Journal of Photochemistry and Photobiology A: Chemistry 218 (2011) 6–10

Contents lists available at ScienceDirect

Journal of Photochemistry and Photobiology A: Chemistry

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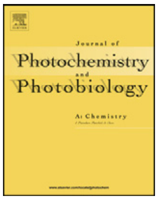

A new highly selective “turn on” fluorescent sensor for zinc ion based on a pyrazoline derivative

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ARTICLE INFO

Article history:
Received 6 August 2010
Received in revised form 27 October 2010
Accepted 22 November 2010
Available online 26 November 2010

Keywords:
Pyrazoline
Fluorescent sensor
Zinc ion
Ratiometric

ABSTRACT

A novel pyrazoline derivative, *2-(4-chloro-2-(1-(6-chloropyridazin-3-yl)-5-phenyl-4,5-dihydro-1H-pyrazol-3-yl)phenoxy)acetic acid*, was synthesized starting from a chalcone and 3-chloro-6-hydrazinylpyridazine and proposed for the determination of Zn^{2+} ion with high selectivity and a low detection limit in CH_3CN:EtOH (90/10, v/v). This sensor formed a 1:1 complex with Zn^{2+} and showed a fluorescent enhancement with good tolerance of other metal ions.

1. Introduction

Fluorescence measurement of specific biological molecules by artificial chemosensors is a versatile technique with high sensitivity, rapid response, and easy performance, offering utility not only for in vitro assays but also for in vivo imaging studies using fluorescence microscopy [1]. During the past few decades, much effort has been devoted to the development of fluorescent chemosensors for various biological substances such as cations, anions, sugars, and proteins [2]. Therein, the monitoring of zinc ion with a selective chemical probe is actively investigated, as zinc is the second most abundant transition metal ion in the human body after iron and an essential cofactor in many biological processes such as brain function and pathology, gene expression, immune function, mammalian reproduction, apoptosis, enzyme regulation, neurotransmission [3–10]. And it is believed that disorder of zinc homeostasis is implicated in a number of pathological processes, such as Alzheimer’s disease, epilepsy, infantile diarrhea, and ischemic stroke [11–13]. Therefore, accurate measurement of Zn^{2+} is very important to decrease the probability of such diseases.

Pyrazoline derivatives are attracting attention in conjugated fluorescent dyes emitting blue fluorescence with high fluorescence quantum yield [14,15] and electroluminescence fields [16,17]. Attempts have been made to synthesize and elucidate the effects of substituent on the absorption and fluorescence properties of this class of compounds [18–22]. Recently interesting papers dealing with solvatochromic effect and the influence of phenyl ring rotation on the UV–vis absorption spectra of pyrazoline containing compounds have been published [23,24]. In our previous reports, we described the UV–vis absorption and fluorescence of a series of novel pyrazoline derivatives [25,26]. Encouraged by these results, we were interested in exploring fluorescent sensor for zinc ion based pyrazoline structure with chelating groups. Herein, we would like to report fortunate results that *2-(4-chloro-2-(1-(6-chloropyridazin-3-yl)-5-phenyl-4,5-dihydro-1H-pyrazol-3-yl)phenoxy)acetic acid* can be used as highly selective “turn on” fluorescent sensor for zinc ion.

2. Experimental

2.1. Apparatus

Thin-layer chromatography (TLC) was conducted on silica gel 60 F_{254} plates (Merck KGaA). ^1H NMR spectra were recorded on a Bruker Avance 400 (400 MHz) spectrometer, using $CDCl_3$ as solvent and tetramethylsilane (TMS) as internal standard. Melting points were determined on an XD-4 digital micro melting point apparatus. IR spectra were recorded with an IR spectrophotometer VERTEX 70 FT-IR (Bruker Optics). HRMS spectra were determined on a Q-TOF6510 spectrograph (Agilent). UV–vis spectra were examined on a U-4100 (Hitachi). Fluorescent measurements were recorded on a Perkin-Elmer LS-55 luminescence spectrophotometer.

