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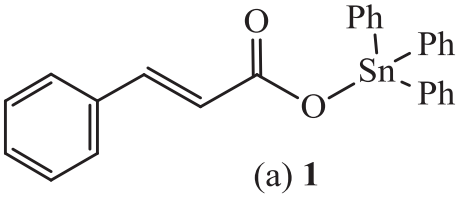

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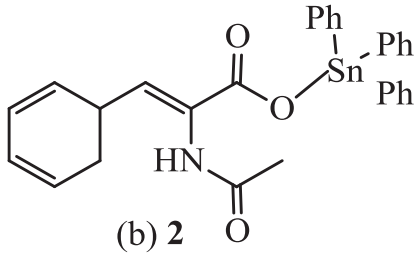

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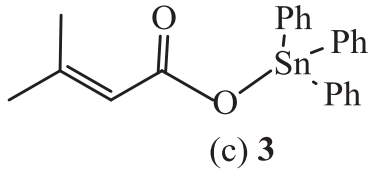

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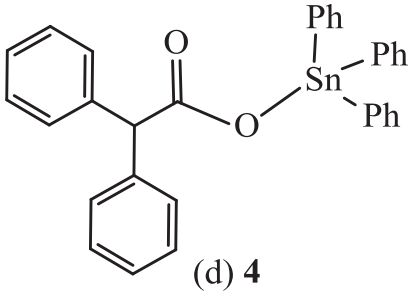

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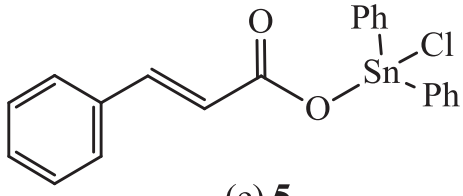

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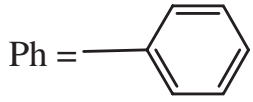

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Antituberculosis study of organotin(IV) complexes: A review

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Abstract: This review emphasized on the antituberculosis activity of organotin complexes. The astonishing antituberculosis activity of organotin complexes of mefenamic acid, 2-[(2,6-dimethylphenyl)amino]benzoic acid (HDMPA), and [bis(2,6-dimethylphenyl)amino]benzoic acid, NSAIDs from the carboxylic acid, oxicams family, meclofenamic acid or (N-(2,6-dichloro-*m*-tolylanthranilic acid), cinnamic acid, (*Z*)-2-acetamido-3-phenylacrylic acid, 3-methyl-but-2-enoic acid, and 2,2-diphenylacetic acid is scrutinized using *Mycobacterium tuberculosis* H37Rv. It showed that there exists a beguiling, range of structural diversity for organotin moiety in all these complexes. Biologically active compounds should have available coordination positions at tin. Antituberculosis activity of organotin complexes is influenced by the nature of the ligand environment, organic groups attached to the tin, compound structure, toxicity, and potential mechanism of action; though generally, an MIC ≤ 1 μg ml^{-1} in a new compound class is considered a good lead. The results of complexes exhibited that triorganotin(IV) complexes have superior antituberculosis activity as compared to diorganotin(IV) complexes. It may be due to the fact that generally toxicity of the organotin compounds is associated with the organic ligand and the toxicity decreases with the order of tri > di > mono-organotins.

Subjects: Physical Science; Bioscience; Medicine, Dentistry, Nursing & Allied Health; Chemistry

Keywords: organotin complexes; antituberculosis activity; *Mycobacterium tuberculosis* H37Rv; Alamar blue; NSAIDs and Rifampicin

ABOUT THE AUTHORS

The group is engaged in diversified research fields, such as material chemistry, bioinorganic chemistry, and synthesis of biodiesel. In bioinorganic chemistry, various organometallic and coordination complexes have been synthesized and characterized by various techniques. Their biological aspects including DNA interaction, enzyme inhibition, anticancer, and antidiabetic studies have been performed.

The biodiesel was synthesized from various non-edible oils and subsequently characterized by various analytical techniques. The catalytic properties of different organometallic compounds in the synthesis of biodiesel have also been investigated. Work is also being carried out for the fabrication of functionalized carbon nanotubes and their uses in polymer matrices to enhance the thermomechanical properties.

PUBLIC INTEREST STATEMENT

The antituberculosis activity of organotin complexes of mefenamic acid, 2-[(2,6-dimethylphenyl)amino]benzoic acid (HDMPA) and [bis(2,6-dimethylphenyl)amino] benzoic acid, NSAIDs from the carboxylic acid, oxicams family, meclofenamic acid or (N-(2,6-dichloro-*m*-tolylanthranilic acid), cinnamic acid, (*Z*)-2-acetamido-3-phenylacrylic acid, 3-methyl-but-2-enoic acid and 2,2-diphenylacetic acid is scrutinized using *Mycobacterium tuberculosis* H37Rv. Bioactivity of the overviewed organotin(IV) indicates potential development of new antituberculosis drugs. This may be considered as good antituberculosis agent in drug development in near feature.

