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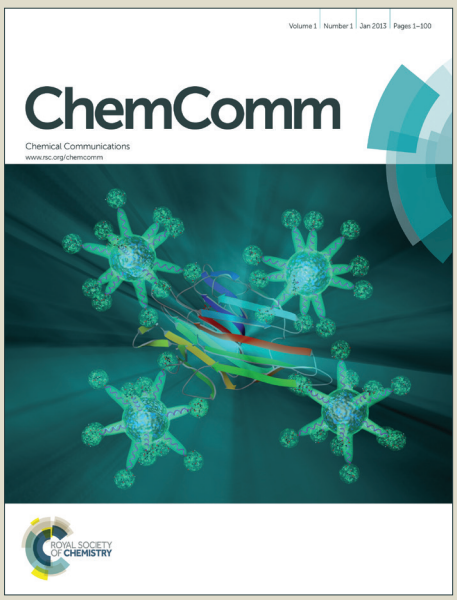

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Theranostic fluorescent agents for Hg^{2+} detection and detoxification treatment†

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Two novel fluorescent theranostic agents 1a and its dimethyl ester 2a for detection and detoxification of mercury ion poisoning are developed.

Hg^{2+} is a highly toxic metal ion which can cause many severe health problems such as kidney failure, central nervous system damage with various cognitive and motor disorders, and even death.[1] The increasing contamination in our living environment and ecosystem has created significant concerns and thus demands for its facile detection and effective treatment (detoxification).[2] In this context, extensive efforts have been made on the development of techniques for its detection[3] particularly fluorescence imaging probes owning to high sensitivity and selectivity and simple operation procedures.[4] A wide range of structurally different recognition groups for Hg^{2+} detection have been reported. These recognition groups are mainly designed to fulfil detection purpose. In other words, reactivity and chemoselectivity are primarily considered while other important properties are often overlooked, such as biocompatibility, bioavailability, and toxicity in bio-related imaging applications. Particularly, some sulfur related probes[5-7] lead to the generation of lipophilic thiolated Hg(II) complexes, which are even more toxic and are more easily redistributed to the body and therefore are difficult to clear out.[1]

On the other hand, very little research work has been conducted in the development of detoxification agents to remove the toxic Hg^{2+} ion from the poisoned body.[8] So far, to the best of our knowledge, few such chelators are available including *meso*-2,3-dimercaptosuccinic acid (DMSA), 2,3-dimercapto-l-propane sulfonic acid (DMPS), and *D*-penicillamine, 2,3-dimercaptopropanol (British anti Lewisite, BAL) (Fig. 1).[9] Particularly DMSA has been used clinically as the effective detoxification agent for the treatment of mercury poisoning (Fig. 1).[1d,10] This agent exhibits an excellent safety profile and potent detoxification ability. In addition, importantly, the DMSA-Hg^{2+} complex formed during chelating process facilitates Hg^{2+} removal through urine or bile secretion without redistribution to lipophilic brain tissues.[10d]

To reduce the significant damage and even save lives once poisoned by Hg^{2+}, it is critically important to rapidly remove the ion from the body, particularly in the first few hours.[1] Therefore, it is necessary to quickly identify the location of the ion in the body and take immediate medication to clean it out. It is expected that a compound endowing diagnostic and therapeutic capacity is highly attractive and valuable in this regard. Recently, there has been a dramatic growing interest in designing theranostic probes/reagents which combine therapeutic effect of a drug with diagnostic power of an imaging probe.[11] They can enhance therapeutic efficacy while minimizing side effects of therapeutics by their capability of spatiotemporal monitoring in imaging-guided drug-delivery, surgery. In addition, these probes can also find important and broad applications in the field of biomedical sciences as powerful tools to study the mechanism of actions of biological targets.

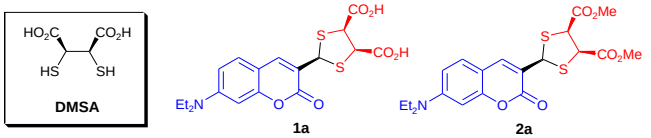
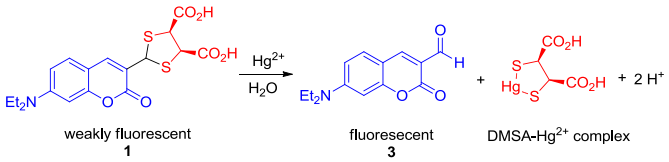


Fig. 1 Detoxifying agent DMSA for Hg^{2+} poisoning and newly designed fluorescent theranostic chemodosimeters **1a** and **2a**.