2.2. Materials

Organic solvents (ethanol, acetonitrile and acetone) used in this study were of analytical grade. All the reagents were purchased

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doi:10.1016/j.jphotochem.2010.11.014

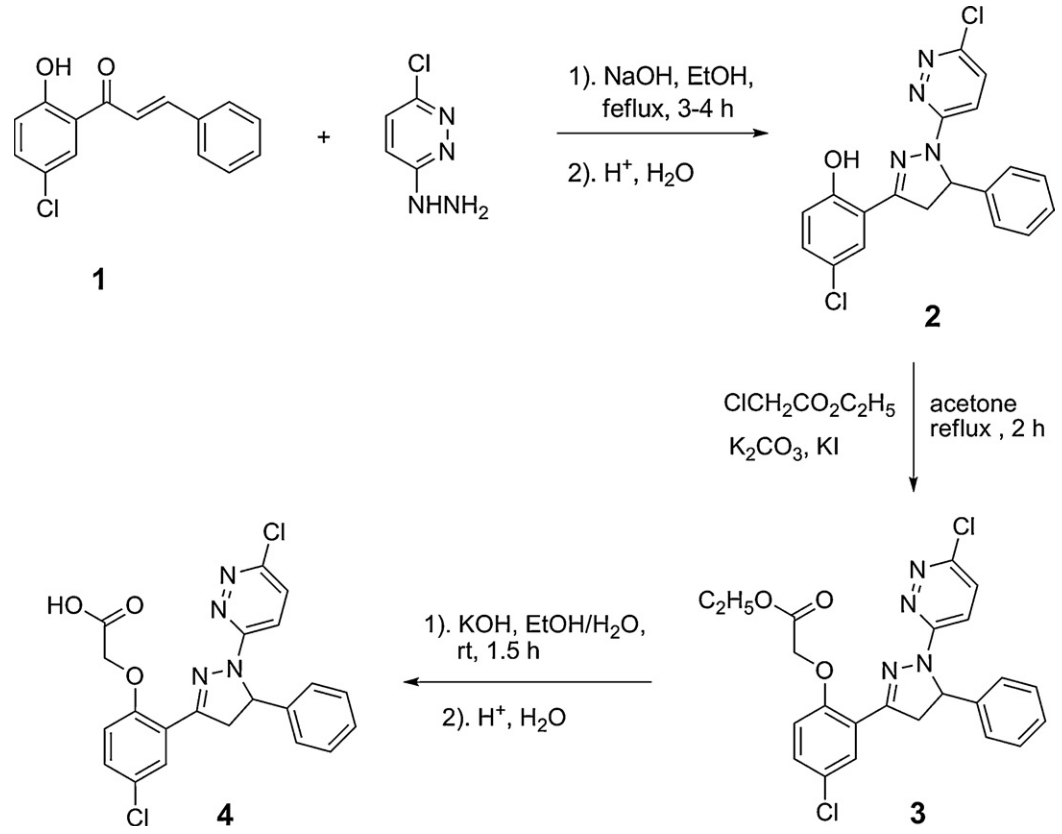

Fig. 1. Synthesis of compound **4**.

from commercial suppliers and used without further purification. The salts used in stock solutions of metal ions were $CoCl_2 \cdot 6H_2O$, $ZnCl_2$, $CaCl_2$, NaCl, $CuCl_2 \cdot 2H_2O$, $NiCl_2 \cdot 6H_2O$, KCl, $CdCl_2 \cdot 2½H_2O$, $HgCl_2$, $FeCl_3 \cdot 6H_2O$, $AgNO_3$, $PbSO_4$, $SnCl_2 \cdot 2H_2O$.

2.3. Synthesis

The synthetic routes are shown in Fig. 1.

