Pesticidal, nematicidal, antifertility and biocidal activity of organotin compounds

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ABSTRACT

This review concern the developments on the biocidal properties of the organotin compounds with an emphasis on the authors's contribution to the field. The organotin compounds with a variety of nitrogen/oxygen and sulfur donor ligands developed mainly during last decade has been reviewed. The article is focused on the design, synthesis and biological peraspective of organotin compounds. Particular attention has been paid to the effectiveness of these compounds as: insecticides, nematicides and antifertility agents and biocides. © 2008 Trade Science Inc. - INDIA

INTRODUCTION

Over the last 40 year's research into the chemistry of organometallic compounds of tin has represented one of the most profilic area of chemical activity. As a result of wide spread industrial applications[1,2] the many facets of this field have attracted the attention of chemists of all persuasions, as well as that of biochemists, biologists, pharmacologists, toxicologist and physicists, to name but a few. Many excellent papers have been published during last two decades and most relevant results have also been reviewed covering this field[3-7]. The chemical reactivity of organotin species and their availability in a wide range of structural features have made the subject of organotin complexes a rich and diverse field of chemistry.

The various aspects of organotin[8-10] compounds reviewed in the last decade include polyhedron organotin compounds[11], bidentate oxygen donor complexes of tin[12], chemistry and applications of organotin(IV) complexes of phosphorus based acids[12], organotin(IV) complexes of aminoacids and peptides[14,15], chalcogenido metalates of the heavier group 14 elements and stannenes[17], toxicity and health effects of organotin compounds[17], toxicological activities of organotin compounds[18], their therapeutic potential[19] and organotin compounds in the environment[20].

The use of some organometallics employed as biocides, i.e. insecticides, pesticides, fungicides, and herbicides and their possible short as well as long-term effects on ecology and environment are attracting the attention of scientists, in many cases arousing deep concern of the society in general of the organometallics of two metals, mercury and tin used extensively for their biocidal properties, the use of the former having been banned in many countries[7]. The pronounced biological effects of organotins led to their wide applications in fields like medicine and agriculture. The ever-increasing practical uses of organometallics as biocides in agriculture, as antiknock agents in automobiles and as catalytic agents in a number of industrial (especially biotechnological processes) have led to an increasing concern about their environmental aspects also[7].

Casaes et al.[21] have reported the synthesis of diorganotin(IV)-promoted deamination of amino acids by pyridoxal; Pyridoxal 5'-phosphate (PLP) and pyridoxal (PL) itself were reacted with diorganotin(IV) derivatives in the presence and absence of aminoacids.

With PLP complexes [SnR$_2$(PLP-2H)] [R=Me, Et, and n-Bu] were isolated and characterized by EI and FAB mass, IR, Raman and mossbauer spectroscopy. The positive findings of antibacterial activity of these compounds against *Pseudomonas aeruginosea* (ATCC 27853), *Staphylococcus aureus*, *Bacillus subtilis*, *E.coli* and a carbapenem-resistant *P.aeruginosa* strain have also been reported.

Ruisi and coworkers[22] have reported the synthesis and *in vitro* antimicrobial activity of organotin(IV) complexes with triazolopyrimidine ligands containing exocyclic oxygen atoms. In vitro anitimicrobial tests were reported on n-Bu$_3$SnPh$_3$Sn(HtpO$_2$) and Ph$_3$Sn(HtpO$_2$) and good antifungal and antibiofilm properties were observed in particular for n-Bu$_3$Sn(HtpO$_2$).

Organotin(IV) complexes of amino acids and their organic derivatives containing the carboxylic O-Sn(IV) bond display significant antitumor activity and promising potential in many other fields like polymer chemistry, pesticidal and antibacterial agents[23-30]. The structural chemistry of organotin(IV) complexes of carboxylic moieties as amino acids and N-protected amino acids with a coordination number higher than four is being extensively studied because of their biological activity, enhanced reactivity and stereochemical non-rigidity[31-39].

Several reports have been cited in the literature by other research groups pertaining the bioactivity as antitumour agents and structural chemistry of di- as well as triorganotin(IV) compounds[31-43]. Ashfag et al.[44] have reported *in vitro* LD$_{50}$, antibacterial, antifungal and antiyeast bio-tests of organotin(IV) complexes of 2-male-imidoacetic acid, which proved them to be powerful biocides. The *in vitro* anti-tumour and analgesic activities also displayed excellent potential of the titled compounds.

Farina[45] and coworker's have reported the synthesis of organotin dithiocarbamates derived from hydroxylated amines, which have been found to be biologically active. The coordination of the Schiff base nitrogen with tin has been investigated in several systems[46-50]. In spite of the reservations arising due to actual as well as potential environmental pollution, a wide variety of organometallic compounds are finding increasing uses as pesticides. For example, tri-phenyl tin hydroxide and acetate are both used in numerous formulations for the control of a variety of fungal growths particularly potato blight. Tricyclohexyltin hydroxide is a very effective acaricide for controlling fruit free red spider mite on apples and pears. Besides these, organotin compounds have been used as antifouling agents, i.e., in protecting various surfaces like that of wood from the growth of mould. The series of organotins, (n-C$_4$H$_9$)$_3$ Sn CH$_2$R (where R is a quaternized amino group) showed herbicidal activity with no phyto-toxicity. n-Tri-butyl tin fluoride was shown to be selective in controlling weeds without damage to corn or rice. The existence of a tin cycle has been investigated extensively since 1970's in view of the larger quantities of organotins entering the environment through their increasing applications as pesticides. A number of pathways, e.g., oxidative methylation of tin(II), environmental methylation of tin and biomethylation of stannic oxide and trimethyltin hydroxide by sediment microorganisms have been suggested in this direction[51]. Tin forms a number of organometallic compound in which tin exists in Sn(II) and Sn(IV) states. Many organo-tin compounds are used as agriculture biocides to protect the crops from fungi, bacteria, insects and weeds. The great advantage of organotin compounds in these applications is that they are nontoxic to mammalians[52].

