IJPSR (2013), Vol. 4, Issue 7 **(Research Article)**

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 26 February, 2013; received in revised form, 28 April, 2013; accepted, 21 June, 2013

SYNTHESIS AND BIOLOGICAL EVALUATION OF CHALCONES FROM 2-ACETYL-5-METHYLFURAN

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Keywords:

2-acetyl-5-methylfuran, Aromatic Aldehydes, Heterocyclic, QSAR

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ABSTRACT: The new chalcones of 2-acetyl-5-methylfuran derivatives are synthesized by reaction with various aromatic and hetero aromatic aldehydes using the method of aldol condensation. Characterization of these synthesized compounds performed with IR, ^{1}H NMR, physical characteristics like molecular mass, melting point and elemental analysis. The data related to structural characterization were given individually with antimicrobial activities. Characterization of these synthesized compounds performed with IR, ^{1}H NMR, physical characteristics like molecular mass, melting point and elemental analysis. The data related to structural characterization were given individually with antimicrobial activities. The literature suggests that chalcones are also useful intermediates for the synthesis of several chemical and pharmacological classes of therapeutic agents having heterocyclic structures in them. Also a number of chalcones with novel substituents synthesized, characterized and biologically evaluated for anti-microbial activity in our laboratory and significant outcome was observed. Thus various novel substituents for chalcone synthesis and QSAR studies will be a promising effort for development of better anti microbials with several significant biological activities.

INTRODUCTION: Chalcones, a group of compounds with two aromatic rings connected by a keto-vinyl chain, constitute an important class of naturally occurring flavonoids exhibiting a wide spectrum of biological activities [1]. Chalcones occur widely in nature particularly in colored flowers.

All the chalcones give pink coloration with concentrated H_2SO_4 (positive Wilson test) and violet coloration with alcoholic ferric chloride solution when substituted with a phenolic hydroxyl [2].

QUICK RESPONSE CODE

DOI: 10.13040/IJPSR.0975-8232.4(7).2629-38

Article can be accessed online on: www.ijpsr.com

Chalcones on heating with traces of iodine in dimethyl sulphoxide (DMSO) for 2 hrs give the corresponding flavones. Chalcones were converted to the corresponding flavonols by their oxidation using hydrogen peroxide in methanolic sodium hydroxide solution and these flavonols showed characteristic greenish yellow fluorescence in ethanolic solution as well as with concentrated sulphuric acid [3].

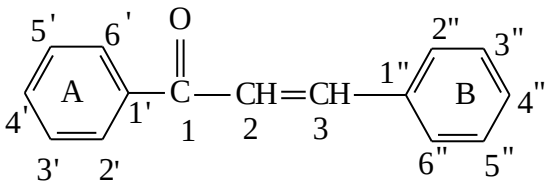
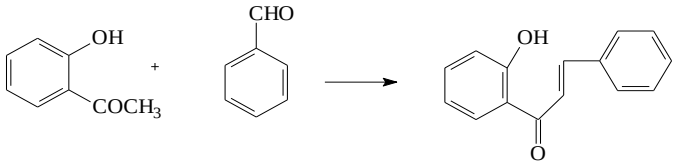


FIGURE 1: GENERAL STRUCTURE OF CHALCONE

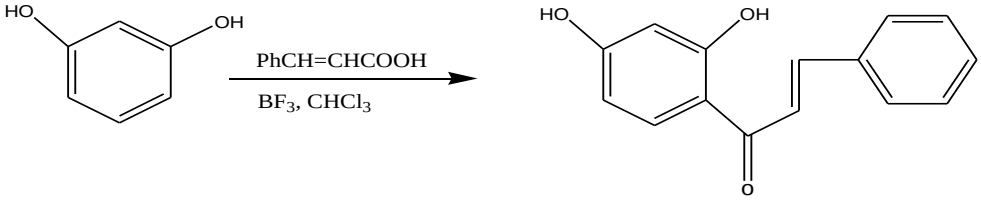
General methods of Synthesis: The chalcones are important intermediates in the synthesis of pyrazoles, isoxazoles and pyrimidines. They can be obtained by

the acid or base catalyzed aldol condensation of 2-hydroxyacetophenones with benzaldehydes [4-6]. For example 2-hydroxyacetophenone and benzaldehyde react in the presence of 0.1M NaOH to give the chalcone [7]. The synthetic reaction was illustrated as **Scheme 1.**

Cinnamic acid condenses with resorcinol in chloroform in the presence of boron trifluoride to yield the chalcone [7]. This reaction procedure for synthesis of chalcone was illustrated as **Scheme 2**.



