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Ratiometric fluorescent determination of Zn(II): a new class of tripodal receptor using mixed imine and amide linkages

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ABSTRACT

We synthesized a novel receptor with a unique combination of sp^2 nitrogen (−CH=N−) and carbonyl groups from amide linkages. These two moieties are judiciously incorporated into the receptor design such that these sites simultaneous binding a metal ion may generate a stable five-member ring. The receptor has been used to selectively detect Zn^{2+} through changes in the fluorescence spectra. Upon Zn^{2+} binding with the receptor, the fluorescence band shifted to enhance fluorescence intensity, allowing ratiometric determination of Zn^{2+} concentration.

1. Introduction

Transition metal ions are an interesting paradox in life.[1] They can be both integral enzyme components necessary for biological activity,[2] and toxic to human life, flora, and fauna. Zinc is one of many transition metal ions necessary for life, and is the second most abundant transition metal ion, after Fe^{2+} or Fe^{3+}, in humans and other mammals.[3] Zn^{2+} plays vital roles in cellular metabolism, neurotransmission, signal transduction and gene expression.[4] Misregulated Zn^{2+} concentrations have been associated with physical growth retardation and neurological disorders, such as cerebral ischemia and Alzheimer's disease.[5]

Developing a chemosensor to estimate Zn^{2+} concentration is important. Fluorescent chemosensors are particularly interesting because of their sensitivity.[6] The design of a Zn^{2+} chemosensor must fulfill some basic criteria: (i) The sensor must have a linear relationship between fluorescence intensity and Zn^{2+} concentration across a broad range of Zn^{2+} concentrations.[7] (ii) The sensor should be selective for Zn^{2+}, not responding to other biological metal ions, and should not be perturbed by the environment.[8] (iii) The sensor should respond quickly, i.e., Zn^{2+} should complex with the coordination sphere quickly and stably.[6c,9] The sensor design is crucial because Zn^{2+} is spectroscopically and magnetically silent due to its $3d^{10}4s^0$ configuration.[10] Many of these qualities have been addressed in several reported Zn^{2+} chemosensors. However, most of these sensors have limited selectivity, and many change intensities at a single wavelength.[11] Measuring at a single wavelength suffers from further errors due to receptor concentration, photobleaching and environmental effects. Alternatively, using the ratio of fluorescence intensity at two wavelengths, or ratiometric fluorescent determination, eliminates these errors, but can only offered by sensors that show shift emission bands upon binding with analytes.

The present investigation aimed to develop a highly sensitive and selective ratiometric chemosensor that works across a wide range of Zn^{2+} concentrations, including low concentrations. Although many Zn^{2+} selective receptors have been reported, few ratiometrically determine Zn^{2+} concentrations.[12] Due to poor design, several of these sensors, mainly di-2-picolylamine (DPA), polyamines, iminodiacetic acid, bipyridine, quinoline, or Schiff-bases, suffer from interference from first row transition metal ions, such as Fe^{2+}, Co^{2+}, Cu^{2+}, etc.[13] These binding sites have similar binding affinities for multiple transition metal ions. The binding sites in this study are based upon X-ray crystallographic analysis of many zinc enzymes.[14] These structures can be used to map out the preferred coordination sphere of Zn^{2+}. The resulting coordination spheres can be broadly categorized as catalytic, cocatalytic, and structural. These categories are sufficient to draw conclusions on the structural identities of zinc binding sites. Imidazole nitrogens, carboxylate oxygens, and cysteine thiols predominate as ligands in catalytic, cocatalytic, and structural sites, respectively.[15] Thus, we

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incorporated a unique combination of sp^2 nitrogens (–CH=N–) and carbonyl groups from amide linkages into our receptor design. Upon these two sites simultaneous binding Zn^{2+} metal ions, a stable five-membered chelate ring forms.[16] Additionally, Zn^{2+} is a border line case in HSAB principle.[17] sp^2 nitrogen is relatively soft, while the carbonyl group is harder binding site. Thus, this unique combination of imine and amide linkages in –CH=N–NH–C(O)– framework could serve our purposes.

2. Results and discussion

Tripodal receptor **5** was synthesized as shown in Scheme 1. Tripodal aldehyde **3** was synthesized as described in the literature.[18] The required receptor **5** was prepared in 98% yield by the condensation of tripodal aldehyde **3** with benzoic hydrazide **4**. The formation of imine linkages was determined from the singlet signal at 8.81 ppm in the ^1H NMR spectrum of compound **5**. To establish the role of tripodal framework to recognize Zn^{2+}, compound **7** was designed and synthesized. The compound **7** has the same type of binding sites as the tripodal receptor **5**.

