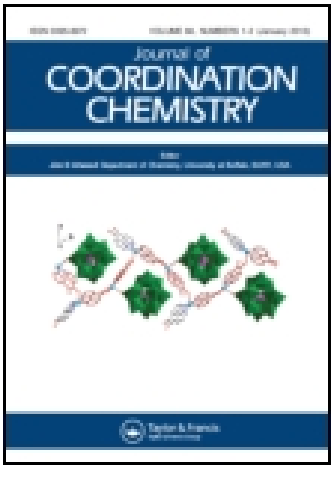


Journal of Coordination Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/gcoo20

Synthesis and structural elucidation of bioactive triorganotin(IV) derivatives of sodium deoxycholate

Farzana Shaheen[a], Saqib Ali[a], Scopelliti Rosario[b] & Naseer Ali Shah[c]

[a] Department of Chemistry, Quaid-i-Azam University, Islamabad, Pakistan

[b] Ecole polytechnique fédérale de Lausanne Institut des sciences et ingénierie chimiques, EPFL SB ISIC LCOM, Lausanne, Switzerland

[c] Department of Biochemistry, Quaid-i-Azam University, Islamabad, Pakistan

Accepted author version posted online: 26 Mar 2014.Published online: 08 May 2014.

To cite this article: Farzana Shaheen, Saqib Ali, Scopelliti Rosario & Naseer Ali Shah (2014) Synthesis and structural elucidation of bioactive triorganotin(IV) derivatives of sodium deoxycholate, Journal of Coordination Chemistry, 67:10, 1851-1861, DOI: 10.1080/00958972.2014.908187

To link to this article: http://dx.doi.org/10.1080/00958972.2014.908187

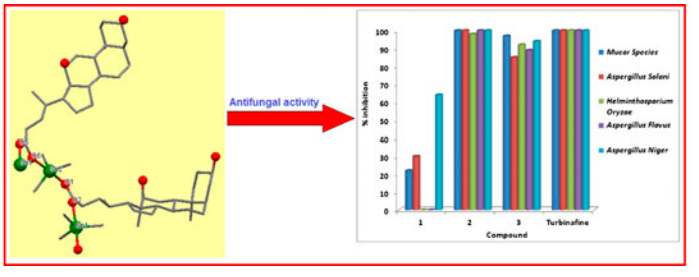
Journal of Coordination Chemistry, 2014
Vol. 67, No. 10, 1851–1861, http://dx.doi.org/10.1080/00958972.2014.908187

Synthesis and structural elucidation of bioactive triorganotin (IV) derivatives of sodium deoxycholate

FARZANA SHAHEEN†, SAQIB ALI*†, SCOPELLITI ROSARIO‡ and NASEER ALI SHAH§

†Department of Chemistry, Quaid-i-Azam University, Islamabad, Pakistan
‡Ecole polytechnique fédérale de Lausanne Institut des sciences et ingénierie chimiques, EPFL SB ISIC LCOM, Lausanne, Switzerland
§Department of Biochemistry, Quaid-i-Azam University, Islamabad, Pakistan

(*Received 10 September 2013; accepted 26 February 2014*)



The synthesized compounds inhibit strong antifungal activity even higher than the standard drug, *Turbinafine*. Keeping in view their antifungal activity, they might be used as potent antifungal agent.

Trimethyl (**1**), tributyl (**2**), and triphenyl tin (**3**) derivatives of sodium (R)-4-((3R,5R,8R, 9S,10S,12S,13R,14S,17R)-3,12-dihydroxy-10,13-dimethyl-hexadecahydro-1H-cyclopenta[a]phenanthren-17-yl)pentanoate (sodium deoxycholate) were synthesized by refluxing sodium deoxycholate with the corresponding triorganotin(IV) chloride in 1 : 1 M ratio. All the three compounds were characterized by elemental analysis, infrared spectroscopy, ^{1}H, ^{13}C, ^{119}Sn NMR, and X-ray diffraction studies. From FT-IR spectra, Δv values proposed bridging or chelating behavior of the ligand. The three compounds gave a trigonal bipyramidal geometry in the solid state and tetrahedral geometry in solution. Single crystal of **1** showed polymeric trigonal bipyramidal geometry. Synthesized compounds obtained were screened for their antimicrobial and antitumor activities against A2780 cell line. Results revealed that only **2** showed significant antibacterial activity. However, all the three compounds exhibited promising antifungal and anticancer activities.

Keywords: Deoxycholate; Triorganotin(IV) complex; Antitumor activity

1. Introduction

Interests in organotin(IV) carboxylates stem from their diverse structural and effective antitumor activity [1, 2]. Organotin(IV) compounds act as pesticidal, antiviral, fungicidal,

*Corresponding author. Email: drsa54@yahoo.com

bactericidal, and antitumor agents [3, 4]. Number and nature of groups attached to tin determine the activity of these compounds [5]. Although organotins with various ligands show exciting properties and activities, results show that oxygen-containing organotins are even more effective than *cis*-platin [6]. The lipophilic and hydrophilic properties of the compounds are very important as lipophilic properties are essential for crossing the cell membrane and hydrophilic character for being accepted by the water-rich cell [7].

