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Crystal Structure and Anti-Kidney Cancer Activity of Two Novel Coordination Polymers $\{[Cu_2(DCTP)_2](H_2O)\}_n$ and $\{[Zn_5(NTB)_4(DMF)_2](NH_2NMe_2)(DMF)_3\}_n$ [1]

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Abstract—Two new coordination polymers, namely $\{[Cu_2(DCTP)_2](H_2O)\}_n$ (**I**) (H_2DCTP = 4'-(3,5-dicarboxyphenyl)-4,2':6',4"-terpyridine) and $\{[Zn_5(NTB)_4(DMF)_2](H_2NMe_2)_2(DMF)_3\}_n$ (**II**) (H_3NTB = 4,4',4"-nitrilotribenzoic acid, DMF = *N*,*N*-dimethylformamide), have been successfully constructed under solvothermal conditions. The structures of two complexes have been successfully determined by single crystal X-ray diffraction (CIF files CCDC nos. 1852377 (**I**) and 1852378 (**II**)). In addition, in vitro antitumor activity of compounds **I** and **II** on four human kidney cancer cells (GRC-1, A-498, ACHN and 786-P) was further determined and the results show that the two compounds showed promising activity.

Keywords: coordination polymer, X-ray diffraction, kidney cancer cell

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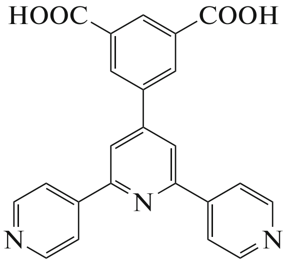
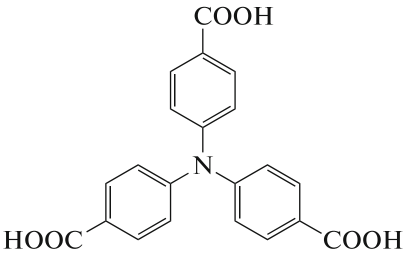
INTRODUCTION

Cancer still remains a threat to human health, figuring among the leading causes of death worldwide [1]. In 2012, cancer was responsible for 8.2 million deaths and it is expected that annual cases will rise from 14 million in 2012 to 22 within the next two decades [2, 3]. In the last years, many efforts have been made to develop new strategies for finding effective ways of treating this disease, which include not only an increase in the understanding of the biological process involved in cancer survival but also the search for more selective and potent chemotherapeutic agents [4, 5].

The design and synthesis of metal-organic coordination network have received significant development over the past decades [6]. Generally, it is important to choose appropriate units to obtain the possible connections between units for the construction of the complexes [7]. Aromatic polyacid ligands have been extensively employed to form complexes due to their excellent coordination capability and greatly influence in the structure of the complexes [8, 9]. In this work, we prepared two new coordination polymer, namely $\{[Cu_2(DCTP)_2](H_2O)\}_n$ (**I**) (H_2DCTP = 4'-(3,5-dicarboxyphenyl)-4,2':6',4"-terpyridine) and $\{[Zn_5(NTB)_4(DMF)_2](H_2NMe_2)_2(DMF)_3\}_n$ (**II**) (H_3NTB = 4,4',4"-nitrilotribenzoic acid, DMF = *N*,*N*-dimethylformamide) under solvothermal conditions and then investigate their in vitro antitumor activity. Schematic representation of the ligands used in this research are given below:



H_2DCTP



H_3NTB

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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 was carried out by an Oxford Xcalibur E diffractometer.

Synthesis complex I. A mixture of H_2DCTP (0.0397 g, 0.1 mmol), $Cu(NO_3)_2 \cdot 6H_2O$ (0.0483 g, 0.2 mmol), H_2O (4 mL) and EtOH (2 mL) was sealed in a Teflon-lined stainless vessel (25 mL) and heated at 160°C for 48 h, and then the vessel was cooled slowly to room temperature at 10°C/min, affording as blue needle like crystals for **I**. The yield was 43% based on the ligand H_2DCTP.

For $C_{23}H_{13}CuN_3O_4$

Anal. calcd., %	C, 59.04	H, 3.02	N, 8.98
Found, %	C, 59.12	H, 3.14	N, 8.69

Synthesis complex II. A mixture of $Zn(NO_3)_2 \cdot 6H_2O$ (14.7 mg, 0.05 mmol), 2,2'-bipyridine (7.5 mg, 0.05 mmol), and H_3NTB (18.7 mg, 0.05 mmol) in DMF–H_2O (6 mL, v/v = 2 : 1) was sealed in a 20 mL Teflon-lined stainless steel vessel at 120°C for 48 h. After cooling to room temperature, light yellow block-shaped crystals suitable for X-ray diffraction were obtained with a yield of 42% (based on H_3NTB).

