

Supporting Information for

Design, Synthesis and Anticonvulsant Activity of New Hybrid Compounds Derived from 2-(2,5-Dioxopyrrolidin-1-yl)propanamides and 2-(2,5-Dioxopyrrolidin-1-yl)butanamides

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1. The NMR data for intermediates 1, 2, and 29

2-(2,5-Dioxopyrrolidin-1-yl)propanoic acid (1). ^1H NMR (300 MHz, CDCl_3) δ 1.45 (d, 3H, $J=6.9$ Hz, $-\text{CH}_3$), 2.81 (s, 4H, imide), 4.55 (q, 1H, $J=7.3$ Hz, $\equiv\text{CH}$), 9.20 (br s, 1H, $-\text{CO}_2\text{H}$).

2-(2,5-Dioxopyrrolidin-1-yl)butanoic acid (2). ^1H NMR (300 MHz, CDCl_3) δ 0.89 (t, 3H, $J=7.4$ Hz, $\underline{\text{CH}_3}-\text{CH}_2-$), 2.08–2.30 (m, 2H, $\text{CH}_3-\underline{\text{CH}_2}-$), 2.77 (s, 4H, imide), 4.86 (dd, 1H, $J=10.4, 5.1$ Hz, $\equiv\text{CH}$), 9.24 (br s, 1H, $-\text{CO}_2\text{H}$).

2-Chloro-3-methoxy-1-[4-[3-(trifluoromethyl)phenyl]piperazin-1-yl]propan-1-one (29). ^1H NMR (300 MHz, CDCl_3) δ 3.13–3.36 (m, 4H, piperazine), 3.42 (s, 3H, $-\text{OCH}_3$), 3.60–3.85 (m, 4H, piperazine), 3.87–4.05 (m, 2H, $-\text{CH}_2-$), 4.56 (t, 1H, $J=6.6$ Hz, $\equiv\text{CH}$), 6.99–7.18 (m, 3H, ArH), 7.31–7.42 (m, 1H, ArH).

2. The NMR data for final compounds 3–28, and 30

1-[1-Oxo-1-(4-phenylpiperazin-1-yl)propan-2-yl]pyrrolidine-2,5-dione (3). ^1H NMR (300 MHz, CDCl_3) δ 1.63 (d, 3H, $J=7.2$ Hz, $-\text{CH}_3$), 2.73 (s, 4H, imide), 3.06–3.22 (m, 4H, piperazine), 3.42–3.55 (m, 2H, piperazine), 3.64–3.83 (m, 2H, piperazine), 5.01 (q, 1H, $J=7.2$ Hz, $\equiv\text{CH}$), 6.82–6.97 (m, 3H, ArH), 7.20–7.35 (m, 2H, ArH); ^{13}C NMR (75 MHz, CDCl_3) δ 14.8, 28.0, 47.5, 49.3, 116.6, 116.6, 120.7, 129.2, 150.7, 167.2, 176.5.

1-{1-[4-(2-Chlorophenyl)piperazin-1-yl]-1-oxopropan-2-yl}pyrrolidine-2,5-dione (4). ^1H NMR (300 MHz, CDCl_3) δ 1.65 (d, 3H, $J=7.2$ Hz, $-\text{CH}_3$), 2.74 (s, 4H, imide), 2.93–3.08 (m, 4H), 3.48–3.80 (m, 4H, piperazine), 5.02 (q, 1H, $J=7.2$ Hz, $\equiv\text{CH}$), 6.96–7.04 (m, 1H, ArH), 7.21 (dd, 1H, $J=7.6, 1.5$ Hz, ArH), 7.24–7.27 (m, 1H, ArH), 7.34–7.40 (m, 1H, ArH).

1-{1-[4-(3-Chlorophenyl)piperazin-1-yl]-1-oxopropan-2-yl}pyrrolidine-2,5-dione (5). ^1H NMR (300 MHz, CDCl_3) δ 1.64 (d, 3H, $J=7.2$ Hz, $-\text{CH}_3$), 2.74 (s, 4H, imide), 3.08–3.23 (m, 8H, piperazine), 5.01 (q, 1H, $J=7.2$ Hz, $\equiv\text{CH}$), 6.76 (ddd, 1H, $J=8.3, 2.3, 0.8$ Hz, ArH), 6.83–6.89 (m, 2H, ArH), 7.14–7.22 (m, 1H, ArH).

1-{1-[4-(4-Chlorophenyl)piperazin-1-yl]-1-oxopropan-2-yl}pyrrolidine-2,5-dione (6). ^1H NMR (300 MHz, CDCl_3) δ 1.64 (d, 3H, $J=7.2$ Hz, $-\text{CH}_3$), 2.74 (s, 4H, imide), 3.02–3.20 (m, 4H, piperazine), 3.45–3.81 (m, 4H, piperazine), 5.01 (q, 1H, $J=7.2$ Hz, $\equiv\text{CH}$), 6.78–6.87 (m, 2H, ArH), 7.18–7.28 (m, 2H, ArH); ^{13}C NMR (75 MHz, CDCl_3) δ 14.8, 28.0, 47.5, 117.9, 125.6, 129.1, 149.3, 167.2, 176.5.

1-{1-[4-(2-Fluorophenyl)piperazin-1-yl]-1-oxopropan-2-yl}pyrrolidine-2,5-dione (7). ^1H NMR (300 MHz, CDCl_3) δ 1.64 (d, 3H, $J=7.2$ Hz, $-\text{CH}_3$), 2.74 (s, 4H, imide), 2.96–3.12 (m, 4H, piperazine), 3.39–3.62 (m, 4H), 5.01 (q, 1H, $J=7.2$ Hz, $\equiv\text{CH}$), 6.83–7.11 (m, 4H); ^{19}F NMR (282 MHz, CDCl_3): δ –123.05 (s., 1F).

1-{1-[4-(3-Fluorophenyl)piperazin-1-yl]-1-oxopropan-2-yl}pyrrolidine-2,5-dione (8).

¹H NMR (300 MHz, CDCl₃) δ 1.64 (d, 3H, *J*=7.2 Hz, –CH₃), 2.74 (s, 4H, imide), 3.08–3.26 (m, 4H, piperazine), 3.45–3.52 (m, 2H, piperazine), 3.68–3.81 (m, 2H, piperazine), 5.01 (q, 1H, *J*=7.2 Hz, ≡CH), 6.50–6.71 (m, 3H, ArH), 7.15–7.25 (m, 1H, ArH); ¹³C NMR (75 MHz, CDCl₃) δ: 14.8, 28.0, 47.5, 103.1, 103.5, 106.7, 107.0, 111.6, 130.2, 130.4, 152.2, 152.3, 165.3, 167.3, 176.5; ¹⁹F NMR (282 MHz, CDCl₃): δ –111.87 (s, 1F).

1-{1-[4-(4-Fluorophenyl)piperazin-1-yl]-1-oxopropan-2-yl}pyrrolidine-2,5-dione (9).

¹H NMR (300 MHz, CDCl₃) δ 1.63 (d, 3H, *J*=7.2 Hz, –CH₃), 2.73 (s, 4H, imide), 2.95–3.15 (m, 4H, piperazine), 3.40–3.89 (m, 4H, piperazine), 5.01 (q, 1H, *J*=7.2 Hz, ≡CH), 6.81–6.90 (m, 2H, ArH), 6.92–7.01 (m, 2H, ArH); ¹⁹F NMR (282 MHz, CDCl₃): δ –123.06 (s, 1F).

1-(1-Oxo-1-{4-[2-(trifluoromethyl)phenyl]piperazin-1-yl}propan-2-yl)pyrrolidine-2,5-dione (10).

¹H NMR (300 MHz, CDCl₃) δ 1.66 (d, 3H, *J*=7.2 Hz, –CH₃), 2.75 (s, 4H, imide), 2.82–3.01 (m, 8H, piperazine), 5.02 (q, 1H, *J*=7.2 Hz, ≡CH), 7.22–7.33 (m, 2H, ArH), 7.48–7.56 (m, 1H, ArH), 7.64 (d, 1H, *J*=7.8 Hz, ArH); ¹⁹F NMR (282 MHz, CDCl₃): δ –60.45 (s, 3F).

1-(1-Oxo-1-{4-[3-(trifluoromethyl)phenyl]piperazin-1-yl}propan-2-yl)pyrrolidine-2,5-dione (11).

¹H NMR (300 MHz, CDCl₃) δ 1.64 (d, 3H, *J*=7.2 Hz, –CH₃), 2.74 (s, 4H, imide), 3.12–3.28 (m, 4H, piperazine), 3.39–3.92 (m, 4H, piperazine), 5.01 (q, 1H, *J*=7.1 Hz, ≡CH), 6.99–7.19 (m, 3H, ArH), 7.29–7.43 (m, 1H, ArH); ¹³C NMR (75 MHz, CDCl₃) δ: 14.8, 28.0, 47.5, 112.8, 112.9, 117.0, 129.7, 131.7, 150.7, 176.3, 176.5; ¹⁹F NMR (282 MHz, CDCl₃): δ –62.76 (s, 3F).

1-(1-Oxo-1-{4-[4-(trifluoromethyl)phenyl]piperazin-1-yl}propan-2-yl)pyrrolidine-2,5-dione (12).

¹H NMR (300 MHz, CDCl₃) δ 1.64 (d, 3H, *J*=7.2 Hz, –CH₃), 2.69–2.79 (m, 4H, imide), 3.25 (td, 4H, *J*=5.1, 2.2 Hz, piperazine), 3.39–3.92 (m, 4H, piperazine), 5.02 (q, 1H, *J*=7.2 Hz, ≡CH), 6.91 (d, 2H, *J*=8.5 Hz, ArH), 7.50 (d, 2H, *J*=8.5 Hz, ArH); ¹⁹F NMR (282 MHz, CDCl₃): δ –61.55 (s, 3F).

1-{1-[4-(3-Methylphenyl)piperazin-1-yl]-1-oxopropan-2-yl}pyrrolidine-2,5-dione (13).

¹H NMR (300 MHz, CDCl₃) δ 1.63 (d, 3H, *J*=7.1 Hz, –CH₃), 2.31 (s, 3H, –CH₃), 2.72 (s, 4H, imide), 3.02–3.22 (m, 4H, piperazine), 3.40–3.90 (m, 4H, piperazine), 5.00 (q, 1H, *J*=7.2 Hz, ≡CH), 6.65–6.77 (m, 3H, ArH), 7.09–7.20 (m, 1H, ArH).

1-{1-[4-(3-Methoxyphenyl)piperazin-1-yl]-1-oxopropan-2-yl}pyrrolidine-2,5-dione (14).

¹H NMR (300 MHz, CDCl₃) δ 1.63 (d, 3H, *J*=7.2 Hz, –CH₃), 2.73 (s, 4H, imide), 3.04–3.28 (m, 4H, piperazine), 3.38–3.84 (m, 7H; 4H, piperazine, 3H, –OCH₃), 5.01 (q, 1H, *J*=7.2 Hz, ≡CH), 6.40–6.55 (m, 3H, ArH), 7.12–7.24 (m, 1H, ArH).

1-[1-(Morpholin-4-yl)-1-oxopropan-2-yl]pyrrolidine-2,5-dione (15). ^1H NMR (300 MHz, CDCl_3) δ 1.60 (d, 3H, $J=7.2$ Hz, $-\text{CH}_3$), 2.73 (s, 4H, imide), 3.21–3.81 (m, 8H, morpholine), 4.94 (q, 1H, $J=7.2$ Hz, $\equiv\text{CH}$).

1-[1-Oxo-1-(4-phenylpiperazin-1-yl)butan-2-yl]pyrrolidine-2,5-dione (16). ^1H NMR (300 MHz, CDCl_3) δ 0.92 (t, 3H, $J=7.4$ Hz, $\underline{\text{CH}_3}-\text{CH}_2-$), 1.99 (ddd, 1H, $J=14.3, 7.4, 5.1$ Hz, $\text{CH}_3-\underline{\text{CH}_2}-$), 2.41 (ddd, 1H, $J=14.3, 10.4, 7.3$ Hz, $\text{CH}_3-\underline{\text{CH}_2}-$), 2.74 (d, 4H, $J=0.6$ Hz, imide), 3.06–3.22 (m, 4H, piperazine), 3.53 (br s, 2H, piperazine), 3.68–3.81 (m, 2H, piperazine), 4.83 (dd, 1H, $J=10.4, 5.1$ Hz, $\equiv\text{CH}$), 6.86–6.95 (m, 3H, ArH), 7.23–7.32 (m, 2H, ArH); ^{13}C NMR (75 MHz, CDCl_3) δ : 11.1, 21.5, 28.0, 53.8, 116.6, 120.7, 129.2, 150.7, 166.9, 176.8.

1-{1-[4-(2-Chlorophenyl)piperazin-1-yl]-1-oxobutan-2-yl}pyrrolidine-2,5-dione (17). ^1H NMR (300 MHz, CDCl_3) δ 0.92 (t, 3H, $J=7.3$ Hz, $\underline{\text{CH}_3}-\text{CH}_2-$), 1.99 (ddd, 1H, $J=14.3, 7.3, 5.1$ Hz, $\text{CH}_3-\underline{\text{CH}_2}-$), 2.43 (ddd, 1H, $J=14.3, 10.5, 7.3$ Hz, $\text{CH}_3-\underline{\text{CH}_2}-$), 2.75 (s, 4H, imide), 2.92–3.08 (m, 4H, piperazine), 3.54 (br s, 2H, piperazine), 3.78 (br s, 2H, piperazine), 4.83 (dd, 1H, $J=10.5, 5.1$ Hz, $\equiv\text{CH}$), 6.92–7.06 (m, 2H, ArH), 7.15–7.28 (m, 1H, ArH), 7.31–7.43 (m, 1H, ArH); ^{13}C NMR (75 MHz, CDCl_3) δ : 11.1, 21.4, 28.0, 42.6, 45.8, 50.9, 51.5, 53.9, 76.6, 120.5, 124.4, 127.7, 128.8, 130.7, 148.3, 167.0, 176.9.

1-{1-[4-(3-Chlorophenyl)piperazin-1-yl]-1-oxobutan-2-yl}pyrrolidine-2,5-dione (18). ^1H NMR (300 MHz, CDCl_3) δ 0.93 (t, 3H, $J=7.3$ Hz, $\underline{\text{CH}_3}-\text{CH}_2-$), 1.99 (ddd, 1H, $J=14.2, 7.3, 5.3$ Hz, $\text{CH}_3-\underline{\text{CH}_2}-$), 2.42 (ddd, 1H, $J=14.3, 10.3, 7.2$ Hz, $\text{CH}_3-\underline{\text{CH}_2}-$), 2.75 (s, 4H, imide), 3.08–3.22 (m, 4H, piperazine), 3.41–3.87 (m, 4H, piperazine), 4.82 (dd, 1H, $J=10.4, 5.1$ Hz, $\equiv\text{CH}$), 6.76 (dd, 1H, $J=8.3, 2.1$ Hz, ArH), 6.83–6.89 (m, 2H, ArH), 7.14–7.21 (m, 1H, ArH).

1-{1-[4-(4-Chlorophenyl)piperazin-1-yl]-1-oxobutan-2-yl}pyrrolidine-2,5-dione (19). ^1H NMR (300 MHz, CDCl_3) δ 0.92 (t, 3H, $J=7.4$ Hz, $\underline{\text{CH}_3}-\text{CH}_2-$), 1.98 (ddd, 1H, $J=14.3, 7.4, 5.2$ Hz, $\text{CH}_3-\underline{\text{CH}_2}-$), 2.42 (ddd, 1H, $J=14.3, 10.4, 7.3$ Hz, $\text{CH}_3-\underline{\text{CH}_2}-$), 2.75 (d, 4H, $J=0.6$ Hz, imide), 3.02–3.20 (m, 4H, piperazine), 3.45–3.86 (m, 4H, piperazine), 4.82 (dd, 1H, $J=10.4, 5.2$ Hz, $\equiv\text{CH}$), 6.77–6.90 (m, 2H, ArH), 7.16–7.30 (m, 2H); ^{13}C NMR (75 MHz, CDCl_3) δ : 11.1, 21.5, 28.0, 53.8, 117.9, 129.1, 149.2, 167.0, 176.8.

1-{1-[4-(2-Fluorophenyl)piperazin-1-yl]-1-oxobutan-2-yl}pyrrolidine-2,5-dione (20). ^1H NMR (300 MHz, CDCl_3) δ 0.93 (t, 3H, $J=7.4$ Hz, $\underline{\text{CH}_3}-\text{CH}_2-$), 1.99 (ddd, 1H, $J=14.3, 7.3, 5.2$ Hz, $\text{CH}_3-\underline{\text{CH}_2}-$), 2.42 (ddd, 1H, $J=14.3, 10.4, 7.3$ Hz, $\text{CH}_3-\underline{\text{CH}_2}-$), 2.75 (s, 4H, imide), 2.94–3.15 (m, 4H, piperazine), 3.65–3.83 (m, 4H, piperazine), 4.83 (dd, 1H, $J=10.4, 5.2$ Hz, $\equiv\text{CH}$), 6.83–7.14 (m, 4H, ArH); ^{19}F NMR (282 MHz, CDCl_3) δ –123.03 (s, 1F).

1-{1-[4-(3-Fluorophenyl)piperazin-1-yl]-1-oxobutan-2-yl}pyrrolidine-2,5-dione (21). ^1H NMR (300 MHz, CDCl_3) δ 0.93 (t, 3H, $J=7.4$ Hz, $\underline{\text{CH}_3}-\text{CH}_2-$), 1.99 (ddd, 1H, $J=14.3, 7.4, 5.2$ Hz, $\text{CH}_3-\underline{\text{CH}_2}-$), 2.42 (ddd, 1H, $J=14.3, 10.4, 7.3$ Hz, $\text{CH}_3-\underline{\text{CH}_2}-$), 2.75 (s, 4H, imide), 3.06–3.25 (m, 4H, piperazine), 3.43–3.84 (m, 4H, piperazine), 4.83 (dd, 1H, $J=10.4, 5.2$ Hz,

$\equiv\text{CH}$), 6.53–6.62 (m, 2H, ArH), 6.65 (ddd, 1H, $J=8.4, 2.1, 0.8$ Hz, ArH), 7.15–7.25 (m, 1H, ArH); ^{19}F NMR (282 MHz, CDCl_3) δ –111.97–(–111.78) (m, 1F).

1-{1-[4-(4-Fluorophenyl)piperazin-1-yl]-1-oxobutan-2-yl}pyrrolidine-2,5-dione (22).

^1H NMR (300 MHz, CDCl_3) δ 0.92 (t, 3H, $J=7.4$ Hz, $\text{CH}_3\text{--CH}_2\text{--}$), 1.90–2.07 (m, 1H, $\text{CH}_3\text{--CH}_2\text{--}$), 2.32–2.52 (m, 1H, $\text{CH}_3\text{--CH}_2\text{--}$), 2.70–2.79 (m, 4H, imide), 2.97–3.12 (m, 4H, piperazine), 3.44–3.80 (m, 4H, piperazine), 4.83 (dd, 1H, $J=10.5, 5.1$ Hz, $\equiv\text{CH}$), 6.81–6.91 (m, 2H, ArH), 6.92–7.02 (m, 2H, ArH); ^{19}F NMR (282 MHz, CDCl_3): δ –123.06 (br s, 1F).

1-(1-Oxo-1-{4-[2-(trifluoromethyl)phenyl]piperazin-1-yl}butan-2-yl)pyrrolidine-2,5-dione (23).

^1H NMR (300 MHz, CDCl_3) δ 0.92 (t, 3H, $J=7.3$ Hz, $\text{CH}_3\text{--CH}_2\text{--}$), 1.99 (ddd, 1H, $J=14.3, 7.3, 5.1$ Hz, $\text{CH}_3\text{--CH}_2\text{--}$), 2.45 (ddd, 1H, $J=14., 10.5, 7.2$ Hz, $\text{CH}_3\text{--CH}_2\text{--}$), 2.76 (s, 4H, imide), 2.81–2.98 (m, 4H, piperazine), 3.41–3.60 (m, 4H, piperazine), 4.83 (dd, 1H, $J=10.5, 5.1$ Hz, $\equiv\text{CH}$), 7.21–7.32 (m, 2H, ArH), 7.47–7.56 (m, 1H, ArH), 7.60–7.66 (m, 1H, ArH); ^{19}F NMR (282 MHz, CDCl_3) δ –62.78 (br s, 3F).

1-(1-Oxo-1-{4-[3-(trifluoromethyl)phenyl]piperazin-1-yl}butan-2-yl)pyrrolidine-2,5-dione (24).

^1H NMR (300 MHz, CDCl_3) δ 0.92 (t, 3H, $J=7.3$ Hz, $\text{CH}_3\text{--CH}_2\text{--}$), 1.99 (ddd, 1H, $J=14.3, 7.3, 5.2$ Hz, $\text{CH}_3\text{--CH}_2\text{--}$), 2.42 (ddd, 1H, $J=14.3, 10.4, 7.2$ Hz, $\text{CH}_3\text{--CH}_2\text{--}$), 2.75 (s, 4H, imide), 3.11–3.28 (m, 4H, piperazine), 3.46–3.89 (m, 4H, piperazine), 4.82 (dd, 1H, $J=10.4, 5.2$ Hz, $\equiv\text{CH}$), 7.00–7.17 (m, 3H, ArH), 7.30–7.41 (m, 1H, ArH); ^{13}C NMR (75 MHz, CDCl_3) δ 11.1, 21.5, 28.0, 53.8, 112.7, 112.8, 112.8, 112.9, 116.8, 116.9, 116.9, 117.0, 119.4, 129.7, 131.3, 131.7, 150.7, 167.0, 176.8; ^{19}F NMR (282 MHz, CDCl_3) δ –62.78 (s, 3F).

1-(1-Oxo-1-{4-[4-(trifluoromethyl)phenyl]piperazin-1-yl}butan-2-yl)pyrrolidine-2,5-dione (25).

^1H NMR (300 MHz, CDCl_3) δ 0.93 (t, 3H, $J=7.3$ Hz, $\text{CH}_3\text{--CH}_2\text{--}$), 1.92–2.08 (m, 1H, $\text{CH}_3\text{--CH}_2\text{--}$), 2.32–2.51 (m, 1H, $\text{CH}_3\text{--CH}_2\text{--}$), 2.71–2.80 (m, 4H, imide), 3.17–3.33 (m, 4H, piperazine), 3.43–3.89 (m, 4H, piperazine), 4.83 (dd, 1H, $J=10.4, 5.2$ Hz, $\equiv\text{CH}$), 6.91 (d, 2H, $J=8.8$ Hz, ArH), 7.50 (d, 2H, $J=8.9$ Hz, ArH); ^{19}F NMR (282 MHz, CDCl_3) δ –61.55 (s, 3F).

1-{1-[4-(3-Methylphenyl)piperazin-1-yl]-1-oxobutan-2-yl}pyrrolidine-2,5-dione (26).

^1H NMR (300 MHz, CDCl_3) δ 0.92 (t, 3H, $J=7.3$ Hz, $\text{CH}_3\text{--CH}_2\text{--}$), 1.99 (ddd, 1H, $J=14.3, 7.4, 5.2$ Hz, $\text{CH}_3\text{--CH}_2\text{--}$), 2.31 (s, 3H, $-\text{CH}_3$), 2.41 (ddd, 1H, $J=14.3, 10.4, 7.3$ Hz, $\text{CH}_3\text{--CH}_2\text{--}$), 2.74 (d, 4H, $J=0.6$ Hz, imide), 3.04–3.20 (m, 4H, piperazine), 3.52 (br s, 2H, piperazine), 3.66–3.83 (m, 2H, piperazine), 4.82 (dd, 1H, $J=10.4, 5.2$ Hz, $\equiv\text{CH}$), 6.67–6.76 (m, 3H, ArH), 7.11–7.20 (m, 1H, ArH); ^{13}C NMR (75 MHz, CDCl_3) δ 11.1, 21.5, 21.7, 28.0, 53.8, 113.7, 117.5, 121.6, 129.0, 139.0, 150.7, 166.9, 176.8.

1-{1-[4-(3-Methoxyphenyl)piperazin-1-yl]-1-oxobutan-2-yl}pyrrolidine-2,5-dione (27).

^1H NMR (300 MHz, CDCl_3) δ 0.92 (t, 3H, $J=7.4$ Hz, $\text{CH}_3\text{--CH}_2\text{--}$), 1.91–2.08 (m, 1H, $\text{CH}_3\text{--CH}_2\text{--}$), 2.39 (dt, 1H, $J=10.4, 7.2$ Hz, $\text{CH}_3\text{--CH}_2\text{--}$), 2.74 (d, 4H, $J=0.6$ Hz, imide), 3.04–3.20 (m, 4H, piperazine), 3.43–3.76 (m, 4H, piperazine), 3.78 (s, 3H, $-\text{OCH}_3$), 4.82 (dd, 1H,

$J=10.4, 5.2$ Hz, $\equiv\text{CH}$), 6.40–6.54 (m, 3H, ArH), 7.13–7.21 (m, 1H, ArH); ^{13}C NMR (75 MHz, CDCl_3) δ 11.1, 21.5, 27.9, 53.8, 55.2, 103.1, 105.3, 109.2, 129.9, 152.0, 160.6, 166.9, 176.8.

