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PAPER

Borondipyrromethene-derived Cu^{2+} sensing chemodosimeter for fast and selective detection†

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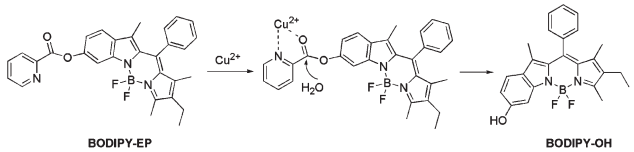
Here, we report a new Cu^{2+}-selective fluorescent turn-on probe **BODIPY-EP**, in which the 2-pyridinecarboxylic acid is connected to a 6-hydroxyindole-based BODIPY platform through an ester linkage. The ester bond of **BODIPY-EP** is selectively hydrolyzed by the reaction with Cu^{2+} under mild and neutral conditions to generate **BODIPY-OH**, showing strong characteristic fluorescence of **BODIPY-OH**. The favorable features of **BODIPY-EP** towards Cu^{2+} include fast response, large fluorescence enhancement and high selectivity. We further demonstrated that the membrane-permeable probe reacts with intracellular Cu^{2+} and exhibits bright fluorescence in living cells.

Introduction

Because of continuing concern over copper in the environment and its critical role in biological systems, development of probes for selective and sensitive quantification of Cu^{2+} by fluorescence techniques has recently emerged as a focal point in the sensing communities.[1] One common approach in the design of fluorescent probes is to attach a ligand to a fluorophore to form Cu^{2+} complexation.[2] Chelating of Cu^{2+} with chemosensors is well known to induce intrinsic fluorescence quenching due to the paramagnetic nature of Cu^{2+}, but turn-off signals are usually less sensitive and offer limited spatial resolution.[3] For practical applications, however, fluorescence probes with fluorescence turn-on signals in the presence of Cu^{2+} are superior to those with turn-off signals. One alternative strategy to achieve fluorescence turn-on involves the use of reaction-based indicator systems, chemodosimeters, and has attracted a great deal of attention.[4–6]

Most of the reported chemodosimeters are based on converting non-emissive molecules to the emissive ones *via* irreversible chemical reactions promoted by Cu^{2+}. Excellent examples of Cu^{2+}-promoted reactions include hydrolysis of esters[4] and amides[5] and oxidation of dihydrorosamine, phenothiazine, and phenol.[6] However, many of the reported chemosensors for Cu^{2+} have limitations such as low Cu^{2+} selectivity in the presence of other metal cations, the requirement for long incubation time, and specific reaction conditions such as high temperature, acidic or basic environment. Therefore, it is of great interest to design a new chemodosimeter that can be used to detect Cu^{2+} rapidly and selectively *in vitro* and *in vivo* under mild and neutral conditions.

BODIPY derivatives are among the most widely studied fluorescent dyes,[7] however, very few investigations have been carried out on 6-hydroxyindole-based BODIPY, as a scaffold for fluorescence probes.[8,9] During our study, we found that 6-hydroxyindole-based BODIPY has excellent photophysical properties. More importantly, it is facile to construct chemodosimeters for highly selective and sensitive detection of analyte by modification of the hydroxyl group in 6-hydroxyindole-based BODIPY.[9] Herein, we report a new Cu^{2+}-selective fluorescent probe **BODIPY-EP** (Scheme 1), in which 2-pyridinecarboxylic acid is connected to a 6-hydroxyindole-based BODIPY platform through an ester linkage. Interestingly, we found that the ester bond of **BODIPY-EP** is selectively hydrolyzed by the reaction with Cu^{2+} under mild and neutral conditions to generate **BODIPY-OH**. The favorable features of **BODIPY-EP** towards Cu^{2+} include fast response, large fluorescence enhancement and high selectivity. We further demonstrated that the membrane-permeable probe reacts with intracellular Cu^{2+} and exhibits bright fluorescence in living systems.



