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# A comparative study on synthesis of some novel α,β-unsaturated carbonyl derivatives and their antioxidant potential

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ABSTRACT

Free radicals are constantly formed in human system either as accidental products during metabolism or deliberately during the process of phagocytosis or due to environmental pollutants, ionizing radiations, ozone, heavy metal poisoning, etc. It is found from literature survey that chalcones (α,β-unsaturated carbonyl derivatives) exhibit great antioxidant activity. Hence, the synthesis of some new chalcone derivatives was undertaken and were synthesized by two methods namely, conventional and microwave irradiation methods. The synthesized chalcone derivatives were tested for their *in vitro* antioxidant activity by using NBT-superoxide free-radical scavenging activity and DPPH radical scavenging activity. The potency of the chalcone derivatives was estimated by $IC_{50}$ values and they have shown promising antioxidant activity. Among all the chalcones synthesized, derivative **3e** showed maximum superoxide inhibition as per NBT method and all the derivatives have shown different percentage inhibitions at different concentrations as per DPPH method. The compounds were characterized by $^1$H NMR and IR spectral analysis.

## 1. Introduction

Chalcones are 1,3-diphenyl-2-propene-1-one [1,2], in which two aromatic rings are linked by a three carbon α,β-unsaturated carbonyl system. These are abundant in edible plants and are considered to be the precursors of flavonoids and isoflavonoids. Chalcones are synthesized by Claisen-Schmidt condensation, which involves cross aldol condensation of appropriate aldehydes and ketones by base catalyzed or acid catalyzed followed by dehydration. Chalcone is a common natural pigment and one of the important intermediate in the biosynthesis of flavonoids [3]. Synthetic and naturally occurring chalcones have been extensively studied and developed as one of the pharmaceutically important molecules [4,5]. Chalcone derivatives are screened for their anti-inflammatory activity [6], chemopreventive activity [7], cardiovascular disease [8], anticancer activity [9], cytotoxic activity [10], antiprolifirative activity [11], antimalarial activity [12], antiviral activity [13], anti-HIV activity [14]. Therefore, in the present investigation it was considered worthwhile to synthesize some new chalcone derivatives by conventional and microwave irradiation methods and comparison 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 effect of microwave irradiation is due to the combination of both thermal and non-thermal effects. It is characterized by spectacular accelerations produced in many reactions, which cannot be observed in classical heating [15-17].

The synthesized compounds were purified by recrystallization and chromatography. The compounds were characterized by $^1$H NMR and IR analysis. The compounds were tested for their potential antioxidant activities by standard methods.

## 2. Experimental

### *2.1. Instrumentation*

All the melting points of the derivatives were determined by digital melting point apparatus (SMP 10). The NMR spectra were recorded on a BRUKER DRX 400 spectrometer at 400 MHz ($^1$H). IR spectra were recorded using an ALPHA FT-IR spectrometer (Bruker). High resolution mass spectra were obtained on Agilent 6100 Series Single Quadrupole LC/MS. Precoated TLC plates from Merck were used. Commercial compounds were purchased from Aldrich Chemical Co.

### *2.2. General procedure for the synthesis of chalcones (3a-3g) by Claisen-Schmidt condensation*

#### *2.2.1. Conventional method*

Claisen-Schmidt condensation [18-23] of chalcones by conventional method involves addition of equimolar quantities (0.001 mol) of 2-acetyl-5-chloro-thiophene and respective aldehydes (0.001 mol) [5].


