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Synthesis, Characteristic Spectral Studies and *in vitro* Antimicrobial and Antitumour Activities of Organotin(IV) Complexes of Schiff Bases Derived from Amino-acids

Mala Nath,[1]* Rakesh Yadav,[1] Marcel Gielen,[2] Hassan Dalil,[2] Dick de Vos[3] and G. Eng[4]

[1] Department of Chemistry, University of Roorkee, Roorkee-247667, India
[2] Free University of Brussels (VUB), Faculty of Applied Sciences, Laboratory for General and Organic Chemistry (AOSC), Room 8G512, Pleinlaan 2, B-1050 Brussels, Belgium
[3] Pharmachemie BV, Medical Department, NL-2003 RN Haarlem, The Netherlands
[4] Department of Chemistry, University of the District of Columbia, Washington, DC 20008, USA

Equimolar reactions of dibutyltin(IV) oxide with Schiff bases derived from amino-acids led to the formation of a new series of dibutyltin(IV) complexes of general formula, Bu_2SnL [L = dianion of tridentate Schiff bases derived from the condensation of 2-hydroxy-1-naphthaldehyde or acetyl acetone with glycine (L-1), L-β-alanine (L-2), DL-valine (L-3), DL-4-aminobutyric acid (L-4), L-methionine (L-5), L-leucine (L-6) and phenylglycine (L-7)]. An attempt has been made to prove the structures of the resulting complexes on the basis of elemental analyses, conductance measurements and electronic, IR, multinuclear magnetic resonance (^1H, ^{13}C and ^{117}Sn) and ^{119}Sn Mössbauer spectral studies. The complexes have been tested against various bacteria [*streptococcus faecalis, Klebsiella pneumoniae, Escherichia coli, Pseudomonas aeruginosa, Staphylococcus aureus* penicillin resistance (2500 units)] and fungi (*Candida albicans, Cryptococcus neoformans, Sporotrichum schenckii, Trichophyton mentagrophytes* and *Aspergillus fumigatus*). All the complexes showed moderate activity. The cytotoxicity of a few compounds has been screened *in vitro* against seven human tumour cell lines, viz. MCF-7, EVSA-T, WiDr, IGROV, M19 MEL, A498 and H226. The activities found experimentally were better than those obtained for cisplatin and carboplatin. © 1997 John Wiley & Sons, Ltd.

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INTRODUCTION

Pyridoxal (Vitamin B_6 aldehyde)–amino-acid Schiff bases are believed to be intermediate in biologically important amination processes.[1] Furthermore, metal ions catalyse transamination reactions involving vitamin B_6.[2,3] These concurrent results seem to indicate that metal complexes of Schiff bases derived from various amino-acids are formed as intermediates in transamination reactions involving vitamin B_6.[4] Most of the work has dealt with transition-metal complexes of salicylideneamino-acid Schiff bases.[5–9] Apart from some papers dealing with transition-metal complexes of Schiff bases in which amino groups are provided by amino-acids,[5–13] little work has been reported on the organotin(IV)–amino-acid Schiff base complexes.[14–16] It was therefore considered of interest to synthesize and characterize new organotin(IV)

† Correspondence to: M. Nath.
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derivatives of Schiff bases derived from amino-acids, and the results of these investigations are reported in this paper. Several classes of organo-tin compounds have been found active against tumours either *in vivo* or *in vitro*.[17] In view of this, the newly synthesized organotin(IV) compounds have been tested *in vitro* against a wide spectrum of bacteria and fungi, and against seven well-characterized human tumour cell lines.

EXPERIMENTAL

All the reactions were carried out under an anhydrous and oxygen-free nitrogen atmosphere. Solvents were pruified, dried and stored under nitrogen. AnalaR-grade 2-hydroxy-1-naphthaldehyde and acetyl acetone (Fluka) were used as received. Dibutyltin oxide (Fluka), glycine (Richie Renolds Chemicals), L-β-alanine and DL-valine (BDH), L-methionine (Sisco Research Laboratory, India), L-leucine (Sigma), phenylglycine and DL-4-aminobuyric acid (Fluka) were used as received.

Synthesis of Schiff bases

Schiff bases were prepared by condensation of 2-hydroxy-1-naphthaldehyde or acetyl acetone (0.01 mol) and the various amino-acids (0.01 mol) in the minimum amount (25 ml) of absolute methanol (Table 1). The solution was stirred for half an hour and then refluxed on a water bath for 3–4 h. The excess of solvent was removed by distillation. The viscous oils thus obtained were purified by repeated washings with petroleum ether (b.p. 60–80 °C). Several attempts to solidify these oils failed. Therefore, the Schiff bases were used *in situ* for the synthesis of the dibutyltin complexes.

Table 1 Schiff bases used in this work

	Abbreviation for Schiff base	
R	H_2L = **I**	H_2L = **II**
$-CH_2-$	H_2L-1(**I**)	H_2L-1(**II**)
$-CH_2-CH_2-$	H_2L-2(**I**)	H_2L-2(**II**)
$>CH-CH(CH_3)_2$	H_2L-3(**I**)	H_2L-3(**II**)
$-CH_2-CH_2-CH_2-$	H_2L-4(**I**)	H_2L-4(**II**)
$>CH-CH_2-CH_2-S-CH_3$	H_2L-5(**I**)	H_2L-5(**II**)
$>CH-CH_2-CH(CH_3)_2$	H_2L-6(**I**)	H_2L-6(**II**)
$>CH-C_6H_5$	H_2L-7(**I**)	H_2L-7(**II**)

Synthesis of dibutyltin(IV) complexes

The complexes were prepared under anhydrous conditions by dropwise addition of a dry, hot benzene–methanol (3:1), v/v; 100 ml) solution of the dibutyltin(IV) oxide (0.0095 mol) in a 1:1 molar ratio to the preformed Schiff base (0.01 mol) in hot absolute methanol (35 ml) *in situ*. The mixture was refluxed with constant stirring giving a clear solution in 10–30 min. Refluxing was continued for 9–10 h with azeotropic removal of water. The excess of solvent was removed under reduced pressure. The oily products thus obtained were solidified and purified by trituration with petroleum ether (b.p. 60–80 °C) and recrystallized from a methanol–petroleum ether mixture. Analytical data of the complexes are presented in Table 2.

