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Fluorogenic Hg^{2+}-Selective Chemodosimeter Derived from 8-Hydroxyquinoline

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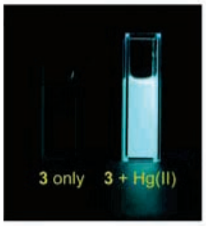
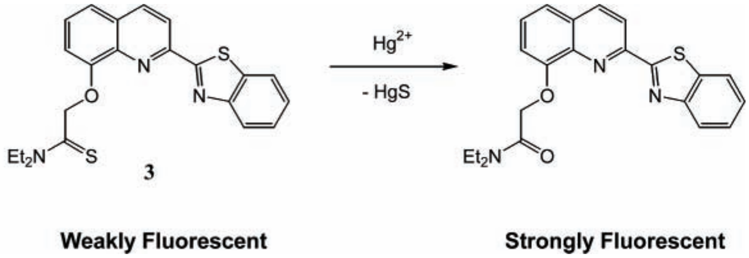
ABSTRACT





A new thioamide derivative of 8-hydroxyquinoline-benzothiazole was prepared, and its fluorogenic chemodosimetric behaviors toward transition-metal ions were investigated. The thioamide derivative showed highly Hg^{2+}-selective fluorescence enhancing properties (167-fold) in 30% aqueous acetonitrile solution. The selective and sensitive signaling behaviors were found to originate from the Hg^{2+} ion induced transformation of the very weak fluorescent thioamide derivative into a highly fluorescent amide analogue.

Development of selective chemosensors for the determination of transition- and heavy-metal ions is very important because they play important roles in living systems and have an extremely toxic impact on the environment.[1] A number of functional ionophores having optical and electrochemical sensing ability have been developed for the analysis of heavy-metal ions of Hg^{2+}, Pb^{2+}, and Cd^{2+}.[2] Among these, optical systems have been particularly attractive because of their sensitive and easy signal detection techniques. On the other hand, the chemodosimetric determination of chemically and biologically important species has also been attracting much research interest recently.[3] Typical examples of the metal ion determinations are Hg^{2+}-selective systems utilizing desulfurization reactions,[4] Cu^{2+}-selective transformation of rhodamine B hydrazide to rhodamine B,[5] and Hg^{2+} signaling by a regenerative chemodosimeter.[6] Also interesting for other important chemical species are the chromo-chemodosimeters for the determination of fluoride and sulfide anions[7] and the heterobimetallic donor−acceptor complex for the selective detection of cyanide, sulfhydryl-containing amino acids, and peptides.[8]

The 8-hydroxyquinoline (8-HQ) scaffold is one of the most widely employed molecular platforms to construct many unique ionophoric systems for the recognition of important metal ions,[9] such as Zn^{2+}, Al^{3+}, Fe^{3+}, and Hg^{2+}, as well as effective light-emitting devices.[10] Among many of the

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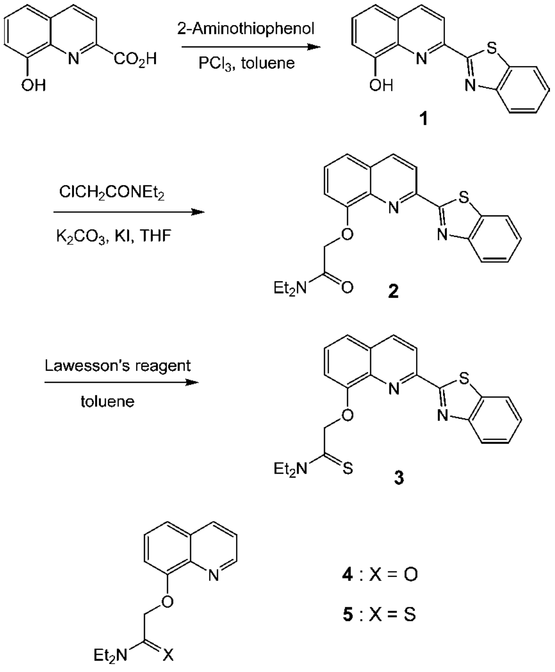
functional transformations, alkylation of the phenolic hydroxyl group of 8-HQ is plausible for the construction of more elaborate functional chemosensors. This might seem unfavorable because of the sacrifice of a very efficient ligating hydroxyl group. However, an extra binding site or signaling unit can be introduced at some well-defined periphery on the appending alkyl group. In this paper, we report on the synthesis and the fluorogenic signaling properties of a new 8-HQ derivative having extra binding sites of benzothiazole and thioamide groups. The thioamide derivative **3** showed a remarkably sensitive Hg^{2+}-selective fluorescence enhancement, which could be used for the chemodosimetric analysis of Hg^{2+} ions[11] in an aqueous environment.

