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PII: S0022-328X(12)00620-1

DOI: 10.1016/j.jorganchem.2012.10.031

Reference: JOM 17752

To appear in: *Journal of Organometallic Chemistry*

Received Date: 28 April 2012

Revised Date: 5 October 2012

Accepted Date: 17 October 2012

Please cite this article as: M. Hong, H. Yin, X. Zhang, C. Li, C. Yue, S. Cheng, Di- and tri-organotin(IV) complexes with 2-hydroxy-1-naphthaldehyde 5-chloro-2-hydroxybenzoylhydrazone: Synthesis, characterization and in vitro antitumor activities, *Journal of Organometallic Chemistry* (2012), doi: 10.1016/j.jorganchem.2012.10.031.

Graphical Abstract-Synopsis

Di- and tri-organotin(IV) complexes with 2-hydroxy-1-naphthaldehyde-5-chloro-2-hydroxybenzoylhydrazone: Synthesis, characterization and in vitro cytotoxicity

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Synopsis

A series of organotin(IV) complexes with 2-hydroxy-1-naphthaldehyde 5-chloro-2-hydroxybenzoylhydrazone have been synthesized and characterized. In vitro cytotoxic activity against three human tumor cell lines is investigated. The results indicate that different alkyl groups organotin(IV) complexes have different effects on cytotoxic activity and selectivity.

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Graphical Abstract-Pictogram

Di- and tri-organotin(IV) complexes with 2-hydroxy-1-naphthaldehyde-5-chloro-2-hydroxybenzoylhydrazone: Synthesis, characterization and in vitro cytotoxicity

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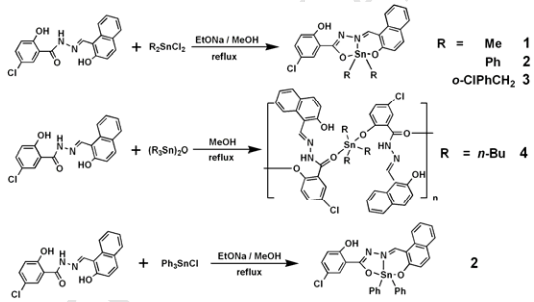
Pictogram



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Highlights:

1. Series of new organotin(IV) complexes have been synthesized and characterized.
2. A novel one-dimensional chain polymeric compound with non-enolic Schiff base ligand was obtained.
3. All compounds exhibit well in vitro cytotoxic activity.

Di- and tri-organotin(IV) complexes with 2-hydroxy-1-naphthaldehyde 5-chloro-2-hydroxybenzoylhydrazone: Synthesis, characterization and in vitro antitumor activities

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Abstract

Series of new organotin(IV) complexes of the types R_2SnL, R is Me (**1**), Ph (**2**), *o*-Cl-$C_6H_4CH_2$ (**3**); and $[R_3SnL]_\infty$, R = *n*-Bu (**4**) (H_2L = 2-hydroxy-1-naphthaldehyde 5-chloro-2-hydroxybenzoylhydrazone) have been synthesized and structurally characterized by means of elemental analysis, FT-IR, UV–Vis spectroscopy, NMR (^1H, ^{13}C and ^{119}Sn) spectra and X-ray single crystal diffraction analyses. Structural analyses reveal that complexes **1**-**3** show similar monomeric structure, in which the tin center is coordinated with the enolic tridentate ligand (L) in the ONO chelate mode and exhibits five-coordinated trigonal bipyramidal geometry. Unexpectedly, complex **4** presents as a rare one-dimensional chain polymeric structure, in which the coordination of Sn is also five-coordinated trigonal bipyramidal geometry and the segment of tri-*n*-butyltin is bridged by the de-protonated phenolate O atom and the carbonyl O atom from the non-enolic Schiff base ligand. All compounds exhibit good in vitro antitumor activity toward human colon cancer cells (HCT-8)**,** lung cancer cells (A549) and human promyelocyticfina leukemic cells (HL-60). The results indicate that alkyl groups bound with tin centers and the structure of organotin compounds have significant effect on their in vitro antitumor activities. Among them, the polymeric tri-*n*-butyltin Schiff base complex **4** is the most active one, and the complex **3** shows high selectivity on the tumor cells HCT-8 and HL-60. For all of the title

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compounds, there was a good dose-effect relationship.

***Keywords*:** Organotin(IV) complexes; Schiff base ligand; Crystal structure; In vitro antitumor activity

1. Introduction

Organotin(IV) complexes have attracted much interest because of their bioactivities, in particular as potential biocidal (e.g., antimicrobial, antifungal) [1] and anticancer agents [2]. Among main-group metal compounds, they appear to exhibit the most potent antitumor activities, in some cases being more effective than cisplatin in vitro tests [3]. It is interesting to combine the anticancer properties exhibited by the organotin(IV) complexes with the established biological effects of hydrazone Schiff base. Organotin(IV) complexes with hydrazone Schiff base ligands have received increasing attention owing to not only their potential applications in biotechnology [4-8], but also their fascinating chemical behavior [9-13]. Structural analyses reveal that hydrazone Schiff base ligands have strong coordination ability, a possibility of keto-enol tautomerism and multi-coordination modes (scheme 1 A、B), and when reacting with organotin(IV) moiety, which adopt an enolic tridentate chelate mode with monomeric or dimeric structure (shown in scheme 2 I and II) [12].

In general, the biochemical activity of organotin(IV) complexes is influenced greatly by the structure of the molecule and the coordination number of the tin atoms [14–16]. In addition, it is well known that the biological activity of organotin complexes is related to the type of alkyl groups attached to the organotin moiety. Usually, *n*-butyltin(IV) complexes display a larger array of biological activity than their methyl-, phenyl- or benzyltin(IV) analogues [17-19]. Meanwhile, as many of the typical antitumor agents, the efficiency and application of organotin derivatives seem to be limited by their poor water solubility [20]. Therefore, the synthesis of organotin complexes with higher water solubility has received particular attention [21–23]. In this context, we design and synthesize a series of organotin(IV) complexes containing hydrophilic hydroxyl ligands and involving different alkyl groups. Interestingly, a polymeric organotin(IV) compound with novel non-enolic coordination mode for Schiff base ligand (shown in scheme 2 III) was

obtained by the reaction of hydrazone ligand with bi(tri-n-butyltin) oxide. In order to compare their activity with that of cisplatin, in vitro cytotoxic activity on human colon cancer cells (HCT-8)**,** lung cancer cells (A549) and human promyelocyticfina leukemic cells (HL-60), have been tested in details. The dependence of the antitumor activity of the complexes on various factors, namely the nuclearity, the organic ligand bound with tin and the coordination type are also discussed.

2. Experimental

2.1. Materials and measurements

All reagents were commercially available and used without further purification. Schiff base ligand and di-o-chlorobenzylltin chloride were prepared by the methods reported in the literature [13,24,25]. All solvents used in the reaction were of AR grade and dried using standard literature procedures.

