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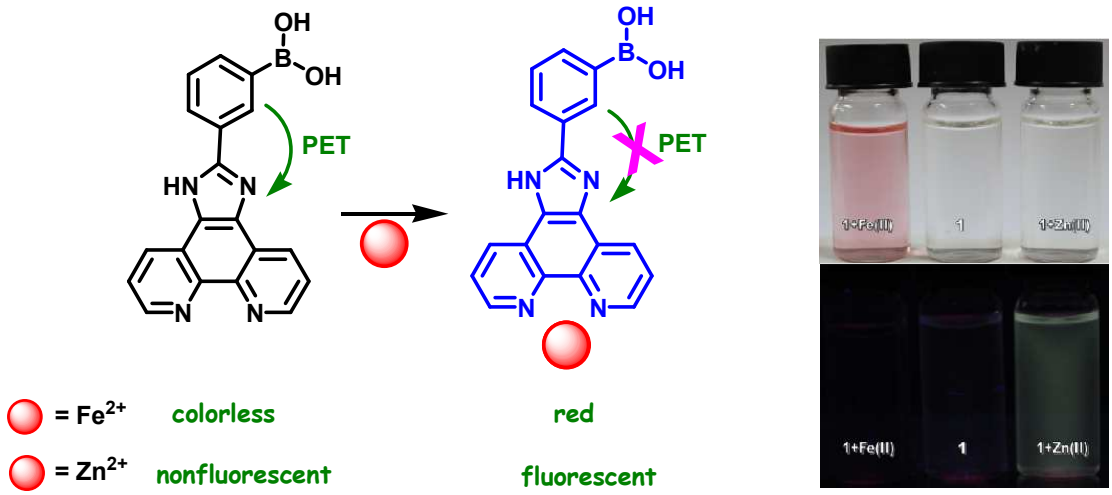
Graphical Abstract

An Imidazo-phenanthroline Scaffold Enables Both Chromogenic Fe(II) and Fluorogenic Zn(II) Detection

Aykut Yoldas, Fatih Algi*



A promising dual channel responsive probe, which can simultaneously induce chromogenic and fluorogenic responses to Fe(II) and Zn(II) ions, respectively, is described.

An Imidazo-phenanthroline Scaffold Enables Both Chromogenic Fe(II) and Fluorogenic Zn(II) Detection

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Abstract

A novel, simple and efficient dual channel probe built on an imidazo-phenanthroline scaffold with boronic acid unit, *viz.* 3-(1H-imidazo[4,5-f][1,10]phenanthrolin-2-yl)phenylboronic acid, is disclosed. It is found that this novel probe induces chromogenic and fluorogenic responses to Fe(II) and Zn(II) ions, respectively. To our best knowledge, this is one of the rare examples of dual channel responsive probes that can be used for visual detection of Fe(II) and turn-on fluorogenic detection of Zn(II) ions, simultaneously.

***Keywords*:** 1,10-phenanthroline, Zn(II), Fe(II), fluorescence, imidazole, sensor, probe.

1. Introduction

Functional organic materials that allow selective and sensitive detection of target metal ions have attracted considerable attention, since metal ions play deleterious and/or essential roles in biological and environmental processes.[1-8] Among these ions, iron is the most abundant transition metal ion, which is naturally present in (II) and (III) oxidation states. It plays vital roles in biological processes such as DNA synthesis, oxidative processes of living tissues, oxygen transport and storage, and mitochondrial electron transfer.[9-13] Also, iron is highly necessary for energy metabolism and enzyme activities. However, either iron deficiency or overload can lead to human disorders and diseases: anemia, diabetes, heart diseases, siderosis, organ damage (liver, kidney etc.), toxicity or even death.[14-24] Furthermore, the discrimination of Fe(II) from Fe(III) might be important, since they represent one of the most important redox couples.[25-32] For that reason, the detection and, if possible, discrimination of Fe(II) from Fe(III) by using simple and efficient methods might be a challenge. In this context, colorimetric iron probes, [33-35] which are capable of giving prominent signals that can easily be visualized by the naked eye without resorting to any instrumentation, offer a facile and prominent strategy.

On the other hand, zinc is the second most abundant transition metal in humans after iron. It is also essential to life as it plays highly crucial roles

in many biological processes; regulation of apoptosis, signal transmission, enzyme function and gene expression.[36] It is also reported that zinc is associated in a number of pathological processes, such as diabetes,[37] Alzheimer's disease,[38] and epilepsy.[39] Therefore, the design of novel molecular sensors, which can recognize zinc selectively among the other metal ions is a challenging task. Fortunately, however, fluorescence spectroscopy offers a highly efficient way of detection of Zn(II) ions. Thus, many examples of fluorescent Zn(II) sensors have been reported to date in the literature.[40-59] However, some of them have disadvantages concerning tedious multistep synthesis, selectivity, sensitivity, and/or interference of other ions especially in aqueous buffer solution. For that reason, design and synthesis of novel and simple yet efficient fluorescent Zn(II) sensors would be welcome.

