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SYNTHESIS AND ANTIOXIDANT ACTIVITY EVALUATION OF TROLOX DERIVATIVES

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To find potent antioxidants, 16 novel Trolox derivatives were designed and synthesized via a reduction and esterification reaction. The chemical structures were characterized by NMR and MS. Trolox derivatives were employed to explore the potential structure–antioxidant activity relationships using three different assays. The results revealed that some of the synthesized compounds exhibited stronger antioxidant activities than L-ascorbic acid and Trolox, which suggests such compounds warrant further study.

Keywords: Trolox, derivatives, synthesis, antioxidant activity, structure activity relationship.

α-Tocopherol (vitamin E) is one of the most effective antioxidants in living organisms. It is the first line of defense against lipid peroxidation in biofilms [1] and plays an important role in the treatment of oxidative stress-related diseases, as supported by more and more clinical research results [2]. Considering its powerful antioxidant effect, vitamin E is an ideal structure for the development of an excellent antioxidant. Trolox (compound **1**) is a representative of its derivatives; it removes the long alkyl chain of vitamin E, retains the antioxidant functional group, and has a certain water solubility due to the presence of carboxyl groups. Thus, it is used more widely as a positive control to measure the antioxidant capacity of other antioxidants [3]. By reducing oxidative stress, compound **1** can reverse manganese-induced neurodevelopmental damage [4], protect the hippocampal nerve after ischemia-reperfusion injury [5], and prevent cigarette smoke-induced lung damage [6]. Compound **1** is used for improving arthritis symptoms [7] and the quality of frozen semen [8], in pig embryo development [9], to reduce the hemolysis of frozen red blood cells [10], and is also employed to protect cold ovarian tissue [11], inhibit glioblastoma growth [12], regulate immunity [13], and treat type 2 diabetes [14] and increase wound healing [15]. It is toxic to cancer cells, such as breast cancer and ovarian cancer [16, 17], and is effective for the treatment of metastatic cancer [18].

In the current study, Trolox was modified, and 16 compounds were designed and synthesized; none of them have previously been reported. Their structures were confirmed through NMR and ESI-MS. The synthesis of Trolox derivatives occurred in two steps. First, $LiAlH_4$ was used as a reducing agent to obtain compound **2** in high yield. Second, DCC and DMAP were used together as a condensing agent and catalyst, respectively, to afford ester products. The esterification reaction proceeded smoothly to obtain the target compound.

DPPH Assay. The radical scavenging activity of Trolox derivatives (**3–18**) compared with those of compound **2**, L-ascorbic acid, and Trolox was determined by DPPH assays, and the results are shown in Table 1. All compounds showed higher antioxidant capacity, ranging from IC_{50} 6.4 to 10.1 μM, than L-ascorbic acid (9.1 μM). Compound **2** (6.4 μM) and **9** (6.5 μM) exhibited good antioxidant activity, which is close to that of Trolox (4.1 μM).

ABTS Assay. The radical scavenging activity of Trolox derivatives (**3–18**) compared with those of compound **2**, L-ascorbic acid, and Trolox was determined by $ABTS^{\cdot+}$ assays is shown in Table 1. Except for compounds **4**, **5**, **9**, and **12**, all other compounds showed greater antioxidant activity (14.9–22.5 μM) than L-ascorbic acid (24.8 μM) and Trolox (22.7 μM).

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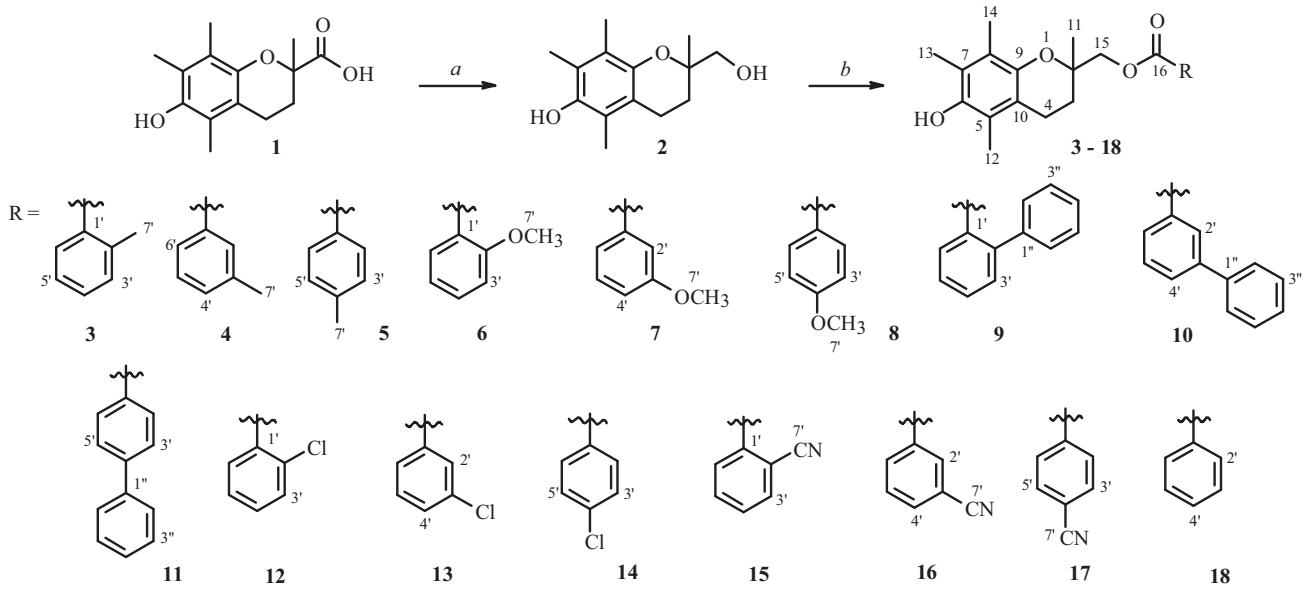
TABLE 1. Antioxidant Activity of Compounds **2–18**

