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Crystal Structure and Biological Activity of Two Novel Coordination Polymers as Anti-Gastric Cancer Agents[1]

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Abstract—Two new coordination polymers, namely $[Cd_2(Mna)_2(Phen)]_n$ (**I**) (H_2Mna = 6-mercaptonicotinic acid, Phen = 1,10-phenanthroline) and $\{[Mn(Ddca)(Phen)](H_2O)\}_n$ (**II**) (H_2Ddca = 6,6'-dithiodinicotinic acid), have been obtained by using H_2Ddca and Phen as the organic building blocks under different reaction conditions. The structures of these complexes have been successfully determined by single crystal X-ray diffraction (CIF files CCDC nos. 1811835 (**I**), 1811836 (**II**)). In addition, in vitro antitumor activity of compounds **I** and **II** on four human gastric cancer cells (MGC-803, BGC-823, SGC-7901 and AGS) was further determined and the results show that the two compounds showed promising activity.

Keywords: coordination polymer, building block, gastric cancer cell

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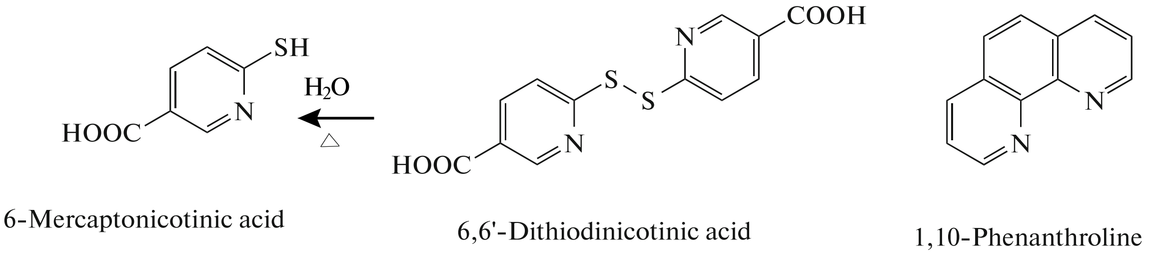
INTRODUCTION

Cancer is a major public health problem in the world [1]. Chemotherapy is still one of the primary modalities for the treatment of cancer. However, the use of this method is limited mainly due to the small number of the available chemotherapeutic agents to choose among them and also because the use of these agents is often accompanied by undesirable side effects [2–4]. This clearly underlies the urgent need for developing novel chemotherapeutic agents with more potent antitumor activities and reduced side effects [5].

The construction of novel organic-inorganic compounds has attracted much attention for their potential applications and interesting structures [6]. Aromatic polyacid and phenanthroline are two kinds of versatile ligands for the construction of polynuclear complexes with transition metal atoms [7]. Most related complexes have been proved to possess effective biological activities, such as antibacterial, antimicrobial, and antitumor activities [8, 9]. In this work, we prepared two new coordination polymers, namely $[Cd_2(Mna)_2(Phen)]_n$ (**I**), where H_2Mna = 6-mercaptonicotinic acid, Phen = 1,10-phenanthroline, and $\{[Mn(Ddca)(Phen)](H_2O)\}_n$ (**II**), where H_2Ddca = 6,6'-dithiodinicotinic acid, by using H_2Ddca and Phen as the organic building blocks under different reaction conditions and their antitumor activities was then evaluated. The ligands used in this work are shown in Scheme 1:



Scheme 1.

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EXPERIMENTAL

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 **I** and **II** was recorded on Mercury CCD diffractometer. The melting points were taken on a XT-4 micro melting apparatus, and the thermometer was uncorrected.

Synthesis of complexes I. A mixture of H_2Ddca (15.4 mg, 0.0494 mmol), 1,10-phenanthroline hydrate (10.0 mg, 0.0505 mmol) and $Cd(NO_3) \cdot 6H_2O$ (29.6 mg, 0.1 mmol) was dissolved in H_2O (6 mL). The resulting solution was kept at 150°C for 3 days. The pale-yellow sheet crystals of **I** were collected by filtration, washed with water, and dried in air. The yield was 32% (based on H_2Ddca).

