

GRIFFINs and GoBleNs: A Non-Fictional Tool for Identifying Trace Controlled Substance Surrogates in Complex Mixtures

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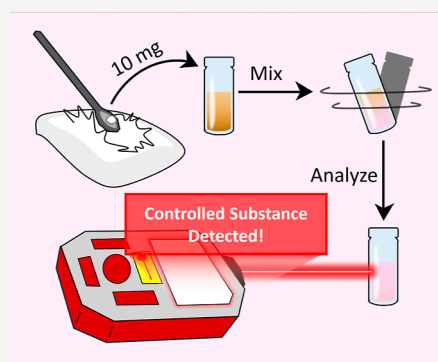
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ABSTRACT: Drug overdose deaths have tripled over the past two decades, and methamphetamine remains the second most frequently identified drug involved in such fatalities. Within the United States, the Drug Enforcement Administration seizes tens of thousands of kg of clandestine powders, tablets, crystals, and liquids that may contain anywhere from 1–100% pure methamphetamine every year. Unfortunately, current portable techniques, such as Raman and infrared spectroscopy, fail to reliably identify methamphetamine and other analogs below ~23 wt % due to interference from cutting agents. We introduce GRIFFINs, a tool for the gold-enhanced Raman identification for forensic field inspection of narcotics. GRIFFINs uses gold-blended nanoparticles (GoBleNs), a novel cationic, lipophilic-specific, and highly selective surface-enhanced Raman spectroscopic (SERS) substrate for the identification of low amounts (<23 wt %) of chemicals like alkylamines in complex matrices that mimic the components of real clandestine samples. Using machine learning, we trained the model on 10 independent dilution series for each of three controlled substance surrogates (phenylethylamine, serotonin, and dopamine) and three other SERS-responsive cutting agents (lidocaine, benzocaine, and caffeine) before testing at least 85 independent mixtures that mimic real evidence samples. The novel SERS substrate, GoBleNs, was mixed with HPLC-compatible samples before being analyzed with a commercially available, portable Raman spectrometer equipped with 830 nm excitation in less than 1 min. Using extreme gradient boosting discriminant analysis, limits of identification ranged between <0.1 and 0.1 wt % depending on the analyte. This study demonstrates the first application of SERS for improving the portable Raman analysis of trace amphetamine and tryptamine surrogates for seized drug analysis.

KEYWORDS: amphetamine, SERS, machine learning, handheld, illicit, drug



1. INTRODUCTION

Drug overdose mortality in the United States has increased substantially from 2003 to 2023 from 8.9 to 31.3 deaths per 100,000 population.¹ Psychostimulants with abuse potential, primarily methamphetamine (MAMP), are now implicated in approximately one-third of overdose deaths in the United States, and MAMP has emerged as the second most frequently identified drug involved in overdose fatalities after fentanyl.¹ Concurrently, the United States Drug Enforcement Administration (DEA) continues to intercept large quantities (~7000–10,000 kg each year for MAMP alone) of illicit substances in the form of powders, tablets, crystals, and liquids during interdiction and trafficking investigations.² These seized materials often exhibit substantial variability in composition and purity, with MAMP-containing samples ranging from trace quantities (1.2 wt %) to nearly pure (~100%) material depending on synthesis route, adulteration, and distribution practices.²

To rapidly screen suspected illicit substances in the field, forensic and law enforcement agencies increasingly rely on portable analytical instrumentation, including Raman spectroscopy, Fourier-transform infrared (FT-IR) spectroscopy, and portable mass spectrometry (MS).^{3,4} Portable Raman and

FT-IR systems offer rapid (i.e., within minutes or less), non-destructive analysis with minimal sample preparation, whereas portable MS generally requires dissolution and ionization of the sample prior to analysis. Despite these operational advantages, currently deployed portable spectroscopic techniques often exhibit reduced reliability when target analytes are present at low concentrations or within chemically complex matrices containing cutting agents, excipients, or other active compounds. For example, Williams et al. reported that portable attenuated total reflectance FT-IR (ATR-FTIR) spectroscopy demonstrated poor performance (<80% accuracy) for the identification of 3,4-methylenedioxymethamphetamine (MDMA) in authentic forensic samples at concentrations below approximately 23 wt %, while amphetamine-containing samples produced some of the lowest spectral match qualities among the tested drug classes.⁵ Similarly, Chang et al. demonstrated that a

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1064 nm portable Raman spectrometer outperformed a conventional 785 nm portable Raman instrument for MAMP detection in the presence of cutting agents; however, the reported limit of identification (LOI) for MAMP remained approximately 25 wt %, whereas portable MS achieved identification at approximately 10 wt %.⁴ Collectively, these studies highlight the persistent challenge of reliably identifying amphetamine-type stimulants at low concentrations in heterogeneous forensic samples.

Surface-enhanced Raman spectroscopy (SERS) represents a promising alternative for trace-level detection.^{6–10} By exploiting localized surface plasmon resonances generated by nanostructured metallic substrates, SERS can enhance Raman scattering intensities by about a million-fold relative to conventional Raman spectroscopy while retaining the molecular specificity and rapid analysis times characteristic of vibrational spectroscopy. As a result, SERS has attracted increasing attention for forensic applications involving trace illicit substance detection. For example, there have been numerous recent studies for the portable SERS detection of fentanyl, tetrahydrocannabinol (THC), and opioids at concentrations as low as 0.05–0.1 wt %.^{11–13} Despite these advances, portable SERS approaches specifically targeting AMP and MAMP remain limited. This gap may partially arise from the relatively weak intrinsic Raman scattering and limited surface affinity of amphetamine-type stimulants compared to more aromatic or highly conjugated illicit compounds, such as fentanyl, cocaine, THC, and morphine.

Previous studies investigating non-portable SERS-based detection of AMP, MAMP, and structurally related alkylamines have reported limits of detection in the $\mu\text{g/mL}$ to ng/mL range using functionalized plasmonic nanoparticles, which correspond to 0.01 and 0.00001 wt % (for a 10 mg/mL sample).^{14–16} Several of these approaches utilized mercaptobenzoic acid-derived ligands, which are sometimes further modified through *N*-hydroxysuccinimide (NHS) chemistry, to promote covalent or affinity-driven interactions with primary and secondary amine-containing analytes such as AMP and MAMP. Although these studies demonstrated substantial improvements in analytical sensitivity compared to conventional Raman, most were conducted using benchtop Raman instrumentation under controlled laboratory conditions, commonly employing high numerical aperture microscope objectives and occasionally excitation wavelengths of 633 nm, which are collectively nonrepresentative of current commercial portable Raman devices. Moreover, limited emphasis was placed on evaluating substrate selectivity against chemically similar interferents or realistic forensic matrices. Consequently, the practical utility of SERS as a portable, selective, and field-deployable technique for amphetamine-type stimulant detection remains insufficiently explored.

In this proof-of-concept study, we investigate the performance of a novel SERS substrate, gold blended nanoparticles (GoBleNs), for the portable Raman detection of AMP and tryptamine structural motifs in the presence of common cutting agents and non-illicit alkylamines that may interfere with forensic identification. In addition, we integrate machine learning-assisted spectral classification to reduce operator subjectivity and improve analytical consistency during spectral interpretation. This combined SERS-machine-learning approach has the potential to substantially improve the sensitivity and selectivity of portable Raman technologies currently used for field

identification of illicit alkylamine-containing substances, including AMP and MAMP.

2. MATERIALS AND METHODS

Information, including product name, catalog number, relative mass, and manufacturer, for reagents can be found in Table S1.

2.1. SERS Substrate

Scheme 1 depicts the underlying mechanisms following the full synthesis of our gold nanoparticle substrates. The following are a more in-depth description of the synthesis from start to finish. Assume all reactions are done in Type I ultrapure milli-Q water.

2.2. Initial Seed Synthesis

After complete dissolution, 250 μL of 10 mM $\text{HAuCl}_4(3 \times \text{H}_2\text{O})$ was added to 9.75 mL water containing 0.3554 g CTAB, stirring at 300 rpm and 30 °C. After 1 min, 600 μL of ice-cold 10 mM NaBH_4 was added and allowed to stir for an additional 2 min. The solution turned from gold to honey-colored upon addition of NaBH_4 , indicating the formation of reduced Au^+ seeds. The seed solution was then allowed to rest in the dark at 30 °C for 1 h before use.

