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ORIGINAL PAPER

A Novel Quinazolinone Derivative as Fluorescence Quenching Off-On Sensor for High Selectivity of Fe^{3+}

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Abstract A novel quinazolinone compound containing quinazoline-fused moiety has been synthesized as fluorescence Off-On sensor QQ. The probe exhibited highly selective and sensitive recognition toward trivalent ferric ion (Fe^{3+}) over other metal ions in HEPES buffer solution (10 mM, pH=7.0, DMF-H_2O, 9:1, v/v). The significant quenching in the fluorescence spectral could be served as a selective fluorescence Off-On sensor. The titration study indicated the formation of 1:1 complex between QQ and Fe^{3+}.

Keywords Quinazolinone · Fe^{3+} · Fluorescent probe · Off-On

Introduction

The development of fluorescent artificial receptors for the recognition of biologically and environmentally important ions (including metal ions and anions) has received numerous attention due to their basic roles in a wide range of chemical, environmental, and biological processes [1–3]. Nowadays, researchers have synthesized some fluorescent probes to determine such metal ions as Cu^{2+}, Fe^{3+}, Zn^{2+}, Cd^{2+}, Hg^{2+}, and Pb^{2+} in organisms [4–7]. Fe^{3+} is widely distributed in nature and is one of the most important elements in biological systems, which participates in many biochemical processes at the cellular level. It is an essential element for the formation of hemoglobin of red cells and plays an important role in the storage and transport of oxygen to tissues. Therefore, research of fluorescent probes for Fe^{3+} detection is of great significance to environmental and biological sciences [8–11]. However, the reports about fluorescent probes for Fe^{3+} are rarely seen in recent years.

The quinazoline ring system along with many alkaloids is a widely recognized moiety in organic syntheses and medioinal applications. It has been reported that modification of quinazoline structure could be applied in many biological studies, such as anticonvulsant, antibacterial, antidiabetic, and anticancer [12, 13]. Quinazoline derivatives act as powerful inhibitors of epidermal growth factor (EGF) receptors of tyrosine kinase. Quinazolinones are excellent reservoir of bioactive substances. Several bio-active natural products such as febrifugine and isofebrifugine contain quinazolinone moieties with potential antimalarial activity [14, 15]. In addition, quinazoline ketone compounds are also good chemical sensors because of their larger fluorescence intensity and good light stability. Therefore, phenyl iso-thiocyanate was introduced to β-position of quinazoline ketone ring. In this paper to synthesize a novel quinazolinone compound containing quinazoline-fused moiety (QQ), which showed favourable recognition response to Fe^{3+} and could be applied as fluorescence Off-On sensor for high selectivity of Fe^{3+}.

Experiment

Materials and General Methods

All the reagents and solvents were purchased from commercial sources and were of analytical grade. Solvents were dried according to standard procedures. All reactions were magnetically stirred and monitored by thin-layer chromatography(TLC). Melting points(M.p.) of prepared compounds were measured on an X4 micromelting point apparatus. A BRUKER DRX500 spectrometer recorded ^1H NMR spectra of objective products. Fluorescence spectra

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were taken on an Perkin Elmer LS −55 type fluorescence photometer.

