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A quinoline based fluorescent probe that can distinguish zinc(II) from cadmium(II) in water

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ABSTRACT

A new quinoline based fluorescent probe (**DQ**) for Zn^{2+} and Cd^{2+} has been designed and synthesized. The new probe shows quite different fluorescence response to Zn^{2+} and Cd^{2+} in aqueous solution. IR and NMR spectra demonstrated that the different response is caused by amide tautomerization of the probe molecule when coordinating with Zn^{2+} and Cd^{2+}. The dissociation constants of Zn^{2+} and Cd^{2+} complex were detected to be 3.36 and 30.62 nM, respectively. Other metal ions have no effect on the fluorescence spectrum of the probe. Thus the new probe can detect Zn^{2+} and Cd^{2+} in water with high selectivity and sensitivity.

Zinc ion is involved in many cellular events such as gene transcription, regulation of enzymes, cell apoptosis, and neuronal signal transmission.[1] Disruption of Zn^{2+} concentration in cells may be associated with a variety of diseases including Alzheimer's disease, epilepsy, and infantile diarrhea.[2] On the other hand, Cd^{2+} has been recognized as a highly toxic metal ion which can cause serious environmental and health problems.[3] Therefore, developing reliable methods for Zn^{2+} and Cd^{2+} detection has attracted considerable attention in recent years.

Fluorescent probes provide the optimal choice to detect biologically relevant species such as metal ions because of the simplicity and high sensitivity of fluorescence.[4] Various probes for Zn^{2+} and Cd^{2+} have been designed based on fluorescein, coumarin, and other fluorophores.[5] However, because Cd^{2+} and Zn^{2+} have very similar chemical properties, they often disturb each other's detection.[6] Hence, it is a challenge to develop fluorescence probes that can discriminate these two ions from each other.

As part of our ongoing research to develop fluorescent probes for metal ions,[7] we report herein a novel fluorescent probe (**DQ**) based on quinoline skeleton. Quinoline and its derivatives have been used as fluorogenic group of many fluorescent probes for its stable optical properties and excellent water solubility.[8] Di-2-picolylamine (**DPA**), a well-known chelator for Zn^{2+} and Cd^{2+}, was linked to quinoline at the 6-position via amide group. In previous reported quinoline-based Zn^{2+} probes,[9] the amide group was modified at the 8-position of quinoline, which undergo deprotonation when coordinating with Zn^{2+}. However, these probes often suffer from the low ability of distinguishing Zn^{2+} from Cd^{2+}. Amide tautomerization has been proved to be an efficient way to improve Zn^{2+}/Cd^{2+} selectivity.[10] So, we anticipate that the change of the location of amide group will make it possible for the probe to bind with Zn^{2+} and Cd^{2+} in different tautomerization forms, and give different fluorescent response signal to Zn^{2+} and Cd^{2+}.

The **DQ** was easily synthesized via four steps from readily available initial materials with an overall yield of 17.7% (Scheme 1). The structures of **DQ** and intermediates were all confirmed by ^{1}H NMR and ^{13}C NMR.[11]

Ion selectivity study was performed in HEPES (4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid) buffer. Metal ions were used in forms of their chloride salts. Due to the abundance of Na^+, K^+, and Ca^{2+} in biological and environmental systems, these ions were tested at the higher concentration (40 times of Cd^{2+} and Zn^{2+}). As shown in Figure 1, no fluorescence emission changed after adding Na^+, K^+, and Ca^{2+}, which means the probe can be used under biological and environmental conditions. The data also show that Ni^{2+}, Mg^{2+}, Cu^{2+}, Hg^{2+}, Co^{2+}, Fe^{2+}, Pb^{2+}, Mn^{2+}, Fe^{3+}, and Cr^{3+} caused negligible response to the fluorescence of **DQ**. As shown in Figure 1b and c, the probe shows high selectivity to Zn^{2+} and Cd^{2+} in water, when the fluorescence intensity at 373 nm and fluorescence intensity ratio of 509/373 nm were used as the detecting signal for Cd^{2+} and Zn^{2+}, respectively. From the pictures of **DQ**, **DQ**-Zn^{2+}, and **DQ**-Cd^{2+} in aqueous solution under UV-lamp (Fig. 1a insert), the dim-green and bright-blue emission for **DQ**-Zn^{2+} and **DQ**-Cd^{2+} can be easily distinguished by naked eyes.