2.3. Gold Nanorods Synthesis and Modification

Add 500 μL of 10 mM HAuCl_4 to 9.5 mL water containing dissolved 0.3554 g CTAB and continue stirring (300 rpm, 30 °C) for 1 min. Then add 100 μL 10 mM AgNO_3 and continue stirring for another minute. Finally, add 70 μL 100 mM L-ascorbic acid and 12 μL 1–2 h aged seed solution. Continue stirring for 15 min and following this, store in dark at 30 °C for 2 h to obtain high-yield gold nanorods (AuNRs). After the AuNRs have formed, the solution should appear almost opaque. Centrifuge the AuNRs at 10,000 rpm for 10 min 3 $\times$, resuspending in 100 mM CTAC, then 50 mM CTAC, and finally 10 mM CTAC. After the final centrifuge, resuspend in 30 mL Type I ultrapure water. To 20 mL of the clarified AuNRs, add 500 μL 20 mM 3-MBA and gently invert 4 $\times$. Sonicate this solution for 1 h in the dark and then transfer to a 30 °C water bath to incubate for an additional 2 h in the dark. Centrifuge the 3-MBA@AuNR solution at 8000 rpm for 10 min 3 $\times$, resuspending in 50 mM CTAC, 10 mM CTAC, and ultrapure water initially, and finally in 5 mL ultrapure water.

2.4. Rugose Gold Nanorod-Blended Nanoparticle Synthesis

The final substrate is a mixture of rugose gold nanorods (rAuNRs) and anisotropic particles with octahedral and globular shapes, which we call GoBleNs for gold-blended nanoparticles. To create them, add 1.35 g of CTAB to 38 mL ultrapure water and mix at 500 rpm at 40 °C for 30 min to completely dissolve the CTAB. Add 1 mL 10 mM HAuCl_4 and continue stirring for 1 min before adding 200 μL 100 mM L-ascorbic acid. Continue stirring for an additional 30 s before transferring the solution to a 50 mL conical tube. While sonicating, add 2 mL of the 3-MBA@AuNR solution and continue sonicating for an additional 3 min. Incubate the solution in a 30 °C water bath in the dark for 1 h. Finally, centrifuge at 4500 rpm for 15 min 3 $\times$, resuspending in 20 mL ultrapure water initially and 4 mL as the final volume.

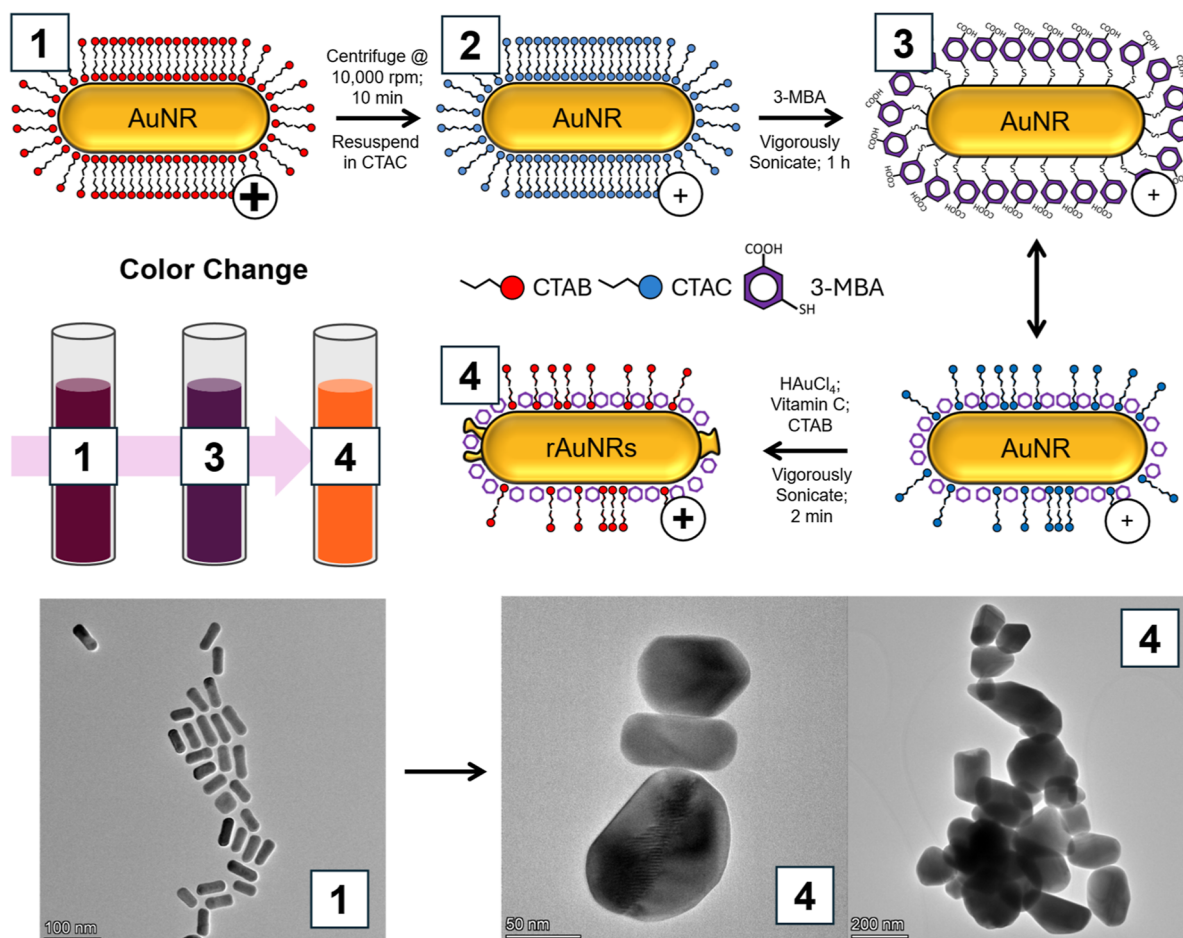
Figures S1 and S2 show transmission electron microscopy (TEM) and energy-dispersive X-ray spectroscopy (EDS) characterizations of AuNRs and GoBleNs.

2.5. Sample Preparation

We chose 2-phenylethylamine (PEA) hydrochloride, serotonin (5-HT) hydrochloride, and dopamine (DOPA) hydrochloride for our proof-of-concept study because their chemical structures closely resemble that of controlled substances, Figure 1.

Our GoBleNs are selective for cationic, lipophilic molecules due to the surface chemistry (3-MBA- COO^-), which are most often nonamide, alkylamines. Therefore, it was important to evaluate the selectivity of the platform not only toward the primary analytes of interest, but also toward potential cutting agents containing similar

Scheme 1. Mechanism of Growth for Gold Nanoparticle Substrate Used for Selective Analysis of Protonatable Controlled Substance Surrogates. (1) Gold Nanorods (AuNRs) are First Synthesized in CTAB, a Strong Surfactant that may Reduce the Binding Efficiency of 3-Mercaptobenzoic Acid (3-MBA) to the Gold Surface via the Thiol. To Circumvent This, (2) AuNRs are Resuspended in CTAC before Adding 3-MBA. (3) Our 3-MBA@AuNRs are Then Used as Seeds when Added to a Solution of Reduced Gold (Au^+ and Au^0) so that Crystallization can Occur in Gaps of Unbound 3-MBA across the AuNR Surface Leading to Creation of (4) Rugose AuNRs (rAuNRs) and Other Anisotropic Species, Termed GoBleNs, for Gold-Blended Nanoparticles. The Images along the Bottom are Transmission Electron Micrographs of Dehydrated Solutions of (1) AuNRs in CTAB and (4) GoBleNs in CTAB.



functional groups, including lidocaine (LAIN) and benzocaine (BAIN). To accomplish this, the model was trained using dilution series prepared for PEA, 5-HT, DOPA, LAIN, and BAIN in methanol. For each dilution series, 10 mg of analyte was dissolved in 1 mL of methanol to prepare the stock solution, followed by serial dilutions to generate concentrations of 3, 1, 0.3, 0.1, 0.03, 0.01, 0.003, and 0.001 mg/mL. The one exception was CAFE which showed a lower responsivity to our GoBleNs and were thus only prepared from 0.01 to 10 mg/mL concentrations. Ten independent dilution series were prepared for each analyte, and each series was freshly prepared immediately prior to Raman analysis. Blanks consisted of methanol and GoBleNs only, and were mixed in the same order and manner as diluted analytes.

Also, to determine whether our technique could reliably identify our analytes under different realistic conditions—in the presence of other analytes and/or common cutting agents, including other non-illicit alkylamines—we prepared 95 unique mixtures so that analytes ranged from 0.01 to 80 wt % in spiked samples. Mixtures were prepared by dissolving the controlled-substance surrogates and soluble interferents at high concentrations and combining the resulting stock solutions at the desired mass ratios. For nontarget compounds with insufficient solubility, the appropriate solid mass was added directly to the mixture to achieve the specified composition. The exact wt % and ingredient for each testing mixture can be found in Table S2. To assess reproducibility

and establish an unbiased evaluation framework, the first 40 mixture compositions were independently prepared in triplicate using separate stock solutions. Spectra from the first replicate were used for model calibration and hyperparameter selection. Spectra from the second replicate were reserved for validation, allowing assessment of model generalizability and determination of empirical probability thresholds from the resulting score distributions. Finally, spectra from the third replicate were held out exclusively for external evaluation of the finalized models. The remaining 55 unique mixtures were also reserved for external evaluation and were not used during model development.

