# Click synthesis of a quinoline-functionalized homooxacalix[3]arene: a turn-on fluorescence chemosensor for Fe$^{3+}$

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**ABSTRACT:** A novel quinoline-functionalized homooxacalix[3]arene **L** was synthesized via Click chemistry and its chemosensing properties with various metal ions were investigated. The chemosensor **L** exhibited a high selectivity and anti-disturbance for Fe$^{3+}$ amongst environmentally and biologically relevant metal ions, leading to a prominent 'off-on' type fluorescent signalling behaviour. Our studies demonstrated that the detection limit on fluorescence response of the sensor to Fe$^{3+}$ is in the $10^{-7}$ M range. The mechanism of the interaction between the **L** and Fe$^{3+}$ has been investigated in detail by $^1$H NMR spectroscopic titration experiments.

**Keywords:** Click synthesis, Quinoline, Homooxacalix[3]arene, Fluorescence chemosensor, Fe$^{3+}$.

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**Graphical Abstract**



Fluorescence "weak"        Fluorescence "on"
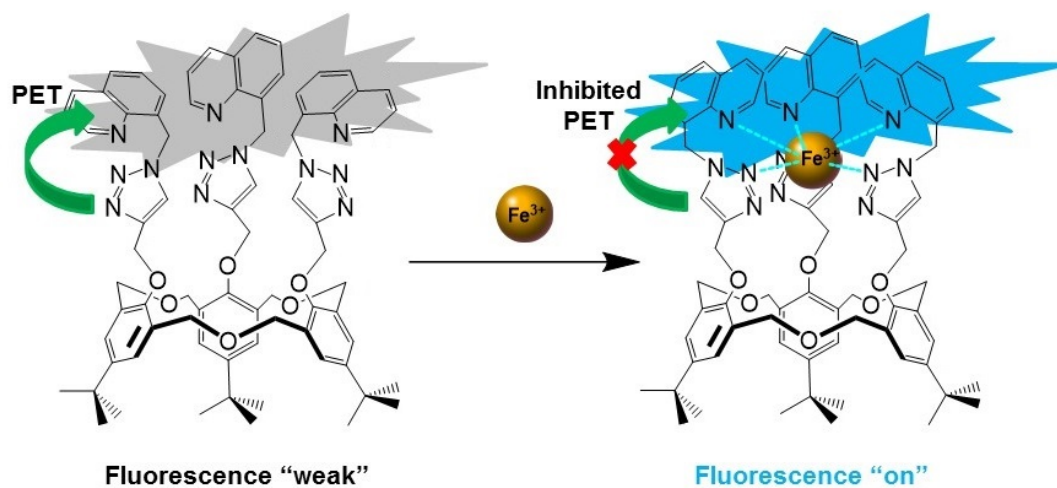
**Highlight:**

1. A quinoline-functionalized homooxacalix[3]arene **L** was synthesized via Click chemistry.

2. Chemosensor **L** exhibited a favourable selectivity for $Fe^{3+}$ ions with a 'turn on' fluorescence emission.

3. The binding behaviour between sensor **L** and $Fe^{3+}$ has been confirmed by $^1H$ NMR spectroscopic titration experiments.

## 1. Introduction

The development of chemosensors capable of recognizing and sensing metal ions has attracted considerable attention because of their fundamental role in biological, environmental, and chemical processes [1–5]. As one of the most essential trace elements, the ferric ion ($Fe^{3+}$) plays important roles in oxygen metabolism, enzyme catalysis, and DNA synthesis [6–9]. Deficiency or overloading of iron can result in various pathological disorders, such as anemia, liver and kidney damages, diabetes, and heart diseases [10,11]. Therefore, the development of simple and effective chemosensors for the detection of $Fe^{3+}$ is of great importance in environmental and life sciences.

A fluorescent chemosensor strategy has proven to be a convenient and efficient approach for metal ion detection due to its superiority over other methods, for example this approach possesses high sensitivity and selectivity, ease of manipulation, non-destructive analysis, and a rapid response [12–14]. Given the paramagnetic nature of $Fe^{3+}$, most reported $Fe^{3+}$ fluorescent chemosensors are based on a fluorescence quenching mechanism, whereas sensors exhibiting fluorescence enhancement (turn-on) sensing behaviour are somewhat limited [15–20]. Nevertheless, turn-on sensors do have some advantages not so easily attainable by turn-off sensors, including the ease of detecting low concentrations against a dark background, reduced false-positive signals, and enhanced sensitivity [21–23]. Thus, the development of

chemosensors that exhibit fluorescence enhancement upon binding with $Fe^{3+}$ would be an attractive target.