Mono-organotin(IV) compounds, considered the least toxic among organotin(IV) derivatives (R$_3$Sn(IV)$^+$ >R$_2$Sn(IV)$^{2+}$>R Sn (IV)$^{3+}$>Sn^{4+}, toxicity scale), have not achieved as much commercial applications as diorgano- and triorganotin(IV) derivatives. However, they are often used as hydrophobic agents for building materials and cellulosic matter and can be present in the aquatic environment as the first step in the alkylation of inorganic Sn[53].

This chapter is particularly concerned in the of biological relevance of organotin compounds. So far, focus has centered on nematicidal, insecticidal, antifertility and biocidal activities of these compounds.

Pesticidal activity

The most common method of pest control is by the use of chemicals, which are known as pesticides. Based on the target organisms, these pesticides are grouped into insecticides, nematicides fungicides, weedicides and rodenticides.

Insecticidal activity

The oldest insecticides used by humans were of plant origin. These were prepared from the roots, stems, leaves, seeds, flowers and oils of various plants. These

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botanical pesticides were followed by the development of inorganic synthetic insecticides like Paris green, lead arsenate and calcium arsenate. In 1867, Paris green, a crystal compound of acetate and arsenite of copper, having approximate composition $Cu_4(CH_3CO_2)_2$ $(AsO_2)_2$ was successfully used for the control of Colorado potato beetle in USA. Another arsenic compound, lead arsenate ($PbHAsO_4$) was first used against Gypsy moth in USA in 1892. Inorganic compounds containing mercury, tin or copper were also used as stomach poisons during this period. In the early 1900s, sodium fluoride and cryolite replaced some arsenicals because of lower phytotoxicity.

With the development of these insecticides, the focus of research in entomology slowly shifted from ecological and cultural control practices to chemical control during the period 1920-1945. The first synthetic organic compounds to be used as insecticides were alkyl thiocyanates prepared by reaction of alkyl halides with sodium thiocyanate during 1930s. Another compound, Lethane, consisting of ether linkages in alkyl chains was prepared in 1936.

The development of these compounds was perhaps prematurely arrested by the dramatic success of DDT [2,2-bis-(p-chlorophenyl)-1,1,1-trichloroethane]. The impact of DDT on pestcontrol is perhaps unmatched by any other synthetic substance and paul muller was awarded Nobel prize in 1948 for discovering the insecticidal properties of DDT. Nearly 1.5 billion kg of DDT was used during the three decades following its introduction in agriculture during 1940s. By 1961, there were over 1200 brands of DDT registered for use on 334 agricultural commodities against 240 species of insect pests in USA. The period since 1940s has rightly been called the 'age of pesticides' and can be divided into three distinct phases the era of optimism, 1946-1962; the era of doubt, 1962-1976; and the era of JPM, 1976-onwards[54].

Trogoderma granarium (Everts) commonly known as khapra beetle belongs to order coleoptera and dermestidae family, is an important pest of both material of plants and animal origin. It is said to be of Indian origin and has spread to whole of world due to ship transactions. It is a major pest of stored wheat in hot and dry parts of the world. The damage is sometimes so serious that whole of grain is reduced to husk and only seed coats with empty cavities are left behind.

Beside wheat it generally infects cereals, pulses, stored malt, rice and coriander seeds[55].

The literature on the insecticidal activity of organotin compounds through 1964 has been reviewed very completely by Ascher and Nissim[56]. Therefore, only the main lines have been discussed here and a few recent publications mentioned.

The first mention of insecticidal properties in organotin compounds was made in a series of patents published around 1929. In addition to compounds of Group V elements, organotin compounds in general were claimed as mothproofing agents[57]. Twenty years later only trialkyltin chlorides were claimed in a patent[58] dealing with the control of insects other than moths. Hueck and Luijten[59] in 1958, found mothproofing activity only in some compounds of the type R_3SnX.

Systematic investigations on the insecticidal activity of organotin compounds started with the work of Blum et al. in 1960. Blum and Bower[60] had already shown that triethyltin hydroxide and some of its salts were hightly toxic when applied topically to house flies (*Musca domestics*). The LD_{50} of the compounds was somewhat higher for DDT-resistant flies than for susceptible flies (e.g. of the hydroxide, 0.40µg as compared with 0.31µg per fly). Blum and Pratt[61] thereupon investigated a series of forty organotin compounds by the same technique. They found a high activity for a trisubstituted compounds, a moderate activity for compounds of the type R_4Sn and R_2 and R_2SnX_2 and a low neither the nature of the group X nor the length of the alky chains (at least up to butyl), had much influence on the insecticidal activity. A similar result was obtained by Gras et al.[62,63] who tested a series of organotin compounds in aqueous solution against mosquito larvae (*Culex pipiens berbericus*). They extended the series of trilky1 compounds somewhat further, however, and found a sudden fall in activity after hexyl. The concentration of trialkyltin compounds killing half of the larvae(LC_{50}) from methy1 through hexy1 was 0.4-0.5 mg/1. This is still ten times the LC_{50} of DDT, lindane, and malathion in the same test. In the above investigations, tripphenyltin compounds had the activity as the lower trialkyltin compounds.

Kochkin et al.[64] likewise investigated a series of organotin compounds, but extended the number of insect to include flies, bed bugs, cockroaches, mosquitos and fleas. The flies were treated topically; the LD_{50}'s

found correspond with those observed by Blum and Pratt[61]. The russian authors moreover found trialkyltin compounds active as contact insecticides against all species. Conflicting results were obtained with triphenltin compounds: Gardnier and Poller[65], when testing a series of ten triphenyltin salts as contact insecticides against *Sitophilus oryzae* adults, found none active. One wonders, however, whether in latter investigation the experimental set-up was favourable. Where Kochkin et al. Used glass plates, Gardiner and Poller used paper discs, and it is known that organotin compounds are fixed cellulose[66]. Kubo[67] who investigated the activity of triphenlytin organphoshates as contact insecticides against the adult Azukibean weevil (*Cellosobruchus chinensis*) again used glass (Petri dishes). Many strong influence of the nature of the acid radical was noted in this case, and Kubo could demonstrate a correlation between the activity and the solubility of the compounds in organic solvents.

