ISSN: 2457-0400

WORLD JOURNAL OF ADVANCE HEALTHCARE RESEARCH

www.wjahr.com

Impact Factor: 7.675

Volume: 10, Issue: 11

Page N. 174-179

Year: 2026

Original Article

Coden USA: WJAMA3

SYNTHESIS OF A NOVEL ESTER DERIVATIVE OF 3-AMINO-4-HYDROXYBENZOIC ACID WITH MENTHOL

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Article Received: 05 October 2026 **Article Revised: 25 October 2026** **Article Published: 03 November 2026**

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DOI: https://doi.org/10.5281/zenodo.23939989

How to cite this Article: Khadija Alsayed*[1], Rushdi Madwar (2026). Synthesis Of A Novel Ester Derivative Of 3-Amino-4-Hydroxybenzoic Acid With Menthol. World Journal of Advance Healthcare Research, 10(11), 174–179.

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ABSTRACT

A novel ester derivative (K) of 3-amino-4-hydroxybenzoic acid was synthesized via Fischer esterification with menthol using DMSO and concentrated H_2 SO_4 as a catalyst at 80 °C for 8 hours. The product was obtained as a brown precipitate in 70% yield. The structure was confirmed by FT-IR, ^{1}H NMR, and ^{13}C NMR spectroscopy. FT-IR revealed the disappearance of the acidic O–H band and the appearance of ester carbonyl (C=O) at 1694 cm^{-1} and C–O–C at 1111 cm^{-1}. ^{1}H NMR showed characteristic signals for aromatic (δ 7.24 ppm), amino (δ 4.16 ppm), and phenolic OH (δ 8.17 ppm) protons, confirming selective esterification at the carboxylic acid group. Signals for menthol protons (δ 3.46–3.41 ppm and δ 2.53 ppm) further supported the structure. ^{13}C NMR displayed the ester carbonyl at δ 162.60 ppm and the menthol C–O carbon at δ 49.07 ppm. These results confirm the successful synthesis of this novel ester derivative, highlighting its potential as a versatile intermediate for pharmaceutical and industrial applications.

KEYWORDS: Fischer esterification; 3-Amino-4-hydroxybenzoic acid; Menthol; Ester derivative; NMR spectroscopy.

1. INTRODUCTION

Nitrogen- and hydroxyl-substituted benzoic acid derivatives serve as essential platforms in heterocyclic chemistry and modern drug design, owing to their flexible spatial structures that enable effective binding to various biological receptors.[1] Among these, 3-amino-4-hydroxybenzoic acid (3,4-AHBA), with the chemical formula C7H7NO4C7H7NO4, stands out as a crucial building block and primary metabolite in both biological and industrial systems.[2] This compound holds exceptional significance in pharmaceutical organic chemistry due to the presence of three chemically active and electronically integrated functional groups on the aromatic ring: carboxyl (-COOH-COOH), phenolic hydroxyl (-OH-OH), and amino (-NH2-NH2) groups.[3]

This unique structural combination endows the compound with high efficiency as a versatile synthetic intermediate, particularly in the synthesis of heat- and stress-resistant polymers such as polybenzoxazole (PBO)[4], in addition to its role as a key element in the biosynthetic pathways of complex natural antibiotics in microorganisms.[5] Numerous reference studies have indicated that chemical modifications of the diverse functional groups of 3-amino-4-hydroxybenzoic acid lead to derivatives with enhanced therapeutic and applicative efficacy; research has demonstrated that these derivatives exhibit excellent antitumor and enzyme-inhibitory activities[7], as well as the ability to act as chelating agents, forming stable complexes with broad-spectrum antibacterial and antifungal activity.[8]

In recent years, however, the ester derivatives of this compound have garnered increasing research interest, as esterification represents one of the most successful strategies for enhancing the lipophilicity of acidic compounds, thereby facilitating their penetration through cellular membranes and improving their bioavailability. Recent literature surveys have revealed that esters derived from hydroxylated aromatic cores exhibit a significant leap in biological activities, particularly as potent antioxidants through free radical scavenging mechanisms and protection against oxidative stress.[6]