FT-IR spectra were recorded on a Nicolet-460 spectrophotometer using KBr discs. ^{1}H, ^{13}C and ^{119}Sn NMR spectra were recorded on a Mercury Plus-400 NMR spectrometer; chemical shifts were given in ppm relative to Me_4Si and Me_4Sn in $CDCl_3$ solvent. Elemental analyses were performed with a PE-2400II elemental analyzer. UV-Vis was performed on a UV-2550 ultraviolet spectrophotometer.

2.2 X-ray crystallography

Diffraction data for the title compounds were obtained on a Bruker Smart 1000 CCD diffractometer (graphite monochromized Mo Kα radiation, λ = 0.71073 Å). All data were corrected using SADABS method and the final refinement was performed by mull-matrix least-square methods with anisotropic thermal parameters for non-hydrogen atoms on F^2 using SHELX-97 program [26]. The hydrogen atoms were added theoretically, riding on the concerned atoms and refined with fixed thermal factors.

2.3 In vitro antitumor activity

The cell lines, human colon cancer cells (HCT-8)**,** lung cancer cells (A549) and human promyelocyticfina leukemic cells (HL-60) were used for screening. HCT-8 and A549 cell lines were grown and maintained in Roswell park memorial institute 1640 (DMEM for HL-60) supplemented with 10% fetal bovine serum (FBS), 1% an antibiotic (gentamycin), and were incubated at 310 K in a 5% CO_2 atmosphere.

Cell proliferation in compound-treated cultures was evaluated by using a system based on the tetrazolium compound (MTT) [27]. All cell lines were seeded into 96 well plates at a concentration of about 5000 cells/mL and were incubated in an atmosphere of 5% CO_2 for 24 h. Then, the samples (organotin complexes) were added and further incubation was carried out at 310 K for 48 h. The complexes were serially diluted with DMSO and added to cell incubation medium at the final concentration of 0.5% DMSO in the medium. MTT was added to each well at the final concentration of 10%. After 4 h incubation, the culture medium was removed, and 100 µl DMSO was added to dissolve the insoluble blue formazan precipitates produced by MTT reduction. The plate was shaken for 10 min on a plate shaker to ensure complete dissolution. The optical density of each well was measured at 570 nm wavelength. The antitumor activity was determined three times in independent experiments, using six replicate wells per toxicant concentration (10, 5, 1, 0.5, 0.1 µg/mL) and we obtained the mean optical densities for drug-treated cells at each concentration.

2.4 Synthesis

2.4.1. Preparation of 2-hydroxy-1-naphthaldehyde 5-chloro-2-hydroxybenzoylhydrazone

The Schiff base of 2-hydroxy-1-naphthaldehyde 5-chloro-2-hydroxybenzoylhydrazone was prepared with 5-chloro-2-hydroxybenzoylhydrazide and 2-hydroxy-1-naphthaldehyde in ethanol solution. 2-hydroxy-1-naphthaldehyde (1.722g, 10.0mmol) was added slowly to an ethanol solution containing 5-chloro-2-hydroxybenzoylhydrazide (1.866g, 10.0mmol) under stirring for 2 h. The yellow solid formed was filtered off, washed with water and ethanol in turn and dried in vacuum. Yield 75%. M.p. >573K. Anal. Calc. for $C_{18}H_{13}N_2O_3Cl$: C, 63.44; H, 3.85; N, 8.22. Found: C, 63.53; H, 3.91; N, 8.11%. IR (KBr, cm^{-1}) *v*: 3185(s, N–H), 3440(m, O–H), 1736(s, C=O), 1631(m, C=N). ^1H NMR (400 MHz, $CDCl_3$, 298 K): 9.49 (1H, s, CH), 3.30 (1H, s, NH),

12.64 (1H, s, naphthalene–OH), 11.89 (1H, s, aromatic–OH). ^{13}C NMR (101 MHz, $CDCl_3$, 298 K): 163.72 (CH=N), 168.62 (CO-N), 113.63–138.90(aromatic carbons).

2.4.2. General procedure for synthesis of complexes

The ethanol solution (2 mL) of sodium ethoxide (0.0272 g, 0.4mmol) was added to 30 mL methanol solution of 2-hydroxy-1-naphthaldehyde 5-chloro-2-hydroxybenzoylhydrazone (0.0682 g, 0.2 mmol) with stirring at room temperature. When the solution changed from yellow solid to clear, diorganotin(IV) dichloride (0.2 mmol) was added. The mixture was heated at reflux for ca. 8 h, and then filtered. The solvent was evaporated under vacuum to leave the yellow solid, which was recrystallized from dichloromethane–petroleum ether (1:1) to give yellow crystal.

*2.4.2.1. $(CH_3)_2SnC_{18}H_{11}N_2O_3Cl$ (**1**)*

Yield 85%. Anal. Calc. for $C_{20}H_{17}ClN_2O_3Sn$: C, 49.27; H, 3.51; N, 5.75. Found: C, 49.38; H, 3.62; N, 5.63%. IR (KBr, cm^{-1}) *v*: 1630(s, C=N), 1606(m, C=N–N=C), 620(m,Sn-O), 563(m, Sn–C), 475(w, Sn–N). ^{1}H NMR (400 MHz, $CDCl_3$, 298 K): 9.50 (1H, t, CH), 0.90 (6H, m, $^2J_{Sn\text{-}H}$ = 68 Hz, $SnCH_3$), 11.84 (1H, s, aromatic–OH). ^{13}C NMR (101 MHz, $CDCl_3$, 298 K): 168.35 (CH=N), 169.51 (CO-N), 13.92 ($^1J_{Sn\text{-}C}$ = 520.4Hz, Sn-CH_3), 107.10–158.17(aromatic carbons). ^{119}Sn NMR (149 MHz, $CDCl_3$, 298 K): -162.3 ppm.

*2.4.2.2. $(C_6H_5)_2SnC_{18}H_{11}N_2O_3Cl$ (**2**)*

Yield 83%. Anal. Calc. for $C_{30}H_{21}ClN_2O_3Sn$: C, 58.90; H, 3.46; N, 4.58. Found: C, 58.98; H, 3.56; N, 4.45%. IR (KBr, cm^{-1}) *v*: 1618(s, C=N), 1600(m, C=N–N=C), 616(m, Sn-O), 570(m, Sn–C), 478(w, Sn–N). ^{1}H NMR (400 MHz, $CDCl_3$, 298 K): 9.52 (1H, s, CH), 11.79 (1H, s, aromatic–OH). ^{13}C NMR (101 MHz, $CDCl_3$, 298 K): 168.43 (CH=N), 170.33 (CO-N), 107.42–158.17(aromatic carbons). ^{119}Sn NMR (149 MHz, $CDCl_3$, 298K): -341.4 ppm.