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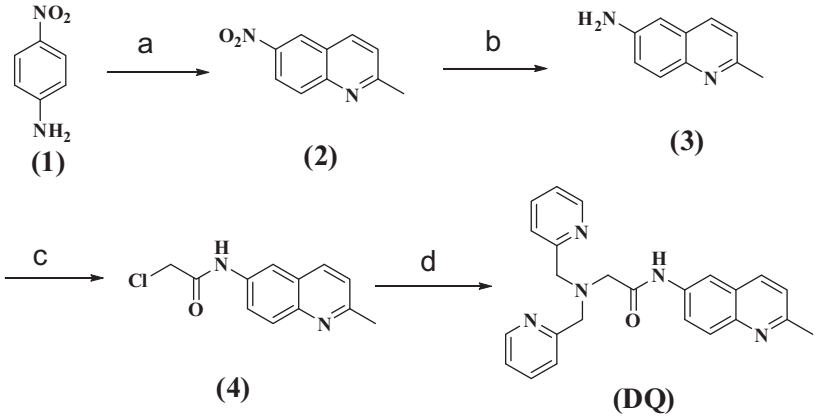


Scheme 1. Reagents and conditions: (a) crotonaldehyde, 6 N HCl, THF,105 °C, 61%; (b) $SnCl_2$, 6 N HCl,105 °C, 74.2%; (c) Et_3N, chloroacetyl chloride, CH_2Cl_2, rt, 60%; (d) DPA, KI, CH_3CN, 78 °C, 65%.

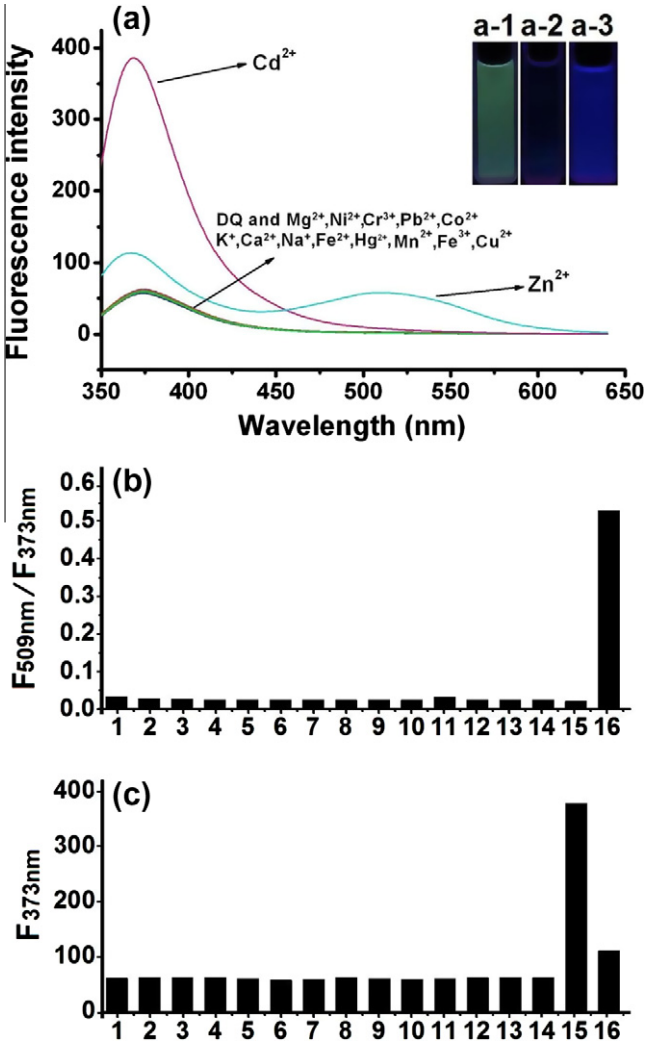


Figure 1. (a) The fluorescence spectra of **DQ** (5 μM) in the presence of various metal ions in HEPES buffer (0.1 M $NaNO_3$, pH 7.4, I = 0.1, λ_{ex} = 330 nm). Inset: the picture of **DQ** in the presence of Cd^{2+} and Zn^{2+} under UV lamp, a-1: **DQ**-Zn^{2+}, a-2: **DQ**, a-3: **DQ**-Cd^{2+}. (b) The fluorescence intensity ratio ($F_{509\ nm}/F_{373\ nm}$) of **DQ** in the presence of various metal ions. (c) The fluorescence intensity at 373 nm of **DQ** upon addition of various metal ions. (1) none; (2) K^+; (3) Na^+; (4) Ca^{2+}; (5) Cr^{3+}; (6) Cu^{2+}; (7) Fe^{3+}; (8) Fe^{2+}; (9) Mg^{2+}; (10) Pb^{2+}; (11) Ni^{2+}; (12) Co^{2+}; (13) Hg^{2+}; (14) Mn^{2+}; (15) Cd^{2+}; (16) Zn^{2+}.

