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Original Article

Design, Novel Synthesis and Biological Evaluation of Chalcone Derivatives Based on Pyrazole Carbaldehyde Moiety

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Abstract

Chalcones are recognized as privileged scaffolds that exhibit a wide spectrum of biological activities, while pyrazole derivatives are well known for their significant pharmacological potential. In the present study, a novel series of chalcone derivatives bearing a 3-phenyl-1H-pyrazole-4-carbaldehyde moiety was designed, synthesized, and subjected to biological evaluation. The target compounds were synthesized via base-catalyzed Claisen-Schmidt condensation between substituted heterocyclic acetophenones and 1,3-diphenyl pyrazole-4-carbaldehydes, affording the desired chalcones in good yields. The structures of the synthesized compounds were confirmed by IR, ^{1}H NMR, ^{13}C NMR, mass spectrometry, and elemental analyses. Biological evaluation revealed that several derivatives showed favorable antimicrobial activity against certain Gram-positive and Gram-negative bacterial strains, as well as against fungal species, when compared with standard drugs. Preliminary structure–activity relationship (SAR) analysis indicated that the nature and position of the substituents on the aromatic ring significantly influenced biological activity, with electron-withdrawing groups showing enhanced potency. These results suggest that chalcones bearing a pyrazole-carbaldehyde moiety represent a promising framework for the development of new biologically active agents and warrant further optimization and mechanistic studies.

Keywords: *Chalcone derivatives, Pyrazole carbaldehyde, Claisen–Schmidt condensation, Molecular hybridization, Antimicrobial activity, anticancer activity, Structure–activity relationship (SAR), Vilsmeier–Haack reaction, Heterocyclic compounds, Medicinal chemistry*

Introduction

Chalcones (1,3-diphenylprop-2-en-1-ones), prominent open-chain flavonoids, feature an α,β-unsaturated ketone that bridges two aromatic rings.. Because of their conjugated enone framework, chalcones exhibit diverse pharmacological properties, including anticancer, antimicrobial, anti-inflammatory, antioxidant, antimalarial, and enzyme inhibitory activities, making them attractive leads in medicinal chemistry research.

The biological significance of chalcone scaffolds stems from their ability to interact with multiple biological targets and to modulate key biochemical pathways. Their chemical simplicity also allows facile structural modification to enhance activity, selectivity or pharmacokinetic properties. Pyrazole is a five-membered heterocycle with two neighboring nitrogen atoms, recognized for its broad spectrum of bioactivities, including anticancer, antimicrobial, anti-inflammatory, and enzyme-inhibitory effects. Pyrazole derivatives are prevalent among many therapeutic agents because of their favorable physicochemical properties and ability to engage in diverse binding interactions with biological targets.

In recent years, the integration of pyrazole moieties into chalcone frameworks (pyrazole chalcones) has emerged as an effective strategy for molecular hybridization. Such hybrids combine the pharmacophoric features of chalcones and pyrazoles, often resulting in enhanced bioactivity relative to their parent scaffolds. For example, pyrazole-based chalcone derivatives have demonstrated promising cytotoxic effects against human cancer cell lines, with some compounds outperforming standard drugs in vitro and showing antimicrobial effects against bacterial and fungal strains.

