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Organotin(IV) derivatives of amide-based carboxylates: Synthesis, spectroscopic characterization, single crystal studies and antimicrobial, antioxidant, cytotoxic, anti-leishmanial, hemolytic, noncancerous, anticancer activities

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Abstract

Four new triorganotin(IV) amide based carboxylates of general formula $R_3SnL^1$and R_3SnL^2, where R= Me(**1**,**3**) and *n*-butyl (**2**,**4**), and L^1= (Z)-4-(*p*-methoxyphenylamino)-4-oxo-2-butenoic acid (**HL^1**) L^2 = (Z)-4-(3,5-bis(trifluoromethyl)phenylamino)-4-oxo-2-butenoic acid (**HL^2**) have been synthesized by refluxing methanolic solution of organtin(IV) chloride and ligand (1:1 molar ratio). The synthesized compounds were characterized by FT-IR, elemental analysis, NMR (^{1}H, ^{13}C, ^{119}Sn &^{19}F) and single crystal X-ray crystallography. The ligands coordinate to tin atom through oxygens (carboxylate and amide) showing distorted trigonal bipyramidal geometry with polymeric bridging behavior in solid state. However, the geometry is switched over from trigonal bipyramidal to tetrahedral upon dissolution as confirmed by multinuclear (^{1}H, ^{13}C, ^{19}F and ^{119}Sn NMR). The prepared ligands and compounds **1**-**4** were screened for antimicrobial, antioxidant, cytotoxicity, hemolysis, antileishmanial and anticancer and noncancerous activities. The results showed significant antimicrobial activities, antioxidant, good cytotoxic LD_{50} values, percent hemolytic values, antileishmanial and anti-cancer activities. Compound **2** and **4** were found the most active antileishmanial and anticancer agent, respectively.

Keywords: Polymeric; Organotin(IV) carboxylates; Intramolecular hydrogen bond; Antileishmanial activity; Anticancer activity

1. Introduction

Cancer, recognized by uncontrolled cell growth, is a reason for million deaths worldwide [1]. It is the leading cause of mortality after the heart disease. In USA every 5th mortality is due to cancer [2]. In year 2005, cancer surpassed the heart diseases in USA. Chemotherapy is one of the strategies used to cure cancer. In this context, the use of metallodrugs as anticancer agents is track back to the fortunate discovery of *cisplatin,* which has shown the ability of halting cell division and since then metallo-anticancer drugs remain the focus of intensive investigations. *Cisplatin* has been approved as anticancer drug for testicular and ovarian malignancies in 1971 [3]. Several other analogues including oxaliplatin, carboplatin, lobaplatin and nedaplatin have got clinical status. Being similar in structure to cisplatin, the mechanism of action of the aforesaid variants is almost the same – they form adduct with DNA [4-6]. However, resistance and damaging side effects, due to their interaction with sulfur containing off-target biomolecules [7], diverted the attention of bioinorganic chemists to find alternate metal-based drugs. Among the known anticancer metallodrugs, organotin(IV) based drugs have received more attention due to their better anticancer activity [8,9]. In this context, organotin(IV) carboxylates have been evaluated and some of them were found more active anticancer agents than other compounds. Furthermore, organotin(IV) carboxylates unveiled a non-cross resistance and might have better activities as compared to platinum complexes [10]**.** The anticancer activity depends on the alkyl/aryl group and ligands attached to Sn atom. The better biological activities of triorganotin(IV) than the di- and mono-organotin(IV) analogues are because of their higher lipophilic characteristics [11,12]. Due to this reason the research on triorganotin(IV) carboxylates got considerable attention. Furthermore, structural modification of ligand and type of ligand's substituents have marked influence on the antiproliferative activity of organotin(IV) carboxylates [13].

Organotin(IV) carboxylates have also shown antileishmanial and antifungal properties [14]. According to WHO, Leishmaniasis is affecting twelve million people inhabitant of hot climatic areas. Appropriate treatment is vital during the growth of this sandy-fly mediated parasite disease otherwise patients may not be able to survive [15]. Scientists have developed several antileishmanial agents (e.g., Miltefosine, Amphotericin B, Glucantine and Pentamidine), that were not effective due to fluctuating degree of effectiveness and toxicity [16,17]. The use of antimony salt has displayed the worst condition [18]. In view of this, there is a dire need to develop new chemotherapeutic agent to treat leishmaniasis. Amide based organotin(IV) carboxylates may be one of the better alternate drug against leishmaniasis. Antibiotic resistance is another leading problem because of various types of bacterial strains. In this context, metal based drugs like organotin(IV) may play an important role in eliminating drug resistance issues. In view of the above, we have synthesized amide based organotin(IV) carboxylates, and characterized their physical and biological activities including anticancer, antileshmanial and antimicrobial activities. These complexes have also been screened for their antibacterial, antifungal, cytotoxic, hemolytic and antioxidant activities. In the current manuscript, we present some notable and novel biological data regarding amide based organotin(IV) carboxylates.

2. Experimental

2.1. Chemicals and procedures

Precursors CH_3SnCl, *n*-$(C_4H_9)_3SnCl$, N-ethyl-3,5-bis(trifluoromethyl)aniline, *p*-anisidine, maleic anhydride and sodium hydroxide were acquired from Sigma Aldrich. Solvents used in the study were procured from Sigma Aldrich and were dried according to published procedures [19]. M.P. was determined using a Melt-Temp (US) electro-thermal apparatus. The FT-IR spectra (in mid-infrared regions) and elemental analysis were recorded on

ThermoNicolett Impact series 10 FT-IR and CE-440 Elemental Analyzer, respectively. ^{1}H,^{13}C, ^{19}F and ^{119}Sn NMR were determined on Bruker (600MHz) Avance III HD,INOVA 400MHz, INOVA 500MHz using DMSO as a solvent. Single crystal X-ray analysis was performed on the Bruker Apex II Cu source CCD diffractometer. All non-hydrogen atoms were refined anisotropically and riding model was used for hydrogen atoms bonded to carbon. Hydrogen atoms bonded to nitrogen and oxygen were calculated from different maps and their coordinates refined. ShelXT was used to solve the structure and ShelXL2014 to polish the structures [20]

2.2 Synthetic procedures

2.2.1. Ligand synthesis: **(Z)-4-(p-methoxyphenylamino)-4-oxo-2-butenoic acid** (**HL^1**)

(Z)-4-(p-methoxyphenylamino)-4-oxo-2-butenoic acid (HL^1) was prepared by the reported method [21-24]. *p*-Anisidine or 4-methoxybenzenamine (1.0 g, 8.1mmol) dissolved in glacial acetic acid (40 mL) was added to round bottom flask (250 mL) containing maleic anhydride (0.8g, 8.1mmol) solution (40 mL) in the same solvent. Yellow precipitates were formed immediately. After 12 hours stirring, the precipitates obtained were filtered off, washed with cold distilled water and air dried. Yellow prism like crystals was obtained by slow evaporation of the acetonic solution at room temperature **(Scheme 1).** Numbering scheme for ligands and Sn attached organic group is given in **Scheme 2**.

$C_{11}H_{11}NO_4$: Yield: 89% (1.6 g): M.P. 199-200 ^{o}C: Mol.Wt: 221.07. FT-IR (cm^{-1}): 3284 ν(OH); 3124 ν(N-H); 1695 ν(NC=O); 1537 ν(COO_{asym}); 1278 ν(COO_{sym}); Δν (COO_{asym} - COO_{sym}) = 259: ^{1}H NMR {DMSO-d_6, δ (ppm)}: 6.27-6.33 (d, H_2,1H, $^{3}J_{(^{1}H,\ ^{1}H)}$ =12.16 Hz; 6.44-6.49 (d, H_3,1H, $^{3}J_{(^{1}H,\ ^{1}H)}$ = 12.14 Hz; 7.51-7.53 (d,$H_{6,6'}$,2H, ^{3}J (^{1}H,^{1}H) =9.4 Hz; 6.66-6.73(d,$H_{7,7'}$,2H, ^{3}J (^{1}H,^{1}H)= 9.14; 3.75 (s, H_9,3H); 10.30 (s,1H, NH,);12.9 (s,1H,COOH).^{13} C NMR (DMSO-d_6) δ(ppm): 167.0 (C_1);131.8 (C_2);.132.09 (C_3); 163.2 (C_4); 131.72 (C_5); 121.6 (C_6); 114.4 (C_7); 156.3 (C_8); 55.6 (C_9).

2.2.2. Synthesis of ligand 2: **(Z)-4-(3,5-bis(trifluoromethyl)phenylamino)-4-oxobut-2-enoic acid(HL^2)**

(Z)-4-(3,5-bis(trifluoromethyl)phenylamino)-4-oxobut-2-enoic acid(HL^2) was synthesized by the following reported procedure [25] using 3,5-*bis*(trifluoromethyl)benzenamine (1.0g, 5.5mmol) and maleic anhydride ((0.54g, 5.5mmol) dissolved in dichloromethane (100 mL). After 8 hours reflux with constant stirring, the solution was left overnight to get white precipitates. After filtration, the precipitates were washed with distilled water and 10 % dilute HCl. White needle like crystals of HL^2 were obtained by the slow evaporation of the methanolic solution at room temperature **(Scheme 1)**.

$C_{12}H_7F_6NO_3$: Yield: 1.31g, 85% M.P.153 ^oC: Mol. Wt: 327.18, FT-IR (cm^{-1}), 3286 ν(OH); 3102 ν(N-H); 1711 ν(NC=O); 1569 ν(COO_{asym}); 1278 ν (COO_{sym}); Δν (COO_{asym} - COO_{sym})= 291 Δ ν.^{1}H NMR (DMSO-d_6) δ(ppm): 6.40-6.36 (d,H_2,1H, ^{3}J (^1_H, ^1_H)=11.91 Hz) ; 6.52-6.48 (d,H_3, 1H, ^{3}J (^1_H, ^1_H)=11.88 Hz); 8.39 (s,$H_{6,6'}$,2H); 7.78 (s,H_8,1H); 10.70 (s,1H,NH); 12.88 (s,1H,COOH).^{13}C NMR (DMSO-d_6) δ(ppm): 170.6 (C_1);130.5 (C_2);140.5 (C_3);166.7 (C_4);132.5 (C_5); 119.7 (C_6);131.9 (C_7); 118.7 (C_8); 124.5 (C_9).^{19}F NMR: (DMSO-d_6), 375 MHz) δ (ppm)= -57.