1. Introduction

Tin is present in numerous inorganic and organometallic compounds, which are distinguished by the presence of at least one covalent carbon–tin bond. Tin has an outer shell with two 5s and two 5p electrons. Basically, it is able to lose the two 5p electrons and form simple Sn^{2+} ions, or acquire the electronic configuration of xenon by sharing all four electrons with other atoms. Yet, the chemistry of tin, especially in aqueous medium, is more convoluted because it uses inert electron pairs to direct its stereochemistry and neither Sn^{4+} nor Sn^{2+} is present in aqueous solutions. Apparently most of the Sn(II) compounds (R_2Sn) are in fact Sn(IV) types with multiple Sn–Sn bonds. Multiple p bonds have not been found in tin compounds. The missing ability of tin to use d orbitals for p binding is demonstrated by the high basicity of $N(SnMe_3)_3$, which is much greater than that of any organic amine. It indicates that although tin may exist either in the Sn^{2+} or in the Sn^{4+} oxidation state, almost all organotins have a tetravalent structure because tin(II) compounds are readily oxidized up to tin(IV) (Figure 1). Solutions of tin(II) that do not contain satisfactorily strong electron donor species are fleetly oxidized with atmospheric oxygen. Thus, the most stable tin compounds belong to the (IV) oxidation state. Rely on the number of organic moieties, organotins are grouped as mono-, di-, tri-, and tetraorganotins ($RSnX_3$, R_2SnX_2, R_3SnX, R_4Sn), in which R is any alkyl or aryl group and X is an anionic species (halide, oxide, hydroxide, carboxylate, or thiolates). The Sn–C bonds are stable in the presence of water, atmospheric O_2, and heat at temperatures up to 200°C, so thermal decomposition has no importance under environmental conditions. The Sn–C bonds are cleaved by UV radiation, strong acids, and electrophilic agents. Transparently, both the number of Sn–C bonds and the length of the alkyl chains influence the chemical and physical properties of organotins.

The structures of tin(II) compounds vary between angular, square pyramidal, trigonal pyramidal, and octahedral. Tin(IV) structures are generally tetrahedral, trigonal pyramidal, or octahedral. In the R_3SnX species, trigonal bipyramidal (five-coordinated) structures remain, while in the R_2SnX_2 complexes, octahedral structures occur more often. Organotins(IV) are easily coordinated to appropriate ligands, giving out highly coordinated species in contrast to the carbon coordination modes. A five-coordinated carbon existing as a transition state in SN^2 reactions, lie on the top of a potential energy surface, while a five-coordinated organotin compound could lie at its bottom due to the participation of the d orbitals, which can be rehybridized to a hypercoordination state (Yasuda, Chiba, & Baba, 2000). Commonly, the solubility of organotins in water decreases with increasing number and length of the organic substituent, but there is also a dependence on the nature of the X group.

The speciation of organotin(IV) species in water is closely related to their reactivity properties. The organotin(IV)$^{(4-n)+}$ moieties are observed as Lewis acid of different strengths, depending on the groups bound to the Sn(IV). Therefore, they show a strong tendency to hydrolysis in aqueous solution.

Organotin(IV) compounds are appraised due to their wide scope of industrial, synthetic, agricultural, and biological applications (Davies, Gielen, Pannell, & Tiekink, 2008; Kroschwitz, 1997). Triorganotin(IV) compounds, including tri-*n*-butyltin tricyclohexyltin, and triphenyltin compounds, immensely considered as industrial and agricultural biocides, in material protection as an antifouling agent, as surface disinfectants, and as catalysts for the production of polyurethanes (Nath, 2008).

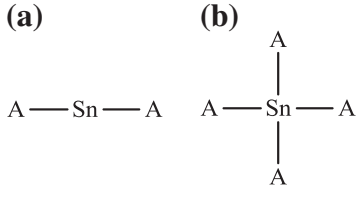

Figure 1. The two possible structures of tin: (a) bivalent and (b) tetravalent where A can be any atom or group.