2.3.1. 4-Chloro-2-(1-(6-chloropyridazin-3-yl)-5-phenyl-4,5-dihydro-1H-pyrazol-3-yl)phenol (2)

Starting material chalcone (**1**) was prepared according to the literature [27,28]. To a stirred solution of chalcone (**1**) (1.032 g, 4.0 mmol) in ethanol (40 mL) was added 3-chloro-6-hydrazinylpyridazine (0.868 g, 5.0 mmol) and NaOH (0.48 g, 12.0 mmol) and the reaction mixture was refluxed for 4.5 h. The progress of the reaction was monitored by TLC. After completion, the reaction mixture was cooled to room temperature and diluted with chilled water, and then aqueous hydrochloric acid was added to neutralize it. The crude product was obtained as yellow precipitates. The precipitates were filtered, washed with water and ethanol. After chromatography on silica gel (petroleum ether/ethyl acetate/dichloromethane = 3/1/1), compound **2** was obtained. Yellow solid, yield 40%; mp 208–209 °C; IR (KBr, cm^{-1}): 3236.7, 3064.0, 3032.8, 1575.0, 1488.4, 1452.4, 1256.6, 1138.1, 1081.8, 823.0; ^1H NMR (400 MHz, $CDCl_3$): δ 3.42 (dd, 1H, J = 5.4, 17.6 Hz, 4-H_{trans}), 3.98 (dd, 1H, J = 12.0, 17.6 Hz, 4-H_{cis}), 5.89 (dd, 1H, J = 5.4, 12.0 Hz, 5-H of pyrazoline), 7.01 (d, 1H, J = 8.8 Hz, Ar-H), 7.18 (d, 1H, J = 2.4 Hz, Ar-H), 7.23–7.30 (m, 6H, Ar-H), 7.32 (d, 1H, J = 9.3 Hz, pyridazine-H), 7.43 (d, 1H, J = 9.3 Hz, pyridazine-H), 10.13 (s, 1H, OH). HRMS: calcd for $[M+H]^+$ $C_{19}H_{15}Cl_2N_4O$: 385.0623; found: 385.0616.

2.3.2. Ethyl 2-(4-chloro-2-(1-(6-chloropyridazin-3-yl)-5-phenyl-4,5-dihydro-1H-pyrazol-3-yl)phenoxy) acetate (3)

To a stirred solution of **2** (0.238 g, 0.6 mmol) and K_2CO_3 (0.166 g, 1.2 mmol) in acetone (20 mL) was added ethyl chloroacetate (0.089 g, 0.72 mmol), then the reaction mixture was refluxed for 3 h. After cooling, the mixture was filtered and the filtrate was evaporated to afford residue. The residue was crystallized from ethanol to afford **3** (0.236 g), yield 83%; mp 165–166 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 1.23 (t, 3H, J = 7.1 Hz, CH_3), 3.54 (dd, 1H, J = 5.5, 18.7 Hz, 4-H_{trans}), 4.15 (dd, 1H, J = 12.2, 18.7 Hz, 4-H_{cis}), 4.22 (q, 2H, J = 7.1 Hz, CO_2CH_2), 4.62 (s, 2H, OCH_2CO), 5.83 (dd, 1H, J = 5.5, 12.2 Hz, 5-H of pyrazoline), 6.75 (d, 1H, J = 8.9 Hz, Ar-H), 7.18–7.22 (m, 1H, Ar-H), 7.26 (d, 1H, J = 9.4 Hz, pyridazine-H), 7.27–7.32 (m, 5H, Ar-H), 7.75 (d, 1H, J = 9.4 Hz, pyridazine-H), 7.99 (d, 1H, J = 2.7 Hz, Ar-H). HRMS: calcd for $[M+H]^+$ $C_{23}H_{21}Cl_2N_4O_3$: 471.0991; found: 471.0986.

