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Short communication

Probing Cr(III) from $Cr(pic)_3$ derivatives in living cell by two rhodamine B-based AIEgens

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ABSTRACT

Two rhodamine B-based compounds **1** and **2** were prepared for application of fluorescence Cr(III) probes, and they inherit aggregation induced emission (AIE) features with strong red emission in water. Fluorescence spectra and cell imaging proved that compounds **1** and **2** were highly responsive to Cr(III), and they were employed to investigate the decomposition of chromium picolinate ($Cr(pic)_3$) in the living cells. As a result, Cr(III) was captured by compound **1** and **2** from $Cr(pic)_3$ in living cell. This result demonstrated that the biological mechanism of $Cr(pic)_3$ could be explored by the fluorescent tracer.

1. Introduction

Chromium(III) was proved to be an essential trace element in the 1960s for its positive effect on cholesterol and glucose metabolism [1]. Henceforth, the biological activity of Cr(III) has been widely investigated[2-5], and Cr(III) compounds have been used as a nutritional supplement for a long time [6]. Although Cr(III) was proved to be non-essential for biochemical and physiological functions in 2014 [7], it was proposed to be a second messenger to amplify insulin signaling for the movement of Cr(III) in response to insulin concentration changes [8]. Besides, Cr(III) supplements exhibited high efficiency in inhibiting TSP-1 expression [9] and lowering the risk of vascular inflammation in diabetes [9–11]. Therefore, Cr(III) is believed to be a hopeful candidate for the prevention and treatment of diabetes and atherosclerosis in recent years [9,11].

There are various chromium supplements on the market, including nicotinate chromium [12], amino acid chromium [13], chromium picolinate ($Cr(pic)_3$) [14] and chromium yeast [15]. Among all the Cr(III) supplements, $Cr(pic)_3$ is the most popular one, and it has sales of over half a billion-dollar, ranked only secondly to calcium supplements for its better bioavailability (~5%) than other Cr(III) supplements [6,16]. However, there are also shortcomings of $Cr(pic)_3$ in biological research. For instance, $Cr(pic)_3$ displayed excessive stability in the organism, and this led to non-ideal bioactivity [17–20]. Also, some research pointed that $Cr(pic)_3$ may pass unhindered through the jejunum for its remarkable stability in an aqueous solution [21] and synthetic gastric fluid [22]. Even some research figured out that $Cr(pic)_3$ is probable to enter the cell and eliminate from the body in the intact form [23], which reduces the bioavailability of $Cr(pic)_3$ incredibly [24,25]. Therefore, many researchers tried to improve the bioavailability of Cr(III) supplements by employing ligands with lower coordination ability than picolinate [26–28]. However, whether $Cr(pic)_3$ release Cr(III) in the organism is still unknown, and factors affecting bioavailability of Cr(III) supplements is ambiguous. Hence, detecting Cr(III) from $Cr(pic)_3$ is of great importance to its biological mechanism exploration and bioavailability improvement. Traditional radioactive tracing of Cr(III) was inapplicable for its side-effect on the organism, and a new method should be employed to the exploration of $Cr(pic)_3$ in vivo.

Fluorescence techniques have attracted many interests for their advantages, such as high sensitivity, specifically selectivity, and real-time monitoring [29–33]. The fluorescent probes could be used as practical tools to research the intracellular fluctuations of metal ions and exerted potential application in biological mechanism detection [33,34]. However, paramagnetic of Cr(III) leads to enhancement of spin–orbit coupling, and it resulted in fluorescence quenching [35]. Up to now, only a few fluorescent turn-on probes were suitable for Cr(III) detection [36–38], and there was scarcely any investigation that has been used to investigate the decomposition of $Cr(pic)_3$. Herein, two rhodamine-based

