

Multimode Selective Detection of Mercury by Chiroptical Fluorescent Sensors Based on Methionine/Cysteine

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ABSTRACT Two multimode Hg(II) sensors, L-MethBQA and L-CysBQA, were obtained by fusing methionine or S-methyl cysteine, into a bis-quinolyl amine-based chiral podand scaffold. Quinolyl groups serve as the fluorophore and possess nitrogen lone pairs capable of chelating metal ions. On exposure to Hg²⁺ or Zn²⁺, these sensors show signal enhancement in fluorescence. However, Cu²⁺ quenches their fluorescence in 30:70 acetonitrile/water. L-CysBQA complexes with Hg²⁺, producing an exciton-coupled circular dichroism spectrum with the opposite sign to the one that is produced by Cu²⁺ or Zn²⁺ complexation. L-CysBQA binds Hg²⁺ more strongly than Zn²⁺ and is shown to differentiate Hg²⁺ from other metal ions, such as Zn²⁺, Cu²⁺, Ni²⁺, and Pb²⁺, exceptionally well. The synergistic use of relatively soft sulfur, quinoline-based chiral ligands and chiroptically enhanced fluorescence detection results in high sensitivity and selectivity for Hg²⁺. *Chirality* 23:916–920, 2011. © 2011 Wiley-Liss, Inc.

KEY WORDS: mercury sensor; S-methyl cysteine; chiral; fluorescence; exciton-coupled circular dichroism

INTRODUCTION

Mercury is an extraordinarily malicious pollutant, which has been of particular environmental and health concern since the Minamata tragedy in the 1950s.¹ Although mercury is introduced into the ecosphere by geochemical processes, global mercury pollution has been rising mainly because of emissions from solid waste incineration and combustion of coal and mining. Mercury concentration is affected by atmospheric conditions including wet and dry deposits. It can be converted to highly toxic methyl mercury in soil and water,² which enters and accumulates in the food chain and reaches the human body mainly through seafood.^{3,4} Mercury poisoning causes serious long-term damage to the central nervous system and other organs.⁵

To curtail mercury contamination and to further understanding of the toxicology of mercury and help bring about remedies, significant effort has been devoted recently to developing powerful sensors for mercury.^{6–26} Mercury sensors need to be highly selective to prevent possible false positive signals from other metal ions.²⁷ They should also be very sensitive because even very low concentrations of mercury can do much harm. Fluorescent sensors have been pursued intensely due to the high sensitivity of fluorescence spectroscopy and microscopy. A number of “switch-on” fluorescent sensors, which are preferred to “switch-off” ones, for Hg²⁺ have been reported.^{15,28–30} However, many of these “switch-on” sensors are complicated by competing metal ions. It is critical to selectively detect mercury in the presence of other metal ions especially Zn²⁺, Pb²⁺, and Cu²⁺ due to their similar chemical properties/electronic configuration. The optical response of many mercury sensors is limited mainly to fluorescence and UV–vis and many metal ions might induce responses similar to mercury. To introduce extra handles in metal ion detection, there are some efforts in using chiroptical spectroscopy including circular dichroism (CD),^{31–33} sometimes in conjunction with fluores-

cence,^{34,35} to study metal complexation. It is not without precedence to influence the behavior of achiral metal ions by using chiral organic ligands.^{13,36,37} Here, we report a strategy wherein both isotropic absorption/emission (such as UV–vis and fluorescence) and anisotropic absorption (such as CD) signals from a single chiral sensor molecule not only detect Hg²⁺ but also differentiate it from multiple analytes.

