Review

Applied Organometallic Chemistry

Received: 18 November 2007 Revised: 12 December 2007 Accepted: 12 December 2007 Published online in Wiley Interscience:

(www.interscience.com) DOI 10.1002/aoc.1378

Antimicrobial activity of organotin(IV) compounds: a review

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A comprehensive review on antimicrobial activity of organotin(IV) compounds is presented.

Keywords: organotin(IV) compounds; antimicrobial activity

Introduction

The use of organotin(IV) compounds in industry has risen dramatically over the years as a result of their wide range of biocidal and industrial applications.[1] However, environmental concerns have caused restrictions in their usage in some instances. Particular attention in this regard has been given to the tri-*n*-butyltin(IV) compounds which are very effective molluscicides and are used in some antifouling paints used for ships. However, serious effects on commercial oyster beds have resulted in their being banned in some jurisdictions. Initially, it was believed that the various toxic organotin(IV) compounds would eventually oxidize to tin(IV) oxide, which would be environmentally benign, but it was discovered that tin(IV) oxide in marine sediments could be methylated by bacterial action, causing the return of organotins to the marine environment. The large-scale usage of organotin(IV) compounds in industry and as biocides has come under increasing scrutiny. However, these macro-scale environmental concerns are probably less serious when considering the antimicrobial uses of organotin(IV) compounds.

The toxicology of organotin(IV) compounds is very complex and has been extensively studied, but, a general pattern does emerge. Tri-substituted alkyl and aryltin(IV) compounds (TOT) are more toxic than di-substituted organotin(IV) compounds (DOT), while mono-substituted organotin(IV) compounds (MOT) are still less toxic. R_4Sn compounds are toxic only if they are metabolized to TOT. Among tri-substituted organotin(IV) compounds *n*-propyl-, *n*-butyl-, *n*-pentyl-, phenyl- and *cyclo*hexyltin(IV) compounds are generally the most toxic to microorganisms. Toxicology data are reported in Smith.[2] Knowledge of the biological chemistry of tin is needed for the rational development of more effective compounds and newer uses. Consequently there has been a growth in the number of publications on the biological effects of tin compounds, including reviews on general aspects,[1,3–6] environmental problems[7–10] and biochemistry and toxicology.[11–13] Toxicity in the R_3Sn series is related to total molecular surface area of the tin compound and to the octanol : water partition coefficient, K_{ow}, which is a measure of hydrophobicity; a high K_{ow} indicates greater hydrophobicity and predicts greater toxicity.[14] Care must be taken when testing the toxicity of tin compounds, for a number of biological, physical and chemical factors can influence the apparent toxicity. Although little is known of the effects of tin compounds on microbial processes, a number of bacterial processes can be inhibited by organotin(IV) compounds and all relate to membrane functions. They include effects on energy transduction, solute transport, retention and oxidation of substrates.[14] Virtually nothing is known of the action of tin compounds on microbial enzymes, but resistant mutants are easy to obtain and should facilitate work to understand modes of microbial interaction with tin compounds and mechanisms of resistance.

This review is particularly concerned with the antimicrobial activity of organotin(IV) compounds. It is impossible to give here a complete picture of the field since an appreciable part of the required information can be traced only from the patent literature. However, an attempt has been made to give the reader some insight into the subject and to enable him or her to consult appropriate sources for future information.

Antimicrobial Activity of Organotin(IV) Compounds of Schiff Bases

A considerable amount of attention has been given to the antimicrobial activity of organotin(IV) Schiff base complexes and brief descriptions of these studies in the form of reviews are available.[15,16] Saxena *et al.*[17] investigated some organotin(IV) (2-fluorobenzaldehyde)-*S*-benzyldithiocarbazates, which showed potential activity at low doses on axenically grown *Entamoeba histolytica trophozoities*, and the compound tri-*n*-butyltin(2-fluorobenzaldehyde)-*S*-benzyldithiocarbazate showed remarkable activity at extremely low doses even after 48 h. A preliminary screening of organotin(IV) complexes of monofunctional bidentate (**1**–**3**) or bi-functional tridentate (**4**) Schiff bases indicated that none of the complexes or ligands is active against Gram-negative bacteria, whereas all the complexes show marked activity against Gram-positive bacteria as compared with their ligands.[18] Organotin(IV) complexes of tetradentate *bis*(salicylaldehyde)ethylenediimine (**5**; R = ^{n}Bu, Bz) exhibited some antibacterial activity and little or no antifungal activity.[19]

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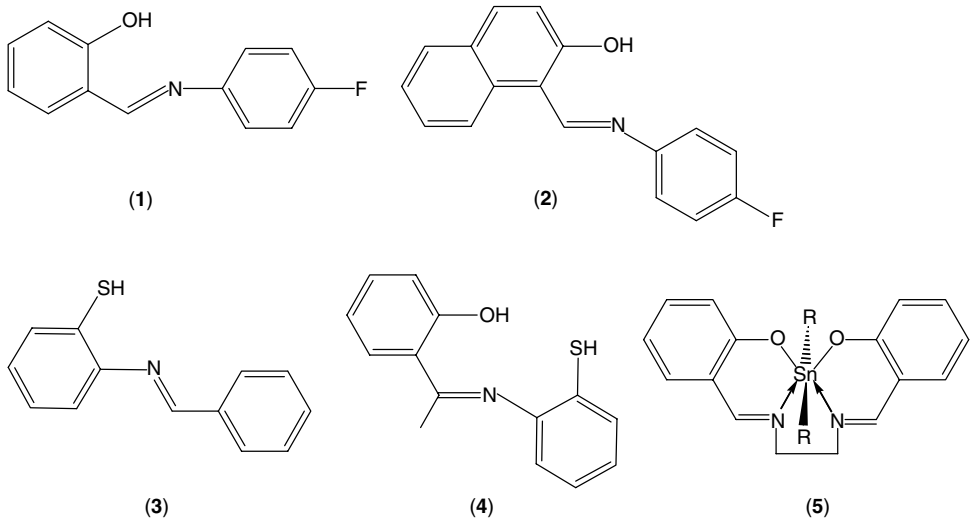


Figure 1. Structures of various Schiff bases derived from substituted anilines (**1**–**4**) used for the synthesis of a variety of organotin(IV) complexes and a diorganotin(IV) complex of the tetradentate Schiff base (**5**).

