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Anti-Lipid-Peroxidative Principles from *Tournefortia sarmentosa*

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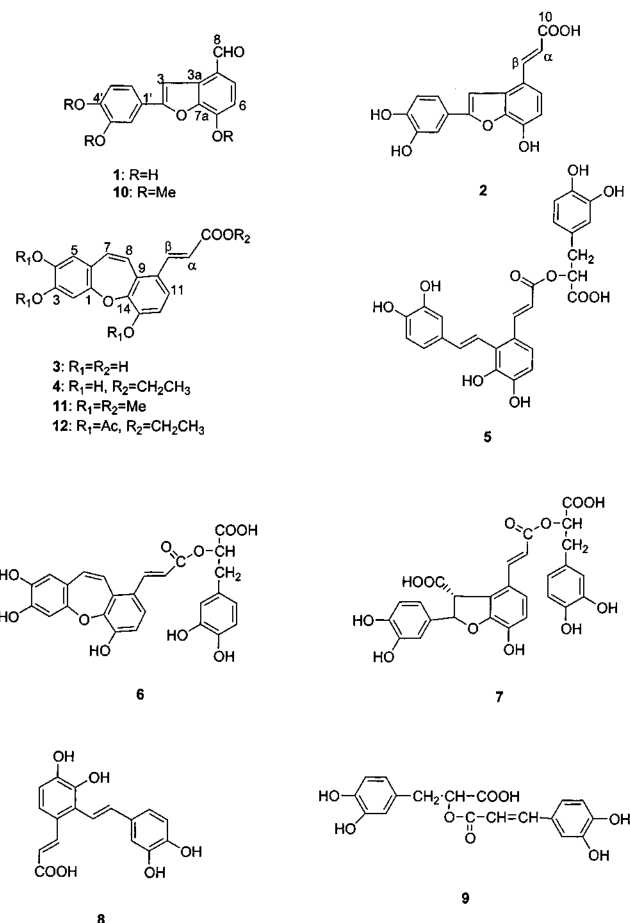
Using the inhibition of Cu^{2+}-induced low-density-lipoprotein (LDL) peroxidation to direct fractionation, four new benzenoids, tournefolal (**1**), tournefolic acids A (**2**) and B (**3**), and B ethyl ester (**4**), together with salvianolic acid A (**5**), isosalvianolic acid C (**6**), lithospermic acid (**7**), salvianolic acid F (**8**), and rosmarinic acid (**9**), were isolated from the stems of *Tournefortia sarmentosa*. The structures of the new compounds **1**−**4** were elucidated on the basis of spectral and chemical methods. Furthermore, the anti-LDL-peroxidative activity of the isolated compounds was determined. All isolated compounds exhibited more potent activity than probucol except for salvianolic acid F (**8**).

Oxidative modification of plasma low-density-lipoprotein (LDL) plays a key role in the initiation and progression of atherogenesis.[1−3] Oxidized LDL (oxLDL) cannot be metabolized by the receptor-mediated pathway of intact LDL and may appear in the circulation and tend to infiltrate into the aortic endothelium[4] and be further oxidized in the intima until finally taken up by the macrophages.[5] The uptake of extensively oxidized LDL by macrophages leads to the formation of foam cells and fatty streaks and is an early event in the pathogenesis of atherosclerosis.[6] Antioxidants which inhibit LDL oxidation may reduce early atherogenesis and slow the progression to advanced stages.[1] Chinese herbs to treat the condition of blood stasis contain antioxidants to prevent LDL oxidation, and many studies have provided supporting evidence of their efficacy.[7−9]

Tournefortia sarmentosa Lam. (Boraginaceae) has been used in Taiwan as a detoxicant, as an anti-inflammatory agent, and for promoting blood circulation for removal of blood stasis.[10] In a previous paper,[11] we reported the isolation of five new phenolic compounds together with salicylic acid and allantoin from an organic soluble extract of this same plant. Our preliminary screening showed that the aqueous ethanolic extract potently inhibited Cu^{2+}-induced LDL peroxidation at 40 μg/mL (100% inhibition). As part of our interest in antioxidative polyphenolic compounds, a further chemical investigation was conducted on a water-soluble fraction of *T. sarmentosa*. In this paper, we report the isolation and structural elucidation of four new benzenoid compounds (**1**−**4**) as well as a series of polyphenols, salvianolic acid A (**5**), isosalvianolic acid C (**6**), lithospermic acid (**7**), salvianolic acid F (**8**), and rosmarinic acid (**9**) from the stems of this plant. A Cu^{2+}-induced oxLDL *in vitro* bioassay was used to evaluate the anti-LDL-peroxidative activity of the compounds obtained.

