



A versatile salicyl hydrazone ligand and its metal complexes as antiviral agents



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ABSTRACT

Acylhydrazones are very versatile ligands and their coordination properties can be easily tuned, giving rise to metal complexes with different nuclearities. In the last few years, we have been looking for new pharmacophores able to coordinate simultaneously two metal ions, because many enzymes have two metal ions in the active site and their coordination can be a successful strategy to inhibit the activity of the metalloenzyme. As a part of this ongoing research, we synthesized the acylhydrazone *H₂L* and its complexes with Mg(II), Mn(II), Co(II), Ni(II), Cu(II) and Zn(II). Their characterization, both in solution – also by means of potentiometric studies – and in the solid state, evidenced the ability of the *o*-vanillin hydrazone scaffold to give rise to different types of metal complexes, depending on the metal and the reaction conditions. Furthermore, we evaluated both the free ligand and its metal complexes in *in vitro* studies against a panel of diverse DNA- and RNA-viruses. In particular, the Mg(II), Mn(II), Ni(II) and Zn(II) complexes had EC₅₀ values in the low micromolar range, with a pronounced activity against vaccinia virus.

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1. Introduction

Acylhydrazone-based ligands and their transition metal complexes are widely studied in catalysis [1], as building blocks in supramolecular chemistry [2,3], as anticancer agents [4,5], and, particularly interesting for our research, antiviral molecules [6,7]. They are often used to build multinuclear metal complexes since they are versatile ligands and their coordination properties can be easily tuned from an electronic and a steric point of view [8–10]. Acylhydrazone ligands, in fact, can act as bidentate or tridentate chelating ligands and even as tetradentates, and can coordinate one or more metal centers [1,3,10,11]. Complexes of salicylaldehyde hydrazones with Mn(II), Cu(II), lanthanide(III), Pd(II), and Ni(II) have been previously studied [1–3, 8–11] and they represent a challenging topic from the coordination point of view. These ligands typically coordinate to the metal ion through the phenolic and carbonyl oxygens and the imine nitrogen

atom. Their degree of deprotonation depends on the reaction conditions and the metal employed and they can give rise to monometallic, bis-chelated complexes or to multimetallic assemblies held together by intermolecular forces [2,3,12].

In this context, we synthesized an acylhydrazone ligand (*H₂L*) (Fig. 1) by condensation of *o*-vanillin with salicyl hydrazide. *H₂L* is diprotic and a potentially ONOO tetradentate ligand; it can coordinate one but also two metal ions (Fig. 1).

Its coordination compounds with Mg(II), Mn(II), Co(II), Ni(II), Cu(II) and Zn(II) were isolated and characterized by IR, elemental analysis and mass spectrometry (complexes 1–6, Fig. 2); the X-ray crystal structures of the tetranuclear copper complex **Cu₄L₄·4CH₃CN** and of the bis-chelated cobalt(III) complex **[CoL₂]NH₄Et₃** (**3**) are also discussed. Moreover, the solution behavior of *H₂L* towards Mg(II), Mn(II), Ni(II), Cu(II) and Zn(II) was investigated by means of potentiometric experiments.

It is well known that the metal complexes of hydrazones have diverse biological and pharmaceutical properties: in fact, they were studied as antimicrobial, anti-inflammatory, antifungal, anti-tubercular, anticancer, antimalarial and antiviral agents [13–16]. In the last few years, the research of new metal-chelating pharmacophores with antiviral activity is at the center of our interest [17–20]. Many enzymes

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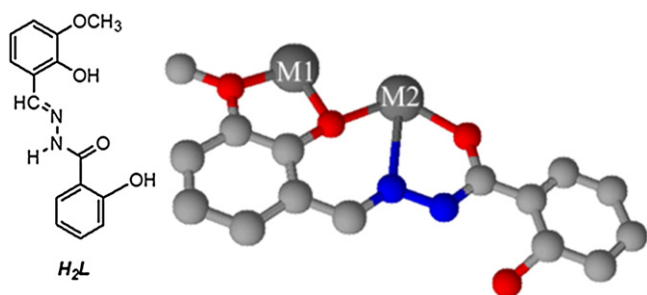


Fig. 1. Chemical structure of the acylhydrazone ligand H_2L (left); the polydentate ligand H_2L can coordinate one or two metal ions (right).

have two metal ions in their active site and coordination of these cofactors can be a successful strategy to inhibit the activity of a given metalloenzyme [21,22]. As a part of this ongoing research, we evaluated H_2L and its metal complexes **1–6** in vitro studies against a panel of diverse DNA- and RNA-viruses, discovering promising activity of this scaffold against herpes simplex virus (HSV) and vaccinia virus (VV).