Tin, nitrogen and sulphur contents of the complexes were determined by gravimetric, Kjeldahl's and Messenger's methods, respectively.[18] The details of analyses of carbon and molar conductance measurement were similar to those reported previously.[18] Infrared spectra (4000–400 cm^{-1}) in KBr discs were recorded on an FTIR spectrophotometer, model FTS 165, at the Institute of Exploration and Petroleum, Dehradun, India. ^1H and ^{13}C NMR spectra were recorded on an FX-100 JEOL FT NMR spectrometer at the Indian Institute of Petroleum, Dehradun, and on a Bruker VM–400 MHz FT NMR spectrometer at the Central Drug Research Institute (CDRI), Lucknow, India, respectively, using deuterochloroform as solvent and tetramethylsilane as the internal standard. The electronic spectra were recorded on a Beckman DU-6 spectrophotometer. The details of ^{119}Sn Mössbauer spectra[18,19] and antimicrobial[18] activity of the complexes were similar to those reported previously. ^{117}Sn NMR spectra were recorded on a Brucker 250 MHz spectrometer at the Free Universtiy of Brussels (VUB), Belgium. The cytotoxicities of three dibutyltin compounds, i.e. Bu_2SnL-1(**I**), Bu_2SnL-2(**I**) and Bu_2SnL-6(**II**) and two diphenyltin analogues,[20] namely Ph_2SnL-1(**I**) and Ph_2SnL-2(**I**), were screened *in vitro* against seven well-characterized human tumour cell lines by applying the microculture sulforhodamine B test (SRB). The

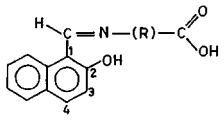
in vitro tests were performed as described previously.[21]

RESULTS AND DISCUSSION

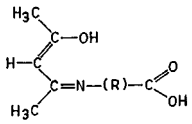
Reactions of dibutyltin(IV) oxide with dianionic tridentate Schiff bases derived from the condensation of 2-hydroxy-1-naphthaldehyde or acetyl acetone with different amino-acids in an equimolar ratio in a benzene–methanol (3:1, v/v) mixture afforded complexes of type Bu_2SnL with azeotropic removal of water (Eqn [1] and Table 2):

$$Bu_2SnO + H_2L \rightarrow Bu_2SnL + H_2O \qquad [1]$$

where H_2L =



(**I**)



(**II**)

This reaction is found to be quite facile and was completed within 9–10 h of refluxing. The resulting complexes (Table 2) were obtained in good yields and are yellow- to brown-coloured solids. In every instance the resulting complexes crystallized with 1:1 stoichiometry regardless of the proportions of Schiff bases and dibutyltin oxide used.

The complexes are soluble in solvents such as chloroform, dimethyl sulphoxide (DMSO), dimethylformamide (DMF) and methanol but insoluble in benzene. The molar conductances of 10^{-3} M solutions of the complexes (Table 2) in $DMF/CHCl_3$ lie in the range

Table 2 Characteristic properties of Bu_2SnL complexes

Complex no.	Complex	Yield (%)	Colour	M.p. (°C)	Analysis (%): Found (Calcd) Sn	N	C	Molar conductance (Ω^{-1} cm^2 mol^{-1})
1	Bu_2SnL-1(**I**) $[C_{21}H_{27}NO_3Sn]$	91	Yellow	155–157	25.60 (25.79)	3.04 (3.04)	54.81 (54.82)	0.02[a]
2	Bu_2SnL-1(**II**) $[C_{15}H_{27}NO_3Sn]$	78	Brown	100–101	30.31 (30.58)	3.60 (3.61)	46.58 (46.43)	7.96[b]
3	Bu_2SnL-2(**I**) $[C_{22}H_{29}NO_3Sn]$	73	Yellow	100–103	25.02 (25.03)	2.75 (2.95)	55.82 (55.73)	1.58[a]
4	Bu_2SnL-2(**II**) $[C_{16}H_{29}NO_3Sn]$	76	Brownish yellow	95–96	29.05 (29.52)	3.79 (3.48)	47.68 (47.79)	18.96[b]
5	Bu_2SnL-3(**I**) $[C_{24}H_{33}NO_3Sn]$	80	Light yellow	120–122	23.58 (23.63)	2.88 (2.79)	57.42 (57.40)	3.16[b]
6	Bu_2SnL-3(**II**) $[C_{18}H_{33}NO_3Sn]$	80	Brownish yellow	90–92	27.83 (27.59)	3.21 (3.26)	50.25 (50.26)	1.58[b]
7	Bu_2SnL-4(**I**) $[C_{23}H_{31}NO_3Sn]$	55	Black	125–128	24.40 (24.31)	2.85 (2.87)	56.57 (56.59)	0.05[a]
8	Bu_2SnL-4(**II**) $[C_{17}H_{31}NO_3Sn]$	70	Reddish brown	120–123	28.02 (28.52)	3.35 (3.37)	49.21 (49.07)	0.08[b]
9	Bu_2SnL-5(**I**) $[C_{24}H_{33}NO_3SSn]$	78	Dark yellow	105–107	22.01 (22.22)	2.59 (2.62)	53.89[c] (53.95)	2.37[b]
10	Bu_2SnL-5(**II**) $[C_{18}H_{33}NO_3SSn]$	86	Browish yellow	110–113	25.79 (25.68)	3.00 (3.03)	46.79[d] (46.77)	17.38[b]
11	Bu_2SnL-6(**I**) $[C_{25}H_{35}NO_3Sn]$	74	Yellow	145–148	22.87 (22.99)	2.68 (2.71)	58.48 (58.17)	1.58[b]
12	Bu_2SnL-6(**II**) $[C_{19}H_{35}NO_3Sn]$	95	Light brown	120–122	26.35 (26.72)	3.14 (3.15)	51.76 (51.38)	3.16[b]
13	Bu_2SnL-7(**I**) $[C_{27}H_{31}NO_3Sn]$	78	Brownish yellow	120–121	22.48 (22.13)	2.79 (2.61)	60.78 (60.48)	0.79[b]
14	Bu_2SnL-7(**II**) $[C_{21}H_{31}NO_3Sn]$	85	Cream	220–223	25.05 (25.57)	3.00 (3.02)	54.80 (54.34)	1.58[a]

[a] In DMF. [b] In $CHCl_3$. [c] S found: 5.98; calcd: 6.00%. [d] S found: 6.98; calcd: 6.94%.

