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Synthesis, characterisation and antimicrobial studies of organotin(IV) complexes with 1,10-phenanthroline derivatives

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ABSTRACT

The synthesis of several diorganotin(IV) dicarboxylate compounds, including acetates and nicotinates as well as diorganotin(IV) dichloride complexes of the ligands phen, dione and dppz were undertaken. Several difficulties in either the syntheses or complexation reactions with the organic ligands were encountered. The diorganotin(IV) dichloride complexes of the ligands (R_2SnCl_2·L where R = Me, n-Bu or Ph and L = phen, dione or dppz) were tested against *Escherichia coli*, *Staphylococcus aureus* and *Pseudomonas aeruginosa*. The dibutyltin(IV) derivatives exhibited the broadest range of activity in comparison to the dimethyltin(IV) or diphenyltin(IV) derivatives. The addition of the nicotinate group did not promote activity against any of the bacteria. Furthermore, only in the case of Ph_2SnCl_2·dione was there improved activity compared to the organic ligand itself.

1. Introduction

The development of new therapeutic agents is paramount in today's society. The role of metal-based drugs in this regard has been understated, with questions being asked regarding the toxicity issues of such compounds. To date, the platinum-based compounds, for example, are among the few metal-based drugs which are available for cancer treatment [1]. However, it should be noted that platinum-based drugs are not effective against all forms of cancer. Therefore, there is an urgent need to develop new metal-based drug therapies against a wide range of diseases.

The investigation of the cytotoxicity/anti-tumour activities of organotin(IV) compounds remains an important area of research [2–4]. The activity of organotin(IV) compounds depends upon the number and nature of the organo group linked to the tin ion as well as on the anionic ligand. Organotin(IV) carboxylates are being extensively studied because of their biological activities, particularly their anti-tumour and anti-cancer activities [5–11]. A significant amount of the work carried out on these organotin(IV) compounds was in relation to their antibacterial activity against a wide range of both Gram-negative and Gram-positive bacteria.

The recent work of McCann and co-workers into the copper(II) and silver(I) complexes of 1,10-phenanthroline and 1,10-phenanthroline-5,6-dione have shown that they are active *in vitro* anti-cancer agents against selected cancer cell lines [12–19]. Our interest in the area of therapeutic agents, especially metal-based drugs, is fuelled by the search for new effective medicines for human health, particularly in the areas of cancer therapy and antimicrobials. To the best of our knowledge, the synthesis and biological activity of 1,10-phenanthroline derivatives of simple organotin(IV) chlorides and acetates against *Escherichia coli*, *Staphylococcus aureus* and *Pseudomonas aeruginosa* has not been reported. Herein, as a part of our ongoing research projects, we report the synthesis, characterisation and biological activities of some diorganotin(IV) chlorides and acetates and their 1,10-phenanthroline derivatives.

2. Experimental

2.1. Methods and materials

^1H and ^{13}C NMR (δ ppm; J Hz) spectra were recorded on a Bruker Avance 300 MHz NMR spectrometer using either saturated $CDCl_3$ or d_6-DMSO solutions with Me_4Si reference with resolutions of 0.18 Hz and 0.01 ppm, respectively. Infrared spectra (cm^{-1}) were recorded as KBr discs using a Perkin Elmer System 2000 FT-IR spectrometer. Melting point analyses were carried out using a Stewart Scientific SMP 1 melting point apparatus and are uncorrected. Microanalyses were carried out at the Microanalytical Laboratory of the National University of Ireland Maynooth. Standard Schlenk techniques were used throughout. Starting materials were commercially obtained and used without further purification. The synthesis of dione [20,21] and dppz [22,23] have been described previously, as has that for Me_2SnCl_2·phen, [24] n-Bu_2SnCl_2·phen

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[25] and Ph_2SnCl_2·phen [26]. ^{1}H NMR data for phen, dione and ddpz are included for comparison purposes.

2.2. Synthesis of ligands

2.2.1. 1,10-Phenanthroline (phen)

^{1}H NMR (300 MHz, d_6-DMSO): 9.10 (2H, dd, *J* = 4.4, 1.8 Hz), 8.49 (2H, dd, *J* = 8.0, 1.8 Hz), 7.99 (2H, s), 7.77 (2H, dd, *J* = 8.0, 4.4 Hz); ^{1}H NMR (300 MHz, $CDCl_3$): 9.17 (2H, d, *J* = 4.3 Hz), 8.22 (2H, d, *J* = 8.0 Hz), 7.76 (2H, s), 7.60 (2H, dd, *J* = 8.0, 4.3 Hz); ^{1}H NMR (300 MHz, d_6-DMSO, 70 °C): 9.06 (2H, dd, *J* = 4.3, 1.7 Hz), 8.37 (2H, dd, *J* = 8.1, 1.7 Hz), 7.86 (2H, s), 7.69 (2H, dd, *J* = 8.1, 4.3 Hz); ^{13}C NMR (75 MHz, d_6-DMSO, 70 °C): 149.8, 145.4, 136.1, 128.4, 126.5, 123.2.

2.2.2. 1,10-Phenanthroline-5,6-dione (dione) [20,21]

^{1}H NMR (300 MHz, d_6-DMSO): 8.98 (2H, dd, *J* = 4.7, 1.7 Hz), 8.39 (2H, dd, *J* = 7.8, 1.7 Hz), 7.68 (2H, dd, *J* = 7.8, 4.7 Hz); ^{1}H NMR (300 MHz, $CDCl_3$): 9.10 (2H, dd, *J* = 4.7, 1.8 Hz), 8.49 (2H, dd, *J* = 7.8, 1.8 Hz), 7.57 (2H, dd, *J* = 7.8, 4.7 Hz).

2.2.3. Dipyridophenazine (dppz) [22,23]

^{1}H NMR (300 MHz, d_6-DMSO): 9.49 (2H, dd, *J* = 8.1, 1.8 Hz), 9.20 (2H, dd, *J* = 4.4, 1.8 Hz), 8.36 (2H, dd, *J* = 6.5, 3.4 Hz), 8.04 (2H, dd, *J* = 6.5, 3.4 Hz), 7.92 (2H, dd, *J* = 8.1, 4.4 Hz); ^{1}H NMR (300 MHz, $CDCl_3$): 9.64 (2H, dd, *J* = 8.1, 1.7 Hz), 9.26 (2H, dd, *J* = 4.5, 1.7 Hz), 8.35 (2H, dd, *J* = 6.5, 3.4 Hz), 7.92 (2H, dd, *J* = 6.5, 3.4 Hz), 7.80 (2H, dd, *J* = 8.1, 4.5 Hz); ^{1}H NMR (300 MHz, d_6-DMSO, 80 °C): 9.41 (2H, dd, *J* = 8.1, 1.7 Hz), 9.13 (2H, d, *J* = 4.3 Hz), 8.27 (2H, dd, *J* = 6.5, 3.4 Hz), 7.98 (2H, dd, *J* = 6.5, 3.4 Hz), 7.85 (2H, dd, *J* = 8.1, 4.3 Hz). ^{13}C NMR (75 MHz, d_6-DMSO, 80 °C): 152.1, 147.7, 141.6, 140.5, 132.9, 131.0, 128.9, 126.7, 124.3; ^{1}H NMR (300 MHz, d_6-DMSO, 95 °C): 9.45 (2H, dd, *J* = 8.1, 1.7 Hz), 9.15 (2H, br s), 8.30 (2H, dd, *J* = 6.5, 3.5 Hz), 7.99 (2H, dd, *J* = 6.5, 3.5 Hz), 7.87 (2H, dd, *J* = 8.1, 4.4 Hz). ^{13}C NMR (75 MHz, d_6-DMSO, 95 °C): 161.6, 151.9, 141.6, 140.4, 132.8, 130.9, 128.8, 126.7, 124.1.

2.3. Synthesis of organotin(IV) acetates

2.3.1. General synthesis of $R_2Sn(O_2CMe)Cl$, R = Me or n-Bu

The appropriate diorganotin(IV) dichloride (4.5 mmol) and acetic acid (9.1 mmol) were dissolved in toluene (25 mL). Triethylamine (10 mmol) was added slowly and the reaction mixture was heated to reflux for 3 h under nitrogen. On cooling, a white solid precititated, which was removed by celite filtration and the filtrate collected. Solvent was removed under reduced pressure to yield the desired product as a white solid.