2. Experimental

2.1. Material and methods

All reagents of commercial quality were used without further purification. Purity of compounds was determined by elemental analysis and verified to be $\geq 96\%$ for all synthesized molecules. NMR spectra were recorded at 25 °C on a Bruker Avance 400 FT spectrophotometer. The ATR-IR spectra were recorded by means of a Nicolet-Nexus (Thermo Fisher) spectrophotometer by using a diamond crystal plate in the range of 4000–400 cm^{-1} . Elemental analyses were performed by using a FlashEA 1112 series CHNS/O analyzer (Thermo Fisher) with gas-chromatographic separation. Electrospray Ionization mass spectral analyses (ESI-MS) were performed with an ESI-TOF (electrospray ionization time-of-flight) Micromass 4LCZ spectrometer. MS spectra were acquired in positive EI mode by means of a DEP-probe (Direct Exposure Probe) mounting on the tip a Re-filament with a DSQII Thermo Fisher apparatus, equipped with a single quadrupole analyzer.

2.2. Synthesis

2.2.1. *N'*-(2-hydroxy-3-methoxybenzylidene)-2-hydroxybenzoylhydrazone (H_2L)

H_2L was obtained by slight modifications of reported procedures [23]. Briefly, an equimolar amount of salicyl hydrazide and aldehyde are dissolved in absolute ethanol. The mixture was refluxed for 6 h, cooled at room temperature and concentrated in vacuum. The resulting precipitate was filtered off, washed with cold ethanol and dried in vacuum. Yield = 89%. $^1\text{H-NMR}$ (DMSO- d_6 , 25 °C), δ : 3.82 (s, 3H, OCH₃), 6.85–7.06 (m, 4H, ArH), 7.17 (d, J = 7.5 Hz, 1H, ArH), 7.45 (t, J = 7.6 Hz, 1H; ArH), 7.89 (d, 2H; J = 7.5, ArH), 8.69 (s, 1H; HC = N), 10.87 (s, br, 1H; NH), 11.99 (s, br, 2H; OH). $^1\text{H-NMR}$ (MeOD- d_4 ,

25 °C), δ : 3.91 (s, 3H, OCH₃), 6.90 (t, J = 7.6 Hz, 1H, ArH); 6.96–7.00 (m, 2H, ArH), 7.06 (d, J = 8.2 Hz, 1H, ArH), 7.21 (d, J = 8.2 Hz, 1H; ArH), 7.47 (t, 2H; J = 7.4, ArH), 7.92 (d, 2H; J = 7.7, ArH), 8.60 (s, 1H; HC = N). $^{13}\text{C-NMR}$ (MeOD- d_4 , 25 °C), δ : 55.27; 113.79; 114.78; 117.10; 118.63; 119.01; 119.06; 121.25; 128.08; 134.02; 148.11; 149.48; 159.73. MS (EI, 70 eV) m/z (%) = 286.0 ([M]⁺, 100); IR (cm^{-1}): $\nu_{\text{NH+OH}}$ = 3202 (br); $\nu_{\text{C=O}}$ = 1606; $\nu_{\text{C=N}}$ = 1560; ν_{OCH_3} = 1256, 1079. Anal. Calcd. for $\text{C}_{15}\text{H}_{14}\text{N}_2\text{O}_4 \cdot 1/2\text{H}_2\text{O}$: C 61.01; H 5.12; N 9.49. Found: C 61.20, H 4.89, N 9.58.

Synthesis of the complexes **1–6**, general procedure. The ligand H_2L (0.5 mmol) was dissolved in 30 ml of methanol and 1 eq. of NEt_3 was added. The yellow solution was stirred at 65 °C for 30 min. 0.5 eq. of acetate of the metal were added and then the reaction mixture was stirred at reflux for 4 h, concentrated in vacuum and cooled overnight. The precipitate was filtered off, washed with water and dried under vacuum.

2.2.2. $\text{Mg}(\text{HL})_2 \cdot 2\text{H}_2\text{O}$ (**1**)

Light yellow powder. Yield: 70%. $^1\text{H-NMR}$ (MeOD, 25 °C), δ : 3.91 (s, 3H, OCH₃); 6.88–7.07 (m, 4H, ArH); 7.20 (d, J = 7.4 Hz, 1H, ArH); 7.46 (t, J = 7.9 Hz, 1H); 7.92 (d, J = 7.9 Hz, 1H); 8.60 (s, 1H; HC = N). MS-ESI, m/z (%) = 595 ([Mg(HL)₂ + H]⁺, 40). IR (cm^{-1}): ν_{NH} = 3267 (br); $\nu_{\text{C=O}}$ = 1627, 1609; ν_{OCH_3} = 1211, 1082. Anal. Calcd. for $\text{C}_{30}\text{H}_{26}\text{N}_4\text{O}_8\text{Mg} \cdot 2\text{H}_2\text{O}$: C 57.11, H 4.79, N 8.88. Found: C 57.33, H 4.33, N 9.00.