SCHEME 1

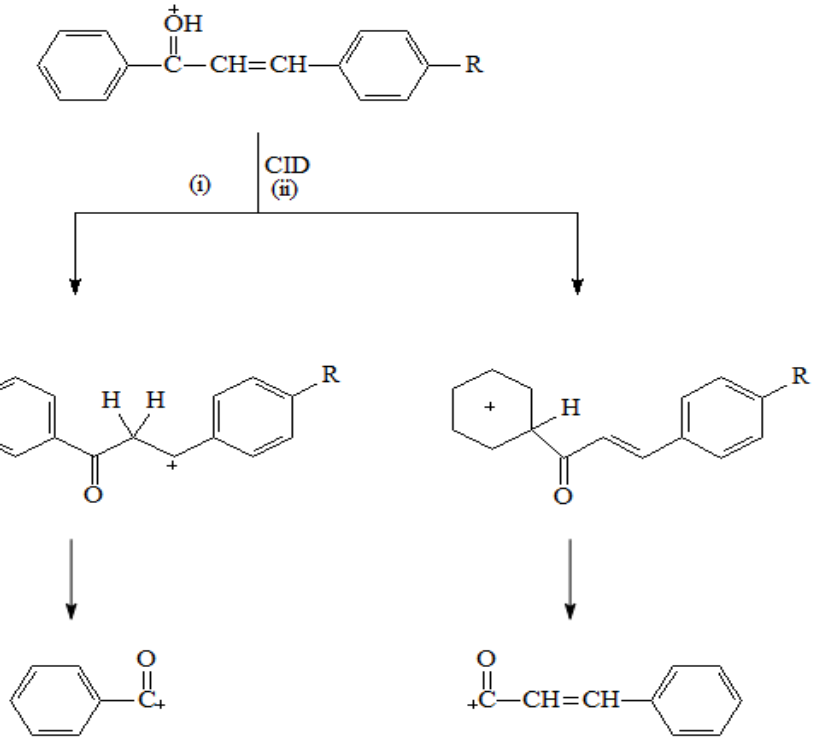


SCHEME 2

The oxygenated chalcones usually possess U.V absorption maxima in the range 340-390 nm and chalcones lacking B-ring oxygenation may have their absorption at considerably shorter wavelengths and a minor peak usually appears in the range 220-270 nm [8]. The infrared spectra of chalcones show usually a band near 1625-1650 cm^{-1}, characteristic of an α, β-unsaturated carbonyl group [9].

The α-H and β-H of chalcones resonate at δ 6.7 – 7.4 and δ 7.3 -7.7 as two doublets (J=17 Hz) respectively in the ^{1}H NMR spectra. This large J value shows that the olefinic bond has *trans* geometry. In the ^{13}C NMR spectra of chalcones, the carbonyl carbon appears between δ 188.6 and 194.6. The α and β carbon atoms give rise to signals in between δ 116.1 – 128.1 and δ 136.9 – 145.4 respectively and can be readily identified by their characteristic appearance as a six line multiplet in the off resonance decoupled spectrum[10].

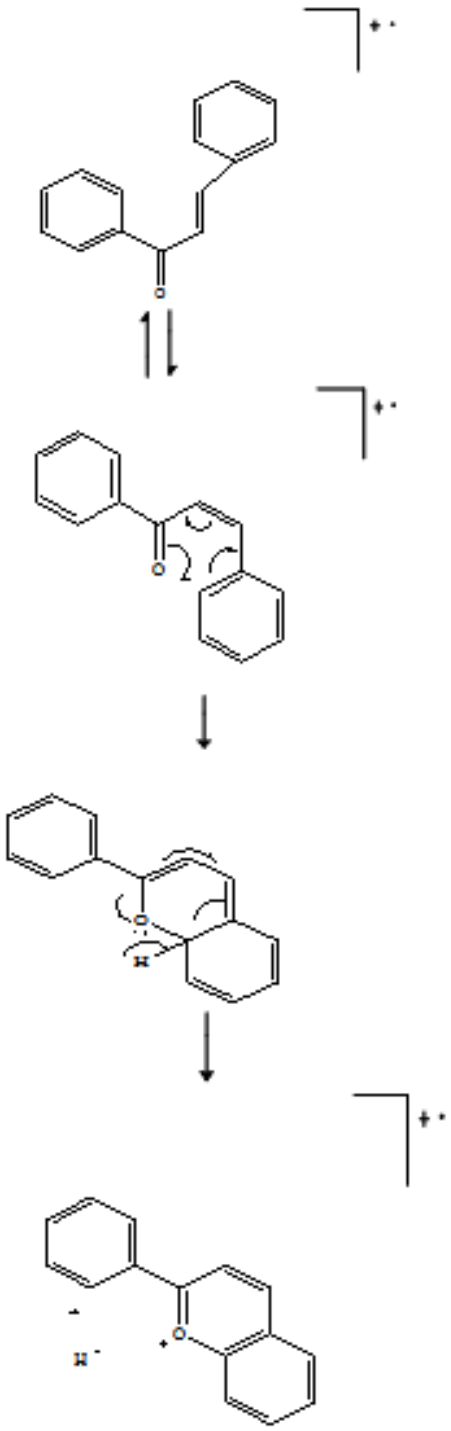
In the collision-induced dissociation (CID), mass spectra of the protonated chalcones reveals loss of benzene from the two ends and elimination of a styrene as the major fragmentation reactions. This fragmentation procedure was clearly illustrated as **Scheme 3** [11].



SCHEME 3: MASS FRAGMENTATION OF PROTONATED CHALCONES

Chalcones also give rise to the unusual fragment ion $[M-H]^+$ in its electron impact mass spectrum. This type of fragmentation is sometimes known as a proximity effect and also occurs in the fragmentation of several categories of ionized heterocycles.