$Me_2Sn(O_2CMe)Cl$ [27]: Yield: 0.80 g, 73%. m.p. >300 °C. ^{1}H NMR (300 MHz, $CDCl_3$): 1.93 (3H, s), 0.78 (3H, s, $^2J(^{119/117}Sn, ^1H)$ = 92.7/82.2 Hz), 0.75 (3H, s, $^2J(^{119/117}Sn, ^1H)$ = 139.8/126.6 Hz).

n-$Bu_2Sn(O_2CMe)Cl$: Yield: 1.30 g, 88%. m.p. 36–39 °C. IR (solid, cm^{-1}): 2958 (s), 2928 (s), 2872 (s), 1637 (s), 1571 (s), 1428 (s), 1376 (s), 1312 (s), 1012(m), 737 (m). ^{1}H NMR (300 MHz, $CDCl_3$): 1.96 (3H, s), 1.64 (4H, m) 1.35 (8H, m), 0.91 (6H, m). ^{13}C NMR (75 MHz, $CDCl_3$): 177.2 (*C*=O), 27.5 (CH_2), 27.2 (CH_2), 26.9 (CH_2), 26.7 (CH_2), 22.9(O_2CCH_3), 13.5 (CH_3). *Anal. Calc.* for $C_{10}H_{21}ClO_2Sn·1/4(C_6H_5CH_3)$: C, 40.27; H, 6.81. Found: C, 39.28; H, 6.84%.

2.3.2. Synthesis of $Ph_2Sn(O_2CMe)Cl$

Diphenyltin(IV) dichloride (4.5 mmol) and acetic acid (9.1 mmol) were dissolved in benzene (25 mL). Potassium carbonate (10 mmol) was added and the reaction mixture refluxed overnight under nitrogen. The reaction mixture was allowed to cool and was filtered through celite. The filtrate was collected and the solvent removed under reduced pressure.

$Ph_2Sn(O_2CMe)Cl$: Yield: 1.29 g, 79%. m.p. >300 °C. IR (solid, cm^{-1}): 3429 (m), 3044 (m), 1551 (s), 1480 (m), 1429 (s), 1076 (m), 728 (s), 696 (s), 443 (m). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.68 (m), 7.43 (m), 2.15 (s). ^{13}C NMR (75 MHz, $CDCl_3$): 178.5 (*C*=O), 136.8 (phenyl *C*H), 129.9 (phenyl *C*H), 128.8 (phenyl *C*H), the quaternary phenyl carbon is believed to be under of these peaks, 20.7 (O_2CCH_3). *Anal. Calc.* for $C_{14}H_{13}ClO_2Sn$: C, 45.76; H, 3.57. Found: C, 45.08; H, 3.24%.

2.4. Synthesis of organotin(IV) nicotinates

2.4.1. General synthesis of $R_2Sn(nicotinate)_2$, R = Me, n-Bu or Ph

The appropriate diorganotin(IV) oxide (1.2 mmol) and nicotinic acid (2.4 mmol) were dissolved in toluene (25 mL). The reaction mixture was then heated to reflux for 2 h under nitrogen. On cooling, the solvent was removed under reduced pressure to yield a white solid. This was then washed with cold methanol and collected by filtration to give the desired product.

$Me_2Sn(nicotinate)_2$: Yield: 0.36 g, 76%. m.p. dec. (>200 °C). IR (solid, cm^{-1}): 3422 (w), 3063 (w), 1605 (s), 1593 (s), 1554 (s), 1441 (sh), 1417 (s), 1399 (s), 1195 (w), 867 (m), 712 (m). ^{1}H NMR (300 MHz, d_6-DMSO): 9.05 (2H, s), 8.71 (2H, d, *J* = 4.7 Hz), 8.24 (2H, dt, *J* = 7.8, 1.9 Hz), 7.78 (2H, dd, *J* = 7.8, 4.7 Hz), 0.94 (6H, s, $^2J(^{119}Sn, ^1H$ = 85.0 Hz). ^{13}C NMR (75 MHz, d_6-DMSO): 170.2 (*C*=O), 152.4 (pyridine *C*H), 150.3 (pyridine *C*H), 136.9 (pyridine *C*H), 128.4 (pyridine *C*, $^1J(^{119}Sn, ^{13}C)$ = 51.8 Hz), 123.5 (pyridine *C*H), 11.4 (CH_3). *Anal. Calc.* for $C_{14}H_{14}N_2O_4Sn$: C, 42.79; H, 3.59; N, 7.13. Found: C, 42.38; H, 3.21; N, 7.32%.

n-$Bu_2Sn(nicotinate)_2$: Yield: 0.41 g, 72%. m.p. 152–158 °C. IR (solid, cm^{-1}): 3426 (w), 2955 (s), 2925 (s), 2867 (w), 1609 (s), 1592 (s), 1434 (sh), 1409 (s), 1196 (m), 863 (m), 756 (m). ^{1}H NMR (300 MHz, $CDCl_3$): 9.07 (2H, s), 8.75 (2H, d, *J* = 4.2 Hz), 8.26 (2H, d, *J* = 7.8 Hz), 7.52 (2H, dd, *J* = 7.8, 4.2 Hz) 1.58 (8H, m), 1.30 (4H, m), 0.81 (6H, t, *J* = 7.3 Hz). ^{13}C NMR (75 MHz, d_6-DMSO): 170.9 (*C*=O), 152.6 (pyridine *C*H), 150.3 (pyridine *C*H), 136.9 (pyridine *C*H), 127.9 (pyridine *C*), 123.6 (pyridine *C*H), 29.8 (CH_2), 26.8 (CH_2, $^1J(^{119}Sn, ^{13}C)$ = 40.5 Hz), 25.6 (CH_2), 13.5 (CH_3). *Anal. Calc.* for $C_{20}H_{26}N_2O_4Sn·H_2O$: C, 48.51; H, 5.70; N, 5.66. Found: C, 49.11; H, 5.52; N, 5.50%.

$Ph_2Sn(nicotinate)_2$: Yield: 0.45 g, 73%. m.p. >300 °C. IR (solid, cm^{-1}): 3422 (m), 3076 (m), 1608 (s), 1592 (s), 1541 (s), 1440 (s), 1412 (s), 1195 (m), 871 (m), 695 (m). ^{1}H NMR (300 MHz, d_6-DMSO): 9.11 (2H, s), 8.77 (2H, d, *J* = 4.8 Hz), 8.31 (2H, d, *J* = 8.4 Hz), 7.80 (4H, d, *J* = 8.5 Hz), 7.52 (2H, dd, *J* = 8.4, 4.8 Hz), 7.34 (6H, m). ^{13}C NMR (75 MHz, d_6-DMSO): *169.3 (*C*=O), 153.1 (pyridine *C*H), 150.4 (pyridine *C*H), *148.6 (phenyl *C*), 137.1 (pyridine *C*H), 134.0 (phenyl *C*H), 128.7 (phenyl *C*H), 128.1 (phenyl *C*H), 127.0 (pyridine *C*), 123.7 (pyridine *C*H). *Anal. Calc.* for $C_{24}H_{18}N_2O_4Sn$: C, 55.74; H, 3.51; N, 5.42. Found: C, 55.91; H, 3.49; N, 5.28%.

*The compound is not very soluble and as a result these signals are very weak.

2.5. Synthesis of phen derivatives of R_2SnCl_2 and $R_2Sn(nicotinate)_2$, R = Me, n-Bu or Ph

The appropriate diorganotin(IV) compound (10 mmol) and phen (10 mmol) were dissolved in ethanol (25 mL) and heated to reflux for 3 h. With the chloride derivatives a solid precipitated on cooling which was removed by filtration and dried, resulting in the desired product. With the $R_2Sn(nicotinate)_2$ (R = Me, n-Bu) derivatives, the resulting solution was cooled and the solvent was removed under pressure to give the desired product. In the case of the phenyl derivative, the resulting suspension was initially filtered to remove unreacted starting materials and the filtrate was then reduced under reduced pressure. The remaining solid was

washed with cold EtOH and the filtrate reduced under reduced pressure to give the desired product.

Me_2SnCl_2·phen (**1**) [24,28]: White solid. Yield: 1.68 g, 92%. m.p. dec. (>200 °C). (lit 264 °C [24,28]). ^{1}H NMR (300 MHz, d_6-DMSO): 9.32 (2H, dd, J = 4.6, 1.7 Hz), 8.74 (2H, dd, J = 8.1, 1.7 Hz), 8.16 (2H, s), 8.00 (2H, dd, J = 8.1, 4.6 Hz), 0.97 (6H, s, $^2J(^{119/117}Sn,^1H)$ = 114.5/109.5 Hz). ^{13}C NMR (75 MHz d_6-DMSO): 148.9 (phen *C*H) 142.4 (phen *C*), 138.2 (phen *C*H), 129.1 (phen *C*), 127.1 (phen *C*H), 124.4 (phen *C*H), 24.0 (*C*H$_3$). ^{1}H NMR (300 MHz, d_6-DMSO, 70 °C): 9.38 (2H, dd, J = 4.6, 1.6 Hz), 8.75 (2H, dd, J = 8.1, 1.6 Hz), 8.15 (2H, s), 8.02 (2H, dd, J = 8.1, 4.6, Hz), 0.99 (6H, s, $^2J(^{119/117}Sn, ^1H)$ = 113.1/108.0 Hz).

