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Characterization and Antimicrobial Activity of Organotin(IV) Complexes of 2-[(2′,6′-diethylphenylamido)]benzoates and 3-[(2′,6′-diethylphenylamido)]propanoates

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New organotin(IV) complexes with 2-[(2′,6′-diethylphenylamido)]benzoic acid (HL^1) and 3-[(2′,6′-diethylphenylamido)]propanoic acid (HL^2) were synthesized by the reaction of di- and triorganotin salts in the presence of triethylamine as base or dioctyltin oxide using a Dean and Stark trap for the removal of azeotropic water. All complexes were characterized by elemental analysis, IR, NMR, and mass spectral studies, and proof that tin-ligand coordination involves only the carboxylate group and complexes show hexa-coordinated geometry in solid state. Multinuclear NMR data show that triorganotin complexes exhibit 4-coordinated geometry while diorganotin complexes show a coordination number greater than 4, probably 5 or 6 in solution state. These complexes were screened to check their antimicrobial activity in vitro. The complexes of 2-[(2′,6′-diethylphenylamido)]benzoic acid (HL^1) were also checked for their insecticidal and anti-leishmanial activity. All the complexes show significant activity with few exceptions.

Key Words: Organotin(IV) carboxylates, spectroscopy, anti-leishmanial, insecticidal antibectrial, antifungal, cytotoxicity

Introduction

The self-assembly of organic ligands coordinated to metal ions or organometallic substances has been extensively studied.[1] The increasing interest in this field is mainly due to the potential relevance of such complexes to catalysis.[2] Organotin compounds show a spectrum to biological effects and have been studied as fungicides, bactericides, acaricides, and wood preservatives.[3] Organotin compounds have also been studied as

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anti-tumor drugs and were reported to exhibit lower toxicity than the related platinum drugs.[4] Organotin compounds bio-accumulate widely in the marine food chain and seafood products. They can also affect the activity of human natural killer cells.[5,6] In recent years, organotin(IV) carboxylates have been a subject of interest for some time because of their biochemical and commercial applications.[7] In general, the biochemical activity of organotin(IV) carboxylates is greatly influenced by the structure of the molecule and the coordination number of the tin atom.[8−10] Therefore, recognition of the importance between the biological properties and the structure of organotin(IV) carboxylates[11] has stimulated the study of carboxylates of tin. In our previous work, we reported several organotin complexes with oxygen and sulfur donor atoms.[12−14] As an extension of this research program and in connection with our current interest in the coordination chemistry of organotin complexes with ligands containing peptide linkage,[15−19] we report here the organotin(IV) complexes of 2-[(2′,6′-diethylphenylamido)]benzoic acid (**HL**^{1}) and 3-[(2′,6′-diethylphenylamido)]propanoic acid (**HL**^{2}) (Figures 1 and 2). These complexes were characterized by elemental analysis, IR, multinuclear NMR (^{1}H, ^{13}C and ^{119}Sn), and mass spectrometry. These complexes were also examined to check their antibacterial, antifungal, cytotoxicity, insecticidal, and anti-leishmanial activity in vitro.

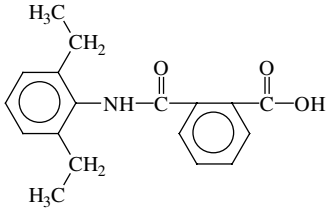


Figure 1. Structure of 2-[(2′,6′-diethylphenylamido)]benzoic acid (HL^1).

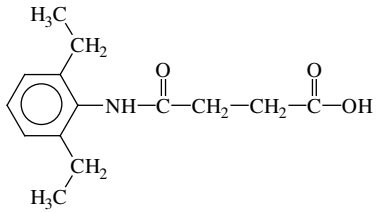


Figure 2. Structure of 3-[(2′,6′-diethylphenylamido)]propanoic acid (HL^2).

Experimental

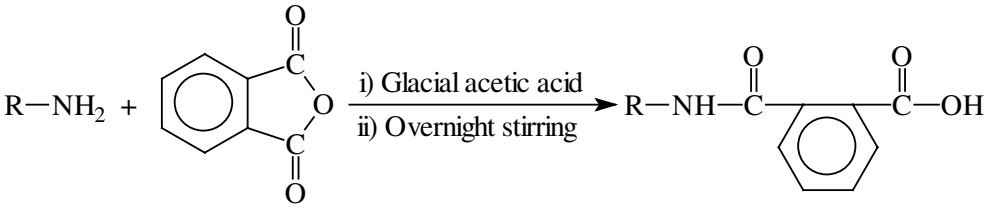
Materials and instrumentation

Glass apparatus with standard quick fit joints was used throughout the work after cleaning and drying at 120 °C. Phthalic anhydride, succinic anhydride, and organotin(IV) chlorides were purchased from Aldrich Chemical Company (USA) and used as such. Dioctyltin oxide was procured from Alfa Aesar. Toluene, acetone, dichloromethane, diethyl ether, methanol, chloroform, and glacial acetic acid were obtained from Merck Chemicals (Germany). All the solvents were purified and dried by the reported methods.[20] Melting points were determined on an electrothermal melting point apparatus, model MP-D Mitamura Riken Kogyo (Japan), by capillary tube and are uncorrected. Elemental analysis was carried out at the Midwest Microlab (Indianapolis, IN, 46250, USA), on a Vario EL model instrument and PE-2400 II apparatus. Infrared spectra were recorded as KBr/CSI pellets or thin film on a Bio-Rad Excaliber FT-IR in the range 4000-400 cm^{-1}.

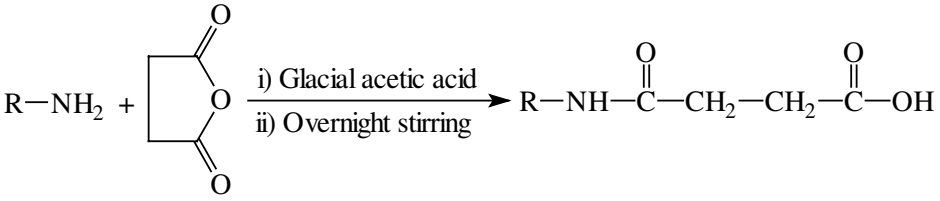
Mass spectra were recorded on a MAT 8500 Finnigan (Germany). The ^{1}H- and ^{13}C-NMR spectra were recorded on a Bruker AM-250 MHz using $CDCl_3$ as an internal surface. ^{119}Sn-NMR spectra were obtained on a Bruker 250 ARX instrument with Me_4Sn as an external reference.

General procedure for the synthesis of carboxylic acid

A solution of phthalic/succinic anhydride (1 mmol) in a HOAc (300 mL) was added to a solution of substituted aniline (1 mmol) in HOAc (150 mL) in a 500 mL round bottom flask and the mixture was stirred at room temperature overnight. The precipitates formed were filtered, washed with cold distilled water (200 mL), and air dried (Eqs. (1) and (2)).

