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A boronate-based ratiometric fluorescent probe for fast selective detection of peroxynitrite

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ABSTRACT

Given that peroxynitrite ($ONOO^-$) is profoundly associated with health and diseases, a new fluorescent probe **ABT** was designed and synthesized for detection of $ONOO^-$. **ABT** manifested not only ratiometric fluorescence signals simultaneously in response to concentrations of $ONOO^-$ (within 10 s), but high selectivity and sensitivity towards $ONOO^-$ over other physiological relevant species (detection limit = 26.3 nM). Moreover, **ABT** worked in a broad pH range with biological relevance. Thus, **ABT** could be used to quantitative detection of $ONOO^-$ concentration and has the potential to efficiently monitor $ONOO^-$ in living organisms.

Introduction

Peroxynitrite ($ONOO^-$), a highly reactive oxidant in living organisms, is mostly produced by a diffusion-controlled reaction between nitric oxide (·NO) and superoxide ($\cdot O_2^-$) in mitochondria.[1] On the one hand, as an oxidant and efficient nitrite agent, $ONOO^-$ plays a vital role in diverse pathophysiological conditions like modulating cell signal transduction.[2–6] For example, $ONOO^-$ oxidizes reactive cysteine residues in proteins, as a result, deactivation or activation of the proteins.[7,8] But on the other hand, abnormality level of $ONOO^-$ in living cells can cause serious damage to cellular biomolecules involving lipids, proteins, and nucleic acids, resulting in cell apoptosis or necrosis. Moreover, abnormal concentrations of $ONOO^-$ is associated with some ailments such as cardiovascular diseases, circulatory shock, inflammation, cancers, and so on.[9,10] Thus, it is significant for assays of $ONOO^-$ detection which may be useful for the diagnosis of relative diseases and the exploration of its various pathophysiologies.

Although peroxynitrite in human health and diseases is of significance, the elucidation of the biological functions of peroxynitrite remains a challenge. One of the main obstacles to explore its roles in organisms is short of suitable approaches to detect it in vivo due to its short lifetime (<10 ms) and numerous antioxidant in cell. Fluorescent probe is of course a promising method to detect $ONOO^-$ in vivo.[11] Recently, a lot of fluorescent probes have been developed for peroxynitrite detection in biological systems.[12–20] Nevertheless, most of these probes are based on a single channel with a turn-on or turn-off fluorescence signal, which limits their applications in quantitative measurement of peroxynitrite concentration in vitro and vivo.[21] By contrast, the fluorescent probes on a basis of independent two-channel ratiometric signal enable reducing of the errors caused by various external conditions: excitation power, fluorescence decay and probe distribution.[22,23] However, it is still a heavy task to distinguish $ONOO^-$ from other reactive oxygen species (ROS) such as H_2O_2 and ClO- with similar properties and selectively detect $ONOO^-$ in the presence of reducing molecules such as hydrogen sulfide and glutathione.[24] Therefore, it is indeed urgent to find more excellent fluorescent probes for detecting and monitoring $ONOO^-$ in vivo.

As $ONOO^-$ can react with arylboronates forming corresponding phenols much faster than H_2O_2 and HClO, arylboronate derivatives are considerable sources for the $ONOO^-$ specific fluorescent probes.[25] Moreover, HMBT (2-(2-hydroxy-3-methoxyphenyl) benzothiazole) is regarded as an available fluorophore used in many fields successfully in light of large Stokes shift, good photostability and ratiometric detection capability.[26,27] Consequently, a new ratiometric fluorescent probe named as **ABT** (4-[(2-(2-benzithiazolyl)-5-methoxy) phenoxymethyl] phenylboronic acid pinacol ester), for detecting $ONOO^-$ was designed and synthesized by modifying HMBT with an arylboronate moiety. This probe **ABT** showed ultra-short response time and highly sensitive quality towards $ONOO^-$. Additionally, **ABT** performed prominent selectivity for $ONOO^-$ over other coexisted ROS such as H_2O_2, HClO, and ·OH.