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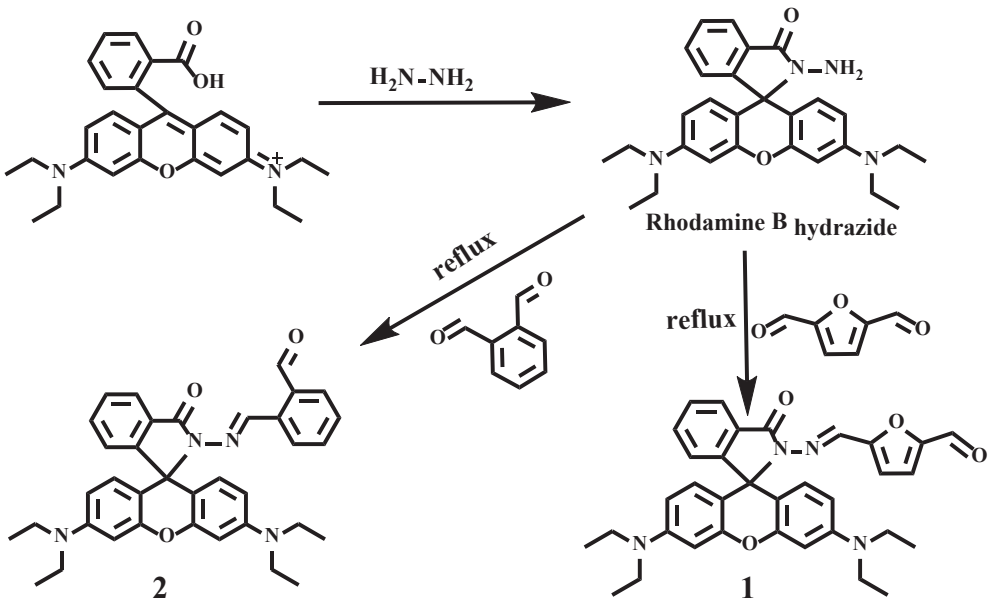

Scheme 1. Synthetic route of compound **1** and **2**.

