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A benzothiazole-based fluorescent probe for hypochlorous acid detection and imaging in living cells

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Abstract

A benzothiazole-based turn-on fluorescent probe with a large Stokes shift (190 nm) has been developed for hypochlorous acid detection. The probe displays prompt fluorescence response for HClO with excellent selectivity over other reactive oxygen species as well as a low detection limit of 0.08 μM. The sensing mechanism involves the HClO-induced specific oxidation of oxime moiety of the probe to nitrile oxide, which was confirmed by HPLC-MS technique. Furthermore, imaging studies demonstrated that the probe is cell permeable and can be applied to detect HClO in living cells.

Keywords: Fluorescent probe, Large Stokes shift, Hypochlorous acid, Cell imaging, Benzothiazole

1. Introduction

Reactive oxygen species (ROS) have received an increasing attention due to their essential roles in biology and their relevance to many diseases [1, 2]. Among the known ROS, hypochlorous acid (HClO), which is biologically produced from hydrogen peroxide (H_2O_2) and chloride ion (Cl^-) enzymatically by MPO (myeloperoxidase), acts as a powerful microbicide agent in the innate immune systems during pathogen invasion [3]. In addition, as a highly potent oxidant, HClO can also react with amino acids, proteins, cholesterol and nucleosides, resulting in the inhibition of various biomolecular functions [4, 5]. Moreover, it is reported that abnormal production of HClO is closely related to a number of diseases, including cardiovascular disease [6], inflammatory disease [7], certain cancers [8] and neurodegenerative disorders [9]. Therefore, the development of accurate and reliable techniques for HClO detection and imaging in living cells is of great important to better understanding its physiological and pathological functions.

Fluorescence imaging based on synthetic probes is a powerful tool for sensing HClO both in vivo and in vitro due to its unique advanteges, such as high sensitivity, capability for spatial and temporal resolution, simplicity for implementation, and rea-time analysis [10-14]. As a potent oxidant and chlorination agent, HClO can mediate specific reactions towards a number of moieties [15, 16], such as chalcogenide (S, Se, Te) atoms, dibenzoylhydrazine, acylhydrazone, hydroxylamine, hydrazone, Schiff bases, electron deficient alkenes, *p*-methoxyphenol, 1,8-diaminonaphthalene and so on. On the basis of these specific reactivities of HClO, a variety of fluorescent probes have been reported for the detection of HClO by using fluorophores, including oxazine [17], Si-rhodamine [18], fluorescein [19-22], BODIPY [11, 23, 24], acedan [10], cyanine dye [25], fluorenone [26], coumarin [27], iridium(III) complex [28],

naphthalimide [29-32], phenanthroimidazole [33], (2-hydroxyphenyl) benzothiazole (HBT) [34], 7-nitro-2,1,3-benzoxadiazole [35]. Among these utilized fluorohpores, HBT and its derivatives have gained a great deal of interets due to their abilities to undergo an excited-state intramolecular photon transfer (ESIPT) process upon photoexcitation through the keto-enol tautomerism which results in a large Stokes shift and/or unique ratiometric fluorescence behaviour [36-38].

Inspired by these insights, we reported a HBT-based turn on fluorescent probe for HClO detection. The probe was obtained by condensation of HBT with NH_2–OH. Due to the non-radiative deactivation *via* C=N isomerization, the probe is weakly fluorescent. The specific HClO-mediated formation of the nitrile oxide could generate a highly emissive derivative. This transformation of the probe induced by HClO was confirmed by high performance liquid chromatography-mass spectrometry (HPLC-MS) technique. The new probe exhibits high sensitivity with a low detection limit of 0.08 μM, as well as excellent selectivity for HClO over other relevant species. Moreover, the probe displays excellent cell membrane permeability and low cell cytotoxicity, and was successfully applied to image HClO in living cells.

