

Fluorinated magnetic covalent organic framework-enhanced laser desorption/ionization mass spectrometry and imaging for determination of perfluoroalkyl ether carboxylic acids

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Abstract

Perfluoroalkyl ether carboxylic acids (PFECAs), an emerging subclass of per- and polyfluoroalkyl substances (PFAS), have raised significant environmental and health concerns due to their prevalence in various samples. We report the room-temperature synthesis of a core-shell magnetic composite, Fe_3O_4 @fluorine-functionalized covalent organic framework (Fe_3O_4 @F-COF), and its application as a dual-functional platform of an efficient adsorbent and an inorganic matrix for the sensitive analysis of PFECAs. It was applied in surface-assisted laser desorption/ionization mass spectrometry (SALDI-MS) to detect three PFECAs, perfluoro (2-methyl-3-oxahexanoate) (GenX), 3H-perfluoro-3-[(3-methoxy-propoxy) propionic acid] (ADONA), and perfluoro [(2-ethyloxy-ethoxy) acetic acid] (EEA), in spring water and human serum. The method showed high sensitivity, with limits of detection (LODs) of 0.075–0.20 ng/L. Furthermore, Fe_3O_4 @F-COF served as an effective matrix for laser desorption/ionization mass spectrometry imaging (LDI-MSI), enabling the visualization and quantification of GenX in exposed animal kidney tissue with a linear range of 0.05–50 $\mu\text{g/L}$ and LOD of 0.01 $\mu\text{g/L}$. These results establish the Fe_3O_4 @F-COF combined LDI-MS as a highly versatile and sensitive platform for the analysis and imaging of PFECAs in environmental and biological matrices.

1. Introduction

Perfluorinated compounds (PFCs) are a class of emerging contaminants characterized by persistence, bioaccumulation, and toxicity, and their environmental behavior and health risks have become a global concern [1]. As traditional perfluorinated compounds, such as PFOS and PFOA, are gradually restricted, novel alternatives have been widely introduced into industrial and consumer products [2]. Perfluoroalkyl ether carboxylic acid (PFECAs) molecules, comprising the ether-based C – O bond with low bioaccumulation capability, were synthesized as alternatives to full carbon-chain precursors like PFASs [3, 4]. Common PFECAs, including perfluoro(2-methyl-3-oxahexanoate) (GenX), 3H-perfluoro-3-[(3-methoxy-propoxy) propionic acid] (ADONA), and perfluoro-[(2-ethyloxy-ethoxy) acetic acid] (EEA), now represent prominent class of emerging PFAS compounds. However, recent toxicological evidence indicates that several PFECAs may exhibit higher toxicity and greater susceptibility to bioaccumulation than perfluorooctanoic acid (PFOA), thereby classifying them as new contaminants of urgent concern [5]. Human exposure to PFECAs occurs through multiple pathways, including drinking water, food, and air, with dietary intake via the food chain being a primary route [6]. Drinking water in specific regions in Europe and North America was reported to contain substantially higher PFECA concentrations than legacy PFASs [7]. The regulations of several organizations have considered different PFECAs in the list of substances of very high concern (SVHC) [8]. The Department of Health and Human Services in North Carolina has set a drinking water health goal for GenX with an equivalent level equal to 140 ng/L [9]. Therefore, developing an effective approach for PFECA detection and quantification for food safety and public health has become of uttermost importance.

Substantial efforts have been devoted to developing analytical technologies for the detection of PFECAs. Currently, liquid chromatography–tandem mass spectrometry (LC–MS/MS) is the most widely employed

technique, prized for its high accuracy and sensitivity for PFECAs detection [10–12]. Nevertheless, this method suffers from limitations such as complex and time-consuming sample pretreatment, high solvent consumption, and the loss of *in-situ* spatial distribution information of analytes on biological tissues' surfaces. Thus, rapid, effective and *in-situ* methods for PFECAs' detection in food and biological samples are essential and currently sought after.

Matrix-assisted laser desorption/ionization mass spectrometry (MALDI-MS) presents a compelling alternative to LC-MS/MS, offering advantages such as high throughput, minimal sample preparation, and rapid analysis speed. Its applicability spans biomedical [13], environmental [14], and food analysis [15]. A critical aspect of MALDI-MS is the selection of an appropriate matrix, which co-crystallizes with analytes to facilitate desorption and ionization. Traditional organic matrices, such as 2,5-dihydroxybenzoic acid (DHB), α -cyano-4-hydroxycinnamic acid (CHCA), and 1,5-diaminoanthracene (DAN), are effective for macromolecules (proteins/peptides), but often produce intense background interference in the low mass/charge (m/z) ratio region, hindering the detection of small molecules [16, 17]. To overcome this limitation, various nanostructured materials, including carbon-based nanomaterials [18], silicon [19], metal [20] and metal oxides [21], covalent organic frameworks (COFs) [22], have been developed as MALDI matrices. These solid matrices typically exhibit low background interference, high salt tolerance and good repeatability in LDI-MS of small molecules [23].

Among these nanostructures, iron oxide (Fe_3O_4) particles have shown promise as an inorganic matrix, owing to their substantial photon absorption cross-section, robust intraparticle bonding, environmentally friendly characteristics, and low cost, which make it a highly valuable matrix for the desorption/ionization process [24, 25]. A major drawback of pristine Fe_3O_4 particles is their tendency to aggregate limitation in selectivity, which affects the reproducibility and sensitivity of the analytical performance [26]. Surface coating with functional materials presents a viable strategy to prevent aggregation. Covalent organic frameworks (COFs), a class of porous crystalline materials, comprise low-molecular-weight elements (C, H, O, and N) [27], feature low density, high stability, ordered pore structures, and easy of functionalization. Fluorinated COFs (F-COFs), in particular, possess extended and highly ordered network structures with strong covalent bonds [28]. The hollow structure of F-COFs facilitates the mass transfer, while fluorinated functional groups enhance their hydrophobicity and strong F–O, F–F, and F– π interactions between strongly electronegative F and O or π electrons, promoting selective adsorption of the fluorinated compounds [29, 30]. Coating Fe_3O_4 with F-COFs can thus prevent nanoparticle aggregation, while providing a large, stable, and selective surface for analyte enrichment.

Herein, we report a facile preparation and systematic characterization of a core-shell Fe_3O_4 @F-COF composite as a dual-functional material, enabling both selective enrichment of PFECAs and their subsequent sensitive analysis by SALDI-MS and MSI. It was successfully applied for the direct and quantitative analysis of PFECAs in complex biological and food samples. Furthermore, the desorption/ionization mechanism of PFECAs on the Fe_3O_4 @F-COF matrix was investigated to elucidate the adsorption and ionization processes, providing insight into the factors influencing the analytical performance for these pollutants.