Me_2Sn(nicotinate)$_2$·phen (**2**): Pink solid. Yield: 1.99 g, 77%. m.p. 212–220 °C. IR (solid, cm^{-1}): 3431 (m), 3055 (w), 1645 (s), 1590 (s), 1428 (s), 1332 (s), 1027 (m), 846 (m), 756 (s). ^{1}H NMR (300 MHz, d_6-DMSO): 9.46 (2H, d, J = 4.7 Hz), 9.15 (2H, br s), 8.73 (4H, m), 8.30 (2H, d, J = 7.7 Hz), 8.15 (2H, s), 8.00 (2H, dd, J = 8.5, 4.7 Hz), 7.50 (2H, dd J = 7.7, 4.4 Hz), 0.92 (6H, s). ^{13}C NMR (75 MHz, d_6-DMSO): 170.3 (*C*═O), 152.1 (pyridine *C*H), 150.5 (pyridine *C*H), 149.5 (phen *C*H), 142.0 (phen *C*), 138.4 (phen *C*H), 136.9 (pyridine *C*H), 129.1 (pyridine *C*), 129.0 (phen *C*), 127.0 (phen *C*H), 124.5 (phen *C*H), 123.4 (pyridine *C*H), 14.5 (*C*H$_3$). *Anal. Calc.* for $C_{26}H_{22}N_4O_4Sn$: C, 54.48; H, 3.87; N, 9.77. Found: C, 54.62; H, 3.85; N, 9.66%.

n-Bu_2SnCl_2·phen (**3**) [29]: White solid. Yield: 2.12 g, 98%. m.p. 192–195 °C (lit 198–199 °C [29]). ^{1}H NMR (300 MHz, d_6-DMSO): 9.44 (2H, dd, J = 4.7, 1.4 Hz), 8.90 (2H, dd, J = 8.2, 1.4 Hz), 8.27 (2H, s), 8.16 (2H, dd, J = 8.2, 4.7 Hz), 1.39 (4H, m), 1.25 (4H, m), 0.99 (4H, m), 0.58 (6H, t, J = 7.3 Hz).

n-Bu_2Sn(nicotinate)$_2$·phen (**4**): Pink solid. Yield: 2.75 g, 93%. m.p. 121–127 °C. IR (solid, cm^{-1}): 3429 (m), 3047 (w), 2948 (s), 2925 (s), 2865 (m), 1648 (s), 1599 (s), 1588 (s), 1552 (m), 1426 (s), 1332 (s), 1143 (m), 848 (s), 424 (m). ^{1}H NMR (300 MHz, d_6-DMSO): 9.48 (2H, d, J = 4.3), 9.17 (2H, br s), 8.77 (2H, d, J = 7.5 Hz), 8.71 (2H, d, J = 4.8 Hz), 8.32 (2H, d, J = 7.7 Hz), 8.17, (2H, s), 8.04 (2H, m), 7.48 (2H, dd, J = 7.7, 4.8 Hz), 1.53 (4H, m), 1.29 (4H, br s), 1.02 (4H, m), 0.52 (6H, t, J = 8.7 Hz). ^{13}C NMR (75 MHz, d_6-DMSO): 170.3 (*C*═O), 152.0 (pyridine *C*H), 150.5 (pyridine *C*H), 149.8 (phen *C*H), 142.3 (phen *C*), 138.5 (phen *C*H), 136.9 (pyridine *C*H), 129.3 (phen *C*), 129.0 (pyridine *C*), 127.1 (phen *C*H), 124.6 (phen *C*H), 123.4 (pyridine *C*H), 31.9 (*C*H$_2$), 26.9 (*C*H$_2$), 25.4 (*C*H$_2$), 13.3 (*C*H$_2$). *Anal. Calc.* for $C_{32}H_{34}N_4O_4Sn{\cdot}2H_2O$: C, 55.43; H, 5.52; N, 8.08. Found: C, 55.08; H, 5.04; N, 7.85%.

Ph_2SnCl_2·phen (**5**) [30]: White solid. Yield: 2.19 g, 93%. m.p. dec. (>200 °C). (lit 235 °C with dec. [30]). ^{1}H NMR (300 MHz, d_6-DMSO): *9.50 (2H, app s), #9.06 (2H, d, J = 8.3 Hz), *8.74 (2H, app s), #8.54 (2H, d, J = 4.7 Hz), #8.43 (2H, br s), #8.25 (2H, d, J = 8.3 Hz), #8.18 (2H, m), *8.12 (2H, br s), *8.05 (2H, app br s), #7.92 (2H, d, J = 7.1 Hz), *7.72 (4H, d, J = 7.1 Hz), #7.49 (6H, m), *7.17 (6H, m). ^{1}H NMR (300 MHz, d_6-DMSO, 70 °C) δ 9.49 (2H, app br s) 8.73 (2H, app br s), 8.08 (4H, m), 7.75 (4H, app br s), 7.17 (6H, app br s). *: trans isomer. #: cis isomer.

Ph_2Sn(nicotinate)$_2$·phen (**6**): Peach solid. Yield: 0.35 g, 10%. m.p. dec. (>200 °C). IR (solid, cm^{-1}): 3432 (s), 3070 (w), 1709 (s), 1655 (s), 1596 (s), 1419 (s), 1324 (s), 1302 (s), 1033 (m), 748 (m). ^{1}H NMR (300 MHz, d_6-DMSO): 9.09 (app bs, 2H), 9.03 (bs, 2H), 8.71 (app bs, 2H), 8.49 (app bs, 2H), 8.24 (app bs, 2H), 7.96 (app bs, 3H), 7.82 (d, J = 6.1 Hz, 2H), 7.78 (app bs, 2H), 7.51 (m, 2H), 7.41 (m, 6H), 7.12 (app bs, 1H). ^{13}C NMR (75 MHz, d_6-DMSO): 167.2 (*C*═O) 153.1 (pyridine *C*H), 150.5 (pyridine *C*H), 150.2 (phen *C*H), 145.5 (phenyl *C*), 143.4 (phen *C*), 137.5 (pyridine *C*H), 136.8 (phen *C*H), 136.5 (phenyl *C*H), 129.3 (phenyl *C*H), 128.8 (phen *C*), 128.7 (phenyl *C*H), 128.3, (pyridine *C*), 127.1 (phen *C*H), 124.2 (pyridine *C*H), 123.9 (phen *C*H). *Anal Calc.* for $C_{36}H_{26}N_4O_4Sn{\cdot}H_2O$: C, 60.44; H, 3.95; N, 7.83. Found: C, 60.44; H, 3.74; N, 8.17%.

2.6. Synthesis of dione derivatives of R_2SnCl_2 and R_2Sn(nicotinate)$_2$, R = Me, n-Bu or Ph

A similar procedure to that employed in Section 2.5 was used. No dione complexes of the R_2Sn(nicotinate)$_2$ compounds were formed.

Me_2SnCl_2·dione (**7**): Yellow solid. Yield: 1.88 g, 97%. m.p. dec. (>200 °C). IR (solid, cm^{-1}): 3442 (s), 3071 (w), 1701 (s), 1573 (s), 1429 (s), 1301 (m), 731 (m). ^{1}H NMR (300 MHz, d_6-DMSO): 9.00 (2H, dd, J = 4.7, 1.8 Hz), 8.41 (2H, dd, J = 7.8, 1.8 Hz), 7.69 (2H, dd, J = 7.8, 4.7 Hz), 1.03 (6H, s, $^2J(^{119/117}Sn, ^1H)$ = 113.7/108.9 Hz). ^{13}C NMR (75 MHz d_6-DMSO): 177.6 (*C*═O), 154.2 (dione *C*H), 152.0 (dione *C*), 135.8 (dione *C*H), 129.1 (dione *C*), 125.3 (dione *C*H), 22.9 (*C*H$_3$, $^1J(^{119/117}Sn, ^{13}C)$ = 1014.0/968.3 Hz). *Anal. Calc.* for $C_{14}H_{12}Cl_2N_2O_2Sn{\cdot}EtOH$: C, 40.38; H, 3.81; N, 5.89. Found: C, 41.24; H, 3.01; N, 6.79%.

n-Bu_2SnCl_2·dione (**8**): Yellow solid. Yield: 2.32 g, 99%. m.p. dec. (>200 °C). IR (solid, cm^{-1}): 3421 (s), 3076 (w), 2955 (m), 2862 (m), 1620 (w), 1584 (s), 1436 (m), 1376 (s), 1069 (s), 1042 (s), 720 (m). *Anal. Calc.* for $C_{20}H_{24}Cl_2N_2O_2Sn{\cdot}H_2O$: C, 45.15; H, 4.93; N, 5.27. Found: C, 45.07; H, 4.69; N, 5.46%.

