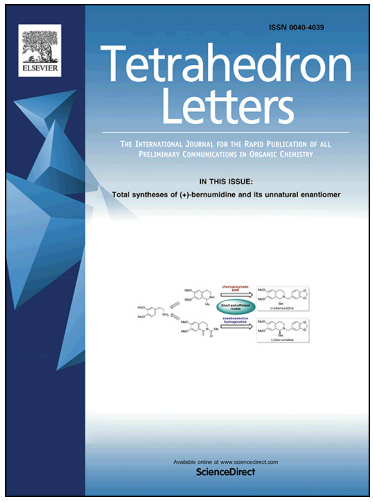

Highly Selective Fluorescent Probe Based on a rhodamine B and furan-2-carbonyl chloride conjugate for Detection of Fe^{3+} in Cells

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Highly Selective Fluorescent Probe Based on a rhodamine B and furan-2-carbonyl chloride conjugate for Detection of Fe^{3+} in Cells

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Abstract

A furan-2-carbonyl chloride modified rhodamine B derivative (RBFC) has been designed and synthesized. The probe RBFC exhibited excellent sensitivity and selectivity for detection of Fe^{3+} with a 1:1 stoichiometry over other tested metal ions in a MeOH/H_2O (1:1, v/v, pH 7.36, HEPES buffer, 1.3 mM) solution. The association constant and the detection limit were calculated to be 7.28×10^3 $M^{-1}$and 0.437 μM based on fluorescence titration analysis. Furthermore, the probe RBFC was successfully applied in living cells, and the results indicated that the probe could monitor intracellular Fe^{3+} in MCF-7 cells.

Key words: fluorescent Probe; rhodamine B; furan-2-carbonyl chloride; iron ions; MCF-7 cells

1. Introduction

Iron is a relatively rich metal element on the earth, which accounts for about 4.1% of its total. Iron not only plays an important role in the modern society, but even more importantly, although iron is a trace element in the human body, but it is the most important of the more than 10 elements necessary in the human body. Therefore, the iron plays the key role for the health of the human body [1]. Iron is widely distributed in the human body. Almost all tissues and organs contain, including blood, muscle tissue, spleen, liver and bone marrow. Iron is an important component of hemoglobin, myoglobin and various enzymes. Therefore, it is an essential trace element in human physiological activities, such as cell metabolism, oxygen metabolism, electron transfer, enzyme catalyzed DNA and RNA synthesis, proton transfer, maintenance of intracellular acid-base balance and osmotic pressure regulation [2-6]. When the iron content in the human body deviates from normal level or abnormal distribution, it will endanger human health. Insufficient or excessive iron content in human body can damage the normal physiological functions, such as immunosuppression, decrease in intelligence, reducing the ability of human body to resist infection, and so on [7], and even a variety of diseases, such as abnormal liver function [8], myocardial injury [9], osteoporosis [10], diabetes [11], and cancer [12]. Therefore, real-time monitoring of iron ions is of great importance to the health of organisms and human beings.

At present, conventional methods like atomic absorption spectroscopy (AAS) [13], colorimetry, [14] voltammetry, [15] and inductively coupled plasma mass spectrometry (ICP-MS) [16] had been used for the detection of Fe^{3+}. However, due to their high cost and complex sample pretreatment, the above methods fail to popularized use. Fluorescent molecular probes are used for the detection of metal ions because of their simple synthesis methods, few sample requirements, short response time, good selectivity and high sensitivity [17-21]. Most of the known Fe^{3+} sensors are based on fluorescence quenching mechanisms due to the paramagnetic nature of Fe^{3+} ions which are not as sensitive as a fluorescence enhancement response.[22] As a result, fluorescence-enhanced probes would be more desirable for Fe^{3+} detection. Rhodamine B is one of the most commonly used dye which has attracted much attention duo to its excellent photophysical properties, such as long absorption and emission wavelengths

extended to the visible region, high fluorescence quantum yield and large extinction coefficient.[23-25] Many fluorescence probes based on Rhodamine B and its derivatives have been developed for Hg^{2+}, Cu^{2+}, Zn^{2+}, Cr^{3+}, Al^{3+} and Pb^{2+}. [26-31]

Herein we have synthesized a fluorescent probe RBFC by combining rhodamine B and furacyl chloride with ethylenediamine. The experimental results show that the probe RBFC has a good detection effect on the specific identification of Fe^{3+} in the solution of EtOH/HEPES (1:1, v/v, 1.3mM, pH=7.36). The cytotoxicity of the human breast cancer cell (MCF-7) is very low and the effect of cell imaging is very good. Therefore, the probe RBFC monitor intracellular Fe^{3+} in the living cells.

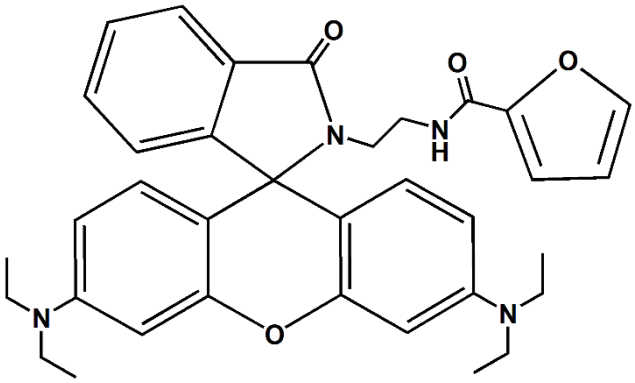
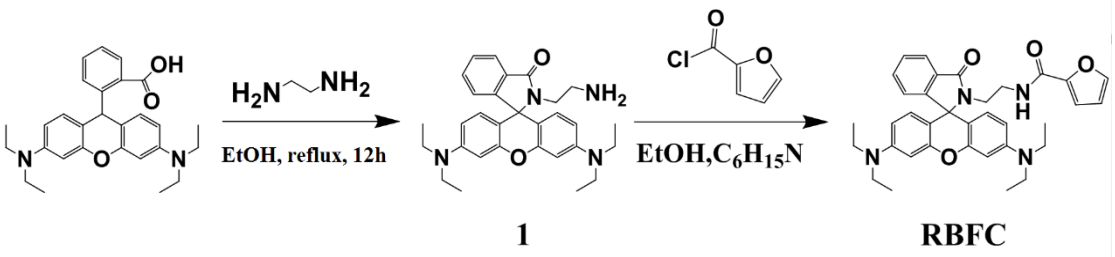


Figure.1 Chemical structure of RBFC

2. Result and discussion

2.1.Synthesis of RBFC

The synthesis procedure of RBFC was shown in **Scheme. 1**. Compound 1 was prepared in 92% yield by refluxing commercially available rhodamine B with ethane -1,2-diamine in EtOH. Then the probe RBFC was isolated from the reaction of compound 1 and N-(Methylaminopyridine) chloroacetamide in EtOH with a good yield (64%). The structure of intermediate and RBFC were confirmed by ^{1}H NMR, ^{13}C NMR and HRMS (Supporting materials).



