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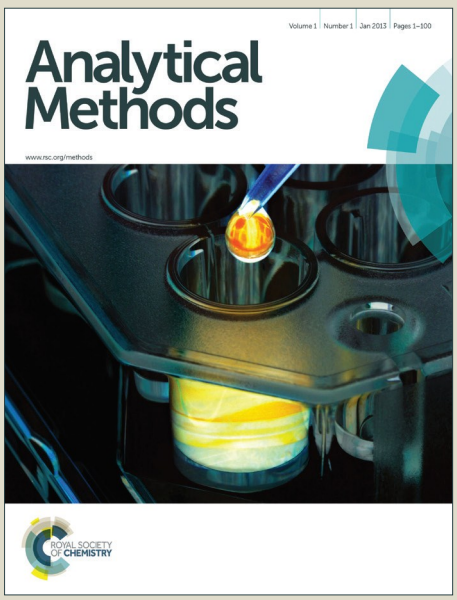

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ARTICLE TYPE

Colorimetric detection of uric acid in human urine and serum based on peroxidase mimetic activity of MIL-53(Fe)

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A porous metal-organic framework MIL-53(Fe) was prepared by a simple solvothermal method using $FeCl_3 \cdot 6H_2O$ and 1,4-benzenedicarboxylic acid as the precursor and characterized by X-ray diffractometer, Fourier transform infrared spectroscopy and scanning electron microscopy. The MIL-53(Fe) was demonstrated to possess intrinsic peroxidase-like activity, and it could catalyze the oxidation of the peroxidase substrate 3,3′,5,5′-tetramethylbenzidine into a blue colored product in the presence of H_2O_2. Based on this phenomenon, MIL-53(Fe) was developed as a colorimetric sensor for the detection of uric acid (UA) in human urine and serum. This method provided a simple and effective for UA detection using uricase and MIL-53(Fe) with a linear range from 4.5 to 60 μM and a detection limit of 1.3 μM (S/N=3). Moreover, the proposed method can be successfully applied to the determination of UA in human urine and serum samples with the recoveries and relative standard deviations between 1.2~4.8% and 89.50~101.44%, respectively.

1. Introduction

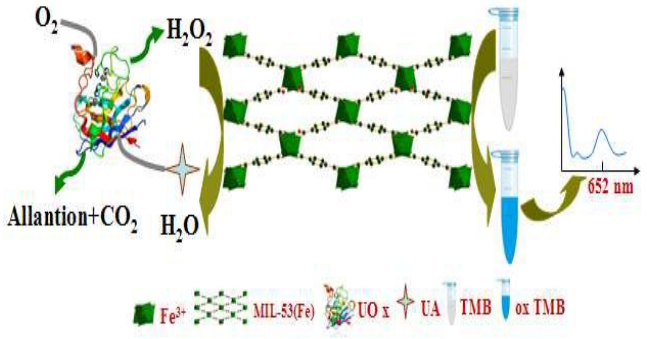
Uric acid (UA), as one of the important biomolecule in humans, is the primary enzymatic degradation product in purine metabolism[1]. In general, its normal physiological level in body fluids is in balance between UA production and excretion[2]. UA has been proposed as a marker for metabolic disorders such as gout, hyperuricaemia, renal failure and Lesch-Nyhan syndrome[3-5]. Thus, it is essential to establish simple and effective analytical method for the sensitive and selective determination of UA in biofluids for health assessment and disease diagnosis.

