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ARTICLE TYPE

“Turn-on” fluorescent sensor for ultrasensitive detection of melamine based on a new fluorescence probe and AuNPs

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In this study, we synthesized a new fluorescence probe which was used to detect melamine by coupling with gold nanoparticles (AuNPs). The new fluorescence probe has good optical stability, and high fluorescence intensity, which can greatly improve the detection sensitivity. Compare to the traditional fluorophore, it is less dependence on the value of pH. And it has a very strong fluorescence emission peak at 550 nm, which has larger overlap with the absorption peak of AuNPs. When the probe incubates with the AuNPs, the fluorescence of the probe can be effectively quenched by AuNPs. Adding melamine into probe-AuNPs mixture caused aggregation of AuNPs and release the adsorbed probe, the fluorescence intensity of probe was recovered. By measuring the changes of fluorescence intensity of the probe, the detection of melamine can be realized. Under optimized conditions, the linear response to melamine in the range of 1.0×10^{-8} - 4.0×10^{-6} mol/L and lower detection limit down to 3.0 nmol/L with the sensor. And this method can realize the detection of melamine in milk and milk-based productions.

1. Introduction

Melamine is an organic base and a trimer of cyanamide, with a 1, 3, 5-triazine skeleton,¹ used mainly in the synthesis of melamine formaldehyde resins for the manufacturing of chemical, industrial products and medical materials.^{2, 3} Because of its high nitrogen level (66% by mass), melamine is sometimes illegally added to milk products by unethical producers to produce an incorrectly high reading in the measurement of protein content based on conventional standard Kjeldahl or Dumas tests. Ingestion of melamine at levels above the safety limit (2.5 ppm in the USA and EU; 1 ppm for infant formula in China)⁴ can induce renal failure and even death in infants.⁵ Therefore, it is very useful to develop simple, rapid and sensitive methods for the detection of melamine in food.

Currently, a number of analytical methods including gas chromatography (GC),⁶ high-performance liquid chromatography (HPLC),⁷ gas chromatography-mass spectrometric (GC-MS) method,^{8, 9} enzyme-linked immunosorbent assay (ELISA),¹⁰⁻¹² mass spectrometry,^{13, 14} electrochemical methods,^{15, 16} colorimetric detection¹⁷⁻¹⁹ have been developed for the determination of melamine. However, these used methods are generally time-consuming, require relatively expensive and complicated instruments, many of these assays are not adaptable to routine analysis. To date, it still remains a great challenge to develop a simple, sensitive and low-cost and reliable detection method for the determination of trace melamine without the use of costly instrumentation or the need for tedious procedures for sample pretreatment or pre-concentration.

As a high sensitivity and easy operation method, fluorimetric methods have been proved to be a powerful optical technique for

the trace detection of analytes. Fluorescence resonance energy transfer (FRET) spectroscopic technique is a kind of non-radiation energy transfer form, which occurs when the emission spectrum of the donor and the absorption spectrum of the acceptor overlapped to a certain extent. Based on the advantages of high extinction coefficient (10^8 - 10^{10} M⁻¹ cm⁻¹, about 3-5 orders of magnitude higher than common organic dyes), gold nanoparticles (AuNPs) were utilized as an ideal acceptor of FRET system.²⁰⁻²² Moreover, when AuNPs as the acceptor, the distances dependence changes from R⁻⁶ to R⁻⁴ and the calculated energy transfer distances can be reach to 70-100 nm (10 times longer than the typical Forster distances).

Herein, a simple, sensitive and reliable “turn-on” fluorescence sensor for melamine in milk products was developed based on the FRET efficiency between AuNPs and a new fluorescent probe 7-(benzylamino)-9,9-dibutyl-9H-fluorene-2-carbaldehyde (BDFC). The synthetic steps of the probe were show in the supporting information). In the presence of AuNPs solution, the BDFC adsorbed on the surface of AuNPs, resulting in the fluorescence quenching due to FRET between BDFC and AuNPs. Upon addition of melamine, melamine can compete with the BDFC to adsorb on the surface of AuNPs caused aggregation of AuNPs and release the BDFC, and as a result the fluorescence of BDFC was recovered. This method reveals many advantages: 1) compared to the traditional fluorophore,^{23, 24} the fluorescence intensity of BDFC was less dependent on the value of pH and had good photostability. 2) BDFC has large Stokes shift (150 nm), which can avoid the self-absorption. 3) The fluorescence emission spectrum of BDFC (the emission maximum at 550 nm) was overlapped with the absorption spectrum of the AuNPs (the absorbance maximum at 520 nm). When the BDFC incubates

with the AuNPs having high extinction coefficient, the fluorescence intensity of the probe can be effectively quenched by AuNPs through FRET. These advantages allow it widely used in biological analysis and benefit improving the detection sensitivity.

