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Synthesis and Characterization of Organotin(IV) Complexes Derived of 2-amino-5-nitrobenzoic Acid: *In vitro* Antibacterial Screening Activity

[1]Yip-Foo Win, [2]Siang-Guan Teoh, [2]M.R. Vikneswaran, [1]Mun-Yee Chan,
[1]Sie-Tiong Ha and [3]Pazilah Ibrahim
[1]Department of Chemical Science, Faculty of Science, University Tunku Abdul Rahman,
Perak Campus, Jalan University, Bandar Barat, 31900 Kampar, Perak, Malaysia
[2]School of Chemical Sciences,
[3]School of Pharmaceutical Sciences,
University Sains Malaysia, 11800 Minden Penang, Pulau Pinang, Malaysia

Abstract: Problem statement: Tremendous studies have been carried out on organotin(IV) complexes derivatives of carboxylate anions. However, the synthesis and characterization as well as the *in vitro* antibacterial screening activity of organotin(IV) carboxylate derived of 2-amino-5-nitrobenzoic acid have not been carried out. **Approach:** Organotin(IV) carboxylate complexes derivative of 2-amino-5-nitrobenzoic acid, 2-NH_2-5-NO_2-C_6H_3COOH have been successfully synthesized. The acid and complexes obtained were characterized quantitatively using C, H, N and Sn elemental analysis as well as spectroscopic methods such as infrared (FTIR) and nuclear magnetic resonance (^1H, ^{13}C, ^1H-^{13}C HMQC and ^{119}Sn NMR). Moreover, the complexes obtained were screened for their *in vitro* antibacterial screening activity. **Results:** Monomeric R_2Sn (2-NH_2-5-NO_2-$C_6H_3COO)_2$ (R = methyl **1**, butyl **2**) and dimeric $\{[(Bu_2Sn(2\text{-}NH_2\text{-}5\text{-}NO_2\text{-}C_6H_3COO)]_2O\}_2$ **3** as well as Ph_3Sn(2-NH_2-5-NO_2-C_6H_3COO) **4** are obtained in solid state. Results of the infrared spectroscopy on the acid and complexes showed that the coordination took place via oxygen atoms from the carboxylate anions. Based on the ^{119}Sn NMR solution study, the tin atom of both complexes **1** and **2** exhibit six-coordination respectively and complex **3** exhibits five- and six-coordination whereas the tin atom of complex **4** exhibits five-coordination. **Conclusion:** Pure complexes derived of 2-amino-5-nitrobenzoic acid have been successfully obtained. Triphenyltin(IV) are found to possess better *in vitro* antibacterial screening activity on two gram-positive bacterial compared to the parent acid.

Key words: Organotin(IV) carboxylate, preparation, antibacterial activity

INTRODUCTION

Organotin(IV) complexes are extensively studied due to the applications in industrial as well as biocidal properties (Molloy *et al*., 1984; Willem *et al*., 1997; Gielen *et al*., 2000). Numerous studies on organotin(IV) complexes have been carried out in order to study its biological properties against bacterial, fungal and cancer cells line (Teoh *et al*., 1997; Novelli *et al*., 1999; Gielen *et al*., 2000; Crouse *et al*., 2004). Up to date, organotin(IV) complexes are still extensively studied due to its coordination geometries as well as structural diversity (monomer, dimeric, hexameric and oligomeric) (Zhang *et al*., 2005; Win *et al*., 2007a; 2008; Amini *et al*., 2009).

In this study, we are focus on synthesis and structural characterization of new organotin(IV) carboxylate complexes derived from 2-amino-5-nitrobenzoic acid. In addition, the *in vitro* antibacterial screening activities of the complexes obtained are carried out and the results are reported herein.

