



Carbon dots-based dual-emission ratiometric fluorescence sensor for dopamine detection

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ABSTRACT

The detection of Dopamine (DA) is significant for disease surveillance and prevention. However, the development of the precise and simple detection techniques is still at a preliminary stage due to their high tester requirements, time-consuming process, and low accuracy. In this work, we present a novel dual-emission ratiometric fluorescence sensing system based on a hybrid of carbon dots (CDs) and 7-amino-4-methylcoumarin (AMC) to quickly monitor the DA concentration. Linked via amide bonds, the CDs and AMC offered dual-emissions with peaks located at 455 and 505 nm, respectively, under a single excitation wavelength of 300 nm. Attributed to the fluorescence of the CDs and AMC in the nanohybrid system can be quenched by DA, the concentration of DA could be quantitatively detected by monitoring the ratiometric ratio change in fluorescent intensity. More importantly, the CDs-AMC-based dual-emission ratiometric fluorescence sensing system demonstrated a remarkable linear relationship in the range of 0–33.6 μ M to detection of DA, and a low detection limit of 5.67 nM. Additionally, this sensor successfully applied to the detection of DA in real samples. Therefore, the ratiometric fluorescence sensing system may become promising to find potential applications in biomedical dopamine detection.

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1. Introduction

Dopamine (DA), an important neurotransmitter, is involved in many biological processes, such as the central nervous, hormonal and cardiovascular systems. Many studies have shown that abnormal DA concentrations may result in serious diseases such as Huntington's, Parkinson's and Alzheimer's diseases and schizophrenia [1–4]. Therefore, the accurate detection of DA has great significance for diagnosing the above diseases. Various methods such as chromatography, ultraviolet spectrophotometry, electrochemistry, chemiluminescence and enzyme methods have been adopted to solve this problem [5–9], but have shown many defects, such as high requirements for testers, time-consuming detection, low accuracy and so on. There is substantial demand for developing a method that is easy to operate, efficient and sensitive for dopamine detection.

Fluorescence-based sensors have been used to detect various target analytes, because of their outstanding advantages, including simple operation, fast testing, low cost and high sensitivity. However, fluorescence emission intensity is normally influenced by many factors, such

as instrument efficiency, probe concentration and environmental interference [10–12], which will affect the analysis results in quantitative testing. Ratiometric fluorescence is a method where changes in the ratio of two fluorescence intensities (FL) with respect to variations in the target analyte are used to quantitatively detect the target analyte, which can effectively eliminate background signal and environmental interference, resulting in high sensitivity and selectivity [13–15].

Carbon dots (CDs), fluorescent materials discovered in 2004, have attracted immense attention in recent years due to their facile preparation, low cost, good water-solubility, excellent biocompatibility and low toxicity. The rich oxygen-containing structure on the surface of CDs not only enables their good dispersion in aqueous solution but also be promising to find potential applications in further modifications [16–20]. To date, different strategies including hydrothermal, chemical oxidation, electrochemical oxidation and laser ablation methods have been developed to synthesize a variety of CDs [21–24]. Traditionally, CDs have been extensively used in bioimaging detection, photocatalysis, optoelectronic devices and so on [25–30]. Recently, some researchers have tried to prepare ratiometric fluorescent probes for chemical sensing by combining CDs with other fluorescent materials to improve detection sensitivity [31–34]. Moon-Jin Cho et al. [32] coupled CDs and rhodamine to prepare a ratiometric probe for glucose detection. Chen et al. [35] reported a ratiometric fluorescent probe synthesized from

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the fluorescent dye ethidium bromide and CDs for perfluorooctane sulfonic acid (PFOS) detection. He et al. [15] fabricated a ratiometric fluorescent probe based on a CDs-gold nanocluster hybrid for the reliable sensing of dopamine.

Here, a novel ratiometric fluorescent probe, combining CDs and 7-amino-4-methylcoumarin (AMC), is proposed to form a CDs-AMC nanohybrid (CDC) for the detection of DA. As shown in Scheme 1, the dual-emission fluorescence CDC with emission peaks located at 455 and 505 nm was synthesized via covalently linking the CDs and AMC. Besides, to completely remove the free AMC from the complex system, the samples were sulfonated to improve the water-solubility of AMC. Attributed to the unique configuration, the concentration of DA can be monitored quickly, by analyzing the relationship between the concentration and FL ratio. What's more, the results revealed good selectivity of the CDC ratiometric fluorescence sensor to DA over other metal ions and amino acids.

