mirabilis* with promising results (MIC, 0.062–0.125 μg/ml) as compared with ciprofloxacin drug [55].

Recently in a study, novel cyanocoumarin-based ligand and its organotin complexes were designed (Fig. 6). The structural relationship and photo physical properties were

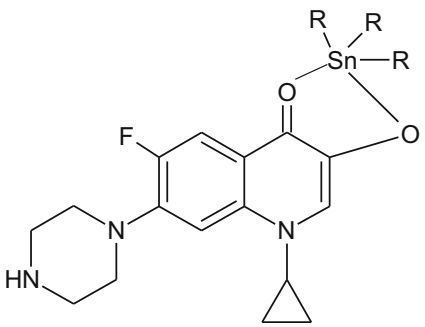


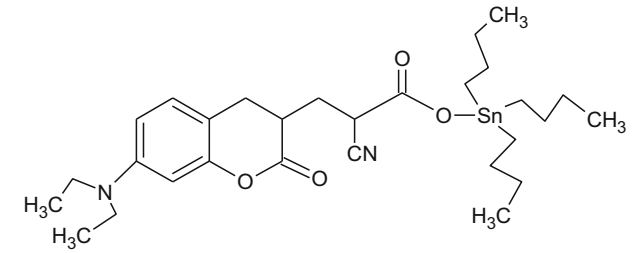
Fig. 5 Anti-microbial activity of organotin (IV) complexes of ciprofloxacin

evaluated both experimentally and theoretically. Complex II with two-photon activity was found to possess highest anti-bacterial activity with MIC value (2 ± 0.14 μg ml^1) than kanamycin (8 ± 0.42 μg ml^1) against gram-positive *B. subtilis*. Importantly, two-photon imaging and super resolution development of bacterial strain suggest that complex II reacts with biological membranes, producing reactive oxygen species (ROS) and leading to cell death [56].

In another study, Andrea et al. reported a series of nine organotin complexes, optically active with C_2 symmetry against *Cryptococcus neoformans* and *Candida albicans*. Complexes with phenyl ligand were found most active against both the strains [34]. Recently, ribavirin-derived organotin complexes (Fig. 7) were evaluated for in vitro biological activities. Interestingly, such complexes have shown remarkable anti-bacterial and anti-fungal tests, as they act by interference with duplication process of viral genetic material, due to their resemblance with building material of RNA [57]. Mechanistic insight (Fig. 8) of organotin anti-microbial action revealed their potential to inhibit transcription, translation, and cell wall synthesis [58–60]. Furthermore, they are found to suppress the activity of bacterial lactamases as well as antibiotic efflux pumps [61].

Anti-cancer Activities

Aryazo Schiff bases exhibit anti-cancer activity; indol-2-carboxaldehyde shows inhibitory activities against KB cell lines [62]. Diorganotin Schiff base complexes exhibit anti-tumor activities in vitro, inhibiting interaction to KB HCT-8 and BEL-7402 cell lines [63]. Low dose of organotin



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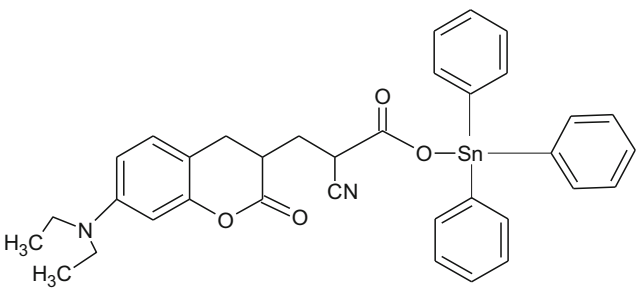

(II)