However, the development of small molecule-based theranostic agents presents a significant challenge. The strategy requires *de nova* design of a new compound with intellectual incorporation of an active drug and imaging moiety in one entity. Critically, the modification should lead to an inactive, non-toxic form of the drug, while it shall be selectively released at the site of interest. Furthermore, ideally, the imaging modality (e.g., fluorophore) produces desired 'off-on' fluorescent signal during the release process. In such a way, the drug can be conveniently and spatiotemporally monitored to ensure the delivery at the desired site to achieve maximum efficacy. In the design of theranostics for Hg^{2+}, high selectivity and reactivity are not the only criteria for selecting Hg^{2+} recognition group. Importantly, low cytotoxicity, biocompatibility, bioavailability, and detoxification effect are also important factors to be considered.

As the proof-of-concept, we designed the first generation theranostic Hg^{2+} agent **1** (Fig. 1 & Scheme 1). It consists of two essential components: DMSA as the recognition moiety and the detoxifying drug, and the widely used 7-*N*-diethyl coumarin as a

fluorescent imaging moiety due to its favorable optical property, stability, simplicity, and low toxicity, which also has been used in several coumarin-based Hg^{2+} chemodosimeters.[6h,7b,12a] These two components are linked through a dithioacetal linkage to create a fluorescent chemodosimeters **1** for Hg^{2+}. The design kills three birds with one stone. First, the dithioacetal functions as a recognition moiety for Hg^{2+} by taking advantage of the unique potent binding affinity of Hg^{2+} to sulfur species. On the other hand, the cleavage Hg^{2+}-DMSA complex can be quickly cleared out by the body without redistribution to ensure the detoxification effect.[10] Finally, the cleavage generates a highly fluorescent coumarin aldehyde molecule from the non-fluorescent dithioacetal form, thus generating a desired 'off-on' signal.[12]



Scheme 1 Design of fluorescent theranostic agents for Hg^{2+}.

The realization of the feasibility of the novel theranostic chemodosimeter started with the synthesis of the newly designed probe **1** (*syn*-isomer **1a** and *trans*-isomer **1b**, Scheme S1†). Similarly, dimethyl ester derivative **2a** was synthesized (see ESI for details) and the structure **2a** with *syn*-configuration was confirmed by 2D-NOESY experiment and X-ray crystallography (Fig. S22†).[13]

With probes **1a**, **1b** and **2a** in hand, the screening of reaction kinetics with Hg^{2+} ion was first performed and their second-order rate constants were determined to be 17.7 $M^{-1}s^{-1}$, 16.9 $M^{-1}s^{-1}$, and 15.1 $M^{-1}s^{-1}$, respectively (see Fig. S1-3†). Notable they showed a quick response with around 15 min. The probe **1a** was then chosen for further investigation.

The reaction stoichiometry of **1a** was determined to be 1:1 by the Job plot experiments (Fig. S4†), supporting the proposed reaction mechanism. The formation of the aldehyde **3** was also proved by ^1H NMR and IR studies (Fig. S20-21†). Then we examined the pH effect of the probe **1a** on Hg^{2+} detection, and found the probe could tolerate a rather broad range of pH (3-11) (Fig. S5†). Physiological pH at 7.4 was used for the studies of the fluorescence and UV-Vis properties. In the absence of Hg^{2+} ion, the probe **1a** at a concentration of 2.0 μM had the maximum excitation at 402 nm and emission at 488 nm (Fig. S6a†). Upon addition of 5.0 equiv. of Hg^{2+}, the maximum excitation and emission wavelength were shifted to 450 and 502 nm, respectively, due to an enhanced ICT process and elongated π-conjugation in Hg^{2+}-induced 1,3-dithiane removal and aldehyde formation (Scheme 1 and S3†).[11] Although the probe **1a** was not an optimal ratiometric fluorescent probe with only 14 nm bathochromic shift in emission upon addition of Hg^{2+}, it turned out to be a great 'turn-on' fluorescent probe as we designed. Notably, the fluorescence intensity was increased by 23-fold upon addition of Hg^{2+} at excitation wavelength of 477 nm where the normalized value in excitation spectrum of **1a** was close to zero (Fig. S6d-e†). For UV-Vis spectra of the probe **1a** upon addition of Hg^{2+} ion, the maximum absorbance was shifted from 403 nm to 445 nm in consistence with elongated π-conjugation (Fig. S7†), which was easily distinguished by a naked eye in color change from almost colorless to yellow (insert of Fig. S7a†).

