New Off–On Sensor for Captopril Sensing Based on Photoluminescent MoO$_x$ Quantum Dots

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ABSTRACT: Molybdenum oxide nanomaterials have recently attracted widespread attention for their unique optical properties and catalytic performance. However, until now, there is little literature on the application of photoluminescent molybdenum oxide nanomaterials in biological and pharmaceuticalsensing. Herein, photoluminescent molybdenum oxide quantum dots (MoO$_x$ QDs) were prepared by a one-pot method and then applied as a new type of photoluminescent probe to design a new off–on sensor for captopril (Cap) detection on the basis of the fact that the quenched photoluminescence of MoO$_x$ QDs by Cu$^{2+}$ was restored with Cap through specific interaction between the thiol group of Cap and Cu$^{2+}$. Under optimal conditions, the restored photoluminescence intensity showed a good linear relationship with the content of Cap, ranging from 1.0 to 150.0 μM, with a limit of detection of 0.51 μM (3σ/k). Additionally, the content of Cap in pharmaceutical samples was successfully detected with the newly developed off–on sensor, and the recoveries were 99.4–101.7%, which suggest that the present off–on sensor has a high accuracy.

INTRODUCTION

Transition metal oxides, including molybdenum oxide,$^{1,2}$ vanadium oxide,$^3$ titanium dioxide,$^4$ germanium dioxide,$^5$ tungsten oxide,$^6$ nickel oxide,$^7$ and zinc oxide,$^8$ have stimulated great interest due to their optical, electrical, and semiconducting properties and catalytic performance. In particular, molybdenum oxide has drawn tremendous attention for its excellent properties, and numerous methods, including the hydrothermal/solvothermal method,$^9$ physical vapor deposition method,$^{10}$ chemical spray pyrolysis,$^{11}$ mechanical grinding and sonication,$^{12}$ thermal oxidation,$^3$ thermal evaporation and decomposition, and electrospinning technologies,$^{13,14}$ have been developed for the synthesis of molybdenum oxide nanomaterials with a variety of morphologies because the physical and chemical properties of molybdenum oxide nanomaterials are closely related to their morphologies. Until now, molybdenum oxide nanomaterials have been used in many applications, including gas sensors,$^{1,2}$ catalysis,$^{15}$ solar cells,$^{16}$ photochromism,$^{17}$ lithium-ion batteries,$^{18}$ thin-film capacitors,$^{19}$ field-effect transistors,$^{19,20}$ antiseptics, and anticancer treatments.$^{14,21}$ However, only a few reports have mentioned the application of molybdenum oxide nanomaterials as a photoluminescent probe in biological and pharmaceutical fields, that is, there is still plenty of room for methodological innovation.

Herein, photoluminescent molybdenum oxide quantum dots (MoO$_x$ QDs) were prepared by a one-pot method at room temperature (Figure 1a) and a new photoluminescent sensor for captopril (Cap) detection was constructed using MoO$_x$ QDs as an effective probe. As an angiotensin-converting enzyme (inhibitor), Cap, 1-(4-(2-thienyl)-3-mercaptop-2-methylpropionyl)-l-proline, plays a crucial biological role in the treatment of hypertension, coronary heart disease, congestive heart failure, and some types of diseases associated with diabetes.$^{22–24}$ Thus far, several methods have been proposed for Cap determination, including voltammetry,$^{25}$ chemiluminescence,$^{26}$ flow injection spectrophotometry,$^{27}$ surface-enhanced Raman spectroscopy,$^{28}$ and mass spectrometry.$^{29}$ However, certain drawbacks limited the application of the above methods. For example, electrochemical methods are sensitive enough, but the preparation of electrodes is relatively tremendous while chemiluminescence methods are simple and rapid, but they possess the limitation of low detection sensitivity. Raman spectroscopy and mass spectrometry are sensitive enough; however, the need for expensive instruments or complicated procedures limits their application in routine analysis. Therefore, it is necessary to establish a facile and sensitive method for Cap determination in biological fluids and pharmaceutical samples. The sensing platform for Cap developed in this manuscript is shown in Figure 1b. The system is a combination...
of MoO$_x$ QDs and Cu$^{2+}$, in which Cu$^{2+}$ can generate a nonluminous complex with the MoO$_x$ QDs, resulting in the quenching of the photoluminescence of the MoO$_x$ QDs (switched off) through static quenching processes. However, the formed MoO$_x$ QDs–Cu$^{2+}$ complex might be dissociated after the introduction of Cap because Cu$^{2+}$ displays a higher affinity toward the $\text{–SH}$ from Cap. As a consequence, the fluorescence of the MoO$_x$ QDs is restored (switched on), providing a facile switch-on assay for Cap detection. On the basis of the proposed switch-on assay, the Cap content in the pharmaceutical samples was successfully determined with high sensitivity and good repeatability.

