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两个含吡咯环酰腙配体的 Cu(Ⅱ)配合物的合成、晶体结构和生物活性

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摘要: 合成并通过元素分析,红外和 X-射线单晶衍射表征了 2 个酰腙铜配合物[Cu(L)$_2$(THF] (**1**)和[Cu(L)(CH$_3$OH)Cl] (**2**)[HL=3,4-二甲基-2-乙氧羰基-吡咯-5-甲醛苯甲酰腙]。结果表明在每个配合物中,HL 脱质子作为阴离子配体,通过烯醇化的氧和亚氨基的氮与中心铜(Ⅱ)离子配位。中心铜(Ⅱ)离子在配合物 **1** 和 **2** 中的配位构型分别为扭曲的四方锥和平面正方形。配合物 **2** 对金黄色葡萄球菌有明显的抑制作用(MIC=1.98 μg·mL^{-1}),而配合物 **1** 则对肝癌细胞 Hep G2 展现出显著的抗肿瘤活性(IC$_{50}$=9.1 μmol·L^{-1})。

关键词: 铜(Ⅱ)配合物; 酰腙; 吡咯; 抗菌活性; 抗肿瘤活性
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Syntheses, Crystal Structures and Biological Activities of Two Cu(Ⅱ) Complexes with an Acylhydrazone Ligand Bearing Pyrrole Unit

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Abstract: Two copper(Ⅱ) complexes, [Cu(L)$_2$(THF] (**1**) and [Cu(L)(CH$_3$OH)Cl]$_2$ (**2**) (where HL=ethyl 5-[(benzoyl) amino-iminomethyl]-3,4-dimethyl-pyrrole-2-carboxylate) have been synthesized and characterized by elemental analyses, infrared spectra and single-crystal X-ray diffraction analyses. The results reveal that the acylhydrazone ligand HL in each complex is deprotonated as an anionic ligand and coordinates to the central Cu(Ⅱ) ion via enolization oxygen and imine nitrogen atoms. The Cu(Ⅱ) center possesses a distorted square-pyramidal geometry and a square-planar geometry in complex **1** and **2**, respectively. Complex **2** shows obvious inhibitory effect to bacterial strain *S. Aureus* (MIC =1.98 μg·mL^{-1}), and complex **1** has excellent antitumor activity towards Hepatocellular carcinoma (Hep G2) cells (IC$_{50}$=9.1 μmol·L^{-1}). CCDC: 1003889, HL·2CH$_3$OH; 1003890, **1**; 1003891, **2**.

Key words: Cu(Ⅱ) complex; acylhydrazone; pyrrole; antibacterial activity; antitumor activity

Recently, acylhydrazone ligands and their metal complexes have generated considerable attention in chemistry and biology due to their attractive and various biological properties, such as antioxidant, anti-inflammatory, anti-proliferative, antibacterial and antitumor activities [1-5]. It is well known that the biological properties of acylhydrazone complexes, which are introduced by the linkage to metal ion, may be modified and differ from those of either the ligand or the metal ion[6-9]. Furthermore, on one hand, a large amount of Cu (II) complexes have found potential medical uses in the treatment of many diseases

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including cancer[10]; on the other hand, Cu(Ⅱ) and Zn(Ⅱ) complexes of imine ligands bearing pyrrole unit have excellent biological properties [11]. Thus, in this paper we report the syntheses, crystal structures, and biological activities of two Cu(Ⅱ) complexes with an acylhydrazone ligand bearing pyrrole unit.

1 Experimental section

1.1 Materials and measurements

Solvents and starting materials for syntheses were purchased commercially and used as received. Melting point was measured on an X-4 digital melting-point apparatus (uncorrected). Elemental analyses were carried out on an Elemental Vario EL analyzer. The ^{1}H NMR spectra were recorded with a Varian VR 300-MHz NMR instrument in $CDCl_3$ with TMS as internal standard. The IR spectra (ν=4 000~400 cm^{-1}) were determined by the KBr pressed disc method on a Bruker V70 FT-IR spectrophotometer.