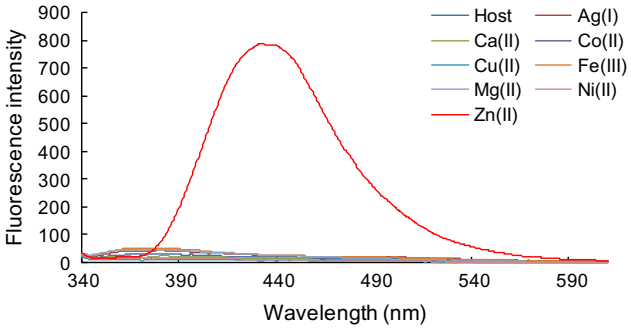
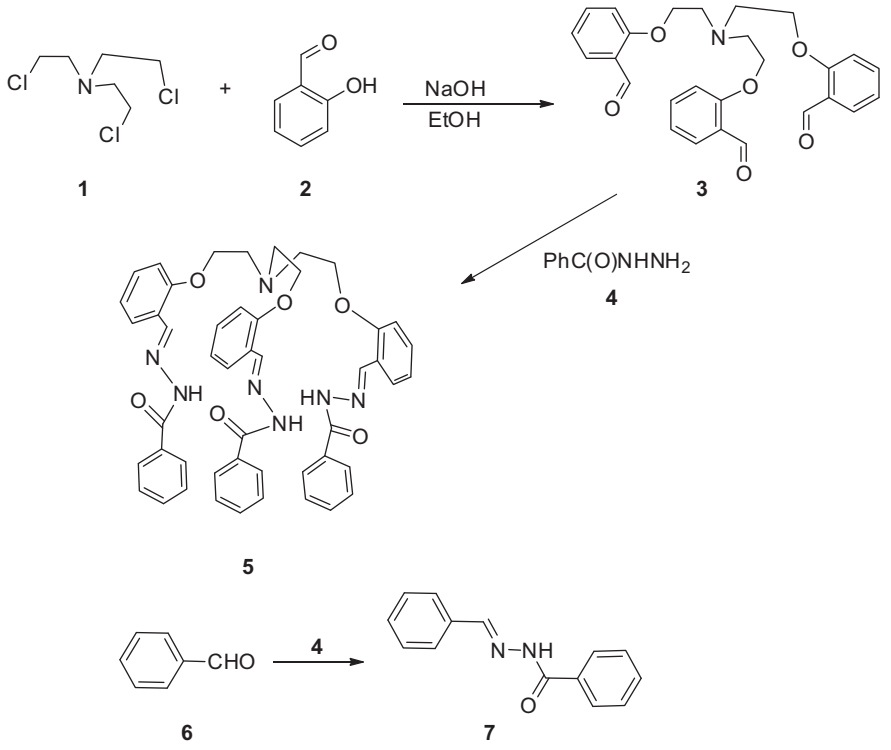


Figure 1. Changes in fluorescence intensity of receptor **5** (10 μM) upon adding particular metal ions (40 μM) in CH_3CN/DMSO=99:1 (λ_{ex}=323 nm).

This enhanced fluorescence intensity in the new band seems to be due to combination of structural rigidity of the metal complex and metal binding close to the fluorophore. These factors might also cooperate to induce the emission band shift. The



Scheme 1.

The photophysical properties of **5** were investigated in CH_3CN/DMSO (99:1, v/v). Receptor **5** displayed a characteristic UV–vis spectrum with three bands at λ_{max}=284, 298, and 323 nm (Fig. S2). The band at λ_{max}=323 nm was designated as an intraligand charge transfer transition in the molecule due to imine linkages. Upon excitation of receptor **5** (10 μM in CH_3CN/DMSO (99:1, v/v)) at λ_{max}=323 nm, the fluorescence spectrum of receptor gives emission at λ_{max}=370 nm.[19a] The binding properties of receptor **5** were evaluated toward various metal ions, such as Ca^{2+}, Mg^{2+}, Fe^{3+}, Co^{2+}, Ni^{2+}, Cu^{2+}, Zn^{2+}, and Ag^{+} (Fig. 1). Upon adding 40 μM Zn^{2+} solution to 10 μM receptor **5**, the emission intensity at λ_{max}=370 nm decreased and a new red-shifted emission band at λ_{max}=432 nm appeared, which increased by more than 40-fold. This is reasonably good brightness to consider this receptor a Zn^{2+} sensor. The other metal ions (as nitrate salts) revealed no such shift in the emission band under the same conditions.

