

Supporting Information

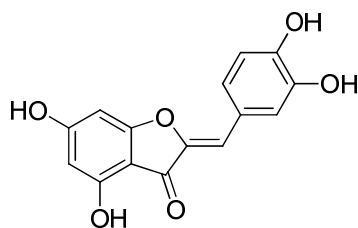
Discovery of Naturally Occurring Aurones that are Potent Allosteric Inhibitors of Hepatitis C Virus RNA-Dependent RNA Polymerase

Romain Haudecoeur, Abdelhakim Ahmed-Belkacem, Wei Yi, Antoine Fortuné, Rozenn Brillet, Catherine Belle, Edwige Nicolle, Coralie Pallier, Jean-Michel Pawlotsky and Ahcène Boumendjel

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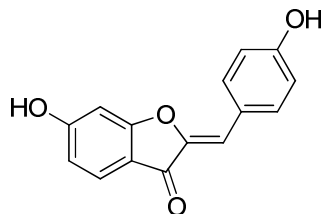
S2-S19: Compounds characterization

Compounds purification and characterization



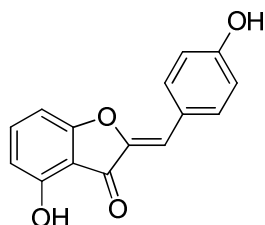
(Z)-2-(3,4-dihydroxybenzylidene)-4,6-dihydroxybenzofuran-3(2H)-one (1).

The crude product was prepared according to general procedure D starting from (Z)-2-(3,4-dimethoxybenzylidene)-4,6-dimethoxybenzofuran-3(2H)-one (**52**), and was washed three times with distilled water to yield a yellow solid, which was analytically pure and used without further purification (61%). m.p. > 260 °C (decomposition). ¹H NMR (400 MHz, MeOD) δ 7.47 (d, 1H, J = 1.4 Hz, H₂'), 7.18 (dd, 1H, J = 8.2 Hz, J = 1.4 Hz, H₆'), 6.82 (d, 1H, J = 8.2 Hz, H₅'), 6.56 (s, 1H, -CH=), 6.19 (s, 1H, H₇'), 6.01 (s, 1H, H₅). ¹³C NMR (100 MHz, MeOD) δ 178.9, 167.4, 166.9, 158.1, 147.4, 145.8, 145.4, 123.9, 123.6, 117.5, 115.9, 109.5, 102.8, 97.5, 90.2. MS (ESI) m/z 287 (M+H)⁺, 309 (M+Na)⁺. Anal. Calcd for C₁₅H₁₀O₆·1.3H₂O: C, 57.57, H, 4.05. Found: C, 57.12, H, 3.81.



(Z)-2-(4-hydroxybenzylidene)-6-hydroxybenzofuran-3(2H)-one (10).

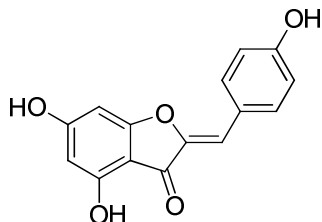
The crude product was prepared according to general procedure A starting from 6-hydroxybenzofuran-3(2H)-one (**2**) and 4-hydroxybenzaldehyde, and was recrystallized from acetonitrile to yield pure bright yellow crystals (77%). m.p. 294-296 °C. ¹H NMR (400 MHz, *d*₆-DMSO) δ 11.14 (br s, 1H, OH), 10.14 (br s, 1H, OH), 7.82 (d, 2H, J = 8.7 Hz, H_{2',6'}), 7.60 (d, 1H, J = 8.4 Hz, H₄), 6.88 (d, 2H, J = 8.7 Hz, H_{3',5'}), 6.78 (d, 1H, J = 1.9 Hz, H₇), 6.73 (s, 1H, -CH=), 6.70 (dd, 1H, J_1 = 8.4 Hz, J_2 = 1.9 Hz, H₅). ¹³C NMR (100 MHz, *d*₆-DMSO) δ 181.2, 167.4, 166.0, 159.2, 145.6, 133.2, 125.6, 123.0, 116.0, 113.1, 112.8, 111.3, 98.4. MS (ESI) m/z 255 (M+H)⁺, 277 (M+Na)⁺. Anal. Calcd for C₁₅H₁₀O₄·½H₂O: C, 68.44, H, 4.18. Found: C, 68.28, H, 4.11.



(Z)-2-(4-hydroxybenzylidene)-4-hydroxybenzofuran-3(2H)-one (11).

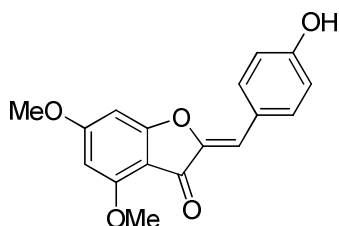
The crude product was prepared according to general procedure A starting from 4-hydroxybenzofuran-3(2H)-one (**5**) and 4-hydroxybenzaldehyde, and was recrystallized from acetonitrile to yield pure orange crystals (37%). m.p. 245-247 °C. ¹H NMR (400 MHz, *d*₆-DMSO) δ 11.05 (s, 1H, OH), 10.13 (s, 1H, OH), 7.81 (d, 2H, J = 8.4 Hz, H_{2',6'}), 7.51 (t, 1H, J

= 8.1 Hz, H₆), 6.88 (d, 2H, J = 8.4 Hz, H_{3',5'}), 6.84 (d, 1H, J = 8.1 Hz, H₇), 6.70 (s, 1H, -CH=), 6.61 (d, 1H, J = 8.1 Hz, H₅). ¹³C NMR (100 MHz, *d*₆-DMSO) δ 181.1, 165.7, 159.2, 156.9, 144.9, 138.2, 133.2, 123.1, 116.0, 110.9, 110.3, 109.4, 102.4. MS (ESI) m/z 255 (M+H)⁺, 277 (M+Na)⁺. Anal. Calcd for C₁₅H₁₀O₄·0.1H₂O: C, 70.37, H, 3.99. Found: C, 70.10, H, 3.96.



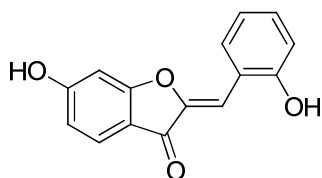
(Z)-2-(4-hydroxybenzylidene)-4,6-dihydroxybenzofuran-3(2H)-one (12).

To a solution of 4-hydroxybenzaldehyde (147 mg, 1.21 mmol) in methanol (10 mL) was added concentrated sulfuric acid (64.2 μ L, 1.21 mmol), and the solution was stirred at room temperature for 30 minutes. 4,6-Dihydroxybenzofuran-3(2H)-one (**3**, 200 mg, 1.21 mmol) was then added, and the solution was refluxed for 4 hours. After cooling, the mixture was concentrated under reduced pressure, then the residue was diluted in water (100 mL), extracted with ethyl acetate and washed with water and brine. The combined organic layers were dried over magnesium sulfate and filtered, and the filtrate was concentrated under reduced pressure to give the crude compound, which was purified by column chromatography on silica gel (eluent: ethyl acetate 3 / cyclohexane 2) to yield a pure yellow solid (17%). m.p. > 295 °C (decomposition). ¹H NMR (400 MHz, *d*₆-DMSO) δ 10.84 (br s, 1H, OH), 10.03 (br s, 1H, OH), 7.75 (d, 2H, J = 8.7 Hz, H_{2',6'}), 6.86 (d, 2H, J = 8.7 Hz, H_{3',5'}), 6.54 (s, 1H, -CH=), 6.20 (d, 1H, J = 1.6 Hz, H₇), 6.06 (d, 1H, J = 1.6 Hz, H₅). ¹³C NMR (100 MHz, *d*₆-DMSO) δ 179.1, 167.6, 167.1, 158.8, 158.2, 146.0, 132.8, 123.4, 116.0, 109.1, 102.9, 97.7, 90.5. MS (ESI) m/z 271 (M+H)⁺, 293 (M+Na)⁺. Anal. Calcd for C₁₅H₁₀O₅: C, 66.67, H, 3.73. Found: C, 66.43, H, 3.83.



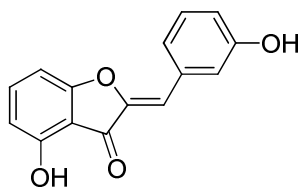
(Z)-2-(4-hydroxybenzylidene)-4,6-dimethoxybenzofuran-3(2H)-one (13).

The crude product was prepared according to general procedure A starting from 4,6-dimethoxybenzofuran-3(2H)-one (**6**) and 4-hydroxybenzaldehyde, and was recrystallized from methanol to yield pure yellow crystals (63%). m.p. > 275 °C (decomposition). ¹H NMR (400 MHz, *d*₆-DMSO) δ 10.11 (s, 1H, OH), 7.79 (d, 2H, J = 8.6 Hz, H_{2',6'}), 6.87 (d, 2H, J = 8.6 Hz, H_{3',5'}), 6.68 (d, 1H, J = 1.1 Hz, H₇), 6.65 (s, 1H, -CH=), 6.33 (d, 1H, J = 1.1 Hz, H₅), 3.91 (s, 3H, OMe), 3.88 (s, 3H, OMe). ¹³C NMR (100 MHz, *d*₆-DMSO) δ 178.9, 168.6, 167.9, 159.1, 158.8, 145.6, 133.0, 123.1, 116.0, 110.4, 104.3, 94.3, 89.7, 56.4, 56.1. MS (ESI) m/z 299 (M+H)⁺, 321 (M+Na)⁺. Anal. Calcd for C₁₇H₁₄O₅: C, 68.46, H, 4.74. Found: C, 68.13, H, 4.78.



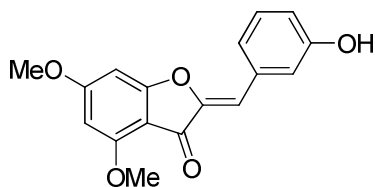
(Z)-2-(3-hydroxybenzylidene)-6-hydroxybenzofuran-3(2H)-one (14).

