

Polarization-Induced Multimode Terahertz Metamaterial for High-Sensitivity and Label-free Drug Monitoring

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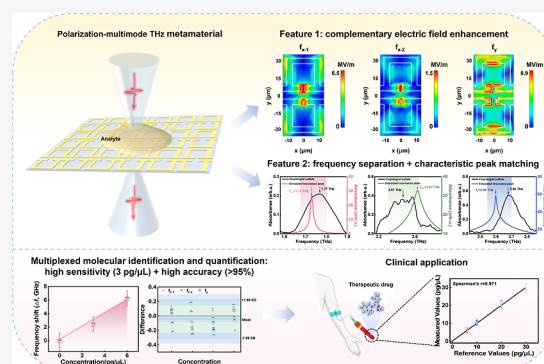


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ABSTRACT: Therapeutic drug monitoring (TDM) requires analytical technologies with high sensitivity, accuracy, and efficiency. Terahertz (THz) metamaterials offer strong THz electromagnetic field–analyte interactions and enable label-free detection with minimal sample consumption. However, most conventional designs rely on a single mode resonance (either single peak or multiple peaks), which limits modal diversity and thus causes in peak instability, sensitivity fluctuations, and a lack of real-time error validation. In this work, we propose a polarization-induced multimode THz metamaterial sensor that enable highly sensitive and accurate detection for TDM applications. By selectively exciting orthogonal electromagnetic modes under *x*- and *y*-polarized THz waves, the sensor generates multiple decoupled resonances with complementary field localization and well-separated spectral peaks. Each resonance mode couples to a distinct molecular vibration of the analyte, enabling multiplexed molecular identification and quantification. Clopidogrel sulfate, a widely used antithrombotic drug, was selected as a representative analyte to validate the sensor performance. The resonance peaks of the polarization-induced multimode sensor were precisely adjusted to match the drug's characteristic absorption bands. An ultralow limit of detection (LOD) of 3.0 pg/μL was achieved, representing a 1000-fold sensitivity improvement over conventional HPLC methods, while maintaining over 95% consistency. When applied to human blood samples, the sensor achieved 93.7% accuracy and a 5 min detection time per sample (postpretreatment), demonstrating its potential for rapid TDM. Overall, the polarization-induced multimode THz metamaterial offers a highly sensitive, accurate, and efficient platform for trace-level drug detection, providing a promising solution for personalized medication management.



INTRODUCTION

Therapeutic drug monitoring (TDM) is essential for individualized therapy,¹ as it allows timely assessment of plasma drug concentrations to optimize treatment regimens, improve therapeutic efficacy, and reduce adverse effects.² TDM is particularly critical for drugs with narrow therapeutic windows or high interindividual pharmacokinetic variability. For example, phenytoin, an antiepileptic agent, requires close monitoring to prevent toxicity or subtherapeutic exposure.^{3,4} Cisplatin, a potent chemotherapeutic agent with dose-limiting nephrotoxicity, requires precise monitoring of blood concentrations to ensure antitumor efficacy while avoiding renal damage.^{5,6} Clopidogrel bisulfate, an antithrombotic agent, requires real-time monitoring to reduce risks of thrombosis and bleeding complications.^{7,8} However, conventional detection techniques, such as chromatography, immunoassays, and electrochemical methods, often suffer from limitations including complex sample preparation,^{9,10} insufficient sensitivity or accuracy,^{11–13} thus restricting their widespread clinical application.^{14,15} Therefore, there is an urgent need for

ultrasensitive, accurate, and efficient detection technologies to address the clinical demands of TDM.

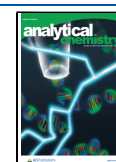
Terahertz (THz) radiation, spanning 0.1 to 10 THz,¹⁶ has attracted growing interest in biomedical applications because of its nonionizing nature and sensitivity to molecular vibrations.^{17–21} Incorporating metamaterials into THz spectroscopy further improves its potential for bioanalysis,^{22–25} as the localized electromagnetic resonances supported by metamaterials strengthen the interaction between THz radiation and target analytes.^{26,27} This approach enables trace-level bioanalysis.^{28–31} However, conventional THz metamaterial sensors often rely on a single resonant peak, which limits their sensitivity and repeatability in complex biological environments.^{32,33} Recent advances have introduced

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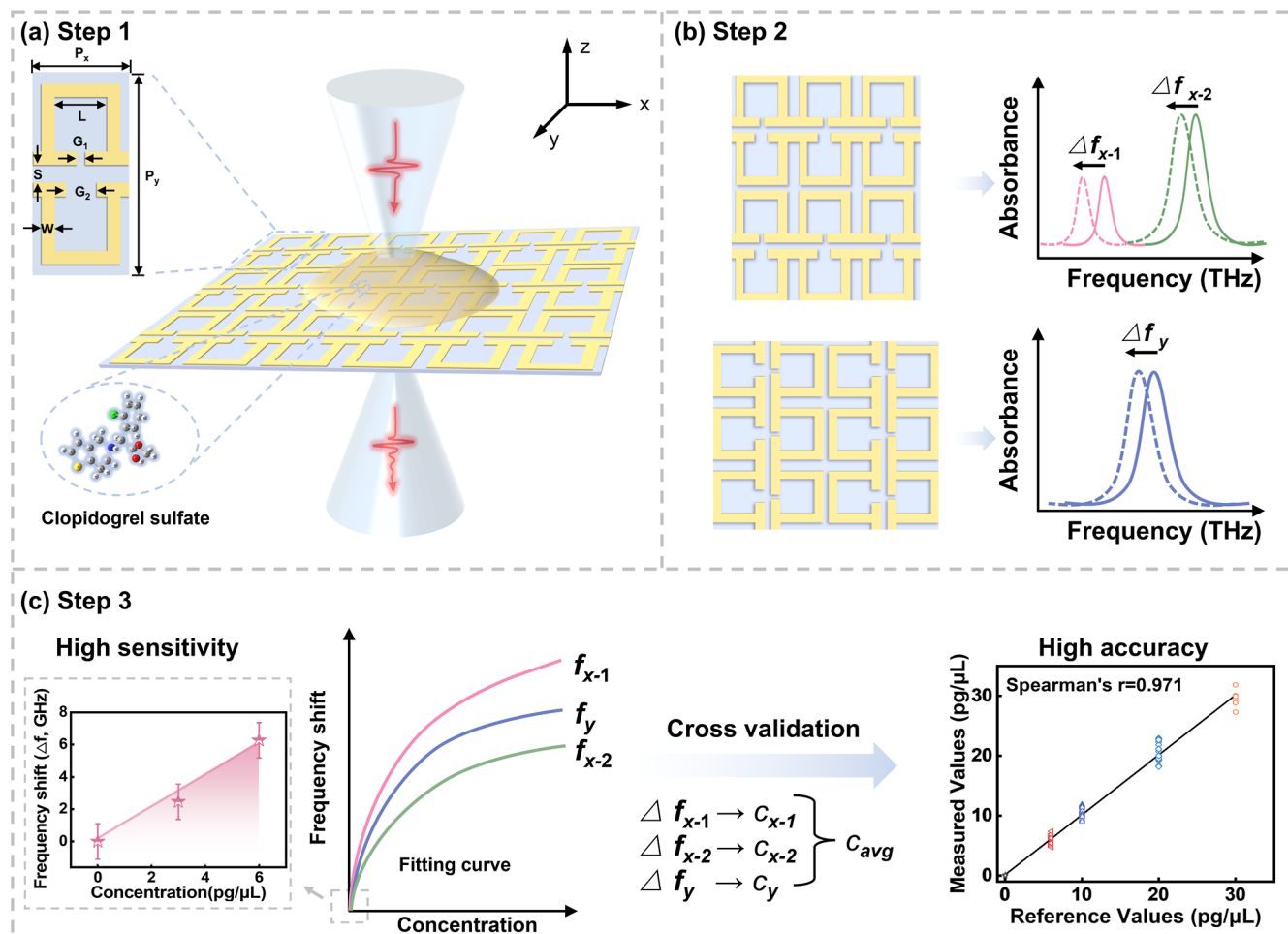


