Cover Page

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# ULTRASOUND-ASSISTED SYNTHESIS OF 3,5-DIARYL-4,5-DIHYDRO-1-PHENYL PYRAZOLINES: A RAPID AND GREEN APPROACH VIA SONOCHEMICAL ACTIVATION

**Dr. Ravikumar Ramlu Vidule**
Associate Professor
Dept. Of Chemistry, Shri Sant Gadge Maharaj Mahavidyalaya Loha, Dist. Nanded

**Abstract:**

Pyrazolines are a significant class of five-membered heterocyclic compounds known for their diverse biological activities. Conventional synthesis of these derivatives often involves prolonged heating and moderate yields. To overcome this in this study, we reporting a rapid and eco-friendly synthesis of 3,5-diaryl-4,5-dihydro-1-phenyl pyrazolines **(2a-d)** via the cyclocondensation of substituted chalcones with **phenyl hydrazine** in an ethanol-acidic medium. The reaction was performed under ultrasonic irradiation, leveraging sonochemical activation to enhance reaction kinetics compared to traditional reflux methods. The synthesized derivatives were characterized using FT-IR, $^{1}$H NMR, $^{13}$C NMR, Mass spectrometry, and elemental analysis. IR spectra confirmed the pyrazoline framework with characteristic -C=N- absorption bands at 1607–1610 cm$^{-1}$. The $^{1}$H NMR analysis revealed a distinct $AB_X$ spin system for the $C_4$ and $C_5$ protons; the methylene protons ($H_A$, $H_B$) appeared as doublets of doublets in the $\delta$ 3.24 to 4.02 ppm range, while the methine proton ($H_X$) appeared as a deshielded doublet of doublets at $\delta$ 5.48 to 5.68 ppm due to the proximity of the aromatic ring. Mass spectral data were in high agreement with the calculated molecular weights, and elemental analysis confirmed a purity level exceeding 95%. The ultrasound-assisted approach proved superior to conventional heating, offering significantly reduced reaction times, simplified work-up procedures, and high yields, aligning with the principles of green chemistry.

**Keywords:** 3,5-Diaryl-4,5-dihydro-1-phenyl pyrazolines; $AB_X$ Spin System; Chalcones; Cyclocondensation; Green Chemistry; Sonochemistry; Ultrasound-Assisted Synthesis.

## 1. Introduction

Heterocyclic compounds, particularly those containing nitrogen, represent the most diverse family of organic compounds with immense biological and industrial importance[1]. Among these, pyrazolines—five-membered di-nitrogenous heterocycles—have emerged as a "privileged scaffold" in medicinal chemistry[2]. The 3,5-diaryl-4,5-dihydro-1-phenyl pyrazoline derivatives are particularly noted for their broad spectrum of pharmacological properties, including antimicrobial, anti-inflammatory, anticancer, antidepressant, and anticonvulsant activities.[3,4] Traditional methods for synthesizing pyrazolines usually involve the cyclocondensation of chalcones with hydrazine under prolonged reflux in acidic or basic media[5]. However, these classical methods often suffer from drawbacks such as long reaction times, high energy consumption, and lower yields[6]. In the modern era, the implementation of Green Chemistry principles has led to the development of non-conventional energy sources like microwave and ultrasound to promote organic transformations[7]. Sonochemistry, the use of ultrasonic waves (20 kHz to 10 MHz) to stimulate chemical reactions, relies on the phenomenon of **acoustic cavitation**[8].

This process involves the formation, growth, and implosive collapse of bubbles in a liquid, creating localized "hotspots" with extreme temperatures and pressures that significantly accelerate reaction kinetics[9,10]. Ultrasound-assisted synthesis (UAS) offers several advantages like higher yields, shorter reaction times, and milder conditions compared to thermal reflux[11,12]. In the present study, we utilize sonochemical activation to synthesize a series of substituted 3,5-diaryl-4,5-dihydro-1-phenyl pyrazolines from chalcones, providing a more efficient and sustainable pathway[13].