2. Experimental

2.1. Materials and Chemicals

Perfluoro(2-methyl-3-oxahexanoate) (GenX), 3H-perfluoro-3-[(3-methoxy-propoxy) propionic acid] (ADONA), and perfluoro[(2-ethyloxy-ethoxy)acetic acid] (EEA) were procured from Tanmo Quality Inspection Technology Co., Ltd. Chromatographic-grade acetonitrile was procured from Merck Ltd. Sodium citrate dihydrate ($C_6H_5O_7Na_3 \cdot 2H_2O$), iron chloride hexahydrate ($FeCl_3 \cdot 6H_2O$), urea, and ethanol were purchased from Sinopharm Chemical Reagent Co., Ltd. Polyacrylamide (nonionic, MW: 5 – 6000000) was obtained from Thermo Fisher Scientific (Acros). 1,3,5-Tris(4-aminophenyl)triazine (TAPT) and 2,3,5,6-tetrafluoroterephthaldehyde (TFTA) were supplied by Zhengzhou Alpha Chemical Co., Ltd. DHB, DAN, and CHCA were obtained from Sigma Reagent Co., Ltd. All chemicals were of analytical grade or higher and utilized without further processing. The standard stock solutions were stored at 4°C.

2.2. Characterization

Microstructural characterization was conducted via scanning electron microscopy (SEM) using a Zeiss SUPRA55 field-emission scanning electron microscope, coupled to an energy dispersive X-ray spectroscopy (EDS) detector for elemental mapping. High-resolution morphological details were captured with transmission electron microscopy (TEM) using a JEM-2010 transmission electron microscope from JEOL, operating at an acceleration voltage equal to 200 kV. Molecular bonding configurations were investigated via a Bruker Vertex 70 Fourier-transform infrared (FTIR) spectrometer in attenuated total reflectance mode. X-ray photoelectron (XPS) spectroscopy was conducted utilizing a Thermo Escalab 250xi system. The magnetic behavior of the sample was evaluated using a Quantum Design SQUID-VSM system for temperature-dependent magnetization measurements across ± 30 kOe field ranges. Brunauer–Elmett–Teller (BET) analysis was performed using a JW-BK300C physisorption analyzer. Porosity characteristics were determined using nitrogen physisorption experiments at a temperature equal to 77 K via a Micromeritics ASAP 2020 analyzer, with specimens degassed at 150°C for a duration equal to 12 h before measurement. All analytical procedures followed standardized protocols to ensure experimental reproducibility.

2.3. Preparation of nanocomposites

Stage I: Preparation of Fe_3O_4 particles. The Fe_3O_4 particles were synthesized using a modified procedure [31]. A homogenous aqueous mixture was prepared by dissolving ferric chloride hexahydrate ($FeCl_3 \cdot 6H_2O$, 2 mmol), trisodium citrate dihydrate ($Na_3C_6H_5O_7 \cdot 2H_2O$, 4 mmol), and urea (6 mmol) in deionized water (40 mL). Subsequently, to improve the stability of Fe_3O_4 , polyacrylamide (300 mg) was gradually added to the solution under constant mechanical agitation maintained for 60 min. The viscous colloidal suspension was hydrothermally processed in a sealed 100 mL stainless-steel reactor at elevated temperature (200°C) for 12 h. Post-reaction purification involved magnetic separation of Fe_3O_4 particles followed by sequential ethanol/water rinsing cycles. The resulting Fe_3O_4 nanoparticles, were vacuum dried at 70°C for 12 h before subsequent functionalization.

Stage II: Fe₃O₄@F-COF preparation. Fe₃O₄ nanoparticles (30 mg) were dispersed in acetonitrile (30 mL) through prolonged sonication for 30 min. The core-shell assembly procedure was performed following a reported method through minor modifications [32]. TAPT (0.24 mmol) was added to the magnetic suspension. The resultant mixture was subjected to a 6-h orbital shaking at 25°C. Subsequent addition of TFTA (0.36 mmol) and acetic acid (6 mL, 12 M) initiated interfacial polycondensation under continuous agitation at room temperature (24 h). The final composite material was magnetically harvested, subjected to methanol washing (3 cycles), and thermally stabilized (70°C, 12 h) to yield the target magnetic Fe₃O₄@F-COF. F-COF was prepared following the above-mentioned procedure without Fe₃O₄ nanoparticles.

2.4. Sample preparation

The concentration of each analyte stock solution was 1 mg/mL. Water was used to prepare the GenX stock solution (100 µg/mL). ADONA and EEA stock solutions (100 µg/mL) were prepared in acetonitrile. Working solutions of different concentrations were obtained using a mixture of acetonitrile and water with a volume ratio of 7:3. All the analytes solutions were stored at 4°C until further use.

The conventional organic matrices (DHB, DAN, or CHCA) were individually prepared in an acetonitrile and water mixture (volume ratio 7:3) at a concentration of 10 mg/mL. The Fe₃O₄, F-COF, and Fe₃O₄@F-COF matrices (10 mg/mL) were individually prepared in water.

Spring water was collected from Baotu Spring in Jinan, China. The prepared sample was filtered via a 0.45-µm filter membrane and cooled to 4°C. Fe₃O₄@F-COF (100 µL 10 mg/mL) was dispersed in blank spring water (1 mL) to enrich PFECAs. The obtained mixture was incubated for 15 min at ambient temperature and magnetically separated using external magnets. The obtained supernatant was discarded, and the obtained residue was re-dispersed in 100 µL of water. The sample (1 µL) was deposited on the MALDI target for analysis. Spring water samples spiked with different concentrations of PFECAs were prepared using the above-mentioned procedure.

The serum specimens were collected from healthy human donors. Acetonitrile (1 mL) was added to 1 mL of a blank human serum sample for high-abundance protein precipitation. The mixture was shaken for a duration equal to 1 min and centrifuged for 5 min at 5000 rpm. Next, the supernatant was mixed with 100 µL of 10 mg/mL Fe₃O₄@F-COF to enrich PFECAs. The mixture, incubated for 15 min at 25°C, was magnetically separated using external magnets. The residue was then dispersed in 100 µL water, while the supernatant was discarded. The sample (1 µL) was deposited on the MALDI target for analysis. Human serum samples spiked with different concentrations of PFECAs were prepared using the above-mentioned procedure.

The experiments using animals were conducted after the approval by the Ethics Committee of Shandong Analysis and Test Center. An adult male mouse was exposed to 100 µg of GenX every day for a week. The mouse kidney was frozen and placed on a sample holder, which was introduced to a frozen table in the microtome. The mouse was sliced into 10 µm-thick slices utilizing a cryostat and a Thermo Cryostar

NX50 cryoslicer. These sliced samples were placed on indium tin oxide (ITO) glass slides. The ITO slides were dried for 15 min using a vacuum dryer before deposition. Later, 5 mL of 0.5 mg/mL $\text{Fe}_3\text{O}_4@\text{F-COF}$ dispersion was prepared in a mixture of acetonitrile: water with a volume ratio equal to 8:2. The mixture was sprayed 10 times onto the tissue surface utilizing a spray gun. The nozzle was maintained 15 cm away from the surface of the tissue while spraying. The prepared ITO slides were dried for 15 min using a vacuum dryer.

