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A Fast-response Fluorescent Probe for Hypochlorite Acid Detection and its Application of Exogenous and Endogenous HOCl Imaging in Living Cells

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A facile fluorescent probe (NBD-DOP) has been developed to detect hypochlorite acid (HOCl) in this study. The probe consists of a NBD fluorophore and a dopamine moiety that reacts with HOCl specifically. The dopamine group quenches the fluorescence of NBD efficiently through photoinduced electron transfer (PET) effect. Experimental data showed that NBD-DOP could detect HOCl with ultrafast response, high sensitivity and high selectivity under a wide pH range. The probe could also be used to detect Myeloperoxidase enzyme that produces HOCl. Moreover, NBD-DOP has been applied to imaging exogenous and endogenous HOCl in living cells by confocal fluorescent microscopy.

Reactive oxygen species (ROS), such as H_2O_2, HOCl, HO•, $O_2^{\bullet -}$, and $^1O_2$, are known to be involved in the killing process of immune cells against microbial cells. ROS could act as good or bad signalling molecules in biological pathways. Excessive ROS could lead to oxidative stress, which cause irreversible damage to DNAs, proteins and lipids, resulting in cell death and drive proliferation for tumour progression.[1] On the other hand, recent biological studies revealed that ROS are capable of regulating normal biological and physiological functions as well.[2] For example, low concentrations of ROS can activate the signalling pathways and trigger important biological progresses such as cellular proliferation and differentiation.[3]

Hypochlorite acid (HOCl) and its conjugate base (OCl^-) are known to be generated by the myeloperoxidase (MPO)-mediated reaction between H_2O_2 and chloride ions *in vivo*.[4] HOCl is a highly reactive species in animal immune systems. Abnormal levels of HOCl can cause tissue damage and lead to a variety of diseases, including cystic fibrosis,[5] atherosclerosis,[6] lung injury,[7] kidney disease,[8] neuron degeneration,[9] and certain cancers.[10] Compared with other ROS species, the role of HOCl in biology remains largely unexplored. Consequently, developing new chemical tools for HOCl detection or imaging in situ is of great importance to better understand its roles in biological systems as well as its relationship with the aforementioned diseases.

Reaction-based fluorescence probes for biomolecule imaging have recently emerged as a highly desired approach due to its advantages of high selectivity and sensitivity, convenient procedure and low costs. The most notable properties of this method are its fast response and its capability to monitor target analytes in living cells in real-time. Due to these prominent features, it has spurred intensive research efforts to design fluorescence-based probes for HOCl detection.[11] However, most of the developed probes suffer from various drawbacks, such as long response time,[11l, 11m] requirement of organic solvent[11o-11q] or narrow pH range.[11h, 11n] These limitations have restricted their usage in biology and medicine.

In this study, we have developed a new fluorescent probe **NBD-DOP** that consists of a 4-nitro-benzo [1,2,5] oxadiazole derivatives (NBD) fluorophore and a dopamine moiety. NBD is chosen in our probe design as this fluorophore has the advantage of minimal self-quenching and photobleaching.[12] Dopamine is a molecule commonly found in neuron cells, and it plays an important role in neurodegenerative pathogenesis such as Parkinson's disease.[13] As shown in Scheme 1, the probe itself shows low fluorescence due to the quenching effect of the dopamine moiety through PET effect. We hypothesize that our probe will react with HOCl specifically and efficiently. After the reaction, the dopamine moiety will be oxidized to form benzoquinone. As a result, PET effect will disappear and fluorescence will be turned on. To our delight, we found that our probe **NBD-DOP** shows fast-response (<30 s), high sensitivity and high selectivity toward HOCl. In addition, the probe also possesses good water solubility, and it is applicable in a wide pH range. These excellent properties make it highly suited for fluorescence imaging microscopy.

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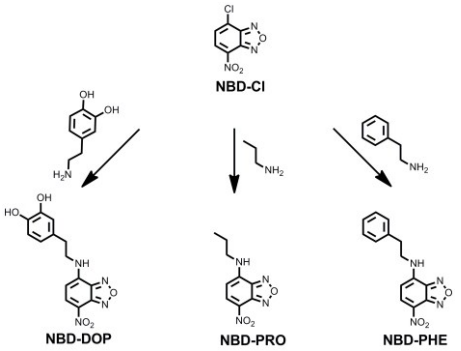
† Footnotes relating to the title and/or authors should appear here.