In the last 15 years, organotin(IV) derivatives are appeared as potential biologically active metallopharmaceuticals exhibiting antitumor activity against a number of tumor cell lines of human origin (Crowe, 1989; de Vos, Willem, Gielen, Van Wingerden, & Nooter, 1998; Nath, Pokharia, Eng, Song, & Kumar, 2003; Nath, Pokharia, Song, et al., 2003). The organotin(IV) derivatives have been amplified as potential biologically active compounds exhibiting antimicrobial (Ayoko et al., 2003; Jabbar et al., 2012; Nath & Yadav, 1998; Nath, Yadav, Eng, & Musingarimi, 1998, 1999; Nath, Yadav, Eng, Nguyen, & Kumar, 1999), anti-inflammatory (Nath, Pokharia, Eng, et al., 2003), cardiovascular (Nath, Pokharia, Song, et al., 2003), trypanocidal (Susperregui et al., 1997, 1999), antiherpes (Nath, Yadav, Eng, & Musingarimi, 1999; Nath, Yadav, Eng, Nguyen, et al., 1999), and antituberculosis activities (Kovala-Demertzi, Dokorou, Ciunik, Kourkoumelis, & Demertzis, 2002). The organotin(IV) derivatives manipulated much attention because of their interactions with drugs, viz. antibacterial agent, such as norfloxacin (Nath, Pokharia, Eng, et al., 2003; Nath, Pokharia, Song, et al., 2003); antibiotics such as cephalexin, penicillin-G (Maggio et al., 1994), amoxicillin (Di Stefano et al., 2002; Pellerito et al., 1995), ampicillin (Di Stefano et al., 2002), chloramphenicol, cycloserine (Pellerito et al., 1998), and tetracyclines (Koza & Nsiah, 2002) and anti-inflammatory drugs, such as tenoxicam (Demertzis, Hadjikakou, Kovala-Demertzi, Koutsodimou, & Kubicki, 2000) and lornoxicam (Galani, Demertzis, Kubicki, & Kovala-Demertzi, 2003). From these studies, it has been observed that the activity of the organotin(IV) derivatives is a function of the structure of organic ligands (containing hetero donor atoms such as O, N, S) bonded to a particular organotin(IV) moiety. Owing to such a structural specificity, efforts have been directed toward the chemotherapeutic importance of organotin(IV) derivatives of biomolecules, such as amino acids and peptides (Jabbar et al., 2012; Nath, Pokharia, Eng, et al., 2003; Nath, Pokharia, Song, et al., 2003; Nath & Yadav, 1998; Nath et al., 1998; Nath, Yadav, Eng, & Musingarimi, 1999; Nath, Yadav, Eng, Nguyen, et al., 1999; Pellerito & Nagy, 2002); carbohydrates; DNA fragments (Pellerito & Nagy, 2002); steroids (Gielen et al., 1992); and coenzymes, such as thiaminepyrophosphate (Fiore et al., 1999).

2. Tuberculosis

Tuberculosis (TB) is originated by gram-positive bacteria known as the *Mycobacterium tuberculosis* complex (MTBC). *Mycobacterium tuberculosis* is a fairly large non-motile rod-shaped bacterium distantly related to the actinomycetes. Many non-pathogenic mycobacteria are components of the normal flora of humans, found most often in dry and oily locales. The rods are 2–4 μm in length and 0.2–0.5 μm in width.

M. tuberculosis is an obligate aerobe. For this reason, in the classic case of tuberculosis, MTBC is always found in the well-aerated upper lobes of the lungs. The bacterium is a facultative intracellular parasite, usually of macrophages and has a slow generation time, 15–20 h, a physiological characteristic that may contribute to its virulence.

Two media are used to grow MTB, Middlebrook's medium which is an agar-based medium and Lowenstein-Jensen medium which is an egg-based medium. MTB colonies are small and buff colored when grown on either medium. Both types of media contain inhibitors to keep contaminants from out-growing MT. It takes 4–6 weeks to get visual colonies on either type of media.

2.1. General properties of Mycobacterium tuberculosis

2.1.1. Special mechanisms for cell entry

The tubercle bacillus can bind directly to mannose receptors on macrophages via the cell wall-consociated mannosylated glycolipid, or indirectly via certain complement receptors.

2.1.2. Intracellular growth

MTB can grow intracellularly. This is an effective means of evading the immune system. In particular, antibodies and complement are ineffective. Once MTB is phagocytosed, it can inhibit phagosome–lysosome fusion by secretion of a protein that modifies the phagosome membrane. It may remain in the phagosome or escape from the phagosome, in either case, finding a protected environment for growth in the macrophage.

2.1.3. Detoxification of oxygen radicals

MTB intermeddled with the toxic effects of reactive oxygen intermediates produced in the process of phagocytosis by three mechanisms:

(1) Compounds including glycolipids, sulfatides.
(2) Macrophage uptake via complement receptors may by pass the activation of a respiratory burst.
(3) The oxidative burst may be compensated by production of catalase and superoxide dismutase enzymes.

2.1.4. Antigen 85 complex

The complex is serenade of a group of proteins secreted by MTB that are known to bind fibronectin. These proteins may help in encaging off the bacteria from the immune system and may promote tubercle formation.

2.1.5. Slow generation time

Because of MTB's slow generation time, the immune system may not readily recognize the bacteria or may not be triggered sufficiently to eliminate them. Many other chronic diseases are caused by bacteria with slow generation times, for example, slow-growing *M. leprae* causes leprosy.