Table 3 Electronic spectral data (in nm) of the Bu_2SnL complexes

Complex no.[a]	$\pi-\pi^*$ (benzenoid)/n$-\pi^*$(COO)	$\pi-\pi^*$ (>C=N–)	Secondary band of the benzene ring
1	200, 240	337	413
2	200, 225	309, 352	—
3	200, 241	337	413
4	200, 216	306, 336	—
5	200, 253	337	416
6	200, 225	308, 336	—
7	198, 238	337	415
8	199, 211	310, 328	—
9	200, 240	337	413
10	200, 219	312, 337	—
11	200, 240	336	413
12	200, 215	312, 333	—
13	200, 240	336	413
14	200, 217	317	383sh

[a] Nos as indicated in Table 2; solvent, methanol

0.02–18.96 Ω^{-1} cm^2 mol^{-1}, indicating their non-electrolytic nature.

The electronic spectral data of all the dibutyltin(IV) complexes in methanol are given in Table 3. The spectra of the complexes exhibit bands in the regions 198–253, 306–352 and 383–416 nm, which may be due to the $\pi-\pi^*$ transition of the benzenoid or $n-\pi^*$ COO, $\pi-\pi^*$ transition of (>C=N–) chromophore and the secondary band of the benzene ring,[14] respectively. Furthermore there is a sharp band observed in the region 253–261 nm in the spectra of the complexes, which could be assigned as a charge-transfer band. It is known[22] that metals/metalloids are capable of forming $d\pi-p\pi$ bonds with ligands containing nitrogen or oxygen as the donor atoms. The tin atom has vacant 5*d* orbitals and hence L⟶M bonding can take place by the acceptance of a pair of electrons from nitrogen or oxygen donor atoms ligand.

Important infrared frequencies (in cm^{-1}) and their assignments are given in Table 4. It has been reported[12] that the Schiff base derived from glycine and 4-methyl-2-hydroxyacetophenone exists predominantly in the keto enamine form as represented in Fig. 1 on the basis of the appearance of an infrared band around 3400 cm^{-1} due to –NH vibration. Two bands at 1675 and 1610 cm^{-1} are also assigned[12] to the

Table 4 Infrared frequencies (in cm^{-1}) of Bu_2SnL complexes

Complex no.[a]	Complex	ν(C=N)	ν_{as}(COO)	ν_s(COO)	$\Delta\nu$(COO)	ν_{as}(SnN–C)	ν_s(Sn–C)	ν(Sn–O)	ν(Sn←N)
1	Bu_2SnL-1(**I**)	1605s	1650vs	1395m	255	581m	515, 525m	560m	415m
2	Bu_2SnL-1(**II**)	1604s	1643vs	1386s	257	575m	532m	550m	418m
3	Bu_2SnL-2(**I**)	1609vs	1673s	1389m	284	580w	530w	564m	486w
4	Bu_2SnL-2(**II**)	1602vs	1650vs	1379m	271	575w	530m	555m	430m
5	Bu_2SnL-3(**I**)	1600vs	1640vs	1400s	240	570m	500m	550m	426w
6	Bu_2SnL-3(**II**)	1610s	1640vs	1370m	270	597w	478m	550m	413w
9	Bu_2SnL-5(**I**)	1610vs	1670vs	1390m	280	595vs	498m	554m	418m
10	Bu_2SnL-5(**II**)	1608s	1659vs	1385m	274	593vs	500m	551m	420m
11	Bu_2SnL-6(**I**)	1603s	1660vs	1380m	280	585m	515w	557m	419m
12	Bu_2SnL-6(**II**)	1605s	1654vs	1379m	275	590m	520w	560m	413m
13	Bu_2SnL-7(**I**)	1605s	1665vs	1393m	272	610m 597sh	532m 542s	565m	434m
14	Bu_2SnL-7(**II**)	1607s	1663vs	1388m	275	590w	530m	553m	422m

[a] Nos as indicated in Table 2; vs, very strong; s, strong; m, medium; w, weak; sh, shoulder.

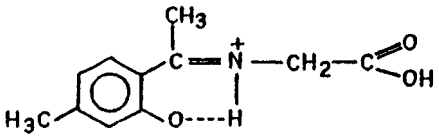


Figure 1 Structure of Schiff base derived from glycine and 4-methyl-2-hydroxyacetophenone

–COO asymmetric stretch and the C=N/C=C ring-stretching modes of vibration, respectively.

