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Journal of Coordination Chemistry

Publication details, including instructions for authors and subscription information:

<http://www.informaworld.com/smpp/title~content=t713455674>

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First published on: 25 September 2007

To cite this Article Shahzadi, S. , Shahid, K. and Ali, S.(2007) 'Spectral characterization and biocidal activity of organotin(IV) (*E*)-3-[(2',6'-dichlorophenylamido)]propenoates', *Journal of Coordination Chemistry*, 60: 24, 2637 – 2648, First published on: 25 September 2007 (iFirst)

To link to this Article: DOI: 10.1080/00958970701288025

URL: <http://dx.doi.org/10.1080/00958970701288025>

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Spectral characterization and biocidal activity of organotin(IV) (*E*)-3-[(2',6'-dichlorophenylamido)]propenoates

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(Received 24 July 2006; in final form 22 October 2006)

Biocidal and spectroscopic aspects of organotin(IV) complexes with (*E*)-3-[(2',6'-dichlorophenylamido)]propenoic acid are described with support of elemental analysis. IR, ¹H, ¹³C, ¹¹⁹Sn NMR and mass spectral data suggest that the ligand is bidentate, coordinating through oxygen atoms and that diorganotin(IV) complexes are six-coordinate. Triorganotin(IV) carboxylates exist as pentacoordinated trigonal bipyramidal complexes in the solid state and tetrahedral ones in solution. The complexes have been screened against bacteria, fungi and brine-shrimp larvae to assess their biological activity.

Keywords: Organotin(IV) carboxylates; (*E*)-3-[(2',6'-dichlorophenylamido)]propenoic acid; Spectral characterization; Biological activity

1. Introduction

The chemistry of organotin(IV) complexes witnessed a quantum leap during the past few decades with wide applications as catalysts, stabilizers, biocides, antifouling paints and wood preservatives [1–3]. Investigations have also been carried out on applications as antitumour agents. Several di- and triorganotin(IV) species, particularly, organotin(IV) carboxylates, are active against various types of cancer [4, 5]. Organotin(IV) chelates with nitrogen, sulfur and oxygen donor ligands have gained attention during the last few years [6]. Use of organotin compounds as reagents or intermediates in organic synthesis prompted preparation of many new organotin compounds [7].

The chemistry of organotin(IV) compounds (R_nSnX_{4-n}) has been extensively studied due to their biopotency [8, 9]. Applications of organotin carboxylates and continuation of our studies of biologically active organotin(IV) derivatives [10, 11], led to synthesis of organotin(IV) derivatives of (*E*)-3-[(2',6'-dichlorophenylamido)]propenoic acid (figure 1). These complexes were characterized by elemental analysis, infrared, multinuclear NMR (¹H, ¹³C, ¹¹⁹Sn) and mass spectrometry. Their biological activity data has also been reported.

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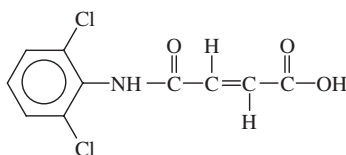


Figure 1. Chemical structure of (*E*)-3-[(2',6'-dichlorophenylamido)]propenoic acid (HL).

2. Experimental

2.1. Material and methods

All reactions were carried out under an anhydrous atmosphere. Solvents were purified and dried before use [12]. All chemicals were of analytical grade and used without further purification. Melting points taken in a capillary tube on a MP-D Mitamura Rikero Kogyo (Japan) are uncorrected. Elemental analysis was carried with a Perkin–Elmer 2400 Series II instrument. IR spectra were recorded on a Bio-Rad FTIR Spectrophotometer as KBr discs. ^1H and ^{13}C NMR spectra were recorded on a Bruker AM-250 spectrometer (Germany) using CDCl_3 as an internal reference. ^{119}Sn NMR spectra were obtained on a Bruker 250 ARX instrument with Me_4Sn as an external reference. Mass spectral data were recorded on a MAT 8500 Finnigan (Germany) at 70 eV.