A difference in the mode of action between trialky1- and triphenyltin compounds is suggested by the results of mothproofing tests by Gardiner and Poller[65]. In these tests, tested samples of wool were exposed to attack by larvae of the common clothes moth (*Tineola bisselliella*). The authors found no attack and 100% kill with 1% of tributyltin oxide in the wool. With triphenyltin salts in the same concentration some wool was always eaten and the percentage kill never attained 100%. The authors conclude that tributyltin oxide acts as a contact insecticide but the triphenyltin salts as stomach poisons. Their observation that the nature of the acid radical in the triphenyltin salts has a distince influence on the insecticidal activity is with Kubo's[67].

A limited series of organotin compounds was tested by Graves et al.[68] against larvae of the bollworm (*Heliothis zea*) and the tobacco bud worm (*Heliothis virescens*). On topical application the following LD_{50}'s were found: trimethyltin hydroxide and acetate about 0.2 µg/larva, tributyltin oxide and diethloctyltin acetate about 5µg/larva and triphenyltin hydroxide and acetate more than 10 µg/larva. A small but consistent difference in sensitivity was noted between insecticide resistant and susceptible strains. A few investigators examined only one compound, in most cases the commercially available tributyltin oxide. Richardson[69] tested tributyltin oxide in powdered biscuits against the larvae if the drug-store beetle (*Stegobium paniceum)* a close

relative to the common furniture beetle (*Anobium punctatum*). One tenth of a percent was sufficient in the long run to kill all larvae.

A compound of the type R_2SnX_2, the commercially available dibutyltin dilaurate (used both as a stabilizer in PVC and as an anthelmintic in poultry), has repeatedly been tested *in vivo* against end parasitic insect larvae in cattle. The larvae of the so-called heel files (*Hypoderma lineatum* and *H.bovis*), known as cattle grubs, live under the skin of cattle. After initial success, however , only negative results have been obtained[70]. An organotin compound of quite another type, viz. hexamethylditin, has recently been introduced as an agricultural insecticide under the trade-name *Pennsalt TD-5032*[71].

Organotin compounds in addition to a toxic effect can exert an antifeeding effect on insects. The antifeeding effect, which is probably based on taste, occurs at very low, sublethal concentrations. It has so far only been described for triphenyltin compounds. After its discovery in field tests in which triphenyltin hydroxide and acetate had been used as agricultural fungicides laboratory experiments have confirmed its existence. Ascher et al.[72] showed that leaves of sugar beet, sprayed with suspensions of triphenyltin acetate of increasing concentrations, were eaten to a decreasing extent by larvae of two kinds of moths. *Prodenia litura* and *Agortis ypsilon*. Protection of the leaves was about 90% at the 0.035% concentration. Further experiments against *P. litura* with triphenyltin hydroxide and acetate showed the latter to be superiorto the former. The results over the capable of quantitative treatment. The superiority of the acetate over the hydroxide was also borne out in experiments with larvae of the potato tuber moth (*Gnorimoschema operculella*) and the striped maize borer (*Chilo agamemnon*). No complete protection against these insects was obtained, however, even at the highest concentration employed (0.05%)[73]. In tests with larvae of the Colorado potato beetle (*leptinotarsa decemlineate*) Byrdy et al.[74] compared the antifeeding activity of a series of triphenyltin compounds. From experiments first with potato leaves and then with whole plants the methoxide, benzoate and acetate emerged as the most active. The antifeeding effect of triphenyltins on housefly larve was again investigated by Acher et al. Triphenlytin hydroxide and acetate were added to moistened wheat bran in concentrations of 10-40 mg/kg. At

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these concentrations, parallel to a moderate antifeeding effect, a toxic effect was observe for both compounds[75]. Also hexamethylditin has been found to possess anti feedant properties[76]. Triphenyltin acetate and chloride according to Kissam and Hays[77] were already quite toxic concentrations reuired for sterilizing house flies.

The mode of action of organotin compounds on insects is not known with certainty. Investigations by Pieper and Casida[78] on the inhibition of adenosine triphosphatases in the house fly, have revealed a correlation between potency for *in vitro* ATPase inhibition and toxicity of triorganotins. The authors suggest that the insectical activity of triorganotins may result from interference with ATPase activity of related processes confers resistance to organotin insecticides and acts as an intensifier of parathion reistance[79]. It has been shown that this gene acts by decreasing the rate of a absorption[80].

Singh et al.[81-89] have reported that the complex $Ph_3Sn(Sa-A-StH)$ is more toxic than other tin complexes. Tin complexes are more active than the parent salicyalanilide sulphathiazole ligand. Dimethyltin complexes are less active than their triphenyltin complexes.

Nematicidal activity

The facile synthesis and studies on the stereochemistry and biochemical aspects of some organosilicon (IV), organotin(IV) and manganese(II) complexes derived from imine having $N\cap N\cap O$ donor system have been cited[89]. These complexes are highly active against nematode (*Meloidogyne incognita*) and insect (*Trogoderma granarium*). These studies demonstrate that the nematicidal activity increased with increasing concentration and the concentrations reached levels which are sufficient to inhibit and kill the pathogens. The tin complexes show better activity than sulphonamide imines and bimolar metal complexes were highly active than unimolar metal complexes. It was also observed that triphenyl metal complexes in 1:1 molar ratio show better activity than diphenyl metal complexes. Knowledge of the mechanism of the action of compound is important from a purely scientific point of view which can be distinguished with three different methods by which complexes can exert their action.

➤ The effect of resonating structures such as benzene rings (in present case) may serve as powerhouse to activate potentially reactive groupings. If toxicity is

dependent on one or more chemical reactions, then any molecule which would increase the rate of chemical reactions must, perforce, enhance toxicity.

➤ The introduction of a lipophilic substituent, either aryl or alkyl, often conferred toxicity as did the substitution of polar groups.

➤ Complexes having amido groups or reactive halogen atoms tend to hydrolyse to form compounds, which have modified activity spectrum. The halogen replaced by hydroxyl ion and as a result of slight alkaline pH the increase in activity was observed.

The indirect nematostatic effects of nonfumigant nematicides resulting from impairment of neuromuscular activity[90], interfere with movement, feeding, invasion, development, reproduction, fecundity and hatching of nematodes are considered more important than their direct killing action and hence, much smaller amounts of non-fumigant than fumigant nematicides are needed in plant protection against nematodes.

