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ORIGINAL PAPER

A Coumarin-Based Fluorescent Chemosensor for Zn^{2+} in Aqueous Ethanol Media

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Abstract A coumarin-based fluorescent chemosensor **1** for Zn^{2+} was designed and synthesized. Compound **1** exhibits lower background fluorescence due to intramolecular photoinduced electron transfer. However, upon mixing with Zn^{2+} in 30% (*v/v*) aqueous ethanol, a "turn-on" fluorescence emission is observed. The fluorescence emission increases linearly with Zn^{2+} concentration in the range 0.5–10 μmol L^{-1} with a detection limit of 0.29 μmol L^{-1}. No remarkable emission enhancement was, however, observed for other metal ions. The proposed chemosensor was applied to the determination of Zn^{2+} in water samples with satisfactory results.

Keywords Zinc(II) ion · Coumarin · Chemosensor · Photoinduced electron transfer

Introduction

Zinc(II) ion, the second most abundant transition-metal ion in the human body, plays critical roles in many biological activities, such as gene expression, apoptosis, enzyme regulation and neurotransmission [1–3]. In addition, elevated levels of Zn^{2+} ions in water could become an environmental problem [4]. Therefore, the design and development of efficient fluorescent chemosensors selective to Zn^{2+} are of considerable interest. Although several fluorescence-based chemosensors for Zn^{2+} have been developed, some of them have shortcomings for practical application such as cross-sensitivities toward other metal ions, susceptibility to pH, difficult synthesis and non-aqueous media requirement [5–14]. It is therefore necessary to develop new chemosensors for Zn^{2+} with high selectivity and sensitivity at physiological pH.

Coumarin dyes are important class of fluorescent compounds and have been widely used to construct a variety of fluorescent probes and chemosensors owing to their excellent photophysical properties [15–24]. Though coumarin-derived chemosensor for Zn^{2+} have been reported by Xi et al. [25], it can work only at CH_3CN solution and is unpractical to real sample analysis. Herein, we report a new coumarin Schiff-based fluorescence chemosensor **1**, which exhibits a high selectivity toward Zn^{2+} ion by utilizing a chelation-enhanced fluorescence (CHEF) mechanism (Scheme 1). The sensor **1** was developed by incorporating a semicarbazide at the 8 position of coumarin ring by a "C=N" bond, which would quench the excited state emission of the coumarin fluorophore via photoinduced electron transfer (PET). Because Zn(II) has a closed-shell d^{10} electronic configuration, we anticipated that its coordination would alleviate PET and provide fluorescence "turn-on." As we expected, upon mixing with Zn^{2+} in aqueous ethanol solution, the fluorescence of **1** is largely enhanced. The fluorescent increase is linear with Zn^{2+} concentration in the range 0.5–10 μmol L^{-1} with a detection limit of 0.29 μmol L^{-1}. The fluorescence sensing process is

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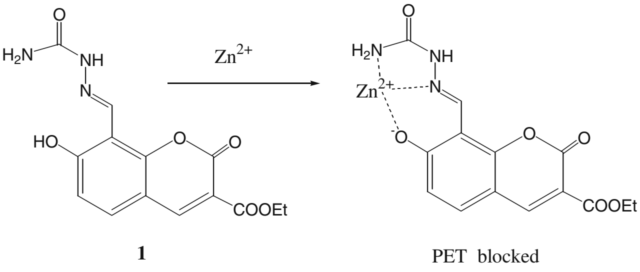


Scheme 1 The proposed binding model of **1** with Zn^{2+} (other possible chelating species are omitted for clarity)

proved to be reversible. The proposed binding mechanism of Zn^{2+} with **1** was studied and proved in a 1:1 binding mode.

Experimental

Reagents

Unless otherwise stated, all reagents were purchased from commercial suppliers and used without further purification. Twice-distilled water was used throughout the experiments. 7-Hydroxycoumarin-3-carboxylic acid ethyl ester (**2**) was obtained from J&K CHEMICAL LTD. The solution of **1** (0.5 mmol L^{-1}) was prepared by dissolving 16.2 mg of **1** in 100 mL DMF. Zn^{2+} solution (1.0 mmol L^{-1}) was prepared by dissolving appropriate amount of $ZnSO_4$ with water. Tris–HCl buffer solutions of different pH were prepared by using proper amount of Tris and HCl under adjustment by a pH meter.

