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Review

Recent advances on non-steroidal anti-inflammatory drugs, NSAIDs: Organotin complexes of NSAIDs

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Abstract

An overview is given of the results of organotin–NSAIDs interactions. Several organotin complexes with NSAIDs, derivatives of the carboxylic acid family and oxicam family, have been synthesized and characterized by spectroscopy and X-ray crystallography at the University of Ioannina. Results concerning the biological activity of these organotin complexes will be referred.

Keywords: NSAIDs; Tolfenamic acid; Diclofenac acid; Mefenamic acid; Flufenamic and oxicam family; Piroxicam; Tenoxicam; Lornoxicam; Crystal structures; Anti-tuberculosis and anti-proliferative activity in vitro

Contents

1. Introduction

Non-steroidal anti-inflammatory drugs, NSAIDs, from the carboxylic acid family, derivatives of *N*-phenylanthranilic acid, such as tolfenamic acid, diclofenac, mefenamic, flufenamic, and from the oxicam family, piroxicam, tenoxicam and lornoxicam, are widely used in inflammatory and painful diseases of rheumatic and non-rheumatic origin.

The anti-inflammatory activity of NSAIDs and most of its other pharmacological effects are related to the inhibition of the conversion of arachidonic acid to prostaglandins, which are mediators of the inflammatory process. NSAIDs are potent inhibitors of cyclo-oxygenase in vitro and in vivo, thereby decreasing the synthesis of prostaglandins, prostacyclin, and thromboxane products. Recently, two different cyclooxygenase isoforms have been characterized Cox-1 and Cox-2. Inhibition of the Cox-2 enzyme system results in anti-inflammatory action, while inhibition of the Cox-1 enzyme system results in anti-inflammatory action as well as gastric irritation [1]. New studies from the last years revealed that in addition to arthritis and pain, cancer and neurodegenerative diseases like Alzheimer's disease could potentially be treated with Cox-2 inhibitors [2].

Synthesis and study of metal complexes with active drugs as ligands is a research area of increasing interest

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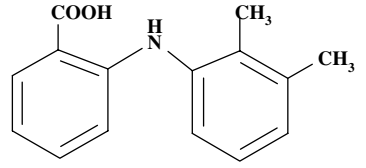
for inorganic, pharmaceutical and medicinal chemistry and has concentrated much attention as an approach to new drug development [3]. The goal is to prepare new compounds with better or different pharmacological profile than that of the free ligand.

Organotin compounds are of interest in view of their considerable structural diversity. Among the compounds, the most ubiquitous are the carboxylates [4]. The increasing interest in organotin(IV) carboxylates that has arisen in the last few decades is attributed to their significantly important biological properties. Several di- and tri-species have shown potential as anti-neoplastic and anti-tuberculosis agents [5].

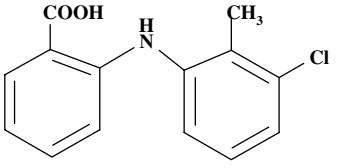
Several organotin complexes with NSAIDs, derivatives of the carboxylic acid family and oxicam family, have been synthesized and characterized by spectroscopy and X-ray crystallography at the University of Ioannina. Some of the organotin complexes exhibit very promising anti-tuberculosis and anti-proliferative activity in vitro.

2. Organotin(IV) complexes with NSAIDs from the carboxylic acid family and derivatives

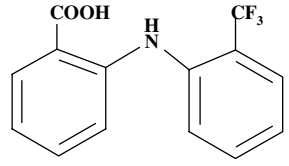
NSAIDs from the carboxylic acid family such as mefenamic (**1**) [7a], tolfenamic (**2**) [6c], flufenamic (**3**) [7c], diclofenac (**4**) [6a,6b], indomethacin (**7**) [7b] and also derivatives such as 2-(2,6-dimethylanilino)benzoic acid (**5**) [8a,5d] and 2-(2,3-dichloroanilino)benzoic acid (**6**) [8b] were used as ligands in order to synthesize organotin complexes [6–8] (see Scheme 1).