1.2 Preparations of the ligand and complexes

As shown in scheme 1, the ligand HL was prepared by condensation of ethyl 5-formyl-3,4-dimethyl-pyrrole-2-carboxylate[12] (0.97 g, 5 mmol) and benzoyl hydrazine[13] (0.68 g, 5 mmol) in ethanol solution (20 mL) at 85 ℃ for 4 h and monitored using TLC[14]. The separated solid was filtered and the single crystals of HL ·2CH_3OH were obtained through recrystallization in methanol solution. Yield: 1.19 g (76%). m.p. 92~94 ℃. Elemental analysis for HL ($C_{17}H_{19}N_3O_3$)(%): Calcd.: C: 61.16; H: 6.11; N: 13.41; Found: C: 61.02; H: 6.24; N: 13.49. FT-IR (cm^{-1}): ν(N-H) 3 236, ν(O=C-O) 1 697, ν(O=C-N) 1 647, ν(C=N-N) 1 610. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 9.95 (1H, s, NH-C=O), 9.23 (1H, s, pyrrole NH), 8.20 (H, s, CH=N), 7.45~7.86 (5H, m, phenyl H), 4.30~4.37 (2H, q, J=7.2 Hz, CH_2-CH_3), 2.27 (3H, s, CH_3), 2.08 (3H, s, CH_3), 1.37 (3H, t, J=7.2 Hz, CH_3-CH_2).

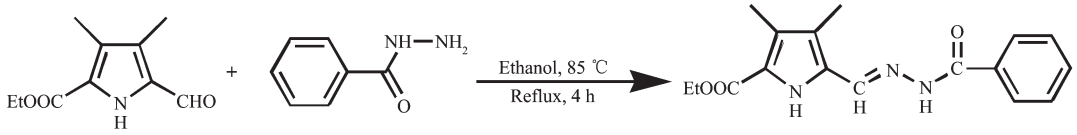
The two titled complexes **1** and **2** were synthesized by reacting moderate HL with $Cu(OAc)_2$·H_2O (molar ratio=2∶1), and with $CuCl_2$·2H_2O (molar ratio=1∶1) in the mixture solvents of THF and methanol (1∶1, *V*/*V*) at room temperature, respectively. After about two weeks, single crystals suitable for X-ray diffraction were obtained from the reaction solutions.

Elemental analysis for **1** ($C_{38}H_{44}CuN_6O_7$)(%): Calcd. C: 60.00, H: 5.79, N: 11.05; Found C: 59.68, H: 5.71, N: 11.25. FT-IR (cm^{-1}): ν(N-H) 3 150, ν(O=C-O) 1 710, ν(N=C-O) 1 610, ν(C=N-N) 1 598. Elemental analysis for **2** ($C_{36}H_{44}Cl_2Cu_2N_6O_8$)(%): Calcd. C: 52.49, H: 5.35, N: 10.21; Found C: 52.26, H: 5.25, N: 10.08. FT-IR (cm^{-1}): ν(N-H) 3 275, ν(O=C-O) 1 710, ν(N=C-O) 1 614, ν(C=N-N) 1 587.

1.3.1 X-ray crystallography

The X-ray diffraction measurements for HL·2CH_3OH, **1** and **2** were performed on a Bruker SMART APEX Ⅱ CCD diffractometer equipped with a graphite monochromatized Mo $K\alpha$ radiation (λ = 0.071 073 nm) by using φ-ω scan mode. Multi-scan absorption correction was applied to the intensity data using the SADABS program[15]. The structures were solved by direct methods and refined by full matrix least-square on F^2 using the SHELXTL-97 program[16]. All non-hydrogen atoms were refined anisotropically. The hydrogen atoms for O4 and O5 in HL·2CH_3OH, O4 and O8 in complex **2** are located from difference Fourier map and refined with restraints in bond length and thermal parameters. All the other H atoms were positioned geometrically and refined using a riding model. Details of the crystal parameters, data collection and refinements for HL·2CH_3OH, **1** and **2** are summarized in Table 1, selected bond lengths and angles are given in Table 2.

CCDC: 1003889, HL·2CH_3OH; 1003890, **1**; 1003891, **2**.



