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Synthesis of novel 1-(4'-fluorophenyl)-3-(4"-aryl)-2-propen-1-ones by conventional and microwave irradiation methods and their pharmacological activities

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ABSTRACT

Chalcones are important starting materials for the synthesis of various classes of five, six and seven memberd heterocyclic compounds. most of these compounds are highly bioactive and are widely used in pharmaceuticals. they belong s to an important class of flavonoids, Chalcones are synthesized by Claisen–Schmidt condensation, which involves cross aldol condensation of appropriate aldehydes and ketones by base or acid catalysed reactions followed by dehydration. 12 new Chalcones were synthesized by conventional and microwave assisted synthesis methods. The structures of newly synthesized compounds were confirmed by spectral evidence.microwave assisted synthesis, a considerable increase in the reaction rate has been observed and that too, with better yields. Prepared compounds were tested for anto microbial activity.

Keywords: *Chalcones, Microwave Irradiation, Antimicrobial Activity,*

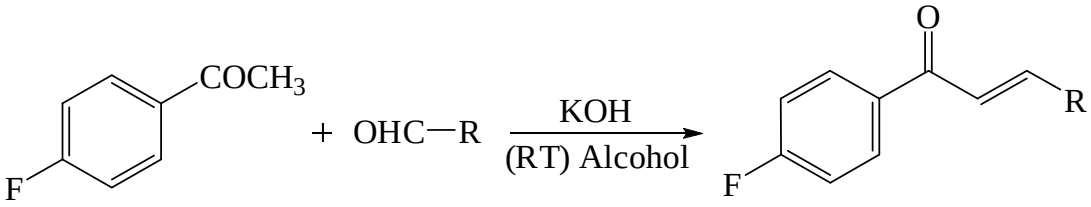
INTRODUCTION

Chalcones[1], 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. The presence of a reactive α,β-unsaturated keto functional group is partly responsible for their activity. Chalcones have also been reported to be antiinflammatory, analgesic and antipyretic, bactericidal, antifungal and insecticidal ,antimutagenic , chemo preventive activity cardiovascular disease, anticancer activity, cytotoxic activity, antiprolifirative activity, antimalarial activity, antiviral activity and anti-HIV activity. Keeping this broad spectrum of biological activities in mind, in the present investigation it has been considered worthwhile to synthesize some new chalcone derivatives by conventional and microwave irradiation methods and to compare between two methods.

Microwave-induced organic reaction enhancement (MORE) chemistry is gaining popularity as a non-conventional technique for rapid organic synthesis. Important features of this technique are easy access to very high temperature, good control over energy input in a reaction, higher yields and rapid synthesis of organic compounds. The synthesized compounds were purified by recrystallization and chromatography. The compounds were characterized by 1H NMR and IR analysis. The compounds were tested for their antimicrobial activity by standard protocals.

MATERIALS AND METHODS

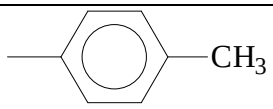
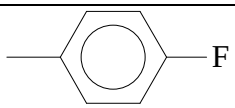
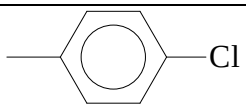
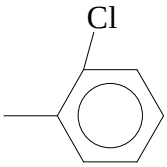
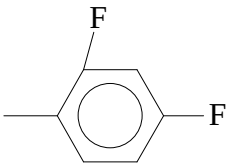
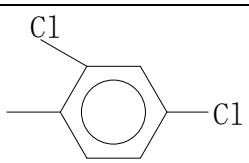
Conventional method: General procedure for the synthesis of chalcones (B_1-B_{12}):
A mixture of 4-fluoroacetophenone (0.001 mole) and the appropriate aryl aldehyde (0.001 mole) was stirred in ethanol (7.5 mL) and to it aqueous solution of KOH (50%, 7.5 mL) was added. The mixture was kept for 24 h and 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.