One of the most prominent phenomena in the design of fluorescent molecular sensors is photoinduced electron transfer (PET).[60-63] In principle, PET might occur in two different directions.[63] In the first case, PET takes place from an excited-state fluorophore to an acceptor unit, which also acts as receptor. This process is termed as oxidative PET.[64-66] In the second case, however, PET takes place from a donor unit to the excited-state fluorophore, which is known as reductive PET. Both of these processes are accompanied by quenching of the fluorophore emission.

In the context of PET based fluorescent probes, we have recently reported that cation-mediated oxidative PET could be modulated in a very

rigid arrangement.[67] We have designed a novel compound which is based on a 1,10-phenanthroline scaffold with cofacial BODIPY units attached orthogonally as the receptor and fluorophore units, respectively. This design afforded a turn-off fluorescent Cd(II) probe. Furthermore, we noted that a simple modification could allow us tailoring the selectivity of the probe from Cd(II) to Zn(II).[68] It is important to note that those analytes, Cd(II) and Zn(II), are in the same group of the periodic table and they show very similar properties.

In the present work, we envisaged that an imidazo-phenanthroline motif with phenyl boronic acid unit could be used to create a simple, selective and viable fluorescent Zn(II) sensor and chromogenic Fe(II) probe. Herein we wish to present our research concerning the design, synthesis and properties of a novel material **1**, *viz.* 3-(1H-imidazo[4,5-f][1,10]phenanthrolin-2-yl)phenylboronic acid. It is found that **1** induces chromogenic response to Fe(II) ions by turning from a colorless state to red color in 0.1 M HEPES buffer containing 0.1% CH_3OH (v/v) (pH = 7.2) solution. It should be noted that **1** can clearly discriminate Fe(II) from Fe(III) in aqueous media. Furthermore, it is noteworthy that **1** can be utilized as a turn-on fluorescent Zn(II) sensor in aqueous buffer solution (0.1 M HEPES buffer containing 0.1% CH_3OH (v/v), pH = 7.2). Importantly, this simple fluorescent sensor is highly selective and it gives fast response to Zn(II) ions. The fluorescence response of **1** is based on cation-mediated inhibition of reductive PET that results in enhancement of

fluorescence emission up to 21-fold in aqueous buffer solution (0.1 M HEPES buffer containing 0.1% CH_3OH (v/v), pH = 7.2). To our best knowledge, this is one of the rare examples of dual channel responsive probes, which can be used for visual detection of Fe(II) and turn on fluorogenic detection of Zn(II) ions, simultaneously.[39, 69-70]

2. Experimental Section

General

All chemicals were purchased from Sigma Aldrich Chemicals or Merck Company and used as received unless otherwise noted. FTIR spectra were recorded on Thermo Scientific Nicolet iS5 FT-IR Spectrometer with iD5-ATR apparatus. ^1H (400 MHz) and ^{13}C (100 MHz) NMR spectra were recorded on a Bruker Ultrashield 400 NMR Spectrometer. Matrix-assisted laser desorbtion/ionization (MALDI TOF) were recorded on Bruker microflex LT MALDI TOF MS system. High resolution mass spectra (HRMS) were recorded on Waters SYNAPT MS system (TOF MS ES). UV/Vis and fluorescence measurements were recorded on Varian Cary 50 and Varian Cary Eclipse spectrophotometers, respectively. Flourescence and UV/Vis spectra were taken at room temperature. Melting points were determined on a Schorrp MPM-H2 model apparatus and are uncorrected. Column chromatography was performed on silica gel (60-200 mesh) from Merck Company. TLC was carried out on Merck 0.2 mm silica gel 60 F254 analytical aluminum plates. The synthesis of **3**[71] was carried out according to a published procedure with slight modifications. Metal solutions were

freshly prepared as 1.0 x 10^{-3} M stocks from the corresponding perchlorate salts [with the exceptions of Au^{3+} (prepared from $AuCl_3$) and Pt^{2+} (prepared from K_2PtCl_4)]. Compound **1** (1 mmol) was dissolved in CH_3OH (10mL). Appropriate amount of this solution was diluted in 0.1 M HEPES buffer (3 mL) at pH 7.2 at room temperature. Proper amount of freshly prepared metal solutions (1.0 x 10^{-3} M) were added to the above solution of **1** for spectrophotometric titrations.

