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A novel quinoline-based colorimetric fluorescent probe for hydrogen sulfide

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Abstract

In this article, a novel fluorescent probe was designed and synthesized based on the quinoline structure for the detection of H_2S. After optical evaluation, the probe showed good characteristics, including a fast response, high sensitivity, and good selectivity. More importantly, the probe could be directly observed by the naked eye after responding to H_2S and has good application value.

Keywords

fluorescent probe, hydrogen sulfide, quinoline structure

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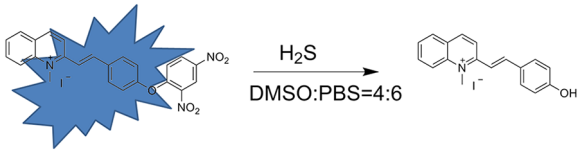

Introduction

Hydrogen sulfide (H_2S), a colorless gas with the smell of rotten eggs, has long been considered a highly toxic gas and environmental pollutant.[1] However, in recent years, numerous studies have shown that hydrogen sulfide has important physiological functions and is an important biological and pharmacological medium[2] at nanomolar to millimolar levels. In mammals, endogenous hydrogen sulfide is mainly derived from the metabolism of L-cysteine and homocysteine.[3] Numerous studies have also shown that hydrogen sulfide has a dual effect on the growth of tumor cells.[4] In addition, hydrogen sulfide has potential therapeutic value for several central nervous system diseases such as Alzheimer's disease (AD),[5] Parkinson's disease (PD),[6] ischemic stroke, and traumatic brain injury (TBI).[7]

Considering the potential of hydrogen sulfide–based treatments, the detection of H_2S is crucial, so various methods have been developed for detection, such as colorimetry,[8] titration,[9] chromatography,[10] electrochemical,[11] and fluorescent probe detection methods.[12] Among these, fluorescent probes have attracted much attention due to their high sensitivity, fast response, and convenient operation. In recent years, significant research into hydrogen sulfide fluorescent probes has been carried out rapidly.[13–17] The main types of fluorescent scaffolds that have been used include coumarins,[18–20] isophoronitriles,[21,22] fluoropyrroles,[23–25] quaternary pyridine salts,[26–28] benzopyrandicarbonitriles,[29,30] naphthalenes,[31] quinolines,[32,33]and the like.

Herein, based on a review of the literature, we report the design of hydrogen sulfide fluorescent probe **6** that has a quinoline group connected to a dinitrophenyl ether through a styrene linker. After reacting with hydrogen sulfide, the dinitrophenyl ether group was removed, releasing a hemicyanine chromophore. The probe is simple and easy to obtain, and the raw materials required for the synthesis are readily available (see Scheme 1). Probe **6** in a phosphate-buffered saline (PBS/dimethyl sulfoxide (DMSO)=6:4, v/v, pH=7.4) solution achieved rapid and selective colorimetric recognition of hydrogen sulfide.

Results and discussion

The synthesis of probe **5** is detailed in the three steps shown in Scheme 1. First, (*E*)-4-(2-(quinolin-2-yl)vinyl) phenyl acetate **3** was synthesized from 2-methylquinoline and 4-hydroxybenzaldehyde and second, compound **3** was hydrolyzed under basic conditions to obtain intermediate **4**. Finally, intermediate **4**, 2,4-dinitrobenzene, and methyl

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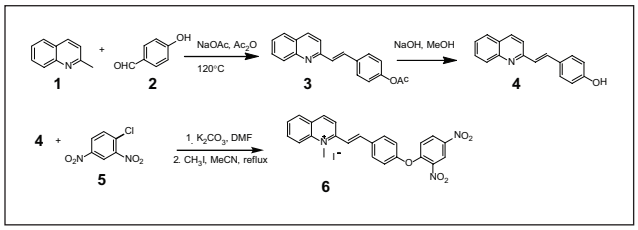


Scheme 1. Synthesis of fluorescent probe **6**.

