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Research Article

MICROWAVE ASSISTED SYNTHESIS AND BIOLOGICAL EVALUATION OF SUBSTITUTED CHALCONES

Sandhya L. Borse[1*], Dr.Mukesh R. Patel[2] ,Laxmikant B. Borse[3]
[1]Shri Jagdishprasad Jhabarmal Tibrewala University, Govn. of Rajasthan, India.
[2]Shri B.M. Shah College of Pharmaceutical Education & Research, Modasa (Guj.), India
[3]P.S.G.V.P.M's College of Pharmacy ,Shahada, Dist.-Nandurbar (M.S.), India.
E mail:sandhyaborse27@rediffmail.com

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Abstract

Microwave induced organic reactions are gaining popularity over conventional technique for rapid organic synthesis. The main features are short reaction time & increased purity of resulting product. The rapid and highly efficient synthesis of chalcones can be achieved under microwave irradiation which results in improvement in yield and shorter reaction time. Among different chalcones, 1-[2',4'-dihydroxyphenyl]-3-[4-chlorophenyl]-2-propen-1-one,and 1-[2',4'dihydroxyphenyl]-3-[2-chlorophenyl]-2-propen-1-one showed good antioxidant activity.

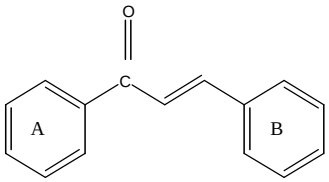
Keywords: Microwave synthesis, chalcones, antioxidant.

Introduction

In recent year, the application of microwave irradiation for promotion of organic reactions has received increasing attention. The technique has been used to assist in transfer hydrogenation, oxidation, aromatic substitution pericyclic reactions and many other process of significance to organic chemistry. In addition, the technique has also found application in the areas of inorganic and solid state synthesis. The application of microwave irradiation to chemical reaction has been shown to enhance significantly the rate of many process .In some cases, the technique has been used to promote reaction previously not observed under conventional thermal activation.

Chalcones

Chalcones are group of yellow pigments that are substituted benzalacetopheno derivatives.



Chalcones basic structure includes two aromatic rings bound by an α, β-unsaturated carbonyl group, a unique template associated with very diverse applications. Due to the presence of the reactive keto vinylenic group, chalcones and their analogues have been reported to be anti-angiogenic, analgesic and anticancer, antioxidant[21] but often they are cytotoxic in vitro. Some chalcones possess bactericidal, antifungal and insecticidal activity and some of their derivatives are reported to be Antimutagenic .Also, chalcones are well-known precursors of many naturally occurring pigments as flavones, and are used in many fields of applications such as UV-absorption filters in polymers, in different kinds of optical materials , in food industry and holographic recording technologies. Chalcones are the object of continuous experimental and theoretical investigations. They are flexible molecules capable of existence in various conformations, and their properties depend on a suitable ring substitution as well as on the presence of α, β -unsaturated ketone moiety. Chalcones exist as either the E- or the Z-isomers, the E-isomer being in most cases the thermodynamically most stable form and consequently, the majority of the chalcones is isolated as the E-isomer. Hydroxyl and phenyl substitutent are associated with antioxidant properties.

Considering the application of microwaves in organic synthesis, it was decided to study the synthesis of chalcones via the microwave method.

Objective

The purpose of this investigation was to synthesize different chalcones by conventional method as well as by microwave method & their biological evaluation and also the comparision between conventional method & microwave method with respect to yield and the reaction time.

Antioxidants

Antioxidants are compounds capable of preventing and even counteracting the damage caused in human tissue by the normal effects of physiological oxidation. Antioxidants can be nutrients such as vitamins and minerals or enzymes, the proteins present in the tissue that assist in certain chemical reactions. A lot of research has shown that antioxidants can play a role in preventing the development of some chronic diseases. Considerable progress in biological and medical research has been made in recent years in relating specific diseases to the oxidation process. In addition to those mentioned previously, diseases such as atherosclerosis, emphysema, iron overload, malaria, muscular dystrophy, retinal degeneration, and rheumatoid arthritis are but a few examples where research has shown the likelihood of direct links and the possibility of positive dietary and perhaps even nutraceutical interventions.