imine linked free sensor may undergo cis–trans isomerism, giving weak fluorescence intensity due to the non-radiative decay of the excited state.[19b–f] Metal binding with the sp^2 nitrogen donor (–CH=N–) hinders this freedom, and consequently blocks the route of non-radiative decay, resulting in enhanced fluorescence. The metal binding close to the fluorophore changes the ICT band.[20a] Receptor **5** binding with Zn^{2+} showed a change in its UV–vis spectrum (Fig. S2) demonstrating the binding of Zn^{2+} in the ground state of the receptor, which also authenticates the shift in CT band.[20b] Thus, the red-shift along with enhanced fluorescence results from two operations. The metal binding modulates fluorescence intensity at two bands. Therefore, receptor **5** can be used for ratiometric fluorescent determination of Zn^{2+}. The ratiometric response of receptor **5** toward the surveyed metal ions is displayed in Figure 2. The results show a highly selective response to Zn^{2+} ions.

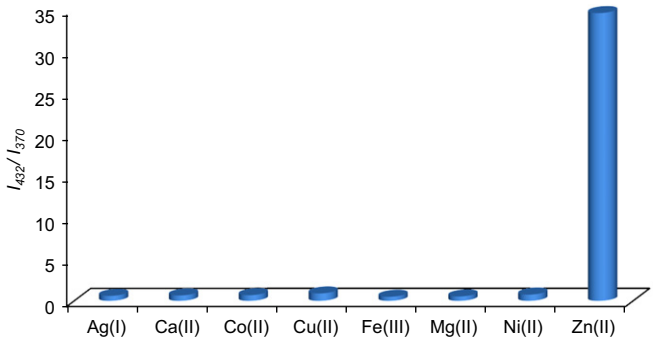


Figure 2. Ratiometric fluorescence (I_{432}/I_{370}) response of receptor **5** (10 μM) upon adding a particular metal salt (40 μM) in CH_3CN/DMSO=99:1.

To evaluate the role of an array of binding sites available in tripodal receptor **5**, receptor **7** was designed and synthesized. Receptor **7** resembles a single pod of receptor **5**. Similar to receptor **5**, receptor **7** displayed a fluorescence emission band at λ_{max}=350 nm at 30 μM in CH_3CN/DMSO (99:1, v/v) upon excitation at λ_{max}=292 nm. For these experiments, we used 30 μM receptor **7** to have approximately equal binding sites as 10 μM receptor **5**. The binding properties of receptor **7** were evaluated toward various metal ions. As expected, adding 40 μM Zn^{2+} ions to 30 μM receptor **7** neither shifted any emission band nor enhanced fluorescent intensity. These experiments clearly authenticate the role of judicial binding in a tripodal framework. In other words, the binding sites in receptor **5** not only provide appropriate binding but also structural rigidity or organization in the pseudocavity.

To gain additional insight into applications for receptor **5** as a Zn^{2+} sensor, a titration was performed as shown in Figure 3. Figure 3 shows the changes in the fluorescence spectrum pattern of receptor **5** upon continuously adding Zn^{2+} ions. The titration shows that continuously adding Zn^{2+} ions to 10 μM receptor **5**, decreased the emission band intensity at λ_{max}=370 nm, while the intensity at λ_{max}=432 nm gradually increased. The titration showed another point at which the fluorescence intensity increased at low Zn^{2+} concentrations and reached a plateau at 40 μM Zn^{2+}. Thus, receptor **5** is very sensitive, and even 2.0 μM Zn^{2+} modulates fluorescence intensity. Moreover, complex formation does not take much time, as all these spectra were recorded immediately after mixing Zn^{2+}. Figure S1 shows the ratiometric response of receptor **5** for Zn^{2+}. The linearity of this graph indicates that the sensor can be used along a specific range of Zn^{2+} concentrations with detection limit as low as 0.9 μM Zn^{2+}.[21] Based on the Benesi–Hildebrand plot, the K_a of receptor **5** for Zn^{2+} was (1.9±0.2)×10^4 M^{-1} (Fig. 4).[22]

