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Synthesis and Anti-Glioma Activity of Two Novel Complexes with Different Schiff Bases

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SUMMARY. By using two flexible Schiff bases (H_2L_1 and H_2L_2), two new Mn(II)- and Ni(II)-coordination compounds, namely, Py_3MnL_1 (**1**) and Py_3NiL_2 (**2**) (Py = pyridine, L_1 = 3,5-$Br_2C_6H_2(O)C{=}NC_6H_3(O)$-4-$NO_2$, L_2 = 4-$BrC_6H_3(O)C$ = $NC_6H_3(O)$-4-Cl), have been synthesized under solvothermal conditions and characterized by single crystal X-ray structural analysis. In addition, the *in vitro* antitumor activities of **1** and **2** and their corresponding organic ligands Py, L_1 and L_2 were studied and evaluated, in which four human glioma cell lines (U251, SHG44, U138 and A172) were used in the screening tests.

RESUMEN. Usando dos bases de Schiff flexibles (H_2L_1 y H_2L_2), dos nuevos compuestos de coordinación de Mn (II) y Ni (II), a saber, Py_3MnL_1 (**1**) y Py_3NiL_2 (**2**) (Py = piridina, L_1 = 3,5-$Br_2C_6H_2(O)C{=}NC_6H_3(O)$-4-$NO_2$, L_2 = 4-$BrC_6H_3(O)C$ = $NC_6H_3(O)$-4-Cl) se han sintetizado en condiciones solvotérmicas y se caracterizaron por análisis estructural de rayos X de cristal único. Además, se estudiaron y evaluaron las actividades antitumorales *in vitro* de **1** y **2** y sus correspondientes ligandos orgánicos Py, L_1 y L_2, en los que se usaron cuatro líneas celulares de glioma humano (U251, SHG44, U138 y A172) en las pruebas de ensayo.

KEY WORDS: coordination compound, liver cancer, Schiff bases.

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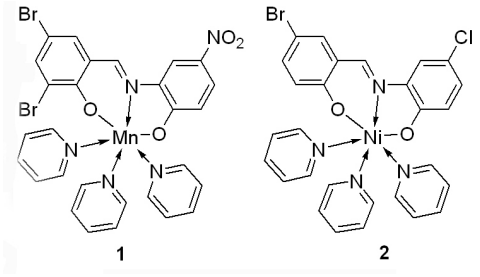

Figure 1. The scheme representation for compounds **1** and **2**.

INTRODUCTION

A tumor, also known as a neoplasm, is an abnormal mass of tissue which may be solid or fluid-filled [1]. There are many different types of tumors and a variety of names for them; their names usually reflect their shape and the kind of tissue they appear in [2,3]. Put simply, a tumor is a kind of lump or swelling, it does not necessarily pose a health threat [4]. A glioma is a type of tumor that starts in the brain or spine. It is called a glioma because it arises from glial cells [5]. The most common site of gliomas is the brain. Gliomas make up about 30% of all brain and central nervous system tumors and 80% of all malignant brain tumors [6].

Schiff bases have played an important role in the development of coordination chemistry since the late 19th century [7]. The metal complexes with Schiff bases have been widely investigated for their versatile structures and potential applications in the fields of medicine, catalyst, and magnetism [8]. Manganese and nickel are two of the most important transition metal ions in biological systems; it plays an important role in transport and activation of molecular oxygen [9]. In this work, two new Mn(II) and Ni(II) complexes Py_3MnL_1 (**1**) and Py_3NiL_2 (**2**) (Fig. 1) (Py = pyridine, L_1 = 3,5-$Br_2C_6H_2(O)C{=}NC_6H_3(O)$-4-$NO_2$, L_2 = 4-$BrC_6H_3(O)C{=}NC_6H_3(O)$-4-Cl) were solvothermally prepared by employment of two different b ase ligands and their antitumor activities was then evaluated.