*2.4.2.3 $(o\text{-}ClC_6H_4CH_2)_2SnC_{18}H_{11}N_2O_3Cl$ (**3**)*

Yield 62%. Anal. Calc. for $C_{32}H_{23}Cl_3N_2O_3Sn$: C, 54.24; H, 3.27; N, 3.95. Found: C, 54.46; H, 3.45; N, 3.63%. IR (KBr, cm^{-1}) *v*: 1613(s, C=N), 1599(m, C=N–N=C), 617(m, Sn-O), 570(m, Sn–C), 473(w, Sn–N). ^{1}H NMR (400 MHz, $CDCl_3$, 298 K): 9.49 (1H, s, CH), 11.76 (1H, s, aromatic–OH). ^{13}C NMR (101 MHz, $CDCl_3$, 298 K): 168.47 (CH=N), 170.29 (CO-N), 33.60

(Sn-CH_2-Ph), 107.35–158.17 (aromatic carbons). ^{119}Sn NMR (149 MHz, $CDCl_3$, 298 K): -281.9 ppm.

*2.4.2.4 Preparation of $[(C_4H_9)_3Sn(C_{18}H_{11}N_2O_3Cl)]_\infty$ (**4**)*

2-Hydroxy-1-naphthaldehyde 5-chloro-2-hydroxybenzoylhydrazone (0.0682 g, 0.2 mmol) was added to 50 ml flask containing 30 mL methanol solution with stirring for 30 minutes at room temperature. After bis(tri-*n*-butyltin) oxide (0.0596g, 0.1mmol) was added to the reactor, the reaction mixture was refluxed for 8 h more. The yellow solution with deposit thus obtained was evaporated under vacuum to form a yellow solid and recrystallized in dichloromethane–petroleum ether to give yellow crystal. Yield 89%. Anal.Calc. for $C_{30}H_{38}N_2O_3ClSn$: C, 57.30; H, 6.09; N, 4.46. Found: C, 57.63; H, 6.27; N, 4.23%. IR (KBr, cm^{-1}) *v*:1617(s, C=N), 1742(s, C=O), 3181(s, N–H), 3441(m, O–H), 601(m, Sn-O), 535(m, Sn–C). ^{1}H NMR (400 MHz, $CDCl_3$, 298 K): 9.46 (1H, t, CH), 3.65 (1H, s, NH), 0.88 (9H, t, $–CH_3$), 1.35–1.68 (18H, m, $SnCH_2CH_2CH_2$), 12.58 (1H, s, naphthalene–OH). ^{13}C NMR (101 MHz, $CDCl_3$, 298 K): 168.54 (CH=N), 170.11 (CO-N), 107.04–158.17 (aromatic carbons), 27.96, 22.63, 16.97, 13.68 (Sn-Bu) ppm. ^{119}Sn NMR (149 MHz, $CDCl_3$, 298 K): -197.1 ppm.

3. Result and discussion

3.1 Syntheses

Complexes **1**–**3** were obtained by reaction of H_2L/EtONa/R_2SnCl_2 in a 1:2:1 molar ratio in methanol at 343 K, while complex **4** was obtained by reaction of H_2L/$(R_3Sn)_2O$ in a 1:1 molar ratio in methanol at reflux. Moreover, when the reaction of 2-hydroxy-1-naphthaldehyde 5-chloro-2-hydroxybenzoylhydrazone with triphenyltin chloride was carried out, complex **2** was also obtained. It is different from the former method of preparation. If like the polymeric structure of complex **4**, triphenyltin next to two large groups has relatively large steric and the formed complex is not stabilizer than the diphenyltin compound. It is similar with the previous complexes we have reported [9]. The synthetic procedures are shown in Scheme 3.

3.2 IR Spectra

In IR spectra of the ligand, the vibration bands of *v*(N-H), *v*(O-H) and *v*(C=O) were observed at 3185, 3440 and 1735 cm^{-1}, respectively. In the complexes **1**–**3**, there was no C=O characteristic stretching vibration absorption, showing that the C=O has enolization and the oxygen atom has coordinated to the tin atom. The strong bands appearing at 1613–1630 and 1598–1610 cm^{-1} in the spectra indicate the presence of C=N and C=N–N=C group [28, 29]. Two new bands at 535–570 and 465–475 cm^{-1} are characteristic of Sn–O and Sn–N absorptions, respectively [10]. However, the *v*(C=O) band of complex **4** remains due to non-enolic Schiff base ligand and there is no absorption to indicate the presence of C=N–N=C groups. There are only Sn-O bands absorptions for complex **4**. All these values are consistent with those detected in a number of organotin(IV) derivatives [30,31]. And the characteristic absorptions of complexes **1**–**3** at 3370–3440 cm^{-1} indicate that the oxygen atoms of phenolic hydroxyl do not participate in the coordination to the Sn atom.

3.3 NMR Spectra

All complexes gave good NMR spectra. In the spectra of ligand, single resonance is observed at 3.30 ppm, which is absent in the spectra of complexes **1**-**3**, indicating deprotonation of–NHN= group and confirming that the ligand coordinates to the tin in the enol form [32]. However, for compound **4**, the single resonance for the proton of –NHN= group remains at 3.6 ppm. The results indicate that –NHN= group of the ligand does not coordinate to the Sn center in complex **4**. It is different from our previous reports [12]. In the ^{1}H NMR spectra of complexes **1**–**3**, there is no signal resonance for naphthalenic OH group, and the single resonances of Ar–OH are observed at 11.76–11.84 ppm, which strongly suggests that the oxygen atoms of naphthalene nucleus participate in coordination to the tin atom, but the phenolic oxygen atoms do not. While for complex **4**, the single resonance of Ar–OH is absent, and the naphthalenic OH group was observed at 12.58 ppm [33].They are in accordance with X-ray single crystal diffraction structural analysis.

The ^{119}Sn chemical shift of tin complexes appears to depend not only on coordination number, but is also very sensitive to the type of donor atoms bonded to the metal ion, so it is a useful tool to determine the chemical environment of the tin atom. Holecek and coworkers studies result

show that in the di- and tri-organotin the ^{119}Sn NMR spectra can be used as an indicator of the coordination number of the tin atom. In the range of +200 to -60, -90 to -190, -210 to -400, -440 to -540 ppm, the coordinate number of the tin are four, five, six and seven [34-36]. The di-organotin complexes of the present investigation exhibit the ^{119}Sn spectra at -162.30 ppm, suggesting that the tin atom is five-coordinate in the complex **1**. However, diphenyltin complexes **2**, **3** show the ^{119}Sn spectra at -341.40, -281.86 ppm, indicating that the tin atoms are five-coordinate [32]. In the tri-organotin, the signal of the ^{119}Sn spectra appear at -197.08 ppm, indicating the tin atoms are five-coordinate in the complex **4**.

3.4 UV–Vis spectra

The UV-Vis absorption spectra of Sn(IV) complexes with multidentate Schiff base ligand (shown in Fig 1) could also be good indicator of their geometry, which give some structural information of organotin(IV) hydrazone Schiff base complexes and exhibit especially the coordination mode of the ligand.