Scheme 1 Synthesis route of NBD-DOP, NBD-PRO and NBD-PHE.

Although a number of HOCl fluorescent probes have been reported by now, most of them have the disadvantages of multi-steps synthesis and low synthetic yields, which have restricted their applications in biological study. Our strategy for designing **NBD-DOP** requires simple one-step synthesis from commercially available compounds with a good reaction yield. For comparison purpose, we also synthesized **NBD-PRO** with a propylamine group and **NBD-PHE** with a benzyl group serving as electron donor. The synthetic route can be found in Scheme 1, and detailed procedure of synthesis is described in Supporting Information. The chemical structures of **NBD-DOP**, **NBD-PRO** and **NBD-PHE** were verified by ^{1}H NMR, ^{13}C NMR and ESI-MS (see supporting information, ESI†).

After synthesis and characterization, the absorption and emission properties of **NBD-DOP** for HOCl detection were studied. The absorption spectrum of **NBD-DOP** showed a major absorption band at 480 nm and a minor band at 350 nm in PBS buffer (10 mM, pH 7.4) (Fig. 1a). Upon addition of NaOCl, which was used as the source of HOCl, the absorption band at 480 nm apparently decreased and showed slight blue-shift to 470 nm. At the same time, the peak at 350 nm also decreased. In the fluorescence emission study, only very weak fluorescence was observed for **NBD-DOP** when excited at 470 nm. After reaction with NaOCl, a new fluorescence emission peak at 540 nm could be readily observed, demonstrating that **NBD-DOP** could sense HOCl efficiently in aqueous solution (Fig. 1a).

One of major challenge for HOCl detection in biological system is to develop highly selective probes that exhibit a notably distinctive response to HOCl over other ROS, such as H_2O_2, HO• and $O_2^{\bullet-}$. To investigate the selectivity of **NBD-DOP**, various ROS were employed in our study. As shown in Figure 1b, all the tested species, except NaOCl, showed very limited fluorescence increase even after 30 min of incubation with 10-fold concentration of NaOCl. Specifically, the fluorescence increase of **NBD-DOP** is 23-fold in PBS buffer (10 mM, pH 7.4). The fluorescence increase of other ROS is all within 5-fold, which is far below that of NaOCl. In addition, we also tested some reactive nitrogen species (RNS) and reactive sulfur species (RSS) for the selectivity test. No obvious fluorescence increase was observed after incubation with **NBD-DOP**. These results clearly demonstrated that **NBD-DOP** could detect HOCl selectively over other ROS, RNS and RSS (Fig. 1b and S1).

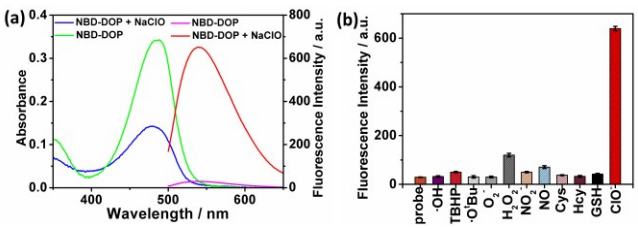


Fig. 1 (a) Absorption and emission of NBD-DOP in the absence and presence of NaOCl. The concentrations of NBD-DOP are 10 μM and 1 μM and the concentrations of NaOCl are 50 μM and 20 μM for absorption and emission respectively; (b) Fluorescence responses of NBD-DOP (1 μM) toward NaOCl and various ROS, RNS and RSS at 540 nm in PBS buffer (10 mM, pH 7.4): HO• (100 μM), •O^{t}Bu (100 μM), TBHP (100 μM), $O_2^{\bullet-}$ (100 μM), H_2O_2 (100 μM), NO_2^- (100 μM), NO (100 μM), Cys (1 mM), Hcy (1 mM), GSH (1 mM), NaOCl (20 μM). All species were incubated with NBD-DOP for 30 min at room temperature.

