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Research Paper

Ephedrine: From Ancient Remedy to Advances in High-Purity Synthesis and Forensic Identification

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ABSTRACT

Background: Ephedrine, the alkaloid of Ephedra (mainly Ephedra sinica, or Ma Huang), has been utilized in traditional Chinese medicine for decades to treat colds, bronchitis, and asthma due to its sympathomimetic and bronchodilator properties. The isolation of Ephedrine in the late 19th century was a milestone in the field of natural product pharmacology. It was first discovered in Western medicine as an orally active adrenergic receptor agonist. Although therapeutically beneficial, Ephedrine is also associated with dose-related toxicities that range from a mild manifestation such as restlessness and insomnia to serious cardiovascular and neurological adverse effects like hypertension, arrhythmias, seizures, and sudden death. In addition, its use as a precursor to illicit methamphetamine manufacture has contributed to control and public health problems.

Methods: A certified analytical procedure was established that combined FTIR and ^{1}H NMR spectroscopy to authenticate the structure and assess the purity of the analgesic drug ephedrine. In ^{1}HNMR spectroscopy, the main goal was the assignment of typical environments for protons in the molecule in an effort to ensure the molecular structure is not compromised. The other technique used was FTIR spectroscopy, which aimed to produce a fingerprint of the functional groups.

Results: The ^{1}H-NMR spectrum of Ephedrine displayed well-resolved and characteristic resonances at δ 7.0–7.4 ppm corresponding to aromatic protons, δ 4.7–5.0 ppm attributed to the hydroxyl (–OH) proton, δ 3.2–3.5 ppm for the methine proton adjacent to the hydroxyl group (–CHOH), and δ 1.0–1.2 ppm corresponding to the methyl group. The absence of extraneous signals confirmed the sample's high chemical purity and structural integrity.

Conclusion: Current analytical advances have enhanced the certainty of ephedrine identification. Fourier transform infrared spectroscopy (FTIR) provides a rapid structural fingerprint and a practical assessment of purity. In contrast, proton nuclear magnetic resonance (^{1}H-NMR) provides detailed information on molecular structure, enabling accurate assignment of functional groups and stereochemistry. When applied in combination, these techniques provide a complementary analytical platform for forensic and clinical confirmation of Ephedrine in complex matrices. Concurrently, modern synthetic methodologies maximize enantioselectivity, high yield, and environmental benignity, thereby extending both pharmacological use and forensic discrimination. Therefore, Ephedrine exemplifies the dual nature of natural products: an ancient medicine of immense therapeutic utility that, in the twentieth century, has also come to be associated with toxicological hazard, regulatory control, and societal harm.

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Introduction

Ephedrine is a sympathomimetic alkaloid that mimics the actions of endogenous catecholamines, producing strong cardiovascular and respiratory effects. Traditionally extracted from Ephedra species, particularly E. sinica (Ma Huang), it has been used in Chinese medicine for more than 5,000 years to treat asthma, bronchospasm, and respiratory infections [1, 2].

The isolation of Ephedrine by Nagai Nagayoshi in the late 19th century marked a turning point from herbal folk remedies to modern pharmacotherapy. Unlike many plant-derived agents, Ephedrine exhibited excellent oral bioavailability and stability, which enabled its widespread adoption during the 20th century [1, 2-5]. It became a mainstay in the treatment of asthma, nasal congestion, intraoperative hypotension, narcolepsy, and even as an adjuvant in weight-loss formulations.

However, the same adrenergic stimulation that provided therapeutic efficacy also caused dose-dependent toxicities, ranging from cardiovascular complications to central nervous system overstimulation. By the mid-20th century, increasing reports of hypertension, arrhythmias, myocardial infarction, stroke, and sudden death raised significant safety concerns [6]. Together with its role as a precursor in clandestine methamphetamine synthesis, Ephedrine became subject to strict global regulation [7, 8].

Today, Ephedrine is restricted to specialized clinical settings, such as anesthesiology for intraoperative hypotension, and its use is tightly monitored. Meanwhile, toxicologists and pharmacologists continue to study its dual nature both as a therapeutic drug and a drug of abuse, highlighting the need for continuous clinical, forensic, and regulatory vigilance [9, 10].