Figure 1. Schematic illustration of the polarization-induced multimode THz metamaterial sensor for therapeutic drug monitoring. (a) Unit cell design featuring a ring–chain-linked resonator structure, with clopidogrel sulfate as the representative analyte. (b) The sensor generates three spectrally separated resonance peaks with spatially complementary field enhancement regions. Each resonance peak corresponds to characteristic absorption peaks of the analyte, enabling multiplexed identification. (c) Quantification of the analyte is achieved by analyzing polarization-dependent resonance shifts. Cross-validation between independent resonance shifts improves detection sensitivity and accuracy.

metamaterials with multiple resonance peaks.^{34–36} However, these multimode designs typically rely on geometric modifications of a single resonator type. As a result, the resonances are generally excited under the same polarization and originate from a single mode mechanism. This often leads to overlapping resonance peaks and spatially coincident field enhancement regions, which in turn induce intermode crosstalk and thereby reduce both sensitivity and accuracy.

To address these challenges, we propose a polarization-induced multimode THz metamaterial sensor. This sensor consists of ring–chain-linked resonators that support distinct resonant modes under *x*- and *y*-polarized THz waves (Figure 1a). Unlike conventional multimode metamaterial sensors, our sensor generates three spectrally well-separated peaks with spatially complementary field enhancement regions, enabling each resonant mode to act as an independent sensing channel (Figure 1b). By providing cross-validation across the multiple modes, this sensor can reduce errors from nonuniform analyte distribution and thereby improve both detection sensitivity and accuracy (Figure 1c). Using the antithrombotic drug clopidogrel sulfate as a representative analyte, we reached pg/ μ L-level detection limits. The quantitative results obtained from the three sensing channels exhibit good agreement with

reference values. These results confirm that our sensor synergistically enhances sensitivity and accuracy in TDM.

MATERIALS AND METHODS

Quantum Chemical Calculation for Clopidogrel Sulfate. To predict the characteristic absorption peaks of clopidogrel sulfate in the 1–4 THz range, quantum chemical calculations were performed. The initial molecular structure was obtained from the Chemical Book database (ID: CB1341210) and imported into Gaussian 09W software,³⁷ which is widely used for vibrational spectral analysis.^{38–40} The DFT calculations were carried out using the B3LYP/3-21G basis set to optimize the molecular geometry and calculate vibrational frequencies.^{41–45} All calculated frequencies were Gaussian-broadened with the fwhm of 4 cm^{-1} to simulate the theoretical spectrum. The vibrational modes corresponding to each peak were further analyzed to assign the spectral features.

Electromagnetic Simulation for THz Metamaterial. The geometry of the proposed THz metamaterial is shown in Figure 1a. Each unit cell consists of a quartz substrate (dielectric constant: 3.9, thickness: 500 μm) and two gold ring–chain-linked resonators.²⁶ The geometric parameters of the gold resonators are as follows: $L = 20 \mu\text{m}$, $W = 5 \mu\text{m}$, $S = 7$

