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2D Co-MOF nanosheet-based nanozyme with ultrahigh peroxidase catalytic activity for detection of biomolecules in human serum samples

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Abstract

A two-dimensional (2D) Co-MOF nanosheet-based nanozyme was developed for colorimetric detection of disease-related biomolecules. The prepared 2D Co-MOFs exhibited ultrahigh peroxidase catalytic activity. 2D Co-MOFs can catalyze the oxidation of colorless 3,3′,5,5′-tetramethylbenzidine (TMB) to the blue product oxTMB, accompanying an obvious change of absorption value at 652 nm. However, alkaline phosphatase can catalyze the hydrolysis of L-ascorbic acid-2-phosphate to produce ascorbic acid which can reduce the oxTMB to TMB, resulting in an obvious color fading. Therefore, by recording the change of absorption value at 652 nm, the 2D Co-MOF nanosheets were used to detect ascorbic acid (AA) and alkaline phosphatase (ALP). The limit of detection for AA and ALP was 0.47 μM and 0.33 U L^{-1}, respectively. The limit of quantification for AA and ALP was 1.56 μM and 1.1 U L^{-1}, respectively. The developed nanozyme was successfully used to determine alkaline phosphatase in clinical human serum samples and the results were consistent with those provided by the hospital. Furthermore, by integrating 2D Co-MOF nanosheets with image recognition and data processing function fixed on a smartphone, a portable test of ascorbic acid was reached.

Keywords 2D co-MOF nanosheets · Colorimetric assay · Ascorbic acid · Alkaline phosphatase · Human serum samples · Portable test

Introduction

Nanozymes are nanoparticles with natural enzyme-like characteristics and have obtained increasing attentions in the last decade [1, 2]. Compared to natural enzymes, nanozymes possess a lot of advantages, including being more robust under harsh conditions, resistance to denaturation, tunable activity,

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and lower cost [3–5]. These features make nanozymes have extensive applications in catalysis, sensing, and therapeutics [6–8]. Up to now, a number of nanoparticles with artificial enzymes characteristics have been developed. However, it is a big challenge for the development of nanozymes with excellent catalytic activity.

Metal-organic frameworks (MOFs), which are hybrid array of metallic nodes interconnected by organic linkers [9], have been widely exploited as artificial enzyme mimics for catalysis application. MOFs possess various unique advantages: (1) MOFs can provide large surface and rich channel for rapid mass transfer [10], (2) the specific pore size in MOFs is good for the adsorption and loading of targets [11], and (3) the metal nodes in MOFs contribute more active sites [12]. For instance, Zhou et al. prepared a PCN-600 (Fe) with effective peroxidase activity to catalyze the co-oxidation reaction [13]. Yang et al. developed 3D Co-MOFs modified electrode for H_2O_2 sensing [14]. However, most of 3D bulk MOFs still exhibit unfulfilling catalytic efficiency. To address this challenge, MOFs with high catalytic ability are urgently needed.

Recently, 2D-MOF nanosheets have been synthetized for application in various fields [15, 16]. Compared to the bulk 3D-MOFs crystals, 2D-MOFs can provide tailorable structures, ultra-large surface areas, and multiple catalytic active sites, resulting in improved catalytic property. Therefore, it can bring gratifying performance for bioassay, biomedicine, and catalysis. For example, Zhang et al. developed a surfactant-assisted preparation strategy to synthetize uniform ultrathin Zn-TCPP MOF nanosheets [17]. Sun and coworkers prepared the Co-MOF nanosheet array on nickel foam via Co^{2+} and terephthalic acid for glucose oxidation electrocatalysis [18]. Although several 2D MOFs have been successfully used as nanozymes for bioassay, the research on the catalytic properties of 2D MOFs and their biomedical applications are remaining in the primary stage. Herein, we try to develop a novel kind of porphyrin-based 2D Co-MOF nanosheets and study their application in testing of disease-related biomolecules.

