Anusandhanvallari
Vol 2023, No.1
August 2023
ISSN 2229-3388

Synthesis of Curcumin Inspired Chalcone and Corresponding Dihydropyrazole Derivatives

Nausheen Amber, Vishwa Deepak Tripathi*

P. G. Department of Chemistry, C. M. Science College Darbhanga (A Constituent Unit of L N Mithila University, Darbhanga) Bihar

Abstract

Molecular hybridization has emerged as a promising strategy for the development of multifunctional therapeutic agents with improved pharmacological profiles. In the present work, a series of curcumin-inspired chalcone and dihydropyrazole were synthesized by integrating the bioactive pharmacophoric features of curcumin and chalcone scaffolds. Initially, aminoalkyl and propargyl substituted benzaldehyde derivatives were prepared from 4-hydroxybenzaldehyde through alkylation reactions. These intermediates were further reacted with dehydroacetic acid under piperidine-catalyzed conditions to afford curcumin-inspired chalcone derivatives in good yields. The synthesized chalcones were subsequently cyclized with phenylhydrazine hydrochloride to obtain corresponding dihydropyrazole derivatives. In addition, propargyl-functionalized chalcones were transformed into triazole analogues through Cu(I)-catalyzed azide–alkyne cycloaddition reactions. All synthesized compounds were characterized using IR, ^{1}H NMR, ^{13}C NMR, elemental analysis, melting point determination, and spectral interpretation. The developed synthetic approach provided structurally diverse hybrid molecules with satisfactory yields and straightforward purification protocols. The study demonstrates an efficient route for the preparation of curcumin-inspired multifunctional scaffolds that may serve as promising candidates for further biological investigations.

Keywords: Molecular hybridization, Curcumin, Chalcones, Dihydropyrazoles, Organocatalysis, Heterocyclic chemistry

1. Introduction

Molecular hybridization has become an important approach in medicinal chemistry for designing compounds with enhanced biological performance by combining two or more pharmacophoric units within a single molecular framework.[1-2] This strategy offers the possibility of improving receptor binding, pharmacokinetic properties, bioavailability, and therapeutic efficacy while simultaneously reducing adverse effects and drug resistance.[3-4] Figure 1 showing the representation of molecular hybridization approach.

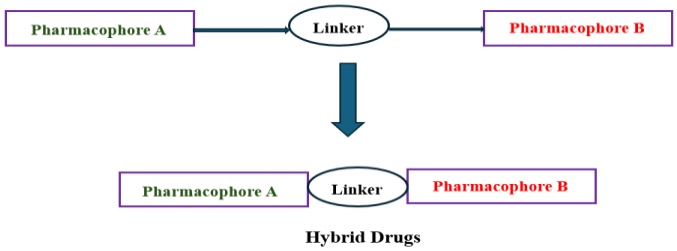


Figure 1: Figure showing the concept of molecular hybridization

Curcumin, a naturally occurring polyphenolic compound isolated from *Curcuma longa*, is widely recognized for its anti-inflammatory, antioxidant, antimicrobial, and anticancer properties.[4-6] Curcumin modulates multiple signaling pathways including NF-κB, PI3K/Akt, JAK/STAT, and p53 pathways. Despite its broad therapeutic potential, the clinical application of curcumin is restricted by poor bioavailability and rapid metabolic degradation.[7-8]

Chalcones represent another important class of bioactive compounds containing an α,β-unsaturated carbonyl system.[9] Their structural flexibility and ease of synthesis make them attractive scaffolds in medicinal chemistry. Chalcone derivatives exhibit diverse biological activities including anticancer, anti-inflammatory, antimicrobial, antiviral, and antioxidant effects.[10-13] The conjugated enone system present in chalcones contributes significantly to their pharmacological properties.

