Interaction of Di- and Triorganotin(IV) Compounds with Carboxylate Ligand: Synthesis, Spectral Characterization, Semi-empirical Study and *In Vitro* Antimicrobial Activities

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Di- and triorganotin(IV) complexes with the general formulae R_nSnL_{4-n}, where R = Me, *n*-Bu, Ph and L = 2-[(2′-methylphenylamido)]benzoic acid have been synthesized by the reaction of triethylammonium salt of 2-[(2′-methylphenylamido)]benzoic acid with di- and triorganotin chloride in dry toluene. All the synthesized complexes were characterized by elemental analysis, FT-IR, multinuclear (^{1}H, ^{13}C, ^{119}Sn) NMR, mass spectrometry and semi-empirical study to assess the binding mode of 2-[(2′-methylphenylamido)]benzoic acid. The diorganotin(IV) derivatives are assessed to adopt distorted octahedral and triorganotin(IV) have linear polymeric trigonal bipyramidal structures in which 2-[(2′-methylphenylamido)]benzoic acid is a monoanionic bidentate, coordinating through C(O)O group. This coordination behaviour is also confirmed by semi-empirical study. The isotopic effect of tin was studied by comparison of experimental data with the simulated isotopic pattern using the Chemtool software package. The insecticidal, antileshmanial, antibacterial, antifungal and cytotoxicity of the synthesized compounds are also reported. Some complexes exhibit good activities comparable to that of standard drugs. Furthermore, triorganotin(IV) derivatives exhibit significantly better activities than the diorganotin(IV) derivatives and have a potential to be used as drug.

Keywords: 2-[(2′-Methylphenylamido)]benzoic acid; Organotin(IV) complexes; Spectral characterization; Isotopic pattern; Semi-empirical study; Biological activities.

INTRODUCTION

The organotin complexes have been of great interest for many years because of their versatile bonding modes. Organotin carboxylates are of interests in view of their considerable structural diversity. Depending on the carboxylic acid used and the stoichiometry of the reactants, several products such as monomers, dimers, tetramers, oligomeric ladders, and hexameric drums can be isolated.[1-4] Steric and electronic attributes of organic substituents on tin and/or the carboxylate moiety impart significant influence on the structural characteristics in tin carboxylates. The biochemical activity of organotin compounds is also influenced greatly by the structure of the molecule and the coordination number of the tin atoms.[5] Therefore, synthesis of new organotin carboxylates with different structural features is beneficial in the development of pharmaceutical organotin and in other properties and application. The syntheses of organotin complexes are research area of increased interest for inorganic, pharmaceutical and medicinal chemistry as an approach to the development of new drugs.[6,7] The coordination chemistry of tin is extensive with various geomertries and coordination numbers known for both inorganic and organometallic complexes.[8] Higher coordination numbers can be generated either by inter- and/or intra-molecular interaction, especially in complexes where tin bonds to electronegative atoms, such as oxygen, nitrogen and sulfur. Studies of adducts of organotin halides continue to provide fundamental information about both the Lewis acid-base model and the reactivity of organotin species.[9] Many amazing structures have been discovered in organotin carboxylates, which include ladder, drum, cube, cluster and cage.[10]

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It has well been established that organotin(IV) compounds are very important in cancer chemotherapy because of their apoptotic inducing character,[11-13] while during the last few year it is noticeable that organotin compounds occupy an important place in cancer chemotherapy reports.[11] Recently, Blower described thirty interesting inorganic pharmaceuticals, four of which are tin compounds.[14] Despite this, the exact mechanism of anti-tumor action of organotin compounds remains unknown. Tin compounds and their therapeutic potentials have been reviewed,[15,16] while a number of early reviews recording advances in the screening for anti-tumor potential of organotins are also available.[17,18]

RESULTS AND DISCUSSION

Organotin(IV) complexes have been prepared by the reaction of the ligand acid and Et_3N with corresponding organotin(IV) chlorides in 1:1 and 1:2 molar ratios in dry toluene. However, prolonged reflux (8-10 h) is required for a good yield. All these complexes 1-5 are solid, with sharp melting points and are stable in air. Physical data are reported in Table 1.

Infrared Spectra

Infrared spectra of the investigated compounds and ligand acid have been recorded as KBr pellets in the range 4000-400 cm^{-1}. The coordinating behaviour of the ligand with the di- and triorganotin(IV) moieties, can be inferred by comparing the infrared spectra of synthesized organotin(IV) compounds with that of free acid. The absorption frequencies assigned to $\nu_{asym}(COO)$, $\nu_{sym}(COO)$ and $\nu(C=O)$ have been identified in free ligand acid and the synthesized compounds are reported together with bands assigned to $\nu(Sn–C)$ and $\nu(Sn–O)$. The absorption bands in the range 1720-1716 cm^{-1} can most likely be attributed to the C=O stretching vibration of the ester group of ligand moiety and confirms the assessment that there is no participation of the ester group C=O in the bond formation with tin atom. This evidence predicts the conclusion that the sharp absorption band at 1555 cm^{-1} is due to carboxyl $\nu(COO)$ stretching and band at 1716 cm^{-1} is absorption frequency of the ester group, $\nu(C=O)$, which contradicts the early report.[19] Moreover, absorption bands in the range 480-415 cm^{-1} and 582-528 cm^{-1}, assigned to Sn–O and Sn–C bonds, respectively, also support the formation of complexes.[20] Data is given in Table 2.

The values of IR stretching vibration frequencies of carboxyl groups [($\nu_{asym}(COO)$ and $\nu_{sym}(COO)$] in organotin(IV) carboxylates are important and may help in elucidation of the structures and bonding mode of the ligand.[21] When the structure changes to higher-coordinated symmetry, the $\nu_{asym}(COO)$ frequencies shift to lower and $\nu_{sym}(COO)$ to higher frequency, which causes decrease in the $\Delta\nu$ value.[22] Thus, a mark decrease in the $\Delta\nu$ values [$\Delta\nu = \nu_{asym}(COO–\nu_{sym}(COO)$] is observed in all the complexes compared to the corresponding free acid, suggesting a bidentate coordination of COO group to tin atom for carboxylate ligand. Di- and triorganotin(IV) complexes approaches six- and five-coordination, respectively in the solid state.