The infrared spectra of the all dibutyltin(IV) complexes do not show a strong band in the region 3500–3300 cm^{-1} due to ν(OH/NH),[11] indicating deprotonation of the phenolic and carboxylic oxygen of the Schiff bases on complexation with the tin metal. This is further confirmed by the appearance in the spectra of the complexes of a sharp band at 558 ± 8 cm^{-1} assignable to the Sn–O stretching vibration.[14] In the sodium salts of the Schiff bases [Na_2L(**I**)/Na_2L(**II**)], two bands at 1675 ± 10 and 1600 ± 5 cm^{-1} are observed and are assigned to the –COO asymmetric stretch and the C=N/C=C ring-stretching vibration modes, respectively. In the spectra of the complexes, the asymmetric –COO stretch is shifted to lower frequency (1657 ± 17 cm^{-1}) whereas the C=N/C=C ring stretch is shifted to higher frequency (1605 ± 5 cm^{-1}) indicating coordination of the ligand through the carboxyl oxygen and the imino nitrogen to the tin. The symmetric stretch of the –COO group undergoes a high-frequency shift from a well-defined peak at 1380 ± 15 cm^{-1} in the ligands to a strong band in the spectra of the complexes at about 1400 ± 15 cm^{-1} which is split, indicating the possibility of metal–oxygen bond formation through the –COO group. Furthermore, the separation between asymmetric and symmetric vibrations is 270 ± 15 cm^{-1}, indicating the covalent nature of the metal–oxygen bond.[12] Ionic bonding and also bridging or chelation can therefore be excluded, and carboxylic groups bonding tin unidentately must be assumed. In the lower-frequency region, the strong band observed in the region 413–486 cm^{-1} in the spectra of all the complexes has been assigned to the ν(Sn←N)[14,18] vibration, lending further support to the proposed

Table 5 ^{1}H NMR data of Bu_2SnL complexes

Complex no.[a]	δ (ppm)
1[b]	H-3: 6.89, d(9); H-4: 7.81, d(9); H-5: 7.67, d(8); H-6: 7.33, dd(7,8); H-7: 7.53, dd(7,8); H-8: 7.88, d(8); H-11: 9.10, s [$^3J(^{119/117}Sn-^1H) = 8952$]; H-13: 4.38, d(1) [$^3J(^{119/117}Sn-^1H) = 8920$]; H-$\alpha$ and H-β: 1.49–1.70, m; H-γ: 1.33, tq (7,7); H-δ: 0.86, t(7)
2	H-1: 1.81, s; H-3: 4.91, s; H-5: 1.93, s; H-7: 3.72, s; H-α, H-β and H-γ: 1.76–1.09, brm; H-δ: 0.86, t
3	H-3, H-4, H-5, H-6, H-7 and H-8: 7.89–6.92, m; H-11: 8.38, s; H-13 and H-14: 3.55, m; H-α, H-β and H-γ: 1.34–0.80, brm; H-δ: 0.65, t
4	H-1 and H-5: 1.50, brm; H-3: 4.52, s; H-7 and H-8: 3.09, m; H-α, H-β and H-γ: 1.24–0.60, brm; H-δ: 0.45, t
5[b]	H-3: 6.92, d(9); H-4: 7.83, d(9); H-5: 7.70, d(8); H-6: 7.34, dd(7,8); H-7: 7.54, dd(7,8); H-8: 7.88, d(8); H-11: 8.99, s [$^3J(^{119/117}Sn-^1H) = 8953$]; H-13: 3.90, d(5) [$^3J(^{119/117}Sn-^1H) = 8936$]; H-14: 2.32, dqq (5,7,7); H-15a: 1.10, d(7); H-15b: 1.06, d(7); H-α and H-β: 1.46–1.72, m; H-γ: 1.25, tq (7,7); H-δ: 0.86, t(7)
9	H-3, H-4, H-5, H-6, H-7 and H-8: 7.90–6.78, m; H-11: 9.13, s; H-13: 4.46, t; H-14: 2.41, q; H-15: 2.71, t; H-16: 2.09, s; H-α, H-β and H-γ: 1.81–1.24, brm; H-δ: 1.05–0.76, brt
10	H-1: 1.90, s; H-3 and H-7: 4.92, m; H-5: 1.96, s; H-8 and H-10: 2.08, m; H-9: 2.66–2.52, brm; H-α, H-β and H-γ: 1.80–1.08, m; H-δ: 0.96, t
11[b]	H-3: 6.91, d(9); H-4: 7.82, d(9); H-5: 7.69, d(8); H-6: 7.34, dd(7,8); H-7: 7.54, dd(7,8); H-8: 7.85, d(8); H-11: 8.98, s [$^3J(^{119/117}Sn-^1H) = 8952$]; H-13: 4.17, d(6,6) [$^3J(^{119/117}Sn-^1H) = 8938$]; H-14: 1.96, ddd (6,6,6); H-16a: 1.00, d(7); H-16b: 0.99, d(7); H-α and H-β: 1.33–1.83, m; H-15 and H-γ: 1.25, tq (7,7); H-δ: 0.86, t(7)
13[b]	H-3: 6.92, d(9); H-4: 7.82, d(9); H-5: 7.66, d(7); H-6 to H-8: 7.24–7.49, m; H-11: 9.07, s [$^3J(^{119/117}Sn-^1H) = 8952$]; H-13: 5.28, s [$^3J(^{119/117}Sn-^1H) = 8930$]; H-15, H-16 and H-17: 7.24–7.49; H-α and H-β: 1.46–1.61, m; H-γ: 1.34, tq (7,7); H-δ: 0.86, t(7)
14	H-1: 1.58, s; H-3: 4.86, s; H-5: 1.94, s; H-9, H-10 and H-11: 7.36–7.00, m; H-7: 3.08, s; H-α, H-β and H-γ: 1.42–1.10, brm centred at 1.26; H-δ: 0.88, t

[a] Nos as indicated in Table 2. s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad.
[b] ^1J and ^3J values (Hz) have been calculated by HMQC (Heteronuclear Multiple-Quantum Correlation) and HMBC (Heteronuclear Multiple-Bond Correlation).

coordination in the complexes. The ν_{as}(Sn–C) and ν_s(Sn–C) bands in the regions 610–570 cm^{-1} and 542–478 cm^{-1}, respectively, have also been assigned.[14,23]