2. Experimental

2.1. Instruments and measurements

Transmission electron microscopy (TEM) was performed using a Tecnai G2 F20 S-TWIN transmission electron microscope (FEI, USA) operated at an accelerating voltage of 200 kV. X-ray photoelectron spectroscopy (XPS) measurements were made on an ESCALAB250Xi spectrometer (ThermoFisher Scientific). Fourier transform infrared (FT-IR) spectra were collected with the aid of a Thermo Scientific FT-IR spectrophotometer (Nicolet iS50 FT-IR). UV-vis absorption spectra were recorded with Shimadzu UV-1800 spectrometer (Shimadzu Inc., Kyoto, Japan). Fluorescence measurements were obtained by using a Hitachi F-4700 fluorescence spectrometer (Hitachi Ltd., Japan).

2.2. Materials

Dopamine hydrochloride, cysteine (Cys), glycine (Gly), alanine (Ala), glutathione (Gsh), 7-amino-4-methylcoumarin (AMC), glutamic acid (Glu), tyrosine (Tyr) and uric acid were purchased from Aldrich

Chemical. Epinephrine, Norepinephrine (NE), and tyrosinase (TYR) were purchased from Shanghai yuanye Bio-Technology Co., Ltd. L-ascorbic acid (AA) and all other reagents were of analytical reagent grade. Nanopure water (18.2 M Ω ; Millipore Co., USA) was used throughout the experiment.

2.3. Synthesis of CDs

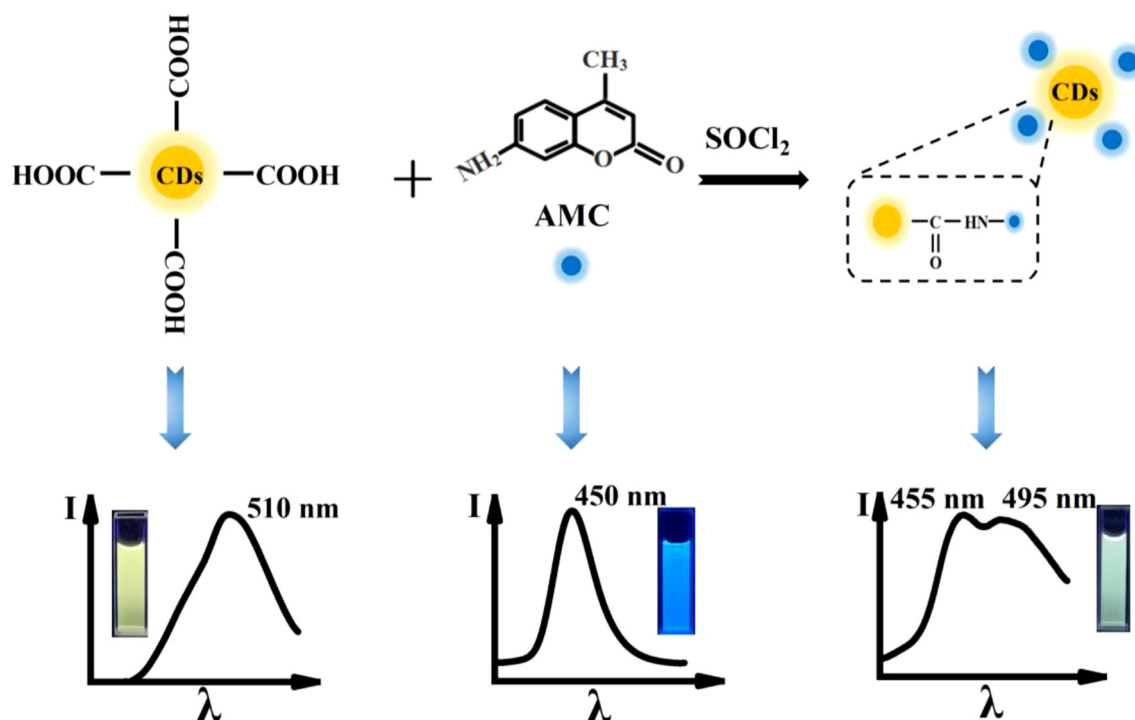
First, 0.4 g of carbon fiber powder was added to 30 mL of a mixed solution of sulfuric acid and nitric acid ($V_{H_2SO_4}:V_{HNO_3} = 1:3$), and the mixed sample was kept boiled under reflux for 4 h, then after the reaction was over, the sample was collected and neutralized with $NaHCO_3$ to bring the pH to approximately 7. The sample was then filtered to remove the formed salt, and the filtrate was collected for further dialyzed. Finally, the sample was ultrafiltered and the fractions equivalent to <3 kDa was investigated in our work.