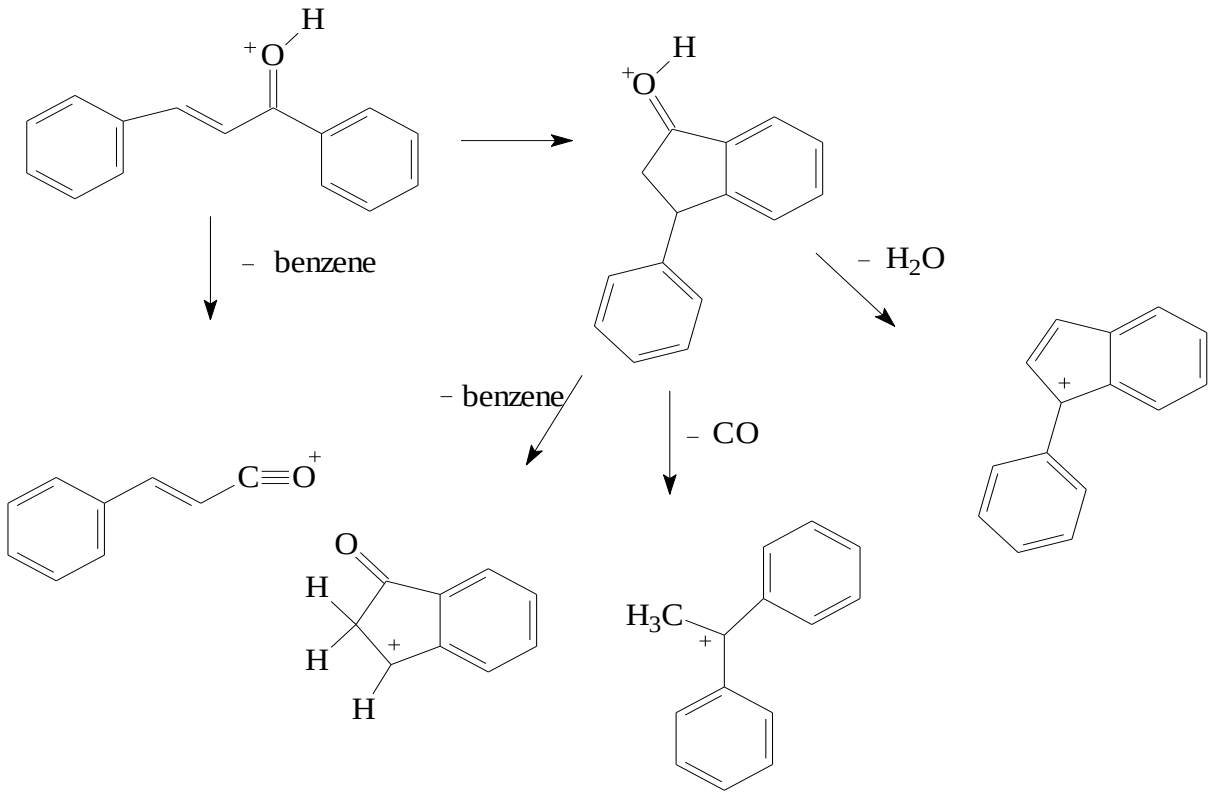
This usually involves the elimination of an *ortho* substituent from an aromatic ring with further cyclization **(Scheme 4)** to give a highly stabilized cation by means of an intramolecular aromatic substitution reaction and this is well documented and reviewed by Grutzmacher [15].



SCHEME 4: MECHANISM OF FORMATION OF $[M-H]^+$ INVOLVING PROXIMITY EFFECT

Recently, the fragmentations of protonated chalcone and substituted analogs were investigated using MS/MS experiments and high resolution accurate mass measurements [13].

Three important fragment ions from protonated chalcone arise due to loss of H_2O, CO and benzene, all of which require rearrangements **(Scheme 5)**.



SCHEME 5: FRAGMENTATION OF ELECTROSPRAY IONIZATION (ESI) GENERATED [M+H] $^{+}$ ION OF CHALCONE

MATERIALS AND METHODS: A brief description of the solvents, chemicals procured, the instruments and the conditions employed for the characterization of the synthesized compounds are presented here.

The organic solvents such as methanol, acetone, chloroform and ethyl acetate were of spectral grade and used as such without further purification. Anhydrous methanol was obtained by fractional distillation and storing over type 4A molecular sieves.

The acetone present in methanol was removed by using the following procedure. A mixture of 500 ml of methanol, 25ml of furfural and 60 ml of 10% sodium hydroxide solution was refluxed for 12 hrs, then the mixture was distilled and the first few millilitres of the distillate was rejected as it contains trace amount of formaldehyde.

Ethanol obtained by distillation of commercial ethyl alcohol was refluxed over ignited calcium oxide for 6 hours and distilled at atmospheric pressure and then used. Some of the solvents were purchased from the local manufacturers and S.D Fine Chem. Ltd, Mumbai, India.

All the chemicals used in the synthesis were obtained from standard commercial sources. 2-acetyl-5-methylfuran was purchased from Aldrich Chemical Co. (Melwaukee, Wisconsin, USA).

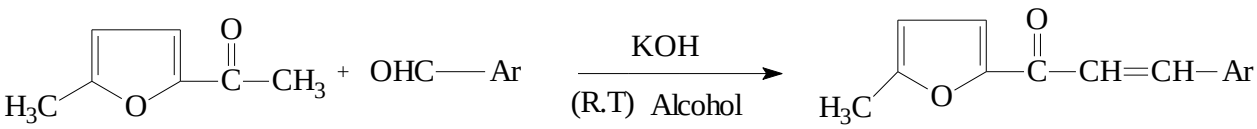
Reactions were monitored by TLC using silica gel-G (Merck grade) as the adsorbent and the solvent systems are indicated at appropriate places. Silica gel (100-200 mesh, Merck grade) has been used for column chromatography. The column was subjected to gradient elution using n-hexane, mixtures of hexane and ethyl acetate (5 %, 10 %, 15 %, 25 %, 50 % and 75 % hexane in ethyl acetate), ethyl acetate and mixtures of ethyl acetate and methanol (1 %, 2 %, 5 % and 10 % ethyl acetate in methanol).

Fractions each of 100 ml were collected. The separation of the compounds was checked on TLC under UV lamp and also by spraying the plates with 10 % sulphuric acid.

The ^{13}C NMR spectra of the compounds were recorded on Bruker AMX 400 MHz NMR spectrophotometer using TMS as an internal standard and the values are expressed in δ ppm.

The mass spectra of the compounds were recorded either on Agilent 1100 ESI-Mass (Turbo Spray) Spectrophotometer using positive mode ionization method. Elemental analyses were carried out with a Perkin-Elmer model 2400 series II apparatus. The results of elemental analyses (C, H and N) were within ± 0.4 % of the calculated values.

Procedure for Synthesis of chalcones of 2-Acetyl-5-methylfuran: A mixture of 2-acetyl-5-methylfuran (0.001mol) and the appropriate aryl aldehyde (0.001 mol) was stirred in ethanol (7.5 ml) and to it aqueous solution of KOH (50 %, 7.5 ml) was added. The mixture was kept for 24 hrs and it was acidified with 1:1 mixture of hydrochloric acid and water, then it was filtered under vacuum and the product was washed with water. This procedure was clearly illustrated in the following **Scheme 6**.