Based on these scientific foundations, and within the framework of searching for hybrid ester compounds combining an effective aromatic scaffold with natural molecular moieties, the present study focuses on the synthesis of a novel ester derivative of 3-amino-4-hydroxybenzoic acid via its chemical coupling with menthol using Fischer esterification, followed by the characterization and structural analysis of the resulting compound using advanced spectroscopic techniques.[6]

2. MATERIALS AND METHODS

2.1. Materials and Instruments

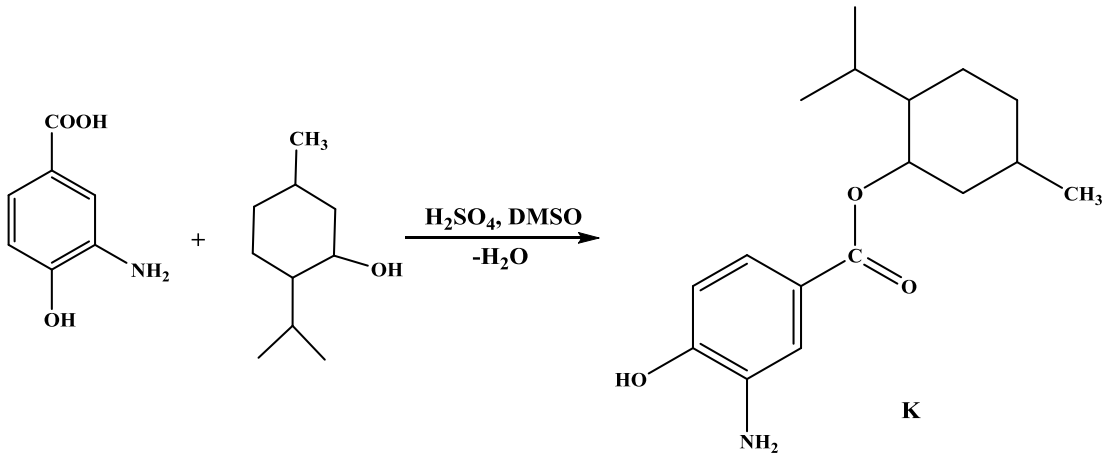
All chemicals and reagents used in this work were of analytical grade, purchased from BDH, Sigma-Aldrich, and Merck, and were used as received without further purification.

The Fourier-transform infrared (FT-IR) spectrum was recorded on a JASCO FT/IR-4100 spectrophotometer in the range of 4000–400 cm^{-1} using potassium bromide (KBr) pellets. ^{1}H and ^{13}C nuclear magnetic resonance (NMR) spectra were recorded on a Bruker spectrometer operating at 400 MHz, using deuterated dimethyl sulfoxide (DMSO-d_6) as the solvent. Chemical shifts (δ) are reported in parts per million (ppm) relative to tetramethylsilane (TMS) as an internal standard.

2.2. Synthesis 2-isopropyl-5-methylcyclohexyl 3-amino-4-hydroxybenzoate (k)

A mixture of 3-amino-4-hydroxybenzoic acid (0.25 g, 1.0 mmol) and menthol (0.17 g, 1.0 mmol) was dissolved in 15 mL of dimethyl sulfoxide (DMSO) in a 100 mL round-bottom flask equipped with a magnetic stirrer and a reflux condenser. A few drops of concentrated sulfuric acid (H_2SO_4) were then added as a catalyst. The reaction mixture was stirred at 80 °C for 8 hours.

The progress of the reaction was monitored by thin-layer chromatography (TLC) using a mixture of ethyl acetate/n-hexane (1: 1 v/v) as the mobile phase. Upon completion, the mixture was allowed to cool to room temperature. The solvent was then evaporated under reduced pressure, and the crude product was purified by extraction with an aqueous basic solution. The pure title compound was obtained as a brown precipitate in 70% yield.