Synthesis of **1**

Compound **1** was synthesized in two steps as shown in Scheme 2.

*Ethyl 7-hydroxy-8-formyl-coumarin-3-carboxylate (***3***)*

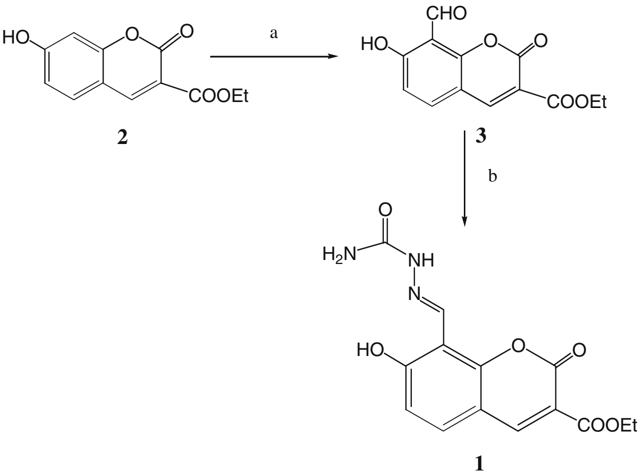
To a stirred TFA (20 mL) was added compound **2** (3.28 g, 14 mmol) and hexamine (2.94 g, 21 mmol). This solution was refluxed for 20 h. Then, 40 mL of water was added to the solution, and the mixture was warmed at 60°C whilst stirring for another 30 min. Upon cooling on ice a yellow solid was precipitated out from the solution, which was collected by filtration and washed several times with water to give the desired product **3** as a yellow solid (2.5 g, 68% yield). IR (KBr, cm^{-1}): 3431, 3045, 1742, 1700, 1659, 1595, 1480, 1445, 1304, 1236; MS (MALDI-TOF): m/z= 262.20 (M^+); M^+ calculated 262.22; ^{1}H NMR (400 MHz, DMSO-d_6): 1.28–1.31 (t, 3H, CH_3), 4.25–4.30 (q, 2H, CH_2), 7.01 (q, 1H, ArH), 8.06 (t, 1H, ArH), 8.75 (s,1H, ArH), 10.40 (s, 1H, CHO), 12.10–12.50(1H, OH);

Compound ***1***

Compound **1** was synthesized by the condensation reaction between compound **3** and semicarbazide. Briefly, semicarbazide hydrochloride (52 mg, 0.46 mmol) was dissolved in 5 mL of ethanol, and the solution was neutralized to pH 7.0 with 1.0 mol L^{-1} of NaOH. The above solution was then mixed with the ethanol solution of compound **2** (60 mg, 0.23 mmol) and refluxed for 4 h. After cooling, the resulting solution was added dropwise into saturated brine. The precipitate was filtered off, washed with water several times and dried to give the desired product as light-yellow solid (30 mg, 43% yield). IR (KBr, cm^{-1}): 3442, 3363, 3265, 1758, 1680, 1615, 1590, 1534, 1461, 1370, 1324, 1299, 1239, 1208, 1092, 1036, 797, 696. MS (MALDI-TOF): m/z=320.59 $(M+H)^+$; M^+ calculated, 320.28;. ^{1}H NMR (400 MHz, DMSO-d_6): 1.29–1.32 (t, 3H, CH_3), 4.25–4.31 (q, 2H, CH_2), 6.48 (s, 2H, NH_2), 6.98 (q, 1H, ArH), 7.80 (t, 1H, ArH), 8.51 (s, 1H, ArH), 8.73 (s,1H, NH), 10.60 (s, 1H, C=NH), 11.99(1H, OH).

