Supporting Information

# Friedel-Crafts Alkylation of Indoles with *p*-Quinols. The role of hydrogen bonding of water for the desymmetrization of the cyclohexadienone system.

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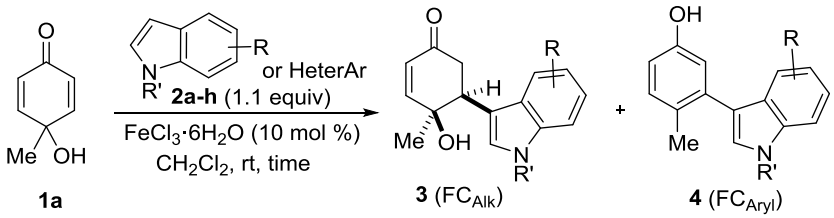
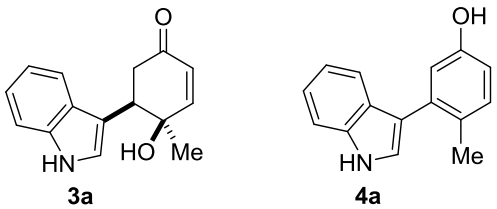
**General Considerations:** $^{1}$H- and $^{13}$C-NMR spectra were generally recorded in a AV-300 Bruker using $CDCl_3$ as solvent at 300 and 75 MHz, respectively. Chemical shifts are reported in ppm relative to $CDCl_3$ (δ 7.26 ppm). Mass spectra (m/z) and HRMS were recorded under the conditions of electron impact (EI) and electrospray (ESI). Unless otherwise stated, analytical HPLC was performed at room temperature, using a commercially available Chiralpack IC on an Agilent 1100 Series HPLC, equipped with a UV-visible variable wavelength. All reactions were monitored by thin-layer chromatography that was performed on precoated sheets of silica gel 60, and column chromatography was done with silica gel 60 (230-400 mesh) of Merck. Eluting solvents are indicated in the text.

**General procedure for diastereoselective Friede-Crafts reaction of heteroaromatic derivatives with *p*-quinols (A)**




To a solution of the corresponding *p*-quinol (1 equiv) and the corresponding heteroaromatic derivative (1.1 equiv) in $CH_2Cl_2$ (0.1 M) at rt, $FeCl_3{\cdot}6H_2O$ (10 mol %) is added and the mixture is stirred until no starting material was observed by TLC. Then, the crude mixture is filtered through a pad of celite and the resulting organic phase is washed with water and dried over anhydrous $MgSO_4$. The solvent is then removed under reduced pressure. The crude product is purified by flash chromatography using the eluent indicated in each case.

**(4*S**,5*S**)-4-Hydroxy-5-(1*H*-indol-3-yl)-4-methylcyclohex-2-enone 3a and 3-(1*H*-indol-3-yl)-4-methylphenol 4a.**

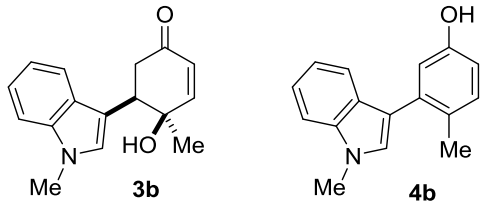



Following the general procedure **A**, the reaction of *p*-quinol **1a** (100 mg, 0.806 mmol), 1*H*-indole **2a** (104.2 mg, 0.887 mmol) and $FeCl_3{\cdot}6H_2O$ (21.8 mg, 0.0806 mmol) in $CH_2Cl_2$ (8 mL) gave a 92:8 mixture of **3a:4a**. After flash column chromatography (eluent Hexane:AcOEt 3:1 - AcOEt) **4a** (less polar fraction) was obtained as a brown oil (9 mg, 5% yield) and **3a** (most polar fraction) was obtained pure as a dark green solid (175 mg, 90% yield). Reaction time: 2 h.

**3a:** M.p.: 147-149 °C. $^1$H-NMR (300 MHz, $CDCl_3$): $\delta$ = 8.42 (bs, 1H), 7.64- 7.61 (d, *J* = 7.8 Hz, 1H), 7.38 – 7.36 (d, *J* = 7.8 Hz, 1H), 7.25 – 7.13 (m, 2H), 7.08 – 7.07 (d, *J* = 2.5 Hz, 1H), 6.84 – 6.80 (d, *J* = 10.1 Hz, 1H), 6.08 – 6.06 (d, *J* = 10.1 Hz, 1H), 3.71 – 3.66 (dd, *J* = 10.6 and 4.2 Hz, 1H), 3.11 – 3.02 (dd, *J* = 16.6 and 10.6 Hz, 1H), 2.70 – 2.63 (dd, *J* = 16.6 and 4.3 Hz, 1H), 1.44 (s, 3H); $^{13}$C-NMR (75 MHz, $CDCl_3$): $\delta$ = 199.9, 153.5, 135.9, 128.5, 127.6, 122.8, 122.5, 119.9, 119.2, 114.1, 111.3, 69.5, 41.9, 41.1, 28.1; MS (EI) *m/z* (%): 241 (12) [$M^+$], 222 (48), 223 (61), 143 (100); HRMS Calcd for $C_{15}H_{15}NO_2$ 241.1103, found 241.1109 [$M^+$].

**4a**: $^{1}$H-NMR (300 MHz, $CDCl_3$): $\delta$ = 8.22 (bs, 1H), 7.56 – 7.54 (d, $J$ = 7.9 Hz, 1H), 7.45 – 7.43 (m, 1H), 7.25 – 7.12 (m, 4H), 6.93 – 6.92 (d, $J$ = 2.8 Hz, 1H), 6.78 – 6.74 (dd, $J$ = 8.2 and 2.8 Hz, 1H), 4.61 (bs, 1H), 2.24 (s, 3H).

**(4*S**,5*S**)-4-Hydroxy-4-methyl-5-(1-methyl-1*H*-indol-3-yl)cyclohex-2-enone 3b and 4-methyl-3-(1-methyl-1*H*-indol-3-yl)phenol 4b.**

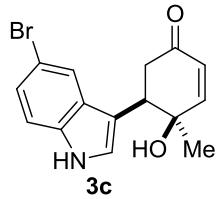



Following the general procedure **A**, the reaction of *p*-quinol **1a** (100 mg, 0.806 mmol), 1-methyl-indole **2b** (110.7 µL, 0.887 mmol) and $FeCl_3{\cdot}6H_2O$ (21.8 mg, 0.0806 mmol) in $CH_2Cl_2$ (8 mL) gave a 75:25 mixture of **3b:4b**. After flash column chromatography (eluent Hexane:AcOEt 3:1 - AcOEt) **4b** (less polar fraction) was obtained as a dark brown oil (50.7mg, 24% yield) and **3b** (most polar fraction) was obtained pure as a brown oil (133.7 mg, 64% yield). Reaction time: 40 min.

**3b**: $^{1}$H-NMR (300 MHz, $CDCl_3$): $\delta$ = 7.55 – 7.51 (dq, $J$ = 8.0 and 1.1 Hz, 1H), 7.26 – 7.15 (m, 2H), 7.10 – 7.04 (m, 1H), 6.89 (s, 1H), 6.76 – 6.72 (dd, $J$ = 10.1 and 1.0 Hz, 1H), 6.00 – 5.97 (d, $J$ = 10.0 Hz, 1H), 3.71 (s, 3H), 3.64 – 3.59 (dd, $J$ = 10.3 and 4.4 Hz, 1H), 3.01 – 2.92 (ddd, $J$ = 16.6, 10.2 and 1.0 Hz, 1H), 2.63 – 2.56 (dd, $J$ = 16.6 and 4.4 Hz, 1H), 1.38 (s, 3H); $^{13}$C-NMR (75 MHz, $CDCl_3$): $\delta$ = 199.8, 153.5, 136.6, 128.4, 128.1, 127.3, 121.9, 119.4, 119.2, 112.5, 109.3, 69.4, 41.8, 41.2, 32.7, 28.0; MS (ESI) *m/z* (%): 278 (12) [$M^+$+Na], 273 (17) [$M^+$+$NH_4$], 238 (44), 256 (100) [$M^+$+H]; HRMS Calcd for $C_{16}H_{18}NO_2$ 256.1332, found 256.1327 [$M^+$+H].

**4b**: $^{1}$H-NMR (300 MHz, $CDCl_3$): $\delta$ = 7.56 – 7.53 (d, $J$ = 7.9 Hz, 1H), 7.37 – 7.36 (d, $J$ = 8.0 Hz, 1H), 7.29 – 7.26 (m, 1H), 7.17 – 7.10 (m, 2H), 7.00 (s, 1H), 6.90 – 6.89 (d, $J$ = 2.8 Hz, 1H), 6.74 – 6.71 (dd, $J$ = 8.2 and 2.9 Hz, 1H), 3.81 (s, 3H), 2.25 (s, 3H); $^{13}$C-NMR (75 MHz, $CDCl_3$): $\delta$ = 153.3, 136.6, 135. 7, 131.3, 128.6, 127.5, 127.3, 121.7, 120.2, 119.4, 117.4, 115.6, 113.4, 109.3, 32.7, 19.8; MS (EI) *m/z* (%): 222 (21), 236 (84), 237 (100) [$M^+$]; HRMS Calcd for $C_{16}H_{15}NO$ 237.1154, found 237.1157 [$M^+$].

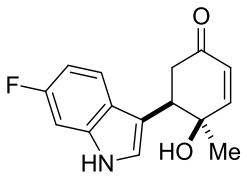
**(4*S**,5*S**)-5-(5-Bromo-1*H*-indol-3-yl)-4-hydroxy-4-methylcyclohex-2-enone 3c.**




Following the general procedure **A**, the reaction of *p*-quinol **1a** (100 mg, 0.806 mmol), 5-bromo-1*H*-indole **2c** (173.9 mg, 0.887 mmol) and $FeCl_3{\cdot}6H_2O$ (21.8 mg, 0.0806 mmol) in $CH_2Cl_2$

(8 mL) gave **3c** as the only product. After flash column chromatography (eluent Hexane:AcOEt 3:1 - AcOEt) **3c** was obtained as a brown solid (223.6 mg, 87% yield). Reaction time: 2.5 h. M.p.: decomposes; $^{1}$H-NMR (300 MHz, $CDCl_3$): $\delta$ = 8.28 (bs, 1H), 7.68 (s, 1H), 7.25 – 7.17 (m, 2H), 7.07 – 7.06 (d, *J* = 2.5 Hz, 1H), 6.77 – 6.73 (dd, *J* = 10.1 and 0.9 Hz, 1H), 6.01 – 5.98 (d, *J* = 10.1 Hz, 1H), 3.57 – 3.52 (dd, *J* = 10.6 and 4.3 Hz, 1H), 3.02 – 2.92 (ddd, *J* = 16.6, 10.6 and 0.9 Hz, 1H), 2.62 – 2.50 (dd, *J* = 16.6 and 4.3 Hz, 1H), 1.37 (s, 3H); $^{13}$C-NMR (75 MHz, $CDCl_3$): $\delta$ = 200.1, 153.7, 134.4, 129.3, 128.4, 125.1, 124.1, 121.7, 113.7, 113.1, 112.8, 69.4, 41.7, 41.0, 27.9; MS (ESI) *m/z* (%): 342 (17) [$M^+$+Na], 300 (59), 320 (100) [$M^+$+H]; HRMS Calcd for $C_{15}H_{15}NO_2Br$ 320.0280, found 320.0281 [$M^+$+H].

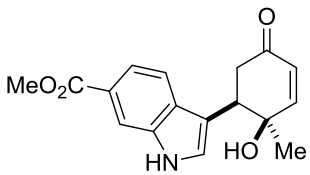
**(4*S**,5*S**)-5-(6-Fluoro-1*H*-indol-3-yl)-4-hydroxy-4-methylcyclohex-2-enone 3d.**




**3d**

Following the general procedure **A**, the reaction of *p*-quinol **1a** (100 mg, 0.806 mmol), 6-fluoro-1*H*-indole **2d** (119.8 mg, 0.887 mmol) and $FeCl_3{\cdot}6H_2O$ (21.8 mg, 0.0806 mmol) in $CH_2Cl_2$ (8 mL) gave **3d** as the only product. After flash column chromatography (eluent Hexane:AcOEt 3:1 - AcOEt) **3d** was obtained as a brown oil (198.3 mg, 95% yield). Reaction time: 50 min. $^{1}$H-NMR (300 MHz, $CDCl_3$); $\delta$ = 8.68 (bs, 1H), 7.52 – 7.47 (dd, *J* = 8.8 and 5.2 Hz, 1H), 7.04 – 7.00 (m, 2H), 6.92 – 6.86 (td, *J* = 9.2 and 2.3 Hz, 1H), 6.83 – 6.80 (d, *J* = 10.1 Hz, 1H), 6.06 – 6.01 (d, *J* = 10.1 Hz, 1H), 3.64 – 3.59 (dd, *J* = 10.7 and 4.2 Hz, 1H), 3.07 – 2.98 (dd, *J* = 16.7 and 10.7 Hz, 1H), 2.65 – 2.59 (dd, *J* = 16.6 and 4.2 Hz, 1H), 1.41 (s, 3H); $^{13}$C-NMR (75 MHz, $CDCl_3$): $\delta$ = 200.1, 161.5 – 158.4 (d, *J* = 238.4 Hz), 153.6, 135.9 - 135.7 (d, *J* = 12.3 Hz), 128.4, 124.2, 123.1 - 123.0 (d, *J* = 3.5 Hz), 119.9 - 119.8 (d, *J* = 10.3 Hz), 114.2, 108.8 - 108.5 (d, *J* = 24.8 Hz), 97.7 - 97.4 (d, *J* = 25.9 Hz), 69.4, 41.8, 41.0, 27.9; $^{19}$F-NMR (282.4 MHz, $CDCl_3$): $\delta$ = -120.28; MS (EI) *m/z* (%): 259 (8) [$M^+$], 241 (16), 161 (100); HRMS Calcd for $C_{15}H_{14}NO_2F$ 259.1009, found 259.1017 [$M^+$].

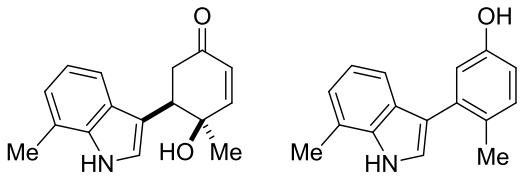
**Methyl-3-[(1*S*,2*S*)-2-hydroxy-2-methyl-5-oxocyclohex-3-en-1-yl]-1*H*-indole-6-carboxylate 3e.**




**3e**

Following the general procedure **A**, the reaction of *p*-quinol **1a** (100 mg, 0.806 mmol), methyl 1*H*-indole-6-carboxylate **2e** (155.4 mg, 0.887 mmol) and $FeCl_3 \cdot 6H_2O$ (21.8 mg, 0.0806 mmol) in $CH_2Cl_2$ (8 mL) gave **3e** as the only product. After flash column chromatography (eluent Hexane:AcOEt 3:1 - AcOEt) **3e** was obtained as a dark brown oil (198 mg, 82%). Reaction time: 2 h. $^1$H-NMR (300 MHz, $CDCl_3$): $\delta$ = 8.76 (bs, 1H), 8.14 (s, 1H), 7.84 – 7.80 (dd, *J* = 8.5 and 1.3 Hz, 1H), 7.65 – 7.62 (d, *J* = 8.5 Hz, 1H), 7.31 – 7.30 (d, *J* = 2.5 Hz, 1H), 6.85 – 6.81 (dd, *J* = 10.1 and 0.9 Hz, 1H), 6.09 – 6.06 (d, *J* = 10.0 Hz, 1H), 3.93 (s, 3H), 3.72 – 3.67 (dd, *J* = 10.8 and 4.2 Hz, 1H), 3.12 – 3.03 (dd, *J* = 16.6 and 10.8 Hz, 1H), 2.70 – 2.63 (dd, *J* = 16.6 and 4.2 Hz, 1H), 1.44 (s, 3H); $^{13}$C-NMR (75 MHz, $CDCl_3$): $\delta$ = 200.2, 168.3, 153.7, 135.1, 131.1, 128.3, 126.7, 123.5, 120.5, 118.7, 114.4, 113.8, 69.4, 52.0, 41.6, 40.9, 27.8; MS (ESI) *m/z* (%): 599 (25) [2$M^+$+H], 300 (100) [$M^+$+H]; HRMS Calcd for $C_{17}H_{18}NO_4$ 300.1230, found 300.1229 [$M^+$+H].

**(4*S**,5*S**)-4-Hydroxy-4-methyl-5-(7-methyl-1*H*-indol-3-yl)cyclohex-2-enone 3f and 4-methyl-3-(7-methyl-1*H*-indol-3-yl)phenol 4f**.




**3f** **4f**

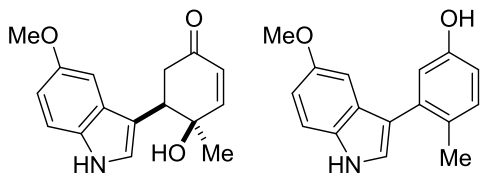
Following the general procedure **A**, the reaction of *p*-quinol **1a** (100 mg, 0.806 mmol), 7-methyl-1*H*-indole **2f** (116.3 mg, 0.887 mmol) and $FeCl_3 \cdot 6H_2O$ (21.8 mg, 0.0806 mmol) in $CH_2Cl_2$ (8 mL) gave a 94:6 mixture of **3f:4f**. After flash column chromatography (eluent Hexane:AcOEt 3:1 - AcOEt)) **4f** (less polar fraction) was obtained as a dark brown oil (9.5 mg, 5% yield and of **3f** (most polar fraction) was obtained pure as a green solid (187 mg, 91% yield). Reaction time: 15 h.

**3f**: M.p.: 159-161°C; $^1$H-NMR (300 MHz, $CDCl_3$): $\delta$ = 8.39 (bs, 1H), 7.49 – 7.47 (d, *J* = 7.7 Hz, 1H), 7.12 – 7.03 (m, 3H), 6.84 – 6.81 (d, *J* = 10.1 Hz, 1H), 6.08 – 6.05 (d, *J* = 10.1 Hz, 1H), 3.71 – 3.66 (dd, *J* = 10.7 and 4.2 Hz, 1H), 3.12 – 3.03 (dd, *J* = 16.6 and 10.7 Hz, 1H), 2.70 – 2.63 (dd, *J* = 16.6 and 4.2 Hz, 1H), 2.49 (s, 3H), 1.44 (s, 3H); $^{13}$C-NMR (75MHz, $CDCl_3$): $\delta$ = 200.0, 153.5, 135.5, 128.5, 127.2, 122.9, 122.5, 120.6, 120.1, 116.9, 114.6, 69.5, 42.0, 41.1, 28.1, 16.5; MS (EI) *m/z* (%): 255 (0.6) [$M^+$], 237 (20), 157 (100); HRMS Calcd for $C_{16}H_{17}NO_2$ 255.1259, found 255.1265 [$M^+$].

**4f**: $^1$H-NMR (300 MHz, $CDCl_3$): $\delta$ = 8.24 (bs, 1H), 7.62 – 7.59 (m, 1H), 7.42 – 7.31 (m, 1H), 7.31 – 7.24 (m, 3H), 7.08 – 7.07 (d, *J* = 2.7 Hz, 1H), 6.96 – 6.93 (dd, *J* = 8.2 and 2.8 Hz, 1H), 5.40 (bs, 1H), 2.70 (s, 3H), 2.43 (s, 3H); $^{13}$C-NMR (75MHz, $CDCl_3$): $\delta$ = 153.1, 135.7, 135.3, 131.3, 128.9, 126.4, 122.7, 122.6, 120.4, 120.1, 117.8, 117.6, 117.4, 113.6, 19.7, 16.5; MS (EI)

*m/z* (%):236 (53), 222 (59), 237 (100) [$M^+$]; HRMS Calcd for $C_{16}H_{15}NO$ 237.1154, found 237.1150 [$M^+$].

**(4*S**,5*S**)-4-Hydroxy-5-(5-methoxy-1*H*-indol-3-yl)-4-methylcyclohex-2-enone 3g and 3-(5-methoxy-1*H*-indol-3-yl)-4-methylphenol 4g.**



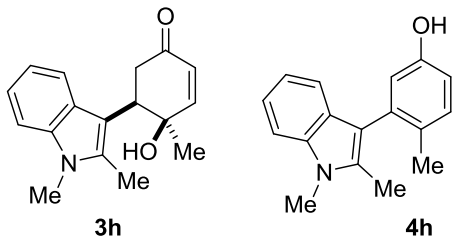

**3g** **4g**

Following the general procedure **A**, the reaction of *p*-quinol **1a** (100 mg, 0.806 mmol), 5-methoxy-1*H*-indole **2g** (130.5 mg, 0.887 mmol) and $FeCl_3{\cdot}6H_2O$ (21.8 mg, 0.0806 mmol) in $CH_2Cl_2$ (8 mL) gave a 90:10 mixture of **3g:4g**. After flash column chromatography (eluent Hexane:AcOEt 3:1 - AcOEt) **4g** (less polar fraction) was obtained as a dark brown oil (20 mg, 9% yield) and **3g** (most polar fraction) was obtained pure as a brown oil (153 mg, 70% yield). Reaction time: 3 d.

**3g**: $^1$H-NMR (300 MHz, $CDCl_3$): $\delta$ = 8.18 (bs, 1H), 7.30 – 7.27 (dd, *J* = 8.9 and 0.7 Hz, 1H), 7.11 – 7.10 (d, *J* = 2.6 Hz, 1H), 7.06 – 7.05 (d, *J* = 2.4 Hz, 1H), 6.91 – 6.88 (dd, *J* = 8.9 and 2.4 Hz, 1H), 6.85 – 6.81 (d, *J* = 10.1 Hz, 1H), 6.09 – 6.06 (dd, *J* = 10.1 and 0.7 Hz, 1H), 3.86 (s, 3H), 3.67 – 3.62 (dd, *J* = 10.5 and 4.3 Hz, 1H), 3.11 – 3.02 (ddd, *J* = 16.6, 10.5 and 0.8 Hz, 1H), 2.72 – 2.64 (ddd, *J* = 16.6, 4.3 and 0.8 Hz, 1H), 1.47 (s, 3H); $^{13}$C-NMR (75 MHz, $CDCl_3$): $\delta$ = 200.4, 154.0, 153.8, 131.0, 128.2, 127.9, 123.7, 113.5, 112.3, 112.0, 101.0, 69.4, 55.8, 41.7, 40.9, 27.9; MS (ESI) *m/z* (%): 294 (9) [$M^+$+Na], 543 (20) [2$M^+$+H], 254 (80) [$M^+$-OH], 272 (100) [$M^+$+H]; HRMS Calcd for $C_{16}H_{18}NO_3$ 272.1281, found 272.1282 [$M^+$+H].

**4g:** $^1$H-NMR (300 MHz, $CDCl_3$): $\delta$ = 8.14 (bs, 1H), 7.33 – 7.30 (d, *J* = 8.7 Hz, 1H), 7.20 – 7.18 (d, *J* = 8.2 Hz, 1H), 7.15 – 7.14 (d, *J* = 2.4 Hz, 1H), 6.96 (d, *J* = 2.5 Hz, 1H), 6.92 – 6.89 (m, 2H), 6.78 – 6.75 (dd, *J* = 8.2 and 2.8 Hz, 1H), 4.81 (bs, 1H), 3.81 (s, 3H), 2.24 (s, 3H); $^{13}$C-NMR (75 MHz, $CDCl_3$): $\delta$ = 154.4, 153.3, 135.7, 131.3, 131.0, 129.0, 127.4, 123.5, 117.4, 117.1, 113.6, 112.6, 111.9, 101.7, 56.0, 19.7; MS (EI) *m/z* (%):254 (20) [$M^+$+H], 222 (26), 210 (27), 238 (80), 253 (100) [$M^+$]; HRMS Calcd for $C_{16}H_{15}NO_2$ 253.1103, found 253.1101 [$M^+$].

**(4*S**, 5*S**)-5-(1,2-Dimethyl-1*H*-indol-3-yl)-4-hydroxy-4-methylcyclohex-2-enone 3h and 3-(1,2-dimethyl-1*H*-indol-3-yl)-4-methylphenol 4h.**



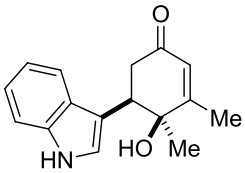

**3h** **4h**

Following the general procedure **A**, the reaction of *p*-quinol **1a** (100 mg, 0.806 mmol), 1,2-dimethyl-1H-indole **2h** (128.6 mg, 0.887 mmol) and $FeCl_3 \cdot 6H_2O$ (21.8 mg, 0.0806 mmol) in $CH_2Cl_2$ (8 mL) gave a 60:40 mixture of **3h:4h**. After flash column chromatography (eluent Hexane:AcOEt 3:1 - AcOEt) **4h** (less polar fraction) was obtained as a dark brown oil (27.6 mg, 11% yield) and **3h** (most polar fraction) was obtained pure as a brown oil (80.7 mg, 30% yield). Reaction time: 20 h.

**3h**: $^1$H-NMR (300 MHz, $CDCl_3$): $\delta$ = 7.77 (d, *J* = 8.0 Hz, 1H), 7.23 (d, *J* = 8.2 Hz, 1H), 7.09 (t, *J* = 7.6 Hz, 1H), 7.00 (t, *J* = 7.6 Hz, 1H), 6.77 (d, *J* = 10.1 Hz, 1H), 6.03 (d, *J* = 10.0 Hz, 1H), 3.76 – 3.68 (m, 1H), 3.63 (s, 3H), 3.37 (dd, *J* = 13.5, 3.7 Hz, 1H), 2.43 – 2.36 (m, 1H), 2.30 (s, 3H), 1.24 (s, 3H); $^{13}$C-NMR (75 MHz, $CDCl_3$): $\delta$ = 200.74, 151.98, 137.12, 134.84, 129.16, 126.68, 120.88, 120.51, 119.48, 108.95, 108.11, 71.02, 43.05, 39.92, 29.76, 28.07, 10.85; MS (ESI) *m/z* (%): 292 (10) [$M^+$+Na], 561 (17) [2$M^+$+Na], 252 (36) [$M^+$-OH], 270 (100) [$M^+$+H]; HRMS Calcd for $C_{17}H_{20}NO_2$ 270.1488, found 270.1485 [$M^+$+H].

**4h**: $^1$H-NMR (300 MHz, $CDCl_3$): δ = δ 7.37 (dd, *J* = 12.8, 8.1 Hz, 2H), 7.23 (d, *J* = 9.2 Hz, 2H), 7.09 (dd, *J* = 16.9, 7.6 Hz, 2H), 6.96 (d, *J* = 8.1 Hz, 1H), 3.77 (s, 3H), 2.37 (s, 3H), 2.33 (s, 3H); $^{13}$C-NMR (75 MHz, $CDCl_3$): $\delta$ = 151.69, 137.01, 135.17, 131.99, 129.30, 129.16, 126.94, 121.52, 120.63, 119.94, 118.86, 114.78, 108.90, 107.16, 29.80, 20.58, 11.00; MS (EI) *m/z* (%):249 (12), 248 (13), 252 (21), 250 (53), 251 (100) [$M^+$]; HRMS Calcd for $C_{17}H_{17}NO$ 251.1310, found 251.1304 [$M^+$].

**(4*R**, 5*S**)-4-Hydroxy-5-(1*H*-indol-3-yl)-3,4-dimethylcyclohex-2-enone 7.**

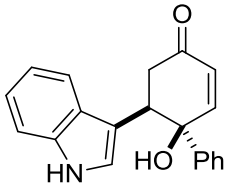



**7**

Following the general procedure **A**, the reaction of *p*-quinol **1b** (147 mg, 1.06 mmol), 1*H*-indole **2a** (137.5 mg, 1.17 mmol) and $FeCl_3 \cdot 6H_2O$ (28.7 mg, 0.106 mmol) in $CH_2Cl_2$ (10 mL) gave **7** as the only product. After flash column chromatography (eluent Hexane:AcOEt 3:1 - AcOEt) **7** was obtained as a brown solid (188 mg, 70% yield). Reaction time: 18 h. M.p.: decomposes; $^1$H-

NMR (300 MHz, $CDCl_3$): $\delta$ = 8.30 (bs, 1H), 7.66 – 7.64 (d, $J$ = 7.9 Hz, 1H), 7.40 – 7.37 (d, $J$ = 8.2 Hz, 1H), 7.26 – 7.13 (m, 2H), 7.04 – 7.03 (d, $J$ = 2.5 Hz, 1H), 5.98 (s, 1H), 3.80 – 3.76 (t, $J$ = 5.8 Hz, 1H), 2.97 – 2.89 (dd, $J$ = 17.0 and 6.3 Hz, 1H), 2.88 – 2.80 (dd, $J$ = 16.9 and 5.3 Hz, 1H), 2.02 (s, 3H), 1.57 (s, 3H); $^{13}$C-NMR (75 MHz, $CDCl_3$): $\delta$ = 198.4, 164.9, 135.8, 127.9, 126.7, 122.7, 122.3, 120.1, 119.1, 114.1, 111.3, 72.9, 43.1, 42.0, 26.3, 19.5; MS (ESI) *m/z* (%): 533 (18), 511 (27) [$M^+$+Na], 256 (100) [$M^+$+H]; HRMS Calcd for $C_{16}H_{18}NO_2$ 256.1332, found 256.1332 [$M^+$+H].

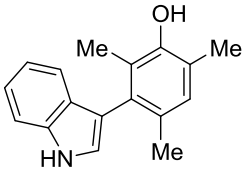
**(1*S**, 2*S**)-1-Hydroxy-2-(1*H*-indol-3-yl)-2,3-dihydro-(1,1'-biphenyl)-4(1*H*)-one 8.**




**8**

Following the general procedure **A**, the reaction of *p*-quinol **1c** (104 mg, 0.56 mmol), 1*H*-indole **2a** (72 mg, 0.61 mmol) and $FeCl_3 \cdot 6H_2O$ (15 mg, 0.06 mmol) in $CH_2Cl_2$ (5.5 mL) gave **8** as the only product. After flash column chromatography (eluent Hexane:AcOEt 3:1 - AcOEt) **8** was obtained as a brown oil (30 mg, 18% yield). Reaction time: 3 h. $^1$H-NMR (300 MHz, $CDCl_3$): $\delta$ = 8.17 (bs, 1H), 7.39 – 7.26 (m, 7H), 7.17 – 7.12 (t, $J$ = 7.6 Hz, 1H), 7.08 – 7.06 (m, 1H), 6.97 – 6.92 (m, 1H), 6.92 – 6.88 (d, $J$ = 10.2 Hz, 1H), 6.36 – 6.33 (d, $J$ = 10.1 Hz, 1H), 4.02 – 3.98 (dd, $J$ = 9.4 and 4.4 Hz, 1H), 3.12 – 3.04 (dd, $J$ = 16.4 and 9.3 Hz, 1H), 2.76 – 2.69 (dd, $J$ = 16.4 and 4.5 Hz, 1H).$^{13}$C-NMR (75 MHz, $CDCl_3$): $\delta$ = 199.5, 151.6, 144.0, 135.7, 129.5, 128.4 (2C), 127.7, 127.4, 125.6 (2C), 122.9, 122.5, 119.9, 119.1, 113.4, 111.0, 74.2, 45.0, 41.0; MS (ESI) *m/z* (%): 326 (7) [$M^+$+Na], 607 (9) [2$M^+$+H], 286 (41) [$M^+$-OH], 304 (67) [$M^+$+H], 244 (100); HRMS Calcd for $C_{20}H_{18}NO_2$ 304.1332, found 304.1343 [$M^+$+H].