1-[1-(Morpholin-4-yl)-1-oxobutan-2-yl]pyrrolidine-2,5-dione (28).

^1H NMR (300 MHz, CDCl_3): δ 0.91 (t, 3H, $J=7.4$ Hz, $\text{CH}_3\text{--CH}_2\text{--}$), 1.95 (ddd, 1H, $J=14.3, 7.4, 5.2$ Hz, $\text{CH}_3\text{--CH}_2\text{--}$), 2.41 (ddd, 1H, $J=14.3, 10.4, 7.3$ Hz, $\text{CH}_3\text{--CH}_2\text{--}$), 2.69–2.79 (m, 4H, imide), 3.25–3.75 (m, 8H, morpholine), 4.76 (dd, 1H, $J=10.4, 5.2$ Hz, $\equiv\text{CH}$).

1-[1-[4-(3-Trifluoromethylphenyl)piperazin-1-yl]-3-methoxy-1-oxopropan-2-

yl]pyrrolidine-2,5-dione (30). ^1H NMR (300 MHz, CDCl_3) δ 2.74 (s, 4H, imide), 3.30 (s, 3H, --OCH_3), 3.32–3.48 (m, 4H, piperazine), 3.82–4.16 (m, 6H; 4H, piperazine, 2H, $\text{--CH}_2\text{--}$), 5.06 (dd, 1H, $J=7.9, 6.2$ Hz, 1H), 7.43–7.59 (m, 2H, ArH), 7.60–7.77 (m, 2H, ArH); ^{19}F NMR (282 MHz, CDCl_3) δ –62.98 (s, 3F).

3. *In vivo* pharmacology. General remarks

Adult male Swiss mice (weighing 22–26 g), that were kept in colony cages with free access to food and tap water, housed under standardized housing conditions, were used. After seven days of adaptation to laboratory conditions, the animals were randomly assigned to experimental groups each comprised of 4 mice. Each mouse was used only once. Procedures involving animals and their care were conducted in accordance with current European Community and Polish legislation on animal experimentation. The experimental protocols and procedures described in this manuscript were approved by the First Local Ethics Committee at the Medical University in Lublin and the Second Local Ethics Committee at the University of Life Sciences in Lublin and complied with the European Communities Council Directive of 24 November 1986 (86/609/EEC). All substances were suspended in a 1% solution of Tween 80 in distilled water and administered intraperitoneally (*i.p.*) as a single injection, in a volume of 5 mL/kg body weight. Fresh solutions were prepared each day of experimentation.

The reference AEDs were obtained from carbamazepine (CBZ, Sigma-Aldrich, St. Louis, MO, USA), ethosuximide (ETX, Sigma-Aldrich, St. Louis, MO, USA), lacosamide (LCM; UCB Pharma, Braine l'Alleud, Belgium), levetiracetam (LEV, UCB Pharma, Braine l'Alleud, Belgium), topiramate (TPM, Tocris, Ellisville, MO, USA), valproic acid (VPA, Sigma-Aldrich, St. Louis, MO, USA).

3.1. Maximal electroshock seizure test (MES)

The maximal electroshock test was performed according to procedure originally described by Toman et al.¹ The compounds tested were administered at 0.25, 0.5, 1 and 2 h before the initiation of maximal electroconvulsions. The pretreatment times before testing of the compounds investigated and the route of *i.p.* administration were based upon information from the Anticonvulsant Screening Program.² Electroconvulsions were produced by a current (0.2 s stimulus duration; 500 V, 50 Hz, fixed current intensity of 25 mA) delivered via ear-clip electrodes by a Rodent Shocker generator (constant current stimulator Type 221, Hugo Sachs Elektronik, Freiburg, Germany). The criterion for the occurrence of seizure activity was

the tonic hind limb extension. The animals were administered with a constant dose of 300 mg/kg for all compounds and 100 mg/kg for 17 derivatives and were subjected to MES-induced seizures.

3.2. Subcutaneous pentylenetetrazole seizure test (*sc*PTZ)

Pentylenetetrazole (PTZ) were purchased from Sigma-Aldrich (St. Louis, MO, USA). PTZ was dissolved in saline solution. *Sc*PTZ-induced seizures were performed by subcutaneously injection of PTZ (100 mg/kg). This produced clonic convulsions lasting for at least five seconds, with accompanying loss of the righting reflex. PTZ was administered 0.25, 0.5, 1 and 2 h after injections of tested compounds and observation were carried out for 30 min. In the control groups the first episode of clonic convulsions was observed between 4–16 min of observation. The absence of clonic convulsions in the observed time period of was interpreted as the compound's ability to protect against PTZ-induced seizure.³ The animals were administered with a constant dose of 300 mg/kg and 100 mg/kg.

3.3. The 6 Hz psychomotor seizure model

This screen was carried out according to the protocol described elsewhere.⁴ Briefly, the 6 Hz model is an alternative electroshock paradigm that uses low-frequency (6 Hz) long-duration (3 s) electrical stimulation. Corneal stimulation (0.2 ms duration monopolar rectangular pulses at 6 Hz for 3 s) was delivered by a constant-current device. During the stimulation, mice were manually restrained and released into observation cage immediately after the current application. The seizures manifested in “stunned” posture associated with rearing, forelimb, automatic movements, and clonus, twitching the vibrissae and Straub-tail. The duration of the seizure activity ranges from 60 s to 120 s in untreated animals. At the end of the seizure, animals resume their normal exploratory behavior. The experimental end point is protection against the seizure. The animal is considered to be protected if it resumes its normal exploratory behavior within 10 s from the stimulation. The animals were administered with a constant dose of 300 mg/kg and 100 mg/kg.

3.4. Chimney test

The chimney test of Boissier et al.⁵ was used to quantify the acute adverse-effect potential of compounds **3–28**, **30** and model AEDs in mice. In this test, the animals had to climb backwards up a plastic tube (3 cm inner diameter, 30 cm length), and motor performance impairment was indicated by the inability of the mice to climb backward up the transparent tube within 60 s.

3.5. Median effective dose (ED₅₀), median toxic dose (TD₅₀) and protective index (PI) determination

The ED₅₀ is defined as the dose of a drug protecting 50% of animals against the MES and PTZ seizures. To evaluate the ED₅₀, at least four groups of animals were injected with various doses of tested compounds. Each group consisted of 8 animals. The neurotoxic effect was expressed as a TD₅₀ value, representing the doses at which the compound resulted in minimal

motor impairment in 50% of the animals in the rotarod test. Similarly, to evaluate the TD₅₀, four groups of animals (each group consisted of 8 mice) were injected with various doses of compound. Both ED₅₀ and TD₅₀ values with 95% confidence limits were calculated by probit analysis.⁶ The protective indexes for the compounds investigated and model AEDs were calculated by dividing a TD₅₀ value, as determined in the chimney test, by the respective ED₅₀ value, as determined in the MES, scPTZ or 6 Hz tests. The protective index is considered as an index of the margin of safety and tolerability between anticonvulsant doses and doses of the compounds exerting acute adverse effects e.g. sedation, motor coordination impairment, ataxia or other neurotoxic manifestations.⁷

4. *In vitro* pharmacology

4.1. Radioligand binding assays

Sodium and calcium channels (N-type, L-type) binding studies were performed commercially in Cerep Laboratories (Poitiers, France) using testing procedures described elsewhere (Na⁺ channel - site 2,⁸ N-type Ca²⁺ channel,⁹ L-type Ca²⁺ channel¹⁰). All experiments were performed in duplicate. The general information is listed in Table 1.

Table 1. Experimental conditions binding assays

Assay	Source	Ligand	Concentration	Kd	Nonspecific binding	Incubation	Detection method
Na ⁺ channel (site 2)	Rat cerebral cortex	[³ H]Batrachotoxinin	10 nM	91 nM	Veratridine (300 µM)	60 min 37 °C	Scintillation counting
Ca ²⁺ channel N, (antagonist radioligand)	Rat cerebral cortex	[¹²⁵ I]ω-Conotoxin GVIA	0.2 nM	0.4 nM	ω-Conotoxin GVIA (10 mM)	30 min Room temp.	Scintillation counting
Ca ²⁺ channel L, dihydro-pyridine site) (antagonist radioligand)	Rat cerebral cortex	[³ H]Nitrendipine	0.001 nM	0.0007 nM	Nifedipine (1 µM)	120 min Room temp.	Scintillation counting

4.2. Antiproliferative assay

Human embryonic kidney HEK–293 cell line (ATCC CRL-1573) was kindly donated by Prof. Dr. Christa Müller (Pharmaceutical Institute, Pharmaceutical Chemistry I, University of Bonn, Germany). The cell lines were cultured in Dulbecco's Modified Eagle's Medium–DMEM (Gibco) with 10% fetal bovine serum (FBS), 100 mg/mL streptomycin and 100 U/mL penicillin at 37 °C in an atmosphere containing 5% CO₂. The cell lines were seeded in 96–well plates at a concentration of 1.5 × 10⁴ cells/well and next cultured in 200 µl of culture medium for 24 h to reach 60% confluence. The stock solution of compound **11** in DMSO (25 mM) was diluted into fresh growth medium to the final concentrations 0.01 µM–250 µM,

added to the culture and incubated for 48 h. The DMSO concentration did not exceed 1%. The EZ4U (EZ4U Non-radioactive cell proliferation and cytotoxicity assay, Biomedica) labeling mixture (20 µl) was next added to each well and the cells were incubated under the same conditions for 5 h. The absorbance of the samples was measured using a microplate reader (EnSpire, PerkinElmer, Waltham, MA, USA) at 492 nm. The activity of the standard drug doxorubicin (DX) was estimated as described previously.¹¹

4.3. Metabolic stability

Reaction with recombinant human liver microsomes (HLMs). Commercial, pooled, human (adult male & female) liver microsomes (HLMs) was obtained from Sigma-Aldrich (St. Louis, MO, USA). The biotransformation was carried out using 1 mg/mL HLMs in 200 µl of reaction buffer containing 0.1 M Tris-HCl (pH 7.4), NADPH Regeneration System (Promega, Madison, WI, USA) and compound **11** with final volume 50 µM. The reaction mixture was preincubated at 37°C for 5 min and then, the reaction was initiated by adding 50 µl of Regeneration System. To terminate the reaction after 120 min, the 200 µl of cold methanol was added. The mixture was next centrifuged at 13 000 rpm for 15 min and the LC/MS analysis of the supernatant was performed. Mass spectra was recorded on LC/MS system consisting of a Waters Acquity UPLC (Waters, Milford, USA), coupled to a Waters TQD mass spectrometer (electrospray ionization mode ESI-tandem quadrupole).

CYP3A4 P450-Glo™ Assay. The luminescent CYP3A4 P450-Glo™ Assay was provided by Promega (Madison, WI, USA). The enzymatic reactions were performed in white polystyrene, flat-bottom Nunc™ MicroWell™ 96-Well Microplates (Thermo Scientific, Waltham, MA USA). The luminescence signal was measured with a microplate reader in luminescence mode (EnSpire, PerkinElmer, Waltham, MA, USA). The CYP3A4 P450-Glo™ protocol was also provided by Promega.¹² The IC₅₀ value of the reference drug ketoconazole was determinate and calculated as reported previously.¹³ The final concentrations of compound **11** was 0.025 µM–25 µM.

5. *In silico* metabolic biotransformation studies

The metabolic biotransformation of compound **11** was studied *in silico* by using computational procedure MetaSite 4.1.1 provided by Molecular Discovery Ltd (2013).^{14,15} The potential sites of metabolism were analyzed using liver model.

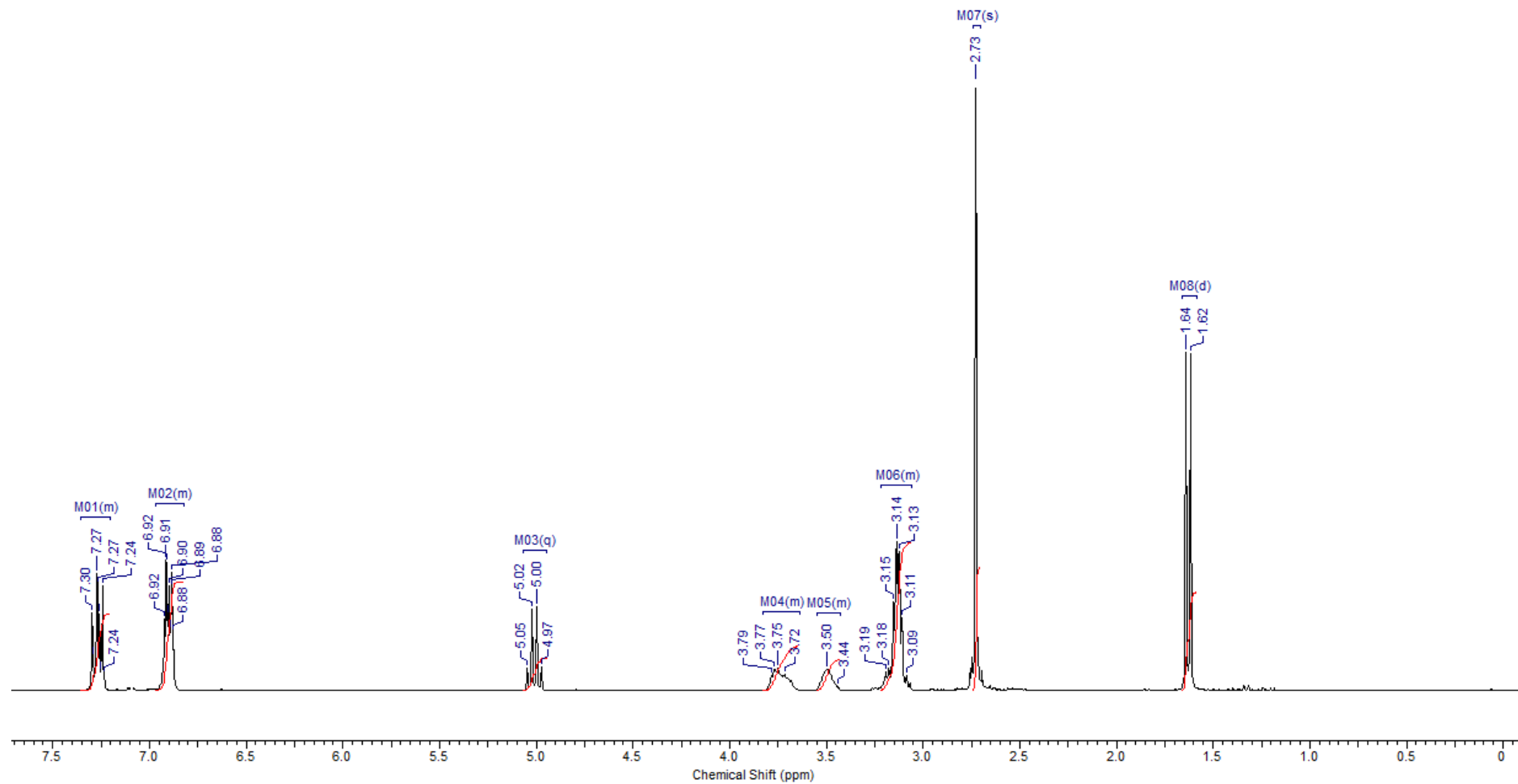
6. References

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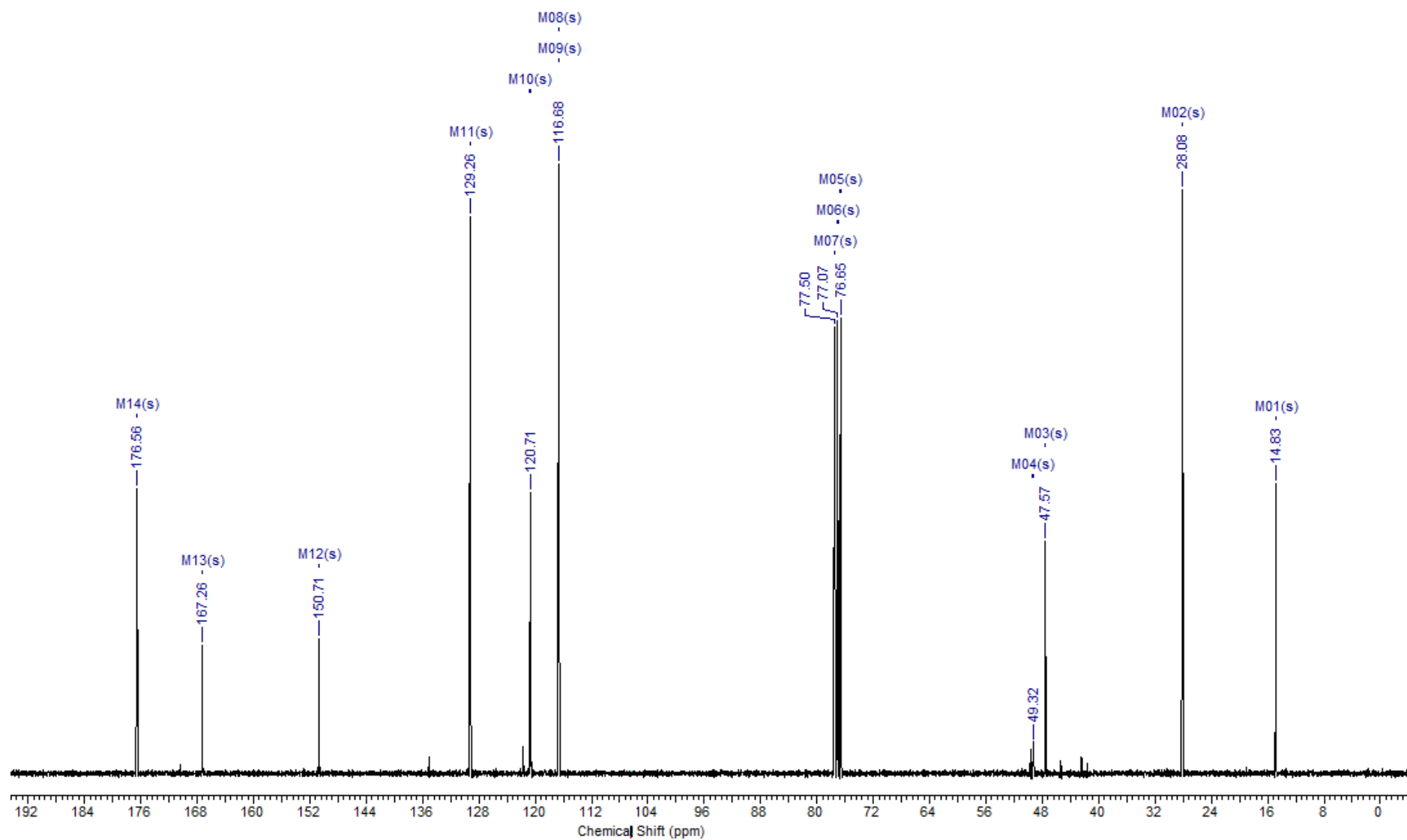
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7. ^1H NMR, ^{13}C NMR, ^{19}F NMR spectra for final compounds 3–28 and 30