2.6. Raman Spectroscopy

The agilent resolve handheld Raman analyzer was selected for this study because it combines true field portability with spatially offset Raman spectroscopy (SORS) capabilities, enabling the non-destructive analysis of samples through optically scattering or partially opaque containers. Unlike conventional handheld Raman instruments that primarily interrogate surface layers, the Resolve system utilizes an 830 nm excitation source coupled with SORS acquisition to suppress container interference and probe subsurface chemical compositions, which is particularly advantageous for forensic analysis of clandestine liquids, powders, and mixtures stored in glass or plastic packaging. In addition, the instrument is equipped with a custom vial attachment accessory capable of securely holding 4 mL, 1-dram glass vials during

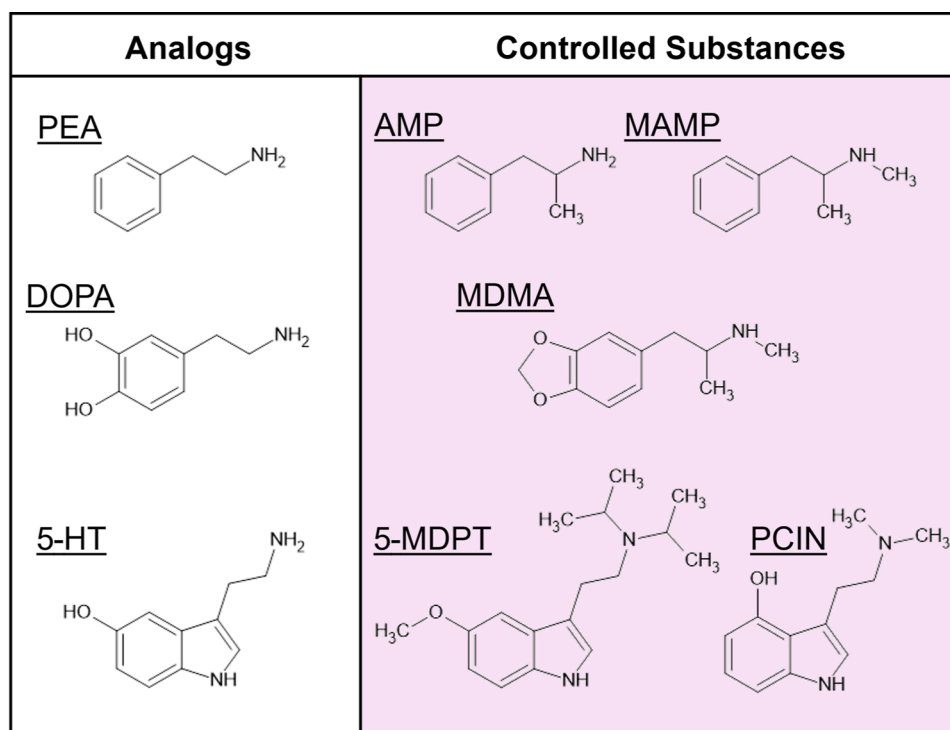


Figure 1. Chemicals used in this study (left) as surrogates for controlled substances (right). PEA: 2-phenylethylamine; DOPA: dopamine; 5-HT: serotonin; AMP: amphetamine; MAMP: methamphetamine; MDMA: 3,4-methylenedioxymethamphetamine; 5-MDPT: 5-methoxy-*N,N*-diisopropyltryptamine; PCIN: psilocin.

spectral acquisition. This configuration provides highly reproducible sample positioning and optical alignment while allowing rapid interchange of samples during high-throughput measurements. The use of standardized vial geometry also minimizes variability associated with focal distance and laser positioning, thereby improving spectral consistency for downstream machine learning analysis. Together, the SORS functionality, portability, and adaptable sampling configuration of the resolve platform make it particularly well-suited for evaluating field-deployable SERS methodologies for illicit drug detection.

Samples were prepared for analysis by mixing 400 μL of GoBleNs with 200 μL of analytes in methanol or methanol alone (for the blank) inside a 4 mL, 1-dram glass vial (Catalog No. 5183–4448, Agilent Technologies, Inc.). All spectra were acquired using the vial measurement mode of the agilent resolve handheld Raman analyzer. The instrument was operated at a maximum laser power setting of 100 mW. Spectral acquisitions were performed with no delay between measurements, and each reported spectrum represented the average of 20 accumulated scans, resulting in an acquisition time of approximately 20 s per spectrum. To assess measurement reproducibility, each sample was analyzed in triplicate through three consecutive spectral acquisitions. All measurements were conducted under ambient laboratory conditions in a well-lit environment with indirect natural light exposure and a controlled temperature of approximately 21–23 $^{\circ}\text{C}$.

2.7. Data Analysis

All spectral processing and analysis was done in Python v3.13. Raman spectra were preprocessed using the following pipeline: trim to 350–1750 cm^{-1} , Savitzky–Golay smoothing (polyorder: 1, window length: 9), and area normalization (as displayed in Figure S3).

6 machine learning classifiers representing both linear and nonlinear modeling approaches were evaluated: partial least squares discriminant analysis (PLSDA), logistic regression discriminant analysis (LRDA), cosine similarity nearest-neighbor classification (CSNNC), random forest discriminant analysis (RFDA), extreme gradient boosting discriminant analysis (XGBDA), and artificial neural network discriminant analysis (ANNDA). These algorithms are among the most widely

applied methods in spectroscopic machine learning and were previously employed during development of the forensic hair dye identification platform developed by our group, DyeSPY.¹⁰ All models were calibrated, validated, and externally evaluated using independent datasets. Hyperparameter grids and Python libraries used for implementation are provided in Table S3.

Model calibration was performed at the spectrum level. Selection of candidate models was guided by recommendations from the 2016 President's Council of Advisors on Science and Technology report, which emphasized the importance of empirically established error rates in forensic methods.¹⁷ Accordingly, model configurations were first required to satisfy an eligibility criterion based on classification error rates. Specifically, the false positive rate (FPR), defined as the proportion of negative samples incorrectly classified as positive, could not exceed 5% for prosecutorial support. Subsequently, each controlled substance surrogate (PEA, 5-HT, and DOPA) could not exceed 1% during calibration initially. In addition, the false negative rate (FNR), defined as the proportion of true positives incorrectly classified as negative for a target analyte, for Blank spectra (negative controls) could not exceed 1%.

Among eligible models, the optimal hyperparameter configuration was selected according to the highest macro-averaged *F1* score (Macro *F1*) for controlled substance surrogates. The *F1* score is the harmonic mean of precision and recall (true positive rate, also TPR), providing a balanced measure of classification performance. Macro *F1* was calculated as the unweighted average *F1* score across all controlled substance surrogates. In cases where multiple configurations produced identical controlled substance surrogate Macro *F1* values, preference was given to the model with the highest Macro *F1* score across all groups: controlled substance surrogates, non-target potential interferences, and blank samples. The only exception was for PLSDA, which contains only 1 tunable parameter; the optimal parameter was chosen using the latent variable (LV) within one standard error of the highest Macro *F1* achieved. This approach is largely responsible for reducing overfitting and increasing parsimony in PLSDA.¹⁸ Selected models were subsequently evaluated using an independent validation set to

confirm that controlled substance surrogate FPRs and blank-sample FNRs did not exceed 5%.

Final model performance was assessed using an external test set at the sample level. This evaluation was used to determine the limit of identification (LOI) for each controlled substance surrogate, defined as the lowest concentration at which the TPR—the proportion of true positive samples correctly identified as positive—remained at or above 95%. Consistent with the validation criteria, models were considered forensically acceptable only if controlled substance surrogate FPRs and blank-sample FNRs did not exceed 5% on the external test set.

3. RESULTS AND DISCUSSION

3.1. Evaluation of GoBleNs Responsivity

First, our novel SERS substrate, GoBleNs, exhibited excellent stability over a 3 week period following purification, as demonstrated using three independently prepared GoBleN batches analyzed with 1 mg/mL PEA in methanol (Figure S4). To evaluate the selectivity of the developed SERS nanosensor toward cationic and lipophilic molecules such as alkylamines, 10 compounds with varying functional groups were analyzed (Figures 2 and 3). 6 analytes possessing protonatable amines were expected to produce measurable SERS responses, whereas four additional compounds containing amides or no amine functionalities were included as potential non-target interferents.

The blank displays strong signals, specifically at about 750, 1050, and 1450 cm^{-1} , which are attributed to the benzoic acid vibrations on the surface of the GoBleNs substrate.^{19,20} Nevertheless, specific vibrations for each GoBleNs-responsive analyte can be observed (Figure 2). For example, Raman bands of $\sim 1600\text{ cm}^{-1}$, represent aromatic and indole ring stretching ($\text{C}=\text{C}$ and $\text{C}-\text{C}$) and are present in both serotonin and lidocaine signatures.²¹ PEA possess a strong peak at $\sim 1000\text{ cm}^{-1}$ and a medium-sized peak at $\sim 1200\text{ cm}^{-1}$ which corresponds to symmetric ring breathing and phenyl-side chain vibrations, respectively.²² The non-interferents were observed to produce indistinct SER signals comparable to the background/blank which consists of only methanol and GoBleNs (Figure 3). This analysis demonstrated that the GoBleN-based handheld Raman platform selectively detected compounds containing protonatable amine groups, while compounds lacking these functionalities produced only background-level responses.