**3-(1*H*-Indol-3-yl)-2,4,6-trimethylphenol 9.**

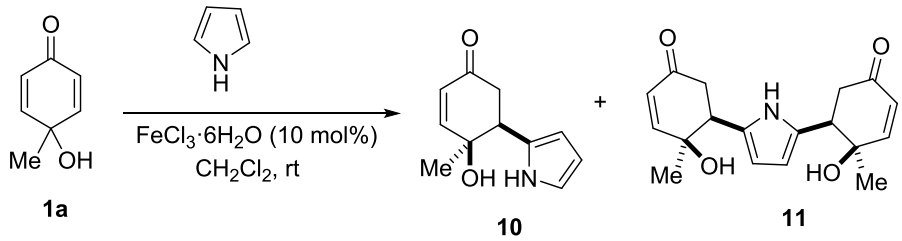



**9**

Following the general procedure **A**, the reaction of *p*-quinol **1d** (90.1 mg, 0.59 mmol), 1*H*-indole **2a** (76.6 mg, 0.65 mmol) and $FeCl_3 \cdot 6H_2O$ (16 mg, 0.059 mmol) in $CH_2Cl_2$ (6 mL) gave **9** as the only product. After flash column chromatography (eluent Hexane:AcOEt 4:1) 38.4 mg (26% yield) of **9**were obtained as a pink oil. Reaction time: 3 d. $^1$H-NMR (300 MHz, $CDCl_3$): $\delta$ = 8.21 (bs, 1H), 7.46 – 7.43 (d, $J$ = 8.0 Hz, 1H), 7.27 – 7.20 (m, 2H), 7.11 – 7.03 (m, 2H), 6.95

(s, 1H), 4.55 (bs, 1H), 2.31 (s, 3H), 2.01 (s, 6H); $^{13}$C-NMR (75 MHz, $CDCl_3$): $\delta$ = 150.0, 135.9, 132. 6, 130.1, 129.1, 127.5, 123.5, 122.6, 121.9, 121.8, 119.9, 119.6, 116.0, 111.0, 20.2, 15.9, 13.5.; MS (ESI) *m/z* (%):220 (31), 236 (70), 251 (100) [$M^+$+H]; HRMS Calcd for $C_{17}H_{17}NO$ 251.1310, found 251.1298 [$M^+$].

**(4*S**,5*S**)-4-Hydroxy-4-methyl-5-(1H-pyrrol-2-yl)cyclohex-2-enone 10 and (4*S**,5*S**)-4-hydroxy-5-(5-((1*R**,2*R**)-2-hydroxy-2-methyl-5-oxocyclohex-3-en-1-yl)-1*H*-pyrrol-2-yl)-4-methylcyclohex-2-enone 11.**

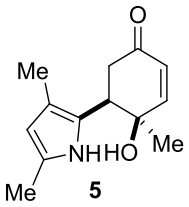



Following the general procedure **A**, the reaction of *p*-quinol **1a** (20 mg, 0.16 mmol), pyrrole (12.3 µl, 0.18 mmol) and $FeCl_3{\cdot}6H_2O$ (4.3 mg, 0.016 mmol) in $CH_2Cl_2$ (1.6 mL) gave a 1:3 mixture of **10**/**11** from a complex mixture of reaction. After flash column chromatography (eluent Hexane:AcOEt 3:1) **10** was obtained as a brown oil (1.6 mg, 5% yield) and **11** was obtained as a brown oil (7.2 mg, 28% yield). Reaction time: 1 h.

**(10)**: $^1$H-NMR (300 MHz, $CDCl_3$): $\delta$ = 8.52 (bs, 1H), 6.79 – 6.76 (m, 2H), 6.317 – 6.15 (m, 1H), 6.04 – 6.00 (m, 2H), 3.37 – 3.32 (dd, *J* = 10.6 and 4.3 Hz, 1H), 3.03 – 2.94 (dd, *J* = 16.7 and 10.6 Hz, 1H), 2.68 – 2.61 (dd, *J* = 16.8 and 4.3 Hz, 1H), 1.43 (s, 3H); $^{13}$C-NMR (75 MHz, $CDCl_3$): $\delta$ = 198.6, 152.5, 129.8, 128.8, 117.9, 108.3, 107.7, 69.6, 44.3, 40.8, 27.8; MS (ESI) *m/z* (%):192 (51) [$M^+$+H], 214 (87) [$M^+$+Na], 174 (100) [$M^+$-OH]; HRMS Calcd for $C_{11}H_{14}NO_2$ 192.1019, found 192.1014 [$M^+$+H].

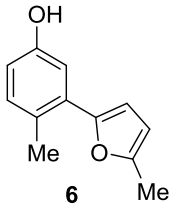
**(11)**: $^1$H-NMR (300 MHz, $CDCl_3$): $\delta$ = 8.86 (bs, 2H), 6.78 – 6.74 (d, *J* = 10.1 Hz, 2H), 6.02 – 5.99 (d, *J* = 10.0 Hz, 2H), 5.94 – 5.93 (d, *J* = 2.7 Hz, 2H), 3.32 – 3.28 (dd, *J* = 10.3 and 4.3 Hz, 2H), 2.99 – 2.90 (dd, *J* = 16.8 and 10.3 Hz, 2H), 2.67 – 2.60 (dd, *J* = 16.8 and 4.4 Hz, 2H), 1.42 (s, 3H); $^{13}$C-NMR (75 MHz, $CDCl_3$): $\delta$ = 198.6, 152.5, 130.0, 128.8, 107.6, 69.5, 44.4, 40.7, 27.8; MS (ESI) *m/z* (%):338 (38) [$M^+$+Na], 316 (84) [$M^+$+H], 279 (100); HRMS Calcd for $C_{18}H_{22}NO$ 316.1543, found 316.1540 [$M^+$+H].

**(4*S**, 5*S**)-5-(3,5-Dimethyl-1*H*-pyrrol-2-yl)-4-hydroxy-4-methylcyclohex-2-enone (5).**




Following the general procedure **A**, the reaction of *p*-quinol **1a** (30 mg, 0.242 mmol), 2,4-dimethylpyrrole (27.4 µl, 0.266 mmol) and $FeCl_3 \cdot 6H_2O$ (6.5 mg, 0.0242 mmol) in $CH_2Cl_2$ (2.4 mL) gave **5** as the only product. After flash column chromatography (eluent Hexane:AcOEt 3:1 - AcOEt) **5** was obtained as a brown oil (31.8 mg, 60% yield). Reaction time: 45 min. $^1$H-NMR (300 MHz, $CDCl_3$): $\delta$ = 8.10 (bs, 1H), 6.84 – 6.80 (d, $J$ = 10.1 Hz, 1H), 6.04 – 6.01 (dd, $J$ = 10.1 and 0.9 Hz, 1H), 5.67 (d, $J$ = 2.8 Hz, 1H), 3.33 – 3.28 (dd, $J$ = 12.2 and 4.1 Hz, 1H), 2.97 – 2.88 (dd, $J$ = 16.7 and 12.2 Hz, 1H), 2.57 – 2.50 (ddd, $J$ = 16.8, 4.2 and 0.9 Hz, 1H), 2.21 (s, 3H), 1.98 (s, 3H), 1.38 (s, 3H); $^{13}$C-NMR (75 MHz, $CDCl_3$): $\delta$ = 199.9, 153.1, 128.6, 126.7, 124.4, 116.4, 107.4, 69.8, 40.9, 40.6, 27.4, 13.0, 10.9. MS (ESI) *m/z* (%): 461 (21) [2$M^+$+Na], 202 (24) [$M^+$-OH], 242 (26) [$M^+$+Na], 220 (100) [$M^+$+H]; HRMS Calcd for $C_{13}H_{18}NO_2$ 220.1332, found 220.1333 [$M^+$+H].

**4-Methyl-3-(5-methylfuran-2-yl)phenol (6).**



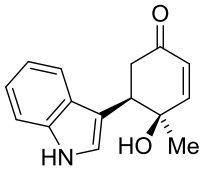

Following the general procedure **A**, the reaction of *p*-quinol **1a** (50 mg, 0.403 mmol), 2-methylfuran (40 µl, 0.43 mmol) and $FeCl_3 \cdot 6H_2O$ (11 mg, 0.0403 mmol) in $CH_2Cl_2$ (4 mL) gave **6** as the only product. After flash column chromatography (eluent Hexane:AcOEt 5:1) **6** was obtained as a brown oil (37.9 mg, 50% yield). Reaction time: 1 min. $^1$H-NMR (300 MHz, $CDCl_3$): $\delta$ = 7.22 – 7.21 (d, $J$ = 2.7 Hz, 1H), 7.09 – 7.06 (d, $J$ = 8.2 Hz, 1H), 6.69 – 6.66 (dd, $J$ = 8.2 and 2.8 Hz, 1H), 6.44 – 6.43 (d, $J$ = 3.2 Hz, 1H), 6.09 – 6.08 (d, $J$ = 3.2 Hz, 1H), 5.13 (s, 1H), 2.40 (s, 3H), 2.37 (s, 3H); $^{13}$C-NMR (75 MHz, $CDCl_3$): $\delta$ = 153.6, 151.5, 151.2, 132.2, 131.3, 126.2, 113.9, 112.9, 109.8, 107.5, 21.1, 13.6. MS (EI) *m/z* (%): 189 (28) [$M^+$+H], 145 (47), 188 (100) [$M^+$]; HRMS Calcd for $C_{12}H_{12}O_2$ 188.0837, found 188.0828 [$M^+$].

## Enantioselective Friedel-Craft Alkylation Reactions:

### GENERAL PROCEDURE B

To a solution of *p*-quinol **1a** (1 equiv) and the indicated indole (1.1 equiv) in $CH_3CN$ (0.1 M) at -20 °C, phosphoric acid (*S*)-**12h** (10 mol %) is added and the mixture is stirred at -20 °C for the time indicated in each case. Then, the crude mixture is washed with water and dried over anhydrous $MgSO_4$. The solvent is then removed under reduced pressure and the crude mixture purified by flash chromatography using the eluent indicated in each case.

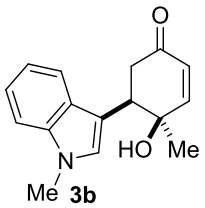
**(4*R*,5*R*)-4-Hydroxy-5-(1*H*-indol-3-yl)-4-methylcyclohex-2-enone (3a).**




**3a**

Following the general procedure **B**, the reaction of *p*-quinol **1a** (15 mg, 0.121 mmol), 1*H*-indole **2a** (15.6 mg, 0.133 mmol) and (*S*)-**12h** (8 mg, 0.0121 mmol) in $CH_3CN$ (0.25 mL) gave **3a** as the only diastereomer. After flash column chromatography (eluent Hexane:AcOEt 3:1 - AcOEt) **3a** was obtained as a dark green solid (21 mg, 72% yield) in a 72% *ee*. Reaction time: 6 d. $[\alpha]_D^{20}$= +9 (*c* 0.184 in $CHCl_3$). HPLC (IC-0.8 mL/min-15% $^i$PrOH-45min). Retention time: 21.42 min (minor) and 33.92 min (major).

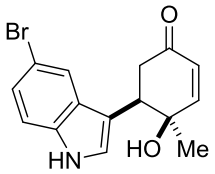
**(4*R*,5*R*)-4-Hydroxy-4-methyl-5-(1-methyl-1*H*-indol-3-yl)cyclohex-2-enone (3b).**




**3b**

Following the general procedure **B**, the reaction of *p*-quinol **1a** (15 mg, 0.121 mmol), 1-methyl-indole **2b** (16.6 µl, 0.133 mmol) and (*S*)-**12h** (8 mg, 0.0121 mmol) in $CH_3CN$ (0.25 mL) gave **3b** as the only diastereomer. After flash column chromatography (eluent Hexane:AcOEt 3:1 - AcOEt) **3b** was obtained as a brown oil (15 mg, 50% yield) in a 8% *ee*. Reaction time: 6 d. HPLC conditions (IC-0,8 mL/min-15% $^i$PrOH-45min). Retention time: 28.53 min and 30.64 min (minor) (major).

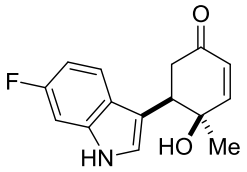
**(4*R*, 5*R*)-5-(5-bromo-1*H*-indol-3-yl)-4-hydroxy-4-methylcyclohex-2-enone (3c).**




**3c**

Following the general procedure **B**, the reaction of *p*-quinol **1a** (15 mg, 0.121 mmol), 5-bromo-1*H*-indole **2c** (26 mg, 0.133 mmol) and (*S*)-**12h** (8 mg, 0.0121 mmol) in $CH_3CN$ (0.25 mL) gave **3c** as the only diastereomer. After flash column chromatography (eluent Hexane:AcOEt 3:1 - AcOEt) of **3c** were obtained as a brown solid (25.8 mg, 67% yield) in a 62% *ee*. Reaction time: 5 d. $[\alpha]_D^{20}$= +11 (*c* 0.051 in $CHCl_3$). HPLC conditions (IC-0.8 mL/min-10% $^i$PrOH-60min). Retention time: 22.38 min (minor) and 31.09 min (major).

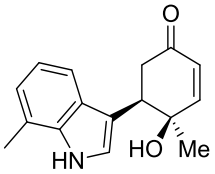
**(4*R*, 5*R*)-5-(6-Fluoro-1*H*-indol-3-yl)-4-hydroxy-4-methylcyclohex-2-enone (3d).**




**3d**

Following the general procedure **B**, the reaction of *p*-quinol **1a** (15 mg, 0.121 mmol), 6-fluoro-1*H*-indole **2d** (18 mg, 0.133 mmol) and (*S*)-**12h** (8 mg, 0.0121 mmol) in $CH_3CN$ (0.25 mL) gave **3d** as the only diastereomer. After flash column chromatography (eluent Hexane:AcOEt 3:1 - AcOEt) **3d** was obtained as a brown oil (12.4 mg, 40% yield) in a 64% *ee*. Reaction time: 6 d. $[\alpha]_D^{20}$= +10 (*c* 0.082 in $CHCl_3$). HPLC conditions (IC-0.8 mL/min-15% $^i$PrOH-45min). Retention time: 14.22 min (minor) and 18.03 min (major).

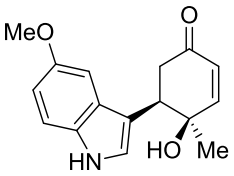
**(4*R*, 5*R*)-4-Hydroxy-4-methyl-5-(7-methyl-1*H*-indol-3-yl)cyclohex-2-enone (3f).**




**3f**

Following the general procedure **B**, the reaction of *p*-quinol **1a** (15 mg, 0.121 mmol), 7-methyl-1*H*-indole **2f** (17.5 mg, 0.133 mmol) and (*S*)-**12h** (8 mg, 0.0121 mmol) in $CH_3CN$ (0.25 mL) gave **3f** as the only diastereomer. After flash column chromatography (eluent Hexane:AcOEt 3:1 - AcOEt) **3f** was obtained as a green solid (18.3 mg, 60% yield) in a 52% *ee*. Reaction time: 6 d. $[\alpha]_D^{20}$= +20 (*c* 0.0702 in $CHCl_3$). HPLC conditions (IC-0.8 mL/min-15% $^i$PrOH-45min). Retention time: 17.73 min (minor) and 25.11 min (major).

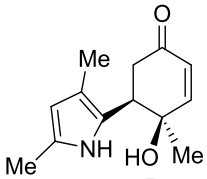
**(4*R*, 5*R*)-4-Hydroxy-5-(5-methoxy-1*H*-indol-3-yl)-4-methylcyclohex-2-enone (3g).**




**3g**

Following the general procedure **B**, the reaction of *p*-quinol **1a** (15 mg, 0.121 mmol), 5-methoxy-1*H*-indole **2g** (19.6 mg, 0.133 mmol) and (*S*)-**12h** (8 mg, 0.0121 mmol) in $CH_3CN$ (0.25 mL) gave **3g** as the only diastereomer. After flash column chromatography (eluent Hexane:AcOEt 3:1 - AcOEt) **3g** was obtained as a brown oil (16.6 mg, 50% yield) in a 62% *ee*. Reaction time: 6 d. $[\alpha]_D^{20}$= +2 (*c* 0.21 in $CHCl_3$). HPLC conditions (IC-0.8 mL/min-17% $^i$PrOH-60min). Retention time: 26.13 min (minor) and 31.43 min (major).

**(4*R*, 5*R*)-5-(3,5-Dimethyl-1*H*-pyrrol-2-yl)-4-hydroxy-4-methylcyclohex-2-enone (5)**




**5**

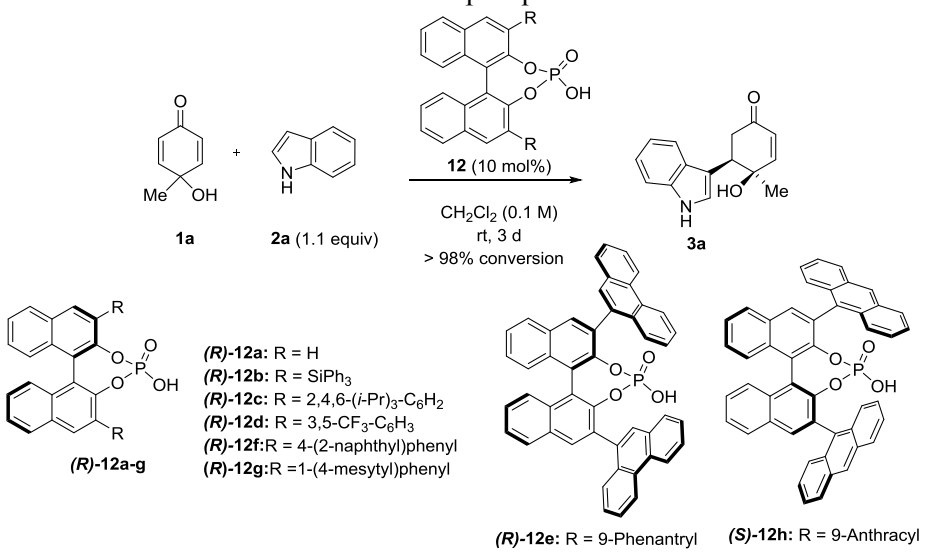
Following the general procedure **B**, the reaction of *p*-quinol **1a** (15 mg, 0.121mmol), 2,4-dimethylpyrrol (14 µg, 0.133 mmol) and (*S*)-**12h** (8 mg, 0.0121 mmol in $CH_3CN$ (0.25 mL) gave the FC alkylation product **9** as the only diastereomer after 24 h. After flash column chromatography (eluent Heptane:AcOEt 3:1-AcOEt) the compound **5** was obtained as a brown oil (20 mg, 75% yield) in 45% *ee*. HPLC-SFC conditions (IB-1 mL/min-5% MeOH-30min). Retention time: 14.45 min (major) and 17.23 min (minor).

# OPTIMIZATION OF THE EXPERIMENTAL CONDITIONS FOR THE ENANTIOSELECTIVE FRIEDEL-CRAFT

## Catalyzed reaction with BINOL derived phosphoric acids 12

Under the conditions shown in Table 1 [$CH_2Cl_2$ (0.1 M), at 25 ºC], (*R*)-**12a-e** catalyzed reactions were completed in 3 days giving the alkylated indole **3a** with null or poor enantiomeric excess. (Table 1, entries 1-5). No evolution was observed with 4-(2-naphthyl)phenyl substituted phosphoric acid **12f**, while a poor conversion (12%) and 0% *ee* resulted in the presence of 1-(4-mesytyl) phenyl substituted **12g** (Table 1, entries 6, 7 respectively). The best enantiomeric excess for **3a** was obtained when 9-anthracenyl substituted phosphoric acid (*S*)-**12h** was use as catalyst (32% *ee*, Table 1, entry 8). The influence of the temperature was then evaluated for the **12h** catalyzed reaction. Decreasing the temperature to -20 ºC, produced an increase of the selectivity giving **3a** with a 55% *ee* (Table 1, entry 9), whereas at -78ºC the enantioselectivity slightly decreased (Table 1, entry 10).

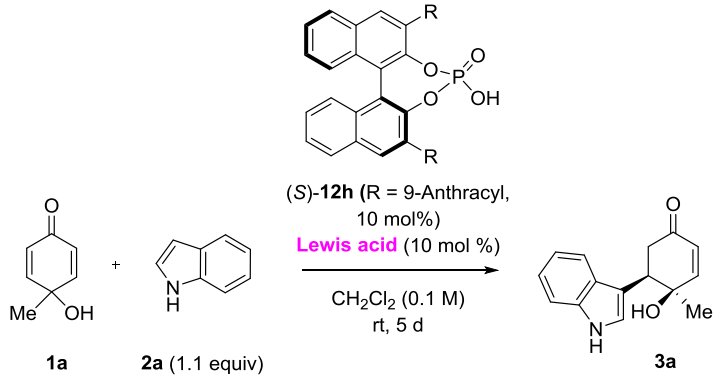
Table 1. Evaluation of chiral BINOL derived phosphoric acids **12**.




| Entry | **12** | R | T (ºC) | t (d) [a] | % *ee*[b] |
|---|---|---|---|---|---|
| 1 | **a** | H | 25 | 3 | 18 |
| 2 | **b** | $SiPh_3$ | 25 | 3 | 0 |
| 3 | **c** | 1,3,5-($^i$Pr)$_3$C$_6$H$_2$ | 25 | 3 | 18 |
| 4 | **d** | 3,5-(CF$_3$)$_2$C$_6$H$_3$ | 25 | 3 | 10 |
| 5 | **e** | 9-phenanthryl | 25 | 3 | 14 |
| 6 | **f** | 4-(2-naphthyl)phenyl | 25 | 7 | NR |
| 7 | **g** | 1-(4-mesytyl) phenyl | 25 | 7 [c] | 0 |
| 8 | **h** | 9-anthracenyl | 25 | 3 | 32 |
| 9 | **h** | 9-anthracenyl | -20 | 3 | 55 |
| 10 | **h** | 9-anthracenyl | -78 | 3 | 40 |

[a] Reaction time controlled by GC-MS. [b]Enantiomeric excess determined by HPLC: IC-0.8 mL/min-15% $^i$PrOH-45 min.[c] Conversion 12%.

Binary acid catalysis was also evaluated, combining different Lewis acids such as $FeCl_3 \cdot 6H_2O$ (10 mol %); $FeCl_3 \cdot 6H_2O$ and AgOTf (30 mol %),[1] $InBr_3$[2] (10 mol %) or $MgF_2$[3] (10 mol %), with the Brønsted acid (*S*)-**12h**.[4] Although good conversions were obtained in most of the cases, the addition of the Lewis acid and (*S*)-**12h** did not produced any improvements in terms of enantioselectivity (Table 2, entries 2-5).




| Entry | Lewis acid | Time | Conversion **3a** | *ee* (%)[a] |
|---|---|---|---|---|
| 1 | - | 3 d | >98% | 32 |
| 2 | $FeCl_3 \cdot 6H_2O$ | 2 d | >98% | 0 |
| 3 | $FeCl_3 \cdot 6H_2O$/AgOTf (30 mol %) | 2 d | >98% | 10 |
| 4 | $InBr_3$ | 2 d | >98% | 0 |
| 5 | $MgF_2$ | 2 d | <50% | 20 |

[a] Enantiomeric ratio measured by HPLC analysis (IC-0.8 mL/min-15% $^i$PrOH-45 min)

## Optimization of the experimental conditions for the enantioselective FC using Chiral phosphoric acid (*S*)-12h

Procedure: To a solution of *p*-quinol **1a** (1 equiv) and indole **2a** (1.1 equiv) in the solvent, concentration and temperature indicated in Table 3, phosphoric acid (*S*)-**12h** (10 mol %) was added and the mixture was stirred for the time indicated in each case. Then, the crude mixture was washed with water and dried over anhydrous $MgSO_4$. The solvent was then removed under reduced pressure and the crude mixture purified by flash chromatography (eluent Hexane:AcOEt 3:1 - AcOEt).

[1] Yang, L.; Zhu, Q.; Guo, S.; Qian, B.; Xia C.; Huang, H. *Chem. Eur. J.* **2010**, *16*, 1638
[2] Lv, J.; Zhang, L.; Zhou, Y.; Nie, Z.; Luo, S.; Cheng, J.-P. *Angew. Chem. Int. Ed.* **2011**, *50*, 6610
[3] Lv, J.; Li, X.; Zhong, L.; Luo, S.; Cheng, J.-P. *Org. Lett.* **2010**, *12*, 1096-1099
[4] Yamamoto, H.; Futatsugi, K. *Angew. Chem., Int. Ed.* **2005**, *44*, 1924.

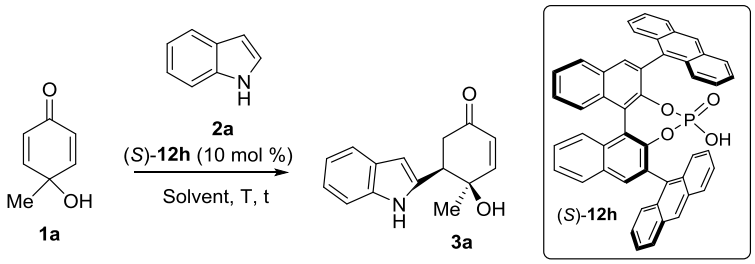



Table 3. Optimization of the experimental conditions for the (*S*)-**12h** catalyzed reaction of **1a** and **2a**

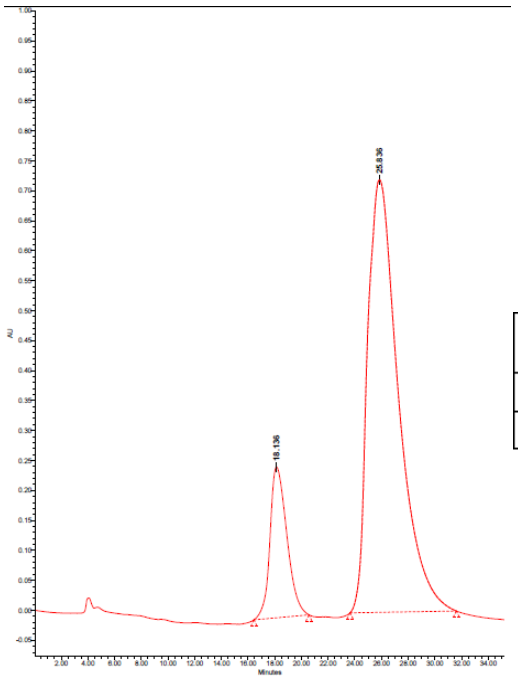
| Entry | Solvent | Conc. (M) | T (ºC) | t (d) | Conversion% | % *ee*[a] |
|---|---|---|---|---|---|---|
| 1 | DCE | 0.1 | 25 | 3 | > 98 | 38 |
| 2 | Toluene | 0.1 | 25 | 2 | > 98 | 28 |
| 3 | THF | 0.1 | 25 | 6 | 65 | 50 |
| 4 | EtOH | 0.1 | 25 | 6 | 50 | 26 |
| 5 | $CH_3CN$ | 0.1 | 25 | 6 | > 80 | 50 |
| 6 | $CH_3CN$ | 0.5 | 25 | 2 | > 98 | 58 |
| **7** | **$CH_3CN$** | **0.5** | **-20** | **6** | **72[b]** | **72** |
| 8 | $CH_3CN$, 4Å MS | 0,5 | -20 | 10 | 17 | 44 |
| 9 | $CH_3CN$ | 0.5 | -40 | 6 | 40 | 70 |
| 10 | AcOEt | 0.5 | -20 | 6 | 50 | 50 |
| 11 | Dioxane | 0.5 | -20 | 6 | 80 | 44 |

[a] Enantiomeric excess was determined by HPLC IC-0.8 mL/min-15% $^i$PrOH-45 min. [b] Isolated yield of pure **3a**.

As shown in Table 3, using a 0.1 M concentration, DCE and toluene gave a complete transformation at 25 ºC after 3 or 2 days, leading to **3a** with modest ee (Table 3, entries 1 and 2). THF produced a slower reaction giving the FC product in 50 % ee. A decrease of reactivity and selectivity was observed with ethanol (Table 1, entry 4). The aprotic polar solvent $CH_3CN$ improved the reactivity and selectivity (Table 1, entry 5), which were even better at higher concentration (0.5 M, Table 1, entry 6). The best result was obtained when the reaction was performed under the above conditions at -20 ºC, allowing the isolation of pure **3a**, after column chromatography in 72 % yield and 72 % *ee* (Table 1, entry 7). Adding 4 Å molecular sieves to this reaction mixture produced a significant delay in the evolution and, after 10 days, only a 17 % of conversion resulted, and 44% of enantiomeric excess was observed (Table 1, entry 8). A lower temperature (-40 ºC) slightly deteriorated the selectivity (Table 1, entry 9). Other solvents such as AcOEt or dioxane neither improved the result of entry 7.

