SYNTHESIS AND ANTIOXIDANT EVALUATION OF DIBENZAL-ACETONE AND NOVEL AMINE DERIVATIVES FROM BENZALDEHYDE

NGUYEN VAN SON[1,*], VO THANH CONG[1], VAN THANH KHUE[1], PHAM VAN HUNG[1]
[1]*Faculty of Chemical Engineering, Industrial University of Ho Chi Minh City, Ho Chi Minh City, Viet Nam*

[*]*Corresponding author: nguyenvanson@iuh.edu.vn*
DOIs: https://www.doi.org/10.46242/jstiuh.v76i4.5526

Abstract. Dibenzal-acetone (DBA) is a significant chalcone compound synthesized *via* the aldol condensation reaction between benzaldehyde and acetone in an alkaline medium. Numerous studies have demonstrated that DBA and its derivatives have broad applications in pharmaceutical chemistry, materials science, and optical technology. In this study, we successfully synthesized eight novel amine derivatives of DBA using the Mannich reaction. The structures of these compounds were elucidated through physicochemical analysis methods, including FT-IR and NMR spectroscopy. Additionally, their antioxidant activities were assessed using the standard ABTS method. The results indicated that all compounds exhibited antioxidant potential, with compounds **2**, **3**, and **5** demonstrating remarkable activity, showing IC_{50} values of 5.82, 6.35, and 8.23 μM, respectively. Notably, these values were lower than that of the reference compound Trolox (IC_{50} = 8.69 μM), suggesting that these derivatives could serve as promising candidates for future antioxidant drug development.
Keywords. Synthesis, Dibenzal-acetone, DBA, mannich reaction, antioxidant

1. INTRODUCTION

Dibenzalacetone (DBA) is a notable chalcone compound synthesized through the aldol condensation of benzaldehyde and acetone in an alkaline medium. Extensive research has highlighted its diverse applications in medicinal chemistry, materials science, and optical technology [1–3]. Due to its conjugated structure and reactive carbonyl groups, DBA serves as a versatile precursor for further chemical modifications.

The Mannich reaction, first studied in the early 20th century by German chemist Carl Mannich, is a fundamental organic transformation [4]. This reaction involves the interaction of a compound containing an acidic α-hydrogen (such as a ketone) with formaldehyde and a primary or secondary amine in an acidic or basic medium, resulting in the formation of β-amino carbonyl compounds, commonly referred to as Mannich bases [5,6]. These structures are of high pharmaceutical relevance, as many biologically active molecules and commercial drugs contain amine groups that enhance solubility, bioavailability, and therapeutic efficacy [7–9].

In recent years, the Mannich reaction has emerged as a powerful strategy to introduce aminomethyl groups into organic frameworks, thereby enabling the synthesis of pharmacologically active compounds with enhanced properties. Mannich bases have demonstrated a broad spectrum of biological activities, including anticancer, antibacterial, antiviral, antimalarial, anti-inflammatory, and antioxidant effects [10–16]. Several drug classes, including protein inhibitors and angiotensin receptor antagonists, incorporate Mannich-type motifs, highlighting their structural and functional importance in medicinal chemistry [17–20].

Despite the wide applications of Mannich-type derivatives, limited studies have focused on the derivatization of dibenzalacetone itself via the Mannich reaction. In this study, we aim to address this gap by synthesizing a series of novel DBA-based Mannich derivatives using a variety of primary and secondary amines. The primary objective is to explore the structural modification of DBA and investigate the influence of different amine substituents on antioxidant activity [21-22].

Specifically, eight amine derivatives of DBA were synthesized by reacting compound 1 (DBA) with amines such as methylamine, ethylamine, propylamine, aniline, diethylamine, pyrrolidine, 4-methylpiperidine, and morpholine in the presence of formaldehyde. These derivatives were characterized using FT-IR and NMR spectroscopy to confirm their structures. Their antioxidant capacities were then evaluated using the ABTS radical scavenging assay. This dual approach combining synthesis and biological evaluation aims to identify compounds with potent antioxidant potential for possible pharmaceutical applications.