Compound	DPPH (IC_{50}, μM)	ABTS (IC_{50}, μM)	FRAP, mmol/g
2	6.4 ± 0.1	22.5 ± 0.2	35.1 ± 0.10
3	8.3 ± 0.1	20.1 ± 0.2	33.4 ± 0.2
4	7.0 ± 0.1	25.3 ± 0.2	32.6 ± 0.3
5	9.6 ± 0.1	31.8 ± 0.1	29.7 ± 0.1
6	7.0 ± 0.1	17.8 ± 0.1	33.8 ± 0.2
7	7.4 ± 0.1	16.5 ± 0.1	34.1 ± 0.2
8	8.9 ± 0.1	19.9 ± 0.2	34.3 ± 0.3
9	6.5 ± 0.0	26.1 ± 0.2	32.3 ± 0.2
10	10.1 ± 0.1	22.4 ± 0.1	31.9 ± 0.3
11	8.5 ± 0.1	17.7 ± 0.1	29.8 ± 0.1
12	8.4 ± 0.1	30.9 ± 0.2	29.9 ± 0.2
13	8.9 ± 0.1	19.0 ± 0.1	31.2 ± 0.2
14	7.3 ± 0.0	18.4 ± 0.1	32.9 ± 0.3
15	7.8 ± 0.1	15.5 ± 0.1	34.5 ± 0.20
16	8.3 ± 0.1	17.1 ± 0.2	37.0 ± 0.3
17	8.6 ± 0.2	14.9 ± 0.1	33.8 ± 0.1
18	7.9 ± 0.2	17.7 ± 0.1	34.2 ± 0.2
L-Ascorbic acid	9.1 ± 0.2	24.8 ± 0.2	19.9 ± 0.2
Trolox	4.1 ± 0.0	22.7 ± 0.2	38.3 ± 0.2



a. $LiAH_4$, THF, reflux, 3 h; *b*. RCOOH, DCC, DMAP, THF, r.t., 12 h

FRAP Assay. The reducing power of Trolox derivatives (**3–18**), as evaluated by the FRAP assay (expressed in millimoles of Fe(II) per gram), compared with those of compound **2**, L-ascorbic acid, and Trolox is summarized in Table 1. All compounds have better antioxidant activity than L-ascorbic acid. Compounds **2** (35.1 mmol/g) and **16** (37.0 mmol/g) were discovered to have an antioxidant capacity close to that of Trolox (38.3 mmol/g).

EXPERIMENTAL

Genaral. Column chromatography was carried out on silica gel (200–300 mesh). Thin-layer chromatography (TLC) was performed using silica gel 60 F_{254} plates. ^1H NMR and ^{13}C NMR spectra were measured on an AV-600 Spectrometer (Bruker, Germany) using tetramethylsilane as internal standard. Electrospray ionization mass spectrometry (ESI-MS) was

performed on an Aglient 6520 Q-TOF spectrometer (Agilent, USA) in positive ionization mode. Melting points were determined in open capillary tubes, and the temperature was uncorrected.

Materials and Instruments. 2,2′-Azino-bis(3-ethylbenzothiazoline-6-sulfonic acid) diammonium salt (ABTS, 98%), dicyclohexylcarbodiimide (DCC, 98%), 4-dimethylaminopyridine (DMAP, 98%), 2,4,6-tris(2-pyridyl)-*s*-triazine (TPTZ, 98%), ferrous sulfate heptahydrate ($FeSO_4 \cdot 7H_2O$, 99%), L-ascorbic acid (98%), and anhydrous tetrahydrofuran (THF, 99.5%) were purchased from Energy Chemical. 6-Hydroxy-2,5,7,8-tetramethylchroman-2-carboxylic acid (Trolox, 98%) was purchased from TCI. 1,1-Diphenyl-2-picrylhydrazyl (DPPH, 95%) was purchased from Alfa Aesar.