Ph_2SnCl_2·dione (**9**): Yellow solid. Yield: 2.42 g, 97%. m.p. dec. (>200 °C). IR (solid, cm^{-1}): 3444 (s), 3058 (w), 1694 (m), 1574 (m), 1430 (m), 1351 (w), 727 (m), 700 (m). ^{1}H NMR (300 MHz, d_6-DMSO): 9.00 (2H, dd, J = 4.7, 1.6 Hz), 8.40 (2H, dd, J = 7.8, 1.6 Hz), 7.90 (4H, d, J = 7.0 Hz), 7.68 (2H, dd, J = 7.8, 4.7 Hz), 7.35 (6H, m). ^{13}C NMR (75 MHz, d_6-DMSO): 177.3 (*C*═O), 155.1 (phenyl *C*), 153.9 (dione *C*H), 151.6 (dione *C*), 136.0 (dione *C*H), 134.5 (Phenyl *C*H, $^2J(^{119}Sn, ^{13}C)$ = 69.8 Hz), 129.3 (dione *C*), 127.8 (phenyl *C*H), 127.3 (phenyl *C*H), 125.3 (dione *C*H). *Anal. Calc.* for $C_{24}H_{16}Cl_2N_2O_2Sn$: C, 52.03; H, 2.91; N, 5.06. Found: C, 52.29; H, 3.34; N, 5.19%.

2.7. Synthesis of dppz derivatives of R_2SnCl_2 and R_2Sn(nicotinate)$_2$, R = Me, n-Bu or Ph

A similar procedure to that employed in Section 2.5 was used.

Me_2SnCl_2·dppz (**10**): Yellow solid. Yield: 2.14 g, 94%. m.p. 269–272 °C. IR (solid, cm^{-1}): 3434 (s), 3066 (w), 1632 (m), 1571 (m), 1494 (s), 1420 (s), 1359 (s), 1075 (s), 772 (s), 734 (s). ^{1}H NMR (300 MHz, d_6-DMSO): 9.42 (2H, dd, J = 8.1, 1.6 Hz), 9.20 (2H, dd, J = 4.4, 1.6 Hz), 8.29 (2H, dd, J = 6.5, 3.4 Hz), 8.01 (2H, dd, J = 6.5, 3.4 Hz), 7.91 (2H, dd, J = 8.1, 4.4 Hz), 1.03 (6H, s). ^{1}H NMR (300 MHz, d_6-DMSO, 80 °C): 9.46 (2H, d, J = 8.0 Hz), 9.21 (2H, app br s), 8.30 (2H, dd, J = 6.5, 3.5 Hz), 7.99 (2H, dd, J = 6.5, 3.5 Hz), 7.91 (2H, dd, J = 8.0, 4.4 Hz), 1.08 (6H, s, $^2J(^{119/117}Sn, ^1H)$ = 108.3/103.8 Hz). ^{13}C NMR (75 MHz, d_6-DMSO, 80 °C): 152.3 (dppz *C*H), 147.8 (dppz *C*), 142.3 (dppz *C*), 141.0 (dppz *C*), 133.8 (dppz *C*H), 131.6 (dppz *C*H), 129.6 (dppz *C*H), 127.6 (dppz *C*), 125.0 (dppz *C*H), 21.4 (*C*H$_3$). *Anal. Calc.* for $C_{20}H_{16}Cl_2N_4Sn$: C, 47.85; H, 3.21; 11.16. Found: C, 47.27; H, 3.04; N, 10.74%.

Me_2Sn(nicotinate)$_2$·dppz (**11**): Yellow solid. Yield: 2.97 g, 98%. m.p. dec. (>200 °C). IR (solid, cm^{-1}): 3427 (m), 3063 (w), 1605 (s), 1592 (s), 1554 (m), 1486 (m), 1415 (s), 1400 (s), 1362 (m), 1336 (w), 1073 (w), 741 (m). ^{1}H NMR (300 MHz, d_6-DMSO): 9.55 (2H, d, J = 7.9 Hz), 9.27 (2H, d, J = 4.7 Hz), 9.07 (2H, d, J = 1.5 Hz), 8.74 (2H, dd, J = 4.9, 1.9 Hz), 8.39 (2H, dd, J = 6.6, 3.5 Hz), 8.26 (2H, app dt, J = 7.8, 1.9 Hz), 8.07 (2H, dd, J = 6.6, 3.5 Hz), 7.98 (2H, dd, J = 7.9, 4.7 Hz), 7.50 (2H, dd, J = 7.8, 4.9 Hz), 0.95 (6H, s). ^{1}H NMR (300 MHz, d_6-DMSO, 80 °C): 9.47 (2H, d, J = 7.9 Hz), 9.22 (2H, app br s), 9.07 (2H, bs), 8.70 (2H, dd, J = 4.8, 1.5 Hz), 8.29 (2H, dd, J = 6.5, 3.4 Hz), 8.25 (2H, d, J = 7.8 Hz), 7.99 (2H, dd, J = 6.5, 3.4 Hz), 7.90 (2H, dd, J = 7.9, 4.3 Hz), 7.46 (2H, dd, J = 7.8, 4.8 Hz), 1.02 (6H, s, $^2J(^{119/117}Sn, ^1H)$ = 101.7/97.5 Hz). ^{13}C NMR (75 MHz, d_6-DMSO, 80 °C): 168.6 (*C*═O), 151.8 (pyridine *C*H), 151.5 (dppz *C*H), 149.9 (pyridine *C*H), 147.0 (dppz *C*), 141.3 (dppz *C*), 140.1

(dppz *C*), 136.2 (pyridine *C*H), 132.7 (dppz *C*H), 130.6 (dppz *C*H), 128.6 (dppz *C*H), 128.2 (pyridine *C*), 126.5 (*C*4'), 123.9 (dppz *C*H), 122.8 (pyridine *C*H), 11.8 (CH_3). *Anal. Calc.* for $C_{32}H_{24}N_6O_4Sn$: C, 56.92; H, 3.58; N, 12.45. Found: C, 56.49; H, 3.57; N, 12.53%.

n-Bu_2SnCl_2·dppz (**12**): Salmon pink solid. Yield: 2.54 g, 96%. m.p. 197–202 °C. IR (solid, cm^{-1}): 3431 (s), 2954 (m), 2916 (m), 2858 (w), 1630 (m), 1493 (s), 1076 (s), 736 (s). ^1H NMR (300 MHz, $CDCl_3$): 9.93 (2H, dd, *J* = 8.2, 1.5 Hz), 9.83 (2H, dd, *J* = 4.9, 1.5 Hz), 8.41 (2H, dd, *J* = 6.6, 3.4 Hz), 8.14 (2H, dd, *J* = 8.2, 4.9 Hz), 8.03 (2H, dd, *J* = 6.6, 3.4 Hz), 1.65 (4H, m), 1.41 (4H, m), 1.07 (4H, m), 0.62 (6H, t, *J* = 6.9 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): 150.5 (dppz *C*H), 142.9 (dppz *C*), 142.7 (dppz *C*), 139.3 (dppz *C*), 136.9 (dppz *C*H), 132.1 (dppz *C*H), 129.7 (dppz *C*H), 129.3 (dppz *C*), 126.3 (dppz *C*H), 41.9 (CH_2), 28.2 (CH_2), 25.9 (CH_2), 13.4 (CH_3). *Anal. Calc.* for $C_{26}H_{28}Cl_2N_4Sn$: C, 53.28; H, 4.81; N, 9.56. Found: C, 52.89; H, 5.22; N, 9.47%.

