

Covalent molecular hybridization of heterocyclic hydrazides with hexamolybdates: Structural, electronic, and antitubercular properties

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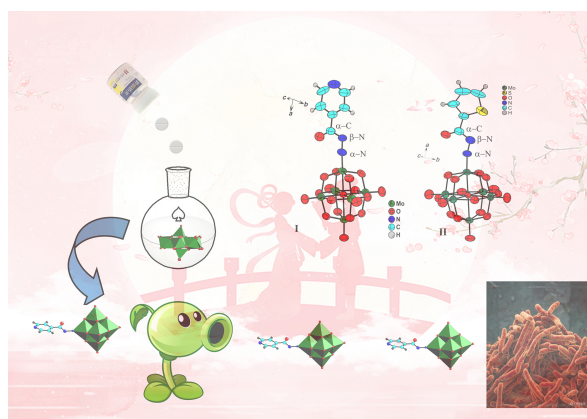


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ABSTRACT: To explore new organically derivatized polyoxometalates (POMs), three heterocyclic hydrazide-functionalized hexamolybdates—**1**: $(\text{TBA})_3[\text{Mo}_6\text{O}_{18}(=\text{N}=\text{NCOC}_5\text{H}_4\text{N})]$, **2**: $(\text{TBA})_3[\text{Mo}_6\text{O}_{18}(=\text{N}=\text{NCOC}_4\text{H}_3\text{S})]$, and **3**: $(\text{TBA})_3[\text{Mo}_6\text{O}_{18}(=\text{N}=\text{NCOC}_4\text{H}_3\text{N}_2)]$; (TBA = tetrabutylammonium)—were synthesized by refluxing the corresponding heterocyclic hydrazides with octamolybdates in dry acetonitrile. Their structures were elucidated by single-crystal X-ray diffraction, Fourier transform infrared spectroscopy, ultraviolet–visible spectroscopy, electrospray ionization mass spectrometry, and ^1H nuclear magnetic resonance spectroscopy. In all compounds, one terminal oxo atom of the hexamolybdate is replaced by a heterocyclic hydrazide via a $\text{Mo}=\text{N}$ multiple bond. Compound **1** contains three conformational isomers of $[\text{Mo}_6\text{O}_{18}(=\text{N}=\text{NCOC}_5\text{H}_4\text{N})]^{3-}$ with approximate C_s or C_1 symmetry, whereas compound **2** contains a single $[\text{Mo}_6\text{O}_{18}(=\text{N}=\text{NCOC}_4\text{H}_3\text{S})]^{3-}$ anion with C_s approximate symmetry. Antitubercular activity assays show that all three compounds exhibit enhanced inhibitory activity compared with hexamolybdate and the thiophene-2-carbohydrazide (**L2**) ligand, although their activity remains lower than that of isoniazid (**L1**) and pyrazine-2-carbohydrazide (**L3**). Given their large molecular weights, the molar inhibitory activities of compounds **1–3** are close to or superior to the corresponding ligands alone. Overall, this work demonstrates that molecular hybridization of organic drug molecules with POMs via covalent bonds provides a promising strategy for developing POM-based agents with enhanced biological activity.



KEYWORDS: hydrazide, polyoxometalates, molecular hybridization, antitubercular

1 Introduction

Tuberculosis (TB)—an infectious disease caused by mycobacteria belonging to the *Mycobacterium tuberculosis* complex [1]—accounted for an estimated 10.7 million incident cases and 1.23 million deaths globally in 2024 [2]. Isoniazid (INH), also known as Rimifon, is a heterocyclic hydrazide and remains a key first-line antitubercular agent due to its potent antimycobacterial activity [3]. However, the increasing prevalence

of drug-resistant *Mycobacterium tuberculosis* strains has created an urgent need for the development of new antitubercular drugs [4]. One promising and straightforward strategy is the molecular hybridization (MH) of INH to generate novel derivatives with enhanced therapeutic potential [5].

MH has become an important strategy in modern drug discovery, aiming to reduce toxicity, increase biocompatibility, strengthen antiviral or antitumor targeting, and increase overall pharmacological activity, while also enabling the development of new therapeutic agents [6]. Pasqualoto [7] and Martins et al. systematically studied functionalized INH derivatives using quantitative structure–activity relationship analysis [8]. To date, several valuable INH derivatives with improved antitubercular activity or low toxicity have been reported [5]. For example, aconiazide—a well-known INH derivative developed in the search for new antitubercular agents—is a hybrid molecule of INH and 2-formylphenoxyacetic acid that exhibits low toxicity [9]. Another

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compound, LL3858 (also known as sudoterb), has demonstrated significant *in vitro* and *in vivo* activity against sensitive and resistant strains of *Mycobacterium tuberculosis* [10]. However, the MH of INH with inorganic molecules remains relatively underexplored. In this context, MH of hydrazides with polyoxometalates (POMs) may offer a promising approach for developing inorganic cluster-based INH hybrids as potential antitubercular agents [11].

POMs are a class of discrete metal oxide clusters primarily composed of early transition metals [12–15]. They have been widely used as fluorescence probes for drugs like ciprofloxacin [16] and exhibit promising anticancer, antibacterial, and antiviral activities [17]. Notably, $[\text{NH}_3\text{Pri}]_6[\text{Mo}_7\text{O}_{24}]$ (PM8) has demonstrated promising antitumor activity against CO-4 human colon cancer and OAT human lung cancer xenografts [18]. In addition, ammonium-5-tungsto-2-antimonate (HPA-23) has shown effective antiviral activity against murine leukemia Virus (MLV), rabies virus (RV), rhabdovirus, and Epstein-Barr virus (EBV) at doses that are nontoxic to cells [19]. Despite these advantages, the large molecular weight and associated tissue toxicity of POMs have limited their clinical application. Therefore, a key challenge in POM-based therapeutics is increasing biological activity while reducing toxicity [20].