To date, various analytical methods for the determination of UA in biological samples have been proposed, such as high performance liquid chromatography (HPLC)[6-9], capillary electrophoresis (CE)[10-12], chemiluminescence (CL)[13-15] and electrochemistry[16-18]etc. Generally, chromatographic techniques such as HPLC and CE make great contributions to UA detection, but required complicated sample pretreatment and expensive instrument. CL and electrochemistry are powerful analytical methods for the determination of UA in real samples and with the advantages of low detection limit and high accuracy[19]. Nevertheless, a simple and effective method for accurate determination of UA is still required. Currently, colorimetric chemosensor based on nanozymes have attracted considerable attention because of its simplicity, feasibility, and low cost as well as the fact that there is no requirement for any sophisticated instrumentation[20]. For example, Zhao et al.[21] have developed a colorimetric method for UA determination based on the intrinsic peroxidase-like activity of BSA-stabilized Au nanoclusters. This method show relatively high sensitivity and good results. However, biomolecules such as biothiols in complex biological fluids are the most likely interference for UA detection due to their strong affinity toward noble metal nanoparticles (including Au, Ag) and affecting their catalytic activity[22,23].

Metal-organic frameworks (MOFs), as a novel class of porous organic-inorganic hybrid materials, have attracted great attention in sensing application due to their high surface areas, versatile structures, tunable pore size, exposed metal sites and high stability[24]. In recent years, PCN-222 with porphyrinic Fe(III) centers[25], Fe(III)-based MOFs[26-30], copper(II)-based MOFs[31] and Ce-MOFs[32] have been reported to show excellent catalytic activity. Up to now, several small molecules such as H_2O_2, glucose and ascorbic acid have been successfully detected based on the Fe(III)-based MOFs colorimetric sensors. Although MOFs-based colorimetric sensors have achieved some success, the development of MOFs as enzyme mimic for bioanalysis applications is still required. Among them, MIL-53 (Fe) show easy synthesis and excellent lattice stability in aqueous solution[33]. Significantly, a small pore structure on the MIL-53(Fe) surface generates a high density of active catalytic centers, which make it suitable for catalytic applications and avoid other molecules interference in biological samples[34]. However, the bioanalysis application of MIL-53(Fe) is far from fully developed and still in its infancy.

In this study, we described that a MIL-53(Fe) with highly peroxidase-like catalytic activity was prepared through a facile solvothermal reaction, and applied to catalyze the oxidation of the peroxidase substrate 3,3′,5,5′-tetramethylbenzidine (TMB) in the presence of H_2O_2, which offered a simple and effective method

for colorimetric detection of UA. The principle of UA detection is shown in Scheme 1. The morphology of MIL-53(Fe) and the parameters affect of UA measurement were all investigated. In addition, the developed method was successfully applied for the detection of UA in human urine and serum samples. Thus, we believed such simple and inexpensive UA sensor will become a potential clinical application in the future.



Scheme.1 Schematic illustration of colorimetric sensor for UA using MIL-53(Fe) as a peroxidase mimetic.

2. Experimental

2.1 Reagents and materials

Uricase (UOx, >2 U/mg) was purchased from Worthington (USA) and stored in a refrigerator at -20 ℃. 3,3′,5,5′-tetramethylbenzidine (TMB), 1,4-benzenedicarboxylic acid (1,4-BDC) and uric acid (UA) were purchased from Alfa Aesar (Ward Hill, MA, USA). L-cysteine, N,N-dimethylformamide (DMF), glucose, acetic acid, absolute alcohol, sodium acetate were purchased from Shanghai Chemical Reagents Co. (Shanghai, China). All the phosphoric acid, iron (III) chloride hexahydrate ($FeCl_3 \cdot 6H_2O$), hydrogen peroxide (H_2O_2), sodium chloride, disodium phosphate dodecahydrate, sodium dihydrogen phosphate, ethanol, urea etc., were in analytical grade. Ultrapure water used for the preparation of solutions was produced by a Milli-Q water system (Millipore, Bedford, MA, USA). Human urine and serum samples were obtained from the Affiliated Hospital of Guilin Medical University (Guilin, China).

