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Organotin (IV) derivative of Piperic acid and Phenylthioacetic acid: Synthesis, Crystal structure, Spectroscopic characterizations and Biological activities

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Abstract

Three new organotin (IV) derivatives have been prepared from piperic and phenylthio acetic acids, the former is obtained by hydrolysis of piperine, which is extracted from black pepper. The three complexes $\{[n\text{-}Bu_2SnO_2C\text{-}(CH{=}CH)_2\text{-}C_7H_5O_2]_2O\}_2$ 1, $\{[n\text{-}Bu_2SnO_2C\text{-}CH_2\text{-}S\text{-}C_6H_4]_2O\}_2$ 2, and $[Ph_3SnO_2C\text{-}(CH{=}CH)_2\text{-}C_7H_5O_2]_n$ 3, have been characterized by IR, ^1H and ^{13}C NMR spectroscopic techniques. Single crystal diffraction studies were made to determine the structures of the three compounds 1, 2 and 3. Compounds 1 and 2 crystallize in the triclinic system ($P\bar{1}$), and the respective cell parameters (Å, °) [a = 10.4427 (19), b = 12.881 (2), c= 15.991 (3), α= 76.840 (7), β= 85.130 (6), γ= 87.278 (6), and [a = 12.237 (3), b = 12.580 (3), c= 13.507 (3), α= 91.146 (8), β= 104.916 (8), γ= 111.307 (8)]. Compound 3 crystallizes in the Monoclinic system ($P2_1/c$) with the cell parameters (Å, °) [a= 12.982 (3), b= 11.282 (2), c= 18.528 (4) and β (°) = 108.572 (7)]. The title compounds were evaluated for their biological activities against a range of cancer cell lines (BT-474, MDA-MB-231, AU565), Chronic myeloid leukemia cell line (K562), Lung cancer cell line (H460) and normal cell line 3T3 mouse fibroblast. Especially complexes 1 and 3 (derivatives of the piperic acid), i.e. Pipericcarboxylate triphenyltin $[Ph_3SnO_2C\text{-}(CH{=}CH)_2\text{-}C_7H_5O_2]_n$ and $\{[n\text{-}Bu_2SnO_2C\text{-}(CH{=}CH)_2\text{-}C_7H_5O_2]_2O\}_2$ were most active against all cancer cell lines. These compounds were also active against 3T3 normal cell line, but the IC_{50} values were high as compared to cancer cell lines

Keywords: Organotin, Carboxylic acids, Piperic acid, Synthesis, Spectroscopy, X-ray crystallography, Cell lines.

1. **Introduction**

Cisplatin was the first inorganic compound clinically approved since 1978 with a great impact in the treatment of cancer and pioneering the use of metal compounds in the cancer treatment [1, 2]. It remains widely employed, due to its significant clinical activity in various kinds of solid neoplasm including bladder, testicular, ovarian, head and neck, esophageal, stomach, breast and cervical cancers [3]. Unfortunately, the use of cisplatin is not totally safe as it was identified to be associated with several disadvantages such as the emergence of cisplatin resistance and certain side effects primarily nephrotoxicity, neurotoxicity and ototoxicity for treated patients [2, 4]. Hence, carboplatin and oxaliplatin, which are also platinum derivative drugs consequently, being introduced just after [2]. To date, cisplatin and its analogue (carboplatin) are amongst the most commonly used antitumor drugs [1]. Besides the Pt complexes, other organometallic compounds, derived mainly from Sn, Au, Ti, Cu, Pd and Ru, have emerged and most of them were found to exhibit potent and comparable cytotoxic properties in different trend of antitumor specificities [5-8]. Particularly, Sn derivatives turned out to be promising anticancer drugs [5]. Indeed, many studies currently show that the organotin compounds induce cell death at very low doses and have better or similar potential than the clinically approved drugs [5, 9-11]. Generally, organotin compounds are coordinated to the ligand through atoms or groups that are bound to the central metallic atom [12]. This has produced numerous di- and triorganotin(IV) derivatives complexes with strong anti-proliferative effects against various types of cancer cell lines [13]. Malignancy is the result from a multiple process by accumulation of mutations and other genetic alteration. Searches for non-platin metal-based antitumor drugs have attracted considerable interests [14-18]. It is well known that organotin(IV) carboxylates adopt a range of molecular structures, such as monomers, dimers, tetramers, oligomers and polymers [19-21]. Many organotin(IV) carboxylates were found to possess anticancer activity in a variety of tumor cells and the structure of these organotin(IV) compounds were characterized in the solid phase, as well as in solution [22]. So, di and triorganotin(IV) carboxylates of the type $\{[R_2Sn(O_2CR')]_2O\}_2$ and R_3SnO_2CR' have been respectively studied in great details owing to their interesting molecular structures and cytotoxic properties [23-25]. Usually triorganotin(IV) compounds display a higher biological activity than their mono- and diorganotin(IV) analogs, which has been related to their ability to bind to proteins [26-28]. The binding ability of organotin compounds to DNA depends on the coordination number and nature of groups bonded to the central tin atom. In general, the antitumor activity of organotin compounds is influenced by their coordination structure [29-33]. These later studies reported mainly on the synthesis and activity of several series of diorganotin (IV) carboxylates synthesized; only di-n-butyltin presents an encouraging "in vivo" antitumor activity, compared with what was observed with the cis-platin [34-40]. Studies of alkyl or aryltin benzoate derivatives reported on compounds of the type $R_3Sn(O_2C_6H_5)$ which turned more active when R is a phenyl, but less when it is an n-butyl. Dibutyltin difluorobenzoate derivatives were more active than their tributyltin counterparts. Several of the compounds gave good results when tested against the colon 26 (C-26) tumor cell implanted in mice, and showed even higher toxicity than cis-platin. Octahedral (+4) complexes of the type $[R_2Sn_2X_2L_2]$ (R= alkyl or phenyl; X= F, Cl, Br, NCS; L= a nitrogen donor such as pyridine) showed activities against the murine P-388 lymphocytic leukemia system, but none for the other models. Dialkyl tin dipeptide complexes have also been studied. The dibutyl glycylglycinate complex increased the life expectancy in animal models with P388 leukaemia (~50%), but not effective against other tested tumor systems [14-18]. Dialkyltin pyridine 2,6-dicarboxylate derivatives have shown better activity than cis-platin against mammary tumor (MDF-7) and colon carcinoma (WiDr) cell lines with the dibutyl compound, proving to be the most active of the series tested [36, 37]. An usual binuclear dibutyltin oxide carboxylate compound has been found to be more active than cis-platin or

carboplatin against human breast (MCF-7), colon (WiDr) and renal (A498) tumor cell lines, as well as against melanoma and non-small cell lung cancer cell lines [37 -40]. Interesting findings from previous research have boosted our curiosity to synthesize and characterize new series of new dibutyltin and triphenyltin compounds from piperic acid and phenylthioacetic acid like the type $\{[(R\text{-}COOSnBu_2)_2O]_2O\}_2$ and $R\text{-}COOSnPh_3$ to study the influence of the nature of ligand on biological activities, either by its structure, or by introducing different substituent's. The piperic acid used to obtain organotin complexes $\{[n\text{-}Bu_2SnO_2C\text{-}(CH{=}CH)_2\text{-}C_7H_5O_2]_2O\}_2$ 1 and $[Ph_3SnO_2C\text{-}(CH{=}CH)_2\text{-}C_7H_5O_2]_n$ 3 is the pure diastereoisomer formed by hydrolysis of piperine extracted from black pepper . We thus report in the present report on the synthesis of these two compounds together with $\{[n\text{-}Bu_2SnO_2C\text{-}CH_2\text{-}S\text{-}C_6H_4]_2O\}_2$ (2). All of them been characterized as to confirm their chemical structures by the IR, ^1H and ^{13}C NMR spectroscopy and the whole data correlated with the experimentally determined crystal structures reported herein. The study is extended to explore the cytotoxicity and the activities of the title compounds against a range of cancer cell lines (i.e. BT-474, MDA-MB-231, AU565), chronic myeloid leukemia cell line (K562), lung cancer cell line (H460) and normal cell line 3T3 mouse fibroblast.

2. Experimental section

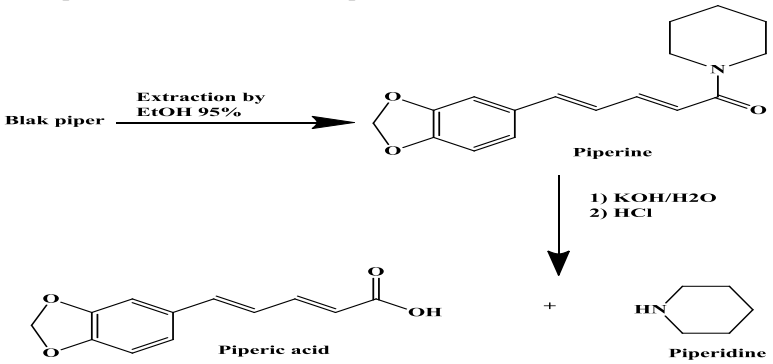
2.1. Extraction and synthesis

We adopted a green synthesis using biological molecule derived from plant source, i.e. black pepper, in the form of extract.