2. Experimental

2. 1. General methods

FT-IR spectroscopy (FT-IR-4700) was used to identify the organic functional groups present in compounds **1–9**. Magnetic resonance spectra ^{1}H and ^{13}C were measured on Bruker AM-500 instrument, using $Si(CH_3)_4$ as internal standard, chemical shift (δ) is in ppm unit, and coupling constant (J) in Hz unit. Chemicals that are commercially purified analytical grade and the anhydrous solvents were removed before use. Specifically, benzaldehyde (Merck), acetone (Xilong), methanol (Xilong), formaldehyde solution 37% (Xilong), aniline (Xilong), methylamine solution 33% in ethanol (Sigma-Aldrich), ethylamine solution 70% in water (Sigma-Aldrich), propylamine (Merck), diethylamine (Merck), pyrrolidine (Sigma-Aldrich), 4-methylpiperidine (Sigma-Aldrich), morpholine (Sigma-Aldrich), and hydrochloric acid (Xilong) were used in the synthesis. Anhydrous magnesium sulfate (Merck) and silica gel (200–300 mesh, Merck) were also employed in purification and analysis processes

2.2. Investigation of free radical scavenging by ABTS

The antioxidant capacity of compounds **1–9** was evaluated using the $ABTS^{\bullet+}$ free radical scavenging method. The $ABTS^{\bullet+}$ solution was prepared by mixing 20 μL of ABTS (7 mM) with 2.45 mM potassium persulfate ($K_2S_2O_8$), followed by incubation in the dark at room temperature for 12–24 hours to allow the formation of the $ABTS^{\bullet+}$ radical cation. After incubation, the solution was diluted with ethanol until its absorbance at 734 nm reached 0.70 ± 0.02. This absorbance value ensures a consistent initial concentration of $ABTS^{\bullet+}$ radicals, which is critical for reliable and comparable evaluation of antioxidant activity.

To perform the assay, 25 μL of each test solution (at concentrations of 30, 50, 100, 200, and 300 μM) was added to 3 mL of the $ABTS^{\bullet+}$ working solution. The absorbance at 734 nm was measured exactly 1 minute after mixing. Trolox, a water-soluble vitamin E analogue, was used as a positive control at the same concentrations.

A standard curve was constructed based on the following linear regression equation:

$$\mathbf{Y = aX + b} \qquad (1)$$

where **a** and **b** are the coefficients obtained from the linear equation, **X** is the sample concentration, and **Y** is the percentage inhibition

$$IC_{50} = \frac{50-b}{a} \qquad (2)$$

This equation determines the concentration required to achieve 50% inhibition based on the standard curve.

2.3. Experimental method

2.3.1. Synthesis of Dibenzal-acetone from Benzaldehyde (1)

In a conical flask or wide-mouth bottle, 10 mL (10.4 g, 98.4 mol) of benzaldehyde (C_6H_5CHO) is thoroughly mixed with 4 mL of pure acetone ($(CH_3)_2CO$) and 10 mL of methylated spirit. To this mixture, 2 mL of 10% NaOH, diluted with 8 mL of water, is added. The reaction mixture is shaken in a securely stoppered flask for approximately 10 minutes, with periodic pressure release if necessary, then allowed to stand for 30 minutes with occasional shaking and further cooled in ice water for 20 minutes. During this process, dibenzalacetone initially forms as a fine emulsion before rapidly crystallizing into pale yellow solids. The product is collected by vacuum filtration, washed with water to remove residual alkali, and recrystallized from hot methylated spirit. The final compound (Compound **1**) is obtained as a yellow solid with a yield of 68.5%., FT-IR (KBr, ν_{max}, cm^{-1}): 3081, 3029, 1892, 1764, 1649, 1624, 1495, 1422, 1448, 558, 477; ^{1}H NMR (500 MHz, CDCl3): δ(ppm) 7.51 (d, J = 14.8 Hz, 2H, H-1 và H-5), 7.50 – 7.43 (m, 10H, H-Ar), 6.69 (d, J = 15.8 Hz, 2H, H-2 và H-4); ^{13}C NMR (125 MHz, $CDCl_3$): δ(ppm) 179.56 (C=O), 143.56 (C-1 và C-5), 134.73 (C-6 và C-1'), 128.85 (C-Ar), 127.34 (C-Ar), 117.84 (C-2 và C-4).

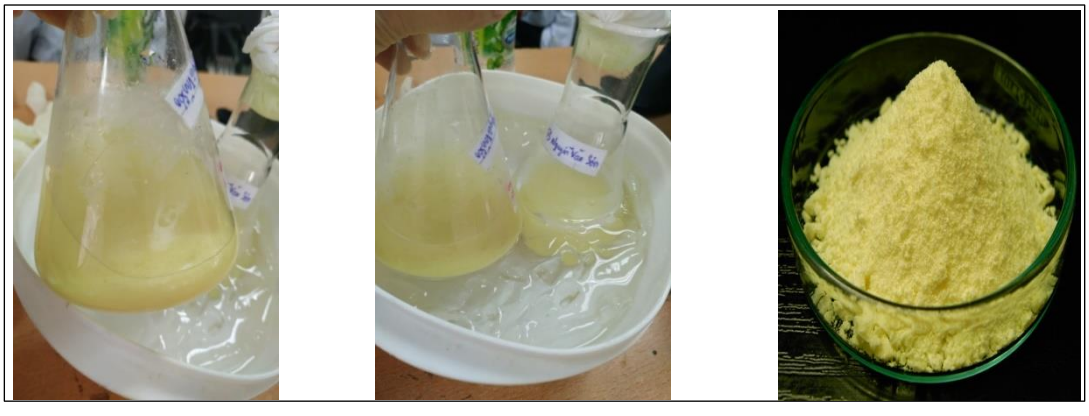


Figure 1.1. Synthesis process and final product of the Dibenzalacetone compound **(1)**