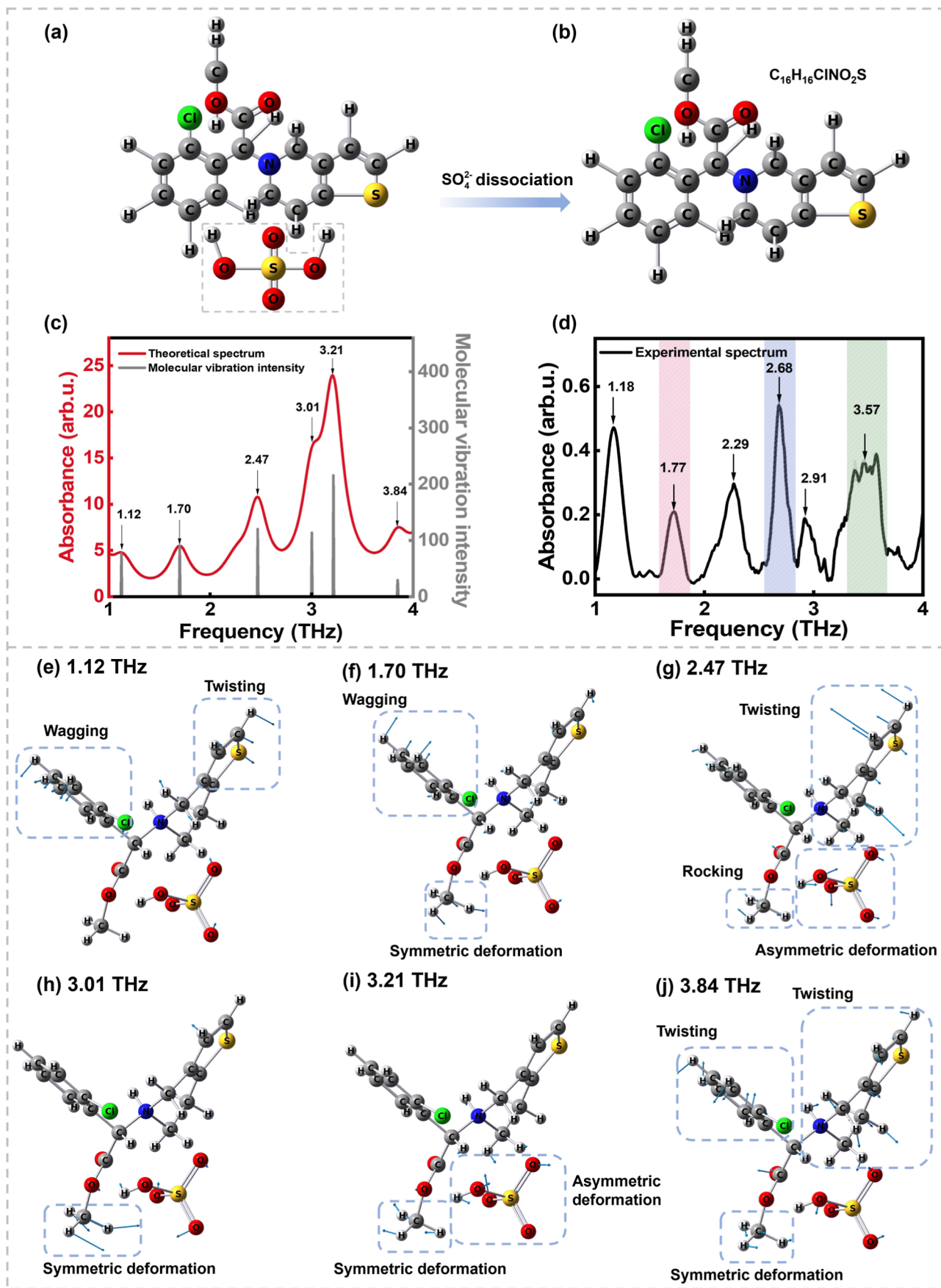


Figure 2. Theoretical and experimental THz spectra of clopidogrel sulfate. Molecular structure of clopidogrel sulfate (a) before and (b) after hydrolysis, (c) theoretical THz absorption spectrum of clopidogrel sulfate based on DFT calculations (gray lines: predicted vibration modes), (d)

Figure 2. continued

Measured THz absorption spectrum of clopidogrel sulfate in the 1–4 THz region, (e–j) vibration modes corresponding to 1.12, 1.70, 2.47, 3.01, 3.21, and 3.84 THz peaks, with vectors representing vibration directions and intensities.

μm , $G_1 = 3 \mu\text{m}$, and $G_2 = 5 \mu\text{m}$, respectively. The unit cell periodicities are $37 \mu\text{m}$ along x -direction (P_x) and $74 \mu\text{m}$ along y -direction (P_y), respectively. Numerical simulations were performed using COMSOL Multiphysics (version 6.2). Floquet periodic boundary conditions were applied along the x - and y -directions, while a perfect matching layer was used as the absorption boundary along the z -direction. The excitation field was a plane wave propagating along the z -direction. To simulate the effect of clopidogrel sulfate on the metamaterial, a dielectric layer (refractive index = 1.3) with varying thicknesses (0, 0.5, 1, 1.5, and $2 \mu\text{m}$) was attached to the metamaterial surface. Field monitors were placed at the characteristic absorption frequencies of clopidogrel sulfate (1.77, 2.68, and 3.57 THz) to monitor electric field variations.

Material and Sample Preparation. Materials. Clopidogrel sulfate ($\text{C}_{16}\text{H}_{16}\text{ClNO}_2\text{S}\cdot\text{H}_2\text{SO}_4$, CAS: 120202-66-6, purity $\geq 98\%$) and dimethyl sulfoxide (DMSO, CAS: 167-68-5, purity $\geq 99\%$) were purchased from Shanghai Aladdin Biochemical Technology Co. Ltd. Potassium dihydrogen phosphate (CAS: 7778-77-0, analytical grade) was purchased from Shanghai Macklin Biochemical Technology Co., Ltd. Methanol (CAS: 67-56-1, HPLC grade) and acetonitrile (CAS: 75-05-8, HPLC grade) were obtained from Sigma-Aldrich (Shanghai) Trading Co., Ltd. All reagents were used as received without further purification.

Solid Samples for Qualitative Analysis. 6 mg of (S)-(+)-clopidogrel sulfate was finely ground and compressed into a 6 mm-diameter tablet at 10 MPa for 4 min. The resulting tablet has smooth and parallel surfaces, with material loss less than 1%. This tablet was stored at 4°C before THz measurement.

Solution Samples for Quantitative Analysis. To cover the reported concentration range of clopidogrel sulfate in human blood,⁴⁶ a series of solutions ranging from 3 pg/ μL to 40 $\mu\text{g}/\mu\text{L}$ were prepared. Briefly, 40 mg of (S)-(+)-clopidogrel sulfate was dissolved in 1 mL of DMSO to prepare a stock solution, which was then diluted to obtain concentrations of 40, 30, 20, 15, 10, 6, 4, 1.5, 0.3, 0.03, 0.003, and 0.0003 $\mu\text{g}/\mu\text{L}$. A 20 μL aliquot of each solution was dropped onto the THz metamaterial sensor and dried under vacuum to form a uniform thin film for THz measurement. For validation, selected concentrations (3 pg/ μL , 6 pg/ μL , 3 ng/ μL , 6 ng/ μL , 9 ng/ μL and 12 ng/ μL) were analyzed using both THz metamaterial sensor and HPLC method.

Blood Samples for THz Analysis. As clopidogrel sulfate is an exogenous compound, it does not naturally occur in the human body. To evaluate the reliability of the THz metamaterial sensor in biological matrices, human blood samples were spiked with clopidogrel sulfate at physiologically relevant concentrations.

Human blood was collected from healthy volunteers at Changhai Hospital with informed consent. Ethical approval was granted by the Ethics Committee of Changhai Hospital (protocol code CHEC2022-113, 6 July 2022), in compliance with the Declaration of Helsinki and relevant national guidelines. Proteins were removed from the blood samples using organic solvent precipitation. In brief, blood was mixed with acetonitrile at a 1:3 (v/v) ratio, vortexed for 30 s, and

centrifuged at 15,000 rpm for 11024utes at 4°C . The supernatant, containing small endogenous molecules, was collected as the blood matrix. Clopidogrel sulfate was dissolved in DMSO and mixed with the blood matrix a 1:1 (v/v) ratio, resulting in final concentrations of 0, 6, 10, 20, and 30 pg/ μL . These samples were labeled as Group 1 to Group 5 for subsequent THz analysis.

Experimental Methods. THz Measurement. A 20 μL droplet of each prepared sample was deposited onto the THz metamaterial sensor and dried to form a uniform film. THz absorption spectra (1–4 THz) were collected using a commercially available THz spectrometer (TAS7400, Advantest Co., Ltd.), with a spectral resolution of 1.9 GHz and 1024 scanning averages. To minimize water vapor interference, all THz measurements were conducted at 20°C under controlled humidity (1%–3%). Each sample was measured four times to ensure repeatability.

