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Graphical Abstract

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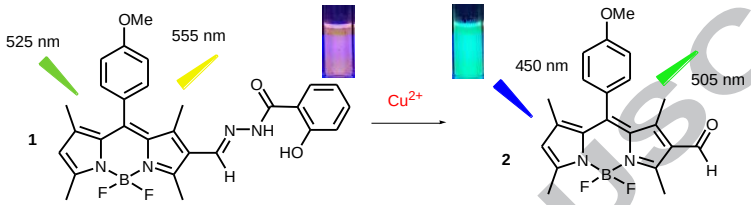

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A new dual-channel ratiometric fluorescent chemodosimeter for Cu^{2+} and its imaging in living cells

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ABSTRACT

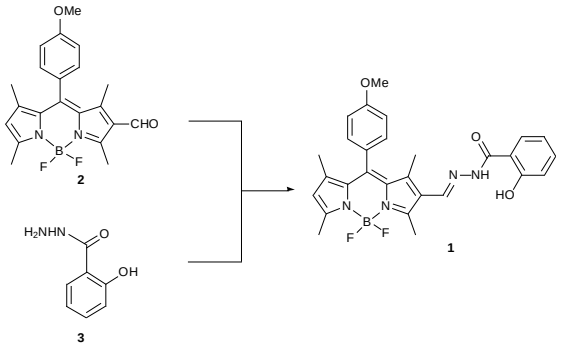
A new BODIPY derivative bearing hydrazone and hydrazide moieties was developed as an efficient dual-channel ratiometric fluorescence chemodosimter **1** for Cu^{2+} in neutral aqueous medium via Cu^{2+}-mediated hydrolsis of C=N bond in hydrazone unit. Confocal microscopy experiments have demonstrated that chemodosimter **1** could also be used in live cells for the fast detection of Cu^{2+}.

1. Introduction

Ratiometric fluorescent technique, which provides built-in correction by simultaneously measuring two different emission signals to minimize or even eliminate these interferences and provide higher analytical accuracy than conventional single-intensity probes, has attracted increasing attention among the various analysis and detection methods in recent years.[1] As far as we know, ratiometric fluorescent detection method has been being utilized for chemo/bio sensing recently.[2] On the other hand, as the third most abundant transition essential element after zinc and iron in the human body, Cu^{2+} plays vital roles in multiple physiological processes dependent on the copper homeostasis in the living organisms.[3] Excess copper intake can result in cancers of the breast, lung, prostate, pancreas, and kidney,[4] and disturbs the cellular homeostasis that will cause Wilson's disease,[5] Alzheimer's disease,[6] and Menkes syndrome[7] owing to the aberrant oxidative and nitrosative stress induced by Cu^{2+}. According to the U.S. Environmental Protection Agency (EPA), the maximum acceptable level of Cu^{2+} in drinking water is 1.3 ppm ($\sim$20 μM).[8] Therefore, there is considerable interest in developing specific fluorescent sensors for sensitive Cu^{2+} detection, especially in environmental and physiological conditions. Even though fluorescent probes for Cu^{2+} have been extensively explored owing to biological significance of this metal ion, there are still only a few examples of ratiometric fluorescent probes available in aqueous systems.[9]

It is well known that Cu^{2+}, being of a catalytic nature, can promote the hydrolysis of amides, esters, lactones and hydrazide, reactions including oxidations, dethioacetalizations, rearrangements, and oxidative cyclizations.[10] The method of copper induced reactions has been an excellent approach for the development of selective chemodosimeters for these ions. Nevertheless, only few of ratiometric chemodosimeters for Cu^{2+} detection have been reported.[9g,10f,g,j,11] Thus the design of new ratiometric chemodosimeters based on Cu^{2+}-selective reaction in aqueous medium is still challenging and very attractive for the demand of the diversified and complicated biological systems.

Recently, we reported a highly sensitive and selective turn-on chemodosimeter for Cu^{2+} based on 4,4-difluoro-4-bora-3a,4a-diaza-s-indacene (BODIPY) containing hydrazone moiety.[10m] Encouraged by this interesting result, we try to design new system for the ratiometric fluorescence detection to the metal ions. In this communication, we describe a new ratiometric chemodosimeter for Cu^{2+} based on the metal ions promoted hydrolysis of C=N bond in hydrazone unit. In this compound **1**, a fluorophore, BODIPY core, was conjugated with hydrazone and hydrazide units. As shown in scheme 1, compound **1** was prepared facilely from condensation of formyl BODIPY **2** with salicylic hydrazide **3** in the yield of 30 % and characterized by ESI-MS, ^{1}H- NMR, ^{13}C-NMR, and elemental analysis.



Scheme 1 Synthesis of chemodosimeter **1**.