The practical utility of this sensing platform must also be considered in the context of authentic seized drug mixtures, which commonly contain a variety of cutting and co-occurring agents. Table 1 summarizes compounds used herein that were reportedly identified in U.S. government-seized powdered samples containing AMP, MAMP, MDMA, or cocaine. Evaluation of these compounds indicates that only a limited subset possess the chemical functionalities necessary to generate appreciable responses from the developed SERS substrate.^{24,25} Furthermore, Fiorentin and colleagues found that lidocaine and procaine (two potential interferents containing responsive amine groups) were identified in only 12.4–13.5% of 515 authentic U.S. seized drug exhibits.²³

Furthermore, the SER spectra acquired across the dilution series for both target analytes and potential interferents indicate that the detection limit for most compounds is at or below 0.001 mg/mL (0.01 wt %) (Figure 4). Notably, 5-HT exhibited the greatest sensitivity on the GoBleN-based portable SERS platform, producing distinct analyte-specific Raman bands above the background even at the lowest concentration evaluated (0.001 mg/mL). However, sensitivity determined from

single-analyte measurements does not necessarily translate directly to complex mixtures, where multiple SERS-responsive compounds may compete for adsorption sites and contribute overlapping spectral features. Consequently, analyte detection limits alone are insufficient predictors of assay performance in realistic multi-component samples.

3.2. GRIFFINs Model Selection and Calibration

To evaluate the robustness of the developed SERS platform for the preliminary and confirmatory detection of controlled substances, a SER spectral library was constructed using the controlled substance surrogates: 2-phenylethylamine (PEA), dopamine (DOPA), and serotonin (5-HT), together with the potential interfering cutting agents caffeine (CAFE), benzocaine (BAIN), and lidocaine (LAIN). The dataset comprised 10 independently prepared dilution series spanning concentrations from 0.01 to 100 wt % encompassing concentrations below the lower range reported for authentic seized methamphetamine exhibits ($\sim 1.2\text{ wt } \%$) through neat material representative of highly pure illicit samples. In addition, two independently prepared replicates of 40 mixture samples were generated, consisting of 10 surrogate-negative samples and 30 surrogate-positive samples with surrogate concentrations ranging from 0.5 to 40 wt %.

Model calibration was performed using 5 randomly selected dilution series, while the remaining five dilution series were reserved for validation. To prevent information leakage, all spectra originating from a given dilution-series replicate were assigned exclusively to either the calibration or validation dataset. The first replicate of the 40 mixture samples was also included in calibration, whereas the second replicate was reserved for validation. 6 machine learning classifiers were evaluated, including PLSDA, LRDA, CSNNC, RFDA, XGBDA, and ANNDA. Initial model eligibility was determined during calibration, with candidate models required to satisfy predefined error-rate criteria before proceeding to validation.

Validation performance for the selected hyperparameter configurations is summarized in Table 2. All six classifiers satisfied the eligibility criteria, achieving controlled substance surrogate FPRs and Blank FNRs below 5%. The Macro *F1*, which incorporates classification performance across both target and non-target classes, ranged from 89.37% for PLSDA to 98.47% for ANNDA. Among the evaluated approaches, ANNDA achieved the highest overall validation Macro *F1* score (98.47%), closely followed by LRDA (98.01%) and CSNNC (97.07%).

Following validation, empirical probability thresholds were determined independently for PEA, 5-HT, and DOPA using the validation dataset. For each model and analyte, the classification threshold was selected as the lowest probability value that maintained a surrogate-specific FPR of $\leq 1\%$. The resulting thresholds are summarized in Table 3.

Notably, substantial differences were observed among the empirically determined thresholds. While PLSDA, RFDA, and LRDA produced intermediate threshold values, XGBDA and ANNDA generated considerably lower thresholds, whereas CSNNC required a threshold of 1.0 for all three analytes. These results demonstrate that equivalent validation performance metrics do not necessarily correspond to equivalent probability-score distributions. Instead, each algorithm exhibited a distinct degree of score calibration, resulting in markedly different operating thresholds despite comparable classification accuracies.

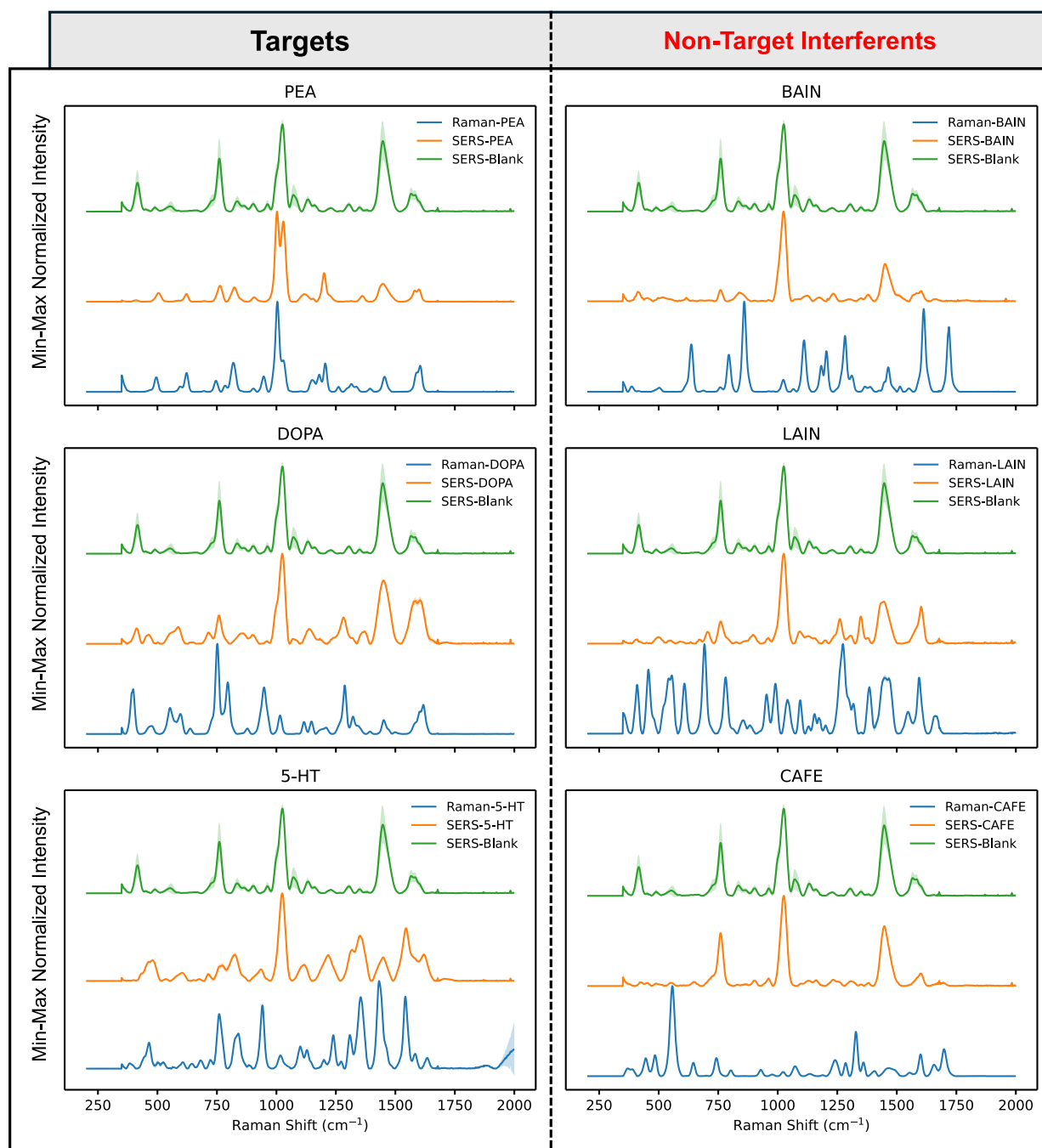


Figure 2. Mean (solid line) raw Raman and SER spectra and standard deviation (filled area) for 1 mg/mL 2-phenylethylamine (PEA), dopamine (DOPA), serotonin (5-HT), benzocaine (BAIN), lidocaine (LAIN), and caffeine (CAFE). Spectra have been min–max normalized to evaluate characteristic peaks, those relative heights of peaks between analyte spectra should not be compared.

