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ScienceDirect
Bioorganic & Medicinal Chemistry Letters
Bioorganic & Medicinal Chemistry Letters 17 (2007) 3774–3777

The crystal structures of copper(II), manganese(II), and nickel(II) complexes of a (*Z*)-2-hydroxy-*N*′-(2-oxoindolin-3-ylidene) benzohydrazide—potential antitumor agents

Xia Zhong,[a] Hu-Lai Wei,[b] Wei-Sheng Liu,[a,*] Da-Qi Wang[c] and Xing Wang[a]

[a]*College of Chemistry and Chemical Engineering and State Key Laboratory of Applied Organic Chemistry, Lanzhou University, Lanzhou 730000, PR China*
[b]*Laboratory Center for Medical Science, Lanzhou University, Lanzhou 730000, PR China*
[c]*Department of Chemistry, Liaocheng University, Liaocheng 252000, PR China*

Received 19 November 2006; revised 1 April 2007; accepted 5 April 2007
Available online 10 April 2007

Abstract—Mononuclear complexes of Cu(II), Ni(II), and Mn(II) with a new Schiff base ligand derived from indoline-2,3-dione and 2-hydroxybenzohydrazide, $[Cu(II)(L)_2]$, $[Ni(II)(L)_2]$, and $[Mn(II)L \cdot (AcO) \cdot 2C_2H_5OH]$ [HL=(*Z*)-2-hydroxy-*N*′-(2-oxoindolin-3-ylidene)benzohydrazide], have been prepared. The complexes have been structurally characterized by X-ray crystallography. Among the three complexes, the Cu(II) complex had the novel highest antitumor activity.
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Whilst most of the reports dealing with metal complexes exhibiting antitumor properties are confined to cisplatin analogues,[1] there are a growing number of non-platinum metal compounds which also exhibit remarkable anticancer activities. Many of these antitumor metal complexes contain thiosemicarbazone or hydrazone pharmacophores derived from the acetyl or formyl pyridines and salicyldehyde moieties.[2–7] Such compounds share a common amidrazone pharmacophore[3] as one of the structural requirements for anticancer activity. To the best of our knowledge until date there is no report on the metal chelating ability and the antitumor activity of this class of ligands (Fig. 1). Since our earlier work had revealed that copper complexation leads to enhancement of the antitumor activity of Schiff base ligands,[8] we were motivated to explore similar trend in case of the Schiff base and its copper complex.

The Schiff base ligand, **HL**, synthesized by condensing indoline-2,3-dione with 2-hydroxybenzohydrazide, on refluxing with copper acetate, manganese acetate, and nickel acetate in ethanol yielded corresponding complexes, respectively. On the basis of elemental analysis, the metal to ligand stoichiometry of 1:2 or 1:1 has been proposed for these complexes. The proposed structures for these complexes have the support of IR and UV spectra. A strong band in the Schiff bases at 1659 cm^{-1} region underwent a shift of 44–70 cm^{-1} in complexes confirming the formation of coordinate bond from azomethine nitrogen to metal ion. From the analytical data and infrared studies, it has been concluded that the ligand has linked through carbonyl oxygen and coordinated through azomethine nitrogen behaving as a tridentate ligand (Fig. 1). The complexes along with their characteristics are recorded in Table 1, their UV spectra in Table 2, their IR spectra in Table 3, and ^1H NMR chemistry shift of the ligand in Table 4.

The crystal structures of Cu(II), Ni(II), and Mn(II) complexes are illustrated in Figure 2. The structure of Cu(II) complex shows that the central Cu ion is surrounded by two nitrogen atoms (N2 and N4) with Cu–N distances of 1.926(7) and 1.958(7) Å, four oxygen atoms (O1, O2, O3, and O4) with Cu–O distances of 2.447(7), 2.314(7), 2.144(6), and 2.051(6) Å. All atoms of the ligand are in one plane, the angle of two ligand is 87.68° which shows that these two planes are almost vertical. The Cu(II) ion is well described as having an octahedron configuration with N2, N4, O1, O2, O3, and O4. The structure of Ni(II) complex is similar to the one of Cu(II) complex. But the structure of Mn(II) complex is

Keywords: Schiff base; Crystal structure; Antitumor activity.
* Corresponding author. Tel.: +86 931 8915151; fax: +86 931 8912582; e-mail: liuws@lzu.edu.cn