Fig. 6 Novel cyanocoumarin-based ligand and its organotin complexes

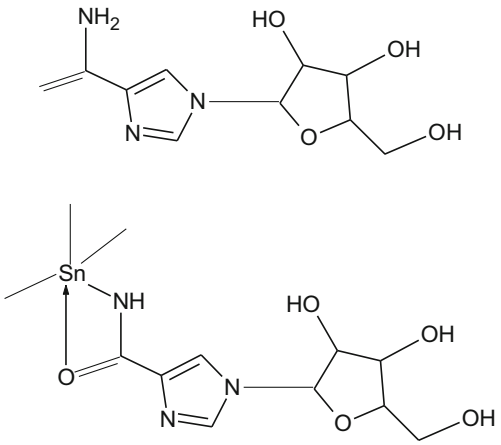

Fig. 7 Ribavirin and its organotin complex

complexes exhibit anti-tumoral activity [64] and suggested an action mode via a gene-mediated pathway in the cancer lines [65]. In a study, Badri et al. reported pyridyl ligand tin complexes and evaluated DNA-binding activity using UV-vis spectroscopy [66]. Intercalative mode of DNA interaction of carboxylate complexes exhibits in vitro anti-cancer activity against lung carcinoma (H-15) and kidney fibroblast (BHK-21) cell line [67]. Carboxylic acid ligands (z)-4-(4-acetylphenylamino)-4-oxobut-2-enoic acid (APA-1) and its triphenyl-(APA-2) and tributyltin–tin complexes have investigated for DNA binding. Experimental results reveal that APA-3 exhibits remarkable anti-tumor activity [68]. Khan et al. reported six hydroxamic acid ligand tin complexes. In vitro cytotoxic activities were evaluated against human leukemic lymphoblastoma K-562, hepatoblastoma HepG2 cells, and mouse fibroblast L929 cell lines [69]. To introduce hydrogen bonds to the biological targets, a novel Schiff isonitcotinohydrazide and p-*N*,*N*-di(2-hydroxyethyl)amino benzaldehyde along with its organotin complexes were evaluated. In vitro cytotoxicity data against A-549, MCF-7, and Hela-tumor cell lines which suggested that compounds are more cytotoxic than *cis*-platin. Roll of steric effect and hydrogen bonding in DNA binding was also highlighted [70]. Biological activity of cyclopentadienyltin derivatives has been recently studied very extensively [71]. Santiago et al. reported four triphenyltin complexes with different cyclopentadienyltin ligands. Cytotoxic activity was tested against 8505C anaplastic thyroid cancer, A252 head and neck tumor, A549 lung carcinoma, A2780 ovarian cancer, and DLD-1 colon carcinoma. All the reported complexes present high activity against evaluated cell lines up to ca. 100 times that of *cis*-platin [72]. In another study, an attempt was made to attenuate the cytotoxic action of structural polyfunctional anti-tumor organotin derivatives by combining the antioxidant 2,6-di-*tert*-butylphenol moiety with Sn atoms. Anti-tumor activity of the complex (Fig. 9) was evaluated against colon carcinoma HCT-116 ($IC_{50} = 2.1 \pm 0.2$) and prostate cancer PC3 ($IC_{50} =$

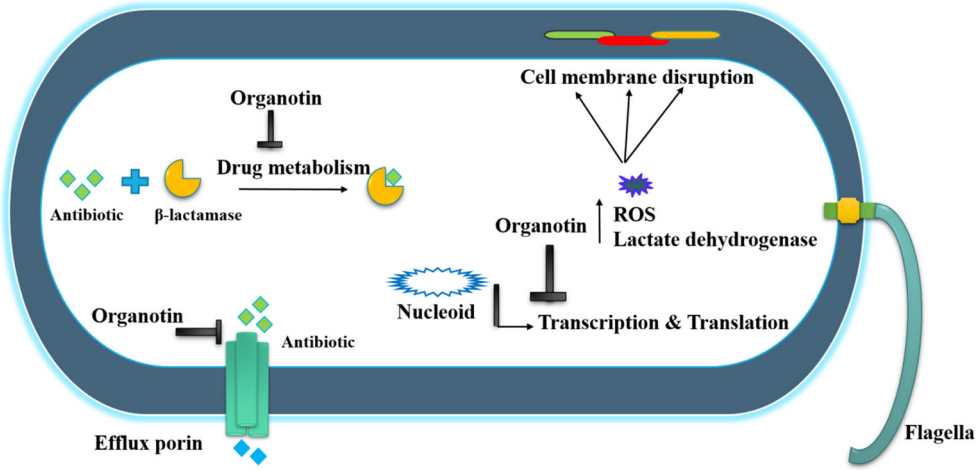

Fig. 8 Schematic representation of anti-bacterial effect of organotin complexes via inhibition of lactamase activity, drug efflux pump, protein cell wall synthesis

4.0 ± 0.3); with such a low toxicity, such complexes may be of pharmacological interest [73].