Synthesis of Compound 2. The synthetic method to prepare compound **2** was reported in Li′s work [19]. Compound **1** (3.06 g, 12 mmol) and anhydrous THF (60 mL) were added to a reaction vessel and dissolved by stirring. $LiAlH_4$ (0.70 g, 18 mmol) was added in batches, and the reaction temperature was maintained below 0°C. After the addition, the ice bath was removed, and the reaction was refluxed for 6 h, after which H_2O (30 mL) was added, and the pH was adjusted to neutral with 2N HCl solution under stirring. The sample was extracted three times with 60 mL of EtOAc. The combined organic phases were then washed sequentially using saturated aqueous solutions of sodium bicarbonate and sodium chloride. The sample was then dried over anhydrous sodium sulfate, filtered, and the solvent evaporated under reduced pressure. The crude product was purified by flash column chromatography on silica gel to give 2.69 g of compound **2**.

Synthesis of Target Compounds 3–18. The synthetic method to prepare compounds **3–18** was reported in our previous work [20]. Substituted benzoic acid (0.4 mmol) and anhydrous THF (1 mL) were added to a dry standard Schlenk tube. DMAP (4.9 mg, 0.04 mmol), compound **2** (99.4 mg, 0.4 mmol), and DCC (90.7 mg, 0.44 mmol) were then added, and the reaction was carried out at room temperature for 12 h. The solvent was evaporated under reduced pressure and the residue dissolved in EtOAc (15 mL). The sample was washed sequentially using saturated aqueous solutions of sodium bicarbonate and sodium chloride. The sample was then dried over anhydrous sodium sulfate, filtered, and the solvent evaporated under reduced pressure. The crude product was purified by flash column chromatography on silica gel to give the desired compound.

2-(Hydroxymethyl)-2,5,7,8-tetramethylchroman-6-ol (2). $C_{14}H_{20}O_3$, light yellow solid, yield 93%, mp 113.8–114.4°C. PMR (600 MHz, $CDCl_3$, δ, ppm, J/Hz): 3.64 (1H, d, J = 11.3, H-15b), 3.59 (1H, d, J = 11.3, H-15a), 2.67 (2H, m, H-4), 2.16 (3H, s, H-13), 2.12 (3H, s, H-12), 2.11 (3H, s, H-14), 1.98 (1H, m, H-3b), 1.73 (1H, m, H-3a), 1.21 (3H, s, H-11).

(6-Hydroxy-2,5,7,8-tetramethylchroman-2-yl)methyl 2-Methylbenzoate (3). $C_{22}H_{26}O_4$, white solid, yield 55%, mp 79.6–81.4°C. PMR (600 MHz, DMSO-d_6, δ, ppm, J/Hz): 7.85 (1H, d, J = 7.6, H-6′), 7.48 (1H, t, J = 7.6, H-4′), 7.44 (1H, s, 6-OH), 7.33 (1H, m, H-5′), 7.32 (1H, m, H-3′), 4.29 (2H, s, H-15), 2.58 (2H, m, H-4), 2.53 (3H, s, H-7′), 2.05 (3H, s, H-13), 2.03 (3H, s, H-12), 1.96 (3H, s, H-14), 1.91 (1H, m, H-3b), 1.84 (1H, m, H-3a), 1.29 (3H, s, H-11). ^{13}C NMR (150 MHz, DMSO-d_6, δ, ppm): 166.6 (C-16), 145.5 (C-6), 143.9 (C-9), 139.2 (C-2′), 132.2 (C-4′), 131.7 (C-3′), 130.1 (C-1′), 129.3 (C-6′), 126.0 (C-5′), 122.7 (C-8), 121.0 (C-7), 120.3 (C-5), 116.5 (C-10), 73.1 (C-2), 68.4 (C-15), 28.3 (C-4), 21.5 (C-3), 21.2 (C-7′), 19.7 (C-11), 12.7 (C-14), 11.8 (C-12), 11.6 (C-13). ESI-MS *m/z* 355.1824 $[M + H]^+$.

