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Original article

# Cascade reaction-based fluorescent probe for detection of H<sub>2</sub>S with the assistance of CTAB micelles

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## ABSTRACT

We report a turn-on fluorescent probe for H<sub>2</sub>S through a cascade reaction using a new trap group 4-(bromomethyl)benzoate, based on excited-state intramolecular proton transfer (ESIPT) sensing mechanism. The probe showed good selectivity and high sensitivity towards H<sub>2</sub>S and it was capable of detecting and imaging H<sub>2</sub>S in living HeLa cells, indicating its potential biological applications.

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## 1. Introduction

For centuries, hydrogen sulfide has been recognized as a toxic molecular. When exposed to this colorless, flammable gas, which has a distinctive smell of rotten eggs, people may suffer from respiratory failure, loss of consciousness, sudden cardiac death, hepatic and olfactory paralysis. However, more recent studies have challenged this traditional view. H<sub>2</sub>S is now identified as the third biological signaling molecular besides nitric oxide (NO) and carbon monoxide (CO) and plays important roles in maintaining normal physiology [1]. Endogenous H<sub>2</sub>S can be produced from sulfur-containing biomolecules such as cysteine and homocysteine, which is catalyzed by cystathionine beta synthase (CBS), cysteine aminotransferase and mercaptopyruvate sulfurtransferase (CAT/MST) [2,3]. These enzymes are widely spread in human tissues ranging from the heart and vasculature, brain, kidney, liver, lungs, indicating the important physiological roles of H<sub>2</sub>S in the body. Besides, H<sub>2</sub>S can also be produced from non-enzymatic processes, including release from sulfur stores and metabolism of polysulfide

[4,5]. The abnormal level of H<sub>2</sub>S can result in many diseases, such as Alzheimer's disease, Down's syndrome, diabetes, and liver cirrhosis [6–9]. Therefore, methods for monitoring the production, trafficking, and consumption of H<sub>2</sub>S in living systems are highly desired.

Compared with the traditional methods including colorimetric assays [10,11] and gas chromatography [12,13], fluorescent probes present lots of advantages, such as rapid response, high sensitivity and excellent selectivity [14–16]. Recently, several fluorescent probes have been reported for the detection of H<sub>2</sub>S in living systems [17–20]. Common strategies include: H<sub>2</sub>S mediated reduction of azide to amine [21,22], H<sub>2</sub>S trapped by nucleophilic addition [23–25], copper sulfide precipitation [26,27], and thiolysis of dinitrophenyl ether [28,29]. Among these, H<sub>2</sub>S trapped by nucleophilic addition strategy has been widely applied. Fluorescent probes based on this strategy usually take advantage of the dual nucleophilicity of H<sub>2</sub>S. Such probes usually contain a H<sub>2</sub>S trap group with two electrophilic reaction sites and a fluorescent reporter, which discriminates the H<sub>2</sub>S from other biothiols.

Recently, excited state intramolecular proton transfer (ESIPT) compounds have been widely used in designing sensors for anions [30,31], cations [32,33], amino acids [34–36] and small neutral molecules [37,38], because of their intrinsic properties, ultra-fast reaction rate and huge bathochromic shift in the emission signal.

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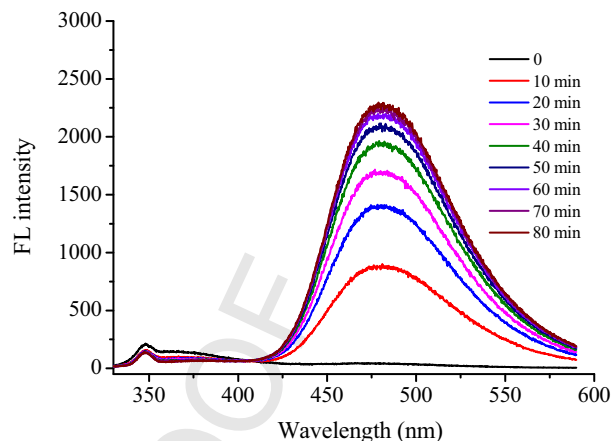
Herein, we reported a fluorescent probe using 2-(hydroxyphenyl)benzothiazole (HBT), a typical ESIPT molecule, as fluorescent reporter, and 4-(bromomethyl)benzoate as trap group, which showed fast response to  $\text{H}_2\text{S}$  through cascade reaction. As the hydroxyl group was protected by 2-(bromomethyl)benzoate, the HBT moiety of the probe showed enol-like fluorescence. The initial nucleophilic attack of  $\text{H}_2\text{S}$  towards bromomethyl group would lead to an intermediate thiol, which was followed by a cyclization cascade reaction towards the adjacent ester carbonyl to release the HBT with keto emission. Thus, the detection of  $\text{H}_2\text{S}$  was realized.