The present study aims to develop and authenticate combined FTIR and ^{1}H-NMR analytical methods for the structural analysis and purity determination of Ephedrine, highlighting their use in forensic science, toxicology, and pharmacy. The study also aims to explore synthetic optimization procedures for synthesizing high-purity ephedrine under environmentally friendly conditions.

Historical Overview: Antiquity through Modern Pharmacology

The earliest records of E. sinica use in ancient China describe its prescription for respiratory diseases, fever, and fatigue. Its persistence across centuries demonstrates its clinical utility long before modern pharmacology [11-13]. In the late 19th century, Ephedrine entered Western medicine, first as a treatment for asthma and later as a component of over-the-counter cold remedies. In the 20th century, its sympathomimetic effects made it the most widely used bronchodilator and decongestant. However, its stimulant properties also encouraged recreational misuse and facilitated diversion into illicit methamphetamine production, cementing its place at the intersection of legitimate medicine and illegal markets [11-14].

Toxicology of Ephedrine

The toxicological profile of Ephedrine is closely tied to its adrenergic activity:

Cardiovascular system: Hypertension, tachyarrhythmias, myocardial infarction, and sudden cardiac death [15].

Central nervous system: Agitation, insomnia, tremor, seizures, and psychosis.

Chronic exposure: Tolerance, dependence, and elevated long-term mortality.

Case reports of ephedrine-related fatalities underscore the importance of rigorous monitoring and justify the extensive regulatory restrictions introduced in recent decades.

Impact on the Immune System and Pathophysiology: Ephedrine acts on adrenergic receptors on immune cells, thereby modulating cytokine signaling and inflammatory cascades [16, 17]. Acute administration can transiently inhibit airway inflammation, but continuous exposure derails immune homeostasis. Evidence shows that Ephedrine affects IL-6, TNF-α, and interferon-γ levels, inhibits the function of T-cells, and aggravates autoimmune diseases like lupus and rheumatoid arthritis. It also affects immunometabolic pathways, such as glucose uptake and lipid metabolism, and is associated with chronic use and systemic inflammation, cardiovascular disease, and metabolic disorders [18-20].

Progress in High-Yield and High-Purity Synthesis

Earlier synthetic strategies for Ephedrine often employed hazardous intermediates and environmentally unfriendly processes. Contemporary innovations now emphasize:

Biocatalysis: Enzyme-catalyzed reductions with high stereoselectivity and reduced energy consumption.

Chiral catalysis and organocatalysis: Offering enantioselective control with fewer byproducts.

Continuous-flow microreactors: Providing greater reaction control, scalability, and industrial safety.

These developments enhance yield and purity while ensuring stereochemical accuracy, which is critical for pharmacological activity and reducing side effects [1-5].

High Purity and High Yield Synthesis Methods

Modern synthetic efforts for ephedrine focus on high purity, stereoselectivity, and environmental sustainability. Strategies frequently combine chiral, organocatalytic, and biocatalytic processes with advanced purification techniques, such as chromatography.

For analytical verification, integrating Fourier-transform infrared spectroscopy (FTIR) and proton nuclear magnetic resonance (^{1}H-NMR) provides complementary confirmation. FTIR delivers a rapid structural fingerprint and identifies functional groups such as hydroxyl (O–H), amine (N–H), and aliphatic/aromatic C–H stretches. Meanwhile, ^{1}H-NMR offers detailed structural resolution, including proton assignments for the hydroxyl group, β-hydroxylated carbon, aromatic protons, and the N-alkyl substituent. Together, FTIR and ^{1}H-NMR ensure precise identification, purity determination, and reproducibility of synthetic Ephedrine, making them indispensable tools in both pharmaceutical development and forensic toxicology [5, 6].

Synthesis of α-Bromopropiophenone

Propiophenone was dissolved in dry benzene in a round-bottom flask to which a condenser was attached. The reaction was carried out slowly under vigorous stirring, adding bromine at a uniform rate to maintain the temperature below 40°C (Figure 1). The initial intense coloration of bromine was discharged on addition, indicating consumption. After completing the addition, the reaction mixture was stirred for an additional 30 minutes to ensure complete conversion. The resulting solution was treated cautiously with aqueous sodium hydroxide to neutralize any excess hydrogen bromide, followed by a water wash. The organic layer was separated and used directly in the next step without purification. α-Bromopropiophenone showed a good yield (>90%).