The crude product was prepared according to general procedure A starting from 6-hydroxybenzofuran-3(2H)-one (**2**) and 3-hydroxybenzaldehyde, and was recrystallized from acetonitrile to yield pure yellow crystals (86%). m.p. 272-274 °C. ¹H NMR (400 MHz, *d*₆-DMSO) δ 11.27 (br s, 1H, OH), 9.69 (br s, 1H, OH), 7.63 (d, 1H, *J* = 8.4 Hz, H₄), 7.36 (m, 2H, H₂,₆), 7.28 (t, 1H, *J* = 7.6 Hz, H₅), 6.84 (d, 1H, *J* = 7.6 Hz, H₄), 6.78 (s, 1H, H₇), 6.72 (d, 1H, *J* = 8.4 Hz, H₅), 6.69 (s, 1H, -CH=). ¹³C NMR (100 MHz, *d*₆-DMSO) δ 181.5, 167.9, 166.6, 157.6, 147.3, 133.1, 129.9, 126.1, 122.4, 117.3, 117.1, 113.1, 112.8, 110.7, 98.5. MS (ESI) *m/z* 255 (M+H)⁺, 277 (M+Na)⁺. Anal. Calcd for C₁₅H₁₀O₄·¼H₂O: C, 69.63, H, 4.06. Found: C, 69.47, H, 3.94.



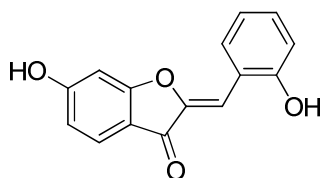
(Z)-2-(3-hydroxybenzylidene)-4-hydroxybenzofuran-3(2H)-one (15).

The crude product was prepared according to general procedure A starting from 4-hydroxybenzofuran-3(2H)-one (**5**) and 3-hydroxybenzaldehyde, and was recrystallized from acetonitrile to yield pure yellow crystals (55%). m.p. 207-209 °C. ¹H NMR (400 MHz, *d*₆-DMSO) δ 11.21 (br s, 1H, OH), 9.69 (br s, 1H, OH), 7.54 (t, 1H, *J* = 8.2 Hz, H₆), 7.36 (m, 2H, H₂,₆), 7.28 (t, 1H, *J* = 7.8 Hz, H₅), 6.84 (m, 2H, H₄,₇), 6.66 (s, 1H, -CH=), 6.64 (d, 1H, *J* = 8.2 Hz, H₅). ¹³C NMR (100 MHz, *d*₆-DMSO) δ 181.4, 166.0, 157.6, 157.2, 146.5, 138.7, 133.2, 129.9, 122.3, 117.2, 117.0, 110.7, 110.2, 109.0, 102.3. MS (ESI) *m/z* 255 (M+H)⁺, 277 (M+Na)⁺. Anal. Calcd for C₁₅H₁₀O₄: C, 70.87, H, 3.97. Found: C, 70.84, H, 4.74.



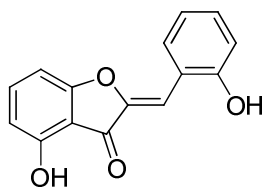
(Z)-2-(3-hydroxybenzylidene)-4,6-dimethoxybenzofuran-3(2H)-one (16).

The crude product was prepared according to general procedure A starting from 4,6-dimethoxybenzofuran-3(2H)-one (**6**) and 3-hydroxybenzaldehyde, and was recrystallized from methanol to yield pure yellow crystals (76%). m.p. > 250 °C (decomposition). ¹H NMR (400 MHz, *d*₆-DMSO) δ 9.65 (s, 1H, OH), 7.34 (m, 2H, H₂,₆), 7.27 (t, 1H, *J* = 8.0 Hz, H₅), 6.83 (d, 1H, *J* = 8.0 Hz, H₄), 6.67 (d, 1H, *J* = 1.2 Hz, H₇), 6.61 (s, 1H, -CH=), 6.35 (d, 1H, *J* = 1.2 Hz, H₅), 3.92 (s, 3H, OMe), 3.89 (s, 3H, OMe). ¹³C NMR (100 MHz, *d*₆-DMSO) δ 179.0, 169.0, 168.3, 159.0, 157.6, 147.2, 133.2, 129.9, 122.1, 117.3, 116.9, 109.8, 104.0, 94.4, 89.8, 56.5, 56.2. MS (ESI) *m/z* 299 (M+H)⁺, 321 (M+Na)⁺. Anal. Calcd for C₁₇H₁₄O₅·H₂O: C, 64.56, H, 5.06. Found: C, 64.31, H, 5.06.



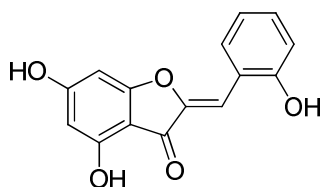
(Z)-2-(2-hydroxybenzylidene)-6-hydroxybenzofuran-3(2H)-one (17).

The crude product was prepared according to general procedure A starting from 6-hydroxybenzofuran-3(2H)-one (**2**) and 2-hydroxybenzaldehyde, and was recrystallized from acetonitrile to yield pure yellow crystals (25%). m.p. > 250 °C (decomposition). ¹H NMR (400 MHz, *d*₆-DMSO) δ 11.21 (br s, 1H, OH), 10.35 (br s, 1H, OH), 8.09 (d, 1H, *J* = 7.0 Hz, H_{6'}), 7.62 (d, 1H, *J* = 8.4 Hz, H₄), 7.26 (t, 1H, *J* = 7.0 Hz, H_{4'}), 7.09 (s, 1H, -CH=), 6.94 (m, 2H, H_{3',5'}), 6.79 (d, 1H, *J* = 1.5 Hz, H₇), 6.72 (dd, 1H, *J* = 8.4 Hz, *J* = 1.5 Hz, H₅). ¹³C NMR (100 MHz, *d*₆-DMSO) δ 181.4, 167.7, 166.3, 157.0, 146.8, 131.3, 130.9, 125.8, 119.6, 118.8, 115.6, 112.9, 104.6, 98.5. MS (ESI) *m/z* 255 (M+H)⁺, 277 (M+Na)⁺. Anal. Calcd for C₁₅H₁₀O₄·¼ H₂O: C, 69.63, H, 4.06. Found: C, 69.81, H, 4.05.

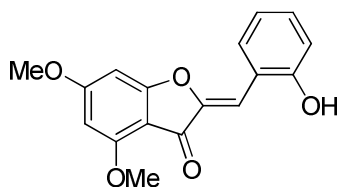


(Z)-2-(2-hydroxybenzylidene)-4-hydroxybenzofuran-3(2H)-one (18).

The crude product was prepared according to general procedure A starting from 4-hydroxybenzofuran-3(2H)-one (**5**) and 2-hydroxybenzaldehyde, and was recrystallized from acetonitrile to yield pure yellow crystals (28%). m.p. > 250 °C. ¹H NMR (400 MHz, *d*₆-DMSO) δ 11.10 (br s, 1H, OH), 10.35 (s, 1H, OH), 8.08 (d, 1H, *J* = 7.2 Hz, H_{6'}), 7.52 (t, 1H, *J* = 7.6 Hz, H₆), 7.24 (t, 1H, *J* = 7.2 Hz, H_{4'}), 7.06 (s, 1H, -CH=), 6.94 (m, 2H, H_{3',5'}), 6.86 (d, 1H, *J* = 7.6 Hz, H₇), 6.62 (d, 1H, *J* = 7.6 Hz, H₅). ¹³C NMR (100 MHz, *d*₆-DMSO) δ 181.2, 165.8, 157.0, 157.0, 146.0, 138.4, 131.2, 130.8, 119.6, 118.9, 115.6, 110.4, 109.1, 104.1, 102.4. MS (ESI) *m/z* 255 (M+H)⁺, 277 (M+Na)⁺. Anal. Calcd for C₁₅H₁₀O₄·¼ H₂O: C, 69.63, H, 4.06. Found: C, 69.19, H, 3.89.

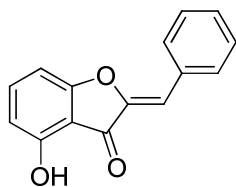


(Z)-2-(2-hydroxybenzylidene)-4,6-dihydroxybenzofuran-3(2H)-one (19). The crude product was prepared according to general procedure D starting from (Z)-2-(2-hydroxybenzylidene)-4,6-dimethoxybenzofuran-3(2H)-one (**20**), and was purified by column chromatography on silica gel (eluent: ethyl acetate 1 / cyclohexane 1) to yield a pure yellow solid (66%). m.p. 262-264 °C. ¹H NMR (400 MHz, *d*₆-acetone) δ 8.12 (d, 1H, *J* = 7.2 Hz, H_{6'}), 7.17 (m, 1H, H_{4'}), 7.12 (s, 1H, -CH=), 6.90 (m, 2H, H_{3',5'}), 6.29 (d, 1H, *J* = 2.0 Hz, H₇), 6.08 (d, 1H, *J* = 2.0 Hz, H₅). ¹³C NMR (100 MHz, *d*₆-acetone) δ 180.9, 167.6, 167.5, 157.9, 156.7, 147.5, 131.2, 130.9, 120.0, 119.6, 115.5, 103.6, 103.4, 97.7, 91.2. MS (ESI) *m/z* 271 (M+H)⁺. Anal. Calcd for C₁₅H₁₀O₅·½ H₂O: C, 65.22, H, 3.86. Found: C, 65.37, H, 4.61.



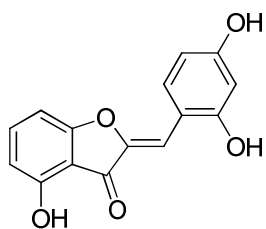
(Z)-2-(2-hydroxybenzylidene)-4,6-dimethoxybenzofuran-3(2H)-one (20).

The crude product was prepared according to general procedure A starting from 4,6-dimethoxy-benzofuran-3(2H)-one (**6**) and 2-hydroxybenzaldehyde, and was recrystallized from methanol to yield pure yellow crystals (51%). m.p. > 250 °C (decomposition). ¹H NMR (400 MHz, *d*₆-DMSO) δ 10.31 (s, 1H, OH), 8.06 (d, 1H, *J* = 7.8 Hz, H_{6'}), 7.24 (t, 1H, *J* = 7.8 Hz, H_{4'}), 7.01 (s, 1H, -CH=), 6.94 (d, 1H, *J* = 7.8 Hz, H_{3'}), 6.92 (t, 1H, *J* = 7.8 Hz, H_{5'}), 6.71 (d, 1H, *J* = 1.4 Hz, H₇), 6.34 (d, 1H, *J* = 1.4 Hz, H₅), 3.91 (s, 3H, OMe), 3.89 (s, 3H, OMe). ¹³C NMR (100 MHz, *d*₆-DMSO) δ 179.0, 168.7, 168.0, 158.8, 156.9, 146.7, 131.1, 130.6, 119.4, 118.8, 115.6, 104.0, 103.6, 94.3, 89.8, 56.4, 56.0. MS (ESI) *m/z* 299 (M+H)⁺, 321 (M+Na)⁺. Anal. Calcd for C₁₇H₁₄O₄: C, 68.46, H, 4.74. Found: C, 68.39, H, 4.77.



