

Synthesis and Structure-Activity Relationship of Griseofulvin Analogues as Inhibitors of Centrosomal Clustering in Cancer Cells

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Table S1. Combustion analysis.

Compound	Formula	Anal. calc'd	Anal. found
2	C ₁₆ H ₁₅ ClO ₆	C 56.73, H 4.46	56.75, 4.49
7	C ₁₇ H ₁₆ ClNO ₈	C 51.33, H 4.05	51.20, 3.98
10	C ₁₈ H ₁₉ ClO ₆	C 58.94, H 5.22	58.78, 5.20
11	C ₁₉ H ₂₁ ClO ₆	C 59.92, H 5.56	59.86, 5.47
12	C ₁₉ H ₂₁ ClO ₆	C 59.92, H 5.56	59.75, 5.60
13	C ₂₀ H ₂₃ ClO ₆	C 60.84, H 5.87	60.71, 5.83
14	C ₂₁ H ₂₅ ClO ₆	C 61.69, H 6.16	61.73, 5.99
15	C ₂₂ H ₂₇ ClO ₆	C 62.48, H 6.44	62.39, 6.37
16	C ₂₀ H ₂₁ ClO ₆	C 61.15, H 5.39	60.95, 5.45
18	C ₁₆ H ₁₄ Cl ₂ O ₅	C 53.80, H 3.95	53.69, 3.88
21	C ₂₃ H ₂₁ ClO ₅ S	C 62.09, H 4.76	62.15, 4.78
27	C ₁₉ H ₂₁ ClO ₆	C 57.23, H 5.93	57.27, 5.90
28	C ₁₇ H ₁₈ ClNO ₆	C 55.52, H 4.93	55.60, 4.96
35	C ₂₃ H ₂₀ ClIO ₆	C 49.80, H 3.63	49.73, 3.67

(2*S*,6'*R*)-(7-Chloro-4,6-dimethoxy-benzofuran-3-on)-2-spiro-1'-(6'-methyl-cyclohex-2',4'-dione) **2**.

To a solution of griseofulvin (7.0 g, 19.8 mmol) in HOAc (50 mL) was added 2 M H₂SO₄ (13 mL). The mixture was stirred at 80 °C for 45 min. where crystals of the product started to separate. The mixture was cooled to 20 °C, the product collected and then washed successively with cold EtOAc. The crystals were dried to afford griseofulvic acid **2**. Yield: 6.2 g (93%) (white crystals); R_f (MeOH:DCM 1:9): 0.31; m.p.: 262-263 °C (Litt.¹); IR(KBr, cm⁻¹): 3244, 1657, 1606 (Litt.²); ¹H NMR(500 MHz, DMSO-*d*₆): δ 11.90 (1H, s), 6.46 (1H, s), 5.31 (1H, s), 4.03 (3H, s), 3.91 (3H, s), 2.89-2.70 (2H, m), 2.52-2.43 (1H, m), 0.85 (3H, d, *J* = 6.2 Hz) (Litt.³); ¹³C NMR(50 MHz, DMSO-*d*₆): δ 191.1, 187.7, 179.3, 170.0, 164.1, 157.4, 104.3, 101.4, 95.2, 94.3, 90.9, 57.5, 56.5, 34.4, 33.0, 14.2; Anal. [C₁₆H₁₅ClO₆]: C, H.

(2*S*,6'*R*)-(7-Chloro-6-methoxy-4-hydroxy-benzofuran-3-on)-2-spiro-1'-(2'-methoxy-6'-methyl-cyclohex-2'-en-4'-one) **4**.

A solution of 2 M MgI₂ was prepared by adding magnesium turnings (0.88 g, 36.0 mmol) and iodine (4.49 g, 17.7 mmol) to anhydrous Et₂O (6 mL) and toluene (12 mL). This solution was refluxed at 80 °C for 2 h, filtered and added to a solution of griseofulvin (3.03 g, 8.5 mmol) in anhydrous toluene (20 mL) at 80 °C. The solution was cooled to 20 °C after 3 h. The mixture was diluted with EtOAc (50 mL) and washed with sat. aq. NH₄Cl (40 mL) and then 10% aq. Na₂S₂O₃ (40 mL). The combined aqueous phases were extracted with EtOAc (3×60 mL) and the organic layer was dried (MgSO₄) and concentrated. The crude mixture was purified by reverse phase chromatography (C-18, MeOH and water gradient) yielding **4**. Yield: 521 mg (18%) (yellow crystals); R_f (MeOH:CH₂Cl₂ 1:9, 1% HOAc): 0.45; IR(KBr, cm): 1627, 1559; ¹H NMR(500 MHz, DMSO-*d*₆): δ 7.68 (1H, s), 6.49 (1H, s), 5.58 (1H, s), 3.89 (3H, s), 3.62 (3H, s), 2.77 (1H, ddq, *J* = 12.6, 6.5, 4.8 Hz), 2.67 (1H, dd, *J* = 16.3, 13.4 Hz), 2.33 (1H, dd,

$J = 16.3, 4.5$ Hz), 0.80 (3H, d, $J = 6.5$ Hz) ^{13}C NMR(50 MHz, DMSO- d_6): δ 195.9, 193.8, 171.1, 170.9, 166.5, 165.8, 106.6, 104.5, 97.3, 89.8 (2C), 56.9, 56.5, 39.4, 35.9, 13.8; HRMS (ESI+) calcd for $[\text{C}_{16}\text{H}_{16}\text{ClO}_6]^+$ 339.0635, found 339.0633.

General procedure for the synthesis of ring A ethers **5** and **6**.

To a solution of **4** (0.7 mmol, 1 equiv.) in DMF (3 mL, 0.2 M) was added NaH (0.7 mmol, 1 equiv.) and tetrabutylammonium iodide (0.1 mmol, 0.1 equiv.). The mixture was stirred at 100 °C and after 20 min. The alkyl bromide (1.1 mmol, 1.5 equiv.) was added. After 24 h the solution was diluted with EtOAc (20 mL) and washed with sat. aq. NH_4Cl (20 mL). The aqueous phase was extracted with EtOAc (3×30 mL), the combined organic phases were dried (MgSO_4) and concentrated. The residue was purified by column chromatography (EtOAc:heptane 1:2) affording the desired product, which was re-crystallized from CH_2Cl_2 /heptane.

(2*S*,6'*R*)-(7-Chloro-4-ethoxy-6-methoxy-benzofuran-3-on)-2-spiro-1'-(2'-methoxy-6'-methyl-cyclohex-2'-en-4'-one) **5**.

Yield: 39 mg (15%) (white crystals); R_f (EtOAc:heptane 5:1): 0.55; m.p.: 205-206 °C (Litt.¹); ^1H NMR(500 MHz, CDCl_3): δ 6.12 (1H, s), 5.53 (1H, s), 4.25-4.15 (2H, m), 4.00 (3H, s), 3.61 (3H, s), 3.04 (1H, dd, $J = 16.8, 13.5$ Hz), 2.84 (1H, ddq, $J = 13.5, 4.7, 6.7$ Hz), 2.42 (1H, dd, $J = 16.8, 4.7$ Hz), 1.52 (3H, t, $J = 7.0$ Hz), 0.96 (3H, d, $J = 6.7$ Hz) (Litt.⁴); ^{13}C NMR(50 MHz, CDCl_3): δ 196.9, 192.2, 170.8, 169.5, 164.4, 157.2, 105.6, 104.7, 97.0, 90.6, 90.3, 65.1, 56.9, 56.6, 40.0, 36.4, 14.3, 14.2; HRMS (ESI+) calcd for $[\text{C}_{18}\text{H}_{20}\text{ClO}_6]^+$ 367.0948, found 367.0944.

(2*S*,6'*R*)-(7-Chloro-4-benzyloxy-6-methoxy-benzofuran-3-on)-2-spiro-1'-(2'-methoxy-6'-methyl-cyclohex-2'-en-4'-one) **6**.

Yield: 40 mg (14%) (white crystals); R_f (EtOAc:heptane 4:1): 0.69; m.p.: 237-239 °C (Litt.¹); ¹H NMR(500 MHz, CDCl₃): δ 7.49-7.46 (2H, m), 7.42-7.38 (2H, m), 7.36-7.31 (1H, m), 6.17 (1H, s), 5.55 (1H, s), 5.27 (2H, s), 3.94 (3H, s), 3.63 (3H, s), 3.05 (1H, dd, $J = 16.6, 13.6$ Hz), 2.85 (1H, m), 2.44 (1H, dd, $J = 16.6, 4.6$ Hz), 0.98 (3H, d, $J = 6.7$ Hz); ¹³C NMR(50 MHz, CDCl₃): δ 196.9, 192.1, 170.8, 169.4, 164.3, 156.6, 135.4, 128.8 (2C), 128.3, 126.8 (2C), 104.8 (2C), 97.4, 91.5, 90.7, 71.1, 56.9, 56.6, 40.0, 36.5, 14.4; HRMS (ESI+) calcd for [C₂₃H₂₂ClO₆]⁺ 429.1105, found 429.1108.

(2*S*,6'*R*)-(7-Chloro-4,6-dimethoxy-5-nitro-benzofuran-3-on)-2-spiro-1'-(2'-methoxy-6'-methyl-cyclohex-2'-ene-4'-one) **7**.

To a solution of griseofulvin (2.0 g, 5.67 mmol) in acetic anhydride (10 mL) was slowly added a solution of nitric acid (2 mL) in acetic anhydride (4 mL) while maintaining the temperature at 0-5 °C. The mixture was stirred at 20 °C for 48 hours and then cooled to 0 °C. A 20% HCl solution was added cautiously to the mixture until a yellow precipitate began to appear, cooling was continued to complete the precipitation of the product and the product was collected by filtration. Additional product was obtained by cautiously adding water to the mother liquor and collected by filtration. The residue was purified by column chromatography (EtOAc:heptane 1:2) to afford the product **7** which was re-crystallized from EtOAc. Yield: 744 mg (33%) (yellow needles); R_f (EtOAc:heptane 5:1): 0.76; m.p.: 195-197 °C (Litt.³); IR (KBr, cm⁻¹): 1719, 1669, 1617, 1577 (Litt.³); ¹H NMR (300 MHz, CDCl₃): δ 5.59 (1H, s), δ 4.22 (3H, s), δ 4.14 (3H, s), δ 3.67 (3H, s), δ 2.99-2.95 (1H, m), δ 2.90-2.86 (1H, m), δ 2.49 (1H, dd, $J = 14.5, 2.4$ Hz), δ 0.98 (3H, d, $J = 6.4$ Hz) (Litt.¹⁷); ¹³C NMR (75 MHz, CDCl₃): δ 196.3, 192.5, 170.0, 169.6, 169.3, 157.4, 149.5, 105.2, 108.9, 91.2, 91.1,

57.2, 64.5, 63.3, 40.0, 36.6, 14.5; EIMS [C₁₇H₁₆ClNO₈] 397, found 397; Anal. (C₁₇H₁₆ClNO₈) C, H.

(2*S*,6'*R*)-(7-Chloro-4,6-dimethoxy-5-amino-benzofuran-3-on)-2-spiro-1'-(2'-methoxy-6'-methyl-cyclohex-2'-ene-4'-one) **8**.

Powdered iron (1.458 g, 26.11 mmol) was added over 3 h to a stirred solution of 5-nitro griseofulvin **7** (744 mg, 1.86 mmol) in 90% aq. acetic acid (18.6 mL). The mixture was refluxed for 1 h and cooled to 20 °C where CH₂Cl₂ (12.6 mL) and then sat. aq. NaHCO₃ was added until pH 7. The aqueous phase was extracted with CH₂Cl₂ (4×100 mL). The combined organic phases were dried (Na₂SO₄) and concentrated. The residue was purified by column chromatography (EtOAc:heptane 1:1) to afford the product **8** which was re-crystallized from EtOAc/heptane. Yield: 369 mg (58%) (yellow crystals); R_f (EtOAc:heptane 5:2): 0.46; m.p.: 120-123 °C (Litt.³); IR (KBr, cm⁻¹): 3471, 3376, 1706, 1664 (Litt.³); ¹H NMR (CDCl₃): δ 5.53 (1H, s), 4.06 (3H, s), 3.98 (3H, s), 3.84 (2H, s), 3.61 (3H, s), 2.95 (1H, dd, *J* = 16.2, 13.3 Hz), 2.87-2.75 (1H, m), 2.41 (1H, dd, *J* = 16.2, 4.2 Hz), 0.91 (3H, d, *J* = 6.6 Hz) (Litt.³); ¹³C NMR (CDCl₃): δ 196.8, 194.4, 171.3, 162.1, 153.0, 142.5, 129.5, 110.0, 105.5, 105.2, 89.8, 62.5, 60.5, 56.9, 40.2, 36.8, 14.6; EIMS [C₁₇H₁₈ClNO₆] 367, found 367.

General procedure for the synthesis of enol ethers by solvolysis (**10-15**).

CSA (0.1 mmol, 0.1 equiv.) was added to a solution of griseofulvic acid (0.6 mmol, 1 equiv.) in the appropriate alcohol (6 mL, 0.1 M). The mixture was stirred at 100 °C for 6 hours, and then cooled to 20 °C. EtOAc (20 mL) was added to the solution and the mixture was washed with sat. NaH₂PO₄ (20 mL) and then water (20 mL). The combined aqueous phases were extracted with EtOAc (3×20 mL), dried (MgSO₄) and then concentrated. The residue was

purified by column chromatography (toluene:CH₂Cl₂:EtOAc 7:7:1) to afford the desired product and the isomer. When possible the product was re-crystallized from EtOAc/Heptane.

(2*S*,6'*R*)-(7-Chloro-4,6-dimethoxy-benzofuran-3-on)-2-spiro-1'-(2'-ethoxy-6'-methyl-cyclohex-2'-en-4'-on) **10**.

Yield: 32 mg (14%) (white crystals); R_f (EtOAc:heptane 5:1): 0.59; m.p.: 202-204 °C (Litt.⁵); IR(KBr, cm⁻¹): 1708, 1661, 1614 (Litt.⁶); ¹H NMR(500 MHz, CDCl₃): δ 6.12 (1H, s), 5.51 (1H, s), 4.03 (3H, s), 3.98 (3H, s), 3.93-3.74 (2H, m), 3.02 (1H, dd, *J* = 16.7, 13.4 Hz), 2.91-2.76 (1H, m), 2.42 (1H, dd, *J* = 16.7, 4.7 Hz), 1.21 (3H, t, *J* = 7.0 Hz), 0.96 (3H, d, *J* = 6.7 Hz) (Litt.⁴); ¹³C NMR(50 MHz, CDCl₃): δ 197.1, 192.6, 169.9, 169.6, 164.4, 157.6, 105.1 (2C), 97.1, 90.8, 89.3, 65.3, 56.9, 56.3, 39.9, 36.3, 14.2, 13.6; HRMS (ESI+) calcd for [C₁₈H₂₀ClO₆]⁺ 367.0949, found 367.0960; Anal. (C₁₈H₁₉ClO₆) C, H.

(2*S*,6'*R*)-(7-Chloro-4,6-dimethoxy-benzofuran-3-on)-2-spiro-1'-(6'-methyl-2'-propoxy-cyclohex-2'-en-4'-on) **11**.

Yield: 41 mg (18%) (white crystals); R_f (EtOAc:heptane 5:1): 0.64; m.p.: 151-153 °C (Litt.⁷) IR(KBr, cm⁻¹): 1706, 1662, 1614 (Litt.⁶); ¹H NMR(500 MHz, CDCl₃): δ 6.13 (1H, s), 5.51 (1H, s), 4.04 (3H, s), 3.98 (3H, s), 3.79-3.66 (2H, m), 3.05 (1H, dd, *J* = 16.7, 13.5 Hz), 2.89-2.80 (1H, m), 2.42 (1H, dd, *J* = 16.7, 4.7 Hz), 1.64-1.55 (2H, m), 0.97 (3H, d, *J* = 6.7 Hz), 0.82 (3H, t, *J* = 7.4 Hz); ¹³C NMR(50 MHz, CDCl₃): δ 197.1, 192.6, 170.0 (2C), 164.4, 157.6, 105.1, 104.8, 96.8, 90.8, 89.3, 70.7, 56.9, 56.3, 39.9, 36.2, 21.5, 14.2, 9.9; HRMS (ESI+) calcd for [C₁₉H₂₂ClO₆]⁺ 381.1105, found 381.1105; Anal. (C₁₉H₂₁ClO₆) C, H.

(2*S*,6'*R*)-(7-Chloro-4,6-dimethoxy-benzofuran-3-on)-2-spiro-1'-(2'-isopropoxy-6'-methyl-cyclohex-2'-en-4'-on) **12**.

Yield: 50 mg (22%) (off-white crystals); R_f (EtOAc:heptane 5:1): 0.62; m.p.: 194-197 °C (Litt.¹); IR(KBr, cm^{-1}): 1714, 1667, 1615 (Litt.⁶); ^1H NMR(500 MHz, CDCl_3): δ 6.12 (1H, s), 5.51 (1H, s), 4.33 (1H, sept., $J = 6.1$ Hz), 4.03 (3H, s), 3.98 (3H, s), 3.02 (1H, dd, $J = 16.7$, 13.4 Hz), 2.87-2.77 (1H, m), 2.41 (1H, dd, $J = 16.7$, 4.7 Hz), 1.23 (3H, d, $J = 6.1$ Hz), 1.11 (3H, d, $J = 6.1$ Hz), 0.95 (3H, d, $J = 6.7$ Hz); ^{13}C NMR(50 MHz, CDCl_3): δ 197.2, 192.6, 169.6, 169.0, 164.3, 157.5, 105.4 (2C), 97.0, 90.9, 89.2, 72.4, 56.9, 56.3, 39.8, 36.2, 21.2, 20.7, 14.3; HRMS (ESI+) calcd for $[\text{C}_{19}\text{H}_{22}\text{ClO}_6]^+$ 381.1105, found 381.1119; Anal. ($\text{C}_{19}\text{H}_{21}\text{ClO}_6$) C, H.

(2*S*,6'*R*)-(7-Chloro-4,6-dimethoxy-benzofuran-3-one)-2-spiro-1'-(2'-butoxy-6'-methyl-cyclohex-2'-ene-4'-one) **13**.

Yield: 72 mg (14%) (white crystals); R_f (EtOAc:heptane 5:1): 0.41; m.p.: 152-154 °C (Litt.⁷); IR (KBr, cm^{-1}): 1706, 1662, 1614; ^1H NMR (300 MHz, CDCl_3): δ 6.11 (1H, s), δ 5.50 (1H, s), δ 4.03 (3H, s), δ 3.97 (3H, s), δ 3.83-3.68 (2H, m), δ 3.03 (1H, dd, $J = 16.5$, 13.5 Hz), δ 2.79 (1H, ddq, $J = 13.3$, 6.6, 4.7 Hz), δ 2.41 (1H, dd), δ 1.59-1.49 (2H, m), δ 1.28-1.19 (2H, m), δ 0.95 (3H, d, $J = 6.7$ Hz), δ 0.74 (3H, t, $J = 7.4$ Hz); ^{13}C NMR (75 MHz, CDCl_3): δ 197.1, 192.9, 170.4, 169.5, 164.7, 157.9, 105.4, 105.2, 97.2, 91.1, 89.6, 69.5, 57.2, 56.6, 40.2, 36.5, 30.2, 19.0, 14.5, 13.8; HRMS (ESI+) calcd for $[\text{C}_{20}\text{H}_{24}\text{ClO}_6]^+$ 395.1261, found 395.1263; Anal. ($\text{C}_{20}\text{H}_{23}\text{ClO}_6$) C, H.

(2*S*,6'*R*)-(7-Chloro-4,6-dimethoxy-benzofuran-3-one)-2-spiro-1'-(6'-methyl-2'-pentoxy-cyclohex-2'-ene-4'-one) **14**.

Yield: 392 mg (17%) (white crystals); R_f (EtOAc:heptane 5:1): 0.52; m.p.: 146-148 °C (Litt.⁷); IR (KBr, cm^{-1}): 1701, 1653, 1613; ^1H NMR (300 MHz, CDCl_3): δ 6.11 (1H, s), 5.48 (1H, s), 4.02 (3H, s), 3.96 (3H, s), 3.79-3.66 (2H, m), 3.03 (1H, dd, $J = 16.5$, 13.5 Hz), 2.82

(1H, ddq, $J = 13.5, 6.8, 4.7$ Hz), 2.40 (1H, dd, $J = 16.5, 4.6$ Hz), 1.61-1.51 (2H, m), 1.20-1.15 (4H, m), 0.95 (3H, d, $J = 6.7$ Hz), 0.77 (3H, t, $J = 6.8$ Hz); ^{13}C NMR (75 MHz, CDCl_3): δ 197.2, 192.8, 170.4, 169.9, 164.7, 157.9, 105.4, 105.1, 97.4, 91.1, 89.5, 69.8, 57.2, 56.6, 40.2, 36.4, 28.0, 27.9, 22.3, 14.5, 14.1; HRMS (ESI+) calcd for $[\text{C}_{21}\text{H}_{26}\text{ClO}_6]^+$ 409.1418, found 409.1412; Anal. ($\text{C}_{21}\text{H}_{25}\text{ClO}_6$) C, H.

(2*S*,6'*R*)-(7-Chloro-4,6-dimethoxy-benzofuran-3-one)-2-spiro-1'-(2'-hexoxy-6'-methyl-cyclohex-2'-ene-4'-one) **15**.

Yield: 450 mg (19%) (white crystals); R_f (EtOAc:heptane 5:1): 0.52; m.p.: 152-154 °C (Litt.⁷); IR (KBr, cm^{-1}): 1701, 1663, 1616; ^1H NMR (300 MHz, CDCl_3): δ 6.11 (1H, s), 5.50 (1H, s), 4.03 (3H, s), 3.97 (3H, s), 3.83-3.66 (2H, m), 3.04 (1H, dd, $J = 16.5, 13.5$ Hz), 2.83 (1H, ddq, $J = 13.3, 6.6, 4.6$ Hz), 2.41 (1H, dd, $J = 16.5, 4.6$ Hz), 1.61-1.49 (2H, m), 1.25-1.16 (6H, m), 0.96 (3H, d, $J = 6.7$ Hz), 0.80 (3H, t, $J = 6.9$ Hz); ^{13}C NMR (75 MHz, CDCl_3): δ 197.2, 192.8, 170.4, 169.8, 164.7, 157.9, 105.5, 105.1, 97.6, 91.1, 89.5, 69.7, 57.2, 56.6, 40.2, 36.4, 31.3, 28.2, 25.4, 22.6, 14.5, 14.0; HRMS (ESI+) calcd for $[\text{C}_{22}\text{H}_{28}\text{ClO}_6]^+$ 423.1574, found 423.1560; Anal. ($\text{C}_{22}\text{H}_{27}\text{ClO}_6$) C, H.

(2*S*,6'*R*)-(7-Chloro-4,6-dimethoxy-benzofuran-3-one)-2-spiro-1'-(2'-chloro-6'-methyl-cyclohex-2'-ene-4'-one) **18**.

Griseofulvic acid (11.3 g, 31.6 mmol) was mixed with LiCl (4.2 g, 0.101 mol) and added to a solution of POCl_3 (15.6 mL, 0.168 mol) in dioxane (40 mL). The mixture was stirred at 100 °C for 30 min, cooled to 0 °C and sat. aq. Na_2CO_3 was added carefully to the solution until slightly basic (pH 7-8). The aqueous phase was extracted with CH_2Cl_2 (4×300 mL) and the combined organic phases were dried (MgSO_4) and concentrated. The residue was purified by column chromatography (toluene: CH_2Cl_2 :EtOAc 35:35:1) affording the desired product

18 and the isomer. The product was re-crystallized from CH₂Cl₂/heptane. Yield: 234 mg (44%) (white crystals); R_f (EtOAc:heptane 5:1): 0.51; m.p.: 196-198 °C (Litt.⁸); IR (KBr, cm⁻¹): 1698, 1615 (Litt.⁸); ¹H NMR (300 MHz, CDCl₃): δ 6.41 (1H, s), 6.14 (1H, s), 4.03 (3H, s), 3.98 (3H, s), 3.12 (1H, dd, *J* = 16.7, 13.9 Hz), 2.89 (1H, ddq, *J* = 13.5, 4.4, 6.7 Hz), 2.45 (1H, dd, *J* = 16.7, 4.4 Hz), 0.98 (3H, *J* = 6.7 Hz); ¹³C NMR (50 MHz, CDCl₃): δ 195.0, 191.1, 169.3, 165.3, 158.1, 152.9, 131.6, 105.4, 97.6, 91.7, 90.0, 57.3, 56.7, 40.3, 37.8, 15.2; EIMS calcd for [C₁₆H₁₄Cl₂O₅] 356, found 356; Anal. (C₁₆H₁₄Cl₂O₅) C, H.

General procedure for the synthesis of enol ethers by addition-elimination. (**19-21**).

To a solution of **18** (0.65 mmol, 1 equiv.) in 1,4-dioxane (3 mL, 0.2 M) was added the desired alcohol (1.30 mmol, 2 equiv.) and DBU (1.63 mmol, 2.5 equiv.). The mixture was heated to 100 °C and stirred for 12 h. The mixture was then cooled to 20 °C and excess reagent was quenched with sat. aq. NH₄Cl (30 mL). The aqueous phase was extracted with EtOAc (3×30 mL) and the combined organic phases were dried (MgSO₄) and then concentrated. The residue was purified by column chromatography (heptane:EtOAc 3:2) affording the product. When possible the product was re-crystallized from EtOAc/heptane.