Scheme 1 Structure of **BODIPY-EP** and the release of **BODIPY-OH** by Cu^{2+} in aqueous solution at room temperature.

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†Electronic supplementary information (ESI) available: Copies of emission spectra, UPLC-MS, HRMS spectra and NMR spectra. See DOI: 10.1039/c2ob06980f

Results and discussion

Synthesis

Our group has reported a 6-hydroxyindole-based BODIPY with excellent photophysical properties.[9] An important advantage of this dye is the facile synthesis of derivatives by modification of the phenol function. Using this strategy, we constructed a chemodosimeter for highly selective and sensitive detection of benzenthiols.[9] On the other hand, the synthetic yield of this indole-based BODIPY is too low for further applications. During our study we found that another 6-hydroxyindole-based BODIPY, **BODIPY-OH**, with phenyl ring in the *meso* position instead of H atom, can be easily obtained. **BODIPY-OH** can be obtained in a routine BODIPY formation, three-step procedure *via* condensation of 2,4-dimethyl-3-ethylpyrrole with 2-benzoyl-3-methyl-6-methoxyindole followed by removal of the methoxy protecting groups (BBr_3, CH_2Cl_2) and boron insertion with $BF_3{\cdot}OEt_2$ (Scheme 2). The overall yield is 53% for the three steps. **BODIPY-EP** was then readily synthesized in one step by reaction of **BODIPY-OH** with 2-pyridinecarboxylic acid (PCA) in the presence of *N*,*N*′-diisopropylcarbodiimide (DIPC) and *p*-(dimethylamino)pyridinium *p*-toluenesulfonate (DPTS) in high yield. The structure was fully characterized by ^{1}H NMR, ^{13}C NMR, and HRMS analysis.

Sensing response of BODIPY-EP to Cu^{2+}

In H_2O–DMSO buffer solution (0.05 M Tris-HCl, 50% DMSO, pH = 7.5), the optical features of **BODIPY-EP** are characteristics of the BODIPY platform (Fig. 1a). The main absorption band of **BODIPY-EP**, attributed to the 0–0 vibrational band of a strong S_0–S_1 transition, is centered at 513 nm. Upon gradual addition of $CuCl_2$ to a solution of **BODIPY-EP** in H_2O–DMSO buffer solution at room temperature, the absorption band at 513 nm decreased and a new band at 546 nm appeared instantly, with a distinct isosbestic point at 523 nm. The spectral change almost stops upon addition of 3 equiv of Cu^{2+} within 20 min. Concomitantly, the color of the solution turned from light pink to reddish purple. The absorption band at 546 nm is the characteristic absorption of **BODIPY-OH** which is red-shifted by 33 nm compared to that of **BODIPY-EP**. Adding an excess amount of EDTA to the solution does not show further spectral change, indicating that **BODIPY-EP** reacts with Cu^{2+} irreversibly.

A fluorescence titration experiment was used to assess the ability of **BODIPY-EP** to detect Cu^{2+} at room temperature (Fig. 1b). Free **BODIPY-EP** shows weak fluorescence at about 577 nm with an emission quantum yield of ~0.07. However, remarkable fluorescence enhancement in the featured emission of **BODIPY-OH** at 577 nm (quantum yield ~0.33) was observed upon gradual addition of $CuCl_2$, and the fluorescence turns out to be stable when 3 equiv of Cu^{2+} was added, higher concentration of Cu^{2+} does not lead to any noticeable change. Consistently, the emission color of **BODIPY-EP** solution turned from dark to bright orange. As shown in Fig. 2a, a linear relationship is observed between the intensity change and the Cu^{2+} amount at concentrations lower than 20 μM. The detection limit for Cu^{2+} was determined as 1.05×10^{-6} M under the experimental conditions, which is sufficiently low to allow the fluorogenic detection of micromolar concentrations of Cu^{2+} in drinking water and living systems. The experiments of the counter anions' effect on the response of **BODIPY-EP** to Cu^{2+} were also investigated, which demonstrated that counter anions have little influence on the response properties (Fig. S1†).

