Supporting information for

Multitargeted Compounds Derived from (2,5-Dioxopyrrolidin-1-yl)(phenyl)-Acetamides as Candidates for Effective Anticonvulsant and Antinociceptive Agents

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Boc-protected 4-phenylpiperazine derivatives A2–A12 and amines A14–A24

***Tert*-butyl 4-(3-(*tert*-butyl)phenyl)piperazine-1-carboxylate (A2)**. Yellow oil, yield 79% (2.42g); TLC: R_f = 0.58 (S_3); UPLC (purity 72%): t_R = 9.19 min. LC-MS (ESI): *m/z* calcd for $C_{19}H_{30}N_2O_2$ $(M+H)^+$ 319.24, found 319.2.

***Tert*-butyl 4-(3-(trifluoromethoxy)phenyl)piperazine-1-carboxylate (A3)**. Yellow oil, yield 78% (2.71 g); TLC: R_f = 0.52 (S_2); UPLC (purity 98%): t_R = 8.73 min. LC-MS (ESI): *m/z* calcd for $C_{16}H_{21}F_3N_2O_3$ $(M+H)^+$ 347.16, found 347.2.

***Tert*-butyl 4-([1,1'-biphenyl]-3-yl)piperazine-1-carboxylate (A4)**. Yellow oil, yield 74% (2.52 g); TLC: R_f = 0.57 (S_2); UPLC (purity 100%): t_R = 8.95 min. LC-MS (ESI): *m/z* calcd for $C_{21}H_{26}N_2O_2$ $(M+H)^+$ 339.23, found 339.2.

***Tert*-butyl 4-(3-(benzyloxy)phenyl)piperazine-1-carboxylate (A5)**. Yellow oil, yield 68% (2.49 g); TLC: R_f = 0.46 (S_3); UPLC (purity 87%): t_R = 8.84 min. LC-MS (ESI): *m/z* calcd for $C_{22}H_{28}N_2O_3$ $(M+H)^+$ 369.22, found 369.2.

***Tert*-butyl 4-(3-(methylthio)phenyl)piperazine-1-carboxylate (A6).** Yellow oil, yield 72% (2.22 g); TLC: R_f = 0.91 (S_2); UPLC (purity 85%): t_R = 7.69 min. LC-MS (ESI): *m/z* calcd for $C_{16}H_{24}N_2O_2S$ $(M+H)^+$ 308.16, found 308.2.

***Tert*-butyl 4-(3-((trifluoromethyl)thio)phenyl)piperazine-1-carboxylate (A7).** Yellow oil, yield 75% (2.72 g); TLC: R_f = 0.74 (S_2); UPLC (purity 91.4%): t_R = 9.14 min. LC-MS (ESI): *m/z* calcd for $C_{16}H_{21}F_3N_2O_2S$ $(M+H)^+$ 363.13, found 363.2.

***Tert*-butyl 4-(3-(difluoromethyl)phenyl)piperazine-1-carboxylate (A8).** Yellow oil, yield 82% (2.57 g); TLC: R_f = 0.86 (S_2); UPLC (purity 87.8%): t_R = 7.83 min. LC-MS (ESI): *m/z* calcd for $C_{16}H_{22}F_2N_2O_2$ $(M+H)^+$ 313.16, found 313.4.

***Tert*-butyl 4-(3,5-dichlorophenyl)piperazine-1-carboxylate (A9).** Yellow oil, yield 71% (2.35 g); TLC: R_f = 0.80 (S_2); UPLC (purity 84.9%): t_R = 9.32 min. LC-MS (ESI): *m/z* calcd for $C_{15}H_{20}Cl_2N_2O_2$ $(M+H)^+$ 331.09, found 331.1.

***Tert*-butyl 4-(3,5-bis(trifluoromethyl)phenyl)piperazine-1-carboxylate (A10).** Yellow oil, yield 62% (2.48 g); TLC: R_f = 0.89 (S_2); UPLC (purity 100%): t_R = 9.34 min. LC-MS (ESI): *m/z* calcd for $C_{17}H_{20}F_6N_2O_2$ $(M+H)^+$ 399.14, found 399.5.

***Tert*-butyl 4-(3,5-bis((trifluoromethyl)thio)phenyl)piperazine-1-carboxylate (A11).** Yellow oil, yield 67% (3.10 g); TLC: R_f = 0.78 (S_2); UPLC (purity 94.2%): t_R = 9.42 min. LC-MS (ESI): *m/z* calcd for $C_{17}H_{20}F_6N_2O_2S_2$ $(M+H)^+$ 463.09, found 463.2.