2.4. Preparation of the CDC nanohybrid [36]

5 mg of CDs and 1 mL of thionyl chloride were added to a round bottom flask and heated to reflux in an acetonitrile solvent. After removing all the liquid, anhydrous acetonitrile was added to the flask to redisperse the sample, and the sample was filtered using an oily filter. The reaction was stirred for 12 h with 0.5 mg of AMC. After the reaction was completed, the sample was evaporated to remove the solvent and redispersed in water for further dialyzed to obtain the CDC nanohybrid.

2.5. Purified CDC nanohybrid

1 mL of CDC solution and 1 g of 1, 3-propane sultone were added to a round bottom flask, then 10 mL of 1, 4-dioxane solvent was added for reaction 24 h at 40 °C. After the reaction was completed, the sample was evaporated to remove the solvent, the resulting sample was dispersed in water and extracted with ethyl acetate to remove free AMC. Then the sample was evaporated to remove the solvent and redispersed in water for further dialyzed to obtain the purified CDC nanohybrid.



Scheme 1. Schematic diagram of the dual-emission ratiometric fluorescence sensor formation

2.6. Detection of DA with the ratiometric sensor

600 μL of CDC (0.1 mg/mL) solutions coupled with 30 μL of different concentrations of DA were mixed thoroughly at room temperature. The final concentrations of DA were 0, 2.4, 4.8, 9.6, 14.4, 19.2, 24, 33.6, 48, 72, 96, 144, 192, 240, 720, 960, 1200 and 2400 μM . Fluorescence spectra were then obtained in the wavelength range of 320–580 nm with excitation at 300 nm. The selectivity of this sensing system for DA was assessed using glucose, L-ascorbic acid, K^+ , Na^+ , urea, uric acid, TRY and other natural amino acids, such as Cys, Ala, Gly, Try, Glu and Gsh.

2.7. Detection of DA in real samples

The serum was diluted 50 times with a PBS buffer solution (pH 6.8, 0.01 M).

Different concentrations of DA were introduced to prepare the spiked samples.

3. Results and discussion

3.1. Synthesis and characterization of the CDC nanohybrid

A chemical oxidation method was used to prepare the CDs, which is suitable for the mass production of CDs. However, further separation and purification are required because of nonuniformity. As shown in Fig. 1A, it is obvious from the TEM image that the prepared <3 k CDs exhibit a regular spherical shape with an average particle diameter of 2.2 ± 0.1 nm (Fig. 1B). Their corresponding high-resolution X-ray photoelectron spectroscopy (XPS) as shown in Fig. 1C illustrates the spectrum of the CDs can be fitted by three peaks located at 284.8, 286.3 and 288.4 eV, corresponding to $\text{C}=\text{C}/\text{C}-\text{C}$, $\text{C}-\text{O}$ and $\text{C}=\text{O}$ bonds, respectively [37], indicating that the surface of the CDs is rich in oxygen-containing functional groups including hydroxyl groups, carbonyl

groups and carboxyl groups. Furthermore, the XRD spectrum of CDs exhibits obvious diffraction peaks at 25° and 42° , corresponding to plane 002 and plane 100 of the facets graphite, respectively [38]. According to Fig. S1 and Fig. S2, the fluorescence quantum yield of the CDs was 2.2% (using fluorescein as a reference).