Synthesis

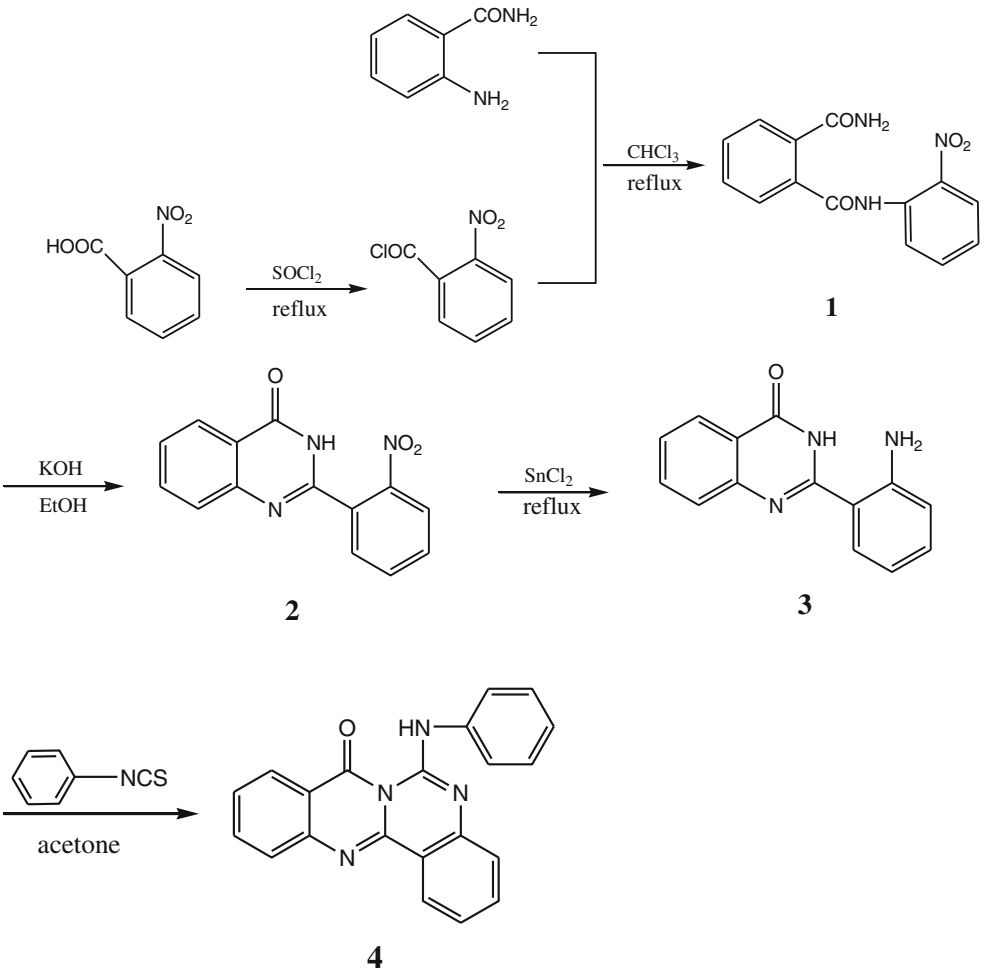
Synthetic procedures of QQ were shown in Scheme 1.

*N-(2-nitrophenyl)phthalamide (**1**)* Anthranilamide (1.04 g, 8.5 mmol), triethylamine (3.1 mL, 17 mmol), and chloroform(25 mL) was added into a 100 mL four-neck flask and stirred at room temperature, then 2-Nitrobenzamide was added dropwise into the solution. the refluxing reaction lasted 4 h at room temperature until TLC indicated the end of reaction, cooling down, recrystallization for filtered solid with methanol would give white crystal (0.68 g, 2.4 mmol, 65.3 %), M.p.,190–192 °C. ^{1}H NMR(500 MHz, DMSO-d6) δ=8.48(d, *J*=8 Hz, 1H), 8.11(d, *J*=8.5 Hz,1H), 8.34(s, 1H), 7.34(s, 1H), 12.49(s, 1H), 7.58(t, *J*=8 Hz, 1H), 7.21–7.24(m, 1H), 7.74–7.90(m, 5H).

*2-(2-nitrophenyl)quinazolin-4(3H)-one (**2**)* **1** (0.68 g, 2.4 mmol), ethanol(10 mL) and potassium hydroxide solution (10 %) were added into a 100 mL four-neck flask, heated to reflux for 15 m. Then ethanol was removed under reduced pressure and heated to reflux, the filtered solid was recrystallized to yield light yellow product(0.53 g, 2.0 mmol, 77.9 %) by column chromatography(petroleum ether:ethyl acetate= 3:1), M.p.,210-212.^{1}H NMR(500 MHz, DMSO-d6) δ= 12.81(s, 1H), 7.66(d, *J*=8 Hz,1H), 7.57–8.23(m, 3H), 7.81–7.93(m, 4H).