In vitro anti-tumor activity of *N*-glycoside-derived ligand, its complex with $SnCl_4.5H_2O$ and $(CH_3)_2$ $SnCl_2$ was screened against A549 (lung), PC3 (prostate), A498 (kidney), DWD (oral), colo205, MCF-7(breast), and A2780 (ovary). Interaction with CT DNA was worked out by using different biophysical techniques. Complexes of $(CH_3)_2$ $SnCl_2$ exhibited good cytotoxicity against DWD (oral) cell lines only [74]. A study on diorganotin pyridinedicarboxylates (di-*n*-butyl tin, di-*t*-butyl tin and diphenyltin-2, 6-pyridinedicarboxylates) screened on human cell lines viz MCF-7, colon carcinoma, and mammary tumor exhibits remarkable anti-tumor activity. Di-*n*-butyl tin-bis(2,5-dihydroxybenzoate) was found to be more effective than *cis*-platin against colon carcinoma cell lines [75]. Anti-cancer ability of Schiff base–derived dibutyltin (IV) oxide complexes was evaluated against MCF-7, colon205, NCL-H460, HeLa, and HepG2. Complex C3 was reported to show significant anti-cancer activity, fluorescence, and UV-Vis, and viscosity measurements demonstrated interaction of complex with calf thymus DNA [17]. In view of biological aspects of hydrozone Schiff base ligands, recently, a series of tin complexes R_2SnI(R = Me 1, Ph. 2, O-Cl-$C_6H_6CH_3$, and R_3SnCl R = *n*-Bu 4) have been evaluated. In vitro anti-tumor activity of complex 1–4 towards HCT-8 (colon), A549 (lung), and HL-60 (promyelocytic cell lines) was

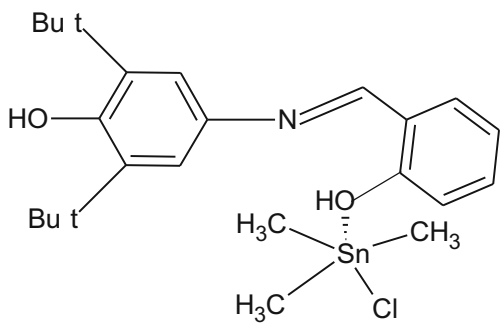

Fig. 9 Anti-tumor activity of the complex

determined by MTT method. Screening reports suggest that complex 4 shows better anti-tumor results [76]. Cytotoxicity of five Sn (IV) complexes of terpyridine against two human carcinoma cell lines has been studied using MTT assay. All the reported complexes showed remarkable cytotoxicity than *cis*-platin and free terpyridine ligand [70]. Interaction of dimethyl tin dichloride with DNA and RNA with different binding approach and mechanistic pathway has been investigated in comparison with other anti-cancer agents like *cis*-platin. The binding constant at different pH for the reported complexes was as for Sn $(CH_3)_2$Cl-DNA (1.47×10^5 M^{-1}) and Sn $(CH_3)_2Cl_2$-RNA (7.33×10^5 M^{-1}) [77]. Han et al. investigated the interaction of organotin (IV) porphinate complexes with DNA; cytotoxicity was screened against P388 and A-549 tumor cell lines. Inhibitory percentage data for the reported complexes have also been described [78]. Anti-tumor activity of bi [(di-*n*-butyl-3-6-dioxaheptaneato) tin] and tri-*n*-butyl tin 3, 6, 9-trioxodecanoate was investigated using circular dichroism spectroscopy, DNA melting experiments, and gel mobility shift assays. Experimental data demonstrates that both the complexes bind to phosphate group of DNA [79]. Isothermal titration calorimetry (ITC), IR spectroscopy, fluorescence/UV, and the binding isothermal and enthalpy curve for Me_2SnCl_2-DNA binding interaction were reported [80]. They concluded that DNA binding at low concentration of the complexes occurs by an exothermic process, unfolding of DNA at higher concentration. Anti-tumor activity of di-*n*-butyl tin {4-(7-oxobicycle[1, 2]-5-heptane-2, 3-dicarboxamide) benzoate} complexes by Zhohu et al. suggested that such complexes have been found to be active towards P388 cell lines (81%) and HL-60 (75.3%) at a concentration of 10^{-8} mol/l [81]. Recently, in vitro anti-tumor profile of organotin complexes containing 1, 2, diamminocyclohexane has been discussed. Reports show that activity towards ZR-75-1, HT-1376, skov-3 colon carcinoma, and PA-1 ovarian cancer increases from diphenyltin (IC_{50} = 7.26 μmol ml^{-1}) to di-butyl tin (IC_{50} = 2.58 μmol ml^{-1}) [82]. Demertzi et al. have investigated organotin complexes of flufenamic acid and flufenamates. [Bu_2(flu) SnOSn (flu) Bu_2]

