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ORIGINAL ARTICLE

A Water-Soluble Fluorescent Probe for SO_2 Derivatives in Aqueous Solution and Serum Based on Phenanthroimidazole Dye

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Abstract A water-soluble fluorescent SO_2 derivatives probe **PI-SO_2** based on a phenanthroimidazole dye, and a sensitive SO_2 recognition site, aldehyde was constructed. The probe **PI-SO_2** exhibits desirable properties such as high sensitivity, high selectivity and good water-solubility. Significantly, we have demonstrated that the probe **PI-SO_2** is suitable for rapidly fluorescence detecting of SO_2 derivatives in aqueous solution and serum. The application of the novel probe **PI-SO_2** proved that it was not only a useful tool for the detection of SO_2 derivatives in vitro, but also a potential assay for investigating the effects of SO_2 derivatives, and demonstrating its value in practical applicationin of complex biological samples.

Keywords Fluorescent probe · Sulfur dioxide · Water-solube · Serum · Phenanthroimidazole

Yang Zhou and Ying Wang contributed equally to this work

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Introduction

Sulfur dioxide (SO_2) has long been recognized to be a toxin found in environmental pollutant. Its toxicological effects are complex, and induce cancer, cardiovascular diseases and neurological disorders, etc. [1]. In recent years, SO_2 has also been found to play important roles in mammalian systems. It is endogenously from in vivo sulfur-containing amino acids and decomposition of sulfinylpyruvate, as a gaseous signalling molecule along with three well-known gasotransmitters: nitric oxide (NO), carbon monoxide (CO) and hydrogen sulfide (H_2S) [2, 3]. In biological environments, SO_2 dissociates to its derivatives, bisulfite and sulfite [HSO_3^-/SO_3^{2-}], and involved in many important physiological and pathological processes. However, the abnormal levels of SO_2 are associated with many types of diseases including lung cancer and cardiovascular diseases [3–5]. Thus, it is of high interest to monitor SO_2 levels in a variety of settings.

Fluorescence sensing is most appealing because of its high sensitivity, high selectivity and simplicity of operation [6–11]. Fluorescent probes capable of the detection of sulfites have received intense attention recently, most of which were developed based on the reaction with the aldehyde [12–15], selective de-protection of levulinate [16–18] and michael addition reaction [19–28]. However, Most of them are not water-soluble, and require an organic co-solvent, which limited their practical applications in a physiological environment. Therefore, it is of great significance to develop the water-soluble fluorescent SO_2 derivatives probes.

The phenanthroimidazole have been regarded as a very attractive molecular platform for the construction of fluorescent probes to achieve different detection purposes, such as H_2S [29–31], Hg^{2+} [32–34], pH [35], F^- [36–38], Cu^{2+} [39], etc. Herein, we constructed a novel water-soluble fluorescent probe **PI-SO_2** (Scheme 1) by using phenanthroimidazole as

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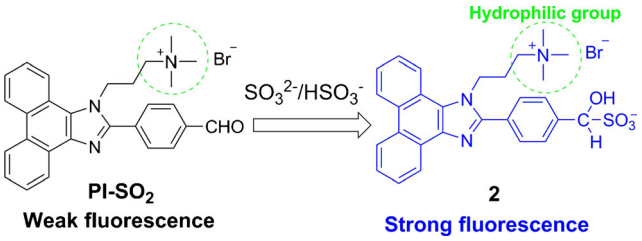


Scheme 1 The detection mechanism of probe **PI-SO_2**

the dyes platform, aldehyde as the reactive site for SO_2 and trimethylamine (TMA) enabled the introduction of the cationic water-solubilizing substituent.