Scheme.1 Synthesis procedure of RBFC

2.2. Effect of pH and response of time

Fluorescence spectra of probe RBFC were inspected at different pH values (**Figure. 2**). Upon excitation at 560 nm, the probe showed almost no fluorescence in a wide pH range (6.0~11.0). Along with the pH varied from 6.0 to 2.0, an emission peak evolved at 582 nm and the fluorescence intensity enhanced gradually. The significant fluorescence increase was ascribed to the ring-opening process of rhodamine spirolactam of RBFC caused by H^+. These results suggested that RBFC was insensitive to pH from 6.0 to 11.0 and could work well in approximate physiological conditions with low background fluorescence. Therefore, the EtOH/HEPES buffer (1:1, v/v, 1.3 mM, pH=7.36) solution was chosen for the following experiments. In addition, the time course of RBFC to 5 equiv of Fe^{3+} was conducted. The fluorescence intensity of RBFC at 582 nm was increased with standing time and leveled off within 70 min (**Figure. 3**).

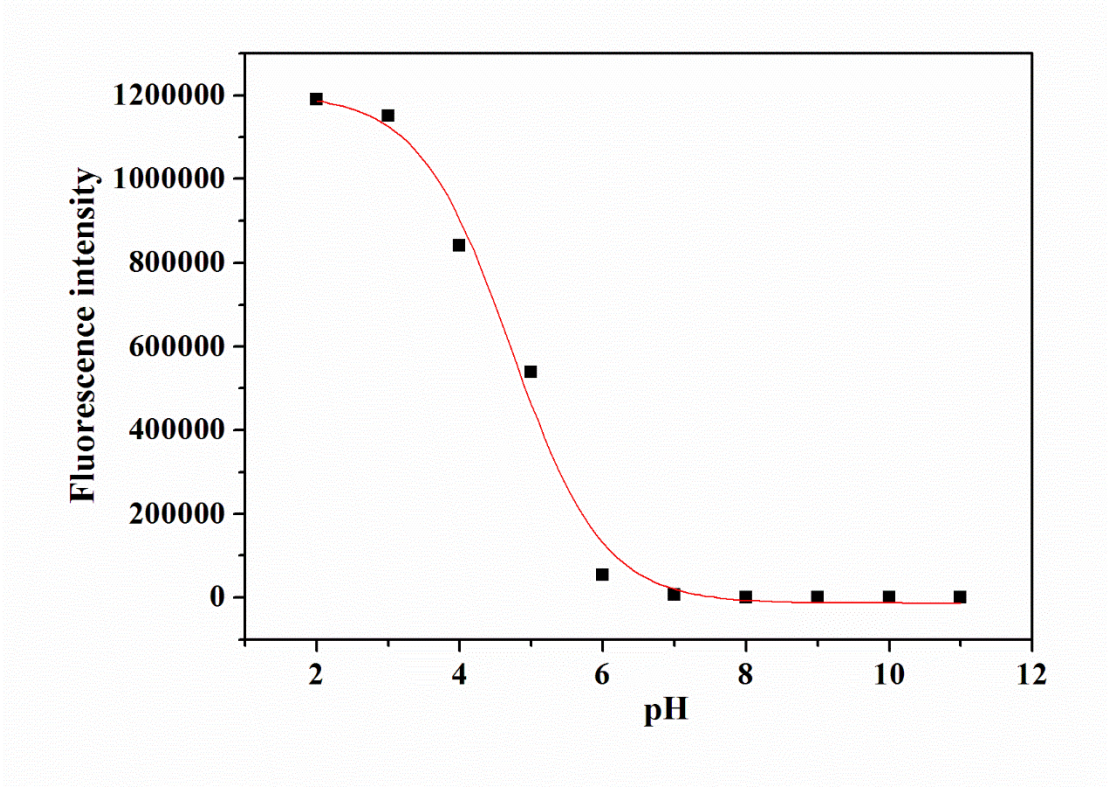


Figure. 2 The effect of the pH on the fluorescence of RBFC (0.02 mM) in MeOH/H_2O solutions (1:1, v/v). The excitation and emission wavelengths were 560 nm and 582 nm.

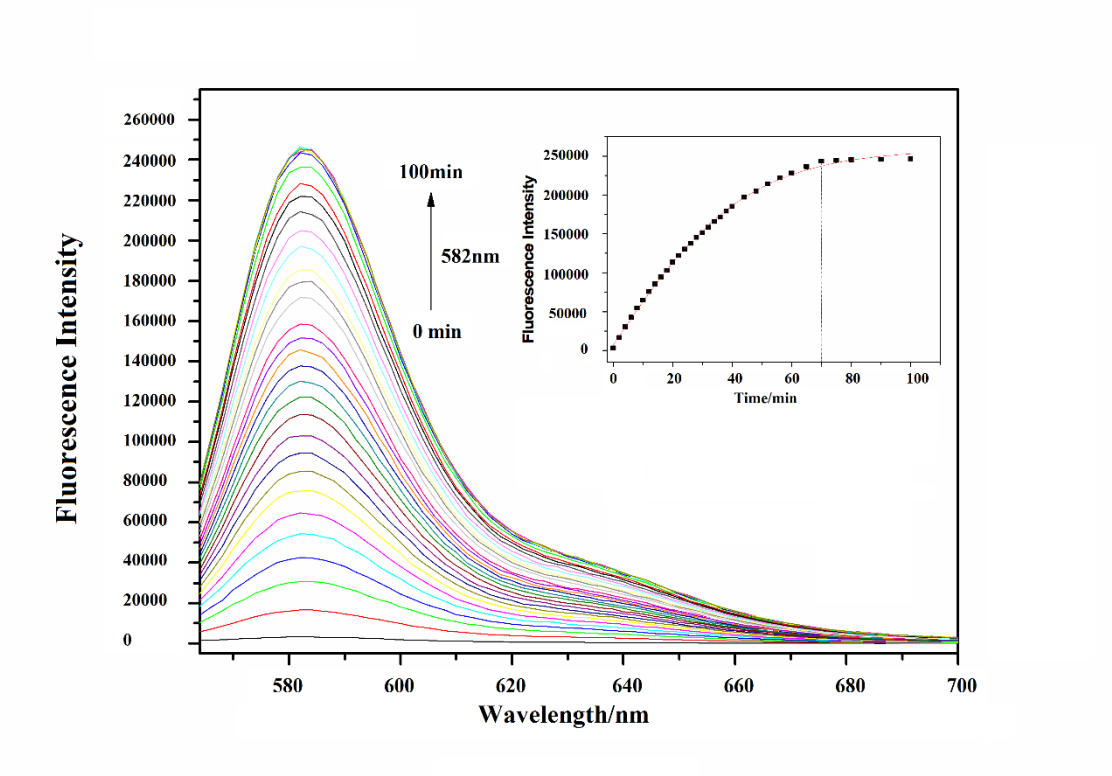


Figure.3 Fluorescence spectra of RBFC (0.02mM) with Fe^{3+} (0.1mM) in MeOH/H_2O (1 : 1, v/v, pH 7.36, HEPES buffer, 1.3mM) solutions. The excitation and emission wavelengths were 560 and 582 nm. Inset: plot of fluorescence intensity at 582 nm over a period of 90 min.

2.3. UV-vis absorption and fluorescence spectra of RBFC toward Fe^{3+}

The photophysical properties of RBFC was evaluated in MeOH/HEPES buffer (1:1, v/v, 1.3 mM, pH=7.36) solution in the presence of different various metal icons. As shown in **Figure. 4**, compound RBFC (0.02mM) showed a strong absorption at around 320 nm. Additions of Cr^{3+}, Cu^{2+}, Mg^{2+}, Cd^{2+}, Fe^{2+}, Ni^{2+}, Mn^{2+}, Co^{2+}, Hg^{2+}, Ba^{2+}, Ca^{2+}, Zn^{2+}, K^{+} and other metal icons showed little or no effect on the absorption of RBFC besides Fe^{3+}. Upon addition of 5 equiv Fe^{3+} ions, a new absorption peak centered at 558 nm appeared because of the rhodamine B ring-opening process. (The molar absorption coefficient raises from $1.0*10^2$ $M^{-1}*cm^{-1}$ to $1.0*10^3$ $M^{-1}*cm^{-1}$.) The above result induced a clear colorimetric change from colorless to pink. Such a dramatic color change demonstrated that the RBFC as a sensitive "off-on" and colorimetric probe for Fe^{3+}.

