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A new "naked-eye" colorimetric and ratiometric fluorescent sensor for imaging Hg^{2+} in living cells

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ABSTRACT

A new oligothiophene-based sensor **3 TH** for monitoring Hg²⁺ has been designed and synthesized based on the intramolecular charge transfer (ICT) mechanism. The **3 TH** shows the significant specificity toward Hg²⁺ through "naked-eye" colorimetric detection as well as via ratiometric fluorescence enhancement response with low detection limit of 62 nM. In addition, sensor **3 TH** shows high selectivity and sensitivity for Hg²⁺ with fast response in a suitable pH range. Moreover, the **3 TH**-based test strips was used to conveniently detect Hg²⁺ ions in water. Furthermore, considering its good "turn-on" fluorescent sensing behavior and low cell cytotoxicity, **3 TH** was successfully applied to detect and image Hg²⁺ in real water samples and living cells, which shows great potentials for application in environmental and biological systems.

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1. Introduction

Toxic effects of metal ions on physiological and pathological processes in living systems have recently attracted considerable research interest, which is considered as one of the forefront research areas in chemistry, biology and medicine [1]. Among the various metal ions, Hg^{2+} is considered as one of the most hazardous heavy metal ions, which can cause severe damages such as kidney failure, liver failure, DNA lesion, cognitive and motor disorders even in a very low concentration [2–7]. Due to its high toxicity and it can lead to serious environmental pollution and health hazard, therefore, building up a convenient, rapid and efficient method for detecting Hg^{2+} is extremely essential.

Apart from the traditional detection techniques, fluorescent sensor as a well-grounded method for detection of various analytes are of growing interest due to its outstanding advantages of great capability of temporal and spatial sampling, high sensitivity, and simple sample pretreatment [8–42]. However, in most practical applications, "turn-on"/"turn-off" type fluorescent sensor is based on the single fluorescence intensity change signal, and is generally influenced by the excitation intensity, sensor concentration,

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https://doi.org/10.1016/j.tet.2019.130687 0040-4020/© 2019 Elsevier Ltd. All rights reserved. photobleaching, and environment around the sensor (pH, polarity, and temperature etc) and stability under illumination, etc [43–48]. In order to eliminate the above-mentioned effects, ratiometric fluorescent sensor is exceptionally useful and is more attractive, which utilizes the ratio of the fluorescence intensity at two different wavelengths, and it also provides built-in correction for environmental factors and provide more accurate and precise measurement results with high sensitivity and inherent reliability [49–52]. To further application in the biological, food and environmental fields, the new ratiometric fluorescent sensor based on the intramolecular charge transfer (ICT) mechanism has recently received great research interest because of its unique ratiometric fluorescence behavior.

In this work, we reported the synthesis of a new thioacetal derivative of thioacetalized oligothiophene **3TH** (Scheme 1) and investigated its sensing behavior toward Hg²⁺. The investigated results indicated that the **3TH** shows highly selective, sensitive, "naked-eye" colorimetric and ratiometric fluorescent turn-on detection of Hg²⁺ in aqueous media based on the ICT mechanism. An obvious ICT process from oligothiophene moiety to aldehyde group causes a significant red-shift of the fluorescence band of the **3TH**, and produces a remarkable ratiometric fluorescent turn-on signal. The **3TH** shows very fast response towards Hg²⁺ with a quite low detection limit of 62 nM. More importantly, the sensor **3TH** was successfully applied to image Hg²⁺ ions in living cells.



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Scheme 1. The synthetic route of sensor 3 TH.

2. Experiment procedure

2.1. Reagents, materials and apparatus

All reagents were purchased from Sigma-Aldrich Chemical Company and used without further purification. Deionized water was used throughout all experiments. NMR spectra were recorded on a Bruker–AVANCE 400 NMR Spectrometer, with tetramethylsilane (TMS) as an internal standard. FTIR spectra were performed on Bruker ALPHA FT-IR spectrometer using KBr pellets. High resolution mass spectra (HRMS) were measured on an Agilent 6510 Accurate–Mass Q–TOF LC/MS system. Absorption and fluorescence spectra were measured on Shimadzu UV-2600 and Hitachi F–4600 spectrofluorometer, respectively. The pH measurements were performed on a Model PHS-3C pH meter. The cell fluorescence images were detected by a Leica TCS SP8 confocal-laser scanning microscope (CL SM) with an objective oil lens of 63X magnification.