Spectroscopic properties were studied in aqueous HEPES buffered solution (pH 7.4). As shown in Figure 2, the free **DQ** in water has very weak fluorescence in water with quantum yield of 0.023. On addition of Zn^{2+}, fluorescence at 373 and 509 nm were both enhanced gradually (Fig. 2a). When 1 equiv of Zn^{2+} was added, the ratio of the fluorescence intensity at 509 and 373 nm ($F_{509\ nm}/F_{373\ nm}$) was enhanced linearly by fivefolds. So this ratio ($F_{509\ nm}/F_{373\ nm}$) could serve as the detection signal for Zn^{2+}. As shown in Figure 2b, on addition of Cd^{2+}, the fluorescence of **DQ** increased linearly at 373 nm until 1 equiv of Cd^{2+} was added. The quantum yield was increased to 0.25 (nearly 11-folds) after addition of 1 equiv of Cd^{2+}. Job's plot (Fig. S3, S4) confirmed that **DQ** adopt a

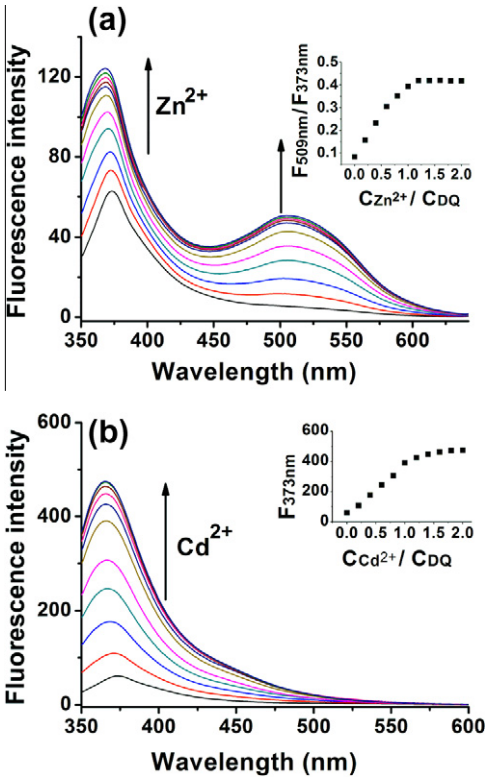
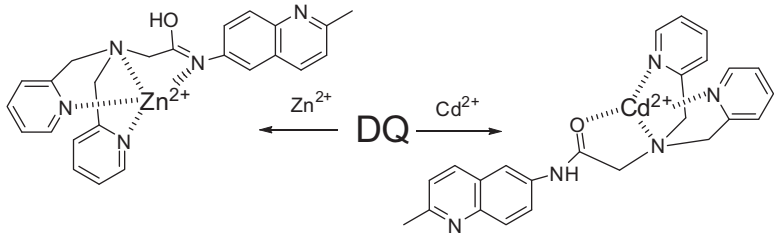


Figure 2. Fluorescence spectra of 5 μM **DQ** upon addition of Zn^{2+} and Cd^{2+} in water (25 mM HEPES, 0.1 M $NaNO_3$, pH 7.4, I = 0.1, λ_{ex}=330 nm): (a) upon addition of Zn^{2+} from 0 to 1.0 equiv. Inset: the ratiometric fluorescence intensity ($F_{509\ nm}/F_{373\ nm}$) as a function of Zn^{2+} concentration. (b) upon addition of Cd^{2+} from 0 to 1.0 equiv. Inset: the fluorescence intensity at 373 nm as a function Cd^{2+} concentration.



Scheme 2. The possible coordination model for **DQ**-Zn^{2+} and **DQ**-Cd^{2+} complex.

