



## ***In-vitro* Antioxidant activity of Diethyl malonate adducts of Phenothiazine**

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### **Abstract**

*A series of novel diethyl malonate adducts 2a-g was prepared by the condensation between chalcones 1a-g and diethyl malonate in presence of KOt-Bu. The products were characterized by their spectral data (UV, IR, NMR and elemental analysis). In-vitro antioxidant activity was carried out for 2a-g which showed good anti-oxidant activity with IC<sub>50</sub> value between 36.15 to 81.00 µg/ml and comparable to the control quercetin with IC<sub>50</sub> value 44.53 (µg/ml). Compound 2a and 2d showed higher activity with IC<sub>50</sub> value of 39.13 and 36.1 µg/ml respectively.*

**Keywords:** Chalcones, michael addition, diethyl malonate adduct, KOt-Bu, antioxidant activity.

### **Introduction**

Chalcone and its derivatives are medicinally important. Michael addition reaction of appropriate carbanionic reagents to  $\alpha$ ,  $\beta$ -unsaturated carbonyl compounds such as chalcone is of synthetic interest for C-C bond formation<sup>1,2</sup>. Addition of 1, 3-dicarbonyl compounds such as malonate esters and acetacetate esters is important for the synthesis of 1, 5-dicarbonyl compounds which are key compounds for the preparation of many biological heterocyclic compounds<sup>3</sup>. In recent years, there has been a growing interest pertaining to the synthesis of bioactive compounds in the field of organic chemistry. Molecules that possess sulfur atoms are universal and crucial in living organisms<sup>4</sup>. Phenothiazine derivatives constitute an important class of compounds possessing diverse type of biological properties including antiviral, antiparasitic, antiparkinsonian, anticonvulsant, antihistaminic as well as anthelmintic properties<sup>5</sup>. Antioxidant is a term widely used but rarely defined; it is difficult these days to open a popular science magazine or medical journal without seeing an article about the role of free radicals in human diseases. Free radicals and reactive oxygen species in general are no longer seen only as destructive factors but also as messengers involved in intracellular and intercellular signaling. In view of the substantial changes in the understanding of the role of reactive oxygen species and antioxidants in living systems, a critical re-evaluation of the methods of determination of the antioxidant activity is necessary. The peroxidase substrate 2, 2'-azino-bis(3-ethyl benzthiazoline-6-sulphonic acid) (ABTS) forming relatively stable radical upon one-electron oxidation has become a popular substrate for estimation of total antioxidant activity<sup>6</sup>.

Furthermore synthesis of novel chemical entities, which are still in resemblance with bioactive molecules by virtue of the presence of some critical structural features, is an essential component of the search for new leads in drug designing programs. Hence careful perusal of literature on antioxidant

properties and our continued interest in the development of simpler and more convenient synthetic routes for achieving the biologically challenging heterocyclic system<sup>5</sup> has induced us to synthesize a class of molecules having diethyl malonate adducts of phenothiazine ring and to evaluate their antioxidant activity.

### **Material and Methods**

**Chemistry:** Melting points (uncorrected) were determined using a Guna melting point apparatus. UV spectra were obtained using a UV 2460 shimadzu spectrophotometer. IR spectra were carried out on a Perkin-Elmer 1650 spectrophotometer. NMR spectra were recorded in CDCl<sub>3</sub> on a Bruker AM 400 MHz spectrometer, using residual CHCl<sub>3</sub> and TMS as an internal standard. Elemental analysis was carried out in a Perkin Elmer 240C model instrument. Column chromatography and TLC were carried out on silica gel 60 -120 mesh and silicagel 'G' respectively. All the chemicals are of AR grade.