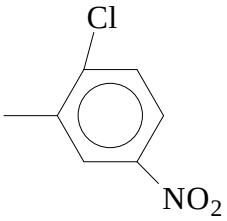
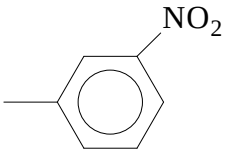
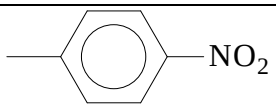
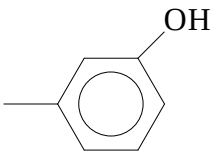
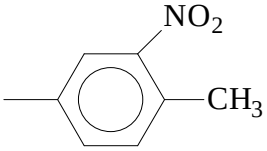
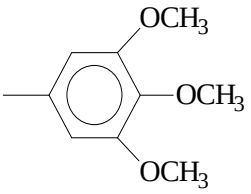


4-Fluoroacetophenone Aromatic/ Heterocyclic Aldehyde Chalcone derivative

(B**) Microwave irradiation method**: Equimolar quantities (0.001 mol) of 4-fluoro acetophenone and respective aldehydes (0.001 mol) were mixed and dissolved in minimum amount (3 ml) of alcohol. To this, pulverized potassium hydroxide (0.003 mol) was added slowly and mixed. The entire reaction mixture was microwave irradiated for about 4 min at 180 watts.

Table 1. Physical characterization data of chalcones (B_1-B_{12})

Compound	R	Molecular Formula	Relative Molecular Mass	Melting Point (°C)	Yield %
B_1		$C_{16}H_{13}FO$	240.27	135-137	88
B_2		$C_{15}H_{10}F_2O$	244.24	88-90	87
B_3		$C_{15}H_{10}ClFO$	260.69	122-124	88
B_4		$C_{15}H_{10}ClFO$	260.69	131-133	79
B_5		$C_{15}H_9F_3O$	262.23	111-113	75
B_6		$C_{15}H_9C_{l2}FO$	295.14	94-96	92

B_7		$C_{15}H_9ClFNO_3$	305.69	132-134	82
B_8		$C_{15}H_{10}FNO_3$	271.24	115-117	85
B_9		$C_{15}H_{10}FNO_3$	271.24	123-125	84
B_{10}		$C_{15}H_{11}FO_2$	242.25	133-135	93
B_{11}		$C_{16}H_{12}FNO_3$	285.27	127-129	85
B_{12}		$C_{18}H_{17}FO_4$	316.32	109-111	89

Spectral data for prepared compounds were given below:

B-1:*1-(4'-fluorophenyl)-3-(4''-methylphenyl)-2-propen-1-one* ***(B_1):***

Mol.wt:, 240.27,yield: 88%,mp: 135-137^{0}C ,IR (KBr) (cm^{-1}) : 1655 (C=O), 1602 (C=C of Ar), 1505(CH=CH), 925 (C-F).^{1}H-NMR ($CDCl_3$) ppm : 2.40 (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 (8H, Ar-H).

B-2: *1-(4'-fluorophenyl)-3-(4''-fluorophenyl)-2-propen-1-one* ***(B_2):***

Mol.wt:, 244.24,yield: 87%,mp: 88-90^{0}C ,IR (KBr) (cm^{-1}) : 1664 (C=O), 1580 (C=C of Ar), 1524 (CH=CH), 928 (C-F).^{1}H-NMR ($CDCl_3$) ppm : 7.15 (1H, d, *J* = 17 Hz, -CO-CH=), 7.62 (1H, d, *J* =17 Hz, =CH-Ar), 7.05-7.71 (8H, Ar-H).

B-3:*1-(4'-fluorophenyl)-3-(4''-chlorophenyl)-2-propen-1-one* ***(B_3):***

Mol.wt:, 260.69,yield: 88%,mp: 122-124^{0}C ,IR (KBr) (cm^{-1}) : 1653 (C=O), 1585 (C=C of Ar), 1505 (CH=CH), 835 (C-Cl), 923 (C-F).^{1}H-NMR ($CDCl_3$) ppm : 7.45 (1H, d, *J* = 17 Hz, -CO-CH=), 7.82 (1H, d, *J* =17 Hz, =CH-Ar), 7.38-8.20 (8H, Ar-H).

B-4:*1-(4'-fluorophenyl)-3-(2''-chlorophenyl)-2-propen-1-one* ***(B_4):***

Mol.wt:, 260.69,yield: 79%,mp: 131-133^{0}C ,IR (KBr) (cm^{-1}) : 1652 (C=O), 1583 (C=C of Ar), 1502 (CH=CH), 833 (C-Cl), 923 (C-F).^{1}H-NMR ($CDCl_3$) ppm : 7.43 (1H, d, *J* = 17 Hz, -CO-CH=), 7.80 (1H, d, *J* =17 Hz, =CH-Ar), 7.36-8.21 (8H, Ar-H).

