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Research paper

A novel dual-responsive fluorescent probe for the detection of copper(II) and nickel(II) based on BODIPY derivatives

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ABSTRACT

A novel dual-responsive fluorescence probe **6** was constructed by introducing a dipicolyamine moiety on the BODIPY-based skeleton *via* Sonogashira coupling reaction and confirmed by ¹H NMR, ¹³C NMR, elemental analysis and high-resolution mass spectroscopy (HRMS). The present probe **6** exhibited high selectivity and sensitivity toward Cu^{2+} and Ni^{2+} detection over other competitive metal ions by fluorescence quenching phenomena, respectively. In addition, the detection limits (DLs) for Cu^{2+} and Ni^{2+} were calculated to be as low as both 0.1 µM respectively, which were lower than the maximum allowable level of the World Health Organization (WHO) limit for the drinking water. The stoichiometric ratio of the probe **6** toward the Cu^{2+} or Ni^{2+} ions was determined to be 1:1 according to the result of the Job's plot and HRMS analysis. These results indicated that probe **6** can be used as a selective "turn-off" fluorescent sensor for the detection of Cu^{2+} and Ni^{2+} .

1. Introduction

Selective and sensitive detection of various heavy metal ions has received increasing attention due to their significant importances in bioanalysis and environmental monitoring. [1,2] Among these metal ions, copper ion (Cu^{2+}) is the third most abundant metal ion after iron and zinc in the human body, which plays important and indispensable roles in physiological and pathological processes such as respiration, enzyme functions, antioxidant defense, and gene expression. [2-5] Trace amount of Cu²⁺ uptake is very necessary for the living system towards growth and development. [6] An undersupply of these metal ions leads to deficiency and oversupply results in toxic effects. [7] However, the imbalance of Cu^{2+} level causes various diseases. [8] Excessive concentration levels of Cu²⁺ in human body can exhibit toxicity and result in many serious diseases such as kidney or liver damage, Alzheimer's disease, Wilson's and Parkinson's diseases and even may cause death. [1,4,9-11] Also, deficiency of Cu^{2+} can cause anemia, hair abnormalities, and arterial abnormalities, and also affect the development of bones and brain. [12-14] In addition, Cu^{2+} is also a

significant environmental pollutant due to the lack of effective management deriving from its widespread use in current agriculture and industry. [12,15] On the other hand, Nickel is also an essential trace element for a variety of enzymes in biological systems such as respiration, biosynthesis, and metabolism. [16,17] However, the excessive uptake of Ni²⁺ in the human body can cause various diseases, such as asthma, acute pneumonitis, dermatitis, and cancer of the lung and sinus. [18] Besides, Ni²⁺ is also a significant environmental pollutant as one of the heavy metals. Consequently, the development of highly sensitive and selective analytical methods for the detection of Cu^{2+} and Ni^{2+} is of great importance for the human health and environment. In the past few years, various analytical methods have been applied for the determination of Cu²⁺ and Ni²⁺ ions. [12,19,20] Compared to those methods, the fluorescence probe has drawn considerable attention due to its good selectivity, high sensitivity, operational simplicity, fast response time, and low cost. [12,21-28] In recent years, a number of fluorescent probes for the detection of Cu2+ and Ni2+ have been reported, such as coumarin, 1,8-naphthalimide, rhodamine and fluorescein, which show high sensitivity and low detection limit toward Cu²⁺ and Ni²⁺.

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in the environment. [26,35,36,38]

reports that show a single fluorescence probe for recognizing both Cu²⁺

and Ni²⁺ simultaneously. [7,8,17,34–37] Therefore, it is still of a great interest and necessary to develop highly sensitive and selective fluo-

rescence probes to detect and estimate the trace levels of \mbox{Cu}^{2+} and \mbox{Ni}^{2+}

are one of the most important fluorescent dyes and possess excellent

photophysical and optoelectronic properties, such as high photo-

stability, large absorption coefficient in the visible and near-IR ranges,

excellent chemical stability, sharp absorption and fluorescence bands,

and high fluorescence quantum yields. [39-41] Also, the spectroscopic

and photophysical properties of the BODIPY derivatives can be tuned by appropriate substitution. [42–45] Furthermore, the parent structure of