Fluorescence spectra of probe RBFC were also inspected in the presence of different various metal icons. As shown in **Figure. 5**, when excited with 560 nm, there was almost non fluorescence due to its ring-closed spirolactam structure. With addition of 5 equiv of Fe^{3+}, around 28-fold fluorescence enhancement at 582 nm was obviously observed. However additions of Cr^{3+}, Cu^{2+}, Mg^{2+}, Cd^{2+}, Fe^{2+}, Ni^{2+}, Mn^{2+}, Co^{2+}, Hg^{2+}, Ba^{2+}, Ca^{2+}, Zn^{2+}, K^{+} and other metal icons exerted a slight enhancement or quenching effect on the emission of RBFC. Commonly, the fluorescence intensity at around 550 nm would be enhanced because of the rhodamine B ring-opening process. Those indicated the compound RBFC can serve as a highly selective fluorescent and colorimetric probe for Fe^{3+} detection in MeOH/HEPES buffer (1:1, v/v, 1.3 mM, pH=7.36) solution.

To further explore selectivity of RBFC toward Fe^{3+}, the metal ions competence assay was carried out by adding Fe^{3+} into the probe RBFC solution in the presence of other metal ions. As depicted in **Figure.6**, the binding of Fe^{3+} by RBFC was hardly interfere by other commonly coexistent ions, which further indicated that the probe RBFC was selective and sensitive for detection of Fe^{3+}. Additionally, the competitive selectivity of RBFC for Fe^{3+} under identical conditions was examined in the presence of other anions. As shown in **Figure.7**, the emission of RBFC with Fe^{3+} shows no significant change when introducing various anions, including I^{-}, F^{-}, Br^{-}, $H_2PO_4^{-}$, HPO_4^{2-}, BrO_3^{-}, S^{2-}, NO_3^{-}, SO_4^{2-}, and $S_2O_8^{2-}$. These results further demonstrate that the presence of anions does not markedly interfere with the detection of Fe^{3+}.

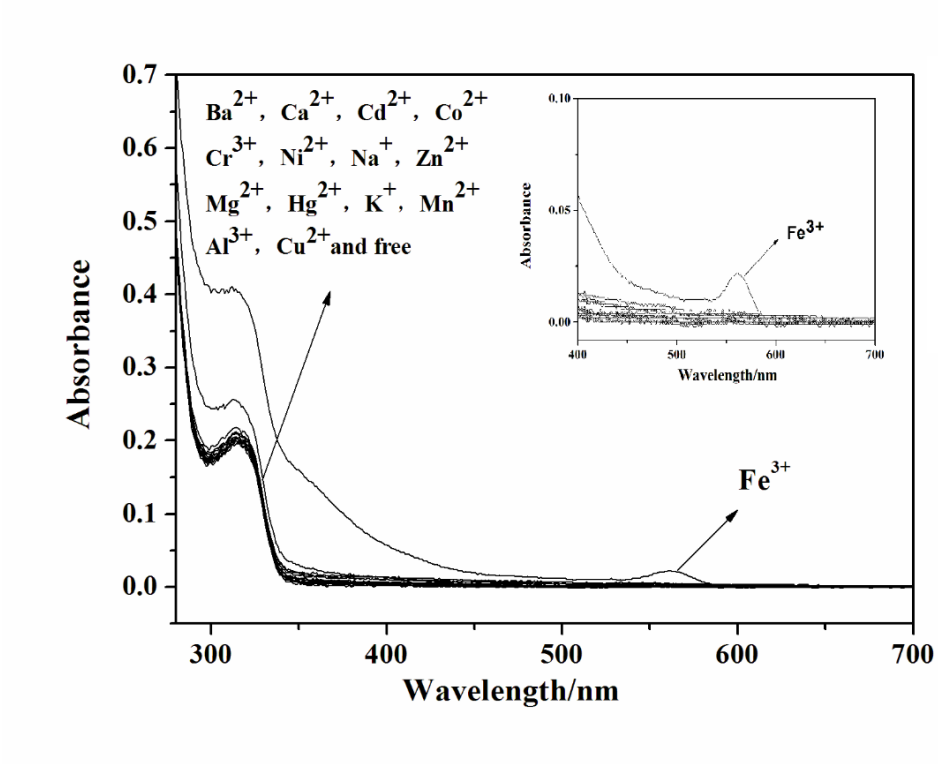


Figure.4 UV–vis absorption spectra of RBFC (0.02mM) in MeOH/H_2O (1:1, v/v, pH 7.36, HEPES buffer, 1.3mM) solutions upon addition of 5 equiv. of various metal icons. Each spectrum was recorded 90 min after the addition of the metal ions.

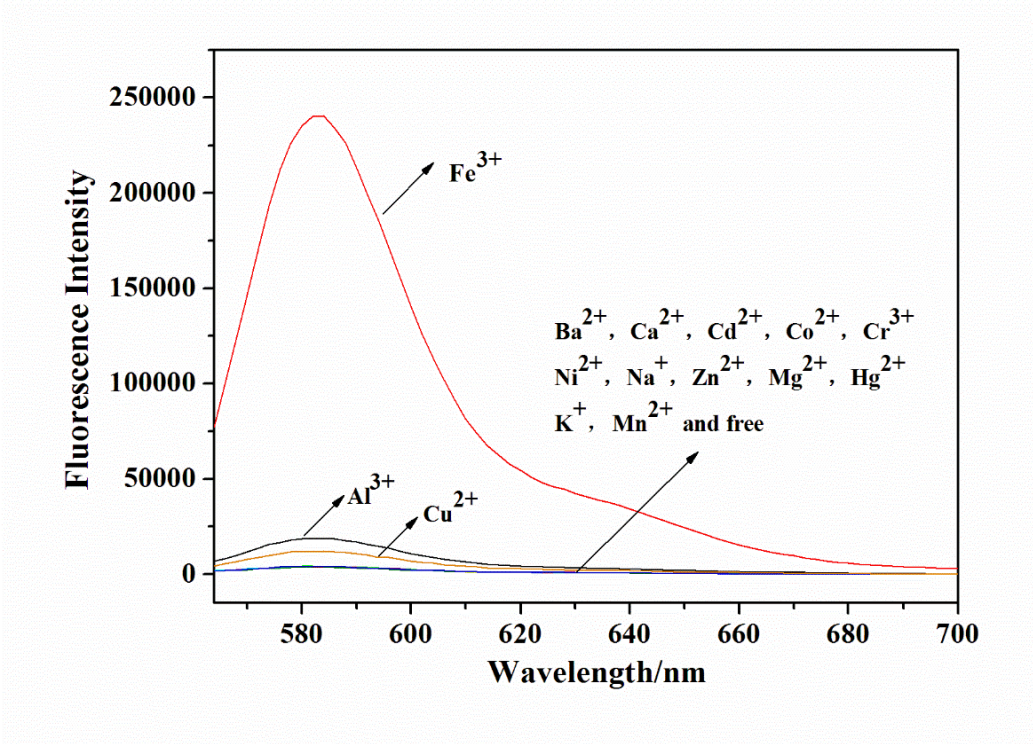


Figure. 5 Fluorescence spectra of RBFC (0.02mM in MeOH/H_2O (1:1, v/v, pH 7.36, HEPES buffer, 1.3mM) solutions upon addition of 5 equiv. of various metal icons with excitation at 582 nm. Each spectrum was recorded 90 min after the addition of the metal ions.