**General procedure for the preparation of compounds 1a-g:** 2-acetyl phenothiazine (0.01 mol) was dissolved in 25 ml methanol and different benzaldehyde derivatives (0.01 mol) were added, heated for 6 hrs with constant stirring in a magnetic stirrer and a catalytic amount of NaOH was added in drops by Claisen-Schmidt condensation<sup>7-9</sup>. The reaction was poured into ice-cold water, neutralized with con.HCl and left over night in a refrigerator. The precipitate was filtered, dried and purity of the compound was checked by TLC using chloroform as the solvent. The compound was purified by column chromatography using silica gel (60-120 mesh).

**General procedure for the preparation of diethyl malonate adducts 2a-g:** Chalcone 1a-g (0.01 mol) was dissolved in 10 ml methanol and diethyl malonate (0.01 mol), and a catalytic amount of KOt-Bu was added and refluxed for 4 hrs by Michael addition reaction<sup>3</sup>. The reaction was poured into ice-cold water, neutralized with con.HCl and left over night in a refrigerator.

The precipitate was filtered, dried and purity of the compound was checked by TLC using chloroform as the solvent. The compound was purified by column chromatography using silica gel (60-120 mesh). The analytical data is given in table-1 and spectral data for each compound is given below.

**Diethyl 2-(1-(4-methoxyphenyl)-3-oxo-3-(10H-phenothiazin-2-yl)propyl)malonate 2a:** UV  $\lambda_{\text{max}}$ : 392.00, 280.50, 244.00; IR (KBr)  $\text{cm}^{-1}$ : 1589 (C = C), 1666 (C = O ketone), 1737 (C = O ester), 3344 (NH);  $^1\text{H-NMR}$  (400MHz  $\text{CDCl}_3$ )  $\delta$ : 3.43, 3.29 (dd,  $J=7.6$ , 16Hz, 2H,  $\text{CH}_2$ ), 4.07-4.04 (td,  $J=4.4\text{Hz}$ , 1H, CH), 3.75 (d,  $J=9.6\text{Hz}$ , 1H, CH), 4.21-4.18 (q,  $J=7.2\text{Hz}$ , 2H,  $\text{OCH}_2$ ), 3.98-3.93 (q,  $J=7.2\text{Hz}$ , 2H,  $\text{OCH}_2$ ), 1.00 (t,  $J=7.2\text{Hz}$ , 3H,  $\text{CH}_3$ ), 1.02 (t,  $J=7.2\text{Hz}$ , 3H,  $\text{CH}_3$ ), 3.73 (1H, s,  $\text{OCH}_3$ ), 6.76-6.74 (m, 3H, Ar-H), 7.00-6.90 (m, 4H, Ar-H), 7.14-7.12 (m, 2H, Ar-H), 7.33(m, 1H, Ar-H);  $^{13}\text{C-NMR}$  (400MHz  $\text{CDCl}_3$ )  $\delta$ : 13.82, 14.04, 61.37, 61.67, 167.77, 168.48, 55.14, 42.72, 40.44, 196.78, 113.03, 135.97, 114.67, 132.12, 132.12, 118.00, 129.22, 126.36, 142.00, 117.00, 141.00, 126.66, 140.90, 127.76, 113.80, 158.58, 57.81.

