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Four transition metal complexes with a semicarbazone ligand bearing pyrazine unit

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ABSTRACT

Four new complexes based on L (where L = 3-ethyl-2-acetylpyrazine semicarbazone), namely $[CoL_2]Cl_2\cdot 0.5H_2O$ (**1**), $[CoL_2](NO_3)_2$ (**2**), $[CdL(H_2O)_2(NO_3)](NO_3)\cdot H_2O$ (**3**) and $[CuL(CH_3OH)Cl_2]\cdot[CuLCl_2]$ (**4**) have been synthesized and characterized by X-ray diffraction analyses. The results show that the semicarbazone acts as a tridentate neutral ligand in all complexes. Each of complex **1** and **2** reveals a distorted octahedral geometry around the metal ion provided by two units of the ligand, while the ratio of the ligand and metal is 1:1 in complexes **3** and **4**. The effect of complexes **1**–**4** on cell proliferation, apoptosis of human pancreatic cancer (Patu8988), human gastric cancer (SGC7901) and human hepatic cancer (SMMC7721) cell lines have been detected by MTT assay, Annexin V/PI double staining flow cytometry and TUNEL assay. The results show that complexes **1**–**4** can inhibit cell proliferation of Patu8988, SGC7901 and SMMC7721 cells, significantly higher than the effect of the ligand. However, the complex **4** reveals higher apoptosis rate, and displays up-regulated expression level of caspase 3, detected by western blotting, which also indicates the complex **4** can induce caspase-dependent cell apoptosis in SMMC7721.

1. Introductions

As one type of Schiff bases, semicarbazones have been attracted much more attention mainly due to their wide spectrum of biological applications. These materials have been used as drugs whose action is attributed to their ability to form metal complexes [1–6]. Generally, the coordination possibilities in the semicarbazones are increased if the substituents of the aldehyde or ketone include additional donor atoms [4–8]. As a result, a number of transition metals with semicarbazones derived from salicylaldehyde, acyl-imidazole, acyl-thiophene and acyl-pyridine have been reported to exhibit anti-inflammatory, antimicrobial, as well as antitumor activities [3,4,7–11].

In fact, transition metal complexes of thiosemicarbazones derived from 2-acylpyrazine have been extensively investigated as potential anticancer agents [12,13]. However, relatively less attention has been devoted to the synthesis and biological properties of their structurally analogous semicarbazones and their metal complexes [9]. In this paper, we report the synthesis and characterization of a semicarbazone ligand, 3-ethyl-2-acetylpyrazine semicarbazone (L; Scheme 1), which is used in the preparation of four transition metal complexes, $[CoL_2]Cl_2\cdot 0.5H_2O$ (**1**), $[CoL_2](NO_3)_2$(**2**), $[CdL(H_2O)_2(NO_3)](NO_3)\cdot H_2O$ (**3**) and $[CuL(CH_3OH)Cl_2]\cdot[CuLCl_2]$ (**4**) (Scheme 2). In addition, the antitumor activities of all compounds are discussed in detail.

2. Experimental

2.1. Physical measurements

Elemental analyses were carried out on an Elemental Vario EL analyzer. The IR spectra ($\nu = 4000–400\ cm^{-1}$) were determined by the KBr pressed disc method on a Bruker V70 FT-IR spectrophotometer. ^1H NMR spectra of L was acquired with Bruker AV400 NMR instrument in d_6-DMSO solution with TMS as internal standard. The