Experimental Section

Materials and Instrumentation

Unless otherwise stated, all reagents were purchased from commercial suppliers and used without further purification. Solvents used were purified by standard methods prior to use. Twice-distilled water was used throughout all experiments. Mass spectra were performed using an LCQ Advantage ion trap mass spectrometer from Thermo Finnigan or Agilent 1100 HPLC/MSD spectrometer and Thermo Fisher Scientific LTQ FT Ultra spectrometer. NMR spectra were recorded on an UltrashiedTM 400 MHZ Plus INOVA-400 spectrometer, using TMS as an internal standard. Electronic absorption spectra were obtained on Shimadzu UV-2600. Photoluminescent spectra were recorded at room temperature with a HITACHI F4600 fluorescence spectrophotometer with a 1 cm standard quartz cell; The pH measurements were carried out on a INESA PHS-25 pH meter; TLC analysis was performed on silica gel plates and column chromatography was conducted over silica gel (mesh 200–300), both of which were obtained from the Qingdao Ocean Chemicals.

General Procedure for the Spectra Measurement

The stock solution of the probe **PI-SO_2** was prepared at 0.5 mM in DMSO. The solutions of various testing species were prepared from NaCl, $NaNO_2$, $NaNO_3$, NaClO, GSH, cysteine, H_2O_2, Na_2SO_4, $Na_2S_2O_3$, Na_3PO_4, Na_2CO_3, $AlCl_3•6H_2O$, $CuCl_2•2H_2O$, CuCl, $Fe(NO_3)_3•9H_2O$, $FeSO_4•7H_2O$, $HgCl_2$, $PbCl_2$, $Cr(NO_3)_3•9H_2O$, $NiCl_2•6H_2O$, $Co(NO_3)_2•6H_2O$, $ZnCl_2$, $CdCl_2$, $NaHSO_3$ and Na_2SO_3 in the twice-distilled water, The test solution of the probe **PI-SO_2** (5.0 μM) in 3 mL HEPES buffer (pH 7.4) was prepared by placing 0.03 mL of the probe **PI-SO_2** stock solution of the aqueous buffer. The resulting solution was shaken well and incubated with appropriate testing species for 0.5 min at room temperture before recording the spectra. Unless otherwise noted, for all measurements, the excitation wavelength was 330 nm, the excitation slit widths were 2.5 nm, and emission slit widths were 2.5 nm.

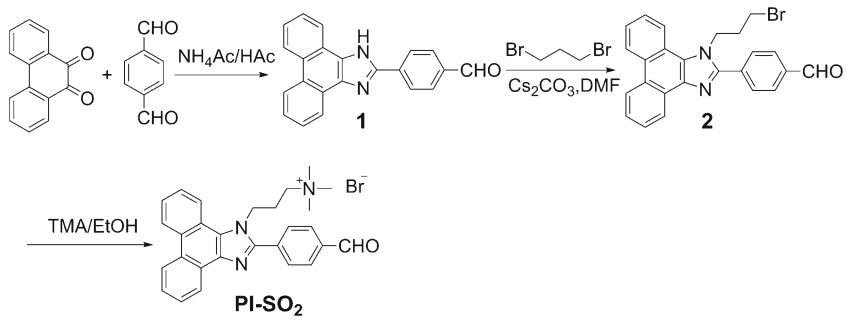
Synthesis of Probe PI-SO_2

Probe **PI-SO_2** was readily synthesized from compound **1** in two steps with a moderate yield, as shown in Scheme 2. The starting materials **1** was prepared based on the reported procedures [32]. The structure of probe **PI-SO_2** and compound **2** were fully characterized by the standard NMR spectroscopy, mass spectrometry.

Synthesis of 4-(1-(3-bromopropyl)-1H-phenanthro[9,10-d]imidazol-2-yl)benzaldehyde(2) Compound **1** (200 mg, 0.62 mmol), 1,3-dibromopropane (873 mg, 4.37 mmol), and Cs_2CO_3 (802 mg, 2.46 mmol) were dissolved in anhydrous DMF (2 mL), and the reaction mixture was heated at 40 °C for 12 h under N_2 atmosphere. The reaction mixture was then poured into 15 mL H_2O, and then extracted with CH_2Cl_2. The organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated. Purification by silica gel column chromatography (CH_2Cl_2: petroleum: ethyl acetate = 10: 8: 1) gave 192 mg (0.43 mmol, 70%) of compound 2 as a yellow solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.41–2.48 (m, 2H), 3.21 (t, J = 6.0 Hz, 2H), 4.89 (t, J = 8.0 Hz, 2H), 7.64–7.74 (s, 4H), 7.97 (d, J = 8.0 Hz, 2H), 8.08 (d, J = 12.0 Hz, 2H), 8.32 (d, J = 8.0 Hz, 1H), 8.71 (d, J = 8.0 Hz, 1H), 8.77 (q, 1H), 8.85 (d, J = 8 Hz, 1H), 10.14 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 191.70, 136.77, 130.80, 130.110, 129.52, 128.38, 127.58, 127.16, 126.13, 125.47, 124.67, 123.14, 122.72, 120.79, 45.82, 32.58, 28.99; MS(EI) m/z = 442.1 $[M]^+$, HRMS (EI) m/z calcd for $C_{25}H_{19}N_2OBr$: 442.0675; Found 442.0677.

