5-Hydroxy-2,3-dihydrobenzofuran-derived polyfunctional antioxidants

1. Synthesis of 2-dodecylthiomethyl-5-hydroxy-2,3-dihydrobenzofurans

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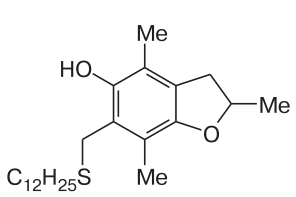
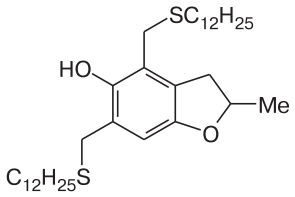
2-Dodecylthiomethyl-5-hydroxy-2,3-dihydrobenzofurans, new sulfur-containing analogs of tocopherols, were synthesized based on methylphenols through the intermediate preparation of 4-alkoxy-2-allylphenols and then 5-alkoxy-2-iodomethyl-2,3-dihydrobenzofurans.

Key words: 5-hydroxy-2,3-dihydrobenzofurans, sulfur-containing antioxidants, iodocyclization.

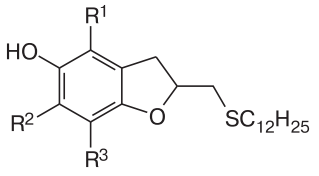
Natural polyphenols and their derivatives (tocopherols, hydroxycoumarans, flavonoids, *etc*.) play a key role in maintaining the redox-homeostasis of living organisms and in protection of cell structures from damaging effect of activated oxygen metabolites.[1,2] Functionalization of the named compounds with sulfur-containing groups is regarded by many researches as a promising way for development of bioantioxidants with polyfunctional mode of antioxidant action for the use in biology and medicine. Thus, in the literature there are described methods for the synthesis and antioxidant properties of α-tocopherol and 5-hydroxy-2,3-dihydrobenzofuran thio derivatives, in the structure of which the oxygen atom in the heterocycle is replaced with a sulfur atom,[3,4] as well as alkylthio-substituted tocopherols[5] and alkylthiomethyl-substituted flavonoids.[6]



A



B



1a—e

1	R^1	R^2	R^3
a	Me	Me	H
b	Me	H	Me
c	H	Me	Me
d	H	H	Me
e	H	H	H

Earlier, we have obtained dodecylthiomethyl-substituted 5-hydroxy-2,3-dihydrobenzofurans **A** and **B** and showed that these compounds considerably exceed α-tocopherol in their ability to inhibit autooxidation of methyl oleate.[7] At the same time, it is known that the presence of thioalkyl substituents at *ortho*-positions relative to the phenol OH group can lead to the decrease in the activity of the latter in the reactions with active radicals because of the formation of the O—H···S hydrogen bond.[8,9]

In this connection, the present work is devoted to the synthesis of structural analogs of compounds **A** and **B** with a dodecylthiomethyl substituent remote from the phenol OH group, namely, 2-dodecylthiomethyl-5-hydroxy-2,3-dihydrobenzofurans **1a—e**.

Results and Discussion

The synthesis of the target compounds **1a—e** was carried out based on methylphenols through the intermediate preparation of 4-alkoxy-2-allylphenols **2a—e** (Scheme 1); allylphenol **2a** was obtained from 2,6-dimethylphenol by a sequence of transformations shown in Scheme 2. The synthesis of allylphenols **2b—e** was described earlier in our work.[7]

Iodocyclization of compounds **2** initially was carried out according to the procedure described earlier[10] in the presence of Na_2CO_3. In this case, the yields of the target iodo derivatives **6** were 65—75%. Later, we obtained com-

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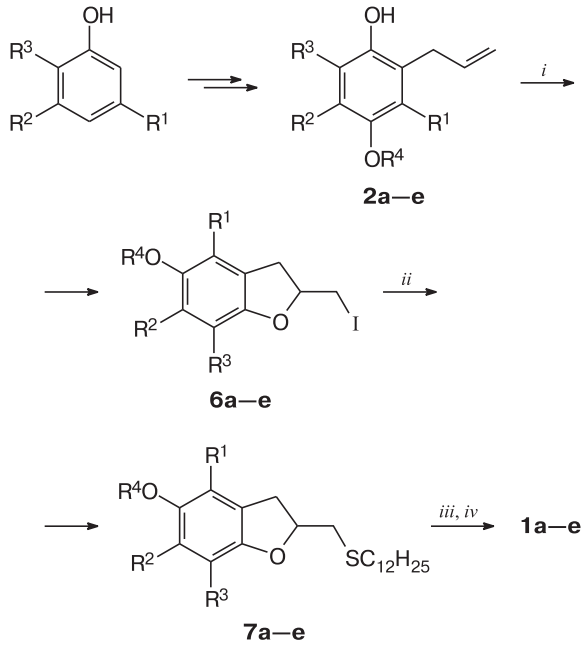
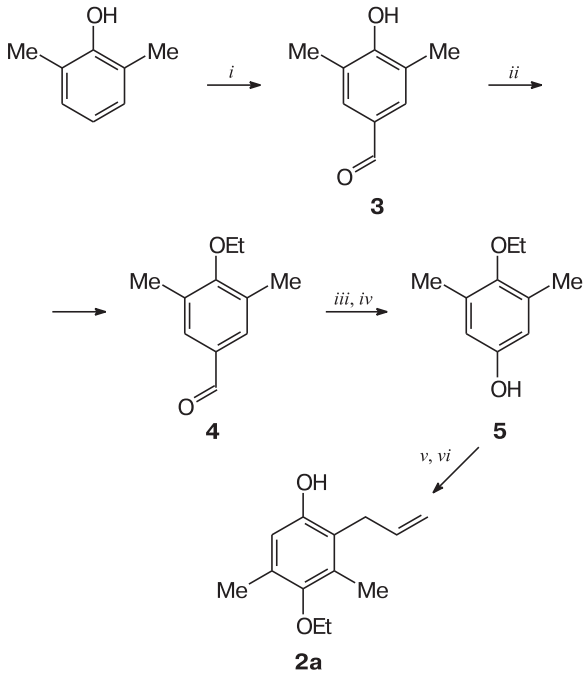
Scheme 1



R^4 = Et (**a—d**), Me (**e**)

Reagents and conditions: *i*. I_2, MeCN, ~20 °C; *ii*. $C_{12}H_{25}SH$, NaOH, EtOH, 60 °C; *iii*. BBr_3, DCM, ~20 °C; *iv*. PhMe, Δ.