## DETERMINATION OF THE ABSOLUTE CONFIGURATION

The (4*R*, 5*R*) absolute configuration of the major enantiomer **3a** formed in the presence of (*S*)-**12h**, was established by comparison of the experimental ECD spectra (in $CH_3CN$) of pure enantiomers (separated by chiral-HPLC from an enantioenriched mixture: Chiral-HPLC conditions: Chiralpak-IC, 0.46 x 25 cm, 5 µm, Hexane-$^i$PrOH (85:15), 0.8 mL/min). Retention time of both enantiomers: major = 25.84 min (peak 2) and minor = 18.14 min (peak 1) with the simulated TD-DFT-ECD spectra (OPBE/PCM ($CH_3CN$)6-31G //B3LYP/6-31G* level).[5]



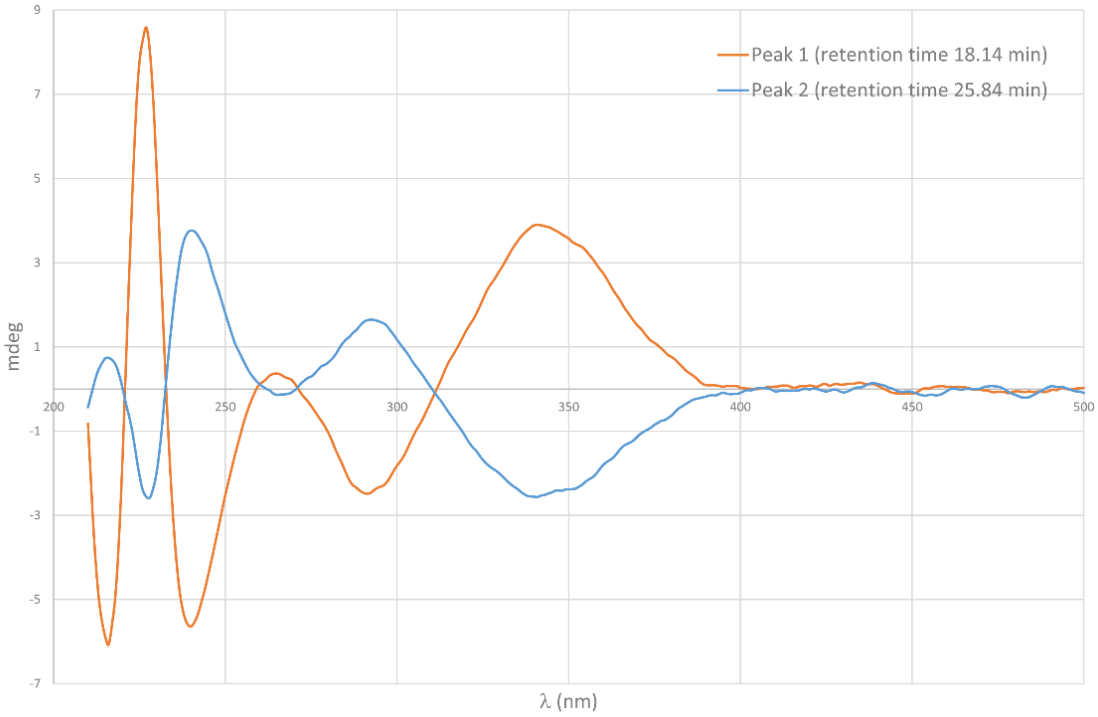
| | Name | Retention Time (min) | Area (µV*sec) | % Area | Height (µV) |
|---|---|---|---|---|---|
| 1 | | 18.136 | 22162050 | 16.03 | 251451 |
| 2 | | 25.836 | 116055097 | 83.97 | 721262 |

Chiral-HPLC 16:84 enantiomer mixture of **3a**

## EXPERIMENTAL ECD SPECTRA

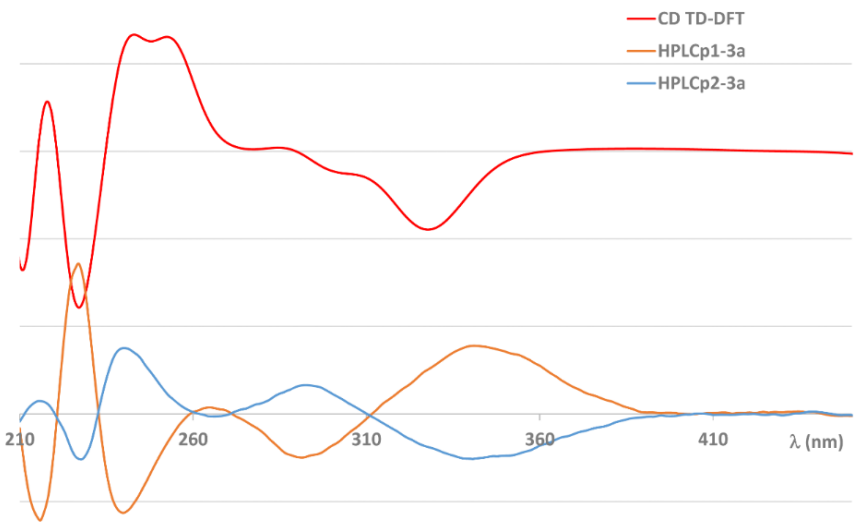
**Figure 2**. Experimental CD spectra (obtained by a JASCO J-815 CD Spectrometer) of **peak 2 (3a)** ($6.84 \times 10^{-3}$M) and **peak 1 (3a)** ($7.25 \times 10^{-3}$M) in $CH_3CN$. A 16:84 enantiomer mixture of **3a** (**peak 1**:**peak 2)** was separated by chiral-HPLC (Chiralpak-IC 0.46 x 25 cm, Hexane-$^i$PrOH 85:15, 0.8 mL/min).

[5] Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Mennucci, B.; Petersson, G. A.; Nakatsuji, H.; Caricato, M.; Li, X.; Hratchian, H. P.; Izmaylov, A. F.; Bloino, J.; Zheng, G.; Sonnenberg, J. L.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Vreven, T.; Montgomery, J. A.; Peralta, J. E.; Ogliaro, F.; Bearpark, M.; Heyd, J. J.; Brothers, E.; Kudin, K. N.; Staroverov, V. N.; Kobayashi, R.; Normand, J.; Raghavachari, K.; Rendell, A.; Burant, J. C.; Iyengar, S. S.; Tomasi, J.; Cossi, M.; Rega, N.; Millam, J. M.; Klene, M.; Knox, J. E.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Martin, R. L.; Morokuma, K.; Zakrzewski, V. G.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Dapprich, S.; Daniels, A. D.; Farkas; Foresman, J. B.; Ortiz, J. V.; Cioslowski, J.; Fox, D. J., Gaussian 09, Revision B.01, Wallingford CT, 2009.




**TD-DFT ECD SPECTRA versus EXPERIMENTAL ECD SPECTRA**

**Figure 3**. TD-DFT (*R*,*R*-**3a**) versus experimental CD-spectra (**3a**, in $CH_3CN$). TD-DFT simulated CD spectrum computed (after UV correction) at the OPBE/PCM ($CH_3CN$)/6-31G//B3LYP/6-31G* level.




The most stable conformations of the (4*R*, 5*R*) enantiomer (enclosed in a 3 kcal/mol window) were subjected to minimization by DFT calculations, in vacuo, at the B3LYP/6-311G* level to evaluate the free energy and the population percentages on ΔG assuming Boltzmann statistic at T = 298 ºK.[5]

| Conformer | ΔEzpve | ΔG | Pop % (ΔG) |
|---|---|---|---|
| **I min_H2O_R_B3LYP** | 3.22 | 2.80 | 0.876 |
| **II min_H2O_R_B3LYP_conf_1** | 0.00 | 0.00 | 99.124 |

Then, electronic excitation energies, oscillator strengths and rotational strengths were calculated for the first 50 excited states at the TD-DFT-OPBE/PCM ($CH_3CN$)/6-311G level.[6] The final simulated ECD spectra was obtained taking into account the populations rations determined assuming Boltzmann statistics.

**I** **II**

**Figure 1.** Most stable conformations computed (B3LYP/6-311G*) for the (4*R*,5*R*) enantiomer.

[6] a) Onsager, L. *J. Am. Chem. Soc.* **1936**, *58*, 1486-1493. b) Becke, A. D. *J. Chem. Phys.* **1993**, 98, 5648-5652. c) Tomasi, J.; Persico, M.*Chem. Rev.* **1994**, *94*, 2027 –2094; d) Tomasi, J.; Mennucci, B.; Cammi, R. *Chem. Rev.* **2005**, *105*, 2999 –3094.

**I**

| | | | |
|---|---|---|---|
| 6 | 5.062301000 | 2.223846000 | -2.091727000 |
| 6 | 4.134395000 | 2.097861000 | -1.038556000 |
| 6 | 3.285297000 | 3.215576000 | -0.781119000 |
| 6 | 3.337368000 | 4.404801000 | -1.514183000 |
| 6 | 4.265791000 | 4.484949000 | -2.542238000 |
| 6 | 5.116822000 | 3.401214000 | -2.825093000 |
| 7 | 2.470101000 | 2.879902000 | 0.270148000 |
| 6 | 2.761071000 | 1.609879000 | 0.680889000 |
| 6 | 3.778319000 | 1.067385000 | -0.083966000 |
| 6 | 4.265198000 | -0.341876000 | 0.175498000 |
| 6 | 4.341617000 | -1.244222000 | -1.068448000 |
| 6 | 5.633249000 | -1.224392000 | -1.867827000 |
| 6 | 6.836840000 | -0.758006000 | -1.162182000 |
| 6 | 6.805471000 | -0.366792000 | 0.125695000 |
| 6 | 5.587178000 | -0.406187000 | 1.015383000 |
| 8 | 5.670628000 | -1.605808000 | -3.029630000 |
| 8 | 5.641750000 | 0.652282000 | 1.958797000 |
| 6 | 5.648382000 | -1.688521000 | 1.852863000 |
| 1 | 7.760280000 | -0.737752000 | -1.742970000 |
| 1 | 7.716434000 | -0.021179000 | 0.621490000 |
| 1 | 3.494517000 | -0.775808000 | 0.828365000 |
| 1 | 3.514269000 | -1.043152000 | -1.757905000 |
| 1 | 5.343752000 | 1.444910000 | 1.489972000 |
| 1 | 4.816707000 | -1.694666000 | 2.567389000 |
| 1 | 5.600171000 | -2.588602000 | 1.232532000 |
| 1 | 6.581382000 | -1.719059000 | 2.426474000 |
| 1 | 2.216216000 | 1.161203000 | 1.504952000 |
| 1 | 1.758004000 | 3.470069000 | 0.667325000 |
| 1 | 5.737606000 | 1.412487000 | -2.341305000 |
| 1 | 5.835508000 | 3.485909000 | -3.640031000 |
| 1 | 2.671993000 | 5.238354000 | -1.287343000 |
| 1 | 4.333950000 | 5.396119000 | -3.136110000 |
| 1 | 4.212437000 | -2.292153000 | -0.755655000 |

**II**

| | | | |
|---|---|---|---|
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| 6 | 1.615002000 | 0.025949000 | -0.249809000 |
| 6 | 2.387627000 | -1.079126000 | 0.198635000 |
| 6 | 3.771938000 | -1.005598000 | 0.371271000 |
| 6 | 4.391523000 | 0.200360000 | 0.080665000 |
| 6 | 3.649370000 | 1.309433000 | -0.368202000 |
| 7 | 1.518021000 | -2.130426000 | 0.387623000 |
| 6 | 0.239179000 | -1.732458000 | 0.066345000 |
| 6 | 0.236372000 | -0.414101000 | -0.325692000 |
| 6 | -0.942226000 | 0.398954000 | -0.814511000 |
| 6 | -2.095255000 | -0.496160000 | -1.315078000 |
| 6 | -2.870498000 | -1.188746000 | -0.201520000 |
| 6 | -3.000549000 | -0.438186000 | 1.062883000 |
| 6 | -2.375473000 | 0.729056000 | 1.258752000 |
| 6 | -1.486810000 | 1.419468000 | 0.245603000 |
| 8 | -3.366783000 | -2.290836000 | -0.349645000 |
| 8 | -0.419477000 | 2.076720000 | 0.932327000 |
| 6 | -2.266816000 | 2.560919000 | -0.419973000 |
| 1 | -3.619553000 | -0.895291000 | 1.829226000 |
| 1 | -2.482659000 | 1.264364000 | 2.199704000 |
| 1 | -0.586722000 | 0.997891000 | -1.660907000 |
| 1 | -1.738165000 | -1.257515000 | -2.010485000 |
| 1 | 0.202813000 | 1.407254000 | 1.246615000 |
| 1 | -1.609181000 | 3.099627000 | -1.106316000 |
| 1 | -3.138385000 | 2.199604000 | -0.967779000 |
| 1 | -2.608509000 | 3.266593000 | 0.339828000 |
| 1 | -0.572773000 | -2.440955000 | 0.126014000 |
| 1 | 1.775026000 | -3.057176000 | 0.682508000 |
| 1 | 1.713715000 | 2.105135000 | -0.854955000 |
| 1 | 4.164979000 | 2.239401000 | -0.584505000 |
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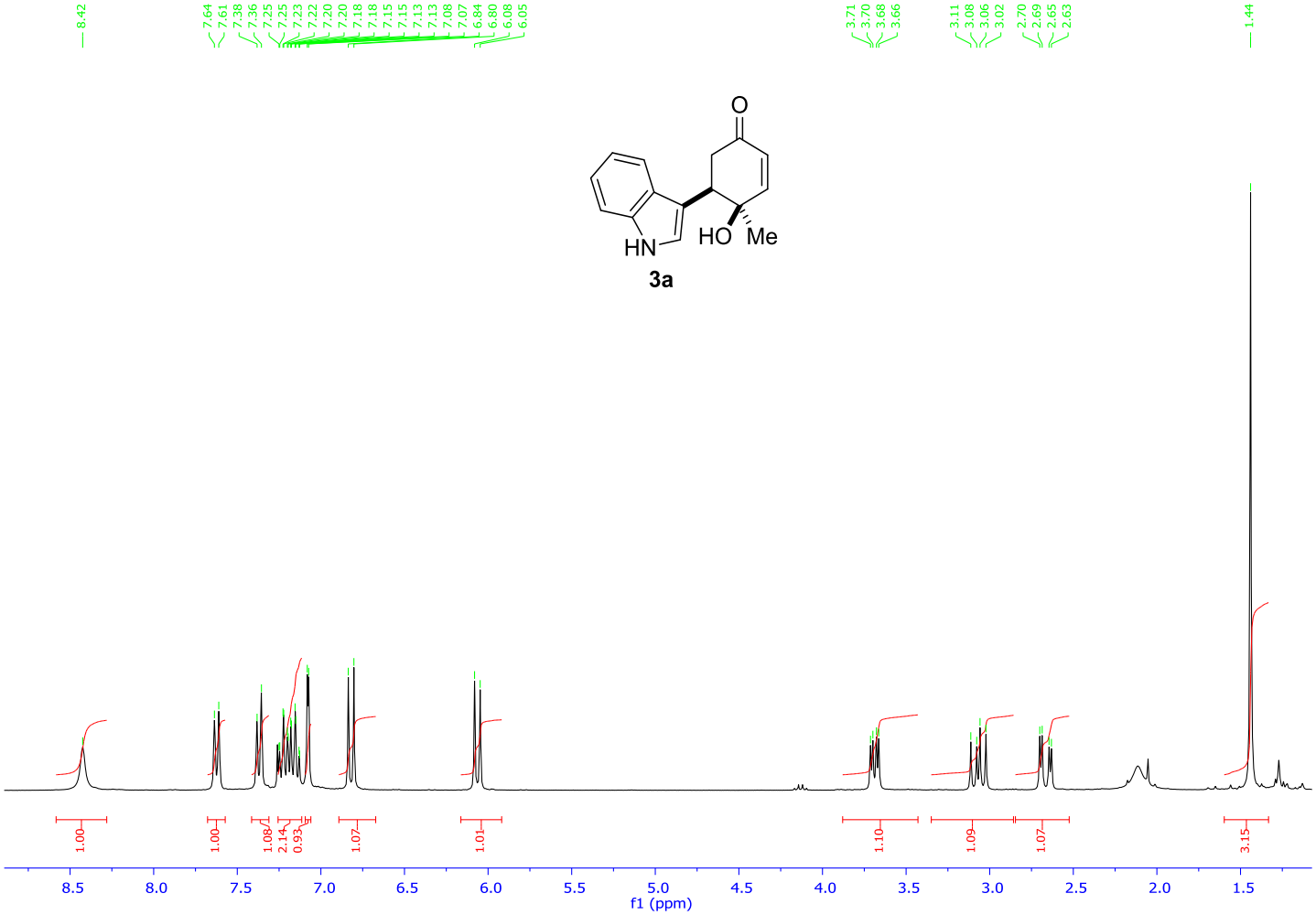
# NMR SPECTRA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2.69
2.65
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HO
Me
3a
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1.00
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0.93
1.07
1.01
1.10
1.09
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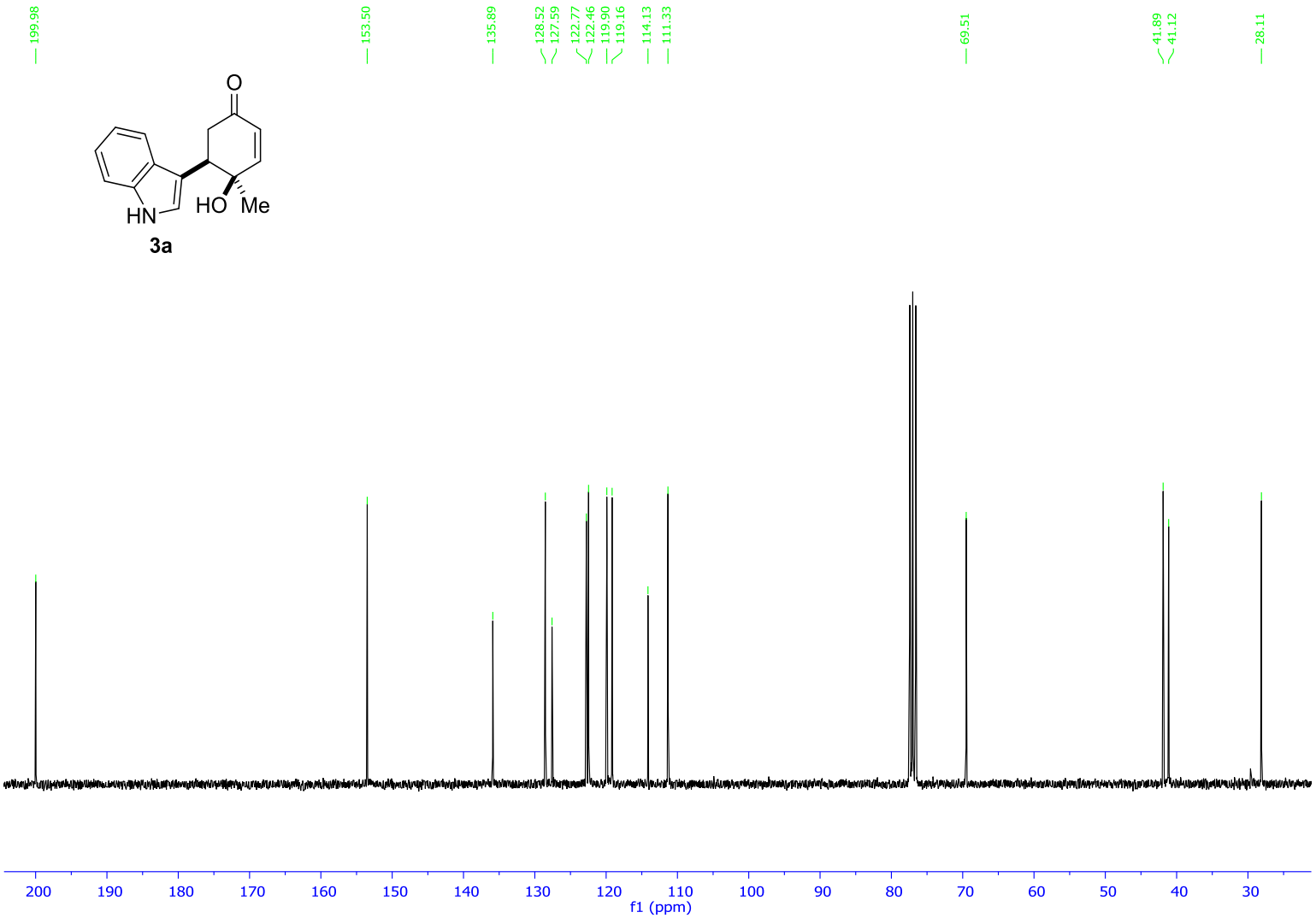
f1 (ppm)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122.46
119.90
119.16
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69.51
41.89
41.12
28.11
O
HN
HO
Me
3a
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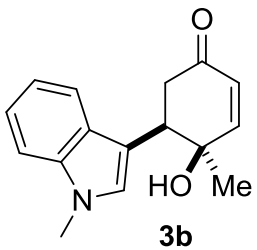
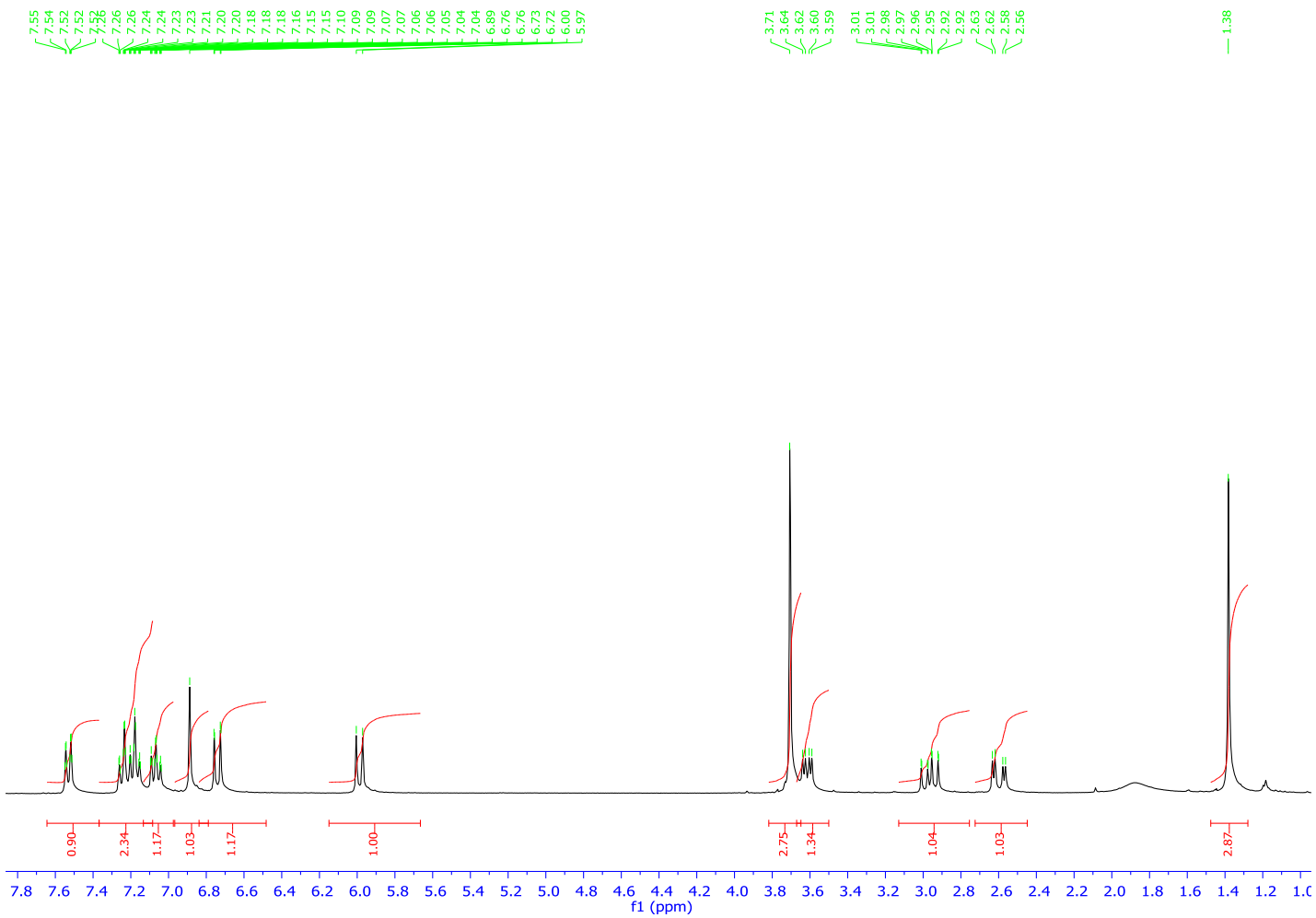
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
f1 (ppm)


O
HO
Me
N

**3b**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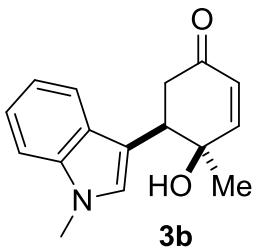
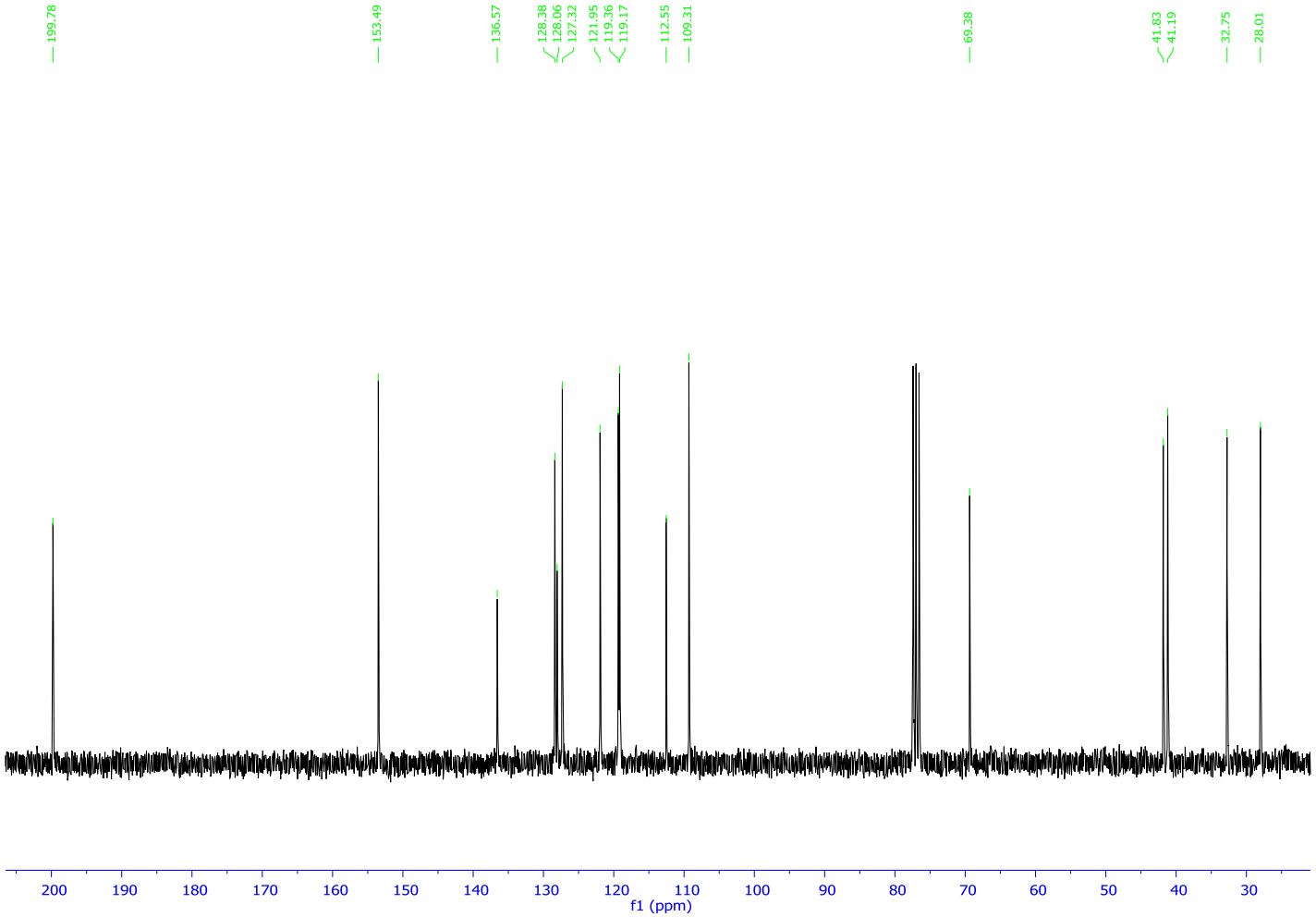
3.71 3.64 3.62 3.60 3.59
3.01 3.01 2.98 2.97 2.96 2.95 2.92 2.92 2.63 2.62 2.58 2.56
1.38
0.90 2.34 1.17 1.03 1.17 1.00 2.75 1.34 1.04 1.03 2.87
7.8 7.6 7.4 7.2 7.0 6.8 6.6 6.4 6.2 6.0 5.8 5.6 5.4 5.2 5.0 4.8 4.6 4.4 4.2 4.0 3.8 3.6 3.4 3.2 3.0 2.8 2.6 2.4 2.2 2.0 1.8 1.6 1.4 1.2
f1 (ppm)