2. Experimental

2.1. Materials

Chloroauric acid (HAuCl_4), sodium citrate and melamine were purchased from Sigma (Shanghai, China). All other chemicals (99%, Merck) used in this work were of analytical grade and Millipore Milli-Q ultrapure water ($\geq 18 \text{ M}\Omega \text{ cm}^{-1}$) was used throughout the experiments.

The detailed synthesis route of the probe 7-(benzylamino)-9,9-dibutyl-9H-fluorene-2-carbaldehyde (BDFC) is shown in Scheme S1, and characterized by ^1H NMR spectra and ^{13}C NMR spectra (Fig. S1).

2.2. Instrumentations

The absorption spectra of AuNPs were recorded on a UV-2450 spectrophotometer (Shimadzu Co., Japan). An F-4500 fluorescence spectrophotometer (Hitachi Co., Japan) was used to collect the fluorescent emission spectra of the probe. Transmission electron microscopy (TEM) images were collected on a JEOL-1230 transmission electron microscope (JEM-3010 Joel, Japan).

2.3. Synthesis of AuNPs

AuNPs were prepared according to the literature.²⁵ Briefly, 50 mL chloroauric acid (HAuCl_4) aqueous solution (containing 1.67 mL 1% HAuCl_4 (w/w)) was firstly heated to boiling, and then 5 mL, of 38.8 mmol/L sodium citrate solution was rapidly added to the boiled HAuCl_4 solution under vigorous stirring. The mixed solution was boiled for 10 min and further stirred without heating for another 15 min. The colors of the solution changed from yellow to wine red, indicating the formation of AuNPs. The obtained wine-red solution was cooled to room temperature and stored in the refrigerator (4°C) for further use. The concentration of the AuNPs was estimated by Beer's law. The size of AuNPs was measured by TEM.

2.4. The detection procedure of melamine

100 μL of AuNPs and 100 μL of probe solution (the final concentration is 7×10^{-7} mol/L) were incubated in the 4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid (HEPES) buffer solution for 10 min (800 μL 10 mmol/L) to form probe-AuNPs complex. Then different concentrations of melamine (50 μL) were incubated with probe-AuNPs mixture (the final volume is 1 mL). The mixture was incubated at room temperature for 30 min. Fluorescence emission spectra were recorded with excitation wavelength at 400 nm.

2.5 Real sample pre-treatment

Pre-treatment of raw milk and milk powder was performed according to the methods stipulated by Chinese National Standard GB/T 22388-2008 (Determination of melamine in raw milk and dairy products). Briefly, 1 mL of CCl_3COOH , 1 mL of CH_3CN ,

and 7 mL (for raw milk)/9 mL (for milk powder) of water was added into 2.0 mL of raw milk or 1.0 g of milk powder. Then the mixture was ultrasonically treated for 10 min, vibratively extracted for 10 min and centrifuged (6000 rpm) for 10 min to deposit protein. After that, the supernatant was filtered through a piece of filter paper soaked by CCl_3COOH (1% w/v), and the filtrate was diluted to 25 mL with CCl_3COOH (1% w/v) to acquire the testing sample for fluorescence analysis according to the proposed analytical method. A certain amount of melamine was doped into the real sample, and then the spiked sample was pretreated in accordance with the above processing steps.