n-Bu_2Sn(nicotinate)$_2$·dppz (**13**): Yellow solid. Yield: 3.07 g, 90%. m.p. dec. (>200 °C). IR (solid, cm^{-1}): 3425 (s), 2955 (s), 2924 (s), 2868 (m), 1627 (sh), 1606 (s), 1593 (s), 1553 (m), 1407 (s), 1361 (m), 1337 (m), 1074 (w), 740 (m). ^1H NMR (300 MHz, d_6-DMSO): 9.40 (2H, d, *J* = 7.8 Hz), 9.31 (2H, app bs), 9.11 (2H, br s), 8.73 (2H, d, *J* = 5.0 Hz), 8.28 (2H, d, *J* = 7.8 Hz), 8.23 (2H, dd, *J* = 6.5, 3.4 Hz), 7.98 (4H, m), 7.51 (2H, dd, *J* = 7.8, 5.0 Hz), 1.56 (8H, m), 1.21 (4H, m), 0.72 (6H, t, *J* = 7.2 Hz). ^1H NMR (300 MHz, d_6-DMSO, 95 °C): 9.38 (2H, dd, *J* = 7.9, 1.7 Hz), 9.14 (2H, d, *J* = 3.9 Hz), 9.03 (2H, d, *J* = 1.7 Hz), 8.68 (2H, dd, *J* = 4.9, 1.7 Hz), 8.22 (4H, m), 7.94 (2H, dd, *J* = 6.6, 3.4 Hz), 7.84 (2H, dd, *J* = 7.9, 3.9 Hz), 7.46 (2H, dd, *J* = 8.0, 4.9 Hz), 1.66 (4H, m), 1.49 (4H, m), 1.30 (4H, m), 0.80 (6H, t, *J* = 7.3 Hz). ^{13}C NMR (75 MHz, d_6-DMSO, 95 °C): 168.4 (*C*=O), 152.2 (pyridine *C*H), 151.9 (dppz *C*H), 150.0 (pyridine *C*H), 147.3 (dppz *C*), 141.6 (dppz *C*), 140.3 (dppz *C*), 136.5 (pyridine *C*H), 132.9 (dppz *C*H), 130.8 (dppz *C*H), 128.8 (dppz *C*H), 128.3 (pyridine *C*), 126.7 (dppz *C*), 124.2 (dppz *C*H), 123.2 (pyridine *C*H), 26.4 (CH_2), 25.6 (CH_2), 12.9 (CH_3). *Anal. Calc.* for $C_{38}H_{36}N_6O_4Sn$: C, 60.10; H, 4.78; N, 11.07. Found: C, 60.91; H, 4.90; N, 10.40%.

Ph_2SnCl_2·dppz (**14**): Light yellow solid. Yield: 2.76 g, 98%. m.p. 272–282 °C. IR (solid, cm^{-1}): 3443 (s), 3067 (m), 1627 (m), 1574 (m), 1494 (s), 1420 (s), 1361 (s), 1078 (s), 735 (s). ^1H NMR (300 MHz, d_6-DMSO): 9.44 (2H, dd, *J* = 8.1, 1.7 Hz), 9.26 (2H, app br s), 8.28 (2H, dd, *J* = 6.5, 3.4 Hz), 8.00 (2H, dd, *J* = 6.5, 3.4 Hz), 7.95 (2H, dd, *J* = 8.1, 4.6 Hz), 7.89 (4H, d, *J* = 6.7 Hz), 7.29 (6H, m). ^{13}C NMR (75 MHz, d_6-DMSO): *155.1 (phenyl *C*), 151.9 (dppz *C*H), *146.9 (dppz *C*), 141.6 (dppz *C*), 140.4 (dppz *C*), 134.5 (phenyl *C*H), 133.5 (dppz *C*H), 131.3 (dppz *C*H), 129.1 (dppz *C*H), 127.7 (phenyl *C*H), 127.3 (phenyl *C*H), 127.1 (dppz *C*), 124.8 (dppz *C*H). *Anal. Calc.* for $C_{30}H_{20}Cl_2N_4Sn$: C, 57.55; H, 3.22; N, 8.95. Found: C, 57.09; H, 3.23; N, 9.22%.

*The compound is not very soluble and as a result these signals are very weak.

2.8. In vitro antimicrobial screening

2.8.1. Materials and methods

Nutrient Broth was obtained from Oxoid, England and made up according to the manufacturer's instructions (13 g in 1 L deionised water). OD_{600nm} values were determined using a spectrophotometer (Biophotometer, Eppendorf). Optical density was read using a microplate reader (Bio-Tek. Synergy HT Spectrophotometer). *S. aureus* (a clinical isolate from a urinary tract infection, St. James Hospital, Dublin), *E. coli* (a clinical isolate from a gastro-intestinal tract infection, St. James Hospital, Dublin) and *P. aeruginosa* (American Type Culture Collection (ATCC) 10145) were used in this study. All bacteria were grown on nutrient broth agar plates at 37 °C and maintained at 4 °C for short term storage. Cultures were routinely sub-cultured every 4–6 weeks. All assays were run in triplicate.

2.8.2. In vitro bacterial susceptibility testing

Fresh solutions (200 μg/mL) of complexes were prepared with distilled water and DMSO (less than 1%) immediately prior to testing. Complexes with low solubility were tested as fine suspensions. Bacteria cultures were grown in nutrient broth at 37 °C and 200 rpm overnight. The cells were diluted to give an OD_{600} = 0.1.

Nutrient broth (100 μL) was added to each well of a 96-well flat-bottomed microtitre plate. An additional 100 μL was added to columns 1 and 2 of the plate. Serial dilutions (1:1) of the test complex were made from column 4–12 giving a test concentration range of 100–0.39 μg/mL. 100 μL of the desired bacteria cell suspension to be tested was added to columns 3–12. Column 3 served as the negative control.

The plate was incubated for 24 h at 37 °C. The optical density was read at λ_{max} 540 nm and growth was then quantified as a percentage of the control. The minimum inhibitory concentration (MIC) values were then determined. The MIC_{80} and MIC_{50} (Minimum Inhibitory Concentration) of any given compound was taken to signify the concentration of compound that would inhibit the growth of that microorganism by 80% or 50%, respectively.

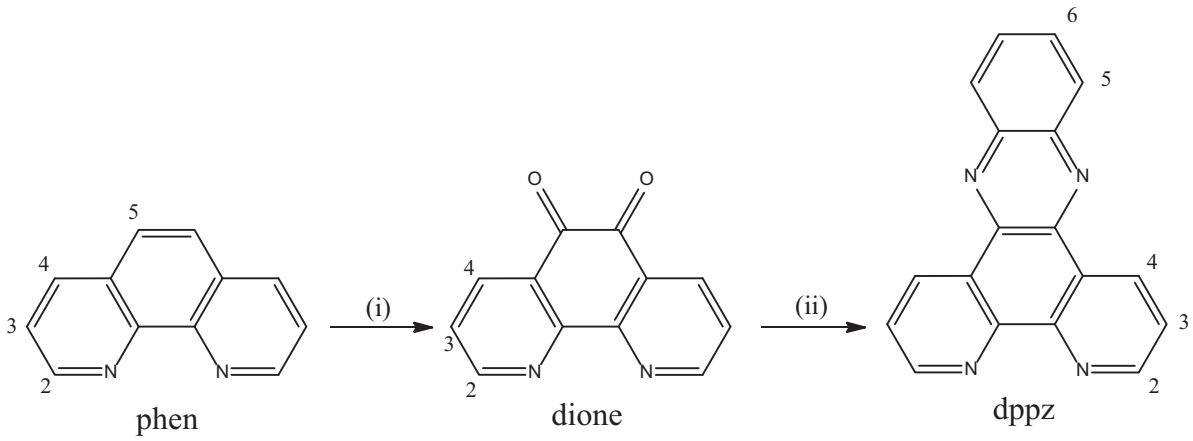
3. Results and discussion

3.1. Synthesis of ligands

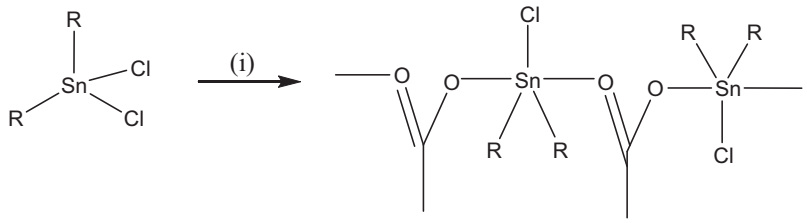
The 1,10-phenanthroline derivatives were chosen for two reasons: firstly, due to their ease of synthesis (see Scheme 1) and secondly, steric and electronic effects are varied between these ligands. 1,10-Phenanthroline (phen) was readily converted to 1,10-phenanthroline-5,6-dione (dione) which can be furthered reacted to give dipyridophenazine (dppz) [22,23]. The simplicity of all the ^1H NMR spectra of the 1,10-phenanthroline derivatives is due to the plane of symmetry in the molecules. The signal for H-5 at 7.99 ppm in phen disappeared in both the ^1H NMR spectra of dione and dppz. Two new signals appeared in the spectrum of dppz due to the H-5 and H-6 protons of the extra aromatic ring. The doublet for H-2 in the ^1H NMR spectra of phen, dione and dppz occurred at 9.10, 8.98 and 9.49 ppm respectively.