2.1.1. Extraction of piperine **[see the scheme 1 below].**

Piperine can be isolated in good yield from ground black pepper as described elsewhere [44-45]. Two methods of extractions of the piperine were used: extraction involving refluxing with C_2H_5OH (95%) or CH_2Cl_2 and by means of a device of Soxhlet (C_2H_5OH 95%). With the extraction involving refluxing, we obtain a mixture of two products (piperine and piperanine). During the recrystallizing in the ethanol, the piperine is soluble in the cold ethanol (Mp: 128 °C), and the other compound is piperanine soluble at hot temperature (Mp: 135 °C). We notice during these various manipulations of extractions, that the piperine is soluble in dichloromethane and in cold ethanol and the piperanine is soluble in dichloromethane and in hot ethanol. The piperine was purified and the structure is confirmed by NMR and IR analysis.

2.1.2. Synthesis of piperic acid [see the scheme 1 below].



Scheme 1: extraction of piperine from black pepper and synthesis of piperic acid from hydrolysis of piperine.

A mixture of an aqueous solution of potassium hydroxide (12g in 15 mL of water) and 3g of piperine in ethanol (25 mL) is refluxed for 2h. After cooling to room temperature, the mixture, which is mostly the resulted salt, is

transferred to a 50 mL Erlenmeyer flask containing 50 mL of water. The acidification of the solution by adding drop wise HCl afforded to the desired piperic acid. After filtration the product is recrystallized in absolute ethanol. Mp= 215°C, almost the same as previously reported (Mp = 216 °C)[46].

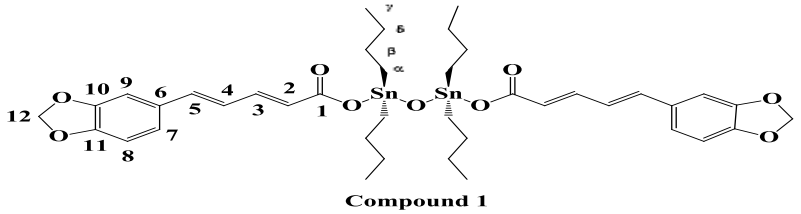
2.1.3. Synthesis of {[n-Bu_2SnO_2C-$(CH=CH)_2$-$C_7H_5O_2$]$_2$O}$_2$ 1

A mixture of Dibutyltin oxide n-Bu_2SnO (1mmol) and piperic acid (1mmol) was heated under reflux in toluene (50 mL) for 10h in a Dean-Stark apparatus for azeotropic removal of the water formed in the reaction (scheme 3). After cooling to room temperature, the solution was filtered. The filtrate was gradually removed by evaporation under vacuum until solid product was obtained. The solid was then dissolved in minimum amount of ethanol and dichloromethane. Yellow cristals, sui**Table** for X-ray analysis, formed up on slow evaporation of the solvent after one week. Yield 68%; M.p. =126- 128°C; 1H NMR (400 MHz, DMSO d6) δ ppm 5,84 (d, 4H, H7); 5,92 (s, 8H, H12); 6,68 (d,d, 4H, H4); 6,84 (d,d, 4H, H5); 6,94 (s,4H, H9); 7,24 (d,d, 4H, H3); 7,67 (d,4H, H2); 7,87 (d,4H, H8); Sn-Bu Skeleton: 1,63 (m, 8H, Hα), 1,32 (m, 16H, Hβ), 1,18 (m, 16H, and Hδ),0,84 (t, 24H, Hγ); 13C NMR (DMSO-d6) δppm: 101,37(C12); 105,91 (C9), 108,71 (C8), 122,66 (C2), 124,09 (C4 and C7), 130,92 (C6); 138,97 (C5), 143,83 (C3), 148,28 (C10 and C11), 174,6 (C1), Sn-Bu skeleton: 27,71 (Cα), 27,31 (Cβ), 26,85 (Cδ), 13,74 (Cγ). IR (KBr, cm-1): 1624 ν_{asy}(COO); 1424 ν_{sym}(COO); 560 ν(Sn–C); 465 ν(Sn–O).

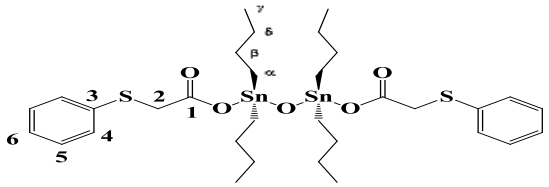
2.1.4. Synthesis of {[n-Bu_2SnO_2C-CH_2-S-C_6H_4]$_2$O}$_2$ 2

The synthesis of the title compound was carried out in an identical manner as described for 1 by using di-n-butyltin oxide (2mmol) and phenyl thioacetic acid (2mmol) (scheme 3). After work-up, the solid was recrystallized from ethanol and dichloromethane, which up on slow evaporation afforded colorless cristals. Yield 65%; M.p. =142-144°C; 1H NMR (400 MHz, DMSO d6) δppm: 3,52 (s, 4H, H2); 7,02-7,26 (m, 12H, H4,H5 and H6 of Ph);Sn-Bu Skeleton: 1,33 (m, 8H, Hα), 1,3 (m, 16H, Hβ), 1,11 (m, 16H, and Hδ),0,78 (t, 24H, Hγ); 13C NMR (DMSO-d6) δppm: 37,62(C2); 125,86 (C6), 127,74 (C5), 128,94 (C4), 136,51 (C3), 174,74 (C1), Sn-Bu skeleton: 29,774(Cα), 27,65(Cβ), 26,82(Cδ), 13,63(Cγ). IR (KBr, cm-1): 1650 ν_{asy}(COO); 1400 ν_{sym}(COO); 530 ν(Sn–C); 460 ν(Sn–O).

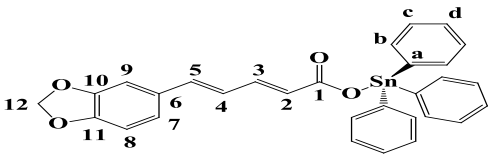
2.1.5. Synthesis of [Ph_3SnO_2C-$(CH=CH)_2$-$C_7H_5O_2$]$_n$ 3



Compound 1



Compound 2



Compuund 3

Schema 2: Numbering scheme in compound 1, 2 and 3 are shown below

The targeted compound was synthesized according to the steps reported on scheme 3. Triphenyltin(IV) hydroxide (2 mmol) and piperic acid (2 mmol) in toluene (50 mL) were refluxed for 8h under azeotropic removal of H_2O by a Dean–Stark trap. After cooling down to the room temperature, the solution was filtered. The filtrate was gradually

removed by evaporation under vacuum until solid product was obtained. The solid was then dissolved in minimum amount of ethanol and dichloromethane. Yellow crystals, suitable for X-ray analysis, formed upon slow evaporation of the solvent after one week.Yield 75%; M.p. =143-145°C; 1H NMR (400 MHz, DMSO d6) δppm: 5,9 (s, 2H, H12); 6,00 (d, 1H, H2); 6,69 (d,1H, H7); 6,71 (d,d, 1H, H4); 6,71 (d, 1H, H8); 6,81 (d,1H, H5); 6,91 (s, 1H, H9); 7,6 (d,d, 1H, H3); 7,38 (m, 15H, H b, H c and H d of SnPh), 13C NMR (DMSO-d6) δppm: 101,54(C12); 105,93 (C9), 108,53 (C8), 120,67 (C2), 122,93 (C7), 124,8 (C4), 128,44 (C6); 139,92 (C5), 146,00 (C3), 148,37 (C10 and C11), 173,58 (C1), Sn-phenyl skeleton: 138,61 (Ca), 130,7 (Cb), 137,18 (Cc), 130,09 (Cd). IR (KBr, cm-1): 1624 ν_{asy}(COO); 1424 ν_{sym}(COO); 530 ν(Sn–C); 450 ν(Sn–O).

2.2. Characterizations

The new synthesized products have been characterized by ^{1}H and ^{13}C-NMR with a 400MHz Bruker AC-250 spectrometer using DMSO-d6 as the solvent and TMS as an internal standard and IR. The results have been compared to the published data [38-40, 44-51].

2.2.1. Infrared

To record IR spectra, pellets were prepared using KBr and measured on Perkin Elmer 1310 spectrometer. The spectra show some supplementary bands compared to the free acids or di-n-butyltin oxide. Indeed, we noticed a fine band at 670 cm^{-1} characteristic of O-Sn bond [46-51]. Recall that the IR spectra of the free ligands show a wide strip ranging between 3200 and 2400 cm^{-1}, which characterize the OH of the carboxylic acid function. In the spectra of di-n-butytin derivatives, we generally notice a disappearance of that OH band, and a displacement of the C=O band towards the low frequencies, as well as the appearance of a band around 670 cm^{-1}, which is associated to O-Sn-O deformation[48-51]. In the spectrum of the triphenyltin carboxylate 3, we noticed the absence of the OH-associated band, either as hydroxide triphenyltin or as carboxylic acid function. Same features as for the previous cases, a displacement towards the low frequencies of the C=O band, as well as the presence of the band at 670 cm^{-1}, which reveals the presence of O–Sn in the structure. These results are conforming well to the single crystal structure data.

