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Some Aryl Sulfonyl Ester-Based Heterocyclic Schiff Bases: Synthesis, Structure Elucidation and Antioxidant Activity

Eyüp BAŞARAN[1*]

ABSTRACT: In this research work, a series of heterocyclic Schiff base compounds bearing arylsulfonyl ester moiety (**2a-i**) were designed, synthesized, characterized by spectral techniques such as 1D NMR (^{1}H and ^{13}C), 2D NMR (COSY and HMQC), and FT-IR; and then examined their antioxidant activity was by using four different methods as DPPH, ABTS, CUPRAC, and *β*-carotene-linoleic acid assays. According to the results obtained, it determined that all synthesized molecules had antioxidant activity. In the DPPH assay, it was found that compound **2e** (IC_{50}: 96.23±0.02 µM/mL) demonstrated the antioxidant activity among all synthesized molecules. In ABTS assay, compounds **2e** (IC_{50}: 41.88±0.21 µM/mL) and **2g** (IC_{50}: 50.75±0.32 µM/mL) were determined to be the molecules with the activity, respectively. Compound **2e** (IC_{50}:73.49±0.00 µM/mL) indicated the best antioxidant activity in the CUPRAC assay compared to other synthesize molecules. In the *β*-carotene-linoleic acid assay, compound **2e** (IC_{50}: 58.79±0.58 µM/mL) displayed antioxidant activity than all other synthesized molecules. Compounds **2d** (IC_{50}: 74.17±0.22 µM/mL) and **2g** (IC_{50}: 66.06±0.13 µM/mL) indicated higher antioxidant activity than the remaining molecules in this series, except for compound **2e**. In conclusion, it is thought that this study will contribute to the ongoing studies on the design and synthesis of new antioxidant agents.

Keywords: Antioxidant activity, 4-Aminoantipyrine, Sulfonyl ester, Schiff base.

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INTRODUCTION

Free radicals and reactive oxygen species (ROS) are both harmful and beneficial structures produced by cells during the normal vital activities of the body (Pham-Huy et al., 2008). The effects of oxidation on human health are known due to damaged cells, proteins, and DNA, contributing to aging. It may also play a role in developing a range of health conditions, including diabetes, cancer, and neurodegenerative diseases such as Alzheimer's (Sıcak et al., 2017). ROS can attack healthy cells, alter the cell structure or cause the cell to lose its ability to function (Uttara et al., 2009). Excessive production of reactive oxygen species leads to oxidative stress, which can cause fatal damage to living cell structures (Puskullu et al., 2016). When free radicals and/or ROS rate reaches uncontrollable levels, they can initially damage cell membranes and tissues, accordingly proteins, lipids, enzymes, and DNA (Sıcak et al., 2019). Antioxidants are used to neutralize free radicals. They play an essential role in stopping radical degradation and scavenging ROS (Sıcak et al., 2021a). When an antioxidant encounters an oxidisable substance, it can significantly retard or inhibit the oxidation of the substrate even at low concentrations (Baytop, 1984; Antolovich et al., 2002). Antioxidants play a significant role in the preventing and treating diverse chronic health problems such as cancer, cardiovascular, diabetes, inflammation, Alzheimer's, autoimmune, atherosclerosis, and stroke (Gutteridge, 1994; Karaaslan et al., 2013). The balance between the body's antioxidant systems and free radicals is essential in maintaining the health status of the organism (Suzen, 2007; Bozkurt et al., 2020). Therefore, there is a need to discover and develop more effective and potent radical scavenging antioxidant agents to prevent the harmful influences of free radicals in the human body (Sıcak et al., 2021b)

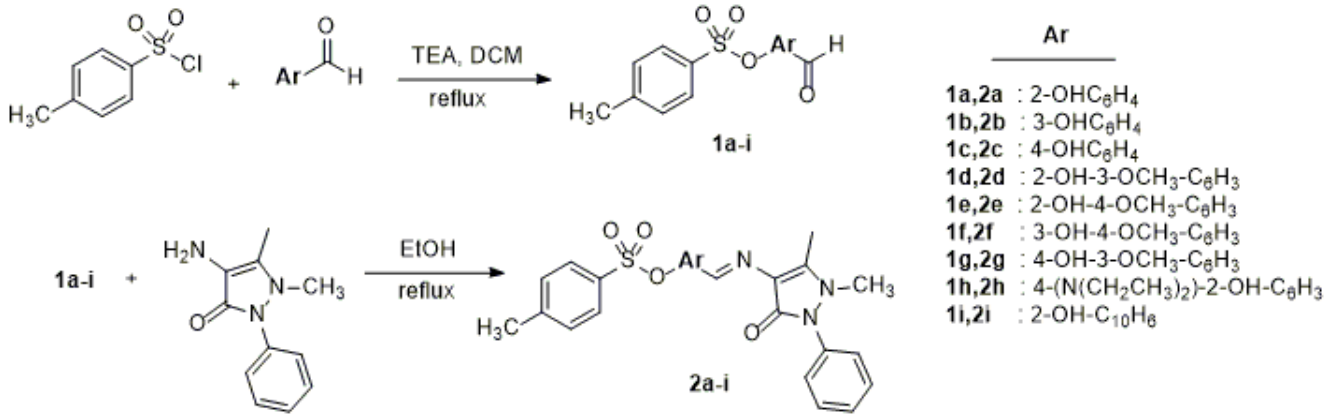
Heterocyclic Schiff base derivatives, synthesized by the condensation of aldehydes with heterocyclic amines, are among the significant compounds in medicinal chemistry (Hashem et al., 2021; Camadan et al., 2021; Orlova et al., 2021). In recent years, compounds of this type have attracted considerable attention due to their remarkable antifungal, antimicrobial, anti-viral, anti-cancer, anti-hyperlipidemic, anti-inflammatory, and antitumor activities (Şener et al., 2021; Lotlikar et al., 2021; Al-Rubaye et al., 2021; Srinivasan et al., 2021). Nowadays, medicinal chemists studying this subject are constantly synthesizing their novel derivatives and investigating their biological activities (Kavitha, 2021; Mohamed et al., 2021; Naureen et al., 2021)

Given the abovementioned findings, this study was carried out to contribute to the continuing researches to design and synthesis new and potent antioxidant agents. This research work's main goal was to synthesize heterocyclic Schiff base compounds containing 4-aminoantipyrine (4-AAP) and evaluate their antioxidant activity. Within the scope of the study, characterization studies of all synthesized target molecules were carried out with some spectroscopic methods.

