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A novel fluorescent probe for rapid and sensitive detection of hydrogen sulfide in living cells

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ABSTRACT

A novel fluorescent probe for H_2S was developed based on a far-red emitting indole-BODIPY, which was decorated with morpholine and 2,4-dinitrobenzenesulfonyl (DNBS) group. This probe showed rapid response ($t_{1/2} = 3$ min), high selectivity and sensitivity for H_2S with significant colorimetric and fluorescence OFF–ON signals, which was triggered by cleavage of 2,4-dinitrobenzenesulfonyl group. This probe could quantitatively detect the concentrations of H_2S ranging from 0 to 60 μM, and the detection of limit was found to be as low as 26 nM. Cell imaging results indicated that the probe could detect and visualize H_2S in the living cells.

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1. Introduction

Hydrogen sulfide (H_2S) is an important gaseous transmitter, which is endogenously generated from cystein with the aid of cystathionine β-synthase [1], cystathionine γ-lyase [2], and 3-mercaptopyruvate sulphur transferase [3]. H_2S plays vital roles in various physiological processes, such as modulation of blood pressure [4], reduction of ischemia reperfusion injury [5,6], exertion of anti-inflammatory effects [7] and reduction of metabolic rate [8]. However, aberrant H_2S production is associated with pathological states including Alzheimer's disease [9], Huntington's disease [10], and Parkinson's disease [11]. Thus, visualization of the production and concentration of H_2S within living cells is beneficial to the early diagnose of these diseases.

Fluorescence-based probe is a powerful tool for the detection and visualization of some biological species [12–18] due to its non-invasiveness, high sensitivity, high temporal and spatial resolution [19,20]. Recently, a number of fluorescent probes for H_2S have been developed on the basis of H_2S-mediated reduction of azides [21–23] and nitros [24,25], nucleophilic addition reaction [26,27], Tandem Michael addition reaction [28,29], copper sulfide precipitation [30,31], and thiolysis of dinitrophenyl ether [32,33]. Xian's group has utilized disulfide exchange mechanism to devise some fluorescent probes for H_2S [34–36]. In addition, enzyme-based probe has also been proposed [37]. Although these probes are innovative, they still have some disadvantages, such as excitation/emission in the ultraviolet or visible region [28,33], and long response time (up to 20 min). Excitation/emission in the visible region might be subjected to the interference from background [38,39]. Long response time is not suitable for real time analysis and bio-imaging of H_2S due to its transient nature. Therefore, it is highly desired to develop some fluorescent probes with long emission wavelength, rapid response and high sensitivity.

Herein we report a new fluorescent probe for H_2S based on indole-BODIPY fluorophore (Scheme 1). This probe exhibited rapid response to H_2S with good selectivity, long emission wavelength ($\lambda_{em} = 635$ nm) and low detection limit. Moreover, the probe has been successfully used for imaging H_2S in living cells with satisfying results.

2. Experimental Section

2.1. Materials

2,4-Dimethylpyrrole, trifluoroacetic acid (TFA), 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ), 1*H*-indole-3-carbaldehyde, piperidine, 2,4-dinitrobenzenesulfonyl chloride, 4-(2-chloroethyl)morpholine, 4-hydroxybenzaldehyde and triethylamine were purchased from commercial suppliers (Aladdin-Reagent, Sigma-Aldrich, TCI), and used without further purifications. 4,4-difluoro-8- (4-hydroxyphenyl)-1,3,5,7–tetramethyl-4-bora-3a,4a-dia-za-*s*-indacene and 1-(2-morpholinoethyl)-1*H*-indole-3-carbaldehyde were synthesized according to literatures [39,40].

2.2. Equipments and Methods

The ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker AV-400 spectrometer with tetramethylsilane (TMS) as the internal standard. The chemical shift was recorded in ppm and the following abbreviations