3. Results and discussion

3.1. Characterization of the probe

BDFC was synthesized according to Scheme S1 and characterized by ^1H and ^{13}C NMR (Fig. S1). The optical properties of the prepared BDFC were characterized using UV-Vis absorbance and fluorescence spectroscopy. The BDFC had a strong absorption peak at around 400 nm which is ascribed to the intramolecular π - π^* transition of BDFC (Fig. S2). A fluorescence (FL) emission maximum at 550 nm is observed when it is excited at 400 nm (Fig. 1). By further investigation, we found that the BDFC exhibited the maximum FL intensity in 37°C (Fig. S3A). Moreover, BDFC in HEPES (pH 7.0) possessed excellent photostability over 10 h under ambient conditions without any protection (Fig. S3B). It is well known that fluorescein is currently the most commonly used fluoresce reagent. A compared study of fluorescein and BDFC was performed. As shown in Fig. S4, fluorescein shows very weak fluorescence under acid condition, which is due to its hydrolysis effect. The FL intensity of BDFC was less dependent on the value of pH when the value of the pH ranged from 5.0-8.0. It means BDFC has good photostability under physiological pH. The Stokes shift of fluorescein is 30 nm. The BDFC has large Stokes shift (150 nm), which can avoid the self-absorption and benefit improving the sensitivity of FL analysis.

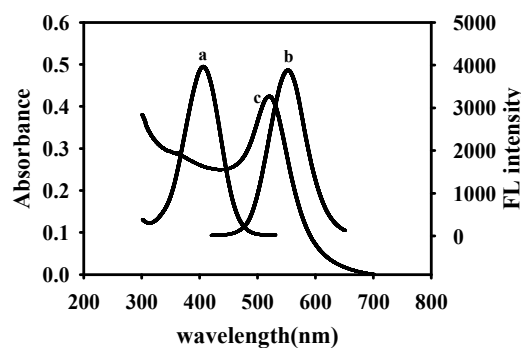


Fig. 1. Excitation spectrum (a) and emission spectrum (b) of BDFC and adsorption spectrum (c) of AuNPs

3.2. Fluorescence quenching effect of probe by AuNPs

AuNPs was used as the acceptor (quencher) because of its high extinction coefficient²⁶ and a broad absorption spectrum in visible light. Fig. 1 shows the absorption spectrum of AuNPs and FL emission spectrum of BDFC, respectively. It is obvious that the FL emission spectrum of BDFC was overlapped with the

absorption spectrum of the AuNPs to an extent, indicated that FRET may take place with BDFC as donor and the AuNPs as acceptor (quencher). Upon addition of AuNPs to the BDFC solution, the electron-rich nitrogen atom of BDFC can bound onto the surface of AuNPs through the coordinating interactions with the electron-deficient surface of AuNPs,^{27, 28} and a BDFC-AuNPs assembly was formed between BDFC and AuNPs. As a result, the FL of BDFC was quenched by AuNPs through FRET. Further study indicated that the FL intensity of the BDFC is inversely proportional to the concentration of AuNPs (shown in Fig. S5A). According to the Stern–Volmer equation:

$$I_0/I = K_{SV} \times c_Q + 1$$

where I_0 and I are the FL intensity of BDFC in the absence and presence of AuNPs, respectively. c_Q is the concentration of the quencher (AuNPs). The plot of the relationship between I_0/I and the c_{AuNPs} was shown in Fig. S5B. It is clear that the plot indicates a good linear relationship in a wide concentration range, and the Stern-Volmer equation was fitted as:

$$I_0/I = 0.3698c_{AuNPs}(\text{nM}) + 1 \quad (R^2 = 0.99)$$

where the quenching constant (KSV) was calculated to be 0.37×10^9 mol/L

3.3 Sensing principle for melamine

BDFC exhibit a maximum FL at 550 nm under excitation at 400 nm. When BDFC was mixed with AuNPs, the FL of BDFC was significantly quenched (curve b in Fig. 2E) *via* FRET and shown an “FRET-off” state. However, upon addition of melamine, melamine could release the adsorbed BDFC and aggregate the AuNPs, which can inhibited the FRET between AuNPs and BDFC and finally “turn-on” the FL of BDFC. To confirm this competition effect between BDFC and melamine, the effect of melamine on the FRET system has been investigated. As shown in Fig. 2 BDFC shows strong FL at 550 nm when excited at 400 nm (curve a in Fig. 2E), and the FL spectra of mixture of BDFC and melamine (curve b in Fig. 2E) were identical to those of BDFC, which illuminated that there was no interaction between BDFC and melamine. Once addition of AuNPs, the FL of BDFC is significantly decreased due to the FRET process between BDFC and AuNPs (curve c in Fig. 2E). However, the FL of BDFC-AuNPs mixture was recovered upon addition of melamine (curve d and e in Fig. 2E), due to melamine can interact with AuNPs through covalent binding of the amino group of melamine to the surface of AuNPs, which prevents the interaction of BDFC and AuNPs, and induce the aggregation of the AuNPs thus reduces the FRET effect, resulting in the recovery of the FL intensity. The melamine-induced aggregation of AuNPs was further confirmed by TEM. As shown in Figs. 2A-D, the AuNPs shows no significant changes compared with the original AuNPs after mixing with the BDFC (Figs. 2A-B), indicated that the adsorption of BDFC onto the AuNPs surface does not influence the dispersibility of AuNPs. However, upon addition of melamine, both the AuNPs (Fig. 2D) and the BDFC-AuNPs (Fig. 2C) obviously aggregated indicated that BDFC were not affect the melamine induced aggregation of AuNPs. The results of TEM observation were consistent with that obtained from FL measurement. Based on the discussion above, the sensing principle of the proposed method for melamine detection is

