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Selective recognition of 6-mercaptopurine based on luminescent metal–organic frameworks Fe-MIL-88NH$_2$

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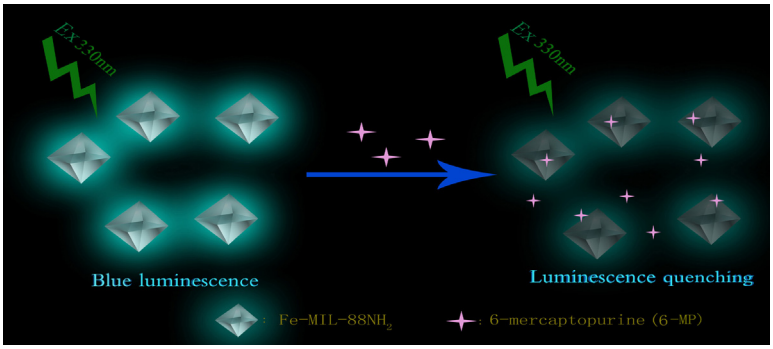
HIGHLIGHTS

- Selective recognition of 6-mercaptopurine against other thiol-containing amino acids was successfully achieved.
- The recognition is based on the fluorescence quenching of metal–organic frameworks Fe-MIL-88NH$_2$.
- This method was successfully used to determine the 6-mercaptopurine in human serum samples.

GRAPHICAL ABSTRACT

A new spectrofluorometry method for rapid and selective detection of 6-mercaptopurine has been developed based on luminescent metal-organic frameworks Fe-MIL-88NH$_2$ as fluorescent probe.



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ABSTRACT

A novel and rapid spectrofluorometry method for the recognition of 6-mercaptopurine (6-MP) has been developed based on luminescent metal–organic frameworks Fe-MIL-88NH$_2$ as fluorescent probe. The strong fluorescence of Fe-MIL-88NH$_2$ at 430 nm could be quenched by 6-MP directly, and the Fe-MIL-88NH$_2$ shows high selectivity for 6-MP compared to other thiol-containing amino acids such as homocysteine (Hcy), cysteine (Cys), glutathione (GSH), etc. Under optimal conditions, the relative fluorescence intensity was linearly proportional to the concentration of 6-MP in the range of 5–600 μM with the detection limit at 1.17 μM (S/N = 3). Furthermore, the present approach has been successfully applied to the determination of 6-MP in human serum samples. The possible fluorescence quenching mechanism has also been investigated, where it is revealed that the quenching was attributed to competition of absorption of the light source energy as well as electron transfer between Fe-MIL-88NH$_2$ and 6-MP.

Introduction

The antimetabolite 6-mercaptopurine (6-MP) has been widely used as an anti-cancer chemotherapy drug to treat acute lymphoblastic leukemia as it can inhibit purine metabolism and then interfere with nucleic acid synthesis [1,2]. However, as a cytotoxic anti-tumor drug, 6-MP always brings about serious side effects. One of the most severe toxic effects of 6-MP was its depressant effect on the bone marrow, and in excessive doses it produces leucopenia, anemia, thrombocytopenia and bleeding [3]. With respect to that, it is necessary and significant for us to monitor the 6-MP

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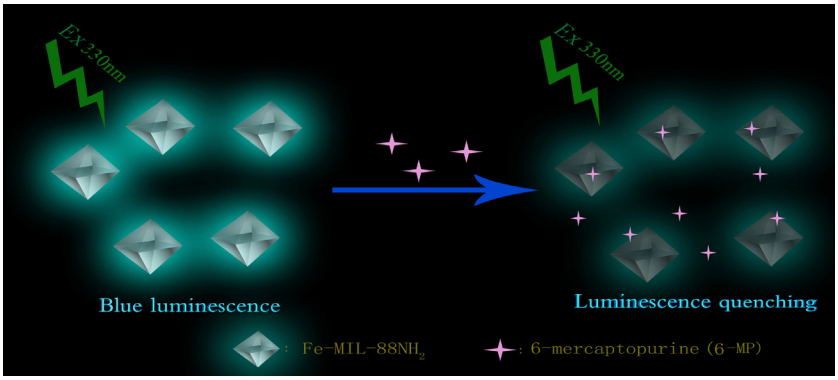

Scheme 1. Schematic illustration of the developed Fe-MIL-88NH_2-based fluorescent probe for 6-MP.

concentration in serum. Until recently, many analytical methods, such as high-performance liquid chromatography [4,5], electrochemical assays [6,7], chemiluminescence analysis [8,9], fluorescence spectroscopy [10–12], have been used for determination of 6-MP. Since spectrofluorometry is among the most sensitive spectrophotometric methods, therefore, spectrofluorometric methods for sensitive analysis of 6-MP have been developed based on the formation of the Au–S covalent bond or the coordination effect between 6-MP and copper ions [10–12]. However, poor selectivity was an issue to be taken into account when considering spectrofluorometric methods since other substances containing thiol groups such as homocysteine (Hcy), cysteine (Cys), glutathione (GSH) would interfere with the determination. Further developing highly selective methods of 6-MP detection is a worthwhile yet challenging undertaking.