Homooxacalix[3]arenes incorporate three ethereal linkages which makes them relatively flexible and thus they can provide a suitable binding environment for species that require trigonal-planar, tetrahedral, or octahedral coordination [24–26]. Based on this excellent structure versatility, homooxacalix[3]arenes have been used as molecular platforms for the development of chemosensors in the molecular recognition of chemical and biological targets [27–29]. On the other hand, we have noted that quinoline derivatives possess desirable photo-physical properties, and that they are usually employed as fluorophores to construct fluorescence chemosensors for heavy and transition metal ions. In particular, the nitrogen atom of the heterocyclic quinoline can act as a chelating site towards metal ions [30–34]. Taking advantage of the easily-synthesized triazole binding site, we were able to readily synthesize the quinoline-functionalized homooxacalix[3]arene by Click chemistry. In the present manuscript, we report a quinoline-functionalized triazole linked homooxacalix[3]arene **L**, which was found to be a selective fluorescence turn on chemosensor for $Fe^{3+}$ with little interference from the other metal ions studied. The role of the calixarene platform has been addressed by making a non-calixarene-based analogue.

## 2. Experimental section

### 2.1. General

Unless otherwise stated, all reagents were purchased from commercial sources and were used without further purification. All solvents were dried and distilled by the usual procedures before use. Melting points were determined using a Yanagimoto MP-S1. $^{1}$H NMR and $^{13}$C NMR spectra were recorded on a Nippon Denshi JEOL FT-300 NMR spectrometer and a Varian-400MRvnmrs400 with SiMe$_4$ as an internal reference: $J$-values are given in Hz. UV spectra were measured by a Shimadzu UV-3150UV-vis-NIR spectrophotometer. Fluorescence spectroscopic studies of compounds in solution were performed in a semi-micro fluorescence cell (Hellma®, 104F-QS, 10 × 4 mm, 1400 μL) with a Varian Cary Eclipse spectrophotometer. Mass spectra were obtained on a Nippon Denshi JMS-01SG-2 mass spectrometer at an ionization energy of 70 eV using a direct inlet system through GLC.

*2.2. General procedure for synthesis of sensor **L**.*

**Insert Scheme 1 in here**

Compound **2** [35] and 8-azidomethyl quinoline [36] were prepared following the reported procedures. Copper iodide (10 mg) was added to compound **2** (200 mg, 0.29 mmol) and 8-azidomethyl quinoline (177 mg, 0.96 mmol) in a 30 mL mixture of THF/H$_2$O (5:1, v/v) and the mixture was heated at 70 °C for 24 h. The resulting solution was cooled and extracted twice with CH$_2$Cl$_2$. The organic layers were combined, dried over MgSO$_4$ and the solvent was removed under reduced pressure. The residue obtained was purified using a silica gel column eluting with 1:1 hexane/ethyl acetate to give the desired compound **L** as a white solid in 65 % yield. m.p. 146–147 °C. $^{1}$H NMR (400

MHz, CDCl$_3$): $\delta$ = 1.03 (s, 27H, $t$Bu), 4.31–4.41 (ABq, 12H, ether bridge, $J$ = 13.2 Hz), 4.54 (s, 6H, ArO–$CH_2$–triazole), 6.08 (s, 6H, triazole–$CH_2$–quinoline), 6.87 (s, 6H, Ar$H$), 7.39-7.45 (m, 6H, Quin–$H$), 7.50 (d, 3H, Quin–$H$, $J$ = 6.8 Hz), 7.74 (d, 3H, Quin–$H$, $J$ = 8.0 Hz), 7.84 (s, 3H, triazole–$H$), 8.10 (d, 3H, Quin–$H$, $J$ = 8.4 Hz), 8.90 (d, 3H, Quin–$H$, $J$ = 2.4 Hz). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ = 31.42, 34.16, 49.65, 67.36, 69.30, 121.50, 124.42, 125.86, 126.36, 128.20, 128.59, 129.59, 130.98, 133.51, 136.14, 143.96, 145.72, 146.21, 150.11, 152.00. HRMS m/z Calcd for C$_{75}$H$_{79}$N$_{12}$O$_6$ [M+H]$^+$: 1243.6246 Found: 1243.6246 [M+H]$^+$.