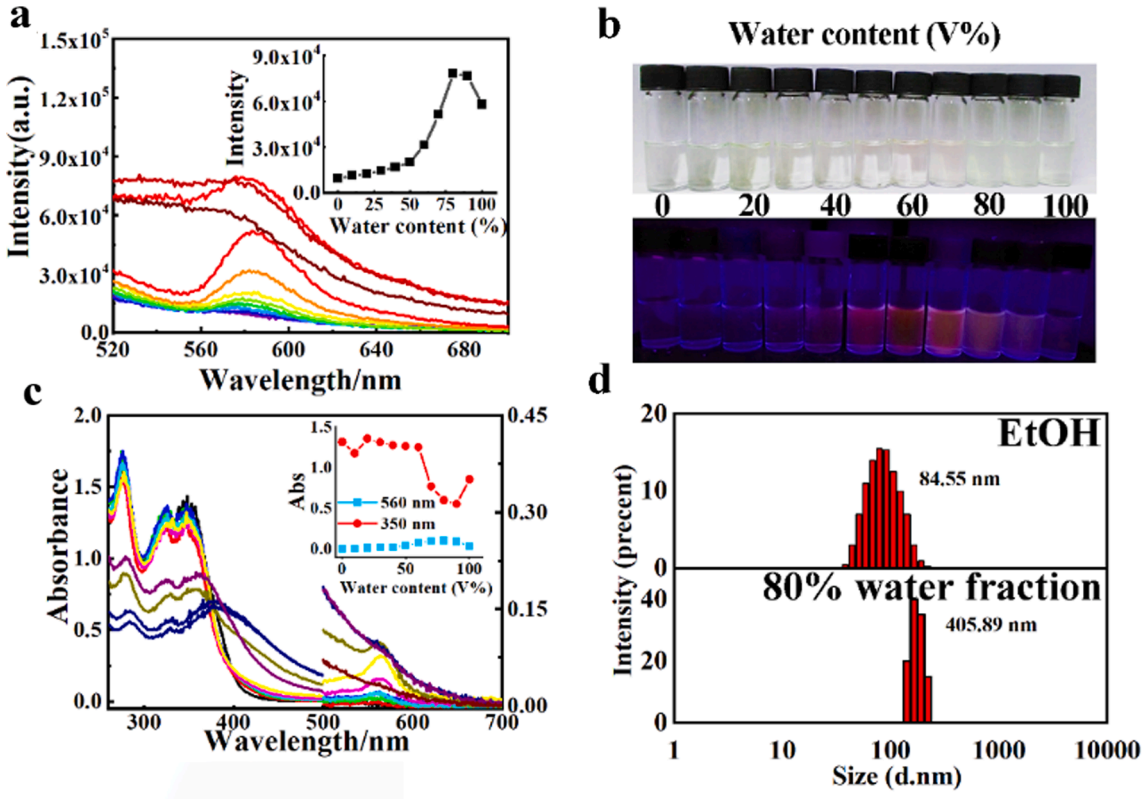

Fig. 1. The AIE properties of compound **1** (50.0 μM). (a) Fluorescence spectra of compound **1** in different water-EtOH fraction, λ_{ex} = 350 nm; (b) Photograph of compound **1** in different water-EtOH fraction under ultraviolet (365 nm) irradiation; (c) UV–vis spectra of compound **1** in different water-EtOH fraction, inset: absorbance of compound **1** in different water fraction at 350 nm and 560 nm, respectively; (d) Particle size of compound **1** in EtOH and 80% water fraction.

Cr(III) probes (compound **1** and **2**) with aggregation-induced emission (AIE) effect were reported, and they showed fluorescence enhancement in response to Cr(III) in 70% water fraction. Cell imaging of compounds **1** and **2** in PC12 cell with $Cr(pic)_3$ administration showed apparent red emission and this result demonstrated decomposition of $Cr(pic)_3$ to Cr (III) in the living cell. This report revealed decomposition of $Cr(pic)_3$ in the living cells and provided a new method to investigate the biological mechanism of $Cr(pic)_3$.

2. Results and discussion

Compounds **1** and **2** were synthesized by the previous method [39] (Scheme 1), and detailed synthetic processes was given in supporting information. The pink solid product was purified by column