3.2. Synthesis of organotin compounds

The diorganotin(IV) chlorides were obtained commercially and used without further purification. The organotin(IV) monoacetate compounds ($R_2Sn(O_2Me)Cl$, R = Me, n-Bu or Ph) were synthesised from the reaction between the corresponding organotin(IV) dichloride with acetic acid in toluene with triethylamine as base (see Scheme 2). Their molecular structure has been elucidated by elemental analyses, ^1H and ^{13}C NMR and IR spectroscopies. Elemental analyses confirmed the presence of a single Cl in each molecule. The ^1H NMR spectra of the three organotin(IV) monoacetate compounds showed a distinct singlet for the acetate signal at 1.93, 1.95 and 2.15 ppm for $Me_2Sn(O_2Me)Cl$, n-$Bu_2Sn(O_2Me)Cl$ and $Ph_2Sn(O_2Me)Cl$, respectively, corresponding to the three protons of the acetate group in all cases. In the ^1H NMR spectrum of $Me_2Sn(O_2Me)Cl$, the $^2J(^{119/117}Sn,^1H)$ coupling constant of 139.8/126.6 Hz indicates six coordination in solution [31–33]. The IR spectra of the three organotin(IV) monoacetate compounds all contained a strong absorption at ca 1700 cm^{-1} corresponding to the ν(C=O) of the carboxyl group. The $\Delta\nu$ difference between $\nu_{asym}(COO)^-$ and $\nu_{sym}(COO)^-$ is important to find out the binding mode of the acetate moiety about the Sn atom. According to the literature, $\Delta\nu$ values greater than 250 cm^{-1} indicates a monodentate binding mode while a value less than 250 cm^{-1} shows a bidentate binding mode of the acetate moiety with the Sn atom. Furthermore, a $\Delta\nu$ value between 150 and 250 cm^{-1} indicates a bridging behaviour



Scheme 1. Reaction conditions: (i) HNO_3, H_2SO_4, KBr, Δ, 3 h; (ii) 1,2-diaminobenzene, methanol, 50 °C for 2 h, then reflux for 12 h. Numbering system for ^1H NMR also shown.



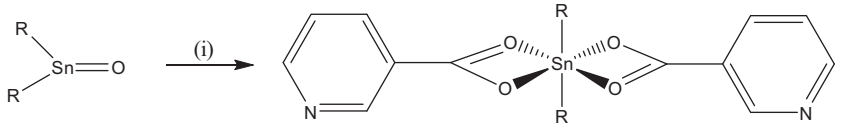
Scheme 2. Reaction conditions: (i) acetic acid, triethylamine, toluene, Δ, 3 h for R = Me, n-Bu, and acetic acid, potassium carbonate, benzene, Δ, 12 h for R = Ph.

[31,34–39]. In the present study, the Δv in the range 160–210 cm^{-1} suggests that compounds $Me_2Sn(O_2Me)Cl$, n-$Bu_2Sn(O_2Me)Cl$ and $Ph_2Sn(O_2Me)Cl$ exhibit a bridging behaviour in the solid state. The crystal structure of $Me_2Sn(O_2Me)Cl$ has been reported [27] and consists of Me_2ClSn units bridged by acetate ligands giving rise to polymeric chains. The Sn atom is in a distorted trigonal bipyramidal environment consisting of two axial O atoms with the equatorial positions occupied by the methyl groups and the chlorine atom.

The synthesis of the diorganotin dinicotinate compounds was carried out as shown in Scheme 3. In all cases, the starting organotin compound was the corresponding diorganotin oxide. In the ^1H NMR spectra of the diorganotin dinicotinate compounds, the absence of the carboxylic acid proton signal at 13.44 ppm was taken to indicate that the reactions had occurred. In the ^1H NMR spectrum of $Me_2Sn(nicotinate)_2$, the $^2J(^{119}Sn, ^1H)$ coupling constant of 85.0 Hz indicates six coordination in solution [32,33]. Furthermore, Lockhart et al. have shown that the coordination geometry about the tin atom results in trans organo groups [40]. The IR spectra of the diorganotin dinicotinate compounds all contained a strong absorption at ca 1600 cm^{-1} corresponding to the ν(C=O) of the carboxyl group. Furthermore, the shift in the C=O band in the IR spectra of the three diorganotin dinicotinate compounds from 1713 cm^{-1} in nicotinic acid to 1605, 1609 and 1608 cm^{-1} was also proof of the formation of the $Me_2Sn(nicotinate)_2$, n-$Bu_2Sn(nicotinate)_2$ and $Ph_2Sn(nicotinate)_2$ products. According to the literature, a Δv difference between $\nu_{asym}(COO)^-$ and $\nu_{sym}(COO)^-$ of a value less than 150 cm^{-1} is indictive of a chelate structure [31,34–39]. The values obtained for the three diorganotin dinicotinate compounds were less than 150 cm^{-1}, implying a chelate structure occurs in the solid state, as shown in Scheme 3. Elemental analysis confirmed, in all cases, the formation of the diorganotin dinicotinate compounds.

3.3. Complexation reactions

The synthesis of the organotin complexes of the 1,10-phenanthroline derivatives generally involved the heating of the two materials in ethanol at reflux temperature for 3 h. After cooling the solution, solids precipitated in most cases. However, no reaction was observed between any of the organotin(IV) monoacetate compounds ($R_2Sn(O_2Me)Cl$, R = Me, n-Bu or Ph) and any of the 1,10-phenanthroline derivatives. This is probably as a result of the organotin monoacetate compounds have achieved a six coordinate geometry in solution. If the 1,10-phenanthroline derivatives are to bind to the organotin compounds, then they must initially disrupt this bridging process, resulting in a seven-coordinate tin species, as outlined in Fig. 1. However, because the 1,10-phenanthroline derivatives are not only large molecules but also very rigid and planar in nature, we believe that they are unable to fit into the



Scheme 3. Reaction conditions: (i) nicotinic acid, toluene, Δ, 8 h; R = Me, n-Bu or Ph.

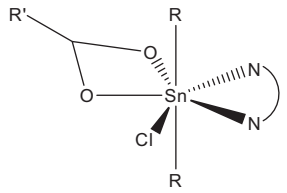


Fig. 1. Proposed seven coordinate organotin structure, where N∩N is the 1,10-phenanthroline derivative, R = Me, n-Bu or Ph and R′ = pyridine.

geometry constraint required by the proposed seven coordination on steric grounds.

Fourteen organotin(IV) complexes were prepared by the one-step reaction of the organotin(IV) dichlorides or the organotin(IV) dinicotinates with the corresponding 1,10-phenanthroline derivatives. In all cases, clear solutions were obtained, from which cream or pale yellow powders resulted on removal of some of the solvent. Elemental analyses indicated that the solids were 1:1 complexes between the organotin(IV) compounds and the 1,10-phenathroline derivatives. In some cases, some solvent molecules of crystallisation were also included. The ^{1}H NMR spectra of the eight R_2SnCl_2 compounds (R = Me, n-Bu or Ph) were obtained using d_6-DMSO as solvent, except for the case of n-Bu_2SnCl_2·dione which was insoluble and for the case of n-Bu_2SnCl_2·dppz which was soluble in $CDCl_3$. All attempts to obtain ^{119}Sn NMR spectra of the complexes obtained during this study always resulted in broad signals being obserrved, no matter what solvent was chosen or the number of scans used – this is despite the fact that clean ^{1}H and ^{13}C spectra were readily obtained on the same samples.

The X-ray structures of Me_2SnCl_2·phen (**1**) [24], n-Bu_2SnCl_2·phen (**3**) [41] and Ph_2SnCl_2·phen (**5**) [26] are known and show that the Sn atom sits in an octahedral geometry with the organo groups sitting in the axial positions. It is expected that the other 1,10-phenanthroline ligands will coordinate to Sn in the same manner (see Fig. 2). In the case of the phen ligand in this study, coordination of the ligand to the organotin(IV) dichloride is obvious with large shifts in the ^{1}H NMR signals associated with the phen ligand. ^{1}H NMR shifts are also observed in the cases of the dppz ligands, although these are much smaller in nature. The $^{2}J(^{119/117}Sn,^{1}H)$ values of reported phen and dppz complexes of Me_2SnCl_2 are similar to those observed in this study, suggesting a *trans*-orientation of the organo groups [26,42].

