Synthesis and Biological Evaluation of Some New Chalcones Containing 2,5-Dimethylfuran Moiety

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Abstract: A series of new chalcones (**3a-g**) were prepared by Claisen-Schmidt condensation of 3-acetyl-2,5-dimethylfuran with various substituted aromatic aldehydes in presence of aqueous solution of potassium hydroxide and ethanol at room temperature. The synthesized chalcones were characterized by means of their IR, ¹H NMR spectral data and elemental analyses. When these chalcones were evaluated for antimicrobial and anti-inflammatory activities, some of them were found to possess significant activity, when compared to standard drugs.

Keywords: Chalcone, Antimicrobial activity, Synthesis, Dimethylfuran moiety.

Introduction

The search for new potent anti-microbial agents with reduced toxicity and lower side effects is of continuous process. One of the most frequently encountered groups of organic compounds in medicinal chemistry is chalcones and their derivatives. Chalcone is a generic term given to compounds bearing the 1,3-diphenylprop-2-en-1-one frame work, which can be functionalized in the propane chain by the presence olefinic, keto and/or hydroxyl groups (Figure 1)¹. Their bactericidal effect has been related to the ability of the α , β - unsaturated ketone to undergo a conjugated addition to a nucleophilic group like a thiol group in an essential protein. In addition, chalcone derivatives showed activity against dermatophytes only but not against other types of fungi. Chalcones are readily synthesized by the base catalysed Claisen-Schmidt condensation of an aldehyde and an appropriate ketone in a polar solvent like ethanol and yields may be variable, ranging²⁻³ from 5% to 80%. The chalcones have a diverse range of biological activities, among which antimalarial, antitubercular, anti-inflammatory, cytotoxic, antioxidant, analgesic, antiviral and antimicrobial⁴⁻¹⁰ properties were widely cited.

Figure 1

As shown in scheme 1, chalcones **3(a-g)** were synthesized by a base catalyzed condensation of 3-acetyl-2,5-dimethylfuran and appropriately substituted aldehydes¹¹. The structures of various synthesized compounds were characterized on the basis of elemental analyses, IR and ¹H NMR spectral data. The compounds were evaluated for their anti-inflammatory activity by carrageenan induced rat paw oedema method and antimicrobial activity by agar cup plate method.

Experimental

Melting points were determined on an open capillary melting point apparatus and are uncorrected. ¹H NMR spectra were recorded in CDCl₃ on Bruker WM 400 MHz spectrometer with TMS as internal standard. Infrared spectra were recorded (KBr) on a Perkin-Elmer AC-1 spectrophotometer. Micro analyses were performed on Carlo Erba E-1108 element analyzer and were within the $\pm 0.4\%$ of the theoretical values. Reaction completion was identified by TLC using silica gel for TLC (Merck). All the chalcones have been purified by column chromatography performed on silica gel columns (100-200 mesh, Merck).

General procedure for the synthesis of 1-(2',5'-dimethyl-3'-furyl)-3-(aryl)-2-propen-1-one (**3a-g**)

A mixture of 3-acetyl-2,5-dimethylfuran (0.005 mol) (**1**) and respective aldehyde (0.005 mol) (**2**) was stirred in ethanol (7.5 mL) and then an aqueous solution of potassium hydroxide (50%, 7.5 mL) was added to it. The mixture was kept for 24 h and it was acidified with 1:1 HCl and H₂O. Then it was filtered under vacuum and the solid was washed with water, purified by column chromatography and crystallized from a mixture of ethyl acetate and hexane (Scheme 1). The physical and spectral data of the chalcones were shown in Table 1 & 2.