Schiff bases derived from 2-amino-4-phenylthiazole and aldehydes (**6**; R =phenyl, 4-methoxyphenyl, 2-hydroxyphenyl, 2-hydroxynaphthyl) yielded complexes of the type $R'_nSnCl_{4-n}\cdot L$ (R′ = Me or Ph). The inhibitory effects were greater in the diorganotin(IV) complexes of the tetradentate Schiff base (**5**) than in the ligands when screened against *Escherichia coli, Bacillus subtilis, Salmonella typhi* and others.[20] The bactericidal and fungicidal activities of the organotin(IV) complexes under experimental conditions decreased in the order: trimethyltin > triphenyltin > diphenyltin, but all were higher than those of the ligands.[20]

In addition, tests of the antimicrobial activity of di- and triorganotin(IV) complexes of thiosemicarbazide[21,22] and 2-amino-5-(*o*-anisyl)-1,3,4-thiadiazole[15] with different imines (similar to **6**) were also carried out against *Streptococcus faecalis, Klebisiella pneumoniae, Escherichia coli, Pseudomonas aeruginosa, Staphylococcus aureus, Penicillin resistance, Candida albicans, Cryptococcus neoformans, Sporotrichum schenkii, Trichophyton mentagrophytes* and *Aspergillus fumigatus*.[15,21,22] This group of complexes has shown remarkable antifungal and antibacterial activities which are higher than those of the Schiff bases. Organotin(IV) complexes of extended systems derived from the condensation of 2-amino-5-(*o*-anisyl)-1,3,4-thiadiazole with salicylaldehyde (**7**), 2-hydroxynaphthaldehyde (**8**) and 2-hydroxyacetophenone (**9**), were also screened *in vitro* against the same panel of bacteria and fungi.[23,24] A series of di-*n*-butyltin(IV) complexes of amino acid Schiff bases (**10**–**12**) (R = alkyl or alkyl-aryl linkages) were also screened against various bacteria and fungi.[25] All the complexes exhibited moderate to good bactericidal and fungicidal activities compared with $^nBu_2SnO$. Furthermore, di-*n*-butyltin(IV) complexes of **10** having the naphthyl skeleton displayed greater activity than those of complexes with **11** in which the Schiff bases are derived from acetyl acetone. On the other hand, di- and triphenyltin(IV) complexes of **10** and **12** exhibited varying degrees of inhibitory effects on the growth of a wide spectrum of bacteria and fungi *in vitro*.[26] The inhibitory effects of the complexes were found to be somewhat greater than those of the parent organotin(IV) compounds. In general, the bactericidal and fungicidal

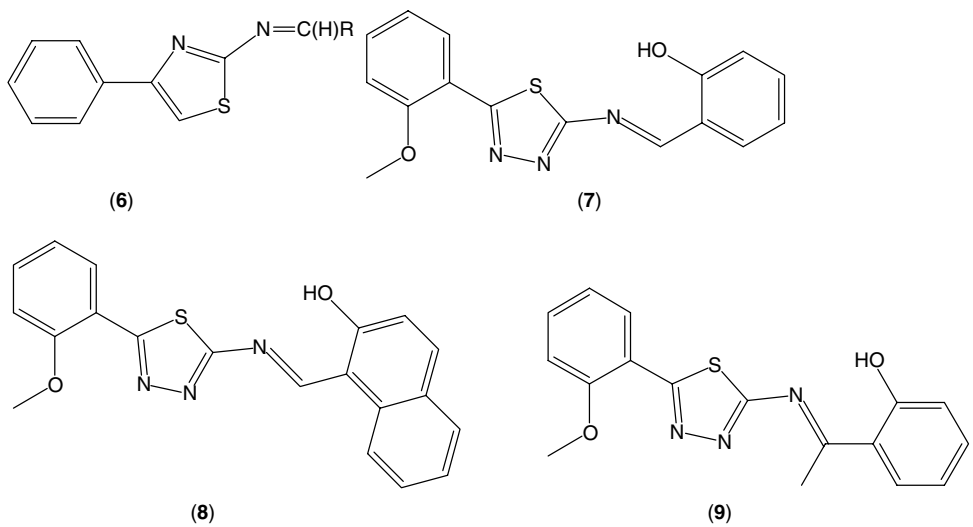


Figure 2. Structures of various Schiff bases derived from 2-aminoarylthiadiazoles (**6**–**9**) used for the synthesis of organotin(IV) complexes.

activities of the triphenyltin(IV) complexes were higher than those of the diphenyltin(IV) complexes.

$^{n}Bu_2Sn(L)_2$ and $^{n}Bu_3SnL$ complexes (L = monoanion of Schiff bases of *S*-benzyldithiocarbazate) were also screened for their antibacterial activities and several of them were found to be quite active.[27] A handful of organotin(IV) complexes of compositions R_3SnL, R_2SnClL and R_2SnL_2 (R = Me, Ph; L = 1-acetylferrocenethiosemicarbazone, **13**) were also subjected to screening for antimicrobial activity.[28] The activity of the ligand was appreciably enhanced on complexation with organotins and this activity could be correlated with chelation theory.[29] The triorganotin(IV) compounds were found to possess higher activity than their diorganotin(IV) counterparts. The complexes were more toxic towards Gram-positive bacteria than Gram-negative bacteria and this has been attributed to differences in the structures of the cell walls.

A more recent investigation of the organotin(IV) complexes of a biologically potent Schiff base ligand 2-acetylfuran-sulfaguanidine (**14**) is described.[30] Organotin(IV) complexes of the type R_3SnL, R_2SnL_2 and R_2SnClL (R = Me or Ph) were more toxic towards the Gram-positive bacteria than the Gram-negative bacteria, as observed for organotin(IV) complexes of **13.**[28] Further, the authors compared the results of the biological activity with a conventional fungicide, *Bavistin*, and a conventional bactericide, *Streptomycin*. A direct relation between the activity and the coordination environment of the tin atom was noted. The six-coordinated tin displayed better results than the five-coordinated tin complex. The compound containing a halogen atom attached directly to the tin atom also showed moderate activity. In general, all the compounds were found to be more active against all the organisms used than the ligand alone. The mode of action of these compounds has been described in terms of hydrogen bonding with the active centres of the cell constituents resulting in an interference with normal cell processes. Since the organotin(IV) complexes inhibited the growth of microorganisms, it has been assumed that the production of an enzyme is being affected; hence, the organisms were less able to metabolize nutrients and, consequently, growth ceased. Those enzymes that require free sulfydryl groups (-SH) for activity, appear to be especially susceptible to deactivation by ions of the complexes.

Antimicrobial Activity of Organotin(IV) Compounds of Amino Acids and Dipeptides

The organotin(IV) derivatives of the amino acids have been of interest as possible biocides[31–33] and as intermediates in peptide synthesis.[34,35] Tri*cyclo*hexyltin(IV) alaninate has been found to be active as a fungicide and bactericide for seeds and plants.[36] Organotin(IV) complexes of amino acids[37–39] of the type R_3SnL and R_2SnL_2 (R = Me, Ph or ^{n}Bu, L = anion of various amino acids) were found to be active against a wide spectrum of bacteria and fungi. In general, organotin(IV) complexes of amino acid derivatives exhibited good activities in comparison with the parent organotin(IV) precursors. The order of the fungicidal and bactericidal activities of these compounds is: triphenyl > diphenyl > di-*n*-butyl > trimethyltin(IV) complexes. Because of the high antifungal activities of the Ph_3Sn derivatives of a few amino acids, $^{n}Bu_2Sn$(*l*-Tyr) and Ph_2Sn(*dl*-Asp) have been screened *in vivo* against a multi-infection fungal model in mice.[36–38] The compounds were tested at 100 and 50 mg kg^{-1}, for 4 days, and proved to be highly toxic at 100 mg kg^{-1}, as most of the animals died during the experimental period, and they did not show promising activity, but both of the compounds were active[37–39] at a dose of 50 mg kg^{-1}.