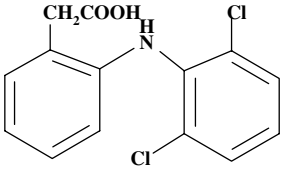
Hmef (**1**)



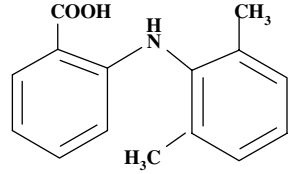
Htolf (**2**)



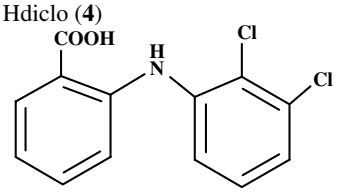
Hfluf (**3**)



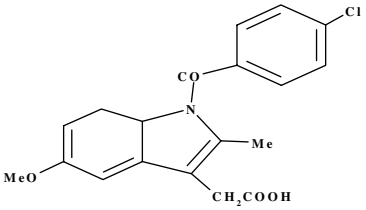
Hdiclo (**4**)



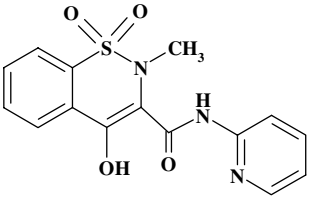
2-(2,6-dimethylanilino)benzoic acid, HDMAB (**5**)



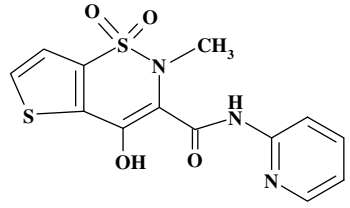
2-(2,3-Dichloroanilino)benzoic acid, HDCAB (**6**)



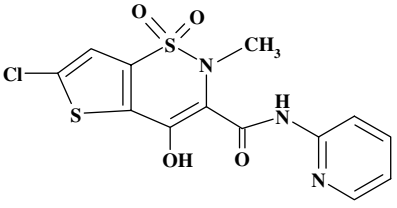
Hindo (**7**), [1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1Hindole-3-acetic acid]



H_2pirox (**8**), [4-hydroxy-2-methyl-N-pyridin-2-yl)-2H-1,2-benzothiazine-3-carboxamide-1,1-dioxide]



H_2tenox (**9**), [4-hydroxy-2,methyl-N-2-pyridyl-2H-thieno(2,3-e)-1,2-thiazine-3-carboxamide-1,1-dioxide]



H_2lornox (**10**), [(8-chloro-4-hydroxy-2-methyl- 2-pyridyl-2H-thieno[2, 3-*e*]-1, 2-thiazine-3- amide-1,1-dioxide]

Scheme 1. NSAIDs from the carboxylic acid family and oxicams (**1**–**10**).

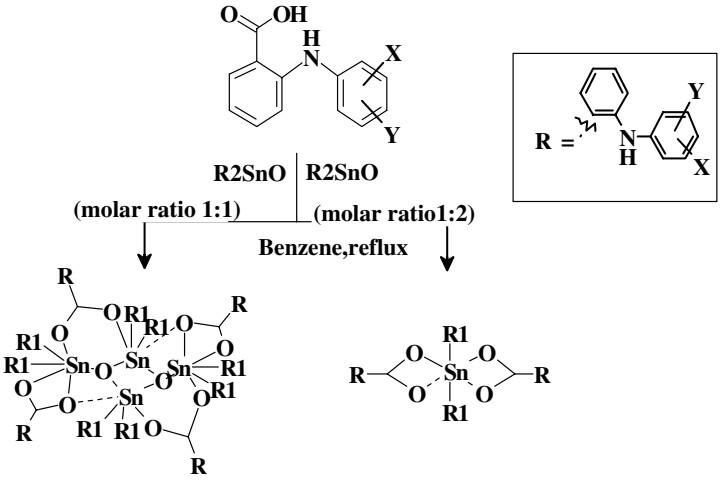
The diorganotin adducts were obtained by azeotropic removal of water produced by the reaction between the diorganotin oxide and mefenamic, tolfenamic, flufenamic, diclofenac or indomethacin acid in the molar ratio 1:1 and 1:2 according to the reactions (1) and (2) and the reaction scheme [6,7] (see Scheme 2)

