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Short communication

A new scheme for rational design and synthesis of polyoxovanadate hybrids with high antitumor activities

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ABSTRACT

A new strategy to construct polyoxovanadate hybrids incorporating amino acid esters in mild conditions was presented in this paper. These new hybrids were not only structurally determined by Single Crystal X-Ray diffraction, but also exhibited higher antitumor activities against laryngeal carcinoma, rhabdomyoma, and breast adenocarcinoma tumor cells compared with the traditional commercial medicine 5-fluorouracil. These results would provide a promising lead scaffold for further design and synthesis of potential anticancer agents.

Polyoxometalates (POMs) are a kind of polynuclear metal-oxide clusters with well-defined structures and potential applications in the fields of catalysis, material science and medicine [1,2]. In the field of pharmaceutical science, POMs have already shown versatile biological activities such as antibacterial, anticancer and antiviral properties and have sparked interest in the applications as bio-inorganic drugs [3,4]. Owing to the great efforts done by Yamase, Dianat and other researchers, various POMs or POM-based hybrids with appealing antitumor activities have been discovered [5–7].

Although POMs have been proved to be excellent and easily accessible inorganic drug prototypes, the low biocompatibility and selectivity have hindered the POM-based medicine from practical use. To overcome these drawbacks, studies on the combination of POMs and bioactive molecules like proteins, peptides and amino acids have been attracted increasing attention during the past decades. On the other hand, the synergistic interactions between POMs and the biomolecules may enhance the bioactivity of the parent POMs [8–10]. However, due to the complexity of the POMs and biomolecules, the relevant researches were usually difficult to make progress. Especially in the research on the covalently bonding of POMs and amino acids, only a few successful examples were reported by Yamase, Kamenar, Hasenknopf and Cronin [11–15]. Systematic studies on how the covalently bonding biomolecules affect the bioactivities of POMs are still rare.

Among the various POM complexes, polyoxovanadates (POVs) have fascinating architectures and unique bio-effects such as ATPases inhibiter, insulin-like effects, anticancer and anti-inflammatory [16–18]. It is worthy to combine polyoxovanadates with bioactive molecules towards the practical applications in pharmacy. However, there are very few examples of polyoxovanadate hybrids containing amino acid or peptide species [19–22]. In this communication, we presented a new method for the design and synthesis of hexavanadate hybrids covalently linked to amino acids. Briefly, carboxyl-derivative of Lindqvist-type hexavanadate $[Bu_4N]_2[V_6O_{13}\{(OCH_2)_3CCH_2OOCCH_2CH_2COOH\}_2]$ (compound **1**), which was prepared according to our previous report [23], was selected as the platform of POMs. By amidation of compound **1**, two new hexavanadate derivatives incorporating with different amino acid esters, β-alanine ethyl ester and L-alanine methyl ester, were obtained as $[Bu_4N]_2[V_6O_{13}\{(OCH_2)_3CCH_2OOCCH_2CH_2CONHCH_2CH_2COOCH_2CH_3\}_2]$ (compound **2**) and $[Bu_4N]_2[V_6O_{13}\{(OCH_2)_3CCH_2OOCCH_2CH_2CONHCH(CH_3)COOCH_3\}_2]$ (compound **3**). The synthetic procedure was shown in the Scheme 1. All the three compounds showed inhibition activities against cell proliferation for Human laryngeal carcinoma epithelial (Hep-2), Rhabdomyoma (RD) and Breast adenocarcinoma (MCF-7) cell lines and compounds **2** and **3** exhibited even more excellent activities than traditional commercial medicine 5-fluorouracil (5-FU).

The structures of compounds **2** and **3** have been determined by single crystal X-ray diffraction. Their anion structures were presented in Fig. 1 and the ORTEP drawings viewed along different axis were shown in Figs. S1 and S2. The well-defined inorganic species were known as Lindqvist-type hexavanadates in which two trialkoxoyl ligands occupied the opposite sites of the octahedron. The succinic ligands were attached to the cluster through the ester groups with C—O bond lengths of 1.343 and

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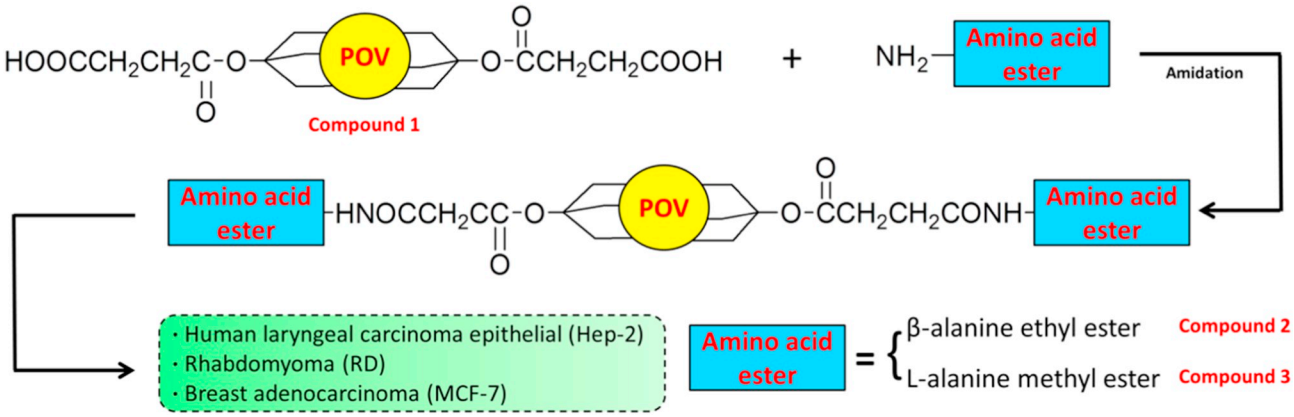