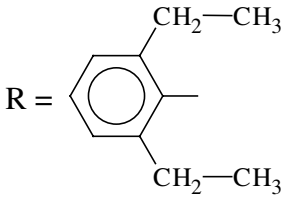


(1)



(2)

where



General procedure for the synthesis of organotin(IV) complexes

From organotin(IV) chloride

Synthesized carboxylic acid was suspended in dry toluene (100 mL) and treated with triethylamine in a 1:1 molar ratio. The mixture was refluxed for 2-3 h. To a solution of triethylammonium salt of the ligand in dry toluene was added diorganotin dichloride (0.5 mmol) or triorganotin chloride (1 mmol) as a solid to a reaction flask with constant stirring and the reaction mixture was refluxed for 8-10 h. The reaction mixture containing Et_3NHCl was filtered off such that the filtrate had the organotin(IV) derivative. The solvent was removed by rotary apparatus under reduced pressure. The mass left behind was recrystallized from $CHCl_3$ and pet-ether (1:1).

From dioctyltin(IV) oxide

Synthesized carboxylic acid (1 mmol) was suspended in dry toluene (100 mL) and treated with equimolar dioctyltin oxide in a reaction flask with constant stirring and the mixture was refluxed for 8-10 h. The water formed was removed by Dean and Stark trap. After completion and cooling of the reaction mixture to room temperature, solvent was removed by rotary apparatus under reduced pressured. The mass left behind was recrystallized from $CHCl_3$ and pet-ether (1:1).

Results and Discussion

Organotin(IV) complexes were 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. Dioctyltin(IV) dicarboxylates were synthesized by the reaction of the ligand acid and Oct_2SnO in 1:2 molar ratio in anhydrous toluene. However, prolonged reflux (8-10 h) is required for a good yield (Eqs. (3)-(5)). All these complexes (**1-12**) are solids, generally with sharp melting points, and are stable in light and dry air. They are more soluble in polar solvents than in non-polar solvents. Physical data are reported in Table 1.

$$R_2SnCl_2 + 2Et_3NHL \xrightarrow[\text{ii) Reflux for 8-10 h}]{\text{i) Toluene}} R_2SnL_2 + 2Et_3NHCl \tag{3}$$

$$R_3SnCl + Et_3NHL \xrightarrow[\text{ii) Reflux for 8-10 h}]{\text{i) Toluene}} R_3SnL + Et_3NHCl \tag{4}$$

$$Oct_2SnO + 2HL \xrightarrow[\text{ii) Reflux for 8-10 h}]{\text{i) Toluene}} Oct_2SnL_2 + H_2O \tag{5}$$

where

R_2	Me_2	Bu_2	Oct_2
HL^1	(**1**)	(**2**)	(**3**)
HL^2	(**7**)	(**8**)	(**9**)
R_3	Me_3	Bu_3	Ph_3
HL^1	(**4**)	(**5**)	(**6**)
HL^2	(**10**)	(**11**)	(**12**)

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

Comp. No.	Quantity Used			mp (°C)	Yield (%)	Elemental Analysis % Calculated (Found)		
	1st Reactant	2nd Reactant	3rd Reactant			C	H	N
(**1**)	HL^1 1 g (3.36 mmol)	Me_2SnCl_2 0.36 g (1.68 mmol)	Et_3N 0.47 mL (3.36 mmol)	141-2	90	61.53 (61.50)	5.66 (5.69)	3.77 (3.70)
(**2**)	HL^1 1 g (3.36 mmol)	Bu_2SnCl_2 0.51 g (1.68 mmol)	Et_3N 0.47 mL (3.36 mmol)	73-74	85	64.00 (64.05)	6.54 (6.56)	3.39 (3.32)
(**3**)	HL^1 1 g (3.36 mmol)	Oct_2SnO 0.60 g (1.68 mmol)	–	183-4	95	66.59 (66.51)	7.47 (7.42)	2.98 (2.91)
(**4**)	HL^1 1 g (3.36 mmol)	Me_3SnCl 0.67 g (3.36 mmol)	Et_3N 0.47 mL (3.36 mmol)	91-92	70	54.78 (54.71)	5.86 (5.81)	3.04 (3.08)
(**5**)	HL^1 1 g (3.36 mmol)	Bu_3SnCl 0.91 g (3.36 mmol)	Et_3N 0.47 mL (3.36 mmol)	130-1	75	61.43 (61.47)	7.67 (7.62)	2.38 (2.31)
(**6**)	HL^1 1 g (3.36 mmol)	Ph_3SnCl 1.29 g (3.36 mmol)	Et_3N 0.47 mL (3.36 mmol)	125-6	67	66.87 (66.80)	5.10 (5.16)	2.16 (2.10)
(**7**)	HL^2 1 g (4.01 mmol)	Me_2SnCl_2 0.44 g (2.00 mmol)	Et_3N 0.56 mL (4.01 mmol)	151-2	95	55.81 (55.79)	6.51 (6.54)	4.34 (4.37)
(**8**)	HL^2 1 g (4.01 mmol)	Bu_2SnCl_2 0.51 g (2.00 mmol)	Et_3N 0.56 mL (4.01 mmol)	171-2	90	59.25 (59.20)	7.40 (7.38)	3.84 (3.80)
(**9**)	HL^2 1 g (4.01 mmol)	Oct_2SnO 0.72 g (2.00 mmol)	–	161-2	65	62.78 (62.70)	8.32 (8.28)	3.32 (3.26)
(**10**)	HL^2 1 g (4.01 mmol)	Me_3SnCl 0.80 g (4.01 mmol)	Et_3N 0.56 mL (4.01 mmol)	53-54	75	49.51 (49.48)	6.55 (6.50)	3.39 (3.33)

Infrared spectroscopy

In order to clarify the mode of the ligand coordination to the tin centre, IR spectra in the 4000-400 cm^{-1} range were recorded. The assignment of IR bands of the synthesized compounds was determined by comparison with IR spectra of the precursors. The most important bands, presented and assigned in Table 2, show the following characteristics. The complexation of tin with the ligand is confirmed by the absence of a broad band in the range of 3425-3449 cm^{-1} due to ν(OH), thus showing the deprotonation of the carboxylic acid group. The C=O band of peptide group appears in the range of 1762-1790 cm^{-1} in the ligands; the complexes show this band in the range 1732-1782 cm^{-1}, which confirms that C=O from the peptide group is not involved in complexation.

Table 2. Assignment of characteristic FT-IR vibrations of 2-[(2′,6′-diethylphenylamido)]benzoic acid (HL^1) and 3-[(2′,6′-diethylphenylamido)]propanoic acid (HL^2) and their organotin(IV) complexes.