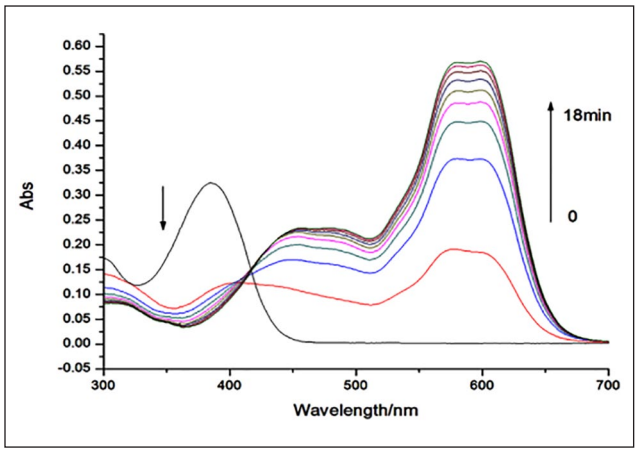


Figure 1. Absorption spectral changes of probe **6** (10 μM) in the absence and presence of sodium sulfide (100 μM) in buffer solution (PBS:DMSO = 6:4, v/v, pH = 7.4) with λ_{ex} at 350 nm.

iodide were used to prepare probe **6** under reflux conditions. Its structure was fully characterized by elemental analysis, UV-Vis, ^{1}H NMR, ^{13}C NMR, and electrospray ionization mass spectra (ESI-MS).

With the probe in hand, 5 equiv. of aqueous sodium sulfide was added to 10 μM of a solution of probe **6** (PBS/DMSO = 6:4, pH = 7.4), and the reaction between the probe and sodium sulfide was observed. The UV absorption spectra at 0, 2, 4, 6, 8, 10, 12, 14, 16, and 18 min are shown in Figure 1. With longer reaction times, the absorption peak of the probe at 390 nm disappeared and a new absorption band appeared at 590 nm. After 14 min, the UV absorption leveled off reaching a maximum after 18 min (Figure 1). Therefore, the reaction between probe **6** and sodium sulfide was complete in 18 min and hydrogen sulfide could be detected quickly.

Next, the emission behavior of the probe with different concentrations of sodium sulfide was investigated. The solution of probe **6** (PBS/DMSO = 6:4, pH = 7.4) was added to different concentrations of solution of sodium sulfide solution (0, 2, 4, 6, 8, 10, 15, 20, 25, 30, 35, 40, 45, 50, 60, and 70 μM), and the absorption spectrum was measured after 20 min. The results are shown in Figure 2. With an increase in sodium sulfide concentration, the absorption peak of the probe at 390 nm gradually decreased and a new absorption band appeared at 590 nm and then gradually increased reaching the maximum when the sodium sulfide concentration was 70 μM. In addition, the color of the solution was observed to change from pale yellow to blue with the naked eye.