2.2.2. Proton and carbon NMR analysis of Compound 1, 2 and 3

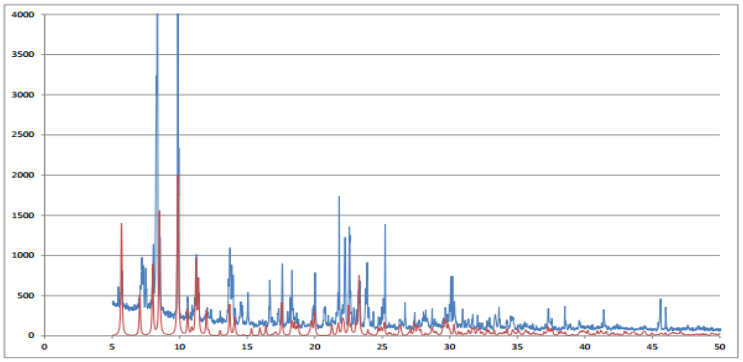
The ^{1}H-NMR spectrum of the oxide form shows two butyl groups. The attribution of the protons was carried out on the basis of multiplicity and integration of the signals or by analogy with some compounds already described in the literature, and which have similar chemical shifts [38-40, 44-51]. The coupling constant J (^{1}H, ^{117}Sn) on the level of butyl, inform on the hybridization of tin´s orbitals. However, in our case, it is not easily measurable, because of the overlapping and the high width of the massif lines. Concerning ^{13}C-NMR, the attribution of the chemical shifts of the ligands´s signals, like those of the butyl radical of all the derivatives, was carried out by comparison with the chemical shifts of the similar derivatives described in literature [38-40, 44-51]. This attribution was done on the basis of spectra obtained by various techniques in which resonances of quaternary carbons, of carbonyls and those of secondary carbons (-CH_2-) remain unchanged whereas those of tertiary carbons (-CH) and of methyl (-CH_3) are reversed. On the ^{13}C-NMR spectrum we observe two resonances very near for each butyl carbon atom related to tin. According to this study, the following structural form might be suggested (scheme 1). The attribution of the chemical shifts of the compound 3 (tripheyltin) was made on basis of multiplicity and integration of the signals or by analogy with some compounds already described in the literature, and which have similar chemical shifts [38-40, 44-51]. The protons of the grouping phenyl appear in the form of solid masses with 7.38 – 7.69 ppm (multiplet). These results are in agreement with the structural known data [48-51]. Moreover, the NMR spectroscopy study results are in agreement

with the crystalline structure of these compounds; compound 1 and 2 show two types of tin sites in the solid state form, while in compound 3 there is only one tin site in accordance with known results[48-52] (see below X-ray).

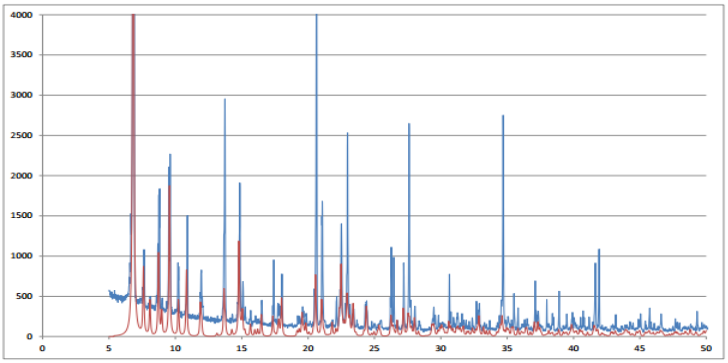
2.3. X-ray crystallography

2.3.1 Powder Diffraction

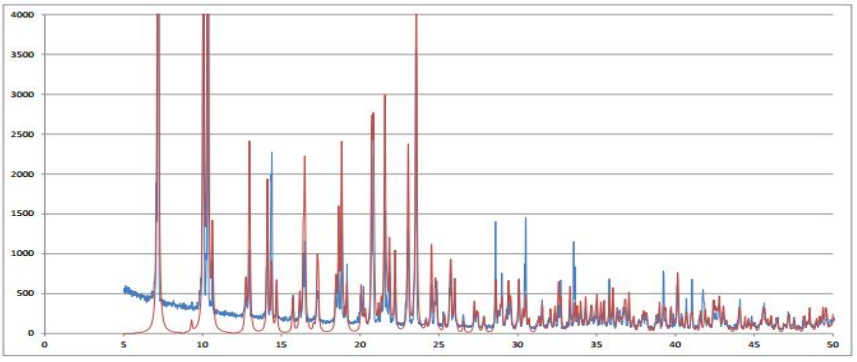
PXRD measurements were carried out at 298 K using a PANalytical X'Pert PRO diffractometer [with a Cu-Kα radiation (λ= 1.5405 Å)] on a mounted bracket sample stage. PXRD patterns were predicted from single crystal structures using Mercury [53].



Powder diffraction pattern for {[n-Bu2SnO2C-(CH=CH)2-C7H5O2]2O}2 (1);experimental drawn in blue, calculated from single crystal structure in red. Counts shown in arbitrary units vs 2Θ



Powder diffraction pattern for {[n-Bu2SnO2C-CH2-S-C6H4]2O}2 (2) experimental drawn in blue, calculated from single crystal structure in red. Counts shown in arbitrary units vs 2Θ



Powder diffraction pattern for [Ph3SnO2C-(CH=CH)2-C7H5O2]n (3) experimental drawn in blue, calculated from single crystal structure in red. Counts shown in arbitrary units vs 2Θ

2.3.2. Single crystal study

Table 1: Crystal data and refinements of the three compounds ({[n-Bu_2SnO_2C-$(CH=CH)_2$-$C_7H_5O_2]_2O\}_2$ (1); {[n-Bu_2SnO_2C-CH_2-S-$C_6H_4]_2O\}_2$ (2) and [Ph_3SnO_2C-$(CH=CH)_2$-$C_7H_5O_2]_n$ (3).Compound

Formula	$C_{80}H_{108}O_{18}Sn_4$	$C_{64}H_{100}O_{10}S_4Sn_4$	$C_{30}H_{24}O_4Sn$
Formula weight ($g.mol^{-1}$)	1832.42	1632.44	567.18
Nomenclature	bis[bis(di-n-butylpipericcarboxylate tin) oxide]	bis[bis (di-n-butyl phenylthioacetate tin) oxide]	Pipericcarboxylate triphenyltin
Cryystals Dimensions (mm)	0.21 × 0.20 × 0.11	0.29 × 0.26 × 0.10	0.34 × 0.24 × 0.13
Colour	Block, yellow	Block, colourless	Block, yellow
λ (MoKα) (Å)	0.71073		
Crystal system & space group	Triclinic, P-1	Triclinic, P-1	Monoclinic, $P2_1/c$
a (Å)	10.4427 (19)	12.237 (3)	12.982 (3)
b (Å),	12.881 (2)	12.580 (3)	11.282 (2)
c (Å),	15.991 (3)	13.507 (3)	18.528 (4)
α(°)	76.840 (7)	91.146 (8)	90
β(°)	85.130 (6)	104.916 (8)	108.572 (7)
γ(°)	87.278 (6)	111.307 (8)	90
Volume ($Å^3$)	2086.0 (7)	1857.0 (8)	2572.4 (9)
T (K)	295		
Z	1	1	4
μ (mm^{-1})	1.25	1.49	1.03
F(000)	932	828	1144
Reflections collected / unique	10302 / 8771 [R_{int} = 0.028]	2647 / 1778 [R_{int} = 0.035]	6363/5658[R_{int}= 0.030]
Data / restraints / parameters	10302 / 0 / 464	9148 / 25 / 378	6363 /0/ 316
Goodness of Fit	1.13	1.045	1.07
R/ wR2	0.031/0.139	0.038/0.104	0.026/0.069
(Δρ max/min(eA^{-3})	-0.50 - 1.40	-1.00 - 1.19	-0.4 - 1.06

Selected single crystals of the three new compounds were selected for X-ray diffraction analysis. Data were collected at room temperature using a Bruker D8 VENTURE diffractometer [using Mo-Kα radiation (λ= 0.71073 Å)], equipped with a Photon II CPAD detector and an IμS 3.0 (dual Cu and Mo) microfocus sealed tube generator. Diffraction data were collected and processed using *APEX3* Ver. 2016.9-0 Bruker-AXS, 2016. The structures were solved using SHELXT [54] and refined using SHELXL [55] within OLEX2 [56]. All non-Hydrogen atoms were refined with anisotropic atomic displacement parameters except partially occupied carbon atoms as part of a disorder model in 2. Hydrogen atoms were placed in geometrically calculated positions and refined as part of a riding model, with isotropic

adps at 1.2U (eq) of the parent carbon atom for all atoms except the Me hydrogen atoms which are 1.5 U(eq).
Details of the data collection and refinement are given in **Table** 1.Theatomic coordinates are reported in **Table**s 2a-c, while **Table**s 3a-c contains the basic geometrical data. CIFs have been deposited with the Cambridge Structure Data base CCDC1838847 (1), 1838849 (2) and 1838844 (3). The structural graphics were created using the software Mercury [53].

Table 2a: Fractional atomic coordinates and isotropic or equivalent isotropic displacement parameters (Å^2) for (1).