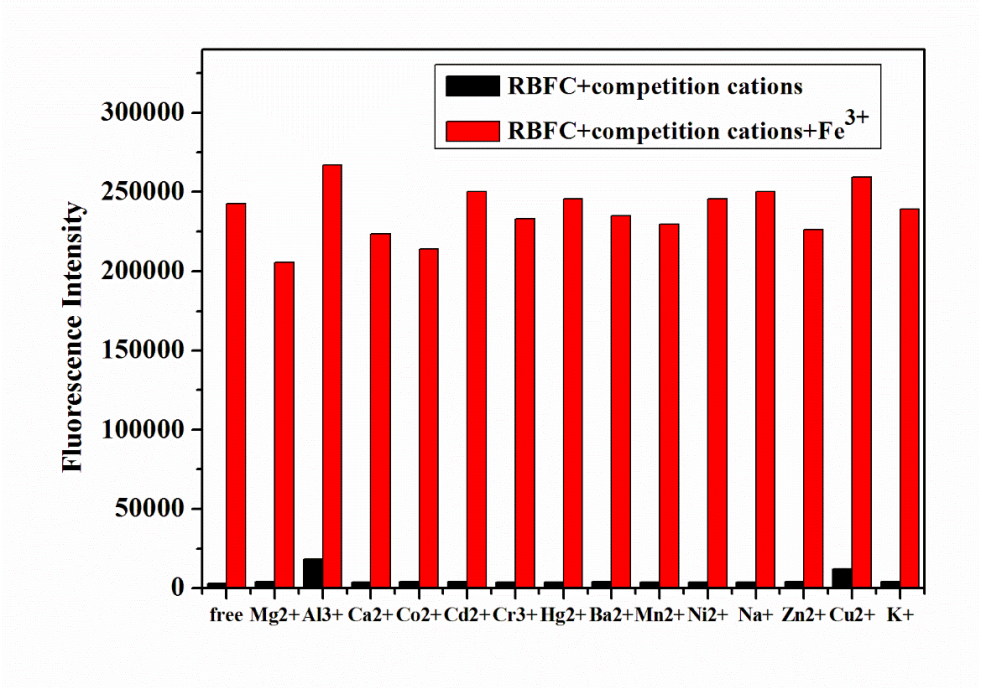


Figure. 6 Metal ion selectivity profiles of RBFC (0.02mM) in the presence of various metal ions in MeOH/H_2O (1:1, v/v, pH 7.36, HEPES buffer, 1.3mM) solution. Black bars represent the fluorescence intensity (582 nm) of RBFC in the presence of 5 equiv of other ions in the absence of Fe^{3+}. Red bars represent the fluorescence intensity (582 nm) in the presence of various metal ions after the addition of Fe^{3+}. Each spectrum was recorded 90 min after the addition of the metal ions.

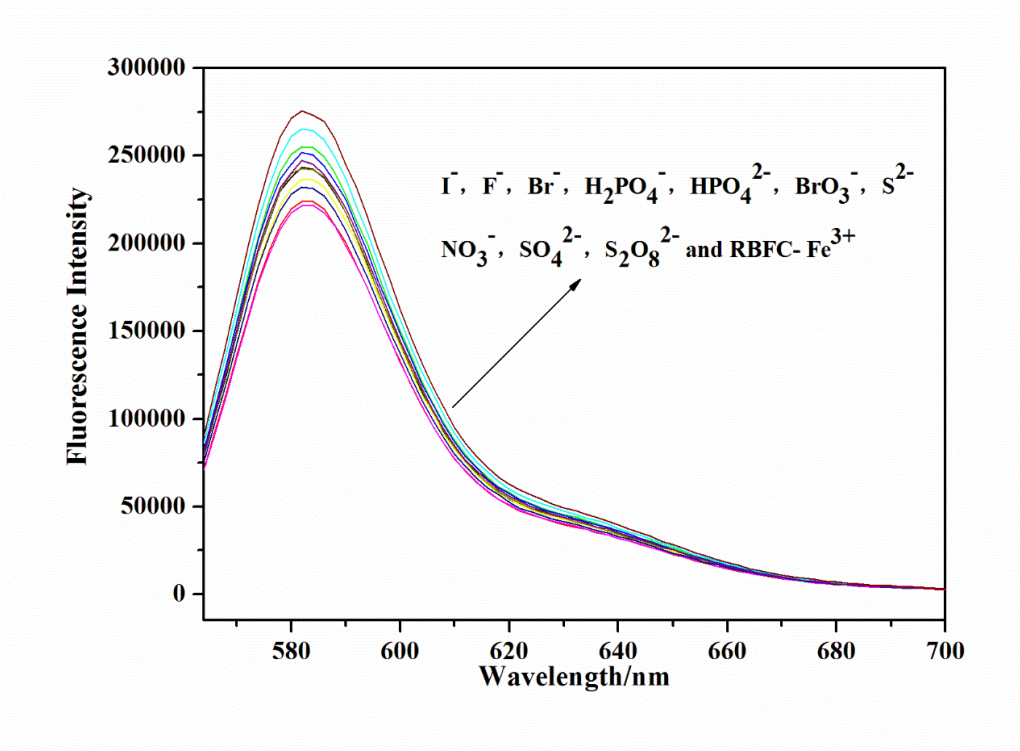


Figure. 7 Fluorescence spectra of RBFC (0.02mM in MeOH/H_2O (1:1, v/v, pH 7.36, HEPES buffer, 1.3mM) solutions upon addition of 5 equiv. of Fe^{3+} and 5 equiv. of various anions icons with excitation at 582 nm. Each spectrum was recorded 90 min after the addition of the metal ions.

2.4. Fluorescence spectral titrations

To get a further insight into the binding of Fe^{3+} with RBFC, the absorbance spectra of RBFC upon titration with Fe^{3+} in MeOH/HEPES buffer (1:1, v/v, 1.3mM, pH=7.36) solution were recorded (**Figure. 8**). Upon addition of increasing amounts of Fe^{3+} ions, a new absorption band centered at 582 nm appeared with increasing intensity. Plotting fluorescence intensity at 582 nm verse Fe^{3+} concentration (3~25μM) afforded a good linear relationship (R=0.98001). According the equation DL=3S/δ, the detection of RBFC for Fe^{3+} was 0.437μM (**Figure. 9**). And the binding constant of RBFC with Fe^{3+} calculated to be $7.28\times10^{3}\ M^{-1}$ (pKa= -3.86) from the fluorescence spectral titrations, according to the Benesi-Hildebrand equation (**Figure. 10**).