MATERIALS AND METHODS

General and instrumental: All the reagents, starting materials as well as the solvents aere purchased commercially and used without any further purification. The melting points were determined in an open capillary and are uncorrected. Elemental C, H and N analyses were carried out on a Perkin-Elmer 2400 CHN Elemental Analyzer. Tin was determined gravimetrically by igniting a known quantity of each complex to SnO_2. Infrared spectra were recorded using a Perkin-Elmer System 2000 FTIR Spectrophotometer

Corresponding Author: Yip-Foo Win, Department of Chemical Science, Faculty of Science, University Tunku Abdul Rahman, Perak Campus, Jalan University, Bandar Barat, 31900 Kampar, Perak, Malaysia

as a KBr disc in the frequency range of 4000-400 cm^{-1}. The spectra for ^{1}H, ^{1}H-^{13}C HMQC and ^{119}Sn NMR were recorded on a Bruker AC-P 400 MHz FTNMR Spectrometer and ^{13}C NMR was recorded on a Bruker AC-P 300MHz FTNMR Spectrometer using deuterated d_6-DMSO as the solvent and tetramethylsilane, TMS as the internal standard.

***In vitro* antibacterial screening activity:** The synthesized complexes and parent acid were screened for their *in vitro* antibacterial activity against three gram-negative (*Escherichia coli*, *Pseudomonas aeruginosa* and *Klebsiella pneumonia*) and two gram-positive (*Bacillus subtilis* and *Staphylococcus aureus*) bacterial strains, by Inhibition Zone Method using agar well diffusion method. The seeded agar (nutrient agar medium) was prepared by cooling the molten agar to 40°C and then adding bacterial inoculums containing approximately 10^4-10^6 Colony Forming Units (CFU) mL^{-1}. The bacterial inoculums were spread on the plate containing agar medium and even coverage was ensured before the agar solidified. The complexes were dissolved in DMSO to prepare 1.0 mg mL^{-1} concentration. By using a sterile metallic borer, the wells (6 mm in diameter) were dug and the standard drugs and complexes were introduced into the respective wells. The plates were incubated immediately at 37°C for 20-24 h. The activity was determined by measuring the diameter of the inhibition zone (in mm).

Preparation of sodium salt and dimethyltin(IV) oxide, Me_2SnO: Dimethyltin(IV) dichloride, Me_2SnCl_2 was dissolve in distilled water and stirred for overnight. Colorless solution was obtained. Ammonia solution (60%) was added into the colorless solution and finally fine white precipitate was obtained and filtered. The precipitate was dried in oven (60°C) for a day until dry white precipitate was obtained. The sodium salt of the acid was obtained by heating under reflux a 1:1 molar mixture of sodium hydroxide, NaOH (0.12 g, 3 mmole) and 2-amino-5-nitrobenzoic acid, NH_2-5-NO_2-C_6H_3COOH (0.55 g, 3 mmole) in ethanol (50 mL) for 2 h. After a few days, yellowish precipitate was obtained. FTIR as KBr disc (cm^{-1}): Selected data: $\nu(COO)_{as}$ 1637, $\nu(COO)_s$ 1334.

Preparation of complexes:

Bis(2-amino-5-nitrobenzoato)dimethyltin(IV), $Me_2Sn(2\text{-}NH_2\text{-}5\text{-}NO_2\text{-}C_6H_3COO)_2$ **(1)**

