



A COMPARATIVE STUDY ON CONVENTIONAL AND MICROWAVE ASSISTED SYNTHESIS OF 1,3-DIPHENYL-2-PROPENE-1-ONES AND THEIR BIOLOGICAL ACTIVITIES

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ABSTRACT

Chalcones are synthesized by conventional and microwave assisted synthesis methods. By microwave assisted synthesis, a considerable increase in the reaction rate has been observed and that too, with better yields. We have reported the synthesis and antifungal activity study on substituent effects of 5 chalcones. A lot of genetically defined strains belonging to different yeast genera and species, namely *Aspergillus niger* and *Candida albicans*, were used as test organisms. Inhibition of chitin biosynthesis was responsible for fungistatic activity, while the fungicidal effect was a consequence of disturbance of β (1 \rightarrow 3) glucan synthase function. The chalcone derivatives may be a useful lead compound for the development of novel antifungal agents.

Key words: Antifungal activity, *Aspergillus niger*, *Candida albicans*, Chalcones.

INTRODUCTION

Chalcones having α , β -unsaturated carbonyl system is one of the most useful Michael acceptor and undergo Michael type nucleophilic addition followed by intramolecular cyclization and aromatization resulting a large number of heterocyclic and cyclic potentially useful systems. The chalcones are considered to be precursors of flavonoids and

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isoflavonoids, when found as naturally- occurring compounds, but it could be considered that their true importance is extended in two branches. The biological activity associated with them, including anti-inflammatory,¹⁻³ antimitotic,⁴ anti-leishmanial,⁵ anti-invasive,^{6,7} anti-tuberculoid,⁸ anti-fungal,⁹ anti-malarial,^{10,11} anti-tumor, and anti-oxidant properties¹² as well as their recognized synthetic utility in the preparation of pharmacologically-interesting heterocyclic systems like pyrazolines, which have also been largely studied owing to their pharmacological activities, which includes anti-tumor,¹³ anti-inflammatory,¹⁴ anti-parasitary,¹⁵ anti-depressive, anticonvulsant,¹⁶ antimicrobial,¹⁷ anti nociceptives¹⁸ and nitric oxide synthase inhibitors, associated with diseases such as Alzheimer, Huntington, and inflammatory arthritis.¹⁹

The structures of the various synthesized compounds were confirmed on the basis of their elemental and spectral (IR, ¹H NMR and MASS) data. Therefore, in the present investigation, it has been considered worthwhile to synthesize some new chalcone derivatives by conventional and microwave irradiation methods and a comparison is made between two methods. The compounds were tested for their antifungal activities by standard methods.

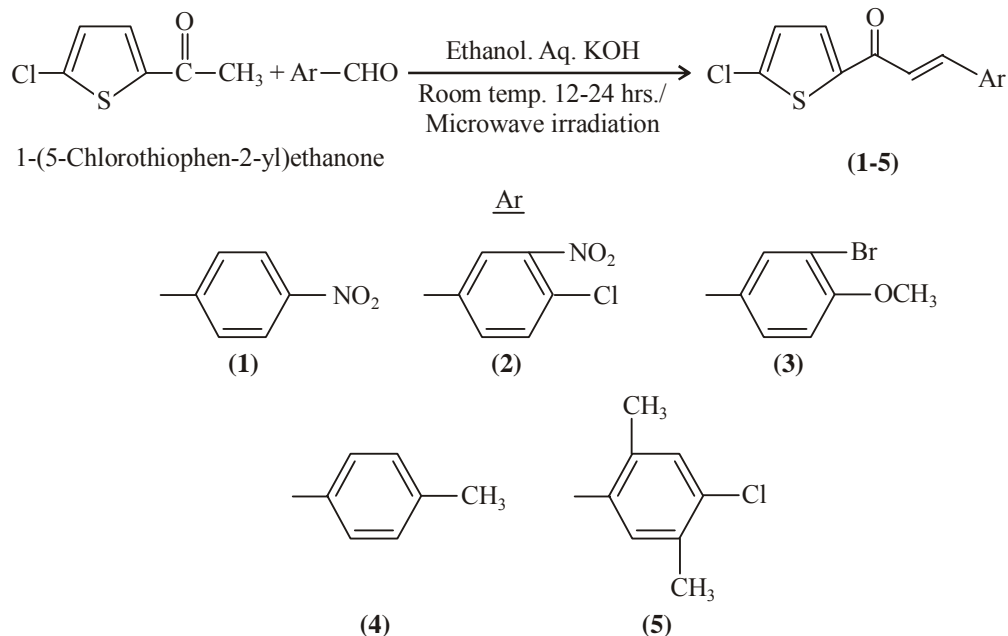
EXPERIMENTAL

General procedure for the synthesis of chalcones by Claisen-Schmidt condensation²⁰⁻²⁵

Synthesis of chalcones (1-5)

(a) Conventional: Equimolar quantities (0.001 mol) of 2-acetyl-5-chloro-thiophene and respective aldehydes (0.001 mol), were mixed and dissolved in minimum amount (3 mL) of alcohol. To this, aqueous potassium hydroxide solution (0.003 mol) was added slowly and mixed occasionally for 24 hrs, at room temperature. Completion of the reaction was identified by observing precoated TLC plates of Merck. After completion of the reaction, the reaction mixture was poured into crushed ice, if necessary, it is acidified with dil HCl. The solid separated was filtered and dried. It was purified by recrystallization or by column chromatography performed on silica gel (100-200 Mesh, Merck), using ethylacetate and hexane mixture as mobile phase.