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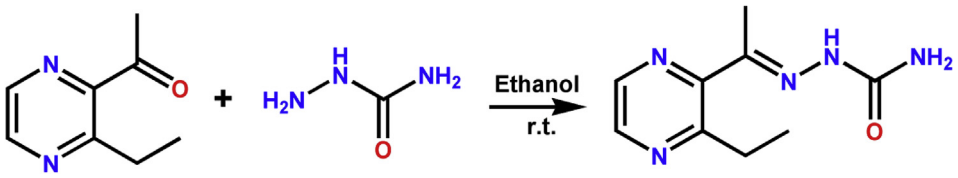
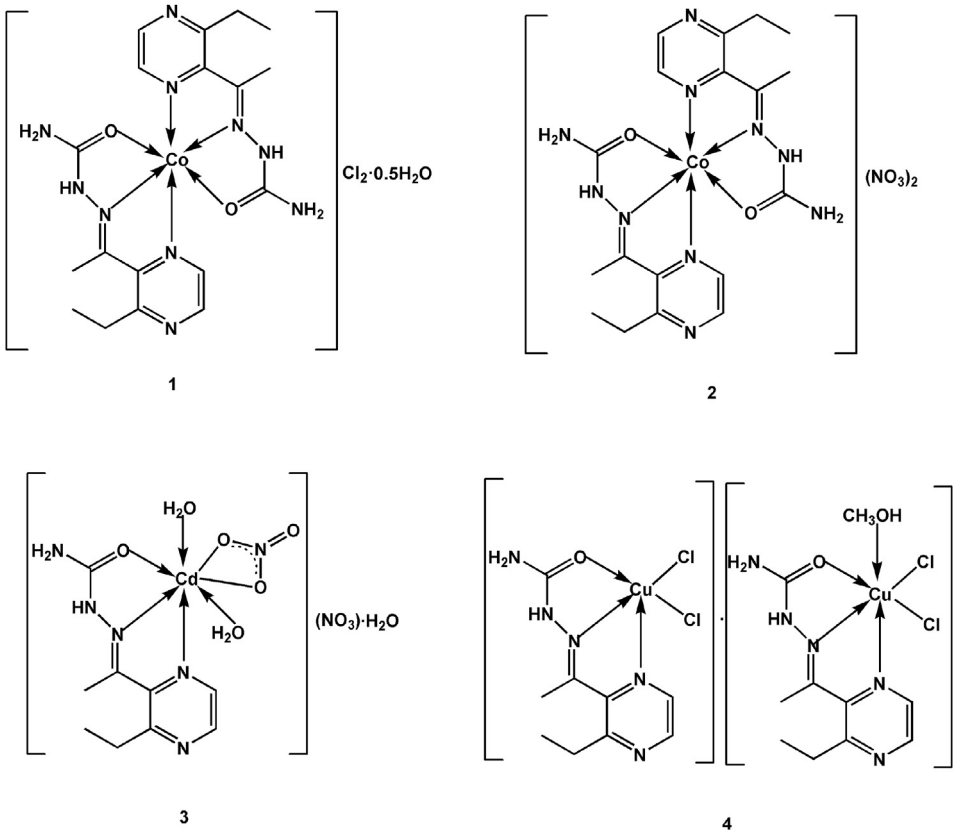


Scheme 1. The synthetic route of the semicarbazone ligand L.



Scheme 2. Molecule structures of complexes **1**–**4**.

X-ray diffraction measurement for complexes **1**–**4** were performed on a Bruker SMART APEX II CCD diffractometer equipped with a graphite monochromatized Mo*K* radiation (λ = 0.71073 Å) by using φ-ω scan mode. Semi-empirical absorption correction was applied to the intensity data using the SADABS program. The structures were solved by direct methods and refined by full matrix least-square on F^2 using the SHELXTL-97 program [1]. H atoms for O1W in complex **1** are not added because of disorder. All the other H atoms were positioned geometrically and refined using a riding model.

2.2. Syntheses of the ligand L

A mixture of 3-ethyl-2-acetylpyrazine (1.50 g, 10 mmol) and semicarbazide hydrochloride (1.11 g, 10 mmol) in ethanol (30 ml) were stirred for 4 h at room temperature. The white solid was precipitated, then filtered and washed three times by cold ethanol. Yield: 1.78 g (86%). M.p.: 128–131 °C. Elemental analysis for HL ($C_{10}H_{15}N_5O$) (%): Calcd: C: 54.28; H: 6.83; N: 31.65; Found: C: 54.00; H: 6.76; N: 31.80. ^{1}H NMR (400 MHz, d_6-DMSO) δ: 9.57 (1H, s)/ 8.42–8.43 (1H, d)/8.46–8.47 (1H, d) for Ar–H, 6.33 (2H, s, NH_2), 2.98–3.03 (2H, q, CH_2), 2.19 (3H, s, CH_3), 1.14–1.18 (3H, t, CH_3). FT-IR (cm^{-1}): *ν*(O=C) 1699, *ν*(N=C, imine) 1670, *ν*(N=C, pyrazine) 1576.

2.3. Syntheses of complexes 1–4

Complexes **1**–**4** were synthesized by reacting the ligand L (0.5 mmol) with equal molar of $CoCl_2·6H_2O$, $Co(NO_3)_2·6H_2O$, $Cd(NO_3)_2·6H_2O$ and $CuCl_2·H_2O$ in methanol (20 ml) solution, respectively. The block crystals suitable for X-ray diffraction analysis were obtained by evaporating the reaction solutions at room temperature.

1: Brown blocks. Yield 52%.Anal.calc. for $C_{18}H_{27}N_{10}O_{2.50}Cl_2Co$ (%):C, 39.07; H, 4.92; N, 25.31. Found (%): C, 39.23; H, 5.00; N, 25.18. IR (KBr) cm^{-1}: ν(C=O) 1680, ν(C=N, imine) 1631, ν(C=N, pyrazine) 1521.
2: Brown blocks. Yield 63%.Anal.calc. for $C_{18}H_{26}N_{12}O_8Co$ (%):C, 36.19; H, 4.39; N, 28.13. Found (%): C, 36.02; H, 4.57; N, 28.04. IR (KBr) cm^{-1}: ν(C=O) 1672, ν(C=N, imine) 1630, ν(C=N, pyrazine) 1528, $\nu_{free}(NO_3^-)$ 1384.
3: Colorless blocks. Yield 58%.Anal.calc. for $C_9H_{19}N_7O_{10}Cd$ (%):C, 21.72; H, 3.85; N, 19.70. Found (%): C, 21.87; H, 3.62; N, 19.95. IR