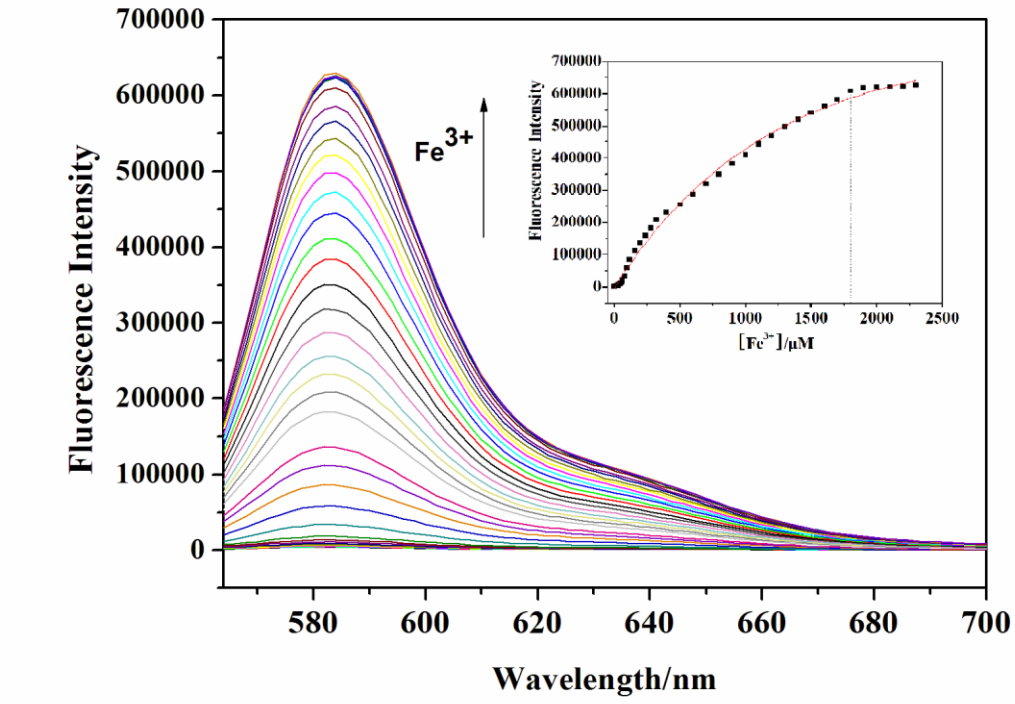


Figure. 8 Fluorescence spectra of 60μL RBFC (1mM) in 3.0mL MeOH/H_2O (1:1, v/v, pH=7.36, HEPES buffer, 1.3mM) solutions at various equiv of Fe^{3+} (0-120equiv). The excitation and emission wavelengths were 560 and 582 nm. Inset: the figure on the right displays the fluorescence intensity at 582 nm vs. the Fe^{3+} concentration. Each spectrum was recorded 90 min after the addition of the metal ions.

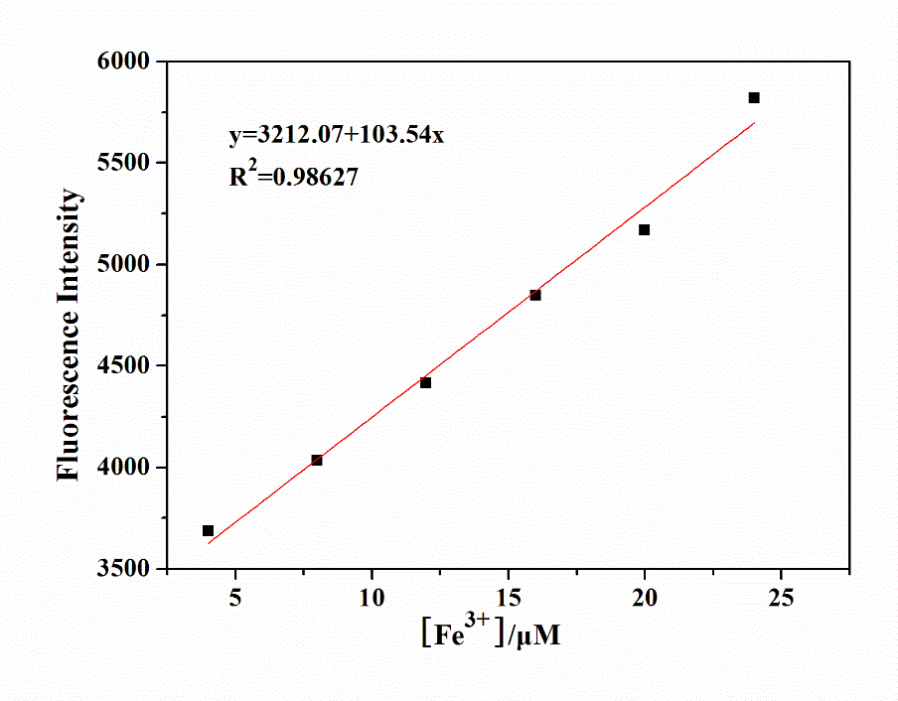


Figure. 9 Fluorescence intensity at 582 nm of RBFC (0.02mM) in MeOH-H_2O solution (1:1, v/v, pH 7.36, HEPES buffer, 1.3mM) with different amounts of Fe^{3+}. Each spectrum was recorded 90 min after the addition of the metal ions.

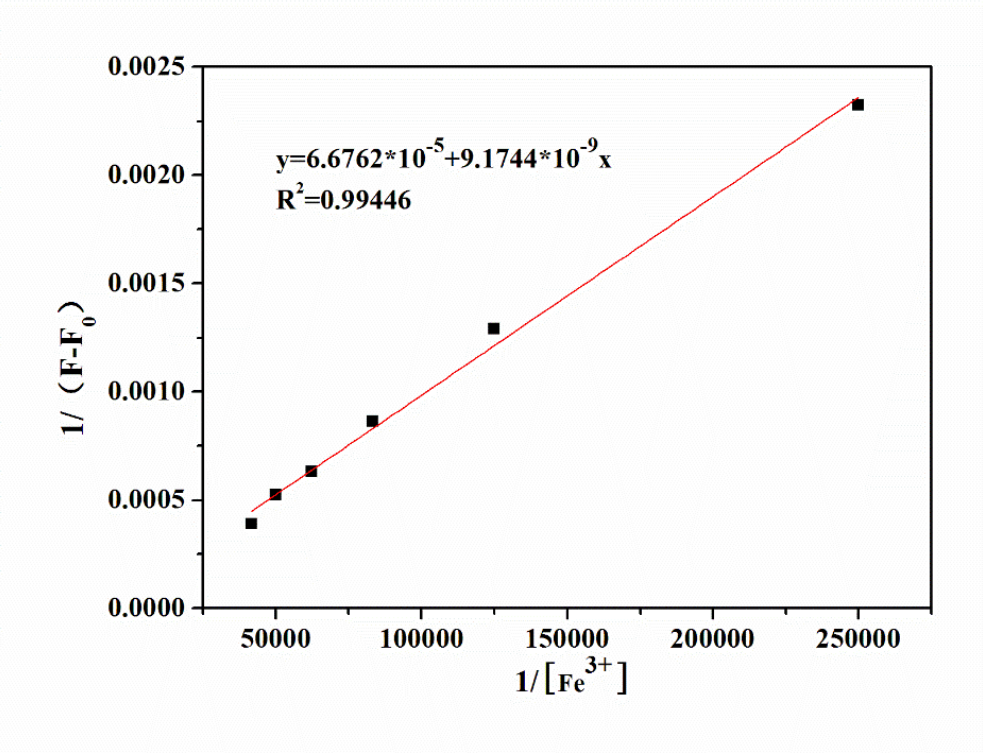


Figure. 10 Benesi–Hildebrand plot (λ_{em}=582 nm) of $1/(F-F_0)$ vs. $1/[Fe^{3+}]$ based on a 1:1 association stoichiometry between sensor RBFC and Fe^{3+}. Each spectrum was recorded 90 min after the addition of the metal ions.