illustrated in Scheme 1. BDFC can exhibit a maximum FL emission at 550 nm under excitation at 400 nm. Upon addition of the AuNPs, the FL of BDFC is obviously quenched *via* FRET to show an “off-state”. Upon addition of melamine, the adsorbed BDFC released from surface of AuNPs and the AuNPs aggregated, resulting in reduction of the FRET effect and “turn-on” the FL of BDFC.

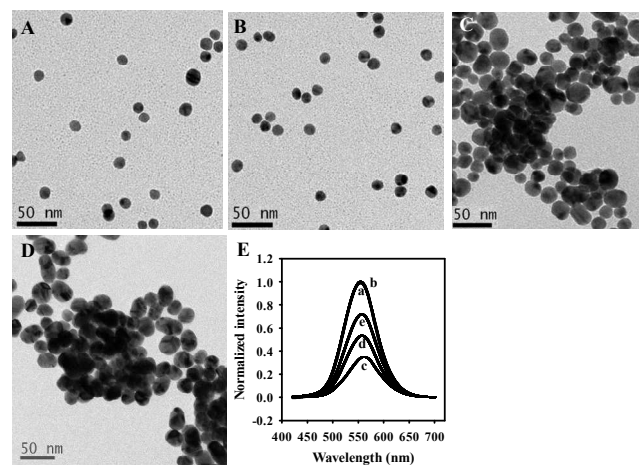
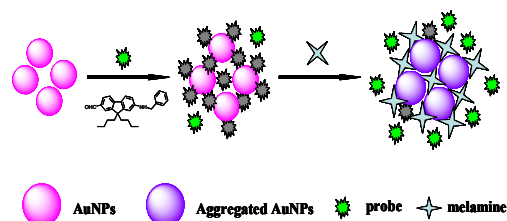


Fig. 2. TEM images of AuNPs: (A) free AuNPs, (B) in the presence of BDFC, (C) in the presence of BDFC and melamine, (D) in the presence of melamine. (E) Fluorescence spectra of (a) BDFC, (b) BDFC + melamine, (c) BDFC + AuNPs, (d) BDFC + AuNPs + 0.5 $\mu\text{mol/L}$ melamine and (e) BDFC + AuNPs + 2 $\mu\text{mol/L}$ melamine. (The pH value is 7, and the concentration of AuNPs, melamine and BDFC were 3.5 nmol/L, 0.5 $\mu\text{mol/L}$ and 0.7 $\mu\text{mol/L}$, respectively)



Scheme 1. Mechanism for the detection of melamine.

3.4. Optimization of the detection conditions

In order to obtain a high-sensitive response for the detection of melamine, the optimization of the conditions such as concentration of AuNPs, pH, incubation temperature and time is essential. First, the effect of the concentration of AuNPs was investigated. As shown in Fig. 3, before the FL of BDFC was fully quenched by AuNPs, the FL recovery efficiency in the presence of melamine was gradually increased with an increasing concentration of AuNPs until the concentration of AuNPs reached 3.5 nmol/L. However, the FL recovery kept a balance when the concentration of the AuNPs beyond 3.5 nmol/L. This was because in the presence of an excess of AuNPs, melamine molecules could not completely substitute BDFC molecules on the surface of AuNPs. For the above reason, 3.5 nmol/L of AuNPs was chosen as the optimum concentration. The effect of pH on the efficiency of FL recovery was investigated in the range from 6.0 to 11.0. As shown in Fig. 3B, the highest recovery efficiency of FL was obtained at pH 7.0. This might be due to the melamine molecules gradually hydrolyze in acidic or alkaline

