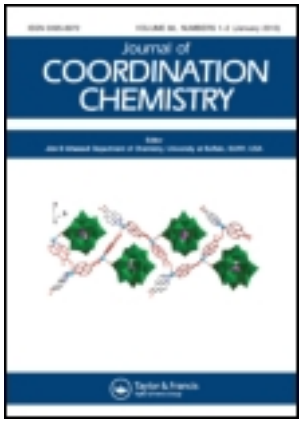

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Synthesis, crystal structures, and cytotoxicity of 2-benzoylpyridine N(4)-cyclohexylthiosemicarbazone and its zinc(II) and diorganotin(IV) complexes

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Synthesis, crystal structures, and cytotoxicity of 2-benzoylpyridine N(4)-cyclohexylthiosemicarbazone and its zinc(II) and diorganotin(IV) complexes

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[$Zn(L)_2$] (**1**) and [$(Ph)_2Sn(L)(CH_3COO)$] (**2**), where HL = 2-benzoylpyridine N(4)-cyclohexylthiosemicarbazone, have been synthesized and characterized. The complexes show different coordination depending on their coordinating preferences. Biological studies carried out *in vitro* against human leukemia K562 cells show that the diorgantin(IV) complex, **2**, has significant cytotoxicity with $IC_{50} = 3.3 \pm 0.5$ μM.

Keywords: Thiosemicarbazone; Crystal structure; Cytotoxicity

1. Introduction

Heterocyclic thiosemicarbazones and their metal complexes have received attention due to their variable coordination [1–5] and pharmacological properties [6, 7], notably antiparasital [8], antibacterial [9], and anticancer activities [10]. 3-Aminopyridinecarbaldehyde thiosemicarbazone (Triapine) is currently undergoing clinical trials [11]. Its mechanism of action is still controversial in many respects and has been identified to involve ribonucleotide reductase inhibition, metal-dependent radical damage, DNA binding, and inhibition of protein synthesis [12–14]. Biological activities of the thiosemicarbazones are closely related to the parent aldehyde or ketone, metal chelation ability and terminal amino substitution [15–18]. In some cases, the highest *in vivo* activity was associated with a metal complex rather than the parent ligand and some side effects may decrease upon complexation [19–21]. Lipophilicity, which controls the rate of entry of molecules into the cell, is modified by coordination [22–24]. Metal compounds could act through dual or even multiple mechanisms of action by combining the pharmacological properties of both the ligand and metal.

Zinc, the second most prominent trace metal in the human body after iron, is essential for growth and development and plays an important role in various biological systems.

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Intracellular distribution of several zinc(II) complexes have been tracked in different cancer cell lines [25]. Zinc(II) complexes are well known for their significant pharmaceutical properties [26–28] and in most cases are more active than their free ligands [29]. Tin complexes are well known for applications as antifungal, antibacterial, and cytotoxic agents [30, 31], but are often toxic [32, 33]. Syntheses of tin complexes with thiosemicarbazones could be a strategy for preparation of new compounds with promising pharmacological profiles.

We have been working on the structural and biological properties of heterocyclic thiosemicarbazones and their metal complexes [34]. These results reveal that the thiosemicarbazones derived from 2-benzoylpyridine and their metal complexes show significant biological activities. Here, we combine zinc(II)/diorganotin(IV) with 2-benzoylpyridine N(4)-cyclohexylthiosemicarbazone and evaluate their coordination chemistry and potential as anticancer agents.

In the present paper, we have tested the biological activities of 2-benzoylpyridine N(4)-cyclohexylthiosemicarbazone (scheme 1), $[Zn(L)_2]$ (**1**), and $[(Ph)_2Sn(L)(CH_3COO)]$ (**2**) against human leukemia K562 cells to compare the variation in biological activity by changing metals. We also describe the synthesis and characterization of **1** and **2**.