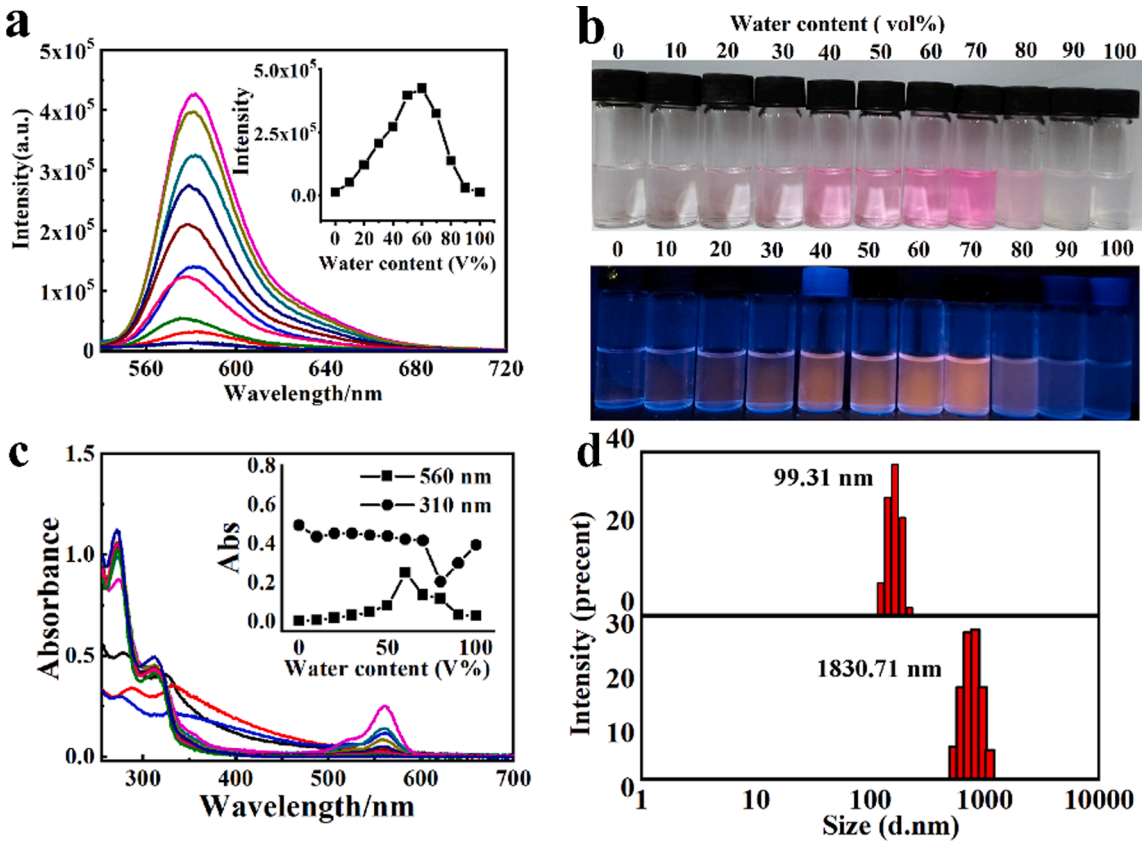

Fig. 2. AIE properties of compound **2** (50.0 μM). (a) Fluorescence spectra of compound **2** in different water-EtOH fraction, λ_{ex} = 350 nm; (b) Images of compound **2** in different water-EtOH fraction under sunlight and UV lamp (365 nm); (c) UV–vis spectra of compound **2** in different water-EtOH fraction; (d) Particle size of compound **2** in EtOH and 70% water fraction.

chromatography, and their structure were characterized by elemental analysis, ESI-MS (Figs. S1 and S3), and ^{1}H NMR (Figs. S2 and S4).

Aggregation-induced emission (AIE) effect of compounds **1** and **2** was investigated by dynamic light scattering (DLS), fluorescent and UV–vis spectroscopy. As shown in Fig. 1a, fluorescence spectrum of compound **1** (50 μM, Ethanol, λ_{ex} = 350 nm) showed weak emission at near 580 nm in pure ethanol (EtOH) solvent, and it persisted low emission before 60% water fraction. Increased emission of compound **1** would be observed at 580 nm with water 70%−90% fraction, and its emission would decrease in pure water comparing to 90% water fraction. Photographs of compound **1** in different EtOH–H_2O mixtures under ultraviolet (365 nm) irradiation and color change of compound **1** in different EtOH–H_2O mixtures were obtained in Fig. 1b. Compound **1** exhibited prominent fluorescence under ultraviolet (365 nm) irradiation with more than 50% water fraction, and this could be attributed to the AIE effect. Besides, UV–vis spectra of compound **1** in different water fractions were shown in Fig. 1c, and the trailing with more than 80% water fraction indicated the aggregation state of compound **1**. Besides, dynamic light scattering (DLS) was used to verify the AIE effect of compound **1**. In Fig. 1d, the particle size of compound **1** in pure EtOH was detected to be 84.5 nm, and it was 405.89 nm in 80% water fractions, which proved the aggregation state of compound **1** in 80% water

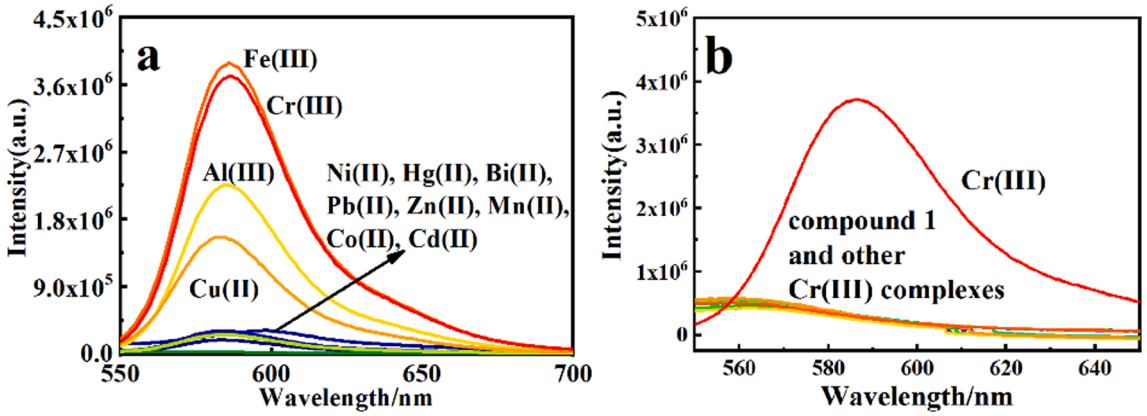

Fig. 3. Fluorescence spectra of compound **1**(10.0 μM) with metal ions (200.0 μM) and Cr(III) compounds (200.0 μM) in Tris(pH 5.0)-EtOH mixture (7:3, V/V): (a) Fluorescence spectra of compound **1** (10.0 μM) with the existence of different metal ions; (b) Interaction of compound **1** (10.0 μM) with varies Cr(III) compounds, λ_{ex} = 350 nm.