As shown in the FT-IR spectra (Fig. S3), the bands at 1685 cm^{-1} and 1530 cm^{-1} are ascribed to the amide I and amide II bands, which proves the successful conjugation of the CDs with the AMC through the existence of amide bond between carboxyl groups and amino groups [36]. Fig. S4 illustrates the UV-vis spectra of the CDs, AMC and CDC nanohybrid. From the spectra, it can be found that the CDC nanohybrid has two absorbance peaks, which correspond to the absorption peaks of CDs and AMC. This indicates that the AMC was successfully coupled to CDs. Moreover, the fluorescence spectra of the CDs, AMC and CDC nanohybrid under an excitation of 300 nm are illustrated in Fig. 2A. The CDC nanohybrid shows dual emission at 455 nm and 505 nm attributable to CDs and AMC, respectively. Compared to the single CDs (510 nm) and AMC (450 nm) both produced a little shift, indicating that the obtained CDC nanohybrid fluorescent spectrum is not the result of the physical mixing between CDs and AMC. Therefore, the results of the FT-IR spectrum, UV-vis spectrum and fluorescent characterization, simultaneously demonstrate the successful preparation of the CDC nanohybrid.

Fig. S5 shows the fluorescence spectra of the CDC nanohybrid at different excitation wavelengths. Under 300 nm excitation, the emission peaks of both CDs and AMC can be observed at the same time. Therefore, all experiments were performed with an excitation wavelength of 300 nm. From Fig. 2B, we can see that there is a spectral overlap between the emission of AMC and the absorption of CDs, which theoretically demonstrates a slight fluorescence resonance energy transfer (FRET) from the CDs to AMC [39]. Moreover, according to previous research, FRET occurs when the distance between the donor and acceptor is less than 10 nm [15]. In our experiment, the CDs (acceptor) and AMC

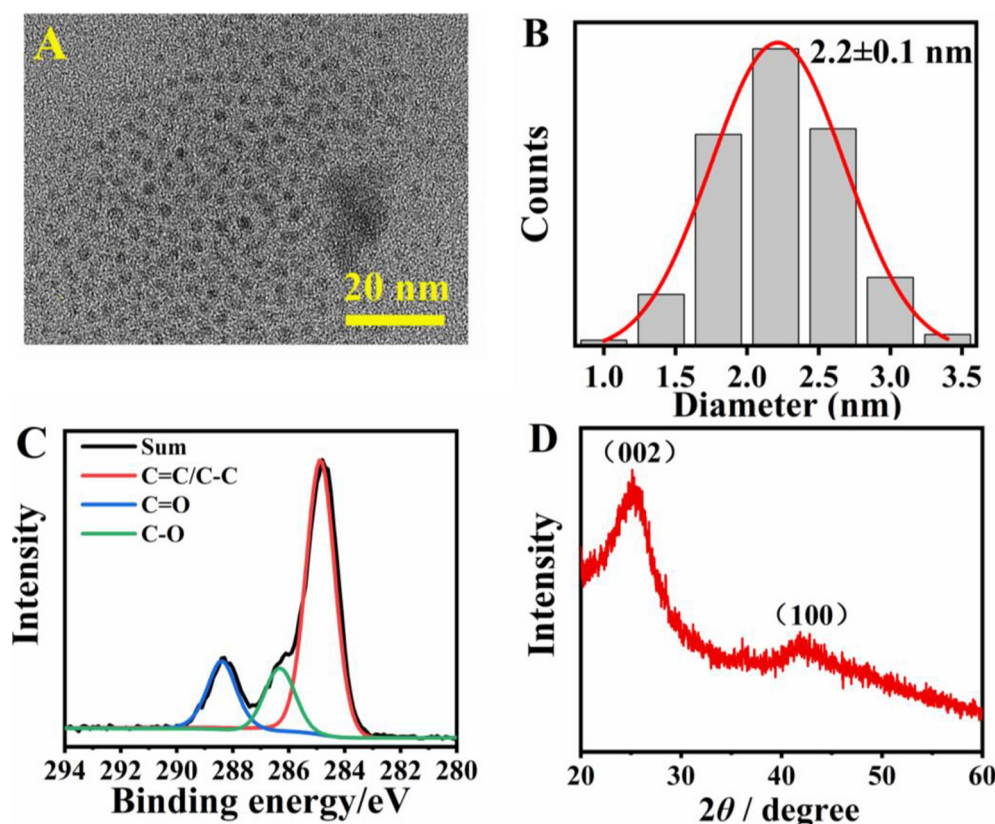


Fig. 1. (A) TEM image of carbon dots, (B) corresponding size distribution of carbon dots, (C) C 1s high-resolution XPS spectrum of carbon dots, (D) XRD spectrum of carbon dots.

