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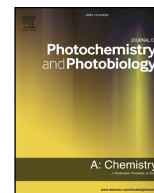

A hydroxyphenylquinazolinone-based fluorescent probe for turn-on detection of cysteine with a large Stokes shift and its application in living cells

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ABSTRACT

A hydroxyphenylquinazolinone-based fluorescent probe DAP-1 with a large Stokes shift (162 nm) was firstly developed for detection of cysteine. The probe DAP-1 with two acrylate as highly Cys-selective sites was designed based on the combination of excited state intramolecular proton transfer (ESIPT) and aggregation-induced emission (AIE) mechanism. Upon the treatment with cysteine, DAP-1 displayed a strong fluorescence enhancement (65-fold). The limit of detection obtained from fluorescent titration was as low as 0.03 μM. DAP-1 could detect cysteine with high selectivity and sensitivity. Significantly, DAP-1 could be used to detect cysteine in living cells.

1. Introduction

Biothiols, such as cysteine (Cys), homocysteine (Hcy) and glutathione (GSH), play crucial roles in protein synthesis, in maintaining biological redox homeostasis, and in post-translational control [1–3]. Normal levels of Cys (30–200 μM) maintain the synthesis of various proteins and act as the source of sulfide in human metabolism [4]. However, abnormal levels of Cys could result in certain diseases including liver damage, slow growth in children and Alzheimer's disease [5,6]. Hence, it is important to track Cys in living system.

Many techniques including, high-performance liquid chromatography [7], electrochemical methods [8], fluorescent probes [9–17], and mass spectroscopy [18] have been developed for the detections of bio-thiols. Among these detection techniques, fluorescent techniques are widely utilized in bio-thiol detection owing to its low detection limit and high sensitivity [11,10–17]. A lot of fluorescent probes based on different sensing mechanisms, including non-emissive Cu(II) complexes [19–22], cleavage reaction [12,23,24], cyclization reaction [25], Michael addition [26] and others [27] have been developed to detect biothiols. Nevertheless, discriminating Cys, GSH and Hcy (Scheme 1) is still challenging due to their structural similarity [28–30]. In the distinguishing Cys from Hcy and GSH, the conjugate addition/cyclization of Cys to acrylate group has demonstrated to be a valid method [31], which has been widely used in conventional chromophores including coumarin [30,32], 2-(2-hydroxyphenyl)quinazolin-4(3 H)-one (HPQ) [33,34], cyanine [35,36], benzothiazole [37,38], naphthalimide [39]. Unlike traditional chromophores suffering from fluorescence quenching in high concentration due to π-π interaction [40–46], aggregation-induced emission (AIE) chromophores such as HPQ and its derivatives are almost non-emissive when molecularly dispersed but become highly emissive in the aggregate state with fluorescence increasing along with the increase of chromophores concentration [47,48]. The AIE probes offer significant advantages of a high signal-to-noise ratio and excellent photostability [49,50].

Continuing on our research in this direction, we have developed a new double acrylate-functionalized fluorescent probe DAP-1 (Scheme 1) for detecting Cys. DAP-1 is derived from HPQ chromophore (compound 2) with two acrylate groups based on addition-cyclization reaction mechanism. Compound 2 displays a large Stokes shift (162 nm). It is known that chromophores with large Stokes shifts are more suitable for the application because they can greatly improve the detection sensitivity by reducing self-quenching and auto-fluorescence caused by the minimal overlap of excitation and emission spectra [51–55]. The acrylate group is commonly used as a functional trigger group to sense Cys [31,56,57], where the reaction with Cys generally exhibited faster reaction kinetics than GSH and Hcy [58–60]. Especially, double

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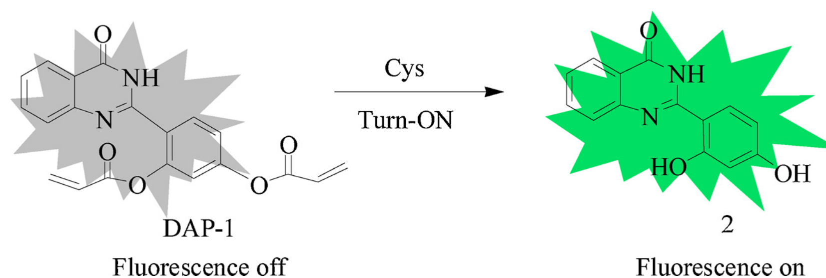
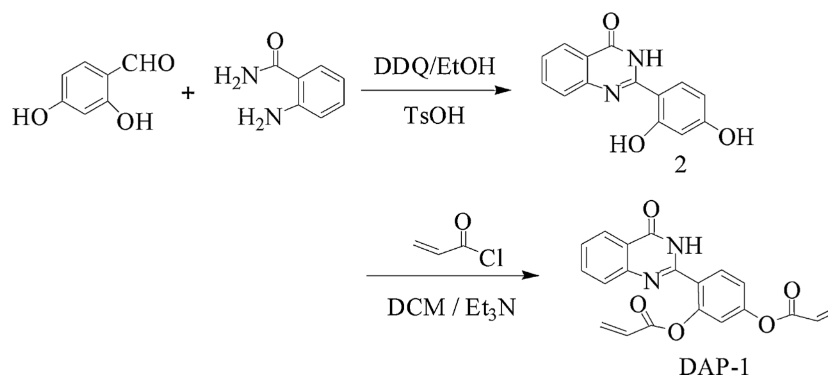


Scheme 1. Rational design of DAP-1.



Scheme 2. Synthesis route of DAP-1.

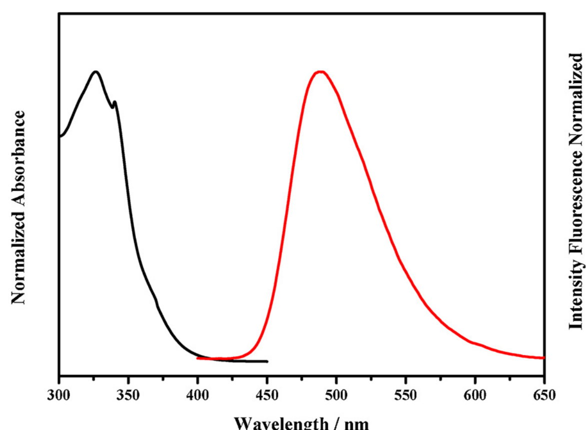


Fig. 1. Normalized absorption (black line) and fluorescence spectra (red line) of compound 2 in PBS/DMSO system (99/1, v/v, pH 7.4). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

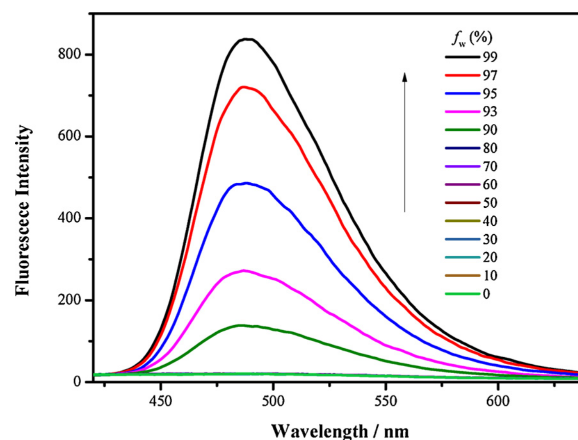


Fig. 2. Fluorescent spectra of compound 2 (10 μM) in water-DMSO mixtures with different fractions of water (f_w).

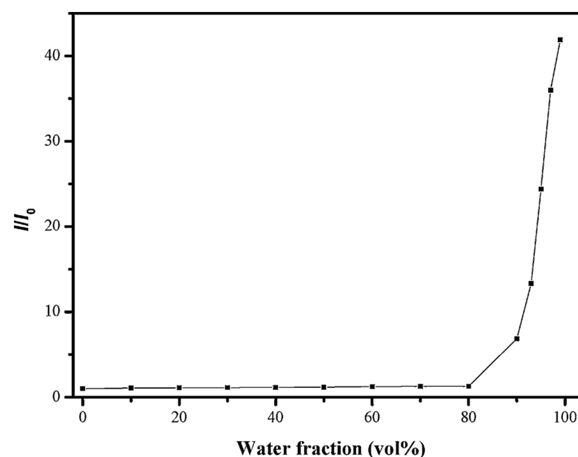


Fig. 3. Plot of relative fluorescent intensity (I/I_0) at 495 nm versus the solvent composition of the water -DMSO mixture of compound 2.

acrylate-functionalized probe DAP-1 can make the distinction of the reaction kinetics with bio-thiols even more evident, thus offering DAP-1 to actualize high sensitivity and selectivity for Cys over GSH and Hcy. To the best of our knowledge, DAP-1 is the firstly use of AIE chromophore HPQ with two acrylate groups to detect Cys. This probe DAP-1 has the following advantages: (1) it can be easily synthesized with good yield; (2) it displays a large Stokes shift; (3) it exhibits high signal-to-noise ratio and excellent photostability. The experiment results showed that DAP-1 could detect Cys with significant and rapid fluormetric response. Moreover, DAP-1 could be conveniently used in living cells imaging.

2. Experimental

2.1. Materials and instruments

All purchased chemicals and reagents are of analytic grade. ^{1}H NMR

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