Comp.	IR Peak (cm^{-1})							
	ν_{OH}	ν_{NH}	$\nu_{C=O}$	ν_{COO}		$\Delta\nu$	ν_{Sn-C}	ν_{Sn-O}
HL^1	3449s	3329s	1762s	1560s[1]	1345s[2]	215	-	-
HL^2	3425s	3362s	1790s	1570s[1]	1330s[2]	240	-	-
1	-	3315m	1774m	1593s	1460m	133	586m	441m
2	-	3320m	1752m	1575m	1452m	123	550m	460m
3	-	3332s	1742m	1552s	1408s	144	542w	432m
4	-	3341s	1758s	1562s	1435m	127	530m	420w
5	-	3353m	1750m	1580m	1422s	158	529w	452m
6	-	3373s	1770s	1585s	1411s	174	-	480m
7	-	3349m	1748s	1562s	1442s	120	522m	425w
8	-	3332m	1732s	1558m	1412m	146	569s	432m
9	-	3356s	1762s	1598s	1420m	178	542m	412s
10	-	3348s	1782s	1545m	1415m	130	515m	452m
11	-	3369m	1750m	1585s	1462s	123	535w	442m
12	-	3376m	1778m	1560s	1402m	158	-	480w

[1]Antisymmetric [2]Symmetric

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

The carboxylates generally have 2 strongly coupled C=O bonds with band strengths intermediate between C=O and C-O. These give a strong asymmetric stretching band near 1545-1598 cm^{-1} and a weaker symmetrical stretching band near 1400 cm^{-1}. The $\Delta\nu$ values [$\Delta\nu = \nu_{asym}$(COO)-ν_{sym}(COO)] were used to predict the mode of tin carboxylate interaction.[21–25] There is a donation of charge density from C=O: $\rightarrow$ to the electropositive tin metal, which slightly increases the C=O bond length. Hence, the absorption frequency decreases and carboxylate acts as a bidentate ligand in the solid state. The IR spectra of the complexes (**1-12**) give a separation value ($\Delta\nu$) less than 200 cm^{-1}, which confirms the bidentate nature of the carboxylate group[22–25] (Figure 3). Bands in the range of 515-586 cm^{-1} and 412-480 cm^{-1} indicate the presence of Sn-C and Sn-O bonds for the complexes (absent in the free ligand).

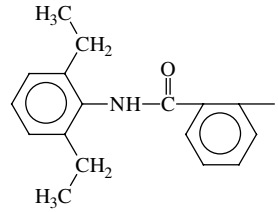
A strong band in the range 3315-3376 cm^{-1}, characteristic for the NH group, is present in the spectra of the ligands. It also persists in the spectra of the complexes, showing that NH groups do not participate via intra/intermolecular modes of interactions. This observation is parallel with the NMR results.

Mass spectrometry

The 70 eV mass spectral data using the Electron Impact (EI) method for the reported complexes (**1-12**) are given in Tables 3 and 4. The molecular ion peak is observed in all triorganotin(IV) carboxylates, while it is absent in all diorganotin(IV) dicarboxylates.[26] The fragmentation ions are in good agreement with the expected structures of the compounds. The other fragment ions containing the Sn atom are also 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 the R group in triorganotin(IV) derivatives, while diorganotin(IV) derivatives manifest slightly different patterns of fragmentation. Sn has 10 naturally occurring isotopes and this effect is pronounced in the mass data presented.[26]

Table 3. Mass spectral data of organotin(IV) complexes of 2-[(2′,6′-diethylphenylamido)]benzoic acid (HL^1) at 70 eV.

Fragment Ion	m/z(%) (**1**)	m/z(%) (**2**)	m/z(%) (**3**)	m/z(%) (**4**)	m/z(%) (**5**)	m/z(%) (**6**)
$R_2SnOO\overset{a}{R}'$	445(12)	529(8)	641(2)	445(6)	529(15)	569(5)
RSnOOCR′	430(3)	472(11)	528(9)	430(3)	472(10)	492(2)
OCOR′	296(8)	296(16)	296(12)	296(9)	296(7)	296(13)
$^{b}R_3Sn^+$	-	-	-	164(17)	290(13)	347(13)
R_2Sn^+	149(12)	233(12)	345(7)	233(78)	233(12)	271(4)
RSn^+	134(20)	176(51)	236(15)	134(39)	176(22)	194(35)
$C_6H_4^+$	76(8)	76(68)	76(94)	76(21)	76(7)	76(78)
Sn^+	120(10)	120(10)	120(10)	120(11)	120(14)	120(12)
$C_8H_{10}^+$	104(19)	104(100)	104(100)	104(57)	104(44)	104(100)
$C_4H_9^+$	57(68)	57(44)	57(64)	57(24)	57(100)	57(64)
$C_8H_{10}N^+$	122(100)	122(97)	122(97)	122(6)	122(8)	122(85)
$C_{10}H_{14}^+$	134(11)	134(20)	134(8)	134(100)	134(10)	134(84)

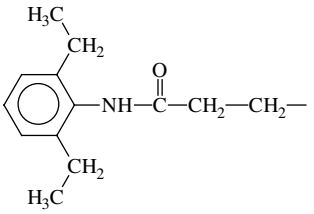
$^{a}R' =$ 

$^{b}R = CH_3$, C_4H_9, C_6H_5 and $CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2$

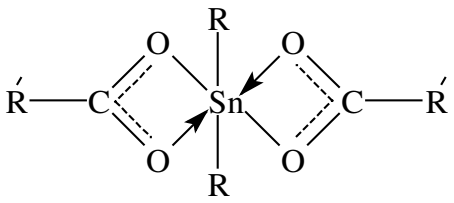
Table 4. Mass spectral data of organotin(IV) complexes of 3-[(2′,6′-diethylphenylamido)]propanoic acid (HL^2) at 70 eV.