2-acetyl-5-methylfuran **Aromatic/ Heterocyclic Aldehyde** **Chalcone derivative**

SCHEME 6

By adopting the above the synthetic procedure, compounds (B_1 to B_{25}) were also synthesized. List of new chalcones synthesized is show in **Table 1**.

TABLE 1: THE LIST OF NEW SYNTHESIZED CHALCONES

S. No.	Compounds	Chemical name
1	B_1	1-(5'-methylfuran-2'-yl)-3-(4"-methylphenyl)-2-propen-1-one
2	B_2	1-(5'-methylfuran-2'-yl)-3-(4"-fluorophenyl)-2-propen-1-one
3	B_3	1-(5'-methylfuran-2'-yl)-3-(4"-chlorophenyl)-2-propen-1-one
4	B_4	1-(5'-methylfuran-2'-yl)-3-(2"-chlorophenyl)-2-propen-1-one
5	B_5	1-(5'-methylfuran-2'-yl)-3-(2",4"-difluorophenyl)-2-propen-1-one
6	B_6	1-(5'-methylfuran-2'-yl)-3-(2",4"-dichlorophenyl)-2-propen-1-one
7	B_7	1-(5'-methylfuran-2'-yl)-3-(2"-chloro-5"nitrophenyl)-2-propen-1-one
8	B_8	1-(5'-methylfuran-2'-yl)-3-(3"-nitrophenyl)-2-propen-1-one
9	B_9	1-(5'-methylfuran-2'-yl)-3-(4"-nitrophenyl)-2-propen-1-one
10	B_{10}	1-(5'-methylfuran-2'-yl)-3-(3"-hydroxyphenyl)-2-propen-1-one
11	B_{11}	1-(5'-methylfuran-2'-yl)-3-(3"-nitro-4"methylphenyl)-2-propen-1-one
12	B_{12}	1-(5'-methylfuran-2'-yl)-3-(3",4",5"-trimethoxyphenyl)-2-propen-1-one
13	B_{13}	1-(5'-methylfuran-2'-yl)-3-(3",4"-methylenedioxyphenyl)-2-propen-1-one
14	B_{14}	1-(5'-methylfuran-2'-yl)-3-(1"-phenyl-3"methylpyrazole-4"-yl)-2-propen-1 one
15	B_{15}	1-(5'-methylfuran-2'-yl)-3-(5"-bromofuran-2"-yl)-2-propen-1-one
16	B_{16}	1-(5'-methylfuran-2'-yl)-3-(4"-dimethylaminophenyl)-2-propen-1-one
17	B_{17}	1-(5'-methylfuran-2'-yl)-3-(3"-methoxy-4"-hydroxyphenyl)-2-propen-1-one
18	B_{18}	1-(5'-methylfuran-2'-yl)-3-(2"-pyridinyl)-2-propen-1-one
19	B_{19}	1-(5'-methylfuran-2'-yl)-3-(3"-pyridinyl)-2-propen-1-one
20	B_{20}	1-(5'-methylfuran-2'-yl)-3-(4"-pyridinyl)-2-propen-1-one
21	B_{21}	1-(5'-methylfuran-2'-yl)-3-(2"-pyrrolyl)-2-propen-1-one
22	B_{22}	1-(5'-methylfuran-2'-yl)-3-(2"-thienyl)-2-propen-1-one
23	B_{23}	1-(5'-methylfuran-2'-yl)-3-(9"-anthracenyl)-2-propen-1-one
24	B_{24}	1-(5'-methylfuran-2'-yl)-3-(4"-hydroxyphenyl)-2-propen-1-one
25	B_{25}	1-(5'-methylfuran-2'-yl)-3-phenyl-2-propen-1-one

All these compounds are new and the physical characterization, elemental analysis, IR and ^{1}H NMR spectral data was presented separately in detail from **Table 2 - 5** respectively.

TABLE 2: PHYSICAL CHARACTERIZATION DATA OF CHALCONES (B_1-B_6)

Compound	Molecular Formula	Relative Molecular Mass	Melting Point (^oC)	% Yield
B_1	$C_{15}H_{14}O_2$	226	152	75
B_2	$C_{14}H_{11}FO_2$	230	148	79
B_3	$C_{14}H_{11}ClO_2$	246	155	71
B_4	$C_{14}H_{11}ClO_2$	246	139	75
B_5	$C_{14}H_{10}F_2O_2$	248	163	81
B_6	$C_{14}H_{10}Cl_2O_2$	280	159	79
B_7	$C_{14}H_{10}ClNO_4$	291	165	74
B_8	$C_{14}H_{11}NO_4$	257	125	79
B_9	$C_{14}H_{11}NO_4$	257	129	74
B_{10}	$C_{14}H_{12}O_3$	228	228	78
B_{11}	$C_{15}H_{13}NO_4$	271	164	73
B_{12}	$C_{17}H_{18}O_5$	302	175	77
B_{13}	$C_{15}H_{12}O_4$	256	185	74
B_{14}	$C_{18}H_{16}N_2O_2$	292	121	69
B_{15}	$C_{12}H_9BrO_3$	281	120	73
B_{16}	$C_{16}H_{17}NO_2$	255	110	75
B_{17}	$C_{15}H_{14}O_4$	258	218	71
B_{18}	$C_{13}H_{11}NO_2$	213	163	78
B_{19}	$C_{13}H_{11}NO_2$	213	171	72
B_{20}	$C_{13}H_{11}NO_2$	213	184	76
B_{21}	$C_{12}H_{11}NO_2$	201	108	70
B_{22}	$C_{12}H_{10}O_2S$	218	113	68
B_{23}	$C_{22}H_{16}O_2$	312	145	75
B_{24}	$C_{14}H_{12}O_3$	228	189	78
B_{25}	$C_{14}H_{12}O_2$	212	138	71

TABLE 3: ELEMENTAL ANALYSIS DATA OF CHALCONES (B_1-B_{25})