*2-(2-aminophenyl)quinazolin-4(3H)-one (**3**)* **2** (0.6 g, 2.2 mmol), $SnCl_2$(1.01 g, 4.5 mmol) and methanol(25 mL) were put into a 100 mL four-neck flask and heated. The refluxing reaction lasted until TLC indicated the complete transformation, then was cooled down. Recrystallization for filtered solid from deionized water would afford yellow crystal (0.52 g, 2.2 mmol, 86.7 %). M.p., 224–226 °C. ^{1}H NMR(500 MHz, DMSO-d6) δ=12.01 (s, 1H), 7.02(s, 2H), 7.71–8.14(m, 4H), 6.59–7.50(m, 4H).

*QQ (**4**)* **3** (0.1 g, 0.4 mmol) and acetone (25 mL) were put into a 100 mL four-neck flask firstly, following phenyl isothiocyanate (0.15 mL/0.17 g, 1.26 mmol) was added in the solution dropwise. The system was heated and refluxed for 12 h until the complete reaction was monitored by TLC, then was cooled down. The filtered result was earthy yellow solid(0.16 g, 0.48 mmol, 60 %). M.p., 288 °C~290 °C. ^{1}H NMR(300 MHz,



Scheme 1 Synthetic procedures of QQ

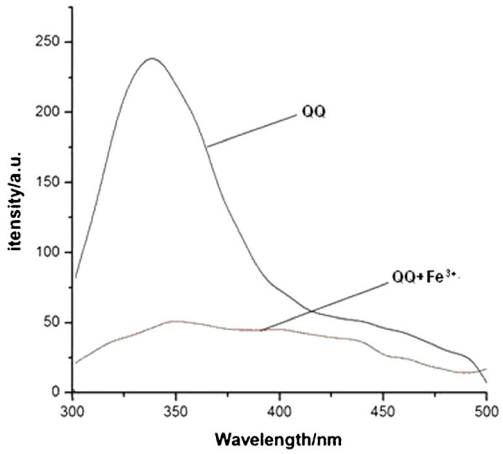


Fig 1 Fluorescence emission spectra of QQ in the presence of Fe^{3+} in HEPES buffer solution (10 mM, pH=7.0, DMF-H_2O, 9:1, v/v), λ_{ex}=344 nm

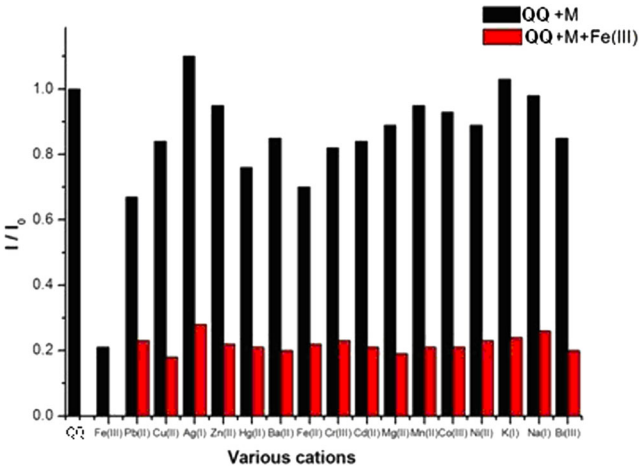


Fig 3 Relative fluorescence intensity changes of QQ in the presence of various metal ions (20 eq.) and Fe^{3+} (20 eq.) in HEPES buffer solution (10 mM, pH=7.0, DMF-H_2O, 9:1, v/v).λ_{ex}=344 nm