Atom	*x*	*Y*	*z*	U_{iso}*/U_{eq}
Sn1	0.43836 (2)	0.24728 (2)	0.58161 (2)	0.04099 (8)
Sn2	0.58595 (2)	0.47533 (2)	0.41404 (2)	0.03938 (8)
O1	0.33084 (19)	0.33845 (15)	0.66627 (12)	0.0534 (4)
O2	0.2593 (2)	0.19168 (17)	0.75495 (15)	0.0697 (6)
O9	0.48025 (15)	0.39831 (13)	0.52331 (10)	0.0413 (4)
O3	-0.3225 (3)	0.6710 (2)	0.99324 (17)	0.0867 (8)
O4	-0.4634 (3)	0.5768 (2)	1.09895 (17)	0.0855 (8)
O5	0.6223 (2)	0.31689 (16)	0.37562 (14)	0.0687 (6)
O6	0.5640 (2)	0.18386 (16)	0.48483 (15)	0.0626 (5)
O7	1.2841 (4)	0.0972 (3)	-0.0276 (2)	0.1157 (13)
O8	1.2819 (4)	-0.0862 (3)	0.0073 (2)	0.1117 (12)
C1	0.2631 (2)	0.2889 (2)	0.73603 (18)	0.0471 (6)
C2	0.1844 (3)	0.3574 (2)	0.78211 (19)	0.0573 (7)
H2	0.191692	0.430876	0.763403	0.069*
C3	0.1036 (3)	0.3206 (3)	0.84894 (19)	0.0589 (7)
H3	0.103774	0.247129	0.870341	0.071*
C4	0.0147 (3)	0.3843 (3)	0.8918 (2)	0.0615 (7)
H4	0.021062	0.458019	0.875161	0.074*
C5	-0.0763 (3)	0.3455 (3)	0.9538 (2)	0.0651 (8)
H5	-0.075942	0.271731	0.973090	0.078*
C6	-0.1756 (3)	0.4046 (3)	0.99451 (19)	0.0582 (7)
C7	-0.2621 (4)	0.3497 (3)	1.0585 (2)	0.0734 (9)
H7	-0.252894	0.275872	1.074944	0.088*
C8	-0.3618 (4)	0.4003 (3)	1.0990 (2)	0.0789 (10)
H8	-0.418042	0.362199	1.142152	0.095*
C9	-0.3728 (3)	0.5087 (3)	1.0721 (2)	0.0651 (8)
C10	-0.2890 (3)	0.5646 (3)	1.00838 (19)	0.0605 (7)
C11	-0.1901 (3)	0.5158 (3)	0.96877 (19)	0.0617 (7)
H11	-0.134242	0.555191	0.926146	0.074*
C12	-0.4282 (4)	0.6808 (3)	1.0541 (3)	0.0805 (10)
H12A	-0.403567	0.721155	1.094247	0.097*
H12B	-0.500222	0.717919	1.024614	0.097*
C21	0.6203 (2)	0.2187 (2)	0.41170 (18)	0.0451 (5)
C22	0.6926 (3)	0.1439 (2)	0.3694 (2)	0.0575 (7)
H22	0.680342	0.071403	0.391182	0.069*
C23	0.7753 (3)	0.1731 (2)	0.3013 (2)	0.0579 (7)
H23	0.784403	0.245915	0.279079	0.070*
C24	0.8526 (3)	0.1016 (2)	0.2587 (2)	0.0603 (7)
H24	0.838613	0.028836	0.276287	0.072*
C25	0.9424 (3)	0.1347 (2)	0.1957 (2)	0.0638 (8)
H25	0.951871	0.208097	0.178662	0.077*
C26	1.0285 (3)	0.0698 (2)	0.1499 (2)	0.0604 (7)
C27	1.0314 (3)	-0.0396 (3)	0.1711 (2)	0.0700 (9)
H27	0.975941	-0.074423	0.216335	0.084*
C28	1.1150 (4)	-0.1007 (3)	0.1272 (3)	0.0771 (10)
H28	1.118174	-0.174794	0.143054	0.093*
C29	1.1919 (4)	-0.0457 (3)	0.0597 (2)	0.0733 (9)
C30	1.1918 (4)	0.0629 (3)	0.0384 (2)	0.0717 (9)
C31	1.1154 (4)	0.1231 (3)	0.0829 (2)	0.0696 (8)
H31	1.119964	0.197047	0.069834	0.084*
C32	1.3198 (6)	0.0036 (4)	-0.0578 (4)	0.124 (2)
H32A	1.277839	0.004299	-0.109815	0.148*
H32B	1.412039	0.000443	-0.071171	0.148*
C1A	0.5576 (3)	0.1640 (2)	0.6772 (2)	0.0529 (6)
H1AA	0.646854	0.170631	0.654845	0.064*
H1AB	0.546556	0.195734	0.726923	0.064*
C2A	0.5256 (3)	0.0462 (2)	0.7048 (2)	0.0576 (7)
H2AA	0.434270	0.040403	0.721301	0.069*
H2AB	0.544145	0.013688	0.655841	0.069*
C3A	0.5988 (4)	-0.0149 (3)	0.7785 (2)	0.0736 (9)
H3AA	0.579327	0.016519	0.827956	0.088*
H3AB	0.690287	-0.008761	0.762470	0.088*
C4A	0.5658 (5)	-0.1332 (3)	0.8037 (3)	0.1053 (15)
H4AA	0.581922	-0.164076	0.754440	0.158*
H4AB	0.476751	-0.139941	0.823997	0.158*
H4AC	0.618164	-0.169653	0.848542	0.158*
C1B	0.2686 (3)	0.1954 (3)	0.5417 (2)	0.0598 (7)
H1BA	0.223964	0.151563	0.592157	0.072*
H1BB	0.214062	0.258080	0.523053	0.072*
C2B	0.2779 (3)	0.1341 (3)	0.4719 (2)	0.0692 (8)
H2BA	0.336056	0.072943	0.487119	0.083*
H2BB	0.312673	0.179103	0.418491	0.083*
C3B	0.1444 (4)	0.0956 (4)	0.4589 (3)	0.0963 (13)
H3BA	0.109758	0.051262	0.512721	0.116*
H3BB	0.086644	0.157071	0.443911	0.116*
C4B	0.1495 (5)	0.0351 (5)	0.3915 (4)	0.136 (2)
H4BA	0.193623	0.075041	0.340022	0.203*
H4BB	0.063591	0.022228	0.379998	0.203*
H4BC	0.194460	-0.031838	0.410423	0.203*
C1C	0.7780 (2)	0.4593 (2)	0.4496 (2)	0.0590 (7)
H1CA	0.834813	0.449306	0.400672	0.071*

H1CB	0.801031	0.524657	0.464264	0.071*
C2C	0.7986 (3)	0.3656 (3)	0.5262 (2)	0.0656 (8)
H2CA	0.733070	0.370388	0.571979	0.079*
H2CB	0.786527	0.299699	0.508472	0.079*
C3C	0.9279 (3)	0.3597 (3)	0.5614 (3)	0.0750 (9)
H3CA	0.993736	0.350797	0.516854	0.090*
H3CB	0.942132	0.426425	0.577109	0.090*
C4C	0.9407 (4)	0.2704 (4)	0.6382 (3)	0.0906 (12)
H4CA	0.942396	0.203614	0.620922	0.136*
H4CB	0.868950	0.273040	0.679439	0.136*
H4CC	1.019060	0.276845	0.663715	0.136*
C1D	0.4581 (3)	0.5091 (2)	0.31478 (18)	0.0568 (7)
H1DA	0.422705	0.581003	0.310396	0.068*
H1DB	0.506367	0.507152	0.260565	0.068*
C2D	0.3473 (4)	0.4324 (3)	0.3279 (2)	0.0712 (9)
H2DA	0.382884	0.361470	0.328078	0.085*
H2DB	0.303480	0.430312	0.384239	0.085*
C3D	0.2501 (4)	0.4592 (4)	0.2621 (3)	0.0993 (14)
H3DA	0.292509	0.458480	0.205844	0.119*
H3DB	0.215681	0.530862	0.260431	0.119*
C4D	0.1398 (5)	0.3826 (5)	0.2799 (4)	0.135 (2)
H4DA	0.077299	0.406916	0.238530	0.203*
H4DB	0.100375	0.379778	0.336837	0.203*
H4DC	0.171965	0.312814	0.275692	0.203*

Table 2b: Fractional atomic coordinates and isotropic or equivalent isotropic displacement parameters (Å^2) for (2).