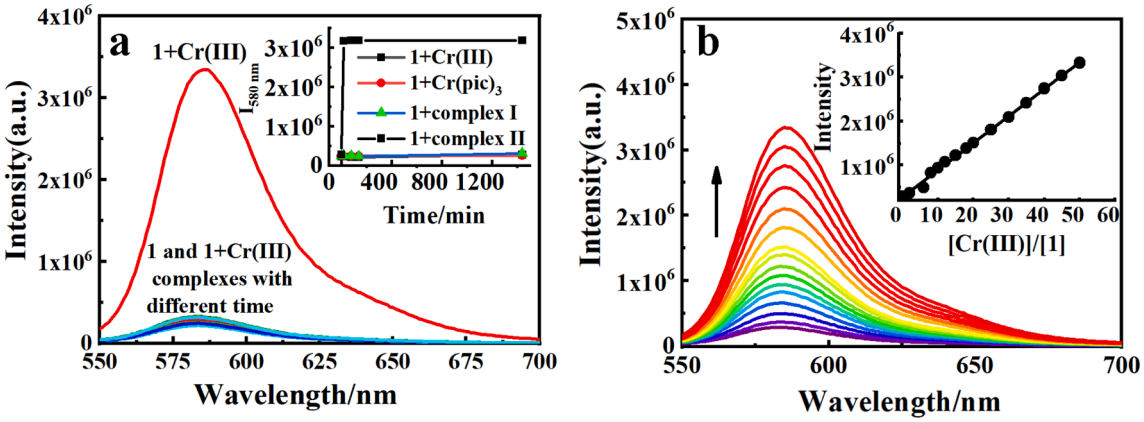

Fig. 4. (a) Kinetic fluorescence enhancement of compound **1**(10.0 μM) in the presence of Cr(III), $Cr(pic)_3$, complex I and complex II (200.0 μM) in Tris(pH 5.0)-EtOH mixture (7:3, V/V), fluorescence intensity were recorded at 580 nm; (b) Fluorescence spectra of compound **1**(10.0 μM) with different concentration of Cr(III) in Tris (pH 5.0)-EtOH mixture (7:3, V/V), λ_{ex} = 350 nm.

fractions. Fluorescence and UV–vis spectroscopy, fluorescence images, and DLS together confirmed AIE effect of compound **1**.

Similar to compound **1**, compound **2** behaved AIE effect in water. Fluorescence spectra of compound **2** (50.0 μM) display weak emission in pure EtOH solution (λ_{ex} = 350 nm), and a new peak appeared at about 580 nm with the addition of water. More addition of water (f_w = 80%) lead to increasement in emission of compound **2**, but the emission significantly decreased when water fraction exceeds 60%. Photographs of compound **2** in different EtOH–H_2O mixtures under ultraviolet (365 nm) and UV–vis spectra in different EtOH–H_2O mixtures also indicated AIE effect of compound **2**. The particle size was 99.31 nm and 1830.71 nm in EtOH and 70% water fraction respectively, which further indicated the aggregation state of compound **2** in 70% water fraction. Therefore, both compounds **1** and **2** were AIEgens, and there are only a few Rh-based AIEgens have been reported [40,41] (see Fig. 2).