2.5. Proposed sensing mechanism

The stoichiometry of a binding event between Fe^{3+} and the RBFC probe was determined to investigate this mechanism. As showed in **Figure.11**, Job's plot (Figure. 11) confirmed the 1:1 stoichiometry for the RBFC-Fe^{3+} complex with an approximate maximum at a mole fraction of 0.5.

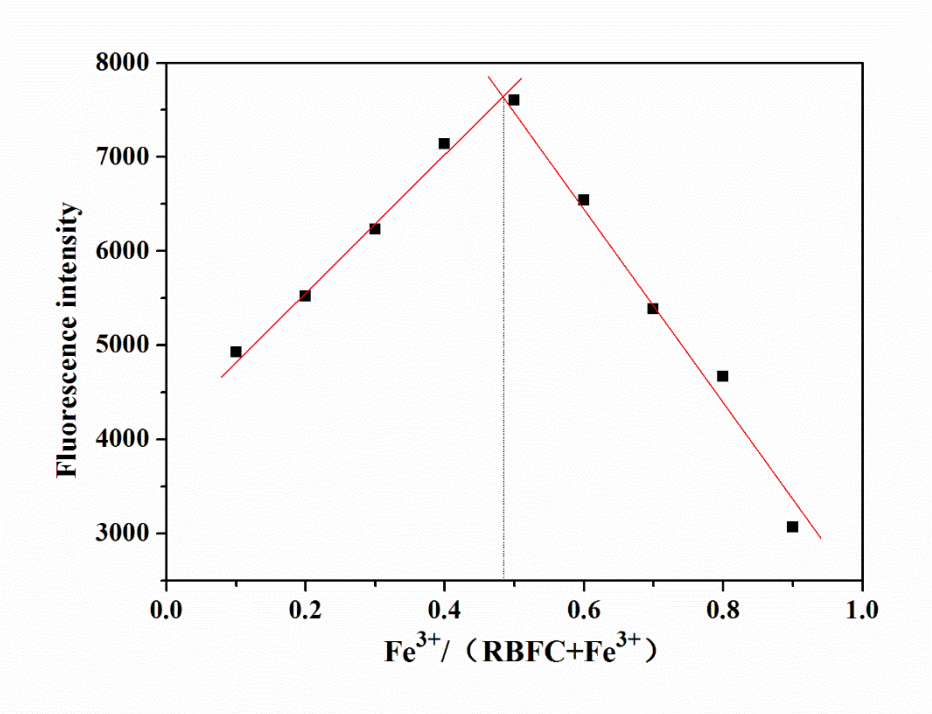


Figure. 11 Job plot of RBFC in MeOH/H_2O (1:1, v/v, pH 7.36, HEPES buffer, 1.3mM) solution with a total concentration of [RBFC]+[Fe^{3+}] =50μM. The emission wavelength was 582 nm (λ_{ex}=560 nm). Each spectrum was recorded 90 min after the addition of the metal ions.

To further elucidate the binding mode of RBFC with Fe^{3+}, 1H NMR spectra of RBFC in the presence and absence of Fe^{3+} were studied. As shown in **Figure.12**, The addition of 0.2 equiv. Fe^{3+} into RBFC in CD_3OD:D_2O (5:1, v/v) solution led to an obvious blue shift of the signals of protons H_e, H_f (H_e: from the peak centered at 6.50 ppm to 6.93 ppm, $\Delta\delta$ = 0.43 ppm; H_f: from the peak centered at 6.26 ppm to 6.50 ppm, $\Delta\delta$ = 0.24 ppm). This was due to the decrease in electron density of the aromatic ring, which proved the delocalization of xanthenes, that is, Fe^{3+} induced the opening of the spirocycle. Next, the proton signals of H_l, H_m, H_n apparent obvious shifts (H_l, H_n: from the peak centered at 7.39 ppm to 7.53 ppm, $\Delta\delta$ = 0.14 ppm; H_m: from the peak centered at 6.21ppm to 6.48pm, $\Delta\delta$ = 0.27ppm). The results indicated that the "O" atoms on the furan group in the string of RBFC participated in the coordination with

Fe^{3+}. Herein, according to above experimental result, we broached a conceivable mechanism of Fe^{3+} complex with RBFC (**Scheme. 2**), in which Fe^{3+} may be coordinated with the oxygen atom of the amide, the oxygen atom of the carbonyl and the oxygen atom of the furan group.

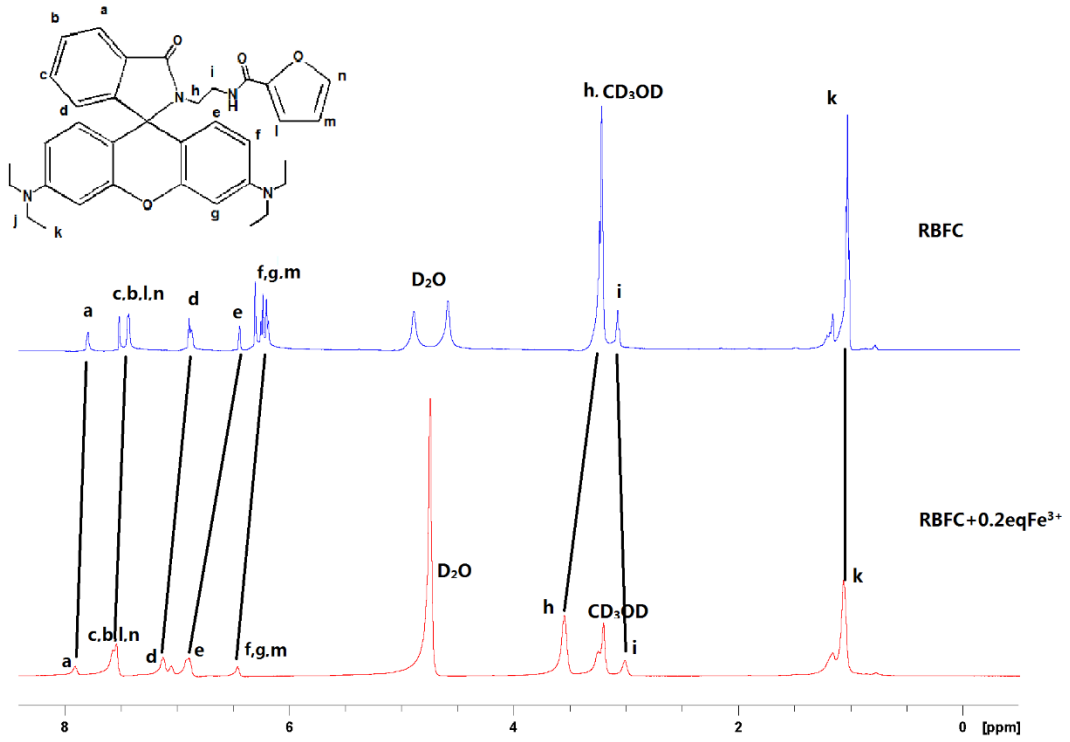
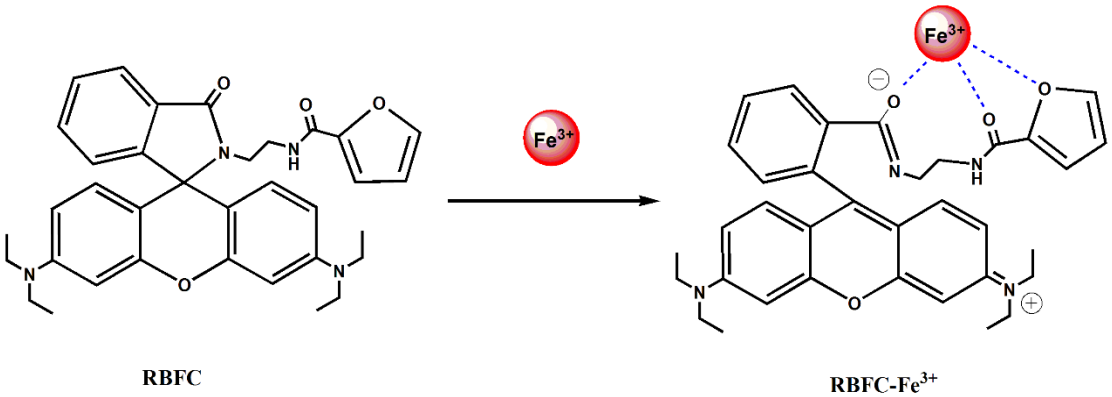