Table 5 shows the chemical shifts (δ in ppm) of various protons in all the dibutyltin(IV) complexes except nos **6**, **7**, **8** and **12** because of their insufficient solubility in $CDCl_3$ and $DMSOd_6$. The absence of a signal due to the –OH proton at δ–12.00–13.00 ppm suggests deprotonation of the phenolic/enolic/carboxylic oxygen atoms of the ligands on complexation.[14] In the PMR spectra of the complexes, the signals at δ 8.74±0.40 and 1.73±0.23 ppm have been assigned to azomethine (–N=CH–) and methyl [–N=C(CH_3)] protons, respectively. The complex patterns due to phenyl protons of the ligands have been assigned to the range δ=7.90–6.78 ppm in the spectra of the complexes. The butyl protons attached to the tin appear in the range δ=1.83–0.60 ppm as complex patterns due to 12H of $-CH_2CH_2CH_2-$ and as a clear triple due to terminal methyl protons in the range δ=1.05–0.45 ppm.[14,24,25] The signals corresponding to $-CH_2$, –CH and $-CH_3$ of the ligand moieties have also been assigned and are presented in Table 5. The number of protons in the various groups calculated from the integration curves and those calculated for the expected molecular formula agree with each other.

^{13}C NMR data for a few representative samples have been recorded and are given in Table 6. The various types of carbon have been assigned and the carbons of butyl groups are observed at positions comparable with other, similar, compounds.[25–27] Compounds **1**, **5**, **9**, **11**, **13**, and **14** show $^1J(^{119}Sn-^{13}C)$ values in the range 607.7–565.2 Hz, which indicates five-coordination around the tin atom in these complexes. Domazetis *et al.* reported[28] a value of 560 Hz for five-coordinate Bu_2Sn complexes of thioamino-acids which is further supported by Mitchell *et al.*[29] Tandon and co-workers[25–27] have also reported $^1J(^{119}Sn-^{13}C)$ values of 560–610 Hz for

Table 6 ^{13}C NMR data of Bu_2SnL complexes

Complex no.[a]	δ (ppm)
1[b]	C-1: 108.2; C-2: 172.7; C-3: 124.6; C-4: 139.6; C-5: 129.5; C-6: 123.8; C-7: 128.9; C-8: 118.3; C-9: 133.9; C-10: 127.0; C-11: 166.3; C-12: 171.4; C-13: 58.2; C-α: 21.7 [$^1J(^{119/117}Sn-^{13}C)$=3D 606/581]; C-β: 26.9 [$^2J(^{119/117}Sn-^{13}C)$=8933]; C-γ: 26.5 [$^3J(^{119/117}Sn-^{13}C)$=8988]; C-δ: 13.5
2	C-1: 29.37; C-2: 198.73; C-3: 45.34; C-4: 166.32; C-5: 25.38; C-6: 173.67; C-7: 49.34; C-α: 21.25; C-β: 26.51; C-γ: 26.15; C-δ: 13.2
3	C-1: 108.43; C-2: 172.61; C-3: 118.35; C-4: 139.52; C-5: 128.87; C-6: 129.56; C-7: 124.66; C-8: 123.78; C-9: 133.93; C-10: 127.06; C-11: 165.66; C-12: 174.76; C-13: 64.32; C-14: 22.10; C-α: 22.83; C-β: 27.06; C-γ: 26.67; C-δ: 13.54
5[b]	C-1: 108.4; C-2: 173.5; C-3: 124.7; C-4: 139.3; C-5: 129.5; C-6: 123.8; C-7: 128.8; C-8: 118.3; C-9: 134.0; C-10: 127.1; C-11: 166.0; C-12: 172.9; C-13: 75.1; C-14: 34.4; C-15a: 19.1; C-15b: 18.5; C-α: 20.1 [$^1J(^{119/117}Sn-^{13}C)$=3D 583/556]; C-β: 26.9 [$^2J(^{119/117}Sn-^{13}C)$=8933]; C-γ: 26.4 [$^3J(^{119/117}Sn-^{13}C)$=897]; C-δ: 13.5
9	C-1: 111.37; C-2: 170.31; C-3: 119.10; C-4: 139.33; C-5: 128.78; C-6: 129.20; C-7: 124.37; C-8: 123.59; C-9: 133.78; C-10: 126.95; C11: 166.72; C-12: 174.68; C-13: 57.30; C-14: 31.34; C-15: 40.71; C-16: 18.69; C-α: 21.90 [$^1J(^{119}Sn-^{13}C)$=607.7]; C-β: 27.01; C-γ: 26.50; C-δ: 13.52
11[b]	C-1: 108.3; C-2: 174.6; C-3: 124.7; C-4: 139.3; C-5: 129.6; C-6: 123.8; C-7: 128.9; C-8: 118.3; C-9: 134.0; C-10: 127.1; C-11: 165.3; C-12: 172.6; C-13: 68.1; C-14: 45.5; C-15: 24.1; C-16a: 22.0; C-16b: 23.0; C-α: 20.7 [$^1J(^{119/117}Sn-^{13}C)$=3D 597/571]; C-β: 26.9 [$^2J(^{119/117}Sn-^{13}C)$=8932]; C-γ: 26.5 [$^3J(^{119/117}Sn-^{13}C)$=8990]; C-δ: 13.5
13[b]	C-1: 108.3; C-2: 174.5; C-3: 124.7; C-4: 139.3; C-5: 129.5; C-6: 123.7; C-7: 128.9; C-8: 118.2; C-9: 134.0; C-10: 127.1; C-11: 165.3; C-12: 172.6; C-13: 68.1; C-14: 139.3; C-15: 129.5; C-16: 128.9; C-17: 124.7; C-α: 20.7 [$^1J(^{119/117}Sn-^{13}C)$=3D 597/572]; C-β: 26.9 [$^2J(^{119/117}Sn-^{13}C)$=8932]; C-γ: 26.5 [$^3J(^{119/117}Sn-^{13}C)$=8990]; C-δ: 13.5
14	C-1: 29.52; C-2: 189.37; C-3: 45.33; C-4: 167.01; C-5: 25.36; C-6: 174.09; C-7: 61.50; C-8: 136.72; C-9: 128.92; C-10: 128.21; C11: 127.58; C-α: 21.56; [$^1J(^{119}Sn-^{13}C)$=565.2]; C-β: 25.33; C-γ: 24.10; C-δ: 11.55

[a] Nos as indicated in Table 2. 3D, 3-dimensional.
[b] ^1J, ^2J and ^3J values (Hz) have been calculated by HMQC and HMBC.

a number of five-coordinate dibutyltin complexes of Schiff bases.

