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ORIGINAL ARTICLE

A highly Sensitive Turn-on Fluorescent Sensor for Ba^{2+} Based on G-Quadruplexes

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Abstract A G-quadruplex-based fluorescent biosensor for highly sensitive detection of barium ion (Ba^{2+}) was constructed for the first time. In the absence of Ba^{2+}, the G-quadruplex-specific fluorescence ligand N-methyl mesoporphyrin IX (NMM) remained weakly fluorescent when coexisted with a single-stranded G-quadruplex sequence AGRO100. Upon addition of Ba^{2+}, AGRO100 was folded into G-quadruplex structures with the aid of Ba^{2+}, which bound with NMM by stacking forces and significantly enhanced its fluorescence. The maximum fluorescence intensity of NMM was increased by ca. 22-fold in response to 1 μM Ba^{2+}. This simple method exhibites a good linear relationship in the range of 0–600 nM with the detection limit of 4 nM. The detection method is turn-on, fast, economic, high in signal-to-noise ratio and free of participation of toxic organic solvents, demonstrating its great potential for on-site and real-time Ba^{2+} detection.

Keywords Barium · Fluorescence · G-quadruplexes · Label-free · Sensors

Introduction

Detection of metal ions is of great importance as they are either beneficial or toxic to biological systems and environment [1, 2]. Soluble barium ion (Ba^{2+}) is a poisonous heavy metal ion. High-level Ba^{2+} exposure causes cardiac arrhythmia, liver and kidney failure, disorders of nervous system, dyspnea, ventricular fibrillation, and paralysis [3]. It is reported that in the US alone, over 150,000 people are exposed to Ba at levels higher than the limit of 2 mg/L defined by the Environmental Protection Agency (EPA) on a continuous basis [3]. Recently, the use of Ba^{2+} in petroleum industry, steel industry, production of semiconductors and medicine has greatly increased [3]. Although current techniques such as inductively coupled plasma mass spectrometry (ICPMS) and electrochemical methods are capable of measuring Ba^{2+} [4–6], it often requires expensive sophisticated instrumentation and complicated sample preparation. Therefore, the development of simple and cost-effective assays for Ba^{2+} detection is very important for water controlling and industrial production.

Fluorescent and colorimetric sensors are often utilized to detect metal ions owing to their simplicity and sensitivity [1, 2]. However, very few sensors for Ba^{2+} have been reported probably due to a lack of specific recognition elements [7–13]. Besides, most of these chemical sensors and nanoparticle-based sensors are subject to the participation of toxic organic solvents, low signal-to-noise ratio, insensitivity and/or poor selectivity. In past decades, the functional nucleic acid-based sensors have shown great potential in the detection of metal ions, such as K^+, Pb^{2+}, Hg^{2+}, and Ag^+ [14–16]. G-quadruplexes are higher four-stranded structures that generate from a planar arrangement of four guanine bases through hydrogen bonds [17]. It is known that the formation of G-quadruplexes is efficiently promoted by monovalent cations, such as K^+ and Na^+ [18]. It has also been reported that some divalent metal ions (such as Pb^{2+} and Ba^{2+}) possess stronger ability than monovalent cations to stabilize G-quadruplexes, mainly because of their appropriate ionic radius and high charge density [19, 20]. Most of these metal ions locate between two G-quartets by coordinating with eight guanines.

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The strong ability to stabilize G-quadruplex structures provides an effective assay method for Ba^{2+} detection [21–23]. Compared with the previous reported sensors based on G-quadruplexes for various metal ions [14–16], biosensors for Ba^{2+} is seldom presented, probably due to the interference from K^+ and Pb^{2+}. To date, only Wu et al. reported a nanopore sensor for Ba^{2+} based on Ba^{2+}-induced formation of G-quadruplex structures from a thrombin binding aptamer (5′-GGTTGGTGTGGTTGG-3′) [24]. Though this nanopore sensing exhibits good sensitivity, expensive and sophisticated protein preparation process and stability of proteins would limit its applications.

In this paper, we demonstrate the Ba^{2+}-induced turn-on fluorescence response of the AGRO100-NMM system and construct a Ba^{2+} sensor using AGRO100 as the sensing element and NMM as the fluorescence indicator molecule through selecting proper buffer solutions. It has been found that the binding of Ba^{2+} to AGRO100 is much stronger than that of monovalent cations, and stronger or comparable compared with the binding of Pb^{2+} and other divalent cations. NMM could efficiently bind with the G-quadruplexes stabilized by Ba^{2+}, exhibiting significant fluorescence enhancement. Under weakly alkaline condition, interference from Pb^{2+} and other metal ions was obviously suppressed. An application for the detection of Ba^{2+} in contaminated lake water was proved.