2.1.6. High lipid concentration in cell wall

This accounts for impermeability and resistance to antimicrobial agents, resistance to killing by acidic and alkaline compounds in both the intracellular and extracellular environment, and resistance to osmotic lysis via complement deposition and attack by lysozyme. *M. tuberculosis* virulence is studied both in tissue culture, using macrophages, dendritic cells, or pneumocytes, and in animal models, primarily mice (Smith, 2003).

2.1.7. Oxidative stress proteins

Most aerobic organisms have enzymes that reduce peroxides and superoxide, which are normal byproducts of aerobic respiration, but also are toxic oxygen radicals. The superoxide dismutases, catalases, and peroxidases enzymes are also important for the response to numerous external oxidative stresses. Since phagocytic cells produce oxygen radicals during the respiratory burst to kill invading bacteria, these enzymes may contribute to *M. tuberculosis* virulence. Enzymes found in *M. tuberculosis* that conflict oxygen radicals include AhpC, an alkyl hydroperoxide reductase that detoxifies organic hydroxyperoxides, and SodA and SodC, two species of superoxide dismutase that degrade superoxides, which are normal byproducts of aerobic respiration and are also generated by the phagocytic respiratory burst.

2.1.8. Nitrate reductase

M. tuberculosis was considered as an obligate aerobe, but there are various experimental indicators for the growth of bacterium in microareophilic environments, especially during the later stages of infection, e.g. in lung granulomas. Blustery *M. tuberculosis* possesses an empirical nitrate reductase (NarG encoded by *narG*) which allows respiration using NO_3 as a final electron acceptor.

2.1.9. Adherence

Few potential adherence factors such as heparin-binding hemagglutinin (HbhA), a fibronectin-binding protein, and a polymorphic acid, glycine-rich protein, called PE-PGRS are known. HbhA is a surface-exposed protein that is implicated in binding *M. tuberculosis* to epithelial cells but not to phagocytes. It can be intricated in extrapulmonary spread after the initial long-term colonization of the host. Fibronectin-binding proteins (FbpA), first known as the α-antigen (Antigen 85 complex), can bind to the extracellular matrix protein fibronectin *in vitro*. The surface-exposed PE-PGRS proteins found in *M. tuberculosis* and *Mycobacterium bovis* also exhibit fibronectin-binding properties. In recent times, *M. tuberculosis* generated pili during human infection, which can be elaborated in

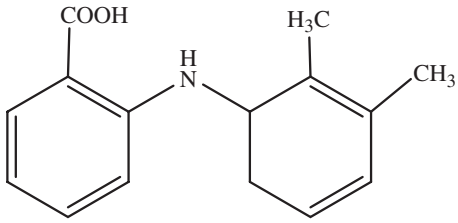

Figure 2. Structure of mefenamic acid (Kovala-Demertzi et al., 2002).

Table 1. Anti-tuberculosis activity of triphenyl and dibutyltin complexes of mefenamic acid

Compound	Inhibition (%)	MIC (μg ml^{-1})	References
$SnPh_3L$	98	0.39	Kovala-Demertzi et al. (2002)
$SnBu_2L_2$	92	6.25	Kovala-Demertzi et al. (2002)

Note: L is the mefenamic acid.

initial colonization of the host (Alteri et al., 2007). Isolated MTP bind to the extracellular matrix protein laminin *in vitro*, suggesting that they act as an adhesin and may be an important host colonization factor of *M. tuberculosis*. Because MTP are produced *in vivo* and the *M. tuberculosis* habitat is the human body from which it is transmitted directly from person to person, it is likely that pili play an important role in some aspect of human TB infection.

3. Antituberculosis activity of organotin(IV) mefenamic complexes against *Mycobacterium tuberculosis* H37Rv

Antibacterial activity was determined using the modified BACTEC-460 system. A screen was performed at 6.25 μg ml^{-1} against *Mycobacterium tuberculosis* H37Rv in BACTEC-12B medium using the BACTEC-460 radiometric system. Compounds influencing <90% inhibition in the primary screen (minimum inhibitory concentration (MIC) > 6.25 μg ml^{-1}) were not evaluated further. Compounds demonstrating at least 90% inhibition in the primary screen were retested at lower concentration (MIC) in a broth microdilution assay with Alamar blue (MABA). The MIC is defined as the lowest concentration effecting a reduction in fluorescence of 90% relative to controls. Rifampicin was used as a positive drug control; the MIC value for Rifampicin is 0.25 μg ml^{-1} with 95% inhibition of H37Rv strain (Kovala-Demertzi et al., 2002).