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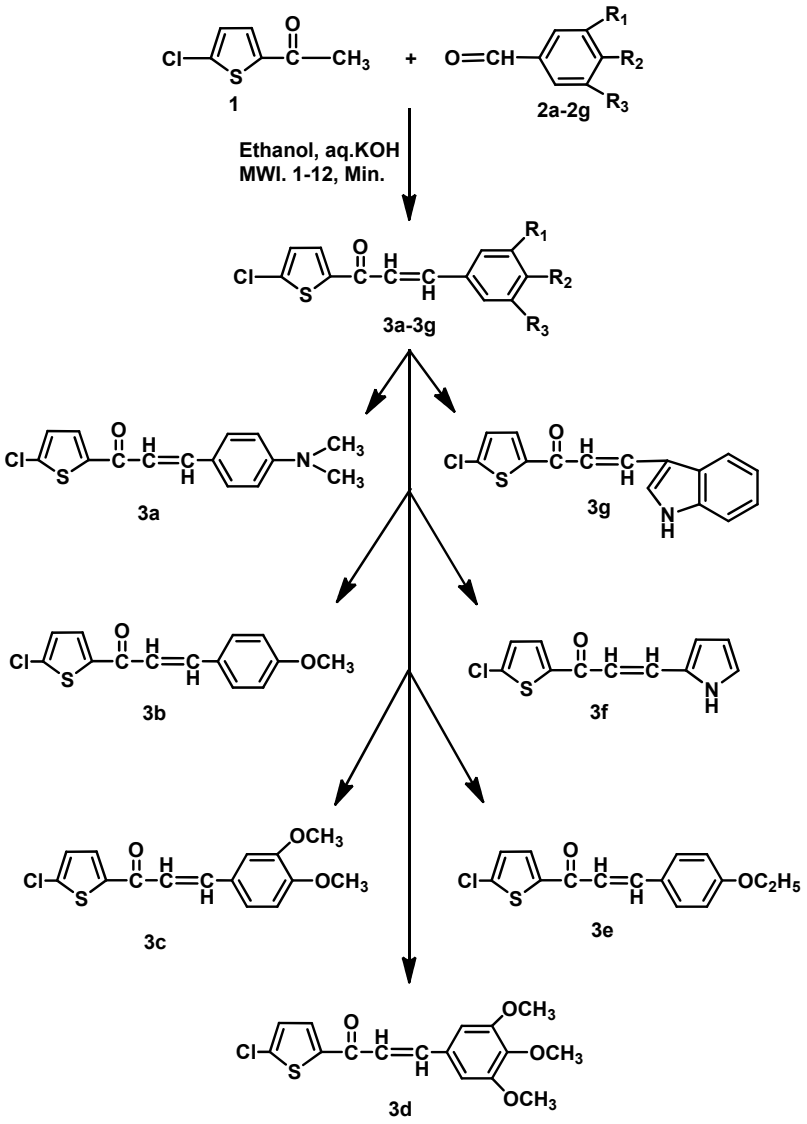


$R_1$ = H (**3a**), H (**3b**), $OCH_3$ (**3c**), $OCH_3$ (**3d**), H (**3e**).
$R_2$ = $NH(CH_3)_2$ (**3a**), $0CH_3$ (**3b**), $OCH_3$ (**3c**), $OCH_3$ (**3d**), $OC_2H_5$ (**3e**).
$R_3$ = H (**3a**), H (**3b**), H (**3c**), $OCH_3$ (**3d**), H (**3e**).

**Scheme 1**

The reaction mixture was mixed and dissolved in minimum amount (3 mL) of alcohol. To this, aqueous potassium hydroxide solution (0.003 mol) was slowly added and mixed occasionally for 24 hrs, at room temperature. Completion of the reaction was identified by observing on precoated thin layer chromatography (TLC) plates. After completion of the reaction, the reaction mixture was poured into crushed ice, acidified with diluted HCl (if necessary). The separated solid was filtered and dried. It was purified by recrystallization or by column chromatography performed on silica gel (100-200 Mesh), using ethylacetate and hexane mixture as mobile phase (Scheme 1), (Tables 1 and 2) [5].

### *2.2.2. Microwave irradiation method (MWI)*

Equimolar quantities (0.001 mol) of acetyl heterocyclic compounds and respective aldehydes (0.001 mol) were mixed and dissolved in minimum amount (3 mL) of alcohol [5]. To this, aqueous potassium hydroxide solution (0.003 mol) was added slowly and mixed. The entire reaction mixture was microwave irradiated in Catalyst Scientific Microwave Oven, Model: CATA 2R, Range: 140-700W, Make: Catalyst System, Pune, India, for about 2-6 minutes at 180 watts [5].