Kinetics measurements of the fluorescence responses of **BODIPY-EP** to Cu^{2+} were studied by time-dependent

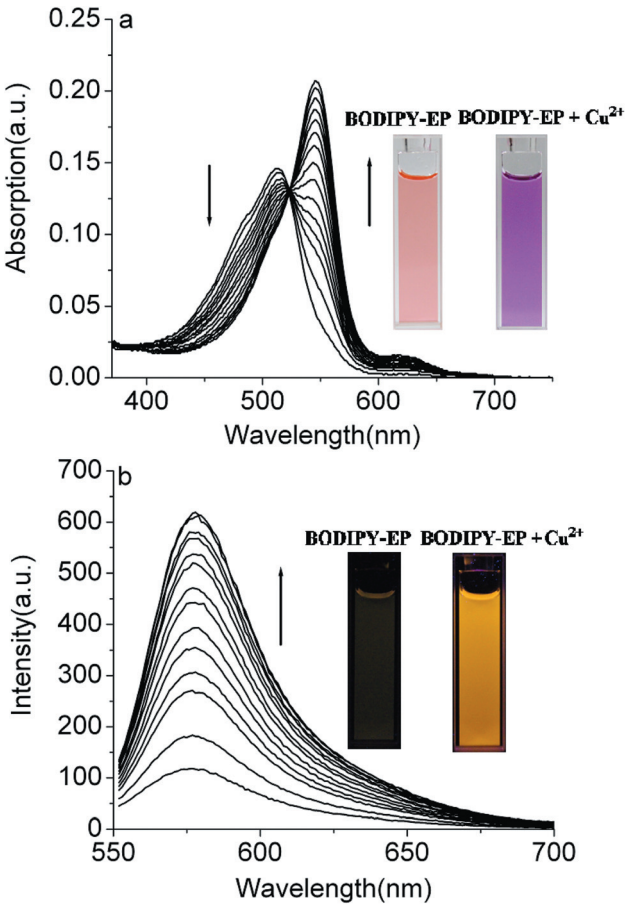
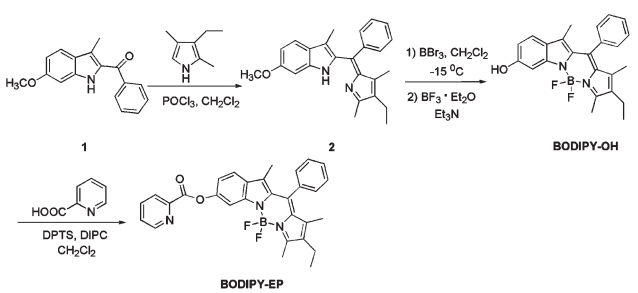


Fig. 1 Spectra of **BODIPY-EP** (5×10^{-6} M) in the presence of different concentrations of $CuCl_2$ (0, 0.15, 0.30, 0.45, 0.60, 0.75, 0.90, 1.05, 1.20, 1.35, 1.50, 1.65, 1.80, 2.25, 3.00 equiv) in H_2O–DMSO buffer solution (0.05 M Tris-HCl, 50% DMSO, pH = 7.5). (a) Absorption spectra. Insets: visible color change of **BODIPY-EP** upon additions of $CuCl_2$ (4 equiv). (b) Fluorescence titration spectra (λ_{ex} = 523 nm). Inset: fluorescence color change of **BODIPY-EP** upon additions of $CuCl_2$ (6 equiv) on excitation at 365 nm using a handheld UV lamp. Each measuring was conducted after 10 min of mixing.



Scheme 2 Synthesis of **BODIPY-EP**.