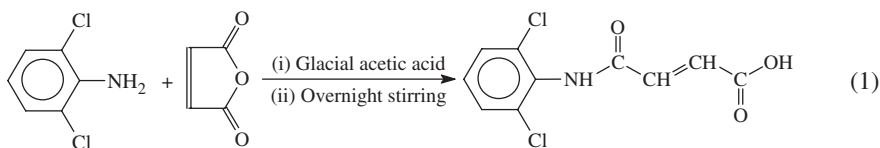
2.2. Procedure for synthesis of ligand acid

A solution of maleic anhydride (50 mmol, 4.9 g) in glacial acetic acid (300 mL) was added to a solution of 2,6-dichloroaniline (50 mmol, 8.05 g) in glacial acetic acid (150 mL) and the mixture was stirred at room temperature overnight. The yellow precipitates formed were washed with cold distilled H_2O (200 mL) and air dried. The general chemical reaction is given in scheme 1 (equation 1).

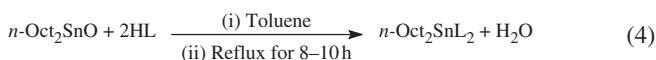
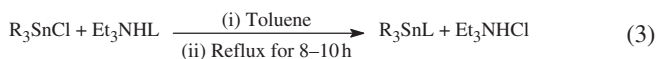
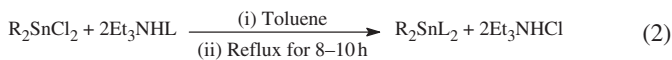
2.3. General procedure for synthesis of complexes

Procedure (a). (*E*)-3-[(2',6'-dichlorophenylamido)]propenoic acid (3.84 mmol, 1 g) was suspended in dry toluene (100 mL) and treated with Et_3N (3.84 mmol, 0.53 mL). The mixture was refluxed for 2–3 h and to this solution, diorganotin dichloride (1.92 mmol) or triorganotin chloride (3.84 mmol) was added as solid (or liquid in case of Bu_3SnCl) with constant stirring and then refluxed for 8–10 h. The reaction mixture containing Et_3NHCl was filtered leaving organotin(IV) derivatives in the filtrate. Solvent was removed by rotary evaporator and the mass left behind was recrystallized from chloroform : *n*-hexane (1 : 1) (equation 2 and 3 in scheme 2).

Procedure (b). (*E*)-3-[(2',6'-dichlorophenylamido)]propenoic acid (3.84 mmol, 1 g) was suspended in dry toluene, (100 mL). To this solution, *n*- Oct_2SnO (1.92 mmole, 0.69 g)



Scheme 1. Synthesis of ligand (HL).



R	Me ₂	<i>n</i> -Bu ₂	<i>n</i> -Oct ₂
Comp. no	(1)	(2)	(3)
R	Me ₃	<i>n</i> -Bu ₃	Ph ₃
Comp. no	(4)	(5)	(6)

Scheme 2. Synthesis of Organotin(IV) carboxylate.

was added as solid with constant stirring and refluxed for 8–10 h. Water formed during the reaction was removed *via* a Dean and Stark trap. The solvent was evaporated through rotary evaporator and the product obtained was recrystallized from chloroform : *n*-hexane (1 : 1) mixture (equation 4 in scheme 2).

3. Results and discussion

Organotin(IV) complexes have been prepared by the reaction of the ligand acid and Et₃N with corresponding organotin(IV) chlorides in 1 : 1 and 1 : 2 molar ratios in dry toluene; the *n*-dioctyltin(IV) dicarboxylates were synthesized by reaction of the ligand acid and *n*-Oct₂SnO in 2 : 1 molar ratio in anhydrous toluene. Prolonged reflux (8–10 h) is required for good yield, equations (2–4). Complexes 1–6 are solids, generally with sharp melting points, stable in light and dry air. They are more soluble in polar solvents than in non-polar. Physical data are reported in table 1.