Scheme 1: Synthetic pathway for the esterification of 3-amino-4-hydroxybenzoic acid with menthol.



Figure 1: Physical appearance of the purified title compound (brown precipitate).



Figure 2: Thin-layer chromatography (TLC) monitoring of the esterification reaction using ethyl acetate/n-hexane (1: 1 v/v) as the mobile phase.

3. RESULTS AND DISCUSSION

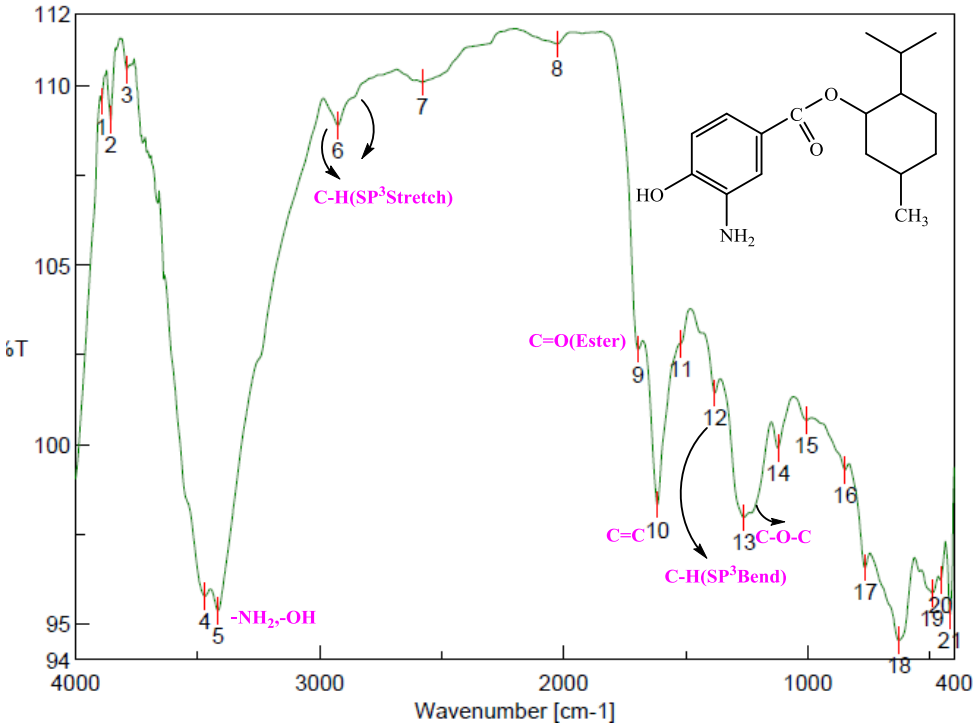
3.1. Spectroscopic Characterization

The molecular structure of the synthesized ester derivative (K) was unequivocally confirmed by comprehensive FT-IR, ^{1}H NMR, and ^{13}C NMR spectroscopic analyses.

3.1.1. FT-IR Spectroscopy

The FT-IR spectrum of the synthesized compound (K) (Figure3) provided strong evidence for the successful formation of the target ester. Characteristic absorption bands were observed at 1694 cm^{-1}, attributed to the ester carbonyl (C=O) stretching vibration, and at 1111 cm^{-1}, corresponding to the C–O–C stretching vibration of the ester linkage. Additionally, a band observed at 1687 cm^{-1} was assigned to the C=N stretching vibration.