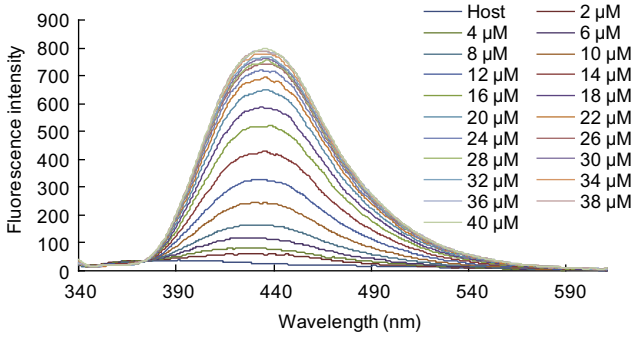


Figure 3. Fluorescence spectra changes of receptor **5** (10 μM) upon adding $Zn(NO_3)_2$ in CH_3CN/DMSO=99:1 (λ_{ex}=323 nm).

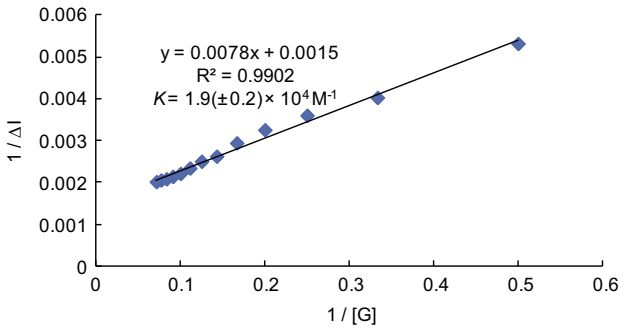


Figure 4. Benesi–Hildebrand plot to determine the stability constant of Zn^{2+} with receptor **5**.

To determine the binding pattern of receptor **5** with Zn^{2+} we began with the stoichiometry of the complex. Continuous variation methods were used to determine the stoichiometric ratios of receptor **5** and Zn^{2+}.[23] Figure 5 shows Job's plot of the fluorescence intensity of free receptor **5** and the intensity of the system with the molar fraction of the host {[*H*]/([*H*]+[*G*])} for a series of solutions in which the total host and Zn^{2+} concentrations were constant and the molar fraction of host continuously varied. The results illustrate that the plot approaches a maximum when the molar fraction of host is about 0.5, meaning that Zn^{2+} forms a 1:1 complex with receptor **5**.

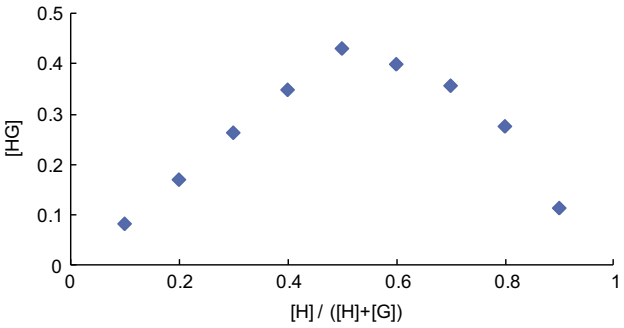


Figure 5. Job's plot between receptor **5** and Zn^{2+}. The [HG] concentration was calculated by the equation [HG]= $\triangle I/I_o \times [H]$.

The exact binding mode was established by ^{1}H NMR while titrating receptor **5** with Zn^{2+} ions (Fig. 6). Upon adding 0.5 equiv of Zn^{2+} ions to receptor **5**, the ^{1}H NMR signals of –CH=N– and –NH–C(O)– showed downfield and upfield shifts, respectively. The methylene (–CH_2–) signals shifted downfield and split in two. Similarly, all signals corresponding to aromatic protons shifted. Adding the next equivalent also shifted the signals except for –CH=N–. At the end of the titration, the NH signal of –NH–C(O)– shifted by $\Delta\delta$=0.34 ppm and –CH=N– signals by $\Delta\delta$=0.04 ppm. The synchronized shifts in CH signal of –CH=N– and NH signal of –NH–C(O)– reveal that these binding sites are participate for coordinating to Zn^{2+} in the receptor pseudocavity.