The dominant vibronic absorption peaks in ~325 and ~370 nm (for the free ligand and complex **4**), and ~350 and ~440 nm (for complexes **1**-**3)** can be ascribed to the ligand-centered (LC) π–π^* transitions. From the spectra data we can see that the absorption spectra of complexes **1**-**3** show the obvious red-shift when compared with that of the free ligand, which should be the result of the enolization of the Schiff base ligand as well as the coordination to the tin center. However, the absorption peaks of complex **4** are almost the same as those of the Schiff base ligand, which should be due to the main body of the Schiff base ligand in **4** having little changes, that is, the phenomenon of enolization does not occur just like in complexes **1**-**3,** and differently the carbonyl and phenolate O atoms of the ligand bond to the tin atoms contributing to the formation of the organotin(IV) polymer **4**. All these values are consistent with their crystal structures.

3.5 Crystal structures

*3.5.1. Crystal structures of complexes **1**, **2** and **3***

Complexes **1**, **2** and **3** have similar molecular structures, as illustrated in Fig 2, 3a and 4a. From the structure descriptions of the complexes, it can be seen that the Schiff base ligands coordinate

to tin center in a tridentate fashion, an enolic O atom, a Schiff base group N atom and an O atom of hydroxyl group of naphthalene nucleus. The tin atom is rendered five-coordinate with a distorted trigonal bipyramidal geometry, surrounded axially by two O atoms from the Schiff base ligand and equatorially by one N atom, two C atoms from the alkyl group. The Sn–O (amide) bond lengths [between 2.121(2) and 2.138(2) Å] and the Sn–O (phenolate) bond lengths [between 2.062(2) and 2.078(2) Å] are in excellent agreement with other previously known acylhydrazone diorganotin(IV) complexes in the literatures [37,38]. The Sn–O (amide) bond length is longer than the Sn–O (phenolate) in the same complex. The Sn-O bond lengths are considerably shorter than the sum of the Van der Waal's radii (2.8 Å) and should be considered as bonding interactions, indicating strong tin–oxygen interactions. The O-Sn-N (equatorial) and O-Sn-O (axial) angles show a large deviation from the ideal values thus, confirming highly distorted trigonal bipyramidal geometry. The distortion from the perfect trigonal bipyramidal geometry is mainly due to the rigidity of the chelate rings and the large covalent radius of the tin(IV) atoms. There are five and six membered Sn–N–N–C–O and Sn–N–C–C–C–O rings imposing the constraints. The dihedral angles between the two rings are 0º for **1**, 5.2º for **2** and 12.5º for **3**. Due to the overall effect of bulk and steric hindrance of the alkyl groups, the dihedral angles have obvious differences. Crystal data and structure refinement parameters for all complexes are shown in Table 1. The selected bond lengths and angles of complexes **1**, **2**, **3** are given in Table 2.

In complexes **1**, **2** and **3**, there also exist intra- and intermolecular hydrogen bonds, which are listed in Table 3. These hydrogen bonds contribute to the crystal stability and compactness and result in different supramolecular structures. For complex **1**, there are intramolecular hydrogen bond (O2-H2···N1) and intermolecular hydrogen bond [C4···O3#2 (x, y, z+1)], and the latter aspect results in a one-dimensional chain arrangement. In complex **2**, there are π··π stacking interactions between the ring (C13-C18) and the ring (C1A,C2A,C3A,C4A,C9A,C10A) found in the structure(shown in Fig 3b), the distance between the ring centroids is 3.714 Å. As can be seen from Fig 3b, the intermolecular hydrogen bond [C30···O2#1(-x+1, -y+1, -z)] and theπ··π stacking interactions between the aromatic rings link the molecules into centrosymmetric (symmetric operation: 1-x, -y, -z) dimers. And the weak interactions (C-H···Cl) link the dimers into the two-dimensional networks [Fig 3c]. For complex **3**, through the intermolecular hydrogen bond

(C32···O1#1), two complexes **3** molecules bind together with each other into a centrosymmetric (symmetric operation: -x+2, -y+1, -z) conformation (shown in Fig 4b).

*3.5.2. Crystal structures of complex **4***

When the reaction of 2-hydroxy-1-naphthaldehyde 5-chloro-2-hydroxybenzoylhydrazone ligand with bis(tri-*n*-butyltin) oxide was carried out, a rare one-dimensional chain polymeric structure complex **4** was obtained (shown in Fig 5b). The molecular structure of the complex **4** is shown in Fig 5a. The selected bond lengths and angles are given in Table 2. The molecular structure is different from the former complexes. In complex **4**, the tin atom is five-coordinate in a distorted trigonal-bipyramid geometry, but the Schiff base ligand coordinated to the tin atom as a bidentate ligand. The central tin atom is surrounded axis by an non-enolic O(3) atom of the carbonyl group and O(2)#1 from the phenolic hydroxyl of the Schiff base, and the equatorial position were occupied by three C atoms from the *n*-butyl group. The Sn(1)–O(2)#1 bond length is 2.169(3) Å and Sn(1)–O(3) bond length is 2.446 Å, which are much less than the sum of the Vander Waals radii for Sn–O (2.8 Å), indicating the significant contacts with the Sn(1) atom. Meanwhile, these Sn–O bond lengths contribute to the angle of O(2)#1–Sn(1)–O(3) which is 174.37(12)º and cause the angle deviated from linear 180º. The packing of the molecules of complex **4** show that the de-protonated phenolate O atom and the carbonyl O atom from the non-enolic Schiff base ligand played as a bridge on forming the unexpected one-dimensional chain polymeric structure. The Schiff base ligand did not follow the traditional way of dehydrocarbylation [11] to coordinate with the tin atom in a tridentate mode. Unexpectedly, the carbonyl O atom chelated to the tin. The explanation of phenomenon may be that the chelation capacity is larger than the ability of dehydroxylation . In other words, the chelation is not enough to destroy the alkyl group. It is different from the previously reported complexes that are obtained by the way of destroying the alkyl group and forming the stable seven-coordinated complexes [9]. In summary, examples of triorganotin Schiff base structure of similar compound **4** are reported less. This result provides the impetus for further exploration of this class of compounds as potential molecular precursors.

3.6 Antitumor activity in vitro

The antitumor activity in vitro of complexes **1**-**4** against human promyelocyticfina leukemic cell

line (HL-60), a human colon cancer cells (HCT-8) and lung cancer cells (A549) were determined by MTT-based assays. This study has been carried out in order to understand the possible relationship between the different tin moieties (bearing methyl, butyl, phenyl or benzyl groups), the coordination geometry and the antitumor activity.

Comparison of inhibition between complexes **1**, **2**, **3** and **4** are shown in Fig 6, 7 and 8. The IC_{50} values, calculated from the dose-survival curves, obtained after 48 h of drug treatment in the MTT test, are summarized in Table 4.