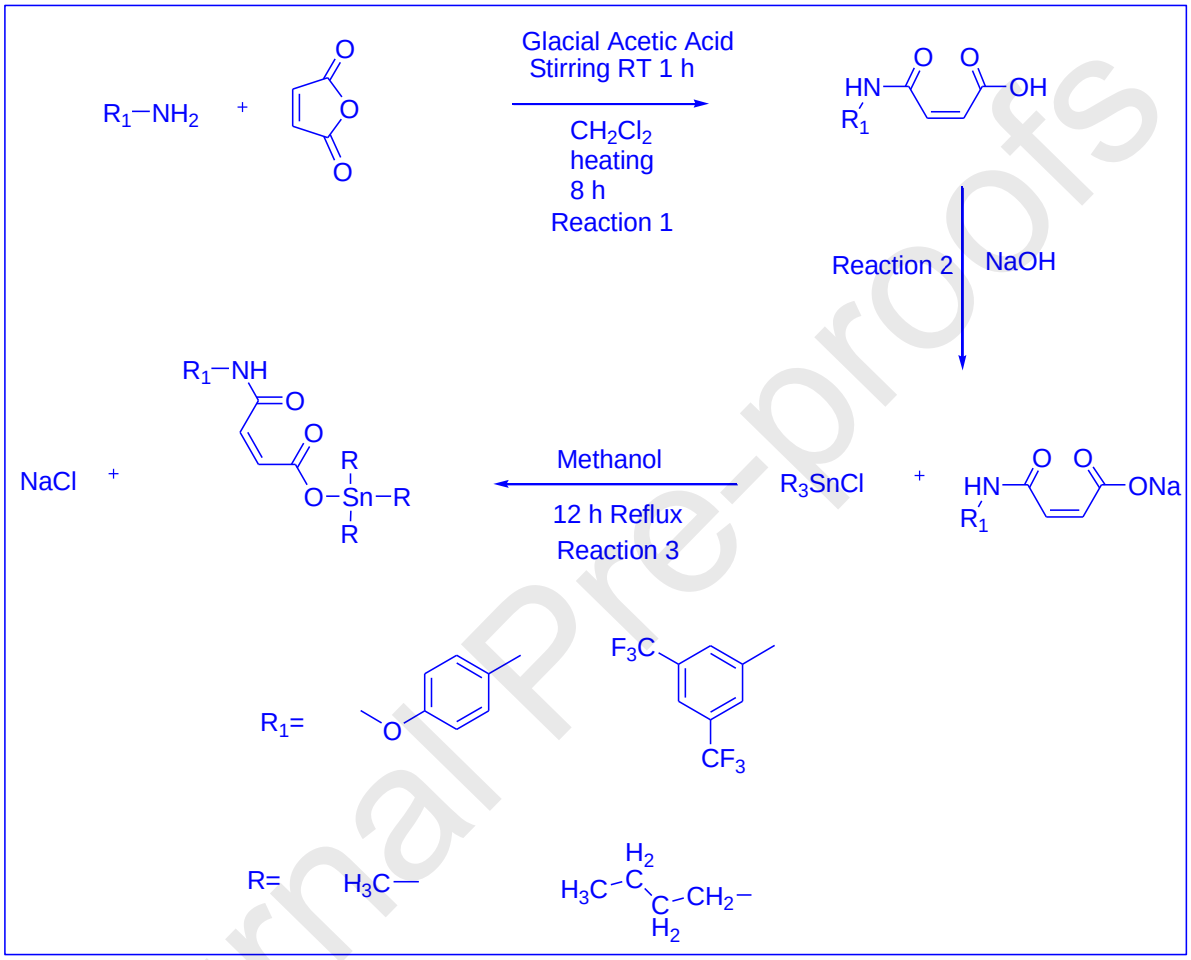
2.2.3. Synthesis of ligand salts

The ligand salts were synthesized by the dropwise addition of an aqueous solution of NaOH (0.16 g, 4 mmol) to the ligand (HL^1 and HL^2) suspension in distilled water (1:1 molar ratio). The resulting solution was stirred at room temperature until a clear solution was obtained, which was then rotary evaporated to get sodium salt of the corresponding ligand (**Scheme 1**).

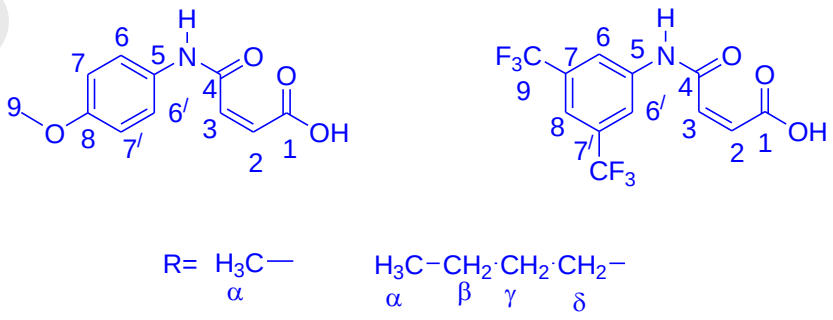
2.2.4. Preparation of oraganotin(IV) complexes

These organotin(IV) compounds were synthesized by refluxing stoichiometric amounts of R_3SnCl {trimethyltin(IV) chloride (0.4g, 2.0 mmol) and Tributyltin(IV) chloride (0.65g, 2.0

mmol) with sodium salt of the ligand {NaL^1 (0.5g, 2.0mmol) and NaL^2 (0.6 g, 2.0mmol) in methanol for 10 hours. The reaction mixture was then left uninterrupted overnight to let the NaCl precipitated. After filtration the solvent was rotary evaporated and the obtained solid product was then recrystallized in chloroform and *n*-hexane mixture (4:1) **(Scheme 1)**.



Scheme 1: Synthesis of ligands, ligand salts and complexes.



Scheme 2: Numbering scheme for ligands and Sn attached organic group.

2.2.5. (*Z*)-trimethylstannyl 4-(4-methoxyphenylamino)-4-oxobut-2-enoate (1)

Yield: 0.62 g, 78%: M.P. 158^{o}C: Mol.Wt: 385.03: Anal cal. for $C_{14}H_{19}NO_4Sn$: C, 43.70(43.79); H, 5.10 (4.99); N, 3.72 (3.65): FT-IR (4000-400 cm^{-1}): 3468 ν(N-H); 1711 ν(NC=O); 1547 $\nu(COO_{asym})$; 1308 $\nu(COO_{sym})$; Δν (COO_{asym} - COO_{sym}) = 239; 530 ν(Sn-C); 460 ν(Sn-O).^{1}H NMR (DMSO-d_6) δ(ppm): 6.19-6.26 (d,H_2,1H, ^{3}J ($^{1}_{H}$, $^{1}_{H}$)=13.44 Hz);6.26-6.33 (d, H_3,1H, ^{3}J ($^{1}_{H}$, $^{1}_{H}$)=13.45 Hz);7.51-7.53 (d,$H_{6,6'}$,2H, ^{3}J ($^{1}_{H}$,$^{1}_{H}$) =12.59 Hz);6.98-6.83 (d,$H_{7,7'}$,2H, ^{3}J ($^{1}_{H}$,$^{1}_{H}$)=13.44 Hz); 3.80 (s,H_9,3H); 11.6 (s,1H,NH); 0.67(s,$H_α$,9H) ^{2}J[^{119}Sn-$^{1}H_α$]=57Hz); ^{13}C NMR (DMSO-d_6) δ(ppm): 170.1 (C_1); 130.89 (C_2); 138.7 (C_3); 162.1 (C_4); 128.92 (C_5); 122.12 (C_6); 113.7 (C_7); 156.4 (C_8); 55.5 (C_9); -2.07 ($C_α$) [^{119}Sn-$^{13}C_α$] =446 Hz; ^{119}Sn NMR: (DMSO-d_6), 225 MHz) δ (ppm)= -16.

2.2.6. (Z)-tributylstannyl 4-(4-methoxyphenylamino)-4-oxobut-2-enoate (2):

Yield:0.82 g, 78%: M.P. 90^{o}C: Mol.Wt: 511.17: Anal cal.for $C_{23}H_{37}NO_4Sn$: C, 54.20 (54.14); H, 7.26 (7.31); N, 2.78 (2.75):FT-IR (cm^{-1}): 3327 ν(N-H); 1693 ν(NC=O); 1570 $\nu(COO_{asym})$; 1289 $\nu(COO_{sym})$; Δν (COO_{asym} - COO_{sym}) = 281Δν; 523 ν(Sn-C); 470 ν(Sn-O).^{1}H NMR (DMSO-d_6) δ(ppm): 6.33 (d,H_2,1H, ^{3}J ($^{1}_{H}$, $^{1}_{H}$)=13.44 Hz); 6.89 (d, H_3,1H, ^{3}J ($^{1}_{H}$, $^{1}_{H}$)=13.45 Hz); 7.52 (d,$H_{6,6'}$,2H, ^{3}J (^{1}H,^{1}H) = 12.59 Hz); 7.25-7.33 (d,$H_{7,7'}$,2H, ^{3}J ($^{1}_{H}$,$^{1}_{H}$) =13.44); 3.73 (s,H_9,3H); 11.5 (s,1H,NH); 1.30 (t,$H_α$,6H);^{3}J($^{1}_{H}$,$^{1}_{H}$)=7.53Hz; 1.36 (m,$H_β$,6H); 1.62 (t,Hγ,6H,); 0.89 (t,Hδ,9H), ^{3}J(^{1}H,^{1}H)=7.33Hz. ^{13}C NMR (DMSO-d_6) δ(ppm): 172.1 (C_1); 131.6 (C_2); 138.0 (C_3); 162.0 (C_4); 127.9 (C_5); 121.3 (C_6); 114.0 (C_7); 156.0 (C_8); 55.4 (C_9); 17 (Cα) ^{1}J[$^{119}_{Sn}$-$^{13}C_α$] =365 Hz; 25 ($C_β$) ^{2}J[$^{119}_{Sn}$-^{13}C] = 75 Hz; 27.7 ($C_γ$) ^{3}J[$^{119}_{Sn}$-^{13}C]= 24 Hz; 13.5 ($C_δ$).^{119}Sn NMR: (DMSO-d_6) , 225 MHz) δ(ppm)= 136.

2.2.7. Trimethylstannyl 4-(3,5-bis(trifluoromethyl)phenylamino-4-oxobut-2-enoate (3)

Yield: 0.72 g, 80%: M.P. 123^{o}C: Mol.Wt: 491: Anal cal. for $C_{15}H_{15}F_6NO_3Sn$: C, 36.89 (36.77); H, 3.2 (3.09); N, 2.74(2.86). FT-IR (cm^{-1}): 3117ν(N-H); 1675ν(NC=O); 1575

ν(COO_{asym}); 1275ν(COO_{sym}); Δν (COO_{asym} - COO_{sym})=300Δν; 546ν(Sn-C); 452ν(Sn-O). ^{1}H NMR (DMSO-d_6) δ(ppm): 6.30-6.35 (d,H_2,1H, ^{3}J (^{1}H, ^{1}H)=13.47 Hz) ; 7.25 (d,H_3, 1H, ^{3}J (^{1}H, ^{1}H)=13.47 Hz); 8.11 (s,$H_{6,6'}$,2H); 7.57 (s,H_8,1H); 9.5 (s,1H,NH); 0.68(s,$H_α$,9H) ^{2}J[^{119}Sn-^{1}Hα]=58Hz);. ^{13}C NMR (DMSO-d_6) δ(ppm): 171.3 (C_1); 130.4 (C_2); 139.5 (C_3);162.9 (C_4);136.7 (C_5); 119.8 (C_6); 131.9 (C_7); 117.2 (C_8); 128.4 (C_9); -1.7 ($C_α$)[^{119}Sn-^{13}Cα] = 392 Hz;. ^{119}Sn NMR: (DMSO-d_6) , 225 MHz) δ (ppm) = 151. ^{19}F NMR: (DMSO-d_6) , 375 MHz) δ (ppm)= -63.