## RESULTS AND DISCUSSION

### Characterization of the Obtained MoO$_x$ QDs

The MoO$_x$ QDs were synthesized at room temperature using commercial MoS$_2$ powder and H$_2$O$_2$ as the precursor and oxidant (Figure 1a), respectively, and the as-prepared MoO$_x$ QDs had an average diameter of around 2.0 nm (Figure 1a) and a height of about 1.5 nm (Figure 1b). From the X-ray
photoelectron spectroscopy (XPS) spectra (Figures 2c,d and S1), it can be clearly seen that Mo⁶⁺ and S²⁻ were both oxidized by H₂O₂ to higher valence states, Mo⁵⁺ (230.6 and 232.8 eV) and Mo⁶⁺ (232.1 and 235.3 eV) and SO₄²⁻ (168.5 and 169.7 eV), respectively. The strongest absorption between 200 and 400 nm, whereas the photoluminescence was gradually quenched as the concentration of Cu²⁺ increased, and the maximal quenching efficiency reached nearly 90% when Cu²⁺ was 75 μM. To elucidate the quenching mechanism, the fluorescence lifetimes of MoO₃-QDs and MoO₃-QDs-Cu²⁺ were measured (Figure 4b and Table S1), and the results show that the average fluorescence lifetimes of MoO₃-QDs and MoO₃-QDs-Cu²⁺ are 4.83 and 5.97 ns, respectively, which indicate that the static quenching mechanism accounts for the decrease in photoluminescence and a nonluminous complex is formed between MoO₃-QDs and Cu²⁺. The formation of MoO₃-QDs-Cu²⁺ complexes was also confirmed by ultrafiltration experiments. For ultrafiltration experiments, MoO₃-QDs-Cu²⁺ solutions were filtered through a 1 kDa MWCO ultrafiltration membrane, through which only free Cu²⁺ ions in the solution could pass, whereas those adhering to MoO₃-QDs could not. The residues were then subjected to XPS measurements, and the Cu₂p peak was clearly observed in the survey spectrum (Figure S4), suggesting the formation of MoO₃-QDs-Cu²⁺ complexes.

**Construction of an Off–On Sensor for Cap Determination.** In view of the effective reaction between Cu²⁺ and the active thiol groups (–SH) in cysteine, the MoO₃-QDs-Cu²⁺ system was utilized to detect the thiol-containing Cap tablets. Figure 5 shows the photoluminescence recoveries of the MoO₃-QDs-Cu²⁺ system with increasing contents of Cap, and it can be clearly seen that the photoluminescence was gradually restored as more and more Cap was added. The reason for the

### Figure 3
Optical spectra of MoO₃-QDs. The black line represents the absorption spectrum of MoO₃-QDs and the other lines are photoluminescence spectra of MoO₃-QDs excited at different wavelengths. The excitation wavelengths are 325, 350, 375, 400, 425, 450, and 475 nm, whereas the maximum emission wavelengths are 470, 500, 510, 517, 525, 534, and 539 nm, respectively. Inset: Photographs obtained under visible (left) and 365 nm UV light (right).

