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Synthesis of coumarin derivatives containing 2-aminothiazole moiety and their recognition of metal ions

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Abstract Two new coumarin derivatives bearing 2-aminothiazole moiety were synthesized and the molecular structures were confirmed by NMR and HRMS. In acetonitrile, **C1** exhibited a selective fluorescence enhancement effect to Mg^{2+} among the metal ions examined. **C2** showed a selective fluorescence quenching effect to Co^{2+}.

Keywords Fluorescent probe · Coumarins · 2-Aminothiazole · Metal ions

Introduction

Metal ions recognition is one of the fast growing fields in supramolecular chemistry due to their fundamental importance to chemistry, biomedicine, and environmental applications. Fluorescent probes for metal ions as a detection method with advantages of simplicity, excellent selectivity, high sensitivity, and fast response time (within minutes) have been widely used, and their design, synthesis, and action mechanisms have received extensive attention and research [1–5]. Currently, the development of fluorescent small molecules for metal ion recognition with excellent selectivity and sensitivity is still a challenging work for many scientists, including chemists, biologists, and clinical biochemists. Fluorescent probes for metal ions generally contain binding sites and a signaling subunit that can respond quickly to the changes in absorption

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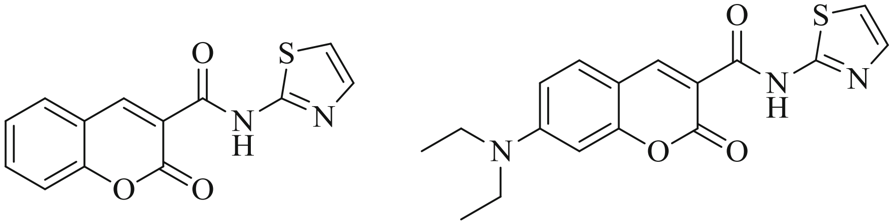
(emission) spectra when binding metal ions. Coumarin derivatives are commonly used as fluorescent chemical probes for the metal ions because they possess many distinctive and desirable properties such as high fluorescence quantum yields, strong absorption (a high molar extinction coefficient), and a large Stokes shifts (up to 160 nm) [6, 7]. These properties have made them desirable components in many fields, including sensors for metal cations [8–17], OLEDs [18–21], laser dyes [22–24], and fluorescent intracellular tags [25, 26]. With these concerns in mind, and in continuation of our ongoing research work on the use of coumarin derivatives as environmentally sensitive fluorescent probes [27], we have recently constructed two fluorescent probes, **C1** and **C2**, by combining a coumarin fragment with 2-aminothiazole (Scheme 1), and studied the properties of their UV–Vis absorption and fluorescence emission spectra in acetonitrile. Compound **C1** displayed a selective fluorescence enhancement effect with Mg^{2+}, on the other hand, compound **C2** displayed a selective fluorescence quenching effect with Co^{2+} among the metal ions examined.

Experimental

Materials and measurements

Unless otherwise stated, all reagents were obtained from commercial suppliers and used without further purification. Solvents employed in this study were of the highest grade and were used as received. Ethyl 2-oxo-2*H*-chromene-3-carboxylate (**1**) and Ethyl 7-diethylamino-2-oxo-2*H*-chromene-3-carboxylate (**2**) were prepared according to literature procedures [27, 29]. Melting points were determined with by a TECH X-4 apparatus and the quoted temperatures were uncorrected. TLC analysis was performed on silica gel plates and column chromatography was carried out on silica gel (mesh 200–300), both of which were purchased from Qingdao Ocean Chemicals. The ^{1}H NMR (600 MHz) and ^{13}C NMR (150 MHz) spectra were recorded on a Bruker AVANCE III 600 spectrometer using DMSO-d_6 as the solvent with tetramethylsilane (TMS) as an internal standard. MS were determined on a Bruker apex ultra 7.0 T spectrometer (the accuracy is 1 ppm). UV spectra were measured on a Purkinje TU-1901 UV–Visible spectrophotometer. Fluorescent spectra were recorded on a HITACHI F-7000 fluorescence spectrophotometer.