Scheme 1 Reaction scheme for the synthesis of HL

Table 1　Crystal data and structure refinement parameters for HL·2CH$_3$OH, 1 and 2

	HL·2CH$_3$OH	1	2
Empirical formula	$C_{19}H_{27}N_3O_5$	$C_{38}H_{44}CuN_6O_7$	$C_{36}H_{44}Cl_2Cu_2N_6O_8$
Formula weight	377.44	760.33	886.75
T / K	296(2)	296(2)	296(2)
λ / nm	0.071 073	0.071 073	0.071 073
Crystal system	Triclinic	Triclinic	Monoclinic
Space group	$P\bar{1}$	$P\bar{1}$	$P2_1/c$
a / nm	0.797 36(2)	0.795 61(10)	1.762 9(4)
b / nm	1.007 49(3)	1.442 28(18)	2.186 3(4)
c / nm	1.362 59(3)	1.715 1(2)	1.015 4(2)
α / (°)	110.008(2)	87.553(3)	90
β / (°)	90.354(2)	76.671(2)	95.010(4)
γ / (°)	91.711(2)	85.052(2)	90
V / nm^3	1.027 93(5)	1.907 4(4)	3.898 6(13)
Z	2	2	4
D_c / (Mg·m^{-3})	1.219	1.324	1.511
Absorption coefficient / mm^{-1}	0.089	0.628	1.286
Crystal size /mm	0.20×0.16×0.15	0.23×0.21×0.18	0.23×0.20×0.18
F(000)	404	798	1 832
θ range for data collection / (°)	1.59~28.33	1.42~25.01	1.16~27.83
Index ranges	$-10 \leqslant h \leqslant 10$, $-13 \leqslant k \leqslant 12$, $-18 \leqslant l \leqslant 17$	$-9 \leqslant h \leqslant 9$, $-10 \leqslant k \leqslant 17$, $-20 \leqslant l \leqslant 20$	$-21 \leqslant h \leqslant 22$, $-24 \leqslant k \leqslant 28$, $-13 \leqslant l \leqslant 12$
Reflections collected	17 426	10 104	24 578
Unique (R_{int})	5 072 (0.037 3)	6 702 (0.016 8)	9 138 (0.057 6)
Data / restraints / parameters	5 072 / 2 / 252	6 702 / 242 / 469	9 138 / 2 / 493
Goodness-of-fit (GOF) on F^2	1.026	1.076	1.028
Final R indices [$I>2\sigma(I)$]	R_1=0.057 2, wR_2=0.155 2	R_1=0.048 2, wR_2=0.128 6	R_1=0.048 1, wR_2=0.096 5
R indices (all data)	R_1=0.121 1, wR_2=0.193 1	R_1=0.061 7, wR_2=0.138 8	R_1=0.108 1, wR_2=0.115 9
Largest peak and hole / (e·nm^{-3})	235 and −219	536 and −753	413 and −395

Table 2　Selected bond lengths (nm) and angles (°) in HL·2CH$_3$OH, 1 and 2

HL·2CH$_3$OH					
O3-C11	0.122 3(2)	O4-C18	0.137 3(4)	N3-C11	0.135 4(3)
N2-C10	0.127 6(3)	C3-O1	0.134 2(3)		
1					
Cu1-O1	0.189 6(2)	Cu1-O4	0.190 1(2)	Cu1-N5	0.202 7(3)
Cu1-N2	0.202 9(3)	Cu1-O7	0.230 1(3)	N5-C8	0.128 6(4)
N4-C7	0.129 3(4)				
O1-Cu1-O4	160.50(11)	O1-Cu1-N5	96.61(10)	O4-Cu1-N5	81.31(10)
O1-Cu1-N2	80.91(10)	O4-Cu1-N2	98.56(10)	N5-Cu1-N2	172.29(11)
O1-Cu1-O7	101.43(11)	O4-Cu1-O7	98.07(11)	N5-Cu1-O7	95.12(11)
N2-Cu1-O7	92.53(11)				
2					
Cu1-O1	0.190 4(2)	Cu1-N2	0.197 4(2)	Cu1-O4	0.200 8(2)

Continued Table 2

Cu1-Cl1	0.223 23(9)	Cu2-O8	0.200 6(2)	Cu2-N5	0.197 3(3)
Cu2-O5	0.190 3(2)	Cu2-Cl2	0.225 5(10)		
O1-Cu1-N2	80.91(10)	N2-Cu1-Cl1	99.25(8)	O5-Cu2-Cl2	176.49(9)
O1-Cu1-O4	88.69(9)	O4-Cu1-Cl1	90.66(7)	N5-Cu2-Cl2	99.52(8)
N2-Cu1-O4	164.59(11)	O5-Cu2-N5	80.77(10)	O8-Cu2-Cl2	90.65(7)
O1-Cu1-Cl1	177.53(8)	O5-Cu2-O8	88.44(9)	N5-Cu2-O8	165.30(12)