O
HO
Me
N

**3b**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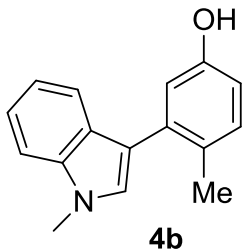
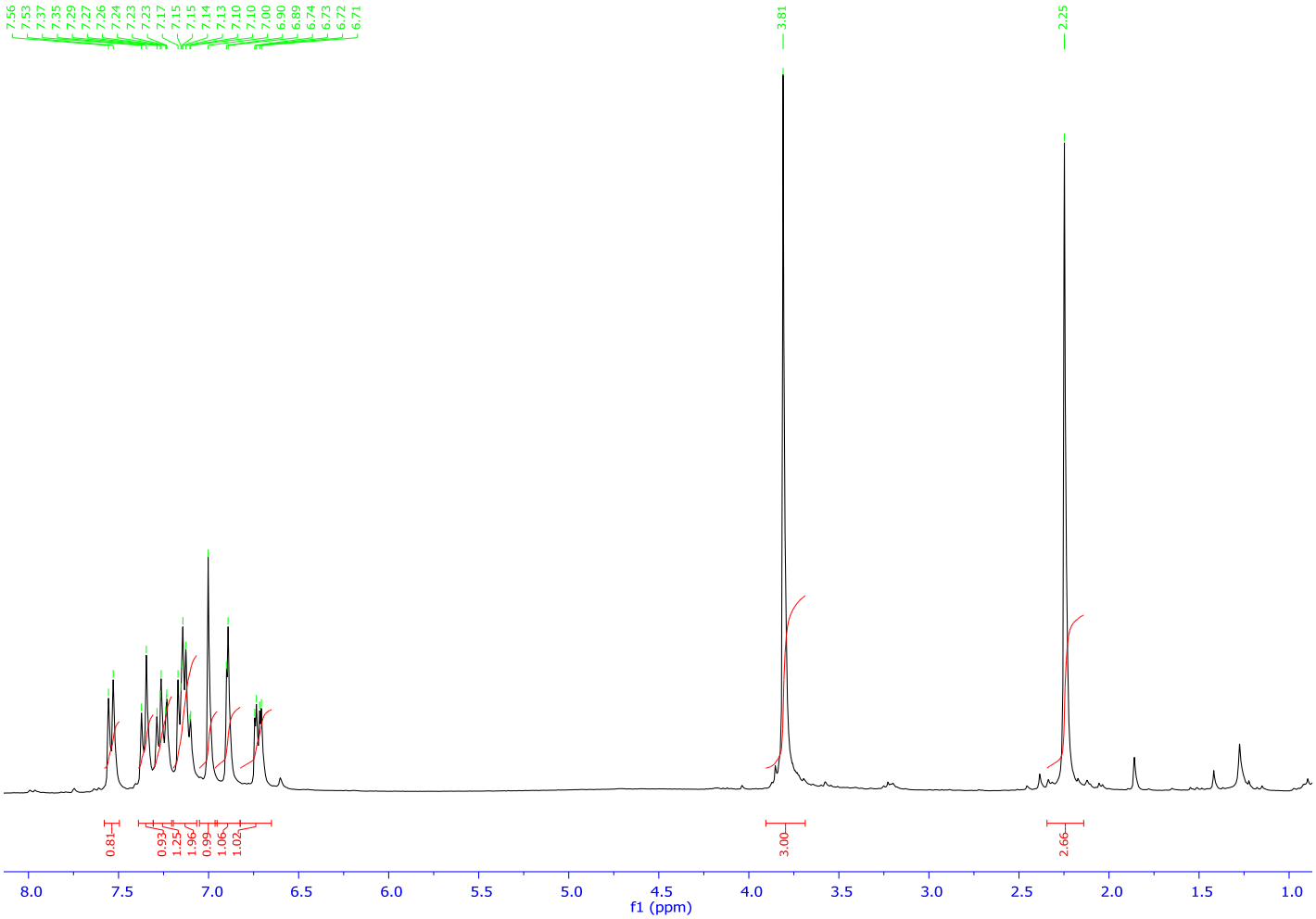
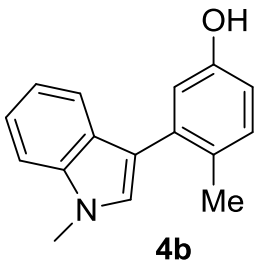
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
f1 (ppm)

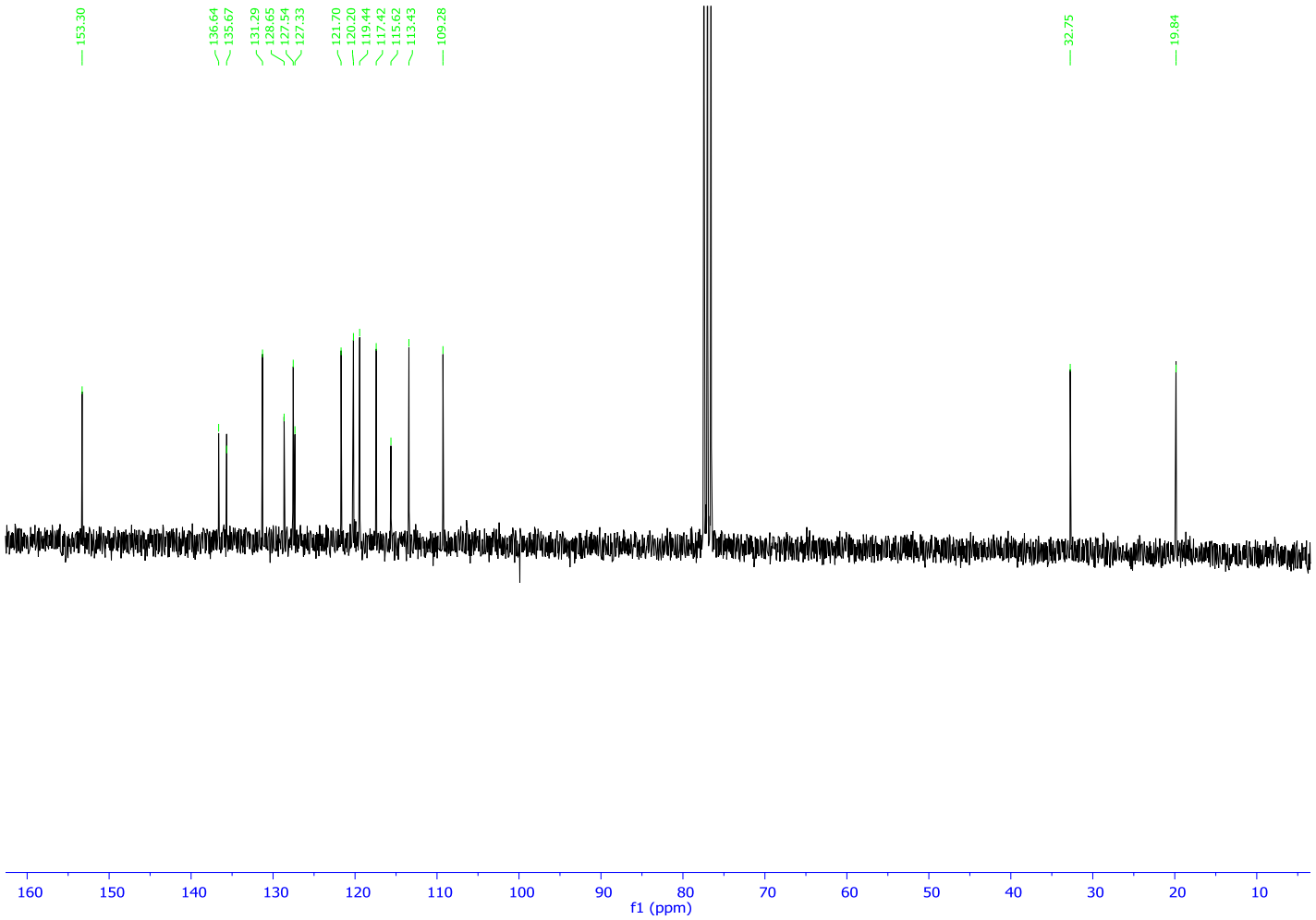

OH
N
Me

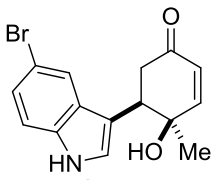
**4b**


7.56
7.53
7.37
7.35
7.29
7.27
7.26
7.24
7.23
7.23
7.17
7.15
7.15
7.14
7.13
7.10
7.10
7.00
6.90
6.89
6.74
6.73
6.72
6.71
3.81
2.25
0.81
0.93
1.25
1.96
0.99
1.06
1.02
3.00
2.66
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
f1 (ppm)

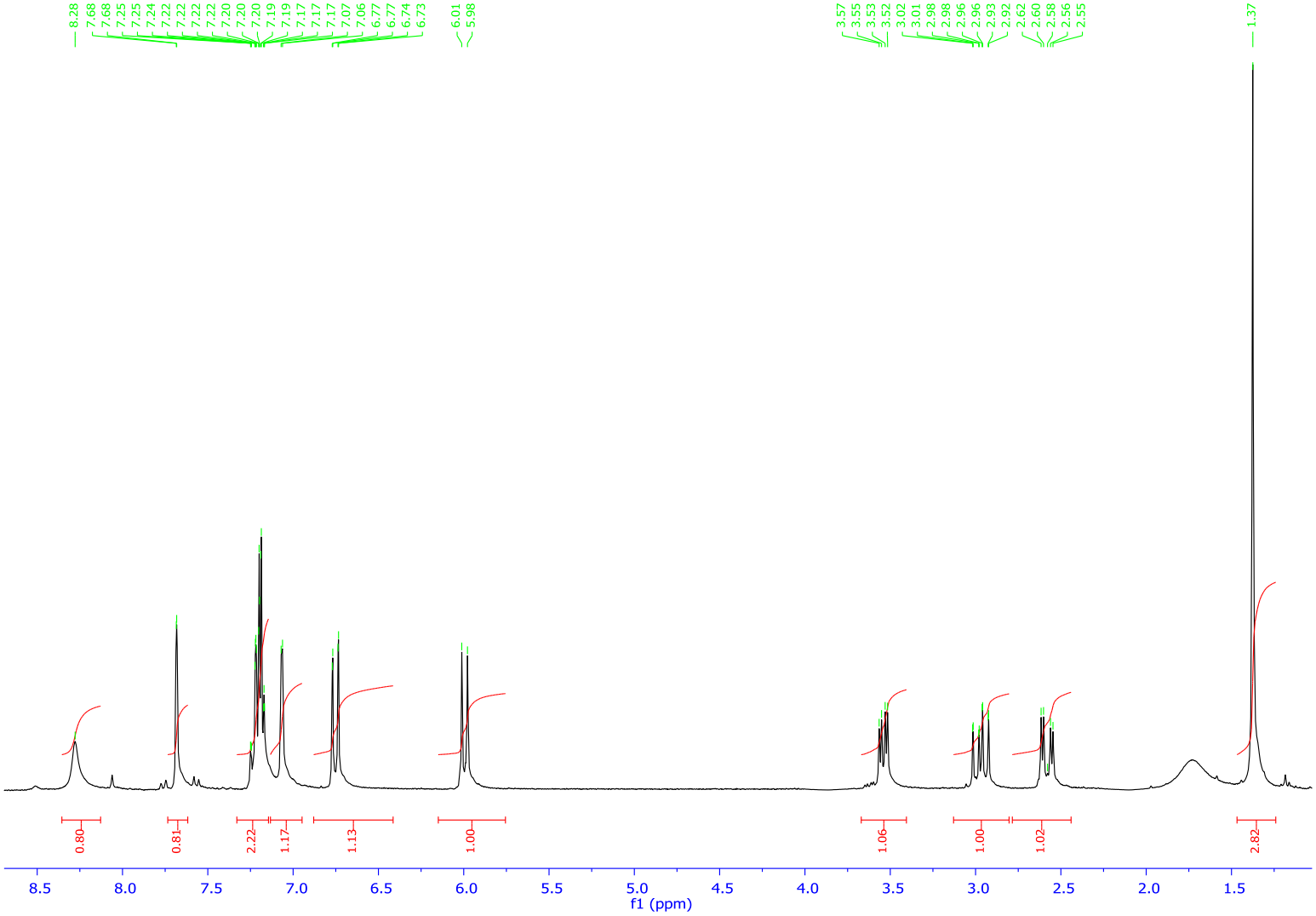

OH
N
Me

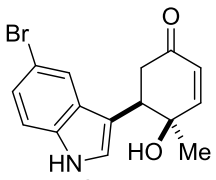
**4b**


153.30
136.64
135.67
131.29
128.65
127.54
127.33
121.70
120.20
119.44
117.42
115.62
113.43
109.28
32.75
19.84
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

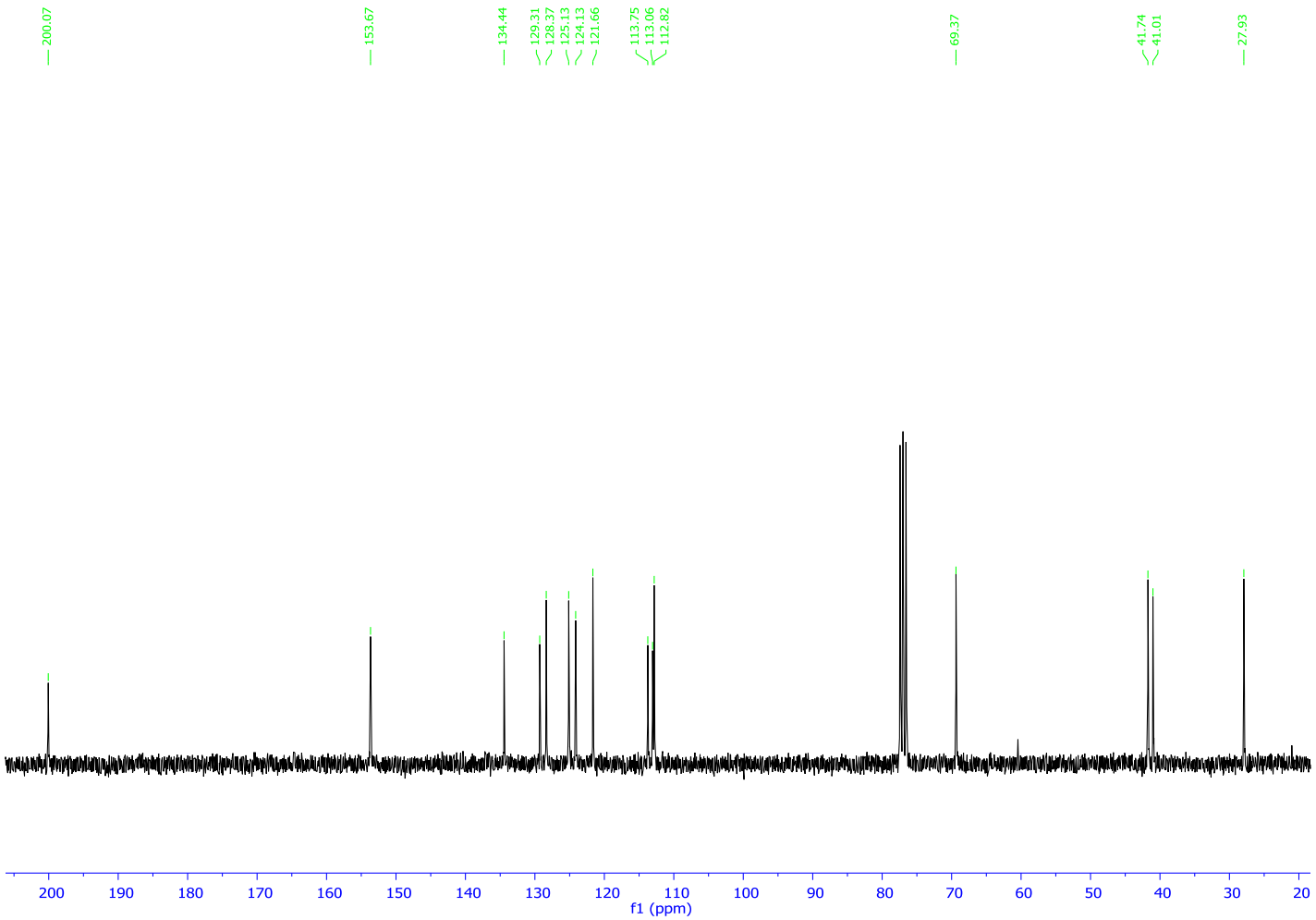

Br
O
HN
HO
Me

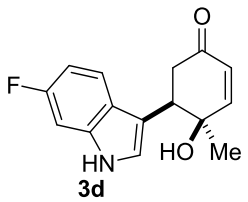
**3c**


8.28
7.68
7.68
7.25
7.25
7.24
7.22
7.22
7.22
7.22
7.20
7.20
7.20
7.19
7.19
7.17
7.17
7.17
7.17
7.07
7.06
6.77
6.77
6.74
6.73
6.01
5.98
3.57
3.55
3.53
3.52
3.02
3.01
2.98
2.98
2.96
2.96
2.93
2.92
2.62
2.60
2.58
2.56
2.55
1.37
0.80
0.81
2.22
1.17
1.13
1.00
1.06
1.00
1.02
2.82
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
f1 (ppm)

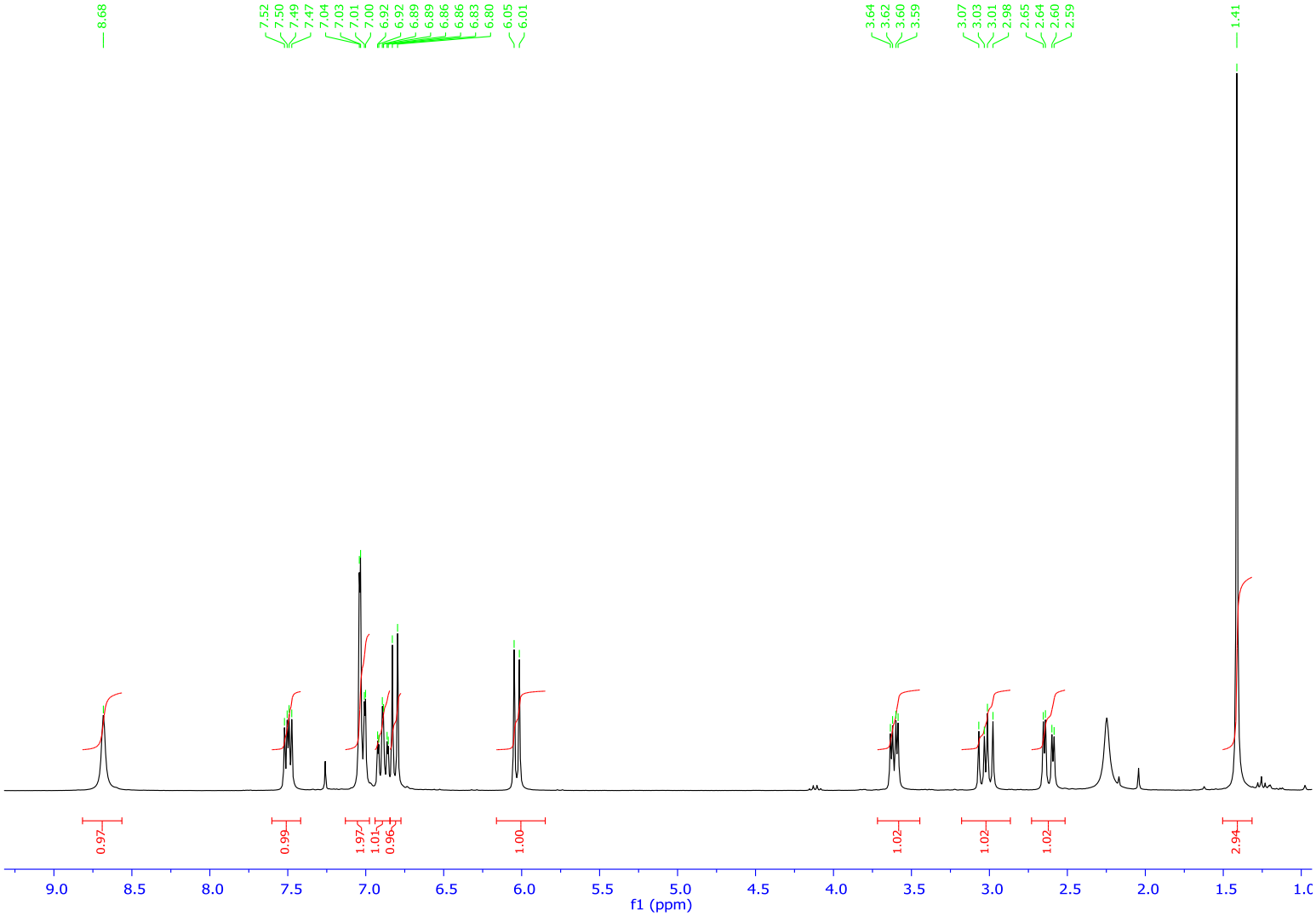

Br
O
HN
HO
Me

**3c**


200.07
153.67
134.44
129.31
128.37
125.13
124.13
121.66
113.75
113.06
112.82
69.37
41.74
41.01
27.93
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
f1 (ppm)


O
F
HN
HO
Me

**3d**


8.68
7.52
7.50
7.49
7.47
7.04
7.03
7.01
7.00
6.92
6.92
6.89
6.89
6.86
6.86
6.83
6.80
6.05
6.01
3.64
3.62
3.60
3.59
3.07
3.03
3.01
2.98
2.65
2.64
2.60
2.59
1.41
0.97
0.99
1.97
1.01
0.96
1.00
1.02
1.02
1.02
2.94
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
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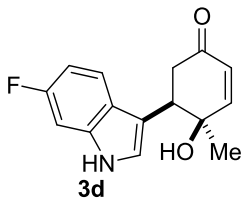
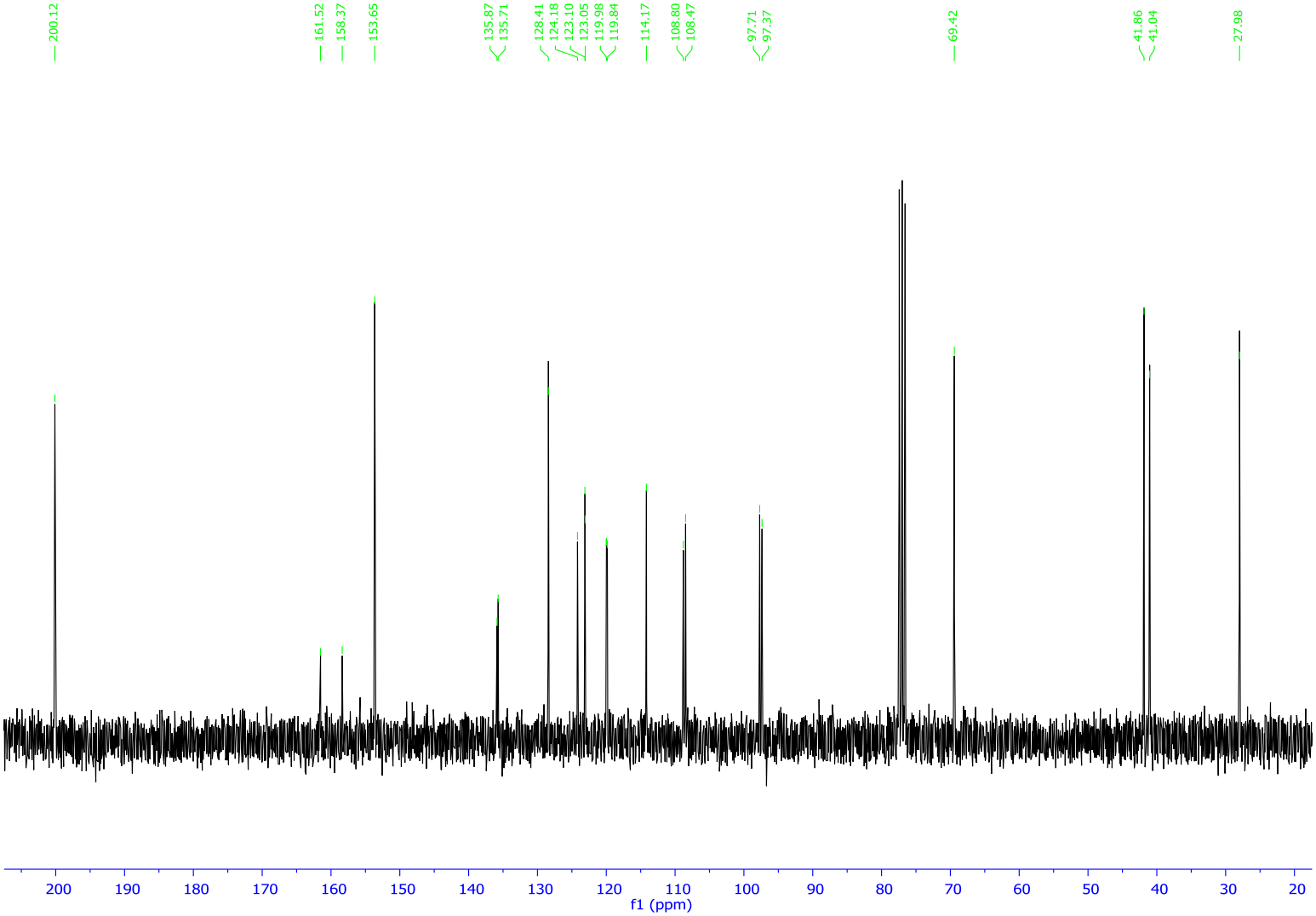
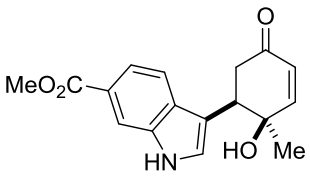
2.5
2.0
1.5
f1 (ppm)

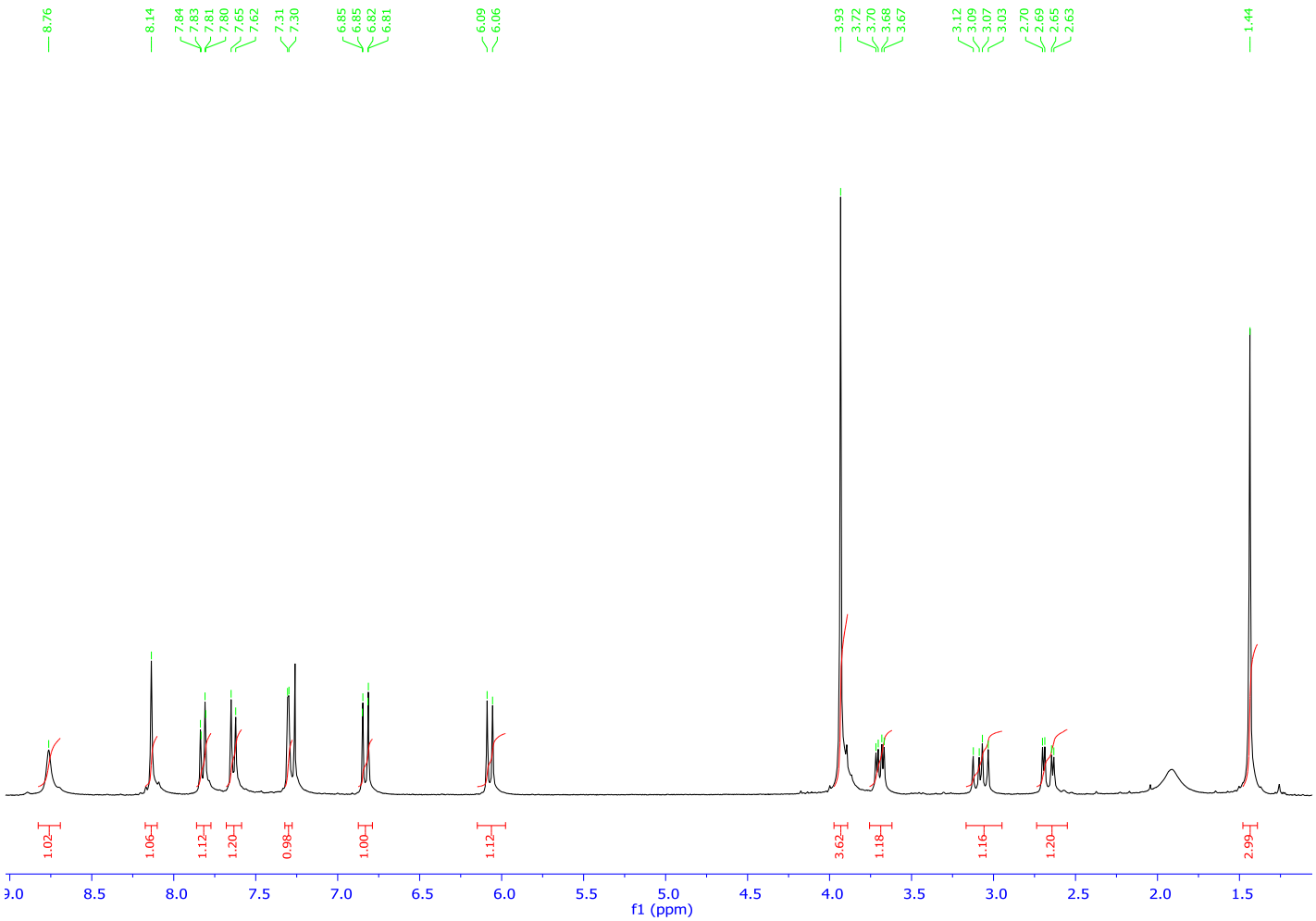

O
F
HN
HO
Me

**3d**


200.12
161.52
158.37
153.65
135.87
135.71
128.41
124.18
123.10
123.05
119.98
119.84
114.17
108.80
108.47
97.71
97.37
69.42
41.86
41.04
27.98
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
f1 (ppm)


O
MeO2C
HN
HO
Me

**3e**


8.76
8.14
7.84
7.83
7.81
7.80
7.65
7.62
7.31
7.30
6.85
6.85
6.82
6.81
6.09
6.06
3.93
3.72
3.70
3.68
3.67
3.12
3.09
3.07
3.03
2.70
2.69
2.65
2.63
1.44
1.02
1.06
1.12
1.20
0.98
1.00
1.12
3.62
1.18
1.16
1.20
2.99
9.0
8.5
8.0
7.5
7.0
6.5
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5.0
4.5
4.0
3.5
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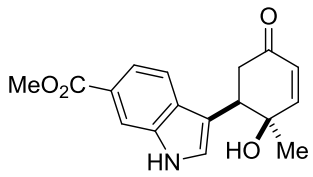
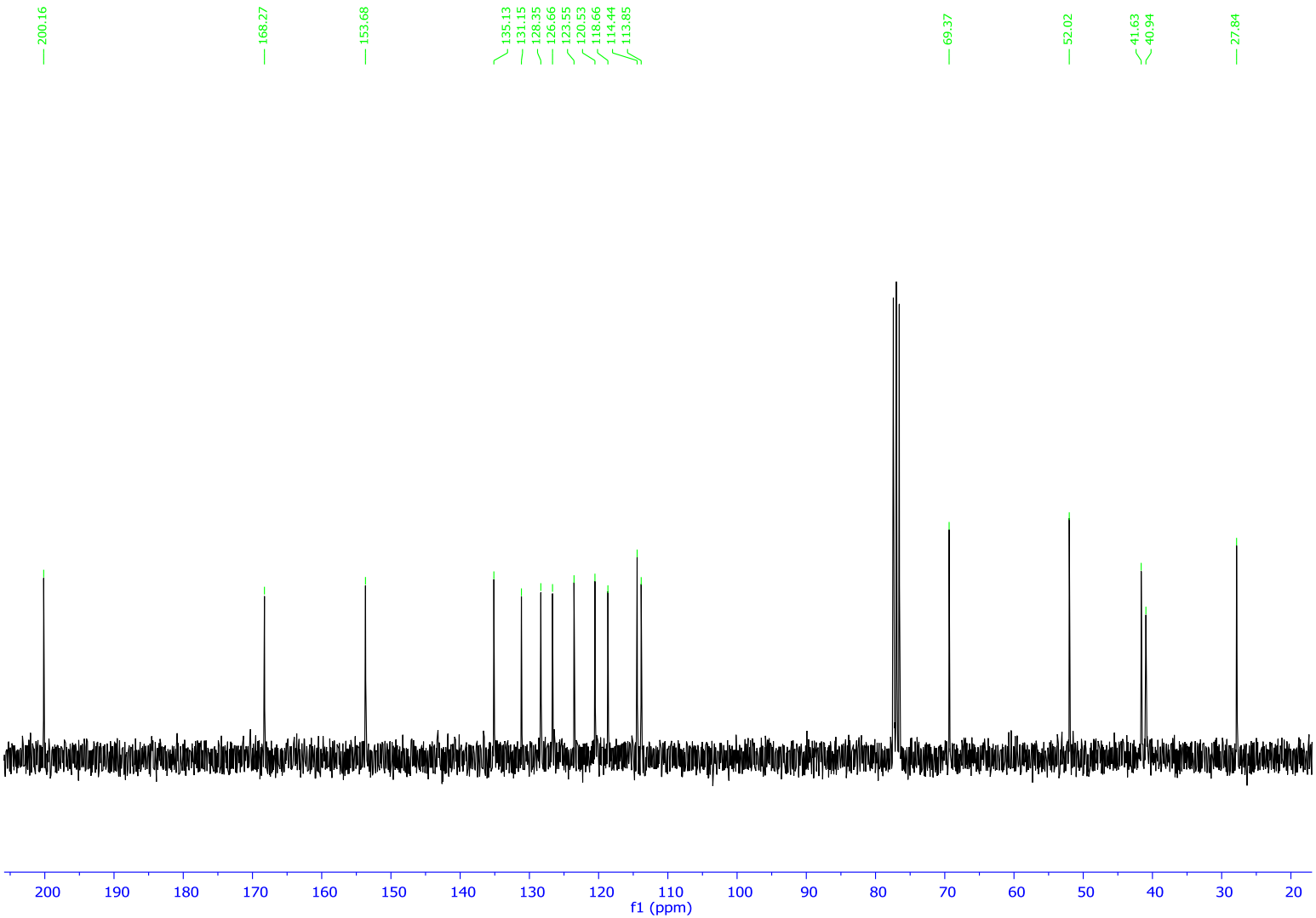
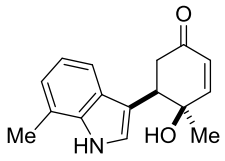
2.5
2.0
1.5
f1 (ppm)