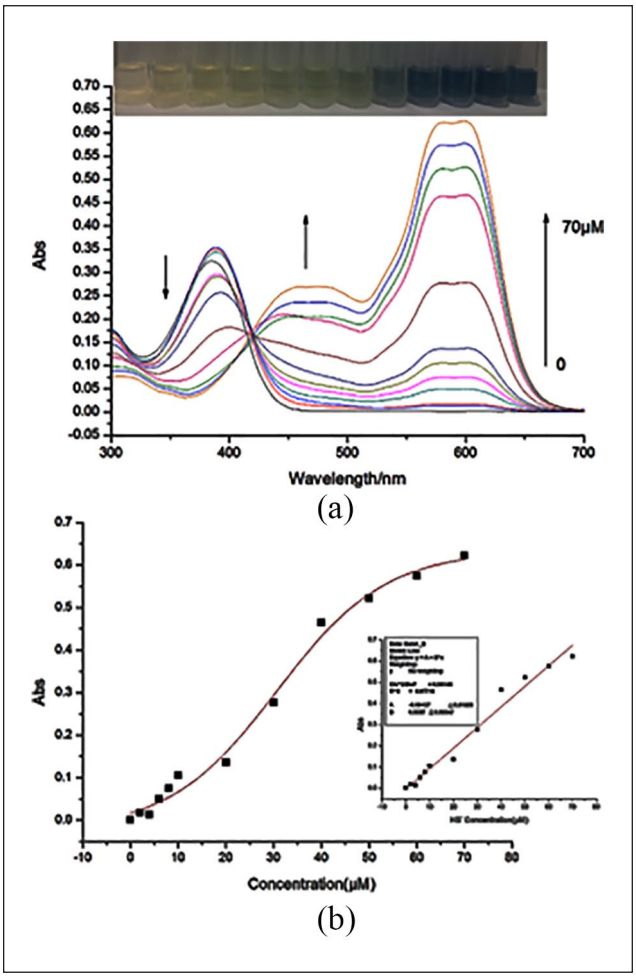


Figure 2. (a) Absorption spectra of **6** (10 μM) on the addition of increasing concentrations of sodium sulfide (0, 2, 4, 6, 8, 10, 15, 20, 25, 30, 35, 40, 45, 50, 60, and 70 μM). (b) Absorption intensity changes of probe **5** at 590 nm as a function of sodium sulfide concentration.

When the sodium sulfide concentration was in the range of 0–70 μM, the absorbance of probe **6** at 590 nm had a linear relationship with the sodium sulfide concentration with a correlation coefficient of 0.977. Moreover, the fluorescence spectrum was measured following the addition of the sodium sulfide solution (0, 2, 4, 6, 8, 10, 20, 30, 40, 50, 60, and 70 μM). As shown in Figure 3, the fluorescence intensity of the probe at 500 nm gradually decreased. When sodium sulfide was added at a concentration of 20 μM, the fluorescence intensity was reduced to the minimum. In addition, the blue fluorescence of the solution was observed to disappear under a UV lamp (365 nm). When the concentration of sodium sulfide is in the range of 0–10 μM, the fluorescence intensity of probe **6** at 500 nm has a good linear relationship with the concentration of sodium sulfide, with a correlation coefficient of 0.991.

Of all the factors, the selectivity of the probe is the most important due to the complexity of biological samples. Therefore, the effects of 11 common anions and reduced thiol Cys on the fluorescence intensity of probe **6** were investigated. After adding 5 equiv. of Na_2S, F^-, Cl^-,

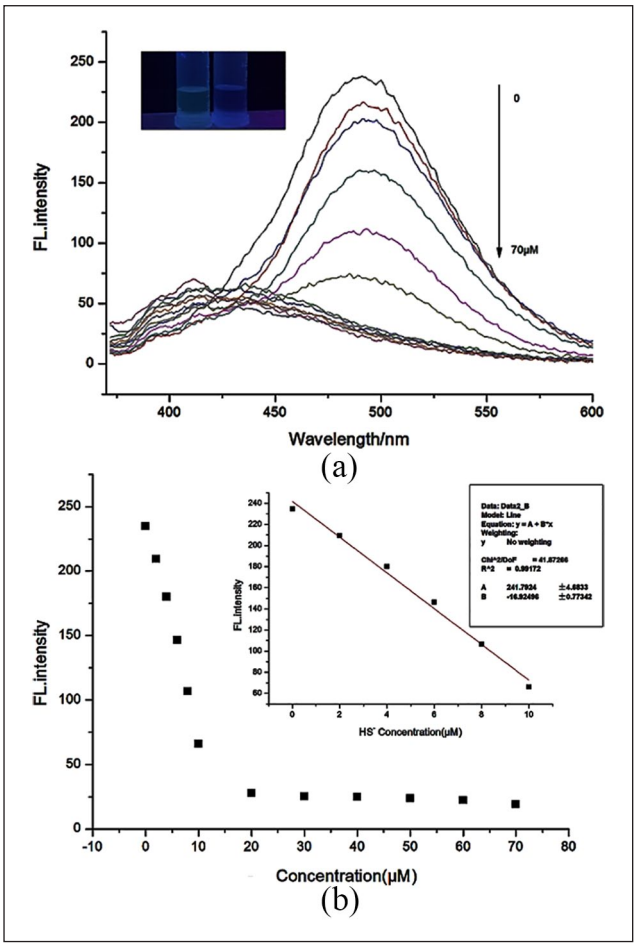


Figure 3. (a) Fluorescence spectra of **6** (10 μM) on the addition of increasing concentrations of sodium sulfide (0, 2, 4, 6, 8, 10, 20, 30, 40, 50, 60, and 70 μM) when excited at 350 nm. (b) Fluorescence intensity changes of probe **6** at 500 nm as a function of sodium sulfide concentration.