MATERIAL AND METHODS

Apparatus and materials

All the starting materials and reagents used in this work were obtained commercially and used without further purification. Element analyses (C, H and N) were determined with an elemental Vairo EL III analyzer. Single-crystal X-ray diffraction data for compounds **1** and **2** was recorded on Mercury CCD diffractometer. The melting points were taken on a XT-4 micro melting apparatus, and the thermometer was uncorrected.

Synthesis and characterization of compounds Py3MnL1 (1) and Py3NiL2 (2)

The 3,5-dibromosalicylaldehyde-2-amino-4-nitrophenol Schiff base (H_2L_1, 1.0 mmol, 0.416 g) and methanol (30 mL) were mixed in the reaction flask. After heating and dissolving in air, 20 mL methanol solution of $MnCl_2$ (50 mmol/L) was also added to the reaction flask. Most of the solvent was removed by evaporators *in vacuo* behind 2 h of reaction. Then pyridine was dropped in the mixture to dissolve, continue to reflux 2 h. The solution was cooled down to room temperature, the brown crystals of **1** was obtain after a few days. Analytical found for compound **1** ($C_{28}H_{21}Br_2MnN_5O_4$): C, 47.65 H, 3.02; N, 9.91%. Calculate: C, 47.62; H, 3.00; N, 9.92%.

The 5-bromosalicylaldehyde-2-amino-4-chlorophenol Schiff base (H_2L_2, 1.0 mmol, 0.326 g) and methanol (30 mL) were mixed in the reaction flask. After heating and dissolving in air, 20 mL methanol solution of $NiCl_2$ (50 mmol/L) was also added to the reaction flask. Most of the solvent was removed by evaporators *in vacuo* behind 2 h of reaction. Then pyridine was dropped in the mixture to dissolve, continue to reflux 2 h. The solution was cooled down to room temperature, the brown crystals of **2** was obtain after a few days. Analytical found for compound **2** ($C_{28}H_{22}BrClN_4NiO_2$): C, 54.20 H, 3.58; N, 9.01%. Calculate: C, 54.19; H, 3.57; N, 9.03%.

Crystal structure determination

Structural measurement was performed on a computer-controlled Mercury CCD diffractometer with graphite-monochromated Mo-Kα radiation (λ = 0.71073 Å) at T = 293 (2) K. Absorption correction was made using the SADABS program. The structure was solved using the direct method and refined by full-matrix least-squares methods on F^2 by using the SHELXS-97 [10] program package. Crystallographic data and structural refinements for compounds **1** and **2** are summarized in Table 1.

Antitumor activity

Four human glioma cell lines (U251, SHG44, U138 and A172) were grown in a RPMI 1460

Formula	$C_{28}H_{21}Br_2MnN_5$	$C_{28}H_{22}BrClN_4Ni$
Mr	O_4	O_2
Temperature / K	706.26	620.57
Crystal system	293 (2)	293 (2)
Space group	Triclinic	Triclinic
a / Å	P-1	P-1
b / Å	8.9193 (14)	8.9747 (19)
c / Å	9.2271 (15)	8.9922 (19)
α / °	17.933 (3)	17.140 (4)
β / °	103.574 (2)	104.069 (3)
γ / °	91.518 (2)	96.547 (2)
V / Å3	98.762 (2)	100.176 (2)
Z	1415.0 (4)	1302.6 (5)
D_{calc} / g•cm^{-3}	2	2
μ (Mo Kα) / mm^{-1}	1.658	1.582
θ range / °	3.333	2.415
Reflections collected	2.30 to 25.10	2.34 to 25.10
No. unique data [*R* (int)]	15027	13400
No. data with I ≥ 2σ(I)	5015 [0.0261]	4572 [0.0357]
R_1	3907	3380
θ range / °	0.0347	0.0673
Reflections collected	0.0863	0.1920
No. unique data [R (int)]	1563365	1563366
ωR_2 (all data)		
CCDC		