2.2.8.Tributylstannyl 4-(3,5-bis(trifluoromethyl)phenylamino)-4-oxobut-2-enoate (**4**)

Yield:0.81 g,71%: M.P. 104^{o}C: Mol.Wt: 617.1: Anal cal. for $C_{24}H_{33}F_6NO_3Sn$: C, 46.92(46.78); H, 5.32 (5.4); N, 2.38 (2.27):FT-IR (cm^{-1}): 3120 ν(N-H); 1683 ν(NC=O); 1576 ν (COO_{asym}); 1274ν(COO_{sym}); Δν (COO_{asym} - COO_{sym})=302Δν; 525ν(Sn-C); 452 ν(Sn-O).^{1}H NMR (DMSO-d_6) δ(ppm): 6.34-6.39 (d,H_2,1H, ^{3}J (^{1}H, ^{1}H)=13.47 Hz) ; 7.25 (d,H_3, 1H, ^{3}J (^{1}H, ^{1}H)=13.47Hz); 8.08 (s,$H_{6,6'}$,2H); 7.58 (s,H_8,1H); 9.7 (s,1H,NH);1.30 (t,$H_α$,6H) ^{3}J(^{1}H,^{1}H)=7.4Hz, ^{2}J[^{119}Sn-^{1}H]=56 Hz); 1.34 (m,$H_β$,6H);1.64 (t,$H_γ$,6H,); 0.91 (t,Hδ,3H) ^{3}J(^{1}H,^{1}H)=7.33 Hz .^{13}C NMR (DMSO-d_6) δ(ppm): 171.5 (C_1);129.8 (C_2);138.9 (C_3);162.5 (C_4);136.1 (C_5); 119.7 (C_6); 132.0 (C_7); 117.2 (C_8); 124.4 (C_9);17.3 ($C_α$) [^{119} Sn-^{13}Cα] =416 Hz; 26.9 ($C_β$) [^{119} Sn-^{13}Cβ]= 68 Hz; 27.6 ($C_γ$) [^{119} Sn-^{13}Cγ]= 24 Hz; 13.3 ($C_δ$).^{119}Sn NMR: (DMSO-d_6) , 225 MHz) δ(ppm)= 137. ^{19}F NMR: (DMSO-d_6 , 375 MHz) δ(ppm) = -63

3. Results and Discussion:

3.1 FT-IR Studies

The infrared spectra of the synthesized ligands and their organotin(IV) complexes were recorded in the mid-infrared region. The appearance of a broad peak (around 3100-2500 cm^{-1}) for OH and relatively sharp peak for NH (3057cm^{-1}= **HL^{1}** and 3102 cm^{-1} = **HL^{2}**) indicate

synthesis of the ligands. For organotin(IV) carboxylates, the absorption frequencies of prime significance are ν(COO^-), ν(Sn-O) and ν(Sn-C). The absence of a broad peak pertinent to OH and a new peak for Sn-O (430-480 cm^{-1}) has been appeared, indicating coordination of carboxylate ligand to organotin moiety. The difference in COO^- asymmetric and symmetric stretch {(Δν= ν(COOasym) - (COOsym) gives valuable information about the approach of coordination of the carboxylate ligands to tin epicenter [26-28]. Δν value falls in the range 302-239 cm^{-1}, signifying monodentate bonding of carboxylate to Sn atom. The presence of Sn-C peak (580-520 cm^{-1}) signifies that the alkyl groups remain intact with Sn during synthesis [29,30].

3.2. ^{1}H, ^{13}C, ^{119}Sn and ^{19}F NMR studies

^{1}H,^{13}C,^{119}Sn and ^{19}F NMR spectra for the synthesized complexes was carried out in DMSO-d_6 solvent and the data is given in the experimental section.

3.2.1.^{1}H NMR

In complexes **1-4**, an absence of the acidic OH peak (10-13 ppm) has confirmed the coordination of carboxylate anion to organotin(IV) moieties. The methyl proton in trimethytin derivatives (**1** and **3**) gave a sharp singlet with $^{2}J_{[^{119}Sn,\ ^{1}H]}$ with coupling values of 57 Hz (**1**) and 58 Hz (**2**), thus confirming tetrahedral geometry around Sn. In tributyltin(IV) complexes (**2** and **4**), β and γ protons of the tributyl were observed as a multiplet, Sn attached CH_2 as a triplet {1.62 ppm (**2**) $^{2}J^{1}_{H}$, $^{1}_{H}$ = 8.0 Hz and 1.64 ppm (**4**) $^{2}J^{1}_{H}$, $^{1}_{H}$ = 8.0 Hz} and terminal CH_3 as an upfield triplet {(0.96 ppm, $^{2}J^{1}_{H}$, $^{1}_{H}$ = 7.3 Hz (**2**) and 0.91 ppm (**4**), $^{2}J^{1}_{H}$, $^{1}_{H}$ = 7.3 Hz } [23]. The presence of NH signal confirms no deprotonation of amide upon ligand coordination to tin. The calculate θ for complexes **1** and **2** using Lockhart equation has confirmed the tetrahedral geometry in solution [31].

3.2.2. ^{13}C NMR

In ^{13}C NMR spectra of the organotin(IV) derivatives, the carboxylic carbon has been observed downfield than the free ligand because of diminution of the electron density at carboxylic carbon upon complexation (**Fig.S1-S4**). This downfield shift is a confirmation for the coordination of carboxylate oxygen to Sn [32]. The signals for aryl, –C-N- and alkyl groups connected to tin appeared in their expected regions [27-28]. By adding value of ^{1}J [^{119}Sn, ^{13}C] in the Lockhart's equation, C-Sn-C bond angle was calculated for methyltin(IV) and butyltin(IV) derivatives (**Table 1**). The complexes **1-4** exhibit ^{1}J[^{119}Sn, ^{13}C], 446 Hz (114.8^{o}), 365 Hz (108.7^{o}), 392 Hz (111.14^{o}) and 416 Hz (113.2^{o}), respectively, which represent tetra-coordinated tin(IV) in solution [33-35].

3.2.3. ^{119}Sn NMR studies

The presence of ^{119}Sn NMR peak at -46 (**1**), 136 (**2**), 151 (**3**) and 137 (**4**) ppm authenticated tetra coordination of tin. The electron withdrawing and donating groups of ligand and the substituent and it's electronegativity effect at the tin atom seem responsible for variation in^{119}Sn NMR value [36-40].

3.2.4.^{19}F NMR

The fluoro bonded ^{13}C gave a specific pattern of ^{13}C chemical shift values. In HL^2 the fluorine signal of CF_3 appeared at -57 ppm, which was shifted upfield (-63 ppm) in complexes **3** and **4**. This upfield shift might be because of the back donation from metal to ligand which in turn increasing electronic density on fluorine atom [41].

3.3. Single crystal X-ray studies

The crystal structures of compounds **1**, **3** and **4** with intramolecular interactions are given in Figures **1-7** and particular geometric parameters, bond lengths and bond angles are given in

Tables 2 and 3. While a related series of compounds (to be published elsewhere) refined well, the anisotropic refinement of the atoms of **3** and **4** here resulted in elongated temperature factors and disordered butyl groups (for compound **4**) in sharp contrast to the other compounds. The inability of these compounds (**3** and **4**) to form well-ordered crystals is probably a consequence of the very weak intermolecular interactions between the CF_3 and CH_2 groups (with very weak H···H and H···F interactions). Compound **4** goes through a phase change on cooling (with the disintegration of the single crystal) and the data were collected at 173 K instead of 100 K. All the compounds having bridging polymeric structure in the solid state and distorted trigonal bipyramidal with one elongated apical Sn-O bond. The three organic groups (methyl and butyl groups) are mutually equatorial and form the base of the bipyramid and the two oxygen atoms, one from carboxylate moiety and other from amide carbonyl, occupy axial positions. It is the amide carbonyl that forms the weak bond to the Sn atom. The Sn atom has a $5s^2 5p^2 4d^{10}$ configuration. The trigonal bipyramidal coordination geometries are best rationalized in terms of electron configuration and the relative large radius of a Sn atom. The four valence electrons are donated primarily to the three Sn-C bonds and the short Sn-O bond. The second Sn—O bond is considered to be a weak hypervalent interaction. Although higher coordination numbers are very rare in carbon and to a greater extent for silicon; higher coordination numbers are accessible to Sn due to its relatively large size. As in Inorganic Chemistry; the relative sizes of the cations and the anions play an important role in the coordination numbers in tin compounds. In an analysis of the coordination geometry in compounds **1** and **3**, the three methyl groups that are connected to tin form the basal plane with C2-Sn1-C1(118.7(2)^o), C3-Sn1-C1(116.9(2)^o), C3-Sn1-C2 (123.2(2)^o), C13-Sn1-C15 (123.7(2)^o), C13-Sn1-C14(115.9(2)^o), C14-Sn1-C15(117.3(2)^o). The two oxygen atoms form the 3-fold axis in an idealized D_{3h} trigonal bipyramid arrangement one from carboxylate moiety and other from amide carbonyl occupy axial

positions with O1-Sn1-O3 (176.48(11)^{o}) and 179.19(11)^{o}) in compounds **1** and **3**, respectively. The pivot atom that best describes the Berry pseudorotation is C(1) in compound **1** and C(14) in compound **3** with a 9% transformation to square pyramidal geometry. In compound **4**, the large values for the anisotropic temperature factors for the butyl groups means that there is a large uncertainty in the ligand-Sn angles and this reflects the considerable flexibility of the L-Sn-L angles. The trigonal carbon atoms have bond angles ranging from 116.5(3)˚ to 120.0(3)˚ while two apical oxygen atoms, one from carboxylate moiety and other from the amide group form angles of 176.48(11)^{o}) and 179.19(11)^{o} with the tin atom. The five-coordination of Sn atom can also be calculated by using Tau value (τ =(β-α) / 60, where β is higher C-Sn-C basal angle and α is the second higher basal angle [42]. The unitary value for τ indicates an exact trigonal bipyramid (β=180^{o} and α=120^{o}) while zero indicates and exact square pyramid (α=β=180^{o}) [19]. For compound **1** the τ value 0.89 (β= O1-Sn1-O3^{1}=176.48^{o} and α= C3-Sn1-C2=123.23^{o}), for the compound **3** the τ = 0.92 (β= O1-Sn1-O3^{1}=179.19^{o} and α= C13-Sn1-C15=123.66^{o}). There are two independent molecules in compound **4**. For molecule 1 the τ = 0.97 (β= O1-Sn1-O3^{1}=178.06^{o} and α = C12(2)-Sn1-C12(8)=116.5). For Sn(2) the τ=0.93 (β= O1-Sn1-O3^{1}=175.76^{o} and α= C12(2)-Sn1-C12(8)=119.86) which designates a relatively undistorted trigonal bipyramidal geometry [43]. The trend of shifting from trigonal bipyramidal to square planar geometry is associated with secondary intermolecular Sn···O interactions [44,45]. One ligand carboxylate oxygen is attached with Sn atom in mono-dentate fashion with tin-oxygen covalent bond [(Sn(1)–O(1) = 2.118 Å and [(Sn(1)–O(1) = 2.169 Å respectively, which is almost near to the covalent radii (2.13Å) and other amide linked oxygen of another carboxylate ligand coordinated with tin-oxygen bond by coordinate covalent bond. The bond distance Sn(1)–O(3^{1}) = 2.399 Å) and Sn(1)–O(3^{1}) = 2.527 Å), are lesser than the totality of the Van der Waals radii of tin and oxygen (3.68 Å) and greater than the totality of

the covalent radii of tin and oxygen (2.13Å) which is feeble type of interaction between these atoms [46]. The two ligands are interrelated with one another by oxygen atoms involving Sn moiety, thus making a 1D polymeric network. Among the two Sn-O bonds, one of the Sn-O bond is longer than its counterpart. As being weak in nature, this Sn-O bond is probably prone to dissociate in solution altering the geometry from trigonal bipyramidal to tetrahedral one (Table 3). The solid state structure of **1** which is depicted in Figures 1 and 2 and interatomic parameters are exhibited in Tables 1 and 2. The crystal structure of this compound is mediated by intramolecular O···H interactions. This interaction makes a seven membered ring in the compound which are rarely seen in organotin(IV) complexes in the polymer chain in solid state. The polymeric chain is alleviated by C-H···π interactions and intramolecular hydrogen bond in a zigzag manner, which is associated into a 3-D network via C-H···π interactions [47,48].

