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Optimizing Hydroxychalcone and Its Derivatives: Evaluating Microwave and Conventional Methods for Synthesis Efficiency

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Abstract: ***A study to access the synthesis of chalcone derivatives from substituted hydroxyacetophenones with substituted benzaldehyde using basic alumina under microwave conditions offers several advantages over traditional methods. This includes a clean reaction process, simple workup and quick reaction times and high product yields. Characterization of the produced compounds was conducted using elemental analysis, ^{1}H NMR, IR and mass spectral data. Our study delves into the multifaceted biological activities of chalcones, shedding light on their potential as antibacterial and antifungal agents in combating a range of diseases. Through comprehensive biological investigations, we elucidate the significance of chalcones in modern drug discovery and development, offering insights into their diverse pharmacological properties and therapeutic potential.***

Keywords: Chalcone, substituted hydroxyacetophenone, substituted benzaldehyde, basic alumina, microwave induced synthesis

1. Introduction

Joseph Tambor and Stanislaw Kostanecki[1] are credited with the coining of the term "Chalcones." These substances are too known as benzylideneacetophenones[2] or benzalacetophenones. The term "chalcone" indicates a fragrant ketone that serves as a foundational component for a course of vital natural compounds known as flavonoids. Ordinarily inferred from consumable plants, chalcones are accepted to act as forerunners to flavones in the biosynthesis of flavonoids and isoflavonoids[3]. The ketoethylenic moiety[4], denoted by -CO–CH═CH–, renders chalcone derivatives particularly desirable.

Chalcones and their derivatives demonstrate a wide spectrum of pharmacological activities[5], agricultural applications, medicinal and biological functions[6], nutritional value, and more, attributable to the presence of a reactive α,β-unsaturated carbonyl group[7]-[8]. Recent breakthroughs in heterocyclic chemistry have facilitated the synthesis of chalcone derivatives, which have been extensively studied for their biological relevance in targeting specific diseases. They are commonly found in natural products, vegetables, tea, flavors, and soy-based nourishments[9]. Their 2'-hydroxy subordinates play a basic part in both the union and biosynthesis of flavonoids, serving as intermediates and last items in these forms.