*1-(5-chlorothiophen-2-yl)-3-[4-(dimethyl amino) phenyl] prop-2-en-1-one* (**3a**): Conventional yield: 54%. Microwave yield: 62%. M.p.: 128-130 $^oC$. FT-IR (KBr, $\nu_{max}$, $cm^{-1}$): 1625 (C=O), 1551 (HC=CH), 1317 (C-N-C), 772 (C-S). $^1H$ NMR (400 MHz, $CDCl_3$, δ, ppm): 3.05 (6H, s, C-4''-$N(CH_3)_2$), 6.77 (2H, d, *J* = 9.6 Hz, C-3'' and 5''-H), 6.98 (1H, d, *J* = 4 Hz, C-4'-H), 7.16 (1H, d, *J* = 16.2 Hz, CO-CH=), 7.52 (2H, d, *J* = 9.2 Hz, C-2'' and 6''-H), 7.61 (1H, d, *J* = 4 Hz, C-3'-H), 7.84 (1H, d, *J* = 16 Hz, Ar-C-H=). Anal. calcd. for $C_{15}H_{14}ClNOS$: C, 61.73; H, 4.62; S, 10.92. Found: C, 61.75; H, 4.64; S, 10.89%.

**Table 1.** Comparative reaction time and percentage yield of chalcone derivatives by conventional and microwave irradiation methods.

| Compound no | Molecular weight (g) | Reaction time | | Yield | |
|---|---|---|---|---|---|
| | | Conventional (hr) | MWI (min) | Conventional (%) | MWI (%) |
| 3a | 291.7 | 24 | 4.5 | 54 | 62 |
| 3b | 278.7 | 24 | 2.5 | 54 | 66 |
| 3c | 308.7 | 24 | 2.5 | 52 | 61 |
| 3d | 338.8 | 24 | 2.5 | 55 | 67 |
| 3e | 292.7 | 24 | 3.0 | 58 | 67 |
| 3f | 237.7 | 24 | 3.5 | 48 | 62 |
| 3g | 287.7 | 24 | 2.5 | 51 | 60 |

**Table 2.** $R_f$ values, melting point (M.p.) and elemental analysis data of chalcone derivatives.

| Compound no | $R_f$ value | M.p., °C | Elemental analysis, % | |
|---|---|---|---|---|
| | | | Calculated | Found |
| 3a | 0.58 | 128 ± 2 | C: 61.73 | C: 61.75 |
| | | | H: 4.62 | H:4.64 |
| | | | S: 10.92 | S:10.89 |
| 3b | 0.64 | 118 ± 2 | C: 60.24 | C: 60.21 |
| | | | H: 3.91 | H: 3.93 |
| | | | S: 11.48 | S: 11.45 |
| 3c | 0.57 | 130 ± 2 | C: 58.36 | C: 58.38 |
| | | | H: 4.07 | H: 4.1 |
| | | | S: 10.3 | S: 10.27 |
| 3d | 0.52 | 110 ± 2 | C: 56.8 | C: 56.78 |
| | | | H: 4.3 | H: 4.33 |
| | | | S: 9.4 | S: 9.43 |
| 3e | 0.61 | 134 ± 2 | C: 61.4 | C: 61.37 |
| | | | H: 4.28 | H: 4.3 |
| | | | S: 10.9 | S: 10.87 |
| 3f | 0.54 | 162 ± 2 | C: 55.53 | C: 55.51 |
| | | | H: 3.18 | H: 3.21 |
| | | | N: 5.86 | S: 5.84 |
| 3g | 0.46 | 158 ± 2 | C: 62.56 | C: 62.53 |
| | | | H: 3.41 | H: 3.38 |
| | | | N: 4.86 | N: 4.89 |

*1-(5-chlorothiophen-2-yl)-3-(4-methoxyphenyl) prop-2-en-1-one* (**3b**): Conventional yield: 54%. Microwave yield: 66%. M.p.: 118-120 °C. FT-IR (KBr, $\nu_{max}$, $cm^{-1}$): 1643 (C=O), 1587 (HC=CH), 1228 (C-O-C), 800 (C-Cl), 722(C-S). $^1$H NMR (400 MHz, $CDCl_3$, δ, ppm): 3.86 (3H, s, C-4''-$OCH_3$), 6.88 (2H, d, *J* = 8.4 Hz, C-3'' and 5''-H), 7.01 (1H, d, *J* = 4 Hz, C-4'-H), 7.18 (1H, d, *J* = 15.6 Hz, CO-CH=), 7.60 (2H, d, *J* = 8.4 Hz, C-2'' and 6''-H), 7.62 (1H, d, *J* = 4.4 Hz, C-3'-H), 7.83 (1H, d, *J* = 15.2 Hz, Ar-C-H=). Anal. calcd. for $C_{14}H_{11}ClO_2S$ : C, 60.24; H, 3.91; S, 11.48. Found: C, 60.21; H, 3.93; S, 11.45%.