(2*S*,6'*R*)-(7-Chloro-4,6-dimethoxy-benzofuran-3-one)-2-spiro-1'-(6'-methyl-2'-phenoxy-cyclohex-2'-ene-4'-one) **19**.

Yield: 199 mg (86%); R_f (EtOAc:heptane 5:1); 0.50; IR (KBr, cm⁻¹): 1704, 1665; ¹H NMR(300 MHz, CDCl₃): δ 7.36-7.29 (2H, m), 7.22-7.16 (1H, m), 7.00-6.95 (2H, m), 6.13 (1H, s), 5.30 (1H, s), 4.01 (3H, s), 3.99 (3H, s) 3.06 (1H, dd, *J* = 16.0, 13.5 Hz), 2.99-2.85 (1H, m), 2.42 (1H, dd, *J* = 16.0, 4.0 Hz), 1.01 (3H, d, *J* = 6.5 Hz); ¹³C NMR(75 MHz, CDCl₃): 197.0, 192.3, 170.9, 169.6, 164.8, 157.8, 152.6, 130.0 (2C), 126.3, 121.1 (2C),

108.8, 105.2, 97.2, 90.6, 89.5, 57.0, 56.4, 40.3, 36.5, 14.3; HRMS (ESI+) calcd for $[C_{22}H_{20}ClO_6]^+$ 415.0948, found 415.0941.

(2*S*,6'*R*)-(7-Chloro-4,6-dimethoxy-benzofuran-3-on)-2-spiro-1'-(2'-benzyloxy-6'-methyl-cyclohex-2'-en-4'-one) **20**.

Yield: 30 mg (55%) (white crystals); R_f (EtOAc:heptane 5:1): 0.49; m.p.: 186-188 °C (Litt.¹); 1H NMR(300 MHz, $CDCl_3$): δ 7.32-7.24 (3H, m), 7.20-7.16 (2H, m), 6.11 (1H, s), 5.60 (1H, s), 4.02 (3H, s), 3.96 (3H, s), 4.92 (1H, d, $J = 12.3$ Hz), 4.82 (1H, d, $J = 12.3$ Hz), 3.06 (1H, dd, $J = 16.7, 13.4$ Hz), 2.87 (1H, ddq, $J = 13.4, 6.7, 4.8$ Hz), 2.44 (1H, dd, $J = 16.7, 4.8$ Hz), 0.99 (3H, d, $J = 6.7$ Hz); ^{13}C NMR(50 MHz, $CDCl_3$): δ 196.9, 192.3, 169.5 (2C), 164.5, 157.7, 134.6, 128.5 (2C), 128.1, 126.6 (2C), 105.9, 105.2, 97.2, 90.7, 89.4, 70.6, 56.9, 56.3, 40.0, 36.6, 14.2; HRMS (ESI+) calcd for $[C_{23}H_{22}ClO_6]^+$ 429.1105, found 429.1103.

(2*S*,6'*R*)-(7-Chloro-4,6-dimethoxy-benzofuran-3-one)-2-spiro-1'-(2'-benzylthio-6'-methyl-cyclohex-2'-ene-4'-one) **21**.

Yield: 349 mg (93%) (white crystals); R_f (EtOAc:heptane 5:1): 0.44; m.p.: 208-210 °C (Litt.⁸); IR (KBr, cm^{-1}): 1703, 1663 (Litt.⁸); 1H NMR (300 MHz, $DMSO-d_6$): δ 7.33-7.27 (5H, m), 6.51 (1H, s), 6.09 (1H, s), 4.17 (1H, d, $J = 12.5$ Hz), 4.05 (1H, d, $J = 12.5$ Hz), 4.03 (3H, s), 3.95 (3H, s), 2.95-2.83 (1H, m), 2.68 (1H, dd, $J = 17.3, 13.3$ Hz), 2.40 (1H, dd, $J = 17.2, 5.3$ Hz), 0.77 (3H, d, $J = 6.6$ Hz); ^{13}C NMR (75 MHz, $DMSO-d_6$): δ 193.4, 191.1, 168.5, 165.2, 160.5, 158.4, 135.3, 129.8 (2C), 129.4 (2C), 128.4, 122.6, 104.1, 95.8, 92.3, 92.2, 58.3, 57.3, 49.9, 37.4, 35.4, 14.9; HRMS (ESI+) calcd for $[C_{23}H_{22}ClO_5S]^+$ 445.0877, found 445.0872; Anal. ($C_{23}H_{21}ClO_5S$) C, H.

(2*S*,6'*R*)-(7-Chloro-4,6-dimethoxy-benzofuran-3-on)-2-spiro-1'-(2'-methoxy-6'-methyl-cyclohex-2'-en-4'-ol) **26**.

A solution of griseofulvin (212 mg, 0.6 mmol) in MeOH (3 mL) was cooled to -40 °C. CeCl₃ (448 mg, 1.8 mmol) was added and the solution stirred for 10 min. after which NaBH₄ (70 mg, 1.8 mmol) was added. After 3 h excess reagent was quenched by the slow addition of acetone (3 mL) and the mixture was allowed to reach 20 °C, diluted with EtOAc (10 mL) and washed with water (20 mL). The aqueous phase was extracted with EtOAc (5×30 mL) and the combined organic phases were dried (MgSO₄) and concentrated. The compound **26** was re-crystallized from MeOH. Yield: 209 mg (98%) (white crystals); R_f (EtOAc:heptane 5:1): 0.25; m.p.: 110-113 °C. (Litt.⁹); ¹H NMR(300 MHz, CDCl₃): δ 6.08 (1H, s), 5.11 (1H, d, *J* = 1.9 Hz), 4.45 (1H, ddd, *J* = 9.3, 5.8, 1.9 Hz), 4.00 (3H, s), 3.96 (3H, s), 3.44 (3H, s), 2.37 (1H, ddq, *J* = 13.1, 3.4, 6.8 Hz), 2.10 (1H, dt, *J* = 9.3, 13.1 Hz), 2.00 (1H, dddd, *J* = 13.1, 5.8, 3.4, 0.9 Hz), 0.87 (3H, d, *J* = 6.8 Hz); ¹³C NMR (from gHSQC, gHMBC, 500 MHz, CDCl₃): δ 195.5, 169.6, 164.8, 157.0, 152.6, 105.8, 105.5, 96.9, 92.0, 88.8, 65.9, 56.5, 56.1, 55.0, 36.3, 35.6, 14.2; EIMS [C₁₇H₁₉ClO₆] M⁺ 354, found 354.

(2*S*,2'*S*,4'*S*,6'*R*)-(7-Chloro-4,6-dimethoxy-benzofuran-3-on)-2-spiro-1'-(2'-methoxy-6'-methyl-cyclohexan-4'-ol) **27**.

To a solution of griseofulvin (107 mg, 0.3 mmol) in MeOH (3 mL) was added 5% Pt on charcoal (24 mg). The mixture was stirred at 20 °C for 12 h under a hydrogen atmosphere. EtOAc (20 mL) was added and the mixture was filtered, dried (MgSO₄), concentrated and purified by column chromatography (EtOAc:heptane 1:1). The product **27** was re-crystallized from EtOAc/heptane. Yield: 94 mg (86%) (white crystals); R_f (EtOAc:heptane 4:1): 0.27; m.p.: 188-190 °C (Litt.^{10,11}); IR(KBr, cm⁻¹): 1696; ¹H NMR(500 MHz, CDCl₃): δ 6.06 (1H, s), 3.99 (3H, s), 3.94 (3H, s), 3.83-3.70 (1H, m), 3.62 (1H, dd, *J* = 12.0, 5.1 Hz), 3.27 (3H, s),

2.29 (1H, m), 2.24 (1H, q, $J = 12.0$ Hz), 2.09 (2H, m), 1.90-1.78 (1H, m), 0.82 (3H, d, $J = 6.1$ Hz); ^{13}C NMR(50 MHz, CDCl_3): δ 195.8, 169.0, 163.6, 156.9, 107.7, 96.6, 94.8, 88.6, 81.5, 67.4, 58.4, 56.7, 56.0, 37.4, 35.0, 34.9, 14.1; Anal. ($\text{C}_{17}\text{H}_{21}\text{ClO}_6$): C, H.

(2*S*,6'*R*)-(7-Chloro-4,6-dimethoxy-benzofuran-3-one)-2-spiro-1'-(2'-methoxy-6'-methyl-cyclohex-2'-ene-4'-one-4'-oxime) **28**.

To a solution of **1** (0.20 mmol, 1.0 equiv.) in EtOH (5 mL, 0.03M) and DMSO (2.5 mL, 0.03M) was added hydroxylamine hydrochloride (0.70 mmol, 3.5 equiv.) and sodium acetate (0.86 mmol, 4.3 equiv.). The mixture was stirred at 75 °C for 24 hours, allowed to reach 20 °C and diluted with CH_2Cl_2 (20 mL). The mixture was washed with distilled water (2×15 mL) and then brine (15 mL). The organic phase was dried (MgSO_4) and concentrated. The crude mixture was purified by column chromatography (toluene: CH_2Cl_2 :EtOAc 2:2:1) to afford the desired product.

Yield: 988 mg (95%) (white needles); R_f (MeOH: CH_2Cl_2 1:10): 0.50; IR (KBr, cm^{-1}): 1706, 1590, 1614 (Litt.³); ^1H NMR (300 MHz, CDCl_3): δ 6.26 (0.5H, s), 6.10 (0.5H, s), 6.10 (0.5H, s), 5.59 (0.5H, s), 4.01 (3H, s), 3.96 (1.5H, s), 3.96 (1.5H, s), 3.61 (1.5H, s), 3.55 (1.5H, s), 3.12 (0.5H, dd, $J = 16.6, 4.7$ Hz), 2.99 (0.5H, dd, $J = 15.0, 13.1$ Hz), 2.70 (0.5H, dd, $J = 16.6, 13.0$ Hz), 2.64-2.48 (1H, m), 2.40 (0.5H, dd, $J = 15.0, 4.2$ Hz), 0.95 (1.5H, d, $J = 6.7$ Hz), 0.94 (1.5H, d, $J = 6.7$ Hz) (Litt.³); ^{13}C NMR (75 MHz, CDCl_3): δ 194.1 (0.5C), 193.9 (0.5C), 169.4 (0.5C), 169.4 (0.5C), 164.3 (0.5C), 164.2 (0.5C), 161.3 (0.5C), 158.6 (0.5C), 157.5 (0.5C), 157.4 (0.5C), 155.0 (0.5C), 151.8 (0.5C), 105.6 (0.5C), 105.5 (0.5C), 98.9 (0.5C), 97.1, 92.6 (0.5C), 91.4 (0.5C), 91.3 (0.5C), 89.1, 56.9 (0.5C), 56.9 (0.5C), 56.3, 56.1 (0.5C), 55.9 (0.5C), 36.4 (0.5C), 35.2 (0.5C), 30.8 (0.5C), 25.5 (0.5C), 14.3 (0.5C), 14.2

(0.5C); HRMS (ESI+) calcd for $[C_{17}H_{19}ClNO_6]^+$ 368.0901, found 368.0891; Anal. ($C_{17}H_{18}ClNO_6$) C, H.

(2*S*,6'*R*)-(7-Chloro-4,6-dimethoxy-benzofuran-3-on)-2-spiro-1'-(3',3',6'-trimethyl-cyclohex-2',4'-dione) **31**.

To a solution of griseofulvin (514 mg, 1.5 mmol) in THF (10 mL) was added K_2CO_3 (410 mg, 3.0 mmol) and MeI (0.2 mL, 3.1 mmol) and the mixture was heated to 80 °C. The solution was cooled to 20 °C after 12 h. The reaction was quenched with sat. aq. NH_4Cl (30 mL) and the aqueous phase was extracted with EtOAc (3×30 mL). The combined organic phases were dried ($MgSO_4$), concentrated and the residue was purified by column chromatography (EtOAc:heptane 1:6) affording the product **31**. Yield: 75 mg (14%) (yellow oil); R_f (EtOAc:heptane 5:1): 0.65; IR(KBr, cm^{-1}): 1695, 1615; 1H NMR(500 MHz, $CDCl_3$): δ 6.11 (1H, s), 4.02 (3H, s), 3.94 (3H, s), 3.44-3.39 (1H, m), 2.88-2.77 (2H, m), 1.39 (3H, s), 1.36 (3H, s), 1.05 (3H, d, $J = 6.5$ Hz); ^{13}C NMR(75 MHz, $CDCl_3$): δ 207.2, 201.6, 190.8, 169.2, 164.8, 157.9, 104.5, 97.3, 96.0, 89.6, 60.2, 57.0, 56.3, 40.4, 32.2, 23.6, 23.5, 14.6; EIMS [$C_{18}H_{19}ClO_6$] 366, found 366.

(2*S*,6'*R*)-(7-Chloro-4,6-dimethoxy-benzofuran-3-one)-2-spiro-1'-(3'-benzyl-6'-methyl-cyclohex-2',4'-dione) **32**.

A solution of griseofulvic acid (5.0 g, 0.015 mol) in H_2O (7.4 mL) containing KOH (0.832 g, 0.015 mol) and NaI (2.22 g, 0.015 mol) was heated to reflux with copper powder (188 mg, 2.97 mmol) and benzyl bromide (2.54 g, 0.015 mol) for 24 hours. The mixture was cooled to 20 °C and the precipitate was filtered off. The filtrate was extracted with EtOAc (3×10 mL) and the organic phase was washed with sat. aq. $NaHCO_3$. The aqueous phase was acidified with 2M HCl and then extracted with EtOAc (3×50 mL). The combined organic phases were

dried (MgSO₄) and concentrated. The residue was purified by column chromatography (toluene:CH₂Cl₂:EtOAc 10:10:1) to yield the product **32** which was re-crystallized from CH₂Cl₂/heptane. Yield: 533 mg (8%) (white crystals); R_f (EtOAc:heptane 5:1): 0.33; m.p.: 202-204 °C (Litt.¹²); IR (KBr, cm⁻¹): 1702, 1616 (Litt.¹²); ¹H NMR (300 MHz, DMSO-*d*₆): δ 11.6 (1H, s), 7.21-7.16 (2H, m), 7.10-7.05 (3H, m), 6.43 (1H, s), 4.01 (3H, s), 3.88 (3H, s), 3.50 (1H, d, *J* = 14.6 Hz), 3.41 (1H, d, *J* = 14.6 Hz), 2.92 (1H, dd, *J* = 16.5, 11.5 Hz), 2.81-2.70 (1H, m), 2.63 (1H, dd, *J* = 16.5, 5.2 Hz), 0.84 (3H, d, *J* = 6.4 Hz); ¹³C NMR (75 MHz, DMSO-*d*₆): δ 190.7, 190.6, 174.4, 168.5, 163.5, 156.9, 140.4, 127.5 (2C), 127.4 (2C), 124.9, 103.8, 95.0, 94.3, 90.4, 90.3, 57.0, 56.0, 34.0, 32.5, 27.3, 13.9; HRMS (ESI+) calcd for [C₂₃H₂₂ClO₆]⁺ 429.1105, found 429.1108.

General procedure for the synthesis of 3' iodo analogues (**33-35**).

To an ice-cooled solution of griseofulvin (1.4 mmol, 1 equiv.) and *N*-iodosuccinimide (2.1 mmol, 1.5 equiv.) in anhydrous CH₂Cl₂ (15 mL, 0.1 M) under an argon atmosphere, was added triethylsilyl trifluoromethanesulfonate (0.35 mmol 0.25 equiv.). The mixture was stirred at 20 °C for 24 h and then diluted with CH₂Cl₂ (60 mL) and washed with sat. aq. NaHCO₃ (60 mL). The aqueous phase was extracted with CH₂Cl₂ (50 mL), the combined organic phases were dried (MgSO₄) and concentrated. The residue was purified by column chromatography (EtOAc:heptane 1:3) to yield the desired product. When possible the product was re-crystallized from EtOAc/heptane.

(2*S*,6'*R*)-(7-Chloro-4,6-dimethoxy-benzofuran-3-one)-2-spiro-1'-(3'-iodo-2'-methoxy-6'-methyl-cyclohex-2'-ene-4'-one) **33**.

Yield: 126 mg (19%) (white crystals); R_f (EtOAc:heptane 5:1): 0.77; m.p.: 188-190 °C (Litt.¹³); IR (KBr, cm⁻¹): 1717, 1664 (Litt.¹³); ¹H NMR (300 MHz, CDCl₃): δ 5.56 (1H, s),

4.10 (3H, s), 4.01 (3H, s), 3.63 (3H, s), 2.95 (1H, dd, $J = 15.6, 13.3$ Hz), 2.90-2.79 (1H, m), 2.46 (1H, dd, $J = 15.6, 3.6$ Hz), 0.94 (3H, d, $J = 6.4$ Hz); ^{13}C NMR (75 MHz, CDCl_3): δ 196.7, 192.5, 170.8, 170.3, 164.6, 157.0, 106.3, 105.4, 97.1, 91.1, 82.1, 63.1, 61.4, 57.1, 40.1, 36.7, 14.6; HRMS (ESI+) calcd for $[\text{C}_{17}\text{H}_{17}\text{ClIO}_6]^+$ 478.9758, found 478.9761.

(2*S*,6'*R*)-(7-Chloro-4,6-dimethoxy-benzofuran-3-one)-2-spiro-1'-(3'-iodo-6'-methyl-2'-propoxy-cyclohex-2'-ene-4'-one) **34**.

Yield: 49 mg (19%) (yellow crystals); R_f (EtOAc:heptane 5:1): 0.53; m.p.: 98-100 °C (Litt.¹³); IR (KBr, cm^{-1}): 1719, 1618 (Litt.¹³); ^1H NMR (500 MHz, CDCl_3): δ 6.13 (1H, s), 4.14-4.11 (2H, m), 4.03 (3H, s), 4.00 (3H, s), 3.80-3.73 (1H, m), 2.94-2.87 (1H, m), 2.92-2.90 (1H, m), 1.75-1.68 (2H, m), 1.05 (3H, d, $J = 5.8$ Hz), 1.00 (3H, t, $J = 7.4$ Hz); ^{13}C NMR (75 MHz, CDCl_3): δ 196.7, 192.1, 188.0, 172.3, 172.3, 165.5, 158.3, 112.2, 103.8, 97.9, 90.1, 67.9, 57.4, 56.8, 39.4, 38.2, 22.3, 12.2, 10.8; HRMS (ESI+) calcd for $[\text{C}_{19}\text{H}_{21}\text{ClIO}_6]^+$ 507.0071, found 507.0069.

(2*S*,6'*R*)-(7-Chloro-4,6-dimethoxy-benzofuran-3-one)-2-spiro-1'-(3'-iodo-2'-benzyloxy-6'-methyl-cyclohex-2'-ene-4'-one) **35**.

Yield: 56 mg (17%) (white crystals); R_f (EtOAc:heptane 5:1): 0.88; m.p.: 172-175 °C (Litt.¹³); IR (KBr, cm^{-1}): 1715, 1666 (Litt.¹³); ^1H NMR (300 MHz, CDCl_3): δ 7.27-7.22 (3H, m), 7.12-7.10 (2H, m), 5.59 (1H, s), 4.90 (1H, d, $J = 12.3$ Hz), 4.81 (1H, d, $J = 12.3$ Hz), 4.07 (3H, s), 3.95 (3H, s), 2.95 (1H, dd, $J = 15.5, 13.2$ Hz), 2.88-2.81 (1H, m), 2.44 (1H, dd, $J = 15.4, 3.3$ Hz), 0.95 (3H, d, $J = 6.4$ Hz); ^{13}C NMR (75 MHz, CDCl_3): δ 196.7, 192.6, 170.9, 168.9, 164.6, 157.0, 134.6, 128.9 (2C), 128.7, 126.9 (2C), 110.4, 106.5, 106.2, 91.2, 82.0, 71.1, 63.1, 61.4, 40.2, 36.5, 14.6; HRMS (ESI+) calcd for $[\text{C}_{23}\text{H}_{21}\text{ClIO}_6]^+$ 555.0071, found 555.0071; Anal. ($\text{C}_{23}\text{H}_{20}\text{ClIO}_6$) C, H.

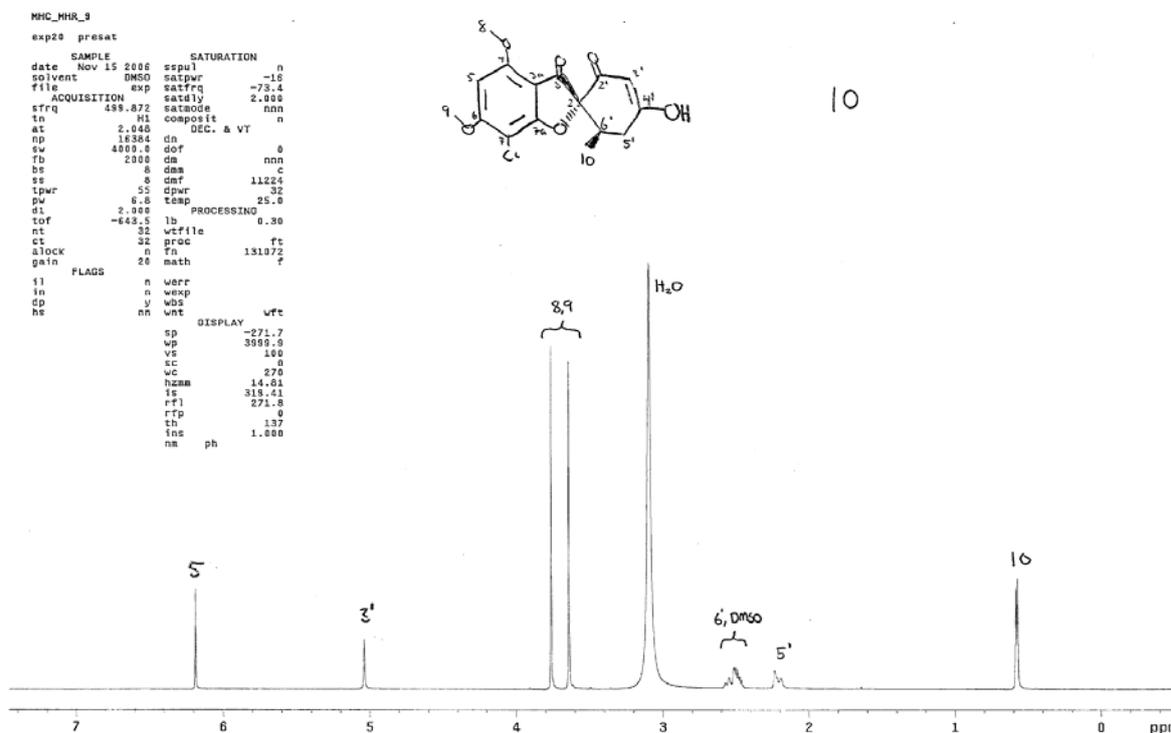
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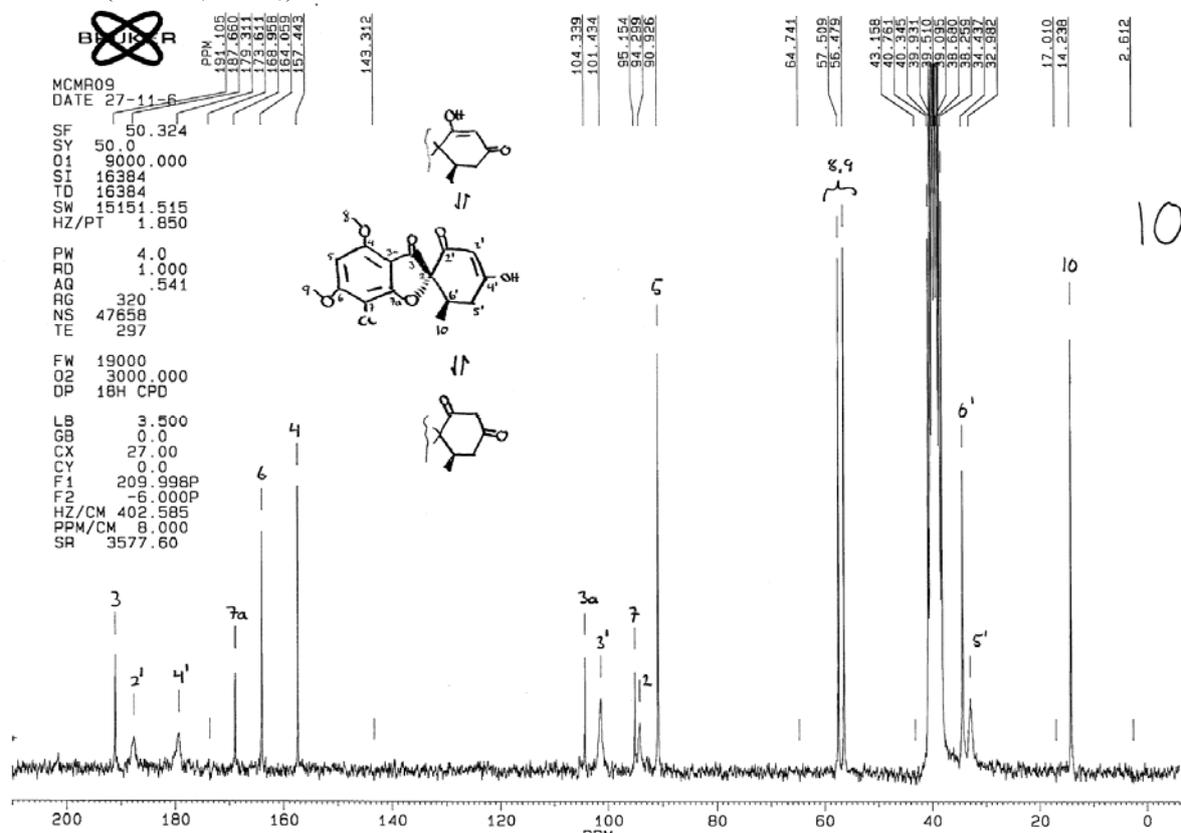
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(2*S*,6'*R*)-(7-Chloro-4,6-dimethoxy-benzofuran-3-on)-2-spiro-1'-(6'-methyl-cyclohex-2',4'-dione) **2**