Scheme 1 Chemical structure of sensors **C1** and **C2**

Synthesis

*Preparation of 2-Oxo-2H-chromene-3-carboxylic acid (**3**)*

To a solution of ethyl 2-oxo-2*H*-chromene-3-carboxylate (**1**) (2.000 g, 9.2 mmol) in EtOH/H_2O 2:1 (v/v, 15 mL) was added 1.5 g NaOH and heated under reflux for 18 min. After cooling to room temperature, the solution was slowly poured into hydrochloric acid solution 20 % (v/v, 30 mL) and cooling to 0 °C gave a white crystalline deposit. The solid was collected by filtration and washed with cold water to afford **3** as white crystals, and finally dried in vacuo. (1.479 g, 84.8 %): m.p. 187–188 °C (lit. value 191–192 °C) [30]. An analogous procedure starting with **2** gave 7-diethylamino-2-oxo-2*H*-chromene-3-carboxylic acid (**4**) (78.6 %); m.p. 236–238 °C (lit. value 228 °C) [31].

*Preparation of 2-oxo-N-(thiazol-2-yl)-2H-chromene-3-carboxamide (**C1**)*

2-Oxo-2*H*-chromene-3-carboxylic acid (**3**) (0.190 g, 1.0 mmol) and 8 mL $SOCl_2$ were added into a 25-mL single-necked flask equipped with a water-cooled condenser and tail gas absorption device and heated under reflux for 4 h. After cooling to room temperature, the $SOCl_2$ was evaporated under reduced pressure. 2-Aminothiazole (0.095 g, 0.95 mmol) in 2 mL of CH_2Cl_2 was added dropwise to the above 2-oxo-2*H*-chromene-3-carbonyl chloride in 10 mL CH_2Cl_2 cooled at 0 °C. The mixture was stirred for 1 h at 0 °C, then for 8 h at r.t. The solvent was evaporated under reduced pressure. The crude product was subjected to chromatography on silica gel (200–300 mesh) and eluted with a mixture of petroleum ether and ethyl acetate to afford **C1** as light yellow crystals (0.099 g, 38.3 % yield). m.p. 278–280 °C. ^{1}H NMR (DMSO-d_6, 600 MHz), δ: 12.05 (s, 1H), 9.04 (s, 1H), 8.05–8.06 (m, 1H), 7.81–7.85 (m, 1H), 7.58–7.59 (m, 2H), 7.50–7.52 (m, 1H), 7.38 (d, $J = 3.5$ Hz, 1H). ^{13}C NMR (DMSO-d_6, 150 MHz), δ: 160.9, 154.5, 149.0, 138.7, 135.4, 131.1, 126.0, 118.8, 116.9, 115.4. HRMS *m*/*z* (ESI): calcd for $C_{13}H_9N_2O_3S$ $[M+H]^+$ 273.0328, found 273.0332.

*Preparation of 7-(diethylamino)-2-oxo-N-(thiazol-2-yl)-2H-chromene-3-carboxamide (**C2**)*

To a solution of 7-diethylamino-2-oxo-2*H*-chromene-3-carboxylic acid (**4**) (0.261 g, 1.0 mmol) in 5 mL CH_2Cl_2, was added EDCI (0.230 g, 1.2 mmol). After stirring for 0.5 h at r.t., the HOBt (0.162, 1.2 mmol) was added and the mixture was stirred for 1.0 h at r.t. 2-Aminothiazole (0.105 g, 1.05 mmol) was added to the above reacting system and stirred for 25 h at r.t. After removal of the solvent by rotary evaporation, the residue was mixed with water (100 mL). The solid was collected by filtration and washed with a small amount of ethyl acetate, then recrystallized from DMF/CH_3OH (5/1, V/V) to afford 7-(diethylamino)-2-oxo-*N*-(thiazol-2-yl)-2*H*-chromene-3-carboxamide (**C2**) as light yellow crystals (0.105 g, 30.6 % yield). m.p. 212–213 °C. ^{1}H NMR (DMSO-d_6, 600 MHz), δ: 11.93 (s, 1H), 8.81 (s, 1H), 7.75 (d, $J = 8.8$ Hz, 1H), 7.53 (d, $J = 2.7$ Hz, 1H), 7.30 (d,