The organic functionalization of POMs through covalent bonding—i.e., substitution of terminal or bridging oxygen atoms—provides a powerful means of tuning their structures and properties [21]. It also offers an efficient strategy for MH of POMs with small-molecule organic drugs. Covalent linkage not only adds value to organic-functionalized POMs through the so-called “bond add value” but may also generate new properties through the synergistic interactions between POMs and organic components [22]. Cronin et al. reported that cells can selectively adhere to Anderson-type POM-based organic–inorganic hybrid materials [23].

To date, organically derivatized hexamolybdate containing Mo–N multiple bonds have been reported by Errington [24], Proust [25], Maatta [26], Peng [27], and our group [28]. We have previously described a series of benzoyldiazene-functionalized hexamolybdates with enhanced antitumor activity [29]. More recently, we found that iodobenzoic hydrazide-functionalized hexamolybdates exhibit enhanced inhibitory activity against Cocksackievirus B3 [30]. These findings suggest that combining POMs and hydrazides through covalent bonds may yield organically functionalized POMs with antitubercular activity. However, the antitubercular activity of POMs and organically derivatized POMs remains largely unexplored.

Herein, we report three organically derivatized hexamolybdates— $(\text{Bu}_4\text{N})_3[\text{Mo}_6\text{O}_{18}(=\text{N}=\text{NCOC}_5\text{H}_4\text{N})]$ (**1**), $(\text{Bu}_4\text{N})_3[\text{Mo}_6\text{O}_{18}(=\text{N}=\text{NCOC}_4\text{H}_3\text{S})]$ (**2**), and $(\text{Bu}_4\text{N})_3[\text{Mo}_6\text{O}_{18}(=\text{N}=\text{N}-\text{COC}_4\text{H}_3\text{N}_2)]$ (**3**)—prepared by the reflux reaction of an octamolybdate with INH (**L1**), thiophene-2-carbohydrazide (**L2**), or pyrazine-2-carbohydrazide (**L3**) in an anhydrous solvent. We characterized the hexamolybdate products using single-crystal X-ray diffraction (XRD), Fourier transform infrared spectroscopy (FTIR), Ultraviolet–visible spectroscopy (UV–Vis), ^1H nuclear magnetic resonance spectroscopy (NMR), electrospray ionization mass spectrometry (ESI-MS), and other techniques. All three compounds exhibit antitubercular activity. To the best of our knowledge, this is the first report of heterocyclic molecules being covalently anchored to the surface of POMs for the exploration of antitubercular activity. This study may provide a new avenue for developing POM-based

medicines through MH with organic drug molecules.

2 Experimental

2.1 Synthesis of compounds 1–3

Mixtures of $(\text{Bu}_4\text{N})_4[\text{Mo}_8\text{O}_{26}]$ (**5**) (2.16 g, 1.00 mmol), dicyclohexylcarbodiimide (DCC) (0.43 g, 2.10 mmol), and corresponding hydrazide—1.33 mmol, 0.18 g **L1** for **1**; 0.19 g **L2** for **2**; 0.18 g **L3** for **3**—were dissolved in anhydrous acetonitrile (10 mL) in dry round-bottom flasks. The resulting solution was refluxed for 6 h under stirring and cooled to room temperature naturally. The black solution was filtered to remove the white precipitate of dicyclohexylurea (DCU), and the resulting black-red filtrate was diffused with ethyl ether. After two weeks, a large number of black block crystals were obtained.

For compound **1**, the yield was 0.17 g (10%). Elemental analysis for $\text{C}_{54}\text{H}_{112}\text{Mo}_6\text{N}_6\text{O}_{19}$: calculated (%) C 37.59, H 6.54, N 4.87; found (%) C 37.58, H 6.54, N 4.75. ^1H NMR (300 MHz, DMSO- d_6 , 300 K): δ = 0.94 (t, 36H, CH_3 -, $[\text{Bu}_4\text{N}]^+$), 1.33 (m, 24H, $-\text{CH}_2-$), 1.58 (m, 24H, $-\text{CH}_2-$, $[\text{Bu}_4\text{N}]^+$), 3.17 (t, 24H, NCH_2 -, $[\text{Bu}_4\text{N}]^+$), 7.63 (d, 2H, ArH), 8.54 (d, 2H, ArH). FTIR (KBr pellet, cm^{-1}): 2961(s), 2874(s), 1592(m), 1538(m), 1483(s), 1382(m), 1343(m), 1314(m), 1275(s), 1205(w), 1153(w), 1108(w), 1060(w), 1028(w), 967(s, shoulder), 946(vs), 883(w), 793(vs), 769(s, shoulder), 695(w), 577(w). UV–Vis (MeCN): λ_{max} = 386 nm.