Synthesis of 3-(2-(4-formylphenyl)-1H-phenanthro[9,10-d]imidazol-1-yl)-N,N,N-trimethyl-propan-1-aminium Bromide (PI-SO_2) A mixture of compound 2 (30 mg, 0.068 mmol), trimethylamine (0.5 mL) in CH_2Cl_2 (2 mL) was stirred at room temperture for 12 h under N_2 atmosphere. The crude product was filtered and washed with n-hexane, filter cake was dried under vacuum to afford 20 mg (60% yield) of **PI-SO_2** as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.27–2.32(m, 2H), 3.00(s, 9H), 3.43(s, 2H), 4.77(t, J = 8 Hz, 2H), 7.68–7.78(m, 3H), 7.86(t, J = 8 Hz, 1H), 8.09(d, J = 8 Hz, 2H), 8.19(d, J = 8 Hz, 2H), 8.45(d, J = 8 Hz, 1H), 8.63(d, J = 8 Hz, 1H), 8.91(d, J = 8 Hz, 1H), 9.03(d, J = 8 Hz, 1H), 10.20 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d6) δ 193.56, 151.26, 137.97, 136.91, 136.21, 131.13, 130.35, 129.02, 128.26, 127.10, 126.50, 126.09, 125.17, 124.13, 123.01, 122.41, 121.73, 62.22, 52.62, 43.87, 24.19. MS(ESI) m/z = 422.1 $[M]^+$, HRMS (ESI) m/z calcd for $C_{28}H_{28}N_3O^+$: 422.2229; Found 422.2227.

Scheme 2 Synthetic route to probe **PI-SO$_2$**



Determination of the Detection Limit

The detection limit was calculated based on the results of fluorescence titration. In the absence of Na_2SO_3, the fluorescence emission spectrum of probe **PI-SO$_2$** was measured five times and the standard deviation of blank measurements was obtained. The detection limit of probe **PI-SO$_2$** for Na_2SO_3 was determined from the following equation:

$$\text{Detection limit} = 3\sigma/k$$

where σ is the standard deviation of blank measurements, k is the slope of fluorescence intensity versus Na_2SO_3 concentration.

Result and Discussion

Sensing of the Probe PI-SO$_2$ to Na_2SO_3

With Probe **PI-SO$_2$** in hand, we firstly examined its optical properties in the absence or presence of Na_2SO_3. The free probe **PI-SO$_2$** (5.0 μM) exhibited a maximal absorption band at around 356 nm (ε = 36,200 M^{-1} cm^{-1}) in pH 7.4 HEPES buffer at ambient temperature (Fig. S1). However, the addition of Na_2SO_3 elicited a significant fluorescence turn-on response at 388 nm (Fig. 1). The titration experiments also showed that the emission intensity of **PI-SO$_2$** at 388 nm was linearly proportional to the amount of Na_2SO_3 (0–100 μM) with a detection limit (S/N = 3) of 1.9 × 10^{-7} M in pH 7.4 HEPES buffer (Fig. 2), indicating that the probe is potentially useful for quantitative detection of SO_2 derivatives over a large dynamic range concentration.