The tin shielding in ^{117}Sn NMR spectra increases markedly with increase in coordination number, from $\delta = -50$ to -100 ppm for four-coordinate to $\delta = -200$ ppm for five-coordinate to $\delta = -330$ ppm for six-coordinate alkyltin compounds.[30] Tin shifts are normally higher for phenyl compared with alkyl substitutents.[30] The compounds Bu_2SnL(**I**)/Bu_2SnL(**II**) give sharp signals in the ^{117}Sn NMR spectra at $\delta = -187.0$ to -201.8 ppm, as given in Table 7. These are in accordance with the proposed five-coordinated structures. Ph_2SnL-1(**I**) and Ph_2SnL-2(**I**) synthesized elsewhere[20] also give sharp signals at $\delta = -334.8$ and -342.2 ppm, respectively, suggesting five-coordination. Sometimes additional signals are observed in ^{13}C NMR spectra of the complexes which could be due to the presence of stereoisomers due to allylic shifting of C=N. For example, one signal at 21.18 ppm has been observed in the ^{13}C spectrum of Bu_2SnL-2(**I**). Similarly, ^{117}Sn NMR spectra of **4**, **6** and **10** gave additional broad peaks at -217, -212, -167 and -212, -167 ppm, respectively, indicating the presence of stereoisomers.

The isomer shift (IS) values indicate the presence of tin in the +IV oxidation state and the presence of quadrupole splitting (QS) shows that the EFG around the tin nucleus is produced by inequalities in the tin–ligand σ-bonds.[22–25] The possible geometry around the tin in Bu_2SnL (where L is an anion of a Schiff bases derived from one of various amino-acids, as indicated in Eqn [1] and Table 1) is distorted trigonal-bipyramidal in which the ligands are bifunctional tridentate coordinating through the ONO donor set derived from the phenolic/enolic oxygen, azomethine nitrogen and carboxyl oxygen atoms as indicated from infrared and ^{1}H NMR studies. The observed values of QS and IS of Bu_2SnL complexes are in the range 2.07–3.09 mm s^{-1} and 1.01–1.34 mm s^{-1}, respectively (table 7). A number of workers obtained QS values in the range 2.40–3.10 mm s^{-1} for R_2SnX(8-hydroxyquinolinate), where R = C_6H_5 or C_2H_5, X = halogen, and for other similar compounds and concluded that the organic groups are in *cis* positions.[31–33] In the light of the above findings, the possible arrangement of the butyl groups in Bu_2SnL will be *cis*, as represented in Fig. 2, since observed QS values are in the same range. The proposed structure is also consistent with the observed multiple, ν(Sn–C) (butyl) vibrations in the infrared spectra (Table 4).

The results of antimicrobial activity of Bu_2SnO and all the Bu_2SnL complexes are compiled in Table 8. In comparison with Bu_2SnO, the starting material, all the complexes exhibited good activity. As is evident from the data compiled in Table 8, complexes of Schiff bases derived from the condensation of

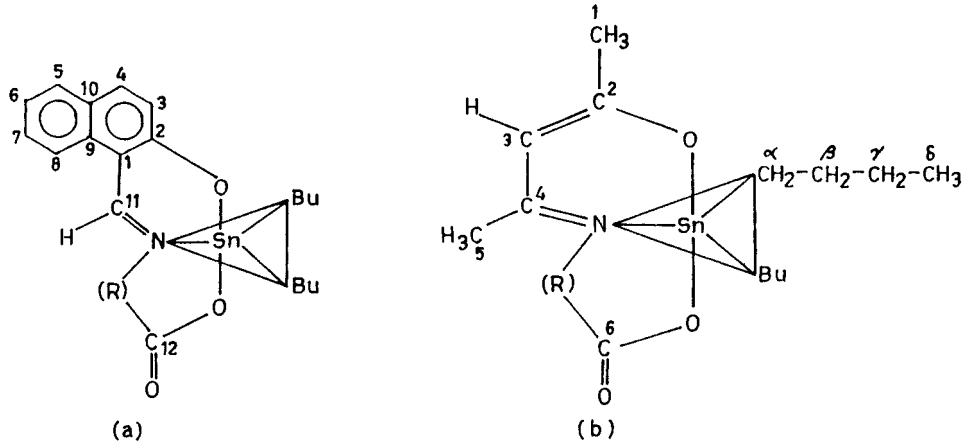
Table 7 ^{117}Sn NMR shifts (δ, ppm and ^{119}Sn Mossbauer data at 80 K) of Bu_2SnL complexes

Complex no.[a]	Complex	δ (^{117}Sn) (ppm)[b]	QS (mm s^{-1})	IS (mm s^{-1})
1	Bu_2SnL-1(**I**)	−195.6	2.90±0.05	1.21±0.01
2	Bu_2SnL-1(**II**)	−197.8	2.56±0.04	1.27±0.01
3	Bu_2SnL-2(**I**)	−201.8	2.96±0.04	1.14±0.01
4	Bu_2SnL-2(**II**)	−192.0	2.82±0.12	1.23±0.06
5	Bu_2SnL-3(**I**)	−200.3	—	—
6	Bu_2SnL-3(**II**)	−192.4	2.55±0.04	1.19±0.01
7	Bu_2SnL-4(**I**)	−187.0	—	—
9	Bu_2SnL-5(**I**)	—	3.09±0.04	1.28±0.01
10	Bu_2SnL-5(**II**)	−191.7	3.05±0.12	1.34±0.06
11	Bu_2SnL-6(**I**)	−200.7	2.98±0.12	1.22±0.06
12	Bu_2SnL-6(**II**)	−192.6	—	—
13	Bu_2SnL-7(**I**)	−200.8	—	—
14	Bu_2SnL-7(**II**)	—	2.07±0.03	1.01±0.01
15	Ph_2SnL-1(**I**)[c]	−334.8	—	—
16	Ph_2SnL-2(**I**)[c]	−342.2	—	—

[a] Nos as indicated in Table 2. [b] In $CDCl_3$. [c] Prepared and reported elsewhere.[20]

2-hydroxy-1-naphthaldehyde with various amino-acids [H_2L-1(**I**) to H_2L-7(**II**)] have been found to exhibit greater activity than those in which the Schiff bases are derived from acetyl acetone and amino-acids. Thus the results indicated that the complexes possess moderate bactericidal and fungicidal activities.