3.1. Infrared spectroscopy

Infrared spectra of 1–6 were recorded in the range of 4000–400 cm⁻¹ as KBr discs. The absorption bands (cm⁻¹) for structural assignments are given in table 2. Carboxylate can coordinate metal by three different modes (see scheme 3).

By comparison to other organotin(IV) complexes with {O} donor ligands, the following assignments were suggested for the complexes studied here. In the 3416 cm⁻¹ region, the ligand exhibit a medium band typical for –OH stretching vibrations which was absent from the spectra of the complexes, indicating deprotonated –COO⁻.

Table 1. Physical data of organotin(IV) carboxylates.

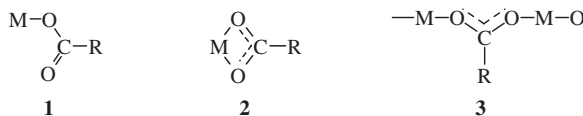
Compound no.	M.p. (°C)	Yield (%)	Elemental analysis % calculated (found)		
			C	H	N
1	121–122	60	39.58 (39.48)	2.69 (2.59)	4.19 (4.07)
2	82–83	70	44.74 (44.68)	3.99 (3.87)	3.72 (3.67)
3	182–183	85	50.17 (50.11)	5.11 (5.23)	3.25 (3.12)
4	92–93	90	36.87 (36.70)	3.54 (3.46)	3.30 (3.18)
5	72–73	93	48.08 (48.21)	6.01 (6.16)	2.55 (2.47)
6	132–133	96	55.17 (55.28)	3.44 (3.34)	2.29 (2.17)

Table 2. Assignment of characteristic FT-IR vibrations of (*E*)-3-[(2',6'-dichlorophenylamido)]propenoic acid and its organotin(IV) complexes.

Compound	IR peak (cm ⁻¹)						
	ν_{OH}	ν_{NH}	$\nu_{\text{C=O}}$	ν_{COO}	$\Delta\nu$	$\nu_{\text{Sn-C}}$	$\nu_{\text{Sn-O}}$
HL	3416s	3319s	1720s	1565s ¹	1322s ²	243	–
1	–	3325s	1726s	1590m	1411s	179	520m
2	–	3321m	1728s	1545m	1420m	125	538m
3	–	3316s	1718s	1578m	1425s	153	525m
4	–	3327s	1714s	1580s	1442s	138	540w
5	–	3315m	1719s	1552s	1422m	130	510w
6	–	3322m	1727s	1535m	1418s	117	–

¹Antisymmetric ²Symmetric.

Abbreviations: s = strong; m = medium; w = weak.



Scheme 3. Possible coordination modes of carboxylate group.

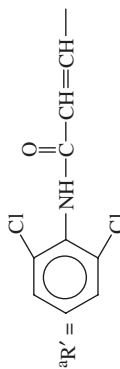
The -C=O stretching vibrations of peptide group in (HL) was observed at 1720 cm^{-1} as strong and sharp band. The difference between $\nu_{\text{asym}}(\text{COO})$ and $\nu_{\text{sym}}(\text{COO})$ is important in the nature of the binding of the ligand [13, 14]. The difference between the two vibration frequencies in the range of $117\text{--}179\text{ cm}^{-1}$, indicate bidentate coordination of the -COO^- in the complexes [15]. In all the complexes, medium to weak bands in the region $435\text{--}480\text{ cm}^{-1}$ are assigned to Sn–O and those in the region $510\text{--}540\text{ cm}^{-1}$ are assigned to Sn–C bonds.

3.2. Mass spectrometry

The 70 eV mass spectral data from the Electron Impact (EI) method for **1–6** are given in table 3. The molecular ion peak is observed in all triorganotin(IV) carboxylates, but absent in all diorganotin(IV) dicarboxylates [16]. The fragmentation ions are in good agreement with expected structures of the compounds. Fragment ions containing the Sn

Table 3. Mass spectral data^a of organotin (*E*)-3-[(2',6'-dichlorophenylamido)]propenoates at 70 eV.