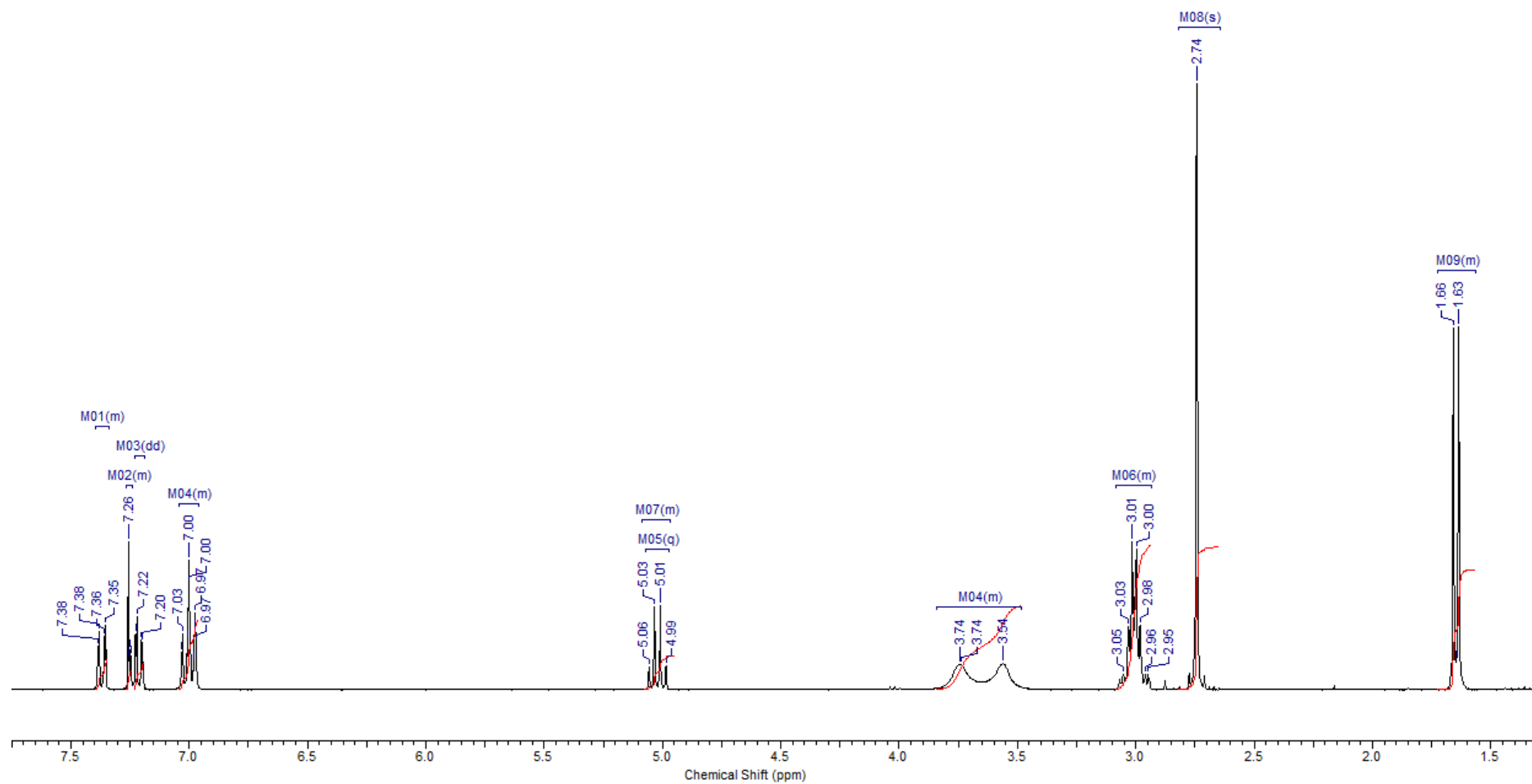
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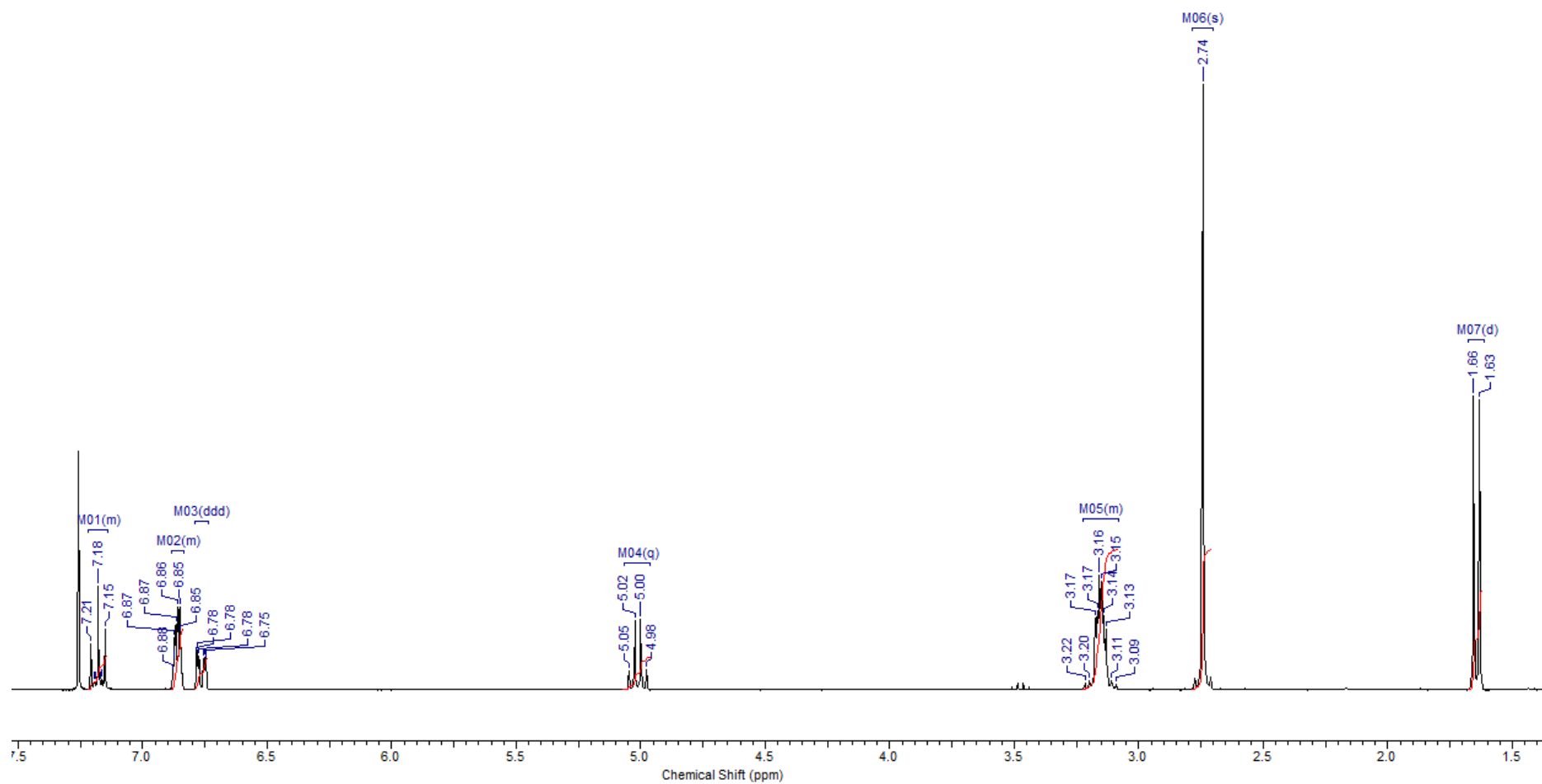
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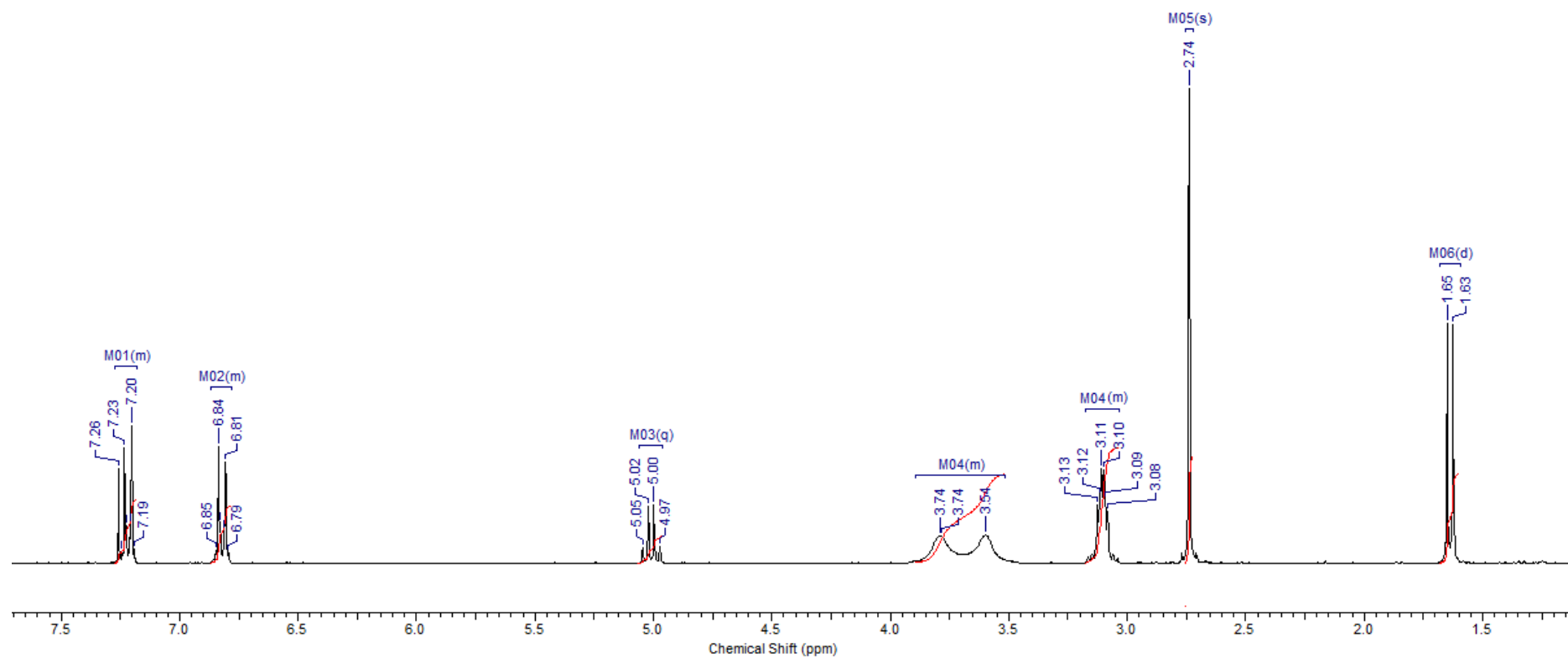
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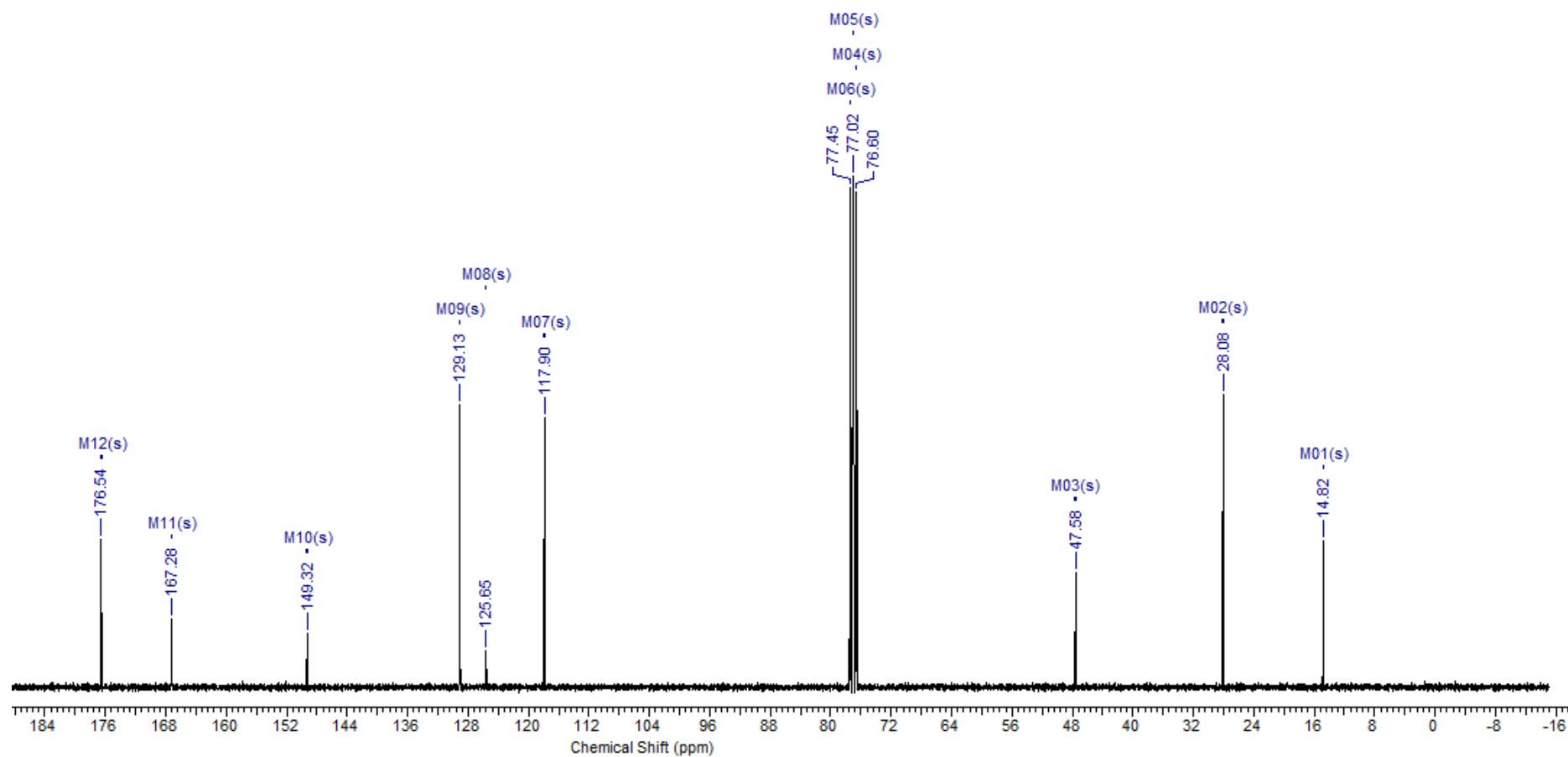
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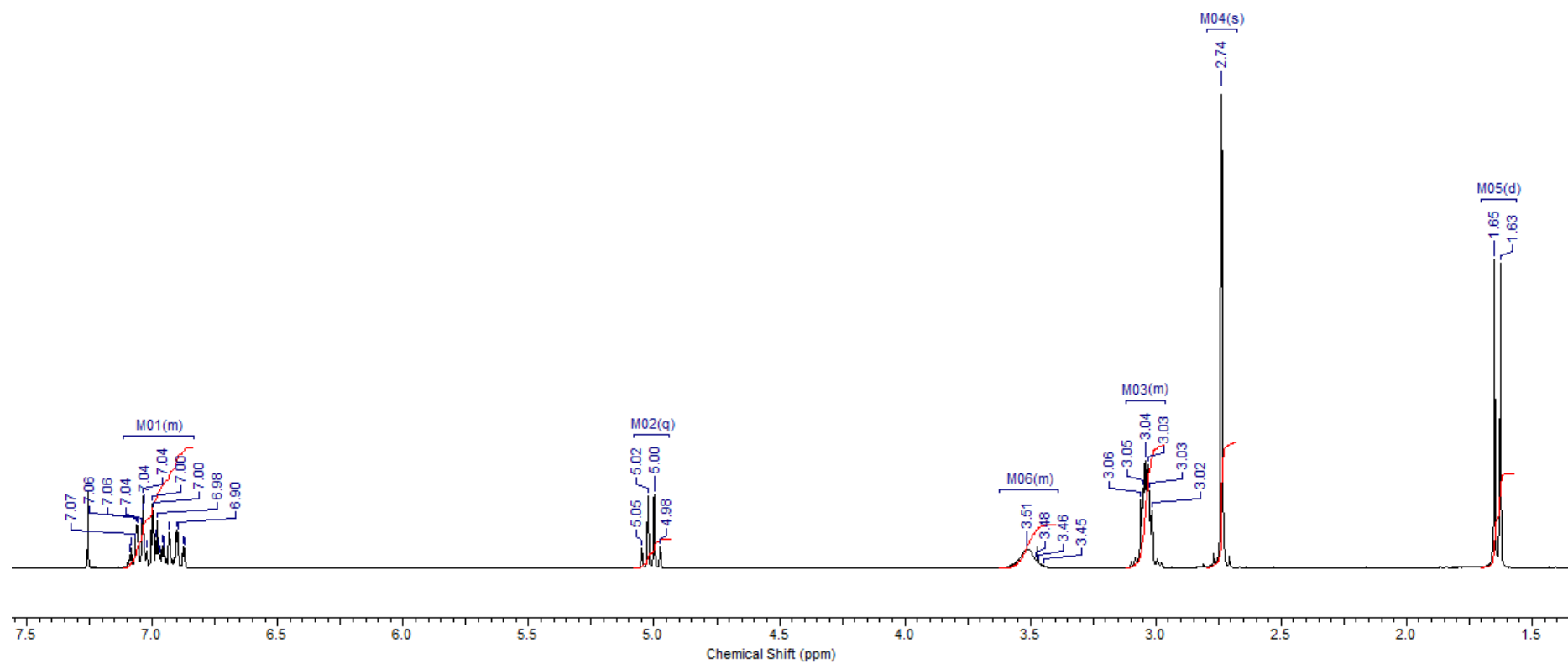
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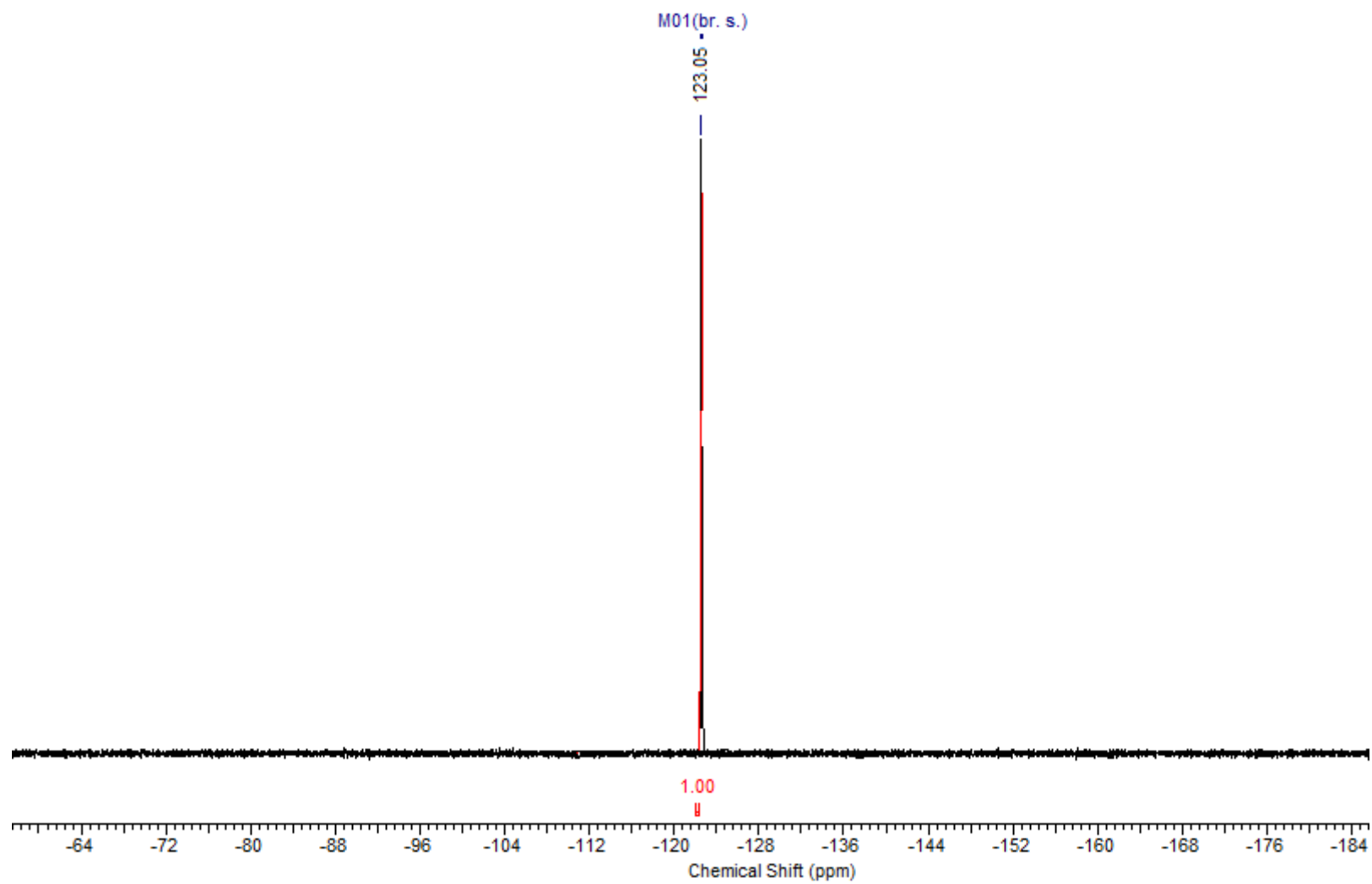
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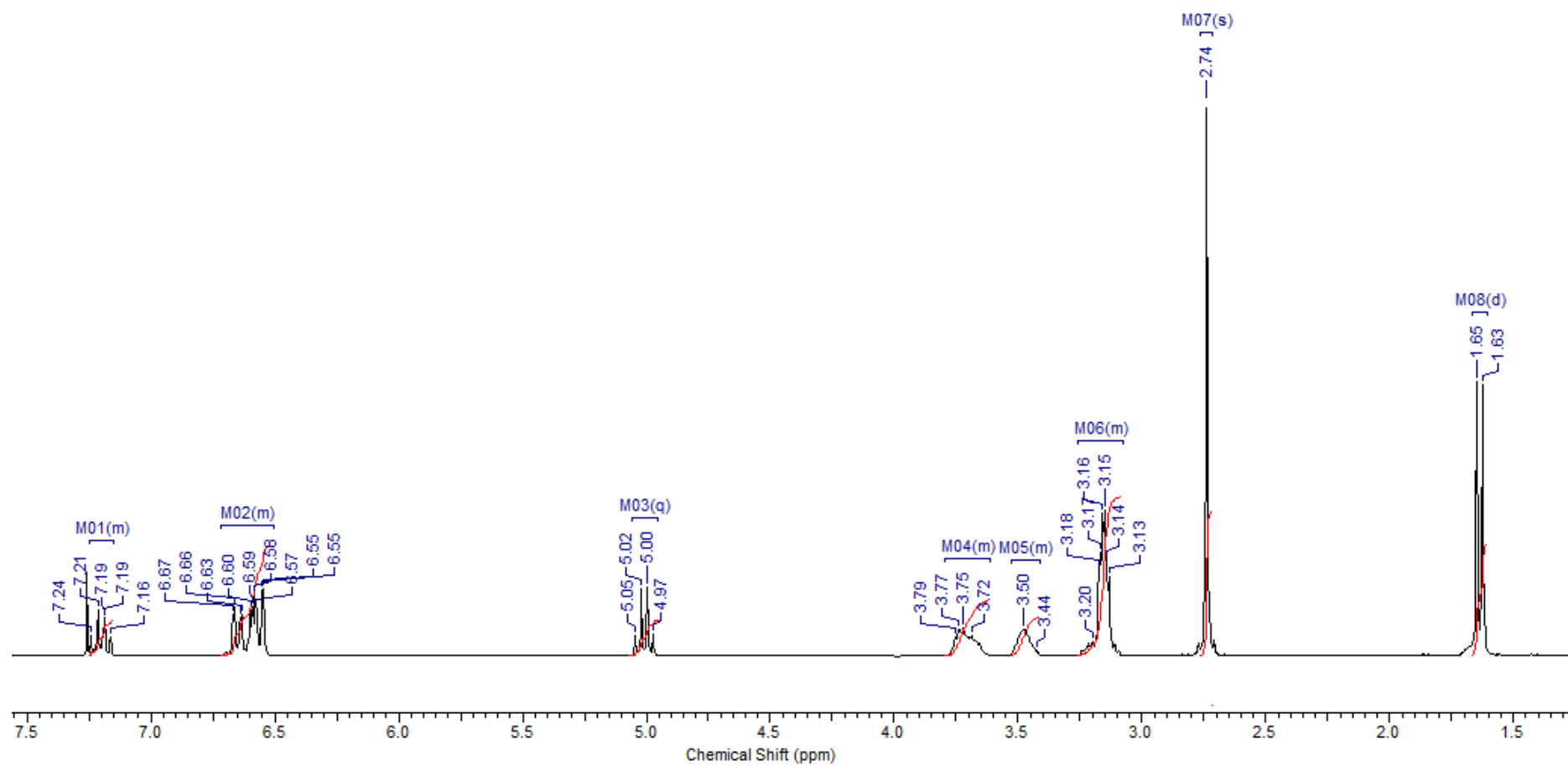
1-{1-[4-(2-Fluorophenyl)piperazin-1-yl]-1-oxopropan-2-yl}pyrrolidine-2,5-dione (**7**) – ^1H NMR