Scheme 1. Synthesis of chalcones

Where Ar =

Table 1. Physical data of the prepared compounds **3(a-g)**

S.No.	Ar	Mol. Formula	RMM	M.P. °C	Yield %	% Calc.			% Found		
						C	H	N	C	H	N
3a	3'',4'',5''-trimethoxyphenyl	C ₁₈ H ₂₀ O ₅	316	154	71	68.34	6.37	-	68.23	6.28	-
3b	4''-chlorophenyl	C ₁₅ H ₁₃ ClO ₂	260	139	68	69.23	5.01	-	69.25	5.03	-
3c	4''-dimethylaminophenyl	C ₁₇ H ₁₉ NO ₂	269	112	73	75.83	7.06	5.20	75.82	7.05	5.22
3d	4''-methylphenyl	C ₁₆ H ₁₆ O ₂	240	153	75	80.02	6.66	-	80.04	6.68	-
3e	2'',4''-dichlorophenyl	C ₁₅ H ₁₂ Cl ₂ O ₂	294	132	71	61.22	4.08	-	61.24	4.06	-
3f	9''-anthracenyl	C ₂₃ H ₁₈ O ₂	326	138	78	84.64	5.56	-	84.65	5.58	-
3g	4''-methoxyphenyl	C ₁₆ H ₁₆ O ₃	256	87	73	75.01	6.25	-	75.02	6.28	-

Table 2. Spectral data of the prepared compounds **3(a-g)**

S.No	IR, $\nu_{\max}$, cm ⁻¹	¹ H NMR (CDCl ₃), δ ppm
3a	1655 (C=O), 1602 (C=C of Ar), 1505 (CH=CH), 1125 (O-CH ₃), 1048 (C-O-C)	3.90-3.95 (9H, s, 3x-OCH ₃), 6.71 (1H, s, C-4'-H), 7.20 (1H, d, J= 17Hz, -CO-CH=), 7.81 (1H, d, J= 17Hz, =CH-Ar), 6.90 (2H, s, C-2''-H and C-6''-H), 2.2(3H,s,Ar-CH ₃), 2.7(3H,s, Ar-CH ₃).
3b	1664 (C=O), 1584 (C=C of Ar), 1520 (CH=CH), 1060 (C-O), 855 (C-Cl)	6.41 (1H, s, C-4'-H), 7.10 (1H, d, J=17Hz,-CO-CH=), 7.70 (1H, d,J= 17Hz, =CH-Ar), 7.58 (2H, d,J= 8Hz, C-3''-H and C-5''-H), 7.40 (2H, d,J= 8Hz, C-2''-H and C-6''-H), 2.3(3H,s, Ar-CH ₃),2.6(3H,s, Ar-CH ₃).
3c	1658 (C=O), 1588 (C=C of Ar), 1502 (CH=CH), 1185 (-N(CH ₃) ₂) 1082 (C-O)	3.05 (6H, s, -N(CH ₃) ₂), 6.58 (1H, s, C-4'-H), 7.25 (1H, d, J=17Hz, -CO-CH=), 7.87(1H, d, J=17Hz, -CH=Ar), 6.75(2H,d, J=8.5 Hz, C-2''-H and C-6''-H), 7.55 (2H,d, J=8.5Hz, C-3''-H andC-5''-H), 2.05 (3H,s, Ar-CH ₃), 2.5(3H,s, Ar-CH ₃).
3d	1641 (C=O), 1583 (C=C of Ar), 1505 (CH=CH), 1076 (C-O)	2.60 (3H, s, Ar-CH ₃), 6.30 (1H, s, C-4'-H), 7.23 (1H, d, J=17Hz, -CO-CH=), 7.77 (1H, d, J= 17Hz, -CH=Ar), 7.56 (2H, d, J=9Hz,C-3''-H and C-5''H), 7.3 (2H, d, J=9Hz, C-2''-H and C-6''-H), 2.3(3H,s, Ar-CH ₃), 2.4(3H,s, Ar-CH ₃).
3e	1648 (C=O), 1609 (C=C of Ar), 1510 (CH=CH), 1080 (C-O), 868 (C-Cl)	6.3 (1H,s,C-4'-H), 7.1 (1H, d, J=17Hz, -CO-CH=), 7.99 (1H, d, J=17Hz, =CH-Ar), 7.3 (1H, d, J=8Hz, C-6''-H), 7.4(1H,s,C-3''-H), 7.6(1H,d, J=9HZ, C-5''-H), 2.3(3H,s, Ar-CH ₃), 2.6(3H,s, Ar-CH ₃).
3f	1633 (C=O), 1591 (C=C of Ar), 1506 (CH=CH), 1070 (C-O)	6.20 (1H, s, C-4'-H), 7.36 (1H, d, J=17Hz, -CO-CH=), 7.68 (1H, d, J=17Hz, =CH-Ar), 7.50-8.90 (9H, Ar-H), 2.3(3H,s, Ar-CH ₃), 2.7(3H,s, Ar-CH ₃).
3g	1664 (C=O), 1585 (C=C of Ar), 1505 (CH=CH), 1133 (O-CH ₃), 1055 (C-O-C)	3.85 (3H, s, OCH ₃), 6.3 (1H, s, C-4'-H), 6.9 (1H, d, J=17Hz, -CO-CH=), 7.1-7.6 (4H, m, C-2'', 3'', 5''and 6''-H), 7.7 (1H, d, J=17Hz, =CH-Ar), 2.3(3H,s, Ar-CH ₃), 2.5(3H,s, Ar-CH ₃).