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doi:10.1016/j.bmcl.2007.04.006

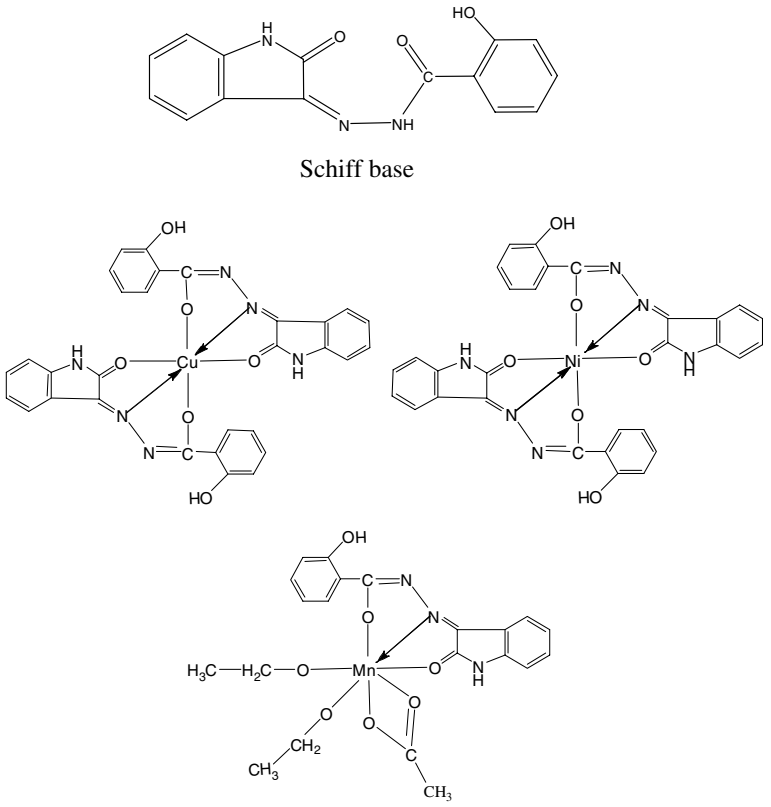

Figure 1. Structures of Schiff base and its transition metal complexes.

Table 1. Data of color, elemental analysis, and molar conductivity of the complexes

Complex	Color	Data of measured (data of theory)%			$\Lambda m/S \cdot cm^{-2} \cdot mol^{-1}$
		C	H	N	
$Cu(L)_2$	Brown	57.53 (57.55)	3.55 (3.54)	13.41 (13.42)	23.41
$MnL \cdot 2\,C_2H_5OH \cdot AcO$	Yellow	51.99 (51.97)	4.96 (4.98)	8.64 (8.66)	21.41
$Ni(L)_2$	Orange	57.98 (58.00)	3.56 (3.57)	13.51 (13.53)	22.21

Table 2. UV spectra of the ligand and the complexes (nm)

Compound	HL	$Cu(L)_2$	$MnL \cdot 2\,C_2H_5OH \cdot AcO$	$Ni(L)_2$
Bands(nm)	342	393	388	391

Table 3. IR spectra of the ligand and the complexes (cm^{-1})

Compound	υ_{N-H}	$\upsilon_{C=N}$	$\upsilon_{C=O}$
HL	3443, 3200	1659	1724
$Cu(L)_2$	—	1589	—
$MnL \cdot 2\,C_2H_5OH \cdot AcO$	—	1612	—
$Ni(L)_2$	—	1615	—

different. Mn ion is surrounded by one nitrogen atom (N2) with Mn–N distance of 2.282(6) Å, six oxygen atoms (O1, O2, O4, O5, O6, and O7) with Mn–O distances of 2.476(5), 2.262(6), 2.271(5), 2.265(6), 2.212(6), and 2.193(6) Å. The ligand and the acetate radical are almost in one plane, and the structure of Mn(II) complex is hepta-coordination.[12]

An ethanolic solution (25 mL) of indoline-2,3-dione (5 mmol) was added dropwise to the solution (10 mL) of 2-hydroxybenzohydrazide (5 mmol) with stirring at ca. 70 °C for 8 h. The yellow precipitate was removed by filtration and recrystallized from 1:1 (v/v) MeOH–EtOH solution. Then a mixture of the ligand (5 mmol) and transition metal (II) acetate (2.5 mmol) in EtOH (80 mL) was stirred at ca. 65 °C for 6 h to give the desired complexes. Suitable X-ray quality crystals were obtained by a slow evaporation of these complexes from MeOH solution.