For $C_{103}H_{99}N_{11}O_{29}Zn_5$

Anal. calcd., %	C, 54.22	H, 4.37	N, 6.75
Found, %	C, 54.67	H, 4.66	N, 6.92

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 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. Selected bond distances and angles are listed in Table 2.

Supplementary material for structures has been deposited with the Cambridge Crystallographic Data Centre (CCDC nos. 1852377 (**I**) and 1852378 (**II**); deposit@ccdc.cam.ac.uk or http://www.ccdc.cam.ac.uk).

Antitumor activity. Four human kidney cancer cells (GRC-1, A-498, ACHN and 786-P) 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 RPMI 1640, 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

Pure crystals of **I** could be obtained by solvothermal treatment of $Cu(NO_3)_2 \cdot 6H_2O$, H_2DCTP in a mixed solvent of H_2O and EtOH at 160°C for 48 h. Single-crystal X-ray diffraction analyses revealed that compound **I** is a 3D twofold interpenetrated framework with a bivalent mononuclear Cu subunits. As shown in Fig. 1a, the asymmetric unit of **I** consists of one Cu^{2+} ion, one $DCTP^{2-}$ anion and half disordered lattice water molecule. The four-coordinated Cu^{2+} ion is completed by two N atoms and two O atoms from four different $DCTP^{2-}$ ligands, resulting in a distorted tetrahedronal $[CuN_2O_2]$ coordination geometry. The Cu(II)–O bond distances range from 1.932(3) to 1.969(3) Å and the Cu(II)–N bond lengths varies from 2.016 to 2.042 Å. As for the $DCTP^{2-}$ ligand, it binds with four Cu^{2+} ions using its two carboxylic groups and two pyridinyl N atoms with two carboxylic groups exhibiting a *trans*-monodentate coordination mode $(\kappa^1\text{-}\kappa^1)\text{-}\mu^1\text{-COO}^-$ (Fig. 1b). The $DCTP^{2-}$ ligand connects with the four coordinated Cu^{2+} ion to afford a diamond-like 3D network with 1D honeycomb-like channels running along the *a* axis (window size 14.3 × 8.24 $Å^2$) which also demonstrates a high solvent-accessible free volume (Fig. 1c), and this net is large enough to accommodate another same net to stabilize the whole framework. There is 1D channel running along the *b* axis which is held by the lattice water molecules. The solvent accessible void for this interpenetrated network is 21.3% as revealed by the PLATON. The network topology of **I** is also investigated by the computer program TOPOS. The Cu(II) subunit is considered as a four-connected node which is linked by four $DCTP^{2-}$ anions, and the whole structure can be simplified as a twofold interpenetrated 4-connected dia net with the point symbol 6^6 and the vertex symbol of (6(2).6(2).6(2).6(2).6(2).6(2)) which

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

Parameter	Value	
	I	**II**
Mr	458.90	2281.87
Crystal system	Triclinic	Monoclinic
Space group	$P\bar{1}$	$P2_1/c$
a, Å	10.2345(7)	14.6611(11)
b, Å	10.8931(11)	23.3118(11)
c, Å	11.6906(10)	15.7765(13)
α, deg	64.013(9)	90
β, deg	82.213(6)	91.104 (3)
γ, deg	72.603(7)	90
V, Å^3	1117.94(18)	5142.7(7)
Z	2	2
ρ_{calcd}, g cm^{-3}	1.363	1.275
μ(MoK_α), mm^{-1}	1.009	1.219
Crystal size, mm	0.32 × 0.26 × 0.14	0.17 × 0.14 × 0.09
θ Range for data collection, deg	2.84–29.206	2.999–26.387
Index ranges hkl	$-13 \le h \le 12$, $-14 \le k \le 13$, $-7 \le l \le 15$	$-18 \le h \le 18$, $-18 \le k \le 29$, $-19 \le l \le 19$
Reflections collected	9046	23580
Unique reflections (R_{int})	5052 (0.0505)	10480 (0.0332)
Reflections with $I > 2\sigma(I)$	3524	8317
GOOF	0.967	1.015
Parameters refined	280	576
Final R indexes ($I > 2\sigma(I)$)	$R_1 = 0.0533$, $wR_2 = 0.1043$	$R_1 = 0.0980$, $wR_2 = 0.2909$
Final R indexes (all data)	$R_1 = 0.0836$, $wR_2 = 0.1160$	$R_1 = 0.1145$, $wR_2 = 0.3090$
Largest diff. peak/hole, e Å^{-3}	0.54/–0.66	2.92/–3.00

belongs to the Class IIa interpenetration mode (Fig. 1d).