The monomeric compound **M** was also synthesized in 68 % yield as a reference compound by following a similar protocol. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ = 1.28 (s, 9H, $t$Bu), 5.14 (s, 2H, ArO–$CH_2$–triazole), 6.24 (s, 2H, triazole–$CH_2$–quinoline), 6.88 (d, 2H, Ar$H$, $J$ = 8.8 Hz), 7.26 (d, 2H, Ar$H$, $J$ = 10.0 Hz), 7.48-7.54 (m, 2H, Quin–$H$), 7.64 (d, 1H, Quin–$H$, $J$ = 6.8 Hz), 7.83 (d, 1H, Quin–$H$, $J$ = 8.4 Hz), 7.86 (s, 1H, triazole–$H$), 8.19 (d, 1H, Quin–$H$, $J$ = 8.4 Hz), 8.97 (d, 1H, Quin–$H$, $J$ = 4.0 Hz). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ = 31.48, 34.05, 49.86, 62.14, 114.17, 121.62, 123.75, 126.21, 126.43, 128.36, 128.91, 129.91, 133.20, 136.39, 143.76, 144.18, 145.82, 150.17, 155.99. HRMS m/z Calcd for C$_{73}$H$_{24}$N$_4$O [M]$^+$: 372.1950 Found: 372.1950 [M]$^+$.

*2.3 General procedure for the UV–vis and fluorescence titrations*

For absorption or fluorescence measurements, compounds were dissolved in acetonitrile to obtain stock solutions (1 mM). The stock solutions were diluted with acetonitrile to afford the desired concentration. Stock solutions ($10^{-3}$ M) of perchlorate salts (Li$^+$, Na$^+$, K$^+$, Cs$^+$, Ag$^+$, Cu$^{2+}$, Pb$^{2+}$, Zn$^{2+}$, Co$^{2+}$, Ni$^{2+}$, Cr$^{3+}$, Al$^{3+}$, Cd$^{2+}$, Hg$^{2+}$, Fe$^{2+}$

and $Fe^{3+}$) were prepared with water. In titration experiments, typically, aliquots of freshly prepared standard solutions ($10^{-3}$ M to $10^{-6}$ M) of various analytes in water were added to record the UV–vis and fluorescence spectra. The fluorescence spectra were performed with the excitation wavelength 314 nm.

## 3. Results and discussion

### 3.1. Synthesis and characterization of chemosensor *L*

### *Insert Scheme 1 in here*

The synthetic route for the current sensor is depicted in Scheme 1. The $Cu^{I}$-catalyzed 1,3-dipolar cycloaddition reaction of compound **2** with 8-azidomethyl quinoline under Click conditions afforded the chemosensor **L** in 65 % yield. All compounds synthesized in this work were fully characterized by spectroscopic data including $^{1}$H, $^{13}$C NMR spectroscopy and HRMS [the corresponding spectra, Figs. S1–S4, see Supporting Information (SI)]. $^{1}$H NMR spectra of **L** revealed the disappearance of the three terminal alkyne protons, whilst the new singlet appearing at around $\delta = 7.84$ ppm was attributed to the protons of the newly formed $H_d$ on the triazole groups. Furthermore, the other peaks were observed as three singlets assignable to the protons $H_a$, $H_c$ and $H_e$, and an AB quartet for the $H_b$ protons. These findings supported the conclusion that the homooxacalix[3]arene skeleton was immobilized in the *cone* conformation and possesses a $C_3$ symmetry. Furthermore, in order to demonstrate the role of calixarene platform clearly, compound **M** was synthesized as a reference.

### 3.2. Chemosensing properties of *L* for $Fe^{3+}$

### **Insert Fig. 1 in here**

The recognition behaviour of chemosensor **L** toward various metal cations was investigated by fluorescence measurements. The fluorescence spectrum of **L** exhibited weak fluorescence emission when excited at 314 nm in $CH_3CN$ solution (Fig. 1). Upon addition of $Fe^{3+}$ ions to the solution of **L**, a remarkable enhancement of emission intensity was observed at 414 nm. Under the same conditions as used for $Fe^{3+}$, no significant change of the fluorescence spectrum was observed in the presence of other metal cations, indicative of $Fe^{3+}$-selective off-on fluorescent signaling behaviour. A possible mechanism for the observed fluorescence enhancement may be explained as follows: before coordinating with $Fe^{3+}$, free **L** exhibited weak fluorescence because of the lone electron pairs of the nitrogen atom in the triazole moieties being located adjacent to the quinoline fluorophores, which resulted in an intramolecular photo-induced electron transfer (PET). The de-excitation of the tautomer occurred mainly via a non-radiative pathway. When **L** was coordinated with $Fe^{3+}$, the non-radiative channel was inhibited simultaneously, and thus the **L**-$Fe^{3+}$ system exhibited the enhanced fluorescence [37, 38].