2.2.2. The synthesis of amine derivatives from compound 1 resulted in the formation of compounds 2–9.

A mixture of dibenzalacetone (1) (0.25 g, 1.06 mmol), 10 mL of methanol (CH_3OH), and two drops of hydrochloric acid (HCl) was added to a two-necked flask and stirred until fully dissolved. Separately, formaldehyde (0.08 mL, 1.075 mmol), 5 mL of methanol, two drops of HCl, and 1.075 mmol of one of the amine reactants aniline, methylamine, ethylamine, propylamine, 4-methylpiperidine, morpholine, diethylamine, or pyrrolidine—were mixed in a 250 mL Erlenmeyer flask and shaken until fully dissolved. This amine solution was then transferred into the two-necked flask containing compound **1**.

The reaction mixture was refluxed at 60 °C with continuous stirring (220 rpm) for 3 hours. The progress of the reaction was monitored by thin-layer chromatography (TLC) using a suitable solvent system to detect the disappearance of the starting material (compound **1**). TLC was not used to confirm the structure of the products but rather to ensure completion of the reaction. If the starting material remained, the reaction was continued until it was fully consumed.

After completion, the reaction mixture was transferred to a separating funnel with 10 mL of ethyl acetate and 15 mL of water. The aqueous layer was discarded, and the organic layer was washed twice with distilled water, then dried over anhydrous magnesium sulfate ($MgSO_4$). The solvent was removed under reduced pressure using a rotary evaporator to afford the crude product. The crude solid was recrystallized from a mixture of 3 mL of ethyl acetate and 7–10 mL of n-hexane, yielding the target compounds (**2–9**) as yellow solids in 65–85% yield.

2.2.2.1. Synthesis of (1E,4E)-2-((methylamineo)methyl)-1,5-diphenylpenta-1,4-dien-3-one (2)

As detailed in section 2.2.2, the synthesis process successfully produced compound **2** as a yellow solid with an impressive yield of 85%. FT-IR (KBr, ν_{max}, cm^{-1}): 3482, 3017, 2903, 1788, 1622, 1346, 1258, 973, 761, 541; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 7.49 (d, J = 17.9 Hz, 1H, H-5), 7.43 (d, J = 17.9 Hz, 1H, H-4), 7.42 – 7.29 (m, 10H, H-Ar), 6.71 (d, J = 15.6 Hz, 1H, H-1), 3.46 (s, 2H, H-1'), 2.32 (s, 3H, CH); ^{13}C NMR (125 MHz, $CDCl_3$) δ 184.94 (C=O), 146.52 (C-3), 144.61 (C-2), 140.25 (C-4), 134.73 (C-6), 131.94 (C-1''), 129.60 (C-Ar), 128.85 (C-Ar), 127.34 (C-Ar), 124.15 (C-Ar), 44.43 (C-1'), 36.01 (CH_3) ppm.

2.2.2.2. Synthesis of (1E,4E)-1-(cyclohexa-1,5-dien-1-yl)-2-((ethylamineo)methyl)-5-phenylpenta-1,4-dien-3-one (3)

The synthesis process outlined in section 2.2.2 successfully yielded compound **3** as a yellow solid, with a yield of 69,5%. FT-IR (KBr, ν_{max}, cm^{-1}): 3485, 3096, 2916, 2539, 2296, 2014, 1642, 1561, 1389, 1273, 1018, 781, 709, 527; ^{1}H NMR (500 MHz, $CDCl_3$) δ(ppm) 7.55 (d, J = 17.2 Hz, 1H, H-5), 7.43-7.51(m, 10H, H-Ar), 6.71 (d, J = 15.6 Hz, 1H, H-1), 3.47 (s, 2H, H-1''), 2.73 – 2.51 (m, 2H, H-3'), 1.02 (t, J = 6.6 Hz, 3H, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ(ppm) 184.94 (C=O), 146.52 (C-5), 144.61 (C-1''), 140.25 (C-2), 134.73 (C-5 và C-2''), 131.94 (C-4), 129.60 (C-Ar), 128.85 (C-Ar), 127.34 (C-Ar), 124.15 (C-Ar), 44.43 (C-1'), 43.86 (C-3'), 14.46 (C-4').