Solvothermal reaction of $Zn(NO_3)_2 \cdot 6H_2O$, H_3NTB and 2,2'-Bipy in a mixed solvent of DMF–H_2O system yields light yellow block-shaped crystals of **II**. It should be noted that H_3NTB is insoluble in water at room temperature but quite soluble in some organic solvents, such as DMF and dimethylacetamide (DMA). Compound **II** crystallizes in the shows a 3D framework structure. The asymmetric unit of **II** contains two and a half Zn^{2+} ions (Zn(1) and Zn(2) with full occupancy and Zn(3) with 50% occupancy), two NTB^{3-} ligand and one coordinated DMF molecule (Fig. 2a). As shown in Fig. 2b, the framework of **II** is composed of apentanuclear $Zn_5(CO_2)_8$ cluster serving as the secondary building unit (SBU) which is formed by the connecting of Zn(1), Zn(2), Zn(3), Zn(1*A*) and Zn(2*A*) (symmetry code: (*A*) $1 - x$, $-1/2 + y$, $1/2 - z$) via the eight bridging carboxylic groups. In the $Zn_5(CO_2)_8$ cluster, three Zn^{2+} ions show different coordination surroundings. The Zn(1) atom is four-coordinated by four carboxylate O atoms from four NTB^{3-} ligands, adopting a tetrahedral coordination geometry; the six-coordinate Zn(2) atom has a distorted octahedral coordination geometry completed by six carboxylate O atoms from five NTB^{3-} ligands; Zn(3) atom adopts the same coordination surrounding with Zn(2). The Zn–O bond distances

Table 2. Selected bond lengths (d, Å) and angles (ω, deg) for **I** and **II***

Bond	d, Å	Bond	d, Å
I			
Cu(1)–O(1)	1.981(2)	Cu(1)–N(3)^2	2.033(3)
Cu(1)–O(4)^1	1.979(2)	Cu(1)–N(2)^3	2.011(3)

* Symmetry codes: ^{1} 1 + x, y, z; ^{2} x, 1 + y, –1 + z; ^{3} 1 + x, y, –1 + z.

Bond	d, Å	Bond	d, Å
II			
Zn(1)–O(8)^1	2.246(6)	Zn(2)–O(8)^4	2.369(7)
Zn(1)–O(5)^2	2.265(7)	Zn(2)–O(3)	2.325(7)
Zn(1)–O(4)^3	2.314(8)	Zn(2)–O(9)^5	2.486(8)
Zn(1)–O(1)	2.181(8)	Zn(2)–O(11)	2.345(19)
Zn(2)–O(10)^5	2.299(9)	Zn(2)–O(12)^6	2.294(9)
Zn(3)–O(7)	2.286(7)	Zn(3)–O(6)	2.214(7)
Zn(3)–O(2)^8	2.323(7)	Zn(3)–O(6)^7	2.214(7)
Zn(3)–O(7)^7	2.286(7)	Zn(3)–O(2)^9	2.323(7)

* Symmetry codes: ^{1} 1 – x, 1/2 + y, 1/2 – z; ^{2} x, 3/2 – y, 1/2 + z; ^{3} –x, 1/2 + y, 1/2 – z; ^{4} –1 + x, y, z; ^{5} –1 + x, 3/2 – y, –1/2 + z; ^{6} –x, 1 – y, 1 – z; ^{7} 1 – x, 1 – y, –z; ^{8} 1 – x, –1/2 + y, 1/2 – z; ^{9} x, 3/2 – y, –1/2 + z.

Angle	ω, deg	Angle	ω, deg
I			
O(1)Cu(1)N(3)^1	103.45(10)	O(4)^{3}Cu(1)O(1)	100.74(10)
O(1)Cu(1)N(2)^2	117.58(11)	O(4)^{3}Cu(1)N(3)^1	115.46(11)
O(4)^{3}Cu(1)N(2)^2	102.38(10)	N(2)^{2}Cu(1)N(3)^1	116.60(12)

* Symmetry codes: ^{1} x, 1 + y, –1 + z; ^{2} 1 + x, y, –1 + z; ^{3} 1 + x, y, z.