Anti-inflammatory activity

Sprague-dawley rats (M/S Gosh Enterprises, Calcutta, West Bengal, India) of either sex weighing between 180-200 g were used in the experiment. 1% carrageenan sodium gel was prepared with saline water for producing inflammation and gel of 1% sodium CMC was prepared with saline water for suspending the test compounds and standard drug.

Rats were divided into nine groups of five animals each. Inflammation was induced by injecting 0.05 mL of 1% carrageenan subcutaneously into the sub plantar region of the right hind paw and 0.05 mL of saline was injected into the sub plantar region of the left hind paw for all groups. 1% sodium CMC gel (1 mL/kg) was given to group-I used as carrageenan treated control and the standard drug aceclofenac (2 mg/kg) was administered to group-II. The groups III-IX treated with compounds **3(a-g)** (10 mg/kg). All the doses were administered orally. Anti-inflammatory activity was evaluated by measuring carrageenan induced paw oedema^{12,13}. The thickness of raw paw was measured before carrageenan injection and after carrageenan injection at time intervals 0.5, 1, 2, 3, 4 and 6 h using Zeitzlin constant loaded lever method¹⁴. The percentage increase of paw oedema thickness was calculated¹⁵. The results and statistical analysis of anti-inflammatory activity of aceclofenac and the compounds tested were shown in Table 3.

Table 3. Anti-inflammatory activity of chalcones **3 (a-g)**

Compound	% inhibition $\pm$ SEM at various time intervals					
	0.5 h	1.0 h	2.0 h	3.0 h	4.0 h	6.0 h
3a	20.58 $\pm$ 0.91	31.65 $\pm$ 1.01	59.84 $\pm$ 1.53	69.13 $\pm$ 1.25	76.55 $\pm$ 1.98	85.15 $\pm$ 2.22
3b	24.19 $\pm$ 0.78*	42.57 $\pm$ 0.99*	65.47 $\pm$ 1.65*	79.87 $\pm$ 1.66*	89.28 $\pm$ 2.01	97.28 $\pm$ 1.99
3c	21.10 $\pm$ 0.65	41.46 $\pm$ 1.12*	53.13 $\pm$ 1.36*	72.91 $\pm$ 1.67	82.65 $\pm$ 2.32	72.55 $\pm$ 2.32
3d	17.13 $\pm$ 0.75*	28.02 $\pm$ 0.89	42.37 $\pm$ 1.45*	67.81 $\pm$ 1.33*	78.74 $\pm$ 1.88	82.70 $\pm$ 2.53
3e	24.78 $\pm$ 0.77*	37.37 $\pm$ 0.92*	51.11 $\pm$ 1.35	62.35 $\pm$ 1.81*	84.10 $\pm$ 2.95	87.30 $\pm$ 3.25
3f	23.01 $\pm$ 0.65*	36.25 $\pm$ 1.23*	57.10 $\pm$ 1.48	78.14 $\pm$ 1.59	80.10 $\pm$ 2.32	85.15 $\pm$ 2.31
3g	21.68 $\pm$ 0.88	34.11 $\pm$ 1.02*	57.45 $\pm$ 1.43	76.16 $\pm$ 1.53	82.46 $\pm$ 1.95	89.52 $\pm$ 2.35
Aceclofenac	28.0 $\pm$ 2.0	20.16 $\pm$ 0.90	43.85 $\pm$ 0.97	58.10 $\pm$ 1.52	77.83 $\pm$ 1.68	77.19 $\pm$ 1.97

