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# A smart “off–on” gate for the *in situ* detection of hydrogen sulphide with Cu(II)-assisted europium emission†

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A water-soluble and emissive Eu-complex (**EuL1**) bearing a DO3A(Eu<sup>3+</sup>)-pyridine-aza-crown motif has been prepared and its Cu<sup>2+</sup> complex has been demonstrated to be a smart luminescence “off–on” gate for H<sub>2</sub>S detection in water with a nano-molar detection limit (60 nM). **EuL1** binds to Cu<sup>2+</sup> ions selectively ( $K_B = 1.2 \times 10^5 \text{ M}^{-1}$ ) inducing 17-fold luminescence quenching and forming a 1 : 1 stoichiometric complex (**EuL1**–Cu<sup>2+</sup>), which responds to H<sub>2</sub>S selectively with restoration of the original Eu emission of **EuL1** followed by a further 40-fold luminescence enhancement, forming a 1 : 1 stoichiometric complex (**EuL1**–Na<sub>2</sub>S,  $K_B = 1.5 \times 10^4 \text{ M}^{-1}$ ). Without Cu<sup>2+</sup> ions, **EuL1** showed non-specific binding towards H<sub>2</sub>S with only a 5-fold luminescence enhancement.

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## Introduction

Hydrogen sulphide (H<sub>2</sub>S) is the smallest bioactive thiol that may act as a gaseous signalling agent,<sup>1</sup> and its production in different tissue types is associated with a wide range of physiological responses such as vascular smooth muscle relaxation,<sup>2</sup> mitochondrial ATP production,<sup>3</sup> insulin-signalling inhibition,<sup>4</sup> regulation of inflammation response<sup>5</sup> and mediation of neurotransmission.<sup>6</sup> Moreover, recent investigations show that abnormal levels of H<sub>2</sub>S are associated with a variety of diseases, such as neurodegenerative diseases,<sup>7</sup> diabetes<sup>8</sup> and cancer.<sup>9</sup> However, the biological targets of H<sub>2</sub>S and the mechanisms of these H<sub>2</sub>S-related physiological phenomena remain unclear. Therefore the development of responsive and reversible luminescence probes for non-invasive real time monitoring of H<sub>2</sub>S may be useful for understanding its biological modes of action.

One of the major approaches for developing luminescence H<sub>2</sub>S detection<sup>10</sup> is based on sulphide-specific chemical reactions, such as reduction of an azide<sup>11</sup> and nucleophilic addition of a sulphide ion.<sup>12</sup> This type of luminescence probe is generally irreversible and usually requires a considerably long incubation

time. An alternative approach is based on CuS precipitation<sup>13</sup> due to the low-solubility of CuS ( $K_{sp} = 6.3 \times 10^{-36}$ ). These luminescence probes are generally reversible with low detection limits. We are particularly interested in developing H<sub>2</sub>S luminescence sensors based on organo-lanthanide complexes due to their water-solubility and unique photophysical properties, including line-like emission spectra and long luminescence lifetimes (micro to milli second scale) that can effectively separate the observing signal from biological autofluorescence noise and are suitable for time-gated detection. Recently, a few studies have been found in the literature with irreversible H<sub>2</sub>S lanthanide probes.<sup>12a</sup> Herein, we report the development of a novel responsive europium-based luminescence “off–on” gate for the *in situ* detection of H<sub>2</sub>S in water.

As illustrated in Fig. 1, **EuL1** contains a DO3A–Eu<sup>3+</sup> complex and an aza-18-crown-6 moiety, which are linked to the 2- and 6-positions of a pyridine-containing chromophore constituting a switch-like structure. In the ground state, **EuL1** should be emissive due to the coordination of the pyridine chromophore

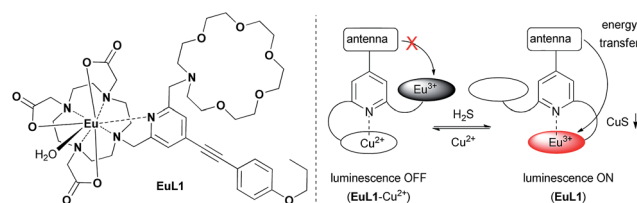


Fig. 1 The structure of **EuL1** and the illustration of the design of a reversible Eu-based luminescence probe (**EuL1**–Cu<sup>2+</sup>) for H<sub>2</sub>S detection.