*1-(5-chlorothiophen-2-yl)-3-(3,4-dimethoxyphenyl) prop-2-en-1-one* (**3c**): Conventional yield: 52%. Microwave yield: 61%. M.p.: 130-132 °C. FT-IR (KBr, $\nu_{max}$, $cm^{-1}$): 3084 (C-H), 1644 (C=O), 1586 (HC=CH), 1259 (C-O-C), 795 (C-Cl), 714(C-S). $^1$H NMR (400 MHz, $CDCl_3$, δ, ppm): 3.93 (3H, s, C-3''-$OCH_3$), 3.95 (3H, s, C-4''-$OCH_3$), 6.89 (1H, d, *J* = 8.2 Hz, C-5''-H), 6.99 (1H, d, *J* = 4 Hz, C-4'-H), 7.16 (1H, d, *J* = I5.2 Hz, CO-CH=), 7.22-7.26 (2H, d, *J* = 9.6 Hz, C-2''and 6''-H), 7.64 (1H, d, *J* = 3.6 Hz, C- 3'-H), 7.81 (1H, d, *J* = 16.2 Hz, Ar-C-H=). Anal. calcd. for $C_{15}H_{13}ClO_3S$: C, 58.36; H, 4.07; S, 10.3. Found: C, 58.38; H, 4.1; S, 10.27%.

*1-(5-chlorothiophen-2-yl)-3-(3,4,5-trimethoxyphenyl) prop-2-en-1-one (***3d**): Conventional yield: 55%. Microwave yield: 67%. M.p.: 110-112 °C. FT-IR (KBr, $\nu_{max}$, $cm^{-1}$): 3095 (C-H), 1646 (C=O), 1585 (HC=CH), 1217 (C-O-C), 819 (C-Cl), 769(C-S). $^1$H NMR (400 MHz, $CDCl_3$, δ, ppm): 1.57 (3H, s, C-4''-$OCH_3$), 3.91 (6H, d, *J* = 8 Hz, C-3'' and 5''-$OCH_3$), 6.84 (2H, s, C-2'' and 6''-H), 7.01 (1H, d, *J* = 4.2 Hz, C- 4'-H),7.22 (1H, d, *J* = 10.6 Hz, CO-CH=), 7.64 (1H, d, *J* = 4 Hz, C- 3'-H), 7.79 (1H, d, *J* = 9.4 Hz, Ar-C-H=). Anal. calcd. for $C_{16}H_{15}ClO_4S$: C, 56.8; H, 4.3; S, 9.4. Found: C, 56.78; H, 4.33; S, 9.43%.

*1-(5-chlorothiophen-2-yl)-3-(4-ethoxyphenyl) prop-2-en-1-one* (**3e**): Conventional yield: 58%. Microwave yield: 67%. M.p.: 134-136 °C. FT-IR (KBr, $\nu_{max}$, $cm^{-1}$): 1643 (C=O), 1585 (HC=CH), 1220 (C-O-C), 772 (C-S). $^1$H NMR (400 MHz, $CDCl_3$, δ, ppm): 1.40 (3H, t, C-4''-$OCH_3$), 4.10 (2H, dd, C-4''-$OCH_2$), 6.93 (2H, d, *J* = 9.6Hz, C-3'' and 5''-H), 6.98 (1H, d, *J* = 3.8 Hz, C-4'-H), 7.21 (1H, d, *J* = 15.8 Hz, CO-CH=), 7.56 (2H, d, *J* = 10 Hz, C- 2'' and 6''-H), 7.62 (1H, d, *J* = 4 Hz, C-3'-H), 7.82 (1H, d, *J* = 16 Hz, Ar-C-H=). Anal. calcd. for $C_{15}H_{13}ClO_2S$: C, 61.4; H, 4.28; S, 10.9. Found: C, 61.37; H, 4.3; S, 10.87%.

