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Short communication

Dimethyltin(IV) and palladium(II) complexes derived from 2-benzoylpyridine *N*(4)-cyclohexylthiosemicarbazone: Synthesis, crystal structures and biological evaluation

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ABSTRACT

Two metal complexes [$(Me)_2Sn(L)(OAc)$] (**1**), and [Pd(L)Cl] (**2**) based on 2-benzoylpyridine *N*(4)-cyclohexylthiosemicarbazone have been synthesized and structurally characterized. X-ray crystallography reveals that in title compounds, each thiosemicarbazone adopts tridentate NNS manner to coordinate with the metal center, and the metal coordination geometry can be described as a distorted pentagonal bipyramid in **1** and a contorted square-planar in **2**, respectively. Growth inhibition assays have indicated that two compounds can effectively inhibit the growth of HepG2 cancer cell lines at micromolar concentrations. In addition, apoptosis mechanisms of **2** on HepG2 cells were further investigated. The results show that **2** can promote the apoptosis of HepG2 cells and the apoptosis is associated with the activation of caspase-3.

Thiosemicarbazones are an important class of Schiff-base compounds well-known for their coordination chemistry and pharmacological properties [1–4]. They can band to a metal center in the neutral or the anionic form owing to their thione-thiol tautomers [2]. Also they have more than one binding site for metals, which makes them display diverse bonding modes such as monodentate, bidentate, bridge, and chelate mode. For thiosemicarbazones, the most famous and distinguishing feature is that they possess a great variety of pharmacological properties, including antimalarial, antifungal, antiviral, antibacterial, and most notable for antitumour activity [2,5–8]. These biological activities are believed to be intensely related to their ability to form stable complexes with a variety of metals [9]. Metal ion, coordination modes, parent aldehyde or ketone and substituents on thiosemicarbazide have marked effects on their biological activities [10–12]. In addition, it is found that lipophilicity controlling the rate of entry of molecules into the cell may be enhanced by coordination [13]. And upon complexation, some metal complex may display higher bioactivities and lower side effects compared to the parent ligand [14,15]. Therefore, it has become one of the most popular research areas to realize the rational synthesis of thiosemicarbazones and their metal complexes with excellent biological activities by modulating the structure of thiosemicarbazones or metal center. In this area, *N*(4)-substituted-α(*N*)-heterocyclic thiosemicarbazone derivatives and their metal complexes have attracted considerable interest owing to their significant biological activities and potential applications in various medicinal fields [16–18].

On the other hand, organotin(IV) and palladium(II) complexes have shown a good application prospect as biologically active metal-based agents. The potential of organotin(IV) complexes as metallopharmaceuticals has been accepted [19–22]. Some studies with interesting results on the *in vitro* anticancer properties of organotin(IV) complexes against human cancer cell lines have been reported [19–22]. Palladium(II) has the similar d^8 system and chemical properties to those of platinum (II), and as a result its complexes may show similar behaviour as platinum complexes did. Moreover, palladium complexes have better solubility than platinum complexes, which makes palladium complexes seem to be more attractive [23]. Hence in search of new alternative of Pt(II)-based drugs for antitumour treatments, much attention has been focused on Pd(II) complexes and some promising results have been achieved [23–25].

In recent years, we have been working on the structure and biological properties of α(*N*) heterocyclic thiosemicarbazones and their metal complexes [26–31]. The study results have revealed that thiosemicarbazones derived from *N*(4)-substituted 2-benzoylpyridine

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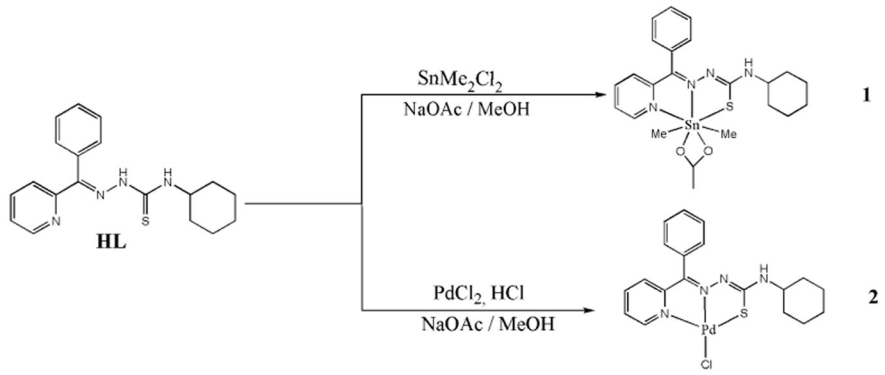

Scheme 1. Synthetic route of complexes **1** and **2**.

and their metal complexes may show significant biological activities [29–31]. Taking into consideration the above facts, and as a continuation of our systemic study, herein we present the synthesis, characterization and structures of Sn(IV) and Pd(II) complexes formulated as $[(Me)_2Sn(L)(OAc)]$ (**1**), [Pd(L)Cl] (**2**) of 2-benzoylpyridine *N*(4)-cyclohexylthiosemicarbazone (HL) (Scheme 1). Their *in vitro* cytotoxicity against human hepatoma HepG2 cells has been evaluated. Moreover, the action mechanism of **2** in HepG2 cells has been studied.