Fragment ion	1 <i>m/z</i> (%)	2 <i>m/z</i> (%)	3 <i>m/z</i> (%)	4 <i>m/z</i> (%)	5 <i>m/z</i> (%)	6 <i>m/z</i> (%)
[R ₂ SnOOR] ⁺	407(65)	491(21)	603(19)	407(33)	491(77)	531(16)
[R ₂ SnOOCR] ⁺	392(13)	434(3)	490(12)	392(8)	434(10)	454(10)
[¹⁰⁷ R ₃ Sn] ⁺ /[¹⁰⁷ R ₃ SnH] ⁺	—	—	—	164(19)/165(2)	290(18)/291(3)	350(13)/351(3)
[R ₂ Sn] ⁺ /[R ₂ SnH] ⁺	149(4)/150(16)	233(2)/234(13)	345(6)/346(18)	149(3)/150(19)	233(3)/234(16)	273(2)/274(18)
[R ₂ Sn] ⁺ /[R ₂ SnH] ⁺	134(19)/135(4)	176(16)/177(2)	232(13)/233(4)	134(15)/135(2)	176(17)/177(3)	196(19)/197(2)
[Sn] ⁺ /[SnH] ⁺	120(16)/121(8)	120(19)/121(3)	120(14)/121(2)	120(15)/121(5)	120(17)/121(4)	120(10)/121(3)
[C ₂ H ₂ COClSn] ⁺	206(100)	206(100)	206(100)	206(100)	206(100)	206(100)



^bR = CH₃, *n*-C₄H₉, C₆H₅ and *n*-C₈H₁₇.

are quite intense. In triorganotin(IV) carboxylates the primary fragmentation is due to the loss of the R group and the same is true for diorganotin(IV) derivatives. However, the secondary and tertiary decomposition is also followed by the loss of R group in triorganotin(IV) derivatives, while diorganotin(IV) derivatives have a slightly different pattern of fragmentation.

3.3. NMR spectroscopy

Tables 4 and 5 summarize the ^1H , ^{13}C and ^{119}Sn NMR spectral parameters, which complement the chemical analyses of the compounds and contributed to their complete characterization.

^1H NMR chemical shifts and coupling constant are (table 4) assigned for all signals in the spectra of the ligand and complexes. Protons 'a' and 'b' give doublets at 7.60 and 7.30 ppm with coupling of 7.6 and 7.5 Hz, respectively. In the complexes, this signal does not show much shift. In the spectra of HL, signals at 6.63 and 7.20 ppm with coupling of 7.7 Hz have been assigned to $\text{CH}=\text{CH}$; $-\text{NH}$ gives a singlet at 6.9 for HL. After complexation the NH proton does not show any shift, which indicates that N is not taking part in coordination.

^{13}C and ^{119}Sn NMR data (table 5) shows the presence of peptide $-\text{C}=\text{O}$ group and $-\text{COO}$ by the signals at 167.2–167.9 ppm and 172.2–175.8 ppm, respectively. Aromatic carbon resonances were at similar positions in the experimental data as those calculated from the incremental method [17]. The coupling constants, $^nJ[^{119}\text{Sn}, ^{13}\text{C}]$ are important for structural characterization of organotin(IV) compounds. For triorganotin(IV) derivatives, the magnitude of $^1J[^{119}\text{Sn}, ^{13}\text{C}]$ coupling suggests tetrahedral geometry around tin in solution [18, 19]. The geometry of the diorganotin dicarboxylates in non-coordinating solvents are not defined with certainty due to the fluxional behaviour of the carboxylate oxygens in coordination with tin [20]. Earlier reports suggest geometry between penta- and hexa-coordination [20, 15].