2. Experimental

2.1. Materials and instrumentations

All reagents were purchased from commercial suppliers and used as received. Deionized water was used throughout the analytical experiments. The fluorescence spectra were carried out on a Varian Cary Eclipse fluorescence spectrophotometer (Agilent Technologies, Santa Clara, USA). The absorbance spectra were recorded with a Cary 60 UV-Vis spectrophotometer Agilent (Agilent Technologies, Santa

Clara, USA). NMR spectra were recorded on a Bruker 400 MHz. Mass spectrometry was performed on a Xevo G2-S Q-TOF mass spectrometer (Waters, Milford, MA, USA). HPLC analysis was performed on a Waters Acquity UPLC H-Class system (Milford, MA, USA) equipped with a quaternary solvent delivery system, a column oven, an auto sampler and a photodiode array detector. The analytes were separated in gradient mode with a Waters Acquity BEH 2.1 × 50 mm C18 1.7 μm column. The column oven was kept at 40 ^{o}C. Flow rate was 0.3 mL/min. Eluent components were water (A) and acetonitrile (B). The mobile phase gradient was as follows: 0.0 min 50% B → 4.0 min 100 % B→ 5.0 min 50 % B.

2.2. General procedure for analysis

A parent stock solution of probe **1** (10 mM) was prepared in absolute ethanol. Test solution of probe **1** was diluted in a mixed solution of phosphate buffer: C_2H_5OH = 9:1 (v/v, pH 7.4, 10 mM) and small aliquots of each testing species solution were added. All spectra were obtained in a quartz cuvette (path length = 1 cm) at room temperature.

2.3. Fluorescence Imaging

The cultured Hela cells were incubated with probe **1** (10 μM), probe **1** (10 μM) and consequently with ClO^- (20 μM) in DMEM (Dulbecco's modified Eagle medium) at 37 ^{o}C, respectively. The incubation time was set at 1 h. After incubation for the corresponding time, the cells were washed with PBS three times to remove free compound and ions before analysis. Fluorescence imaging was performed with an Olympus IX 71 with xenon lamp and Olympus digital camera. Fluorescence in green channels was visualized with the appropriate emission filters.

2.4. Cell viability assay

The toxicity of probe **1** towards living cells was determined by MTT (3-(4,5-dimethyl-2-thiazolyl)-2,5-diphenyl-2-H-tetrazolium bromide) assays. Three kinds of cell liens (HeLa, L929, and MDA-MB-231 cells) were evaluated. The cells were seeded in 96-well plates at a density of 5×10^3 cells per well and cultured for 24 h at 37 ^oC with 5% CO_2 in humidified environment. Then a series of different concentrations of probes (0, 5, 10, 15, and 20 μM) were added to the separated wells, and the cells were incubated for an additional 24 h. MTT solution was then added into each well and then residual MTT solution was removed after 4 h. The MTT-formazan crystals were dissolved in 200 μL DMSO. The absorbance of each well was measured by a microplate reader (Bio-TekELx800) at the wavelength of 490 nm. The cell viability was assessed using the following Equation:

Cell viability (%) = $A_T/A_0 \times 100\%$

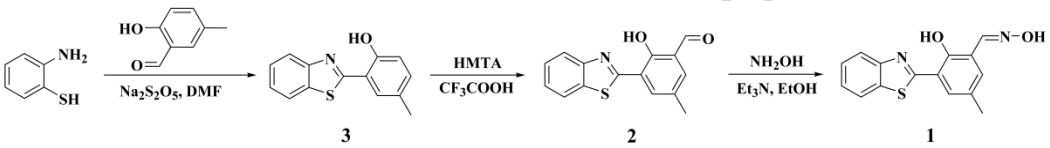
where A_T is the absorbance of treated cells and A_0 is the control absorbance. Data of cell viability are given as mean ± standard deviation (S.D.) (three replicate measurements).

*2.5. Synthesis of probe **1***

The preparation of probe **1** was shown in scheme 1. Compounds **2** and **3** were synthesized according the previously reported procedures [39].