Experimental Section

Reagents and Chemicals

The synthesized DNA was purchased from Sangon Biotechnology Co., Ltd. (Shanghai, China). DNA samples were prepared in ultrapure water, and the concentrations of DNA were quantified using 260 nm UV absorbance. N-methyl mesoporphyrin IX (NMM) was purchased from Frontier Scientific, Inc. (Logan, Utah). The concentration of NMM was determined using UV-VIS spectrophotometer (λ = 379 nm, extinction coefficient = 1.45×10^5 M^{-1} cm^{-1}). $Ba(NO_3)_2$ and other chemicals were of analytical grade and bought from Sinopharm Chemical Reagent Co. Ltd. (Shanghai, China). Fluorescence and circular dichroism (CD) measurements were performed in 10 mM Tris-HAc buffer. Milli-Q water was used to prepare solutions throughout the experiment.

Apparatus

DNA concentration was determined by spectrophotometry using an Eppendorf biophotometer (Eppendorf, Hamburg, Germany). Fluorescence spectra were recorded on a F-4600 spectrofluorometer (Hitachi, Tokyo, Japan). The excitation wavelength was fixed at 399 nm and emission spectra were collected from 550 to 750 nm at 1 nm increments. The slit widths for excitation and emission were set at 10 nm and 10 nm, respectively. The maximum emission intensity for NMM was observed at ca. 611 nm. The CD spectra were collected by a Chirascan-plus Circular Dichroism Spectrometer (Applied Photophysics Ltd., Surrey, UK). Three scans from 205 to 320 nm at 1 nm intervals were accumulated and averaged.

Fluorescence Measurements

For the typical fluorescence detection of Ba^{2+}, the AGRO100 stock solution (10 μM) prepared in Milli-Q water was first heated to 50 °C for 10 min, then cooled slowly to room temperature. 7.5 μL AGRO100 was withdrawn from this solution and diluted with Tris-HAc (10 mM, pH 8.5) buffer to a final concentration of 0.5 μM. After that, 4.5 μL NMM (10 μM) was added to the buffer solution. Different concentration of $Ba(NO_3)_2$ was finally added to the above mixture solution and incubated for 20 min in the dark at room temperature before fluorescence spectra measurement. In the selectivity experiment, KNO_3, $CaCl_2$, $MgCl_2{\cdot}6H_2O$, $Al(NO_3)_3{\cdot}9H_2O$, $Fe(NO_3)_3{\cdot}9H_2O$, $CuSO_4{\cdot}5H_2O$, $Pb(NO_3)_2$, $Cr(NO_3)_3{\cdot}9H_2O$, $Co(NO_3)_2{\cdot}6H_2O$, $AgNO_3$, $Cd(NO_3)_2.4H_2O$ and $Hg(NO_3)_2$ were utilized to evaluate the selectivity of this sensor towards Ba^{2+}. The assay procedures for these metal ions were the same as those for Ba^{2+}.

Water samples were collected from Dushu Lake of Suzhou and filtered through a 0.22 μm membranes before using. Then artificially contaminated water samples were prepared through spiking different concentrations of Ba^{2+} (5 μM and 10 μM) into the filtered water samples. These samples were added into the sensing system and fluorescence spectra were recorded according to the aforementioned procedure.

Circular Dichroism Measurements

The AGRO100 stock solution (50 μM) prepared in Milli-Q water was first heated to 50 °C for 10 min, then cooled slowly to room temperature. 24 μL AGRO100 was diluted with Tris-HAc (10 mM, pH 8.5) buffer to a final concentration of 4 μM. 2.4 μL Ba^{2+} (1 mM) was then added into the mixture solution and incubated for 20 min at room temperature before CD spectra were measured.