Mass Spectrometry

Mass spectra for the investigated compounds are recorded at 70 eV for all di- and triorganotin(IV) derivatives. The molecular ion peaks of very low intensity are observed in few complexes.[23] In di- and triorganotin(IV) derivatives a rather similar pattern of fragmentation is observed. In both cases primary fragmention is due to the successive loss of R groups followed by the elimination of CO_2 from the ligand and then the remaining part of the ligand which leaves Sn^+ or SnH^+ as an end product. Mass data is given in Table 3. Another possible route is disintegration of the ligand and stepwise elimination of R groups to Sn^+ or SnH^+ as a residue. Some common and different peaks (with *m/z* and % abundance) which were observed in di- and triorganotin(IV) derivatives are reported in Experimental part. Isotopic patterns in mass spectra were studied as given in the Experimental and representative spectrum is given in Fig. 1. They show the isotopic effect on M^+ ions in complex **4**. As Sn has 10 naturally occurring isotopes this effect is pronounced in the mass spectra presented in (Fig. 1).

NMR Spectroscopy

The ^1H NMR spectral data (in $CDCl_3$) identifies almost all the protons of ligand and complexes by their intensity and multiplicity pattern. ^1H NMR chemical shifts and coupling constant for reported compounds are summarized in Table 4.

In ^1H NMR spectra of all the complexes studied, the CO(OH) resonance of the ligand is absent which suggests the replacement of the carboxylic proton by the organotin(IV) moiety. The –NH signal remains almost unchanged which indicates that this group is not involved in inter/intramolecular hydrogen bonding or in bonding to organo-

Table 1. Physical data of organotin(IV) carboxylates

Comp. No.	Quantity Used			M.P. (°C)	Yield (%)	Elemental Analysis % Calculated (Found)		
	1st Reactant	2nd Reactant	3rd Reactant			C	H	N
HL	o-Toluidine 7.2 mL (6.75 mmol)	Phthalic anhydride 10 gm (6.75 mmol)	-	160-161	88	70.58 (70.67)	5.09 (5.23)	5.49 (5.59)
1	HL 1 gm (3.92 mmol)	Me_2SnCl_2 0.43 gm (1.96 mmol)	Et_3N 0.54 mL (3.92 mmol)	132-133	85	58.44 (58.35)	4.56 (4.43)	4.26 (4.17)
2	HL 1 gm (3.92 mmol)	Bu_2SnCl_2 0.59 gm (1.96 mmol)	Et_3N 0.54 mL (3.92 mmol)	95-98	80	60.25 (60.12)	5.85 (5.74)	3.90 (3.79)
3	HL 1 gm (3.92 mmol)	Me_3SnCl 0.78 gm (3.92 mmol)	Et_3N 0.54 mL (3.92 mmol)	142-144	75	51.67 (51.52)	5.02 (5.13)	3.34 (3.24)
4	HL 1 gm (3.92 mmol)	Bu_3SnCl 1.06 gm (3.92 mmol)	Et_3N 0.54 mL (3.92 mmol)	112-114	70	59.55 (59.46)	7.16 (7.29)	2.57 (2.44)
5	HL 1 gm (3.92 mmol)	Ph_3SnCl 1.51 gm (3.92 mmol)	Et_3N 0.54 mL (3.92 mmol)	75-77	92	65.56 (65.47)	4.47 (4.33)	2.31 (2.19)

Table 2. Assignment of characteristic FT-IR vibrations of 2-[(2′-methylphenylamido)]benzoic acid and their organotin(IV) complexes

Comp. No.	IR Peak (cm^{-1})							
	ν_{OH}	ν_{NH}	$\nu_{C=O}$	ν_{COO}		$\Delta\nu$	ν_{Sn-C}	ν_{Sn-O}
HL	3440s	3335s	1716s	1555s[1]	1320s[2]	235	-	-
1	-	3330m	1719s	1548m	1459m	189	582w	415m
2	-	3337s	1711s	1585m	1422s	163	528m	462m
3	-	3333s	1709m	1535s	1410s	125	560m	480w
4	-	3335m	1715s	1572s	1380s	192	535s	472m
5	-	3338m	1720s	1567m	1381s	186	226m	445w

[1]Antisymmetric [2]Symmetric
Abbreviations: s = strong, m = medium, w = weak

tin moiety. All the protons present in the synthesized compounds **1-5** have been identified in position and number with the protons calculated from increamental method.[24] Triphenyltin(IV) complexes show a multiplet in the aromatic region of spectra at 7.64-7.68 ppm. Methyl protons appeared as sharp singlet in both di-*n*- and tri-methyltin(IV) compounds at 0.26 ppm and -0.03 ppm in solution state in coordinating solvent, respectively while other protons show a complex pattern and are assigned according to earlier reports[25] in butyl compounds **2** and **4**, protons of α-carbon show a triplet at 0.87 and 0.94, respectively with $^nJ(^{119}Sn\text{-}^1H)$ of 78-56 Hz showing the four coordinated nature of this compound in solution.

To confirm the expected structure of the title compounds, ^{13}C NMR data was also recorded for the reported compounds. ^{13}C NMR data for reported compounds are given in Table 5. These parameters are useful for the determination of the coordination number of tin, its molecular geometry and stereochemistry. In case of diorganotin dicarboxylates, the geometry around tin could not be deter-

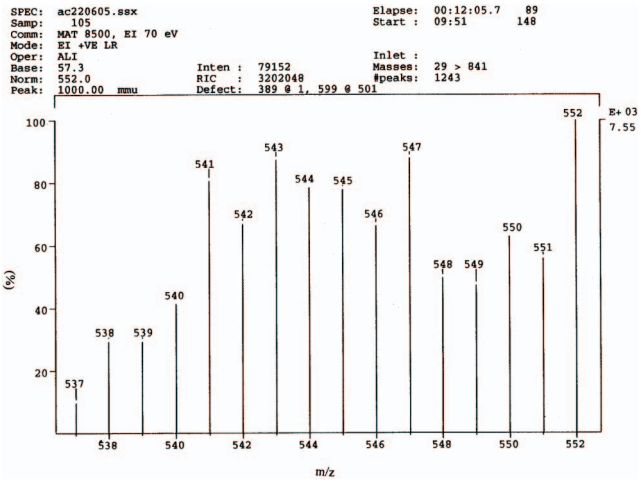
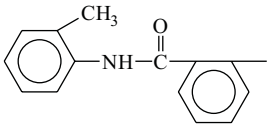


Fig. 1. Isotopic pattern of M^+ ions for compound **4**.

