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Synthesis and characterization of substituted chalcone derivatives via pyrazole intermediates

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Abstract
This study explores the synthesis and characterization of a series of substituted chalcone derivatives via a multi-step synthetic methodology. The process involves the initial condensation of hydrazine derivatives with ethyl acetoacetate to form pyrazole derivatives as critical intermediates. Subsequent functionalization, including acylation and cyclization, was performed to yield the target chalcone derivatives. Reaction conditions were meticulously optimized, resulting in high-yield and high-purity compounds. The prepared compounds were characterized using Fourier-transform infrared (FT-IR) spectroscopy, proton nuclear magnetic resonance (^{1}H-NMR), and carbon-13 nuclear magnetic resonance (^{13}C-NMR) spectroscopy, confirming their structures.

Keywords: Chalcone derivatives, pyrazole intermediates, acylation and cyclization.

Introduction
Chalcones are natural compounds belonging to the flavonoid family, first introduced by Stanislaw Kostanecki and Joseph Tambor in 1899 [1]. These aromatic compounds serve as parent molecules for various bioorganic precursors in medicinal chemistry. Structurally, chalcones consist of two aromatic rings linked by a highly electrophilic α, β-unsaturated carbonyl system. They are valuable intermediates in synthesizing various heterocyclic compounds with significant biological activities [2], such as pyrazoline [3-13] and isoxazole [14-19] (Figure 1).

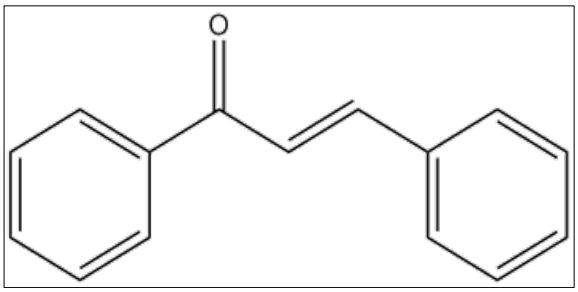


Fig1: Structural Framework of Chalcone

The parent chalcone is known by its IUPAC name, (E)-1, 3-diphenylprop-2-en-1-one. It is also referred to by other names, including benzylideneacetophenone, phenyl styryl ketone, benzalacetophenone, and α-phenyl-β-benzoylethylene, among others [20].
The chalcone skeleton is commonly found in numerous natural products, known for their significant bioactivities. These include antioxidant properties, which help prevent chronic diseases in humans by protecting DNA and proteins from damage, thereby reducing the risk of various cancers, cardiovascular disorders, and neurological diseases [21, 22]. Additionally, chalcones exhibit a wide range of applications, serving as anti-inflammatory agents [23, 24], xanthine oxidase inhibitors [25], antihistaminic compounds [26, 27], anticancer agents [28-30], antimalarial drugs [31], antiviral agents [32], antimicrobial compounds [33-35], antioxidants [36], and antidiabetic agents [37].

Materials and Methods

All the chemicals used in this study were of high purity and sourced from reputable suppliers, including Sigma-Aldrich, BDH, Fluka, Merck, Alpha Aesar, and Aldrich.

The melting points of the synthesized compounds were determined using a Stuart SMP10 apparatus in the laboratories of the Department of Chemistry at the College of Science, Tikrit University.

Infrared spectra of the synthesized organic compounds were recorded using a Shimadzu FT IR-8400S instrument in the range of 4000-400 cm^{-1}, with potassium bromide (KBr) discs as the sample medium. These measurements were performed in the Chemistry Laboratory at the College of Science, Tikrit University.

Proton Nuclear Magnetic Resonance (NMR) spectra were obtained using a Bruker 500 MHz spectrometer, with d6-DMSO as the solvent. These experiments were conducted in the central laboratories at Tehran University, Iran.

Procedure

Preparation of Pyrazolone-5-One Derivative (M1)

A mixture of 0.015 mol (3.6 g) of hydrazide acid (M1) was added to a 100 mL round-bottom flask, and 5 mL of ethyl acetoacetate was then added. To this mixture, 36 mL of absolute ethanol and 6 drops of glacial acetic acid were introduced. Small boiling stones were placed in the flask, which was then set in a water bath at 70-75°C and connected to a condenser. The reaction was allowed to proceed for 3 hours, with intermittent shaking and swirling of the flask. Afterward, the mixture was cooled, poured into a beaker, and crushed ice was added, resulting in the formation of a yellowish-white precipitate. The precipitate was filtered, washed with distilled water, and dried. The yield was 83%, and the melting point was 150-152°C.

