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A new Pb(II)-based coordination polymer constructed by 5-((4-carboxyphenoxy)methyl)benzene-1,3-dioic acid and N-donor co-ligand: crystal structure and anti-glioma activity

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Abstract: A new lead(II)-organic architecture [Pb(HL)(dipyrido[3,2-a:2',3'-c]phenazine (dppz))](H₂O)₂ (**1**) was successfully prepared under hydrothermal conditions by using organic-acid linker 5-((4-carboxyphenoxy)methyl)benzene-1,3-dioic acid (H₃L) and N-donor chelating ligand dppz. The as-prepared complex was characterized by single-crystal X-ray structural analysis, powder X-ray diffraction (PXRD), and elemental analyses, which reveals that complex **1** shows a one-dimensional (1D) chain-like structure that is further extended to the 3D supermolecular network through H-bond and π - π interactions. Complex **1** was transformed to the nanoscale regime (ca. 190 nm) by mechanical grinding to yield the nano-**1**, maintaining its structure and crystallinity. Furthermore, the anticancer activity of the nano-**1** toward the human neuroglioma cells (U251, U87, SHG-44, and A172) was evaluated via the MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide) assay.

Keywords: coordination polymer; MTT assay; nanoscale regime; X-ray diffraction.

Introduction

Though possible remedial measures are available at present to tackle any disease, continuous search in trying to find better and more effective drugs is on the increase worldwide

(Dasari and Bernard Tchounwou, 2014). This is particularly true in the treatment of patients with cancer where they receive cisplatin and its analogs such as carboplatin and oxaliplatin during chemotherapy that has drawbacks, including intrinsic or acquired resistance, and toxicity. So, the efforts to mitigate the drawbacks have prompted chemists to synthesize a variety of analogs, which is valuable not only for providing better anticancer drugs but also for offering useful tools for studying the molecular mechanisms underlying tumor development (Docì et al., 1996; Wang and Lippard, 2005; Zhang et al., 2015).

Coordination polymers received considerable attention because of their intriguing topologies and potential applications as functional materials. So far, a large number of coordination polymers were prepared using various organic ligands, such as carboxylate acids, imidazoles, and pyridine derivatives (Luo et al., 2015; Li et al., 2017a,b; Li and Li, 2018). Because of the versatile coordination modes, aromatic carboxylate linkers are most used to construct coordination polymers, and the typical example is using rigid linear dicarboxylate acids of various lengths to construct a family of isorecticular coordination polymers with pcu topology based on Zn₄O-based SBUs (Han et al., 2015). Compared with rigid aromatic ligands, flexible multicarboxylate linkers enable the formation of frameworks with uncommon or even novel topologies and special properties because of their flexibility and conformational diversity (Shen et al., 2016). Furthermore, great attentions were paid to the study of the interactions between the polypyridyl-based metal coordination complexes and the cancer cells since the last century. Ligands derived from various modifications of 2,2'-bipyridine and 1,10-phenanthroline (phen) were employed to study the ligand effects on the anticancer activities of the coordination complexes. As the variation of the phen ligand, the dipyrdo[3,2-a:2',3'-c]phenazine (dppz)-based metal-organic complexes were seldom studied in the anticancer activities, which might be due to their difficulty in the formation of diversiform coordination complexes for the large rigidity of the ligands and the disadvantageous geometry of the coordination atoms. It was obvious that the employment of organic carboxylate and the N-donor organic ligands could result in novel coordination polymers with interesting structural diversity (Luo et al., 2015; Rancan and Armelao, 2015; Zhou et al.,