In vitro antitumour activities (ID_{50} values in ng ml^{-1}) against MCF-7 and EVSA-T (two breast cancers), WiDr (a colon cancer), IGROV (an ovarian cancer), M19 MEL (a melanoma), A498 (a renal cancer) and H226 (a lung cancer) of Bu_2SnL-1(**I**), Bu_2SnL-2(**I**), Bu_2SnL-6(**II**), Ph_2SnL-1(**I**) and Ph_2SnL-2(**I**) as well as the ID_{50} values of some reference compounds[21] used clinically, and of tri-n-butyltin pentafluorocinnamate,[34] are presented in Table 9. All five organotin compounds are more active *in vitro* against all the cell lines than carboplatin and cisplatin. Three of them, i.e. Bu_2SnL(**I**), Bu_2SnL-2(**I**) and Bu_2SnL-6(**II**), are even more active than 5-fluorouracil. However, they are all less active than methotrexate and doxorubicin, and much less active than the tri-n-butyltin carboxylates reported recently,[34] such as pentafluorocinnamate, of which the ID_{50} value is also given in Table 9. Further, data reveal that dibutyltin derivatives of the Schiff bases derived from amino-acids are more active than the corresponding diphenyltin derivatives.



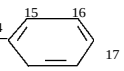
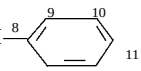
R	Compd no.	R	Compd no.
$-\overset{13}{C}H_2-$	**1**	$-\overset{7}{C}H_2-$	**2**
$-\overset{13}{C}H_2-\overset{14}{C}H_2-$	**3**	$-\overset{7}{C}H_2-\overset{8}{C}H_2-$	**4**
$>\overset{13}{C}H-\overset{14}{C}H(\overset{15}{C}H_3)_2$	**5**	$>\overset{7}{C}H-\overset{8}{C}H(\overset{9}{C}H_3)_2$	**6**
$-\overset{13}{C}H_2-\overset{14}{C}H_2-\overset{15}{C}H_2-$	**7**	$-\overset{7}{C}H_2-\overset{8}{C}H_2-\overset{9}{C}H_2-$	**8**
$>\overset{13}{C}H-\overset{14}{C}H_2-\overset{15}{C}H_2-S-\overset{16}{C}H_3$	**9**	$>\overset{7}{C}H-\overset{8}{C}H_2-\overset{9}{C}H_2-S-\overset{10}{C}H_3$	**10**
$>\overset{13}{C}H-\overset{14}{C}H_2-\overset{15}{C}H(\overset{16}{C}H_3)_2$	**11**	$>\overset{7}{C}H-\overset{8}{C}H_2-\overset{9}{C}H(\overset{10}{C}H_3)_2$	**12**
$>\overset{13}{C}H-\overset{14}{}$ 	**13**	$>\overset{7}{C}H-\overset{8}{}$ 	**14**

Figure 2 Structures of (a) Bu_2SnL(**I**) and (b) Bu_2SnL(**II**).

Table 8 Antimicrobial activity of Bu_2SnL complexes

Complex no.	Complex	Minimum inhibitory concn, MIC,[a] (μg ml^{-1}) against: Bacteria 1	2	3	4	5	Fungi 6	7	8	9	10
	Bu_2SnO	50	—	—	—	—	—	50	50	—	50
1	Bu_2SnL-1(**I**)	< 12.5	—	25	50	< 12.5	—	12.5	50	25	25
2	Bu_2SnL-1(**II**)	—	—	—	50	—	—	50	—	50	50
3	Bu_2SnL-2(**I**)	—	50	—	—	50	—	25	25	—	50
4	Bu_2SnL-2(**II**)	50	—	—	—	50	—	50	—	50	25
5	Bu_2SnL-3(**I**)	< 12.5	—	—	50	25	—	25	50	25	25
6	Bu_2SnL-3(**II**)	25	—	—	—	—	—	25	—	50	25
7	Bu_2SnL-5(**I**)	< 12.5	—	50	50	25	—	25	50	25	50
8	Bu_2SnL-5(**II**)	25	—	—	50	50	—	50	—	50	25
9	Bu_2SnL-6(**I**)	< 12.5	—	—	50	25	—	< 12.5	50	25	50
10	Bu_2SnL-6(**II**)	25	—	—	—	25	50	50	—	50	25
11	Bu_2SnL-7(**I**)	< 12.5	—	25	50	12.5	—	25	50	25	50
12	Bu_2SnL-7(**II**)	25	—	—	—	25	—	50	—	—	—

[a] The samples were not screened below 12.5 μg ml^{-1}. Key: 1, *Streptococcus faecalis*; 2, *Klebsiella pneumoniae*; 3, *Escherichia coli*; 4, *Pseudomonas aeruginosa*; 5, *Staphylococcus aureus* [penicillin resistance (2500 units)]; 6, *Candida albicans*; 7, *Cryptococcus neoformans*; 8, *Sporotrichum schenckii*; 9, *Trichophyton mentagrophytes*; 10, *Aspergillus fumigatus*. Solvent, DMSO.