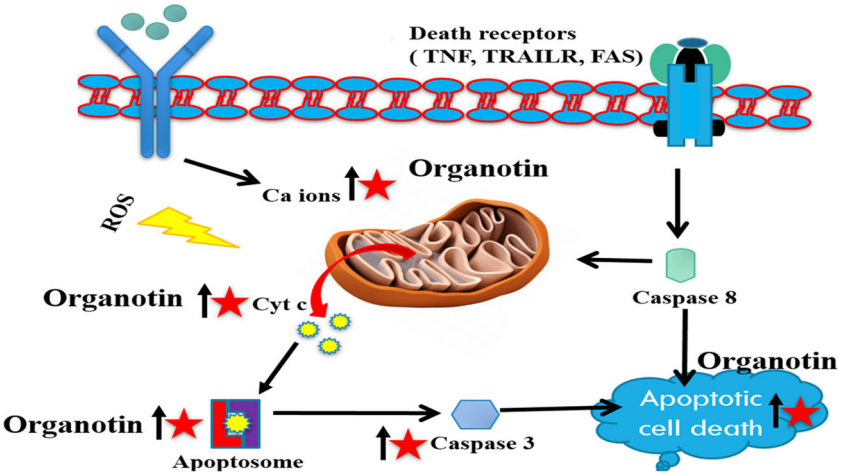

Fig. 10 Organotin complexes induce apoptotic cell death in cancer by activating cyt C release and caspase functions

and [Bu_2Sn (flu) $_2$] (HL = *N*-[(3-trifluoromethyl)-phenyl-anthranilic acid] show significant cytotoxicity against lung carcinoma (A549) cell lines. Interaction of di- and triorganotin complexes of meso-tetra-(4-sulfonato phenyl) porphine $[Me_2Sn]_4$ TPPS, $(Me_2Sn)_4$ TPPS, and $(Bu_3Sn)_4$TPPS with DNA was analyzed. Spectrophotometric and spectrofluorometric results have suggested that all complexes strongly interact with DNA. Fluorescence quenching and viscosity results suggest $(Bu_3Sn)_4$ TPPS are able to noticeably alter DNA conformation [83]. Cytotoxicity of organotin complexes of 2, 6-di-*tert*-butylphenol moiety with various thioamides has been evaluated. Selective activity of [(*tert*-bu-)$_2$-(HO-Ph.)]2 against MCF-7(IC_{50} = 0.58 ± 0.1 μM), indicates involvement of estrogen receptor (ER) in their anti-tumor mechanism [84]. Organotin complexes with carbazole ligands were tested in vitro for their cytotoxic activity towards human hepatocellular carcinoma (BEL-7402) and hepatocellular liver carcinoma (Hep G2) cell lines. Complexes $\{[nBu2SnOL]_2O\}_2$ show the best cytotoxicity (HepG2 = 1.93 ± 0.12, BEL-74 = 0.60 ± 0.02) values, and can be considered for further investigation [85]. In another study, Balas et al. reported triphenyl and tri-*n*-butyl tin complexes of thiobarbituric acid. In vitro cytotoxic activity results showed that tri-*n*-butyl tin (IV) complexes exhibited highest cytotoxic activity in comparison with triphenyl against HeLa, OAW-42, MFC-7, MB-231, and A549 human cancer cell lines. In this study, both complexes were found to interfere with lipooxygenase (LOX), preventing oxidation of fatty acids, thus interacting indirectly with DNA [86]. Recently, 4-fluorophenyl-selenoacetic acid–derived noval organotin (IV) complexes were evaluated for their in vitro cytotoxic activity against human breast cancer cell lines (MDA-MB-231) [87]. Anti-cancer mechanisms suggested the ability of organotin complexes to induce apoptotic cancer cell death (Fig. 10) by increasing ROS production, release of Ca^{2+} ions, disturbed mitochondrial membrane potential, and discharge of cytochrome C [88, 89].