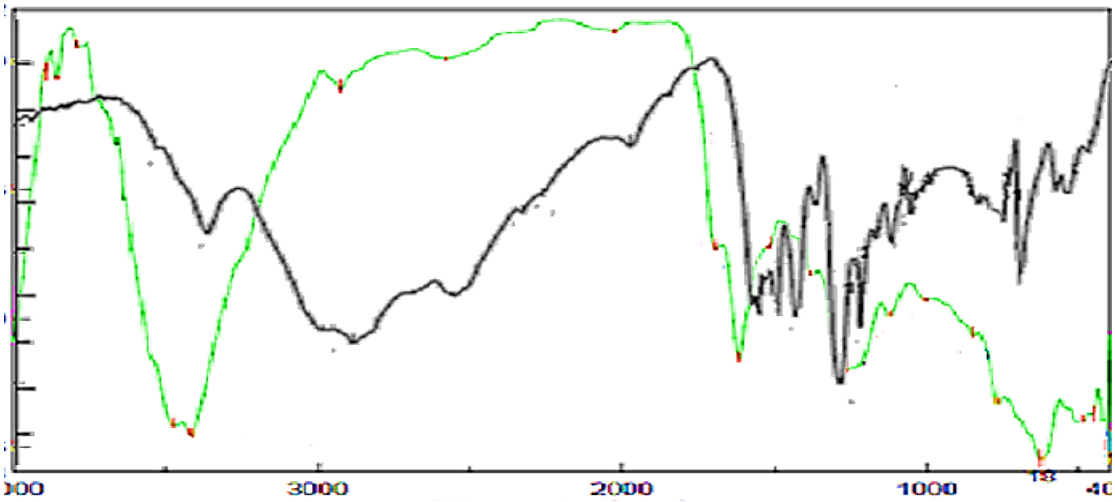
Comparison of the FT-IR spectrum of the product with (3-amino-4-hydroxybenzoic acid) revealed a significant change(Figure4): the disappearance of the characteristic broad absorption band of the acidic hydroxyl (O–H) group of the carboxylic acid, which typically appears in the range of 2500–3300 cm^{-1}. This disappearance, along with the appearance of the new carbonyl and C–O–C bands, confirms the successful esterification of the carboxylic acid group. The phenolic hydroxyl group remained intact, as evidenced by the broad band centered around 3300–3500 cm^{-1} (O–H stretching of the phenolic group), indicating that esterification occurred selectively at the carboxylic acid moiety without affecting the phenolic hydroxyl functionality.



Figuer(3): IR spectrum for product (k).

Table 1: Characteristic FT-IR Absorption Bands of Compound (K)

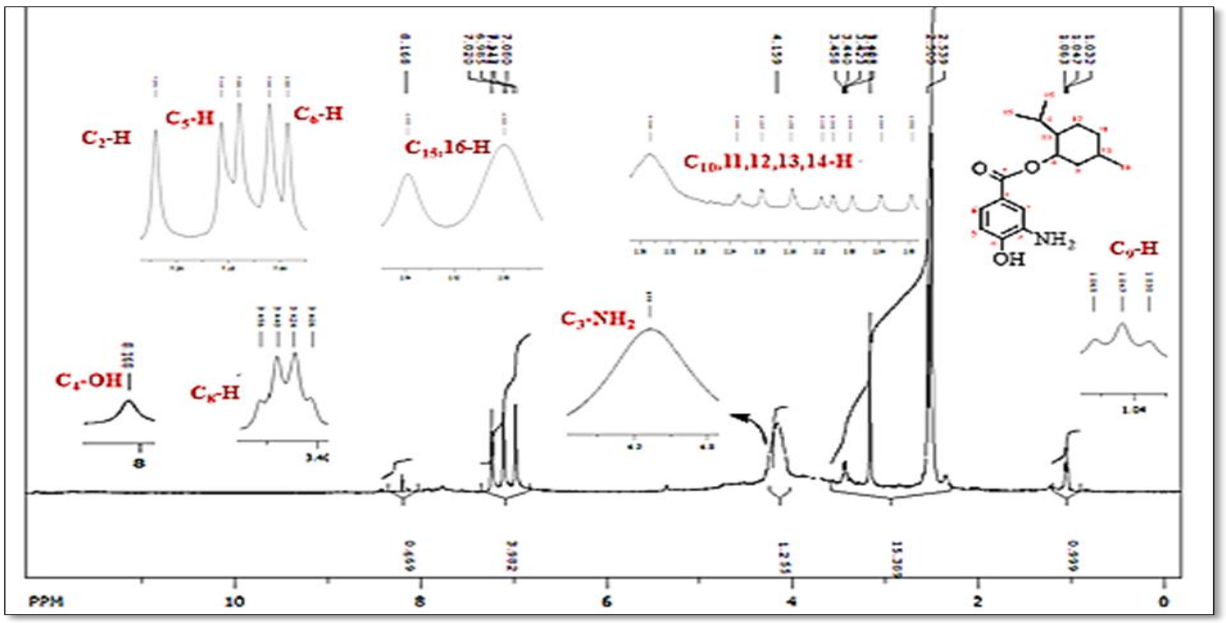
Wavenumber (cm^{-1})	Assignment
3300–3500 (broad)	O–H stretching (phenolic)
1694	C=O stretching (ester carbonyl)
1687	C=N stretching
1111	C–O–C stretching (ester linkage)



