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Sayima Siddika
Chemistry Department,
Rajshahi University,
Rajshahi, Bangladesh.

Mst. Mahmuda Akter Reshma
Chemistry Department,
Rajshahi University,
Rajshahi, Bangladesh.

Mymuna Sabrina
Chemistry Department,
Rajshahi University,
Rajshahi, Bangladesh.

Md. Badrul Islam
Principal Scientific Officer &
Division In-Charge, Natural
Products Research Division,
BCSIR Laboratories,
Rajshahi, Bangladesh.

M. Azizul Islam
Chemistry Department,
Rajshahi University,
Rajshahi, Bangladesh.

Bilkis Jahan Lumbiny
Chemistry Department,
Rajshahi University,
Rajshahi, Bangladesh.

Correspondence:
Bilkis Jahan Lumbiny
Chemistry Department,
Rajshahi University,
Rajshahi, Bangladesh.

Effect of Radical Scavenging and Reducing Power Capacity Screening of Some Synthesized Substituted Methoxy Chalcones to Establish Their Potency as Additives

Sayima Siddika, Mst. Mahmuda Akter Reshma, Mymuna Sabrina, Md. Badrul Islam, M. Azizul Islam, Bilkis Jahan Lumbiny

Abstract
Different functional groups which are attached to the benzene ring of chalcones can be varied to enhance activity. Thus, the present study has been carried out by synthesizing four substituted methoxy chalcones; 4′– methyl – 2 – methoxychalcone (3a), 4′– benzyloxy – 2′, 4 – dihydroxy – 3 – methoxychalcone (3b), 3′, 4′, 5′, 2, 3, 4 – hexamethoxychalcone (3c), 2′, 6 – dihydroxy – 3 – methoxychalcone (3d) based on Claisen-Schimdt condensation method and characterized by spectral data UV, IR and ^{1}H NMR. The synthesized chalcones (3a-3d) were evaluated for *in vitro* radical scavenging activity using diphenylpicrylhydrazyl (DPPH) model as well as antioxidant activity using Fe reducing power capacity. Compound 3d showed highest activity in DPPH method (IC_{50}, 3.17) due to the presence of two phenolic –OH groups, capable to generate phenoxy radicals easily and stabilized by $–OCH_3$ over the wide delocalized π- system. All the chalcones especially dihydroxy methoxy chalcones showed appreciable reducing activity at lower concentration. Reducing power capacity also highest (3d, absorbance 0.016 at 10 µg/mL). Therefore, compound 3d has a high potency in the future new template for antioxidant as well as health beneficiary chemical additive.

Keywords: Methoxy Chalcones, Claisen-Schmidt method, Radical Scavenging, Reducing power capacity, Antioxidant, Chemical Additives.

1. Introduction

Bangladesh is an agrobased economic country and mostly rely on agriculture as well as rapid advancing industries like textile, leather, food, cosmetics etc.[1] Tropical climate of Bangladesh is a major challenge for the storage and proper management of all these agro or industrial products as it allows quick spoilage of food and other products due to microbial growth and air oxidation.[2] Health beneficiary chemical preservatives[3] having antioxidant properties are highly needed to reduce autoxidation process thus to achieve a sustainable economic growth.

Chalcones [4] is a collective name of natural and synthetic color pigment like compounds with a Benzylideneacetophenones or 1,3-diaryl-2-propen-1-one (IUPAC name) moiety (Fig. 1). Chalcone molecule is a class of flavonoid intermediates often obtained from natural or synthetic sources.[5] Chalcone (polyhydroxylated) bears a very good synthon, especially reactive ketoethylenic group –CO–CH=CH– so that variety of novel heterocyclic with good pharmaceutical profile can be designed.

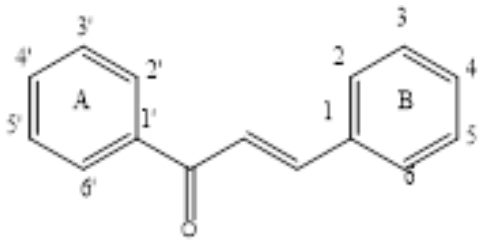


Fig. 1: General structure of chalcone.