The results of in vitro cytotoxic effects of compounds **1**-**4** demonstrate these compounds are active against three tumor cell lines (A549, HCT-8 and HL-60) that are either sensitive to or have acquired resistance to cisplatin, the clinically used drug. From Fig 6, 7 and 8, we can also see that there was a good dose-effect relationship for all complexes, the percentage inhibition grows with the increasing of the concentration of organotin(IV) complexes. *n*-Butyltin(IV) complex **4** exhibits a greater activity than complexes **1**, **2** and **3** against three cancer cells examined, which is well consistent with the results reported in the literature [39-41]. As for the identical coordination geometry, the IC_{50} values of complexes **1**, **2** and **3** (shown in Table 4) follow different trends for three cancer cell line, that is **1** > **3** > **2** for A549 and HCT-8, but **3** > **1** > **2** for HL-60. Also, the data analysis reveals that different complexes demonstrate different anticancer activities against the same cell line, and the inhibitory potencies of the same complex against three different tumor cells exhibit a high selectivity. For example, di-*o*-chlorobenzyltin(IV) complex **3** demonstrates significant activities for tumor cells HL-60 and HCT-8, while exhibits no activity for tumor cell A549.

Therefore, possible structure-activity relationships could be recognized as follows: (i) with the increasing concentration, the inhibition of cancer cells was also increased; (ii) the polymeric complex **4** with the long carbon chain butyl ligand is the most active one, in comparison with other organotin(IV) complexes; (iii) the organic ligand R plays an important role, the dimethyl complexes exhibiting a stronger antitumor activity than the diphenyl analogues, while the effects of the benzyltin complexes on different tumor cells are different. The results indicate that complexes act against cells selectively and the type of alkyl groups attached to the organotin moiety has effects on antitumor activity; (iv) the contribution from coordination geometry to tin atom in the present compounds towards the cytotoxic effects may not be rules out.

4. Conclusions

Four new organotin(IV) complexes were obtained by the reaction of 2-hydroxy-1-naphthaldehyde 5-chloro-2-hydroxybenzoylhydrazone Schiff base ligand and organotin(IV) salts in methanol. Complexes **1**-**3**, characterized by X-ray analysis, showed the structure with tridentate chelate ligand through the oxygen of deprotonated phenolic and enolic hydroxyl group and the nitrogen atoms. In complex **4**, a novel non-enolic bidentate O,O-coordination of Schiff base ligand in synthesized tri-n-butyltin(IV) complex was documented for the first time.

Moreover, the results of in vitro antitumor activity screening also indicate that *n*-butyltin(IV) complex **4** shows better antitumor activity on three cancer cell lines than the methyl-, phenyl- or benzyltin(IV) derivatives. Otherwise, benzyltin(IV) complex **3** show high selectivity between cancer cell lines HCT-8, HL-60 and A549.

Acknowledgement

We acknowledge the National Natural Foundation of China (21105042), the National Basic Research Program (No. 2010CB234601), the Natural Science Foundation of Shandong Province (ZR2011BM007, ZR2010BQ021) for financial support. And this work was supported by Shandong "Tai–Shan Scholar Research Fund".

Appendix A. Supplementary data

CCDC-836674 (for **1**), -836672 (for **2**), -836675 (for **3**), and -836673 (for **4**), contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via http://www.ccdc.cam.ac.uk/data_request/cif, or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: (+44) 1223-336-033; or e-mail: deposit@ccdc.cam.ac.uk.

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Fig 1. Absorption spectra of L1 (a) and complex **1** (c), **2** (e), **3** (d), **4** (b) at 298 K in methanol.

Fig 2. Molecular structure of **1** with 30% probability ellipsoids. All H atoms are omitted for clarity.

Fig 3. Molecular structure of **2** with 30% probability ellipsoids (a). The view of the dimer via the intermolecular hydrogen bond and π··π stacking interactions (b). A perspective view of the 2D supramolecular structures via the intermolecular hydrogen bond, π··π stacking interactions and C-H···Cl interactions (c).

Fig 4. Molecular structure of **3** with 30% probability ellipsoids (a). The dimer structure by intermolecular hydrogen bond interactions (b).

Fig 5. Structure of segments of the 1D chain of complex **4**. (a). A perspective view of the one-dimensional chain polymeric structure (b).

Fig 6. In vitro antitumor activity against A549 (human lung cancer cell line). *Inhibition* vs C_{VOL} (*Inhibition* = $(A_0\text{-}A)/A$; A_0 and A represent the optical density of each well in the absence and presence of the sample, respectively; C_{VOL} relates to the concentration of the sample). From left to right, C_{VOL} = 0.1, 0.5, 1, 5, 10 μg/mL.

Fig 7. In vitro antitumor activity against HCT-8 (human colon cancer cells).

Fig 8. In vitro antitumor activity against HL-60 (human promyelocyticfina leukemic cell line).

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

Table 2. Selected bond lengths (Å) and angles (º) for complexes **1**, **2, 3** and **4**

Table 3. Hydrogen bonding geometries for complexes **1**, **2**, **3** and **4**

Table 4. In vitro cytotoxicity assay for complexes **1-4** against tumor cell lines

Scheme 1. Different coordination sites of the Schiff base group.

Scheme 2. Different modes of the Schiff base group.

Scheme 3. Synthetic routes to complexes **1-4**.

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

Complexes	**1**	**2**	**3**	**4**
EmpiricalFormula	$C_{20}H_{17}ClN_2O_3Sn$	$C_{30}H_{21}ClN_2O_3Sn$	$C_{32}H_{23}Cl_3N_2O_3Sn$	$C_{30}H_{38}ClN_2O_3Sn$
Formula mass	487.50	611.63	708.56	628.76
Crystal system	Orthorhombic	Monoclinic	Triclinic	Monoclinic
Space group	Pnma	P2(1)/c	P-1	P2(1)/c
a [Å]	24.265(2)	9.3991(8)	8.1570(8)	9.7397(8)
b [Å]	7.2450(8)	11.1000(10)	13.3971(12)	16.3895(15)
c [Å]	10.8311(11)	26.143(2)	13.9919(13)	18.6474(17)
α[°]	90	90	91.2830(10)	90
β[°]	90	108.9920(10)	104.414(2)	93.289
γ[°]	90	90	98.1300(10)	90
V [Å^3]	1904.1(3)	2579.0(4)	1463.4(2)	2971.8(5)
Z	4	4	2	4
F(000)	968	1224	708	1292
$D_{calcd.}$ [g·cm^{-3}]	1.701	1.575	1.608	1.405
θ range [°]	3.14 - 25.02	2.47 - 25.02	2.66 - 25.02	2.44 - 25.02
Number of Reflections	7336	12592	7587	14705
Number of Parameters	163	335	371	338
Final *R* indices [$I > 2\sigma(I)$]	0.0264	0.0335	0.0317	0.0379
wR_2 [$I > 2\sigma(I)$]	0.0623	0.0686	0.0716	0.0839
Goodness of fit on F^2	1.011	1.062	1.086	1.118

Table 2. Selected bond lengths (Å) and angles (°) for complexes **1**, **2, 3** and **4**

