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ENVIRONMENTAL FRIENDLY SYNTHESIS AND ANTIMICROBIAL ANALYSIS OF FLUORINATED CHALCONE FROM FORMYL PYRAZOLE UNDER ULTRASONIC IRRADIATION

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ABSTRACT
Chalcone is α, β-unsaturated carbonyl system having basic skeleton. These are 1, 3-diphenyl-2-propene-1-one made up of two aromatic rings are joined by a three carbon. These are found in plenty of amount in edible plants and flavonoids and isoflavonoids are made up from chalcones as precursors. Under sonochemical irradiation the synthesis of Chalcones is carried out by a base catalyzed Claisen-Schmidt condensation is the basic reaction. The newly prepared compounds were evaluated for their antimicrobial and antifungal activity against Gram +ve and Gram-ve microorganisms. Moderate activity was shown by some compounds against standard drugs.

Keywords: *Chalcones, Sonochemical irradiation*

INTRODUCTION
The chalcones have attracted a pronounced interest due to their uses as antibacterial, anti-inflammatory and anticancer pharmacological agents [1, 2]. Chalcones are important intermediates in the preparation of many pharmaceuticals. They are commonly made by the Claisen-Schmidt condensation between acetophenone and benzaldehyde. This reaction is catalyzed by acids and bases under homogeneous conditions. There are numerous methods existing for the synthesis of chalcones. The most commonly used is the base-catalyzed such as potassium hydroxide (KOH), sodium hydroxide (NaOH), lithium hydroxide ($LiOH{\cdot}H_2O$). and barium hydroxide $Ba(OH)_2$ Synthesizing chalcones with the help of the acid-catalyst like dry HCl, aluminum trichloride ($AlCl_3$), titanium tetrachloride ($TiCl_4$), boron trifluoride-etherate (BF_3- Et_2O), and ruthenium trichloride ($RuCl_3$)
Now a day's powerful technique emerging is Ultrasonic-assisted organic synthesis as a green synthetic approach that is being extensively used more and more to accelerate organic reactions [3]. This method is much convenient as compared with traditional methods, and reactions give higher yield, less reaction time and milder conditions. [4]
Ultrasonic irradiation leads to the acceleration of numerous catalytic reactions as well as in homogeneous and heterogeneous systems [5]. Furthermore, significant improvements can be realized as regards to the yields [6]. The sonochemical phenomena initiate from the contact between a appropriate field of acoustic waves and a possibly reacting chemical system; the interaction proceeds through the transitional phenomenon of acoustic cavitation. Three significant factors have to be measured when an ultrasonic prompted reaction is done: the acoustic field, the bubbles field and the chemical system [7].
Chalcones are also synthesized by condensing substituted o-hydroxy acetophenones with substituted pyrazole carbaldehyde in presence of suitable condensing agents. They undergo various chemical reactions and are found valuable in synthesis of important heterocyclic compounds. Chalcones have been used as intermediate for the preparations of compounds having therapeutic value. Based on the above observation it is worthwhile to prepare newer compounds for their antimicrobial and anti-inflammatory activities. In the view of the varied biological and pharmacological application, we synthesized some new heterocyclic derivatives of chalcones. Synthesis of chalcones has been carried out by Claisen–Schmidt condensation under sonochemical irradiation. Heterocycles containing nitrogen and sulphur moieties constitute the core structure of a number of biologically interesting compounds. During last three decades, Ultrasound has progressively been used in organic synthesis. A large number of organic reactions can be carried out in higher yields, shorter reaction time or milder conditions under ultrasound irradiation. As a part of our investigations on the application of ultrasound in organic synthesis, we wish to report an efficient and practical procedure for the synthesis of chalcones from fluorinated formyl pyrazole.

EXPERIMENTAL
Melting points were recorded in open capillaries in liquid paraffin bath and are uncorrected. TLC is used for the monitoring completion of reaction. IR spectra were recorded in KBr disc on Schimadzu-FT-IR Spectrophotometer. ^{1}H NMR spectra were recorded on Brucker Avance II 400 MHz instrument in DMSO-d_6 and an internal standard used is TMS. Peak values are shown in δ (ppm). Mass spectra were recorded on micromass Q-Tof Micro mass spectrophotometer. Bandelin Sonorex (with a frequency of 35 KHz and a

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nominal power of 200W) ultrasonic bath was used for ultrasonic irradiation. The reaction vessel placed inside the ultrasonic bath containing water.

