



Ratiometric two-photon excited photoluminescence of quantum dots triggered by near-infrared-light for real-time detection of nitric oxide release *in situ*



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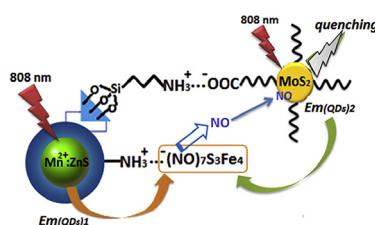
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HIGHLIGHTS

- $\text{Mn}^{2+}:\text{ZnS}@\text{SiO}_2/\text{MoS}_2\text{-RBS}$ nanocomposites were developed as a novel ratiometric two-photon excited fluorescence probe.
- This probe could conduct real-time detection of nitric oxide release *in situ*.
- High feasibility of this probe was confirmed in tumor intracellular microenvironments.

GRAPHICAL ABSTRACT



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ABSTRACT

Probe-donor integrated nanocomposites were developed from conjugating silica-coated $\text{Mn}^{2+}:\text{ZnS}$ quantum dots (QDs) with MoS_2 QDs and photosensitive nitric oxide (NO) donors ($\text{Fe}_4\text{S}_3(\text{NO})_7$, RBS). Under excitation with near-infrared (NIR) light at 808 nm, the $\text{Mn}^{2+}:\text{ZnS}@\text{SiO}_2/\text{MoS}_2\text{-RBS}$ nanocomposites showed the dual-emissive two-photon excited photoluminescence (TPEPL) that induced RBS photolysis to release NO *in situ*. NO caused TPEPL quenching of $\text{Mn}^{2+}:\text{ZnS}$ QDs, but it produced almost no impact on the TPEPL of MoS_2 QDs. Hence, the nanocomposites were developed as a novel QDs-based ratiometric TPEPL probe for real-time detection of NO release *in situ*. The ratiometric TPEPL intensity is nearly linear ($R^2 = 0.9901$) with NO concentration in the range of 0.01–0.8 μM , which corresponds to the range of NO release time (0–15 min). The detection limit was calculated to be approximately 4 nM of NO. Experimental results confirmed that this novel ratiometric TPEPL probe possessed high selectivity and sensitivity for the detection of NO against potential competitors, and especially showed high detection performance for NIR-light triggered NO release in tumor intracellular microenvironments. These results would promote the development of versatile probe-donor integrated systems, also providing a facile and efficient strategy to real-time detect the highly controllable drug release *in situ*, especially in physiological microenvironments.

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1. Introduction

As a diatomic free radical generated in human body, nitric oxide (NO) regulates the biological functions in cardiovascular,

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respiratory and nervous systems [1,2]. NO has been actively involved in immune responses and mediates macrophage against the destruction from foreign pathogens [3]. Additionally, NO has been confirmed to be implicated both in the growth suppression of tumors and selective killing of neoplastic tissues [4]. In biological systems, NO is yielded in endothelial cells from L-arginine by NO synthases of different forms, which only generate limited endogenous NO for practical demand [5]. Currently, the complex and extensive actions of NO in physiological systems partially promote the development of extrinsic NO donors towards storing more NO and releasing stored NO, based upon a highly controllable manner.

Among extrinsic NO donors, photosensitive donors have attracted considerable attention due to photoactivated NO release and NO delivery to specific targets [6–9]. Compared with spontaneous NO release from diazeniumdiolate donors under physiological situation [10–12], light-induced NO release from photosensitive NO donors is more promising since it can highly controllably release NO into biomedical systems [13–15]. Ultraviolet (UV) or visible light-triggering of photosensitive NO donors can perform precise control of location, time and dosage for NO administration [16]. However, UV or visible light to trigger drug release has inevitable defects in biosystems, such as limited tissue penetration depth and higher photon energy (be harmful to biosystems). Using the first near-infrared light (NIR-I, 700–900 nm) to trigger the release of NO is one feasible solution to overcome this limitation [17,18]. When compared to UV or visible light, NIR light has a higher tissue penetration depth and lower photon energy, thus improving its biomedical uses.

The integration of photosensitive NO donors and probes is attractive as it can release and detect NO synchronously, showing a great potential in synergistic diagnose and therapy. Tan et al. [19] reported CdTe quantum dots (QDs)-carboxymethyl chitosan composites that could spontaneously release NO and monitor NO release (induced photoluminescence (PL) quenching of QDs) *in situ*. Chitosan-conjugated fluorescein derivatives spontaneously released NO and detected NO *in situ*, resulting in PL enhancement of fluorescein derivatives [20,21]. In addition, the donors-QDs dual-loaded chitosan was synthesized and released NO under excitation of 1160 nm laser [22]. Xu et al. [23] prepared photodonor-QDs composites that could release NO under excitation of 1130 nm laser, without the report of NO detection *in situ*. In biomedical applications, NIR light wavelength should not exceed 900 nm, so as to avoid water absorption (limited penetration depth). Excitation at a wavelength of 700–900 nm provides a larger penetration depth and higher spatial resolution. Therefore, the nanocomposites that can perform NO release triggered by NIR-I light are promising [7,24]. Although the *in situ* detection of NO from the NO donor-probe nanocomposites have been reported [19–21,25], the relative detection mechanism only depend on quenching or enhancement of single PL from QDs or organic dyes. To obtain the exact PL intensity in real samples is difficult since its fluctuation at reagent concentrations. However, the introduction of a second chromophore to acquire ratiometric dual-PL can overcome this difficulty since it is independent of the content of reagents or chromophores [26,27]. Organic dyes-based ratiometric PL detection of NO has been reported [28–30], with dual-PL excited only by visible light. So far, there is still no literature that has reported the NIR-I light triggered ratiometric PL *in situ* detection of NO release.