By employing the surfactant-assisted preparation strategy, porphyrin-based 2D Co-MOF nanosheets were prepared for the first time. In this work, $CoCl_2 \cdot 6H_2O$ was chosen as the metal source and TCPP was chosen as the ligand. Polyvinylpyrrolidone (PVP) was introduced as a surfactant to control the size and morphology of 2D MOFs. Compared to previously reported 3D Co-MOFs, the new prepared 2D Co-MOF nanosheets have uniform size and possess many highly accessible active sites on their surface. The obtained 2D Co-MOF nanosheets showed attractive intrinsic peroxidase-like activities and were successfully employed for biomolecules detection in clinical human serum samples. Furthermore, a paper-based strip sensor was also fabricated based on the 2D Co-MOF nanosheets for quantitative detection of ascorbic acid under the help of a smartphone. Therefore, we believed that this nanoplatform may provide a new direction for the utilization of 2D MOFs-based nanomaterial as peroxidase mimics to build a facile and reliable platform for portable test application (Scheme 1).

Experimental section

Reagents

Cobalt chloride ($CoCl_2 \cdot 6H_2O$), tetrakis(4-carboxyphenyl) porphyrin, N-Ethylmaleimide, 3, 3′, 5, 5′ tetramethylbenzidine, L-ascorbic acid-2-phosphate, and ascorbic acid were provided by J&K Scientific Co, Ltd. (Beijing, China, www.jkchemical.com). Dimethyl sulfoxide, trifluoroacetic acid, L-cysteine, glutathione, glutamic acid, proline, histidine, lysine, L-aspartic acid, and DL-methionine were obtained from Aladdin Reagent Co, Ltd. (Shanghai, China, www.aladdin-e.com). Alkaline phosphatase

(10,000 U mL^{-1}) was obtained from New England Biolabs (Beijing, China, www.neb.com).

Instruments

The morphology of 2D Co-MOF nanosheets was confirmed by SU8000 scanning electron microscopy (Hitachi, Japan, www.hitachi.com.cn). The size distribution was analyzed by the Zetasizer Nano series (ZEN3700, Malvern Instruments, www.malvernpanalytical.com). UV-Vis absorption was obtained from U-3900H ultraviolet spectrophotometer (Hitachi, Japan, www.hitachi.com.cn).

Synthesis of 2D Co-MOF nanosheets

The synthesis of 2D Co-MOF nanosheets was according to the previous report with slight modification [17]. The detailed preparation process is presented in the electronic supporting material.

Investigation of the peroxidase activity of 2D Co-MOF nanosheets

The peroxidase activity of 2D Co-MOF nanosheets was investigated by catalytic oxidation of TMB in the presence of H_2O_2. Briefly, 1 μL of H_2O_2 (20 mM), 32 μL of TMB solution (5 mM in DMSO), and 7 μL of 2D Co-MOF nanosheets (3.9 mg mL^{-1}) were added into 200 mM acetate buffer with a total volume of 200 μL. After incubation for 80 min, the sample was transferred into a quartz cell and then placed in the UV spectrophotometer to record its UV-vis spectra (652 nm). To obtain the optimal catalytic condition, the concentration of 2D Co-MOF nanosheets, pH of the buffer, reaction time, the concentration of H_2O_2, and temperature were carefully investigated.

The application of 2D Co-MOF nanosheets in the assay of biomolecules

The colorimetric detection for biomolecules was built in the 2D Co-MOF nanosheet-TMB-H_2O_2 reaction system. Firstly, different concentrations of ascorbic acid (AA) were mixed with 5 mM TMB (32 μL) in acetate buffer (pH, 4.0). Then, both H_2O_2 (20 mM, 1 μL) and 2D Co-MOF nanosheets (3.9 mg mL^{-1}, 7 μL) were added into the above reaction solution with a final volume of 200 μL. After 80 min, the UV-vis spectra of these solutions were recorded.

In a typical detection of alkaline phosphatase (ALP), different concentrations of ALP were first incubated with 10 mM L-ascorbic acid-2-phosphate (AAP, 2 μL, 10 mM) in buffer (10 mM Tris, pH 8.0) with a volume of 30 μL at 37 °C for 20 min. The following step was similar to that for AA detection.