**Diethyl 2-(3-oxo-3-(10H-phenothiazin-2-yl)-1-phenylpropyl)malonate 2b:** UV  $\lambda_{\text{max}}$ : 282.00, 248.00, 211.50; IR(KBr)  $\text{cm}^{-1}$ : 1597 (C = C), 1680 (C = O ketone), 1730 (C = O ester), 3350 (NH);  $^1\text{H-NMR}$  (400MHz  $\text{CDCl}_3$ )  $\delta$ : 3.45, 3.29 (dd,  $J=7.6$ , 16Hz, 2H,  $\text{CH}_2$ ), 4.14-4.06 (td,  $J=4.4\text{Hz}$ , 1H, CH), 3.74 (d,  $J=9.6\text{Hz}$ , 1H, CH), 3.98 (q,  $J=7.2\text{Hz}$ , 2H,  $\text{OCH}_2$ ), 4.15 (q,  $J=7.2\text{Hz}$ , 2H,  $\text{OCH}_2$ ), 1.04 (t,  $J=7.2\text{Hz}$ , 3H,  $\text{CH}_3$ ), 1.22 (t,  $J=7.2\text{Hz}$ , 3H,  $\text{CH}_3$ ), 6.74-6.70 (m, 3H, Ar-H), 7.00-6.84 (m, 5H, Ar-H), 7.12-7.10 (m, 2H, Ar-H), 7.28(m, 1H, Ar-H);  $^{13}\text{C-NMR}$  (400MHz  $\text{CDCl}_3$ )  $\delta$ : 13.89, 14.10, 61.37, 61.43, 169.00, 168.00, 57.00, 25.40, 45.67, 199.00, 136.00, 115.89, 118.90, 132.00, 122.0, 118.40, 132.10, 117.76, 127.5, 119.7, 142.50, 143.34, 149.65, 126.23, 128.50, 126.12.

**Diethyl 2-(1-(4-chlorophenyl)-3-oxo-3-(10H-phenothiazin-2-yl)propyl)malonate 2c:** UV  $\lambda_{\text{max}}$ : 282.00, 245.00, 207.50; IR (KBr)  $\text{cm}^{-1}$ : 1595 (C = C), 1660 (C = O ketone), 1741 (C = O ester), 3332 (NH);  $^1\text{H-NMR}$  (400MHz  $\text{CDCl}_3$ )  $\delta$ : 3.45, 3.27 (dd,  $J=7.6$ , 16Hz, 2H,  $\text{CH}_2$ ), 4.13-4.07 (td,  $J=4.4\text{Hz}$ , 1H, CH), 3.75 (d,  $J=9.6\text{Hz}$ , 1H, CH), 3.98 (q,  $J=7.2\text{Hz}$ , 2H,  $\text{OCH}_2$ ), 4.15 (q,  $J=7.2\text{Hz}$ , 2H,  $\text{OCH}_2$ ), 1.04 (t,  $J=7.2\text{Hz}$ , 3H,  $\text{CH}_3$ ), 1.24 (t,  $J=7.2\text{Hz}$ , 3H,  $\text{CH}_3$ ), 6.52-6.50 (dd, 1H, Ar-H), 7.33-7.30 (dd, 1H, Ar-H), 6.83-6.79 (td, 1H, Ar-H), 7.00-6.90 (m, 5H, Ar-H), 7.21-7.16 (m, 4H, Ar-H);  $^{13}\text{C-NMR}$  (400MHz  $\text{CDCl}_3$ )  $\delta$ : 13.81, 14.03, 61.55, 61.81, 167.55, 168.19, 57.37, 42.27, 40.36, 196.23, 112.88, 135.77, 114.65, 132.98, 132.98, 122.91, 125.63, 122.54, 141.68, 116.92, 140.67, 126.69, 140.90, 127.81, 128.59, 129.64.

**Diethyl 2-(3-oxo-3-(10H-phenothiazin-2-yl)-1-p-tolylpropyl)malonate 2d:** UV  $\lambda_{\text{max}}$ : 278.50, 243.50, 218.50; IR(KBr)  $\text{cm}^{-1}$ : 1597 (C = C), 1668 (C = O ketone), 1738 (C = O ester), 3356 (NH);  $^1\text{H-NMR}$  (400MHz  $\text{CDCl}_3$ )  $\delta$ : 3.43, 3.27 (dd,  $J=7.6$ , 16Hz, 2H,  $\text{CH}_2$ ), 4.09 (td,  $J=4.4\text{Hz}$ , 1H, CH), 3.75 (d,  $J=9.6\text{Hz}$ , 1H, CH), 3.98-3.93 (q,  $J=7.2\text{Hz}$ , 2H,  $\text{OCH}_2$ ), 4.21-4.17 (q,