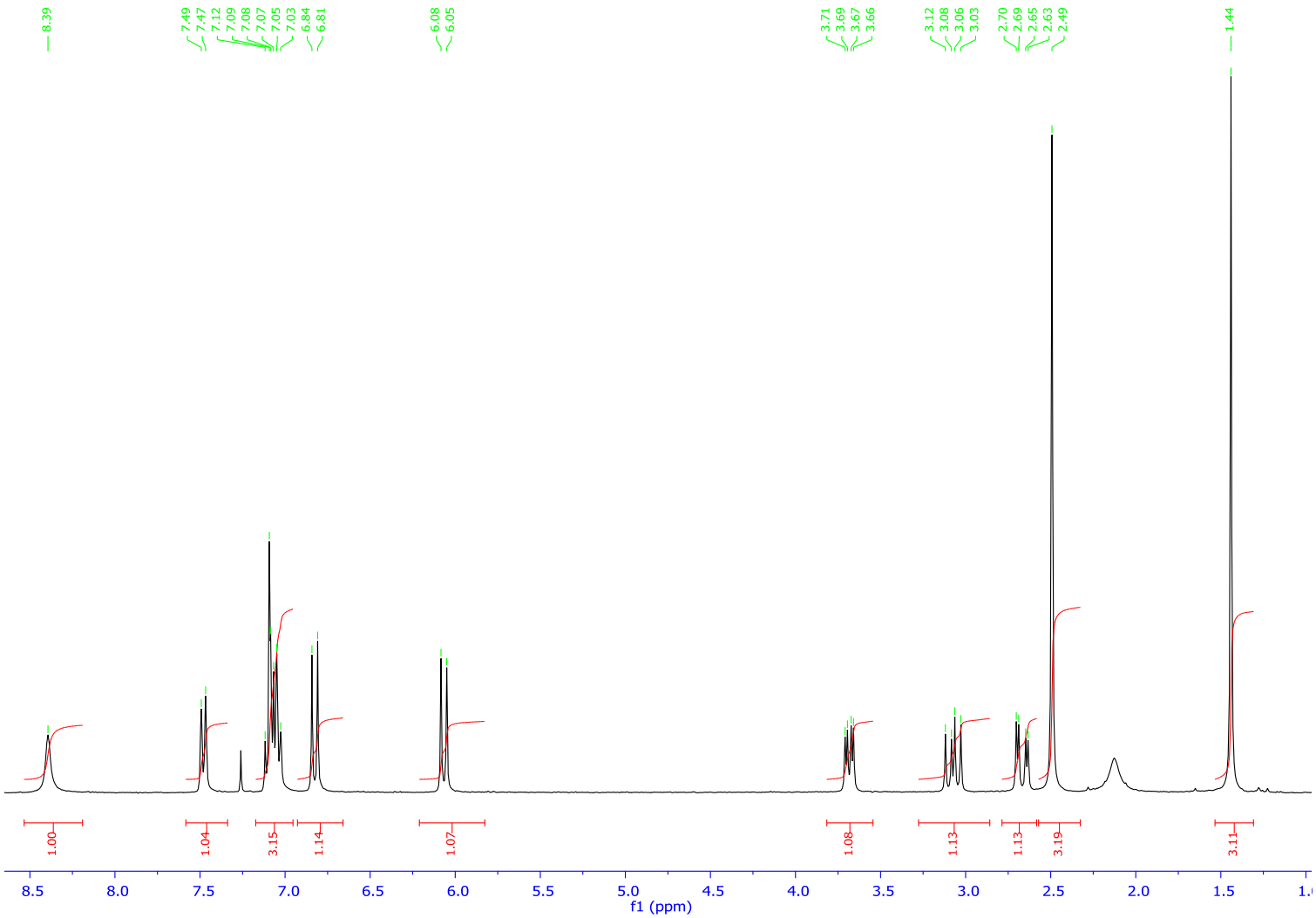

O
MeO2C
HN
HO
Me

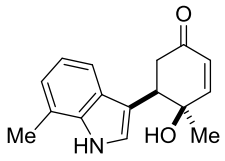
**3e**


200.16
168.27
153.68
135.13
131.15
128.35
126.66
123.55
120.53
118.66
114.44
113.85
69.37
52.02
41.63
40.94
27.84
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
f1 (ppm)

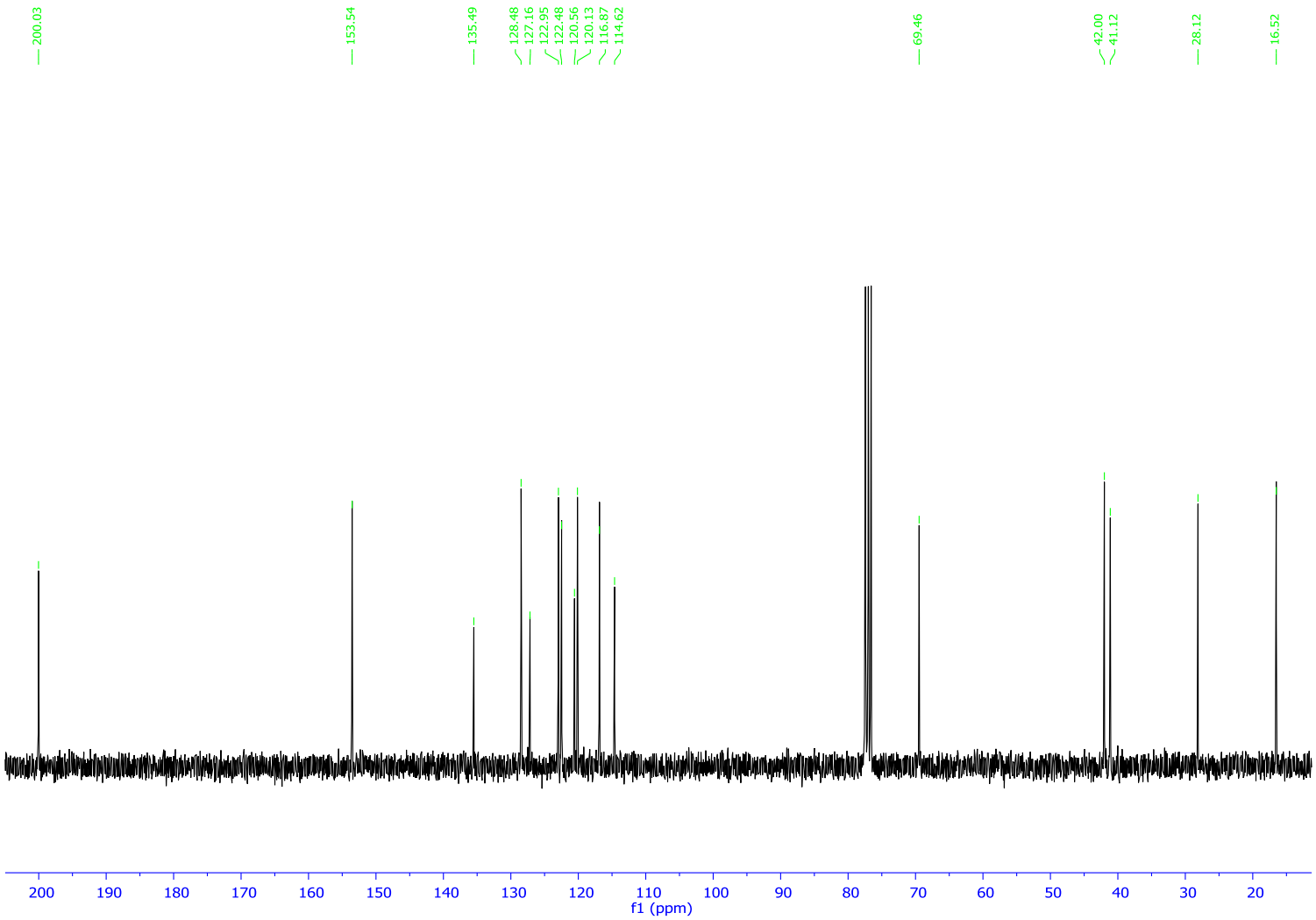

O
Me
HN
HO
Me

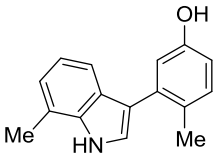
**3f**


8.39
7.49
7.47
7.12
7.09
7.08
7.07
7.05
7.03
6.84
6.81
6.08
6.05
3.71
3.69
3.67
3.66
3.12
3.08
3.06
3.03
2.70
2.69
2.65
2.63
2.49
1.44
1.00
1.04
3.15
1.14
1.07
1.08
1.13
1.13
3.19
3.11
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
f1 (ppm)

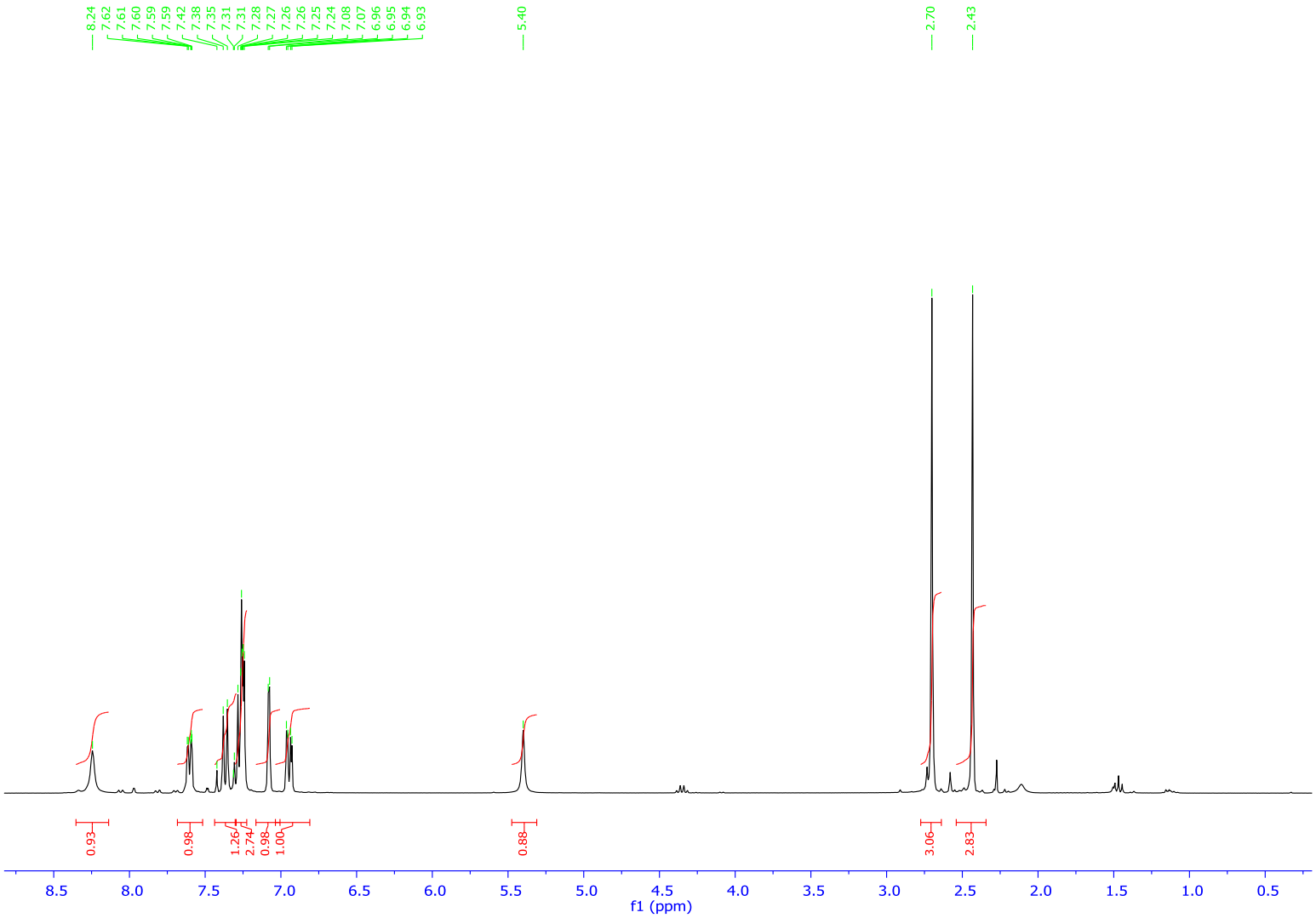

O
Me
HN
HO
Me

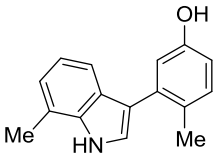
**3f**


200.03
153.54
135.49
128.48
127.16
122.95
122.48
120.56
120.13
116.87
114.62
69.46
42.00
41.12
28.12
16.52
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
f1 (ppm)

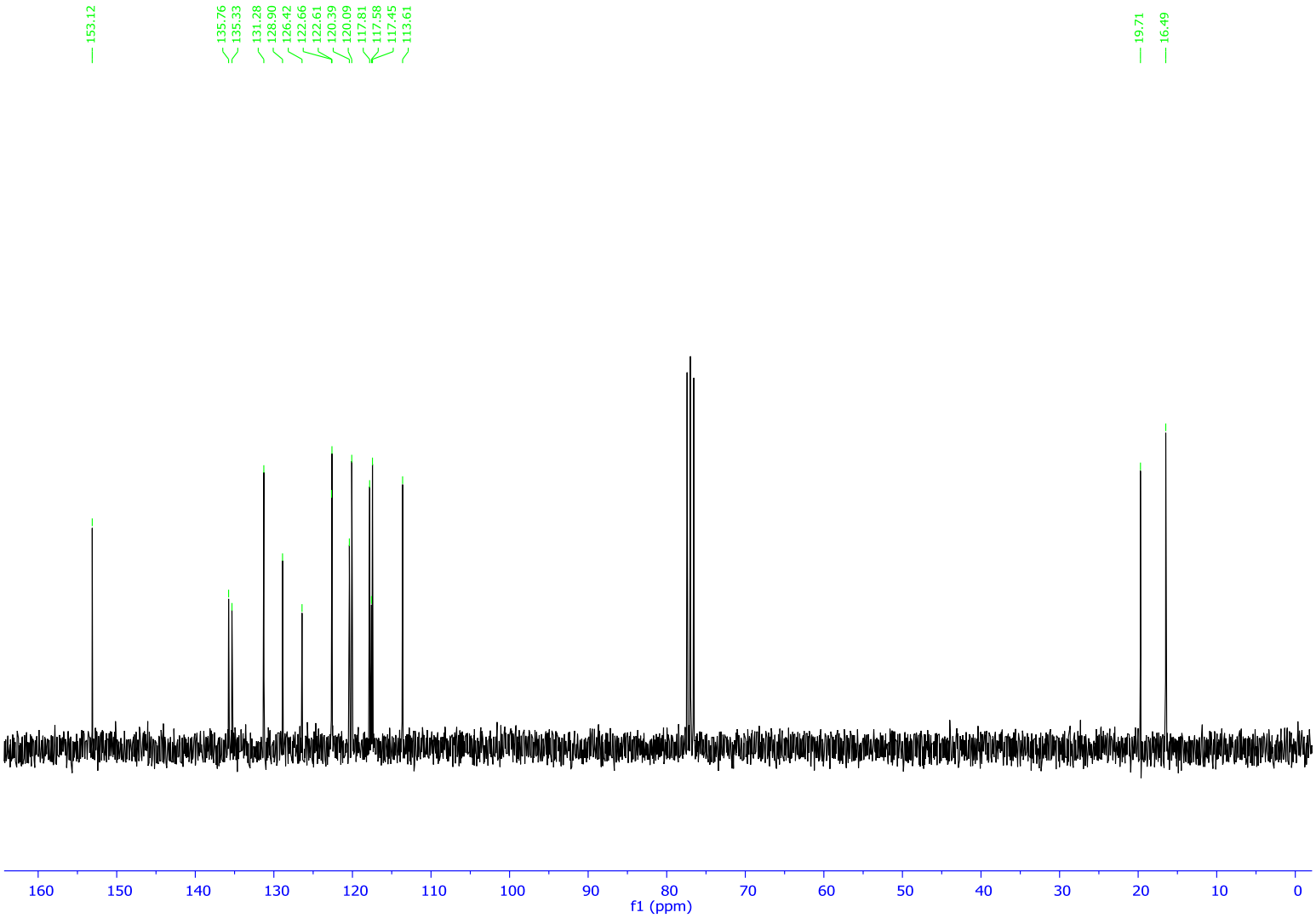

OH
Me
HN
Me

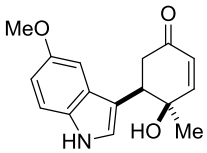
**4f**


8.24
7.62
7.61
7.60
7.59
7.59
7.42
7.38
7.35
7.31
7.31
7.28
7.27
7.26
7.26
7.25
7.24
7.08
7.07
6.96
6.95
6.94
6.93
5.40
2.70
2.43
0.93
0.98
1.26
2.74
0.98
1.00
0.88
3.06
2.83
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

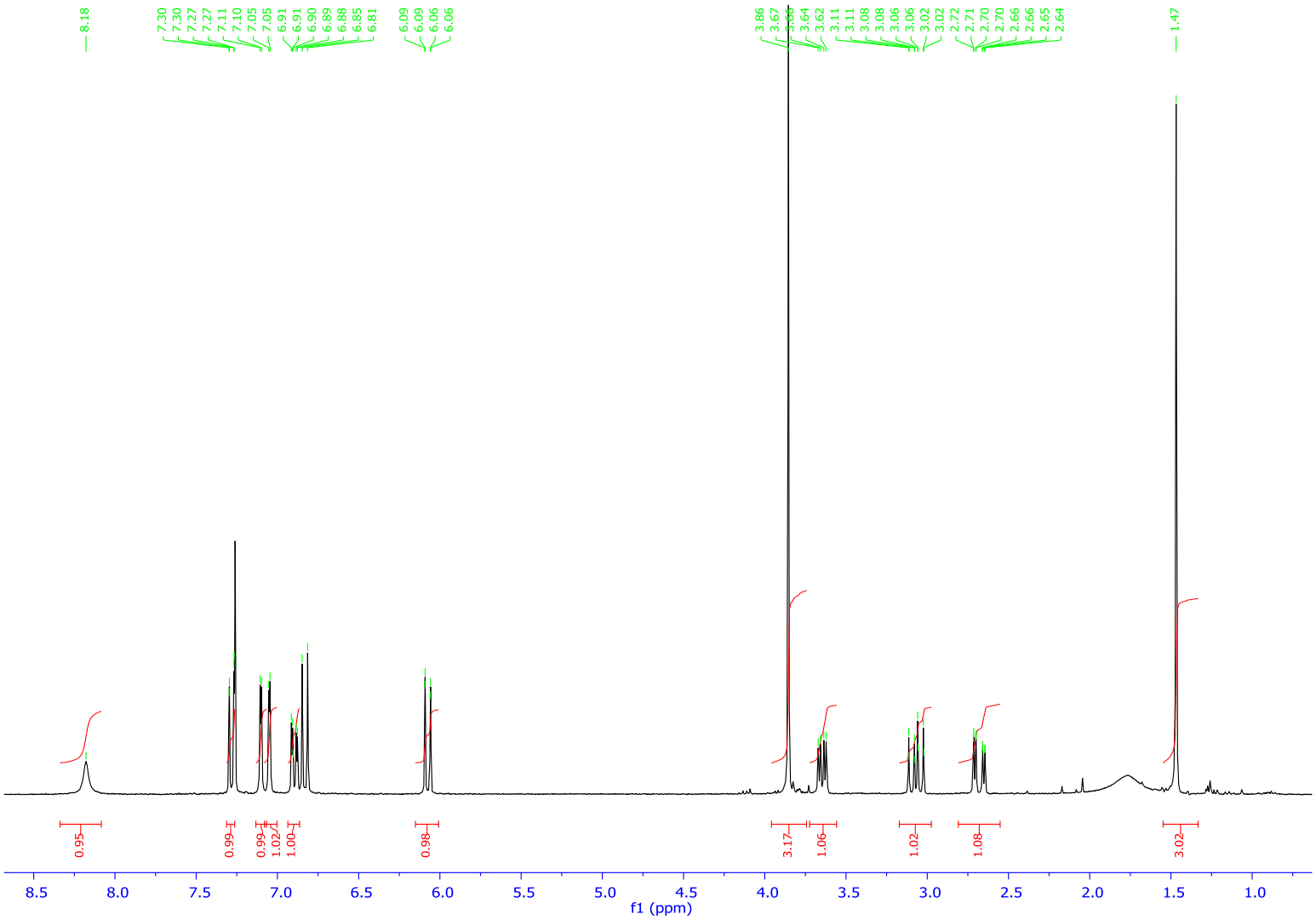

OH
Me
HN
Me

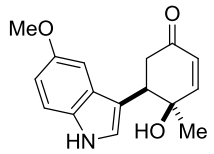
**4f**


153.12
135.76
135.33
131.28
128.90
126.42
122.66
122.61
120.39
120.09
117.81
117.58
117.45
113.61
19.71
16.49
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

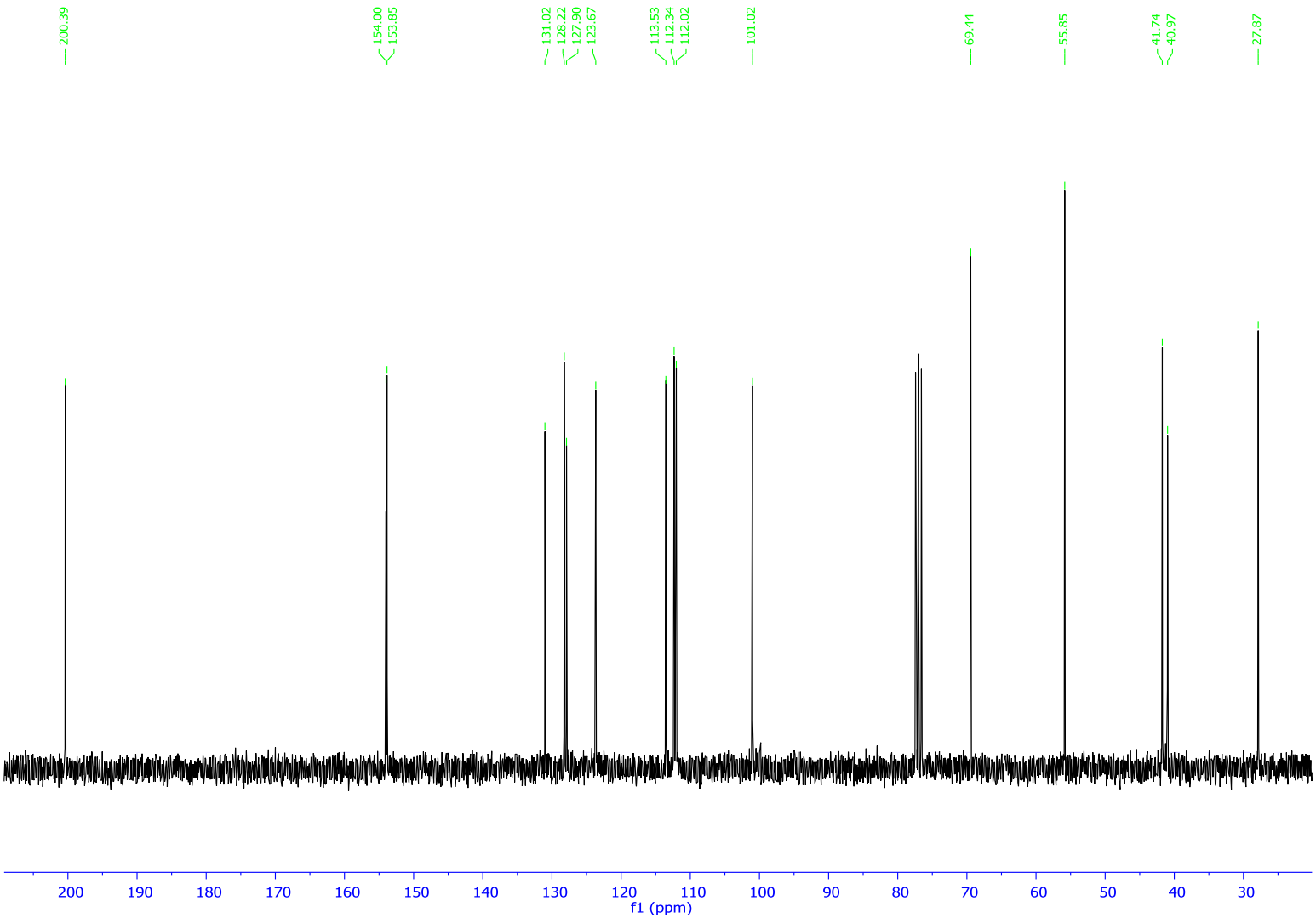

MeO
O
HN
HO
Me

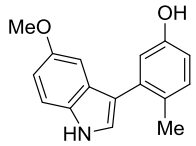
**3g**


8.18
7.30
7.30
7.27
7.27
7.11
7.10
7.05
7.05
6.91
6.91
6.90
6.89
6.88
6.85
6.81
6.09
6.09
6.06
6.06
3.86
3.67
3.66
3.64
3.62
3.11
3.11
3.08
3.08
3.06
3.06
3.02
3.02
2.72
2.71
2.70
2.70
2.66
2.66
2.65
2.64
1.47
0.95
0.99
0.99
1.02
1.00
0.98
3.17
1.06
1.02
1.08
3.02
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
f1 (ppm)

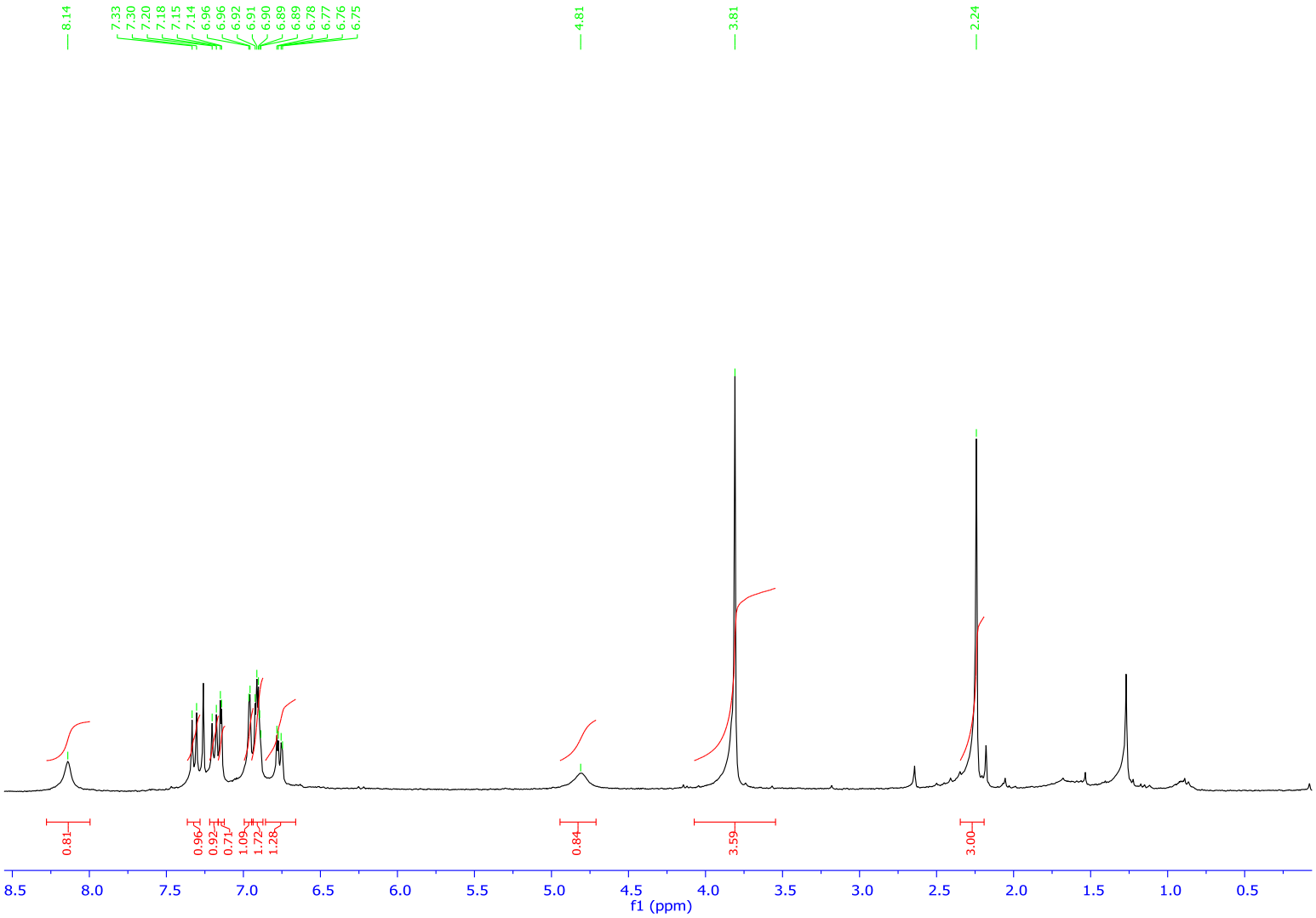

MeO
O
HN
HO
Me

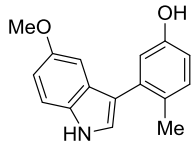
**3g**


200.39
154.00
153.85
131.02
128.22
127.90
123.67
113.53
112.34
112.02
101.02
69.44
55.85
41.74
40.97
27.87
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
f1 (ppm)