For compound **2**, the yield was 0.44 g (25%). Elemental analysis for $\text{C}_{53}\text{H}_{111}\text{Mo}_6\text{N}_5\text{O}_{19}\text{S}$: calculated (%) C 36.79, H 6.47, N 4.05; found (%) C 36.63, H 6.42, N 3.93. ^1H NMR (300 MHz, DMSO- d_6 , 300 K): δ = 0.88 (t, 36H, CH_3 -, $[\text{Bu}_4\text{N}]^+$), 1.28 (m, 24H, $-\text{CH}_2-$, $[\text{Bu}_4\text{N}]^+$), 1.52 (m, 24H, $-\text{CH}_2-$, $[\text{Bu}_4\text{N}]^+$), 3.15 (t, 24H, NCH_2 -, $[\text{Bu}_4\text{N}]^+$), 6.99 (s, 1H, ArH), 7.37 (s, 1H, ArH), 7.41 (d, 1H, ArH). FTIR (KBr, cm^{-1}): 2961(s), 2874(s), 1583(s), 1483(s), 1367(w), 1344(m), 1254(s), 1214(m), 1152(w), 1088(w), 1068(w), 1025(w), 964(s, shoulder), 939(vs), 884(w), 791(vs), 767(s, shoulder), 603(w). UV–Vis (MeCN): λ_{max} = 385 nm.

For compound **3**, the yield was 0.17 g (10%). Elemental analysis for $\text{C}_{53}\text{H}_{111}\text{Mo}_6\text{N}_7\text{O}_{19}$: calculated (%) C 36.88, H 6.48, N 5.68; found (%) C 36.73, H 6.44, N 5.73. ^1H NMR (300 MHz, DMSO- d_6 , 300 K): δ = 0.93 (t, 36H, CH_3 -, $[\text{Bu}_4\text{N}]^+$), 1.31 (m, 24H, $-\text{CH}_2-$), 1.57 (m, 24H, $-\text{CH}_2-$, $[\text{Bu}_4\text{N}]^+$), 3.17 (t, 24H, NCH_2 -, $[\text{Bu}_4\text{N}]^+$), 8.58 (d, 2H, ArH), 8.92 (d, 2H, ArH). FTIR (KBr pellet, cm^{-1}): 2961(s), 2874(s), 1584(w), 1557(w), 1483(s), 1380(m), 1346(m), 1297(m), 1261(w), 1205(w), 1163(w), 1120(w), 1047(w), 1016(w), 968(s, shoulder), 945(vs), 883(w), 791(vs), 767(s, shoulder), 667(w), 584(w). UV–Vis (MeCN): λ_{max} = 389 nm.

2.2 Antitubercular test

The minimum inhibitory concentration (MIC) of the target compounds against *Mycobacterium tuberculosis* H37Rv was determined by the agar proportion method using Middlebrook 7H10 agar medium. Two-fold serial dilutions of each test compound were prepared in 7H10 medium. A bacterial suspension of H37Rv was adjusted to a 1.0 McFarland standard (equivalent to ~ 1 mg/mL) and then further diluted to 10^{-3} mg/mL. One loopful (0.01 mL) of the diluted inoculum was streaked onto both drug-containing and drug-free control plates. All plates were incubated at 37 °C for up to 4 weeks. The MIC was defined as the lowest concentration of the test compound required to inhibit at least 99% of visible bacterial growth relative to the drug-free control. All

assays were performed in triplicate and confirmed in at least two independent experiments.

2.3 In vitro cytotoxicity assay

The *in vitro* cytotoxicity of compounds 1–3, hexamolybdates (4), and octamolybdate against Vero cell lines was evaluated using the CCK-8 assay [31]. Briefly, the compounds were first dissolved in dimethyl sulfoxide (DMSO, Sigma Aldrich) and then diluted with Dulbecco's modified Eagle's medium (HyClone) containing 2% fetal calf serum for testing. The final DMSO concentration did not exceed 0.05%, and the same concentration of DMSO was used in the control wells. Vero cells (African green monkey kidney epithelial cells) were seeded in 96-well plates (Corning Costar) at a density of 2×10^4 cells per well and cultured to subconfluence. After removal of the growth medium, cells were exposed to serial concentrations of each compound (400, 200, 100, 50, 25, 12.5 $\mu\text{g/mL}$), with four replicates per concentration. The plates were incubated at 37 °C in a humidified atmosphere containing 5% CO_2 . After 48 h of exposure, cell viability was assessed by adding 10 μL of CCK-8 reagent to each well, incubating in a culture incubator for 1–4 h until the negative control turned distinctly yellow, and measuring the optical density at a wavelength of 450 nm using a microplate reader. The cell viability was then calculated using the formula: $\text{Cell viability\%} = [(A_{\text{treatment}} - A_{\text{blank}})/(A_{\text{control}} - A_{\text{blank}})] \times 100\%$. All data were analyzed using SPSS software, and the 50% cytotoxic concentrations (CC_{50}) of each compound were determined using a single cell line. All assays were performed in triplicate across three independent experiments; the results are presented as mean $\pm$ SD.

2.4 X-ray crystallographic analyses

Suitable crystals were mounted on glass fibers and quickly transferred to the diffractometer. XRD data of 1 and 2 were collected on a Rigaku RAXIS-SPIDER IP diffractometer using graphite-monochromatized Mo $K\alpha$ radiation ($\lambda = 0.71073$ Å) at room temperature (293 ± 2 K). Data collection and reduction, cell refinement, and empirical absorption correction were performed using the Rigaku RAPID AUTO software package (Rigaku, 1998, Ver2.30). The structures of all compounds were solved by direct or heavy atom methods using SHELXT [32] and refined by the full-matrix least-squares refinement on F^2 using SHELXL-2018 [33]. All non-hydrogen atoms, except for some disordered atoms, were refined anisotropically. All calculations were carried out using OLEX1.5 [34]. Table S1 in the Electronic Supplementary Material (ESM) summarizes the crystallographic data and structural refinement details for both compounds.