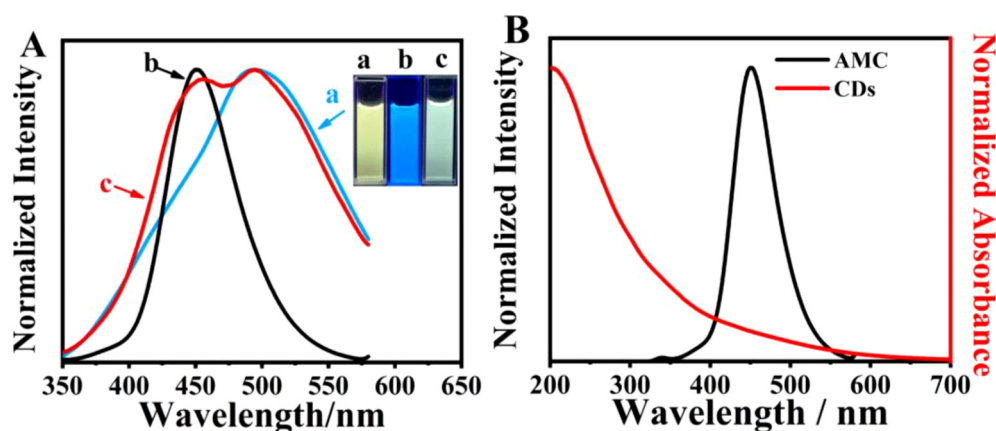


Fig. 2. (A) Fluorescent emission spectra ($\lambda_{\text{ex}} = 300$ nm) of (a) CDs, (b) AMC, (c) CDC nanohybrid, (B) Fluorescent emission spectra of AMC (black line) and absorbance of CDs (red line).

(donor) were conjugated together via amide bonds, so the distance between the components was sufficient to perform FRET.

3.2. Possible sensing mechanism

In neutral conditions, DA behaves like a positively charged particle with $-\text{NH}_3^+$ [39], while CDs behave as negatively charged particles due to their rich oxygen-containing functional groups on the surface, such as hydroxyl and carboxyl groups. Thus, CDs and DA can be attached by noncovalent interactions, including electrostatic interactions, π - π stacking, and hydrogen bonding [40,41]. Therefore, the quenching effect may be caused by photoinduced electron transfer. When the amine and hydroxyl functional groups of DA interact with the oxygen-containing groups on the surface of CDs, the lone pair of electrons in the oxygen-containing group can undergo intramolecular charge transfer or photoinduced electron transfer, resulting in a decrease in the emission amount and further quenching the CDs fluorescence [42]. To verify this conclusion, the fluorescence lifetime of the samples before and after the addition of DA was investigated. As Fig. S6 shown, the fluorescence lifetime of CDC nanohybrid decreased after the addition of DA, indicating that dynamic quenching contributes to the CDC nanohybrid toward DA detection. Moreover, it can be seen from Fig. S7 that there is no overlap between the absorption spectrum of DA and the emission spectrum of CDC nanohybrid, so fluorescence resonance energy transfer (FRET) mechanism can be excluded. Thus, the quenching effect was more likely caused by photoinduced electron transfer.