Next fluorescence and UV-Vis titration experiments with Hg^{2+} ion were conducted (Fig. 3a & S8†). To a 2.0 μM probe **1a** in PBS buffer solution (pH = 7.4) was added Hg^{2+} to the final concentrations in the range of 0.0-10.0 μM, emission spectra were recorded at λ_{ex} 477 nm. The emission at 502 nm gradually increased up to 23 folds. The fluorescent detection limit of probe **1a** was determined to be 2.4 nM (Fig. S8†). For UV-Vis titration, a ratiometric response of decreasing 403 nm and increasing 445 nm absorptions was observed (Fig. S9a†). The UV-Vis detection limit based on the ratio of Abs (445 nm)/Abs (403 nm) was calculated to be 12.0 nM (Fig. S9b†). Notably, both fluorescence and UV-Vis detection limits of probe **1a** were below or close to the maximum mercury contamination level (2.0 ppb, 10 nM) allowed in drinking water defined by the US EPA.[14]

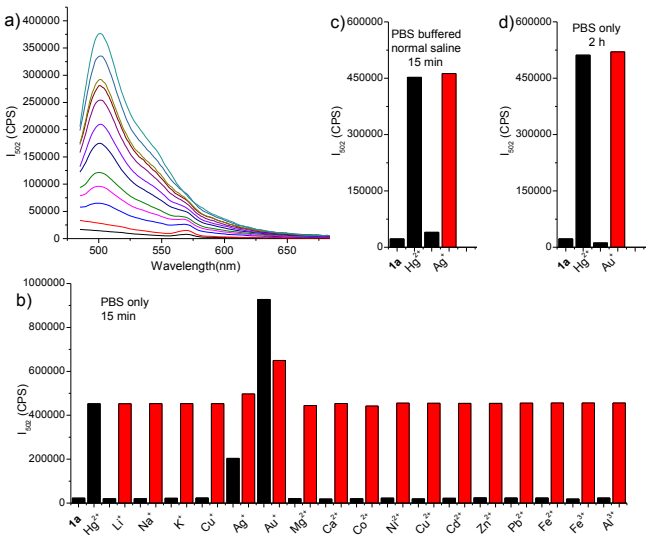


Fig. 3 a) Fluorescent spectra of probe **1a** (2 μM) upon addition of increased concentrations of Hg^{2+} ions (0.0 - 5.0 equiv.); b-d) Emission intensity of probe **1a** (2 μM) upon the addition of different competing metal ions (50 equiv., each) and Hg^{2+} (5 equiv.). Black bars: free probe **1a**, or treated with the marked metal ions (50 equiv.); red bars: the probe treated with the marked metal ions (50 equiv.) followed by Hg^{2+} (5 equiv.). (All fluorescence responses were obtained after 15 min incubation time in 20 mM PBS buffer containing 0.2 % DMSO at 25 °C with λ_{ex} = 477 nm and λ_{em} = 502 nm unless otherwise stated; 20 mM PBS buffered normal saline containing 0.2 % DMSO and 154 mM NaCl was used in Fig. 3c; incubation time was 2h for Fig. 3d.)