Table 1. Crystal data and structure refinements for compounds **1** and **2**.

medium supplemented with 10% fetal calf serum, 100 μg/mL penicillin and 100 μg/mL streptomycin. They were incubated at 37 °C in a moist incubator and 95% air and 5% CO_2. Cells at the exponential growth were diluted to 5 × 10^4 cells/mL with RPMI1640, and then seeded in 96-well cell culture at a volume of 100 μL per cell, respectively, and incubated for 24 h at 37 °C in 5% CO_2. After incubation of cells for up to 96 h, medium was removed from each cell and 150 μL of MTT (0.5 mg/mL) solution, diluted 10-fold by RPMI 1460 was subsequently added. The IC_{50} values were measured by depicting the ratio viability versus concentration on a logarithmic chart and reading off the concentration where 50% of cells viable involved in the control. In order to get the mean values, it is requested that each experiment was conducted at least three times in the same way.

RESULTS AND DISCUSSION

Molecular structure

The crystal structures were determined by single-crystal X-ray diffraction, it showed that **1** and **2** both crystallize in the triclinic system, space group P-1∠For **1**, the asymmetric unit comprises one Mn(II) atom, one 3,5-dibromosalicylaldehyde-2-amino-4-nitrophenol Schiff base ligand and three pyridine molecular. For **2**, the asymmetric unit comprises one Ni(II) atom, one 5-bromosalicylaldehyde-2-amino-4-chlorophenol Schiff base ligand and three pyridine molecular.

As shown in Fig. 2(a) and Fig. 3(a), the center Mn1 and Ni1 atom are both six-coordinate in a distorted octahedral geometry, they are surrounded by two oxygen atoms (O1 and O2), one nitrogen atom (N2 for **1**; N1 for **2**) from the ligand and three nitrogen atoms (N3, N4, and N5 for **1**; N2, N3, and N4 for **2**) from three different pyridine. The axis position was occupied by two nitrogen atoms (N2 and N3 for **1**; N1 and N3 for **2**) from their corresponding Schiff base ligands and one pyridine molecular, respectively. For **1** and **2**, the angle of N2–Ni1–N3