*1-(5-chlorothiophen-2-yl)-3-(1H-pyrrol-2-yl) prop-2-en-1-one* (**3f**): Conventional yield: 48%. Microwave yield: 62%. M.p.: 162-164 °C. FT-IR (KBr, $\nu_{max}$, $cm^{-1}$): 3242 (N-H), 1635 (C=O), 1545 (HC=CH), 1284 (C-N-C), 771 (C-S), 731 (C-Cl). $^1$H NMR (400 MHz, $CDCl_3$, δ, ppm): 4.10 (1H, m, N-H), 6.20 (2H, d, *J* = 8 Hz, C-3'' and 5''-H), 6.91 (1H, d, *J* = 8 Hz, C-4''-H), 7.21 (1H, d, *J* = 4 Hz, C-4'-H), 7.32 (1H, d, *J* = 15.6 Hz, CO-CH=), 7.61 (1H, d, *J* = 4.2 Hz, C- 3'-H), 7.84 (1H, d, *J* = 16 Hz, Ar-C-H=). Anal. calcd. for $C_{11}H_8ClNOS$: C, 55.53; H, 3.18; N, 5.86. Found: C, 55.51; H, 3.21; N, 5.84%.

*1-(5-chlorothiophen-2-yl)-3-(1H-indol-3-yl) prop-2-en-1-one* (**3g**): Conventional yield: 51%. Microwave yield: 60%. M.p.: 158-160 °C. FT-IR (KBr, $\nu_{max}$, $cm^{-1}$): 3212 (N-H), 1633 (C=O), 1519 (HC=CH), 1220 (C-N-C), 770(C-S). $^1$H NMR (400 MHz, $CDCl_3$, δ, ppm): 7.20 (1H, d, *J* = 4 Hz, C-4'-H), 7.22-7.27 (4H, m, C-4'', 5'', 6''and 7''-H), 7.53 (1H, d, *J* = 15.2 Hz, CO-CH=), 8.15 (1H, d, *J* = 4.2 Hz, C-3'-H), 8.28 (1H, d, *J* = 16 Hz, Ar-C-H=), 9.95 (1H, s, C- 3''-H), 12.13 (1H, s, N-H). Anal. calcd. for $C_{15}H_{10}ClNOS$: C, 62.56; H, 3.41; N, 4.86. Found: C, 62.53; H, 3.38; N, 4.89%.

### *2.3. Pharmacological activity*

#### *2.3.1. Antioxidant activity*

Free radicals are constantly formed in human system either as accidental products during metabolism or deliberately during the process of phagocytosis or due to environmental pollutants, ionizing radiations, ozone, heavy metal poisoning, cigarette smoking and chronic alcohol intake. Free radicals being highly reactive can oxidize biomolecules leading to tissue injury and cell death. In the present study, two *in vitro* antioxidant models 1,1-diphenyl-2-picrylhydrazyl radical ($DPPH^{\bullet}$) scavenging activity (as it is a model for lipophilic radicals which initiate lipid peroxidation) and nitro blue tetrazolium (NBT)-Riboflavin photo reduction method were used. The $IC_{50}$ values of chalcones, tested for their antioxidant

activity were also calculated. Solvent used in both the tests for compounds was DMSO (Dimethylsulfoxide).

### 2.3.2. Procedure for superoxide free-radical scavenging activity

#### 2.3.2.1. NBT-Riboflavin photo reduction method

Superoxide scavenging activity of the compounds was determined by McCord and Fridovich method [24], which depends on light induced superoxide generation by riboflavin and corresponding reduction of NBT [25-27]. The assay mixture contained EDTA (Ethylenediamine tetra-acetic acid) solution (6.6 mM) containing NaCN (3 µg), riboflavin (2 µM), NBT (50 µM), test substances and phosphate buffer (67 mM, pH = 7.8) in a final volume of 3 mL. The absorbances at 560 nm were measured, before and 15 minutes after illumination. All tests were run in triplicate and mean values were used to calculate percentage scavenging ability and $IC_{50}$ values were calculated (using linear regression analysis). The inhibitory effects of samples on the generation of superoxide anions were estimated by the equation (1).

$$\text{Percentage Inhibition} = [(A_0 - A_1) \times 100] / A_0 \quad (1)$$

where $A_0$ is the absorbance with no addition of sample $A_1$ is the absorbance with addition of sample.

#### 2.3.2.2. DPPH free-radical scavenging activity

DPPH (1,1-diphenyl-2-picrylhydrazyl) radical scavenging activity was measured by the method of Lamaison [28]. The reaction mixture contained 1.5 x $10^{-7}$ M methanolic solution of DPPH and various concentrations of the test substances and were kept in darkness for 50 minutes. Optical density (OD) of samples was measured at 517 nm against a blank, and $IC_{50}$ values were calculated (using linear regression analysis) by plotting a graph, taking concentration on X-axis and percentage inhibition on Y-axis. The $IC_{50}$ values were obtained by drawing a line from Y-axis and aligning with the concentration on X-axis at 50% of percentage inhibition.