Compound **2** (0.135 g, 0.5 mmol) and hydroxylamine hydrochloride (0.069 g, 1.0 mmol) was dissolved in absolute ethanol (30 mL). Triethylamine (0.11 g, 1.1 mmol) was added to the solution, and then the mixture was refluxed under 80 ^oC for 5 h. The volatiles were then removed under reduced pressure, and the residue was taken up in DCM (dichloromethane) and washed with H_2O for three times. The organic layer was

dried over Na_2SO_4, filtered, and then dried under vacuum. Purification *via* column chromatography using DCM/MeOH as eluent (100:3, v/v) afforded **1** as a white solid (0.183 mg, 65%). ^{1}H NMR (400 MHz, DMSO): δ 12.20 (s, 1H), 11.63 (s, 1H), 8.46 (s, 1H), 8.18 (s, 1H), 8.10 (s, 1H), 7.98 (s, 1H), 7.55 (s, 2H), 7.49 (s, 1H), 2.36 (s, 3H) (see Fig. S1). ^{13}C NMR (101 MHz, DMSO) δ 165.68, 153.28, 151.68, 147.40, 134.38, 131.73, 130.04, 129.29, 127.18, 125.93, 122.66, 122.60, 120.19, 118.83, 20.39 (see Fig. S2). MS [ESI]: m/z, calcd for $[M+H]^+$ 258.06; found 285.01 (see Fig. S3).



Scheme 1 Synthesis of probe 1.

3. Results and Discussion

*3.1. Spectral response of probe **1** to ClO⁻*

The spectral responses of probe **1** towards ClO^- were investigated by both UV-Vis and fluorescence titration in a H_2O-EtOH solution (9:1, v/v, 10 mM phosphate buffer, pH 7.4). As shown in Fig. 1, Probe **1** displays a main absorption band around 350 nm. Upon addition of ClO^-, a weak shoulder absorption band at 410 nm was gradually emerged with a slight decrease of originally absorption at 350 nm. This bathochromic shift can be attributed to the enhanced ICT (intramolecular charge transfer) process within the oxidized product of **1** by ClO^-, as the generated nitrile oxide is a stronger electron-withdrawing group compared with the unreacted hydroxylamine. Fig. 1B shows the fluorescent responses of probe **1** to ClO^-. Probe **1** exhibits weak fluorescence in the absence of HClO at the excitation of 350 nm due to the C=N isomerization involved decay process. The introduction of HClO into the solution of **1**

led to an obvious fluorescence enhancement at 540 nm, which can be ascribed to the conversion of the quenching group of hydroxylamine by ClO^-. Additionally, a good linear relationship was obtained between the fluorescence intensities at 540 nm and the HClO concentrations in a range of 0.5–18.0 μM (inset in Fig. 1B). The detection limit was estimated to be 0.08 μM based on 3σ. The performance of probe **1** is compared with various hydroxylamine-based fluorescent ClO^- (listed in Table S1). The proposed probe exhibits comparable or superior analytical performance in the aspects of detection medium, Stokes shift and detection limit.