Scheme 1. Synthetic procedure of the novel scheme for the rational design of POV-based amino acid ester hybrids and their antitumor activities.

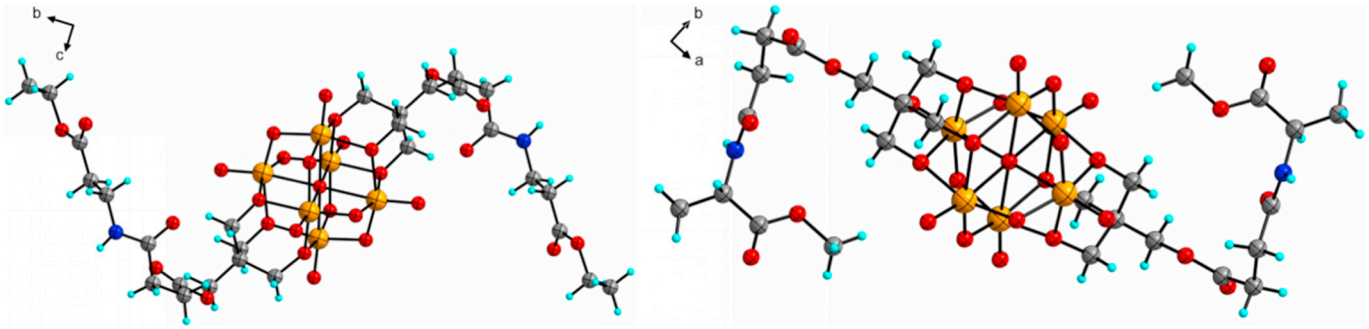

Fig. 1. ORTEP drawings of the anion structures of compounds **2** (left) and **3** (right). Red sphere: O; light blue sphere: H; grey sphere: C; blue sphere: N; orange sphere: V.

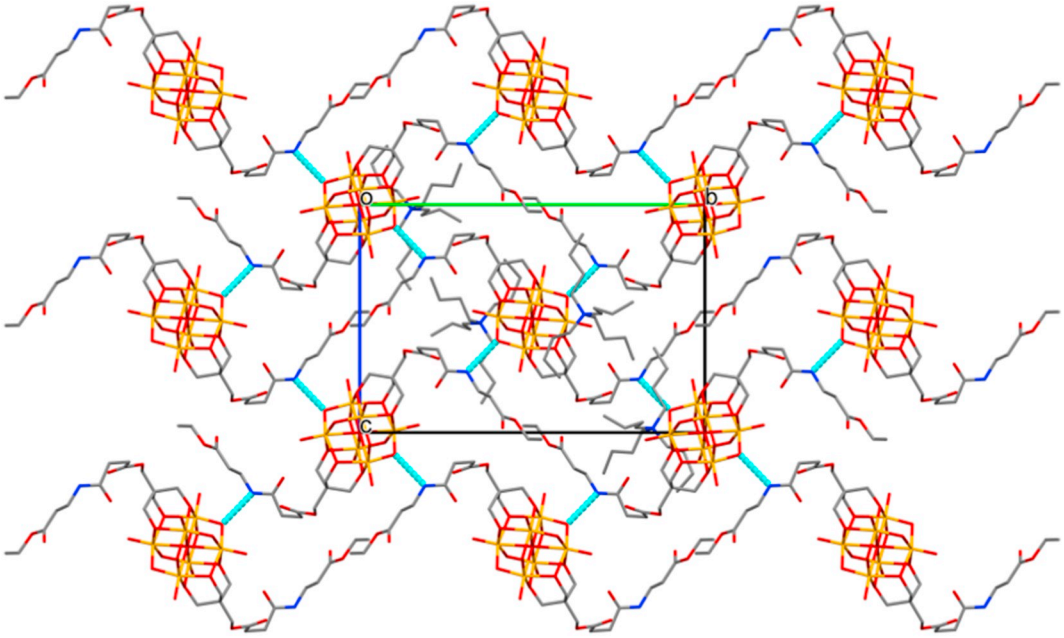

Fig. 2. 2D network formation *via* N—H···O hydrogen bonding interactions in the crystal of compound **2** (orange sticks: V; red sticks: O; grey sticks: C; blue sticks: N; hydrogen atoms were purified for clarity).

1.433 Å in compounds **2** and **3**, while the other acryl group was linked to the amino acid esters *via* amidic bonds in length of 1.338 and 1.324 Å, respectively. Moreover, the crystal packing of compound **2** and **3** showed a novel 2D network *via* weak hydrogen-bonding interactions between the amido N—H and the bridging oxygen of the cluster with the distance of 2.836 and 3.038 Å, respectively (Figs. 2, S3 and S4).