Synthesis of 1,10-phenanthroline-5,6-dione (3).[71]

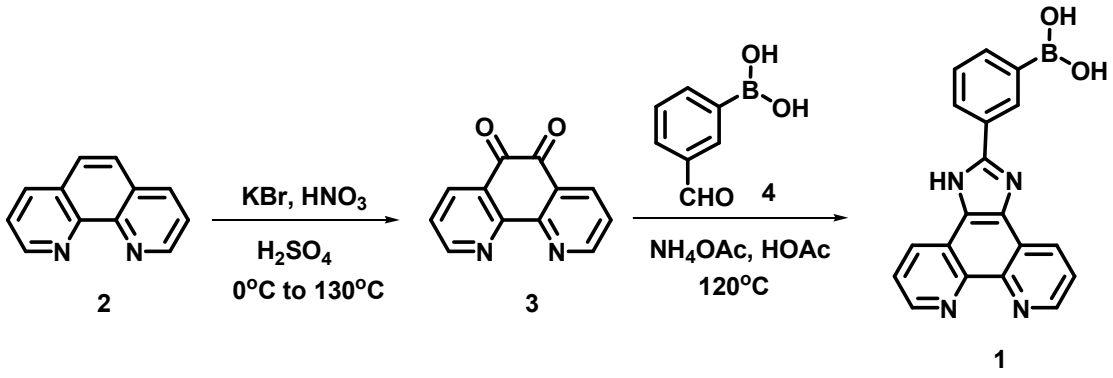
A cooled mixture of H_2SO_4 (10 ml) and HNO_3 (5 ml) was prepared and KBr (1g, 8.4 mmol) was added in small partions to this mixture at 0 ^oC while stirring. This was followed by the addition of 1,10-phenanthroline (**2**, 1 g, 5.5 mmol). Then, the reaction mixture was heated up to 130 °C for 3 hours. Then, the solution was transferred into a beaker containing crushed ice and carefully neutralised with NaOH (10% aqueous solution). The product was extracted by CH_2Cl_2 (3x50 ml), dried over $MgSO_4$ and the solvent was removed under vacuum to give a yellow solid. The yellow solid was recrystallized from ethanol; 972 mg, yield 80%, m.p. 259 ^oC (lit[8] 257^oC). ^1H NMR (400 MHz, $CDCl_3$, 25 ^oC, TMS): δ= 9.05 (dd, J= 4.6-1.7 Hz, 2H), 8.44 (dd, J=7.8-1.7 Hz, 2H), 7.53 (dd, J=7.8-4.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 ^oC, TMS): δ= 178.5, 156.3, 152.8, 137.2, 128.0, 124.9; FTIR (cm^{-1}): 3061, 1701, 1682, 1559, 1458, 1412, 1315, 1292, 1205, 1010, 925, 806, 697.

Synthesis of 3-(3a,11b-dihydro-1H-imidazo[4,5-f][1,10]phenanthrolin yl)phenylboronic acid (1)

1,10-phenanthroline-5,6-dione (**3**, 211 mg, 1 mmol), 3-formylphenylboronic acid (149 mg, 1 mmol), and ammonium acetate (950 mg, 13.32 mmol) were dissolved in glacial acetic acid (10 mL) and the mixture was heated to 120 ^{o}C for 6 h under N_2 atmosphere. After completion of the reaction, the mixture was cooled to room temparature and a majority of the solvent was removed under reduced pressure. Next, 10% aqueous solution of NaOH was used for neutralization (pH=7.0). A yellow precipitate was formed, which was washed with water, CH_2Cl_2 and dried under vacuum overnight; 330 mg, yield 97%, m.p.>360 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$, 25 ^{o}C, TMS): δ= 13.82 (s, NH), 9.03 (dd, J= 4.2-1.5 Hz, 2H), 8.99-8.92 (m, 2H), 8.71 (s, 1H), 8.32 (bs, 3H), 7.95 (d, J=7.3 Hz, 1H), 7.86-7.80 (m, 2H), 7.59 (t, J=7.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 ^{o}C, TMS): δ= 146.3, 142.5, 138.4, 130.3, 130.1, 127.2, 125.1, 124.2, 123.8, 123.1, 122.8, 121.3, 118.1; FTIR (cm^{-1}) : 3372, 3198, 3072, 1609, 1546, 1419, 1275, 1067, 1037, 973, 804, 735, 692, 667; HRMS Anal. Calcd. For $C_{20}H_{15}BN_3O_2$ 340.1257 $[M]^+$; found: 341.1205 $[M+H]^+$.

3. Results and Discussion

The synthesis of the target compound was carried out via a two-step reaction sequence. In the first step, 1,10-phenanthroline (**2**) was treated with KBr, HNO_3 and H_2SO_4 to afford dione **3** in 80% yield according to a known procedure (Scheme 1) (see Supporting Information Figures S1-S2).[71] Next, condensation of **3** with 3-formylphenylboronic acid (**4**) in the presence of NH_4OAc and HOAc resulted in the formation of **1** in a yield of 97%. Compound **1** was initially characterized on the basis of ^1H and ^{13}C NMR spectroscopy, elemental and HRMS analysis, which firmly established the structure (see Supporting Information Figures S3-S5).



Scheme 1. Synthesis of compound **1**.