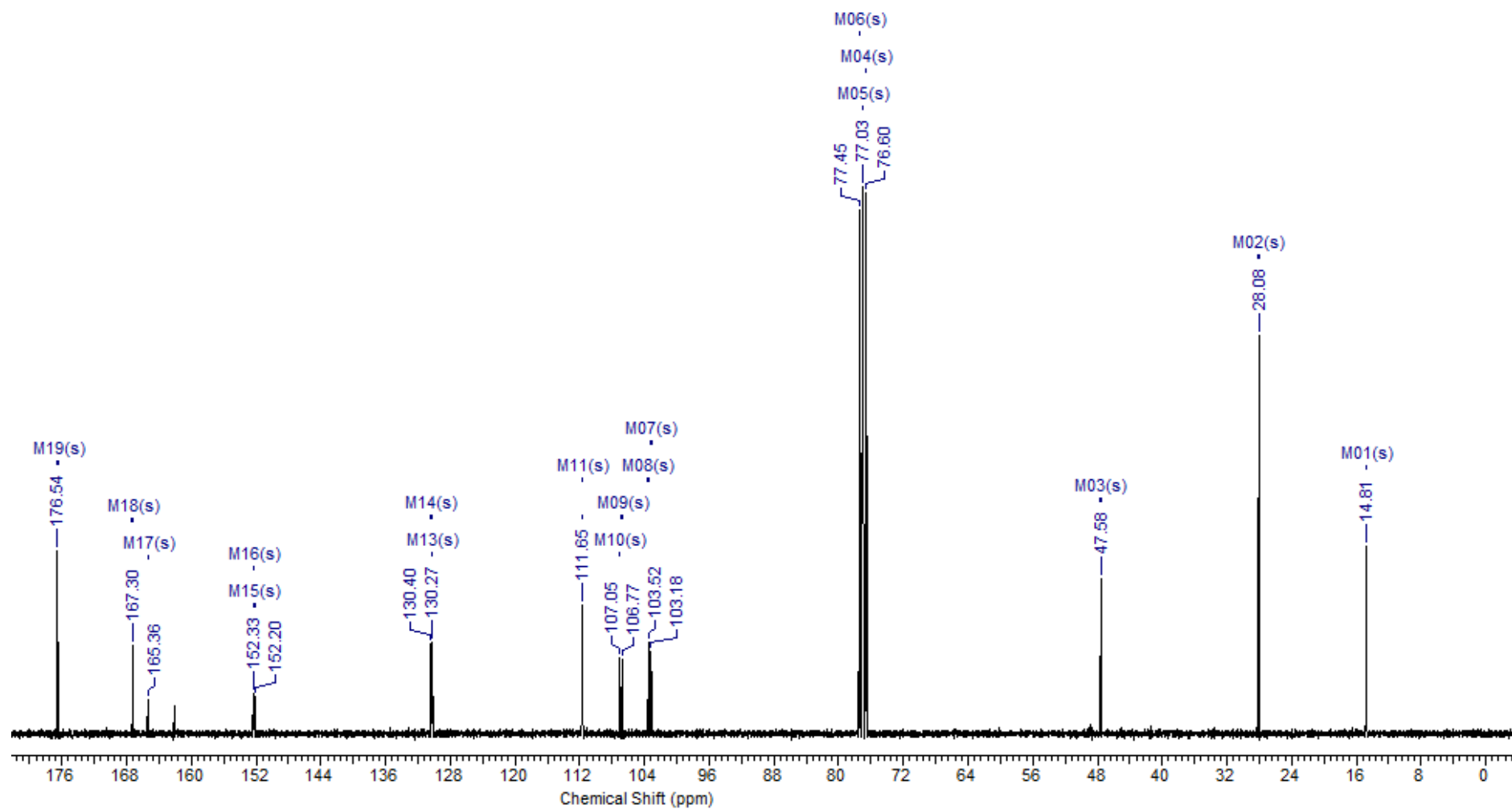
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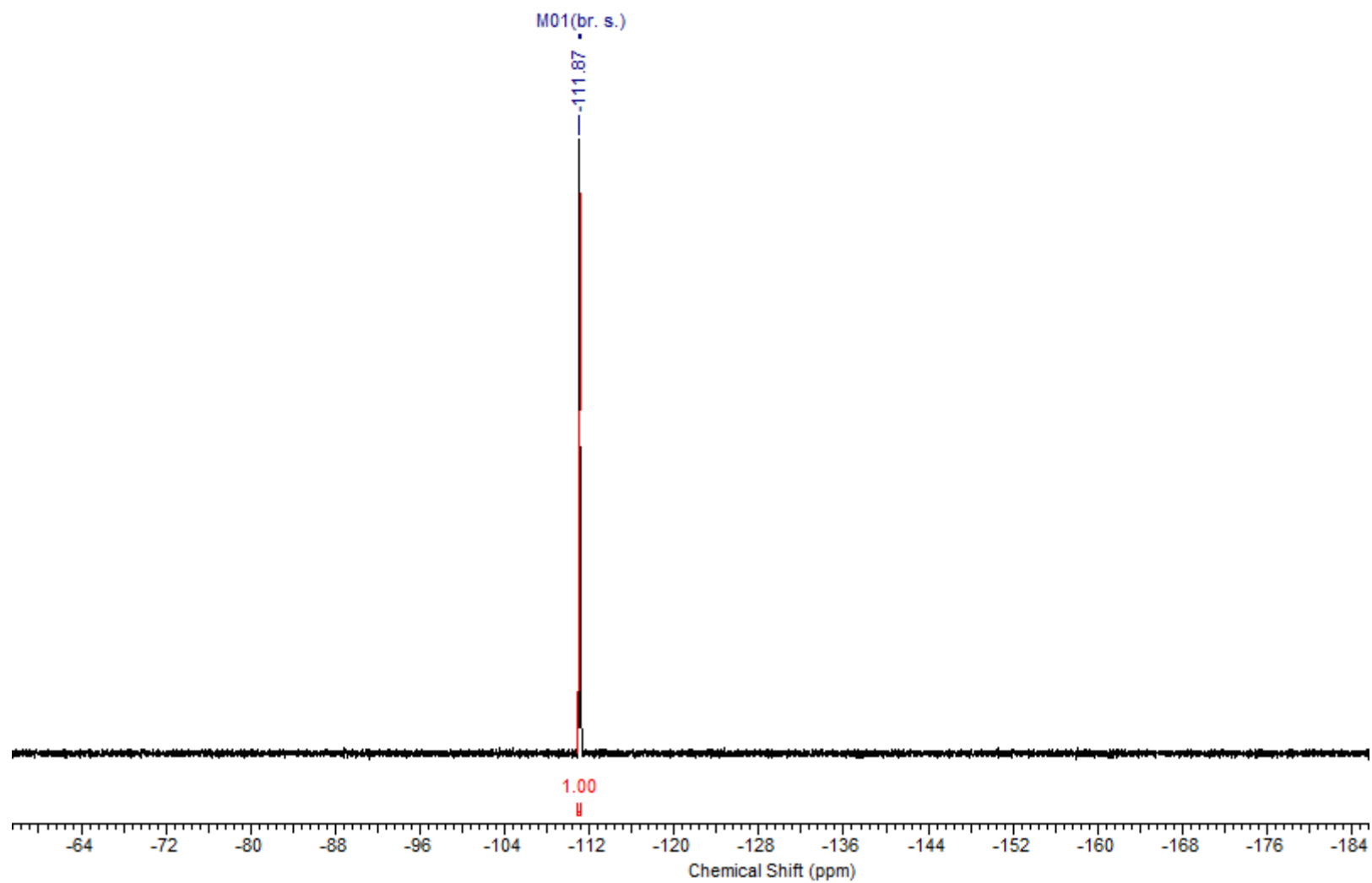
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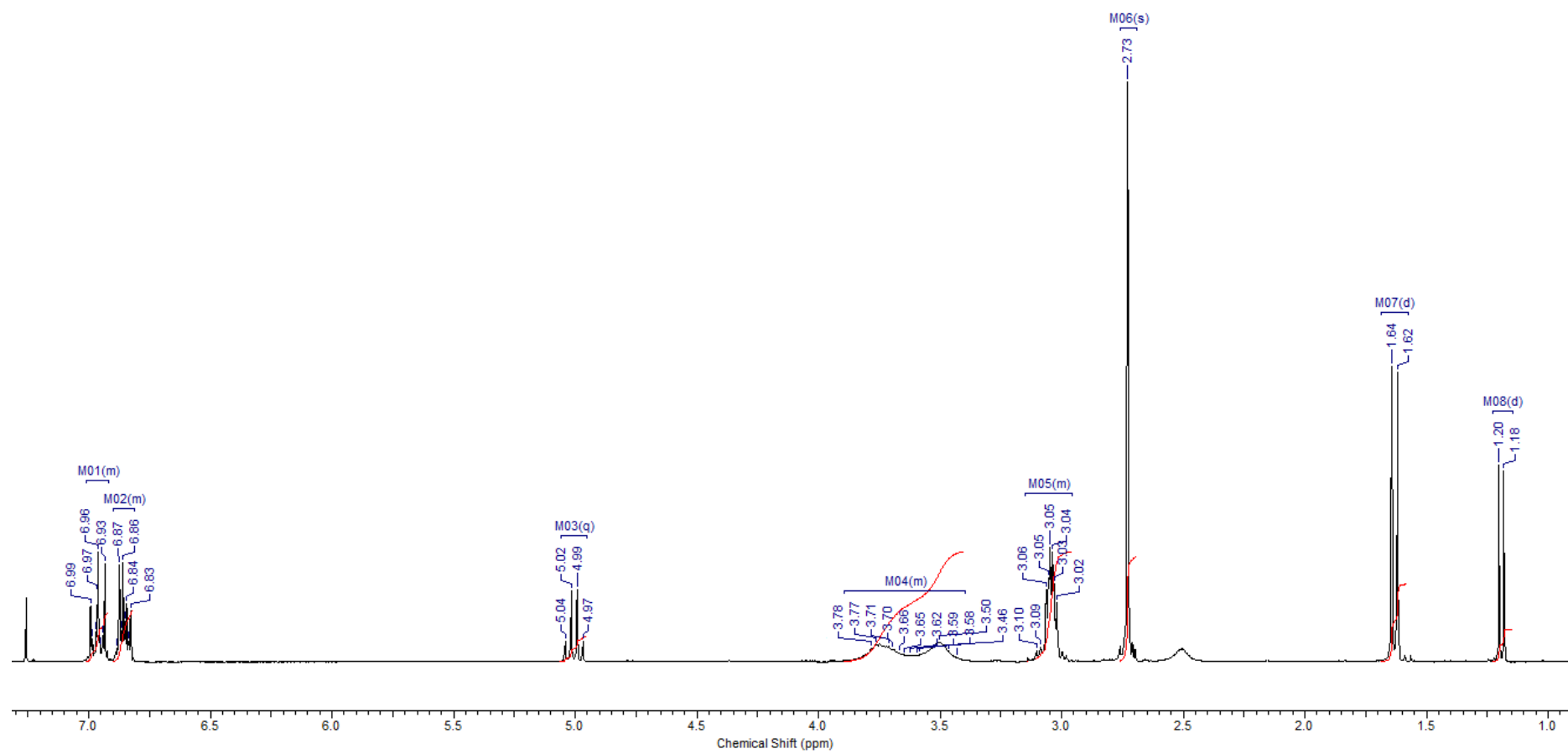
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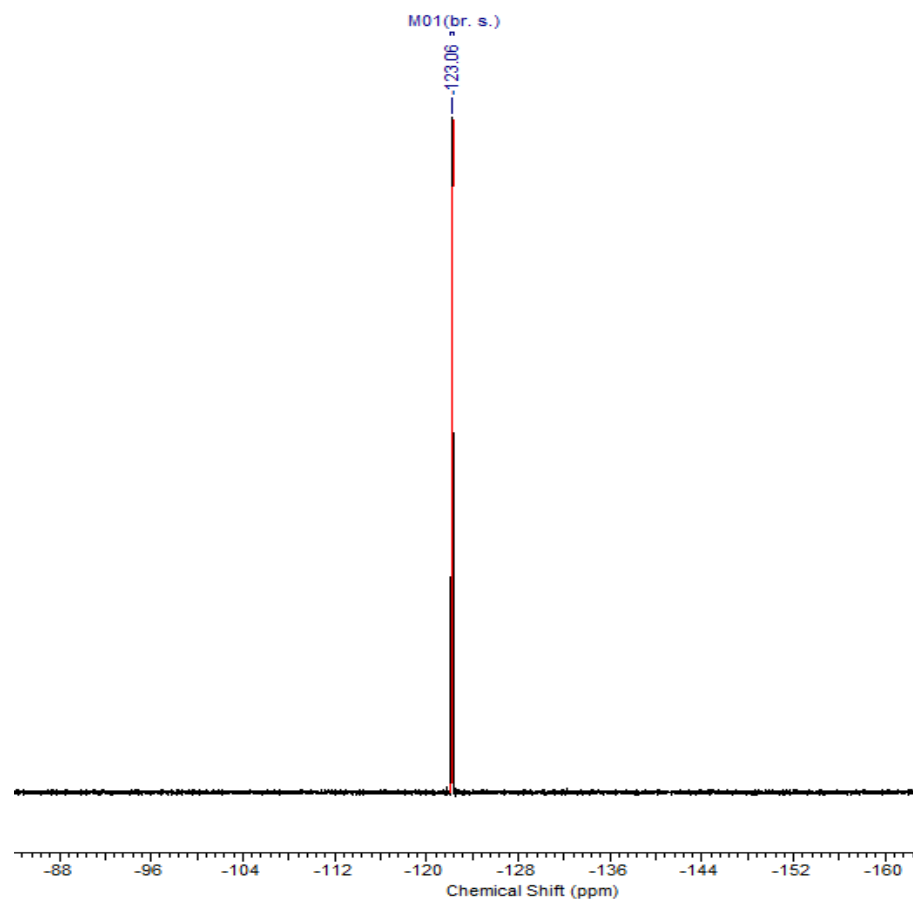
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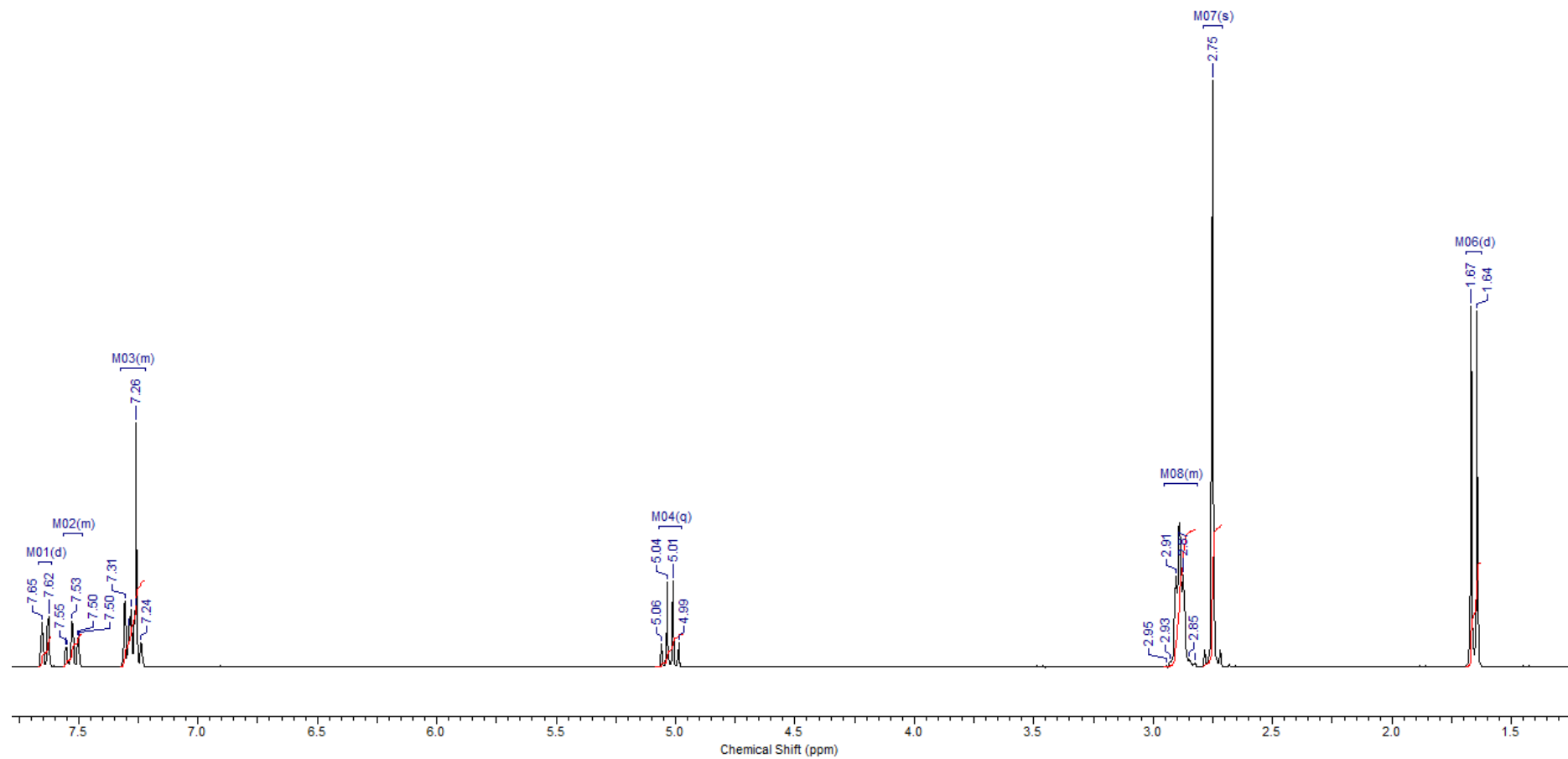
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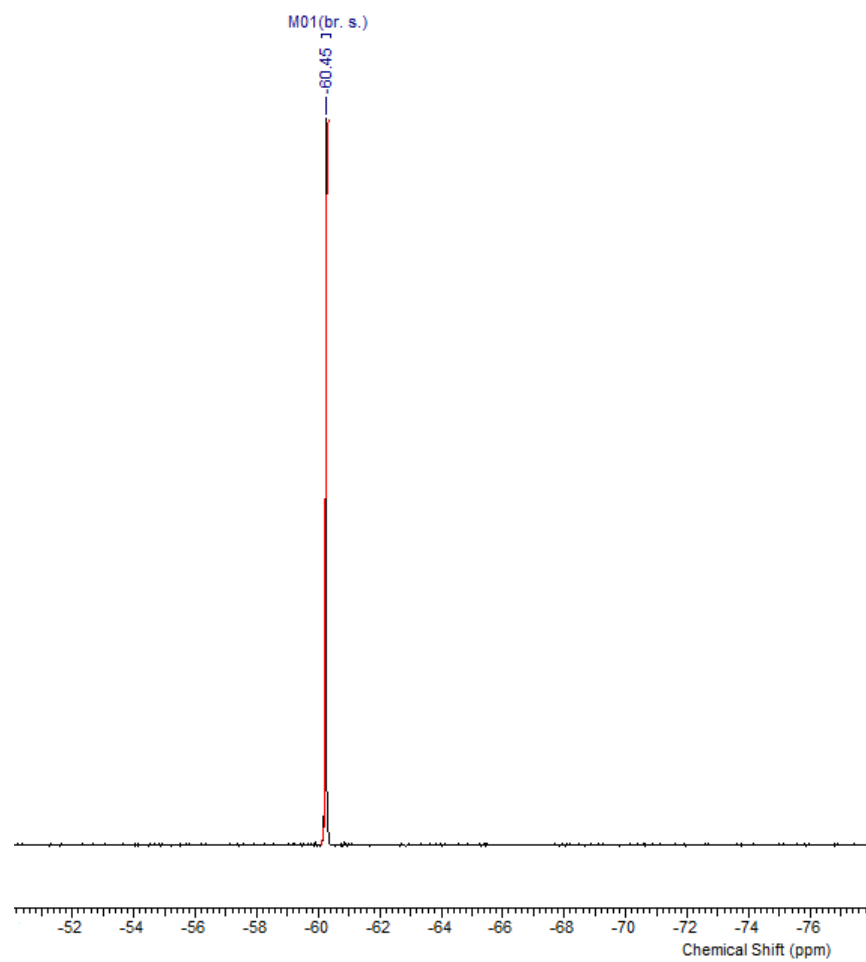
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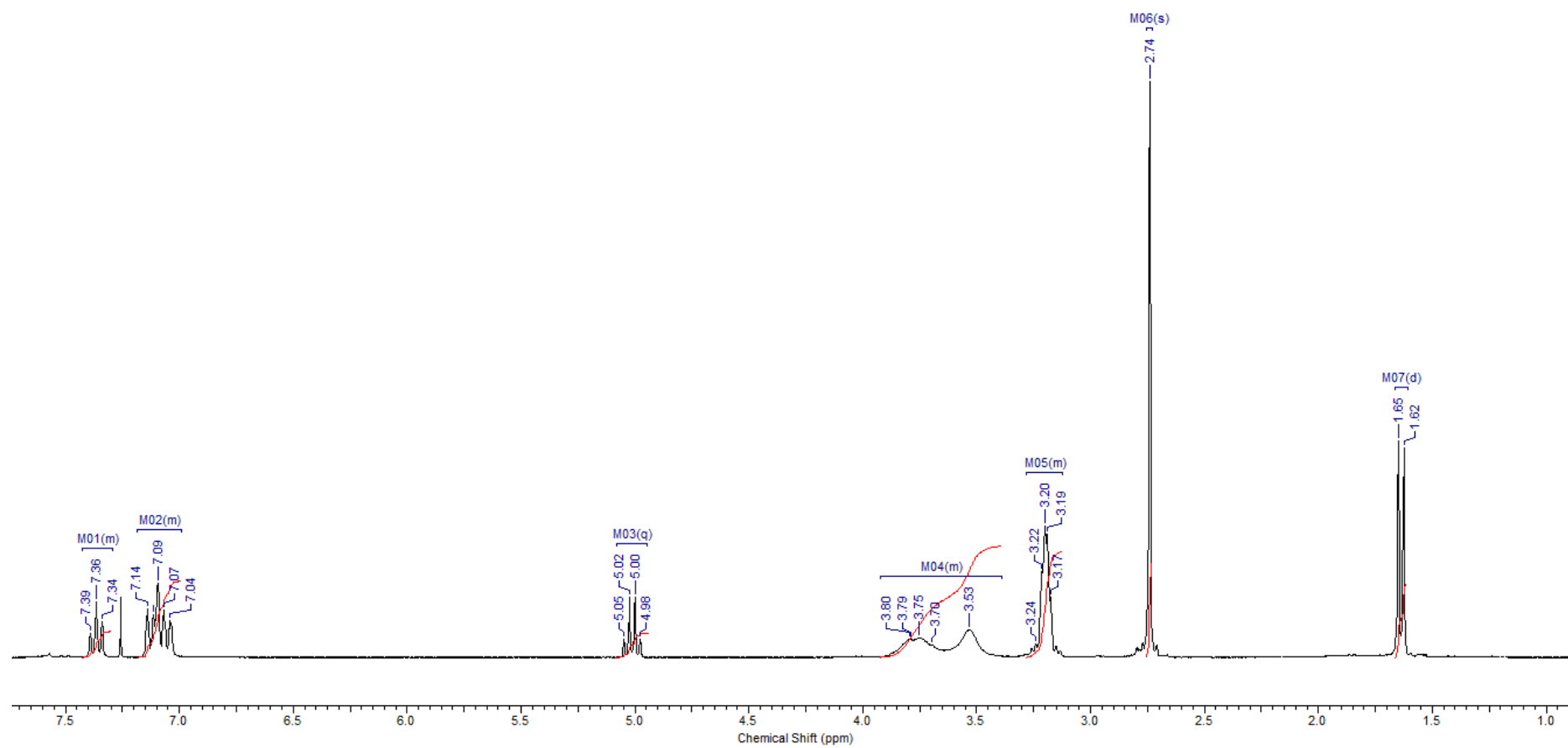
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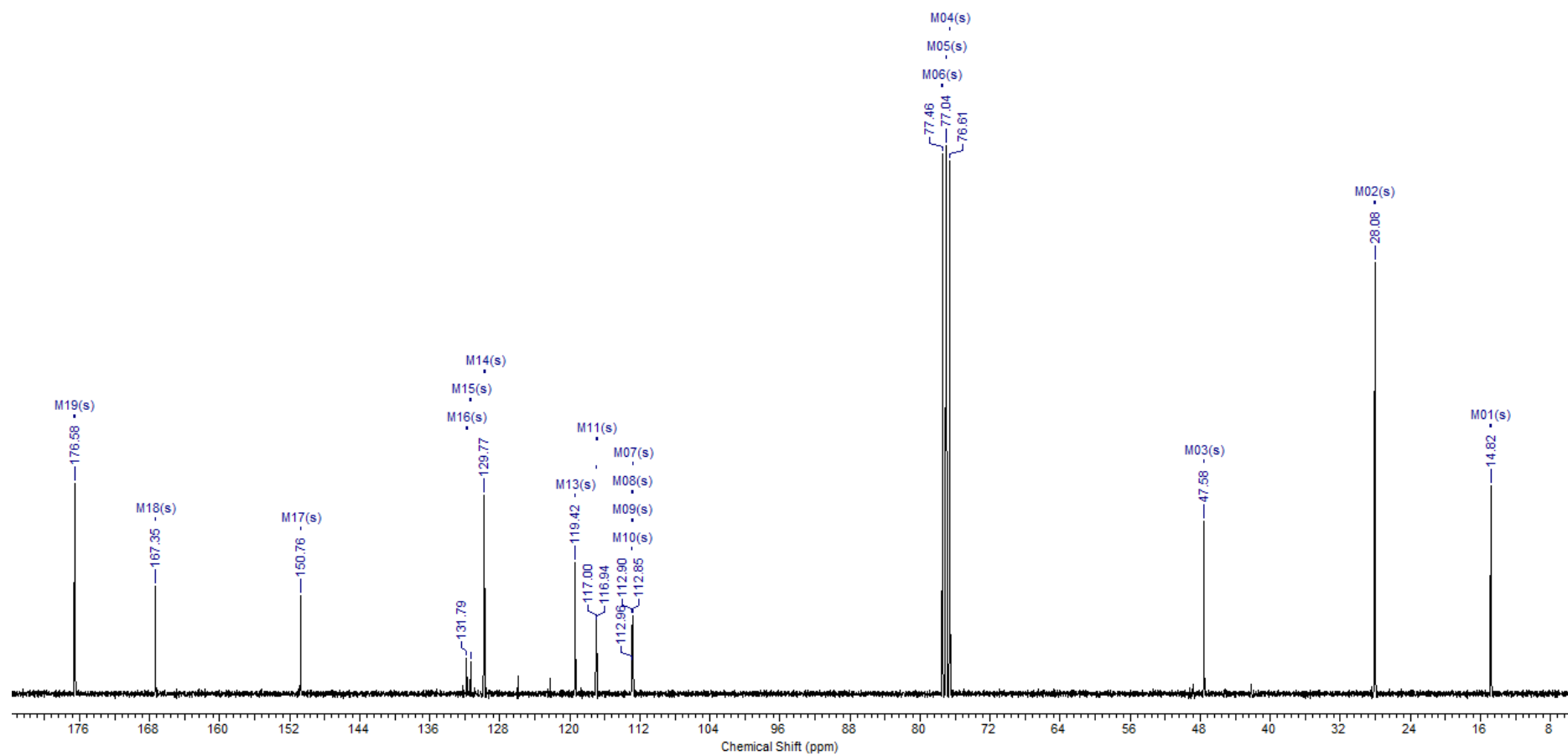
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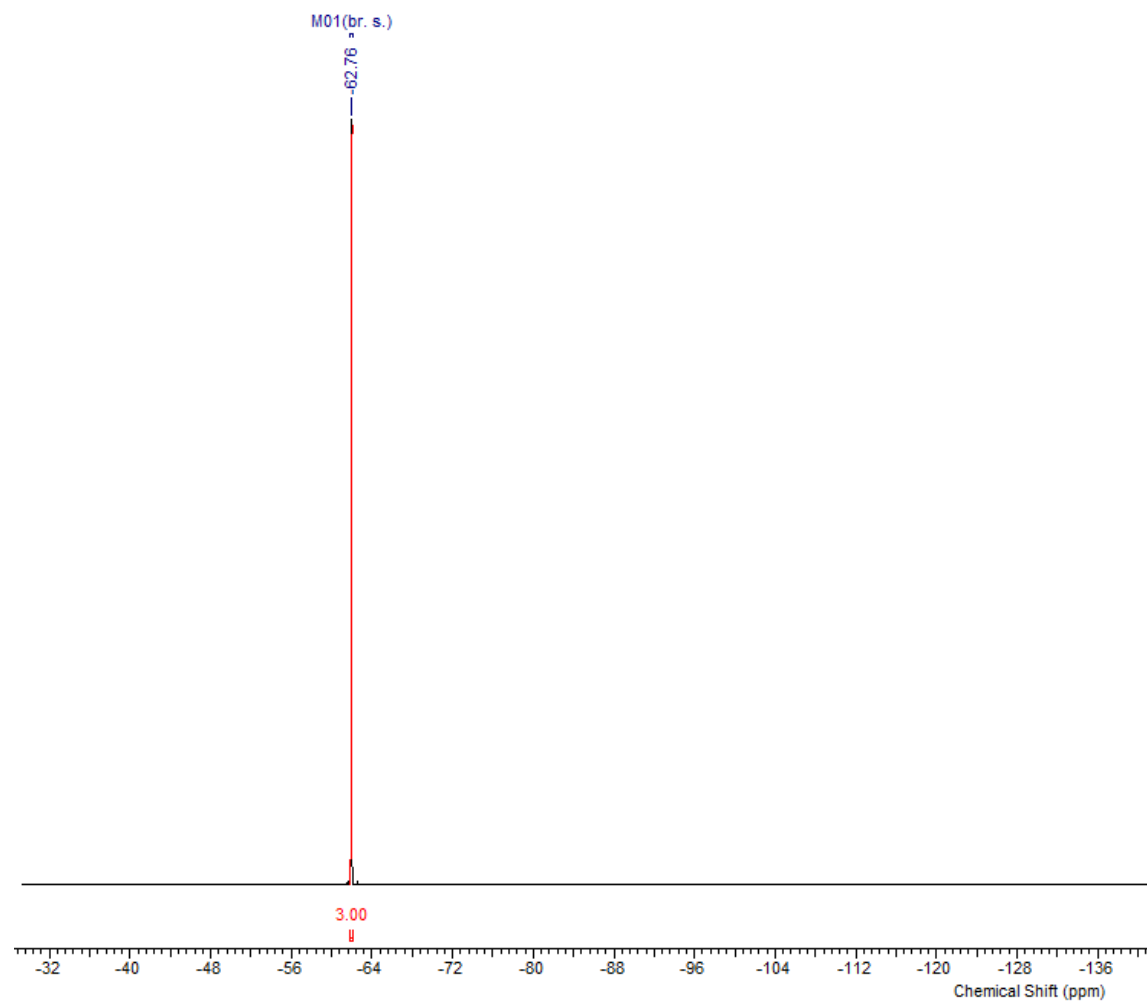
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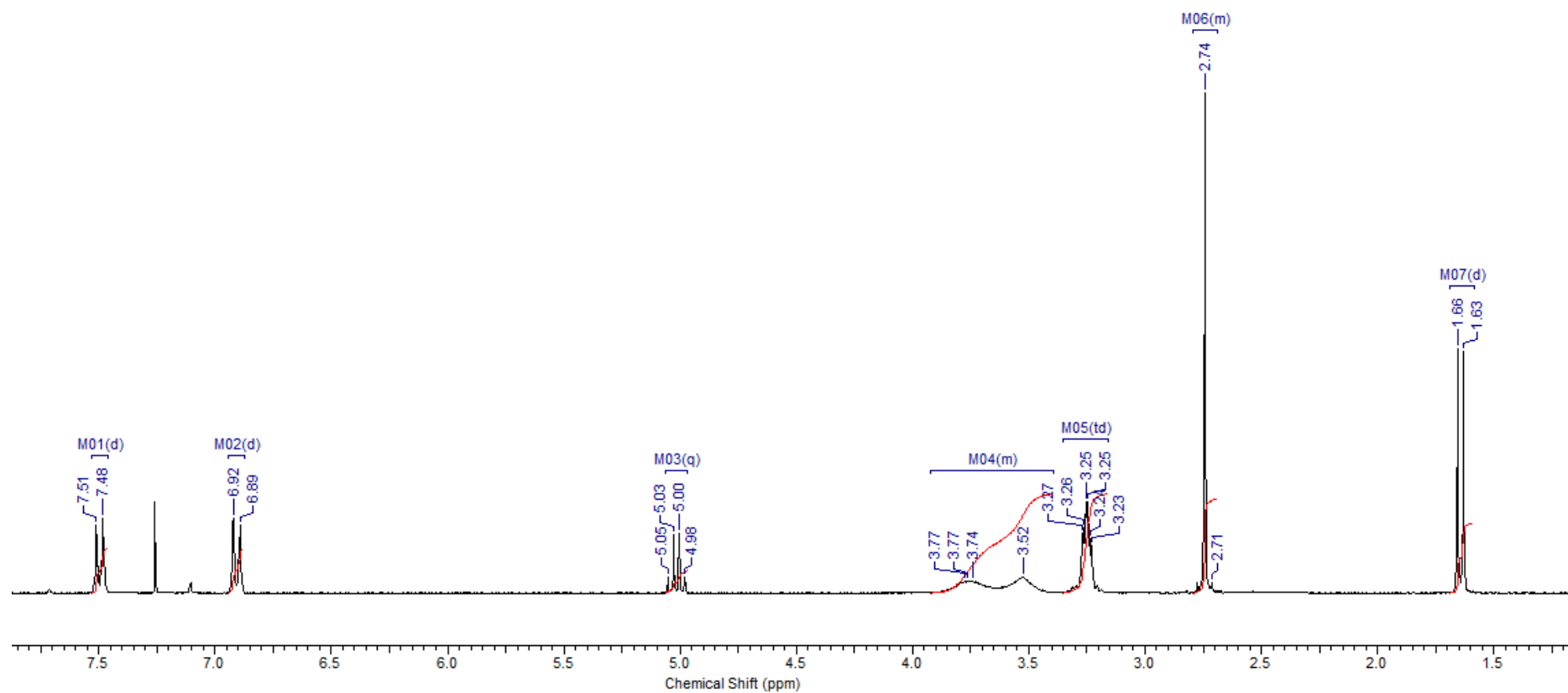
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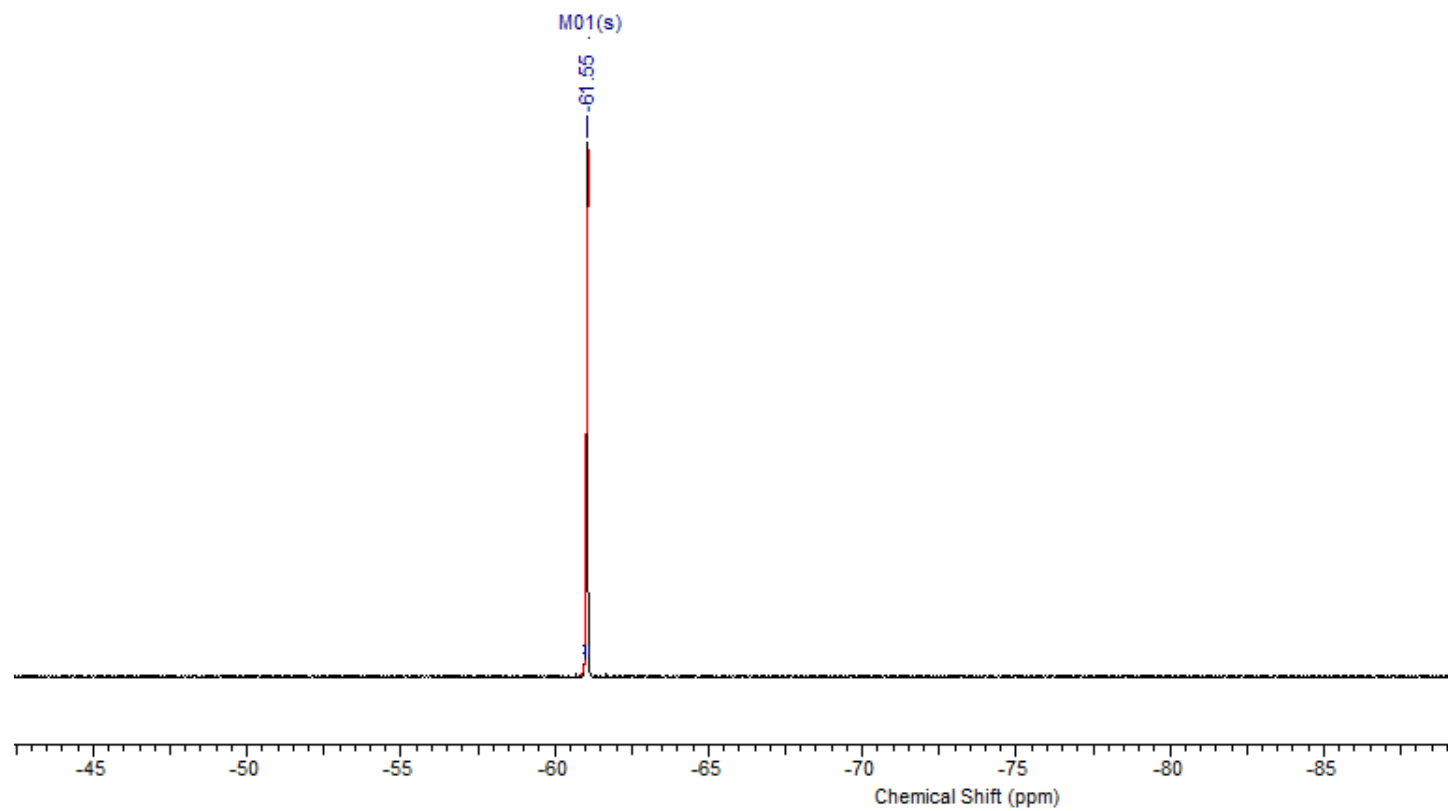
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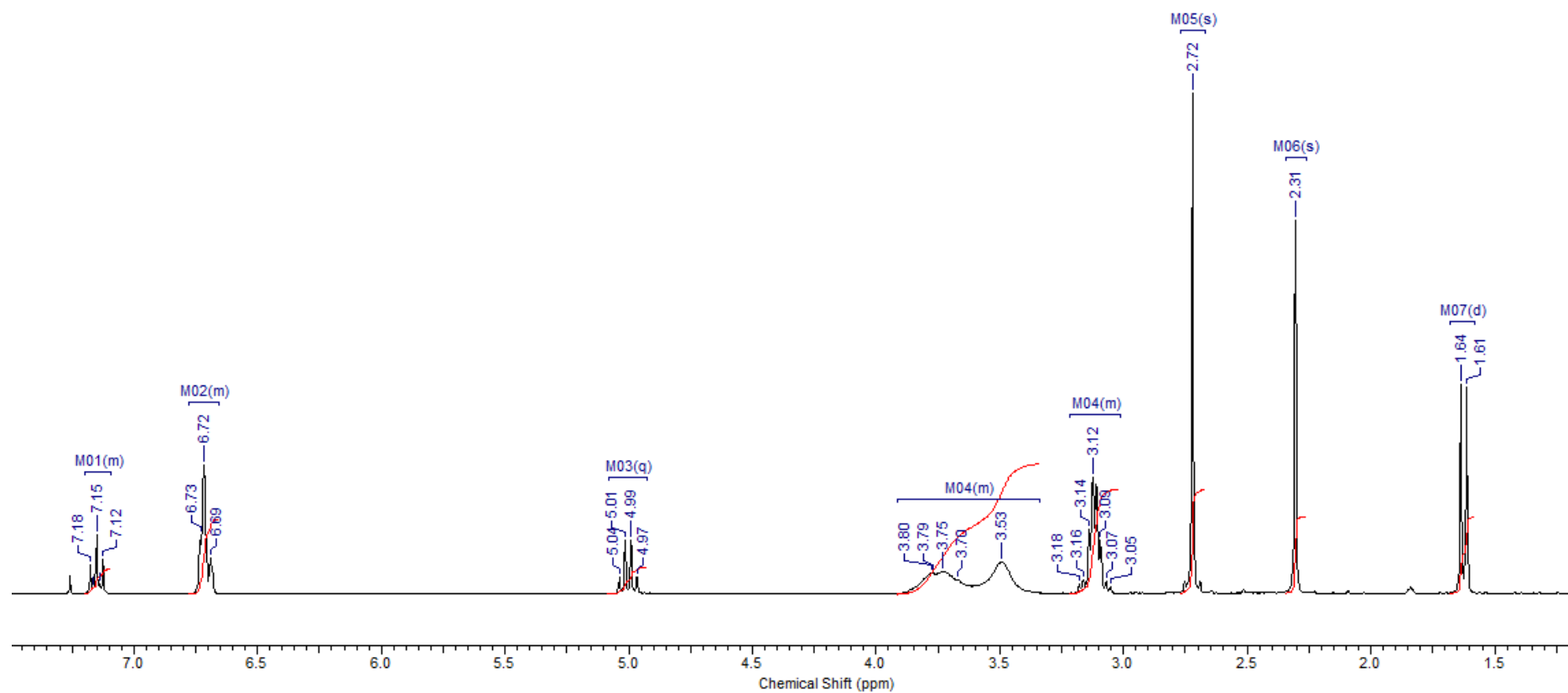
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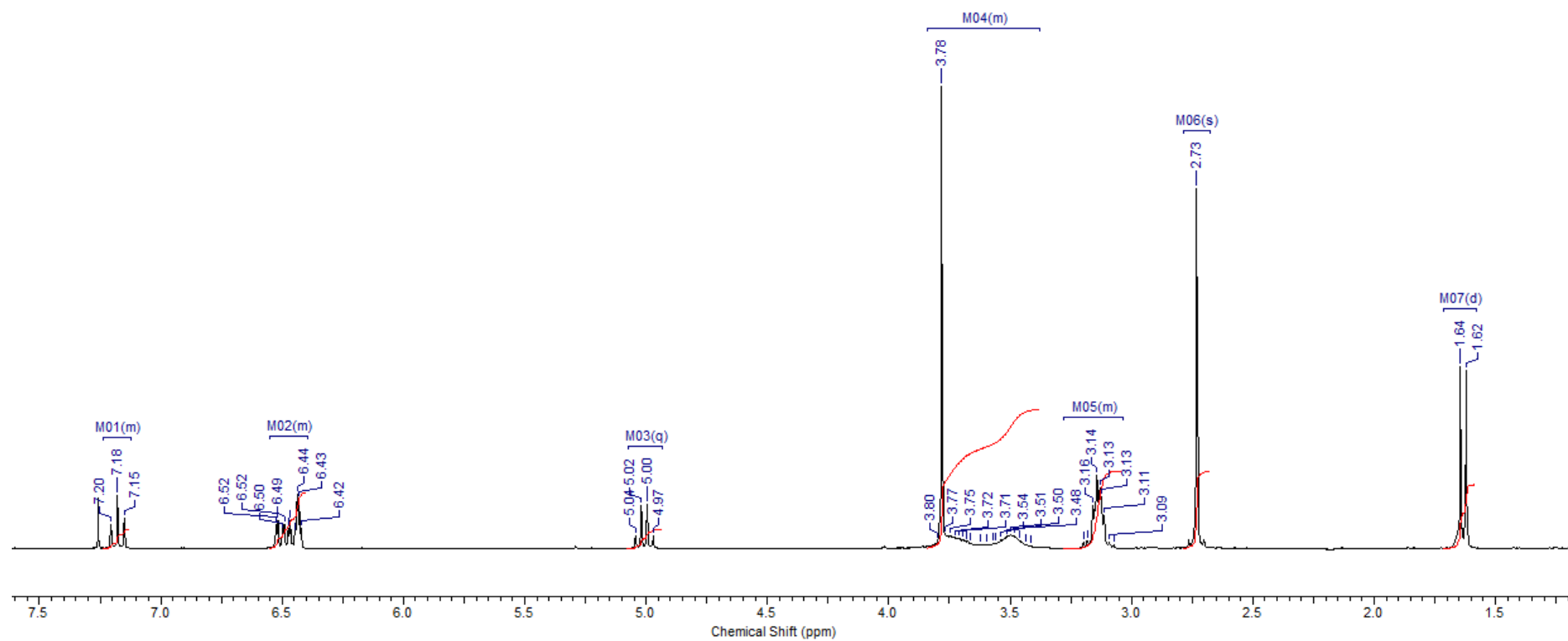
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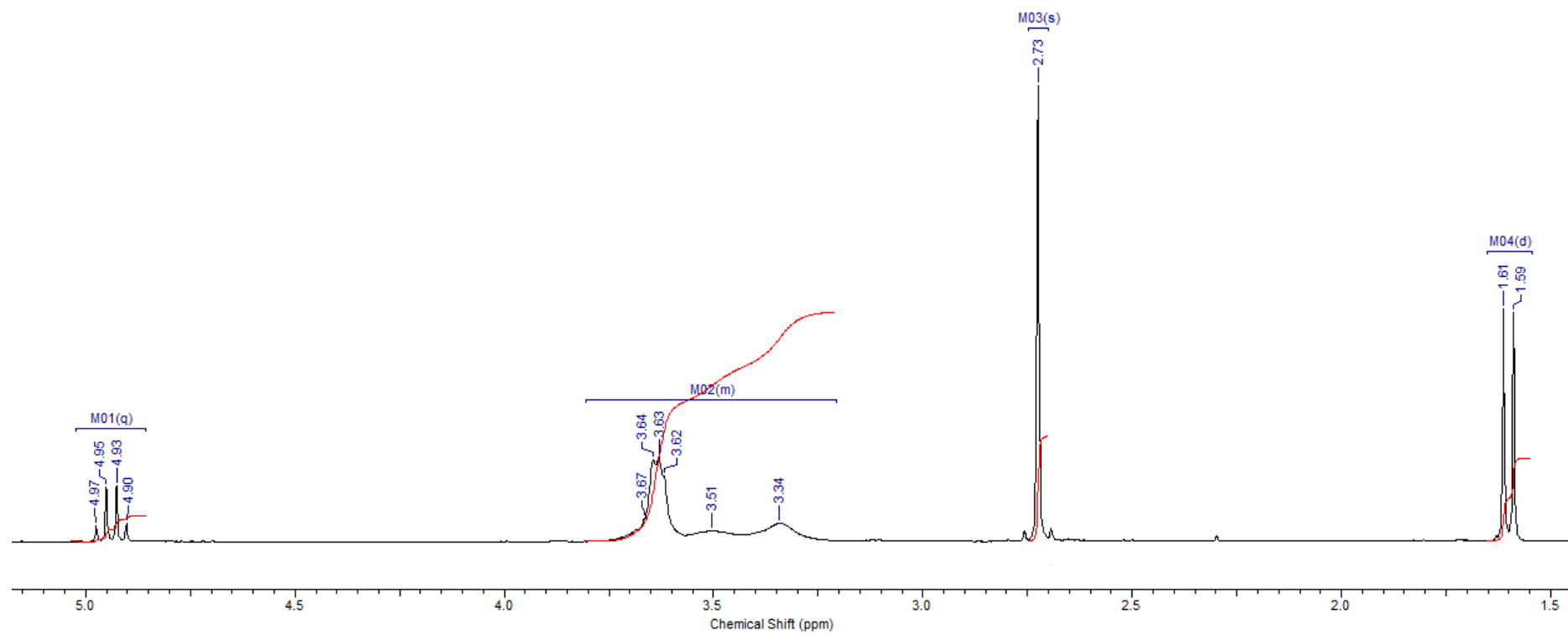
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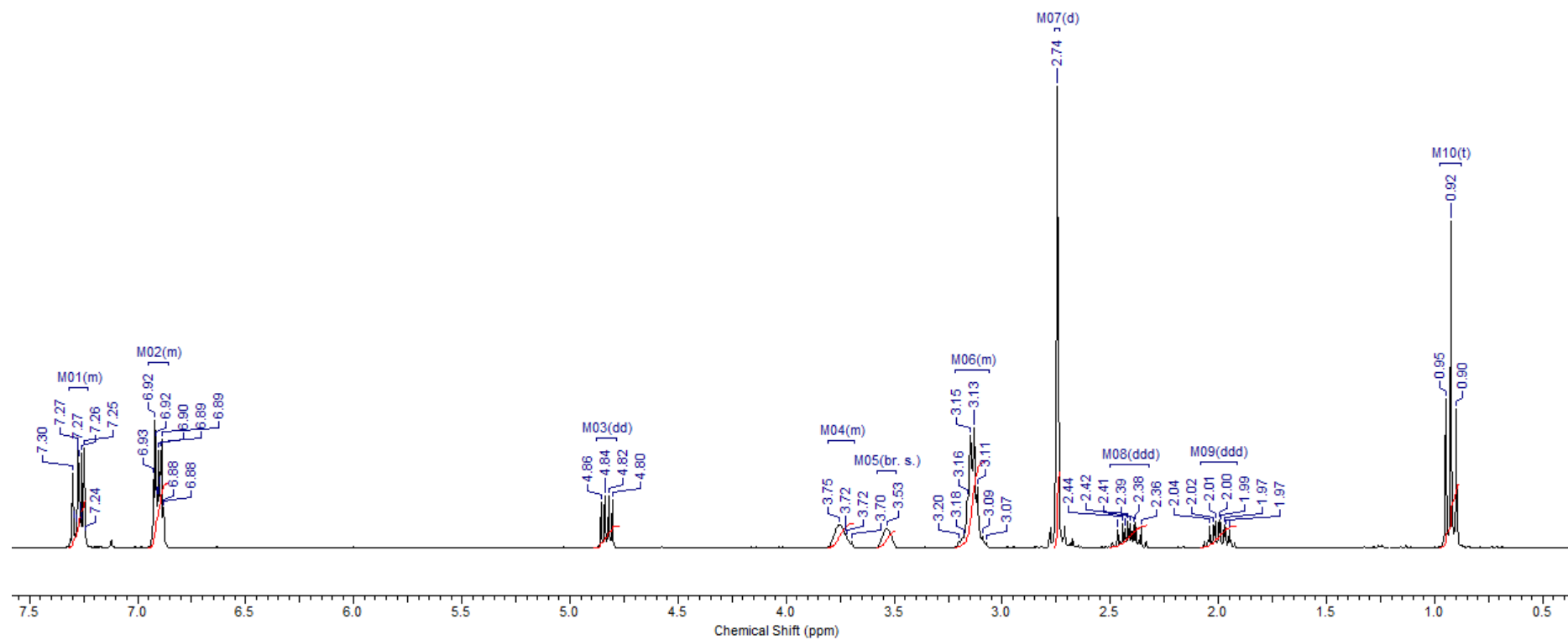
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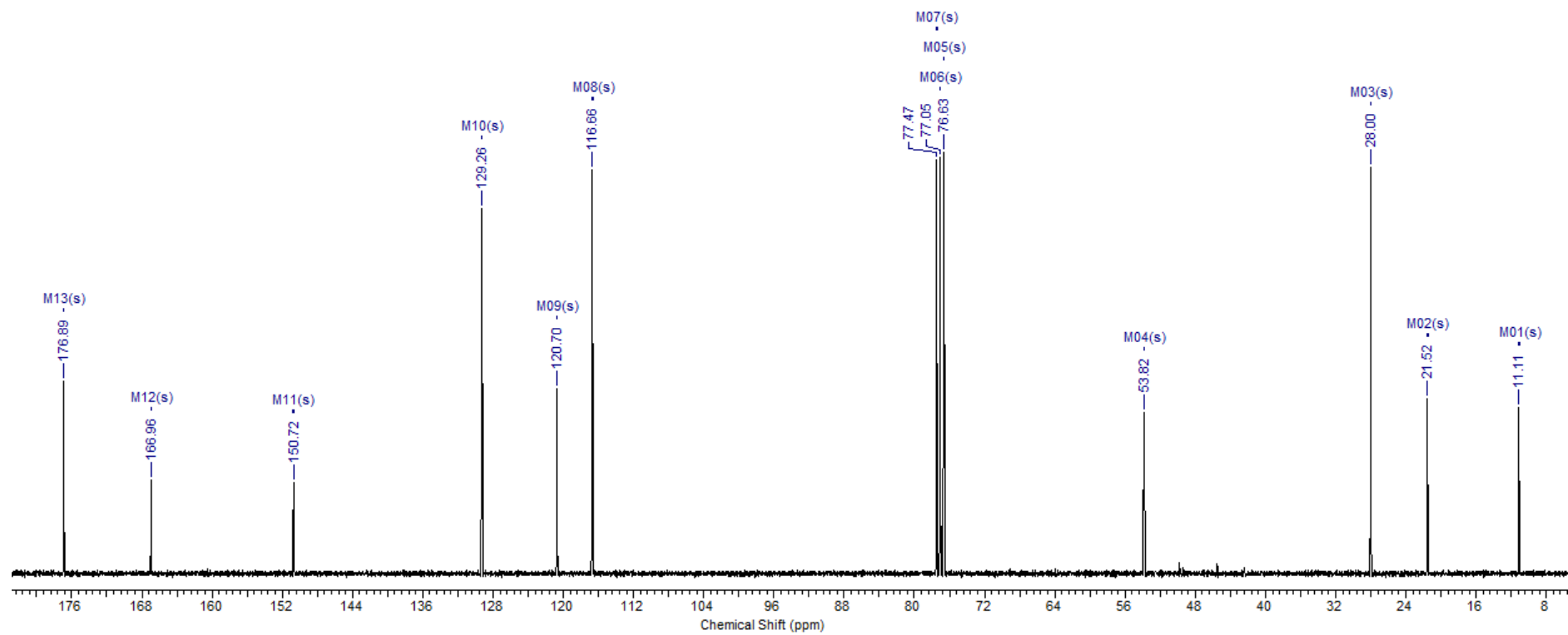
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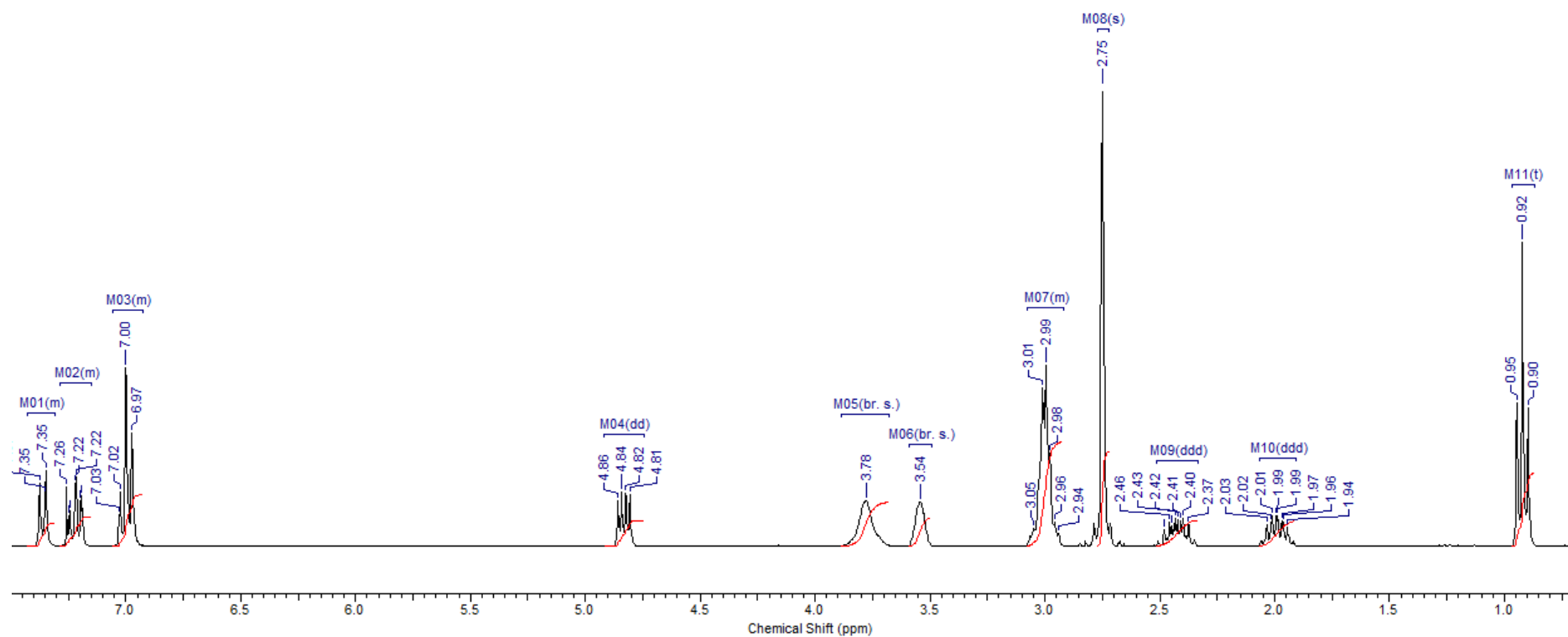
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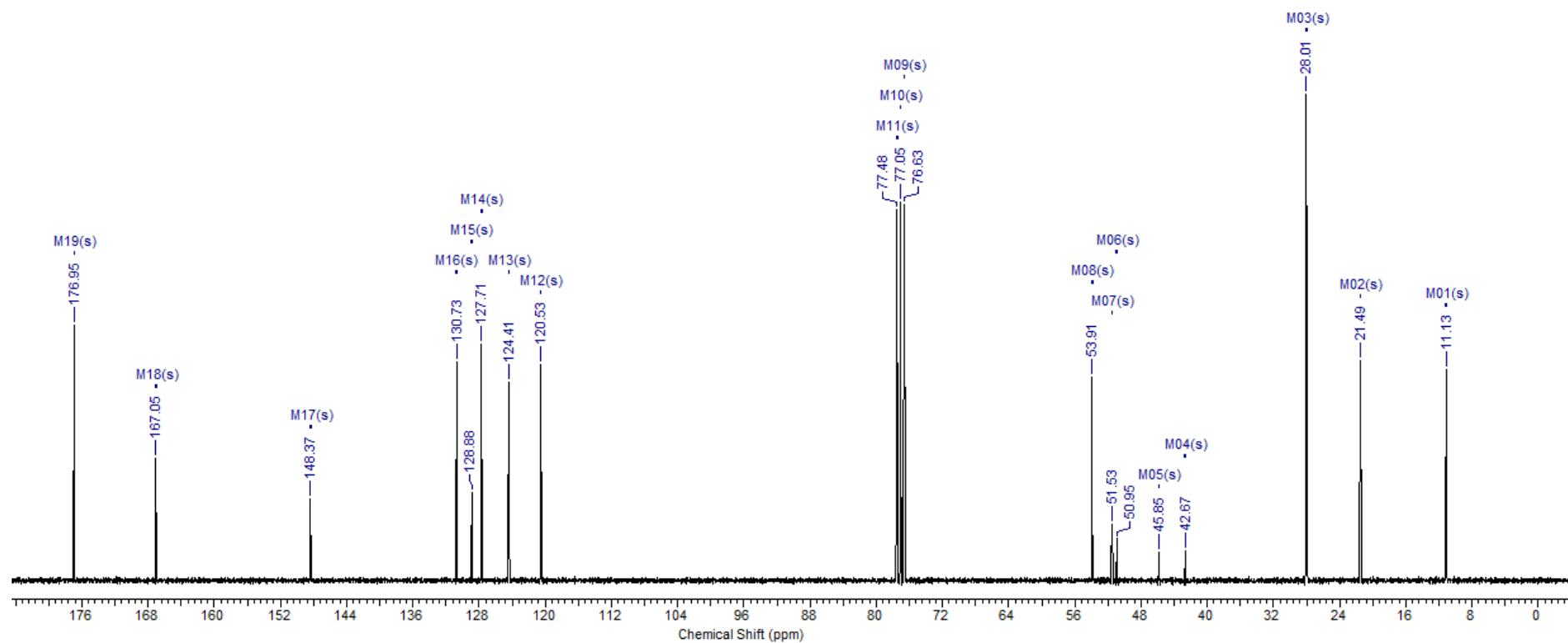
1-[1-Oxo-1-(4-phenylpiperazin-1-yl)butan-2-yl]pyrrolidine-2,5-dione (**16**) – ^{13}C NMR