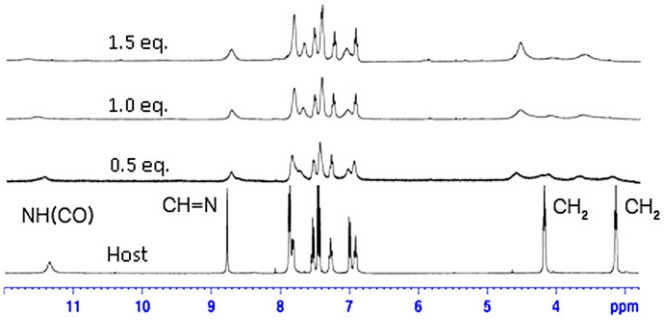


Figure 6. Family of ^{1}H NMR spectra of receptor **5** upon adding Zn^{2+} ions in DMSO-d_6.

Every attempt failed to obtain a single crystal of the complex; this limited us to comment on the exact structure of the complex and the conformation of amide moiety. We performed MacroModel calculations for the binding mode of receptor **5** with Zn^{2+} (Fig. 7).[24] The calculated structures support our hypothesis that the imine and amide linkages are responsible for Zn^{2+} coordination as demonstrated by NMR studies and these binding sites are projected toward the metal ion in the energy minimized Zn^{2+} complex of receptor **5**. The energy minimized calculations also reveal that the C=N bonds exist in *E* configuration and the rotamers with respect to the carbon–nitrogen hydrazide bond are in *Z* conformation in the complex formed.[25]

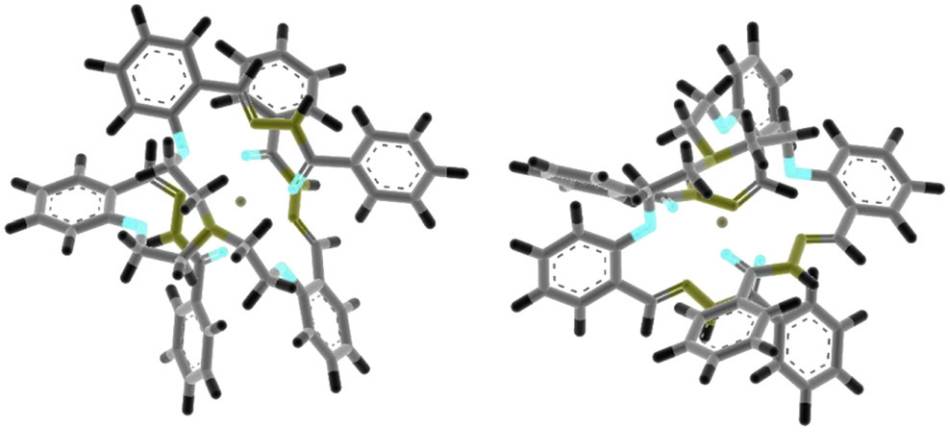


Figure 7. Energy minimized structure of Zn^{2+} complex with receptor **5** as obtained by MacroModel calculation (two views of the same metal complex).

Finally, we analyzed the utility of receptor **5** as a Zn^{2+} sensor in a competitive medium, a medium that contains other metal ions (Fig. 8). In these experiments, fluorescence intensity was measured in a series of solutions containing receptor **5**, with different amounts of Zn^{2+} and other metal ions all at the same concentration. The fluorescence intensity was almost identical to that in the absence of other metal ions. Therefore, receptor **5** is highly selective for, and can be used to recognize Zn^{2+}.

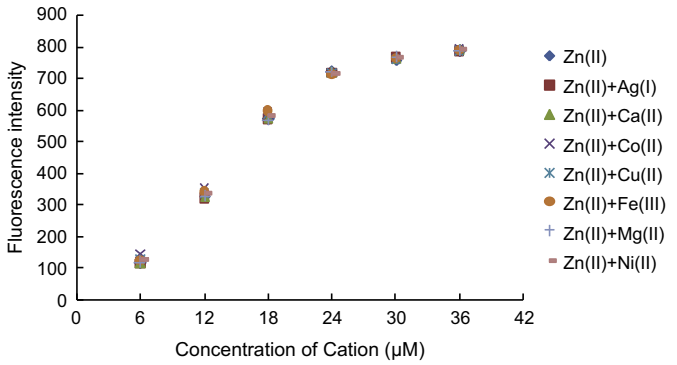


Figure 8. Estimating Zn^{2+} ions with receptor **5** (10 μM) in the presence of equimolar metal ions in CH_3CN/DMSO (99:1, v/v) at 432 nm.