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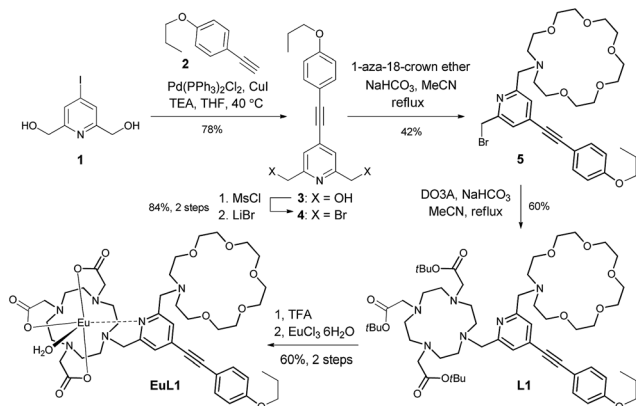
† Electronic supplementary information (ESI) available: Detailed experimental procedures, characterization of compounds, NMR spectra and supplementary fluorometric titration studies. See DOI: 10.1039/c5sc04091d

to a  $\text{Eu}^{3+}$  ion, which favours energy transfer from the organic chromophore to the  $\text{Eu}^{3+}$  ion. Upon binding of the aza-18-crown-6 moiety with a  $\text{Cu}^{2+}$  ion, pyridine is expected to coordinate with the  $\text{Cu}^{2+}$  ion, resulting in luminescence quenching. The europium emission should be recovered after the displacement of the  $\text{Cu}^{2+}$  ion upon copper sulphide precipitation.

## Results and discussion

### Synthesis and photophysical properties of L1 and EuL1

Ligand **L1** was readily prepared from (4-iodopyridine-2,6-diyl) dimethanol (**1**)<sup>14</sup> via a desymmetrization synthetic strategy. As shown in Scheme 1, a pyridine-containing chromophore (based on a D- $\pi$ -A motif) was established via a Sonogashira cross-coupling reaction between **1** and 1-ethynyl-4-propoxybenzene (**2**).<sup>15</sup> After converting both hydroxyl groups of **3** into the corresponding bromide, the aza-18-crown-6 and DO3A moieties were incorporated into **4** sequentially under basic conditions and afforded **L1** in good yields. **L1** was fully characterized using  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectroscopy and HRMS. Finally, acid hydrolysis of the *t*-butyl esters followed by Eu complex formation provided **EuL1**, which was characterized unambiguously using HRMS and HPLC (Table S1 and Fig. S1†).



Scheme 1 Synthesis of L1 and EuL1.

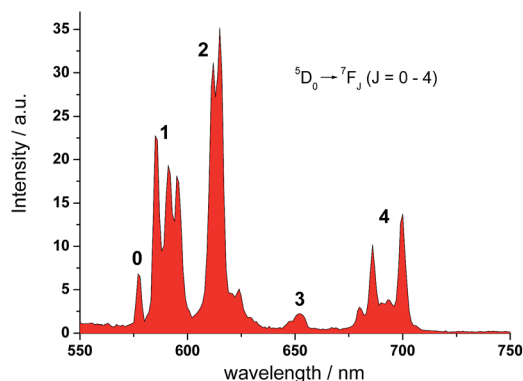


Fig. 2 Emission spectrum of **EuL1** ( $\text{H}_2\text{O}$ ,  $\lambda_{\text{ex}} = 325$  nm, 10  $\mu\text{M}$ ).

In the UV-vis absorption spectrum, **L1** showed strong absorption bands at 235 and 310 nm in methanol which are attributed to the  $\pi$  to  $\pi^*$  transitions. The absorption bands were broadened and red-shifted in **EuL1** (245 and 333 nm,  $\epsilon_{333 \text{ nm}} = 7560 \text{ M}^{-1} \text{ cm}^{-1}$ ) in water (Fig. S2†). The excitation spectrum of **EuL1** at 615 nm showed maxima at 240 and 340 nm (Fig. S2†), evidencing an antenna effect due to energy transfer from the ligand to the  $\text{Eu}^{3+}$  ion. The  $^5\text{D}_0 \rightarrow ^7\text{F}_J$  transitions of **EuL1** ( $\lambda_{\text{ex}} = 325$  nm) were found at 578 ( $J = 0$ ), 585–603 ( $J = 1$ ), 604–637 ( $J = 2$ ), 646–658 ( $J = 3$ ), and 673–712 nm ( $J = 4$ ) in the emission spectrum (Fig. 2). The quantum yield of **EuL1** corresponding to the  $^5\text{D}_0 \rightarrow ^7\text{F}_2$  transitions of  $\text{Eu}^{3+}$  ions in water is 0.5% (Table S2†).