2. Experimental

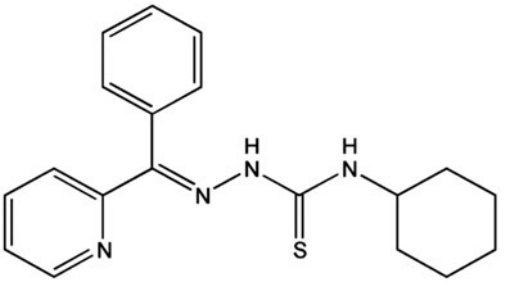
2.1. *General procedures*

All chemicals were of reagent grade quality obtained from commercial sources and used without purification. Instrumentation: C, H, and N elemental analyses were performed with a Perkin–Elmer 240 analyzer. IR spectra were recorded from KBr disks on a Nicolet 170 FT-IR spectrophotometer. Electronic spectra were obtained with a Hitachi U4100 spectrometer. ^{1}H NMR spectra were recorded using a Bruker AV-400 spectrometer. Mass spectrometry (MS) was carried out on an Esquire 3000 LC-MS mass spectrometer.

2.2. *Synthesis*

2.2.1. Synthesis of HL. HL was synthesized according to the literature method [35].

2.2.2. Synthesis of 1. An ethanol solution containing $Zn(ClO_4)_2 \cdot 6H_2O$ (0.074 g, 0.2 mM) was added dropwise to an ethanol solution (20 mL) of 2-benzoylpyridine N(4)-cyclohexyl-



Scheme 1. 2-Benzoylpyridine N(4)-cyclohexylthiosemicarbazone, HL.

thiosemicarbazone (0.136 g, 0.4 mM) and NaOAc (0.032 g, 0.4 mM). After refluxing for 1 h of stirring, the mixture was allowed to cool to room temperature and filtered. The obtained solid product was subsequently purified by recrystallization from ethanol and dried over P_4O_{10} in vacuum. Yield: 70%. Anal. Calcd (%) for $C_{38}H_{42}N_8S_2Zn$: C, 61.65; H, 5.72; N, 15.14. Found: C, 61.48; H, 5.84; N, 15.03. ^{1}H NMR (DMSO-d_6, δ ppm): 8.50 (s, 1H, NH), 7.53–7.47 (m, 9H, 4H of Py, 5H of Ph), 1.79–1.62 (m, 11H, C_6H_{11}); IR [KBr, ν (cm^{-1})]: 2926 and 2851 (NH), 1587 (C=N), 1147 (N–N), 787 (C=S); UV–vis [λ(nm), C_2H_5OH]: 260, 306, 410; ESI-MS (m/z): 741.3 $[Zn(L)(HL)]^+$, Calcd: 741.3. Yellow crystals suitable for X-ray studies were obtained by slow evaporation of an ethanol solution of **1**.

2.2.3. Synthesis of 2. An ethanol solution containing $(Ph)_2SnCl_2$ (0.070 g, 0.2 mM) was added dropwise to an ethanol solution (20 mL) of 2-benzoylpyridine N(4)-cyclohexylthiosemicarbazone (0.068 g, 0.2 mM) and NaOAc (0.016 g, 0.2 mM). The mixture was heated at reflux for 1 h and allowed to cool slowly to room temperature. Yellow powder formed, was collected by filtration, purified by recrystallization from ethanol, and dried in vacuum. Yield: 65%. Anal. Calcd (%) for $C_{33}H_{34}N_4SO_2Sn$: C, 59.21; H, 5.12; N, 8.37. Found: C, 59.08; H, 5.34; N, 8.53. ^{1}H NMR (DMSO-d_6, δ ppm): 9.16 (s, 1H, NH), 7.95–7.90 (m, 2H, Py), 7.56–7.48 (m, 7H, 2H of Py, 5H of Ph), 7.20–7.14 (m, 10H, Ph), 1.99–1.55 (m, 11H, C_6H_{11}); IR [KBr, ν (cm^{-1})]: 2931 and 2852 (NH), 1575 (C=N), 1152 (N–N), 785 (C=S); UV–vis [λ(nm), C_2H_5OH]: 330, 406; ESI-MS (m/z): 569.2 $[(Ph)Sn(L)(OH)(H_2O)]^+$, Calcd: 569.1. Yellow crystals suitable for X-ray studies were obtained by slow evaporation of an ethanol solution of **2**.