The 8-HQ scaffold having an appended benzothiazole group was first modified by O-alkylation to introduce an amide group to the side chain, and the structure was further transformed into a thioamide derivative for the selective recognition of thiophilic metal ions such as Hg^{2+} and Cd^{2+} ions.[12] Benzothiazole derivative **1** was prepared by the reaction of 8-hydroxyquinoline-2-carboxylic acid with 2-aminothiophenol (PCl_3, toluene, 75%).[13] Reaction of the benzothiazole derivative **1** with *N*,*N*-diethyl chloroacetamide (K_2CO_3, KI, THF) afforded diethylamide **2** (63%). Thioamide **3** was prepared from the amide by the reaction with Lawesson's reagent in good yield (62%).[12a] 8-HQ-based derivatives **4** and **5** were also prepared as control compounds following similar procedures (Scheme 1).

It is well-known that the fluorescent behavior of 8-HQ itself is not strong.[14] However, the complexation with suitable metal ions or alkylation of the phenolic moiety generally resulted in a significant enhancement of the fluorescence intensity of the resulting compounds.[15] As expected, O-alkylated amide **2** exhibited a large enhancement of fluorescence compared to **1** itself (quantum yield of **2** = 0.38 in Tris buffered H_2O-CH_3CN (70:30, v/v) at pH 8.1). Interestingly, however, transformation of the amide function into a thioamide resulted in a very weak emission behavior. The thioamides are in general readily oxidized, and in the present system, the thioamide group might act as a strong intramolecular quenching entity for the 8-HQ-based fluorophore.[4a.]

Scheme 1. Synthesis of Chemodosimeter



First, the fluorescence behaviors of **2** and **3** in the presence of varying metal ions were surveyed. Among the solvent systems tested, aqueous acetonitrile was found to be well-optimized for the realization of selective signaling of a specific target metal ion of Hg^{2+}. To have a more optimized condition for the signaling of Hg^{2+} ions, the effects of water content on the metal ion selectivity were surveyed (Figure 1). In more realistic 100% aqueous solution, the fluorescence enhancements induced by the addition of Hg^{2+} ions were very sluggish and about 24 h was required to reach a stable signal. On the other hand, in a mixed solvent system of 30% aqueous acetonitrile, where more pronounced selectivity and

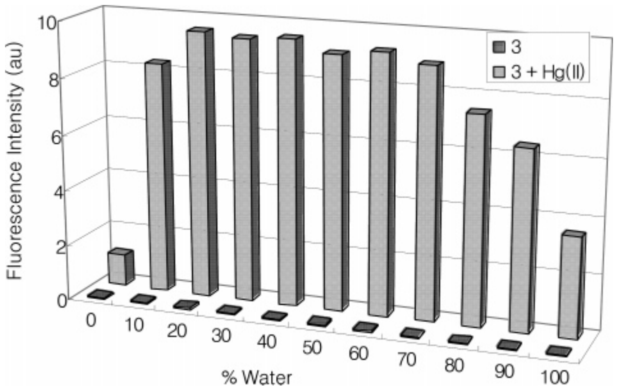


Figure 1. Effects of water content on the fluorescence intensity of **3** at 479 nm in the absence and presence of Hg^{2+} ions in aqueous acetonitrile solution. $[\mathbf{3}] = 5.0 \times 10^{-6}$ M, $[Hg^{2+}] = 5.0 \times 10^{-4}$ M. $\lambda_{ex} = 345$ nm. Buffered at pH 8.1 (Tris, 10 mM).