Table 9 ID_{50} values (in ng ml^{-1}) of selected diorganotin derivatives of Schiff bases derived from amino-acids, and of some reference compounds

Complex	ID_{50} (ng ml^{-1}) against[a]: MCF-7	EVSA-T	WiDr	IGROV	MI9 MEL	A498	H226
Bu_2Sn-1(**I**)	75	35	480	75	90	170	190
Bu_2SnL-2(**I**)	20	17	114	27	71	62	160
Bu_2SnL-6(**II**)	60	120	420	130	70	130	200
Ph_2SnL-1(**I**)	170	70	490	120	530	230	350
Ph_2SnL-2(**I**)	600	150	1750	480	620	690	1100
Carboplatin[b]	10 500	4500	3500	2400	5500	18 000	25 000
Cisplatin[b]	1400	920	1550	230	780	1200	3160
5-Fluorouracil[b]	350	720	440	850	310	340	5300
Methotrexate[b]	15	26	7	20	18	16	70
Doxorubicin[b]	25	13	18	150	21	55	180
$F_5C_6CH{=}CHCO_2SnBu_3$[c]	13	< 3	14	11	45	54	33

[a] MCF-7 and EVSA-T, two breast cancers; Widr, a colon cancer; IGROV, an ovarian cancer; M19 MEL, a melanoma; A498, a renal cancer; H226, a non-small cell lung cancer. [b] Ref. 21. [c] Ref. 34.

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REFERENCES

1. D. E. Metzler, *J. Am. Chem.* **79**, 485 (1957).
2. D. E. Metzler and E. E. Snell, *J. Am. Chem. Soc.* **74**, 979 (1952).
3. D. E. Metzler and E. E. Snell, *J. Biol. Chem.* 353 and 363 (1952).
4. G. L. Eichhorn and J. W. Dawes, *J. Am. Chem. Soc.* **76**, 5663 (1954).
5. L. A. Zyzyck, H. Frummer and J. F. Villa, *J. Inorg. Nucl. Chem.* **37**, 1653 (1975).
6. R. C. Burrows and J. C. Bailar Jr, *J. Am. Chem. Soc.* **88**, 4150 (1966).
7. G. N. Weinstein, M. J. O'Connor and R. H. Holm, *Inorg. Chem.* **9**, 2104 (1970).
8. G. O. Carlisle and L. J. Theriot, *J. Inorg. Nucl. Chem.* **35**, 2093 (1973).
9. V. V. Ramanujam and B. Sivasankar, *J. Ind. Chem. Soc.* **58**, 1152 (1981).
10. V. V. Ramanujam and B. Sivasankar, *Ind. J. Chem.* **20**, 749 (1981).
11. M. Singh, *Synth. React. Inorg. Met.—Org. Chem.* **15**, 235 (1985).
12. N. S. Biradar, V. L. Roddabasanagoudar and T. M. Aminabhavi, *Polyhedron* **3**, 575 (1984).
13. T. M. Aminabhavi, N. S. Biradar, G. V. Karajagi and W. E. Rudzinski, *Inorg. Chim. Acta* **91**, 49 (1984).
14. M. Nath, C. L. Sharma and N. Sharma, *Synth React. Inorg. Met.—Org. Chem.* **21**, 807 (1991).
15. H. P. S. Chauhan, A. Bhargava and R. J. Rao, *Ind. J. Chem.* **32A**, 157 (1993).
16. J. Wang, Y. Zhang, Y. Xu, Z. Wang and H. Youji, *Heteroat. Chem.* **13**, 289 (1993).
17. M. Gielen, P. Lelieveld, D. de Vos and R. Willem, *In vitro* antitumour activity of organotin compounds. In: *Metal-based Antitumor Drugs*, Vol. 2, Gielen, M. (ed.), Freund, Tel Aviv, 1992, pp 29–54.
18. M. Nath, S. Goyal and C. L. Sharma, *Main Group Met. Chem.* **18**, 51 (1995).
19. M. Nath and S. Goyal, *Main Group Met. Chem.* **16**, 167 (1993).
20. M. Nath and R. Yaldav, *Bull. Chem. Soc. Jpn.* **70**, June (1997).
21. Y. P. Keepers, P. E. Pizao, G. J. Peters, J. Van Ark-otte, B. Winograd and H. M. Pinedo, *Eur. J. Cancer* **27**, 897 (1991).
22. A. Saxena, J. P. Tandon, K. C. Molloy and J. J. Zuckerman, *Inorg. Chim. Acta* **63**, 71 (1982).
23. S. S. Sandhu, S. S. Sandhu Jr, G. K. Sandhu, R. V. Parish and O. Parry, *Inorg. Chim. Acta* **58**, 251 (1982).
24. R. Tiwari, G. Srivastava, R. C. Mehrotra and A. J. Crowe, *Inorg. Chem. Acta* **111**, 161 (1986).
25. A. Saxena and J. P. Tandon, *Polyhedron* **3**, 681 (1984).
26. A. Saxena and J. P. Tandon, *Polyhedron* **2**, 443 (1983).
27. A. Saxena, J. P. Tandon and A. J. Crowe, *Polyhedron* **4**, 1085 (1985).
28. G. Domazetis, R. J. Magee and B. D. James, *J. Organomet. Chem.* **148**, 339 (1978).
29. T. N. Mitchell, *J. Organomet. Chem.* **71**, 39 (1974).
30. B. S. Saraswat and J. Mason, *Polyhedron* **5**, 1449 (1986).
31. R. C. Poller and J. N. R. Ruddick, *J. Chem. Soc. (A)* 2273 (1969).
32. M. V. Garad, M. P. Gupta, S. Gopinathan and C. Gopinathan, *Ind. J. Chem.* **20A**, 363 (1981).
33. M. A. Mullins and C. Curran, *Inorg. Chem.* **7**, 2584 (1968).
34. R. Willem, A. Bouhdid, M. Biesemans, J. C. Matrins, D. de Vos, E. R. T. Tiekink and M. Gielen, *J. Organomet. Chem.* **514**, 203 (1996).

