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Microwave-Assisted Efficient Synthesis of Ortho Hydroxy Chalcones as Probes for Biological Activities

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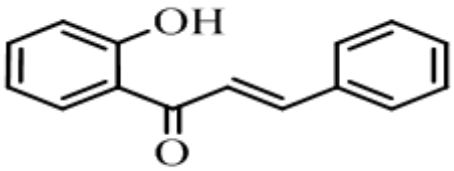
ABSTRACT

Novel series of chalcones(1-10) were synthesized by Claisen-Schmidt condensation of 2-hydroxy, 5-Chloro acetophenone with several aromatic aldehydes in presence of aqueous solution of sodium hydroxide using microwave irradiations. The reaction is clean with shorter reaction time, eco-friendly, mild reaction condition, excellent yield as compared to conventional methods and reduces the use of volatile organic compounds (VOCs). Variety of functional groups such as chloro, hydroxy, nitro, bromo, and ether survived under the reaction conditions. The synthesized chalcones compounds were characterized by physical and spectral methods such as melting point, IR, ^{1}H-NMR and Mass analysis. All the synthesized compounds have been screened and evaluated for antibacterial activity against *Staphylococcus aureus* gr +ve, *Escherichia coli* gr –ve *Bacillus subtilis* gr +ve, *Salmonella typhi* gr –ve , and antifungal activity against *Aspergillus oryzoe*, *Aspergillus niger*, DMSO was used as solvent control for their antimicrobial activity using disc diffusion method. The antioxidant activity of these chloro substituted also studied using the DPPH radical scavenging. Synthesis and biological evaluation of chalcone derivatives have been a topic of special interest to organic and medicinal chemists. The new structural classes of compounds may prove as lead molecules and good candidates for the future investigations.

1.0 INTRODUCTION

The chemistry of chalcones has generated intensive scientific studies throughout the world. Especially interest has focused on the synthesis and biodynamic activities of chalcones. The name 'Chalcone' was given by Kostanecki and Tambor (1). Chalcones are 1,3-diphenyl-2-propene-1-one in which two aromatic rings are linked by a three carbon α, β unsaturated carbonyl system.



Chalcone

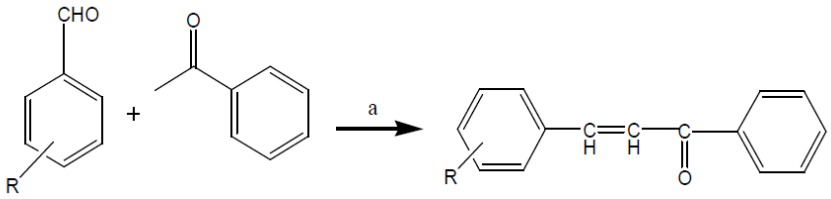
Chalcones possess conjugated double bond and a completely delocalised π electron system on both benzene rings. Molecules possessing such system have relatively low redox potentials and have a greater probability of undergoing electron transfer reactions. Chalcones bear a very good synthon, so that variety of novel heterocycles with good pharmaceutical profile can be designed. Chalcones represent an important class of natural compounds with a variety of biological activities (2). Recent studies on biological evaluation of chalcones revealed some to be antimicrobial (3), anti-inflammatory (4), analgesic (5), antiplatelet (6), anticulcerative (7),(14), antimalarial (8), anticancer (9), antiviral (10), antihyperglycemic (11), antioxidant (12), antitubercular (13), immunomodulatory (15), inhibition of chemical mediator release (16), inhibition of leukotriene B4 (17), inhibition of tyrosinase (18) and inhibition of aldose reductase (19) activities. In recent years, microwave assisted solid support-solvent free organic synthesis has attracted much attention as they offer several advantages such as simple procedure, fast reaction rate, mild reaction conditions, eco friendly and improved yields as compared to the conventional methods. Further the reaction in dry media conditions, are especially appealing as they provide an opportunity to work with open vessels, thus avoiding the risk of high pressure development and offer the possibility of carrying out reactions that can be scaled up by the industries (20). Dry media reaction or solid state reaction or solventless reaction is a chemical reaction system in the absence of solvent. The drive for the development of the dry media reaction in chemistry is

- Economics
- Ease of purification
- High reaction rate
- Environment friendly

All these factors have developed an academic interest in solid phase reaction and have led to developing methodologies for solvent free reactions with considerable success.

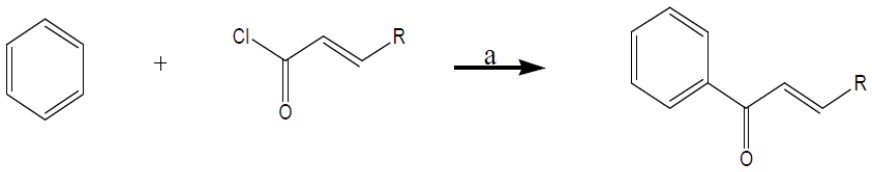
1.1 Review of Literature

Chalcones have been synthesized by Claisen-Schmidt condensation. The aromatic or aliphatic ketones are condensed with an aldehyde in the presence of soluble alkaline hydroxides of EtONa to afford chalcones. (21).