Figure 1. Bromination of propiophenone in anhydrous benzene to produce α-bromopropiophenone (>90%).

Figure 2. Alkylation of α-bromopropiophenone to ketone intermediate by reaction with methylamine in restricted conditions.

Synthesis of the Ketone Intermediate (Methcathinone)

The solution of α-bromopropiophenone in benzene from the previous reaction was treated with water. Aqueous methylamine (or an equimolar solution of base and methylamine hydrochloride) was added in portions with stirring over a long time period (about 12 hours) at a temperature of about 30°C under sealed conditions to prevent loss of volatile methylamine. Upon completion, upon appearance of a color change, a saturated aqueous base was added, and the mixture was heated to 70°C to liberate any amine product from its salt form (Figure 2). The mixture was cooled, and the aqueous layer was decanted. The benzene layer was sequentially washed with brine and water to furnish a solution of the ketone intermediate, which was used directly in the succeeding reduction.

Reduction to Ephedrine

Sodium borohydride was slowly added to the agitated benzene solution of the ketone intermediate in small portions to control foaming and exotherm. After addition, the reaction mass was shaken well at room temperature for 24 hours, then heated to 40-50 °C for 3 hours to complete the reduction. The solution was then chilled, and a concentrated aqueous alkali solution was added to decompose the excess borohydride and coagulate the inorganic salts, facilitating filtration. The solution was filtered, and the residue was washed with benzene. The organic filtrates were washed with cold water (Figure 3). The reduction product (freebase

Figure 3. Reduction of ketone intermediate to produce the ephedrine freebase in restricted conditions.

ephedrine) was then extracted from the organic phase with the help of a dilute acidic aqueous solution. The aqueous acid-combined extracts were washed with an organic solvent to remove neutral impurities. The aqueous fraction was basified to pH > 11 with solid alkali, liberating ephedrine freebase as an oil. The freebase was retransferred into dichloromethane. The combined organic extracts were washed with brine and water, and the solvent was then reduced in pressure to obtain a crude oil [11, 17].

Crystallization of Ephedrine Hydrochloride from Pure Freebase Oil

Isopropyl alcohol (IPA) was used to dissolve the freebase oil, which was then converted to its hydrochloride salt by gradual addition of concentrated hydrochloric acid until the mixture was slightly acidic. Isopropyl alcohol was evaporated, leaving a thick residue. The residue was re-dissolved in fresh IPA and re-evaporated to dryness to remove all water. The solid so obtained was made to crystallize by cooling and agitating in a jet of air. The crystal mass was mixed with cold acetone, filtered, and washed with additional cold acetone to yield ephedrine hydrochloride as a white, fine crystalline powder. The product was thoroughly dried (Figure 4).

^{1}H-NMR Profile and Forensic Uses

^{1}H-NMR spectroscopy provides structural characterization in detail of Ephedrine, complementing vibrational spectroscopic methods. In the recorded

Figure 4. Crystallization of hydrochloride salt from freebase oil to produce ephedrine hydrochloride as a fine white crystalline powder.

spectrum (Figure 5), characteristic resonances were observed:

δ 7.0–7.4 ppm (m, 5H) – phenyl ring aromatic protons' multiplets, confirming monosubstituted benzene moiety.

δ 4.7–5.0 ppm (br s, 1H) – hydroxyl proton (–OH), exchangeable and vanishing on D_2O shake, confirming secondary alcohol group.

δ 3.2–3.5 ppm (m, 1H) – the methine proton next to the hydroxyl group (–CHOH–).

δ 2.9–3.1 ppm (m, 2H) – methylene protons next to the nitrogen (–CH_2–N).

δ 1.0–1.2 ppm (d, 3H) – the methyl group bonded to the methine carbon.

This spectral fingerprint confirms the molecular identity of Ephedrine and distinguishes it from close analogues such as pseudoephedrine. The absence of additional peaks confirmed the high purity of the analytical sample, thereby establishing the success of the synthesis and purification process.