(6-Hydroxy-2,5,7,8-tetramethylchroman-2-yl)methyl 3-Methylbenzoate (4). $C_{22}H_{26}O_4$, white solid, yield 54%, mp 118.6–120.2°C. PMR (600 MHz, DMSO-d_6, δ, ppm, J/Hz): 7.78 (1H, d, J = 7.6, H-6′), 7.77 (1H, s, H-2′), 7.46 (1H, d, J = 7.6, H-4′), 7.44 (1H, s, 6-OH), 7.41 (1H, t, J = 7.6, H-5′), 4.31 (1H, d, J = 11.2, H-15b), 4.28 (1H, d, J = 11.2, H-15a), 2.58 (2H, m, H-4), 2.36 (3H, s, H-7′), 2.04 (3H, s, H-13), 2.03 (3H, s, H-12), 1.96 (3H, s, H-14), 1.93 (1H, m, H-3b), 1.84 (1H, m, H-3a), 1.30 (3H, s, H-11). ^{13}C NMR (150 MHz, DMSO-d_6, δ, ppm): 165.5 (C-16), 145.5 (C-6), 144.0 (C-9), 138.2 (C-3′), 134.0 (C-4′), 129.6 (C-2′), 129.5 (C-1′), 128.6 (C-5′), 126.3 (C-6′), 122.7 (C-8), 121.1 (C-7), 120.3 (C-5), 116.7 (C-10), 73.2 (C-2), 68.4 (C-15), 28.4 (C-4), 21.7 (C-3), 20.8 (C-7′), 19.7 (C-11), 12.7 (C-14), 11.8 (C-12), 11.6 (C-13). ESI-MS *m/z* 355.1804 $[M + H]^+$.

(6-Hydroxy-2,5,7,8-tetramethylchroman-2-yl)methyl 4-Methylbenzoate (5). $C_{22}H_{26}O_4$, light yellow oil, yield 51%. PMR (600 MHz, DMSO-d_6, δ, ppm, J/Hz): 7.86 (2H, d, J = 8.0, H-2′, 6′), 7.44 (1H, s, 6-OH), 7.33 (2H, d, J = 8.0, H-3′, 5′), 4.28 (2H, s, H-15), 2.58 (2H, m, H-4), 2.37 (3H, s, H-7′), 2.04 (3H, s, H-13), 2.03 (3H, s, H-12), 1.94 (3H, s, H-14), 1.92 (1H, m, H-3b), 1.84 (1H, m, H-3a), 1.30 (3H, s, H-11). ^{13}C NMR (150 MHz, DMSO-d_6, δ, ppm): 165.4 (C-16), 145.5 (C-6), 143.9 (C-9), 143.7 (C-4′), 129.3 (C-2′, 6′), 129.1 (C-3′, 5′), 126.9 (C-1′), 122.7 (C-8), 121.1 (C-7), 120.3 (C-5), 116.6 (C-10), 73.1 (C-2), 68.2 (C-15), 28.3 (C-4), 21.6 (C-3), 21.1 (C-7′), 19.7 (C-11), 12.7 (C-14), 11.7 (C-12), 11.6 (C-13). ESI-MS *m/z* 355.1829 $[M + H]^+$.

(6-Hydroxy-2,5,7,8-tetramethylchroman-2-yl)methyl 2-Methoxybenzoate (6). $C_{22}H_{26}O_5$, light yellow oil, yield 50%. PMR (600 MHz, DMSO-d_6, δ, ppm, J/Hz): 7.66 (1H, m, H-6′), 7.55 (1H, m, H-4′), 7.43 (1H, s, 6-OH), 7.16 (1H, d, J = 8.4, H-3′), 7.02 (1H, t, J = 7.5, H-5′), 4.23 (2H, s, H-15), 3.81 (3H, s, H-7′), 2.58 (2H, m, H-4), 2.04 (3H, s, H-13), 2.03 (3H, s, H-12), 1.96 (3H, s, H-14), 1.93 (1H, m, H-3b), 1.82 (1H, m, H-3a), 1.29 (3H, s, H-11). ^{13}C NMR (150 MHz, DMSO-d_6, δ, ppm): 165.4 (C-16), 158.4 (C-2′), 145.5 (C-6), 144.0 (C-9), 133.7 (C-4′), 130.7 (C-6′), 122.7 (C-8), 121.1 (C-7), 120.3 (C-5),

120.1 (C-5′), 119.9 (C-1′), 116.6 (C-10), 112.7 (C-3′), 73.2 (C-2), 68.2 (C-15), 55.7 (C-7′), 28.2 (C-4), 21.6 (C-3), 19.7 (C-11), 12.7 (C-14), 11.8 (C-12), 11.6 (C-13). ESI-MS *m/z* 371.1779 $[M + H]^+$.

(6-Hydroxy-2,5,7,8-tetramethylchroman-2-yl)methyl 3-Methoxybenzoate (7). $C_{22}H_{26}O_5$, white solid, yield 74%, mp 95.6–97.6°C. PMR (600 MHz, DMSO-d_6, δ, ppm, J/Hz): 7.56 (1H, d, J = 7.8, H-6′), 7.46 (2H, m, H-2′, 5′), 7.44 (1H, s, 6-OH), 7.24 (1H, m, H-4′), 4.32 (1H, d, J = 11.2, H-15b), 4.28 (1H, d, J = 11.2, H-15a), 3.81 (3H, s, H-7′), 2.59 (2H, m, H-4), 2.04 (3H, s, H-13), 2.03 (3H, s, H-12), 1.95 (3H, s, H-14), 1.92 (1H, m, H-3b), 1.85 (1H, m, H-3a), 1.30 (3H, s, H-11). ^{13}C NMR (150 MHz, DMSO-d_6, δ, ppm): 165.2 (C-16), 159.3 (C-3′), 145.5 (C-6), 143.9 (C-9), 131.0 (C-1′), 130.0 (C-5′), 122.7 (C-8), 121.3 (C-6′), 121.1 (C-7), 120.3 (C-5), 119.2 (C-4′), 116.6 (C-10), 113.9 (C-2′), 73.1 (C-2), 68.5 (C-15), 55.3 (C-7′), 28.3 (C-4), 21.6 (C-3), 19.7 (C-11), 12.7 (C-14), 11.8 (C-12), 11.6 (C-13). ESI-MS *m/z* 371.1774 $[M + H]^+$.