$J = 2.2$ Hz, 1H), 6.88 (d, $J = 8.3$ Hz, 1H), 6.69 (s, 1H), 3.52–3.53 (m, 4H), 1.16 (t, $J = 6.7$ Hz, 6H); ^{13}C NMR (DMSO-d$_6$, 150 MHz), δ: 162.6, 160.8, 158.2, 157.5, 153.9, 149.3, 138.5, 132.7, 114.8, 111.3, 108.5, 107.1, 96.6, 45.0, 12.8. HRMS *m/z* (ESI): calcd for $C_{17}H_{17}N_3NaO_3S$ $[M+Na]^+$ 366.0883, found 366.0883.

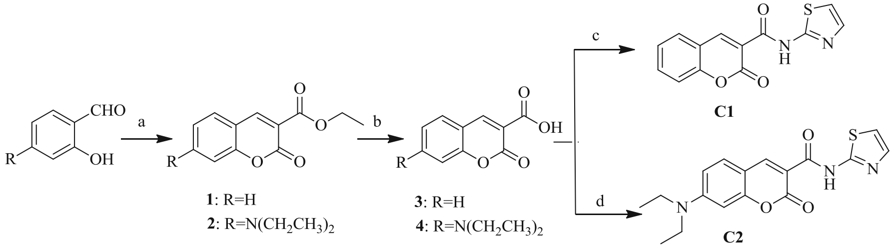
Results and discussion

Aminothiazole-based probes **C1** and **C2** were synthesized by condensation of 2-aminothiazole with 2-oxo-2*H*-chromene-3-carboxylic acid or 7-diethylamino-2-oxo-2*H*-chromene-3-carboxylic acid, respectively. The target molecules and their precursors were synthesized according to the procedure shown in Scheme 2. The synthesis of reaction intermediates **1** and **2** has been reported by us previously [27]. Reaction of **1** or **2** with NaOH in EtOH/H_2O resulted in the desired key intermediates, **3** and **4,** respectively. Treatment of compounds **3** with $SOCl_2$ in CH_2Cl_2 led to 2-oxo-2*H*-chromene-3-carbonyl chloride. After the solvent was evaporated under reduced pressure, 2-aminothiazole was reacted with the above carbonyl chloride in CH_2Cl_2 to give compound 2-oxo-*N*-(thiazol-2-yl)-2*H*-chromene-3-carboxamide (**C1**) in 38.3 % yield as yellow crystals after purification by flash chromatography. 7-(Diethylamino)-2-oxo-*N*-(thiazol-2-yl)-2*H*-chromene-3-carboxamide (**C2**) was synthesized in 30.6 % yields from compounds **4** and 2-aminothiazole by a one-step reaction in the presence of HOBt/EDCI in CH_2Cl_2 at r.t. Compounds **C1** and **C2** were fully characterized by ^{1}H NMR, ^{13}C NMR, and HRMS.

To evaluate the photo-physical properties of probes **C1** and **C2**, their UV–Vis absorption spectra were recorded at 10 mM concentration in acetonitrile (Fig. 1). Probe **C1** displayed a milder strong absorbance band centered at 343 nm and a milder weak absorbance band on the shorter wavelength side centered at about 307 nm. Probe **C2** exhibited a strong band centered at 436 nm and a weaker absorption band at about 269 nm. The large difference in the absorption between **C1** and **C2** is attributed to the strongly electron-donating *N*,*N*-diethylamino moiety groups on the side aromatic ring of **C2**.

