"A convenient, rapid and eco-friendly synthesis of Chalcones N-[4-Chloro-2-(2-fluorobenzoyl)phenyl]-3-(substitutedphenyl) acrylamides as well as their antimicrobial activity"

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ABSTRACT

In this work, an attempt was made to synthesize chalcones N-[4-Chloro-2-(2-fluorobenzoyl)phenyl]-3-(substitutedphenyl)acrylamide derivatives by the condensation of aromatic aldehyde with N-[4-chloro-2-(2-fluorobenzoyl)phenyl]acetamide under basic conditions by using both conventional and microwave irradiation methods. A simple condensation of aromatic aldehyde and N-[4-Chloro-2-(2-fluorobenzoyl)phenyl]acetamide using sodium methoxide as a base was carried out for the study. The synthesized compounds were characterized for IR, ^{1}H NMR, ^{13}C NMR and mass spectral analysis. It was observed that completion of a reaction occurred in 10-12 min by microwave irradiation method and in 10-12 hr by conventional method. Finally, it was observed that microwave irradiation method is more convenient, rapid and eco-friendly as compare to conventional method. The reaction time has been brought down from hours to seconds with improved yield as compared to conventional method.

KEY WORDS

Chalcone, Conventional method, Microwave irradiation method, Antimicrobial activity.

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INTRODUCTION

In the last few years Microwave-assisted Organic Synthesis(MAOS) has gained popularity as a non-conventional technique for rapid organic synthesis [1] and many researchers have described accelerated organic reactions, and a large number of papers have appeared proving the synthetic utility of Microwave in routine organic synthesis [2,3]. It is convenient, rapid, economical and eco-friendly and is believed to be a step towards green chemistry.

Chalcones come under an aromatic ketone that forms the central core for a variety of important biological compounds. Chalcone derivatives are very versatile as physiologically active compounds and substrates for the evaluation of various organic synthesis. Chalcone and their derivatives are of high interest materials due to their antioxidant, antibacterial, antifungal, antitumor and anti-inflammatory properties [4–7]. Chalcones are valuable intermediates in the synthesis of many active pharmaceutical drugs like biosynthesis of

flavonoids [8] and Auwers synthesis of flavones [9]. Having such varied pharmacological activities, these molecules have attracted medicinal chemists and therefore several strategies have been developed to synthesize them. Claisen–Schmidt condensation between acetophenone and benzaldehyde gives chalcone [7]. Herein we report the Chalcone derivatives by synthesizing a series of ten molecules (3a–j) using both Microwave and conventional synthesis method. The effect of microwaves on % yield and reaction time of synthesized chalcones has been studied to understand the role of microwaves (microwave energy) in the synthesis of chalcones.

MATERIALS AND METHODS

All the melting points of the synthesized compounds were determine by open capillaries and are uncorrected. The progress of the reactions were monitored by TLC plates using silica gel (Merck grade) as absorbent, solvent systems (ethyl acetate : n-hexane, 2:8) and visualized under iodine vapor. IR spectra were recorded on a Shimadzu FT-IR 8400S spectrophotometer using KBr pellet method. ^{1}H NMR and ^{13}C NMR spectra of the compounds were recorded on BRUKER DRX-300 instrument using DMSO as solvent and TMS as internal standard and the values are expressed in δ ppm. Mass spectra of the compounds were obtained on an AGILENT 6520(Q-TOF) mass spectrometer.

General procedure for the synthesis of *N*-[4-Chloro-2-(2-fluoro benzoyl) phenyl] acetamide [2]

A mixture of (2-Amino-5-chlorophenyl)-(2-fluorophenyl)methanone **1** and acetic anhydride in a glacial acetic acid was taken in a R.B.F. The reaction mixture was reflux for 2 hrs on sand bath. Progress of the reaction was monitored by TLC **(mobile phase: ethyl acetate : toluene 3:7).** The reaction mixture was then cooled, treated with crushed ice to give the solid product which was filtered, dried and purified by recrystallization from acetone.