2. Results and discussion

The absorption spectra of probe **1** in the presence of varying Cu^{2+} concentrations were recorded first in DMF-H_2O (7:3, v:v) solution. As shown in Figure 1, the solution of probe **1** alone (1.0×10^{-5} M) exhibits a maximum absorption peak at 526 nm, consistent with the pink coloration of the solution. Upon addition of Cu^{2+}, the probe **1** solution showed a new maximum absorption wavelength at 495 nm, which can be ascribed to the fluorophore containing the moieties of BODIPY hydrazone and salicylic hydrazide. Meanwhile, the absorption band centered at 526 nm decreased gradually was observed (Fig. S3). In addition, the absorption behavior changes the color of the resultant solution from pink into pale yellow, allowing "naked-eye" detection (Fig. S7). The addition of various other transition and alkali metal ions did not alter the absorption spectrum of receptor **1** and the color of the metal ions solution, initially indicating the special selectivity towards Cu^{2+}.

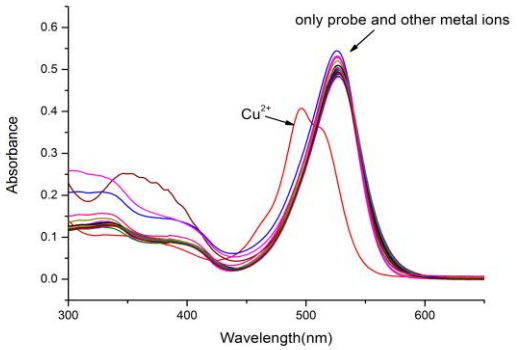


Fig.1 Absorption spectra of chemodosimeter **1** (10 μM) with Cu^{2+} or other different metal ions (100 μM, 10 equiv.) including Li^+, Na^+, K^+, Mg^{2+}, Ca^{2+}, Ba^{2+}, Al^{3+}, Pb^{2+}, Cr^{3+}, Mn^{2+}, Bi^{3+}, Ni^{2+}, Sn^{2+}, Fe^{2+}, Fe^{3+}, Ag^+, Zn^{2+}, Cd^{2+}, Hg^{2+} and Co^{2+} in DMF:H_2O (7:3, v:v) medium.

Next, the titrations of the novel ratiometric probe **1** (10 μM) with Cu^{2+} were conducted in DMF-H_2O (7:3, v:v) solution. In a solution of probe **1**, very weakly fluorescent emission was observed around 505 nm in the featured emission of formyl-BODIPY under the excitation in 450 nm. Upon the increasing addition of Cu^{2+}, a drastic increase in the featured emission of formyl-BODIPY around 505 nm was observed, and the fluorescence intensity enhancement was up to 8-fold (Fig. 2a; Fig. S2b). Interestingly, as shown in Figure 1b, upon excitation at 525 nm, the free probe **1** displays a single emission band centered at 555 nm and the fluorescence intensity decreases smoothly upon the addition of Cu^{2+} (Fig. 2b; Fig. S2c).

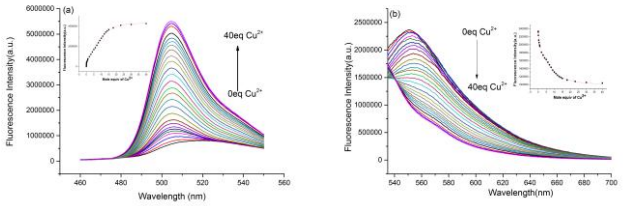


Fig.2 Fluorescence spectra of chemodosimeter **1** (10 μM) towards Cu^{2+} (0, 0.02, 0.04, 0.08, 0.1, 0.3, 0.5, 0.8, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 18, 23, 30, 40 equiv) in DMF:H_2O (7:3, v:v) medium, (a) λ_{ex} = 450 nm, (b) λ_{ex} = 525 nm.

We then proceeded to examine the selectivity of the probe. The ratiometric fluorescent response of probe **1** (10 μM) to other metal cations of interest has also been determined (Fig. S2b,S2b), and the results showed that other tested metal ions (400 μM, 40 equiv.) including Li^+, Na^+, K^+, Mg^{2+}, Ca^{2+}, Ba^{2+}, Al^{3+}, Pb^{2+}, Cr^{3+}, Mn^{2+}, Bi^{3+}, Ni^{2+}, Sn^{2+}, Fe^{2+}, Fe^{3+}, Ag^+, Zn^{2+}, Cd^{2+}, Hg^{2+} and Co^{2+}, did not induce any distinct change of F_{505}, and F_{555}. Furthermore, the examination of the fluorescence response of probe **1** toward Cu^{2+} in the presence of other potentially competing ions was carried out to investigate the applicability of the developed ratiometric chemodosimeter **1** to the analysis of Cu^{2+} ions in a practical sample (Fig. 3; Fig. S5a-5c). As shown in Fig. 3, the ratiometric response induced by Cu^{2+} was almost intact even in the presence of various competitive metal ions. This is also supported by the absorption spectra which showed the similar selectivity to the species. All these results indicate that probe 1 is able to sense Cu^{2+} in a ratiometric manner in aqueous media with high selectivity. Moreover, the detection limit of this sensor was determined to be 0.2 μM (Fig. S6),[12] much lower than the allowable Cu^{2+} level in drinking water and the typical concentration of blood copper (11.8-23.6 μM) in normal individuals.[8,13]