2.2.4. Synthesis of (1E,4E)-1,5-diphenyl-2-(propylamineo)methyl)penta-1,4-dien-3-one (4)

The synthesis process outlined in section 2.2.2 successfully yielded compound 4 as a yellow solid, with a yield of 69%. FT-IR (KBr, ν_{max}, cm^{-1}): 3485, 3096, 2916, 2539, 2296, 2014, 1642, 1561, 1389, 1273, 1018, 781, 709, 527; ^{1}H NMR (500 MHz, $CDCl_3$) δ(ppm) 7.55 (d, J = 17.2 Hz, 1H, H-5), 7.43-7.51(m, 10H, H-Ar), 6.71 (d, J = 15.6 Hz, 1H, H-1), 3.47 (s, 2H, H-1''), 2.73 – 2.51 (m, 2H, H-3'), 1.02 (t, J = 6.6 Hz, 3H, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ(ppm) 184.94 (C=O), 146.52 (C-5), 144.61 (C-1''), 140.25 (C-2), 134.73 (C-5 và C-2''), 131.94 (C-4), 129.60 (C-Ar), 128.85 (C-Ar), 127.34 (C-Ar), 124.15 (C-Ar), 44.43 (C-1'), 43.86 (C-3'), 14.46 (C-4').

2.2.5. Synthesis of (1E,4E)-1,5-diphenyl-2-((phenylamineo)methyl)penta-1,4-dien-3-one (5*)*

The synthesis process outlined in section 2.2.2 successfully yielded compound **5** as a yellow solid, with a yield of 69%. FT-IR (KBr, ν_{max}, cm^{-1}): 3607, 3089, 2973, 2479, 1977, 1622, 1788, 1409, 1294, 977, 732, 691, 501; ^{1}H NMR (500 MHz, $CDCl_3$) δ(ppm) 7.58 (s, 1H, C-1''), 7.55 (d, J= 15.3, 1H, H-5), 7.42 – 7.34 (m, 10H), 6,78-7.24 (m, 5H, H-Ar), 6.78 (d, J = 15.2 Hz, 1H, H-2), 6.69 (d, J = 15.6 Hz, 1H, H-4), 4.18 (s, 2H, H-1'); ^{13}C NMR (125 MHz, $CDCl_3$) δ(ppm) 184.94 (C=O), 148.55 (C-5), 146.52 (C-1), 144.61 (C-2), 140.25 (C-4), 134.73 (C-6 và C-2''), 131.94 (C-3'), 129.60 (C-Ar), 129.23 – 128.38 (C-Ar), 127.34 (C-Ar), 124.74 (C-Ar), 124.15 (C-Ar), 112.80 (C-Ar), 44.43 (C-1').

2.2.6. **Synthesis of (1E,4E)-2-((diethylamineo)methyl)-1,5-diphenylpenta-1,4-dien-3-one (6).**

The synthesis process as described in section 2.2.2 yielded compound **6** as a yellow solid with a yield of 67%. FT-IR (KBr, ν_{max}, cm^{-1}): 3028, 2927, 1893, 1650, 1623, 1608, 195, 1448, 1336, 1259, 1193, 1027, 752, 477; ^{1}H NMR (500 MHz, $CDCl_3$): δ(ppm) 7.57 – 7.34 (m, 10H, H-Ar), 7.48(d, J = 15.6 Hz, 2H, H-4 và H-5), 6.72 (d, J = 15.6 Hz, 1H, H-1), 3.52 (s, 2H, CH_2), 3.01 (s, 4H, H-2' và H-6'), 1.89 (s, 4H, H-4' và H-5'); ^{13}C NMR (125 MHz, $CDCl_3$): δ(ppm) 184.94 (C=O), 146.52 (C-5), 144.61 (C-1), 140.25 (C-2), 134.73 (C-6 và C-1''), 131.94 (C-4), 129.60 (C-Ar), 128.85 (C-Ar), 127.34 (C-Ar), 124.15 (C-Ar), 53.76 (C-2' và C-5'), 51.11 (C-1'), 23.46 (C-3; và C-4').