Complex **1** was obtained by heating under reflux a 1:2 molar mixture of dimethyltin(IV) oxide (0.17 g, 1 mmole) and acid (0.363 g, 2 mmole) in ethanol (50 mL) for an hour. A clear yellow transparent solution was separated by filtration and kept in a bottle. After four days, fine yellow solids (0.45 g, 88.0% yield) were collected. Melting point: >300°C (decomposed). Analysis for $C_{16}H_{16}N_4O_8Sn$: C, 37.66; H, 3.01; N, 11.04; Sn, 23.26%. Calculated for $C_{16}H_{16}N_4O_8Sn$: C, 37.61; H, 3.16; N, 10.96; Sn, 23.23 %. FTIR as KBr disc (cm^{-1}): $\nu(NH_2)$ 3468, 3358; ν(C-H) aromatic 3091, ν(C-H) saturated 2955, $\nu(COO)_{as}$ 1626, $\nu(COO)_s$ 1315, $\nu(NO_2)$ 1552, ν(O-Sn-O) 644, ν(Sn-C) 506, ν(Sn-O) 404. ^{1}H-NMR (ppm) (d_6-DMSO): δ: benzene protons 6.82 (d, 9.3 Hz, 2H); 8.03 (dd, 2.8 Hz, 9.2 Hz, 2H); 8.63 (d, 2.8 Hz, 2H); methyl, CH_3 0.93 (s, 6H), $^{2}J(^{119}Sn - {}^{1}H)$= 95.2 Hz. ^{13}C-NMR (ppm) (d_6-DMSO): δ: benzene carbons 112.43, 116.91, 128.94, 129.99, 135.98, 156.82; methyl 12.25; COO 172.24. ^{119}Sn-NMR (ppm) (d_6-DMSO):δ: -281.39:

Bis(2-amino-5-nitrobenzoato)dibutyltin(IV), $Bu_2Sn(2\text{-}NH_2\text{-}5\text{-}NO_2\text{-}C_6H_3COO)_2$ (**2**)

Complex **2** was obtained by heating under reflux a 1:2 molar mixture of dibutyltin(IV) oxide (0.75 g, 3 mmole) and acid (1.09 g, 6 mmole) in methanol (50 mL) for 4 h. After two weeks, yellow crystals (1.60 g, 90.0% yield) were collected. Melting point: 209.3-209.7°C. Analysis for $C_{22}H_{28}N_4O_8Sn$: C, 44.42; H, 4.19; N, 9.38; Sn, 19.91%. Calculate for $C_{22}H_{28}N_4O_8Sn$: C, 44.39; H, 4.74; N, 9.41; Sn, 19.94%. FTIR as KBr disc (cm^{-1}): $\nu(NH_2)$ 3484, 3313, 3334; ν(C-H) aromatic 3059, ν(C-H) saturated 2951, 2922, 2854; $\nu(COO)_{as}$ 1619, $\nu(COO)_s$ 1314, $\nu(NO_2)$ 1541, ν(O-Sn-O) 642, ν(Sn-C) 515, ν(Sn-O) 420. ^{1}H-NMR (ppm) (d_6-DMSO):δ: benzene protons 6.94 (d, 9.3 Hz, 2H); 8.15 (dd, 2.8 Hz, 9.3 Hz, 2H); 8.73 (d, 2.8 Hz, 2H); butyl, CH_3 0.91 (t, 7.3 Hz, 6H); CH_2 1.40 (sx, 7.1 Hz, 4H); CH_2 1.64-1.80 (m, 8H). ^{13}C-NMR (ppm) (d_6-DMSO):δ: benzene carbons 111.84, 116.98, 129.15, 130.04, 135.93, 156.81; butyl 14.42, 26.47, 27.72, 31.02; COO 173.05. ^{119}Sn-NMR (ppm) (d_6-DMSO):δ: -310.76:

Bis(2-amino-5-nitrobenzoato)tetrabutyldistannoxane (IV) dimer, $\{[(Bu_2Sn(2\text{-}NH_2\text{-}5\text{-}NO_2\text{-}C_6H_3COO)]_2O\}_2$ (**3**)