General Procedure for the synthesis of 3-(2, 4-difluorophenyl)-1-(4-fluorophenyl)-1*H*-pyrazole-4-carbaldehyde (4):

A mixture of 4-fluoro acetophenone **1** (0.1mole), 4-fluorophenyl hydrazine **2** (0.1 mole), absolute ethanol (20ml) and catalytic amount of glacial acetic acid was stirred on magnetic stirrer with hot plate for ten minutes. The resulting faint yellow colour product was separated by filtration and washed with cold ethanol (50%) and dried under vacuum to get the compound **3**.

A mixture of dimethylformamide (0.1mole) and phosphorous oxychloride (0.6mole) was stirred at 0^{o}C for 30 minutes and then (Z)-2-(4-fluorophenyl)-1-(1-(4-fluorophenyl) ethylidene) hydrazine **3** (0.2 mole) was added at 0^{o}C with constant stirring. The reaction mixture was stirred overnight at room temperature and then poured over crushed ice; resulting product was separated by filtration and washed with cold sodium bicarbonate solution (10%) followed by water and crystallized from ethanol to get 1,3-bis(4-fluorophenyl)-1*H*-pyrazole-4-carbaldehyde compound **4.**

CONVENTIONAL METHOD

General procedure for the synthesis of (*E*)-3-(1, 3-bis (4-fluorophenyl)-1*H*-pyrazol-4-yl)-1-(5-chloro-2-hydroxyphenyl) prop-2-en-1-one (6c): A mixture of **4** (0.01 mol) and **5** (0.01 mol) was dissolved in 25 ml ethanol and contents were cooled to 0^{o}C in ice bath. To this reaction mixture, powdered 1.5g KOH was added and temperature is maintained below 5^{o}C. At room temperature the reaction mixture was stirred for 40hr. Then reaction mixture was diluted with water containing crushed ice and 2M HCl is added to acidify the mixture. Resulting product was separated by filtration and washed with ice cold water. Product was recrystallized from ethanol. This typical experimental procedure was followed to prepare other analogs of this series. Their physical data are given in **Table 1**

NONCONVENTIONAL METHOD

A mixture of **4** (0.01 mol) and **5** (0.01 mol) was dissolved in 25 ml ethanol in 100ml round bottom flask. To this reaction mixture, 1.5g powdered KOH was added. The mixture was irradiated by ultrasonic generator in a water bath keeping temperature 30-70^{o}C for 4hr. The reaction mixture containing solid product was poured over crushed ice and contents were acidified with 2M HCl. Resulting product was separated by filtration and washed with cold water. Product was crystallized from ethanol. This typical experimental procedure was followed to prepare other analogs of this series. Their physical data are given in **Table 1**and Antimicrobial data given in **Table 2 & 3.**

Compound 4: m.p.194-196^{o}C

IR(4) (cm^{-1}): 1102(Ar-F), 1524(C=C), 1647(C=N), 1685(C=O), 3190(CHO).

^{1}H NMR(4) (DMSO-d_6) δ ppm: 7.2299-7.2349(d, 1H, Ar-H), 7.2470-7.2519(d, 1H, Ar-H ,*J*=Hz), 7.2980-7.3034(d, 1H, Ar-H, *J*=Hz), 7.3200-7.3415(d, 1H, Ar-H, *J*=Hz), 7.9774-7.9868(d,1H, Ar-H, *J*= Hz),7.9912-7.9989(d,1H, Ar-H, *J*= Hz),8.0039-8.0095(d,1H,Ar-H),8.0132-8.0212(d,1H,Ar-H), 9.2155(s, 1H, pyrazoyl proton), 9.9916 (s, 1H, Ar-CHO).

ES-MS (4) (m/z): 285(M+1).

6c: m.p 173^{o}C

IR(6c) (cm^{-1}): 1014 (C-Cl), 1101 (C- F), 1158 (C-O), 1535 (C=C), 1472, 1575 (Ar C=C), 1644 (C=O), 3415 (-OH)

^{1}H NMR(6c)**:** 6.9608-6.9917(d, 1H, Ar-H, *J*=12.36Hz), 7.0136-7.3767 (m, 4H, Ar-H), 7.4653-7.5294 (m, 1H, Ar-H), 7.6510-7.7192(m, 2H, Ar-H), 7.7511-7.9798(4H, d, CH=C, *J*=15.2 Hz), 8.1180-8.1854(d, 1H, Ar-H, *J*=8.8Hz), 9.3890 (s, 1H, pyrazole =CH), 12.6417 (s, 1H, -OH).