Antifertility activity

With the ever growing world population, contraception is an important health issue for the 21st century. Fertility is an issue of global and national public issues concerning the rapid growth of the country. The total world population of this century, the rate of increase of the population was about 10 million per year. Now it is increasing at a much faster rate of 100 million per year. If the rate of increase remains continuous at the same pace, it is expected to reach 7 billion by the end of the present century. The rapid increase of population has got an adverse effect on the international economy and as the increase is only limited to the developing countries, the problem becomes an acute on the fruits of improvement in the different sectors, which are being eroded by the growing population. Moreover, increasing number of births has got a deleterious effect on the health of mother and child and hinders social and economic progress. The regulation of human fertility has global consequences in terms of resources depletion, population and poverty. Now, it has become one of the priorities of the National Family Programs and therefore, there is an urgent need to improve the access and the quality of contraceptive service in the country.

An ideal chemical contraceptive for male would be one which effectively arrests the production of sperms (spermatogenesis) or inhibits sperm fertilizing

capacity without altering libido, accessory sex organs and pituitary function and one which is easily administrable. The facts reported above are true in case of human beings. However, similar treatment is possible in case of animals. Since the present studies are related to the development of new pesticides, the experiments have been done on the rats and not on the human beings. The preliminary studies on rats are in positive direction and need further deep studies in the subject. Here the studies *in vivo* for one ligand and its silicon, tin and manganese complexes have been attempted and the obtained results have been described:

Diorganotin(IV) complexes of sulphonamide imine

Male rats exposed to ligand; SaH-A-StH (salicyl anilidesulphathiazole) and its tin complexes showed altered reproductive activity.

Body and organ weight

There were no significant differences in the body weight at the end of the experimental period away the treated groups as compared with control in TABLE 1. However, the weights of testes, epididymis, seminal vesicle and ventral prostate were decreased significantly in ligand ($P \leq 0.01$) and its various complexes ($P \leq 0.01$ to 0.001) as shown in TABLE 1.

Sperm dynamics and fertility

The sperm motility in cauda epididymis was decreased significantly in ligand ($P \leq 0.01$) and its complexes treated animals ($P \leq 0.001$) as shown in TABLE 2. Also, a significant decrease in sperm density in testes and cauda epididymis ($P \leq 0.01$ to 0.001) were observed in ligand and its various complexes treated rats.

Biochemical changes

Marked reductions ($P \leq 0.01$ to 0.001) in sialic acid and protein contents of testes, epididymis, ventral prostate, and seminal vesicle were observed in the ligand and its complexes treated animals when compared with control in TABLE 3. However, a sharp increase in tes-

TABLE 1 : Effects of ligand and its tin complexes on the body and reproductive organ weights of male rats

Comp.	Body weight (g) Initial	Body weight (g) Final	Testes	Epididymis	Seminal vesicle	Ventral prostate
			← mg / 100 g body weight →			
Control GroupA (SaH-A-St)	235.0 ± 15.0	245.0 ± 17.0	1350.0 ± 30.8	460.0 ± 13.0	505.0 ± 32.0	480.0 ± 21.0
GroupB	220.0 ± 17.0	230.0 ± 15.0	1210.0 ± 15.0^a	410.0 ± 10.0^a	422.0+15.0^a	400.0 ± 20.0^a
Me$_2$Sn (Sa-A-St) GroupC	227.0 ± 16.0	238.0 ± 15.0	1040.0 ± 19.0^b	280.0 ± 15.0^b	308.0 ± 16.0^b	310.0 ± 16.0^b
Ph$_2$Sn (Sa-A-St) GroupD	232.0 ± 14.0	239.0 ± 17.0	900.0 ± 30.0^b	250.0 ± 20.0^b	300.0 ± 17.0^b	290.0 ± 15.0^b
Ph$_3$Sn (Sa-A-StH) GroupE	228.0 ± 15.0	235.0 ± 16.0	870.0 ± 18.0^b	210.0 ± 21.0^b	285.0 ± 18.0^b	270.0 ± 17.0^b

TABLE 2 : Altered sperm dynamics and fertility after treatment with ligand and its tin complexes

Compound	Sperm motility cauda epididymis	Sperm density (million/ml) Testes	Sperm density (million/ml) Epididymis	Fertility test
Control Group A	70.0 ± 6.10	1.90 ± 0.20	51.0 ± 1.85	98.1 +ve
(SaH-A-StH) Group B	60.0 ± 3.0^a	1.08 ± 0.10^a	42.0 ± 1.70^a	65% -ve
Me$_2$Sn(Sa-A-St) Group C	38.0 ± 6.0^b	0.61 ± 0.18^b	25.0 ± 1.80^b	95% -ve
Ph$_2$Sn(Sa-A-St) Group D	35.0 ± 7.0^b	0.51 ± 0.20^b	22.0 ± 1.30^b	98% -ve
Ph$_3$Sn(Sa-A-StH) Group E	30.0 ± 7.1^b	0.35 ± 0.10^b	20.5 ± 1.60^b	100% -ve

Values are mean+SEM six determinations: a = P ≤ 0.01 ; b = P ≤ 0.001, Group A compared with Group B; Group C compared with Group B.; Groups D, E, F, G, H and I compared with Group B