A large number of organotin(IV) complexes of compositions $Ph_3SnL{\cdot}bipy$ and $Me_2SnLCl{\cdot}bipy$ (L = anion of amino acid, e.g. tyrosine or phenylalanine) have been screened against a number of fungi and bacteria to assess their growth inhibition potential.[40] The antimicrobial screening results were compared with the conventional fungicides, *Bavistin*, and a conventional bactericide, *Streptomycin*. The complexes show greater antimicrobial activity as compared with the starting materials. The complexes containing a halogen atom directly coordinated to the metal atom showed

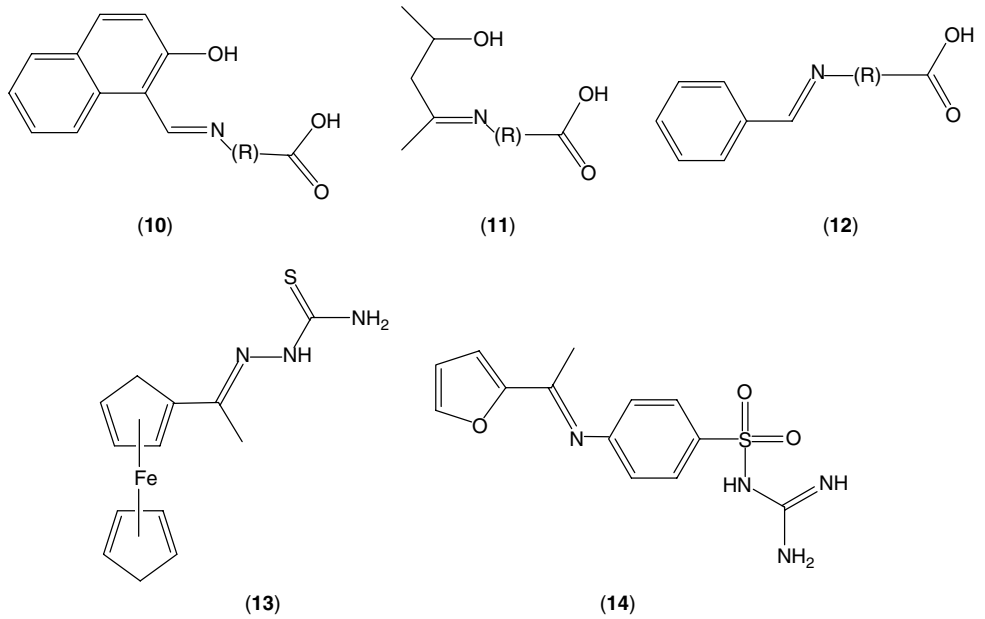


Figure 3. Structures of various Schiff bases derived from amino acids (**10–12**), 1-acetylferrocene (**13**) and sulfaguanidine (**14**) used for the synthesis of organotin(IV) complexes.

moderate activity. The mode of action of these compounds was associated with the formation of a hydrogen bond with the active centres of the cell constituents, thereby interfering with normal cell processes.

Recently, the antimicrobial and antiinflammatory activities of R_2SnL (R = ^{n}Bu and Ph; L = Ala–Phe, Phe–Leu, Phe–Phe, Gly–Leu and Gly–Ile) have been reported by Nath *et al*.[41] The minimum inhibitory concentration (MIC, in μg ml^{-1}) values indicated that the di-*n*-butyltin(IV) complexes are more active than $^nBu_2SnO$ whereas the diphenyltin(IV) derivatives are less active than Ph_2SnCl_2, except Ph_2Sn(Gly–Ile), against *Pseudomonas putida* and *Verticillium dahliae* and Ph_2Sn(Ph–Leu) against *Auerobasidium pullulans*. The relationship between the activity and the nature of the substituents present in the dipeptide chain has also been discussed.[41] Further, it has been reported that the toxicity of the diorganotin(IV) dipeptides is much lower than those of the di- and tri-organotin(IV) derivatives of the amino acids,[37,38] indicating that the bigger biomolecules lower the toxicity but enhance the activity of the resulting organotin(IV) complexes. Systematic efforts were also made for synthesizing and studying the antimicrobial activities of triorganotin(IV) complexes of dipeptides containing *N*-terminal glycine residues.[42] The complexes of the type R_3Sn(HL) (R = Me, ^{n}Bu or Ph; HL = monoanion of Gly–Gly, Gly–Val, Gly–Leu, Gly–Trp and Gly–Tyr) were screened for their *in vitro* antimicrobial activity against *Staphylococcus aureus* Mau, *Bacillus subtilis, Escherichia coli, Candida albicans* and *Microsporum gypseum* and *Euglena gracillis*. Most of the compounds displayed appreciable antibacterial activity but showed no antifungal activity when compared with *ampicillin* and *norfloxacin* and, in particular, Ph_3Sn(Gly–Gly) and Ph_3Sn(Gly–Val) were the most active compounds. The change in the organic residue in the side chain at the methylene carbon adjacent to C (carboxyl) has little influence on the activity, and the presence of a bulky group, viz., imidazole, at methylene carbon lowers the activity considerably.

Antimicrobial Activity of Other Organotin(IV) Compounds

In the previous two sections, particular emphasis was given to the antimicrobial activities of Schiff bases and, amino acids and dipeptides. The present section deals with the antimicrobial activities of organotin(IV) compounds of various ligands which are not covered earlier.

Kupchik *et al*.[43] studied the fungicidal activity of *N*-Substituted *N*-(triphenylstannyl)cyanamides (**15**) and found them to be better antifungal agents than the previously tested *N*-substituted *N*′-cyano-S-(triphenylstannyl)isothioureas (**16**) and *N*-substituted *N*′-cyano-*O*-(triphenylstannyl)isoureas (**17**; R = Ph, *cyclo*Hexyl). They were similar in activity to the previously tested ethyl *N*-aryl-*S*-(triphenylstannyl)isothiocarbamates (**18**). The antifungal activity of triethylammonium (organocyanoamino)chlorotriphenylstannates (**19**), which are the triethylammonium chloride complexes of (**15**), was similar to or better than that of **15**.[43] Although they inhibited Gram-positive bacteria, they showed little inhibitory activity toward Gram-negative bacteria. As compounds **19**, which are the triethylammonium chloride complexes of **15**, exhibited higher antifungal activity than the compounds **15**,[43] the authors further investigated the triethylammonium chloride complexes of **17**, i.e. **20**.[44] Indeed, the compounds (**20**; R = Et, *cyclo*hexyl, Ph, *p*-fluoro Ph) exhibited higher antifungal and antibacterial activity than its parent compounds (**17**).[45]

In view of this, the antifungal activity of triorganotin(IV) 5-nitro-2-furoates of composition R_3SnL (**21**) (R = Me, ^{n}Bu, Ph, NeoPh, *cyclo*hex) were compared with that of the compounds **15**–**19**.[46] The compound $^nBu_3SnL$ was found to be the best antifungal agent that completely inhibited the growth of six of 10 test fungi at a concentration of 1 μg ml^{-1}, and all of the test fungi at 10 μg ml^{-1}. Both compounds Ph_3SnL and $^nBu_3SnL$ completely inhibited the Gram-positive bacteria *Bacillus megaterium* and *Staphylococcus*