the BODIPY dyes is easily modified on all possible positions of the core, and various functional groups can be introduced to the BODIPY core for

different applications. [46–48] As a result, the BODIPY dyes are widely

used for the design and synthesis of fluorescent probes for detecting

different ions. [49–53] For example, a few fluorescent probes for detecting Cu^{2+} were constructed by integrating bis(pyridin-2-ylmethyl)

amine (DPA) to the 3-position of BODIPY fluorophore. [45,54,55] Also,

substitution at the 2- and/or 6-position(s) on the BODIPY core can cause

significant shifts in the absorption and fluorescence spectra. [49,56]

However, few studies have been conducted on substituent effects at the

2- and/or 6-position(s) of BODIPY to obtain metal ion probes. [49,57]

Herein, we have now synthesized a new ratiometric fluorescent probe 6

by the introduction of a cation receptor DPA at the 2-position of BODIPY

core, which can act as a dual chemosensor for selective/sensitive

4,4-Difluoro-4-borato-3a,4a-diaza-s-indacene (BODIPY) derivatives

[1,17,29–32] However, some probes for Cu^{2+} and Ni^{2+} still are confronted with some thorny problems, such as complicated synthetic procedures, difficult purification, and strict testing conditions. [26,31,33] In addition, to the best of our knowledge, there are only a few

2. Results and discussion

2.1. Synthesis of probe 6

The synthetic route of probe 6 was shown in Scheme 1. Probe 6 was synthesized by the Sonogashira coupling reaction of BODIPY derivatives 2 with bis(pyridin-2-ylmethyl)amine derivatives 5. The product of each step of the synthesis has been characterized by ¹H NMR spectroscopic technique. The target product 6 was also characterized by HRMS. All the detailed characterization data were presented in the Supporting Information (Figs. S1–S7).

2.2. Selectivity detection studies of 6 towards various metal ions

The sensing abilities of the probe **6** towards various biologically and environmentally affected ions such as Zn^{2+} , Ni^{2+} , Cd^{2+} , Cu^{2+} , Pd^{2+} , Fe^{3+} , Mn^{2+} , Mg^{2+} , K^+ , Na^+ , Cr^{3+} , Ag^+ , Hg^{2+} , and Co^{2+} were investigated in methanol by UV–Vis absorption and fluorescence spectra. Different metal ions (10 equiv.) were separately added into the solution of probe **6** (1×10^{-5} mol/L). As shown in Figure S8, the probe **6** shows the typical maximum absorption wavelength of BODIPY at 542 nm which is ascribed to $S_0 \rightarrow S_1 (\pi - \pi^*)$ transition of BODIPY conjugated system. [41] However, slight changes can be observed in the UV–Vis absorption spectra in the presence of different ions (Fig. S8). As seen from Fig. 1, different from the UV–Vis absorption spectra, the probe **6** shows considerable changes of the fluorescence intensity upon with the addition of different metal ions. The probe **6** alone exhibited an intense emission band at 589 nm with a quantum yield value of 0.065 upon the



Scheme 1. The synthetic route for 6.





Fig. 1. Fluorescence emission spectra of probe 6 (1×10^{-5} mol/L) and in the presence of 11 kinds of metal ions such as Cu²⁺, Ni²⁺, Zn²⁺, Cd²⁺, Pd²⁺, Fe³⁺, Mn²⁺, Mg²⁺, K⁺, Na⁺, Co²⁺, Cr³⁺, Ag⁺ and Hg²⁺ (10.0 equiv) in methanol solution. (Excitation wavelength: 542 nm).

excitation at 542 nm, and the fluorescence lifetimes were determined to be 3.98 ns. The addition of the Cu^{2+} and Ni^{2+} ions to the methanol solution of probe **6** resulted in a remarkable fluorescence quenching at the wavelength of 589 nm; and the addition of Zn^{2+} , Cd^{2+} , and Pd^{2+} caused a prominent fluorescence enhancement, and slightly quenched or no fluorescence spectral changes were observed upon the addition of other metal ions under the same conditions. The observed fluorescent quenching might be attributed to the excited state electrons of probe **6** transfer to the unoccupied 3d orbital of Cu^{2+} or Ni^{2+} . [36] The significant spectra changes suggested that probe **6** should be more sensitive to the presence of Cu^{2+} and Ni^{2+} ions than other mentioned ions due to their higher binding interaction with the chelator of probe **6** that resulted in the formation of stable complexes between probe **6** and the Ni^{2+} or Cu^{2+} . [8,58] Consequently, the result clearly indicates that probe **6** can be used as a fluorescent probe to detect the Ni²⁺ and Cu²⁺.