The cytotoxicity assay was in four kinds of cells line (SPCA-1, Tb, MGC, and K562). Cells were cultured

Table 4. ^1H NMR chemistry shift of the ligand (ppm) (solvent:DMSO-d_6)

Ligand	δ	δ	δ	δ
HL	7.35 (s, 8 H, Ar)	10.85 (s, H, NH)	11.15 (s, H, NH)	12.19 (s, H, OH)

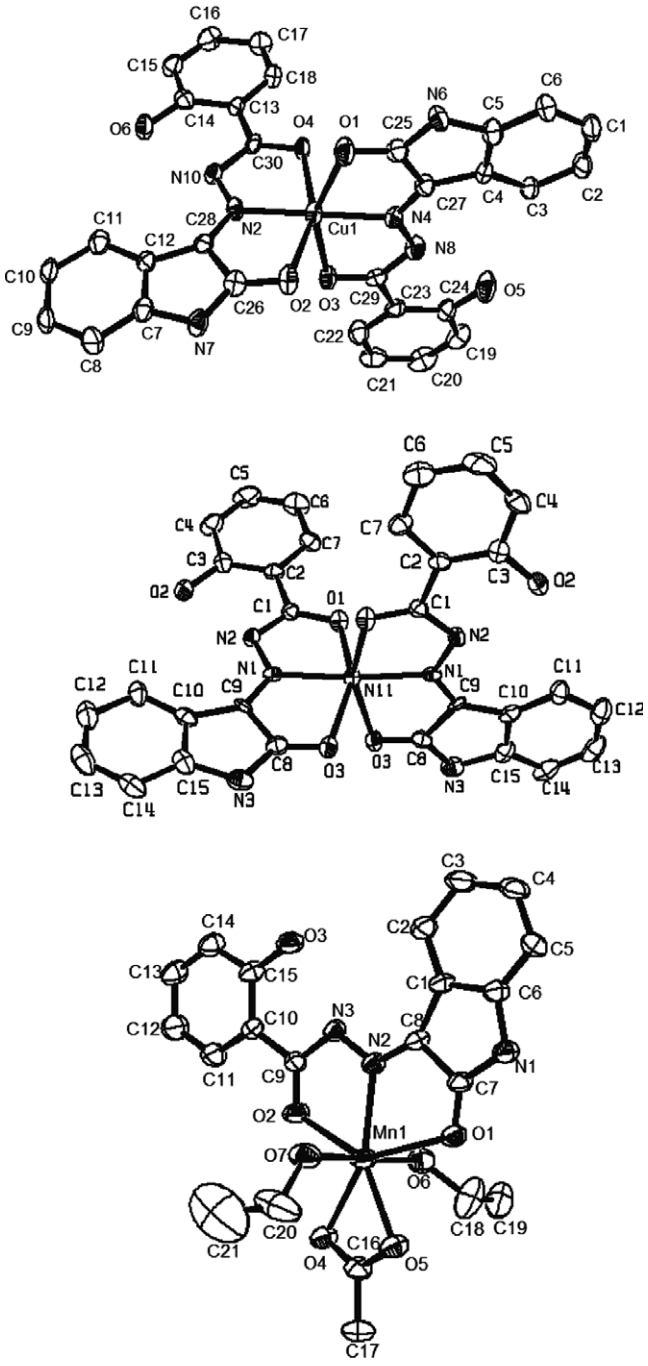

Figure 2. Crystal structures of the complexes.

at 37 °C under a humidified atmosphere of 5% CO_2 in RPMI 1640 medium supplemented with 10% fetal serum and dispersed in replicate 96-well plates with 1×10^4 cells/well. Compounds were then added. After 24-h, 48-h, 72-h exposure to the toxins, cells viability were determined by the [3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide] (MTT) cytotoxicity assay by measuring the absorbance at 570 nm with an ESILA reader. Each test was performed in triplicate. From the data in Table 5, it can be inferred that the Cu, Mn, and Ni complexes all have antitumor activities in a way, but its copper(II) complex is substantially more active than other compounds reported before.[9,10] The copper compound is found to exhibit higher antitumor activity which may be due to the generation of cytotoxic Cu(I) species through intracellular enzymatic reduction.[11]