Scheme 2



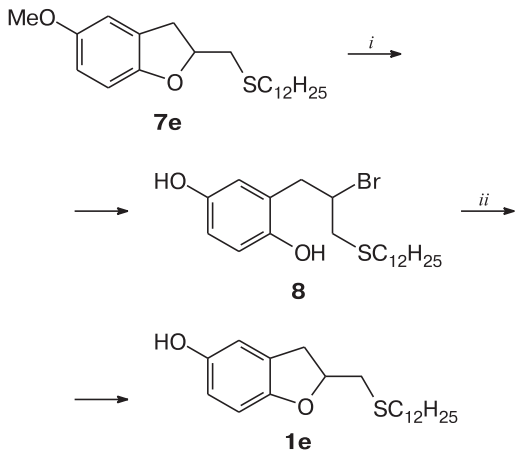
Reagents and conditions: *i*. $C_6H_{12}N_4$, AcOH, H_2O; *ii*. EtI, K_2CO_3, Δ; *iii*. H_2O_2, HCOOH, DCM, Δ; *iv*. NaOH, EtOH, ~20 °C; *v*. C_3H_5Br, NaOH, DMF; *vi*. 200—220 °C.

pounds **6** in higher yields (87—93%) by carrying out iodocyclization of compounds **2** with a larger excess of I_2 in O_2 atmosphere and in the absence of bases.

The reaction of compounds **6** with dodecanthiol was carried out under conditions suggested earlier for the synthesis of nonsymmetrical sulfides based on 4-(3-bromopropyl)-2,6-dimethylphenol,[11] that allowed us to obtain thio derivatives **7** in good yields (77—90%).

The attempts to convert benzofurans **7** to the target compounds **1** upon treatment with HBr under conditions used for the transformation of 2-ethoxyphenols to the corresponding alkylpyrocatechols[12] in good yields were unsuccessful: the reaction led to the formation of a large number of side products and resinification of the reaction mixture. The application of BBr_3, yet another reagent widely used for selective cleavage of phenyl alkyl ethers, turned out to be more efficient. The search of conditions for the transformation of benzofurans **7** to compounds **1** was carried out on a model compound **7e**. The reaction of **7e** with BBr_3 under conditions described in the work[13] led not only to the O-dealkylation of **7e**, but also to the ring opening with the formation of 2-[2-bromo-3-(dodecylthio)-propyl]hydroquinone (**8**) (Scheme 3). The conversion of hydroquinone **8** to the target benzofuran **1e** required a "recyclization", which initially was carried out by the reflux with K_2CO_3 in acetone.[14,15] Under these conditions, the synthesis of **1e** was accompanied by the formation of side products; after a complete conversion of **8** the content of **1e** in the reaction mixture, according to the HPLC and GC/MS data, did not exceed 85%. At the same time, we made an observation that compound **8** upon storage gradually loses HBr and converts to compound **1e**. Taking into account this fact, we tested a thermal version of the cyclization: after the reflux of a solution of compound **8** in toluene for 2 h, the HPLC and GC/MS data showed that the content of **1e** in the reaction mixture reached 98%.

Scheme 3

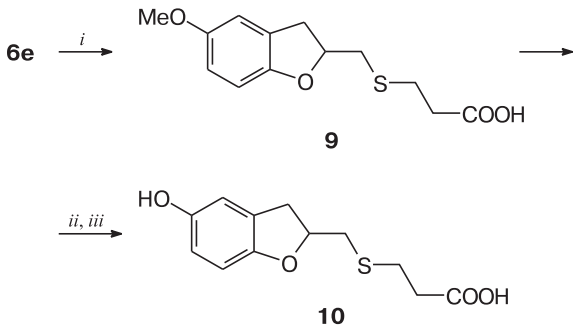


Reagents and conditions: *ii*. BBr_3, DCM, ~20 °C; *ii*. PhMe, Δ.

In the preparation of compounds **1a—d**, the products of the reaction of alkoxy derivatives **7a—d** with BBr_3 were involved in the thermal cyclization without additional purification.

It is obvious that the approach to the synthesis of sulfur-containing benzofurans **1a—e** suggested in the present work can be also used for the preparation of their structural analogs containing additional functional groups in the alkylthiomethyl substituent. Thus, we used compound **6e** to obtain a thiopropionic acid derivative **10**, which is a hydrophilic analog of compound **1e** (Scheme 4).

Scheme 4



Reagents and conditions: *i*. $HSCH_2CH_2COOH$, NaOH, EtOH, 60 °C; *ii*. BBr_3, DCM, ~20 °C; *iii*. PhMe, Δ.

Experimental

Commercially available reagents and solvent used in the work were purchased from Sigma-Aldrich, Merck, and Reakhim. Solvents before use were purified and dried according to the standard procedures.[16]

^{1}H NMR spectra were recorded on a Bruker DRX 600 spectrometer (600 MHz) in $CDCl_3$ (for compounds **1—9**) and DMSO-d_6 (for compound **10**). IR spectra were recorded on an Agilent Cary 600 Series FTIR spectrometer for solutions with a concentration of (1.5—2.5) • 10^{-2} mol L^{-1} in CCl_4 (for compounds **1**, **2**, **4—7**), in a mixture of $CHCl_3$—CCl_4 (1 : 1, for compound **8**), in $CHCl_3$ (for compounds **3** and **9**) in 0.5-mm thick cells with KBr and in KBr pellets (for compound **10**). UV spectra were recorded on a Shimadzu UV-1800 spectrometer in solution of EtOH. GC analysis was carried out on an Agilent 7820A chromatograph (HP-5, 30 m×0.25 mm and HP-FFAP, 50 m×0.32 mm; carrier gas nitrogen), HPLC was performed on an Agilent Infinity 1220 chromatograph (ZORBAX SB-C18, 5 μm, 150×4.6 mm), GC/MS analysis was carried out on an Agilent 7890B chromatograph (HP-5MS UI, 30 m×0.25 mm, carrier gas helium) with an Agilent 5977A mass detector (EI, 70 eV). The peaks of ions with ≥ 10% intensity including the most abundant isotopes are reported in the description of mass spectra. Silufol plates (UV 254) were used for TLC. Melting points were measured in a capillary tube on a MP50 Mettler Toledo heating stage (the rate of heating 0.5 °C min^{-1}). All the reaction, if not stated otherwise, were carried out under inert atmosphere and in anhydrous solvents.