$J=7.2\text{Hz}$ , 2H,  $\text{OCH}_2$ ), 1.00 (t,  $J=7.2\text{Hz}$ , 3H,  $\text{CH}_3$ ), 1.24 (t,  $J=7.2\text{Hz}$ , 3H,  $\text{CH}_3$ ), 2.23 (s, 3H,  $\text{CH}_3$ ), 6.52-6.50 (dd, 1H, Ar-H), 6.82-6.78 (td, 1H, Ar-H), 7.10 (d, 2H, Ar-H), 7.33-7.31 (dd, 1H, Ar-H), 7.02-6.90 (m, 6H, Ar-H);  $^{13}\text{C-NMR}$  (400MHz  $\text{CDCl}_3$ )  $\delta$ : 13.77, 14.03, 61.35, 61.64, 167.76, 168.48, 57.70, 42.58, 40.72, 196.68, 113.03, 135.99, 114.65, 129.10, 129.10, 122.81, 125.27, 122.61, 141.60, 116.96, 140.78, 126.66, 140.90, 126.35, 128.00, 136.71, 21.00.

**Diethyl 2-(1-(3-nitrophenyl)-3-oxo-3-(10H-phenothiazin-2-yl)propyl)malonate 2e:** UV  $\lambda_{\text{max}}$ : 280.00, 245.00, 206.00; IR(KBr)  $\text{cm}^{-1}$ : 1591 (C = C), 1660 (C = O ketone), 1737 (C = O ester), 3340 (NH);  $^1\text{H-NMR}$  (400MHz  $\text{CDCl}_3$ )  $\delta$ : 3.53, 3.39 (dd,  $J=7.6$ , 16Hz, 2H,  $\text{CH}_2$ ), 4.17 (td,  $J=4.4\text{Hz}$ , 1H, CH), 3.83 (d,  $J=9.6\text{Hz}$ , 1H, CH), 4.00 (q,  $J=7.2\text{Hz}$ , 2H,  $\text{OCH}_2$ ), 4.23 (q,  $J=7.2\text{Hz}$ , 2H,  $\text{OCH}_2$ ), 1.07 (t,  $J=7.2\text{Hz}$ , 3H,  $\text{CH}_3$ ), 1.26 (t,  $J=7.2\text{Hz}$ , 3H,  $\text{CH}_3$ ), 6.52-6.49 (dd, 1H, Ar-H), 6.82-6.78 (td, 1H, Ar-H), 6.92-6.90 (dd, 1H, Ar-H), 7.00-6.94 (m, 3H, Ar-H), 7.32-7.30 (dd, 1H, Ar-H), 7.44 (t, 1H, Ar-H), 7.66 (d, 1H, Ar-H), 8.06-8.03 (dd, 1H, Ar-H), 8.15-8.14 (t, 1H, Ar-H);  $^{13}\text{C-NMR}$  (400MHz  $\text{CDCl}_3$ )  $\delta$ : 13.83, 14.02, 61.73, 62.01, 167.35, 167.88, 56.91, 41.83, 40.26, 195.73, 112.77, 135.52, 114.65, 129.32, 129.32, 122.96, 125.99, 122.45, 141.74, 116.85, 140.58, 126.48, 148.21, 122.83, 135.16, 142.81, 127.85, 116.85.