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degree of fluorescence enhancement were observed (Supporting Information, Figure S9), the signaling was completed within 5 min (Supporting Information, Figure S10a). On the basis of these, all the fluorescence signaling experiments were carried out in 30% aqueous acetonitrile solution (H_2O/CH_3CN = 70:30, v/v) buffered at pH 8.1 with Tris buffer.

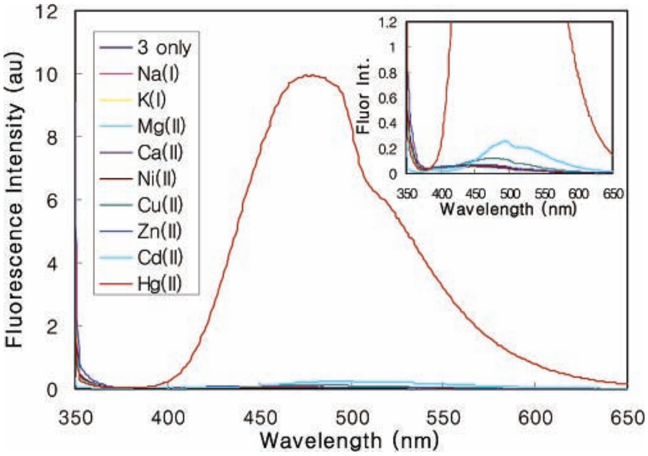


Figure 2. Fluorescence spectra of **3** in response to the metal ions. [**3**] = 5.0 × 10^{-6} M, [M^{n+}] = 5.0 × 10^{-4} M, in H_2O-CH_3CN (70:30, v/v). λ_{ex} = 345 nm. Buffered at pH 8.1 (Tris, 10 mM).

Thioamide **3** showed a very weak fluorescence centered around 475 nm in 30% aqueous acetonitrile solution (Supporting Information, Figure S11). Upon interaction with varying metal ions of alkali (Na^+, K^+), alkaline earth (Mg^{2+}, Ca^{2+}), and transition-metal ions (Ni^{2+}, Cu^{2+}, Zn^{2+}, Cd^{2+}, Hg^{2+}), only Hg^{2+} ions induced a sizable enhancement in fluorescence intensity (Figure 2). The enhancement was so effective that with only 1 equiv of Hg^{2+} ions the fluorescence intensity at 479 nm increased 167-fold with a moderate shift in the emission maximum from 468 to 479 nm. Other representative metal ions, except for the slightly responding Cd^{2+} ions (3.8-fold increase, inset of Figure 2), revealed almost insignificant responses with a relatively constant fluorescence enhancement factor of less than 2.0-fold. The fluorescence behaviors of the possibly interfering Ag^+ and Pb^{2+} ions were also measured by treating more dilute solutions (10 equiv) due to slight precipitate formation, and no significant interferences were confirmed (Supporting Information, Figure S12). To check the time-dependent effects of other possibly interfering metal ions, the time course of the fluorescence changes was followed. In addition to Hg^{2+} ions, Cd^{2+} ions also induced somewhat slowly developed fluorescence enhancements of 2.2-fold and 20-fold after 1 h and 1 day, respectively (Supporting Information, Figure S10d). However, the selectivity toward Hg^{2+} ions was not deteriorated by the fluorescence measurements carried out within 1 h of the sample preparation. Other metal ions exhibited no appreciable time-dependent effects.