^{119}Sn chemical shifts of organotin compounds cover a range of ± 600 ppm. The chemical shifts of ^{119}Sn for organotin(IV) derivatives were recorded in CDCl_3 (table 5). These values lie inside the range for four-coordinate organotin(IV) complexes. Coupling parameter (J) can easily be measured in solution, while can be calculated by using Lockhart's equation [21] (5).

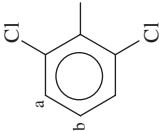
$$\theta = 0.0161[{}^2J]^2 - 1.32[{}^2J] + 133.4 \quad (5)$$

This equation is used for non-coordinating solvents. Similarly on substituting value of θ in the Lockhart's equation [21] (6), $^1J[^{119}\text{Sn}, ^{13}\text{C}]$ can be calculated.

$$^1J[^{119}\text{Sn}, ^{13}\text{C}] = 11.4\theta - 875 \quad (6)$$

To gain further information about the possible coordination geometries in solution, a close examination of $^1J[^{119}\text{Sn}-^{13}\text{C}]$ and $^2J[^{119}\text{Sn}-^1\text{H}]$ coupling constants was undertaken since $\text{C}-\text{Sn}-\text{C}$ bond angles, can be obtained by literature methods [22, 23]. Data are summarized in table 6. As indicated by Nadvornik and co-workers [23, 24] and $^1J[^{119}\text{Sn}-^{13}\text{C}]$ coupling constant is quite amenable for predictions about the geometry around tin. For the *n*-tributyltin(IV) derivative, with the $^1J[^{119}\text{Sn}-^{13}\text{C}]$ value being 350.6 Hz a $\text{C}-\text{Sn}-\text{C}$ value of 111.6° was calculated by the use of the Holecek and Lycka equation [25] which corresponds to a quasi-tetrahedral geometry

Table 4. ^1H NMR data^a of (*E*)-3-[2',6'-dichlorophenylamido]propenoic acid and their organotin complexes.

Proton	Chemical shift (ppm)						
	HL	1	2	3	4	5	6
	(a) 7.60d (7.6)	(a) 7.62d (7.6)	(a) 7.64d (7.7)	(a) 7.66d (7.7)	(a) 7.65d (7.6)	(a) 7.65d (7.7)	(a) 7.66d (7.8)
	(b) 7.30t (7.5)	(b) 7.32t (7.5)	(b) 7.34t (7.6)	(b) 7.33t (7.5)	(b) 7.36t (7.7)	(b) 7.38t (7.8)	(b) 7.40t (7.9)
-NH	6.9s	6.9s	6.6s	6.9s	6.9s	6.9s	6.9s
-CH=CH-	6.63d (7.7)	7.38d (7.9)	7.24d (8.0)	7.20d (8.2)	7.35d (8.1)	7.17d (8.0)	7.38d (8.3)
	7.20d (7.7)	7.50d (7.9)	7.41d (8.0)	7.50d (8.2)	7.49d (8.1)	7.31d (8.0)	7.52d (8.3)
R	-	0.26s [78.5]	1.78t [72.9] 1.39-1.42m 1.40ps (7.4) 0.86t (7.2)	0.85t [73.6] 1.81-1.96m	-0.02s [58.0]	0.89t [60.1]	7.70-7.74m 1.26-1.40m

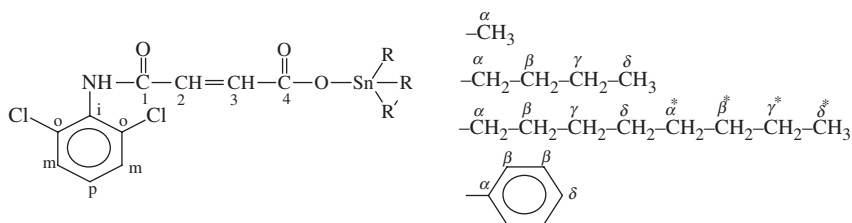
^aChemical shifts (δ) in ppm, $^2J(^{19}\text{Sn}, ^1\text{H})$ and $^3J(^1\text{H}, ^1\text{H})$ in Hz are listed in square brackets and parenthesis, respectively. Multiplicity is given as: s = singlet, d = doublet, t = triplet, m = multiplet, ps = pseudosextet.