Scheme 1 Schematic illustration of (**a**) the surfactant-assisted synthesis of 2D Co-MOF nanosheets and (**b**) 2D MOF nanosheet-based colorimetric and portable detection of ascorbic acid
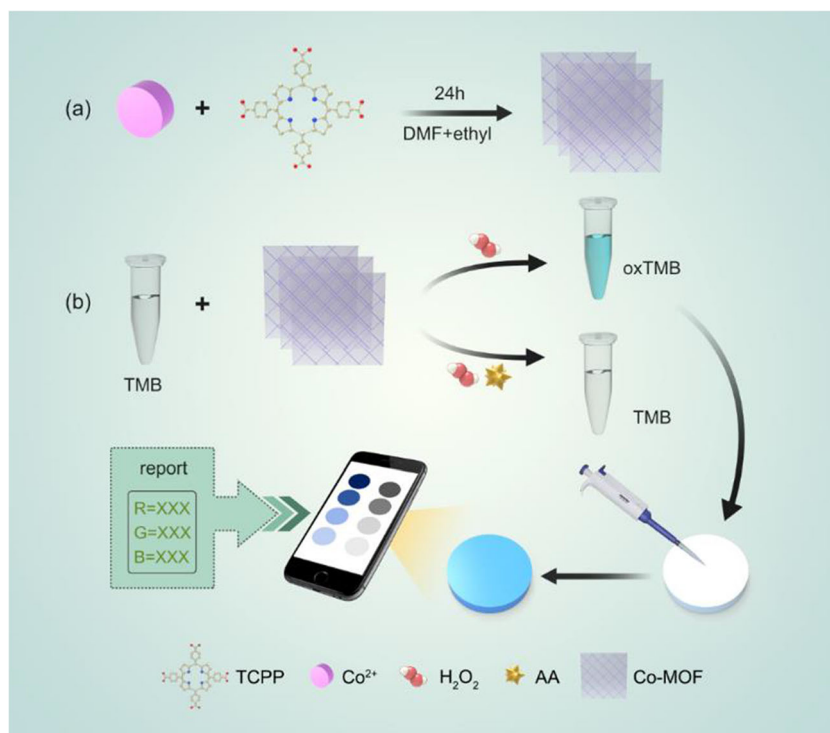
The application of 2D Co-MOF nanosheets in real samples

To investigate the performance of the prepared nanozyme in real samples, the prepared 2D Co-MOF nanosheets were used to detect ALP in clinical serum samples. Samples were provided by the First Affiliated Hospital of Zhengzhou University (Zhengzhou, China) and used in compliance with protocols approved by the Life-Science Ethics Review Committee of Zhengzhou University. First, the collected human serum samples were pretreated with 2 mM N-Ethylmaleimide (NEM) to remove the sulfhydryl compounds. Then, 2 µL AAP stock solution (10 mM) and 3 µL serum sample were incubated in buffer with a volume of 30 µL at 37 °C for 20 min, the subsequent step was similar to that for AA detection.

Smartphone imaging-based detection of AA

A paper-based test kit was developed for visual sensing of AA. To prepare the kit, 200 µL solution (including 0.136 mg mL^{-1} Co-MOF nanosheets and 0.8 mM TMB) was first spotted on filter paper strips (1×1 cm^2). These strips were then dried in vacuum. For the detection of AA, different concentrations of AA with 100 µM H$_2$O$_2$ were dropped on these prepared strips. After 15 min, the appeared blue color was captured by a camera and then a smartphone with image recognition and data processing function fixed was used to record the RGB value of the obtained images.

Results and discussions

Preparation and characterization of 2D Co-MOF nanosheets

The 2D Co-MOF nanosheets were synthesized via a top-down synthetic method. In this work, PVP was chosen as surfactant molecules. PVP can selectively adsorb on the surface of Co-MOFs and regulate the growth of MOFs crystals, resulting in the anisotropic growth of nanoparticles and formation of ultrathin Co-MOF nanosheets. In addition, PVP can effectively prevent the agglomeration of nanoparticles, resulting in improved catalytic activity for Co-MOF nanosheets.