Preliminary complexation properties of sensors **C1** and **C2** were studied toward metal ions (Na^+, K^+, Mg^{2+}, Ca^{2+}, Zn^{2+}, Cu^{2+}, Co^{2+}, Ni^{2+}, Fe^{3+}, Mn^{2+}, Cd^{2+}, Ag^+, Hg^{2+}, and Pb^{2+}) by fluorescence spectra in acetonitrile. As shown in Fig. 2, the addition of ten equiv. of metal ions, such as Na^+, K^+, Zn^{2+}, Cu^{2+}, Co^{2+}, Mn^{2+}, Cd^{2+}, Hg^{2+}, and Pb^{2+} resulted in negligible changes in the emission spectrum of **C1**. When Ni^{2+} was added to **C1**, the intensity of the emission band at 380 nm increased by 5.6-fold in acetonitrile. In addition, Fe^{3+}, Ag^+, and Ca^{2+} also showed increased emission bands at 380 nm, but the intensity was lower than that with Ni^{2+}. On the other hand, a fluorescence enhancement effect at 400 nm was observed in the case of **C1** Mg^{2+}. The inset in Fig. 2 exhibits the fluorescent intensity ratio (I400/I380) of free **C1** and **C1** in the presence of 10.0 equiv. of different metal ions.

The fluorescence emission changes of sensor **C2** after addition of the above ions are depicted in Fig. 3. Compound **C2** presents a different extent of fluorescence quenching upon the addition of Mg^{2+} (41.5 %), Ni^{2+} (60.1 %), and Co^{2+} (81.7 %)



(a) Diethyl malonate/EtOH/Piperidine, reflux; (b) i:NaOH/EtOH/H_2O, reflux; ii: H^+. (c) i: $SOCl_2$, reflux; ii: CH_2Cl_2, 2-aminothiazole. (d) HOBt/EDCI, CH_2Cl_2, 2-aminothiazole.

Scheme 2 Synthetic approach for sensors C1 and C2

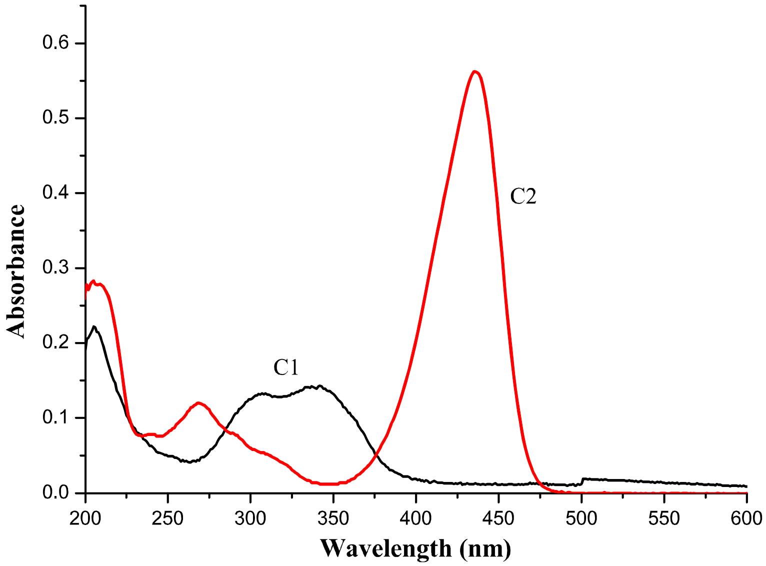


Fig. 1 UV–Vis spectra of sensor C1 and C2 in acetonitrile

among the metal ions examined. Under the same conditions, upon the addition of metal ions such as Na^+, K^+, Ca^{2+}, Zn^{2+}, Cu^{2+}, Fe^{3+}, Mn^{2+}, Cd^{2+}, Ag^+, Hg^{2+}, and Pb^{2+} (10 equiv.) to the solutions of **C2**, no significant fluorescence changes were observed. The inset in Fig. 3 exhibits the fluorescent intensity ratio (I0/I) of free **C2** and **C2** in the presence of 10.0 equiv. of different metal ions at 477 nm.