Materials & Methods

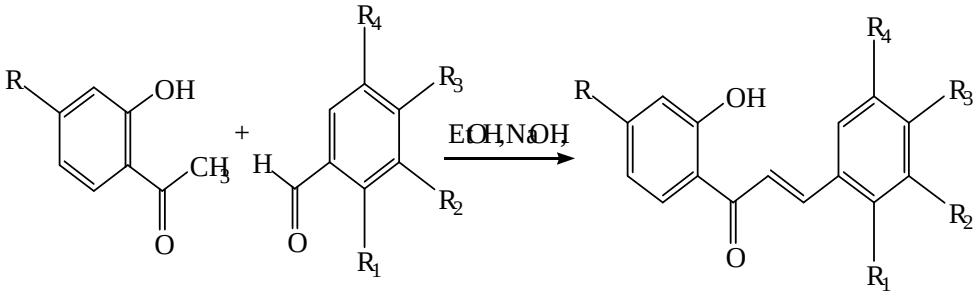
Melting points were taken in open glass capillary using Elico melting point apparatus and were uncorrected. Thin layer chromatography was done with silica gel G as adsorbent. The spots were detected by exposure to iodine vapours and UV cabinet. Infra–red spectra of compounds were recorded on "Schimadzu I.R.408" spectrophotometer model. GC-MS spectra were recorded on Perkin Elmer Auto System exel gas chromatography in MGV'S college of pharmacy, Nashik. Proton ^{1}H Nuclear Magnetic Resonance spectra of compounds were recorded on Brooot spectrophotometer(300MHz) using $CDCl_3$ as solvent at IIT, Bombay. All microwave reactions were carried on Raga's Electromagnetic system with automatic power setting from p-1 to p-10. Initially reactions were started at every 10 seconds and after every 10seconds reaction mixture was monitored for completion of the reaction with the help of TLC.

Following solvent systems were used for thin layer chromatography.

Benzene:Ethyl acetate 8:2

Synthesis of Chalcones (Conventional method)

Scheme:



A) Synthesis of 1-(2',4'-dihydroxyphenyl)-3-phenyl-2-propen-1-one.

Mixture of corresponding acetophenone (1 mole) and the corresponding aldehyde (1mole) in anhydrous ethanol was stirred at room temperature during 5mins. Then NaOH (3moles) was added. The reaction mixture was stirred at room temperature until aldehyde consumption. After that , HCL was added until neutrality. In case of the precipitated chalcones , they were filtered and recrystalized from ethanol.

B) Synthesis of 1-(2',4'-dihydroxyphenyl)-3-(4-methoxyphenyl)-2-propen-1-one.

Compound B was prepared by reacting 1mole of 4-methoxybenzaldehyde and 1mole of 2,4-dihydroxyacetophenone using similer procedure as given for the preparation of A.

C) Synthesis of 1-(2',4'-dihydroxyphenyl)-3-(4-chlorophenyl)-2-propen-1-one.

Compound C was prepared by reacting 1mole of 4-chlorobenzaldehyde and 1mole of 2,4-dihydroxyacetophenone using similer procedure as given for the preparation of A. The

D) Synthesis of 1-(2',4'-dihydroxyphenyl)-3-(2-chlorophenyl)-2-propen-1-one.

Compound D was prepared by reacting 1mole of 2-chlorobenzaldehyde and 1mole of 2,4-dihydroxyacetophenone using similer procedure as given for the preparation of A.

E) Synthesis of 1-(2',4'-dihydroxyphenyl)-3-(4-dimethylaminophenyl)-2-propen-1-one

Compound E was prepared by reacting 1mole of 4-dimethylaminobenzaldehyde and1mole of 2-hydroxyacetophenone using similer procedure as given for the preparation of A.

F) Synthesis of 1-(2'- hydroxyphenyl)-3-(4-dimethylaminophenyl)-2-propen-1-one

Compound F was prepared by reacting 1mole of 4-dimethylaminobenzaldehyde and 1mole of 2,4-dihydroxyacetophenone using similer procedure as given for the preparation of A.

G) Synthesis of 1-(2'-hydroxyphenyl)-3-(4-chlorophenyl)-2-propen-1-one.

Compound G was prepared by reacting 1mole of 4-chlorobenzaldehyde and 1mole of 2,4-dihydroxyacetophenone using similer procedure as given for the preparation of A.