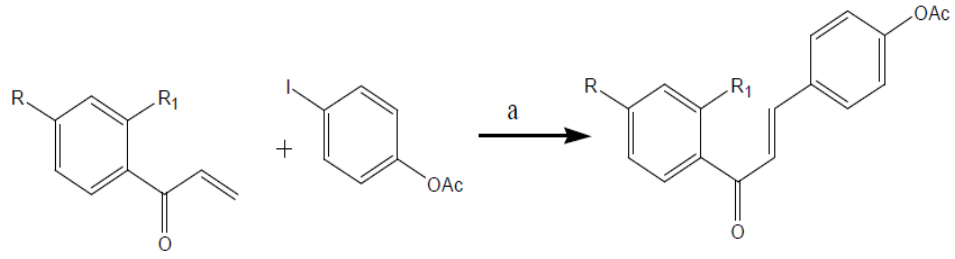
Reagents (a). EtONa ,Alkaline hydroxides.

Various heterogeneous solid bases are also employed to obtain chalcones. These include alumina (22), $Ba(OH)_2$ (23). Hydrotalcites (24), MgO and Calcinised $NaNO_3$/ Natural phosphate (25,26). The acid catalysed methodologies include the use of $AlCl_3$ (27), BF_3 (28), dry HCl (29), $TiCl_4$ (30), CP_2ZrH_2/ $NiCl_2$ (31), Zeolites (32) and $RuCl_3$ (33). Chalcones are also synthesized by Friedal-Craft Acylation, in which aromatic hydrocarbons were acylated using α, β- unsaturated acid chloride in the presence of the Lewis acid (34,35).



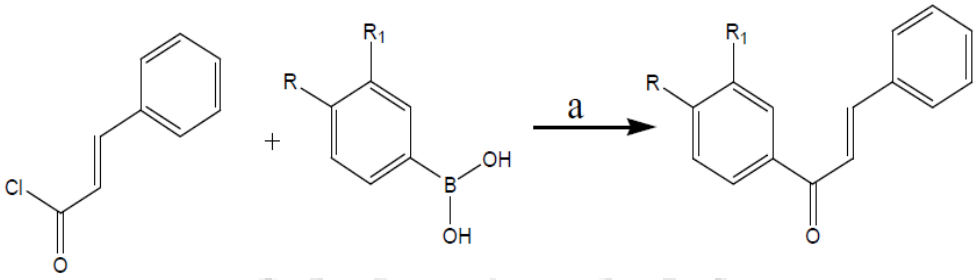
Reagents (a): Anhydrous $AlCl_3$.

Heck reaction is also employed for the synthesis of chalcones. Heck reaction is a reaction of alkenes and aryl halides catalysed by Pd Metal complexes (36).



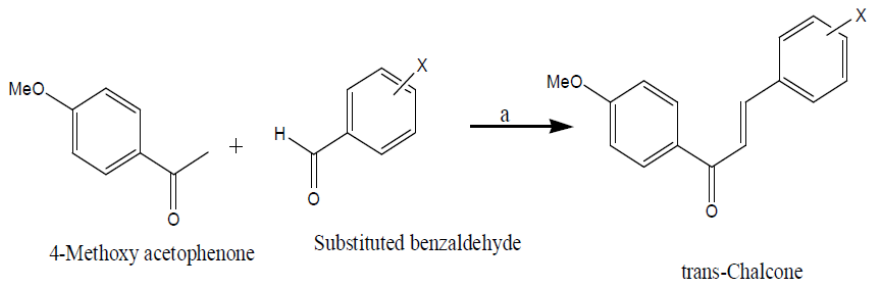
Reagents (a): Pd-Metal Complex.

Chalcones are also synthesized by Suzuki coupling reaction between benzyl chlorides and phenyl vinyl boronic acid. (37).



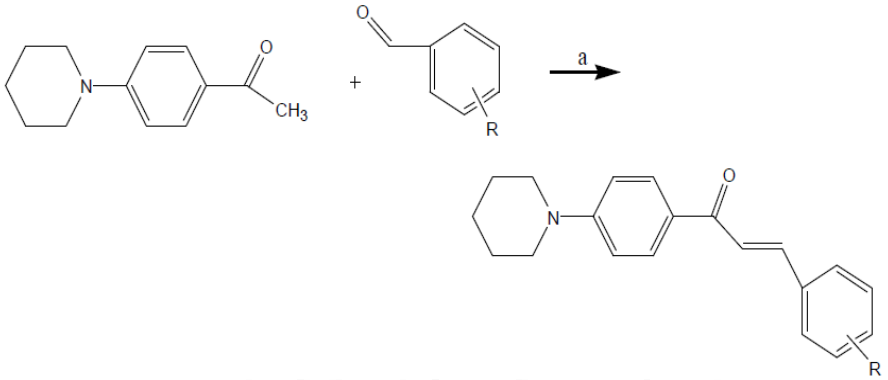
Reagents (a): $(PPh_3)_4$ Pd(O), Cs_2CO_3, toluene.