The fluorogenic affinity of **C1** with Mg^{2+} ions was evaluated by a fluorescence titration experiment (Fig. 4). Probe **C1** has a milder weak fluorescence emission at about 400 nm with excitation at 343 nm. Upon addition of Mg^{2+} ion (0–4 N), relative fluorescence intensity increased significantly at 400 nm. The binding constant (K_a) for the interaction of **C1** with Mg^{2+} estimated from the fluorescence titration data was found to be 7.9×10^4 M^{-1} [28]. The inset in Fig. 4 exhibits the

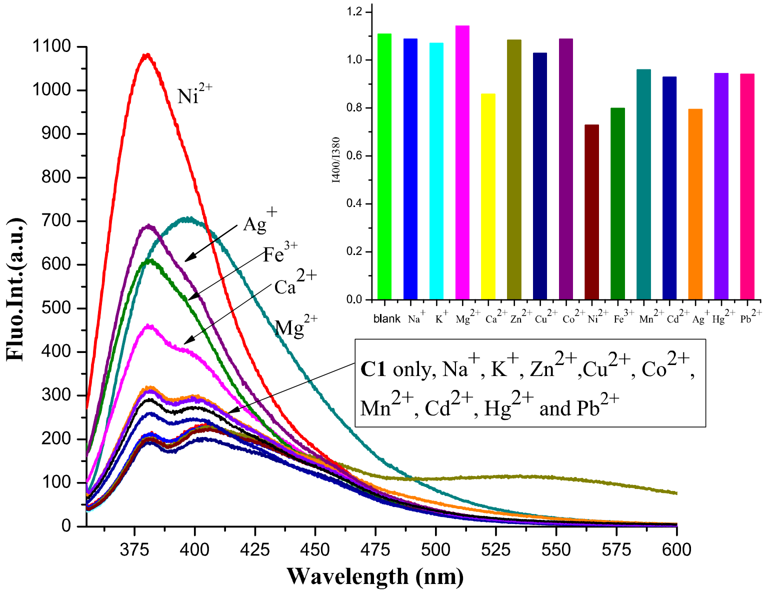


Fig. 2 Fluorescence spectra of free C1 and C1 in the presence of 10 equiv. of various metal ions in acetonitrile. [C1] = 1.0 × 10^{-5} M. Excitation wavelength: 343 nm; bandwidth (E_x): 5 nm; bandwidth (E_m): 10 nm. *Inset* fluorescent intensity ratio (I400/I380) of free C1 and C1 with different metal ions