TABLE 3 : Effects of ligand and its tin complexes on tissue biochemistry

Compound	Total protein (mg/g) Testes	Total protein (mg/g) Epididymis	Total protein (mg/g) Seminal vesicle	Total protein (mg/g) Ventral prostate	Siliac acid (mg/g) Testes	Siliac acid (mg/g) Epididymis	Siliac acid (mg/g) Seminal vesicle	Siliac acid (mg/g) Ventral prostate	Cholesterol (mg/g) testes	Fructose (mg/g) seminal vesicle	Phosphatases (mg/ip liberated/hr/mg tissue) Acid	Phosphatases (mg/ip liberated/hr/mg tissue) Alkaline
Control Group A	25.0±17.0	230.0±20.0	240.0 ±18.0	220.0 ±15.0	7.60±0.7	6.70±0.5	6.89±0.4	6.95±0.6	7.70±0.2	460.0±30.0	2.9±0.18	10.50±0.65
(SaH-A-StH) Group B	210.0±15.0^a	180.0±10.0^a	190.0 ±10.0^a	170.0 ±10.0^a	6.56±6.3^a	5.1±0.3^a	5.2±0.3^a	5.1±0.5^a	8.5±0.1^a	400.0±10.0^a	3.5±0.10^a	13.0±0.50^a
Me$_2$Sn(Sa-A-St) Group C	130.0±9.5^b	124.0±13.0^b	120.0 ±16.0^b	110.0 ±14.0^b	3.9±0.2^b	3.5±0.1^b	3.8±0.2^b	3.1±0.3^b	11.9±0.2^b	224.0±17.8^b	4.8±0.11^b	17.0±0.60^b
Ph$_2$Sn(Sa-A-St) Group D	125.0±9.7^b	120.0±14.0^b	117.0 ±17.0	108.0 ±18.0^b	3.5±0.1^b	3.4±0.2^b	3.5±0.3^b	3.0±0.3^b	12.1±0.3^b	200.0±13.0^b	4.7±0.12^b	17.1±0.65^b
Ph$_3$Sn(Sa-A-StH) Group E	110.0±5.0	107.0±6.0	108.0 ±7.0^b	100.0 ±17.0^b	3.0±0.5^b	3.1±0.6^b	3.8±0.5^b	3.2±0.3^b	12.5±0.8^b	180.0±15.0^b	5.0±0.90^b	18.0±0.90^b

Values are mean+SEM six determinations; a = P ≤ 0.01 ; b = P ≤ 0.001 Group A compared with Group B, Group C compared with Group B, Groups D, E, F, G, H and I compared with Group B.

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TABLE 4 : Blood analysis after treatment with salicylanilide-S-benzyldititithiocarbzate (Sal. BenzH$_2$)

Treatment	Total Erythrocyte count	Total Leukocyte Count	Hemoglobin (Hb)	Hematocrit (PCV)	Mean corpuscular volume (MCV)	Mean corpuscular Hemoglobin (MCH)	Mean corpuscular hemoglobin concentration (MCHC)	Blood urea
	Million / mm^3	per cu.mm	gm%	%	fl	Pg	%	mg/100ml
Control	5.1	8853.33	14.5	40.6	82.0	28.7	30.50	38.9
Group I	± 0.43	± 405.4	± 0.34	± 2.9	± 3.5	± 2.1	± 2.3	± 3.6
2mg/day for	4.87^{ns}	8770.0^{ns}	13.51^{ns}	37.5^{ns}	81.5^{ns}	24.0^{ns}	31.66^{ns}	42.4^{ns}
60 days Group II	± 0.80	± 460.01	± 0.41	± 1.5	± 3.66	± 2.2	± 0.57	± 4.02
4mg/day for	4.41^{ns}	8708.1^{ns}	14.29^{ns}	34.9^{ns}	87.1^{ns}	27.34^{ns}	31.9^{ns}	42.0^{ns}
60 days Group III	± 0.35	± 205.3	± 2.7	± 2.3	± 4.28	± 0.39	± 1.52	3.81
7mg/day for	4.2^{ns}	8450^{ns}	13.89^{ns}	43.2^{ns}	89.6^{ns}	25.5^{ns}	32.5^{ns}	40.9^{ns}
60 days Group IV	± 0.21	± 530.0	± 0.92	± 2.5	± 8.4	± 0.59	± 0.5	± 5.1

Mean+SEM of 6 animals: ns = non significant

TABLE 5: Blood analysis after treatment with (CH$_3$)$_3$Sn(Sal. Benz. H)

Treatment	Total Erythrocyte count	Total Leukocyte Count	Hemoglobin (Hb)	Hematocrit (PCV)	Mean corpuscular volume (MCV)	Mean corpuscular Hemoglobin(MCH)	Mean corpuscular Hemoglobin concentration (MCHC)	Blood urea
	million / mm^3	per cu.mm	gm%	%	fl	Pg	%	mg/100ml
Control	5.3	8013.1	13.8	43.9	79.89	25.9	30.26	35.84
Group I	± 0.14	± 402.1	± 0.08	± 0.47	± 4.6	± 1.23	± 1.9	± 3.7
2mg/day for 60	4.9^{ns}	7889.4^{ns}	11.7^{ns}	40.26^{ns}	87.2^{ns}	27.5^{ns}	31.2^{ns}	48.05^{ns}
days Group II	± 0.29	± 320.4	±0.65	±1.31	±4.1	± 3.0	± 3.1	± 2.31
4mg/day for 60	4.1*	8161.4^{ns}	11.3*	39.6*	83.3^{ns}	27.1^{ns}	32.9^{ns}	64.06*
days Group III	± 0.29	± 394.2	± 0.61	± 1.26	± 4.9	± 3.1	± 2.1	± 4.1

Mean+SEM of 6 animals: ns = non significant* = significant

ticular cholesterol, acid and alkaline phosphatase contents were observed in various treated groups. Seminal vesicular fructose contents were decreased significantly in TABLE 3.

Here, ligand and its complexes were adminstered to rats at the dose levels 9-50 mg/kg/day for 60 days which brought about marked alterations in the weights of testes, epididymis, seminal vesicle and ventral prostate. Significant decline in the testes weight may be due to the decrease in number of spermatogenic elements and spermatozoa. Reduction in weight of sex accessory organs directly support the reduced availability of androgens[91]. Suppression of gonadotropins might have caused decrease in sperm density in testes. Low candal epididymal sperm density may be due to alterations in androgen metabolism[92] and 65% to 100% negative fertility may be attributed to lack of forward progression and reduction in density of spermatozoa and altered biochemical millieu of cauda epididymis[93]. Decline in total protein concentration in testis and other accessory reproductive organs indicated suppressed androgen activity. Further, reduced contents of sialic acid in various reproductive organs reported herein suggest adverse effects on the metamorphosis and maturational stages of spermatid[94]. The rise in the testicular cholesterol contents due to various compounds treatment suggests suppressed androgen biosynthesis[95]. An increase in testicular acid and alkaline phosphatase activities indicate metabolic disturbance and impairement of the functional integrity of the testes.

