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Research Article

Exploring Efficient Synthetic Routes to Flavanones from Substituted O-Hydroxychalcones And O-Benzoyloxyacetophenones

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The synthesis of flavanones is a significant area of research due to their diverse biological activities and potential pharmaceutical applications. This study focuses on the synthesis of flavanones using substituted o-hydroxychalcones and substituted o-benzoyloxyacetophenones as starting materials. Both pathways offer efficient and selective routes to flavanone derivatives. In the first approach, substituted o-hydroxychalcones undergo cyclization under acidic or basic conditions to yield the desired flavanones. The presence of electron-donating or electron-withdrawing substituents on the aromatic rings influences the reaction rate and yield. The second pathway involves the synthesis of substituted o-benzoyloxyacetophenones, which then undergo acid catalysed cyclization to form flavanones. This method provides an alternative route that can accommodate a wide range of substituents, potentially enhancing the versatility of the synthetic process. Comparative analysis of these methods reveals differences in reaction conditions, yields, and substrate scope, highlighting the importance of choosing the appropriate starting material based on the desired flavanone derivative. The resulting flavanone derivatives exhibits varied pharmacological properties, underscoring the potential of these synthetic routes in drug discovery and development. This study contributes to the field by offering optimized protocols for flavanone synthesis, facilitating the exploration of their therapeutic potential.

Keywords: Flavanones; o-hydroxychalcones; o-benzoyloxyacetophenones; acid catalysed cyclization; therapeutic activity.

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INTRODUCTION

Flavanones are an important subclass of flavonoids, a large family of polyphenolic compounds[1] commonly found in plants. Structurally, flavanones are characterized by a 15-carbon skeleton consisting of two aromatic rings (A and B) connected by a three-carbon heterocyclic ring (C)[2]. This distinctive structure

is crucial for their biological activity[3] and potential therapeutic applications.

Naturally occurring flavanones, such as naringenin, hesperetin, and eriodictyol[4], are abundant in citrus fruits like oranges, lemons, and grapefruits[5]. These compounds are responsible for some of the characteristic flavors and health benefits associated with citrus fruits. The biological activities of flavanones are diverse and have been well-documented in scientific literature:

1. **Antioxidant Activity:** Flavanones can neutralize free radicals and reduce oxidative stress, which is linked to chronic diseases such as cancer[6], cardiovascular diseases, and neurodegenerative disorders. Their antioxidant properties[7] are due to their ability to donate hydrogen atoms or electrons and to chelate metal ions.
2. **Anti-inflammatory Effects:** Flavanones have been shown to inhibit the production of proinflammatory cytokines and enzymes, such as cyclooxygenase-2 (COX-2), thereby reducing inflammation[8]. This makes them potential candidates for treating inflammatory conditions like arthritis.
3. **Anticancer Properties:** Studies suggest that flavanones can induce apoptosis (programmed cell death) in cancer cells, inhibit cell proliferation[9], and prevent metastasis. Their mechanisms include the modulation of signaling pathways such as NF-κB and PI3K/Akt.
4. **Antimicrobial Activity:** Flavanones exhibit antimicrobial effects against a range of pathogens, including bacteria, fungi, and viruses[10]. This activity can be attributed to their ability to disrupt microbial cell membranes and inhibit the synthesis of nucleic acids and proteins.
5. **Cardioprotective Effects:** Flavanones contribute to cardiovascular health by improving endothelial function, reducing blood pressure, and lowering cholesterol levels[11]. These effects are mediated through mechanisms like the enhancement of nitric oxide bioavailability and the inhibition of LDL oxidation.

Despite their promising pharmacological properties[12], the exploration of flavanones in clinical settings is often limited by their low natural abundance and challenges associated with their extraction and purification from plant sources. This highlights the need for efficient synthetic methods to produce flavanone and its derivatives in sufficient quantities for research and therapeutic use.

Traditional synthetic methods for flavanone production typically involve multi-step processes and stringent reaction conditions, which can be time-consuming and inefficient. Consequently, there is a strong interest in developing more straightforward and versatile synthetic routes.

Substituted o-hydroxychalcones[13] and substituted o-benzoyloxyacetophenones have emerged as valuable starting materials for flavanone and its derivatives synthesis. Substituted o-hydroxychalcones, featuring hydroxyl groups ortho to the chalcone moiety, can cyclize under acidic or basic conditions to form flavanones. The cyclization reaction is influenced by the substituents on the aromatic rings, with electron-donating groups generally facilitating the process.