To gain insight into the signaling properties of **3** toward the most responding metal ions of Hg^{2+}, fluorescence titrations were carried out (Figure 3). The fluorescence intensity at 479 nm increased in response to the increases in concentration of the added Hg^{2+} ions up to 1 equiv and then remained relatively constant. From the titration results, the detection limit of **3** for the analysis of Hg^{2+} ions in 30% aqueous acetonitrile was estimated to be 5.4 × 10^{-7} M.

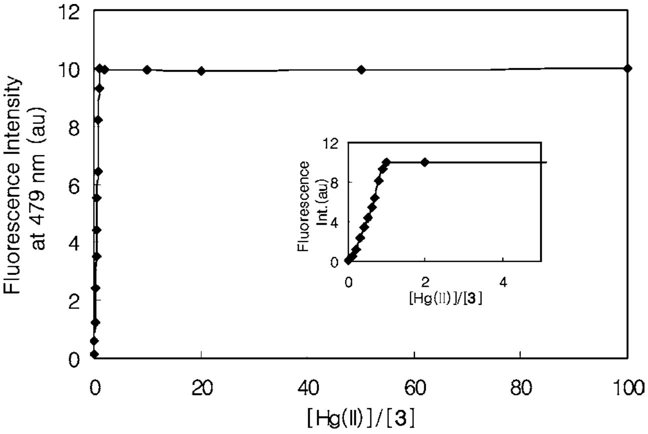
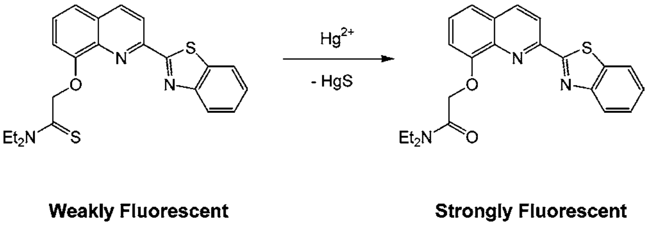


Figure 3. Fluorescence titration of **3** with Hg^{2+} ions in H_2O-CH_3CN (70:30, v/v). [**3**] = 5.0 × 10^{-6} M. Buffered at pH 8.1 (Tris, 10 mM).

Scheme 2. Fluorescence Enhancement of **3** in Response to the Hg^{2+} Ion Induced Desulfurization



The large Hg^{2+}-selective fluorescence enhancement of **3** was caused by the Hg^{2+} induced transformation of the thioamide function into an amide group as depicted in Scheme 2. The hydrolytic conversion of thioamides into amides catalyzed by certain metal ions has been known to be very efficient.[16] In the present case, the conversion was effective exclusively with Hg^{2+} ions under the condition of aqueous acetonitrile. This behavior is quite reminiscent of Czarnik's Hg^{2+}-selective chemodosimeter that is based on the thioamide derivative of anthracene.[4a] Fortunately, the presence of Hg^{2+} ions having an intrinsic quenching nature[17] did not significantly affect the fluorescence of transformed amide derivative **2**,[18] which favorably resulted in an efficient OFF−ON-type signaling of Hg^{2+} ions (Supporting Information, Figure S13). The rationale for the presence of the

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benzothiazole function in **3** is supported by the insignificant fluorescence signaling behavior of the 8-HQ-based control compound **5** toward any of the metal ions (Supporting Information, Figure S14).

To gain further insight into the fluorescent signaling behavior of **3** toward Hg^{2+} ions, the effect of EDTA on the fluorescence signaling of the **3**−Hg^{2+} system was investigated. It was interesting to observe that the enhancement in fluorescence intensity was dependent on the order of addition of EDTA and Hg^{2+} ions (Figure 4). For example, an addition of 100 equiv Hg^{2+} ions induced large fluorescence enhancements of **3**, which was not so significantly affected by the subsequent addition of EDTA solution (1000 equiv). On the other hand, the addition of Hg^{2+} ions (100 equiv) into the solution of **3** in the presence of EDTA (1000 equiv) induced no significant fluorescence enhancement. This may be attributed to the strong complexation of Hg^{2+} ions with EDTA that prevents the interaction of guest Hg^{2+} ions with chemodosimeter **3**.