Complex **3** was prepared from a 1:1 molar mixture of dibutyltin(IV) oxide (0.50 g, 2 mmole) and 2-amino-5-nitrobenzoic acid (0.36 g, 2 mmole) in ethanol (50 mL). Dibutyltin(IV) oxide was first dissolved in ethanol (20 mL) and heated for an hour until clear solution was obtained. Then, 2-amino-5-nitrobenzoic acid dissolved in ethanol (30 mL) added to the dibutyltin(IV) oxide solution. The resulting mixture was heated under reflux

for 2 h. A clear yellow transparent solution was isolated by filtration and kept in a bottle. After four days, yellow solids (0.61 g, 73.0% yield) were collected. Melting point: 240.7-241.5°C. Analysis for $C_{60}H_{92}N_8O_{18}Sn_4$: C, 42.74; H, 5.79; N, 6.57; Sn, 27.98%. Calculated for $C_{60}H_{92}N_8O_{18}Sn_4$: C, 42.66; H, 5.49; N, 6.64; Sn, 28.12%. FTIR as KBr disc (cm^{-1}): ν(NH_2) 3457, 3344, 3314; ν(C-H) aromatic 3059, ν(C-H) saturated 2956, 2926, 2870; ν($COO)_{as}$ 1622, ν($COO)_s$ 1310, ν(NO_2) 1537, ν(Sn-O-Sn) 630, ν(Sn-C) 531, ν(Sn-O) 391. ^{1}H-NMR (ppm) (d_6-DMSO):δ: benzene protons 6.92 (d, 9.3 Hz, 4H); 8.12 (dd, 2.4 Hz, 9.2 Hz, 4H); 8.72 (s, 4H); butyl, CH_3 0.84 (t, 7.3 Hz, 12H); 0.90 (t, 7.3 Hz, 12H); CH_2 1.28-1.43 (m, 32H); CH_2 1.64-1.80 (m, 16H). ^{13}C-NMR (ppm) (d_6-DMSO):δ: benzene carbons 112.27, 116.50, 128.49, 129.47, 135.55, 156.49; butyl 13.71, 13.91, 26.09, 26.77, 27.02, 27.29, 29.90; COO 172.11. ^{119}Sn-NMR (ppm) (d_6-DMSO):δ: -173.87, -213.71:

2-Amino-5-nitrobenzoatotriphenyltin(IV), $Ph_3Sn(2\text{-}NH_2\text{-}5\text{-}NO_2\text{-}C_6H_3COO)$ **(4)**

Complex **4** was obtained by heating under reflux a 1:1 molar mixture of triphenyltin(IV) hydroxide (0.73 g, 2 mmole) and 2-amino-5-nitrobenzoic acid (0.36 g, 2 mmole) in methanol (60 mL) for an hour. A clear yellow transparent solution was separated by filtration and kept in a bottle. After six days, yellow crystals (0.51 g, 96.0% yield) were collected. Melting point: 208.5-208.9°C. Analysis for $C_{25}H_{20}N_2O_4Sn$: C, 56.41; H, 3.48; N, 5.23; Sn, 22.03%. Calculated for $C_{25}H_{20}N_2O_4Sn$: C, 56.53; H, 3.80; N, 5.27; Sn, 22.35%. FTIR as KBr disc (cm^{-1}): ν(NH_2) 3442, 3328; ν(C-H) aromatic 3058, ν($COO)_{as}$ 1618, ν($COO)_s$ 1310, ν(NO_2) 1556, ν(Sn-O) 443. ^{1}H-NMR (ppm) (d_6-DMSO):δ: phenyl protons 7.53-7.59 (m, 9H); 7.95-7.97 *(m, 6H); benzene 6.82 (d, 9.2 Hz, 1H); 8.07 (dd, 2.8 Hz, 9.2 Hz, 1H); 8.73 (d, 2.9 Hz, 1H). ^{13}C-NMR (ppm) (d_6-DMSO):δ: phenyl carbons C_{ipso} 142.87 (839.3 Hz), C_{ortho} 136.11 (45.6 Hz), C_{meta} 128.43, C_{para} 129.03 (18.4 Hz); benzene 112.77, 115.75, 127.72, 127.97, 134.89, 155.92; COO 169.52. ^{119}Sn-NMR (ppm) (d_6-DMSO):δ: -265.89.