Table 5. ^{13}C and ^{119}Sn NMR data^{a,b} of (*E*)-3-[(2',6'-dichlorophenylamido)]propenoic acid and their organotin(IV) complexes.

Carbon	HL	1	2	3	4	5	6
i	134.6	134.5	134.7	134.2	134.8	134.3	134.1
o	127.9	127.7	127.5	127.8	127.2	126.6	127.1
m	134.0	135.5	135.4	135.2	135.7	135.3	135.9
p	130.6	131.1	131.2	131.5	131.4	131.8	131.7
1	167.2	167.8	167.5	167.4	167.3	167.1	167.9
2	124.4	124.9	124.5	124.7	124.2	124.1	124.6
3	119.6	119.8	119.6	119.4	119.2	119.9	119.7
4	172.2	175.8	175.5	175.3	175.7	175.6	175.4
(C- α)	–	29.6	29.6	37.4	–1.9	16.7	137.3
		[659.8]	[589.0]	[462.8]	[394.8]	[350.6]	[661.5]
(C- β)	–	–	27.2	31.9	–	27.8	135.7
			[19.7]			[20.3]	
(C- γ)	–	–	26.6	30.1	–	26.0	136.2
			[98.7]			[62.4]	
(C- δ)	–	–	14.1	29.6	–	14.1	130.2
(C- α^*)	–	–	–	29.1	–	–	–
(C- β^*)	–	–	–	26.3	–	–	–
(C- γ^*)	–	–	–	22.6	–	–	–
(C- δ^*)	–	–	–	14.0	–	–	–
δ ^{119}Sn	–	–179.3	–138.6	–138.8	169.6	155.2	–46.1

^aChemical shifts (δ) in ppm: $^nJ[^{119}\text{Sn}, ^{13}\text{C}]$ in Hz is listed in parenthesis.

^b



R' = R for triorganotin, R' = L for diorganotin.

Table 6. C–Sn–C angles ($^\circ$) estimated from NMR.

Compound	$^1J[^{119}\text{Sn}-^{13}\text{C}]$ (Hz)	$^2J[^{119}\text{Sn}-^1\text{H}]$ (Hz)	C–Sn–C angles ($^\circ$) calculated from	
			1J	2J
1	659.8	78.5	134.6	129.0
2	589.0	72.9	136.6	122.7
3	462.8	73.6	122.1	123.4
4	394.8	58.0	111.4	111.0
5	350.6	60.1	111.6	112.2
6	661.5	–	116.8	–

in CDCl_3 solution. The geometric data calculated, as just described, are consistent with tetrahedral geometries for the triorganotin(IV) species, i.e. monomers 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 asymmetric coordination of the carboxylate ligand.

3.4. Biological activity

Compounds 1–6 and HL were also screened for their antibacterial activity by the Agar well diffusion method [26]. The results are reported in table 7 and figure 2. All the compounds show significant antibacterial activity. Antifungal activity data is given in table 8 and figure 3 for which the tube dilution method [27] was used.

Compound 6 shows maximum activity while the other compounds were also found active against fungi with few exceptions. Bioactive compounds are often toxic to Shrimp larvae. Hence *in vivo* lethality to Shrimp larvae can be used as rapid and simple preliminary monitor for bioactive compounds during the isolation of natural products. Brine Shrimp's method [28] has been used for the determination of toxicity of the organotin carboxylates. The results are reported in table 9 and figure 4.

Table 7. Antibacterial activity^{a-c} (diameter of inhibition zone after 20 h) of (*E*)-3-[(2',6'-dichlorophenylamido)]propenoic acid and their organotin(IV) complexes.