(b) Microwave irradiation (MWI): Equimolar quantities (0.001 mol) of acetyl heterocyclic compound and respective aldehydes (0.001 mol) were mixed and dissolved in minimum amount (3 mL) of alcohol. To this, aqueous potassium hydroxide solution (0.003 mol) was added slowly and mixed. The entire reaction mixture was irradiated with microwave for about 2-6 minutes at 180 Watts.



Scheme 1

(1) 1-(5-Chlorothiophen-2-yl)-3-phenylprop-2-en-1-one (1)**Physical data**

Molecular formula	M. Wt.	M.P.	Time and % Yield				Elemental analysis (%)	
			Conventional		Micro wave Irradiation		Calculated	Found
			T	% Y	T	% Y		
C ₁₃ H ₉ ClOS	248.7	106 ± 2°C	24 hrs	85	1.5 min	94	C 62.7	C 62.9
10 % Ethyl acetate / Hexane; TLC- R _f : 0.60							H 3.60	H 3.57
							S 12.86	S 12.88

Spectral data

IR (cm⁻¹): 643 (C=O), 1587 (HC=CH), 3093 (C-H aromatic ring stretching), 802 (C-Cl), 756 (C-S).

¹H NMR (δ ppm): 6.99 (1H, d, J = 8.4 Hz, C-4'-H), 7.26 (1H, d, J = 15.6 Hz, CO-CH=), 7.3-7.5 (5H, m, Ph-H), 7.68 (1H, d, J = 9.6 Hz, C-3'-H), 7.82 (1H, d, J = 16 Hz, Ar-C-H=).

(2). 3-(3-Bromophenyl)-1-(5-chlorothiophen-2-yl) prop-2-en-1-one (2)**Physical data**

Molecular formula	M. Wt.	M.P.	Time and % Yield				Elemental analysis (%)	
			Conventional		Microwave irradiation		Calculated	Found
			T	% Y	T	% Y		
C ₁₃ H ₈ Br ClOS	327.6	102 ± 2°C	24 hrs	80	2.0 min	91	C 47.68 H 2.44	C 47.7 H 2.46
10 % Ethyl acetate/Hexane; TLC - R _f : 0.67							S 9.76	S 9.73

Spectral data

IR (cm⁻¹): 1645 (C=O), 1588 (HC=CH), 3078, 3062 (C-H), 807 (C-Br), 785 (C-S).

¹H NMR (δ ppm): 7.01 (1H, d, J = 4 Hz, C-4'-H), 7.26 (1H, d, J = 16 Hz, CO-CH=), 7.30 (1H, d, J = 4 Hz, C-6''-H), 7.53 (1H, t, J = 8 Hz, C-5''-H), 7.64 (1H, d, J = 4 Hz, C-3'-H), 7.69 (1H, s, C-2''-H), 7.75 (1H, d, J = 16 Hz, Ar-C-H=).

(3). 1-(5-chlorothiophen-2-yl)-3-(4-fluorophenyl) prop-2-en-1-one (3)**Physical data**

Molecular formula	M. Wt.	M.P.	Time and % Yield				Elemental analysis (%)	
			Conventional		Microwave irradiation		Calculated	Found
			T	% Y	T	% Y		
C ₁₃ H ₈ ClFOS	266.7	114 ± 2°C	24 hrs	76	2.5 min	87	C 58.49 H 2.99	C 58.47 H 2.96
10 % Ethyl acetate / Hexane; TLC - R _f : 0.58							S 11.99	S 12.02

IR (cm⁻¹): 1646 (C=O), 1586.9 (HC=CH), 3093 (C-H), 803 (C-F), 724 (C-S).

¹H NMR (δ ppm): 7.0 (1H, d, J = 4 Hz, C-4'-H), 7.12 (2H, d, J = 8.6 Hz, C-3'' and 5''-H), 7.21 (1H, d, J = 16 Hz, CO-CH=), 7.61 (2H, d, J = 8.4 Hz, C-2'' and 6''-H), 7.63 (1H, d, J = 4 Hz, C-3'-H), 7.81 (1H, d, J = 16 Hz, Ar-C-H=).