**Diethyl 2-(1-(4-bromophenyl)-3-oxo-3-(10H-phenothiazin-2-yl)propyl)malonate 2f:** UV  $\lambda_{\text{max}}$ : 281.50, 244.50, 206.50; IR(KBr)  $\text{cm}^{-1}$ : 1598 (C = C), 1660 (C = O ketone), 1743 (C = O ester), 3334 (NH);  $^1\text{H-NMR}$  (400MHz  $\text{CDCl}_3$ )  $\delta$ : 3.44, 3.29 (dd,  $J=7.6$ , 16Hz, 2H,  $\text{CH}_2$ ), 4.09 (td,  $J=4.4\text{Hz}$ , 1H, CH), 3.73 (d,  $J=9.6\text{Hz}$ , 1H, CH), 4.05 (q,  $J=7.2\text{Hz}$ , 2H,  $\text{OCH}_2$ ), 4.21 (q,  $J=7.2\text{Hz}$ , 2H,  $\text{OCH}_2$ ), 1.04 (t,  $J=7.2\text{Hz}$ , 3H,  $\text{CH}_3$ ), 1.24 (t,  $J=7.2\text{Hz}$ , 3H,  $\text{CH}_3$ ), 7.32 (dd, 1H, Ar-H), 6.52 (d, 1H, Ar-H), 6.80 (t, 1H, Ar-H), 6.99-6.90 (m, 3H, Ar-H), 7.13-7.10 (m, 2H, Ar-H), 7.36-7.33 (m, 2H, Ar-H);  $^{13}\text{C-NMR}$  (400MHz  $\text{CDCl}_3$ )  $\delta$ : 13.81, 14.03, 61.56, 61.81, 167.54, 168.18, 57.31, 42.20, 40.44, 196.20, 112.91, 135.81, 114.65, 132.24, 131.55, 122.54, 125.67, 122.93, 141.69, 116.96, 140.68, 126.45, 140.90, 129.79, 131.55, 121.13.

**Diethyl 2-(1-(4-formylphenyl)-3-oxo-3-(10H-phenothiazin-2-yl)propyl)malonate 2g:** UV  $\lambda_{\text{max}}$ : 280.00, 244.00, 211.50; IR (KBr)  $\text{cm}^{-1}$ : 1598 (C = C), 1689 (C = O ketone), 1756 (C = O ester), 3358 (NH);  $^1\text{H-NMR}$  (400MHz  $\text{CDCl}_3$ )  $\delta$ : 3.50, 3.33 (dd,  $J=7.6$ , 16Hz, 2H,  $\text{CH}_2$ ), 4.18 (td,  $J=4.4\text{Hz}$ , 1H, CH), 3.80 (d,  $J=9.6\text{Hz}$ , 1H, CH), 3.97 (q,  $J=7.2\text{Hz}$ , 2H,  $\text{OCH}_2$ ), 4.21 (q,  $J=7.2\text{Hz}$ , 2H,  $\text{OCH}_2$ ), 1.00 (t,  $J=7.2\text{Hz}$ , 3H,  $\text{CH}_3$ ), 1.26 (t,  $J=7.2\text{Hz}$ , 3H,  $\text{CH}_3$ ), 9.91 (s, 1H, CHO), 6.51 (d, 1H, Ar-H), 6.79 (td, 1H, Ar-H), 6.97-6.77 (m, 4H, Ar-H), 7.29 (m, 1H, Ar-H), 7.43 (d, 2H, Ar-H), 7.75 (d, 2H, Ar-H);  $^{13}\text{C-NMR}$  (400MHz  $\text{CDCl}_3$ )  $\delta$ : 13.78, 14.01, 61.50, 61.61, 167.41, 168.02, 57.04, 42.02, 40.94, 196.04, 112.81, 135.64, 114.67, 129.83, 129.83, 122.44, 125.78, 122.87, 141.77, 116.81, 140.66, 126.65, 166.64, 126.39, 129.04, 135.08, 191.75.