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2015). Lead is a toxic metal, has lesser value in medicinal chemistry, but study on the drug activity of such compound would pave the way to understand the structural requirements or the role of a metal ion in drugs (Elbaz et al., 2008; Beqa et al., 2011). In this work, a new lead(II)-organic architecture $[\text{Pb}(\text{HL})(\text{dppz})](\text{H}_2\text{O})_2$ (**1**) was successfully prepared under hydrothermal conditions using organic-acid linker 5-((4-carboxyphenoxy)methyl)benzene-1,3-dioic acid (H_3L) and N-donor chelating ligand dppz. The as-prepared complex was characterized by single-crystal X-ray structural analysis, powder X-ray diffraction (PXRD), and elemental analyses, which reveals that complex **1** shows a one-dimensional (1D) chain-like structure that is further extended to the 3D supermolecular network through H-bond and π - π interactions. Complex **1** was transformed to the nanoscale regime (ca. 190 nm) by mechanical grinding to yield the nano-**1**, maintaining its structure and crystallinity. Furthermore, the anticancer activity of the nano-**1** toward human neuroglioma cells (U251, U87, SHG-44, and A172) was evaluated via the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide (MTT) assay.

Results and discussion

Molecular structure

The colorless crystals of **1** were obtained by the solvothermal reaction of $\text{Pb}(\text{NO}_3)_2$, H_3L , and dppz acid in a mixed solvent of DMF and H_2O . X-ray crystallographic analysis reveals that **1** bears a 1D chain-like network, crystallizing in triclinic P-1 space group. The asymmetric unit of **1** contains one crystallographically independent Pb(II) cation, one HL anion, one dppz ligand, and two disordered lattice water molecules at general positions. As shown in Figure 1, the coordination surrounding the six-coordinated Pb(II)

cation is formed by four carboxylic O atoms from two different HL anions, and the remaining two sites are finished by the two chelating N atoms from the dppz ligand (Figure 2A). The Pb(II)-O bond distances are in the range of 2.371(2)–2.716(3) Å, and the Pb(II)-N bond distances are in the range of 2.564(4)–2.777(3) Å, which are all comparable to those of the reported similar complexes (Yang et al., 2007; Sadeghzadeh and Morsali, 2009; Zhang et al., 2011). Each HL anion coordinates to two Pb(II) cations with one kind of coordination mode ($\mu^1\text{-}\eta^1$; η^1), with two phenyl rings in the ligand that are exactly perpendicular to each other (Figure 2B). In this manner, an infinite 1D chain consisting of HL anions and Pb(II) cations can be obtained. Meanwhile, one dppz ligand is located between two HL ligands by chelating with the Pb(II) ion (Figure 2C). The 1D chain is stabilized by intramolecular π - π interactions between the phenyl group of the dppz ligand with a face-to-face distance of 3.550 Å and a centroid-to-centroid distance of 3.847 Å. Furthermore, there also exists H-bond interactions between the adjacent 1D chains with the $\text{O}\cdots\text{O}$ distance of 2.704 Å ($\text{O-H}\cdots\text{O}$ distance of 1.956 Å) (Figure 2D). The combination of the H-bond interactions and the π - π interactions make the framework of **1** a 3D tightly packed supermolecular structure with no solvent-accessible volume.

To check the purity and homogeneity of the bulk products of **1**, the as-synthesized samples of the compound were measured by X-ray powder diffraction (XRPD) at room temperature. As shown in Figure 3A, the peak positions of the experimental patterns are in good agreement with the simulated ones, which clearly indicate the good purity and homogeneity of the compounds. To produce a stable dispersion in terms of biological perspectives, we used the simple mechanical grinding route to produce the nanosized **1** (noted as **1**-nano). The scanning electron microscope (SEM) reveals that the size of the as-prepared nano-**1** is around 190 nm (Figure 3B). Furthermore, the PXRD reflection of the obtained nanocrystalline **1** corresponds well with the simulated pattern, readily indexing a high crystallinity of the obtained **1** nanomaterial.

Figure 1: Chemical structures for the H_3L and dppz linkers employed in this study.

Antitumor activity

The successful preparation of the nanosized **1** encouraged us to test its cytotoxicity against a panel of human neuroglioma cells (U251, U87, SHG-44, and A172) by MTT assay method. Compounds were dissolved in DMSO, and blank samples containing the same volume of DMSO were taken as controls to identify the activity of the solvent in this cytotoxicity experiment. Cisplatin was used as a positive control to assess the cytotoxicity of the test compounds.