$$4SnR_2O + 4HL \rightarrow 2[R_2LSnOSnLR_2]_2 + 2H_2O \quad (1)$$

$$SnR_2O + 2HL \rightarrow [SnR_2(L)_2] + H_2O \quad (2)$$

The dimeric ladders $[R_2LSnOSnLR_2]_2$, are tetranuclear, centro-symmetric and features a central rhombus Sn_2O_2 unit with two additional tin atoms linked at the O atoms. The "external' tin atoms have their coordination geometry completed by a bridging bidentate carboxylate ligand or by a monodentate carboxylate ligand. Five rings, each containing two tin atoms, are present in the dimeric tetraorganodistannoxanes and the geometry around the four tin centers is distorted octahedral or distorted trigonal bipyramidal [6,7]. The overall geometry found in these structures, allowing for differences in chemistry, is similar to that found in the common motif adopted by compounds with the general formula $[R_2LSnOSnLR_2]_2$ [4]. An unusual feature of the *dimeric distannoxane* of diclofenac is the crystallographic 2-fold symmetry as it is usually the case that the $[R_2LSnOSnLR_2]_2$ structures are centrosymmetric [6a,6b]. In the dimeric distannoxane of tolfenamic the dihedral angles between the aminobenzoate aromatic ring and the other ring are 78.0(3)° and 47.8(2)°, respectively. Remarkably, these are comparable to the angles of 73° and 46°, respectively, found in the two white and yellow forms of free tolfenamic acid [6c]. Significant $\pi \rightarrow \pi$ stacking interactions, C–H–π interactions and intramolecular hydrogen bonds stabilize these structures and the organotin complexes are self-assembled via C–H–π and $\pi \rightarrow \pi$ stacking interactions, Fig. 1 [7a].

The complexes $[SnR_2(L)_2]$ consist discrete molecular units. The two monodeprotonated ligands are co-ordinated to the SnR_2 fragment and the ligands act as anisobidentate



Scheme 2. Synthesis of diorganotin complexes with (**1**–**5**), where R = Me or Bu.

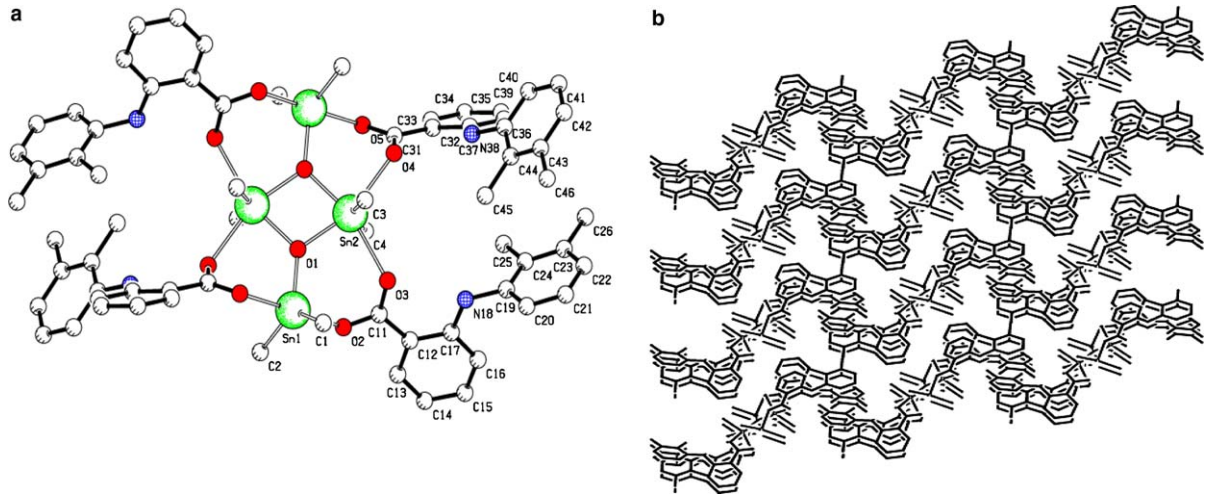


Fig. 1. (a) Perspective view of $[Me_2Sn(mef)O(mef)SnMe_2]_2$. (b) Packing diagram of the complex of $[Me_2Sn(mef)O(mef)SnMe_2]_2$ viewed along the *b*-axis.

chelating agents, thus rendering the tin atom six-coordinated. Significant $\pi \rightarrow \pi$, C–H $\rightarrow \pi$ stacking interactions and intramolecular hydrogen bonds stabilize the structures $[SnR_2(L)_2]$, Fig. 2 [8a].

Derivatives of substituted phenylanthranilic acid, **5** and **6**, which resembles to fenamates, were synthesized according to Ullmann–Goldberg condensation from substituted-benzenamine and potassium 2-bromobenzoate in the presence of 4-ethylmorpholine and copper acetate [8].

When 2-(2,3-dichloroanilino)benzoic acid, DCAB (**6**), was used, another ladder-type carboxylates were formed and the insertion of μ^2-OH or μ^2-OC_2H_5 group was observed (Scheme 3, Fig. 3). This unusual result was interpreted in terms of a competition between the strength different donors, in which the –OH or the –OC_2H_5 groups show higher donor capacity than the carboxylato group of DCAB (**6**) [8b].

The electron withdrawing effect of the two chloride substituents, at 2′,3′ position, may be weaken the donor strength of DCAB and prevent it from further condensation and the formation of the dimeric tertaorganodistannoxane $[R_2Sn(DCAB)OSn(DCAB)R_2]_2$ [8b].