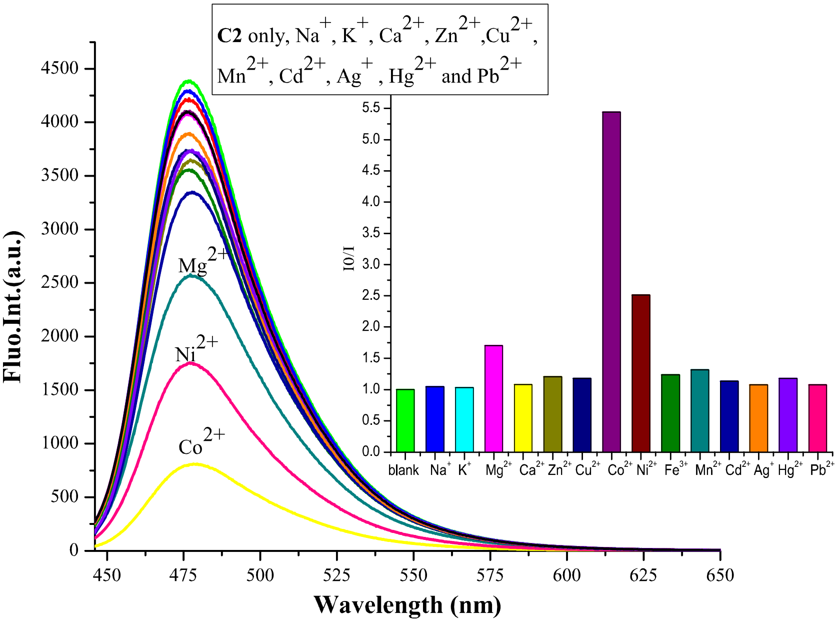


Fig. 3 Fluorescence spectra of free C2 and C2 in the presence of 10 equiv. of various metal ions in acetonitrile. [C2] = 1.0 × 10^{-5} M. Excitation wavelength: 436 nm; bandwidth (E_x): 5 nm; bandwidth (E_m): 5 nm. *Inset* fluorescent intensity ratio (I0/I) of free C2 and C2 with different metal ions at 477 nm

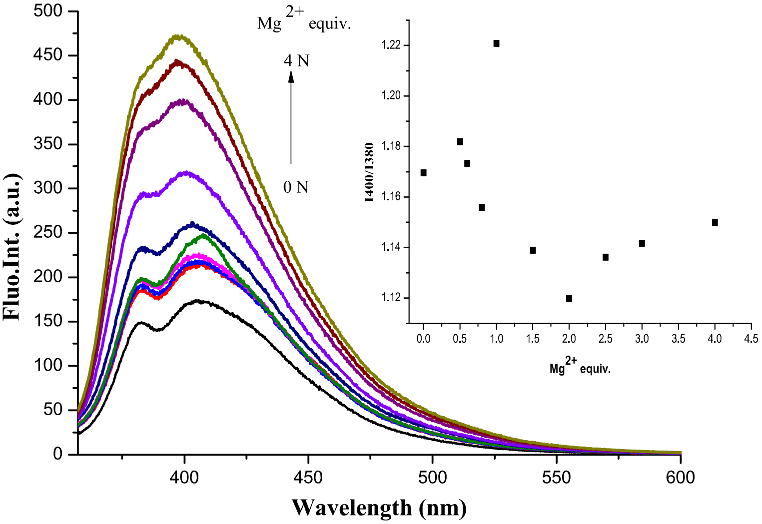


Fig. 4 Fluorescence spectral changes of C1 (1.0×10^{-5} M) upon addition of Mg^{2+} in acetonitrile. Excitation wavelength: 343 nm; bandwidth (E_x): 5 nm; bandwidth (E_m): 10 nm. *Inset* the plot of ratio fluorescence intensity of C1 (I400/I380) versus the concentrations of Mg^{2+}

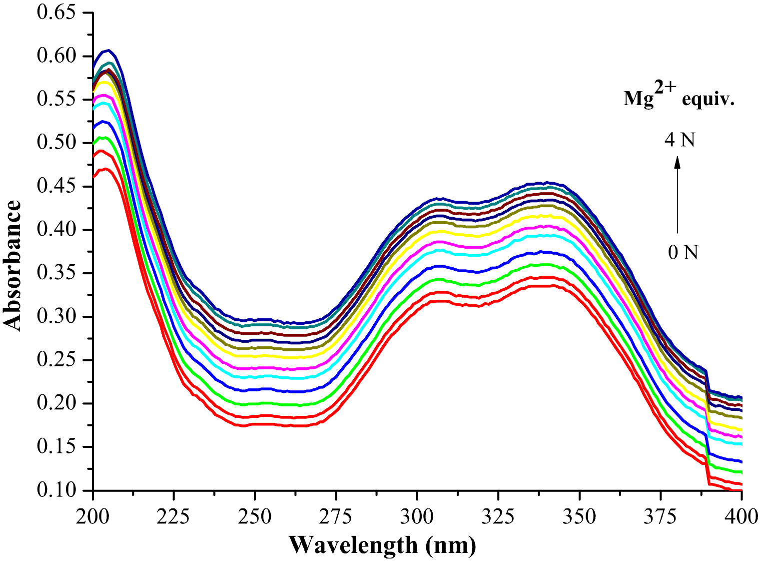


Fig. 5 Absorption spectral changes of C1 (1.0×10^{-5} M) upon addition of Mg^{2+} in acetonitrile