4-Hydroxy-3,5-dimethylbenzaldehyde (3) was obtained according to the known procedure.[17] A solution of 2,6-dimethylphenol (45.8 g, 0.375 mol), urotropine (105.2 g, 0.75 mol) in a mixture of AcOH (640 mL) and H_2O (140 mL) was refluxed for 4 h, cooled to room temperature, and poured into water (4 L). A precipitate formed (44.1 g) was separated and recrystallized from PhMe (180 mL) to obtain compound **3** (39.8 g, 70%) as colorless crystals with m.p. 115.5—117 °C (*cf.* Ref. 17: 109—112 °C). Found (%): C, 72.09; H, 6.64. $C_9H_{10}O_2$. Calculated (%): C, 71.98; H, 6.71. UV, λ_{max}/nm (logε): 230 (4.32), 292 (4.20). IR, ν/cm^{-1}: 3598 (OH), 1684 (C=O). ^{1}H NMR, δ: 2.30 (s, 6 H, $ArCH_3$); 5.40 (br.s, 1 H, ArOH); 7.48 (s, 2 H, ArH); 9.75 (s, 1 H, C(O)H). MS (EI, 70 eV), *m/z* (I_{rel} (%)): 150 $[M]^+$ (70), 149 $[M - H]^+$ (100), 121 $[M - H - CO]^+$ (16), 91 (27), 77 (27).

4-Ethoxy-3,5-dimethylbenzaldehyde (4). Anhydrous K_2CO_3 (22.1 g, 0.16 mol) was added to a solution of benzaldehyde **3** (30.0 g, 0.2 mol) and EtI (48.4 g, 0.31 mol) in EtOH (160 mL) and the mixture was refluxed for 4 h. Then, the solvent was evaporated on a rotary evaporator, toluene (100 mL) and water (50 mL) were added to the residue, the aqueous layer was separated and treated with toluene (3×20 mL). The organic phases were combined, washed with 5% aqueous solution of NaOH (3×50 mL), water (3×50 mL), and a saturated solution of NaCl, then dried with Na_2SO_4. The solvent was evaporated and the residue was distilled *in vacuo* to obtain the product (33.4 g, 93%) as a colorless light liquid, b.p. 91—94 °C (1 Torr). Found (%): C, 74.31; H, 8.02. $C_{11}H_{14}O_2$. Calculated (%): C, 74.13; H, 7.92. UV, λ_{max}/nm (logε): 267 (4.10). IR, ν/cm^{-1}: 1698 (C=O). ^{1}H NMR, δ: 1.42 (t, 3 H, OCH_2CH_3, J = 7.2 Hz); 2.29 (s, 6 H, $ArCH_3$); 3.85 (q, 2 H, OCH_2CH_3, J = 7.2 Hz); 7.46 (s, 2 H, ArH); 9.79 (s, 1 H, C(O)H). MS (EI, 70 eV), *m/z* (I_{rel} (%)): 178 $[M]^+$ (54), 149 $[M - Et]^+$ (100), 121 $[M - Et - CO]^+$ (11).

4-Ethoxy-3,5-dimethylphenol (5) was obtained according to the known procedure.[18] A mixture of benzaldehyde **4** (82.8 g, 0.465 mol), formic acid (98 mL, 91%, 2.34 mol), H_2O_2 (133 mL, 33%, 1.45 mol), and DCM (2.35 L) was refluxed for 15 h. Then, the reflux condenser was replaced with a Liebig one and DCM was distilled off from the reaction mixture, followed by the addition of EtOH (1 L) and a solution of NaOH (113 g, 2.83 mol) in water (1.9 L) with cooling. The mixture was stirred at room temperature for 1 h, EtOH was evaporated. The mixture was acidified with aqueous HCl, extracted with DCM (3×150 mL), washed with aqueous NaCl, and dried with Na_2SO_4. The solvent was evaporated, the residue was distilled *in vacuo*, the main fraction was crystallized from a mixture of light petroleum ether (120 mL) and toluene (100 mL) to obtain compound **5** (63.4 g, 82%) as colorless crystals, m.p. 84.5—86 °C, with b.p. 113—116 °C (1 Torr). Found (%): C, 72.61; H, 8.37. $C_{10}H_{14}O_2$. Calculated (%): C, 72.26; H, 8.49. UV, λ_{max}/nm (logε): 282 (3.43). IR, ν/cm^{-1}: 3615 (OH). ^{1}H NMR, δ: 1.37 (t, 3 H, OCH_2CH_3, J = 7.2 Hz); 2.17 (s, 6 H, $ArCH_3$); 3.73 (q, 2 H, OCH_2CH_3, J = 7.2 Hz); 4.70 (br.s, 1 H, ArOH); 6.34 (s, 2 H, ArH). MS (EI, 70 eV), *m/z* (I_{rel} (%)): 166 $[M]^+$ (54), 137 $[M - Et]^+$ (100), 123 (16), 109 (12).

1-Allyloxy-4-ethoxy-3,5-dimethylbenzene. A reaction of phenol **5** (24.9 g, 0.15 mol), allyl bromide (36.3 g, 0.3 mol), NaOH (6.6 g, 0.165 mol) in DMF (270 mL), according to the known procedure,[19] gave 1-allyloxy-4-ethoxy-3,5-dimethylbenzene (28.3 g, 92%), b.p. 113—114 °C (1 Torr). Found (%): C, 74.94; H, 8.31. $C_{13}H_{18}O_2$. Calculated (%): C, 75.69; H, 8.80. UV, λ_{max}/nm (logε): 280 (3.66). ^{1}H NMR, δ: 1.37 (t, 3 H, OCH_2CH_3, J = 7.2 Hz); 2.21 (s, 6 H, $ArCH_3$); 3.73 (q, 2 H, OCH_2CH_3,

J = 7.2 Hz); 4.41 (dt, 2 H, C$\underline{H}_2$CH=CH$_2$, J = 5.4 Hz, J = 1.8 Hz); 5.21 (dq, 1 H, CH$_2$CH=C$\underline{H}_2$ J = 10.8 Hz, J = 1.8 Hz); 5.34 (dq, 1 H, CH$_2$CH=C$\underline{H}_2$ J = 17.4 Hz, J = 1.8 Hz); 5.98 (m, 1 H, CH$_2$C$\underline{H}$=CH$_2$); 6.45 (s, 2 H, ArH). MS (EI, 70 eV), m/z (I_{rel} (%)): 206 [M]$^+$ (31), 165 [M – C$_3$H$_5$]$^+$ (18), 137 [M – C$_3$H$_5$ – – C$_2$H$_4$]$^+$ (100).