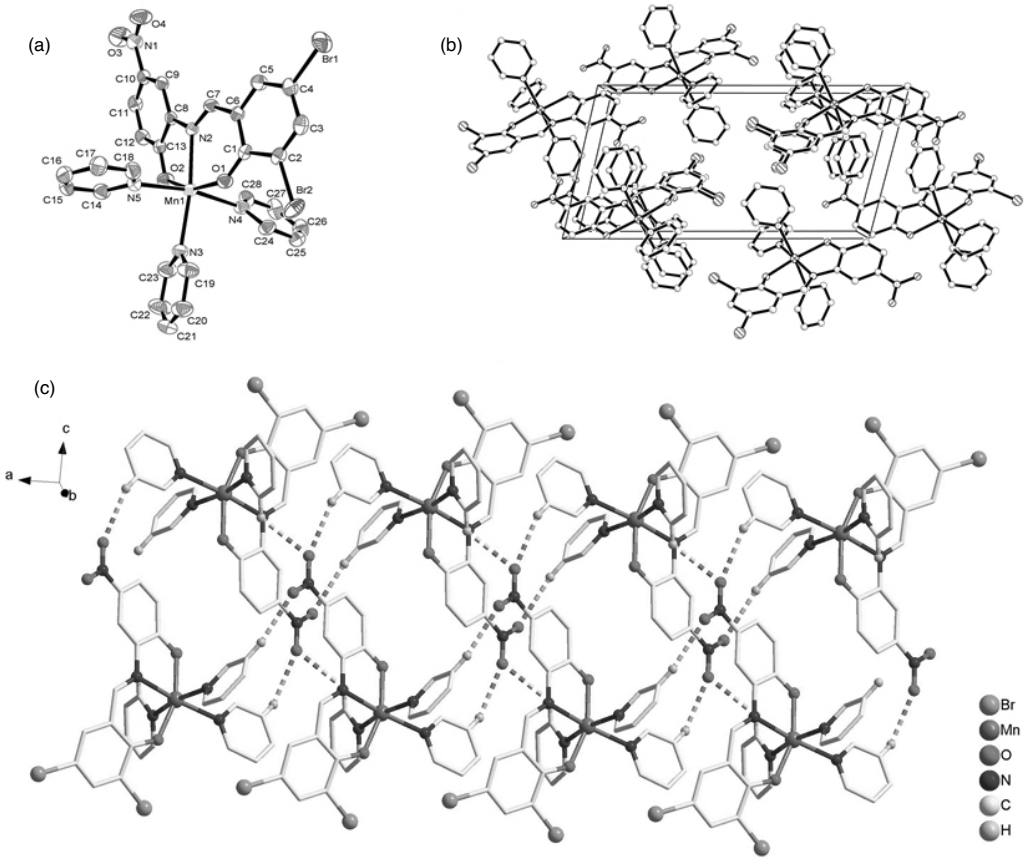

Figure 2. (**a**) Molecular structure of the compound **1**; (b) Packing of the compound **1** in unit cell; (**c**) one-dimensional infinite ribbon structure of the compound **1** was formed by the C–H…O interactions.

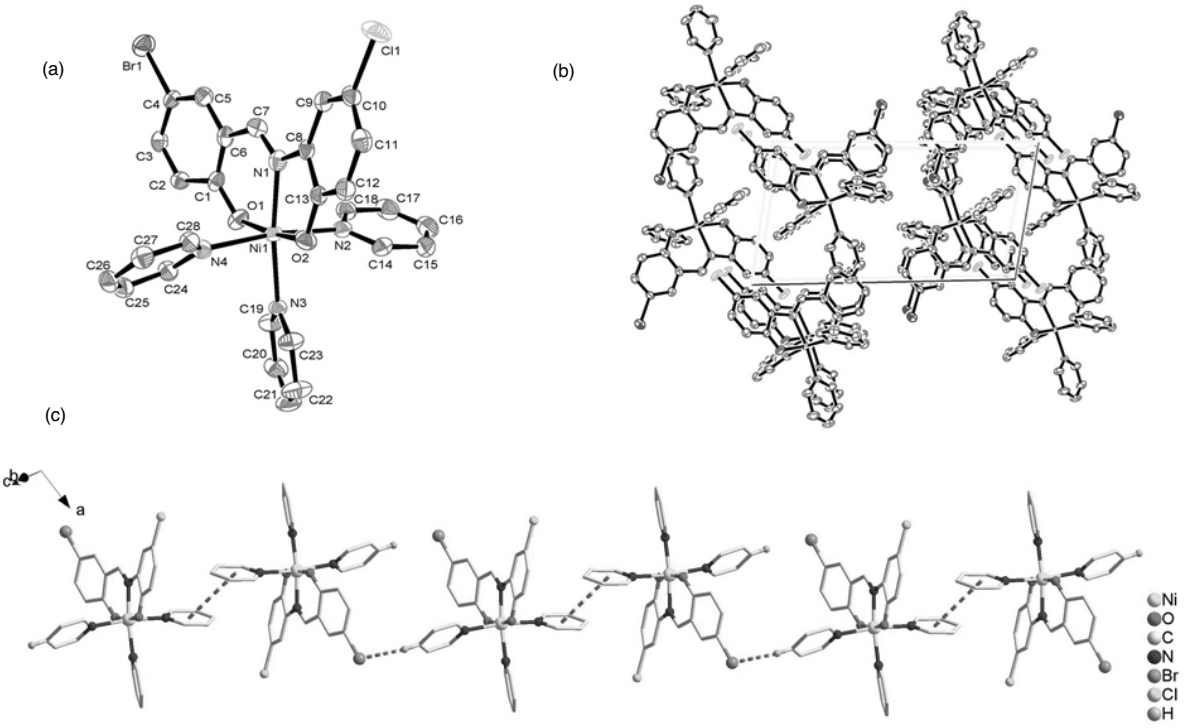

Figure 3. (**a**) Molecular structure of the compound **2**; (**b**) Packing of the compound **2** in unit cell; (**c**) one-dimensional infinite chain structure of the compound **2** was formed by the π…π and C–H…Br interactions.