Herein, semiconductor QDs-based versatile nanocomposites were prepared through conjugating silica-coated Mn²⁺:ZnS QDs with MoS₂ QDs and photosensitive NO donors (Fe₄S₃(NO)₇, RBS) under electrostatic interactions. Upon an excitation of 808 nm laser, the nanocomposites exhibited dual two-photon excited photoluminescence (TPEPL) with peaks at 489 nm for MoS₂ (QD₂) and 591 nm for Mn²⁺:ZnS (QD₁). Both TPEPL could trigger *in situ* release

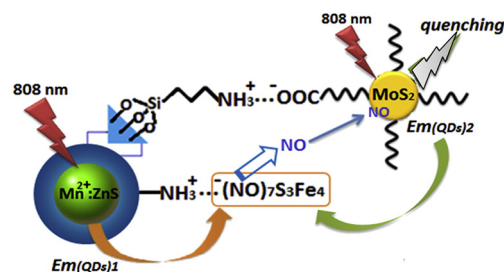
of NO, ascribed to TPEPL-induced RBS photolysis. Released NO caused TPEPL quenching of QD₂ due to NO coordinating with Mo atoms on the QD₂ surface, but it produced no effect on TPEPL of QD₁ since the silica-coating prevented the contact of NO with QD₁. Hence, we rationally developed a novel ratiometric TPEPL method for real-time detection of NO release *in situ* from the versatile NO probe-donor integrated nanocomposites, *i.e.* QD₁@SiO₂/QD₂-RBS (Scheme 1).

2. Experimental

2.1. Synthetic details of Mn²⁺:ZnS QDs and silica-coated QDs

Mn²⁺:ZnS QDs were prepared based on a modified version of the previously reported method [31]. In brief, 0.4 mmol of Zn(CH₃COO)₂ and 0.02 mmol of Mn(CH₃COO)₂ were used as Zn²⁺ and Mn²⁺ precursors respectively, while 1.0 mmol of 3-mercaptopropionic acid (MPA) was used for the capping agent. Both the precursors and MPA were loaded into a three-necked flask, where the air was pumped off and replaced with N₂. Then, 50 mL of ultrapure water was added with a syringe to form homogeneous reaction solution, whose pH was adjusted to be 11.0 by dropwise addition of 1.0 M of NaOH. Under N₂ atmosphere and vigorous stirring, the reaction solution was incubated for 30 min. After that, the aqueous solution of Na₂S (0.4 mmol) was rapidly added into the flask to allow the nucleation of QDs for 20 min at room temperature with continuous stirring. Afterward, the reaction solution was aged at 50 °C under N₂ atmosphere for 2 h to improve the quality of MPA-capped Mn²⁺-doped ZnS QDs. The purification was performed by precipitation of QDs with ethanol in a centrifuge at 5000 rpm for 5 min. Finally, the resulting QDs were dried in vacuum to obtain the solid powder of QDs, or were dispersed in ultrapure water to form aqueous suspension of QDs for the use in subsequent experiments.

Silicon-coated Mn²⁺:ZnS QDs were synthesized by a modified version of stöber method [32]. In a typical experiment, 50 mL of ethanol, 1 mL of distilled water, 2 mL of aqueous ammonia, and 0.2 mL of tetraethyl orthosilicate (TEOS) were injected into a conical flask (100 mL). The mixed solution was stirred for 10 min at room temperature. After that, cetyltrimethylammonium bromide (CTAB, 0.1 g) and Mn²⁺:ZnS QDs (10 mg) were ultrasonically dispersed in 10 mL of distilled water, which was then added into the foregoing solution. The reaction mixture was continuously stirred for 2 h at room temperature. The resulting products were isolated by centrifugation and washed with hot deionized water to remove the excess QDs and CTAB. The crude products were centrifuged, repeatedly washed with water and ethanol. The products were transferred into 50 mL of ethanol with 0.1 mL of 3-aminopropyltriethoxysilane (APTS), and the mixture was stirred at 25 °C for 6 h. The products were collected by centrifugation and washed with ethanol several times. Finally, the –NH₂ modified



Scheme 1. Schematic illustration of the fabrication of QD₁@SiO₂/QD₂-RBS nanocomposites and their application for the ratiometric TPEPL detection of NO *in situ*.

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