2.2. General procedure for the spectra measurement

3 TH was dissolved in ethanol to prepare the 1.0 mM of stock solution. The appropriate amount of each inorganic metallic salts $(K^+, Na^+, Ag^+, Ca^{2+}, Mg^{2+}, Ba^{2+}, Al^{3+}, Co^{2+}, Cu^{2+}, Ni^{2+}, Pb^{2+}, Hg^{2+}, Zn^{2+}, Cd^{2+}, Cr^{3+}, Sr^{2+}, Fe^{2+}, and Fe^{3+})$ was dissolved in deionized water at a concentration of 1.0 mM. Test solutions were prepared by placing the stock solutions and diluted to the desired analytical concentrations with a mixed solution of EtOH/H₂O (1/1, v/v). All measurements were carried out at room temperature, the excitation wavelength was 360 nm with excitation and emission slit widths of 5 and 5 nm, respectively.

2.3. Synthesis of sensor 3 TH

Compound **3T-CHO** (50 mg, 0.18 mmol) and 1.3-malonylthiol (39 mg, 0.36 mmol) were dissolved in dry dichloromethane (10 mL), a catalytic amount of BF₃·Et₂O (0.02 mL, 0.15 mmol) as the Lewis acid added into the above solution. The reaction mixture was stirred at room temperature for 10 h under an atmosphere of argon. Then, the reaction mixture was evaporated in vacuo, and the crude product was purified by column chromatography to obtain compound 3TH, which is as a yellow solid (45 mg, 68% yield). Mp 136.8–137.5 °C; FTIR (KBr, cm⁻¹) v = 1059 (C–S–C), 1503 (C=C, thiophene ring); ¹H NMR (400 Hz, DMSO- d_6 , ppm): $\delta = 7.53$ (d, J = 4.8 Hz, 1H), 7.34 (d, J = 3.2 Hz, 1H), 7.26 (s, 2H), 7.18 (d, J = 3.6 Hz, 1H), 7.09 (m, J = 8.8 Hz, 2H), 5.73 (s, 1H), 3.05 (t, J = 11.6 Hz, 2H), 2.89 (d, J = 14 Hz, 2H), 2.08 (d, J = 14 Hz, 1H), 1.76 (d, J = 14 Hz, 1H); ¹³C NMR (100 Hz, DMSO- d_6 , ppm): $\delta = 142.2$, 135.9, 135.8, 135.6, 134.8, 128.4, 127.2, 125.7, 125.1, 124.9, 124.3, 123.6, 79.6, 43.4, 30.1, 24.6; HRMS (ESI) *m/z* calcd for C₁₆H₁₄S₅ [M+H]⁺: 369.9777; Found 366.9782.

2.4. Fluorescence imaging of Hg^{2+} in living cells

The HeLa cells were cultured in DMEM supplemented with 10% FBS at 37 °C (under 5% CO₂), which were chosen for the cell imaging experiments. Firstly, the living HeLa cells and sensor **3 TH** (10 μ M) were cultured in cell culture media for 1 h at 37 °C, washed with PBS buffer (pH = 7.4) for three times, and then imaging. Next, Hg²⁺ (10 μ M) was added to the pre-cultured cells of the **3 TH**, cultured for 30 min at 37 °C, and washed with PBS for three times, then imaging. After 60 min, imaging the cells that loaded Hg²⁺ again were detected under CLSM. The excitation wavelength was 488 nm, and the emission filter was 500–550 nm.

3. Results and discussion

3.1. Design and synthesis of **3 TH**

As described in Scheme 1, compound 3 TH was facilely synthesized from 3T-CHO [53] and 1,3-malonylthiol. The structure of 3 TH was well confirmed by ¹H NMR, ¹³C NMR, FTIR and HRMS (Figs. S1–4). Our design strategy was based on the well-known Hg2+-promoted desulfurization reaction of thioacetal to the corresponding aldehyde.