2.3.3. 2-(4-Chloro-2-(1-(6-chloropyridazin-3-yl)-5-phenyl-4,5-dihydro-1H-pyrazol-3-yl)phenoxy)acetic acid (4)

To a solution of **3** (0.141 g, 0.3 mmol) in ethanol (6 mL) was added 0.3 N aqueous potassium hydroxide solution (2 mL). The solution was stirred at room temperature for 1.5 h. The progress of the reaction was monitored by TLC. After completion, the solvent was evaporated. Then chilled water (10 mL) was added and aqueous hydrochloric acid was added to neutralize it to obtain yellow precipitates. The precipitates were filtered, washed with water and ethanol to afford **4** (0.123 g). White solid, yield 93%; mp 192–194 °C; ^1H NMR (400 MHz, DMSO-d_6): δ 3.43 (dd, 1H, J = 5.2, 18.8 Hz, 4-H_{trans}), 4.13 (dd, 1H, J = 12.2, 18.8 Hz, 4-H_{cis}), 4.77 (s, 2H, OCH_2CO), 5.80 (dd, 1H, J = 5.2, 12.2 Hz, 5-H of pyrazoline), 7.09 (d, 1H, J = 8.9 Hz, Ar-H), 7.21–7.33 (m, 5H, Ar-H), 7.43 (dd, 1H, J = 2.6, 8.9 Hz, Ar-H), 7.60 (d, 1H, J = 9.4 Hz, pyridazine-H), 7.90 (d, 1H,

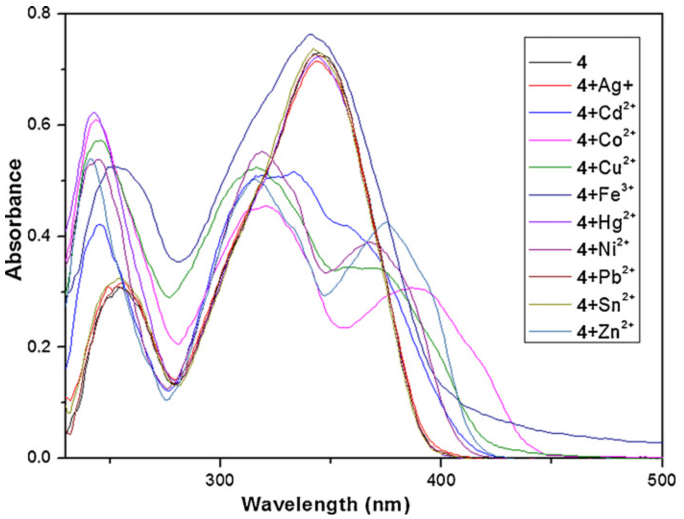

Fig. 2. UV–vis spectral changes of compound **4** (5×10^{-5} M) in CH_3CN:EtOH solution (90/10, v/v) upon addition of 1.0 equiv. of various metal ions.

$J = 9.4$ Hz, pyridazine-H), 7.99 (d, 1H, $J = 2.6$ Hz, Ar-H), 13.10 (s, 1H, CO_2H). HRMS: calcd for $[M+H]^+$ $C_{21}H_{17}Cl_2N_4O_3$: 443.0678; found: 443.0671.