2-Benzoylpyridine *N*(4)-cyclohexylthiosemicarbazone was prepared as described in the literature [32], and complexes **1** and **2** were synthesized by reaction of equivalents amount of the ligand with $(Me)_2SnCl_2$ or $PdCl_2$ in methanol solution for 1 h under refluxing [33, 34]. Crystals of **1** and **2** suitable for X-ray studies were obtained by slow evaporation of their methanol solutions.

X-ray crystallography [35] reveals that complex **1** crystallizes in the triclinic system with space group $P\bar{1}$. As shown in Fig. 1 (a), **1** contains the mononuclear neutral molecule composed of one anionic thiosemicarbazone ligand, one dimethyltin(IV) group and one acetato group wrapped around tin(IV) ion. The tin(IV) ion is seven-coordinated in a distorted pentagonal bipyramidal geometry with the pentagonal plane defined by one tridentate N_2S thiosemicarbazone and one bidentate acetato group, whereas the axial positions are occupied by two methyl groups. The bond angles N(3)—Sn(1)—S(1) 73.65(10)°, N(4)—Sn(1)—N(3) 67.11(13)°, N(4)—Sn(1)—O(2) 82.72(14)°, O(1)—Sn(1)—O(2) 53.89(13)°, and O(1)—Sn(1)—S(1) 82.92(10)°, deviate markedly from the theoretical value of 72°, suggesting contortion from the regular pentagonal bipyramidal geometry. Meanwhile, the axial C(20)—Sn(1)—C(21) segment deviate 17.8° from linearity, bending towards the vacant equatorial position and away from the bite of the thiosemicarbazone moiety [36]. In **1**, each ligand coordinates to tin(IV) ion in a N_2S tridentate manner, resulting in forming two 5-membered fused chelate rings with dihedral angle of 5.6°. The Sn—C bond distances (2.098(5) Å and 2.101(6) Å) are normal for $SnME_2^{2+}$-thiosemicarbazone compounds [36,37]. The shorter bond length of $Sn–N_{imine}$ (2.393(4) Å) relative to that of $Sn–N_{pyridine}$ (2.462(4) Å), similar to other related tin(IV)-thiosemicarbazone complexes [36–40], may be due to the fact that the imine nitrogen is a stronger base compared with the pyridine nitrogen [41]. The C(7)–S(1) bond distance (1.746(5) Å) corresponds to a single bond character, while C(7)–N(2) bond distances (1.318(6)) Å) accounts for the double bond character of this bond [42]. In addition, pairs of intermolecular hydrogen bonds are formed between the terminal nitrogen atom N(1) and sulfur atom

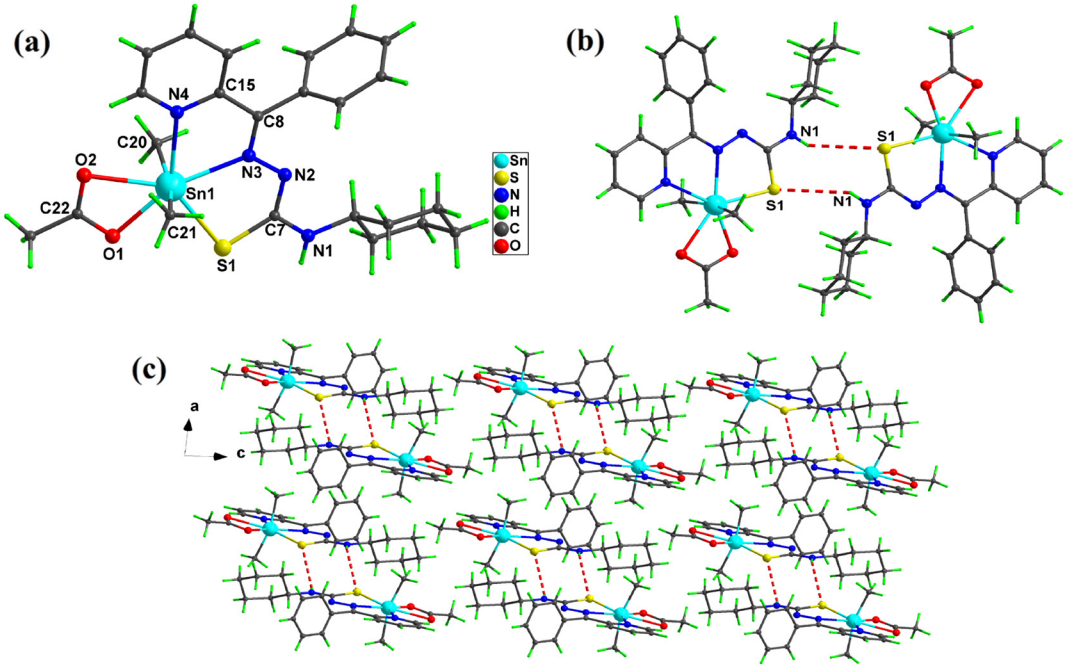

Fig. 1. (a) Molecular structure of complex **1** with atomic labeling scheme. (b) Intermolecular interactions *via* hydrogen bonds (indicated by dashed line). (c) The molecular packing projected along the *b*-axis.