¹H NMR (500 MHz, DMSO-*d*₆)

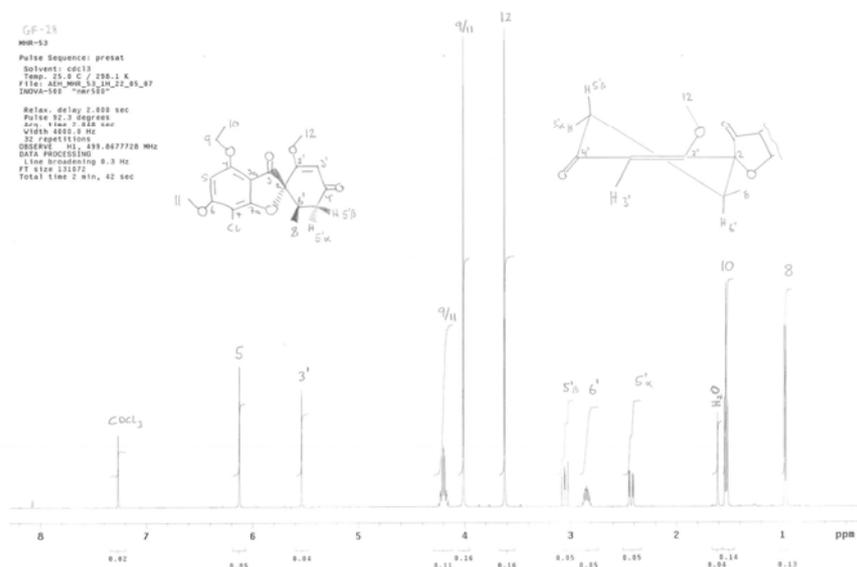


¹³C NMR (50 MHz, CDCl₃)

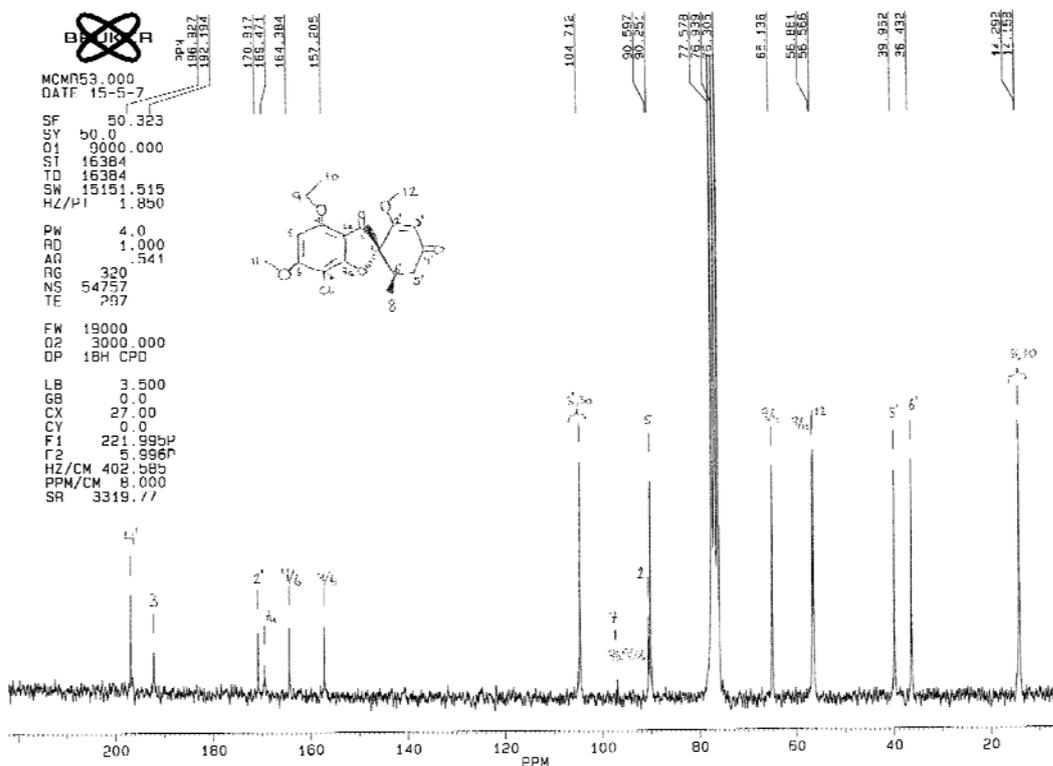


(2*S*,6'*R*)-(7-Chloro-4-ethoxy-6-methoxy-benzofuran-3-on)-2-spiro-1'-(2'-methoxy-6'-methyl-cyclohex-2'-en-4'-one) **5**

¹H NMR (500 MHz, CDCl₃)

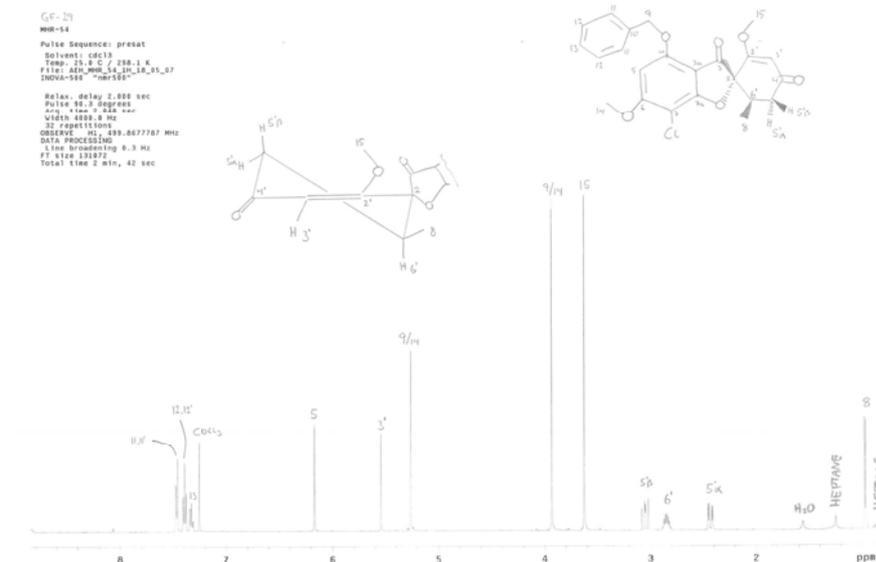


¹³C NMR (50 MHz, CDCl₃)

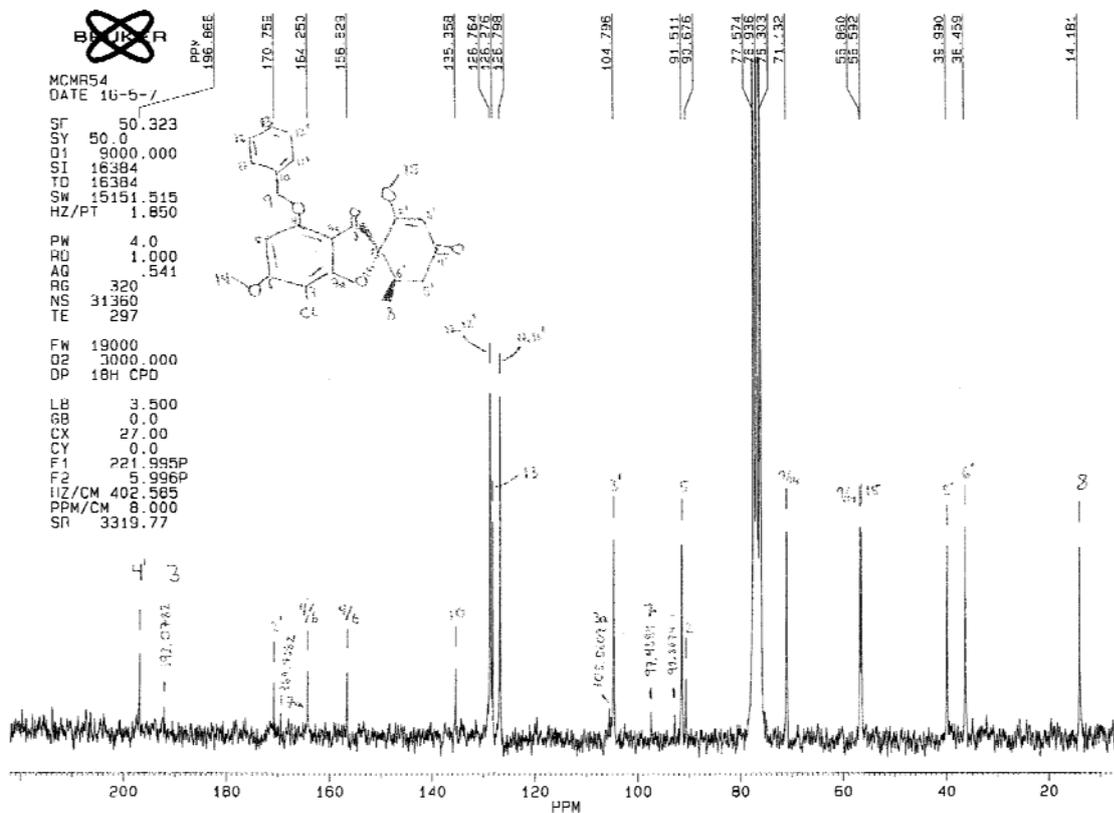


(2*S*,6'*R*)-(7-Chloro-4-benzyloxy-6-methoxy-benzofuran-3-on)-2-spiro-1'-(2'-methoxy-6'-methyl-cyclohex-2'-en-4'-one) **6**

¹H NMR (500 MHz, CDCl₃)

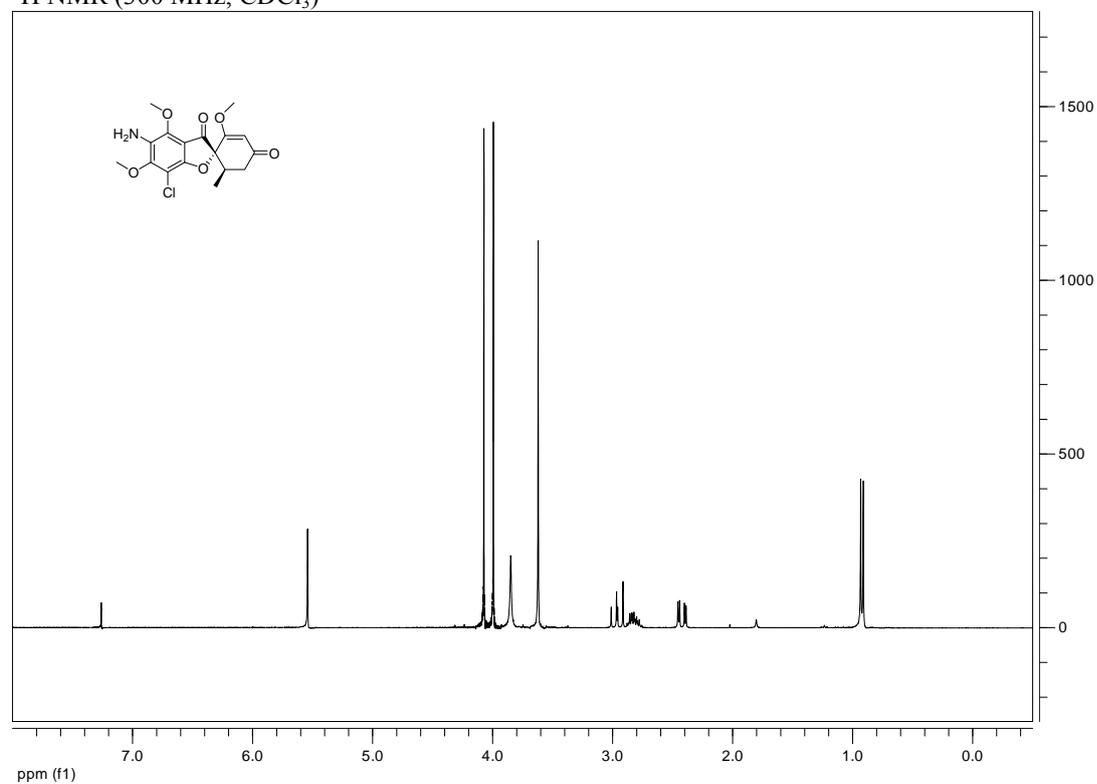


¹³C NMR (50 MHz, CDCl₃)

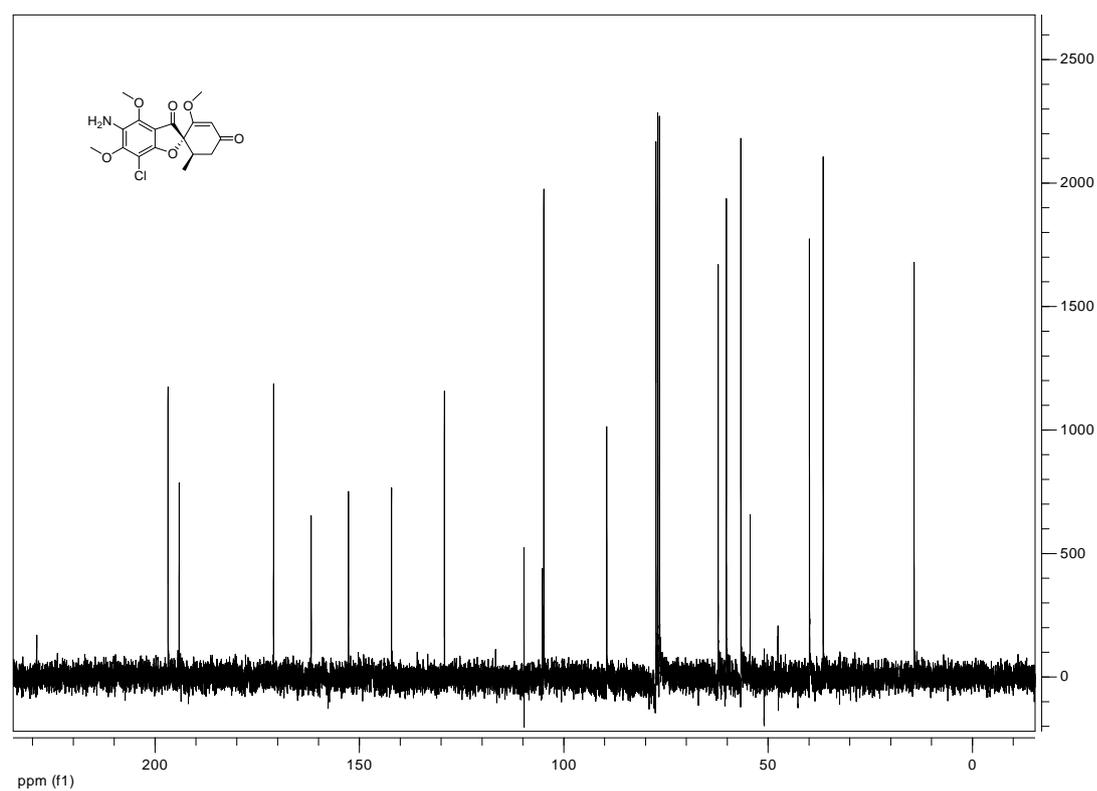


(2*S*,6'*R*)-(7-Chloro-4,6-dimethoxy-5-amino-benzofuran-3-on)-2-spiro-1'-(2'-methoxy-6'-methyl-cyclohex-2'-ene-4'-one) **8**

¹H NMR (300 MHz, CDCl₃)

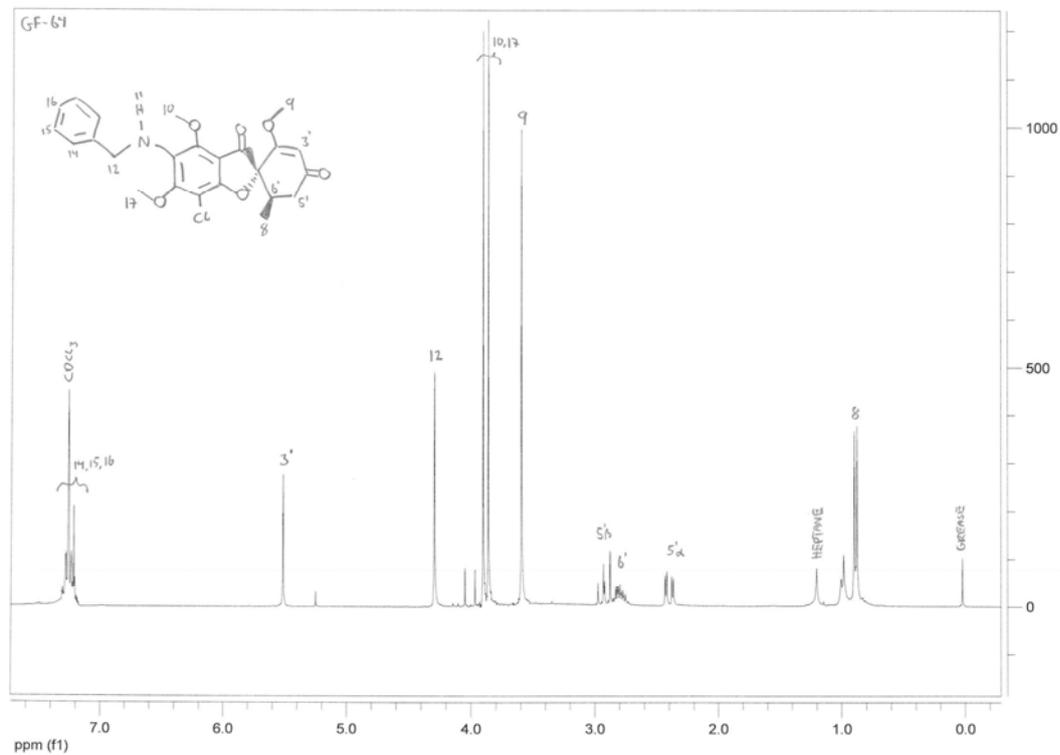


¹³C NMR (75 MHz, CDCl₃)

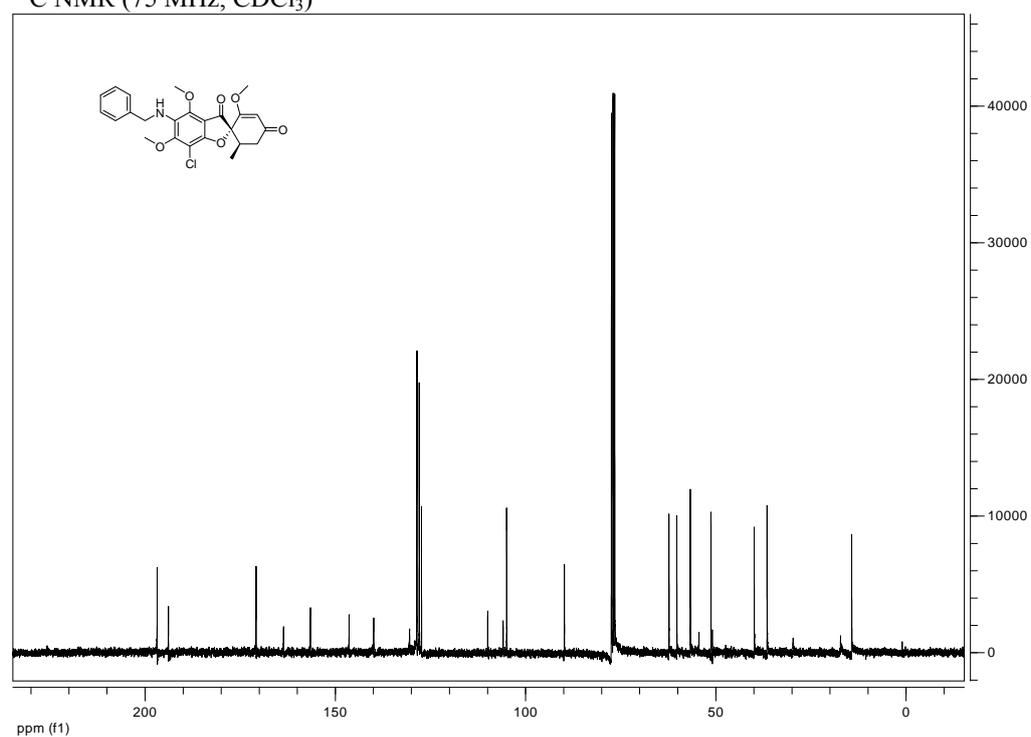


(2*S*,6'*R*)-(7-Chloro-4,6-dimethoxy-5-benzylamino-benzofuran-3-on)-2-spiro-1'-(2'-methoxy-6'-methyl-cyclohex-2'-ene-4'-one) **9**

¹H NMR (300 MHz, CDCl₃)

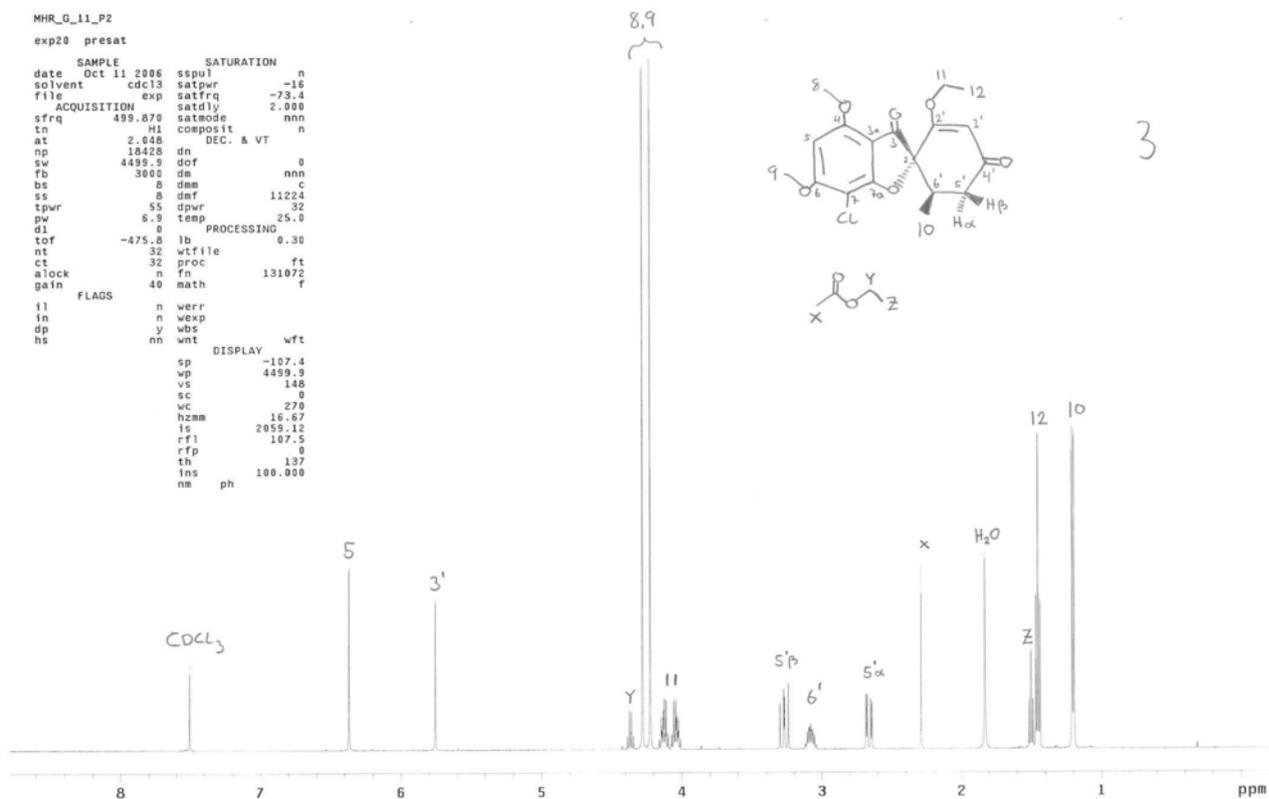


¹³C NMR (75 MHz, CDCl₃)