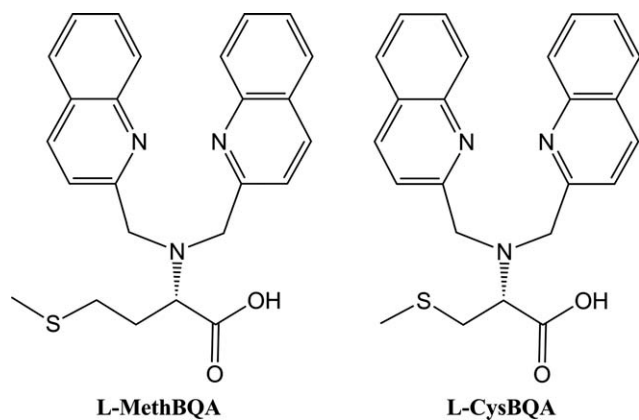
MATERIALS AND METHODS

The two sensors reported here (Scheme 1), (S)-N,N-bis(2-quinolylmethyl)methionine (L-MethBQA) and (R)-N,N-bis(2-quinolylmethyl)-S-methyl cysteine (L-CysBQA), were either a gift from Prof. Canary of NYU or synthesized following published protocols.^{38,39} Analytical grade HgCl₂, CuCl₂, ZnCl₂, Cu(ClO₄)₂, Zn(ClO₄)₂, Ni(ClO₄)₂, Pb(ClO₄)₂, and other reagents were obtained from commercial sources and used as received unless noted otherwise. Solvents (acetonitrile and water) used in spectroscopic studies are of spectrometric grades. Aliquots of 1 mM metal salt solution, 3 μL per addition, were titrated into 3 mL of 10 μM of sensor solution and mixed thoroughly before all spectra were taken. Electronic absorbance spectra were recorded on Beckman DU-640 spectrophotometer. CD spectra were acquired on an Aviv 212 CD instrument. Fluorescence measurements were performed on a Hitachi F-2500 spectrophotometer. Excitation wavelength (spectral bandwidth: 5 nm) was set at 300 nm and emission spectra (spectral bandwidth: 5 nm) between 320 and 500 nm were recorded. In all measurements, 1 cm quartz cells were used. All measurements were performed at 298 K.^{38,39}

RESULTS AND DISCUSSION

We prepared L-MethBQA and L-CysBQA by S_N2 reactions between 2 equiv. of 2-bromomethylquinoline and 1 equiv. of

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Scheme 1. Structures of L-MethBQA and L-CysBQA.

(L)-methionine methyl ester or (L)-S-methyl cysteine methyl ester followed by hydrolysis.^{38,40} In these sensors, we incorporated pyridine/quinoline-based binding sites, which have been reported to selectively recognize relevant heavy metals⁴¹ such as Hg^{2+} .²⁶ Chiral sulfur-containing^{14,15,23,25,28,29} binding motifs, such as the natural amino acids (L)-methionine and (L)-S-methyl cysteine, were incorporated into chiral podand scaffolds to generate these chiral fluorescent sensors for Hg^{2+} . Such tripodal ligands and their copper complexes have been reported as electron-driven chiroptical switches.^{32,38,40} Other chiral tripodal ligands have been widely used in asymmetric synthesis and chiral discrimination.^{38,42–44} Few have been used previously expressly for metal sensing⁴⁵ and none has been used for Hg^{2+} sensing.^{13,36,37} An advantage of using chiral tripodal ligands is that they form complexes with metal ions with defined configuration and their chirality can be utilized to control the stereochemistry of metal complexes.^{32,42,46} In addition, their metal complexes can yield more spectroscopic information such as CD, exciton-coupled CD, and fluorescence-detected CD on top of fluorescence change.³⁵ The fluorescence- and exciton-coupled CD properties of the complexes may provide data to identify a metal ion, support the binding mechanism and the specificity of the binding. The sensing of Hg^{2+} by L-MethBQA was initially investigated in acetonitrile. As shown

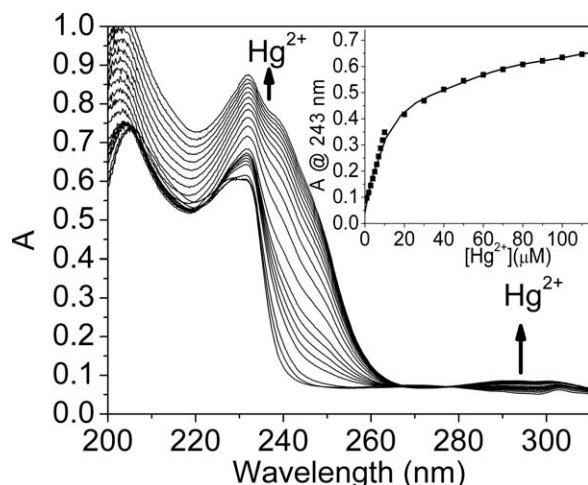


Fig. 1. UV-vis spectral response of 10 μM L-MethBQA to HgCl_2 in acetonitrile. Inset: Plot of absorbance at 243 nm against Hg^{2+} concentration.