2.2.3. $\text{Mg}_2\text{L}_2 \cdot 4\text{H}_2\text{O}$ (**1a**)

0.5 mmol of H_2L was dissolved in 30 ml of methanol and 2.5 eq. of NaOH 4 M were added. The yellow solution was stirred at 65 °C for 30 min. 1 eq. of magnesium acetate was added and the reaction mixture was stirred at reflux for 4 h, concentrated in vacuum and cooled overnight. The precipitate was filtered off and washed with water. Intense yellow powder. Yield: 64%. $^1\text{H-NMR}$ (MeOD, 25 °C), δ : 3.84 (s, br, 3H, OCH₃); 6.45 (s, br, 1H, ArH), 6.68–6.82 (m, br, 5H, ArH); 7.20 (s, br, 1H, ArH); 7.90 (s, br, 1H); 8.24 (s, br, 1H; HC=N). MS-ESI, m/z (%) = 309 ([MgL]⁺, 100); 617 ([Mg₂L₂]⁺, 50); 640 ([Mg₂L₂ + Na]⁺, 40). IR (cm^{-1}): ν_{OH} = 3420–3500 (br); $\nu_{\text{C=O}}$ = 1609; ν_{OCH_3} = 1211, 1082. Anal. Calcd. for $\text{C}_{30}\text{H}_{24}\text{N}_4\text{O}_8\text{Mg}_2 \cdot 4\text{H}_2\text{O}$: C 52.28, H 4.68, N 8.13. Found: C 52.67, H 4.63, N 8.03.

2.2.4. $\text{Mn}_2\text{L}_2 \cdot 2\text{H}_2\text{O}$ (**2**)

Brown powder. Yield: 70%. MS-ESI, m/z (–, %) = 624 ([Mn(HL)₂][–], 95); 677 ([Mn₂L₂][–], 100). IR (cm^{-1}): ν_{NH} = 3267 (br); $\nu_{\text{C=O}}$ = 1607; ν_{OCH_3} = 1208. Anal. Calcd. for $\text{C}_{30}\text{H}_{24}\text{N}_4\text{O}_8\text{Mn}_2 \cdot 2\text{H}_2\text{O}$: C 50.43, H 3.95, N 7.84. Found: C 50.68, H 4.27, N 7.87.

2.2.5. $[\text{CoL}_2](\text{NHEt}_3)$ (**3**)

Brown powder. Yield: 64%. $^1\text{H-NMR}$ (DMSO- d_6 , 25 °C), δ : 0.99 (t, 9H, CH₃, NEt_3), 2.50 (overlapping with solvent signal, CH₂, NEt_3), 3.36 (s, 3H, OCH₃), 6.41 (t, 1H; J = 7.6, ArH), 6.51 (d, 1H; J = 7.7, ArH), 6.67 (t, 1H, J = 8, ArH), 7.22 (m, 2H, ArH), 7.47 (d, 1H, J = 7.9, ArH), 7.70 (d, 1H, J = 8, ArH), 8.93 (s, 1H; HC = N), 12.64 (s, 1H, NHEt₃). MS-ESI, m/z (–, %) = 627 ([CoL₂][–], 100). IR (cm^{-1}): ν_{NH} = 3206 (br); $\nu_{\text{C=O}}$ = 1624; $\nu_{\text{C=N}}$ = 1598. Anal. Calcd. for $\text{C}_{36}\text{H}_{40}\text{N}_5\text{O}_8\text{Co}$: C 59.26, H 5.53, N 9.60. Found: C 59.55, H 5.48, N 9.41. Crystals suitable for X-ray diffraction analysis were obtained by slow evaporation of a methanol solution of the complex.

2.2.6. $\text{Ni}(\text{HL})_2 \cdot 2\text{H}_2\text{O}$ (**4**)

Green powder. Yield: 87%. MS-ESI, m/z (+, %) = 629 ([Ni(HL)₂]⁺, 70); 652 ([Ni(HL)₂ + Na]⁺, 50). IR (cm^{-1}): $\nu_{\text{NH+OH}}$ = 3150–3200 (br); $\nu_{\text{C=O}}$ = 1629; ν_{OCH_3} = 1201. Anal. Calcd. for $\text{C}_{30}\text{H}_{26}\text{N}_4\text{O}_8\text{Ni} \cdot 2\text{H}_2\text{O}$: C 54.16, H 4.55, N 8.42. Found: C 54.51, H 4.84, N 8.34.

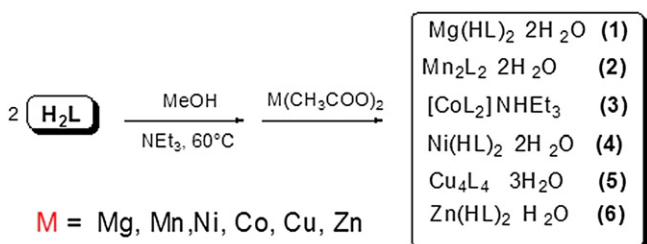


Fig. 2. Synthesis of complexes **1–6**.

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