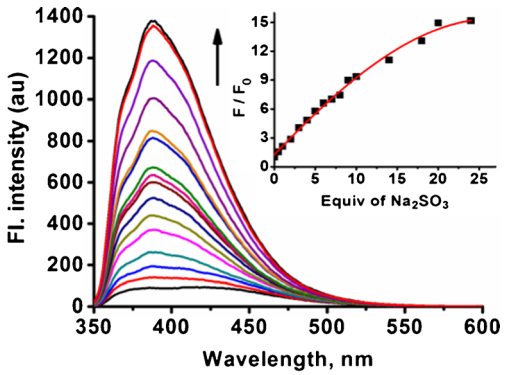


Fig. 1 Fluorescence spectra of **PI-SO$_2$** (5.0 μM) in pH 7.4 HEPES buffer in the absence or presence of Na_2SO_3(0–24 equiv.). Inset: fluorescence intensity ratio (F/F_0) changes at 388 nm of **PI-SO$_2$** (5.0 μM) with the amount of Na_2SO_3. The spectra were recorded after incubation of the probe with Na_2SO_3 for 0.5 min. Excitation at 330 nm, Slit: 2.5 nm/2.5 nm

Mechanism Studies

To verify the above proposed sensing mechanism, we decided to monitor the progress of the reaction of **PI-SO$_2$** with Na_2SO_3 by mass spectroscopy. After treatment of **PI-SO$_2$** with Na_2SO_3 in pH 7.4 HEPES buffer, Three groups of peaks corresponding to the probe **PI-SO$_2$** (m/z 422.22 $[M\text{-}Br^-]^+$ and 492.27$[M\text{-}Br^-\text{+}2Cl^-]^-$), the final products (m/z 538.3 $[M\text{-}Br^-\text{+}Cl^-]^-$ were obtained (Fig. S2). This is consistent with the previous report that Na_2SO_3 reacts with aldehyde group [12–15].

Effects of Reaction Time on Sensing Na_2SO_3

The time course of the fluorescent intensity (F_{388}) in the absence or presence of Na_2SO_3 was displayed in Fig. 3. Upon introduction of Na_2SO_3, a dramatic enhancement in the emission intensity was noted, and the intensity essentially reached the maximumin 30 s. Thus, an assay time of 30 s was selected

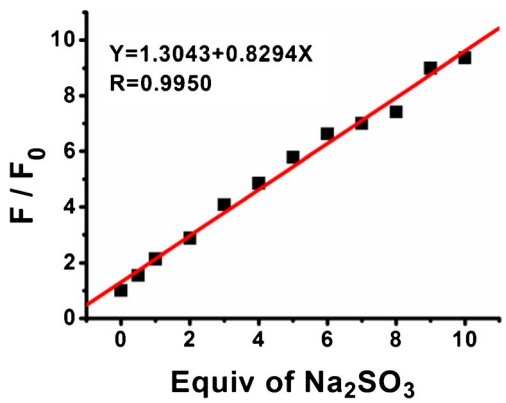


Fig. 2 The fluorescence intensity ratio (F/F_0) of **PI-SO$_2$** vs. increasing concentrations of Na_2SO_3 in pH 7.4 HEPES buffer

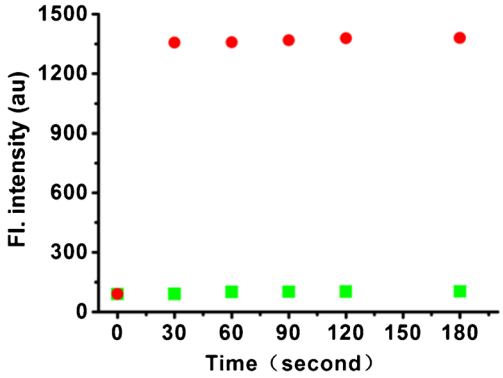


Fig. 3 Reaction-time profiles of **PI-SO_2** (5 μM) in the absence (*green square*) or presence of Na_2SO_3 (100 μM, [*red circle*]). The fluorescence intensities at 388 nm were continuously monitored at time intervals in pH 7.4 HEPES buffer at ambient temperature. Time points represent 0, 30, 60, 90, 120 and 180 s

in the evaluation of the selectivity and sensitivity of the probe to Na_2SO_3.