environment to produce the cyanuric acid which can not interact with the AuNPs.^{29, 30} Therefore, the ideal pH value for melamine detection is 7.0. The effect of the incubation time of melamine was investigated as well. Fig. 3C shows the time dependent fluorescent response in the presence of melamine. The FL response remained a stable value when the incubation time reached to 30 min, suggesting that the competitive reaction of melamine and BDFC reached equilibrium within 30 min. Therefore, 30 min was employed as the incubation time of melamine. Fig. 3D illustrates the FL response of the sensor under different incubation temperatures. It was observed that the FL intensity sharply increased with the increasing in the incubation temperature from 4 °C to 37 °C, and then declined lightly while further raising the temperature. These results suggested that temperature lower or higher than 37 °C would be not good for the detection of melamine.

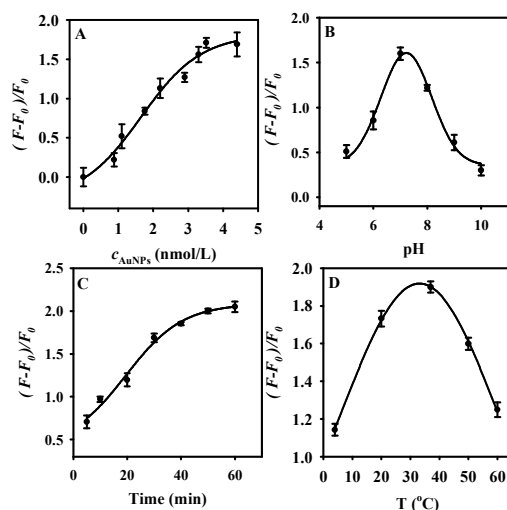


Fig. 3. Effects of (A) AuNPs concentration, (B) pH, (C) incubation time and (D) temperature on the fluorescence responses of the sensor for melamine detection. (The concentrations of BDFC and melamine were 0.7 μ mol/L and 0.5 μ mol/L. λ_{ex} = 400 nm, λ_{em} = 550 nm)

3.5. The analytical performance of the sensor

Under the optimal assay conditions, the analytical performance of the proposed method for melamine detection was then evaluated.

The FL spectra of the mixture in the presence of different amounts of melamine were shown in Fig. 4A. The FL of the mixture was enhanced as the concentration of melamine was increased, and even as low a concentration as 10×10^{-8} mol/L of melamine can give a distinct fluorescent recovery. In order to simplify the calibration process and widened the detection concentration range, we followed a reported method by Hakonen.³¹ In the range of 1.0×10^{-8} to 4.0×10^{-6} mol/L, the FL recovery efficiency undergoes square root change with respect to the concentration of melamine, where the square root calibration equation was: $(F-F_0)/F_0 = 0.87944\sqrt{c} - 0.03421$ (Fig. 4B). The limit of detection (LOD) was the concentration of analyte which produces an analytical signal equal to 3 times the standard deviation of the background fluorescence,³² which was calculated to be 3.0 nmol/L. For comparative purpose, the linear range and LOD of some other methods^{1, 7, 8, 12, 15, 22, 29, 33, 34} for the detection of melamine are listed in Table S1. It is obvious that the LOD are

lower than that of the reported methods and the linear response ranges are wider than reported (shown in Table S1).

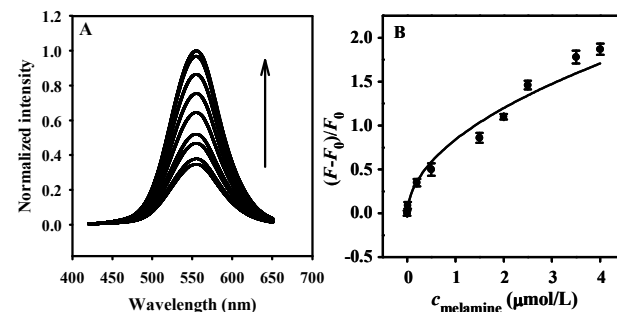


Fig. 4. (A) Fluorescent spectra of BDFC-AuNPs mixture in the presence of different concentrations of melamine. The concentrations of melamine were 0, 1.0×10^{-8} , 0.2×10^{-6} , 0.5×10^{-6} , 1.5×10^{-6} , 2.0×10^{-6} , 2.5×10^{-6} , 3.5×10^{-6} , and 4.0×10^{-6} mol/L, respectively; pH 7.0; the concentrations of BDFC and AuNPs were 0.7 μ mol/L and 3.5 nmol/L, respectively; temperature: 37 °C; incubating time: 30 min. (B) Effect of the concentration of melamine on the fluorescent recovery efficiency.