MATERIALS AND METHODS

Materials

All chemicals required to synthesize antioxidant agents and biological activity assays in this research were procured from Merck, Sigma Aldrich companies. These chemicals purchased were employed without any further purification. Spectroscopic data of all synthesized molecules were recorded on the following instruments: FT-IR: Cary 630 FTIR spectrometer (Agilent Technologies, Inc., Danbury, CT) with the diamond ATR module at a scan range of 4000-400 cm^{-1}, ^{1}H- and ^{13}C- NMR (in $CDCl_3$ solutions): Bruker AVANCE III (Bruker, Germany) 400 MHz spectrometer using tetramethylsilane as the internal reference at 400 and 100 MHz, respectively. Melting points were determined by melting point apparatus (Barnstead IA9100 Electrothermal Digital Melting Points Apparatus, Staffordshire, Great Britain), and they are uncorrected.



Scheme 1. Synthetic pathway of targeted heterocyclic Schiff base compounds (**2a-i**)

Experimental Procedure

General procedure for synthesis of sulfonyl esters derivatives (1a-i)

The solution of a phenolic aldehyde (9.2 mmol) and triethylamine (18.4 mmol) in 20 mL of CH_2CI_2 WASstirred at room temperature (RT) for 1 h (Selvi et al., 2020). Then, the mixture was added dropwise 4-methylbenzenesulfonyl chloride (9.2 mmol) in 20 mL of CH_2CI_2, and the resulting mixture was refluxed for 5 h. TLC was used for followed the progress of the reaction. Upon completing the reaction, the obtained solution was extracted two times with 2 M HCI. The organic phase obtained was dried over Na_2SO_4 and then filtered. Finally, the crude product acquired was crystallized from ethanol.

2-Formylphenyl 4-methylbenzenesulfonate (1a)

Off white solid, yield: 84%, m.p. 63-65 °C, lit.: m.p. 63-64°C (Freudenberg and Hess,1926). FT-IR (ATR, cm^{-1}) υ_{max}: 3077, 3038 (C-H_{arom}), 2952, 2930 (C-H_{aliph}), 2884, 2754 (C-$H_{aldehyde}$), 1688 (C=$O_{aldehyde}$), 1373 ($SO_{2antisym}$), 1175 (SO_{2sym}) (Figure S1). ^{1}H NMR ($CDCl_3$, δ/ppm): 10.02 (s, 1H, H_{12}), 7.89 (dd, *J* = 7.6, 1.8 Hz, 1H, H_{10}), 7.73 (d, *J* = 8.4 Hz, 2H, H_4), 7.60 (td, *J* = 8.4, 2.0 Hz, 1H, H_8), 7.42 (t, *J* = 7.6 Hz, 1H, H_9), 7.36 (d, *J* = 8.4 Hz, 2H, H_3), 7.23 (d, *J* = 8.4 Hz, 1H, H_7), 2.48 (s, 3H, H_1) (Figure S2).

3-Formylphenyl 4-methylbenzenesulfonate (1b)

White solid, yield: 84%, m.p. 68-70 °C, lit.: m.p. 64-66°C (Piller et al., 2009). FT-IR (ATR, cm^{-1}) υ_{max}: 3072, 3038 (C-H_{arom}), 2978, 2922 (C-H_{aliph}), 2812, 2731 (C-$H_{aldehyde}$), 1698 (C=$O_{aldehyde}$), 1368 ($SO_{2antisym}$), 1170 (SO_{2sym}) (Figure S3). ^{1}H NMR ($CDCl_3$, δ/ppm): 9.93 (s, 1H, H_{12}), 7.78 (t, *J* = 4.2 Hz, 1H, H_8), 7.72 (d, *J* = 8.0 Hz, 2H, H_4), 7.50 (d, *J* = 12.6 Hz, 2H, H_3), 7.36 – 7.28 (m, 3H, H_7, H_9 and H_{11}), 2.46 (s, 3H, H_1) (Figure S4).

4-Formylphenyl 4-methylbenzenesulfonate (1c)

Off white, yield: 89%, m.p. 75-76 °C, lit.: m.p. 72-73°C (Collado et al., 2006). FT-IR (ATR, cm^{-1}) υ_{max}: 3101, 3063 (C-H_{arom}), 2978, 2921 (C-H_{aliph}), 2821, 2729 (C-$H_{aldehyde}$), 1704 (C=$O_{aldehyde}$), 1368 ($SO_{2antisym}$), 1145 (SO_{2sym}) (Figure S5). ^{1}H NMR ($CDCl_3$, δ/ppm): 9.99 (s, 1H, H_{10}), 7.85 (d, *J* = 8.8 Hz, 2H, H_8), 7.74 (d, *J* = 8.4 Hz, 2H, H_4), 7.74 (d, *J* = 8.0 Hz, 2H, H_3), 7.03 (d, *J* = 8.4 Hz, 2H, H_7), 2.48 (s, 3H, H_1) (Figure S6).

2-Formyl-6-methoxyphenyl 4-methylbenzenesulfonate (1d) (Nadler et al., 2015)

Light yellow solid, yield: 91%, m.p. 97-98 °C. FT-IR (ATR, cm^{-1}) υ_{max}: 3095, 3027 (C-H_{arom}), 2977, 2938 (C-H_{aliph}), 2880, 2759 (C-$H_{aldehyde}$), 1691 (C=$O_{aldehyde}$), 1378 ($SO_{2antisym}$), 1150 (SO_{2sym}) (Figure S7). ^{1}H NMR ($CDCl_3$, δ/ppm): 10.12 (s, 1H, H_{13}), 7.78 (d, *J* = 8.4 Hz, 2H, H_4), 7.52 – 7.48 (m, 1H, H_{10}), 7.38 – 7.32 (m, 3H, H_3 and H_9), 7.14 – 7.10 (m, 1H, H_7), 3.58 (s, 3H, H_{12}), 2.48 (s, 3H H_1) (Figure S8).