Apparatus

Absorption spectra were determined with a Shimadzu UV-1700 spectrophometer (Tokyo, Japan). The fluorescence spectra and relative fluorescence intensity were performed on a Sanco CRT-970 spectrofluorimeter (Shanghai, China) with a 10 mm quartz cuvette. Unless specific noted, the excitation and emission wavelength bandpasses were both set at 10 nm. The pH was measured with a Model pHs-3B meter (Shanghai, China). Infrared (IR) were taken in KBr pellets on a Bruker Tensor 27 FTIR spectrometer. Mass spectra were obtained with AXIMA-CFR plus MALDI-TOF Mass Spectrophotometer. ^{1}H NMR spectra were recorded on an INOVA-400 spectrometer (Varian Unity), using tetramethyl-



Scheme 2 Synthesis of compound **1**. (*a*) Hexamine, TFA; (*b*) Semicarbazide hydrochloride, ethanol

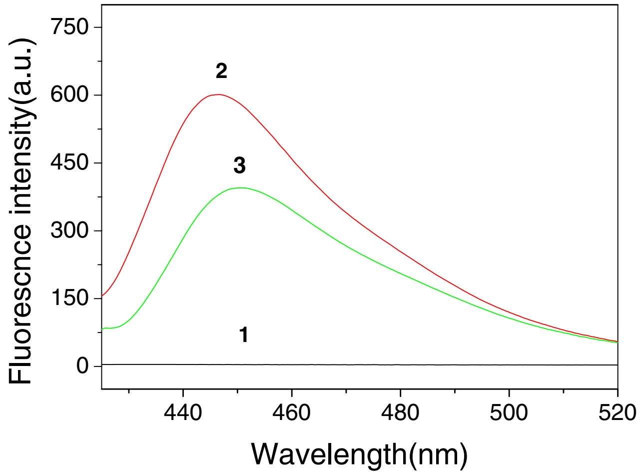


Fig. 1 Fluorescence spectra (excited at 395 nm) of compound **1, 2** and **3** in ethanol–water (30/70, *v/v*) at pH 7.4 (Tris–HCl, 10 mmol L^{-1}). The concentration of **1**, **2** and **3** are both 1.0 μmol L^{-1}. Both the excitation and emission slit widths were set at 5.0 nm

silane(TMS)as internal standard. All of the measurements were operated at room temperature at about 298 K.

Procedure

Typically, to a 10-mL test tube containing 3.0 mL ethanol, 1.0 mL of Tris-HCl buffer (0.1 mol L^{-1}, pH=7.4) and 0.1 mL of compound **1** (1.0 mmol L^{-1}), an appropriate aliquot of Zn^{2+} was added and the reaction mixture was diluted to 10.0 mL with water. The resulting solution was allowed to stand at room temperature for 5 min, and then the absorption and emission spectra were recorded. For fluorescence intensity measurements, the excitation and emission wavelengths were at 400 nm and 457 nm, respectively.

Results and discussion

Spectral characteristics

It is well-known that coumarin dyes are strongly fluorescent. In this study, we formylated compound **2** at its 8 position via Duff reaction [26, 27] and found that its fluorescence was slightly decreased and the emission maximum shifted from 446 to 452 nm. However, upon coupling with semicarbazide, **3**'s fluorescence was dramatically quenched (Fig. 1). This quenching is due to a PET process from the electron-donating semicarbazide moiety to the coumarin ring. Experimentally, it was observed that the fluorescence of compound **1** is largely enhanced with the addition of Zn^{2+}, differentiated from other metal ions, indicating that it is a selective chemosensor for Zn^{2+}.