Alternatively, substituted o-benzoyloxyacetophenones offer a different route through acid catalysed cyclization. The direct conversion of o-benzoyloxyacetophenone to flavanone eliminates the need for intermediate steps, streamlining the synthetic process. This method typically involves the selective cleavage of the benzoyloxy group followed by cyclization to form the flavanone scaffold. The direct synthesis not only reduces the number of synthetic steps but also minimizes the generation of chemical waste, making it an attractive strategy for the efficient production of flavanones. Additionally, this approach allows for the modification of reaction conditions to optimize yield and selectivity, offering flexibility in the synthesis of diverse flavanone derivatives with tailored biological activities.

Our research not only seeks to expand the synthetic toolbox for flavanone derivatives but also aims to enhance the understanding of their synthesis, facilitating further exploration of their therapeutic potential. Through these efforts, we contribute to the development of new flavanone-based pharmaceuticals, supporting advancements in health and disease treatment.

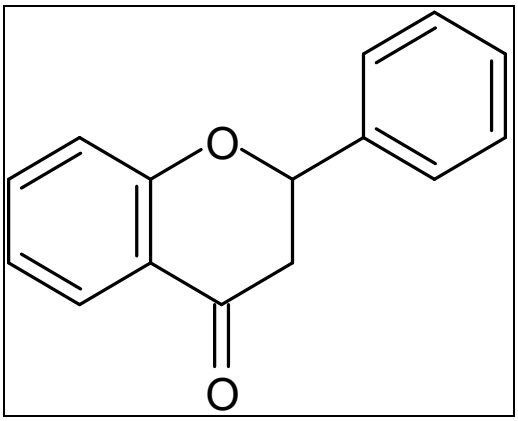


Figure 1. Basic Structure of Flavanone

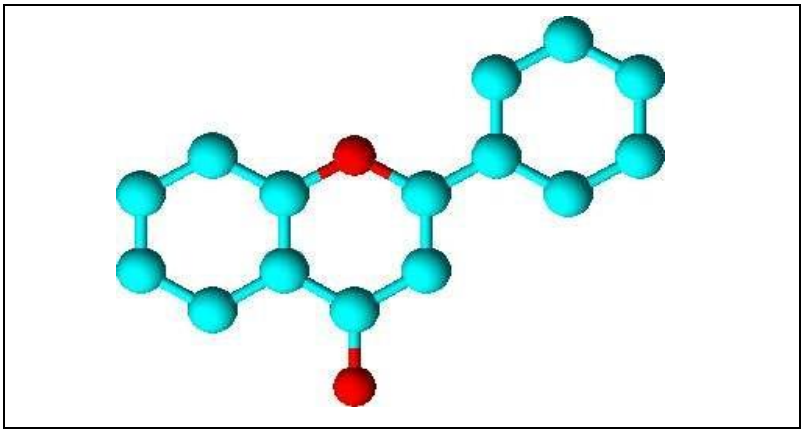


Figure 2. 3D Structure of Flavanone

EXPERIMENTAL METHOD

Analytical-grade chemicals were purchased for the experiment and used straight out of the containers. We estimated melting points with the uncorrected open capillary method. All synthesized compounds' structural confirmation was obtained by elemental analysis along with spectrum data analysis, which included nuclear magnetic resonance (NMR), mass spectrometry, and infrared (IR) spectroscopy. Using thin layer chromatography on silica gelG plates and an eluent consisting of a toluene:ethyl acetate (9:1) solvent mixture, more compound structure clarification was accomplished. Using KBr as the medium, infrared spectra were acquired with a Perkin Elmer 175P spectrophotometer. Using a Brucker DRX300 spectrophotometer, ^{1}H NMR spectra were obtained using $CDCl_3$ as the solvent and Tetramethylsilane (TMS) as the internal standard. A Jeol SX-102 spectrophotometer was used to get mass spectra. All reactions were conducted in a household microwave oven.