In the case of the dione ligand, the signals for the complexes are very similar to those of the starting dione ligand. It is strange that this should happen as the ligands are all 1,10-phenanthroline derivatives and therefore should chelate through the two nitrogen atoms. If the size of the ligand was an issue, then it would be expected that the dppz ligand would cause problems and not the dione ligand. However, the size of the ligand cannot really be an issue, as the binding site is remote from the rest of the molecule and is consistent amongst the series. A second explanation for the lack of interaction in all the cases of the dione ligand may be down to the fact that the dione ligand contains two potential binding sites, one through the two nitrogen atoms and the second through the two oxygen atoms (see Scheme 1). This dual binding of the ligand could be the reason for the lack of solubility of the n-Bu_2SnCl_2·dione (**8**) complex as a result of the possible polymeric nature of the 1:1 complex formed, through the formation of 8-coordinate tin atoms as a result of coordination to two organic groups, two chlorine atoms and the two nitrogen atoms and the two oxygen atoms of the ligand. Alternatively, it may just be that the dione ligand is a weakly binding ligand and only associates weakly in solution. When the solvent is removed at the end of the reaction, what we are left with is simply a mixture of the two starting materials rather than the formation of a new complex. The elemental analyses of the dione complexes all suggest the presence of a 1:1 complex but this could equally be a simple 1:1 mixture of the starting materials, which is why the ^{1}H NMR spectra of these "complexes" show no shift in the proton signals of the dione ligand.

The ^{1}H NMR spectra of the five $R_2Sn(nicotinate)_2$ compounds (R = Me, n-Bu or Ph) were also obtained using d_6-DMSO as solvent. Unlike Me_2SnCl_2·phen (**1**) [24], n-Bu_2SnCl_2·phen (**3**) [41] and Ph_2SnCl_2·phen (**1**) [26] where the X-ray structures are known, there is no X-ray structural data available for $R_2Sn(nicotinate)_2$·phen (R = Me, n-Bu or Ph) or any other 1,10-phenanthroline derivative. However, from the ^{1}H NMR data given in the experimental section, it is obvious that the 1,10-phenanthroline derivatives are binding to the tin atom as can be clearly seen from signal shifts. The IR spectra of the organotin(IV) dinicotinate complexes of the 1,10-phenanthroline derivatives all contained a strong absorption at ca 1600 cm^{-1} corresponding to the ν(C=O) of the carboxyl group. The $\Delta\nu[\nu_{asym}(COO) - \nu_{sym}(COO)]$ values for these complexes of >200 cm^{-1} suggested a monodentate chelating (bridging through one oxygen atom) coordination mode of the carboxyl group in these complexes [38,43]. This imples that the Sn(IV) centre in these complexes is coordinated by two C atoms from the two organic groups, two N atoms from the 1,10-phenanthroline derivative and two O atoms from separate nicotinate groups, forming an octahedral geometry about the Sn atom (see Fig. 3).

3.4. Antimicrobial activity

In order to study the bioactivity of all these organotin(IV) complexes, the starting materials and the organotin(IV) complexes were screened for their ability to inhibit the growth of the Gram-negative bacteria *E. coli* and *P. aeruginosa* and the Gram-positive bacterium *S. aureus*. The minimum inhibitory concentration (MIC) is the concentration of a complex (expressed as either a μM solution or a μg/mL solution) required to totally inhibit the growth of the microorganism at 37 °C. The MIC_{80} (Minimum Inhibitory Concentration) of any given compound was taken to signify the concentration of compound that would inhibit the growth of

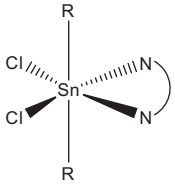


Fig. 2. Expected structure of 1:1 complex of organotin(IV) dichloride and 1,10-phenathroline derivatives, where R = Me, n-Bu or Ph; N-N = 1,10-phenathroline derivative.

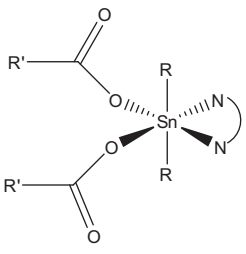


Fig. 3. Expected structure of 1:1 complex of organotin(IV) dinicotinate and 1,10-phenathroline derivatives, where R = Me, n-Bu or Ph; N-N = 1,10-phenathroline derivative; R′CO_2 = nicotinate group.

that microorganism by 80%. The results are summarised in Tables 1 and 2. Compounds, other than starting materials, that required more than a μM solution of the complex to show activity against all the bacteria are not included in the tables.

The only reagent to show good broad spectrum activity against all three bacteria was the dione ligand. This ligand has been previously shown by McCann and co-workers to be very active against several microbes, as well as the yeast *Candida Albicans* [12,15,16]. Furthermore, when they made silver(I) complexes with the dione ligand, they found that the activity against all the bacteria was increased.

Of the active compounds listed in Table 2, phen, Me_2SnCl_2·phen (**1**) and Ph_2SnCl_2·dppz (**14**) were inactive against *E. coli* and Me_2SnCl_2, Ph_2SnCl_2, Me_2SnO, Me_2SnCl_2·phen (**1**) and Ph_2Sn(nicotinate)$_2$ were inactive against *S. aureus*. The majority of complexes synthesised exhibited little or no activity against *P. aeruginosa*. However, of the active compounds, only Me_2SnCl_2·dione (**7**) and Ph_2SnCl_2·dione (**9**) exhibited good activity against *P. aeruginosa* with an MIC_{50} range of 22–29 and 23–34 μM, respectively. In both cases, the values were slightly greater than for the dione ligand on it's own, so it could be concluded that the complex was breaking up in solution before affecting the activity. However, if this was the case that the dione complexes were breaking up before entering the cell, then the value for n-Bu_2SnCl_2·dione (**8**) should also be very similar, which is not the case. *P. aeruginosa* produces a thick capsule which retards the entry of antibiotics [44]. It is possible that it is having the same action here and preventing the entry of the organotin complexes.

Most complexes demonstrated good to moderate activity against both *E. coli* and *S. aureus*. *S. aureus* is Gram-positive and the complexes may be directly interacting with the cell wall and disrupting its function. *E. coli* is a Gram-negative bacterium surrounded by a lipid bi-layer and it is this bi-layer which may be easily disrupted by the organotin(IV) complexes. Graphs 1–4 show the activity profiles for both the phen and dione families of compounds against both *E. coli* and *S. aureus*.

If we consider the cases of n-Bu_2SnCl_2·phen (**3**) and Ph_2SnCl_2·dione (**9**) and their respective activities against *S. aureus*, as shown in Graphs 1 and 3, there could be a synergistic effect occurring in each of these cases. The organotin compound n-Bu_2SnCl_2 is clearly active against *S. aureus* reaching a maximum at 25 μg/mL while the organic ligand phen has poor activity. The

Table 1
Antimicrobial activities as MIC_{80} range (μM and μg/mL).[a]

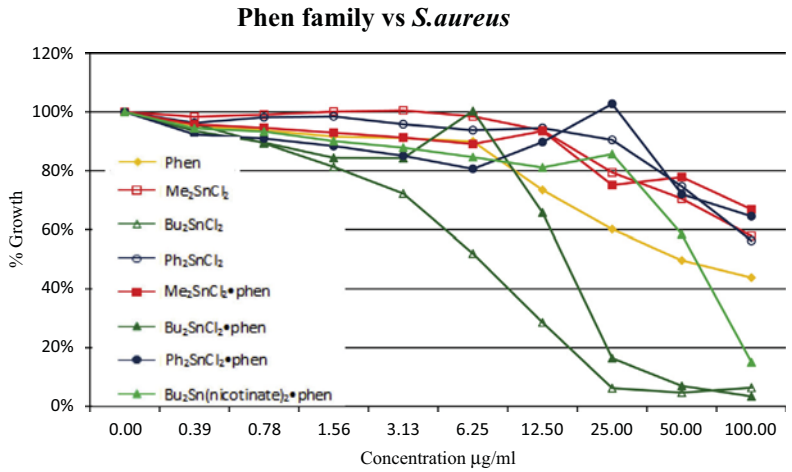
Compound	*E. coli*		*P. aeruginosa*		*S. aureus*	
	μM	μg/mL	μM	μg/mL	μM	μg/mL
Vancomycin hydrochloride	2–3	3–5	>67	>100	3–4	5–6
Dione	30–45	6–9	22–30	5–6	45–60	9–12
Me_2SnCl_2	>455	>100	341–455	75–100	>455	>100
n-Bu_2SnCl_2	41–62	13–19	>329	>100	41–62	13–19
Ph_2SnCl_2	218–291	75–100	>291	>100	>291	>100
n-Bu_2SnCl(OAc)	114–152	37–50	>305	>100	114–152	37–50
Ph_2SnCl(OAc)	136–204	50–75	>272	>100	68–102	25–37
n-Bu_2SnCl_2·phen (**3**)	77–103	37–50	155–207	75–100	39–52	19–25
Me_2SnCl_2·dione (**7**)	>233	>100	44–59	19–25	44–58	19–25
n-Bu_2SnCl_2·dione (**8**)	36–49	19–25	>195	>100	146–195	75–100
Ph_2SnCl_2·dione (**9**)	>181	>100	34–45	19–25	17–23	9–12
n-Bu_2SnCl_2·dppz (**12**)	64–85	37–50	>171	>100	32–43	19–25
n-Bu_2Sn(nicotinate)$_2$	105–157	50–75	>209	>100	78–105	37–50
n-Bu_2Sn(nicotinate)$_2$·phen (**4**)	114–152	75–100	>152	>100	114–152	75–100
n-Bu_2Sn(nicotinate)$_2$·dppz (**13**)	99–132	75–100	>132	>100	>132	>100

[a] Values are mean of three experiments.