Figure(4): FT-IR spectrum Comparison of the Product (K1) with 3-Amino-4-hydroxybenzoic Acid.

3.1.2. ^{1}H NMR Spectroscopy

The ^{1}H NMR spectrum of compound K (Figure 5), recorded in DMSO d_6, provided clear evidence for the successful formation of the target ester. Two signals observed at δ 2.50 ppm and δ 3.16 ppm are attributed to residual water and the solvent, respectively. Three characteristic singlet signals were observed: a singlet at δ 7.24 ppm (s, 1H) assigned to the aromatic proton (C2–H); a singlet at δ 4.16 ppm (s, 2H) corresponding to the amino protons ($–NH_2$) at C3, confirming the regioselectivity of the reaction[1]; and a singlet at δ 8.17 ppm (s, 2H) attributed to the phenolic hydroxyl proton (C4–OH), confirming that esterification occurred selectively at the carboxylic acid group without affecting the phenolic hydroxyl functionality.[2] Additionally, a characteristic quartet at δ 3.46–3.41 ppm (q, 1H, J = 4 Hz) was assigned to the methine proton attached to the ester oxygen in the menthol ring (C8–H). A broad doublet overlapping with the solvent signal at δ 2.53 ppm (d, 9H, J = 12 Hz) corresponded to the methyl protons of the menthol moiety. Table 2 presents the complete ^{1}H NMR chemical shift assignments for compound K.



Figuer (5): ^{1}H NMR spectrum of compound K.

Tablet (2): ^{1}H NMR Spectral Data of Compound (K) in DMSO-d_6.