**Insert Fig. 2 in here**

To further investigate the chemosensing properties of **L** towards $Fe^{3+}$, UV-vis and fluorescence titration experiments were performed on 5.0 µM and 1.0 µM solutions of **L** in $CH_3CN$ respectively. The UV-vis spectrum of compound **L** exhibited absorption bands at 255, 261, 280 and 314 nm. Upon the addition of $Fe^{3+}$, the absorption bands at 255, 261 and 280 nm gradually decreased, while the absorption intensity at 314 nm increased (Fig 2). The isosbestic point observed at 293 nm indicates a transition

between the unbound and the complexed species. The stoichiometry of the complex formed between **L** and $Fe^{3+}$ has been derived to be 1:1 based on Job's plot analysis (Fig. S5, SI).

**Insert Fig. 3 in here**

As seen in Fig 3, upon the stepwise addition of $Fe^{3+}$ to a solution of **L**, the fluorescence emission intensity of **L** at 414 nm gradually increased. When the concentration of $Fe^{3+}$ approached 20.0 equiv, the fluorescence intensity of **L** reached a plateau and almost remained constant. From the fluorescence titration profiles, the association constant between **L** and $Fe^{3+}$ was calculated to be $1.18 \times 10^5$ $M^{-1}$ according to the Benesi–Hildebrand method by plotting $1/(I\text{-}I_0)$ against $1/[M]$ (Fig. S6, SI) [39–41]. Moreover, the corresponding detection limit for $Fe^{3+}$ was estimated to be $2.25 \times 10^{-7}$ M on the basis of reported methods (Fig. S7, SI) [36,42,43], which is much lower than the maximum level (0.3 mg $L^{-1}$, equivalent to 5.4 μM) of $Fe^{3+}$ permitted in drinking water as reported by the U.S. Environmental Protection Agency [44].

**Insert Fig. 4 in here**

In order to explore the practical utility of **L** for detecting $Fe^{3+}$ selectively, *ie* even in the presence of other metal ions, competition experiments were carried out (Fig. 4). No significant variation was observed in the presence of other competitive metal ions in comparison to the solution containing only $Fe^{3+}$. Thus it may be concluded that **L** could be used as a potential $Fe^{3+}$ selective fluorescent chemosensor. The potency of the synthesized chemosensor **L** for the detection of $Fe^{3+}$ was evaluated and compared with that of previously described sensors in the literature (Table S1).

*3.3. Sensing mechanism of **L** for Fe³⁺*

**Insert Fig. 5 in here**

**Insert Table 1 in here**

In order to obtain insight into the sensing mechanism of sensor **L** with $Fe^{3+}$, the interaction of sensor **L** with $Fe^{3+}$ was further investigated by $^1H$ NMR spectroscopic titration experiments. As shown in Fig. 5, the $^1H$ NMR signals for the protons of both the quinoline and triazole moieties of **L** experienced downfield shifts in the presence of $Fe^{3+}$; detailed chemical shifts are summarized in Table 1. This phenomenon may be attributed to the electron shielding effect of $Fe^{3+}$ on protons in its proximity. Furthermore, the AB quartet of the methylene bridge protons $H_b$ was split into a pair of doublet, which indicated that there must be a conformational change of sensor **L** on binding with $Fe^{3+}$ ions. As a matter of fact, it is believed that the conformation of homooxacalix[3]arene can be pre-organized for the binding of metal cations in solution in a manner that is similar to the examples described by previous reports [45,46].

**Insert Scheme 2 in here**

The reference compound **M**, which lacks the calixarene platform, showed no appreciable fluorescence changes in the presence of $Fe^{3+}$. This phenomenon suggested that the three triazole ligands and three quinoline moieties exhibited a synergistic action to bind $Fe^{3+}$, and hence supports the necessity of the calixarene platform for the selective recognition of $Fe^{3+}$. Based on the above results, we deduced that the triazole and quinoline moieties of **L** jointly coordinated with

$Fe^{3+}$ to form the **L**-$Fe^{3+}$ complex as illustrated in Scheme 2, which inhibited the intramolecular photoinduced electron transfer (PET) from the electron-donating group triazole to the electron-receptor quinoline group and thus led to the observed enhanced fluorescence of **L**-$Fe^{3+}$ system.

## 4. Conclusions

In summary, we have demonstrated that incorporation of the quinoline fluorophore at the lower rim of a homooxacalix[3]arene *via* the "Click"-generated triazole linker enables excellent fluorescence turn-on sensing towards $Fe^{3+}$. Comparison with a non-calixarene analogue **M** indicates the necessity of the homooxacalix[3]arene platform for $Fe^{3+}$ sensing. Chemosensor **L** formed a 1:1 complex with $Fe^{3+}$ and the sensing mechanism may be ascribed to the inhibition of the PET process on coordination of $Fe^{3+}$ with **L**. This work illustrates that homooxacalix[3]arene with its unique $C_3$ symmetry is beneficial to the design and synthesis of highly selective chemosensors for metal cations.