(6-Hydroxy-2,5,7,8-tetramethylchroman-2-yl)methyl 4-Methoxybenzoate (8). $C_{22}H_{26}O_5$, white solid, yield 60%, mp 69.1–71.2°C. PMR (600 MHz, DMSO-d_6, δ, ppm, J/Hz): 7.92 (2H, d, J = 8.8, H-2′, 6′), 7.43 (1H, s, 6-OH), 7.06 (2H, d, J = 8.9, H-3′, 5′), 4.27 (1H, d, J = 11.2, H-15b), 4.24 (1H, d, J = 11.2, H-15a), 3.83 (3H, s, H-7′), 2.58 (2H, m, H-4), 2.04 (3H, s, H-13), 2.03 (3H, s, H-12), 1.94 (3H, s, H-14), 1.92 (1H, m, H-3b), 1.84 (1H, m, H-3a), 1.30 (3H, s, H-11). ^{13}C NMR (150 MHz, DMSO-d_6, δ, ppm): 165.1 (C-16), 163.2 (C-4′), 145.5 (C-6), 144.0 (C-9), 131.2 (C-2′, 6′), 122.7 (C-8), 121.8 (C-1′), 121.1 (C-7), 120.3 (C-5), 116.6 (C-10), 114.1 (C-3′, 5′), 73.2 (C-2), 68.1 (C-15), 55.5 (C-7′), 28.3 (C-4), 21.7 (C-3), 19.7 (C-11), 12.7 (C-14), 11.8 (C-12), 11.6 (C-13). ESI-MS *m/z* 371.1790 $[M + H]^+$.

(6-Hydroxy-2,5,7,8-tetramethylchroman-2-yl)methyl [1,1′-Biphenyl]-2-carboxylate (9). $C_{27}H_{28}O_4$, white solid, yield 61%, mp 111.2–113.4°C. PMR (600 MHz, DMSO-d_6, δ, ppm, J/Hz): 7.76 (1H, dd, J = 7.6, 1.2, H-6′), 7.62 (1H, td, J = 7.6, 1.2, H-4′), 7.50 (1H, td, J = 7.6, 1.2, H-5′), 7.43 (1H, s, 6-OH), 7.42 (1H, d, J = 7.6, H-3′), 7.38 (2H, m, H-2″, 6″), 7.34 (1H, m, H-4″), 7.29 (2H, m, H-3″, 5″), 4.03 (1H, d, J = 11.0, H-15b), 3.99 (1H, d, J = 11.0, H-15a), 2.39 (2H, m, H-4), 2.03 (3H, s, H-13), 2.00 (3H, s, H-12), 1.92 (3H, s, H-14), 1.49 (2H, t, J = 7.0, H-3), 0.99 (3H, s, H-11). ^{13}C NMR (150 MHz, DMSO-d_6, δ, ppm): 167.9 (C-16), 145.5 (C-6), 143.8 (C-9), 141.3 (C-1″), 140.6 (C-2′), 131.5 (C-4′), 130.7 (C-6′), 130.7 (C-1′), 129.3 (C-4″), 128.3 (C-3″, 5″), 128.1 (C-2″, 6″), 127.4 (C-5′), 127.2 (C-8), 122.7 (C-7), 121.0 (C-3′), 120.2 (C-5), 116.5 (C-10), 72.7 (C-2), 68.6 (C-15), 27.8 (C-4), 21.5 (C-3), 19.6 (C-11), 12.7 (C-14), 11.8 (C-12), 11.6 (C-13). ESI-MS *m/z* 417.1984 $[M + H]^+$.