Figure. 12 ^{1}H NMR spectra (500 MHz, 298K, CD_3OD/D_2O (5:1,v/v)) of RBFC, and RBFC+0.2equiv Fe^{3+}. Each spectrum was recorded 90 min after the addition of the metal ions.



Scheme. 2 Proposed mechanism for the binding of compound RBFC to Fe^{3+}.

2.6. Fluorescence imaging in living cells

Finally, to investigate the potential biological application of the probe RBFC in living cells, imaging inside MCF-7 cells were monitored by florescence microscopy.

To begin with, the cytotoxicity of probe RBFC was evaluated using a conventional MTT assay. As shown in **Figure. 13**, when MCF-7 cells are treated with probe RBFC at a concentration of no more than 30 μM for 24 h, no significant cytotoxic response (cell viability ⩾85%) is observed. Thereby, 10 μM of probe RBFC is used for cell imaging.

Then fluorescence imaging of RBFC was conducted in MCF-7 cells. Bright-field measurements after the treatment with RBFC confirmed that the cells were viable throughout the imaging experiments. As shown in **Figure.14A2**, RBFC cells display almost no fluorescence. The cells treated with both the Fe^{3+} and probe RBFC exhibit strong fluorescence (shown in **Figure.14C2**), while the cells treated only with probe RBFC show weak fluorescence (shown in **Figure.14B2**). These results indicated that probe RBFC is cell membrane-permeable, effective intracellular imaging agent for Fe^{3+} ions, and valuable for studying the uptake, bioaccumulation, and bioavailability of Fe^{3+} in living organisms.

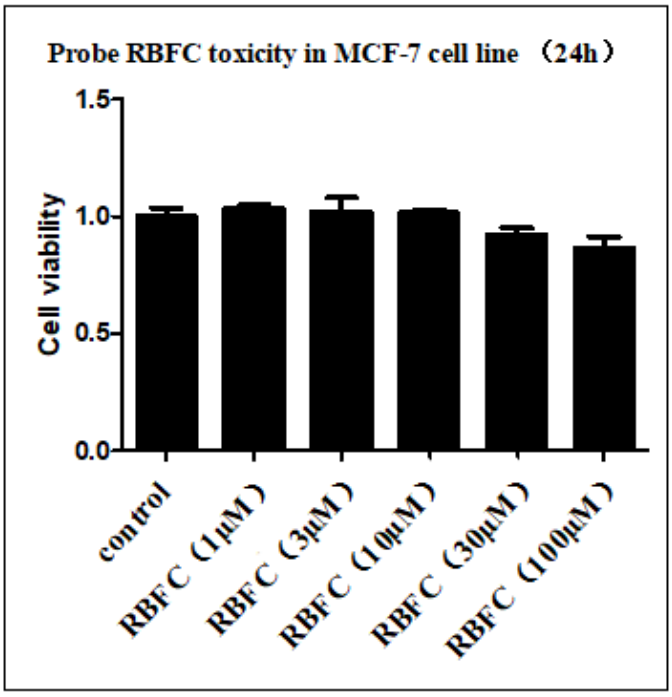


Figure. 13 Cytotoxic effect of RBFC in MCF-7 cells incubated for 24 h.

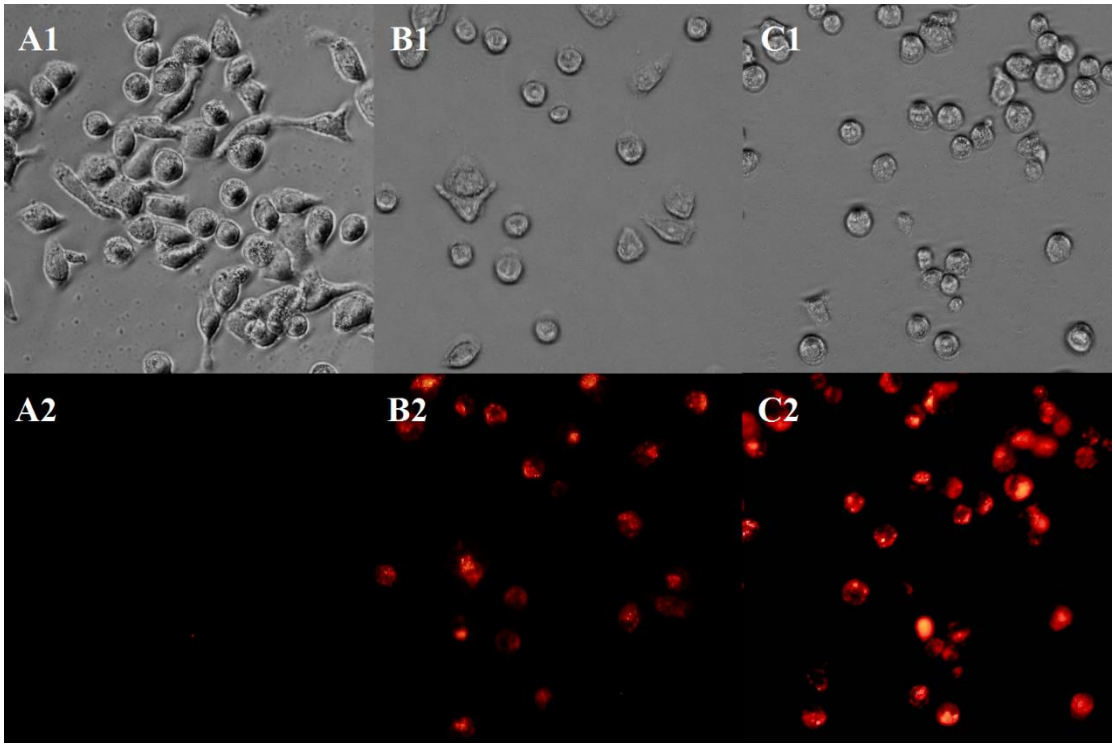


Figure.14 Fluorescence images of MCF-7 cells incubated with RBFC and/or Fe^{3+}. MCF-7 cells were incubated with 100 μM $FeCl_3$ for 60 min at 37 °C, followed by 10 μM RBFC for additional 5 h. (A) Fluorescence image of MCF-7 Cells; (B)Cells treated with only probe RBFC; (C)Cells incubated with $FeCl_3$ for 1h,followed by treatment with probe RBFC for an additional 5h;(1) Bright field .(2) Red channel.