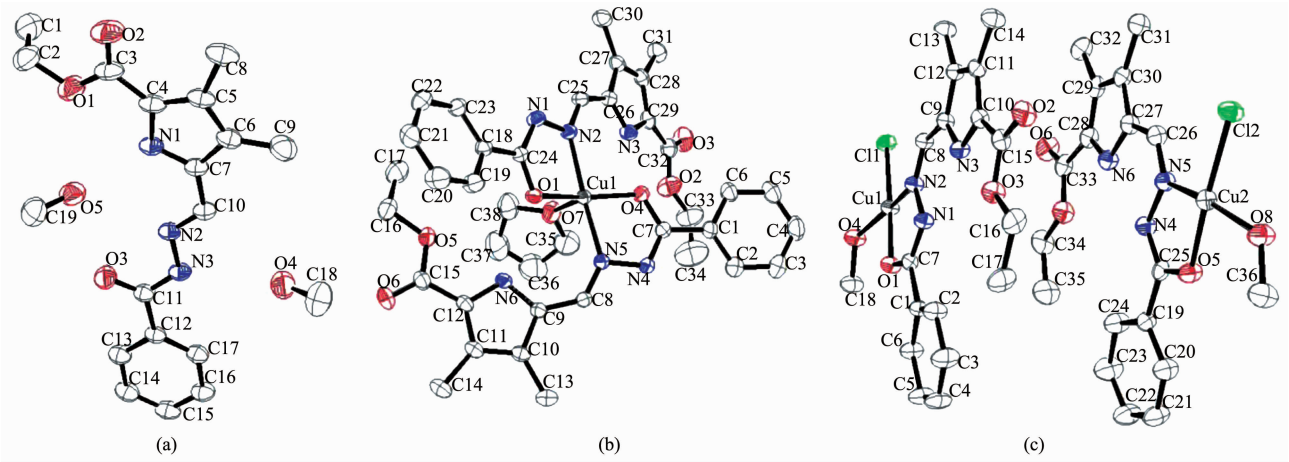
2 Results and discussion

2.1 Crystal structures of HL·2CH$_3$OH, 1 and 2

As shown in Fig.1a, the acylhydrazone ligand in HL·2CH$_3$OH is in a ketone form, in which the bond length of carbonyl C11-O3 (0.122 3(2) nm) is similar as that of other previously known acylhydrazone ligand (0.122 09(17) nm)[17]. In the crystal of HL·2CH$_3$OH, the acylhydrazone molecules are linked into centrosymmetric dimers by methanol molecules via intermolecular O–H···O, O–H···N and N–H···O hydrogen bonds (Fig.2a, Table 3).