Fragment Ion	m/z(%) (**1**)	m/z(%) (**2**)	m/z(%) (**3**)	m/z(%) (**4**)	m/z(%) (**5**)	m/z(%) (**6**)
$R_2SnOO\overset{a}{R}'$	430(8)	514(11)	626(5)	430(18)	514(7)	554(5)
RSnOOCR′	415(11)	457(7)	513(7)	415(2)	457(3)	477(3)
OCOR′	281(10)	281(16)	281(6)	281(22)	281(18)	281(20)
$^bR_3Sn^+$	-	-	-	164(29)	290(9)	350(9)
R_2Sn^+	149(7)	233(25)	345(10)	149(52)	233(27)	273(2)
RSn^+	134(8)	176(30)	232(16)	134(58)	176(8)	196(8)
Sn^+	120(24)	120(10)	120(5)	120(12)	120(14)	120(11)
$C_6H_4^+$	76(4)	76(3)	76(4)	76(18)	76(16)	76(38)
$C_8H_{10}^+$	106(100)	106(2)	106(3)	106(63)	106(42)	106(65)
$C_{10}H_{14}^+$	134(6)	134(100)	134(100)	134(100)	134(100)	134(100)
$C_8H_{12}N^+$	122(4)	122(3)	122(5)	122(12)	122(8)	122(2)

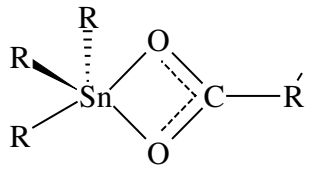
^{a}R′ =



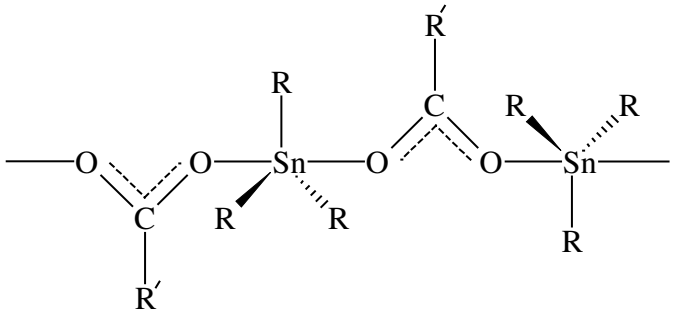
^{b}R = CH_3, C_4H_9, C_6H_5 and $CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_3$



(a)



(b)



(c)

Figure 3. Proposed structures of (a) diorganotin(IV) dicarboxylates, (b) triorganotin(IV) carboxylate, (c) polymeric structure of triorganotin(IV) carboxylate.

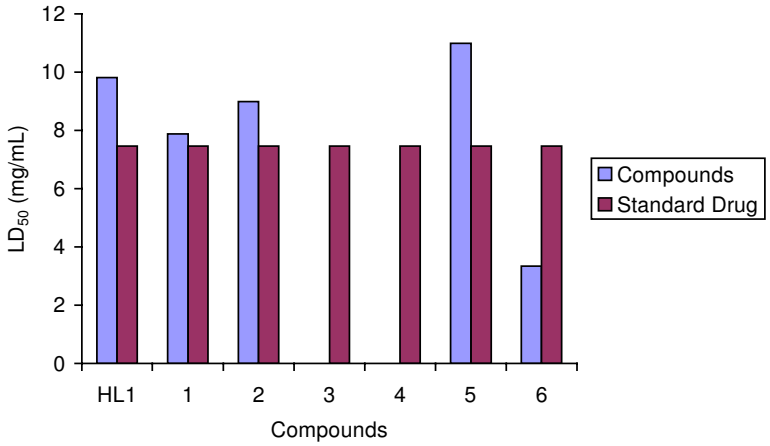


Figure 4. Cytotoxicity data of HL^1 and its organotin(IV) derivatives.

NMR spectroscopy

^{1}H-NMR spectroscopy

^{1}H-NMR spectral data of the synthesized ligands and reported compounds (**1-12**) are given in Tables 5 and 6. The signals are assigned by their peak multiplicity, intensity pattern, integration, and satellites.

Table 5. ^{1}H-NMR data^a of 2-[(2′,6′-diethylphenylamido)]benzoic acid (HL^1) and its organotin complexes.

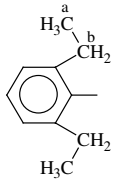
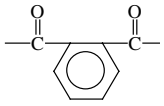
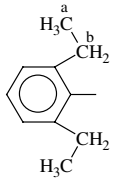
Proton	Chemical Shift (ppm)						
	HL^1	(**1**)	(**2**)	(**3**)	(**4**)	(**5**)	(**6**)
	a) 0.93t (7.0) b) 2.50q (9.2) 6.72-6.75m	a) 0.95t (7.2) b) 2.49q (9.1) 6.70-6.73m	a) 0.94t (7.3) b) 2.51q (9.0) 6.72-6.74m	a) 0.93t (7.1) b) 2.52q (9.2) 6.73-6.75m	a) 0.96t (7.3) b) 2.50q (9.1) 6.74-6.76m	a) 0.91t (7.3) b) 2.50q (9.1) 6.74-6.76m	a) 0.90t (7.1) b) 2.52q (9.3) 6.69-6.71m
–NH	7.28s	7.28s	7.28s	7.28s	7.28s	7.28s	7.28s
	7.48-7.52d,d (8.0) 8.34-8.38d,d (8.0)	7.53-757d,d (7.9) 8.37-8.40d,d (7.9)	7.85-7.88d,d (8.2) 8.23-8.26d,d (8.2)	7.40-7.43d,d (8.0) 8.32-8.35d,d (8.0)	7.81-8.76d,d (8.3) 8.32-8.35d,d (8.3)	7.91-7.95d,d (8.2) 8.28-8.32d,d (8.2)	7.87-7.91d,d (8.0) 7.98-8.01d,d (8.0)
R	–	0.27t ^2J[80.1]	0.87t(7.5) 1.30-1.42m	0.86-1.92m	-0.03s [55.7,58.2]	0.92t(7.7) 1.30-1.41m	7.25-7.32m

Table 6. ^{1}H-NMR data[a] of 3-[(2′,6′-diethylphenylamido)]propanoic acid (HL^2) and its organotin complexes.

Proton	Chemical Shift (ppm)						
	HL^2	(**7**)	(**8**)	(**9**)	(**10**)	(**11**)	(**12**)
	a) 0.96t (7.3) b) 2.53q (9.5) 6.74-6.80m	a) 0.94t (7.2) b) 2.55q (9.6) 6.82-6.85m	a) 0.93t (7.1) b) 2.54q (9.6) 6.86-6.89m	a) 0.91t (7.0) b) 2.51q (9.5) 6.76-6.83m	a) 0.95t (7.4) b) 2.52q (9.4) 6.84-6.87m	a) 0.96t (7.5) b) 2.53q (9.3) 6.70-6.73m	a) 0.91t (7.1) b) 2.54q (9.4) 6.75-6.79m
–NH	2.84s	2.82s	2.80s	2.86s	2.84s	2.84s	2.84s
$-CH_2-CH_2-$	7.10-7.18d (8.3) 7.35-7.38 (8.3)	7.07-7.12d (8.2) 7.23-7.35d (8.2)	7.04-7.09d (7.7) 7.24-7.36d (7.7)	7.08-7.13d (7.8) 7.26-7.34d (7.8)	7.12-7.20d (8.6) 7.30-7.36d (8.6)	7.06-7.25d (8.5) 7.31-7.38d (8.5)	7.12-7.16d (8.0) 7.34-7.36d (8.0)
R	–	0.25t ^{2}J[79.8]	0.89t(7.6) 1.30-1.36m	0.87-1.69m	-0.04s [55.8,58.8]	0.94t(7.8) 1.31-1.37m	7.60-7.68m