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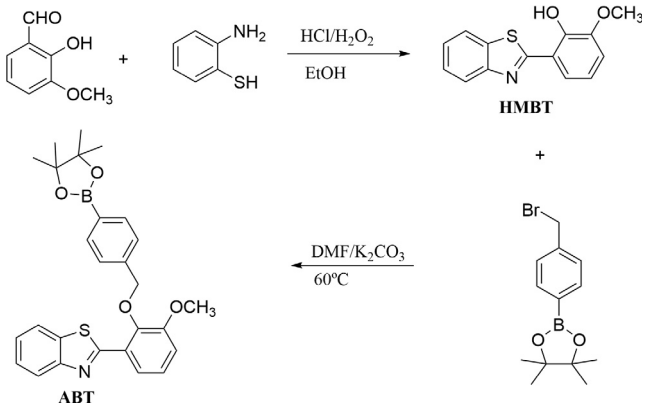

Scheme 1. Synthetic route of the probe **ABT**.

Results and discussion

Synthesis of probe ABT

Probe **ABT** was easily synthesized through two steps outlined in Scheme 1, and the details for synthetic data were given in Supporting information.

Spectral response of the probe to ONOO⁻

As the probe **ABT** and HMBT were in hand, their UV–vis absorption spectra and fluorescence emission spectra were investigated in PBS buffer (10 mM, pH 7.4, 40% ethanol) at room temperature. **ABT** showed maximal absorption/emission bands at 309 nm/405 nm, however, upon addition of $ONOO^-$ (2 equiv), the absorption band at λ = 309 nm was red-shifted to 317 nm and the emission