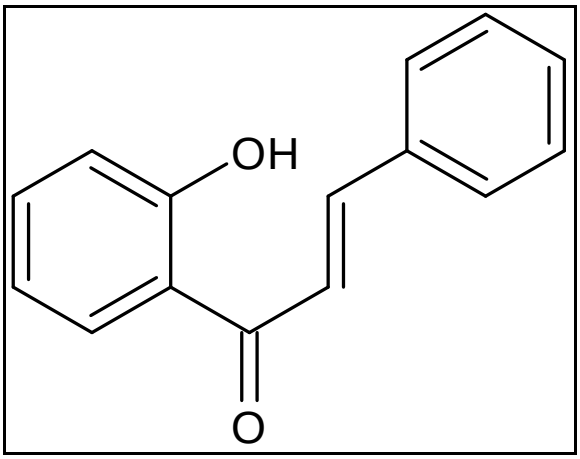


Figure 1: General Structure of Hydroxychalcone

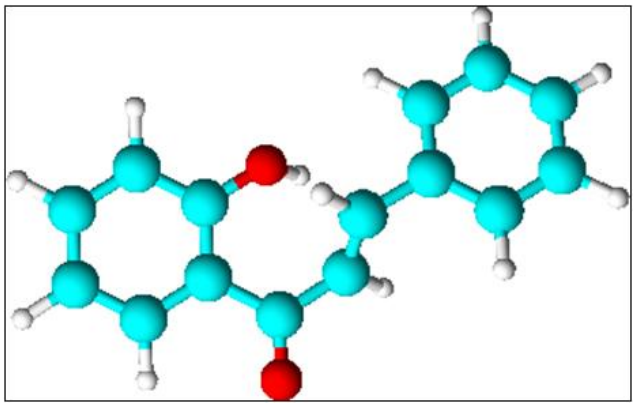


Figure 2: 3D Structure of Hydroxychalcone

For numerous decades, chalcones have been intertwined with the traditional medicinal practices involving plants and herbs[10], employed to address a diverse array of ailments. Recent studies suggest that chalcones may exhibit a myriad of significant pharmacological properties, including antimicrobial[11], anti-tuberculosis, antioxidant, antileishmanial[12], antiallergic, anti-inflammatory, antibacterial, antifungal, antimalarial, antiviral[13]-[14], anticancer[15] and anti-HIV[16] activities. One prevalent method for synthesizing chalcones from hydroxyacetophenones and benzaldehydes is the Claisen-Schmidt condensation, which occurs in the presence of a base within a polar solvent. This process is also integral to the biosynthesis of flavones and flavanones. The predominant structural feature of flavonoids, characterized by the 1-benzopyran-4-one ring, encompasses flavones, flavonols, and isoflavones.

Experimental Method

The chemicals procured for experimentation were of analytical grade and were utilized directly from their containers. Melting points were estimated using the uncorrected open capillary method. Structural confirmation of all synthesized compounds was achieved through spectrum data analysis, including infrared (IR), nuclear magnetic resonance (NMR), and mass spectrometry, along with elemental analysis. Further elucidation of compound structures was carried out using thin layer chromatography on silica gel-G plates, employing a toluene:ethyl acetate (9:1) solvent system as the eluent. Infrared spectra were obtained using a Perkin Elmer 175P spectrophotometer with KBr as the medium. ^1H NMR spectra were recorded utilizing $CDCl_3$ as the solvent and Tetramethylsilane (TMS) as the internal standard on a Brucker DRX-300 spectrophotometer. Mass spectra were acquired using a Jeol SX-102 spectrophotometer. All reactions were conducted in a household microwave oven.

General Method

Method A: Traditional (Conventional) Method:

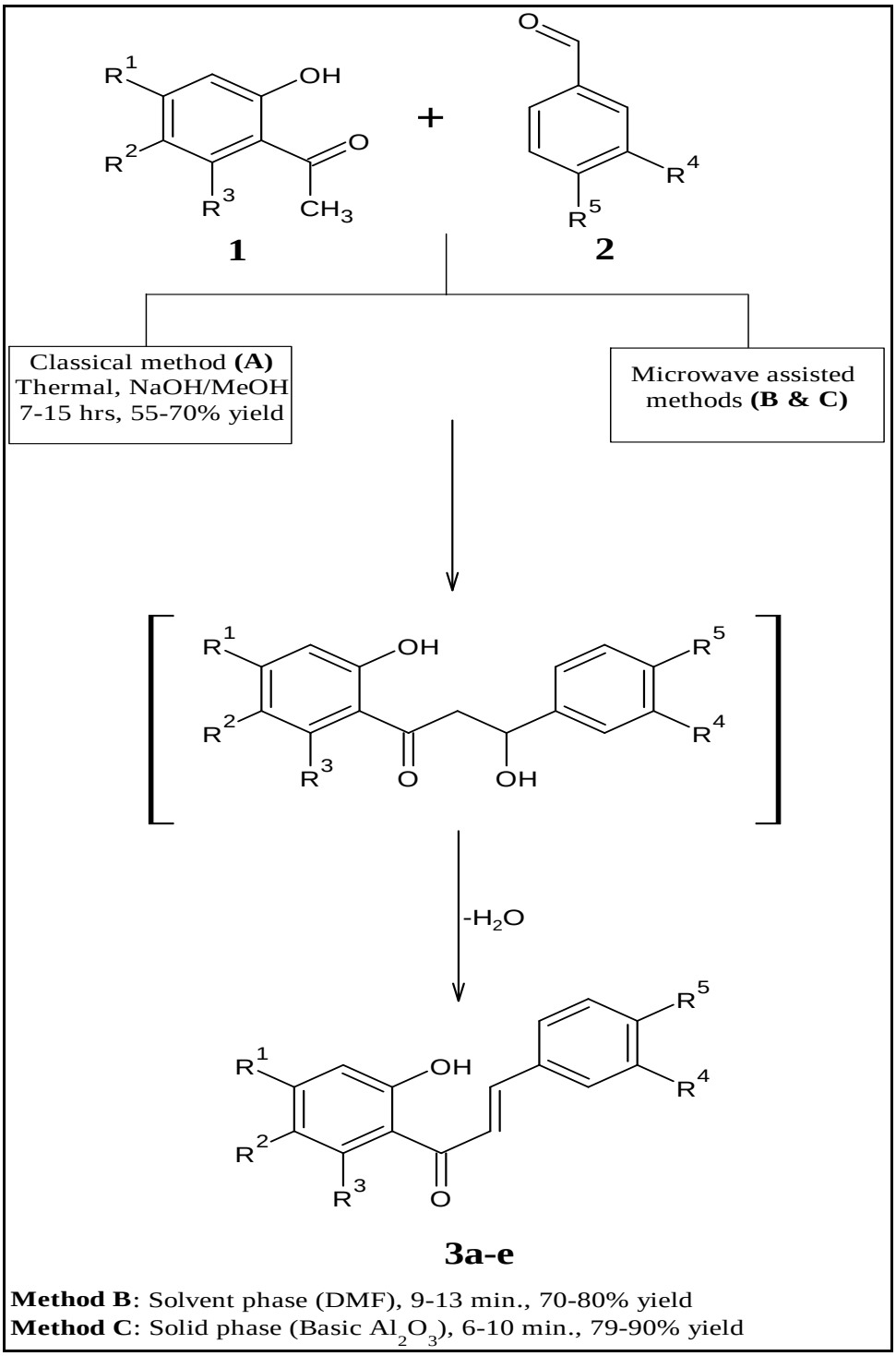
For the amalgamation of hydroxychalcones, the most compelling strategy involves utilizing the Claisen-Schmidt condensation. This prepare includes refluxing equimolar amounts of substituted hydroxyacetophenone and substituted benzaldehyde in the nearness of fluid alcoholic antacid on a water bath. The response is permitted to continue for 7 to 15 hours at a temperature extending from 20 to 80℃. Taking after completion of the response, the coming about product is cooled, washed, dried, and subjected to recrystallization for consequent analysis.