In an attempt to prepare diphenyl derivatives of mefenamic [5c] or flufenamic acid [8c] a relatively insoluble white solid resulted that has a high melting point, >300 °C, and an elemental analysis indicating the loss of a benzene molecule. A facile dearylation of diphenyltin(IV) oxide takes place in the presence of mefenamic acid or flufenamic acid, reaction (3) [5c,8c]. Such dearylations have previously reported and found to have a role in the inter-conversion of phenyltin trichloroacetate complexes [9]

$$n\mathrm{SnPh_2O} + 2\mathrm{nHL} \rightarrow [\mathrm{SnPh(O)L}]\mathrm{n} + n\mathrm{C_6H_6} \quad (3)$$

When 2-(2,6-dimethylanilino)benzoic acid, DMAB (**5**) was used for synthesis of diphenyl and triphenyl derivatives the dimeric tetraorganostannoxane $[Ph_2(DMAB)SnOSn(DMAB)Ph_2]_2$ (5.3.1), the monomeric $[SnPh_2(DMAB)_2]$

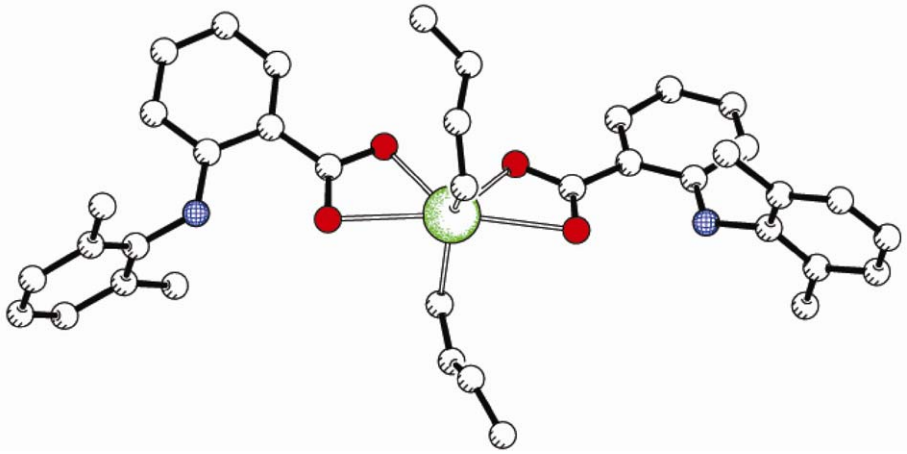
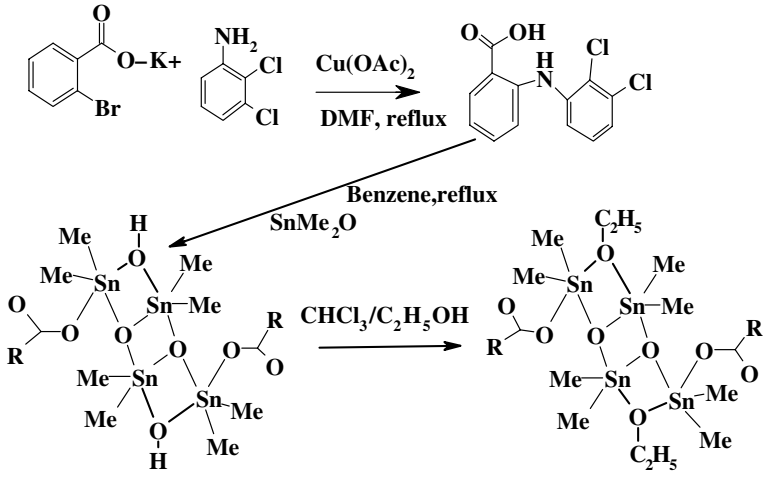


Fig. 2. Perspective view of $[Bu_2Sn(DMPA)_2]$.



Scheme 3. Synthesis of the organotin ladders $[(Me_2Sn)_4(DCAB)_2O_2(OH)_2]$ and $[(Me_2Sn)_4(DCAB)_2O_2(OC_2H_5)_2]$.