2.1. Fluorescence selectivity of compound 1 and 2 to Cr(III)

The selectivity of compound **1** was first studied by fluorescence spectroscopy with metal ions such as Fe(III), Cr(III), Ni(II), Hg(II), Bi(II), Pb(II), Al(III), Mg(II), Cu(II) in the mixture of Tris(pH 5.0)-EtOH (7:3, V/V). In Fig. 3a, fluorescence spectra of compound **1** showed strong pink fluorescence (a maximum at 580 nm) with the addition of Fe(III) and Cr (III). Nevertheless, other metal ions have little influence on the emission of compound **1**. Whereafter, the sensing response of compound **1** to different Cr(III) complexes (including $Cr(en)_3$, $Cr(pic)_3$, Cr(Salen)(en) and $Cr(pic)_3$ derivatives) was also tested. In Fig. 3b, fluorescence spectra of compound **1** (10 μM) displayed strong fluorescence with the addition of Cr(III) and the addition of Cr(III) complexes did not influence the fluorescence spectrum of compound **1**. The selectivity of compound **2** to Cr(III) was also tested by fluorescence spectroscopy, and the result was given in supplementary material (Fig. S5 and S6). This result indicated compounds **1** and **2** put up excellent selectivity to Cr(III), and no significant spectral change of compound **1** was observed with the appearance of Cr(III) complexes. Besides, effect of pH on the Cr(III) detection by compound **1** and **2** was tested by fluorescence spectra (Fig. S7 and S8). As a result, pH 5.0 and pH 5.5 was selected as optimal working solution for detection of Cr(III) by compounds **1** and **2**, respectively. The reason is that acidic conditions may prevent hydrolysis of Cr(III) rather than in neutral and alkaline conditions. Jobs' plots of compound **1** and **2** were also detected by fluorescence spectra (Figs. S9 and S10), and an approximate maximum at a mole fraction of 0.5 indicated the stoichiometry of **2**-Cr^{3+} complex is 1:1. The abnormal fluorescence emission in Jobs' plot of compound **1** was observed, which may be due to the AIE effect of compound **1** in 70% water fraction. The sensing mechanism of compound **1** and **2** to Cr(III) could be an irreversible break of N-N bond and ring open triggered by Cr(III) ions. It was supported by the peak at *m/z* = 442.2487 and *m/z* 442.24906 in ESI–MS analysis of **1**-Cr(III) and **2**-Cr(III), respectively (Figs. S11 and S12).

Table 1
Comparison of analytical methods and parameters of proposed Cr(III) sensor with other reported chemosensors of Cr(III).

Linear range ($mol \cdot L^{-1}$)	Limit of Detection ($mol \cdot L^{-1}$)	pH	Analytical Method	Reference
$8.06–52.6 \times 10^{-5}$	2.42×10^{-6}	2–8	UV–vis spectra	[42]
$0.96–19.23 \times 10^{-6}$	3.85×10^{-7}	12.7	chemiluminescence	[43]
$0– 20 \times 10^{-6}$	1.3×10^{-7}	—	Fluorescent spectra	[38]
$0.001–1000 \times 10^{-6}$	5.0×10^{-11}	—	UV–vis spectra	[44]
$1–21 \times 10^{-6}$	7.5×10^{-8}	4.5–9.0	Fluorescent spectra	[45]
$0.0125–6.815 \times 10^{-6}$	1.5×10^{-6}	8.0	Fluorescent spectra	[46]
$0.5–40 \times 10^{-6}$	3.4×10^{-8}	—	Fluorescent spectra	[47]
$0.1–500 \times 10^{-6}$	3.6×10^{-6}	5.0–5.5	Fluorescent spectra	This report

Fluorescence spectra of compound **1**(10.0 μM) in the presence of Cr (III), $Cr(pic)_3$, complex I and complex II (200.0 μM) were monitored as a function of time till constant. In Fig. 4a, compound **1** reacted with Cr(III) entirely within 5 min, and emission of compound **1** stayed unchanged with the presence of $Cr(pic)_3$, complex I ($Cr(5\text{-}CF_3\text{-}pic)_2(H_2O)_2 \cdot NO_3$) and complex II ($Cr(3\text{-}CH_3\text{-}pic)_2(H_2O)_2 \cdot NO_3$) till 1200 min. This result provided a possibility for cell trace of Cr(III) from $Cr(pic)_3$ by compound **1**. Fluorescence spectra of compound **1** (10.0 μM) upon the gradual addition of different concentrations of Cr(III) were recorded in Fig. 4b. Fluorescence spectra of compound **1** displayed weak emission in mixture of EtOH and Tris mixture (3:7, V/V), and the addition of Cr(III) ions to compound **1** gradually increased intensity at 580 nm. As inset of Fig. 4b, there is an excellent linear relationship between the fluorescence intensity and the concentration of Cr(III) in the range from 1×10^{-6} to 5.00×10^{-4} M, and the limit of detection was calculated to be 3.6 μM. A similar result could be obtained in Cr(III) detection by compound **2**, and the fluorescence spectra were recorded in Figs. S13 and S14. Therefore, compound **1** and compound **2** could be used as sensors for intracellular Cr(III) recognition.