All values are represented as mean $\pm$ SEM (n=6). *P<0.01 compared to reference standard Aceclofenac Student's t-test. Dosage: Aceclofenac-2 mg/kg and test compounds-10 mg/kg body weight of rat

Antimicrobial activity

Cup plate method^{16,17} using Mueller-Hinton agar medium was employed to study the preliminary antibacterial activity of (**3a-g**) against *B. subtilis*, *B. pumilis*, *S. aureus*, *E. coli* and *P. vulgaris*. The agar medium was purchased from HI-media Laboratories Ltd., Mumbai, India. Preparation of nutrient broth, subculture, base layer medium, agar medium and peptone water was done as per the standard procedure. Each test compound (5 mg) was dissolved in 5 mL of dimethyl sulfoxide. Benzylpenicillin was employed as reference standard (1000 μ g/mL) to compare the results. The pH of the all the test solutions and control was maintained at 2-3 by using conc. HCl, because the compounds were not diffused through agar medium at pH below 3. All the compounds were tested at a concentration of 0.05 mL (50 μ g) and 0.1 mL (100 μ g) level and DMSO as control did not show any inhibition.

Same cup plate method using PDA (Potato-Dextrose-Agar) medium was employed to study the preliminary antifungal activity of (**3a-g**) against *A. niger*, *C. albicans* and *R. oryzae*. The PDA medium was purchased from HI-media Laboratories Ltd., Mumbai, India. Preparation of nutrient broth, subculture, base layer medium and PDA medium was done as per the standard procedure. Each test compound (5 mg) was dissolved in 5 mL of dimethyl sulfoxide. Fluconazole employed as reference standard (1000 μ g/mL) to compare the results. The pH of the all the test solutions and control was maintained at 2-3 by using conc. HCl, because the compounds were not diffused through agar medium at pH below 3. All the compounds were tested at a concentration of 0.05 mL (50 μ g) and 0.1 mL (100 μ g) level and DMSO as control did not show any inhibition.

The cups each of 7 mm diameter were made by scooping out medium with a sterilized cork borer in a Petri dish which was streaked with the organisms. The solutions of each test

compound, control and reference standards (0.05 and 0.1 mL) were added separately in the cups and Petri dishes were subsequently incubated at 37 ± 1 °C for 24 h for antibacterial activity and kept aside at room temperature for 48 h for antifungal activity. Zone of inhibition produced by each compound was measured in mm and the results are presented in Table.4 for antibacterial activity and in Table.5 for antifungal activity.

Table 4. Antibacterial activity of chalcones **3(a-g)**

Compound	Zone of inhibition, in mm									
	Quantity in µg/mL									
	50	100	50	100	50	100	50	100	50	100
3a	12	11	09	10	08	11	11	12	13	08
3b	15	21	17	20	18	23	14	15	14	18
3c	16	18	18	23	20	23	18	23	21	26
3d	20	23	19	16	11	19	18	19	17	18
3e	11	13	14	14	17	21	12	16	11	14
3f	14	16	18	23	14	21	15	17	16	20
3g	19	22	20	24	18	22	16	17	13	16
Benzylpenicillin	27	32	30	31	26	29	24	26	27	31
Control	-	-	-	-	-	-	-	-	-	-

Table 5. Antifungal activity of chalcones **3(a-g)**

Compound	Zone of inhibition, in mm					
	Quantity in µg/mL					
	<i>A. niger</i>		<i>C. albicans</i>		<i>R. oryzae</i>	
	50	100	50	100	50	100
3a	16	20	17	21	17	19
3b	17	21	15	20	15	18
3c	17	23	24	25	16	18
3d	14	17	16	21	13	18
3e	15	17	20	22	13	16
3f	18	20	22	20	14	19
3g	17	20	21	22	15	18
Fluconazole	23	27	23	27	21	26
Control	-	-	-	-	-	-