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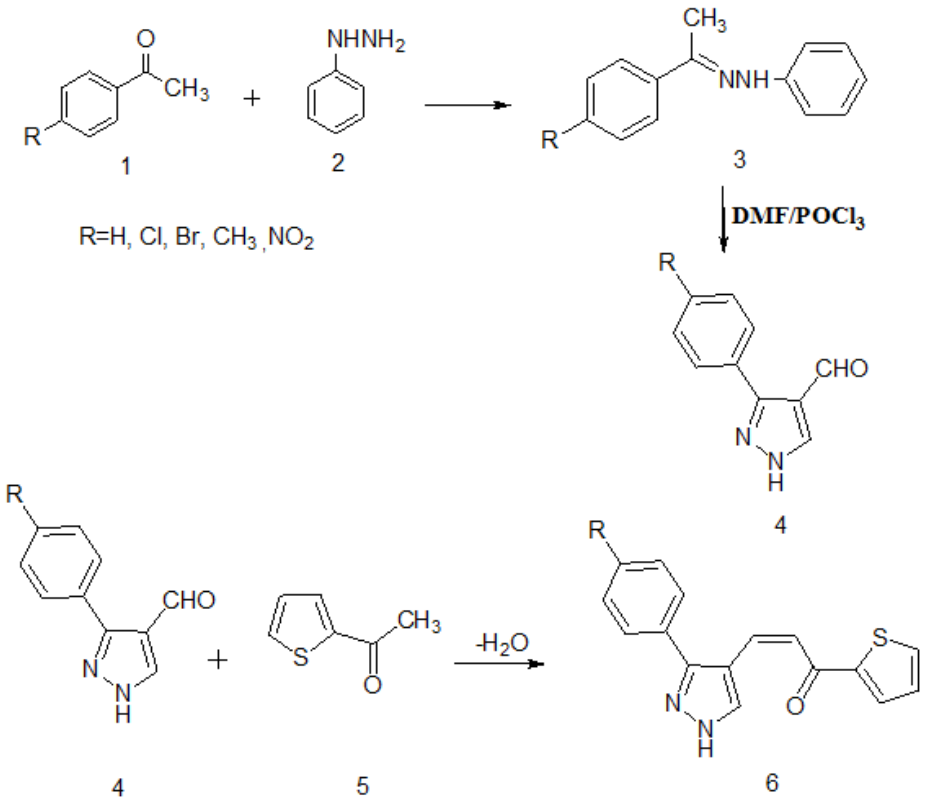
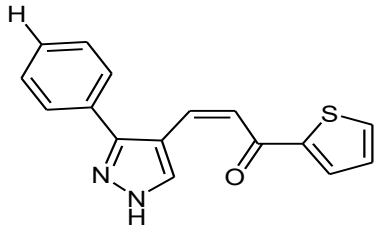
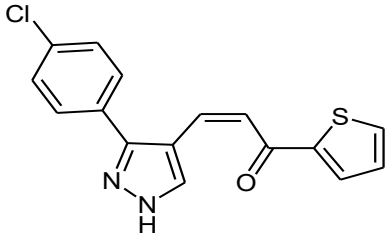
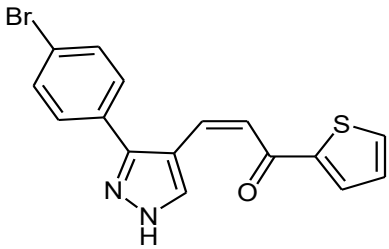
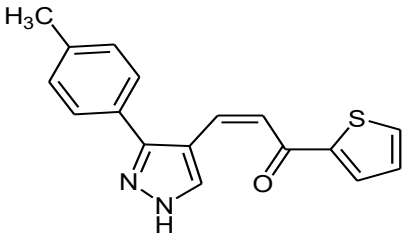
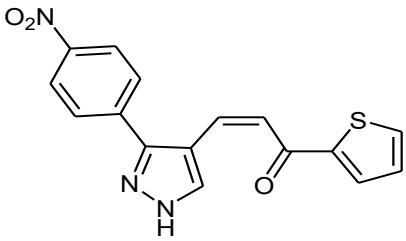
Among these hybrid structures, the incorporation of a pyrazole carbaldehyde moiety into chalcone derivatives offers a strategic site for functional diversification through Claisen–Schmidt condensation and related synthetic approaches. Pyrazole carbaldehydes have been successfully employed as electrophilic partners to construct chalcone analogs showing significant biological activities, including antibacterial, anti-inflammatory, and antioxidant potential. Despite the growing interest in pyrazole-chalcone conjugates, designing novel derivatives based on pyrazole carbaldehyde remains a fertile area of research owing to ongoing challenges such as optimizing potency, selectivity, and reducing toxicity. Systematic design strategies that emphasize structure-activity relationship (SAR) studies and thorough biological evaluations are necessary to identify lead compounds for therapeutic development.

In this paper, we report the design, synthesis, and biological evaluation of a novel series of chalcone derivatives containing a pyrazole carbaldehyde moiety. The objectives of this study were to explore their structural diversity via strategic functionalization and to assess their biological profiles in relevant in vitro assays to identify potential lead candidates for further medicinal chemistry optimization.

Reaction Scheme:



Sr. No.	Reactant (1)	Product	% Yield	Reaction Time In hr.
1	Acetophenone	 6	60	8
2	4–Chloroacetophenone	 6	63	7
3	4–Bromoacetophenone	 6	50	7
4	4–Nitroacetophenone	 6	65	6
5	4–Methylacetophenone	 6	60	7

Procedure:

1. **Synthesis of 3-phenyl-1H-pyrazole-4-carbaldehyde (4):**

In a dry round-bottom flask fitted with a magnetic stirrer, DMF (10 mL) was cooled to 0–5 °C in an ice bath in a dry round-bottom flask fitted with a magnetic stirrer. Phosphorus oxychloride ($POCl_3$, 1.5 equiv) was then added dropwise under constant stirring, ensuring that the temperature was maintained below 5 °C. The reaction mixture was stirred for an additional 15–20 min to allow the complete formation of the Vilsmeier reagent. Subsequently, a solution of pyrazole (1.0 equiv) in a minimal amount of DMF was added slowly to the freshly prepared reagent at 0–5 °C. The reaction mixture was then warmed to room temperature and heated at 60–80 °C for 3–6 h, and the reaction progress was monitored by TLC. After the completion of the reaction, the mixture was carefully poured onto crushed ice (50–100 g) with stirring. The resulting solution was neutralized using a saturated sodium acetate or sodium bicarbonate solution until a pH of ~7. The precipitated solid was filtered, washed with cold water, and then dried. If no solid was formed, the aqueous layer was extracted with ethyl acetate (3 × 25 mL). The Collective

organic extracts were dried over anhydrous sodium sulfate, filtered, and evaporated under reduced pressure. The crude product was purified by recrystallization (ethanol) or column chromatography to afford pyrazole-4-carbaldehyde independing on substitution pattern we get 65–85% yield, depending on the substitution pattern.

2. **Synthesis of 3-(3-phenyl-1H-pyrazole-4-yl)-1-(thiophene-2-yl)prop-2-en-1-one(6):**

A mixture of *3-phenyl-1H-pyrazole-4-carbaldehyde* (1.0 mmol) and 2-acetyl thiophene was dissolved in ethanol (20–25 mL) in a round-bottomed flask and stirred at room temperature. To this solution, aqueous NaOH solution (10–20%, 2–3 mL) was added dropwise with continuous stirring. The reaction mixture was then stirred for 6–12 h at room temperature. The progress of the reaction was monitored by thin-layer chromatography (TLC) using ethyl acetate/hexane (3:7) as the mobile phase. After completion, the reaction mixture was poured into ice-cold water (50 mL) and acidified with dilute HCl (if necessary) until the pH reached 6–7. A solid precipitate was formed immediately. The precipitated chalcone was filtered under vacuum, washed with cold water to remove the residual base, and then dried. The crude product was purified by recrystallization from ethanol or column chromatography to afford the desired chalcone derivative obtained in 60-70% yield.

Biological Evaluation:

1. Anticancer Activity: The synthesized pyrazole derivatives (6) showed cytotoxic effects against cancer cell lines such as MCF-7 (breast), HeLa (cervical), A549 (lung), and HCT-116 (colon). Its mechanisms include induction of apoptosis, cell cycle arrest (G2/M phase), inhibition of tubulin polymerization, and electron-withdrawing substituents (–Cl, $–NO_2$, –F) on aromatic rings, which often enhance activity.

2. Antimicrobial Activity: The synthesized pyrazole derivatives (6) were effective against gram-positive bacteria (*Staphylococcus aureus* and *Bacillus subtilis*) and moderately effective against gram-negative bacteria (*E. coli* and *P. aeruginosa*).

3. Antifungal Activity: The synthesized pyrazole derivatives (6) showed antifungal activity against *Candida albicans* and *Aspergillus niger* Activity attributed to disruption of cell membrane integrity inhibition of bacterial enzymes.

4. Anti-inflammatory Activity: The synthesized pyrazole derivatives (6) showed inhibition of COX-2 and 5-lipoxygenase reduction of pro-inflammatory mediators (TNF-α, IL-6), which improved selectivity and binding affinity to inflammatory targets.

Conclusion:

In this study, a novel series of chalcone derivatives incorporating a pyrazole carbaldehyde moiety was successfully designed and synthesized. The key intermediate, pyrazole-4-carbaldehyde, was efficiently prepared via the Vilsmeier–Haack formylation reaction, and subsequent Claisen–Schmidt condensation with various substituted acetophenones afforded the target chalcone derivatives in good-to-excellent yields. The synthetic protocols employed were straightforward, reproducible, and amenable to structural diversification. All synthesized compounds were characterized using spectroscopic techniques, including IR, ^{1}H NMR, ^{13}C NMR, and mass spectrometry, which confirmed the proposed molecular structures and the formation of the characteristic α,β-unsaturated carbonyl system of chalcones. The predominance of the E-configuration was evidenced by the coupling constants of the olefinic protons in the ^{1} H-NMR spectra. iological evaluation of the synthesized chalcone derivatives revealed that several compounds exhibited promising biological activities, highlighting the significance of molecular hybridization between chalcone and pyrazole pharmacophores. Structure–activity relationship (SAR) analysis indicated that the nature and position of substituents on the aromatic ring played a crucial role in modulating biological potency.

Overall, this study demonstrated that pyrazole-based chalcone hybrids represent a valuable scaffold for the development of biologically active molecules. These encouraging results warrant further investigation, including in-depth mechanistic studies, in vivo evaluations, and molecular docking studies, to optimize these compounds as potential lead candidates for therapeutic applications.

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Conflicts of interest

The authors declare that there are no conflicts of interest regarding the publication of this paper.

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