The triphenyltin and dibutyltin adducts of mefenamic acid, 2-[bis(2,3-dimethylphenyl) amino]benzoic acid (Figure 2) were screened against *Mycobacterium tuberculosis* H37Rv in BACTEC-12B medium using the BACTEC-460 radiometric system at the single concentration of 6.25 μg ml^{-1}. Both of these complexes exhibited the highest inhibitory activities, 98 and 92%, respectively, and are considered as active compounds. The compounds were checked by serial dilution beginning at 6.25 μg ml^{-1}. The third column in Table 1 lists the measured MIC values, viz. 0.39 μg ml^{-1} and >6.25 μg ml^{-1} for triphenyltin and dibutyltin complexes of mefenamic acid, respectively. The significance of these values based on several factors, such as compound structure, novelty, toxicity, and potential mechanism of action, though generally, an MIC ≤ 1 μg ml^{-1} in a new compound class is considered a good lead. The triphenyltin derivative of mefenamic acid with a value of 0.39 μg ml^{-1} is marked as a good lead compound and the results of this study represent the discovery of triphenyltin derivatives as a potential new class of antituberculosis agent (Kovala-Demertzi et al., 2002).

4. Antituberculosis activity of 2-[(2,6-dimethylphenyl)amino]benzoic acid (HDMPA) and its triphenyltin(IV) derivative

In vitro evaluation of the activity of HDMPA and [$Sn(Ph)_3$(DMPA) against *Mycobacterium tuberculosis* H37Rv was observed with the modified BACTEC-460 system. A screen was conducted at 6.25 μg ml^{-1} against *Mycobacterium tuberculosis* H37Rv in BACTEC-12B medium, using the BACTEC-460 radiometric system. Both of these compounds were investigated at lower concentration in a broth

Table 2. Antituberculosis activity of 2-[(2,6-dimethylphenyl)amino]benzoic acid (HDMPA) and its triphenyltin(IV) derivative

Compound	Inhibition (%)	MIC (μg ml^{-1})	References
HDMPA	0	0.78	Dokorou et al. (2004)
[Sn(Ph)$_3$(DMPA)]	100	0.39	Dokorou et al. (2004)
Rifampicin	95	0.25	Dokorou et al. (2004)

microdilution assay with Alamar blue (MABA). Rifampicin, considered as a positive drug control, was dissolved in DMSO and added to BACTEC-12 broth to achieve a range of concentrations for the determination of the MIC value, the lowest concentration inhibiting 99% of the inocula. The MIC value of Rifampicin is 0.25 μg ml^{-1}, with 95% inhibition of the H37Rv strain.

Compounds HDMPA and [Sn(Ph)$_3$(DMPA)] were examined against *Mycobacterium tuberculosis* H37Rv in BACTEC-12B medium, using the BACTEC-460 radiometetric system at the single concentration of 6.25 μg ml^{-1}. HDMPA did not exhibit any inhibitory effect and was not screened any further. [Sn(Ph)$_3$(DMPA)] exhibited the highest inhibitory activity (100%) and can be considered an active compound (Table 2) (Dokorou, Kovala-Demertzi, Jasinski, Galani, & Demertzis, 2004). Generally, an MIC ≤ 1 g ml^{-1} in a novel compound depending on several factors, such as compound structure, novelty, toxicity, and potential mechanism of action, is considered as an excellent effort (Kovala-Demertzi, 2006).

5. Antituberculosis activity of NSAIDs from the carboxylic acid, oxicams family, and their organotin derivatives

Selected NSAIDs and organotin complexes were scrutinizing against *Mycobacterium tuberculosis* H37Rv in BACTEC-12B medium using the BACTEC-460 radiometetric system at the single concentration of 6.25 μg ml^{-1} (Table 3) (Figures 3 and 4). Rifampicin was used as a positive drug control. The parent drugs and the dimeric tetraorganostannoxanes and the triphenyltin ester of flufenamic acid

Table 3. Antituberculosis activity of NSAIDs from the carboxylic acid, oxicams family, and their organotin derivatives

Compound	Inhibition (%)	MIC (μg ml^{-1})	References
H$_2$tenox	21	>6.25	Kovala-Demertzi (2006)
H$_2$pirox	11	>6.25	Kovala-Demertzi (2006)
H$_2$lorno	2	>6.25	Kovala-Demertzi (2006)
Hfluf	0	>6.25	Kovala-Demertzi (2006)
HDMAB	0	>6.25	Dokorou et al. (2004), Kovala-Demertzi (2006)
[Me$_2$(dicl)SnOSn(dicl)Me$_2$]$_2$	0	>6.25	Kovala-Demertzi (2006)
[Ph$_2$(dicl)SnOSn(dicl)Ph$_2$]$_2$	0	>6.25	Kovala-Demertzi (2006)
[Sn(Ph)$_3$(Flu)]	0	>6.25	Kovala-Demertzi (2006)
[SnMe$_2$(dicl)$_2$]	100	3.13	Kovala-Demertzi (2006)
[SnBu$_2$(dicl)$_2$]	100	3.13	Kovala-Demertzi (2006)
[Sn(Ph)$_3$(pirox)]	100	1.56	Kovala-Demertzi (2006)
[Sn(Ph)$_3$(lorno)]	100	3.13	Kovala-Demertzi (2006)
[Sn(Ph)$_3$(indo)]	100	0.78	Kovala-Demertzi (2006)
[Sn(Ph)$_3$(tenox)]	100	0.78	Kovala-Demertzi (2006)
[Sn(Ph)$_3$(DMAB)]	100	0.78	Kovala-Demertzi (2006)
Rifampicin	95	0.25	Kovala-Demertzi (2006)