UV/Vis absorption spectrum of **1** was recorded in 0.1 M HEPES buffer containing 0.1% CH_3OH (v/v) (pH = 7.2) solution. The absorption spectrum of **1** (1.30×10^{-5} M) in this solution is characterized by a broad band between 275-350 nm with λ_{max} at 276 nm and 308 nm (Figure 1, black line). Spectrophotometric titrations of **1** with different metal ions were carried out in order to determine the metal cation complexing

properties of **1**. It was found that the addition of Ag^{+}, Al^{3+}, Au^{3+}, Cd^{2+}, Co^{2+}, Cu^{+}, Cu^{2+}, Fe^{3+}, Hg^{2+}, K^{+}, Li^{+}, Mn^{2+}, Mg^{2+}, Na^{+}, Ni^{2+}, Pb^{2+}, Pt^{2+}, Pd^{2+} and Zn^{2+} ions (3.0 equiv) did not alter the color of the solution of **1** in spite of the fact that small changes were observed in the absorption spectrum as depicted in Figure 1 (blue line). Gratifyingly, however, it was noted that the addition of Fe^{2+} ions (3.0 equiv) revealed significant changes in the original absorption spectrum of **1** (Figure 1, red line).

The absorption spectral changes of **1** as a function of Fe^{2+} concentration in 0.1 M HEPES buffer containing 0.1% CH_3OH (v/v) (pH = 7.2) at room temperature is depicted in Figure 2. Notably, a progressive increase in absorbance in the Visible region of the electromagnetic spectrum was observed with simultaneous formation of new red shifted absorption bands (λ_{max} = 528 nm). Remarkably, the formation of these new red shifted absorption bands (λ_{max} = 528 nm). Remarkably, the formation of these new red shifted absorption bands was enough to change the color of the solution from a colorless state to red color. This allowed the naked-eye (colorimetric) detection of Fe^{2+} ions among the others (Figure 1 inset). In addition, **1** could clearly discriminate Fe(II) from Fe(III) in aqueous media. Competition experiments indicated that **1** is responsive to Fe^{2+} even in the presence of other metal ions (Figure 1, green line). It is important to note that color change is one of the most convenient visual detection methods used in classical chemical analysis, which is straightforward and inexpensive.

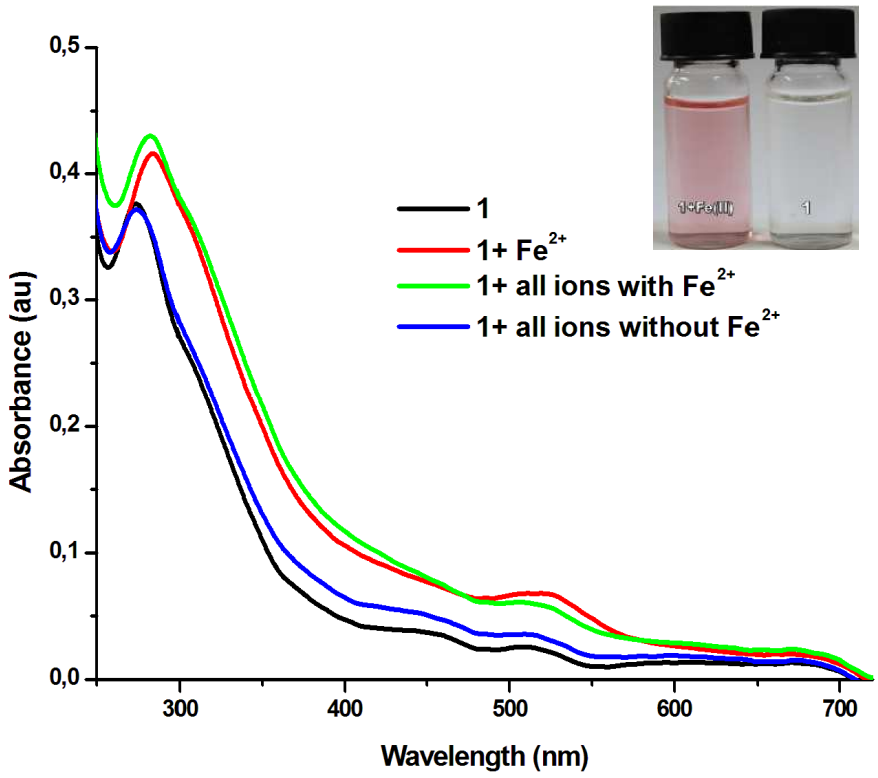


Figure 1. UV/Vis absorption spectra of **1** (1.30 x 10^{-5} M) in the absence and presence of Fe^{2+} and other metal ions (Ag^{+}, Al^{3+}, Au^{3+}, Cd^{2+}, Co^{2+}, Cu^{+}, Cu^{2+}, Fe^{3+}, Hg^{2+}, K^{+}, Li^{+}, Mn^{2+}, Mg^{2+}, Na^{+}, Ni^{2+}, Pb^{2+}, Pt^{2+}, Pd^{2+} and Zn^{2+}) (3.0 equiv) in 0.1 M HEPES buffer containing 0.1% CH_3OH (v/v), pH = 7.2, 25°C. Inset: Color of **1** (1.30 x 10^{-5} M) in the absence and presence of Fe^{2+} ions under room light in 0.1 M HEPES buffer containing 0.1% CH_3OH (v/v), pH = 7.2, 25°C.