In order to further explore the high selectivity of probe 6 for Cu²⁺ and Ni²⁺ sensing, competition experiments were carried out with other competitive co-existing metal ions. Fig. 2 and Fig. 3 showed the fluorescence emission of probe 6 (1×10^{-5} mol/L) in the presence of both 10 equiv. Ni²⁺/Cu²⁺ and 10 equiv. other metal ions (Zn²⁺, Cd²⁺, Pd²⁺, Fe³⁺, Mn²⁺, Mg²⁺, K⁺, Na⁺, Cr^{3+,} Ag⁺, Hg²⁺ and Co²⁺). This fluorescence quenching by the solutions of Cu²⁺ (Fig. 2) and Ni²⁺ (Fig. 3) in methanol was not affected significantly by the presence of the other metal ions. This result strongly revealed that the binding affinity between probe 6 and Cu²⁺ or Ni²⁺ was stronger than that between probe 6 and other metal ions. Therefore, this also indicated that the recognition of Ni²⁺ and Cu²⁺ by probe 6 was hardly interfered by other coexisting metal ions. Thus, the probe 6 can be used as a selective fluorescent sensor for Cu²⁺ and Ni²⁺ ions over other competing metal ions in a methanol solution.

2.3. Titration analysis probe 6 with Cu^{2+} and Ni^{2+}

To get a better insight into the sensitive response of probe **6** towards Ni²⁺ and Cu²⁺, titration experiments between probe **6** and the metal ions (Ni²⁺ and Cu²⁺) were also performed in methanol by fluorescence spectra. A methanolic solution of probe **6** (1×10^{-5} mol/L) was titrated with Cu²⁺ (0–1 equiv.) or Ni²⁺ (0–1 equiv.) solutions in methanol. The changes in the fluorescence intensity as a function of the concentration of Cu²⁺ and Ni²⁺ ions were shown in Figs. 4 and 5, respectively. The fluorescence intensity gradually decreased at 589 nm with the



Fig. 2. The selectivity of probe **6** in MeOH $(1 \times 10^{-5} \text{ mol/L})$ for Ni²⁺ in the presence of other metal ions (10 equiv.) (Zn²⁺, Cd²⁺, Pd²⁺, Fe³⁺, Mn²⁺, Mg²⁺, K⁺, Na⁺, Co²⁺, Cr³⁺, Ag⁺ and Hg²⁺). (excitation wavelength: 542 nm, emission wavelength: 589 nm).



Fig. 3. The selectivity of probe 6 in MeOH (1 \times 10⁻⁵ mol/L) for Cu²⁺ in the presence of other metal ions (10 equiv.) (Zn²⁺, Cd²⁺, Pd²⁺, Fe³⁺, Mn²⁺, Mg²⁺, K⁺, Na⁺, Co²⁺, Cr³⁺, Ag⁺ and Hg²⁺). (excitation wavelength: 542 nm, emission wavelength: 589 nm).

incremental addition of a solution of the metal ion (Ni²⁺ or Cu²⁺) into the solution of the probe **6**, and then reached minimum and remained almost constant after the addition of 1.0 equiv. of Cu²⁺ or Ni²⁺, respectively, which suggests the formation of 1:1 complexes between probe **6** and either metal ion. Based on the concentration-dependent experiments, a good linearity relationship between the fluorescence intensities and the metal ion concentration of Cu²⁺ or Ni²⁺ in the range of 0–1.0 equiv. was obtained, which were shown in Figs. 6 and 7 respectively. The regression equations were y = -429.818x + 707 ($R^2 =$ 0.984) for Cu²⁺ and y = 354.583x + 690 ($R^2 = 0.987$) for Ni²⁺, where yreferred to the fluorescence emission intensity and $\times x$ referred to the concentration of Ni²⁺ or Cu²⁺. Furthermore, the detection limit (DL) values for Cu²⁺ and Ni²⁺ were calculated to be both 0.1 μ M,



Fig. 4. Fluorescence emission spectra of probe 6 (2×10^{-5} mol/L, excitation wavelength: 542 nm) in MeOH upon addition of 0–1 equiv. of Ni²⁺.