Notes: Alamar assay; drug concentration 6.25 μg ml^{-1}.

(Hfluf) not exhibit any inhibitory effect and were not examined further. The rest of the organotin compounds exhibited highest inhibitory activity of 92–100%, respectively, and considered as active compounds. The MIC values are in the range of 3.13–0.78 μg ml^{-1}. Several factors such as structure of compound, novelty, toxicity, and implicit mechanism of action affect the significance of these values, although an MIC ≤ l μg ml^{-1} in a novel compound class is advised as an excellent value. The triphenyltin esters of anthranilic acid are considered excellent lead compounds and the results of this study represent the discovery of triphenyltin derivatives as a potential new class of antituberculosis agent (Kovala-Demertzi, 2006).

6. Meclofenamic acid or N-(2,6-dichloro-*m*-tolylanthranilic acid) and its organotin(IV) complex

In vitro evaluation of the activity of meclofenamic acid and 2-[(2,6-dichloro-3-methylphenyl)amino] benzoate)triphenyltin(IV) [(Ph_3Sn(Meclo)] against *Mycobacterium tuberculosis* H37Rv was determined with the modified BACTEC-460 system. A screen was conducted at 6.25 μg ml^{-1} against *M.tuberculosis* H37Rv in BACTEC-12B medium, using the BACTEC-460 radiometric system. Compounds effecting <90% inhibition in the primary screen (MIC > 6.25 μg ml^{-1}) were not evaluated further. Compounds demonstrating at least 90% inhibitions were reinvestigated at lower concentration in a broth microdilution assay with Alamar blue (MABA).

Rifampicin, used as a positive drug control, was dissolved in DMSO and added to BACTEC-12 broth to achieve a range of concentrations for the determination of the MIC value, the lowest concentration inhibiting 99% of the inoculums. The MIC value of Rifampicin is 0.25 μg ml^{-1}, with 95% inhibition of the H37Rv strain. Meclofenamic acid (Hmeclo) did no exhibit any inhibitory effect and was not further tested. The compound [(Ph_3Sn(Meclo)] exhibited highest inhibitory activity of 100% and considered as active compound. Generally, the compounds which exhibit <90% inhibition in the primary screen (MIC > 6.25 μg ml^{-1}) are not evaluated further. Compound [(Ph_3Sn(Meclo)] effecting >90% inhibition in the primary screen at 6.25 μg ml^{-1} was retested at lower concentrations against *Mycobacterium tuberculosis* H37Rv to determine the actual minimum inhibitory concentration in a