Atom	*x*	*y*	*z*	*Uiso*/Ueq*	Occ. (<1)
Sn1	0.70950 (2)	0.41614 (2)	0.49820 (2)	0.05540 (8)	
Sn2	1.02020 (2)	0.63769 (2)	0.51068 (2)	0.04543 (7)	
S1	0.64130 (14)	0.02711 (12)	0.30461 (15)	0.1098 (6)	
S2	0.7495 (3)	0.8324 (3)	0.6590 (4)	0.1210 (18)	0.439(4)
O1	0.7336 (2)	0.25779 (19)	0.4684 (2)	0.0570 (6)	
O2	0.5434 (2)	0.1718 (2)	0.4753 (2)	0.0703 (7)	
O3	0.8809 (3)	0.7192 (3)	0.5047 (3)	0.0856 (9)	
O4	0.7164 (3)	0.5959 (3)	0.5341 (4)	0.1146 (15)	
O5	0.88583 (18)	0.47766 (17)	0.49505 (17)	0.0433 (5)	
C1	0.6367 (4)	0.1665 (3)	0.4624 (3)	0.0598 (9)	
C2	0.6470 (4)	0.0545 (3)	0.4362 (4)	0.0812 (13)	
H2A	0.581002	−0.007703	0.451570	0.097*	
H2B	0.723513	0.054564	0.479983	0.097*	
C3	0.4854 (5)	−0.0270 (4)	0.2354 (4)	0.0830 (13)	
C4	0.3900 (5)	−0.0380 (4)	0.2761 (4)	0.0846 (13)	
H4	0.406849	−0.012431	0.345541	0.102*	
C5	0.2705 (6)	−0.0859 (5)	0.2161 (5)	0.1023 (17)	
H5	0.207280	−0.094105	0.245265	0.123*	
C6	0.2443 (8)	−0.1218 (7)	0.1127 (6)	0.137 (3)	
H6	0.163433	−0.154101	0.071980	0.164*	
C7	0.3357 (10)	−0.1101 (8)	0.0708 (6)	0.148 (3)	
H7	0.317210	−0.133644	0.000685	0.177*	
C8	0.4576 (8)	−0.0636 (6)	0.1299 (5)	0.120 (2)	
H8	0.519836	−0.056878	0.099804	0.144*	
C11	0.7794 (4)	0.6942 (3)	0.5220 (3)	0.0659 (10)	
C12	0.7366 (4)	0.7893 (4)	0.5321 (5)	0.0932 (17)	
H12C	0.695215	0.776223	0.585678	0.112*	0.561(4)
H12D	0.676823	0.785938	0.467763	0.112*	0.561(4)
H12A	0.651700	0.764630	0.491700	0.112*	0.439(4)
H12B	0.783992	0.854684	0.503637	0.112*	0.439(4)
C13	0.9017 (8)	0.9067 (10)	0.7231 (11)	0.076 (3)*	0.439(4)
C14	0.9404 (18)	0.919 (2)	0.8301 (16)	0.150 (7)*	0.439(4)
H14	0.886434	0.884435	0.868281	0.180*	0.439(4)
C15	1.0631 (18)	0.984 (2)	0.8779 (12)	0.135 (8)*	0.439(4)
H15	1.093883	0.991805	0.949292	0.162*	0.439(4)
C16	1.1375 (15)	1.0369 (17)	0.8198 (11)	0.105 (5)*	0.439(4)
H16	1.221189	1.072024	0.851313	0.127*	0.439(4)
C17	1.0917 (12)	1.0406 (13)	0.7113 (10)	0.093 (4)*	0.439(4)
H17	1.140223	1.090371	0.675639	0.112*	0.439(4)
C18	0.9755 (11)	0.9691 (10)	0.6629 (9)	0.080 (3)*	0.439(4)
H18	0.944970	0.961236	0.591435	0.096*	0.439(4)
S2A	0.8536 (2)	0.93184 (19)	0.5621 (2)	0.0927 (9)	0.561(4)
C1A	0.5860 (4)	0.4101 (4)	0.3541 (4)	0.0836 (13)	

H1AA	0.510145	0.405501	0.367165	0.100*	
H1AB	0.618933	0.483241	0.328728	0.100*	
C2A	0.5547 (6)	0.3197 (5)	0.2703 (4)	0.1027 (18)	
H2AA	0.517914	0.245968	0.293403	0.123*	
H2AB	0.629933	0.322170	0.257282	0.123*	
C3A	0.4690 (7)	0.3253 (6)	0.1695 (5)	0.125 (2)	
H3AA	0.395244	0.326431	0.182821	0.150*	
H3AB	0.507493	0.397262	0.144370	0.150*	
C4A	0.4350 (11)	0.2337 (9)	0.0900 (6)	0.211 (6)	
H4AA	0.374213	0.239996	0.031869	0.316*	
H4AB	0.402299	0.161487	0.115380	0.316*	
H4AC	0.505663	0.237811	0.069230	0.316*	
C13A	0.9319 (10)	0.9379 (9)	0.6922 (7)	0.070 (2)*	0.561(4)
C14A	0.8996 (16)	0.8910 (17)	0.7762 (15)	0.158 (6)*	0.561(4)
H14A	0.820754	0.838891	0.769991	0.189*	0.561(4)
C15A	0.9915 (17)	0.9251 (17)	0.8737 (14)	0.160 (6)*	0.561(4)
H15A	0.978468	0.894676	0.933763	0.192*	0.561(4)
C16A	1.1004 (16)	1.0066 (15)	0.8701 (13)	0.124 (5)*	0.561(4)
H16A	1.158408	1.024575	0.934291	0.148*	0.561(4)
C17A	1.1480 (17)	1.0692 (17)	0.7987 (15)	0.152 (8)*	0.561(4)
H17A	1.221984	1.130475	0.806512	0.182*	0.561(4)
C18A	1.0516 (17)	1.0130 (19)	0.7110 (16)	0.177 (9)*	0.561(4)
H18A	1.073282	1.030410	0.650420	0.213*	0.561(4)
C1B	0.7016 (5)	0.3909 (5)	0.6563 (4)	0.0916 (16)	
H1BA	0.730265	0.329889	0.676505	0.110*	
H1BB	0.758821	0.460667	0.701125	0.110*	
C2B	0.5845 (6)	0.3629 (6)	0.6755 (5)	0.1103 (19)	
H2BA	0.529840	0.287218	0.639496	0.132*	
H2BB	0.549839	0.417758	0.647439	0.132*	
C3B	0.5915 (8)	0.3636 (6)	0.7884 (5)	0.129 (3)	
H3BA	0.632859	0.314237	0.818624	0.154*	
H3BB	0.638689	0.441068	0.823798	0.154*	
C4B	0.4673 (9)	0.3229 (8)	0.8026 (8)	0.172 (4)	
H4BA	0.425009	0.369498	0.769709	0.258*	
H4BB	0.473702	0.328599	0.874983	0.258*	
H4BC	0.422845	0.244227	0.772198	0.258*	
C1C	1.0190 (4)	0.6918 (3)	0.3623 (3)	0.0620 (9)	
H1CA	1.043068	0.774617	0.368645	0.074*	
H1CB	1.079774	0.673960	0.339053	0.074*	
C2C	0.8960 (4)	0.6368 (5)	0.2805 (3)	0.0860 (14)	
H2CA	0.866292	0.554041	0.280229	0.103*	
H2CB	0.837514	0.663281	0.298543	0.103*	
C3C	0.9026 (6)	0.6646 (7)	0.1738 (4)	0.117 (2)	
H3CA	0.961468	0.638461	0.156046	0.140*	
H3CB	0.932187	0.747378	0.174188	0.140*	
C4C	0.7814 (8)	0.6103 (11)	0.0918 (5)	0.183 (5)	
H4CA	0.793234	0.624479	0.024997	0.274*	
H4CB	0.725620	0.643105	0.103826	0.274*	
H4CC	0.748338	0.528924	0.094456	0.274*	
C1D	1.0926 (4)	0.6990 (3)	0.6701 (3)	0.0653 (10)	
H1DA	1.170628	0.691032	0.695077	0.078*	
H1DB	1.107921	0.780346	0.678909	0.078*	
C2D	1.0122 (4)	0.6389 (4)	0.7357 (3)	0.0762 (12)	
H2DA	0.987408	0.556513	0.720262	0.091*	
H2DB	0.938936	0.656175	0.718039	0.091*	
C3D	1.0754 (6)	0.6743 (5)	0.8506 (4)	0.1050 (19)	
H3DA	1.146039	0.653041	0.869275	0.126*	
H3DB	1.104007	0.757157	0.865724	0.126*	
C4D	0.9914 (10)	0.6183 (8)	0.9139 (6)	0.187 (5)	
H4DA	0.928375	0.648676	0.903827	0.280*	
H4DB	1.036908	0.633424	0.985526	0.280*	
H4DC	0.954910	0.536776	0.892864	0.280*	

Table 2c: Fractional atomic coordinates and isotropic or equivalent isotropic displacement parameters (Å2) for (3).