Results and Discussion

Sensing Mechanism

It has been reported that Ba^{2+} efficiently stabilized G-quadruplexes from guanosine derivatives and a thrombin

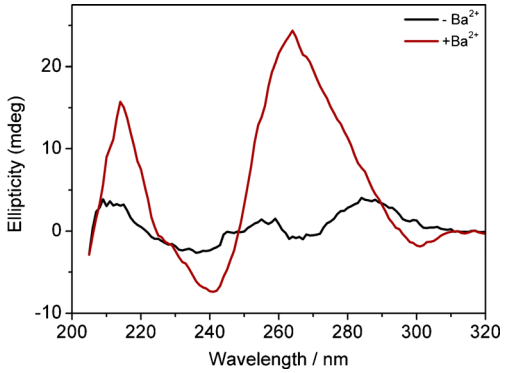

Fig. 1 Circular dichroism (CD) spectra of AGRO100 (4 μM) in the absence and presence of Ba^{2+} (8 μM) in a 10 mM Tris-HAc (pH 8.5) buffer

binding aptamer sequence [25, 26]. Previous reports showed that the AGRO100-NMM system insensitively responded to K^+ [27, 28]. To eliminate the common interference from K^+, AGRO100 was selected as the sensing element for this G-quadruplex-based Ba^{2+} sensor. AGRO100, also known as AS1411, is a nucleolin targeting aptamer (5′-GGTG GTGGTGGTTGTGGTGGTGGTGG-3′) [29]. Compared with the widely reported interaction of AGRO100 with K^+ and Pb^{2+}, the binding of AGRO100 with Ba^{2+} still remained unknown. To confirm the conformation conversion of AGRO100 in response to Ba^{2+}, circular dichroism (CD) spectra of AGRO100 were measured in the absence and presence of Ba^{2+}. As shown in Fig. 1, in the absence of Ba^{2+}, the small peak in the wavelength range of 205–320 nm indicated the random-coil structure of AGRO100 in solution. In the presence of Ba^{2+}, a large positive peak at 264 nm was observed, demonstrating the presence of G-quadruplex structures [30].

Here we utilized a fluorescence ligand NMM to monitoring the formation of Ba^{2+}-stabilized G-quadruplexes. NMM is a commercially available G-quadruplex-specific fluorescence dye. NMM is weakly fluorescent, but exhibits a significant enhancement in its fluorescence upon binding to G-quadruplex structures [31, 32]. Figure 2 outlines the sensing mechanism of this Ba^{2+} sensor. The fluorescence of NMM itself is weak. Upon adding AGRO100 in its random-coil structure into a NMM solution, the fluorescence still remained weak. When Ba^{2+} was added, the conformation of AGRO100 converted into G-quadruplex structures which could bind to NMM and enhance its fluorescence. As a consequence, the presence of Ba^{2+} was indicated by the fluorescence enhancement.

To confirm the feasibility of the present strategy, the fluorescence spectra of NMM, AGRO100-NMM and AGRO100-NMM-Ba^{2+} complexes were first determined. As shown in Fig. 3, AGRO100 in its random-coil structure led to a slight increase in the fluorescence of NMM. With the adding 1 μM Ba^{2+}, the maximum fluorescence at 611 nm of AGRO100-NMM was increased by ca. 22-fold. The significant fluorescence enhancement obtained here ensures a high signal-to-noise ratio. Given that NMM is a G-quadruplex-specific fluorescent dye, the fluorescence enhancement suggested the formation of G-quadruplex structures stabilized by Ba^{2+}. Contrary to the previous supposition that Ba^{2+}-mediated G-quadruplex structures are not stable enough to afford turn-on fluorescent sensing [24], our results above confirmed that the G-quadruplexes stabilized by Ba^{2+} could switch on fluorescence of appropriate ligands.

Optimization of Sensing Conditions

The incubation time of the AGRO100-NMM complex with Ba^{2+} was studied to achieve maximum and stable fluorescence responses. 0.6 μM Ba^{2+} was mixed with AGRO100