2.2 Instrumentation

The morphology of MIL-53(Fe) was characterized by scan electron microscope (SEM, FEI Quanta 200 FEG). The characterization of the crystalline phase was performed on a Rigaku D/max 2500/PC (Japan) X-ray diffractometer (XRD) with Cu Kα source. Fourier transform infrared (FT-IR) spectroscopy was conducted on a PE Spectrum One FT-IR spectrometer (PE, USA) over the range of 4000-500 cm^{-1}. UV-vis absorption spectra were recorded with a Cary 60 UV-vis spectrophotometer (Agilent, USA). The pH of solution was measured with a DHSJ-4A pH-meter (Shanghai, China).

2.3 Preparation of MIL-53(Fe)

The MIL-53(Fe) was synthesized by a solvothermal reaction in a Teflon-lined bomb according to the reported approaches with modifications[35]. Typically, 0.334 g of 1,4-BDC and 0.545 g of $FeCl_3 \cdot 6H_2O$ were dissolved in 10 mL of DMF, and the mixture was stirred for 10 min under room temperature. The resulting solution was transfer into a Teflon-lined bomb, then sealed and placed in an oven at 150 ℃ for 17 h. After cooling to room temperature, the yellow precipitate was collected by centrifugation at 6000 rpm for 3 min and rinsed thoroughly with ultrapure water to remove the excessive reactants. The product was vacuum-dried at 60 ℃ for 24h. Finally, the MIL-53(Fe) was characterized by FT-IR, XRD and SEM.

2.4 Catalytic activity of MIL-53(Fe)

In order to evaluated the peroxidase-like activity of the synthesized MIL-53(Fe), the catalytic oxidation of TMB in the presence of H_2O_2 with and without MIL-53(Fe) as the catalyst was tested. Experiment was carried out as follows: 920 μL of acetate buffer solution (0.1 M, pH 4.0), 20 μL of TMB (10 mM, ethanol solution), 40 μL of H_2O_2 (0.1mM) and 20 μL of MIL-53(Fe) dispersion (1 $mg \cdot mL^{-1}$) were added into 1.5 mL EP vial. The mixed solution was incubated at 40℃ for 40 min. After cooling to room temperature, the UV-vis spectra were measured using a Cary 60 spectrophotometer.

2.5 Preparation of human urine and serum samples

For UA detection in human urine and serum, the samples were collected from several volunteers and immediately prepared according to the procedures as described in our previous work[36]. Before subsequent use, the urine and serum sample was diluted 25 and 30 times, respectively. After that, the subsequent procedure for UA analysis was the same with UA standard solutions.

2.6 Colorimetric detection of UA

A stock solution of UA (1 mM) was prepared in 0.1 M phosphate buffer solution (PBS, pH 9.0) and different concentrations of UA (100, 80, 60, 50, 40, 30, 10, and 5 μM) were obtained by serial dilution of the stock solution. The principle of UA detection is shown in Scheme 1. (1) 50 μL of 2 U/mL UOx was added to 100 μL of UA solution with different concentrations (or pre-diluted urine and serum samples) and the mixture was incubated at 37℃ for 15 min. (2) Subsequently, 40 μL of TMB, 790 μL of PBS, 20 μL of MIL-53(Fe) dispersion were added into the above reaction solution (pH 4.0, adjusted with PBS) and incubated at 55 °C for 40 min. (3) The resultant solution was used for the UV-vis spectra measurement. To investigate interference experiments, the concentrations of urea, L-cysteine, ascorbic acid, tryptophan, glutathione, glucose and sodium chloride were all 100 μM, 50 μM for UA and their mixture were used as anti-interference experiments.