3 Results and discussions

To date, the substitution of oxygen ligands in hexamolybdate by nitrogen has been successfully used to obtain imido [21] and hydrazine derivatives [35]. However, no heterocyclic compound-functionalized POMs have been reported. We attempted to functionalize POMs using heterocyclic amines as organic ligands, but only azo compounds were obtained (POMs played only a catalytic role) [36]. The lower basicity of the heterocyclic ligands may reduce their reactivity. In reactions between heterocyclic hydrazides and octamolybdate, the solution turned red rapidly upon addition of the reactants to dry acetonitrile. As the temperature increased, the solution color changed from red to black-

red. The target compounds were obtained after refluxing for 6 h. However, when the reaction time was extended to 20 h, hexamolybdate and octamolybdate were obtained instead.

Single-crystal XRD was used to determine the molecular structure of compounds 1 and 2 (Fig. 1), whereas the crystal data of compound 3 could not be collected because of poor diffraction quality. Compound 1 crystallizes in the monoclinic system with the noncentrosymmetric space group $P2_1$; its asymmetric unit contains three hybrid anion clusters of $[\text{Mo}_6\text{O}_{18}(=\text{N}=\text{NCOC}_5\text{H}_4\text{N})]^{3-}$ and nine tetrabutylammonium (TBA) cations. Compound 2 also belongs to the monoclinic system but crystallizes in the centrosymmetric space group $P2_1/n$; its asymmetric unit contains one hybrid anion cluster of $[\text{Mo}_6\text{O}_{18}(=\text{N}=\text{NCOC}_4\text{H}_3\text{N})]^{3-}$ and three TBA cations. In both compounds, the hexamolybdate core adopts the classical Lindqvist structure, consisting of six octahedrally coordinated molybdenum centers linked by one μ_6 -oxygen atom, twelve bridging oxygen atoms, and six terminal O/N ligands, forming a spherical metal-oxide cluster. The pyridinyldiazenido and thiophenyldiazenido ligands each replace one terminal oxygen atom, giving rise to monosubstituted hexamolybdate derivatives with covalent Mo–N multiple bonds. As in aryldiazenido-functionalized hexamolybdates [35], the hybrid anions in compounds 1 and 2 carry a -3 negative charge due to deprotonation at the β -N atom.

The three $[\text{Mo}_6\text{O}_{18}(=\text{N}=\text{NCOC}_5\text{H}_4\text{N})]^{3-}$ clusters in compound 1 differ primarily in the dihedral angle between the pyridine ring and the Mo_4O_4 plane of the Lindqvist cluster (Fig. S1 in the ESM): 46.8° for cluster A, 16.2° for cluster B, and 5.5° for cluster C. Clusters A and C adopt approximate C_s symmetry, with dihedral angles close to 45° and 90° , respectively. Contrastingly, the dihedral angle of cluster B reduces its symmetry to C_1 . These different dihedral angles give rise to three conformational isomers, which also reduces the likelihood of anion clusters crystallizing in a higher symmetric space group; this is likely responsible for the crystallization of compound 1 in a noncentrosymmetric space group. In compound 2, the dihedral angle between the thiophene ring and the Mo_4O_4 plane is 41.4° (close to 45°), suggesting approximate C_s symmetry for $[\text{Mo}_6\text{O}_{18}(=\text{N}=\text{NCOC}_4\text{H}_3\text{N})]^{3-}$. Overall, the mono-substitution of hexamolybdates reduces their symmetry from O_h to C_s or C_1 .

The Mo–N bond lengths in both compounds (1.736(6)–1.742(7) Å for 1, 1.747(2) Å for 2) are slightly shorter than those in hydrazine derivatives (1.739–1.768 Å) and slightly longer than those in imido derivatives (1.702–1.750 Å) of hexamolybdate (Table S2 in the ESM). The Mo–N–N bond angles are close to linear

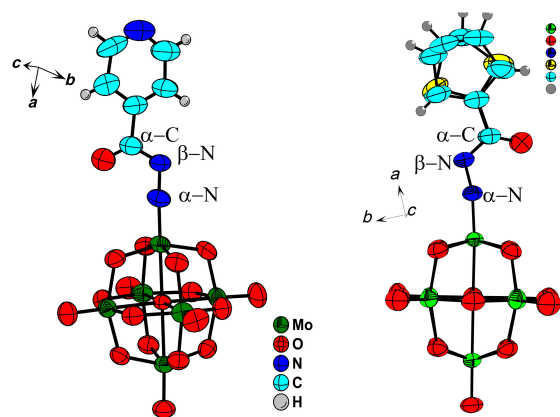


Figure 1 ORTEP drawings of the anions in 1 and 2 with ellipsoid probabilities of 50%.

(172.8(4)°–174.4(4)° for **1**; 168.3(3)° for **2**), indicating that α -N adopts a typical sp -hybridized geometry. The N–N bond lengths and N–N–C bond angles (Table S1 in the ESM) support the double-bond character of N–N and the sp^2 -hybridized character of the β -N atom. Moreover, the C–N bond lengths in both compounds are shorter than a typical C–N single bond and close to a C–N double bond, confirming strong electron delocalization between the ligands and hexamolybdate (1.333(9)–1.368(8) Å in **1**; 1.320(7) Å in **2**).