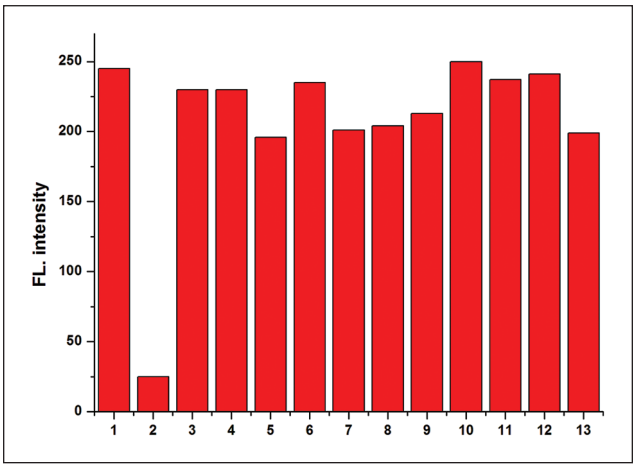


Figure 4. Fluorescence enhancements at 450 nm of probe **6** (10 μM) on addition of 10 equiv. of interfering analytes.
1: blank; 2: Na_2S; 3: NaF; 4: NaCl; 5: $NaHSO_3$; 6: NaOAc; 7: NaH_2PO_4; 8: Na_2SO_4; 9: $NaHCO_3$; 10: Na_2CO_3; 11: $NaNO_2$; 12: NaI; 13: Cys.

Conclusion

In this article, the design and synthesis of the colorimetric fluorescence–enhanced probe **6** for the selective detection of hydrogen sulfide are reported. By adding sodium sulfide, the color of the solution of probe **6** could be observed with the naked eye to change from pale yellow to blue. With the increase in sodium sulfide concentration, the maximum fluorescence emission intensity of probe **6** at 490 nm gradually decreased. A good linear relationship was found between the sodium sulfide concentration (0–10 μM) and the fluorescence intensity (R^2=0.991). More importantly, the probe could be used as a colorimetric and highly selective fluorescent probe for the rapid detection of sulfur hydrogen.

Experiments

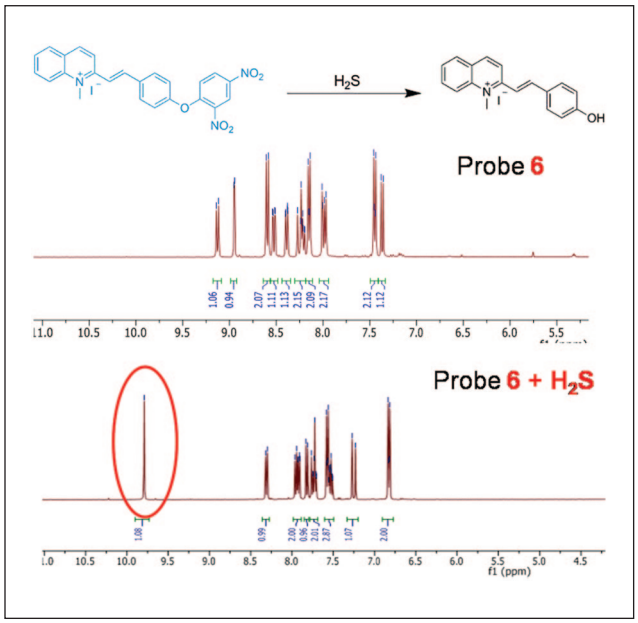
All the reagents and solvents were purchased from commercial suppliers and used without further purification. The compounds used for the selectivity studies were Na_2S, NaF, NaCl, NaI, NaH_2PO_4, NaOAc, Na_2SO_4, Na_2CO_3, $NaHCO_3$, $NaNO_2$, Cys, and $NaHSO_3$. The water used in the experiments was ultrapure water purified by a Millipore water purification system. ^{1}H nuclear magnetic resonance (NMR) and ^{13}C NMR were measured on a Bruker AVANCE III400 MHz spectrometer with tetramethylsilane (TMS) as an internal standard, and chemical shifts were reported in ppm. UV absorption spectra were taken on a PERSEE TU-1900 spectrophotometer. Fluorescence spectra were recorded using a CARY Eclipse fluorescence spectrophotometer.