Method B: Microwave Assisted Solvent Phase Method:

Microwave irradiation was employed to facilitate the synthesis of substituted hydroxychalcones from a reaction mixture comprising substituted hydroxyacetophenone and substituted benzaldehyde in the presence of anhydrous NaOH. Initially, a conical flask containing the acetophenone and aldehyde was utilized. Subsequently, the NaOH solution was added to the mixture and combined thoroughly before being placed inside the microwave reactor. The mixture underwent exposure to 300 watts of microwave radiation for a duration ranging from 9 to 13 minutes. The advancement of the reaction was observed via thin layer chromatography (TLC). Following completion of the reaction, the reaction mixture was diluted with ice-cold water, and the compounds were subsequently extracted using methanol after an acidification step involving diluted HCl. The solvent was evaporated after the methanol layer was purified with water, dried using anhydrous Na_2SO_4, and allowed to cool. The resulting product was subjected to recrystallization for further analysis.

Method C: Microwave Assisted Solid Phase Method:

Basic Al_2O_3 served as the solid support for the synthesis of substituted hydroxychalcones. The mixture comprising substituted hydroxyacetophenone and substituted benzaldehyde was adsorbed onto the surface of the solid support in ethanol under continuous stirring. Subsequently, the adsorbed material was thoroughly air-dried and transferred into the microwave reactor. Following heating for a duration of 6 to 10 minutes, the reaction mixture was extracted using methanol. The resulting product was subjected to recrystallization for subsequent analysis.



Reaction Scheme I

2. Result and Discussion

A plethora of techniques for synthesizing hydroxychalcone and its derivatives can be found in the literature. However, many of these methods suffer from drawbacks such as prolonged reaction times, elevated reaction temperatures, low yields, the use of expensive and toxic reagents, and cumbersome work-up procedures. Therefore, there is a continuing need to develop innovative techniques that offer higher yields, enhanced efficiency, and simplified procedures. In recent decades, chemists have been compelled to reevaluate traditional approaches in light of growing environmental concerns. In this project, the use of solid-supported reagents has emerged as a pioneering strategy, resulting in significantly reduced waste effluent while preserving the natural environment. Additionally, the application of microwave irradiation has facilitated reactions on dry media, simplifying the experimental process.