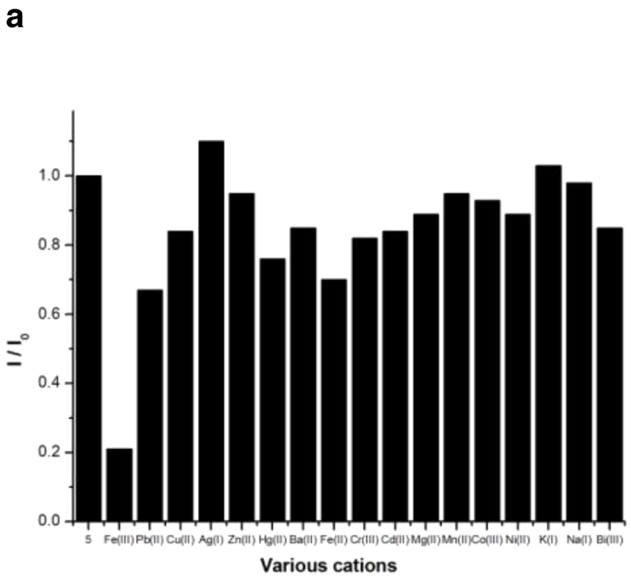
DMSO-d6)δ=12.28 (s, 1H), 8.57(d, *J*=8.1 Hz,1H), 8.34(d, *J*= 8.1 Hz, 1H), 8.01(t, *J*=7.8 Hz, 1H), 7.15 ppm(t, *J*=7.5 Hz, 1H), 7.33–7.46(m, 4H), 7.59–7.90(m, 5H).

Fluorescence Sensing of QQ for Metal Ions

Deionized water was used throughout all experiments. Solutions of Fe^{3+}, Pb^{2+}, Cu^{2+}, Ag^{+}, Zn^{2+}, Hg^{2+}, Ba^{2+}, Fe^{2+}, Cr^{3+}, Cd^{2+}, Mg^{2+}, Mn^{2+}, Co^{3+}, Ni^{2+}, K^{+}, Na^{+}, and Bi^{3+} were prepared from their nitrate salts. A 1 mM stock solution of QQ was prepared by dissolving in DMF. All measurements of fluorescence spectra(FS) were obtained with a Perkin Elmer LS-55 fluorescence spectrophotometer linked to a Pentium PC running SpectraCalc software package. All measurements were carried out in HEPES buffered (10 mM, pH=7.0, DMF-H_2O, 9:1, v/v).

Chemical Complexion Stoichiometric Ratio of QQ and Fe^{3+}

In the titration experiments, a 2.5 mL solution of QQ (10 mM and 1 mM) was poured into a quartz optical cell of 1 cm optical path length each time, and Hg^{2+}solution was added into the quartz optical cell gradually with a micro-pipette. FS data were recorded in an indicated time after the addition.



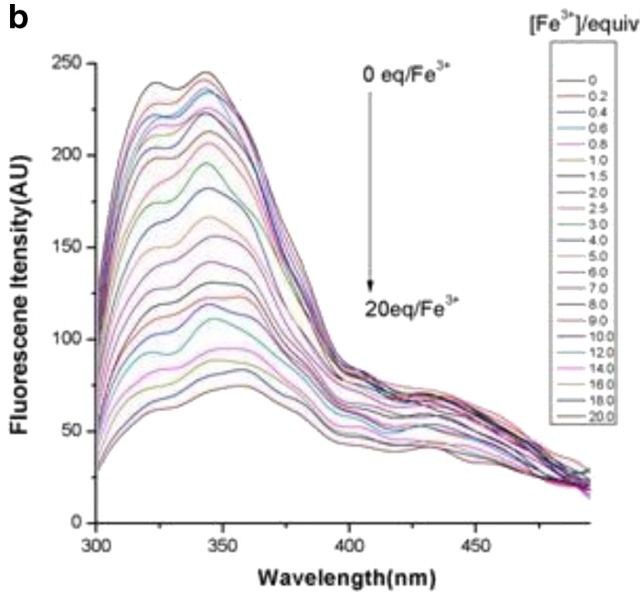


Fig 2 **a** Relative fluorescence intensity changes of QQ in the presence of various metal ions(10 eq.) in HEPES buffer solution (10 mM, pH=7.0, DMF-H_2O, 9:1, v/v), λ_{ex}=344 nm. **b** Fluorescence spectra of QQ in the presence of various equiv of Fe^{3+} in HEPES buffer solution (10 mM, pH=7.0, DMF-H_2O, 9:1, v/v).λ_{ex}=344 nm