Table 3. Mass spectral data of organotin(IV) complexes of 2-[(2′-methylphenylamido)]benzoic acid at 70 eV

Fragment Ion	**1** *m/z* (%)	**2** *m/z* (%)	**3** *m/z* (%)	**4** *m/z* (%)	**5** *m/z* (%)
$R_2SnOO\overset{a}{R}'$	403(8)	487(5)	403(16)	487(8)	527(9)
RSnOOCR′	388(6)	430(11)	388(20)	430(10)	450(12)
OCOR′	254(76)	254(81)	254(30)	254(12)	254(8)
$^bR_3Sn^+$	-	-	164(25)	290(25)	347(16)
R_2Sn^+	149(56)	233(18)	149(62)	233(50)	271(21)
RSn^+	134(62)	176(42)	134(50)	176(35)	194(31)
$C_6H_4^+$	76(18)	76(14)	76(30)	76(18)	76(12)
Sn^+	120(11)	120(2)	120(8)	120(6)	120(9)
$C_{14}H_{11}O_2^+$	219(100)	219(100)	219(43)	219(100)	219(26)
$C_4H_9^+$	57(17)	57(10)	57(100)	57(17)	57(37)
$C_{12}H_9^+$	154(20)	154(31)	154(52)	154(24)	154(38)
HOCOR′	256(41)	256(53)	256(72)	256(80)	256(100)

[a] R′ = 

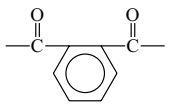
[b] R = CH_3, *n*-C_4H_9 and C_6H_5

mined with certainty due to the fluxional behavior of the carboxylate oxygens with coordination to tin atom; however, earlier reports suggest geometry in between penta- and hexa-coordination.

The alkyl carbons attached to the tin occurs at the normal values in case of methyl and butyl tin compounds.[26] The aromatic carbon resonances were assigned by the comparison of experimental chemical shift with those calculated from incremental method[24] and with literature values.[27] The resonance of the carboxylic carbons in organotin compounds showed downfield shift (175.5-175.9 ppm) than in the ligand (172.8 ppm) suggesting the coordination of the ligand through the carboxylic oxygen, to the organotin(IV) moiety. In ^{13}C NMR data, the measurement of coupling constant helps to determine the molecular structure of compounds. The value $^1J(^{119}Sn\text{-}^{13}C)$ is different in di- and tri-organotin compounds for tetra and penta-coordinated nature of tin.

For the *n*-tributyltin(IV) derivative, with the $^1J[^{119}Sn\text{-}^{13}C]$ value being 350 Hz and by the use of the Holecek and Lycka equation,[27,28] a C-Sn-C value of 111.6° was calcu-

Table 4. ^1H NMR data[a] of 2-[(2′-methylphenylamido)]benzoic acid and their organotin(IV) complexes

Proton	Chemical Shift (ppm)					
	HL	**1**	**2**	**3**	**4**	**5**
	2.14(2.3) 7.34-7.41m	2.16(2.5) 7.32-7.41m	2.15(2.5) 7.34-7.39m	2.15(2.4) 7.32-7.41m	2.14(2.3) 7.35-7.42m	2.17(2.6) 7.37-7.42m
- NH	2.24s	2.25s	2.24s	2.24s	2.23s	2.28s
	7.78-7.82d,d (8.1) 7.95-7.99d,d (8.1)	7.79-7.83d,d (8.0) 7.97-8.00d,d (8.0)	7.80-7.83d,d (8.1) 7.96-7.99d,d (8.1)	7.80-7.86d,d (8.2) 7.96-8.00d,d (8.2)	7.77-7.80d,d (7.9) 7.95-7.99d,d (7.9)	7.81-7.84d,d (8.3) 7.98-8.02d,d (8.3)
R	-	0.26t ^2J[78.9]	0.87t(7.6) 1.35-1.44m	-0.03s [56]	0.94t(7.6) 1.31-1.34m	7.64-7.68m

[a] Chemical shifts (δ) in ppm. $^2J[^{117/119}Sn, ^1H]$; $^2J[^{119}Sn, ^1H]$ and $^3J(^1H, ^1H)$ in Hz are listed in square brackets and parenthesis, respectively. Multiplicity is given as: s = singlet, d = doublet, d,d = doublet of doublet, t = triplet, m = multiplet.

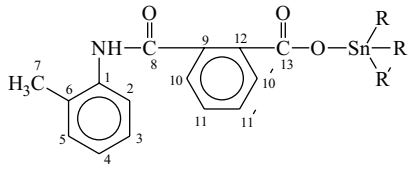
Table 5. ^{13}C and ^{119}Sn NMR data[a-c] of 2-[(2′-methylphenyl-amido)]benzoic acid and their organotin(IV) complexes

Carbon	HL	1	2	3	4	5
1	136.2	136.4	136.3	136.7	136.6	136.9
2	131.8	131.9	131.8	131.5	131.3	131.7
3	134.2	134.3	134.4	134.7	134.6	134.8
4	128.5	128.6	128.7	128.9	128.3	128.8
5	127.2	127.6	127.5	127.9	127.0	127.3
6	126.5	126.7	126.6	126.3	126.2	126.1
7	28.9	28.2	28.4	28.6	28.7	28.3
8	167.2	167.3	167.5	167.7	167.6	167.4
9	130.4	130.3	130.6	130.7	130.2	130.5
10,10′	123.6	123.4	123.8	123.3	123.7	123.9
11,11′	118.6	118.4	118.3	118.6	118.8	118.5
12	131.0	131.2	131.3	131.1	131.6	131.7
13	172.6	175.8	175.6	175.5	175.7	175.9