The aqueous ethanolic extract from the stems of *T. sarmentosa* was partitioned between ethyl acetate and water. The antioxidative water-soluble fraction was separated by Diaion HP-20 and Sephadex LH-20 column chromatography to yield the new compounds tournefolal (**1**), tournefolic acids A (**2**) and B (**3**), and B ethyl ester (**4**), together with salvianolic acid A (**5**),[12] isosalvianolic acid C



(**6**),[13] lithospermic acid (**7**),[14] salvianolic acid F (**8**),[12] and rosmarinic acid (**9**).[15] Lithospermic acid was the major constituent of *T. sarmentosa*, with its content being about 0.62% w/w on the basis of the dried herb.

Tournefolal (**1**) was isolated as pale yellow crystals with a highly conjugated system and exhibited UV absorption bands at 276 and 350 nm. It was assigned a molecular formula of $C_{15}H_{10}O_5$, on the basis of its HREIMS and ^{13}C NMR spectral data, with 11 indices of hydrogen deficiency (IHD). The IR spectrum showed hydroxyl (3450 and 1150 cm^{-1}), conjugated aldehyde (1690 cm^{-1}), and phenyl (1600 and 1520 cm^{-1}) group absorptions. The ^1H NMR spectrum revealed two *ortho*-coupled phenyl protons [δ 6.79 and 7.59

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(1H each, d, $J = 8.4$ Hz)], one set of ABX-type phenyl protons [δ 6.86 (d, $J = 8.1$ Hz), 7.34 (dd, $J = 8.1$, 2.0 Hz), 7.36 (d, $J = 2.0$ Hz)], an isolated aromatic proton (δ 7.51), and a conjugated aldehyde proton (δ 9.88). In the ^{13}C NMR spectrum were observed five oxygenated aromatic carbons (δ_C 145.0, 147.0, 148.5, 150.9, and 161.2). Methylation of **1** with CH_3I/K_2CO_3 in acetone yielded the trimethoxyl product **10** (δ 3.93, 3.99, and 4.13). The NOESY spectrum of **10** showed NOE correlations of three methoxyl groups as follows: δ 4.13/H-6 (δ 6.87); δ 3.99/H-5′ (δ 6.93); and δ 3.93/H-2′ (δ 7.40). The remaining two oxygenated olefinic carbons were linked to one oxygen. On the basis of the above evidence, compound **1** was assigned with a benzofuranoid skeleton along with a 3,4-dihydroxylphenyl unit, as well as a hydroxyl group and an aldehyde group. The ^{1}H and ^{13}C NMR data indicated that the aldehyde (δ_H 9.88; δ_C 192.7) was conjugated with the benzene ring, having a NOE correlation with H-5, and HMBC correlations were observed from the aldehyde to C-3a, C-4, and C-5. The signal at δ 7.51 was assigned as H-3 due to deshielding by the aldehyde group and exhibited a HMBC correlation with C-1′, C-2, C-3a, C-4, and C-7a. From the above results, compound **1** was assigned as 7-hydroxy-2-(3,4-dihydroxyphenyl)benzofuran-4-al. This was also in agreement with the results of the HMBC correlations.

Tournefolic acid A (**2**) had an exact mass at *m/z* 312.0636 from its HREIMS, indicating the molecular formula $C_{17}H_{12}O_6$. The presence of hydroxyl, phenyl, and carboxylic groups was evident from observed IR absorption bands. The ^{1}H NMR spectrum was similar to that of compound **1** except that signals for the presence of an (*E*)-2-propenoic acid group [δ_H 6.43 and 7.75 (1H each, d, $J = 16.0$ Hz); δ_C 116.0 (C-α), 141.8 (C-β), 168.0 (−*C*OOH)] were evident in place of the aldehyde group signal in **1**. The HMBC spectrum showed diagnostic correlations as follows: δ 7.75 (H-β)/carbonyl (δ_C 168.0), C-3a, C-4, and C-5; and H-3/C-1′, C-2, C-3a, C-4, and C-7a. Thus, the structure of **2** was assigned as 7-hydroxy-2-(3,4-dihydroxyphenyl)-4-(1*E*-propenoyl-3-oic acid)benzofuran.

