New Dihydrostilbene Derivatives from the Leaves of *Glycyrrhiza glabra* and Evaluation of Their Antioxidant Activity

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Five new prenylated dihydrostilbenes, α,α′-dihydro-3,5,4′-trihydroxy-4,5′-diisopentenylstilbene (**1**), α,α′-dihydro-3,5,3′,4′-tetrahydroxy-4,5′-diisopentenylstilbene (**2**), α,α′-dihydro-3,5,4′-trihydroxy-5′-isopentenylstilbene (**3**), α,α′-dihydro-3,5,3′-trihydroxy-4′-methoxy-5′-isopentenylstilbene (**4**), and α,α′-dihydro-3,5,3′,4′-tetrahydroxy-5′-isopentenyl stilbene (**5**), along with four known flavonoids, glabranin (**6**), pinocembrin, (**7**), licoflavone (**8**), and wighteone (**9**), were isolated from a lipid extract of the leaves of Sicilian *Glycyrrhiza glabra*. The structures of the compounds were elucidated by spectroscopic methods. The antioxidant activities of the crude extracts and the isolated compounds were tested.

Glycyrrhiza glabra (liquorice) (Leguminose) is a plant with a rich ethnobotanical tradition. The roots are used as a folk medicament both in Europe and in eastern countries, particularly China, where it is found in the Official Pharmacopoeia. The main components are the triterpene saponins glycyrrhizin and glycyrrhetic acid, which are believed to be partly responsible for its antiulcer, antiinflammatory, expectorant, antiphlogistic, and antiallergic properties, as well as its ability to "fight" low blood pressure.[1] Moreover, *Glycyrrhiza* root extracts have antimicrobial[2−5] and antioxidant[6] activities due to the presence of a variety of phenolic compounds including flavonoids, isoflavonoids, chalcones, and bibenzyls.

The aerial parts of the plant are scarcely used and always considered as waste products. However, recent studies[7−9] on the aerial parts of plant belonging to different species of this genus have highlighted the antimicrobial and anti-HIV properties of their extracts, ascribable to flavonoids[7] and bibenzylic[8] compounds, respectively.

In our ongoing program aimed at the isolation of new antioxidant natural substances from Sicilian wild flora, we report here the structural determination of five new dihydrostilbenes from *G. glabra* and the evaluation of their antioxidant effects in a model system.

Results and Discussion

Fresh leaves of *Glycyrrhiza glabra* were defatted with hexane and then extracted with ethyl acetate at room temperature as detailed in the Experimental Section. The concentration of total phenols, determined by the Folin-Ciocalteau method, was 1903 mequiv/L as gallic acid. This result prompted us to evaluate the efficacy of the liquorice extract to inhibit peroxide formation in a common seed oil. Figure 1 shows the increase of the peroxide value (PV) of commercial sunflower oil in a 40-day period. The behavior of *G. glabra* extract is comparable to the effects of butyl hydroxyl toluene (BHT), a well-known food antioxidant. Accordingly, repeated chromatographic fractionations (see Experimental Section) of the lipid extract were carried out to give five new dihydrostilbene derivatives, namely, α,α′-dihydro-3,5,4′-trihydroxy-4,5′-diisopentenylstilbene (**1**), α,α′-dihydro-3,5,3′,4′-tetrahydroxy-4,5′-diisopentenylstilbene (**2**), α,α′-dihydro-3,5,4′-trihydroxy-5′-isopentenylstilbene (**3**), α,α′-dihydro-3,5,3′-trihydroxy-4′-methoxy-5′-isopentenylstilbene (**4**), and α,α′-dihydro-3,5,3′,4′-tetrahydroxy-5′-isopentenyl stilbene (**5**). The separations also afforded four known flavonoids, glabranin (**6**), pinocembrin, (**7**), licoflavone (**8**), and wighteone (**9**), whose structures were elucidated on the basis of comparison with literature data.[7,10,11]

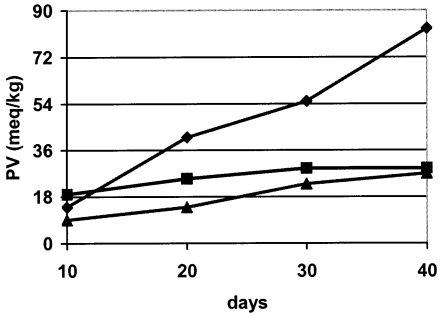
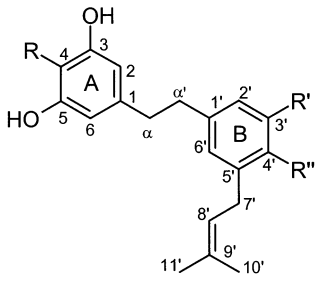


Figure 1. Peroxide value variation of sunflower seed oil: with BHT (▲), with liquorice leaves extract (■), blank (◆); standard deviation (SD = ±10%).