For $C_{24}H_{14}N_4O_4S_2Cd_2$

Anal. calcd., %	C, 40.52	H, 1.98	N, 7.88
Found, %	C, 40.65	H, 2.19	N, 7.49

Synthesis of complexes II. A mixture of H_2Ddca (15.4 mg, 0.0494 mmol), 1,10-phenanthroline hydrate (10.0 mg, 0.0505 mmol) and $MnCl_2 \cdot 6H_2O$ (24 mg, 0.1 mmol) was dissolved in H_2O (4 mL). The resulting solution was kept at 100°C for 3 days. The pale-yellow needle-like crystals of **II** were collected by filtration, washed with water, and dried in air. The yield was 36% (based on H_2Ddca).

For $C_{24}H_{16}N_4O_5S_2Mn$

Anal. calcd., %	C, 51.52	H, 2.88	N, 10.01
Found, %	C, 51.65	H, 2.19	N, 10.49

X-ray structure determination. Suitable single crystal of compounds **I** and **II** was carefully selected under optical microscope and glued on thin glass fibers. The intensity data of **I** and **II** was collected on Oxford Xcalibur E diffractometer. The empirical absorption corrections were applied to the data using the SADABS system. This structure was solved by direct method and refined by full-matrix least-squares method on F^2 using the SHELXS-97 program [10]. All non-hydrogen atoms of **I** and **II** were refined anistropically, and all the hydrogen atoms attached to carbon atoms were fixed at their ideal positions. Pertinent crystal data and structural refinement results for compounds **I** and **II** were summarized in Table 1.

Supplementary material for structures has been deposited with the Cambridge Crystallographic Data Centre (CCDC nos. 1811835 (**I**), 1811836 (**II**); deposit@ccdc.cam.ac.uk or http://www.ccdc.cam.ac.uk).

Antitumor activity. Four human gastric cancer cells (MGC-803, BGC-823, SGC-7901 and AGS) were grown in a RPMI 1460 medium supplemented with 10% fetal calf serum, 100 μg/mL penicillin and 100 μg/mL streptomycin. They were incubated at the temperature of 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

Hydro(solvo)thermal synthesis is a powerful method for preparation of coordination polymers due to their low solubilty in common solvents. Complex **I** was successfully obtained from the hydrothermal reaction of H_2Ddca and cadmium ion at 150°C where the starting H_2Ddca ligand can be converted into a functional (Mna)-ligand characteristic of mixed nitrogen, oxygen and sulfur donors. X-ray crystallography reveals that in complex **I**, the asymmetric unit consists of two Cd^{2+} ions, two Mna^{2-} ligands and two Phen ligands as shown in Fig. 1a. The $Hmna^{2-}$ ligand comes from *in situ* decomposition of H_2Ddca molecule during the hydrothermal synthesis reaction. The two Cd(II) centers show different coordination environments (Fig. 1b): Cd(1) is six-coordinated by two sulfur atoms from two Mna^{2-} ligands (Cd–S 2.591(2) to 2.6447(2) Å), three N atoms from the Phen ligand and one Mna^{2-} ligand (Cd–N 2.3835(2) to 2.4617(2) Å), while the remaining site is finished by the oxygen atom on the Mna^{2-} ligand. The Cd(1) is located in distorted $[CdON_3S_2]$ octahedral coordination environment; In comparison, the coordinating surrounding of Cd(2) is built up from two sulfur atoms from two Mna^{2-} ligands (Cd–S 2.6169(2) to 2.7344(2) Å), two O atoms from from two Mna^{2-} ligands (Cd–O 2.384(2) to 2.462(2) Å), while the remaining site is finished by the N atom on the Mna^{2-} ligand. The Cd(2) is located in distorted $[CdO_2NS_2]$ trigonal bipyramidal coordination environment. Two adjacent Cd^{2+} ions are held together by the carboxylic acid group and one bridged S atom to afford a Cd(2) dimer with a Cd–Cd distance of 3.976 Å. Such Cd(2) dimers are further connected by the Mna^{2-} ligands along the *bc* plane to afford a 2D layered structure with the Phen molecules cover the two sides of the planes (Fig. 1c). The total solvent accessible volume for **I** is 12.5%, which locates in the interlayer of the packing layers (Fig. 1d).