***Tert*-butyl 4-(3-chloro-5-(trifluoromethyl)phenyl)piperazine-1-carboxylate (A12).** Yellow oil, yield 73% (2.66 g); TLC: R_f = 0.82 (S_2); UPLC (purity 85.7%): t_R = 9.27 min. LC-MS (ESI): *m/z* calcd for $C_{16}H_{20}ClF_3N_2O_2$ $(M+H)^+$ 365.12, found 365.2.

1-(3-(*Tert*-butyl)phenyl)piperazine (A14). Yellow oil, yield 98% (1.62 g); TLC: R_f = 0.30 (S_3); UPLC (purity 89%): t_R = 4.46 min. LC-MS (ESI): *m/z* calcd for $C_{14}H_{22}N_2$ $(M+H)^+$ 219.18, found 219.2. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.28–1.36 (m, 10H; 9H, C(C<u>H</u>$_3$)$_3$, 1H, piperazine), 3.07–3.28 (m, 8H, piperazine), 6.77 (dd, 1H, *J*=2.4, 0.8 Hz, ArH), 6.90–7.04 (m, 2H, ArH), 7.22 (t, 1H, *J*=7.9 Hz, ArH).

1-(3-(Trifluoromethoxy)phenyl)piperazine (A15). Yellow oil, yield 97% (1.87 g); TLC: R_f = 0.25 (S_3); UPLC (purity 85%): t_R = 3.99 min. LC-MS (ESI): *m/z* calcd for $C_{11}H_{13}F_3N_2O$ $(M+H)^+$ 247.10, found 247.1. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.23 (s, 1H, piperazine) 2.91–3.16 (m, 8H, piperazine) 6.59–6.85 (m, 3H, ArH), 7.19 (t, 1H, *J*=8.3 Hz, ArH).

1-([1,1'-Biphenyl]-3-yl)piperazine (A16). Yellow oil, yield 95% (1.68 g); TLC: R_f = 0.82 (S_3); UPLC (purity 100%): t_R = 4.39 min. LC-MS (ESI): *m/z* calcd for $C_{16}H_{18}N_2$ $(M+H)^+$ 239.15, found 239.2. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.15–1.28 (m, 1H, piperazine), 3.14–3.76 (m, 8H, piperazine), 6.65–7.73 (m, 9H, ArH).

1-(3-(Benzyloxy)phenyl)piperazine (A17). Yellow oil, yield 94% (1.71 g); TLC: R_f = 0.35 (S_3); UPLC (purity 86%): t_R = 4.59 min. LC-MS (ESI): *m/z* calcd for $C_{17}H_{20}N_2O$ $(M+H)^+$ 269.16, found 269.2. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.28 (s, 1H, piperazine), 2.58–3.59 (m, 8H, piperazine), 4.89–5.16 (m, 2H, -C<u>H</u>$_2$-O-), 6.22–6.73 (m, 3H, ArH), 6.85–7.76 (m, 6H, ArH).

1-(3-(Methylthio)phenyl)piperazine (A18) Yellow oil, yield 98% (1.47 g); TLC: R_f = 0.51 (S_4); UPLC (purity 98.6%): t_R = 3.20 min. LC-MS (ESI): *m/z* calcd for $C_{11}H_{16}N_2S$ $(M+H)^+$ 209.10, found 209.1. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.65–1.71 (m, 1H, piperazine), 2.46 (s, 3H, CH_3), 3.00–3.02 (m, 4H, piperazine), 3.12–3.14 (m, 4H, piperazine), 6.70 (m, 1H, ArH), 6.74 (d, 1H, *J*=7.6 Hz, ArH), 6.81 (t, 1H, *J*=2.0 Hz, ArH), 7.17 (t, 1H, *J*=7.9 Hz, ArH)

1-(3-((Trifluoromethyl)thio)phenyl)piperazine (A19) Yellow oil, yield 95% (2.04 g); TLC: R_f = 0.57 (S_4); UPLC (purity 97%): t_R = 3.69 min. LC-MS (ESI): *m/z* calcd for $C_{11}H_{13}F_3N_2S$ $(M+H)^+$ 263.08, found 263.1. ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.65–2.71 (m, 1H, piperazine), 3.10–3.16 (m, 3H, piperazine), 3.18–3.31 (m, 5H, piperazine), 6.99–7.01 (m, 1H, ArH), 7.09–7.16 (m, 2H, ArH), 7.25–7.30 (m, 1H, ArH).

