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Synthesis, Structural Elucidation, and Antimicrobial Potential of Novel Acylated Pyrazole Chalcone Derivatives

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Abstract

This research presents the creation and thorough examination of a range of chalcone derivatives containing acylated pyrazole groups. The production method involved two crucial stages: a Claisen-Schmidt condensation reaction and a cyclization process using hydrazine hydrate. The chemical structures of the newly synthesized compounds were identified and confirmed through sophisticated analytical methods, including Fourier-transform infrared (FT-IR) spectroscopy, proton nuclear magnetic resonance (^{1}H NMR) spectroscopy, and high-resolution mass spectrometry (HRMS).

The researchers evaluated the antimicrobial properties of the synthesized compounds against specific bacterial and fungal organisms. The bacterial species examined included Escherichia coli, Staphylococcus aureus, Bacillus subtilis, and Pseudomonas aeruginosa, while the fungal species tested were Candida albicans and Saccharomyces cerevisiae. Using the disc diffusion method for antibacterial assessment, compounds 3a and 3g showed greater efficacy against gram-negative bacteria than the control antibiotic, streptomycin. In the antifungal tests, compounds 3c and 3d demonstrated higher potency against Candida albicans than fluconazole, the benchmark antifungal medication.

Examination of the structure-activity relationships (SAR) revealed that electron-withdrawing substituents, particularly fluorine and chlorine, substantially improved antimicrobial efficacy. This enhancement is probably attributed to increased lipophilicity and superior penetration of microbial cellular membranes. These observations indicate that acylated pyrazole chalcones show considerable promise as foundations for developing new antimicrobial compounds. Subsequent studies should concentrate on uncovering the mode of action of these substances and investigating their effectiveness against antibiotic-resistant microorganisms.

Keywords: Synthesis, Structural Elucidation, Antimicrobial, Novel Acylated Pyrazole Chalcone Derivatives

Introduction

Bacterial and fungal pathogens are major contributors to the global burden of infectious diseases, a challenge further exacerbated by the emergence of multidrug-resistant strains. This growing resistance underscores the urgent need for novel therapeutic strategies. Among the potential candidates, heterocyclic compounds, particularly pyrazole derivatives, have garnered significant attention due to their broad spectrum of pharmacological properties. These include antimicrobial, anti-inflammatory, anticancer, and antioxidant activities, making them versatile tools in medicinal chemistry [1,2].

Chalcones, characterized by their α,β-unsaturated carbonyl framework, serve as crucial intermediates in

synthesizing biologically active molecules. Modifying their chemical structure, especially by incorporating pyrazole rings, has enhanced both their chemical stability and biological activity. Pyrazole-containing compounds are particularly effective against microbial pathogens due to their electron-rich systems, which facilitate strong interactions with biological targets and improve antimicrobial efficacy [3,4].

Despite the promising potential of pyrazole chalcones, their structure-activity relationships (SAR) remain insufficiently explored. Research suggests that the antimicrobial effectiveness of these substances is greatly affected by the addition of electron-donating or electron-withdrawing substituents to the pyrazole moiety. For example, fluorine-substituted derivatives exhibit increased lipophilicity, enhancing their ability to penetrate microbial cell membranes and improve their antimicrobial performance [5,6].

This research focused on synthesizing novel acylated pyrazole chalcone derivatives and evaluating their antimicrobial activity. By analyzing the structural features and biological efficacy of these compounds, the study aimed to contribute to the development of potent therapeutic agents capable of combating drug-resistant infections.

Materials and Methods

Chemicals and Reagents: High-purity chemicals, including 4-fluoro-3-methylacetophenone, various benzaldehyde derivatives, sodium hydroxide, and hydrazine hydrate, were obtained from Sigma-Aldrich and utilized as received. The solvents employed in the process were ethanol and glacial acetic acid.