Table 5. Antitumor activity data of the compounds

Cell	Time (h)	L · Cu	L · Mn	L · Ni
K562 IC_{50} (μM)	24	4.78	100[a]	91.65
	48	3.77	100[a]	91.53
	72	2.84	100[a]	90.66
MGC IC_{50} (μM)	24	3.65	100[a]	76.85
	48	3.52	100[a]	75.91
	72	2.43	100[a]	74.85
Tb IC_{50} (μM)	24	5.06	100[a]	90.75
	48	4.05	100[a]	89.83
	72	3.01	100[a]	87.92
SPCA-1 IC_{50} (μM)	24	6.07	100[a]	92.03
	48	5.23	100[a]	91.72
	72	3.85	100[a]	90.68

Antitumor activities are expressed as IC_{50} (50% inhibitory concentration) in four kinds of cells (SPCA-1, Tb, MGC, and K562). Data are average data of triplicate assay.

[a] When the inhibition was below 50% at the highest test concentration.

Acknowledgment

We acknowledge financial support from the NSFC (Grants 20431010, 20021001, and J0630962).

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12. Crystal data: $C_{30}H_{22}CuN_6O_8$, $M = 658.08$, Orthorhombic, crystal dimensions $0.20\times 0.06\times 0.08$ mm, space group P_{bca}, $a = 13.531(3)$, $b = 14.293(3)$, $c = 31.115(6)$ Å, $\alpha = 90.00$, $\beta = 90.00$, $\gamma = 90.00$, $\lambda = 0.71073$Å, $T = 294(2)$ K, $V = 6017.82(19)$ Å^3, $Z = 8$, $D_c = 1.453\text{gcm}^{-3}$, $\mu = 0.787\ \text{mm}^{-1}$, $F(000) = 2696$; 3162 reflections used, 429 refined parameters. The final discrepancy factors were $w_R = 0.1560$, $R = 0.0801$, goodness of fit $S = 1.074$ on F^2, largest difference peak and hole 0.466 and $-0.372\ \text{eÅ}^{-3}$, CCDC 634807 contains the supplementary crystallographic data for this paper.
$C_{31}H_{28}N_6NiO_9$, $M = 687.30$, Monoclinic, crystal dimensions $0.36\times 0.10\times 0.07$ mm, space group C2/c, $a = 16.800(10)$, $b = 20.435(12)$, $c = 9.396(6)$Å, $\alpha = 90.00$, $\beta = 105.082(9)$, $\gamma = 90.00$, $\lambda = 0.71073$Å, $T = 298(2)$ K, $V = 3115(3)$ Å^3, $Z = 4$, $D_c = 1.466\text{gcm}^{-3}$, $\mu = 0.688\ \text{mm}^{-1}$, $F(000) = 1424$;

2691 reflections measured, 222 refined parameters. The final discrepancy factors were $w_R = 0.1415$, $R = 0.0778$, goodness of fit $S = 1.006$ on F^2, largest difference peak and hole 0.724 and -0.576 eÅ^{-3}, CCDC 634808 contains the supplementary crystallographic data for this paper.

$C_{21}H_{23}MnN_3O_7$, $M = 484.36$, Triclinic, crystal dimensions $0.18 \times 0.10 \times 0.04$ mm, space group P-1, $a = 8.909(8)$, $b = 12.368(5)$, $c = 12.624(5)$Å, $\alpha = 118.426(6)$, $\beta = 93.613(9)$, $\gamma = 107.154(9)$, $\lambda = 0.71073$Å, $T = 294(2)$ K, $V = 1134.1(12)$ Å^3, $Z = 2$, $D_c = 1.418$gcm^{-3}, $\mu = 0.628$ mm^{-1}, $F(000) = 502$; 3989 reflections measured, 295 refined parameters. The final discrepancy factors were $w_R = 0.1853$, $R = 0.0867$, goodness of fit $S = 1.034$ on F^2, largest difference peak and hole 0.66 and -0.51 eÅ^{-3}, CCDC 634809 contains the supplementary crystallographic data for this paper.

These data can be obtained free of charge from the Cambridge Crystallographic Data Center via www.ccdc.cam.ac.uk/data-request/cif.