3. Results and discussion

3.1 Characterization of MIL-53(Fe)

The as-synthesized MIL-53(Fe) was characterized by FT-IR, XRD and SEM (Fig. 2). Fig. 2A describes the FT-IR spectra of MIL-53(Fe). As can be seen that the band at 546 cm^{-1} is assigned to the Fe-O vibrations. The bands at 746 and 1288 cm^{-1} can be ascribed to aromatic C-H and C=C stretching vibration. Two bands at 1393 and 1547 cm^{-1} are attributed to C-O asymmetric and symmetric vibration, this result indicate that the presence of a dicarboxylate linker within the sample. Besides, the bands located

at 1688 cm^{-1} is ascribed to carboxyl group of unreacted free 1,4-BDC that trapped in the cavities of MIL-53(Fe). The crystalline structure of MIL-53(Fe) was investigated by XRD and the result shown in Fig.2B. Most of the reflection peaks of the synthesized MIL-53(Fe) crystals were in good agreement with the simulated one, indicating the successful synthesis of MIL-53(Fe). The crystal morphology of the as-synthesized MIL-53(Fe) was further characterized by SEM (Fig.2C). The as-synthesized MIL-53(Fe) crystals displayed a cubic shape with a proper size distribution, which are consent with the previous report [37].

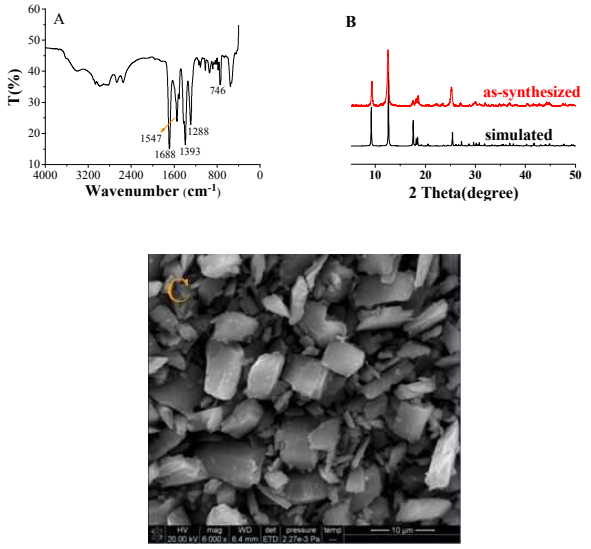


Fig. 2. Characterisation data for MIL-53(Fe): (A) FT-IR spectrum; (B) XRD pattern; (C) SEM image.

3.2 Catalytic activity

To evaluate the peroxidase-like activity of the as-synthesized MIL-53(Fe), the catalytic oxidation of peroxidase substrate TMB to generate a blue color reaction was tested in the presence of H_2O_2. As shown in Fig. 3A, the UV-vis spectra of reaction systems of TMB, TMB-MIL-53(Fe), TMB-H_2O_2, and TMB-MIL-53(Fe)-H_2O_2 in acetate buffer solution (0.1M, pH 4.0). Clearly, TMB alone showed no absorbance at 652nm (curve a), even in the presence of MIL-53(Fe) (curve b) or H_2O_2 (curve c), which reveal that no oxidation reaction occurred. Conversely, a strong absorbance was found for TMB-H_2O_2 in the presence of MIL-53(Fe) (curve d). These results demonstrate that MIL-53(Fe) exhibits peroxidase-like catalytic activity. This is similar to the phenomena observed for the commonly used horseradish

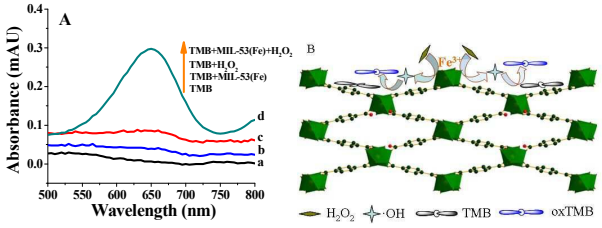


Fig. 3. (A) The UV/Visible absorption spectra of (a) the TMB solution, (b) TMB and MIL-53(Fe), (c) TMB and H_2O_2, (d) TMB, MIL-53(Fe) and H_2O_2. (B) Scheme of TMB oxidation by H_2O_2.

peroxidase (HRP). Compared to other commonly used nanomaterials, MIL-53(Fe) showed unique chemical and physical properties. The peroxidase-like activity of MIL-53(Fe) can be attributed to their metal centers. In addition, the peroxidase substrate TMB can possibly adsorb on the surface of MIL-53(Fe) via the π-π and hydrogen bonding interactions. A possible reaction mechanism was depicted in Fig. 3B. H_2O_2 molecules collide with metal centers Fe^{3+} and converted to ·OH radicals, and then catalyze the oxidation of colorless TMB to a blue colored product.