4. Biological activities

4.1. Antibacterial activities

The ligands (**HL^1** and **HL^2**) and their complexes (**1-4**) were screened against three Gram negative bacterial strains (*B. bronchiseptica* ATCC#4617, *S. typhimurium* ATCC#14028 and *E. aerogenes* ATCC#13048) according to the formerly described procedure [49] and the statistics are represented in Figure 8a. A criterion for the activity was based on zone of inhibition. All the compounds, except compound **3,** showed activity against all strains. A mixed behavior of activity was observed among ligands and their complexes-sequence varies from strain to strain. The data revealed that triorganotin(IV) compounds are more active than their corresponding ligands, an observation in consonance with the earlier reports [50]. Furthermore, ligand **HL^1** and its organotin compounds were found more active than the ligand **HL^2** and its organotin compounds. Compound **1** was found active against all the three

strains, however, **2** showed better activity than **1** against *B.Bronchiseptaca*. Higher activity of **4** than **3** can be attributed to more lipophilic nature of the tributyltin than trimethyltin [51].

4.2. Antifungal activities

Antifungal activity of extracts was evaluated following previously described standard protocol [52]. The antifungal activity (Figure 8b) of the synthesized ligands (**HL^1**&**HL^2**) and complexes (**1**-**4**) were tested against three fungal strains (*A. fumigatus* FCBP#66, *F. solani* FCBP#0291, *N.niger* FCBP#0300). Antifungal activity of the complexes was found greater than the ligands with few exceptions. Tributyltin(IV) derivatives were found more active than the trimethyltin(IV) derivatives, a behavior reasonably consistent with the earlier report [56].

4.3. Antioxidant Activities

Total antioxidant activity of extracts was evaluated by method [53]. The antioxidant activities of the prepared compounds were evaluated by the method described in earlier reports. The antioxidant activities of the prepared compounds were evaluated by the method described in earlier reports. A significant antioxidant capacity 25.0, 22.0, 21.0 and 11.5 μg Ascorbic acid Equivalent (AAE)/mg extract was found in compound **2, 4, 1** and **3,** respectively as depicted in Figures 9a. In total reducing power (TRP) assay, the highest reducing power potential was observed for **HL^2**, followed by **2, HL^1**, **4, 3** and **1** (Figure 9b). DPPH free radical scavenging potential was found by the ability of antioxidants to decolorize 2,2-diphenyl-2-picryl-hydrazyl. Among all compounds analyzed the %inhibition ranged from 55 to 33.1. The activity varies the following sequence **2** > **1** > **HL^2** > **HL^1** > **3** > **4** (Figure 9c). The results are comparable to the earlier reports [54].

4.4. Cytotoxicity

Lethality test was performed in a 96 well plate against brine shrimp (*Artemia salina*) larvae as previously described [53] with slight modification. *A. salina* eggs (Ocean star, USA) were incubated for 24-48 h under light at 30-32°C in simulated sea water (38 g/L supplemented with 6 mg/L dried yeast) in a specially designed two-compartment plastic tray. Ten mature phototropic nauplii were harvested with the help of Pasteur pipette and transferred to each well of plate. Corresponding volume of each extract containing ≤ 1% DMSO in sea water at final concentrations of 500 and 200 µg/mL was transferred to the wells containing sea water and shrimp larvae. The final volume in each well was kept 300 µL. Positive and negative control wells included serial concentrations of doxorubicin and 1% DMSO, respectively. After 24 h incubation, live shrimps were counted and percentage of deaths was determined. Median lethal concentration (LC_{50}) was calculated using table curve 2D v5.01 software.

The synthesized ligands (**HL^1 & HL^2**) and complexes**1-4** were also screened for cytotoxicity using Brine shrimp (Artemia asalina) bioassay lethality method [55] and results are shown in the Figure 9b. The data illustrate that all compounds are cytotoxic and the LD_{50} values decreased in following sequence: **1**>**3**>**2**>**4**.

4.5. Hemolysis Assay

Hemolysis assay was performed in order to check the cytotoxicity of the compounds on human blood erythrocytes. For this 8mL of the blood was taken from an anonymous human donor with prior consent and as per ethical guidelines provided by ethical committee of the Department of Biotechnology Abdul Wali Khan University Mardan and pour directly into K_2-EDTA tubes to prevent coagulation. The blood was diluted 1:3 with autoclaved Phosphate Buffer Saline (PBS) pH 7.04 by. Erythrocytes were collected by centrifugation at 1500rpm for 10 minutes. The supernatant was discarded and pellet was washed with PBS three times

and centrifuged after each wash with above-mentioned condition. The pellet was transferred into a 50mL conical flask and PBS was added three times to the actual volume of the blood. The screening compounds **HL^1, HL^2, 1, 2, 3 and 4** were added into Eppendorf tubes already containing 1 mL of blood erythrocytes to make three different concentrations i.e. 25ppm, 50ppm and 100ppm. Triton X-100 (0.5%) was used as positive control as it has 100% hemolysis ration while DMSO was taken as negative control. The Eppendorf tube containing the target compound and blood erythrocytes were incubated for one hour at 37ºC. After incubation, the erythrocyte suspensions were centrifuged at 1000 ×g for 10 min and the cell lysis (haemoglobin release) was determined spectrophotometrically at 576 nm on spectrophotometer (Agilent-DAD, 8453, Agilent Tech., Germany) [1,2]. The results were determined by evaluating the percentage of hemolysis compared to the negative and positive controls using the following formula;

Hemolysis (%) = [(O.D. 576 nm in the sample solution – O.D. 576 nm in DMSO)/ (O.D. 576 nm in 0.5% Triton X-100 – O.D. 576 nm in DMSO)] x 100

Hemolysis assay was done in order to evaluate the cytotoxicity of the compounds on human blood erythrocytes. The synthesized compounds were checked for it's cytotoxic activity and was likened with Triton X-100 (0.5%). The results (Table 4) showed that **HL^2** was found to be the least toxic in term of percent hemolysis, followed by **1**, **3** and **HL^1**, while **4** and **2** were observed to be highly toxic as compared to Triton X-100 with high percent hemolysis ratio. In nutshell, compound with low percent hemolysis and high IC_{50} (HL^1, HL^2 and 3) value is considered the best.

4.6. Antileishmanial assay

The promastigote forms of *L. tropica* (1 x 10^4 cells/well) were seeded in 96-well microtiter plates in RPMI-1640 (Gibco®) supplemented with 10% FBS (Gibco®) and 1% antibiotics and allowed to grow either in the presence of various concentrations (1000, 500 and 250 µg/mL) of test compounds (I-C-30, I-C-11, L-7, L-9, I-C-19 and I-C-20) or in the absence (negative control) of the test compound for 72 hours at 25ºC. After the incubation period was completed, viability of the promastigote form was assessed by MTT (3-(4,5- dimethylthiazol-2yl)-2,5-diphenyltetrazolium bromide) colorimetric method (Mosmann, 1983). For this a 100µl of the MTT dye were added to each well and the plates were incubated for 3 hours at 37ºC. In last, 40µl of the DMSO as solubilization solution was added into each well and the readings were recorded using an ELISA plate reader (Biotek Elx800) at 570 nm. Amphotericin-B was taken as positive control. The experiment was performed in triplicates while counting of leishmania promastigote was done using neubauer chamber.

For the anti-leishmanial assay, the synthesized ligands (**HL^1 & HL^2**) and complexes **1**-**4** were solubilized in DMSO. The percent inhibition and IC_{50} values are given in the Table 5 and represented in Figure 10a. All compounds showed good result except **HL^1** in terms of percentage inhibition. Interestingly, **HL^2** showed high percentage inhibition at higher concentration but its potency lowers at low concentrations. It is worth mentioning that compound **4** also showed high anti-leishmanial **activity which decreases with the decrease in concentration. Amphotericin-B used as positive control showed 100% inhibition at all the concentration tested.** The observed anti-leishmanial activity order is **2** > **3** > **4** > **1**.

4.7. Anticancer and non-cancerous cells activity

Breast cancer cell line (MCF-7) and human endometrial stromal cells (hESCs) were used for cytotoxic analysis. MCF-7 was grown in EMEM with 1% penicillin/streptomycin, 10% FBS and 0.01 mg/ml insulin. hESCs were grown in DMEM/Ham's F12 with 10 % FBS and 1%

penicillin/streptomycin. Both the cells were maintained in a humidified incubator with 5% CO_2.For cytotoxic analysis, 4 X 10^4 cells were seeded per well in a 96 well plate and allowed to reach 80% confluence. The salts were dissolved in DMSO, added to the cells (final concentrations of 1000, 500, 250, 125, 62.5, 31.25 & 15.63 µM) and incubated for 48 h. The cell survival was determined by MTT assay according to the manufacturer's instruction (Vybrant^{TM} MTT Cell Proliferation Assay Kit, Thermofisher).

In order to determine the cytotoxic effect of compounds on cancer and normal cell line, the cells were treated with ligands (**HL^1**, **HL^2**) and complexes **1**-**4** at various concentrations and determined the cytotoxicity by MTT assay. The IC_{50} values of the compounds are given in Table 6 and represented in Figure 10b. The compounds **2** and **3** have shown strong growth inhibition properties with IC_{50} < 15.6. However, **4** can be a good anticancer compound for further evaluation as it is twenty times more active against anticancer cells as compared to normal cells.

5. Structure-activity relationship

The biological action of organotin(IV) carboxylates depends on their geometry and types ligands coordinated to tin atom. It is well documented fact that triorganotin(IV) compounds are being more active than their di-analogues owing to more lipophilic character enabling them to cross lipid layer of the cell membrane of microbes with more ease [48]. For complexes **2** and **4**, the better antimicrobial, anti-oxidant, anti-leishmanial, hemolytic and anticancer activity, despite of few exceptions, are due to more lipophilic organic groups and presence of electronegative substituent i.e. fluoro. The latter enable the complexes to bind strongly with cell vital components altering their structural and functional chemistry-ultimately death of the microbe [49].

6. Conclusion

Four new triorganotin(IV) amide based carboxylates {$R_3SnL^1$and R_3SnL^2, Where R= Me(**1**,**3**) and n-butyl(**2**,**4**), and L^1=(Z)-4-(4-methoxyphenylamino)-4-oxobut-2-enoic acid (**HL^1**) L^2= (Z)-4-(3,5-bis(trifluoromethyl)phenylamino)-4-oxobut-2-enoic acid (**HL^2**)} of biological significance have been synthesized and characterized by FT-IR, elemental analysis, and NMR (^{1}H, ^{13}C, ^{119}Sn, & ^{19}F). In solid state, these complexes are polymeric in nature in which each Sn atom is five-coordinated (IR and X-ray single crystal), however, in solution, one of the two Sn-O bonds is no more intact rendering monomeric form having Sn atom in four-coordination environment (NMR). The compounds **1**-**4** were screened for antimicrobial, antioxidant, cytotoxicity, hemolysis, antileishmanial, and anticancer activities. The results showed significant antimicrobial activities, good cytotoxic LD_{50} values, percent hemolytic values and good IC_{50} values for anti-cancer activities with few exceptions. Remarkably compound **4** is twenty times more anticancerous as compared to normal cells.

Supplementary material

Single-crystal X-ray diffraction data for the structural analyses have been deposited with the Cambridge Crystallographic Data Center, CCDC Nos. 1941613 (**1**), 1941614 (**2**) and 1941615 **(4)** A copy of this information may be obtained free of charge from the Director, CCDC, 12 Union Road, Cambridge, CBZ 1EZ, UK (Fax: +44 1223 336033; Email: deposit@ccdc.cam.ac.uk or www: http://www.ccdc.cam.ac.uk). Further experimental details regarding the materials used and the methods employed, together with anticancer and antioxidant assay data are also given here.