2.4. *Analytical procedure*

A 1.0×10^{-3} M of stock solution of compound **4** in CH_3CN was prepared. The cationic stocks were all in C_2H_5OH with a concentration of 1.0×10^{-3} M for fluorescence and UV–vis spectra analysis. The UV–vis absorption spectra were recorded in acetonitrile and the mixture of acetonitrile and ethanol (analytical grade) solutions (5×10^{-5} M) in a standard 1 cm path length quartz cell in range 220–600 nm with spectral resolution 1 nm. For all measurements of fluorescence spectra, excitation was at 347 nm with excitation and emission slit widths at 10.0 nm and scan speed was set at 800 nm min^{-1} using 1×10^{-5} M of compound **4** in CH_3CN:EtOH solution (90/10, v/v). Moreover, for fluorescence titration experiments, each time a 3 mL solution of compound **4** was filled in a quartz cell of 1 cm optical path length, and the stock solution of Zn^{2+} was added into the quartz cell gradually by using a micro-syringe. After each addition of Zn^{2+}, the solution was stirred for 3 min. The volume of cationic stock solution added was less than 100 μL with the purpose of keeping the total volume of testing solution without obvious change. In order to determine stoichiometry of the complex formed from compound **4** and Zn^{2+}, solutions of compound **4** and Zn^{2+} salt were prepared as 1:9, 2:8, 3:7, 4:6, 5:5, 6:4, 7:3, 8:2 and 9:1 in CH_3CN keeping the total concentration is 1.0×10^{-4} M. These solutions were kept at room temperature for 3 h, and the absorbance at 347 nm was used for calculations.

3. Results and discussion

3.1. *UV–vis studies*

Fig. 2 records the UV–vis spectral changes of compound **4** (50 μM) in CH_3CN:EtOH solution (90/10, v/v) upon addition of 1.0 equiv. of various metal ions. As can be seen from Fig. 2, when Ag^+, Fe^{3+}, Pb^{2+}, Hg^{2+} and Sn^{2+} were added, no absorption curve changes were observed, whereas the absorption intensity at 347 nm can be decreased to some extent when Cd^{2+}, Co^{2+}, Cu^{2+}, Ni^{2+}, Zn^{2+} were added, accompanied by an obviously new absorption peaks appeared.

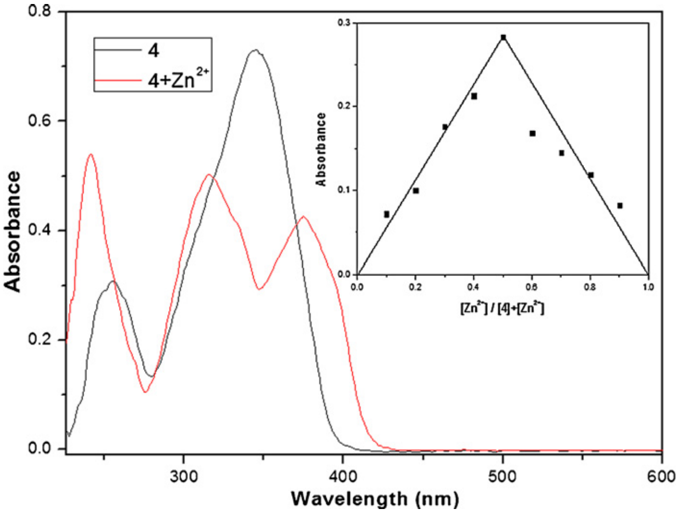

Fig. 3. UV–vis spectra of compound **4** (5×10^{-5} M) and compound **4** (5×10^{-5} M) upon addition of 1.0 equiv. of Zn^{2+} in CH_3CN:EtOH solution (90/10, v/v). Inset: Job's plots according to the method for continuous variations in CH_3CN, indicating the 1:1 stoichiometry for 4-Zn^{2+} (the total concentration of 4 and Zn^{2+} is 1.0×10^{-4} M).

The spectra of compound **4** were recorded in CH_3CN:EtOH solution (90/10, v/v). It can be found from Fig. 3 that the maximal absorbance of compound **4** is at 347 nm ($\varepsilon = 1.43 \times 10^4$ M^{-1} cm^{-1}). Upon addition of Zn^{2+} (1.0 equiv.), the absorption intensity at 347 nm decreases, accompanied by the obvious hypsochromic shift of the absorption peak (from 347 to 316 nm). Simultaneously, a new shoulder-like peak appears around 375 nm with several isosbestic points at 256, 282, 318 and 370 nm, indicating the formation of a new complex between compound **4** and Zn^{2+}. The Job's plot in Fig. 3 (inset) gives a 1:1 stoichiometric ratio between compound **4** and Zn^{2+} ion.