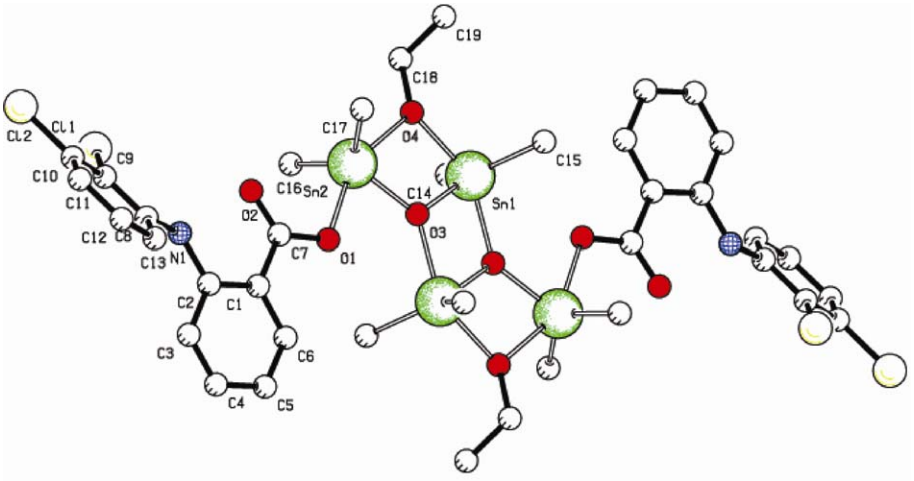


Fig. 3. Perspective view of $[(Me_2Sn)_4(DCAB)_2)O_2(OC_2H_5)_2]$.

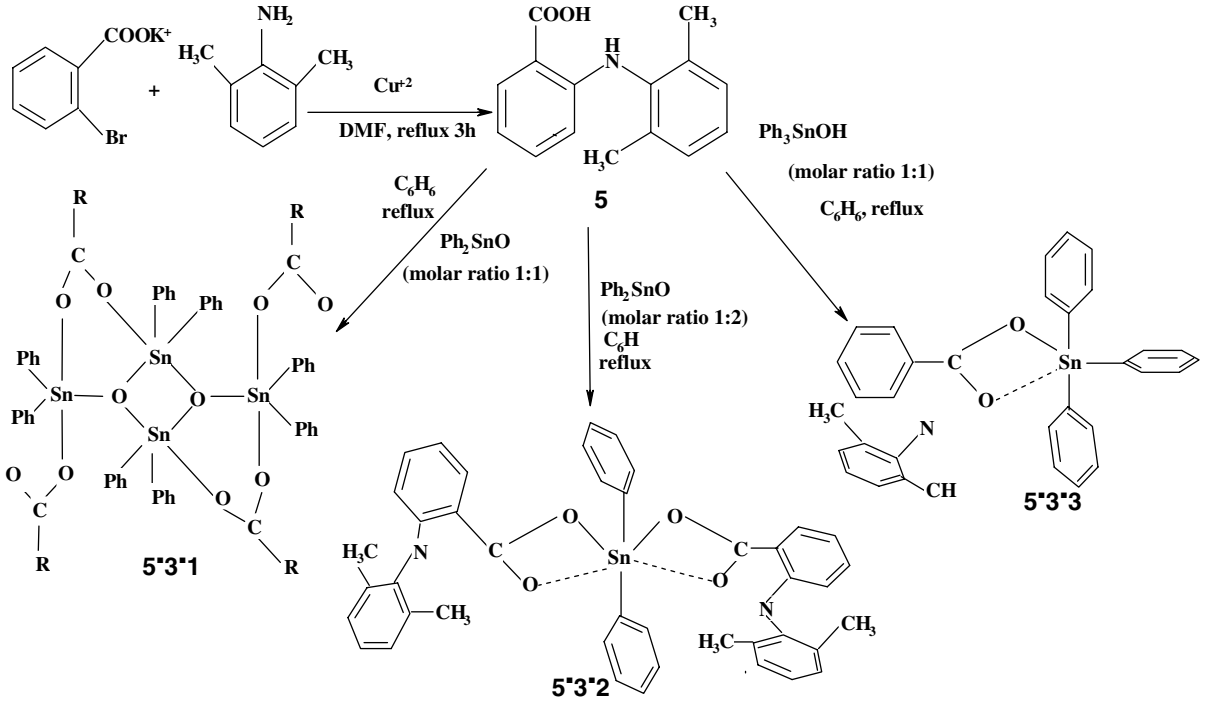
(5.3.2) and the triphenyl complex $[SnPh_3(DMAB)$ (5.3.3)], were obtained [5d] (see Scheme 4).

The crystallographically determined molecular structure of 5.3.3 is shown in Fig. 4 [5d].

The triphenyl ester of DMAB comprises discrete molecular units in which the COO group functions as an anisobidentate chelating ligand, thus rendering the Sn-atom five-coordinated. The geometry at the tin atom is intermediate between square pyramidal and *cis*-trigonal bipyramidal, in which the carboxylato-ligand spans equatorial and axial sites. A similar structure was found in the tripheneyl ester of mefenamic acid $[Ph_3Sn(mef)]$ [5c].