H) Synthesis of 1-(2'-hydroxyphenyl)-3-(4-dimethylaminophenyl)-2-propen-1-one.

Compound Hwas prepared by reacting 1mole of 4-chlorobenzaldehyde and 1mole of 2,4-dihydroxyacetophenone using similer procedure as given for the preparation of A.

Synthesis of Chalcones (Under microwave)

A) Synthesis of 1-(2',4'-dihydroxyphenyl)-3-phenyl-2-propen-1-one.

To a solution of 2,4-dihydroxyacetophenone (1mole) and benzaldehyde (1mole) in dry ethanol (20ml), 3 moles of sodium hydroxide pallets were added and the reaction mixture was irradiated under microwave. The reaction was monitored by TLC for completion of reaction. After TLC shows different spots it was poured in cold water containing 10% HCl and allowed to precipitate the product, then washed with water until neutral to litmus. The product was recrystallised from ethanol.

B) Synthesis of 1-(2',4'-dihydroxyphenyl)-3-(4-methoxyphenyl)-2-propen-1-one.

Compound B was prepared by reacting 1mole of 4-methoxybenzaldehyde and 1mole of 2,4-dihydroxyacetophenone using similer procedure as given for the preparation of A.

C) Synthesis of 1-(2',4'-dihydroxyphenyl)-3-(4-chlorophenyl)-2-propen-1-one.

Compound C was prepared by reacting 1mole of 4-chlorobenzaldehyde and 1mole of 2,4-dihydroxyacetophenone using similer procedure as given for the preparation of A.

D) Synthesis of 1-(2',4'-dihydroxyphenyl)-3-(2-chlorophenyl)-2-propen-1-one.

Compound D was prepared by reacting 1mole of 2-chlorobenzaldehyde and 1mole of 2,4-dihydroxyacetophenone using similer procedure as given for the preparation of A.

E) Synthesis of 1-(2',4'-dihydroxyphenyl)-3-(4-dimethylaminophenyl)-2-propen-1-one.

Compound E was prepared by reacting 1mole of 4-dimethylaminobenzaldehyde and 1mole of 2-hydroxyacetophenone using similer procedure as given for the preparation of A.

F) Synthesis of 1-(2'- hydroxyphenyl)-3-(4-dimethylaminophenyl)-2-propen-1-one.

Compound F was prepared by reacting 1mole of 4-dimethylaminobenzaldehyde and 1mole of 2,4-dihydroxyacetophenone using similer procedure as given for the preparation of A.

G) Synthesis of 1-(2'-hydroxyphenyl)-3-(4-chlorophenyl)-2-propen-1-one.

Compound G was prepared by reacting 1mole of 4-chlorobenzaldehyde and 1mole of 2,4-dihydroxyacetophenone using similer procedure as given for the preparation of A.

H) Synthesis of 1-(2'-hydroxyphenyl)-3-(4-dimethylaminophenyl)-2-propen-1-one.

Compound H was prepared by reacting 1mole of 4-chlorobenzaldehyde and 1mole of 2,4-dihydroxyacetophenone using similer procedure as given for the preparation of A.

Antioxident activity:

a. DPPH scavenging activity:

Antiradical activity of Compounds was performs by DPPH model stock solution of DPPH (1.3mg/ml) in methanol was prepared. 100µl of stock solution of DPPH was added in 3ml of methanol and absorbance at 516nm was taken. The various concentrations of Compounds (25, 50, 75, 100, 125 µg/ml) were prepared. In all diluted Solutions, 100µl of stock solution of DPPH was added than absorbance was recorded at 516nm and Ec_{50} was calculated against methanol as a blank. % Inhibition = [Blank – Test]/Blank ×100

b. **Nitric oxide scavenging activity**:

To each solution, 1ml Sodium Nitroprusside solution was added and incubated for 2.5hrs. At 37^0C.After incubation baseline was taken with methanol and 1ml Sodium nitroprusside Solution was used as blank. Griess reagent and methanol was added immediately before recording of readings. Readings were recorded at 546nm. % Inhibition = [Blank – Test]/Blank ×100

c. Hydrogen peroxide scavenging activity:

Hydrogen peroxide scavenging activity was measured with titrimetric method of estimation.1ml of compunds concentration was mixed with 1ml of 0.1mM of H_2O_2 , 2 drops of 3% Ammonium molybate indicator ,10ml sulphuric acid and 7ml of 2M KI .The mixed solution was titrated with 5mM sodium thiosulphate until yellow color disappeared ,Ascorbic acid was used as positive control and percentage hydrogen scavenging was determined.