The coloration and biological effects of chalcone pigments were found to be highly dependent on the presence, the number and position of electron donating or withdrawing functional groups such as methoxy, glycosides, hydroxyl, halogens in both A and B rings. Some of the compounds namely 2-hydroxy- 4-methoxy-3',4'-(2"- hydroxy methyl-1", 4" - dioxano) chalcone and 2-hydroxy- 4, 6 - dimethoxy-3',4'-(2"- hydroxy methyl-1", 4"- dioxano) chalcone showed a potent antihepatotoxic activity.[6] Chalcones with proper substitution have recently been isolated from *Broussonetia papyrifera* known to selectively inhibit enzymes like protein tyrosine phosphatase 1B (PTP1B) and aldose reductase.[6] Their antioxidant property attracted to explore hybrid structures as antihyperglycemic agents, because oxidative stress also plays an important role in diabetic patients leading to vascular complications. Mono methoxy series showed blood glucose lowering activity. Compounds vicinally deoxygenated as dimethoxy and methylenedioxy substitution showed the best antihyperglycemic activity when compared to the corresponding monomethoxy compounds. 3, 4-Dimethoxy compound displayed significant antihyperglycemic effect.[6] Licochalcone A, an oxygenated chalcone with methoxy moiety, a chalconoid derived from root of *Glycyrrhiza inflata*, has been known to possess a wide range of biological functions such as antitumor, anti-angiogenesis, antiparasitic, anti-oxidant, antibacterial and anti-inflammatory effects. [7]

Modification as well as improved biological activities can be achieved by laboratory synthesis of compounds like chalcones. Insertion of new substituent groups in different position specially in benzene ring may produce many analogues of naturally occurring chalcones and their derivatives. Introduction of hydrophilic functionality methoxy group at different position of benzene nucleus moiety of chalcone were done by synthesis. Important information about positional and electronic contribution effect of methoxy group being studied by their bioactivity. Finally its efficacy as preservative and chemical additives being determined by various antioxidant activity.

In the present study four substituted chalcones were synthesized: 4′– methyl – 2 – methoxychalcone (3a), 4′– benzyloxy – 2′, 4 – dihydroxy – 3 – methoxychalcone (3b), 3′, 4′, 5′, 2, 3, 4– hexamethoxychalcone (3c), 2′, 6 – dihydroxy – 3 – methoxychalcone (3d) using Claisen-Schmidt condensation synthetic strategy (Scheme. 1). The synthesized chalcones (3a-3d) were evaluated for *in vitro* radical scavenging activity using 1, 1-diphenyl-2-picrylhydrazyl (DPPH) model. Observation for antioxidant activity is expressed in terms of percent scavenging of DPPH radical and the inhibitory concentration 50% (IC_{50}). The antioxidant activity was also measured in another method using reducing power capacity.

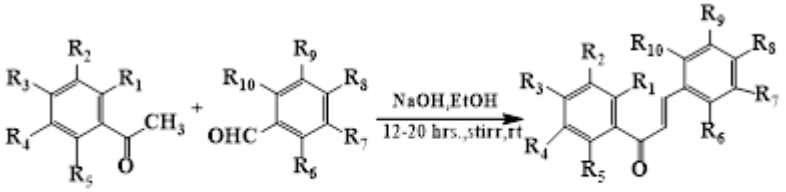
2. Materials and methods

2.1 Chemicals and apparatus

The substituted acetophenones (1a-1d) and substituted benzaldehydes (2a-2d) were purchased and employed together for the synthesis of substituted chalcones (3a-3d). Other necessary chemicals and reagent grade solvent were purchased from E-Merck or Sigma-Aldrich company and purified if required.

2.2 Synthesis of Substituted Chalcones (3a-3d)[8,9]

Four substituted chalcones were synthesized: 4′– methyl – 2 – methoxychalcone **(3a)**; 4′– benzyloxy – 2′, 4 – dihydroxy – 3 – methoxychalcone **(3b)**; 3′, 4′, 5′, 2, 3, 4– hexamethoxychalcone **(3c)**; 2′, 6 – dihydroxy – 3 – methoxychalcone **(3d)** using Claisen-Schmidt condensation method, a classical, very simple, inexpensive and easy to conduct synthetic strategy. The chalcones **(3a-3d)** were obtained from equimolar quantities of the corresponding acetophenones **(1a-1d)** as well as aldehydes **(2a-2d)** in presence of NaOH/EtOH as shown in (Scheme 1). The structures of the above compounds were assigned on the basis of spectral data; UV, IR and ^{1}H NMR.