2-Amino-5-nitrobenzoic acid: The parent acid, 2-amino-5-nitrobenzoic acid, $2\text{-}NH_2\text{-}5\text{-}NO_2\text{-}C_6H_3COOH$ was purchased from Acros Organics and used without any further purification. FTIR as KBr disc (cm^{-1}): selected data: ν(OH) 2892-2616, ν($COO)_{as}$ 1685, ν($COO)_s$ 1330. ^{1}H-NMR (ppm) (d_6-DMSO):δ: benzene protons 6.96 (d, 9.3 Hz, 1H); 8.17 (dd, 2.8 Hz, 9.3 Hz, 1H); 8.68 (d, 2.8 Hz, 1H). ^{13}C-NMR (ppm) (d_6-DMSO):δ: benzene carbons 109.31, 117.34, 129.54, 129.58, 135.87, 156.99; COO 168.95.

RESULT

Physical and elemental analysis: Elemental analysis C, H, N and Sn data obtained were in agreement with the predicted formula and complexes **1-4** gave a sharp melting point indicated the isolation of fairly pure complexes.

Structural and *in vitro* antibacterial screening activity: An outline of the proposed structure for complexes **1-4** are depicted in Fig. 1. The *in vitro* antibacterial screening activity of complexes **1-4** are given in Table 1.

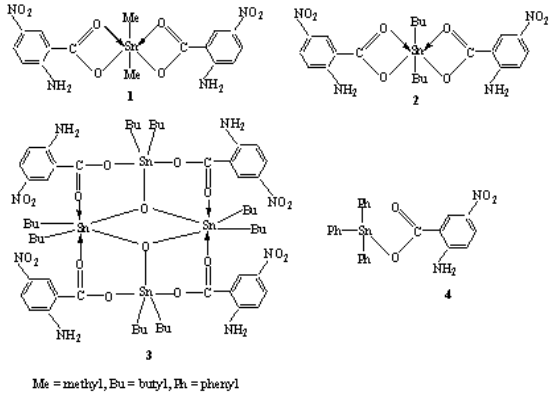

Fig. 1: The proposed structure for complexes **1-4**

Table 1: *In vitro* antibacterial screening activity of parent acid and complexes **1-4**

	Inhibition zone (mm)				
Complexes	*Bacillus subtilis*	*Escherichia coli*	*Klebsiella pneumonia*	*Pseudomonas aeruginosa*	*Staphylococcus aureus*
Acid	-	-	-	-	-
1	10	9	12	10	12
2	13	9	-	-	11
3	13	7	-	-	11
4	18	-	-	-	19
Chloramphenicol	29	-	23	34	30
Doxycycline	34	24	21	40	28
Rifampicin	25	24	23	29	37

Agar well diffusion method (*in vitro*) = 1.0 mg mL^{-1}; Reference drug = Chloramphemicol, Doxycycline and Rifampicin

DISCUSSION

In this study, complexes **1-4** derived of 2-amino-5-nitrobenzoic acid have been obtained in solid state. Complexes **2** and **4** were obtained as single yellow crystals and the X-ray crystal structure of both complexes have been reported (Win *et al*., 2006; 2007b).

The ν(O-H) bands which appeared in the range of 2892-2616 cm^{-1} for the acid, were absent in the infrared spectra of salt and complexes **1-4** showed the deprotonation and coordination of the carboxylate anion. The infrared spectra of complexes **1-4** revealed that the $\nu(COO)_{as}$ was shifted to a lower wave length number compared to the parent acid which signify that the coordination took place via the oxygen atoms of the carboxylate anion. Complex **4** showed the $\nu(COO)_{as}$ and $\nu(COO)_{s}$ are in the range of 1618-1626 and 1310-1315 cm^{-1} respectively.