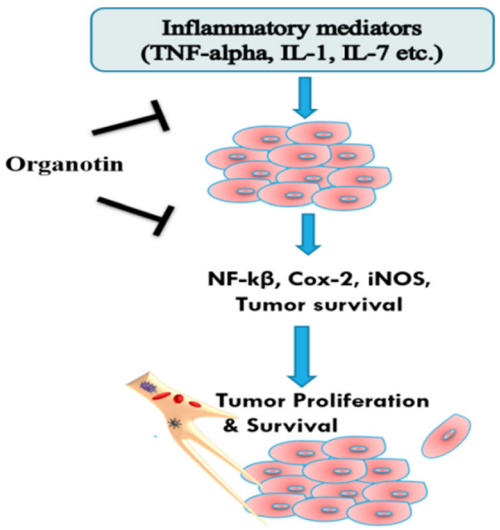

Fig. 11 Inhibition of inflammatory mediators (iNOS, COX) by organotin complexes to suppress tumor growth and survival

Anti-leishminial Activity

Leishminia is a genus of trypanosome protozoa, the parasite responsible for the disease leishmaniasis transmitted through sand flies. Organotin derivatives have been widely explored against *Leishminia* major. Anti-leishminial activity of organotin complexes of dimethyl (1), diethyl (2), diphenyl (3), di-*n*-octyl (4), di-*tert*-butyl (5), and *n*-butyl chlorotin (6) derivatives of *N*-(2-hydroxy-3-methoxybenzylidene) formohydrazide ligand was evaluated using Amphotericin B as standard drug. Complex nos. 3 and 5 have shown comparable activity, which may be attributed to their lipophilic nature [90]. In a study using the classic microscopic in vitro model, organotin complexes were screened against *Leishminia amazonesis*. Remarkable IC_{50} values (0.17 ± 0.03 and 0.10 ± 0.11 μg/ml) were reported for [(L) (Ph_3Sn)] and (Ph_3SnCl_2) respectively. Di- and triorganotin (IV) dithiocarbamates (n-Bu_2SnCl_2) L, $(Ph_2SnCl)_2$ L, $(Ph_3Sn)_2$ L, and $(Bz_3Sn)_2$L were tested towards pathogenic *Leishminia* major B. Docking method analysis suggests noticeable anti-leishminial activity of $(Bz_3Sn)_2$ L due to low binding energy with enzyme