To obtain the 2D Co-MOFs with larger surface area and high uniformity, three different ratios of DMF and ethanol (3:1, 2:1, and 1:1) for preparation of Co-MOF nanosheets were carefully investigated. Powder X-ray diffraction was first carried out to study the component of three kinds of Co-MOFs. As described in Fig. S1, with the increase of DMF proportion, the characteristic peaks increase obviously, indicating that they are different compounds. SEM was further used to analyze the morphology of three kinds of compounds. As shown in Fig. S2, only the Co-MOFs prepared by DMF and ethanol with the ratio of 3:1 exhibits ultrathin structure and uniform size. The reason may be that the coordination assembly of Co^{2+} and TCPP was influenced by the solvent from both kinetic and thermodynamic aspects [19].

Then, the morphology, chemical component, and size of optimized 2D Co-MOF nanosheets were characterized by

TEM, DLS, XPS, and elemental mapping. As described in Fig. 1a, the TEM result shows the sheet-like structure of the prepared Co-MOFs with an average diameter of about 100 nm, which is agreed with the DLS result (Fig. S3). In addition, the composition and structure of Co-MOF nanosheets was also investigated by elemental mapping (Fig. S4) and the X-ray photoelectron spectroscopy (XPS). As revealed in Fig. 1b and Fig. S5, XPS analysis detects that the Co-MOF nanosheets are composed of C, O, N, and Co, and two peaks at 781.9 and 797.8 eV can be assigned to the Co $2p^{3/2}$ and Co $2p^{1/2}$, respectively. The two peaks at 786.8 and 804.1 eV are well matched with two shakeup satellites, respectively, suggesting the existence of Co^{2+} [18].

Investigation the peroxidase property of 2D Co-MOF nanosheets

The peroxidase property of three different kinds of Co-MOFs was studied by employing TMB as the chromogenic substrate. As presented in Fig. S6, TMB is oxidized to oxTMB with the addition of Co-MOF nanosheets and H_2O_2. However, there is no obvious color change when only the presence of H_2O_2. The results indicate that Co-MOF nanosheets possess intrinsic peroxidase property. In addition, as shown in Fig. S7, the optimized 2D Co-MOF nanosheets show the best peroxidase catalytic activity, demonstrating that the structure has large effect on the peroxidase property.

To further elucidate the catalytic mechanism of Co-MOF nanosheets, some experiments were carried out to authenticate the possible reaction intermediates. Here, 2, 2′-(anthracene-9, 10-diylbis(methylene)) dimalonic acid (ADMA) was chosen as an indicator of $O_2^{·-}$ to verify the presence of $O_2^{·-}$ in the Co-MOF nanosheets involved catalytic process. As shown in Fig. S8, the typical absorption bands (379 and 405 nm) of ADMA in 2D Co-MOFs solution were degraded by the oxidation of $O_2^{·-}$. Furthermore, isopropanol was chosen as ·OH scavengers to identify the presence of ·OH. As described in Fig. S9, the absorbance of oxTMB in the presence of scavengers was much lower than that in the absence of scavengers, suggesting

the presence of ·OH in this process. Based on these results, we infer that a lot of H_2O_2 was coated on the surface of the 2D Co-MOF nanosheets and subsequently turned to $O_2^{·-}$ and ·OH by the catalysis of Co-MOF nanosheets. And then the strong oxidizing ability of $O_2^{·-}$ and ·OH catalyze TMB to oxidized TMB.

Steady-state kinetic assay of 2D Co-MOF nanosheets as peroxidase

Furthermore, the peroxidase properties of three different kinds of Co-MOF nanosheets were checked through the steady-state kinetic experiments. The detailed experimental process and the results were shown in electronic supporting material (Fig. S10, Fig. S11, Fig. S12, and Table S1). As presented in Table 1, the K_m for 2D Co-MOF nanosheets is much lower and the ν_m is higher than the most reported 3D MOFs-based peroxidases.