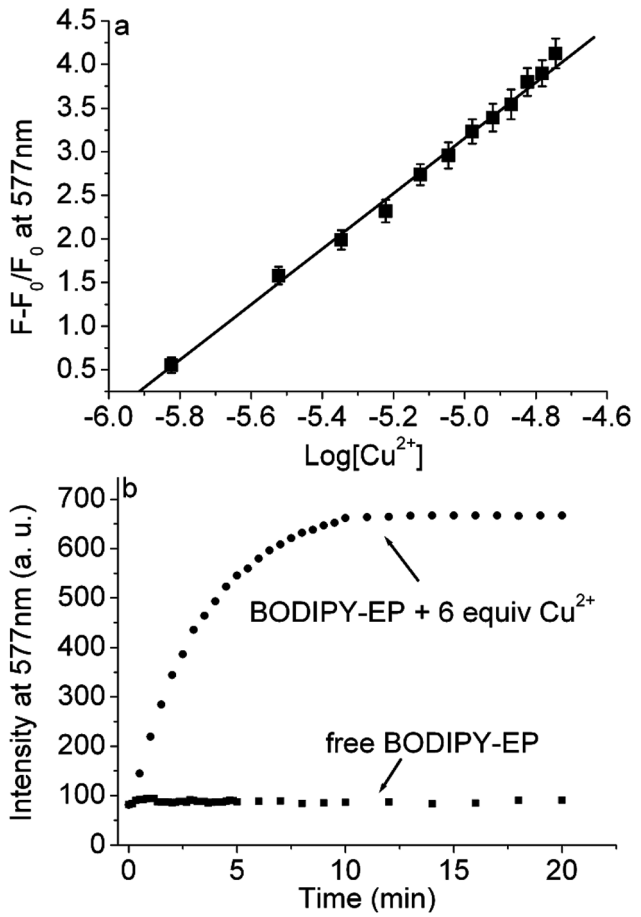


Fig. 2 (a) Fluorescence change of **BODIPY-EP** (5 μM) in intensity at 577 nm as a function of Cu^{2+} concentration. Error bars represent the standard deviation of three measurements. Each measuring was conducted after 10 min of mixing. (b) Kinetics of fluorescence enhancement profile of **BODIPY-EP** at 577 nm in the absence and presence of Cu^{2+}. The experiment was carried out in H_2O–DMSO buffer solution (0.05 M Tris-HCl, 50% DMSO, pH = 7.5) at room temperature. λ_{ex} = 523 nm.

fluorescence spectra (λ_{ex} = 523 nm, λ_{em} = 577 nm). Fig. 2b and S2† display the representative kinetics plots for **BODIPY-EP** in the presence of different amounts of Cu^{2+}. The fluorescence intensity increase displays in a concentration dependent fashion. Higher concentrations of Cu^{2+} afforded a quicker and more dramatic response. Observed rate constants for Cu^{2+}-mediated deprotection of **BODIPY-EP** are in the range of 0.06–0.37 min^{-1}. Notably, a drastic characteristic of **BODIPY-EP** is the rapid reaction with excess of Cu^{2+}. As shown in Fig. 2b, **BODIPY-EP** (5 μm) exhibited no observable changes in the emission intensities at 577 nm in the absence of Cu^{2+} within 2 hours. By contrast, a pronounced enhancement at 577 nm was noted even after 1 min upon the addition of 6 equiv of Cu^{2+} and the enhancement reached equilibrium within 10 min, indicative of a fast reaction of **BODIPY-EP** with Cu^{2+} to release **BODIPY-OH**. The Cu^{2+}-induced fluorescence enhancement of **BODIPY-EP** occurs in a pH range from 5 to 8 (Fig. S3†), although the reaction time is much longer in an acid environment, suggesting that **BODIPY-EP** enables Cu^{2+} detection at a physiological pH range.