2.5. SALDI-MS and MSI analysis

Laser-assisted ionization and spatial mapping analyses were conducted using a Bruker rapifleX™ MALDI-TOF platform (Bruker Daltonics, Bremen) integrated with a Smartbeam II Nd:YAG excitation source (355 nm wavelength). Spectral acquisition involved accumulating 200-laser pulses per sampling point at a pulse frequency of 500 Hz, with detection sensitivity optimized across the 150–600 Da mass range. Spatial resolution for molecular imaging studies was configured at 100- μm step intervals. Instrumental voltage parameters were calibrated using the mentioned parameters: primary ionization potential at 20 kV, secondary ion acceleration at 19.55 kV, and reflector potentials sequentially at 22, 1.5, and 9 kV. Optical configurations included a LasAtten intensity modulator at 15% transmission efficiency, with focusing parameters fixed at Lens 11 and PIE 2.5. A controlled signal delay interval of 100 ns was implemented to enhance mass resolution.

For mouse kidneys, the irradiation protocol consisted of a single-pulse mode with a $50 \times 50 \mu\text{m}$ beam raster pattern, generating composite images across $10^4 \times 10^4 \mu\text{m}$ fields. Laser energy output was stabilized at 80% maximum capacity throughout the experiments. Post-acquisition spectral processing used Bruker Flex Analysis Suite (v4.0) for baseline correction and peak identification, while spatial data normalization was performed through total ion current adjustment using SCLS 2018b software. All instrumental configurations and computational workflows adhered to manufacturer-specified protocols to ensure analytical reproducibility.

3. Results and discussion

3.1 Characterization of $\text{Fe}_3\text{O}_4@\text{F-COF}$

The as-synthesized Fe_3O_4 nanoparticles exhibited a uniform distribution, spherical shape, and mean diameter of $\sim 150 \text{ nm}$ (Fig. 1a, 1d). F-COF exhibited an urchin-like structure, with a uniform size distribution and morphology (Fig. 1b, 1e). Scanning electron microscopy (SEM) image of $\text{Fe}_3\text{O}_4@\text{F-COF}$ revealed that the urchin-like structure of F-COF was maintained through hybridization (Fig. 1c). The transmission electron microscopy (TEM) image of $\text{Fe}_3\text{O}_4@\text{F-COF}$ exhibited core-shell structure with an even surface on the coated shell (Fig. 1f). X-ray photoelectron spectroscopy (XPS) in Figure 1g was performed to detect the chemical composition and state of elements of $\text{Fe}_3\text{O}_4@\text{F-COF}$. Nitrogen (N) 1s, iron (Fe) 2p, Fe 3p, fluorine (F) 1s, oxygen (O) 1s, and carbon (C) 1s were detected with binding energy

values of 398.7, 711.4, 33.7, 687.7, 532.1, and 284.5 eV, respectively. Figure 1h shows the F 1s fine spectrum of the $\text{Fe}_3\text{O}_4@\text{F-COF}$, indicating successful modification with fluoride [33].

Moreover, the elemental mapping images of $\text{Fe}_3\text{O}_4@\text{F-COF}$ were obtained via energy-dispersive spectroscopy (EDS) (Fig. 2a–2f). Fe, F, C, N, and O are uniformly distributed on the surface of $\text{Fe}_3\text{O}_4@\text{F-COF}$, with multiple fluorinated affinity sites [34]. Brunauer–Emmett–Teller (BET) measurement allowed to determine the surface area of Fe_3O_4 , F-COF, and $\text{Fe}_3\text{O}_4@\text{F-COF}$ as high as 113, 723, 534 m^2/g , and the main pore size distribution of $\text{Fe}_3\text{O}_4@\text{F-COF}$ was 2.6 nm in diameter (Fig. 2g). The results of BET and N_2 adsorption–desorption isotherm proved the formation of $\text{Fe}_3\text{O}_4@\text{F-COF}$, which is expected to adsorb the target material and exhibit charge transfer properties during the laser-desorption ionization (LDI) process. Furthermore, the hybridization of Fe_3O_4 and F-COF is expected to allow rapid removal of the sorbent from sample solutions using an external magnet. The magnetic hysteresis curves were measured, and the saturated magnetization values of Fe_3O_4 and $\text{Fe}_3\text{O}_4@\text{F-COF}$ were 85 and 16 emu/g, respectively (Fig. 2h). No remnant magnetization or coactivity was observed in the two magnetic hysteresis curves, indicating their superparamagnetic property. Fig. S1 depicts the FTIR spectra of F-COF, Fe_3O_4 , and $\text{Fe}_3\text{O}_4@\text{F-COF}$. The peak appearing at 1710 cm^{-1} is due to the C=O stretching vibrations of TFTA, while the peaks appearing at 446 and 568 cm^{-1} correspond to the Fe–O vibration of Fe_3O_4 . The peaks at 3420 and 1359 cm^{-1} represent N–H stretching and C–N vibrations of the triazine ring structure of TAPT, respectively. The peak representing the –C=N– stretching vibration of $\text{Fe}_3\text{O}_4@\text{F-COF}$ and F-COF appears at 1627 cm^{-1} , indicating the formation of an imine bond. Compared to Fe_3O_4 and F-COF, the UV–vis spectrum of $\text{Fe}_3\text{O}_4@\text{F-COF}$ showed a strong absorption at 300–700 nm (Fig. S2). These results proved that the formation of the $\text{Fe}_3\text{O}_4@\text{F-COF}$ enhanced the UV–vis absorbance and expected to improve the ionization efficiency of analytes in the LDI/MS process.

3.2 LDI performance of $\text{Fe}_3\text{O}_4@\text{F-COF}$

Matrices comparison: The analytical efficacy of $\text{Fe}_3\text{O}_4@\text{F-COF}$ as an inorganic matrix in laser desorption/ionization mass spectrometry (LDI-MS) was assessed through a comparative analysis of its PFECA response signals against those generated by commonly employed commercial matrices (CHCA, DAN, and DHB) as well as the individual components i.e. Fe_3O_4 and F-COF. The organic matrices CHCA, DAN, and DHB showed pronounced background interferences, which considerably reduced the ion signals of the target analytes (Fig. 3a–c). By using these matrices, only four weak PFECA-related peaks were observed. In particular, CHCA facilitated the detection of merely two compounds: GenX (m/z 329.08, $[\text{M-H}]^-$) and ADONA (m/z 377.07, $[\text{M-H}]^-$). Although DAN and DHB allowed for the identification of three PFECAs including GenX (m/z 329.08, $[\text{M-H}]^-$), EEA (m/z 345.05, $[\text{M-H}]^-$), and ADONA (m/z 377.07, $[\text{M-H}]^-$), their spectral profiles remained obscured by substantial matrix-derived noise. By contrast, both Fe_3O_4 (Fig. 3d) and F-COF (Fig. 3e) exhibited clearly resolved signals for the three PFECAs, accompanied by a noticeable reduction in background interference. Interestingly, the $\text{Fe}_3\text{O}_4@\text{F-COF}$

composite (Fig. 3f) demonstrated superior performance, delivering high-intensity analyte signals with negligible background contamination. Quantitative comparison revealed that the signal/noise (S/N) obtained using $\text{Fe}_3\text{O}_4@\text{F-COF}$ were typically 5 to 15 times higher than those achieved with conventional organic matrices. These outcomes underscore the favorable laser energy absorption and efficient charge transfer characteristics of $\text{Fe}_3\text{O}_4@\text{F-COF}$, affirming its suitability as a high-performance inorganic matrix in LDI-MS applications.