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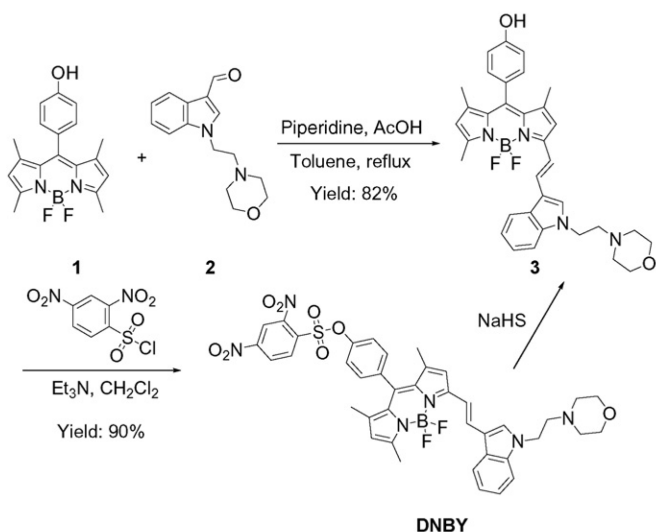

Scheme 1. Synthetic scheme of the probe **DNBY**.

were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, m = multiplet. Mass spectra were measured by a HP-1100 LC-MS spectrometer. UV–vis spectra were recorded on a Hitachi UV 3310 spectrometer. Fluorescence spectra were recorded on a Hitachi FL-4700 fluorometer. Fluorescent images were acquired on a Nikon A1 confocal laser-scanning microscope with a 100× objective lens. Solvents used for UV–vis and fluorescence measurements were of HPLC grade. Column chromatography was performed on silica gel (mesh 200–300), which was purchased from Qingdao Ocean Chemicals Corporation.

2.3. Synthesis and Characterization

2.3.1. Synthesis of Compound 3

4,4-Difluoro-8-(4-hydroxyphenyl)-1,3,5,7-tetramethyl-4-bora-3a,4a-diaza-s-indacene (170.0 mg, 0.50 mmol), 1-(2-morpholinoethyl)-1*H*-indole-3-carbaldehyde (168.0 mg, 0.65 mmol) and two drops of piperidine were dissolved in 30 mL of toluene. The reaction mixture was heated to 110 °C under nitrogen atmosphere, then two drops of acetic acid were added. The reaction mixture was stirred at 110 °C for 16 h. After the reaction was finished, the solvent was removed under reduced pressure. The residue was purified by silica gel column chromatography ($CH_2Cl_2/C_2H_5OH = 60/1$) to afford compound **3** as a dark blue solid (179.9 mg, 0.31 mmol, 62%). ^1H NMR (400 MHz, DMSO-d_6) δ 9.82 (s, 1H), 7.93 (s, 2H), 7.79 (d, *J* = 16.4 Hz, 1H), 7.62 (d, *J* = 7.2 Hz, 1H), 7.46 (d, *J* = 16.4 Hz, 1H), 7.28 (m, 2H), 7.15 (d, *J* = 8.2 Hz, 2H), 6.99 (s, 1H), 6.93 (d, *J* = 8.2 Hz, 2H), 6.10 (s, 1H), 4.38 (t, *J* = 5.7 Hz, 2H), 3.56 (s, 4H), 2.70 (s, 2H), 2.48 (s, 6H), 1.50 (s, 3H), 1.42 (s, 3H)·^{13}C NMR (100 MHz, DMSO-d_6) δ 158.47, 155.61, 151.25, 143.37, 139.94, 139.55, 137.75, 133.39, 132.80, 131.22, 129.87, 125.95, 125.19, 123.12, 121.52, 120.48, 120.18, 118.27, 116.39, 113.78, 113.59, 111.46, 66.64, 57.99, 53.73, 43.49, 15.01, 14.73, 14.47. HR-MS (ESI): calcd for $C_{34}H_{35}BF_2N_4O_2$ + H 581.2905; Found 581.2906.