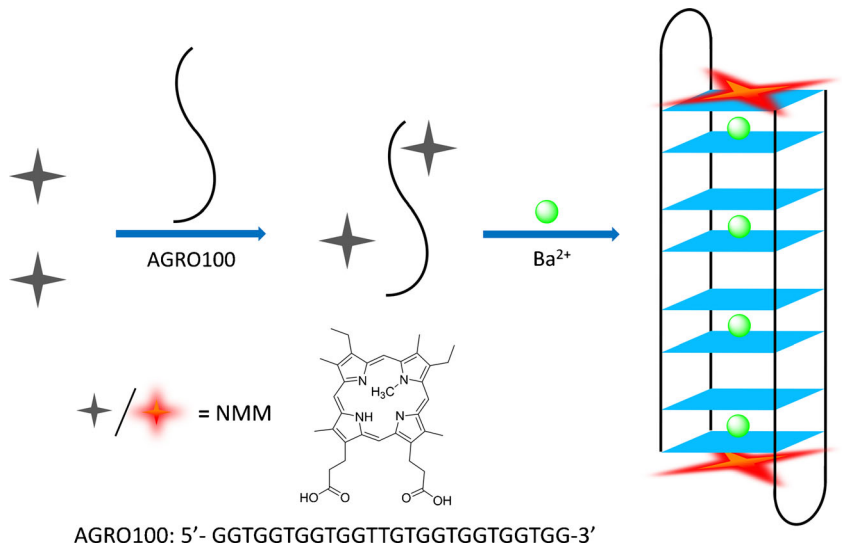

Fig. 2 Schematic of the highly sensitive turn-on fluorescent sensor for Ba^{2+} based on G-quadruplex

and NMM, incubated in the dark for different time, and finally fluorescence intensity at 611 nm was recorded. As illustrated in Fig. 4, the fluorescence intensity was increased with prolonging the incubation time after adding Ba^{2+} and reached a plateau after ca. 20 min. Therefore an incubation time of 20 min was used in this experiment.

A further study was performed to investigate the effect of pH of the Tris-HAc buffer on the fluorescence responses of the AGRO100-NMM complex to Ba^{2+}. As K^+ was also known to induce the formation of G-quadruplexes, the effect of pH on fluorescence changes in the presence of K^+ was simultaneously investigated. With the increase of pH value from 7.0 to 9.0, the fluorescence response remained almost unchanged to Ba^{2+}, whereas obviously increased to K^+ from pH 8.5 to pH 9.0 (Fig. 5a). Besides, it is known that Pb^{2+} could obviously turn on the fluorescence of the AGRO100-NMM complex at pH 7.4 [27]. However, the fluorescence response to Pb^{2+} was apparently suppressed at pH 8.5 (Fig. 5b), which was supposed to be caused by the low solubility product constant (Ksp) of $Pb(OH)_2$ (1.43×10^{-15}) [33]. To eliminate the interference from K^+ and Pb^{2+}, a buffer solution of pH 8.5 was selected.

Sensitivity and Selectivity

The fluorescence responses to different concentrations of Ba^{2+} were measured under optimal conditions. The fluorescence intensity at 611 nm was increased as a function of the added Ba^{2+} and reached a plateau at ca. 1500 nM (Fig. 6). The inset in Fig. 6b shows a good linear relationship between fluorescence intensities and Ba^{2+} concentrations in the range of 0–600 nM. The limit of detection was estimated to be 4 nM for Ba^{2+} based on a signal-to-noise ratio (S/N) of 3 in the test conditions. It is more than 3600-fold lower than the EPA limit (2 mg/L) for Ba^{2+} in drinking water, exhibiting the high sensitivity of the sensor. Compared with the reported Ba^{2+} sensors, this sensor provides better sensitivity than most of those

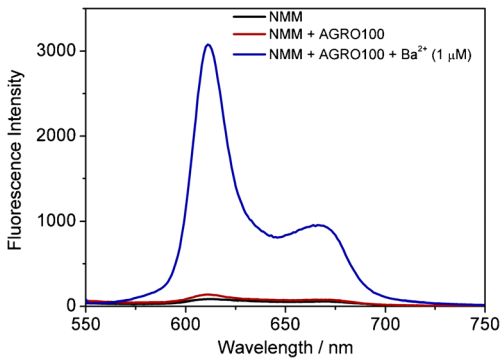

Fig. 3 Fluorescence emission spectra of NMM, AGRO100-NMM and AGRO100-NMM-Ba^{2+} complexes in 10 mM Tris-HAc buffer (pH 8.5). [NMM] = 0.3 μM, [AGRO100] = 0.5 μM, [Ba^{2+}] = 1 μM

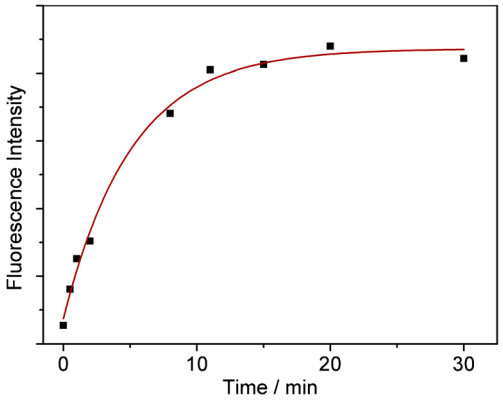

Fig. 4 Fluorescence response of NMM-AGRO100 complexes with Ba^{2+} (0.6 μM) as a function of incubation time in a 10 mM Tris-HAc (pH 8.5) buffer. [NMM] = 0.3 μM, [AGRO100] = 0.5 μM

previously reported methods. Besides, as shown in Table 1, compared with ICP-MS, this sensor has comparable sensitivity, but with the advantage of low cost.