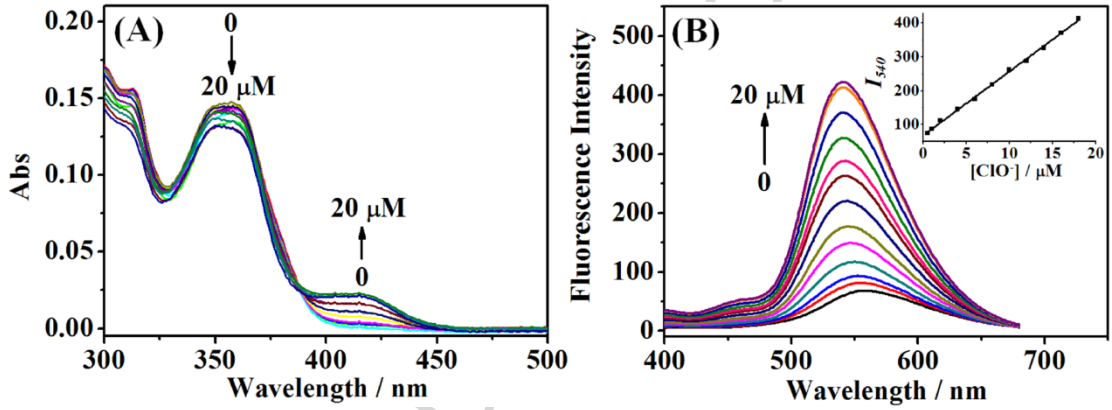


Fig. 1. UV-Vis spectra (A) and fluorescence spectra (B) of probe **1** (10 μM) in H_2O-EtOH solution (9:1, v/v, 10 mM phosphate buffer, pH 7.4) upon addition of various concentrations of ClO^- (0, 0.5, 1.0, 2.0, 4.0, 6.0, 8.0, 10.0, 12.0, 14.0, 16.0 18.0, and 20.0 μM). Inset shows the linear fitting curve between the fluorescence intensity at 540 nm and the concentration of ClO^-. λ_{ex} = 350 nm.

Subsequently, the time-dependence of fluorescence response of the probe for HClO was evaluated. In the presence of ClO^-, the probe solution reveals a dramatic enhancement in the emission intensity at 540 nm (Fig. S4). Under pseudo-first-order conditions, the reaction rate constant (*k*') was calculated to be 3.9×10^{-3} s^{-1}. And the

emission intensity reached the maximum in 15 min, indicating that probe **1** has the capability for real-time detection of ClO^-. The selectivity of probe **1** toward various ROS and other interferences was investigated. The probe possesses a 100-fold higher response for ClO^- over other species, such as ^tBuOOH, Fe^{3+}, H_2O_2, NO, $^1O_2$, •OH, $•O_2^-$ and TBHP (tert-butyl hydroperoxide), indicating that probe **1** is highly selective for ClO^- (see Fig. 2). This specific fluorescence response of probe **1** towards ClO^- also can be visualized under a Handheld UV Lamp (Fig. 2B, inset).

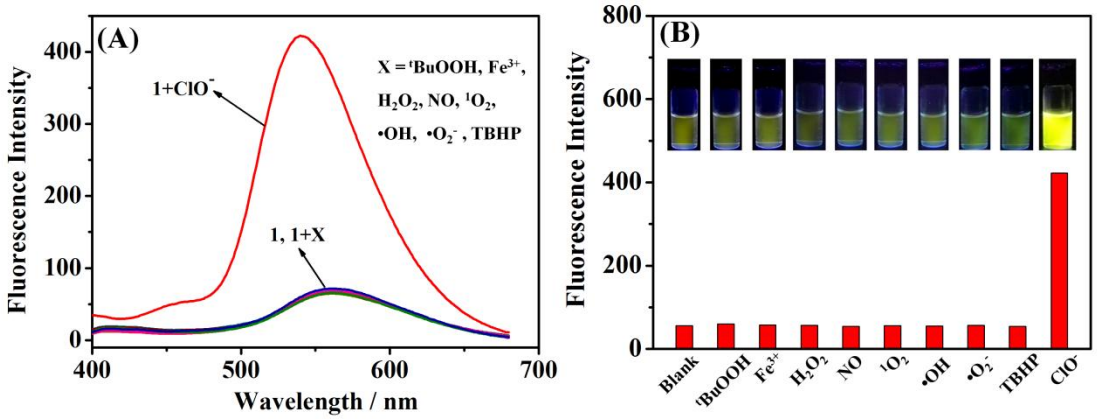


Fig. 2. (A) Fluorescence spectra of probe **1** (10 μM) in H_2O-EtOH solution (9:1, v/v, 10 mM phosphate buffer, pH 7.4) in the presence of various ROS and other interferences (20 μM); (B) Fluorescence intensity changes at 540 nm (λ_{ex} = 350 nm). The inset shows the corresponding visual fluorescence change photograph of the probe solution for ClO^- and interferences under a Handheld UV Lamp (λ_{ex} = 365 nm).