Sodium deoxycholate is commonly known as a bile salt and is recognized to kill localized body fat by emulsification [8]. Bile salts are steroidal detergents which facilitate fat digestion and absorption through intestinal wall by the formation of mixed micelles with lipids/fats/cholesterol [9]. They have been used as a delivery vehicle in medications [10]. Mammary tumor is considered as directly related to fat intake during initiation or promotion stages [11]. Organotin(IV) compounds are already known for their role in anticancer drugs. Deoxycholate in conjugation with tin may improve liposolubility for better interaction within the cells.

Thus, we have developed some new organotin(IV) deoxycholate derivatives. Their interesting topologies mediate exciting antitumor and antifungal properties.

2. Experimental setup

2.1. *Materials and methods*

All the chemicals used for synthesis were of analytical grade and used without purification. Solvents were dried and distilled before use. All compounds were synthesized in nitrogen under reflux in toluene for 7–8 h. IR spectra were recorded on a Perkin-Elmer FT-IR 2000 system from 4000 to 200 cm^{-1}. Elemental analyses were performed by using a Thermo Scientific Flash 2000 CHN/S organic elemental analyzer. ^{1}H and ^{13}C NMR spectra were recorded on an AvanceIII 400 MHz BBFO-Plus 5 mm TOPSPIN 3. ^{119}Sn NMR spectra were recorded on an Avance 400 MHz TXO 10 mm XWINNMR. ^{1}J (^{119}Sn–^{13}C) and ^{2}J (^{119}Sn–^{1}H) coupling constants are expressed in Hertz and are provided in square brackets.

2.2. *Synthesis*

Triorganotin(IV) compounds of sodium deoxycholate were synthesized by reacting equimolar ratios of sodium deoxycholate with triorganotin(IV) chlorides in dry distilled toluene, refluxing for 7–8 h. Sodium chloride was removed by filtration and the soluble product was separated by evaporating toluene under vacuum using rotoevaporation. The product obtained was recrystallized in chloroform: *n*-hexane (1 : 2).

2.2.1. Synthesis of (R)-trimethylstannyl 4-((3R,5R,8R,9S,10S,12S,13R,14S,17R)-3,12-dihydroxy-10,13-dimethyl-hexadecahydro-1H-cyclopenta[a]phenanthren-17-yl)pentanoate [$Me_3SnC_{24}H_{39}O_4]_n$ (1). (Yield: 0.97 g, 73.4%). m.p. 118–119 °C. Elemental analysis, % Calculated (Found) for $[C_{27}H_{48}O_4Sn]_n$: C, 58.39 (57.68); H, 8.71 (8.56). FT-IR (cm^{-1}): 1564 $\nu(COO)_{asym}$, 1407 $\nu(COO)_{sym}$, $\Delta\upsilon = 157$, 557 ν(Sn–C), 439 ν(Sn–O), 615 (O–Sn–O). ^{1}H NMR (ppm): 1.27–2.05 (m, $H_{cycloalkane}$), 0.84–1.14 (m, H_2–H_5, H_{20}, H_{25}), 3.43 (bs, H_{16}, H_{24}), 0.37 (s, Sn–CH_3 [$^{2}J = 51.0$], $\theta = 107.6°$). ^{13}C NMR (ppm): 177.9 (C-1), 12.3, 15.2, 17.3, 23.3, 24.4, 25.4, 25.4, 26.2, 26.9, 28.5, 30.3, 31.6, 33.2, 34.1, 35.5, 36.1,

40.6, 42.2, 46.4, 47.7, 48.0 (C_2–C_{14}, C_{17}–C_{22}, C_{25}–C_{26}), 73.3 (C_{15}), 72.2 (C_{23}), 10.2 (Sn–CH_3), ^1J [^{119}Sn–^{13}C = 352, θ = 107.6°] ^{119}Sn (ppm): 340.

2.2.2. Synthesis of (R)-tributylstannyl 4-((3R,5R,8R,9S,10S,12S,13R,14S,17R)-3, 12-dihydroxy-10,13-dimethyl-hexadecahydro-1H-cyclopenta[a]phenanthren-17-yl)pentanoate [$Bu_3SnC_{24}H_{39}O_4]_n$ (2). (Yield: 1.36 g, 83.9%). m.p. 63–65 °C. Elemental analysis, % Calculated (Found) for $[C_{36}H_{66}O_4Sn]_n$: C, 63.44 (62.94); H, 9.76 (9.66). FT-IR (cm^{-1}): 1571 $\nu(COO)_{asym}$, 1404 $\nu(COO)_{sym}$, $\Delta\upsilon$ = 167, 572 ν(Sn–C), 439 ν(Sn–O), 618 (O–Sn–O). ^{1}H NMR (ppm): 1.24–2.07 (m, $H_{cycloalkane}$), 0.85–1.15 (m, H_2–H_5, H_{20}, H_{25}), 3.47 (bs, H_{16}, H_{24}), 0.33–0.81 (m, $H_{\alpha,\ \beta,\ \gamma,\ \delta}$). ^{13}C NMR (ppm): 178.3 (C-1), 12.2, 15.1, 17.2, 23.4, 24.5, 25.2, 25.7, 26.2, 27.5, 28.5, 30.4, 31.5, 33.4, 34.0, 35.5, 36.1, 40.1, 42.7, 46.3, 47.5, 48.3 (C_2–C_{14}, C_{17}–C_{22}, C_{18}–C_{23}, C_{25}–C_{26}), 73.4 (C_{15}), 72.5 (C_{24}), 28.1 (C_α), 26.9 (C_β), 17.5 (C_γ), 20.5 (C_δ). ^{119}Sn (ppm): 310.