3.3 Optimization of experimental conditions

Since MIL-53(Fe) is similar to other nanomaterials peroxidase mimetics and HRP, the catalytic activity of MIL-53(Fe) was dependent on the reaction temperature and pH. The peroxidase-like activity of the MIL-53(Fe) was investigated by vary reaction temperatures from 15 to 65℃. As can be seen from Fig. 4(a), the catalytic activity of MIL-53(Fe) gradually increased with increasing the reaction temperature up to 55℃. This is probably due to the increase in reaction temperature, the H_2O_2 molecules increased kinetic energy and fast diffusion, which induce an increase in the collisions between H_2O_2 and the catalytic centers of MIL-53(Fe). Nevertheless, when the reaction temperature passed 55℃, the catalytic efficiency has a significant decrease. This is probably due to the fact that H_2O_2 molecules are not very steady and converted to other products before it collide with catalytic centers of MIL-53(Fe). Meanwhile, the pH is another important parameter that affects the catalytic efficiency. Fig. 4(b) displays the effect of pH on the catalytic activity of the MIL-53(Fe). From Fig. 4(b), experiments were carried out at a pH range from 1.0 to 5.5, the catalytic activity of the MIL-53(Fe) increases with increasing pH from 1.0 to 4.0 and then decreases with a further increase pH to 5.5. This phenomenon likely attributed to the MIL-53(Fe) framework construction exhibits higher effective catalytic sites at pH 4.0 and achieves significantly activity. Therefore, the optimal reaction temperature and pH obtained in the catalytic activity tests was 55℃ and 4.0, respectively. This result is similar to previously reported for nanostructure-based peroxidase mimetics[38,39].

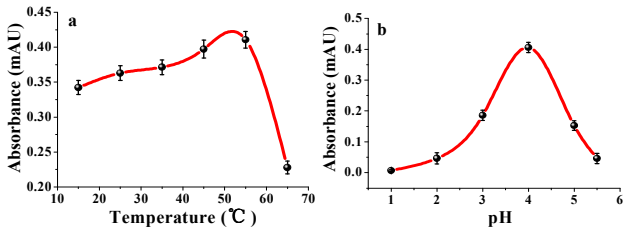


Fig. 4. Effects of the MIL-53(Fe) catalytic activity on (a) reaction temperature and (b) pH. Error bars show the standard deviation from three parallel measurements.

3.4 Quantitative determination of UA

Under the optimal experimental conditions, a colorimetric method was used for the detection of UA due to the absorbance of oxidized TMB, which is linearly dependent on H_2O_2

concentration. As we known, H_2O_2 is the main product of UA oxidation by uricase, which means that the proposed colorimetric