The UV–vis and fluorescence spectra of the **BODIPY-EP**–Cu^{2+} system are characteristic of **BODIPY-OH**. Therefore, the sensing mechanism can be proposed as the Cu^{2+}-induced selective hydrolysis of **BODIPY-EP** to release **BODIPY-OH** (Scheme 1). This mechanism is confirmed by identifying the same mass of **BODIPY-EP** + Cu^{2+} as that of **BODIPY-OH** (Fig. S4†). In UPLC-Mass spectra, **BODIPY-EP** gave a retention time at 3.63 min, and peak of $[M - H]^-$ with 508.2032. Likewise, **BODIPY-EP** + Cu^{2+} gave a retention time at 3.43 min, and peak of $[M - H]^-$ with 403.1841, identical to that of **BODIPY-OH**. ^{1}H-NMR spectrometry also revealed the identity of the fluorescent product to be **BODIPY-OH** (Fig. S5†). Absorption and fluorescence spectra titration of **BODIPY-EP** (5 μM) in the presence of 0–30 μM Cu^{2+} also demonstrated that Cu^{2+}-promoted hydrolysis was a stoichiometric reaction rather than a Cu^{2+}-catalyzed reaction, because Cu^{2+}–PCA chelate produced by the hydrolysis reaction inhibited the reactivity of the Cu^{2+}. This was further confirmed by adding Cu^{2+} ions to the solution of **BODIPY-EP** in the presence of excess 2-pyridinecarboxylic acid (PCA, 1000 equiv), where no apparent fluorescence changes were observed (Fig. S6–S7†). The inhibition of Cu^{2+}–PCA chelate clearly demonstrated that the coordination of Cu^{2+} to pyridinecarboxylate ester is requisite for hydrolysis of the probe, supporting the mechanism proposed above.

Selectivity studies of BODIPY-EP toward Cu^{2+}

The selectivity of **BODIPY-EP** towards Cu^{2+} over relevant cations was then evaluated by measuring the changes in the optical spectra upon addition of excess amount of various cations with an assay time of 10 min. The unique absorption change with appearance of the characteristic absorption of **BODIPY-OH** was observed only by the addition of $CuCl_2$, which can be ascribed to the Cu^{2+}-promoted hydrolysis of **BODIPY-EP** to give **BODIPY-OH**. By contrast, no noticeable change in the UV spectra was noted with other cations such as K^+, Na^+, Ca^{2+}, Ag^+, Zn^{2+}, Hg^{2+}, Cd^{2+}, Co^{2+}, Fe^{2+}, Fe^{3+}, Ni^{2+}, Mn^{2+}, Pb^{2+} (Fig. 3a).

The fluorescence response of **BODIPY-EP** with various cations and its selectivity for Cu^{2+} are shown in Fig. 3b. The weak fluorescence of **BODIPY-EP** was only marginally increased upon addition of representative cations such as K^+, Na^+, Ca^{2+}, Ag^+, Zn^{2+}, Hg^{2+}, Cd^{2+}, Co^{2+}, Fe^{2+}, Fe^{3+}, Ni^{2+}, Mn^{2+}, Pb^{2+}. Only when Cu^{2+} was added was the unique fluorescent characteristic of **BODIPY-OH** detected. It is noted that the unique absorbance and fluorescence bands resulting from the addition of the Cu^{2+} ions were not influenced by other cations. We further examined the fluorescence response of **BODIPY-EP** toward Cu^{2+} in the presence of other potentially competing cations (Fig. 4). The titration of Cu^{2+} and **BODIPY-EP** in the presence of various metal ions was conducted, and the experimental results indicate that most of the relevant metal ions only display minimum interference. The selectivity was also conducted at an elevated temperature (37 °C), and no noticeable changes in UV and emission spectra were observed upon addition of the competitive cations. These results indicate the excellent selectivity of **BODIPY-EP** towards Cu^{2+} over the other competitive cations.