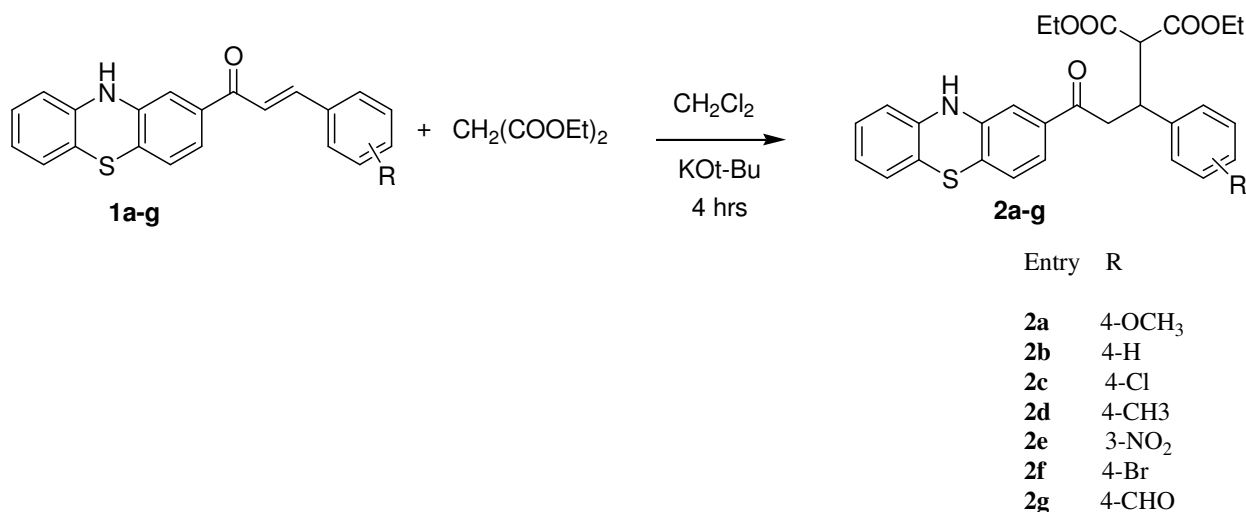
**In-vitro ABTS<sup>+</sup> radical scavenging assay:** ABTS<sup>+</sup> radical scavenging activity was determined for compounds (**2a-g**) accordingly<sup>10</sup>. ABTS<sup>+</sup> radical was freshly prepared by adding 5 ml of 4.9 mM ammonium persulfate solution to 5 ml of 14 mM ABTS solution and kept for 16 h in dark. This solution was diluted with ethanol (99.5%) to yield an absorbance of 0.70±0.02 at 734 nm and the same was used for the assay. To 950 µl of ABTS radical solution, added 50 µl of prepared solutions (25-500 µg/ml) and the reaction mixture was vortexed for 10 sec. After 6 minutes the absorbance was recorded at 734 nm and compared with the control ABTS solution. Quercetin was used as a control. The experiment was carried in triplicates. Percentage inhibition was calculated from the formula

Percentage inhibition = [1 - (absorbance of test/absorbance of control)]

## Results and Discussion

**Spectral values of diethyl malonate adduct 2a-g:** A series of seven chalcone diethyl malonate derivatives 2a-g was prepared by Michael addition reaction of diethyl malonate to chalcones

1a-g as shown in scheme-1. Diethyl malonate adducts were obtained in good yields of 68-83%. The analytical data were summarized in Table-1. The structures of all seven adducts of diethyl malonate 2a-g synthesized were characterized by UV, IR, <sup>1</sup>H, <sup>13</sup>C-NMR, elemental analysis. The addition of diethyl malonate to chalcones 1a-g leads to the generation of a chiral center in the structure of adducts 2a-g and confirmed by its <sup>1</sup>H-NMR spectral data. In <sup>1</sup>H-NMR spectrum the protons present in the CH<sub>2</sub> group appeared as a doublet of doublets at δ 3.43 (1H, J = 7.6Hz) and 3.29 (1H, J = 16Hz) with different coupling constant values. For this two signals at δ 1.00 and 1.24 were attributed to the methyl groups. The two OCH<sub>2</sub> groups present in the structures 2a-g appeared as a pair of quartets at δ 4.00 and 4.23. All the aromatic protons appeared between δ 6.51 to 8.06. In <sup>13</sup>C-NMR spectrum, keto carbonyl group appeared at δ 196.00 and two ester carbonyl groups appeared at δ 167.00 and 168.00. All the aromatic or C = C unsaturated carbon appeared between δ 100.00 to 160.00. IR spectra showed a sharp strong band at 1730cm<sup>-1</sup> (ν<sub>C=O</sub> ester), at 1680cm<sup>-1</sup> (ν<sub>C=O</sub> keto), at 1598cm<sup>-1</sup> for C = C and at 3358cm<sup>-1</sup> N-H group.