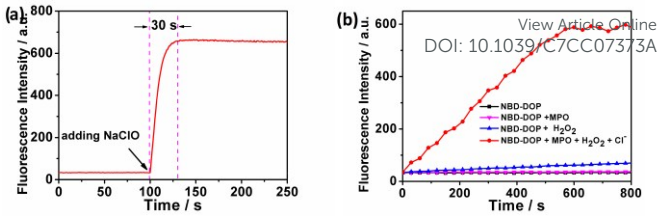


Fig. 2 (a) Time-dependent fluorescence intensity of probe NBD-DOP (1 μM) before and after the addition of NaOCl (20 μM) in PBS buffer (10 mM, pH 7.4). The arrow indicates the time when NaOCl was added; (b) Fluorescence responses of NBD-DOP toward HOCl generated in MPO/H_2O_2/Cl^- system (30 μM H_2O_2, 3 U/mL MPO) in PBS buffer (pH 7.4). Ex = 470 nm, Em = 540 nm.

Due to the short lifetime of HOCl in biological environment, fast response is highly desired for real-time monitoring of HOCl fluctuation in biological applications. Inspired by the preliminary result, we next investigated time-dependent fluorescence changes of **NBD-DOP** in the presence of NaOCl. As shown in Fig. 2a and S2, a fast response of **NBD-DOP** toward HOCl was observed by the fluorescence enhancement at 540 nm within 30s. In addition, the fluorescence intensity of **NBD-DOP** remained unchanged before and after the reaction, indicating that **NBD-DOP** and the reaction product of **NBP-DOP** and HOCl have excellent stability. Furthermore, we also tested the possibility of detecting HOCl generated in an enzyme system of MPO/H_2O_2/Cl^-. A fast response of fluorescence intensity was observed after adding **NBD-DOP** into the MPO/H_2O_2/Cl^- system. Nevertheless, almost no obvious change or slight increment was observed with MPO or H_2O_2 only, which demonstrated that our probe could sense the generation of HOCl catalyzed by MPO (Fig. 2b). This also proved that our probe was capable of detecting MPO activity in real time.

To better understand the effects of pH value on the sensing of HOCl by **NBD-DOP**, **NBD-DOP** was incubated in buffers of different pH values in the absence or presence of NaOCl. As indicated by Fig. S3, almost no fluorescence change was observed in the absence of NaOCl, suggesting the stability of **NBD-DOP** under different pH. Meanwhile, in the presence of NaOCl under the pH range of 4.0-9.0, the corresponding product exhibited fluorescence enhancement without significant change (Fig. S3 and S4), demonstrating that **NBD-DOP** is compatible with a wide pH range.

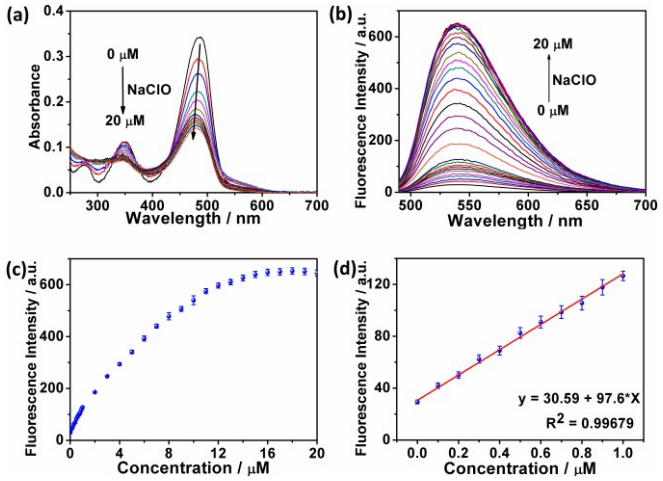


Fig. 3 (a) Absorption spectra of NBD-DOP (10 μM) in the presense of various concentrations of NaOCl (0-20 μM) in PBS buffer (10 mM, pH 7.4) at room temperature; (b) Fluorescence spectra of NBD-DOP (1 μM) in the presence of different concentrations of NaOCl (0-20 μM) in PBS buffer (10 mM, pH 7.4) at room temperature (Ex: 470 nm); (c) Fluorescence intensity changes of NBD-DOP (1 μM) at 540 nm in the presence of different concentrations of NaOCl (0-20 μM); (d) Fluorescence intensity changes of NBD-DOP (1 μM) at 540 nm in the presence of different concentrations of NaOCl (0-1.0 μM); Ex: 470 nm, Em: 540 nm. Note: Incubation time: 1 min.