3.2. *Selective detection of zinc ion*

As depicted in Fig. 4 compound **4** showed a very weak fluorescence centered around 480 nm in CH_3CN:EtOH solution (90/10, v/v). Upon interaction with varying metal ions (Ag^+, Cd^{2+}, Co^{2+}, Cu^{2+}, Fe^{3+}, Hg^{2+}, Ni^{2+}, Pb^{2+}, Sn^{2+}, Zn^{2+}), only Zn^{2+} ion induced a siz-

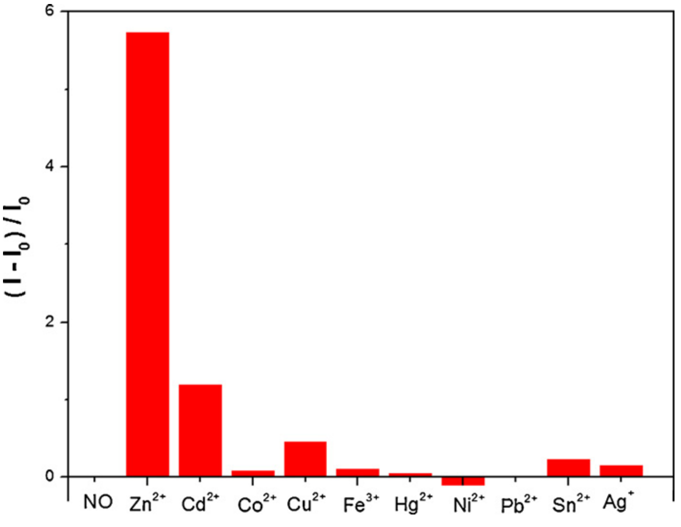

Fig. 4. Fluorescence spectra of free compound **4** (1×10^{-5} M) in CH_3CN:EtOH solution (90/10, v/v) upon addition of 1.0 equiv. of various metal ions with an excitation wavelength of 347 nm. (I and I_0 denote fluorescence intensity of compound **4** at 480 nm in the presence and absence of Zn^{2+}, respectively).

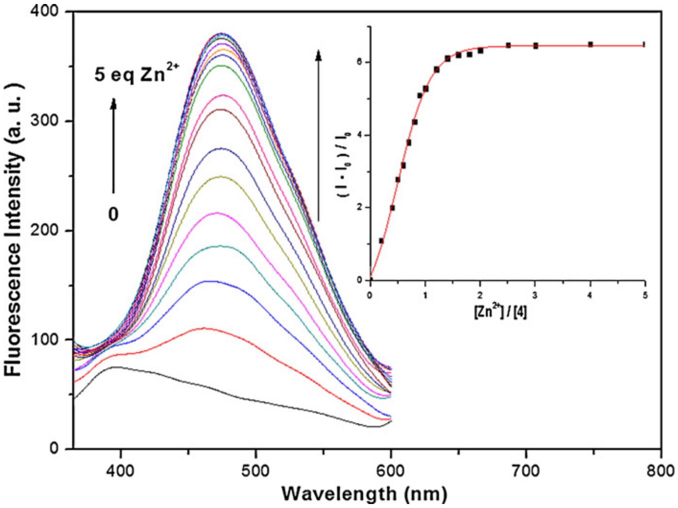

Fig. 5. Fluorescence emission spectra of compound **4** (1×10^{-5} M) was titrated with Zn^{2+} (0–5 equiv.) in CH_3CN:EtOH solution (90/10, v/v). Excitation wavelength was 347 nm. Inset: Variations of fluorescence intensity of compound **4** (1×10^{-5} M) at 480 nm vs. equiv. of $[Zn^{2+}]/[\mathbf{4}]$. (I and I_0 denote fluorescence intensity of compound **4** in the presence and absence of Zn^{2+}, respectively).