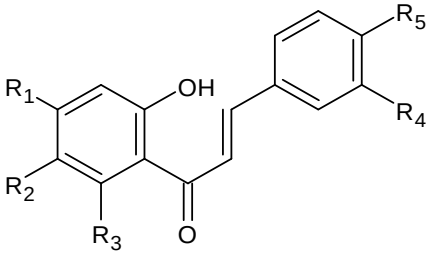
The conventional method involves refluxing substituted acetophenones with substituted aromatic aldehydes in the presence of a base to generate hydroxychalcone and its derivatives under varying conditions. Refluxing typically extends over a duration of 7 to 15 hours. This traditional approach is characterized by its lengthy duration, low yield, labor-intensive nature, and high solvent consumption. Consequently, efforts were made to conduct reactions

utilizing microwave irradiation under solvent-free conditions over basic alumina, aiming to establish a novel, environmentally friendly synthesis process. Both reactants were subjected to microwave radiation after being adsorbed onto a solid support of basic alumina. With a reaction time ranging from 6 to 10 minutes, the yield of the reaction reached 79 to 90%. In these reactions, solid supports functioned as both energy transfer media and catalysts. It was observed that reaction technique C, employing basic alumina, outperformed solvent-phase microwave irradiation (method B) and the standard method (method A). Due to its simplified work-up procedure and higher yield, basic alumina emerged as a favorable choice for the synthesis of hydroxychalcone and its derivatives (3a-e) (Reaction Scheme-I).

According to the findings, the synthesis of substituted hydroxychalcone was found to be more favorable when employing microwave-assisted synthesis compared to the classical method, resulting in a superior yield.

Biological Activity: The antibacterial and antifungal analyses of synthesized samples was done using the paper disc diffusion method. The tested bacteria and fungi included B. subtilis, S. aureus, T. mentagrophytes, and E. floccosum at a concentration of 50mg/ml in DMF. All synthesized compounds were compared for efficiency against standard streptomycin and fluconazole. The incubation period was 24 hours at a temperature of 25°C. Through rigorous comparison with established antibiotics like streptomycin and fluconazole, we discerned a notable trend: compounds enriched with chloro or bromo functional groups demonstrated heightened efficacy against both bacterial and fungal strains. In contrast, the effectiveness of other compounds ranged from moderate to weak, highlighting the distinct advantage of halogenated derivatives in combating microbial pathogens.

Apart from antibacterial and antifungal activities, these synthesized substituted hydroxychalcones exhibit various other biological properties (predicted using way2drug tool), such as, antiprotozoal, anti-inflammatory, antimutagenic, chemopreventive, vasoprotector, antihypotensive, antituberculosic, antiparasitic, antiallergic, antihypercholesterolemic, antioxidant, chalcone isomerase inhibitor, retinoprotector, histidine kinase inhibitor, melanin inhibitor, free radical scavenger, antihelmintic, hepatoprotectant, antiulcerative, etc.
The synthesized compounds and their spectral analysis were shown below:



(3a-e)

3a: $R^1=OCH_3$, $R^2=R^4=H$, $R^3=Cl$, $R^5=CH_2C_6H_5OCH_3$
3b: $R^1=COCH_3$, $R^2=R^4=H$, $R^3=OH$, $R^5=OC_6H_5$
3c: $R^1=R^3=R^4=H$, $R^2=NO_2$, $R^5=OCH_2C_6H_5$
3d: $R^1=NO_2$, $R^2=R^5=H$, $R^3=Br$, $R^4=C_6H_5Cl$
3e: $R^1=Cl$, $R^2=R^5=H$, $R^3=OH$, $R^4=C_6H_5Br$