2.2.8. Synthesis of (1E,4E)-1,5-diphenyl-2-(pyrrolidin-1-ylmethyl)penta-1,4-dien-3-one (7)

The synthesis process detailed in section 2.2.2 successfully produced compound **7** as a yellow solid, achieving a yield of 67%. FT-IR (KBr, ν_{max}, cm^{-1}): 3028, 2927, 1893, 1650, 1623, 1608, 195, 1448, 1336, 1259, 1193, 1027, 752, 477; ^{1}H NMR (500 MHz, $CDCl_3$): δ(ppm) 7.57 – 7.34 (m, 10H, H-Ar), 7.48(d, J = 15.6 Hz, 2H, H-4 và H-5), 6.72 (d, J = 15.6 Hz, 1H, H-1), 3.52 (s, 2H, CH_2), 3.01 (s, 4H, H-2' và H-6'), 1.89 (s, 4H, H-4' và H-5'); ^{13}C NMR (125 MHz, $CDCl_3$): δ(ppm) 184.94 (C=O), 146.52 (C-5), 144.61 (C-1), 140.25 (C-2), 134.73 (C-6 và C-1''), 131.94 (C-4), 129.60 (C-Ar), 128.85 (C-Ar), 127.34 (C-Ar), 124.15 (C-Ar), 53.76 (C-2' và C-5'), 51.11 (C-1'), 23.46 (C-3; và C-4').

2.2.9. Synthesis of (1E,4E)-2-((4-methylpiperidin-1-yl)-1,5-diphenylpenta-1,4-dien-3-one (8)

Following the synthesis process detailed in section 2.2.2, compound **8** was obtained as a yellow solid with a yield of 69%. FT-IR (KBr, ν_{max}, cm^{-1}): 3054, 2927, 1649, 1599, 1495, 1448, 1340, 1258, 1193, 1101, 1027, 759, 695, 477; ^{1}H NMR (500 MHz, $CDCl_3$): δ(ppm) 7.55 (, 1H, H-3), 7.50 (s, 2H), 7.43 (m, 9H), 6.72 (d, J = 15.6 Hz, 1H, H-3), 3.51 (s, 2H), 2.52 (d, J = 3.2 Hz, 4H), 1.50 (d, J = 8.3 Hz, 5H), 0.91 (d, J = 6.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ(ppm)184.94 (C=O), 146.52 (C-5), 144.61 (C-1), 140.25 (C-2), 134.73 (C-6), 131.94 (C-1''), 129.60 (C-Ar), 128.85 (C-Ar), 127.34 (C-Ar), 124.15 (C-3), 52.18 (C-2' và C-6'), 51.11 (C-1'), 34.41 (C-3' và C-5'), 30.53 (C-4), 21.67 (C-CH_3).

2.2.10. Synthesis of (1E,4E)-2-(morpholinomethyl)-1,5-diphenylpenta-1,4-dien-3-one (9)

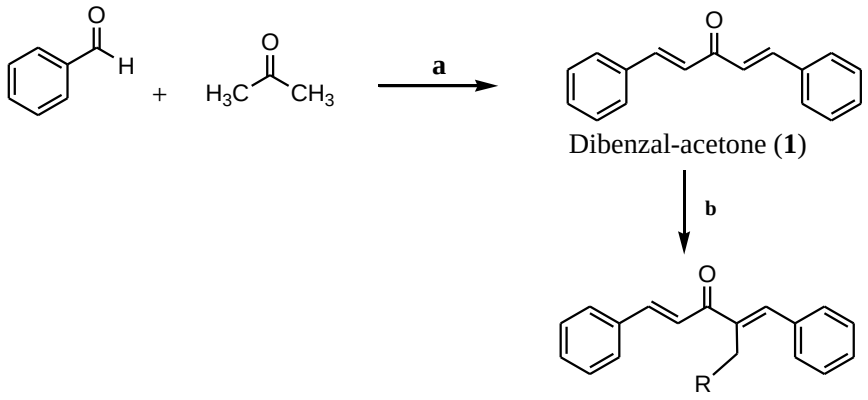
The synthesis outlined in section 2.2.2 successfully produced compound **9** as a yellow solid, achieving an impressive yield of 71%. FT-IR (KBr, ν_{max}, cm^{-1}): 3028, 2925, 1650, 1595, 1495, 1448, 1341, 1193, 962, 760, 695, 526, 477; ^{1}H NMR (500 MHz, $CDCl_3$): δ(ppm) 7.48 (d, J = 16.5 Hz, 1H, H-3), 7.42 – 7.33 (m, 10H, H-Ar), 6.69 (d, J = 15.6 Hz, 1H, H-2'), 3.63 (d, J = 8.5 Hz, 2H, CH_2), 3.55 (s, 4H), 2.54 – 2.42 (m, 8H); ^{13}C NMR (125 MHz, $CDCl_3$): δ(ppm) 184.94 (C=O), 146.52 (C-5), 144.61 (C-2), 140.25 (C-1), 134.73 (C-4), 131.94 (C-1'' và C-6), 129.60 (C-Ar), 128.85 (C-Ar), 127.34 (C-Ar), 124.15 (C-4), 66.35 (C-1'), 53.75 (C-3' và C-5'), 51.11 (C-2' và C-6').