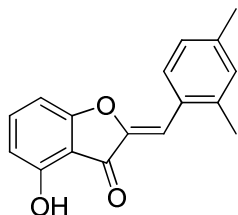
(Z)-2-benzylidene-4-hydroxybenzofuran-3(2H)-one (21).

The crude product was prepared according to general procedure A starting from 4-hydroxybenzofuran-3(2H)-one (**5**) and benzaldehyde, and was purified by column chromatography on silica gel (eluent: dichloromethane) to yield a pure yellow solid (72%). m.p. 148 °C. ¹H NMR (400 MHz, *d*₆-DMSO) δ 11.19 (s, 1H, OH), 7.95 (d, 2H, *J* = 7.2 Hz, H_{2',6'}), 7.54 (t, 1H, *J* = 8.1 Hz, H₆), 7.46 (m, 3H, H_{3',4',5'}), 6.87 (d, 1H, *J* = 8.1 Hz, H₇), 6.77 (s, 1H, -CH=), 6.64 (d, 1H, *J* = 8.1 Hz, H₅). ¹³C NMR (100 MHz, *d*₆-DMSO) δ 181.4, 166.1, 157.2, 146.6, 138.8, 132.2, 131.0, 129.6, 129.0, 110.7, 109.9, 109.0, 102.5. MS (ESI) *m/z* 239 (M+H)⁺, 261 (M+Na)⁺. Anal. Calcd for C₁₅H₁₀O₃·²/₃H₂O: C, 72.00, H, 4.53. Found: C, 71.99, H, 4.15.



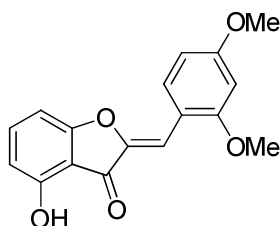
(Z)-2-(2,4-dihydroxybenzylidene)-4-hydroxybenzofuran-3(2H)-one (22).

The crude product was prepared according to general procedure D starting from (Z)-2-(2,4-dimethoxybenzylidene)-4-hydroxybenzofuran-3(2H)-one (**24**), and was washed three times with distilled water to yield a yellow solid, which was analytically pure and used without further purification (61%). m.p. > 230 °C (decomposition). ¹H NMR (400 MHz, *d*₆-DMSO) δ 10.94 (s, 1H, OH), 10.29 (s, 1H, OH), 10.02 (s, 1H, OH), 7.96 (d, 1H, *J* = 8.2 Hz, H_{6'}), 7.48 (t, 1H, *J* = 8.0 Hz, H₆), 7.03 (s, 1H, -CH=), 6.83 (d, 1H, *J* = 8.0 Hz, H₇), 6.59 (d, 1H, *J* = 8.0 Hz, H₅), 6.40 (m, 2H, H_{3',5'}). ¹³C NMR (400 MHz, *d*₆-DMSO) δ 181.0, 165.6, 160.9, 159.1, 156.8, 144.3, 137.8, 132.4, 110.7, 110.1, 109.7, 108.3, 105.6, 102.5, 102.3. MS (ESI) *m/z* 271 (M+H)⁺, 293 (M+Na)⁺. Anal. Calcd for C₁₅H₁₀O₅·H₂O: C, 62.50, H, 4.17. Found: C, 62.64, H, 3.70.



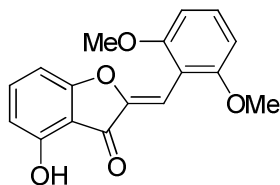
(Z)-2-(2,4-dimethylbenzylidene)-4-hydroxybenzofuran-3(2H)-one (23).

The crude product was prepared according to general procedure A starting from 4-hydroxybenzofuran-3(2H)-one (**5**) and 2,4-dimethylbenzaldehyde, and was recrystallized from methanol to yield pure yellow crystals (76%). m.p. 193-194 °C. ¹H NMR (400 MHz, *d*₆-DMSO) δ 11.14 (s, 1H, OH), 8.01 (d, 1H, *J* = 7.9 Hz, H_{6'}), 7.52 (t, 1H, *J* = 8.1 Hz, H₆), 7.12 (m, 2H, H_{3',5'}), 6.84 (d, 1H, *J* = 8.1 Hz, H₇), 6.78 (s, 1H, -CH=), 6.63 (d, 1H, *J* = 8.1 Hz, H₅), 2.40 (s, 3H, Me), 2.29 (s, 3H, Me). ¹³C NMR (100 MHz, *d*₆-DMSO) δ 181.2, 166.0, 157.1, 146.2, 139.4, 138.5, 138.4, 131.3, 130.3, 127.6, 127.1, 110.6, 109.1, 106.5, 102.4, 21.0, 19.6. MS (ESI) *m/z* 267 (M+H)⁺, 289 (M+Na)⁺. Anal. Calcd for C₁₇H₁₄O₃·¹/₃H₂O: C, 75.00, H, 5.39. Found: C, 74.96, H, 5.35.



(Z)-2-(2,4-dimethoxybenzylidene)-4-hydroxybenzofuran-3(2H)-one (24).

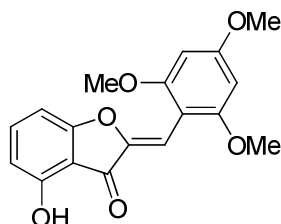
The crude product was prepared according to general procedure A starting from 4-hydroxybenzofuran-3(2H)-one (**5**) and 2,4-dimethoxybenzaldehyde, and was recrystallized from methanol to yield pure yellow crystals (76%). m.p. 234-235 °C. ¹H NMR (400 MHz, *d*₆-DMSO) δ 11.05 (s, 1H, OH), 8.11 (d, 1H, *J* = 8.6 Hz, H_{6'}), 7.51 (t, 1H, *J* = 8.0 Hz, H₆), 6.99 (s, 1H, -CH=), 6.84 (d, 1H, *J* = 8.0 Hz, H₇), 6.70 (d, 1H, *J* = 8.6 Hz, H_{5'}), 6.66 (s, 1H, H_{3'}), 6.62 (d, 1H, *J* = 8.0 Hz, H₅), 3.90 (s, 3H, OMe), 3.84 (s, 3H, OMe). ¹³C NMR (100 MHz, *d*₆-DMSO) δ 181.2, 165.8, 162.4, 159.8, 157.0, 145.3, 138.3, 132.2, 113.2, 110.5, 109.4, 106.7, 103.9, 102.6, 98.3, 56.0, 55.6. MS (ESI) *m/z* 299 (M+H)⁺, 321 (M+Na)⁺, 619 (2M+Na)⁺. Anal. Calcd for C₁₇H₁₄O₅·¹/₂H₂O: C, 66.44, H, 4.92. Found: C, 66.60, H, 4.88.



(Z)-2-(2,6-dimethoxybenzylidene)-4-hydroxybenzofuran-3(2H)-one (25).

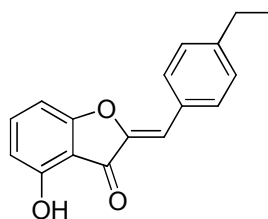
The crude product was prepared according to general procedure A starting from 4-hydroxybenzofuran-3(2H)-one (**5**) and 2,6-dimethoxybenzaldehyde, and was purified by column chromatography on silica gel (eluent: dichloromethane) to yield pure yellow solid (34%). m.p. 152-153 °C. ¹H NMR (400 MHz, CDCl₃) δ 7.95 (br s, 1H, OH), 7.45 (t, 1H, *J* = 8.1 Hz, H₆), 7.34 (t, 1H, *J* = 8.4 Hz, H_{4'}), 7.09 (s, 1H, -CH=), 6.66 (d, 1H, *J* = 8.1 Hz, H₇), 6.61 (d, 2H, *J* = 8.4 Hz, H_{3',5'}), 6.58 (d, 1H, *J* = 8.1 Hz, H₅), 3.88 (s, 6H, OMe). ¹³C NMR (100 MHz, CDCl₃) δ 185.5, 165.1, 159.1, 156.7, 147.5, 139.2, 131.5, 110.1, 109.9, 109.3,

106.5, 104.0, 103.5, 56.0. MS (ESI) m/z 299 (M+H)⁺, 321 (M+Na)⁺, 619 (2M+Na)⁺. Anal. Calcd for C₁₇H₁₄O₅·½H₂O: C, 66.45, H, 4.88. Found: C, 66.45, H, 4.78.



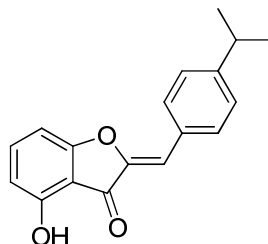
(Z)-2-(2,4,6-trimethoxybenzylidene)-4-hydroxybenzofuran-3(2H)-one (26).

The crude product was prepared according to general procedure A starting from 4-hydroxybenzofuran-3(2H)-one (**5**) and 2,4,6-trimethoxybenzaldehyde, and was recrystallized from methanol to yield pure yellow crystals (71%). m.p. 139-140 °C. ¹H NMR (400 MHz, *d*₆-DMSO) δ 11.00 (s, 1H, OH), 7.46 (t, 1H, *J* = 8.1 Hz, H₆), 6.68 (d, 1H, *J* = 8.1 Hz, H₇), 6.66 (s, 1H, -CH=), 6.57 (d, 1H, *J* = 8.1 Hz, H₅), 6.31 (s, 2H, H_{3,5}), 3.84 (s, 3H, OMe), 3.83 (s, 6H, OMe). ¹³C NMR (100 MHz, *d*₆-DMSO) δ 181.1, 165.9, 162.8, 159.5, 156.9, 146.1, 138.4, 109.9, 109.5, 103.4, 102.2, 91.1, 55.9, 55.5. MS (ESI) m/z 329 (M+H)⁺, 351 (M+Na)⁺, 679 (2M+Na)⁺. Anal Calcd for C₁₈H₁₆O₆·½H₂O: C, 64.67, H, 4.99. Found: C, 64.58, H, 5.03.



(Z)-2-(4-ethylbenzylidene)-4-hydroxybenzofuran-3(2H)-one (27).