HPLC Measurement. Detailed HPLC procedures are provided in the Supporting Information (Text S1).

RESULTS AND DISCUSSION

THz Absorption Characteristics of Clopidogrel Sulfate. Following oral administration, clopidogrel sulfate undergoes enzymatic hydrolysis, generating clopidogrel, its pharmacologically active thiol metabolite (Figure 2a,b). The THz absorption features of clopidogrel sulfate (1–4 THz) were investigated through both density functional theory (DFT) simulations and THz measurements. DFT simulations predicted six vibrational peaks at 1.12, 1.70, 2.47, 3.01, 3.21, and 3.84 THz (Figure 2c). The measured THz absorption spectrum exhibited corresponding peaks at 1.18, 1.77, 2.29, 2.68, 2.91, and 3.57 THz (Figure 2d). All frequency deviations were within 0.33 THz (Table S2), confirming good agreement between simulation and experiment.

Each measured peak was further assigned based on its vibrational origin derived from DFT simulations. The 1.18 THz peak corresponds to the theoretical 1.12 THz mode, involving wagging of the chloro-substituted phenyl ring and twisting of the thiophene moiety (Figure 2e). The 1.77 THz peak corresponds to the theoretical 1.70 THz mode, attributed to the wagging of the phenyl ring and symmetric deformation of the methyl group (Figure 2f). The 2.29 THz peak corresponds to the theoretical 2.47 THz mode, related to the twisting of thienopyridine scaffold, rocking of the methyl group, and antisymmetric deformation of the sulfate group (Figure 2g). The 2.68 THz peak corresponds to the theoretical 3.01 THz mode, arising from the symmetric stretching of the methyl group (Figure 2h). The 2.91 THz peak corresponds to the theoretical 3.21 THz mode, attributed to the deformation of both methyl and sulfate groups (Figure 2i). The 3.57 THz peak corresponds to the theoretical 3.84 THz mode, originating from twisting of both phenyl and thienopyridine rings, along with symmetric deformation of the methyl group (Figure 2j).

The peaks at 1.77, 2.68, and 3.57 THz were selected as target frequencies in the THz metamaterial design, as they correspond to distinct functional groups within the drug

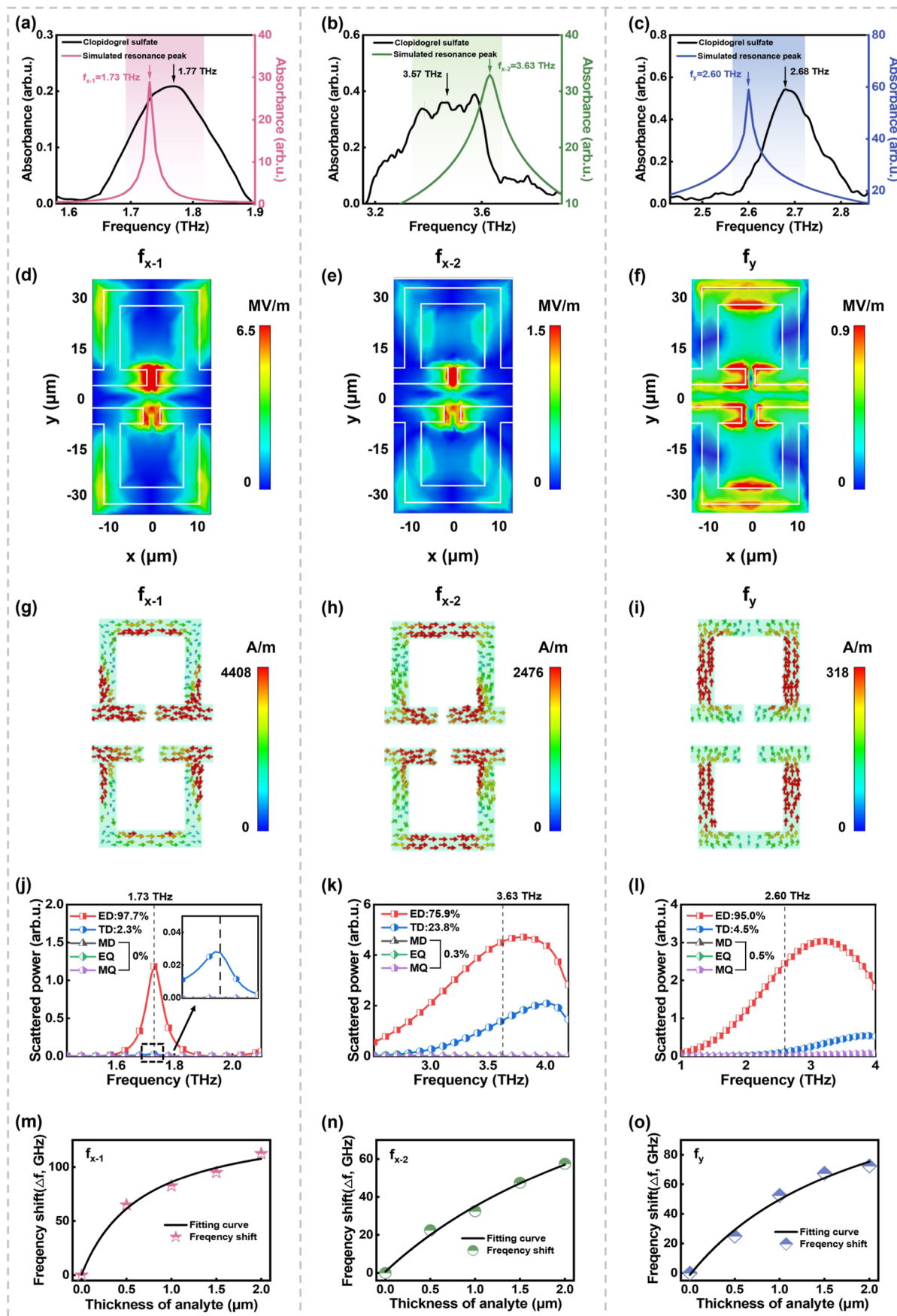


Figure 3. Resonance characteristics of the polarization-induced multimode THz metamaterial sensor. (a–c) Simulated resonance peaks (f_{x-1} , f_{x-2} , and f_y) spectrally matched to the characteristic absorption peaks of clodipogrel sulfate. (d–f) Electric field distributions, (g–i) Surface current

Figure 3. continued

distributions, and (j–l) Multipole decomposition for f_{x-1} , f_{x-2} , f_y resonances. (m–o) Nonlinear redshift behavior of the three resonances (f_{x-1} , f_{x-2} , and f_y) with increasing analyte thickness (refractive index = 1.3).

molecule, including the chloro-substituted phenyl ring, the thienopyridine scaffold, and the sulfate groups. By selectively enhancing these vibrational modes, the THz metamaterial sensor can capture multidimensional molecular information, enabling more robust and specific identification of clopidogrel sulfate, even in the presence of structurally similar compounds or complex biological matrices.