Bacterium (ATCC No.)	Inhibition zone diameter (mm)							Reference drug
	HL	1	2	3	4	5	6	
<i>Escherichia coli</i>	14	–	15	13	12	15	16	35
<i>Bacillus subtilis</i> (11774)	–	12	15	–	14	10	11	38
<i>Shigella flexneri</i> (700390)	12	10	12	–	16	15	14	32
<i>Staphylococcus aureus</i> (25923)	11	–	10	15	16	13	–	38
<i>Pseudomonas aeruginosa</i> (10145)	10	–	8	–	10	–	–	29
<i>Salmonella typhi</i> (10749)	8	12	10	9	–	–	–	28

^a*In vitro*, agar well diffusion method, conc. 3 mg mL^{-1} of DMSO.

^bReference drug, Imipenem.

^cClinical Implication: *E. coli*, infection of wounds, urinary tract and dysentery; *B. subtilis*, food poisoning; *S. flexneri*, blood diarrhoea with fever and severe prostration; *S. aureus*, food poisoning, scaled skin syndrome, endocarditis; *P. aeruginosa*, infection of wounds, eyes, septicemia, *S. typhi*, typhoid fever, localized infection.

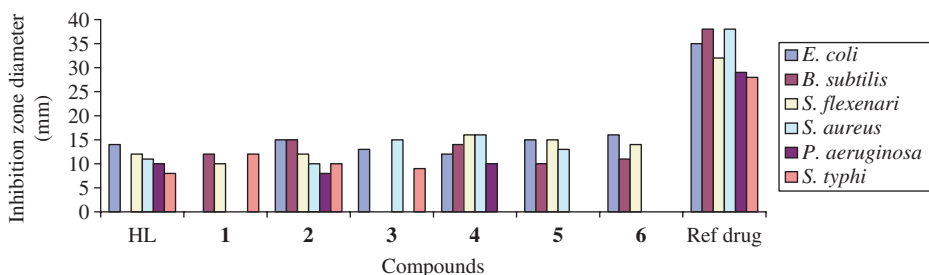


Figure 2. Antibacterial activity of HL and its organotin(IV) derivatives against various bacteria.

Table 8. Antifungal activity^{a-c} (% inhibition) of (*E*)-3-[(2',6'-dichlorophenylamido)]propenoic acid and their organotin(IV) complexes.

Fungi (ATCC No.)	Inhibition (%)							MIC($\mu\text{g mL}^{-1}$)
	HL	1	2	3	4	5	6	
<i>Trichophyton longifusus</i> (22397)	40.2	0	0	30.8	0	58.9	0	70.0
<i>Candida albicans</i> (2192)	60.5	60.2	0	50.2	40.5	72.5	30.5	110.8
<i>Aspergillus flavis</i> (1030)	80.2	79.8	0	50.9	67.8	40.9	20.9	20.0
<i>Microsporium canis</i> (9865)	0	50.5	60.5	70.2	66.8	82.5	0	98.4
<i>Fusarium solani</i> (11712)	0	0	80.8	75.6	50.2	65.4	30.5	73.2
<i>Candida glaberata</i>	0	0	90.1	80.2	43.2	75.2	0	110.8

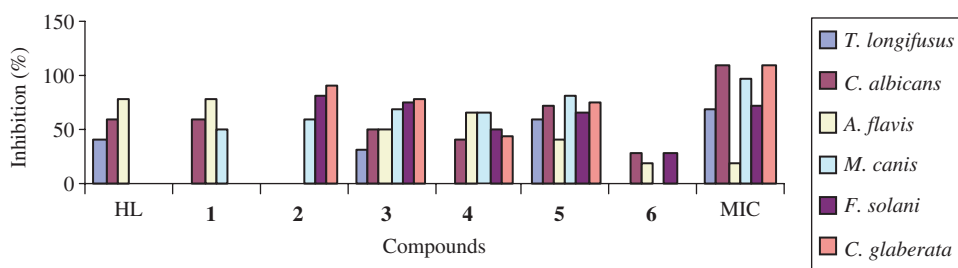
^aConcentration: 100 $\mu\text{g mL}^{-1}$ of DMSO.^bMIC: Minimum inhibitory concentration.^cPercent inhibition (standard drug) = 100.