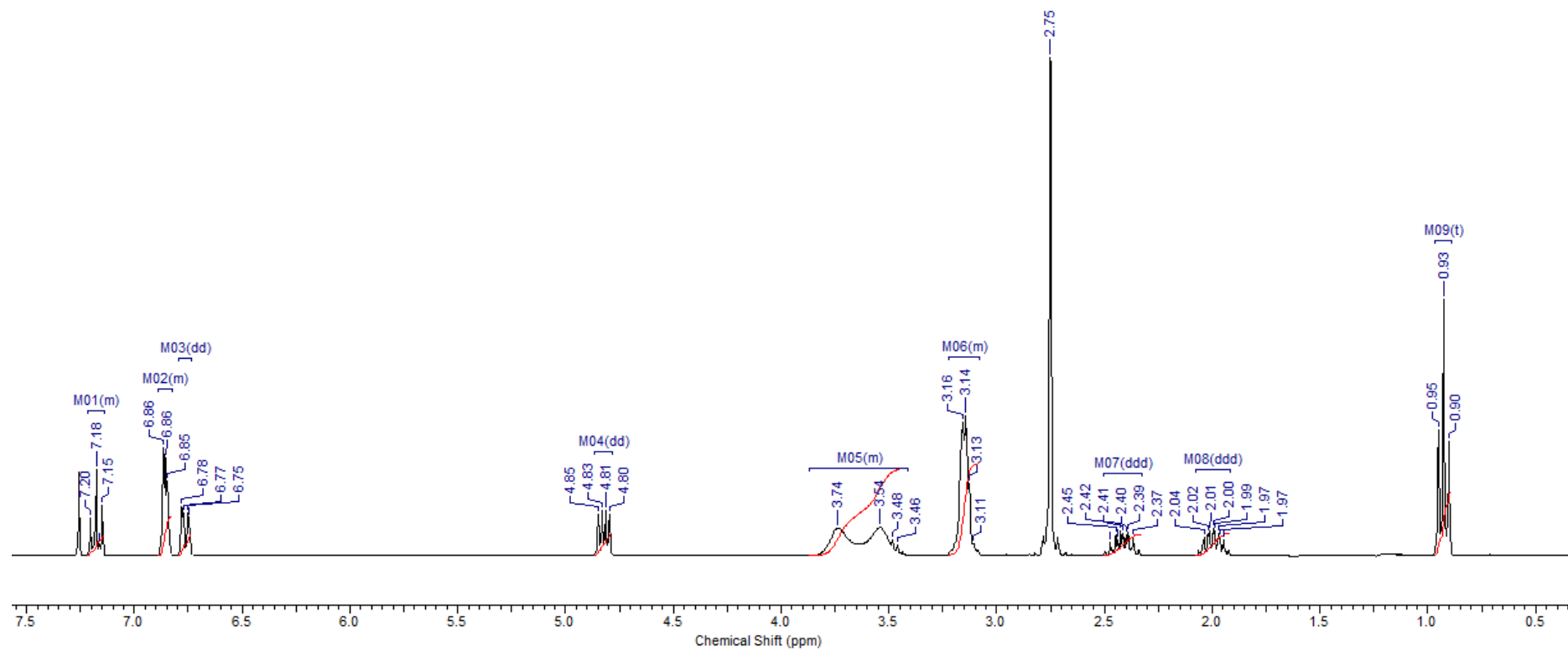
1-{1-[4-(2-Chlorophenyl)piperazin-1-yl]-1-oxobutan-2-yl}pyrrolidine-2,5-dione (**17**) - ^1H NMR