dependence of the intensity ratios of emission at 400 nm to that at 380 nm (I400/I380) on Mg^{2+}.

To understand the coordination behavior between **C1** and the Mg^{2+} ion, the UV–Vis absorption spectral titration experiment of **C1** (10 mM) with Mg^{2+} ion

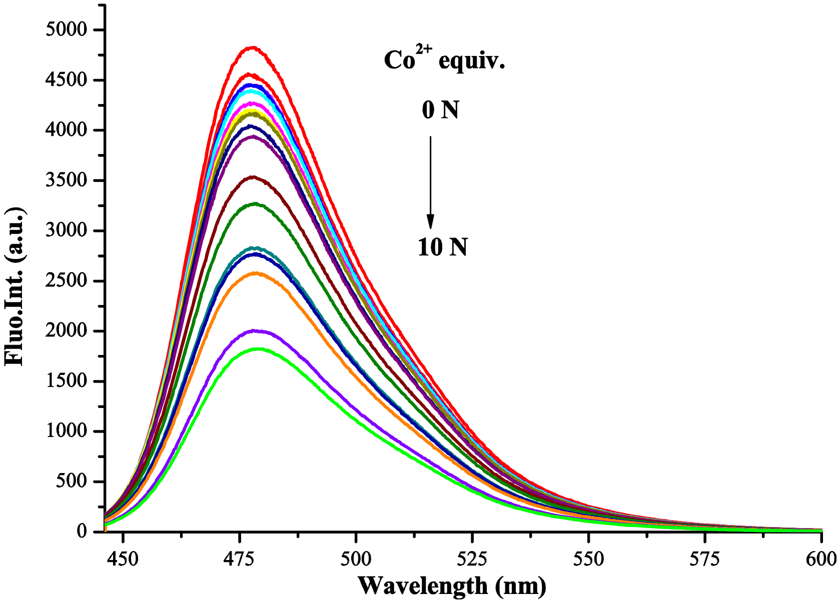


Fig. 6 Fluorescence spectral changes of C2 (1.0×10^{-5} M) upon addition of Co^{2+} in acetonitrile. Excitation wavelength: 436 nm; bandwidth (E_x): 5 nm; bandwidth (E_m): 5 nm

(0–40 mM) in acetonitrile was carried out. With the stepwise addition of Mg^{2+} ion, the absorbance increased gradually and then remained constant after adding approximately 40 mM Mg^{2+} (Fig. 5).

Figure 6 displays fluorescence changes of **C2** upon addition of increasing concentrations of Co^{2+} (0–10 N) in acetonitrile. Probe **C2** has a very strong fluorescence emission at about 477 nm with excitation at 436 nm. The fluorescence intensity gradually decreased at 477 nm upon addition of Co^{2+}. From the fluorescent titrations (Fig. 6), the associated constant (K_a) for the interaction of **C2** with Co^{2+} was calculated as 1.25×10^5 M^{-1} [28].

Conclusions

In summary, two new coumarin derivatives (**C1**, **C2**) bearing 2-aminothiazole moiety were synthesized as fluorescent sensors for metal ions. Compound **C1** displayed enhanced fluorescent effects upon the addition of Mg^{2+} among the metal ions examined. On the other hand, sensor **C2** with the *N*,*N*-diethylamino donor group showed selective fluorescence quenching effect with Co^{2+}.

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