Figure 3. Antifungal activity of HL and its organotin(IV) derivatives against various fungus.

Table 9. Brine Shrimp (*Artemia salina*) lethality bioassay of (*E*)-3-[(2',6'-dichlorophenylamido)]propenoic acid and their organotin(IV) complexes.

Compound	Dose ($\mu\text{g mL}^{-1}$)	No. of shrimps	No. of survivors	LD ₅₀ ($\mu\text{g mL}^{-1}$)	Standard drug	LD ₅₀ ($\mu\text{g mL}^{-1}$)
HL	100	30	10	–	Etoposide	7.46
	10	30	12			
	1	30	10			
1	100	30	6	–	Etoposide	7.46
	10	30	8			
	1	30	11			
2	100	30	0	10.19	Etoposide	7.46
	10	30	0			
	1	30	8			
3	100	30	0	10.00	Etoposide	7.46
	10	30	0			
	1	30	14			
4	100	30	12	65.02	Etoposide	7.46
	10	30	25			
	1	30	30			
5	100	30	0	64.08	Etoposide	7.46
	10	30	11			
	1	30	20			
6	100	30	6	–	Etoposide	7.46
	10	30	30			
	1	30	30			

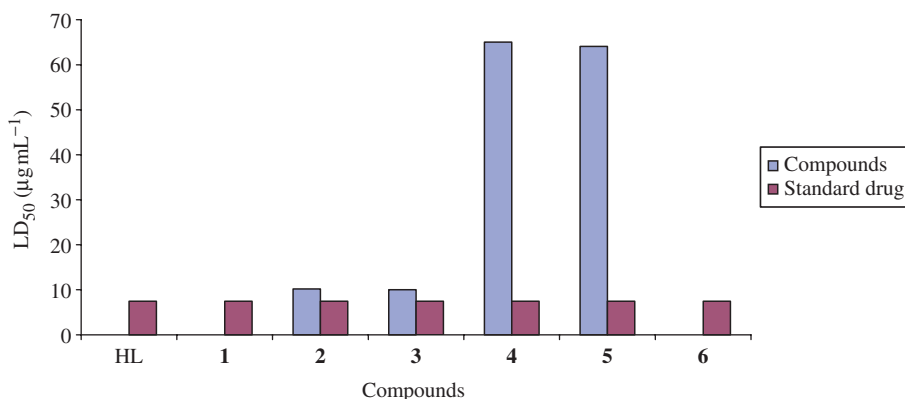


Figure 4. Cytotoxicity data of HL and its organotin(IV) derivatives.

Compounds **2–5** show positive lethality while **1** and **6** do not. A previous report [26] shows that toxicity of organotin compounds depends on the nature of R.

4. Conclusions

Organotin(IV) derivatives have been synthesized in quantitative yield by refluxing the carboxylic acid and respective organotin(IV) chloride/organotin(IV) oxide in dry toluene for 8–10 h. Elemental analyses show good agreement between the calculated and observed % of C, H and N. The FT–IR spectra clearly demonstrate that the organotin(IV) moieties react with [O, O] atoms of the ligand and ligand are bidentate towards tin. Mass spectrometry reveals that the primary fragmentation is due to loss of the alkyl or aryl group followed by elimination of CO₂ and the remaining part of the ligand, which leaves Sn⁺ as the end product. NMR data show that in solution the bidentate nature of carboxylate is lost and the resulting monomer contains tin with a tetrahedral arrangement in case of triorganotin(IV) derivatives while for diorganotin(IV) derivatives the geometry is between penta- and hexa-coordination.

Biological activity data show that all the complexes are biologically active with few exceptions.

Acknowledgement

Financial support from the University Research Fund (URF) of Quaid-i-Azam University is acknowledged.

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