Salt tolerance of $\text{Fe}_3\text{O}_4@\text{F-COF}$: The high salt content often present in real-world samples can significantly interfere with MALDI processes, making salt tolerance a critical parameter for analyses conducted in complex environments. To assess the salt resistance of the $\text{Fe}_3\text{O}_4@\text{F-COF}$ composite in LDI-MS, varying concentrations of KCl were added into a standard mixture with three PFECAs (GenX, EEA, and ADONA). Even at a KCl concentration of 500 mM, the signal intensities of GenX, EEA, and ADONA remained at 86.1%, 89.6%, and 86.3% of their original values (Fig. 4a), respectively, indicating only moderate signal suppression. These findings demonstrate that $\text{Fe}_3\text{O}_4@\text{F-COF}$ maintains effective performance under high-salinity conditions, supporting its utility as a robust matrix for SALDI-MS detection of PFECAs in salt-rich samples.

Repeatability of $\text{Fe}_3\text{O}_4@\text{F-COF}$: Signal reproducibility is another essential criterion for evaluating the suitability of an inorganic matrix in LDI-MS applications. The shot-to-shot reproducibility was assessed, yielding relative standard deviations (RSDs) of 10.9% for GenX, 7.05% for EEA, and 11.1% for ADONA (Fig. 4b). Meanwhile, sample-to-sample reproducibility tests resulted in RSDs of 9.89% for GenX, 5.95% for EEA, and 11.3% for ADONA (Fig. 4c). The consistently low RSD values across both measurement scales confirmed that $\text{Fe}_3\text{O}_4@\text{F-COF}$ provides reliable and repeatable signal, underscoring its potential as a practical matrix for SALDI-MS-based analytical applications.

3.3 Quantitative analysis of PFECAs

The performance of $\text{Fe}_3\text{O}_4@\text{F-COF}$ as an adsorbent and matrix to detect PFECAs was evaluated in spring water and human serum samples. The water of Baotu Spring (China) is frequently consumed directly by people. The analysis of spring water holds paramount importance in public health research, as it represents a critical and direct pathway for human exposure to ubiquitous contaminants. A linearity of 0.50–500 ng/L, 0.30–500 ng/L, and 0.50–500 ng/L for GenX, EEA and ADONA in blank spring water was obtained (Fig. 5a-c). The R^2 values of the three analytes are respectively 0.9958, 0.9931, 0.9936. The limit of detection (LOD) values of GenX, EEA, and ADONA in the blank spring water (Table S1) are 0.10, 0.075, and 0.15 ng/L, while the limit of quantitation (LOQ) values are 0.35, 0.25, and 0.45 ng/L, respectively. The RSDs of 4.22–9.48% and 5.46–10.2% represent shot-to-shot and sample-to-sample, respectively. Some coexisting compounds in spring water sample are detected, and their signals had a negligible effect on the analyte signals (Fig. 5d). When each concentration of 300 ng/L of three PFECAs mixture (GenX, EEA and ADONA) was spiked, the signals were detected with $\text{Fe}_3\text{O}_4@\text{F-COF}$ as a matrix (Fig. 5e), and the signals were much higher with $\text{Fe}_3\text{O}_4@\text{F-COF}$ as a matrix and adsorbent (Fig. 5f).

After contaminated animals and plants by PFECAs enter the human body as food, harmful substances will enter the bloodstream, further contaminating the blood. They will cause damage to the blood and affect its normal function. For the blank human serum sample (Table S2), a limit of detection (LOD) of GenX, EEA and ADONA was 0.15, 0.10, 0.20 ng/L, respectively. A limit of quantitation (LOQ) of GenX, EEA and ADONA was 0.50, 0.25, 0.75 ng/L, respectively. A linearity of 0.75–500 ng/L, 0.50–500 ng/L, and 1.00–500 ng/L for GenX, EEA and ADONA was obtained. The determined RSD values for shot-to-shot and sample-to-sample are 6.18–8.65% and 7.23–10.2%, respectively.

Our method was used to determine the level of PFECAs in real samples (Table S3). The recoveries of the GenX in spring water and human serum samples were respectively in the ranges of 83.28–96.32% and 84.76–107.3%. The recoveries of the EEA in spring water and human serum samples were in the ranges of 87.34–101.3% and 83.65–114.4%, respectively. The recoveries of the ADONA in spring water and human serum samples were in the ranges of 92.36–109.4% and 83.43–107.6%, respectively. Thus, $\text{Fe}_3\text{O}_4\text{@F-COF}$ is an effective matrix for LDI-MS analysis of PFECAs in spring water and human serum samples

3.4 Spatial distribution of PFECAs in animal tissue

As a label-free analytical technique, LDI-MSI enables direct visualization of molecular spatial distribution within biological tissues without the need for complex sample pretreatment. In this work, the spatial distribution of GenX in mouse kidney sections was investigated using $\text{Fe}_3\text{O}_4\text{@F-COF}$ matrix. A series of GenX standard solutions (0.05, 0.5, 5, 25, and 50 $\mu\text{g/L}$) were spotted onto blank mouse kidney tissue at 1 μL per spot (Fig. 6a). A good linear response was achieved over the concentration range of 0.05–50 $\mu\text{g/L}$, with a linear correlation coefficient (R^2) of 0.9937 and a limit of detection (LOD) of 0.01 $\mu\text{g/L}$. There was no signal of GenX in mouse kidney of the control group as shown in Fig. 6b. The cross-sectional structure diagram of mouse kidney is depicted in Fig. 6c. The spatial distribution of GenX was revealed in the exposure group in Fig. 6d. Furthermore, we found that GenX has different degrees of distribution in different parts such as renal cortex, renal sinus, renal medulla, renal pelvis and ureter. There is less distribution of GenX in the renal cortex; this is likely due to the lack of efficient and specific renal transporters, which cannot actively "capture" and retain GenX within the cortical tubular cells. The latter functions more like a highly efficient "conduit" or "filter," allowing contaminants to pass through rapidly, ultimately reaching the downstream regions responsible for urine concentration and collection—the renal medulla, renal pelvis, and renal sinus. GenX exhibits a higher concentration in the urter and renal sinus, especially in the urter, and the core reason for its ability to adsorb contaminants lies in its unique anatomical structure. It is a "functional complex" tightly interwoven by the urinary collection system, adipose reservoirs, and vascular-lymphatic networks. The renal pelvis/calices provide exposure via the urinary pathway; the sinus fat serves as a reservoir for lipophilic distribution; and the blood and lymphatic vessels offer pathways for transport and capture. This enables the renal sinus to function not merely as a passage for urine outflow, but as a key site capable of effectively adsorbing and enriching various contaminants. The high-resolution imaging of the distribution of GenX using $\text{Fe}_3\text{O}_4\text{@F-COF}$ as a matrix demonstrated that the $\text{Fe}_3\text{O}_4\text{@F-COF}$ -assisted LDI-MSI method not only effectively maps the

spatial distribution of PFECAs in biological tissues, but also provides quantitative capability for assessing their concentration levels in the kidney.