Compound	(% Calc.)			C, H, N (% found)		
	C	H	N	C	H	N
B_1	79.64	6.19	-	79.62	6.15	-
B_2	73.04	4.78	-	73.00	4.75	-
B_3	68.29	4.47	-	68.58	4.69	-
B_4	68.29	4.47	-	68.25	4.43	-
B_5	67.74	4.03	-	67.71	4.00	-
B_6	60.00	3.57	-	60.01	3.55	-
B_7	57.73	3.43	4.81	57.70	3.40	4.79
B_8	65.36	4.28	5.44	65.31	4.25	5.41
B_9	65.36	4.28	5.44	65.32	4.24	5.42
B_{10}	73.68	5.26	-	73.65	5.23	-
B_{11}	66.42	4.79	5.16	66.40	4.75	5.13
B_{12}	67.54	5.96	-	67.51	5.91	-
B_{13}	70.31	4.68	-	70.29	4.65	-
B_{14}	73.97	5.47	9.58	73.96	5.44	9.56
B_{15}	51.24	3.20	-	51.21	3.19	-
B_{16}	75.29	6.66	5.49	75.27	6.64	5.47
B_{17}	69.76	5.42	-	69.71	5.40	-
B_{18}	73.23	5.16	6.57	73.20	5.14	6.54
B_{19}	73.23	5.16	6.57	73.21	5.14	6.55
B_{20}	73.23	5.16	6.57	73.20	5.13	6.52
B_{21}	71.64	5.47	6.96	71.61	5.44	6.92
B_{22}	66.05	4.58	-	66.01	4.51	-
B_{23}	84.61	5.12	-	84.59	5.09	-
B_{24}	73.68	5.26	-	73.65	5.22	-
B_{25}	79.24	5.66	-	79.21	5.63	-

TABLE 4: IR (KBr DISC) SPECTRAL DATA OF CHALCONES (B_1-B_{25})

Compound	Position of absorption band (cm^{-1})
B_1	1655 (C=O), 1602 (C=C quadrant of Ar), 1505(CH=CH), 1085 (C-O-C)
B_2	1664 (C=O), 1580 (C=C of Ar), 1524 (CH=CH), 1065 (C-O-C), 925 (C-F)
B_3	1653 (C=O), 1585 (C=C of Ar), 1505 (CH=CH),1083 (C-O-C), 835 (C-Cl)
B_4	1652 (C=O), 1583 (C=C of Ar), 1502 (CH=CH), 1076 (C-O-C), 833 (C-Cl)
B_5	1655 (C=O), 1581 (C=C of Ar), 1510 (CH=CH), 1073 (C-O-C), 925 (C-F)
B_6	1663 (C=O), 1578 (C=C of Ar), 1506 (CH=CH), 1082 (C-O-C), 833 (C-Cl)
B_7	1658 (C=O), 1603 (C=C of Ar), 1515 (CH=CH), 1048 (C-O-C), 824 (C-Cl),1525 (N=O, asymmetric), 1348 (N=O, symmetric)
B_8	1655 (C=O), 1605 (C=C of Ar), 1508 (CH=CH), 1045 (C-O-C), 1533 (N=O, asymmetric), 1345 (N=O, symmetric)
B_9	1652 (C=O), 1610 (C=C of Ar), 1502 (CH=CH), 1063 (C-O-C), 1541 (N=O, asymmetric), 1346 (N=O, symmetric)
B_{10}	3520 (O-H), 1648 (C=O), 1612 (C=C of Ar), 1505 (CH=CH), 1058 (C-O-C),
B_{11}	1655 (C=O), 1605 (C=C of Ar), 1500 (CH=CH), 1048 (C-O-C), 1545 (N=O, asymmetric), 1343 (N=O, symmetric)
B_{12}	1652 (C=O), 1585 (C=C of Ar), 1462 (CH=CH), 1127 (-O-CH_3), 996 (C-O-C)
B_{13}	1643 (C=O), 1574 (C=C of Ar), 1500 (CH=CH), 1240 (O-CH_2-O),1036 (C-O-C)
B_{14}	1663 (C=O), 1610 (C=N), 1588 (C=C of Ar), 1510 (CH=CH), 1391 (C-N), 1060 (C-O-C)
B_{15}	1652 (C=O), 1585 (C=C of Ar), 1503 (CH=CH), 1082 (C-O-C), 823 (C-Br)
B_{16}	1650 (C=O), 1586 (C=C of Ar),1505 (CH=CH), 1178 (-N(CH_3)$_2$),1076 (C-O-C)
B_{17}	3450 (O-H), 1648 (C=O), 1606 (C=C of Ar), 1510 (CH=CH), 1225 (-OCH_3), 1083 (C-O-C)
B_{18}	1653 (C=O), 1605 (C=C of Ar), 1595 (C=N), 1508 (CH=CH), 1385 (C-N), 1079 (C-O-C)
B_{19}	1645 (C=O), 1603 (C=C of Ar), 1590 (C=N), 1502 (CH=CH), 1370 (C-N), 1085 (C-O-C)
B_{20}	1650 (C=O), 1605 (C=C of Ar), 1581 (C=N), 1505 (CH=CH), 1373 (C-N), 1083 (C-O-C)
B_{21}	1652 (C=O), 1605 (C=C of Ar), 1588 (C=N), 1506 (CH=CH), 1375 (C-N), 1085 (C-O-C)
B_{22}	1655 (C=O), 1610 (C=C of Ar), 1505 (CH=CH), 1078 (C-O-C), 624 (C-S)
B_{23}	1658 (C=O), 1605 (C=C of Ar), 1503 (CH=CH), 1085 (C-O-C)
B_{24}	3460 (O-H), 1648 (C=O), 1606 (C=C of Ar), 1505 (CH=CH), 1083 (C-O-C)
B_{25}	1650 (C=O), 1605 (C=C of Ar), 1502 (CH=CH), 1075 (C-O-C)

TABLE 5: ^{1}H NMR SPECTRAL DATA OF CHALCONES (B_1-B_{25})