Triorganotin(IV) complexes of hydrazinecarbo dithioic acids

No significant changes were noticed in the body weight after the treatment of ligand (Sal.Benz.H$_2$) and its complexes at 2 mg, 4 mg and 7 mg dose levels/per day for 60 days, similarly no significant changes were observed at 2 mg, and 4 mg dose level of (CH$_3$)$_3$Sn (Sal.Benz.H)and (C$_6$H$_5$)$_3$Sn(Sal.Benz.H) in the body weight of rats, when compared with their initial body weight. Oral administration of ligand and complexes caused significant reduction (P ≤ 0.01) in the weight of testes and accessory sex organs whereas no changes were observed in the weight of kidney and adrenal glands. Sperm motility of cauda epididymides and sperm density of the testes and cauda epididymides was decreased significantly (P ≤ 0.001) in rats treated with ligand and its complexes at all the dose levels. 40 to 65 percent negative fertility was observed at different dose levels of ligand and its various complexes.

Total erythrocyte count (TEC), total leukocyte count (TLC), hemoglobin concentration, hematocrit and blood urea values were in normal range after ligand treatment, whereas tin complexes (CH$_3$)$_3$Sn(Sal.

TABLE 6 : Blood analysis after treatment with $(C_6H_5)_3Sn(Sal.Benz.H)$

Treatment	Total Erythrocyte count (million / mm^3)	Total Leukocyte Count (Per cu.mm)	Hemoglobin (Hb) (gm%)	Hematocrit (PCV) (%)	Mean corpuscular volume (MCV) (fl)	Mean corpuscular hemoglobin (MCH) (Pg)	Mean corpuscular hemoglobin concentration (MCHC) (%)	Blood urea (mg/100ml)
Control Group I	5.23 ± 0.25	8086.3 ± 303.32	14.1 ± 0.13	47.6 ± 1.76	82.0 ± 5.5	29.2 ± 2.10	30.29 ± 2.3	39.0 ± 6.1
2mg/day for 60 days Group II	4.3^{ns} ± 0.65	8280.0^{ns} ± 406.20	12.6^{ns} ±0.95	38.5^{ns} ±4.7	84.5^{ns} ±3.5	25.2^{ns} ± 2.1	31.66^{ns} ± 1.52	42.2^{ns} ± 4.0
4mg/day for 60 days Group III	3.9* ± 0.16	9210.0^{ns} ± 393.80	11.2* ± 0.77	36.5* ± 2.5	81.0^{ns} ± 4.2	27.3^{ns} ± 0.3	32.9^{ns} ± 1.5	67.1* ± 3.8

Mean+SEM of 6 animals ns = non significant ,* = significant

TABLE 7: Tissue biochemistry after treatment with salicylanilide-S-benzyldititthiocarbzate (Sal. BenzH$_2$)

Treatment	Cholesterol Testes	Cholesterol Liver	Glycogen Testes	Glycogen Liver	Protein Testes	Protein Epididy-mides	Protein Seminal vesicle	Protein Prostate gland	Sialic acid Testes	Sialic acid Epididy-mides	Sialic acid Seminal Vesicle	Sialic acid Prostate gland
Control Group I	10.13 ± 0.27	15.96 ± 0.18	2.58 ± 0.13	6.90 ± 0.39	192.4 ± 7.6	208.00 ± 6.7	204.7 ± 5.8	170.0 ± 6.7	5.3 ± 0.10	4.8 ±.0.40	5.4 ± 0.4	5.27 ± 0.30
2mg/day for 60 days Group II	10.09^{ns} ± 0.3	15.4^{ns} ± 2.01	2.47^{ns} ± 0.10	6.03^{ns} ± 0.8	164.0^{ns} ± 5.5	199.6^{ns} ± 8.0	197.6^{ns} ± 4.7	163.3^{ns} ± 6.1	5.0^{ns} ± 0.20	4.2^{ns} ± 0.26	4.78^{ns} ± 1.5	4.91^{ns} ± 1.2
4mg/day for 60 days Group III	9.16* ± 0.05	15.39^{ns} ± 0.26	2.11* ± 0.08	5.65^{ns} ± 2.3	148.1* ± 7.2	180.1* ± 4.6	180.5* ± 4.9	140.1* ± 6.0	4.9^{ns} ± 0.3	4.06^{ns} ± 0.7	4.05^{ns} ± 0.40	4.2^{ns} ± 0.09
7mg/day for 60 days Group IV	8.8* ± 0.02	14.91^{ns} ± 0.44	2.01* ± 0.14	5.10^{ns} ± 2.2	113.1* ± 15.3	145.6* ± 14.09	168.6* ± 8.3	127.2* ± 10.2	4.0* ± 0.30	3.5* ± 0.22	3.9* ± 0.02	3.64* ± 0.2

(Mean ± SEM of 6 animals): ns = Non significant, * = P≤ 0.01 – significant, ** = P ≤ 0.001 – Highly significant

TABLE 8 : Tissue biochemistry after treatment with $(CH_3)_3$ Sn(Sal. Benz. H)

Treatment	Cholesterol Testes	Cholesterol Liver	Glycogen Testes	Glycogen Liver	Protein Testes	Protein Epididy-mides	Protein Seminal vesicle	Protein Prostate gland	Sialic acid Testes	Sialic acid Epididy-mides	Sialic acid Seminal vesicle	Sialic acid Prostate gland
Control Group I	11.13 ± 0.37	16.59 ± 0.18	2.53 ± 0.13	6.29 ± 0.39	199.57 ± 12.0	240.0 ± 11.11	214.2 ± 7.4	180.1 ± 13.9	5.02 ± 0.06	5.94 ± 0.07	4.86 ± 0.09	4.6 ± 0.15
2mg/day for 60 days Group II	9.06* ± 0.3	16.02^{ns} ± 0.29	1.19** ± 0.19	5.91^{ns} ± 0.19	158.0* ± 4.2	190.8* ± 5.4	182.01* ± 6.6	111.0* ± 10.3	3.82** ± 0.13	4.79* ± 0.2	3.9** ± 0.05	3.5** ± 0.04
4mg/day for 60 days Group III	6.7** ± 0.82	14.26* ± 0.44	1.11** ± 0.02	4.56* ± 0.09	136.1** ±5.9	160.0** ± 10.9	138.0** ± 11.8	106.31** ± 5.0	3.67** ± 0.05	4.18** ± 0.19	3.58** ± 0.04	3.30** ± 0.07