Moreover, in the last two decades, use of microwave energy for conducting organic reactions has become very popular and emerging technique as it has several advantages over classical organic reactions such as shortening reaction time, improving yields and promoting environment friendly (Green chemistry) new reactions. The combination of supported reagents and microwave irradiation has gained much interest to carry out a wide range of reactions in a short time and with high conversion and selectivity without the need of solvent. The solvent free approach involves the exposure of neat reaction to microwave irradiation (MWI) in conjunction with the use of supported reagent or catalyst which are primarily of mineral origin. The salient features of these high yield protocols are the enhanced reaction rates, greater selectivity and the experimental ease of manipulation (38). Recently various modified methods have been reported for solvent free synthesis of chalcones using different catalysts. Solid NaOH was first time used by Palleros (39) in 2004 for Aldol condensation to obtain trans chalcones by grinding technique.



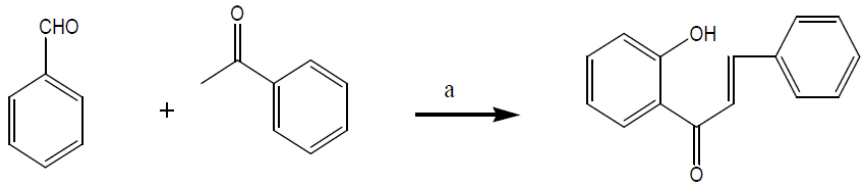
Reagents (a): NaOH (solid) Where X= NO_2, OCH_3, Cl

Chalcones have been synthesized under microwave irradiation by Claisen –Schmidt condensation between 4-piperidino-acetophenone and appropriately substituted benzaldehydes using NaOH-Al_2O_3 under solvent free conditions by Jayant P. Singh et al (40). Neat reaction on MWI under solvent free condition resulted in enhancement of yield and reaction rates.



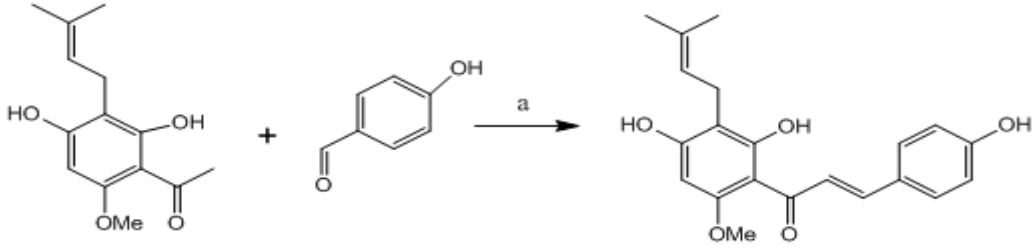
Reagents (a): Basic alumina/MWI.

Y.K. Shrivasta (41), successfully carried out Clasein-Schmidt condensation to afford desired chalcones in 83-90% yield. Various substituted o-hydroxy acetophenones were condensed with aromatic aldehyde in the presence of anhydrous K_2CO_3 under microwave irradiations. The reaction was completed within 3-5 min.



Reagents: (a) Anhydrous K_2CO_3, 3-5 min.

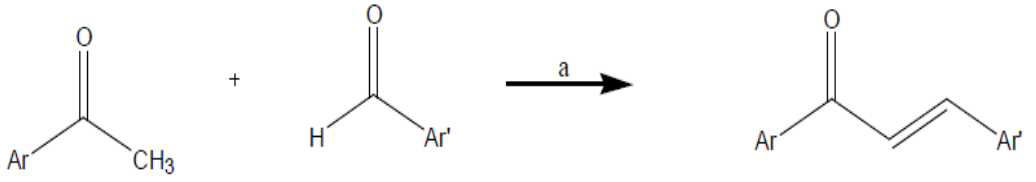
Kaketi D. et al (42) have developed a simple, eco-friendly and cost-effective methodology, for the solvent free condensation of aryl ketones and aldehydes using iodine impregnated alumina under microwave irradiation. This protocol has been applied to variety of substituted aryl carbonyls with excellent yield of substituted 1,3,diphenyl propenones.



Reagents (a): I2-Al_2O_3, MWI, 90 sec.

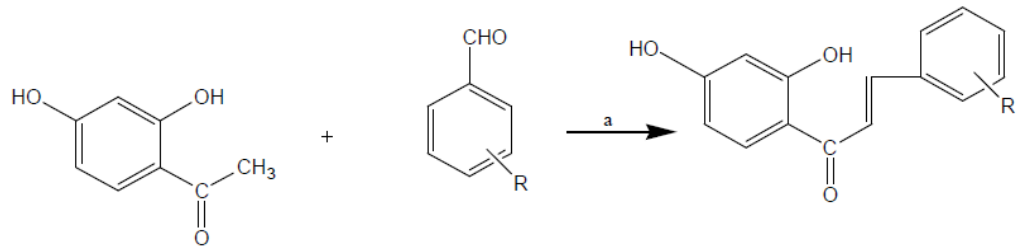
Riady Y. et al (43), have successfully demonstrated Animal Bone Meal (ABM) as new heterogenous catalysts for simple and convenient synthesis of various chalcones.