Figure 2: Structural features of compound 1.

(A) View of the atoms that shape the coordination surrounding the Pb(II) ion. (B) View of connecting model of HL ligand in 1. (C) The 1D chain-like network of 1. (D) View of the H-bond interaction and the π - π interaction of 1.

Figure 3: PXRD profiles.

(A) The PXRD patterns for 1. (B) The SEM image of sphere morphology for nanoscale 1.

The results were analyzed by means of cell inhibition expressed as IC_{50} values and they are shown in Figure 4A. The IC_{50} value showed that the nano-1 exhibited significant activity against U251 and U87 cell lines, which is almost equal to the activity of the well-known anticancer drug cisplatin. Interestingly, on comparison of the IC_{50} value of the complex with cisplatin against SHG-44 and A172 cell lines, the inhibitory activity of the nano-1 against SHG-44 and A172 is about six and 10 times higher than that of cisplatin, respectively. The better cytotoxic activity of the nano Pb(II) complex compared to that of cisplatin

against SHG-44 and A172 cell lines may be attributed to the extended planar structure induced by the π - π conjugation resulting from the chelating of the Pb(II) ion with the ligand. Furthermore, the PXRD measurement result shows that the nano-1 maintains its structural integrity after the MTT assay (Figure 3A). In addition, we also performed the filtration experiment to probe the active substrate using the filtrate of nano-1 dispersed in fetal bovine serum (FBS) for 12 h, and the MTT result indicates that the filtrate did not reveal any anticancer activity. All the above results confirm that the coordination complex nano-1 is

Figure 4: MTT assay results.

(A) The cytotoxic activity of nano-1 and cisplatin. (B) The cytotoxic activity of Pb(NO₃)₂ and the organic ligands. (C) The time-dependent cell viability of the A172 cell lines at a concentration of 25 μg/mL nano-1.

responsible for the anticancer activity. It is to be noted that the two organic ligands and Pb(NO₃)₂ did not show any significant activity on all the four cancer cells (IC₅₀ = above 420–640 μM), which confirmed that the chelation of the ligand with the Pb(II) ion is the only responsible factor for the observed cytotoxic properties of the new polymeric Pb(II) complex (Figure 4B). To probe the therapeutic time of nano-1, the time-dependent cell viability of the A172 cell lines was recorded based on the substrate concentration of 25 μg/mL, and the results are plotted in Figure 4C. It could be observed that the therapeutic time is 20 h, which reaches the lowest cell viability of the cancer cells.

Conclusion

In summary, a new lead(II)-organic architecture was successfully prepared under hydrothermal conditions using the organic-acid linker H₃L and N-donor chelating ligand dppz. The as-prepared complex shows a 1D chain-like structure that is further extended to the 3D supermolecular network through H-bond and p-p interactions. Complex **1** was transformed to the nanoscale regime (ca. 190 nm) by

mechanical grinding to yield nano-1, maintaining its structure and crystallinity. Furthermore, the anticancer activity of nano-1 was evaluated via the MTT assay, which indicates its obvious cytotoxicity toward the cancer cells studied.

Experimental

Chemicals and instruments

All reagents were purchased and used without further purification. A PANalytical X'Pert Pro (PANalytical B.V, Almelo, Holland) powder X-ray diffractometer was used to record PXRD patterns. The single-crystal X-ray data was collected using an Agilent Technologies Super Nova (Agilent Technologies, Santa Clara, CA, USA) single-crystal diffractometer. The size and morphology of particles were observed using a Hitachi S4800 SEM (Hitachi, Tokyo, Japan). IR spectra were recorded on a Thermo Fisher Nicolet iS10 spectrometer (Thermo Fisher Scientific, Waltham, MA, USA) as KBr pellets.