Scheme-1  
Synthesis of diethyl malonate adducts 2a-g

Table-1  
Analytical data for compounds 2a-g

Compound	Molecular formula	Yield (%)	Mp °C	Elemental analysis					
				Calculated			Found		
				C	H	N	C	H	N
2a	C <sub>29</sub> H <sub>29</sub> O <sub>6</sub> NS	72	132	67.06	5.58	2.69	67.14	5.52	2.60
2b	C <sub>28</sub> H <sub>27</sub> O <sub>5</sub> NS	78	143	68.72	5.51	2.86	68.79	5.45	2.90
2c	C <sub>28</sub> H <sub>26</sub> O <sub>5</sub> NSCl	83	137	64.20	4.96	2.67	64.23	4.85	2.73
2d	C <sub>29</sub> H <sub>29</sub> O <sub>5</sub> NS	79	128	68.73	5.72	2.76	68.77	5.82	2.68
2e	C <sub>28</sub> H <sub>26</sub> O <sub>7</sub> N <sub>2</sub> S	68	166	62.54	4.83	5.20	62.66	4.75	5.15
2f	C <sub>28</sub> H <sub>26</sub> O <sub>5</sub> NSBr	75	149	58.82	4.54	2.45	58.94	4.47	2.49
2g	C <sub>29</sub> H <sub>27</sub> O <sub>6</sub> NS	80	150	66.88	5.18	2.68	66.97	5.12	2.74

**Anti-Oxidant Activity (ABTS method):** *In vitro* anti-oxidant activity was evaluated by ABTS<sup>+</sup> radical scavenging assay for 2a-g and IC<sub>50</sub> value was determined as shown in table-2. Quercetin was used as a control. Synthesized compounds 2a-g showed a good anti-oxidant activity with IC<sub>50</sub> value between 36.15 to 81.00 µg/ml when compared to the control quercetin with IC<sub>50</sub> value 44.53 µg/ml. From the table-2, Compound 2b does not have any substituents and the IC<sub>50</sub> value is 40.00 µg/ml. When electron donating groups are introduced in fourth position in 2a and 2d it increases the electron density and have marginally high anti-oxidant property with IC<sub>50</sub> value of 39.13 and 36.15 µg/ml respectively. The compound with electron donating group contributes more to the anti-oxidant activity; with respect to electron withdrawing groups when they are in para position the effect is more. This may be due to the resonance effect. When electron withdrawing group is in the meta position the effect is less and showed a better activity. The presence of NH and CO group in diethyl malonate adducts of phenothiazine nucleus helps in antioxidant activity.

**Table-2**  
**In-vitro antioxidant assay of compounds 9a-g**

S.No	Compound	IC <sub>50</sub> value in (µg/ml)
1	2a	39.13
2	2b	40.00
3	2c	61.02
4	2d	36.15
5	2e	41.23
6	2f	81.00
7	2g	43.00
8	Quercetin	44.53

## Conclusion

In conclusion, a series of diethyl malonate adducts 2a-g were synthesized by Michael addition reaction. *In-vitro* antioxidant activity was evaluated for all synthesized compounds which showed a good activity with an IC<sub>50</sub> value between 36.15 to 81.00 µg/ml, when compared to the control quercetin with IC<sub>50</sub> value of 44.53 µg/ml.

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