The ANNDA and XGBDA models produced particularly low probability thresholds, indicating that their prediction scores were strongly concentrated near zero even for correctly identified positive samples. Conversely, the CSNNC model generated highly discrete similarity scores, requiring perfect similarity (1.0) to maintain the desired $\leq 1\%$ FPR criterion. These findings highlight the importance of empirically determining classification thresholds for each modeling approach rather than relying on a universal threshold of 0.5. Although all six models demonstrated acceptable validation performance, the threshold analysis revealed substantial differences in how confidently each

classifier separated positive and negative classes, which ultimately influenced performance during external evaluation.

3.3. Testing on Complex Mixtures

To minimize the potential for overoptimistic performance estimates arising from spectrum-level model development, all selected classifiers were evaluated using an independent sample-level test set consisting of 85 unique mixtures. The test set included 10 surrogate-negative samples and 75 surrogate-positive samples comprising 25 samples each containing PEA, 5-HT, or DOPA. Surrogate concentrations ranged from 0.01 to

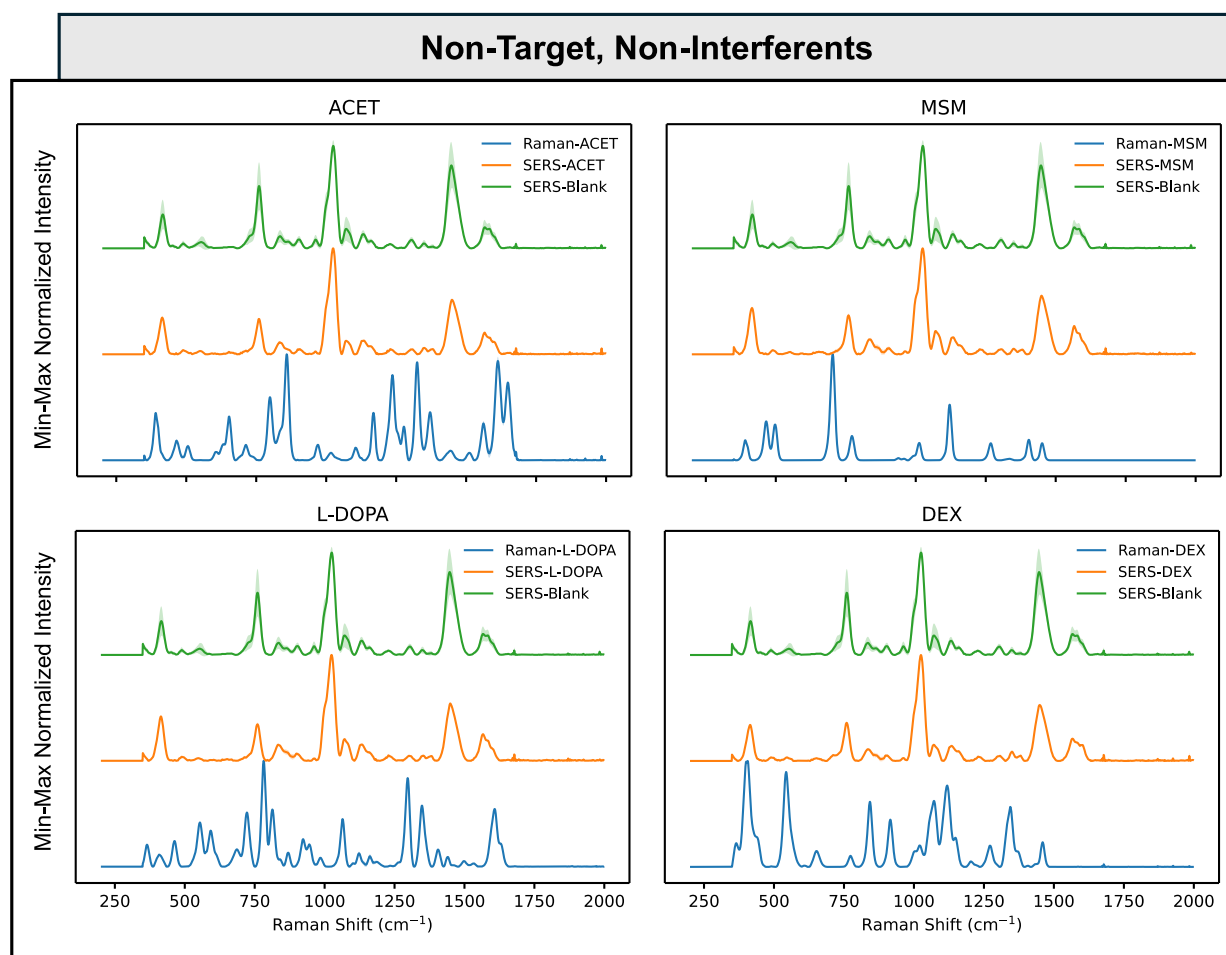


Figure 3. Mean (solid line) raw Raman and SER spectra and standard deviation (filled area) for 1 mg/mL levodopa (L-DOPA), acetaminophen (ACET), methylsulfonylmethane (MSM) and dextrose (DEX). Spectra have been min–max normalized to evaluate characteristic peaks, those relative heights of peaks between analyte spectra should not be compared.

80 wt % when present, whereas concentrations of non-target potential interferents (LAIN, BAIN, and CAFE) ranged from 10 to 70 wt % (Table S2). Additional non-reactive cutting agents were incorporated at concentrations ranging from 10 wt % to greater than 99.9 wt %, with at least one such component present in 95% of all test mixtures. Consequently, the external test set represented a substantially more challenging and realistic evaluation of model performance than the calibration and validation datasets.

Performance metrics obtained from external evaluation are summarized in Table 4. Two models, PLSDA and XGBDA, satisfied the predefined forensic acceptance criteria of surrogate FPRs and a Blank FNR not exceeding 5%. Although LRDA, CSNNC, RFDA, and ANNDA demonstrated strong validation performance, each exceeded at least one error-rate threshold during external testing. These findings underscore the importance of independent sample-level evaluation, as validation performance alone was not always predictive of generalization to previously unseen mixtures.

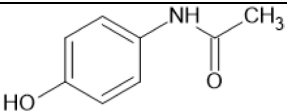
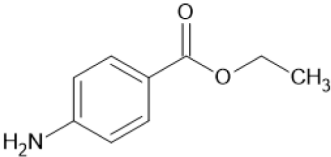
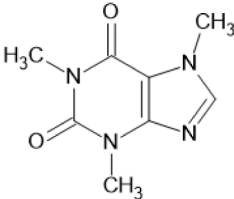
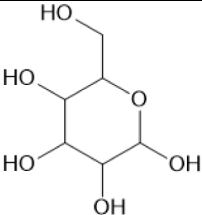
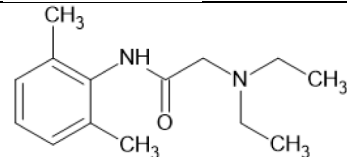
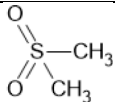
Notably, DOPA represented the most challenging analyte across all modeling approaches. Every classifier generated at least one false-positive DOPA identification among surrogate-negative samples, suggesting that DOPA-associated spectral features were more susceptible to overlap with those of other mixture components than were PEA- or 5-HT-associated

features. This trend was particularly pronounced for CSNNC, which exhibited one of the lowest validation error rates yet produced the highest DOPA FPR during external testing, further illustrating the limitations of relying solely on validation metrics for model selection.

Among the two eligible models, PLSDA achieved a lower DOPA FPR than XGBDA. However, this increased conservatism was accompanied by substantially lower overall classification performance, reflected by a Macro F1 score of 81.91% compared with 95.31% for XGBDA. Examination of the prediction outcomes revealed that PLSDA was more likely to classify low-concentration surrogate-positive samples as negative, whereas XGBDA maintained substantially higher sensitivity while remaining within the predefined forensic error-rate limits. Collectively, these results indicate that XGBDA provided the most favorable balance between sensitivity and specificity for the identification of controlled substance surrogates in complex mixtures.

The LOIs determined from external evaluation are presented in Table 5. The LOI was defined as the lowest concentration at which the TPR remained at or above 95%. Across all models, lower LOIs were generally observed for 5-HT and PEA than for DOPA, indicating that DOPA was the most challenging analyte to identify reliably in mixed samples. Among the eligible models, PLSDA failed to achieve an LOI of 1 wt % or lower for all

Table 1. List of Cutting Agents Reportedly Detected in Authentic Seized Drug Samples and Their Affinity for Our GoBleN-Based Assay

Substance	Structure	Reference	Nanosensor Detectability
Acetaminophen		Fiorentin et al. (2018) ²³	Not detectable
Benzocaine		Broséus et al. (2016); ²⁴ Fiorentin et al. (2018) ²³	Detectable
Caffeine		Broséus et al. (2016); ²⁴ Fiorentin et al. (2018) ²³	Detectable
Dextrose (<i>D</i> -Glucose)		Broséus et al. (2016) ²⁴	Not detectable
Lidocaine		Broséus et al. (2016); ²⁴ Fiorentin et al. (2018) ²³	Detectable
Methylsulfonylmethane		DEA (2025) ²⁵	Not detectable

analytes, exhibiting a DOPA LOI of 30 wt %. In contrast, XGBDA achieved LOIs of 0.1 wt % for PEA and 5-HT and less than 0.1 wt % for DOPA, representing the best overall identification performance observed in this study.