2.2.3. Synthesis of (R)-triphenylstannyl 4-((3R,5R,8R,9S,10S,12S,13R,14S,17R)-3, 12-dihydroxy-10,13-dimethyl-hexadecahydro-1H-cyclopenta[a]phenanthren-17-yl)pentanoate [$Ph_3SnC_{24}H_{39}O_4]_n$ (3). (Yield 1.49 g, 84.6%). m.p. 67–70 °C. Elemental analysis, % Calculated (Found) for $[C_{42}H_{54}O_4Sn]_n$: C, 68.02 (68.03); H, 7.34 (7.34). FT-IR (cm^{-1}): 1521 $\nu(COO)_{asym}$, 1408 $\nu(COO)_{sym}$, $\Delta\upsilon$ = 113, 282 ν(Sn–C), 440 ν(Sn–O), 610 (O–Sn–O). ^{1}H NMR (ppm): 1.26–2.03 (m, $H_{cycloalkane}$), 0.83–1.13 (m, H_2–H_5, H_{20}, H_{25}), 3.43 (bs, H_{16}, H_{24}), 7.77 (H_{ortho}, d) 7.42 (H_{meta}, dd), 7.48–7.56 (H_{para}, dd). ^{13}C NMR (ppm): 181.4 (C-1), 12.6, 15.4, 17.3, 23.1, 24.4, 25.1, 25.7, 26.1, 27.2, 28.6, 30.5, 31.7, 33.6, 34.1, 35.3, 36.0, 40.2, 42.1, 46.5, 47.4, 48.2 (C_2–C_{14}, C_{17}–C_{22}, C_{25}–C_{26}), 73.1 (C_{16}), 72.2 (C_{24}), 138.5 (C_{ipso}), 136.9 (C_{ortho}), 129.4 (C_{meta}), 131.3 (C_{para}). ^{119}Sn (ppm): 95.

2.3. *Antibacterial assay*

The organotin(IV) compounds were tested against different bacterial strains, *Escherichia coli* (8739), *Klebsiella pneumonia* (700603), *Bacillus subtilis* (6633), and *Staphylococcus aureus* (25923), by agar well diffusion method [12]. *Cefixime* was used as a standard drug. One milliliter of Broth culture containing 10^4–10^6 colony forming units per mL was added to 100 mL of nutrient agar medium at 45 °C, mixed well, and then poured into a 14 cm sterile petri plate. The medium was allowed to solidify, and then 6 mm wells were dug with a sterile metallic borer (which is used to cut the agar plate). Then, a DMSO solution of the test sample (100 µL) at 1 mg mL^{-1} was added to the wells. DMSO served as a negative control, and the standard antibacterial drug *Cefixime* (1 mg mL^{-1}) was used as positive control. The plates were incubated aerobically at 37 °C for 24 h. The activity was determined by measuring the diameter of the zone showing complete inhibition (mm). Growth inhibition was calculated with reference to the positive control.

2.4. *Antifungal assay*

Synthesized compounds were screened for their antifungal activities against five different strains of fungi [*Mucor species* (90364), *Fusarium solani* (62877), *Helminthosporium oryzae* (38851), *Aspergillus flavus* (9643), and *Aspergillus Niger* (16404)] by using agar tube dilution method [12]. *Turbinafine* was used as standard drug.

Stock solutions of pure compounds 200 μg mL^{-1} were prepared in sterilized DMSO. A stock solution of sabouraud dextrose agar (SDA) medium was prepared in distilled water. SDA medium (4 mL) was then dispensed in screw-caped test tubes and autoclaved at 121 °C for 15 min. The tubes were allowed to cool to 50 °C and non-solidified SDA was loaded with known amounts of test compounds from the stock solution. The tubes were then allowed to solidify in a slanting position at room temperature. Each tube was inoculated with a 4 mm diameter piece of inoculum from seven-days-old fungal culture. Media supplemented with DMSO and *Turbinafine* (200 μg mL^{-1}) were used as a negative and a positive control, respectively. The tubes were incubated at 28 °C for 7 days and growth was determined by measuring the linear growth (mm), and growth inhibition was calculated with reference to growth in the control as shown in the equation below:

$$\%\,\text{Growth inhibition} = 100 + \left(\frac{\text{linear growth in test sample (mm)}}{\text{linear growth in control (mm)}} \times 100\right)$$

2.5. *Cytotoxic activity*

Cytotoxic activities of the three compounds were performed by MTT-Method [13] to assess the effect of compounds on the growth of cells. The human ovarian carcinoma cell line (A2780) was chosen. This method is based on the principle of reduction of yellow-colored tetrazolium salt, MTT [3-(4,5-dimethylthiazolyl-2)-2,5-diphenyl tetrazoleum bromide] to purple formazan product, by mitochondrial dehydrogenase of metabolically active cells. MTT solution was prepared by dissolving it at 5 g mL^{-1} in phosphate buffer saline. About 20 μL of this solution was added to each of 96 well plates containing 100 μL of culture medium and was incubated at 37 °C for 3–4 h. The medium was aspirated carefully without disruption of purple-colored formazan crystals. The resulting purple color zone was solubilized in 100 μL of DMSO and quantified by spectrophotometer. Micro ELISA plate was used to read the plate at 590 nm to determine the IC_{50} value.