3.3. Detection of DA with the ratiometric sensor

The detection of DA by the CDC nanohybrid system was performed in a PBS solution (pH 6.8, 0.01 M), and different concentrations of DA were used to study the sensitivity of the nanohybrid sensor. This reaction is particularly quick and can be completed in less than 10 s. As shown in Fig. 3A, the excitation wavelength was 300 nm, and when the concentration of DA increased, the fluorescence of the CDs and AMC in the nanohybrid system could be quenched by DA to different degrees. When the DA concentration was increasing to 2400 μM , the CDs fluorescence at 505 nm was almost completely quenched. As shown in Fig. S8, according to the degree of quenching by adjusting the concentration of DA, the CDC nanohybrid showed different colors under a UV-lamp ($\lambda_{\text{ex}} = 360$ nm), when increasing the DA concentration, the color of the CDC nanohybrid would change from dark yellow to light yellow, indicating that the CDC nanohybrid could enable naked-eye visualization DA detection qualitatively. Fig. 3B shows a plot of the FL ratio (I_{505}/I_{455}) against the DA concentration. When the concentration of DA is in the range of 0–33.6 μM , the FL ratio (I_{505}/I_{455}) and DA concentration have a good linear relationship, the linear regression equation is $I_{505}/I_{455} = 1.02142 - 0.00419 [C_{\text{DA}}]$ ($R^2 = 0.992$). The limit of detection (LOD), defined as 3 times the standard deviation of background [12,34,43], was calculated as 5.67 nM. As Table S1 reveals, compared with other methods, this sensing platform has obvious advantages in detection sensitivity. Moreover, the ratiometric fluorescence probe has excellent accuracy compared with a single fluorescent

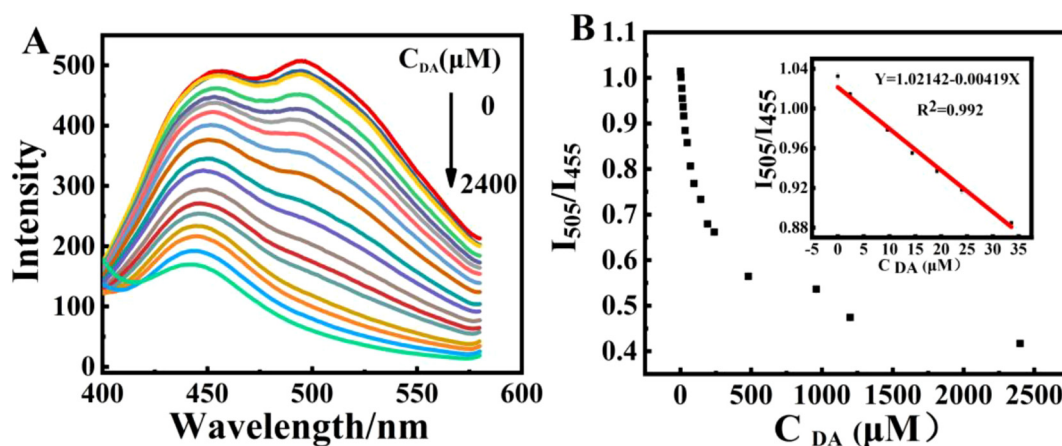


Fig. 3. (A) Fluorescent emission spectra ($\lambda_{\text{ex}} = 300$ nm) of CDC nanohybrid with different concentrations of DA. (B) The linear relationship between the ratiometric fluorescence intensity (I_{505}/I_{455}) and various concentrations of DA (0–33.6 μM), (inset) graph showing the linear relations between I_{505}/I_{455} and the concentrations of DA.