Because XGBDA demonstrated both acceptable forensic error rates and the lowest LOIs, it was selected as the final model for further interpretation. Analysis of the external test results revealed no evidence that any individual non-target potential interferent disproportionately contributed to DOPA false-positive identifications (Figure 5, all other models: Figures S5–S9). Instead, the single DOPA false positive occurred equally across interferent categories, suggesting that misclassification arose from the combined spectral complexity of the mixtures rather than from a specific interferent. Similar trends were observed for false-negative identifications, where PEA- and 5-HT-containing samples exhibited comparable susceptibility to misclassification in the presence of LAIN and BAIN, whereas CAFE had little apparent effect on performance.

Importantly, all four misclassified samples (IDs 51, 54, 66, and 69) contained surrogate concentrations at or below 0.1 wt %. No misclassifications were observed above this concentration. Consequently, when only samples above the experimentally

determined LOIs were considered, the observed TPR for all controlled substance surrogates increased to 100%. These findings emphasize the practical value of establishing analyte-specific LOIs, as classification performance was highly reliable above these thresholds despite the complexity of the tested mixtures.

3.4. Testing Multi-Label Capabilities

Finally, ten independent test samples containing two or more controlled substance surrogates were evaluated to determine whether the selected XGBDA model could simultaneously identify multiple target analytes within a single mixture. These samples represented particularly challenging test cases, as individual surrogate concentrations did not exceed 15 wt % and were frequently accompanied by potential interferents (Table 6).

Overall, the XGBDA model successfully detected the presence of at least one true surrogate in all ten mixtures; however, complete identification of every surrogate present within a sample proved substantially more challenging. In mixtures containing two surrogates, the model typically identified the component present at higher concentration while failing to

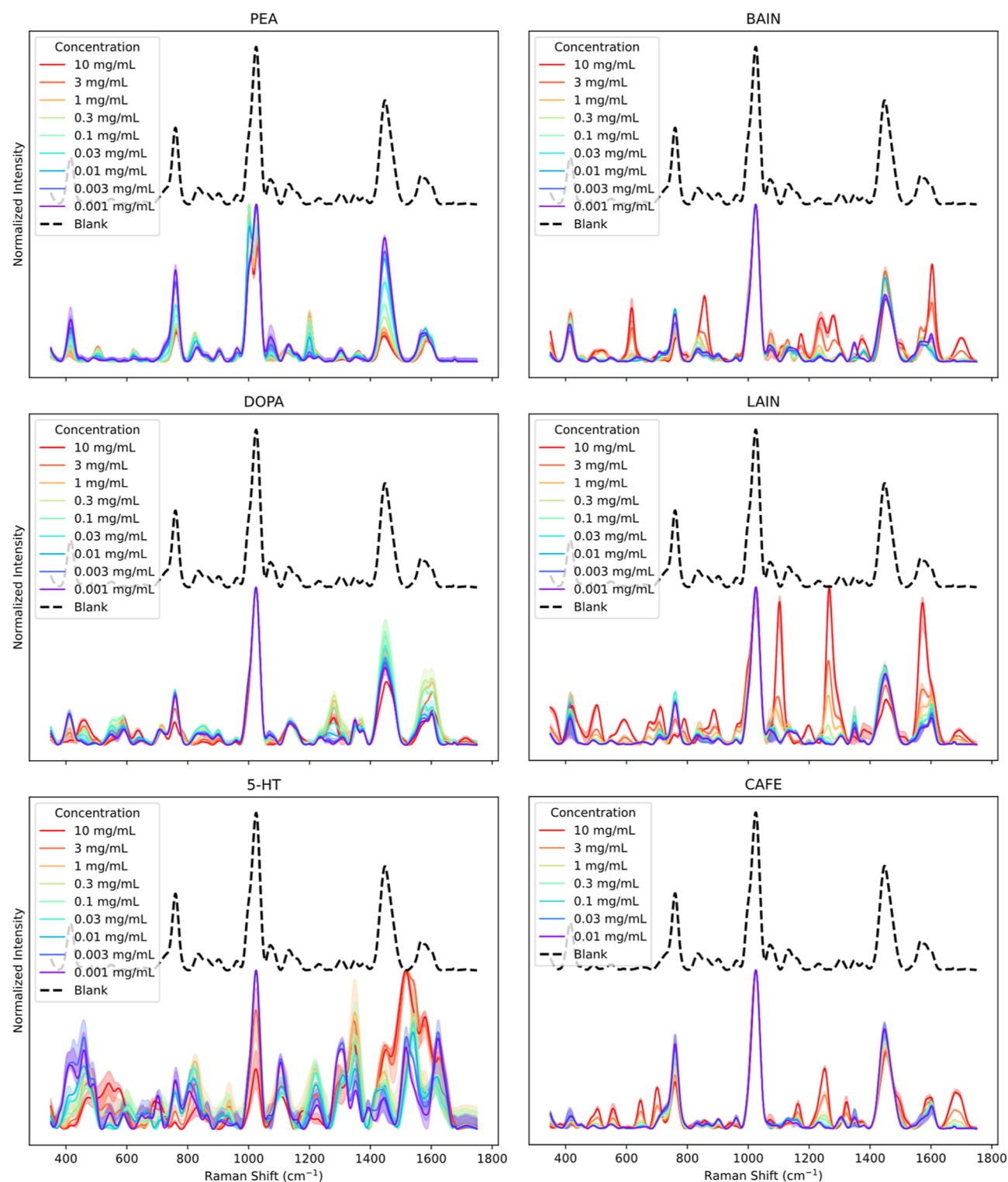


Figure 4. Mean and SD SER spectra for each dilution series for PEA, 5-HT, DOPA, BAIN, LAIN, and CAFE.

detect the lower-concentration surrogates. For example, in samples containing PEA and 5-HT at a 2:10 ratio (Samples 41 and 46), only 5-HT was identified, whereas in samples containing PEA and DOPA at a 10:2 ratio (Samples 43 and 48), only PEA was consistently detected. Similar behavior was observed for mixtures containing 5-HT and DOPA at a 2:10 ratio (Samples 42 and 47), where the higher-concentration analyte was preferentially identified.

The greatest challenge for XGBDA was observed in samples containing all three surrogates simultaneously (Samples 44, 45, 49, and 50). In 3 out of 4 of these complex mixtures, the model typically detected only the most prominent component(s) while failing to identify one or more lower-abundance analytes. The outlier was Sample 50, which contained identical PEA:5-HT/DOPA ratios (15:4.5:0.5 wt %) to Sample 45 but differed in the cutting agent and its relative abundance. Sample 45 contained

Table 2. Model Validation Summary of Calibration-Selected Models

model	hyperparameter(s)	validation macro $F1^a$ (%)	PEA FPR (%)	5-HT FPR (%)	DOPA FPR (%)	blank FNR (%)	eligible? ^b
PLSDA	LVs: 14	89.37	0.88	0.88	0.88	3.02	Yes
LRDA	C: 10; iter: 200; penalty: L1	98.01	0.88	0.88	0.88	3.67	Yes
CSNNC	K: 1; W: uniform	97.07	0.13	0.13	0.13	0.43	Yes
RFDA	Depth: 5; trees: 200; feat: sqrt; SPL: 5	95.91	0.88	0.88	0.88	4.10	Yes
XGBDA	LR: 0.05; depth: 3; trees: 500; L1:0.0001	96.60	0.88	0.88	0.88	4.10	Yes
ANNDA	HD: 256; drop: 0.3; L1: 0.0 optimizer; RMSprop LR; 0.0001	98.47	0.88	0.88	0.88	3.24	Yes

^aA: validation macro $F1$ includes BAIN, LAIN, and CAFE model classification performance. ^bB: eligibility is determined by possessing controlled substance surrogate FPR and blank FNR $\leq 5\%$.

Table 3. Empirically-Determined Probability Thresholds for Each Hypertuned Model Following Validation

model	PEA probability threshold	5-HT probability threshold	DOPA probability threshold
PLSDA	0.306319	0.181567	0.290151
LRDA	0.1838	0.025284	0.048573
CSNNC	1.0	1.0	1.0
RFDA	0.256791	0.30954	0.300092
XGBDA	0.025607	0.014464	0.025144
ANNDA	0.004454	0.000124	0.001

Table 4. Final Model Evaluation Summary across 85 Independent Samples (10 Blank and 75 Surrogate Samples)

model	macro $F1^a$ (%)	PEA FPR (%)	5-HT FPR (%)	DOPA FPR (%)	blank FNR (%)	eligible? ^b
PLSDA	81.91	0	0	1.67	0	yes
LRDA	92.36	0	1.67	10	0	no
CSNNC	83.72	0	0	11.67	0	no
RFDA	85.06	1.67	0	8.33	20	no
XGBDA	95.31	0	0	5	0	yes
ANNDA	94.13	0	0	10	0	no

^aA: macro $F1$ is the unweighted average $F1$ scores for all surrogate and Blank samples. ^bB: eligibility is determined by possessing controlled substance surrogate FPR and Blank FNR $\leq 5\%$.