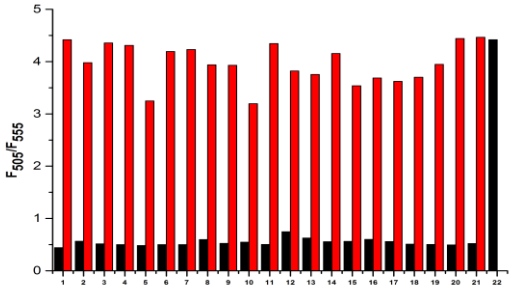


Fig.3 Ratio of emission at 505 nm to that at 555 nm for **1** (10 μM) in in DMF:H_2O (7:3, v:v) medium, F_{505}/F_{555}, determined in the absence and presence of different metal ions: 1, none; 2, Li^+; 3, Na^+; 4, K^+; 5, Mg^{2+}; 6, Ca^{2+}; 7, Ba^{2+}; 8, Al^{3+}; 9, Pb^{2+}; 10, Cr^{3+}; 11, Mn^{2+}; 12, Fe^{3+}; 13, Bi^{3+}; 14, Co^{2+}; 15, Ni^{2+}; 16, Sn^{2+}; 17, Fe^{2+}; 18, Ag^+; 19, Zn^{2+}; 20, Cd^{2+}; 21, Hg^{2+}; 22, Cu^{2+}. 100 μM. Black bars: free sensor, or sensor treated with the marked metal ions. Red bars: sensor treated with the marked metal cations (100 μM, 10 equiv.) followed by Cu^{2+} (100 μM, 10 equiv).

The effect of pH on the fluorescence of the probe was evaluated due to the great importance of the probe solution for the practical application. As shown in Fig. S4, the pH value of the solution has a great influence on the free probe **1** in the range of 4.0-10.0 for the two emission channels. However, no remarkable change of two emission fluorescence intensities of probe **1** upon the addition of Cu^{2+} was observed from about 5.0 to 8.0 pH range. That is to say, the ratiometric probe works well

under physiological conditions. Moreover, to understand the sensing mechanism of the chemodosimeter **1** toward Cu^{2+}, we carried out the ^1H NMR experiments for the probe **1** solution followed by the addition of Cu^{2+}. As shown in Fig. 4, two singlet peaks at 8.46 ppm (H_a) and 12.01 ppm (H_b) corresponding to the protons on the hydrazone (H_aC=N)and hydrazide ($CONH_b$) moieties in probe **1** respectively disappeared upon the addition of Cu^{2+}. Meanwhile, the singlet peak at 9.96 ppm (H_c) corresponding to the proton of the CHO moiety in the major hydrolysis products fomyl-BODIPY was observed. This result integrated with significant emission enhancement around 505 nm, the featured fluorescence emission band, confirms that the C=N bond in the hydrazone unit of probe **1** was hydrolyzed effectively in the presence of Cu^{2+} to generate the green fluorescence product fomyl-BODIPY.

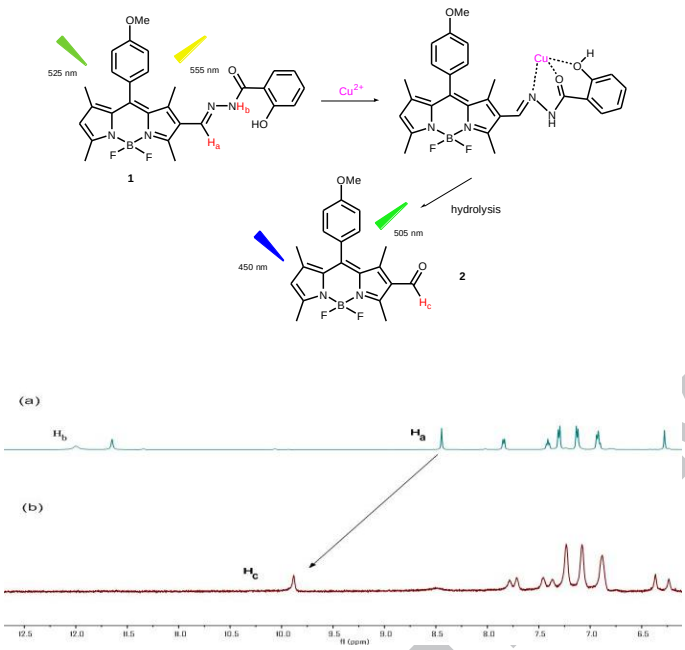


Fig.4 Proposed sensing mechanism and partial ^1H NMR spectra of **1** (1 mM) in $DMSO_{d6}$-D_2O upon addition of (a) 0, (b) 1 equiv. of Cu^{2+}.