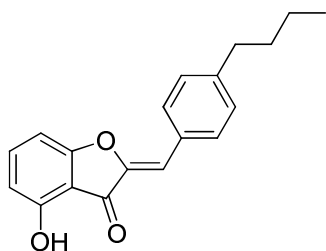
The crude product was prepared according to general procedure A starting from 4-hydroxybenzofuran-3(2H)-one (**5**) and 4-ethylbenzaldehyde, and was recrystallized from methanol to yield pure yellow crystals (50%). m.p. 141-142 °C. ¹H NMR (400 MHz, *d*₆-DMSO) δ 11.16 (s, 1H, OH), 7.86 (d, 2H, *J* = 8.0 Hz, H_{2,6}), 7.53 (t, 1H, *J* = 8.1 Hz, H₆), 7.32 (d, 2H, *J* = 8.0 Hz, H_{3,5}), 6.86 (d, 1H, *J* = 8.1 Hz, H₇), 6.74 (s, 1H, -CH=), 6.64 (d, 1H, *J* = 8.1 Hz, H₅), 2.64 (q, 2H, *J* = 7.5 Hz, PhCH₂CH₃), 1.19 (t, 3H, *J* = 7.5 Hz, PhCH₂CH₃). ¹³C NMR (100 MHz, *d*₆-DMSO) δ 181.3, 166.0, 157.1, 146.2, 145.8, 138.6, 131.1, 129.6, 128.4, 110.6, 110.1, 109.1, 102.4, 28.2, 15.3. MS (ESI) m/z 267 (M+H)⁺, 289 (M+Na)⁺. Anal. Calcd for C₁₇H₁₄O₃·½H₂O: C, 76.04, H, 5.31. Found: C, 75.93, H, 5.26.



(Z)-2-(4-isopropylbenzylidene)-4-hydroxybenzofuran-3(2H)-one (28).

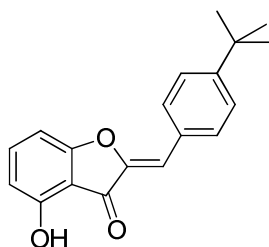
The crude product was prepared according to general procedure A starting from 4-hydroxybenzofuran-3(2H)-one (**5**) and 4-isopropylbenzaldehyde, and was recrystallized from methanol to yield pure yellow crystals (44%). m.p. 126-127 °C. ¹H NMR (400 MHz, *d*₆-DMSO) δ 11.16 (s, 1H, OH), 7.86 (d, 2H, *J* = 7.9 Hz, H_{2,6}), 7.54 (t, 1H, *J* = 8.1 Hz, H₆), 7.36 (d, 2H, *J* = 7.9 Hz, H_{3,5}), 6.86 (d, 1H, *J* = 8.1 Hz, H₇), 6.74 (s, 1H, -CH=), 6.64 (d, 1H, *J* =

8.1 Hz, H₅), 2.92 (sept., 1H, $J = 6.8$ Hz, PhCH(CH₃)₂), 1.21 (d, 6H, $J = 6.8$ Hz, PhCH(CH₃)₂). ¹³C NMR (100 MHz, *d*₆-DMSO) δ 181.3, 166.0, 157.1, 150.4, 146.2, 138.6, 131.2, 129.8, 127.0, 110.6, 110.1, 109.1, 102.4, 33.5, 23.6. MS (ESI) m/z 281 (M+H)⁺, 303 (M+Na)⁺. Anal. Calcd for C₁₈H₁₆O₃· $\frac{1}{4}$ H₂O: C, 75.92, H, 5.79. Found: C, 75.55, H, 5.62.



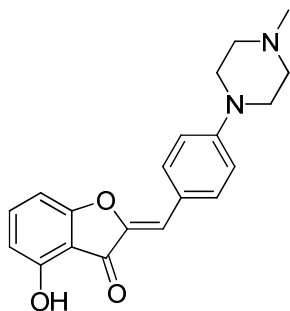
(Z)-2-(4-butylbenzylidene)-4-hydroxybenzofuran-3(2H)-one (29).

The crude product was prepared according to general procedure A starting from 4-hydroxybenzofuran-3(2H)-one (**5**) and 4-butylbenzaldehyde, and was recrystallized from methanol to yield pure yellow crystals (56%). m.p. 121-122 °C. ¹H NMR (400 MHz, *d*₆-DMSO) δ 11.15 (s, 1H, OH), 7.85 (d, 2H, $J = 7.9$ Hz, H_{2',6'}), 7.53 (t, 1H, $J = 8.1$ Hz, H₆), 7.30 (d, 2H, $J = 7.9$ Hz, H_{3',5'}), 6.86 (d, 1H, $J = 8.1$ Hz, H₇), 6.74 (s, 1H, -CH=), 6.63 (d, 1H, $J = 8.0$ Hz, H₅), 2.61 (t, 2H, $J = 7.4$ Hz, PhCH₂CH₂CH₂CH₃), 1.56 (quint., 2H, $J = 7.4$ Hz, PhCH₂CH₂CH₂CH₃), 1.30 (sext., 2H, $J = 7.4$ Hz, PhCH₂CH₂CH₂CH₃), 0.89 (t, 3H, $J = 7.4$ Hz, PhCH₂CH₂CH₂CH₃). ¹³C NMR (100 MHz, *d*₆-DMSO) δ 181.3, 166.0, 157.1, 146.2, 144.5, 138.6, 131.1, 129.6, 129.0, 110.6, 110.2, 109.1, 102.4, 34.8, 32.9, 21.8, 13.8. MS (ESI) m/z 295 (M+H)⁺, 317 (M+Na)⁺. Anal. Calcd for C₁₉H₁₈O₃: C, 77.53, H, 6.17. Found: C, 77.32, H, 6.33.



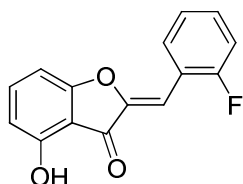
(Z)-2-(4-tert-butylbenzylidene)-4-hydroxybenzofuran-3(2H)-one (30).

The crude product was prepared according to general procedure A starting from 4-hydroxybenzofuran-3(2H)-one (**5**) and 4-tert-butylbenzaldehyde, and was recrystallized from methanol to yield pure yellow crystals (61%). m.p. 167-168 °C. ¹H NMR (400 MHz, *d*₆-DMSO) δ 11.16 (s, 1H, OH), 7.86 (d, 2H, $J = 8.0$ Hz, H_{2',6'}), 7.54 (t, 1H, $J = 8.1$ Hz, H₆), 7.49 (d, 2H, $J = 8.0$ Hz, H_{3',5'}), 6.85 (d, 1H, $J = 8.1$ Hz, H₇), 6.74 (s, 1H, -CH=), 6.64 (d, 1H, $J = 8.1$ Hz, H₅), 1.28 (s, 9H, Ph(CH₃)₃). ¹³C NMR (100 MHz, *d*₆-DMSO) δ 181.3, 166.0, 157.2, 152.6, 146.3, 138.6, 130.9, 129.4, 125.8, 110.6, 110.0, 109.2, 102.4, 34.6, 30.9. MS (ESI) m/z 295 (M+H)⁺, 317 (M+Na)⁺. Anal. Calcd for C₁₉H₁₈O₃: C, 77.53, H, 6.17. Found: C, 77.22, H, 6.24.



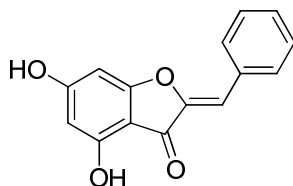
(Z)-2-(4-(4-methylpiperazin-1-yl)benzylidene)-4-hydroxybenzofuran-3(2H)-one (31).

The crude product was prepared according to general procedure A starting from 4-hydroxybenzofuran-3(2H)-one (**5**) and 4-(4-methylpiperazin-1-yl)benzaldehyde, and was washed three times with distilled water to yield an orange solid, which was the analytically pure hydrochloride salt, used without further purification (71%). m.p. > 260 °C (decomposition). ¹H NMR (400 MHz, *d*₆-DMSO) δ 11.14 (s, 1H, OH), 11.14 (br s, 1H, NH⁺) 7.85 (d, 2H, *J* = 8.4 Hz, H_{2',6'}), 7.51 (t, 1H, *J* = 8.1 Hz, H₆), 7.10 (d, 2H, *J* = 8.4 Hz, H_{3',5'}), 6.84 (d, 1H, *J* = 8.1 Hz, H₇), 6.72 (s, 1H, -CH=), 6.66 (d, 1H, *J* = 8.1 Hz, H₅), 4.02 (m, 2H, CH₂), 3.48 (m, 2H, CH₂), 3.24 (m, 2H, CH₂), 3.13 (m, 2H, CH₂), 2.80 (s, 3H, NMe). ¹³C NMR (100 MHz, *d*₆-DMSO) δ 180.8, 165.5, 156.9, 149.9, 145.0, 137.9, 132.4, 122.8, 115.1, 110.6, 110.3, 109.3, 102.2, 51.7, 44.2, 41.8. MS (ESI) *m/z* 337 (M+H)⁺. Anal. Calcd for C₁₅H₁₀O₄·HCl·1.75H₂O: C, 57.14, H, 5.83, N, 6.67. Found: C, 57.22, H, 5.95, N, 6.76.



(Z)-2-(2-fluorobenzylidene)-4-hydroxybenzofuran-3(2H)-one (32).

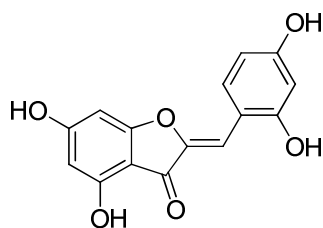
The crude product was prepared according to general procedure A starting from 4-hydroxybenzofuran-3(2H)-one (**5**) and 2-fluorobenzaldehyde, and was recrystallized from methanol to yield pure yellow crystals (30%). m.p. 162-163 °C. ¹H NMR (400 MHz, *d*₆-DMSO) δ 11.29 (s, 1H, OH), 8.21 (m, 1H, H_{6'}), 7.56 (t, 1H, *J* = 8.1 Hz, H₆), 7.50 (m, 1H, H_{3'}), 7.35 (m, 2H, H_{4',5'}), 6.87 (d, 1H, *J* = 8.1 Hz, H₇), 6.75 (s, 1H, -CH=), 6.66 (d, 1H, *J* = 8.1 Hz, H₅). ¹³C NMR (100 MHz, *d*₆-DMSO) δ 181.1, 166.1, 160.6 (d, *J* = 251.6 Hz), 157.4, 147.6, 139.1, 131.7 (d, *J* = 8.0 Hz), 131.1, 125.2, 119.9 (d, *J* = 11.5 Hz), 115.8 (d, *J* = 21.5 Hz), 111.0, 108.8, 102.5, 99.8 (d, *J* = 7.3 Hz). MS (ESI) *m/z* 257 (M+H)⁺, 279 (M+Na)⁺. Anal. Calcd for C₁₅H₉FO₃·²/₃H₂O: C, 67.16, H, 3.85. Found: C, 66.80, H, 3.58.



(Z)-2-benzylidene-4,6-dihydroxybenzofuran-3(2H)-one (33).