As shown in Fig. 2, compound **1** exhibits an absorption maximum at 416 nm, which undergoes a hypsochromic shift to 407 nm upon Zn^{2+} binding. Furthermore, to gain more insight into the chemosensing properties of **1** toward Zn^{2+}, a fluorescence titration with Zn^{2+} in 30% aqueous ethanol solution were carried out. In the absence of Zn^{2+}, the fluorescence emission maximum of **1** is centered at about 483 nm. Upon the gradual addition of the Zn^{2+} from 0 to 10 equiv, the λ_{em} undergoes a blue shift to 457 nm, and the fluorescence emission at 457 nm increases with increasing Zn^{2+} concentration, which forms the base of fluorimetric determination of Zn^{2+} (Fig. 3). The blockage of PET process from the semicarbazide amine to coumarin ring induced by Zn^{2+} coordination is responsible for Zn^{2+}-induced emission enhancement. Additionally, similar results are obtained when divalent zinc salts, such as $ZnSO_4$, $ZnCl_2$, $Zn(NO_3)_2$ and $Zn(Ac)_2$ are used (Fig. S1). Therefore, it appears that counter anions have no perceptible effects on the fluorescence response of the proposed chemosensor.

Binding of 1 with Zn^{2+}

Before the application of **1** in the detection of Zn^{2+}, the binding interaction of **1** with Zn^{2+} was investigated. First, EDTA, a very strong cation chelating agent, was added to the solution of **1**-Zn^{2+}, and it was observed that the fluorescence intensity almost decreased to its original intensity of free ligand (Fig. S2), indicating that the coordination of **1** with Zn^{2+} is chemically reversible. Next, Job's method for the emission changes at 457 nm was applied to study the binding stoichiometry of **1** and Zn^{2+} (Fig. 4) [28–30]. The data of Job's plots using a total concentration of 20 μmol L^{-1} **1** and Zn^{2+} in 30% (*v/v*) aqueous ethanol solution exhibited a maximum fluorescence signal when the molecular fraction of compound **1** was close to 50%, indicating a 1: 1 complexation between

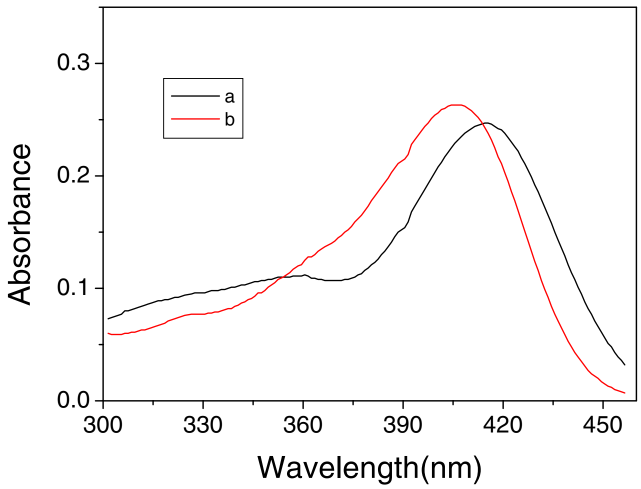


Fig. 2 UV-Vis spectra of **1** (10 μmol L^{-1}) in the absence (*a*) and presence (*b*) of 1 equiv of Zn^{2+} in ethanol–water (30/70, *v/v*) at pH 7.4 (Tris–HCl, 10 mmol L^{-1})

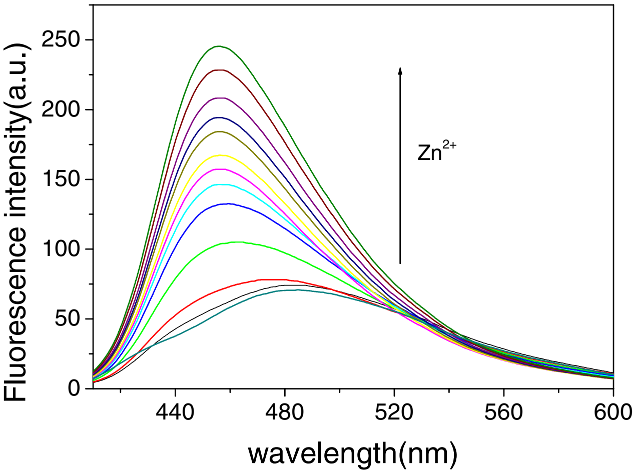


Fig. 3 Fluorescence spectra of **1** (10 μmol L^{-1}) in the presence of different concentrations of Zn^{2+} (0,0.5,1.0,2.0,3.0,4.0,5.0,6.0,7.0,8.0, 10.0,15.0,20.0 μmol L^{-1}) in ethanol–water (30/70, *v/v*) at pH 7.4 (Tris–HCl, 10 mmol L^{-1}). Excitation wavelength was set at 400 nm

Zn^{2+} and **1** (Scheme 1). The binding constant of **1** to Zn^{2+} was calculated by nonlinear least-squares analysis (Fig. S3) to be (9.15±3.50)×10^5 L mol^{-1} with a good correlation (r=0.9979) [31, 32].