Tournefolic acid B (**3**) exhibited hydroxyl, aromatic, and carboxyl IR absorption bands. It gave a molecular formula of $C_{17}H_{12}O_6$, representing 12 IHD from the HREIMS at *m/z* 312.0632. The ^{13}C NMR spectrum revealed five oxygenated carbons and a conjugated carboxyl carbon. In the ^{1}H NMR spectrum were signals for two *ortho*-coupled phenyl protons, two isolated phenyl protons, two *trans*-olefinic protons, and two olefinic proton signals at δ 6.78 and 6.86 with a coupling constant of 11.4 Hz. These data supported **3** as being a dibenzooxepin derivative[13] and were similar to those of isosalvianolic acid C (**6**). Methylation (CH_3I/K_2CO_3) of **3** yielded the trimethoxyl product **11**, which was identified as a trimethoxydibenzooxepin product, previously derived from isosalvianolic acid C (**6**).[13] Therefore, the structure of **3** was established as 3-(4,7,8-trihydoxydibenzo-[*b,f*]oxepin-1-yl)acrylic acid.

Tournefolic acid B ethyl ester (**4**) was obtained as yellow crystals. The IR spectrum showed the presence of hydroxyl, aromatic, and ester absorption bands. The ^{1}H and ^{13}C NMR spectra were similar to those of **3**, with there being additional evidence of an ethyl ester replacement of a free carboxylic acid group in **4**. The structure was confirmed through the measurement of HMQC and HMBC spectra, and acetylation of **4** yielded the triacetate **12** (δ 2.25, 2.27, and 2.43). Therefore, compound **4** was assigned as an ethyl ester of **3**.

OxLDL obtained by incubation of LDL with Cu^{2+}/O_2 exhibits biological, immunological, and physiochemical properties that are remarkably similar to those of *in vivo* lipid peroxidation.[16] Cu^{2+}/O_2-induced oxLDL is recognizable by scavenger receptors and causes cholesterol ester accumulation in macrophages.[5,6,17] The hypocholesterolemic drug probucol was used as a positive control to evaluate the relative potency in this study. All of the isolated compounds were effective in preventing Cu^{2+}-induced LDL oxidation (see Table 1). On the basis of the IC_{50} values obtained, all of the isolated compounds were more potent than probucol except for salvianolic acid F. The relative antioxidative activities of salvianolic acid A, lithospermic acid, and compound **4** were 7.3-, 4.3-, and 8.6-fold of probucol, respectively. Compound **4** is a more lipophilic antioxidant, which could be inserted into LDL particles in a favorable orientation so that its antioxidative functionality is more exposed to the lipid−water interface than compound **3**. Therefore, the antioxidative activity was much more potent than that of compound **3**. Water-soluble antioxidants are unable to adhere to LDL particles. However, several studies suggest that water-soluble antioxidants, such as vitamin C, are effective in inhibiting LDL oxidation by the preservation of endogenous antioxidants in LDL through scavenging free radicals.[18,19] We suggest therefore that these polyphenolic compounds in *T. sarmentosa* may indirectly protect LDL from oxidative modification by free radical scavenging.

Table 1. Antioxidative Activities of Isolated Compounds and Probucol in a Cu^{2+}-Induced LDL Peroxidation Assay

compound	IC_{50} (μM)[a]	relative potency[b]
probucol	4.30[c] ± 0.12	1.0
tournefolal (**1**)	4.70 ± 0.09	1.09
tournefolic acid A (**2**)	4.81± 0.15	1.1
tournefolic acid B (**3**)	2.32 ± 0.05	1.9
tournefolic acid B ethyl ester (**4**)	0.51± 0.08	8.6
salvianolic acid A (**5**)	0.59 ± 0.10	7.3
isosalvianolic acid C (**6**)	2.72 ± 0.21	1.6
lithospermic acid (**7**)	1.00 ± 0.08	4.3
salvianolic acid F (**8**)	5.44 ± 0.17	0.8
rosmarinic acid (**9**)	1.81 ± 0.14	2.2

[a] IC_{50} values indicated the concentration of antioxidant required to inhibit the formation of conjugated dienes in Cu^{2+}-induced LDL oxidation by 50% from the concentration curves. Probucol was used as a positive control. [b] For comparison, the potency of probucol was set at 1.0. The relative potency of each antioxidant was expressed as IC_{50} (probucol)/IC_{50} (compound). [c] Data represent mean values of three determinations.