ES-MS (6c) (m/z 435(M-1),437(M+2)

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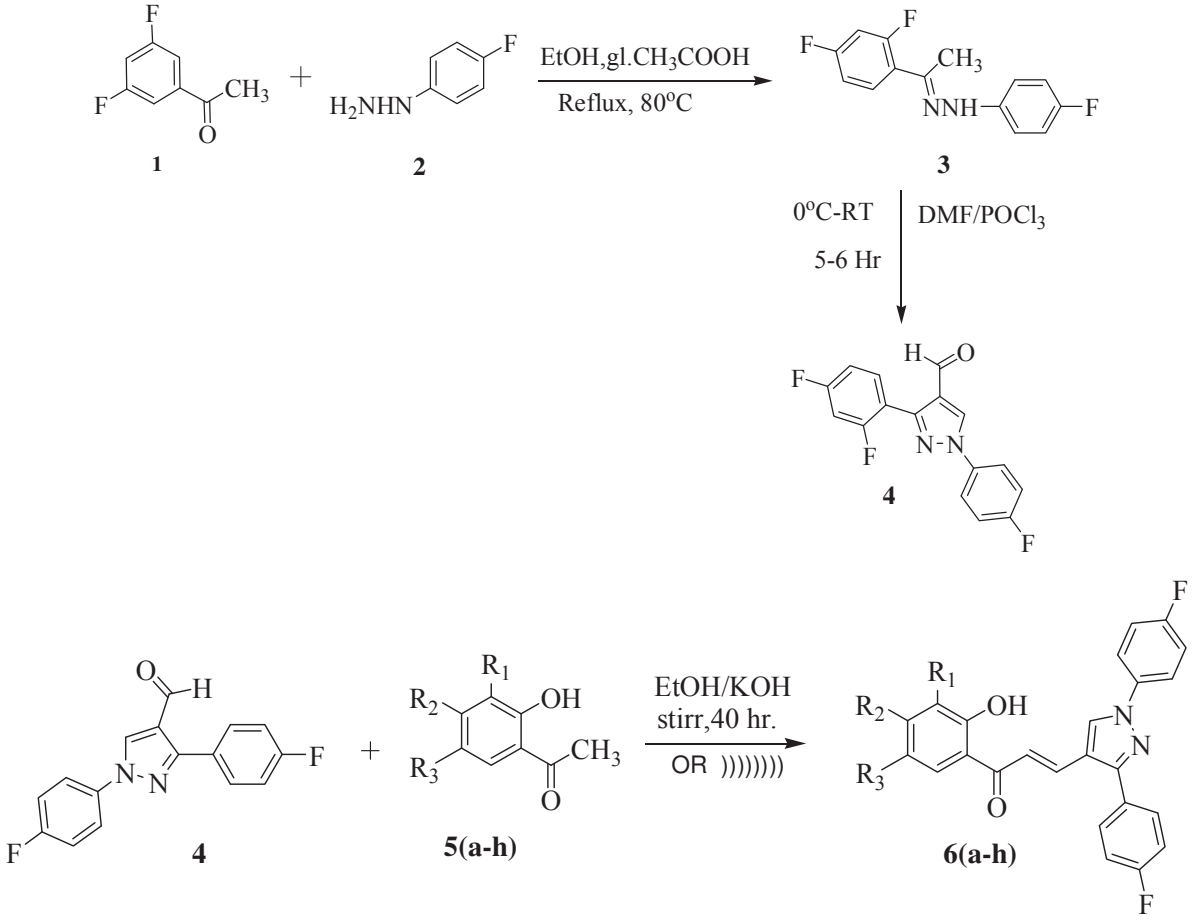
Scheme



Scheme-1: Synthesis of various substituted (*E*)-3-(1, 3-bis (4-fluorophenyl)-1*H*-pyrazol-4-yl)-1-(5-chloro-2-hydroxyphenyl) prop-2-en-1-one

Table-1: Physical data of compounds 6(a-h)

					Conventional Method		Nonconventional Method	
Compd.	**R_1**	**R_2**	**R_3**	**M.P. (°C)**	**Time (hr)**	**Yield (%)**	**Time (min)**	**Yield (%)**
6a	H	H	H	172-174	48	71	240	78
6b	H	H	CH_3	178-180	40	76	240	78
6c	H	H	Cl	194-196	40	60	240	65
6d	Cl	H	Cl	202-204	40	85	240	88
6e	H	H	F	200-202	40	62	240	69
6f	H	CH_3	Cl	138-140	40	64	240	70
6g	H	H	Br	226-228	40	76	240	80
6h	CH_3	H	CH_3	222-224	40	70	240	74