3. Results and discussion

3.1. *IR data*

IR spectra of these compounds were recorded from 200 to 4000 cm^{-1}. Peaks of interest in IR spectrum are that of ν(COO), ν(Sn–C), and ν(Sn–O). IR stretching vibrations of carboxylate are useful in defining the structure of complexes. ν_{asym} (CO_2) appeared at

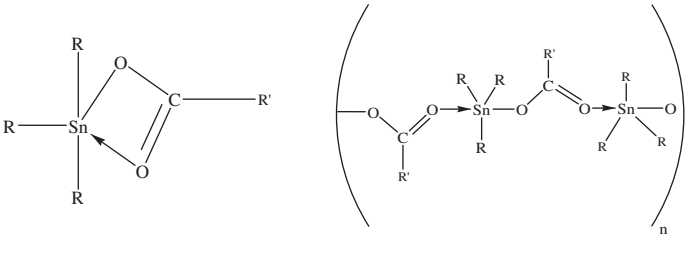


Figure 1. Proposed structures of triorganotin(IV) compounds.

1521–1571 cm^{-1}, while vibrations observed at 1404–1418 cm^{-1} are characteristic of ν_{sym} (CO_2); $\Delta\nu$ (CO_2) ($\Delta\nu = \nu_{asym} - \nu_{sym}$) between 150 and 250 cm^{-1} suggests a bridging coordination, while difference below 150 cm^{-1} suggests a chelating mode of coordination [14]. The $\Delta\nu$ for **2** and **3** indicates bidentate bridging and chelating coordination, respectively.

Two possible solid state structures are shown in figure 1. For **1**, polymeric bridging mode is confirmed by single-crystal analysis. FT-IR data suggest two types of geometry in solid state, five-coordinate polymeric, or chelated compound.

3.2. *Multinuclear NMR data*

^{1}H, ^{13}C, and ^{119}Sn NMR spectra of the compounds were recorded in $CDCl_3$. However, due to complex structure, no fine pattern was observed. Owing to their multiplicity and intensity in a narrow range, multiplets and broad signals were obtained. In **1,** methyl group protons gave a sharp singlet at 0.37 ppm with well-defined satellites due to Sn–^{1}H coupling in region expected for tetrahedral geometry [15], which shows dissociation of the polymeric structure in solution. For **2** and **3**, due to complex peak pattern, no couplings were observed.

In ^{13}C NMR spectra, new peaks for alkyl and aryl groups favor the formation of compounds. However, the environment of different carbons does not differ too much, and does not resonate at very different frequencies and appear in a narrow range. Methyl groups attached to Sn gave a peak in the upfield region. Coupling constant value of 352 for **1** suggests a tetrahedral geometry in solution [15], in agreement with ^{1}H NMR spectroscopic results. Carbons of butyl groups were assigned peak values by comparison to the literature. In **3**, ipso carbon gave a signal at 138.5 ppm, which is a characteristic of tetrahedral geometry [16].

Confirming solution state geometry, their ^{119}Sn NMR spectra were taken in chloroform, where the chemical shift value gave information about geometry in solution. Increase in coordination number gives a large upfield shift. Only tetrahedral complexes are reported to show a positive chemical shift value and appear in the most downfield region. An increase in electron-releasing power of the alkyl group results in shifting of ^{119}Sn value to higher field, as a consequence of increased shielding [17]. Appearance of single peaks in ^{119}Sn NMR spectra supports the formation of one species and purity of the compounds. According to Holecek and co-workers, four, five, six, and seven coordination compounds give chemical shifts in the range of +200 to −60, −90 to −190, −210 to −400, and −440 to −540 ppm, respectively [18].

Compounds **1** and **2** gave resonances at a very downfield region at 340 and 310 ppm, respectively, which could be due to tetrahedral geometry. A peak appearing at 95 ppm for **3** suggests tetrahedral geometry in solution. It is evident from the ^{1}H, ^{13}C, and ^{119}Sn NMR spectra that all three compounds do not retain their five-coordinate geometry and exist as tetrahedra in solution.

3.3. *X-ray crystal structure of 1*

The crystal structure of the monomeric unit along with atom numbering scheme and polymeric unit of **1** are shown in figures 2 and 3, respectively. Packing diagram is shown in figure 4. Crystallographic data, selected bond lengths, and angles are collected in tables 1