2-Formyl-5-methoxyphenyl 4-methylbenzenesulfonate (1e) (Motherwell and Vázquez, 2000)

White solid, yield: 90%, m.p. 89-90 °C. FT-IR (ATR, cm^{-1}) υ_{max}: 3098, 3053 (C-H_{arom}), 2955, 2906 (C-H_{aliph}), 2850, 2781 (C-$H_{aldehyde}$), 1676 (C=$O_{aldehyde}$), 1597 (C=C_{arom}), 1366 ($SO_{2antisym}$), 1143 (SO_{2sym}) (Figure S9). ^{1}H NMR ($CDCl_3$, δ/ppm): 9.80 (s, 1H, H_{13}), 7.82 (d, *J* = 8.8 Hz, 1H, H_{10}), 7.75 (d, *J* = 8.4 Hz, 2H, H_4), 7.36 (d, *J* = 8.0 Hz, 2H, H_3), 6.93 – 6.89 (m, 1H, H_7), 6.78 (d, *J* = 2.4 Hz, 1H, H_9), 3.86 (s, 3H, H_{12}), 2.47 (s, 3H, H_1) (Figure S10).

5-Formyl-2-methoxyphenyl 4-methylbenzenesulfonate (1f)

White solid, yield: 88%, m.p. 145-146 °C, lit.: 148-151°C (Reddy et al., 2008). FT-IR (ATR, cm^{-1}) υ_{max}: 3089, 3067 (C-H_{arom}), 3014, 2940 (C-H_{aliph}), 2841, 2793 (C-$H_{aldehyde}$), 1684 (C=$O_{aldehyde}$), 1357 ($SO_{2antisym}$), 1176 (SO_{2sym}) (Figure S11). ^{1}H NMR ($CDCl_3$, δ/ppm): 9.84 (s, 1H, H_{13}), 7.81 – 7.75 (m, 3H, H_4 and H_{11}), 7.64 (d, *J* = 2.0 Hz, 1H, H_9), 7.34 (d, *J* = 8.0 Hz, 2H, H_3), 7.00 (d, *J* = 8.4 Hz, 1H, H_8), 3.71 (s, 3H, H_{12}), 2.47 (s, 3H, H_1) (Figure S12).

4-Formyl-2-methoxyphenyl 4-methylbenzenesulfonate (1g)

Off white solid, yield: 89%, m.p. 126-128 °C, lit.: m.p. 126-128°C (Reddy et al., 2010). FT-IR (ATR, cm^{-1}) υ_{max}: 3056, 3018 (C-H_{arom}), 2989, 2956 (C-H_{aliph}), 2818, 2774 (C-$H_{aldehyde}$), 1696 (C=$O_{aldehyde}$), 1359 ($SO_{2antisym}$), 1149 (SO_{2sym}) (Figure S13). ^{1}H NMR ($CDCl_3$, δ/ppm): 9.94 (s, 1H, H_{13}), 7.77 (d, *J* = 8.4 Hz, 2H, H_4), 7.45 (dd, *J* = 8.4, 1.6 Hz, 1H, H_8), 7.40 – 7.36 (m, 2H, H_7 and H_{10}), 7.33 (d, *J* = 8.0 Hz, 2H, H_3), 3.65 (s, 3H, H_{12}), 2.47 (s, 3H, H_1) (Figure S14).

5-(Diethylamino)-2-formylphenyl 4-methylbenzenesulfonate (1h) (Liu et al., 2016)

Light brown solid, yield: 87%, m.p. 102-103 °C. FT-IR (ATR, cm^{-1}) υ_{max}: 3111, 3067 (C-H_{arom}), 2969, 2928 (C-H_{aliph}), 2866, 2772 (C-$H_{aldehyde}$), 1670 (C=$O_{aldehyde}$), 1367 ($SO_{2antisym}$), 1172 (SO_{2sym}) (Figure S15). ^{1}H NMR ($CDCl_3$, δ/ppm): 9.62 (s, 1H, H_{14}), 7.77 (d, *J* = 8.4 Hz, 2H, H_4), 7.69 (d, *J* = 9.2 Hz, 1H, H_{10}), 7.34 (d, *J* = 8.0 Hz, 2H, H_3), 6.56 (dd, *J* = 9.0, 2.4 Hz, 1H, H_9), 6.39 (d, *J* = 2.4 Hz, 1H, H_7), 3.39 (q, *J* = 7.2 Hz, 4H, H_{12}), 2.46 (s, 3H, H_1), 1.19 (t, *J* = 7.2 Hz, 6H, H_{13}) (Figure S16).

1-Formylnaphthalen-2-yl 4-methylbenzenesulfonate (1i) (Lei et al., 2015)

Off white solid, yield: 92%, m.p. 136-138 °C. FT-IR (ATR, cm^{-1}) υ_{max}: 3071, 3058 (C-H_{arom}), 2970, 2922 (C-H_{aliph}), 2877, 2775 (C-$H_{aldehyde}$), 1692 (C=$O_{aldehyde}$), 1369 ($SO_{2antisym}$), 1170 (SO_{2sym}) (Figure S17). ^{1}H NMR ($CDCl_3$, δ/ppm): 10.41 (s, 1H, H_{16}), 9.16 (d, *J* = 8.4 Hz, 1H, H_9), 8.07 (d, *J* = 8.4 Hz, 1H, H_{14}), 7.88 (d, *J* = 8.0 Hz, 1H, H_{12}), 7.75 (d, *J* = 8.0 Hz, 2H, H_4), 7.70 – 7.66 (m, 1H, H_{10}), 7.59 (t, *J* = 7.6 Hz, 1H, H_{11}), 7.39 – 7.32 (m, 3H, H_3 and H_{15}), 2.47 (s, 3H, H_1) (Figure S18).

General procedure for synthesis of heterocyclic Schiff bases (2a-i)

The target molecules **(2a-i)** were easily obtained by refluxing an equimolar ethanolic solution of 4-aminoantipyrine (5 mmol), and the corresponding 4-methylbenzenesulfonyl ester derivatives (**1a-i**) (5 mmol) was refluxed for 1 h. Subsequently, the reaction medium was cooled to RT. The acquired crude product was quickly removed by filtration, rinsed with petroleum ether, and then crystallized from ethanol.