2-Allyl-4-ethoxy-3,5-dimethylphenol (2a). 1-Allyloxy-4-ethoxy-3,5-dimethylbenzene (28.3 g) was stirred for 3 h at 200—220 °C, then distilled *in vacuo* and crystallized from hexane (40 mL) to obtain product **2a** (25.9 g, 84%), m.p. 95.5—96.5 °C, with b.p. 119—121 °C (1 Torr). Found (%): C, 76.12; H, 8.92. C$_{13}$H$_{18}$O$_2$. Calculated (%): C, 75.69; H, 8.80. UV, λ_{max}/nm (logε): 287 (3.49). IR, ν/cm^{-1}: 3616 (OH). ^{1}H NMR, δ: 1.38 (t, 3 H, OCH$_2$C$\underline{H}_3$, J = 7.2 Hz); 2.16 (s, 3 H, ArCH$_3$); 2.17 (s, 3 H, ArCH$_3$); 3.33 (dt, 2 H, C$\underline{H}_2$CH=CH$_2$, J = 5.4 Hz, J = 1.8 Hz); 3.71 (q, 2 H, OC$\underline{H}_2$CH$_3$, J = 7.2 Hz); 4.57 (s, 1 H, ArOH); 4.94 (dq, 1 H, CH$_2$CH=C$\underline{H}_2$, J = 16.8 Hz, J = 1.8 Hz); 4.99 (dq, 1 H, CH$_2$CH=C$\underline{H}_2$, J = 10.2 Hz, J = 1.8 Hz); 5.88 (m, 1 H, CH$_2$C$\underline{H}$=CH$_2$); 6.36 (s, 1 H, ArH). MS (EI, 70 eV), m/z (I_{rel} (%)): 206 [M]$^+$ (58), 177 [M – Et]$^+$ (100), 163 (15), 121 (12).

5-Ethoxy-2-iodomethyl-4,6-dimethyl-2,3-dihydrobenzofuran (6a). A solution of I_2 (3.80 g, 15 mmol) and compound **2a** (1.55 g, 7.5 mmol) in MeCN (50 mL) was stirred for 48 h at ~20 °C in O_2 atmosphere; MeCN was evaporated on a rotary evaporator, the residue was dissolved in DCM (15 mL), washed with aqueous solution of $Na_2S_2O_3$, and dried with Na_2SO_4, the solvent was evaporated. Compound **6a** (2.22 g, 89%) was obtained as light yellow crystals (with purity >99% by GC), m.p. 52.5—54.5 °C. Found (%): C, 46.31; H, 5.22; I, 37.54. C$_{13}$H$_{17}$IO$_2$. Calculated (%): C, 47.00; H, 5.16; I, 38.20. UV, λ_{max}/nm (logε): 290 (3.56). ^{1}H NMR, δ: 1.37 (t, 3 H, OCH$_2$C$\underline{H}_3$, J = 7.2 Hz); 2.13 (s, 3 H, ArCH$_3$); 2.18 (s, 3 H, ArCH$_3$); 2.87 (m, 1 H, H(3)); 3.19—3.26 (m, 2 H, H(3) + CH$_2$I); 3.39 (m, 1 H, CH$_2$I); 3.70 (q, 2 H, OC$\underline{H}_2$CH$_3$, J = 7.2 Hz); 4.83 (m, 1 H, H(2)); 6.32 (s, 1 H, H(7)). MS (EI, 70 eV), m/z (I_{rel} (%)): 332 [M]$^+$ (100), 303 [M – Et]$^+$ (96), 175 [M – Et – HI]$^+$ (57), 161 (36), 133 (16).

Compounds **6b—e** were obtained similarly to iodo derivative **6a**.

5-Ethoxy-2-iodomethyl-4,7-dimethyl-2,3-dihydrobenzofuran (6b). The yield was 93%. M.p. 61.0—63.0 °C. Found (%): C, 47.34; H, 5.24; I, 37.88. C$_{13}$H$_{17}$IO$_2$. Calculated (%): C, 47.00; H, 5.16; I, 38.20. UV, λ_{max}/nm (logε): 294 (3.58). ^{1}H NMR, δ: 1.44 (t, 3 H, OCH$_2$C$\underline{H}_3$, J = 7.2 Hz); 2.13 (s, 3 H, ArCH$_3$); 2.18 (s, 3 H, ArCH$_3$); 2.98 (m, 1 H, H(3)); 3.30 (m, 1 H, CH$_2$I); 3.35 (m, 1 H, H(3)); 3.49 (m, 1 H, CH$_2$I); 3.96 (q, 2 H, OC$\underline{H}_2$CH$_3$, J = 7.2 Hz); 4.90 (m, 1 H, H(2)); 6.42 (s, 1 H, H(6)). MS (EI, 70 eV), m/z (I_{rel} (%)): 332 [M]$^+$ (100), 303 [M – Et]$^+$ (25), 205 [M – I]$^+$ (21), 175 [M – Et – HI]$^+$ (35), 161 (19), 149 (13), 131 (11).

5-Ethoxy-2-iodomethyl-6,7-dimethyl-2,3-dihydrobenzofuran (6c). The yield was 91%. M.p. 48.3—50.3 °C. Found (%): C, 47.29; H, 5.11; I, 38.71. C$_{13}$H$_{17}$IO$_2$. Calculated (%): C, 47.00; H, 5.16; I, 38.20. UV, λ_{max}/nm (logε): 296 (3.63). ^{1}H NMR, δ: 1.39 (t, 3 H, OCH$_2$C$\underline{H}_3$, J = 7.2 Hz); 2.08 (s, 3 H, ArCH$_3$); 2.09 (s, 3 H, ArCH$_3$); 2.99 (m, 1 H, H(3)); 3.23 (m, 1 H, CH$_2$I); 3.34 (m, 1 H, H(3)); 3.41 (m, 1 H, CH$_2$I); 3.89 (q, 2 H, OC$\underline{H}_2$CH$_3$, J = 7.2 Hz); 4.80 (m, 1 H, H(2)); 6.47 (s, 1 H, H(4)). MS (EI, 70 eV), m/z (I_{rel} (%)): 332 [M]$^+$ (100), 303 [M – Et]$^+$ (18), 205 [M – I]$^+$ (21), 176 [M – Et – I]$^+$ (34), 161 (25), 131 (13).

5-Ethoxy-2-iodomethyl-7-methyl-2,3-dihydrobenzofuran (6d). The yield was 92%. Found (%): C, 45.11; H, 4.87; I, 40.13. C$_{12}$H$_{15}$IO$_2$. Calculated (%): C, 45.30; H, 4.75; I, 39.89. UV, λ_{max}/nm (logε): 297 (3.60). ^{1}H NMR, δ: 1.35 (t, 3 H, OCH$_2$C$\underline{H}_3$, J = 7.2 Hz); 2.13 (s, 3 H, ArCH$_3$); 2.99 (m, 1 H, H(3)); 3.23 (m, 1 H, CH$_2$I); 3.34 (m, 1 H, H(3)); 3.41 (m, 1 H, CH$_2$I); 3.88 (q, 2 H, OC$\underline{H}_2$CH$_3$, J = 7.2 Hz); 4.81 (m, 1 H, H(2)); 6.39 (d, 1 H, H(6), J = 1.8 Hz); 6.45 (d, 1 H, H(4), J = 1.8 Hz). MS (EI, 70 eV), m/z (I_{rel} (%)): 318 [M]$^+$ (100), 191 [M – I]$^+$ (33), 163 [M – C$_2$H$_4$ – I]$^+$ (30), 161 [M – Et – HI]$^+$ (18), 148 (14), 135 (24).