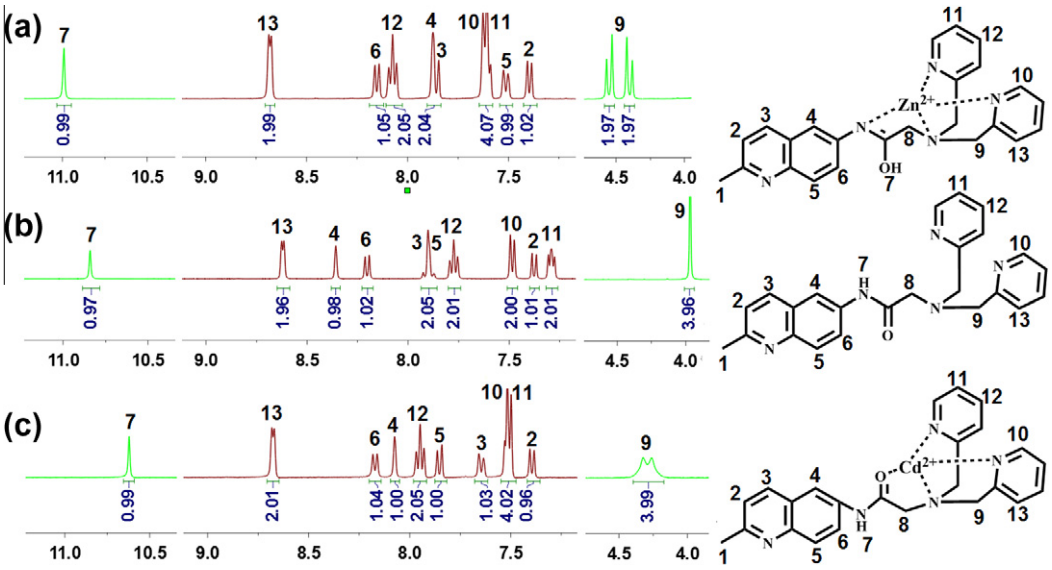


Figure 3. ^{1}H NMR spectra of DQ in the presence of Zn^{2+} and Cd^{2+} in DMSO-d_6: (a) **DQ**-Zn^{2+}, (b) **DQ**, and (c) **DQ**-Cd^{2+}.

1:1 binding model with Cd^{2+} and Zn^{2+}. The dissociation constant (K_d) of **DQ**-Zn^{2+} and **DQ**-Cd^{2+} complex was calculated to 3.36 and 30.62 nM according to the reported method.[12] Thus the new probe could serve as a high sensitive fluorescent probe for both Cd^{2+} and Zn^{2+} in water.

We deem that the different fluorescence response of **DQ** to Cd^{2+} and Zn^{2+} may originate from the different coordination model. As shown in Scheme 2, Zn^{2+} binds to the imidic acid tautomer of **DQ**, which results in an enlarged conjugate system and gives a new emission at 509 nm. Meanwhile, the intra-molecule PET (photoinduced electron transfer) process is blocked, resulting in the fluorescence enhancement. However, Cd^{2+} binds to the amide tautomer of **DQ**. The coordination just blocks the intra-molecule PET process and causes the enhancement of the fluorescence intensity.

To confirm the different binding modes of **DQ** to Zn^{2+} and Cd^{2+}, H NMR spectra were tested for the **DQ**-Zn^{2+} and **DQ**-Cd^{2+} complex. Chemical shift of the amide NH can be used to distinguish the different bonding site (i.e., carbonyl oxygen or imidic acid nitrogen) of **DQ** to metal ions.[13] As shown in Figure 3, when coordinating with Zn^{2+}, the chemical shift of the proton of NH (10.84) was downfield shifted to 10.99. Meanwhile, a large upfield shift (from 8.36 to 7.88) of proton at the 4-position of quinoline was observed. In contrast, on addition of Cd^{2+}, the NH proton shows an upfield shift (from 10.84 to 10.62) and the proton at 4-position of quinoline shows a smaller upfield shift (form 8.36 to 8.07). The result is consistent with previous reports.[10a]

IR test provided further evidence to support the different bonding model. In Figure 4, **DQ**-Zn^{2+} complex shows typical stretching

