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# Complexes of 2-thiophenecarbonyl and isonicotinoyl hydrazones of 3-(*N*-methyl)isatin. A study of their antimicrobial activity

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**Abstract**

Cobalt(II), nickel(II), copper(II) and zinc(II) complexes of 2-thiophenecarbonyl and isonicotinoyl hydrazones of 3-(*N*-methyl)isatin ($HL^1$ and $HL^2$, respectively) were synthesized and characterized, being the crystal structures of $HL^1$, $HL^2$ and $[Ni(L^1)_2]\cdot 2CHCl_3$ elucidated by X-ray diffraction techniques. The *in vitro* antimicrobial activity of all these compounds was tested against several bacteria and fungi. $HL^1$and its complexes exhibited a strong inhibition of the growth of *Haemophilus influenzae* (MIC 0.15–1.50 μg/mL) and good antibacterial properties towards *Bacillus subtilis* (MIC 3–25 μg/mL). The minimal inhibitory concentration (MIC) was defined as the lowest concentration of compound inhibiting the growth of each strain. The antibacterial effectiveness was confirmed against a number of Gram positive bacteria, including methicillin-resistant *Staphylococcus aureus.* Yeasts and moulds showed a low susceptibility, except the dermatophyte mould *Epidermophyton floccosum* that is inhibited at concentrations ranging from 6 to 50 μg/mL. In general, the antimicrobial activity of the thiophene derivatives was greater than that of the isonicotinic analogues.


*Keywords:* Zinc; Copper; Nickel; Cobalt; Hydrazones; Antibacterial activity; Antifungal activity

## 1. Introduction

During the last years we have been working on the coordination chemistry and biological properties of different metal complexes of isatin- and *N*-alkylisatin thiosemicarbazones [1–3], bisthiocarbonohydrazones [4], semicarbazones [5,6] and hydrazones [7] in order to establish a possible relationship between chemical structure and biological activity.

Following this research line, here we report the synthesis and characterization of 2-thiophenecarbonylhydrazone of 3-(*N*-methyl)isatin, $HL^1$ (Fig. 1), and isonicotinoylhydrazone of 3-(*N*-methyl)isatin, $HL^2$ (Fig. 2), as well as some of their cobalt(II), nickel(II), cooper(II) and zinc(II) complexes. We also describe a study of the antibacterial and antifungal properties of all the synthesized compounds.

## 2. Experimental

Elemental analyses were performed with a Carlo-Erba 1108 analyser. Estimation of chlorine content in complexes

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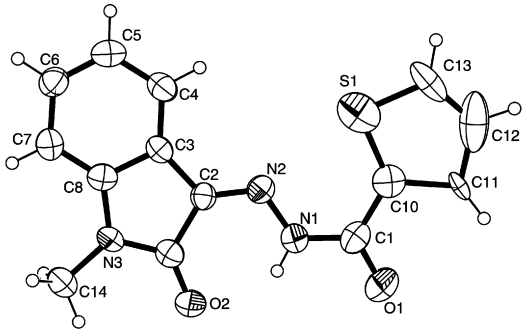


Fig. 1. ORTEP drawing of ligand $HL^1$. Ellipsoids are drawn at 50% probability. Parentheses are omitted for clarity.

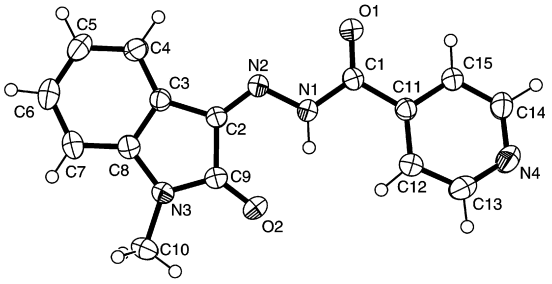


Fig. 2. ORTEP drawing of ligand $HL^2$. Ellipsoids are drawn at 50% probability. Parentheses are omitted for clarity.

were performed on a Siemens SRS3000 XRF, using 1-chloro-2,4-dinitrobenzene as reference. Melting points were determined with a Gallenkamp NFB-595 apparatus. Conductivities were measured on a Crison GLP 32 conductivimeter using $10^{-3}$ M dimethylformamide (DMF) solutions. The conductivity value of $[CuCl_2(HL^2)_2]\cdot H_2O$ was obtained using a $9.8\times10^{-4}$ M solution. Infrared (IR) spectra in the range 400–4000 $cm^{-1}$ were recorded on a Bruker V-22 spectrophotometer using KBr disks. Low frequency vibrations (500–100 $cm^{-1}$) were recorded on a Bruker IFS-66 V spectrophotometer, using nujol and polyethylene windows. The nuclear magnetic resonance (NMR) spectra were recorded on a Bruker ARX-400 using dimethyl sulfoxide-$d_6$ (DMSO-$d_6$) as solvent. Magnetic susceptibility measurements were performed on pulverised samples at room temperature (RT) with an Alfa MSB-MK1 balance. Diffuse reflectance spectra in the range 200–2000 nm were recorded on a Shimadzu UV-3101 PC spectrophotometer.

### 2.1. Synthesis of compounds

All reagents and solvents were reagent grade.