Resonance Mechanisms of Polarization-Induced Multimode THz Metamaterial Sensor. To achieve selective detection of clopidogrel sulfate, the THz metamaterial sensor was designed to resonate at frequencies corresponding to the drug's characteristic absorption peaks (1.77, 2.68, and 3.57 THz). The simulated spectra of the metamaterial under x - and y -polarized THz excitation are shown in Figure 3a–c. Under x -polarized excitation, two resonances appear at 1.73 and 3.63 THz (f_{x-1} and f_{x-2}), closely matching the molecular absorption peaks at 1.77 and 3.57 THz (Figure 3a,b). Under y -polarized excitation, a resonance peak (f_y) appears at 2.60 THz, corresponding to the molecular absorption peak at 2.68 THz (Figure 3c).

To elucidate the underlying resonance mechanisms, we systematically investigated the mode characteristics of f_{x-1} , f_{x-2} , and f_y by simulating their electric field distributions, surface current patterns, and multipole contributions (Figure 3d–l).

At the f_{x-1} resonance (1.73 THz), the electric field is strongly localized at the gap region, forming a high-energy-density hotspot (Figure 3d). The corresponding surface current exhibits a typical closed-loop distribution (Figure 3g). Multipole decomposition (Figures 3j and S2a) reveals a dominant electric dipole contribution (ED: 97.7%) with a small toroidal dipole contribution (TD: 2.3%). The frequencies of the ED and TD components closely match f_{x-1} resonance, indicating that the f_{x-1} resonance arises from a strongly coupled ED–TD hybrid mode.

In contrast, the f_{x-2} resonance (3.63 THz) exhibits a more uniform field enhancement, with hotspots localized near the resonator gaps (Figure 3e). The surface current is concentrated between the cantilevers and gaps, forming a dipole-like symmetric distribution along the x -axis (Figure 3h). Multipole decomposition (Figures 3k and S2b) shows that the f_{x-2} mode is also ED-dominated (75.9%) with a TD component (23.8%). However, the frequencies of ED and TD components are shifted from f_{x-2} resonance by 0.17 THz and 0.39 THz, suggesting a weakly coupled ED–TD hybrid mode. Consequently, the f_{x-2} resonance exhibits weaker localized field energy and a broader full width at half-maximum (fwhm) than the f_{x-1} resonance (Table S3).

Different from the x -polarized resonances, the f_y resonance (2.60 THz) exhibits field hotspots at the resonator junction (Figure 3f). This hotspot has the largest area among the three resonances, and is spatially complementary to those of the x -polarized resonances. The surface current is mainly distributed along the y -axis cantilevers (Figure 3i). Multipole decomposition (Figures 3l and S2c) shows that f_y resonance is dominated by the ED contribution (95.0%) with a small TD contribution (4.5%). Both components exhibit obvious frequency deviates from the f_y resonance (0.59 THz and 1.28 THz), confirming that it is an ED mode. Although the

field confinement of f_y resonance is weaker than that of f_{x-1} and f_{x-2} , its effective sensing area is the largest.

To evaluate the sensing performance of the proposed metamaterial sensor, we numerically investigated its sensitivity by varying both analyte thickness and refractive index. First, we simulated the frequency shifts of the three resonance peaks under varying analyte thicknesses (0–2 μm) at a fixed refractive index of 1.3 (consistent with the dielectric property of clopidogrel sulfate). All three resonances exhibited a nonlinear redshift trend as the analyte thickness increased, with the most significant redshifts observed in the 0–0.5 μm (Figure S3a–c). This indicates that the sensor has high sensitivity at low concentrations. Among the three resonances, f_{x-1} showed the largest redshift, followed by f_y and f_{x-2} (Figure 3m–o), revealing a theoretical sensitivity order of $f_{x-1} > f_y > f_{x-2}$. Furthermore, we evaluate the sensor's versatility by varying the refractive indices at a fixed analyte thickness of 0.5 μm . The refractive index sensitivity (GHz/RIU) and figure of merit (FoM) were calculated for each resonance. The results showed that both refractive index sensitivity and FoM follow the order of $f_{x-1} > f_y > f_{x-2}$ (Table S3), confirming that f_{x-1} as the most sensitivity mode.

These differences in sensing performance originate from the intrinsic resonance mechanisms of the three resonances. The f_{x-1} resonance exhibits strong modal coupling and pronounced field confinement, making it highly sensitive to analyte-induced microenvironmental changes. The f_{x-2} resonance has weaker coupling and field confinement, limiting its sensitivity. The f_y resonance, with moderate field energy but the largest hotspot area, enables efficient analyte capture and thus intermediate sensitivity. These three resonances form a multimode sensing platform, offering a robust basis for ultrasensitive and multiplexed detection.

Drug Quantitative Detection Based on Polarization-Induced Multimode THz Metamaterial. Figure 4a shows the optical micrographs of the fabricated metamaterial sensor. The fabricated structure exhibits high fidelity to the design, with dimensional deviations below 0.5 μm . Figure 4b,d compare the measured and the simulated resonance peaks of the sensor. Measured peaks appear at 1.78, 2.58, and 3.67 THz, with frequency deviations of 0.02–0.05 THz relative to the simulated peaks. These deviations are attributed to fabrication tolerances, including intrinsic material losses and dimensional inaccuracies. Nevertheless, the measured resonance peaks remain well-aligned with the characteristic absorption peaks of clopidogrel sulfate, enabling selective enhancement of THz wave–drug interaction.