Preparation of a Substituted Pyrazolone-5-One Derivative (M2)

0.005 mol of pyrazolone-5-one (M1) was dissolved in 5 mL of dioxane, and then 0.005 mol of calcium hydroxide was added with stirring and heating. Acetyl chloride (0.004 mol) was gradually added dropwise while stirring, causing the mixture to thicken and react for 35 minutes, as shown in the equation. After the reaction was complete, 9.2 mL of 2 M hydrochloric acid (7%) was added to the reaction mixture, followed by the addition of crushed ice. A white precipitate formed, which was then filtered, washed with cold water, and dried. The melting point of the product was found to be 141-142°C, and the product was white in color.

Preparation of Chalcones Derivative from a Substituted Pyrazolone-5-One Derivative (M3-M6)

0.0008 mol of the substituted pyrazolone-5-one (M2) was mixed with 0.0008 mol of substituted benzaldehydes in 10 mL of absolute ethanol. Then, 0.0008 mol of sodium hydroxide dissolved in 4 mL of absolute ethanol was added to the mixture. The mixture was stirred at room temperature for 6 hours, then placed in the refrigerator for 15 hours. The reaction was neutralized using a diluted hydrochloric acid solution, resulting in the formation of a precipitate, which was then filtered, washed with distilled water, and dried. The product was recrystallized from ethanol, and its melting point was measured. Table 1 presents some of the physical properties and yield percentages of the synthesized compounds.

Table 1: The physical properties of synthesis chalcones derivative (M3-M6)

Compound	X	Molecular Formula	Melting point, °C	Color	Yield%
M3	H	$C_{20}H_{15}O_5N_3$	209-211	Yellow	87
M4	Br	$C_{20}H_{14}O_5N_3Br$	193-195	brown	67
M5	Cl	$C_{20}H_{14}O_5N_3Cl$	185-186	Orange	72
M6	NO_2	$C_{20}H_{14}O_7N_3$	192-194	White	70

Results and Discussion

This investigation focuses on the synthesis and characterization of a series of substituted chalcones derivatives through a multi-step synthetic approach. The process begins with the condensation of hydrazine derivatives with ethyl acetoacetate, which leads to the formation of pyrazole derivatives as key intermediates. These pyrazole derivatives are then subjected to further functionalization steps, including acylation and cyclization, to produce the desired chalcones derivatives. The reaction conditions were carefully optimized to ensure high yields and excellent purity of the target compounds.

The synthesized chalcones derivatives were characterized using advanced spectroscopic techniques such as NMR, IR, and UV, confirming their structural integrity and purity. Due to the presence of diverse functional groups, these chalcones derivatives hold significant potential for various applications in pharmaceutical and chemical research.

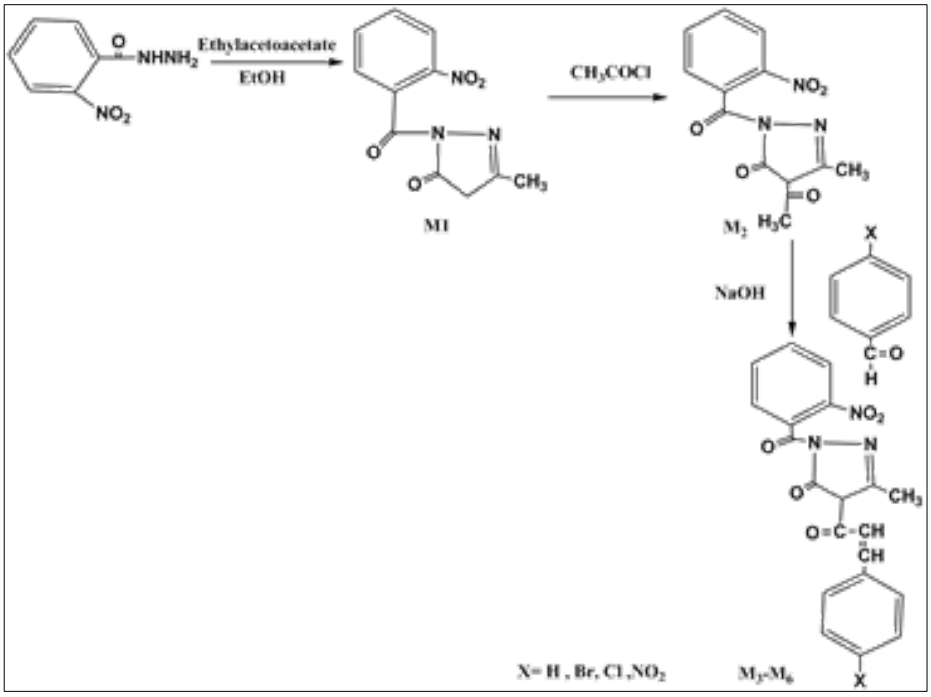
All synthesized compounds were purified, dried, and fully characterized to confirm their chemical structures and purity. The details of the synthesized compounds are presented in Scheme 1.