B-5:*1-(4'-fluorophenyl)-3-(2'',4''-difluorophenyl)-2-propen-1-one* ***(B_5):***

Mol.wt:, 262.23,yield: 75%,mp: 111-113^{0}C ,IR (KBr) (cm^{-1}) : 1655 (C=O), 1581 (C=C of Ar), 1510 (CH=CH), 925 (C-F), 926 (C-F).^{1}H-NMR ($CDCl_3$) ppm : 7.40 (1H, d, *J* = 17 Hz, -CO-CH=), 7.73 (1H, d, *J* =17 Hz, =CH-Ar), 7.15-8.10 (7H, Ar-H).

B-6:*1-(4'-fluorophenyl)-3-(2",4"-dichlorophenyl)-2- propen-1-one* ***(B_6):***
Mol.wt:, 295.14,yield: 92%,mp: 94-96^{0}C ,IR (KBr) (cm^{-1}) : 1663 (C=O), 1578 (C=C of Ar), 1506 (CH=CH), 833 (C-Cl), 921 (C-F).^{1}H-NMR ($CDCl_3$) ppm : 7.68 (1H, d, *J* = 17 Hz, -CO-CH=), 7.85 (1H, d, *J* =17 Hz, =CH-Ar), 7.42-8.20 (7H, Ar-H).

B-7: *1-(4'-fluorophenyl)-3-(2"-chloro-5"-nitrophenyl)-2-propen-1-one* ***(B_7):***
Mol.wt:, 305.69,yield: 82%,mp: 132-134^{0}C ,IR (KBr) (cm^{-1}) : 1658 (C=O), 1603 (C=C of Ar), 1515 (CH=CH), 824 (C-Cl),1525 (N=O, asymmetric), 1348 (N=O, symmetric), 929 (C-F).^{1}H-NMR ($CDCl_3$) ppm : 7.49 (1H, d, *J* = 17 Hz, -CO-CH=), 7.65 (1H, d, *J* =17 Hz, =CH-Ar), 7.12-8.60 (7H, Ar-H).

B-8:*1-(4'-fluorophenyl)-3-(3"-nitrophenyl)-2-propen-1-one* ***(B_8):***
Mol.wt:, 271.24,yield: 85%,mp: 115-117^{0}C ,IR (KBr) (cm^{-1}) : 1655 (C=O), 1605 (C=C of Ar), 1508 (CH=CH), 1533 (N=O, asymmetric), 1345 (N=O, symmetric), 925 (C-F).^{1}H-NMR ($CDCl_3$) ppm : 7.40 (1H, d, *J* = 17 Hz, -CO-CH=), 7.62 (1H, d, *J* =17 Hz, =CH-Ar), 7.20-8.55 (8H, Ar-H)

B-9:*1-(4'-fluorophenyl)-3-(4"-nitrophenyl)-2-propen-1-one* ***(B_9):***
Mol.wt:, 271.24,yield: 84%,mp: 123-125^{0}C ,IR (KBr) (cm^{-1}) : 1652 (C=O), 1610 (C=C of Ar), 1502 (CH=CH), 1541 (N=O, asymmetric), 1346 (N=O, symmetric), 923 (C-F).^{1}H-NMR ($CDCl_3$) ppm : 7.43 (1H, d, *J* = 17 Hz, -CO-CH=), 7.68 (1H, d, *J* =17 Hz, =CH-Ar), 7.21-8.59 (8H, Ar-H)

B-10:*1-(4'-fluorophenyl)-3-(3"-hydroxyphenyl)-2-propen-1-one* ***(B_{10}):***
Mol.wt:, 242.25,yield: 93%,mp: 133-135^{0}C ,IR (KBr) (cm^{-1}) : 3520 (O-H), 1648 (C=O), 1612 (C=C of Ar), 1505 (CH=CH), 923 (C-F).^{1}H-NMR ($CDCl_3$) ppm : 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 (8H, Ar-H)

B-11:*1-(4'-fluorophenyl)-3-(3"-nitro-4"methylphenyl)-2-propen-1-one* ***(B_{11}):***
Mol.wt:, 285.27,yield: 85%,mp: 127-129^{0}C ,IR (KBr) (cm^{-1}) : 1655 (C=O), 1605 (C=C of Ar), 1500 (CH=CH), 1545 (N=O, asymmetric), 1343 (N=O, symmetric), 922 (C-F).^{1}H-NMR ($CDCl_3$) ppm ; 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 (7H, Ar-H).