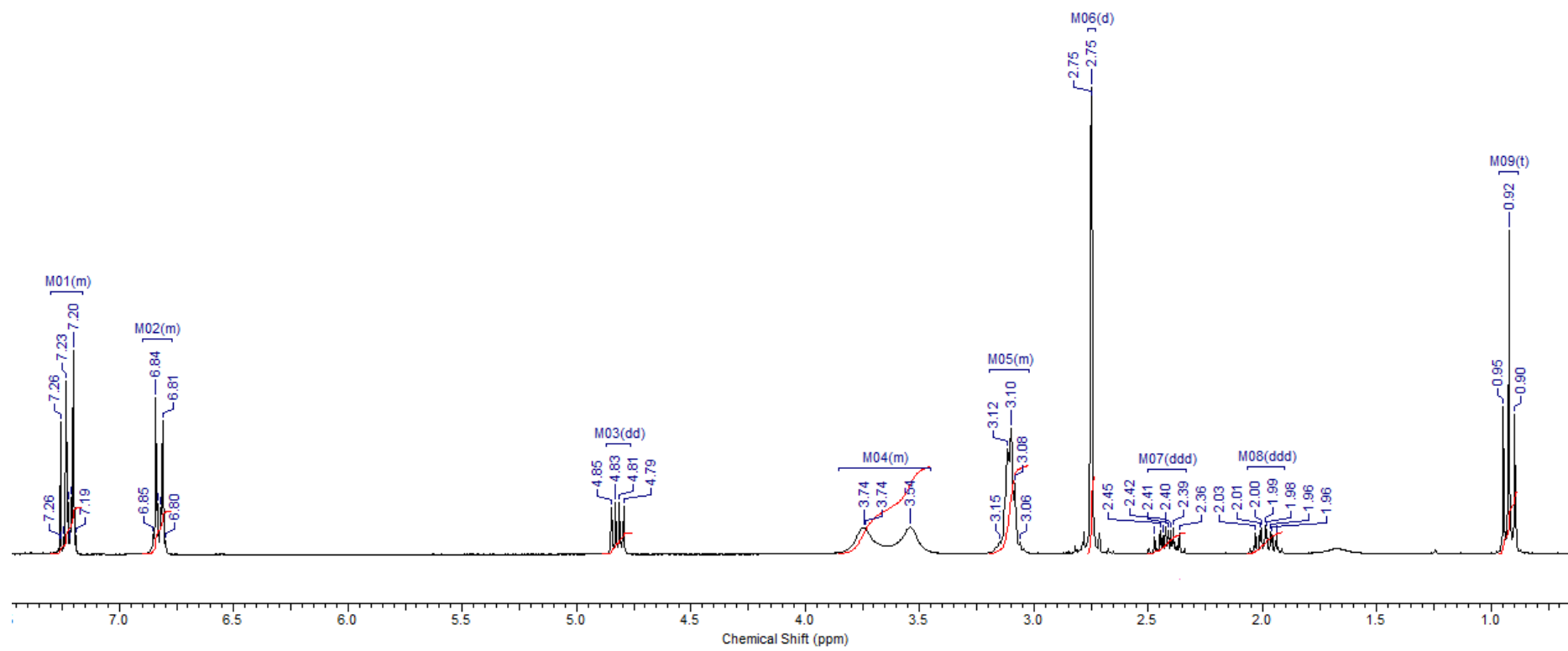
1-{1-[4-(2-Chlorophenyl)piperazin-1-yl]-1-oxobutan-2-yl}pyrrolidine-2,5-dione (**17**) – ^{13}C NMR



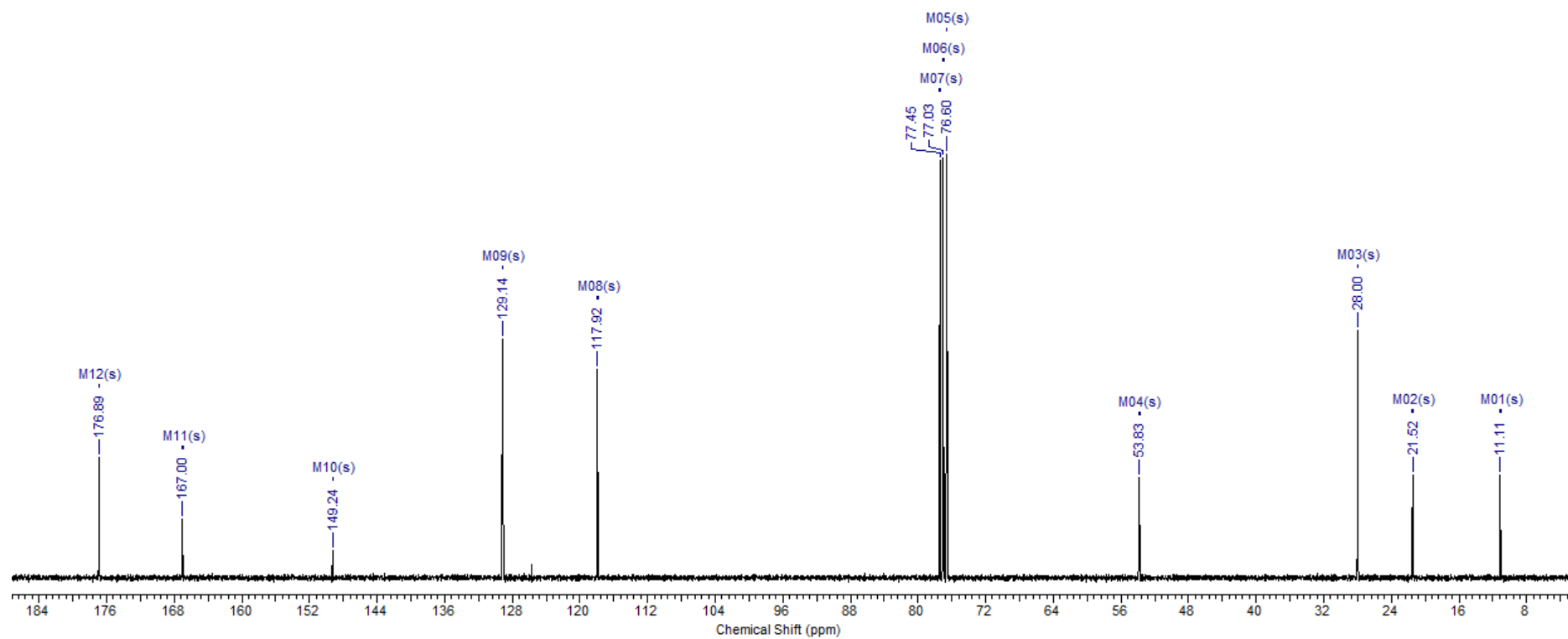
1-{1-[4-(3-Chlorophenyl)piperazin-1-yl]-1-oxobutan-2-yl}pyrrolidine-2,5-dione (**18**) – ^1H NMR



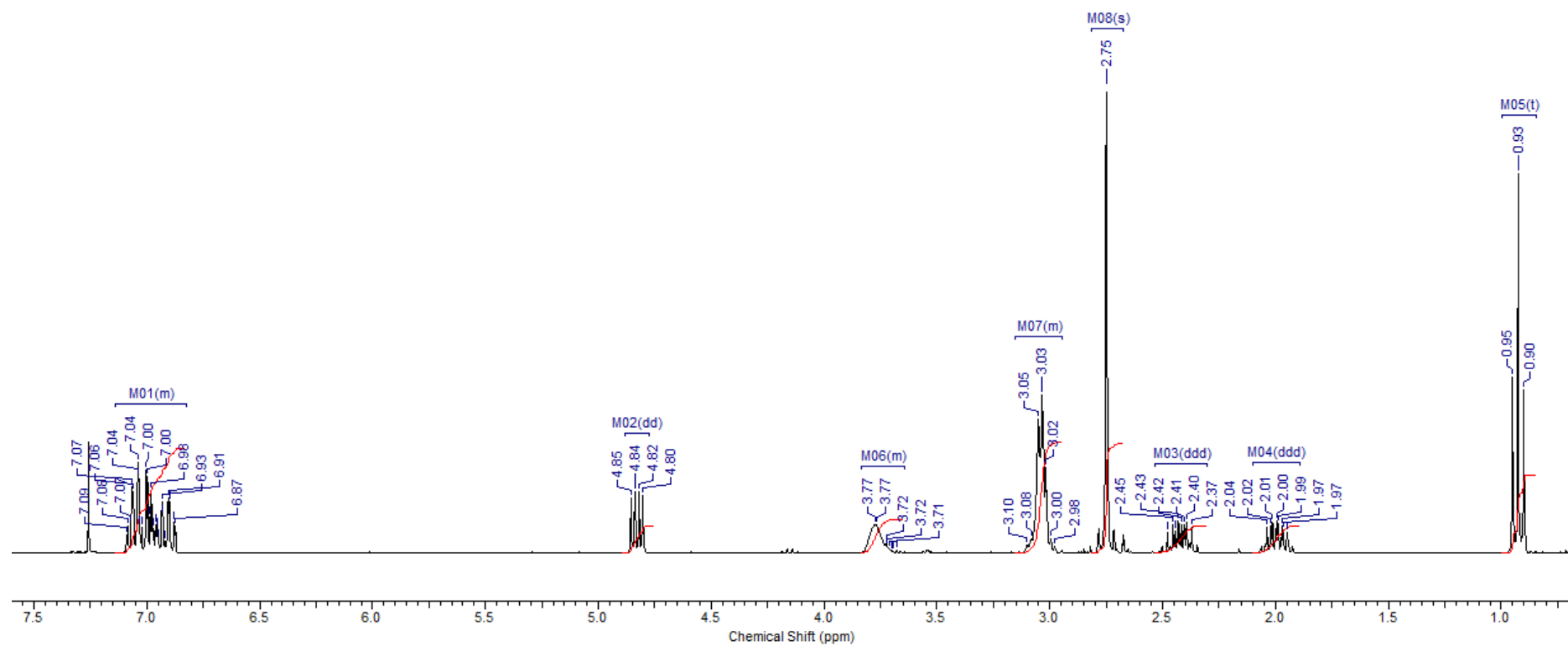
1-{1-[4-(4-Chlorophenyl)piperazin-1-yl]-1-oxobutan-2-yl}pyrrolidine-2,5-dione (**19**) – ^1H NMR



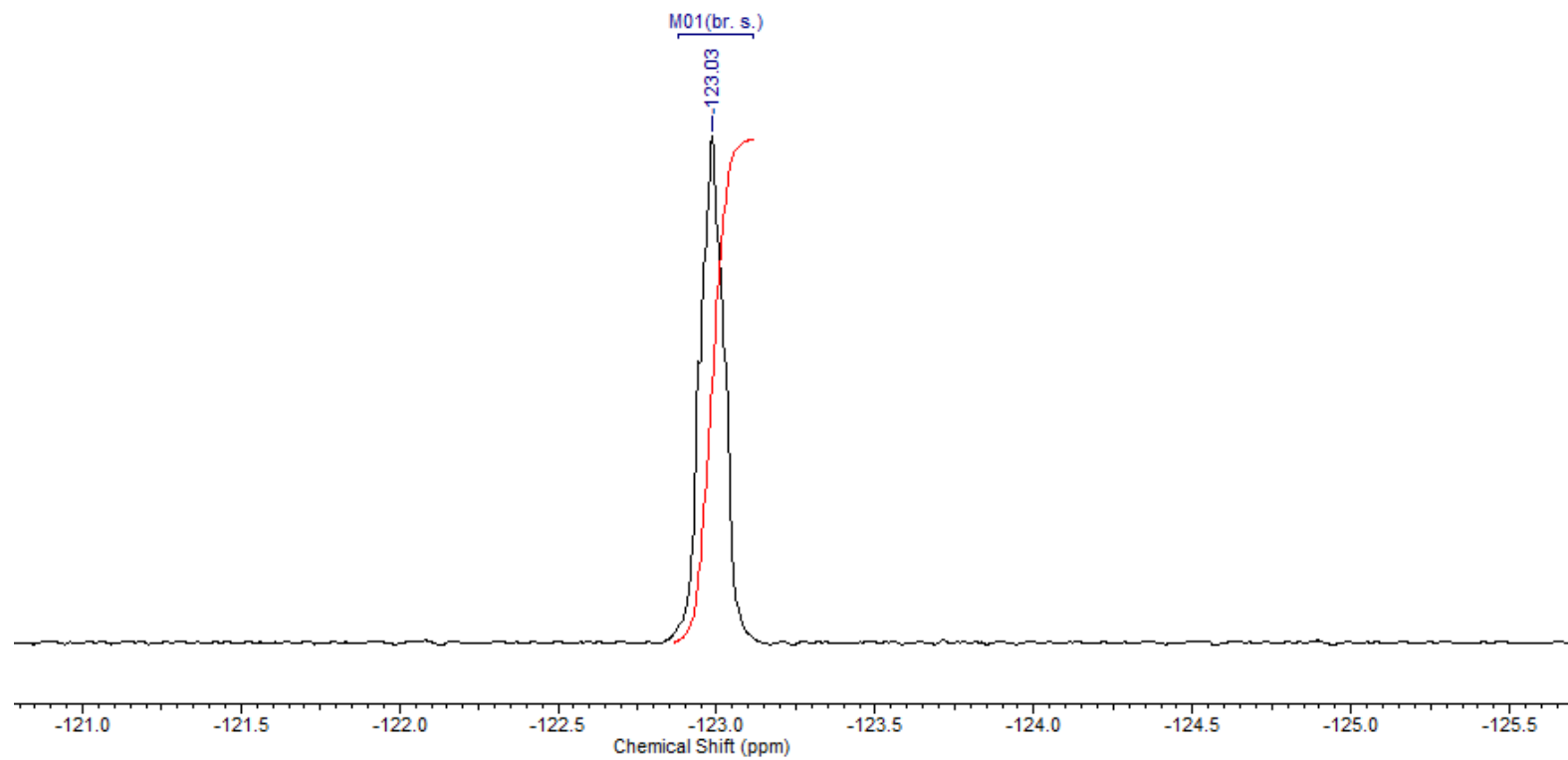
1-{1-[4-(4-Chlorophenyl)piperazin-1-yl]-1-oxobutan-2-yl}pyrrolidine-2,5-dione (**19**) – ^{13}C NMR



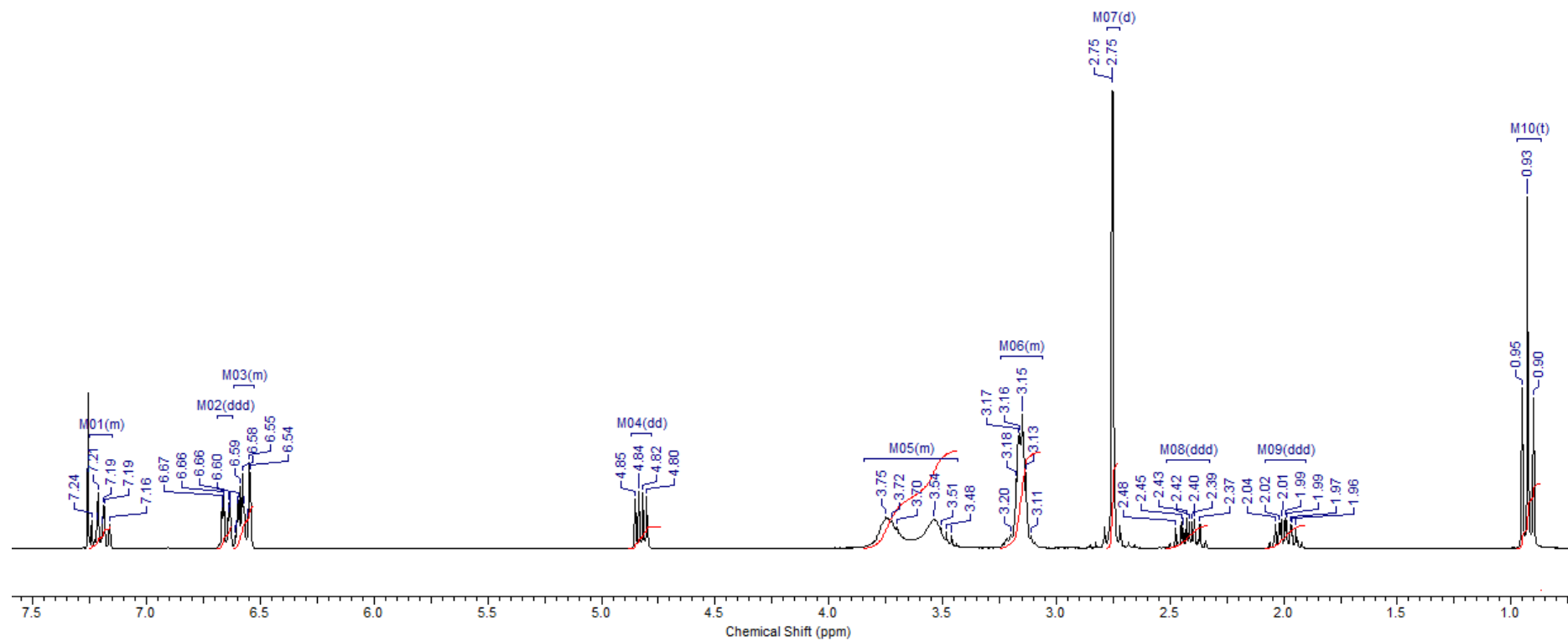
1-{1-[4-(2-Fluorophenyl)piperazin-1-yl]-1-oxobutan-2-yl}pyrrolidine-2,5-dione (**20**) – ^1H NMR