2-(((Antipyrine-4-yl)imino)methyl)phenyl 4-methylbenzenesulfonate (2a)

Light yellow solid, yield: 80%, m.p. 216-217 °C. FT-IR (ATR, cm^{-1}) υ_{max}: 3060, 3034 (C-H_{arom}), 2963, 2926 (C-H_{aliph}), 1647 (C=$O_{antipyrine}$), 1589 (C=N_{imino}), 1368 ($SO_{2antisym}$), 1150 (SO_{2sym}) (Figure S19). ^{1}H NMR ($CDCl_3$, δ/ppm): 9.66 (s, 1H, H_{12}), 8.08 (d, *J* = 7.6 Hz, 1H, H_{10}), 7.84 (d, *J* = 8.0 Hz, 2H, H_4), 7.53 (t, *J* = 7.6 Hz, 2H, H_{20}), 7.45 (d, *J* = 8.4 Hz, 2H, H_{19}), 7.38 – 7.31 (m, 5H, H_3, H_8, H_9 and H_{21}), 7.21 (d, *J* = 8.0 Hz, 1H, H_7), 3.17 (s, 3H, H_{17}), 2.46 (s, 3H, H_1), 2.34 (s, 3H, H_{16}) (Figure S20). ^{13}C NMR ($CDCl_3$, δ/ppm): 160.38 (C_{14}), 152.50 (C_{12}), 150.72 (C_6), 148.74 (C_{15}), 145.00 (C_2), 134.96 (C_{18}), 132.06 (C_8), 131.28 (C_5), 130.81 (C_{10}), 129.70 (C_4), 129.26 (C_3), 129.02 (C_{20}), 127.01 (C_{21}), 126.95 (C_9), 126.88 (C_{11}), 124.31 (C_{19}), 123.56 (C_7), 118.74 (C_{13}), 35.89 (C_{17}), 21.66 (C_1), 10.06 (C_{16}) (Figure S21).

3-(((Antipyrine-4-yl)imino)methyl)phenyl 4-methylbenzenesulfonate (2b) (Chen and Yu, 2006a**)**

Light yellow solid, yield: 77%, m.p. 155-156 °C. FT-IR (ATR, cm^{-1}) υ_{max}: 3069, 3042 (C-H_{arom}), 2997, 2921 (C-H_{aliph}), 1641 (C=$O_{antipyrine}$), 1575 (C=N_{imino}), 1357 ($SO_{2antisym}$), 1171 (SO_{2sym}) (Figure S22). ^{1}H NMR ($CDCl_3$, δ/ppm): 9.63 (s, 1H, H_{12}), 7.74 (d, *J* = 8.0 Hz, 2H, H_4), 7.70 (d, *J* = 7.6 Hz, 1H, H_9), 7.52 – 7.48 (m, 3H, H_{11} and H_{20}), 7.42 – 7.31 (m, 6H, H_3, H_8, H_{19} and H_{21}), 7.03 (dd, *J* = 8.0, 8.4 Hz, 1H, H_7), 3.19 (s, 3H, H_{17}), 2.48 (s, 3H, H_1), 2.46 (s, 3H, H_{16}) (Figure S23). ^{13}C NMR ($CDCl_3$, δ/ppm): 160.59 (C_{14}), 154.81 (C_{12}), 152.24 (C_6), 150.08 (C_{15}), 145.38 (C_2), 140.01 (C_{18}), 134.57 (C_{10}), 132.36 (C_5), 129.81 (C_4), 129.67 (C_8), 129.26 (C_3), 128.54 (C_{20}), 127.13 (C_{21}), 126.59 (C_7), 124.55 (C_{19}), 123.72 (C_9), 120.69 (C_{11}), 118.03 (C_{13}), 35.67 (C_{16}), 21.77 (C_1), 10.03 (C_{17}) (Figure S24).

4-(((Antipyrine-4-yl)imino)methyl)phenyl 4-methylbenzenesulfonate (2c)

Light yellow solid, yield: 83%, m.p. 181-182 °C. FT-IR (ATR, cm^{-1}) υ_{max}: 3055, 3027 (C-H_{arom}), 2963, 2926 (C-H_{aliph}), 1638 (C=$O_{antipyrine}$), 1591 (C=N_{imino}), 1344 ($SO_{2antisym}$), 1194 (SO_{2sym}) (Figure S25). ^{1}H NMR ($CDCl_3$, δ/ppm): 9.71 (s, 1H, H_{10}), 7.78 (d, *J* = 8.4 Hz, 2H, H_8), 7.72 (d, *J* = 8.4 Hz, 2H, H_4), 7.50 (t, *J* = 7.8 Hz, 2H, H_{18}), 7.41 (d, *J* = 7.6 Hz, 2H, H_{17}) 7.36-7.31 (m, 3H, H_3 and H_{19}), 7.03 (d, *J* = 8.4 Hz, 2H, H_7), 3.18 (s, 3H, H_{15}), 2.49 (s, 3H, H_1), 2.46 (s, 3H, H_{14}) (Figure S26). ^{13}C NMR ($CDCl_3$, δ/ppm): 160.66 (C_{12}), 155.20 (C_{10}), 152.09 (C_6), 150.77 (C_{13}), 145.44 (C_2), 136.87 (C_{16}), 134.67 (C_5), 132.30 (C_9), 129.79 (C_{19}), 129.23 (C_{18}), 128.83 (C_4), 128.55 (C_8), 127.06 (C_3), 124.51 (C_{17}), 122.50 (C_7), 118.28 (C_{11}), 35.72 (C_{15}), 21.71 (C_1), 10.04 (C_{14}) (Figure S27).

2-(((Antipyrine-4-yl)imino)methyl)-6-methoxyphenyl 4-methylbenzenesulfonate (2d)

Light yellow solid, yield: 81%, m.p. 206-207 °C. FT-IR (ATR, cm^{-1}) υ_{max}: 3063, 3010 (C-H_{arom}), 2967, 2927 (C-H_{aliph}), 1649 (C=$O_{antipyrine}$), 1567 (C=N_{imino}), 1367 ($SO_{2antisym}$), 1143 (SO_{2sym}) (Figure S28). ^{1}H NMR ($CDCl_3$, δ/ppm): 9.59 (s, 1H, H_{13}), 7.85 (d, *J* = 8.4 Hz, 2H, H_4), 7.72 (d, *J* = 8.0 Hz, 1H, H_{10}), 7.50 (t, *J* = 7.8 Hz, 2H, H_{21}), 7.44 – 7.40 (m, 2H, H_{20}), 7.33 (t, *J* = 7.2 Hz, 1H, H_9), 7.27 – 7.23 (m, 3H, H_3 and H_{22}), 6.96 (d, *J* = 8.0 Hz, 1H, H_8), 3.73 (s, 3H, H_{12}), 3.16 (s, 3H, H_{18}), 2.47 (s, 3H, H_1), 2.32 (s, 3H, H_{17}). (Figure S29). ^{13}C NMR ($CDCl_3$, δ/ppm): 160.20 (C_{15}), 152.87 (C_{13}), 152.58 (C_7), 151.58 (C_6), 144.58 (C_2), 138.53 (C_{16}), 135.00 (C_{19}), 133.55 (C_5), 133.13 (C_{10}), 129.44 (C_4), 129.14 (C_3), 128.72 (C_{20}), 127.15 (C_{21}), 126.62 (C_9), 124.07 (C_{22}), 118.96 (C_8), 118.43 (C_{14}), 113.79 (C_{11}), 55.97 (C_{12}), 35.95 (C_{18}), 21.57 (C_1), 10.11 (C_{17}) (Figure S30).