After confirming the structural fidelity and spectral alignment of the fabricated sensor, we then we tested the sensor with clopidogrel sulfate solutions (0–40 $\mu\text{g}/\mu\text{L}$). The sensing response of the three resonance peaks were comprehensively analyzed. Figure 4e,h,k present the redshifts of the f_{x-1} resonance peak at different clopidogrel sulfate concentrations. As the concentration increases, the f_{x-1} peak exhibits a redshift, with the redshift (Δf) increasing nonlinearly (Figure 4e), consistent with the theoretical simulations (Figure S3a). Based on these observations, a nonlinear regression model was established to relate Δf to clopidogrel sulfate concentration

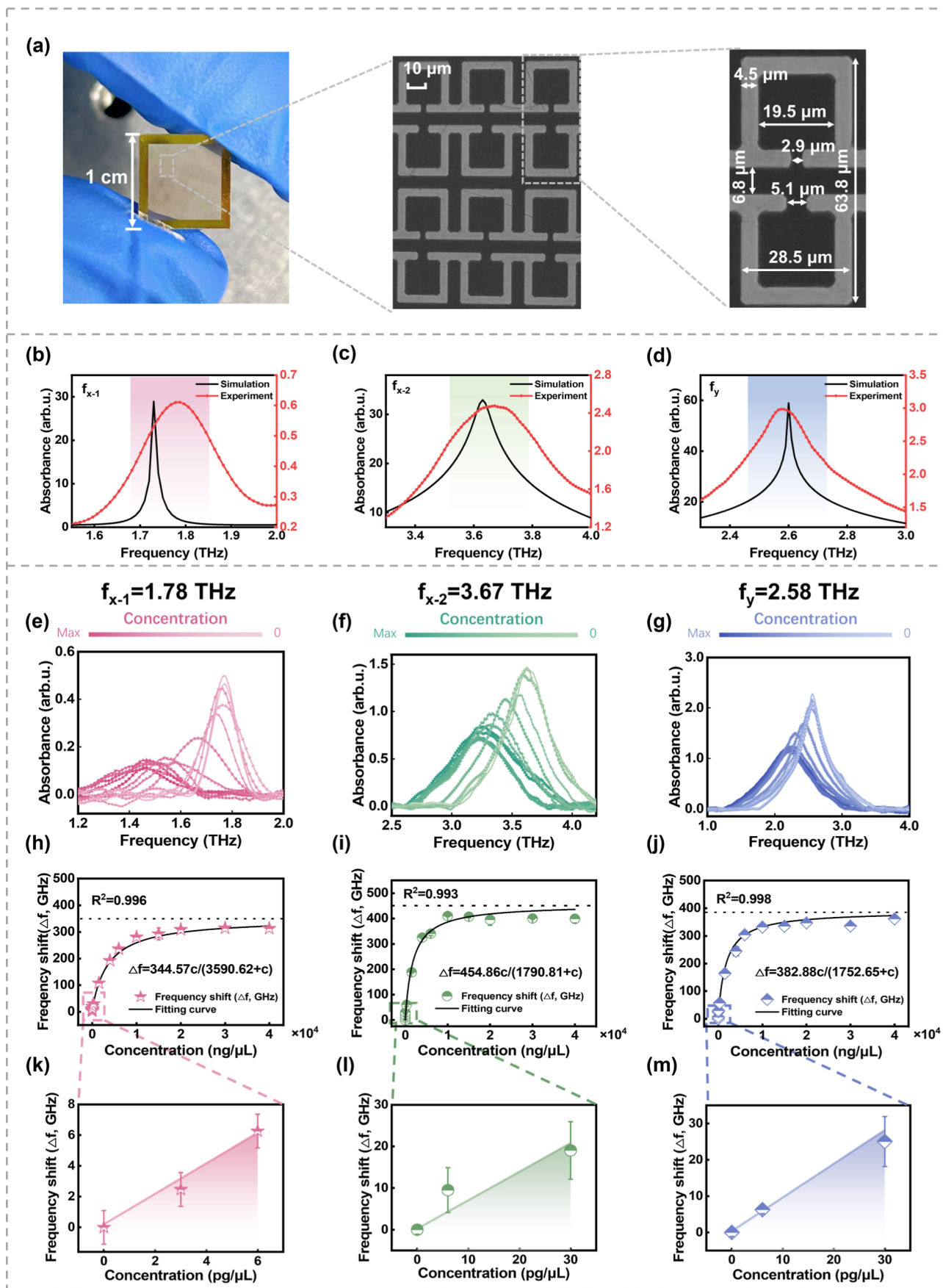


Figure 4. Quantitative detection of clopidogrel sulfate using the polarization-induced multimode THz metamaterial sensor. (a) Optical micrograph of the fabricated sensor. (b,d) Comparison between the measured (black) and simulated (red) resonance spectra for f_{x-1} , f_{x-2} , and f_y . (e–g)

Figure 4. continued

Measured spectra at each resonance under varying clopidogrel sulfate concentrations. (h–j) Nonlinear redshift–concentration relationships at each resonance. (k–m) Magnified redshift response at low concentrations.

Table 1. Sensing Performance of the Polarization-Induced Multimode THz Metamaterial Sensor for Clopidogrel Sulfate Detection

resonance	analyte's characteristic peak (THz)	resonance frequency (THz)	$\Delta f_{\max}^a$ (GHz)	S^a (GHz· $\mu\text{L}/\text{pg}$)	LOD ^a (pg/ μL)
f_{x-1}	1.77	1.78	345.1	1044	3.0
f_{x-2}	3.57	3.67	455.4	686	5.3
f_y	2.68	2.58	385.3	927	3.9

^a $\Delta f_{\max}$: Maximum redshift, defined as the maximum redshift relative to the baseline (0 $\mu\text{g}/\mu\text{L}$). S : Sensitivity at low concentration, defined as the slope of the linear fitting curves (unit: GHz· $\mu\text{L}/\text{pg}$). This unit corresponds to the frequency redshift (GHz) per analyte concentration (pg/ μL). LOD: Limit of detection, calculated according to Text S3.