3.5 Possible mechanism of $\text{Fe}_3\text{O}_4@\text{F-COF}$ for enhanced SALDI-MS performance

The effective LDI-MS performance of $\text{Fe}_3\text{O}_4@\text{F-COF}$ is owing to the following reasons

- i. The synergistic effect of the Schottky junction and internal electric field prevents electron–hole recombination. The position of the bonding orbitals in $\text{Fe}_3\text{O}_4@\text{F-COF}$ is above the Fermi level, facilitating electron acceptance (Fig. 7a). A Schottky barrier develops at the $\text{Fe}_3\text{O}_4\text{-F-COF}$ interface when they come in contact. The electrons under laser radiation are excited and transferred from the conduction band (CB) of F-COF to Fe_3O_4 . Thus, a positively charged area is formed in F-COF. The valence band (VB) of F-COF comprises the generated holes, with the formation of a negatively charged region close to Fe_3O_4 . This phenomenon boosts the transfer of photogenerated carriers across the Schottky barrier. The created internal electric field propels the spatial separation of electrons and holes, remarkably prolonging the charge carrier lifetime.
- ii. Specific recognition via fluorine-fluorine interactions. The $\text{Fe}_3\text{O}_4@\text{F-COF}$ matrix functions as a fluorinated sorbent that enhances both selectivity and detection sensitivity toward PFECAs through strong F-F interaction affinity. PFECAs exhibit a marked tendency to phase-separate from hydrocarbon-rich environments, thereby reducing nonspecific interactions with non-fluorinated species (Fig. 7b). This selective enrichment not only improves ionization efficiency but also elevates overall sensitivity of the developed method.
- iii. High photothermal and photochemical energy conversion/transfer. The desorption and ionization capabilities, governed by photothermal and photochemical conversion, were assessed with sodium tetraphenylborate and juglone as probes. $\text{Fe}_3\text{O}_4@\text{F-COF}$ showed the strongest desorption signal at m/z 319.06 $[\text{M-H}]^-$ for tetraphenylborate (Fig. 7c, 7d). For ionization, juglone acted as an electron acceptor, generating characteristic ions such as m/z 174.03 ($\text{M}^\cdot$) and 173.02 ($[\text{M-H}]^-$), among others at m/z 329.02, 345.02, and 346.03 (Fig. 7e); these findings are consistent with our earlier work [35]. The superior ionization capacity of $\text{Fe}_3\text{O}_4@\text{F-COF}$ was further validated by its total ion intensity metrics (Fig. 7f), confirming its enhanced and balanced functionality in both key processes. Thus, the $\text{Fe}_3\text{O}_4@\text{F-COF}$ matrix features stronger desorption and ionization ability.

4. Conclusion

This work demonstrates that the core-shell $\text{Fe}_3\text{O}_4@\text{F-COF}$ functions as a dual-functional platform that integrates efficient sample enrichment with high-performance LDI-MS and MSI analysis, offering a streamlined and sensitive approach for PFECA detection in complex matrices. It exhibited higher sensitivity and lower background interference peaks than the commonly used organic matrices (CHCA, DAN, and DHB) in the detection of PFECAs (GenX, EEA, and ADONA) by LDI-MS. The $\text{Fe}_3\text{O}_4@\text{F-COF}$ matrix exhibited high repeatability, salt resistance, and allowed the PFECAs to be detected at a low

detection limit. This matrix exhibited excellent performance in (i) SALDI-MS for quantifying PFECAs in spring water and human serum samples, and (ii) SALDI-MSI for detecting GenX distribution in animal kidney samples. This work also explored a potential mechanism of LDI processes with $\text{Fe}_3\text{O}_4@\text{F-COF}$. $\text{Fe}_3\text{O}_4@\text{F-COF}$ should have potential as an inorganic matrix in the efficient analysis of other PFECAs in food and biological samples.

Declarations

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Competing interest

The authors declare no competing interests.

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Author Contribution

Yanfang Zhao: Methodology, Writing—original draft; Jun Wang: Investigation; Rabah Boukherroub: Methodology, Language edit; Ke Jia & Sabine Szunerits: Methodology; Lu Liu & Xiangrong Chen: Formal analysis; Xiangfeng Chen: Project administration, Funding acquisition.

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Data availability

No datasets were generated or analysed during the current study.

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Figures

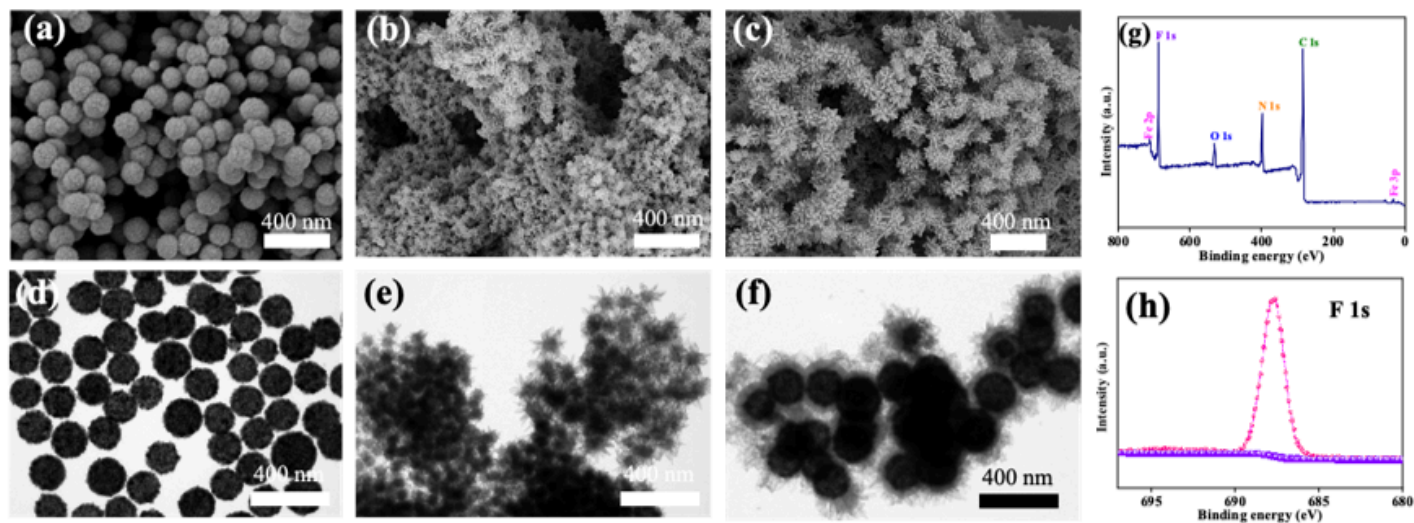


Figure 1

SEM of (a) Fe₃O₄, (b) F-COF and (c) SEM and Fe₃O₄@F-COF; TEM images of (d) Fe₃O₄, (e) F-COF and (f) Fe₃O₄@F-COF; (g) XPS survey scan of Fe₃O₄@F-COF; (h) XPS high-resolution spectrum of F 1s of Fe₃O₄@F-COF