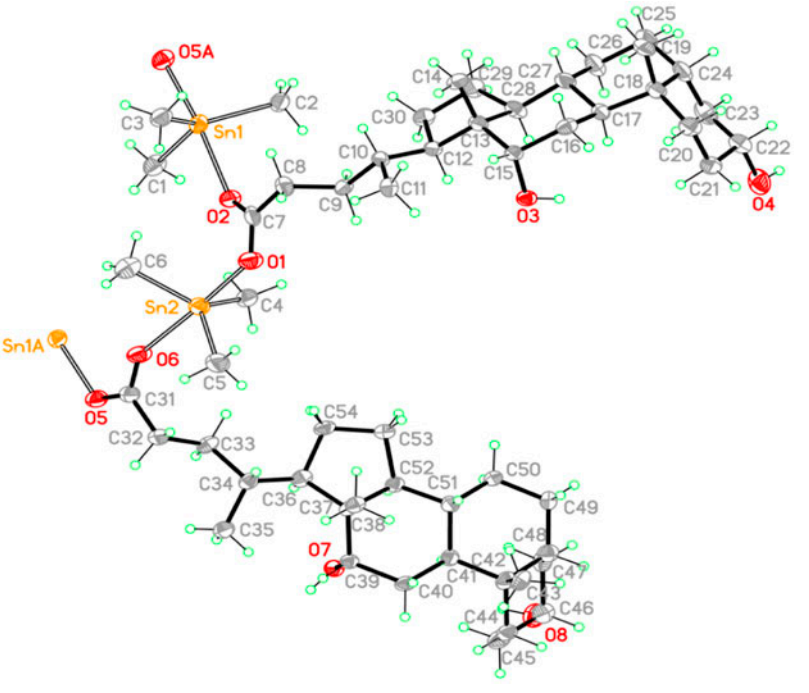


Figure 2. ORTEP diagram of **1** with atom numbering scheme. Labels with letter A refer to equivalent atoms obtained by symmetry.

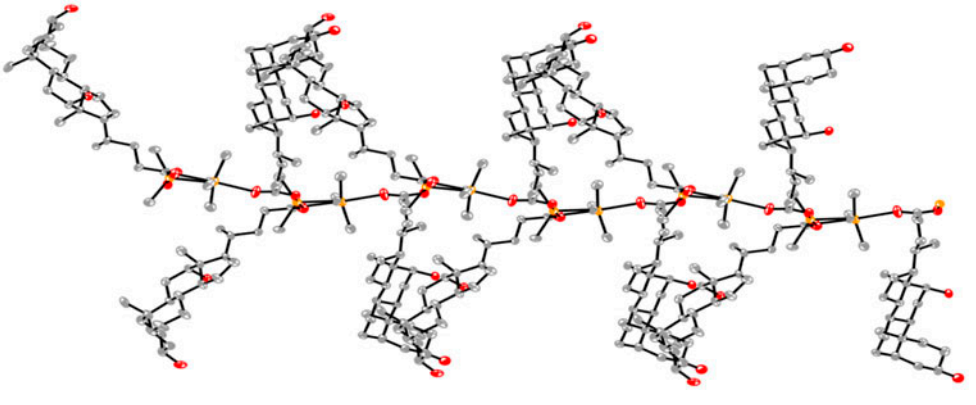


Figure 3. ORTEP view of polymeric structure of **1**.

and 2, respectively. The apparent geometry around tin is five-coordinate. Exact geometry can be best described by the τ value,

$$\tau = \frac{(\beta - \alpha)}{60}$$

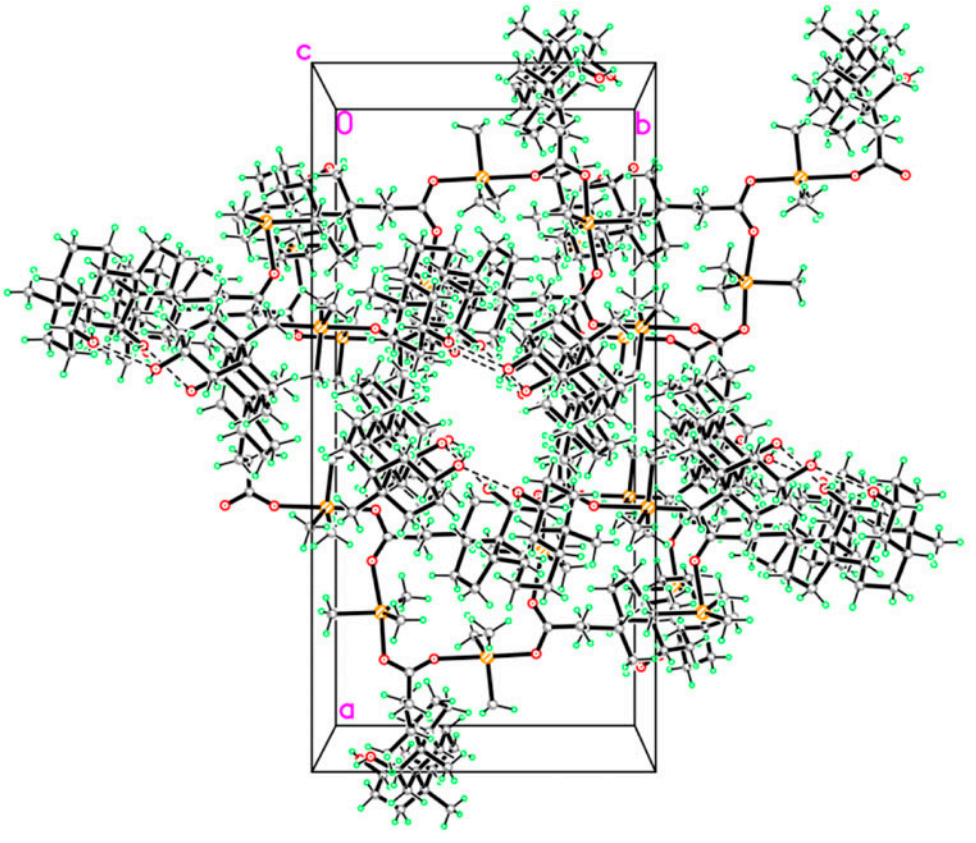


Figure 4. Packing diagram of **1**, viewed down the *c*-axis, showing its H-bond network.