Method I: General Method for the Synthesis of Substituted Flavanone from Substituted O-hydroxychalcone

Method A: Traditional (Conventional) Method:

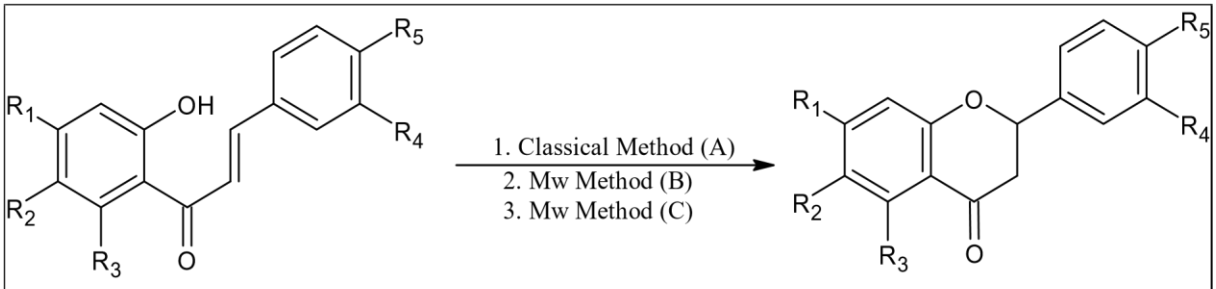
To synthesize substituted flavanones from substituted o-hydroxychalcones reaction used is acid catalysed cyclization reaction. For this process dissolve equimolar quantities of substituted o-hydroxychalcone in ethanol. Now add a catalytic amount of p-toluenesulfonic acid in the reaction mixture which acts as an acid catalyst. Reflux the reaction mixture at 60-100°C for about 6-8 hours. Thin Layer Chromatography (TLC) is used to track the course of the reaction. After the reaction is finished, let it cool to room temperature and, neutralize it with sodium bicarbonate. Extract the obtained precipitate using an organic solvent such as dichloromethane. Now dry the organic layer using anhydrous sodium sulphate, concentrate it again, and purify the product by recrystallization. The obtained product is then used for further analysis.

Method B: Microwave Assisted Solvent Phase Method:

Dissolve equimolar amount of substituted o-hydroxychalcone in ethanol and add a catalytic amount of p-toluenesulfonic acid. Place the mixture in a microwave reactor and heat it at around 120-160°C for 8-12 minutes to induce cyclization. Monitor the reaction progress using Thin Layer Chromatography (TLC). Once the reaction is complete, cool the mixture to room temperature, neutralize with sodium bicarbonate, and extract the product with an organic solvent such as dichloromethane. Dry the organic layer over anhydrous sodium sulfate, concentrate the solution again, and purify the product by recrystallization. The obtained product is then used for further analysis.

Method C: Microwave Assisted Solid Phase Method:

Mix substituted o-hydroxychalcone with a catalytic amount of p-toluenesulfonic acid which acts as a solid acid catalyst. Place the mixture in a microwave reactor and heat it at around 110-150°C for 5-8 minutes to induce cyclization. Monitor the reaction progress using Thin Layer Chromatography (TLC). Once the reaction is complete, allow the mixture to cool to room temperature. Extract the product with dichloromethane. Dry the organic layer over anhydrous sodium sulfate, concentrate the solution, and purify the product by recrystallization. The obtained product is then used for further analysis.



(I) **(II a-e)**

IIa. $R_1 = OCH_3$, R_2, R_4 = H, R_3 = Cl, $R_5 = CH_2C_6H_5OCH_3$
IIb. $R_1 = COCH_3$, R_2, R_4 = H, R_3 = OH, $R_5 = OC_6H_5$
IIc. R_1, R_3, R_4 = H, $R_2 = NO_2$, $R_5 = OCH_2C_6H_5$
IId. $R_1 = NO_2$, R_2, R_5 = H, R_3 = Br, $R_4 = C_6H_5Cl$
IIe. R_1 = Cl, R_2, R_5 = H, R_3 = OH, $R_4 = C_6H_5Br$

Reaction Scheme I.

Method II: General Method for the Synthesis of Substituted Flavanone from Substituted O-benzoyloxyacetophenone

This method contains two steps:

Step I. Synthesis of substituted o-benzoyloxyacetophenone from substituted o-hydroxyacetophenone

Step II. Synthesis of substituted flavanone from substituted o-benzoyloxyacetophenone

Step I: General Method for the Synthesis of Substituted O-benzoyloxyacetophenone from Substituted O-hydroxyacetophenone

Dissolve equimolar amount of substituted o-hydroxyacetophenone in pyridine solution. Add benzoyl chloride dropwise to the solution while stirring, maintaining the reaction mixture at a low temperature using an ice bath. Allow the reaction to proceed at room temperature for 3-6 hours. Once complete, pour the reaction mixture into water and extract the product with an organic solvent such as dichloromethane. Wash the organic layer with water, then dry it over anhydrous sodium sulfate. Concentrate the solution, and purify the crude product by recrystallization. The obtained product is then used for further process.