Potassium fluoride or sodium nitrate doped ABM increased catalytic activity remarkably under solventless microwave chalcone synthesis.



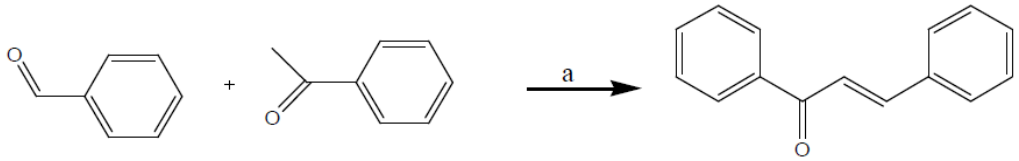
Reagents (a): $NaNO_2$, ABM/ KF-ABM, MWI.

JayaPal M. R et al (44), have synthesized a series of α, β -unsaturated ketones derived from 2,4-dihydroxy acetophenone with various substituted benzaldehydes under solvent free conditions using silica-sulphuric acid as a reagent in oven.



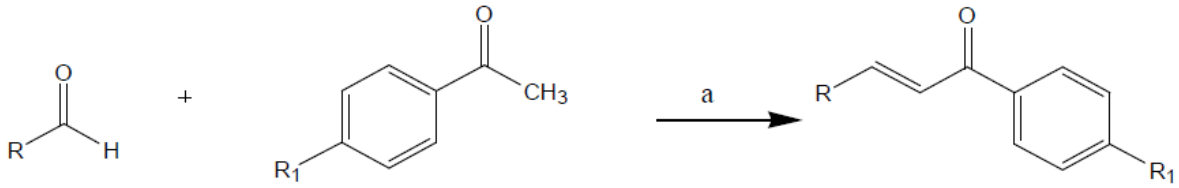
Reagents (a): SiO_2-H_2SO_4, solvent free, 80^0C. R= 2-Cl, 4, -OH, 3-OH, 4-NO_2

Achraf Lahyani et al (45), have presented an improved synthesis of transchalcones and bis-(aryl-methylidene) cycloalkanones under ultrasound irradiation in the presence of commercial acid-resins as catalysts in solvent free conditions.



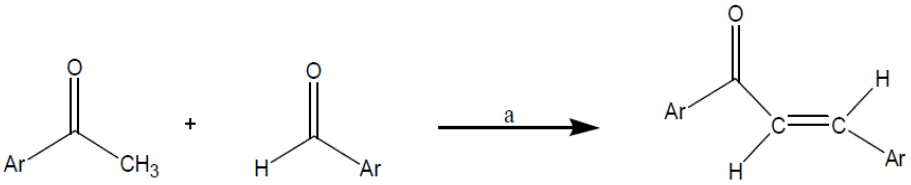
Reagents (a) Resin, Ultrasonic. 2h, 25-30^{0}C.

Dhruva Kumar et al (46), have reported an environmentally benign protocol for the synthesis of chalcones by Claisen-Schmidt condensation of aldehydes with the ketones using eco-friendly non-toxic Bismuth (III) Chloride catalyst under solvent free condition. In this protocol, yields are high and there are no other pollutants formed.



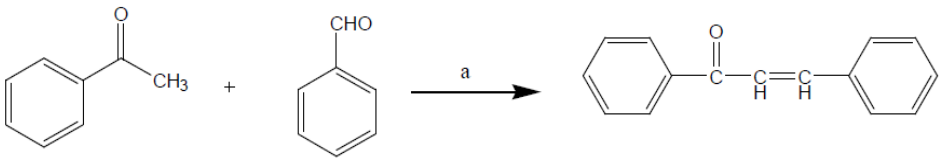
Reagent (a) $BiCl_3$, solvent free.

R Arulkumaran et al (47), have synthesized a series of substituted styrl 3,5- dichloro-2'-hydroxy phenyl ketones using thionyl chloride assisted crossed aldol reaction.



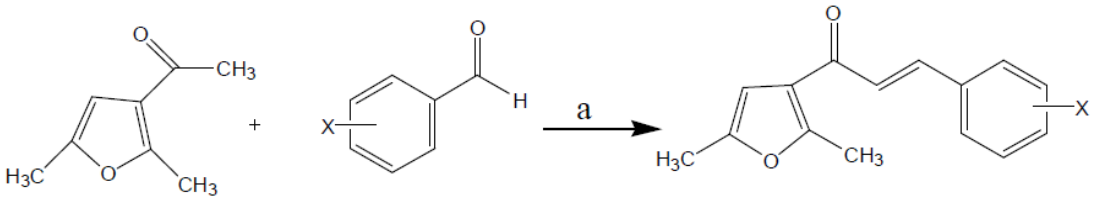
Reagents (a) $SOCl_2$, EtOH, R.T.