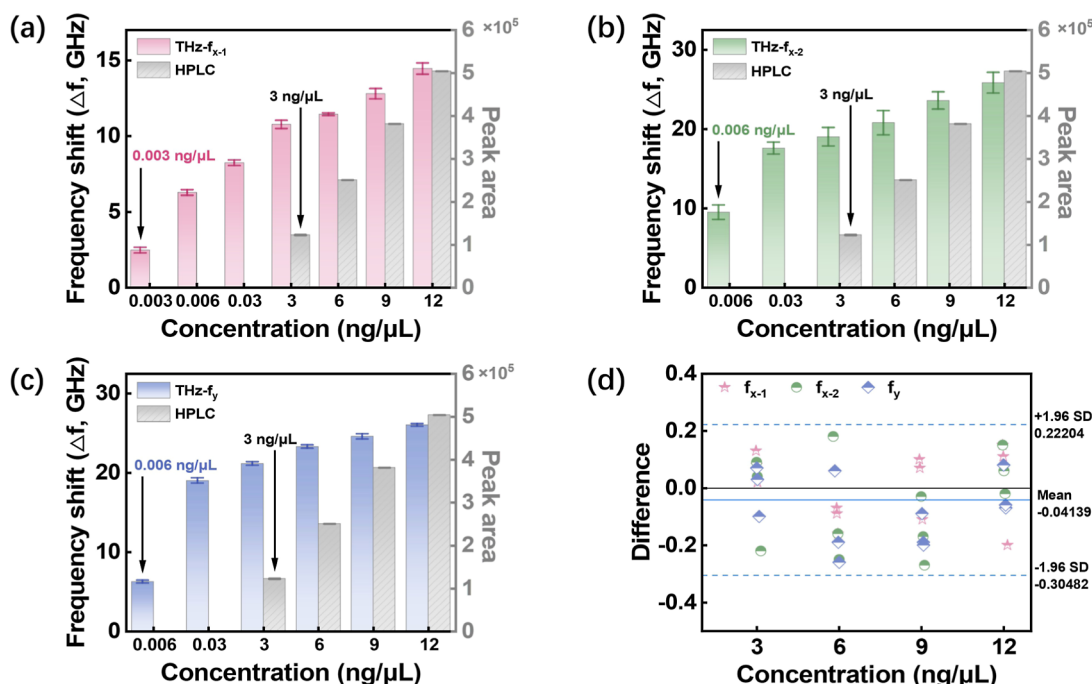


Figure 5. Comparison of sensitivity and accuracy between THz metamaterial sensor and HPLC for clopidogrel sulfate detection. (a–c) Sensitivity comparison for f_{x-1} , f_{x-2} , and f_y resonance modes. (d) Bland–Altman analysis evaluating consistency between the two methods.

(Figure 4h). The high fitting coefficient ($R^2 = 0.996$) indicates strong agreement between the fitting model and the experimental data. Similarly, the redshifts of the f_{x-2} and f_y resonance peaks at different clopidogrel sulfate concentrations were investigated. As concentration increases, both peaks exhibit nonlinear redshifts (Figure 4f,g), consistent with theoretical simulations (Figure S3b,c). The corresponding nonlinear fitting curves are presented in Figure 4i,j, with R^2 values of 0.993 and 0.998, respectively.

The Δf –Concentration relationships below 30 pg/ μL are presented in Figure 4k–m. In this low-concentration region, the redshifts of three peaks exhibit an approximating linear trend. Therefore, the detection sensitivity (S) can be assessed as the slope of the linear fitting curves.⁴⁷ The LODs for clopidogrel sulfate were determined to be 3.0 pg/ μL for f_{x-1} peak, 5.3 pg/ μL for f_{x-2} peak, and 3.9 pg/ μL for f_y peak (Table 1). These LODs are within the reported clinical blood concentration range of clopidogrel sulfate (0.04–4.04 pg/ μL),⁴⁶ demonstrating that the proposed THz metamaterial

sensor meets the sensitivity requirements for clinical applications.

Comparison Between the Polarization-Induced Multimode THz Metamaterial and HPLC. To evaluate the accuracy of the proposed THz sensor, clopidogrel sulfate solutions analyzed in parallel by THz sensor and HPLC. Calibration curves for THz sensor were established by correlating the redshifts of the three resonance peaks (f_{x-1} , f_{x-2} and f_y) with the clopidogrel sulfate concentrations (Figure 4h–j). Meanwhile, HPLC calibration curves were established by correlating the peak areas with clopidogrel sulfate concentrations (Figure S1). Figure 5 compares the detection results by both methods. The THz sensor exhibited higher sensitivity, with LODs of 3, 6, and 6 pg/ μL for the f_{x-1} , f_{x-2} , and f_y peaks, respectively. These LODs are 3 orders of magnitude lower than that of HPLC (Figure 5a–c). Furthermore, the consistency between the two methods was confirmed by Bland–Altman analysis (Figure 5d). The limit of agreement (LOA) was calculated as the mean difference ± 1.96 standard deviations of the differences (Text S4), ranging from –0.30 to

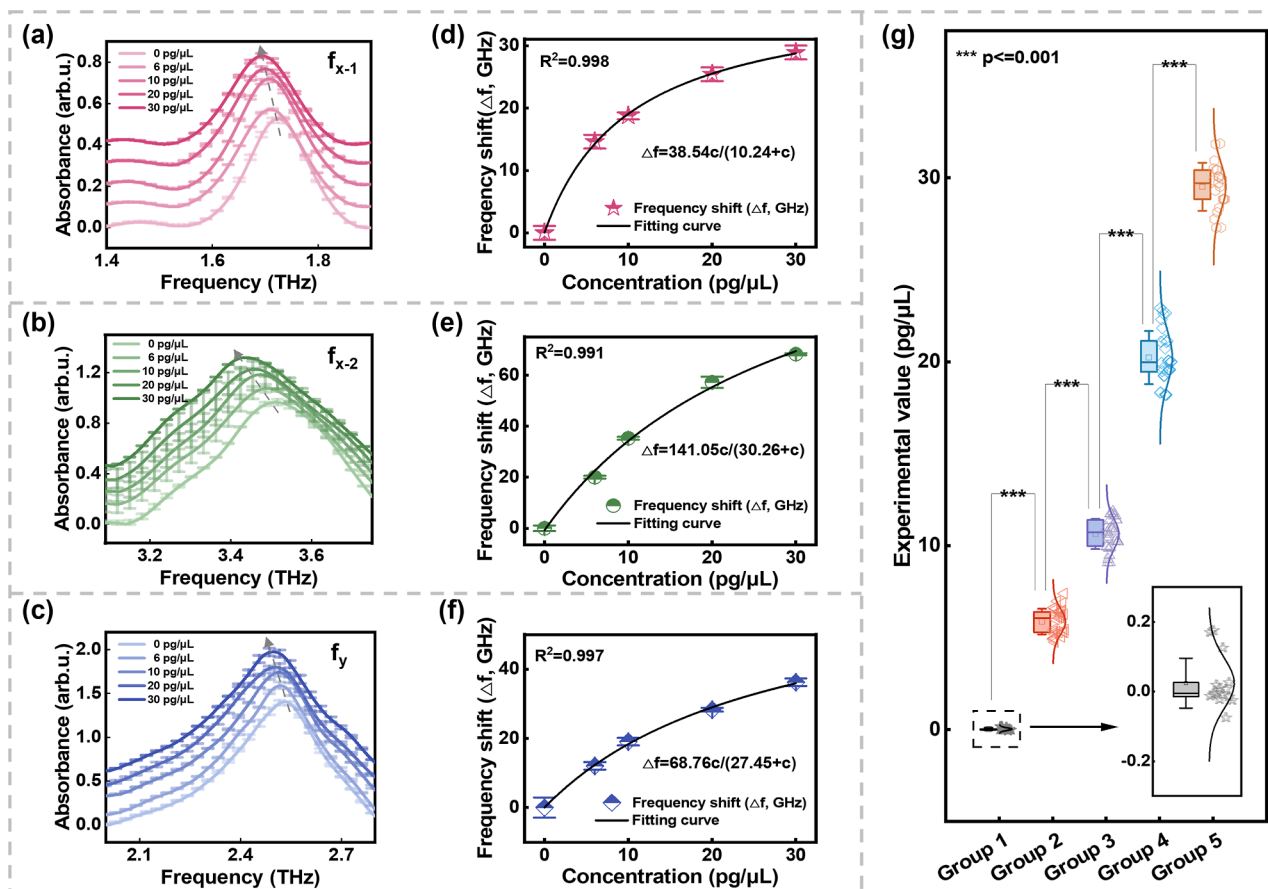


Figure 6. Quantitative detection of clopidogrel sulfate in blood using the THz metamaterial sensor. (a–c) Measured spectra at each resonance for blood sample with varying clopidogrel sulfate concentrations. Each spectrum was vertically offset to improve visual comparison. (d–f) Nonlinear redshift–concentration relationships at each resonance for blood samples. (g) Clopidogrel sulfate detection accuracy in blood samples by the THz metamaterial sensor.

