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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 both alkyl groups bound with tin centers and the structural 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 compounds, there was a good dose–effect relationship.

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 1A, 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) analogs [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.

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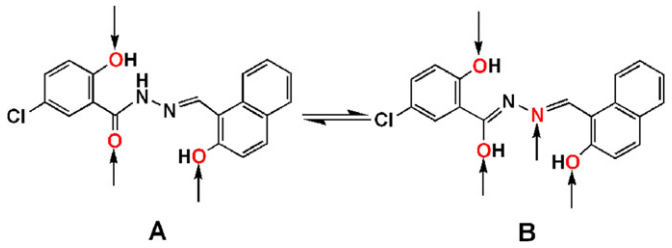


Scheme 1. Different coordination sites of the Schiff base group.

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, $\lambda = 0.71073$ 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.

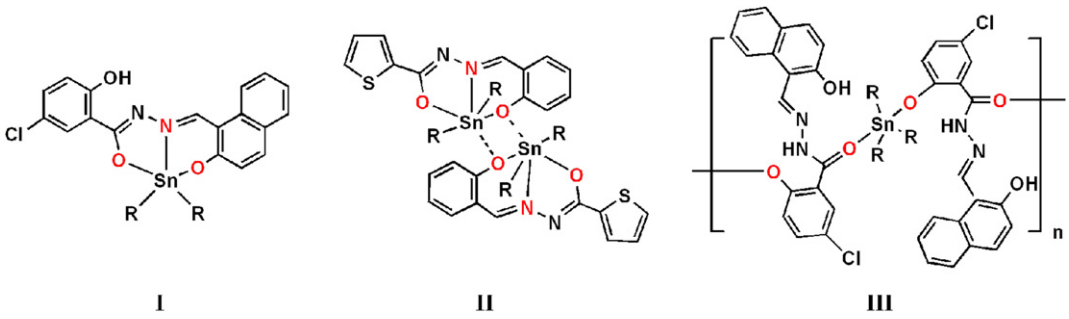
2.4. Synthesis

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 (1.722 g, 10.0 mmol) was added slowly to an ethanol solution containing 5-chloro-2-hydroxybenzoylhydrazide (1.866 g, 10.0 mmol) 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. >573 K. 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). ^{1}H 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, 0.4 mmol) was added to 30 mL methanol solution of 2-hydroxy-1-



Scheme 2. Different modes of the Schiff base group.