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Research Article

SYNTHESIS AND PHARMACOLOGICAL EVALUATION OF A NOVEL SERIES OF 1-(2',5'-DIMETHYL-3'-FURYL)-3-(SUBSTITUTED ARYL)-2-PROPEN-1-ONES

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ABSTRACT

In the present study, a series of new 1-(2',5'-dimethyl-3'-furyl)-3-(substituted aryl)-2-propen-1-ones were prepared by Claisen-Schmidt condensation of 3-acetyl-2,5-dimethylfuran with various substituted aromatic and heterocyclic aldehydes in presence of aqueous solution of potassium hydroxide and ethanol at room temperature. The synthesized compounds were characterized by means of their IR, ^{1}H NMR spectral data and elemental analyses. When these compounds 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.

INTRODUCTION

The development of new antimicrobial agents has been a very important step for researchers. Most of the research programme efforts are directed toward the design of new drugs, because of the unsatisfactory status of present drugs with side effects and the acquisition of the resistance by the infecting organisms to present drugs. The resistance of common pathogens to standard antibiotic therapy is rapidly becoming a major health problem throughout the world. There is real perceived need for the discovery of new compounds endowed with antimicrobial property. Synthesis of chalcones and their derivatives has attracted considerable attention due to their significant biological activities including antimicrobial, antileishmanial, antimalrial, antimycobacterial, anti-inflammatory, cytotoxic, antioxidant, analgesic and antiviral activities[1-6]. 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[7]. 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 catalyzed claisen-schmidt condensation of an aldehyde and an appropriate ketone in a polar solvent like ethanol and yields may be variable, ranging from 5% to 80%. In view of these observations and in continuation of our research

programme on the synthesis of chalcones[8], we report here in, the synthesis of some new chalcones **(scheme1)** which have been found to possess an interesting profile of antimicrobial and anti-inflammatory activities.

EXPERIMENTAL

Melting points were determined on an open capillary melting point apparatus and are uncorrected. ^{1}H NMR spectra were recorded in $CDCl_3$ 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 with in the ± 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 preparation of Synthesis of 1-(2',5'-dimethyl-3'-furyl) -3-(substituted aryl)-2-propen-1- one (3a-h)

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 hours and it was acidified with 1:1 HCl and H_2O. Then it was filtered under vaccum and the solid was washed with water, purified by column chromatography and crystallized from a mixture of ethyl acetate and hexane.

Antimicrobial activity

Cup plate method[9,10] using Mueller-Hinton agar medium was employed to study the preliminary antibacterial activity of **(3a-h)** 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 µg/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 µg) and 0.1 mL (100 µg) 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-h)** 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 µg/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 µg) and 0.1 mL (100 µg) level and DMSO as control did not show any inhibition.

The cups each of 7mm 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^{0}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.3 for antibacterial activity and in table.4 for antifungal activity.

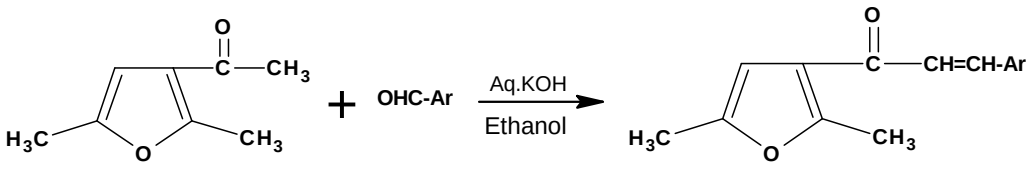
Anti-inflammatory activity

Spraygue-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 ten groups of five animals each. Inflammation was induced by inducing 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. One hour prior to carrageenan injection, the groups III-X treated

with compounds **3(a-h)** (10 mg/kg). 1% sodium CMC gel (1 mL/kg) was given to group-I used as carrageenan treated control and the standard drug aceclofenac (2mg/kg) was administered to group-II. All the doses were administered orally. Anti-inflammatory activity was evaluated by measuring carrageenan induced paw oedema[11,12]. 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 Zeitlin constant loaded lever method. The percentage increase of paw oedema thickness was calculated. The results and statistical analysis of anti-inflammatory activity of aceclofenac and the compounds tested were shown in Table 5.