Experimental Section

General Experimental Procedures. Melting points were determined on a Yanagimoto micromelting point apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer 781 spectrophotometer. UV spectra were measured on a Hitachi U-3200 spectrophotometer. NMR spectra were run on a Varian unity INOVA-500 spectrometer. Mass spectra (EIMS and HREIMS) were taken on a JEOL JMS-100 and a JEOL SX-102A instrument, respectively.

Plant Material. The stems of *T. sarmentosa* Lam. were collected from Nei-Men, Kaohsiung County, Taiwan, in August 1998. The plant was identified by comparison with the voucher specimens deposited earlier at the Herbarium of the Department of Botany, National Taiwan Unversity, Taipei, Taiwan (no. TAI 175693, collected on April 1, 1979).

Extraction and Isolation. The stems of *T. sarmentosa* (20 kg) were extracted three times with 85% EtOH (each 100 mL) at 50 °C. The combined 85% EtOH extract was evaporated under reduced pressure. The concentrate was taken up in H_2O and partitioned with EtOAc (×3). The aqueous fraction (650 g) was subjected to Diaion HP-20 column chromatography using a gradient of methanol/water. Fractions (50% and 75%

methanol/water and methanol) rich in bioactive polyphenolic compounds were then separated over a Sephadex LH-20 column and eluted with 80% methanol. Each fraction was further purified by passage over a Sephadex LH-20 column (MeOH) to afford **1** (26 mg), **2** (21 mg), **3** (125 mg), and **4** (150 mg), together with salvianolic acid A (**5**) (186 mg), isosalvianolic acid C (**6**) (512 mg), lithospermic acid (**7**) (125 g), salvianolic acid F (**8**) (32 mg), and rosmarinic acid (**9**) (12.5 g).

Tournefolal (1): pale yellow crystals from ethanol, mp 210−212 °C; IR (KBr) ν_{max} 3450, 1690, 1630, 1600, 1520, 1200, 1150, 820 cm^{-1}; UV (MeOH) λ_{max} (log ϵ) 350 (4.00), 276 (4.01) nm; ^{1}H NMR (CD$_3$OD, 500 MHz) δ 6.79 and 7.59 (1H each, d, J = 8.4 Hz, H-6, H-5), 6.86 (1H, d, J = 8.1 Hz, H-5′), 7.34 (1H, dd, J = 8.1, 2.0 Hz, H-6′), 7.36 (1H, d, J = 2.0 Hz, H-2′), 7.51 (1H, s, H-3), 9.88 (1H, s, −C*H*O); ^{13}C NMR (125 MHz, CD$_3$OD) δ 100.8 (d, C-3), 111.8 (d, C-6), 113.7 (d, C-2′), 117.0 (d, C-5′), 119.1 (d, C-6′), 122.5 (s, C-4), 123.4 (s, C-1′), 132.4 (s, C-3a), 133.8 (d, C-5), 145.0 (s, C-7a), 147.0 (s, C-3′), 148.5 (s, C-4′), 150.9 (s, C-7), 161.2 (s, C-2), 192.7 (s, −*C*HO); HMBC correlations H-3/C-2, C-3a, C-4, C-7a, C-1′; −C*H*O/C-4, C-3a, C-5; H-5/C-4, C-6, C-7, C-8, C-3a; H-5′/C-1′, C-3′, C-4′; H-6′/C-2, C-2′, C-4′; H-2′/C-2, C-3′, C-4′, C-6′; EIMS *m/z* 270 [M]$^+$ (100), 241 (18), 213 (10), 135 (12), 129 (14); HREIMS *m/z* 270.0521 (calcd for $C_{15}H_{10}O_5$, 270.0528).