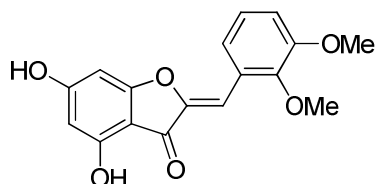
The crude product was prepared according to general procedure D starting from (Z)-2-benzylidene-4,6-dimethoxybenzofuran-3(2H)-one (**54**), and was purified by column chromatography on silica gel (eluent: toluene 9 / methanol 1) to yield a pure yellow solid (33%). m.p. > 225 °C (decomposition). ¹H NMR (400 MHz, *d*₆-DMSO) δ 10.99 (br s, 2H, OH), 7.89 (d, 2H, *J* = 7.4 Hz, H_{3',5'}), 7.47 (m, 2H, H_{2',6'}), 7.39 (m, 1H, H_{4'}), 6.61 (s, 1H, -

CH=), 6.23 (s, 1H, H₇), 6.08 (s, 1H, H₅). ¹³C NMR (100 MHz, *d*₆-DMSO) δ 180.0, 167.8, 158.4, 147.7, 132.3, 130.6, 129.1, 128.9, 108.0, 102.4, 97.7, 90.6. MS (ESI) *m/z* 255 (M+H)⁺, 277 (M+Na)⁺. Anal. Calcd for C₁₅H₁₀O₄·²/₃H₂O: C, 67.67, H, 4.26. Found: C, 67.67, H, 4.15.

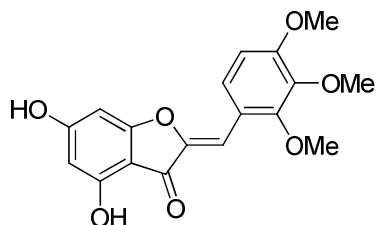


(Z)-2-(2,4-dihydroxybenzylidene)-4,6-dihydroxybenzofuran-3(2H)-one (34).

The crude product was prepared according to general procedure D starting from (Z)-2-(2,4-dimethoxybenzylidene)-4,6-dimethoxybenzofuran-3(2H)-one (**53**), and was washed three times with distilled water to yield an orange solid, which was analytically pure and used without further purification (58%). m.p. > 270 °C (decomposition). ¹H NMR (400 MHz, *d*₆-DMSO) δ 10.77 (s, 1H, OH), 10.74 (s, 1H, OH), 10.16 (s, 1H, OH), 9.90 (s, 1H, OH), 7.89 (d, 1H, *J* = 8.4 Hz, H₆'), 6.88 (s, 1H, -CH=), 6.37 (m, 2H, H₃', 5'), 6.18 (d, 1H, *J* = 1.6 Hz, H₇), 6.05 (d, 1H, *J* = 1.6 Hz, H₅). ¹³C NMR (100 MHz, *d*₆-DMSO) δ 179.1, 167.4, 166.7, 160.3, 158.6, 158.0, 145.4, 132.0, 110.8, 108.1, 103.6, 103.1, 102.3, 97.5, 90.4. MS (ESI) *m/z* 287 (M+H)⁺, 309 (M+Na)⁺. Anal. Calcd for C₁₅H₁₀O₆·1.1H₂O: C, 58.86, H, 3.99. Found: C, 58.78, H, 3.98.

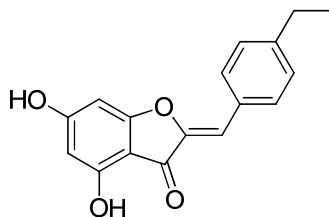


(Z)-2-(2,3-dimethoxybenzylidene)-4,6-dihydroxybenzofuran-3(2H)-one (35). The crude product was prepared according to general procedure B starting from 4,6-dihydroxybenzofuran-3(2H)-one (**3**) and 2,3-dimethoxybenzaldehyde, and was purified by column chromatography on silica gel (eluent: cyclohexane 2 / ethyl acetate 1 / acetic acid 0.005) to yield a pure yellow solid (72%). m.p. 272-273 °C. ¹H NMR (400 MHz, *d*₆-DMSO) δ 11.00 (s, 1H, OH), 10.94 (s, 1H, OH), 7.73 (dd, 1H, *J*₁ = 8.0 Hz, *J*₂ = 0.8 Hz, H₆'), 7.19 (t, 1H, *J* = 8.0 Hz, H₅'), 7.12 (dd, 1H, *J*₁ = 8.0 Hz, *J*₂ = 0.8 Hz, H₄'), 6.80 (s, 1H, -CH=), 6.21 (d, *J* = 1.6 Hz, 1H, H₇), 6.08 (d, *J* = 1.6 Hz, 1H, H₅), 3.84 (s, 3H, OMe), 3.80 (s, 3H, OMe). ¹³C NMR (100 MHz, *d*₆-DMSO) δ 178.9, 167.7, 167.4, 158.5, 152.5, 148.3, 147.8, 125.9, 124.4, 122.0, 114.0, 102.4, 101.4, 97.8, 90.6, 60.9, 55.8.

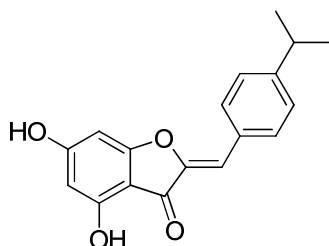


(Z)-2-(2,3,4-trimethoxybenzylidene)-4,6-dihydroxybenzofuran-3(2H)-one (36). The crude product was prepared according to general procedure B starting from 4,6-dihydroxybenzofuran-3(2H)-one (**3**) and 2,3,4-trimethoxybenzaldehyde, and was purified by column chromatography on silica gel (eluent: cyclohexane 2 / ethyl acetate 1 / acetic acid 0.005) to yield a pure yellow solid (80%). m.p. 245-246 °C. ¹H NMR (400 MHz, *d*₆-DMSO) δ

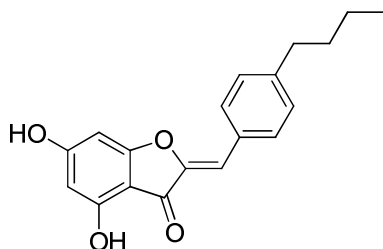
11.13 (s, 2H, OH), 7.87 (d, 1H, $J = 7.6$ Hz, $H_{6'}$), 6.97 (d, 1H, $J = 7.6$ Hz, $H_{5'}$), 6.72 (s, 1H, -CH=), 6.27 (s, 1H, H_7), 6.23 (s, 1H, H_5), 3.86 (s, 3H, OMe), 3.85 (s, 3H, OMe), 3.76 (s, 3H, OMe). ^{13}C NMR (100 MHz, d_6 -DMSO) δ 181.0, 169.5, 169.5, 160.4, 156.6, 154.6, 149.3, 143.7, 127.9, 120.6, 110.6, 104.5, 103.7, 99.9, 92.5, 63.6, 62.5, 58.0.



(Z)-2-(4-ethylbenzylidene)-4,6-dihydroxybenzofuran-3(2H)-one (37). The crude product was prepared according to general procedure B starting from 4,6-dihydroxybenzofuran-3(2H)-one (**3**) and 4-ethylbenzaldehyde, and was purified by column chromatography on silica gel (eluent: cyclohexane 2 / ethyl acetate 1 / acetic acid 0.005) to yield a pure yellow solid (83%). m.p. 237-238 °C. ^1H NMR (400 MHz, d_6 -DMSO) δ 10.94 (s, 2H, OH), 7.81 (d, 2H, $J = 8.0$ Hz, $H_{2',6'}$), 7.31 (d, 2H, $J = 8.0$ Hz, $H_{3',5'}$), 6.58 (s, 1H, -CH=), 6.22 (s, 1H, H_7), 6.08 (s, 1H, H_5), 2.64 (q, 2H, $J = 7.6$ Hz, CH_2CH_3), 1.18 (t, 3H, $J = 7.6$ Hz, CH_2CH_3). ^{13}C NMR (100 MHz, d_6 -DMSO) δ 181.1, 169.8, 169.4, 160.4, 149.3, 147.3, 132.8, 131.8, 130.4, 110.3, 104.6, 99.7, 92.6, 30.1, 17.4. Anal. Calcd for $\text{C}_{17}\text{H}_{14}\text{O}_4 \cdot \frac{1}{4}\text{H}_2\text{O}$: C, 71.20, H, 5.06. Found: C, 71.47, H, 5.19.



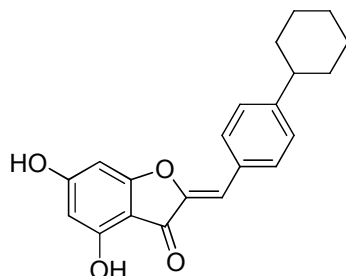
(Z)-2-(4-isopropylbenzylidene)-4,6-dihydroxybenzofuran-3(2H)-one (38). The crude product was prepared according to general procedure B starting from 4,6-dihydroxybenzofuran-3(2H)-one (**3**) and 4-isopropylbenzaldehyde, and was purified by column chromatography on silica gel (eluent: cyclohexane 2 / ethyl acetate 1 / acetic acid 0.005) to yield a pure yellow solid (88%). m.p. 229-230 °C. ^1H NMR (400 MHz, d_6 -DMSO) δ 10.94 (s, 2H, OH), 7.80 (d, 2H, $J = 8.0$ Hz, $H_{2',6'}$), 7.32 (d, 2H, $J = 8.0$ Hz, $H_{3',5'}$), 6.58 (s, 1H, -CH=), 6.23 (d, 1H, $J = 2.0$ Hz, H_7), 6.09 (d, 1H, $J = 2.0$ Hz, H_5), 2.89 (sept, 1H, $J = 6.8$ Hz, $\text{CH}(\text{CH}_3)_2$), 1.19 (d, 6H, $J = 6.8$ Hz, $\text{CH}(\text{CH}_3)_2$). ^{13}C NMR (100 MHz, d_6 -DMSO) δ 181.1, 169.8, 169.4, 160.4, 151.8, 149.4, 132.8, 132.0, 128.9, 110.3, 104.6, 99.7, 92.6, 35.4, 25.6. Anal. Calcd for $\text{C}_{18}\text{H}_{16}\text{O}_4 \cdot \frac{1}{4}\text{H}_2\text{O}$: C, 71.88, H, 5.49. Found: C, 71.99, H, 5.52.



(Z)-2-(4-butylbenzylidene)-4,6-dihydroxybenzofuran-3(2H)-one (39).