Validation of ^{1}H-NMR Method for Ephedrine Detection

The ^{1}H-NMR method was validated according to spectroscopic criteria:

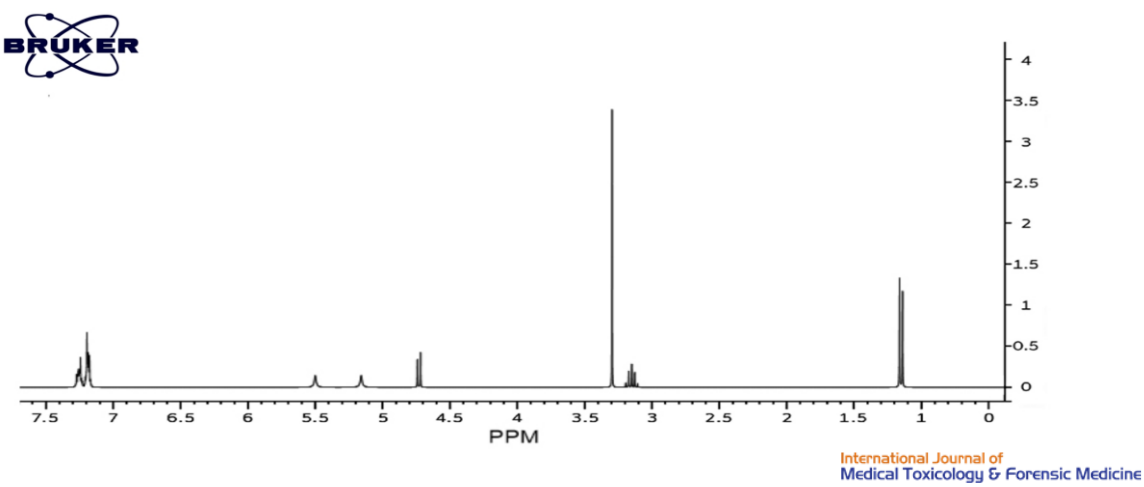

Figure 5. ^{1}HNMR spectrum of ephedrine.

Table 1. ^{1}H-NMR chemical shift assignments for Ephedrine.

δ (ppm)	Multiplicity	Integration	Assignment	Notes
7.0 – 7.4	m	5H	Aromatic protons (phenyl)	Monosubstituted benzene ring
4.7 – 5.0	br s	1H	–OH proton	Exchangeable, disappears in D_2O
3.2 – 3.5	m	1H	–CHOH methine	Adjacent to hydroxyl group
2.9 – 3.1	m	2H	$–CH_2–N$	Methylene next to secondary amine group
1.0 – 1.2	d	3H	$–CH_3$	Coupled to methine proton (isopropanol)

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Specificity: All expected signals were recorded without interference from solvent or impurities.

Reproducibility: Chemical shifts were reproducible across replicate acquisitions, varying by ≤ ±0.02 ppm.

Resolution: Multiplet splitting patterns were well resolved, allowing confident assignment of all protons.

Stability: Spectra did not change following repetitive scans, indicating no degradation under analysis conditions.

Conclusion: ^{1}H-NMR spectroscopy provided unequivocal structural identification and stereochemical confirmation of Ephedrine, making it highly suitable for forensic authentication and purity determination.

FTIR Profile and Forensic Applications

Fourier-transform infrared spectroscopy (FTIR) gave confirmatory data on Ephedrine's functional groups (Figure 6). The spectrum showed:

3737–3729 cm^{-1}: O–H stretch (secondary alcohol).

3302 cm^{-1}: N–H stretch (secondary amine).

2920, 2853 cm^{-1}: aliphatic C–H stretches.

1638–1543 cm^{-1}: N–H bending and skeletal vibrations.

1255–1061 cm^{-1}: C–N and C–O stretching vibrations.

Fingerprint region (924, 722, 626 cm^{-1}): aromatic C–H out-of-plane bending, which established the substitution pattern.

The FTIR spectrum enabled rapid screening of ephedrine crystals or powders without extensive preparation. In forensic applications, it provides rapid identification of authentic pharmaceutical-grade material and adulterated or illicit preparations from the presence or absence of extra peaks.

Validation of FTIR Method

Validation parameters ensured the integrity of FTIR analysis for Ephedrine:

Specificity: No interfering peak was observed; all functional group peaks overlapped with reference spectra.

Reproducibility: Peak positions varied by less than ±2 cm^{-1} between copies.

Stability: Spectral fine structure did not alter when scanned repeatedly.

Results

The improved ^{1}H-NMR and FTIR systems demonstrated higher analytical performance in the structural analysis and purity determination of Ephedrine.