	R	R'	R"
1		H	OH
2		OH	OH
3	H	H	OH
4	H	OH	OCH_3
5	H	OH	OH

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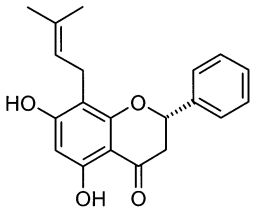
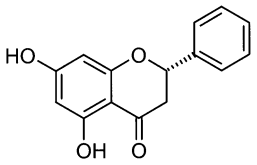
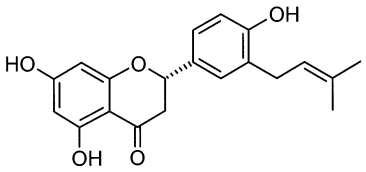


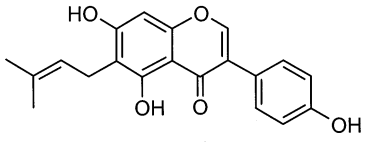
Glabranin (**6**)



Pinocembrin (**7**)



Licoflavone (**8**)



Wighteone (**9**)

The first compound, α,α′-dihydro-3,5,4′-trihydroxy-4,5′-diisopentenylstilbene (**1**), is an amorphous solid. The molecular formula $C_{24}H_{30}O_3$ was established by HREIMS ([M^+] 366.2190). UV absorptions at 210, 230, and 280 nm, ascribable to aromatic ring chromophores, were indicative of this class of compounds.[12] The IR spectrum showed absorptions at 3692 and 3582 cm^{-1} (OH) and 1603 cm^{-1} (benzenoids), which indicated the compound's phenolic nature. ^{1}H NMR (Table 1) showed resonances at δ 1.77 and 1.83 (each 3H, s) and at δ 1.78 (6H, bs), characteristic of four methyl groups; two triplets partially overlapped at δ 5.27 and 5.32 (2H, t, J = 7 Hz) are indicative of the presence of two vinyl groups, and the signals at δ 3.40 and 3.34 (each 2H, d, J = 7 Hz) are attributable to allyl groups. In the complex, these signals indicated the presence of two isopentenyl substituents. The analysis of the aromatic region of the spectrum led us to establish the substitution pattern of the aromatic rings. In particular, the signal at δ 6.25 (2H, bs) relative to two meta-coupled protons characteristics of a 1,3,4,5-tetrasubstitued benzene ring was attributed to the A ring, whereas a 1,4,5-trisubstitution pattern was assigned to the aromatic B ring owing to the presence of the signals of three aromatic protons at δ 6.73 (1H, d, J = 8 Hz), 6.90 (1H, d, J = 2 Hz), and 6.92 (1H, dd, 2, 8 Hz). Finally, the ^{1}H NMR spectrum showed a resonance at δ 2.75 (4H, m) relative to α,α′-methylenes. The ^{13}C NMR spectrum, along with the DEPT experiment, showed 20 signals, in contrast with the molecular weight as determined by the mass spectra; hence the presence of some overlapped signals in the spectra was assumed. This was confirmed through the study of the direct correlations (HMQC) and long-range correlations (HMBC). The signals at δ 18.3 and 26.2 were assigned to the couples C-10−C-10′ and C-11−C-11′, respectively, relative to the methyl groups of the isopentenyl moieties. The same analysis allowed us to assign the signal at δ 108.0 to the C-2 and C-6 carbons and the signal at δ 155.2 to the C-3 and C-5 carbons, unequivocally establishing the presence of nine quaternary carbons, seven CH, four CH_2, and four CH_3. The final confirmation of the substitution pattern of both rings, as well as of the whole structure, was provided by the HMBC correlations, of which some of the more significant are shown in Figure 2.