Table 1 Birds eye view of various bioactivities of organotin compounds

	Organotin complexes	Dosage/IC_{50}	Subject	Ref.
Anti-cancerous activity	Ph3Sn(CEMPD)	0.22–0.53 μM	HeLa, K562, MDA-MB-453	[107]
	Derivatives with O-hydroxy-benzoic or P-hydroxybenzoic acids	1. 31 ± 1.6 2. 108 ± 2.6 3. 97 ± 2.1 4. 21 ± 1.1 nM	1. LMS 2. MCF-7 3. U2-0S 4. HeLa cell lines	[108]
	Triethyltin lupinylsulfide hydrochloride	28 mg/kg	P288 lymphocytic leukemia, B16F10 melanoma, and 3LL lung carcinoma	[109]
	Triorganotin 3, 5-di-*tert*-butyl-4-hydroxybenzoates	0.22 ± 0.03, 0.08 ± 0.01, 0.46 ± 0.03, and 3.24 ± 0.12 μ $mol.l^{-1}$	Human tumor cell lines A549	[110]
	Triphenyltin esters	0.2–60 to 0.4–7 and 0.3–5 to 0.2–27 μM	A-549 and L-929 and T-24 and MCF-7 cell lines respectively	[111]
	Derivatives of propyl gauate and 1, 10 phenanthroline	ca. 0.84 μM	MCF-7 cell lines	[112]
	Diphenyltin dithiocarbamate	4.8 ± 0.2 and 7.5 ± 0.3 μM	HEP-3B and IMR cell lines	[113]
	Dimethyltin derivatives of *N* (4)-methyl thiosemicarbazone	6 μM/ml	MCF-7	[114]
	Di and tri derivatives of arylhydrazone of methylene	0.0284 ± 0.0001 and 0.287 ± 0.0001 μM	HCT-116 and HePG2 cell lines respectively	[115]
	$[(C_6H_5)_3Sn(Cmbzt)]$	4×2 mg/kg every 5 days and 3×2.6 mg/kg every 10 days	Wistar rats	[116]
	Triorganotin compound with 2-mercapto-nicotinic acid ligand.	4.5 mg/kg every 3 days	Female Wistar rats	[117]
	Derivatives with O or P-hydroxybenzoic aids	11, 19, and 24 μM	Sarcoma cell lines	[118]
	$[n\text{-}Bu_2Sn$ (imda) (H2O)$]_2$ Bpy and $[n\text{-}Bu_2Sn$ (imda) (H2O)$]_2$ phen	10^{-4}M	P388, HL-60, and A-549	[119]
	Derivatives with amide carboxylic acid ligands	120 μg/ml	HePG2 cell lines	[120]
	Me_2SnL^1, ($MeSnL^2$), (Me_2SnL^3), (Ph_3SnL1H), and (Ph_3SnL^3H) L = (2S) = 2-(E)-[(Z)-4-hydroxypent-3-en-2-ylidene]-3-(1H-indole-3yl) propanoate	10 to 100 μM	A375 (melanoma), HeLa (epithelial), and MDAMB-231 (ovarian carcinoma)	[121]
	$R2Sn[(5\text{-}GMP)H2O]_n$ and $[(R3Sn)_2(5GMP)H2O]_n$	40 mg/kg	Albino rats	[122]
Anti-inflammatory activity.	Derivatives from pyrimidine Schiff base ligand	0.031 to 1.0 μ mol	Mouse ear edema	[90]
	Derivatives of 3-maleimidopropionic acid	10–100 mg/kg	Albino mice	[123]
	Organotin tryptophanylglycinates	≥400 mg/kg	Edema bioassay in rats	[100]
	Di and tri derivatives with imidazole ligand	40–80 mg/kg		[102]
	Tri-*i*-propyltin and di-derivatives of guanosine.	40 mg/kg	Albino rats	[86]
	Organotin chlorides with fexofenadine ligand	50 mg/kg	Hind paw of the rats of both sex	[124]
	Derivatives with salicylaldehyde and adenine	≥50 mg kg^{-1}	Rats of both sex	[84]
	Derivatives with *N*-(2-methoxyphenyl)-4-oxo-4-[oxy] butanamide	5 μl	M. species, *A. niger*, *A. fumigates*, *A. flavus*, *Fusarium solani*	[81]
Anti-microbial activity.	Derivatives with carboxylate ligand 4-(4-methoxyanilino)-4-oxobutanoic acid	40 mg	*S. aureus*, *B. subtilis*, *E. coli*, *B. bronchiseptica*, *S. typhimurium*, and *K. aerogenes*	[70]
	Derivatives with triazole Schiff base ligand	4.0 mg/ml	*S. aureus*, *B. subtilis*, *E. coli*, *S. aeruginosa*	[30]

Table 1 (continued)

Organotin complexes	Dosage/IC_{50}	Subject	Ref.
Derivatives with 4-(4-hydroxy-3-methoxy-benzylideneamino-*N* (pyrimidine 2-yl) benzene sulfonamide	200 μg/ml	*E. coli*, *S. aureus*, *R. salanacearum*, and *A. niger* and *A. solani* (fungi)	[13]
Organotin isopropoxide with thymol derivatives	8–33 μg ml^{-1}	*S. aureus*, *B. subtilis*, *E. coli*, and *Pseudomonas aeruginosa*	[31]
Di-derivatives with *N*-methyl-4-bromobenzohydroxamic acid	4 mg/ml in DMSO	*Salmonella typhi*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, and *Escherichia coli*	[29]
Derivatives with carboxylate ligands	0.25–4.68 μg/ml	*A. fumigatus*, *F. avenaceum*	[125]
With amino acid and 2, 2-bipyridine ligands	500–1000 ppm in methanol	*Pseudomonas capacicola*, *Staphylococcus aureus*	[4]
With azo-imino carboxylic acid ligands	625–4.7 μg/ml	*Candida albicans*	[126]
Organotin complex of $NASAID_S$	1.89 μg/ml	*Mycobacterium tuberculosis*	[127]
Triphenyl tin salicylanilde thiosemicarbazone	0.05 ± 0.01 mg/l	*Leishminia donovani*	[78]