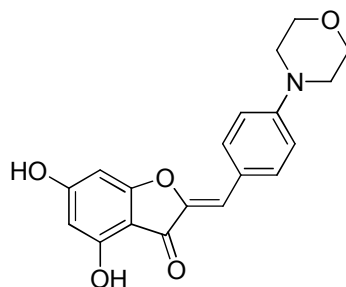
The crude product was prepared according general procedure D starting from (Z)-2-(4-butylbenzylidene)-4,6-dimethoxybenzofuran-3(2H)-one (**44**), and was purified by column

chromatography on silica gel (eluent: ethyl acetate 1 / cyclohexane 1) to yield a pure yellow solid (52%). m.p. 221-222 °C. ¹H NMR (400 MHz, *d*₆-DMSO) δ 10.95 (br s, 2H, OH), 7.79 (d, 2H, *J* = 8.1 Hz, H_{2',6'}), 7.29 (d, 2H, *J* = 8.1 Hz, H_{3',5'}), 6.57 (s, 1H, -CH=), 6.21 (s, 1H, H₇), 6.07 (s, 1H, H₅), 2.61 (t, 2H, *J* = 7.5 Hz, PhCH₂CH₂CH₂CH₃), 1.56 (quint., 2H, *J* = 7.5 Hz, PhCH₂CH₂CH₂CH₃), 1.31 (sext., 2H, *J* = 7.5 Hz, PhCH₂CH₂CH₂CH₃), 0.89 (t, 3H, *J* = 7.5 Hz, PhCH₂CH₂CH₂CH₃). ¹³C NMR (100 MHz, *d*₆-DMSO) δ 179.0, 167.8, 167.6, 158.5, 147.4, 143.9, 130.7, 129.9, 128.9, 108.3, 102.6, 97.8, 90.5, 34.8, 32.9, 21.8, 13.8. MS (ESI) *m/z* 311 (M+H)⁺, 333 (M+Na)⁺, 643 (2M+Na)⁺. Anal. Calcd for C₁₉H₁₈O₄· $\frac{1}{3}$ H₂O: C, 72.15, H, 5.91. Found: C, 72.00, H, 5.83.

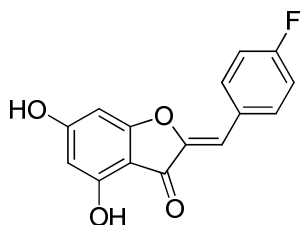


(Z)-2-(4-cyclohexylbenzylidene)-4,6-dihydroxybenzofuran-3(2H)-one (40).

The crude product was prepared according to general procedure D starting from (Z)-2-(4-cyclohexylbenzylidene)-4,6-dimethoxybenzofuran-3(2H)-one (**45**), and was purified by column chromatography on silica gel (eluent: ethyl acetate 1 / cyclohexane 1) to yield a pure yellow solid (64%). m.p. > 215 °C (decomposition). ¹H NMR (400 MHz, *d*₆-DMSO) δ 10.98 (br s, 2H, OH), 7.79 (d, 2H, *J* = 8.3 Hz, H_{2',6'}), 7.31 (d, 2H, *J* = 8.3 Hz, H_{3',5'}), 6.56 (s, 1H, -CH=), 6.20 (d, 1H, *J* = 1.5 Hz, H₇), 6.07 (d, 1H, *J* = 1.5 Hz, H₅), 2.54 (m, 1H, *c*-Hex), 1.79 (m, 4H, *c*-Hex), 1.70 (m, 1H, *c*-Hex), 1.39 (m, 4H, *c*-Hex), 1.31 (m, 1H, *c*-Hex). ¹³C NMR (100 MHz, *d*₆-DMSO) δ 179.0, 167.8, 167.5, 158.5, 149.0, 147.4, 130.7, 130.0, 127.3, 108.2, 102.5, 97.7, 90.5, 43.7, 33.7, 26.3, 25.5. MS (ESI) *m/z* 337 (M+H)⁺, 359 (M+Na)⁺, 695 (2M+Na)⁺. Anal. Calcd for C₂₁H₂₀O₄· $\frac{1}{2}$ H₂O: C, 73.03, H, 6.13. Found: C, 72.95, H, 6.01.

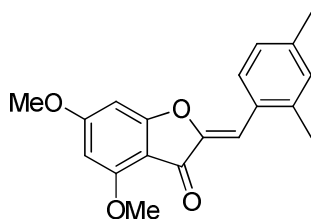


(Z)-2-(4-morpholinobenzylidene)-4,6-dihydroxybenzofuran-3(2H)-one (41). The crude product was prepared according to general procedure B starting from 4,6-dihydroxybenzofuran-3(2H)-one (**3**) and 4-morpholinobenzaldehyde, and was purified by column chromatography on silica gel (eluent: cyclohexane 2 / ethyl acetate 1 / acetic acid 0.005) to yield a pure red solid (32%). m.p. 273-273 °C. ¹H NMR (400 MHz, *d*₆-DMSO) δ 10.83 (s, 1H, OH), 10.79 (s, 1H, OH), 7.77 (d, 2H, *J* = 8.6 Hz, H_{2',6'}), 7.02 (d, 2H, *J* = 8.6 Hz, H_{3',5'}), 6.55 (s, 1H, -CH=), 6.20 (d, 1H, *J* = 0.8 Hz, H₇), 6.06 (d, 1H, *J* = 0.8 Hz, H₅), 3.74 (t, 4H, *J* = 4.8 Hz, CH₂O), 3.23 (t, 4H, *J* = 4.8 Hz, CH₂N). ¹³C NMR (100 MHz, *d*₆-DMSO) δ 180.9, 169.4, 168.9, 160.1, 153.3, 147.9, 134.2, 124.4, 116.4, 111.3, 104.9, 99.6, 92.4, 67.9, 49.2. Anal. Calcd for C₁₉H₁₇NO₅· $\frac{1}{3}$ H₂O: C, 66.08, H, 5.12, N, 4.05. Found: C, 66.44, H, 5.54, N, 3.37.



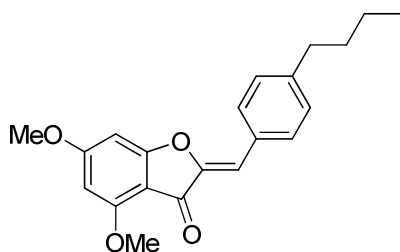
(Z)-2-(4-fluorobenzylidene)-4,6-dihydroxybenzofuran-3(2H)-one (42).

The crude product was prepared according to general procedure D starting from (Z)-2-(4-fluorobenzylidene)-4,6-dimethoxybenzofuran-3(2H)-one (**55**), and was purified by column chromatography on silica gel (eluent: dichloromethane 9 / methanol 1) to yield a pure yellow solid (50%). m.p. > 270 °C (decomposition). ¹H NMR (400 MHz, *d*₆-DMSO) δ 11.00 (br s, 1H, OH), 10.97 (br s, 1H, OH), 7.96 (m, 2H, H_{2',6'}), 7.31 (m, 2H, H_{3',5'}), 6.64 (s, 1H, -CH=), 6.22 (d, 1H, *J* = 1.6 Hz, H₇), 6.08 (d, 1H, *J* = 1.6 Hz, H₅). ¹³C NMR (100 MHz, *d*₆-DMSO) δ 179.0, 167.9, 167.5, 162.3 (d, *J* = 248.4 Hz), 158.5, 147.5, 132.9 (d, *J* = 8.2 Hz), 129.1, 116.0 (d, *J* = 21.7 Hz), 107.1, 102.5, 97.8, 90.7. MS (ESI) *m/z* 273 (M+H)⁺, 295 (M+Na)⁺. Anal. Calcd for C₁₅H₉FO₄·½H₂O: C, 64.74, H, 3.48. Found: C, 64.58, H, 3.67.



(Z)-2-(2,4-dimethylbenzylidene)-4,6-dimethoxybenzofuran-3(2H)-one (43).

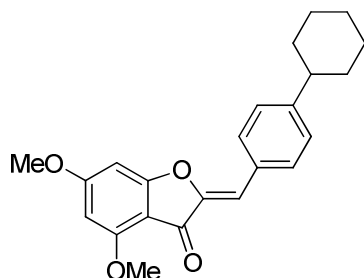
The crude product was prepared according to general procedure A starting from 4,6-dimethoxybenzofuran-3(2H)-one (**6**) and 2,4-dimethoxybenzaldehyde, and was recrystallized from methanol to yield pure pale yellow crystals (86%). m.p. 216 °C. ¹H NMR (400 MHz, CDCl₃) δ 8.07 (d, 1H, *J* = 8.0 Hz, H_{6'}), 7.10 (d, 1H, *J* = 8.0 Hz, H_{5'}), 7.06 (s, 1H, H_{3'}), 6.97 (s, 1H, -CH=), 6.37 (d, 1H, *J* = 1.7 Hz, H₇), 6.12 (d, 1H, *J* = 1.7 Hz, H₅), 3.95 (s, 3H, OMe), 3.90 (s, 3H, OMe), 2.46 (s, 3H, Me), 2.35 (s, 3H, Me). ¹³C NMR (100 MHz, CDCl₃) δ 180.9, 169.2, 169.0, 159.6, 147.8, 139.8, 139.0, 131.6, 131.0, 128.4, 127.2, 108.1, 105.6, 94.2, 89.4, 56.4, 56.3, 21.6, 20.4. MS (ESI) *m/z* 311 (M+H)⁺, 333 (M+Na)⁺, 643 (2M+Na)⁺. Anal. Calcd for C₁₉H₁₈O₄: C, 73.54, H, 5.85. Found: C, 73.04, H, 5.92.



(Z)-2-(4-butylbenzylidene)-4,6-dimethoxybenzofuran-3(2H)-one (44).

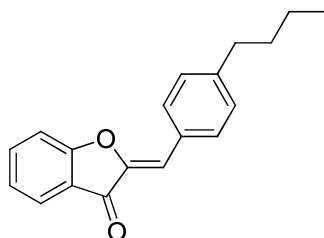
The crude product was prepared according to general procedure A starting from 4,6-dimethoxybenzofuran-3(2H)-one (**6**) and 4-butylbenzaldehyde, and was recrystallized from methanol to yield pure white crystals (75%). m.p. 153 °C. ¹H NMR (400 MHz, CDCl₃) δ 7.78 (d, 2H, *J* = 8.1 Hz, H_{2',6'}), 7.24 (d, 2H, *J* = 8.1 Hz, H_{3',5'}), 6.77 (s, 1H, -CH=), 6.38 (d, 1H, *J* = 1.7 Hz, H₇), 6.12 (d, 1H, *J* = 1.7 Hz, H₅), 3.95 (s, 3H, OMe), 3.91 (s, 3H, OMe), 2.65 (t, 2H, *J* = 7.6 Hz, PhCH₂CH₂CH₂CH₃), 1.61 (quint., 2H, *J* = 7.6 Hz, PhCH₂CH₂CH₂CH₃), 1.37 (sext., 2H, *J* = 7.6 Hz, PhCH₂CH₂CH₂CH₃), 0.96 (t, 3H, *J* = 7.6 Hz, PhCH₂CH₂CH₂CH₃). ¹³C NMR

(100 MHz, CDCl₃) δ 181.0, 169.2, 169.1, 159.6, 147.7, 145.0, 131.3, 130.2, 129.1, 111.3, 105.5, 94.2, 89.4, 56.4, 56.3, 35.8, 33.6, 22.5, 14.1. MS (ESI) m/z 339 (M+H)⁺, 361 (M+Na)⁺, 699 (2M+Na)⁺. Anal. Calcd for C₂₁H₂₂O₄: C, 74.54, H, 6.56. Found: C, 74.46, H, 6.33.