[a] Compound **1**: Sn-CH_3, (C- α) 29.5. δ ^{119}Sn = -101.6. Compound **2**: Sn-$CH_2CH_2CH_2CH_3$, (C- α) 29.5, (C- β) 27.4, (C- γ) 26.8, (C- δ) 14.0. δ ^{119}Sn = -129.6. Compound **3**: Sn-CH_3, (C- α) -2.2 ^1J[379,398]. δ ^{119}Sn = +144.4. Compound **4**: Sn-$CH_2CH_2CH_2CH_3$, (C- α) 29.5 [350], (C- β) 27.2 ^2J[21.3], (C- γ) 26.7 ^3J[63.5], (C- δ) 14.2. δ ^{119}Sn = +155.25. Compound **5**: Sn-C_6H_5, (C- α) 137.8 ^1J[640.2,660.2], (C- β) 137.5 ^2J[49.0], (C- γ) 136.0, (C- δ) 129.32. δ ^{119}Sn = -83.6.

[b] Chemical shifts (δ) in ppm: ^nJ[^{119}Sn, ^{13}C] in Hz is listed in parenthesis.

[c]



R′ = R for triorganotin, R′ = L for diorganotin

lated, which corresponds to a quasi-tetrahedral geometry in $CDCl_3$ solution. The geometric data calculated, as just described, are consistent with tetrahedral geometries for the triorganotin(IV) species, i.e., monomer in solution. For the diorganotin(IV) species, for which earlier results indicate five coordination, the calculated C-Sn-C angles are consistent with the skew-trapezoidal bipyramidal geometries, with the lower apparent coordination number arising from the asymmetric coordination mode of the carboxylate ligand. The value of δ ^{119}Sn defines the region of various coordination number of central tin atom.[29] The results are listed in Table 5.

In all complexes, ^{119}Sn spectra show only a sharp singlet indicting the formation of single species. ^{119}Sn chemical shift δ(^{119}Sn) of organotin compounds cover a range of over 600 ppm and are quoted relative to tetramethyltin with downfield shifts from the reference compound having a positive sign. As the electron-releasing power of the alkyl group increases the tin atom becomes progressively more shielded and δ(^{119}Sn) value moves to higher field. These values are also dependent upon the nature of X in R_nSnX_{4-n} and generally move to lower field as the electronegativity of the latter increases. A very important property of the ^{119}Sn chemical shift is that an increase in coordination number of the tin atom from four to five, six or seven usually produces a large upfield shift of δ(^{119}Sn).[29] In triorganotin(IV) complexes, ^{119}Sn chemical shifts value lie in the tetrahedral environment around the tin atom as in non-coordinating solvent whereas the diorganotin(IV) compounds show the higher coordination, probably five or six. These values are strongly dependent upon the nature and orientation of the organic groups bonded to tin. The shifts observed in complexes can be explained quantitatively in terms of an increase in electron density on the tin atom as the coordination number increases.[29]

As increase in coordination number is accompanied by an appropriate upfield shift. It is generally accepted that compounds with a specific geometry about the tin atom produce shifts in moderately well defied ranges.

Semi-empirical study

In 2-[(2′-methylphenylamido)]benzoic acid **HL**, the mean planes of the two phenyl rings make an angle of 48.72° with each other. The two C-O bonds are 1.21 and 1.35 Å, respectively. The C=O and C-N bond length of NH-CO group being 1.22 and 1.41 Å, respectively. The selected bond length and angles of the optimized structure are given in Table 6. The optimized and chemical structure is shown in Fig. 2.

In all the five compounds **1**-**5**, the carboxylate group binds in an anisobidentate mode to the Sn atom. The bond lengths and angles are similar to those in the literature.[30] In compound **1**, the Sn atom is 2.01 and 2.70 Å away from the oxygen's of the carboxylic group. The two long Sn-O bond being trans to each other. The C-O bond are also unequal they are 1.31, 1.23 Å the shorter C-O bond corresponding to the weakly coordinating oxygens. The two methyl groups are equidistant from Sn (2.07 Å) and complete the coordination sphere of Sn. The Me(C)-Sn-(C)Me angles are 114.3°. The O-Sn-O and O-C-O angles are 50.4 and 110.6°, respectively for both the carboxylic ligands. The mean planes of the two phenyl groups of the carboxylic ligand make an angle of 47.8° with each other for one

Table 6. Bond lengths (Å) and angles (°) for **HL**

C4	C3	1.40		C3	C2		1.40
C2	C7	1.39		C2	C1		1.48
C3	N12	1.44		N12	C14		1.41
C14	C16	1.50		O27	C26		1.21
C3	C2	C7	118.82	C3	C2	C1	122.30
C4	C3	N12	119.62	C2	C3	N12	120.23
C5	C4	C3	120.02	C2	C7	C6	120.94
C3	N12	C14	124.77	N12	C14	O15	122.17

Table 7. Bond lengths (Å) and angles (°) for compound **1**

Sn1	O2	2.01		Sn1	C33		2.07
Sn1	C37	2.07		Sn1	O41		2.01
O2	C3	1.31		C3	O4		1.23
C61	C62	1.38		Sn1	O43		2.70
C33	Sn1	C37	114.29	C33	Sn1	O41	101.37
O2	Sn1	O43	83.39	C33	Sn1	O43	148.89
C33	Sn1	O4	90.30	C37	Sn1	O4	148.83
O41	Sn1	O43	50.37	O41	Sn1	O4	83.29

ligand and 47.3° for the other. The selected bond length and angles of the optimized structure are tabulated in Table 7. The optimized and chemical structure is shown in Fig. 3.