#### 2.1.1. Synthesis of ligands

The ligands, 2-thiophenecarbonylhydrazone of 3-(*N*-methyl)isatin ($HL^1$, Fig. 1) and isonicotinoylhydrazone of 3-(*N*-methyl)isatin ($HL^2$, Fig. 2) were obtained by refluxing in ethanol solution *N*-methylisatin and the corresponding hydrazide (2-thiophenecarboxylic acid or isonicotinic acid hydrazide), following a general procedure [8]. When a powdery solid of $HL^1$ was recrystallized in DMF, single crystals could be isolated after several weeks, whereas yellow crystals suitable for X-ray diffraction studies were isolated from the mother liquor of $HL^2$.

*2.1.1.1. $HL^1$.* Anal. found of yellow solid: C, 58.9; H, 4.0; N, 14.8; S, 10.9. Calc. for $C_{14}H_{11}N_3O_2S$: C, 58.9; H, 3.9; N, 14.7; S, 11.2%, m.p. 220 °C. IR (KBr, $cm^{-1}$, vs: very strong, s: strong, m: medium, w: weak, sh: shoulder and br: broad): $\nu$(NH) 3485m,br, 3420m,br; $\nu$(CO) 1717m, 1664m; $\nu$(CN) 1605s; $\nu$CN + $\delta$NH 1512m. NMR $\delta$ ($^1$H, DMSO-$d_6$, 400 MHz, ppm, s: singlet, d: doublet, t: triplet) = 11.73 (1H, s, *H*N1), 8.17 (1H, d, *H*C11), 8.11 (1H, d, *H*C4), 8.03 (1H, d, *H*C13), 7.50 (1H, t, *H*C6), 7.27 (1H, t, *H*C12), 7.14 (1H, t, *H*C5), 7.12 (1H, d, *H*C7), 3.20 (1H, s, *H*C14); NMR $\delta$ ($^{13}$C, DMSO-$d_6$, 400 MHz, ppm) = 163.12 (C9) 144.95 (C8), 134.95 (C13), 134.30 (C10), 134.00 (C11), 132.59 (C6), 127.62 (C12), 126.09 (C4), 122.16 (C5), 114.59 (C3), 109.18 (C7), 25.91 (C14). $\lambda$ (nm) = 234, 282, 338, 440.

*2.1.1.2. $HL^2$.* Anal. found of yellow solid: C, 63.9; H, 4.1; N, 20.0. Calc. for $C_{15}H_{12}N_4O_2$: C, 64.3; H, 4.3; N, 20.0%, m.p. 216 °C. IR ($cm^{-1}$, KBr): $\nu$(NH) 3369w, 3227w,br, 3190w,br; $\nu$(CO) 1702s, 1680s; $\nu$(CN) 1617s, 1595m; $\nu$CN ss $\delta$NH 1518m,br. NMR $\delta$ ($^1$H, DMSO-$d_6$, 400 MHz, ppm) = 13.95 (1H, s, *H*N1), 8.87 (2H, d, *H*C14, *H*C13), 7.79 (2H, d, *H*C15, *H*C12), 7.64 (1H, d, *H*C4), 7.51 (1H, t, *H*C6), 7.20 (2H, m, *H*C5, *H*C7), 3.25 (1H, s, *H*C10); NMR $\delta$($^{13}$C, DMSO-$d_6$, 400 MHz, ppm) = 161.03 (C9) 150.81 (C14, C13), 143.88 (C8), 139.05 (C11), 132.04 (C6), 123.31 (C5), 121.02 (C15, C12), 120.77 (C4), 118.78 (C3), 110.07 (C7), 25.90 (C10). $\lambda$ (nm) = 274, 340, 374, 444.

#### 2.1.2. Synthesis of complexes

The complexes were prepared by refluxing (in the range 8–24 h) an ethanol suspension of a metal(II) salt (chloride or acetate) and the corresponding ligand in the adequate molar ratio (see Table 1). Powdered solids obtained by cooling were filtrated, washed with ethanol and dried under vacuum. A slow evaporation of a $[Ni(L^1)_2]$ chloroform solution afforded crystals suitable for X-ray diffraction studies that were identified later as $[Ni(L^1)_2]\cdot 2CHCl_3$.

*2.1.2.1. $[Zn(L^1)_2]$.* Anal. found of orange solid: C, 52.8; H, 3.3; N, 13.2; S, 10.5. Calc. for $C_{28}H_{20}N_6O_4S_2Zn$: C, 53.0; H, 3.2; N, 13.3; S, 10.1%, m.p. >300 °C. IR ($cm^{-1}$, KBr): $\nu$(CO) 1689s,sh; $\nu$(CN) 1608s,sh. NMR $\delta$ ($^1$H, DMSO-$d_6$, 400 MHz, ppm) = 8.28 (1H, br, *H*C11), 8.00 (1H, br, *H*C4), 7.92 (1H, br, *H*C13), 7.53 (1H, br, *H*C6), 7.31 (1H, br, *H*C12), 7.25 (2H, br, *H*C5, *H*C7), 3.20 (1H, s, *H*C14).

*2.1.2.2. $[Cu(L^1)_2]\cdot H_2O$.* Anal. found of brown solid: C, 51.3; H, 3.2; N, 12.6; S,10.0. Calc. for $C_{28}H_{22}CuN_6O_5S_2$: