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A ratiometric fluorescent probe for sensitive and selective detection of hydrogen sulfide and its application for bioimaging

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ABSTRACT

A new 4-hydroxy-1,8-naphthalimide-based ratiometric fluorescent probe for hydrogen sulfide (H_2S) detection was designed and synthesized. The probes showed fast response, high sensitivity and selectivity for hydrogen sulfide over other reactive sulfur species. The mechanism is based on H_2S-mediated nucleophilic addition followed by an intramolecular cyclization to give the product, 4-hydroxy-1,8-naphthalimide, which showed outstanding intramolecular charge transfer (ICT). Therefore, ratiometric signal was observed and with a H_2S detection of 1–10 μM. Furthermore, the probe successfully applied to bioimaging, demonstrating its potential applications in biological systems.

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1. Introduction

Hydrogen sulfide (H_2S) is best known for its characteristic smell of rotten eggs and has been traditionally viewed as toxic. Recent studies have shown that the typical concentration of H_2S play important roles in many biological processes[1–6], altered levels of H_2S has been influenced various physiological processes including vasodilation, anti-inflammatory, anti-oxidant, and antiapoptotic [7–12], and linked to many diseases, such as Alzherimer's disease, Down's syndrome, diabetes, and liver cirrhosis [13–16]. Previous studies have shown H_2S can be endogenously produced by enzymes such as cystathionine b-synthase (CBS), cystathionine g-lyase (CSE), and 3-mercaptopyruvate sulfurtransferase (3MST) [17–21]. It was reported that mitochondrial sulfide quinone oxidoreductase (SQR) and persulfide dioxygenase (ETHE1) are involved in the consumption of H_2S [22,23]. Therefore, H_2S have been recognized as the third gaseous transmitter besides nitric oxide (NO) and carbon monoxide (CO) [24,12,25,26], an efficient method for sensitively and selectively probing H_2S in living systems is highly required.

Fluorescent probes have been recognized as the efficient molecular tools, in particular, the exploitation of the reaction-based fluorescent probes have attracted increasing attention and become an active research field in recent years [27–31]. To date, many H_2S responsive fluorescence probes have been rationally developed based on specific reactions between probes and H_2S, including: H_2S reductive reactions, H_2S nucleophilic reactions, and copper sulfide precipitation reaction [32]. Among these, the probes based on bis-nucleophilic addition are attractive because H_2S is regard as a nonsubstituted thiol, can undergo two nucleophilic reactions, whereas thiols compounds (RSH) that can only undergo one time nucleophilic reaction. Therefore, a high selectivity for H_2S versus other biothiols can be guaranteed. Based on this strategy, M. Xian's group and several other groups presented some probes containing bis-electrophilic centers for the detection of H_2S [33–37]. However, most of them show turn-off or turn-on response in emission spectra which might be influenced in quantitative detection by many factors, such as the efficiency of excitation and emission, variabilities in probe distribution, the environment of the probe (temperature, pH, solvent polarity, etc.), and effective cell thickness in the optical beam [38,39]. So, ratiometric fluorescent probes for H_2S are urgently required because they can eliminate numerous ambiguities by self-calibration of two emission bands. Very few ratiometric fluorescent sensors for H_2S are known [40,41], it still remains a challenge to develop a ratiometric fluorescence probe for H_2S.

To develop a ratiometric fluorescence probe for H_2S, we used 1,8-naphthalimide, a typical intramolecular charge transfer (ICT) fluorophore, because of its desirable optical properties, such as high photostability, large Stokes' shift, insensitivity to pH [42–45]. 2,2′-Dipyridyl disulfide owning to its high sensitivity and rapid response to H_2S [46] was employed as the effective electrophile for trapping H_2S and benzene to be an appropriate linker as shown in Scheme 1. The results of this work show that the probe can be employed to

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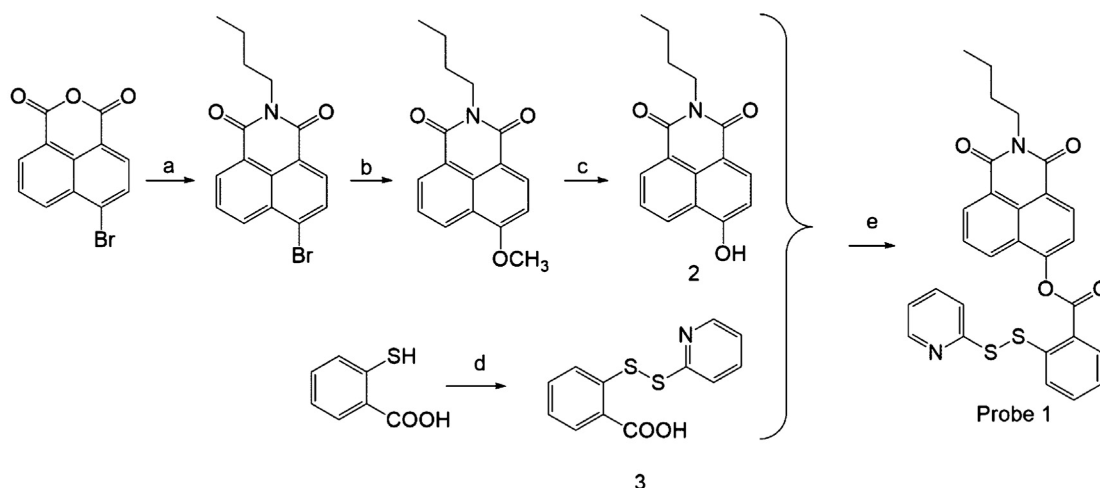

Scheme 1. The synthesis route of probe 1.
(a) n-BuNH_2, EtOH, reflux, 89%; (b) CH_3ONa/CH_3OH, reflux, 89%; (c) HBr, reflux, 65%; (d) CH_3OH, PySSPy, 78%; (e) EDC, DMAP, 52%.

detect H_2S in a ratiometric manner with high sensitivity and selectivity. In addition, we have demonstrated an application of probe for ratiometric detection of H_2S in cell imaging.

2. Experimental

2.1. Materials

4-Bromo-1,8-naphthalic anhydride, EDC (1-(3-dimethylamino-propyl)-3-ethylcarbodiimide hydrochloride), DMAP (4-dimethyl-aminopyridine) and other chemicals were purchased from Sigma-Aldrich or Aldrich and were used as received. Solvents were dried according to standard procedures. Probe 1 was synthesized using a modification of a literature method [33,34,39]. All other reactive sulfur species, including cysteine (Cys), homocysteine (Hcy) and glutathione (GSH) were analytical grade.

2.2. Instruments

^{1}H-NMR and ^{13}C-NMR spectra were collected on a 300 MHz spectrometer. Absorption spectra were recorded on a Lambda 20 UV/Vis spectrophotometer using 1 cm quartz cells. Fluorescence excitation and emission spectra were measured on a Cary Eclipse fluorescence spectrophotometer. High resolution mass spectra were obtained on a Varian QFT-ESI mass spectrometer. Fluorescence imaging was performed with a fluorescence microscope with a GFP light cube for fluorescence channel and 40× objectives.

2.3. Preparation and characterization of probe

Synthesis of probe (1) is summarized in Scheme 1. 4-Hydroxy-1,8-naphthalimide (2) and 2,2′-dipyridyl disulfide benzoic acid (3) were synthesized by the literature methods [33,34,39].

Dry CH_2Cl_2 (5 mL) was added to a mixture of compound 3 (52 mg, 0.2 mmol), compound 2 (54 mg, 0.2 mmol), EDC (38 mg, 0.2 mmol), and DMAP (2.5 mg, 0.02 mmol) in a 25 mL round-bottomed flask at room temperature. The mixture was stirred for overnight. Solvent was removed under reduced pressure and the residue was purified by column chromatography using petroleum ether/dichloromethane/ethyl acetate (5:5:1, v/v/v) to afford the desired probe as a white solid (50 mg, 52%).

^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS) δ 8.66 (t, J = 7.1 Hz, 2H), 8.48 (d, J = 7.3 Hz, 2H), 8.34 (d, J = 8.4 Hz, 1H), 8.05 (d, J = 8.2 Hz, 1H), 7.72–7.82 (m, 2H), 7.52–7.67 (m, 3H), 7.44 (t, J = 7.5 Hz, 1H), 7.12 (t, J = 7.9 Hz, 1H), 4.32–4.15 (t, J = 7.6 Hz, 2H), 1.69–1.76 (m, 2H), 1.43–1.50 (m, 2H), 1.00 (t, J = 7.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C, TMS) δ = 164.3, 164.2, 163.7, 158.8, 151.6, 151.0, 142.7, 137.6, 134.7, 132.4, 132.0, 131.9, 129.6, 127.9, 127.7, 126.8, 126.4, 125.6, 125.5, 123.3, 121.4, 121.0, 120.1, 120.0, 40.6, 30.4, 20.6, 14.1 ppm. HRMS $[M + Na]^+$ calcd for $C_{28}H_{22}O_4N_2S_2Na$, 537.09187, found, 537.09058. $[M + H]^+$ calcd for $C_{28}H_{23}O_4N_2S_2$, 515.10992, found, 515.10754 (Fig. S5–S7).

2.4. General UV–vis and fluorescence spectra measurements

Stock solutions of probe 1 (0.25 mM) were prepared in DMF (N,N-Dimethylformamide). Aqueous Na_2S (as a H_2S donor) and other biothiols solutions were also prepared using the deionized water. UV–vis and fluorescence spectra were obtained in DMF: water (1:9 v/v, PES buffer, pH 7.4) solutions. Fluorescence measurements were carried out with a slit width of 5 nm (λ_{ex} = 385 nm).

2.5. Cell imaging experiments with H_2S

HeLa cells were cultured in Dulbecco's modified Eagle's Medium (DMEM, Cellgro company) supplemented with 10% fetal bovine serum, 4 mM glutamine, 100 IU/mL penicillin, and 100 μg/mL streptomycin at 37 °C and with 5% CO_2 for two days. Cells were transferred to 24-well plates one day before imaging. Before use, the adherent cells were washed once with FBS-free DMEM. Then the cell was treated with Na_2S (100 μM) in culture media for 30 min at 37 °C and washed with phosphate-buffered saline (PBS). After washing with PBS to remove the remaining Na_2S, the cells were further incubated with probe 1 (25 μM) for 15 min in PBS buffer (pH 7.4, containing 100 μM CTAB). Cell imaging was carried out after washing the cells with PBS (pH 7.4). All of the microscopy images were taken on a fluorescence microscope with blue and green channels.

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