The second compound, α,α′-dihydro-3,5,3′,4′-tetrahydroxy-4,5′-diisopentenylstilbene (**2**), had a molecular formula $C_{24}H_{30}O_4$ ([M^+] 382.2141) as established by HREIMS. UV absorptions were at 212, 230, and 281 nm, similar to those of the previous compound, while the IR spectrum showed characteristic absorptions of hydroxyl groups and benzenoids. With respect to the previous compound, the mass spectrum of **2** showed 16 mass units more; the ^{1}H NMR showed the lack of an aromatic proton, while in the ^{13}C NMR spectrum an aromatic CH was replaced by a quaternary carbon at δ 140.8. These indications led us to establish the presence of a further hydroxyl group in the new compound, which was placed on the B ring on the basis of the following considerations. The NMR data of the portion relative to the A ring were superimposable with those of compound **1**, but mainly because the B ring bears only two protons, whose signals at δ 6.46 and 6.59 are meta-coupled (J = 2 Hz) and indicative of a 1,3,4,5-tetrasubstitution pattern. The ortho relationship of the two oxygenated functions was established by the HMBC correlations, which at the same time confirmed the whole structure.

Compound **3** was a monoprenylated dihydrostilbene, α,α′-dihydro-3,5,4′-trihydroxy-5′-isopentenylstilbene (**3**), with molecular formula $C_{19}H_{22}O_3$ ([M^+] 298.1563). The UV and IR spectra showed absorptions very similar to those of **1**. The lack of one isopentenyl substituent was indicated by the mass spectra and confirmed by ^{1}H and ^{13}C NMR data, which in turn showed an aromatic proton signal more with respect to compound **1**. In this case, the signals relative to the B ring were the same as in **1**, while the COSY, HMQC, and HMBC correlations confirmed the presence of a proton instead of the isopentenyl group on position 4 of the A ring.

The fourth compound was α,α′-dihydro-3,5,4′-trihydroxy-4′-methoxy-5′-isopentenylstilbene (**4**), with the molecular formula $C_{20}H_{24}O_4$ ([M^+] 328.1670). The UV and IR absorptions were similar to those of the previous compounds. The NMR spectra of **4** showed the presence of one isopentenyl group and, unlike the previous compounds, the presence of a methoxy group (δ 3.76 and 61.6). The analysis of the ^{1}H NMR spectra together with COSY and hetero long-range data revealed that the A ring substitution in compound **4** is similar to that of **3**, whereas the B ring had a substitution similar to that of compound **2**. Furthermore, a NOE experiment was carried out in order to establish the exact position of the methoxy group. Figure 3 shows the significant NOEs, which allowed unambiguously to place the methoxy group on position 4′ of the B ring.

The last and most polar compound was α,α′-dihydro-3,5,3′,4′-tetrahydroxy-5′-isopentenylstilbene (**5**). Its molecular formula is $C_{19}H_{22}O_4$ ([M^+] 314.1512), and its UV and IR spectra showed absorptions similar to those of the previous compounds. The ^{1}H and ^{13}C NMR spectra were almost superimposable on those of compound **4**, the only difference being the lack of the signals relative to the

Table 1. ^{1}H and ^{13}C Data of Compounds **1**−**5**[a]