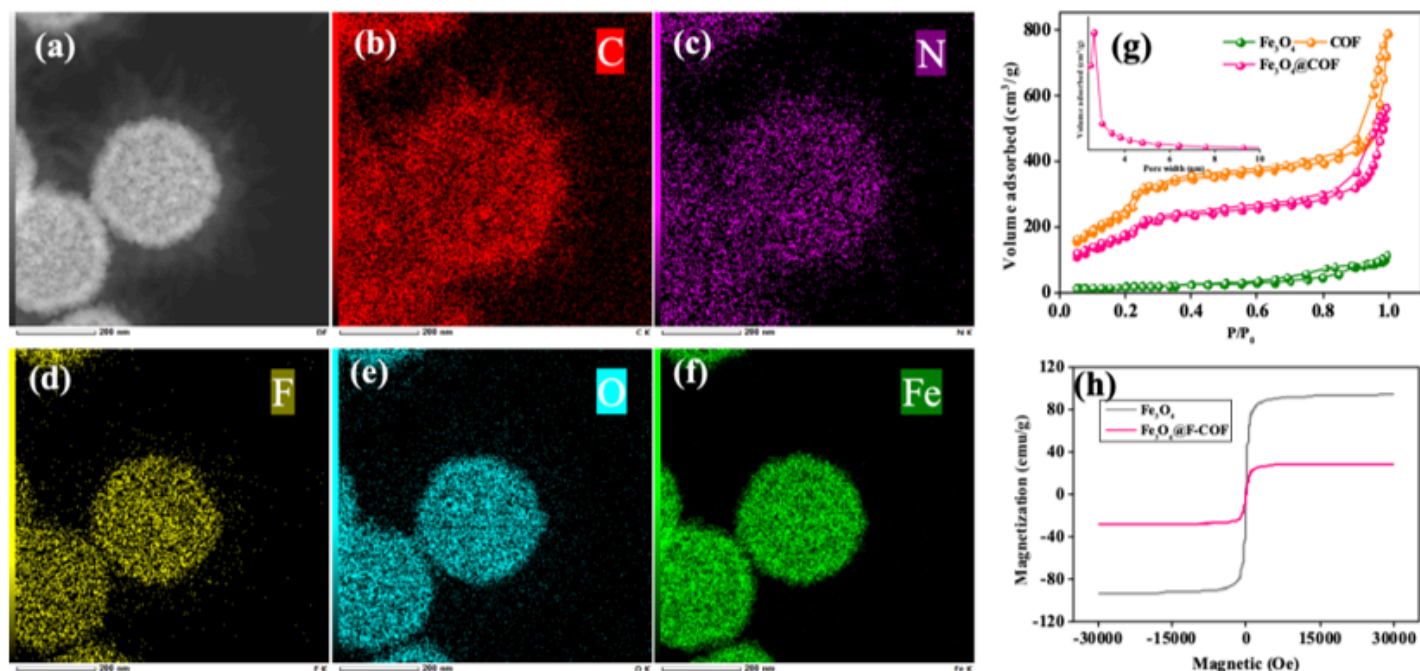


Figure 2

(a-f) Elemental mapping images of $\text{Fe}_3\text{O}_4@\text{F-COF}$; (g) Nitrogen adsorption-desorption isotherms of Fe_3O_4 , F-COF, and $\text{Fe}_3\text{O}_4@\text{F-COF}$; (h) magnetic curves of Fe_3O_4 and $\text{Fe}_3\text{O}_4@\text{F-COF}$

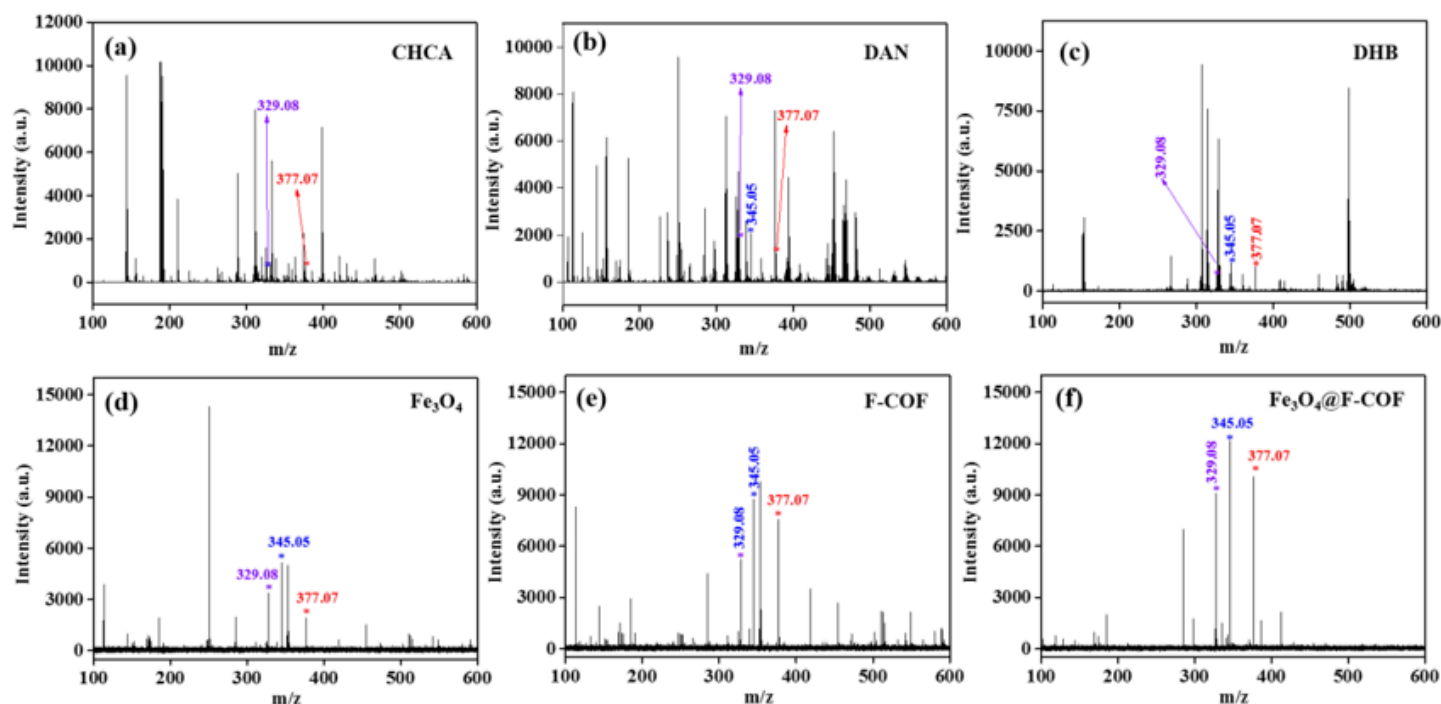


Figure 3

The mass spectra of PFECAs (GenX, EEA and ADONA) recorded employing (a) CHCA, (b) DAN, (c) DHB, (d) Fe_3O_4 , (e) F-COF, and (f) Fe_3O_4 @F-COF matrices. The concentration of each analyte=100 ng/L