Characterization of Pyrazolone-5-One Derivative (M1)

The analysis revealed distinct physical characteristics in the synthesized compound compared to the starting materials, as evidenced by infrared spectroscopy. The spectra exhibited various functional group vibrations, including aromatic C-H stretching at 3062 cm^{-1}, aliphatic C-H stretching at 2954 cm^{-1}, and a carbonyl group stretch between 1718-1660 cm^{-1}. Additionally, aromatic C=N vibrations were observed at 1562 cm^{-1}, and a C=C stretching vibration appeared at 1519 cm^{-1}, as shown in Figure 2 [38].

Characterization of a Substituted Pyrazolone-5-One Derivative (M2)

The analysis revealed distinct physical characteristics in the synthesized compound compared to the starting materials, as evidenced by infrared spectroscopy. The spectra exhibited various functional group vibrations, including aromatic C-H stretching 3087cm^{-1}, aliphatic C-H stretching at 2929 cm^{-1}, and a carbonyl group stretch between 1672-1728 cm^{-1}. Additionally, aromatic C=N vibrations were observed at 1606 cm^{-1}, and a C=C stretching vibration appeared at 1552 cm^{-1}, as shown in Figure 3.



Scheme 1: Preparation of Chalcones from Pyrazolone-5-One Derivative (M_3-M_6)

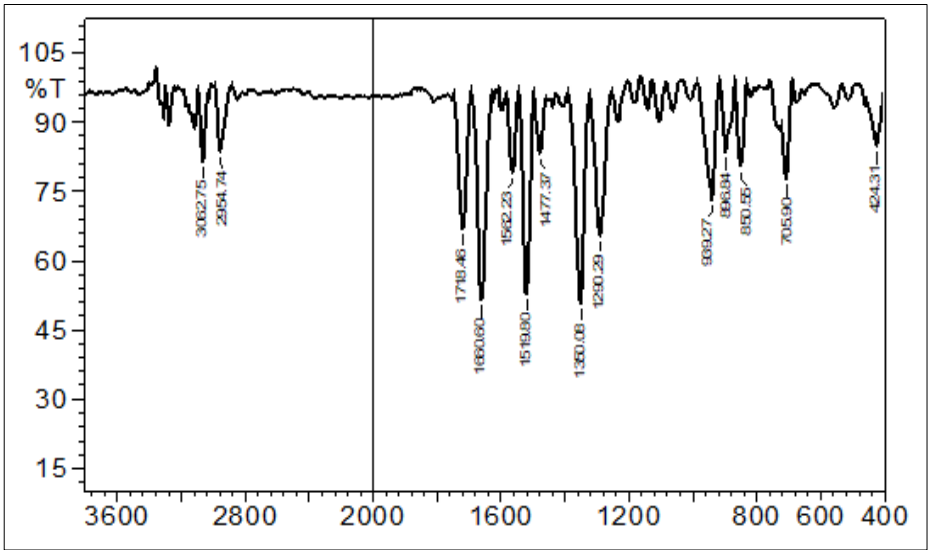


Fig 2: The FT-IR spectrum of compound M1.