	1		**2**		**3**		**4**		**5**	
pos	δ ^{13}C	δ ^{1}H *J*(Hz)	δ ^{13}C	δ ^{1}H *J*(Hz)	δ ^{13}C	δ ^{1}H *J*(Hz)	δ ^{13}C	δ ^{1}H *J*(Hz)	δ ^{13}C	δ ^{1}H *J*(Hz)
1	142.1 s		141.6 s		144.3 s		145.4 s		144.6 s	
2	108.0 d	6.25 bs	108.2 d	6.24 bs	107.3 s	6.21 d (2)	108.7 d	6.24 d (2)	107.2 d	6.19 d (2)
3	155.2 s		154.8 s		158.4 s		156.8 s		158.8 s	
4	111.5 s		111.0 s		100.6 d	6.18 d (2)	101.1 d	6.20 d (2)	100.6 d	6.17 d (2)
5	155.2 s		154.8 s		158.4 s		156.8 s		158.8 s	
6	108.0 d	6.25 bs	108.2 d	6.24 bs	107.3 d	6.21 d (2)	108.7 d	6.24 d (2)	107.2 d	6.19 d (2)
α	37.1 t	2.75 m	37.6 t	2.70 m	37.2 t	2.70 m	37.1 t	2.73 m	37.4 t	2.66 m
α′	38.2 t	2.75 m	37.9 t	2.70 m	38.7 t	2.70 m	37.7 t	2.73 m	38.5 t	2.66 m
1′	134.6 s		134.2 s		132.7 s		139.0 s		133.2 s	
2′	127.6 d	6.92 dd (2, 8)	113.1 d	6.46 d (2)	126.8 d	6.92 dd (2, 8)	114.1 d	6.61 d (2)	113.2 d	6.56 d (2)
3′	116.1 d	6.73 d (8)	140.8 s		115.0 d	6.83 d (8)	143.4 s		144.8 s	
4′	152.7 s		143.0 s		152.9 s		148.6 s		141.6 s	
5′	127.2 s		127.3 s		127.9 s		135.2 s		128.2 s	
6′	130.4 d	6.90 d (2)	121.2 d	6.59 d (2)	130.0 d	6.92 d (2)	122.0 d	6.48 d (2)	120.8 d	6.46 d (2)
7	22.8 t	3.40 d (7)	22.3 t	3.38 d (7)						
8	122.4 d	5.27 t (7)	122.0 d	5.25 t (7)						
9	135.0 s		134.5 s							
10	18.3 q	1.83 s	17.8 q	1.82 s						
11	26.2 q	1.77 s	25.8 q	1.75 s						
7′	30.2 t	3.34 d (7)	29.6 t	3.31 d (7)	28.6 t	3.27 d (7)	28.7 t	3.31 d (7)	28.6 t	3.27 d (7)
8′	122.3 d	5.32 t (7)	121.8 d	5.28 t (7)	123.5 d	5.31 t (7)	123.1 d	5.24 t (7)	123.6 d	5.26 t (7)
9′	135.5 s		135.0 s		131.1 s		133.0 s		131.2 s	
10′	18.3 q	1.78 bs	17.8 q	1.78 bs	17.4 q	1.69 bs	18.2 q	1.74 s	17.3 q	1.74 s
11′	26.2 q	1.78 bs	25.8 q	1.78 bs	25.4 q	1.69 bs	26.1 q	1.72 s	25.4 q	1.73 s
O-Me							61.6 q	3.76 s		

[a] The assignments were based on COSY, DEPT, HMQC, and HMBC experiments.

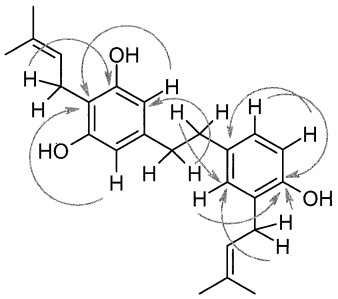


Figure 2. Selected HMBC correlations for compound **1**.

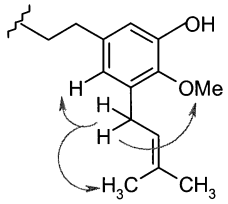


Figure 3. Selected NOE correlations for compound **4**.

methoxy group, which was replaced by a hydroxyl group. Definitive confirmation of the structure was obtained through the analysis of the homo and hetero 2D NMR spectra.

The new dihydrostilbenes (**1**−**5**) isolated from *G. glabra* were tested for their antioxidant effects. These tests were carried out by applying a recently described methodology in a homogeneous model system, which allows measuring the absolute inhibition rate constants of the oxidation process using a linoleic acid solution as substrate.[13] The values of the inhibition rate constants of the five new metabolites were the following: compound **1** $k_{inh} = 7 \times 10^4$ M^{-1} s^{-1}; compound **2** $k_{inh} = 11 \times 10^4$ M^{-1} s^{-1}; compound **3** $k_{inh} = 6 \times 10^4$ M^{-1} s^{-1}; compound **4** $k_{inh} = 8 \times 10^4$ M^{-1} s^{-1}, and compound **5** $k_{inh} = 9 \times 10^4$ M^{-1} s^{-1}. Considering that very effective antioxidants show inhibition rate constants[14,15] in the range 10^5−10^6 M^{-1} s^{-1}, the new phenolic constituents of *G. glabra* can be regarded as good antioxidant molecules. Compounds **2** and **5** showed relatively higher inhibition rate constants. Both compounds bear a catechol-like moiety on the B ring, confirming the greater protective effect of these particular polyphenols against lipid peroxidation.[16]