In the FTIR spectra, the peak at 952 cm^{-1} for hexamolybdate corresponds to the stretching vibration of the $\text{Mo}=\text{O}_t$ bond (Fig. 2). When one terminal oxygen atom of hexamolybdate is substituted by a hydrazide ligand, the $\text{Mo}=\text{O}_t$ stretching vibration peaks in the FTIR spectra split into a shoulder peak at $\sim 968 \text{ cm}^{-1}$ and a strong peak at $\sim 946 \text{ cm}^{-1}$; the former is attributable to the vibration of $\text{Mo}=\text{N}$, whereas the latter is ascribed to the stretching vibration of $\text{Mo}=\text{O}_t$. Due to the conjugation interaction between the ligands and POMs, the stretching vibration of C=O shifts considerably from 1700 to 1592 cm^{-1} .

The ^1H NMR spectra of compounds **1–3** in DMSO- d_6 solution show well-resolved signals (Figs. S5–S7 in the ESM). Four signals (0.94, 1.33, 1.58, and 3.17 ppm in **1**; 0.88, 1.28, 1.52, and 3.15 ppm in **2**; 0.93, 1.31, 1.57, and 3.17 ppm in **3**) correspond to the TBA cations. The aromatic protons of the pyridine ring in compound **1** appear at 7.63 and 8.54 ppm, those of the thiophene ring in compound **2** appear at 6.99, 7.37, and 7.41 ppm, and those in the pyrazine ring of compound **3** appear at 8.58 and 8.57 ppm. These signals show slight downfield shifts relative to the corresponding free ligands, suggesting that the $[\text{Mo}_6\text{O}_{18}(=\text{N}=\text{N})]$ POM fragment acts as an electron-donating group in compounds **1–3**. The integrated proton signals are consistent with the molecular formulas of all three compounds.

ESI-MS further confirmed the structures of compounds **1–3** (Figs. S8–S13 in the ESM). In the negative-ion regime of compound **1**, the peak at $m/z = 1482.9510$ corresponds to the $[\text{M-TBA}]^-$ cation (calculated: 1482.9489), whereas the peak at $m/z = 1242.6707$ is assigned to the $[\text{M-2TBA+H}]^-$ cation (calculated: 1242.6715). For compound **3**, the peak at $m/z = 1482.9506$ is assigned to $[\text{M-TBA}]^-$ (calculated: 1482.9440), and the peak at $m/z = 1239.6722$ to $[\text{M-2TBA+H}]^-$ ion (calculated: 1239.6667). For compound **2**, the peak at $m/z = 1487.9435$ is assigned to $[\text{M-TBA}]^-$ (calculated: 1487.9099), the peak at $m/z = 1245.6765$ to $[\text{M-2TBA+H}]^-$ (calculated: 1245.6324), and the peak at $m/z = 1004.4012$ to $[\text{M-3TBA+2H}]^-$ (calculated: 1004.3551). In the positive-ion regime, $[\text{M+TBA}]^+$ was

detected at $m/z = 1967.5236$ for compound **1** (calculated: 1967.5195), $m/z = 1972.5318$ for compound **2** (calculated: 1972.4084), and $m/z = 1967.5150$ for compound **3** (calculated: 1967.5145). The measured molecular weights of compounds **1–3** were in good agreement with the theoretical values, further validating their molecular structures.

The UV–Vis spectra of compounds **1–3** demonstrated similar absorption bands, with the maximal absorption at around 386 nm for **1**, 385 nm for **2**, and 389 nm for **3** (Fig. 3). The maximal absorption bands are attributed to charge transfer from the organic ligands to the POM core. The pronounced bathochromic shift relative to hexamolybdate likely results from the expansion of the delocalized π -system upon substitution of one terminal oxo ligand by a hydrazide ligand. The overall similarity between the spectra can be explained by the electronic structure around the β -N atom; this nitrogen center possesses two lone pairs of electrons: One participates in conjugation with the $[\text{Mo}_6\text{O}_{18}(=\text{N}-)]$ moiety, whereas the other is conjugated with the carbonyl group. Because the β -N atom is sp^2 hybridized, these two conjugation systems are nearly perpendicular such that the delocalized π -system is largely confined to the $[\text{Mo}_6\text{O}_{18}(=\text{N}=\text{N})]$ fragment, and the hydrazide ligand exerts only an inductive effect on the core unit.

The optical band gaps (E_g) of compounds **1–3** and hexamolybdate were determined using the absorption onset method (Tauc plot-derived E_g values were also calculated for comparison and are given in Table S8 in the ESM). The onset wavelengths (λ_{onset}) were obtained through the tangent method (479.07 nm for **1**; 476.80 nm for **2**; 503.12 nm for **3**). The band gap was then calculated as $E_g \text{ (eV)} = 1240/[\lambda_{\text{onset}} \text{ (nm)}]$ [37], yielding 2.588, 2.601, and 2.465 eV, respectively, for compounds **1–3**. E_g for hexamolybdate was larger (3.07 eV) than for compounds **1–3**, demonstrating that E_g can be tuned by modifying the attached organic ligands.