(6-Hydroxy-2,5,7,8-tetramethylchroman-2-yl)methyl [1,1′-Biphenyl]-3-carboxylate (10). $C_{27}H_{28}O_4$, light yellow oil, yield 57%. PMR (600 MHz, DMSO-d_6, δ, ppm, J/Hz): 8.20 (1H, s, H-2′), 7.97 (1H, d, J = 7.8, H-6′), 7.95 (1H, d, J = 7.8, H-4′), 7.67 (2H, d, J = 7.7, H-2″, 6″), 7.63 (1H, t, J = 7.7, H-5′), 7.50 (2H, t, J = 7.7, H-3″, 5″), 7.45 (1H, s, 6-OH), 7.41 (1H, t, J = 7.7, H-4″), 4.37 (1H, d, J = 11.2, H-15b), 4.31 (1H, d, J = 11.2, H-15a), 2.59 (2H, m, H-4), 2.04 (3H, s, H-13), 2.03 (3H, s, H-12), 1.97 (3H, s, H-14), 1.94 (1H, m, H-3b), 1.86 (1H, m, H-3a), 1.32 (3H, s, H-11). ^{13}C NMR (150 MHz, DMSO-d_6, δ, ppm): 165.3 (C-16), 145.5 (C-6), 143.9 (C-9), 140.7 (C-3′), 139.1 (C-1″), 131.6 (C-4′), 130.3 (C-1′), 129.6 (C-2′), 129.1 (C-3″, 5″), 128.1 (C-6′), 128.0 (C-4″), 127.1 (C-5′), 126.7 (C-2″, 6″), 122.7 (C-8), 121.1 (C-7), 120.3 (C-5), 116.7 (C-10), 73.2 (C-2), 68.6 (C-15), 28.4 (C-4), 21.7 (C-3), 19.7 (C-11), 12.7 (C-14), 11.8 (C-12), 11.6 (C-13). ESI-MS *m/z* 417.1956 $[M + H]^+$.

(6-Hydroxy-2,5,7,8-tetramethylchroman-2-yl)methyl [1,1′-Biphenyl]-4-carboxylate (11). $C_{27}H_{28}O_4$, white solid, yield 49%, mp 146.2–147.6°C. PMR (600 MHz, DMSO-d_6, δ, ppm, J/Hz): 8.05 (2H, d, J = 8.3, H-2′, 6′), 7.83 (2H, d, J = 8.3, H-3′, 5′), 7.73 (2H, d, J = 7.6, H-2″, 6″), 7.51 (2H, t, J = 7.6, H-3″, 5″), 7.44 (1H, s, 6-OH), 7.43 (1H, t, J = 7.6, H-4″), 4.34 (1H, d, J = 11.2, H-15b), 4.32 (1H, d, J = 11.2, H-15a), 2.59 (2H, m, H-4), 2.04 (6H, s, H-12, 13), 1.96 (3H, s, H-14), 1.94 (1H, m, H-3b), 1.87 (1H, m, H-3a), 1.32 (3H, s, H-11). ^{13}C NMR (150 MHz, DMSO-d_6, δ, ppm): 165.3 (C-16), 145.5 (C-6), 144.8 (C-1′), 144.0 (C-9), 138.8 (C-4′), 129.8 (C-3″, 5″), 129.1 (C-2″, 6″), 128.4 (C-1″), 127.0 (C-3′, 5′), 127.0 (C-2′, 6′, 4″), 122.7 (C-8), 121.1 (C-7), 120.3 (C-5), 116.6 (C-10), 73.2 (C-2), 68.5 (C-15), 28.3 (C-4), 21.7 (C-3), 19.7 (C-11), 12.7 (C-14), 11.8 (C-12), 11.6 (C-13). ESI-MS *m/z* 417.1969 $[M + H]^+$.

(6-Hydroxy-2,5,7,8-tetramethylchroman-2-yl)methyl 2-Chlorobenzoate (12). $C_{21}H_{23}ClO_4$, light yellow oil, yield 56%. PMR (600 MHz, DMSO-d_6, δ, ppm, J/Hz): 7.81 (1H, d, J = 7.6, H-6′), 7.59 (2H, m, H-3′, 5′), 7.47 (1H, m, H-4′), 7.44 (1H, s, 6-OH), 4.32 (2H, s, H-15), 2.58 (2H, m, H-4), 2.04 (3H, s, H-13), 2.03 (3H, s, H-12), 1.96 (3H, s, H-14), 1.92 (1H, m, H-3b), 1.83 (1H, m, H-3a), 1.29 (3H, s, H-11). ^{13}C NMR (150 MHz, DMSO-d_6, δ, ppm): 164.7 (C-16), 145.5 (C-6), 143.9 (C-9), 133.3 (C-4′), 131.9 (C-2′), 131.1 (C-1′), 130.9 (C-6′), 129.8 (C-3′), 127.4 (C-5′), 122.8 (C-8), 121.1 (C-7), 120.3 (C-5), 116.5 (C-10), 73.0 (C-2), 69.1 (C-15), 28.2 (C-4), 21.5 (C-3), 19.6 (C-11), 12.7 (C-14), 11.8 (C-12), 11.7 (C-13). ESI-MS *m/z* 375.1198 $[M + H]^+$.