Figure 3: Substituted Hydroxychalcone Derivatives

3a: Anal. Calcd for $C_{24}H_{21}ClO_4$ (408.89): C 70.44, H 5.12, Cl 8.68. (Ar) 3009, (C=O) 1692, (C=C) 1652, (C-O-C) 1075, (OCH_3) 1262, (Cl) 674. (M+100) 373. 3.82 [d, 6H], 4.04 [d, 2H], 6.49 [d, 1H], 6.82 [m, 3H], 7.16 [d, 2H], 7.43 [dd, 2H], 7.41 [m, 2H], 7.53 [d, 1H].
3b: Anal. Calcd for $C_{23}H_{18}O_5$ (374.33): C 72.73, H 4.82. (Ar) 3042, (OH) 3357, (C=O) 1685, (C=C) 1612, (C-O-C) 1082, (OCH_3) 1079. (M+100) 353. 2.53 [s, 3H], 7.06 [s, 5H, 1H], 7.13 [tt, 1H], 7.38 [m, 2H], 7.45 [dd, 2H], 7.54 [m, 3H], 7.71 [d, 2-OH].
3c: Anal. Calcd for $C_{22}H_{17}NO_5$ (375.39): C 70.35, H 4.55, N 3.75. (Ar) 3098, (C-N) 1257, (C=O) 1689, (C=C) 1647, (C-O-C) 1119. (M+100) 403. 5.05 [d0, 2H], 6.77 [m,2H], 7.13 [m, 2H, 1-OH], 7.37 [m, 5H, 1H], 7.52 [d, 2H], 7.75 [dd, 1H], 8.17-8.56 [d, 2H].
3d: Anal. Calcd for $C_{21}H_{13}BrClNO_4$ (458.65): C 54.92, H 2.87, N 3.09, Cl 7.76, Br 17.45. (Ar) 3035, (C-N) 1368, (C=O) 1725, (C=C) 1679, (Cl) 674, (Br) 547. (M+100) 523. 7.57 [m, 4H, 2H, 1H], 7.68 [m, 2H], 7.83 [m, 1H], 8.26 [d, 1H].
3e: Anal. Calcd for $C_{21}H_{14}BrClO_3$ (429.68): C 58.66, H 3.27, Cl 8.29, Br 18.55. (Ar) 3092, (OH) 3309, (C=O) 1654, (C=C) 1665, (Cl) 699, (Br) 583. (M+100) 503. 6.77 [s, 2H], 7.63 [m, 2H, 3H, 4H], 7.73 [s, 2-OH], 7.84 [t, 1H].

3. Conclusion

In conclusion, among the three methods employed in this study, Method C demonstrated the shortest reaction time and yielded the highest product yield. Furthermore, our investigation into the biological activities of the synthesized compounds revealed that those containing chloro or bromo groups exhibited the highest effectiveness as antibacterial and antifungal agents. Among these compounds, 3a, 3b, and 3e emerged as the most potent agents, showcasing their potential for further exploration as therapeutic candidates.

Table I: Comparison of reaction time and yields of synthesized substituted hydroxychalcone

S. No.	Comp. Name	Reaction Time			% Yield		
		Classical method (A) (hrs)	MW methods (min)		Classical method (A)	MW methods	
			B	C		B	C
3a	(2*E*)-1-(2-chloro-6-hydroxy-4-methoxyphenyl)-3-{4-[(4-methoxyphenyl)methyl]phenyl}prop-2-en-1-one	11.50	10.50	7.50	69.12	80.34	89.68
3b	(2*E*)-1-(4-acetyl-2,6-dihydroxyphenyl)-3-(4-phenoxyphenyl)prop-2-en-1-one	11	11	8	58.05	77.45	87.59
3c	(2*E*)-3-[4-(benzyloxy)phenyl]-1-(2-hydroxy-5-nitrophenyl)prop-2-en-1-one	9.50	13	7	60.54	72.64	81.74
3d	(2*E*)-1-(2-bromo-6-hydroxy-4-nitrophenyl)-3-(4'-chloro[1,1'-biphenyl]-3-yl)prop-2-en-1-one	12	9.50	9	61.97	76.68	86.33
3e	(2*E*)-3-(4'-bromo[1,1'-biphenyl]-3-yl)-1-(4-chloro-2,6-dihydroxyphenyl)prop-2-en-1-one	8.50	10	8	65.25	78.55	85.94

Table II: Antibacterial and Antifungal activity of substituted hydroxychalcones

Comp. Name	Antibacterial Activity		Antifungal Activity	
	B. subtilis	S. aureus	T. mentagrophytes	E. floccosum
3a	0.23	0.19	0.33	0.15
3b	0.03	0.17	0.29	0.32
3c	0.06	0.22	0.18	0
3d	0.13	0.2	0.31	0
3e	0.22	0.18	0.34	0
Streptomycin	0.67	0.53	0.61	0
Fluconazole	0.38	0	0.41	0.82

