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A NIR-BODIPY derivative for sensing copper(II) in blood and mitochondrial imaging

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ABSTRACT

In order to develop NIR BODIPY for mitochondria targeting imaging agents and metal sensors, a side chain modified BODIPY (BPN) was synthesized and spectroscopically characterized. BPN has NIR emission at 765 nm when excited at 704 nm. The emission at 765 nm responded differently to Cu^{2+} and Mn^{2+} ions, respectively. The BPN coordinated with Cu^{2+} forming $[BPNCu]^{2+}$ complex with quenched emission, while Mn^{2+} induced aggregation of BPN with specific fluorescence enhancement. Moreover, BPN can be applied to monitor Cu^{2+} in live cells and image mitochondria. Further, BPN was used as sensor for the detection of Cu^{2+} ions in serum with linear detection range of 0.45 μM–36.30 μM. Results indicate that BPN is a good sensor for the detection of Cu^{2+} in serum and image mitochondria. This study gives strategies for future design of NIR sensors for the analysis of metal ions in blood.

1. Introduction

Mitochondria supply energy; provide building blocks for new cells and control redox homeostasis. Indeed, mitochondrial biogenesis and quality control are often upregulated in cancers [1]. Thus, mitochondria play an important role in suppression of tumor growth as they could determine the aberrant energetic metabolism of malignant cells and regulate cell death by apoptosis and necrosis. Cancer cells exhibit an extensive metabolic reprogramming that renders them more susceptible to mitochondrial perturbations than non-immortalized cells [2]. In particular, mitochondrion has been reported as an important target in heavy metal toxicity [3]. For example, Fe and Cu induced phospholipid peroxidation depended on the mitochondrial production of H_2O_2 and O_2^- [4]. Moreover, the generation of oxidative stress and mitochondrial dysfunction may determine heavy metal-induced cytotoxicity. Therefore, mitochondrial targeting metal sensors are meaningful to the assessment of metal-induced cytotoxicity.

Recently, fluorescence sensing and imaging has emerged as one of the most powerful techniques to monitor levels, localization, and movement of biomolecules in living systems [5]. The long wavelength (far-red to NIR) analyte-responsive fluorescent probes are advantageous for in vivo bioimaging because of minimum photo-damage to biological samples, deep tissue penetration, and minimum interference from background auto-fluorescence by biomolecules in the living systems [6]. BODIPYs (4,4′-difluoro-4-bora-3a,4a-diaza-s-indacenes) are fascinating dyes with large molar absorption coefficients, high fluorescence quantum yields, and excellent stability [7]. BODIPYs with absorption/emission at the NIR region have been reported as fluorescent imaging probes and photodynamic therapy agents [8,9]. The conjugation of metal chelator and BODIPY produces metal ion sensitive fluorescence probes [10,11,13]. For example, di(picolyl)amine (DPA) conjugated BODIPY can be Cu^{2+} sensitive fluorescence probe based on the ICT effect [14]. Previously, we found that the conjugation of BODIPY with DPA (di(pyridylmethyl)amine) results Cu^{2+} responsive sensors based on PET effect [15]. Cu(II) ion plays a crucial role in chronic neurological disorders such as Alzheimer's disease. BODIPY derivative with an —NH_2 and —OH substituted *meso*-phenyl group was reported as a colorimetric chemosensor for Cu^{2+} based on a specific cation induced *J*-aggregation [16]. Aggregation induced emission (AIE) fluorophores, a particular class of fluorophore, exhibits the change of fluorescence emission upon aggregation. Most fluorophores associated with quenched fluorescence upon aggregation, due to restricted intermolecular rotations in the self-assembled state [17]. Furthermore, a dye aggregation and the resulting changes in the fluorescence emission could be highly sensitive probes. In order to develop NIR BODIPY for mitochondria targeting imaging agents and metal sensors in serum, here, we report a new NIR BODIPY compound, which exhibits metal-induced quenched emission in the presence of Cu^{2+} and specific fluorescence enhancement for Mn^{2+}.