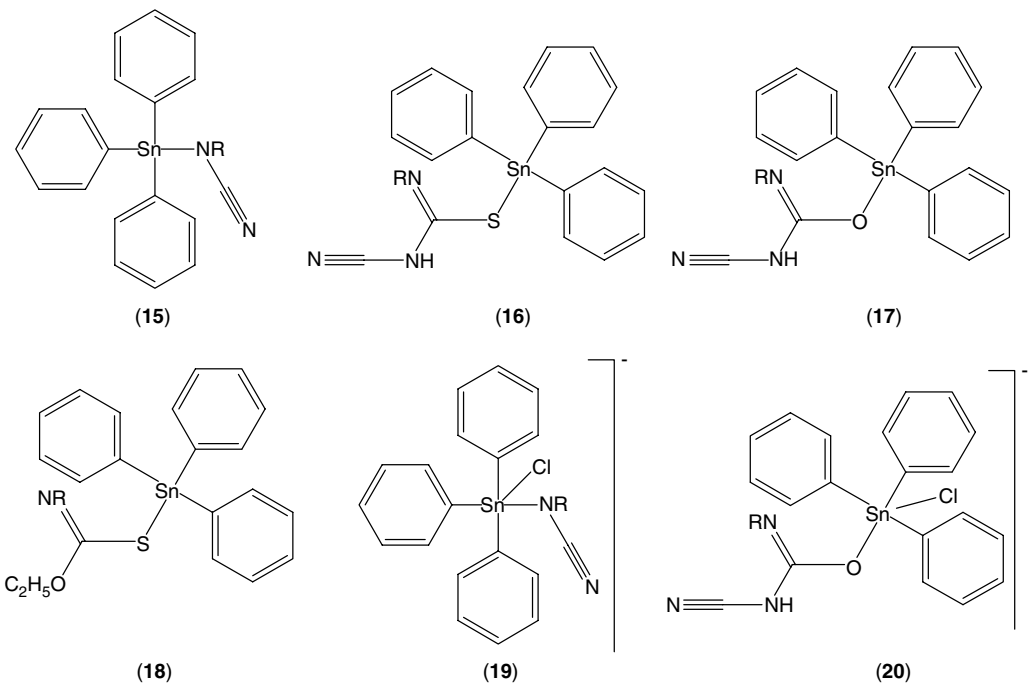
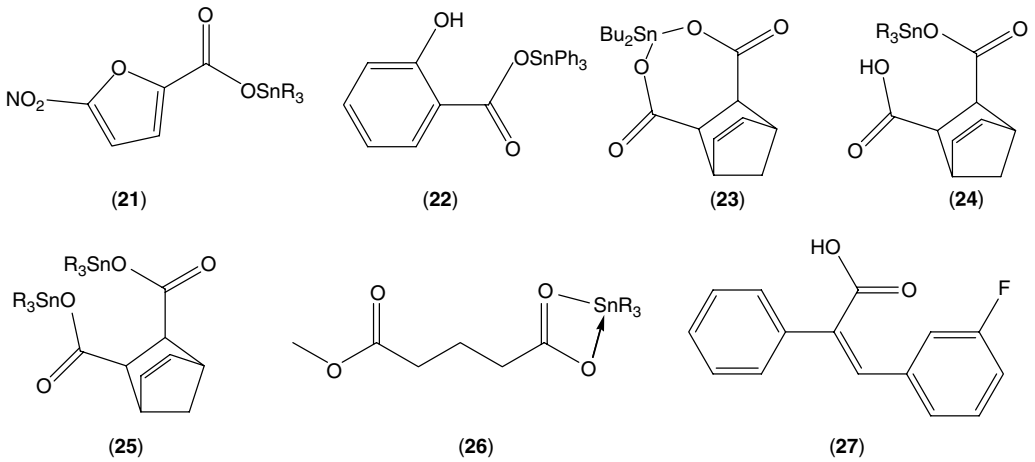


Figure 4. Triphenyltin(IV) complexes of *N*-substituted cyanamides (**15**), isothioureas (**16**), isoureas (**17**), isothiocarbamates (**18**) and related triethylammonium chloride complexes (**19**–**20**).



(**21**) (**22**) (**23**) (**24**) (**25**) (**26**) (**27**)

Figure 5. Organotin(IV)-furoates (**21**), -salicylates (**22**), -endiconates (**23**–**25**), -glutarates (**26**) and 3-(3-Fluorophenyl)-2-phenylopropenoic acid (**27**).

aureus at the minimum concentration of organotin(IV) compound (1 μg ml^{-1}).

The effect of triphenyltin(IV) salicylate (**22**) was tested against six bacteria, *Escherichia coli, Staphylococcus aureus, Shigella flexneri, Pseudomonas aeruginosa, Klebsiella pneumoniae* and *Salmonella typhi* and five fungi, *Aspergillus flavus, Aspergillus fumigatus, Aspergillus niger, Rhodotorula* spp. and *Saccharomyces* spp.[47] Sensitivity tests were determined with 5–500 μg ml^{-1} of **22** and all organisms were found to be sensitive except *Klebsiella pneumoniae, Pseudomonas aeruginosa, Rhodotorula* spp. and *Saccharomyces* spp. The minimum dose of **22** required to kill 50% of the susceptible microorganisms was in the range 5–50 μg ml^{-1}. Membrane-bound pyrophosphatase(s) from the organisms was non-competitively inhibited by 5 μM **22** with K_i (substrate inhibition constant) values of 7.6, 18, 8.8 and 6.9 μM for *Escherichia coli, Shigella flexneri, Aspergillus niger* and *Aspergillus fumigatus*, respectively. The physiological index of efficiency of the enzyme (V_{max}/KM, i.e. Michaelis–Menten constant/maximum velocity) for **22** was reduced by 17–68% in the presence of 5–10 μM of **22**. In contrast, the index for the non-susceptible organisms was unaffected. Several triphenyltin(IV) carboxylates and diorganotin(IV) dicarboxylates were also tested against different fungal strains, viz., *Gaeumannomyces graminis f. tritici, Botrytis cinerea, Fusarium nivale, Fusarium avenacearum, Phytophthora* (cryptogea) and *Rhizoctonia*, and against two bacterial strains, *Xanthomonas campestris* and *Pseudomonas syringae*.[48] Triphenyltin(IV) 5-methoxysalicylate was the most active compound. Organotin(IV) compounds, such as *bis*[tri-*n*-butyltin(IV)]oxide, tri-*n*-butyltin(IV) acetate, tri-*n*-butyltin(IV) oleate, tri-*n*-butyltin(IV) benzoate, tri-*n*-butyltin(IV) laurate, triphenyltin(IV) acetate and tri-*n*-butyltin(IV) chloride exhibited variable effectiveness against fungi, bacteria and yeast.[49] The recommended dose for these compounds in water was given as 3 μg l^{-1}. The di- and triorganotin(IV) endiconates (**23**–**25**; R = Me, Et, ^{n}Bu or Ph) were also prepared and copolymerized with unsaturated compounds to give polymers having antimicrobial activity and fungus-resistance.[50]

Organotin(IV) complexes of monomethyl glutarate (**26**; R = Me, ^{n}Bu) have also shown antibacterial activity against Gram-positive and Gram-negative bacteria.[51] The organotin(IV) compounds showed higher activity than the ligand but lower than the standard drug imipinem.