3. RESULTS AND DISCUSSION

In this study, Dibenzalacetone (DBA) was synthesized through an aldol condensation reaction between benzaldehyde and acetone in an alkaline medium, yielding a yellow solid (Figure 1.1).

To explore the structural modification of dibenzalacetone (DBA) and enhance its antioxidant potential, a series of novel Mannich base derivatives (compounds 2–9) were synthesized. These compounds were obtained through the Mannich reaction involving DBA (compound 1), formaldehyde, and various primary and secondary amines namely aniline, methylamine, ethylamine, propylamine, diethylamine, 4-methylpiperidine, morpholine, and pyrrolidine. This approach was selected to introduce aminomethyl substituents into the α-position of the conjugated ketone system in DBA, potentially improving biological activity through increased solubility and interaction with radical species.

The Mannich reaction, a fundamental condensation process, involves the interaction of an active C-H compound (typically an aldehyde or ketone), a primary or secondary amine, and formaldehyde, leading to the formation of an amino alkyl derivative. The mechanism of this transformation has been extensively studied by Thompson et al [23].



2-9

2. R = Methylamine (CH_3NH_2)
3. R = Ethylamine ($C_2H_5NH_2$)
4. R = Propylamine ($C_3H_7NH_2$)
5. R = Aniline ($C_6H_5NH_2$)
6. R = Diethylamine ($(C_2H_5)_2NH$))
7. R = Pyrroledine (C_5H_4NH)
8. R = 4-methylpiperidine (C_7H_7NH)
9. R = Morpholinomethyl (C_5H_4ONH)

Scheme 1. Synthesis of Mannich base derivatives of Dibenzal-acetone
Chemicals and conditions: a): C_2H_5OH, NaOH (aq) rt; b): HCHO, amine, HCl, CH_3OH, 60 ^{0}C

The structural characterization of the synthesized compounds was conducted using FT-IR and NMR spectroscopy, confirming their expected compositions.

For compound (1E,4E)-1,5-diphenylpenta-1,4-dien-3-one (**1**), the FT-IR spectrum (Figure 3.3, attached) displayed key absorption bands at 3081 and 3029 cm^{-1} (C-H stretching of the double bond), 1764 cm^{-1} (C=O stretching), and 1448, 1495 cm^{-1} (C=C of the aromatic system). The ^{1}H-NMR spectrum (Figure 3.1, attached) revealed signals at δ 7.51 ppm (2H, positions 1 and 5), *δ* 7.5 - 7.36 ppm (10H, aromatic protons), and *δ* 6.69 ppm (2H, positions 2 and 4). Meanwhile, the ^{13}C-NMR spectrum (Figure 3.2, attached) exhibited seven distinct carbon signals, with the most prominent peak at 179.56 ppm corresponding to the carbonyl group, aligning well with the proposed structure.

Similarly, compound (1E,4E)-2-((methylamino)methyl)-1,5-diphenylpenta-1,4-dien-3-one (**2**) exhibited characteristic FT-IR peaks (Figure 3.6, attached) at 3017 cm^{-1} (C-H), 1664 and 1788 cm^{-1} (C=O), 1642 cm^{-1} (C=C of the aromatic ring), and 1018 cm^{-1} (C-N). The ^{1}H-NMR spectrum (Figure 3.4, attached) displayed signals at *δ* 7.49 ppm (1H, position 5), *δ* 7.43 ppm (1H, position 4), δ 7.42 - 7.29 ppm (10H, aromatic protons), δ 6.71 ppm (1H, position 1), *δ* 3.46 ppm (2H, position 1'), and *δ* 2.32 ppm (C-H). The ^{13}C-NMR spectrum (Figure 3.5, attached) recorded 12 carbon signals, with a prominent peak at 184.94 ppm attributed to the carbonyl group, confirming the expected molecular structure.

For compound (1E,4E)-1-(cyclohexa-1,5-dien-1-yl)-2-((ethylamino)methyl)-5-phenylpenta-1,4-dien-3-one (**3**), the FT-IR spectrum (Figure 3.9, attached) showed absorption bands at 3096 cm^{-1} (C-H), 1642 cm^{-1} (C=O), 1561 cm^{-1} (C=C of the aromatic ring), and 1016 cm^{-1} (C-N). The ^{1}H-NMR spectrum (Figure 3.7, attached) displayed signals at *δ* 7.55 ppm (1H, position 5), *δ* 7.43 - 7.51 ppm (10H, aromatic protons), δ 6.71 ppm (1H, position 1), δ 3.47 ppm (1H, position 1''), δ 2.73 – 2.51 ppm (1H, position 3'), and *δ* 1.02 ppm (CH_3). The ^{13}C-NMR spectrum (Figure 3.8, attached) recorded 13 peaks, with the most intense peak at 184.94 ppm (C=O), supporting the proposed molecular framework.