where β is the largest basal angle around tin, while α is the second largest angle. The τ value is zero for a perfect square pyramid ($\alpha = \beta = 180°$) and unity for perfect trigonal bipyramidal geometry ($\alpha = 120$ and $\beta = 180°$) [19]. For **1**, τ is 0.81 (β = O(5)A–Sn(1)–O(2) = 173.1(2) and α = C(3)–Sn(1)–C(2) = 124.2(4)), which shows that geometry is distorted trigonal bipyramidal where O1 and O5 of two ligands occupy the axial positions and three methyl groups lie in the equatorial plane. Sn1–O2 and Sn1–O5 bond lengths 2.356(5) and 2.173(6) Å, respectively, are less than the sum of the covalent radii (2.56 Å) and van der Waals radii of Sn and O (3.68 Å), which shows a strong interaction of oxygen with tin [20].

Thus, **1** adopts a linear polymeric geometry with *trans*-R_3SnO_2 structural motif, in which adjacent SnR_3 moieties are bridged by a single bidentate carboxylate. This geometry is frequently shown by many triorganotin carboxylates as reported [21, 22].

3.4. *Antimicrobial and cytotoxic activity*

3.4.1. Antimicrobial studies. Antibacterial activities of **1–3** were tested against four bacterial strains (table 3). *Cefixime* was used as a standard drug. Generally, inhibition zone above 20 mm is considered as significant; 18–20 mm is thought to be good and below 11–14 mm

Table 1. Crystal data and structure refinement for **1**.

Empirical formula	$C_{54}H_{96}O_8Sn_2$
Formula weight	1110.69
Temperature	140(2) K
Wavelength	0.71073 Å
Crystal system	Orthorhombic
Space group	$P2_12_12$
a (Å)	29.202(6)
b (Å)	14.136(3)
c (Å)	17.265(4)
α (°)	90
β (°)	90
γ (°)	90
Volume	7127(2) Å^3
Z	4
Density (Calcd)	1.035 mg m^{-3}
Absorption coefficient	0.739 mm^{-1}
F (0 0 0)	2336
Crystal size	0.29 × 0.17 × 0.14 mm^3
Theta range for data collection	2.74°–25.57°
Index ranges	$-35 \le h \le 35$, $-17 \le k \le 17$, $-20 \le l \le 20$
Reflections collected	12,814
Independent reflections	12,814 [R(int) = 0.0000]
Completeness to $\theta = 25.00°$	97.6%
Absorption correction	None
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	12,814/0/579
Goodness-of-fit on F^2	0.984
Final R indices [$I > 2\sigma(I)$]	R_1 = 0.0687, wR_2 = 0.1783
R indices (all data)	R_1 = 0.0860, wR_2 = 0.1894
Absolute structure parameter	0.06(3)
Extinction coefficient	0.0134(7)
Largest diff. peak and hole	0.743 and −0.504 e Å^{-3}

Table 2. Selected bond lengths (Å) and angles (°) for **1**.

Bond lengths (*Å*)			
Sn(1)–C(3)	2.12(1)	Sn(1)–C(1)	2.190(8)
Sn(1)–C(2)	2.166(8)	Sn(1)–O(2)	2.356(5)
Sn(1)–O(5)A	2.173(6)		
Bond angles (°)			
C(3)–Sn(1)–C(2)	124.2(4)	O(5)A–Sn(1)–C(1)	89.5(3)
C(3)–Sn(1)–O(5)A	93.8(3)	C(3)–Sn(1)–O(2)	88.3(3)
C(2)–Sn(1)–O(5)A	94.5(3)	C(2)–Sn(1)–O(2)	89.6(3)
C(3)–Sn(1)–C(1)	115.6(4)	O(5)A–Sn(1)–O(2)	173.1(2)
C(2)–Sn(1)–C(1)	119.5(4)	C(1)–Sn(1)–O(2)	83.6(3)

Note: Letter A refers to the symmetry $-x+1/2$, $y-1/2$, $-z+1$, used to generate equivalent atoms.

is considered as insignificant [23]. All compounds display less activity than the standard drug. Compounds **1** and **3** did not show any significant activity against any of the four bacterial strains, however, **2** showed some activity against *B. subtilis* and *S. aureus*; **2** showed insignificant activity against *K. pneumoniae* and *E. coli*.

Similarly, compounds **1–3** were tested against five different types of fungi to establish their antifungal activity. The results are shown in table 4 and a graphical picture is presented in figure 5. Compound **1** was ineffective against *H. oryzae* and *A. flavus* and showed some reasonable activity against *M. species*, while **2** and **3** exhibited good activities. Compound **2** was competitive with standard drug.