1a. $R_3 = -CH_3$, 2a. $R_6 = -OCH_3$, 3a. $R_3 = -CH_3$, $R_6 = -OCH_3$
1b. $R_1 = -OH$, $R_3 = -OBz$, 2b. $R_7 = -OCH_3$, $R_8 = -OH$, 3b.
$R_1 = -OH$, $R_3 = -OBz$, 2b. $R_7 = -OCH_3$, $R_8 = -OH$
1c. R_2, R_3, $R_4 = -OCH_3$, 2c. R_6, R_7, $R_8 = -OCH_3$,
3c. R_2, R_3, R_4, R_6, R_7, $R_8 = -OCH_3$
1d. $R_1 = -OH$, 2d. $R_7 = -OCH_3$, $R_{10} = -OH$. 3d. R_1, $R_{10} = -OH$, $R_7 = -OCH_3$

Scheme 1 General synthetic root of chalcone (3a-3d).

2.3 Characterization of Synthesized Chalcones (3a-3d)

(i) 4′– methyl –2 – methoxychalcone, 3a

$C_{17}H_{16}O_2$, Solid and brown, yield 58%; m. p. 95-97 ºC, λ_{max} ($CHCl_3$ nm) ; 372.5, 256.1, IR (KBr, cm^{-1}): 3029.00 (C=C–H, olefinic, str), 2921.22 (aliphatic –C–H, asym.-str.), 2835.20 (aliphatic –C–H, sym-str.), **1636.05 (C=O, conjugated keto group)**, 1606.25, 1581.79 (C=C, aromatic), 1511.35, 1489.77, 1442.97, 1370.71 (–CH_3 bend), 1341.35, 1303.95, 1275.50, 1241.61, 1204.28, 1160.25, 1126.15 (C–O–C, str), 1024.72, 984.70, 833.20 (C–O str), 751.67, 661.74, 564.29 (C–H, bending aromatic),

(ii) 4′– benzyloxy – 2′, 4 – dihydroxy – 3 – methoxy chalcone, 3b

$C_{23}H_{20}O_5$, light brown solid, yield 60%; m. p. 86-88 ºC, λ_{max} ($CHCl_3$, nm) ; 273.5, 230.3, IR (KBr, cm^{-1}); 3428.90 (–OH, broad), 3029.00 (C=C –H, olefinic, str), 2930.96 (aliphatic –C–H, asym.-str.), 2860.73 (aliphatic –C–H, sym-str.), **1603.17 (C=O, conjugated keto group)**, 1507.14 (C=C, aromatic), 1453.05, 1434.78, 1365.33, 1325.75 (–CH_3 bend), 1250.87, 1184.80, 1133.62 (C–O–C, str), 1066.80, 1025.94, 1006.89, 982.75, 956.30 (C–O str), 913.06, 837.93, 815.27, 764.00, 714.83, 696.10, 653.99 (C–H, bending aromatic), ^{1}H NMR, δ_H (500 MHz, $CDCl_3$, 20H); 12.782 (s, 2H, –OH), 7.825 (d, 1H, *J* = 5.0 Hz), 7.630 (d, *J* = 10.0 Hz, 1H) 7.595 (d, *J* =15.0 Hz, 1H, C_β–H), 7.465 (d, *J* =15.0 Hz, 1H, C_α–H), 7.440 – 7.380 (m, 7H), 7.360 – 7.300 (m, 2H), 5.107 (bs, 2H, –$C\underline{H}_2$ – $C_6\underline{H}_5$), 3.968 (s, 3H, –$OC\underline{H}_3$)

(iii) 3′, 4′, 5′, 2, 3, 4– hexamethoxy chalcone, 3c

$C_{21}H_{24}O_7$; lemon yellow solid, yield 55%; m. p. 91-93 ºC , λ_{max} ($CHCl_3$, nm) ; 295.0, 232.1, IR (KBr, cm^{-1}): 3097.40 (C=C–H, olefinic, str.), 2940.89 (aliphatic C–H, asym.-str.) 2838.21 (aliphatic C–H, sym-str.), 1653.37 (s, C=O, conjugated keto group), 1586.07 (C=C, aromatic), 1496.05, 1465.65, 1416.43, 1343.80 (CH_3 bend), 1298.49, 1257.38, 1229.70, 1198.33, 1163.36, 1125.8 (C–O–C, str), 1093.77, 1037.14, 1000.60 (C–O str), 946.02, 852.98, 833.18, 805.27, 771.41, 692.96 (C–H, bending aromatic), ^{1}H NMR, δ_H (500 MHz, $CDCl_3$, 21H) ; 8.005 (d. 1H, *J* = 15.0 Hz C_β – H), 7.525 (d, *J* = 15.0 Hz, 1H, C_α– H), 7.415 (d. 1H *J* =5.0 Hz), 7.340 – 7.290 (m, 2H), 6.755 (d. 1H *J* =5.0 Hz) 3.990 (s, 18H, –OCH_3)