3.2. Sensing mechanism

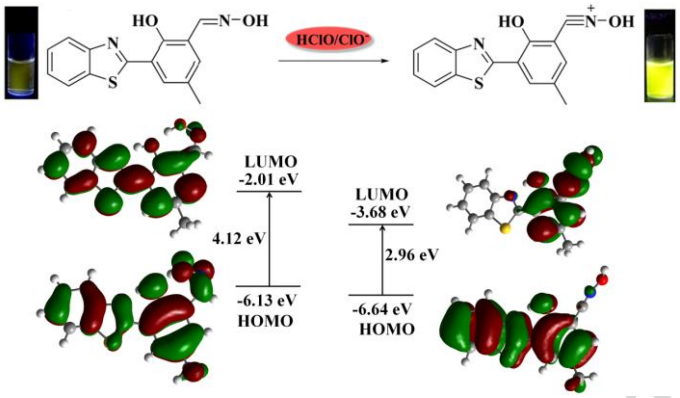


Fig. 3. Proposed sensing mechanism of probe **1** towards ClO^- and the frontier orbital diagram of probe **1** and its speculated products.

Hydroxylamine has been successfully employed as a recognition moiety for the construction of fluorescent ClO^- probes [16]. But this hydroxylamine group in different probes can probably be oxidized into different species by ClO^-, such as aldehyde [40-42], nitrile oxide [43, 44], carboxylic acid [45, 46]. To better understand the sensing mechanism of probe **1** towards ClO^-, the reaction process was monitored by HPLC-MS (see Fig. S5). The HPLC chromatogram of probe **1** shows a single peak with retention time (Rt) at 3.17 min, which corresponds to a m/z value of 258.01. After incubation with ClO^- (1 equiv.) for 15 min (Fig. S5B), a new chromatographic peak was emerged (R_t = 3.60 min) with a m/z value of 252.99, which can be ascribed to the generated nitrile oxide derivative (cal. 253.05). These HPLC-MS results clearly indicates the conversion of probe **1** into its nitrile oxide product as depicted in Fig. 3. To further inspect the relationship between the electronic structure changes and optical response of probe **1** to ClO^-, a theoretical calculation was carried out by Density Functional Theory (DFT) with the B3LYP/6-31+G(d,p) method basis set using the Gaussian 09 program. Fig. 3 presents the frontier orbital diagram, highest occupied molecular orbital (HOMO) and lowest unoccupied molecular orbital

(LUMO), of probe **1** and the corresponding products. Due to the generated nitrile oxide group, the product displays decreases in the energy levels of both LOMO and HOMO, and a smaller energy gap, in good agreement with the red shift of the UV-Vis spectra.