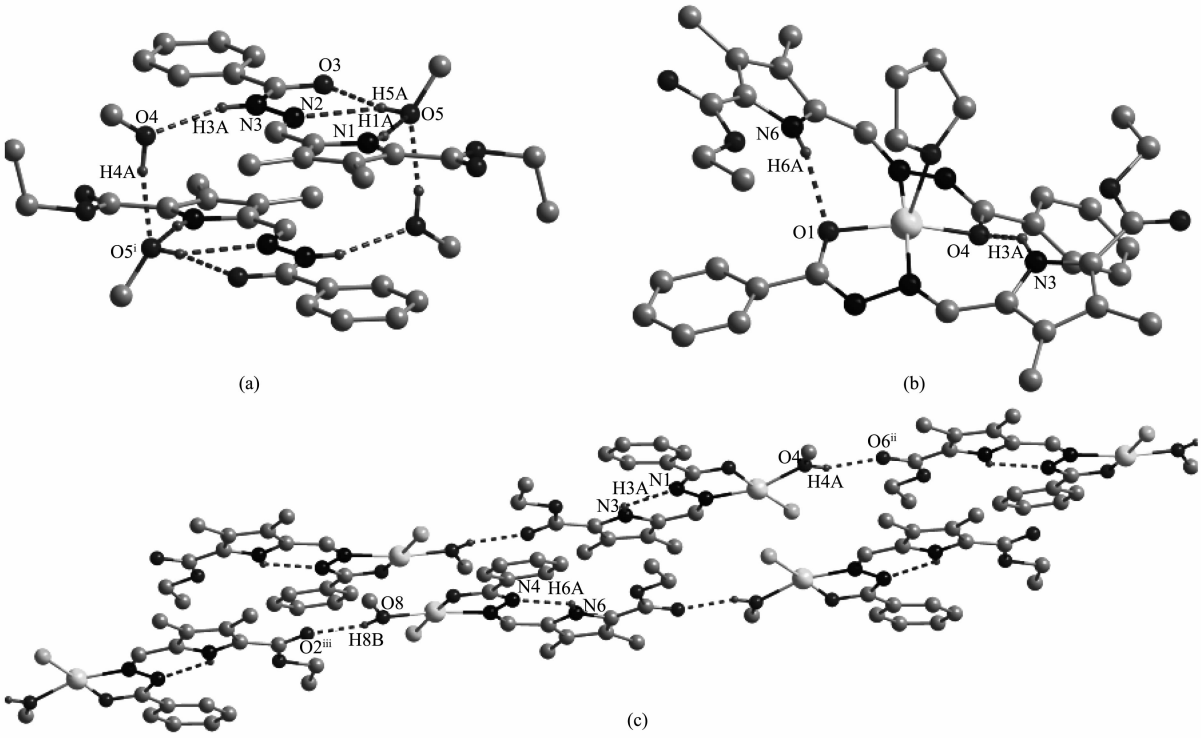
Once coordinating with metal ion, the acylhydrazone ligand HL is deprotonated. The central copper ion in complex **1** is coordinated with two L$^-$ anions by NO donor sets and an additional binding of solvated THF molecular (Fig.1b). The maximal two angles between the coordination atoms and Cu(Ⅱ) ion are 172.29(11)° and 160.50(11)°, respectively. According to the Addison rule[18], the geometric index τ value is 0.197, which is indicating that the irregular coordination geometry of the five-coordinated copper ion in **1** should be described as a distorted square-pyramidal geometry. The basal plane is made up of two NO donor sets (from two independent ligands) including O1, N2, O4 and N5 atoms. The bond lengths from Cu(Ⅱ) center to these atoms are in the range of 0.189 6(2)~0.202 9(3) nm. The fifth coordination site is occupied by O7 (from THF molecular) located axially at 0.230 1(3) nm. Obviously, as shown in Fig.2b, there are two types of classical intramolecular N–H···O hydrogen bonds (Table 3) in complex **1**.

However, in complex **2**, the central copper ion is four coordinated and possesses a distorted square-planar geometry. The four coordinated atoms are consist of one chloride anion, one oxygen atom from one CH$_3$OH molecular and a NO donor set from one enolization ligand L$^-$ (Fig.1c). In the crystal of **2**, intermolecular O–H···O hydrogen bonds link the complex molecules into 1D chains (Fig.2c).



H atoms have been omitted for clarity

Fig.1 Molecular structures of the complexes HL·2CH$_3$OH (a), **1** (b) and **2** (c) shown with 30% probability displacement ellipsoids and atomic numbering scheme



H atoms of C-H bonds were omitted for clarity; Symmetry code: in (a) $^{i}-x+1, -y+2, -z+1$; in (c) $^{ii}-x+1, -y+1, -z+1$; $^{iii}-x+2, -y+1, -z+3$

Fig.2　(a) Dimer formed by hydrogen bonds (dashed line) in HL·2CH_3OH; (b) Classical intramolecular hydrogen bonds in complex **1**; (c) 1D Chain-like structure formed by hydrogen bonds in complex **2**

Table 3　Classical hydrogen bonds for HL·2CH_3OH, 1 and 2

D–H···A	*d*(D-H) / nm	*d*(H···A) / nm	*d*(D···A) / nm	∠DHA / (°)
HL·2CH_3OH				
N3–H3A···O4	0.086	0.217	0.299 9(3)	160.9
N1–H1A···O5	0.086	0.217	0.301 7(3)	169.9
O5–H5A···O3	0.085 3(19)	0.196(2)	0.280 4(2)	169(4)
O5–H5A···N2	0.085 3(19)	0.247(4)	0.296 4(3)	118(4)
O4–H4A···O5^{i}	0.086 9(19)	0.193(2)	0.277 9(3)	166(4)
1				
N3–H3A···O4	0.086	0.199	0.272 4(4)	142.5
N6–H6A···O1	0.086	0.195	0.268 4(3)	142.5
2				
O4–H4A···O6^{ii}	0.084 0(10)	0.202(2)	0.278 4(3)	151(4)
O8–H8B···O2^{iii}	0.084 7(10)	0.204(2)	0.279 5(3)	148(4)
N3–H3A···N1	0.086	0.219	0.272 4(4)	119.8
N6–H6A···N4	0.086	0.220	0.273 6(4)	119.8

Symmetry code: $^{i}-x+1, -y+2, -z+1$; $^{ii}-x+1, -y+1, -z+1$; $^{iii}-x+2, -y+1, -z+3$

Meanwhile, strong intramolecular N–H···N hydrogen bonds were also presented (Table 3).