### Fluorimetric titration studies of EuL1

With **EuL1** in hand, its binding properties towards  $\text{Cu}^{2+}$  ions were investigated. Upon the addition of 1 equiv. of  $\text{Cu}^{2+}$  ions ( $\text{CuCl}_2$  as the source of  $\text{Cu}^{2+}$  ions), the absorption maximum of **EuL1** showed a slight red shift and the absorption ability slightly decreased due to the effect of the copper metal. In a titration study, **EuL1** exhibited a 17-fold quenching of the

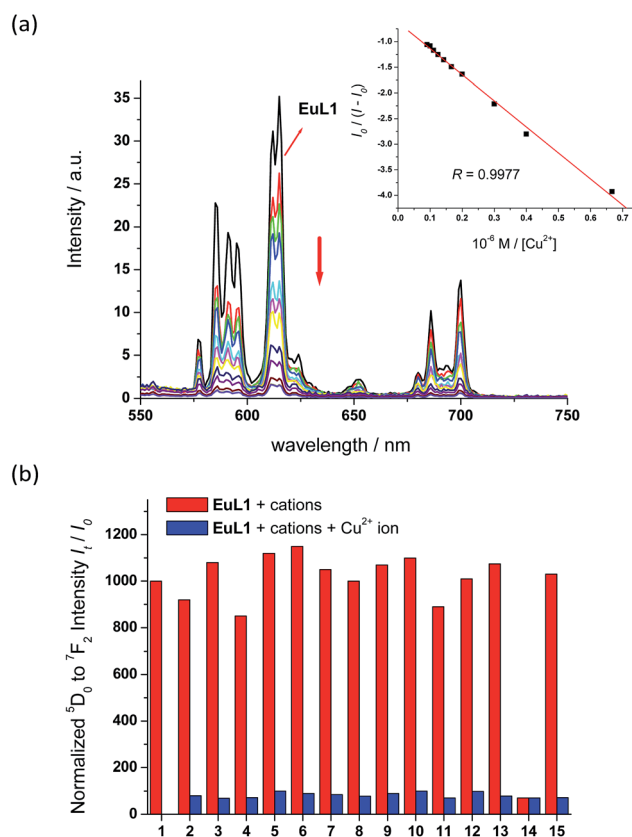


Fig. 3 (a) Fluorimetric titration of **EuL1** (10  $\mu\text{M}$ ) towards  $\text{Cu}^{2+}$ . The inset shows the plot of  $I_0/(I - I_0)$  vs.  $[\text{Cu}^{2+}]$  (0–20  $\mu\text{M}$ ).  $I$  and  $I_0$  stand for intensity of europium emission  $^5\text{D}_0 \rightarrow ^7\text{F}_2$ . (b) Effects of various metal ions on the luminescence intensity of **EuL1** (10  $\mu\text{M}$ ). 1: **EuL1** only; 2:  $\text{Na}^+$ ; 3:  $\text{K}^+$ ; 4:  $\text{Ca}^{2+}$ ; 5:  $\text{Mg}^{2+}$ ; 6:  $\text{Ba}^{2+}$ ; 7:  $\text{Co}^{2+}$ ; 8:  $\text{Zn}^{2+}$ ; 9:  $\text{Ni}^{2+}$ ; 10:  $\text{Fe}^{2+}$ ; 11:  $\text{Mn}^{2+}$ ; 12:  $\text{Cu}^+$ ; 13:  $\text{Li}^+$ ; 14:  $\text{Cu}^{2+}$ ; 15: all of the above metal ions except  $\text{Cu}^{2+}$ . All spectra were acquired in water with excitation at 325 nm.



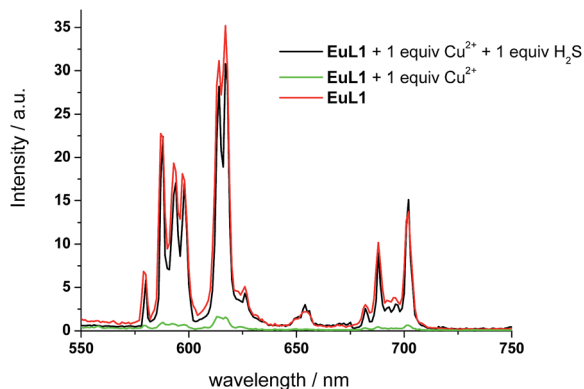


Fig. 4 The emission spectra of **EuL1** (10  $\mu$ M) (red), with 1 equiv. of  $\text{Cu}^{2+}$  ions (green), and with 1 equiv. of  $\text{Cu}^{2+}$  ions and 1 equiv. of  $\text{H}_2\text{S}$  (black). All spectra were acquired in water with  $\lambda_{\text{ex}}$  at 325 nm.

europium emission with an excess of  $\text{Cu}^{2+}$  ions and the Benesi-Hildebrand plot showed a 1 : 1 binding stoichiometry with  $K_B = 1.2 \times 10^5 \text{ M}^{-1}$  (inset of Fig. 3a).<sup>16</sup> The Job's plot also supported the formation of a **EuL1**- $\text{Cu}^{2+}$  complex in a 1 : 1 ratio (Fig. S3†).