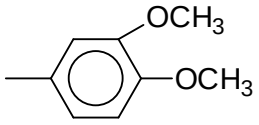
Scheme 1:



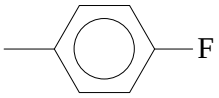
1 **2 a-h** **3 a-h**

Scheme 1

Where Ar =



3a



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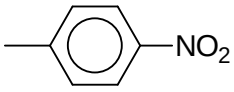
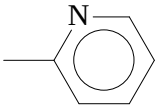
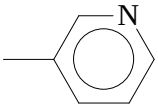


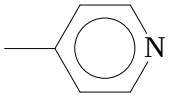
3c



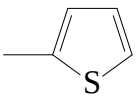
3d



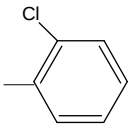
3e



3f



3g



3h

Table 1: Physical data of the prepared compounds 3 (a-h)

S. No.	Mol. Formula	RMM	M.P (°C)	Yield%	(% Calc.) C	H	N	(% found) C	H	N
3a	$C_{17}H_{18}O_4$	286	121	69	71.32	6.29	-	71.34	6.30	-
3b	$C_{15}H_{13}FO_2$	244	113	75	73.77	5.32	-	73.78	5.34	-
3c	$C_{15}H_{13}NO_4$	271	219	73	66.42	4.79	-	66.43	4.80	-
3d	$C_{14}H_{13}NO_2$	227	157	76	74.01	5.72	6.16	74.04	5.73	6.18
3e	$C_{14}H_{13}NO_2$	227	171	81	74.01	5.72	6.16	74.02	5.74	6.17
3f	$C_{14}H13NO_2$	227	168	72	74.01	5.72	6.16	74.04	5.72	6.18
3g	$C_{13}H_{12}SO_2$	232	82	75	67.24	5.17	-	67.25	5.18	-
3h	$C_{15}H_{13}ClO_2$	260	151	68	69.23	5.01	-	69.24	5.02	-

Table 2: Spectral data of the prepared compounds 3 (a-h)

S. No.	IR(υ_{max}, cm^{-1})	^{1}H NMR ($CDCl_3$), δ ppm
3a	1656 (C=O), 1590 (C=C), 1513 (CH=CH), 1166 (O-CH3), 1062 (C-O-C)	3.92 (6H, s, -OCH_3), 6.35 (1H, s, C-4'-H), 6.89 (1H, d, J=16Hz, -CO-CH=), 7.02-7.3 (2H, m, C-5″and 6″-H),7.18 (1H,s, C-2″-H), 7.7 (1H, d, J=16Hz, =CH-Ar), 2.3(3H,s, Ar-CH_3), 2.6(3H,s, Ar-CH_3).
3b	1664 (C=O), 1588 (C=C), 1520 (CH=CH), 1120 (C-F), 1060 (C-O)	6.35(1H, s, C-4'-H),7.0-7.1 (2H, d, J=8.8Hz, C-3″and 5″-H), 7.1 (1H,d, J=17Hz, -CO-CH=) , 7.5 (2H, d, J=8.8Hz, C-2″and 6″-H), 7.7 (1H, d, J=17Hz, =CH-Ar), 2.25(3H,s, Ar-CH_3), 2.65(3H,s, Ar-CH_3).
3c	1656 (C=O), 1585(C=C of Ar), 1519 (N=O, asymmetric), 1505 (CH=CH), 1335 (N=O, symmetric), 1062 (C-O)	6.3 (1H, s, C-4'-H), 7.79 (2H, d, J=8.4Hz,C-2″and 6″-H), 7.55 (2H,d, J=8.5Hz, C-3″-H andC-5″-H) 7.2 (1H, d, J=16Hz, -CO-CH=),8.23 (1H, d, J=16Hz, =CH-Ar), 2.2(3H,s, Ar-CH_3), 2.7(3H,s, Ar-CH_3).
3d	1641 (C=O), 1590 (C=N), 1503 (CH=CH), 1076 (C-O)	6.35 (1H,s,C-4'-H), 7.11 (1H, d, J=14.6Hz,-CO-CH=) 8.10 (1H, d, J=14Hz, =CH-Ar) 7.2-7.7 (4H, m, C-3″,4″,5″and 6″-H), 2.35(3H,s, Ar-CH_3), 2.6(3H,s, Ar-CH_3).
3e	1645 (C=O), 1598 (C=N), 1505 (CH=CH), 1075 (C-O)	6.15 (1H, s, C-4'-H), 7.1 (1H,d,J=15Hz, -CO-CH=) 7.25-7.6 (4H, m, C-2″,4″,5″&6″-H) 7.2 (1H, d , J=15.5Hz, =CH-Ar), 2.02(3H,s, Ar-CH_3), 2.35(3H,s, Ar-CH_3).
3f	1653 (C=O), 1595 (C=N), 1510 (CH=CH), 1079 (C-O)	6.2 (1H, s, C-4'-H), 6.85 (1H, d, J=15.2Hz,-CO-CH=) 7.09 (2H, d, J=7.8Hz,C-3″and 5″-H) 7.25 (2H, d, J=7.4Hz, C-2″and 6″-H), 7.35 (1H, d, J=15Hz, =CH-Ar), 2.3(3H,s, Ar-CH_3), 2.6(3H,s, Ar-CH_3).
3g	1658 (C=O), 1503 (CH=CH), 1076 (C-O), 665 (C-S)	6.6 (1H, s, C-4'-H), 7.22 (1H, d, J=15.6Hz, -CO-CH=), 7.41(1H, d, J=8Hz, C- 5″-H), 7.08-7.06 (1H,t,C-4″-H), 7.63(1H, d, J=6.2Hz, C-3″-H), 7.9(1H, d, J=15.8Hz, =CH-Ar), 2.3(3H,s, Ar-CH_3), 2.7(3H,s, Ar-CH_3).
3h	1660 (C=O), 1582(C=C of Ar), 1512 (CH=CH), 1059 (C-O), 860(C-Cl)	6.3 (1H, s, C-4'-H), 7.15 (1H, d, J=17Hz,-CO-CH=) 7.7 (1H, d,J= 17Hz, =CH-Ar), 7.1-7.9 (4H, m, C-3″,4″,5″and 6″-H), 2.3(3H,s, Ar-CH_3), 2.65(3H,s, Ar-CH_3).