A variety of other transition metal ions also display affinities, but these ions did not elicit the fluorescence response of probe **BODIPY-EP** within an assay time of 10 min (Fig. 3), which

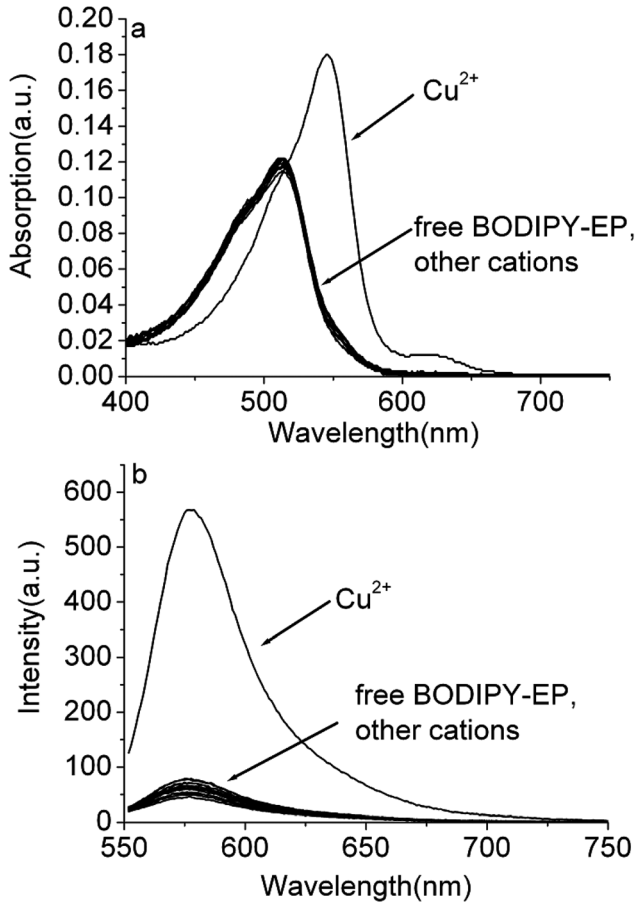


Fig. 3 (a) Absorption and (b) fluorescence spectra (λ_{ex} = 523 nm) of **BODIPY-EP** (5 μM) in the absence and presence of 6 equiv of various cations in H_2O–DMSO buffer solution (0.05 M Tris-HCl, 50% DMSO, pH = 7.5). The assay time was 10 min.

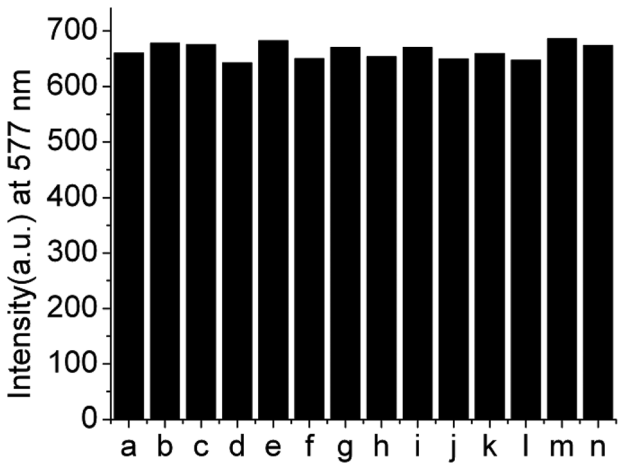


Fig. 4 Fluorescence response to 6 equiv of Cu^{2+} in the presence of 6 equiv of other cations (λ_{ex} = 523 nm). (a) Cu^{2+}, (b) K^+, (c) Na^+, (d) Ca^{2+}, (e) Ag^+, (f) Zn^{2+}, (g) Hg^{2+}, (h) Cd^{2+}, (i) Co^{2+}, (j) Fe^{2+}, (k) Fe^{3+}, (l) Ni^{2+}, (m) Mn^{2+}, (n) Pb^{2+}. The assay time was 10 min.

allows the probe to exhibit the high selectivity for Cu^{2+}. This high selectivity could be attributed to reaction time and conditions required for the hydrolysis of pyridinecarboxylate ester