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References

[1] A. Attanzio, M. Ippolito, M.A. Girasolo, F. Saiano, A. Rotondo, S. Rubino, L. Mondello, M.L. Capobianco, P. Sabatino, L. Tesoriere, G. Casella, *J. Inorg. Biochem.* 188 (2018) 102.

[2] W.A. Wani, S. Prashar, S. Shreaz, S. Gomez-Ruiz, *Coord. Chem. Rev.* 312 (2016) 67.

[3] H. Khan, A. Badshah, G. Murtaza, M. Said, M., Zia-ur-Rehman, C. Neuhausen, M. Todorova, B.J. Jean-Claude, I.S. Butler, *Eur. J. Med. Chem*. 46 (2011) 4071.

[4] W. Wu, L. Fan, Z. Bao, Y. Zhang, Y. Peng, M. Shao, L. Tao, *Biochem. Biophys. Res. Commu*. 487 (2017) 292.

[5] J. Poljaková, T. Eckschlager, J. Hraběta, J. Hřebačková, S. Smutný, E. Frei, M. Stiborová, *Biochem. Pharm*. 77 (2009) 1466.

[6] T.C. Johnstone, G.Y. Park, S.J. Lippard, *Anticancer. Res.* 34 (2014) 471.

[7] M.K. Amir, S. Khan, Zia-ur-Rehman, A. Shah, I.S. Butler, Inorg. Chim. Acta. 423 (2014) 14.

[8] C. Pellerito, P. D'Agati, T. Fiore, C. Mansueto, V. Mansueto, G. Stocco, L. Pellerito, *J. Inorganic. Biochem*. 99 (2005) 1294.

[9] M. Hussain, S. Ali, A. Rauf, M. Helliwell, *Inorg. Chim. Acta*. 370 (2011) 27.

[10] F. Arjmand, S. Parveen, S. Tabassum, C. Pettinari, *Inorg. Chim. Acta*. 423 (2014) 26.

[11] J. Liu, Y. Lin, M. Liu, S. Wang, Y. Li, X. Liu, L. Tian, App. Organomet. Chem xx (2019) xx-xx DOI: 10.1002/aoc.4715.

[12] M. Gielen, M. Boualam, A. Meriem, B. Mahieu, M. Biesemans, R. Willem, *Heteroatom. chem*. 3 (1992) 449.

[13] F.F. Yan, Q. Zhu, Q.L. Li, R.F. Zhang, C.L. Ma, *J. Organometal. Chem*. 880 (2019) 156.

[14] D. Waseem, A.F. Butt, I.U. Haq, M.H. Bhatti, G.M. Khan, *DARU J. Pharm. Sci.* 25 (2017) 8.

[15] P. Desjeux, *Trans. R. Soc. Trop. Med. Hyg*. 95 (2001) 239.

[16] H.W.Murray, *Antimicrob. Agents. Chemother.* 45 2001, 2185.

[17] P. Marty, E. Rosenthal, *Expert Opin. Pharmacother*. 3 (2002) 1101.

[18] S. Sundar, *Trop. Med. Int. Health*. 6 (2001) 849.

[19] W.L. Armarego, C.L.L. Chai, Purification of Laboratory Chemicals, 5th edn. Butterworth-Heinemann, London, New York, 5th edn, 2003.

[20] O.V. Dolomanov, L.J. Bourhis, R.J. Gildea, J.A. Howard, H. Puschmann, OLEX2: a complete structure solution, refinement and analysis program. *J. Appl.Crystallogr.* 42 (2009) 339.

[21] B.T. Gowda, M. Tokarčík, K. Shakuntala, J. Kožíšek, H. Fuess, *Acta. Cryst. E. Structure Reports Online*, 66 (2010) 1529.

[22] I. Rojas-Oviedoa, C. Camacho-Camachoa, L. Sánchez-Sánchezb, J. Cárdenasc, H. López-Muñozb, H. Eugenio-Robledoa, I. Velázquezaand R.A. Toscano, App. Organomet. Chem. 28 (2014) 884.

[23] M. Sirajuddin, S. Ali, V. McKee, S. Zaib, J. Iqbal, *RSC Advances* 4. 101 (2014) 57505.

[24] M. H. Bhatti, U. Yunus, N. Mussarat, M. Helliwell, R. Prendergast, Acta. Cryst. E. Structure Reports Online, 69 (2013) 427

[25] R. Callahan, O. Ramirez III, K. Rosmarion, R. Rothchild, K.C. Bynum, *J. Heterocycl. Chem.* 42 (2005) 889.

[26] H. Khan, A. Badshah, G. Murtaza, M. Said, M., Zia-ur-Rehman, C. Neuhausen, M. Todorova, B.J. Jean-Claude, I.S. Butler, *Eur. J. Med. Chem*. 46 (2011) 4071

[27] Zia-urRehman, A. Shah, N. Muhammad, S. Ali, R. Qureshi, A. Meetsma, I.S. Butler, *Eur. J. Med. Chem.*44 (2009) 3986.

[28] Zia-ur-Rehman, A. Shah, N. Muhammad, S. Ali, R. Qureshi, I.S. Butler, *J. Organometal. Chem.* 694 (2009) 1998.

[29] N. Muhammad, Zia-ur-Rehman, , Ali, S., Meetsma, A., Shaheen, F., *Inorg. Chim. Acta.* 2009, **362**, 2842.

[30] Muhammad, N., Shah, A., Zia-ur-Rehman, S. Shuja, S. Ali, R. Qureshi, A. Meetsma, M.N. Tahir, *J. Organometal. Chem.* 694 (2009) 3431.

[31] D. Kovala-Demertzi, V.N. Dokorou, J.P. Jasinski, A. Opolski, J. Wiecek, M. Zervou, M.A. Demertzis, *J. Organometal. Chem*. 690 (2005) 1800.

[32] H.D. Yin, C.H. Wang, C.L. Ma, *Chin. J. Org. Chem.* 23 *(*2003) 475.

[33] G. Eng, X. Song, A. Zapata, A.C. de Dios, L. Casabianca, R.D. Pike, *J. Organometal. Chem.* 692 (2007) 1398.

[34] Y. Farina, A. Graisa, E. Yousif, *Mod. Appl. Sci*. 3 (2009) 215.

[35] T.P. Lockhart, W.F. Manders, E.M. Holts, *J. Am. Chem. Soc*. 108 (1986) 6611.

[36] S. Tabassum, R.A. Khan, F. Arjmand, A.S. Juvekar, S.M. Zingde, *Eur. J. Med. Chem.* 45 (2010) 4797.

[37] B. Wrackmeyer, Application of ^{119}Sn NMR parameters. In *Annual Reports on NMR Spectroscopy*. 38 (1999) 203. Academic Press.

[38] V.N. Torocheshnikov, A.P. Tupciauskas, A.Y. Ustynyuk, *J. Organometal. Chem*. 81 (1974) 351.

[39] M. Iqbal, S. Ali, N. Muhammad, M. Parvez, P. Langer, A. Villinger, *J. Organometal. Chem*. 723 (2013) 214.

[40] W.F. Howard Jr, R.W. Crecely, W.H. Nelson, *Inorg. Chem*. 24 (1985) 2204.

[41] M. Gielen, A. El Khloufi, M. Biesemans, F. Kayser, R. Willem, Appl. Organomet. Chem. 7 (1993) 201.

[42] A.W. Addison, T.N. Rao, J. Reedijk, J. van Rijn, G.C. Verschoor, *J. Chem. Soc. Dalton. Transactions*. 7 (1984) 1349.

[43] S. Shujha, A. Shah, Zia-ur-Rehman, N. Muhammad, S. Ali, R. Qureshi, N. Khalid, A. Meetsma, *Eur. J. Med. Chem*. 45 (2010) 2902.

[44] M. Tariq, S. Ali, N.A. Shah, N. Muhammad, M.N. Tahir, N. Khalid, M.R. Khan, *Inorg. Chim.Acta*. 405 (2013) 444.

[45] H. Masood, S. Ali, M. Mazhar, S. Shahzadi, K. Shahid, *Turk. J. Chem*. 28 (2004) 75.

[46] M. Hussain, Zia-ur-Rehman, M. Hanif, M. Altaf, Aziz-ur-Rehman, S. Ali, K.J. Cavell, *Appl. Organometal. Chem*. 25 (2011) 412.

[47] M. Hussain, S. Ali, T. Zahur, M. Hanif, H. Stoeckli-Evans, *Acta. Crystallogr. Sec E: Structure Reports Online*, 62 (2006) o4618.

[48] N. Muhammad, S. Shujha, A. Shah, Zia-ur-Rehman, S. Ali, A. Meetsma, *J. Coord.. Chem*. 67 (2014) 1110.

[49] M.S. Ahmad, M. Hussain, M. Hanif, S. Ali, M. Qayyum, B. Mirza, *Chem. Biol. Drug Des*. 71 (2008) 568.

[50] M. Ahmad, M. Hussain, M. Hanif, S. Ali, B. Mirza, *Molecules*. 12 (2007) 2348.

[51] A.S.L. Barbosaetal, *J. Inorg. Biochem.* 180 (2018) 80.

[52] C.C. Camacho, D. de Vos, B. Mahieu, M. Gielen, M. Kemmer, M. Biesemans, R. Willem, *Main. Group. Met. Chem*. 23 (2000) 381.

[53] S.Naz, F. Shams, S. Tabassum, M. Ashraf, M. Zia, IET nanobiotechnology.11 (2017) 1040.

[54] S. Tabassum, M. Ahmed, B. Mirza, M. Naeem, M. Zia, Z.K. Shanwari, G.M. Khan, *BMC. Complementary. Alternative. Medicine*. 17 (2017) 146.

[55] T. Mosmann, *J. Immunol. Methods*. 65 (1983) 55.

[56]. M. Tariq, S. Ali, N.A. Shah, N. Muhammad, M.N. Tahir, N. Khalid, M.R. Khan, *Polyhedron.* 57 (2013) 127.

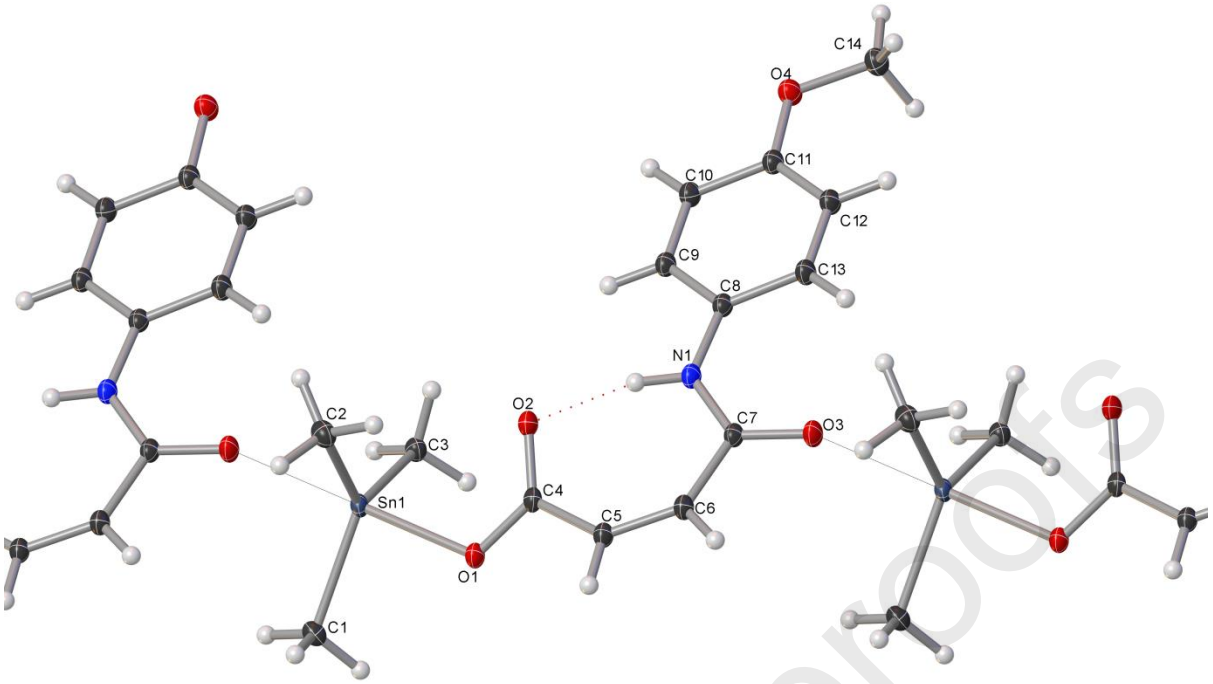


Figure 1. A perspective of one of the linear polymeric chains of compound **1**. The displacement ellipsoids are drawn at the 50% probability level and H atoms are shown as small circles of arbitrary radii.