(iv) 2′, 6 – dihydroxy – 3 – methoxychalcone 3d

$C_{16}H_{14}O_4$; yellow solid, yield 65%, m. p. 122-124 ºC ; λ_{max} ($CHCl_3$, nm); 392.6, 311.7, IR (KBr, cm^{-1}): 3317.90 (–OH), 3034.70 (C=C–H, aromatic, str.), 3011.90 (C=C–H, olifinic, str.), 2954.83 (aliphatic C–H, asym.-str.), 2834.91 (aliphatic C–H, sym-str.), 1626.76 (C=O, conjugated keto group), 1581.31 (C=C, aromatic), 1559.58, 1502.90, 1472.44, 1448.19, 1424.73, 1357.57, 1318.84 (–CH_2 bend), 1286.86, 1260.37, 1239.03, 1200.45 (C–O–C, str), 1156.38, 1025.97 (C–O, str) , 984.17, 957.17, 849.32, 818.39, 746.82, 715.45 (C–H, bending aromatic) ^{1}H NMR, δ_H (500 MHz, $CDCl_3$, 14H) ; 12.921(s, 2H, –OH), 8.185 (d. 1H, *J* = 15.0 Hz C_β – H), 7.950 (d, 1H, *J* = 10 Hz), 7.825 (d, *J* = 15.0 Hz, 1H, C_α– H), 7.530 – 7.500 (m, 1H), 7.120 (bs, 1H), 7.050 (d, 1H, J = 10 Hz), 6.840 – 6.809 (m. 3H), 3.813 (s, 18H, –OCH_3)

2.4 Antioxidant Activity

Antioxidants are the agents, which can inhibit or delay the oxidation of an oxidisable substrate in a chain reaction.[6] Antioxidants may be defined as radical scavengers which protect the human body against free radicals that may cause pathological conditions such as ischemia, anemia, asthma, arthritis, inflammation, neuro degeneration, Parkinson's diseases, mongolism, aging process and perhaps dementias. [10] Antioxidant activity in terms of Radical scavenging activity is measured by DPPH method. [1,2, 3, 11] It has been reported that there is a direct correlation between antioxidant activities and reducing power of certain compounds. The reducing properties are generally associated with the presence of reductants, which have been shown to exert antioxidant action by breaking the free radical chain by donating a hydrogen atom. So, antioxidant activity is also measured by reducing power capacity.

2.4.1 Antioxidant Activity by DPPH method

The radical scavenging activity was measured using the method of Hatano *et al*. with some modifications.[12] Summarily, firstly, the stock solution of test samples were prepared by dissolving 1mg of test samples (3a-3d) in 1 mL of 70 % methanol. Six test tubes were taken to make aliquots of six kinds (1, 2, 5, 10, 15, 20 µg/mL) of concentrated solution. DPPH (0.004%) solution in 70% methanol was prepared and 2.5 mL of this solution was added to the equal volume of each test sample solution. After shaking, the mixture was maintained in dark for 30 mins. Then, the absorbance was measured at 517 nm against a blank. Ascorbic acid was used as standard references. The scavenging activity was calculated using the formula:

Scavenging Activity (%) = $[(A_{control} - A_{sample}) / A_{control}] \times 100$

Finally radical scavenging activities (%) are plotted against concentration of the sample solutions under investigation in MS Excel. The concentration for 50% scavenging, IC_{50} being determined from regression equation (Table 1) and compared with that of the standard (ascorbic acid). Smaller the IC_{50} value higher the activity.