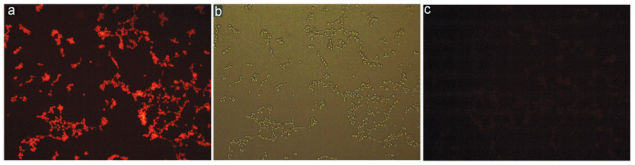


Fig. 5 (a) Fluorescence microscopy image of HEK293A cells pre-treated with Cu^{2+} (50 μM) for 30 min, washed with PBS, and then incubated with **BODIPY-EP** (10 μM) for another 30 min at room temperature. (b) Bright-field image of the cells shown in (a). (c) Fluorescence image of cells incubated with 10 μM **BODIPY-EP** for 30 min.

by different metal ions. For instance, solutions containing **BODIPY-EP** (5 μM) and Zn^{2+} (30 μM) in buffer solutions were allowed to react for 2 hours to reach equilibrium (Fig. S8†). However, Cu^{2+} ion promotes the hydrolysis at rates much greater than other metal ions, only several minutes are needed. At the same time, the fluorescence enhancement is much stronger than that of **BODIPY-EP** + other cations.

Detection of Cu^{2+} in living HEK293A cells

We next assessed the ability of our probe for fluorescence imaging of Cu^{2+} in living HEK293A cells (Fig. 5). HEK293A cells incubated with 10 μM of **BODIPY-EP** for up to 120 min at 37 °C show negligible intracellular fluorescence image. However, if cells were pre-treated with Cu^{2+} in the culture medium for 30 min, washed with phosphate buffered saline to remove extracellular Cu^{2+} and further incubated with 10 μM **BODIPY-EP** for 30 min, a bright fluorescence image was then observed from these cells. These results demonstrate that **BODIPY-EP** is cell membrane permeable and can be used as a possible sensor to detect Cu^{2+} within living cells.

Conclusions

In conclusion, a borondipyrromethene-derived fluorescence turn-on probe for Cu^{2+}, **BODIPY-EP**, was developed. This probe was constructed by the modification of the hydroxyl group in 6-hydroxyindole-based BODIPY through an ester linkage to 2-pyridinecarboxylate. The ester bond is selectively hydrolyzed by the reaction with Cu^{2+} under mild and neutral conditions. Therefore, **BODIPY-EP** displays favorable features towards Cu^{2+}, including: (1) fast response to Cu^{2+} under mild and neutral conditions within several minutes, enabling Cu^{2+} detection rapidly; (2) remarkable fluorescence enhancement in the featured emission of **BODIPY-OH** at 577 nm (quantum yield increased from ~0.07 to ~0.33) upon addition of Cu^{2+}; (3) high selectivity based on reaction time, due to Cu^{2+} ion promoting the hydrolysis at rates much greater than other metal ions. Importantly, the probe is membrane-permeable and can react with intracellular Cu^{2+}, displaying bright fluorescence in living systems.

The probe constructed here has absorption and emission wavelengths in the visible range. In contrast, near-infrared (NIR) fluorescent sensors are advantageous due to less photodamage, minimum fluorescence background, and less light scattering by NIR light. Given the fact that the anion form of **BODIPY-OH** is highly fluorescent around 650 nm (falling in NIR region),[8]

construction of a chemodosimeter with release of the anion form *via* a reaction may open an avenue for the development of NIR fluorescent sensors. As modulation of the p*K*a of **BODIPY-OH** is a key point to get the brightest fluorescence emission of the phenolate species in aqueous media under physiological conditions, further study to reduce the p*K*a of the phenol and to improve the water-solubility[10] of these BODIPY derivatives is currently underway.

Experimental section

General methods

All chemical reagents and solvents for synthesis were purchased from commercial suppliers and were used without further purification. Dichloromethane was dried with CaH_2 and distilled immediately prior to use. All moisture-sensitive reactions were carried out under an atmosphere of argon. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker AV-400 spectrometer with chemical shifts reported in ppm (in $CDCl_3$, TMS as internal standard) at room temperature. Mass spectra were measured on a HP 1100 LC-MS spectrometer.