2.2　IR spectra

In the IR spectra of the ligand HL, the vibration bands of ν(N-H), ν(C=O-O), ν(C=O-N) and ν(C=N-N) were observed at 3 236, 1 697, 1 647 and 1 610 cm^{-1}, respectively. However, O=C-N characteristic stretching vibration absorption in both complexes are disappeared, meanwhile, new (N=C-O) stretching vibration absorption are observed at 1 610 and 1 614 cm^{-1} in complexes

1 and **2**, respectively, which revealing that in both complexes the C=O groups in O=C-N moieties have enolizated and the oxygen atom coordinates to the central copper ion[8,13]. The ν(C=N) of the ligand at 1 610 cm^{-1} shifts to 1 598 and 1 587 cm^{-1} in complexes **1** and **2**, respectively, indicating that imine nitrogen atom in the ligand also takes part in the coordination with central copper ions[11]. It is consistent with the X-ray diffraction analyses result.

2.3 Antibacterial activities

In view of the antibacterial activities of acylhydrazone and their metal complexes, antibacterial activities of all compounds were investigated in details by using the disc diffusion method[19]. We can learn from the results that both **1** and **2** exhibit potential inhibition activity as shown in Table 4. Precisely speaking, complex **2** showed obvious inhibitory effect to bacterial strain *S. Aureus* with an excellent MIC value 1.98 $\mu g \cdot mL^{-1}$, which is even exceeded to positive control antibiotics Amp, Cm and Kan. However, inhibition activity against bacterial strains S. *Aureus* of complex **1** (MIC=250 $\mu g \cdot mL^{-1}$) is much lower than that of HL (MIC =15.62 $\mu g \cdot mL^{-1}$). Although the bactericidal mechanisms of acylhydrazones and their metal complexes are still not very clear. The structures and the lability of Cu-Cl bond may explain the mentioned trends. Complex **1** is a square pyramidal and has only one coordination site to bind with bio-molecules of bacterial cell wall. However, Complex **2** are square planar, two axial coordination sites are vacant and may interact with donor centers available in bio-molecules and are responsible for better anti-bacterial[20].

Table 4 Antibacterial activities of the titled complexes and the positive control antibiotics

Microoganism	MIC / ($\mu g \cdot mL^{-1}$)					
	1	**2**	HL	Amp	Cm	Kan
B. subtilis	1 000	—	125	0.24	15.62	15.62
S. lutea	—	—	—	0.48	62.5	7.81
S. aureus	250	1.98	15.62	—	31.25	62.5
B. cereus	250	—	—	0.48	15.62	125
A. tumefaciens	—	—	—	1.95	31.25	3.90
E. coli	—	—	—	125	31.25	31.25
P. aeruginosa	500	—	—	250	31.25	31.25
S. typhimurium	250	—	—	0.48	15.62	3.90

—: no inhibition or MIC>1 000 $\mu g \cdot mL^{-1}$

2.4 Antitumor activities

It is reported that arylhydrazone and their metal complexes show particularly effective antitumor activities possibly for their NO bidentate systems[21]. In view of this reason, in vitro cytotoxicity assays about inhibit tumor cell growth against Hep G2 cells were carried out by using MTT method[22]. Surprisingly, antitumor activity of complex **1** (IC_{50}=9.1 $\mu mol \cdot L^{-1}$) is much better than that of complex **2** (20% at 6 $\mu mol \cdot L^{-1}$ for less soluble) and HL (IC_{50}>100 $\mu mol \cdot L^{-1}$). In some cases, the antitumor activity has been related to the chelating property of the ligand and the coordinated central metal ion. Comparing with that of complex **2**, the better antitumor activity of complex **1** is probably due to the additional enolization acylhydrazone ligand[21].

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