## Appendix A. Supplementary data

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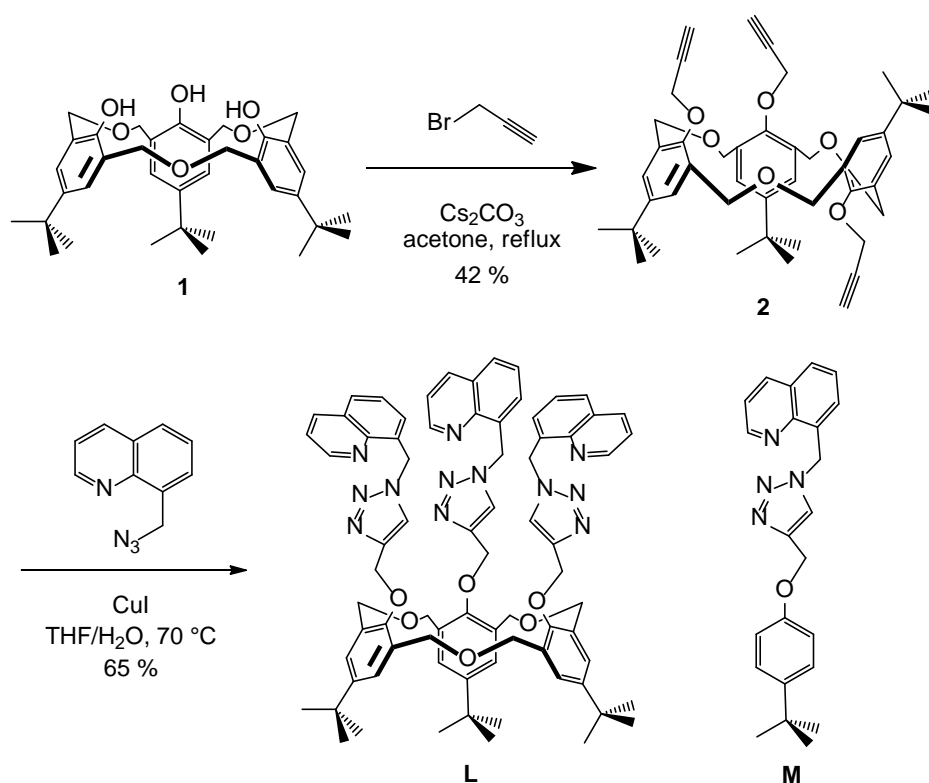
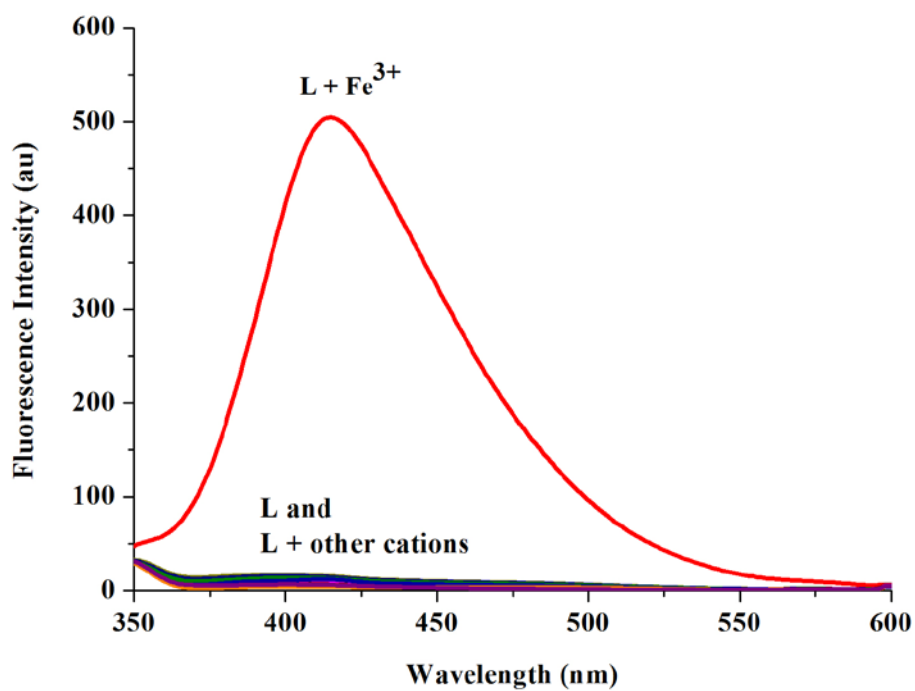