Angle	ω, deg	Angle	ω, deg
II			
O(8)^{1}Zn(1)O(5)^2	125.0(3)	O(8)^{1}Zn(1)O(4)^3	119.4(3)
O(1)Zn(1)O(8)^1	123.0(4)	O(1)Zn(1)O(4)^3	87.4(3)
O(1)Zn(1)O(5)^2	103.4(4)	O(5)^{2}Zn(1)O(4)^3	87.7(3)
O(8)^{4}Zn(2)O(9)^5	77.3(3)	O(10)^{5}Zn(2)O(3)	135.4(3)
O(3)Zn(2)O(8)^4	79.2(2)	O(10)^{5}Zn(2)O(9)^5	54.0(3)
O(3)Zn(2)O(9)^5	85.0(3)	O(10)^{5}Zn(2)O(11)	88.7(6)
O(3)Zn(2)O(11)	92.9(4)	O(12)^{6}Zn(2)O(8)^4	82.9(3)
O(10)^{5}Zn(2)O(8)^4	104.5(3)	O(12)^{6}Zn(2)O(3)	134.0(4)
O(12)^{6}Zn(2)O(10)^5	90.1(4)	O(12)^{6}Zn(2)O(9)^5	131.4(3)
O(12)^{6}Zn(2)O(11)	95.3(5)	O(11)Zn(2)O(8)^4	166.7(6)
O(7)Zn(3)O(7)^7	180.0	O(7)^{7}Zn(3)O(2)^8	88.3(3)
O(7) Zn(3)O(2)^8	91.7(3)	O(7)Zn(3)O(2)^9	88.3(3)
O(7)^{7}Zn(3)O(2)^9	91.7(3)	O(6)^{7}Zn(3)O(7)^7	93.4(3)
O(6)^{7}Zn(3)O(7)	86.6(3)	O(6)Zn(3)O(7)	93.4(3)
O(6)Zn(3)O(7)^7	86.6(3)	O(6)Zn(3)O(6)^7	180.0
O(6)^{7}Zn(3)O(2)^9	88.3(3)	O(6)Zn(3)O(2)^8	88.3(3)
O(6)^{7}Zn(3)O(2)^8	91.7(3)	O(6)Zn(3)O(2)^9	91.7(3)

* Symmetry codes: ^{1} 1 – x, 1/2 + y, 1/2 – z; ^{2} x, 3/2 – y, 1/2 + z; ^{3} –x, 1/2 + y, 1/2 – z; ^{4} –1 + x, y, z; ^{5} –1 + x, 3/2 – y, –1/2 + z; ^{6} –x, 1 – y, 1 – z; ^{7} 1 – x, 1 – y, –z; ^{8} x, 3/2 – y, –1/2 + z; ^{9} 1 – x, –1/2 + y, 1/2 – z.