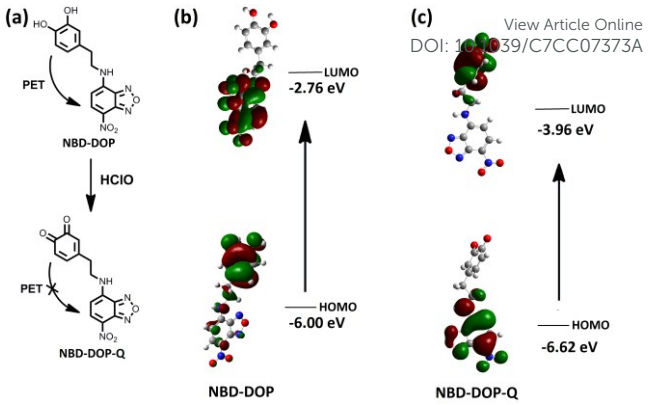


Fig. 4 (a) Proposed mechanism of NBD-DOP sensing HOCl; Frontier orbital energy representation of NBD-DOP (b) and NBD-DOP-Q (c).

The concentration-dependent absorption and fluorescence response of **NBD-DOP** with HOCl was further examined. As seen in Fig. 3a, the absorbance at 480 nm decreased with increasing amount of NaOCl, indicating the conversion of **NBD-DOP** to the reaction product. At the same time, the maximum absorption wavelength moved from 480 nm to 470 nm. The absorption and the fluorescence of the control compounds, **NBD-PRO** and **NBD-PHE**, were tested as well. The results clearly confirmed that the peak at 480 nm belongs to the NBD fluorophore (Fig. S5). Fluorescence titration experiments showed that the fluorescence intensity increased with the addition of NaOCl (0-20 μM) (Fig. 3b). Upon addition of NaOCl, the fluorescence intensity at 540 nm enhanced gradually and reached a plateau when 15 μM NaOCl was added (Fig. 3c). The fluorescence intensity at 540 nm and the NaOCl concentration in the range of 0-1 μM can be fitted to the regression equation y=30.59+97.6*x with R^2=0.99679. The excellent linear relationship suggests that **NBD-DOP** can be used as a highly sensitive fluorescent probe for HOCl detection (Fig. 3d). Based on the regression equation, the detection limit of the probe towards HOCl was calculated to be 9.7 nM based on 3σ/slope method (0-1000 nM), indicating that **NBD-DOP** is suitable for quantitative detection of HOCl in aqueous media.[14]

The outstanding performance of **NBD-DOP** to detect HOCl drives us to explore its sensing mechanism. We hypothesized that the *ortho*-benzenediol group in dopamine displays PET effect to NBD and quenches the fluorescence of NBD. After the reaction with HOCl, **NBD-DOP** was converted to **NBD-DOP-Q**. The PET effect diminished and the fluorescence was turned on (Fig. 4a). The above hypothesis was confirmed by ESI-MS analysis (Fig. S6). The main peak at m/z 337.2, which corresponds to [**NBD-DOP-Q**+Na]$^+$, was observed.

In addition, the quenching mechanism of dopamine was explained using the frontier orbital energy diagrams. We applied density functional theory (DFT) method to calculate the energy of ground state and excited state at the B3LYP/6-31G (d, p) level using the Gaussian 09 program. The highest occupied molecular orbital (HOMO) of **NBD-DOP** is mainly delocalized on the dopamine part, while the lowest occupied molecular orbital (LUMO) is mainly delocalized on the NBD part. This corresponds to electron cloud distribution of the PET mechanism process (Fig. 4b). However, when **NBD-DOP** is converted to **NBD-DOP-Q** using HOCl, HOMO of **NBD-DOP-Q** is mainly delocalized on the NBD part, while the LUMO is mainly delocalized on the dopamine part. Under this circumstance, the PET process is prohibited (Fig. 4c).[15] Additionally, before the reaction with HOCl, the HOMO energy level of the 1,2-benzenediol (−5.63 eV) was higher than the HOMO energy level (−6.26 eV) of 4-metylamino-7-nitrobenzofurazan (Fig. S7a). Thus, the fluorescence of **NBD-DOP** could be quenched through PET process. After reaction, the HOMO energy level of 1,2-benzoquinone moiety was −6.79 eV, which is lower than that of the 4-metylamino-7-nitrobenzofurazan (−6.26 eV) (Fig. S7b).[11a] Therefore, the PET process was prohibited, and NBD-DOP-Q displayed enhanced fluorescence.