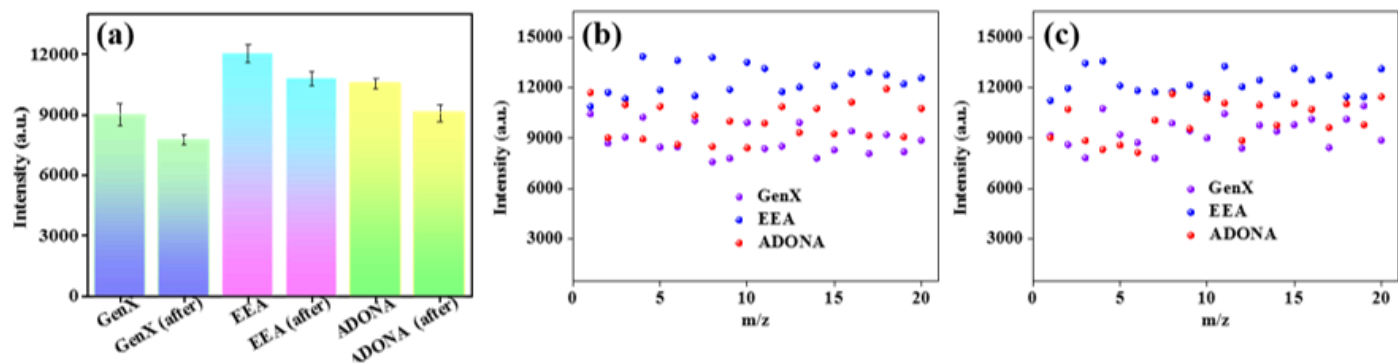


Figure 4

(a) MS intensity of PFECAs (GenX, EEA and ADONA) adopting Fe_3O_4 @F-COF as the matrix for SALDI-MS at different KCl concentrations in negative ion mode, MS intensity values of PFECAs (GenX, EEA and ADONA) from (b) 20 locations in one sample, and (c) 20 samples. Each PFECA concentration=100 ng/L

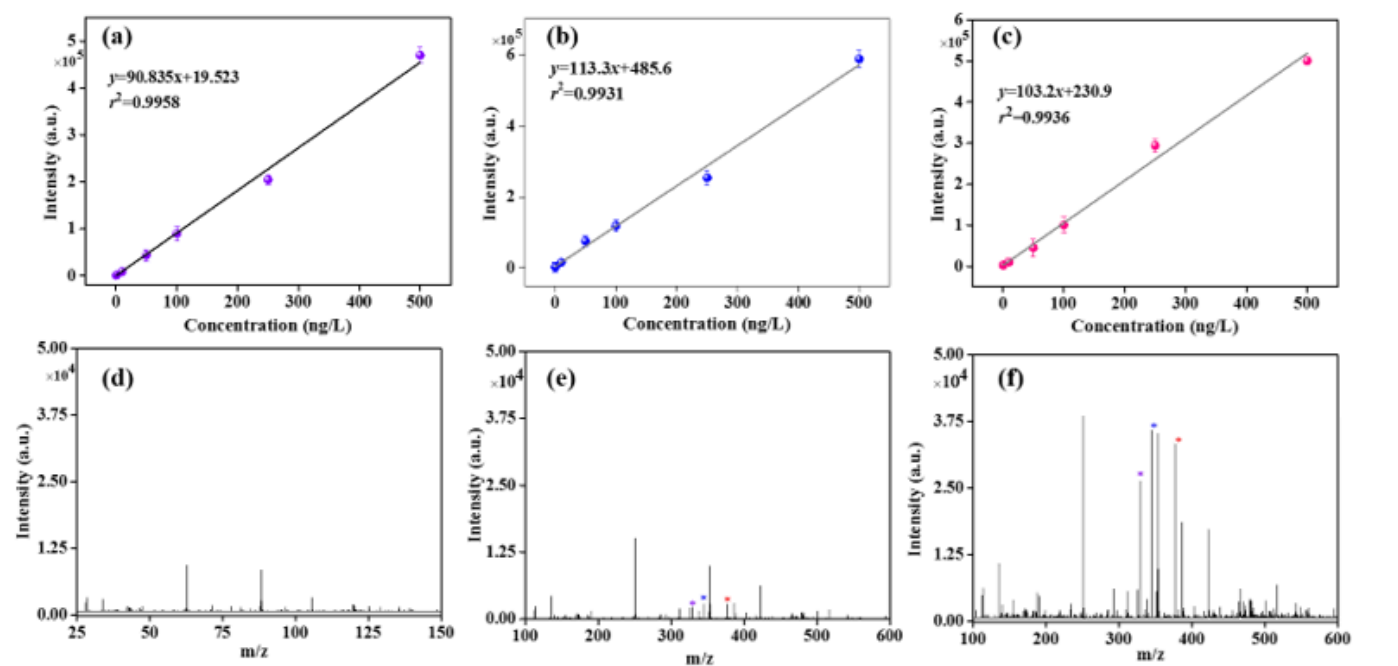


Figure 5

Calibration curve obtained by plotting the (a) GenX, (b) EEA, and (c) ADONA concentration versus MS signal intensity; The recorded mass spectra for the (d) blank spring water sample using $\text{Fe}_3\text{O}_4\text{@F-COF}$ as a matrix, (e) blank spring water sample spiked with PFECAs (GenX, EEA and ADONA), (f) after enrichment spiked with PFECAs (GenX, EEA and ADONA) with $\text{Fe}_3\text{O}_4\text{@F-COF}$