Cyclic voltammetry (CV) of compounds **1–3** and hexamolybdate was performed in $\sim 1 \text{ mmol/L}$ dichloroethane solutions using $[\text{n-Bu}_4\text{N}]\text{PF}_6$ (0.1 mol/L) as the supporting electrolyte (Figs. S2–S4 in the ESM and Table 1). In the -1.6 to $+1.8 \text{ V}$ range (vs. saturated calomel electrode), compounds **1–3** demonstrated two reversible reductive processes in the cathodic region and one irreversible oxidative process in the anodic region. The half-wave potentials ($E_{1/2}$) of the first reversible redox process—associated with the $\text{A}^{3-}/\text{A}^{4-}$ (A^{3-} = anion cluster of title compounds; A^{4-} = single-electron-reduced anion cluster)—are

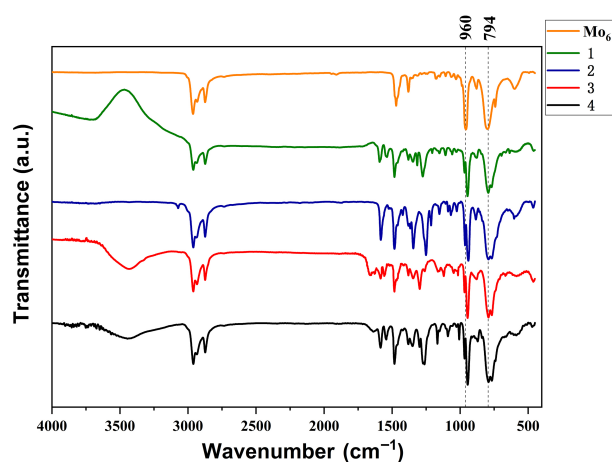


Figure 2 FT-IR spectra of compounds **1–3** and hexamolybdates.

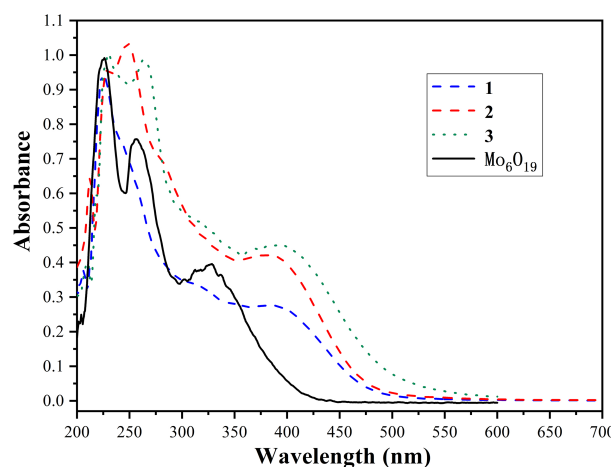


Figure 3 UV-Vis spectra of compounds **1–3** and hexamolybdates.

Table 1 Cyclic voltammetry data of compounds 1–3

Compound	[Mo ₆ O ₁₉] ²⁻	1	2	3
Solvent	DCE	DCE	DCE	DCE
E_{pcI} (V)	−0.266	−0.445	−0.331	−0.378
E_{paI} (V)	−0.163	−0.291	−0.310	−0.323
$E_{\text{paI}} - E_{\text{pcI}}$ (V)	0.103	0.154	0.021	0.055
$E_{1/2}$ (V)	−0.214	−0.368	−0.316	−0.350
Cath. shift (V)	0	0.154	0.102	0.136
E_{pcII} (V)		−0.970	−1.001	−0.945
E_{paII} (V)		−0.748	−1.745	−0.771
$E_{\text{paII}} - E_{\text{pcII}}$ (V)		0.222	0.256	0.174
$E_{1/2}$ (V)		−0.859	−0.873	−0.858
Cath. shift (V)		0.645	0.658	0.688
E_{pOI} (V)		0.804	0.752	0.810
E_{pOII} (V)			1.212	

found at −0.368 V for **1**, −0.316 V for **2**, and −0.350 V for **3**. The $E_{1/2}$ of the second reversible redox process—associated with A^4/A^{5-} (A^{5-} = two-electron reduced anion cluster)—are found at −0.859 V for **1**, −0.873 V for **2**, and −0.858 V for **3**. The parent [Bu₄N]₂[Mo₆O₁₉] shows one reversible redox process at $E_{1/2} \approx -0.214$ V; the $E_{1/2}$ cathodic shifts for compounds **1–3** are thus 0.154 V (**1**), 0.102 V (**2**), and 0.136 V (**3**) for the first reversible redox process, and 0.645 V (**1**), 0.658 V (**2**), and 0.688 V (**3**) for the second reversible redox process. These large cathodic shifts indicate that compounds **1–3** are more difficult to reduce than hexamolybdate. The irreversible peaks at 0.804 V (**1**), 0.752 V (**2**), and 0.810 V (**3**) are likely associated with the oxidation of the organic ligands in these compounds.

Density functional theory (DFT) calculations (details are provided in the ESM) were conducted to analyze the highest occupied molecular orbital (HOMO) and lowest unoccupied molecular orbital (LUMO) and Mulliken charge distribution of compounds **1–3**. The anion models of compounds **1** and **2** were built from their single-crystal XRD data. The structural model of compound **3** was modified from that of compound **2**. All calculations were performed using the Gaussian 16 package [38] and the calculated results were analyzed with the Multiwfn package [39, 40]. The HOMO–1 and HOMO of compounds **1–3** are primarily distributed at the Mo=N–N–CO– moiety between the Lindqvist cluster and the heterocyclic ligands (Fig. 4). There is a node between the N1 and N2 atoms, and the Mo=N molecular orbital is perpendicular to the NC=O molecular orbital. This further corroborates the UV–Vis spectra analyses; the conjugation involving the Mo=N multiple bond is mainly confined to the POM cluster, and there is no conjugation between the Mo=N π bond and the appended heterocyclic hydrazide. Meanwhile, the LUMO and LUMO+1 of compounds **1–3** are predominantly localized on the anti-bonding orbitals of the heterocyclic ligand and the Lindqvist cluster, indicating that the electron transitions in these compounds involve a charge transition from the Mo=N–N–CO– moiety to the Lindqvist cluster mixed with intramolecular ligand charge transfer.