Generally, the $\Delta\nu = [\nu(COO)_{as} - \nu(COO)_{s}]$ value is used to determine the bonding properties of carboxylate anion to tin atom in organotin(IV) carboxylate complexes. Sandhu and Verma (1987) in their studies and reports have shown that the Δν value of complexes greater by 65-90 cm^{-1} than in their sodium salts indicates either asymmetric or monodentate bonding of the carboxylate group to tin(IV) atom. Complexes **1-3** showed that the Δν is comparable to the sodium salt ($\Delta\nu$ = 303 cm^{-1}) indicating bidentate bonding of the carboxylate group to tin(IV) atom. Moreover, for complexes derived from triphenyltin(IV) carboxylate, Δν below 200 cm^{-1} would be expected for bridging or chelating carboxylates, but greater than 200 cm^{-1} for the monodentate bonding carboxylate anions (Yeap and Teoh, 2003). Hence, carboxylate anion in complex **4** would be expected to bond to the tin atom in monodentate manner since the Δν above 200 cm^{-1}. Based on the infrared spectroscopy study, both complexes **1** and **2** exhibit six-coordinated tin atom; complex 3 exhibits five- and six-coordinated whereas complex **4** exhibits four-coordinated tin atom.

The upfield regions of the ^{1}H NMR spectra of the complexes **1-3** showed the signal of the methyl and butyl protons in the range of 0.93 and 0.84-1.80 ppm respectively. In addition, complex **1** showed $^{2}J(^{119}Sn\text{-}^{1}H)$ at 95.2 Hz and based on the application of the Lockhart-Manders equation, the C-Sn-C angle is 153.61° (Lockhart and Manders, 1986). Based on the $^{2}J(^{119}Sn\text{-}^{1}H)$ and C-Sn-C angle, the tin atom of complex **1** is believed to exist in distorted octahedral geometry and six-coordinated. In general, complex **3** is one of the distannoxane dimer types and should exhibited two unresolved sets of butyl signals, one of the butyl groups linked to the endo-cyclic tin atom and the other one linked to the exo-cyclic tin atom respectively (Danish *et al*., 1995). However, complex **3** only showed two unresolved sets of CH_3 signal at 0.84 and 0.90 ppm respectively and two set of methylene signals of butyl groups in the range of 1.28-1.43 and 1.64-1.80 ppm in the spectra. This may due to a very similar environment or overlapping of methylene signals multiplicity in the NMR spectra. For complex **4**, the resonances appearing as two well separated sets of multiplets in the regions centering around δ≈ 7.55 ppm and 7.96 ppm ascribed to phenyl protons. At the low field arising from ortho and at higher field arising from meta and para phenyl protons respectively (Sau and Holmes, 1981).

Evidence of the formation of the complexes is clearly displayed in the ^{13}C NMR spectra. The ^{13}C NMR spectra of complexes **1-4** showed the δ(COO) signal shifted to the downfield region which is lower compared to that of the acid (168.95 ppm) indicating the carboxylate anion is bonded to tin atom upon complexation. Complex **1** showed a sharp signal at 12.25 ppm indicated the present of methyl groups in the $SnMe_2$ moiety. In the upfield region of ^{13}C NMR spectra, complexes **2** and **3** showed the occurrence of CH_3 and CH_2 in the range of 13.71-14.42 and 26.09-29.90 ppm respectively (Danish *et al*., 1995; Holecek *et al*., 1986). In addition, complex **3** exhibited two sets of butyl signals in ^{13}C NMR spectra. This attributed to the butyl groups linked to the exo- and endo-cyclic tin atom respectively. The ^{13}C NMR spectra of complex **4** showed that the chemical shifts of the $\delta(^{13}C)_{ipso}$ at 142.87 ppm indicative of a five-coordinated Sn atom (Holecek *et al*., 1983a; 1983b; Baul *et al*., 2001).