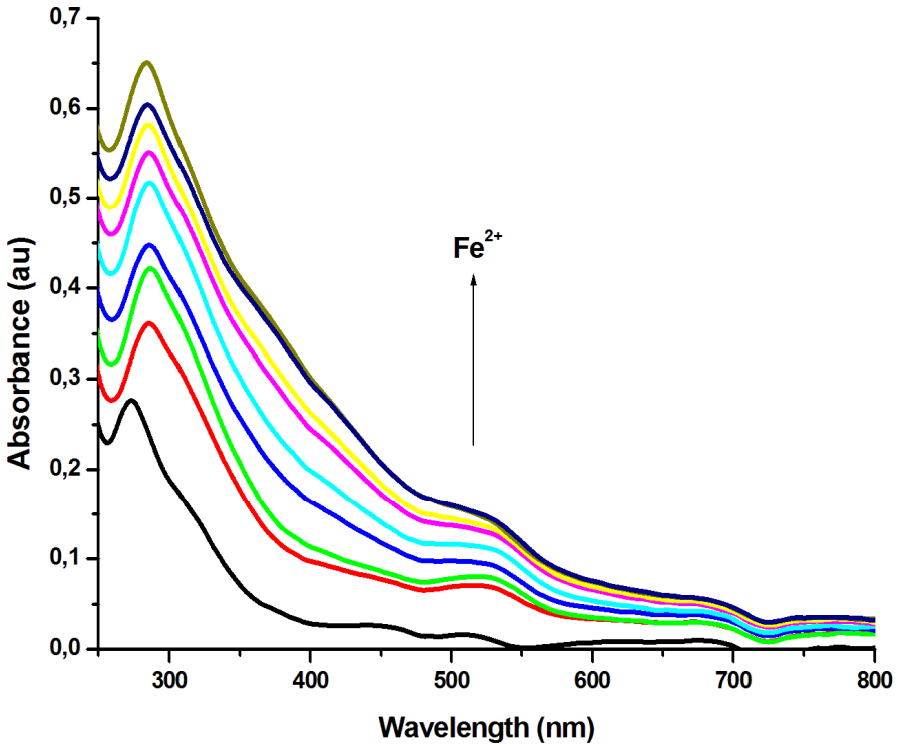


Figure 2. Absorption spectral changes of **1** (0.95 x 10^{-5} M) as a function of Fe^{2+} concentration (0.0-8.0 equiv) in 0.1 M HEPES buffer containing 0.1% CH_3OH (v/v), pH= 7.2, 25°C.

Binding assays were performed by using Job's method, which indicated a 1:1 stoichiometry for the interaction between **1** and Fe^{2+} (see Supporting Information, Figure S6). On the basis of the above spectrophotometric titrations, the detection limit of **1** was calculated to be 4.89 x 10^{-6} M (Figure S7). Moreover, the binding constant (Ka) of **1** with Fe^{2+} was determined to be 4.77 x 10^3 M^{-1} (Figure S8).

On the other hand, **1** (1.30 x 10^{-5} M) was practically nonluminescent under the given conditions [0.1 M HEPES buffer containing 0.1% CH_3OH (v/v), pH= 7.2, 25°C]. The metal cation complexing properties of **1** were investigated by spectrophotometric titrations with different metal cations. It was found that the addition of Ag^+, Al^{3+}, Au^{3+}, Cd^{2+}, Co^{2+}, Cu^+, Cu^{2+}, Fe^{2+}, Fe^{3+}, Hg^{2+}, K^+, Li^+, Mn^{2+}, Mg^{2+}, Na^+, Ni^{2+}, Pb^{2+}, Pt^{2+} and Pd^{2+} ions (1.0 equiv) did not induce any significant change in the emission profile of **1** (Figures 3 and 4). However, the emission intensity of **1** (1.30 x 10^{-5} M) was dramatically increased upon addition of Zn^{2+} ions (1.0 equiv) (turn-on).