We then evaluated the sensor's selectivity to Ba^{2+}. As shown in Fig. 7, when metal ions existed alone, a large amount of excess of others ions (except Pb^{2+}) did not obviously change the fluorescence intensity of the NMM-AGRO100

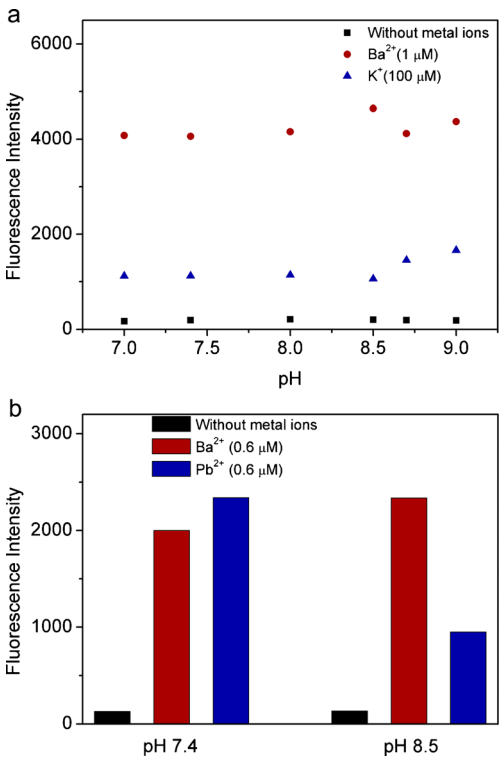

Fig. 5 **a** Effect of pH of 10 mM Tris-HAc buffer on the fluorescence response of the AGRO100-NMM complex in the absence and presence of Ba^{2+}(1 μM) or K^+ (100 μM) ions. [NMM] = 0.5 μM, [AGRO100] = 0.5 μM. **b** Effect of pH of Tris-HAc buffer on the fluorescence response of the AGRO100-NMM complex in the absence and presence of Ba^{2+}(0.6 μM) or Pb^{2+} (0.6 μM) ions. [NMM] = 0.3 μM, [AGRO100] = 0.5 μM

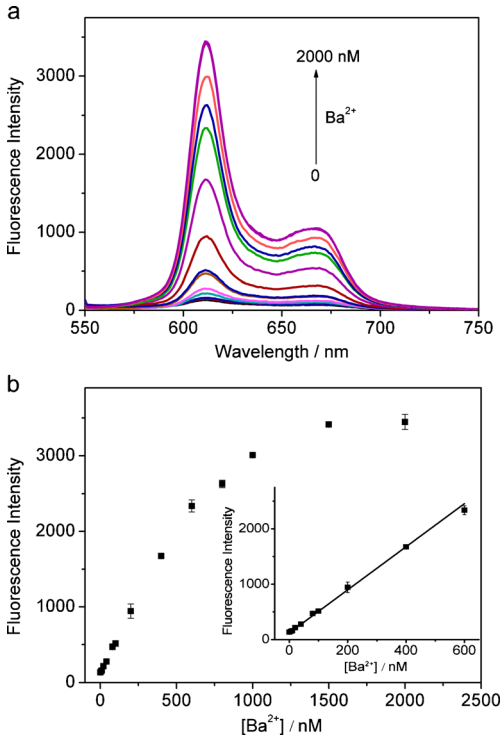

Fig. 6 **a** Fluorescence emission spectra of the AGRO100-NMM complex in the presence of different concentrations of Ba^{2+} from 0 to 2000 nM. **b** Fluorescence intensities at 611 nm of the AGRO100-NMM complex in the presence of different concentrations of Ba^{2+} from 0 to 2000 nM. Inset: The linear relationship in the Ba^{2+} concentration range from 0 to 600 nM. [NMM] = 0.3 μM, [AGRO100] = 0.5 μM