In ^{1}H-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 organotin moiety. All the protons present in the synthesized compounds (**1-12**) were identified in position and number with the protons calculated from incremental method.[27] The methyl protons of dimethyl- and trimethyltin(IV) derivatives appear as sharp singlets with well defined satellites in the range 0.27 to 0.25 and -0.04 to -0.03 ppm, respectively. The coupling constants are included in Tables 5 and 6. The protons of n-butyltin(IV) and triphenyltin(IV) derivatives mostly show a complex pattern and were assigned according to the literature.[28,29] Despite the complex pattern of ^{1}H-NMR spectra of di- and tri-n-butyltin(IV) derivatives, a clear triplet due to terminal methyl group appears in the range of 0.84-0.95 ppm.[30,31]

The methylene protons (CH_2) of $n-$octyltin(IV) moiety exhibit somewhat different behavior compared with the n-butyl groups of the respective complexes. The α-CH_2, β-CH_2, and γ-CH_2 to γ'-CH_2 protons give broad/multiplet signals at 0.86-1.92 ppm, which are consistent with the values calculated by the incremental method.[27]

^{13}C-NMR spectroscopy

^{13}C-NMR data of the synthesized ligands and their respective di- and triorganotin(IV) derivatives are given in Tables 7 and 8.

The aromatic resonances were assigned by comparing with values calculated from the incremental method.[27] The carboxylate carbon shifts to a lower field region in almost all the complexes (**1-12**), indicating participation of the carbonyl group (COO) in coordination to tin(IV).[32] The magnitudes for $^{n}J[^{119}Sn,^{13}C]$

coupling are also observed and are given in Tables 7 and 8. The coupling constants, $^{n}J[^{119}Sn,^{13}C]$, are important parameters for the structural characterization of organotin(IV) compounds. For triorganotin(IV) compounds, the magnitude of $^{1}J[^{119}Sn,^{13}C]$ coupling suggests tetrahedral geometry around the tin atom in solution.[33,34] As far as the geometry of the diorganotin dicarboxylates in non-coordinating solvents is concerned, it is not defined with certainty due to the fluxional behavior of the carboxylate oxygens in their coordination with the tin atom.[35] However, earlier reports suggest geometry between penta- and hexa-coordination.[36,37]

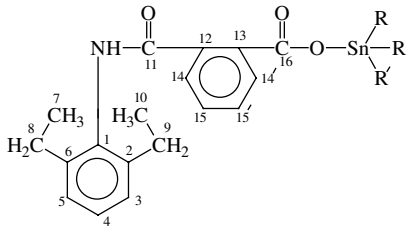
Table 7. ^{13}C- and ^{119}Sn-NMR data[a−c] of 2-[(2′,6′-diethylphenylamido)]benzoic acid (HL^1) and its organotin(IV) complexes.

Carbon	HL^1	(**1**)	(**2**)	(**3**)	(**4**)	(**5**)	(**6**)
1	136.2	136.5	136.7	136.6	136.9	136.4	136.5
2/6	133.7	133.8	133.4	133.9	133.2	133.5	133.1
3/5	132.0	132.6	132.3	132.5	132.1	132.4	132.9
4	127.9	127.4	127.8	127.6	127.1	127.5	127.4
7/10	24.7	24.9	24.1	24.6	24.8	24.5	24.3
8/9	10.9	12.1	12.4	12.7	12.9	12.8	12.6
11	162.7	162.8	162.4	162.6	162.4	162.3	162.4
12	130.9	130.4	130.5	130.7	130.1	130.8	130.3
13	131.1	131.3	131.5	131.2	131.5	131.6	131.4
14,14′	125.6	126.7	126.4	126.2	126.6	126.8	126.4
15,15′	119.4	117.3	117.8	117.5	117.7	117.6	117.9
16	170.1	174.2	174.5	174.4	174.3	174.7	174.6

[a]Compound **1**: Sn-CH_3, (C-α) 29.6. δ ^{119}Sn = -37.6. Compound **2**: Sn-$CH_2CH_2CH_2CH_3$, (C-α) 29.6, (C-β) 27.2 ^{2}J[21.2], (C-γ) 26.7 ^{3}J[63.1], (C-δ) 14.1. $\delta^{119}Sn$ = -132.7. Compound **3**: Sn-$CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_3$, (C-$\alpha$) 37.4 ^{1}J[555, 580], (C-β) 31.8 ^{2}J[36.8] (C-γ) 30.0 ^{3}J [92.5], (C-δ) 29.4 (C-α^*) 29.1, (C-β^*) 26.8, (C-γ^*), 22.6, (C-δ^*) 14.0. $\delta^{119}Sn$ = -138.8. Compound **4**: Sn-CH_3, (C-α) -2.0 ^{1}J[376.5, 395.8]. $\delta^{119}Sn$ = +55.7. Compound **5**: Sn-$CH_2CH_2CH_2CH_3$, (C-α) 29.6, (C-β) 27.8 ^{2}J[22.6], (C-γ) 26.8 ^{3}J[63.1], (C-δ) 14.2. $\delta^{119}Sn$ = +140.8. Compound **6**: Sn-C_6H_5, (C-α) 138.2 ^{1}J[640.2, 662.2], (C-β) 137.2 ^{2}J[47.9], (C-γ) 136.2, (C-δ) 130.8. δ ^{119}Sn = -80.0.

[b]Chemical shifts (δ) in ppm. $^{n}J[^{119}Sn, ^{13}C]$ in Hz are listed in parentheses.

[c]



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

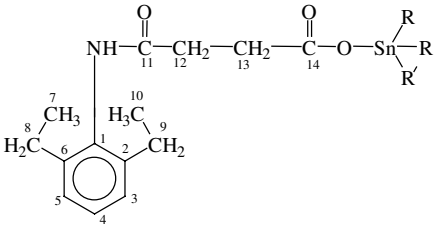
Table 8. ^{13}C- and ^{119}Sn-NMR data^{a-c} of 3-[(2′,6′-diethylphenylamido)]propanoic acid (HL^2) and its organotin(IV) complexes.