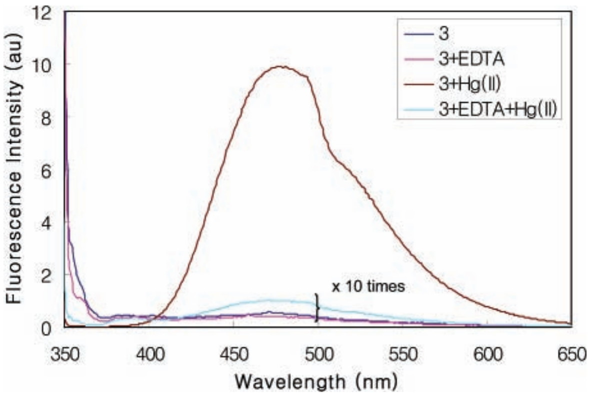

Figure 4. Effects of EDTA on the fluorescence signaling of Hg^{2+} ions of **3**. [**3**] = 5.0×10^{-6} M, [Hg^{2+}] = 5.0×10^{-4} M, [EDTA] = 5.0×10^{-3} M. λ_{ex} = 345 nm. Buffered at pH 8.1 (Tris, 10 mM). The indicated species were added in sequence.

The Hg^{2+} ion induced transformation of the thioamide **3** into the amide **2** was evidenced by NMR, IR, and mass spectroscopic measurements. After treating **3** with 5 equiv of Hg^{2+} ions in 30% aqueous acetonitrile, the recovered residue was characterized. Of all the other evidences, most importantly, the ^1H NMR (Supporting Information, Figure S15) and ^{13}C NMR spectra of the extracted compound were identical to those of the amide derivative **2**. The EI-MS measurement of the residue also confirmed the suggested transformation by showing a prominent peak at $m/z = 391.1$ for the compound **2**.

The utilization of the present system for the analysis of Hg^{2+} ions in a practical sample was also tested. The possible interferences by other metal ions were assessed by measuring Hg^{2+} induced fluorescence changes of **3** in the presence of background metal ions. Among the tested metal ions, Cd^{2+} and Ag^{+} ions were found to interfere by diminishing the fluorescence intensity of the **3**−Hg^{2+} system up to 10% and 13%, respectively (Supporting Information, Figure S16), which might limit the practical applicability of **3** for the analysis of samples having high concentrations of these two ions. However, a nice profile of a Hg^{2+} ion-dependent fluorescence change was observed in the presence of physiologically important metal ions as background[19] that is suitable for the analysis of real samples in a pseudophysiological environment (Supporting Information, Figure S17).

In summary, a new ionophore based on the 8-hydroxyquinoline molecular framework was prepared, and its fluorogenic chemodosimetric behavior was investigated. The transformation of the thioamide function into an amide group selectively exerted by Hg^{2+} ions resulted in a pronounced OFF−ON-type fluorescent signaling behavior. The prepared compound may be utilized as a new chemodosimeter for the analysis of Hg^{2+} ions in the micromolar concentration range in an aqueous environment.

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Supporting Information Available: Experimental details and characterization for new compounds, NMR spectra, and fluorescence data are reported. This material is available free of charge via the Internet at http://pubs.acs.org.

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(18) The desulfurized product **2** has a significant affinity toward Hg^{2+} ions. The association constant (K_{assoc}) of the amide **2** toward Hg^{2+} ions was found to be 2.4×10^4 M^{-1} in H_2O−dioxane (90:10, v/v). The interaction of **2** with Hg^{2+} ions was also evidenced by UV−vis measurements of **2** and **2**−Hg^{2+} systems in H_2O−dioxane (90:10, v/v) (Supporting Information, Figure S18). The fluorescence and UV-vis absorption behaviors of **2** and **2**−Hg^{2+} systems were quite sensitive to the employed solvent systems. The H_2O−dioxane solvent system was chosen because more pronounced spectral changes were observed than in H_2O−acetonitrile.

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