2-Iodomethyl-5-methoxy-2,3-dihydrobenzofuran (6e). The yield was 87%. M.p. 62.0—63.3 °C. Found (%): C, 41.49; H, 3.77; I, 43.94. C$_{10}$H$_{11}$IO$_2$. Calculated (%): C, 41.40; H, 3.82; I, 43.75. UV, λ_{max}/nm (logε): 229 (3.87), 299 (3.63). ^{1}H NMR, δ: 3.01 (m, 1 H, H(3)); 3.23 (m, 1 H, CH$_2$I); 3.34 (m, 1 H, H(3)); 3.39 (m, 1 H, CH$_2$I); 3.70 (s, 3 H, OCH$_3$); 4.82 (m, 1 H, H(2)); 6.55 (dd, 1 H, H(6), J = 7.8 Hz, J = 2.4 Hz); 6.57 (d, 1 H, H(7), J = 7.8 Hz); 6.64 (d, 1 H, H(4), J = 2.4 Hz). MS (EI, 70 eV), m/z (I_{rel} (%)): 290 [M]$^+$ (100), 163 [M – I]$^+$ (46), 148 [M – Me – – I]$^+$ (11), 135 (22), 131 (12).

2-Dodecylthiomethyl-5-ethoxy-4,6-dimethyl-2,3-dihydrobenzofuran (7a). Sodium hydroxide (0.063 g, 1.58 mmol) was added to a solution of C$_{12}$H$_{25}$SH (0.32 g, 1.58 mmol) in EtOH (1.5 mL). The mixture was stirred for 0.5 h at 60 °C, then cooled to 40 °C, followed by the addition of a solution of **6a** (0.50 g, 1.50 mmol) in EtOH (1.5 mL) and stirring for 2 h at 40 °C. The reaction mixture was cooled, acidified with aqueous solution of HCl, and extracted with toluene (3×20 mL). The organic phase was washed with aqueous solution of NaCl and dried with Na_2SO_4, the solvent was evaporated, the residue was purified on a SiO_2 plate (eluent a mixture of toluene—hexane (2 : 3)) to obtain the product (0.50 g, 82%). M.p. 35.5—36.5 °C. Found (%): C, 72.29; H, 10.54; S, 8.01. C$_{25}$H$_{42}$O$_2$S. Calculated (%): C, 73.84; H, 10.41; S, 7.88. UV, λ_{max}/nm (logε): 291 (3.56). ^{1}H NMR, δ: 0.88 (t, 3 H, S(CH$_2$)$_{11}$C$\underline{H}_3$, J = 7.2 Hz); 1.25—1.31 (m, 18 H, S(CH$_2$)$_2$(C$\underline{H}_2$)$_9$CH$_3$); 1.37 (t, 3 H, OCH$_2$C$\underline{H}_3$, J = 7.2 Hz); 1.57 (m, 2 H, SCH$_2$C$\underline{H}_2$); 2.12 (s, 3 H, ArCH$_3$); 2.17 (s, 3 H, ArCH$_3$); 2.55 (t, 2 H, SC$\underline{H}_2$C$_{11}$H$_{23}$, J = 7.2 Hz); 2.65 (m, 1 H, C$\underline{H}_2$SC$_{12}$H$_{25}$); 2.83 (m, 1 H, C$\underline{H}_2$SC$_{12}$H$_{25}$); 2.88 (m, 1 H, H(3)); 3.16 (m, 1 H, H(3)); 3.71 (q, 2 H, OC$\underline{H}_2$CH$_3$, J = 7.2 Hz); 4.80 (m, 1 H, H(2)); 6.30 (s, 1 H, H(7)). MS (EI, 70 eV), m/z (I_{rel} (%)): 406 [M]$^+$ (80), 377 [M – Et]$^+$ (14), 191 [M – CH$_2$SC$_{12}$H$_{25}$]$^+$ (14), 175 [M – Et – C$_{12}$H$_{25}$SH]$^+$ (100), 163 (12).

Compounds **7b—e** were obtained similarly to benzofuran **7a**.

2-Dodecylthiomethyl-5-ethoxy-4,7-dimethyl-2,3-dihydrobenzofuran (7b). The yield was 90%. M.p. 46.7—48.5 °C. Found (%): C, 73.38; H, 10.36; S, 7.81. C$_{25}$H$_{42}$O$_2$S. Calculated (%): C, 73.84; H, 10.41; S, 7.88. UV, λ_{max}/nm (logε): 295 (3.60). ^{1}H NMR, δ: 0.88 (t, 3 H, S(CH$_2$)$_{11}$C$\underline{H}_3$, J = 7.2 Hz); 1.25—1.31 (m, 18 H, S(CH$_2$)$_2$(C$\underline{H}_2$)$_9$CH$_3$); 1.37 (t, 3 H, OCH$_2$C$\underline{H}_3$, J = 7.2 Hz); 1.58 (m, 2 H, SCH$_2$C$\underline{H}_2$); 2.04 (s, 3 H, ArCH$_3$); 2.09 (s, 3 H, ArCH$_3$); 2.57 (t, 2 H, SC$\underline{H}_2$C$_{11}$H$_{23}$, J = 7.2 Hz); 2.66 (m, 1 H, C$\underline{H}_2$SC$_{12}$H$_{25}$); 2.85 (m, 1 H, C$\underline{H}_2$SC$_{12}$H$_{25}$); 2.91 (m, 1 H, H(3)); 3.20 (m, 1 H, H(3)); 3.88 (q, 2 H, OC$\underline{H}_2$CH$_3$, J = 7.2 Hz); 4.80 (m, 1 H, H(2)); 6.31 (s, 1 H, H(6)). MS (EI, 70 eV), m/z (I_{rel} (%)): 406 [M]$^+$ (100), 204 [M – C$_{12}$H$_{25}$SH]$^+$ (27), 191 [M – CH$_2$SC$_{12}$H$_{25}$]$^+$ (26), 175 [M – Et – C$_{12}$H$_{25}$SH]$^+$ (38), 163 (13).