Selectivity and Competition Studies

The probe **PI-SO_2** was treated with various relevant analytes including anions, reactive oxygen species, reducing agents, small-molecule thiols, metal ion, and Na_2SO_3 in pH 7.4 HEPES buffer to investigate the selectivity over a period of 30 s. As exhibited in Figs. 4 and S3, introduction of representative species including ClO^-, H_2O_2, Cl^-, CO_3^{2-}, PO_4^{3-}, NO_2^-, NO_3^-, $S_2O_3^{2-}$, SO_4^{2-}, GSH, Cys, Zn^{2+}, Cd^{2+}, Fe^{2+}, Fe^{3+}, Cr^{3+}, Cu^{2+}, Cu^+, Al^{3+}, Co^{2+}, Ni^{2+}, Pb^{2+} and Hg^{2+}elicited essentially no fluorescence response. By contrast, importantly, introduction of Na_2SO_3 or $NaHSO_3$ caused a large fluorescent enhancement in 30 s. These data indicate that the probe is selective for SO_2 derivatives over other tested species. In addition, we further examined the fluorescence response of the probe toward SO_2 derivatives in the presence of other potentially competing species. The other species only displayed minimum interference (Fig. 5). This suggests that

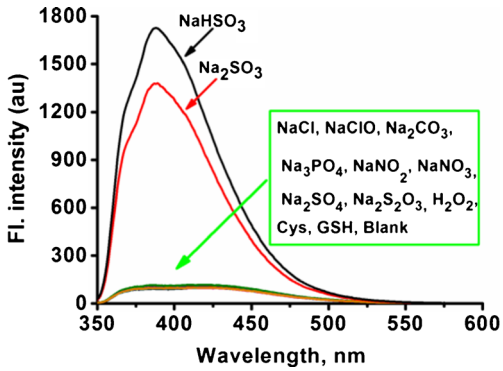


Fig. 4 The fluorescent responses of the probe **PI-SO_2** (5 μM) to various relevant species (100 μM for H_2O_2, ClO^-, $S_2O_3^{2-}$,NO_3^-, Cl^-, CO_3^{2-}, PO_4^{3-}, NO_2^-, SO_4^{2-}, Na_2SO_3, $NaHSO_3$ and Cys, 1 mM for GSH) in pH 7.4 HEPES buffer at ambient temperature

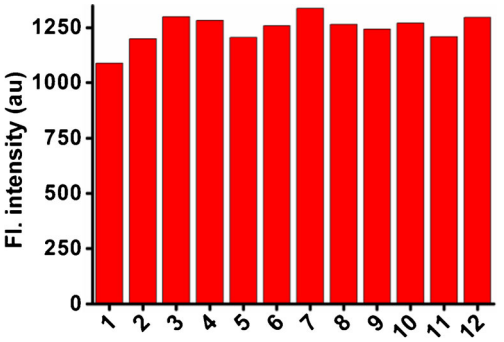


Fig. 5 The fluorescent responses of the probe **PI-SO_2** (5 μM) to Na_2SO_3 in the presence of various relevant species (100 μM for H_2O_2, ClO^-, $S_2O_3^{2-}$, Cl^-, CO_3^{2-}, PO_4^{3-}, NO_2^-, NO_3^-, SO_4^{2-}, cysteine, 1 mM for GSH,) in pH 7.4, 25 mM PBS buffer. 1. Na_2SO_3 + ClO^-; 2. Na_2SO_3 + CO_3^{2-}; 3. Na_2SO_3 + cysteine; 4. Na_2SO_3 + GSH; 5. Na_2SO_3 + H_2O_2; 6. Na_2SO_3 + Cl^-; 7. Na_2SO_3 + SO_4^{2-}; 8. Na_2SO_3 + NO_2^-; 9. Na_2SO_3 + NO_3^-; 10. Na_2SO_3 + PO_4^{3-}; 11. Na_2SO_3 + $S_2O_3^{2-}$; 12. Na_2SO_3. The spectra were recorded after incubation of the probe with various relevant species for 0.5 min

PI-SO_2 is potentially useful for sensing SO_2 derivatives in the presence of other related species.

pH Effect on Probe PI-SO_2 and PI-SO_2 + Na_2SO_3 Complex

The effect of pH on the fluorescence response of **PI-SO_2** to Na_2SO_3 was investigated. As shown in Fig. 6, in the absence of Na_2SO_3, almost no change in fluorescence intensity was observed in the free probe over a wide pH range of 6.0–8.5, indicating that the free probe **PI-SO_2** was stable in the wide pH range. Upon treatment with Na_2SO_3, the maximal fluorescence signal was observed in the pH range of 6–7.5, suggesting that the probe functions properly at physiological pH.