Atom	*x*	*y*	*z*	*U*iso*/*U*eq
Sn1	0.54790 (2)	0.83162 (2)	0.24580 (2)	0.02942 (5)
O1	0.63821 (13)	0.66618 (11)	0.24360 (10)	0.0409 (3)
O2	0.53459 (11)	0.51891 (12)	0.26024 (8)	0.0366 (3)
O3	1.1593 (2)	0.0966 (2)	0.05800 (17)	0.0948 (8)
O4	1.05382 (18)	0.03333 (19)	0.12941 (16)	0.0838 (7)
C1	0.61226 (16)	0.55790 (17)	0.24050 (11)	0.0334 (4)
C2	0.67802 (18)	0.47471 (18)	0.21239 (13)	0.0421 (5)
H2	0.654425	0.396484	0.204818	0.051*
C3	0.76854 (18)	0.5021 (2)	0.19689 (13)	0.0432 (5)
H3	0.791336	0.580688	0.201488	0.052*
C4	0.83289 (19)	0.4150 (2)	0.17323 (14)	0.0481 (5)
H4	0.811245	0.336203	0.171925	0.058*
C5	0.92050 (19)	0.4381 (2)	0.15315 (15)	0.0509 (6)
H5	0.941136	0.517198	0.153931	0.061*
C6	0.98746 (19)	0.3513 (2)	0.13000 (15)	0.0476 (5)
C7	1.0545 (2)	0.3878 (3)	0.08895 (16)	0.0565 (6)
H7	1.058479	0.468263	0.079152	0.068*
C8	1.1164 (2)	0.3085 (3)	0.06173 (19)	0.0673 (8)
H8	1.160279	0.334177	0.033797	0.081*
C9	1.1090 (2)	0.1923 (3)	0.07818 (19)	0.0627 (8)
C10	1.0454 (2)	0.1542 (2)	0.12053 (17)	0.0559 (6)
C11	0.9844 (2)	0.2302 (2)	0.14729 (16)	0.0532 (6)
H11	0.942118	0.202892	0.176004	0.064*
C12	1.1261 (3)	−0.0049 (3)	0.0908 (2)	0.0812 (10)
H12A	1.090111	−0.061312	0.051305	0.097*
H12B	1.188847	−0.043305	0.126190	0.097*
C1A	0.64829 (16)	0.91372 (16)	0.18972 (11)	0.0332 (4)
C2A	0.6060 (2)	0.9985 (2)	0.13388 (13)	0.0451 (5)
H2A	0.533565	1.020790	0.121975	0.054*
C3A	0.6705 (2)	1.0504 (2)	0.09555 (15)	0.0579 (7)
H3A	0.641331	1.107569	0.058536	0.069*
C4A	0.7768 (3)	1.0175 (3)	0.11216 (17)	0.0686 (8)
H4A	0.819709	1.051296	0.085909	0.082*
C5A	0.8201 (2)	0.9345 (3)	0.1675 (2)	0.0712 (8)
H5A	0.892726	0.912940	0.179214	0.085*
C6A	0.75621 (19)	0.8824 (2)	0.20645 (15)	0.0520 (6)
H6A	0.786320	0.826095	0.243920	0.062*
C1B	0.39790 (16)	0.76311 (16)	0.17330 (11)	0.0334 (4)
C2B	0.32685 (19)	0.7021 (2)	0.20165 (14)	0.0444 (5)
H2B	0.345256	0.688632	0.253746	0.053*
C3B	0.2286 (2)	0.6608 (2)	0.15343 (19)	0.0634 (7)
H3B	0.181157	0.620329	0.173145	0.076*
C4B	0.2011 (3)	0.6800 (3)	0.07595 (19)	0.0674 (8)
H4B	0.134434	0.653935	0.043595	0.081*
C5B	0.2715 (2)	0.7367 (3)	0.04699 (15)	0.0641 (8)
H5B	0.253760	0.747484	−0.005318	0.077*
C6B	0.3693 (2)	0.7786 (2)	0.09510 (13)	0.0497 (6)
H6B	0.416809	0.817678	0.074736	0.060*
C1C	0.58507 (16)	0.83349 (16)	0.36626 (11)	0.0322 (4)
C2C	0.5950 (2)	0.9395 (2)	0.40647 (13)	0.0472 (5)
H2C	0.586482	1.011381	0.380708	0.057*
C3C	0.6176 (3)	0.9380 (3)	0.48506 (14)	0.0621 (7)
H3C	0.625340	1.008910	0.511841	0.074*
C4C	0.6286 (3)	0.8318 (3)	0.52325 (15)	0.0647 (8)
H4C	0.641121	0.830782	0.575534	0.078*
C5C	0.6212 (3)	0.7282 (3)	0.48434 (15)	0.0622 (7)
H5C	0.630163	0.656650	0.510503	0.075*
C6C	0.6003 (2)	0.7281 (2)	0.40604 (13)	0.0450 (5)
H6C	0.596675	0.656603	0.380301	0.054*

Table 3a: Selected bond lengths (Å) and angles (°) in compounds 1 (Symmetry code: (i) -*x*+1, -*y*+1, -*z*+1).

Sn1—O1	2.1939 (19)	O9—Sn1—C1B	113.28 (10)	O5	
Sn1—O6	2.217 (2)	C1A—Sn1—O1	94.77 (10)	O9—Sn2—C1C	104.12 (9)
Sn1—O9	2.0077 (16)	C1A—Sn1—O6	88.41 (11)	O9—Sn2—C1D	106.10 (10)
Sn2—O9	2.0597 (15)	C1B—Sn1—O1	92.97 (10)	C1C—Sn2—O9^{i}	98.69 (11)
Sn2—O9^{i}	2.1562 (17)	C1B—Sn1—O6	93.04 (11)	C1C—Sn2—O5	86.24 (11)
Sn2—O5	2.268 (2)	O9—Sn2—O9^{i}	76.05 (7)	C1D—Sn2—O9^{i}	97.37 (10)
O1—Sn1—O6	169.29 (7)	O9^{i}—Sn2—O5	165.21 (7)	C1D—Sn2—O5	85.08 (11)
O9—Sn1—O1	77.66 (6)	O9—Sn2—O5	89.24 (7)	C1D—Sn2—C1C	148.38 (12)
O9—Sn1—O6	91.82 (7)				
O9—Sn1—C1A	118.23 (9)				

Table 3b: Selected bond lengths (Å) and angles (°) in compounds 2 (Symmetry code: (i) -*x*+2, -*y*+1, -*z*+1).

Sn1—O1	2.162 (2)	O5—Sn1—C1B	109.66 (15)	C1D	
Sn1—O4	2.269 (3)	C1A—Sn1—O1	98.63 (15)	C1C—Sn2—O3	84.37 (14)
Sn1—O5	2.023 (2)	C1A—Sn1—O4	86.16 (18)	C1C—Sn2—O5^{i}	97.55 (12)
Sn2—O5^{i}	2.165 (2)	C1A—Sn1—C1B	137.1 (2)	C1D—Sn2—O3	87.91 (16)
Sn2—O5	2.049 (2)	O5^{i}—Sn2—O3	166.24 (10)	C1D—Sn2—O5^{i}	98.52 (14)
Sn2—O3	2.273 (3)	O5—Sn2—O3	90.07 (10)	O5^{i}—Sn2—O3	166.24 (10)
O1—Sn1—O4	171.00 (11)	O5—Sn2—O5^{i}	76.42 (9)	C1D—Sn2—C1C	142.15 (16)
O1—Sn1—C1B	94.60 (18)	O5—Sn2—C1C	109.47 (13)		
O5—Sn1—O1	79.16 (8)	O5—Sn2—C1D	107.53 (12)		
O5—Sn1—O4	91.97 (10)				
O5—Sn1—C1A	112.81 (16)				

Table 3c: Selected bond lengths (Å) and angles (°) in compounds 3 (Symmetry codes: (i) -*x*+1, *y*+1/2, -*z*+1/2).

Sn1—O1	2.2114 (14)	C1A—Sn1—O2^{i}	85.76 (6)	C1B—Sn1—O2^{i}	89.15 (6)
Sn1—O2^{i}	2.3554 (14)	C1A—Sn1—C1B	115.52 (8)	C1B—Sn1—C1C	121.47 (8)
Sn1—C1A	2.1211 (19)	C1A—Sn1—C1C	122.68 (8)	C1C—Sn1—O1	94.78 (7)
Sn1—C1B	2.128 (2)	C1B—Sn1—O1	93.77 (7)	C1C—Sn1—O2^{i}	89.36 (6)
Sn1—C1C	2.128 (2)				
O1—Sn1—O2^{i}	172.74 (5)				
C1A—Sn1—O1	86.98 (7)				

2.4. Biological activities

As to have to test compounds with the same chemical compositions as revealed by the crystal structure study, respective crystals have been grounded and measured. The Supplementary file S1 reports the diffractograms of the studied compounds, they are fully indexed by the cell parameters and symmetries obtained by the single crystal study.

2.4.1. Cytotoxicity Assay

For the assay, cell culturing was carried out at 37 ^{o}C in DMEM which contained FBS (10%), penicillin and streptomycin having 100 IU/ml and 100 ug/ml, respectively followed by incubation in CO_2 incubator. 96 well plate was utilized for assay purpose by pipetting 100 μL of cell culture. After overnight incubation at 37 ^{o}C, test compounds were prepared of 50 uM concentration in a fresh media and introduced in place of older media, and plate was incubated further for 48 h. Following this incubation, fresh media containing MTT dye hving 0.5 mg/ml concentration was introduced after removing old media containing test compounds. Plate was incubated further for 3 hrs, followed by adding DMSO. ELISA UV plate reader (Spectra Max-384, Molecular Devices, CA, USA) was utilized to quantify the formazan produced after MTT reduction. Index of cytotoxicity was quantified as concentration of compound with 50% growth inhibition (IC_{50}). DMSO and media were used as vehicle control and blank, respectively.

2.4.1.1. Butyryl Cholinesterse Activity

To determine the inhibitory potential of compounds Ellman's assay was performed with slight modifications [57].Assay starts when we add 10 μL of test compound (0.5 mM) (solvent: methanol) in 150 μL of NaH_2PO_4 buffer (100 mM) (pH 8.0) in 96 well plate. After this incubate the plate for 15 minutes with 20 μL of BChE enzyme (51.732 mU) (Sigma) at 25°C. Prepared butyrylthiocholine chloride (0.5 mM) (Sigma) substrate and rest in the dark for 15 minutes. The reaction starts by the addition of 10 μL of substrate, and DTNB (0.5 mM) (Sigma), which is a chemical reagent used to identify thiol groups in the sample. The plate was then read at 412 nm in spectrophotometer.

2.4.1.2. Protocol for Carbonic Anhydrase Activity (CA)

For this assay, protocol of Richard P. Shank was used with slight modifications [58].The assay was based upon the colorimetric estimation of 4-nitrophenol produced after hydrolysis of 4-NPA. The estimation reaction was performed at 25 ^{o}C in the presence of a buffering solution of 7.2 pH containing HEPES and Tris with concentration of 20 mM. Reaction mixture was prepared by addition of 140 μL of aforementioned buffer solution with 20 μL of freshly prepared bovine erythrocyte CA-II. Test compounds and substrate (0.7 mM) were dissolved in DMSO and ethanol, respectively. 20 µL solution of both was added in reaction mixture.