3. Conclusion

In summary, we developed a fluorescent probe RBFC for sensing Fe^{3+} based on rhodamine derivative. The probe could specifically recognize Fe^{3+} in a MeOH/H_2O (1:1, v/v, pH 7.36, HEPES buffer, 1.3mM) solution by UV–vis and fluorescence response. The probe RBFC displayed a 28-fold fluorescence enhancement upon complexation with Fe^{3+} under in vitro. The detection limit of the probe RBFC for Fe^{3+} was calculated to be 0.437μM and the association constant was 7.28×10^3 M^{-1}. The probe was site-specifically internalized in Fe^{3+} due to the opening of the spirolactam rings occurs upon RBFC coordination with Fe^{3+}. Additionally, the probe has been applied to the microscopic imaging for monitor intracellular Fe^{3+} in MCF-7 cells with little cytotoxity.

4. Experimental

4.1. Materials and instruments

For details, see the Supporting Information.

4.2. Synthesis of 2-(2-aminoethyl)-30,60-bis(diethylamino)spiro-[isoindoline-1,90-xanthen]-3-one (compound 1)

Syntheses and characterizations of compound 1 were described in Supporting Information.

4.3. Synthesis of RBFC

A mixture of compound 1 (174.2 mg, 0.36 mmol), furan-2-carbonyl chloride (0.03 mL, 0.30 mmol) and triethylamine (0.05mL, 0.36mmol) were dissolved in EtOH (5.0mL) with stirring at room temperature under nitrogen for 4 h. After completion of the reaction, the solvent was removed under reduced pressure. The residue was purified by flash silica gel column chromatography using MeOH–CH_2Cl_2 (2:98, v/v), yielding a pink solid RBFC (112.0 mg, 64%).

^{1}H NMR ($CDCl_3$), δ 8.02（s, 1H, N-H), 7.94(m, 1H, Ar-H), 7.59(m, 1H, Ar-H), 7.44(m, 2H, Ar-H), 7.09(m, 1H, Ar-H), 7.05(d, J=3.5, Ar-H, 1H), 6.45(m, 3H), 6.38(d, J=2, 2H), 6.27(dd, J_1=2, J_2=8.5, 2H), 3.40(t, J=5, 2H), 3.35(q, J=7, 8H), 3.21(q, J=4.5, 2H), 1.29(m, 2H), 1.18(t, J=7, 12H) ppm. ^{13}C NMR ($CDCl_3$), δ 170.15, 158.64, 154.05, 153.42, 149.08, 148.41, 144.24, 132.90, 130.58, 128.41, 124.03, 123.07, 113.55, 111.73, 108.41, 104.85, 97.92, 77.16, 65.87, 44.49, 40.41, 29.82, 12.74 ppm. FTMS（M）found，579.2939，calculated for $C_{35}H_{39}N_4O_4$，579.2893.

4.4. General spectroscopic procedures

Stock solutions (5.0mM) of the metal chloride salts or nitrate of (Fe^{3+}, Cr^{3+}, Cu^{2+}, Mg^{2+}, Cd^{2+}, Fe^{2+}, Ni^{2+}, Mn^{2+}, Co^{2+}, Hg^{2+}, Ba^{2+}, Ca^{2+}, Zn^{2+} , K^+, Na^+) in water were prepared. Stock solutions of RBFC (1.0mM) were prepared in MeOH/H_2O (1:1, v/v, pH 7.36, HEPES buffer, 1.3mM). All spectra were recorded 90min after the addition at room temperature with the excitation wavelength set at 560 nm and emission was collected from 564 to 702 nm (excitation /emission slit widths: 2 nm)

4.5. Calculations for the detection limit and the binding association constant

Calculations for the detection limit and the binding association constant were described in Supporting Information.

4.6. Cell studies of RBFC in the presence of Fe^{3+}

MCF-7 cells were incubated in Dulbecco`s modified Eagle`s medium (high glucose, HyClone) supplemented with 15% FBS (fetal bovine serum), 100 units/mL

penicillin, and 100 units/mL streptomycin in a 5% CO_2/95% air incubator at 37 ℃. The MCF-7 cells (2×10^4 cells per well) were seeded into 24 well plates overnight before imaging. Then the cells were incubated with 10 μM RBFC in culture medium for 4 h in an air incubator at 37 ℃. In the control experiment, cells were pretreated with 100 μM Fe^{3+} for 1 h and then incubated with 10 μM RBFC in culture medium for an additional 4 h. After washing triple with PBS, the cells was imaged under an inverted fluorescence microscope with the red channel.

4.7. Cell cytotoxicity assay

To determine the cell viability of RBFC, MTT (3-(4,5-dimethyl-2-thiazolyl) -2,5-diphenyl-2-H-tetrazolium bromide) assay was performed according to the procedure described. MCF-7 cells (6×10^3 cells per well) were cultured in a 96 well plate at 37 ℃, and exposed to varying concentrations of RBFC (5, 10, 20, 30, 40, 60 and 80 μM) respectively, for 24 h. 50 μL of MTT solution (1 mg ml^{-1}) was added to each well of a 96-well culture plate and incubated again at 37 ℃ for a period of 4 h. All media were removed from wells and DMSO (150 μL/well) was added to dissolve the formazan. Absorbance was measured at 550 nm with a microplate reader (Infinite M200 Pro). All experiments were performed in quadruplicate and the relative cell viability (%) was expressed as a percentage relative to the untreated control cells.

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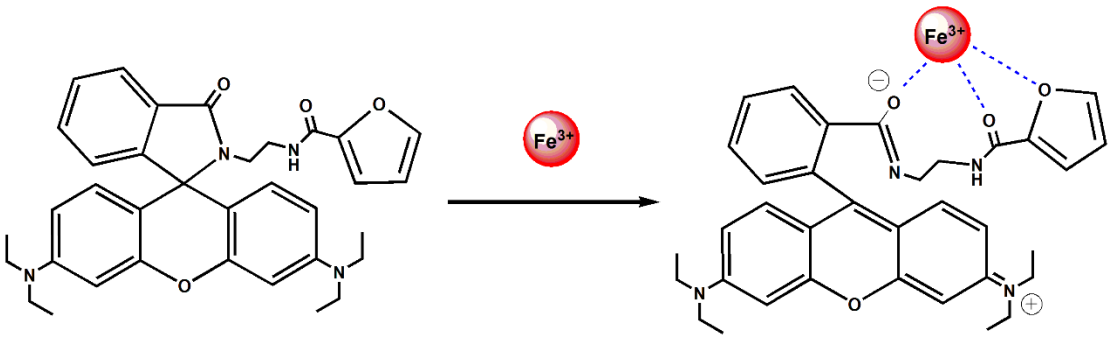
Highlights

- A fluorescent probe synthesized with rhodamine B and furan-2-carbonyl chloride
- The probe exhibited a high selectivity and sensitivity towards Fe^{3+} in solution
- UV-vis absorption and fluorescence spectroscopic are used to characterize the probe
- The probe could be applied to monitor intracellular Fe^{3+} in living cells



RBFC **RBFC-Fe^{3+}**

A furan-2-carbonyl chloride modified rhodamine B derivative has been designed and synthesized. The probe exhibited excellent sensitivity and selectivity for detection of Fe^{3+} in a MeOH/H_2O solution. And it could monitor intracellular Fe^{3+} in MCF-7 cells.