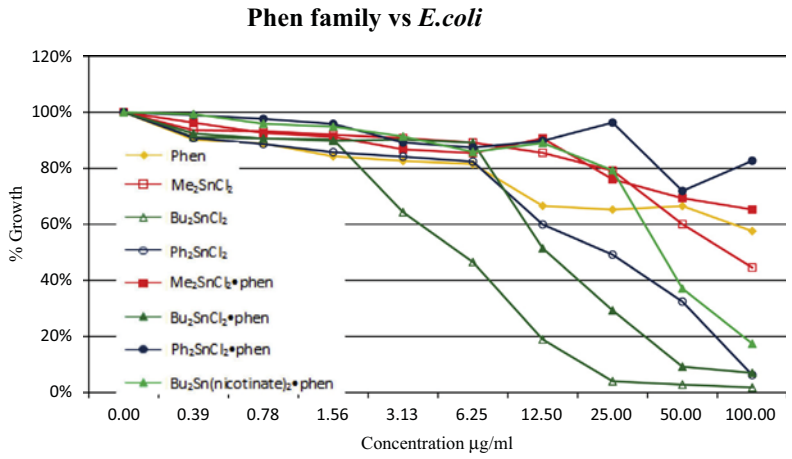
Table 2
Antimicrobial activities as MIC_{50} range (μM and μg/mL).[a]

Compound	*E. coli*		*P. aeruginosa*		*S. aureus*	
	μM	μg/mL	μM	μg/mL	μM	μg/mL
Vancomycin hydrochloride	1–2	2–3	>67	>100	1–2	2–3
Phen	>555	>100	416–555	75–100	278–416	50–75
Dione	15–22	3–5	15–22	3–5	30–45	6–9
Me_2SnCl_2	341–455	75–100	341–455	75–100	>455	>100
n-Bu_2SnCl_2	15–21	5–6	165–247	50–75	21–31	6–9
Ph_2SnCl_2	55–73	19–25	>291	>100	>291	>100
Me_2SnO	452–603	75–100	452–603	75–100	>603	>100
n-Bu_2SnCl(OAc)	29–38	9–12	>305	>100	37–57	12–19
Ph_2SnCl(OAc)	26–34	9–12	>272	>100	17–26	6–9
Me_2SnCl_2·phen (**1**)	>250	>100	125–188	50–75	>250	>100
n-Bu_2SnCl_2·phen (**3**)	26–39	12–19	103–155	50–75	26–39	12–19
Me_2SnCl_2·dione (**7**)	44–58	19–25	22–29	9–12	29–44	12–19
n-Bu_2SnCl_2·dione (**8**)	18–24	9–12	146–195	75–100	49–73	25–38
Ph_2SnCl_2·dione (**9**)	23–34	12–19	23–34	12–19	6–9	3–5
n-Bu_2SnCl_2·dppz (**12**)	16–21	9–12	>171	>100	21–32	12–19
Ph_2SnCl_2·dppz (**14**)	>160	>100	80–120	50–75	60–80	37–50
n-Bu_2Sn(nicotinate)$_2$	39–52	19–25	>209	>100	26–39	12–19
Ph_2Sn(nicotinate)$_2$	72–97	37–50	>193	>100	>193	>100
n-Bu_2Sn(nicotinate)$_2$·phen (**4**)	57–76	37–50	>152	>100	76–114	50–75
n-Bu_2Sn(nicotinate)$_2$·dppz (**13**)	33–49	25–37	>132	>100	99–132	75–100

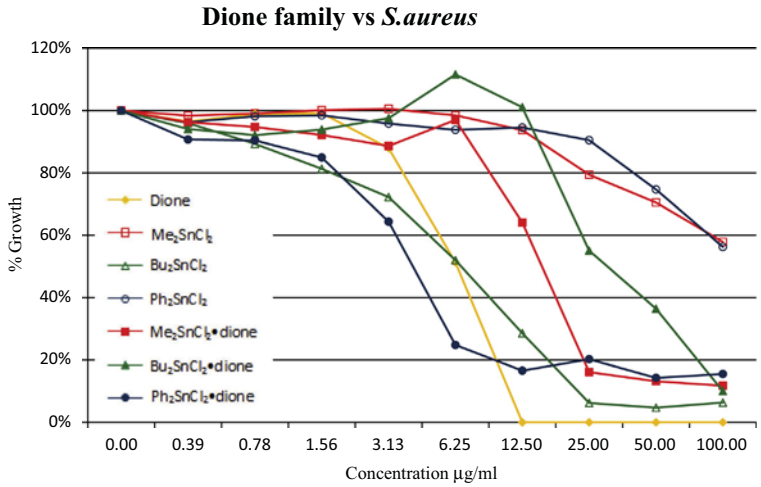
[a] Values are mean of three experiments.



Graph 1. Activity profile for phen compounds vs. *S. aureus*.

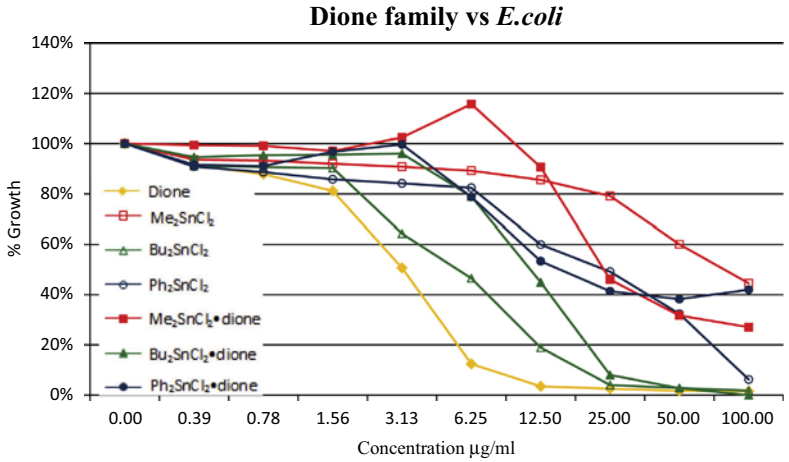


Graph 2. Activity profile for phen compounds vs. *E. coli*.



Graph 3. Activity profile for dione compounds vs. *S. aureus*.

complex n-Bu_2SnCl_2·phen (**3**) is between both, as it reaches the same level of activity as n-Bu_2SnCl_2 at a concentration of 25 μg/mL. In the case of Ph_2SnCl_2·dione (**9**), it is a similar story. In this case, however, the dione ligand shows a complete inhibition at 12.5 μg/mL. The Ph_2SnCl_2·dione (**9**) complex has more activity than dione at low concentrations, but never reaches complete inhibition and seems to achieve its maximum actitivy at ~80% inhibition at 12.5 μg/mL.



Graph 4. Activity profile for dione compounds vs. *E. coli*.

In the cases of the nicotinate compounds, either as the simple diorganotin compound or as the complex, very little activity was observed against any of the three bacteria except in the case of n-Bu_2Sn(nicotinate)$_2$ which exhibited reasonable activity against *S. aureus*.

4. Conclusions

The synthesis of diorganotin(IV) dichloride complexes of the ligands phen, dione and dppz were undertaken and characterised by CHN analyses and ^{1}H NMR spectroscopy. We also synthesised several diorganotin(IV) dicarboxylate compounds, including acetates and nicotinates. However, we encountered several difficulties in these syntheses and furthermore, complexation reactions with the organic ligands rarely occurred. This is probably due to the difficulty in breaking the intermolecular interactions involved in diorganotin(IV) dicarboxylate compounds.

Overall, the organotin(IV) compounds tested here demonstrated greatest activity against *E. coli* and *S. aureus* and were almost inactive against *P. aeruginosa*. The dibutyltin(IV) derivatives exhibited the broadest range of activity in comparison to the dimethyltin(IV) or diphenyltin(IV) derivatives. The addition of either the nicotinate group did not promote activity against any of the bacteria. Furthermore, only in the case of Ph_2SnCl_2·dione (**9**) was there improved activity compared to the organic ligand itself.

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