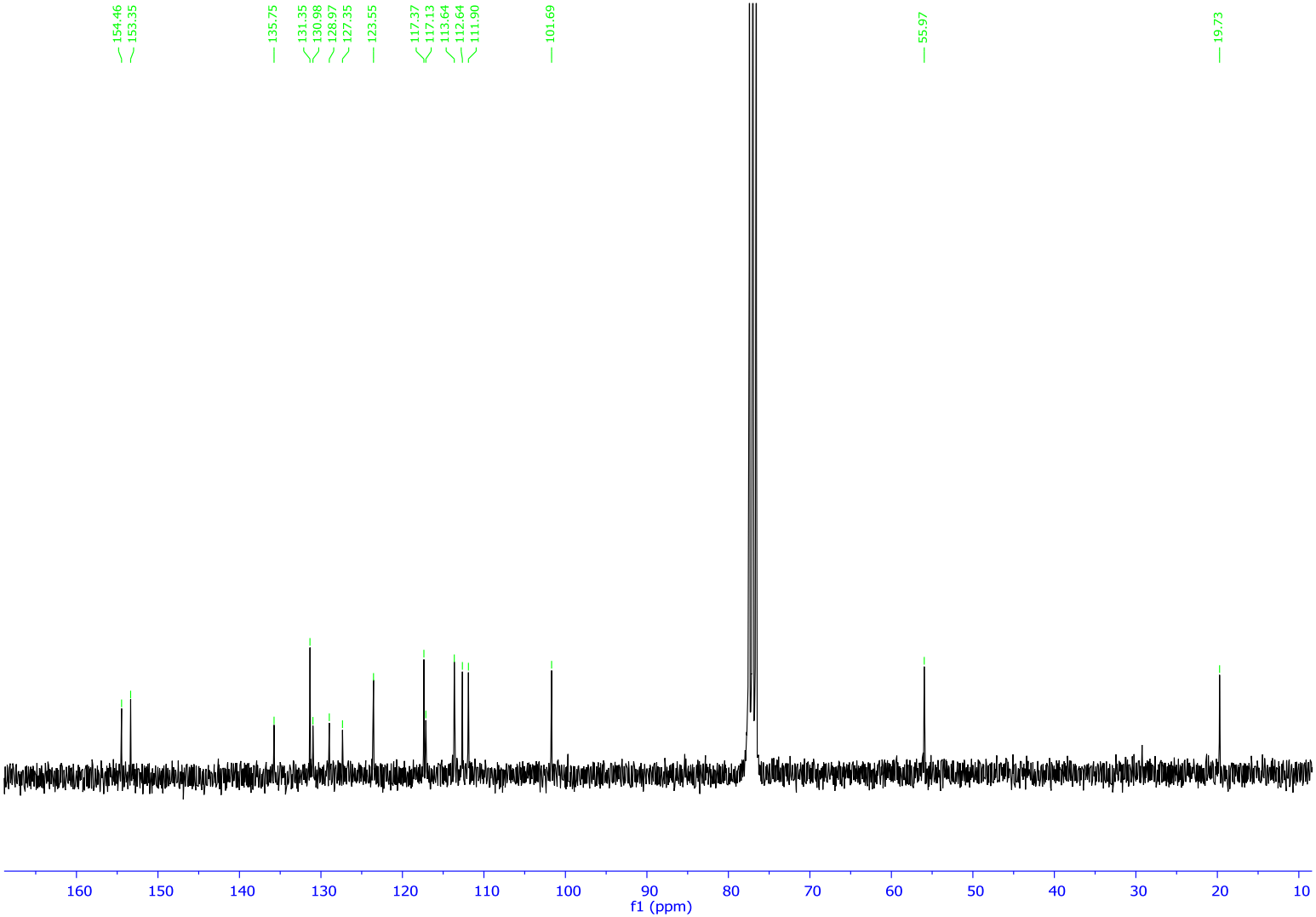

MeO
OH
HN
Me

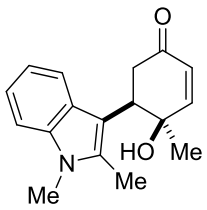
**4g**


8.14
7.33
7.30
7.20
7.18
7.15
7.14
6.96
6.96
6.92
6.91
6.90
6.89
6.89
6.78
6.77
6.76
6.75
4.81
3.81
2.24
0.81
0.96
0.92
0.71
1.09
1.72
1.28
0.84
3.59
3.00
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

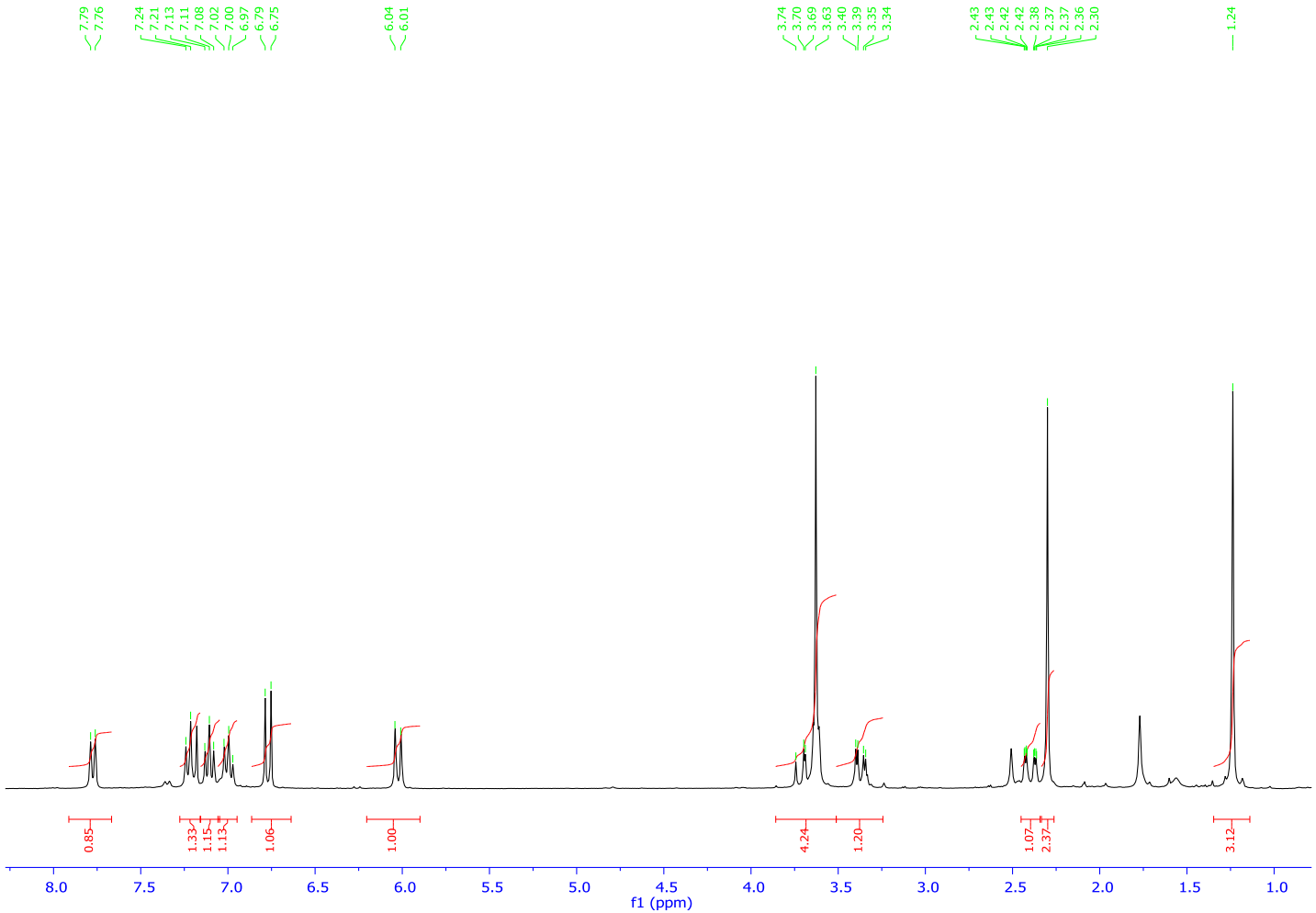

MeO
OH
HN
Me

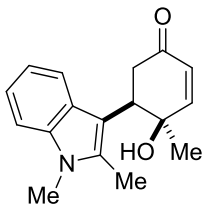
**4g**


154.46
153.35
135.75
131.35
130.98
128.97
127.35
123.55
117.37
117.13
113.64
112.64
111.90
101.69
55.97
19.73
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

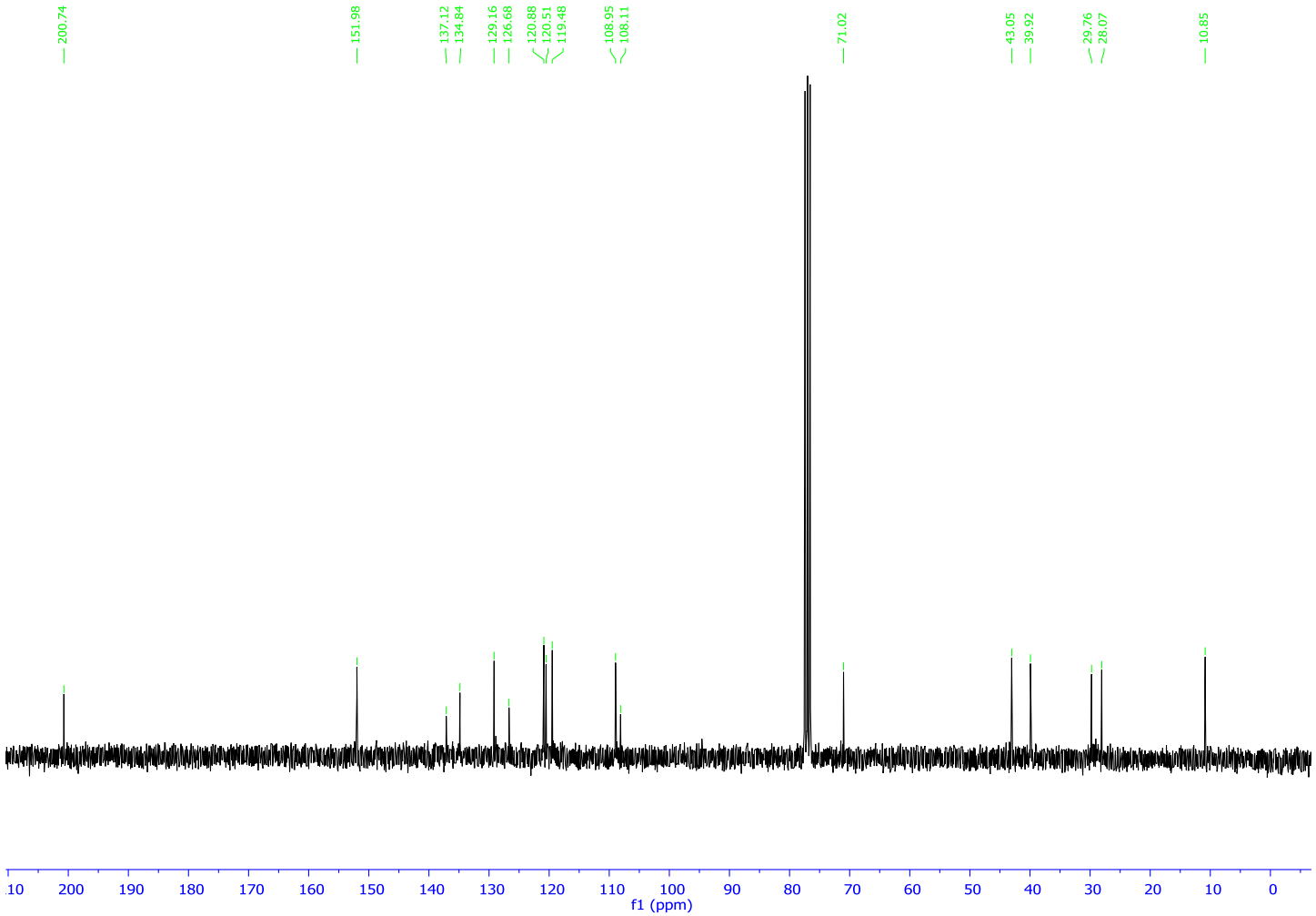

O
HO
Me
N
Me
Me

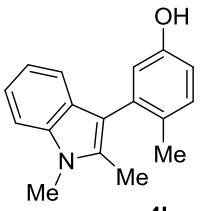
**3h**


7.79
7.76
7.24
7.21
7.13
7.11
7.08
7.02
7.00
6.97
6.79
6.75
6.04
6.01
3.74
3.70
3.69
3.63
3.40
3.39
3.35
3.34
2.43
2.43
2.42
2.42
2.38
2.37
2.37
2.36
2.30
1.24
0.85
1.33
1.15
1.13
1.06
1.00
4.24
1.20
1.07
2.37
3.12
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
f1 (ppm)

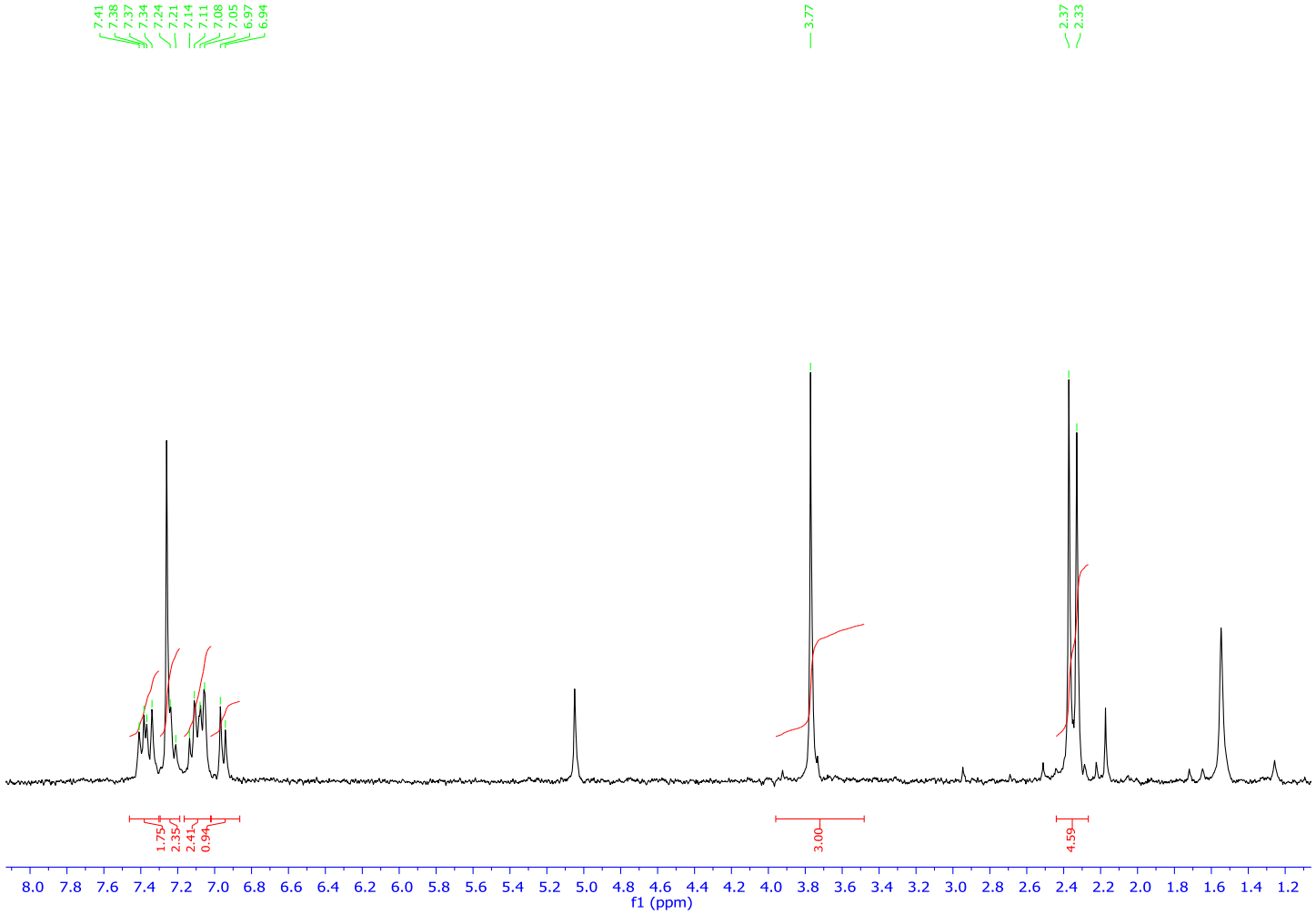

O
HO
Me
N
Me
Me

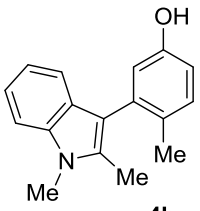
**3h**


200.74
151.98
137.12
134.84
129.16
126.68
120.88
120.51
119.48
108.95
108.11
71.02
43.05
39.92
29.76
28.07
10.85
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

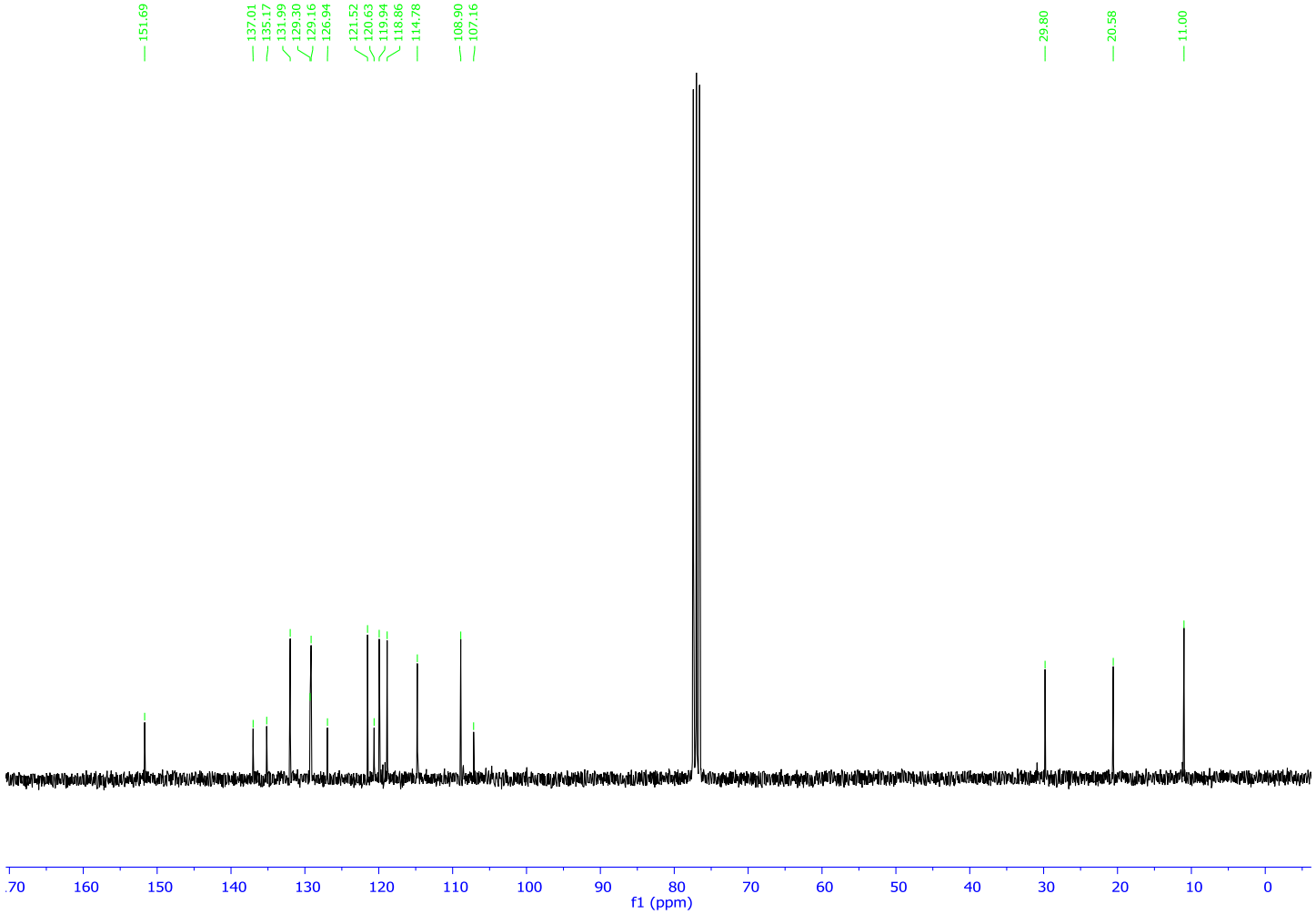

OH
Me
N
Me
Me

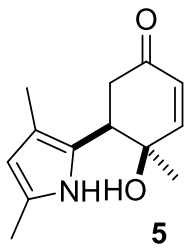
**4h**

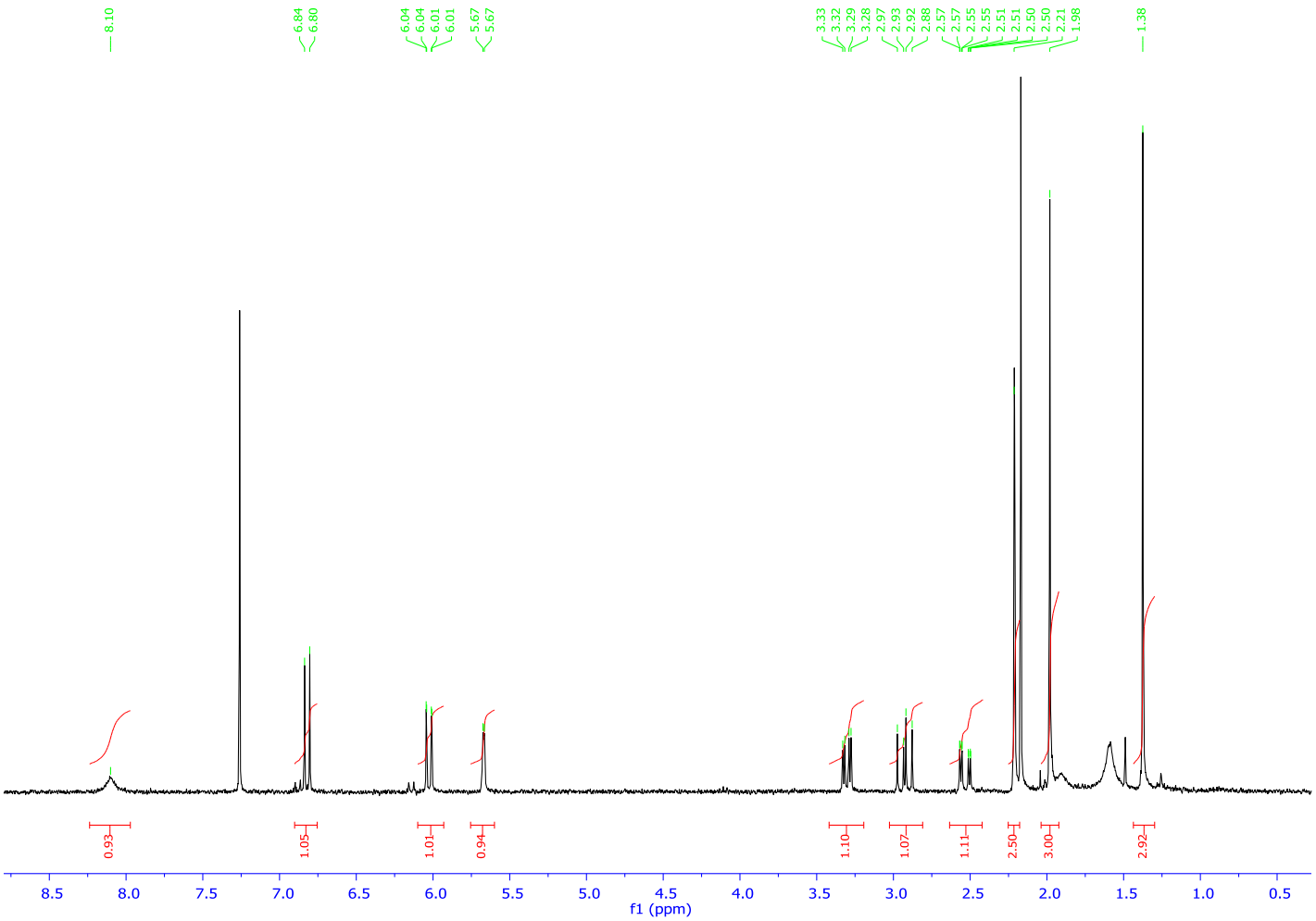

7.41
7.38
7.37
7.34
7.24
7.21
7.14
7.11
7.08
7.05
6.97
6.94
3.77
2.37
2.33
1.75
2.35
2.41
0.94
3.00
4.59
8.0 7.8 7.6 7.4 7.2 7.0 6.8 6.6 6.4 6.2 6.0 5.8 5.6 5.4 5.2 5.0 4.8 4.6 4.4 4.2 4.0 3.8 3.6 3.4 3.2 3.0 2.8 2.6 2.4 2.2 2.0 1.8 1.6 1.4 1.2
f1 (ppm)

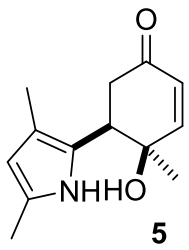

OH
N
Me
Me
Me

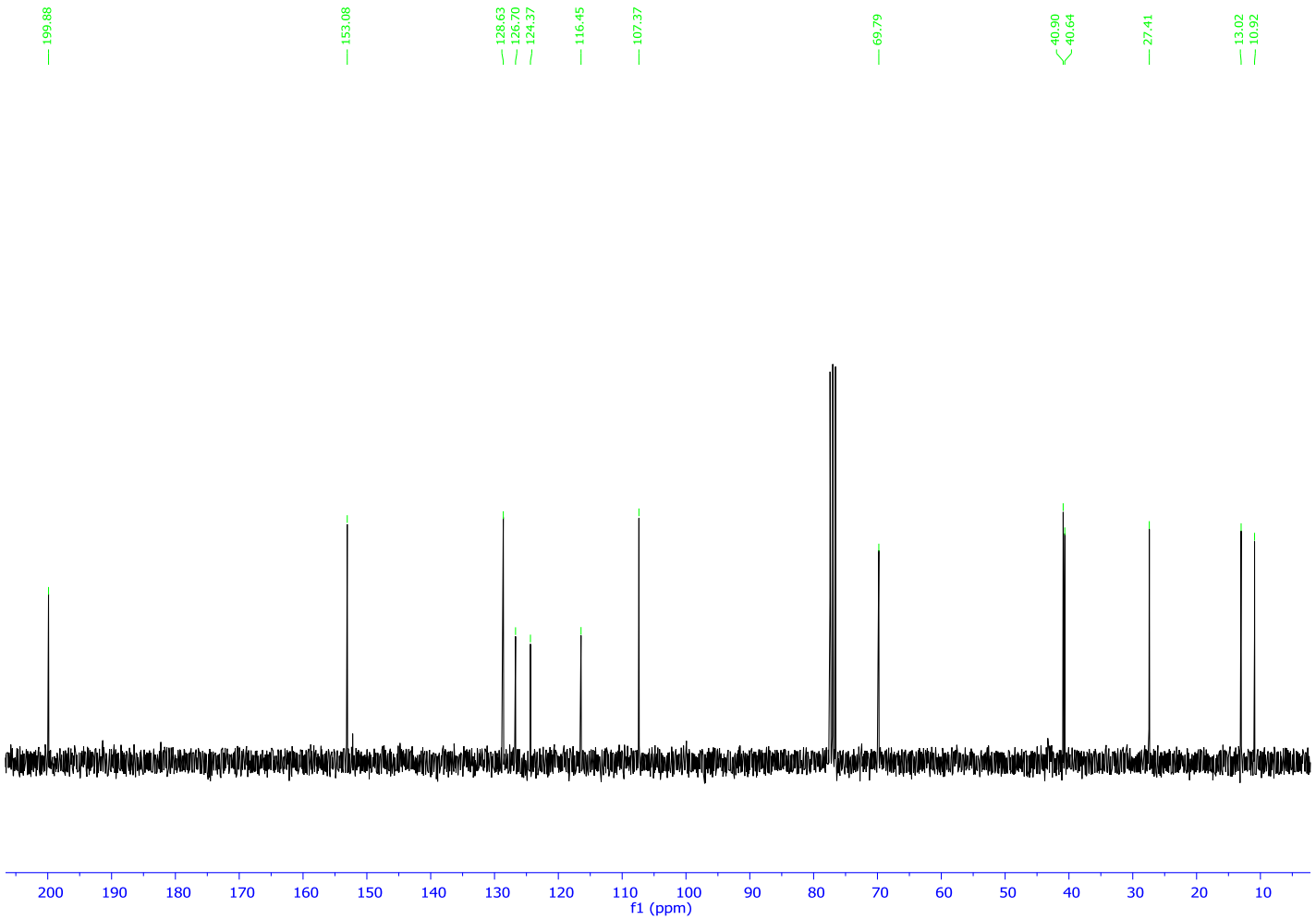
**4h**

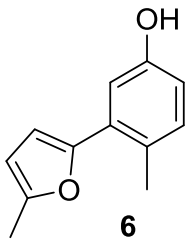

151.69
137.01
135.17
131.99
129.30
129.16
126.94
121.52
120.63
119.94
118.86
114.78
108.90
107.16
29.80
20.58
11.00
.70
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