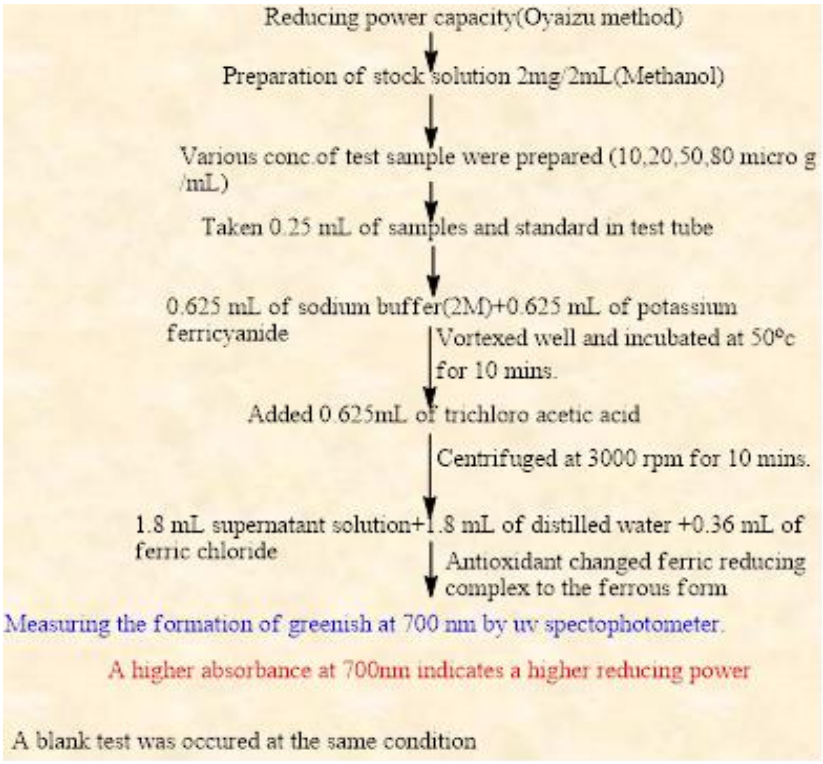
2.4.2 Antioxidant Activity by reducing power capacity

The reducing power of chalcones was determined by Oyaizu method.[2] The presence of reductants such as antioxidant substances in the samples causes the reduction of the Fe^{3+} - ferricyanide complex to the ferrous form by donating an electron. The amount of Fe^{2+} complex can then be monitored by the formation of Purl's Prussian blue or greenish color at 700 nm. The amount of Fe^{2+} complex can then be determined by measuring the formation of Purl's Prussian blue or greenish solution from yellow at 700 nm.

Fe^{3+}- ferricyanide + e^- = Fe^{2+} - ferricyanide

The stock solution of test samples were prepared by dissolving 1mg of test samples (3a-3d) in 1 mL of methanol. Four test tubes were taken to make aliquots of four kinds (10, 20, 50, 80 µg/mL) of concentrated solution. The schematic representation of the present study is mentioned in detailed in Scheme 2. The change in color from yellowish (before reduction) to greenish (after reduction) is shown in (Fig. 2).

Then, the absorbance was measured at 700 nm and against a blank as well. Butylated Hydroxytoluene (BHT) was used as standard references. The reducing power capacity is proportional to the absorbance at 700 nm. Higher the absorbance value higher the activity.



Scheme 2 Schematic Representation of Fe Reducing power Assay.

I II

Fig. 2: Test sample solution (Yellowish, I), turn into Greenish after reduction (II).

3. Results & Discussion

Chalcones basic structure includes two aromatic rings bound by α, β-unsaturated carbonyl group, a unique template associated with diverse application. Due to the presence of the reactive keto, vinylinic group, chalcones and their analogues have been reported to be antioxidant. Hydroxyl, methoxy and benzyloxy substituents are associated with antioxidant properties.

Methoxylated and hydroxylated chalcones are also well known for their powerful antioxidant activities. In fact, it has been reported in literature that natural chalcones carrying methoxyl and hydroxyl substitutions such as butein, isoliquiritigenin, cardamonin, flavokawain A and B are able to scavenge reactive oxygen species (ROS). Normally living organisms are protected against highly reactive oxygen species by an endogenous system of enzymes like superoxide dismutase or other naturally occurring antioxidants widely distributed in the biological system such as ascorbic acid or vitamin E for instance. In fact a high level of ROS can attack essential biological molecules like lipids, proteins, and DNA, and it has been already demonstrated that in case of disease the production of ROS is increased. As a consequence, natural and synthetic molecules possessing multifunctional antioxidant activities such as flavonoids are of great interest and important in disease prevention and in therapy. Apart from these promising aspects, little is known about the reactivity and response of methoxy chalcones towards reactive oxygen species. Thus, an evaluation of the potential biological applications of the substituted methoxy chalcone compounds will give more insights into their mode-of-action. Therefore, they could represent in the future new templates for antioxidants as well as chemical additives.