Table 3. Antibacterial activity of organotin(IV) derivatives of sodium deoxycholate.[a–c]

Compound (ATCC No.)	Average zone of inhibition (mm) inhibition ± SD			
	Escherichia coli (8739)	*Klebsiella pneumonia* (700603)	*Bacillus subtilis* (6633)	*Staphylococcus aureus* (25923)
1	–[a]	–	–	–
2	–	13	20	18
3	–	–	–	–
Cefixime[b]	40	40	30	40

[a] Insignificant activity.
[b]Reference drug used for antibacterial evaluation.
[c]Clinical implication: *E. coli*, infection of wounds, urinary tract, dysentery; *K. pneumonia*, urinary tract infection (UTI), cholecystitis, diarrhea, upper respiratory tract infection, wound infection, osteomyelitis, meningitis, bacteremia, septicemia; *B. subtilis*, food poisoning; *S. aureus*, food poisoning, scaled skin syndrome, endocarditis.

Table 4. Antifungal activity of organotin(IV) complexes of sodium deoxycholate.[a,b]

Compound (ATCC No.)	Mean value of percent growth inhibition				
	Mucor species (90364)	*Fusarium solani* (62877)	*Helminthosporium oryzae* (38851)	*Aspergillus flavus* (9643)	*Aspergillus niger* (16404)
1	22 ± 0.91	30 ± 0.51	0	0	64 ± 0.19
2	100	100	98 ± 0.66	100	100
3	97 ± 0.51	85 ± 0.63	92 ± 0.34	89 ± 0.43	94 ± 0.78
[a]*Turbinafine*	100	100	100	100	100

[a]Reference drug for antifungal activity.
[b]Clinical implication: *M. species*, opportunistic, necrotizing infections known as zygomycosis; *F. Solani*, keratitis, fungal infections; *H. oryzae*, none; *A. flavus*, hepatitis, immunosuppression, hepatocellular carcinoma, neutropenia, infarction; *A. niger*, *Aspergillosis*, Otomycosis (fungal ear infections).

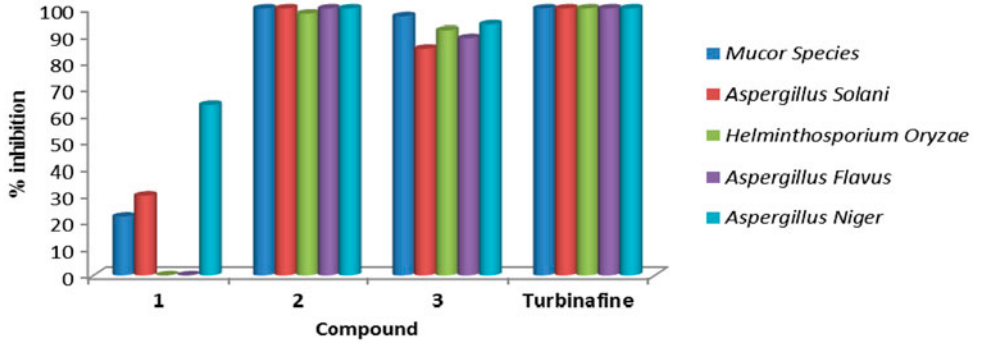


Figure 5. Antifungal activity of organotin(IV) derivatives of sodium deoxycholate against various fungi.

3.4.2. Cytotoxic activity. All synthesized compounds were tested for their cytotoxic activity against cell line A2780 and results are presented in table 5. Compounds **1–3** present less IC_{50} than *cis*-platin which shows that **1–3** are more active than standard drug. Electron acceptor properties of organotin(IV) compounds make it possible for them to interact with electron donor sites of biomolecules [24].

Table 5. IC_{50} values ($\mu g\,mL^{-1}$) of compounds tested against human ovarian tumor cell lines A2780.[a]

Compound	IC_{50}
1	2.66
2	1.58
3	1.67
[a]*cis*-Platin	3.28

[a]Standard drug *cis*-$[Pt(NH_3)_2Cl_2]$.

Lipophilic characters of drugs also play a part in improving such an interaction. Lipophilic character increases with increasing chain length, so tributyl tin complex is assumed to be more active than trimethyl complex; however, taking advantage of small size, it is easier for **1** to diffuse more rapidly into the membrane. The cytotoxic activity of these compounds against given cancer cells showed that coupling of ligand with R_3Sn(IV) metal center results in remarkable cytotoxic activity. Bulky phenyl groups in **3** can interact through π–π interactions with biomolecules in cells.

Because of their lipophilicity, organotins are considered as interacting with cellular membranes. There is evidence that the intracellular as well as cytoplasmic membrane could be the possible site of action of organotin compounds. However, it is not known whether cell surface adsorption or accumulations within the cell or even both actions are liable for its toxicity [25].

4. Conclusion

New organotin(IV) compounds of sodium (R)-4-((3R,5R,8R,9S,10S,12S,13R,14S,17R)-3,12-dihydroxy-10,13-dimethyl-hexadecahydro-1H-cyclopenta[a]phenanthren-17-yl)pentanoate have been synthesized and characterized. The compounds exhibited five-coordinate geometry in solids, while dissociated in solution to four-coordinate. Crystal structure of **1** shows that the compound exists as a polymer and exhibits a slightly distorted trigonal bipyramidal geometry, for which three methyl groups lie in the equatorial plane, while single oxygen from two carboxylates occupies axial positions. Packing diagrams are stabilized by non-covalent interactions. Antimicrobial and cytotoxic assay showed that compounds do not show appreciable antibacterial activity. Only **2** showed activity against *B. subtilis* and *S. aureus*. However, all compounds displayed good activity against fungal strains. Cytotoxic studies revealed that compounds **1–3** exhibit good antitumor properties.