2. Experimental Section

2.1. Materials and Measurements

Chemicals (AR purity), unless indicated, were purchased from Sinopharm Chemical Reagent Co., Ltd. Anisic aldehyde (98%), 4-

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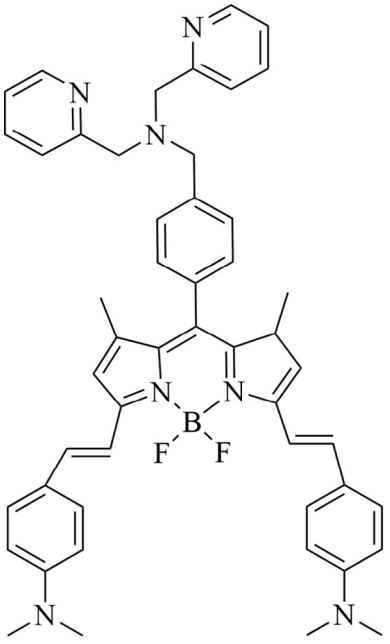

BPN

Scheme 1. The chemical structure of BPN.

dimethylaminobenzaldehyde (99%), 2,4-dimethylpyrrole (98%) were purchased from Energy Chemical Reagent Co., Ltd. 8-(3-Chlorobenzyl)-4,4-difluoro-1,3,5,7-tetramethyl-4-bora-3a,4a-diaza-s-indacene was synthesized according to literature procedures [14]. FT-IR characterization was performed using a Nicolet Nexus 470 FT-IR spectrophotometer in the wave number range of 4000–400 cm^{-1}. The electronic absorption spectrum was recorded using a UV-2450 UV–vis spectrophotometer at room temperature. Fluorescence measurements were performed on a fluorescence spectrofluorometer Model CARY Eclipse (VARIAN, USA), a 1.0 cm quartz cell (ex = 704 nm, slit width = 5 nm). The electrospray mass spectra (ES-MS) were determined on a Finnigan LCQ mass spectrograph. The ^1H (400 MHz) data was recorded on a Bruker AVANCE II 400 MHz spectrometer using $CDCl_3$ as a solvent. The chemical shifts (δ) were reported in ppm and coupling constants (J) in Hz.

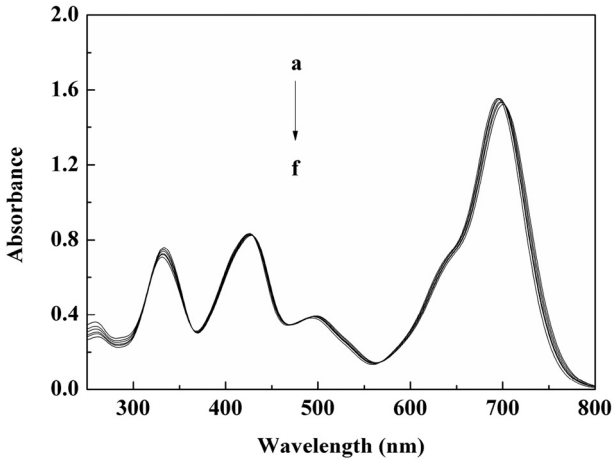

Fig. 1. Changes in the absorption spectrum of BPN (10 μM in MeCN) as the Cu^{2+} concentration is increased (C_{Cu2+} a–f = 0, 0.2, 0.4, 0.6, 0.8, 1.0 μM).