## 2. Experimental

Probe **1** was synthesized using a simple procedure with HBT and 2-(bromomethyl)benzoic acid as starting materials, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDCI) as a coupling reagent, and 4-dimethylaminopyridine (DMAP) as catalyst (Scheme 1).

**2-(2'-Hydroxy-3'-methoxyphenyl)benzothiazole (HMBT):** A solution of 2-aminothiophenol (0.3 mL, 4.2 mmol) and *o*-vanillin (0.48 g, 3.15 mmol) in EtOH (10 mL), aq.  $\text{H}_2\text{O}_2$  (30%, 18.9 mmol) and aq. HCl (37%, 9.45 mmol) was stirred at rt for 90 min. The solution was quenched by 10 mL  $\text{H}_2\text{O}$ . The precipitate was filtered, dried under vacuum and recrystallized from EtOH to afford the desired product as a light brown solid (0.64 g, 79% yield).  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz, ppm):  $\delta$  12.75 (s, 1H), 8.01 (d, 1H,  $J = 7.6$  Hz), 7.91 (d, 1H,  $J = 7.2$  Hz), 7.51 (t, 1H,  $J = 6.8$  Hz), 7.42 (t, 1H,  $J = 7.2$  Hz), 7.33 (dd, 1H,  $J_1 = 1.2$  Hz,  $J_2 = 8.0$  Hz), 6.99 (dd, 1H,  $J_1 = 1.2$  Hz,  $J_2 = 8.0$  Hz), 6.91 (t, 1H,  $J = 8.0$  Hz), 3.96 (s, 1H).

**Probe 1:** To a solution of EDCI (0.346 g, 1.5 mmol) in  $\text{CH}_2\text{Cl}_2$  (20 mL) was added 2-bromodimethylbenzoic acid (0.312 g, 1.5 mmol) followed by DMAP (0.012 g, 0.1 mmol) and HMBT (0.346 g, 1 mmol). The mixture was stirred at room temperature for 12 h and then filtered, washed with water. The filtrate was concentrated to afford the crude product, then purified by silica gel column chromatography (PE: $\text{CH}_2\text{Cl}_2 = 1:1$ ) to afford compound **1** as a white solid (0.24 g, 40%).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ , ppm):  $\delta$  8.41 (d, 1H,  $J = 4.0$  Hz), 7.93–7.99 (m, 2H), 7.83 (d, 1H,  $J = 4.0$  Hz), 7.34–7.56 (m, 6H), 7.15 (d, 1H,  $J = 4.0$  Hz), 4.94–5.14 (d, 2H), 3.90 (s, 3H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ): 164.2, 162.3, 153.0, 152.1, 140.0, 139.8, 138.1, 135.5, 134.0, 133.3, 132.3, 132.0, 130.9, 129.0, 128.7, 128.5, 128.2, 127.7, 126.9, 126.3, 125.8, 125.3, 123.4, 122.1, 121.1, 121.5, 121.4, 114.2, 69.6, 56.4, 44.1, 31.0. HRMS: calcd: 454.010, found: 454.011.