In compound **2**, the Sn atom is 2.01 and 2.71 Å away from the oxygen's of the carboxylic group. The two long Sn-O bond being trans to each other. The C-O bonds are nearly equal (1.31 Å). The two butyl groups are equidistant from Sn (2.10 Å) and complete the coordination sphere of Sn. The Bu(C)-Sn-(C)Bu angles are 117.2°. The O-Sn-O and O-C-O angle are 50.2 and is 110.8°, respectively for both the carboxylic ligands. The mean planes of the two phenyl groups of the carboxylic ligand make an angle of 35.3° with each other for one ligand and 44.8° for the other. The selected bond length and angles of the optimized structure are given in Table 8. The optimized and chemical structure is shown in Fig. 4.

In compound **3**, the Sn atom is asymmetrically attached to carboxylic acid with displacement of Sn atom from the O atoms being 2.02, 2.74 Å. The C-O bonds are also unequal being 1.23 and 1.31 Å with the shorter C-O bond for the weakly coordinated longer Sn-O. The three methyl groups are equidistant from Sn (2.10 Å) and complete the coordination. The Me-Sn-Me angles are 110.0, 114.3 and 110.5°. The O-Sn-O and O-C-O angles are 49.7 and 111.4°, respectively. The mean planes of the two phenyl groups of the carboxylic ligand make an angle of 76.7° with each other. The selected bond length and angles of the optimized structure are tabulated in Table 9. The optimized and chemical structure is shown in Fig. 5.

In compound **4**, the Sn atom is asymmetrically attached to carboxylic acid with displacement of Sn atom from the O atoms being 2.02, 2.74 Å. The C-O bonds are also unequal being 1.23 and 1.31 Å with the shorter C-O bond for the weakly coordinated longer Sn-O. The three butyl groups are equidistant from Sn (2.14 Å) and complete the coordination. The Bu-Sn-Bu angles are 112.2, 111.4

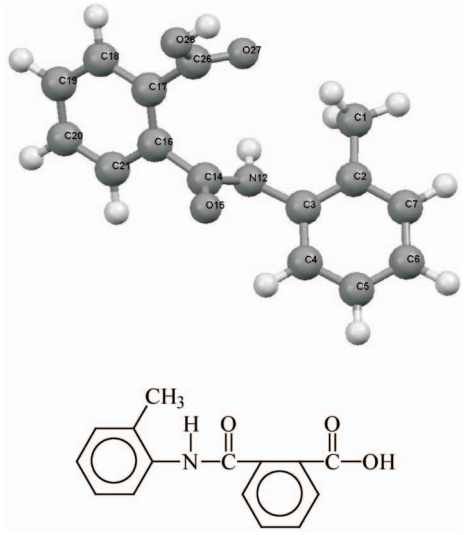


Fig. 2. Geometry optimised and chemical structure of 2-[(2′-methylphenylamido)]benzoic acid **HL**.

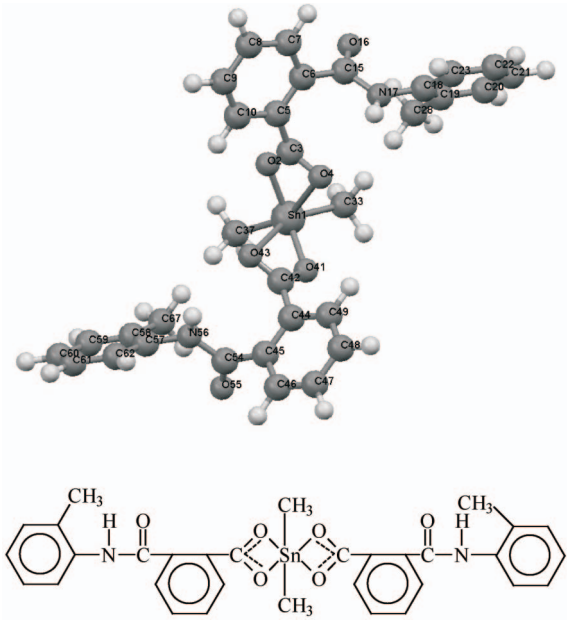


Fig. 3. Geometry optimised and chemical structure of compound **1**.

Table 8. Bond lengths (Å) and angles (°) for compound **2**

Sn1	O2	2.01			Sn1	C33	2.10
Sn1	C46	2.11			Sn1	O59	2.01
O2	C3	1.31			Sn1	O61	2.71
C38	C37	1.51			C18	C23	1.40
O2	Sn1	C33	109.34	O2	Sn1	O59	121.67
O2	Sn1	O61	82.55	C33	Sn1	C46	117.20
C46	Sn1	O41	47.92	O59	Sn1	O61	50.25
O59	Sn1	O4	83.22	O61	Sn1	O4	76.80

Table 9. Bond lengths (Å) and angles (°) for compound **3**

C9	C10	1.39			O2	C3	1.23
Sn1	O2	2.74			Sn1	O32	2.02
Sn1	C33	2.10			O23	C6	1.22
C6	C5	1.50			C5	C4	1.39
O2	Sn1	O32	49.68	O2	Sn1	C33	86.46
O2	Sn1	C37	86.67	O2	Sn1	C41	146.64
O32	Sn1	C41	96.95	C33	Sn1	C37	114.38
C4	C27	C26	120.24	C9	C8	N7	119.94

and 108.3°. The O-Sn-O and O-C-O angles are 49.7 and 111.4°, respectively. The mean planes of the two phenyl groups of the carboxylic ligand make an angle of 77.3° with each other. The selected bond length and angles of the optimized structure are tabulated in Table 10. The optimized and chemical structure is shown in Fig. 6.