% Inhibition = [Blank – Test]/Blank ×100

d. Assay for phenyl hydrazine induced haemolysis of erythrocytes (membrane stabilization study):

The erythrocyte suspension 20% PCV (packed cell volume) of human blood was prepared and assay was carried out according to the procedure described by Cazana et al. The method involves the incubation of mixture containing 1 ml of phenyl hydrazine hydrochloride (0.5 mM), different concentration of compounds and 0.1 ml of 20 % erythrocyte suspension and final volume made to 3.0 ml by phosphate buffer solution. The mixture was incubated at 37^0 C for 1 hour and then centrifuged at 1000 g for 10 min. The absorbance of supernatant was measured at 540 nm. Suitable blank was also carried out to nullify the effect of solvents and inherent haemolysis. α-tocopherol was used as a positive control for the inhibition of phenylhydrazine induced haemolysis of erythrocytes. % Inhibition was calculated using following formula.

% Inhibition = [Blank – Test]/Blank ×100

Results and Discussion

Synthetic aspect

In the present investigation some new hydroxychalcones were successfully synthesized using both conventional method and microwave method.In the conventional method 2'-hydroxychalcones were synthesized by Claisen-Schmidt reaction by catalytic condensation of substituted benzaldehydes with ortho-hydroxyacetophenone using sodium hydroxide as a catalyst and ethanol as a solvent such a condensation essentially requires active methylene moiety in the ketone used in the reaction. This reaction takes 12-15 hours in conventional method whereas in microwave method they have been optimally synthesized within 1-5 mins. with appropriate power setting and time

setting. Thus microwave synthesis of chalcones are found to be undoubtedly more Economic, Efficient, Ecofriendly and Convenient than other reported methods as the equipment is cheap, and reagents required are also cheap.

Table 1: Comparison between conventional and microwave method in synthesis of Chalcones.

Comp code	R	R1	R2	R3	R4	Reaction Time		Yield [%]		Practical Melting point [◦c]	Lit. melting Point [◦c]	Rf Value
						X [Hrs]	Y [Min]	X	Y			
1	OH	H	H	H	H	12	2.5	78	89	170-172	170	0.42
2	OH	H	H	OCH_3	H	12	2.4	72	82	195-196	194	0.7
3	OH	H	H	Cl	H	12	3	76	89	118-120	-	0.76
4	OH	Cl	H	H	H	12	2.5	82	92	105-108	-	0.58
5	OH	H	H	$N(CH_3)_2$	H	12	2.8	80	90	92-94	-	0.6
6	H	H	H	OCH_3	H	15	2.5	75	86	90-92	90-95	0.86
7	H	H	H	Cl	H	15	3	76	88	145-146	146-149	0.7
8	H	H	H	$N(CH_3)_2$	H	15	3	80	90	78-80	80-82	0.68

Biological evaluation:

All synthesized hydroxychalcones were found to possess antioxidant activity compared to that of standard [ascorbic acid and α-tocopherol] which was evaluated on four different methods namely.

1. DPPH [Diphenyl Picryl Hydrazine]

2. Hydrogen peroxide.

3. Nitric oxide scavenging model and

3. Phenyl hydrazine induced hemolysis of erythrocytes.

In the series of synthesized and evaluated 2',4'-dihydroxychalcones, 1-[2',4'-dihydroxyphenyl]-3-[4-chlorophenyl]-2-propen-1-one,and1-[2',4'dihydroxyphenyl]-3-[2-chlorophenyl] -2-propen-1-one, showed good activity compared to others.

In the series of synthesized and evaluated compounds of Flavanoid, electron withdrawing group at position four showed good activity.

The catechol (O-dihydroxy) group in the ring confers great scavenging ability. The 4-oxo (keto double bond at position 4 of the C ring), especially in association with the C2-C3 double bond, increases scavenger activity by delocalizing electrons from B ring.

Evaluation of Antioxidant activity:

Table 2: Observation for antioxidant activity in terms of DPPH method.