Step II. General Method for the Synthesis of Substituted Flavanone from Substituted O-benzoyloxyacetophenone

Method A: Traditional (Conventional) Method:

The most effective method for synthesizing substituted flavanones is to employ the intramolecular aldol condensation. Equimolar quantities of substituted o-benzoyloxyacetophenone and KOH as base are refluxed on a water bath in this formulation. The reaction can last between 5-10 hours at a temperature between 50-80°C. Following the completion of the response, the resultant product is chilled and acidified using diluted hydrogen chloride in order to neutralize the precipitate and base. After filtering, the precipitate is cleaned, dried, and then recrystallized for further analysis.

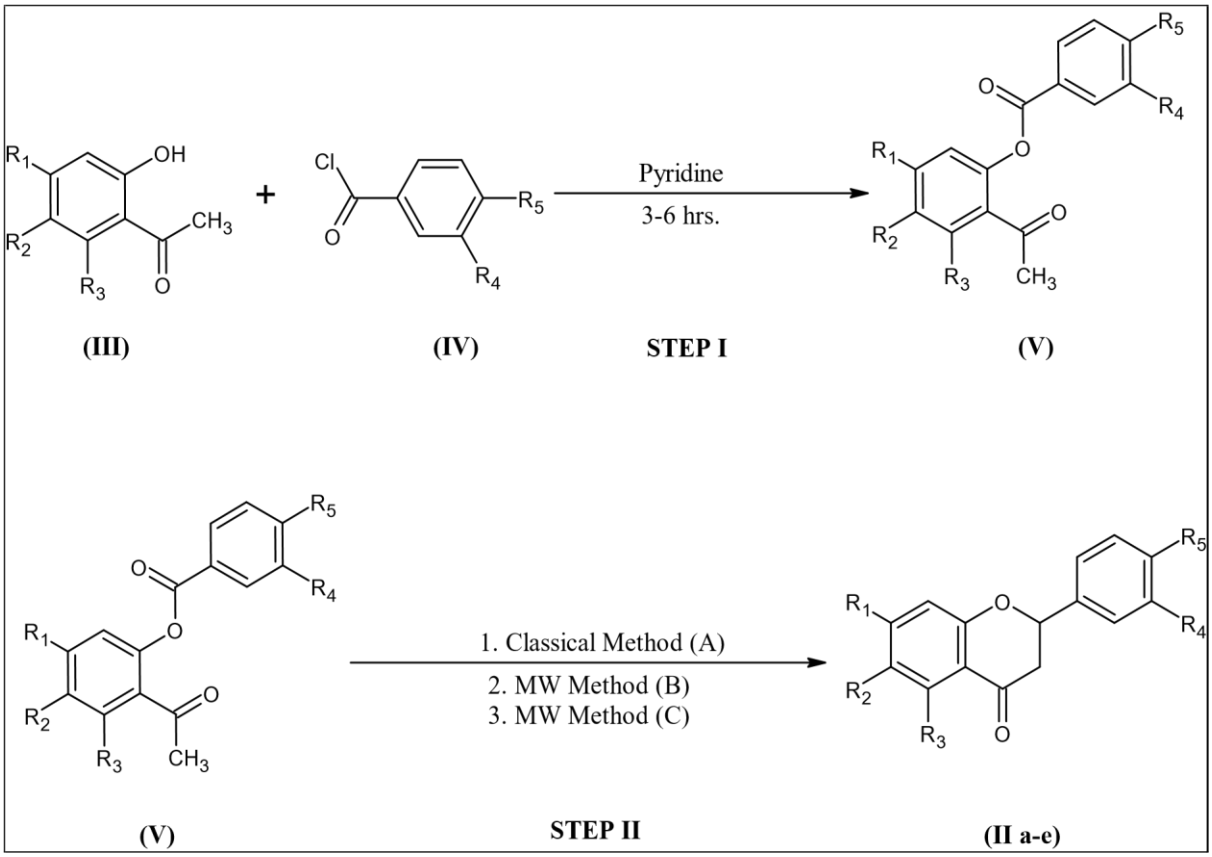
Method B: Microwave Assisted Solvent Phase Method:

In a microwave-safe reaction vessel, dissolve substituted o-benzoyloxyacetophenone using a solvent, such as methanol. After adding KOH as a base to the mixture in an equimolar proportion, put the reaction vessel inside the microwave reactor. The reaction mixture is heated for 12-15 minutes under microwave radiation with a power of 300 W and a temperature of 100-150°C. Using TLC, track the reaction's progress and modify the reaction's duration as necessary. Once the reaction is finished, allow the mixture to cool to room temperature before acidifying it with diluted HCl to precipitate the flavanone and neutralize the base. To get rid of any remaining base and contaminants, filter the precipitated product and give it a water wash. To isolate and purify the crude flavanone product, dry it out at the end.