The theoretical HOMO–LUMO gaps for compounds **1–3** are 2.719, 2.686, and 2.349 eV, respectively, representing a significant reduction compared to hexamolybdate (3.945 eV) (Table S8 in the

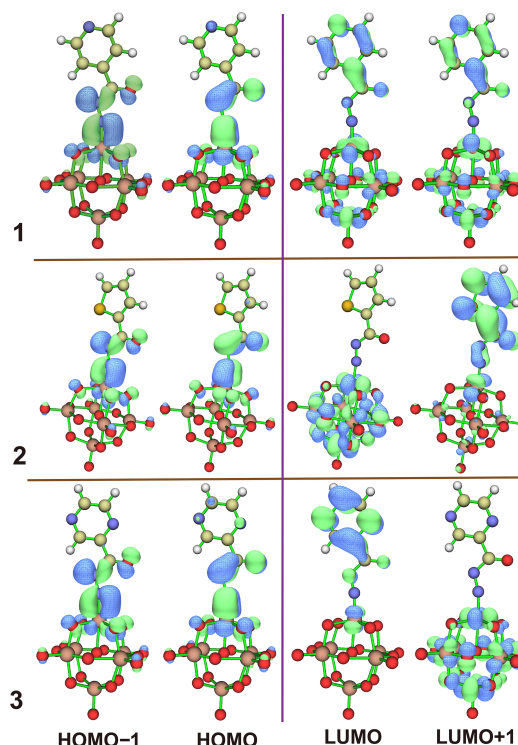


Figure 4 Frontier molecular orbitals (HOMO–1, HOMO, LUMO, LUMO+1) of compounds **1–3**.

ESM). These values are close to the experimental E_g values and follow the same decreasing trend from compounds **1** to **3**. The Mulliken charges for the α -N and β -N atoms are −0.363 and −0.322 for compound **1**, −0.363 and −0.328 for compound **2**, and −0.360 and −0.321 for compound **3**, respectively (Table S4 in the ESM). Notably, the Mulliken charge on the hydrazide-substituted Mo atom (1.558 for **1**, 1.557 for **2**, and 1.560 for **3**) is slightly lower than that on the other unsubstituted Mo atoms (1.726–1.783), indicating that the hydrazide ligand is a stronger electron donor than the terminal oxygen ligand, resulting in reduced electropositivity of the substituted Mo centers. Additionally, the LUMO is primarily localized on the POM framework and the bridging nitrogen atom. This electronic distribution is important because the activation of INH-like drugs often involves single-electron transfer processes [41].

Compounds **1–3**, along with their parent hexamolybdate (**Mo6**) and octamolybdate (**Mo8**), were evaluated for *in vitro* cytotoxicity against Vero cells using the CCK-8 assay [42] with 5-fluorouracil (5-FU) as a positive control (Table S9 in the ESM). The preliminary cytotoxicity results are summarized in Fig. 5. The cell viability histogram clearly shows that compounds **1–3**, **Mo6**, and **Mo8** exhibited lower cytotoxicity than 5-FU (Table S9 in the ESM). Overall, they displayed mild cytotoxicity at 200 $\mu\text{g/mL}$, while the toxicity was negligible or very weak at lower concentrations. Contrastingly, 5-FU exhibited significant toxicity even at low concentrations.

Mycobacterium tuberculosis H37Rv was used for all susceptibility testing. The MIC was determined using the broth dilution method [43, 44]. The measured MICs of compounds **1–3** and hexamolybdate (**4**) are listed in Table 2, and the MICs of **L1–L3** are cited from [7]. The MICs of compounds **1–3** are all lower than that of **4**, but higher than those of **L1** and **L3**. These results suggest that covalent organic modification of hexamolybdates with heterocyclic

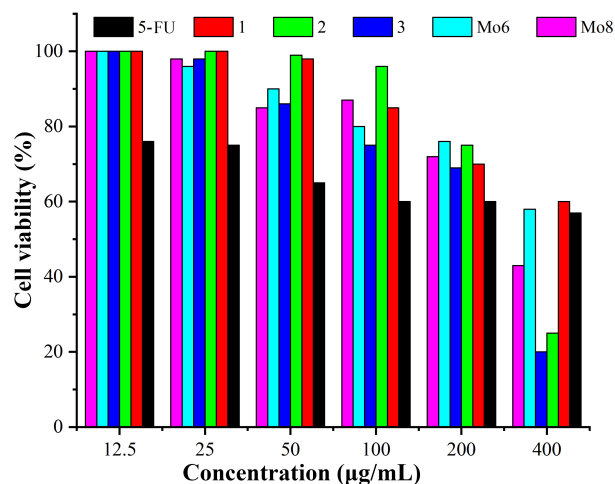


Figure 5 Inhibition activities against Vero arrays for compounds 1–3, Mo6, Mo8 and 5-fluorouracil at different concentration.