Titration experiments were carried out and Job's analyses [16] was applied to calculate the stoichiometric ratio of QQ-Fe^{3+} complex according to the following equation.

$$\log\frac{F-F_{min}}{F_{max}-F} = n\log\left[Fe^{3+}\right] + B$$

In above equation, F_{min} , F_{max} and F were the fluorescent intensity of metal-free QQ, QQ with excessive $Fe^{3+}$and QQ with Fe^{3+}at any concentration between the former two, resperively. n meant the stoichiometry of QQ- Fe^{3+}complex.

Results and Discussion

Spectroscopic Properties of QQ

Fluorescence and UV–vis studies were performed using a solution of quinazoline QQ in HEPES buffer (DMF-H_2O 9:1, v/v) at an excitation wavelength of 344 nm. Figure 1 shows a change in the fluorescence spectra of QQ. When no metal ion was added to the solution, almost no fluorescence signal in the range from, 300 nm to 500 nm could be observed, whereas a significant quenching of the characteristic fluorescence could be found soon after Fe^{3+} was injected into the solution.

Fluorescence Sensing of QQ for Fe^{3+}

The Fig. 2a is fluorescence spectra of quinazoline QQ in HEPES buffer with appropriate amounts of metal ions. Solutions were shaken for 30 min before measuring the absorption and fluorescence in order to make the metal ions chelate with the sensors sufficiently. Under the identical condition, no obvious response could be observed upon the addition of other ions including Al^{3+}, Ba^{2+}, Cd^{2+}, Cr^{3+}, Fe^{2+}, Hg^{2+}, K^{+}, Mg^{2+}, Mn^{2+}, Na^{+}, Pb^{2+} and Zn^{2+}. It shows that the fluorescence selective of QQ to Fe^{3+} is very