Fig. 5. Fluorescence emission spectra of probe 6 (2 \times 10⁻⁵ mol/L, excitation wavelength: 542 nm) in MeOH upon addition of 0–1 equiv. of Cu²⁺.



Fig. 6. Calibration curve of 6-Ni $^{2+}$ (emission wavelength: 589 nm).



Fig. 7. Calibration curve of **6**-Cu²⁺ (emission wavelength: 589 nm).

respectively, which were determined reasonably by the equation $DL = 3\sigma/K$. [8] Moreover, these detection limits were significantly lower than the permitted levels of Cu²⁺ (30 μ M) and Ni²⁺ (17 μ M) in drinking water set by the World Health Organization (WHO). [8,59] The result indicated that the probe could be used as an excellent fluorescent sensor for the recognition and detection of the Cu²⁺ and Ni²⁺ in biological and environmental systems.

In addition, to further determine the binding stoichiometry between probe 6 and Cu^{2+} or Ni^{2+} , Job's plot titration experiments of probe 6 with Cu²⁺ and Ni²⁺ and HRMS mass spectral analysis were carried out. As shown in Fig. S9 and S10, the maximum point was measured at a molar fraction of ca. 0.5, indicating the formation of a complex between probe 6 and Cu^{2+} or Ni^{2+} in a 1:1 ratio. In the HRMS spectra (Fig. S11 and S12), the formation of a 1:1 complex between probe 6 and Ni^{2+} or Cu^{2+} was confirmed by the emergence of the peak at m/z = 801.1256 $[probe 6 + Cu^{2+} + Cl^{-}]^+$ or 820.1774 $[probe 6 + Ni^{2+} + CH_3CO_2^{-}]^+$. The results obtained from the mass spectral analysis correlated well with those obtained by the Job's method. Therefore, based on the fluorescence titration experiments, HRMS, and Job's plot analysis, the possible binding mechanism between probe 6 and Cu^{2+} or Ni^{2+} was provided in Scheme 2 [61–63]. The ¹H NMR titration was also performed (Fig. S13). However, no signal was observed after adding ions due to the formations of paramagnetic Cu (II) and Ni (II) complexes. The FT-IR spectra for Cu (II) complex, Ni (II) complex and probe 6 were presented in Fig. S15. The C=N bond vibrations of pyridine in the corresponding Ni (II) and Cu (II) complexes can be observed at 1606 and 1610 cm⁻¹, respectively. Compared with probe 6, the C=N stretching frequency shifted to a higher frequency by ca. 15 and 19 cm⁻¹ for Ni (II) and Cu (II) complexes, respectively, indicating forming the coordination bond between the metal ion and the pyridine-N lone pair. Besides, the new stretching frequency at 539 cm^{-1} for Ni (II) complexes and 509 cm^{-1} for Cu (II) complexes can be attributed to v(Ni-N) and v(Cu-N), respectively. The NMR titration and FT-IR spectra further confirmed the binding mechanism between probe 6 and Cu^{2+} or Ni^{2+} .

3. Conclusion

In summary, a new "turn-off" dual responsive fluorescence chemosensor containing BODIPY and DPA units for the detection of Cu²⁺ and Ni²⁺ in a methanol solution was successfully synthesized and structurally characterized by ¹H NMR, ¹³C NMR, Esi-HRMS and elemental analysis, which was investigated in detail by employing fluorescence spectra. The investigations showed that probe **6** exhibits high selectivity and sensitivity for the detection of Cu²⁺ and Ni²⁺ ions over several other metal ions with the detection limit of as low as 0.1 μ M for both Cu²⁺ and

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Scheme 2. Proposed binding modes of probe 6 with Cu²⁺ and Ni²⁺ (L are solvent molecules or coordinating anions).

