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# Turn-on detection of cysteine by a donor-acceptor type quinoline fluorophore: Exploring the sensing strategy and performance in bioimaging

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ABSTRACT

Tracking the biothiol cysteine (Cys) in living systems is a significant responsibility to balance the redox environment and oxidative stress. A quinoline-7-nitro-1,2,3-benzoxadiazole (**Q-NBD**) fluorophore has been synthesized and characterized towards examination of Cys. The probe forms a quinoline-substituted phenol (**Q-Ph-OH**) after thiolysis of the NBD ether bond, leading to an increase of fluorescence at green channel. The turn-on sensing mechanism originates from the change in intramolecular charge transfer (ICT-OFF) along with an aggregation-induced emission (AIE) as suggested by spectroscopy measurements in solutions, time-dependent density-functional theory (TD-DFT) calculations and $^{1}$H NMR titration examination. Importantly, **Q-NBD** exhibited great sensitivity with a low limit of detection value of 89.5 nM and remarkable selectivity in various biothiols towards Cys. The sensor probe was successfully used for detecting both endogenous and exogenous Cys in PC3 living cells and spiked Cys in human urine samples.



## 1. Introduction

Biothiols, namely cysteine (Cys), homocysteine (Hcy) and glutathione (GSH), are sulfhydryl (SH) containing amino acids that play significant roles in physiological and pathological systems. The concentration of intracellular Cys is associated with protein synthesis [1], the biosynthesis of GSH and cysteine, and retaining intracellular redox homeostasis [2–5]. Deficiency of Cys can cause slow growth, liver damage, skin lesions, Parkinson's, Alzheimer's and cardiovascular disease, and oxidative stress [6–9]. Additionally, Cys is one of the most important precursors for lanthionine, taurine, coenzyme A, biotin and gaseous hydrogen sulfide [4], and plays an important role as an antioxidant within mitochondria in balancing the redox environment to sense and respond to oxidative modifications of the Cys thiol group [4, 10]. Consequently, an ability to effectively and selectively monitor changes in the concentration of Cys molecules is an essential research goal in biosensor research.

A series of conventional analytical techniques have been developed to detect Cys, such as capillary electrophoresis [11], potentiometry [12], high-performance liquid chromatography [13], mass spectrometry [14] and UV–visible absorption and fluorescence emission spectroscopy [6]. There has been a particularly strong focus on fluorescent probes for the detection of Cys biomolecules due to their high selectivity and sensitivity, simplicity of use, and the scope for real-time monitoring, and non-invasive detection of Cys during sensing and bioimaging both *in vitro* and *in vivo* [15–17]. Fluorescence optical detection provides a set of favorable properties, such as the importance of the possible analyte molecule, and the ability to target Cys at the subcellular level due to its temporal and spatial resolution capability in living cells [18,19].

In recent years, a diverse array of fluorophores have been developed for the recognition and imaging of Cys. The cumulative effect of their SH and adjacent amino ($NH_2$) groups facilitate specific reactions with the probes, such as cyclization with aldehydes, Michael addition reaction, cyclization with acrylates, nucleophilic aromatic ($S_NAr$) substitution

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