Table 1. Crystallographic data and structure refinements for compounds **I** and **II**

Parameter	Value	
	I	**II**
Mr	711.31	609.52
Crystal system	Triclinic	Triclinic
Space group	$P\bar{1}$	$P\bar{1}$
a, Å	9.0068 (6)	9.9367 (8)
b, Å	11.8542 (8)	11.7317 (7)
c, Å	12.4925 (9)	12.5826 (11)
α, deg	97.485 (6)	111.545 (7)
β, deg	90.665 (6)	106.335 (7)
γ, deg	103.202 (5)	94.786 (6)
V, Å^3	1286.31 (16)	1280.28 (19)
Z	2	2
ρ_{calcd}, g cm^{-3}	1.837	1.581
μ(MoK_α), mm^{-1}	1.853	0.733
θ Range, deg	2.983 to 24.998	3.154 to 24.998
Reflections collected/ unique data (R_{int})	8606/4519 (0.0209)	7948/4498 (0.0206)
Reflections with $I \geq 2\sigma(I)$	3808	3652
R indices ($I > 2\sigma(I)$)	$R_1 = 0.0266$, $wR_2 = 0.0554$	$R_1 = 0.0335$, $wR_2 = 0.0768$
R indices (all data)	$R_1 = 0.0357$, $wR_2 = 0.0587$	$R_1 = 0.0459$, $wR_2 = 0.0822$
Largest diff. peak/hole, e Å^{-3}	0.49/–0.35	0.42/–0.43

The asymmetric unit of **II** is made up of one unique Mn(II) atom, one Ddca ligand, one Phen ligand, one coordinated water molecule and one coordinated EtOH molecule as well as one lattice water molecule (Fig. 2a). The Mn(II) atom adopts a six-coordinate mode with a distorted [MnO_4N_2] octahedral arrangement. Each Mn(II) atom is coordinated by four oxygen atoms from two monodentate carboxylate groups of two Ddca^{2-} ligands and two nitrogen atom from one Phen ligand as well as two O atoms from the coordinated water and EtOH molecules. The Mn–O distances fall in the range of 2.157 (2)–2.205(2) Å, and the Mn–N bond lengths are in the region of 2.276(17)–2.339(3) Å, which are all in good agreement with previous studies. In **II**, the H_2Ddca molecules are completely deprotonated and are largely bent at the C–S–S bond site. The torsion angle of the Ddca molecule (C–S–S–C) is 89.53°, and the dihedral angle of two pyridine rings is 104.32° (Fig. 2b). Two Mn(II) atoms are bridged by two carboxylates in a monodentate fashion to give a metallocyclic motif with the Mn···Mn distance of 13.115(2) Å. More remarkably, the formed metallocyclic motifs are further extended into a 2D layered structure by the H-bonds form by the lattice water, pyridine N atom (H···N 2.24 Å), coordinated water molecule (H···O 2.24 Å) and coordinated EtOH molecule (H···O 2.083 Å, Fig. 2c). From the topological point of view, the coordinated water molecule could be viewed as a four-connected node, the Mn^{2+} ion could be viewed as a five-connected node and the ligand could be judged as a six-connected node, so the whole network of **II** could be considered as a (4,6)-connected network whose topology has not been encountered in coordination polymers (CP) chemistry (Fig. 2d).