Compounds	IC_{50} (mM)			
	U251	**SHG44**	**U138**	**A172**
Py	>100	>100	>100	>100
L_1	>100	>100	>100	>100
L_2	>100	>100	>100	>100
1	22	24	33	31
2	30	27	25	36

Table 2. Growth inhibitory effects of **1**, **2**, Py, L_1 and L_2 on U251, SHG44, U138 and A172 cells.

and N1–Ni1–N3 are 172.12(10)° and 172.5(2)° respectively, which are obviously deviates from linear angle 180°. The four atoms (O1, O2, N4, and N5 for **1**; O1, O2, N2, and N4 for **2**) were placed in equatorial sites, the sum of the angles [O1–Mn1–N4=86.72(9)°, O1–Mn1–N5=93.76(9)°, O2–Mn1–N4=89.33(9)°, O2–Mn1–N5=88.27(9)° for **1**; O1–Ni1–N2=93.4(2)°, O1–Ni1–N4= 8 6.95(19)°, O2–Ni1N2 = 91.80(19)°, O2–Ni1–N4 = 88.91(18)° for **2**] is 358.08° and 361.06° respectively, which shows that five atoms (Mn1, O1, O2, N4, and N5 for **1**, Ni1, O1, O2, N2, and N4 for **2**) are basically planar, however, the bond lengths [Mn1–O1=2.076(2) Å, Mn1–O2=2.123(2) Å, Mn1–N4=2.310(3) Å, Mn1–N5=2.338(3) Å for **1**; Ni1–O1=2.012(4) Å, Ni1O2=2.047(5) Å, Ni1–N2=2.157(5) Å, Ni1–N4=2.154(5) Å for **2**] are unequal, it indicated that the central Mn and Ni atom are six-coordinate in a distorted pentagonal pyramid geometry.

The packing of the compounds **1** and **2** in unit cell were shown in Fig. 2(b) and Fig. 3(b). Moreover, for 1, the C–H…O interactions [C15–H15…O4=2.587Å, C15–H15…O4=169.10°; C22–H22…O3=2.531Å, C22–H22…O3=135.10°; C28–H28…O3=2.633Å, C28–H28…O3=129.75°] were observed between adjacent molecular, which lead to the forming of a interesting one-dimensional infinite ribbon structure [Fig. 2(c)]; for **2**, the π…π interactions [π (N2–C18)…π ($N2^{i}$-$C18^{i}$, i: 1-x, -y, -z) 4.3474(10)Å] and the C-H…Br interactions [C26–H26…Br1=3.037Å, C26–H26…Br1=126.93°] were observed between adjacent molecular, which lead to the forming of a interesting one-dimensional infinite chain structure [Fig. 3(c)].

Anticancer activity

The cytotoxicities of the title compounds **1** and **2**, organic ligands Py, L1 and L2 against U251, SHG44, U138, and A172 cell lines were evaluated by MTT assay, and the IC_{50} values derived from the experimental data were concluded in Table 2. It is obvious that the three organic ligands were inactive against all of these cell lines (IC_{50} > 100 μM). At this concentration, the three organic ligands should exert high cytotoxicity against the cells, thus we infered that it did not exert any inhabitation selectivity towards these cell lines.

However, after the cancer cells were incubated in the presence of compounds **1** and **2** for 72 h, the IC_{50} values for the compound ranged from 22 to 36 μM, indicating that the title compounds **1** and **2** exhibited anticancer activity against all of these cell lines in different de-