2D Co-MOF nanosheet-based colorimetric probe for AA and ALP detection

AA is a momentous reactive biological molecule in human body and plays various important roles, including enzyme cofactor, antioxidant against oxidative damages, and involvement in neurotransmitter-related enzymes [3]. However, the abnormal level of AA is connected with a number of diseases, such as scurvy, depression, urinary stone, and diarrhea. ALP is widely found in liver, bones, and intestines, which can catalyze the hydrolysis of phosphate groups on biomolecules. ALP possesses a vital role in the normal growth of mammals and acts as an important biomarker for a variety of diseases in clinical diagnosis [4]. Therefore, development of simple and efficient method for AA and ALP detection in complex biological systems is of great significance for clinical diagnosis, treatment, and biomedical research. Based on the knowledge that ALP can catalyze the hydrolysis of AAP to produce AA, and AA can reduce the oxTMB to TMB, resulting in an obvious color change. Herein, we developed a colorimetric

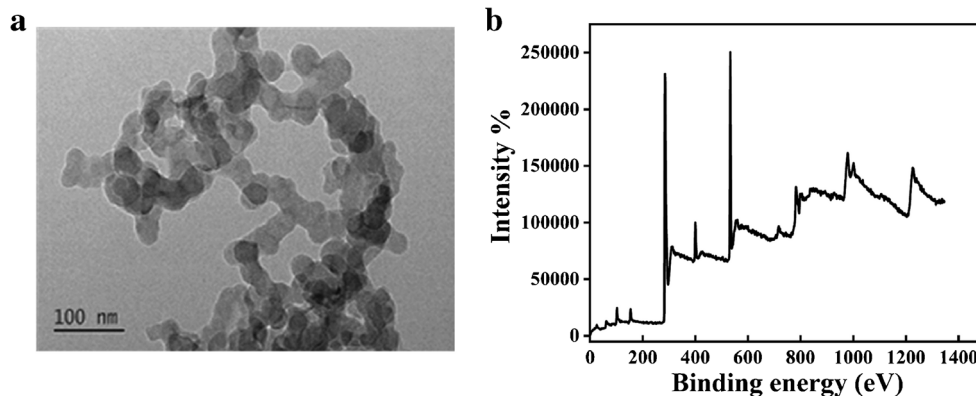Fig. 1 The characterization of prepared 2D Co-MOF nanosheets. a TEM. b XPS

Table 1 The comparison of the apparent K_m and ν_m of 2D Co-MOF nanosheets and other peroxidase mimetics

Catalyst	Substrate	K_m [mM]	ν_m (10^{-7} Ms.$^{-1}$)	Ref
Fe-MIL-88NH$_2$	TMB	0.28	1.05	[20]
	H$_2$O$_2$	0.21	0.70	
MIL-53(Fe)	TMB	1.08	0.88	[21]
	H$_2$O$_2$	0.04	0.19	
Ag@Zn-MOF	TMB	0.16	0.14	[22]
	H$_2$O$_2$	0.162	0.20	
Pt/CeO$_2$	TMB	0.41	8.84	[23]
	H$_2$O$_2$	16.18	10.82	
HRP	TMB	0.43	1.00	[24]
	H$_2$O$_2$	3.70	0.87	
2D Co-MOFs	TMB	0.26	6.44	This work
	H$_2$O$_2$	0.24	5.01	

probe for AA and ALP sensing by employing the peroxidase activity of Co-MOF nanosheets.