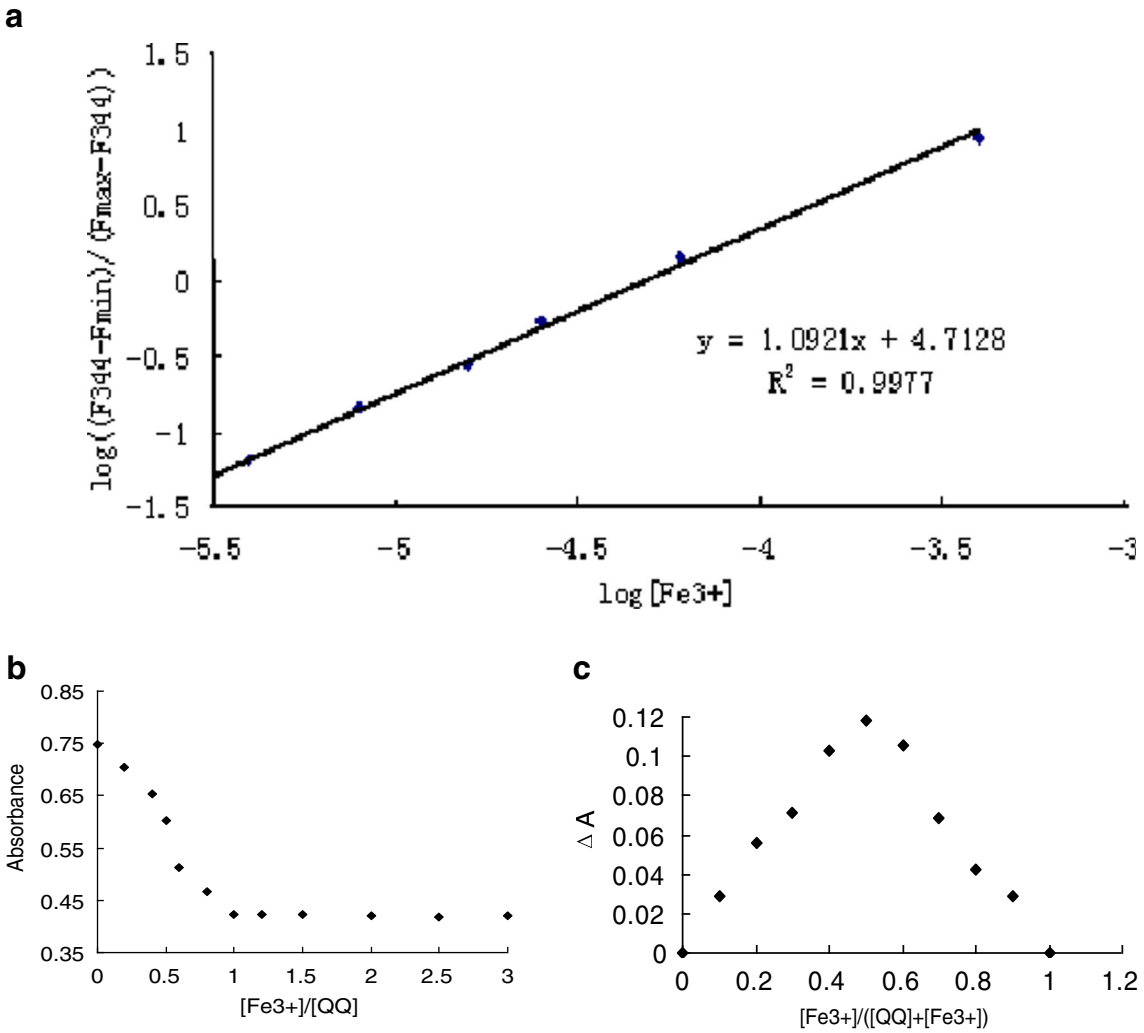


Fig 4 **a** Curve of fluorescence intensity at 344 nm of QQ versus increasing concentration of Fe^{3+}. **b** Absorbance of QQ-Fe^{3+} complex in different [Fe3+]/[QQ] ratio. **c** Job's plot for the QQ-Fe^{3+} complex ([QQ]+[Fe^{3+}]=5×10^{-5} mol dm^{-3})

specificity. It is probably due to several combined influences cooperating to achieve the unique selectivity for the Fe^{3+} ion, such as the suitable coordination geometry conformation of the receptor, the radius of the Fe^{3+} ion and the amide deprotonation ability of the Fe^{3+} ion.

With gradual addition of Fe^{3+} ion to the solution of QQ, the fluorescence intensity was decreased obviously. Due to the formation of chelate Fe^{3+} with cavity of N and polycyclic in molecular structure of QQ, it caused the decline of coplanarity and molecular rigidity of QQ result in the fluorescence quenching. Figure 2b shows that emission peak recede gradually with the addition of Fe^{3+}, but the peak patterns do not shift. When the titration achieves a balance, the fluorescence tensity declines three times.

Interference Test

The solution of QQ showed almost no changes in the presence of other metal ions, such as Al^{3+}, Cu^{2+}, Ba^{2+}, Cd^{2+}, Cr^{3+}, Fe^{2+}, Hg^{2+}, K^{+}, Mg^{2+}, Mn^{2+}, Na^{+}, Pb^{2+} and Zn^{2+}. The results show that the selective recognition of QQ to Fe^{3+} is hardly interfered with common metal ions. The evidence supports that QQ can serve as a selective OFF-ON fluorescence (Fig. 3).