Compound	Chemical shift (δ) in ppm
B_1	2.40 (3H, s, Ar-CH_3), 2.62 (3H, s, Ar-CH_3), 7.23 (1H, d,J= 17 Hz, -CO-CH=), 7.73 (1H, d, J=17 Hz, =CH-Ar), 7.20-7.78 (6H, Ar-H)
B_2	2.60 (3H, s, Ar-CH_3), 7.15 (1H, d, J= 17 Hz, -CO-CH=), 7.62 (1H, d, J=17 Hz, =CH-Ar), 7.05-7.71 (6H, Ar-H)
B_3	2.65 (3H, s, Ar-CH_3), 7.45 (1H, d, J= 17 Hz, -CO-CH=), 7.82 (1H, d, J=17 Hz, =CH-Ar), 7.38-8.20 (6H, Ar-H)
B_4	2.63 (3H, s, Ar-CH_3), 7.43 (1H, d, J= 17 Hz, -CO-CH=), 7.80 (1H, d, J=17 Hz, =CH-Ar), 7.36-8.21 (6H, Ar-H)
B_5	2.55 (3H, s, Ar-CH_3), 7.40 (1H, d, J= 17 Hz, -CO-CH=), 7.73 (1H, d, J=17 Hz, =CH-Ar), 7.15-8.10 (5H, Ar-H)
B_6	2.62 (3H, s, Ar-CH_3), 7.68 (1H, d, J= 17 Hz, -CO-CH=), 7.85 (1H, d, J=17 Hz, =CH-Ar), 7.42-8.20 (5H, Ar-H)
B_7	2.65 (3H, s, Ar-CH_3), 7.49 (1H, d, J= 17 Hz, -CO-CH=), 7.65 (1H, d, J=17 Hz, =CH-Ar), 7.12-8.60 (5H, Ar-H)
B_8	2.62 (3H, s, Ar-CH_3), 7.40 (1H, d, J= 17 Hz, -CO-CH=), 7.62 (1H, d, J=17 Hz, =CH-Ar), 7.20-8.55 (6H, Ar-H)
B_9	2.62 (3H, s, Ar-CH_3), 7.43 (1H, d, J= 17 Hz, -CO-CH=), 7.68 (1H, d, J=17 Hz, =CH-Ar), 7.21-8.59 (6H, Ar-H)
B_{10}	2.61 (3H, s, Ar-CH_3), 7.38 (1H, d, J= 17 Hz, -CO-CH=), 7.52 (1H, d, J=17 Hz, =CH-Ar), 6.89 (1H, s, Ar-OH), 7.18-7.79 (6H, Ar-H)
B_{11}	2.62 (3H, s, Ar-CH_3), 2.50 (3H. s, Ar-CH_3), 7.40 (1H, d, J= 17 Hz, -CO-CH=), 7.65 (1H, d, J=17 Hz, =CH-Ar),7.15-8.53 (5H, Ar-H)
B_{12}	2.65 (3H, s, Ar-CH_3), 7.15 (1H, d, J= 17 Hz, -CO-CH=), 7.64 (1H, d, J=17 Hz, =CH-Ar), 7.12-7.58 (4H, Ar-H), 3.78 (3H,s,Ar-OCH_3), 3.88 (6H,s,2x Ar-OCH_3)
B_{13}	2.69 (3H, s, Ar-CH_3), 6.10 (2H,s,-O-CH_2O-), 6.88 (1H, d, J= 17 Hz, -CO-CH=), 7.69 (1H, d, J=17 Hz, =CH-Ar), 7.10-7.29 (5H, Ar-H)
B_{14}	2.60 (3H, s, Ar-CH_3), 2.45 (3H, s, Ar-CH_3), 6.85 (1H, d, J= 17 Hz, -CO-CH=), 7.65 (1H, d, J=17 Hz, =CH-Ar), 6.58-7.90 (7H, Ar-H)
B_{15}	2.60 (3H, s, Ar-CH_3), 7.23 (1H, d, J= 17 Hz, -CO-CH=), 7.71 (1H, d, J=17 Hz, =CH-Ar), 7.18-7.95 (4H, Ar-H)
B_{16}	3.10 (6H,s,-N(CH_3)$_2$, 2.45 (3H, s, Ar-CH_3), 6.88 (1H, d, J= 17 Hz, -CO-CH=), 7.75 (1H, d, J=17 Hz, =CH-Ar), 6.65-7.90 (6H, Ar-H)
B_{17}	2.62 (3H, s, Ar-CH_3), 7.21 (1H, d, J= 17 Hz, -CO-CH=), 7.68 (1H, d, J=17 Hz, =CH-Ar), 7.20-7.93 (5H, Ar-H), 6.75 (1H.s, Ar-OH), 3.82 (3H,s,Ar-OCH_3)

B_{18}	2.60 (3H, s, Ar-CH_3), 7.15 (1H, d, J= 17 Hz, -CO-CH=), 7.65 (1H, d, J=17 Hz, =CH-Ar), 6.30-8.15 (6H, Ar-H)
B_{19}	2.60 (3H, s, Ar-CH_3), 7.18 (1H, d, J= 17 Hz, -CO-CH=), 7.70 (1H, d, J=17 Hz, =CH-Ar), 7.12-8.20 (6H, Ar-H)
B_{20}	2.58 (3H, s, Ar-CH_3), 7.15 (1H, d, J= 17 Hz, -CO-CH=), 7.75 (1H, d, J=17 Hz, =CH-Ar), 7.20-8.15 (6H, Ar-H)
B_{21}	2.60 (3H, s, Ar-CH_3), 7.10 (1H, d, J= 17 Hz, -CO-CH=), 7.70 (1H, d, J=17 Hz, =CH-Ar), 6.35-7.90 (5H, Ar-H)
B_{22}	2.62 (3H, s, Ar-CH_3), 7.12 (1H, d, J= 17 Hz, -CO-CH=), 7.70 (1H, d, J=17 Hz, =CH-Ar), 6.62-8.10 (5H, Ar-H)
B_{23}	2.65 (3H, s, Ar-CH_3), 7.35 (1H, d, J= 17 Hz, -CO-CH=), 7.60 (1H, d, J=17 Hz, =CH-Ar), 7.20-8.90 (11H, Ar-H)
B_{24}	2.58 (3H, s, Ar-CH_3), 7.28 (1H, d, J= 17 Hz, -CO-CH=), 7.59 (1H, d, J=17 Hz, =CH-Ar), 6.85 (1H,s,Ar-OH),7.21-7.89 (6H, Ar-H)
B_{25}	2.60 (3H, s, Ar-CH_3), 7.21 (1H, d, J= 17 Hz, -CO-CH=), 7.62 (1H, d, J=17 Hz, =CH-Ar), 7.11-7.90 (7H, Ar-H)