Figure 1: Graph showing DPPH scavenging activity of chalcone

Table 3: Observation for antioxidant activity in terms of Nitric oxide method.

Figure 2 :Graph showing Nitric oxide scavenging activity of chalcone

Table 4: Observation for antioxidant activity in terms of H_2O_2 method.

Figure 3: Graph showing H_2O_2 scavenging activity of chalcone

Table 5: Observation for antioxidant activity in terms of phenyl hydrazine hydrochloride induced hemolysis method.

Figure 4: Graph showing scavenging activity of chalcone by phenyl hydrazine hydrochloride induced hemolysis method**.**

Table-2: Observation for antioxidant activity in terms of DPPH method.

Comp	code	% Scavenging± SEM					IC_{50} ug/ml
		25ug/ml	50ug/ml	75ug/ml	100ug/ml	125ug/ml	
	1	14.09±0.349	26.03±0.058	40.01±0.211	54.19±0.086	65.68±0.151	94.03
	2	12.11±0.143	25.29±0.197	38.03±0.265	60.59±0.199	64.16±0.130	92.86
	3	18.05±0.889	35.10±0.070	58.56±0.161	66.19±0.185	72.13±0.065	75.13
	4	18.56±0.468	40.39±0.228	46.12±0.221	62.09±.135	68.12±0.186	81.09
	5	11.82±0.325	25.50±0.168	36.69±0.229	46.78±0.18	60.13±0.106	104.39
	6	12.10±0.172	22.40±0.14	28.52±0.217	40.16±0.336	56.60±0.164	117.26
	7	11.08±0.197	24.05±.0819	32.05±0.156	43.36±0.117	58.19±0.085	111.02
	8	8.46±0.201	15.39±0.102	32.13±0.167	45.19±0.367	50.32±0.176	118.8

STD (Ascorbic acid)	24.19±0.135 (5µg/ml)	43.21±0.066 (10µg/ml)	54.15±0.073 (15µg/ml)	75.1±0.127 (20µg/ml)	93.97±0.055 (25µg/ml)	12.00

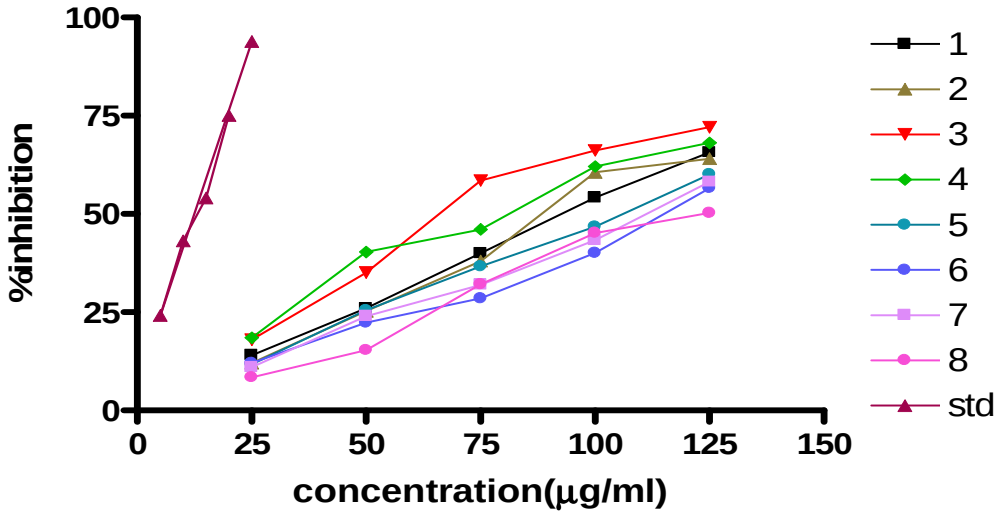


Figure 1: Graph showing DPPH scavenging activity of chalcone.

Table-3: Observation for antioxidant activity in terms of Nitric oxide method.