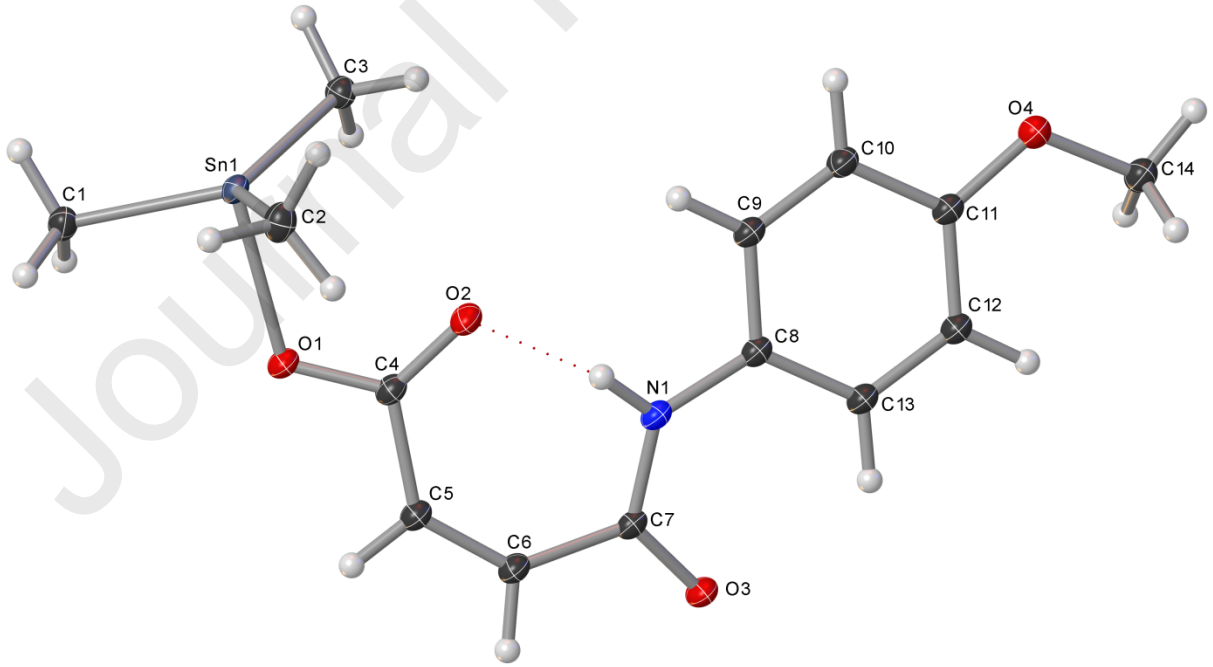


Figure 2. A perspective of the monomeric structural unit of compound **1**.

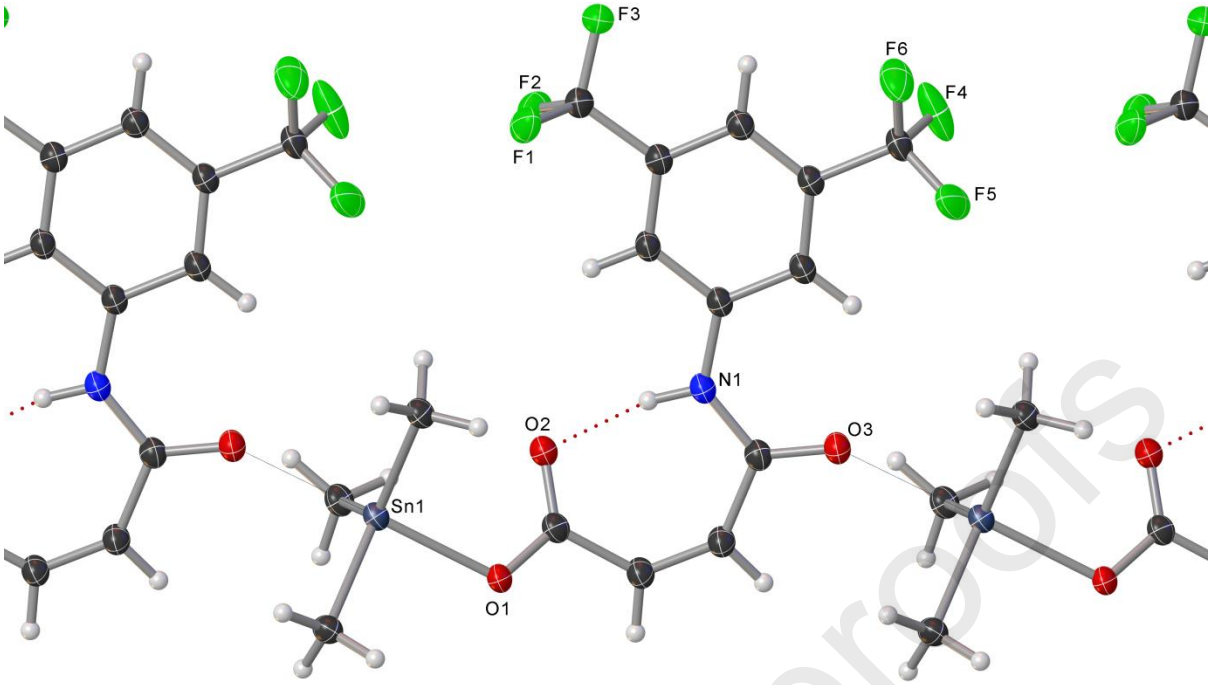


Figure 3. A perspective of one of the linear polymeric chains of compound **3**. The displacement ellipsoids are drawn at the 50% probability level and H atoms are shown as small circles of arbitrary radii.

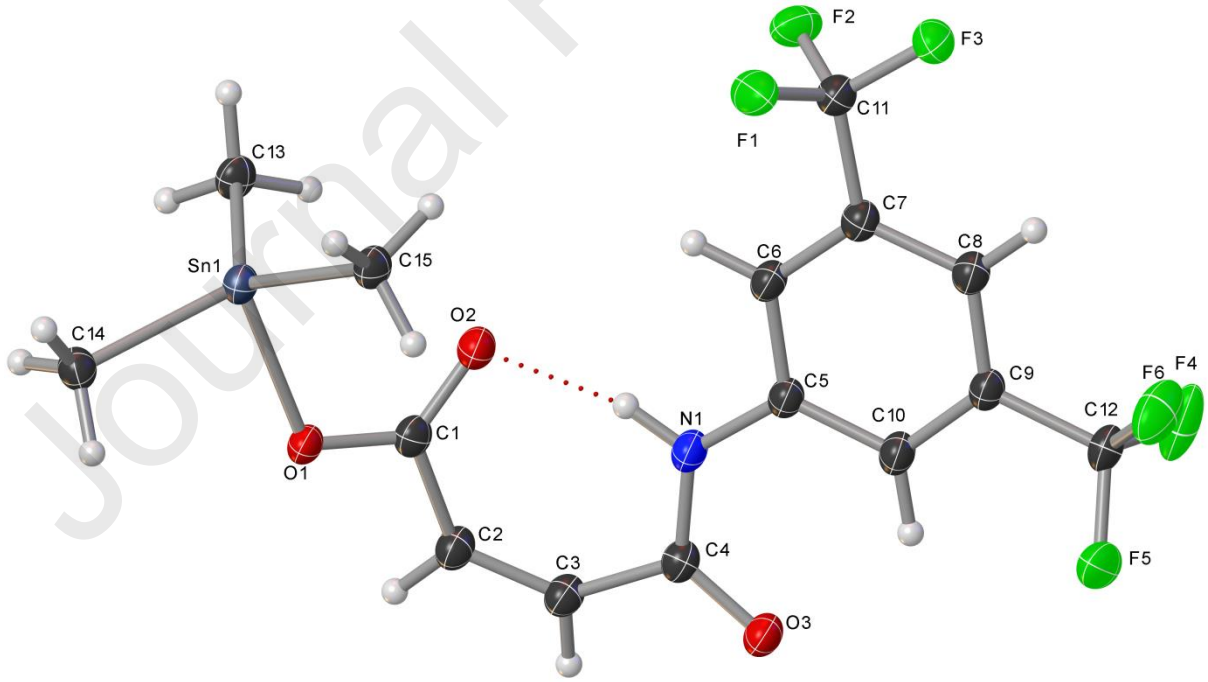


Figure 4. A perspective of the monomeric structural unit of compound **3**.

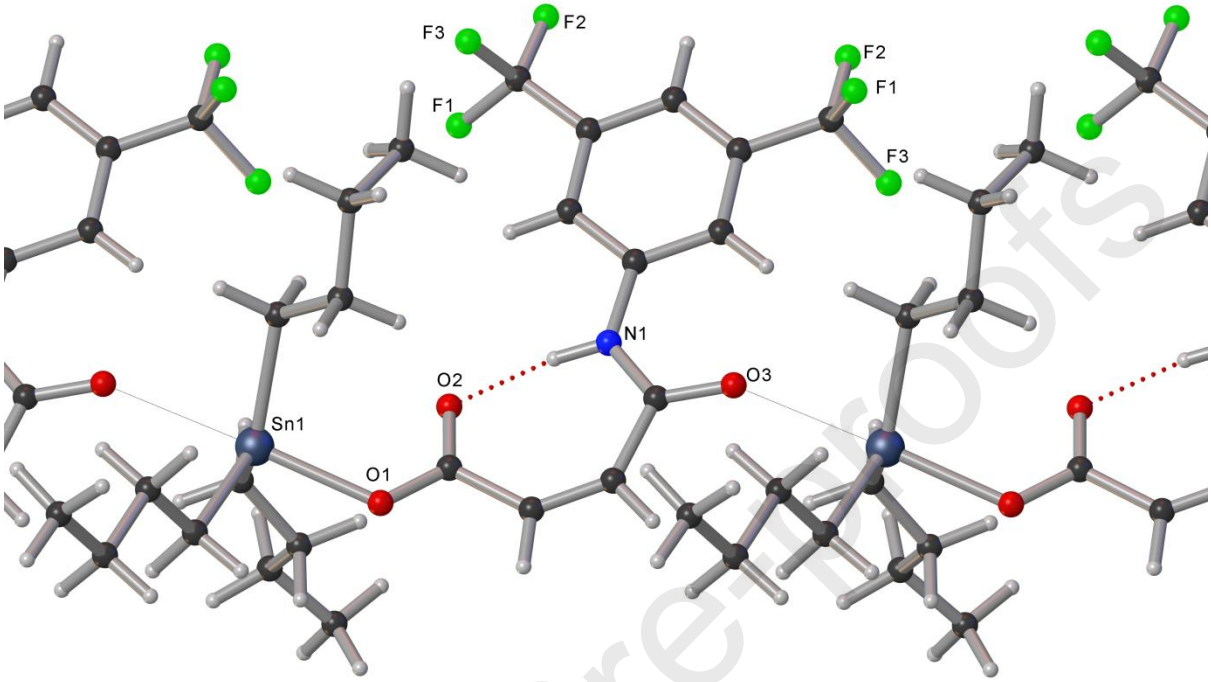


Figure 5. A perspective of one of the two crystallographically distinct one-dimensional polymeric chains of the crystal structure of compound **4**.