The Practical Application of the Probe PI-SO_2 in Complex Biological Samples

Finally, to test the feasibility of the practical application of the probe **PI-SO_2**, we further conducted the SO_2 derivatives

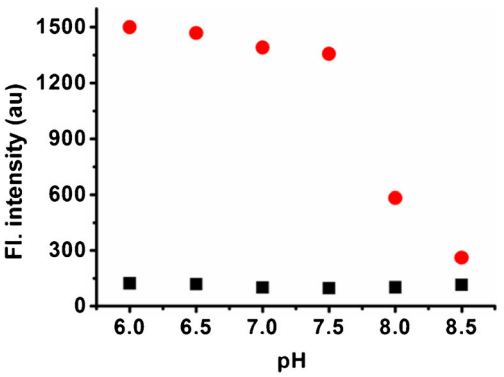


Fig. 6 The pH influence on the fluorescence intensity of **PI-SO_2** (5 μM) in absence (■) or presence (*red circle*) of Na_2SO_3. Emission at 388 nm

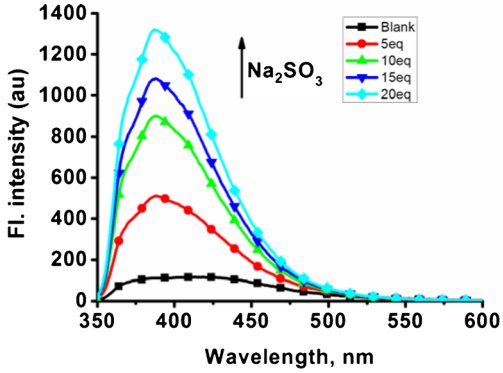


Fig. 7 Fluorescence spectra of **PI-SO_2** (5.0 μM) in pH 7.4 HEPES buffer (contain 1 mg/mL bovine serum albumin (BSA)) in the absence or presence of Na_2SO_3(0–20 equiv.). The spectra were recorded after incubation of the probe with Na_2SO_3 for 0.5 min. Excitation at 330 nm, Slit: 2.5 nm/2.5 nm

detection in bovine serum albumin (BSA) and calf serum samples. As shown in Fig. 7, the free probe **PI-SO_2** (5.0 μM) exhibited weak fluorescence in pH 7.4 HEPES buffer (contain 1 mg/mL BSA) at ambient temperature. Upon addition of Na_2SO_3 to the probe **PI-SO_2** solution in pH 7.4 HEPES buffer (contain 1 mg/mL BSA), **PI-SO_2** showed a significant increase of the fluorescence intensity at 388 nm. The fluorescence intensity of the serum sample with probe **PI-SO_2** increases as the Na_2SO_3 concentration increases. We then examined the fluorescence response of the probe **PI-SO_2** in pH 7.4 HEPES buffer (contain 30% calf serum) to Na_2SO_3, the probe **PI-SO_2** exhibited a fluorescence turn-on signal toward Na_2SO_3(Figure S4). These results indicate that probe **PI-SO_2** can be used to detect SO_2 derivatives in complex biological serum samples.

Conclusion

In summary, we have developed **PI-SO_2** as the novel fluorescent SO_2 derivatives probe based on phenanthroimidazole dye. The prominent features of **PI-SO_2** include high sensitivity, high specificity, and good water-solubility. Significantly, we have demonstrated that the probe **PI-SO_2** is suitable for rapidly fluorescence detecting of SO_2derivatives in aqueous solution and serum. The application of the probe **PI-SO_2** proved that it was not only a good tool for the detection of SO_2 derivatives in vitro, but also a potential assay for investigating the effects of SO_2 derivatives, and demonstrating its value in practical application of biological samples.

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