3. Conclusions

A novel receptor has been synthesized to determine Zn^{2+} concentrations. The receptor has the unique combination of sp^2 nitrogen (−CH=N−) and carbonyl groups from amide linkages that provide perfect binding sites for Zn^{2+}. Upon Zn^{2+} binding with receptor **5**, the fluorescence band shifted and increased in intensity. Therefore, receptor **5** can be used to ratiometrically determine Zn^{2+} concentration. The receptor is selective for Zn^{2+} even in competition with other metal ions.

4. Experimental section

4.1. General information

All solvents were dried by standard methods. Unless otherwise specified, chemicals were purchased from commercial suppliers, and used without further purification. TLC was performed on glass sheets pre-coated with silica gel (Kieselgel 60 F_{254}, Merck). The ^1H and ^{13}C NMR spectrum were performed in DMSO-d_6 with TMS as an internal reference on a Bruker 400 NMR spectrometer, which operated at 400 MHz for ^1H and 100 MHz for ^{13}C nuclei. The chemical shifts were reported as δ values (ppm) relative to TMS. The CHN analyses were obtained on a CE Instrument EA1110. The fluorescence measurements were performed on a Perkin–Elmer LS55 Luminescence Spectrometer.

4.2. Synthesis of compound 5

A solution of 2,2′,2″-((nitrilotris(ethane-2,1-diyl))tris(oxy))tribenzaldehyde (100 mg, 0.22 mmol) in THF (10 mL) was added to benzoic hydrazide (103 mg, 0.76 mmol) and a catalytic amount of $Zn(ClO_4)_2$ in MeOH (10 mL) under argon at room temperature. After stirring for 3 h at room temperature, a precipitated solid was filtered and washed with THF and MeOH, yielding 176 mg (98%) of compound **5**: White solid; mp: 254∼257 °C, ^1H NMR (400 MHz, DMSO-d_6): δ 3.15 (t, 6H, J=5.2 Hz, CH_2), 4.20 (t, 6H, J=5.2 Hz, CH_2), 6.95–6.98 (m, 3H, Ar), 7.07–7.10 (m, 3H, Ar), 7.27–7.31 (m, 3H, Ar), 7.47–7.50 (m, 6H, Ar), 7.55–7.59 (m, 3H, Ar), 7.83–7.87 (m, 9H, Ar), 8.81 (s, 3H, CH=N), 11.82 (br, 3H, −NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 53.8, 67.1, 112.9, 120.8, 122.7, 125.7, 127.6, 128.4, 131.4, 131.7, 133.5, 143.5, 157.0, 163.1. Anal. Calcd for $C_{48}H_{45}N_7O_6$: C, 70.66; H, 5.56; N, 12.02. Found C, 70.68; H, 5.57; N, 11.99.

4.3. Metal binding studies

Metal binding ability of receptor **5** was performed using 10 μM of receptor **5** in CH_3CN/DMSO (99:1, v/v). Measuring flasks each contained 10 μM of receptor **5** along with varied amounts of a particular salt in CH_3CN/DMSO (99:1, v/v). The solutions were kept at 25±1 °C for 3 h, and were shaken occasionally. Fluorescence spectra were recorded with excitation at 323 nm.

4.4. Stability constant determination

The stability constant of receptor **5** with zinc was determined by preparing solutions containing 10 μM of receptor **5** and varying

amounts (0–40 μM) of zinc salt in CH_3CN/DMSO (99:1, v/v). The emission was measured at 432 nm.

4.5. Stoichiometry determination

Mixtures of receptor–zinc salt were prepared at 1:9, 2:8, 3:7, 4:6, 5:5, 6:4, 7:3, 8:2, 9:1. These solutions were kept at 25±1 °C before recording their spectra. The plot of [HG] versus $[H]/[H]+[G]$ was used to determine the stoichiometry of the complex. [HG] was calculated by the equation $[HG]=\triangle I/I_o\times[H]$.

4.6. Competitive Zn^{2+} binding

Solutions were prepared containing receptor **5** (10 μM) and equimolar interfering metal ions and Zn^{2+} ions (6, 12, 18, 24, 30, and 36 μM). The fluorescence intensity of each solution was recorded at 432 nm.

Acknowledgements

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Supplementary data

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.tet.2010.08.024. These data include MOL files and InChIKeys of the most important compounds described in this article.

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