Method C: Microwave Assisted Solid Phase Method:

The solid support basic alumina used should first be loaded with substituted o-benzoyloxyacetophenone by soaking it in its chemical solution and drying it to remove the solvent. Inside the microwave reactor, place the prepared solid support. Add the KOH base, either solid or absorbed by the solid support as a solution. Under microwave radiation, heat the mixture to 100-120°C for 8-12 minutes while using thin-layer chromatography (TLC) to
track the reaction's development. Allow the mixture to cool to room temperature after the reaction is finished. To dissolve and extract the flavanones, wash the solid support with methanol as a solvent. To extract the solid support from the flavanone-containing solvent, strain the mixture using a filter. Crude flavanone can be

obtained by reducing the pressure as the solvent evaporates.



Reaction Scheme II.

RESULT and DISCUSSION

The literature contains numerous methods for producing flavanone and its derivatives. Nevertheless, many of these techniques have disadvantages such high reaction temperatures, long reaction times, poor yields, costly and hazardous reagent usage, and laborious work-up procedures. Thus, there is a constant need to create novel methods that provide improved yields, streamlined processes, and increased efficiency. Because environmental concerns have grown over the past few decades, chemists have been forced to reconsider their conventional methods. Using solid-supported reagents has proven to be an innovative approach in this project, leading to a large reduction in waste effluent and the preservation of the environment. Furthermore, the use of microwave irradiation has made reactions on dry media easier, which has simplified the experimental procedure.

The synthesis of flavanone and its derivatives from substituted o-hydroxychalcone and substituted o-benzoyloxyacetophenone was investigated using three different methods: the classical method, microwave-assisted solvent phase method, and microwave-assisted solid phase method.

In the classical method, the synthesis of flavanone and its derivatives involved conventional heating in a suitable solvent with an acid catalyst. This method, while well-established, often requires long reaction times and high temperatures. The reaction proceeds via acid-catalyzed cyclization of the o-hydroxychalcone or o-benzoyloxyacetophenone, leading to the formation of the flavanone ring structure. However, the classical method may suffer from limitations such as low yields and the need for extensive purification steps.

The microwave-assisted solvent phase method utilized microwave irradiation to accelerate the cyclization reaction of substituted o-hydroxychalcone or substituted o-benzoyloxyacetophenone in a solvent medium. This approach offers several advantages, including shorter reaction times, higher reaction rates, and improved yields compared to the classical method. By heating the reaction mixture under microwave irradiation, the cyclization process was expedited, resulting in faster formation of flavanones and their derivatives. Additionally, microwave irradiation can enhance reaction efficiency and reduce energy consumption.

The microwave-assisted solid phase method represents a novel approach to synthesizing flavanones from substituted o-hydroxychalcone or substituted o-benzoyloxyacetophenone. In this method, the precursor molecule is immobilized on a solid support and subjected to microwave irradiation under specific reaction conditions. This approach offers advantages such as improved reaction selectivity, ease of product separation, and reduced solvent usage. By utilizing solid-phase synthesis, the synthesis process was streamlined, and the formation of by-products minimized. Microwave irradiation facilitated rapid

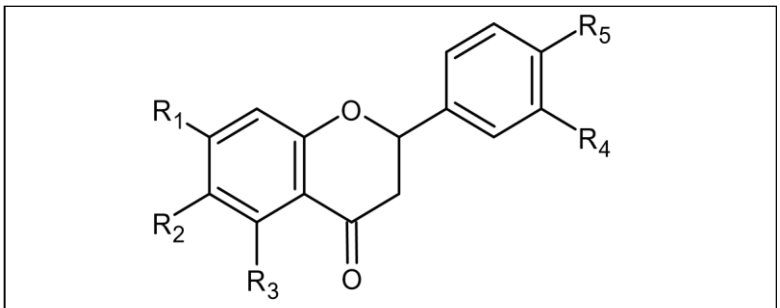
heating and efficient cyclization, leading to enhanced yields and purity of the flavanone products.

Comparing the three methods, the microwave-assisted solid phase method emerged as the most efficient and environmentally friendly approach for synthesizing flavanones and their derivatives from both substituted o-hydroxychalcone and substituted o-benzoyloxyacetophenone. This method offers advantages such as shorter reaction times, higher yields, and reduced solvent usage compared to the classical and solvent phase
methods. Additionally, the microwave-assisted solid phase method provides a convenient platform for conducting organic synthesis reactions, allowing for improved control over reaction parameters and enhanced reproducibility.