Organotin(IV) complexes of the type R_3SnL, R_2SnL_2 and $\{[R_2Sn(L)]_2O\}_2$ (R = Me, Et, ^{n}Bu, ^{n}Oct, Ph, Bz; L = anion of 3-(3-Fluorophenyl)-2-phenylpropenoic acid, **27**)[52–55] also displayed comparable or slightly better activity against different bacteria (e.g. *Escherichia coli, Bacillus subtilis, Shigella flexenari, Staphylococcus aureus, Pseudomonas aeruginosa, Salmonella typhi*) and different fungi (e.g. *Trichophyton longifusus, Candida albicans, Aspergillus flavus, Microsporum canis, Fusarium solani, Candida glaberata*) populations than the reference drugs. In general, the triorganotin(IV) compounds were more active than diorganotin(IV) derivatives and the ligand itself, particularly against *Trichophyton longifusus, Aspergillus flavusi* and *Microsporum canis*, and the activity was correlated to the geometry of the complexes.[55] In addition, some di- and tri-organotin(IV) triorganogermyl (substituted) propionates also exhibited promising activity towards bacteria and fungi.[56,57]

Ph_2SnCl_2 complexed with dimethylacetamide, dimethylformamide or diphenylacetamide was more effective *in vitro* against *Bacillus subtilis* and several fungus species than was the Ph_2SnCl_2 alone or the Lewis bases alone.[58]

A useful review with 31 references is also available on the antifungal and antibacterial activities of organotin(IV) compounds used commercially and industrially as preservatives and (or) disinfectants.[59] *Bis*(tri-*n*-butyltin(IV))oxide, a widely used organotin compound, was shown to have a synergistic effect with chlorinated aromatic hydrocarbons against fungi. Reaction of $(^nBu_3Sn)_2O$ with alkanedisulfonic acids $HOSO_2(CH_2)_nSO_3H$ (n = 1–6) afforded $^nBu_3SnO_3S(CH_2)_nSO_3Sn^nBu_3$, which showed antimicrobial activity comparable to $(^nBu_3Sn)_2O$ against bacteria, yeasts and molds, as well as against wood-rotting fungi.[60]

Most of a group of complexes of the types $[RNH]^+$ $[Ph_3SnCl_2]^-$ and $[RNH]^+$ $[Ph_2SnCl_3]^-$ (RN = pyridine, aniline, quinoline, α- and β-naphthylamines and β- and γ-picolines) showed appreciable antimicrobial activity.[61] A series of interesting organotin(IV) compounds obtained from the reactions of 2,6-diacetylpyridine nicotinoyl- and isonicotinoylhydrazones (**28**–**29**) with tri- and di-organotin(IV) chlorides were tested[62] on different microbial species including bacteria, yeasts, and molds. In all cases, the complexes showed a reduced antimicrobial activity as compared with those of the corresponding organotin(IV) precursors. In addition, two interesting organotin(IV) compounds, $[PhSn(L)Cl_2]$ and $[Ph_3SnCl(OH_2)]\cdot LH$ (LH = di-2-pyridylketone-2-thenoylhydrazone, **30**), have been prepared and characterized crystallographically.[63] The mode of coordination is different with the ligand **29**. The di- and tri-phenyltin(IV) compounds showed antibacterial activity preferentially against Gram-positive bacteria.

The triphenyltin(IV) compound proved to have a very strong activity against *Bacillis subtilis* and *Staphylococcus aureus* and also toward several *Bacilli* with minimum inhibitory concentrations ranging from 1.5 to 3 μg ml^{-1}. This compound was also effective against the fungi tested; a remarkable activity was found against *Aspergillus niger*. In general, parent organotins showed a higher antimicrobial activity compared with the corresponding complexes. The results were found to be consistent with the hypothesis that complexation by a polyfunctional ligand (**30**) decreases its biological activity.[62] Along these lines, a couple of interesting polyfunctional ligands, e.g. di-2-pyridylketone 2-aminobenzoylhydrazone, LH (**31**) and phenyl(2-pyridyl)ketone 2-aminobenzoylhydrazone, L′H (**32**) were reacted with di- and tri-organotins.[64] The complexes exhibited antimicrobial *in vitro* activity against Gram-positive bacteria. Ph_2SnCl_2, Ph_3SnCl and their complexes Ph_2SnCl_2(LH) and $Ph_3SnCl(OH_2)\cdot$(LH) were the most active compounds with MIC values in the 0.3–3 μg ml^{-1} range. In contrast, only Ph_2SnCl_2 and its complex Ph_2SnCl_2(LH) gave a good antimicrobial response against *Escherichia coli*. All the compounds were inactive against fungi, with the exception of Ph_2SnCl_2, Ph_3SnCl and $Ph_3SnCl(OH_2)$.(LH). The two latter compounds possess a very strong toxicity against both yeast and molds (MIC = 0.7–1.5 μg ml^{-1}). Strong antimicrobial activity towards all the phytopathogens used was demonstrated for the compounds Ph_2SnCl_2, Ph_3SnCl, Bz_2SnCl_2 and its derivatives, but the ligands **31** and **32** were inactive at doses ≤20 μg ml^{-1}. The activity of Ph_2SnCl_2 is reduced in all the complexes described. On the contrary, the strong fungicidal activity of Ph_3SnCl is maintained in the LH complex (EC_{50} = 0.1–5.0 μg ml^{-1}). As for organotins, it is interesting to note that the substitution of the phenyl group with benzyl groups produced a quantitative variation in both the antibacterial and the antifungal activities. Bz_2SnCl_2 showed a lower inhibition against bacteria than phenyl derivatives but no antifungal activity. This observation is in agreement with the general assumption that organotin(IV) toxicity is related to their hydrophobicity.[14] Both ligands **31** and **32** showed a light antimicrobial activity. However, **31** gave a better response than **32** against Gram-positive bacteria, thus demonstrating quantitative differences related to the presence of the pyridine or benzene ring in the nucleus. In contrast, no significant difference in activity was observed against Gram-negative bacteria and fungi.

In summary, the complexes exhibited a good antimicrobial potency, higher than those of the corresponding ligands, but lower than those of the parent organotins. This clearly indicates that the complexation, i.e. the introduction of hindering organic molecules or groups strongly bonded to tin, decreases the biological activity of the parent organotin. Only $Ph_3SnCl(OH_2)\cdot$(LH) exhibits comparable biological activity to that of Ph_3SnCl against all tested