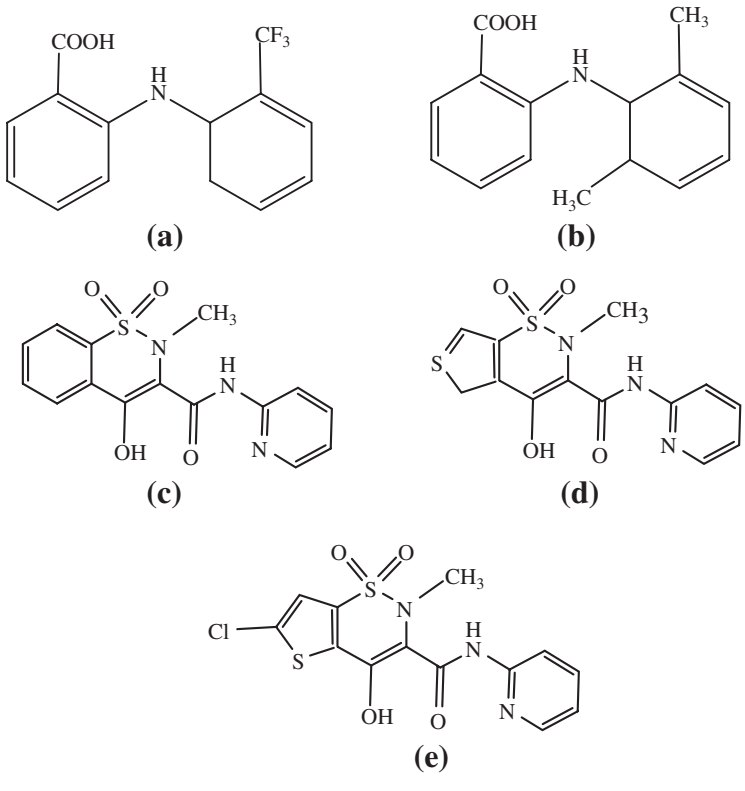

Figure 3. (a) [Flufenamic acid, (fluf)], (b) 2-(2,6-dimethylanilino)benzoic acid, HDMAB, (c) (4-hydroxy-2-methyl-N-pyridine-2-yl)-2H-1,2-benzothiazine-3-carboxamide-1,1-dioxide (H_2pirox), (d) 4-hydroxy-2,methyl-N-2-pyridyl-2H-thieno(2,3-*e*)-1,2-thiazine-3-carboxamide-1,1-dioxide (H_2tenox), (e) 8-chloro-4- hydroxy-2,methyl-2-pyridyl-2H-thieno(2,3-e)-1,2-thiazine-3-amide-1,1-dioxide (H_2lorox).

Figure 4. Structure of [Sn(Ph)$_3$(DMAB)] complex (Kovala-Demertzi, 2006).

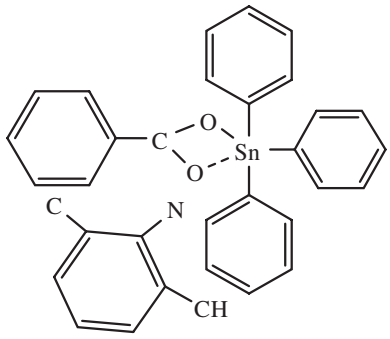

Table 4. Antituberculosis activity of meclofenamic acid and its organotin complex

Compound	Inhibition (%)	MIC (μg ml^{-1})	References
Hmeclo	0	>6.25	Kovala-Demertzi et al. (2009)
[Sn(Ph)$_3$(Meclo)]	99	99	Kovala-Demertzi et al. (2009)
Rifampicin	95	0.25	Kovala-Demertzi et al. (2009)

broth microdilution assay using Alamar blue. The MIC value is 0.78 for [(Ph$_3$Sn(Meclo)] and [SnPh$_3$(DMPA)], where DMPA is the deprotonated 2-[(2,6-dimethylphenyl)amino]benzoic acid (HDMPA) (Dokorou et al., 2004), (Tables 2 and 4).

The interplanar angle between the two aromatic rings is 88.2° and 86.7° for two conformers of HDMPA, respectively, in meclofenamic acid the corresponding angle being 81° (Krishna Murthy & Vijayan, 1981). It seems clearly that the conformation of the molecules is determined by steric interactions between the substituent on the phenyl groups. Besides the amino group in meclofenamic acid and HDMPA, there are two equivalent Cl$^-$ atoms and two Me groups, respectively, and the molecules are in a conformation where the two phenyl rings are almost perpendicular to minimize steric interactions. The dihedral angle between the planes of the phenyl rings of DMPA in [SnPh$_3$(DMPA)] is 68.6° (Fox, 1990) and for [(Ph$_3$Sn(Meclo)] is 65.9° (Kovala-Demertzi, 2006). It seems that structural and electronic effects of the anthranilic derivative play important role in the activity. [SnPh$_3$(Meclo)] is considered as an excellent lead compound and the results of this study represent the triphenyltin derivatives as a potential new class of antituberculosis agent (Kovala-Demertzi et al., 2009).

7. Antituberculosis activity of di- and triorganotin(IV) complexes of cinnamic acid, (*Z*)-2-acetamido-3-phenylacrylic acid, 3-methyl-but-2-enoic acid, and 2,2-diphenylacetic acid

Di- and triorganotin(IV) complexes of cinnamic acid, (*Z*)-2-acetamido-3-phenylacrylic acid, 3-methyl-but-2-enoic acid, and 2,2-diphenylacetic acid were checked for their antituberculosis activity against the logarithmic phase culture of *Mycobacterium tuberculosis* H37Rv by rapid colorimetric XXT method (Figure 5). The compounds were found to be active at 10 μg ml^{-1}. Minimum inhibitory concentrations (MIC) were found to be in the range of 0.078–1.25 μg ml^{-1}. Triorganotin(IV) complexes of cinnamic acid, (*Z*)-2-acetamido-3-phenylacrylic acid, 3-methyl-but-2-enoic acid, and 2,2-diphenylacetic acid exhibited activity at concentration 0.078 μg ml^{-1}, whereas diorganotin(IV) complex of cinnamic acid showed activity at 1.25 μg ml^{-1} (Table 5) (Hussain et al., 2012).