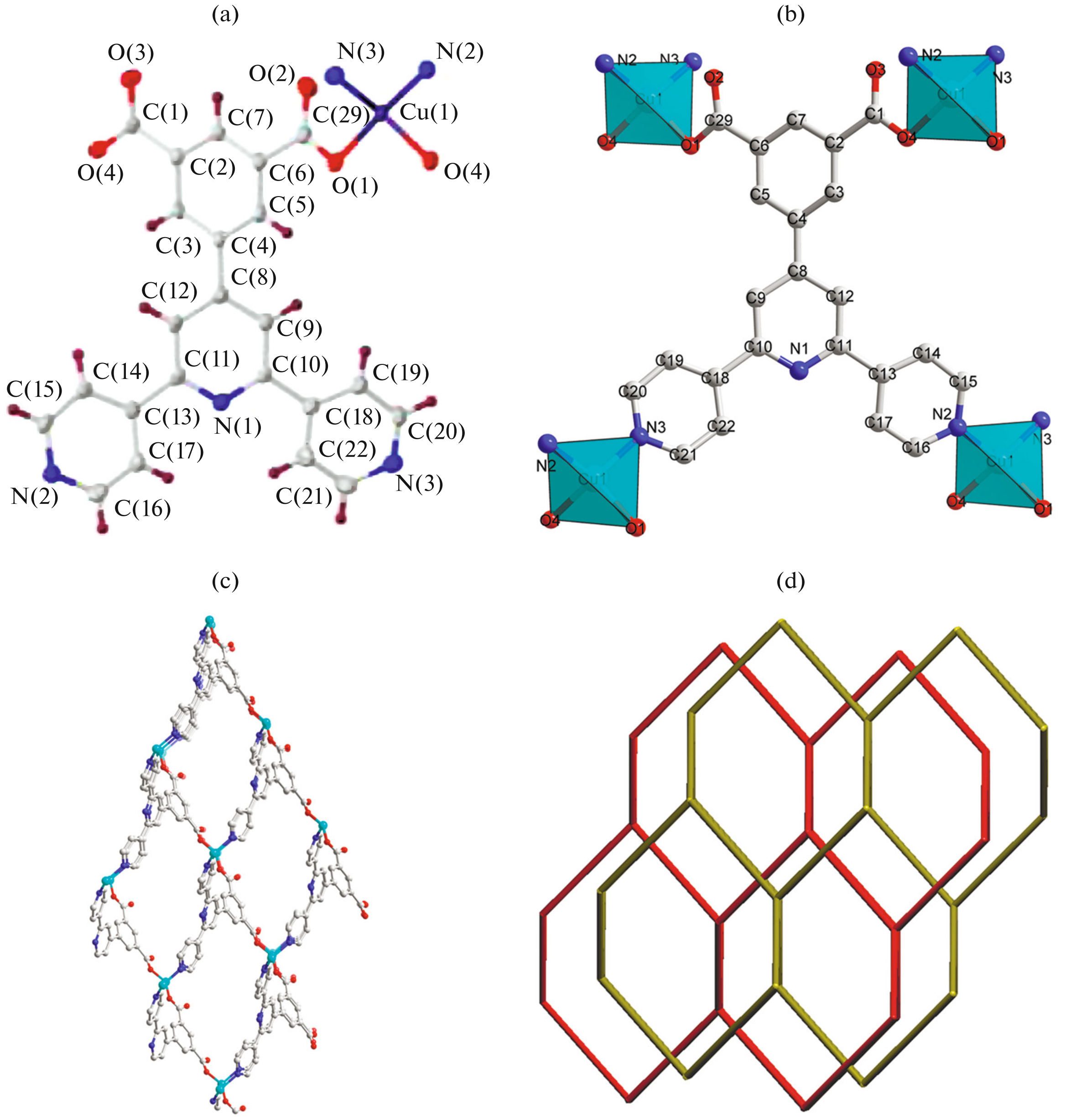

Fig. 1. View of the asymmetric unit of **I** (a), view of the four-connected $DCTP^{2-}$ anion in **I** (b), view of the single framework of **I** (c), view of the twofold interpenetrated 4-connected dia net of **I** (d).

range from 1.983 to 2.381 Å. The $Zn_5(CO_2)_8$ clusters are connected by the NTB^{3-} ligand to afford a 3D network structure (Fig. 2c). The three dimensional space-filling view of the MOF illustrates a porous 1D channel with a cavity dimension, 6.405 × 6.405 Å along the *c* axis which is filled by DMF molecules and $H_2NMe_2^+$ cations (Fig. 2d). From the topological point of view, the whole framework can be simplified as a (3,3,12)-connected 3-nodal net with a Schläfli symbol of $\{4^{16} \cdot 6^{36} \cdot 8^{14}\}\{4^2 \cdot 6\}_2\{4^3\}_2$ if taking the pentanuclear Zn(II) cluster and NTB^{3-} ligand as the 12-connected and 3-connected nodes, respectively.

The cytotoxicities of the title compounds **I** and **II** and their corresponding organic ligands H_2DCTP and H_3NTB against GRC-1, A-498, ACHN and 786-P cell lines were evaluated by MTT assay, and the IC_{50} values derived from the experimental data were concluded in Table 3. It is obvious that the two 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**