Ni²⁺. The 1:1 binding mode between probe **6** and the Cu²⁺ or Ni²⁺ ions have been well demonstrated by HRMS spectra and Job's method. Therefore, the probe **6** is a dual-responsive and sensitive fluorescence chemosensor for the detection of Cu²⁺ and Ni²⁺ ions and can be potentially applied in various applications in the area of biology and environment.

4. Experimental section

4.1. Materials and measurements

All chemicals and solvents were of analytical reagent grade and used directly as received unless otherwise noted. Dry CH₂Cl₂ and triethylamine was (TEA) were distilled from CaH2 under nitrogen. Dry tetrahydrofuran (THF) was distilled from sodium/benzophenone under nitrogen. ¹H NMR spectra were collected on a Bruker DRX-600 AVANCE III spectrometer. Chemical shifts for ¹H NMR spectra were recorded in ppm relative to CDCl₃ (δ = 7.26 ppm) as the internal standard. Highresolution mass spectra data were obtained using a Thermo Fisher LTQ Orbitrap XL (HR-ESI) spectrometer. UV-vis spectra were carried out on a Shimadzu UV-3100 spectrophotometer. Fluorescent spectra were recorded on a LS 55 Fluorescence Spectrometer (Perkin Elmer). The PLQY were measured in FluoroLog-UltraFast (HORIBA Instrument Inc, Edison) equipped with a 450 W CW xenon lamp and an Open-Electrode TECooled CCD Detector (Syncerity). Nanosecond lifetime was conducted using a TCSPC MCA model equipped with a picosecond photo detector (<200 ps) (PPD850) and picosecond laser (duration is 180 ps, Deltadiode, 100 MHz laser). The fluorescence lifetime values were obtained from deconvolution and distribution lifetime analysis. IR spectra were recorded using a Bruker Vertex80 FT-IR spectrometer with KBr discs in the range 400–4000 cm^{-1} range.

4.2. Synthesis of Compounds 1-6

Compounds 1, 3, 4 and 5 were synthesized referring to the previously reported methods. [60 61] Detailed information can be found in the supplementary data.

4.2.1. Compound 2

Compound 1 (117.92 mg, 0.3 mmol) and N-iodosuccinimide (NIS)

(81 mg, 0.36 mmol) were added into dry 30 mL of CH₂Cl₂ and stirred at room temperature for 30 min. The reaction mixture was washed with saturated aqueous Na₂S₂O₃ (3 × 30 mL), dried over anhydrous Na₂SO₄, and then concentrated under reduced pressure. The crude product was purified by column chromatography on silica with CH₂Cl₂/petroleum ether = 3:2 as the eluent, affording the desired compound **2**. Yield (52.7 mg, 34%). ¹H NMR (600 MHz, CDCl₃, ppm), δ 7.47 (d, ³*J*_{*H*+*H*} = 7.8 Hz, 2H), 7.40 (t, ³*J*_{*H*+*H*} = 7.2 Hz, 1H), 2.65 (s, 3H), 2.59 (s, 3H), 1.51 (s, 3H), 1.49 (s, 3H). (Fig. S2)