2.3.2. Synthesis of Compound DNBY

Compound **3** (81.0 mg, 0.14 mmol) and triethylamine (60.0 μL, 0.35 mmol) were dissolved in 20 mL of anhydrous CH_2Cl_2. To this solution, 2,4-dinitrobenzenesulfonyl chloride (74 mg, 0.28 mmol) in 2 mL of anhydrous CH_2Cl_2 was added dropwise in 0.5 h at 0 °C. Then, the temperature was raised to 40 °C, and the reaction mixture was stirred for 2 h. After the reaction completed, the solvent was removed under reduced pressure. The residue was purified by silica gel column chromatography ($CH_2Cl_2/C_2H_5OH = 100/1$) to afford the probe **DNBY** as a dark blue solid (70.0 mg, 0.09 mmol, 64%). ^1H NMR (400 MHz, DMSO-d_6) δ 9.15 (d, *J* = 2.0 Hz, 1H), 8.60 (dd, *J* = 8.7, 2.2 Hz, 1H), 8.17 (d, *J* = 8.7 Hz, 1H), 7.96 (s, 1H), 7.94 (d, *J* = 6.9 Hz, 1H), 7.84 (d, *J* = 15.1 Hz, 1H), 7.63 (d, *J* = 8.2 Hz, 1H), 7.56–7.34 (m, 6H), 7.28 (m, 2H), 7.05 (s, 1H), 6.12 (s, 1H), 4.38 (s, 2H), 3.55 (s, 4H), 2.70 (s, 2H), 2.48 (s, 6H), 1.35 (s, 3H), 1.28 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 156.42, 152.06, 151.64, 149.39, 148.67, 143.12, 139.43, 137.77, 136.54, 135.13, 134.34, 133.72, 132.79, 131.39, 130.57, 130.33, 127.70, 125.99, 123.33, 123.22, 121.62, 120.78, 120.18, 118.90, 113.87, 113.35, 111.52, 66.46, 57.78, 53.62, 43.30, 15.05, 14.72, 14.46. HR-MS (ESI): calcd for $C_{40}H_{37}BF_2N_6O_8S$ + H 811.2533; Found 811.2532.

2.3.3. Conversion of Compound DNBY by NaHS

NaHS (10.0 mg, 0.18 mmol) and compound **DNBY** (30.0 mg, 0.037 mmol) were dissolved in 3.0 mL absolute ethanol at room temperature. 30 min later, the solvent was removed under reduced pressure. The residue was purified by flash column chromatography (CH_2Cl_2/C_2H_5OH = 60/1) to give a dark blue solid (11.6 mg, 0.02 mmol, 54%).

2.4. Fluorescence Analysis

The solutions of various testing species were prepared from $CaCl_2$, $MgCl_2$, KI, NaCl, KBr, NaF, NaN_3, Na_2SO_4, Na_2SO_3, CH_3COONa, NaH_2PO_4, GSH, Cys, Hcy, H_2O_2 in double-distilled water. Hydroxyl radicals were generated from the reaction of Fe^{2+} with H_2O_2. Singlet oxygen ($^1O_2$) was generated from ClO^- and H_2O_2. The stock solution of **DNBY** (10 μM) was prepared in 10 mM PBS buffer solution (pH 7.4) with 30% fraction of ethanol. For all measurements, the excitation wavelength was 560 nm, the excitation and emission slit widths were 5 nm.

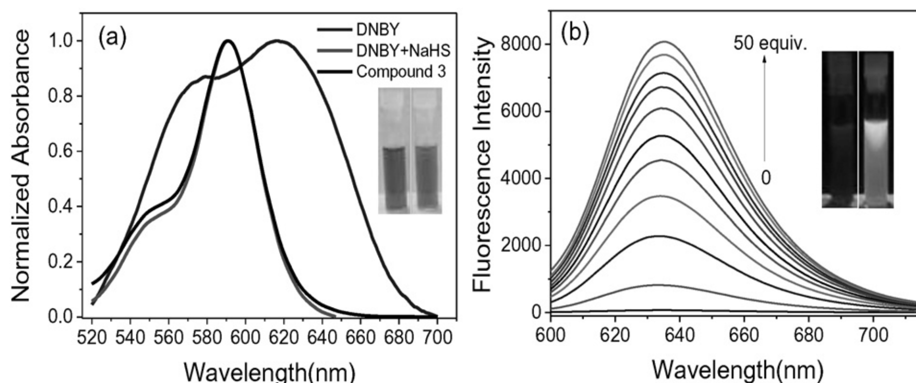

Fig. 1. (a) Absorption spectra of **DNBY** (10 μM) in the absence (blue line) or presence (red line) of NaHS (500 μM) in PBS aqueous solution (C_2H_5OH/PBS = 3:7, pH 7.4). Inset: color changed from blue to red. (b) Fluorescence spectra changes of **DNBY** (10 μM) upon the addition of NaHS (0–500 μM) in PBS aqueous solution (C_2H_5OH/PBS = 3:7, pH 7.4). Slits: 5/5 nm.

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