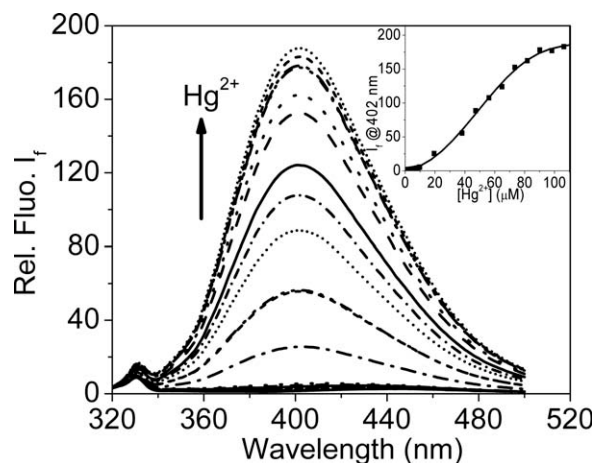


Fig. 2. Fluorescence (Ex: 300 nm) response of 10 μM L-MethBQA to HgCl_2 in acetonitrile. Inset: Plot of relative fluorescence intensity at 402 nm against Hg^{2+} concentration.

in Figure 1, addition of Hg^{2+} was accompanied by the increase of UV absorbance in the range of 200–268 nm and 277–320 nm. It exhibits “switch-on” fluorescence signaling behavior on exposure to Hg^{2+} , as is shown in Figure 2. Exposure to Zn^{2+} and Cu^{2+} in acetonitrile similarly results in fluorescence enhancement. L-CysBQA behaves similarly.

Titration of L-MethBQA with Hg^{2+} in acetonitrile was also monitored by CD spectroscopy (Figure 3). The sensor itself exhibits a negative Cotton effect (CE) around 234 nm. With the addition of Hg^{2+} , the amplitude of this CE gradually becomes smaller.

In acetonitrile, L-MethBQA and L-CysBQA shows linear response to different concentration ranges of Hg^{2+} when monitored by different spectroscopic tools such as UV-vis, fluorescence, and CD. It seems that complexation of Hg^{2+} to these sensors in a pure organic solvent such as acetonitrile might be very complicated and additional investigation is underway to further our understanding.

In order to optimize the conditions for practical applications in environmental and biological samples, sensing of mercury ions was investigated in an aqueous solvent that contains 30% acetonitrile aqueous (i.e., 30:70 acetonitrile/

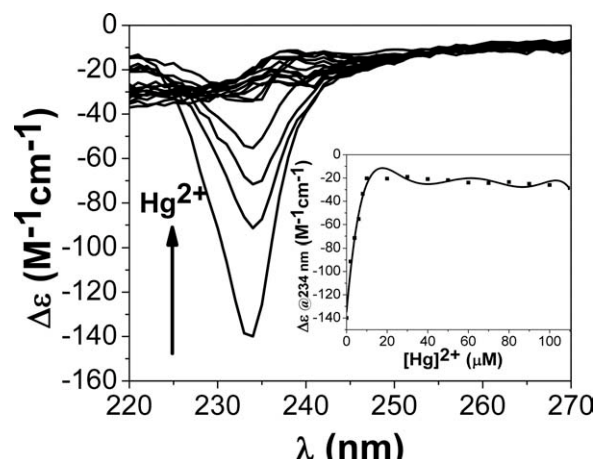


Fig. 3. Circular dichroism response of 10 μM L-MethBQA to HgCl_2 in acetonitrile. Inset: Plot of $\Delta\epsilon$ at 234 nm against Hg^{2+} concentration.

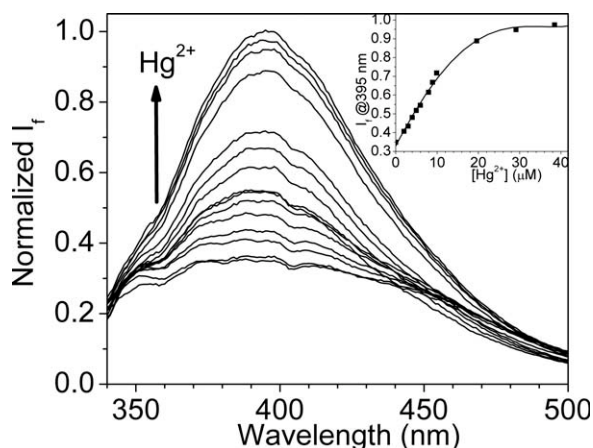


Fig. 4. Normalized fluorescence (Ex: 300 nm) response of 10 μM L-MethBQA to HgCl_2 in 30:70 acetonitrile/water. Inset: Plot of normalized fluorescence intensity at 395 nm against Hg^{2+} concentration.