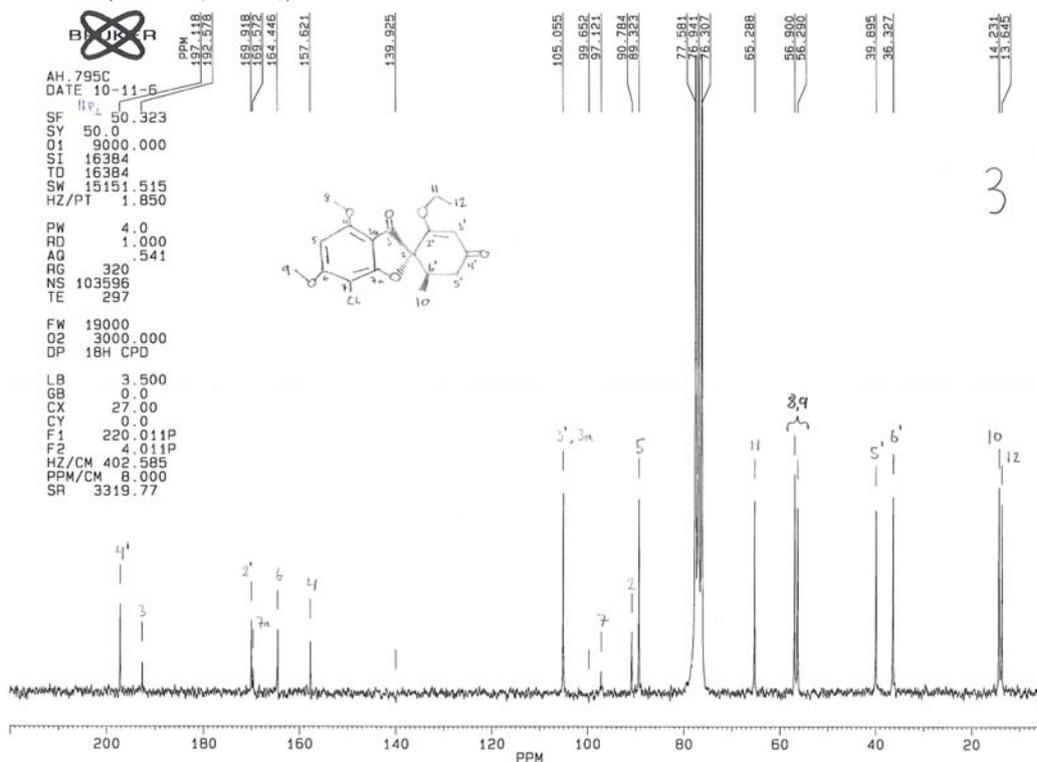


(2*S*,6'*R*)-(7-Chloro-4,6-dimethoxy-benzofuran-3-on)-2-spiro-1'-(2'-ethoxy-6'-methyl-cyclohex-2'-en-4'-on) **10**

¹H NMR (500 MHz, CDCl₃)



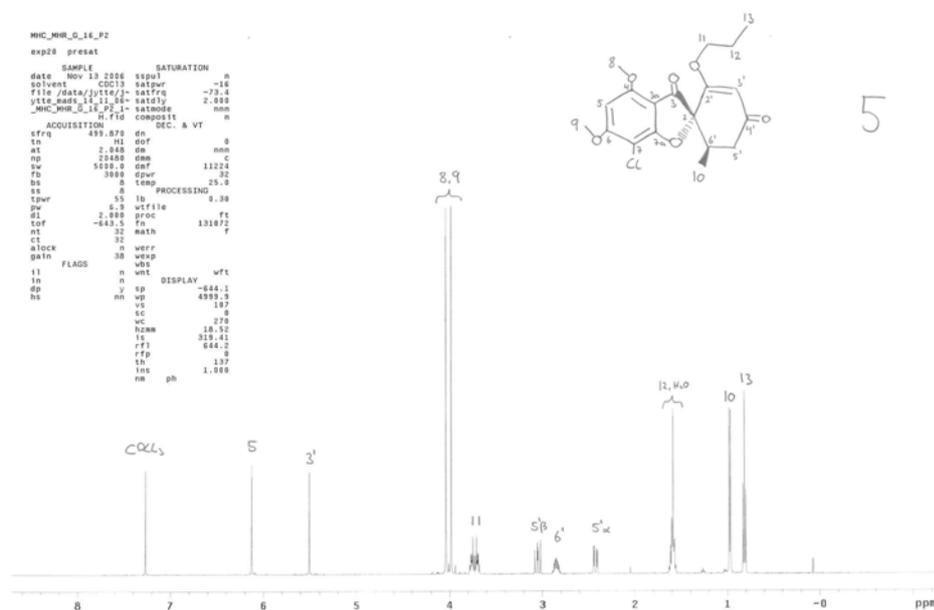
¹³C NMR (50 MHz, CDCl₃)



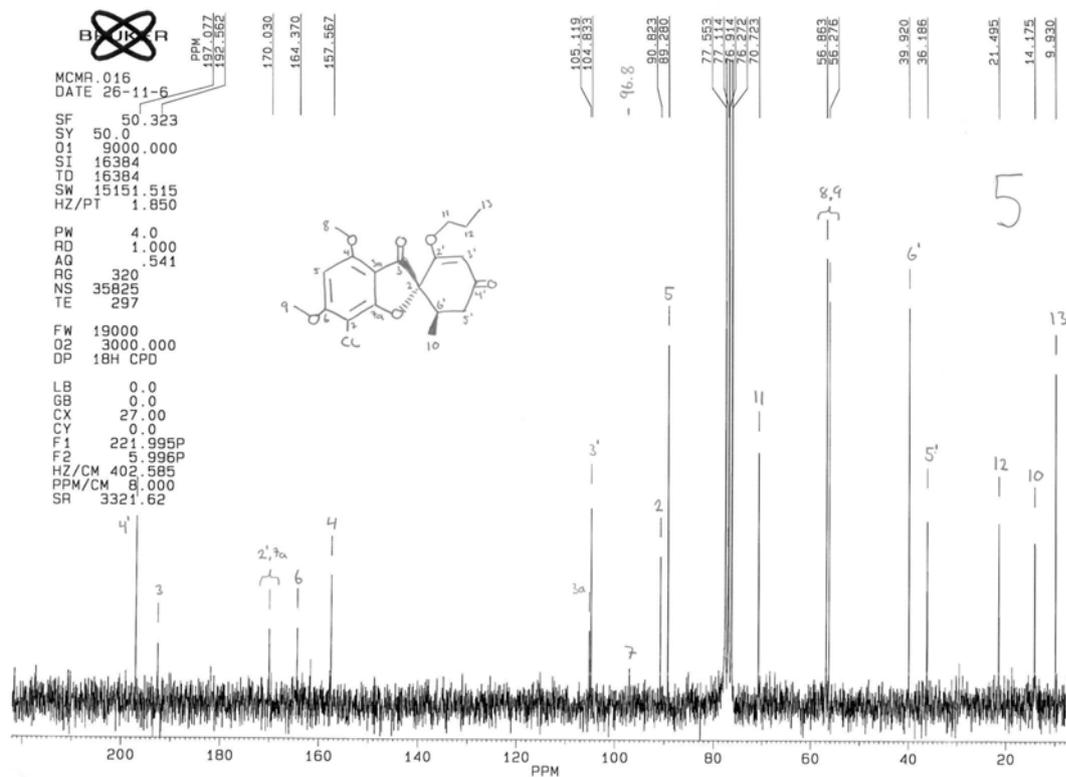
(2*S*,6'*R*)-(7-Chloro-4,6-dimethoxy-benzofuran-3-on)-2-spiro-1'-(6'-methyl-2'-propoxy-cyclohex-2'-en-4'-on)

11

¹H NMR (500 MHz, CDCl₃)

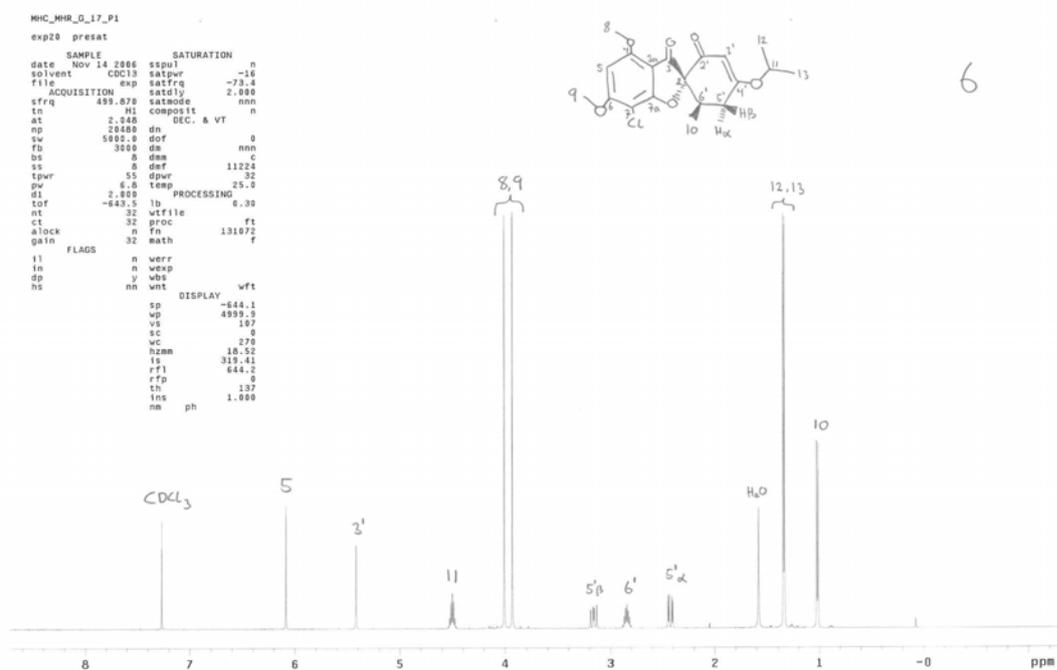


¹³C NMR (50 MHz, CDCl₃)

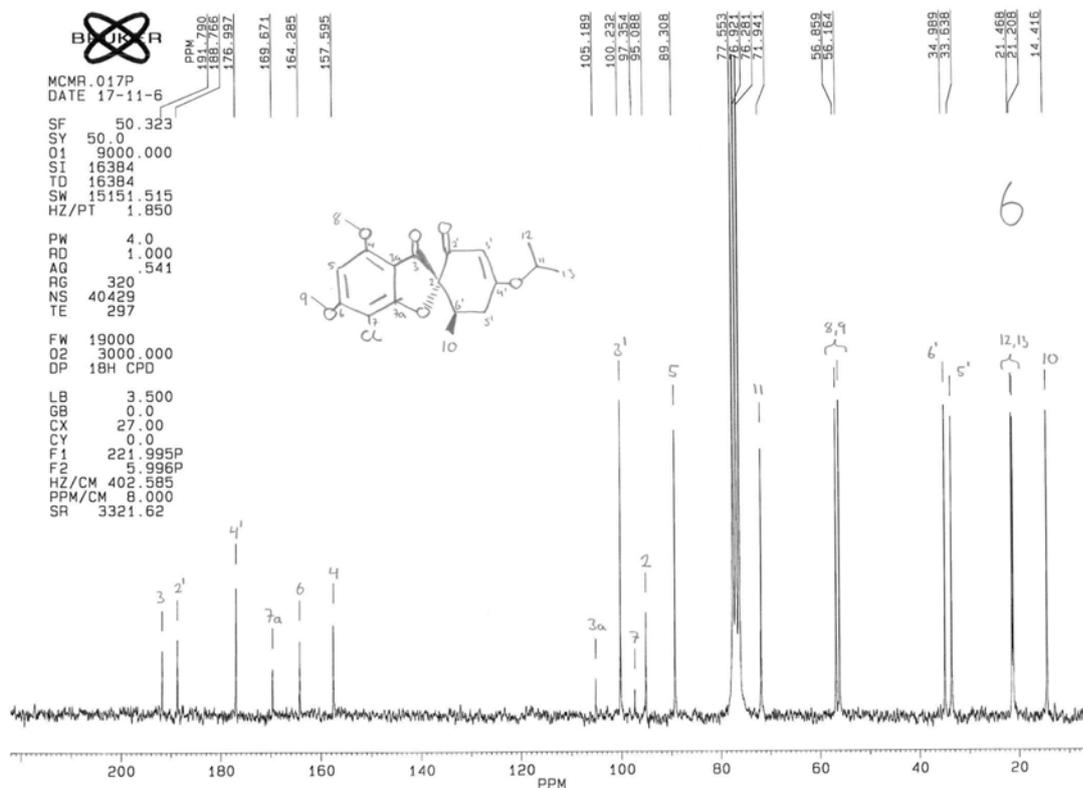


(2*S*,6'*R*)-(7-Chloro-4,6-dimethoxy-benzofuran-3-on)-2-spiro-1'-(2'-isopropoxy-6'-methyl-cyclohex-2'-en-4'-on) **12**

¹H NMR (500 MHz, CDCl₃)



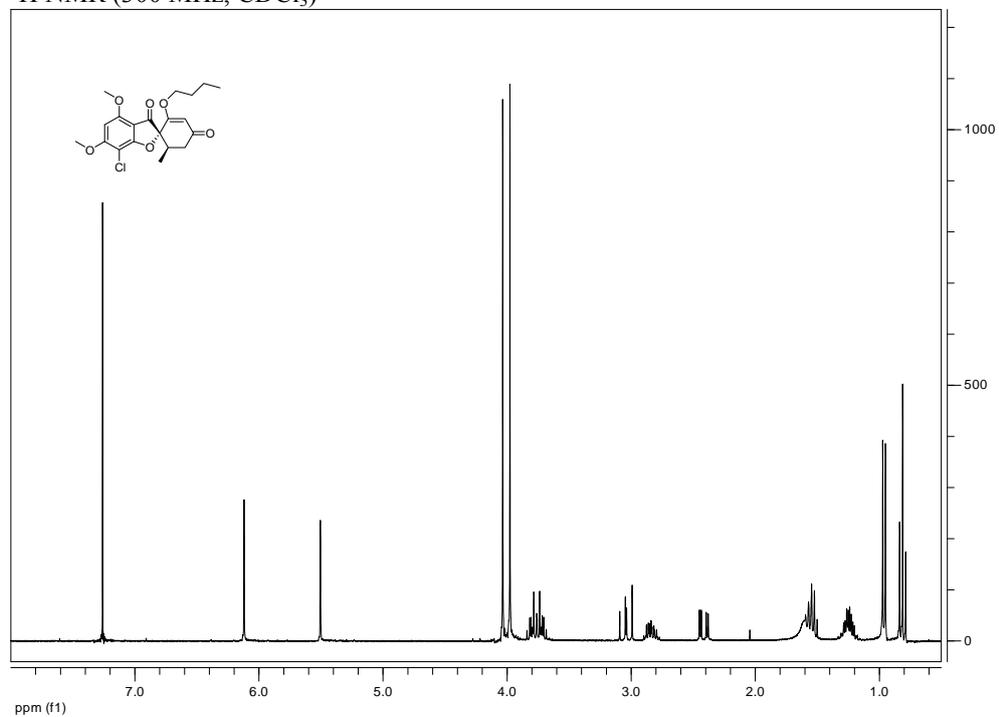
¹³C NMR (50 MHz, CDCl₃)



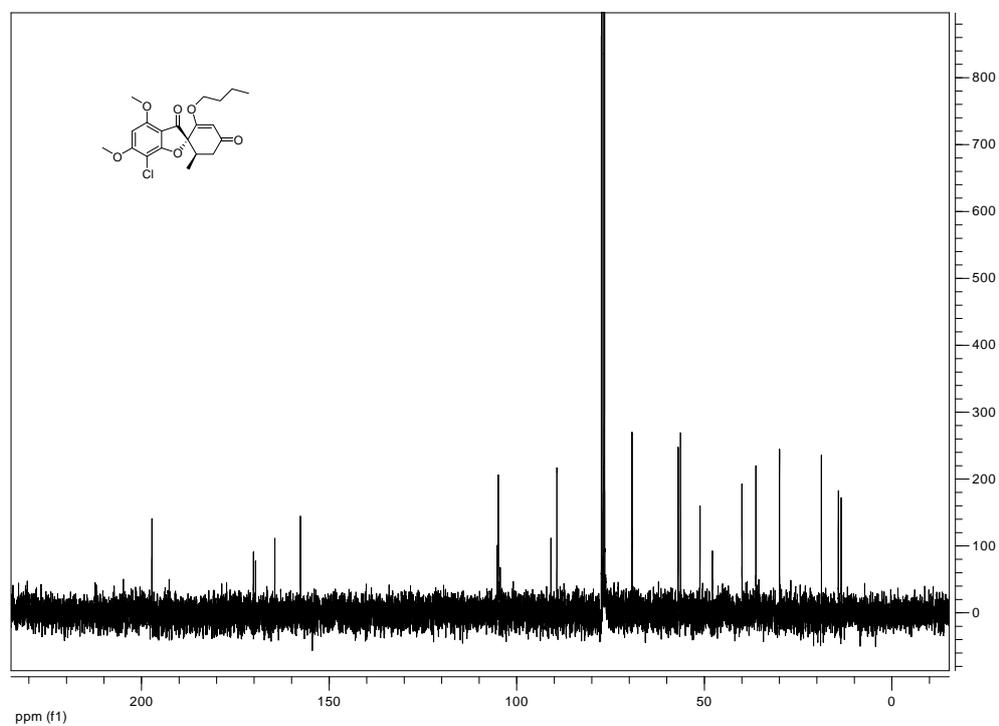
(2*S*,6'*R*)-(7-Chloro-4,6-dimethoxy-benzofuran-3-one)-2-spiro-1'-(2'-butoxy-6'-methyl-cyclohex-2'-ene-4'-one)

13

¹H NMR (300 MHz, CDCl₃)

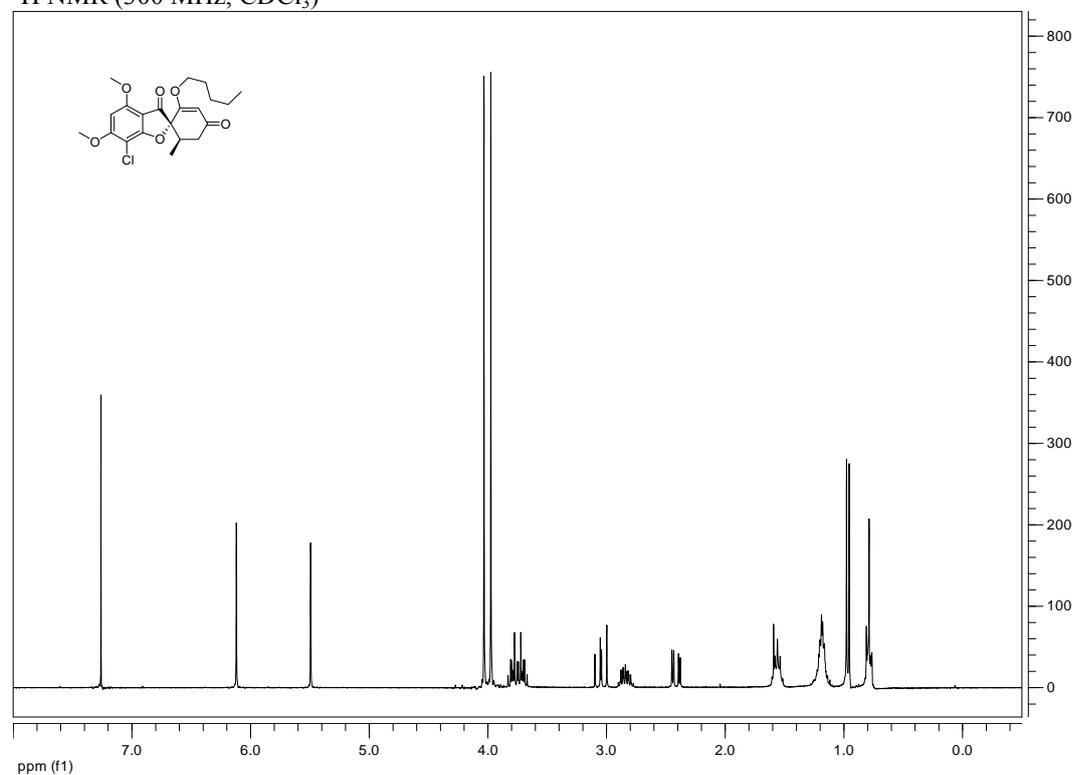


¹³C NMR (75 MHz, CDCl₃)

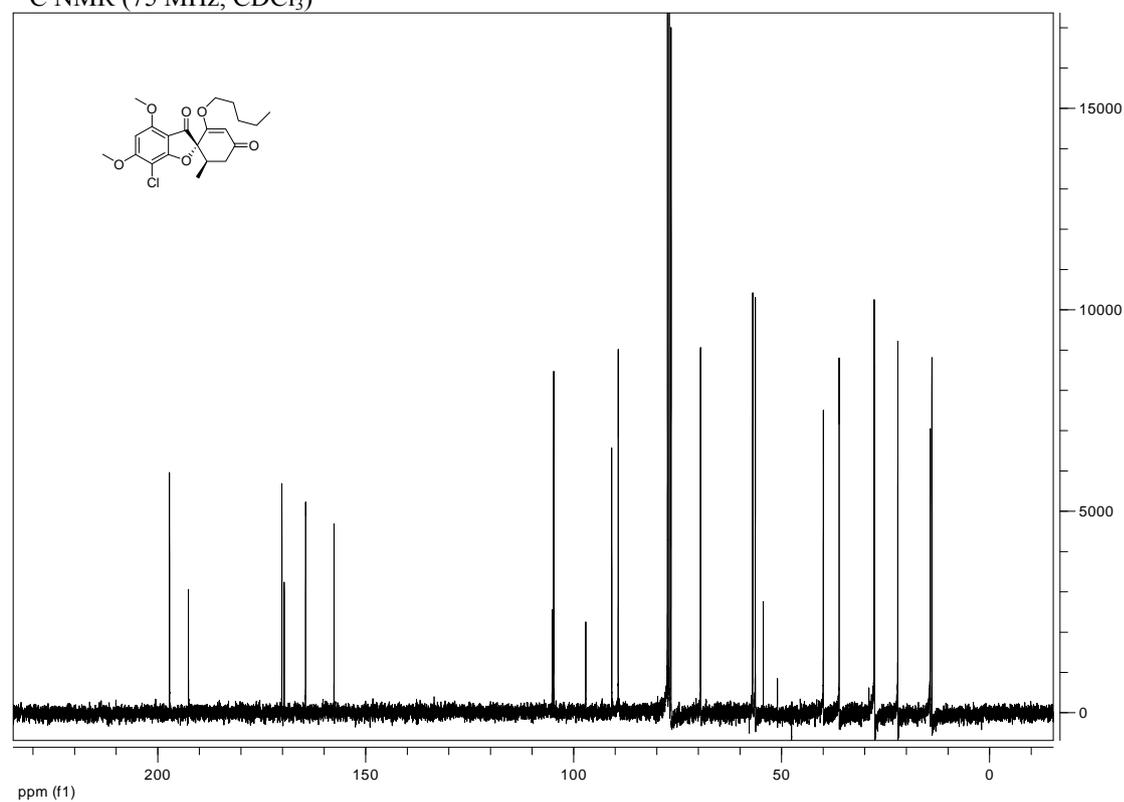


(2*S*,6'*R*')-(7-Chloro-4,6-dimethoxy-benzofuran-3-one)-2-spiro-1'-(6'-methyl-2'-pentoxy-cyclohex-2'-ene-4'-one) **14**

$^1\text{H NMR}$ (300 MHz, CDCl_3)



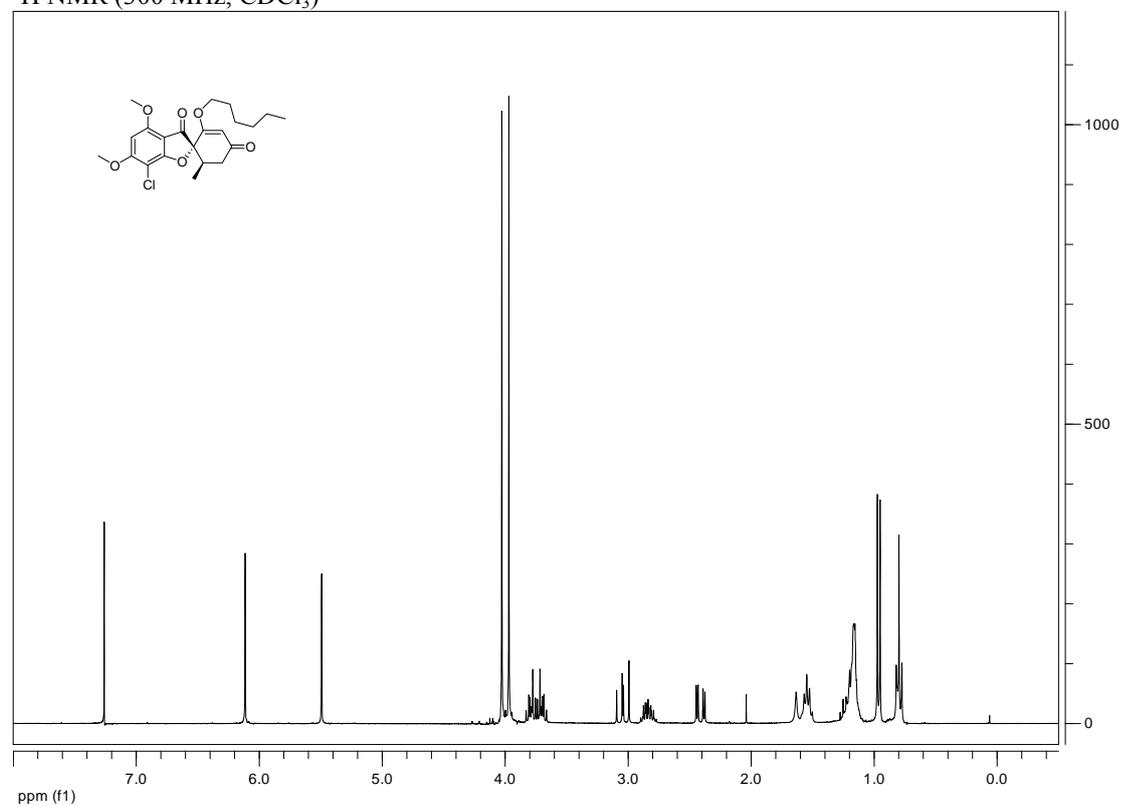
$^{13}\text{C NMR}$ (75 MHz, CDCl_3)