able enhancement in fluorescence intensity. With only 1.0 equiv. of Zn^{2+} ion, the fluorescence intensity at 480 nm increased 6-fold; other representative metal ions, except for the slightly responding Cd^{2+} ion increasing about 1-fold, revealed almost insignificant responses to the fluorescence intensity of compound **4**. The system shows selective chelation enhanced fluorescence (CHEF) in the presence of Zn^{2+} ion and the phenomenon is consistent with the literature concerning zinc ion sensors [29–32]. The enhancement of fluorescence is attributed to the strong binding of Zn^{2+} evident from a large binding constant value ($2.5\times10^6\ M^{-1}$) that would impose rigidity and hence decrease the nonradiative decay of the excited state. It is know that transition and post-transition ions with open shell *d*-orbitals often quench the fluorescence of fluorophores due to the electron or energy transfer between the metal ions and fluorophores, providing a fast and efficient nonradiative decay of the excited states [33]. In contrast, the transition ions with close shell *d*-orbitals, such as Zn^{2+}, do not introduce low-energy metal-centered or charge-separated excited states into the molecule, so energy and electron-transfer processes cannot take place [34]. Thus, when Zn^{2+} was added, the fluorescence intensity of compound **4** was increased obviously.

3.3. Fluorescence titration studies

The titration of Zn^{2+} was carried out by adding small aliquots of $ZnCl_2$ ethanol stock solution (1.0×10^{-3} M) into the solution of compound **4** (1×10^{-5} M) in CH_3CN:EtOH solution (90/10, v/v). We observed an almost 6-fold enhancement of fluorescence intensity upon titration of 10 μM $ZnCl_2$ ethanol solution (Fig. 5). When more $ZnCl_2$ ethanol solution was titrated, the fluorescence intensity showed negligible changes and the curve (inset) remained relatively constant, which also gives a 1:1 stoichiometric ratio between compound **4** and Zn^{2+} similar to Job's plot in Fig. 3. The binding constant of the complex of **4** with Zn^{2+} was determined by the nonlinear curve fit according to the fluorescent titration data in Fig. 5 (coefficient of determination: $R^2 = 0.997$) with a 1:1 association equation in CH_3CN:EtOH solution (90/10, v/v) and it was calculated to be $2.5\times10^6\ M^{-1}$ according to the literature [35]. In addition, the detection limit of compound **4** for the analysis of Zn^{2+} ion was estimated to be 4×10^{-7} M. Moreover, the MS analysis has been used to determine the stoichiometry of complex [36–38]. Thus, in present study, the $[(\mathbf{4}\text{-H})/Zn]^+$ complex was calculated at *m*/*z* 504.9813 and measured at *m*/*z* 504.9885. These results support the idea that compound **4** forms a 1:1 complex with Zn^{2+} as proposed in Fig. 6

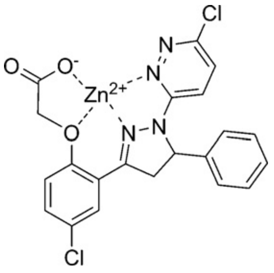

Fig. 6. Proposed complex structure of 4 with Zn^{2+}.