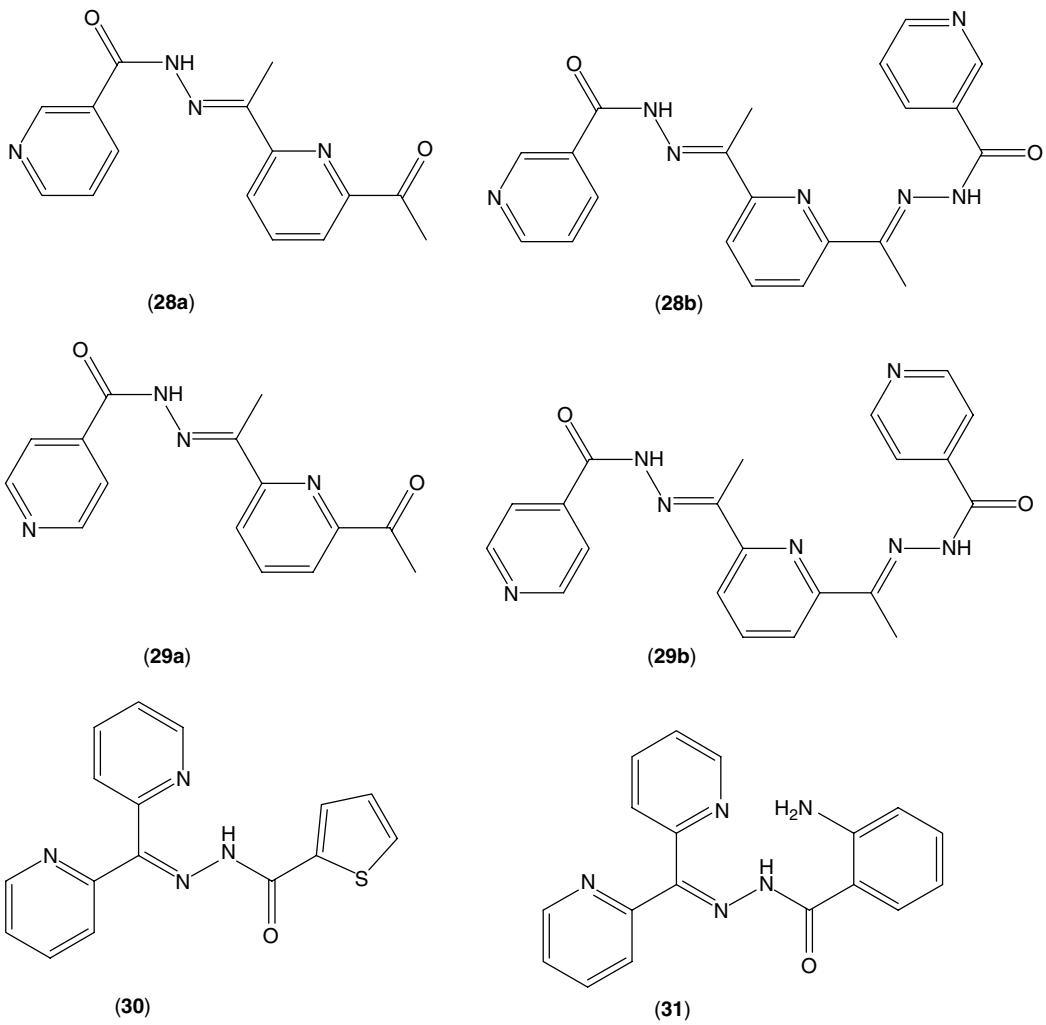


Figure 6. Structures of various acylhydrazones (**28–37**) used for the synthesis of organotin(IV) complexes.

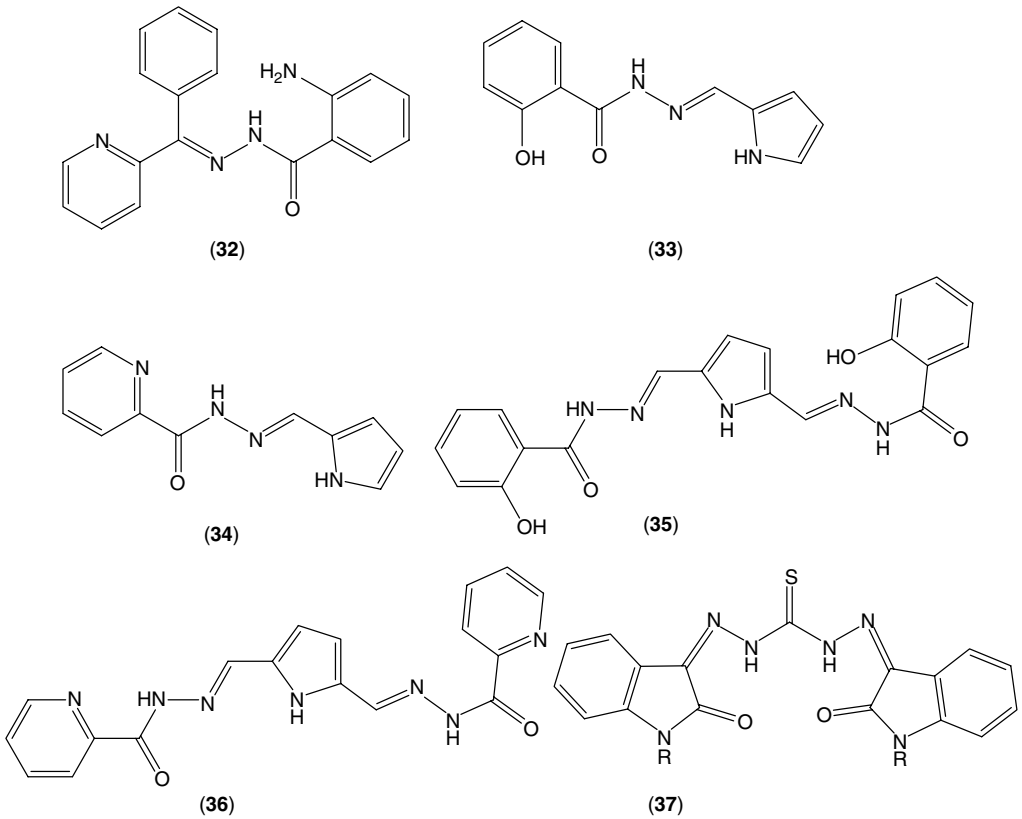


Figure 6. (*Continued*).

microorganisms. Since in this complex the component molecules are held together uniquely by hydrogen bonds, the observed activity could be due to their disruption with the formation of the parent compound Ph_3SnCl. A different antibacterial activity, particularly against *Escherichia coli*, was observed between two chelates obtained from Ph_2SnCl_2 and **31**, i.e. $PhSnCl_2(L)$ and $Ph_2SnCl_2(LH)$. The high activity of the latter was attributed to the hydrophobicity of the molecule. Further, it has also been stated that the presence of two phenyl groups in the latter compound makes it more soluble in lipids which can cross biological membranes with higher efficiency than $PhSnCl_2(L)$.