2-(((Antipyrine-4-yl)imino)methyl)-5-methoxyphenyl 4-methylbenzenesulfonate (2e)

Shiny yellow solid, yield: 84%, m.p. 186-187 °C. FT-IR (ATR, cm^{-1}) υ_{max}: 3043, 3015 (C-H_{arom}), 2986, 2921 (C-H_{aliph}), 1633 (C=$O_{antipyrine}$), 1592 (C=N_{imino}), 1343 ($SO_{2antisym}$), 1179 (SO_{2sym}) (Figure S31). ^{1}H NMR ($CDCl_3$, δ/ppm): 9.56 (s, 1H, H_{12}), 8.00 (d, *J* = 9.6 Hz, 1H, H_{10}), 7.85 (d, *J* = 8.0 Hz, 2H, H_4), 7.52 (t, *J* = 7.8 Hz, 2H, H_{21}), 7.44 (d, *J* = 7.6 Hz, 2H, H_{20}), 7.34 (t, *J* = 7.2 Hz, 1H, H, H_{22}), 7.21 (d, *J* = 8.0 Hz, 2H, H_3), 6.87 (d, *J* = 6.8 Hz, 2H, H_7 and H_9), 3.83 (s, 3H, H_{12}), 3.13 (s, 3H, H_{18}), 2.43 (s, 3H, H_1), 2.32 (s, 3H, H_{17}) (Figure S32). ^{13}C NMR ($CDCl_3$, δ/ppm): 161.68 (C_{15}), 160.52 (C_8), 152.15 (C_{13}), 150.42 (C_6), 149.73 (C_{16}), 145.16 (C_2), 135.06 (C_{19}), 131.85 (C_5), 129.74 (C_4), 129.21 (C_3), 129.03 (C_{21}), 127.76 (C_{10}), 126.71 (C_{22}), 124.17 (C_{20}), 123.96 (C_9), 118.84 (C_{14}), 114.04 (C_{11}), 108.21 (C_7), 55.69 (C_{12}), 36.00 (C_{18}), 21.65 (C_1), 10.04 (C_{17}) (Figure S33).

5-(((Antipyrine-4-yl)imino)methyl)-2-methoxyphenyl 4-methylbenzenesulfonate (2f) (Chen and Yu, 2006b**)**

Yellow solid, yield: 78%, m.p. 199-200 °C. FT-IR (ATR, cm^{-1}) υ_{max}: 3063, 3012 (C-H_{arom}), 2980, 2930 (C-H_{aliph}), 1647 (C=$O_{antipyrine}$), 1594 (C=N_{imino}), 1370 ($SO_{2antisym}$), 1172 (SO_{2sym}) (Figure S34). ^{1}H NMR ($CDCl_3$, δ/ppm): 9.62 (s, 1H, H_{13}), 7.80 (d, *J* = 8.4 Hz, 2H, H_4), 7.72 (d, *J* = 1.6 Hz, 1H, H_{11}), 7.61 (dd, *J* = 8.4, 1.6 Hz, 1H, H_9), 7.50 (t, *J* = 7.6 Hz, 2H, H_{21}), 7.41 (d, *J* = 7.2 Hz, 2H, H_{20}), 7.34 – 7.28 (m, 3H, H_3 and H_{22}), 6.88 (d, *J* = 8.4 Hz, 1H, H_8), 3.64 (s, 3H, H_{12}), 3.17 (s, 3H, H_{18}), 2.47 (s, 3H, H_1), 2.46

(s, 3H, H_{17}) (Figure S35). ^{13}C NMR ($CDCl_3$, δ/ppm): 160.83 (C_{15}), 154.94 (C_7), 153.36 (C_{13}), 151.93 (C_6), 144.99 (C_2), 138.85 (C_{16}), 134.75 (C_{19}), 133.31 (C_5), 131.41 (C_{10}), 129.40 (C_4), 129.20 (C_3), 128.64 (C_{21}), 128.46 (C_{22}), 126.92 (C_9), 124.38 (C_{20}), 121.93 (C_{11}), 118.43 (C_{14}) , 112.22 (C_8), 55.74 (C_{12}), 35.85 (C_{18}), 21.71 (C_1), 10.05 (C_{17}) (Figure S36).

4-(((Antipyrine-4-yl)imino)methyl)-2-methoxyphenyl 4-methylbenzenesulfonate (2g)

Light yellow solid, yield: 82%, m.p. 192-193 °C. FT-IR (ATR, cm^{-1}) υ_{max}: 3069, 3038 (C-H_{arom}), 2963, 2939 (C-H_{aliph}), 1639 (C=$O_{antipyrine}$), 1562 (C=N_{imino}), 1347 ($SO_{2antisym}$), 1172 (SO_{2sym}) (Figure S37). ^{1}H NMR ($CDCl_3$, δ/ppm): 9.69 (s, 1H, H_{13}), 7.76 (t, *J* = 7.6 Hz, 2H, H_{21}), 7.50 (d, *J* = 6.8 Hz, 2H, H_4), 7.41 (d, *J* = 8.0 Hz, 2H, H_{20}), 7.35-7.26 (m, 5H, H_3, H_8, H_{10} and H_{22}), 7.20 (d, *J* = 7.6 Hz, 1H, H_7), 3.63 (s, 3H, H_{12}), 3.19 (s, 3H, H_{18}), 2.50 (s, 3H, H_1), 2.46 (s, 3H, H_{17}) (Figure S38). ^{13}C NMR ($CDCl_3$, δ/ppm): 160.66 (C_{15}), 155.68 (C_{13}), 151.99 (C_{11}), 151.93 (C_6), 145.05 (C_2), 139.71 (C_{16}), 137.77 (C_{19}), 134.62 (C_5), 133.10 (C_9), 129.36 (C_4), 129.25 (C_3), 128.69 (C_{21}), 127.07 (C_{22}), 124.47 (C_{20}), 124.01 (C_8), 120.86 (C_7), 118.30 (C_{14}), 110.53 (C_{10}), 55.53 (C_{12}), 35.77 (C_{18}), 21.70 (C_1), 10.15 (C_{17}) (Figure S39).