B Krishnakumar and M Swaminathan (48), have used Sulfated Degussa titania as a novel solid acid catalyst for the synthesis of quinaxalines, dipyridophenazines and chalcones under microwave irradiation. The catalyst Degussa [Sulfated TiO_2-P25] is a commercial titania powder, prepared by sol-gel method using H_2SO_4.



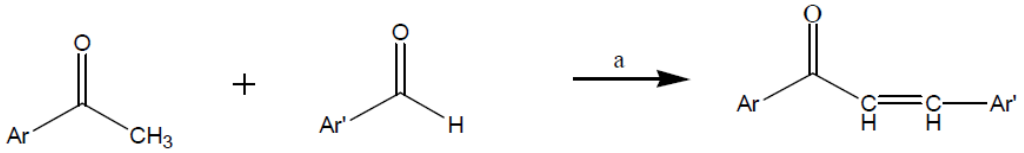
Reagents (a): Sulfated TiO_2-P25/ MWI, 1min.

M Subramanian et al (49), have synthesized 3-furyl chalcones by hydroxyapatite catalysed aldol condensation.



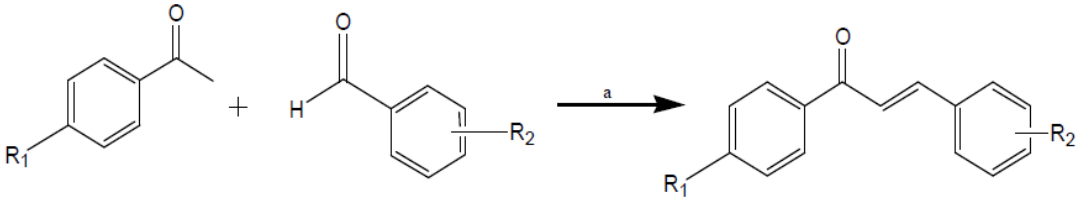
Reagents(a): Hydroxyapetite, H_2O, MWI.

Thirunarayanan G et al (50), have developed fly-ash H_2SO_4 catalysed solvent free synthesis of some aryl chalcones under microwave irradiation.



Reagent (a) Fly-ash, H_2SO_4, MWI, 480W.

Qiong Xu et al (51), discovered a novel solid acid catalyst, bamboochar sulfonic acid, prepared and applied in the synthesis of chalcones at high yields in a heterogeneous acid system under solvent free conditions.

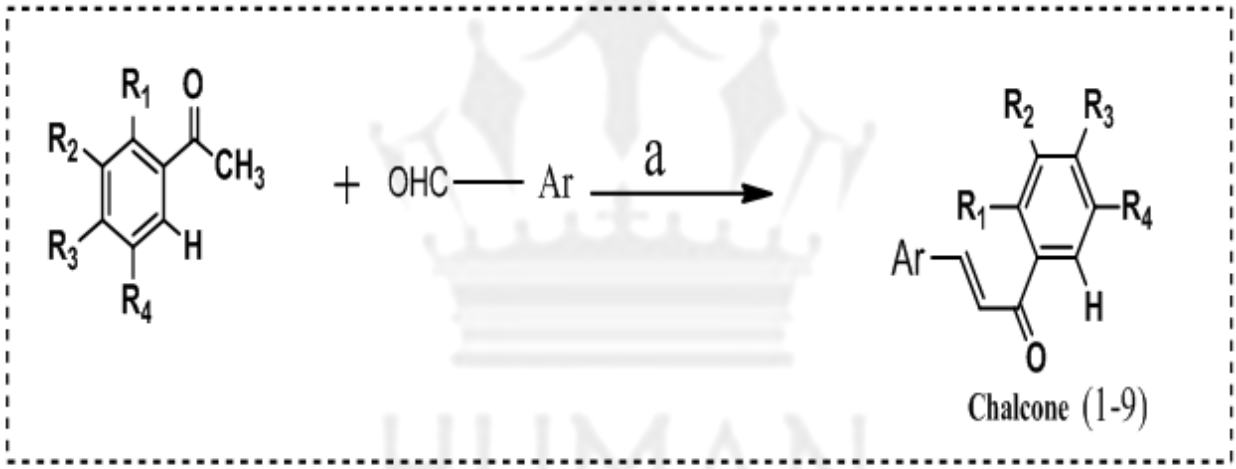


Reagents (a) Bamboochar sulfonic acid.