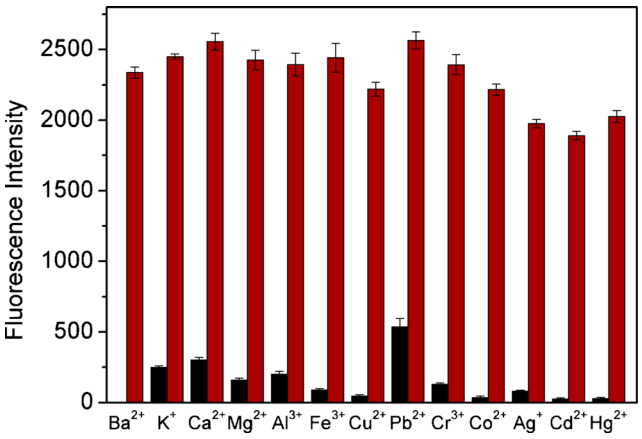

Fig. 7 Selectivity of the Ba^{2+} sensor. Black bars represent fluorescence responses after addition of individual metal ion (0.6 μM Ba^{2+}, 50 μM K^{+}, 10 μM Ca^{2+}, 100 μM Mg^{2+}, 100 μM Al^{3+}, 100 μM Fe^{3+},100 μM Cu^{2+},0.2 μM Pb^{2+}, 10 μM Cr^{3+}, 10 μM Co^{2+}, 10 μM Ag^{+}, 10 μM Cd^{2+}, and 10 μM Hg^{2+}). Red bars represent fluorescence responses after addition of Ba^{2+} together with one other metal ion (100 μM K^{+}, 10 μM Ca^{2+}, 100 μM Mg^{2+}, 10 μM Al^{3+}, 10 μM Fe^{3+}, 1 μM Cu^{2+}, 0.2 μM Pb^{2+}, 10 μM Cr^{3+}, 0.6 μM Co^{2+}, 0.6 μM Ag^{+}, 0.6 μM Cd^{2+}, and 0.6 μM Hg^{2+}). [NMM] = 0.3 μM, [AGRO100] = 0.5 μM

complex, compared with the significant fluorescence enhancement in the presence of Ba^{2+}. Pb^{2+} (0.2 μM) led to a slightly increase in the fluorescence due to its ability to stabilize G-quadruplex structures [24, 27]. Coexistence of other metal ions with Ba^{2+} in the test conditions did not apparently affect Ba^{2+} detection. The good selectivity mainly results from the strong ability of Ba^{2+} to stabilize G-quadruplex structures [21, 22], and the utilization of NMM as an effective fluorescence indicator. As the content of Pb^{2+} was usually much less than that of Ba^{2+} in common environment, Pb^{2+} would bring little interference with the detection of Ba^{2+} in real samples. For example, the maximum contamination level of Pb^{2+} in drinking water is defined to be 72 nM by EPA [27]. Besides, it is worth noting that when the AGRO100-NMM system interacts with Pb^{2+} at pH 7.4, the incubation time is less than 2 min [27], compared with ca. 20 min required here to reach the maximum fluorescence response to Ba^{2+} (Fig. 4). As for Pb^{2+} detection, the interference from Ba^{2+} may be reduced by shortening the incubation time and using a masking agent.

Table 1 The Ba^{2+} concentrations detected by ICP-MS and this fluorescent sensor

	Original sample	Diluted 10-Fold sample
ICP-MS	108 nM	11.7 nM
This method	94.2 nM	12.5 nM

Application

To evaluate the performance for practical application of the proposed method, the AGRO100-NMM probe was applied to the detection of Ba^{2+} in artificially contaminated water samples. 5 μM and 10 μM Ba^{2+} were added to water samples respectively and the recovery values obtained were in the range of 105–110 %, demonstrating that this novel probe could be applied to detect Ba^{2+} in environmental samples.

Conclusions

In summary, we have developed a G-quadruplex-based turn-on fluorescent Ba^{2+} sensor using NMM as a signal reporter. The limit of detection was 4 nM, which is over 3600-fold lower than the EPA limit for Ba^{2+} in drinking water. This detection strategy is much simpler, faster, more economic, higher in signal-to-noise ratio, and free of participation of toxic organic solvents. This system holds great potential for on-site and real-time Ba^{2+} detection in environmental and medical diagnostic applications, and ion-responsive molecular devices.

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