The combination of curcumin and chalcone pharmacophores through molecular hybridization offers an opportunity to generate structurally diverse molecules with improved biological potential.[14-16] In addition, transformation of chalcones into heterocyclic derivatives such as pyrazolines and triazoles further enhances structural diversity and medicinal relevance. Pyrazoline-containing molecules are known for their anticancer and anti-inflammatory activities, whereas triazole derivatives are widely recognized for their metabolic stability and therapeutic versatility.[17-19] In the present study, curcumin-inspired chalcone derivatives incorporating aminoalkyl and propargyl functionalities were synthesized using organocatalytic methodologies. These chalcones were further transformed into corresponding dihydropyrazole derivatives to generate multifunctional hybrid molecules.[20-21] Figure 2 demonstrating the designing of curcumin based chalcone derivatives.

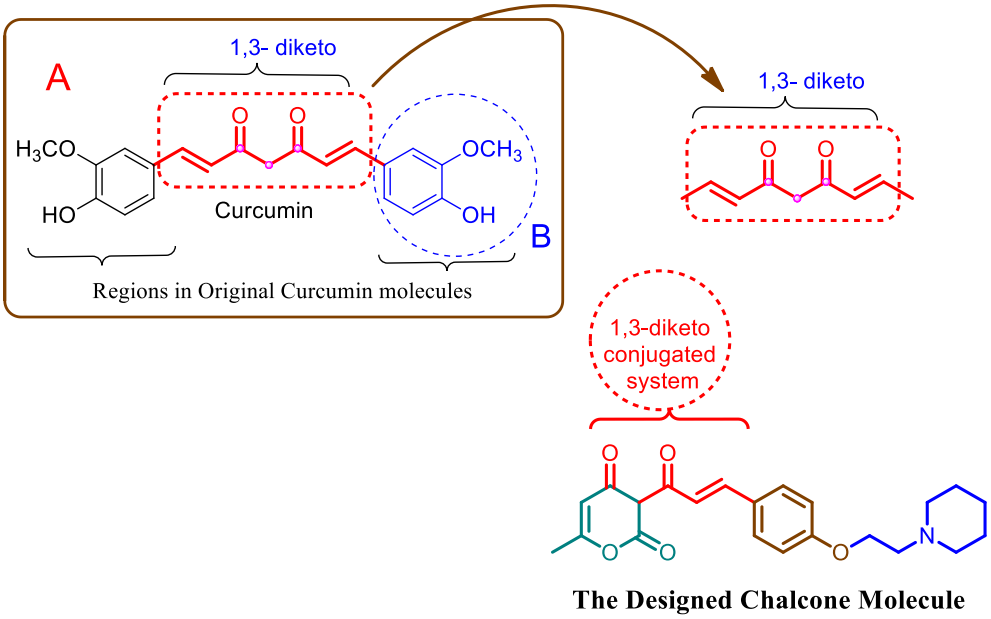


Figure 2: The designing of Curcumin Inspired Chalcone derivatives

2. Materials and Methods

2.1 Chemicals and Instrumentation

All reagents and solvents were of analytical grade and used without further purification unless otherwise stated. Thin-layer chromatography (TLC) was carried out using silica gel plates for monitoring the progress of reactions. Melting points were determined using open capillary tubes and are uncorrected. IR spectra were recorded in cm^{-1}. ^{1}H NMR and ^{13}C NMR spectra were recorded using CDCl3 as solvent and tetramethylsilane (TMS) as internal standard.

2.2 General Procedure for the Synthesis of Benzaldehyde Derivatives

4-Hydroxybenzaldehyde (1 mmol) was reacted with corresponding aminoalkyl halides (1.2 mmol) or propargyl bromide (1.2 mmol) in the presence of suitable bases such as sodium hydride or anhydrous potassium carbonate using dry THF or acetone as solvent. The reaction mixtures were stirred or refluxed until completion as monitored by TLC. After completion, the reaction mixtures were extracted using organic solvents and purified without chromatographic separation.

Table 1: Synthesized Benzaldehyde Derivatives

Compound	Substituent	Yield
2a	Piperidine analogue	78%
2b	Pyrrolidine analogue	82%
2c	Morpholine analogue	80%
3	Propargyl analogue	83%

2.3 General Procedure for the Synthesis of Curcumin-Inspired Chalcone Derivatives

Dehydroacetic acid (1 mmol) and the synthesized benzaldehyde derivatives (1 mmol) were dissolved in dry chloroform followed by the addition of catalytic piperidine. The reactions were carried out under reflux conditions for approximately 8 h. After completion, the solvent was evaporated and the products were isolated through extraction and recrystallization.