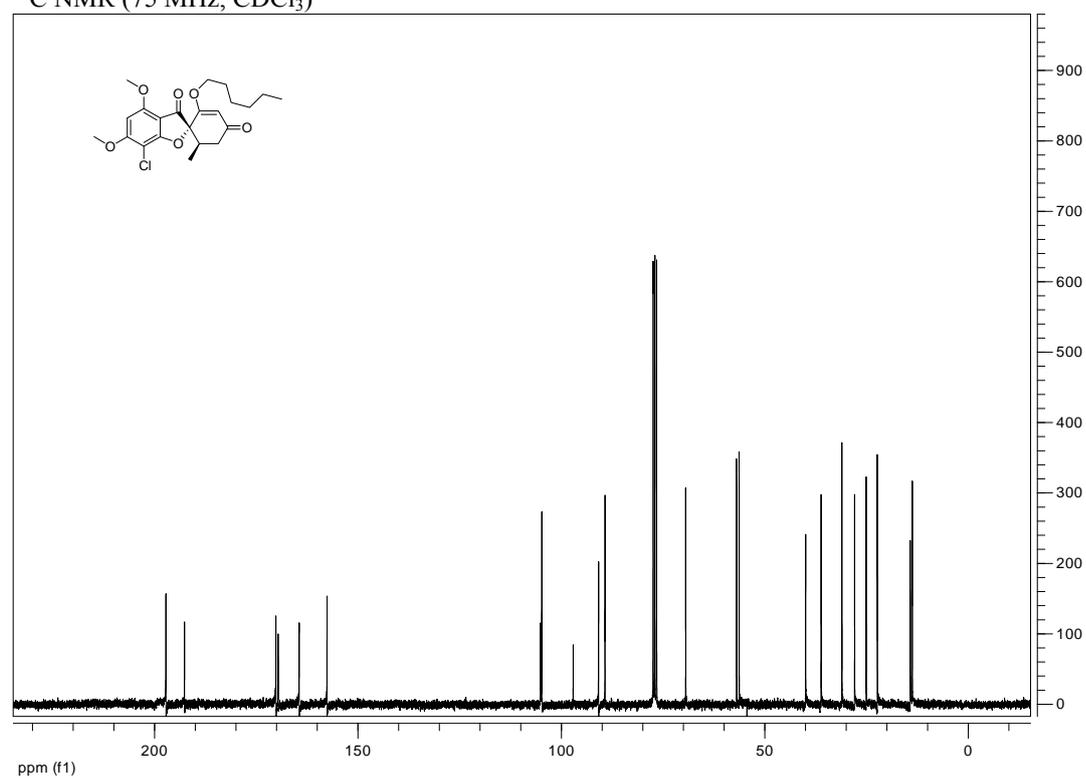
(2*S*,6'*R*)-(7-Chloro-4,6-dimethoxy-benzofuran-3-one)-2-spiro-1'-(2'-hexoxy-6'-methyl-cyclohex-2'-ene-4'-one)

15

¹H NMR (300 MHz, CDCl₃)

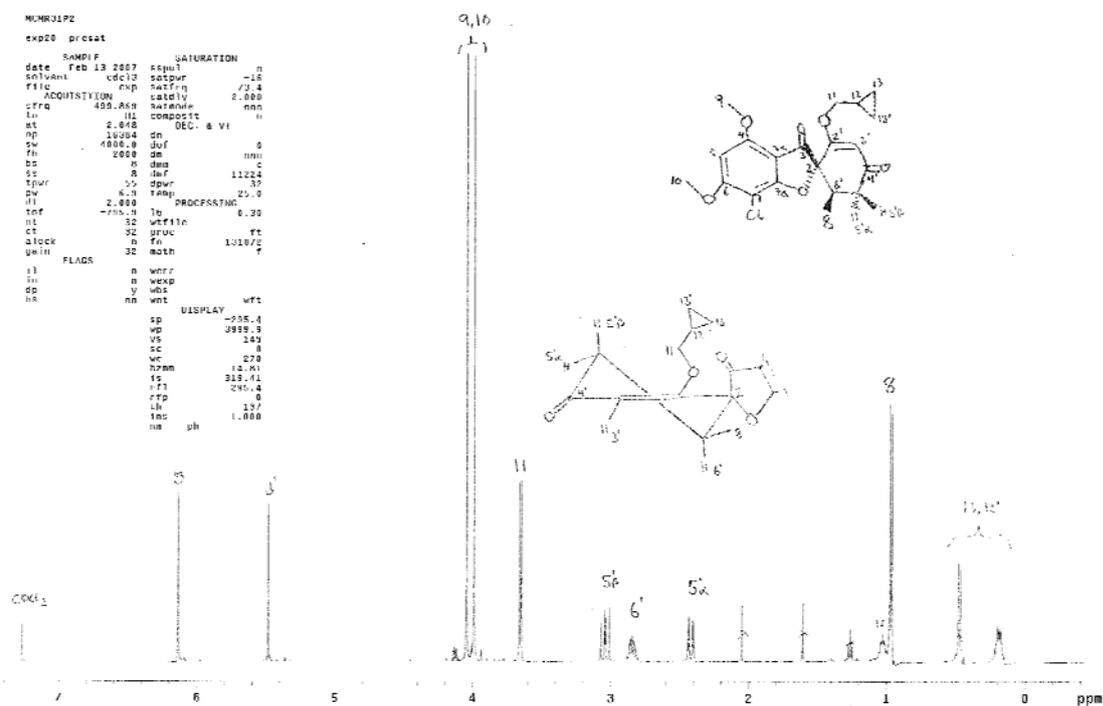


¹³C NMR (75 MHz, CDCl₃)

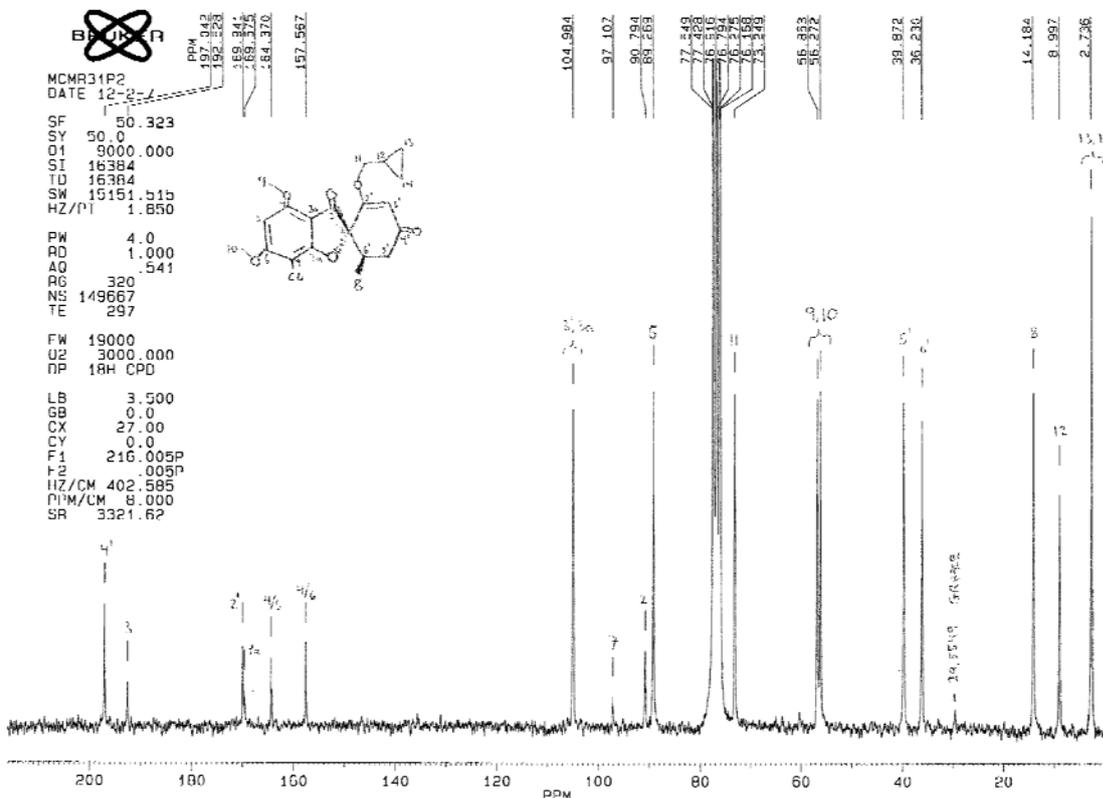


(2*S*,6'*R*)-(7-Chloro-4,6-dimethoxy-benzofuran-3-on)-2-spiro-1'-(2'-cyclopropylmethoxy-6'-methyl-cyclohex-2'-en-4'-one) **16**

¹H NMR (500 MHz, CDCl₃)



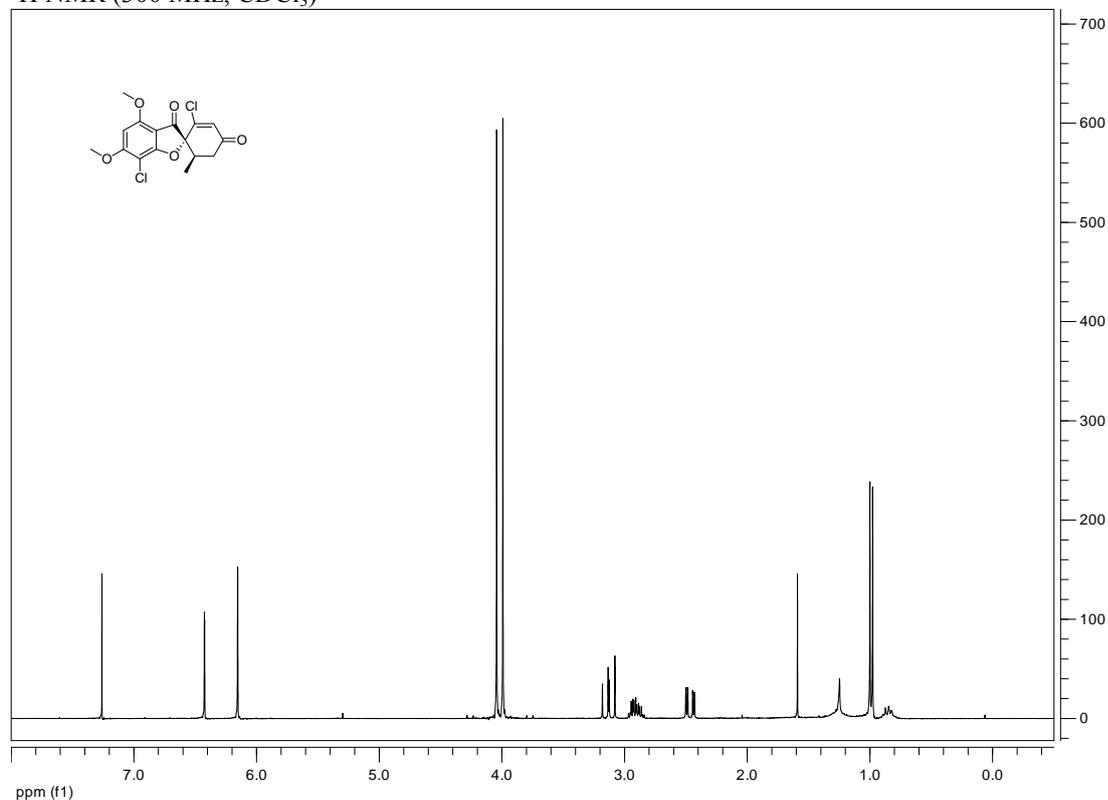
¹³C NMR (50 MHz, CDCl₃)



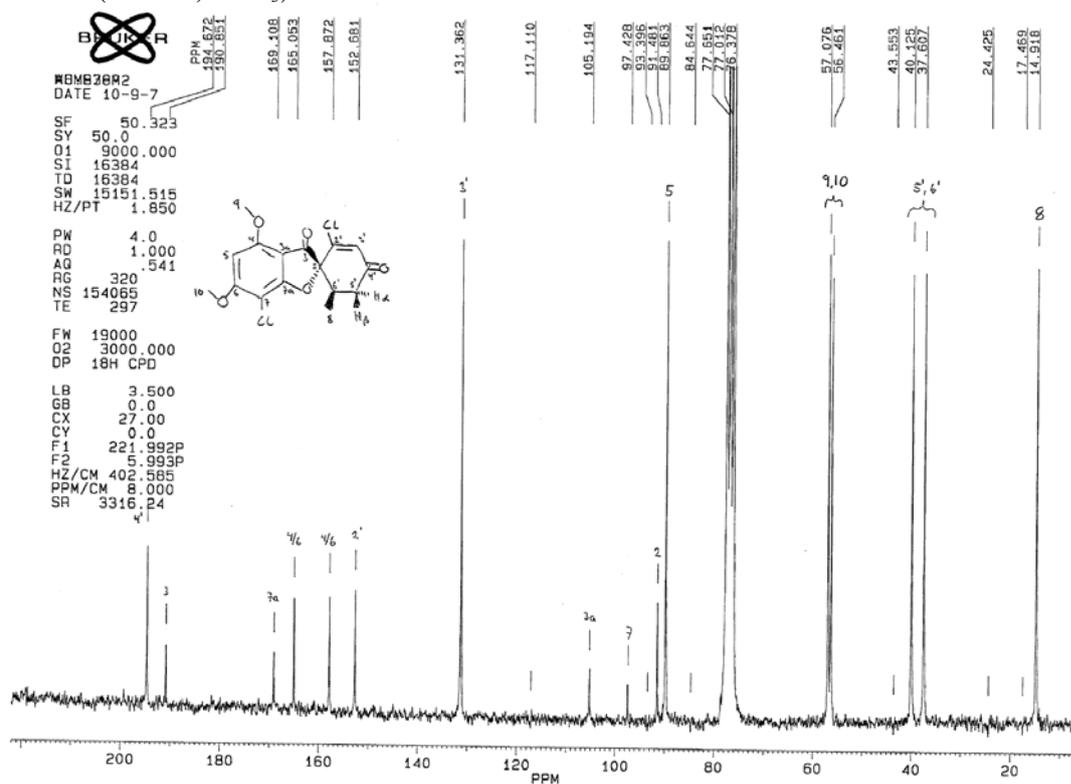
(2*S*,6'*R*)-(7-Chloro-4,6-dimethoxy-benzofuran-3-one)-2-spiro-1'-(2'-chloro-6'-methyl-cyclohex-2'-ene-4'-one)

18

¹H NMR (300 MHz, CDCl₃)

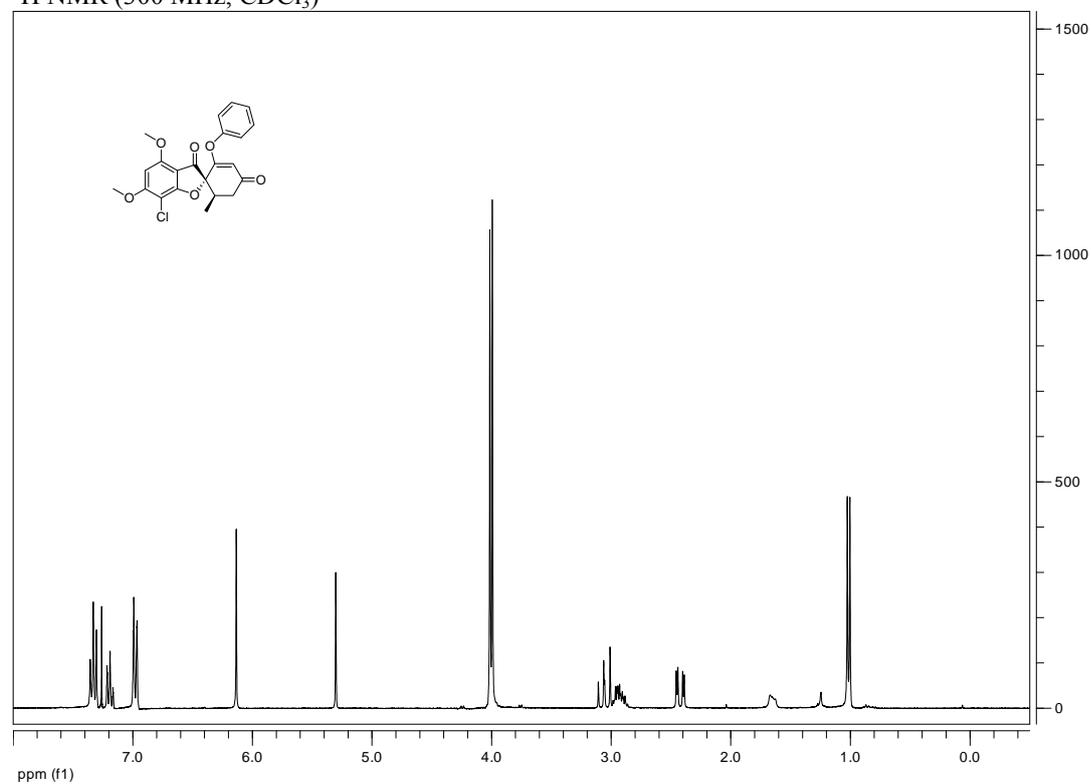


¹³C NMR (50 MHz, CDCl₃)

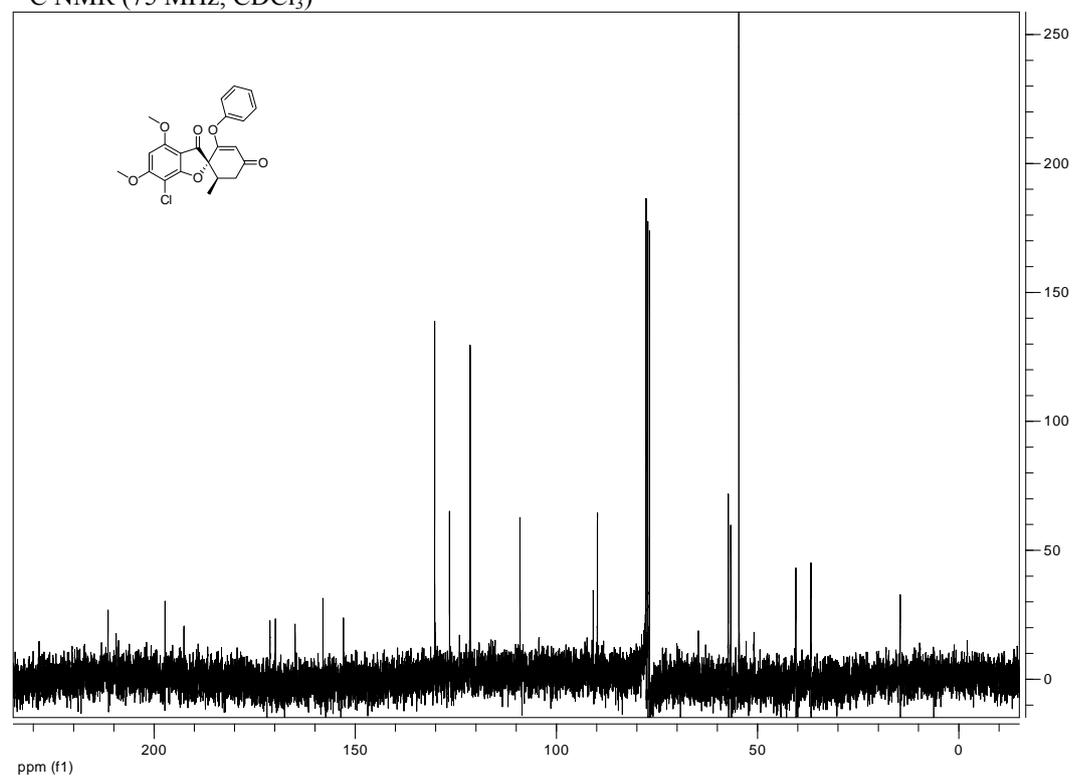


(2*S*,6'*R*)-(7-Chloro-4,6-dimethoxy-benzofuran-3-one)-2-spiro-1'-(6'-methyl-2'-phenoxy-cyclohex-2'-ene-4'-one) **19**

¹H NMR (300 MHz, CDCl₃)

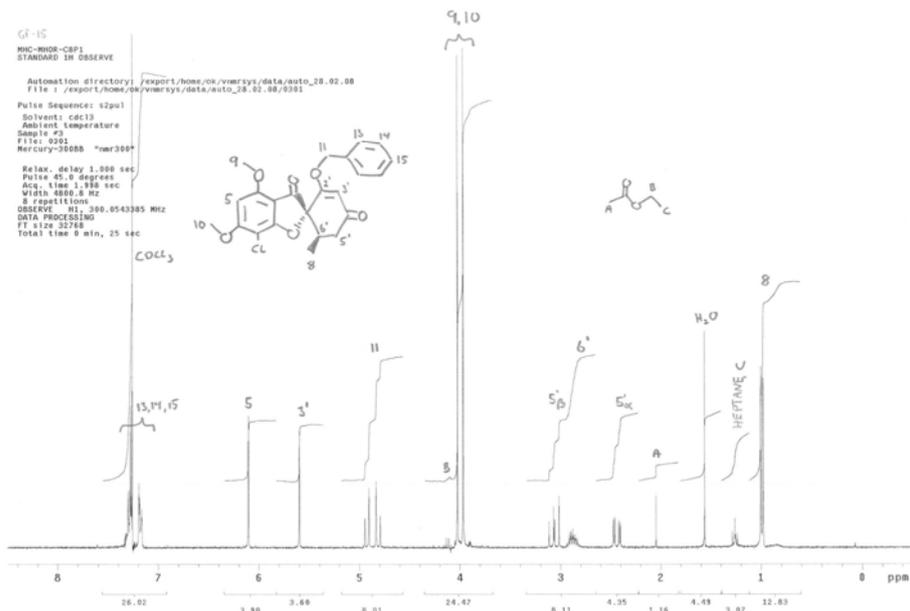


¹³C NMR (75 MHz, CDCl₃)

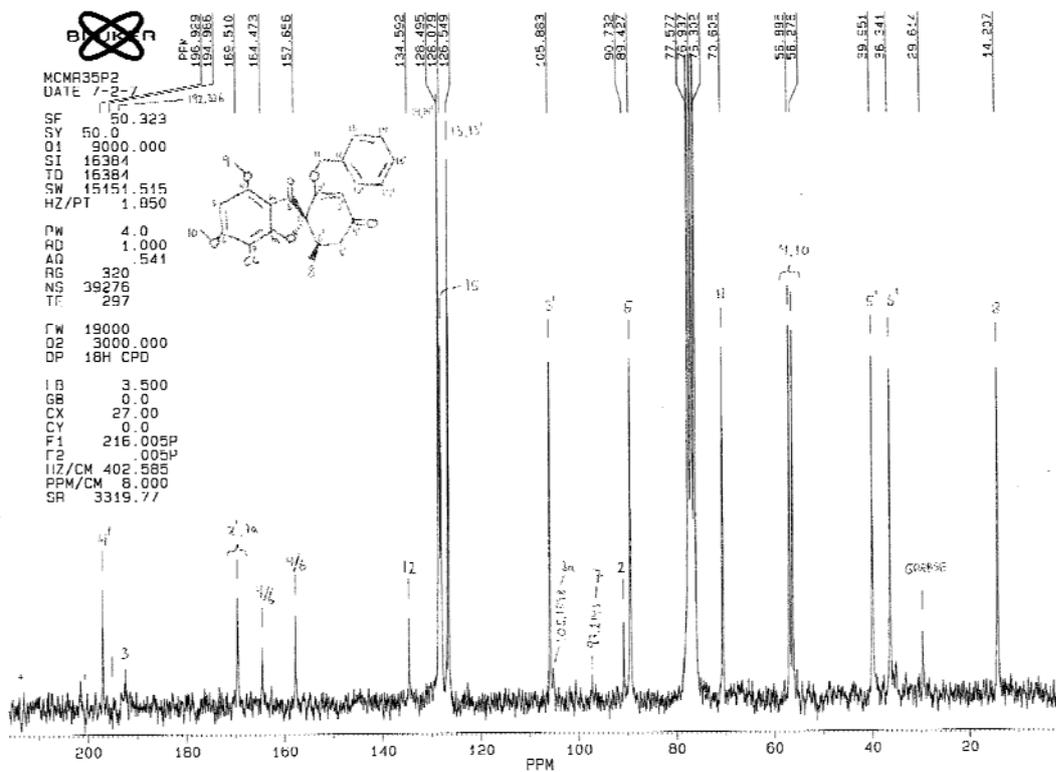


(2*S*,6'*R*)-(7-Chloro-4,6-dimethoxy-benzofuran-3-on)-2-spiro-1'-(2'-benzyloxy-6'-methyl-cyclohex-2'-en-4'-one) **20**

¹H NMR (300 MHz, CDCl₃)