2.3. *Single-crystal X-ray diffraction*

Single-crystal X-ray diffraction data were collected with a Siemens SMART-CCD diffractometer with graphite-monochromated Mo-$K\alpha$ radiation (λ = 0.71073 Å). The structures were solved by direct methods and refined by full-matrix least-squares on F^2 with anisotropic displacement parameters for all non-hydrogen atoms using SHELXTL [36]. The hydrogens were added in idealized geometrical positions.

2.4. In vitro *cytotoxicity*

3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay was carried out to evaluate cytotoxicity in K562 leukemia cells. Cells were plated in 96-well plates at a cell density of 1×10^4 cells per well and allowed to grow in a CO_2 incubator. After 24 h, the medium was removed and replaced by fresh medium containing the tested compounds that were dissolved in DMSO at 0.01 M and diluted to various concentrations with phosphate-buffered saline before the experiment such that the final concentration of DMSO was lower than 1%. After 24 h of incubation, cultures were incubated in 100 µL of the medium with 10 µL of a 5 mg mL^{-1} MTT solution for 4 h at 37 °C. The medium with MTT was removed and 100 µL of DMSO was added to each well to dissolve the formazan. The absorbance at 570 nm was measured with a microplate reader (Bio-Tek ELX800, USA). The inhibitory percentage of each compound at various concentrations was calculated, and the IC_{50} value was determined.

3. Results and discussion

3.1. *X-ray crystallography*

Crystallographic data of **1** and **2** are summarized in table 1 and selected bond distances and angles in table 2.

Complex **1** (figure 1A) is a mononuclear six-coordinate with the basic formula $[Zn(L)_2]$. The zinc(II) is N_4S_2 coordination by two mono-deprotonated ligands, forming four five-membered chelate rings. One sulfur, one imine nitrogen, and one pyridine nitrogen from one ligand and one imine nitrogen atom from another ligand occupy the basal position; the two axial positions in the octahedral geometry are occupied by one sulfur and one pyridine nitrogen from the second ligand. The measured C–S bond distances *ca* 1.725(4) and 1.737(4) Å are within the normal range of C–S single bonds, indicating that the thiosemicarbazones adopt the thiol tautomeric form and act as mono-negative ligands [37]. As shown in figure 1B, **1** is stabilized by intermolecular hydrogen bonds involving terminal nitrogen N(5) and S(2) with N(5)···S(2) 3.503(3) Å and the angle N(5)–H(5A)···S(2) of 162.4° (symmetry code: $-x + 1/2, -y + 1/2, -z$), respectively.

As shown in figure 2(A), **2** contains one anionic thiosemicarbazone, one diorganotin(IV), and one acetate. Tin(IV) is seven-coordinate, distorted pentagonal bipyramidal with the pentagonal plane defined by the tridentate N_2S thiosemicarbazone and the bidentate acetate, whereas the axial positions are occupied by two *trans* phenyl rings. The distortion from pentagonal bipyramidal geometry is evident from the bond angles N(3)–Sn(1)–S(1) 74.86 (11)°, N(4)–Sn(1)–N(3) 68.07(14)°, N(4)–Sn(1)–O(1) 82.90(13)°, O(1)–Sn(1)–O(2) 54.33 (13)°, and O(2)–Sn(1)–S(1) 80.08(10)°, respectively. The axial C(20)–Sn(1)–C(26) angle is far from linear (l65.1(2)°). The significant deviations from regular geometry are primarily

Table 1. Summary of crystal data and refinement results for **1** and **2**.

Crystal data	**1**	**2**
Empirical formula	$C_{38}H_{42}N_8S_2Zn$	$C_{33}H_{34}N_4O_2SSn$
Formula weight	740.29	669.42
Crystal size /mm	0.32×0.16×0.14	0.57×0.41×0.17
Crystal system	Monoclinic	Monoclinic
Space group	*C2/c*	$P2_1/c$
T/K	293(2)	293(2)
a/Å	29.439(4)	8.4271(15)
b/Å	14.744(2)	23.907(4)
c/Å	18.670(3)	15.808(3)
V/Å^3	7680.7(19)	3170.2(10)
β (°)	108.595(2)	95.485(3)
D_c/g cm^{-3}	1.280	1.403
Z	8	4
μ/mm^{-1}	0.786	0.907
θ (°)	2.07–25.00	2.14–25.00
F_{000}	3104	1368
Index ranges	$-34 \le h \le 33, -17 \le k \le 16, -22 \le l \le 21$	$-9 \le h \le 10, -19 \le k \le 28, -18 \le l \le 18$
Refl. collected	6748	5553
Refl. unique	5072	4141
R_{int}	0.1045	0.0692
Parameters	442	370
R_1, wR_2 [$I \ge 2\sigma(I)$]	0.0690, 0.2086	0.0487, 0.1318
R_1, wR_2 (all data)	0.0836, 0.2193	0.0643, 0.1390
Goodness-of-fit on F^2	1.014	1.060
$\Delta\rho_{max}$, $\Delta\rho_{min}$/e Å^{-3}	2.964, −0.627	1.301, −0.673