water). L-MethBQA exhibits Hg^{2+} selective “switch-on” fluorescence signaling behavior in this aqueous solution (Figure 4). Its response is linear up to 1 equiv. of Hg^{2+} and rapidly saturates above 1 equiv. of Hg^{2+} (inset of Figure 4), indicating the formation of a 1:1 complex. The dissociation constant, K_d , is determined by nonlinear curve fitting of the fluorescence titration results and is found to be 3.8×10^{-6} M for the 1:1 complex of L-MethBQA- Hg^{2+} in this aqueous solvent. Zn^{2+} also enhances its fluorescence while Cu^{2+} quenches its fluorescence in this solvent (Figure 5). L-CysBQA behaves similarly, although its fluorescence enhancement on exposure to Hg^{2+} is not as large as that of L-MethBQA. Both Ni^{2+} and Pb^{2+} quench the fluorescence of L-CysBQA. The detection limits of both L-MethBQA and L-CysBQA are low enough for the detection of micromolar Hg^{2+} ions.

In addition, mercury sensing in 30:70 acetonitrile/water by these chiral fluorescent sensors was also monitored by UV-vis and CD. Although there are only very small changes in the UV-vis spectrum of L-CysBQA when it is titrated with HgCl_2 (Figure 6A), Hg^{2+} complexation with L-CysBQA induces significant changes in CD (Figure 6B). L-CysBQA shows a small positive CE in this aqueous solution. On addition of Hg^{2+} , a positive CE at 239 nm shows up, followed by a negative CE at 228 nm, which is characteristic of a positive exci-

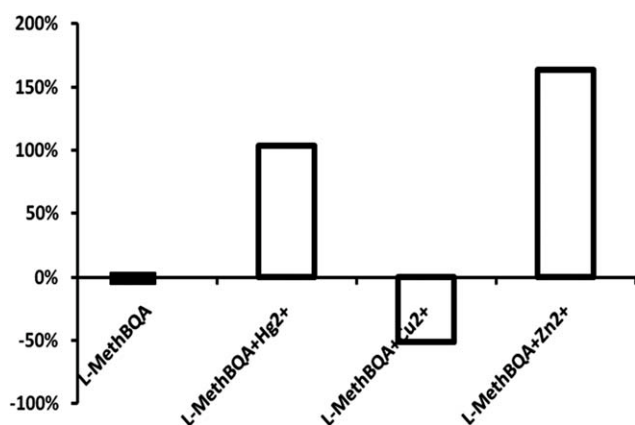


Fig. 5. Percentage of change in fluorescence intensity at emission maxima (Ex: 300 nm) when 10 μM L-MethBQA was exposed to 10 μM HgCl_2 , CuCl_2 and ZnCl_2 , respectively, in 30:70 acetonitrile/water.

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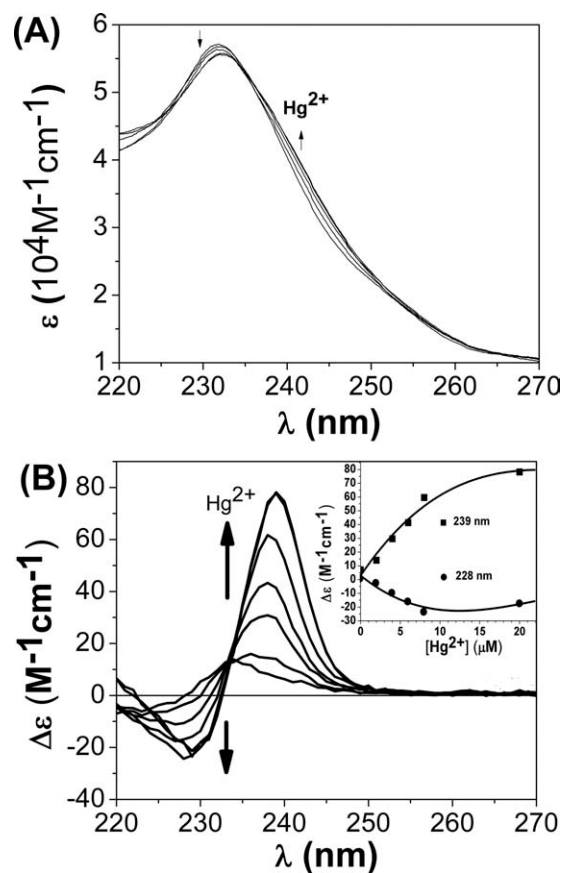