Triorganotin(IV) complexes of cinnamic acid, (*Z*)-2-acetamido-3-phenylacrylic acid, 3-methylbut-2-enoic acid, and 2,2-diphenylacetic acid possessing the same triphenyl group have imperious antituberculosis activity than diorganotin(IV) complex of cinnamic acid possessing two phenyl groups which may be due to the fact that generally toxicity of the organotin compounds is associated with the organic ligand and the toxicity decreases with the order of tri > di > mono-organotins (Basu Baul, 2008; Gielen, 2002). *M. tuberculosis* is endowed with lipid and waxed cell envelop and is hard to treat.

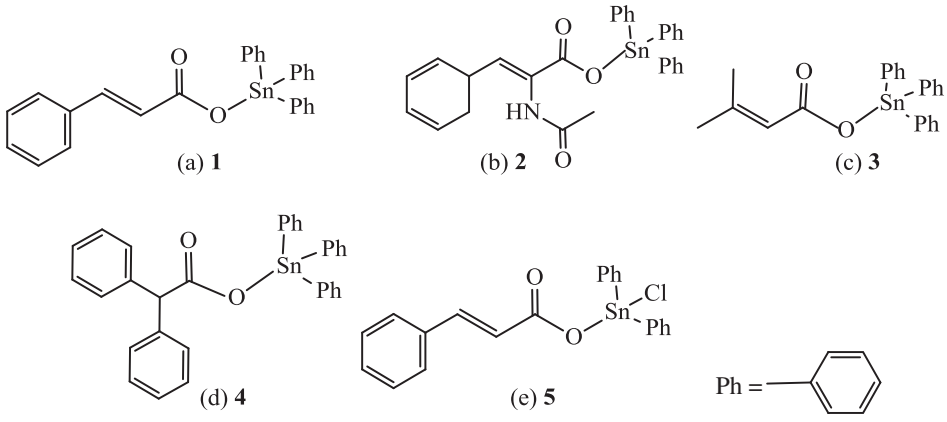

Figure 5. Structures of tirorganotin(IV) complexes of (a) cinnamic acid, (b) (*Z*)-2-acetamido-3-phenylacrylic acid, (c) 3-methylbut-2-enoic acid, (d) 2,2-diphenylacetic acid, (e) chlorodiorganotin complex of cinnamic acid.

Table 5. Antituberculosis activity of chlorodi- and triorganotin(IV) complexes

Compound	MIC (μg ml^{-1})	References
1	0.078	Hussain et al. (2012)
2	0.078	Hussain et al. (2012)
3	0.078	Hussain et al. (2012)
4	0.078	Hussain et al. (2012)
5	1.25	Hussain et al. (2012)
Isoniazid	0.1	Hussain et al. (2012)
Rifampicin	0.2	Hussain et al. (2012)

The outer most structure is the cell wall which is comprised of peptidoglycan-arabinogalactan backbone. Lipids and carbohydrate molecules are attached to this backbone structure, make the cell envelop highly complex and diverse in nature. This composition of *M. tuberculosis* cell wall renders most of the antibiotics unable to penetrate (Brennan, 2003; Briken, Porcelli, Besra, & Kremer, 2004). Unlike various conventional antimicrobial compounds, organotin compounds because of their lipophilic properties have the ability to penetrate and assembled in the lipid bilayers. Thus, they can be a potential source of developing new class of completely encouraging antimycobacterial agents. Promising antituberculosis activities of organotin mefanamic complexes and organotin complexes of the non-steroidal anti-inflammatory drugs (NSAIDs) of carboxylic acid family have also revealed in previous studies (Cooney & Wuertz, 1989; Kovala-Demertzi et al., 2002). Organotin compounds exert their antimicrobial activity mainly by interfering with the membrane function including effect on energy transduction, in and out transportation of the solute molecules (Fox, 1990). Furthermore, these compounds get solubilized in phospholipid bilayers and hence, they change the physiological composition of the lipids.

8. Conclusion

The surprising antituberculosis activity of organotin complexes of mefenamic acid, 2-[(2,6-dimethylphenyl)amino]benzoic acid (HDMPA), and [bis(2,6-dimethylphenyl)amino]benzoic acid, NSAIDs from the carboxylic acid, oxicams family, meclofenamic acid or (N-(2,6-dichloro-*m*-tolylanthranilic acid), cinnamic acid, (*Z*)-2-acetamido-3-phenylacrylic acid, 3-methyl-but-2-enoic acid, and 2,2-diphenylacetic acid is overviewed using *Mycobacterium tuberculosis* H37Rv. It exhibited that there exists a fascinating range of structural diversity in all these organotin complexes. Bioactivity of the overviewed organotin(IV) indicates potential development of new antituberculosis drugs. This may be considered as good antituberculosis agent in drug development in near feature.

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