2.0 MATERIALS AND METHODS

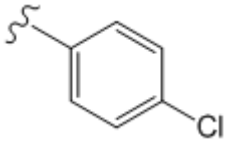
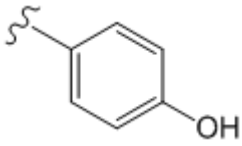
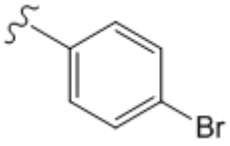
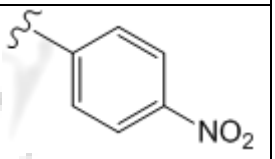
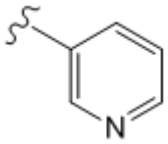
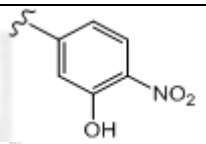
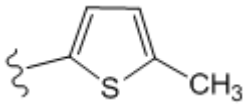
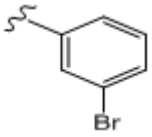
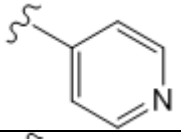
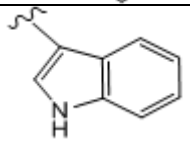
2.1 Experimental

Equimolar quantities of orthohydroxy acetophenone (0.01mol) and aromatic aldehyde (0.01mol) along with solid NaOH (0.02 mol) were homogenized in a mortar. The reaction mixture was poured onto an inert silica gel (mesh 230-400) 2.5gm. The reaction mixture was irradiated in a domestic microwave oven for 2-8min with a regular interval of 30 sec. After completion of the reaction (monitored by TLC) the content of the flask was cooled to R.T. Acetone (10ml) was added to the reaction mixture and filtered through filter paper to separate the solid catalyst (i.e. silica). The filtrate was poured onto crushed ice HCl to afford the solid product i.e. chalcones. The chalcones were recrystallized from glacial acetic acid.



Reagents (a): Solid NaOH, SiO_2, EtOH, MWI

Scheme-1. Synthesis of Chalcones

Comp. no	R_1	R_2	R_3	R_4	Ar
1	OH	I	H	Cl	
2	OH	I	H	Cl	
3	OH	I	H	Cl	
4	OH	I	H	Cl	
5	OH	I	H	Cl	
6	OH	I	H	Cl	
7	OH	I	H	Cl	
8	OH	I	H	Cl	
9	OH	I	H	Cl	
10	OH	I	H	Cl	

RESULTS AND DISCUSSION

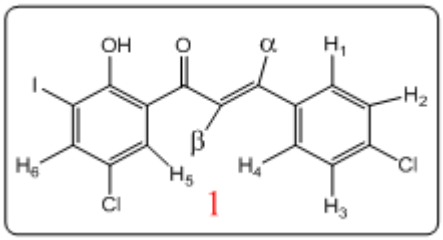
The synthesis of the chalcones was accomplished according to Claisen-Schmidt condensation of ortho hydroxy ketones with several aromatic aldehyde under microwave irradiation, as indicated to Scheme 1. The corresponding reactions proceeded smoothly and in good to excellent yields (75-90%). The newly synthesized chalcones were characterized by their chemical, physical and spectral analysis data and are further subjected to antimicrobial studies which exhibit moderate to good activity.

Table-1 Comparison of compounds under classical and microwave methods.

Comp. No	Mol. Formula	Reaction time	Yield %	Reaction time	Yield %	M.P.(°C)
		MW/Min	Yield%	Classical/ hrs	Yield %	
1	$C_{15}H_9O_2ICl_2$	5	80	24	72	120-122
2	$C_{15}H_{10}O_3ICl$	5	85	24	68	108-110
3	$C_{15}H_9O_2IBrCl$	7	75	24	70	190
4	$C_{15}H_9O_4INCl$	8	76	24	55	188-190
5	$C_{15}H_9O_2NICl$	6	78	24	65	136-138
6	$C_{15}H_9O_5INCl$	8	82	24	68	110-112
7	$C_{14}H_{10}ClO_2IS$	8	90	24	66	102-104
8	$C_{15}H_9O_2IBrCl$	5	85	24	70	170
9	$C_{15}H_9NIO_2Cl$	6	84	24	65	125-130
10	$C_{17}H_{11}O_2ClNI$	7	88	24	75	110

Spectral analysis of the compounds

The structure of the compounds were done by spectral analysis (IR, ^{1}H NMR, MASS) and the results of some chalcones are shown below :

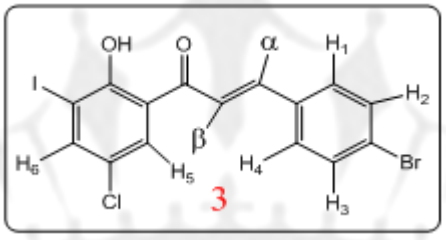


(E)-1-(5-chloro-2-hydroxy-3-iodophenyl)-3-(4-chlorophenyl)prop-2-en-1-one

Compound 1:- FTIR (KBr, cm^{-1}): 1639(C=O) ,1558(C=C), 1424(C-C Aromatic str) ,820(C-Cl).

^{1}HNMR:- 7.26(d, 1H,H_4), 7.34(d, 1H, H_2), 7.36(d,1H, H_α,J=15Hz,), 7.51(d, 1H,H_1), 7.86(d,1H, H_β,J=15Hz), 7.97(d,1H ,H_3), 8.27(s, 1H, H_5), 8.46(s, 1H, H_6), 13.29 (s, 1H, OH)

M.S. (m/z): (M)= 419(M^+) ,417 (M-2) .