3.2. UV-vis spectral response of **3** TH to Hg^{2+}

Initially, the selectivity study of sensor **3 TH** towards Hg^{2+} was evaluated. The UV–vis response of **3 TH** (10 μ M) was carried out after addition of a series of 2.0 equiv. metal ions (K⁺, Na⁺, Ag⁺, Ca²⁺, Mg²⁺, Ba²⁺, Al³⁺, Co²⁺, Cu²⁺, Ni²⁺, Pb²⁺, Hg²⁺, Zn²⁺, Cd²⁺, Cr³⁺, Sr²⁺, Fe²⁺, and Fe³⁺) in EtOH/H₂O (1:1, v/v) solution. As shown in Fig. 1, the **3 TH** (10 μ M) exhibited a maximal absorption band at 360 nm, which should be ascribed to the absorption of oligothiophene moiety. Upon addition of various metal ions (2.0 equiv.), only Hg²⁺ induced great changes: a typical absorption at 360 nm reduced significantly while a new red-shift absorption band is created at 400 nm along with the solution color change from colorless to pale yellow. Whereas, other metal ions caused no significant color and spectral changes. These results indicated that the colorimetric sensor **3 TH** has high selectivity towards Hg²⁺.



Fig. 1. The UV–vis absorption spectra of **3 TH** (10 μ M) after addition of 2.0 equiv. of various metal ions in EtOH/H₂O (1/1, v/v) solution; **Inset:** Colorimetric responses of **3 TH** (10 μ M) in an EtOH/H₂O (1:1, v/v) solution upon the addition of 2.0 equiv. of various metal ions.

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Fig. 2. The absorption spectra of $3\,\text{TH}$ (10 $\mu\text{M})$ exposed to various concentrations of Hg^2+ (0–2.0 equiv.) in EtOH/H_2O (1/1, v/v) solution.

To insight into the colorimetric response of the **3 TH** toward Hg^{2+} , the absorption spectra of **3 TH** with various concentrations of Hg^{2+} (0–2.0 equiv.) in EtOH/H₂O (1:1, v/v) solution were recorded. As displayed in Fig. 2, with increasing concentration of Hg^{2+} , the absorption intensity at 360 nm decreased gradually and the absorption band at 400 nm increased progressively. Meanwhile, the ratio (A₄₀₀/A₃₆₀) of the absorbance shows a gradual increase with the increased concentrations of Hg^{2+} , and reached saturation at 10 μ M of Hg^{2+} . In addition, a clear well-formed isobestic point at 381 nm was clearly observed, suggesting the formation of **3 TH**.

3.3. Ratiometric fluorescence response of **3 TH** to Hg^{2+}

Next, the fluorescence response of **3 TH** was examined with the above of metal ions (2.0 equiv.). As shown in Fig. 3, with the excitation at 360 nm, sensor **3 TH** showed a blue emission centered



Fig. 3. Fluorescence spectra of **3 TH** (10 μ M) in the presence of various metal ions (2.0 equiv.) in EtOH/H₂O (1/1, v/v) solution; **Inset:** Fluorimetric responses of **3 TH** (10 μ M) in an EtOH/H₂O (1:1, v/v) solution upon the addition of 2.0 equiv. of various metal ions.



Fig. 4. Fluorescence titration spectra of **3 TH** (10 μ M) with different concentrations of Hg²⁺ (0–2.0 equiv) in EtOH/H₂O (1/1, v/v) solution.



Fig. 5. Fluorescence intensity ratio (I_{552}/I_{448}) of sensor **3 TH** upon gradual addition of Hg²⁺ (0–2.0 equiv); **insets:** Fluorescence photographs of sensor **3 TH** in the presence of different concentration of Hg²⁺.



Fig. 6. ¹H NMR spectra of 3TH, 3TH upon the addition of 1.0 equiv. Hg²⁺ (3TH + Hg²⁺) and 3T-CHO in DMSO-d_6.

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Scheme 2. Proposed complexation model of 3 TH with Hg²⁺ and the observed colorimetric change.



Fig. 7. Fluorescence intensity ratio (I_{552}/I_{448}) of $3\,\text{TH}~(10\,\mu\text{M})$ exposed to 2.0 equiv various metal ions and to the mixture of 2.0 equiv. Hg^{2+} in EtOH/H_2O (1/1, v/v) solution.

about 448 nm. With the addition of metal ions except for Hg^{2+} to **3 TH** in EtOH/H₂O (1:1, v/v) solution, almost no spectral and solution color changes were observed. Fascinatingly, the addition of Hg^{2+} to sensor **3 TH** resulted in a considerable enhancement of



Fig. 8. Fluorescence intensity ratio (I_{552}/I_{448}) of sensor **3 TH** (10 μ M) at various pH values in an EtOH/H₂O solution (1/1, v/v) in the absence and presence of Hg²⁺ (2.0 equiv.) at room temperature.