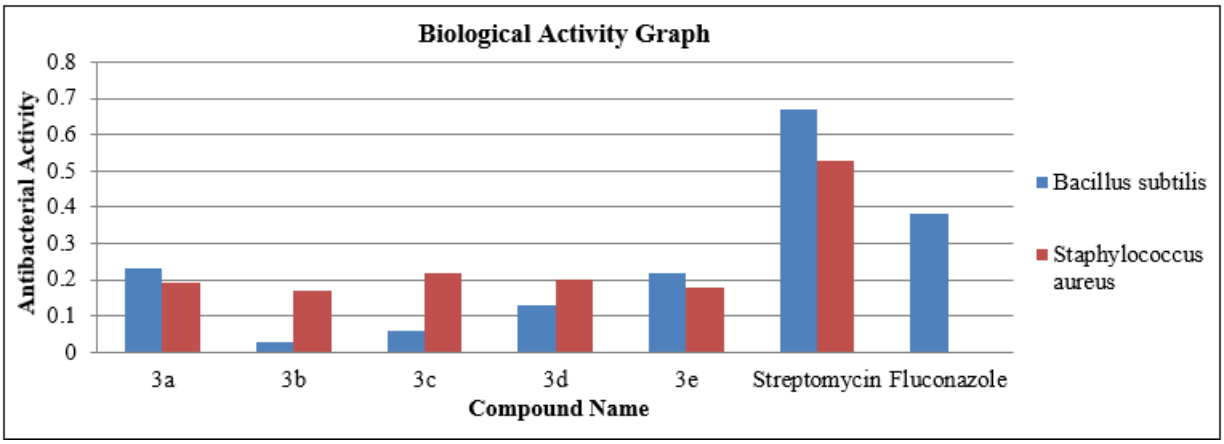


Figure 4: Antibacterial Activity Chart of Synthesized Hydroxychalcone Derivatives

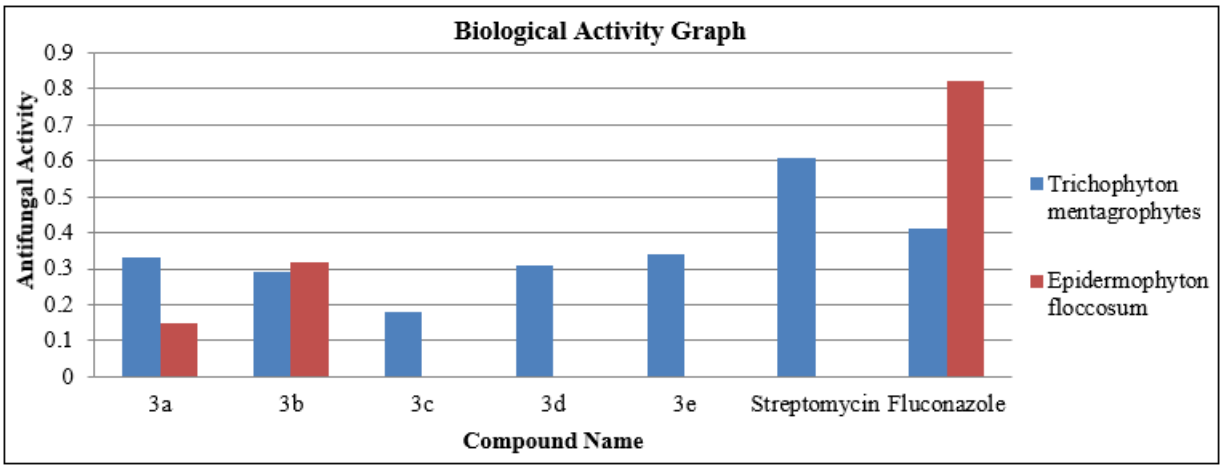


Figure 5: Antifungal Activity Chart of Synthesized Hydroxychalcone Derivatives

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References

[1] Kostanecki S., Tambor J. Ueber die sechs, "Isomeren Monooxybenzalacetophenone (Monooxychalkone)," Ber. Dtsch. Chem. Ges, XXXII, pp. 1921-1926, **1899.**

[2] Fana-Maria Coman, Armelle T. Mbaveng and Coworkers, "Heterocycles 44. Characterization, Synthesis, and Anticancer Activity of New Thiazole Ortho-hydroxychalcones," Medicinal Chemistry Research, XXVII, pp. 1396-1407, **2018**.

