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Cadmium(II) and indium(III) complexes derived from 2-benzoylpyridine *N*(4)-cyclohexylthiosemicarbazone: Synthesis, crystal structures, spectroscopic characterization and cytotoxicity

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ABSTRACT

Two metal complexes $[Cd(L)_2]\cdot 0.275H_2O$(**1**) and $[In(L)_2]NO_3$ (**2**) (HL = 2-benzoylpyridine *N*(4)-cyclohexylthiosemicarbazone) have been synthesized and structurally characterized by elemental analysis, a number of spectroscopic methods (IR, UV-vis, NMR), mass spectrometry, and X-ray crystallography. The Schiff's base ligand forms hexacoordinated complexes having octahedral geometry for Cd(II) and In(III) complexes, respectively. The synthesized compounds were tested for antiproliferative activity and showed the ability to kill HepG2 cells (human hepato cellular carcinoma) significantly, especially **2** with $IC_{50} = 2.02 \pm 0.14$ μM. Of particular note is the fact that complex **1** has *ca* 12-fold lower toxicity in the normal hepatocyte QSG7701 cells than in the hepatocellular carcinoma HepG2 cells. In addition, complex **2** also exhibited excellent luminescent property. Upon the addition of 1 equiv of In^{3+} ion, 200-fold fluorescence enhancement of HL at $\lambda_{em} = 504$ nm has been observed. Moreover, the fluorescent color change (from transparent to light-green) could be observed by naked eyes under the light of 365 nm. These findings can expand the applications of thiosemicarbazone derivatives in the fields of colorimetric and fluorescent probes.

1. Introduction

From the early 1950s to the present, the chemistry of thiosemicarbazones has shown considerable interest in analytical chemistry, pharmacological properties and spectrophotometry [1–5]. The best known member of this family, 3-aminopyridine carboxaldehyde thiosemicarbazone (3-AP), is a potent ribonucleotide reductase inhibitor that is currently in phase II clinical trials for the treatment of a number of forms of cancer, including non-small-cell lung cancer and renal carcinoma [6]. This compound shows therapeutic activity over a certain range of dosages in preclinical tumor models without imposing intolerable host toxicity [7]. In more cases, the involvement of mixed nature of the N and S donor atoms in coordination with metal ions is responsible for increasing biological activities of thiosemicarbazones [8,9]. Their mechanism of action is still controversial in many respects, including ribonucleotide reductase inhibition, metal dependent radical damage, DNA binding, and inhibition of protein synthesis [10,11].

Cadmium is an extremely toxic element whose deleterious actions influence the majority of human tissues and is often present in the environment [12]. Its toxicity derives from the fact that it is rapidly localized intracellularly, mainly in the liver, and then is bound to metallothionein forming a complex that is slowly transferred to the bloodstream to be deposited in the kidneys. Even so, cadmium complexes have attracted more and more attentions due to their widely reported bioactivities, such as DNA binding ability [13], antibacterial activities [14] and antitumor activities [15,16]. Moreover, the compounds which are able to form stable complexes with cadmium could be employed as detoxificating agents [14].

Indium is an auger electron emitter, potentially enabling its complexes to be dual imaging-therapeutic agents [17]. However, indium complexes remain relatively unexplored to date [18–21]. Therefore, detailed investigations of indium complexes will be valuable.

As part of our systematic studies on heterocyclic thiosemicarbazones and their metal complexes [8,22–25], here we report the synthesis, characterization and *in vitro* cytotoxicity of Cd(II)

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and In(III) complexes formulated as $[Cd(L)_2]\cdot 0.275H_2O$ (**1**), $[In(L)_2]NO_3$ (**2**) (HL = 2-benzoylpyridine *N*(4)-cyclohexylthiosemicarbazone) (Scheme 1). In addition, luminescent studies have been carried out.

2. Experiment

2.1. Materials and methods

All solvents and reagents used in this study were reagent grade and used without further purification. The melting points were determined with a Gallenkamp electrically heated apparatus. Elemental analyses (C, H and N) were performed on a Perkin–Elmer 2400–II analyzer. Inductively coupled plasma (ICP) analysis was performed on a Jarrel-AshJ-A1100 spectrometer. The IR spectrum was recorded on a Nicolet FT–IR 360 spectrometer using KBr pellets in the range of 4000–400 cm^{-1}. The UV–vis absorption spectrum was obtained with a U-4100 spectrometer at room temperature. The mass spectra (MS) were taken out on an Esquire 3000 LC–MS mass spectrometer. ^1H NMR spectra were recorded in DMSO-d_6 using a BrukerAV-400 spectrometer. The fluorescent emission spectrums were collected on a HITACHI F–7000 model instrument.

2.2. Synthesis

2.2.1. Synthesis of ligand (HL)

The ligand HL was synthesized according to the literature [26] and confirmed by the IR spectrum.