General procedure for the synthesis of N-[4-chloro-2-(2-fluorobenzoyl)phenyl]-3-(substitutedphenyl) acrylamides [3a-j]

Conventional Method: A mixture of *N*-[4-Chloro-2-(2-fluoro benzoyl) phenyl] acetamide **2** (1.0mol), various aromatic aldehyde (1.2 mol) and 5% sodium methoxide solution in methanol (30ml) was taken in a R.B.F. The reaction mixture was stirred overnight at room

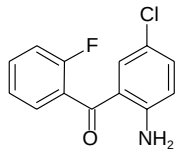
temperature. The progress of reaction was monitored by TLC (Mobile Phase Ethyl Acetate : n-Hexane 2:8). The solid thus obtained was filtered, washed with chilled methanol and purified by recrystallization from methanol.

Microwave Method: In a 250 ml R.B.F., A mixture of *N*-[4-Chloro-2-(2-fluorobenzoyl) phenyl] acetamide **2** (1.0mol), various aromatic aldehyde (1.2 mol) and 5% sodium methoxide solution in methanol (30ml) was subjected to microwave irradiation for specified time of 10-12 min at power level 450W. The progress of reaction was monitored by TLC (Mobile Phase Ethyl Acetate : n-Hexane 2:8). The solid thus obtained was filtered, washed with chilled methanol and purified by recrystallization from methanol.

[3a] IR (KBr cm^{-1}) : 3335.03(-NH), 1619.29 (-C=O), 756.12 (C-Cl), 1101.39 (C-F), 1670.41 (Ar-CO-Ar) . **^{1}H NMR (DMSO) δ :** 6.903-6.933 (d, 2H, -CO-CH=CH), 7.355(s, 1H, -NH), 7.315-7.345 & 7.379-7.645(m, 12H, Ar-H). **^{13}C NMR :** 156.47 (C1), 115.87(C2), 132.48(C3), 119.16(C4), 131.85(C5), 117.25(C6), 193.03(C7), 129.48(C8), 129.44(C9), 127.74(C10), 132.38(C11), 116.80(C12), 140.09(C13), 159.73(C14), 116.15(C15), 149.74(C16), 134.91(C17), 124.80(C18), 127.51(C19), 124.84(C20), 127.51(C21), 124.80(C22). **Mass (m/z):** 379.5 (M), 381.5 (M+2), 301.0360, 291.0247, 276.6414, 257.0630, 250.0429, 177.0069, 154.8051, 131.0018 .

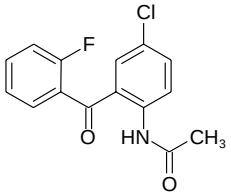
[3e] IR (KBr cm^{-1}) : 3245.34(-NH), 1605.79(-C=O), 766.73(C-Cl), 1096.57(C-F), 1667.52 (Ar-CO-Ar) . **^{1}H NMR (DMSO) δ :** 7.185-7.214 (d, 2H, -CO-CH=CH), 7.351(s, 1H, -NH), 7.301-7.326 & 7.418-7.997(m, 12H, Ar-H). **^{13}C NMR :** 162.46(C1), 114.71(C2), 132.98(C3), 125.48(C4), 131.68(C5), 125.11(C6), 190.29(C7), 131.53(C8), 130.95(C9), 128.81(C10), 131.80(C11), 124.41(C12), 135.28(C13), 161.88(C14), 116.02(C15), 140.30(C16), 132.12(C17), 128.23(C18), 115.00(C19), 165.75(C20), 115.00(C21), 128.23(C22). **Mass (m/z):** 397.7807 (M), 399.7807 (M+2), 301.1348, 275.1609, 250.0421, 155.0645, 149.0012 .