Results and Discussion

The results of anti-inflammatory activity revealed that the compounds (**3a-g**) exhibited moderate to considerable activity when compared to reference standard aceclofenac. In addition, it was found that **3b** showed maximum activity and this may be due to presence of chloro group at 4th position on aromatic ring-B of chalcone. Moreover, it was also observed that the compounds **3e** and **3g**, carrying 2,4-dichlorophenyl and 4-methoxy phenyl rings as ring-B of chalcone, respectively, showed remarkable activity.

Compounds (**3a-g**) showed significant antibacterial activity at both 0.05 mL (50 µg) and 0.1 mL (100 µg) concentration levels when compared with standard drug benzylpenicillin. However, the chalcones **3b**, **3c** and **3g** were found to be more potent on all the bacterial strains. Compounds (**3a-g**) also showed significant antifungal activity at both 0.05 mL (50 µg) and 0.1 mL (100 µg) concentration levels when compared with standard drug fluconazole. Compounds **3c** and **3g** showed maximal antifungal activity. The results clearly revealed the contribution of electron withdrawing groups and electron releasing groups on the aromatic ring in enhancing the antibacterial and antifungal activity.

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References

1. Oyvind M A and Kenneth R M, Flavonoids: Chemistry, Biochemistry and Applications, CRC Press: New York, 2006, 1004.
2. Prasad Y R, Ravikumar P, ASHA Deepti CH and Ramana M V, *Asian J Chem.*, 2007, **19**(6), 4799-4804.
3. Prasad Y R, Ravikumar P, Srivani N and Rao A S, *Int J Chem Sci.*, 2006, **4**(4), 905-909.
4. Tomar V, Bhattacharjee G, Kamaluddin and Kumar A, *Bioorg Med Chem Lett.*, 2007, **17**(19), 5321-5324.
5. Solankee A, Kapadia K, Ciric A, Sokovic M, Doytchinova I and Geronikaki A, *Eur J. Med Chem.*, 2010, **45**(2), 510-518.
6. Mei L, Prapon W, Simon L C, Agnes L-C T and Mei-Lin G, *Bioorg Med Chem.*, 2003, **11**(13), 2729-2738.
7. Trivedi A R, Dodiya D K, Ravat N R and Shah V H, *ARKIVOC*, 2008, **xi**, 131-141.
8. Jen-Hao C, Chi-Feng H, Shyh-Chyun Y, Jih-Pyang W, Shen-Jeu W and Chun-Nan L, *Bioorg Med Chem.*, 2008, **16**(15), 7270-7276.
9. Bhat B A, Dhar K L, Puri S C, Saxena A K, Shanmugavelb M and Qazi G N, *Bioorg Med Chem Lett.*, 2005, **15**, 3177.
10. Jalpa C T, Jitender B B, Kuldip D U, Yogesh T N, Sudhir K J, Christophe C P, Erik De C and Anamik K S, *Tetrahedron Lett.*, 2007, **48**(48), 8472-8474.
11. Dhar D N, The Chemistry of Chalcones and related compounds; John Wiley and Sons, New York, 1981.
12. Turner R A, Screening Methods in Pharmacology; Demic Press: New York, 1965, 152.
13. Winter C A, Risley E A and Nuss G W, *Proc Soc Exp Biol Med.*, 1962, **111**, 544-547.
14. Al-Haboubi H A and Zeitlin I J, *Eur J Pharmacol.*, 1983, **88**, 169-176.
15. Duwiejua M, Zeitlin I J, Watermanand P G and Gray A I, *J Pharm Pharmacol.*, 1994, **46**, 286-290.
16. Banty A L, The antimicrobial Susceptibility test: Principle and practice; Edited by Illus, Lea and Febiger, Philadelphia, PA: USA, 1976, 180.
17. Seely H W and Van Demark P J, Microbes in Action: A Laboratory Manual of Microbiology; D.B. Taraporewala Sons and Co., Bombay, 1975, 55.