Fig. 9. Time-dependent of the fluorescence intensity ratios (I_{552}/I_{448}) of **3 TH** (10 μ M) upon addition of 2.0 equiv Hg²⁺ in EtOH/H₂O (1/1, v/v) solution.

fluorescence intensity at 552 nm via fluorescence turn-on response and a significant decrease of fluorescence intensity at 448 nm, along with the solution color change from blue to bright green under 365 nm lamp. The result revealed that **3 TH** can function as a fluorescent turn-on sensor for highly selective detection of Hg^{2+} .

To examine the sensitivity of **3 TH** for Hg^{2+} sensing, the fluorescence titration of **3 TH** (10 μ M) with Hg^{2+} (0–2.0 equiv.) was performed as shown in Fig. 4. With increasing of concentration of Hg²⁺, a gradual decrease of the emission peak occurred at 448 nm and a progressive increase of new red-shift emission band at 552 nm along with a distinct isoemission point at 495 nm, which gives measurable ratiometric fluorescent signals. The emission intensity ratios at 552 nm and 448 nm (I552/I448) underwent a remarkable change with 13-fold emission enhancement with increasing Hg²⁺ and reached the platform at 10 μ M (Fig. 5). The large red-shift (104 nm) and the distinct ratiometric fluorescent enhancement signals in **3 TH** were due to electron-rich dithioacetal moiety which could be removed by Hg^{2+} to release the electrondeficient aldehyde group, and produced strong push-pull electronic system, leading to the ICT process from oligothiophene moiety to aldehyde group switched on. A preferable linearity $(R^2 = 0.98686)$ between the $[Hg^{2+}]$ and emission ratios (I_{552}/I_{448}) was clearly observed along with sensitive solution color changes from blue to green (Fig. 5), indicating that **3 TH** was a Hg²⁺-specific ratiometric fluorescent turn-on sensor for quantitatively and qualitatively detecting Hg^{2+} . The detection limit of **3 TH** was determined to be 62 nM (LOD = $3\sigma/k$), which is lower than those of most reported ratiometric fluorescent sensors previously [54-56], further indicating **3** TH has high sensitivity to Hg^{2+} .

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Table 1

Determination of Hg²⁺ in environmental water samples by the proposed method.

Sample	Added (µM)	Detect $(x \pm SD) (\mu M)$	Recovery (%)	Relative error (%)	RSD (%)
Tap water	5.0	4.87 ± 0.14	97.4	2.6	2.8
	10.0	10.22 ± 0.19	102.2	2.2	1.8
River water	5.0	5.13 ± 0.11	102.6	2.6	2.1
	10.0	9.77 ± 0.29	97.7	2.3	2.9
Distilled Water	5.0	4.85 ± 0.13	97.0	3.0	2.6
	10.0	10.31 ± 0.14	103.1	3.1	1.4
The Yellow River	5.0	4.89 ± 0.11	97.8	2.2	2.2
	10.0	10.33 ± 0.34	103.3	3.3	3.3
Lake Water of Ji'nan Garden Expo	5.0	5.14 ± 0.15	102.8	2.8	2.9
	10.0	10.32 ± 0.10	103.2	3.2	0.9



Sunlight









UV light (365)

Fig. 10. Photographs showing the color changes of sensor **3 TH** before and after addition of Hg²⁺ and other ions on filter papers (**a**) and TLC plates (**b**).