B-12:*1-(4'-fluorophenyl)-3-(3",4",5"-trimethoxyphenyl)-2-propen-1-one* ***(B_{12}):***
Mol.wt:, 316.32,yield: 89%,mp: 109-111^{0}C ,IR (KBr) (cm^{-1}) : 1652 (C=O), 1585 (C=C of Ar), 1462 (CH=CH), 1127 (-O-CH_3), 927 (C-F).^{1}H-NMR ($CDCl_3$) ppm : 7.15 (1H, d, *J* = 17 Hz, -CO-CH=), 7.64 (1H, d, *J* =17 Hz, =CH-Ar), 7.12-7.58 (6H, Ar-H), 3.78 (3H,s,Ar-OCH_3), 3.88 (6H,s,2x Ar-OCH_3).

Antimicrobial Activity:
Since the chalcones were reported to possess antimicrobial activity, the chalcones prepared during the course of the present work were tested for antibacterial and antifungal activity.

Antibacterial activity:
The antibacterial activity was tested by determining the minimum inhibitory concentration (MIC) for each compound using serial tube dilution technique[59].The following organisms were used.

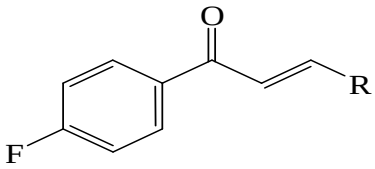
Test organisms: Gram positive bacteria:*Staphylococcus aureus* (NCIM-2079),*Bacillus subtilis* (NCIM-2063), **Gram negative bacteria**: *Escherichia coli* (NCIM-2068),*Proteus vulgaris* (NCIM-2027)

Antifungal activity The antifungal activity was tested by the same procedure as described in the antibacterial activity, except using Potato-Dextrose-Agar medium. These two organisms were used.*Aspergillus* niger (ATCC-6275),*Candida tropicalis* (ATCC-1369)

The results are shown in tables 2 in the case of antibacterial activity and table 3 in the case of antifungal activity.

Table 2. Antibacterial activity of chalcones (compounds B_1 to B_{12}):

(Expressed as MIC in µg/mL)



Compound	R	*B.subtilis*	*S.aureus*	*E.coli*	*P.vulgaris*
B_1	4"-methylphenyl	128	128	64	64
B_2	4"-fluorophenyl	64	128	64	128
B_3	4"-chlorophenyl	64	128	128	64
B_4	2"-chlorophenyl	64	128	128	64
B_5	2",4"-difluorophenyl	32	64	32	32
B_6	2",4-dichlorophenyl	64	64	32	128
B_7	2"-chloro-5"-nitrophenyl	32	128	128	128
B_8	3"-nitrophenyl	128	256	128	256
B_9	4"-nitrophenyl	128	256	128	128
B_{10}	3"-hydroxyphenyl	256	256	128	256
B_{11}	3"-nitro-4"-methylphenyl	128	64	128	128
B_{12}	3",4",5"-trimethoxyphenyl	64	64	64	32
Standard (Ampicillin)		< 1	< 1	< 1	< 1

Table 3. Antifungal activity of chalcones (compounds B_1 to B_{12}): (Expressed as MIC in µg/mL)

Compound	R	*Aspergillus* niger	*Candida tropicalis*
B_1	4"-methylphenyl	128	64
B_2	4"-fluorophenyl	64	64
B_3	4"-chlorophenyl	64	128
B_4	2"-chlorophenyl	128	64
B_5	2",4"-difluorophenyl	16	32
B_6	2",4-dichlorophenyl	32	32
B_7	2"-chloro-5"-nitrophenyl	32	64
B_8	3"-nitrophenyl	64	128
B_9	4"-nitrophenyl	128	128
B_{10}	3"-hydroxyphenyl	128	64
B_{11}	3"-nitro-4"-methylphenyl	64	64
B_{12}	3",4",5"-trimethoxyphenyl	32	16
Standard Fluconazole		< 2	< 2

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 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 chalcone 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.

Antifungal activity:

Among the compounds tested for antifungal activity, compounds B_5 and B_{12} 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 fovourably to antifungal activity along with antibacterial as seen earlier. The chalcones B_6, and B_7 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.

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