In the ^{1}H-NMR spectrum (Figure 5), characteristic resonances were seen at δ 7.0–7.4 ppm (m, 5H, aromatic protons), δ 4.7–5.0 ppm (br s, 1H, –OH proton), δ 3.2–3.5 ppm (m, 1H, –CHOH methine proton), δ 2.9–3.1 ppm (m, 2H, $–CH_2–N$), and δ 1.0–1.2 ppm (d, 3H, methyl group). This spectral fingerprint is in reasonable conformity with published reference spectra, confirming the stereochemical configuration and structural integrity of Ephedrine. The absence of extraneous peaks ensured high sample purity and a low level of environmental or synthetic impurities. Replication analysis revealed excellent reproducibility with chemical shift variations within ±0.02 ppm.

The FTIR spectrum (Figure 6) provided confirmatory molecular identification. Significant absorption bands were observed at 3737–3729 cm^{-1} (O–H stretching), 3302 cm^{-1} (N–H stretching), 2920 and 2853 cm^{-1} (aliphatic C–H stretching), and 1061 cm^{-1} (C–O stretching). Certain broad peaks were observed in the fingerprint region (1543, 1463, 1412, 1255, 924, 722, and 626 cm^{-1}), indicating the presence of secondary alcohol, amine, and aromatic functionalities. Reproducibility of peak positions (≤ ±2 cm^{-1}) between replicate scans testified to the robustness

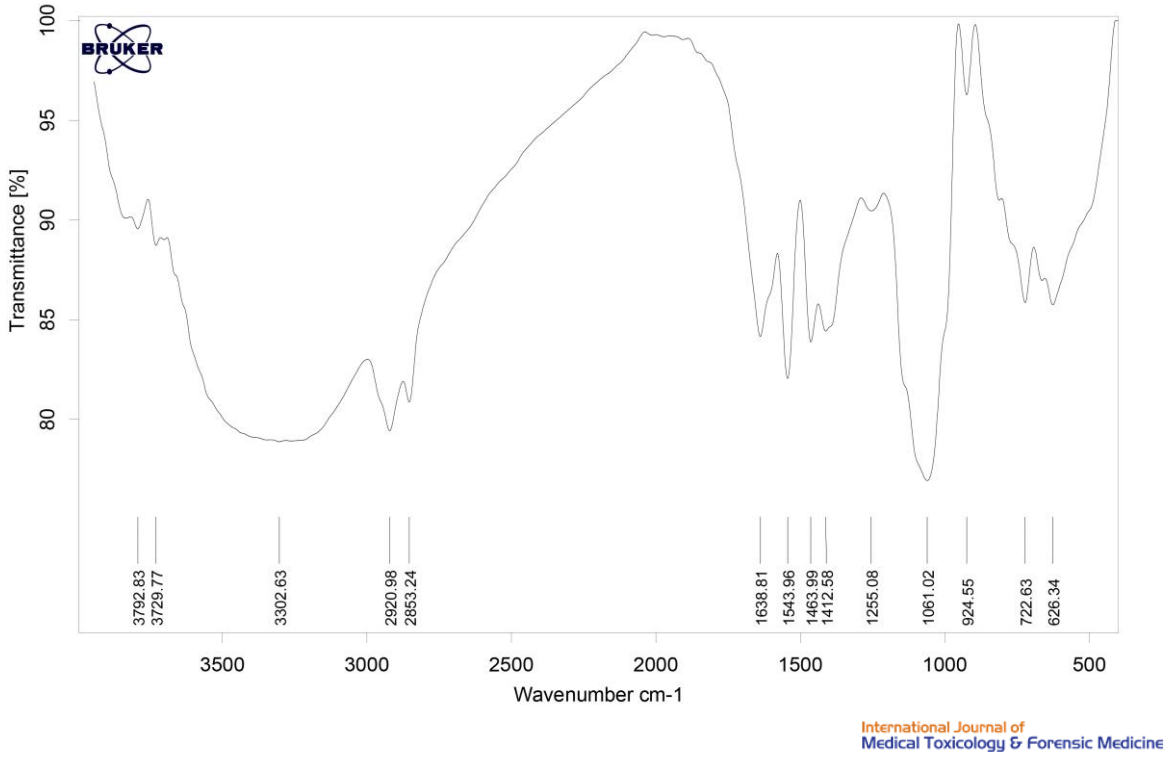

Figure 6. FTIR spectrum of Ephedrine (KBr pellet).

and consistency of the spectroscopic method.