Biological Activity: Flavanones, a subclass of flavonoids found in various plants, exhibit diverse biological activities that make them valuable targets for pharmacological research. Studies have shown that flavanones possess antioxidant properties, helping to scavenge free radicals and protect cells from oxidative stress-related damage. Additionally, flavanones demonstrate anti-inflammatory effects by inhibiting inflammatory mediators and pathways, making them potential candidates for treating inflammatory conditions such as arthritis and inflammatory bowel disease. Furthermore, flavanones have been investigated for their potential anticancer properties, with studies suggesting their ability to inhibit tumor growth and induce apoptosis in cancer cells. Moreover, flavanones exhibit antimicrobial activity against bacteria, fungi, and viruses, highlighting their potential as antimicrobial agents. Overall, the diverse biological activities of flavanones underscore their importance in drug discovery and development for various health conditions.

The paper disc diffusion method was used to analyze the synthetic materials for antibacterial and antifungal properties. B. subtilis, S. aureus, T. mentagrophytes, and E. floccosum were among the bacteria and fungi that were evaluated; their concentrations were 50 mg/ml in DMF. The effectiveness of each synthesized compound was evaluated by comparison with standard fluconazole and ciprofloxacin. At 25°C, the incubation time lasted for 24 hours. We identified a noteworthy pattern by doing a thorough comparison with well-known antibiotics such as fluconazole and ciprofloxacin: compounds that were enriched with functional groups such as chloro or bromo showed increased activity against strains of bacteria as well as fungi. The significant advantage of halogenated derivatives in fighting microbial infections is shown by the moderate to weak efficiency of other agents.

These synthesized substituted flavanones, in addition to their antibacterial and antifungal activities, have a variety of other biological properties (as predicted by the way2drug tool) including antituberculosic, antihypotensive, antiparasitic, antiallergic, antihypercholesterolemic, antioxidant, retinoprotector, chalcone isomerase inhibitor, free radical scavenger, antihelmintic, hepatoprotectant, antiulcerative, etc.



(II a-e)

IIa. R_1= OCH_3, R_2, R_4= H, R_3 = Cl, R_5 = $CH_2C_6H_5OCH_3$

IIb. R_1= $COCH_3$, R_2, R_4= H, R_3 = OH, R_5 = OC_6H_5

IIc. R_1, R_3, R_4 = H, R_2 = NO_2, R_5 = $OCH_2C_6H_5$

IId. R_1= NO_2, R_2, R_5= H, R_3 = Br, R_4 = C_6H_5Cl

IIe. R_1= Cl, R_2, R_5= H, R_3 = OH, R_4 = C_6H_5Br

Figure 3. Substituted Flavanone Derivatives

IIa: Anal. Calcd for $C_{24}H_{21}ClO_4$ (408.89): C 70.45, H 5.13, Cl 8.69. (Ar) 3085, (C=O) 1690, (C=C) 1535, (C-O-C) 1180, (OCH_3) 1275, (Cl) 692. (M+100) 423. 2.87-3.13 [dd, 2H], 3.80 [d, 6H], 4.02 [p, 2H], 5.45 [td, 1H], 6.55 [d, 1H], 6.87 [m, 2H], 6.93 [d, 1H], 7.07-7.15 [dt, 6H], 7.28 [dd, 2H].

IIb: Anal. Calcd for $C_{23}H_{18}O_5$ (374.33): C 72.75, H 4.84. (Ar) 3092, (OH) 3275, (C=O) 1715, (C=C) 1480, (C-O-C) 1095. (M+100) 376. 2.54 [d, 3H], 2.82-3.09

[dd, 2H], 5.47 [tt, 1H], 6.85 [m, 3H], 7.01-7.37 [m, 8H], 7.13 [tt, 1H].

IIc: Anal. Calcd for $C_{22}H_{17}NO_5$ (375.39): C 70.37, H 4.58, N 3.76. (Ar) 3005, (C-N) 1253, (C=O) 1708, (C=C) 1498, (C-O-C) 1153. (M+100) 379. 2.89-3.12 [dd, 2H], 5.05-5.47 [d, 2H], 6.85 [m, 2H], 7.27-7.42 [m, 8H], 8.32 [dd, 1H], 8.69 [d, 1H].