Cover Page

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## 2. Experimental

### 2.1 Materials and Methods:

All reagents and chemicals were of analytical grade. Melting points were determined using the open capillary method and are uncorrected. FT-IR spectra were recorded on a Shimadzu 8700 spectrometer using KBr pellets. $H^1$NMR and $C^{13}$ NMR spectra were recorded on a Bruker 400 MHz spectrometer in *$CDCl_3$* with TMS as the internal standard. Mass spectra were recorded on an EI-SHIMADZU-GC-MS.

### 2.2 General Procedure for Synthesis (2a-d):

**A. Conventional Method:**

A mixture of substituted chalcone (**1a-d**, 1 mmol) and phenyl hydrazine (3 mmol) was refluxed for 3 to 4 hrs in ethanol (10 mL) containing a few drops of glacial acetic acid. The progress was monitored by TLC.

**B. Ultrasound-Assisted Method:**

The same mixture was placed in a sonication bath and irradiated at room temperature 35°C. The reaction was completed within 15–30 minutes (monitored by TLC). After completion, the mixture was poured into ice-cold water. The resulting solid was filtered, washed with cold ethanol-water, and recrystallized from ethanol.

**Scheme: I**

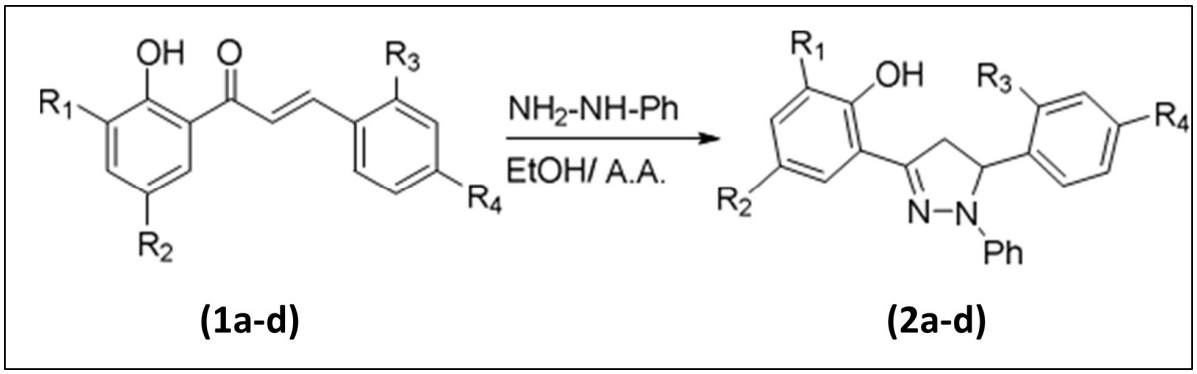


**Table 1: Substituent data and physical constants of synthesized compounds**

| Sr. No. | Product | Substituent (R) | Time (min) [US][a] | Time (h) [Conv][b] | Yield (%) [US]c | M.P. (°C) |
|---|---|---|---|---|---|---|
| 1 | **2a** | -H | 20–30 | 3.5 | 92 | 118–120 |
| 2 | **2b** | 4-Cl | 25–35 | 4.0 | 89 | 142–144 |
| 3 | **2c** | 4-Br | 25–35 | 4.0 | 88 | 156–158 |
| 4 | **2d** | 4-$OCH_2CH_3$ | 30–40 | 4.0 | 90 | 134–136 |

**Ultrasound-Assisted Method Time (min) [US][a]**: This refers to the reaction performed using an ultrasonic bath or probe (Sonochemistry). The time is measured in minutes because the reaction is significantly faster.

**Conventional Reflux Method Time (h) [Conv][b]** : This refers to the traditional laboratory method of heating the reaction mixture at its boiling point using a round-bottom flask and a condenser. The time is measured in hours because it takes much longer to complete.

Cover Page

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**Ultrasound Method Yield Yield (%) [US]$^c$** : This represents the percentage of the final pure product obtained specifically when using the ultrasonic method.