(Mean ± SEM of 6 animals): ns = Non significant, * = P≤ 0.01 – significant, = P ≤ 0.001 – Highly significant**

TABLE 9 : Tissue biochemistry after treatment with $(C_6H_5)_3Sn(Sal.Benz.H)$

Treatment	Cholesterol Testes	Cholesterol Liver	Glycogen Testes	Glycogen Liver	Protein Testes	Protein Epididy-mides	Protein Seminal vesicle	Protein Prostate gland	Sialic acid Testes	Sialic acid Epididy-mides	Sialic acid Seminal Vesicle	Sialic acid Prostate gland
Control Group I	9.81 ± 0.50	16.59 ± 0.4	2.69 ± 0.22	4.66 ± 0.57	209.2 ± 14.3	220.0 ± 15.12	161.1 ± 8.19	198.4 ± 13.18	5.16 ± 0.05	5.7 ± 0.18	5.3 ± 0.01	4.96 ± 0.06
2mg/day for 60 days Group II	4.9* ± 1.2	16.9^{ns} ± 0.18	1.59** ± 0.05	3.85^{ns} ± 0.02	118.09** ± 9.17	128.1** ± 7.9	107.6* ± 11.17	110.8** ± 5.2	2.80** ± 0.03	4.54** ± 0.07	4.02** ± 0.03	4.36** ± 0.02
4mg/day for 60 days Group III	3.6** ± 0.17	15.34* ± 0.2	1.32** ± 0.07	3.23* ± 0.2	105.0** ± 10.0	113.7** ± 9.4	97.02** ± 9.8	100.0** ± 9.9	2.72** ± 0.02	4.26** ± 0.09	3.04** ± 0.2	4.17** ± 0.06

(Mean ± SEM of 6 animals): ns = Non significant, * = P≤ 0.01 – significant, ** = P ≤ 0.001 – Highly significant

Benz.H) and $(C_6H_5)_5Sn(Sal.Benz.H)$ showed increased values in total leukocyte(TLC), and blood urea. No change was observed in total erythrocyte count (TEC), hemoglobin concentration and hematocrit at all the dose levels (TABLES 4-6). Total protein contents and sialic acid concentration of testes and accessory sex organs were significantly reduced after the ligand and its complexes. Administration reduced level of testicular glycogen and cholesterol were noticed following the administration of the ligand and its tin complexes at all dose levels (TABLES 7-9). Histopathology of testes treated with different doses exhibited drastic changes.

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TABLE 10: Effects of various compounds of sperm dynamics and fertility of male rats

Compound	Sperm motility (%) (Cauda epididymis)	Sperm density		Fertility test
		Testes	Cauda epididymis	
Vehicle alone (olive oil)	78.5 ± 4.8	4.3 ± 0.42	61.1 ± 4.8	100% Positive
L^2H	42.5 ± 3.5^b	2.4 ± 0.10^b	49.5 ± 3.5^b	80% Negative
$Ph_2Sn[L^2]_2$	34.0 ± 4.8^a	1.2 ± 0.12^c	30.0 ± 3.2^c	95% Negative
$Ph_2Sn[L^2]Cl$	38.0 ± 3.6^b	1.6 ± 0.14^c	$33.6 \pm 5.5b$	91% Negative
$Ph_3Sn[L]$	35.0 ± 4.2^c	1.3 ± 0.18^b	31.4 ± 6.1^c	92% Negative

Values are expressed as mean $\pm$ S.E., $^a p < 0.001$, $^b p < 0.01$, $^c p < 0.02$, $^d p < 0.05$

Most of the tubules showed more or less spermatogenic arrest. However, the damage was not uniform. Residual sperms and the cell debris were present in the lumen of some tubules. Interstitial stroma had slight atrophy and nacrotic nuclei. The epididymis showed normal epithelium. The intertubular stroma appeared to be degenerated. The lumen was having less number of sperm.

Organotin derivatives of benzothiazoline

The results of experiments (TABLE 11) with benzo thiozoline derivatives may also be correlated with the well-known fact that sulphur-containing compounds produce infertility in male rats[96] Thus it can be postulated that chelation through sulphur atoms induces the sterilizing activity in the biological systems.

Biocidal activity

A system investigation on the antifungal activity of organotin compounds was started in 1950 at the Institute for Organic Chemistry TNO, Utrecht, the Netherlands. Van der Kerk and Luijten soon found that among organotin compounds of the several possible types.

R_4Sn R_3SnX R_2SnX_2 $RSnX_3$
(R= hydrocarbon radical; X= anionic group); (Some representatives of the type R_3SnX possessed a high fungitoxicity)

Initially tests were carried out with series tetraethyltin, triethyltin chloride, diethyltin dichloride and ethyltin trichloride. Only triethyltin chloride inhibited the growth of test fungi at concentrations below 10mg/l. Variation of the acid radical had only a minor influence on the activity of triethyltin salts. Subsequent examination of a series of tri-n-alkyltin acetates, on the other

TABLE 11 : Antifungal activity of some triorganotin acetates

	Minimal concentration in mg/1 causing complete inhibition of growth of the fungi				
$R_3SnOCOCH_3R$	*Botryits allii*	*Penicillium italicum*	*A. niger*	*T. nigricans*	Refs.
CH_3	200	500	200	500	[99]
C_2H_5	1	10	2	2	[99]
$n\text{-}C_3H_7$	0.5	0.5	0.5	0.5	[99]
$n\text{-}C_4H_7$	0.1	0.5	1	1	[99]
$n\text{-}C_4H_9$	0.5	0.5	1	1	[99]
$i\text{-}C_4H_9$	1	1	10	1	[99]
$n\text{-}C_5H_{11}$	5	2	5	5	[99]
Cyclo- C_5H_9	0.5	0.5	5	0.5	[100]
$n\text{-}C_6H_{13}$	500	500	500	500	[110]
Cyclo- C_6H_{11}	20	20	50	20	[239]
C_6H_5	10	1	0.5	5	[147]

hands, showed a considerable influence of the length of the alkyl groups (TABLE 11). The data given in this TABLE differ somewhat from those given in the original publication. They were obtained in later, careful testing using a prolonged incubation time and a richer vulture medium. The most active compounds in the series of tri-n-alkyltin acetates were tripropyl-and tributyltin aceate. They inhibited the growth of the test fungi at concentrations of 1 mg/l or lower[97].