Selectivity of 1

The selectivity of **1** toward Zn^{2+} was investigated by treating **1** with other ions such as Cu^{2+}, Ni^{2+}, Co^{2+}, Fe^{2+}, Mn^{2+}, K$^+$, Na$^+$, Ba^{2+}, Li$^+$, Cd^{2+}, Hg^{2+}, Cr^{3+}, Al^{3+}, Pb^{2+}, Ag$^+$, Mg^{2+}, and Ca^{2+} in 30% aqueous ethanol buffered at pH 7.4 (Fig. 5). The addition of Mn^{2+}, K$^+$, Na$^+$, Ba^{2+}, Li$^+$, Hg^{2+}, Cr^{3+}, Al^{3+}, Pb^{2+}, Ag$^+$, Mg^{2+} and Ca^{2+} gave no significant changes to the fluorescence spectra of **1**, while Cu^{2+}, Co^{2+}, Ni^{2+}, Fe^{2+} caused a dramatic fluorescence quenching. The observation that the fluorescence emission of **1** is slightly enhanced with the addition of Cd^{2+}, which is due to Cd^{2+} and Zn^{2+} are in the same group of the periodic table and they have many similar properties. By contrast, the addition of Zn^{2+} to the solution of **1** results in a drastic fluorescence emission change. The fluorescence peak at 483 nm blue-shifts to 457 nm with a marked fluorescence intensity enhancement.

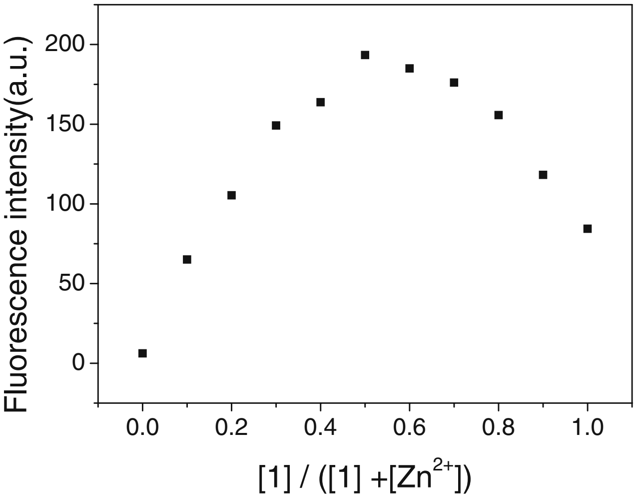


Fig. 4 Job's plots of **1** and Zn^{2+}. The total concentration of **1** and Zn^{2+} were kept at a constant 20.0 μmol L^{-1}. Other conditions are same as those described in the procedure