Carbon	HL^2	(**7**)	(**8**)	(**9**)	(**10**)	(**11**)	(**12**)
1	136.0	136.4	136.8	136.5	136.2	136.9	136.7
2/6	133.2	133.4	133.0	133.8	133.7	133.5	133.3
3/5	132.9	132.8	132.6	132.4	132.5	132.7	132.2
4	128.4	128.6	128.2	128.9	128.5	128.4	128.3
7/10	23.8	23.5	23.7	23.3	23.2	23.4	23.9
8/9	11.2	12.5	12.4	12.7	12.1	12.6	12.8
11	167.9	168.2	168.4	168.8	168.5	168.3	168.7
12	32.9	33.2	33.5	33.7	33.3	33.6	33.7
13	30.8	30.4	30.6	30.2	30.1	30.5	30.6
14	176.7	180.6	180.3	180.0	180.5	180.8	180.9

[a]Compound **7**: Sn-CH_3, (C-α) 29.7. δ ^{119}Sn = -101.6. Compound **8**: Sn-$CH_2CH_2CH_2CH_3$, (C-α) 29.4, (C-β) 27.1 ^2J[21.1], (C-γ) 26.4 ^3J[62.9], (C-δ) 14.0. δ ^{119}Sn = -143.6. Compound **9**: Sn-$CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_3$, (C-$\alpha$) 37.2 ^1J[554,581], (C-β) 31.7 ^2J[36.5], (C-γ) 30.1 ^3J[92.6], (C-δ) 29.6, (C-α^*) 29.2, (C-β^*) 26.8, (C-γ^*) 22.5, (C-δ^*) 14.0. δ ^{119}Sn = -146.2. Compound **10**: Sn-CH_3, (C-α) -2.1 ^1J[376.9,395.4]. δ ^{119}Sn = +140.1. Compound **11**: Sn-$CH_2CH_2CH_2CH_3$, (C-α) 29.5, (C-β) 27.6 ^2J[22.4], (C-γ) 26.8 ^3J[63.2], (C-δ)14.2. δ ^{119}Sn = -144.1. Compound **12**: Sn-C_6H_5, (C-α) 138.1 ^1J[640.0,662.1], (C-β) 137.5 ^2J[50.1], (C-γ) 136.5, (C-δ) 130.0. δ ^{119}Sn = -52.9.

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

[c]



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

^{119}Sn-NMR spectroscopy

The value of δ^{119}Sn defines the region of various coordination numbers of the central tin atom.[37] The results are listed in Tables 7 and 8.

In all complexes, ^{119}Sn spectra show only a sharp singlet indicting the formation of single species. ^{119}Sn chemical shift $\delta(^{119}$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 the $\delta(^{119}$Sn) value moves to a higher field. These values are also dependent upon the nature of X in R_nSnX_{4-n} and generally move to a 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 4 to 5, 6, or 7 usually produces a large upfield shift of $\delta(^{119}$Sn)[37]. 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 higher coordination, probably 5 or 6. 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.[37]

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 defined ranges.

Biological activity

Cytotoxicity

The Brine Shrimp method[38] was used to check the toxicity of the synthesized compounds by using Etoposide as standard drug. Cytotoxicity data are given in Tables 9 and 10 and presented in Figures 4 and 5. The highest toxicity was shown by compound **5**, whose LD_{50} value was 10.99 μg/mL, while the lowest toxicity was shown by compound **6**, whose LD_{50} value was 3.34 μg/mL as compared to standard drug.

Table 9. Brine Shrimp (*Artemia salina*) lethality bioassay of 2-[(2′,6′-diethylphenylamido)]benzoic acid (HL^1) and its organotin(IV) derivatives.

Comp.	Dose (μg/mL)	No. Shrimps	No. Survivors	LD_{50} (μg/mL)	Standard Drug	LD_{50} (μg/mL)
HL^1	100	30	0	9.81	Etoposide	7.46
	10	30	11			
	1	30	21			
1	100	30	0	7.88	Etoposide	7.46
	10	30	0			
	1	30	22			
2	100	30	0	8.99	Etoposide	7.46
	10	30	4			
	1	30	12			
3	100	30	6	-	Etoposide	7.46
	10	30	10			
	1	30	9			
4	100	30	23	-	Etoposide	7.46
	10	30	21			
	1	30	30			
5	100	30	0	10.99	Etoposide	7.46
	10	30	11			
	1	30	17			
6	100	30	0	3.34	Etoposide	7.46
	10	30	1			
	1	30	29			

Table 10. Brine Shrimp (*Artemia salina*) lethality bioassay of 3-[(2′,6′-diethylphenylamido)]propanoic acid (HL^2) and its organotin(IV) derivatives.

Comp.	Dose (μg/mL)	No. Shrimps	No. Survivors	LD_{50} (μg/mL)	Standard Drug	LD_{50} (μg/mL)
HL^2	100	30	0	14.21	Etoposide	7.46
	10	30	12			
	1	30	18			
7	100	30	0	13.92	Etoposide	7.46
	10	30	7			
	1	30	20			
8	100	30	6	-	Etoposide	7.46
	10	30	10			
	1	30	8			
9	100	30	0	5.18	Etoposide	7.46
	10	30	0			
	1	30	4			
10	100	30	0	9.14	Etoposide	7.46
	10	30	10			
	1	30	19			
11	100	30	0	8.65	Etoposide	7.46
	10	30	0			
	1	30	14			
12	100	30	0	7.99	Etoposide	7.46
	10	30	2			
	1	30	12			

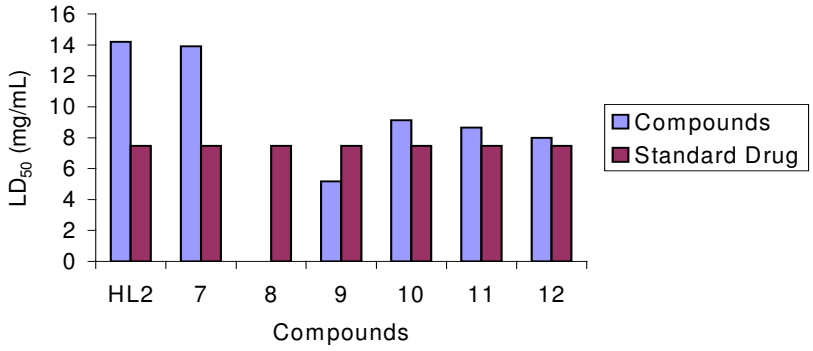


Figure 5. Cytotoxicity data of HL^2 and its organotin(IV) derivatives.

Antifungal activity

The present inhibition of the synthesized ligands and compounds are given in Tables 11 and 12 and presented in Figures 6 and 7. Miconazole and Ketoconazole were used as standard drugs. When the reported compounds were screened against different plant pathogens using the tube diffusion method,[39] it

was observed that all compounds show significant antifungal activity as compared to synthesized ligands with few exceptions.

Table 11. Antifungal activity[a−c] (% inhibition) of 2-[(2′,6′-diethylphenylamido)]benzoic acid (HL^1) and its organotin(IV) complexes.