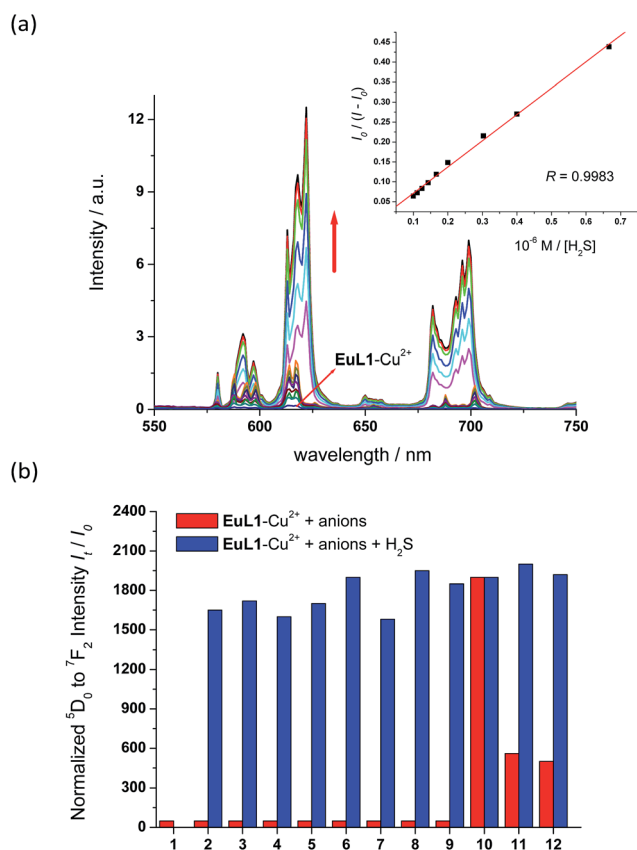


Fig. 5 (a) Fluorimetric titration of **EuL1**- $\text{Cu}^{2+}$  (10  $\mu$ M, generated *in situ* with 2 equiv. of  $\text{Cu}^{2+}$ ) towards  $\text{H}_2\text{S}$  (0–100  $\mu$ M). The inset shows the plot of  $I_0/(I - I_0)$  vs.  $[\text{Na}_2\text{S}]$  (0–100  $\mu$ M).  $I$  and  $I_0$  stand for intensity of europium emission  ${}^5\text{D}_0 \rightarrow {}^7\text{F}_2$ . (b) Effects of various anions on the luminescence intensity of **EuL1** (10  $\mu$ M). 1: **EuL1** only; 2:  $\text{Cl}^-$ ; 3:  $\text{SO}_4^{2-}$ ; 4:  $\text{HSO}_4^-$ ; 5:  $\text{I}^-$ ; 6:  $\text{CO}_3^{2-}$ ; 7:  $\text{HPO}_4^{2-}$ ; 8:  $\text{Br}^-$ ; 9:  $\text{HCO}_3^-$ ; 10:  $\text{S}^{2-}$ ; 11: GSH; 12: cysteine. All spectra were acquired in water with excitation at 325 nm.

In a competitive study, the addition of a large excess of various metal ions, such as  $\text{Na}^+$ ,  $\text{K}^+$ ,  $\text{Ca}^{2+}$ ,  $\text{Mg}^{2+}$ ,  $\text{Ba}^{2+}$ ,  $\text{Co}^{2+}$ ,  $\text{Zn}^{2+}$ ,  $\text{Ni}^{2+}$ ,  $\text{Fe}^{2+}$ ,  $\text{Mn}^{2+}$ ,  $\text{Cu}^+$  and  $\text{Li}^+$  ions, to **EuL1** resulted in only slight luminescence changes (red columns in Fig. 3b). The subsequent addition of excess  $\text{Cu}^{2+}$  ions caused significant luminescence quenching (blue columns in Fig. 3b). These results indicate the high selectivity of **EuL1** towards  $\text{Cu}^{2+}$  ions and that the binding between **EuL1** and  $\text{Cu}^{2+}$  ions is not interfered by other metal ions. In a pH study, **EuL1** remains highly emissive and was quenched by  $\text{Cu}^{2+}$  ions in the pH range 6 to 8 (Fig. S4†), indicating that **EuL1** is stable and can bind to  $\text{Cu}^{2+}$  ions under physiological conditions.