2-(((Antipyrine-4-yl)imino)methyl)-5-(Diethylamino)-phenyl 4-methylbenzenesulfonate (2h)

Shiny yellow solid, yield: 80%, m.p. 159-160 °C. FT-IR (ATR, cm^{-1}) υ_{max}: 3086, 3063 (C-H_{arom}), 2964, 2926 (C-H_{aliph}), 1652 (C=$O_{antipyrine}$), 1585 (C=N_{imino}), 1366 ($SO_{2antisym}$), 1170 (SO_{2sym}) (Figure S40). ^{1}H NMR ($CDCl_3$, δ/ppm): 9.47 (s, 1H, H_{14}), 7.90-7.88 (m, 3H, H_4 and H_{10}), 7.53-7.45 (m, 4H, H_{21} and H_{22}), 7.33 (t, *J* = 7.2 Hz, 1H, H_{23}), 7.21 (d, *J* = 8.0 Hz, 2H, H_3), 6.57 (d, *J* = 8.8 Hz, 1H, H_9), 6.50 (d, *J* = 2.1 Hz, 1H, H_7), 3.37 (q, *J* = 7.0 Hz, 4H, H_{12}), 3.09 (s, 3H, H_{19}), 2.42 (s, 3H, H_1), 2.32 (s, 3H, H_{18}), 1.18 (t, *J* = 7.0 Hz, 6H, H_{13}) (Figure S41). ^{13}C NMR ($CDCl_3$, δ/ppm): 160.89 (C_{16}), 151.85 (C_{14}), 151.41 (C_8), 150.66 (C_6), 150.02 (C_{17}), 144.76 (C_2), 135.35 (C_{20}), 132.38 (C_5), 129.63 (C_4), 129.12 (C_3), 129.02 (C_{22}), 127.97 (C_{10}), 126.37 (C_{23}), 123.86 (C_{21}), 119.84 (C_{11}), 117.77 (C_{15}), 110.24 (C_9), 105.23 (C_7), 44.66 (H_{12}), 36.35 (H_{19}), 21.63 (C_1), 12.55 (C_{13}), 10.14 (C_{18}) (Figure S42).

1-(((Antipyrine-4-yl)imino)methyl)naphthalen-2-yl 4-methylbenzenesulfonate (2i)

Light yellow solid, yield: 83%, m.p. 207-208 °C. FT-IR (ATR, cm^{-1}) υ_{max}:3105, 3061, 3034 (C-H_{arom}), 2972, 2922 (C-H_{aliph}), 1647 (C=$O_{antipyrine}$), 1582 (C=N_{imino}), 1342 ($SO_{2antisym}$), 1163 (SO_{2sym}) (Figure S43). ^{1}H NMR ($CDCl_3$, δ/ppm): 10.03 (s, 1H, H_{16}), 9.05 (d, *J* = 8.0 Hz, 1H, H_{14}), 7.86 (d, *J* = 8.8 Hz, 2H, H_4), 7.80 (d, *J* = 8.4 Hz, 2H, H_{24}), 7.57-7.52 (m, 4H, H_9, H_{10}, H_{11} and H_{12}), 7.50 – 7.44 (m, 3H, H_{23} and H_{25}), 7.39 (d, *J* = 7.6 Hz, 1H, H_{15}), 7.16 (d, *J* = 8.0 Hz, 2H, H_3), 3.22 (s, 3H, H_{21}), 2.51 (s, 3H, H_1), 2.33 (s, 3H, H_{20}) (Figure S44). ^{13}C NMR ($CDCl_3$, δ/ppm): 160.27 (C_{18}), 153.32 (C_{16}), 152.65 (C_6), 147.17 (C_{19}), 145.03 (C_2), 134.94 (C_5), 132.46 (C_{14}), 131.70 (C_8), 131.26 (C_{13}), 129.58 (C4), 129.29 (C24), 128.90 (C_{23}), 128.27 (C_3), 127.50 (C_{12}), 126.86 (C_{10}), 126.50 (C_{22}), 126.25 (C_{11}), 125.85 (C_9), 124.19 (C_{25} and C_{15}), 121.92 (C_{17}), 119.22 (C_7), 35.93 (C_{21}), 21.68 (C_1), 10.25 (C_{20}) (Figure S45).

Antioxidant activity assays of all synthesized molecules

In the total antioxidant activity assay, the synthesized compounds were assessed by employing *β*-carotene-linoleic acid model assay system (Miller, 1971). Additionally, the free radical scavenging activity and cation radical scavenging activity was established by DPPH (1,1-diphenyl-2-picrylhydrazyl) (Blois, 1958), and $ABTS^{+\cdot}$(2,2'-azino-bis(3-ethylbenzothiazoline-6-sulphonic acid) (Re et al., 1989) assay, respectively**.** The cupric-reducing antioxidant capacity was determined according to the method of Apak et al. (2004). DMSO was employed as negative control, while butylated hydroxy toluene (BHT) and butylated hydroxyl anisole (BHA) were utilized as positive controls.

RESULTS AND DISCUSSION

Chemistry

This study consists of two parts. In the first part of the study, target molecules whose biological importance is examined were synthesized. Also, The corresponding Schiff base derivatives were obtained in good yields (77-84%). The reaction sequence of the formation of all synthesized 4-methylbenzenesulfonyl ester derivatives (**1a-i)** and heterocyclic Schiff base analogs from 4-AAP (**2a-i)** in the scope of this research is outlined in Scheme 1. In the first step, sulfonyl ester derivatives were prepared via the treatment of 4-methylbenzenesulfonyl chloride with some phenolic aldehydes in dichloromethane medium in the presence of trimethylamine (TEA). In the second step of the synthesis process, heterocyclic Schiff base compounds were acquired via condensation reaction of 4-aminoantipyrine with sulfonyl ester derivatives in ethanol medium. As a result, six of the synthesized Schiff bases are new (**2c-e** and **2g-i**), two are known (**2b** and **2f**), and one is commercial (**2a**). All synthesis reactions were refluxed for 1 h with a magnetic stirrer and monitored by thin-layer chromatography. In the second part of the study, the antioxidant activity of target molecules was examined in detail using methods known in the literature (Sıcak et al., 2019; Sıcak 2021). All molecules were characterized by employing spectroscopic techniques such as 1D NMR (^{1}H and ^{13}C), 2D NMR (COSY and HMQC for only **2c**), and FT-IR.