Tournefolic acid A (2): yellow crystals (EtOH), mp 197−198 °C; IR (KBr) ν_{max} 3360−2400, 1690, 1600, 1510, 1180, 1150 cm^{-1}; UV (MeOH) λ_{max} (log ϵ) 285 (4.08), 316 (4.01) nm; ^{1}H NMR (DMSO-d_6, 500 MHz) δ 6.43 and 7.75 (1H each, d, J = 16.0 Hz, H-9, H-8), 6.73 and 7.38 (1H each, d, J = 8.1 Hz, H-6, H-5), 6.84 (1H, d, J = 8.1 Hz, H-5′), 7.35 (1H, dd, J = 8.1, 2.0 Hz, H-6′), 7.38 (1H, d, J = 2.0 Hz, H-2′); ^{13}C NMR (125 MHz, DMSO-d_6) δ 98.7 (d, C-3), 110.7 (d, C-6), 112.5 (d, C-2′), 116.0 (d, C-5′), 116.0 (d, C-α), 117.1 (s, C-6′), 117.5 (s, C-4), 121.0 (s, C-1′), 125.1 (s, C-3a), 130.5 (d, C-5), 141.0 (s, C-7a), 141.8 (d, C-β), 144.3 (s, C-3′), 145.6 (s, C-4′), 146.8 (s, C-7), 157.1 (s, C-2), 168.0 (s, −*C*OOH); EIMS *m/z* 312 [M]$^+$ (25), 267 (12), 239 (100); HREIMS *m/z* 312.0636 (calcd for $C_{17}H_{12}O_6$, 312.0634).

Tournefolic acid B (3): yellow crystals (EtOH), mp 242−245 °C; IR (KBr) ν_{max} 3540, 3350−2400, 1697, 1610, 1510, 1196, 1115, 865 cm^{-1}; UV (MeOH) λ_{max} (log ϵ) 260 sh (3.91), 285 sh (3.91), 329 (3.95) nm; ^{1}H NMR (DMSO-d_6, 500 MHz) δ 6.22 and 7.76 (1H each, d, J = 15.9 Hz, H-α, H-β), 6.61 and 6.84 (1H each, s, H-2, H-5), 6.78 and 6.86 (1H each, d, J = 11.4 Hz, H-7, H-8), 6.88 and 7.36 (1H each, d, J = 8.4 Hz, H-12, H-11), 8.80, 9.29, and 9.81 (1H each, brs, OH); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 108.9 (d, C-5), 114.4 (d, C-2), 116.7 (d, C-11), 118.4 (d, C-α), 121.0 (s, C-6), 123.1 (d, C-8), 123.5 (d, C-12), 124.0 (s, C-10), 130.7 (d, C-7), 131.4 (s, C-9), 140.4 (d, C-β), 142.5 (s, C-3), 145.2 (s, C-4),147.1 (s, C-13), 150.0 (s, C-1), 150.5 (s, C-14), 167.5 (s, −*C*OOH); HMBC correlations H-3/C-1, C-2, C-4; H-6/C-1, C-2, C-4, C-5; H-11/C-β, C-9, C-10, C-12, C-13; H-α/C-β, C-10, −*C*OOH; EIMS *m/z* 312 [M]$^+$ (25), 268 (100), 249 (55), 221 (40), 165 (18); HREIMS *m/z* 312.0632 (calcd for $C_{17}H_{12}O_6$, 312.0633).

Tournefolic acid B ethyl ester (4): yellow crystals (EtOH), mp 225−227 °C; IR (KBr) ν_{max} 3540, 3470−2400, 1695, 1620, 1590, 1530, 1180, 1155, 860 cm^{-1}; UV (MeOH) λ_{max} (log ϵ) 260 sh (3.92), 287 sh (3.93), 329 (4.10) nm; ^{1}H NMR (DMSO-d_6, 500 MHz) δ 1.25 (3H, t, J = 6.9 Hz, $-CH_2CH_3$), 4.17 (2H, q, J = 6.9 Hz, $-CH_2CH_3$), 6.30 and 7.81 (1H each, d, J = 15.9 Hz, H-α, H-β), 6.62 (1H, s, H-5), 6.80 and 6.87 (1H each, d, J = 11.1 Hz, H-7, H-8), 6.86 (1H, s, H-2), 6.89 and 7.38 (1H each, d, J = 8.5 Hz, H-12, H-11); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 14.6 (t, $-CH_2CH_3$), 60.6 (t, $-CH_2CH_3$), 109.3 (d, C-5), 114.9 (d, C-2), 117.3 (d, C-11), 117.7 (d, C-α), 121.6 (s, C-1), 123.3 (d, C-8), 124.0 (d, C-12), 124.8 (s, C-10), 131.4 (d, C-7), 132.2 (s, C-9), 141.4 (d, C-β), 142.8 (s, C-3), 145.6 (s, C-4), 147.5 (s, C-13), 150.6 (s, C-2), 151.3 (s, C-14), 167.1 (s, −*C*OO−); EIMS *m/z* 340 [M]$^+$ (45), 311 (15), 295 (15), 267 (100), 250 (50), 221 (38); HREIMS *m/z* 340.0954 (calcd for $C_{17}H_{12}O_6$, 340.0947).