Supplementary material

CCDC 996466 contains the supplementary crystallographic data for 1. These data can be obtained free of charge via http://www.ccdc.cam.ac.uk/conts/retrieving.html, or from the Cambridge Crystallographic Data Center, 12 Union Road, Cambridge CB2 1EZ, UK; Fax: (+44)1223-336-033; or E-mail: deposit@ccdc.cam.ac.uk.

Acknowledgement

Authors are highly thankful to Higher Education Commission of Pakistan for providing financial support.

References

[1] L. Tian, Y. Sun, H. Li, X. Zheng, Y. Cheng, X. Liu, B. Qian. *J. Inorg. Biochem.*, **99**, 1646 (2005).
[2] W. Rehman, M.K. Baloch, A. Badshah. *J. Braz. Chem. Soc.*, **16**, 827 (2005).
[3] J.T. Lu, S.S. Chen, M. Du, L.F. Tang. *Appl. Organomet. Chem.*, **20**, 448 (2006).
[4] M.I. Khan, M.K. Bloach, M. Ashfaq. *J. Organomet. Chem.*, **689**, 3370 (2009).
[5] S. Hadi, M. Rilyanti, N. Nurhasanah. *Modern Appl. Sci.*, **3**, 12 (2009).
[6] V. Valla, M.B. Christianopoulou. *Synth. React. Inorg. Met.-Org. Nano.-Met. Chem.*, **37**, 507 (2007).
[7] M. Gielen, M. Biesemans, R. Willem. *Appl. Organomet. Chem.*, **19**, 440 (2005).
[8] G. Salti, I. Ghersetich, F. Tantussi, B. Bovani, T. Lotti. *Dermatol. Surg.*, **34**, 60 (2008).
[9] S. Mukhopadhyay, U. Maitra. *Curr. Sci.*, **87**, 1666 (2004).
[10] A.M. Rotunda, H. Suzuki, R.L. Moy, M.S. Kolodney. *Dermatol. Surg.*, **30**, 1001 (2004).
[11] G. Ray, S.A. Husain. *Clin. Biochem.*, **34**, 71 (2001).
[12] A. Rehman, M.I. Choudhary, W.J. Thomsen. *Bioassay Techniques for Drug Development*, Vol. 9, Harwood Academic Publishers, Amsterdam, (2001).
[13] T. Mosmann. *J. Immunol. Methods*, **65**, 55 (1983).
[14] B.S. Manhas, A.K. Trikha. *J. Indian Chem. Soc.*, **LIX**, 315 (1982).
[15] T.P. Lockhart, W.F. Manders, E.M. Holt. *J. Am. Chem. Soc.*, **108**, 6611 (1986).
[16] C.C. Camacho, I.R. Oviedo, M.A.P. Sandoval, J. Cárdenas, A. Toscano, M. Gielen, L.B. Sosa, F.S. Bártez, I.G. Mora. *Appl. Organomet. Chem.*, **22**, 171 (2008).
[17] S. Shahzadi, S. Ali, K. Shahid, M. Yousaf, S.K. Sharma, K. Qanungo. *J. Chin. Chem. Soc.*, **57**, 659 (2010).
[18] J. Holeček, M. Nádvorník, K. Handlíř, A. Lyčka. *J. Organomet. Chem.*, **315**, 299 (1986).
[19] A.W. Addison, T.N. Rao, J. Reedijk, J. van Rijn, G.C. Verschoor. *J. Chem. Soc., Dalton Trans.*, 1349 (1984).
[20] J. Li, H. Yin, M. Hong. *ISRN Org. Chem.*, **2011,** 5 (2011).
[21] S.M. Abbas, S. Ali, S.T. Hussain, S. Shahzadi. *J. Coord. Chem.*, **66**, 2217 (2013).
[22] C.L. Ma, S.L. Zhang, Z.S. Hu, R.F. Zhang. *J. Coord. Chem.*, **65**, 2569 (2012).
[23] M. Sirajuddin, S. Ali, A. Haider, N.A. Shah, A. Shah, M.R. Khan. *Polyhedron*, **40**, 19 (2012).
[24] F. Ahmad, S. Ali, M. Pervez, A. Munir, M. Mazhar, K.M. Khan, T.A. Shah. *Heteroatom Chem.*, **13**, 638 (2002).
[25] V.O. White, J.A. Eisen, J.F. Heidelberg, E.K. Hickey, J.D. Peterson, R.J. Dodson, D.H. Haft, M.L. Gwinn, W.C. Nelson, D.L. Richardson, K.S. Moffat, H. Qin, L. Jiang, W. Pamphile, M. Crosby, M. Shen, J.J. Vamathevan, P. Lam, L. McDonald, T. Utterback, C. Zalewski, K.S. Makarova, L. Aravind, M.J. Daly, K.W. Minton, R.D. Fleischmann, K.A. Ketchum, K.E. Nelson, S. Salzberg, H.O. Smith, J.C. Venter, C.M. Fraser. *Science*, **286**, 1571 (1999).