3. Organotin(IV) complexes with NSAIDs from the oxicam's family

Tenoxicam, piroxicam and lornoxicam (**8**–**10**) are members of oxicams. Piroxicam is a derivative of oxicams with a benzene ring replacing the thiophene ring in tenoxicam and Lornoxicam with a chloro atom at position 8, Scheme 1. Both piroxicam and tenoxicam are the most famous members of this group. In vitro experiments have demonstrated that lornoxicam is more than 100 times more potent than tenoxicam and 40 times more potent than piroxicam in its ability to inhibit cyclooxygenase. To date, piroxicam is



Scheme 4. Synthesis of di- and tri-phenylorganotin complexes $[Ph_2(DMAB)SnOSn(DMAB)Ph_2]_2$ (5.3.1), $[SnPh_2(DMAB)_2]$ (5.3.2) and $[SnPh_3(DMAB)]$ (5.3.3).

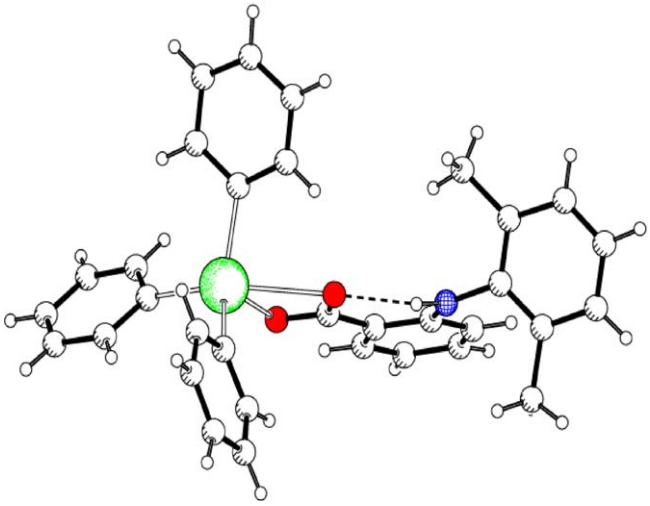


Fig. 4. The molecular structure of [$SnPh_3$(DMAB)] (5.3.3).

among the top 10 NSAIDs in the market. The drug, with four donor atoms and several possible isomers, is known to react as a monodentate ligand through the pyridyl nitrogen towards platinum(II) and as a singly deprotonated bidentate chelate ligand, through the pyridyl nitrogen and the amide oxygen, towards copper(II) and cadmium(II) [11].

Tenoxicam, piroxicam and lornoxicam were used as ligands to synthesize organotin complexes. The diorganotin adducts were prepared according to the reactions (4) and (5), in benzene solution [10]

$$n\mathrm{SnR_2O} + n\mathrm{H_2L} \rightarrow [\mathrm{SnR_2L}]n + n\mathrm{H_2O} \quad (4)$$

$$\mathrm{SnR_2O} + 2\mathrm{H_2L} \rightarrow [\mathrm{SnR_2(HL)_2}] + \mathrm{H_2O} \quad (5)$$

The stoichiometries of the complexes indicate that organotin(IV) is coordinated by the singly charged anion in $[SnR_2(HL)_2]$ and by the doubly charged anion in $[SnR_2L]n$. In $[SnR_2L]$n the doubly deprotonated ligand is coordinated as a tridentate ligand via the enolic oxygen O, the amide and pyridyl nitrogen atoms. Two carbon atoms complete the fivefold coordination at the diorganotin(IV) fragments. The di-anionic, tridentate ligand has an *EZZ* configuration and the metal coordination geometry is therefore described as distorted square pyramidal with the amide nitrogen occupying the apical position. Molecules of $[SnR_2L]$ are joined into dimers in a head-to-tail fashion by intermolecular bonds between tin and the neighbouring ketonic oxygen atom, with distances of Sn–O 2.971–2.611 Å [10a,10b,10c]. The dimers are arranged in polymers with a stacking of alternate parallel chains. Extended networks of Sn–O–Sn, C–H–O and C–H–π contacts lead to aggregation and a supramolecular assembly, Fig. 5 [10c].

The crystal structure of $[Ph_2Sn(Hpir)_2]$ (Fig. 6) has been solved [10d]. The tin atom is coordinated in a very distorted octahedral configuration through its enolate and amide oxygen atoms in a *trans*-$O_{enolate}$-*cis*-O_{amide}-*cis*-C_2 configuration. The two phenyl groups are cis but the C–Sn–C angle is much greater than 90°; indeed, it is closer to the tetrahedral value. In the present structure, the amide nitrogen atoms remain protonated, as they are not coordinated. This is in sharp contrast to the behaviour of piroxicam with di-*n*-butyltin, which forms [Bu2Sn(pir)]*n* with doubly deprotonated, tridentate piroxicam [10a].