2.4 General Procedure for the Synthesis of Dihydropyrazole Derivatives

The synthesized chalcone derivative (1 mmol) was reacted with phenylhydrazine hydrochloride in ethanol under reflux conditions on a water bath for approximately 6 h. The reaction mixtures were concentrated under reduced pressure followed by extraction with ethyl acetate and water. The products were isolated as crystalline solids after recrystallization.

3. Results and Discussion

3.1 Synthesis of Benzaldehyde Derivatives

The synthesis of benzaldehyde derivatives was achieved through O-alkylation of 4-hydroxybenzaldehyde using different aminoalkyl halides and propargyl bromide. The reactions proceeded smoothly under basic conditions and produced the desired derivatives in good to excellent yields. Sodium hydride

and potassium carbonate proved effective in generating the corresponding alkoxide intermediates required for nucleophilic substitution. The aminoalkyl derivatives bearing piperidine, pyrrolidine, and morpholine functionalities were isolated as pale-yellow solids or viscous oils without requiring chromatographic purification. Similarly, the propargyl derivative was obtained in high yield and served as a valuable intermediate for further click chemistry transformations. **Figure 3** shows the synthesis of designed benzaldehyde derivatives.

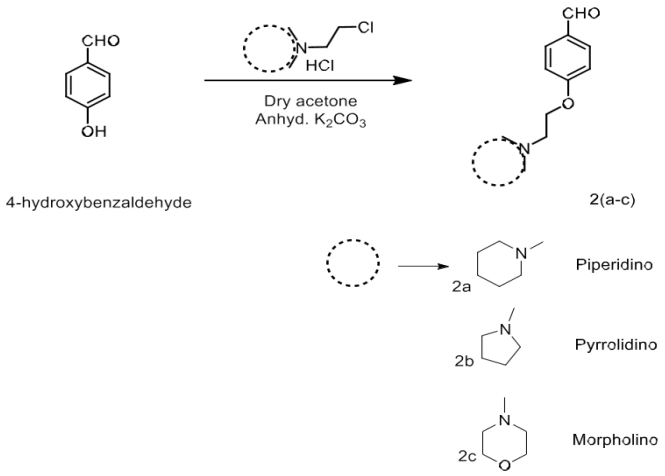


Figure 3: Synthesis of designed benzaldehyde analogues

Spectral characterization confirmed successful functionalization of the benzaldehyde scaffold. In the IR spectra, characteristic aldehydic C=O stretching frequencies were observed around 1721 cm^{-1}. The propargyl derivative additionally displayed a distinct alkyne stretching band near 2113 cm^{-1}. ^1H NMR spectra showed characteristic aldehydic proton signals around δ 9.9 ppm along with aromatic and alkoxy methylene resonances.

3.2 Synthesis of Curcumin-Inspired Chalcone Derivatives

The prepared benzaldehyde analogues were successfully converted into curcumin-inspired chalcone derivatives through condensation with dehydroacetic acid in the presence of catalytic piperidine. The reactions were operationally simple and provided the desired chalcones in satisfactory yields ranging from 78–88%. The organocatalytic approach using piperidine was found to be efficient and reproducible. The chalcone derivatives were isolated as pale-yellow crystalline solids after recrystallization from ethanol. Among the synthesized compounds, the pyrrolidine-containing derivative showed the highest yield, while the propargyl-substituted chalcone displayed slightly lower conversion, possibly due to steric and electronic factors associated with the alkyne substituent. **Figure 4** demonstrates the synthesis of chalcone derivatives.