2.4.1.3. Thymidine Phosphorylase "TP" Activity

Inhibition potential of tested compounds Bera *et al*. was used with few changes [59].The reaction mixture was of 200 µL having TP enzyme (20 µL, 0.058 unit/well) and tested compound (10 µL, 0.5 mM) followed by incubation at 30 °C for 10 minutes. After the incubation thymidine (20 µL; 1.5 mM) was introduced to observe the absorbance dynamics for 10 min. at 290 nm. Each reaction was repeated thrice for reproducibility purpose. As standard compound Tipiracil-HCl was utilized.

2.4.1.4. Alpha Glucosidase and Lipase Activity

For in vitro, enzyme inhibiton activity phosphate buffer saline of PH (6.8) was used. α-Glucosidase enzyme was dissolved in (PBS), of concentration 0.01U/well, while test compounds concentration 0.5mM were dissolved in 70%

DMSO. Inhibiton activity for α-glucosidase enzyme was carried out by adding 135 µL PBS/well, 20 µL test compounds and 20 µL enzyme, and incubated for 15 mn at 37 ^{0}C. After incubation Substrate p-nitro phenyl-α-D-glucopyranoside of concentration (0.7 mM), 25 µL/well was added and absorbance was recorded at 400 nm for 30 mn, while Acarbose was used as a standard[60].For Lipase assay same procedure was followed as in, but reaction buffer was used Tris-HCl (PH), 169 µL/well, enzyme was dissolved in MOPS EDTA (PH), 6 µL/well, test compounds were dissolved in DMSO, 20 µL/well and Substrate was dissolved in DMF, 5 µL/well. Absorbance was recorded at 405 nm and Orlistate was used as a standard [61].

2.4.1.5. Prolyl Endopeptidase Assay

Prolyl endopeptidase (PEP, EC 3.4.21.26) is a proline specific endopeptidase, also known as Prolyl oligopeptidase. Its highest concentration is reported in the brain that cleaves proline containing bioactive peptides implicated in neurodegeneration, memory, and learning [62]. The highest expression of PEP in the brain indicates that it is associated with neurotransmission, memory and learning. PEP inhibitors are neuroprotective in certain experimental settings [63]. PEP activity elevates the accumulation (*in-vitro*) of α-synuclein. Additionally, Several PEP inhibitors have demonstrated potent reversal in case of loss of memory in such regards scopolamine has been utilized for patients suffering from brin ischemia [64].

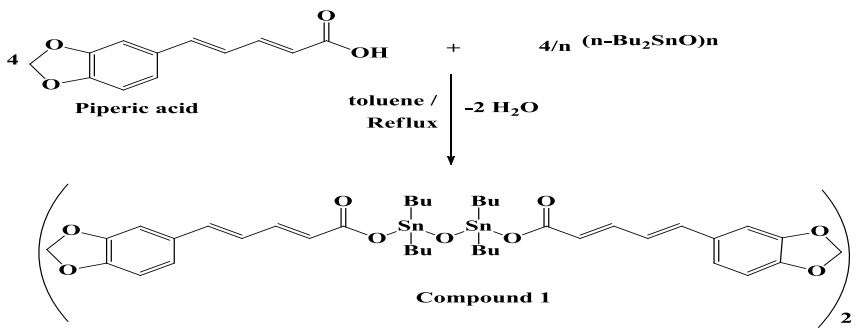
2.4.1.6. In vitro Prolyl Endopeptidase Inhibition Assay

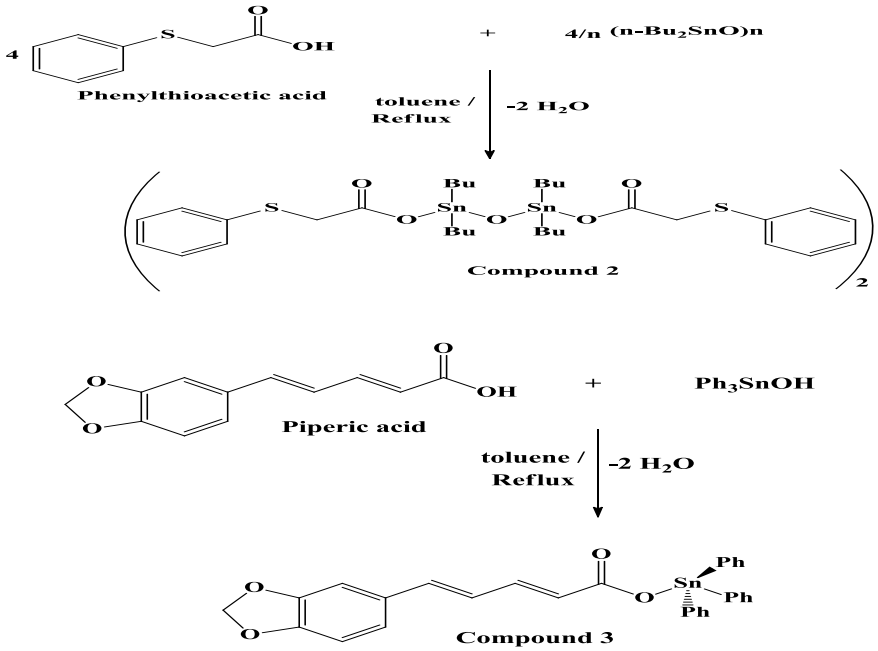
The PEP inhibition activity was measured by a slight modification of the Yoshimoto *et al.* method [65]. Using 96-well plates, 200 µL of total reaction volume containing 20 µL of PEP enzyme (*Flavobacterium* source), 140 µL phosphate buffer (50 *µM* at pH 7.0) and 20 µL test compound (0.5 mM) were incubated at 30 °C. Z-Gly-Pro-pNA 20 µL (0.4 *µM* in 40% 1, 4 dioxane) as a substrate was added after 10 minutes of incubation. Reaction mixtures were allowed for 30 min catalysis and the change in OD at 410 nm was measured by using Multiskan GO (Thermo Fisher Scientific OyRatastie 2, P.O. Box 100 FI-01621 FINLAND). EZ-FIT enzyme kinetics software (Perrella Scientific, Inc., Amherst, NH 03031, USA) was used to calculate the IC_{50} values.

3. Results and discussion

3.1. Synthesis

Compounds 1 and 2 have been synthesized from di-n-butyltin oxide in the presence of piperic acid and Phenylthioacetic acid respectively, however the compound 3 has been prepared by the reaction of piperic acid with triphenyltin hydroxide (see the scheme 3 below: synthesis of compound 1, 2 and 3).





Scheme 3: Synthesis of compounds 1, 2 and 3.

3.2. Crystal structure description

3.2.1 Bis[bis(di-n-butylpipericcarboxylate tin) oxide] 1 and bis [bis (di-n-butyl phenylthioacetate tin) oxide] 2

Both compounds form centrosymmetric diorganotin tetranuclear complexes with a planar Sn_4O_2 core. A central Sn_2O_2 ring containing the symmetry related Sn2 endocyclic Sn centres is linked via two μ^3-oxo groups to each of the exocyclic Sn centres (Sn1). These Sn centres are each further bridged by a chelating carboxylate (μ^2-η^1:η^1). Each of the exocyclic Sn centres is further coordinated by a carboxylate oxygen which additionally forms a long interaction via an asymmetric bidentate bridge to the endocyclic Sn2 centre (2.601(2) and 2.748(2) Å in 1 and 2 respectively) (**Fig**s. 1 and 2). The second carboxylate oxygen is much further from Sn1 at 3.168(2) and 2.962(2) Å in 1 and 2 respectively. The coordination of each Sn atom is completed by 2 n-butyl groups above and below the Sn_4O_2 plane. The exocyclic Sn atom (Sn1) in each case is 5-coordinate with a slightly distorted trigonal bipyramidal geometry (with the two carboxylate atoms the apical sites and the two C atoms and oxo oxygen in the equatorial positions) and excluding the long Sn-O interaction the endocyclic Sn centre can also be considered as 5-coordinate although the close approach of the bridging carboxylate oxygen distorts the coordination considerably from ideal trigonal bipyramidal geometry. In the case of Sn2 the apical sites are one of the oxo and the chelating carboxylate oxygen atoms with the n-butyl carbon atoms and the other symmetry related oxo anion forming the equatorial plane (**Fig**s. 1 and 2).The value of the trigonality index τ of 0.68 for Sn1 and 0.28 for Sn2 in compound 1 illustrates the greater distortion from trigonal bipyramidal for Sn2 (a value of 1.0 means an ideal trigonal bipyramid, while τ= 0.0 is for an ideal square pyramid)[41].In compound 2, the values are respectively 0.56 and 0.40 for Sn1 and Sn2, which are both considerably distorted but the higher value for Sn2 possibly reflects Sn…carboxylate distance is longer in 2 than 1. A survey of related structures in the Cambridge Structural Database (CSD) [42] shows that the bis(dicarboxylatetetraorganodistannoxane) structure is frequently adopted in dialyltin(IV) carboxylate complexes.

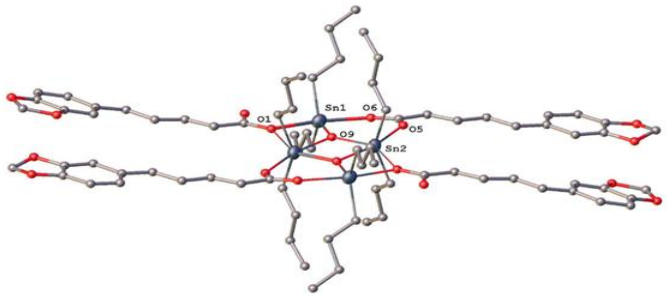


Fig.1: View showing the structure of 1{[n-Bu2Sn2O2C-(CH=CH)4-C7H5O2]2O}2, Hatoms are omitted for clarity (Sn atomsdrawnwith displacementellipsoids drawnat 50% probabilitylevel,all other atoms drawn as spheres of arbitrary radius).