The above-mentioned work of Pelizzi and co-workers[62–64] reported the antimicrobial properties of organotin(IV) compounds of acylhydrazones containing the pyridine ring, which is substituted in the 2-position. At this stage, the authors decided to replace the pyridine ring by the pyrrole ring [pyrrole-2-carboxaldehyde 2-hydroxybenzoylhydrazone, H_3L (**33**) and pyrrole-2-carboxaldehyde 2-picolinoylhydrazone, H_2L' (**34**)] in order to examine the ligand behavior towards organotins and thereby the antimicrobial properties.[65] The complexes exhibited antibacterial properties higher than those of the corresponding ligands but they turn out to be less potent than the parent organotin(IV) compounds. $Ph_2SnCl_2(H_3L).2H_2O$ and $^nBu_2SnCl(HL')$ were the most active antibacterial compounds, showing MIC values between 3 and 6 μg ml^{-1} against *Bacillus subtilis* and *Staphylococcus aureus* and between 6 and 25 μg ml^{-1} against *Escherichia coli*; the diphenyltin(IV) compound also strongly inhibits the growth of *Aspergillus niger*. Both ligands **33** and **34** were devoid of antimicrobial activity (MIC $\geq$ 100 μg ml^{-1}), perhaps because of their polarity and their poor lipophilic character. Good antibacterial properties were noted for organotin(IV) compounds, and among these, the most active was Ph_2SnCl_2, whose effectiveness is extended to fungi. Inhibitory activity increases in the order Et < ^{n}Bu < Ph and is attributed to lipophilicity, which facilitates microorganism membrane crossing, in agreement with the knowledge that the toxicity of the organotins is related to their hydrophobicity.[14] The lipophilicity seems to be one of the prevalent factors connected with the toxicity of the complexes. However, the different acid properties of the two ligands and the presence of polar groups (one or two chlorine atoms) should also be considered. Nevertheless the low number of active compounds together with their different stoichiometries prevented a rational assessment of the data. All the ligands and complexes were devoid of DNA-damaging activity in the *Bacillus subtilis rec*-assay. The strong antimicrobial properties and the lack of genotoxicity of $Ph_2SnCl_2(H_3L)\cdot 2H_2O$ and $^nBu_2SnCl(HL')$ suggested their practical use as safe preservative, bactericide and fungicide agents for industrial and agricultural purposes. Bearing these points in mind, Pelizzi and co-workers further investigated organotin(IV) complexes of pyrrole-2,5-dicarboxaldehyde bis(acylhydrazones) [H_5L; (**35**)- H_3L; (**36**)][66] in order to compare their properties with those of the corresponding monoacylhydrazones described above. Amongst several mono- and bi-metallic diorganotin(IV) complexes, $Ph_2SnCl_2(H_3L)\cdot Me_2SO$ (characterized crystallographically) was found to be the most active compound and the results were almost comparable to that of Ph_2SnCl_2, exhibited MIC values of 3 and 12 μg ml^{-1} against Gram-positive and Gram-negative bacteria, respectively. The higher antimicrobial activity of $Ph_2SnCl_2(H_3L)\cdot Me_2SO$ was explained in terms of the involvement of both the hydrazonic chains in the coordination to tin, producing more stable complexes. Conversely, bimetallic complexes of **36** were found to be inactive, owing to the involvement of both the

hydrazonic chains in coordination to tin, producing more stable complexes. Lastly authors concluded that the replacement of the pyridine with the pyrrole ring does not enhance the antimicrobial activity. All the compounds tested are devoid of antifungal activity. Both the ligands **35** and **36** were found inactive up to 100 μg ml^{-1}, owing to their poor lipophilicity. None of the ligands (**35**–**36**) or complexes produced DNA damage in the *Bacillus subtilis rec*-assay or showed mutagenic activity in the *Salmonella*-microsome test.

Pelizzi and co-workers[67–69] reported that some organotin(IV) complexes of 1,5-*bis*(isatin)thiocarbonohydrazone and of its *N*-alkyl derivatives (**37**)[70] exhibited good antibacterial activity, better than that of the corresponding *N*-Bu and *N*-pentylisatin derivatives. Gram-positive bacteria were the most sensitive microorganisms. No growth inhibition of fungi was detected up to the concentration of 100 μg ml^{-1}. Ligand (**37**, R = Me) demonstrated mutagenic activity with and without metabolic activation, whereas no mutagenicity was found for its organotin(IV) complexes and for the other compounds.

Organotin(IV) complexes of triazolo-pyrimidine derivatives (**38**–**40**) were also subjected to *in vitro* antimicrobial tests.[71] A good activity with an MIC value of 3.1 μg ml^{-1} was displayed by the tri-*n*-butyltin(IV) complex of **40** against *Staphylococcus epidermidis* and was better than the parent $^{n}Bu_3SnOCH_3$. On the other hand, the triphenyltin(IV) complex of the same ligand possessed a good anti Gram-positive activity, while its parent Ph_3SnOH, was inactive at the maximum tested concentration. A good antifungal activity was also noted for the triphenyltin(IV) complex with MIC values of 0.78 μg ml^{-1} against both strains of *Candida albicans* and *Candida tropicalis*. Good antifungal activity was also shown by the tri-*n*-butyltin(IV) complex with MIC values of 0.78 and 1.5 μg ml^{-1} against *Candida albicans* and *Candida tropicalis*, respectively, but its organotin(IV) precursor $^{n}Bu_3SnOCH_3$ was equally active (MIC = 0.78 μg ml^{-1}). Some more diorganotin(IV) complexes of triazolo-pyrimidines (**41**–**42**) were also screened.[72] Both the ligands **41** and **42** were inactive at concentration of 100 μg ml^{-1}, but their complexation with organotin led to better antimicrobial activity, but the results were not as good as those of the parent organotin(IV) compounds. $^{n}Bu_2SnCl_2$.42 provided an improved activity against *Escherichia coli* and *Staphylococcus aureus* with MIC value of 6.2 μg ml^{-1} in both cases. A good activity (MIC equal to 3.1 μg ml^{-1}) against *Staphylococcus epidermidis* was also noted for Ph_2SnCl_2.42. Most compounds were inactive as antifungal agents at a screening concentration of 100 μg ml^{-1}.

Di-*n*-butyltin(IV) complexes of heterocyclic ketones and *N*-phthaloyl amino acids are reported to be more active than the ligands (**43**, R = 4-halo Ph, CF_3) and (**44**, R = H, Me) and the higher activities of the complexes were attributed to the chelation.[73]

Triorganotin(IV) derivatives of the types $Me_3Sn(SCZ)$ (SCZ^- is the anion of a semicarbazone ligand) were evaluated for their antimicrobial effects on different species of pathogenic fungi and bacteria.[74]

All the compounds are highly active against pathogens, even at low concentrations, and the inhibition of the growth of microorganisms was dependent on the concentration of the complexes. Furthermore, all the compounds exert the greatest toxicity against the fungus *Aspergillus niger* and bacterium *Bacillus subtilis*, but are least toxic towards the fungus *Fusarium oxysporum* and the bacterium *Escherichia coli*.

Triorganotin(IV) complexes with benzothiazolines, e.g. 2-acetyl(2-pyridyl)benzothiazoline (**45**) and 2-acetyl(2-furyl) benzothiazoline (**46**) showed moderate activity against *Helminthosporium graminium, Aspergillus niger* and *Alternaria alternate*.[75]

Triorganotin(IV) derivatives of thiolupinine(1-mercaptolupinane), 2-mercaptobenzoxazole and 2-mercaptobenzothiazole were also tested against several bacteria, fungi and protozoa.[76] Most of the compounds exhibited high activity; the activity of triethyltin(IV) lupinylsulfide was the best on Gram-negative strains.

The triorganotin(IV) complexes of umbelliferone (**47**) (R_3SnL and $R_3SnL{\cdot}L'$ where R = Me, ^{n}Bu and Ph; L = anion of umbelliferone; L′ = 1,10-phenanthroline) showed mild activities *in vitro* against Gram-positive and Gram-negative bacteria as well as yeast and mold.[77] R_3SnL (R = Me and Ph) show good activity against *Staplylococcus aureus* and *Bacillus subtilis, Candida albicans* and *Microsporum gypseum*, and this was enhanced upon adduct formation with 1,10-phenanthroline, i.e. in $R_3SnL{\cdot}L'$.