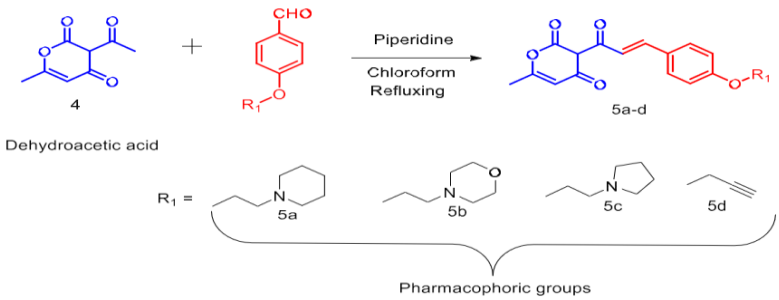
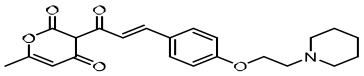
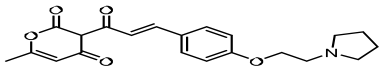
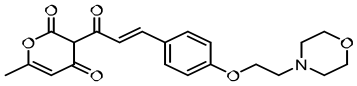
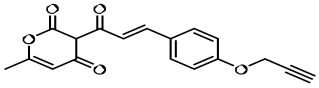


Figure 4: Synthesis of Chalcone derivatives

Table 2: The summary of synthesized chalcone derivatives

S. No.	Comp. No.	Structure	Yield
1	5a		88%
2	5b		84%
3	5c		82%
4	5d		78%

IR spectral analysis confirmed the formation of α,β-unsaturated carbonyl systems through characteristic C=O stretching bands around 1670–1676 cm^{-1} and conjugated C=C absorptions near 1655 cm^{-1}. The 1H-NMR spectra exhibited diagnostic olefinic proton doublets with coupling constants close to 16 Hz, indicating the formation of trans-configured chalcones. The synthesized chalcone framework successfully integrated the bioactive features of curcumin and dehydroacetic acid while also incorporating aminoalkyl or clickable propargyl substituents. This molecular arrangement may contribute to enhanced pharmacological behavior and improved molecular interactions.

Proposed Mechanism of Chalcone Formation

The chalcone synthesis is proposed to proceed through piperidine-mediated organocatalysis as shown in the figure **5**. Piperidine initially forms an enamine intermediate with the aldehydic carbonyl group, which subsequently reacts with activated dehydroacetic acid to generate the desired α,β-unsaturated carbonyl system after elimination and catalyst regeneration.

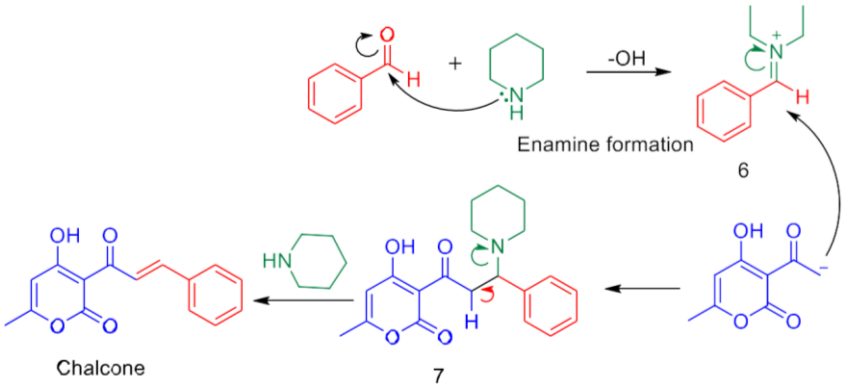


Figure 5: Proposed mechanism for synthesis of chalcone derivatives

3.3 Synthesis of Dihydropyrazole Derivatives

The chalcone derivatives were further transformed into corresponding dihydropyrazole analogues through cyclization with phenylhydrazine hydrochloride. The reactions proceeded efficiently under reflux conditions in ethanol and afforded the target heterocycles in moderate to good yields. The figure 5 shows the synthesis of dihydropyrazole derivatives. Formation of the pyrazoline ring was confirmed by the disappearance of olefinic proton signals and the appearance of characteristic methine and methylene resonances in the ^{1}H NMR spectra. The synthesized dihydropyrazole derivatives appeared as brownish crystalline powders and displayed satisfactory purity after recrystallization.