FT-IR spectra of all synthesized sulfonyl ester derivatives (**1a-i**) showed absorption peaks in the 1670-1704 cm^{-1} range, representing the presence of the C=O group of the aldehyde (-CHO) and aliphatic C-H stretching band signal (two weak) of -CHO group was observed at 2812-2884 cm^{-1} and 2729-2793 cm^{-1}, respectively (Collado et al., 2006; Reddy et. al., 2010). Also, 3018-3111 cm^{-1} and 2906–3014 cm^{-1} determined in the range of weak absorption bands correspond aromatic and aliphatic C-H stretching vibrations, respectively. Besides, asymmetrical and symmetrical stretching bands of the SO_2 (S=O) were observed at 1357-1378 cm^{-1} and 1143-1176 cm^{-1}, respectively (Yadav et al., 2006; Piller et al., 2009). ^{1}H NMR spectra of all arylsulfonyl ester derivates (**1a-i)** were established in $CDCl_3$ as solvent. In ^{1}H NMR spectra of **1a-i**, the proton peak signal of the -HC=O (**1a-b**;H_{12}, **1c**;H_{10}, **1d-g**;H_{13}, **1h**;H_{14}, **1i**;H_{16}) was determined as singlet peaks at 9.80-10.41 ppm (Collado et al., 2006; Yadav 2006; Reddy et al., 2010). The proton peak signals of protons in the aromatic rings were observed between 6.39 and 9.16 ppm (Collado et al., 2006). Furthermore, the tosyl group's methyl protons (-CH_3) (for all compounds-H_1) resonated as singlet peaks at 2.46-2.48 ppm (Collado et al., 2006; Yadav et al., 2006; Piller et al., 2009). These results of the structures of arylsulfonyl ester compounds (**1a-i**) were found to be compatible with the literature.

In FT-IR spectrum results for targeted heterocyclic Schiff base molecules (**2a-i**), the characteristic carbonyl group (C=O) on the antipyrine ring were defined around 1633-1652 cm^{-1}, and the imino group (-C=N-) molecular scaffold showing formation Schiff base of the stretching absorption bands are determined around 1562-1594 cm^{-1} (Shukla et al., 2010). Sulfonate ester moiety displayed S=O asymmetrical and symmetrical stretching vibrations representing the presence of SO_2 functional group in all synthesized compounds were observed around 1342–1370 cm^{-1} and 1143-1194 cm^{-1}, respectively (Selvi et al., 2020). ^{1}H NMR spectra of **2a-i** indicated a clear singlet for the imino (-N=CH–) proton (**1a-b**;H_{12}, **1c**;H_{10}, **1d-g**;H_{13}, **1h**;H_{14}, **1i**;H_{16}) at 9.62-9.63 ppm (Shukla et al., 2010; Selvi et al., 2020). Methyl protons –N-CH_3 in 1st position (**2a-b**;H_{17}, **2c**;H_{15}, **2d-g**;H_{18}, **2h**;H_{19}, **2i**;H_{21}) and =C-CH_3 in 5th position (**2a-b**;H_{16}, **2c**;H_{14}, **2d-g**;H_{17}, **2h**;H_{18}, **2i**;H_{20}) of the antipyrine ring were observed as singlet around 3.09–3.19 and 2.32–2.46 ppm, respectively, and each equivalent to three protons (Shukla et al., 2010; Tok et al., 2019). The protons of aromatic rings were resonated in the aromatic region between 6.50 and 9.05 ppm (Tok et al., 2019; Selvi et al., 2020). ^{13}C NMR spectra results of **2a-i** were detected to be suitable with the structures of the target molecules. The signals at 10.03–10.25 ppm and 35.67–36.35 ppm for **2a-i** were described to be methyl carbons (=C-CH_3) (**2a-b**;C_{16}, **2c**;C_{14}, **2d-g**;C_{17}, **2h**;C_{18}, **2i**;C_{20}) and (–

N-CH_3) (**2a-b**;C_{17}, **2c**;C_{15}, **2d-g**;C_{18}, **2h**;C_{19}, **2i**;C_{21}) on antipyrine ring, respectively (Shukla et al., 2010; Tok et al., 2019). The signals at 105.23–160.52 ppm for the compounds were identified to carbons of the aromatic rings. The signals at 160.20–161.68 ppm for synthesized target molecules were observed to C=O carbon (**2a-b**;C_{14}, **2c**;C_{12}, **2d-g**;C_{15}, **2h**;C_{16}, **2i**;C_{18}) of the antipyrine ring (Shukla et al., 2010; Tok et al., 2019). The signals at 151.85–155.68 ppm for the final molecules belonged to the imino -N=CH– carbon (**2a-b**;C_{12}, **2c**;C_{10}, **2d-g**;C_{13}, **2h**;C_{14}, **2i**;C_{16}), which supports the formation of the Schiff base (Tok et al., 2019; Selvi et al., 2020). The spectroscopic data obtained to elucidate the structures of heterocyclic Schiff bases (**2a-i**), which are the target compounds, were found to be compatible with the literature, and it was proven that the compounds were synthesized. Also, FT-IR, NMR (^{1}H, and ^{13}C) spectra were given in the Supplementary Materials.

Three spin systems were observed in the COSY spectrum (H_3-H_4 and H_7-H_8) of compound **2c**, which was selected as a model molecule for the 2D NMR spectrum (Figure 1a).