Together, ^{1}H-NMR and FTIR analysis provided a robust analytical platform for ephedrine identification and assurance of purity: ^{1}H-NMR offered detailed structural and stereochemical information, whereas FTIR provided rapid, non-destructive fingerprinting suitable for purity determination and mass screening of pharmaceutical or seized material.

Discussion

Results confirm the stability and reliability of the hybrid ^{1}H-NMR–FTIR technique for the forensic profiling and structural determination of Ephedrine in biological and pharmaceutical samples. The typical NMR signals, particularly the methine proton adjacent to the hydroxyl group (δ 3.2–3.5 ppm) and the aromatic signals (δ 7.0–7.4 ppm), are in full agreement with literature-reported reference data, ensuring analytical specificity and definitive identification of the compound. Also, the generic FTIR bands for O–H, N–H, and C–O vibrations provide strong evidence for functional group identification and compound purity.

While ^{1}H-NMR is not as sensitive as chromatographic techniques for trace-level quantitation, it is unparalleled in its ability for stereochemical confirmation and structure elucidation. It is thus beneficial for discriminating between Ephedrine and pseudoephedrine, as well as other sympathomimetic analogs. FTIR, by contrast, allows rapid, non-destructive screening of powders, tablets, or crystalline residues, with immediate detection of impurities or adulterants, vital for forensic analysis and quality control.

From a forensic perspective, the synergy of ^{1}H-

Table 2. Characteristic FTIR absorption bands of Ephedrine.

Wavenumber (cm^{-1})	Intensity	Functional group assignment	Interpretation / Notes
3737, 3729	Medium	O–H stretch (free OH)	Secondary alcohol group
3302	Strong	N–H stretch	Secondary amine functionality
2920, 2853	Strong	C–H stretch (aliphatic)	–CH_2– and –CH_3 groups
1638	Medium	N–H bending / C=C skeletal vibration	Amine bending and aromatic contribution
1543	Medium	C–N stretching + N–H bending	Amine-related band
1463, 1412	Medium	C–H bending (CH_2, CH_3)	Aliphatic bending
1255	Medium	C–N stretching	Aliphatic amine
1061	Strong	C–O stretch (alcohol)	Secondary alcohol functional group
924, 722, 626	Medium	Aromatic C–H out-of-plane bending	Characteristic aromatic substitution patterns

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NMR and FTIR provides greater analytical confidence for structural confirmation and functional identification. Simultaneous application of the methods allows efficient detection protocols in toxicology and forensic crime laboratories, particularly when rapid screening must be followed by definitive molecular identification. Future improvements, such as the use of chiral NMR techniques and chemometric FTIR spectroscopy, can presumably enhance discrimination between ephedrine enantiomers (d- vs. l-ephedrine) and the identification of counterfeit or adulterated drug products.

Conclusion

This study establishes and verifies a tandem ^{1}H-NMR and FTIR analytical stage for the correct identification and purity analysis of Ephedrine in pharmaceutical, biological, and forensic specimens. The two techniques were very selective, reproducible, and accurate in molecular structure and purity verification.

The email service also provided distinct, diagnostic resonance patterns that enabled unambiguous structural assignment and purity determination, thereby enabling efficient discrimination between Ephedrine, pseudoephedrine, and analogs. The FTIR spectrum also provided immediate, non-destructive identification of functional groups and fingerprint confirmation. It was particularly valuable for preliminary screening of bulk and seized material before confirmatory NMR analysis.

Together, when used in combination, ^{1}H-NMR and FTIR provide a robust complementary toolkit that combines molecular-level specificity with rapid functional characterization. The two-step process maximizes forensic insight by enabling source attribution, verifying pharmaceutical-grade purity, and detecting counterfeit or illicit variants.

In addition to analytical significance, the findings underscore the dual nature of Ephedrine, a therapeutic drug by historical tradition but with extreme toxicological and regulatory relevance in modern contexts. The synergistic use of advanced spectroscopic techniques such as FTIR and ^{1}H-NMR not only ensures improved analytical precision but also helps law enforcement and public health agencies prevent ephedrine misuse and diversion into illicit methamphetamine production.

Conflicts of Interest

The authors report there are no competing interests to declare.

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