2-Dodecylthiomethyl-5-ethoxy-6,7-dimethyl-2,3-dihydrobenzofuran (7c). The yield was 82%. M.p. 41.5—43.0 °C. Found (%): C, 73.62; H, 10.32; S, 7.69. C$_{25}$H$_{42}$O$_2$S. Calculated (%): C, 73.84; H, 10.41; S, 7.88. UV, λ_{max}/nm (logε): 297 (3.66). ^{1}H NMR, δ: 0.89 (t, 3 H, S(CH$_2$)$_{11}$C$\underline{H}_3$, J = 7.2 Hz); 1.25—1.31 (m, 18 H, S(CH$_2$)$_2$(C$\underline{H}_2$)$_9$CH$_3$); 1.37 (t, 3 H, OCH$_2$C$\underline{H}_3$, J = 7.2 Hz); 1.58 (m, 2 H, SCH$_2$C$\underline{H}_2$); 2.05 (s, 3 H,

$ArCH_3$); 2.06 (s, 3 H, $ArCH_3$); 2.56 (t, 2 H, $SC\underline{H}_2C_{11}H_{23}$, J = 7.2 Hz); 2.64 (m, 1 H, $C\underline{H}_2SC_{12}H_{25}$); 2.83 (m, 1 H, $C\underline{H}_2SC_{12}H_{25}$); 2.98 (m, 1 H, H(3)); 3.25 (m, 1 H, H(3)); 3.87 (q, 2 H, $OC\underline{H}_2CH_3$, J = 7.2 Hz); 4.77 (m, 1 H, H(2)); 6.45 (s, 1 H, H(4)). MS (EI, 70 eV), m/z (I_{rel} (%)): 406 $[M]^+$ (100), 204 $[M - C_{12}H_{25}SH]^+$ (30), 191 $[M - CH_2SC_{12}H_{25}]^+$ (22), 175 $[M - Et - C_{12}H_{25}SH]^+$ (31), 163 (12).

2-Dodecylthiomethyl-5-ethoxy-7-methyl-2,3-dihydrobenzofuran (7d). The yield was 77%. Found (%): C, 74.09; H, 10.35; S, 8.08. $C_{24}H_{40}O_2S$. Calculated (%): C, 73.42; H, 10.27; S, 8.17. UV, λ_{max}/nm (logε): 234 (3.58), 299 (3.61). ^{1}H NMR, δ: 0.88 (t, 3 H, $S(CH_2)_{11}C\underline{H}_3$, J = 7.2 Hz); 1.25—1.30 (m, 18 H, $S(CH_2)_2(C\underline{H}_2)_9CH_3$); 1.35 (t, 3 H, $OCH_2C\underline{H}_3$, J = 7.2 Hz); 1.58 (m, 2 H, $SCH_2C\underline{H}_2$); 2.12 (s, 3 H, $ArCH_3$); 2.56 (t, 2 H, $SC\underline{H}_2C_{11}H_{23}$, J = 7.2 Hz); 2.66 (m, 1 H, $C\underline{H}_2SC_{12}H_{25}$); 2.84 (m, 1 H, $C\underline{H}_2SC_{12}H_{25}$); 2.99 (m, 1 H, H(3)); 3.26 (m, 1 H, H(3)); 3.87 (q, 2 H, $OC\underline{H}_2CH_3$, J = 7.2 Hz); 4.80 (m, 1 H, H(2)); 6.36 (d, 1 H, H(6), J = 1.8 Hz); 6.45 (d, 1 H, H(4), J = 1.8 Hz). MS (EI, 70 eV), m/z (I_{rel} (%)): 392 $[M]^+$ (100), 190 $[M - C_{12}H_{25}SH]^+$ (69), 177 $[M - CH_2SC_{12}H_{25}]^+$ (44), 161 $[M - Et - C_{12}H_{25}SH]^+$ (40), 149 (21).

2-Dodecylthiomethyl-5-methoxy-2,3-dihydrobenzofuran (7e). The yield was 80%. M.p. 40.0—41.4 °C. Found (%): C, 71.87; H, 10.03; S, 8.92. $C_{22}H_{36}O_2S$. Calculated (%): C, 72.48; H, 9.95; S, 8.79. UV, λ_{max}/nm (logε): 230 (3.84), 300 (3.62). ^{1}H NMR, δ: 0.88 (t, 3 H, $S(CH_2)_{11}C\underline{H}_3$, J = 7.2 Hz); 1.25—1.35 (m, 18 H, $S(CH_2)_2(C\underline{H}_2)_9CH_3$); 1.57 (m, 2 H, $SCH_2C\underline{H}_2$); 2.55 (t, 2 H, $SC\underline{H}_2C_{11}H_{23}$, J = 7.2 Hz); 2.67 (m, 1 H, $C\underline{H}_2SC_{12}H_{25}$); 2.83 (m, 1 H, $C\underline{H}_2SC_{12}H_{25}$); 3.01 (m, 1 H, H(3)); 3.27 (m, 1 H, H(3)); 3.70 (s, 3 H, OMe); 4.82 (m, 1 H, H(2)); 6.54 (dd, 1 H, H(6), J = 7.8 Hz, J = 2.4 Hz); 6.56 (d, 1 H, H(7), J = 7.8 Hz); 6.65 (d, 1 H, H(4), J = 2.4 Hz). MS (EI, 70 eV), m/z (I_{rel} (%)): 364 $[M]^+$ (100), 162 $[M - C_{12}H_{25}SH]^+$ (84), 149 $[M - C_{12}H_{25}SCH_2]^+$ (73), 137 (12), 121 (16).

2-[2-Bromo-3-(dodecylthio)propyl]hydroquinone (8). The reagent BBr_3 (0.57 mL, 6.0 mmol) dissolved in DCM (5 mL) was added to a solution of compound **6e** (0.73 g, 2.0 mmol) in DCM (15 mL) cooled to −10 °C. The cooling was removed after 0.5 h and the mixture was stirred at room temperature for 12 h. Then water (10 mL) was added, the mixture was stirred for 20 min and diluted with DCM (20 mL). The organic phase was separated, washed with water, and dried with Na_2SO_4. The solvent was evaporated, the residue was dried *in vacuo* (1 Torr) to obtain the product (0.84 g, 98%). UV, λ_{max}/nm (logε): 299 (3.62). IR, ν/cm^{-1}: 3608 (OH). ^{1}H NMR, δ: 0.88 (t, 3 H, $S(CH_2)_{11}C\underline{H}_3$, J = 7.2 Hz); 1.23—1.40 (m, 18 H, $S(CH_2)_2(C\underline{H}_2)_9CH_3$); 1.58 (m, 2 H, $SCH_2C\underline{H}_2$); 2.58 (t, 2 H, $SC\underline{H}_2C_{11}H_{23}$, J = 7.2 Hz); 2.90—2.98 (m, 2 H, $C\underline{H}_2SC_{12}H_{25}$); 3.05 (m, 1 H, $ArC\underline{H}_2$); 3.46 (m, 1 H, $ArC\underline{H}_2$); 4.24 (s, 1 H, ArOH); 4.81 (m, 1 H, $C\underline{H}Br$); 4.87 (s, 1 H, ArOH); 6.54 (dd, 1 H, H(5), J = 8.4 Hz, J = 2.4 Hz); 6.59 (d, 1 H, H(3), J = 2.4 Hz); 6.62 (d, 1 H, H(6), J = 8.4 Hz).