Synthesis

Synthesis of BODIPY-OH. To a solution of 2-benzoyl-3-methyl-6-methoxyindole (1 g, 3.76 mmol) in CH_2Cl_2 (60 mL) was added $POCl_3$ (1.05 mL, 11.28 mmol) at 0 °C, the resulted solution was stirred for another 5 min, followed by the addition of 2,4-dimethyl-3-ethylpyrrole. The resulting mixture was warmed to room temperature and stirred for 3 days, cooled to 0 °C, neutralized with saturated Na_2CO_3, and washed with H_2O. The organic phase was dried with Na_2SO_4, and the solvent was removed to give dark oil. To the resulting oil in anhydrous CH_2Cl_2 was added BBr_3 (3.48 mL, 37.6 mmol) at −15 °C. The reaction mixture was further stirred for 1 hour at −15 °C, warmed to room temperature, quenched with H_2O, extracted with CH_2Cl_2, and washed with H_2O. The combined organic extracts were dried with Na_2SO_4, and Na_2SO_4 was removed by filtration. Then Et_3N (5.6 mL) was added to the solution at room temperature, and the resulting mixture was stirred for 5 min, cooled to 0 °C, followed by addition of $BF_3{\cdot}OEt_2$, and stirred for another 30 min. The reaction mixture was extracted with CH_2Cl_2, washed with H_2O, dried over Na_2SO_4, and the solvent was removed *in vacuo*. The crude product was purified by flash chromatography (silica gel, eluent: CH_2Cl_2 then EtOAc–CH_2Cl_2 1 : 10) to afford 800 mg (53%) **BODIPY-OH**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.03 (t, 3H), 1.40 (s, 3H), 1.60 (s, 3H), 2.35–2.41 (q, 2H), 2.69 (s, 3H), 6.61–6.65 (dd, 1H), 7.1 (m, 1H), 7.34–7.37 (m, 3H), 7.54–7.56 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.8, 157.7, 146.5, 141.6, 141.5, 136.8, 135.3, 133.3, 132.7, 129.3, 129.1, 128.3, 127.0, 122.7, 112.4, 98.7, 17.2, 14.2, 13.4, 12.2, 11.3; HRMS (ESI-TOF) *m*/*z* calcd for $C_{24}H_{22}BF_2N_2O$ $[M - H]^-$: 403.1793. Found: 403.1825.

Synthesis of BODIPY-EP. A mixture of **BODIPY-OH** (404 mg, 1.0 mmol), 2-pyridinecarboxylic acid (127 mg, 1.03 mmol), DPTS (780 mg, 2.5 mmol), and DIPC (315 mg, 2.5 mmol) in CH_2Cl_2 were refluxed overnight. The solvent was removed *in vacuo*, and the residual solid was purified by flash chromatography (silica gel) to afford 446 mg (88%) of **BODIPY-EP**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.05–1.01 (t, 3H), 1.40 (s, 3H), 1.62 (s, 3H), 2.40–2.34 (m, 2H), 2.69 (s, 3H), 6.97–6.94 (dd, 1H), 7.36–7.34 (m, 2H), 7.50–7.48 (d, 1H), 7.57–7.55 (m, 4H), 7.64 (s, 1H), 7.95–7.90 (m, 1H), 8.32–8.30 (d, 1H), 8.87–8.86 (d, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.07, 162.76, 150.50, 149.08, 146.59, 143.42, 141.76, 141.04, 136.93, 136.16, 135.84, 133.94, 132.76, 129.88, 129.70, 128.61, 128.36, 127.77, 127.24, 127.10, 126.28, 124.79, 120.66, 114.46, 106.33, 21.95, 16.14, 13.06, 11.28, 10.13. HRMS (ESI-TOF) *m*/*z* calcd for $C_{30}H_{25}BF_2N_3O_2$ $[M - H]^-$: 508.2008, found 508.2015.

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