trypanothione synthetase [91]. In vitro anti-leishminial activity of organotin carboxylate derivatives of germatranyl,4-(4-methoxyanilino)-4-oxobutanoic acid and tri-butyl tin(iv) were screened against *Leishminia* major and donovani types. Presence of R groups in germatranyl tin carboxylates plays a significant role in anti-leishminial activities. Para methyl–substituted aromatic ring of carboxylate ligand is more significant than other substituted complexes. Diethyl tin derivatives are more active than tribenzyl tin compounds [92–94]. In another study, triphenyl tin salicylanilde thiosemicarbazone [Ph_3Sn (OSal.TSCZH)] has been evaluated towards visceral leishmaniasis. Anti-leishminial activity was found to be effective both in vitro and in vivo with IC_{50} value 0.05 ± 0.01 mg/l [95]. MTT assay was employed to determine the in vitro anti-leishminial activity of organotin carboxylate derivatives of *N*-[(2-methoxy-5-nitrophenyl)]-4-oxo-4-[oxy] butanamide. Complex which is potent against Leishminia major was found to exhibit an IC_{50}value of 0.98 ± 0.06 μM in comparison with amphotericin B (0.29 ± 0.05 μM). Activity of the complexes was suggested due to interference with parasite mitochondria [96]. In a comparative study, anti-leishminial aspects of organotin derivatives of 4-[(2, 4-dinitrophenyl) amino)]-4-oxo-2-butenic acid, 2-{(2,4-ditrophenyl) amino] carbonyl} benzoic acid [97], and *N*-[(2-methoxyphenyl)]-4-oxo-4-[oxy] butanamide [98] towards *Leishminia* major were evaluated.

Anti-inflammatory Activity

Organotin complexes from carboxylic acid and oxicam family have widely evaluated as non-steroidal anti-inflammatory drugs [99]. Anti-inflammatory action of di- and triorganotin derivatives of tryptophanyl glycine (H_2trp-Gly) using carrageenan-induced paw edema bioassay in rats were conducted by a group of researchers. Among the reported complexes, R_2Sn (trp-Gly) shows higher anti-inflammatory activities in comparison with phenylbutazone [100]. In a study, organotin Schiff base complexes have been stemmed for their anti-inflammatory activity [101]. Di- and triorganotin complexes derived from condensation of tis (2-amino ethyl) amine and 4-methyl-5-imidazole-carboxaldehyde have been tested for anti-inflammatory effect. Tri derivative $Me_3Sn(H_2L)$ (8.89% inhibition) was found to be more active than diorganotin Me_2Sn (HL)(6.38% inhibition) [102].Tri-*i*-propyltin and diorganotin derivatives of guanosine tested towards albino rats display a low range of anti-inflammatory action (7.51–9.21% inhibition) [103]. In vivo anti-inflammatory activity of tri- and diorganotin orotates was investigated by Malanath and co-workers. Data suggests that diorganotin orotates are more efficient than tri derivatives. The active role of $Ph_3Sn(H_2Or)$ is due to Ph_3Sn (IV) $^{+}$ion formation and transportation through cell membranes [104]. There is an anti-inflammatory character of ibuprofen and cinnamic acid–derived tin complexes by cyclooxygenases

(COX-1 and COX-2) pathway. In silico affinity and selectivity were screened towards cyclooxygenase enzyme involved in the inflammatory activities [105]. Hapta-coordinated tin derivatives containing pyridine moieties were evaluated in vivo applying TPA-induced ear edema bioassay in mice samples. Data indicates that the rate of drug action is dependent on dosage [106]. A schematic representation of anti-inflammatory mechanisms of action of organotic complexes has been shown in Fig. 11, Table 1.

Conclusion

Organotin and its derivatives are biologically active agents that have been widely recognized. The above discussed text has suggested its anti-microbial, anti-leishmanial, anti-cancer, and anti-inflammatory activity. Therefore, organotin complexes could not only be used in the industry but also in the treatment of various diseases. In the future, complexes of organotin with different ligands could bring hope to lower down the mortality rate of various dreadful diseases. We should focus on extending its applications by introducing nanotechnology and various nanotechnological tools.

Compliance with Ethical Standards

Conflict of Interest There authors declare that there is no conflict of interest.

Human and Animal Rights Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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