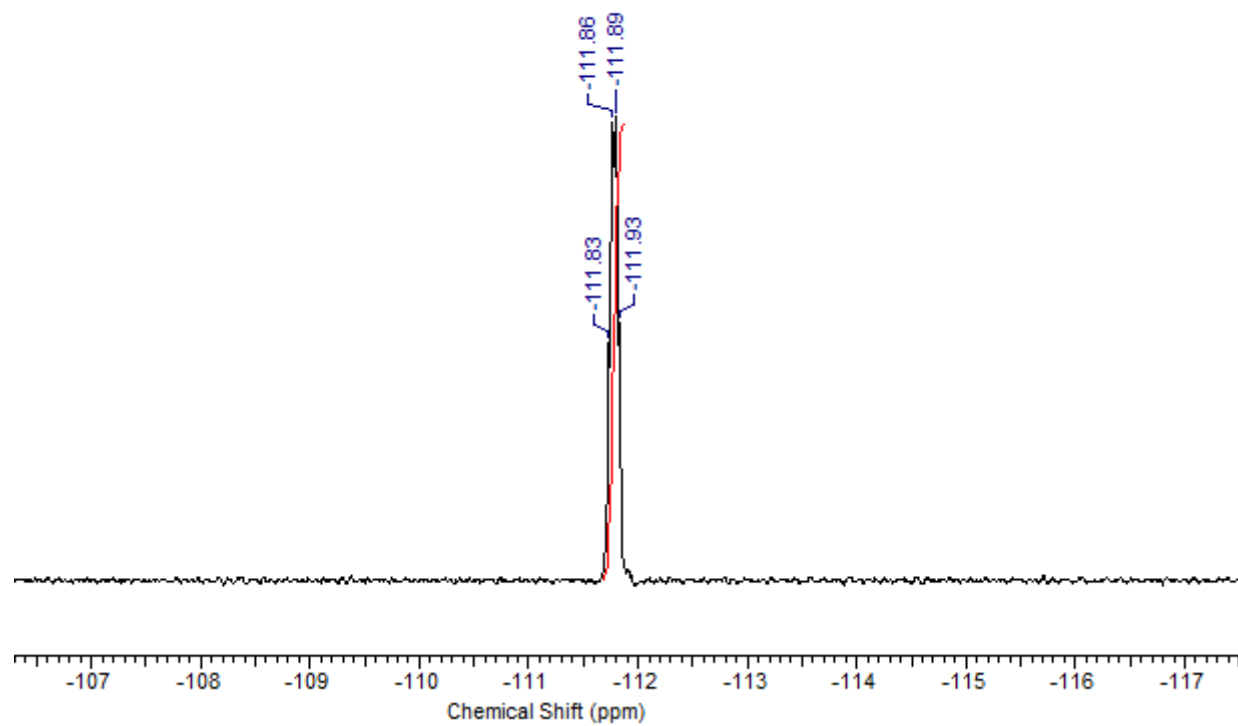
1-{1-[4-(2-Fluorophenyl)piperazin-1-yl]-1-oxobutan-2-yl}pyrrolidine-2,5-dione (**20**) – ^{19}F NMR



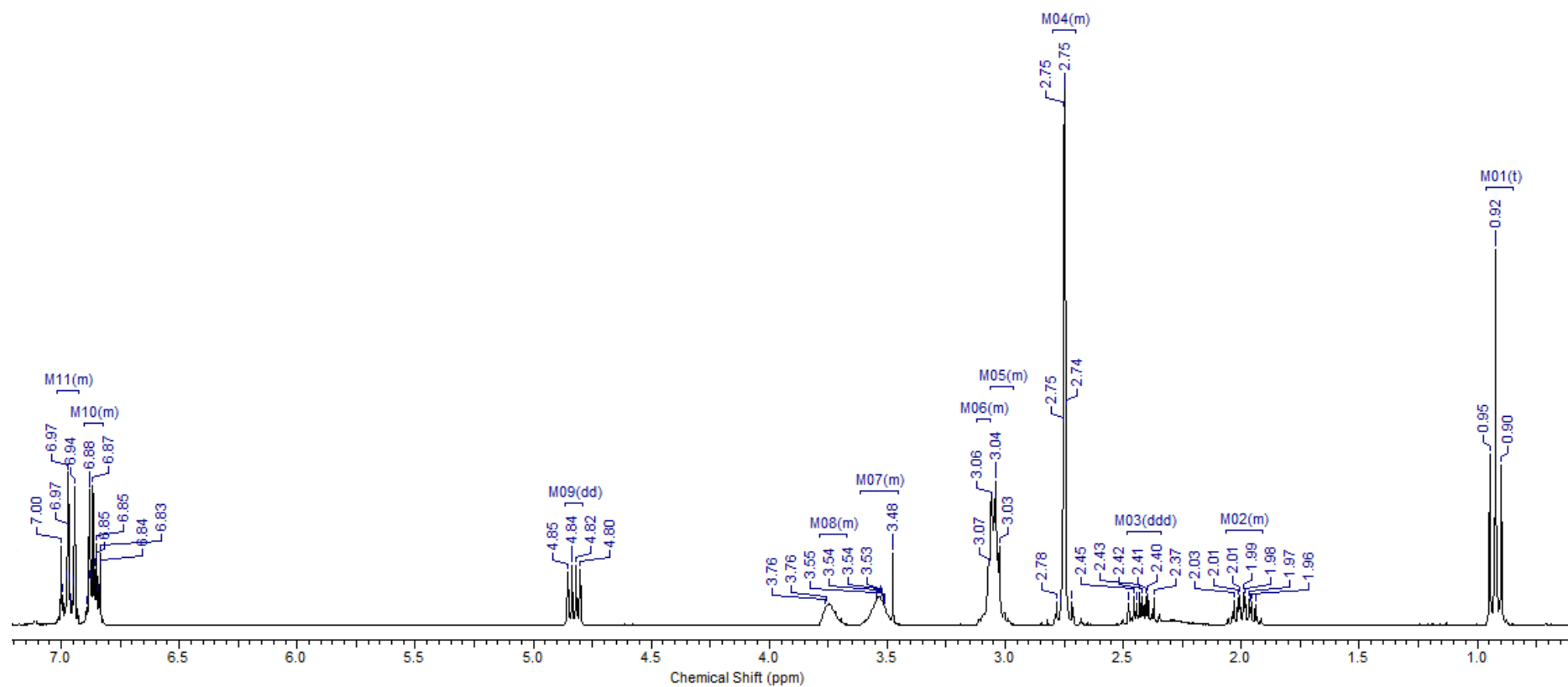
1-{1-[4-(3-Fluorophenyl)piperazin-1-yl]-1-oxobutan-2-yl}pyrrolidine-2,5-dione (**21**) – ^1H NMR



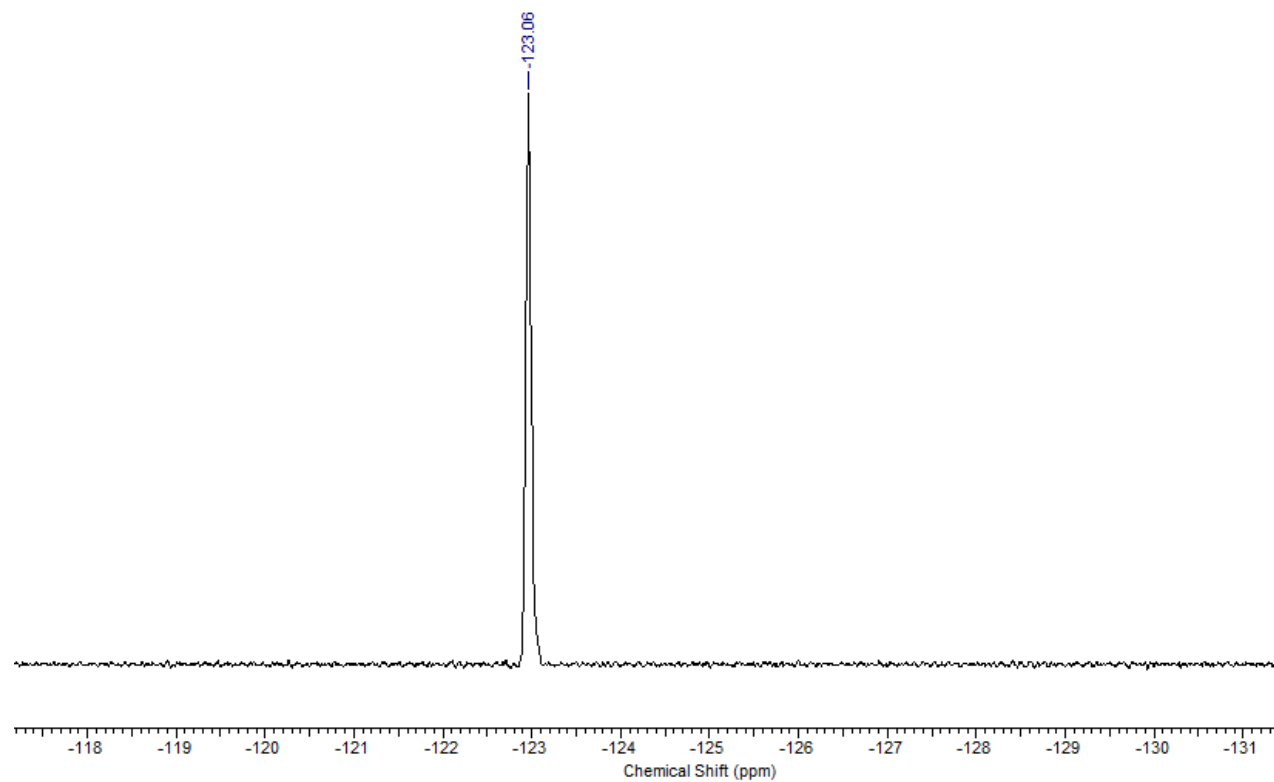
1-{1-[4-(3-Fluorophenyl)piperazin-1-yl]-1-oxobutan-2-yl}pyrrolidine-2,5-dione (**21**) – ^{19}F NMR



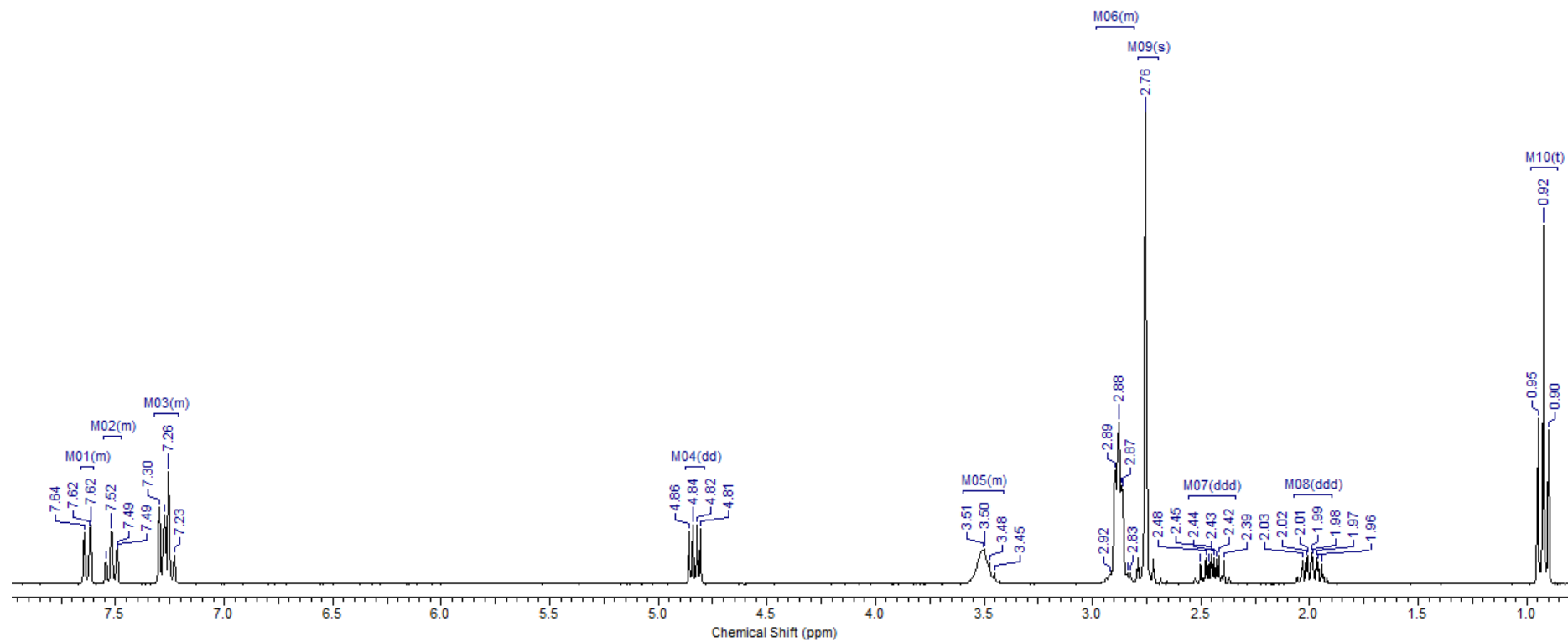
1-{1-[4-(4-Fluorophenyl)piperazin-1-yl]-1-oxopropan-2-yl}pyrrolidine-2,5-dione (**22**) – ^1H NMR



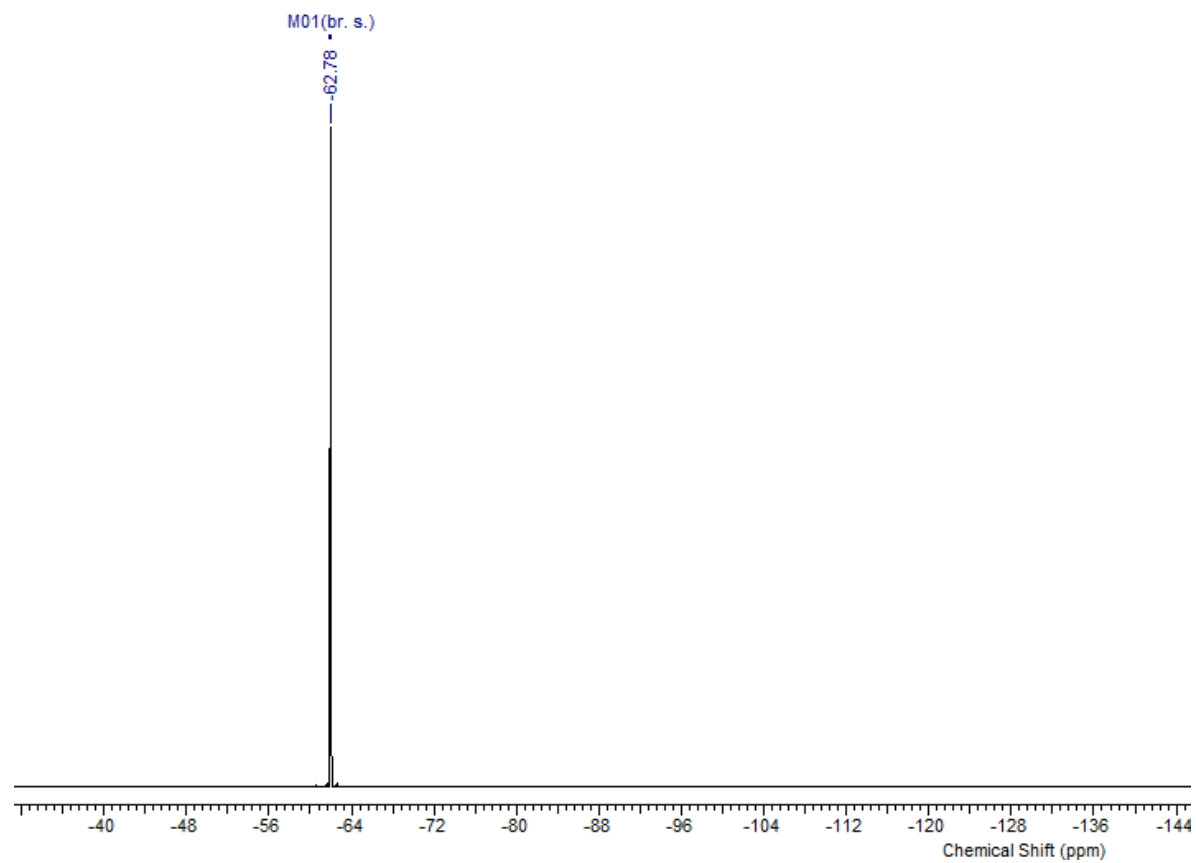
1-{1-[4-(4-Fluorophenyl)piperazin-1-yl]-1-oxopropan-2-yl}pyrrolidine-2,5-dione (**22**) – ^{19}F NMR



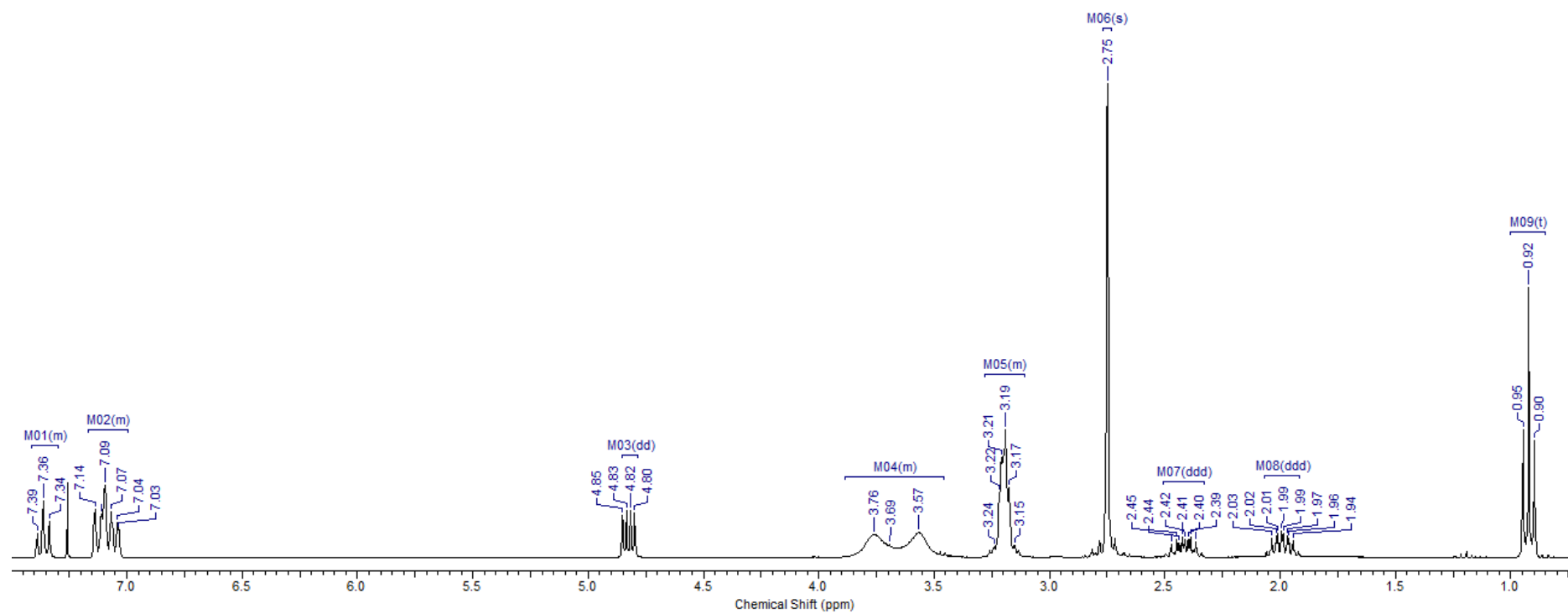
1-(1-Oxo-1-{4-[2-(trifluoromethyl)phenyl]piperazin-1-yl}butan-2-yl)pyrrolidine-2,5-dione (**23**) – ^1H NMR



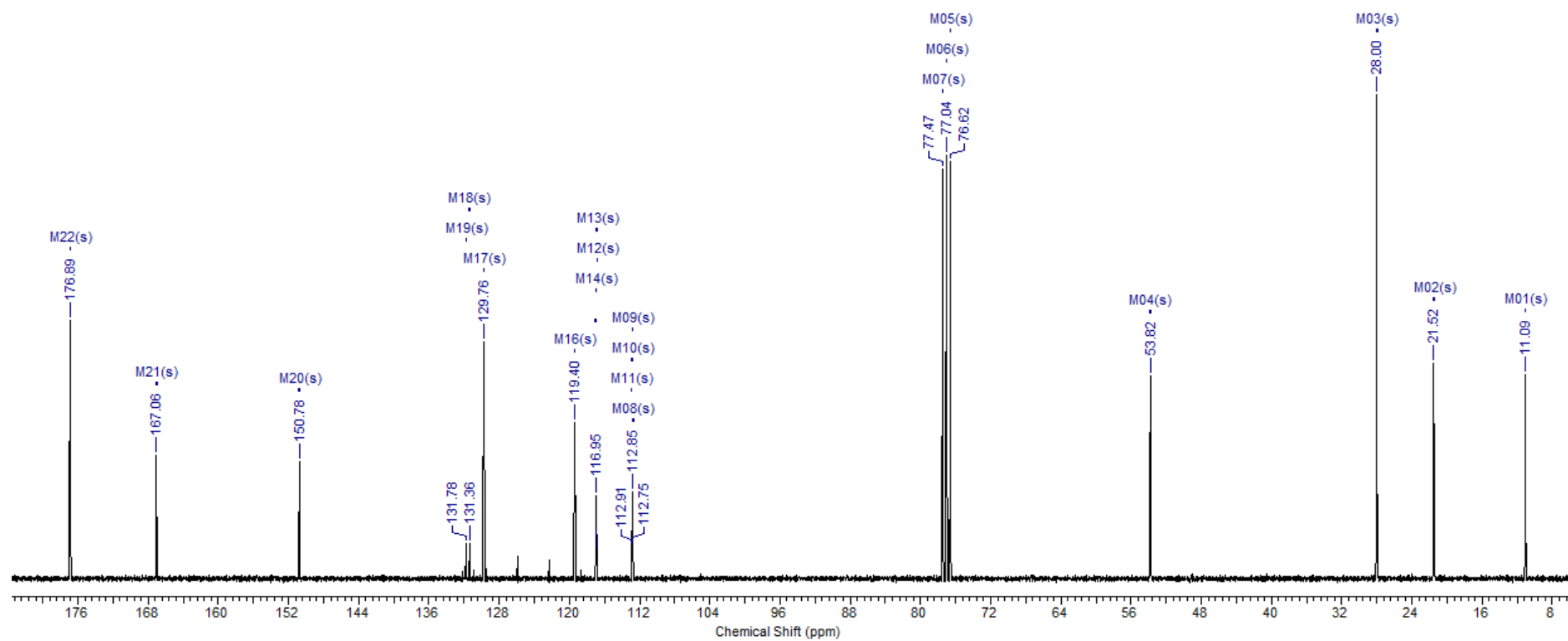
1-(1-Oxo-1-{4-[2-(trifluoromethyl)phenyl]piperazin-1-yl}butan-2-yl)pyrrolidine-2,5-dione (**23**) – ^{19}F NMR



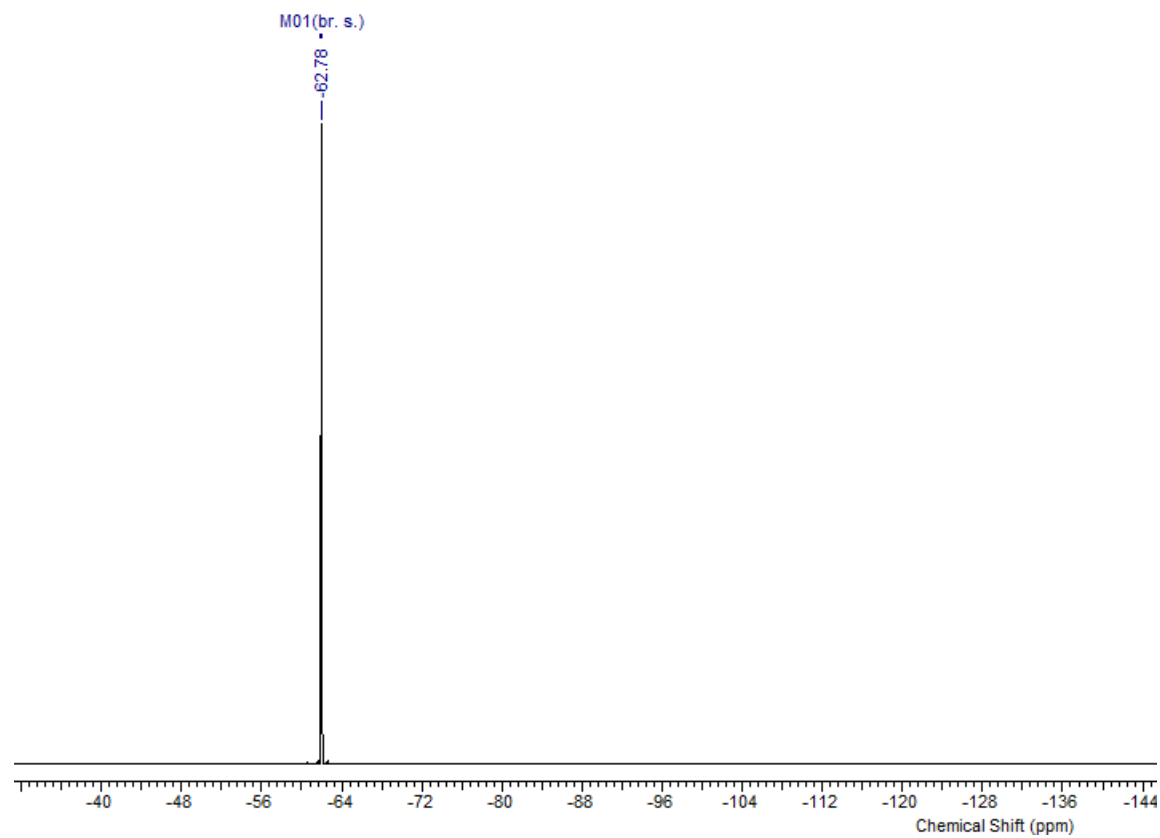
1-(1-Oxo-1-{4-[3-(trifluoromethyl)phenyl]piperazin-1-yl}butan-2-yl)pyrrolidine-2,5-dione (**24**) – ^1H NMR