Complex **1**			
Sn1-O3	2.068(3)	N1-C1	1.309(4)
Sn1-C20	2.096(3)	N1-N2	1.388(4)
Sn1-C20#1	2.096(3)	N2-C8	1.312(5)
Sn1-O1	2.121(3)	O1-C1	1.296(4)
Sn1-N2	2.149(3)	O2-C3	1.357(5)
O3-Sn1-C20	95.55(10)	O3-Sn1-N2	82.41(12)
O3-Sn1-C20#1	95.55(10)	C20-Sn1-N2	118.72(9)
C20-Sn1-C20#1	122.40(19)	C20#1-Sn1-N2	118.72(9)
O3-Sn1-O1	155.96(10)	O1-Sn1-N2	73.56(10)
C20-Sn1-O1	95.96(9)	C20#1-Sn1-O1	95.96(9)
Complex **2**			
Sn1-O1	2.062(2)	N2-C12	1.317(4)
Sn1-C19	2.111(4)	N1-C11	1.300(4)
Sn1-N1	2.158(3)	O3-C12	1.290(4)
Sn1-O3	2.121(2)	N1-N2	1.399(4)
Sn1-C25	2.111(4)	O1-C1	1.307(4)

O1-Sn1-C25	93.72(13)	C19-Sn1-O3	96.24(13)
O1-Sn1-C19	99.36(13)	O1-Sn1-N1	82.26(10)
C25-Sn1-C19	126.38(14)	C25-Sn1-N1	122.72(13)
O1-Sn1-O3	154.67(10)	C19-Sn1-N1	110.53(13)
C25-Sn1-O3	92.92(13)	O3-Sn1-N1	73.61(10)
Complex **3**			
Sn1-N2	2.167(3)	O3-C25	1.324(4)
Sn1-C26	2.137(3)	C1-N1	1.321(4)
Sn1-O2	2.138(2)	N1-N2	1.394(4)
Sn1-C8	2.137(3)	C1-O2	1.296(4)
Sn1-O3	2.078(2)	C15-N2	1.309(4)
O3-Sn1-C26	101.90(12)	C8-Sn1-O2	92.49(12)
O3-Sn1-C8	92.18(12)	O3-Sn1-N2	81.68(10)
C26-Sn1-C8	125.02(14)	C26-Sn1-N2	101.29(12)
O3-Sn1-O2	149.09(10)	C8-Sn1-N2	133.44(12)
C26-Sn1-O2	100.28(11)	O2-Sn1-N2	73.04(9)
Complex **4**			
Sn1-C27	2.130(5)	O2-Sn1#2	2.169(3)
Sn1-C23	2.146(5)	O3-C7	1.239(5)
Sn1-O2#1	2.169(3)	N2-C7	1.354(6)
Sn1-C19	2.136(5)	N1-N2	1.389(5)
Sn1-O3	2.446(3)	N1-C8	1.2886
C27-Sn1-C19	131.9(2)	C27-Sn1-C23	110.5(2)
C19-Sn1-C23	116.1(2)	C27-Sn1-O2#1	97.00(17)
C19-Sn1-O2#1	92.23(17)	C23-Sn1-O2#1	92.63(16)
C27-Sn1-O3	85.11(16)	C19-Sn1-O3	82.51(17)
C23-Sn1-O3	91.51(16)	O2#1-Sn1-O3	174.37(12)
C4-O2-Sn1#2	125.7(3)		

Symmetry transformations used to generate equivalent atoms: Complex 1: #1 x, -y+1/2, z;
Complex 4: #1 -x+2, y+1/2, -z+1/2, #2 -x+2, y-1/2, -z+1/2

Table 3. Hydrogen bonding geometries for complexes 1, 2, 3 and 4

D-H...A	*D-H*	*H...A*	*D...A*	*D-H...A*
Complex **1**				
C(4)-H(4)...O(3)#2	0.93	2.43	3.359(5)	175.3
O(2)-H(2)...N(1)	0.82	1.86	2.576(4)	145.6
C(7)-H(7)...O(1)	0.93	2.46	2.774(5)	99.8
Complex **2**				
C(30)-H(30)...O(2)#1	0.93	2.58	3.332(5)	138.7
O(2)-H(2)...N(2)	0.82	1.92	2.638(4)	145.9
C(18)-H(18)...O(3)	0.93	2.40	2.728(4)	100.5
C(30)-H(30)...O(1)	0.93	2.57	3.120(5)	118.4

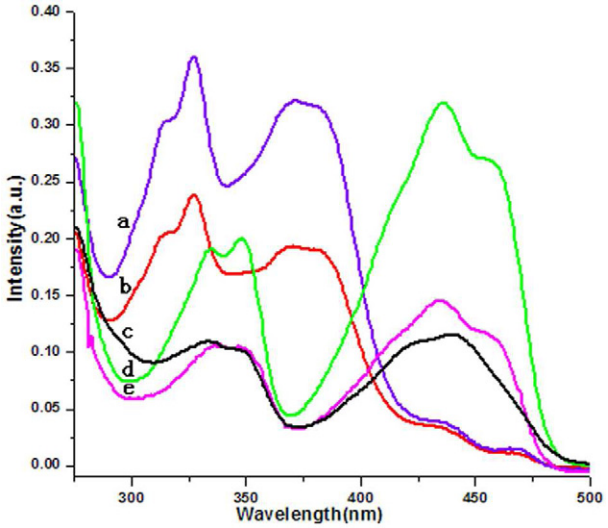
Complex **3**				
O(1)-H(1)...N(1)	0.82	1.86	2.576(4)	144.8
C(32)-H(32)...O(1)#1	0.93	2.46	3.215(4)	138.4
Complex **4**				
C(2)-H(2)...O(3)	0.93	2.42	2.748(6)	100.6
O(1)-H(1)...N(1)	0.82	1.89	2.609(5)	146.3

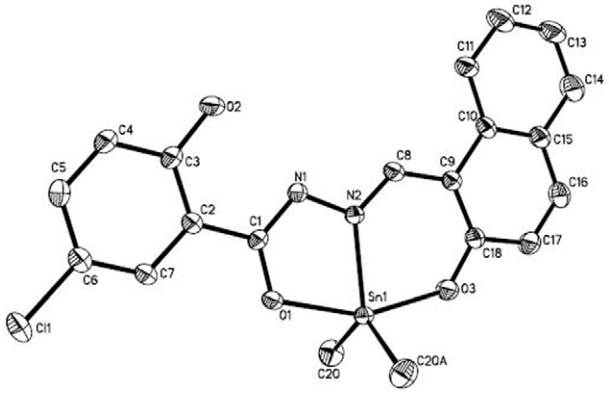
Symmetry transformations used to generate equivalent atoms:complex 1: #2 x, y, z+1

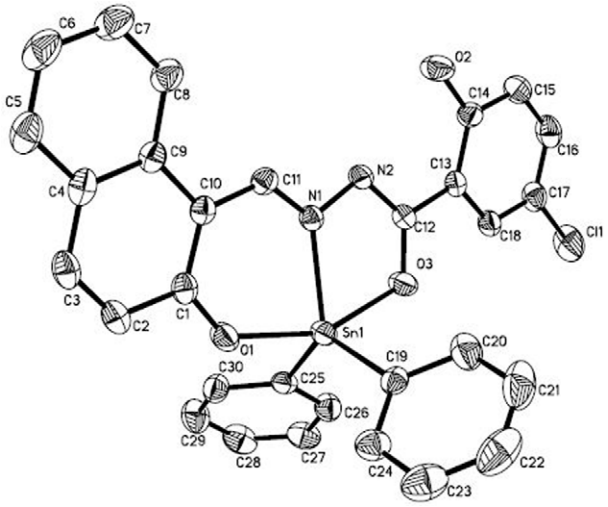
complex 2: #1 -x+1, -y+1, -z; complex 3: #1 -x+2, -y+1, -z