Metal–organic frameworks (MOFs), in which metal ions are linked together by organic bridging ligands, have attracted great excitement because of their infinite tunability, high porosity, and structural rigidity [13–15]. Some of them show good characteristics and have wide applications such as catalysis [16,17], separation [18–22], analytes enrichment [23–26], gas storage [27,28], drug delivery [29,30], molecular recognition [31,32]. Over the past few years, a large number of luminescent MOFs have been used for sensing metal ions [33], anions [34], gases [35], small solvents molecules [36]. Recently, we found that the luminescent iron-containing metal–organic frameworks Fe-MIL-88NH_2 can function as an efficient peroxidase mimic and for colorimetric determination of glucose [37]. Due to the competitive reaction between TMB and thiol compounds with H_2O_2, Fe-MIL-88NH_2 can also be used for detecting thiol compounds [38]. Here, we observe that the fluorescence of Fe-MIL-88NH_2 could be quenched by 6-MP directly (Scheme 1) while other thiol compounds such as Hcy, Cys, GSH, etc could not interfere with the determination. Moreover, the decrease of the fluorescence intensity was proportional to the concentration of 6-MP. Based on the phenomenon above, a new assay for selective recognition of 6-MP involving the use of luminescent metal–organic frameworks Fe-MIL-88NH_2 as fluorescent probe has been established.

Experimental

Instrumentation

The fluorescence and the absorption spectra were recorded with a Hitachi F-2500 fluorescence spectrophotometer (Tokyo, Japan) and a Hitachi U-3010 spectrophotometer (Tokyo, Japan), respectively. The fluorescence lifetimes were measured with a FL-TCSPC fluorescence spectrophotometer (Horiba Jobin Yvon Inc., France). A constant-temperature water-base boiler (Jiangsu, China) was used to control the reaction temperature. All pH measurements were performed with a pH-510 digital pH-meter with a combined glass electrode (California, USA) and a vortex mixer QL-901 (Haimen, China) was used to blend the solution.

Chemicals and materials

6-Mercaptopurine was purchased from Aladdin (Shanghai, China). Homocysteine (Hcy), cysteine (Cys), glutathione (GSH) and other amino acids were purchased from Beijing Dingguo Changsheng Biotech Co., Ltd. Serum samples were obtained from the Southwest University Hospital (Chongqing, China). Fe-MIL-88NH_2 was synthesized according to the method reported in our previous work [37]. All reagents were of analytical reagent grade and used as received unless otherwise stated. The stock solutions of 6-MP were prepared by first dissolving solid 6-MP in 2 mL 0.1 mol/L NaOH and then diluting it to the final concentration of 1.175×10^{-2} M with doubly distilled water. The stock solution of 6-MP should be stored at 4 °C. Tris–HCl buffer solution was used to control the acidity of the solutions. Millipore purified water (18.2 MΩ) was used throughout this experiment.

Preparation of serum sample

For 6-MP determination in serum, the serum samples of three healthy adults were first treated by spin dialysis at 12,000 rpm for 30 min, and then the eluents were diluted to half of the initial concentration with doubly distilled water and directly used for experimental test.

General procedure

50 μL Fe-MIL-88NH_2 solution (0.2 mg mL^{-1}) and 50 μL Tris–HCl buffer solution (pH 7.45) were added to a 1.5 mL EP vial. Subsequently, the appropriate amount of 6-MP or serum solution was added, and then the solution was diluted to a final volume of 500 μL. At last, the foregoing ultima solution was incubated at 40 °C for 25 min before measurements. The fluorescence spectrum was recorded at the F-2500 spectrophotometer with the PMT voltage of 400 V.

Results and discussions

Spectral characteristic

The metal–organic frameworks Fe-MIL-88NH_2 display two excitation peaks at 250 nm and 330 nm, and the emission wavelength is centered at 430 nm (Fig. 1A). When excited at 330 nm, a significant quenching of the fluorescence was observed upon the addi-