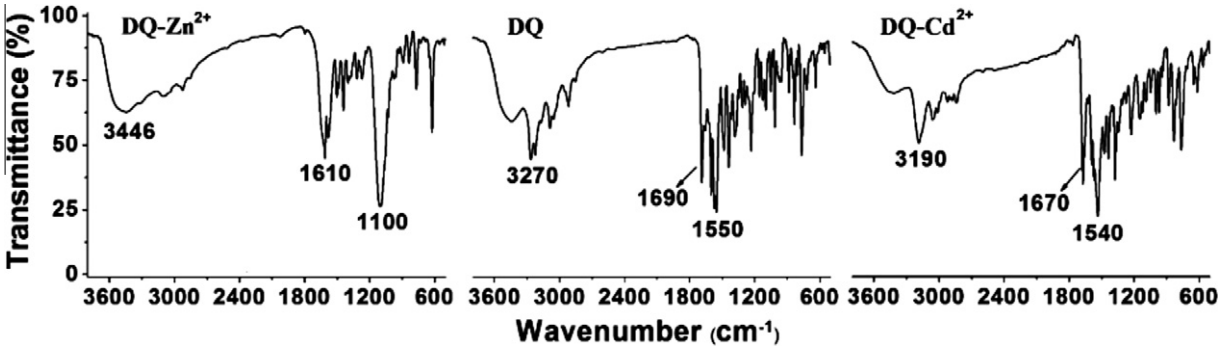


Figure 4. The IR spectra of **DQ**-Zn^{2+}, **DQ**, and **DQ**-Cd^{2+} in KBr tablet.

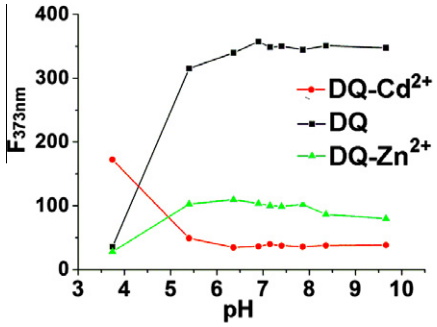


Figure 5. The pH effect on **DQ** and its complex with Cd^{2+} and Zn^{2+}.

absorptions of O–H (3446 cm^{-1}), C=N (1610 cm^{-1}), and C–O (1100 cm^{-1}) of imidic acid tautomer. For **DQ** and **DQ**-Cd^{2+} complex, the typical stretching absorptions of N–H (3270 cm^{-1}, 3190 cm^{-1}) and C=O (1690 cm^{-1}, 1670 cm^{-1}) of amide tautomer were observed.

Furthermore, pH effect on fluorescence of **DQ** was investigated in water. As shown in Figure 5, in the pH range of 6–9, **DQ** and its complex with Zn^{2+} and Cd^{2+} show very stable fluorescence, indicating that the probe could be used under common environmental and physiological condition.

In conclusion, a water-soluble quinoline-based fluorescent probe (**DQ**) for Cd^{2+} and Zn^{2+} was designed and synthesized. The new probe coordinates with Zn^{2+} and Cd^{2+} in different binding models and gives quite different fluorescent signals for these two ions. Moreover, the probe shows nanomole affinity and high selectivity to Zn^{2+} and Cd^{2+}. All these make **DQ** an excellent candidate fluorescent probe that can distinguish Zn^{2+} from Cd^{2+} for biological and environmental applications.

Acknowledgments

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Supplementary data

Supplementary data (synthetic and experimental details) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.12.054.

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11. *Data for* ***DQ***: ^{1}H NMR (400 MHz, DMSO-d_6, ppm): δ 2.63 (3H, s), 3.52 (2H, s), 3.97 (4H, s), 7.28–7.31 (2H, m), 7.37–7.39 (1H, d, J = 8.46 Hz), 7.47–7.79 (2H, d, J = 7.73 Hz), 7.76–7.79 (2H, t, J = 7.63 Hz), 7.87–7.93 (2H, m), 8.19–8.21 (1H, d, J = 8.44 Hz), 8.36 (1H, s), 8.61–8.63 (2H, d, J = 4.52 Hz), 10.84 (1H, s). ^{13}C NMR (100 MHz, DMSO-d_6, ppm): δ 24.81, 58.85, 60.40, 115.62, 122.36, 122.63, 123.32, 123.62, 127.02, 128.53, 136.12, 136.57, 136.72, 144.30, 149.42, 157.35, 157.97, 170.21. Anal. Calcd for $C_{24}H_{23}ON_5$: C, 72.52; H, 5.83; N, 17.62. Found: C, 71.49; H, 5.88; N, 17.65. The detail experiment and the data of other intermediates are in the Supplementary data.
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