**Scheme 1.** The synthetic route to chemosensor **L**.

**Fig. 1** Fluorescence emission spectra of **L** (1.0 μM) in the presence of various metal ions ($Li^+$, $Na^+$, $K^+$, $Cs^+$, $Ag^+$, $Cu^{2+}$, $Pb^{2+}$, $Zn^{2+}$, $Co^{2+}$, $Ni^{2+}$, $Cr^{3+}$, $Fe^{3+}$, $Al^{3+}$, $Cd^{2+}$, $Hg^{2+}$ and $Fe^{2+}$, 20.0 μM) in $CH_3CN$.
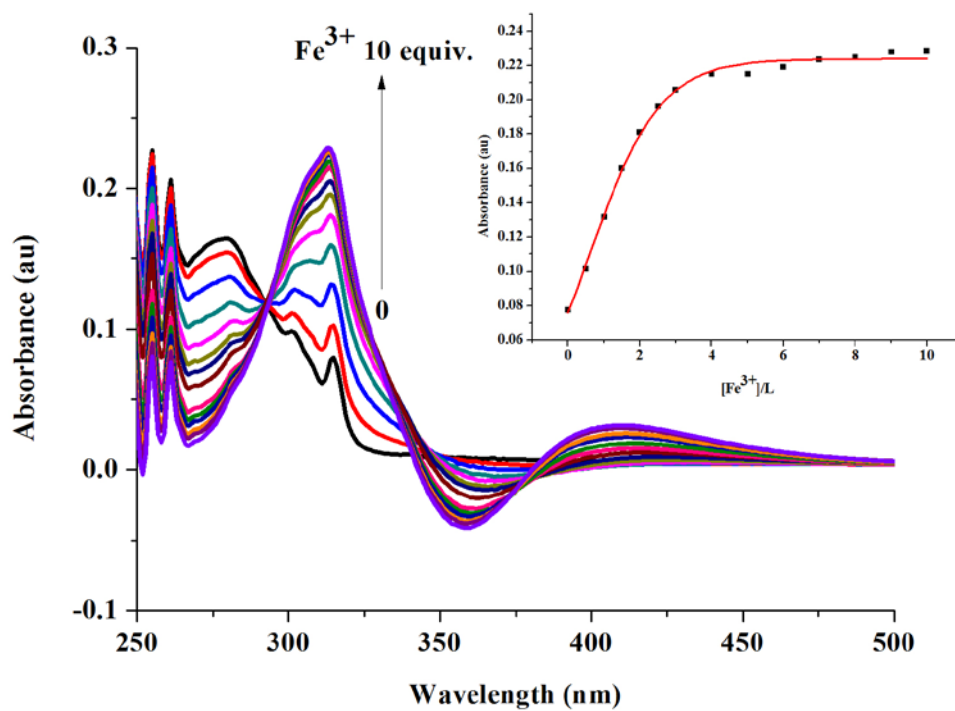
**Fig. 2** Absorption spectra obtained during the titration of **L** (5.0 μM) with $Fe^{3+}$ in $CH_3CN$. The inset shows the plot of absorbance at 314 nm *vs* $[Fe^{3+}]/[L]$ mole ratio.
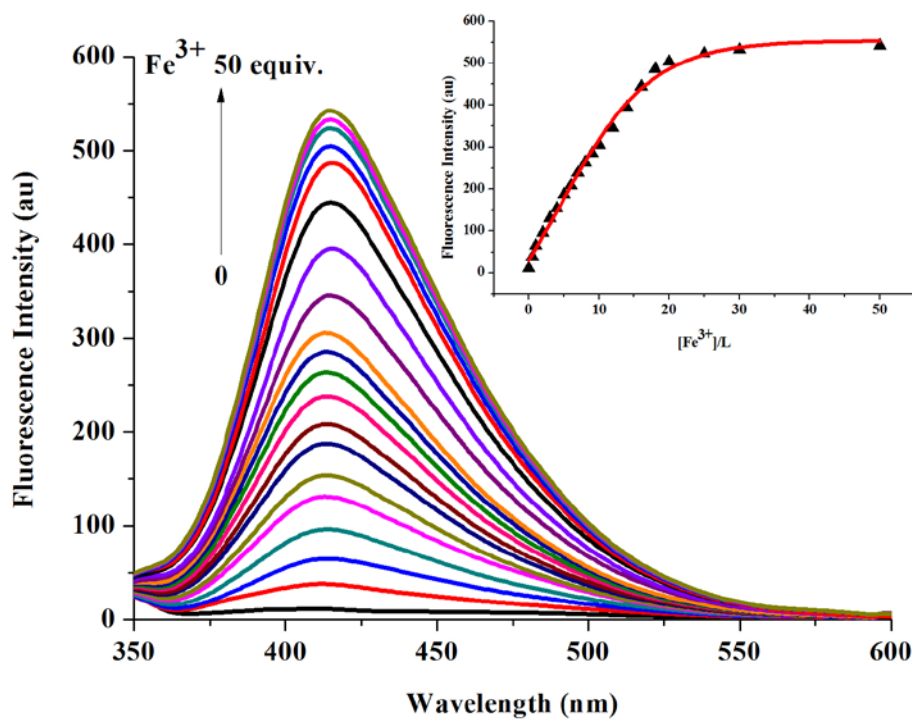
**Fig. 3** Fluorescence spectra obtained during the titration of **L** (1.0 μM) with $Fe^{3+}$ in $CH_3CN$. The inset shows the relative fluorescence intensity as a function of the $[Fe^{3+}]/[\mathbf{L}]$ mole ratio.