To study the reversibility of the binding between **EuL1** and  $\text{Cu}^{2+}$  ions, a small amount of  $\text{H}_2\text{S}$  ( $\text{Na}_2\text{S}$  as the source of  $\text{H}_2\text{S}$ ) was added. The **EuL1**- $\text{Cu}^{2+}$  complex responded instantaneously (requiring only 40 s to reach saturation without stirring or shaking) (Fig. S5†), and Eu emission resumed with a similar profile for the emission spectrum to that of **EuL1** (Fig. 4). This result indicated that the  $\text{DO3A-Eu}^{3+}$  complex was not displaced by a  $\text{Cu}^{2+}$  ion, forming the **EuL1**- $\text{Cu}^{2+}$  complex in the previous step. More interestingly, Eu emission was further enhanced (40-fold) with an excess of  $\text{H}_2\text{S}$  and the  $\text{Eu}^{3+}$  emission profile showed significant changes, suggesting binding between **EuL1** and  $\text{H}_2\text{S}$  (Fig. 5a). The Benesi-Hildebrand plot showed a 1 : 1 binding stoichiometry with  $K_B = 1.5 \times 10^4 \text{ M}^{-1}$  (inset of Fig. 5a).<sup>16</sup> The detection limit of **EuL1** towards  $\text{H}_2\text{S}$  was calculated according to the  $3S_D/\text{slope}$  as low as 60 nM. Surprisingly, direct titration of **EuL1** against  $\text{H}_2\text{S}$  resulted in only about a 5-fold luminescence enhancement with a non-linear relationship in the 1 : 1 Benesi-Hildebrand plot (Fig. 6). These results indicated that the  $\text{Cu}^{2+}$  ion facilitates the specific 1 : 1 binding of **EuL1** and  $\text{H}_2\text{S}$ , presumably *via* pre-organizing the conformation of **EuL1**. On the other hand, non-specific binding (possibly a mixture of 1 : 1 and 2 : 1 binding) between **EuL1** and  $\text{H}_2\text{S}$  resulted without the favourable conformation that is induced by

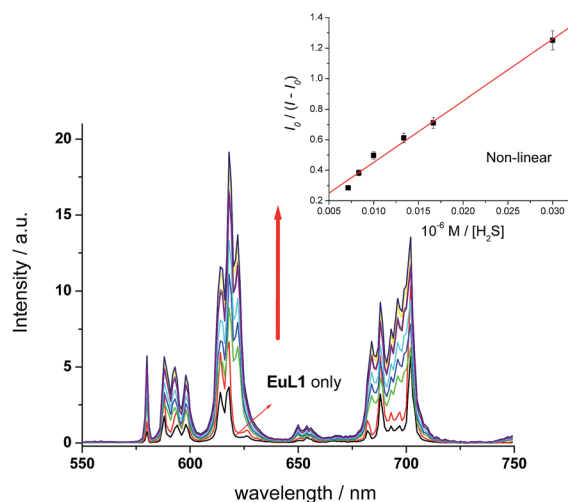


Fig. 6 Fluorimetric titration of **EuL1** (10  $\mu$ M) towards  $\text{H}_2\text{S}$  (0–300  $\mu$ M). The inset shows the plot of  $I_0/(I - I_0)$  vs.  $[\text{H}_2\text{S}]$  (0–300  $\mu$ M).  $I$  and  $I_0$  stand for intensity of europium emission  ${}^5\text{D}_0 \rightarrow {}^7\text{F}_2$ . All spectra were acquired in water with  $\lambda_{\text{ex}}$  at 325 nm.