### Figure 4
(a) Photoluminescence of the MoO₃-QDs quenched by Cu²⁺. Cu²⁺ concentrations from top to bottom are 0, 1.0, 2.5, 5.0, 10.0, 20.0, 40.0, 60.0, 80.0 μM, respectively. Inset is the plot of photoluminescence intensities vs Cu²⁺ concentration. (b) Fluorescence lifetimes of MoO₃-QDs, MoO₃-QDs-Cu²⁺ complexes, and MoO₃-QDs-Cu²⁺-Cap. The data were obtained from three parallel samples.
photoluminescence recovery might be as follows: a Cu\textsuperscript{2+}—S bond can be formed between the thiol group of Cap and Cu\textsuperscript{2+}, resulting in the removal of Cu\textsuperscript{2+} from the surface of MoO\textsubscript{x} QDs via competitive adsorption interactions (Figure 1b),\textsuperscript{41} which enhanced the photoluminescence. The desorption of Cu from MoO\textsubscript{x} QDs—Cu\textsuperscript{2+} complexes was also confirmed by XPS, and the results showed that the Cu2p peak of the residues disappeared after the MoO\textsubscript{x} QDs—Cu\textsuperscript{2+}—Cap solutions were passed through a 1 kDa MWCD ultrafiltration membrane (Figure S5).

The photoluminescence recovery was affected by pH and time, and the photoluminescence intensity reached its maximum value at pH 7.5 within 5 min (Figures S2 and S3). Under optimal conditions, the photoluminescence follows a linear relationship with the Cap content, ranging from 1.0 to 150.0 \textmu M, with a limit of detection of 0.51 \textmu M (3\sigma/k), which is comparable to that of other methods, as shown in Table S2.

**Detection of Cap in Pharmaceutical Samples Based on the New Off–On Sensor.** To further evaluate the selectivity of the new off–on sensor for Cap, the photoluminescence responses to other common ions and excipients in antihypertensive pills were investigated. As shown in Figure 5b, the photoluminescence of other detected substances showed no significant increase even when their concentrations were 10-fold higher than those of Cap, illustrating the high selectivity of the developed off–on sensor, which might be employable for Cap determination in real samples. Therefore, the Cap contents in real pharmaceutical samples were detected to further illustrate the feasibility. To avoid any interference from the sample matrix, a standard addition method was used, spiking each pharmaceutical sample with a known concentration of Cap. The results clearly showed that the sample matrix has no obvious interference, and the actual Cap concentration of the pharmaceutical sample could be obtained from the linear trend produced by the standard addition method (Figure S6). Meanwhile, Cap contents in pharmaceutical samples were successfully detected (Table 1), and the standard deviations and recovery (99.4—101.7\%) demonstrated that the proposed method for Cap detection has a high accuracy and good repeatability, which can fulfill the needs of real applications.

### Table 1. Determination of Cap in Pharmaceutical Samples

| sample nos. | measured (\pm SD, \textmu M)\textsuperscript{a} | value added (\textmu M)\textsuperscript{a} | value found (\pm SD, \textmu M)\textsuperscript{a} | recovery (%) |
|-------------|---------------------------------|-----------------|---------------------------------|-------------|
| 1           | 19.2 ± 1.05                     | 25.0            | 44.09 ± 0.86                    | 99.4        |
| 2           | 19.19 ± 1.04                    | 50.0            | 69.52 ± 1.05                    | 101.7       |
| 3           | 19.17 ± 1.29                    | 50.0            | 69.28 ± 1.08                    | 100.6       |

\textsuperscript{a}The data were obtained from three parallel samples.

### CONCLUSIONS

In summary, photoluminescent MoO\textsubscript{x} QDs were synthesized at room temperature and a new “off–on” photoluminescent sensor was designed for Cap detection in pharmaceutical samples based on MoO\textsubscript{x} QDs—Cu\textsuperscript{2+}. The quenching and recovery mechanisms were carefully explored. On the one hand, the photoluminescence of MoO\textsubscript{x} QDs was quenched by Cu\textsuperscript{2+} by a static quenching process, which was attributed to the formation of nonluminous MoO\textsubscript{x} QDs—Cu\textsuperscript{2+} complexes. On the other hand, Cu\textsuperscript{2+} might be dissociated from MoO\textsubscript{x} QDs due to the stronger binding affinity of Cu\textsuperscript{2+} to the thiol group of Cap, resulting in restoration of the photoluminescence of the MoO\textsubscript{x} QDs. Moreover, the content of Cap in the pharmaceutical samples was successfully detected with the newly developed off–on sensor; the standard deviations and recoveries (99.4—101.7\%) demonstrated high accuracy and good repeatability of the off–on sensor, which fulfill the requirements for real-time applications.