The main structural features of chalcones required for antioxidant activity supposed to be influenced by three fundamental factors: (1) presence of phenolic hydroxy or benzyloxy group favors the free electron generation and methoxy group supports electron delocalization as well. (2) an unsaturated 2-3 bond in conjugation with a keto group provides electron delocalization from one ring to another ring to stabilize radical. (3) hydroxyl groups may form intramolecular hydrogen bonding to the keto group (**C**).

These effects lead to the increases of the radical scavenging by delocalization of electrons or by donation of hydrogen.

The synthesized chalcones (3a-3d) were evaluated for *in vitro* antioxidant activity using DPPH model. Observation for antioxidant activity is expressed in terms of percent scavenging of DPPH radical and the inhibitory concentration 50% (IC_{50}) as presented in Table-1.DPPH solution of sample 3b is made 0.002% and for 3a, 3c and 3d is 0.004%. It is presented as Bar diagram in Fig. 2 and 5 is added to IC_{50} for clarity and better visualization.

The trend for antioxidant activity (IC_{50})

Ascorbic acid (0.08) > 3d (3.17) > 3b (9.03) > 3c (25.08) > 3a (32.27)

Smaller the IC_{50} value higher the antioxidant activity. Compound 3d showed highest activity in DPPH method (**IC_{50}, 3.17)**. Presence of two phenolic –OH groups generate phenoxy radicals easily and stabilized by $–OCH_3$ over the wide delocalized π- system. As in ring B $–OCH_3$ and –OH are located in para position to each other electronic contribution is higher. Compound 3b also showed higher activity in DPPH method (**IC_{50}, 9.03)**. Presence of two phenolic –OH groups generate phenoxy radicals easily and favored by $–OCH_3$ and –OBz groups over the wide delocalized π- system. As in ring A, –OBz is located meta position to –OH so less activity is observed than that of 3d. Absence of Phenolic –OH groups Compound 3a and 3c showed slightly reduced activity but moderately good values. As the steric congestion favors radical generation so 3c has slightly higher antioxidant value (**IC_{50} , 25.08 for 3c and 32.27 for 3a)**.

Table- 1: DPPH radical scavenging data of synthesized chalcones **(3a-3d)** and their corresponding IC_{50} values.

Compound No.	Conc. µg /mL	Absorbance at 517 nm	%Inhibition	IC_{50}* (µg /mL)
3a	2	0.186	43.64	32.27
	5	0.182	44.85	
	10	0.181	45.15	
	20	0.173	47.56	
	blank	0.330		
3b	2	0.238	45.54	9.03
	5	0.221	49.43	
	10	0.213	51.26	
	20	0.199	54.46	
	blank	0.437		
3c	1	0.257	24.85	25.08
	2	0.241	29.53	
	10	0.234	31.58	
	15	0.210	38.59	
	20	0.181	47.08	
	blank	0.342		
3d	1	0.248	19.74	3.17
	5	0.036	88.35	
	10	0.023	92.56	
	blank	0.309		

* Ascorbic acid is the standard and IC_{50} 0.08 (µg /mL)

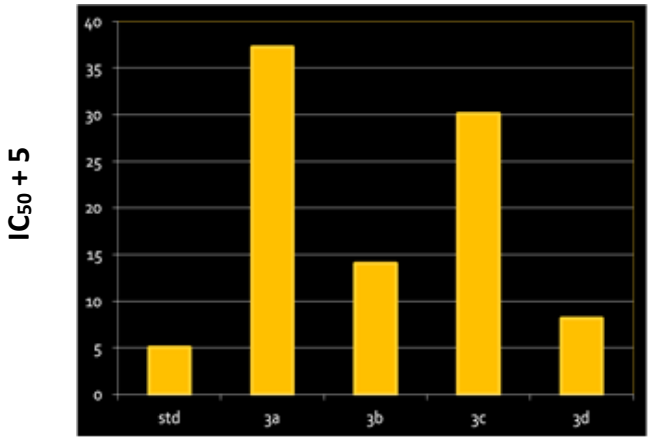


Fig. 3: Bar Diagram of IC_{50} values of (3a-3d).