2.2.2. Synthesis of complex *1*

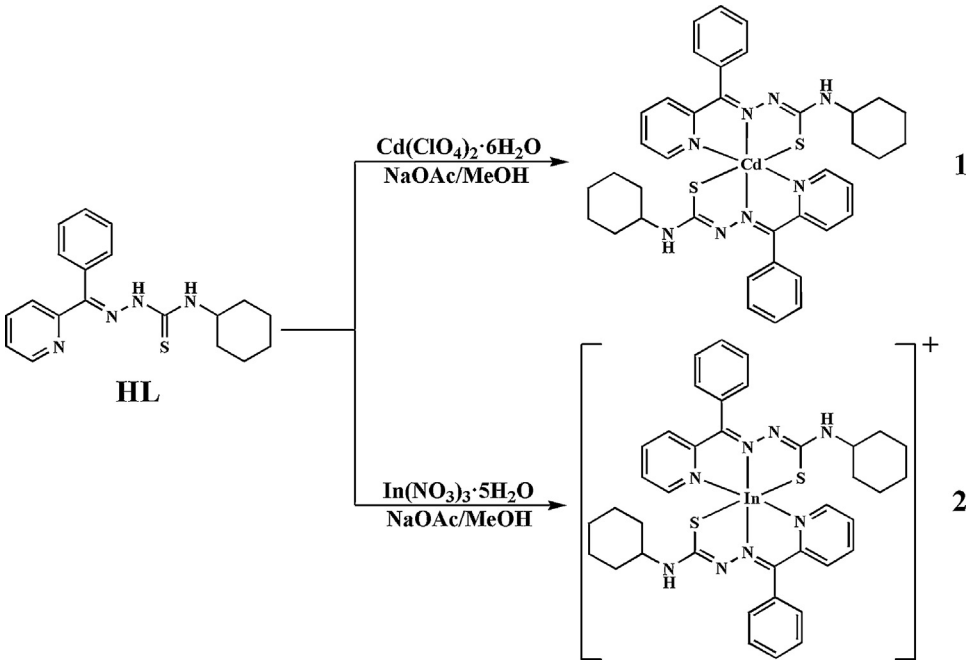
A methanol solution containing $Cd(ClO_4)_2\cdot 6H_2O$ (0.084 g, 0.2 mmol) was added dropwise to a methanol solution (20 mL) of 2-benzoylpyridine *N*(4)-cyclohexylthiosemicarbazone (0.136 g, 0.4 mmol) and NaOAc (0.032 g, 0.4 mmol). After refluxing for 1 h with stirring, the resultant mixture was filtered. The obtained solid product was subsequently purified by recrystallization from methanol and dried over P_4O_{10} *in vacuo*. Yield: 70%, M.P. 245−246 °C, Elemental analysis calcd for $C_{38}H_{42.55}CdN_8O_{0.275}S_2$(**1**): C, 57.61; H, 5.41; N, 14.14; Cd, 14.19. Found: C, 57.85; H, 5.46; N, 14.05; Cd, 14.26. ESI–MS (*m*/*z*): 789.2 = $[Cd(L)(HL)]^+$(Fig. S1 in the Supporting information). calc: mass = 789.2. ^1H NMR(DMSO-d_6, δppm) 8.48 (s, 1H, NH), 8.09 (s, 1H, Py), 7.79 (s, 1H, Py), 7.52–7.46 (m, 3H, Ph), 7.38(d, *J* = 4 Hz, 2H, Ph), 7.25–7.22(m, 1H, Py), 7.07(d, *J* = 5.6 Hz, 1H, Py), 1.75(s, 11H, C_6H_{11}). Yellow crystals suitable for X-ray studies were obtained by the slow evaporation of a methanol solution of **1**.

2.2.3. Synthesis of complex

Complex **2** was prepared by a similar procedure to that of complex **1** using $In(NO_3)_2\cdot 5H_2O$ (0.078 g, 0.2 mmol) in place of $Cd(ClO_4)_2\cdot 6H_2O$ (0.084 g, 0.2 mmol). Yield: 85%, M.P. 224−227 °C, Elemental analysis calcd for $C_{38}H_{42}InN_9O_3S_2$(**2**): C, 53.58; H, 4.97; N, 14.80; In, 13.48. Found: C, 53.38; H, 4.72; N, 14.85; In, 13.58. ESI–MS (*m*/*z*): 789.2 $[In(L)_2]^+$ (Fig. S2 in the Supporting information), calc: 789.2. ^1H NMR(DMSO-d_6, δppm) 8.12 (s, 1H, NH), 7.75 (t, *J* = 6.4 Hz, 2H, Py), 7.62–7.54 (m, 4H, Ph), 7.46 (d, *J* = 8 Hz, 1H, Py),7.32 (t, *J* = 8.8 Hz, 1H, Ph), 7.21 (d, *J* = 8 Hz, 1H, Py), 1.81–1.00 (m, 11H, C_6H_{11}). Yellow crystals suitable for X-ray studies were obtained by the slow evaporation of a methanol solution of **2**.

2.3. X-ray crystallography

Crystallographic data were collected with a Bruker SMART-CCD APEX II diffractometer with graphite-monochromated Mo *Kα* 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 [27]. Although the higher R_{int} value of 0.1251 (>0.10) for **1** is somewhat large, owing to poor crystal quality, the molecule skeleton is well behaved, and there are no unusual temperature factors in the structure. The atoms of O1, O2, O3 and N9 of the nitrate anion from **2** were refined isotropically to avoid the ADP errors. The hydrogen atoms were added in idealized geometrical positions. Crystal data, experimental details, and refinement results are listed in Table 1.



Scheme 1. 2-benzoylpyridine *N*(4)-cyclohexylthiosemicarbazone (HL) and the reaction scheme for the synthesis of **1** and **2**.