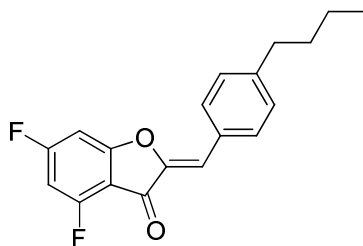
(Z)-2-(4-cyclohexylbenzylidene)-4,6-dimethoxybenzofuran-3(2H)-one (45).

The crude product was prepared according to general procedure A starting from 4,6-dimethoxybenzofuran-3(2H)-one (**6**) and 4-cyclohexylbenzaldehyde, and was recrystallized from methanol to yield pure white crystals (78%). m.p. 174 °C. ¹H NMR (400 MHz, CDCl₃) δ 7.78 (d, 2H, J = 8.2 Hz, H_{2',6'}), 7.27 (d, 2H, J = 8.2 Hz, H_{3',5'}), 6.76 (s, 1H, -CH=), 6.37 (d, 1H, J = 1.6 Hz, H₇), 6.11 (d, 1H, J = 1.6 Hz, H₅), 3.94 (s, 3H, OMe), 3.90 (s, 3H, OMe), 2.53 (m, 1H, *c*-Hex), 1.86 (m, 4H, *c*-Hex), 1.76 (m, 1H, *c*-Hex), 1.42 (m, 4H, *c*-Hex), 1.35 (m, 1H, *c*-Hex). ¹³C NMR (100 MHz, CDCl₃) δ 180.9, 169.1, 169.0, 159.5, 150.0, 147.7, 131.4, 130.3, 127.5, 111.2, 105.5, 94.1, 89.4, 56.4, 56.3, 44.7, 34.4, 27.0, 26.2. MS (ESI) m/z 365 (M+H)⁺, 751 (2M+Na)⁺. Anal. Calcd for C₂₃H₂₄O₄: C, 75.81, H, 6.64. Found: C, 75.40, H, 6.78.



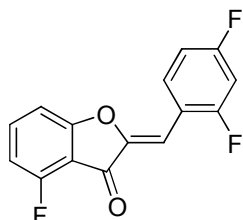
(Z)-2-(4-butylbenzylidene)-benzofuran-3(2H)-one (46).

The crude product was prepared according to general procedure C starting from benzofuran-3(2H)-one and 4-butylbenzaldehyde, and was purified by column chromatography on silica gel (eluent: dichloromethane 1 / cyclohexane 1) to yield a pure pale yellow solid (44%). m.p. 77-78 °C. ¹H NMR (400 MHz, CDCl₃) δ 7.87 (d, 2H, J = 8.3 Hz, H_{2',6'}), 7.83 (d, 1H, J = 8.3 Hz, H₄), 7.67 (t, 1H, J = 8.3 Hz, H₆), 7.35 (d, 1H, J = 8.3 Hz, H₇), 7.30 (d, 2H, J = 8.3 Hz, H_{3',5'}), 7.24 (t, 1H, J = 8.3 Hz, H₅), 6.92 (s, 1H, -CH=), 2.68 (t, 2H, J = 7.5 Hz, PhCH₂CH₂CH₂CH₃), 1.65 (quint., 2H, J = 7.5 Hz, PhCH₂CH₂CH₂CH₃), 1.40 (sext., 2H, J = 7.5 Hz, PhCH₂CH₂CH₂CH₃), 0.96 (t, 3H, J = 7.5 Hz, PhCH₂CH₂CH₂CH₃). ¹³C NMR (100 MHz, CDCl₃) δ 185.0, 166.2, 146.7, 145.7, 136.9, 131.8, 129.9, 129.3, 124.8, 123.6, 122.0, 113.7, 113.1, 35.9, 33.6, 22.6, 14.2. MS (ESI) m/z 279 (M+H)⁺. Anal. Calcd for C₁₅H₁₀O₄·1/4H₂O: C, 80.71, H, 6.55. Found: C, 80.96, H, 6.77.



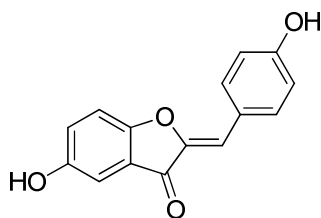
(Z)-2-(4-butylbenzylidene)-4,6-difluorobenzofuran-3(2H)-one (47).

The crude product was prepared according to general procedure C starting from 4,6-difluorobenzofuran-3(2H)-one (**8**) and 4-butylbenzaldehyde, and was purified by column chromatography on silica gel (eluent: dichloromethane 1 / cyclohexane 1) to yield a pure white solid (56%). m.p. 93-94 °C. ¹H NMR (400 MHz, CDCl₃) δ 7.80 (d, 2H, *J* = 8.1 Hz, H_{2',6'}), 7.29 (d, 2H, *J* = 8.1 Hz, H_{3',5'}), 6.91 (s, 1H, -CH=), 6.88 (m, 1H, H₇), 6.63 (m, 1H, H₅), 2.68 (t, 2H, *J* = 7.5 Hz, PhCH₂CH₂CH₂CH₃), 1.65 (quint., 2H, *J* = 7.5 Hz, PhCH₂CH₂CH₂CH₃), 1.39 (sext., 2H, *J* = 7.5 Hz, PhCH₂CH₂CH₂CH₃), 0.96 (t, 3H, *J* = 7.5 Hz, PhCH₂CH₂CH₂CH₃). ¹³C NMR (100 MHz, CDCl₃) δ 179.5, 170.1 (*J* = 13.0 Hz), 167.5 (*J* = 13.0 Hz), 160.8 (*J* = 16.2 Hz), 158.2 (*J* = 16.2 Hz), 146.4, 146.3, 131.9, 129.4, 129.2, 114.5, 100.0 (*J*₁ = 27.0 Hz, *J*₂ = 23.4 Hz), 97.5 (*J*₁ = 27.0 Hz, *J*₂ = 4.5 Hz). MS (ESI) *m/z* 315 (M+H)⁺. Anal. Calcd for C₁₉H₁₆F₂O₂: C, 72.61, H, 5.14. Found: C, 72.86, H, 5.47.



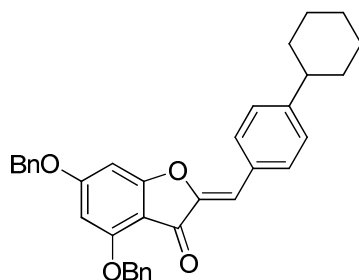
(Z)-2-(2,4-difluorobenzylidene)-4-fluorobenzofuran-3(2H)-one (48).

The crude product was prepared according to general procedure C starting from 4-fluorobenzofuran-3(2H)-one (**9**) and 2,4-difluorobenzaldehyde, and was purified by column chromatography on silica gel (eluent: dichloromethane 1 / cyclohexane 1) to yield a pure white solid (83%). m.p. 164-165 °C. ¹H NMR (400 MHz, CDCl₃) δ 8.29 (dt, 1H, *J*₁ = 8.6 Hz, *J*₂ = 6.5 Hz, H_{6'}), 7.65 (dt, 1H, *J*₁ = 8.3 Hz, *J*₂ = 5.5 Hz, H₆), 7.13 (d, 1H, *J* = 8.3 Hz, H₇), 7.11 (s, 1H, -CH=), 7.01 (m, 1H, H_{5'}), 6.90 (dt, 1H, *J*₁ = 8.7 Hz, *J*₂ = 2.6 Hz, H_{3'}), 6.88 (t, 1H, *J* = 8.3 Hz, H₅). ¹³C NMR (100 MHz, CDCl₃) δ 180.6, 166.3 (*J* = 6.0 Hz), 164.4 (*J*₁ = 171.8 Hz, *J*₂ = 12.3 Hz), 161.9 (*J*₁ = 174.6 Hz, *J*₂ = 12.2 Hz), 160.1, 157.5, 146.9, 138.7 (*J* = 9.4 Hz), 133.2 (*J* = 9.5 Hz), 117.0 (*J*₁ = 12.0 Hz, *J*₂ = 4.1 Hz), 112.4 (*J*₁ = 21.2 Hz, *J*₂ = 2.9 Hz), 110.7 (*J* = 19.0 Hz), 109.0 (*J* = 4.1 Hz), 104.5 (*J* = 25.6 Hz), 103.9 (*J* = 5.7 Hz). MS (ESI) *m/z* 277 (M+H)⁺. Anal. Calcd for C₁₅H₇F₃O₂: C, 65.23, H, 2.56. Found: C, 65.36, H, 2.57.



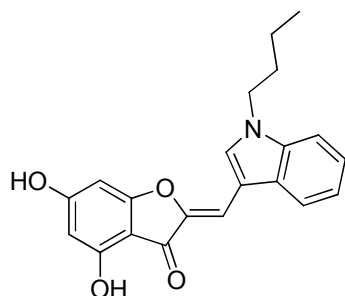
(Z)-2-(4-hydroxybenzylidene)-5-hydroxybenzofuran-3(2H)-one (49).

The crude product was prepared according to general procedure A starting from 5-hydroxybenzofuran-3(2H)-one (**4**) and 4-hydroxybenzaldehyde, and was recrystallized from acetonitrile to yield pure yellow crystals (17%). m.p. > 300 °C (decomposition). ¹H NMR (400 MHz, *d*₆-DMSO) δ 10.21 (br s, 1H, OH), 9.76 (br s, 1H, OH), 7.85 (d, 2H, *J* = 7.8 Hz, H_{2',6'}), 7.38 (d, 1H, *J* = 8.5 Hz, H₆), 7.20 (d, 1H, *J* = 8.5 Hz, H₇), 7.01 (s, 1H, H₄), 6.89 (d, 2H, *J* = 7.8 Hz, H_{3',5'}), 6.83 (s, 1H, -CH=). ¹³C NMR (100 MHz, *d*₆-DMSO) δ 183.4, 159.5, 158.8, 153.6, 145.5, 133.5, 125.2, 122.9, 121.5, 116.0, 113.7, 112.8, 107.4. MS (ESI) *m/z* 255 (M+H)⁺, 277 (M+Na)⁺. Anal. Calcd for C₁₅H₁₀O₄·²/₃H₂O: C, 67.67, H, 4.29. Found: C, 67.56, H, 4.10.