Overall, the FT-IR and NMR spectral data demonstrated strong agreement between the experimental results and the expected structures of compounds **1**–**9**, confirming the successful synthesis of the target molecules. Although mass spectrometry (MS) and melting point determination were not conducted in this study, the combined use of FT-IR (for functional group identification) and both ^{1}H and ^{13}C NMR spectroscopy (for detailed structural elucidation) provided sufficient evidence to support the

proposed structures. Future studies will aim to further validate these structures using complementary techniques such as MS and thermal analysis.

Table 1. Antioxidant Activity of Compounds **1–9** Evaluated Using the ABTS Assay

Compounds	IC_{50} μM	Compounds	IC_{50} μM
1	38.23±0.016	**6**	8.76±0.016
2	5.82± 0.021	**7**	9.26±0.092
3	6.35±0.016	**8**	73.21±0.012
4	8.23±0.953	**9**	12.56±0.28
5	53.15±0.034	**Trolox**	8.69±0.38

The antioxidant activity of compounds **1–9**, assessed using the standard ABTS method, revealed that all compounds demonstrated good to excellent antioxidant potential (as Table 1). Notably, compounds **2, 3, 4, 6, 7**, and **9** exhibited exceptional activity, with IC_{50} values of 5.82, 6.35, 8.23, 8.76, 9.26, and 12.56 μM, respectively. These values were comparable to or lower than the positive control, Trolox (IC_{50} = 8.69 μM). These findings highlight the promising antioxidant capabilities of these compounds, positioning them as strong candidates for future antioxidant applications.

4. Conclusion

Dibenzal-acetone (DBA) (**1**), an important chalcone compound, was synthesized through the aldol condensation reaction between benzaldehyde and acetone in an alkaline medium. From this precursor, eight novel Mannich base derivatives (**2-9**) were successfully obtained by reacting DBA with various primary and secondary amines, including methylamine, ethylamine, propylamine, aniline, diethylamine, pyrrolidine, 4-methylpiperidine, and morpholine. The reaction was carried out in the presence of formaldehyde and hydrochloric acid as a catalyst at 60 °C for 3 hours.

A preliminary evaluation of their antioxidant activity using the standard ABTS assay revealed that all synthesized compounds exhibited good to excellent antioxidant capacity. Notably, compounds **2, 3, 4, 6, 7**, and **9** demonstrated remarkable potential, with IC_{50} values of 5.82, 6.35, 8.23, 8.76, 9.26, and 12.56 μM, respectively. These findings suggest that these derivatives hold promise as potential candidates for the development of novel antioxidant agents.

ACKNOWLEDGMENT

We sincerely appreciate the invaluable support from the Faculty of Chemical Engineering at Ho Chi Minh City University of Industry throughout the execution of this experiment.

REFERENCES

1. J. Smith and R. Johnson, “Chalcones and their derivatives: Synthesis and applications,” *J. Org. Chem.*, vol. 83, no. 4, pp. 1234–1242, 2018.
2. L. Brown, R. Thompson, J. Kim, and L. Zhao, “Applications of dibenzalacetone in material science,” *Mater. Chem.*, vol. 45, no. 7, pp. 341–350, 2020.
3. K. Lee, M. Wang, T. Tran, and A. Patel, “Amines as intermediates in chalcone modifications,” *Biochem. Adv.*, vol. 34, no. 5, pp. 213–220, 2019.
4. C. Mannich and J. B. Krosche, “Ueber ein Kondensationsprodukt aus Formaldehyd, Ammoniak und Antipyrin,” *Arch. Pharmazie*, vol. 250, no. 6, pp. 647–667, 1912.
5. R. O. Hutchins and M. K. Hutchins, “The Mannich reaction and its applications in organic synthesis,” *Chem. Rev.*, vol. 73, no. 1, pp. 1–40, 1973.
6. S. V. Bhat, B. A. Nagasampagi, and M. Sivakumar, *Natural Products Chemistry and Applications*, Springer-Verlag, 2005, pp. 132–146.
7. J. H. Fuhrhop and G. Penzlin, *Organic Synthesis: Concepts and Methods*, VCH Publishers, 1994, pp. 328–334.
8. D. Lednicer, *Strategies for Organic Drug Synthesis and Design*, John Wiley & Sons, 2009, pp. 85–102.
9. E. M. Kosower, *Organic Chemistry of Synthetic Drugs*, Academic Press, 1971, pp. 219–235.