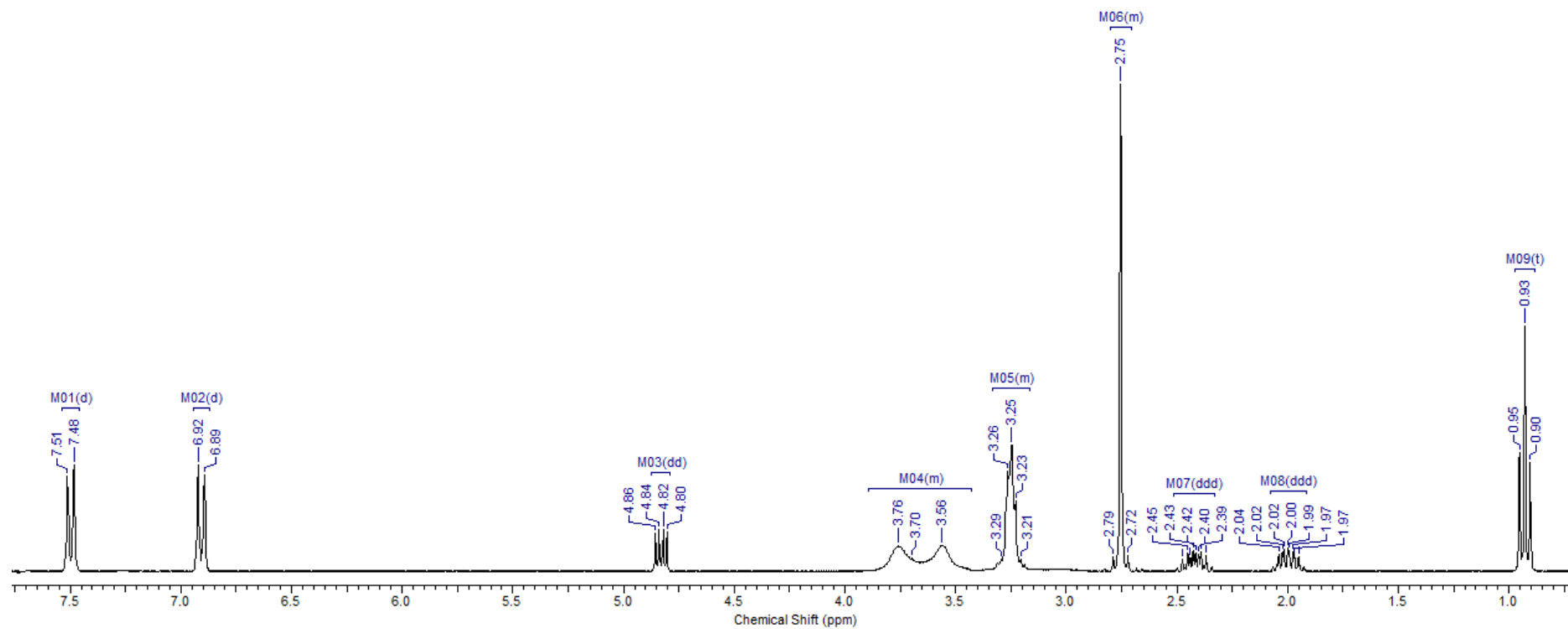
1-(1-Oxo-1-{4-[3-(trifluoromethyl)phenyl]piperazin-1-yl}butan-2-yl)pyrrolidine-2,5-dione (**24**) – ^{13}C NMR



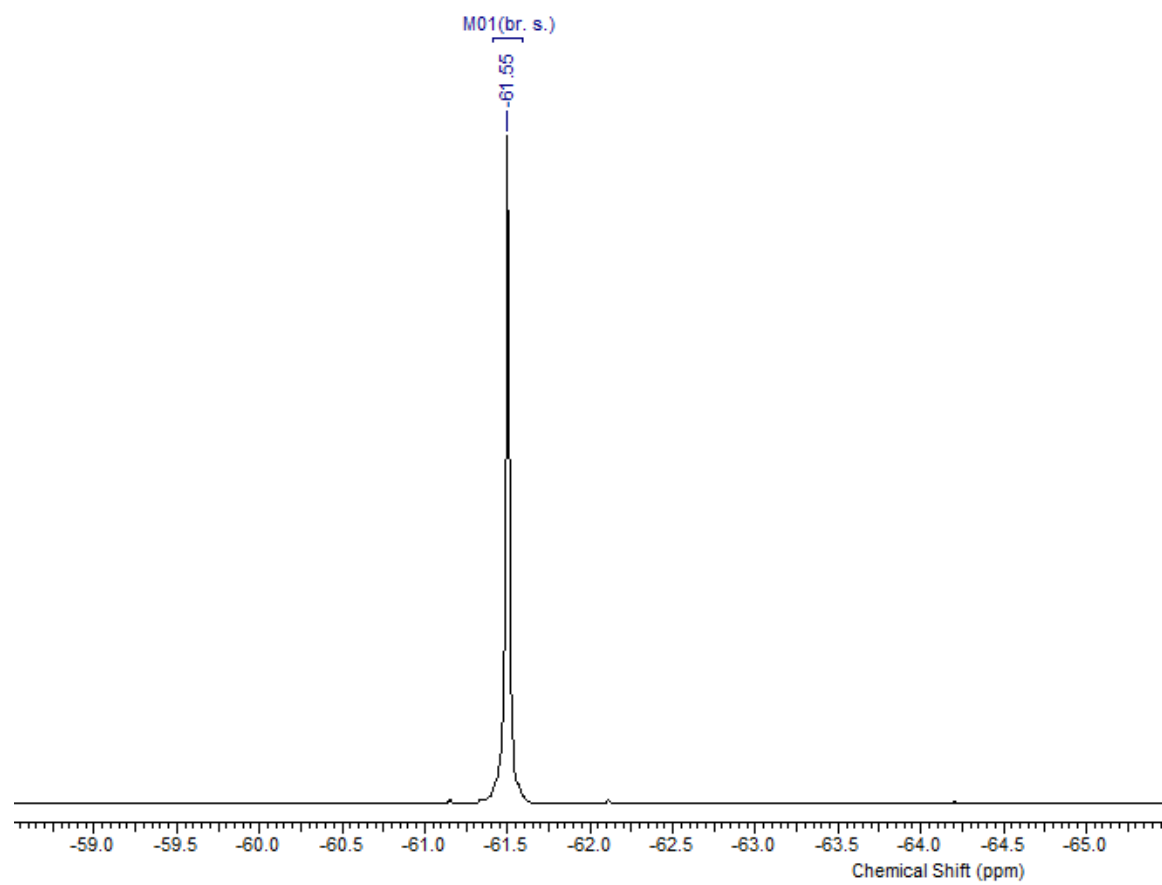
1-(1-Oxo-1-{4-[3-(trifluoromethyl)phenyl]piperazin-1-yl}butan-2-yl)pyrrolidine-2,5-dione (**24**) – ^{19}F NMR



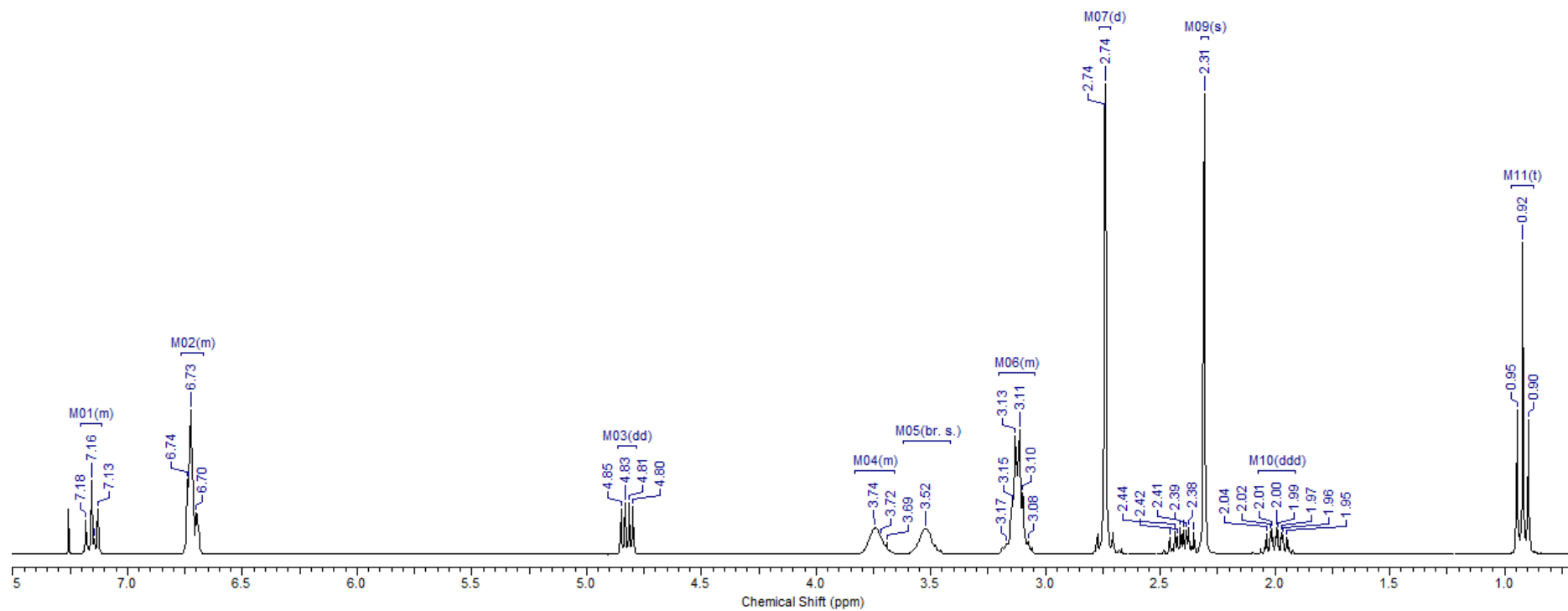
1-(1-Oxo-1-{4-[4-(trifluoromethyl)phenyl]piperazin-1-yl}butan-2-yl)pyrrolidine-2,5-dione (**25**) – ^1H NMR



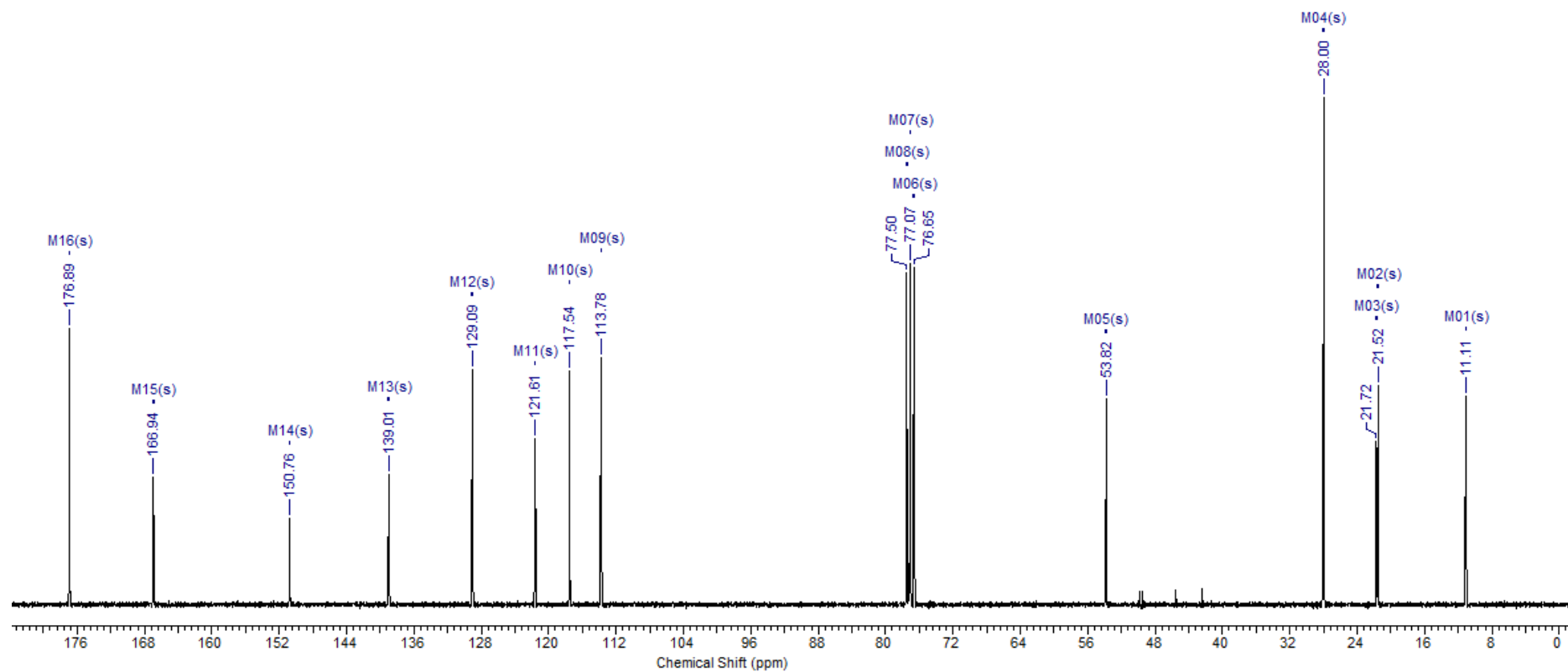
1-(1-Oxo-1-{4-[4-(trifluoromethyl)phenyl]piperazin-1-yl}butan-2-yl)pyrrolidine-2,5-dione (**25**) – ^{19}F NMR



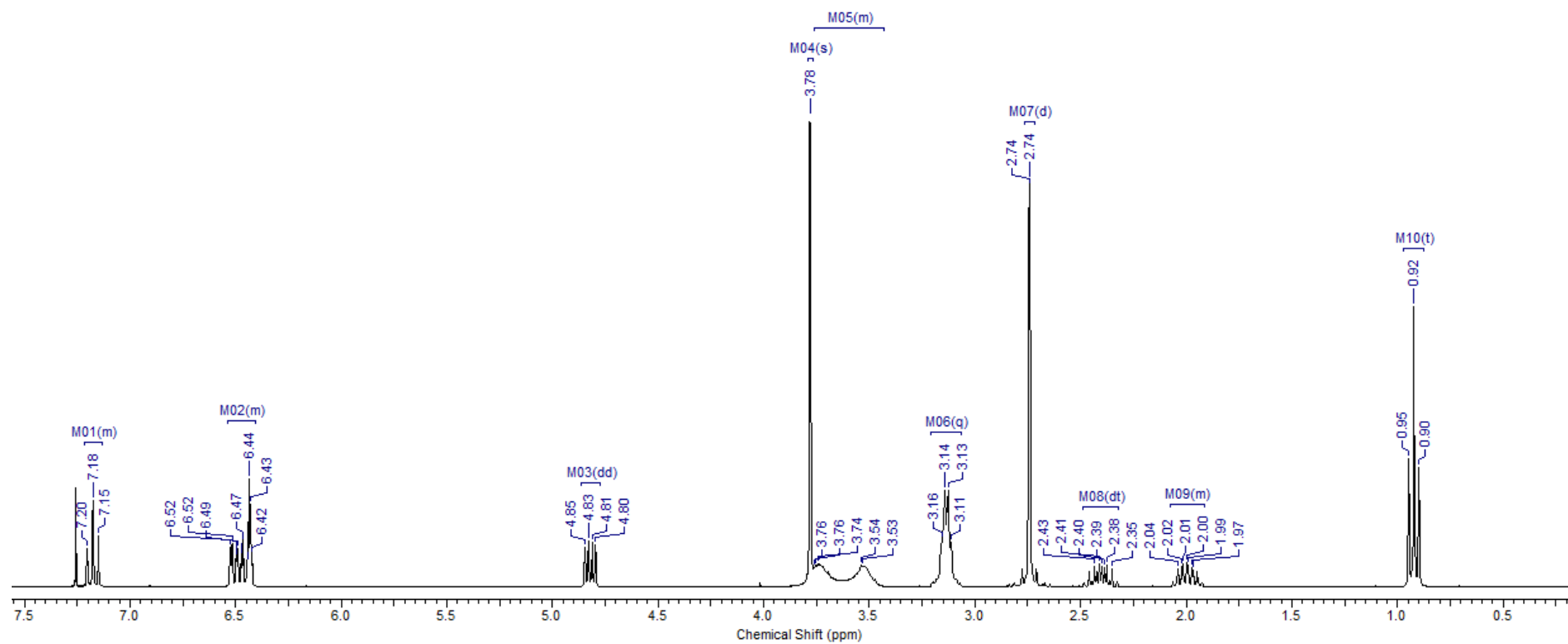
1-{1-[4-(3-Methylphenyl)piperazin-1-yl]-1-oxobutan-2-yl}pyrrolidine-2,5-dione (**26**) – ^1H NMR



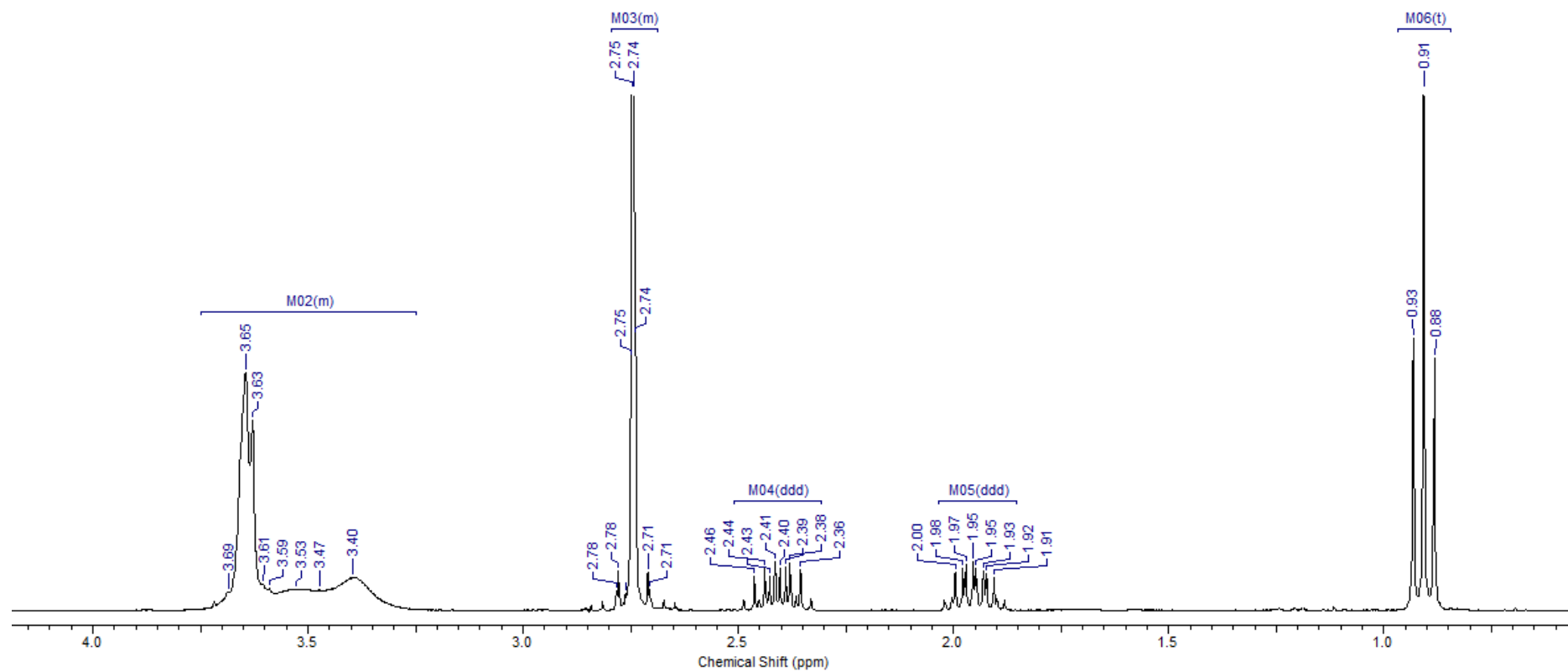
1-{1-[4-(3-Methylphenyl)piperazin-1-yl]-1-oxobutan-2-yl}pyrrolidine-2,5-dione (**26**) – ^{13}C NMR



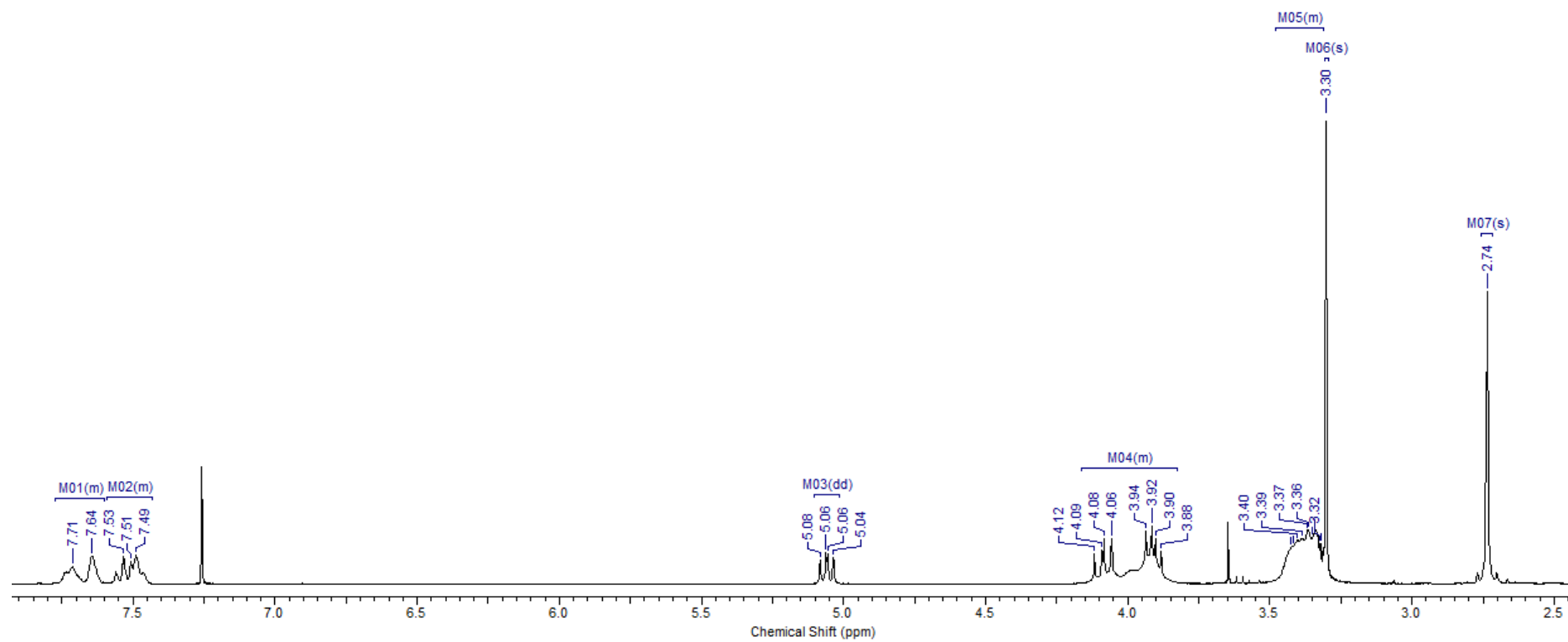
1-{1-[4-(3-Methoxyphenyl)piperazin-1-yl]-1-oxobutan-2-yl}pyrrolidine-2,5-dione (**27**) – ^1H NMR



1-[1-(Morpholin-4-yl)-1-oxobutan-2-yl]pyrrolidine-2,5-dione (**28**) – ^1H NMR



1-{1-[4-(3-Trifluoromethylphenyl)piperazin-1-yl]-3-methoxy-1-oxopropan-2-yl}pyrrolidine-2,5-dione (**30**) – ^1H NMR



1-{1-[4-(3-Trifluoromethylphenyl)piperazin-1-yl]-3-methoxy-1-oxopropan-2-yl}pyrrolidine-2,5-dione (**30**) – ^{19}F NMR