The FT-IR spectra of compounds **2**–**3** in the range of 4000–500 cm^{-1} were shown in Figs. S5 and S6. The very strong and obvious band near 950 cm^{-1} was assigned to the vibration of V═O in both of the compounds. The ester group (between the inorganic core and succinic acid ligands) gave apparent signals at 1735 and 1737 cm^{-1} while the carbonyl in the acylamino (between succinic acid ligands and amino acids) gave

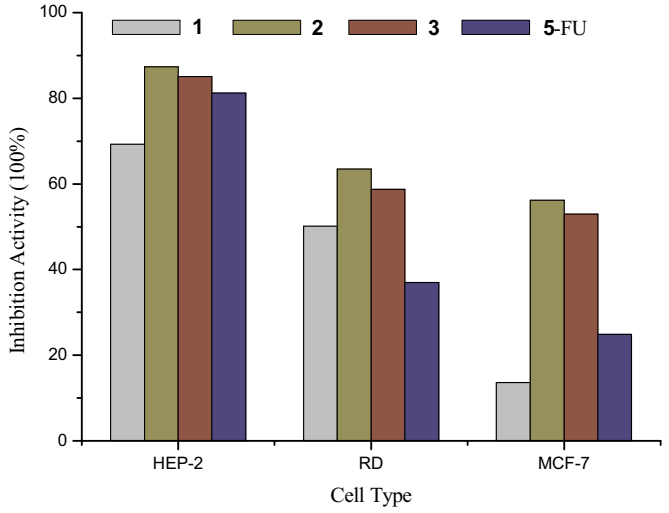

Fig. 3. Inhibition activities against cell proliferation for compounds **1–3** and 5-fluorouracil at 50 μM.

signals at 1667 and 1671 cm^{-1} in compounds **2** and **3**, respectively. In addition, ^{1}H NMR spectra of compounds **2–3** were presented in Figs. S7 and S8, which showed clearly resolved signals for all protons in both of the two hybrids. High solution electrospray mass spectra (HR-ESI-MS) exhibited *m/z* peak at 1178.87485 for compound **2** and 1150.84333 for compound **3** (Figs. **S11** and **S12**), which corresponded to the anions of $H[V_6O_{13}\{(OCH_2)_3CCH_2OOCCH_2CH_2CONHCH_2CH_2COOCH_2CH_3\}_2]^-$ (theoretical value 1178.87456) and 1150.84333 $H[V_6O_{13}\{(OCH_2)_3CCH_2OOCCH_2CH_2CONHCH(CH_3)COOCH_3\}_2]^-$ (theoretical value 1150.84327), respectively. These results also supported the presumed structures, indicated that such designs and syntheses have successfully introduced the amino ester groups to the POV hybrids covalently and the topologic structures of inorganic clusters were not damaged after reaction.

Compounds **1–3** have been subjected to *in vitro* cytotoxic effects evaluation against laryngeal carcinoma (Hep-2), rhabdomyoma (RD) and breast adenocarcinoma (MCF-7) cell lines by the standard MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) assay using 5-fluorouracil (5-FU) as a positive control. The preliminary antitumor results are summarized in Fig. 3. Both of compounds **2** and **3** displayed higher inhibitory activities against Hep-2, RD and MCF-7 cells compared with compound **1** and 5-FU. Notably, in MCF-7 cells, the inhibitory activities of compound **2** (56.19%) and compound **3** (52.96%) were twice more than that of compound **1** (13.66%) and 5-FU (24.87%). The results indicated that these novel amino acids-functional POMs might be used as a high potential active scaffold for optimization of anticancer agents.

In order to further investigate the potential activities, the IC_{50} values for compounds **1–3** were evaluated and presented in Table S3. The IC_{50} value represented the drug concentration required to inhibit cell growth by 50%. The results further testified that compounds **2** and **3** exhibited better anticancer activities than the reference drug 5-FU under the same conditions. Besides, compound **2** exhibited the strongest inhibitory effects against Hep-2 and MCF-7 cells, with IC_{50} values of 11.40 and 53.01 μM respectively. From these results, it can be demonstrated that the covalently incorporation of amino acid species could improve the bioactivities of POVs.

In conclusion, this communication reported two novel POV hybrids covalently bonded to amino acid esters by a new and convenient scheme under mild conditions. Interestingly, these hybrid materials exhibited enhanced antitumor activity against three kinds of human tumor cells compared to their parent POV platform and even better than traditional commercial drug 5-FU. This work would provide a new vision to the rational design and synthesis of POV-based drugs.

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Appendix A. Supplementary data

Details about the experiments, general characterizations, crystal data and FT-IR, ^{1}H NMR, ESI-MS spectra were provided in Electric Supporting Information. CCDC numbers 1814827 and 1814833 contains the supplementary crystallographic data for compounds **2** and **3**, respectively. Supplementary data to this article can be found online at https://doi.org/10.1016/j.jinorgbio.2019.01.013.

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