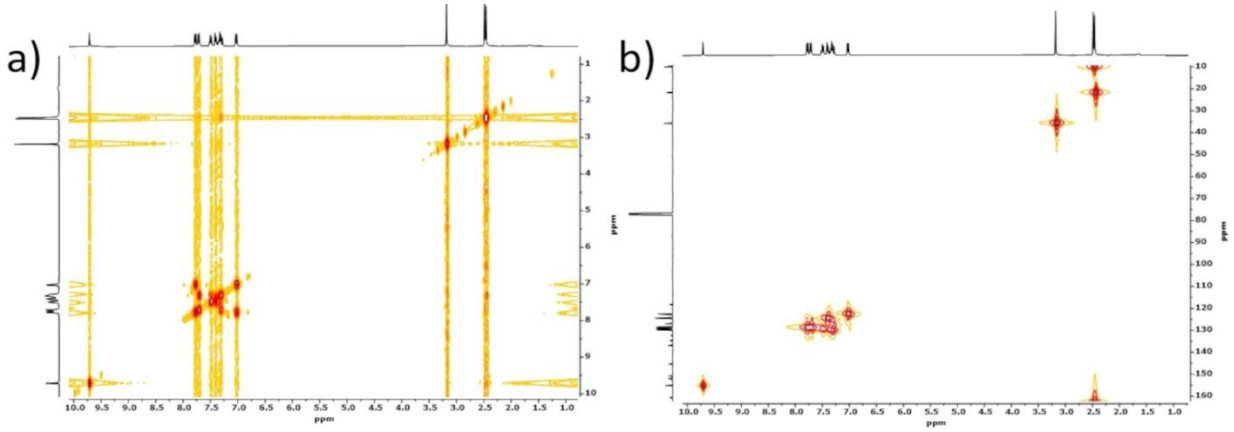


Figure 1. a) COSY spectrum of compound **2c**; **b)** HMQC spectrum of compound **2c**

The HMQC spectrum of compound **2c** displayed that H_1 was in correlation with C_1, and H_3 with C_3, H_4 with C_4, H_7 with C_7, H_8 with C_8, H_{10} with C_{10}, H_{14} with C_{14}, H_{15} with C_{15}, H_{17} with C_{17}, H_{18} with C_{18} and H_{19} with C_{19} (Figure 1b).

Antioxidant activity results

Understanding the relationship between free radicals and diseases has led to a significant increase in researchers' interest in antioxidants. In recent years, it has been seen in literature research that many studies have been conducted on obtaining antioxidants from natural sources or producing them synthetically. In this study, the antioxidant activity of sulfonyl ester (**1a-i**) and Schiff base (**2a-i)** derivatives at 50, 100, 200, and 400 µM concentrations were determined according to DPPH· and $ABTS^+$, *β*-carotene-linoleic acid and CUPRAC assays. The antioxidant activity of synthesized molecules is given in Table 1.

When examined in Table 1, in general, it is seen that Schiff base (**2a-i**) derivatives exhibit better antioxidant activity than sulfonyl ester (**1a-i**) derivatives. In the *β*-carotene-linoleic acid assay, compound **2e** showed the highest antioxidant activity among the synthesized molecules. In the DPPH assay, all synthesized molecules showed lower antioxidant activity than the molecules used as reference. However, compound **2e** (IC_{50}: 96.23±0.02 µM/mL) demonstrated other molecules' highest antioxidant activity. In the ABTS assay, compounds **2e** (IC_{50}: 41.88±0.21 µM/mL) and **2g** (IC_{50}: 50.75±0.32 µM/mL) from the synthesized compounds were determined to be the molecules with the highest activity compared to others. In the CUPRAC assay, among the synthesized molecules, compounds **2e** (IC_{50}: 73.49±0.00 µM/mL), **1e** (IC_{50}: 82.17±0.01 µM/mL) and **2g** (IC_{50}: 82.69±0.01 µM/mL) indicated the highest antioxidant activity, respectively.

Table 1. Antioxidant activity results of synthesized compounds **(1a-i)** and **(2a-i)**[a]

Compound	Antioxidant Activity			
	***β*-carotene-linoleic acid (IC_{50} µM/mL)**	**DPPH· activity (IC_{50} µM/mL)**	**$ABTS^{\cdot+}$ activity (IC_{50} µM/mL)**	**CUPRAC capacity ($A_{0.5}$ µM)**
1a	111.31±0.63	162.54±0.71	94.12±0.29	129.44±0.03
1b	99.61±0.86	146.74±0.33	88.01±0.16	117.80±0.00
1c	118.46±0.31	180.17±0.52	100.61±0.27	136.28±0.02
1d	86.27±0.55	128.91±0.30	71.34±0.79	93.75±0.01
1e	77.15±0.80	114.41±0.76	61.26±0.40	82.17±0.01
1f	94.80±0.67	139.66±0.24	78.86±0.26	107.72±0.01
1g	81.56±0.19	119.28±0.42	67.89±0.35	89.34±0.04
1h	90.38±0.51	133.76±0.11	72.09±0.77	104.89±0.00
1i	94.80±0.67	139.66±0.24	78.86±0.26	107.72±0.01
2a	100.46±0.09	153.61±0.82	89.76±0.74	117.21±0.00
2b	96.17±0.69	142.18±0.23	85.68±0.50	112.15±0.03
2c	103.30±0.76	158.42±0.66	94.80±0.61	122.88±0.01
2d	74.17±0.22	124.64±0.31	64.45±0.38	91.37±0.00
2e	58.79±0.58	96.23±0.02	41.88±0.21	73.49±0.00
2f	91.67±0.62	139.91±0.75	80.37±0.84	109.25±0.01
2g	66.06±0.13	105.33±0.19	50.75±0.32	82.69±0.01
2h	81.34±0.06	130.08±0.77	70.36±0.44	99.41±0.03
2i	87.03±0.94	135.35±0.51	74.27±0.55	104.34±0.02
BHA[b]	1.34±0.04	19.40±0.47	4.10±0.06	35.71±0.02
BHT[b]	2.34±0.09	54.97±0.99	2.91±0.55	4.00±0.04

[a]Values expressed are means ± S.E.M. of three parallel measurements. $p< 0.05$, significantly different with student's *t*-test.
[b]Reference compounds: BHA: butylated hydroxyl anisole, BHT: butylated hydroxy toluene.

CONCLUSION

In this study, 4-aminoantipyrine based Schiff base derivatives have been prepared. The antioxidant activity of the molecules was widely investigated by using four different methods. The structures of molecules were elucidated by utilizing FT-IR, ^{1}H- and ^{13}C- NMR, COSY, and HMQC. When study results were examined, it was determined that the molecules synthesized have antioxidant activity. It is thought that this study will shed light on the ongoing studies on the discovery of new antioxidant agents.

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Conflict of Interest

The author declares that there is no conflict of interest.

Author's Contributions

I hereby declare that the planning, execution and writing of the article was done by me as the sole author of the article.

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