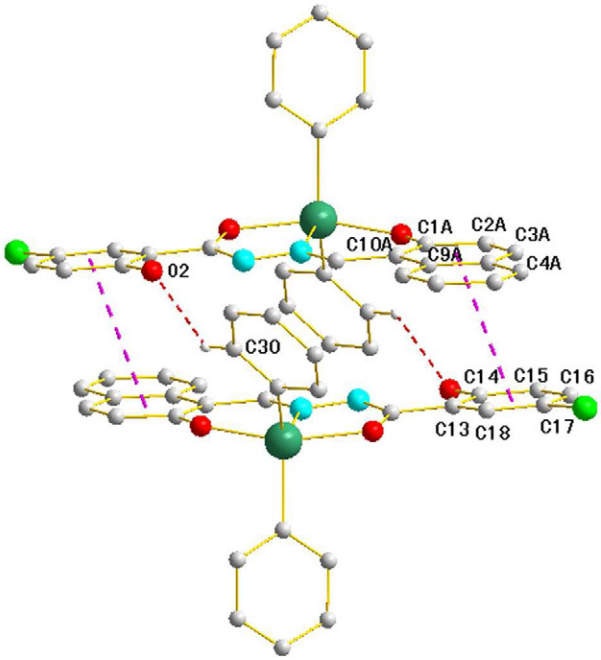
Table 4. In vitro cytotoxicity assay for complexes **1-4**, organotin(IV) chlorides and H_2L against tumor cell lines.

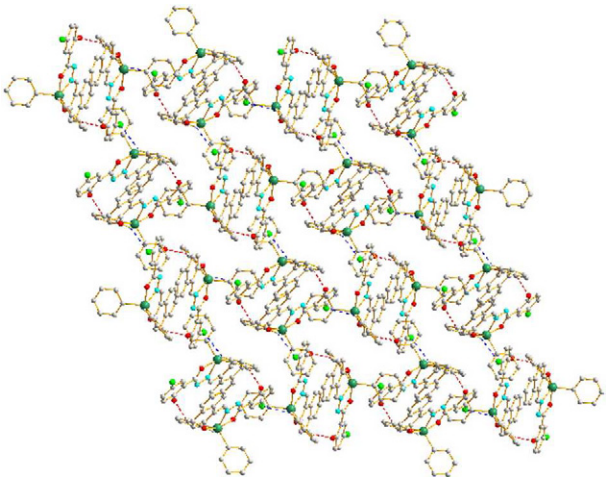
Complex	IC_{50}(μg/mL)		
	A549	HCT-8	HL-60
1	0.9 ±0.14	0.5±0.13	9.3±0.82
2	>10	4.1±0.25	>10
3	>10	3.9±0.05	0.6±0.04
4	0.09±0.03	0.5±0.13	0.4±0.06
Me_2SnCl_2	>10		
Ph_2SnCl_2	4.23±0.46		
(o-$ClC_6H_4CH_2)_2$ $SnCl_2$	0.48±0.12		
n-Bu_3SnCl	0.81±0.21		
H2L	0.95±0.06		
cisplatin	2.1±0.44	0.9±0.26	0.7±0.23