Table 3: Antibacterial activity of chalcones 3 (a-h)

Compound	Zone of inhibition (in mm)									
	Quantity in µg/mL									
	B. subtilis		*B. pumilis*		*S. aureus*		*E. coli*		*P. vulgaris*	
	50	100	50	100	50	100	50	100	50	100
3a	19	20	18	21	17	17	18	24	25	23
3b	19	21	19	16	21	24	19	21	19	20
3c	12	13	13	15	18	19	11	15	12	14
3d	18	20	17	20	16	21	16	18	15	20
3e	16	20	15	19	15	20	16	18	14	16
3f	14	16	17	20	15	20	18	20	16	18
3g	13	16	15	19	18	19	15	18	20	19
3h	19	21	20	24	21	26	21	23	20	25
Benzylpenicillin	27	32	30	31	26	29	24	26	27	31
Control	-	-	-	-	-	-	-	-	-	-

Table.4: Antifungal activity of Chalcones 3 (a-h)

Compound	Zone of inhibition (in mm)					
	Quantity in µg/mL					
	A. niger		*C. albicans*		*R. oryzae*	
	50	100	50	100	50	100
3a	17	20	22	23	15	18
3b	16	19	21	23	15	19
3c	14	18	19	22	16	21
3d	16	18	20	19	16	18
3e	15	18	19	21	11	16
3f	10	12	12	14	10	15
3g	15	18	18	20	11	17
3h	15	17	17	19	14	16
Fluconazole	23	27	23	27	21	26
Control	-	-	-	-	-	-

Table 5: Anti-inflammatory activity of chalcones 3 (a-h)

S. No.	% inhibition ± SEM at various time intervals					
	0.5 h	1.0 h	2.0 h	3.0 h	4.0 h	6.0 h
3a	23.17±1.02	35.39±1.10*	53.58±1.03	65.53±1.66	76.60±2.02	87.57±2.12
3b	18.34±0.75	29.45±0.89	46.40±1.15*	52.75±1.75	71.18±1.80	89.25±2.32
3c	26.50±0.93	45.36±1.01	56.76±1.35*	78.74±1.77*	82.14±2.05	95.20±2.36
3d	18.80±0.69*	25.11±0.69*	44.79±1.85*	62.45±2.03	78.55±2.32*	86.25±2.98
3e	25.19±1.02	26.14±1.05	56.95±1.36*	78.31±2.06	81.70±2.31	85.86±2.85
3f	26.32±1.23*	31.69±1.32	46.74±1.52*	67.21±1.98	75.11±2.05*	87.16±2.56
3g	24.62±0.75	48.65±0.85	56.36±1.32*	76.17±1.92	72.40±2.35	88.16±2.65
3h	19.34±0.25	29.64±0.79	46.54±1.23*	53.45±1.77	71.58±1.98	89.76±2.24
std	20.16±0.90	28.0±2.01	43.85±0.97	58.10±1.52	77.83±1.68	77.19±1.97

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

RESULTS AND DISCUSSION

The results of antibacterial activity revealed that the compounds **(3a-h)** showed significant activity at both 0.05 mL (50 µg) and 0.1 mL (100 µg) concentration levels when compared with standard drug benzylpenicillin. However, the compounds **3b** and **3h** containing halogens were found to be more potent on all the bacterial strains. Compounds **(3a-h)** 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 **3a** and **3b** showed maximal antifungal activity. From the results, it is interesting to note that the diaryl chalcones, which are having substituents like methoxy, fluoro and chloro groups of aromatic ring-B showed moderate to considerable antibacterial and antifungal activities, when compared to other chalcones.The results of anti-inflammatory activity revealed that the compounds **(3a-h)** exhibited moderate to considerable activity when compared to reference standard aceclofenac. In addition, it was found that **3C** showed maximum activity and this may be due to presence of nitro group at 4th position on aromatic ring–B of chalcone. Moreover, it was also observed that the compounds **3b** and **3h**, carrying 4-fluoro and 2-chloro phenyl rings as ring-B of chalcone, respectively, showed remarkable activity.

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