Binding Constant

According to the literature16, the chelation formula of fluorescent probe and metal ions is:

F_{min}, F_{max} and F in the formula refer to the fluorescence intensity of QQ with blank, excess and any concentration of Fe^{3+} respectively. n is the binding constant of ligand and Fe^{3+}. Chelation curve of $\log((F\text{-}F_{min}/(F_{max}\text{-}F))$ and $\log[Fe^{3+}]$ is shown in Fig. 4a. The curve is linear when the addition capacity of QQ within 0.2 eq to 20 eq, and the linear slope is 1.0921, it indicates that the binding constant of QQ and Fe is 1:1 approximate. The complexation between QQ and Fe^{3+} was also studied by UV–vis spectroscopy, and the result is showed in Fig. 4b and c. Figure 4b is the plot of the absorbance for QQ-Fe3+ complex with different [Fe3+]/[QQ] ratio in 356 nm. As shown in Fig. 4b, when the [Fe3+]/[QQ] ratio is 1:1, the plot appears the turning point and begines to flatten. It indicates that 1:1 QQ-Fe3+ complex formed. The Job's plot (Fig. 4c) indicates that QQ-Fe3+ binds in a 1:1 stoichiometry as well.

According to the literature [17], the binding constant of QQ with Fe^{3+} is calculated to be $K_{\alpha}=6.89\times10^{3}$.

Conclusions

In conclusion, a quinazoline ketone compound has been synthesised as fluorescence probe QQ for Fe^{3+} detecting. The ion binding properties of this receptor with a large number of metal ions have been investigated and the ion recognition events have been monitored by fluorescence spectral changes. Our study revealed that the fluorescence selective of QQ to Fe^{3+} is high selectivity and anti-disturbance. The calculation confirmed that a stable 1:1 QQ-Fe^{3+}complex formed.

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References

1. Zhang D, Zou RY, Wang M, Chai MM, Wang XB, Ye Y, Zhao YF (2013) J Fluoresc 23:13–19
2. Chai MM, Zhang D, Wang M, Hong HJ, Ye Y, Zhao YF (2012) Sensors Actuators B Chem 174:231–236
3. Callan JF, de Silva AP, Magri DC (2005) Tetrahedron 61:8551–8588
4. Liu ZP, He WJ, Guo ZJ (2013) Chem Soc Rev 42:1568–1600
5. Liu YL, Lv X, Zhao Y, Liu J, Sun YQ, Wang P, Guo W (2012) J Mater Chem 22:1747–1750
6. Khatua S, Samanta D, Bats JW, Schmittel M (2012) Inorg Chem 51: 7075–7086
7. Tang LJ, Wang NN, Zhang Q, Guo JJ, Nandhakumar R (2013) Tetrahedron Lett 54:536–540
8. Li ZX, Zhou W, Zhang LF, Yuan RL, Liu XJ, Wei LH, Yu MM (2013) J Lumin 136:141–144
9. Dong L, Wu C, Zeng X, Mu L, Xue SF, Tao Z, Zhang JX (2010) Sensors Actuators B Chem 145:433–437
10. Li ZY, Xia JL, Liang JH, Yuan JJ, Jin GJ, Yin J, Yu GA, Liu SH (2011) Dyes Pigments 90:290–296
11. Patra S, Lo R, Chakraborty A, Gunupuru R, Maity D, Ganguly B, Paul P (2013) Polyhedron 50:592–601
12. Zhang LX, Ren LG, Bai MH, Weng LW, Huang J, Wu L, Deng MG, Zhou X (2007) Bioorgan Med Chem 15:6920–6926
13. Song Y, Wang P, Wu JJ, Zhou X, Zhang XL, Weng LH, Cao XP, Liang F (2006) Bioorg Med Chem Lett 16:1660–1664
14. Kumar A, Sharma P, Kumari P, Kalal BL (2011) Bioorg Med Chem Lett 21:4353–4357
15. Ferrini S, Ponticelli F, Taddei M (2007) Org Lett 9:69–72
16. Li JB, Li NN, Yu XL (2010) J Wuhan Inst Tech 32:11–14
17. Sessler JL, Katayev E, Pantos GD, Scherbakov P, Reshetova MD, Khrustalev VN, Lynch VM, Ustynyuk YA (2005) J Am Chem Soc 127:11442–11446