Table 5. Limits of Identification (LOIs) Determined from Final Model Evaluation across 85 Independent Samples

model	PEA LOI (wt %)	5-HT LOI (wt %)	DOPA LOI (wt %)
PLSDA	1	1	30
LRDA	1	0.1	<0.1
CSNNC	30	1	10
RFDA	1	0.1	none ^a
XGBDA	0.1	0.1	<0.1
ANNDA	1	0.1	<0.1

^aDOPA was not sufficiently identified at or above 95% for all concentration bins.

10 wt % LAIN and was correctly predicted to contain both PEA and 5-HT, whereas Sample 50 contained 70 wt % BAIN and was predicted to contain only DOPA. These observations are consistent with the interferent-specific false-negative trends shown in Figure 5, where the only false negatives produced by XGBDA occurred for PEA and 5-HT in samples containing

either LAIN or BAIN. Notably, these errors were associated with mixtures containing substantially higher interferent-to-surrogate ratios. The transition from a 10:15:4.5:0.5 LAIN/PEA:5-HT:DOPA composition to a 70:15:4.5:0.5 BAIN/PEA:5-HT:DOPA composition markedly increased the relative contribution of the potential interferent, thereby reducing the detectability of PEA and 5-HT and leading to the observed false-negative classifications.

Importantly, although complete multilabel identification was not achieved for any of the ten samples, the model consistently identified at least one true controlled substance surrogate and did not exhibit a systematic bias toward any specific potential interferent. Collectively, these results indicate that the XGBDA model is capable of detecting the presence of at least one controlled substance surrogate in complex multi-component mixtures, but that reliable identification of all individual analytes within such mixtures remains a challenge, particularly when one or more components are present at substantially lower concentrations than competing SERS-responsive species.

4. LIMITATIONS

Several limitations should be resolved before the GoBleN-based assay is considered for operational use in field or laboratory drug screening. Most importantly, because the platform was evaluated with structural surrogates rather than authentic controlled substances or authentic seized-drug samples, the present findings are best interpreted as proof-of-concept rather than as a casework-ready validation. That distinction matters because real seized materials are chemically complex and often contain adulterants or diluents that interfere with analytical signatures, while the contemporary drug supply also includes emerging substances that test selectivity and robustness. Consistent with that concern, recent forensic validation literature emphasizes casework-relevant testing.^{26,27} Future studies should therefore establish sensitivity, specificity, false-positive and false-negative performance, and limits of detection using genuine controlled substances and authentic casework matrices across powders, tablets, and mixtures.

Another limitation is that only hydrochloride salt forms were examined. In forensic practice, however, salt form is analytically consequential: DEA guidance notes that some controlled substances are commonly encountered in multiple salt forms and requires salt-form verification for substances such as cocaine and methamphetamine, while other forensic laboratory manuals require confirmation or molecular-weight correction when the unknown and the comparison standard

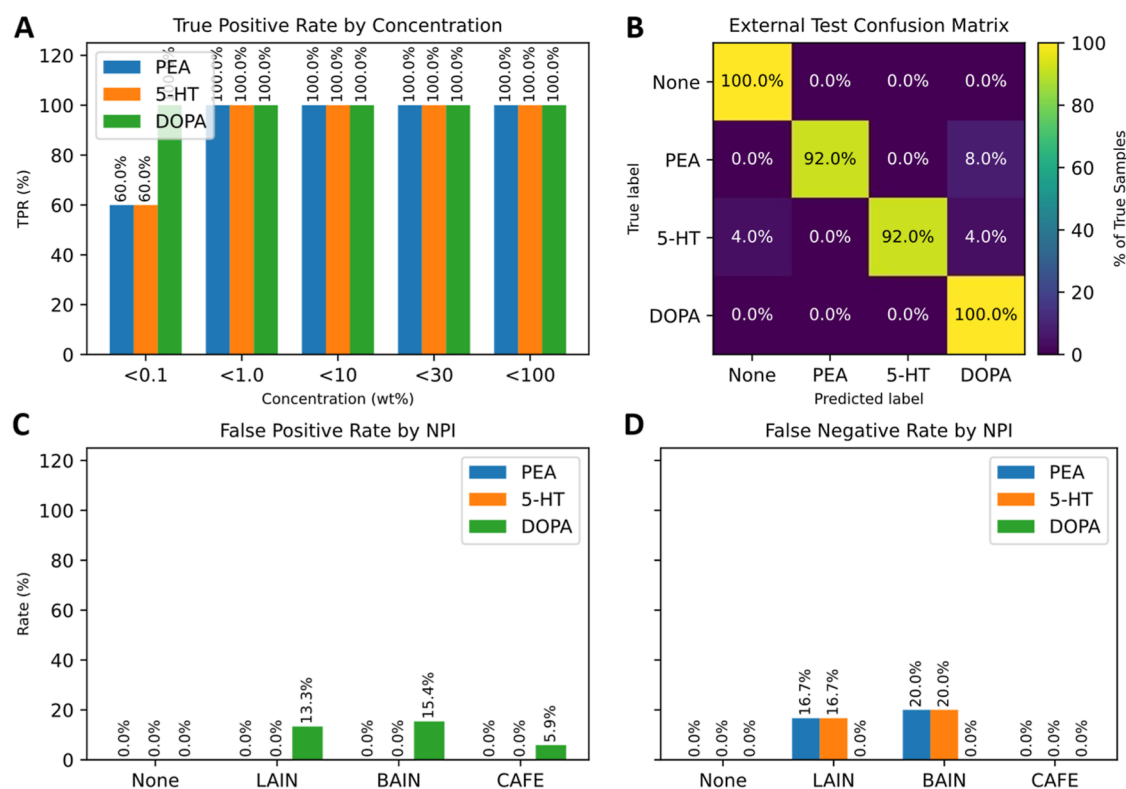


Figure 5. External evaluation summary of the selected XGBDA model using 85 independent mixture samples. (A) TPRs as a function of analyte concentration, demonstrating limits of identification (LOIs) of 0.1 wt % for PEA and 5-HT and <0.1 wt % for DOPA. (B) Classification performance across PEA-, 5-HT-, DOPA-containing, and Blank samples, showing recall values $\geq 92\%$ for all classes and only four total misclassifications among the 85 evaluated samples. (C) FPRs for controlled substance surrogates stratified by the presence of non-target potential interferents (LAIN, BAIN, or CAFE). The sole DOPA false-positive identification occurred across multiple interferent categories, indicating no single interferent was disproportionately associated with misclassification. (D) FNRs for PEA and 5-HT as a function of non-target potential interferents composition. Misclassifications were observed primarily in mixtures containing LAIN or BAIN. All misclassified samples contained analyte concentrations at or below 0.1 wt %, consistent with the experimentally determined LOIs. NPI: non-target potential interferent.

Table 6. External Evaluation Results for the Selected XGBDA Model on Test Samples Containing Two or More Controlled Substance Surrogates^{a,b}

sample ID	true PEA present	predicted PEA present	true 5-HT present	predicted 5-HT present	true DOPA present	predicted DOPA present	true PEA:5-HT:DOPA ratio	true NPI present
41	yes	no	yes	yes	no	no	2:10:0	CAFE
42	no	no	yes	yes	yes	no	0:2:10	CAFE
43	yes	yes	no	no	yes	no	10:0:2	CAFE
44	yes	no	yes	yes	yes	no	0.5:15:4.5	none
45	yes	yes	yes	yes	yes	no	15:4.5:0.5	LAIN
46	yes	no	yes	yes	no	no	2:10:0	BAIN
47	no	no	yes	no	yes	yes	0:2:10	LAIN
48	yes	yes	no	yes	yes	no	10:0:2	LAIN
49	yes	no	yes	yes	yes	no	0.5:15:4.5	BAIN
50	yes	no	yes	no	yes	yes	15:4.5:0.5	BAIN

^aIndividual surrogate concentrations did not exceed 15 wt % in any mixture. ^bNPI: non-target potential interferent.

differ in salt form.³ Amphetamine-type stimulants may be encountered as hydrochloride, sulfate, phosphate, or bromide salts, and methamphetamine is commonly seized as the hydrochloride whereas amphetamine is often encountered as the sulfate in DEA seizure profiling.³ Because salt selection can alter physicochemical behavior such as solubility and stability, and because counterions measurably affect gold–nanoparticle interactions and SERS features, the GoBleN-based method should be evaluated across the salt forms most likely to appear

in exhibits, such as hydrochloride and sulfate, where chemically relevant to the target analytes.