Compound code	**% Scavenging ±SEM**				**IC_{50} ug/ml**
	50 ug/ml	**100 ug/ml**	**200 ug/ml**	**400 ug/ml**	
1	21.01±0.297	30.33±0.146	55.02±0.200	73.03±0.231	222.18
2	19.89±0.163	25.62±0.122	58.89±0.121	67.03±0.225	238.7
3	22.89±0.261	30.32±0.13	72.86±0.147	80.92±0.180	177.3
4	21.76±0.234	38.43±0.097	67.68±0.150	78.88±0.215	176.68
5	18.01±0.110	23.56±0.222	58.01±0.170	70.22±0.219	236.29
6	20.01±0.100	28.39±0.065	59.01±0.139	64.20±0.236	243.34
7	19.32±0.127	24.10±0.160	55.52±0.078	65.32±0.171	252.92
8	15.56±0.195	28.56±0.117	50.13±0.211	61.02±0.173	277.23
STD [Ascorbic acid]	47.84±0.100 25ug/ml	58.14±0.0917 50ug/ml	72.12±0.199 75ug/ml	88.49±0.102 100ug/ml	28.66

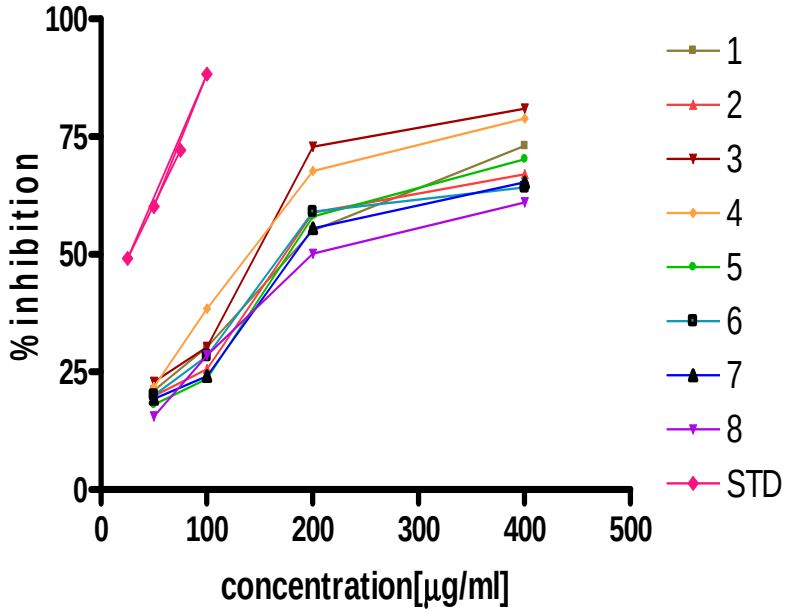


Figure 2: Graph showing Nitric oxide scavenging activity of chalcone.

Table-4: Observation for antioxidant activity in terms of H_2O_2 method.

Compound code	% Scavenging ±SEM				IC_{50} ug/ml
	50 ug/ml	100 ug/ml	200 ug/ml	400 ug/ml	
1	20.10±0.121	41.03±0.112	56.50±0.165	70.07±0.194	311.39
2	21.29±0.117	40.09±0.169	57.68±0.257	70.95±0.288	206.62
3	26.56±0.197	44.46±0.184	64.04±0.176	76.11±0.286	166.25
4	22.10±0.206	45.01±0.128	60.05±0.165	74.58±0.197	184.02
5	17.13±0.239	35.56±0.187	54.40±0.185	66.07±0.176	239.68
6	16.18±0.207	30.01±0.140	53.84±0.293	56.00±0.138	289.92
7	17.15±0.325	34.68±0.297	55.39±0.190	68.12±0.517	232.83
8	13.19±0.192	24.09±0.170	45.66±0.266	54.09±0.202	326.44
STD [Ascorbic acid]	30.88±0.278 25ug/ml	64.09±0.0954 50ug/ml	75.66±0.142 75ug/ml	90.10±0.105 100ug/ml	39.30