The experimental conditions for AA and ALP detection were first carefully investigated to obtain the best analytical performance. As shown in Fig. S13, the optimized conditions were 0.136 mg mL^{-1} Co-MOFs, 100 μM H$_2$O$_2$, 800 μM TMB, and pH 4.0. Figure 2a clearly illustrates the UV-vis spectra of the solution with the addition of different concentrations of AA. Figure 2b exhibits the relationship between the absorption value at 652 nm and the concentration of AA. The

regression equation is $A = 0.0297$ [AA] + 0.0312 (R^2 = 0.9941), with the limit of detection (LOD) of 0.47 μM (based on 3δ/slope ruler). Meanwhile, the system was also used to detect ALP according to the similar procedure as that for AA detection. Figure 2c and d show the response of 2D Co-MOF nanosheets to ALP. The linear regression equation between absorbance and concentration of ALP is $A = 0.0591$[ALP] + 0.1183 ($R^2 = 0.9923$) with the LOD of 0.33 U L^{-1}. Compared to many previous reports for ALP detection, the detection performance of the 2D Co-MOF nanosheets showed comparable or slightly lower LOD for AA and ALP detection (Table 2).

To investigate the selectivity of the system, the response of 2D Co-MOF nanosheets to several interferences with higher concentrations were studied. Here, glutathione (GSH, 5 mM), cysteine (Cys, 5 mM), some amino acids (5 mM), and some metal ions (150 mM) were investigated. As displayed in Fig. 3, obvious change in absorbance at 652 nm can be observed with the addition of AA or ALP. In contrast, other interferences show negligible effect, even existing in a much higher concentration, although some reductive substances, for example, GSH, may have some impact on the detection of AA and ALP in the human body. N-NEM can effectively reduce these interferences thanks to its ability to perfectly mask sulfhydryl compound. Therefore, the system can be used to detect AA and ALP after simple pretreatment the sample.

Fig. 2 **a** UV-vis absorbance of the TMB-H$_2$O$_2$-Co-MOF (0.136 mg mL^{-1} Co-MOFs, 100 μM H$_2$O$_2$, 800 μM TMB, and pH 4.0) reaction system upon the addition of 0.5–25 μM AA, **b** the relationship between the absorption value at 652 nm and the concentration of AA, **c** the UV-vis absorbance spectra of TMB-H$_2$O$_2$-Co-MOFs (0.136 mg/mL Co-MOFs, 100 μM H$_2$O$_2$, 800 μM TMB, and pH 4.0) in the presence of ALP with different activity and AAP (10 mM), and **d** the relationship between the absorption value at 652 nm and the concentration of ALP
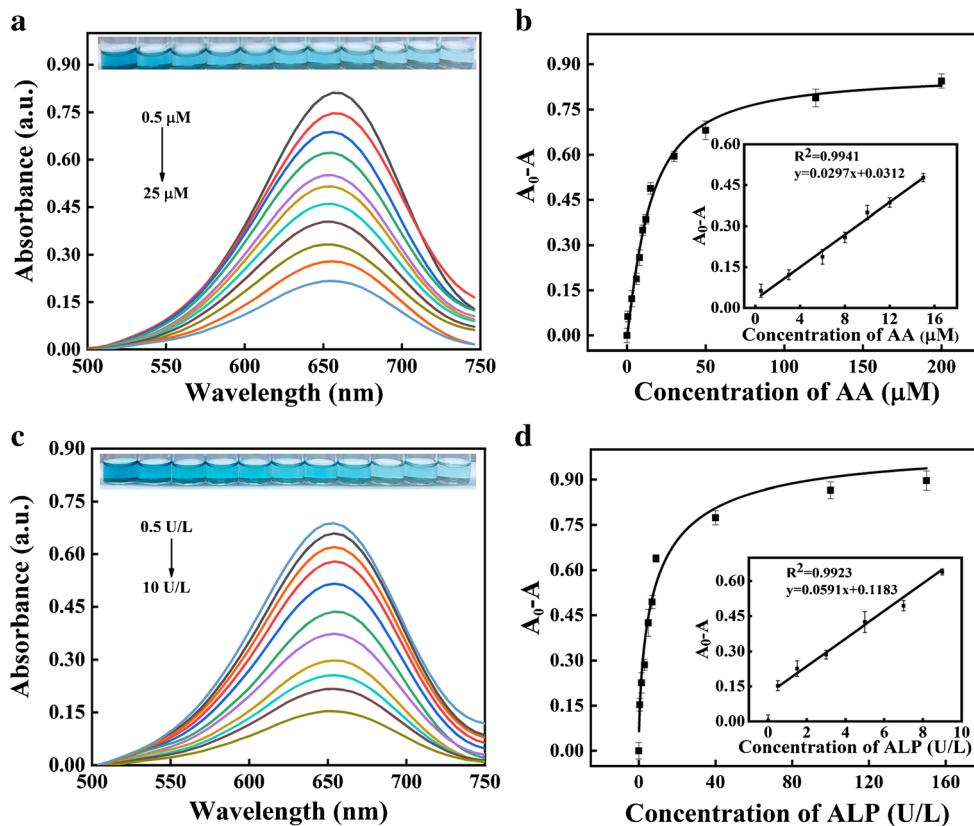
Table 2 The comparison of recently reported colorimetric methods for AA and ALP determination