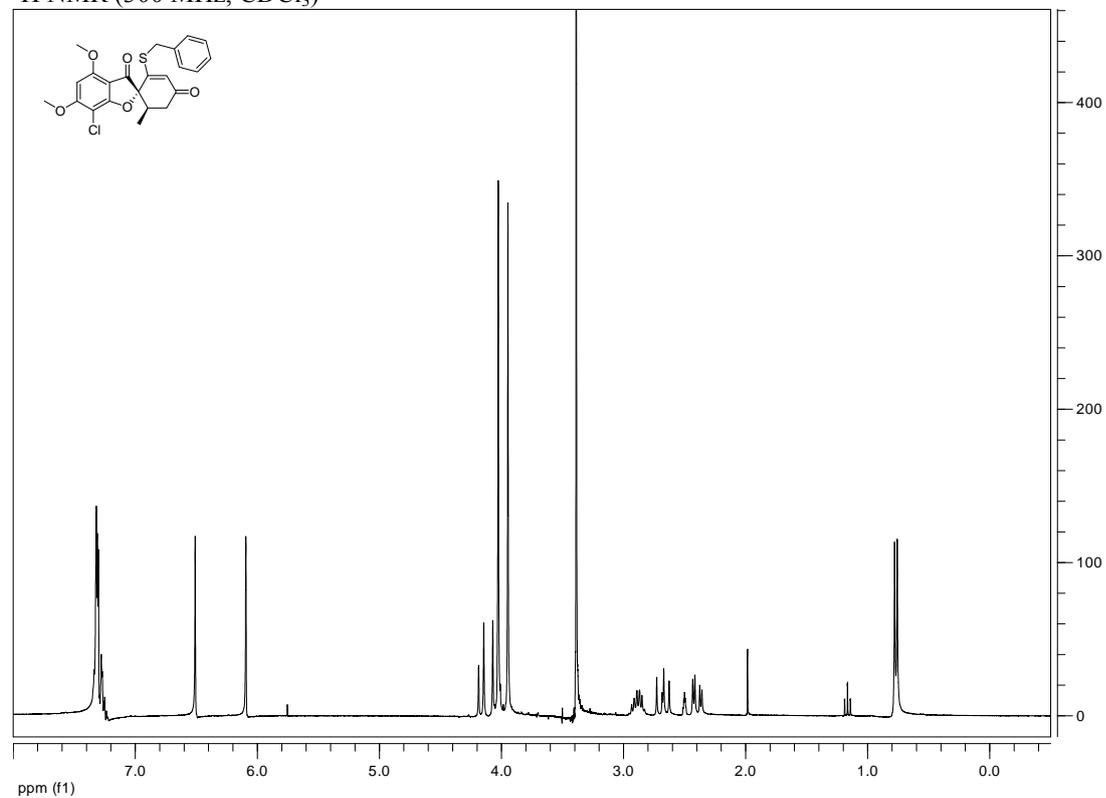


¹³C NMR (75 MHz, CDCl₃)

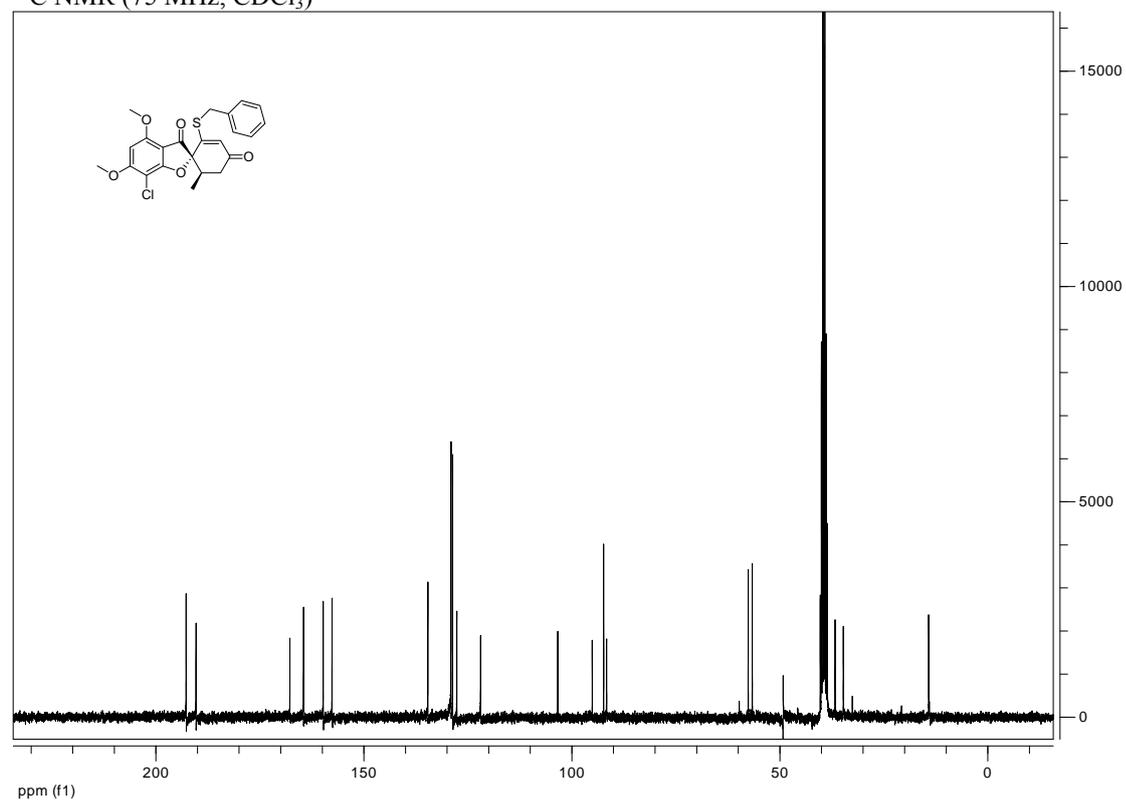


(2*S*,6'*R*)-(7-Chloro-4,6-dimethoxy-benzofuran-3-one)-2-spiro-1'-(2'-benzylthio-6'-methyl-cyclohex-2'-ene-4'-one) **21**

¹H NMR (300 MHz, CDCl₃)

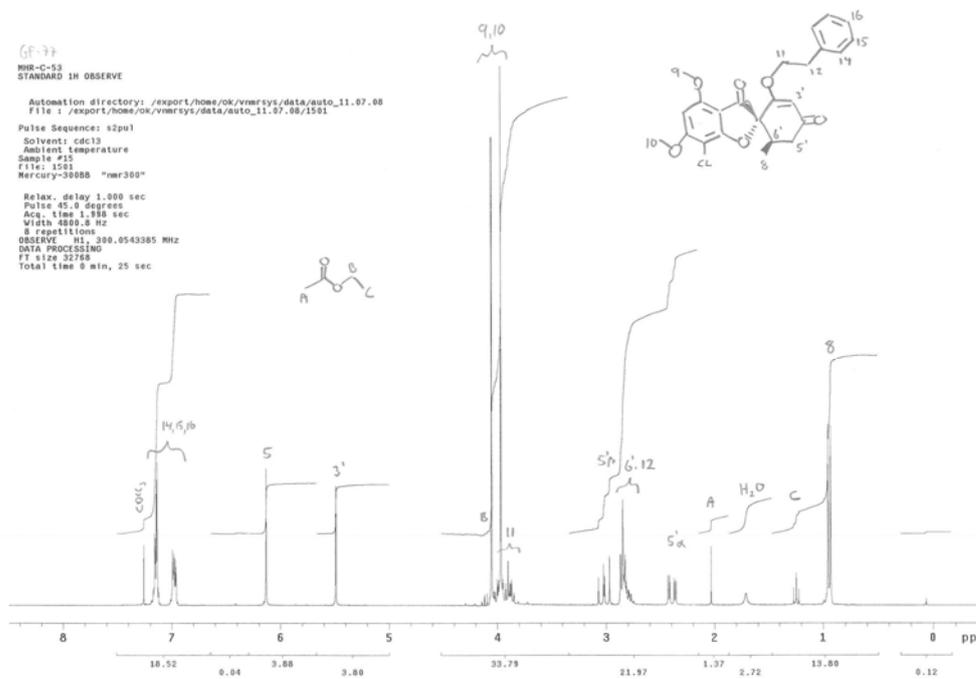


¹³C NMR (75 MHz, CDCl₃)

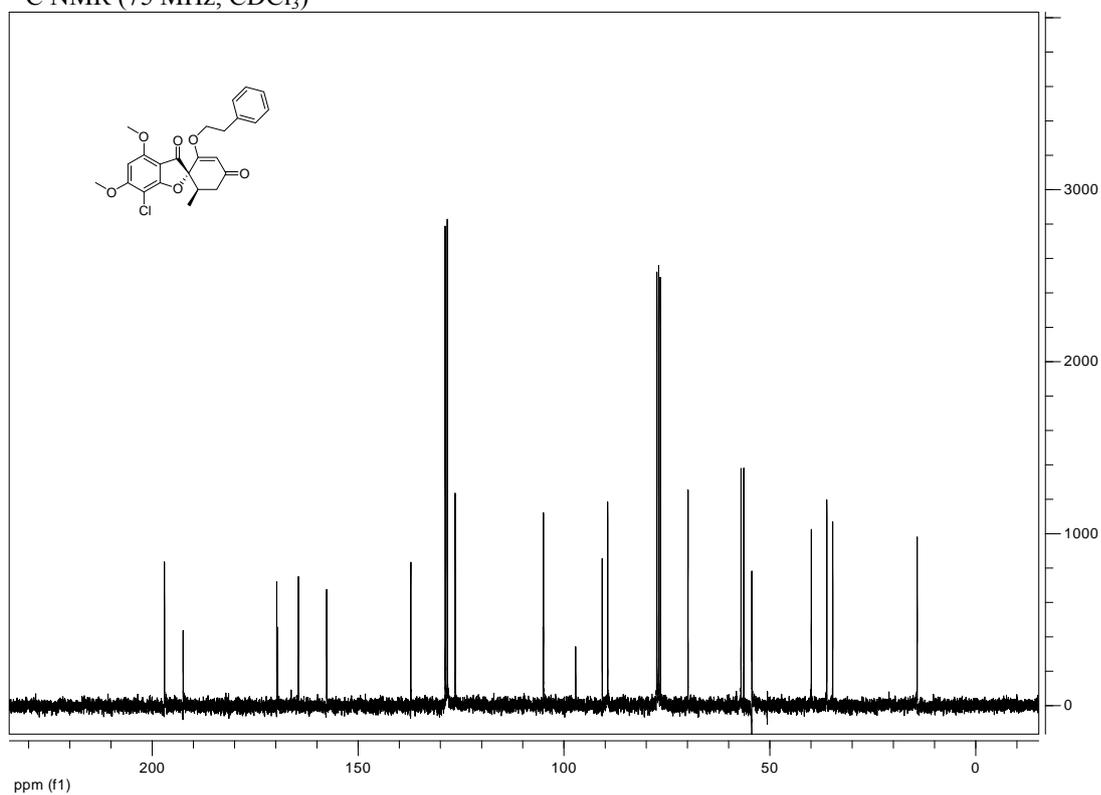


(2*S*,6'*R*)-(7-Chloro-4,6-dimethoxy-benzofuran-3-on)-2-spiro-1'-(2'-(2-phenylethoxy)-6'-methyl-cyclohex-2'-en-4'-one) **22**

¹H NMR (300 MHz, CDCl₃)

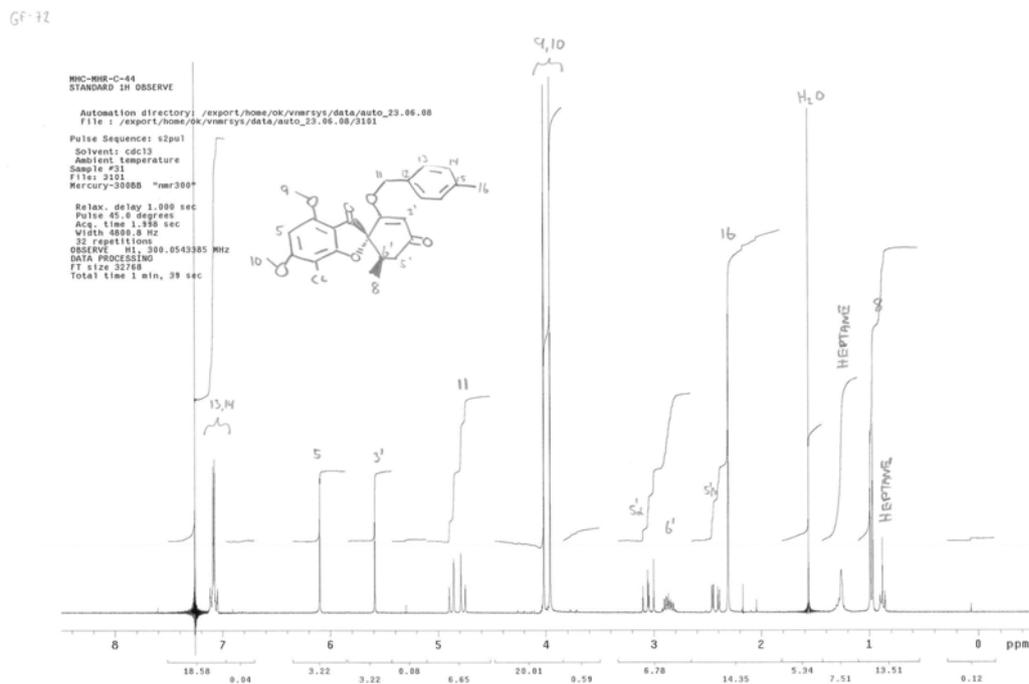


¹³C NMR (75 MHz, CDCl₃)

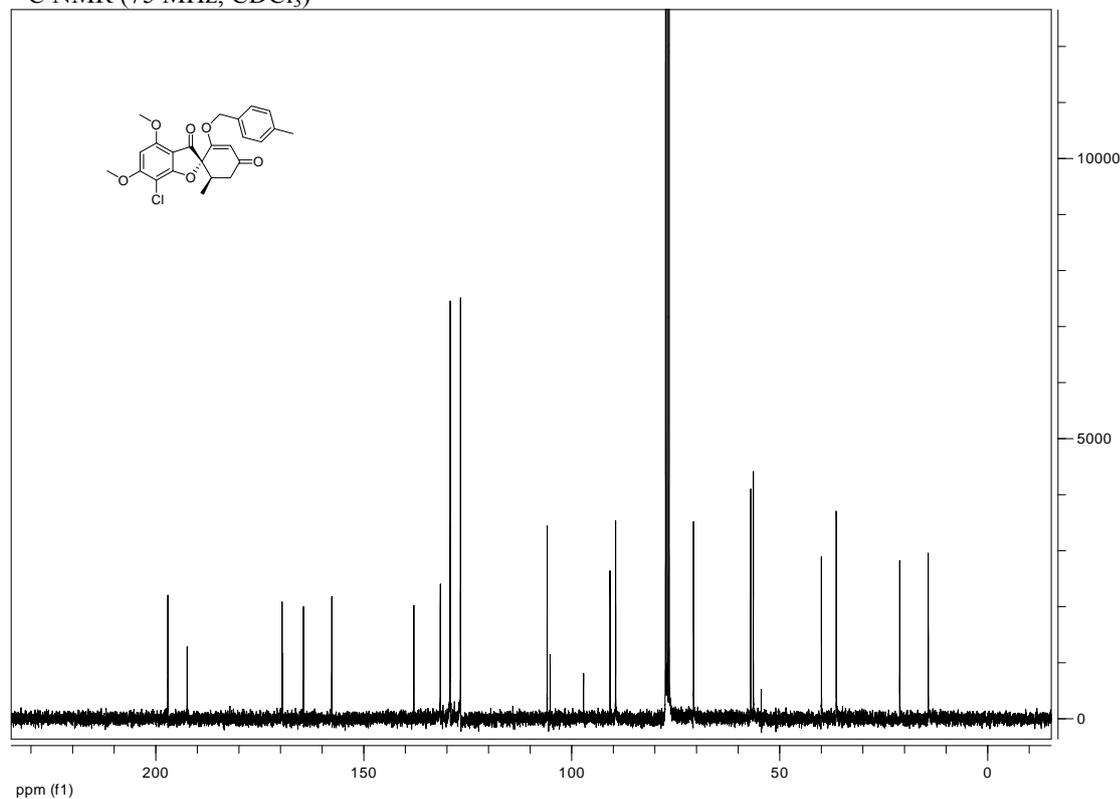


(2*S*,6'*R*)-(7-Chloro-4,6-dimethoxy-benzofuran-3-one)-2-spiro-1'-(2'-4-methylbenzyloxy-6'-methyl-cyclohex-2'-ene-4'-one) **23**

¹H NMR (300 MHz, CDCl₃)



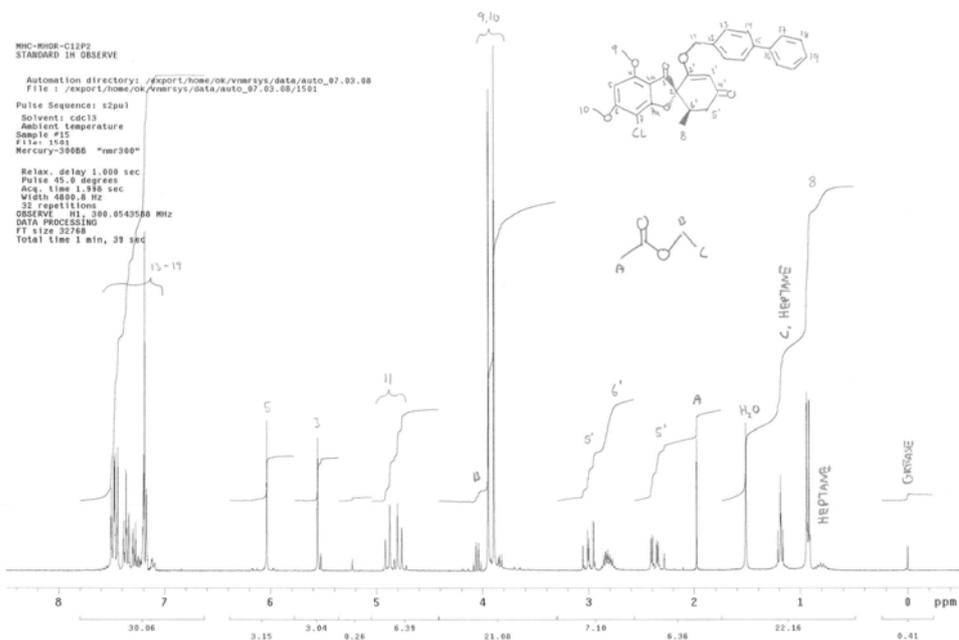
¹³C NMR (75 MHz, CDCl₃)



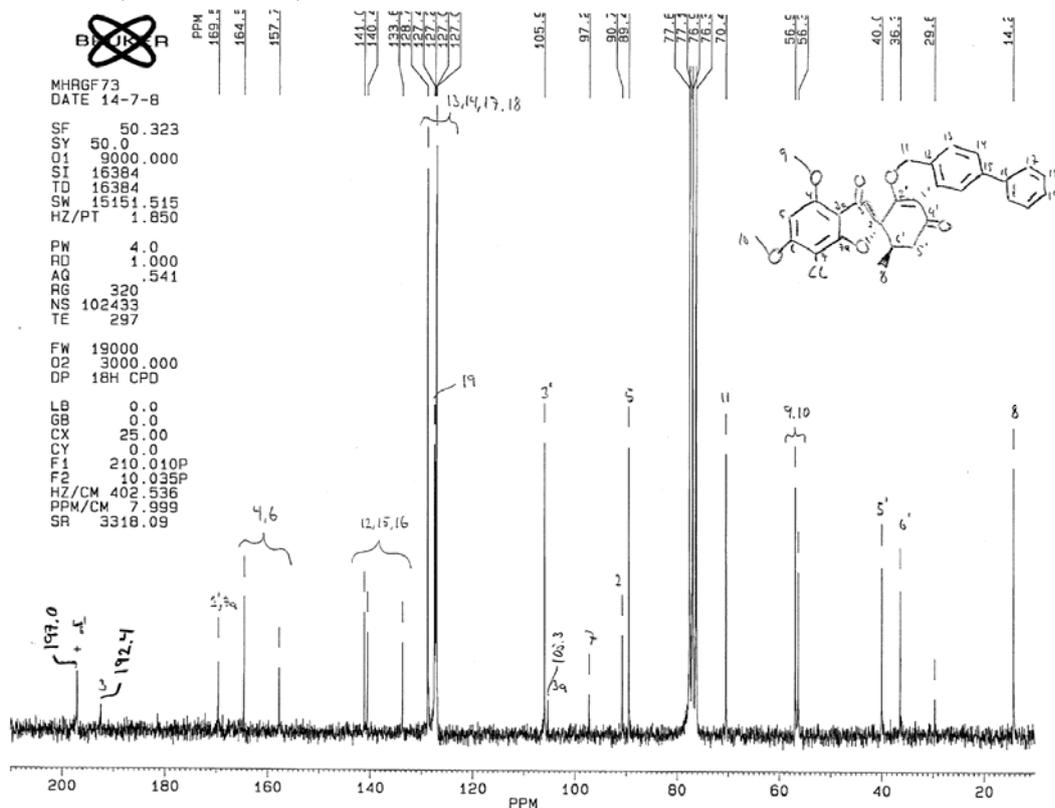
(2*S*,6'*R*)-(7-Chloro-4,6-dimethoxy-benzofuran-3-one)-2-spiro-1'-(2'-(4-biphenylmethoxy)-6'-methyl-cyclohex-2'-ene-4'-one) **24**

¹H NMR (300 MHz, CDCl₃)

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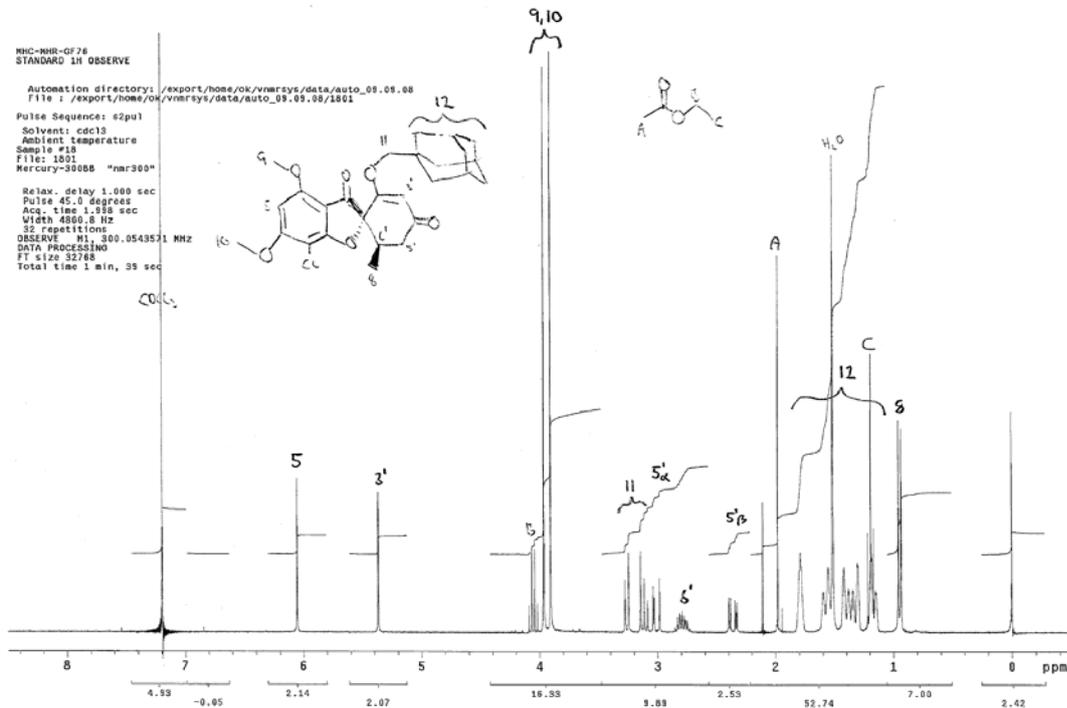


¹³C NMR (75 MHz, CDCl₃)

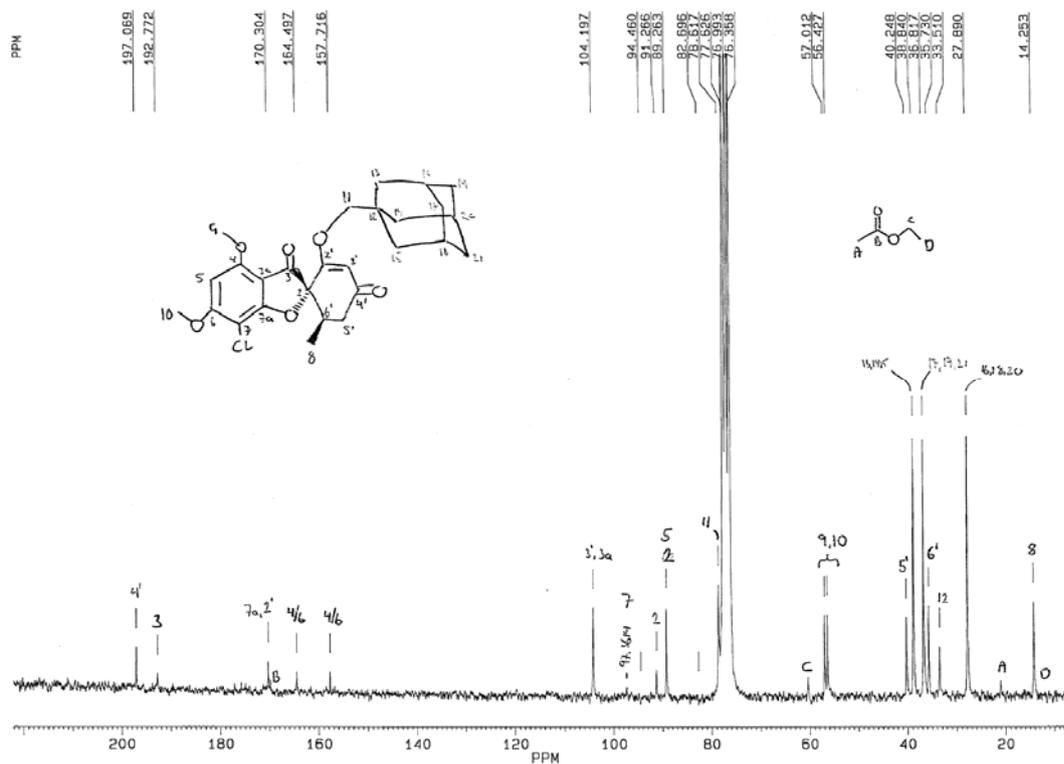


(2*S*,6'*R*)-(7-Chloro-4,6-dimethoxy-benzofuran-3-one)-2-spiro-1'-(2'-(1-adamantylmethoxy)-6'-methyl-cyclohex-2'-ene-4'-one) **25**