Experiments with unsymmetrical trialkyltin acetates, i.e., compounds in which the tin atom bore mutually different alkyl groups, revealed that not the nature of the individual groups, but the total number of carbon atmos in the three groups was decisive. Dimethyloctyltin acetate, for example, had the same high activity as tripropyltin aceate, whereas both trimethyl tin acetate and trioctyltin acetate had a low activity. For a high antifungal activity the total number of carbon atoms in the alkyl groups of a trialkyltin compound should be about 9-12[98].

In addition to the tri-n-alkyltin acetates, numerous other triorganotin acetates were tested for antifungal activity. Triisoalkyltin acetates had an activity which was comparable to that of the normal isomers[99]. Tricyclo pentyl- and tricyclohexyltin acetate, however, were more active than the n-alkyl derivatives[100]. Triphenyltin acetate had about the same activity as triethylting acetate. Tri-m-tolyl-and tri-p-tolytin acetate different little from triphenyltin acetate but tribenzyl- and tris (2-phenylethyl) tin acetate were somewhat less active. Tri-α-naphthyltin acetate, probably because of its low solubility, did not show any antifungal activity[101].

When, through the addition reactions of organotin hydrides to olefins functionally substituted organotin

compounds became available, a number of then, both of the type R_4Sn and R_3EnX, were tested for antifungal activity. It turned out, however, that in no case did a functionally substituted compound has a higher activity than a comparable unsubstituted compound. On the contrary, in most cases the introduction of a functional group severely reduced antifungal activity, especially, hydrophilic groups had an adverse effect[102].

No active compounds were ever found among the types R_4Sn, R_2SnX_2, and $RSnX_3$ in spite of careful screening. The sole exception is diphenyltin dichloride which inhibits the growth of the fungi mentioned in TABLE 1 at concentrations of 10-20mg/1[103]. In a few cases in which a compound of the type R_4Sn showed some activity, either a compound of the R_2SnX was present as an impurity or an easy cleaveage of one of the R groups probably occurred. An example of the latter is tributyl (cyanomethyl) tin which easily loses the cyanomethyl group under hydrolytic circumstances[102].

Several other groups of workers have studied the antifungal properties of organotin. Independent research on simple alkyl- and aryltin compounds with a practical aim has been carried out by Baumann[104] and Hartel [105,106] at Farbwerks Hoechst, Frankfort, Germany. This work has led to the triphenyltin acetate. Other workers have extended the above results. In most cases the influences of varying the acid radical in triorganotin salts was studied[11,12]. Results at variance with the rules formulated above were only obtained when compounds with highly fungitoxic acid radicals were tested[107,108].

The action of the organotin compounds at the low concentrations employed in the tests in fungistatic rather than fungicidal. The mode of action of the organotin compounds is still not understood, although it has been suggested[99,103] that inhibition of oxidative phosphorylation in the case of the trialkyltin compounds may be the cause of the observed inhibition of fungal growth. The differences in activity among the several trialkyltin compounds might then be attributed both to differences in intrinsic activity on the enzyme system and to differences in permeability into the cells. Permeability in its turn may be dependent on the partition coefficient of the organotin compounds between water and lipids.

Antibacterial tests with organotin compounds have been carried out by Kaars Sijpesteijn[109,110]. Organotin compounds are, in general, much more active towards Gram-positive bacteria like *Bacillus subtilis*, *Micobac-*

terium phlei and *Streptococcus lactis* than towards gram-negative ones like *Escherichia coli* and *Pseudomons fluorescens*. The most active compounds, inhibiting growth of the gram-positive species at 0.1-5 mg/1, again belong to the type R_3SnX. Among the trialkyltin acetates maximal activity is associated with the propy1 and buty compounds, although tripentyltin acetate is still, highly active against *Mycobacterium phlei*. Triphenyltin acetate is as active as the most active trialkyltin acetates.

It is remarkable that, for the gram-negative bacteria, triehyl-and tripropyltin aceate are the most active trialkyltin acetates. They inhibit their growth at 20-50mg1. Dipropy1-, and dipentyltin dichloride have no antifungal properties, but they inhibit the growth of gram-positive bacteria at a concentration of 20-50 mg/1.

Trialkyltin compounds have also been tested against pathogenic bacteria, notably *staphylococcus aureus* (Gram-positive) and some *Pseudomonas species* (Gram-negative). The results[111,112] confirm the trends signalized above.

As to the mode of action of the organotin compounds against bacteria, the same remarks can be made as in the case of their action against fungi. It is supposed[103,111] that the triorganotin compounds act by their inhibition on enzymes containing thiol groups. Evidence for the latter has recently been presented.

The fungicidal activity of the ligand hydrazine carbothioamide and its tin complexes have been reported[81,83]. The need for further study and research in the field of chemotherapy has been felt with a view to develop more and more drugs with high efficacy against variety of pathogens. Besides, investigations into the *modus operandi* of existing drugs have also been carried out to facilitate the study of microbiology. The exclusive characteristics of non-transition and transition metal chelates with their applications in multispheres have opened new vistas in the field of inorganic biochemistry. We have reported[81-89] some derivatives of tin(IV) with biologically active ligands such as sulphonamide imine and study their activity *in vitro* as well as *in vivo* against a number of pathogenic fungi and bacteria The results show that the activity is enhanced on undergoing chelation. It is a well known fact that the concentration plays a vital role in increasing the degree of inhibition. As the concentration increases, the activity increased. The fungicidal activity was better as compared to the

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bactericidal activity

Future prospects

The importance of ligands in modifying the biological effects of metal based drugs can not be overestimated. Ligands can modify the oral systemic bio availability of metal ions, can assist the targeting specific tissues or enzymes and can deliver, protect or sequester a particular metal ion, depending on the requirements, for the therapy and diagnosis. To summarize, we can state that several organotin compounds exhibit rather promising *in vivo* and *in vitro* nematicidal, insecticidal and antifertility activity. However, more work has to be done on the synthesis and testing of organotin molecules that might become useful nematicidal, insecticidal and antifertility agents in future.

ACKNOWLEDGMENT

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