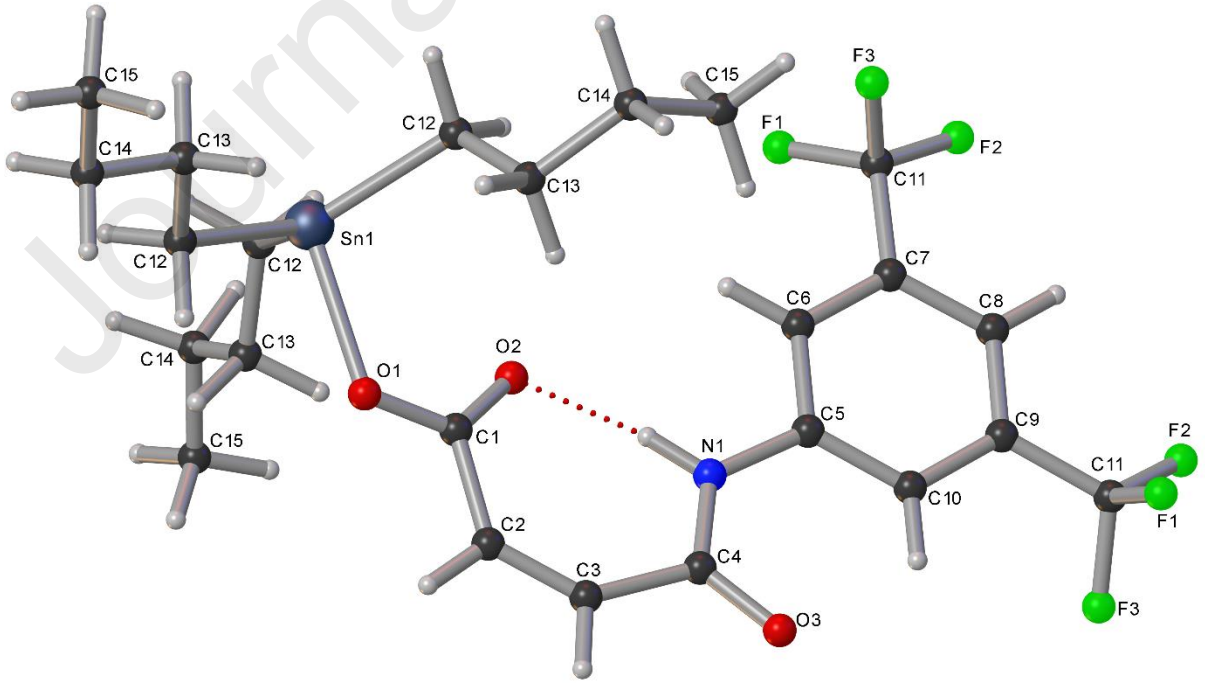


Figure 6. A perspective of one of the two crystallographically distinct the monomeric structural unit of compound **4**.

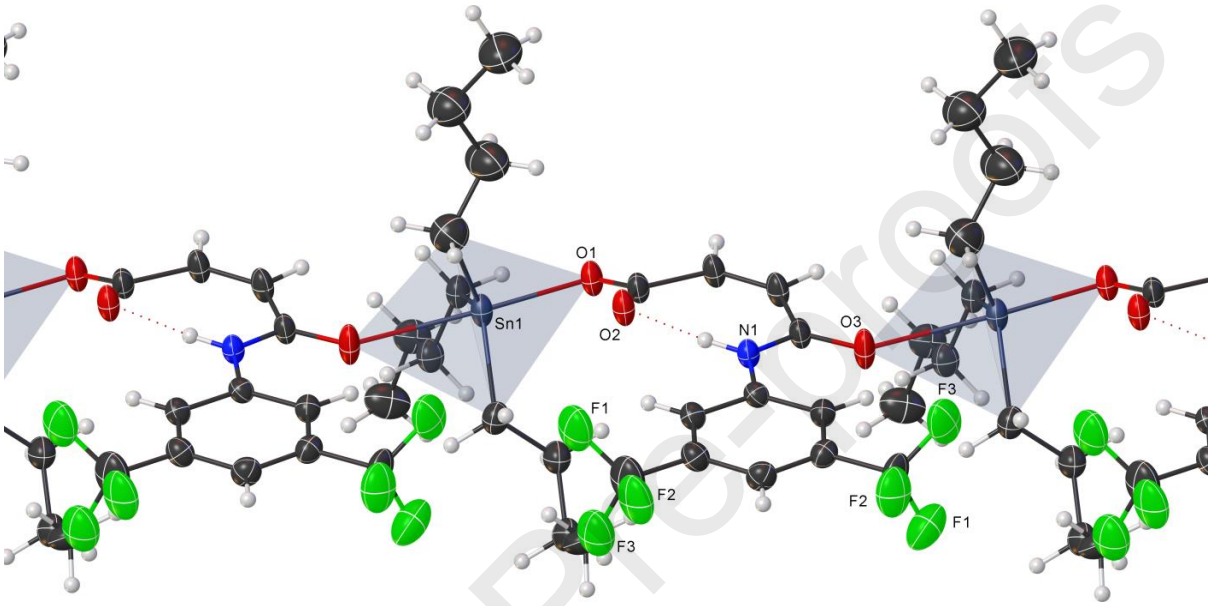


Figure 7. Perspective view of 1D monomeric structure of compound 4

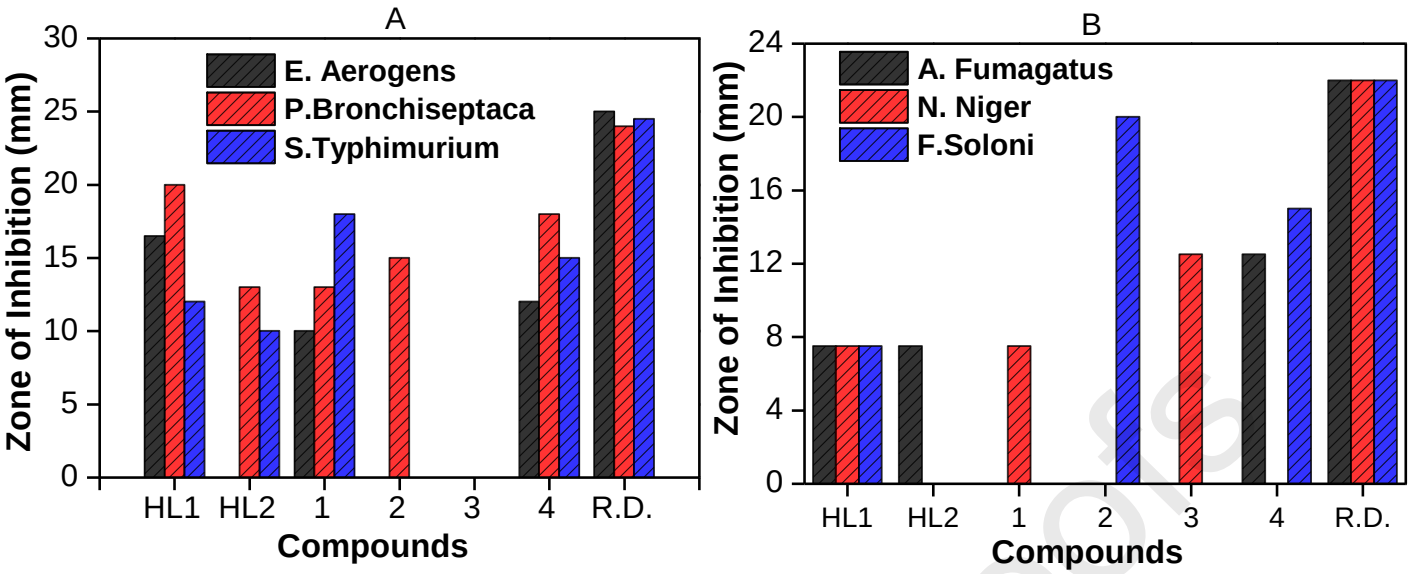


Fig 8. Antibacterial (b) and Antifungal (b) activities of ligands and organotin(IV) derivatives.

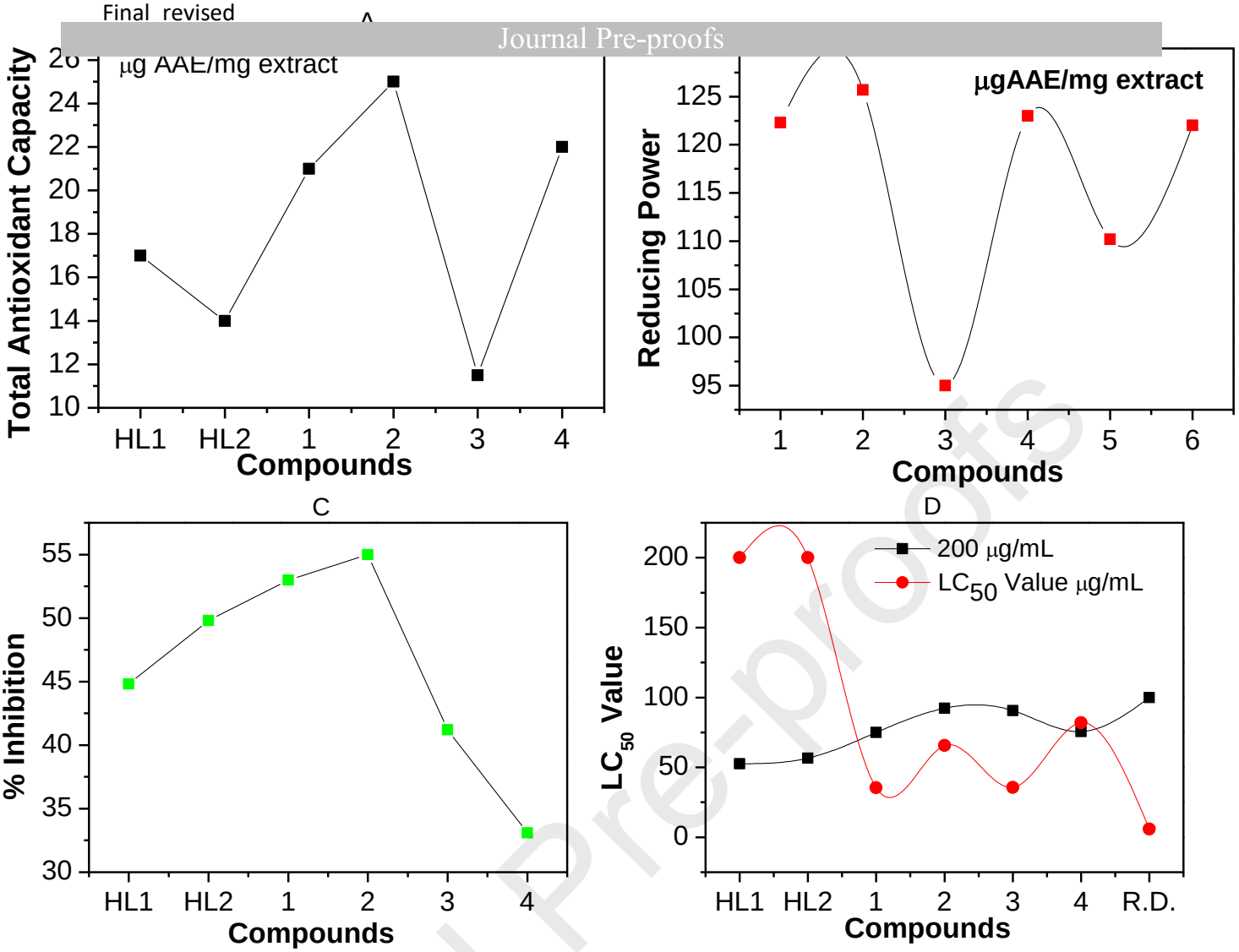


Figure 9. Antioxidant (A,B,C) and Brine shrimp lethality (D) bioassay of ligands and complexes