For diorganotin(IV) carboxylate complexes, the $\delta(^{119}Sn)$ value for four-coordinated complexes fall in the range between +200 to -60 ppm; for five-coordinated complexes between -90 to -190 ppm and for six-coordinated complexes between -210 to -400 ppm (Holecek *et al*., 1986). Complexes **1** and **2** showed that the $\delta(^{119}Sn)$ are -281.39 and -310.76 ppm respectively, indicated that the tin atom in complexes **1** and **2** are six-coordinated. Complex **3** showed two well separated resonances of $\delta(^{119}Sn)$ at -173.87 and -213.71 ppm respectively. These two low- and high-field resonances respectively are attributed to the exo- and endo-cyclic tin atoms in complex 3 as observed in distannoxane dimer (Danish *et al*., 1995). As a result, complex **3** showed that the exo- and endo-cyclic tin atoms are five- and six-coordinated respectively (Danish *et al*., 1995; Holecek *et al*., 1986). The

coordination number of tin in triphenyltin(IV) carboxylate could be determined by the studies of $^{1}J(^{119}Sn\text{-}^{13}C)$ coupling constant (Holecek *et al*., 1983a; 1983b; Baul *et al*., 2001). Basically, the tin atom of triphenyltin(IV) compounds with higher $\delta(^{119}Sn)$ and $^{1}J(^{119}Sn\text{-}^{13}C)$ value lie in the range of -200 to -260 ppm and 750-850 Hz respectively are believed to exhibit five-coordinated and in trigonal bipyramid geometry of the substituents and ligand, $Ph_3SnX{\bullet}L$ and L is a monodentate ligand (Holecek *et al*., 1983b). The three phenyl groups lie in the equatorial positions with the substituent, X and the ligand, L lie in the axial positions to form *trans*-trigonal bipyramid geometry (Holecek *et al*., 1983b). Complex **4** showed that the $\delta(^{119}Sn)$ and $^{1}J(^{119}Sn\text{-}^{13}C)$ are -265.89 ppm and 839.3 Hz respectively indicated that the tin atom in complex 4 is five-coordinated and having trans-trigonal bipyramid geometry. This due to one d_6-DMSO molecule coordinated to the tin atom in complex **4** resulting the complex exhibited five-coordinated tin atom in solution state.

The *in vitro* antibacterial screening activity of parent acid and complexes **1-4** are given in Table 1. Inhibition zones with a diameter less than 10 mm are considered as weak; larger than 10 mm but less than 16 mm are considered as moderate and finally larger than 16 mm and above are active (Chohan *et al*., 2006). Complex **1** showed a significant result against all the tested bacterial strains even though the activities obtained were from weak to moderate activity. Meanwhile, complexes **2-4** were found to be significantly active against gram-positive bacterial strains. Against *Bacillus subtillis* and *Staphylococcus aureus* at 1.0 mg mL^{-1}, the inhibition zones obtained for complex **4** were 18 and 19 mm respectively indicating that the *in vitro* antibacterial activity was in the active mode. Moreover, the inhibition zone diameters of complexes **1-3** in the range of 9-13 mm indicated that their activities were weak. Hence, complex **4** was more active compared to diorganotin(IV) complexes derivatives. In this study, the tin atom moiety of complex **4** is five-coordinated and exists in trans-R_3SnO_2 geometry in solution form; hence causing it's activity to be greater compared to complexes **1-3** (Danish *et al*., 1995; Baul *et al*., 2002). Although complex **4** showed significant *in vitro* antibacterial activity against gram-positive bacterial strains but the value obtained was lower compared to the reference drugs.

CONCLUSION

Complexes **1-4** have been successfully synthesized. The structural as well as the coordination number of tin moieties of complexes **1-4** have been successfully characterized quantitatively and qualitatively. Based on the *in vitro* antibacterial screening activity, complex **4** showed significant activity on *Bacillus subtilis* and *Staphylococcus aureus* compared to complexes **1-3** but lower compared to reference drugs.

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