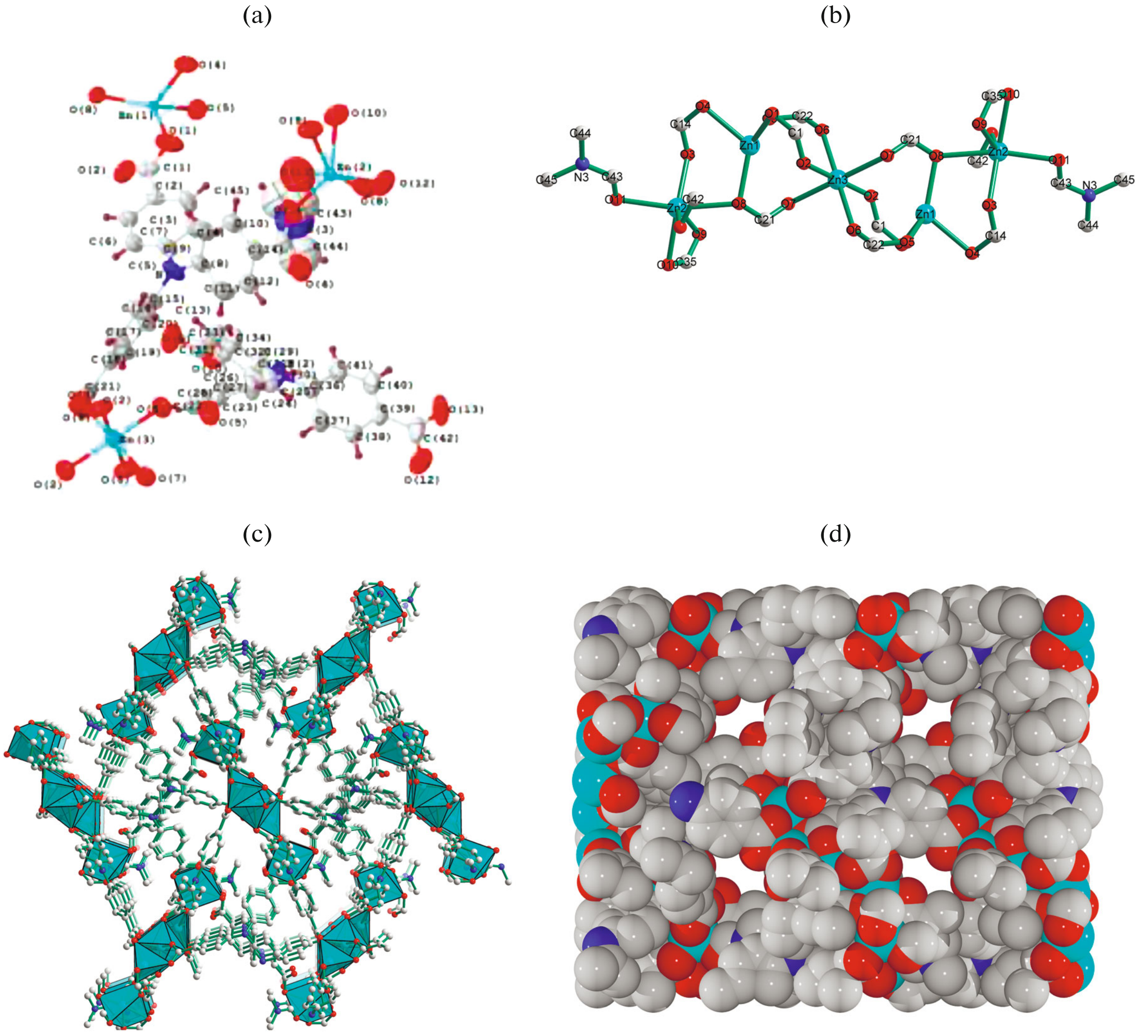

Fig. 2. View of the asymmetric unit of **II** (a), view of the Zn(5) cluster in **II** (b), view of the 3D network of **II** (c), the space filling mode of **II** (d).

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.

The single-crystal X-ray diffraction study reveals that compound **I** is a 3D twofold interpenetrated framework locating, whose framework could be viewed as a twofold interpenetrated 4-connected dia net. The structural analysis of **II** reveals a 3D framework structure based on a pentanuclear $Zn_5(CO_2)_8$ cluster serving as SBU. In addition, antitumor activity of compounds **I** and **II** has been advanced greatly when their related organic ligands are in coordination with Cu and Zn ion, respectively.

Table 3. Growth inhibitory effects of **I**, **II**, H_2DCTP and H_3NTB on GRC-1, A-498, ACHN and 786-P cells

Compound	IC_{50}, μM			
	GRC-1	A-498	ACHN	786-P
H_2DCTP	>100	>100	>100	>100
H_3NTB	>100	>100	>100	>100
I	20	28	27	35
II	25	23	30	33

ACKNOWLEDGMENTS

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