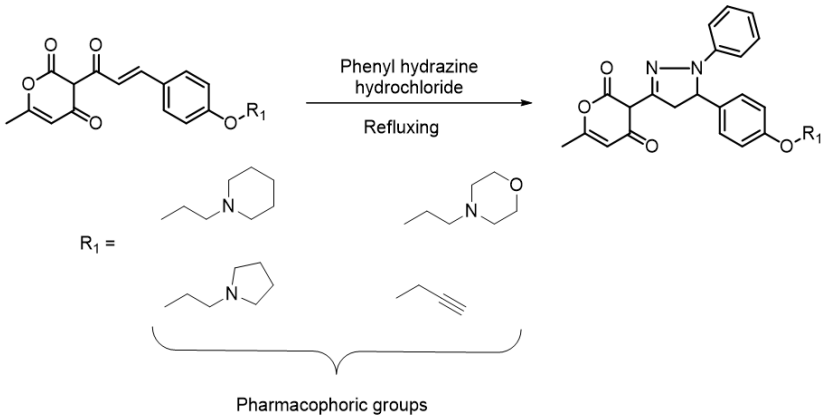
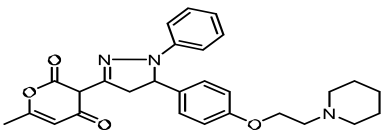
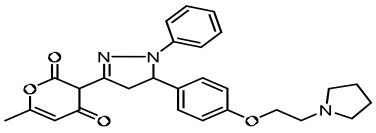
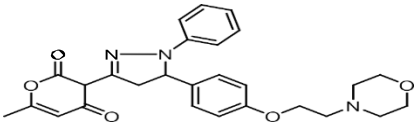
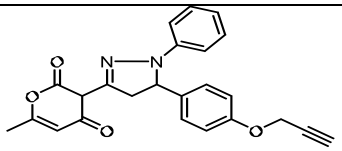


Figure 5: Synthesis of dihydropyrazole derivatives

Table 3: The summary of synthesized Dihydroyrazole derivatives

S. No.	Comp. No.	Structure	Yield
1	8a		74%
2	8b		77%
3	8c		79%
4	8d		71%

Introduction of the pyrazoline moiety significantly increased the structural diversity of the synthesized hybrids. Incorporation of aminoalkyl substituents such as pyrrolidine, piperidine, and morpholine may further improve molecular flexibility and potential biological interactions. The propargyl-containing dihydropyrazole derivative also retained the reactive alkyne functionality for future derivatization.

4. Conclusion

The present study demonstrates the successful synthesis of a series of curcumin-inspired chalcone, dihydropyrazole, and 1,2,3-triazole derivatives through molecular hybridization strategies. The synthetic routes employed were straightforward, reproducible, and provided the desired products in good yields with minimal purification requirements. The incorporation of aminoalkyl and triazole functionalities into curcumin-inspired chalcone scaffolds generated structurally diverse hybrid molecules with potential medicinal significance. Spectral characterization and elemental analysis confirmed the successful synthesis of all target compounds. The developed compounds combine important pharmacophoric features associated with chalcones, dihydropyrazoles and curcumin analogues, making them promising candidates for further biological screening and pharmacological evaluation.

Acknowledgements

The authors are thankful to the Lalit Narayan Mithila University research laboratory and institutional facilities for providing instrumental and synthetic support during the course of this work.

Conflict of Interest

The authors declare no conflict of interest.

References

[1] Mishra, S.; Singh, P.; Gupta, R.; Sharma, A. Curcumin Analogues and Derivatives in Cancer Therapy: Current Molecules and Clinical Status. *ACS Omega* 2022, 7, 32613–32636.

[2] Akram, M.; Shahab-Uddin; Ahmed, A.; Usmanghani, K.; Hannan, A.; Mohiuddin, E.; Asif, M. Curcumin: Synthesis, Chemistry, and Medicinal Properties. *Chem. Eur. J.* 2019, 25, 163–188.