In compound **5**, the Sn atom is asymmetrically attached to carboxylic acid with displacement of Sn atom from the O atoms being 2.01, 2.74 Å. The C-O bonds are also unequal being 1.23 and 1.31 Å with the shorter C-O bond for the weakly coordinated longer Sn-O. The three phenyl groups are are nearly equidistant from Sn (2.06 Å) and complete the coordination. The Ph(C)-Sn-(C)Ph angles are 110.3, 108.8 and 116.1°, respectively. The O-Sn-O and O-C-O angles are 49.6 and 111.2°, respectively. The mean planes of the two phenyl groups of the carboxylic ligand make an angle of 75.5° with each other. The selected

Table 10. Bond lengths (Å) and angles (°) for compound **4**

C13	C12	1.38			O23	C6	1.22
Sn1	O2	2.74			Sn1	O32	2.02
Sn1	C33	2.14			Sn1	C46	2.13
Sn1	C59	2.13			C11	C10	1.38
O2	Sn1	O32	49.65	O2	Sn1	C33	86.79
O2	Sn1	C46	86.26	O2	Sn1	C59	146.54
O32	Sn1	C33	113.81	O32	Sn1	C59	96.91
C46	Sn1	C59	111.42	Sn1	C33	C34	110.02

bond length and angles of the optimized structure are tabulated in Table 11. The optimized and chemical structure is shown in Fig. 7.

Microbial Assay

Antibacterial activity

Organotin(IV) complexes were tested against the three Gram-positive bacterial strains, *Bacillus subtilis*

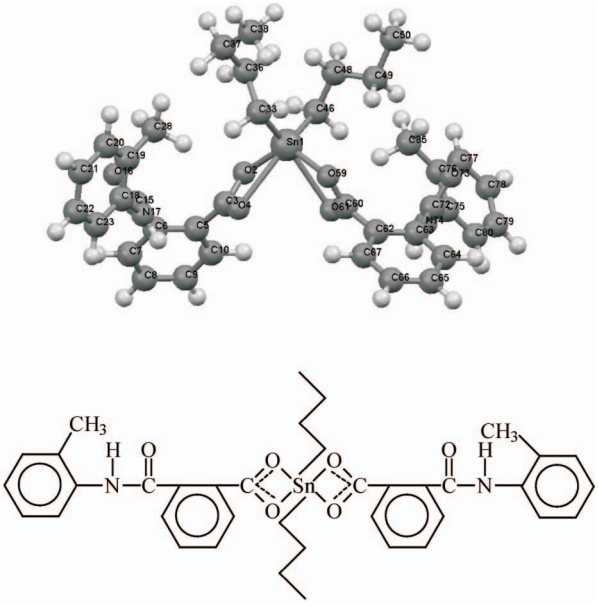


Fig. 4. Geometry optimised and chemical structure of compound **2**.

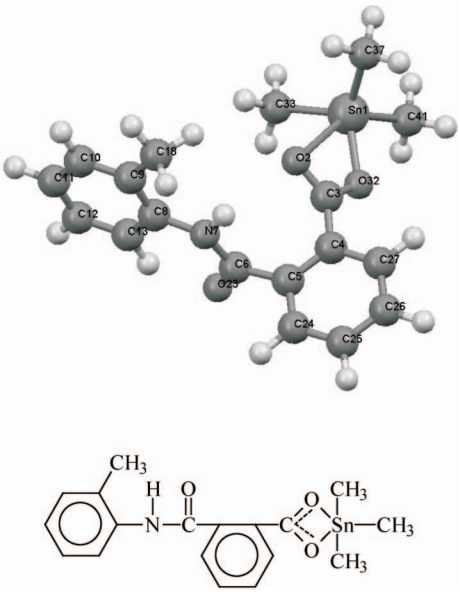


Fig. 5. Geometry optimised and chemical structure of compound **3**.

(ATCC 6633), *Micrococcus leuteus* (ATCC 10240) and *Staphlococcus aureus* (ATCC 6538)] and three Gram-negative bacterial strains, *Escherichia coli* (ATCC 15224), *Enterobactor aerogenes* (ATCC 13048) and *Bordetella bronchiseptica* (ATCC 4617). The agar well-diffusion method[31] was used in this assay and each experiment was done in triplicate. The results are listed in Table 12. The antibacterial studies exhibited that the complex **3** and **4** does not show activity towards *Escherichia coli*. But the complex **5** shows the significant activity against all bacterial strains.

Cytotoxicity

Brine Shrimp method[31] has been used to check the toxicity of the synthesized compounds by using Etoposide as standard drug. Cytotoxicity data are given in Table 13. Highest toxicity was shown by compound **1**, whose LD_{50} value is 17.99 μg/mL, while the lowest toxicity is shown by compound **4**, whose LD_{50} value is 5.18 μg/mL as compared to standard drug.

Antifungal Ativity

The present inhibition of the synthesized ligand and compounds are given in Table 14. Miconazole, Ketoconazole and Amphotercin B. were used as standard drugs. When the reported compounds were screened against different plant pathogens using tube diffusion method,[31] it was observed that all compounds show the significant antifungal activity as compared to synthesized ligand.

Table 11. Bond lengths (Å) and angles (°) for compound **5**

Sn1	O2	2.01			Sn1	C33	2.06
Sn1	C55	2.06			O2	C3	1.31
C5	C6	1.39			C3	O4	1.23
C3	C5	1.48			C18	C19	1.40
O2	Sn1	C33	111.05	O2	Sn1	C55	97.39
C33	Sn1	C44	116.06	C44	Sn1	C55	108.84
C55	Sn1	O4	147.03	Sn1	C33	C34	119.96
Sn1	O2	C3	116.78	O2	C3	O4	111.22

Insecticidal Activity

Insecticidal activity data was collected by contact toxicity method[31] and the data is reported in Table 15 for complexes **1-5**. Premethrin was used as standard drug with concentration 235.7 μg/cm^2. Complex **1**, **4** and **5** shows the activity against all insects while the complex **2** and **3** does not show any insecticidal activity against *Tribolium castaneum*.

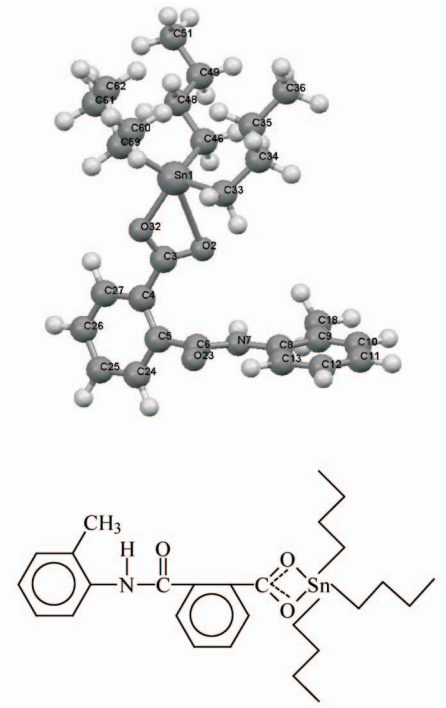


Fig. 6. Geometry optimised and chemical structure of compound **4**.