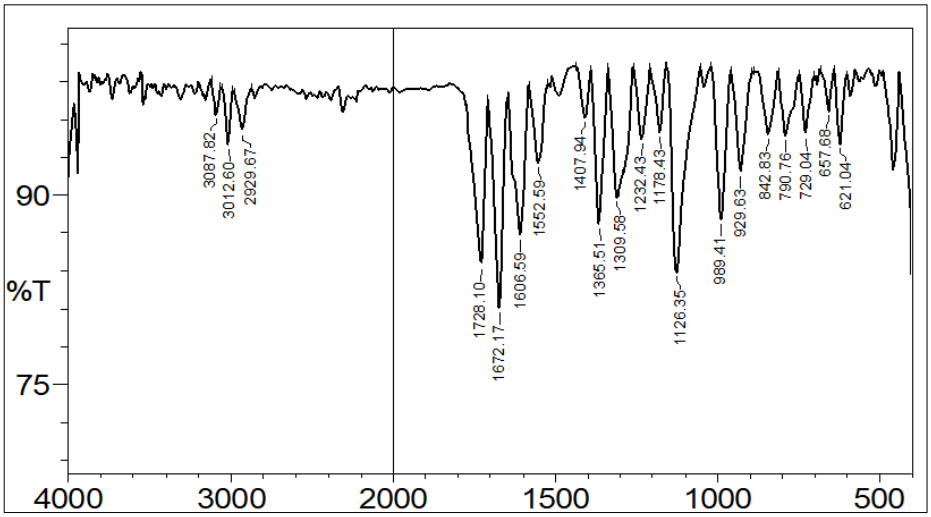


Fig 3: The FT-IR spectrum of compound M2

Characterization of Chalcones Derivative (M3-M6)

The analysis revealed distinct physical characteristics in the synthesized compound compared to the starting materials, as evidenced by infrared spectroscopy. The spectra exhibited various functional group vibrations, including aromatic C-H stretching 3093cm^{-1}, aliphatic C-H stretching at 2962 cm^{-1}, and a carbonyl group stretch between 1683-1737 cm^{-1}. Additionally, aromatic C=N vibrations were observed at 1604 cm^{-1}, and a C=C stretching vibration appeared at 1525 cm^{-1}, as shown in Figure 4 [39, 40].

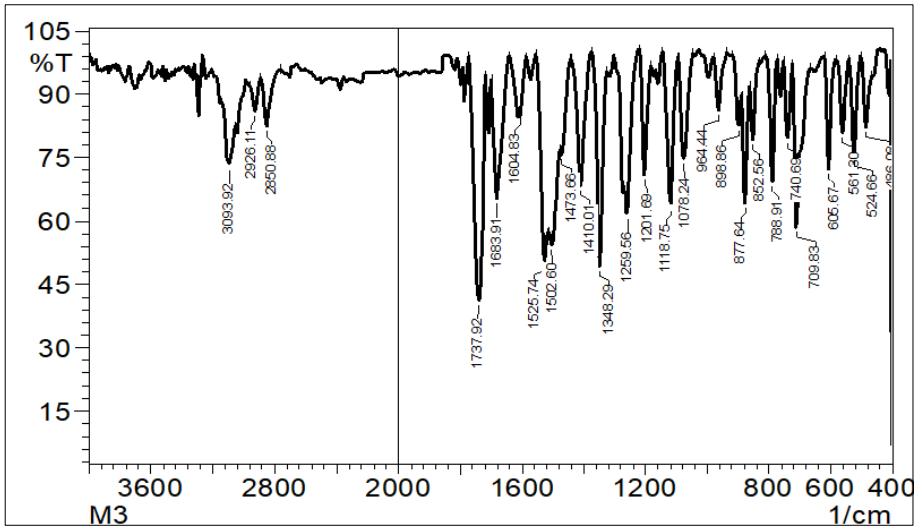


Fig 4: The FT-IR spectrum of compound M3

The compound M3 was obtained from the reaction of 4-(3-(4-bromophenyl)acryloyl)-5-methyl-2-(2-nitrobenzoyl)-2,4-dihydro-3H-pyrazol-3-one according to the general synthesis method.