0.22. The 95% confidence interval for the LOA was estimated using the delta method, demonstrating strong agreement between the two methods. These results indicate that the proposed THz sensor is a reliable alternative to HPLC for drug quantification.

Application of Polarization-Induced Multimode THz Metamaterial in Human Blood. To evaluate the applicability of the proposed THz sensor in clinic, we analyzed human blood samples spiked with clopidogrel sulfate at five concentrations (Group 1–5). Representative THz absorption spectra are shown in Figure 6, with the complete data sets provided in Figures S4 and S5. As drug concentration increased. As the drug concentration increased, progressive redshifts were observed across all three resonance peaks (f_{x-1} , f_{x-2} and f_y), peak was observed (Figure 6a–c), consistent with the nonlinear trend observed in standard solutions.

The redshifts (Δf) were calculated relative to blank blood samples (Group 1, 0 pg/ μL). The nonlinear fitting models established using standard samples (Figure 4) were also applicable to human blood samples (Figure 6d–f), despite slight deviations in the fitting parameters. These deviations are likely attributable to residual endogenous substances in blood that were not completely removed during protein precipitation. Nevertheless, the models demonstrated good robustness, indicating its suitability for analysis in complex biological matrices.

Basing on these nonlinear fitting model, clopidogrel sulfate concentrations in blood samples were analyzed. The results are summarized in Figure 6g. For Group 1 (0 pg/ μL), the measured drug concentration was 0.024 ± 0.071 pg/ μL , indicating a low background and high signal stability of the sensor. For Group 2 to 5, the measured concentrations were 5.87 ± 0.70 pg/ μL , 10.63 ± 0.82 pg/ μL , 20.23 ± 1.44 pg/ μL and 29.51 ± 1.31 pg/ μL , respectively. The relative error between the measured and nominal concentrations ranged from 1.14% to 6.30%, corresponding to a detection accuracy exceeding 93.7%. Compared to HPLC analysis, our THz sensing method significantly reduces the detection time (5 min vs 20 min per sample, postpretreatment). This 5 min duration includes four repeated THz measurements per sample, with the averaged results used for subsequent analysis. These results confirm that the proposed sensor provides an accurate, reliable and rapid detection approach for blood drug analyses.

Table 2 summarizes the detection performance of our polarization-induced multimode THz metamaterial sensor in comparison with recently reported representative devices (single- and multiresonance devices). Unlike conventional THz metamaterials that often rely on complex resonator geometries or auxiliary materials, our sensor employs a simple split-ring resonator to generate multiple polarization-dependent resonance modes. These modes are spectrally well-separated under orthogonal polarizations, and exhibit spatially complementary in field distribution. Therefore, our sensor

Table 2. Comparison of Current THz Metamaterial Strategies for Biochemical Samples

resonance peak (THz)	sample	auxiliary signal enhancement	LOD (pg/ μ L)	reference
0.85	bovine serum albumin	none	100	48
0.88	imidacloprid	none	11.2	49
1.44	D-glucose	none	840	50
0.63, 1.16	whey protein	graphene	6.25	51
0.64, 1.24	human epidermal growth factor receptor 2	nanoparticles graphene aptamer	0.1	34
1.83, 2.03	vanillin melamine	none	52.8, 78.5	52
0.98, 1.245	total prostate-specific antigen	graphene colloidal gold antibody	0.00001	53
1.77, 2.68, 3.57	clopidogrel sulfate	none	3.0	this work

enables cross-validation between multiple modes and significantly reduces measurement errors caused by nonuniform sample distribution. This self-validated multimode sensing leads to improved detection sensitivity and accuracy. Moreover, our sensor operates without any auxiliary materials, which facilitates fabrication. Additionally, our sensor has strong extensibility, because its resonance frequencies can be readily tuned by adjusting geometric parameters, such as the gap size of resonator. This spectral tunability enables spectral alignment with characteristic absorption peaks of various drugs. The successful application of the sensor to human blood samples further demonstrates its practical applicability for blood drug analysis. Owing to these advantages, the proposed sensor shows great potential for therapeutic drug monitoring.

CONCLUSION

Here we developed a polarization-induced multimode THz metamaterial sensor for the highly sensitive and accurate detection of clopidogrel sulfate, a widely used antithrombotic drug. Quantum chemical calculations and THz spectroscopy (1–4 THz) identified three vibrational fingerprints of the drug at 1.77, 2.68, and 3.57 THz, corresponding to vibration modes of different functional groups. To enable label-free detection, the THz metamaterial was designed to exhibit resonance peaks at 1.70, 3.49 THz (f_{x-1} , f_{x-2} under x -polarization) and 2.63 THz (f_y under y -polarization), which were spectrally aligned with the drug's vibrational fingerprints. Electromagnetic simulations and multipolar decomposition revealed that the f_{x-1} resonance originates from a strongly coupled electric–toroidal hybrid mode, while f_{x-2} and f_y resonances mainly arise from orthogonally polarized dipolar modes. These distinct resonance mechanisms produce spectrally separated peaks and spatially complementary field enhancement regions, thereby enabling multiplexed molecular identification and quantification. The proposed sensor achieved LODs of 3.0 pg/ μ L (f_{x-1}), 5.3 pg/ μ L (f_{x-2}), and 3.9 pg/ μ L (f_y), representing a 1000-fold sensitivity improvement over conventional HPLC. The detection results also showed >95% consistency with HPLC, confirming the high accuracy of the sensor. Furthermore, in human blood samples, the sensor demonstrated >93.7% accuracy and a rapid detection time of less than 5 min per sample (postpretreatment). These results confirm the strong potential of the polarization-induced multimode THz meta-

material sensor as a highly sensitive, accurate, and label-free platform for therapeutic drug monitoring.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/acs.analchem.5c04376>.

HPLC measurement, multipolar scattering analysis, definition of the limits of detection, definition of the limits of agreement, analysis of terahertz spectra from different blood samples (PDF)

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Notes

The authors declare no competing financial interest.

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