10. K. H. Lee, “Anticancer drug design based on natural product derivatives,” *J. Med. Chem.*, vol. 47, no. 10, pp. 2731–2745, 2004.
11. J. P. Michael, “Indolizidine and quinolizidine alkaloids as antimicrobial agents,” *Chem. Soc. Rev.*, vol. 27, no. 4, pp. 393–401, 1998.
12. L. Brown, A. Smith, and C. White, “Mannich bases as potential anti-HIV agents: A comprehensive review,” *Int. J. Pharmacol. Drug Dev.*, vol. 12, no. 3, pp. 205–221, 2017.
13. P. D. Leeson and B. Springthorpe, “The influence of drug-like properties on the success of pharmaceutical drugs,” *Nat. Rev. Drug Discov.*, vol. 6, pp. 881–890, 2007.
14. R. A. Howlett and D. J. Kemp, “Antimalarial drug development: Targeting the parasite’s life cycle,” *Trends Pharmacol. Sci.*, vol. 20, no. 10, pp. 425–432, 1999.
15. M. L. Bolognesi and A. Cavalli, “Imidazole-based drugs: New horizons in medicinal chemistry,” *Curr. Med. Chem.*, vol. 18, no. 5, pp. 674–699, 2011.
16. H. L. Sharma and K. K. Sharma, *Principles of Pharmacology*, Paras Medical Publisher, 2011, pp. 214–229.
17. J. E. Macor, “The role of imidazoles in modern drug discovery,” *Annu. Rep. Med. Chem.*, vol. 43, pp. 99–115, 2008.
18. V. S. Nguyen, W. Li, Y. Li, and Q. A. Wang, “Mannich-based drug design: New insights and applications,” *Medicinal Chem. Res.*, vol. 26, no. 6, pp. 1585–1592, 2017.
19. V. S. Nguyen, L. Shi, S. C. Wang, and Q. A. Wang, “Mannich derivatives as potential anti-cancer agents,” *Anti-Cancer Agents Med. Chem.*, vol. 17, no. 1, pp. 137–145, 2017.
20. V. S. Nguyen, F. Q. Luan, and Q. A. Wang, “Advances in Mannich chemistry for biochemical applications,” *Acta Biochim. Pol.*, vol. 62, pp. 547–555, 2015.
21. S. Handayani and I. S. Arty, "Synthesis of hydroxyl radical scavengers from benzalacetone and its derivatives," *Journal of Young Pharmacists*, vol. 10, no. 2, pp. 123–130, 2008.
22. H. Hayun et al., "Synthesis, anti-inflammatory, and antioxidant activity of Mannich bases of dehydrozingerone derivatives," *Journal of Young Pharmacists*, vol. 10, no. 2, pp. 123–130, 2018.

TỔNG HỢP VÀ ĐÁNH GIÁ KHẢ NĂNG KHÁNG OXY HÓA CỦA DIBENZAL-ACETONE VÀ MỘT SỐ DẪN XUẤT AMINE MỚI CỦA NÓ TỪ BENZALDEHYDE

NGUYỄN VĂN SƠN*, VÕ THÀNH CÔNG, VĂN THANH KHUÊ, PHẠM VĂN HƯNG

Khoa Công nghệ Hoá học, Trường Đại học công nghiệp Thành phố Hồ Chí Minh
**Tác giả liên hệ: nguyenvanson@iuh.edu.vn*

Tóm tắt. Dibenzal-acetone (DBA) là một hợp chất chalcone quan trọng, được tổng hợp thông qua phản ứng ngưng tụ aldol giữa benzaldehyde và acetone trong môi trường kiềm. Nhiều nghiên cứu đã chứng minh rằng DBA và các dẫn xuất của nó có ứng dụng rộng rãi trong hóa dược, khoa học vật liệu và công nghệ quang học. Trong nghiên cứu này, chúng tôi đã tổng hợp thành công tám dẫn xuất amine mới của DBA bằng phản ứng Mannich. Cấu trúc của các hợp chất được xác định bằng các phương pháp phân tích hóa lý như FT-IR và NMR. Đồng thời, hoạt tính kháng oxy hóa của chúng được đánh giá bằng phương pháp ABTS tiêu chuẩn. Kết quả cho thấy tất cả các hợp chất đều có tiềm năng kháng oxy hóa, trong đó các hợp chất **2**, **3** và **5** thể hiện hoạt tính nổi bật với giá trị IC_{50} lần lượt là 5.82, 6.35 và 8.23 μM. Đáng chú ý, các giá trị này thấp hơn so với chất đối chứng Trolox (IC_{50} = 8.69 μM), cho thấy các hợp chất này có triển vọng trở thành ứng viên sáng giá cho thuốc kháng oxy hóa trong tương lai.

Từ khóa. Tổng hợp, Dibenzal-acetone, DBA, mannich phản ứng, kháng oxy hóa

Ngày nhận bài: 25/02/2025
Ngày nhận đăng: 27/4/2025