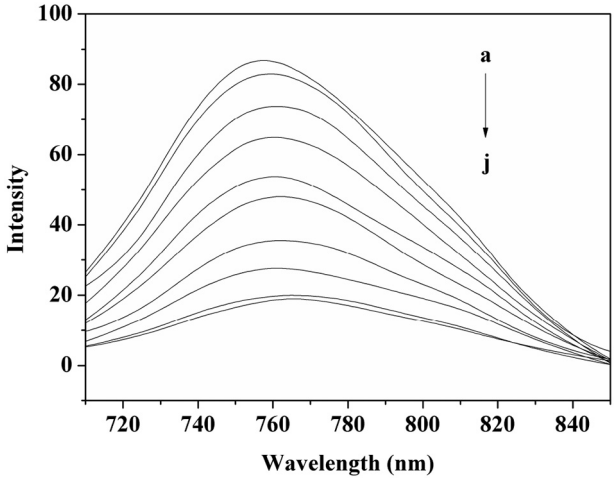

Fig. 2. Emission spectra of BPN (1 μM, CH_3CN) in the presence of various amount of Cu^{2+} (C_{Cu2+} a–j = 0, 0.2, 0.4, 0.6, 0.8, 1.0, 1.2, 1.4, 1.6, 1.8 μM). The excitation wavelength was 704 nm.

2.2. Synthesis of BPN (Scheme 1)

8-[Di(2-picolyl)amine-4-benzyl]-4,4-difluoro-1,3,5,7-tetramethyl-4-bora-3a,4a-diaza-s-indacene (245 mg, 0.46 mmol) was dissolved in toluene (10 ml) under nitrogen at room temperature, 4-*N*,*N*-dimethylaminobenzaldehyde (170 mg, 1.14 mmol) and piperidine (18.7 mg, 0.22 mmol) were added. The reaction was stirred at 120 °C for 8 h. The solvent was removed in vacuum and residue was dissolved in chloroform. The organic layer was washed with saturated sodium chloride (3 × 10 ml), dried with sodium sulfate, and then the solution was concentrated to give blue solid (257 mg) after column chromatography on silica gel. Yield. 70%. MS (EsI^+): Calcd for $C_{50}H_{51}BF_2N_2O_7C$, 75.18; H, 6.44; N, 12.27; Found. (%): C, 75.23; H, 6.38; N, 12.24·^{1}HNMR (400 MHz $CDCl_3$). δ = 8.57–8.56 (d, J = 4 Hz, 2H), 7.74–7.72 (t, J = 8 Hz, 2H), 7.60–7.54 (m, 10H), 7.32–7.30 (d, J = 8 Hz, 2H), 7.22–7.18 (m, 4H), 6.74–6.72 (d, J = 8 Hz, 4H), 6.59 (s, 2H), 3.86 (s, 4H), 3.79 (s, 2H), 3.05 (s, 12H), 1.39 (s, 6H). ES-MS (ESI^+, MeOH): calcd for $[C_{50}H_{51}BF_2N_7]^+$: 798.81, found:799.00.

2.3. Cell Imaging

MCF-7 cancer cells (hepatoma cancer cell) was inoculated into culture plate with 2.4×10^4 cells in each well and incubated for 24 h. Compounds were purified with semipermeable membrane and diluted to an appropriate concentration with culture solution respectively, and then inoculated with MCF-7 cancer cells for 6 h at 37 °C. The medium was washed with PBS buffer to remove the free compound, then it was detected with Nikon i-E 2000 microscope. The excitation wavelength was 643 nm.

Table 1
Spectroscopic properties of BPN in different solvents at room temperature.

Compound	Solvent	$\lambda_{Abs.}$ (nm)	λ_{ex} (nm)	λ_{em} (nm)	$\Delta\lambda$ (nm)	$\varepsilon \times 10^5$ ($l \cdot mol^{-1} \cdot cm^{-1}$)
BPN	CH_2Cl_2	703	704	762	58	1.31
	MeCN	696	704	765	61	1.33
	THF	695	704	748	44	1.48
	DMSO	716	704	786	82	1.40
	CH_3CH_2OH	698	704	763	59	15.1
	Tris–HCl buffer 7.4	724	704	786	82	1.19