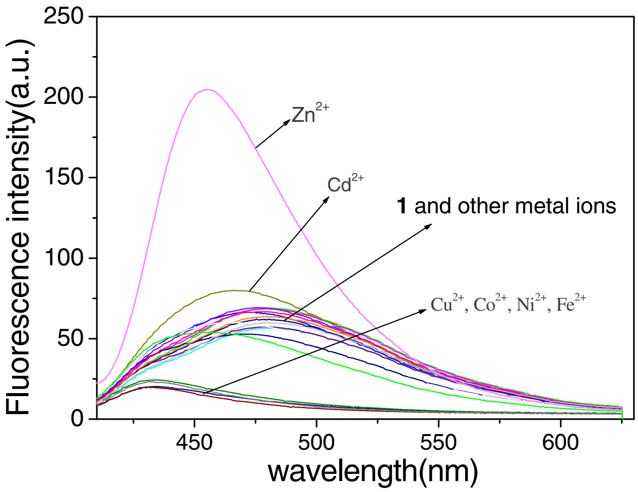


Fig. 5 Fluorescence spectra (excitation at 400 nm) of **1** (10 μmol L^{-1}) in ethanol–water (30/70, *v/v*) at pH 7.4 (Tris–HCl, 10 mmol L^{-1}) in the presence of 1 equiv of Cu^{2+}, Ni^{2+}, Co^{2+}, Fe^{2+}, Al^{3+}, Mn^{2+}, K$^+$, Na$^+$, Ba^{2+}, Li$^+$, Cd^{2+}, Hg^{2+}, Cr^{3+}, Pb^{2+}, Ag$^+$, Mg^{2+} and Ca^{2+}

Furthermore, the competition experiments were carried by adding Zn^{2+} to the solution of **1** in the presence of Cu^{2+}, Ni^{2+}, Co^{2+}, Mn^{2+}, K$^+$, Na$^+$, Li$^+$, Cd^{2+}, Al^{3+}, Pb^{2+}, Ag$^+$, Mg^{2+}, and Ca^{2+}, respectively, and the results were shown in

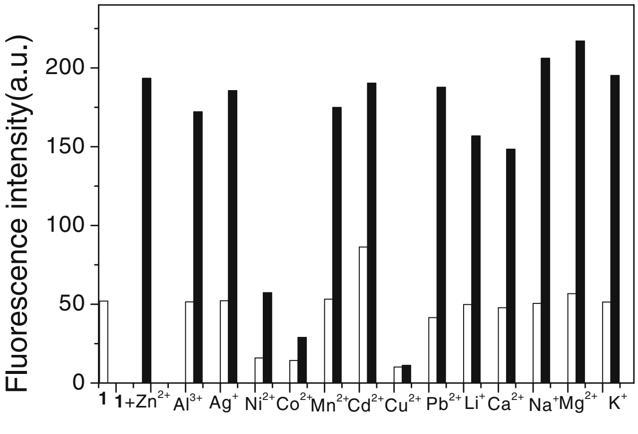


Fig. 6 Fluorescence response of **1** (10 μmol L^{-1}) in the presence of Zn^{2+} (10 μmol L^{-1}) and / or various metal ions in ethanol–water (30/70, *v/v*) at pH 7.4 (Tris–HCl, 10 mmol L^{-1}). All metal ions were evaluated at one equiv to Zn^{2+} except Na$^+$, K$^+$, which were used at 1 mmol L^{-1}. White bars represent the addition of the appropriate metal ion to the solution of **1**. Black bars represent the subsequent addition of Zn^{2+} to the solution

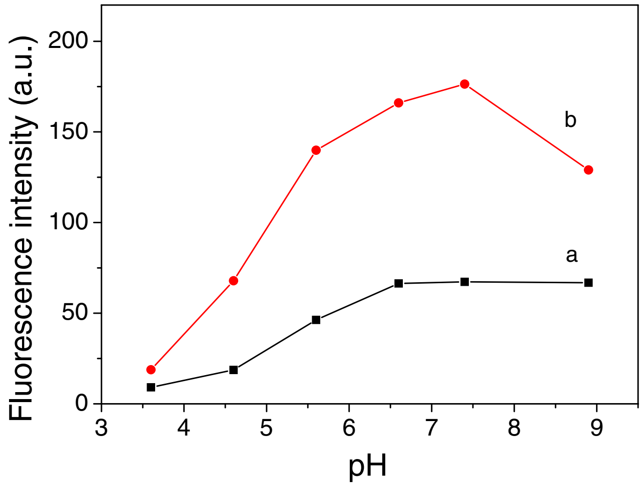


Fig. 7 Effect of pH on the fluorescence intensity of **1** (10 µmol L^{-1}) upon the addition of 1 equiv of Zn^{2+} in ethanol–water (30/70, *v/v*). The concentration of Tris was fixed to 10 mmol L^{-1}. (*a*) **1** only; (*b*) **1** + Zn^{2+}