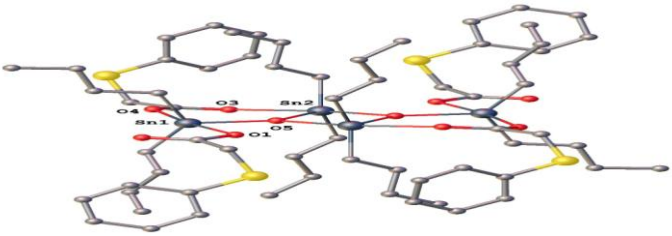


Fig.2: Views howing the structure of 2{[n-Bu2Sn2O2C-CH2-S-C6H4]2O}2,Handminor disorder componentatoms areomitted for clarity,atoms drawn as spheres of arbitraryradius.

3.2.2 Pipericcarboxylate triphenyltin 3

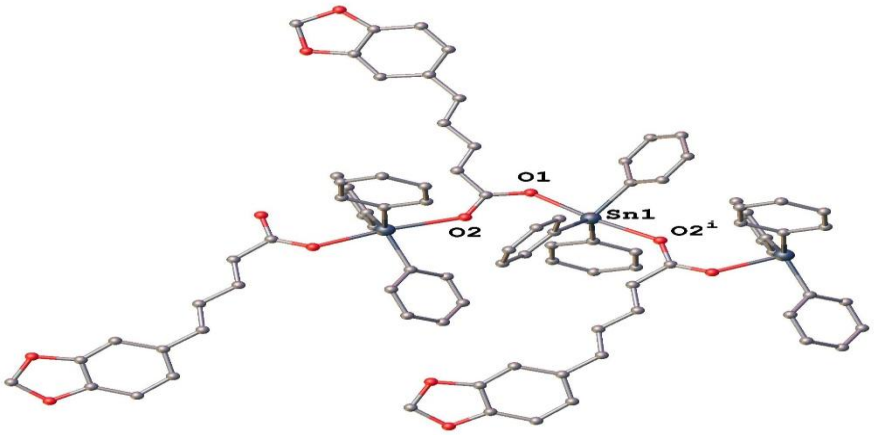


Fig3.View showing the polymeric structure of [Ph3SnO2C-(CH=CH)2-C7H5O2]*n*; hydrogenatoms omittedfor clarity,atoms drawn as spheres of arbitraryradius (i= *1-x,½+y, ½-z*).

The crystal structure of the triorganotin complex pipericcarboxylate triphenyltin shows a 1D polymer $[Ph_3SnO_2C-(CH=CH)_2-C_7H_5O_2]_n$ (**Fig** 3). The asymmetric unit contains one Sn centre, one pipericcarboxylate and three phenyl groups. The Sn atom has trigonal bipyramidal geometry, which is much less distorted than in the previous compounds (trigonality index τ_5= 0.83), with the coordination sphere containing three C atoms derived from three phenyl groups in the equatorial plane, and two oxygen atoms from two different (symmetry related) pipericcarboxylates in the apical positions, which form syn:anti chelating bridges linking Sn centres. Triorganotin polymers linked by syn:anti carboxylate chelating bridges often show an asymmetry in the Sn-O distances. The CSD database shows the Sn-

O(syn) to have a mean distance of 2.197 Å and the Sn-O(anti) of 2.398 Å with which the Sn1-O1 (syn) distance of 2.2114(14) Å and Sn1-O2^{i} (i = *1-x, ½+y, ½-z*) (anti) distance of 2.3554(14) Å respectively in 3 agree well.

3.3. Biological Activities

The synthesized compounds were further checked for their biological activities against cancer cell lines including breast cancer cell lines (BT-474, MDA-MB-231, AU565), Chronic myeloid leukemia cell line (K562), Lung cancer cell line (H460) (**Table** 4). The compounds showed potent activity against cancer cell lines. Moreover, results showed that compounds 1 and 3 were most active against all cancer cell lines. The title compounds turned however less active towards Butyrylcholinesterase (BchE). They were also evaluated for their carbonic anhydrase inhibitory activity. There is in fact no significant difference between the activity of compound 1 and 2, which exhibited good activity with IC_{50} values 86.6 ± 6.5 μM and 69.8 ± 2.01 μM respectively. Whereas, compound 3 showed weak activity with IC_{50} value of 190.48 ± 2.5 μM, which might be due to the presence of bulky group *i.e.*, triphenlytin. While, rest of the compounds were found to be inactive. Regarding the Thymidine Phosphorylase Activity, all 3 compounds were tested but only compound 1 has shown a weak TP inhibitory activity, with IC_{50} value of 213.6 ± 1.23 μM, as compared to standard inhibitor *i.e.* tipiracil-HCl (0.014 ± 0.018 μM).

Table 4: Results of the biological activities of the tested compounds 1-3.

Enzymes Inhibition and Cytotoxicity assay

Comp.#	Thymidine Phosphorylase (TP) IC_{50} ± SEM [μM]	Prolylndopeptidase (PEP) IC_{50} ± SEM [μM]	α-G1ucosidase (anti-diabetic) IC_{50} ± SEM [μM]	Pancreatic Lipase assay (anti-obesity) IC_{50} ± SEM [μM]	Cytotoxicity assay: Against 3T3 cell line IC_{50} ± SEM [μM]
1	213.60 ± 1.23	Insoluble	NA	186.40 ± 2.87	10.70 ± 0.05
2	NA	13.4 ± 1.73	NA	353.59 ± 2.87	10.70 ± 0.07
3	NA	16.3 ± 0.92	118.35 ± 1.10	329.90 ± 2.33	10.10 ± 0.005
STD	Tipiracil-HCl 0.014 ± 0.001	Z-Pro prolinal 1.50 ± 0.94	Acarbose 875.75 ± 2.08	Orlistat 0.014 ± 0.13	Cyclo-examide 0.8 ± 0.10

Anti-Cancer assay

Comp .#	BT-474 IC_{50} ± SEM [μM]	H-460 IC_{50} ± SEM [μM]	K562 IC_{50} ± SEM [μM]	MDA-MB231 IC_{50} ± SEM [μM]	AU565 IC_{50} ± SEM [μM]
1	6.50 ± 0.80	0.10 ± 0.03	2.60 ± 0.15	6.50 ± 0.80	3.73 ± 0.65
2	0.25 ± 0.02	NA	1.30 ± 0.10	0.25 ± 0.00	0.23 ± 0.01
3	0.17 ± 0.05	NA	0.14 ± 0.00	0.17 ± 0.05	0.12 ± 0.01
STD	Doxoru-bicin 2.10 ± 0.01	Doxoru-bicin 0.20 ± 0.03	Imatinib 1.72 ± 0.29	Doxoru-bicin 0.57 ± 0.07	Doxoru-bicin 0.08 ± 0.003

All the synthetic compounds were evaluated against α-Glucosidase and Lipase enzymes. Lipase and α-Glucosidase are the key metabolic enzymes of carbohydrates and lipids digestion, and has a key role in the development of therapy for type 2 Diabètes mellitus as well as for Obesity [43]. All compounds were found active against lipase, with IC_{50} values186.4 ± 2.87 µM, 353.59 ± 2.87 µM, and 329.9 ± 2.33 µM. Compound 3 showed a potent inhibitory activity (IC_{50} = 118.35 ± 11 µM), against α-Glucosidase as compared to acarbose (IC_{50} = 875.75 ± 2.03 µM), and was found to be a dual inhibitor, while compounds 1 and 3 were found inactive against α-glucosidase enzyme. Compounds 1, and compound 3 showed a potent inhibitory potential against Prolyl endopeptidase (PEP), with IC_{50} values 13.4 ± 1.73,

16.3 ± 0.92 *μM*, in comparison with standard *i.e.* Z-Pro prolinal 1.50 ± 0.94 *μM*. Cytotoxicity was checked by using normal (3T3) mouse fibroblast cell line, and all compounds showed a weak cytotoxic activity.

4. Conclusions

Three new organotin (IV) derivatives have been prepared from piperic and phenylthio acetic acids. Piperic acid was prepared by hydrolysis from piperine and used in the synthesis of two new compounds :{[n-Bu_2SnO_2C-$(CH=CH)_2$-$C_7H_5O_2$]$_2$O}$_2$ and [Ph_3SnO_2C-$(CH=CH)_2$-$C_7H_5O_2$]$_n$. The third {[n-Bu_2SnO_2C-CH_2-S-C_6H_4]$_2$O}$_2$ was formed by Phenylthioacetic acid. The complexes have been characterized by IR, ^{1}H and ^{13}C NMR spectroscopic techniques, and their crystal structures fully elucidated. All the synthesized compounds were evaluated for their biological activities against a range of the cancer cell lines (BT-474, MDA-MB-231, AU565), Chronic myeloid leukemia cell line (K562), and Lung cancer cell line (H460). The compounds showed potent activity against cancer cell lines. The Pipericcarboxylate triphenyltin [Ph_3SnO_2C-$(CH=CH)_2$-$C_7H_5O_2$]$_n$ and {[n-Bu_2SnO_2C-$(CH=CH)_2$-$C_7H_5O_2$]$_2$O}$_2$ were most active against all cancer cell lines.

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