Preparation and characterization of [Pb(HL)(dppz)](H₂O)₂ (**1**)

A mixture of H₃L (32 mg, 0.1 mmol), dppz (28 mg, 0.1 mmol), Pb(NO₃)₂ (33 mg, 0.1 mmol), and 6 mL of water was sealed in a 15-mL Teflon

reactor and heated at 160°C for 72 h. After cooling to ambient temperature, colorless crystals of **1** were obtained in 65% yield. Anal. Calc. for $C_{34}H_{24}N_4O_9Pb$ (Mr = 839.79): C, 48.63; H, 2.88; N, 6.67. Found: C, 48.21; H, 2.80; N, 6.93. IR (cm^{-1}): 3063(s), 1604(w), 1511(w), 1455(w), 1410(m), 1380(m), 1314(m), 1161(m), 1124(s), 1101(s), 1071(m), 927(s), 850(m), 791(s).

Preparation and characterization of nanoscale **1**

The downsizing of **1** was prepared according to the reported literature (Kundu et al., 2014). The as-synthesized **1** (50 mg) was ball milled using a Retsch (MM400) operated at 30 Hz for 30 min to obtain a light yellow powder of mechanically ground **1**.

Structural determination of **1** via X-ray diffraction analysis

Single-crystal X-ray diffraction data for compound **1** was performed on Oxford Diffraction Gemini R Ultra diffractometer with graphite-monochromated Mo K α radiation ($\lambda = 0.71073$ Å) at 293 K. The structure was solved and refined by SHELXL-97 program within wingx. The ordered non-hydrogen atoms in each structure were refined with anisotropic displacement parameters, while the hydrogen atoms were placed in idealized positions and allowed to ride on the relevant atoms. The detailed crystallographic data and structure-refinement parameters for compound **1** are summarized in Table 1.

Antitumor activity

Cytotoxicity studies of the compounds along with cisplatin were carried out on human neuroglioma cells (U251, U87, SHG-44, and

A172), which were obtained from the National Centre for Cell Science, Pune, India. Cell viability was carried out using the MTT assay method. The U251, U87, SHG-44, and A172 cells were grown in Eagles minimum essential medium containing 10% FBS. For the screening experiment, the cells were seeded into 96-well plates in 100 mL of the respective medium containing 10% FBS, at a plating density of 10,000 cells/well, and incubated at 37°C, under conditions of 5% CO₂, 95% air, and 100% relative humidity for 24 h prior to the addition of compounds. The compounds were dissolved in DMSO and diluted in the respective medium containing 1% FBS. After 24 h, the medium was replaced with the respective medium with 1% FBS containing the compounds at various concentrations and incubated at 37°C under conditions of 5% CO₂, 95% air, and 100% relative humidity for 48 h. Triplication was maintained, and the medium not containing the compounds served as the control. After 48 h, 10 mL of MTT (5 mg/mL) in phosphate-buffered saline (PBS) was added to each well and incubated at 37°C for 4 h. The medium with MTT was then flicked off, and the formed formazan crystals were dissolved in 100 μ L of DMSO. The absorbance was then measured at 570 nm using a microplate reader. The percentage of cell inhibition was determined using the formula, % inhibition = [mean OD of untreated cells (control)/mean OD of treated cells (control)] $\times$ 100, and a graph was plotted with the percentage of cell inhibition versus concentration. From this, the IC₅₀ value was calculated.

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Table 1: Crystallographic parameters for compound **1**.

Formula	$C_{34}H_{24}N_4O_9Pb$
Mr	804.74
Crystal system	Triclinic
Space group	P-1
a/Å	6.0108 (3)
b/Å	9.8838 (6)
c/Å	24.0821 (14)
$\alpha/^\circ$	96.079 (1)
$\beta/^\circ$	91.895 (2)
$\gamma/^\circ$	105.129 (1)
V/Å ³	1370.60 (13)
Z	2
$D_{calc}/g \cdot cm^{-3}$	1.950
$\mu(Mo K\alpha)/mm^{-1}$	6.218
θ range/ $^\circ$	0.852–25.008
Reflections collected	11211
No. unique data [R(int)]	4739 [0.0405]
No. data with $I \geq 2\sigma(I)$	4186
R_1	0.0379
ωR_2 (all data)	0.1156
CCDC	1848436

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