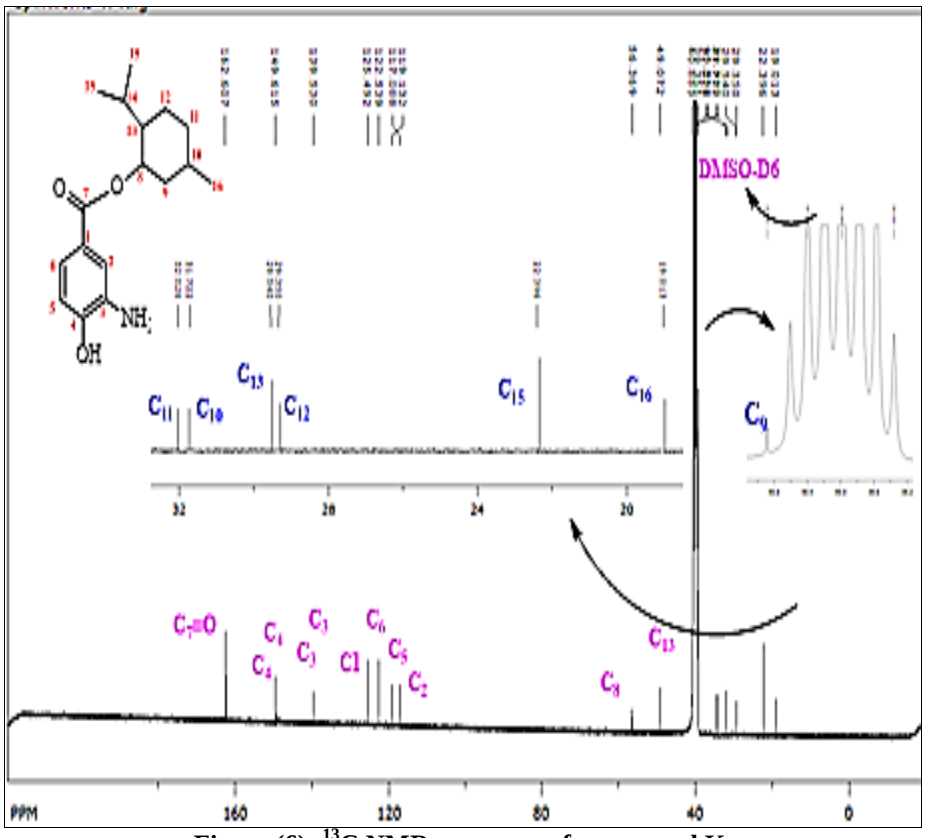
Chemical Shift (δ, ppm)	Multiplicity	Integration	Assignment
2.50	–	–	Residual solvent (DMSO-d_6)
3.16	–	–	Residual water
4.16	s	2H	–NH_2 (C3)
7.24	s	1H	Aromatic C2–H
8.17	s	2H	Phenolic –OH (C4)
3.46–3.41	q (J = 4 Hz)	1H	Menthol C8–H (O–CH)
2.53	d (J = 12 Hz)	9H	Menthol –CH_3 protons
0.90–2.10	m	–	Other menthol aliphatic protons

3.1.3. ^{13}C NMR Spectroscopy

The ^{13}C NMR spectrum of compound K (Figure 6), recorded in DMSO-d_6, further supported the proposed structure.

The most diagnostic signal appeared at δ 162.60 ppm, corresponding to the ester carbonyl carbon (C=O) conjugated with the aromatic ring, providing direct evidence for ester formation. The aromatic carbon signals were observed in the range of δ 117.09–149.62 ppm, consistent with the aromatic ring carbons of the benzoic acid moiety.

Additional confirmation of successful esterification was provided by the signal at δ 49.07 ppm, assigned to the menthol carbon directly attached to the ester oxygen (C–O–). The remaining aliphatic carbon signals of the menthol cyclohexane ring appeared in the range of δ 19.01–40.88 ppm, as detailed in Table 3.



Figuer (6): ^{13}C NMR spectrum of compound K.

Tablet(3): ^{13}C NMR Spectral Data of Compound (K) in DMSO-d_6.

Chemical Shift (δ, ppm)	Assignment
162.60	Ester carbonyl carbon (C=O)
149.62–117.09	Aromatic carbons (C1–C6)
49.07	Menthol carbon attached to ester oxygen (C–O–)
40.88–19.01	Menthol cyclohexane aliphatic carbons

4. CONCLUSION

In this study, a novel ester derivative of 3-amino-4-hydroxybenzoic acid was successfully synthesized via Fischer esterification with menthol. The reaction was carried out under mild conditions using DMSO as a solvent and concentrated H_2SO_4 as a catalyst, affording the target compound in 70% yield. The structure of the synthesized compound (K1) was unequivocally confirmed by comprehensive spectroscopic analyses, including FT-IR, ^1H NMR, and ^{13}C NMR. The FT-IR spectrum confirmed the disappearance of the acidic O–H band and the emergence of characteristic ester carbonyl (C=O) and C–O–C stretching bands, while ^1H and ^{13}C NMR spectra provided unambiguous evidence for the selective esterification at the carboxylic acid group without affecting the phenolic hydroxyl or amino functionalities. The successful synthesis of this ester derivative opens new avenues for further biological and industrial applications, particularly in the development of pharmacologically active compounds and functional polymers.

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