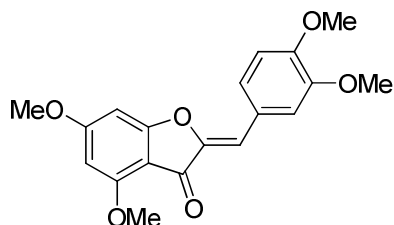


(Z)-2-(4-cyclohexylbenzylidene)-4,6-dibenzoyloxybenzofuran-3(2H)-one (50).

The crude product was prepared according to general procedure C starting from 4,6-dibenzoyloxybenzofuran-3(2H)-one (**7**) and 4-cyclohexylbenzaldehyde, and was purified by column chromatography on silica gel (eluent: dichloromethane 2 / cyclohexane 1) to yield a pure pale yellow solid (43%). m.p. 155-157 °C. ¹H NMR (400 MHz, CDCl₃) δ 7.81 (d, 2H, *J* = 8.2 Hz, H_{2',6'}), 7.32-7.50 (m, 10H, OCH₂Ph), 7.29 (d, 2H, *J* = 8.2 Hz, H_{3',5'}), 6.78 (s, 1H, -CH=), 6.46 (d, 1H, *J* = 1.6 Hz, H₇), 6.24 (d, *J* = 1.6 Hz, H₅), 5.28 (s, 2H, OCH₂Ph), 5.11 (s, 2H, OCH₂Ph), 2.53 (m, 1H, *c*-Hex), 1.89 (m, 4H, *c*-Hex), 1.78 (m, 1H, *c*-Hex), 1.43 (m, 4H, *c*-Hex), 1.30 (m, 1H, *c*-Hex). ¹³C NMR (100 MHz, CDCl₃) δ 180.8, 169.0, 167.8, 158.5, 150.0, 147.7, 136.2, 135.7, 131.4, 130.3, 129.0, 128.9, 128.7, 128.1, 127.8, 127.5, 127.0, 111.2, 106.1, 96.6, 90.7, 71.0, 70.9, 44.8, 34.4, 27.1, 26.3. MS (ESI) *m/z* 517 (M+H)⁺. Anal. Calcd for C₃₅H₃₂O₄·¹/₃H₂O: C, 80.46, H, 6.26. Found: C, 80.30, H, 6.67.

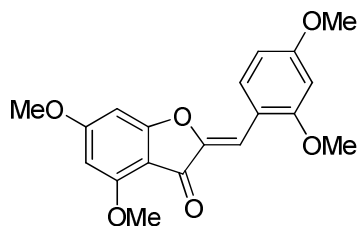


(Z)-2-((1-butyl-1H-indol-3-yl)methylene)-4,6-dihydroxybenzofuran-3(2H)-one (51). The crude product was prepared according to general procedure B starting from 4,6-dihydroxybenzofuran-3(2H)-one (**3**) and 1-butyl-1H-indole-3-carbaldehyde, and was purified by column chromatography on silica gel (eluent: cyclohexane 2 / ethyl acetate 1 / acetic acid 0.005) to yield a pure red solid (65%). m.p. 248-249 °C. ¹H NMR (400 MHz, *d*₆-DMSO) δ 10.75 (s, 2H, OH), 8.13 (s, 1H, H₂), 7.97 (d, 1H, *J* = 7.7 Hz, H₄), 7.56 (d, 1H, *J* = 7.7 Hz, H₇), 7.25 (t, 1H, *J* = 7.7 Hz, H₆), 7.18 (t, 1H, *J* = 7.7 Hz, H₅), 6.97 (s, 1H, -CH=), 6.27 (d, 1H, *J* = 1.2 Hz, H₇), 6.08 (d, 1H, *J* = 1.2 Hz, H₅), 4.28 (t, 2H, *J* = 7.2 Hz, CH₂CH₂CH₂CH₃), 1.76 (quint., 2H, *J* = 7.2 Hz, CH₂CH₂CH₂CH₃), 1.27 (sext., 2H, *J* = 7.2 Hz, CH₂CH₂CH₂CH₃), 0.88 (t, 3H, *J* = 7.2 Hz, CH₂CH₂CH₂CH₃). ¹³C NMR (100 MHz, *d*₆-DMSO) δ 180.3, 168.9, 168.5, 159.9, 147.3, 138.0, 134.9, 129.2, 124.5, 122.7, 121.1, 112.6, 109.4, 105.7, 104.2, 99.5, 92.5, 47.9, 33.9, 21.5, 15.6. Anal. Calcd for C₂₁H₁₉NO₄: C, 72.19, H, 5.48, N, 4.01. Found: C, 71.81, H, 5.79, N, 3.79.



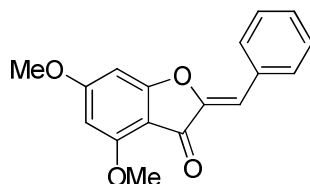
(Z)-2-(3,4-dimethoxybenzylidene)-4,6-dimethoxybenzofuran-3(2H)-one (52).

The crude product was prepared according to general procedure A starting from 4,6-dimethoxybenzofuran-3(2H)-one (**6**) and 3,4-dimethoxybenzaldehyde, and was recrystallized from methanol to yield pure pale yellow crystals (83%). m.p. 173-174 °C. ¹H NMR (400 MHz, CDCl₃) δ 7.44 (m, 2H, H_{2',6'}), 6.91 (d, 1H, *J* = 8.1 Hz, H_{5'}), 6.73 (s, 1H, -CH=), 6.34 (s, 1H, H₇), 6.12 (s, 1H, H₅), 3.96 (s, 3H, OMe), 3.95 (s, 3H, OMe), 3.93 (s, 3H, OMe), 3.91 (s, 3H, OMe). ¹³C NMR (100 MHz, CDCl₃) δ 180.5, 168.7, 159.3, 150.3, 148.9, 146.8, 125.5, 125.3, 113.5, 111.3, 111.1, 105.4, 93.9, 89.1, 56.2, 56.1, 55.9, 56.0. MS (ESI) *m/z* 343 (M+H)⁺, 707 (2M+Na)⁺.



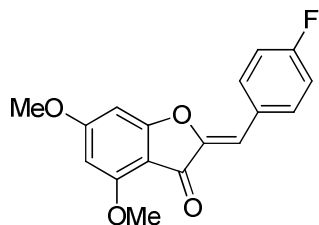
(Z)-2-(2,4-dimethoxybenzylidene)-4,6-dimethoxybenzofuran-3(2H)-one (53).

The crude product was prepared according to general procedure A starting from 4,6-dimethoxybenzofuran-3(2H)-one (**6**) and 2,4-dimethoxybenzaldehyde, and was recrystallized from methanol to yield pure pale yellow crystals (91%). m.p. 213-214 °C. ¹H NMR (400 MHz, CDCl₃) δ 8.19 (d, 1H, *J* = 8.7 Hz, H_{6'}), 7.27 (s, 1H, -CH=), 6.57 (dd, 1H, *J* = 8.7 Hz, *J* = 2.3 Hz, H_{5'}), 6.45 (d, 1H, *J* = 2.3 Hz, H_{3'}), 6.36 (d, 1H, *J* = 1.7 Hz, H₇), 6.11 (d, 1H, *J* = 1.7 Hz, H₅), 3.94 (s, 3H, OMe), 3.90 (s, 3H, OMe), 3.87 (s, 3H, OMe), 3.86 (s, 3H, OMe). ¹³C NMR (100 MHz, CDCl₃) δ 180.6, 168.5, 168.4, 162.2, 160.1, 159.2, 146.8, 132.8, 114.6, 105.6, 105.5, 105.3, 97.9, 93.7, 89.0, 56.1, 56.0, 55.5, 55.4. MS (ESI) *m/z* 343 (M+H)⁺, 707 (2M+Na)⁺.



(Z)-2-benzylidene-4,6-dimethoxybenzofuran-3(2H)-one (54).

The crude product was prepared according to general procedure A starting from 4,6-dimethoxybenzofuran-3(2H)-one (**6**) and benzaldehyde, and was recrystallized from methanol to yield pure pale yellow crystals (61%). m.p. 156-157 °C. ¹H NMR (400 MHz, CDCl₃) δ 7.91 (d, 1H, *J* = 7.3 Hz, H_{2',6'}), 7.39-7.48 (m, 3H, H_{3',4',5'}), 6.68 (s, 1H, -CH=), 6.66 (d, 1H, *J* = 1.5 Hz, H₇), 6.31 (d, 1H, *J* = 1.5 Hz, H₅), 3.91 (s, 3H, OMe), 3.89 (s, 3H, OMe). ¹³C NMR (100 MHz, CDCl₃) δ 179.0, 168.9, 168.3, 158.9, 147.3, 132.1, 130.8, 129.3, 128.8, 109.3, 104.0, 94.3, 89.8, 56.4, 56.1. MS (ESI) *m/z* 283 (M+H)⁺, 587 (2M+H)⁺.



(Z)-2-(4-fluorobenzylidene)-4,6-dimethoxybenzofuran-3(2H)-one (55).

The crude product was prepared according to general procedure A starting from 4,6-dimethoxybenzofuran-3(2*H*)-one (**6**) and 4-fluorobenzaldehyde, and was recrystallized from methanol to yield pure pale yellow crystals (64%). m.p. 186-187 °C. ¹H NMR (400 MHz, CDCl₃) δ 7.87 (m, 2H, H_{2',6'}), 7.12 (m, 2H, H_{3',5'}), 6.74 (s, 1H, -CH=), 6.40 (d, 1H, *J* = 1.8 Hz, H₇), 6.15 (d, 1H, *J* = 1.8 Hz, H₅), 3.97 (s, 3H, OMe), 3.93 (s, 3H, OMe). ¹³C NMR (100 MHz, CDCl₃) δ 180.8, 168.2, 163.2 (d, *J* = 251.4 Hz), 159.6, 147.7, 133.2 (d, *J* = 8.2 Hz), 129.1, 116.2 (d, *J* = 21.7 Hz), 109.8, 105.4, 94.3, 89.4, 56.4, 56.4. MS (ESI) *m/z* 301 (M+H)⁺, 623 (2M+Na)⁺.