O
NHHO
5

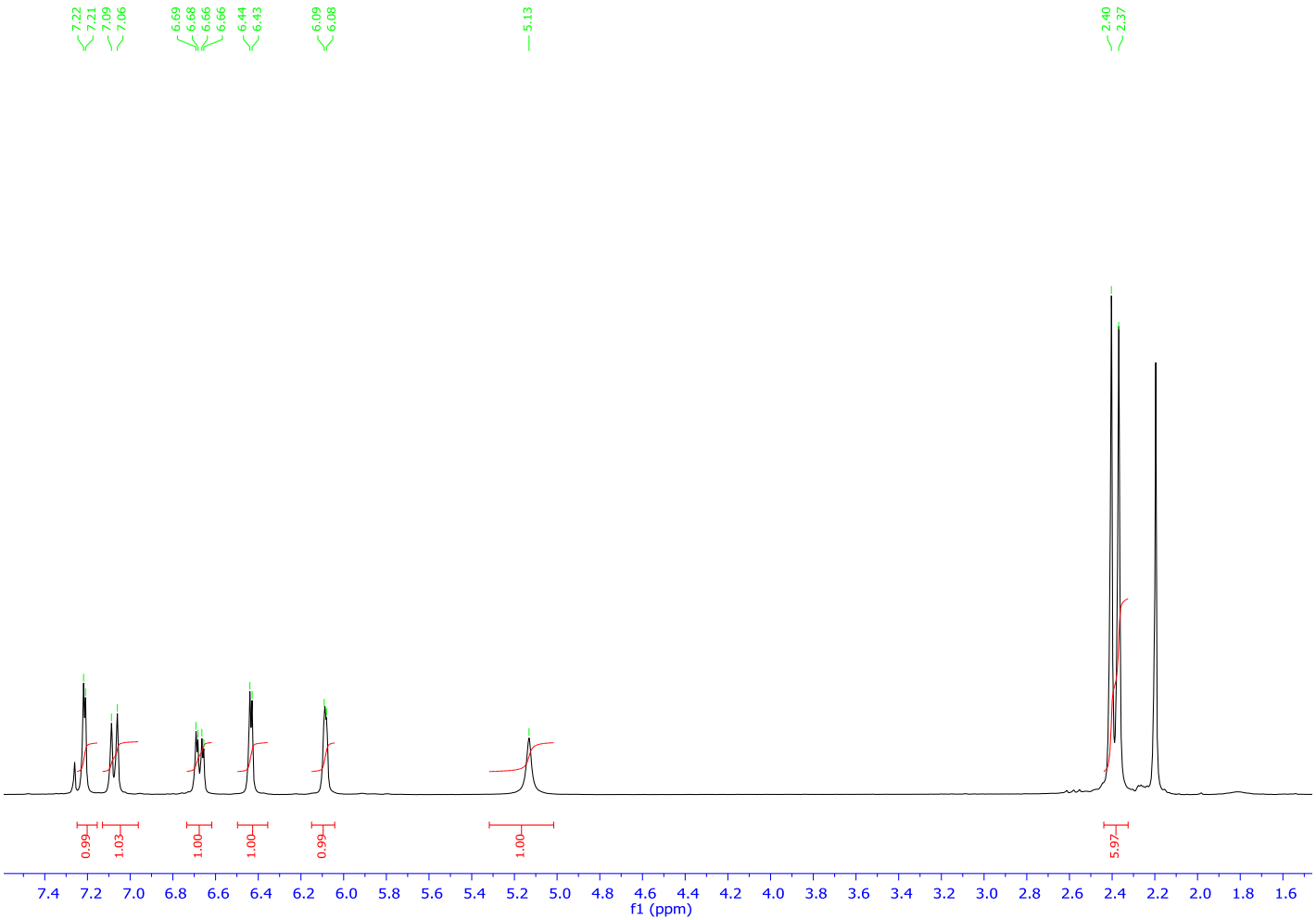

8.10
6.84
6.80
6.04
6.04
6.01
6.01
5.67
5.67
3.33
3.32
3.29
3.28
2.97
2.93
2.92
2.88
2.57
2.57
2.55
2.55
2.51
2.51
2.50
2.50
2.21
1.98
1.38
0.93
1.05
1.01
0.94
1.10
1.07
1.11
2.50
3.00
2.92
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

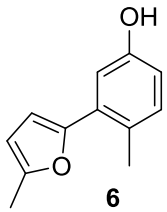

O
NHHO
5


199.88
153.08
128.63
126.70
124.37
116.45
107.37
69.79
40.90
40.64
27.41
13.02
10.92
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
f1 (ppm)

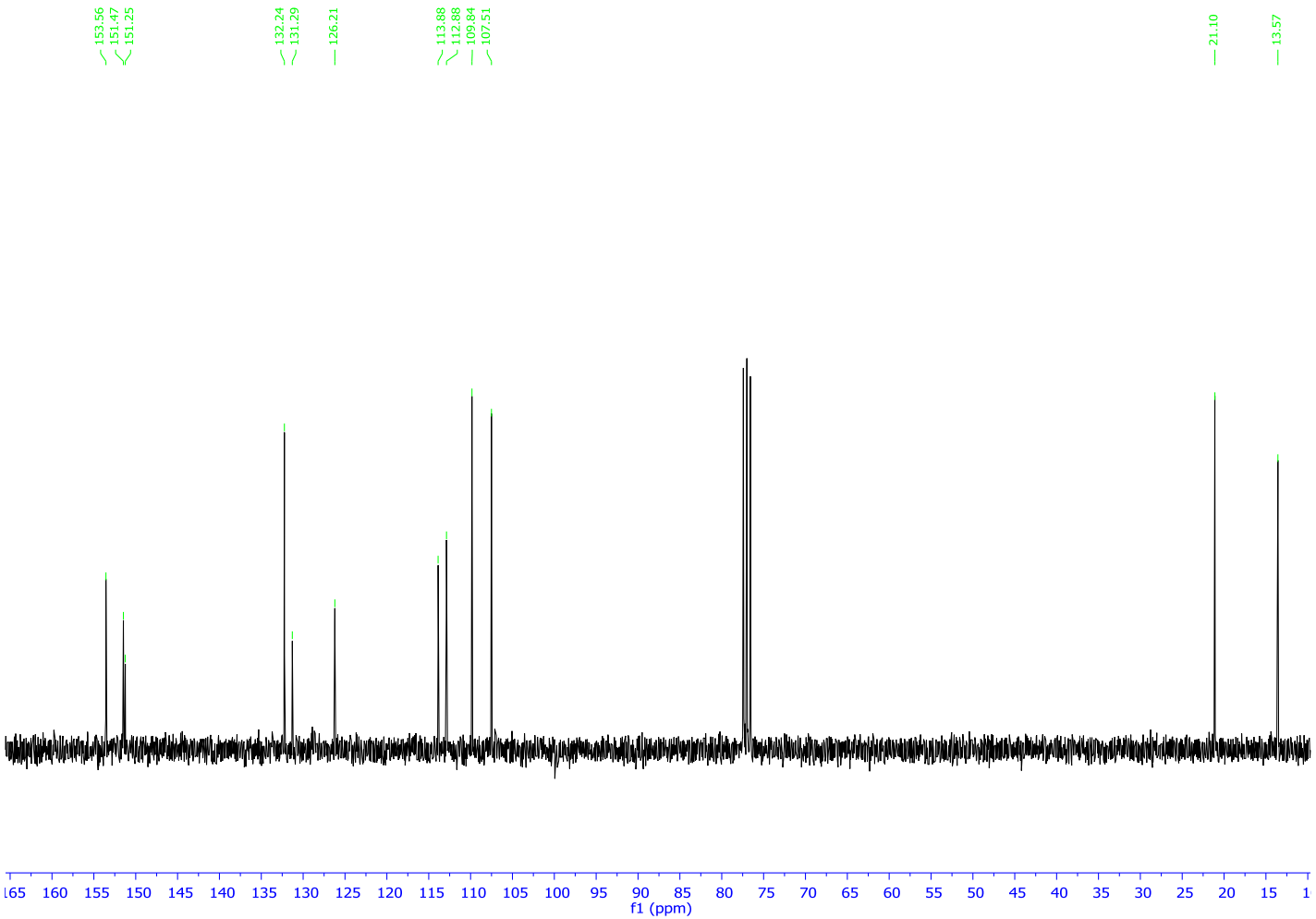

OH
O

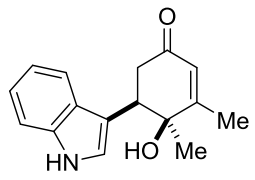
**6**


7.22
7.21
7.09
7.06
6.69
6.68
6.66
6.66
6.44
6.43
6.09
6.08
5.13
2.40
2.37
0.99
1.03
1.00
1.00
0.99
1.00
5.97
7.4 7.2 7.0 6.8 6.6 6.4 6.2 6.0 5.8 5.6 5.4 5.2 5.0 4.8 4.6 4.4 4.2 4.0 3.8 3.6 3.4 3.2 3.0 2.8 2.6 2.4 2.2 2.0 1.8 1.6
f1 (ppm)

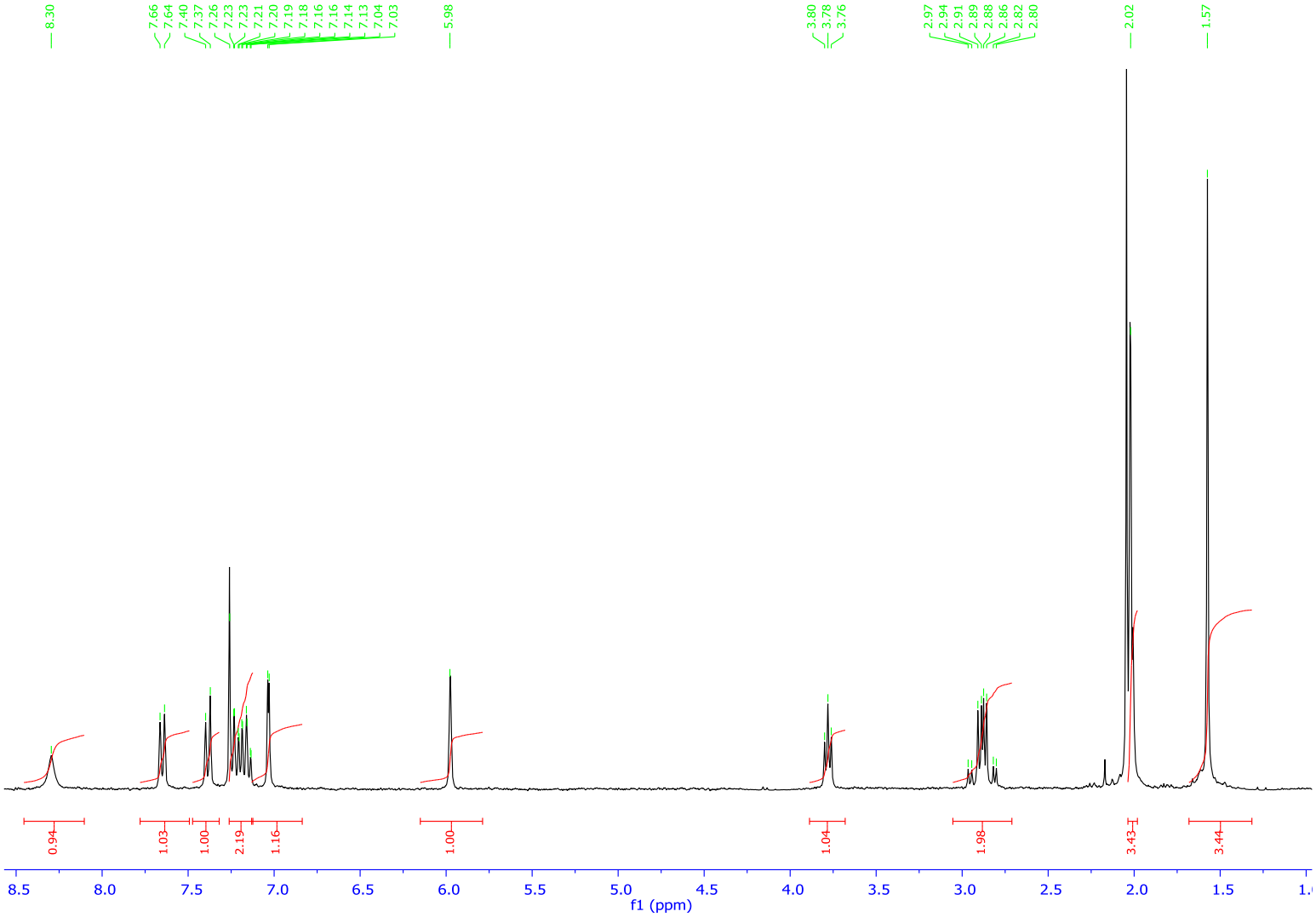

OH
O

**6**


153.56
151.47
151.25
132.24
131.29
126.21
113.88
112.88
109.84
107.51
21.10
13.57
165 160 155 150 145 140 135 130 125 120 115 110 105 100 95 90 85 80 75 70 65 60 55 50 45 40 35 30 25 20 15 1
f1 (ppm)


O
Me
HO
Me
HN

**7**


8.30
7.66
7.64
7.40
7.37
7.26
7.23
7.23
7.21
7.20
7.19
7.18
7.16
7.16
7.14
7.13
7.04
7.03
5.98
3.80
3.78
3.76
2.97
2.94
2.91
2.89
2.88
2.86
2.82
2.80
2.02
1.57
0.94
1.03
1.00
2.19
1.16
1.00
1.04
1.98
3.43
3.44
8.5
8.0
7.5
7.0
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5.0
4.5
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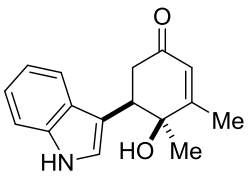
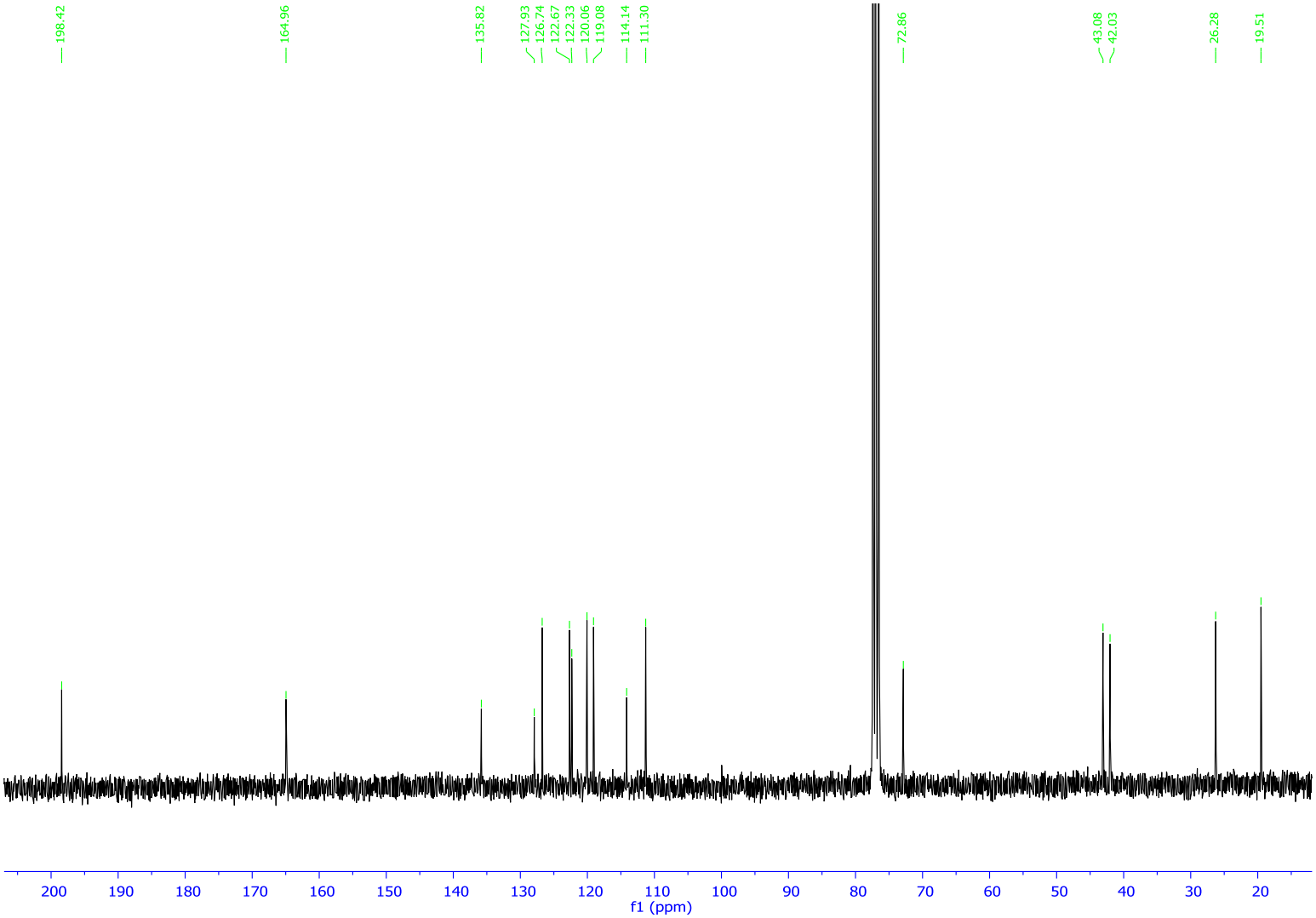
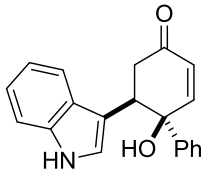
3.5
3.0
2.5
2.0
1.5
f1 (ppm)

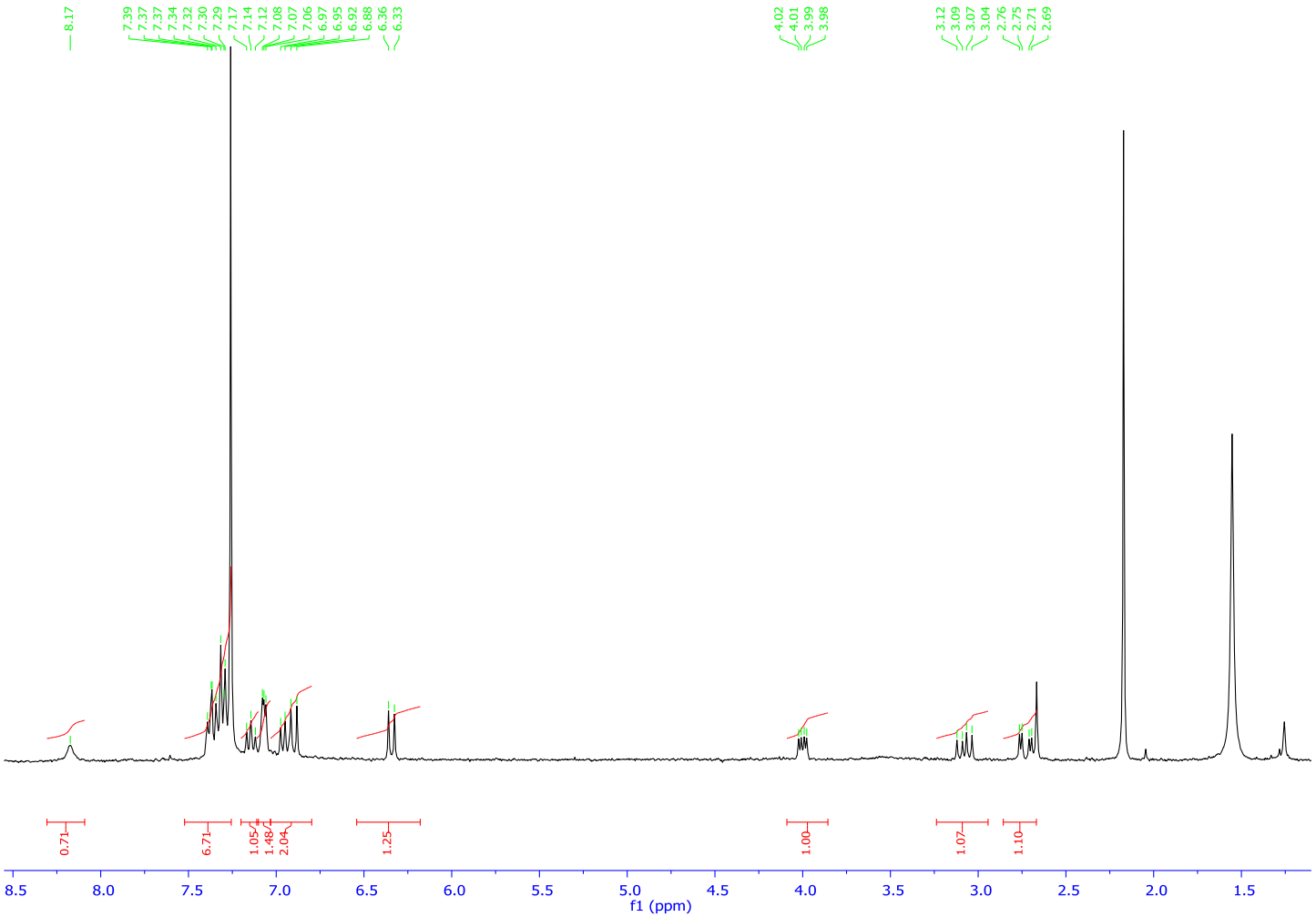

O
Me
HO
Me
HN

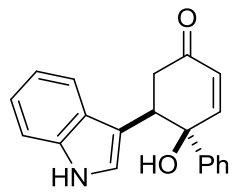
**7**


198.42
164.96
135.82
127.93
126.74
122.67
122.33
120.06
119.08
114.14
111.30
72.86
43.08
42.03
26.28
19.51
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
f1 (ppm)

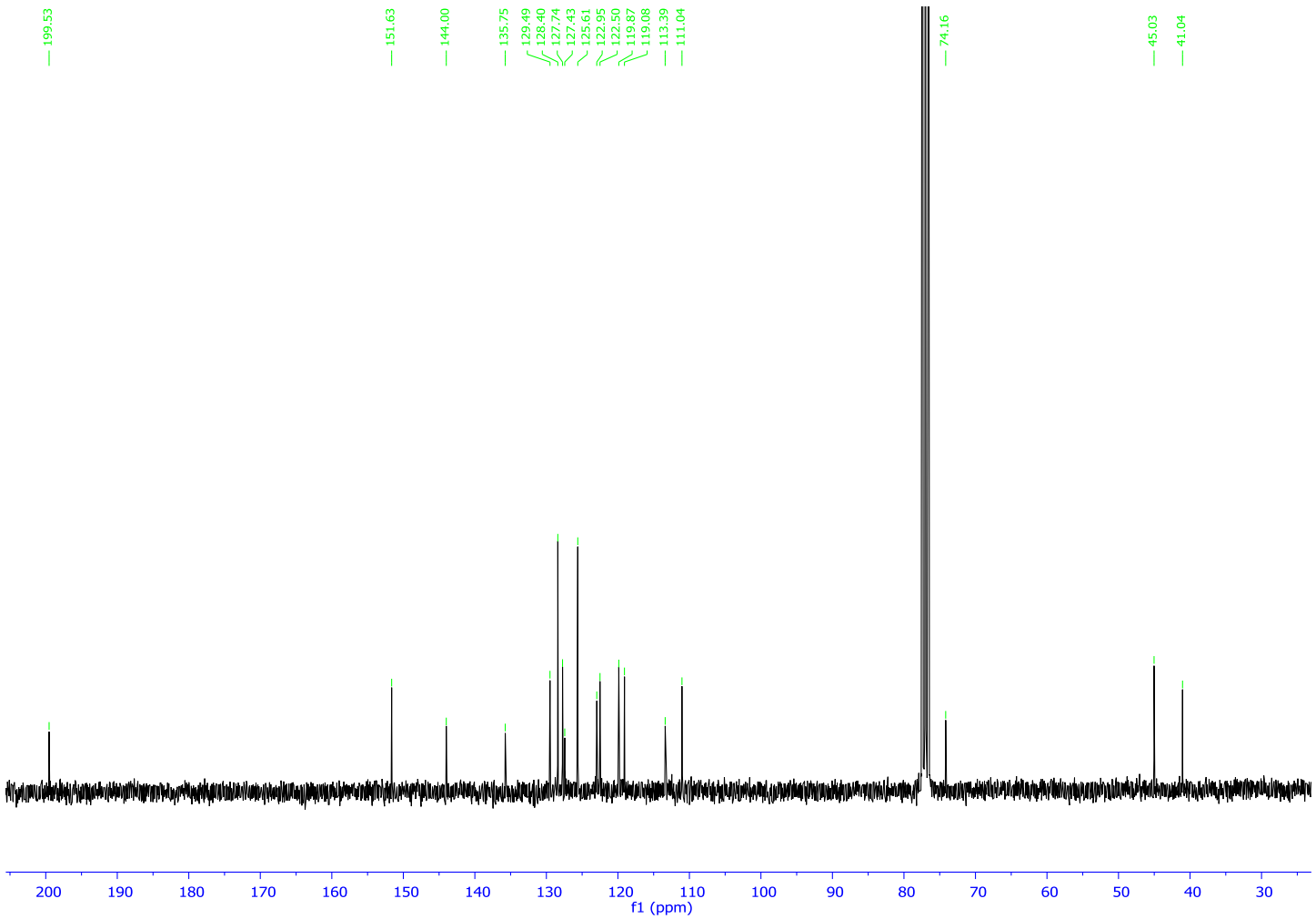

O
HN
HO
Ph

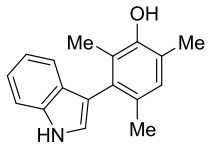
**8**


8.17
7.39
7.37
7.37
7.34
7.32
7.30
7.29
7.17
7.14
7.12
7.08
7.07
7.06
6.97
6.95
6.92
6.88
6.36
6.33
4.02
4.01
3.99
3.98
3.12
3.09
3.07
3.04
2.76
2.75
2.71
2.69
0.71
6.71
1.05
1.48
2.04
1.25
1.00
1.07
1.10
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
f1 (ppm)

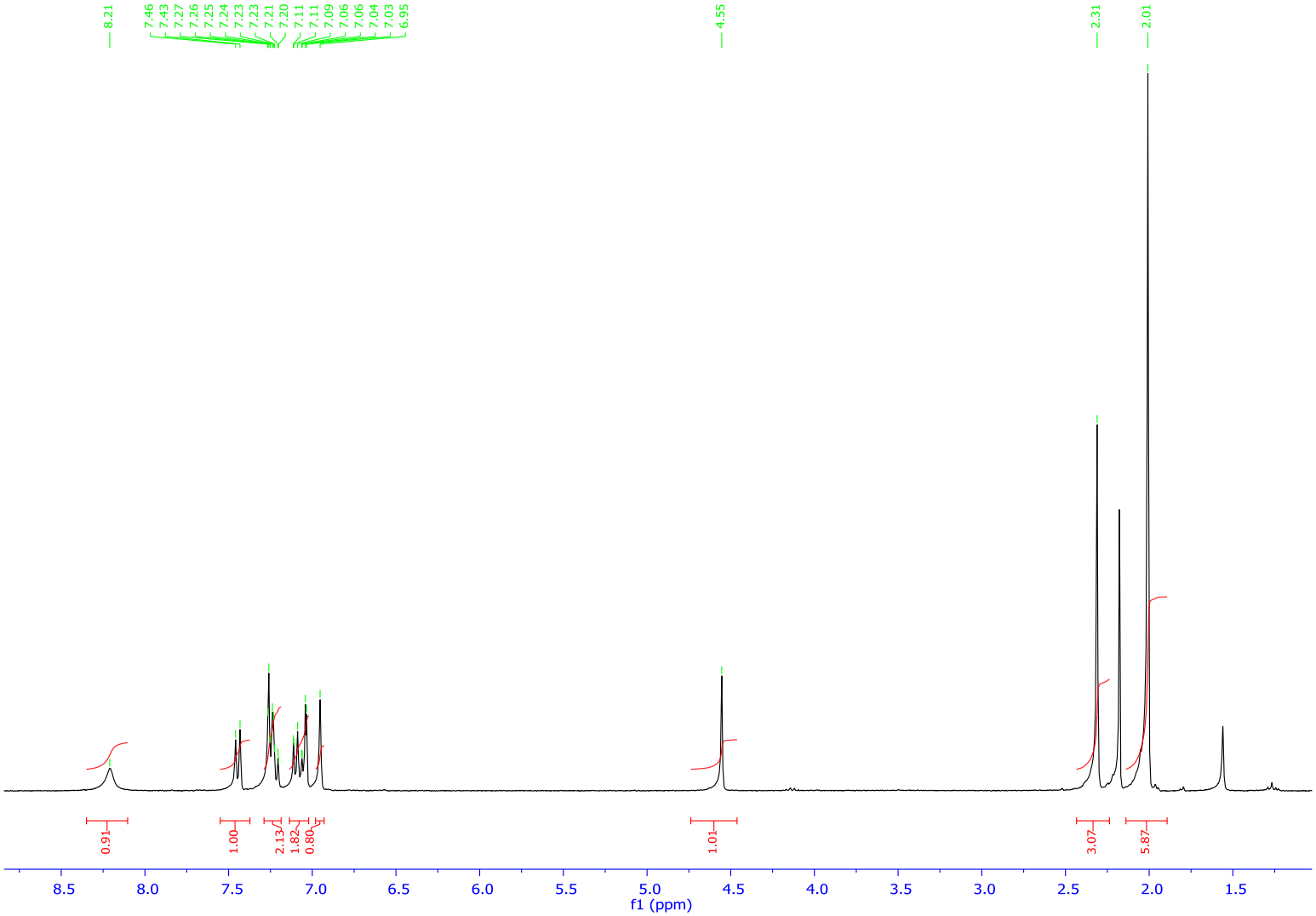

O
HN
HO
Ph

**8**


199.53
151.63
144.00
135.75
129.49
128.40
127.74
127.43
125.61
122.95
122.50
119.87
119.08
113.39
111.04
74.16
45.03
41.04
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
f1 (ppm)