IR (KBr, cm^{-1}): ν=3093 (C-H$_{arom}$), 2926(C-H$_{aliph}$), 1638-1737(C=O),1604(C=N) 1525(C=C$_{arom}$). 1H NMR: δ=7.615-8.663 (m, 9H, CH$_{arom}$), 6.091 and 5.226 (d, H, CH), 3.351 (s, 2H, CH$_2$), 1.970 (s, 3H, CH$_3$.^{13}C-NMR: δ= 183.13, 174.40, 170.09 (C=O), 122.35, 123.32, 124.03,126.13, 128.93,130.22, 132.10,135.41, 137.87 and 145.01(C$_{arom}$), 118.36, 110.76(CH=CH), 28.73(CH$_3$).

The compound M4 was obtained from the reaction of 4-(3-(4-bromophenyl)acryloyl)-5-methyl-2-(2-nitrobenzoyl)-2,4-dihydro-3H-pyrazol-3-one according to the general synthesis method.

IR (KBr, cm^{-1}): ν=3105 (C-H$_{arom}$), 2977(C-H$_{aliph}$), 1661-1745(C=O),1620(C=N) 1566 (C=C$_{arom}$). 1H NMR: δ=7.634-8.733 (m, 8H, CH$_{arom}$), 6.121 and 5.342 (d, H, CH), 3.356 (s, 2H, CH$_2$), 1.993 (s, 3H, CH$_3$.^{13}C-NMR: δ= 186.12, 175.16, 171.15 (C=O), 123.12, 124.55, 124.82,126.82, 127.99,131.42, 133.21,136.02, 138.12 and 146.12 (C$_{arom}$), 119.06, 113.45(CH=CH), 29.41(CH$_3$).

The compound M5 was obtained from the reaction of 4-(3-(4-chlorophenyl)acryloyl)-5-methyl-2-(2-nitrobenzoyl)-2,4-dihydro-3H-pyrazol-3-one according to the general synthesis method.

IR (KBr, cm^{-1}): ν=3095 (C-H$_{arom}$), 2959(C-H$_{aliph}$), 1668-1752(C=O), 1613(C=N) 1555 (C=C$_{arom}$). 1H NMR: δ=7.596-8.624 (m, 8H, CH$_{arom}$), 6.092 and 5.278 (d, H, CH), 3.329 (s, 2H, CH$_2$), 1.982 (s, 3H, CH$_3$.^{13}C-NMR: δ= 185.09, 174.29, 171.23 (C=O), 124.87, 125.63, 125.91,126.89, 127.23,132.11, 133.65,135.92, 139.07 and 145.48 (C$_{arom}$), 117.34, 111.78(CH=CH), 28.22(CH$_3$).

The compound M6 was obtained from the reaction of 4-(3-(4-nitrophenyl)acryloyl)-5-methyl-2-(2-nitrobenzoyl)-2,4-dihydro-3H-pyrazol-3-one according to the general synthesis method.

IR (KBr, cm^{-1}): ν=3088 (C-H$_{arom}$), 2965(C-H$_{aliph}$), 1659-1738(C=O), 1626(C=N) 1535 (C=C$_{arom}$). 1H NMR: δ=7.627-8.767 (m, 8H, CH$_{arom}$), 6.128 and 5.308 (d, H, CH), 3.347 (s, 2H, CH$_2$), 1.889 (s, 3H, CH$_3$.^{13}C-NMR: δ= 187.12, 175.53, 172.07(C=O), 124.91, 125.87, 126.20,126.93, 127.68,133.23, 133.85,136.22, 139.22 and 147.60 (C$_{arom}$), 119.89, 112.89(CH=CH), 30.13(CH$_3$).

Conclusion

This study successfully demonstrates the synthesis of a series of substituted chalcone derivatives through a multi-step approach, starting with the condensation of hydrazine derivatives and ethyl acetoacetate to form pyrazole intermediates. Further functionalization steps, including acylation and cyclization, led to the production of the target chalcones with high yield and purity. The synthesized compounds were thoroughly characterized using advanced spectroscopic techniques, confirming their structural integrity. Given their diverse functional groups, these chalcone derivatives show significant promise for applications in pharmaceutical and chemical research, offering valuable potential for further exploration and development.

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