RESULTS AND DISCUSSION

Antimicrobial Activity:-Compounds **6** were screened for their in vitro antimicrobial activity against *Escherichia coli, Pseudomonas aeruginosa, Staphylococcus albus, Staphylococcus aureus, Klebsiella pnuemoniae, Pseudomonas sp.*using Ciprofloxacin as a reference standard drug by paper disc diffusion method and agar well method. Antifungal activity was evaluated against *Candida sp.* using Fluconazole as standard drug. All the tests were evaluated at 100 µg/ml concentration. The culture media was Muller hinton agar. The zone of inhibition was measured in mm after 24 hr. of incubation at 37°C. **6a, 6e, 6f, 6g** shows moderate antifungal activity. All the compounds show good to moderate antibacterial activity against above mentioned bacterial species. DMSO is used as control.

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Table-2: Antimicrobial data of compounds 6(a-h)
Disc Diffusion Method

Sample	Inhibition Zone Diameter (mm)					
	Candida sp.	***Staphylococcus aureus***	***Staphylococcus albus***	***Klebsiella pnuemoniae***	***Escherichia coli***	***Pseudo monas sp.***
6a	8	7	9	1	14	10
6b	No zone	8	10	11	12	10
6c	No zone	8	12	11	12	No zone
6d	8	No zone	9	9	No zone	No zone
6e	11	9	7	10	8	No zone
6f	10	No zone	7	10	10	No zone
6g	10	No zone	No zone	10	10	No zone
6h	No zone	No zone	10	No zone	9	No zone
Control (DMSO)	8	3	3	6	7	10
Ciprofloxacin	---	20	22	22	21	23
Fluconazole	23	---	---	---	---	---

Table-3: Antimicrobial data of compounds 6(a-h)
Agar Well Method

Sample	Inhibition Zone Diameter (mm)					
	Candida sp.	***Staphylococcus aureus***	***Staphylococcus albus***	***Klebsiella pnuemoniae***	***Escherichia coli***	***Pseudo monas sp.***
6a	No zone	8	6	No zone	3	2
6b	No zone	11	10	3	5	4
6c	No zone	6	4	6	4	10
6d	No zone	7	12	8	5	No zone
6e	No zone	9	7	8	No zone	No zone
6f	10	13	No zone	7	8	10
6g	11	7	No zone	10	8	No zone
6h	8	9	13	12	10	No zone
Control	8	3	3	4	6	10
Ciprofloxacin	---	20	22	22	21	23
Fluconazole	23	---	---	---	---	---

CONCLUSION

All the synthesized compounds were screened for antimicrobial activity. In-*vitro* activity data is presented in **Table 2 &3**. All the compounds screened showed moderate to good antibacterial and antifungal activity comparable with that of standard drug tested.

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REFERENCES

1. M. Liu, P. Wilairat, M.L. Go, (2001), Antimalarial alkoxylated and hydroxylated chalcones : structure-activity relationship analysis. J. Med. Chem. 44(25), 4443-4452.
2. J. Rojas, J. N. Domı´nguez, J.E. Charris, G. Lobo, M. Paya, M.L. Ferra´ndiz, (2002), Synthesis and inhibitory activity of dimethylamino-chalcone derivatives on the induction of nitric oxide synthase, Eur. J. Med. Chem. 37, 699–705.
3. Xu, H., Liao, W. M., & Li, H. F. (2007), A mild and efficient ultrasound-assisted synthesis of diaryl ethers without any catalyst. Ultrasonics Sonochemistry, 14, 779–782.

ISSN 2394 - 7780

4. Mason, T. J.; Peters, D.; Practical Sonochemistry, Power Ultrasound Uses and Applications, (2002), 2nd ed., Ellis Horwood Publishers: Chicherster, 89-91.
5. T. J. Mason, (1990), Chemistry with Ultrasound, T. J. Mason (Ed.); Elsevier Applied Science, London, Ch. 1, 1–26.
6. J. Berlan, T.J. Mason, (1992), Sonochemistry from research laboratories to industrial plants. Ultrasonics, 30, 203-212.
7. M. A. Margulis, (1992), Fundamental aspects of Sonochemistry, Ultrasonics, 30, 152-155.