Fig. 6. (A) UV-vis response of 10 μM L-CysBQA to HgCl_2 in 30:70 acetonitrile/water. (B) Circular dichroism response of 10 μM L-CysBQA to HgCl_2 in 30:70 acetonitrile/water. Inset: Plot of (ϵ at 239 and 228 nm, respectively, against Hg^{2+} concentration.

ton couplet. The CD amplitudes at both 239 nm and 228 nm are linear to the concentration of the added Hg^{2+} until it reached 1:1 Hg^{2+} /L-CysBQA saturation, indicating the formation of a 1:1 complex. The dissociation constant, K_d , is determined by nonlinear curve fitting of the CD titration results and is found to be 4.7×10^{-7} M for the 1:1 complex of L-CysBQA- Hg^{2+} and 1.7×10^{-6} M for the 1:1 complex of L-CysBQA- Zn^{2+} in 30:70 acetonitrile/water. L-CysBQA binds

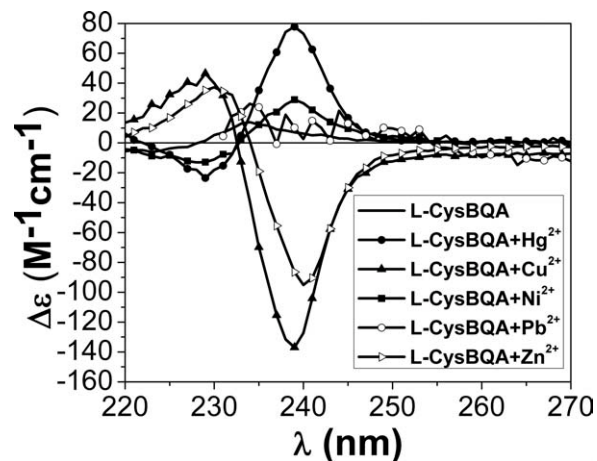


Fig. 7. Circular dichroism response of 10 μM L-CysBQA to 50 μM HgCl_2 , $\text{Cu}(\text{ClO}_4)_2$, $\text{Zn}(\text{ClO}_4)_2$, $\text{Pb}(\text{ClO}_4)_2$, $\text{Ni}(\text{ClO}_4)_2$ respectively, in 30:70 acetonitrile/water.

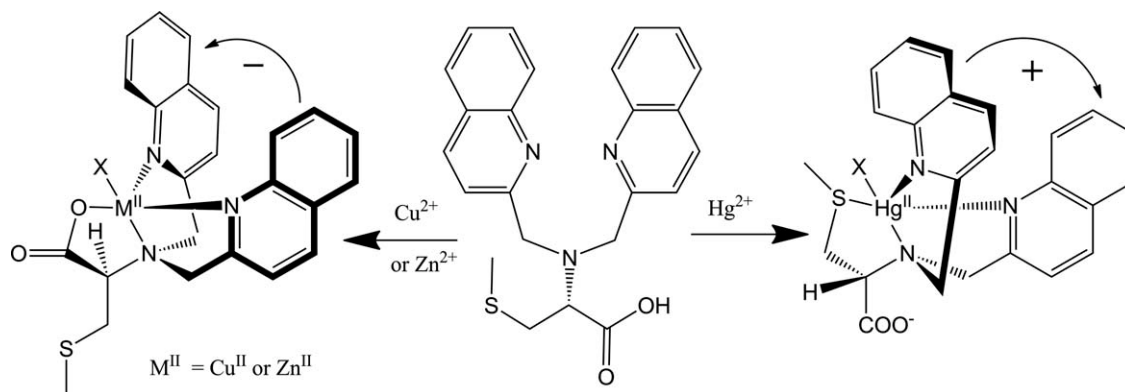


Fig. 8. (R)-*N,N*-Bis(2-quinolylmethyl)-*S*-methyl cysteine (L-CysBQA) complexes with $\text{Cu}^{2+}/\text{Zn}^{2+}$ and Hg^{2+} . The chiral center of the amino acid dictates the orientation of the quinoline chromophores via a gearing mechanism as illustrated. The transition dipoles in the quinolines in the two complexes invert in the sense of absolute orientation and therefore give opposite exciton coupled CD spectra.