Furthermore, the competition assays of probe **1a** were conducted by addition of Hg^{2+} (5.0 equiv.) to the solution of 50.0 equiv. of other metal ions including Li^+, Na^+, K^+, Cu^+, Ag^+, Au^+, Mg^{2+}, Ca^{2+}, Co^{2+}, Ni^{2+}, Cu^{2+}, Zn^{2+}, Cd^{2+}, Pb^{2+}, Fe^{2+}, Fe^{3+}, and Al^{3+}. The probe **1a** showed excellent selectivity toward Hg^{2+} over most of metal ions except Ag^+ and Au^+, two known metal ions with good sulfur affinity. The addition of other metal ions neither resulted in a significant increase of fluorescence response of probe **1a** alone, nor interfered with fluorescence response of **1a** towards Hg^{2+} ions at much higher concentrations (Fig. 3b). Similar conclusions were also drawn from UV-Vis studies (Fig. S10†). Further investigation to improve the selectivity for Ag^+ and Au^+ led to the interesting findings that the potential interferences from these two ions were manageable either by using PBS buffered normal saline solution for Ag^+ (Fig. 3c & Fig. S11b†)) or by increasing the incubation time from 15 min to 2 h for Au^+ (Fig. 3d & Fig. 12b†). For probe **2a**, similar selectivity profile was observed from the competition assays except for its difficulty to differentiate Hg^{2+} from Au^+ even at an increased incubation time up to 2h (Fig. S13†).

Based on above fluorescence and UV-Vis studies, the probe **1a** had demonstrated its high reactivity and specificity as a feasible 'turn-on' chemodosimeter for detection of Hg^{2+} ion. We then

conducted cellular imaging studies. MCF-7 cells were used as a model in fluorescence imaging experiments. However, it was found that probe **1a** gave low fluorescent 'turn-on' response for detection of Hg^{2+} inside MCF-7 cells (Fig. 4h), compared with non-treated cells (Fig. 4f). We believed such observation was caused by low cell penetration of probe **1a**, likely due to low lipophilicity of the probe **1a** containing two carboxylic acid groups. We then switched to the diester **2a** for cell imaging studies. Diester **2a** is more lipophilic and would be able to enter into cells more readily. Furthermore, the ester groups would be easily hydrolyzed back to carboxylic acid by esterase inside cells, and regenerate probe **1a**. Indeed, probe **2a** gave satisfactory results with much brighter imaging by pretreatment with Hg^{2+} (Fig. 4l vs 4h).

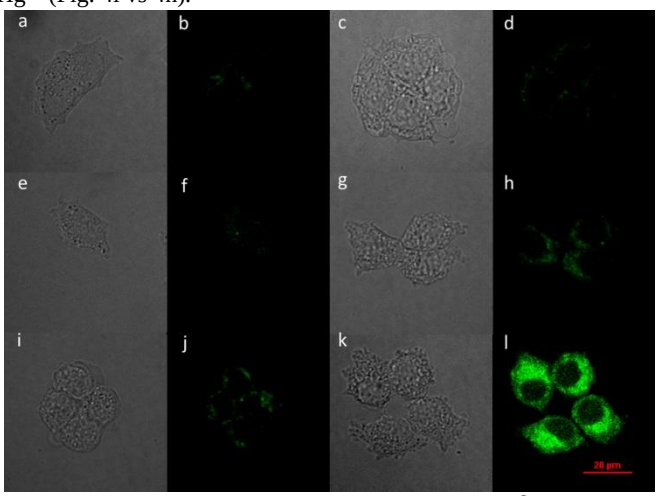


Fig. 4 Top: confocal images of MCF cells without Hg^{2+} pretreatment (a & b) and with Hg^{2+} pretreatment (c & d); Middle: confocal images of MCF-7 cells treated with probe **1a** for 4 h without Hg^{2+} pretreatment (e & f) and with Hg^{2+} pretreatment (g & h); Bottom: confocal images of MCF cells treated with probe **2a** for 30 min without Hg^{2+} pretreatment (i & j) and with Hg^{2+} pretreatment (k & l). (Hg^{2+} pretreatment concentration: 10 μM; probe concentration: 20.0 μM; a, c, e, g, i, k: bright field; b, d, f, h, j, l: green channel; scale bar = 20 μm, see ESI for details).