Spectral solution studies suggest that the diorganotin adducts 1:2 lose one ligand and after rearrangement, give the 1:1 adducts according to reaction (6) [10c]

$$[\mathrm{SnR_2(HL)_2}] \rightleftharpoons [\mathrm{H_2L}] + [\mathrm{SnR_2(L)}] \quad (6)$$

4. Biological activity

Tuberculosis (TB) caused by *Mycobacterium tuberculosis* remains a leading cause of mortality worldwide into

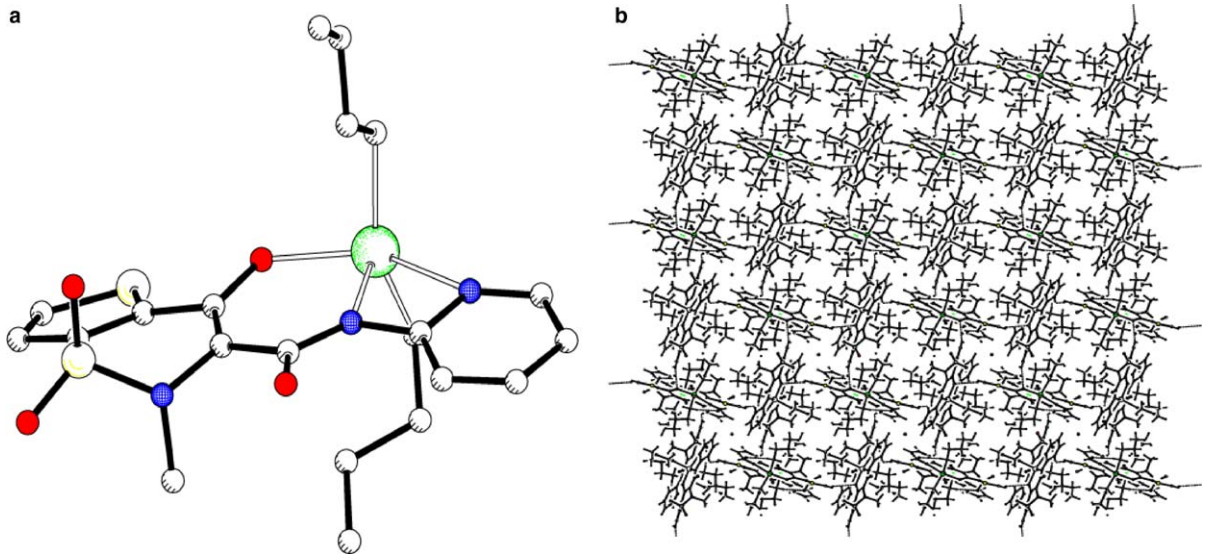


Fig. 5. (a) Perspective view of [Bu_2Sn(tenox)]*n*. (b) Packing diagram of the complex [Bu_2Sn(tenox)]*n* viewed along the *c*-axis.

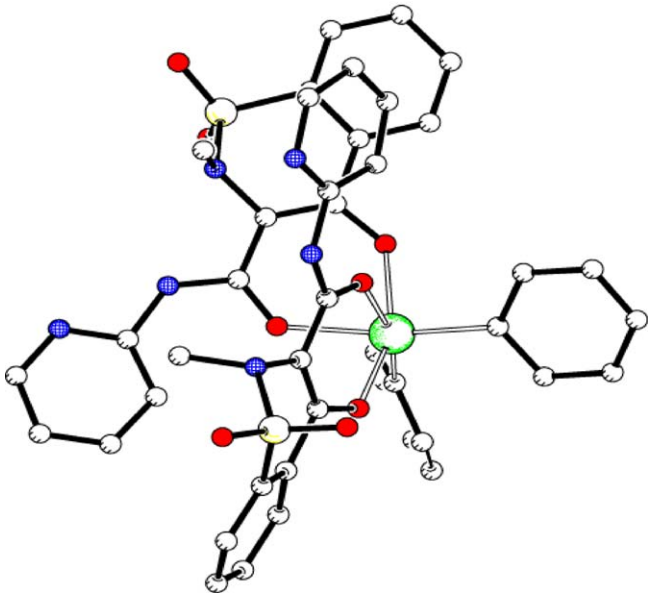


Fig. 6. Perspective view $[Ph_2Sn(Hpir)_2]$.

21st century. The mortality and spread of this disease has further been aggravated because of synergy of this disease with HIV. A number of anti-TB drugs are ineffective against this disease because of development of resistance strains. Internationally efforts are being made to develop new anti-tubercular agents [12].