OH
Me
Me
Me
HN

**9**


8.21
7.46
7.43
7.27
7.26
7.25
7.24
7.23
7.23
7.21
7.20
7.11
7.11
7.09
7.06
7.06
7.04
7.03
6.95
4.55
2.31
2.01
0.91
1.00
2.13
1.82
0.80
1.01
3.07
5.87
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
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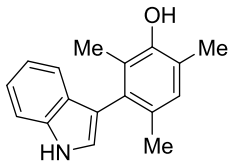
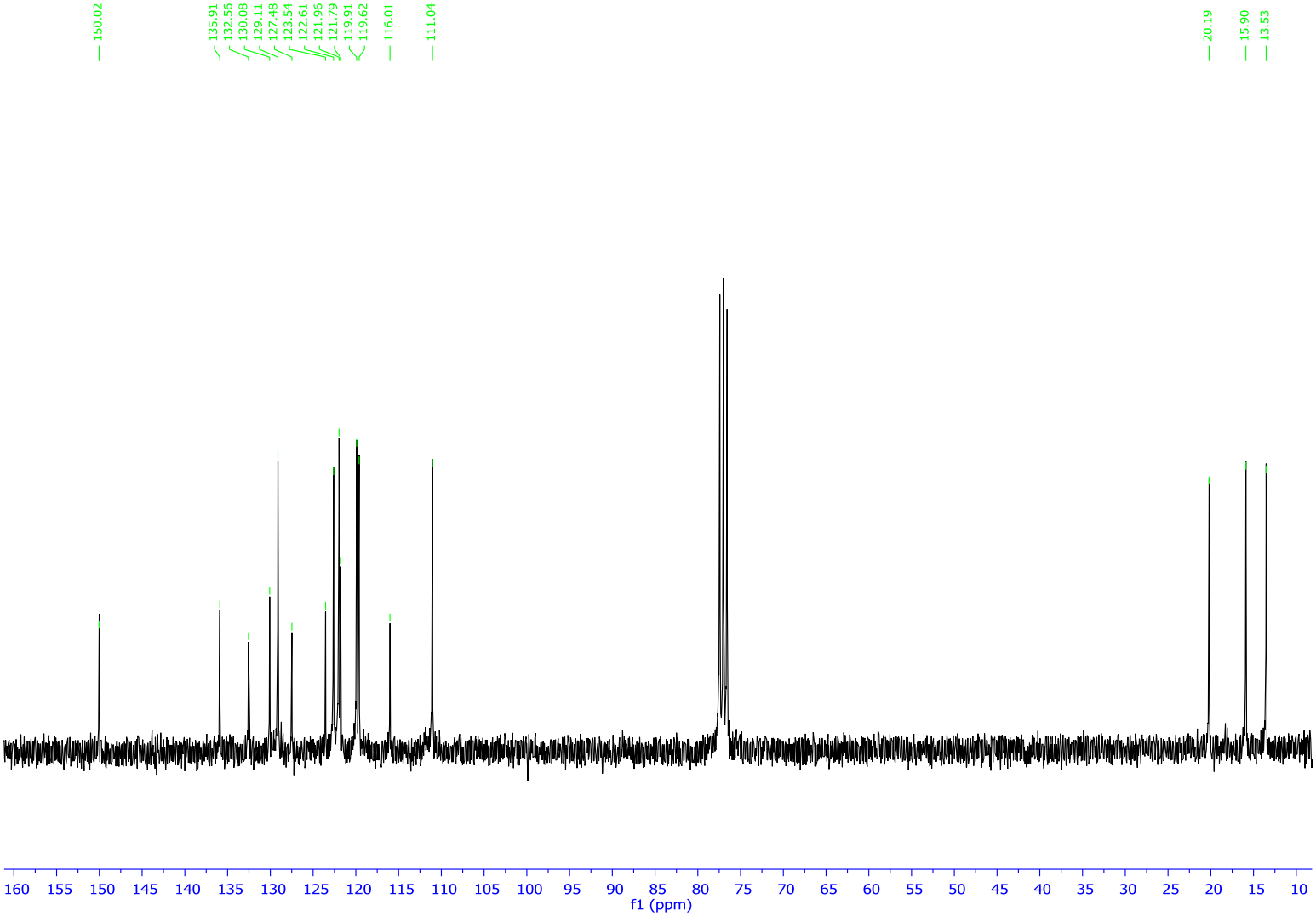
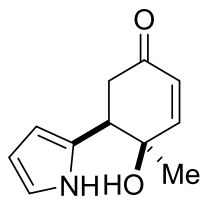
2.5
2.0
1.5
f1 (ppm)

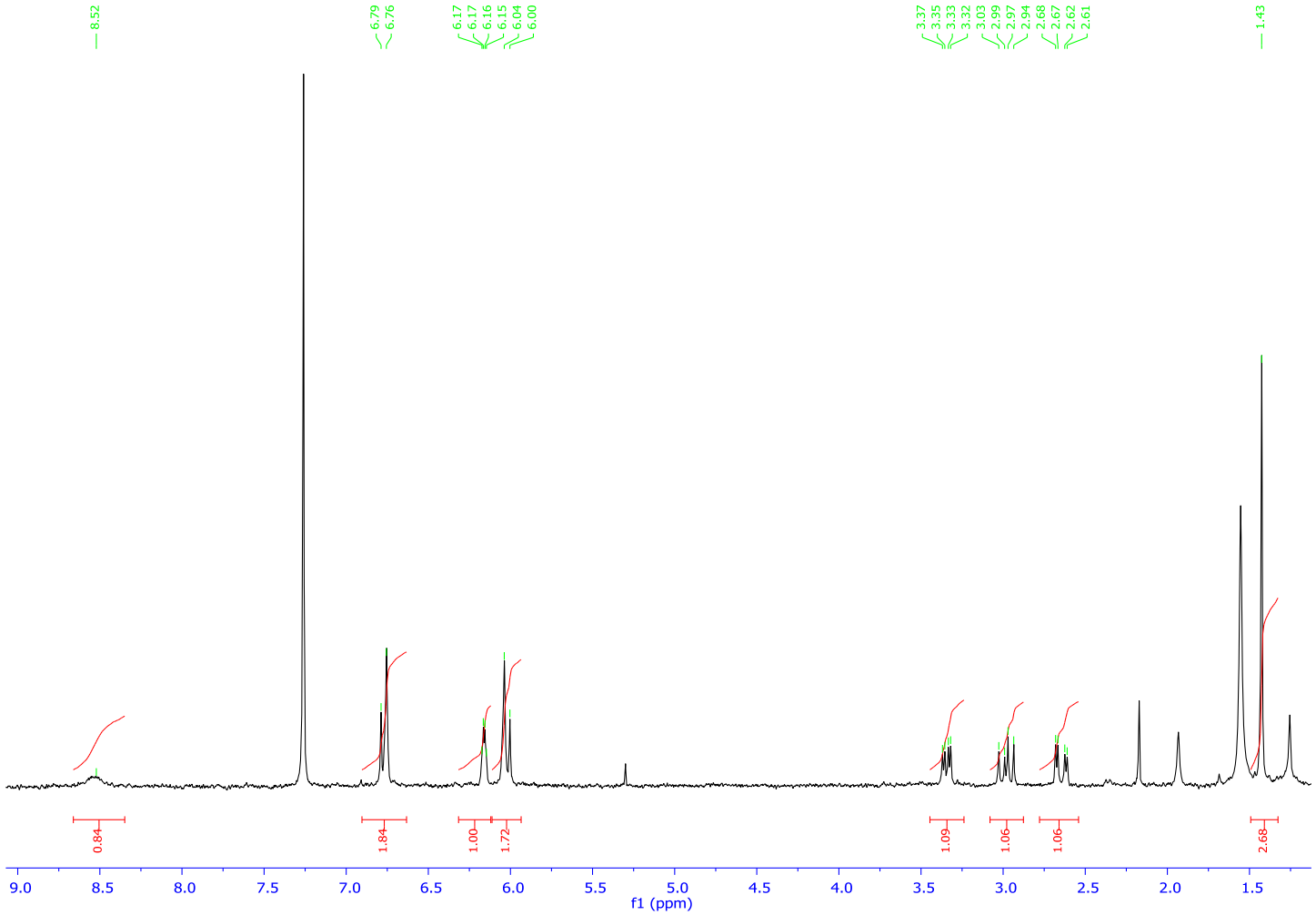

OH
Me
Me
Me
HN

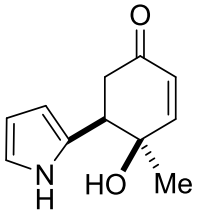
**9**


150.02
135.91
132.56
130.08
129.11
127.48
123.54
122.61
121.96
121.79
119.91
119.62
116.01
111.04
20.19
15.90
13.53
160 155 150 145 140 135 130 125 120 115 110 105 100 95 90 85 80 75 70 65 60 55 50 45 40 35 30 25 20 15 10
f1 (ppm)

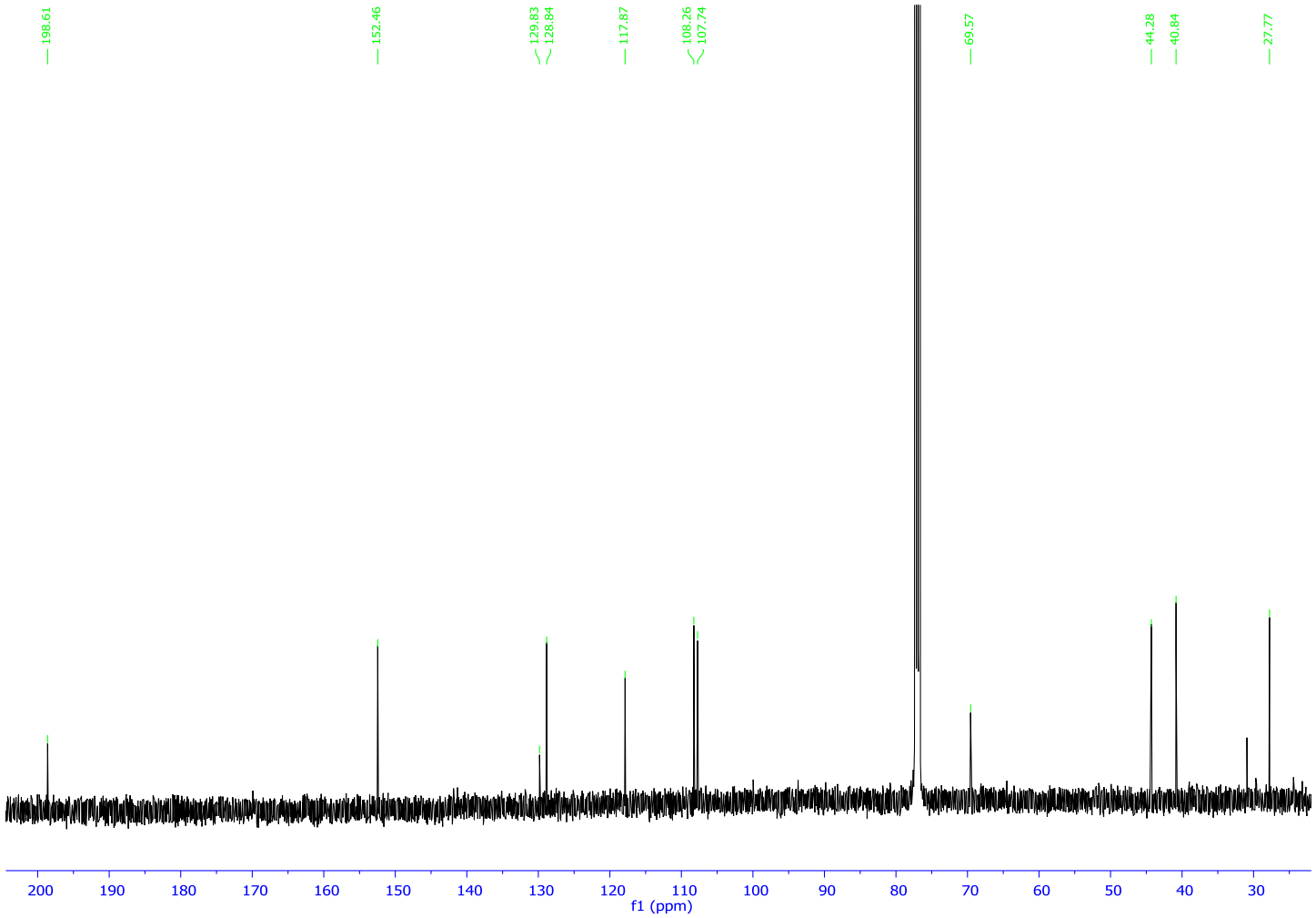

O
NH
HO
Me

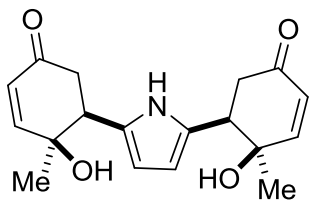
**10**


8.52
6.79
6.76
6.17
6.17
6.16
6.15
6.04
6.00
3.37
3.35
3.33
3.32
3.03
2.99
2.97
2.94
2.68
2.67
2.62
2.61
1.43
0.84
1.84
1.00
1.72
1.09
1.06
1.06
2.68
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
f1 (ppm)

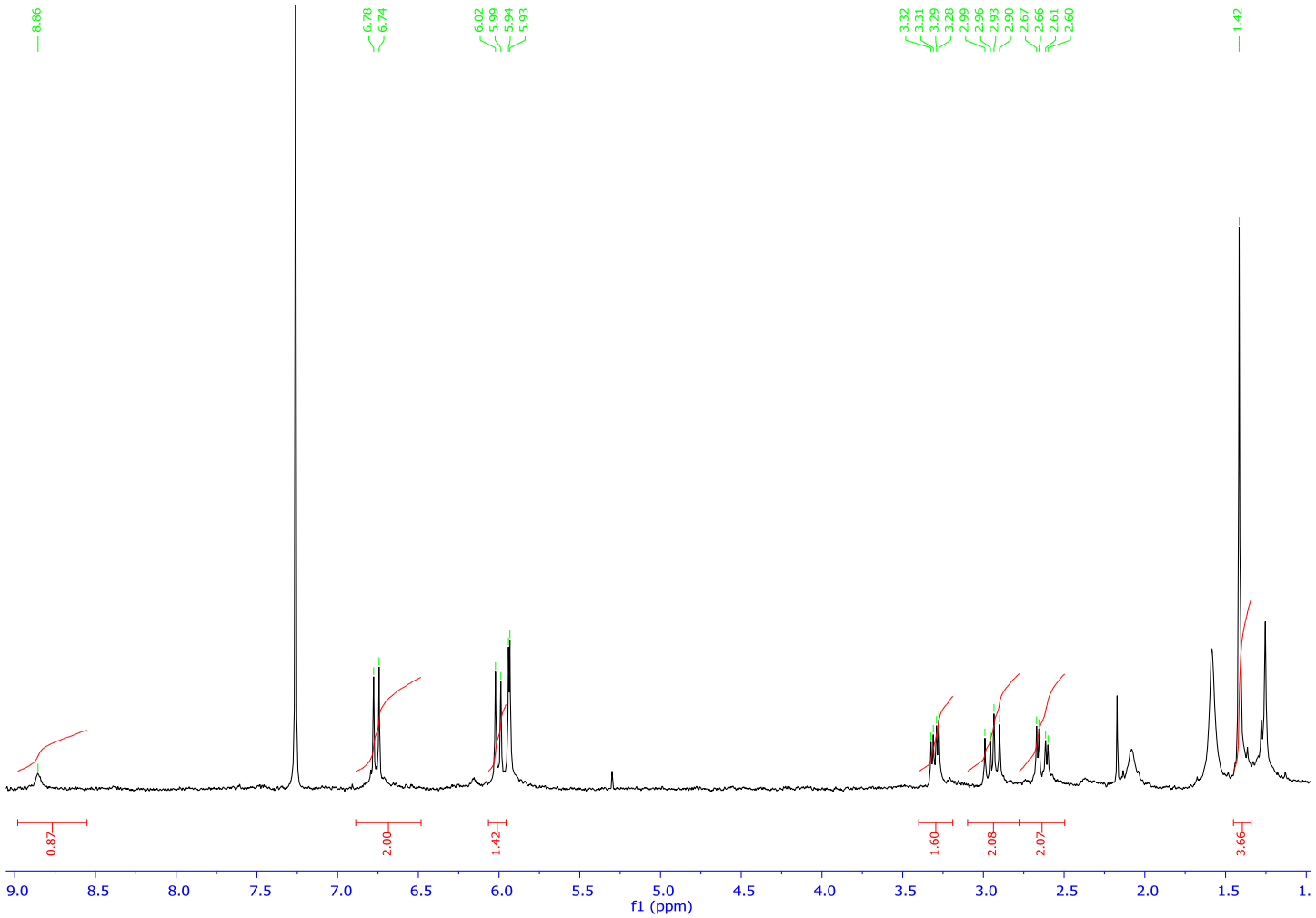

O
N
H
HO
Me

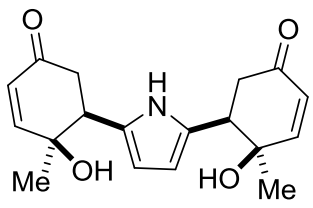
**10**


198.61
152.46
129.83
128.84
117.87
108.26
107.74
69.57
44.28
40.84
27.77
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
f1 (ppm)

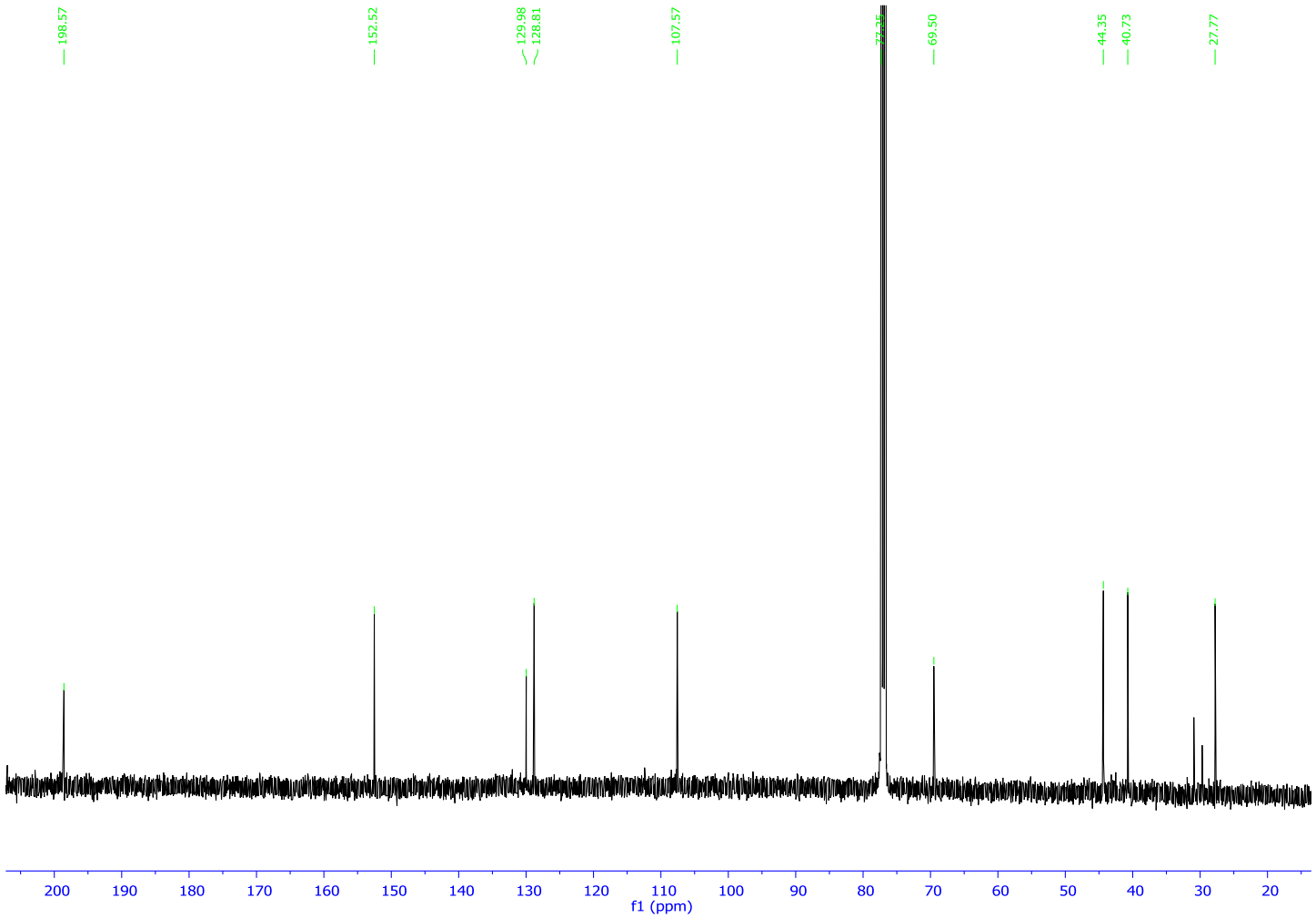

O
O
H
N
Me
OH
HO
Me

**11**


8.86
6.78
6.74
6.02
5.99
5.94
5.93
3.32
3.31
3.29
3.28
2.99
2.96
2.93
2.90
2.67
2.66
2.61
2.60
1.42
0.87
2.00
1.42
1.60
2.08
2.07
3.66
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.
f1 (ppm)

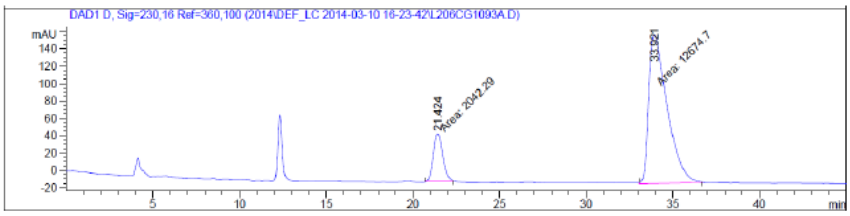

O
O
H
N
Me
OH
HO
Me

**11**


198.57
152.52
129.98
128.81
107.57
77.35
69.50
44.35
40.73
27.77
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
f1 (ppm)

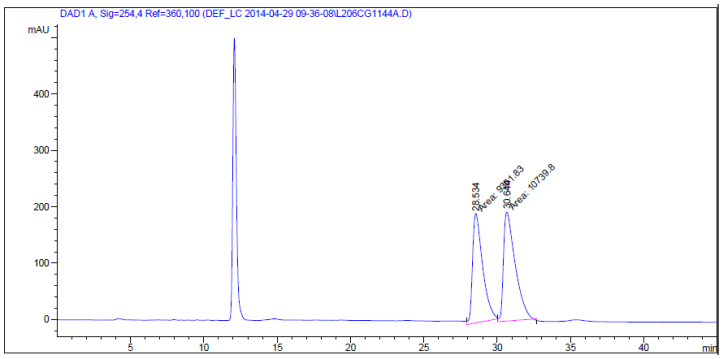
# HPLC CHROMATOGRAPHS

HPLC data for **3a**: IC-0.8 mL/min-15% $^{i}$PrOH. Retention time: 21.42 min (minor) and 33.92 min (major). The peak at 12.5 min is *p*-quinol **1a**



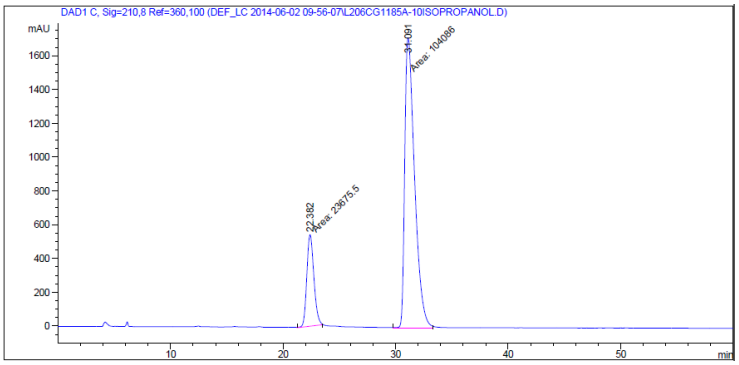

| Peak # | RetTime [min] | Type | Width [min] | Area [mAU*s] | Height [mAU] | Area % |
|---|---|---|---|---|---|---|
| 1 | 21.424 | MM | 0.6267 | 2042.28662 | 54.31218 | 13.8771 |
| 2 | 33.921 | MM | 1.2352 | 1.26747e4 | 171.01950 | 86.1229 |

HPLC data for **3b**: IC-0.8 mL/min-15% $^{i}$PrOH



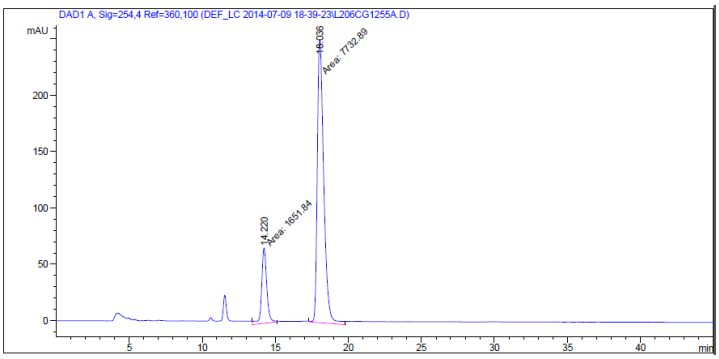

| Peak # | RetTime [min] | Type | Width [min] | Area [mAU*s] | Height [mAU] | Area % |
|---|---|---|---|---|---|---|
| 1 | 28.534 | MM | 0.7983 | 9301.82520 | 194.19296 | 46.4124 |
| 2 | 30.644 | MM | 0.9246 | 1.07398e4 | 193.59590 | 53.5876 |

HPLC data for **3c**: IC-0.8 mL/min-10% $^{i}$PrOH



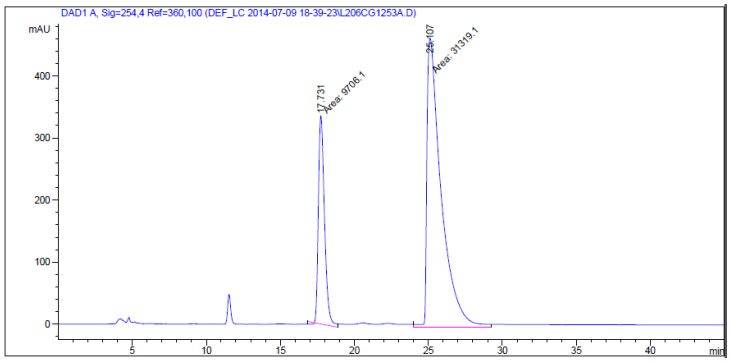

| Peak # | RetTime [min] | Type | Width [min] | Area [mAU*s] | Height [mAU] | Area % |
|---|---|---|---|---|---|---|
| 1 | 22.382 | MM | 0.7280 | 2.36755e4 | 542.01678 | 18.5310 |
| 2 | 31.091 | MM | 1.0104 | 1.04086e5 | 1716.97144 | 81.4690 |

HPLC data for **3d**: IC-0.8 mL/min-15% $^{i}$PrOH



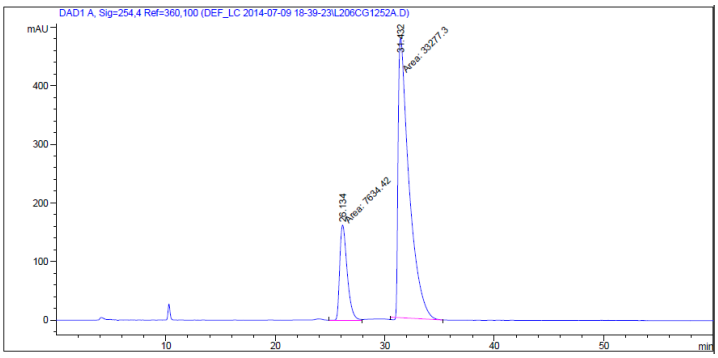

| Peak # | RetTime [min] | Type | Width [min] | Area [mAU*s] | Height [mAU] | Area % |
|---|---|---|---|---|---|---|
| 1 | 14.220 | MM | 0.4112 | 1651.84216 | 66.95544 | 17.6014 |
| 2 | 18.036 | MM | 0.5120 | 7732.88770 | 251.74472 | 82.3986 |

HPLC data for **3f** IC-0.8 mL/min-15% $^{i}$PrOH



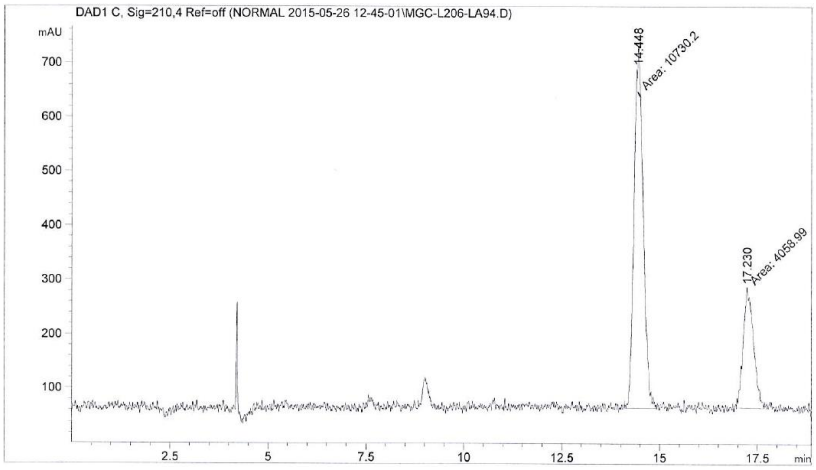

| Peak # | RetTime [min] | Type | Width [min] | Area [mAU*s] | Height [mAU] | Area % |
|---|---|---|---|---|---|---|
| 1 | 17.731 | MM | 0.4816 | 9706.10254 | 335.87253 | 23.6589 |
| 2 | 25.107 | MM | 1.1183 | 3.13191e4 | 466.74698 | 76.3411 |

HPLC data for **3g** IC-0.8 mL/min-17% $^{i}$PrOH




| Peak # | RetTime [min] | Type | Width [min] | Area [mAU*s] | Height [mAU] | Area % |
|---|---|---|---|---|---|---|
| 1 | 26.134 | MM | 0.7847 | 7634.42139 | 162.15430 | 18.6607 |
| 2 | 31.432 | MM | 1.1612 | 3.32773e4 | 477.64175 | 81.3393 |

The enantiomeric excess of the compound **5** was determined by supercritical fluid chromatography (SFC) using mixtures of supercritical CO2 and methanol and Chiralpack IB columns as chiral stationary phases 1 mL/min-5% MeOH-30 min.




| Peak # | RetTime [min] | Type | Width [min] | Area [mAU*s] | Height [mAU] | Area % |
|---|---|---|---|---|---|---|
| 1 | 14.448 | MM | 0.2680 | 1.07302e4 | 667.32941 | 72.5543 |
| 2 | 17.230 | MM | 0.3033 | 4058.99390 | 223.04100 | 27.4457 |