We then evaluated the potential therapeutic/protective effects of probes **1a** and **2a** against Hg^{2+}-induced cytotoxicity through cell viability assays.[15] To demonstrate the concept of our design, the detoxifying drug DMSA was selected as the positive or therapeutic control, while known fluorescent chemodosimeters **4**[11a] (structure shown in Fig. 5) was used as the nontherapeutic control. First, the cytotoxicity of Hg^{2+} and probes **1a**, **2a**, and **4** together with DMSA for MCF-7 cells in different concentrations were evaluated. IC_{50} for Hg^{2+} was measured at 25.01±3.16 μM. The Hg^{2+} at 10 μM concentration was chosen since it induced modest toxicity to MCF-7 cells (cell survival rate: 65.13±4.11% after 24 incubation) (Fig. S14†), allowing an optimal Hg^{2+} concentration for evaluation of protective effects of these probes. Among three probes, probe **1a** showed the lowest toxicity with no appreciable toxicity up to 250 μM, while probe **4** displayed the highest toxicity with IC_{50} = 28.44 ±2.05 μM and probe **2a** lied in between with IC_{50} = 214.13±6.14 μM (Fig. S15-16†). The cell toxicity assay clearly demonstrated that the recognition group contributes significantly to overall toxicity of the probes. We then evaluated the protective effect of these probes against acute Hg^{2+} poisoning. MCF-7 cells were pretreated with 10 μM Hg^{2+} for 2 h before different concentrations of the probes (up to 10 μM) were added directly into the media containing Hg^{2+} (Fig. 5). This experimental setting was designed to mimic acute Hg^{2+} poisoning, in which body fluids contained high concentration of the Hg^{2+} with some Hg^{2+} already entered cells. Experiment results indicated probe **1a** had almost the same protective effect as DMSA in all concentrations tested and probe **2a** showed even better protection against Hg^{2+} induced cytotoxicity in the range of 0.5-5.0 μM, probably due to a better cell penetration. We would expect probe **4** gave the similar result as probe **2a** as it has a good cell penetration as well. Intriguingly, at lower concentrations below 2.5 μM, probe **4** showed significant less protective effects than DMSA, while at higher concentrations (5 μM and 10 μM) probe **4** induced significant toxicity (Fig. 5). We believed the unexpected anti-protective effect of probe **4** at higher concentration was due to potential redistribution effect. Mercury ethylene bisdithioate, the Hg^{2+} chelating product formed from probe **4**, was relatively non-polar and facilitated mercury uptake into cells, where it might be entrapped in intracellular lipid membrane, deactivated proteins on the membrane, and caused cell damage. On the contrary, DMSA-Hg^{2+} complex, the chelating product formed from probe **1a** and Hg^{2+}, is much polar and without redistribution effect. These observations agreed well with the chelating mechanism, which mainly targeting nonchelating or loosely chelated Hg^{2+}. Furthermore, probe **2a** showed better cell protective effects than probe **1a** and DMSA, likely due to less cell penetration of probe **1a** and DMSA.

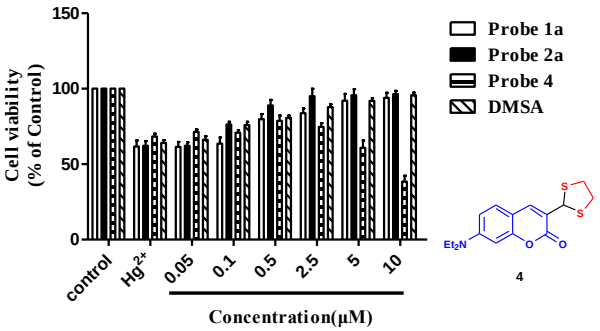


Fig. 5 Cell viability (24 h) of probe **1a**, **2a**, **4**, and DMSA at various concentrations for MCF-7 cells pretreated with 10.0 μM Hg^{2+} for 2 h.

In conclusion, we have developed the theranostic agents for Hg^{2+} detection and poisoning treatment. Two novel fluorescent theranostic agents **1a** and **2a** have been designed, synthesized, and evaluated. As demonstrated experimentally, the first generation theranostics display the excellent reactivity, selectivity, and sensitivity toward Hg^{2+}. The more cell permeable dimethyl ester probe **2a** can be used to track the drug release inside cells by fluorescence spectroscopy. Furthermore, both **1a** and **2a** could effectively protect MCF-7 cell against Hg^{2+} induced toxicity with similar potency to DMSA. To the best of our knowledge, this is the first example of small-molecule based theranostic agents encompassing the dual functions of detection and medication for heave metal poisoning.[16] The study may open a new direction on the development of novel therapeutics for treatment of heavy metal poisoning, an underexplored area, which constitutes our further endeavor.

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† Electronic Supplementary Information (ESI) available: Synthetic procedures, NMR, and other UV-Vis and fluorescent spectra. See DOI: 10.1039/b000000x/

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