Fungus	Inhibition (%)							MIC
(ATCC No.)	HL^1	**1**	**2**	**3**	**4**	**5**	**6**	(μg/mL)
Trichophyton longifusus (22397)	60.5	55.8	0	0	45.8	73.4	0	70.0
Candida albicans (2192)	72.2	55.6	0	43.2	32.9	89.6	0	110.8
Aspergillus flavis (1030)	30.8	0	0	49.5	59.6	96.2	22.5	20.0
Microsporum canis (9865)	0	80.2	76.8	62.5	0	0	0	98.4
Fusarium solani (11712)	0	60.9	55.3	0	89.2	0	33.5	73.2
Candida glaberata	80.5	70.8	69.2	0	43.2	97.8	56.2	110.8

[a]Concentration: 100 μg/mL of DMSO

[b]MIC: Minimum inhibitory concentration

[c]Percent inhibition (standard drug) = 100

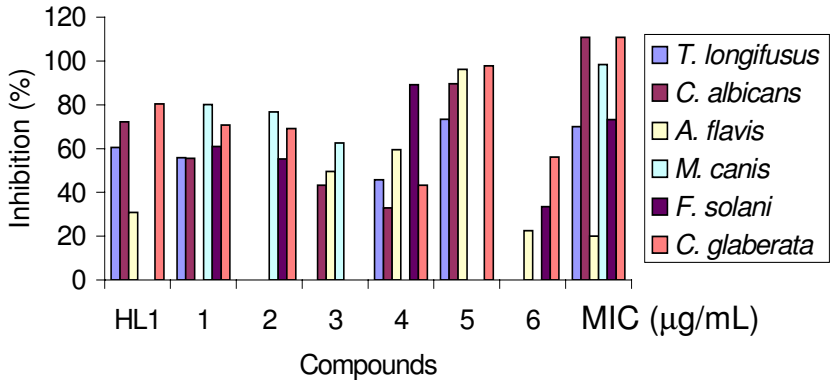


Figure 6. Antifungal activity of HL^1 and its organotin(IV) derivatives against various fungi.

Antibacterial activity

The synthesized ligands and compounds were screened for antibacterial activity by the agar well diffusion method[39] and the zone of inhibition is measured in millimeters and the data are reported in Tables 13 and 14 and presented in Figures 8 and 9. All the synthesized compounds show significant antibacterial activity

against the tested bacteria with few exceptions. The synthesized ligands were found to be active and their organotin(IV) carboxylates showed more significant antibacterial activity as compared to the ligands.

Table 12. Antifungal activity[a−c] (% inhibition) of 3-[(2′,6′ diethylphenylamido)]propanoic acid (HL^2) and its organotin(IV) complexes.

Fungus (ATCC No.)	Inhibition (%)							MIC
	HL^1	**1**	**2**	**3**	**4**	**5**	**6**	(μg/mL)
Trichophyton longifusus (22397)	85.2	40.0	0	0	38.2	0	0	70.0
Candida albicans (2192)	60.5	40.0	0	20.5	20.8	0	0	110.8
Aspergillus flavis (1030)	80.5	60.5	75.8	20.8	60.5	20.5	0	20.0
Microsporum canis (9865)	80.0	40.3	58.2	0	18.2	20.5	0	98.4
Fusarium solani (11712)	0	30.5	0	20.5	20.5	0	0	73.2
Candida glaberata	80.2	65.3	0	0	40.2	0	55.6	110.8

[a]Concentration: 100 μg/mL of DMSO

[b]MIC: Minimum inhibitory concentration

[c]Percent inhibition (standard drug) = 100

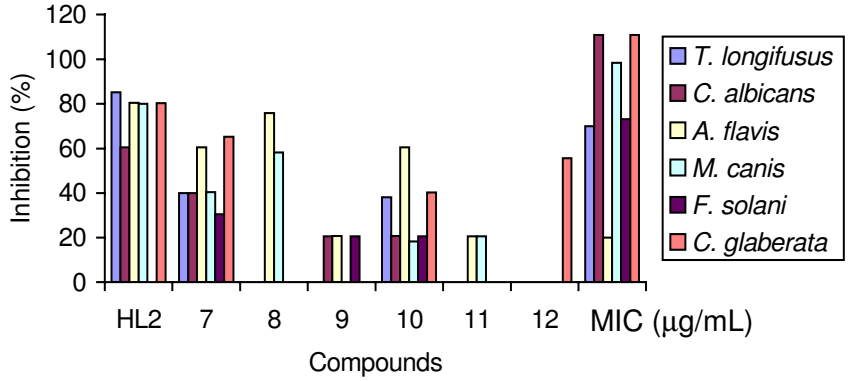


Figure 7. Antifungal activity of HL^2 and its organotin(IV) derivatives against various fungi.

Insecticidal activity

Insecticidal activity data were collected by the contact toxicity method[39] and the data are reported in Table 15 and Figure 10 for complexes **1-6**. Premethrin was used as standard drug with concentration 235.7 μg/cm^2. Compound **1** shows the activity against *Rhypertha dominica* and *Callosbruchus analis* while **3-5** show the insecticidal activity against *Rhypertha dominica* only. Compounds **2** and **6** do not show any insecticidal activity.

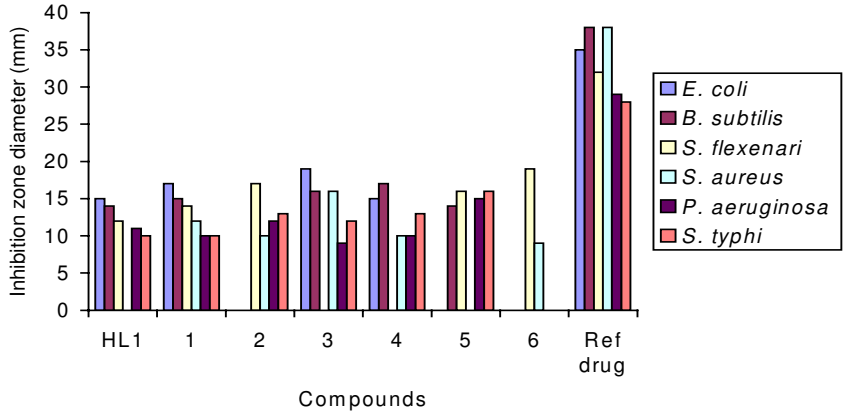


Figure 8. Antibacterial activity of HL^1 and its organotin(IV) derivatives against various bacteria.

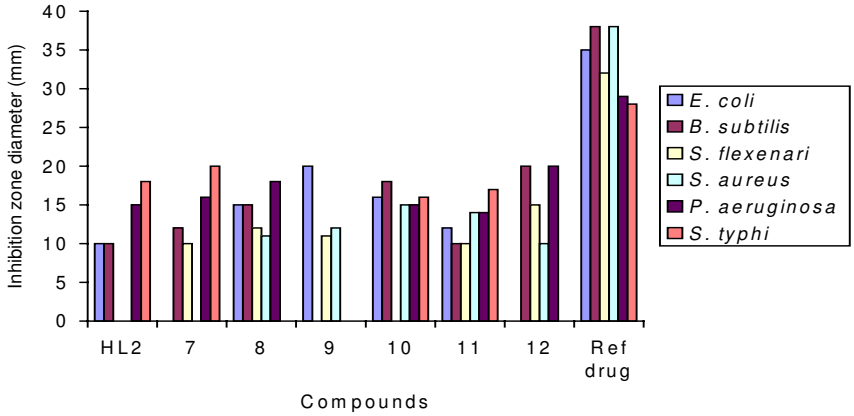


Figure 9. Antibacterial activity of HL^2 and its organotin(IV) derivatives against various bacteria.