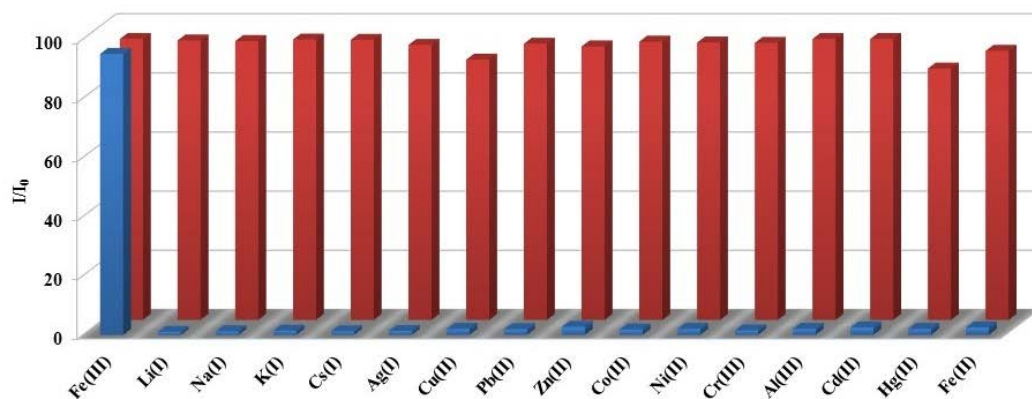
**Fig. 4** Fluorescence response of **L** (1.0 μM) to 20 equiv. of metal cations (the blue bar) and to the mixture of 20 equiv. of other metal ions with $Fe^{3+}$ (the red bar). $I_0$ is fluorescent emission intensity at 414 nm of free **L**, and I is the fluorescent intensity after adding metal cations.
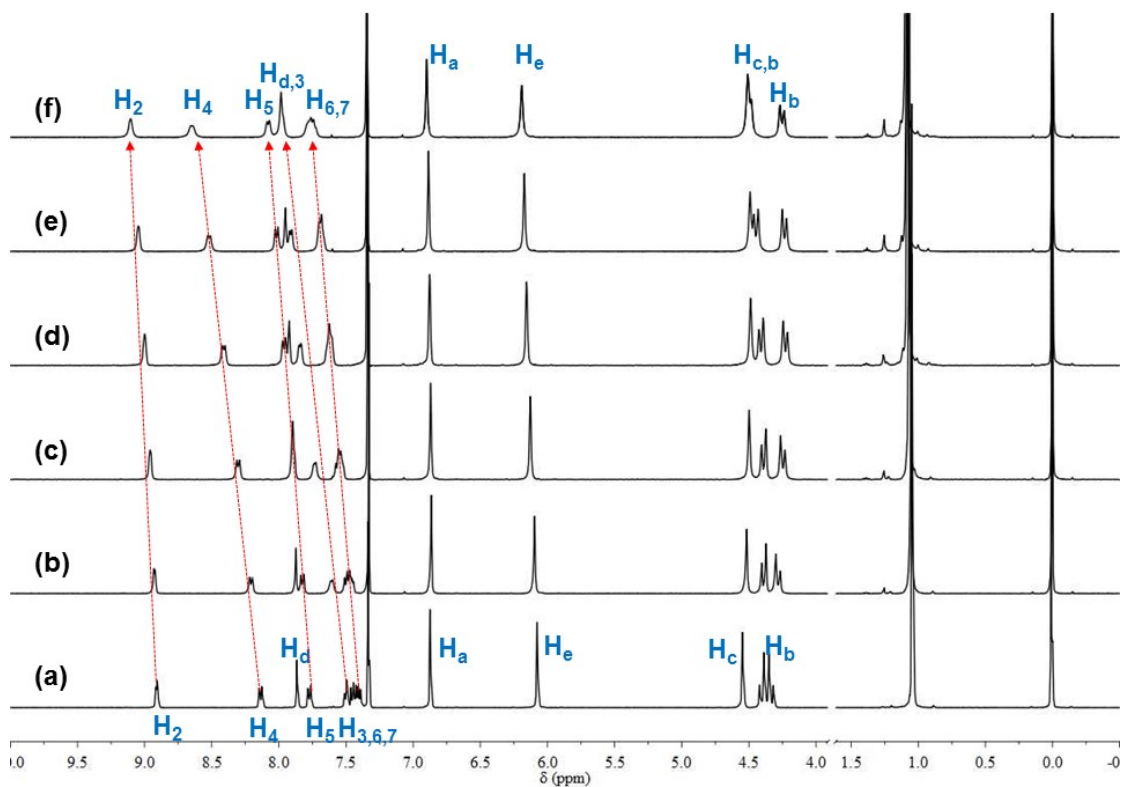
**Fig. 5** $^1$H NMR titration spectra of **L** (5.0 mM) in the presence of increasing amounts of $Fe^{3+}$ in $CDCl_3/CD_3CN$ (10:1, v/v). (a) **L** only, (b c d e and f) in the presence of 0.2, 0.4, 0.6, 0.8 and 1.0 equiv. of $Fe^{3+}$, respectively.
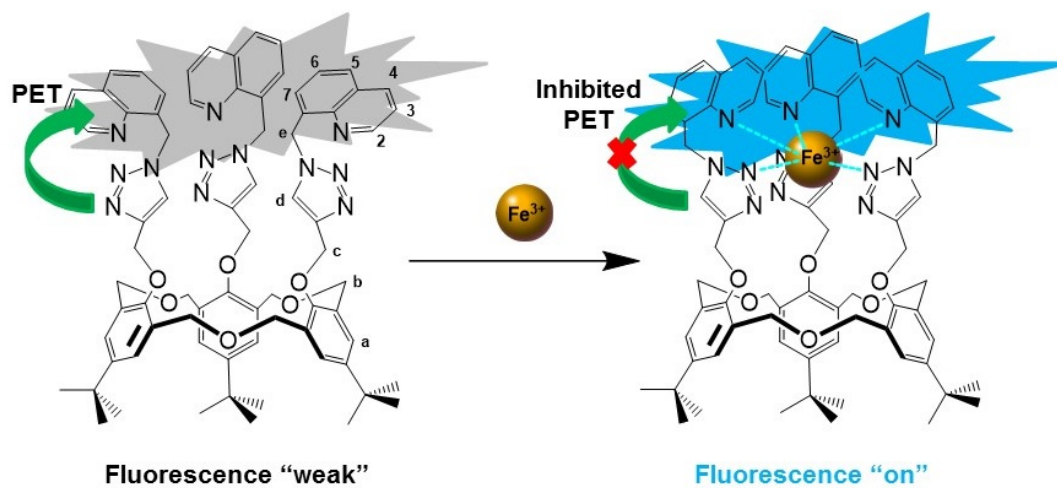
**Table 1** Selected proton chemical shifts ($\delta$, ppm) of **L** and the **L**-$Fe^{3+}$ complex.[a]

| Compound | $H_2$ | $H_3$ | $H_4$ | $H_5$ | $H_6$ | $H_7$ | $H_d$ |
|---|---|---|---|---|---|---|---|
| **L** | 8.90 | 7.43 | 8.10 | 7.74 | 7.43 | 7.50 | 7.84 |
| **L**-$Fe^{3+}$ | 9.10 | 7.98 | 8.64 | 8.07 | 7.76 | 7.76 | 7.98 |
| $\Delta\delta$ [b,c] | +0.20 | +0.55 | +0.54 | +0.33 | +0.33 | +0.26 | +0.14 |

[a] The midpoint values of multiplets are indicated.

[b] $\Delta\delta$ value is the difference of the chemical shift between **L** and the **L**-$Fe^{3+}$ complex.

[c] A plus sign (+) denotes a shift to lower magnetic field.

**Scheme 2.** Proposed sensing mechanism of **L** towards $Fe^{3+}$.