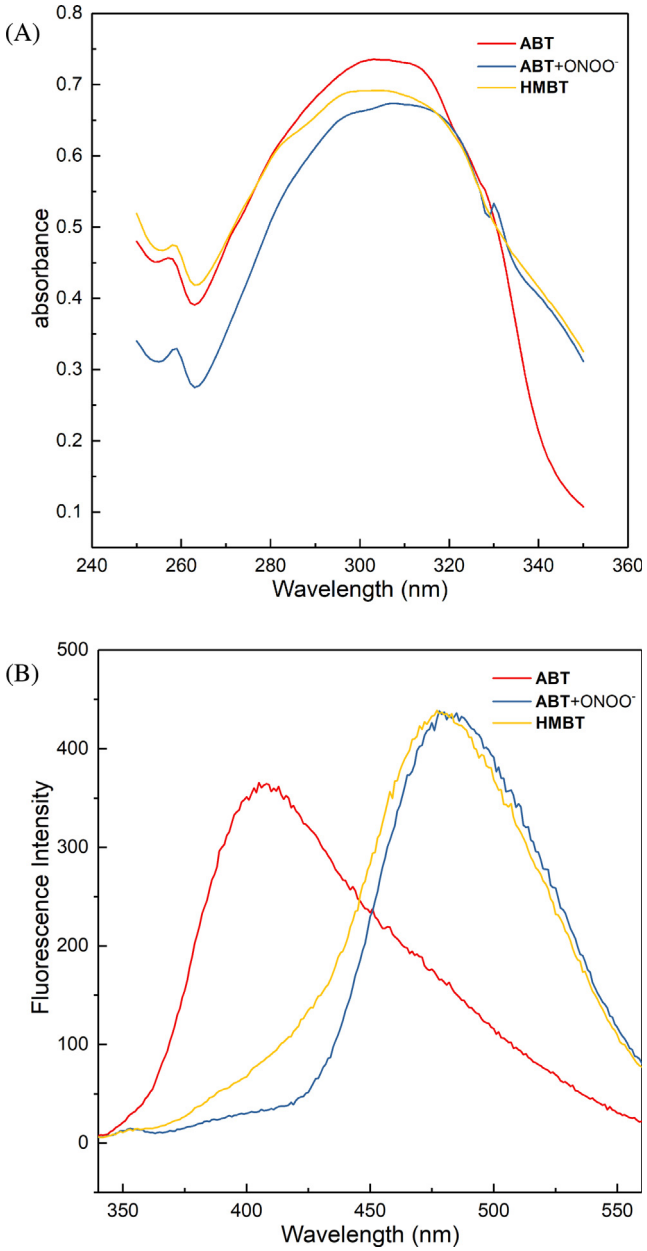

Fig. 1. The spectral profiles were obtained in PBS buffer (10 mM, pH 7.4, 40% ethanol). (A) UV–vis absorption spectra of **ABT** (50 μM), HMBT (50 μM) and **ABT** (50 μM) in the presence of 2 equiv of $ONOO^-$. (B) Fluorescence spectra of **ABT** (5 μM), HMBT (5 μM) and **ABT** (5 μM) in the presence of 2 equiv of $ONOO^-$, $\lambda_{ex.}$ = 317 nm, slits: 5. 5.

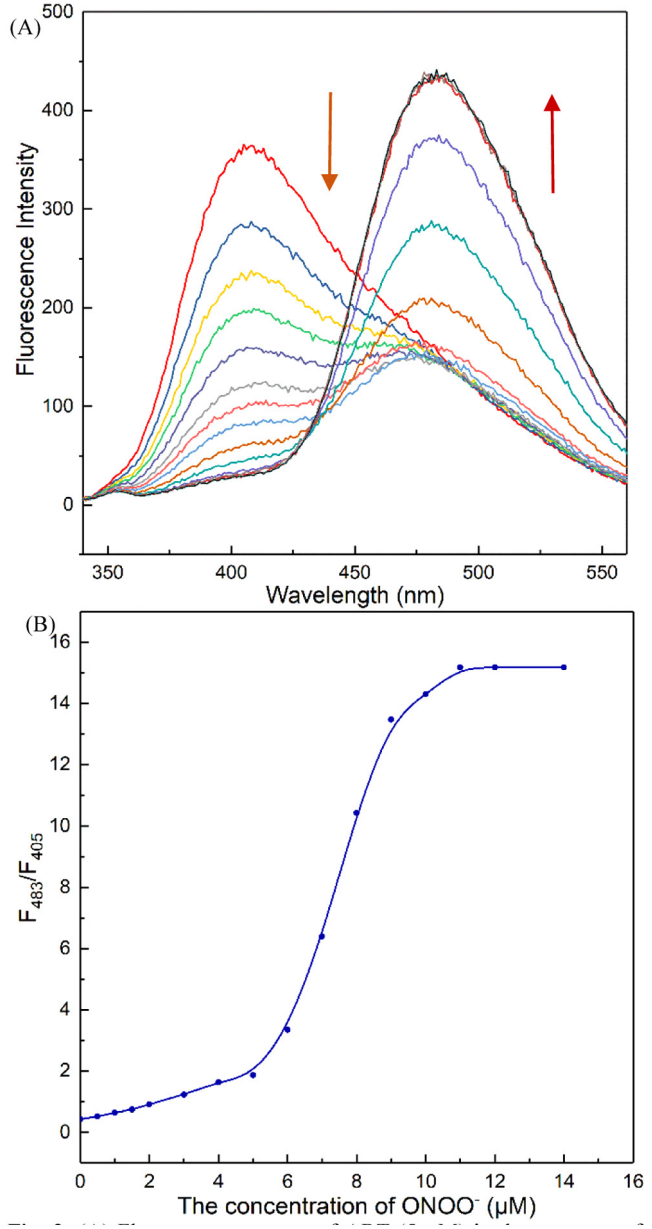

Fig. 2. (A) Fluorescence spectra of **ABT** (5 μM) in the presence of various concentrations of $ONOO^-$ (0–14 μM). (B) The relationship between fluorescence emission intensity ratio (F_{483}/F_{405}) and $ONOO^-$ concentration (0–14 μM). Profiles were obtained in PBS buffer (10 mM, pH 7.4, 40% ethanol), $\lambda_{ex.}$ = 317 nm, slits: 5. 5.