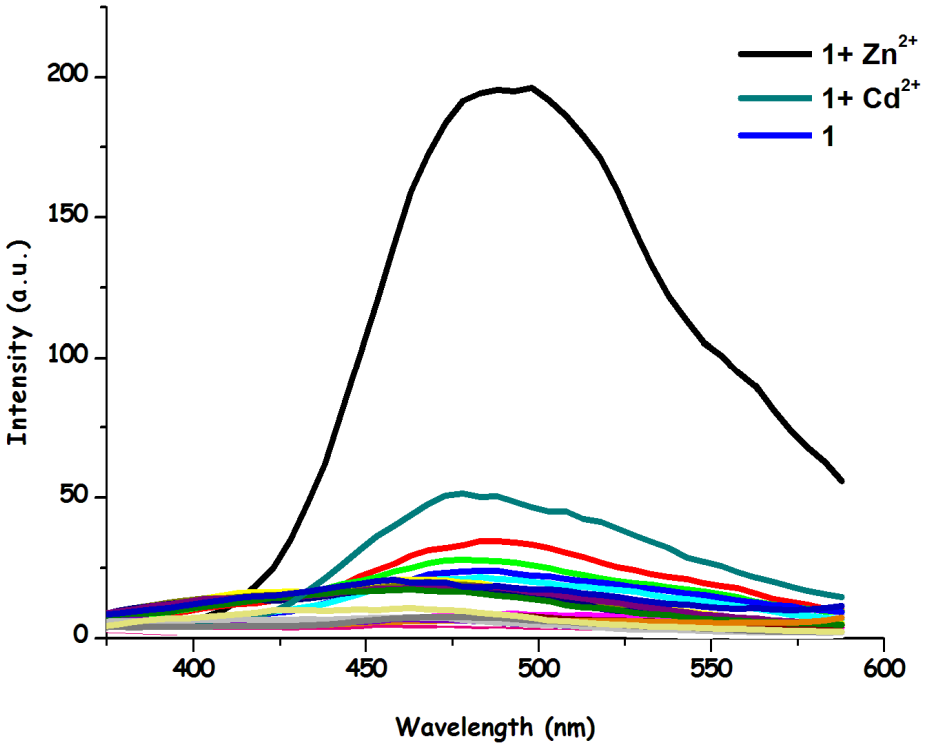


Figure 3. Fluorescence spectrum of compound **1** (1.30 x 10^{-5} M) with various metal ions (Ag^+, Al^{3+}, Au^{3+}, Cd^{2+}, Co^{2+}, Cu^+, Cu^{2+}, Fe^{2+}, Fe^{3+},

Hg^{2+}, K^{+}, Li^{+}, Mn^{2+}, Mg^{2+}, Na^{+}, Ni^{2+}, Pb^{2+}, Pt^{2+}, Pd^{2+} and Zn^{2+}) (1.0 equiv) in 0.1 M HEPES buffer containing 0.1% CH_3OH (v/v), pH= 7.2, 25°C, λ_{exc}=308 nm. Inset: Color of **1** (1.30 x 10^{-5} M) in the absence and presence of Zn^{2+} ions under UV illumination (365 nm) in 0.1 M HEPES buffer containing 0.1% CH_3OH (v/v), pH = 7.2, 25°C.

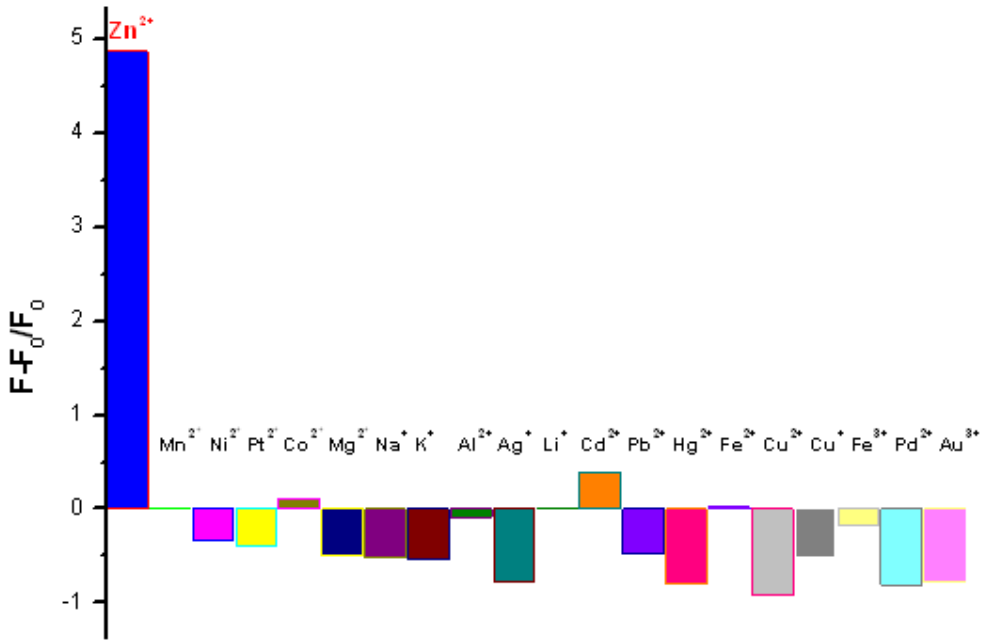


Figure 4. Relative fluorescence spectral changes for **1** (1.30 x 10^{-5} M) with various metal ions (1.0 equiv) in 0.1 M HEPES buffer containing 0.1% CH_3OH (v/v), pH= 7.2, 25°C, λ_{exc}=308 nm.