Finally, The ratiometric imaging ability of probe **1** for intracellular Cu^{2+} has been confirmed in HeLa cells by confocal fluorescence imaging with a dual channel mode (green channel, 491–540 nm, λ_{ex} = 488 nm; red channel, 546–650 nm, λ_{ex} = 543 nm) and the ratiometric image was obtained via mediating the red channel image with the related green channel image (Fig. 5, Fig. S9). After HeLa cells were incubated with 5 μM Probe **1** (15 min), the ratiometric image displayed a deep blue color in the cytosol, indicating the low intracellular chelatable Cu^{2+} level (Fig. 5d). After the probe **1**-stained cells were incubated with a 30 μM Cu^{2+} solution (15 min), the related ratiometric image showed a remarkable ratio enhancement in the cytosol (Fig. 5h), implying that the chelatable cytosolic Cu^{2+} level can be effectively enhanced *via* incubation with Cu^{2+} solution. The bright fluorescence inside the cells shown in both green and red channel images indicated that probe **1** can be loaded into cells in 15 minutes, displaying the excellent membrane permeability of probe **1**. These results suggest that probe **1** is cell permeable and an effective intracellular Cu^{2+} ion imaging agent with ratiometric fluorescence emission characteristic.

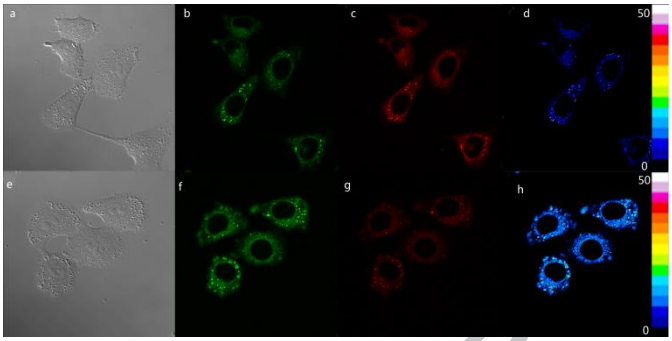


Fig.5 Confocal fluorescence images of living Hela cells: Hela cells incubated with compound **1** (5 μM) for 15 min (a, b, c, d) at 37 ℃. The stained cells were exposed to 30 μM Cu^{2+} solution for 30min (e, f, g, h). (a, e) Bright-field transmission images. (b, f) Fluorescence images obtained according to the emission collected by the green channel (λ_{ex}: 488 nm, band path 491-540 nm). (c, g) Fluorescence images obtained from the red channel (λ_{ex}: 543 nm, band path 546-650 nm). (d, h) Ratiometric images generated from (b, f) and (c, g).

3. Conclusion

In conclusion, the new fluorescent ratiometric chemodosimeter **1** for Cu^{2+} sensing exhibits a specific Cu^{2+}-induced blue shift from 555 to 505 nm. The key point is that the ratiometric sensing is conducted through Cu^{2+}-promoted hydrolysis of the C=N bond in the hydrazone unit in aqueous medium. Moreover, the emissive blue shifting comes from dual excitation channels (λ_{em} = 505 nm, λ_{ex} = 450 nm; λ_{em} = 555 nm, λ_{ex} = 525 nm). Further, chemodosimeter **1** can also be used as a ratiometric fluorescent probe for intracellular imaging of Cu^{2+} ions with tunable emission (green and red) which will help in the understanding of biological processes at the molecular level. This study displays also an effective rationale to design ratiometric chemodosimeters for rapid Cu^{2+} sensing and bioimaging.

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Supplementary data

Supplementary material associated with this article can be found, in the online version, at doi:

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Highlights

- A new **ratiometric** chemodosimeter **1 was developed for** recognizing Cu^{2+} efficiently;
- Chemodosimeter **1 works well** within a wide range pH and physiological conditions;
- **1** shows high selectivity and low detection limitation (0.2 μM) in aqueous medium;
- **1** can be successfully utilized in fluorescent imaging in living cells for the Cu^{2+} detecting.