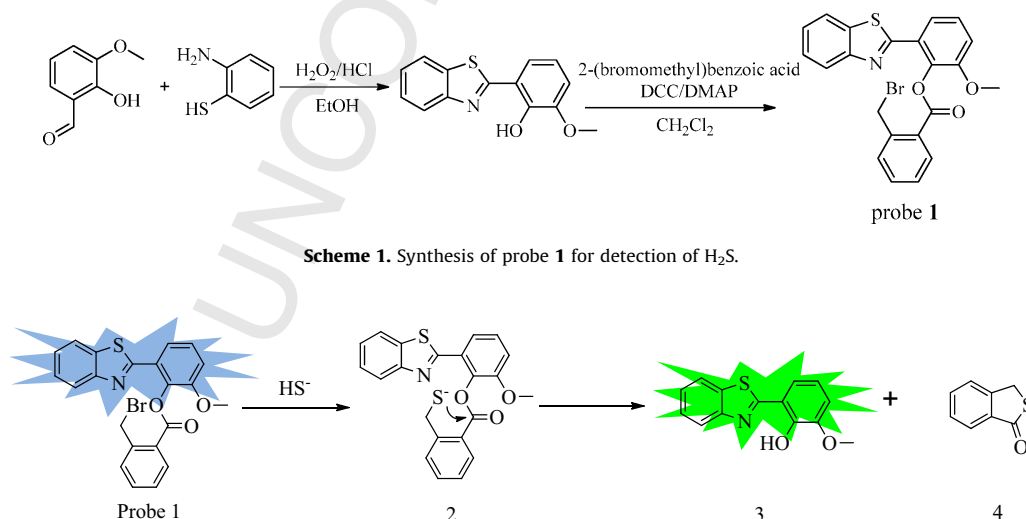


**Fig. 2.** Time-dependent fluorescence response of probe **1** (10  $\mu\text{mol/L}$ ) upon addition of NaHS (200  $\mu\text{mol/L}$ ) in HEPES buffer (20 mmol/L, pH 7.4, containing 1 mmol/L CTAB).  $\lambda_{\text{ex}} = 310$  nm,  $\lambda_{\text{em}} = 484$  nm. Slits: 5/5 nm.

## 3. Results and discussion

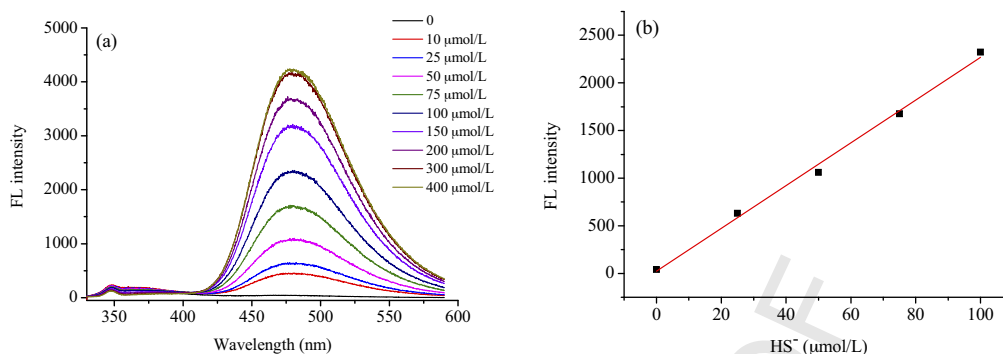
The proposed sensing mechanism is shown in Fig. 1. As the hydroxyl group is protected by 2-(bromomethyl)benzoate, the excited state intramolecular proton transfer (ESIPT) process was forbidden. As a result, the HBT moiety of probe **1** shows enol-like fluorescence. The initial nucleophilic attack of  $\text{H}_2\text{S}$  towards bromomethyl group would lead to an intermediate thiol, which is followed by a cyclization cascade reaction towards the adjacent ester carbonyl to release the HBT. Upon irradiation, the resulting HBT generated the excited state intramolecular proton transfer (ESIPT) tautomer, which shows keto emission. To identify the proposed sensing mechanism, probe **1** was treated with excess NaHS and  $\text{Et}_3\text{N}$  in  $\text{CH}_3\text{CN}$ . After the reaction, the HBT was released, with the formation of cyclization product **4**. All products were separated and confirmed with  $^1\text{H}$  NMR (Figs. S1 and S2 in Supporting information).

We first tested the absorption spectra of probe **1** in HEPES buffer. However, the obvious variation of the absorption spectra of **1** in 12 h suggested that it was unstable in HEPES buffer, probably due to its poor solubility in pure water (Fig. S3 in Supporting information). Then we used 50% ethanol as co-solvent, and the stability of **1** was improved (Fig. S4 in Supporting information). As



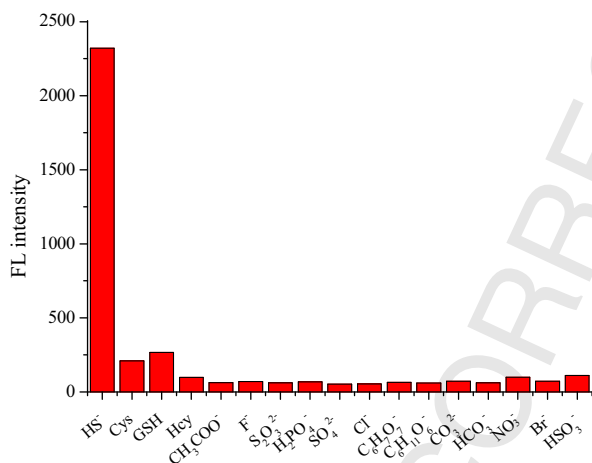
**Scheme 1.** Synthesis of probe **1** for detection of  $\text{H}_2\text{S}$ .