Methylation of 1 and 3. A mixture of compound **1** (3 mg), methyl iodide (0.5 mL), dried acetone (0.5 mL), and potassium carbonate (0.5 g) was refluxed overnight. The mixture was subsequently purified by preparative TLC to afford the colorless amorphous trimethoxy compound **10** (2.0 mg). Compound **10**: ^{1}H NMR (CDCl$_3$, 500 MHz) δ 3.93, 3.99, and 4.13 (3H each, s, OC*H*$_3$), 6.87 and 7.65 (1H each, d, J = 8.1 Hz, H-6, H-5), 6.93 (1H, d, J = 8.4 Hz, H-5′), 7.40 (1H, d, J = 2.0 Hz, H-2′), 7.54 (1H, dd, J = 8.4, 2.0 Hz, H-6′), 7.69 (1H, s, H-3), 10.04 (1H, s, −C*H*O). Compound **3** (3 mg) was methylated under the same conditions as done above to yield the tetramethoxy compound **11** (1.8 mg). Compound **11**: ^{1}H NMR (CDCl$_3$, 500 MHz) δ 3.66, 3.94, 4.00, and 4.12 (3H each, s, OC*H*$_3$), 6.26 and 7.86 (1H each, d, J = 15.9 Hz, H-α, H-β), 6.77 and 6.97 (1H each, d, J = 11.4 Hz, H-7, H-8), 7.01 and 7.31 (1H each, d, J = 8.4 Hz, H-12, H-11), 6.94 and 7.01 (1H each, s, H-2, H-5).

Acetylation of 4. Compound **4** (5 mg) was treated with Ac_2O (0.5 mg) and pyridine (0.5 mL) to yield **12** (4 mg): colorless needles, mp 165−167 °C (from EtOH); IR (KBr) ν_{max} 1770, 1710, 1640, 1500, 1200, 1180, 1150, 1090, 1040, 910 cm^{-1}; ^{1}H NMR (CDCl$_3$, 500 MHz) δ 1.32 (3H, t, J = 7.2 Hz, $-CH_2CH_3$), 2.25, 2.27, and 2.43 (3H each, s, $-COCH_3$), 4.25 (2H, q, J = 7.2 Hz, $-CH_2CH_3$), 6.27 and 7.86 (1H each, d, J = 15.9 Hz, H-α, H-β), 6.78 and 6.97 (1H each, d, J = 11.4 Hz, H-7, H-8), 6.95 and 7.00 (1H each, s, H-2, H-5), 7.08 and 7.30 (1H each, d, J = 8.4 Hz, H-12, H-11).

LDL Peroxidation and Screening for Antioxidants. Fasting plasma samples were collected from healthy male adult humans who were not using vitamin supplements. LDL was obtained by following a previously reported method.[16] The LDL assay was carried out in a 96-well microtiter plate as described.[21] Each plate was incubated with $CuSO_4$ (final concentration 10 μM) at 37 °C to induce lipid peroxidation.[22] In a typical assay, incubation was carried out at 37 °C for 2 h in a gyrorotary incubator shaker at 120 rpm. For screening, LDL was preincubated with test compounds at 37 °C for 1 h before adding Cu^{2+}. Probucol (10 μM, 10% ethanol solution, 10 μL) was used as a positive control. The conjugated diene formation in the supernatant was determined by UV absorption at 232 nm.

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