(4). 3-(4-Chlorophenyl)-1-(5-chlorothiophen-2-yl) prop-2-en-1-one (4)**Physical data**

Molecular formula	M. Wt.	M.P.	Time and % Yield				Elemental analysis (%)	
			Conventional		Microwave irradiation		Calculated	Found
			T	% Y	T	% Y		
C ₁₃ H ₈ Cl ₂ OS	283	144 ± 2°C	24 hrs	87	1.5 min	96	C 55.1 H 2.82	C 55.13 H 2.80
10 % Ethyl acetate / Hexane; TLC - R _f : 0.66							S 11.30	S 11.27

Spectral data

IR (cm⁻¹): 1647 (C=O), 1592 (HC=CH), 797 (C-Cl), 768 (C-S).

¹H NMR (δ ppm): 7.03 (1H, d, J = 4 Hz, C-4'-H), 3.1 (1H, d, J = 15.6 Hz, CO-CH=), 7.42 (2H, d, J = 8.4 Hz, C-3'' and 5''-H), 7.59 (2H, d, J = 8.6 Hz, C-2'' and 6''-H), 7.71 (1H, d, J = 3.8 Hz, C-3'-H), 7.85 (1H, d, J = 16 Hz, Ar-C-H=).

(5). 1-(5-Chlorothiophen-2-yl)-3-(2,4-dichlorophenyl) prop-2-en-1-one (5)**Physical Data**

Molecular formula	M. Wt.	M.P.	Time and % Yield				Elemental analysis (%)	
			Conventional		Microwave irradiation		Calculated	Found
			T	% Y	T	% Y		
C ₁₃ H ₇ Cl ₃ OS	317.6	140 ± 2°C	24	88	1.5	98	C 49.1 H 2.20	C 49.07 H 2.23
10 % Ethyl acetate / Hexane; TLC - R _f : 0.52							S 10.07	S 10.09

Spectral data

IR (cm⁻¹): 1643 (C=O), 1588 (HC=CH), 792 (C-Cl), 771 (C-S).

¹H NMR (δ ppm): 7.02 (1H, d, J = 4 Hz, C-4'-H), 7.30 (1H, s, C-3''-H), 7.32 (1H, d, J = 16 Hz, CO-CH=), 7.46 (1H, d, Hz, C-5''-H), 7.61 (1H, d, J = 8.4 Hz, C-6''-H), 7.67 (1H, d, J = 4.2 Hz, C-3'-H), 8.08 (1H, d, J = 15.8 Hz, Ar-C-H=).

Antifungal activity

All the 5 compounds were screened for their antifungal activity. The fungi employed for screening were *Aspergillus niger* and *Candida albicans*. Fluconazole was employed as standard to compare the results. The test organisms were sub-cultured using potato-dextrose-agar (PDA) medium.

Each test compound (5 mg) was dissolved in dimethyl sulphoxide (5 mL, Analytical R grade) at concentration of 1000 µg/mL. Fluconazole solution was also prepared at a concentration of 1000 µg/mL in sterile distilled water.

All the 5 compounds were tested at a concentration of 0.025 mL (25 µg), 0.05 mL (50 µg), and 0.1 mL (100 µg) level. DMSO was used as a control. The solutions of each test compound, control and reference standards (0.025, 0.05 and 0.1 mL) were added separately in cups and plates. These were kept undisturbed for at least 2 hours in refrigerator to allow diffusion of the solution properly into potato dextrose agar media. Petri dishes were subsequently kept at room temperature for 48 hours. After that, the diameter of zone of inhibition in mm surrounding each of the cups was measured with the help of an antibiotic zone reader. All experiments were carried out in triplicate. The results were presented in Table 1.

Table 1: Antifungal activity of chalcone derivatives (1-5)

Comps.	Zone of inhibition (in mm)					
	<i>Aspergillus niger</i>			<i>Candida albicans</i>		
	25 µg/mL	50 µg/mL	100 µg/mL	25 µg/mL	50 µg/mL	100 µg/mL
1	-	4	8	-	5	9
2	-	5	10	-	5	10
3	-	6	9	-	6	10
4	-	6	12	-	7	14
5	-	7	13	-	8	15
Fluconazole		11	17	-	14	19
Control		-	-	-	-	-

(-) No zone of inhibition

RESULTS AND DISCUSSION

Antifungal activity

All the compounds (**1-5**) were screened for their antifungal activity by using cup plate method for the fungi employed screening *Aspergillus niger* and *Candida albicans*. Fluconazole was employed as standard to compare the results.

Compounds (**1-5**) exhibited significant antifungal activity at both the concentrations; 50 µg/mL and 100 µg/mL, when compared with the standard drugs. In particular, compounds (**3**) possessed maximum activity on both the fungi strains. It may be due to the presence of nitro at C-4; nitro at C-3 and chlorine at C-4, bromo, methoxy at C-3, C-4 ; methyl at C-4; respectively on aromatic ring-B. Other compounds also showed mild to moderate activity at both the concentration levels on both organisms. The results and complete data of test were presented in Table 1.

It is interesting to know that the diaryl chalcones, having electron releasing and withdrawing substituents like nitro, nitrochloro, bromomethyl and dimethyl. Pharmacophore present especially at C-4 position of aromatic ring-B, showed excellent antifungal activities, when compared to other substituted chalcones.

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