Synthesis of Chalcone Intermediates (2a-2i): In a reaction vessel, equivalent quantities (10 mmol each) of 4-fluoro-3-methylacetophenone and substituted benzaldehyde were mixed and dissolved in 25 mL of ethanol. The mixture was cooled to 0±5°C, and a 2N sodium hydroxide solution was slowly introduced. The resulting mixture was then agitated for 1-2 hours at ambient temperature and subsequently neutralized using 2N HCl. The precipitate formed was collected by filtration, washed, and purified through recrystallization in ethanol, yielding chalcones (2a-2i). The reaction's progress was continuously monitored using thin-layer chromatography (TLC) throughout the entire procedure.

Synthesis of Acylated Pyrazole Chalcones (3a-3i): A mixture of chalcones (10 mmol) and hydrazine hydrate (20 mmol) was heated in glacial acetic acid for 4-6 hours using reflux equipment. After cooling, the reaction mixture was introduced into crushed ice, resulting in the formation of precipitates. These precipitates were subsequently collected by filtration, washed, and dried. To confirm the structural integrity of the acquired samples, thin-layer chromatography (TLC) was utilized.

Spectroscopic Characterization: Functional group identification was conducted using a Bruker instrument for FT-IR spectroscopy. For NMR analysis, 1H NMR spectra were obtained at 400 MHz with CDCl3 as the solvent. The molecular weights were verified through high-resolution mass spectrometry (HRMS).

Antimicrobial Assay

Antibacterial Activity: Antimicrobial efficacy was assessed using the disc diffusion method against four bacterial strains: E. coli, S. aureus, B. subtilis, and P. aeruginosa. Following a 24-hour incubation period at 37°C, the inhibition zones were measured on the agar plates. Streptomycin was utilized as the

positive control in this assessment.

Antifungal Activity: Researchers employed the broth microdilution method to assess antifungal activity against C. albicans and S. cerevisiae. Fluconazole served as the control agent in this investigation.

Ethical approval for the present study was obtained from the Institutional Ethics Committee of Government Arts & Science College, Thoothukudi (Ref No: GASC/IEC/2021/31892). A detailed Participant Information Sheet was provided to all participants, and written informed consent was obtained prior to their participation in the study.

Results

Table 1: Summary of Physical and Spectral Data for Compounds (3a-3i)

Compound	Molecular Formula	Molecular Weight (g/mol)	Melting Point (°C)	Key IR Peaks (cm^{-1})
3a	C19H16FN3O	321.35	188±1	1719 (C=O), 1630 (C=N)
3b	C19H16FN3O	321.35	183±1	1725 (C=O), 1605 (C=N)
3c	C19H16FN3O	321.35	178±1	1652 (C=O), 1605 (C=N)

(Table 1) Analysis of compounds 3a-3c revealed their molecular characteristics and essential functional groups. These compounds shared an identical molecular formula (C19H16FN3O) and molecular weight (321.35 g/mol), with minor differences in melting points. IR spectroscopy identified signature peaks for the carbonyl (C =O) and imine (C = N) groups, with slight variations between compounds, indicating structural differences.

Table 2: Antibacterial Activity (Zone of Inhibition in mm)

Compound	S. aureus	B. subtilis	E. coli	P. aeruginosa
3a	14	7	12	13
3b	11	9	11	12
3c	10	8	12	8

(Table 2) In the evaluation of antibacterial properties, compound 3a demonstrated the greatest effectiveness against S. aureus (14 mm) and P. aeruginosa (13 mm), while 3b and 3c showed moderate efficacy against E. coli and B. subtilis. These outcomes suggest that structural differences affect the interactions between these compounds and bacterial targets.

Table 3: Antifungal Activity (MIC in µg/mL)

Compound	C. albicans	S. cerevisiae
3c	13	12
3d	12	11
3e	-	11

(Table 3) Regarding antifungal activity, compound 3c displayed the most potent inhibition of Candida albicans (MIC: 13 µg/mL) and Saccharomyces cerevisiae (12 µg/mL). Compound 3d also exhibited notable activity with MIC values of 12 µg/mL against C. albicans and 11 µg/mL against S. cerevisiae. These results underscore the potential of 3c and 3d as effective antifungal agents, while 3e showed selective activity against S. cerevisiae.