Experimental Section

General Experimental Procedures. Melting points were determined using an LD Mel-Temp II apparatus and are uncorrected. Optical rotations were measured on a Jasco DIP-370 digital polarimeter. UV and FTIR spectra were measured on Perkin-Elmer model Lambda 25 and model Spectrum BX spectrophotometers, respectively. ^{1}H NMR spectra were measured on a Varian INOVA operating at 499.883 MHz and a Bruker AC-250 at 250 MHz, whereas ^{13}C NMR spectra were run at 63 MHz on a Bruker AC-250 instrument. Multiplicities of ^{13}C were determined by distortionless enhancement of polarization transfer (DEPT), nuclear Overhauser enhancement spectroscopy (NOESY), heteronuclear multiple-quantum correlation (HMQC), and heteronuclear multiple-bond correlation (HMBC) performed using standard Bruker software. High-resolution electron impact mass spectra (HREIMS) were obtained at 70 eV on a Kratos M50S mass spectrometer. Thin-layer chromatography (TLC) were carried out on precoated silica gel F254 plates (Merck); flash chromatography on Diol and LiChroprep (Merck).

Plant Material. *G. glabra* L. was collected on the banks of the Simeto river in April 2000. A voucher specimen was deposited in the Herbarium of the Department of Botany, Catania, Italy.

Extraction and Isolation. Fresh plant was ground and freeze-dried to obtain 630 g of dried material, which was defatted three times with hexane, and the residual material was extracted with ethyl acetate three times at room temperature with continuous stirring. After concentration, 107 g of extract was obtained, 40 g of which was then subjected to chromatography over MN Polyammide SC6<0.07 mm. Elution with stepwise gradient from 60% MeOH/H_2O to 100% MeOH gave 15 fractions (A−Q).

Fraction H (4 g) was rechromatographated by flash chromatography over Diol (40−63 μm), the eluents used were a gradient of (70%) CH_2Cl_2/hexane to 100% and then 3% acetone/

CH_2Cl_2, to 5% and finally 100% of acetone. This fractionation yielded glabranin (**6**, 140 mg), pinocembrin (**7**, 380 mg), and another three fractions, which were rechromatographed. The first fraction was subjected to a flash column over Diol 40−63 μm, using a gradient starting from 15 to 28% acetone/hexane to provide licoflavone (**8**, 520 mg). The second fraction was chromatographed over flash column using Diol 25−40 μm and Et_2O/hexane from 20 to 70% to obtain compounds **3** (190 mg) and **4** (830 mg). Eventually from the third fraction the more polar compound (**5**, 590 mg) was purified with 24% of acetone in hexane.

Fraction I (7 g), coming from the polyammide column and eluted with MeOH, was purified by open column chromatography over acetylated polyammide (MN-Polyammide SC6-Ac 0.05−0.06 mm) by gradient elution of 40 to 100% acetone in hexane to give 10 fractions. Fraction 6 was subjected to further flash column chromatography using silica gel LiChroprep 25−40 μm and 40% Et_2O/hexane as the eluent to obtain compound **1** (380 mg). Fraction 10 was purified over Diol 25−40 μm with 15−23% of acetone/hexane to give compound **2** (140 mg) and wighteone (**9**, 120 mg).

α,α′-Dihydro-3,5,4′-trihydroxy-4,5′-diisopentenylstilbene (1): orange-yellow oil (yield 0.16%, fresh wt); HREIMS *m/z* 366.2190 (calcd for $C_{24}H_{30}O_3$ 366.2195); EIMS *m/z* (%) 366 [M^+] (8), 192 (5), 175 (100), 133 (9), 119 (5), 91 (6); UV (MeOH) λ_{max} (log ϵ) 210 (4.68), 230 (4.36), 280 (3.64) nm; IR (CH_2Cl_2) ν_{max} 3692, 3582, 3054, 2987, 1603, 1551, 1422, 896 cm^{-1}; ^1H and ^{13}C NMR data in Table 1.