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

1		**2**	
Zn(1)–N(3)	2.227(3)	Sn(1)–N(3)	2.352(4)
Zn(1)–N(4)	2.270(3)	Sn(1)–N(4)	2.443(4)
Zn(1)–N(7)	2.211(3)	Sn(1)–S(1)	2.552(1)
Zn(1)–N(8)	2.248(3)	Sn(1)–O(1)	2.502(4)
Zn(1)–S(1)	2.461(1)	Sn(1)–O(2)	2.284(4)
Zn(1)–S(2)	2.464(1)	Sn(1)–C(20)	2.152(5)
S(1)–C(7)	1.725(4)	Sn(1)–C(26)	2.155(5)
S(2)–C(26)	1.737(4)	S(1)–C(7)	1.745(6)
N(3)–C(8)	1.296(5)	N(2)–N(3)	1.369(6
N(7)–C(27)	1.306(5)	N(3)–C(8)	1.296(6)
		N(3)–Sn(1)–N(4)	68.07(14)
N(3)–Zn(1)–N(4)	71.93(12)	N(3)–Sn(1)–S(1)	74.86(11)
N(3)–Zn(1)–S(1)	76.68(9)	O(2)–Sn(1)–S(1)	80.08(10)
N(3)–Zn(1)–N(7)	145.0(1)	N(4)–Sn(1)–O(1)	82.90(13)
N(4)–Zn(1)–N(7)	84.29(12)	O(2)–Sn(1)–O(1)	54.33(13)
N(8)–Zn(1)–S(2)	145.1(1)	C(20)–Sn(1)–C(26)	165.1(2)

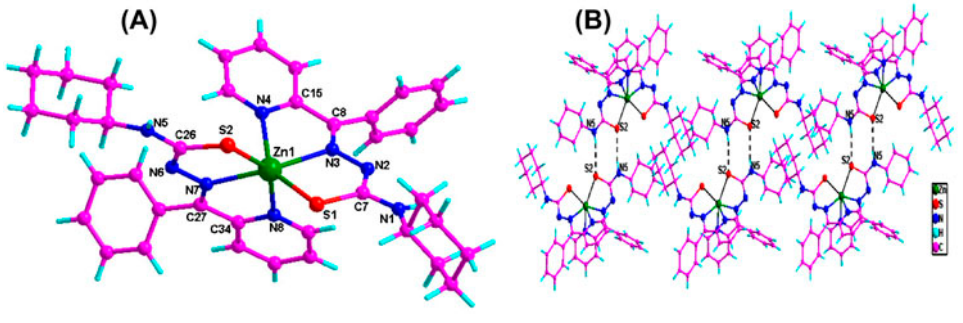


Figure 1. (A) Structure of **1** with the atom numbering scheme. (B) Hydrogen bond in dashed lines in **1**.