**Fig. 1.** The proposed sensing mechanism of probe **1** for  $\text{H}_2\text{S}$ .



**Fig. 3.** (a) Fluorescence spectra of probe **1** (10  $\mu\text{mol/L}$ ) upon addition of NaHS (0–400  $\mu\text{mol/L}$ ) in HEPES buffer (20 mmol/L, pH 7.4, containing 1 mmol/L CTAB). (b) Fluorescence response of probe **1** at 484 nm to NaHS concentration (0–100  $\mu\text{mol/L}$ ). Spectra were recorded after incubation with different concentrations of NaHS for 1 h.  $\lambda_{\text{ex}} = 310 \text{ nm}$ ,  $\lambda_{\text{em}} = 484 \text{ nm}$ . Slits: 5/5 nm.

shown in Fig. S5 in Supporting information, with the addition of 200  $\mu\text{mol/L}$  NaHS in ethanol/HEPES buffer (1:1, v/v, 20 mmol/L, pH 7.4), the emission at 350 nm (which is attributed to the enol form) decreased, followed by a new peak appearing at 484 nm (which is attributed to the keto form). However, the fluorescence at 484 nm was quite weak, as the intramolecular hydrogen bond is strongly disturbed in polar solvents [39]. We speculated that the ESIPT would be enhanced in the nonpolar core of CTAB micelles. Probe **1** was stable in HEPES buffer (20 mmol/L, pH 7.4) containing 1 mmol/L CTAB (Fig. S6 in Supporting information). As we expected, upon addition of NaSH to probe **1**, the original emission at 350 nm decreased, and a significant fluorescence enhancement at 484 nm of approximately 60-fold was observed (Fig. 2). In contrast, an enhancement of only 5-fold was observed in ethanol/HEPES buffer (1:1, v/v, 20 mmol/L, pH 7.4) (Fig. S5). The results



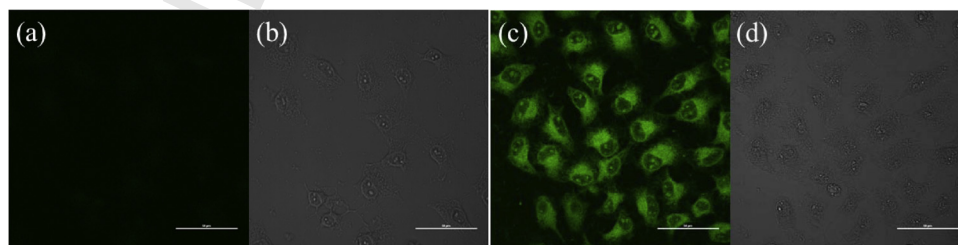
**Fig. 4.** Fluorescence response of probe **1** (10  $\mu\text{mol/L}$ ) upon addition of various species in HEPES buffer (20 mmol/L, pH 7.4, containing 1 mmol/L CTAB).  $\lambda_{\text{ex}} = 310 \text{ nm}$ ,  $\lambda_{\text{em}} = 484 \text{ nm}$ . Slits: 5/5 nm.

indicated that ESIPT process was greatly enhanced with the assistance of CTAB micelles. Therefore, the following studies were carried out in HEPES buffer (20 mmol/L, pH 7.4, containing 1 mmol/L CTAB). The probe **1** (10  $\mu\text{mol/L}$ ) upon reaction with NaHS (2 mmol/L) in HEPES buffer (20 mmol/L, pH 7.4, containing 1 mmol/L CTAB) exhibited a pseudo first order reaction kinetics with rate constant  $k = 0.59 \text{ min}^{-1}$  ( $t_{1/2} = 1.17 \text{ min}$ ), indicating the fast response of **1** towards  $\text{H}_2\text{S}$  (Fig. S7 in Supporting information).