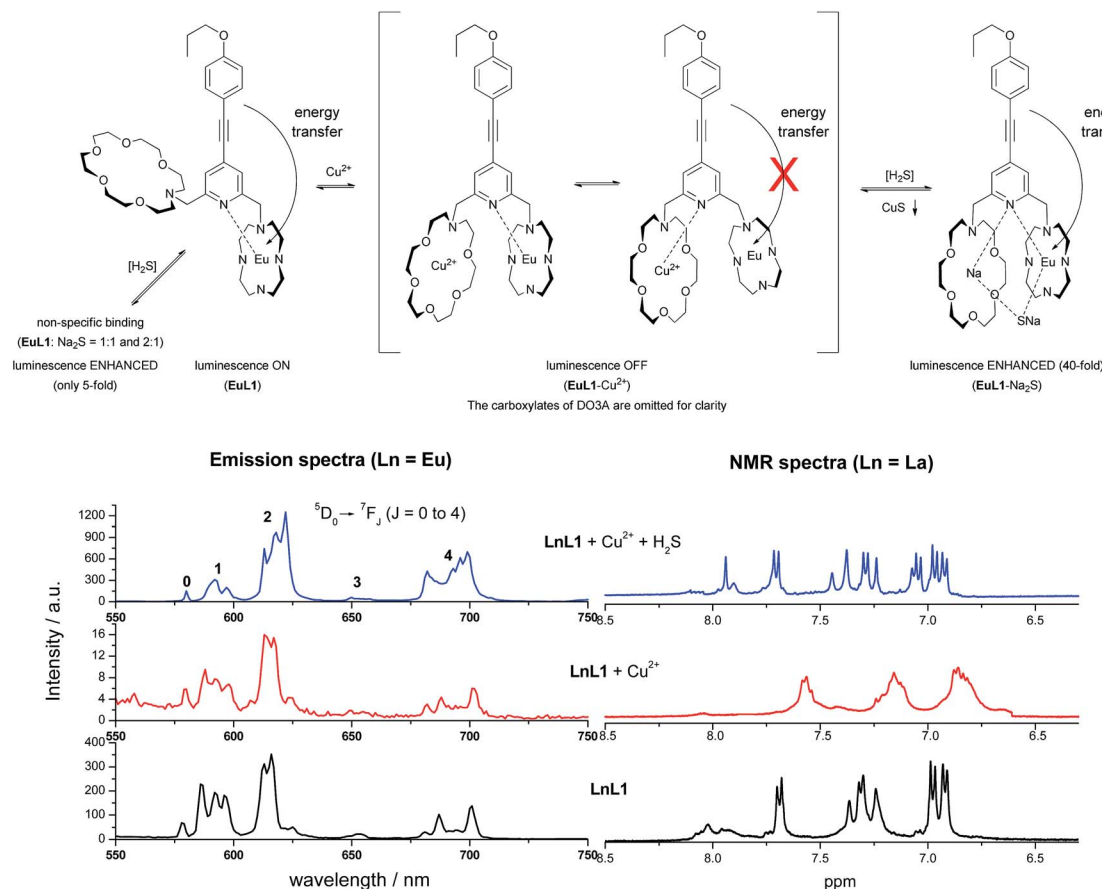


Fig. 7 Top: proposed binding mechanism of **EuL1** towards Cu<sup>2+</sup> and H<sub>2</sub>S (Na<sub>2</sub>S as the source of H<sub>2</sub>S). Bottom left: emission spectra of the Eu complexes ( $\lambda_{\text{ex}} = 325$  nm). Bottom right: <sup>1</sup>H NMR spectra of the La complexes (6.5–8.5 ppm).

the pre-complexation of a Cu<sup>2+</sup> ion. This proposal was further supported by the dramatic luminescence drop of the **EuL1**–Na<sub>2</sub>S complex upon heating (>70 °C) (Fig. S6†). This type of Cu<sup>2+</sup>-assisted luminescence enhancement of Eu emission is unprecedented. In a competitive study, **EuL1**–Cu<sup>2+</sup> showed insignificant changes in luminescence with a large excess of anions, including Cl<sup>–</sup>, SO<sub>4</sub><sup>2–</sup>, HSO<sub>4</sub><sup>–</sup>, I<sup>–</sup>, CO<sub>3</sub><sup>2–</sup>, HPO<sub>4</sub><sup>2–</sup>, Br<sup>–</sup> and HCO<sub>3</sub><sup>–</sup>, and only small changes for GSH and cysteine (red columns in Fig. 5b). Upon the addition of H<sub>2</sub>S, the Eu emissions were recovered in all the above cases, indicating a high selectivity of **EuL1**–Cu<sup>2+</sup> towards H<sub>2</sub>S.

### Mechanistic studies

The binding mechanisms of **EuL1** towards Cu<sup>2+</sup> ions and the **EuL1**–Cu<sup>2+</sup> complex towards H<sub>2</sub>S were studied using

Table 1 The ratio of <sup>5</sup>D<sub>0</sub> → <sup>7</sup>F<sub>J</sub> (J = 0 to 4) emission bands of **EuL1**, **EuL1** + Cu<sup>2+</sup> and **EuL1** + Cu<sup>2+</sup> + H<sub>2</sub>S<sup>a</sup>

<sup>5</sup> D <sub>0</sub> →	<sup>7</sup> F <sub>0</sub>	<sup>7</sup> F <sub>1</sub>	<sup>7</sup> F <sub>2</sub>	<sup>7</sup> F <sub>3</sub>	<sup>7</sup> F <sub>4</sub>
<b>EuL1</b>	0.01	1	1.22	0.08	0.55
<b>EuL1</b> + Cu <sup>2+</sup>	0.08	1	1.86	0.15	0.91
<b>EuL1</b> + Cu <sup>2+</sup> + H <sub>2</sub> S	0.48	1	3.98	0.15	1.95

<sup>a</sup> All spectra were acquired in water with excitation at 325 nm.