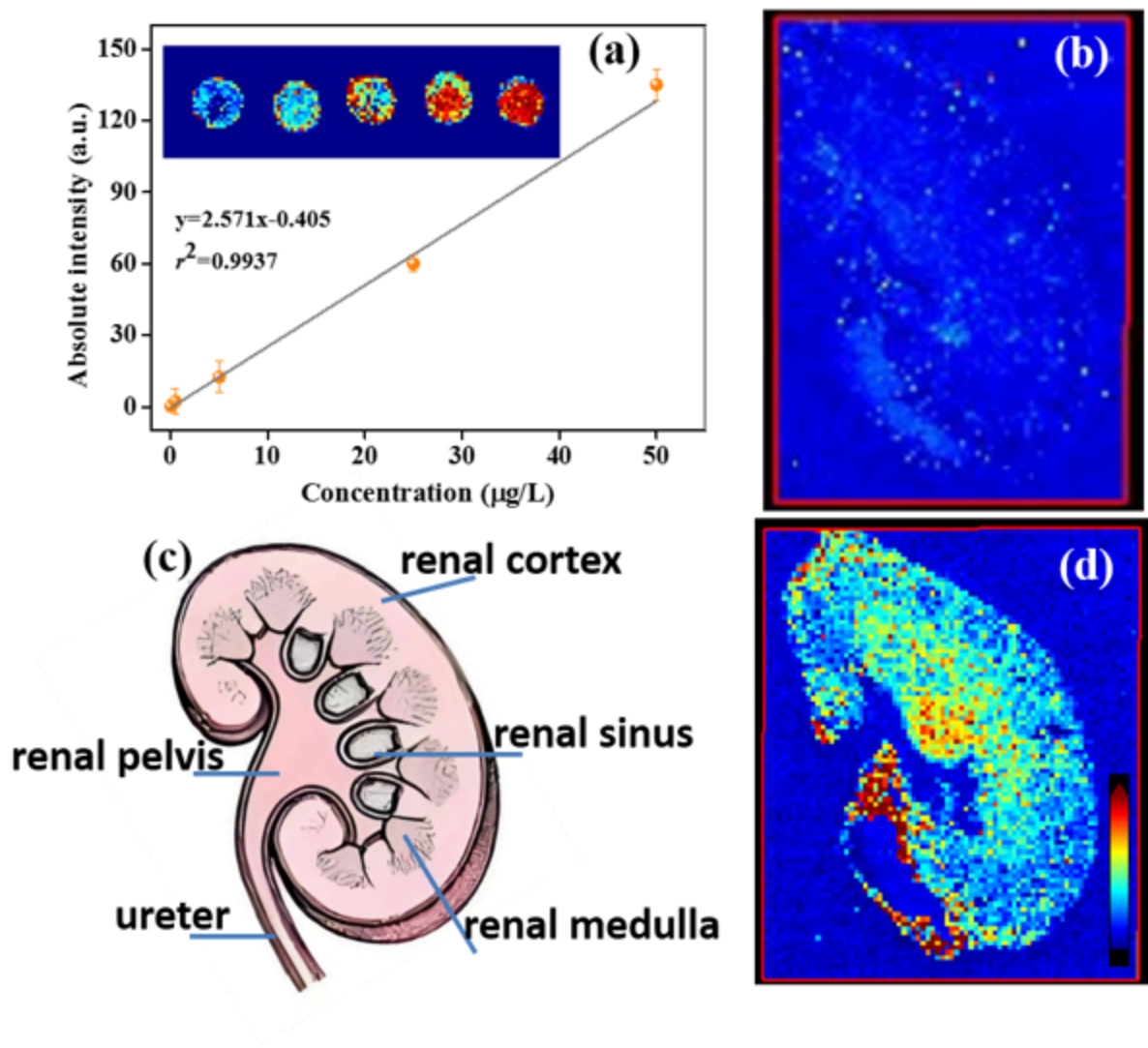


Figure 6

(a) SALDI-MSI for different concentrations of GenX and calibration curve for GenX using $\text{Fe}_3\text{O}_4\text{@F-COF}$ matrix; (b) blank rat kidney; (c) cross-sectional structure diagram of mouse kidney; (d) the acquired SALDI-MS images for the spatial distribution of GenX in rat kidney using $\text{Fe}_3\text{O}_4\text{@F-COF}$ matrix

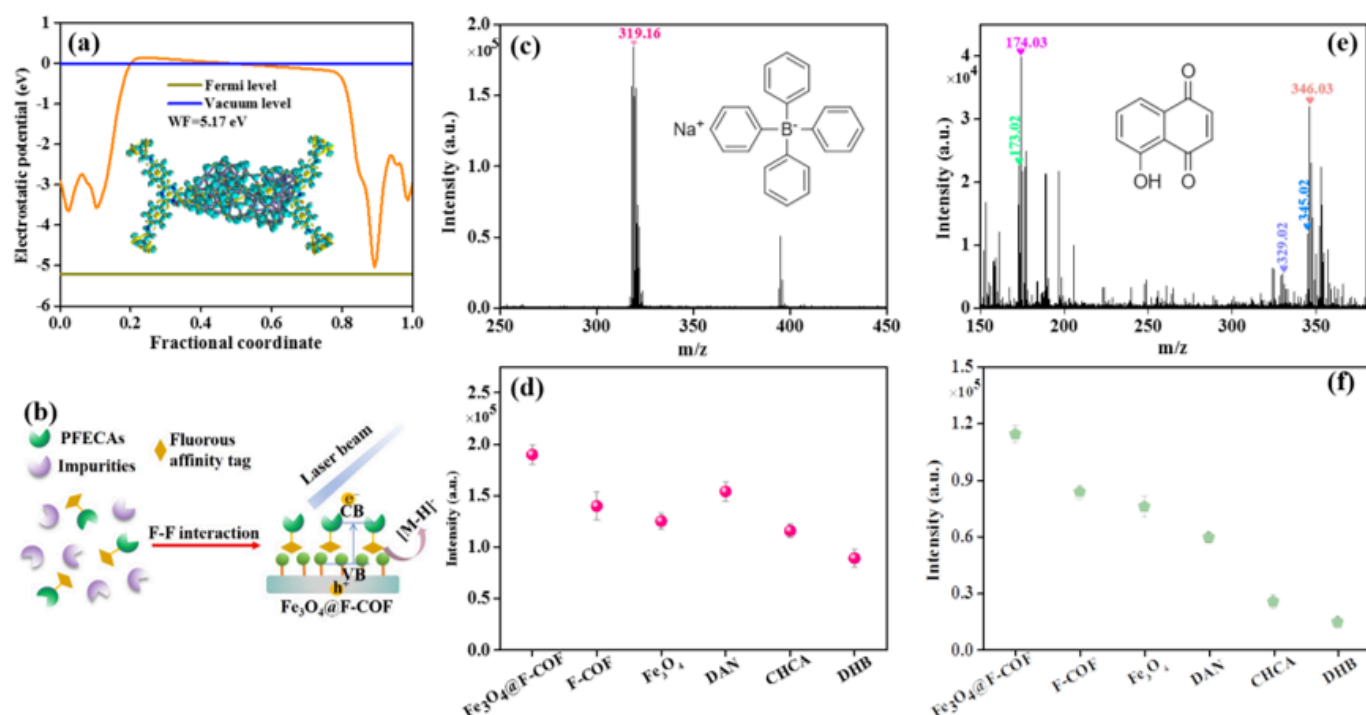


Figure 7

(a) The work function and charge density difference of $\text{Fe}_3\text{O}_4@\text{F-COF}$; (b) desorption/ionization under the F-F interaction; (c) LDI mass spectra of 1 mM terphenylborate recorded with $\text{Fe}_3\text{O}_4@\text{F-COF}$; (d) Ion intensity of MS peaks at m/z 319.16 with various substrates (n=5); (e) LDI mass spectra of 5 mM juglone acquired using $\text{Fe}_3\text{O}_4@\text{F-COF}$; (f) Total ion intensity of MS peaks at 173.02, 174.03, 329.02, 345.02, and 346.03 with various substrates (n=5).

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