REACTION SCHEME



(2-Amino-5-chlorophenyl)-(2-fluorophenyl)methanone **1**

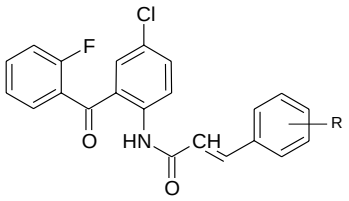
Gla. Acetic Acid
Acetic Anhydride
Reflux, 2 hrs



N-[4-chloro-2-(2-fluorobenzoyl)phenyl]acetamide **2**

Microwave Method
10-12 mnt , 450 W

Conventional Method
Aro. Aldehyde
5%CH_3ONa



***N*-[4-chloro-2-(2-fluorobenzoyl)phenyl]-3-(sub. phenyl)acrylamide 3a-j**

Table:1 Physical data of compounds 3a-j

Sr No.	R	Mol. Formula	Mol. Wt. gm/mol	Conventional Method		Microwave Method		M.P ^{0}C (Con)	M.P. ^{0}C (Mic)
				Time (hr)	Yield (%)	Time (min)	Yield (%)		
3a	H	$C_{22}H_{15}NO_2ClF$	379.5	12-14	80	10-12	83	100	102
3b	2-Cl	$C_{22}H_{14}NO_2Cl_2F$	414.0	12-14	82	10-12	86	92	94
3c	3-Cl	$C_{22}H_{14}NO_2Cl_2F$	414.0	12-14	80	10-12	82	100	98
3d	4-Cl	$C_{22}H_{14}NO_2Cl_2F$	414.0	12-14	82	10-12	88	96	96
3e	4-F	$C_{22}H_{14}NO_2ClF_2$	397.5	12-14	78	10-12	83	104	106
3f	4-OH	$C_{22}H_{15}NO_3ClF$	395.5	12-14	80	10-12	86	110	109
3g	4-OH-3-OCH_3	$C_{23}H_{17}NO_4ClF$	425.5	12-14	85	10-12	88	108	110
3h	4-OCH_3	$C_{23}H_{17}NO_3ClF$	409.5	12-14	76	10-12	81	120	118
3i	3,4-$(OCH_3)_2$	$C_{24}H_{19}NO_4ClF$	439.5	12-14	78	10-12	85	122	122
3j	3,4,5-$(OCH_3)_3$	$C_{25}H_{21}NO_5ClF$	469.5	12-14	75	10-12	84	116	118

ANTIMICROBIAL ACTIVITY

Following common standard strains were used for screening of antibacterial and antifungal activities: *E. Coli* (MTCC 442), *P. Aeruginosa* (MTCC 441), *S. Aureus* (MTCC 96), *S. Pyogenus* (MTCC 443), *C. Albicans* (MTCC 227), *A. Niger* (MTCC 282), *A. Clavatus* (MTCC 1323). The strains were procured from Institute of Microbial Technology, Chandigarh. DMSO was used as diluent to get desired concentration of drugs to test upon standard bacterial strains. Each synthesized drug was diluted for obtaining 2000 μg/ml concentration, as a stock solution. In primary screening 1000 μg/ml, 500 μg/ml and 250 μg/ml concentrations of the synthesized drugs were taken. The actively synthesized drugs found in this primary screening were further tested in the second set of dilution against all microorganisms. The drugs found active in primary screening were similarly diluted to obtain 200 μg/ml, 100 μg/ml, 50 μg/ml, 25 μg/ml, 12.5 μg/ml and 6.250 μg/ml concentrations. The highest dilution showing at least 99 % inhibition zone is taken as MIC. The result of this is much affected by the size of the inoculums. Gentamycin, Ampicillin, Chloramphenicol, Ciprofloxacin, Norfloxacin, Nystatin and Gresiofulvin were used as a standard drugs. The

Comparative activities of the newly synthesized compounds and the control antibiotics on bacterial and fungal strains respectively were summarized in **table 2** and **table 3**.