a comparative analysis of the emission spectra of the Eu complexes and the <sup>1</sup>H NMR spectra of La complexes.<sup>17</sup> As shown in Fig. 7, the profile of the emission spectrum of **EuL1** did not change significantly upon the addition of Cu<sup>2+</sup> ions. Comparing [**EuL1**], [**EuL1** + Cu<sup>2+</sup>] and [**EuL1** + Cu<sup>2+</sup> + H<sub>2</sub>S], measured under the same solution conditions, similar spectra were observed for [**EuL1**] and [**EuL1** + Cu<sup>2+</sup>] (<sup>5</sup>D<sub>0</sub> → <sup>7</sup>F<sub>1</sub>:<sup>7</sup>F<sub>2</sub>:<sup>7</sup>F<sub>4</sub> of [**EuL1**] = 1 : 1.122 : 0.55 and <sup>5</sup>D<sub>0</sub> → <sup>7</sup>F<sub>1</sub>:<sup>7</sup>F<sub>2</sub>:<sup>7</sup>F<sub>4</sub> [**EuL1** + Cu<sup>2+</sup>] = 1 : 1.186 : 0.91, Table 1). This is correlated with the NMR data and shows that the Cu<sup>2+</sup> ion is coordinated in the aza-crown. However, signal broadening was observed in the <sup>1</sup>H NMR spectrum of **LaL1**, indicating rapid metal–ligand exchange. These results suggested that the pyridine moiety of the organic chromophore is rapidly switching between the DO3A–Eu<sup>3+</sup> and

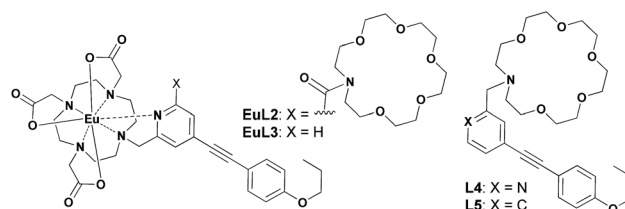


Fig. 8 The structures of the negative control compounds **EuL2**, **EuL3**, **L4** and **L5**.

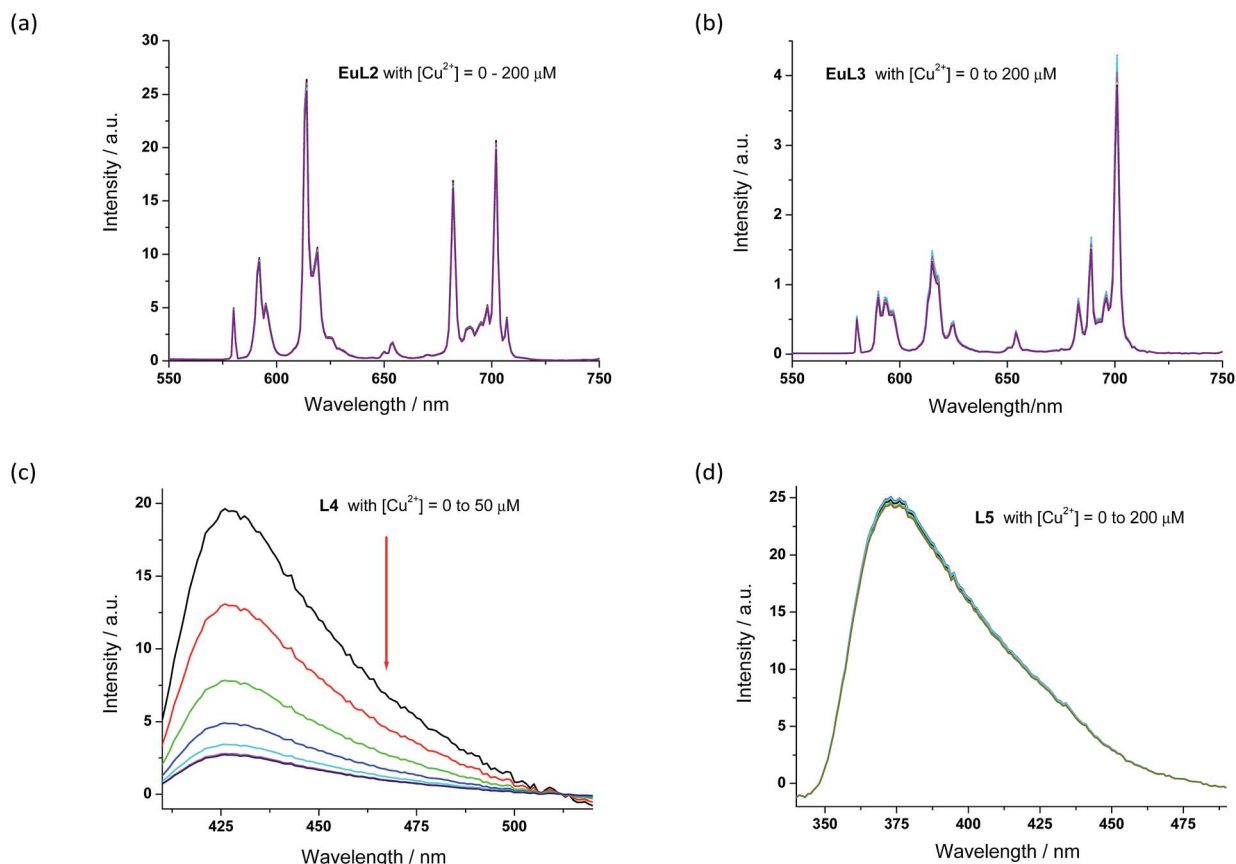


Fig. 9 The emission spectra of negative control compounds (10  $\mu\text{M}$ ) with various concentration of  $\text{Cu}^{2+}$  ions. (a): **EuL2**; (b): **EuL3**; (c): **L4**; (d): **L5**. All spectra were acquired in water with  $\lambda_{\text{ex}}$  at 325 nm.