3-{[(5-Methoxy-2,3-dihydrobenzofuran-2-yl)methyl]thio}-propionic acid (9) was obtained according to the known procedure.[20] Sodium hydroxide (0.41 g, 10.3 mmol) was added to a solution of 3-mercaptopropionic acid (0.56 g, 5.3 mmol) in EtOH (25 mL) and the mixture was stirred at 70 °C until complete dissolution of the alkali. Then, a solution of compound **6e** (1.45 g, 5.0 mmol) in EtOH (5 mL) was added, followed by stirring for 4 h. The reaction mixture was cooled, acidified with aqueous solution of HCl, and treated with toluene (3×20). The organic phase was washed with water to pH = 7 and aqueous solution of NaCl, dried with Na_2SO_4. The solvent was evaporated, the residue (1.27 g) was crystallized from toluene (25 mL) to obtain the product (1.03 g, 77%) with m.p. 103.9—104.9 °C. Found (%): C, 58.25; H, 5.97; S, 12.13. $C_{13}H_{16}O_4S$. Calculated (%): C, 58.19; H, 6.01; S, 11.95. UV, λ_{max}/nm (logε): 230 (3.90), 300 (3.65). IR, ν/cm^{-1}: 1713 (C=O). ^{1}H NMR, δ: 2.66 (t, 2 H, $C\underline{H}_2COOH$, J = 7.2 Hz); 2.75 (m, 1 H, $C\underline{H}_2SCH_2CH_2COOH$); 2.84—2.89 (m, 3 H, $C\underline{H}_2CH_2COOH$, $C\underline{H}_2SCH_2CH_2COOH$); 3.01 (m, 1 H, H(3)); 3.27 (m, 1 H, H(3)); 3.71 (s, 3 H, OCH_3); 4.86 (m, 1 H, H(2)); 6.55 (dd, 1 H, H(6), J = 8.4 Hz, J = 2.4 Hz); 6.58 (d, 1 H, H(7), J = 8.4 Hz); 6.65 (d, 1 H, H(4), J = 2.4 Hz).

2-Dodecylthiomethyl-5-hydroxy-4,6-dimethyl-2,3-dihydrobenzofuran (1a). The reagent BBr_3 (0.145 mL, 1.50 mmol) dissolved in DCM (1 mL) was added to a solution of **7a** (209 mg, 0.514 mmol) in DCM (4.5 mL) cooled to −10 °C. After 0.5 h, the cooling was removed and the mixture was stirred for 12 h at room temperature. After addition of distilled water (2 mL), the mixture was stirred for 20 min and diluted with DCM (20 mL). The organic phase was separated, washed with water, and dried with Na_2SO_4. The solvent was evaporated, the residue was dissolved in toluene (50 mL) and refluxed for 2 h. Toluene was evaporated, the residue was purified on a column with SiO_2 (eluent 12% EtOAc in hexane) and crystallized from MeCN (5 mL) to obtain compound **1a** (150 mg, 79%). M.p. 75.8—76.6 °C. Found (%): C, 72.32; H, 10.27; S, 8.38. $C_{23}H_{38}O_2S$. Calculated (%): C, 72.96; H, 10.12; S, 8.47. UV, λ_{max}/nm (logε): 296 (3.62). IR, ν/cm^{-1}: 3624 (OH). ^{1}H NMR, δ: 0.88 (t, 3 H, $S(CH_2)_{11}C\underline{H}_3$, J = 7.2 Hz); 1.25—1.38 (m, 18 H, $S(CH_2)_2(C\underline{H}_2)_9CH_3$); 1.56 (m, 2 H, $SCH_2C\underline{H}_2$); 2.11 (s, 3 H, $ArCH_3$); 2.16 (s, 3 H, $ArCH_3$); 2.55 (t, 2 H, $SC\underline{H}_2C_{11}H_{23}$, J = 7.2 Hz); 2.65 (m, 1 H, $C\underline{H}_2SC_{12}H_{25}$); 2.82 (m, 1 H, $C\underline{H}_2SC_{12}H_{25}$); 2.91 (m, 1 H, H(3)); 3.19 (m, 1 H, H(3)); 3.96 (s, 1 H, ArOH); 4.79 (m, 1 H, H(2)); 6.29 (s, 1 H, H(7)). MS (EI, 70 eV), m/z (I_{rel} (%)): 378 $[M]^+$ (100), 176 $[M - C_{12}H_{25}SH]^+$ (83), 163 $[M - C_{12}H_{25}SCH_2]^+$ (90), 135 (22).

Compounds **1b—e** and **10** were obtained similarly to benzofuran **1a**.

2-Dodecylthiomethyl-5-hydroxy-4,7-dimethyl-2,3-dihydrobenzofuran (1b) was purified on a column with SiO_2 (eluent 15% EtOAc in hexane) and crystallized from MeCN. The yield was 75%. M.p. 92.5—93.5 °C. Found (%): C, 72.55; H, 10.19; S, 8.31. $C_{23}H_{38}O_2S$. Calculated (%): C, 72.96; H, 10.12; S, 8.47. UV, λ_{max}/nm (logε): 299 (3.60). IR, ν/cm^{-1}: 3619 (OH). ^{1}H NMR, δ: 0.88 (t, 3 H, $S(CH_2)_{11}C\underline{H}_3$, J = 7.2 Hz); 1.25—1.35 (m, 18 H, $S(CH_2)_2(C\underline{H}_2)_9CH_3$); 1.58 (m, 2 H, $SCH_2C\underline{H}_2$); 2.06 (s, 3 H, $ArCH_3$); 2.07 (s, 3 H, $ArCH_3$); 2.57 (t, 2 H, $SC\underline{H}_2C_{11}H_{23}$, J = 7.2 Hz); 2.66 (m, 1 H, $C\underline{H}_2SC_{12}H_{25}$); 2.85 (m, 1 H, $C\underline{H}_2SC_{12}H_{25}$); 2.92 (m, 1 H, H(3)); 3.20 (m, 1 H, H(3)); 3.96 (s, 1 H, ArOH); 4.82 (m, 1 H, H(2)); 6.26 (s, 1 H, H(6)). MS (EI, 70 eV), m/z (I_{rel} (%)): 378 $[M]^+$ (100), 176 $[M - C_{12}H_{25}SH]^+$ (93), 163 $[M - C_{12}H_{25}SCH_2]^+$ (97), 151 (13), 147 (13), 135 (25).