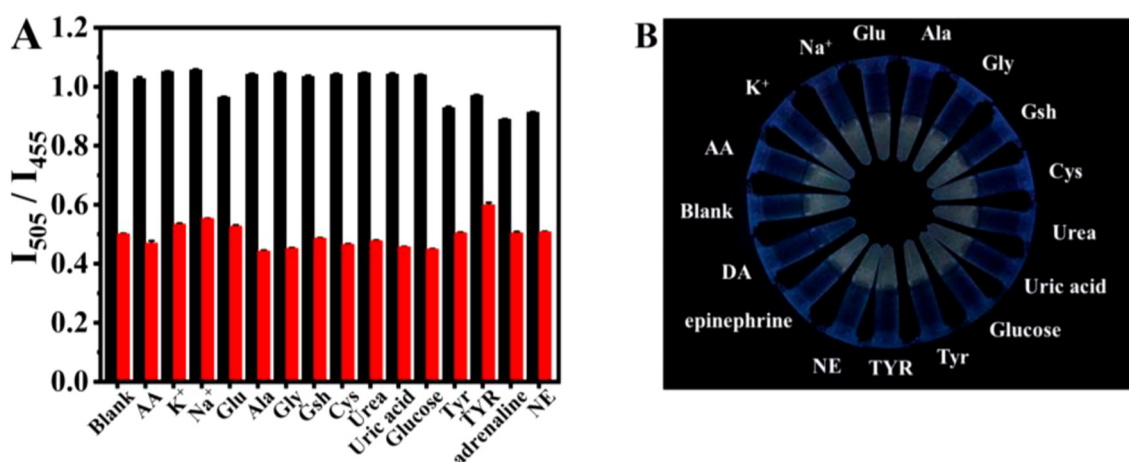


Fig. 4. (A) The interference studies of the CDC nanohybrid sensor toward DA. The black bars represent the fluorescence response of the sensor to the different interfering substances. The red bars represent the fluorescence of the aforementioned solution upon subsequent addition of DA. (B) FL images of the aqueous suspension of CDC nanohybrid with a different substances, excited by a 365 nm of UV-lamp.

probe, which can effectively eliminate background signal and environmental interference, resulting in high sensitivity and selectivity.

3.4. Selectivity and interference studies

The selectivity of fluorescent probes is one of the key parameters used to evaluate the feasibility of a sensor system. To investigate the specificity of the CDC nanohybrid probe, we tested some potentially interfering substances (100 mM, Na^+ , K^+ , AA, Cys, Ala, Glu, Gly, Gsh, Try, urea, uric acid and glucose, 10 mM, epinephrine and NE, 1 mg/mL, TRY) under the same conditions. As shown in Fig. 4A, no significant difference between the black bars group and the interference bars group was observed when the DA concentration was zero, indicating that the interfering substances have no significant effect on the sensing system. When DA and potential interferences coexist, even if the concentration of various substances is more than 5 times that of DA, their relative error in DA detection is also small. Moreover, Fig. 4B shows a photograph of different interfering substances added to the nanohybrid under a UV-lamp ($\lambda_{\text{ex}} = 360 \text{ nm}$). The FL of the nanohybrid is clearly not affected by other interferences except DA compared with the black bars group. Therefore, the prepared CDC nanohybrid probe displays high selectivity for DA determination.

3.5. Detection of DA in real samples

To evaluate the feasibility of the constructed CDC nanohybrid sensor platform for detecting DA in real samples. The concentration of DA in human serum samples was measured by the standard method. The results are displayed in Table 1. The recovery for the three different samples was 102–105%, and the RSDs $\leq 1.8\%$. The above results imply that this sensor platform has excellent potential for sensing DA in real serum samples.

4. Conclusion

In summary, a novel CDC nanohybrid ratiometric fluorescent probe prepared by covalently linking CDs and AMC through amide bonds,

which was successfully applied in on-site naked-eye detection of DA. Specifically, due to the FL of AMC and CDs is quenched to different degrees when adjusting the DA concentration, a significant color change (dark yellow-light yellow) can be easily observed by the naked eye under a UV-lamp. This CDC nanohybrid probe showed excellent sensitivity and selectivity for the detection of DA with a detection limit as low as 5.67 nM. Compared with previously reported methods, our nanohybrid probe has several important advantages, such as easy fabrication (less than 10 s), rapid detection, low interference and reliable results. Additionally, such CDC nanohybrid probe does not contain toxic semiconductor quantum dots or organic solvents and is therefore more environmentally friendly.

CRediT authorship contribution statement

Jia An: Conceptualization, Methodology, Validation, Writing - original draft. **Meizhu Chen:** Writing - review & editing. **Nan Hu:** Writing - review & editing. **Yongqin Hu:** Investigation, Resources. **Rubing Chen:** Investigation, Resources. **Ying Lyu:** Investigation, Resources. **Wenxi Guo:** Writing - review & editing. **Lijie Li:** Writing - review & editing. **Yufei Liu:** Conceptualization, Supervision, Project administration, Funding acquisition, Writing - review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.saa.2020.118804>.

Table 1
Detection of DA in real samples.

Sample	Spiked (μM)	Measured (μM)	Recovery (%)	RSD (% , n = 3)
1	14	14.69 ± 0.27	105	1.8
2	16	16.42 ± 0.19	103	1.2
3	25	25.46 ± 0.32	102	1.3

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