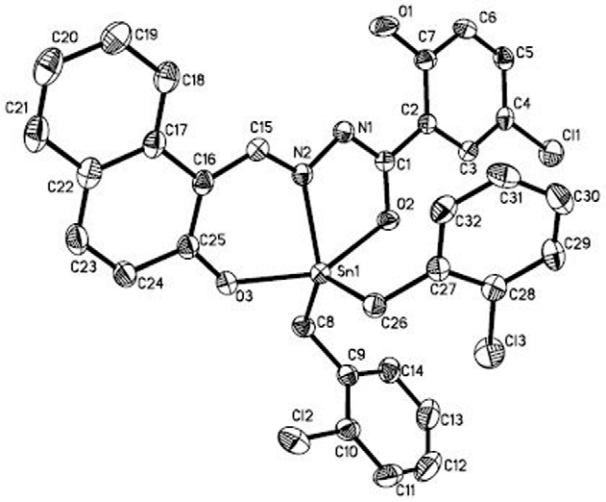


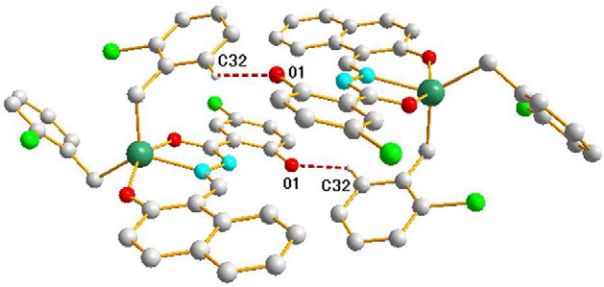


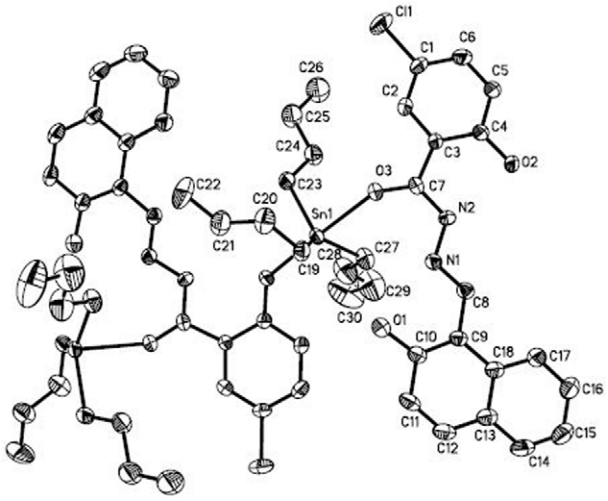


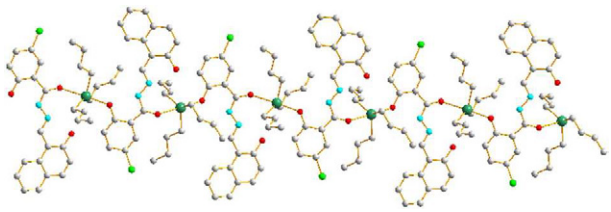


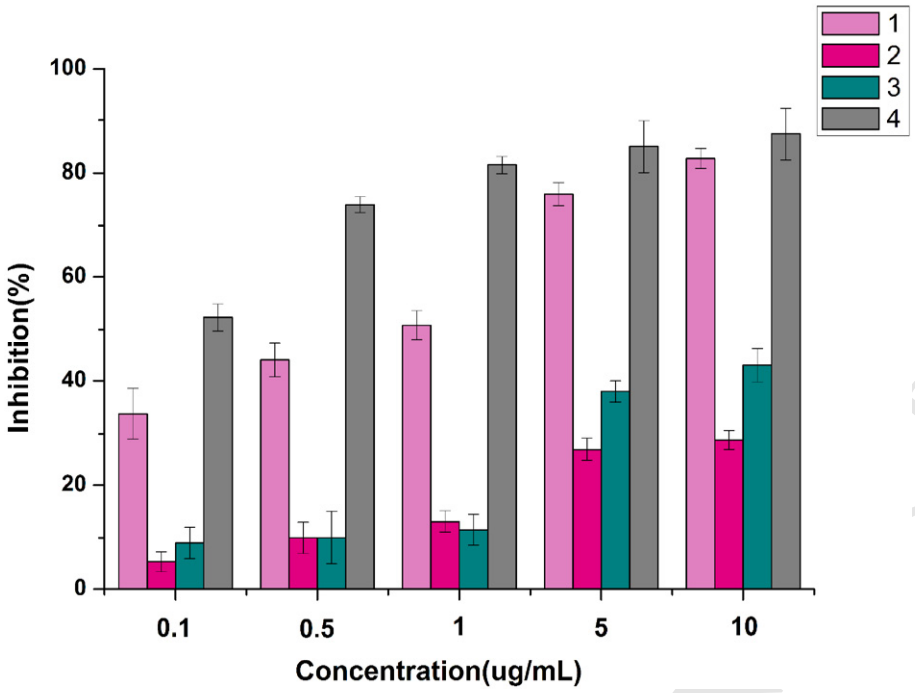


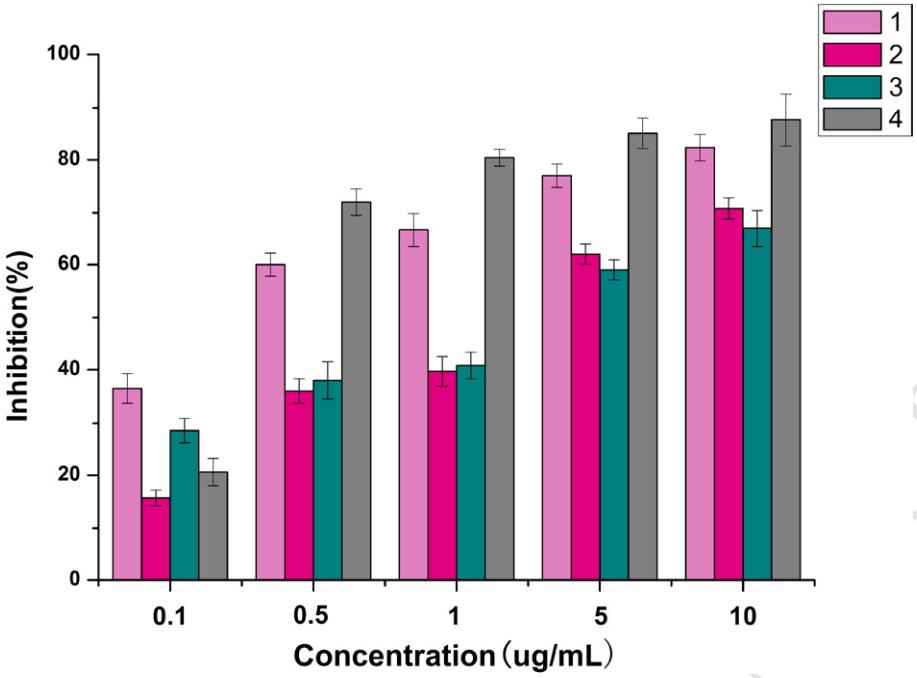


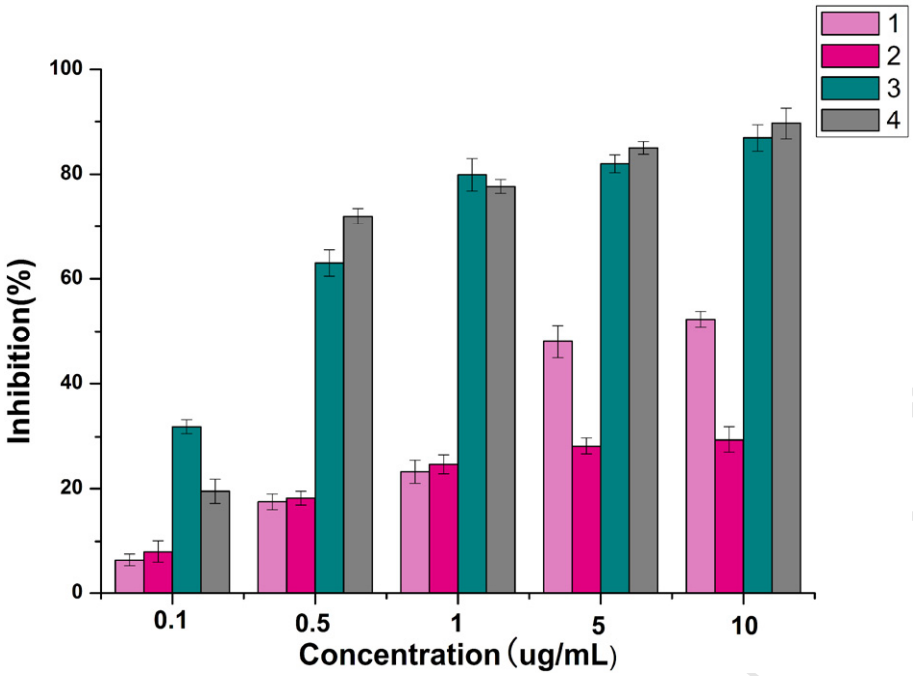


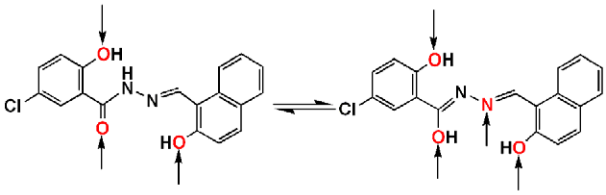


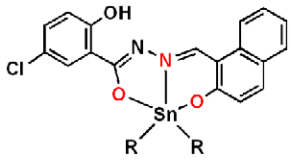




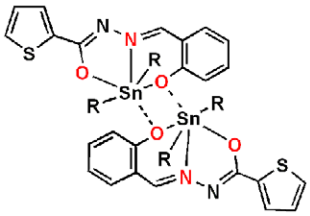




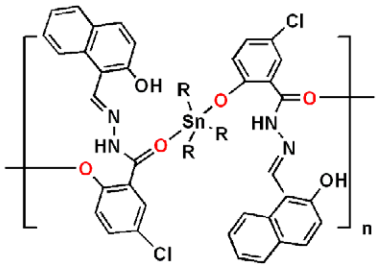




I



II



III