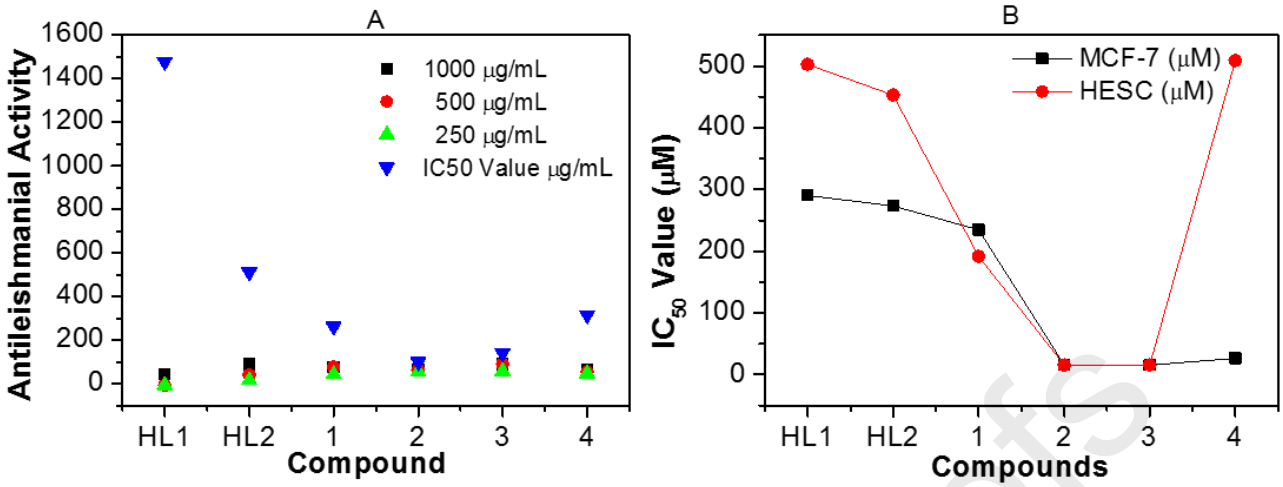


Figure 10. Antileshmanial (A) and anticancer (B) activity of ligands and complexes.

Table 1. C-Sn-C angles (θ) based on NMR parameters of selected organotin(IV) compounds.

Compound. no.	$^{2}J[^{119}Sn\text{-}^{1}H]$ (Hz)	$^{1}J[^{119}Sn\text{-}^{13}C]$ (Hz)	$^{2}J(\theta)$	$^{1}J(\theta)$
1	57	446	111	116
2		365		109
3	58	392	110	111
4		416		113

Table 2. Crystal data and structure refinement parameters for complexes 1, 3 and 4.

Empirical Formula	$C_{14}H_{19}NO_4Sn$	$C_{15}H_{15}F_6NO_3Sn$	$C_{24}H_{33}F_6NO_3Sn$
$D_{calc.}$/ g cm^{-3}	1.657	1.851	1.467
μ/mm^{-1}	13.321	12.291	0.979
Formula Weight	383.99	489.97	616.20
Colour	colourless	colourless	Colourless
Shape	needle	prism	needle
Size/mm^3	0.32×0.10×0.05	0.44×0.39×0.20	0.32 × 0.174 × 0.156
T/K	99.93(16)	100.00(10)	173.00(10)
Crystal System	monoclinic	monoclinic	triclinic
Space Group	$P2_1/c$	C2/c	P-1
a/Å	9.5424(3)	15.3177(5)	9.67709(14)
b/Å	6.9070(2)	10.9589(3)	14.1678(2)
c/Å	23.3651(8)	22.7379(7)	21.1430(3)
α/°	90	90	94.4266(13)
β/°	91.774(3)	112.868(4)	94.1105(12)
γ/°	90	90	104.0913(13)
V/Å^3	1539.25(9)	3516.9(2)	2790.85(7)
Z	4	8	4
Z'	1	1	1
Wavelength/Å	1.54184	1.54184	0.710743
Radiation type	CuKα	CuKα	MoKα

$\Theta_{min}/^{\circ}$	3.785	5.042	2.978
$\Theta_{max}/^{\circ}$	70.073	68.220	54.964
Measured Refl.	15835	16612	56312
Independent Refl.	2933	3197	12815
Reflections with I > 2σ(I)	2770	3091	1248
R_{int}	0.0667	0.0889	0.0339
Parameters	185	238	767
Restraints	120	129	544
Largest Peak	1.728	3.564	1.82
Deepest Hole	-1.150	-1.187	-1.42
GooF	1.077	1.084	1.054
wR_2 (all data)	0.1083	0.1575	0.1807
wR_2	0.1067	0.1563	0.1731
R_1 (all data)	0.0418	0.0592	0.0695
R_1	0.0402	0.0584	0.0601

Table 3. Selected bond lengths (Å) and bond angles (θ) for compound **1**, **3** and **4**.

Bond lengths

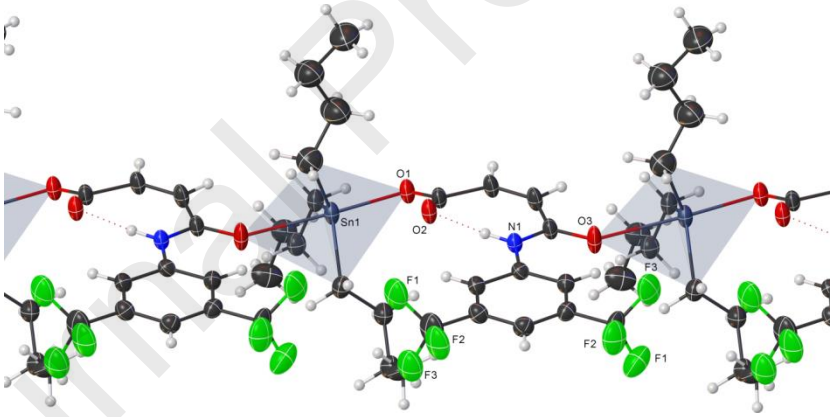
Sn1-O1	2.188(3)	Sn1-O1	2.169(3)	Sn1-O1	2.147(3)
Sn1- $O3^1$	2.399(3)	Sn1-$O3^1$	2.527(3)	$Sn1^1$-O3	2.556(3)
Sn1-C3	2.118(4)	Sn1-C13	2.123(5)	Sn1C12_2	2.092(7)
Sn1-C2	2.127(5)	Sn1-C14	2.128(4)	Sn1-C13_3	2.163(6)
Sn1-C1	2.131(4)	Sn1-C15	2.127(5)	Sn1-C12_8	2.138(4)
O3-$Sn1^2$	2.399(2)	O3-$Sn1^2$	2.527(3)	Sn2-O1B	2.154(3)
Bond angles					
O1-Sn1-O3	176.48(10)	O1-Sn1-O3	179.19(12)	O1-Sn1-O3	178.06(14)
C3-Sn1-O1	98.99(12)	C13-Sn1-O1	95.89(18)	O1-Sn1-C12_3	148.7(4)
C3-Sn1-O3	83.95(12)	C13-Sn1-O3	84.66(17)	C12_2-Sn1-C12_3	99.8(6)
C3-Sn1-C2	123.23(15)	C13-Sn1-C14	115.94(19)	C12_2-Sn1-C12_8	140.0(9)
C3-Sn1-C1	116.86(16)	C13-Sn1-C15	123.66(19)	C12_8-Sn1-C12_3	88.43(15)
C2-Sn1-O1	93.10(12)	C14-Sn1-O1	92.01(15)	C12_8-Sn1-C12_4	106.0(4)
C2-Sn1-$O3^1$	83..64(13)	C14-Sn1-$O3^1$	87.21(15)	C12_1-Sn1-C12_8	79.0(3)

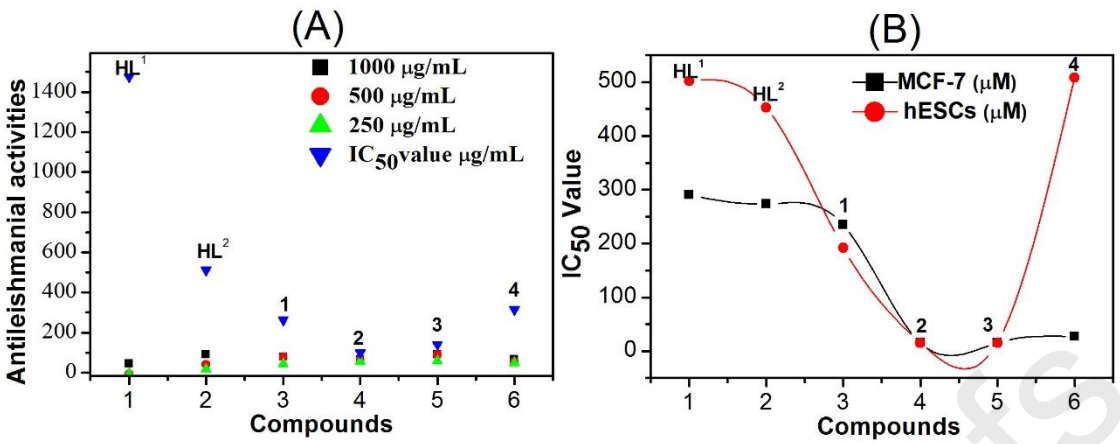
Table 4. % Hemolysis and IC_{50} Values of ligands and complexes.

Name	25 (µg/mL)	50 (µg/mL)	100 (µg/mL)	IC_{50} (µg/mL)
HL^1	13.34 ± 0.012	16.64 ± 0.04	21.46 ± 0.115	>1000
HL^2	2.61 ± 1.617	3.51 ± 1.73	6.32 ± 0.037	>1000
1	8.22 ± 0.918	14.34 ± 0.019	15.64 ± 0.045	379.46
2	96.36 ± 0.035	354.45 ± 0.041	395.36 ±0.046	0.80
3	13.34 ± 0.033	13.54 ± 0.290	15.44 ± 0.661	>1000
4	123.13 ± 0.039	163.64 ± 2.012	298.91 ± 0.059	0.447

Graphical Abstract

We report herein four new bioactive triorganotin (IV) amide based carboxylates.





Highlights

Synthesis of amide based triorganotin(IV) carboxylates complexes.IV

Spectroscopic characterization of the synthesized complexes.

Structural Chemistry of organotin(IV) complexes in solution and solid states.

Complexes 1-4 showed novel 1D polymeric structures.

Complexes 2, 3 and 4 showed good anticancer activities while compound 2 is the most active compound against antileshmanial activity.

Author Statement

The manuscript is submitted solely to this journal and the material discussed herein has not been published elsewhere in any medium including electronic journals and computer databases of a public nature.