Table 1
Biological activities of NSAIDs and organotin complexes of NSAIDs towards *Mycobacterium tuberculosis* H37Rv

Compound	Inhibition (%)	MIC (μg/ml)	IC_{50} (μg/ml)	SI
H_2tenox (**9**)[a]	21	>6.25		
H_2pirox (**8**)[a]	11	>6.25		
H_2lorno (**10**)[a]	2	>6.25		
Hfluf (**3**)[a]	0	>6.25		
HDMAB (**5**)[c]	0	>6.25		
$[Me_2(dicl)SnO\text{-}Sn(dicl)Me_2]_2$[a]	0	>6.25		
$[Ph_2(dicl)SnO\text{-}Sn(dicl)Ph_2]_2$[a]	0	>6.25		
$[Sn(Ph)_3(Flu)]$[a]	0	>6.25		
$[SnPh_3(mef)]$[b] [5c]	98	0.39		
$[SnBu_2(mef)_2]$[b] [5c]	92	>6.25		
$[SnMe_2(dicl)_2]$[a]	100	3.13		
$[SnBu_2(dicl)_2]$[a]	100	3.13		
$[SnPh_3(pirox)]$[a]	100	1.56	0.07	0.04
$[SnPh_3(lorno)]$[a]	100	3.13	0.19	0.06
$[SnPh_3(indo)]$[a]	100	0.78	0.07	0.09
$[SnPh_3(tenox)]$[a]	100	0.78	0.08	0.10
$[Sn(Ph)_3(DMAB)]$[c]	100	0.78	1.89	2.42
Rifampicin[d]	95	0.25	113.6	

Alamar assay; drug concentration 6.25 μg/ml.
For details, see Refs. [5c,5d].
[a] Ref. [13].
[b] Ref. [5c].
[c] Ref. [5d].
[d] Positive drug control.

Selected NSAIDs and organotin complexes were screening against *Mycobacterium tuberculosis* H37Rv in BACTEK 12B medium using the BACTEC 460-radiometetric system at the single concentration of 6.25 μg/ml. Rifampicin, RMP, was included as a positive drug control (Table 1).

The parent drugs, the dimeric tetraorganostannoxanes, and the triphenyl ester of flufenamic did not exhibit any inhibitory effect and were not screened further. The rest of the organotin compounds exhibited highest inhibitory activity of 92–100%, respectively, and considered as active compounds. The column labeled MIC, lists the measured minimum inhibitory concentration. The MIC values are in the range of 3.13–0.78 μg/ml. The significance of this value depends on several factors such as compound structure, novelty, toxicity, and potential mechanism of action, though generally an MIC $\leqslant$ 1 μg/ml in a novel compound class is considered as an excellent lead.

The triphenyl esters of NSAIDs were also tested for cytotoxicity (IC_{50}) in Vero cells at concentrations equal to and greater than the MIC value *Mycobacterium tuberculosis* H37Rv. The IC_{50} value was found to a concentration level of 1.89 μg/ml for $[Sn(Ph)_3(DMAB)]$. The selectivity index ($SI = IC_{50}/MIC$) was calculated to be 2.42, showing that this compound not only displaying a considerable activity, but also had increased cytotoxicity.

The triphenyl esters of anthranilic acids are considered excellent lead compounds and the results of this study represent the discovery of triphenyl derivatives as a potential new class of anti-tuberculosis agent.

Flufenamic acid and organotin adducts were evaluated for anti-proliferative activity in vitro. Among the compounds tested $[Bu_2(flu)SnOSn(flu)Bu_2]_2$ and $[Bu_2Sn(flu)_2]$ exhibited high cytotoxic activity against the cancer cell line A549 (non-small cell lung carcinoma) [7c]. The ID_{50} value for $Bu_2(flu)SnOSn(flu)Bu_2]_2$, and $[Bu_2Sn(flu)_2]$ is 0.24 ± 0.1 and 0.35 ± 0.1, respectively (where ID_{50} is the dose of compound (in μg/ml) that inhibits a proliferation rate of the tumor cells by 50% as compared to control untreated cells). The ID_{50}values for $[Bu_2(flu)SnOSn(flu)Bu_2]_2$ and $[Bu_2Sn(flu)_2]$ are lower to the international activity criterion for synthetic agents (4 μg/ml) [14]. Thus, these compounds are considered as agents with potential anti-tumor activity, and can therefore be candidates for further stages of screening in vitro and/or in vivo.

Acknowledgements

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Disease Center, Colorado State University, Birmingham, AL, USA) for the in vitro evaluation of anti-mycobacterial activity.

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