3.3. Cellular imaging

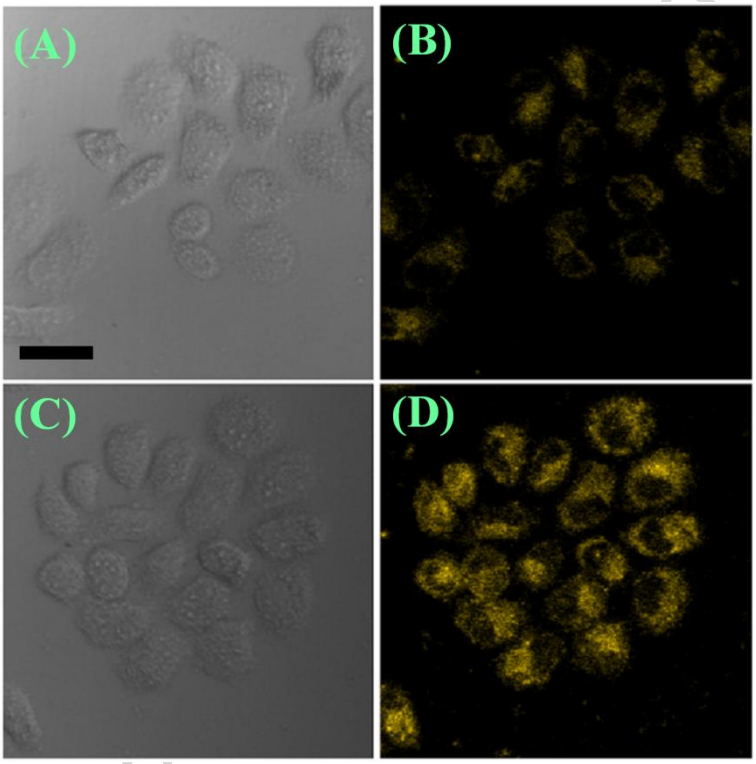


Fig. 4. Fluorescence images of live Hela cells. Cells incubated with 10 μM probe **1** for 60 min at 37 °C (A, B). Probe **1** loaded cells after treatment with 20 μM ClO^- for 60 min at 37 °C (C, D). (A) and (C) are bright-field images. Scale bar represents 20 μm in all images.

We further sought to apply probe **1** for fluorescence imaging of ClO^- in living cells. HeLa cells loaded with 10 μM probe **1** for 1 h at 37 ^oC showed faint fluorescence indicate that the probe is cell-permeable (Fig. 4B). Addition of 20 μM ClO^- to HeLa

cells loaded with probe **1** led to a significant increase in intracellular fluorescence compared to control cells without treatment by ClO^- (Fig. 4D). Furthermore, the cytotoxicities of probe **1** towards different types of cells were evaluated using MTT assay. All these inspected cells remained in good condition after 24 h incubation with various concentrations (0–20 μM) of probe **1** (Fig. S6), implying the low cytotoxicity of probe **1**. These cell experiments demonstrate that probe **1** is biocompatible, cell membrane permeable, and can be utilized for monitoring ClO^- in live cells.

4. Conclusion

In summary, a new turn-on fluorescent probe (**1**) for ClO^- by condensation of aldehyded HBT fluorophore with the recognition moiety of hydroxylamine was presented. Probe **1** displays sensitive and selective fluorescence response toward ClO^- over other ROS *via* the ClO^--induced specific transformation of the quenching group of hydroxylamine into nitrile oxide within probe **1**. The reaction mechanism was confirmed by HPLC-MS. Furthermore, probe **1** exhibits excellent biocompatibility and cell membrane permeability, and can be utilized for monitoring ClO^- in live cells. This novel probe provides a new model for detection and bioimaging of ROS in living cells.

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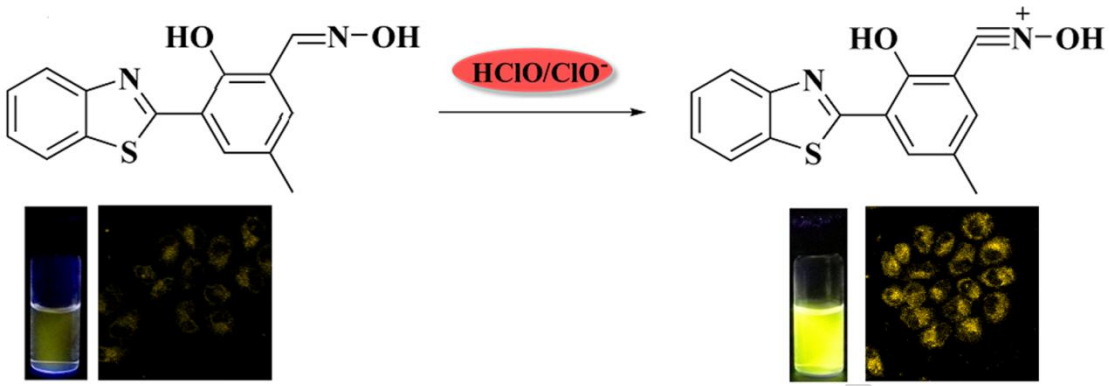

Graphical Abstract

Highlights

- A new benzothiazole-based turn-on fluorescent probe **1** was developed for ClO^-.
- Probe **1** features high sensitivity (LOD: 0.08 μM) and selectivity to ClO^-.
- The sensing mechanism was confirmed by HPLC-MS technique.
- Probe **1** was utilized for monitoring ClO^- in live cells.