### 3.0 Spectral interpretation of 3,5-diaryl-4,5-dihydro-N-phenyl pyrazolines (2a-d):

### 3.1 IR Spectra of 3,5-diaryl-4,5-dihydro-N-phenyl pyrazolines:

The IR spectra of selected products showed the absorption bands in the region of 1607-1610 $cm^{-1}$ due to –C=N– of pyrazoline ring[14], a band in the range between 1370-1355 $cm^{-1}$ indicates the presence of (-$OCH_2CH_3$) group. The absorption band in the region 3083-3094 $cm^{-1}$ is due to –OH stretching. The bands 809 $cm^{-1}$ due to C-Cl stretching, 505 $cm^{-1}$ due to C-Br appears whenever present in the respective compound[15]. All these observations are in agreement with those observed earlier.

### 3.2 $^1$H NMR Analysis: The ABX Spin System:

The most defining feature of 2-pyrazolines is the ABX spin system formed by the three protons at the C4 and C5 positions of the ring[16]. $^1$H NMR spectra revealed that the three protons $H_A$, $H_B$ and $H_X$ attached to C-4 and C-5 carbon atoms of the pyrazol ring gave an $AB_X$ spin system and they appeared as doublet of The methylene proton of pyrazoline ring ($H_A$, $H_B$) exhibited a typical $AB_X$ spin system with $H_X$ as a doublet of doublet.

**Methylene Protons ($H_A$, $H_B$):** The two non-equivalent protons at C4 coupled with each other and the vicinal methine proton ($H_X$). $H_A$ appeared as a doublet of doublets (dd) at $\delta$ 3.96–4.02 ppm, and $H_B$ appeared as a dd at $\delta$ 3.24–3.94 ppm[17].

**Methine Proton ($H_X$):** The proton at C5 appeared as a highly deshielded dd at $\delta$ 5.48–5.68 ppm due to the magnetic anisotropy of the adjacent aromatic ring[18].

**Additional Signals:** The ethoxy group showed a triplet for -$OCH_3$ $\delta$ 1.23–1.30 ppm and a quartet for -$OCH_2$ at $\delta$ 4.03–4.17 ppm. The ortho-hydroxyl proton was observed as a singlet at $\delta$ 10.14–11.73 ppm[19].

**Mass spectra:**

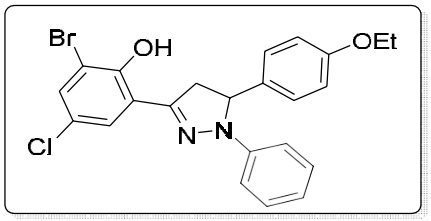
The mass spectra of synthesized products (N-Phenyl-2-pyrazolines) are also in agreement with their molecular formulae weights.

### 4. Conclusion

The present study successfully demonstrated a "Green" sonochemical approach for the synthesis of 3,5-diaryl-4,5-dihydro-1-phenyl pyrazolines. Ultrasound irradiation significantly reduced the reaction time from hours to minutes and provided higher purity and yields compared to the conventional reflux method. The structures were unequivocally established using modern spectroscopic techniques, confirming the formation of the pyrazoline scaffold and the presence of the characteristic $AB_X$ spin system. This protocol adheres to the tenets of green chemistry by minimizing energy consumption and hazardous waste.

**Spectral data of synthesized compounds:**

1. **3-(3-bromo-5-chloro-2-hydroxyphenyl)-5-(4-ethoxyphenyl)-4,5-dihydro-1-phenyl pyrazolines (2a):**



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**IR (KBR $cm^{-1}$)** : 3383, 1610, 1355, 809, 505 $cm^{-1}$;