IId: Anal. Calcd for $C_{21}H_{13}BrClNO_4$ (458.65): C 54.94, H 2.89, N 3.07, Cl 7.74, Br 17.43. (Ar) 3064, (C-N) 1389, (C=O) 1695, (C=C) 1529, (Cl) 675, (Br) 549. (M+100) 457. 2.88-3.13 [dd, 2H], 5.57 [t, 1H], 7.44-7.57 [m, 7H], 7.65 [t, 1H], 7.88 [d, 1H], 8.25 [d, 1H].

IIe: Anal. Calcd for $C_{21}H_{14}BrClO_3$ (429.68): C 58.65, H 3.29, Cl 8.27, Br 18.57. (Ar) 3075, (OH) 3342, (C=O) 1748, (C=C) 1592, (Cl) 692, (Br) 574. (M+100) 432. 2.82-3.23 [dd, 2H], 5.58 [td, 1H], 6.77-6.89 [d, 2H], 7.43-7.65 [m, 9H].

CONCLUSION

In conclusion, our study demonstrates the versatility of different synthetic methods for the preparation of flavanone and its derivatives from both substituted o-hydroxychalcone and substituted o-benzoyloxyacetophenone. While each method has its advantages and limitations, the microwave-assisted solid phase method offers the most efficient and sustainable approach for synthesizing flavanones in a controlled and environmentally friendly manner. These findings contribute to the development of efficient synthetic methodologies for accessing flavanone-based compounds with potential applications in pharmaceuticals, agrochemicals, and materials science. Comparing the two synthetic routes, the synthesis from substituted o-hydroxychalcones emerged as the more efficient and reliable method for flavanone production. This route offers simplicity, versatility, and high yields, making it suitable for large-scale synthesis and structural diversification. In contrast, while the synthesis from o-benzoyloxyacetophenones presents an alternative approach, it requires more optimization and control to achieve comparable results. Nevertheless, both routes contribute to the expanding toolbox of synthetic methodologies for flavanone synthesis, offering flexibility for different synthetic needs and target molecules.

Table I: Comparison of reaction time and yields of substituted flavanones synthesized from o-hydroxychalcone

S.No.	Comp. Name	Reaction Time			% Yield		
		Classical method (A) (hrs)	MW methods (min)		Classical method (A)	MW methods	
			B	C		B	C
IIa	5-chloro-7-methoxy-2-{4-[(4methoxyphenyl)methyl]phenyl}-2,3dihydro-4*H*-1-benzopyran-4-one	7	10	6.50	69.15	82.34	90.68
IIb	7-acetyl-5-hydroxy-2-(4phenoxyphenyl)-2,3-dihydro-4*H*-1benzopyran-4-one	8	11	8	65.05	78.45	88.68
IIc	2-[4-(benzyloxy)phenyl]-6-nitro-2,3dihydro-4*H*-1-benzopyran-4-one	7.50	9	7	62.54	76.64	87.59
IId	5-bromo-2-(4'-chloro[1,1'-biphenyl]3-yl)-7-nitro-2,3-dihydro-4*H*-1benzopyran-4-one	6	9.50	7.50	68.97	77.68	89.76
IIe	2-(4'-bromo[1,1'-biphenyl]-3-yl)-7chloro-5-hydroxy-2,3-dihydro-4*H*-1benzopyran-4-one	6.50	8.50	8	70.25	84.55	91.25

Table II: Comparison of reaction time and yields of substituted flavanones synthesized from o-benzoyloxyacetophenone

S.No.	Comp. Name	Reaction Time			% Yield		
		Classical method (A) (hrs)	MW methods (min)		Classical method (A)	MW methods	
			B	C		B	C
IIa	5-chloro-7-methoxy-2-{4-[(4methoxyphenyl)methyl]phenyl}2,3-dihydro-4*H*-1-benzopyran-4one	6	14	7	68.55	80.34	88.76
IIb	7-acetyl-5-hydroxy-2-(4phenoxyphenyl)-2,3-dihydro-4*H*-1benzopyran-4-one	9	13	7.50	62.88	75.96	87.59
IIc	2-[4-(benzyloxy)phenyl]-6-nitro2,3-dihydro-4*H*-1-benzopyran-4one	9.50	14.50	11	60.54	72.64	85.38
IId	5-bromo-2-(4'-chloro[1,1'biphenyl]-3-yl)-7-nitro-2,3-dihydro-4*H*-1-benzopyran-4-one	6	12	9	64.75	78.43	86.74

IIe	2-(4'-bromo[1,1'-biphenyl]-3-yl)-7chloro-5-hydroxy-2,3-dihydro-4*H*-1-benzopyran-4-one	7.50	12.50	10.50	69.37	81.58	89.64