Reducing power assay method is based on the principle that substances, which have reduction potential, react with potassium ferricyanide (Fe^{3+}) to form potassium ferrocyanide (Fe^{2+}), which then reacts with ferric chloride to form ferric–ferrous complex that has an absorption maximum at 700 nm. The reducing power of the hydro alcoholic extracts and standard increases with the increase in amount of sample and standard concentrations. The

amount of Fe^{2+} complex can then be monitored by measuring the formation of Purl's Prussian blue or greenish solution from yellow at 700 nm. Thus higher the absorbance higher the activity (Table 2). The results are also presented by Bar Diagram (Fig. 4).

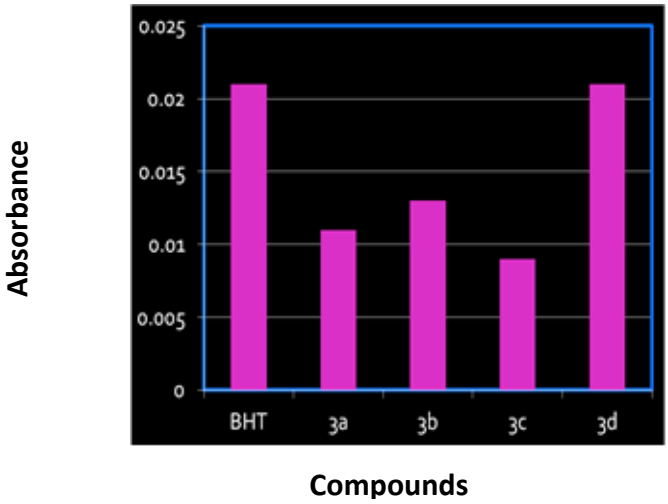


Fig. 4: Reducing power of chalcones **(3a-3d)** in 10 µg/mL concentration.

The trend for antioxidant activity (reducing power assay) in absorbanc at 10 µg/mL

BHT (0.021) > 3d (0.016) > 3b (0.013) > 3c (0.011) > 3a (0.009)

Highest activity is found in case of 3d (absorbance 0.016 at 10 µg/mL). Reducing power capacity of 3b is also next to 3d (**3b, 0.013 at** 10 µg/mL) as in DPPH method. On the other hand, due to steric effect reducing power is smaller in 3c than that of 3a (absorbance of 3a, 0.011 and 3c 0.009 at 10 µg/mL)

Table- 2: Reducing power of chalcones **(3a-3d)** with standard Butylated Hydroxytoluene (BHT).

Compound no.	Conc.(µg/mL)	Absorbance
3a	**10**	**0.011**
	20	**0.138**
	50	**0.154**
	80	**0.267**
3b	**10**	**0.013**
	20	**0.032**
	50	**0.036**
	80	**0.155**
3c	**10**	**0.009**
	20	**0.023**
	50	**0.047**
	80	**0.180**
3d	**10**	**0.016**
	20	**0.036**
	50	**0.112**
	80	**0.344**
BHT	**10**	**0.021**
	20	**0.052**
	50	**0.169**
	80	**0.304**

4. Conclusions

Natural and synthetic molecules possessing multifunctional antioxidant activities such as flavonoids are of great interest and important in disease prevention and in therapy. Apart from these promising aspects, little is known about the reactivity/response of methoxychalcones towards reactive oxygen species.Thus, an evaluation of the potential biological applications of the substituted methoxy chalcone compounds will give more insights into their mode-of-action.

The present study includes design a suitable method for the synthesis of chalcones, with methoxy substituents present commonly and varying hydroxy, benzyloxy and methyl groups. Finally, SAR being studied through antioxidant screening in two different methods DPPH Modeling and Reducing Power Assay

Especially compound 3d and 3b showed very high activity in both the method. Since benzyloxy group is in meta position with hydroxyl group in 3b so showed lesser activity than that of 3d. On the other hand, 3c showed higher activity than 3a in DPPH method and lesser activity than 3a in reducing power assay. Steric congestion might be the possible reason for such observation. Therefore, they could represent in the future new templates for antioxidants specially 3d has a high potency as chemical additives.

5. Acknowledgments

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