3.4. Reaction mechanism studies

To study the reaction mechanism, ¹H NMR titration was firstly carried out. As shown in Fig. 6, upon the addition of Hg^{2+} (1.0 equiv.) into **3TH** (10 µM) in DMSO-*d*₆, the characteristic 1,3-dithiane methine proton signal at 5.73 ppm disappeared with a concomitant appearance of a new proton signal at 9.80 ppm, which assigned to the corresponding aldehyde proton of **3T-CHO**. The ¹H NMR spectrum of **3TH** + Hg²⁺ was well identical to that of **3T-CHO**, further proved the production of **3T-CHO** from the reaction between **3TH** and Hg²⁺. Then, the reaction product of **3TH** with Hg²⁺ has been further confirmed by FTIR spectra (Fig. S5). The FTIR

spectra shows a new typical and prominent absorption peak of aldehyde group at 1650 cm^{-1} in the presence of Hg²⁺ (1.0 equiv), which is similar to that of **3T-CHO**, giving another proof that the resulting product is essentially identical to that of **3T-CHO**. In addition, upon the addition of Hg²⁺ to the sensor, the optical spectra of **3TH** along with the distinct color changes are the same as that of **3T-CHO** (Figs. S6 and S7), further demonstrating that **3TH** was indeed converted into **3T-CHO** by Hg²⁺. Based on these investigated results, the reaction mechanism between **3TH** with Hg²⁺ occurs as shown in Scheme 2, the **3TH** for selectively sensing of Hg²⁺ is based on the Hg²⁺-triggered deprotection reaction of oligothiophene thioacetals [57–61], which resulted in the ICT on

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Fig. 11. Cellular activity of $3\,\text{TH}$ against HeLa cells at different concentrations (0–25 $\mu\text{M}).$



Fig. 12. Confocal microscopy images of HeLa cells. (a) Fluorescent image of HeLa cells with **3 TH** for 1 h; (b) Bright-field image of HeLa cells with **3 TH** for 1 h; (c) Fluorescent images of HeLa cells incubated with **3 TH** and Hg²⁺ for 30 min; (d) for 60 min.

and thus caused a large red-shift and distinct ratiometric fluorescent enhancement in emission spectra.

3.5. Competition studies

To check the high selectivity of sensor **3 TH** sensing response to Hg^{2+} , the competition experiments was carried out in the presence of Hg^{2+} ions (2.0 equiv.) mixed with other relevant tested metal ions (2.0 equiv.) in EtOH/H₂O (1:1, v/v) solution. As shown in Fig. 7, there was no significant variation on the Hg^{2+} -induced emission ratiometric signal (I_{552}/I_{448}) of **3 TH** for detection of Hg^{2+} mixed

with other competitive metal ions. The investigation suggests that **3 TH** behaves as a highly selective ratiometric fluorescent turn-on sensor for Hg^{2+} and is quite useful for selectively detecting Hg^{2+} in environmental and biological systems.

3.6. Effect of pH

To ensure that the sensor **3 TH** is suitable for detecting Hg^{2+} under a physiological pH range, the pH-dependent experiment with different pH values was recorded in EtOH/H₂O (1:1, v/v) solution (Fig. 8). It is found that no dramatic change in the fluorescence ratios (I_{552}/I_{448}) of **3 TH** during the pH range 5.0–9.0. By treatment with Hg^{2+} (2.0 equiv.), from pH 5.0 to 7.0, the fluorescence ratios (I_{552}/I_{448}) showed a gradual increase, while it showed a decreasing trend from pH 7.0 to 9.0, which may be due to hydrolysis of Hg^{2+} at pH 7.0–9.0. The proposed ratiometric fluorescent sensor **3 TH** is applicable in a wide range of pH (5.0–9.0), which indicates that it can monitor Hg^{2+} under physiological pH conditions.

3.7. Reaction time on sensing Hg^{2+}

A short response time is a key factor for a designed sensor [62,63], therefore, the time dependent fluorescence responses of **3 TH** toward Hg²⁺ (2.0 equiv.) were investigated in EtOH/H₂O (1:1, v/v) solution. As shown in Fig. 9, a dramatic enhancement in the emission ratios (I_{552}/I_{448}) was quickly detected, reached the maximum within 1 min, and then remained stable with increasing time. The result indicated that the fluorescence assay time of 1 min was s elected in the evaluation of the selectivity and sensitivity of the **3 TH** toward Hg²⁺ under mild conditions and without any catalyst.