2.2. Comparison with other methods

The proposed fluorescence probes of Cr(III) (compounds **1** and **2**) in this paper was compared with other chemosensors, and the data were

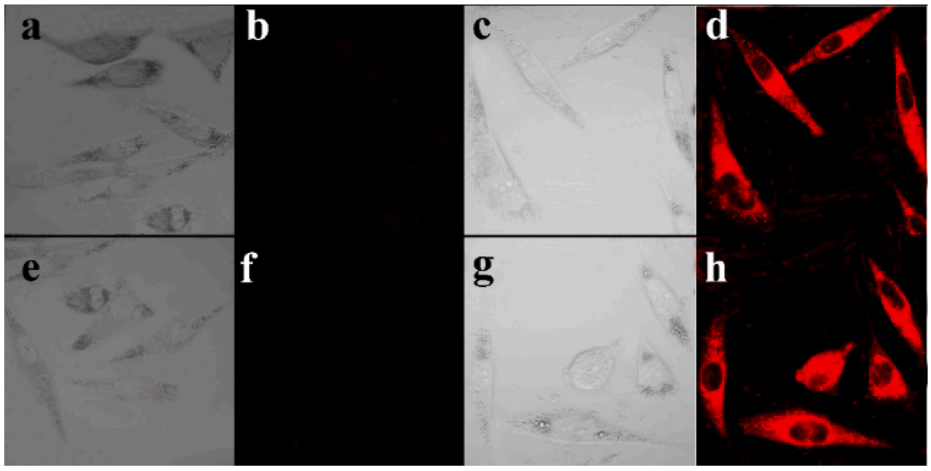

Fig. 5. Confocal fluorescence images of HeLa cells treated by compound **1** and **2** (10.0 μM) with Cr(III): Cells were incubated with compound **1** and **2** for 30 min in 37 °C (brightfield: a, e; darkfield: b, f); Cells incubated with compound **1** and **2** for 30 min and subsequently with $CrCl_3$ (0.1 mM) for another 30 min (brightfield: c, g; darkfield: d, h).

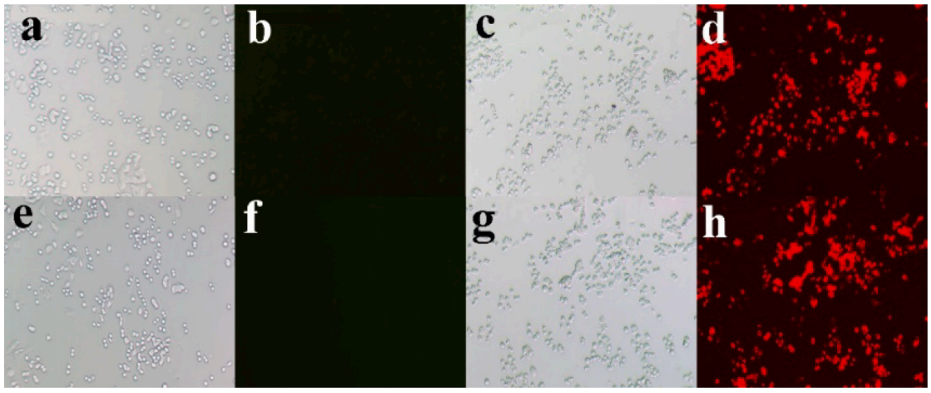

Fig. 6. Fluorescence images of PC12 cell lines: Images of PC12 cells treated by compound **1** (10.0 μM) for 30 min (brightfield: a, e; darkfield: b and f). Images of PC12 cell treated with compound **1** (10.0 μM) for 30 min and subsequently with $Cr(pic)_3$ (10.0 μM) for another 30 min (brightfield: c; Darkfield: d); Images of PC12 cell treated with compound **1** (10.0 μM) for 30 min and subsequently with $[Cr(5CF_3\text{-}pic)_2(H_2O)_2{\cdot}H_2O]NO_3$ (10.0 μM) for another 30 min (brightfield: g; Darkfield: h).

listed in Table 1. Although probes in this report were less sensitive than some probes reported previously, and it showed a wider linear relationship in Cr(III) detection. However, application of compounds **1** and **2** would be limited in real samples for its acidic condition required in Cr (III) probing, and this side-effect would be improved.