Finally, as discussed in Section 3.4, testing multi-label capabilities, the poor classification of mixtures containing multiple surrogates indicates that the current GRIFFINs framework is best suited as a rapid preliminary screening tool rather than a confirmatory method. SERS enhancement depends strongly on analyte–substrate interactions, meaning that compounds with favorable surface affinity may be preferentially enhanced while

other mixture components are suppressed or undetected. Similar portable SERS methods have therefore been described as targeted or nontargeted screening approaches for seized drugs.²⁸ Although conventional Raman spectroscopy is classified by SWGDRUG as a Category A technique (for its high selectivity), a forensic identification still requires a validated analytical scheme incorporating at least one additional technique. Accordingly, positive GRIFFINs results would require confirmation using an established laboratory method such as gas or liquid chromatography-MS.

5. CONCLUSIONS

In summary, the GoBleN-based portable SERS platform, GRIFFINs, demonstrated the ability to rapidly detect and identify controlled substance surrogates at concentrations relevant to forensic drug analysis, even in the presence of common cutting agents and structurally related interferents. Among the six machine learning approaches evaluated, XGBDA provided the best balance between sensitivity and specificity during external evaluation, achieving acceptable forensic error rates while maintaining limits of identification of ≤ 0.1 wt % for PEA, 5-HT, and DOPA in complex mixtures. These findings demonstrate the potential of combining selective SERS substrates with machine learning to provide rapid, field-deployable screening and preliminary identification of illicit alkylamine-containing substances. Future studies will focus on expanding the analyte library to include authentic controlled substances and additional cutting agents, improving multilabel classification of samples containing multiple controlled substances, and validating performance using seized drug exhibits obtained from forensic laboratories. Such efforts will be critical for establishing the robustness, generalizability, and forensic utility of this approach in real-world casework.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/acs.analchem.6c05866>.

Reagent and sample information, as well as microscopic images of the nanostructures are provided in the Supporting Information. Supporting Information is available free of charge on the ACS Publications website. Experimental details can be seen in the Supporting Information (DOCX)

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Notes

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■ REFERENCES

- (1) Garnett, M. F.; Cisewski, J. A.; Ahmad, F. B. Drugs Most Frequently Involved in Drug Overdose Deaths: United States, 2017–2023. In *National Vital Statistics Reports [Internet]*; National Center for Health Statistics (US), 2026.
- (2) Drug Enforcement Administration. *Annual Methamphetamine Report: DEA Laboratory System Reporting, CY 2024. Special Testing and Research Laboratory, Office of Forensic Sciences* 2025.
- (3) Drug Enforcement Administration. *Analysis of Drugs Manual; Virginia Department of Forensic Science: Controlled Substances Procedures Manual*.
- (4) Chang, C.; Monjardez, G.; Davidson, J. T. Assessment of a combined handheld Raman spectroscopy and transportable mass spectrometry approach for the analysis of seized drug mixtures. *Forensic Sci. Int.* **2025**, 372, 112512.
- (5) Williams, S. F.; Stokes, R.; Tang, P. L.; Blanco-Rodriguez, A. M. Detection & identification of hazardous narcotics and new psychoactive substances using Fourier transform infrared spectroscopy (FTIR). *Anal. Methods* **2023**, 15 (26), 3225–3232.
- (6) Holman, A. P.; Kurouski, D. Surface-enhanced Raman spectroscopy in forensic analysis. *Rev. Anal. Chem.* **2024**, 43 (1), 20230079.
- (7) Holman, A. P.; Peterson, M.; Linhart, E.; Kurouski, D. Using surface-enhanced Raman spectroscopy to probe artificial dye degradation on hair buried in multiple soils for up to eight weeks. *Sci. Rep.* **2024**, 14 (1), 6469.
- (8) Holman, A. P.; Kurouski, D. Role of race/ethnicity, sex, and age in surface-enhanced Raman spectroscopy and infrared spectroscopy-based analysis of artificial colorants on hair. *ACS Omega* **2023**, 8 (23), 20675–20683.
- (9) Holman, A. P.; Kurouski, D. DyeSPY-LINK: The first likelihood-based inference of near-source kinship for dyed hair evidence comparisons. *Forensic Chem.* **2026**, 49, 100746.
- (10) Holman, A. P.; Maalouf, A.; Kurouski, D. DyeSPY: Establishing the First Forensic SERS Reference for Hair Dye Colorant Evidence. *Anal. Chem.* **2025**, 97, 27862–27878.
- (11) Wang, H.; Xue, Z.; Wu, Y.; Gilmore, J.; Wang, L.; Fabris, L. Rapid SERS quantification of trace fentanyl laced in recreational drugs with a portable Raman module. *Anal. Chem.* **2021**, 93 (27), 9373–9382.
- (12) Smith, M.; Logan, M.; Bazley, M.; Blanchfield, J.; Stokes, R.; Blanco, A.; McGee, R. A Semi-quantitative method for the detection of fentanyl using surface-enhanced Raman scattering (SERS) with a handheld Raman instrument. *J. Forensic Sci.* **2021**, 66 (2), S05–S19.
- (13) Wilson, N. G.; Raveendran, J.; Docoslis, A. Portable identification of fentanyl analogues in drugs using surface-enhanced Raman scattering. *Sens. Actuators, B* **2021**, 330, 129303.

- (14) Cai, J.; Wu, Y.; Bai, H.; He, Y.; Qin, Y. SERS and machine learning based effective feature extraction for detection and identification of amphetamine analogs. *Heliyon* **2023**, 9 (12), e23109.
- (15) Su, J.; Zhao, L.; Yang, R.; Zhang, X.; Wang, C.; Li, L.; Wang, L.; Sun, X.; Wei, W.; Wang, Y. Sensitive SERS detection of trace methamphetamine in complex samples through sharp-spiked gold nanostructure. *Spectrochim. Acta, Part A* **2025**, 336, 126037.
- (16) Sulk, R. A.; Corcoran, R. C.; Carron, K. T. Surface-enhanced Raman scattering detection of amphetamine and methamphetamine by modification with 2-mercaptosuccinic acid. *Appl. Spectrosc.* **1999**, 53 (8), 954–959.
- (17) President's Council of Advisors on Science and Technology. *Forensic Science in Criminal Courts: Ensuring Scientific Validity of Feature-comparison Methods*. In *Executive Office of the President of the United States*, 2016.
- (18) Holman, A. P.; Kurouski, D. Cross-Study Validation and Guidance for Resampling Approaches for Partial Least Squares Discriminant Analysis in Spectral Machine Learning. *Anal. Chim. Acta* **2026**, 1414, 345655.
- (19) Michota, A.; Bukowska, J. Surface-enhanced Raman scattering (SERS) of 4-mercaptobenzoic acid on silver and gold substrates. *J. Raman Spectrosc.* **2003**, 34 (1), 21–25.
- (20) Scarpitti, B. T.; Morrison, A. M.; Buyanova, M.; Schultz, Z. D. Comparison of 4-mercaptobenzoic acid surface-enhanced Raman spectroscopy-based methods for pH determination in cells. *Appl. Spectrosc.* **2020**, 74 (11), 1423–1432.
- (21) Shende, C.; Smith, W.; Brouillette, C.; Farquharson, S. Drug stability analysis by Raman spectroscopy. *Pharmaceutics* **2014**, 6 (4), 651–662.
- (22) Taplin, F.; O'Donnell, D.; Kubic, T.; Leona, M.; Lombardi, J. Application of Raman spectroscopy, surface-enhanced Raman scattering (SERS), and density functional theory for the identification of phenethylamines. *Appl. Spectrosc.* **2013**, 67 (10), 1150–1159.
- (23) Fiorentin, T. R.; Krotulski, A. J.; Martin, D. M.; Browne, T.; Triplett, J.; Conti, T.; Logan, B. K. Detection of cutting agents in drug-positive seized exhibits within the United States. *J. Forensic Sci.* **2018**, 64 (3), 888–896.
- (24) Broséus, J.; Gentile, N.; Esseiva, P. The cutting of cocaine and heroin: a critical review. *Forensic Sci. Int.* **2016**, 262, 73–83.
- (25) Drug Enforcement Administration. In *Dimethyl Sulfone (Also Known as MSM, DMS, Methyl Sulfone or DMSO2) is Used as a Cutting Agent for Methamphetamine*; 2025.
- (26) Sisco, E.; Burns, A.; Schneider, E.; Bobka, L.; Ikpeama, I. A template for the validation of DART-MS for qualitative seized drugs analysis. *Forensic Chem.* **2022**, 29, 100415.
- (27) Couch, A. N.; Tyler Davidson, J. Development of a novel seized drug screening method utilizing DART-MS and used weigh paper. *Forensic Chem.* **2024**, 39, 100572.
- (28) Ott, C. E.; Wilcox, A.; Kalb, S.; McConnell, A.; Sisco, E.; Arroyo, L. E. Development and evaluation of a nontargeted electrochemical surface-enhanced Raman spectroscopy (EC-SERS) screening method applied to forensic seized drug casework samples. *Forensic Chem.* **2024**, 41, 100621.