¹H NMR (300 MHz, CDCl₃)



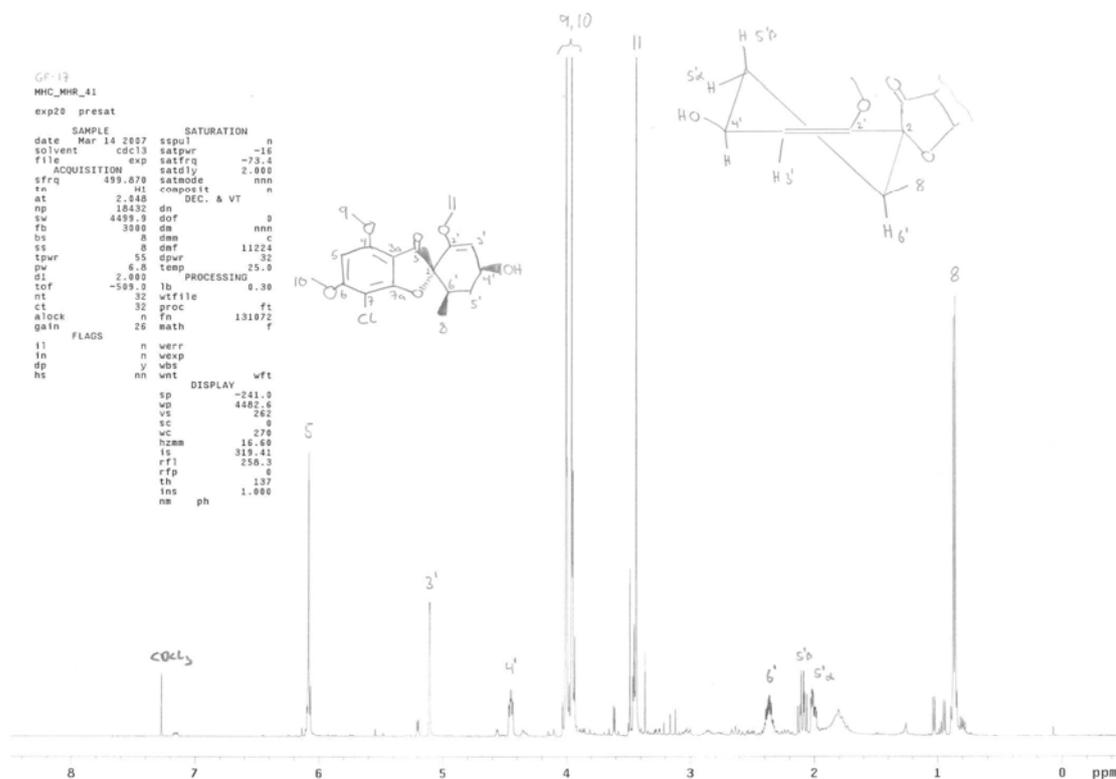
¹³C NMR (50 MHz, CDCl₃)



(2*S*,6'*R*)-(7-Chloro-4,6-dimethoxy-benzofuran-3-on)-2-spiro-1'-(2'-methoxy-6'-methyl-cyclohex-2'-en-4'-ol)

26

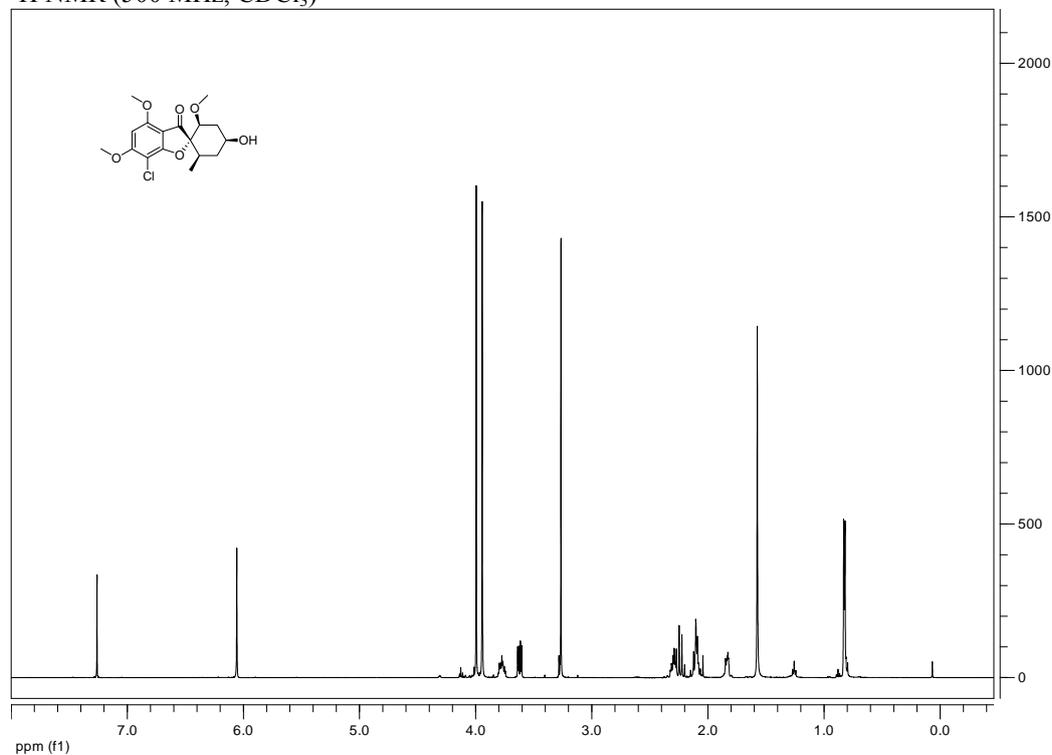
¹H NMR (300 MHz, CDCl₃)



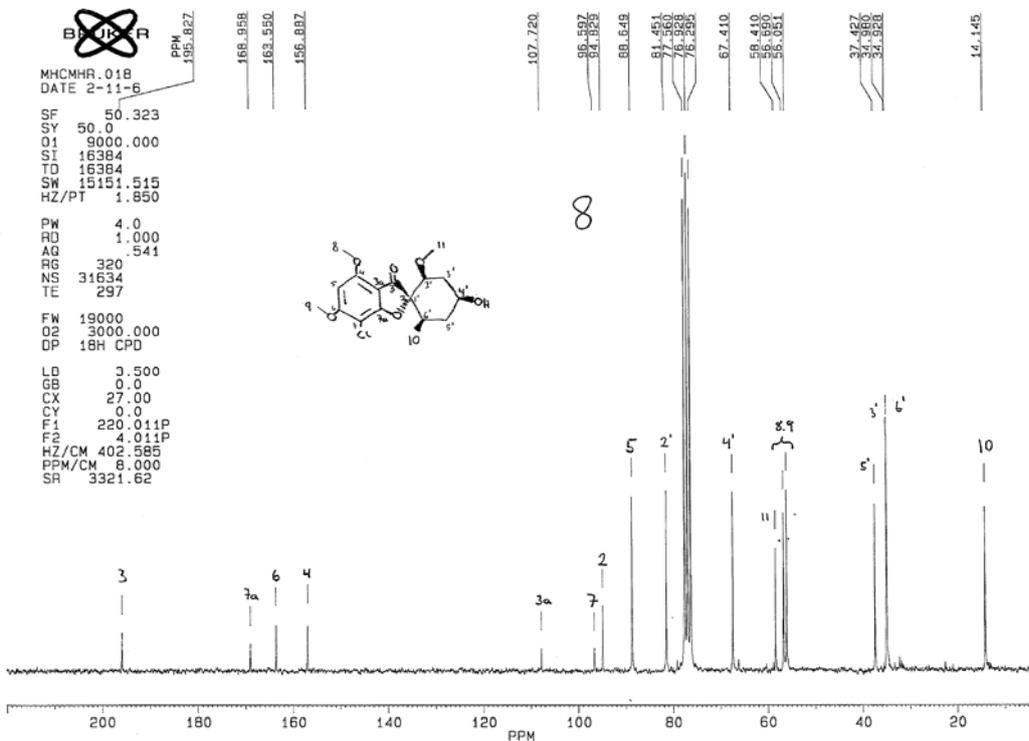
Carbon shifts from gHSQC, gHMBC

(2*S*,2'*S*,4'*S*,6'*R*)-(7-Chloro-4,6-dimethoxy-benzofuran-3-on)-2-spiro-1'-(2'-methoxy-6'-methyl-cyclohexan-4'-ol) **27**

¹H NMR (500 MHz, CDCl₃)

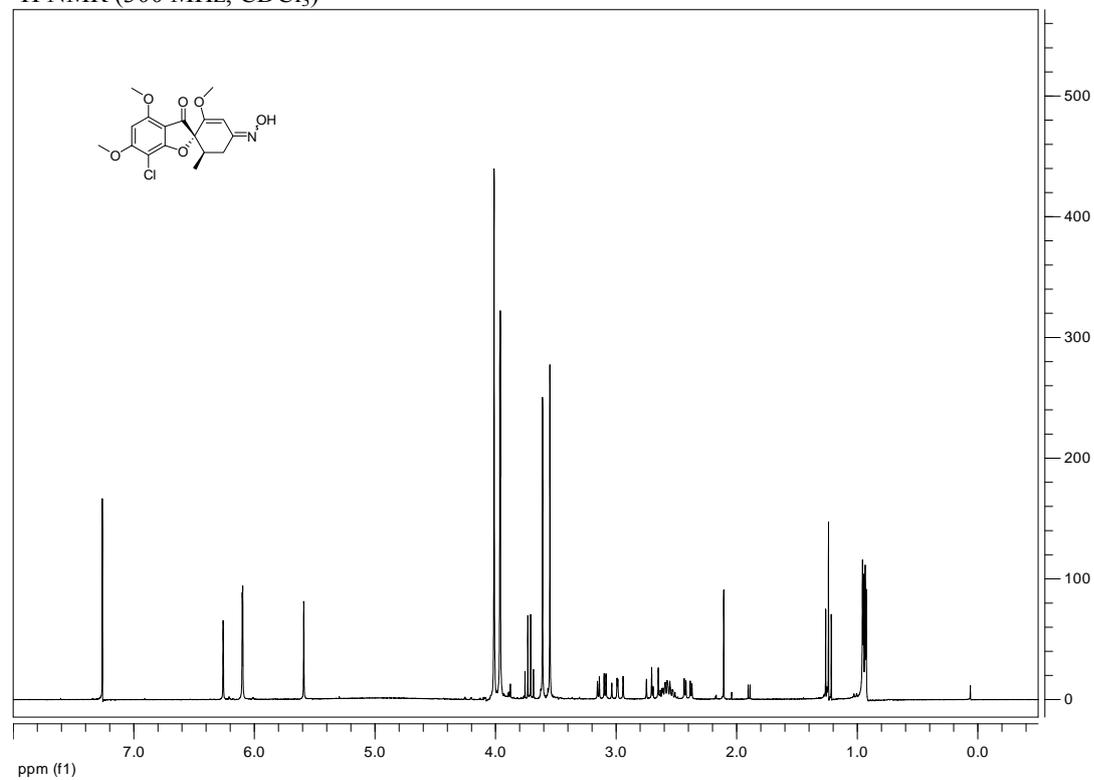


¹³C NMR (50 MHz, CDCl₃)

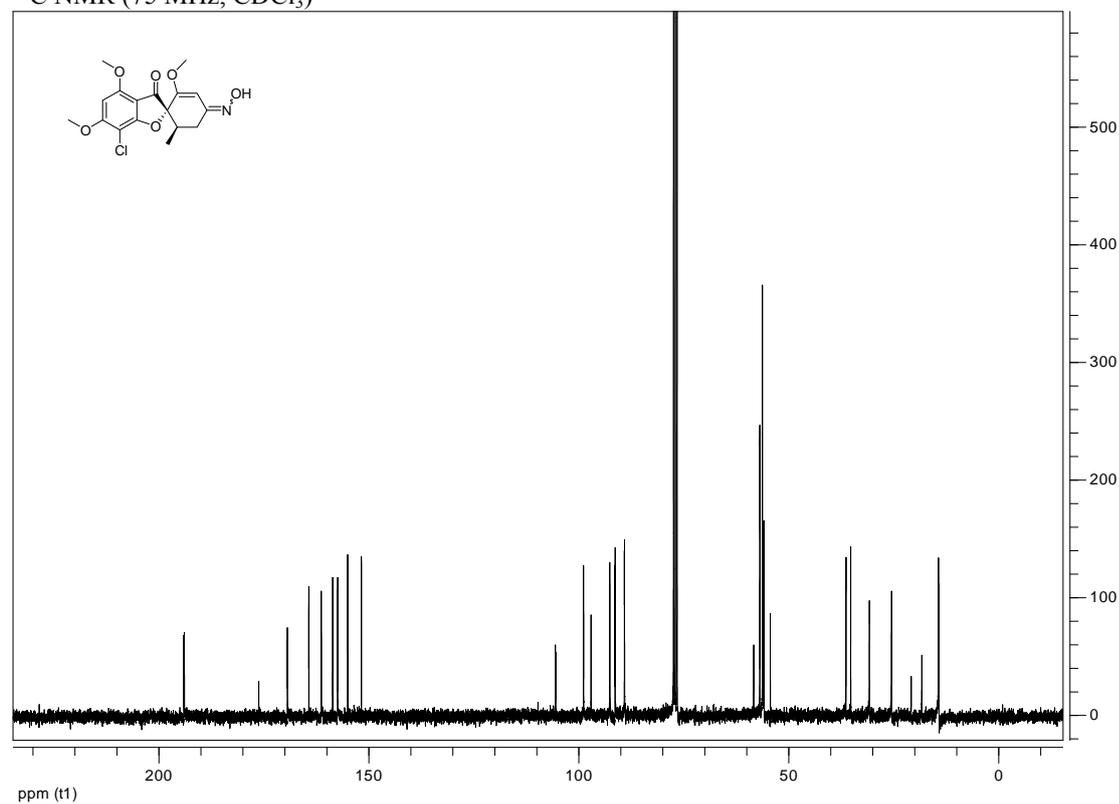


(2*S*,6'*R*)-(7-Chloro-4,6-dimethoxy-benzofuran-3-one)-2-spiro-1'-(2'-methoxy-6'-methyl-cyclohex-2'-ene-4'-one-4'-oxime) **28**

¹H NMR (300 MHz, CDCl₃)

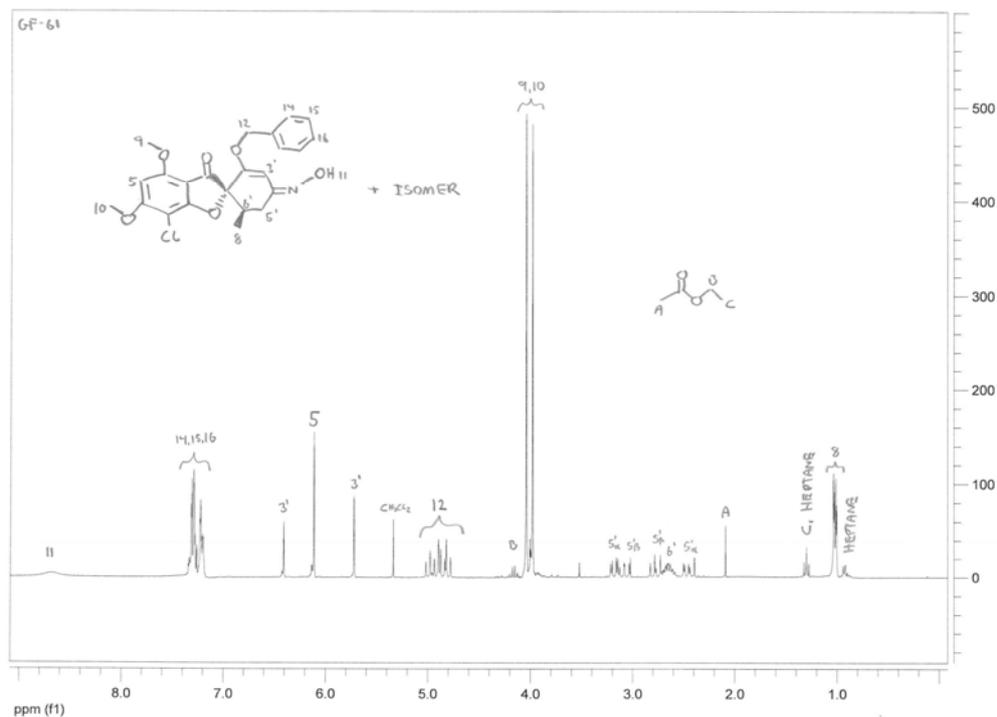


¹³C NMR (75 MHz, CDCl₃)

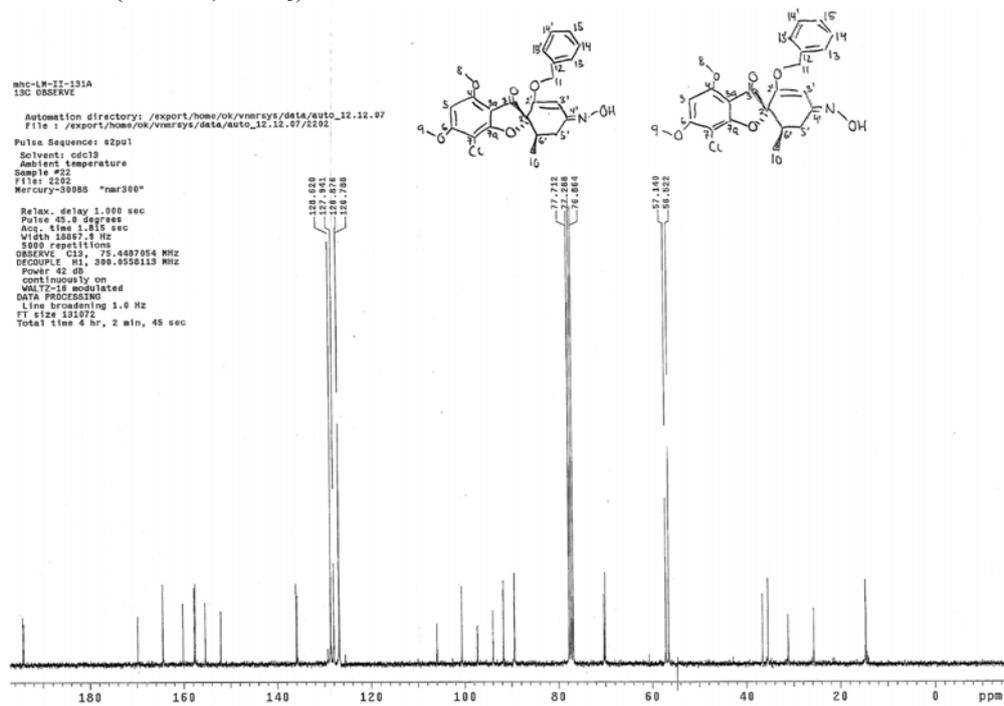


(2*S*,6'*R*)-(7-Chloro-4,6-dimethoxy-benzofuran-3-one)-2-spiro-1'-(2'-benzyloxy-6'-methylcyclohex-2'-ene-4'-one-4'-oxime) **29**

¹H NMR (300 MHz, CDCl₃)

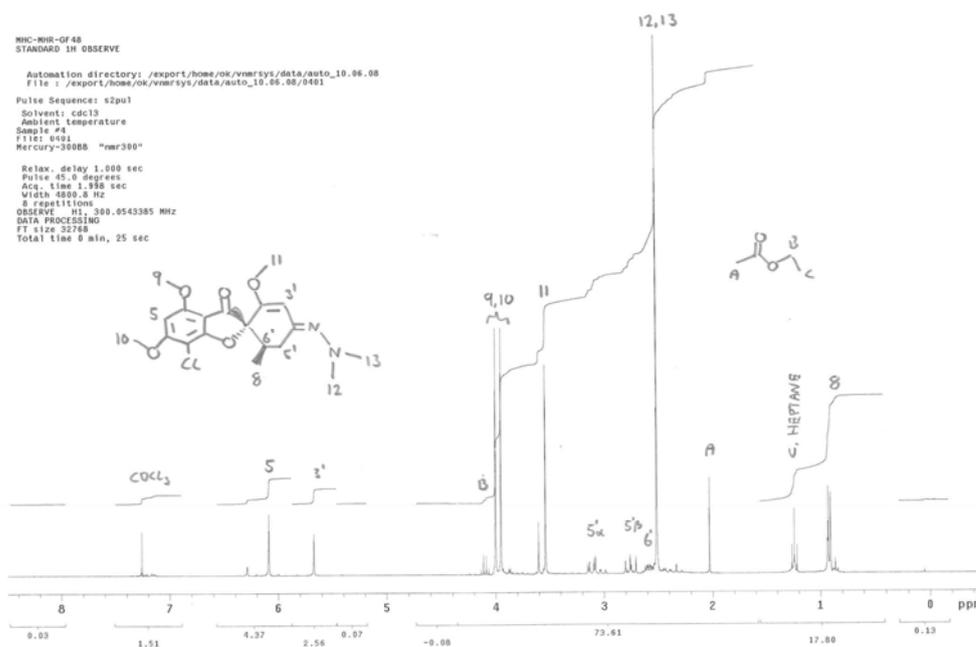


¹³C NMR (75 MHz, CDCl₃)

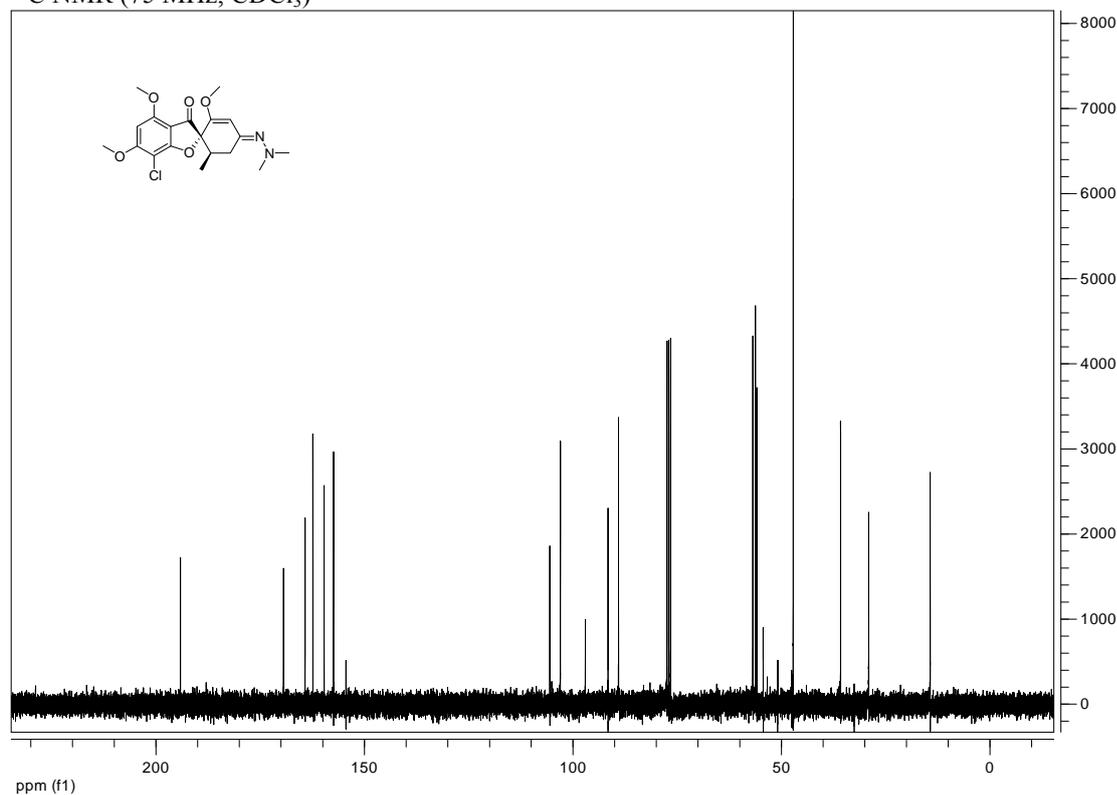


(2*S*,6'*R*,*E*)-(7-Chloro-4,6-dimethoxy-benzofuran-3-one)-2-spiro-1'-(2'-methoxy-6'-methyl-cyclohex-2'-ene-4'-one-4'-dimethylhydrazine) **30**

¹H NMR (300 MHz, CDCl₃)