Table III: Antibacterial and Antifungal activity of substituted flavanones

Comp. Name	**Antibacterial Activity**		**Antifungal Activity**	
	B. subtilis	**S. aureus**	**T. mentagrophytes**	**E. floccosum**
IIa	0.06	0.01	0.33	0.10
IIb	0.16	0.15	0.24	0.14
IIc	0.03	0.07	0.07	-
IId	0.01	0.24	0.24	-
IIe	0.05	0.39	0.27	-
Fluconazole	0.43	-	0.39	0.80
Ciprofloxacin	0.53	0.76	-	-

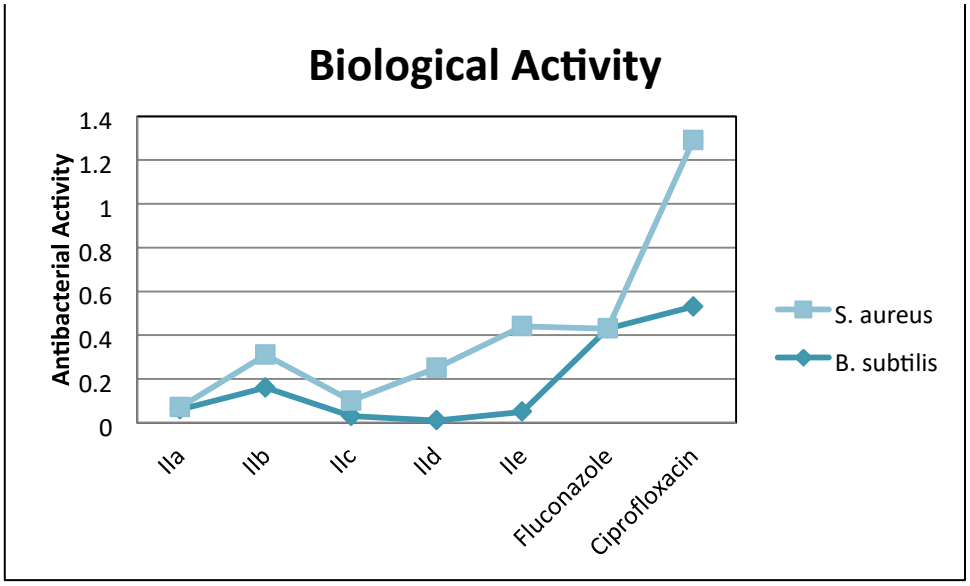


Figure 4. Antibacterial Activity Chart of Synthesized Flavanone Derivatives

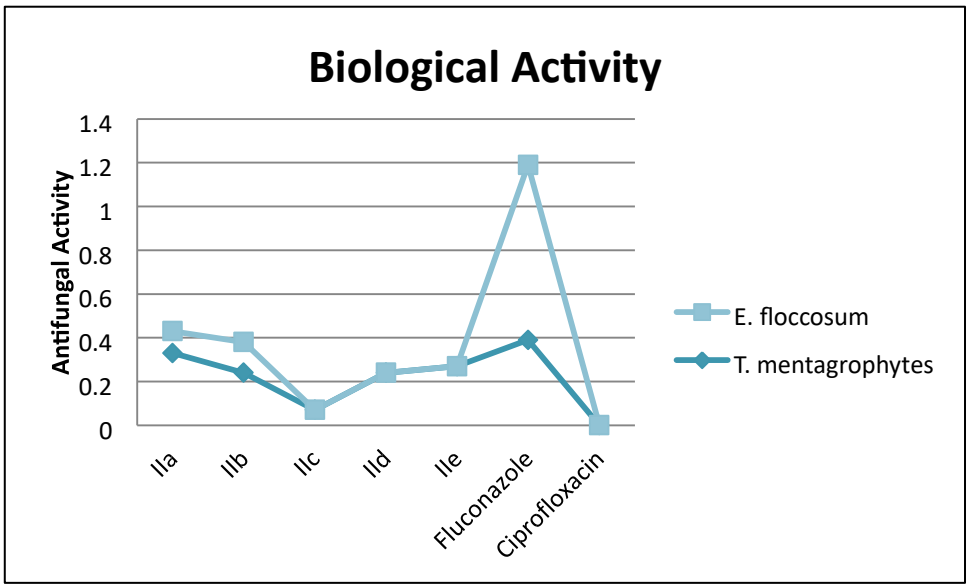


Figure 5. Antifungal Activity Chart of Synthesized Flavanone Derivatives

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