2-Dodecylthiomethyl-5-hydroxy-6,7-dimethyl-2,3-dihydrobenzofuran (1c) was purified on a column with SiO_2 (eluent 7% EtOAc in hexane) and crystallized from hexane. The yield was 71%. M.p. 82.1—82.5 °C. Found (%): C, 73.18; H, 10.05; S, 8.54. $C_{23}H_{38}O_2S$. Calculated (%): C, 72.96; H, 10.12; S, 8.47. UV, λ_{max}/nm (logε): 301 (3.71). IR, ν/cm^{-1}: 3620 (OH). ^{1}H NMR, δ: 0.88 (t, 3 H, $S(CH_2)_{11}C\underline{H}_3$, J = 7.2 Hz); 1.25—1.37 (m, 18 H, $S(CH_2)_2(C\underline{H}_2)_9CH_3$); 1.57 (m, 2 H, $SCH_2C\underline{H}_2$); 2.07 (s, 6 H, $ArCH_3$); 2.56 (t, 2 H, $SC\underline{H}_2C_{11}H_{23}$, J = 7.2 Hz); 2.65 (m, 1 H, $C\underline{H}_2SC_{12}H_{25}$); 2.84 (m, 1 H, $C\underline{H}_2SC_{12}H_{25}$); 2.96 (m, 1 H, H(3)); 3.23 (m, 1 H, H(3)); 4.02 (s, 1 H, ArOH); 4.78 (m, 1 H, H(2)); 6.39 (s, 1 H, H(4)). MS (EI, 70 eV), m/z (I_{rel} (%)): 378 $[M]^+$ (100), 176 $[M - C_{12}H_{25}SH]^+$ (94), 163 $[M - C_{12}H_{25}SCH_2]^+$ (78), 151 (11), 147 (13), 135 (19).

2-Dodecylthiomethyl-5-hydroxy-7-methyl-2,3-dihydrobenzofuran (1d) was purified on a column with SiO_2 (eluent 12% EtOAc in hexane) and crystallized from hexane. The yield was 80%. M.p. 58.8—59.3 °C. Found (%): C, 72.11; H, 10.07; S, 9.18. $C_{22}H_{36}O_2S$. Calculated (%): C, 72.48; H, 9.95; S, 8.79. UV, λ_{max}/nm (log ε): 301 (3.63). IR, ν/cm^{-1}: 3618 (OH). ^{1}H NMR, δ: 0.88 (t, 3 H, $S(CH_2)_{11}C\underline{H}_3$, J = 7.2 Hz); 1.25—1.37 (m, 18 H, $S(CH_2)_2(C\underline{H}_2)_9CH_3$); 1.57 (m, 2 H, $SCH_2C\underline{H}_2$); 2.10 (s, 3 H, $ArCH_3$); 2.56 (t, 2 H, $SC\underline{H}_2C_{11}H_{23}$, J = 7.2 Hz); 2.65 (m, 1 H, $C\underline{H}_2SC_{12}H_{25}$); 2.84 (m, 1 H, $C\underline{H}_2SC_{12}H_{25}$); 2.98 (m, 1 H, H(3)); 3.24 (m, 1 H, H(3)); 3.99 (s, 1 H, ArOH); 4.80 (m, 1 H, H(2)); 6.29 (d, 1 H, H(6), J = 2.4 Hz); 6.38 (d, 1 H, H(4), J = 2.4 Hz). MS (EI, 70 eV), m/z (I_{rel} (%)): 364 $[M]^+$ (90), 162 $[M - C_{12}H_{25}SH]^+$ (100), 149 $[M - C_{12}H_{25}SCH_2]^+$ (81), 121 (21).

2-Dodecylthiomethyl-5-hydroxy-2,3-dihydrobenzofuran (1e) was purified on a column with SiO_2 (eluent 12% EtOAc in hexane) and crystallized from hexane. The yield was 80%. M.p. 72.2—73.2 °C. Found (%): C, 72.15; H, 9.62; S, 9.03. $C_{21}H_{34}O_2S$. Calculated (%): C, 71.95; H, 9.78; S, 9.15. UV, λ_{max}/nm (log ε): 228 (3.96), 302 (3.73). IR, ν/cm^{-1}: 3617 (OH). ^{1}H NMR, δ: 0.88 (t, 3 H, $S(CH_2)_{11}C\underline{H}_3$, J = 7.2 Hz); 1.25—1.36 (m, 18 H, $S(CH_2)_2(C\underline{H}_2)_9CH_3$); 1.57 (m, 2 H, $SCH_2C\underline{H}_2$); 2.55 (t, 2 H, $SC\underline{H}_2C_{11}H_{23}$, J = 7.2 Hz); 2.66 (m, 1 H, $C\underline{H}_2SC_{12}H_{25}$); 2.83 (m, 1 H, $C\underline{H}_2SC_{12}H_{25}$); 2.99 (m, 1 H, H(3)); 3.25 (m, 1 H, H(3)); 4.24 (s, 1 H, ArOH); 4.81 (m, 1 H, H(2)); 6.45 (dd, 1 H, H(6), J = 8.4 Hz, J = 2.4 Hz); 6.50 (d, 1 H, H(7), J = 8.4 Hz); 6.58 (d, 1 H, H(4), J = 2.4 Hz). MS (EI, 70 eV), m/z (I_{rel} (%)): 350 $[M]^+$ (73), 148 $[M - C_{12}H_{25}SH]^+$ (100), 135 $[M - C_{12}H_{25}SCH_2]^+$ (90), 123 (13), 107 (25).

3-[2-(5-Hydroxy-2,3-dihydrobenzofuran-2-yl)methylthio] propionic acid (10). The yield was 43%. M.p. 123.5—125.0 °C. Found (%): C, 56.76; H, 5.51; S, 12.80; $C_{12}H_{14}O_4S$. Calculated (%): C, 56.68; H, 5.55; S, 12.61. UV, λ_{max}/nm (log ε): 229 (3.81), 302 (3.61). IR, ν/cm^{-1}: 3404 (OH), 1685 (C=O). ^{1}H NMR, δ: 2.51 (t, 2 H, $C\underline{H}_2COOH$, J = 7.2 Hz); 2.74 (t, 2 H, $SC\underline{H}_2CH_2COOH$, J = 7.2 Hz); 2.79 (m, 1 H, $C\underline{H}_2SCH_2CH_2COOH$); 2.85 (m, 1 H, $C\underline{H}_2SCH_2CH_2COOH$); 2.89 (m, 1 H, H(3)); 3.21 (m, 1 H, H(3)); 4.82 (m, 1 H, H(2)); 6.44 (dd, 1 H, H(6), J = 8.4 Hz, J = 3.0 Hz); 6.50 (d, 1 H, H(7), J = 8.4 Hz); 6.60 (d, 1 H, H(4), J = 3.0 Hz); 8.78 (s, 1 H, ArOH); 12.27 (br.s, 1 H, COOH).

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