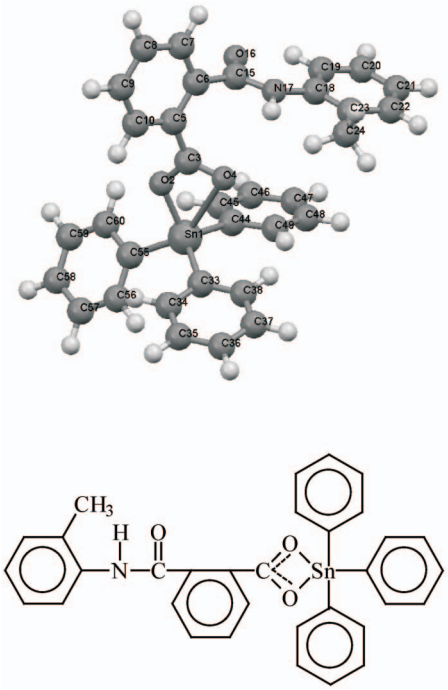


Fig. 7. Geometry optimised and chemical structure of compound **5**.

Table 12. Antibacterial activity[a-c] (diameter of inhibition zone after 20 h) of 2-[(2′-methylphenyl-amido)]benzoic acid and their organotin(IV) complexes

Bacterium (ATCC No.)	Inhibition Zone Diameter (mm)						Reference Drug
	HL	**1**	**2**	**3**	**4**	**5**	
Escherichia coli (11229)	-	15	16	-	-	12	35
Bacillus subtilis (11774)	-	20	-	-	15	18	38
Shigella flexenari (10782)	-	11	13	-	14	16	32
Stephlococcus aureus (25923)	-	-	12	10	16	12	38
Pseudomonas aeruginosa (10145)	-	-	10	9	-	15	29
Salmonella typhi (10749)	-	14	10	13	-	16	28

[a] *In vitro*, agar well diffusion method, conc. 3 mg/mL of DMSO
[b] Reference drug, Imipenum
[c] Clinical Implication: *Escherichia coli*, infection of wounds, urinary tract and dysentery; *Bacillus subtilis*, food poisoning; *Shigella flexenari*, blood diarrhea with fever and severe prostration; *Staphlococcus aureus*, food poisoning, scaled skin syndrome, endrocarditis; *Pseudomonas aeruginosa*, infection of wounds, eyes, septicemia, *Salmonella typhi*, typhoid fever, localized infection.

Table 13. Brine Shrimp (Artemia salina) lethality bioassay of 2-[(2′-methylphenylamido)]benzoic acid and their organotin(IV) derivatives

Comp. No.	Dose (μg/mL)	No. of Shrimps	No. of Survivors	LD_{50} (μg/mL)	Standard Drug	LD_{50} (μg/mL)
	100	30	0			
HL	10	30	14	-	Etoposide	7.46
	1	30	22			
	100	30	0			
1	10	30	13	17.99	Etoposide	7.46
	1	30	25			
	100	30	0			
2	10	30	8	13.92	Etoposide	7.46
	1	30	21			
	100	30	6			
3	10	30	10	-	Etoposide	7.46
	1	30	10			
	100	30	0			
4	10	30	0	5.18	Etoposide	7.46
	1	30	4			
	100	30	0			
5	10	30	10	9.14	Etoposide	7.46
	1	30	17			

Antileishmanial Activity

The antiprotozoal activity of the compounds **1-5** against the pathogenic Leishmania was obtained and data are given in Table 16. Reported compounds produced a significant reduction in viable promastigotes. The minimum protozoa concentration for promastogotes, defined as that concentration which produced 50% reduction in parasites after 72 h of incubation.[31] Compounds **1-5** show good antileishmanial activity. Amphotericin B. was used as standard drug with the concentration 0.19 μg/mL.

The results obtained support the earlier reports that there is direct relation between the activity and the coordination environment of the metal. Function of the ligand is to support the transport of the active organotin moiety to the site of the action where it is released by hydrolysis.[32] The anionic ligand also plays an important role in determining the degree of the activity of organotin compounds. As the triorganotin(IV) compounds show tetrahedral geometry in solution and they show significant activity which is consistent with literature that species generating the tetrahedral geometry in solution are more active.[33,34]

Thus the presence of an organic group directly attached to tin is an important factor which is responsible for enhanced activity of organotin(IV) complexes. This indicates that the alkyl group directly appended to the central tin atom is important contributor to the activity.

EXPERIMENTAL

Physical measurements

Melting points were determined in capillary tubes using a MP-D Mitamura Riken Kogyo (Japan) electrothermal melting point apparatus and are uncorrected. Infrared absorption spectra were recorded as KBr (4000-400 cm^{-1}) pellets on Bio-red FTIR spectrophotometer.