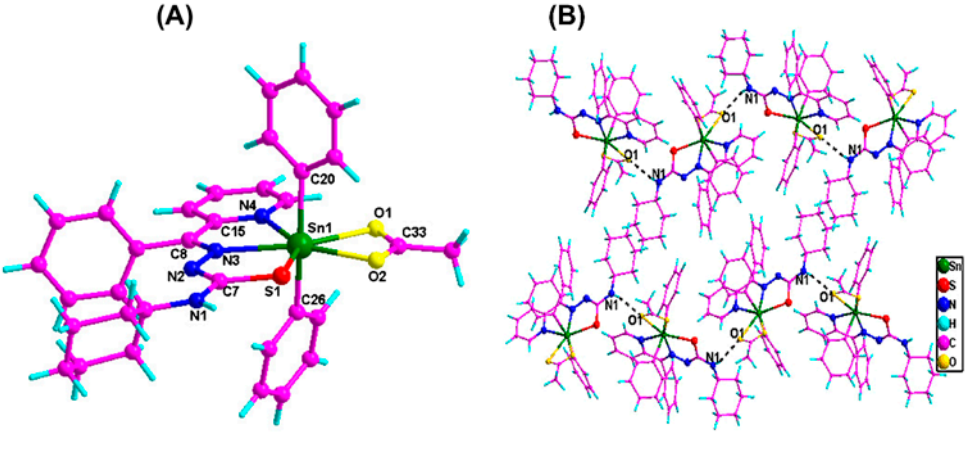


Figure 2. (A) Structure of **2** with the atom numbering scheme. (B) Hydrogen bond in dashed lines in **2**.

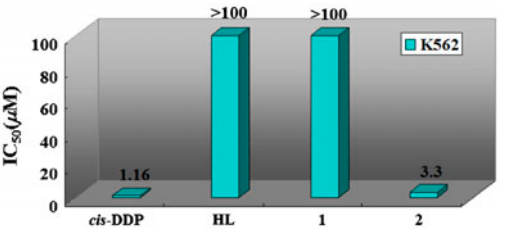


Figure 3. The cytotoxicity of HL, **1**, and **2** against human leukemia K562 cells.

due to the short bite of acetate which results in an O(1)–Sn(1)–O(2) angle of 54.33(13)° instead of the theoretical value of 72°. The shortening of the bond lengths of the Sn–N (imine), relative to the bond distances of the Sn–N(pyridine), may be attributed to the imine nitrogen being a stronger base compared with the pyridine nitrogen [38, 39]. Intermolecular hydrogen bonds of **2** link the different components to stabilize the crystal structure (figure 2B). The terminal nitrogen N(1) of the thiosemicarbazone is a hydrogen bond donor while O(1) of an acetate is an acceptor with N(1)···O(1) 2.953(6) Å and the angle N(1)–H(1A)···O(1) being 141.5° (symmetry code: x, $-y + 1/2$, $z - 1/2$).

3.2. *Cytotoxicity*

Heterocyclic substituted thiosemicarbazones and their metal complexes show particularly effective cytotoxicity, due to the NNS tridentate system [40]. Therefore, we have tested the ability of the obtained compounds to inhibit cancer cell growth against human leukemia K562 cells. In our experiments, IC_{50} values (compound concentration that produces 50% of cell death) in micro molar units were calculated (figure 3). The lower the IC_{50} value, the greater the cytotoxicity. The human clinical drug, cisplatin, was used as reference compound for comparison. Complexation with metals has a synergistic effect on the cytotoxicity of these compounds and the growth inhibitory activity depends on the type of metal ion. Coupling of the thiosemicarbazone with tin(IV) leads to enhancement of cytotoxicity of the Schiff base, similar to other bioactive tin complexes [30b-30e, 31d]. The higher cytotoxicity of **2** (IC_{50} = 3.3 ± 0.5 μM) may be due to the presence of phenyls, which facilitate binding to biological molecules by π–π interactions [30e]. Further screening *in vitro* and *in vivo* of **2** will be essential for medical application. Surprisingly, the introduction of zinc(II) makes no significant contribution to the bioactivity, inconsistent with previously reported zinc cases [41].

4. Conclusions

Zinc(II) and tin(IV) complexes with 2-benzoylpyridine N(4)-cyclohexylthiosemicarbazone have been synthesized and structurally characterized. Two new complexes show distinctly different coordination modes. Biological studies indicate that coordination of organotin(IV) enhances the biological activities of the free ligand. Further investigations of organotin(IV) complexes with substituted thiosemicarbazone ligands should be performed, in particular on the spectrum of their antitumor activities and mechanism of action.

Supplementary material

CCDC 784105 and 827310 contain the Supplementary crystallographic data for **1** and **2**, respectively. These data can be obtained free of charge from the Cambridge Crystallographic Centre via www.ccdc.cam.ac.uk/data_request/cif.

Acknowledgments

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