To determine melamine in real samples such as raw milk and milk powder, the potential interfering substances including common ions and amino acids were investigated to evaluate the selectivity of the proposed method. As shown in Fig. 5, the FL recovery by melamine was larger than the other compounds, which indicated that the potential interfering substances could hardly produce distinct interference for the detection of melamine. Similar to previous reports,^{30, 35} the amino-group ($-\text{NH}_2$) of amino acids can interact with AuNPs, and also recovery the FL of the BDFC-AuNPs mixture. But the recovery efficiency was much lower than that of melamine. Combining with proper pre-treatment or separation technology, it is promising to apply this method to detect melamine in milk products.

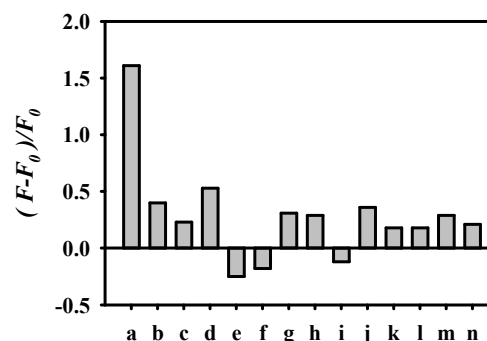


Fig. 5. Fluorescent recovery efficiency of BDFC-AuNPs mixture upon addition of melamine or other substances: (a) melamine, (b) Na^+ , (c) K^+ , (d) histidine, (e) SO_4^{2-} , (f) Cl^- , (g) Mg^{2+} , (h) Cu^{2+} , (i) NO_3^- , (j) Ca^{2+} , (k) glucose, (l) lysine, (m) tryptophan, (n) dopamine. (The concentration of melamine was 3.0×10^{-6} mol/L, other substances concentration is 1.5×10^{-5} mol/L)

3.6. Analysis of melamine in real samples

To validate the proposed method to selectively detect melamine in real samples, the amounts of melamine in commercial in raw milk and milk powder were measured by standard addition method under the optimized conditions. Certain amounts of melamine standard solution were directly spiked into the real

samples before sample pre-treatment because the existing milk products in the market are free of melamine. Then the samples were treated and determined according to the procedures described in Section 2.4 and 2.5. The results of real samples by standard addition method are summarized in Table 1. As shown in Table 1, excellent recoveries in the range from 92 to 108% were obtained for all samples, suggesting that the proposed method is reliable and suitable for real applications.

Table 1. Results of the determination of melamine in real samples.

Sample	Added (μM)	Detected (μM)	Recovery (%)	RSD (%)
Milk power	1.00	0.92	92.00	0.80
	2.00	2.10	105.00	3.37
	4.00	4.20	105.00	4.21
Raw milk	1.00	1.08	108.00	3.68
	2.00	2.11	105.50	2.75
	4.00	3.94	98.50	4.06

4. Conclusions

An effective and sensitive FRET-based detection method for melamine was developed based on BDFC as donor and AuNPs as acceptor. BDFC can adsorb on the surface of AuNPs, which lead to the FL of BDFC was quenching via FRET. Upon addition of melamine, BDFC could be released due to the competitive adsorption of AuNPs between melamine and BDFC, resulting the FL recovery of BDFC. The FL recovery was linearly increased with the increase of the concentration melamine in the range of 1.0×10^{-8} - 4.0×10^{-6} mol/L, and the detection limit was calculated to be 3.0 nmol/L. The proposed method displays high sensitivity and excellent selectivity for the determination of melamine and can be applied to the determination of melamine in real samples with satisfactory recoveries.

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Notes and references

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⁵⁰ † Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/b000000x/

⁵⁵ ‡ Jiangna Zhao and the first author made equal contributions to this work.

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