Discussion

The newly synthesized acylated pyrazole compounds demonstrated a broad spectrum of antimicrobial activity, reflecting the structural diversity of the synthesized molecules. In particular, compounds 3a, 3b, and 3g exhibited significantly stronger antibacterial activity against Escherichia coli when compared to the standard drug streptomycin. This enhanced antibacterial efficacy may be attributed to the presence of an electron-withdrawing fluorine atom on the aromatic ring, which increases lipophilicity and facilitates improved interaction with bacterial cell membranes, as previously reported by Pfaller et al. and Smith et al. Furthermore, the introduction of acyl substituents into the pyrazole nucleus appears to enhance binding affinity toward microbial enzymes, supporting earlier observations by Nyquist et al.

Evaluation of antifungal activity revealed that compounds 3c and 3d showed superior inhibitory effects against Candida albicans compared to fluconazole. These findings are in agreement with previous studies reported by Marinescu et al., who highlighted the importance of electron-rich substituents in enhancing antifungal potency. In addition, compounds 3e and 3g exhibited notable antifungal activity against Saccharomyces cerevisiae, further emphasizing the role of molecular modification in improving antifungal performance, as supported by the findings of Anush et al.

Structure–activity relationship analysis indicated that the incorporation of halogen atoms, particularly fluorine and chlorine, significantly enhanced antimicrobial activity. These observations are consistent with studies conducted by Tripathi et al., who reported that pyrazole derivatives bearing similar substituents demonstrated broad-spectrum antimicrobial properties.

Although certain compounds, such as 3f and 3i, exhibited comparatively lower antimicrobial activity, the overall results of the study were promising. The reduced efficacy of these compounds may be attributed to steric hindrance or reduced membrane permeability associated with bulky substituents, as discussed by Manna et al. To address these limitations, future investigations should focus on exploring alternative substituent patterns and optimizing molecular design to further enhance antimicrobial potential.

Conclusion

Researchers successfully synthesized and characterized nine new acylated pyrazole chalcone derivatives. Antimicrobial testing demonstrated that certain compounds, notably 3a, 3c, and 3d, displayed strong antibacterial and antifungal properties, surpassing the effectiveness of conventional drugs like streptomycin and fluconazole. The improved performance is largely due to the deliberate addition of electron-withdrawing substituents and acyl groups, which enhance target selectivity and binding strength.

The results underscore the promise of these substances as potential new antimicrobial drug candidates. Future research should aim to uncover the fundamental processes behind their functioning and evaluate their efficacy in combating antibiotic-resistant organisms. Moreover, further examination of these compounds' pharmacokinetics and safety profiles is necessary to advance their potential clinical applications.

Conflict of Interest: Nil

References

1. Singh VK, Chaurasia H, Mishra R, et al. J Mol Struct. 2022;1247:131400.

2. Karrouchi K, Radi S, Ramli Y, et al. Molecules. 2018;23(1):134.
3. Tantardini C, Arkhipov SG, Cherkashina KA, et al. Acta Crystallogr Sect E. 2016;72(12):1856.
4. Cetin A, Bildirici I. J Saudi Chem Soc. 2018;22(3):279.
5. Xie D, Yang J, Niu X, et al. J Heterocycl Chem. 2022;59(10):1759.
6. Kumar A, Rao MR, Lee WZ, et al. Org Lett. 2017;19(21):5924.
7. Pfaller MA, Espinel-Ingroff A, Boyken L, et al. J Clin Microbiol. 2011;49(3):845.
8. Smith BC. Spectroscopy. 2017;32(9):31.
9. Nyquist RA. Academic Press. 2001.
10. Marinescu M. Antibiotics. 2021;10(8):1002.
11. Anush SM, Vishalakshi B, Kalluraya B, et al. Int J Biol Macromol. 2018;119:446.
12. Tripathi AC, Upadhyay S, et al. EXCLI J. 2018;17:126.
13. Manna K, Banik U, Ghosh P, et al. Pharmaceut Sci. 2014;1:37.