Table 13. Antibacterial activity[a−c] (diameter of inhibition zone after 20 h) of 2-[(2′,6′-diethylphenylamido)]benzoic acid (HL^1) and its organotin(IV) complexes.

Bacteria	Inhibition (%)							Reference
(ATCC No.)	HL^1	**1**	**2**	**3**	**4**	**5**	**6**	Drug
Escherichia coli	15	17	-	19	15	-	-	35
Bacillus subtilis (11774)	14	15	-	16	17	14	-	38
Shigella flexenari (700390)	12	14	17	-	-	16	19	32
Staphylococcus aureus (25923)	-	12	10	16	10	-	9	38
Pseudomonas aeruginosa (10145)	11	10	12	9	10	15	-	29
Salmonella typhi (10749)	10	10	13	12	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; *Staphylococcus aureus*, food poisoning, scaled skin syndrome, endrocarditis; *Pseudomonas aeruginosa*, infection of wounds, eyes, septicemia, *Salmonella typhi*, typhoid fever, localized infection.

Table 14. Antibacterial activity[a−c] (diameter of inhibition zone after 20 h) of 3-[(2′,6′-diethylphenylamido)]propanoic acid (HL^2) and its organotin(IV) complexes.

Bacteria	Inhibition (%)							Reference
(ATCC No.)	HL^1	**1**	**2**	**3**	**4**	**5**	**6**	Drug
Escherichia coli	10	-	15	20	16	12	-	35
Bacillus subtilis (11774)	10	12	15	-	18	10	20	38
Shigella flexenari (700390)	-	10	12	11	-	10	15	32
Staphylococcus aureus (25923)	-	-	11	12	15	14	10	38
Pseudomonas aeruginosa (10145)	15	16	18	-	15	14	20	29
Salmonella typhi (10749)	18	20	-	-	16	17	-	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; *Staphylococcus aureus*, food poisoning, scaled skin syndrome, endocarditis; *Pseudomonas aeruginosa*, infection of wounds, eyes, septicemia, *Salmonella typhi*, typhoid fever, localized infection.

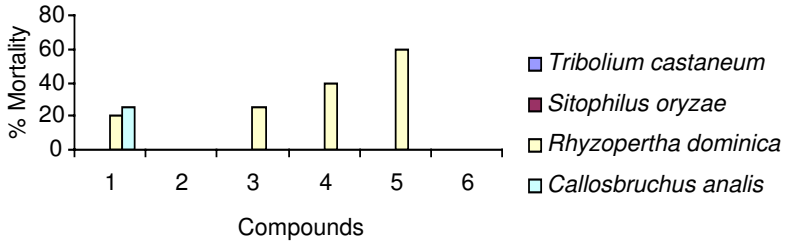


Figure 10. Insecticidal bioassay of organotin(IV) complexes of HL^1.

Table 15. Insecticidal bioassay[a−c] of organotin(IV) complexes of 2-[(2′,6′-diethylphenylamido)]benzoic acid (HL^1).

Insects	Compound					
	1	**2**	**3**	**4**	**5**	**6**
Tribolium castaneum	-	-	-	-	-	-
Sitophilus oryzae	-	-	-	-	-	-
Rhyzopertha dominica	20	-	25	40	60	-
Callosbruchus analis	25	-	-	-	-	-

[a]Concentration of sample: 1571.2 $\mu g/cm^2$

[b]Standard drug: Permethrin

[c]Conc. of Standard drug: 235.7 $\mu g/cm^2$

Anti-leishmanial activity

The antiprotozoal activity of the compounds **1-6** against the pathogenic Leishmania was obtained and the data are given in Table 16 and Figure 11. The reported compounds produced a significant reduction in viable

promastigotes. The minimum protozoa concentration for promastogotes was defined as the concentration that produced 50% reduction in parasites after 72 h of incubation.[40] Compounds **1**, **2**, **4-6** show good anti-leishmanial activity, while compound **3** shows low activity. Amphotericin B was used as standard drug with the concentration 0.19 μg/mL.

Table 16. Antileishmanial activity[a−d] of organotin(IV) complexes of 2-[(2′,6′-diethylphenylamido)]benzoic acid (HL^1).

	Compound					
	1	**2**	**3**	**4**	**5**	**6**
% Inhibition	100	100	100	100	100	100
IC_{50} (μg/mL)	68.5	68.1	60.0	67.7	68.1	68.5
Standard drug (μg/mL)	0.19	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 °CC

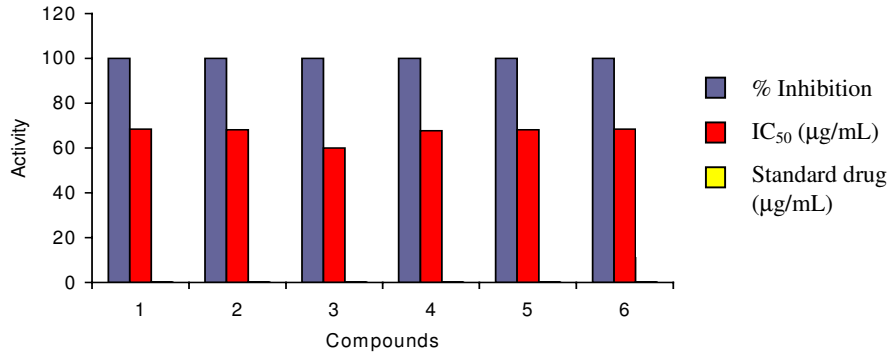


Figure 11. Anti-leishmanial activity of organotin(IV) complexes of HL^1.

The results obtained support the earlier reports that there is a direct relation between the activity and the coordination environment of the metal. The 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.[41] The anionic ligand also plays an important role in determining the degree of the activity of organotin compounds. The triorganotin(IV) compounds show tetrahedral geometry in solution and they show significant activity, which is consistent with literature that species generating tetrahedral geometry in solution are more active.[42]

Conclusion

Organotin(IV) derivatives were synthesized in quantitative yield by refluxing the synthesized carboxylic acid and respective organotin(IV) chloride/organotin(IV) oxide in dry toluene for 8-10 h. Elemental analysis shows good agreement between the calculated and observe % 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 ligands behave as a bidentate group for coordination to tin. 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 4 coordinated tin with a tetrahedral arrangement. Biological activity data show that all the complexes are biologically active with few exceptions.

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