## 3. Results and discussion

The *in vitro* antioxidant activity and scavenging effects of the seven chalcones were evaluated by using different reactive species assay containing NBT-superoxide free-radical scavenging activity and DPPH free-radical scavenging activity. The potency of the chalcone derivatives was estimated by $IC_{50}$ values.

### 3.1. NBT-superoxide radical scavenging activity

All the chalcones (**3a**-**3g**) were found to scavenge the superoxides generated by photo-reduction of riboflavin. Among them, compounds **3e** showed maximum inhibition of superoxide radicals at concentrations of 25, 50 and 100 µg/mL and also the $IC_{50}$ values were found to be the best of all the synthesized derivatives. The remaining compounds (Table 3), exhibited less activity when compared to the above compounds at similar concentration levels.

Gallic acid, the known antioxidant was employed in the study for comparing the results, at concentrations of 0.25, 0.50 and 0.75 µg/mL; compound **3e** appeared to be the best among all the tested compounds. Few of the chalcone derivatives showed good percentage inhibition but their $IC_{50}$ values were more. Hence they were less potent among the tested compounds with respect to $IC_{50}$ values.

**Table 3.** Percentage inhibition of superoxide radical using NBT-riboflavin photo reduction method (Compounds **3a**-**3g**).

| Compounds | Quantity (µg/mL) | | | |
|---|---|---|---|---|
| | 25 µg/mL | 50 µg/mL | 100 µg/mL | $IC_{50}$, µg/mL |
| 3a | 30.18 | 41.55 | 64.40 | >100 |
| 3b | 16.04 | 18.45 | 20.23 | >100 |
| 3c | 28.07 | 32.51 | 34.68 | 90.97 |
| 3d | 23.58 | 33.33 | 53.69 | >100 |
| 3e | 17.03 | 11.85 | 4.36 | 20.33 |
| 3f | 30.18 | 40.93 | 54.66 | 76.25 |
| 3g | 37.85 | 43.69 | 59.74 | 83.71 |
| Gallic acid | 31.21 | 40.00 | 59.83 | 0.61 |
| | 0.25 µg/mL | 0.50 µg/mL | 0.75 µg/mL | |

### 3.2. DPPH-radical scavenging activity

The free radical scavenging activity of all the chalcones (**3a**-**3g**) were evaluated through their ability to quench the DPPH• using ascorbic acid as reference. All the synthesized derivatives have shown different percentage inhibitions at concentrations of 25, 50 and 100 µg/mL and also their $IC_{50}$ values were also calculated (Table 4). The percentage inhibitions of ascorbic acid were found at concentrations of 1.0, 2.5, 5.0 µg/mL.

**Table 4.** Percentage inhibition of free radicals using DPPH method (Compounds **3a**-**3g**).

| Compounds | Quantity (µg/mL) | | | |
|---|---|---|---|---|
| | 25 µg/mL | 50 µg/mL | 100 µg/mL | $IC_{50}$, µg/mL |
| 3a | 5.92 | 9.30 | 9.14 | >100 |
| 3b | 9.51 | 10.78 | 18.68 | >100 |
| 3c | 3.54 | 8.25 | 16.54 | >100 |
| 3d | 18.76 | 25.32 | 34.62 | >100 |
| 3e | 0.90 | 1.17 | 11.16 | >100 |
| 3f | 5.55 | 9.30 | 10.15 | >100 |
| 3g | 12.69 | 14.02 | 28.37 | >100 |
| Ascorbic acid | 16.13 | 38.11 | 62.34 | 3.81 |
| | 1.0 µg/mL | 2.5 µg/mL | 5.0 µg/mL | |

## 4. Conclusion

The synthesis of chalcones by conventional method and microwave irradiation method showed that MWI is a preferable method because of rapid synthesis and also higher yield of products. All the synthesized compounds were purified by recrystallization or by column chromatography. The characterization of compounds was established by single spot TLC, melting point and by spectral analysis involving IR, $^1$H NMR, Mass and elemental analysis. Since chalcones were widely reported to possess promising antioxidant activity. All the chalcone derivatives (**3a**-**3g**) were evaluated for the above mentioned activity. It was found that **3e** showed maximum inhibition of superoxide radicals, as per NBT method and all the derivatives have shown different percentage inhibitions at different concentrations as per DPPH method.

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