2.3. Probing Cr(III) from $Cr(pic)_3$ by compound *1* and *2*

To monitor decomposition of $Cr(pic)_3$, compounds **1** and **2** were first used to examine Cr(III) in Hela cell. Hela cell was cultured in Dulbecco's modified Eagle's medium (DMEM) supplemented with 10% fetal calf serum (FCS, Gibco) (penicillin/streptomycin 100 μg/mL) for 12 h to allow adherence. Compound **1** and **2** (10 μM) was added to cell lines for 30 min incubation, and fluorescence images was obtained under laser confocal. Then, Cr(III) (0.1 mM) was added to cells treated by compound **1** and **2** subsequently for another 30 min incubation, and images were obtained under laser confocal. As shown in Fig. 5, fluorescence images of Hela cells treated by compound **1** and compound **2** showed weak emission both in brightfield and darkfield (Fig. 5a, b and e, f), and strong red emission could be observed with the addition of Cr(III) to Hela cell (Fig. 5d and h). This result indicated the excellent fluorescence enhanced sensing of compounds **1** and **2** to Cr(III) in living cells.

Whereafter, the decomposition of $Cr(pic)_3$ and its derivatives were studied by cells imaging. In this experiment, commercial used Cr(III) supplements $Cr(pic)_3$, and $[Cr(5CF_3\text{-}pic)_2(H_2O)_2{\cdot}H_2O]NO_3$ was employed in nerve cell PC12 to investigate the decomposition $Cr(pic)_3$ and its derivatives. PC12 cells were cultured in DMEM for 14 h, and compound **1** (10.0 μM) was added to cells for 30 min incubation. Fluorescence image of PC12 cells treated with compound **1** for 30 min showed weak emission (Fig. 6a, b and e, f), and addition of $Cr(pic)_3$ or $[Cr(5CF_3\text{-}pic)_2(H_2O)_2{\cdot}H_2O]NO_3$ to cell lines for another 30 min incubation led to strong red emission in the red channel (Fig. 6c, d and g, h). This result indicated the generation of Cr(III) by $Cr(pic)_3$ and $[Cr(5CF_3\text{-}pic)_2(H_2O)_2{\cdot}H_2O]NO_3$, and it demonstrated decomposition of $Cr(pic)_3$ and $[Cr(5CF_3\text{-}pic)_2(H_2O)_2{\cdot}H_2O]NO_3$ in the living cell. Compound **2** was also used to recognize Cr(III) from $Cr(pic)_3$ and $[Cr(5CF_3\text{-}pic)_2(H_2O)_2{\cdot}H_2O]NO_3$, and the same result was obtained by cell imaging (Fig. S15). This result demonstrated the generation of Cr(III) by $Cr(pic)_3$ in the living cells, and this result is different from the previous reports [22]. As a result, Cr(III) fluorescent sensor might be used as a tracer for mechanism detection of $Cr(pic)_3$.

Metabolism of $Cr(pic)_3$ and biological target of Cr(III) have always been pendent, and Cr(III) has been traced by radioactive ^{51}Cr [48]. However, radiological analysis is harmful to the organisms, which is dangerous and high consumption. According to the result above, fluorescence probes could be used to investigate the metabolism of $Cr(pic)_3$.

3. Conclusion

In this paper, two fluorescent probes (compound **1** and **2**) with AIE

effect were prepared by rhodamine B. AIE effect of two probes was confirmed by fluorescence spectra, UV–vis spectra and DLS. Besides, compounds **1** and **2** responded to Cr(III) within 5 min with a limit of detection of 3.6 μM. Cells imaging indicated effective response of compounds **1** and **2** to Cr(III) in cell line and decomposition of $Cr(pic)_3$. This result provides a new thought for $Cr(pic)_3$ research, and Cr(III) probe could be used to detect the metabolism of Cr(III) in *vivo*.

CRediT authorship contribution statement

Jie Chai: Investigation, Writing - original draft. **Jinlong Dong:** Investigation. **Binsheng Yang:** Supervision. **Pengli Guan:** Investigation. **Xiaoqin Wei:** Writing - review & editing. **Yien Du:** Funding acquisition. **Bin Liu:** Conceptualization, Supervision, Funding acquisition, Writing - review & editing. **Guangming Wen:** Writing - review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.inoche.2021.108579.

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