[3] Barreca, M.; Spanò, V.; Rocca, R.; Bivona, S.; Montalbano, A.; Raimondi, M. V.; Diana, P.; Cirrincione, G.; Daidone, G. Curcumin-Inspired Microtubule-Targeting Agents: Design and Anticancer Profiles. *Molecules* 2021, 26, 1689.

[4] Matos, M. J.; Vilar, S.; Uriarte, E.; Santana, L. "Golden Triads" in Medicinal Chemistry: From Curcumin to New Multifunctional Leads. *Pharmaceuticals* 2024, 17, 1180.

[5] Singh, P.; Anand, A.; Kumar, V. The Anticancer Profile of Chalcones: An Update. *Molecules* 2023, 28, 3950.

[6] Zhuang, C.; Zhang, W.; Sheng, C.; Zhang, W.; Xing, C.; Miao, Z. Chalcone-Based Anticancer Agents: New Insights (2015–2020). *RSC Adv.* 2021, 11, 18777–18811.

[7] Singh, J.; Kaur, M.; Silakari, O. Fusion of Chalcones with Heterocycles: Emerging Chemotypes in Drug Discovery. *Molecules* 2020, 25, 4559.

[8] Kaur, R.; Sharma, M.; Kumar, S. Chalcone–Pyrazoline Hybrids: Synthetic Strategies and Bioactivities. *Molecules* 2023, 28, 4321.

[9] Ubaid, J. M.; Haridas, K. R.; Anilkumar, G. Benzothiazole–Pyrazoline Hybrids: Synthesis and Anticancer Evaluation. *Molecules* 2024, 29, 2456.

[10] Göksu, G.; Çelik, İ.; Arslan, M. Green and Sustainable Synthesis of Chalcones: Advances and Outlook. *Catalysts* 2022, 12, 1170.

[11] Sharma, S.; Gupta, N.; Verma, P. Microwave-Assisted Claisen–Schmidt Condensation in Benign Media. *Green Chem.* 2024, 26, 3012–3029.

[12] Wang, D.; Gao, F.; Wang, S. Dihydropyrazole (Pyrazoline) Derivatives as Anticancer Agents. *ACS Omega* 2019, 4, 10557–10571.

[13] Zhan, P.; Liu, X.; Fang, Z.; Li, Z. Pyrazoline-Embedded Scaffolds with Potent Antitumor Activities. *Sci. Rep.* 2021, 11, 22155.

[14] Othman, I.; Gad-Elkareem, M. A. M.; Anouar, E. H. Pyrazoline Derivatives: Recent Therapeutic Applications. *Eur. J. Med. Chem.* 2024, 263, 115707.

[15] Maji, B.; Ghosh, S.; Roy, S. Claisen–Schmidt Condensation in Water Mediated by a Cationic DAIL Micellar System. *J. Org. Chem.* 2024, 89, 8525–8534.

[16] Moses, J. E.; Moorhouse, A. D. Click Chemistry in Drug Discovery: CuAAC in Pharmaceuticals. *Org. Lett.* 2021, 23, 5321–5331.

[17] Pashkina, E.; Sokolov, V.; Kalinin, V. Greener Azide–Alkyne Cycloadditions: Aqueous/Copper Protocols. *Synlett* 2024, 35, 781–794.

[18] Kumar, S.; Bawa, S.; Gupta, H. Click Chemistry for Medicinal Chemists: Practical Aspects. *Asian J. Org. Chem.* 2021, 10, 2175–2198.

[19] Abdel-Rahman, H.; Al-Abd, A.; El-Naggar, M. 1,2,3-Triazole Hybrids as Anticancer Leads: Progress and Prospects. *Molecules* 2023, 28, 5587.

[20] Nahar, S.; Mosaddik, A.; Alam, M. A. Chalcone–Triazole Hybrids against *Mycobacterium tuberculosis*. *Med. Chem. Commun.* 2019, 10, 100–112.

[21] Sasse, F.; Steinmetz, H.; Höfle, G. Copper-Mediated Direct Assembly of 1,2,3-Triazoles: Methods and Scope. *Chemistry–Methods* 2021, 1, 119–131.