The antimicrobial activity of a number of organotin(IV) diethyldithiocarbamates has been evaluated *in vitro* against (a) *Colletotrichum falcatum, Sclerotium rolfsii* and *Gloeocercospora sorghi* fungal pathogens of sugar producing crops, (b) *Candida albicans, Cryptococcus neoformans, Microsporum canis* and *Trichophyton mentagrophytes*, fungi responsible for mycotic infections in animals, and (c) *Bacillus subtilis, Escherichia coli, Salmonella typhi*

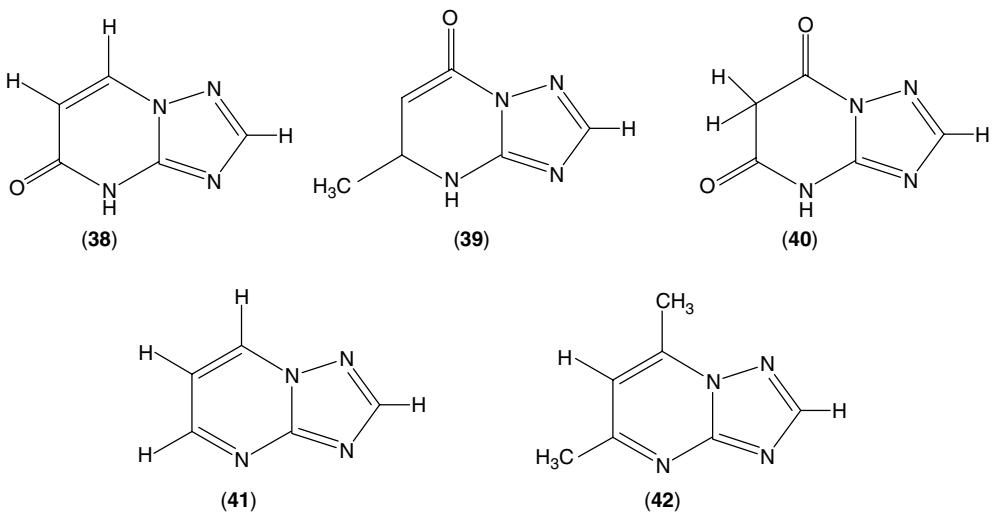


Figure 7. Structures of various triazolo-pyrimidine derivatives (**38**–**42**) used for the synthesis of organotin(IV) complexes.

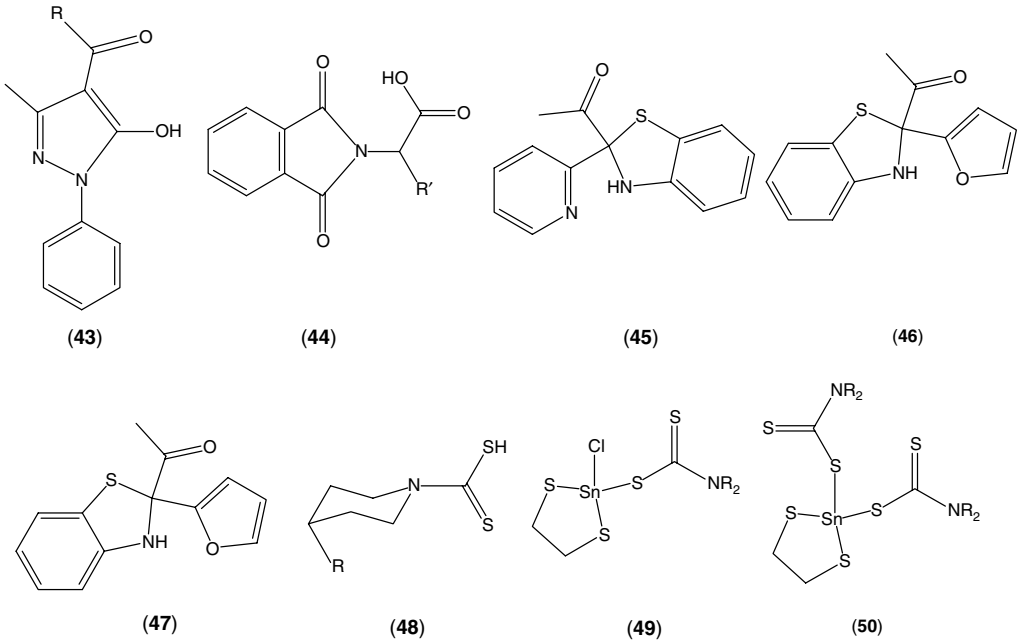


Figure 8. Structure of various heterocyclic ketones (**43**), *N*-phthaloyl amino acids (**44**), heterocyclic benzothiazolines (**45** and **46**), umbelliferone (**47**) and pipyridyl dithiocarbamates (**48**), used for the synthesis of organotin(IV) complexes, and 1,3-dithia-2-stannacyclopentane derivatives with dimethyldithiocarbamate (**49** and **50**).

and *Staphylococcus aureus* bacterial test species.[78] The nature of the organic group and the metal atom in the compounds appear to have a significant bearing on the fungitoxicity of a compound. Antimicrobial activities of triaryltin(IV) diethyldithiocarbamates were found to be superior to the corresponding diaryltin(IV) diethyldithiocarbamates.[79] Substitution of an electron-releasing methyl group in the benzene nucleus enhanced the activity. In view of the promising results, some new organotin(IV) dithiocarbamates of the formula $R_nSn(SCSNR_1R_2)_{4-n}$ (R = Ph or Bz; $R_1 = R_2$ = alkyl or aryl; n = 1 or 2) were synthesized as well and evaluated *in vitro* against five fungi and four bacteria.[80] Triphenyltin(IV) phenylthiocarbamate had the best overall antimicrobial activity. A series of organotin(IV) complexes of pipyridyl dithiocarbamates of the types R_2SnL_2, R_3SnL[81] and R_2SnLCl[82,83] also exhibited high activity compared to free ligand (**48**, R = H, Me) against bacteria and fungi.

The free ligands and mixed sulfur ligand tin complexes (**49** and **50,** R = Me, Et, CH_2-CH_2) derived from 1,3-dithia-2-stannacyclopentane derivatives with dimethyldithiocarbamate were tested against a panel of bacterial species and fungi and compared with the activities of some reported antibiotics such as terbinafin (antifungal agent) and chloramphenicol (antibacterial agent).[84] The mixed sulfur ligand tin complexes (**49**) and (**50**) have lower activity towards all tested bacteria than the free ligands and are concentration-dependent. The same analogies were applicable in the case of fungi. The decrease in the activities for the complexes was ascribed to chelation. However, no structure–activity relationship between antimicrobial activities could be derived. Both free ligands and complexes exhibited greater antibacterial effect than antibiotic.

Conclusion

A great deal of work describing the antimicrobial activities of organotin(IV) compounds is available in the literature; however, there are few defined reports of mode of action of organotin(IV) compounds towards various microorganisms such as bacteria and fungi. Pelizzi and co-workers have tried to give precise information on the mode of action of organotin(IV) compounds in relations to genetoxic potential which are important in predicting the structure–activity relationship, but the low number of active compounds together with their different stoichiometries prevented a rational valuation of the data. Even though the organotin(IV) compounds and their complexing agents described above have shown a wide range of activities towards various microorganisms, this advantage can also lead to confusion and misconceptions in general. It is inappropriate to generalize that all organotins have similar antimicrobial properties. When used responsibly, they can provide performance and value in a variety of end uses. For work in this area to be truly effective, it is necessary to combine chemical and biological knowledge and to create interdisciplinary teams.

Acknowledgments

The financial support of the Department of Science & Technology, New Delhi, India (Grant No. SR/SI/IC-03/2005, TSBB) is gratefully acknowledged.

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