[3] Kibrom Mezgebe, Yadessa Melaku, and Endale Mulugeta, "Synthesis and Pharmacuetical Activities of Chalcone and its Derivatives Bearing N-Heterocyclic Scaffolds: A Review," ACS Omega, VII, pp. 27769−27786, **2022**.

[4] Kamya Goyal, Rajwinder Kaur, Anju Goyal, Rajendra Awasthi, "Chalcones: A Review on Synthesis and Pharmacological Activities," Journal of Applied Pharmaceutical Science, XI, pp. 001-014, **2021**.

[5] Santosh L. Gaonkar, U. N. Vignesh, "Synthesis and Pharmacological Properties of Chalcones: A Review," Research on Chemical Intermediates, XLIII, pp. 6043-6077, **2017**.

[6] Yanqing Du, Fengying Liang, Mixia Hu, Ren Bu, Meiling Wang, Akihiko Tsuda and Chaolu Eerdun, "Dyes of Hydroxychalcone that serve as Coulor indicators for pH and Fluoride ions," RSC Adv., X, pp. 37463–37472, **2020**.

[7] Jing Zhang, Xin-Ling Fu, Nan Yang and Qiu-An Wang, "Synthesis and Cytotoxicity of Chalcones and 5-Deoxyflavonoids," The Scientific World Journal., MMXIII, pp. 1-6, **2013**.

[8] Mangalshree Dulawat, Jyoti Prajapati, Arpita Matta, Renu Rathore and Shiv Singh Dulawat, "Microwave Induced Novel Synthesis and Characterization of 3,5-diaryl-Δ^2-isoxazoline" from α, β-unsaturated Carbonyl Compounds," Res. J. Chem. Sci., VII, pp. 33-38, **2017**.

[9] Zahraa Haithem, Yasameen K. Al-Majedy, Majid S.Jabir, "Designing and Synthesis of Chalcone's and Chromone's Derivatives as an Effective Antimicrobial Agents," J. Popul. Ther. Clin. Pharmacol., XXX, pp. 324–329, **2023**.

[10] Salehi B, Quispe C and Coworkers, "Biological Properties of Chalcones: A Review of Preclinical Analysis Including Molecular Mechanisms and Clinical Evidence," Front Pharmacol., XI, pp. 1-21, **2021**.

[11] U. B. Chougale, P. R. Kharade, S. R. Dhongade, "Synthesis of Various Chalcone Derivatives and Analysis of Their Antimicrobial Activity," Life Science Informatics Publications, V, pp. 343-349, **2019**.

[12] B. B. Chavan, A. S. Gadekar, P. P. Mehta, P. K. Vawhal, A. K. Kolsure, A. R. Chabukswar, "Synthesis and Medicinal Signiicance of Chalcones-A Review," Asian Journal of Biomedical and Pharmaceutical Sciences., VI, pp. 01-07, **2016**.

[13] Laxmi Lal Dangi, Mangal S. Dulawat, Parul Tiwari and Shiv Singh Dulawat, "Novel Substituted m-Phenoxy Chalcones: Their Synthesis through Microwave Irradiation and Evaluation of Antifungal Activity," Asian J. Research Chem., VI, pp. 461-463, **2013**.

[14] Tran Thanh Dao, Tran Thai Son, Nguyen Thi Cam Vi, Le Minh Tri and Thai Khac Minh, "Synthesis, in situ Acetylcholinesterase Inhibitory Activity Evaluation and Docking Investigation of different Aromatic Chalcones," Med. Pharm. Res, I, pp. 15-25, **2017**.

[15] Jyoti Prajapati, Mangalshree Dulawat, Prakash Prajapat, Renu Rathore & Shiv S. Dulawat, "Microwave Irradiated Synthesis of Pyrazoline Compounds Containing Substituted Benzyloxy Phenyl Ring System," International Journal of Applied Sciences., IV, pp. 145-151, **2016**.

[16] Kunal Dhankhar, D. P Pathak, "Methods of Synthesis of Chalcones with Green methods and Recent updates in Anticancer and Anti-HIV activities of Chalcones: A Review," Saudi J Med Pharm Sci., V, pp. 512-526, **2019**.