(6-Hydroxy-2,5,7,8-tetramethylchroman-2-yl)methyl 3-Chlorobenzoate (13). $C_{21}H_{23}ClO_4$, white solid, yield 73%, mp 59.8–60.2°C. PMR (600 MHz, DMSO-d_6, δ, ppm, J/Hz): 7.91 (1H, d, J = 7.9, H-2′), 7.89 (1H, d, J = 1.5, H-6′), 7.72 (1H,

d, J = 7.9, H-4′), 7.56 (1H, t, J = 7.9, H-5′), 7.44 (1H, s, 6-OH), 4.32 (1H, s, H-15b), 4.31 (1H, s, H-15a), 2.58 (2H, br.s, H-4), 2.04 (3H, s, H-13), 2.03 (3H, s, H-12), 1.95 (3H, s, H-14), 1.92 (1H, s, H-3b), 1.84 (1H, s, H-3a), 1.30 (3H, s, H-11). ^{13}C NMR (150 MHz, DMSO-d_6, δ, ppm): 164.2 (C-16), 145.6 (C-6), 143.9 (C-9), 133.5 (C-1′), 133.2 (C-3′), 131.6 (C-4′), 130.9 (C-5′), 128.6 (C-2′), 127.8 (C-6′), 122.7 (C-8), 121.0 (C-7), 120.3 (C-5), 116.6 (C-10), 73.1 (C-2), 68.9 (C-15), 28.3 (C-4), 21.6 (C-3), 19.7 (C-11), 12.7 (C-14), 11.8 (C-12), 11.6 (C-13). ESI-MS *m/z* 375.1179 $[M + H]^+$.

(6-Hydroxy-2,5,7,8-tetramethylchroman-2-yl)methyl 4-Chlorobenzoate (14). $C_{21}H_{23}ClO_4$, white solid, yield 56%, mp 121.3–122.9°C. PMR (600 MHz, DMSO-d_6, δ, ppm, J/Hz): 7.95 (2H, d, J = 8.8, H-2′, 6′), 7.59 (2H, d, J = 8.8, H-3′, 5′), 7.44 (1H, s, 6-OH), 4.30 (2H, s, H-15), 2.58 (2H, m, H-4), 2.03 (3H, s, H-13), 2.02 (3H, s, H-12), 1.93 (3H, s, H-14), 1.91 (1H, m, H-3b), 1.84 (1H, m, H-3a), 1.30 (3H, s, H-11). ^{13}C NMR (150 MHz, DMSO-d_6, δ, ppm): 164.6 (C-16), 145.5 (C-6), 143.9 (C-9), 138.4 (C-4′), 130.9 (C-2′, 6′), 129.0 (C-3′, 5′), 128.4 (C-1′), 122.7 (C-8), 121.1 (C-7), 120.3 (C-5), 116.6 (C-10), 73.1 (C-2), 68.7 (C-15), 28.3 (C-4), 21.6 (C-3), 19.7 (C-11), 12.7 (C-14), 11.7 (C-12), 11.6 (C-13). ESI-MS *m/z* 375.1163 $[M + H]^+$.

(6-Hydroxy-2,5,7,8-tetramethylchroman-2-yl)methyl 2-Cyanobenzoate (15). $C_{22}H_{23}NO_4$, white solid, yield 70%, mp 141.2–142.3°C. PMR (600 MHz, DMSO-d_6, δ, ppm, J/Hz): 8.13 (1H, m, H-6′), 8.03 (1H, m, H-5′),7.86 (2H, m, H-3′, 4′), 7.43 (1H, s, 6-OH), 4.38 (2H, s, H-15), 2.59 (2H, m, H-4), 2.03 (6H, s, H-12, 13), 2.03 (3H, s, H-12), 1.98 (1H, m, H-3b), 1.94 (3H, s, H-14), 1.87 (1H, m, H-3a), 1.34 (3H, s, H-11). ^{13}C NMR (150 MHz, DMSO-d_6, δ, ppm): 163.3 (C-16), 145.5 (C-6), 143.9 (C-9), 135.3 (C-4′), 133.6 (C-5′), 133.4 (C-3′), 131.4 (C-6′), 130.9 (C-1′), 122.7 (C-8), 121.1 (C-7), 120.3 (C-5), 117.3 (C-7′), 116.6 (C-10), 111.6 (C-2′), 73.1 (C-2), 69.4 (C-15), 28.3 (C-4), 21.7 (C-3), 19.7 (C-11), 12.7 (C-14), 11.8 (C-12), 11.6 (C-13). ESI-MS *m/z* 366.1622 $[M + H]^+$.