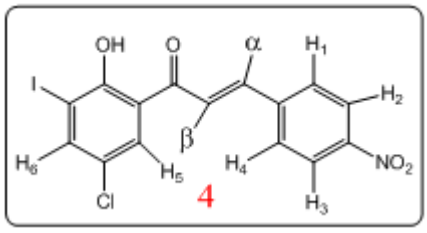


(E)-3-(4-bromophenyl)-1-(5-chloro-2-hydroxy-3-iodophenyl)prop-2-en-1-one

Compound 3:- FTIR (KBr, cm^{-1}): 1639(C=O) ,1570(C=C), 1427(C-C Aromatic str), 815(C-Cl), 860(C-Br).

^{1}HNMR:- 7.25(d, 1H,H_4), 7.51(d, 1H, H_1), 7.51(d, 1H,H_1) , 7.62(d,1H, H_α,J=15Hz,), 7.63(d,1H ,H_3), 7.90(d,1H, H_3), 8.00(d,1H, H $_\beta$,J=15Hz), 8.14(s, 1H, H_5), 8.50(s, 1H, H_6), 13.46 (s, 1H, OH).

M.S. (m/z): (M)= 462(M-1) ,464 (M+1) .



(E)-1-(5-chloro-2-hydroxy-3-iodophenyl)-3-(4-nitrophenyl)prop-2-en-1-one

Compound 4:- FTIR (KBr, cm^{-1}): 1657(C=O),1593(C=C), 1421(C-C Aromatic str), 1341(N-O symmetric), 697(C-Cl).

^{1}HNMR:- 7.21(d, 1H,H_2), 7.31(d, 1H, H_1), 7.32(d,1H, H_α,J=15Hz), 7.46(d, 1H,H_4), 7.54(d,1H ,H_3), 7.91(d,1H, H_β,J=15Hz), 8.1 (s, 1H, H_5), 8.39(s, 1H, H_6), 12.96 (s, 1H, OH) .

M.S. (m/z): (M)= 442(M+2).

Biological Evaluation of Synthesized Compounds:-

(A) Antimicrobial activity

Antimicrobial screening was done using disc diffusion method (52) at a concentration of 500µg/ml.

Procedure:- The test was performed according to the disk diffusion method (52) adopted with some modification for the prepared compound using Penicillin and streptomycin as references. The prepared compounds were tested against one strain of Gram +ve bacteria, Gram –ve bactria, fungi. Whatman filter paper disk of 5mm diameter was sterilized by autoclaving for 15 min at 121^0C. The sterile disk was impregnated with different compounds (600gm/disk). Agar plates were surface inoculated uniformly from the both culture of the tested microorganism. The disk was placed on the medium suitably spaced apart on the plate were incubated at 50^0C for 1 hr to permit good diffusion and then transferred to an incubator at 37^0C for 24hr for bacteria and 28^0C for 72hrs for fungi.

The compounds were evaluated for antibacterial activity against *Staphylococcus aureus* gr +ve, *Escherichia coli* gr –ve *Bacillus subtilis* gr +ve, *Pseudomonas aeruginosa* gr –ve , and antifungal activity against *Aspergillus oryzoe*, *Aspergillus niger*, DMSO was used as solvent control. The results of antimicrobial data are summarized in table 3. Most of compounds show good activity against bacteria and fungus.

Table 3. Antimicrobial activity of synthesized compounds

compounds	Gram positive bacterias		Gram negative bacterias		Fungus	
	Staph aureus	***Bacillus subtilis***	***Escherichia coli***	***Pseudomonas aeruginosa***	***Aspergillus oryzoe***	***Aspergillus niger,***
1	++	++	-	-	+	+
2	+	+	-	-	+	++
3	+	+	-	-	-	-
4	+	+	-	-	-	-
5	++	++	-	-	+	++
6	+	+	-	-	-	++
7	-	+	-	-	-	+
8	++	++	-	-	-	-
9	+	+	-	-	+	+
10	+	+	-	-	+	+
DMSO	-	-	-	-	-	-
Penicillin 1	++	-	-	+	x	x
Streptomycin 2	++	++	++	++	x	x
Greseofulvin	x	x	x	x	-	-

++ = Clear Zone of Inhibition, + = Minimum Zone of Inhibition, - = No Effect, X = Not applicable

Standard 1 Penicillin +, Standard 2 Streptomycin ++ (bacteria), Greseofulvin (fungus).