Figure 5 shows the fluorescence spectral changes of **1** (1.30 x 10^{-5} M) as a function of Zn^{2+} concentration in 0.1 M HEPES buffer containing 0.1% CH_3OH (v/v, pH= 7.2) at room temperature. It is important to note that a

progressive increase in the fluorescence emission intensity at 498 nm was observed as the concentration of the ion was increased. Chromogenic and fluorogenic responses of **1** to Fe^{2+} and Zn^{2+} ions, respectively, were depicted in Figure S9.

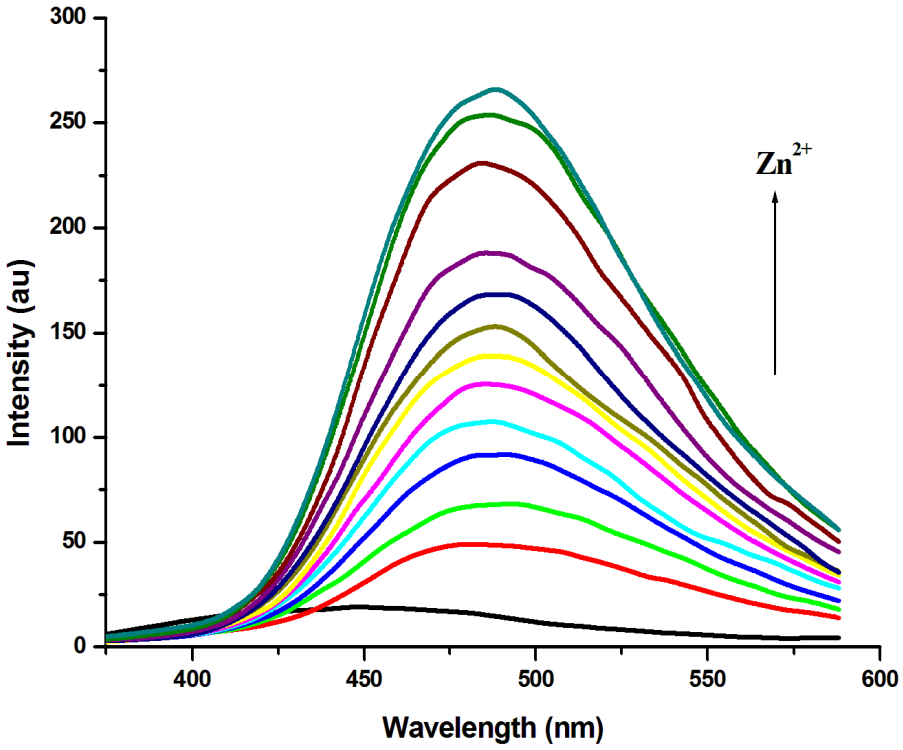


Figure 5. Fluorescence spectrum of compound **1** (1.30 x 10^{-5} M) as a function of Zn^{2+} concentration (0.0, 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 1.0, 2.0, 3.0, 4.0 equiv) in 0.1 M HEPES buffer containing 0.1% CH_3OH (v/v), pH= 7.2, 25°C, λ_{exc}=308 nm.

Clearly, the changes in the emission profile of **1** upon addition of Zn^{2+} ions indicated the formation of a well-defined complex between **1** and Zn^{2+}. Upon binding of Zn^{2+} ions to **1**, the fluorescence emission intensity of the imidazophenanthroline unit was dramatically increased probably by blocking PET between imidazophenanthroline and phenyl boronic acid units. It is reasonable to assume that both the HOMO and LUMO energy levels of the metal-bound form of the ligand **1** disfavors PET when compared to the metal-free state, thus providing efficient radiative decay of the excited state. Interestingly, evaluation of Job plot for the determination of the stoichiometry of the interaction between **1** and Zn^{2+} revealed a 1:2 ratio (see Supporting Information, Figure S10). Remarkably, the formation of the complex between **1** and Zn^{2+} was also evidenced by ^{1}H NMR (Figure S11). It was found that all the proton signals of **1** showed down field shifts between 0.03 and 0.40 ppm due to the interaction with Zn^{2+} (Figure S12). Furthermore, MALDI TOF MS analysis proved the formation of the complex between **1** and Zn^{2+}. Figure S13 depicts MALDI TOF MS spectrum of **1**+Zn^{2+} complex, which indicated the presence of three hydrated form of the complex with an $[M^{+}]$ ion peak (*m/z*) of 458.925.