Method	Materials used	Applied	LOD of AA (μM)	LOD of ALP (U L^{-1})	Ref
Colorimetric	Co$_3$O$_4$	AA	1.09	No	[25]
Colorimetric	Au/Cu NRs	AA	25	No	[26]
Colorimetric	Cu-Ag	AA	3.6	No	[27]
Colorimetric	polydiacetylene	ALP	No	5.4	[28]
Colorimetric	gold nanoclusters	ALP	No	0.5	[29]
Colorimetric	DNA-Cu	ALP	No	0.84	[30]
Colorimetric	2D Co-MOFs	ALP/AA	0.47	0.33	This work

These results demonstrated that the prepared 2D Co-MOF nanosheets possess high selectivity toward AA and ALP, which enhances its potential in real complex samples analysis.

The application of 2D Co-MOF nanosheets in real samples

To estimate the application of the proposed approach in real samples, the developed 2D Co-MOF nanosheets were used to quantify ALP in clinical serum samples. The collected human serum samples were first pretreated with 2 mM NEM to remove the sulfhydryl compounds and then performed according to that in buffer. As shown in Table 3, the results for all real samples are in good agreement with the results provided by the First Affiliated Hospital at Zhengzhou University with a relative error less than ± 8%. These results suggest that the 2D Co-MOF nanosheet-based colorimetric platform possess great potential for clinical application due to its high accuracy and low cost.
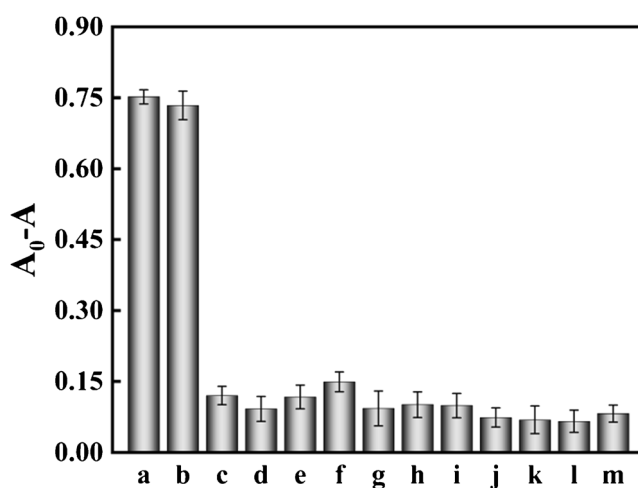

Fig. 3 Selectivity of the developed 2D Co-MOF nanosheets for AA and ALP assay: (a) AA (20 μM), (b) ALP (10 U L^{-1}), (c) blank, (d) Cys (5 mM) + NEM (10 mM), (e) GSH (5 mM) + NEM, (f) Glu (5 mM), (g) His (5 mM), (h) Lys (5 mM), (i) MET (5 mM), (j) Pro (5 mM), (k) Asp (5 mM), (l) Mg^{2+} (150 mM), and (m) Na$^+$ (150 mM)