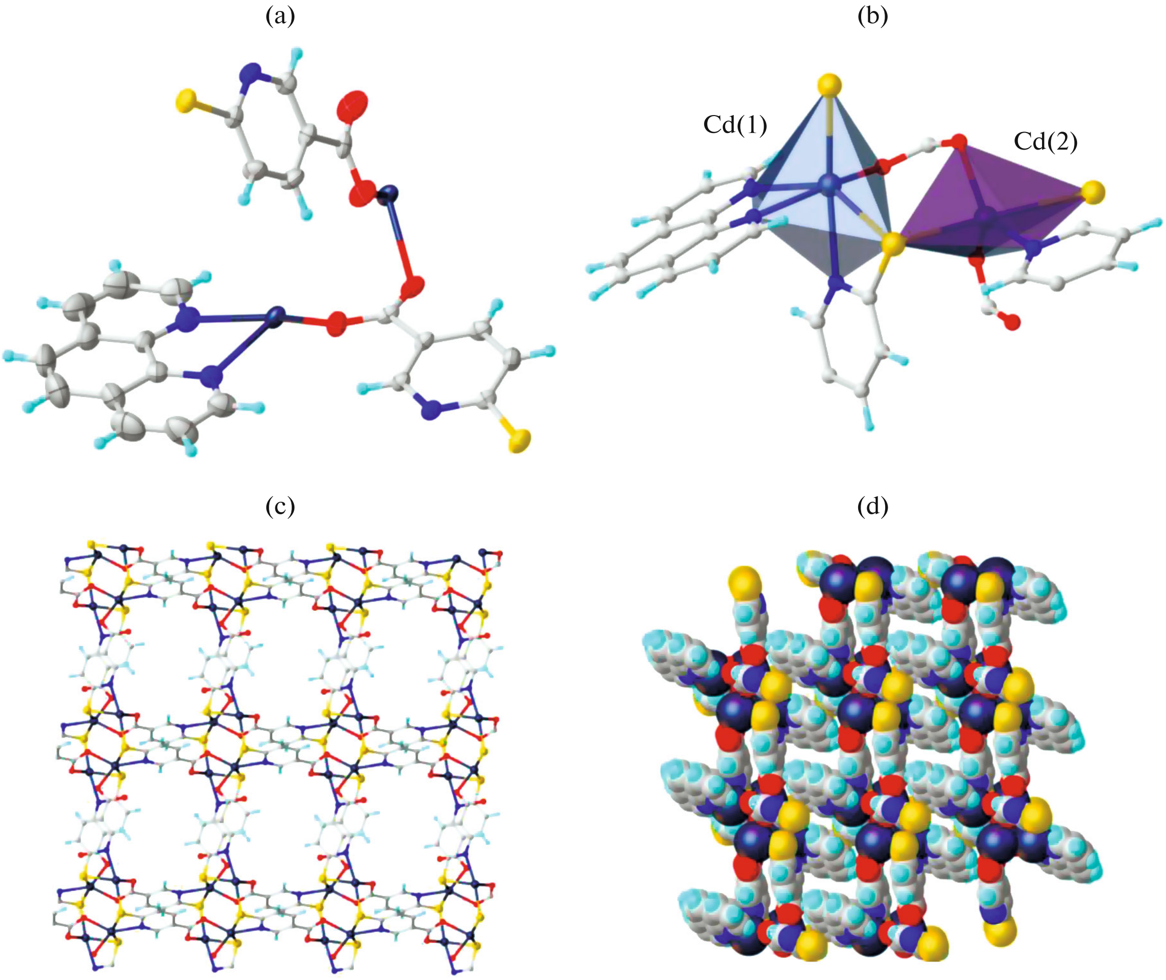

Fig. 1. View of the asymmetric unit of **I** (a); view of coordinating surrounding of Cd^{2+} ions in **I** (b); view of the 2D layered structure of **I** (c); view of packing mode of **I** (d).

Table 2. Growth inhibitory effects of **I**, **II**, H_2Mna, Phen and H_2Ddca on MGC-803, BGC-823, SGC-7901 and AGS cells

Compounds	IC_{50}, μM			
	MGC-803	BGC-823	SGC-7901	AGS
H_2Mna	>100	>100	>100	>100
Phen	>100	>100	>100	>100
H_2Ddca	>100	>100	>100	>100
I	20	28	27	35
II	25	23	30	33

The cytotoxicities of the title compounds **I** and **II** and their corresponding organic ligands H_2Mna, Phen and H_2Ddca against MGC-803, BGC-823, SGC-7901 and AGS 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, they should exert high cytotoxicity against these cells, thus we infered that it did not exert any inhabitation selectivity towards these cell lines. However, after the tumor cells were incubated in the presence of compounds **I** and **II** for 72 h, the IC_{50} values for the compound ranged from 20 to 35 μM, indicating that the two title compounds **I** and **II** exhibited antitumor activity against all of these cell lines in different degrees.