Fig. 6. It was observed that the presence of some metal ions such as K^+, Na^+, Al^{3+}, Ag^+, Mn^{2+}, Cd^{2+}, Pb^{2+}, Li^+, Ca^{2+}, Mg^{2+} does not interfere with the Zn^{2+}-enhanced fluorescence. When 1 equiv of Zn^{2+} was added to the solution of **1** in the presence of 1 equiv of Cu^{2+}, Co^{2+}, Ni^{2+}, however, no fluorescence response was observed, possibly because the formed complex between these metal ions and **1** is too stable to be replaced by Zn^{2+}, which indicates that the signaling of Zn^{2+} by **1** is significantly interfered by these metal ions.

Effect of pH

The effect of pH on the fluorescence response of **1** to Zn^{2+} was studied in 10 mmol L^{-1} Tris-HCl buffer solution (30% water/ethanol, *v/v*), and the results were shown in Fig. 7. It can be observed that the fluorescence emission of **1**-Zn(II) and free **1** are both increased with increasing pH from 3.6 to 7.4. However, when the pH is higher than 7.4, the fluorescence of **1**-Zn^{2+} is decreased but the free **1** remained stable. In order to obtain a higher signal-to-noise, Tris-HCl buffer (pH 7.4, 10 mmol L^{-1}) was employed for Zn^{2+} assay throughout the experiment.

Analytical characteristics of **1** for Zn^{2+} ion

Under the selected optimized conditions, the fluorescence enhancement (ΔF) is linear with Zn^{2+} concentration (C) in the range 0.5–10.0 µmol L^{-1} (Fig. S4). The linear regression equation was determined to be $\Delta F = 1.44 \times 10^7 C$ [mol L^{-1}]+ 9.92 (n=7, r=0.9989). According to IUPAC, the detection limit was determined from three times the standard deviation of the blank signal (3σ) as 0.29 µmol L^{-1}. The relative standard deviation (R.S.D) for eight repeated measurements of 5.0 µmol L^{-1} of Zn^{2+} is 2.3%.

Preliminary application of **1** for Zn^{2+} assay in water samples

Synthesized water (by adding Zn^{2+} and other metal ions to tap water) and Rongshi Drinking Mineralized Water obtained from the local supermarket were analyzed by the proposed chemosensor under optimized conditions (Table 1). From the above results, it can be seen that **1** can measure the concentration of Zn^{2+} in water samples with good recovery results. Therefore, compound **1** can be employed for Zn^{2+} assay in a water setting.

Conclusion

In summary, a coumarin-based chemosensor **1** was designed and synthesized. Upon treatment with Zn^{2+} in 30% aqueous ethanol buffer at 7.4, the sensor showed a “turn-on” fluorescence response and the emission blue-shifted from 483 nm to 457 nm. The significantly enhanced fluorescence of **1** with the addition of Zn^{2+} is due to the formation of a 1:1 complex **1**-Zn^{2+} in which the PET from a semicarbazide amine to coumarin fluorophore is hindered. The high selectivity of **1** for Zn^{2+} is evidenced as its exceptional fluorescence enhancement from various metal ions. Moreover, compound **1** can be prepared from cheap starting materials with easy preparation in organic synthesis, which is important for practical application.

Table 1 Determination of Zn^{2+} concentrations in water samples

Sample	Zn^{2+} added (µmol L^{-1})	Zn^{2+} found (µmol L^{-1})	Recovery (%)	RSD (%) (n=3)
Synthesized Water[a]	0.0	2.13	106.5	2.7
	4.0	5.95	99.2	2.2
	6.0	8.40	105.0	1.2
Drinking Mineralized Water	0.0	3.60	–	4.2
	4.0	7.50	97.5	1.5
	6.0	9.50	98.3	1.1

[a] Synthesized by tap water, 2.0 µmol L^{-1} $ZnSO_4$, 8.0 µmol L^{-1} $CdCl_2$, 50 µmol L^{-1} NaCl, KCl, $MgSO_4$, and $CaCl_2$

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