The intermediates **3** and **4** were synthesized according to the routes reported in the literature.[34]

Compound **4** (494 mg, 2 mmol), 2,4-dinitrochlorobenzene (425 mg, 2.2 mmol), and anhydrous potassium carbonate (331 mg, 2.4 mmol) were sequentially added to 5 mL of dimethylformamide (DMF) and allowed to react overnight at room temperature. After the reaction was completed, 20 mL of water was added to the reaction mixture that was then extracted with ethyl acetate (3 × 20 mL). The organic phases were

I^-, $H_2PO_{4^-}$, AcO^-, SO_4^{2-}, CO_3^{2-}, HCO_{3^-}, NO_{2^-}, Cys, and HSO_3^- sodium salts to the solution of probe, the fluorescence spectra were measured. The results are shown in Figure 4. Only Na_2S significantly reduced the fluorescence intensity of probe **6**. Therefore, probe **6** can selectively detect hydrogen sulfide.

It is well known that H_2S can induce the departure of 2,4-dinitrobenzene in aqueous solution, and this strategy has been successfully applied to construct various reaction-based fluorescence sensors for the detection of H_2S.[12,15,21] Probe **6** may be cleaved to release a quinoline on action with H_2S, resulting in detectable changes in the fluorescence spectrum. In addition, probe **6** itself had an intramolecular charge transfer (ICT) under the action of an electron-withdrawing group (2,4-dinitrobenzene) and had the highest fluorescence intensity. When hydrogen sulfide reacts with the probe, 2,4-dinitrobenzene is expelled, and the mechanism of ICT action disappears so that the fluorescence intensity was decreased. In addition, we used a ^{1}H NMR titration experiment to prove that H_2S can cause the departure of 2,4-dinitrobenzene and the appearance of a hydroxyl at 9.83 ppm (Scheme 2).



Scheme 2. Proposed mechanism for detection of H_2S by probe **6** and ^1H NMR titration experiment.

combined, washed with water to remove DMF, and dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure to give crude compound. Then, the crude compound (206 mg, 0.5 mmol) and methyl iodide (142 mg, 1 mmol) were dissolved in 3 mL of acetonitrile, and the reaction mixture was refluxed for 8 h. After cooling to room temperature, precipitation occurred and filtration, washing the filter cake with a small amount of acetonitrile, and drying the solid under vacuum gave the fluorescent probe **6**, 200 mg yellow solid, yield 72%. m.p. 310 °C–312 °C. UV-Vis (in DMSO, nm): 375. Anal. calcd C, 51.91; H, 3.27; N, 7.57%; found: C, 51.995; H, 3.25; N, 7.59%. ^1H NMR (400 MHz, DMSO-d_6) δ 9.13 (d, J=8.8 Hz, 1H), 8.95 (d, J=2.8 Hz, 1H), 8.60 (d, J=8.8 Hz, 2H), 8.52 (dd, J=9.2, 2.8 Hz, 1H), 8.39 (dd, J=8.1, 1.6 Hz, 1H), 8.30–8.18 (m, 2H), 8.18–8.11 (m, 2H), 8.04–7.94 (m, 2H), 7.49–7.41 (m, 2H), 7.37 (d, J=9.2 Hz, 1H), 4.60 (s, 3H).^{13}C NMR (100 MHz, DMSO-d_6) δ 156.71, 156.55, 154.39, 145.88, 144.86, 142.59, 140.41, 139.70, 135.51, 133.05, 132.09, 130.58, 130.23, 129.62, 128.41, 122.49, 121.69, 121.03, 120.87, 120.27, 119.87, 40.59. MS (ESI) m/z for $C_{24}H_{18}IN_3O_5$, 428.1 $[M-I]^+$; found: 427.8.

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Declaration of conflicting interest

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