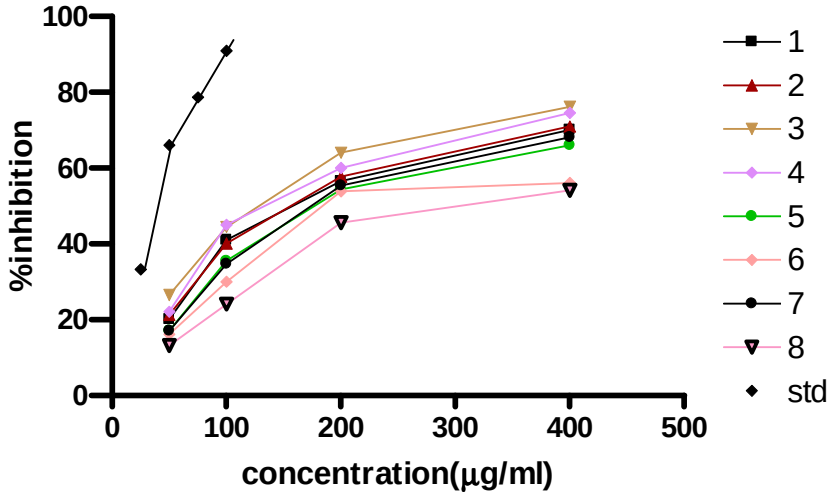


Figure 3: Graph showing H_2O_2 scavenging activity of chalcone

Table-5: Observation for antioxidant activity in terms of phenyl hydrazine hydrochloride induced hemolysis method.

Compound code	% Scavenging ±SEM				IC_{50} ug/ml
	50 ug/ml	100 ug/ml	200 ug/ml	400 ug/ml	
1	20.10±0.244	35.1±0.176	47.85±0.440	55.85±0.379	298.59
2	12.62±0.105	25.09±0.158	39.78±0.246	51.66±0.271	356.12
3	29.96±0.343	34.23±0.193	56.23±0.247	65.50±0.204	221.29
4	31.01±0.182	46.73±0.344	58.50±0.213	67.28±0.255	177.93
5	10.89±0.308	24.11±0.204	40.39±0.251	46.03±0.406	399.02
6	10.83±0.160	22.07±0.197	34.74±0.351	42.39±0.249	455.87
7	12.61±0.140	24.58±0.286	36.34±0.419	45.47±0.295	421.07
8	15.09±0.251	28.95±0.323	35.84±0.380	45.20±0.312	434.49
STD [toco pherol]	39.4±0.162 25ug/ml	47.2±0.185 50ug/ml	65.6±0118. 75ug/ml	76.1 ±0.137 100ug/ml	41.98

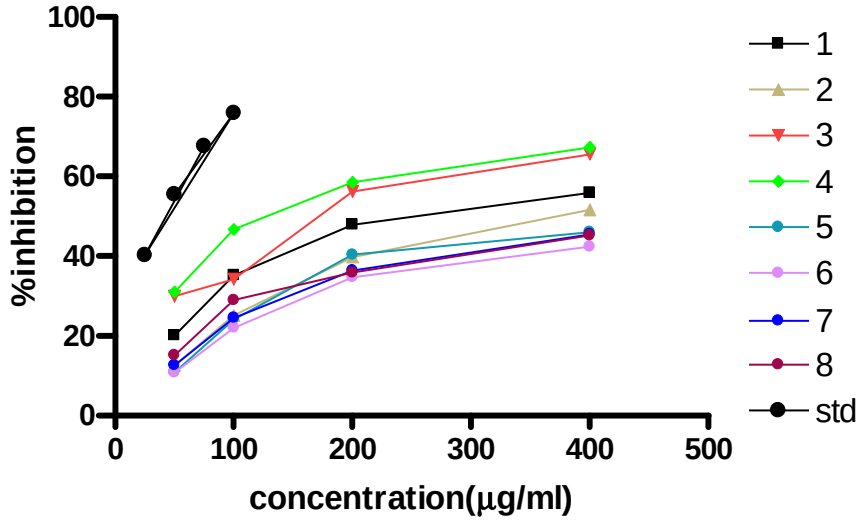


Figure 4: Graph showing scavenging activity of chalcone by phenyl hydrazine hydrochloride induced hemolysis method.

Conclusion:

- The rapid and highly efficient synthesis of chalcones can be achieved under microwave irradiation which results in improvement in yield and shorter reaction time.
- Among different chalcones, 1-[2',4'-dihydroxyphenyl]-3-[4-chlorophenyl]-2-propen-1-one,and1-[2',4'dihydroxyphenyl]-3-[2-chlorophenyl]-2-propen-1-one, showed good antioxidant activity.

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Corresponding Author:

Sandhya L. Borse[1*],

E mail:sandhyaborse27@rediffmail.com