Hg^{2+} more strongly than it binds Zn^{2+} in this aqueous solution. While the Hg^{2+} complex of L-CysBQA shows a positive couplet, its Cu^{2+} and Zn^{2+} complexes both show negative exciton couplets in this aqueous solvent (Figure 7). Ni^{2+} complexation with L-CysBQA induces a positive exciton-coupled CD, which is consistent with that of the Ni^{2+} -L-MethBQA complex.⁴⁷ While Pb^{2+} induces little change in CD signal, it does not produce exciton coupling. This remarkable differentiation of Hg^{2+} from Cu^{2+} and Zn^{2+} can be explained by the structures of the CD active products, which are illustrated in Figure 8. Tetradentate metalochelates form involving the Cu^{2+} ion, the tertiary amine, the two quinolines, and the carboxylate. The stereocenter of the *S*-methyl cysteine arm dictates the orientation of the quinoline groups by a “gear” with the methylenes of the achiral arms such that a propeller forms from the planar carboxylate and quinoline groups. The Hg^{2+} complex gives a propeller complex with the opposite configuration due to the preference of Hg^{2+} for coordination by the sulfur atom. As shown in Figure 8, for the sulfide to come proximal to the metal center, the amino acid arm must pivot about the C–N bond. This inverts the gearing, and therefore the orientation, of the quinoline moieties, leading to an exciton-coupled CD with

the opposite sign. Although crystals of L-CysBQA complexes with these metal ions has yet to be obtained, crystal structures of Zn^{2+} and Cu^{2+} complexes of L-MethBQA and other similar compounds, which show strong exciton-coupled CD in organic solvents, showed that these metal ions coordinate with the carboxylate instead of the sulfide.^{38,40,47,48} NMR spectra of the Cu^{+} complexes and other evidence demonstrated Cu^{+} -S coordination,^{38–40} which indicates that Hg^{2+} should coordinate the sulfur atom as like the soft Cu^{+} , the soft- Hg^{2+} should prefer the soft sulfur.

Figure 9 visually highlights metal ion sensing by the chiroptical fluorescent sensor L-CysBQA through both fluorescence enhancement and anisotropic absorption distinguish, for example, Hg^{2+} (enhanced fluorescence with strong positive exciton-coupled CD), Zn^{2+} (enhanced fluorescence and strong negative exciton-coupled CD), Cu^{2+} (strong negative exciton-coupled CD but quenched fluorescence), Ni^{2+} (strong positive exciton-coupled CD but quenched fluorescence), and Pb^{2+} (quenched fluorescence but no exciton-coupled CD). L-MethBQA offers similar advantages. These results further illustrate that recognition involving both isotropic and anisotropic detection tools may be utilized to maximize the information transmitted by a single sensor molecule.³⁴

CONCLUSIONS

In summary, we have reported the sensing capabilities of two multimode Hg^{2+} sensors, L-MethBQA and L-CysBQA. L-CysBQA binds Hg^{2+} are more strongly than Zn^{2+} . These chiroptical fluorescent sensors differentiate Hg^{2+} from other metal ions, such as Zn^{2+} , Cu^{2+} , Ni^{2+} , and Pb^{2+} , exceptionally well through a combinatorial fluorescence-exciton-coupled CD recognition. The synergistic use of relatively soft sulfur, quinoline based chiral ligands and chiroptically enhanced fluorescence detection results in high sensitivity and selectivity for Hg^{2+} .

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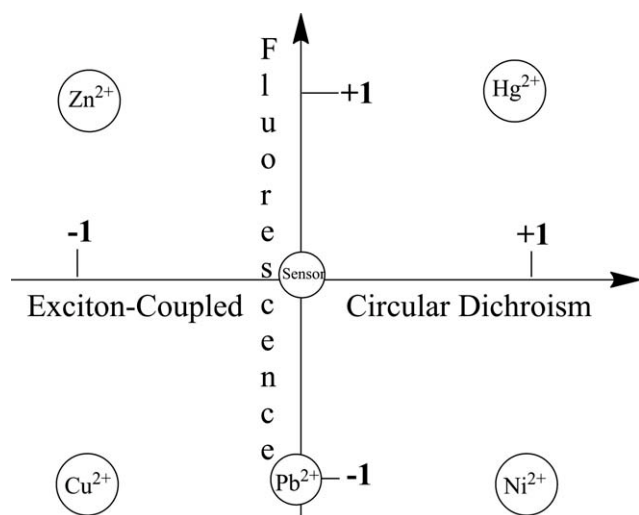


Fig. 9. Chiroptically enhanced fluorescence detection and differentiation of different metal ions by LCysBQA.

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