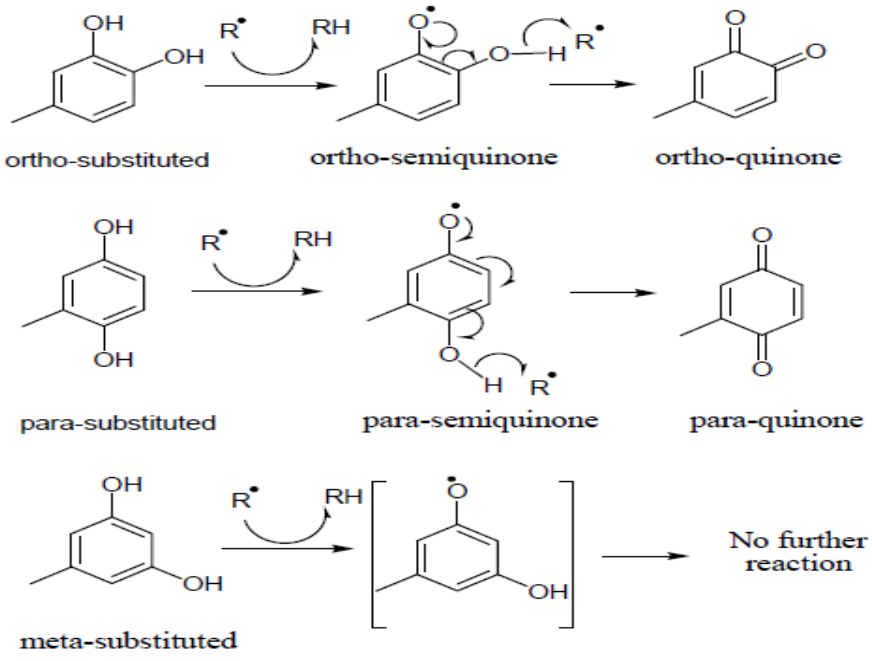
(B) Antioxidant Activity

Free radicals, including the superoxide radical (O2.-), hydroxyl radical (.OH), hydrogen peroxide (H_2O_2), and lipid peroxide radicals have been implicated in a number of disease processes, including asthma, cancer, cardiovascular disease, cataracts, diabetes, gastrointestinal inflammatory diseases, liver disease, macular degeneration, periodontal disease and other inflammatory processes. These radical oxygen species (ROS) are produced as a normal consequence of biochemical processes in the body and as a result of increased exposure to environmental and/or dietary xenobiotics. Antioxidants are the agents, which can inhibit or delay

the oxidation of an oxidisable substrate in a chain reaction. Chalcones belongs to the largest class of plant secondary metabolites. Which, in many cases, serve in plant defense mechanisms to counteract reactive oxygen species (ROS) in order to survive and prevent molecular damage and damage by microorganisms, insects, and herbivores. They are known to possess antioxidant character at various extents. The antioxidant activity of natural compounds like chalconoids is related to a number of different mechanisms such as free radical scavenging, hydrogen donation singlet oxygen quenching, metal ion chelation and acting as a substrate for free radicals such as superoxide and hydroxide.

Mechanism of antioxidant activity of chalcones (53)

When the chalcone molecules react with the radicals, they are readily converted to the phenoxy radicals due to the high reactivity of hydroxyl groups of chalcones. The ortho (i.e. catechol structure) and paradihydroxylated benzene ring system are generally known to delocalize electrons. As the phenoxy radicals occurring at the ortho- (i.e. catechol structure) or para-dihydroxylated benzene ring system are much more readily converted to a fairly stable semiquinone radicals while, meta dihydroxylated benzene ring system is comparatively less efficient to delocalize electrons as the phenoxy radicals occurring at the meta dihydroxylated ring system is converted to quinone structure which is not much stable.



The aliquot of different concentrations (50 to 100 µg/ml) of the test sample was added to 0.5ml of 0.003M DPPH in methanol. Final volume was adjusted to 3ml. Quercetin was used as a positive control. Negative control was prepared by using the same amount of DPPH mixed with only methanol devoid of samples. Absorbance values were measured at 517nm using Ultraviolet –Visible Spectrophotometer.

Absorbance was converted into % Antioxidant activity using the following equation [35]. The antioxidant activity data is presented in graphical pattern.(Table-3.1.1)

$$\text{Inhibition S (\%)} = \frac{100(A_0 - A_s)}{A_0}$$

Where A0 = Absorbance of control
(Containing all reagents except the test compound) AS= Absorbance of the test Compound

Comp no	Concentration (µg/ml)		
	50	**75**	**100**
1	40.52	48.54	62.69
2	40..96	45.64	60.56
3	38.66	40.87	60.89
4	47.68	56.62	74.52
5	44.91	51.83	66.56
6	46.51	53.82	69.77
7	35.73	37.52	58.62
8	35.96	36.51	56.65
9	41.61	50.68	64.69
10	45.68	52.61	67.73
Querecetin (standard)	56.73 5(µg/ml)	74.96 10(µg/ml)	89.96 20(µg/ml)

CONCLUSION

In the present study, an easy and useful method to synthesize biologically active chalcone, we have demonstrated the synthesis of chalcones using microwave irradiation. Antibacterial, antifungal and antioxidant ability of these compounds were evaluated. The newly synthesized chalcones were confirmed by spectral analysis and further evaluated for their antimicrobial activity. Antibacterial activity revealed that of the compounds showed good activity against the pathogens used. Compounds **4,6** showed excellent antioxidant activity. Since analogs **5,9,10** are showing promising results, studies to establish their *in vivo* efficacy and safety are being planned for further development.

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