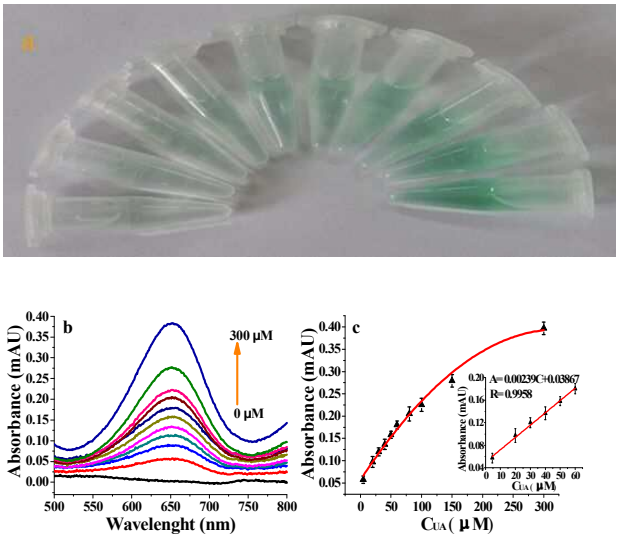


Fig. 5. (a) Image of colored products in the presence of different concentrations of UA (From left to right: 4.5, 20, 30, 40, 50, 60, 80, 100, 150, 300 μM). (b) The UV/Visible absorption spectra of the colorimetric sensor in the presence of different concentrations of UA. (c) A dose-response curves for UA detection in the range of 4.5 to 300 μM using MIL-53(Fe) as a peroxidase mimic. Inset: The linear calibration plot for UA. Error bars show the standard deviation from three parallel measurements.

method could be used to quantitatively determine UA content combining with uricase. As showed in Fig. 5a, the color variation for the sensing system from light-blue to deep-blue can be directly observed by the naked eye. The limit of detection (LOD) observed by the naked eye is as low as 4.5 μM. As can be seen from Fig. 5b, the absorbance increased gradually while the UA concentration increased from 0 to 300 μM. Fig. 5c describes the absorbance of the colored oxidized product of TMB (652 nm) at different UA concentrations. The linear regression equations for UA was expressed as A=0.00239C+0.03867 with a correlation coefficient of 0.9958 (Fig. 5c inset), where C is the UA concentration, A is the absorbance. The linear range for UA was from 4.5 to 60 μM, and the LOD was calculated to be 1.3 μM. Moreover, we compared the linear range and LOD with the previous reports on UA detection. As shown in Table 1, the proposed method was sensitive enough for UA detection, which showed comparably or even better than other reported[14,18,40]. Though the LOD and linear range of this assay is inferior to the method obtained using BSA-stabilized Au nanoclusters as peroxidase mimetic[21], the proposed method showed better precision and much strong resistance to common interferences. Because some special components such as biothiols (including cysteine, homocysteine and glutathione) are commonly existed in serum and have strong interaction with Au nanoclusters via Au-S bonds, causing the decrease of catalytic activity[23, 41].

3.5 Interference experiments

To evaluate the selectivity of detection of UA by using MIL-53(Fe) as peroxidase mimic, the absorbance responses of the sensing system were measured for other coexisting substances such as urea, L-cysteine, ascorbic acid, tryptophan, glutathione, glucose, sodium chloride, UA and their mixture. The results were shown in Fig. 6, it can be found that the absorbance obtained for urea, L-cysteine, ascorbic acid, tryptophan, glutathione, glucose and sodium chloride were still weak. However, only the addition of UA can result in a high absorbance, and no obvious absorbance changes were found upon the addition of coexisting substances. The results indicated that the coexistence of these interfering substances do not affect the detection of UA and further demonstrated the high selectivity for UA detection. Thus, the proposed sensing system showed great potential for the determination of UA in human urine and serum samples.

3.6 Analysis of human urine and serum samples

In addition, human urine and serum samples were selected as the real sample to examine the practicability of the proposed method. The results were shown in Table 2, the recoveries of UA in human urine ranged from 89.50 to 99.38%, while the recoveries ranged from 93.70 to 101.44% were obtained for serum samples. The relative standard deviations (RSD, n=3)are all less than 4.8%.