aza-18-crown-6- $\text{Cu}^{2+}$  complexes, causing significant luminescence quenching. Moreover, the binding of  $\text{Cu}^{2+}$  would also provide a favourable conformation for forming a new 1 : 1 complex with  $\text{H}_2\text{S}$ . Upon the addition of  $\text{H}_2\text{S}$ , the emission profile of **EuL1** changed significantly,  $\Delta J = 2/\Delta J = 1$  for [**EuL1** +  $\text{Cu}^{2+}$  +  $\text{H}_2\text{S}$ ],<sup>18</sup> and the intensity ratio was about >200% higher for [**EuL1**] and [**EuL1** +  $\text{Cu}^{2+}$ ]. This increase can be attributed to the lower symmetry of the complexes with the addition of sulphide ions (Fig. 7) and the  $^1\text{H}$  NMR signals of **LaL1** were sharpened. These results suggested new complex formation after the displacement of the  $\text{Cu}^{2+}$  ion *via*  $\text{CuS}$  precipitation. This proposal is further supported by the HRMS spectrum of the **EuL1**- $\text{Na}_2\text{S}$  complex (Fig. S7†) and the change in the quantum yields (Table S2†). The **EuL1**- $\text{Na}_2\text{S}$  complex is highly emissive probably due to its rigid structure.

The proposed binding mechanism was also examined using a series of negative control compounds (Fig. 8).<sup>19</sup> **EuL2** showed no luminescence quenching upon the addition of  $\text{Cu}^{2+}$  ions (Fig. 9a). This result indicated that the carbonyl linker of aza-18-crown-6 may be too rigid for coordination between  $\text{Cu}^{2+}$  and pyridine, which could be essential for Eu emission quenching. Without the aza-crown moiety, **EuL3** also showed no luminescence quenching towards  $\text{Cu}^{2+}$  (Fig. 9b), suggesting DO3A- $\text{Eu}^{3+}$  is stable with  $\text{Cu}^{2+}$  and the aza-crown motif is important for the  $\text{Cu}^{2+}$  binding. **L4** bearing the pyridine-chromophore showed

profound luminescence quenching, but its phenyl analogue (**L5**) showed no significant change in luminescence upon the addition of  $\text{Cu}^{2+}$  ions (Fig. 9c and d). These results indicated that the pyridine moiety of the chromophore is essential for the binding of  $\text{Cu}^{2+}$  to the aza-crown moiety. The results of this series of negative control compounds are in full agreement with the proposed mechanism in Fig. 7.

## Conclusions

In summary, we have prepared a water-soluble and emissive Eu-complex (**EuL1**) based on a DO3A( $\text{Eu}^{3+}$ )-pyridine-aza-crown motif, and studied its consecutive binding properties towards  $\text{Cu}^{2+}$  and  $\text{H}_2\text{S}$  extensively. **EuL1** binds to  $\text{Cu}^{2+}$  ions selectively ( $K_{\text{B}} = 1.2 \times 10^5 \text{ M}^{-1}$ ) inducing 17-fold luminescence quenching and forming a 1 : 1 stoichiometric complex (**EuL1**- $\text{Cu}^{2+}$ ), which responds to  $\text{H}_2\text{S}$  selectively with restoration of the original **EuL1** emission followed by a further 40-fold luminescence enhancement and a nano-molar detection limit (60 nM). Mass spectroscopic analysis showed the formation of a 1 : 1 stoichiometric complex (**EuL1**- $\text{Na}_2\text{S}$ ) with  $K_{\text{B}} = 1.5 \times 10^4 \text{ M}^{-1}$ . Without  $\text{Cu}^{2+}$  ions, **EuL1** shows non-specific binding towards  $\text{H}_2\text{S}$  with only a 5-fold luminescence enhancement. These results indicate that the  $\text{Cu}^{2+}$  ion may pre-organize the conformation of **EuL1** and facilitate the formation of the **EuL1**- $\text{Na}_2\text{S}$  complex. The studies





on this unprecedented Cu<sup>2+</sup>-assisted luminescence enhancement of Eu emission are still ongoing. With long-lived Eu emission, reversible binding properties, an instantaneous response and high selectivity towards H<sub>2</sub>S, this Eu-based luminescence “off-on” gate could find suitable applications for H<sub>2</sub>S imaging in biological systems.

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