(6-Hydroxy-2,5,7,8-tetramethylchroman-2-yl)methyl 3-Cyanobenzoate (16). $C_{22}H_{23}NO_4$, white solid, yield 64%, mp 116.2–118.1°C. PMR (600 MHz, DMSO-d_6, δ, ppm, J/Hz): 8.31 (1H, s, H-2′), 8.24 (1H, d, J = 7.9, H-6′), 8.13 (1H, d, J = 7.7, H-4′), 7.75 (1H, t, J = 7.8, H-5′), 7.43 (1H, s, 6-OH), 4.36 (1H, d, J = 11.2, H-15b), 4.33 (1H, d, J = 11.2, H-15a), 2.59 (2H, m, H-4), 2.03 (6H, s, H-12, 13), 1.98 (1H, m, H-3b), 1.94 (3H, s, H-14), 1.86 (1H, m, H-3a), 1.32 (3H, s, H-11). ^{13}C NMR (150 MHz, DMSO-d_6, δ, ppm): 163.9 (C-16), 145.5 (C-6), 143.9 (C-9), 136.8 (C-4′), 133.6 (C-6′), 132.6 (C-2′), 130.7 (C-1′), 130.3 (C-5′), 122.7 (C-8), 121.0 (C-7), 120.3 (C-5), 117.9 (C-7′), 116.6 (C-10), 112.2 (C-3′), 73.1 (C-2), 69.0 (C-15), 28.3 (C-4), 21.7 (C-3), 19.7 (C-11), 12.7 (C-14), 11.8 (C-12), 11.6 (C-13). ESI-MS *m/z* 366.1602 $[M + H]^+$.

(6-Hydroxy-2,5,7,8-tetramethylchroman-2-yl)methyl 4-Cyanobenzoate (17). $C_{22}H_{23}NO_4$, white solid, yield 61%, mp 153.8–155.4°C. PMR (600 MHz, DMSO-d_6, δ, ppm, J/Hz): 8.10 (2H, d, J = 8.2, H-2′, 6′), 8.02 (2H, d, J = 8.2, H-3′, 5′), 7.44 (1H, s, 6-OH), 4.35 (2H, br.s, H-15), 2.59 (2H, m, H-4), 2.02 (6H, s, H-12, 13), 1.97 (1H, m, H-3b), 1.92 (3H, s, H-14), 1.86 (1H, m, H-3a), 1.31 (3H, s, H-11). ^{13}C NMR (150 MHz, DMSO-d_6, δ, ppm): 164.2 (C-16), 145.5 (C-6), 143.9 (C-9), 133.5 (C-1′), 132.9 (C-3′, 5′), 129.8 (C-2′, 6′), 122.7 (C-8), 121.0 (C-7), 118.0 (C-7′), 116.6 (C-10), 115.6 (C-5), 109.5 (C-4′), 73.1 (C-2), 69.1 (C-15), 28.3 (C-4), 21.6 (C-3), 19.7 (C-11), 12.7 (C-14), 11.8 (C-12), 11.6 (C-13). ESI-MS *m/z* 366.1593 $[M + H]^+$.

(6-Hydroxy-2,5,7,8-tetramethylchroman-2-yl)methyl Benzoate (18). $C_{21}H_{24}O_4$, white solid, yield 59%, mp 133.8–134.2°C. PMR (600 MHz, DMSO-d_6, δ, ppm, J/Hz): 7.98 (2H, d, J = 8, H-2′, 6′), 7.67 (1H, m, H-4′), 7.54 (2H, m, H-3′, 5′), 7.44 (1H, s, 6-OH), 4.32 (1H, d, J = 11.2, H-15b), 4.29 (1H, d, J = 11.2, H-15a), 2.59 (2H, m, H-4), 2.03 (3H, s, H-13), 2.03 (3H, s, H-12), 1.94 (3H, s, H-14), 1.93 (1H, m, H-3b), 1.85 (1H, m, H-3a), 1.31 (3H, s, H-11). ^{13}C NMR (150 MHz, DMSO-d_6, δ, ppm): 165.4 (C-16), 145.5 (C-6), 143.9 (C-9), 133.4 (C-4′), 129.6 (C-1′), 129.1 (C-2′, 6′), 128.8 (C-3′, 5′), 122.7 (C-8), 121.1 (C-7), 120.3 (C-5), 116.6 (C-10), 73.2 (C-2), 68.4 (C-15), 28.3 (C-4), 21.6 (C-3), 19.7 (C-11), 12.7 (C-14), 11.8 (C-12), 11.6 (C-13). ESI-MS *m/z* 341.1651 $[M + H]^+$.

Antioxidant Activities. DPPH Assay. DPPH scavenging activity was assayed according to our previously published method [20].

ABTS Assay. ABTS radical cation ($ABTS^{\cdot+}$) scavenging activity was assayed according to our previously published method [20].

FRAP Assay. FRAP assay was assayed according to our previously published method [20].

Statistical Analysis. All the experiments were carried out in triplicate, and the data were analyzed using SPSS v22.0 (IBM, Armonk, NY, USA).

In summary, a series of Trolox derivatives has been synthesized and screened for antioxidant activity. All compounds showed good antioxidant activity; compounds **2**, **9**, **15–17** showed the highest antioxidant activity. The compounds synthesized in this study may be used for the development of new antioxidants.

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