4.2.2. Compound 6

Compound 5 (45 mg, 0.15 mmol), compound 2 (50 mg, 0.1 mmol) and CuI (1.2 mg, 0.006 mmol) were dissolved in dry triethylamine (5 mL). The mixture was deoxygenated with argon, and then Pd(PPh₃)₄ (88 mg, 0.07 mmol) was added into the mixture under Ar. The reaction mixture was heated at 80 °C for 12 h. After completion of the reaction, the solvent was removed under reduced pressure and the crude product was purified by column chromatography on silica gel with CH2Cl2/ $CH_3OH = 99.5:0.5$ as the eluent, affording the desired compound 6. Yield (21.7 mg, 43%). ¹H NMR (600 MHz, CDCl₃, ppm), δ 8.54 (d, ³J_{H-H} = 3.6 Hz, 2H), 7.70–7.65 (m, 4H), 7.58–7.54 (m, 3H), 7.50–7.45 (m, 3H), 7.40 (s, 3H), 7.19-7.17 (m, 2H), 6.06 (s, 1H), 3.92 (s, 4H), 3.80 (s, 2H), 2.70 (s, 3H), 2.60 (s, 3H), 1.60 (s, 3H), 1.50 (s, 3H). ¹³C NMR (150 MHz, CDCl₃, ppm), δ 151.9, 148.4, 141.9, 136.7, 134.9, 130.5, 129.6, 127.7, 127.6, 125.8, 124.4, 124.2, 123.9, 123.6, 122.6, 121.7, 116.2, 115.4, 115.2, 114.0, 52.7, 50.7, 22.7, 9.0, 8.3, 7.9, 6.4. (Fig. S14). Anal. Calcd. for C₄₀H₃₄BCl₂F₂N₅(%): C, 68.20; H, 4.87; N, 9.94; Found(%): C, 68.24; H, 4.91; N, 9.91. HRMS (ESI): m/z calcd for C40H35BCl2F2N5 [M + H⁺]: 704.2325; found: 704.2348. (Fig. S7).

4.3. UV-vis and fluorescence titration

Compound **6** (1.4 mg, 0.002 mmol) was dissolved in 100 mL MeOH to form 2×10^{-5} mol/L solution. CuCl₂·2H₂O (3.4 mg) and NiCl₂·6H₂O (4.7 mg) were dissolved in 10 mL MeOH to form 2×10^{-3} mol/L solution. 3 mL probe **6** solution was added into a cuvette, then 3 µL (0.1 equiv.), 6 µL (0.2 equiv.), 9 µL(0.3 equiv.), 12 µL (0.4 equiv.), 15 µL(0.5 equiv.), 18 µL (0.6 equiv.), 21 µL (0.7 equiv.), 24 µL (0.8 equiv.), 27 µL (0.9 equiv.), 30 µL (1 equiv.) of Cu²⁺ or Ni²⁺ solution were added, respectively. After mixing for a few seconds, UV–vis and fluorescence

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spectra were taken at room temperature.

4.4. UV-vis and fluorescence for selectivity and competition with other mental ions

Compound **6** (0.7 mg, 0.001 mmol) was dissolved in 100 mL MeOH to form 1×10^{-5} mol/L solution. ZnCl₂ (13.6 mg), CdCl₂ (18.3 mg), Pd (OAc)₂ (22.4 mg), FeCl₃ (16.2 mg), MnCl₂·4H₂O (19.8 mg), MgCl₂·6H₂O (20.3 mg), KCl (7.4 mg), NaCl (5.8 mg), CoCl₂·6H₂O (0.0238 mg), NiCl₂·6H₂O (23.8 mg), CuCl₂·2H₂O (17.0 mg), Cr (OAc)₃ (22.9 mg), AgNO₃ (17.0 mg) and Hg(OAc)₂ (31.9 mg) were dissolved in 10 mL MeOH to form 0.01 mol/L solution, respectively. Then 30 µL (10 equiv.) of 0.01 mol/L ions solution was added into 3 mL solution of probe **6** (1 × 10^{-5} mol/L). After mixing for a few seconds, UV–Vis and fluorescence spectra were taken at room temperature to detect the selectivity. Furthermore, 30 µL (10 equiv) of 0.01 mol/L Cu²⁺ or Ni²⁺ solution was firstly added into 3 mL 1 × 10^{-5} mol/L probe **6** solution. Then the other ions were added into the solution above. After mixing for a few seconds, fluorescence spectra were taken at room temperature to measure the competition with other metal ions.

4.5. Calculation of detection limit

The detection limit was calculated by $3\sigma/K$. Ten times of fluorescence intensity of compound **6** was test and σ could be calculated. The fluorescence intensity data were obtained according to the fluorescence titrating for Cu²⁺ and Ni²⁺ (Excitation was provided at 542 nm and emission intensity was measured at 589 nm). The linear regression curve of probe **6** was then fitted to these fluorescence intensity data to calculate the slope *K*.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ica.2020.120099.

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