Thus, we can see that compound **I** is a 2D layered structure containing a Cd(2) dimer as the secondary building unit, in which the starting H_2Ddca reagent was unprecedentedly converted into H_2Mna ligands

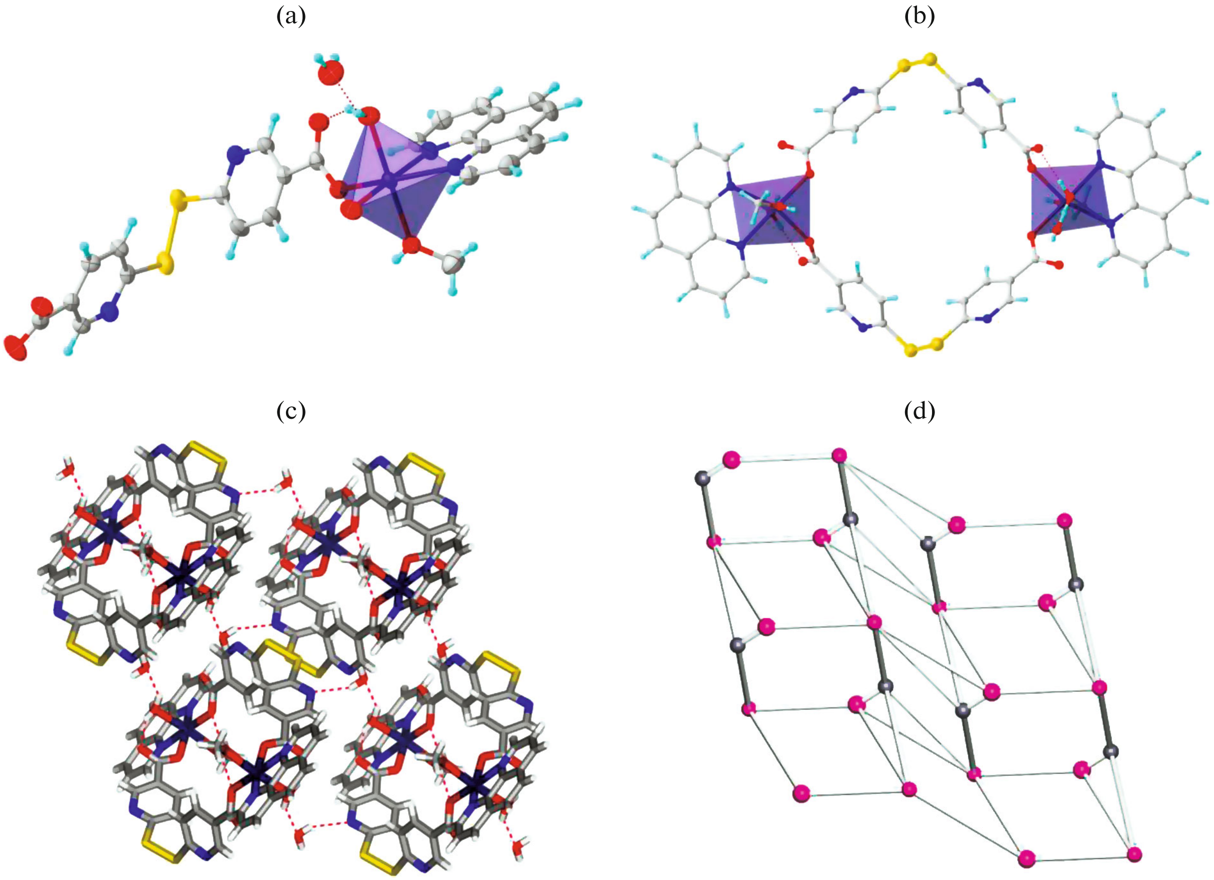

Fig. 2. View of the asymmetric unit of **II** (a); view of metallocyclic motif in **II** (b); view of the H-bonding interactions in **II** (c); view of (4,6)-connected network of **II** (d).

via in situ cleavage of S–S bonds during the course of hydrothermal treatment; compound **II** exhibits a 2D H-bonding layered structure with a (4,6)-connected network whose topology has not been encountered in CP chemistry. In addition, antitumor activity of compounds **I** and **II** has been advanced greatly when their related organic ligands are in coordination with Cd^{2+} or Mn^{2+} ion, respectively.

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