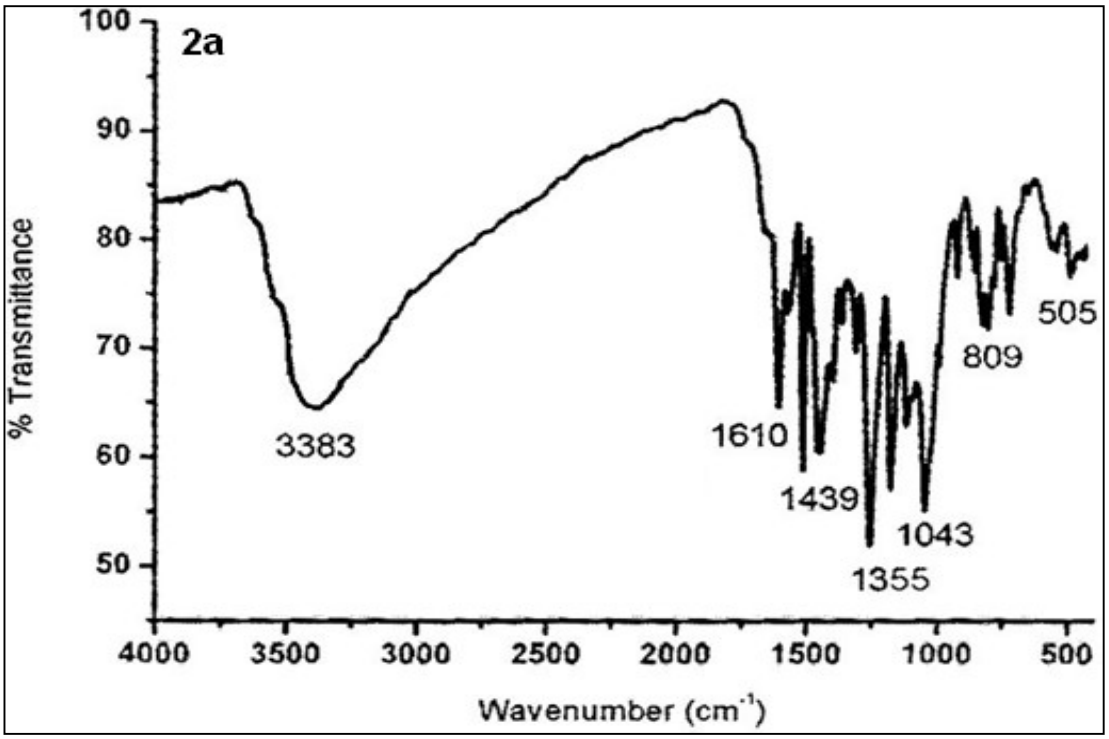
**$^1$H NMR (400 MHz, $CDCl_3$, ppm)** : δ 10.14 (s, 1H, OH), 6.69-7.68 (m, 11H, Ar-H), 5.48-5.53 (t,1H, $H_X$), 4.03-4.07 (q, 2H, $-OCH_2$), 3.99-4.02 (dd,1H,$H_A$), 3.94-3.98 (dd,1H,$H_B$), 1.27-1.30 (t, 3H).

**$^{13}$C-NMR ($CDCl_3$)** : *δ* 162.2. 156.1, 150.9, 143.5, 135.9, 134.8, 130.3, 130.1, 129.9, 129.8, 126.1, 125.9, 123.6, 121.3, 117.3, 117.2, 115.8, 115.4, 115.3, 65.2, 60.6, 40.6, 14.4;

**LCMS (m/z)** : 471.

**CHN analysis** : Calculated for $C_{23}H_{20}BrClN_2O_2$ : C, 58.56; H, 4.27; N, 5.94; found C, 58.65; H, 4.23; N, 4.89.