Subsequently, quantitative response of probe **1** in HEPES buffer (20 mmol/L, pH 7.4, containing 1 mM CTAB) towards  $\text{H}_2\text{S}$  was estimated. As shown in Fig. 3a, with the increasing concentrations of NaHS, the original emission at 350 nm decreased, and a significant fluorescence enhancement at 484 nm was observed. Moreover, the fluorescence intensity of 484 nm showed linear relationship with NaHS concentrations ranging from 0 to 100  $\mu\text{mol/L}$ , suggesting the potential application for quantitative determination of  $\text{H}_2\text{S}$  (Fig. 3b). The detection limit for  $\text{HS}^-$  was estimated to be 0.50  $\mu\text{mol/L}$  ( $S/N = 3$ ), which is much lower than the concentration required to cause physiological response [40].

To evaluate the selectivity of the probe to  $\text{H}_2\text{S}$ , emission spectra changes upon addition of 20 equivalents of different interfering species, such as cysteine (Cys), glutathione (GSH), homocysteine (Hcy), sodium acetate ( $\text{CH}_3\text{COONa}$ ), sodium fluoride (NaF), sodium persulfate ( $\text{Na}_2\text{S}_2\text{O}_8$ ), sodium dihydrogen phosphate ( $\text{NaH}_2\text{PO}_4$ ), sodium sulfate ( $\text{Na}_2\text{SO}_4$ ), sodium chloride (NaCl), sodium tartrate ( $\text{C}_4\text{H}_4\text{Na}_2\text{O}_6$ ), sodium gluconate ( $\text{C}_6\text{H}_{11}\text{NaO}_7$ ), sodium carbonate ( $\text{Na}_2\text{CO}_3$ ), sodium bicarbonate ( $\text{NaHCO}_3$ ), sodium nitrate ( $\text{NaNO}_3$ ), sodium bromide (NaBr), sodium hydrogen sulfite ( $\text{NaHSO}_3$ ) were studied. As shown in Fig. 4, in most cases, little change in emission intensity was observed. In contrast, a great enhancement in emission intensity was only observed when adding NaHS. Thus, these results demonstrated that probe **1** has a high selectivity towards  $\text{H}_2\text{S}$ .

We further examined the capability of probe **1** to  $\text{H}_2\text{S}$  in living cells (Fig. 5). After incubated with probe **1** (20  $\mu\text{mol/L}$ ) for 45 min in culture medium, HeLa cells showed almost no fluorescence in



**Fig. 5.** Images of  $\text{H}_2\text{S}$  in HeLa cells using probe **1** (20  $\mu\text{mol/L}$ ) at 37  $^\circ\text{C}$ . (a) Fluorescence and (b) bright-field images of HeLa cells incubated with probe **1** for 45 min. (c) Fluorescence and (d) bright-field images of HeLa cells incubated with NaHS (200  $\mu\text{mol/L}$ ) for 30 min and further incubated with probe **1** for 45 min. Scale bar: 50  $\mu\text{m}$ .



green channel. By contrast, when HeLa cells were pretreated with NaHS (200  $\mu\text{mol/L}$ ) before incubated with probe **1** (20  $\mu\text{mol/L}$ ) for 45 min, the obvious fluorescence was observed. It revealed that probe **1** has potential for visualizing  $\text{H}_2\text{S}$  levels in living cells.

#### 4. Conclusion

In conclusion, we designed and synthesized a novel fluorescent probe **1** for the detection of  $\text{H}_2\text{S}$  based on ESIPT mechanism with the assistance of CTAB. As the hydroxyl group is protected by 2-(bromomethyl)benzoate, probe **1** showed weak enol-like fluorescence at 350 nm. The 2-(bromomethyl)benzoate group showed fast response to  $\text{H}_2\text{S}$  through cascade reaction and released free HBT, which showed strong fluorescence at 484 nm in CTAB micelles. The emission at 484 nm showed linear relationship with the  $\text{H}_2\text{S}$  concentration at 0–100  $\mu\text{mol/L}$  with the detection limit of 0.50  $\mu\text{mol/L}$ . The high selectivity and sensitivity of our probe to  $\text{H}_2\text{S}$  may give new insights for the development of fluorescent probe to selectively detect  $\text{H}_2\text{S}$  in biological systems.

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