### EXPERIMENTAL SECTION

**Reagents.** MoS\textsubscript{2} powder was commercially obtained from Sigma-Aldrich. NaOH, 30% H\textsubscript{2}O\textsubscript{2}, HCl, CuCl\textsubscript{2}, NaCl, Fe\textsubscript{3}(SO\textsubscript{4})\textsubscript{3}, NaNO\textsubscript{3}, CaCl\textsubscript{2}, Mg(NO\textsubscript{3})\textsubscript{2}, KCl, and Zn(SO\textsubscript{4})\textsubscript{2} were provided by Shanghai Maikun Chemical Reagents Co., Ltd (Shanghai, China). Tris (C\textsubscript{4}H\textsubscript{11}O\textsubscript{3})\textsubscript{HCl} was purchased from Solarbio Company. Cap was supplied from Wanji (China). Starch, lactose, glucose, sucrose, and dextrin were purchased from Guangzhou Yuwei Chemical Reagents Co., Ltd (Guangzhou, China). All chemicals and solvents were of analytical grade and were used without further purification. Deionized water was used in all experiments.
Apparatus. A JEM-2010 TEM (JEOL Ltd., Japan) with a 200 kV accelerating voltage and an AFM in the ScanAsyst mode were used to obtain the size and height of the MoO$_3$ QDs, whereas XPS (Thermo) was used to characterized the elemental composition and bonding configuration. The fluorescence lifetime was measured by an FL-TCSPC fluorescence spectrophotometer (Horiba Jobin Yvon Inc., France). The absorption was measured using a Shimadzu UV-2450 spectrophotometer (Tokyo, Japan), whereas a Hitachi F-7000 fluorescence spectrophotometer (Tokyo, Japan) or a USB-4000FL spectrophotometer (Ocean Optical) was utilized to record the fluorescence spectra.

Preparation of MoO$_3$ QDs. MoO$_3$ QDs were prepared using a one-pot method at room temperature according to our previous studies, in which MoS$_2$ and 30% hydrogen peroxide were selected as the precursor and oxidant, respectively. Briefly, 10.0 mg of the MoS$_2$ powder was incubated with 10 mL of the mixing solution (H$_2$O−30% H$_2$O$_2$ = 3:2) for 30 min at room temperature. Thereafter, the pH of the mixture was adjusted to 7.0 using sodium hydroxide (NaOH), with slow stirring for 20 min. Finally, MoO$_3$ QDs were obtained by centrifuging the resulting mixture at 8000 rpm for 10 min.

Fluorescence Sensing of Cu$^{2+}$ and Cap. For the detection of Cu$^{2+}$, 20 μL of MoO$_3$ QD solution (1 mg/mL), 20 μL of Tris−HCl buffer solution (50 mM, pH 7.5), Cu$^{2+}$, and H$_2$O were added to a final volume of 200 μL. The final concentration of Cu$^{2+}$ ranged from 0 to 80 μM. The resulting solutions were excited with a 405 nm laser, and their fluorescence spectra were recorded using a Shimadzu UV-2450 spectrophotometer.

For the detection of Cap, 20 μL of MoO$_3$ QDs (1 mg/mL); 20 μL of Tris−HCl buffer solution (50 mM pH 7.5); 15 μL of Cu$^{2+}$ (1 mM), with a final concentration of 75 μM; and deionized water were added to a final volume of 200 μL. The final concentration of Cap ranged from 0 to 150 μM. After incubation for 5 min, the fluorescence spectra were recorded using a USB-4000FL spectrophotometer equipped with a 405 nm laser light source.

Pharmaceutical Sample Preparation. The three pharmaceutically relevant samples were obtained from Henan Yu pharmaceuticals, Ltd., Shanghai pharmaceutical Co., Ltd., and Hangzhou Mingsheng pharmaceutical Co., Ltd., respectively. Four tablets of each sample were ground to a homogenized powder. A portion of the powder containing 12.5 mg of Cap was accurately weighed and dissolved in 10 mL of H$_2$O. After ultrasonication for 20 min, the supernatant was obtained by centrifuging at 500g for 5 min. The obtained sample solutions were diluted 300 fold before use. The standard Cap solution was added into the diluted sample solutions for recovery tests to evaluate the accuracy of the present off−on sensor.

ASSOCIATED CONTENT

Supporting Information The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acsomega.7b00088.

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