**IR spectra of : 2a**



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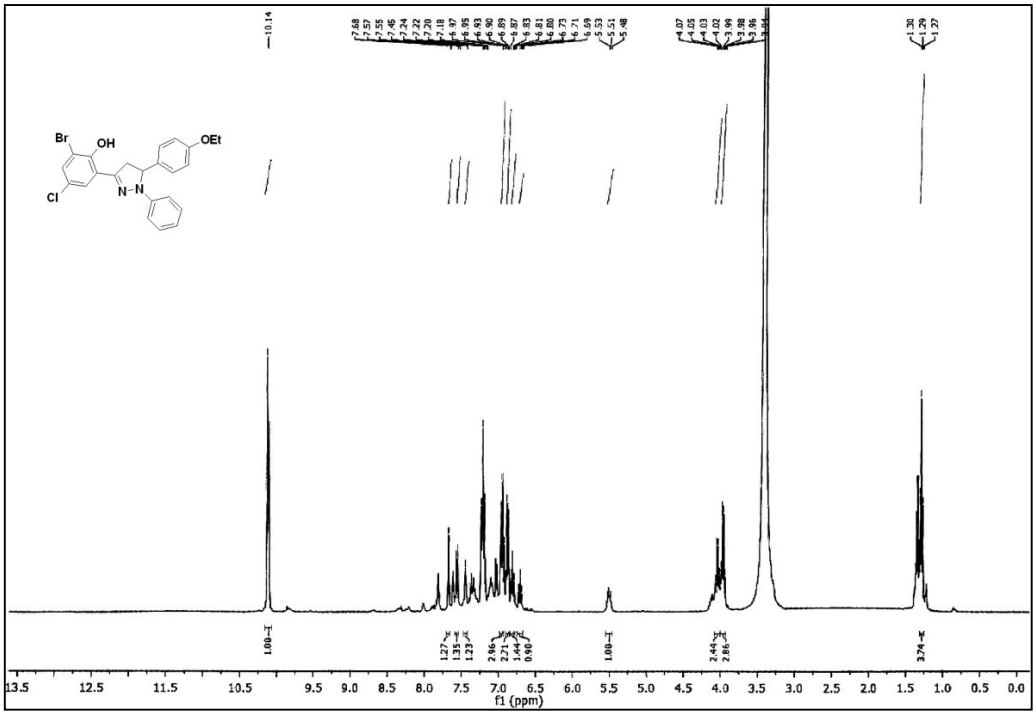
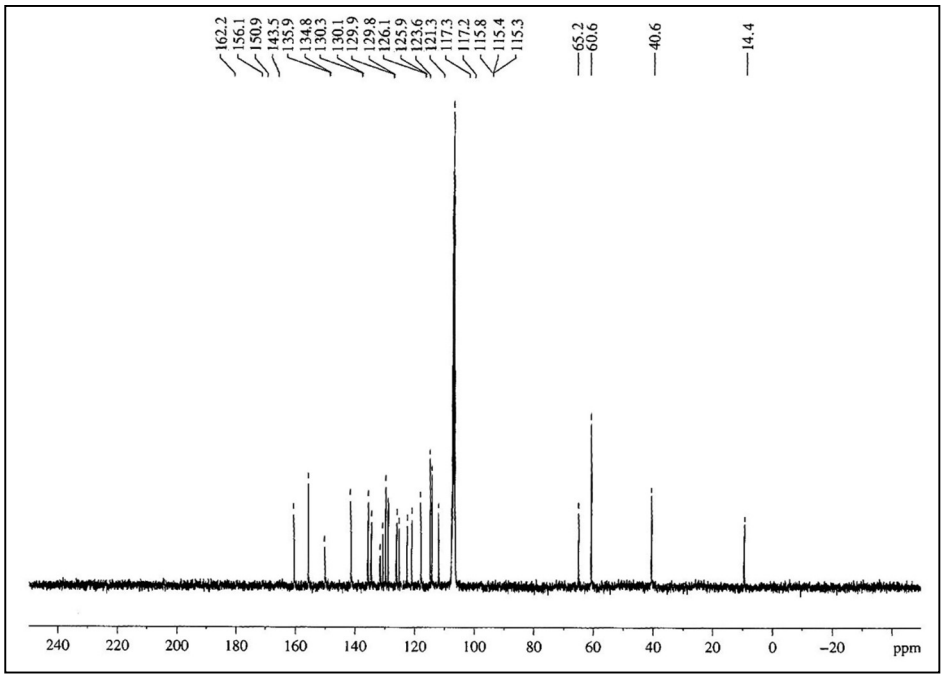
**$^{1}$H-NMR spectra of : 2a**