Biological Studies:

Anti-microbial activity of Chalcones:

Antibacterial activity: Chalcones are proved anti-microbial agents [14] and antibacterial activity of the synthesized chalcones (B_1 to B_{25}) was assessed by determining the MIC, which is defined as the lowest concentration of the compound that completely inhibited the growth of each strain after overnight incubation. MIC values can be determined by a number of standard test procedures. The most commonly employed methods are the tube dilution and agar dilution methods [15].

Minimum inhibitory concentrations are important in diagnostic laboratories to confirm resistance of microorganisms to an antimicrobial agent and also to monitor the activity of new antimicrobial agents.

Procedure: The test bacteria grown at 37^{o}C in nutrient agar medium were diluted in sterile nutrient broth medium in such a manner that the suspension contains about 10^7cells/mL. This suspension was used as the inoculum.

Serial broth dilution procedure was adopted to determine MIC of the synthesized Chalcones.

11 test tubes were taken, 9 of which were marked 1, 2, 3, 4, 5, 6, 7, 8, 9 and the rest two were assigned as T_M (medium), and T_{MI} (medium + inoculum). 1 mL of nutrient broth medium was poured into each of the 11 test tubes. These test tubes were cotton plugged and sterilized in an autoclave at 15 lbs/sq.inch pressure. After cooling, 1 mL of the sample solution was added to the first test tube and mixed well and then followed by serial dilution method. 10 µL of the inoculum was added to the test tube T_{MI} to observe the growth of the organism in the medium used. The controlled test tube T_M containing only the medium was used to confirm the sterility of the medium. All the test tubes were incubated at 37^{o}C for 18 hrs.

A similar experiment with medium, methanol and inoculum without compound was also performed to ensure that the methanol has no inhibitory effect in the dilutions used. The test tube number in which the first sign of growth of the organism observed was noted. The MIC was taken as that concentration used in the test tube number just prior to the test tube number where the first sign of growth observed. This procedure was followed to determine the MIC values for all the compounds.

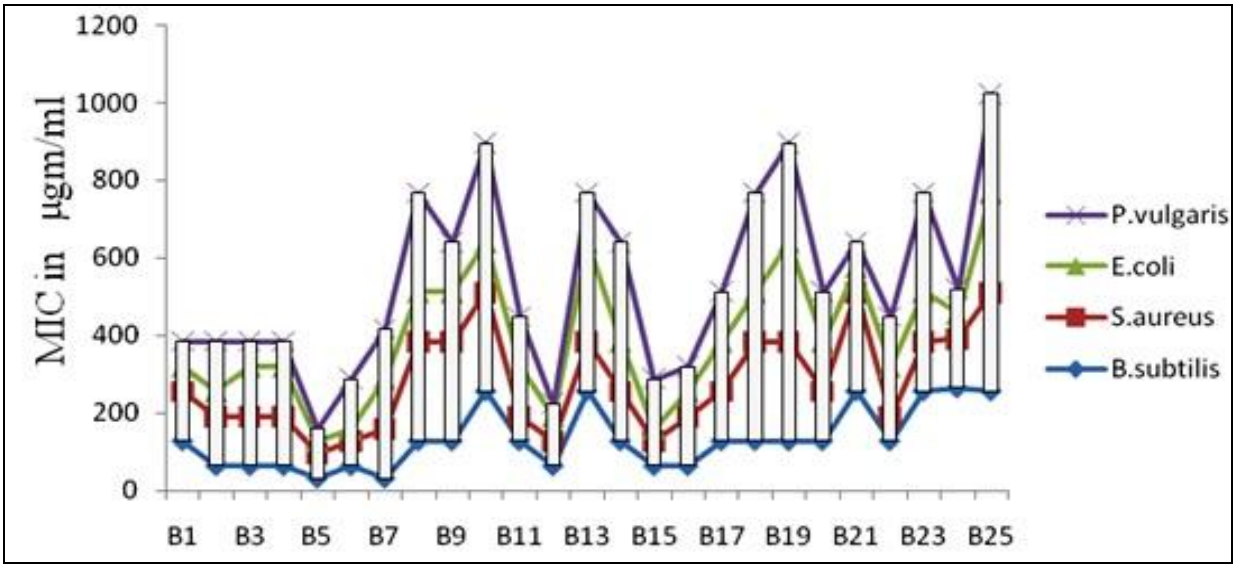
The results are shown as **Graph 1** in the case of antibacterial activity and as **Graph 2** in the case of antifungal activity.

RESULTS AND DISCUSSION:

Antibacterial activity: From the above results it is evident that all the chalcones synthesized, showed antibacterial activity with different MIC values against the tested organisms, but not comparable with that of the standard. Among the compounds tested, B_5 with difluorophenyl moiety was found to be the most potent against *B. subtilis*, *E. coli* and *P. vulgaris* having a MIC value of 32 µg/mL in each case.