^{1}H, ^{13}C and ^{119}Sn NMR spectra were recorded on a

Table 14. Antifungal activity[a-c] (% inhibition) of 2-[(2′-methylphenylamido)]benzoic acid and their organotin(IV) complexes

Fungus (ATCC No.)	Inhibition (%)						Standard Drug	MIC (μg/mL)
	HL	**1**	**2**	**3**	**4**	**5**		
Trichophyton longifusus (22397)	0	0	79.8	0	100	0	Miconazole Ketoconazole	70.0
Candida albicans (2192)	0	72.5	85.5	0	100	100	Miconazole	110.8
Aspergillus flavis (1030)	0	66.6	89.2	0	90.0	70.2	Amphotercin B.	20.0
Microsporum canis (9865)	0	0	0	100	80.2	0	Miconazole	98.4
Fusarium solani (11712)	0	0	95.8	100	0	86.4	Miconazole	73.2
Candida glaberata (90030)	0	90.2	0	0	0	95.4	Miconazole	110.8

[a] Concentration: 100 μg/mL of DMSO
[b] MIC: Minimum inhibitory concentration
[c] Percent inhibition (standard drug) = 100

Table 15. Insecticidal biassay[a-c] of organotin(IV) complexes of 2-[(2′-methylphenylamido)]benzoic acid

Insects	% Mortality				
	1	**2**	**3**	**4**	**5**
Tribolium castaneum	20	–	–	18	20
Sitophilus oryzae	20	25	25	22	18
Rhyzopertha dominica	25	20	20	19	16
Callosbruchus analis	30	–	30	25	28

[a] Concentration of sample: 1571.3 μg/cm^2
[b] Standard drug: Permethrin
[c] Concentration of standard drug: 237.7

Table 16. Antileishmanial activity biassay[a-d] of organotin(IV) complexes of 2-[(2′-methylphenylamido)]benzoic acid

	Compound No.				
	1	**2**	**3**	**4**	**5**
% Inhibition	100	100	100	100	100
IC_{50} (μg/mL)	68.1	67.1	67.1	67.5	67.5
Standard drug (μg/mL)	0.19	0.19	0.19	0.19	0.19

[a] Test organism: Leishmania major (DESTO)
[b] Standard drug: Amphotericin.B
[c] Incubation period: 72 h
[d] Incubation temperature: 22 °C

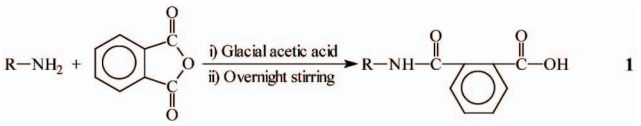
Bruker AM-250 spectrometer (Germany), using $CDCl_3$ as an internal reference [δ ^{1}H($CDCl_3$) = 7.25 and δ ^{13}C($CDCl_3$) = 77.0]. ^{119}Sn NMR spectra were obtained with Me_4Sn as external reference [δ(Sn) = 37.290665]. Mass spectral data were measured on a MAT 8500 Finnigan 70 eV mass spectrometer (Germany). The stimulated isotopic distribution was computed with the CHEMTOOL Software Package.[35] The HL and complexes **1**-**5** were modeled by MOPAC 2007[36] program in gas phase using PM3 method.[37,38] The newer PM6 method gave unsatisfactory results for compounds **1**-**5**, therefore for sake of uniformity PM3 method was used for the free ligand **HL** as well. Selected parts of the complexes not containing the metal ion were pre-optimised using molecular mechanics methods. Several cycles of energy minimisation had to be carried for each of the molecules. Molecular Mechanics correction was applied to the -CO-NH- barrier. Geometry was optimized using Eigen vector following the Root Mean Square Gradient for molecules was found to be (HL) 0.035 (1) 0.073 (2) 0.009 (3) 0.100 (4) 0.093 and (5) 0.052. Self consistent field was achieved in each case. The final heat of formation of molecules (in Kcal.) are as follows **HL** -80.10415, **1** -86.78979, **2** -127.8883, **3** -162.0344 **4** -190.6807 and **5** 18.43217.

Materials and chemicals

All the glass apparatus with standard quick fit joints were used throughout the work after cleaning and drying at 120 °C. Di- and triorganotin(IV) salts were purchased from Aldrich. All other reagents were of the purest grade available. Solvents were purified as in previously published methods.[39] The *o*-toluidine and phthalic anhydride were commercial products and used without further purification.

General Procedure for Synthesis of 2-[(2′-methylphenylamido)]benzoic acid HL

A solution of phthalic anhydride (5 mmol) in HOAc (300 mL) was added to a solution of *o*-toluidine (5 mmol) in HOAc (150 mL) and the mixture was stirred overnight at room temperature. The pale yellow precipitates were filtered, washed with cold distilled H_2O (200 mL) and air dried.



R =

$R_2SnCl_2 + 2Et_3NHL \xrightarrow[\text{ii) Reflux for 8-10 hrs}]{\text{i) Toluene}} R_2SnL_2 + 2Et_3NHCl$ **2**

$R_3SnCl + Et_3NHL \xrightarrow[\text{ii) Reflux for 8-10 hrs}]{\text{i) Toluene}} R_3SnL + Et_3NHCl$ **3**

Where

R_2	**Me_2**	**Bu_2**	-
HL	**1**	**2**	-
R_3	**Me_3**	**Bu_3**	**Ph_3**
HL	**3**	**4**	**5**

General Procedure for Synthesis of Organotin(IV) complexes

2-[(2′-methylphenylamido)]benzoic acid (1 mmol) was suspended in dry toluene (100 mL) and treated with Et_3N (0.29 mL, 1 mmol). The mixture was refluxed for 2-3 hours. To this stirring solution, diorganotin dichloride (0.5 mmol) or triorganotin chloride (1 mmol) was added as solid and the reaction mixture was refluxed for 8-10 hours. The reaction mixture contained Et_3NHCl was filtered off. The solvent was removed through rotary apparatus. The mass left behind was recrystallized from $CHCl_3$ and *n*-hexane (1:1).

CONCLUSIONS

Organotin(IV) derivatives have been synthesized in the quantitative yield by refluxing the synthesized carboxylic acid and respective organotin(IV) chlorides in dry toluene for 8-10 hours. The FT-IR spectra clearly demonstrate that the organotin(IV) moieties react with [O,O] atoms of the ligand and ligand behave as bidentate group for coordination to tin. Semi-empirical study shows that in the compounds **1**-**5**, the carboxylate group binds in an anisobidentate mode to the Sn atom. Mass spectrometry reveals that the primary fragmentation is due to the loss of the alkyl or aryl group followed by elimination of CO_2 and the remaining part of the ligand, which leaves Sn^+ as the end product. NMR shows that in solution the bidentate carboxylate group is cleaved and the resulting monomer contains four coordinated tin with a tetrahedral arrangement. Biological activity data shows that all the complexes are biologically active with few exceptions and can be used as drug.

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