**$^{13}$C-NMR spectra of : 2a**



Cover Page

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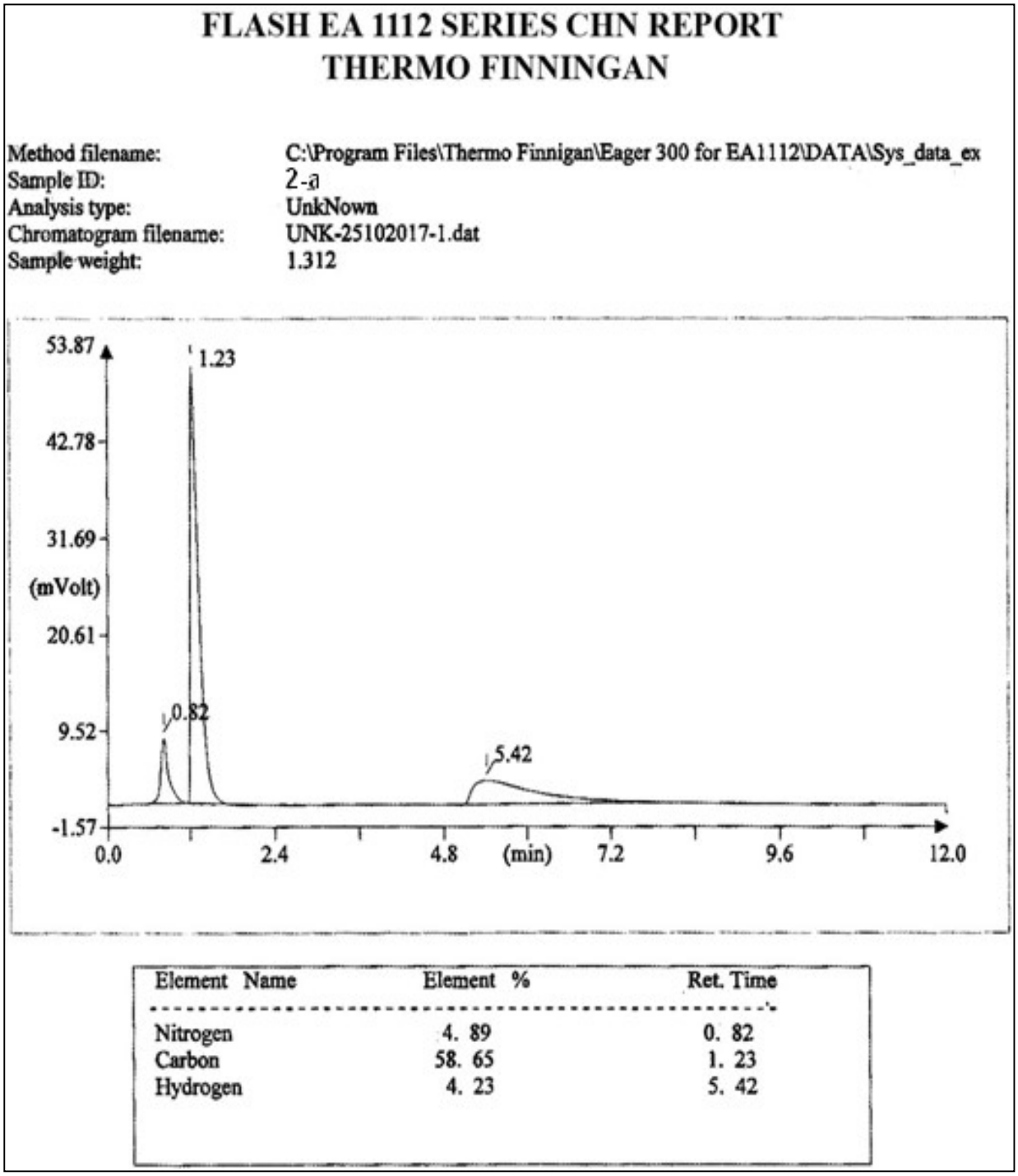
**LCMS spectra of : 2a**




**CHN analysis spectra of : 2a**

Cover Page

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