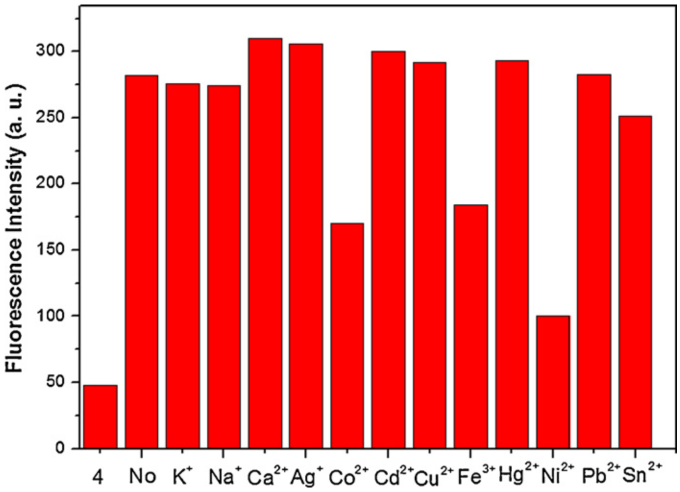

Fig. 7. Fluorescent response of sensor compound **4** (1×10^{-5} M) containing 10 μM Zn^{2+} to the selected metal ions (Ag^+, Co^{2+}, Cd^{2+}, Cu^{2+}, Fe^{3+}, Hg^{2+}, Ni^{2+}, Pb^{2+} and Sn^{2+} (1×10^{-5} M, respectively) and K^+, Na^+, Ca^{2+} (1×10^{-4} M, respectively)) in CH_3CN:EtOH solution (9/1, v/v). Excitation wavelength was 347 nm, and emission wavelength was 480 nm.

3.4. Interference from other ions

To further detect the selectivity for zinc ion over other metal ions, we also examined metal ions/zinc coexisted systems. By

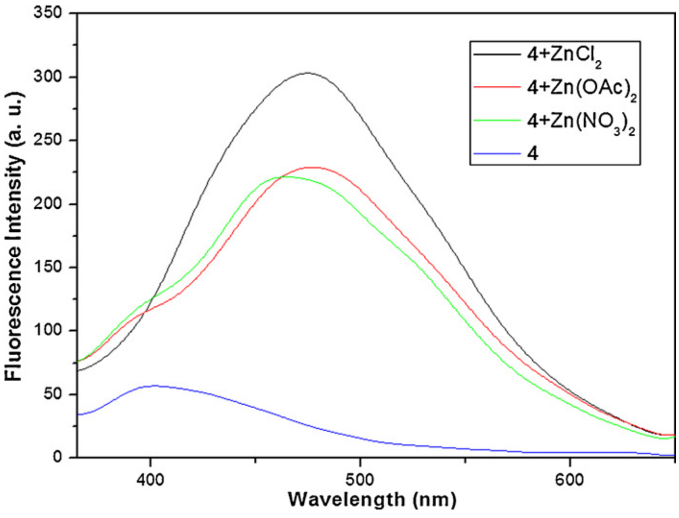

Fig. 8. Fluorescence emission spectra of free compound **4** (1×10^{-5} M) in CH_3CN:EtOH solution (90/10, v/v) upon addition of 1.0 equiv. of different zinc salts.

monitoring fluorescence intensity at 480 nm, zinc ions could be distinguished apparently from other transition metal ions. Furthermore, only Ni^{2+}, Fe^{3+} and Co^{2+} have a little impact on the 480 nm value of the zinc complex as shown in Fig. 7. The results imply the sensor bears high selectivity for zinc ions in the presence of other competitive metal ions.

Interestingly, similar fluorescence enhancement was observed for compound **4** after the addition of Zn^{2+} salts with different counteranions (NO^{3-}, Cl^-, and CH_3COO^-) as shown in Fig. 8. So the zinc salts with different anions all can enhance the fluorescence intensity of compound **4**.

4. Conclusions

In summary, a novel fluorescent sensor based on pyrazoline with 2-(4-chlorophenoxy)acetic acid and 3-chloropyridazine substituent was synthesized and proposed for the determination of Zn^{2+} ion with high selectivity and a low detection limit in CH_3CN:EtOH (90/10, v/v). This sensor formed a 1:1 complex with Zn^{2+} and showed a fluorescent enhancement with good tolerance of other metal ions. Further fluorescent probe exploration for zinc ion in live cell will be reported in due course.

Acknowledgments

This study was supported by 973 Program (2010CB933504) and the National Natural Science Foundation of China (20972088).

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