3.8. Application of **3 TH** to real water samples

To evaluate the applicability of the sensor **3 TH** to real samples, water samples including tap water, river water, distilled water, the Yellow River, and lake water of Ji'nan Garden Expo were analyzed using a standard addition method. A series of various concentrations of Hg²⁺ are spiked in these test samples. As displayed in Table 1, the analytical results obtained from the water samples show satisfactory recoveries ranging between 97.8% and 103.3% with low relative standard deviation (RSD) below 3.3%. These determined values were in good agreement with the added values, confirming the applicability of the proposed sensor **3 TH** in the environmental water samples with high sensitivity, good reliability and efficiency.

3.9. Sensor 3 TH-based test strips

Ease of applicability of a developed sensor is a performance index that makes it more convenient to use. To further investigate the practical application of sensor **3 TH**, we prepared test strips by dipping filter paper/TLC plate into the EtOH solution of **3 TH** (1.0 mM) and then dried in air. When these test strips coating **3 TH** immersed into the solution of each metal ion (1.0 mM) in water, we found that only Hg^{2+} ions induced immediate and apparent color changes under sunlight and 365 nm UV lamp, respectively, other metal ions caused almost no change (Fig. 10). Therefore, these **3 TH**based test strips could be conveniently handled at any moment for the selective colorimetric detection of Hg^{2+} ions by the naked eyes.

3.10. Cellular imaging of Hg^{2+}

Inspired by the excellent "turn-on" fluorescent sensing behavior of sensor **3TH** for Hg^{2+} , the cellular imaging capability in living

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Table 2

The comparisons of **3 TH** for Hg^{2+} with other Hg^{2+} -sensitive sensors.

Compound	Sensing method	LOD (µM)	pH range	Test Strips	Response time	Cells Imaging	Ref.
	fluorescence turn-on	0.42	no data	no date	no date	yes	[64]
N HO S	fluorescence turn-on	3.20	3.0-10.0	no date	10 min	yes	[65]
S HO S	fluorescence turn-on	0.20	3.0-5.0	no date	no date	no date	[66]
N S OH	fluorescence turn-on	1.16	no data	no date	1 min	yes	[67]
S S S	naked-eye colorimetric/ratiometric fluorescent turn-on	0.062	5.0-9.0	Yes	1 min	yes	This work

HeLa cells was further studied. Firstly, the cytotoxicity of **3TH** towards HeLa cells at different concentrations $(0-25 \,\mu\text{M})$ were tested using MTT assay (Fig. 11). The tested result indicates that **3 TH** has low cytotoxicity to the living cells, because the cellular viability is nearly 90% over 24 h even at high concentration. Next, HeLa cell imaging experiments were measured with sensor 3 TH at the concentration of $10 \,\mu$ M. Sensor **3TH** incubation alone for 60 min gave no fluorescence in the related regions (Fig. 12a and b). Then, the HeLa cells were firstly incubated with 3TH for 30 min and washed off the excess sensors that did not enter the cells, then the Hg²⁺ were added and incubated for 30 min, significant green fluorescence was observed (Fig. 12c). As the incubation time prolonged to 60 min, a stronger green fluorescence was displayed in the cytoplasm (Fig. 12d). Therefore, these cell imaging results demonstrated that sensor **3 TH** can effectively image Hg^{2+} in living cells.

3.11. Comparison with other reported sensitive- Hg^{2+} sensors

Compared with other reported sensitive Hg²⁺ fluorescent sensors [64-67], and the analytical results were listed in Table 2. Our designed sensor 3TH showed some outstanding advantages including naked-eye colorimetric and ratiometric fluorescent turnon detection, low detection limit, fast response, wide working pH range, and multifunctional applications in test strips, environmental water and live-cell imaging.

4. Conclusion

In summary, we developed a new oligothiophene-based sensor **3**TH based on the ICT mechanism, which shows fast, "naked-eye" colorimetric and ratiometric fluorescent turn-on detection of $\check{\text{Hg}^{2+}}$ in aqueous media. The low-cost sensor 3TH with low toxicity exhibited high sensitivity and superior selectivity toward Hg^{2+} in a favorable working pH range. Due to its excellent features, the sensor **3 TH** was successfully applied to detect and image Hg²⁺ in environmental water, test strips and living cells, which provided a convenient, reliable and accurate method for Hg²⁺ analysis.

Declaration of competing interest

The authors declared that they have no conflicts of interest to this work.

We declare that we do not have any commercial or associative interest that represents a conflict of interest in connection with the work submitted.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tet.2019.130687.

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