Before we moved on to cell imaging study, MTS tests were performed to examine the toxicity of **NBD-DOP.** As shown in Fig. S8, after 24 h of incubation with 5 μM probe, more than 95% of the cells remained viable. In addition, the cell viability was as high as 90% when 20 μM **NBD-DOP** was incubated for 24 h. The results indicated that **NBD-DOP** exhibits low cytotoxicity at concentrations of 0-20 μM.

Finally, we evaluated the suitability of the probe for visualizing HOCl in living cells. The HeLa cells incubated with **NBD-DOP** (5 μM) for 10 min show very weak fluorescence at 520-570 nm (Fig. 5a-c). In contrast, after treating cells with NaOCl (50 μM) and incubation for another 10 min, a strong fluorescence was clearly observed, indicating that **NBD-DOP** can penetrate the cell membranes and react with exogenous HOCl in the cellular environment (Fig. 5d-f). Subsequently we tested the feasibility of **NBD-DOP** to image endogenous HOCl in living cells. Lipopolysaccharide (LPS) and phorbol 12-myristate 13-acetate (PMA), which are the stimulator and the activator for generating ROS, were used for producing endogenous HOCl in the cell imaging experiment.[11b, 11q, 16] Significant fluorescence increase was observed after the cells were stimulated by LPS/PMA (Fig. 5g-i). Taken together, these data demonstrate

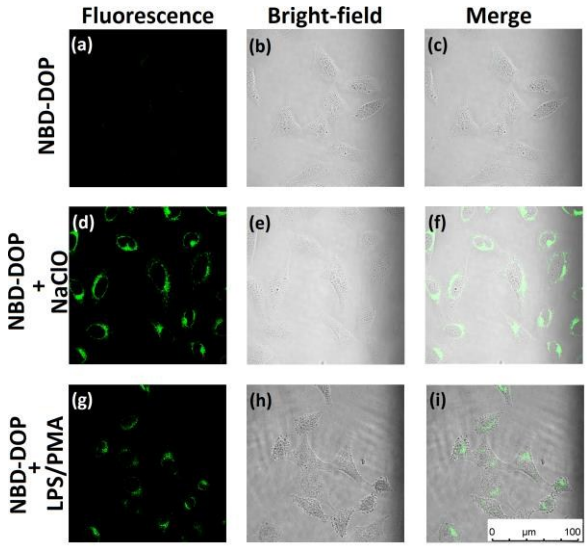


Fig. 5 Confocal fluorescence imaging for ClO^- detection in HeLa cells using NBD-DOP. (a-c) images of HeLa cells incubated with NBD-DOP for 20 min; (d-f) images of HeLa cells after treatment with NBD-DOP (5 μM) for 20 min, and subsequent treatment with NaOCl (50 μM) for 20 min; (g-i) images of HeLa cells incubated with LPS (2 μg/mL) for 24 h, further incubated with PMA (2 μg/mL) and then with NBD-DOP (2 μM) for 20 min.

that **NBD-DOP** is capable of detecting exogenous or endogenous HOCl in living cells.

To conclude, we have synthesized a facile fluorescent probe **NBD-DOP** to detect HOCl. **NBD-DOP** can be obtained through one-step synthesis. The dopamine moiety has dual functions: 1. The *ortho*-benzenediol group of dopamine plays PET effect on the NBD fluorophore. This provides the weak fluorescence background of **NBD-DOP** and high fluorescence enhancement after reacting with HOCl; 2. The dopamine group could react with HOCl specifically and efficiently. Our data supports that **NBD-DOP** functions as a practical fluorescent probe that features fast response (within 30 s), high selectivity and sensitivity to HOCl, and wide pH range in applications. Importantly, **NBD-DOP** has been successfully applied for imaging exogenous or endogenous HOCl in living cells.

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Conflicts of interest

There are no conflicts to declare.

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