Table-2 : Antibacterial activity data of compounds 3a-j

Compound No.	(R)	MINIMAL INHIBITION CONCENTRATION FOR BACTERIA (µg/ml)			
		Gram Positive		Gram Negative	
		S. aureus MTCC 96	***S. pyogenus MTCC 443***	***E. coli MTCC 442***	***P. aeruginosa MTCC 441***
3a	(H)	250	200	250	100
3b	**(2-Cl)**	**100**	**125**	**62.5**	**62.5**
3c	(3-Cl)	250	250	100	100
3d	**(4-Cl)**	**100**	**125**	250	**62.5**
3e	(4-F)	125	200	200	125
3f	(4-OH)	200	250	125	200
3g	(4-OH-3-OCH_3)	250	200	125	250
3h	(4-OCH_3)	200	250	200	200
3i	(3,4-$(OCH_3)_2$)	**200**	**100**	200	100
3j	(3,4,5-$(OCH_3)_3$)	500	500	250	200
Gentamycin	-	**0.25**	**0.50**	**0.05**	**1**
Ampicillin	-	**250**	**100**	**100**	**--**
Chloramphenicol	-	**50**	**50**	**50**	**50**
Ciprofloxacin	-	**50**	**50**	**25**	**25**
Norfloxacin	-	**10**	**10**	**10**	**10**

Table-3 : Antifungal activity data of compounds 3a-j

Compound No.	(R)	MINIMAL INHIBITION CONCENTRATION FOR FUNGI (µg/ml)		
		C. albicans MTCC 227	***A. niger MTCC 282***	***A. clavatus MTCC 1323***
3a	(H)	>1000	>1000	>1000
3b	(2-Cl)	**500**	500	500
3c	(3-Cl)	1000	500	500
3d	(4-Cl)	1000	>1000	>1000
3e	(4-F)	**500**	>1000	>1000
3f	(4-OH)	**250**	500	500
3g	(4-OH-3-OCH_3)	1000	500	500
3h	(4-OCH_3)	>1000	>1000	>1000
3i	(3,4-$(OCH_3)_2$)	>1000	250	250
3j	(3,4,5-$(OCH_3)_3$)	1000	1000	1000
NYSTATIN	-	**100**	**100**	**100**
GRESEOFULVIN	-	**500**	**100**	**100**

RESULTS AND DISCUSSION

Compound N-[4-chloro-2-(2-fluorobenzoyl)phenyl]acetamide **2**, were synthesized from (2-Amino-5-chlorophenyl)-(2-fluorophenyl)methanone **1**, which upon reaction with various aromatic aldehyde yields N-[4-chloro-2-(2-fluorobenzoyl)phenyl]-3-(substitutedphenyl) acrylamides **3a-j** inpresence of 5% sodium methoxide using methanol as a solvent. The proposed structures of all the synthesized compounds were supported by IR, ^{1}H NMR, ^{13}C NMR and Mass spectral data. The formation of newly synthesized compounds 3a-j was confirmed by the appearance of doublet signal at δ 7.185-7.214 for –CO-CH=CH system.

CONCLUSION

In summary, N-[4-chloro-2-(2-fluorobenzoyl)phenyl]-3-(substitutedphenyl)acrylamides **3a-j** derivatives have been synthesized and characterized. *In vitro* antimicrobial testing of the compounds were carried out by microdilution method. Amongst the synthesized compounds excellent activity was observed in compound **3b** (against *E.Coli, P.Aeruginosa, S.Aureus, and S.Pyogenus*), compound **3d** (against *P.aeruginosa, S.Aureus, and S.Pyogenus*) and compound **3i** (against *S.Aureus, S.Pyogenus*). Excellent to good activity observed in compounds **3b, 3e, 3f** (against *C.Albicans*). The remaining compounds were found effective

at a much higher concentration against all bacterial and fungal strain as compared to the standard drugs.

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