Table 2 MICs of title compounds and their ligands^a

Compounds	MICs (µg/mL)	MICs (µg/mL) (anion part)	MICs (nmol/mL) ^a	Data source
1	1.14	0.66	0.66	This work
L1	0.02	0.02	0.15	
2	4.55	2.64	2.63	This work
L2	8.00	8.00	56.34	
3	2.27	1.31	1.32	This work
L3	1.50	1.50	10.87	
4	4.55	2.93	3.33	This work

^aMolar MICs = (Mass MICs)/M.W.; anion MICs = (anion M.W./M.W.) × mass MICs.

hydrazides improves their antitubercular activity.

The antitubercular activity of **1** is still inferior to that of **L1** based on mass MICs. TBA is well-known to lack antitubercular activity; therefore, the antitubercular activity of compounds **1–3** can be attributed to their anion clusters. The anion-based MICs of compounds **1–3** (Table 2) demonstrate a similar trend to the mass MICs. Moreover, considering their large molecular weights, the molar MICs of compounds **1–3** were also calculated (Table 1). The molar antitubercular activities of compounds **1–3** (0.66, 2.63, and 1.32 mmol/mL, respectively) are close to or lower than that of the corresponding ligands (0.15, 56.34, and 10.87 mmol/mL, respectively), indicating that higher molecular antitubercular efficiency results from the covalent MH of heterocyclic hydrazides with hexamolybdates.

The blank 7H10 medium and 7H10 medium containing compounds **1–3** were opaque, with pH values of 6.81, 6.90, 6.93, and 6.86, respectively (Table S12 in the ESM). After the biological assay, UV–Vis analysis of the remaining culture medium revealed that the characteristic peak of the Mo=N multiple bond disappeared (Fig. S14 in the ESM), indicating that the compounds decomposed during the biological test. Similar decomposition of organically derivatized Anderson–Evans POMs in the aqueous solution was reported by Parac-Vogt [45].

4 Conclusions

In summary, we synthesized three heterocyclic hydrazide covalently-

functionalized hexamolybdates (compounds **1–3**) via reflux of octamolybdates with corresponding hydrazide ligands. Single-crystal XRD revealed three conformational isomers of $[\text{Mo}_6\text{O}_{18}(=\text{N}=\text{NCOC}_5\text{H}_4\text{N})]^{3-}$ in the asymmetric unit of compound **1** and one anion cluster of $[\text{Mo}_6\text{O}_{18}(=\text{N}=\text{NCOC}_4\text{H}_3\text{S})]^{3-}$ in compound **2**. In both cases, one terminal oxygen atom of hexamolybdate is replaced by a heterocyclic hydrazide via a Mo=N multiple bond. This substitution reduces the symmetry of the anion cluster from the O_h symmetry of hexamolybdate to C_s or C_1 symmetry. The coexistence of multiple conformational isomers in combination with this symmetry reduction leads to crystallization in the non-centrosymmetric $P2_1$ space group. Their structures were further confirmed by UV–Vis, FTIR, ^1H NMR, and ESI-MS. The optical band gaps of compounds **1–3** were found to be 2.588, 2.601, and 2.465 eV, respectively. Cyclic voltammetry showed two reversible reduction processes in the cathodic region and one irreversible oxidative process in the anodic region. DFT studies indicated that the electron transitions involve charge transfer from the Mo=N–N–CO– moiety to the Lindqvist cluster, mixed with intramolecular charge transfer within the attached organic ligands. Compounds **1–3** also exhibited enhanced antitubercular properties relative to hexamolybdate. Although their antitubercular activity is still lower than that of INH, their molar MICs are close to or superior to those of the corresponding ligands alone. This work demonstrates that covalent MH of hydrazides with POMs can simultaneously tune the structures and electronic properties of POMs and improve their biological activities, thereby providing a simple and effective strategy for developing POM-based medicines.

Electronic Supplementary Material: Supplementary material (experimental details, crystallographic data, ^1H NMR, ESI-MS, CV data, energy gap, and biological test) is available in the online version of this article at <https://doi.org/10.26599/POM.2026.9140142>.

Data availability

All data needed to support the conclusions in the paper are presented in the manuscript and/or the Electronic Supplementary Material. Additional data related to this paper may be requested from the corresponding author upon request.

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Declaration of competing interest

Yong-Ge Wei is the editor-in-chief of this journal, but he is not involved in the peer-review or decision of this article. The other contributing authors report no conflict of interests in this work.

Author contribution statement

The manuscript was written through contributions of all authors. L.-S. W. and P.-C. Y. performed the synthetic experiments, data

analysis, X-ray structure refinement, and revised the paper; Z.-H. F. and Z.-Y. L. conducted some synthetic experiments, finished the ¹H NMR, CV, FT-IR and UV-Vis test and corresponding data analyses, and prepared the original draft; C.-L. L. and F.-P. X. revised the paper, theoretical calculation and data analysis; Y.-G. W. supervised the research and revised the paper; X. Q. W. and H.-M. L. performed the antitubercular test, supervised the research, and revised the paper. All authors had read and approved the final manuscript.

Informed consent

Not applicable.

Ethics statement

Not applicable.

Use of AI statement

During the preparation of this work, the author used QianWen in order to generate the 3D figure of mycobacterium tuberculosis in the TOC using the SEM photo of mycobacterium tuberculosis. After using this service, the author reviewed and edited the content as needed and takes full responsibility for the content of the publication.

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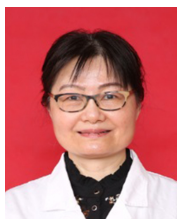
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