Finally, the reversibility of the fluorogenic response of **1** to Zn^{2+} ions was tested by titration of **1**+Zn^{2+} complex with EDTA, which is known as a strong chelator for Zn^{2+}. It was noticed that the fluorescence emission of complex (Figure 6, red line) is turned off by the addition of EDTA into a

solution of complex (Figure 6, green line) in 0.1 M HEPES buffer containing 0.1% CH_3OH (v/v), pH = 7.2, 25°C. However, the emission intensity is reconfigured almost to the original state after addition of Zn^{2+} ions to this mixture (Figure 6, blue line). These results clearly suggests that the fluorogenic response of **1** to Zn^{2+} ions is completely reversible. Furthermore, competition experiments indicated that **1** (5.20 x 10^{-5} M) is still responsive to Zn^{2+} (10 equiv) even in the presence of other competing ions (10 equiv) albeit with lower emission intensity (Figure S14).

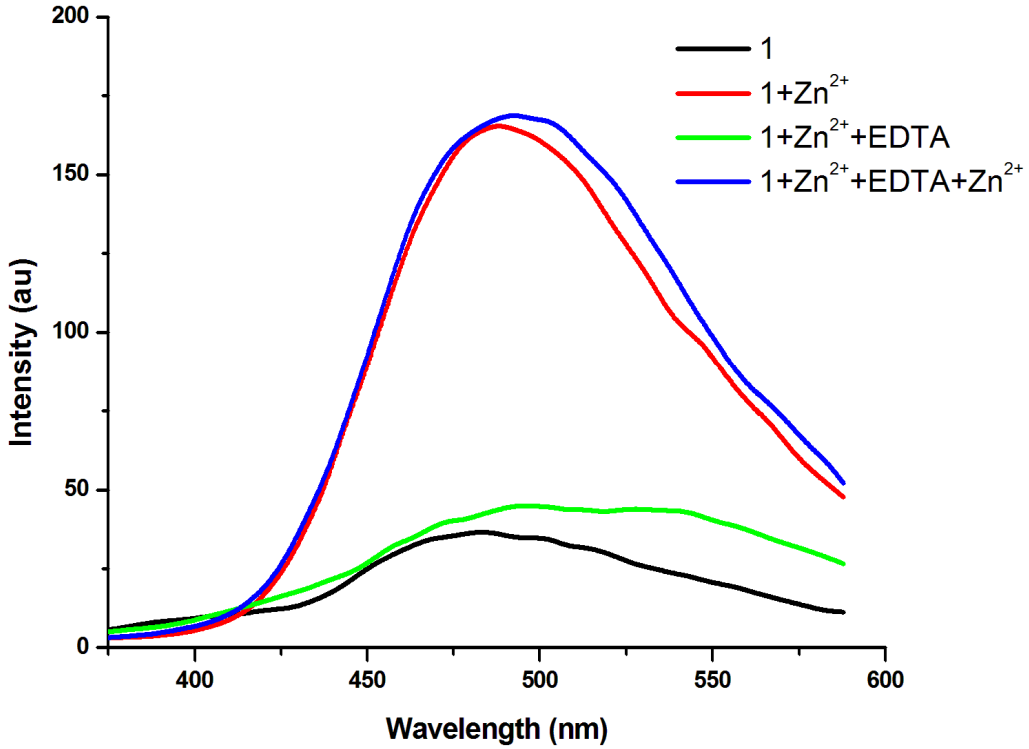


Figure 6. Fluorescence emission spectra of **1** (1.30 x 10^{-5} M) in the absence and presence of Zn^{2+} (1 equiv) or EDTA (1 equiv) in 0.1 M HEPES buffer containing 0.1% CH_3OH (v/v), pH = 7.2, 25°C, λ_{exc}=308 nm.

On the basis of the above spectrofluorimetric titrations, the detection limit[6-7] of **1** was calculated to be 6.74 x 10^{-7} M (Figure S15). Furthermore, the binding constant (Ka) of **1** with Zn^{2+} was determined from the emission intensity data following the steady-state fluorometric method[6-8] in which I_0 referred to the fluorescence intensities of solutions of **1**. When $I_0/(I-I_0)$ is plotted against $[M]^{-1}$, K_a was calculated to be 1.50 x 10^5 from the ratio of intercept/slope with a good correlation coefficient (R=0.99695) (Figure S16).

4. Conclusions

In summary, the design, syntheses, optical and metal ion recognition features of a novel compound (**1**) are investigated. The compound is built on an imidazo-phenanthroline scaffold with phenyl boronic acid unit. It is noteworthy that **1** is not only a simple and selective metal ion probe, but also it is a promising dual channel responsive material. **1** can simultaneously induce chromogenic and fluorogenic responses to Fe(II) and Zn(II) ions, respectively. To our best knowledge, this is one of the rare examples of dual channel responsive probes that can be used for both visual detection of Fe^{2+} and turn-on fluorogenic detection of Zn^{2+}

ions simultaneously. Further work is currently underway in our laboratories.

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