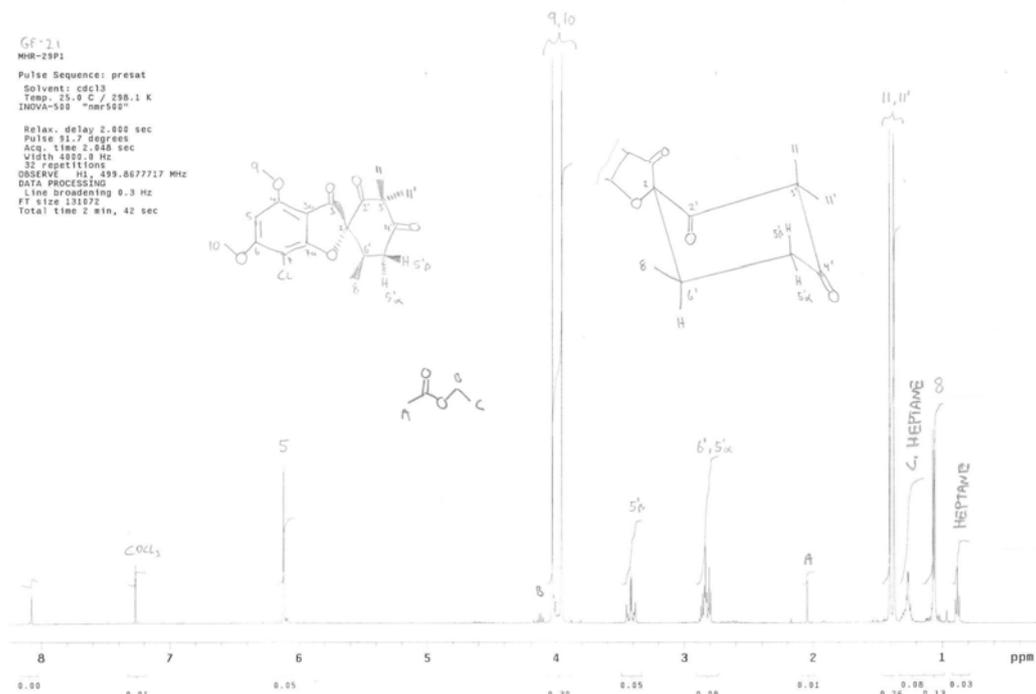


¹³C NMR (75 MHz, CDCl₃)

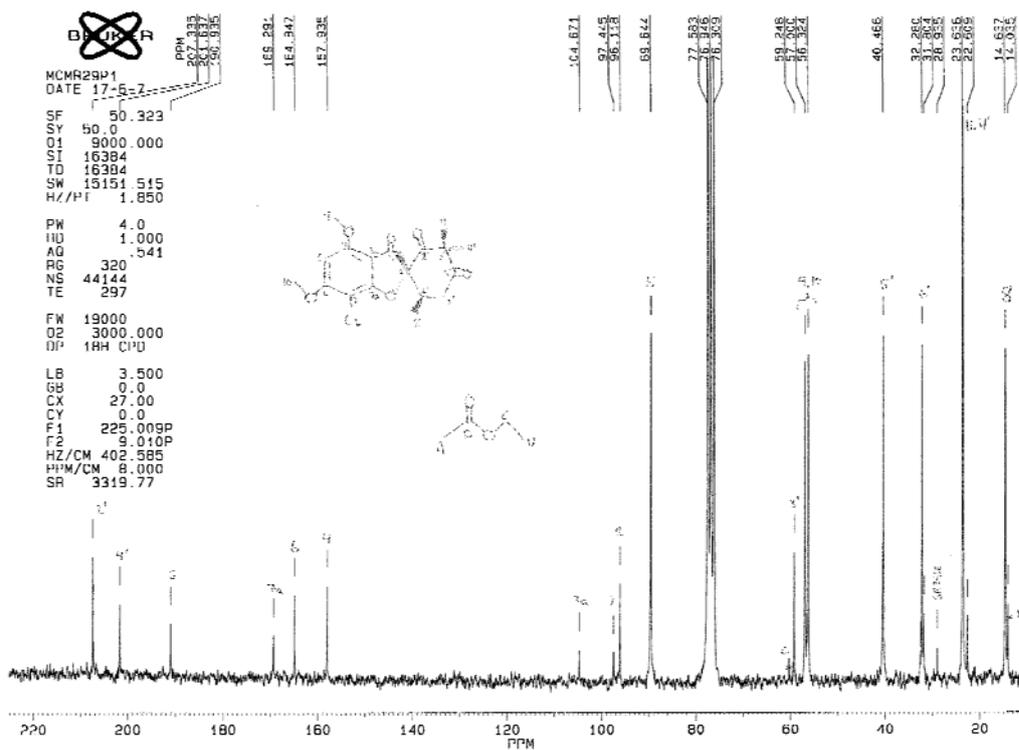


(2*S*,6'*R*)-(7-Chloro-4,6-dimethoxy-benzofuran-3-on)-2-spiro-1'-(3',3',6'-trimethyl-cyclohex-2',4'-dione) **31**

¹H NMR (500 MHz, CDCl₃)

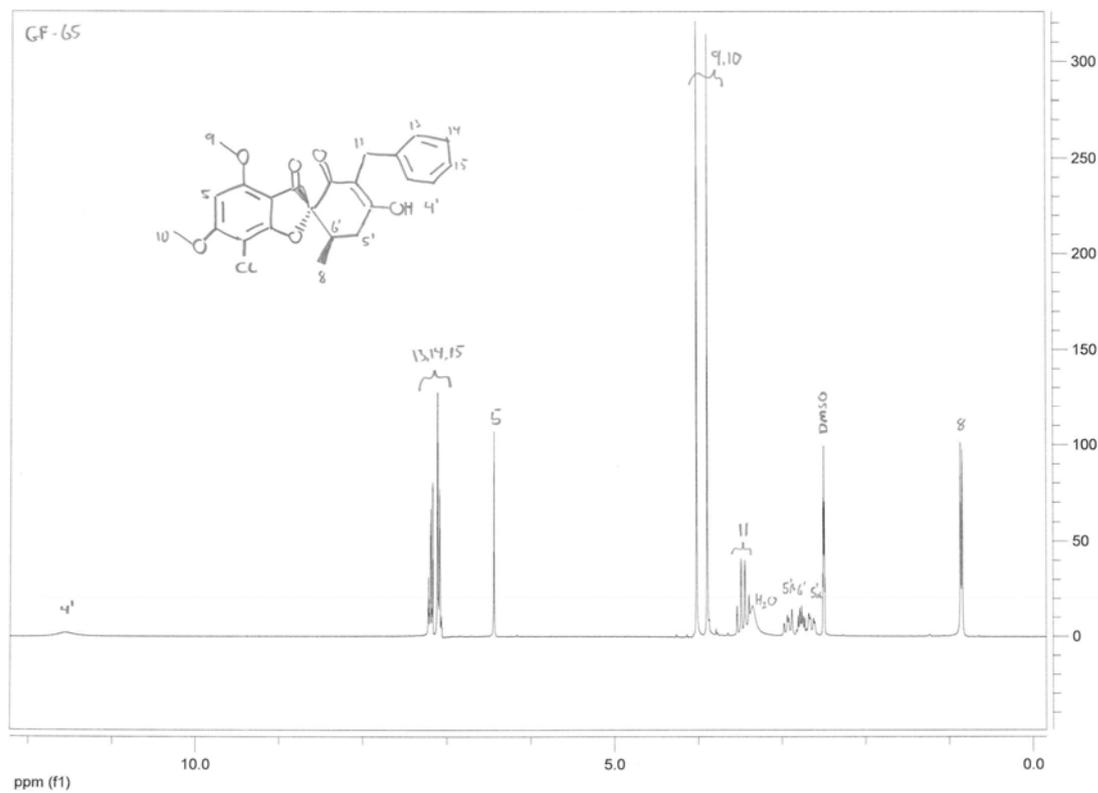


¹³C NMR (75 MHz, CDCl₃)

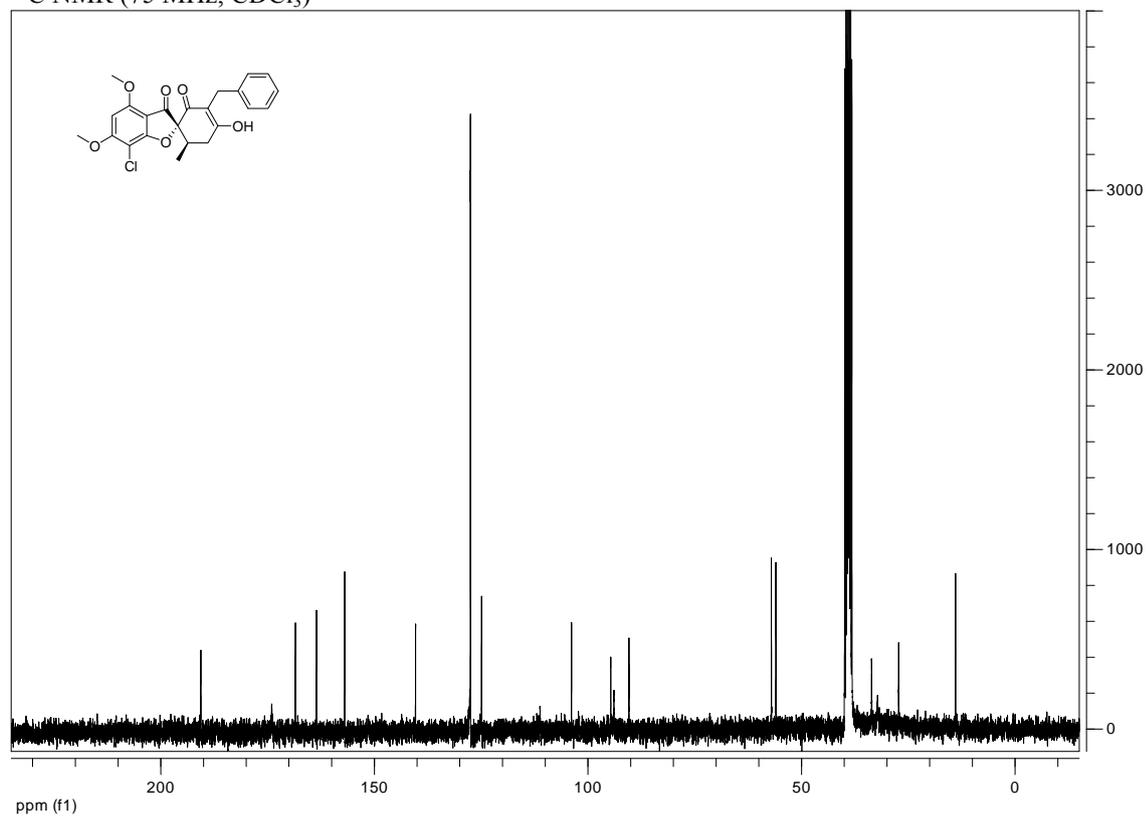


(2*S*,6'*R*)-(7-Chloro-4,6-dimethoxy-benzofuran-3-one)-2-spiro-1'-(3'-benzyl-6'-methyl-cyclohex-2',4'-dione) **32**

^1H NMR (300 MHz, CDCl_3)

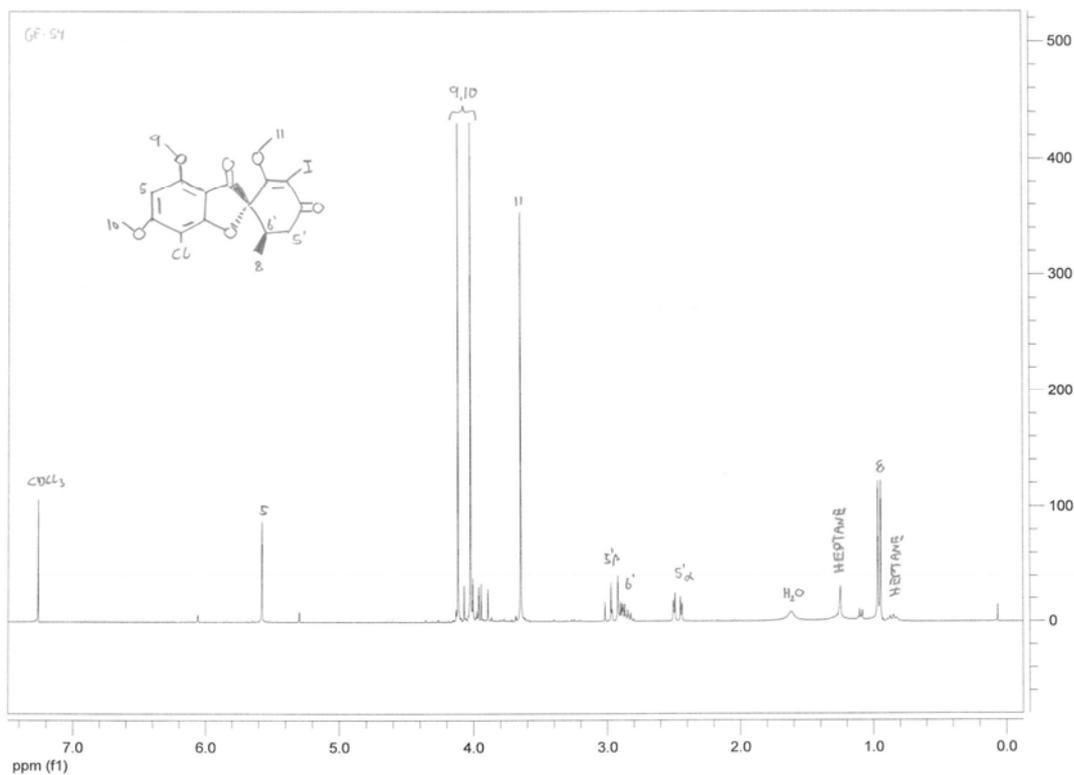


^{13}C NMR (75 MHz, CDCl_3)

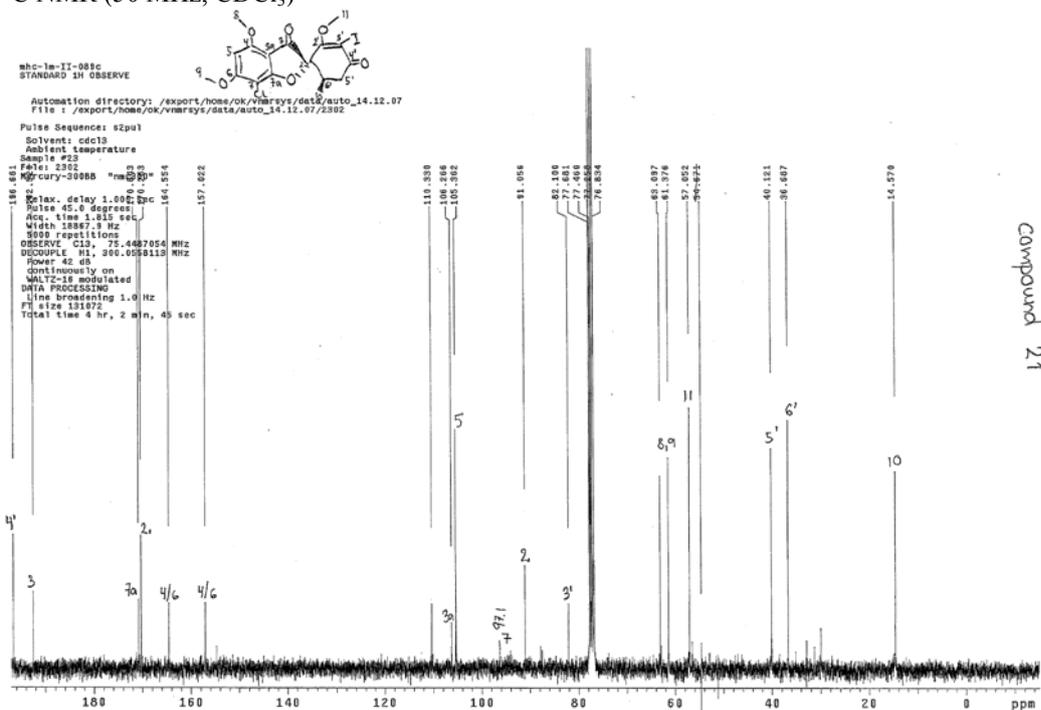


(2*S*,6'*R*)-(7-Chloro-4,6-dimethoxy-benzofuran-3-one)-2-spiro-1'-(3'-iodo-2'-methoxy-6'-methyl-cyclohex-2'-ene-4'-one) **33**

¹H NMR (300 MHz, CDCl₃)

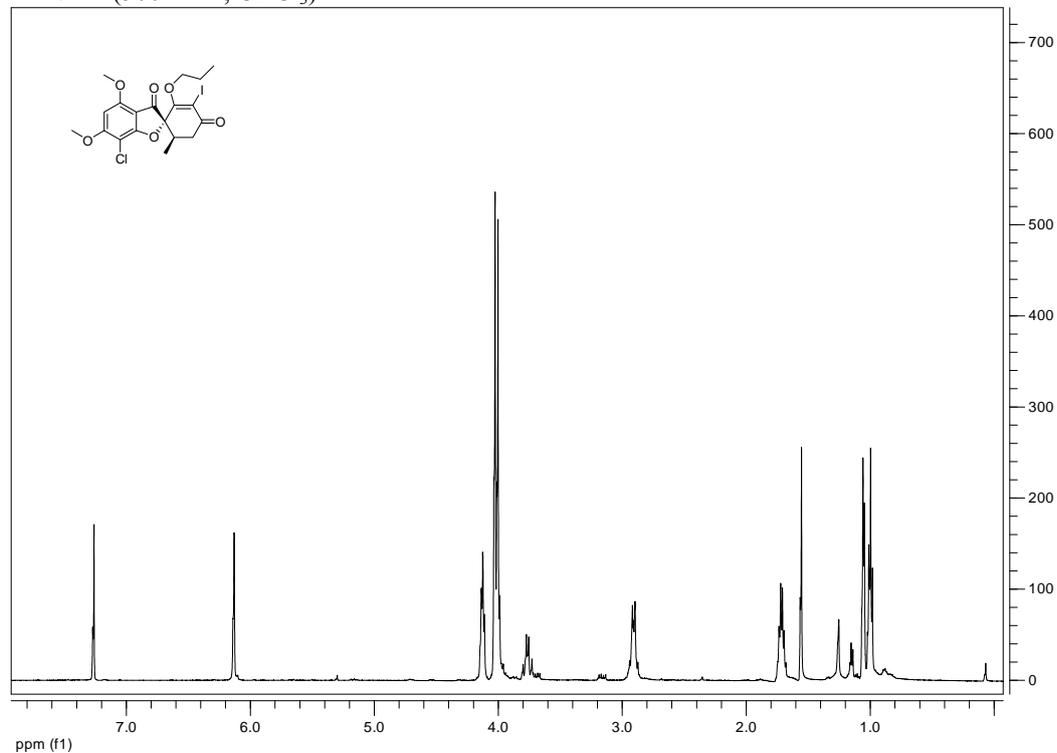


¹³C NMR (50 MHz, CDCl₃)



(2*S*,6'*R*)-(7-Chloro-4,6-dimethoxy-benzofuran-3-one)-2-spiro-1'-(3'-iodo-6'-methyl-2'-propoxy-cyclohex-2'-ene-4'-one) **34**

¹H NMR (500 MHz, CDCl₃)



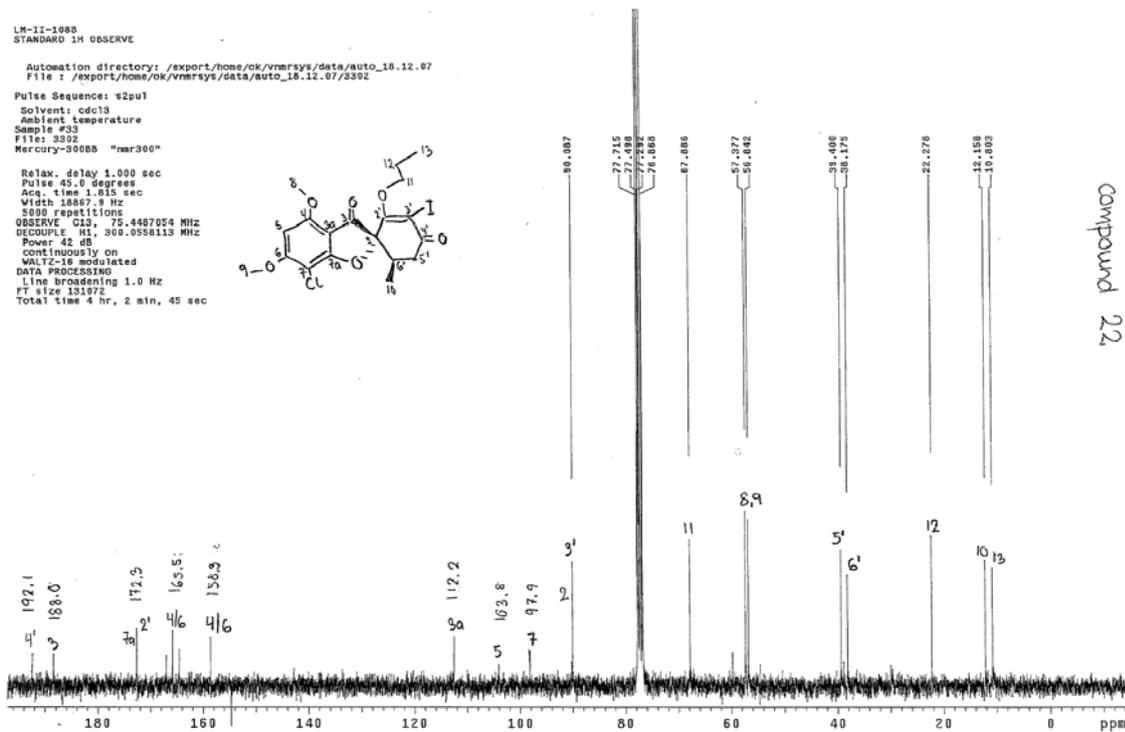
¹³C NMR (75 MHz, CDCl₃)

LM-II-1088
STANDARD 1H OBSERVE

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Ambient temperature
Sample #33
File: S302
Mercury-S9085 "mar300"

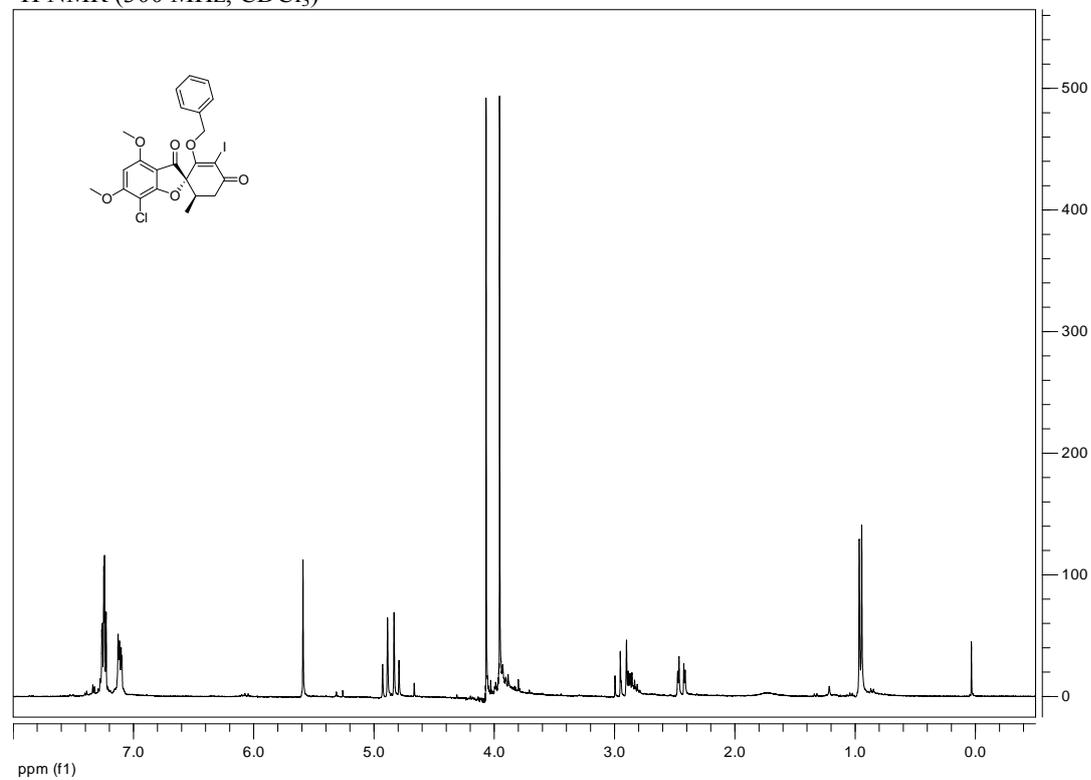
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3000 repetitions
OBSERVE c13, 75.4487054 MHz
DECOUPLE H1, 300.0558113 MHz
Power 42 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 1.0 Hz
F1 size 131872
Total time 4 hr, 2 min, 45 sec



Compound 22

(2*S*,6'*R*)-(7-Chloro-4,6-dimethoxy-benzofuran-3-one)-2-spiro-1'-(2'-benzyloxy-3'-iodo-6'-methyl-cyclohex-2'-ene-4'-one) **35**

¹H NMR (300 MHz, CDCl₃)



¹³C NMR (75 MHz, CDCl₃)