α,α′-Dihydro-3,5,3′,4′-tetrahydroxy-4,5′-diisopentenylstilbene (2): amorphous solid (yield 0.06%, fresh wt); HREIMS *m/z* 382.2141 (calcd for $C_{24}H_{30}O_4$ 382.2144); EIMS *m/z* (%) 382 [M^+] (10), 247 (3), 191 (100), 149 (7), 135 (6), 91 (1), 77 (2); UV (MeOH) λ_{max} (log ϵ) 212 (4.44), 230 (4.16), 281 (3.33) nm; IR (CH_2Cl_2) ν_{max} 3578, 3052, 2927, 2856, 1630, 1586, 1446, 1269, 1178, 1044 cm^{-1}; ^1H and ^{13}C NMR data in Table 1.

α,α′-Dihydro-3,5,4′-trihydroxy-5′-isopentenylstilbene (3): amorphous solid (yield 0.08%, fresh wt); HREIMS *m/z* 298.1563 (calcd for $C_{19}H_{22}O_3$ 298.1569); EIMS *m/z* (%) 298 [M^+] (13), 207 (6), 175 (100), 133 (11), 107 (10), 91 (7); UV (MeOH) λ_{max} (log ϵ) 209 (4.62), 225 (4.32), 281 (3.74) nm; IR (CH_2Cl_2) ν_{max} 3578, 2928, 2855, 1646, 1500, 1330, 1269, 1148, 833 cm^{-1}; ^1H and ^{13}C NMR data in Table 1.

α,α′-Dihydro-3,5,3′-trihydroxy-4′-methoxy-5′-isopentenylstilbene (4): colorless oil (yield 0.35%, fresh wt); HREIMS *m/z* 328.1670 (calcd for $C_{20}H_{24}O_4$ 328.1674); EIMS *m/z* (%) 328 [M^+] (23), 281 (9), 205 (100), 173 (4), 44 (22); UV (MeOH) λ_{max} (log ϵ) 206 (5.06), 229 (4.20), 280 (3.30) nm; IR (CH_2Cl_2) ν_{max} 3579, 2930, 2959, 1602, 1496, 1452, 1333, 1148, 998 cm^{-1}; ^1H and ^{13}C NMR data in Table 1.

α,α′-Dihydro-3,5,3′,4′-tetrahydroxy-5′-isopentenylstilbene (5): yellow oil (yield 0.25%, fresh wt); HREIMS *m/z* 314.1512 (calcd for $C_{19}H_{22}O_4$ 314.1518); EIMS *m/z* (%) 314 [M^+] (22), 247 (2), 173 (5), 149 (14), 135 (11), 123 (8), 91 (6); UV (MeOH) λ_{max} (log ϵ) 206 (4.67), 228 (4.10), 282 (3.54) nm; IR (CH_2Cl_2) ν_{max} 3624, 3478, 3054, 2945, 2837, 1468, 1337, 1263, 1018 cm^{-1}; ^1H and ^{13}C NMR data in Table 1.

Glabranin (6): crystalline material (yield 0.06%, fresh wt); physicochemical properties as reported in the literature.[10]

Pinocembrin (7): pale yellow needles (yield 0.16%, fresh wt).[7]

Licoflavon (8): pale yellow needles (yield 0.22%, fresh wt).[7]

Wighteone (9): colorless prisms (yield 0.05%, fresh wt).[11]

Folin-Ciocalteau Assay. The measurement of the phenolic content of the extracts was performed using the Folin-Ciocalteau procedure as previously described.[17,18]

Antioxidant Assay. The antioxidant activity of the extract was carried out by measuring the peroxide value (PV) evolution of commercial sunflower seed oil kept at 30 °C for a 40-day period. A sample of oil was added with *G. glabra* ethyl acetate extract (0.03 % wt/wt); another sample of oil was added with BHT (0.03 % wt/wt); a third aliquot of oil was used as control. The PV values were obtained by standard tritation.[19] The analyses were carried out in triplicate.

The antioxidant activity of the purified compounds was evaluated by measuring their inhibition rate constant (k_{inh}) following the increase in absorbance at 254 nm due to the conjugated diene hydroperoxides formed from the oxidation process of a dilute solution of linoleic acid at 50 °C containing an aliquot of the tested compound and the radical initiator ($\sim 3 \times 10^{-3}$ M). The final concentration of antioxidants in the reaction system was $(2-3) \times 10^{-5}$ M. The analyses were carried out in triplicate.

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