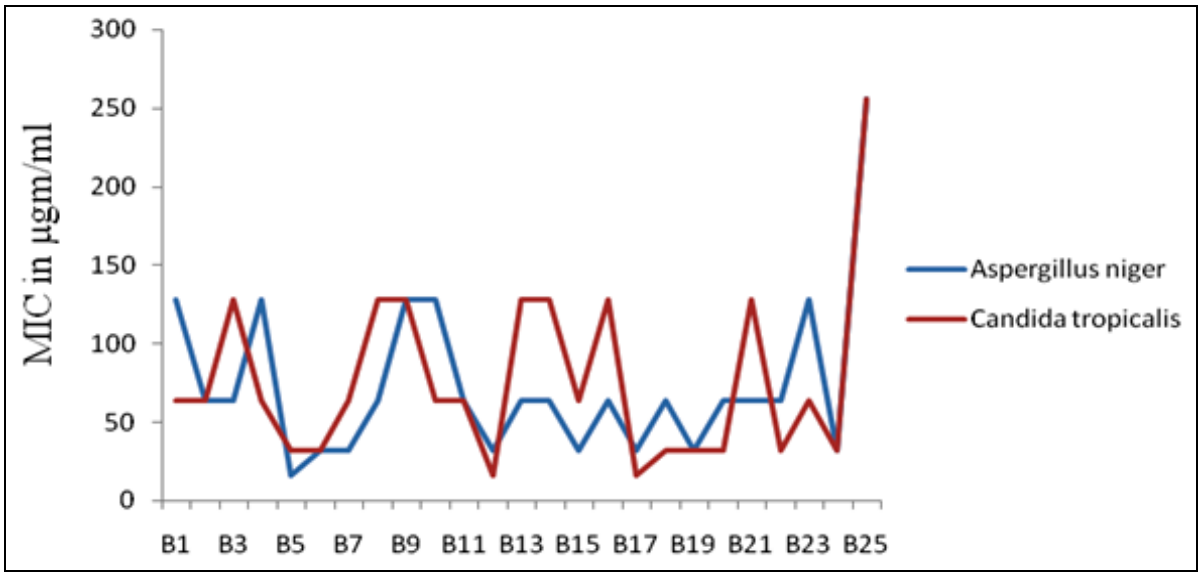
The chalcones, B_6 having a dichlorophenyl substitution, B_7 having 2-chloro-5-nitrophenyl substitution and B_{15} having bromofuran substitution were also found to be equipotent with a MIC value of 32 µg/mL against *E. coli*, *B. subtilis* and *E. coli* respectively. Some of the chalcones with mono halogen substitution (B_2, B_3 and B_4) on the phenyl ring showed a MIC of 64 µg/mL against both Gram-positive and Gram-negative bacteria. The chalcones B_{12} with trimethoxyphenyl moiety also showed similar MIC values. All the other chalcones were also found to be somewhat potent against selective organisms with a MIC of 64 µg/mL, but most of them showed a MIC value in between 128-256 µg/mL.

The structure-activity relationship study based on the above results clearly indicated the importance of electron withdrawing groups in enhancing the antibacterial activity. When more than one such group present on the phenyl ring, a cumulative effect was observed as seen in the case of B_5 and B_6 having difluoro and dichloro substitution respectively. However, compounds with electron releasing substituents as seen in the case of B_{12} and B_{16} also enhanced the activity. Compounds with more number of electron releasing or electron with drawing substituents on the aromatic or heteroaromatic ring at different positions can be synthesized to draw meaningful conclusions with respect to the influence of electronic effects on the antimicrobial activity was show in **Graph 1**.



GRAPH 1: ANTIBACTERIAL ACTIVITY OF CHALCONES (B_1 TO B_{25})

Antifungal activity: Among the compounds tested for antifungal activity, compounds B_5, B_{12} and B_{17} found to be the most potent with a MIC value of 16 µg/mL against *A.niger* in the case of B_5 and against *C.tropicalis* in the case of other two compounds. Again compound B_5 possessing a difluorophenyl moiety could contribute favorably to antifungal activity along with antibacterial as seen earlier. The chalcones B_6, B_7, B_{15}, B_{19}, B_{22} and B_{24} carrying different electron withdrawing or electron releasing substituents also enhanced the antifungal activity. The other compounds also found to be somewhat potent with MIC values ranging from 64-256 µg/mL was show in **Graph 2**.



GRAPH 2: ANTIFUNGAL ACTIVITY OF CHALCONES (B_1 TO B_{25})

A Structure-Activity-Relationship study based on the above results indicated the necessity of fluorine at different positions of the phenyl ring. Since the fluorine substitution has contributed favorably to the inhibitory activity, a chalcone with two or more such substituents on the aromatic ring at different positions can be synthesized with a hope to get promising antifungal compounds. Compound having the phenyl ring substituted with three methoxyls at 3, 4 and 5 positions has also enhanced the activity.

Compounds having this type of substitution at other positions can be attempted as part of SAR studies and similarly chalcones with different substituents on furan moiety can also be synthesized in order to enhance the activity.

CONCLUSION: The results also indicated the contribution of α, β-unsaturated carbonyl group present in chalcones in enhancing the activity, as this structural feature was distinctive for the chalcones synthesized. Influence of the same reactive group for probable anti-microbial activity of chalcones must be investigated further in detail. However, the change in the resulting physico-chemical properties, need to be established by proper QSAR studies in each case.

ACKNOWLEDGEMENT: I, Pavan Kumar Padarthi would like to express our gratitude to all those who gave us the possibility to complete this report. We are deeply indebted to Dr. Reddy Rambabu of Chebrolu Hanumaiah Institute of Pharmaceutical Sciences, Guntur and Prof. Y. Rajendra Prasad of Andhra University, Visakahapatnam, for stimulating suggestions, knowledge, experience and encouragement helped us in all the times of study and analysis of the project.

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How to cite this article:
Padarthi PK and Namasivayam E: Synthesis and Biological evaluation of Chalcones from 2-acetyl-5-methylfuran. *Int J Pharm Sci Res* 2013: 4(7); 2629-2638. doi: 10.13040/IJPSR. 0975-8232.4(7).2629-38