Fabrication of 2D Co-MOF nanosheet-based portable device

The excellent peroxidase-like activity and the successful application in real samples of Co-MOF nanosheets inspired us to explore its potential in developing portable device either using the naked eye or a smartphone. As one of the commonly used portable devices, paper strips possess many advantages including low cost, easy operation, simple storage, and transport. Based on the above advantages, a paper-based portable device for AA detection was explored by using 2D Co-MOF nanosheets. As shown in Fig. 4a, an apparent color change from dark blue to light blue is observed with the naked eye and the color can stay stable within 30 min (Fig. S14). Then, these images were digitized with an RGB application which were pre-downloaded onto a smartphone. As shown in Fig. 4b, the ratio of red (R) and blue (B) also shows a linear relationship with the concentration of AA ranging from 1 to 30 μM ($R/B = -0.1970[AA] + 6.455$, $R^2 = 0.9904$) with a LOD of 0.69 μM. These results show that the developed 2D Co-MOF nanosheet-based portable device holds a great potential to be used for quick and reliable biomarker detection. The 2D Co-MOF nanosheet-based nanozyme exhibits significant application in clinical samples with many advantages such as easy operation and low cost. However, this method is somehow time-consuming and should be further improved in the future studies.

Conclusion

In this work, we have successfully synthesized novel 2D Co-MOF nanosheets with significant enhancement of peroxidase catalytic activity compared with the widely explored 3D

Table 3 The comparison of 2D Co-MOF nanosheets and hospital method for ALP assay in human serum samples

Sample	Detected (U L^{-1})	Clinical result (U L^{-1})	RE (%)
1#	58.1 ± 0.26	61	−4.7
2#	51.1 ± 0.18	55	−7.1
3#	33.4 ± 0.13	31	+7.7

Fig. 4 **a** Photographs of test trips after addition of 2D Co-MOF nanosheets with different concentrations of AA (1, 5, 8, 12, 16, 20, 25, 30 μM). **b** The relationship between the R/B ratio provided by APP and the different concentrations of AA. Error bars indicate standard deviations ($n = 3$)
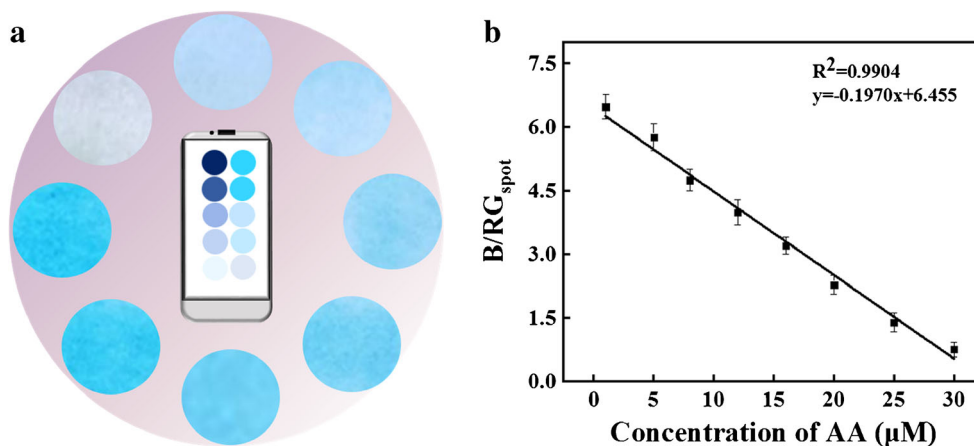
MOFs. Based on the fact that the 2D Co-MOF nanosheets can catalyze the oxidation of TMB to produce oxTMB and AA can induce the reduction of oxTMB, the developed 2D Co-MOF nanosheets were successfully used to detect AA and ALP. Moreover, integrating these Co-MOF nanosheets with a smartphone, easy test of AA with extremely reliability was achieved, showing its tremendous potential for practical application in public security, emergency rescue, and related fields. Our findings herein afford new insight into the construction of 2D MOFs with excellent catalytic activity as well as durability. This work may advance the construction of portable test devices and accelerate the protein-free biotransformation in biomedicine applications.

Declarations

Conflict of interest The authors declare no competing interests.

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