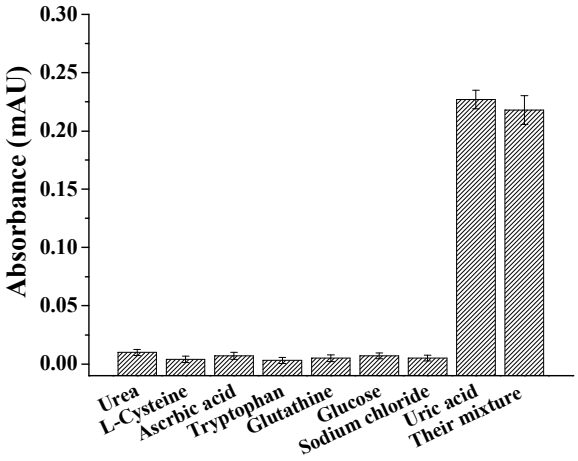


Fig. 6. Absorbance response of the colorimetric sensor to urea, L-cysteine, ascorbic acid, tryptophan, glutathine, glucose, sodium chloride, UA and their mixture. The concentrations of UA and other coexisting substances are 50 μM and 100 μM, respectively. Error bars show the standard deviation from three parallel measurements.

In order to check further the accuracy of the method and the reliability of the reaction system, measuring UA in two human serum samples have been validated through comparison between the proposed method and routine clinical methods. The results showed that the UA concentrations in serum 1 and serum 2 were 644.31 μM and 631.76 μM, which were consistent with the values measured by the routine clinical methods in the local hospital (serum 1: 641.00 μM, serum 2: 623.00 μM). Good recovery and precision of UA determination confirmed that the developed colorimetric method here is suitable for UA detection in real clinical samples.

4. Concluding remarks

In this study, we have confirmed that MIL-53(Fe) exhibits

peroxidase-like activity and can catalyze the oxidization of TMB

Table 1. Comparison of linear ranges and detection limits for MIL-53(Fe) with other analytical method.

Analytical method	Linear range(μM)	Detection limit(μM)	Reference
Luminol-$K_3[Fe(CN)_6]$	4.8-179	3	[14]
uricase/AuNP/MWCNT Au electrode	10-800	10	[18]
uricase/BSA-stabilized Au nanoclusters	2.0-200	0.36	[21]
uricase/HRP-CdS quantum dots	125-1000	125	[40]
uricase/MIL-53(Fe)	4.5-60	1.3	This work

Table2. Determination of UA in human urine and serum samples.

Samples	Founded (μM)	Value of this method	Value of clinical method [a]	Added (μM)	Detected (μM)	Recovery (%)	RSD (n=3, %)
Urine 1	22.22	555.5	--	8.0	29.75	94.13	3.1
				12.8	34.36	94.84	4.0
				16.0	36.54	89.50	2.8
Urine 2	19.38	484.5	--	8.0	27.33	99.38	1.5
				12.8	31.94	98.13	1.2
				16.0	35.28	99.38	1.8
Urine 3	16.87	421.75	--	8.0	24.69	97.75	2.3
				12.8	28.59	91.56	1.7
				16.0	31.52	91.56	3.5
Serum 1	21.48	644.31	641.00	10.0	30.85	93.70	2.1
				15.0	35.93	96.33	2.4
				25.0	46.16	98.72	2.0
Serum 1	21.06	631.76	623.00	10.0	30.85	97.90	4.8
				15.0	35.70	97.60	2.1
				25.0	46.42	101.44	1.3

[a] Data supported by the Affiliated Hospital of Guilin Medical University

by H_2O_2 with high efficiency. Experimental results indicated that the catalytic activity of MIL-53(Fe) was dependent on the reaction temperature and pH, similar to HRP. As a mimic peroxidase, the MIL-53(Fe) showed several advantages, such as inexpensive, stability, easy preparation and high catalytic efficiency. Based on the intrinsic peroxidase-like activity of MIL-53(Fe), a simple and effective method for colorimetric detection of UA in human urine and serum samples was explored by using UOx and MIL-53(Fe). Therefore, we believe that the use of MOFs nanomaterial as peroxidase mimics for UA determination is a promising candidate for bioassays and medical diagnostics.

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Notes and references

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