1-(3-(Difluoromethyl)phenyl)piperazine (A20) Yellow oil, yield 97% (1.69 g); TLC: R_f = 0.71 (S_4); UPLC (purity 96.3%): t_R = 3.01 min. LC-MS (ESI): *m/z* calcd for $C_{11}H_{14}F_2N_2$ $(M+H)^+$ 213.11, found 212.9. ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.63–2.66 (m, 1H, piperazine), 3.15–3.18 (m, 4H, piperazine), 3.27–3.30 (m, 4H, piperazine), 6.40–6.55 (m, 1H, CHF_2), 6.60–6.73 (m, 1H, ArH), 6.96–7.03 (m, 1H, ArH), 7.05–7.11 (m, 1H ArH), 7.15–7.23 (m, 1H, ArH).

1-(3,5-Dichlorophenyl)piperazine (A21) Yellow oil, yield 94% (1.53 g); TLC: R_f = 0.62 (S_4); UPLC (purity 83.4%): t_R = 3.99 min. LC-MS (ESI): *m/z* calcd for $C_{10}H_{12}Cl_2N_2$ $(M+H)^+$ 231.04, found 231.0. ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.02–2.18 (m, 1H, piperazine) 2.97–3.00 (m, 4H, piperazine), 3.11–3.14 (m, 4H, piperazine), 6.72 (s, 2H, ArH), 6.77 (s, 1H, ArH).

1-(3,5-Bis(trifluoromethyl)phenyl)piperazine (A22) Yellow oil, yield 98% (1.81 g); TLC: R_f = 0.57 (S_4); UPLC (purity 100%): t_R = 4.80 min. LC-MS (ESI): *m/z* calcd for $C_{12}H_{12}F_6N_2$ $(M+H)^+$ 299.09, found 299.3. ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.63 (br. s, 1H, piperazine), 3.03–3.05 (m, 4H, piperazine), 3.23–3.25 (m, 4H, piperazine), 7.22 (s, 2H, ArH), 7.25–7.26 (m, 1H, ArH).

1-(3,5-Bis((trifluoromethyl)thio)phenyl)piperazine (A23) Yellow oil, yield 95% (2.30 g); TLC: R_f = 0.62 (S_4); UPLC (purity 98.2%): t_R = 4.62 min. LC-MS (ESI): *m/z* calcd for $C_{12}H_{12}F_6N_2S_2$ $(M+H)^+$ 363.03, found 363.2. δ 2.63–2.70 (m, 1H, piperazine), 3.08–3.12 (m, 4H, piperazine), 3.21–3.34 (m, 4H, piperazine), 6.95–7.03 (m, 1H, ArH), 7.12–7.22 (m, 1H, ArH), 7.26–7.29 (m, 1H, ArH).

1-(3-Chloro-5-(trifluoromethyl)phenyl)piperazine (A24) Yellow oil, yield 98% (1.89 g); TLC: R_f = 0.57 (S_4); UPLC (purity 97.1%): t_R = 4.53 min. LC-MS (ESI): *m/z* calcd for $C_{11}H_{12}ClF_3N_2$ $(M+H)^+$ 265.06, found 265.2. ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.64–2.73 (m, 2H, piperazine), 3.01–3.06 (m, 3H, piperazine), 3.20–3.26 (m, 4H, piperazine), 6.97 (d, 2H, *J*=9.68 Hz, ArH), 7.00–7.03 (m, 1H, ArH).

Intermediate succinamic acids 2–5

4-((1-Carboxy-2-phenylethyl)amino)-4-oxobutanoic acid (2). White solid. Yield: 88% (7.00 g); mp. 143.8–144.9ºC; TLC: R_f = 0.52 (S_4); UPLC (purity 100%): t_R = 3.25 min. LC-MS (ESI): *m/z* calcd for $C_{13}H_{15}NO_5$ $(M+H)^+$ 266.10, found 266.1.

4-((Carboxy(3-fluorophenyl)methyl)amino)-4-oxobutanoic acid (3). White solid. Yield: 80% (6.46 g); mp. 136.2–137.5ºC; TLC: R_f = 0.45 (S_4); UPLC (purity 100%): t_R = 3.21 min. LC-MS (ESI): *m/z* calcd for $C_{12}H_{12}FNO_5$ $(M+H)^+$ 270.08, found 270.1.

4-((Carboxy(4-fluorophenyl)methyl)amino)-4-oxobutanoic acid (4). White solid. Yield: 85% (6.86 g); mp. 125.7–126.9ºC; TLC: R_f = 0.42 (S_4); UPLC (purity 100%): t_R = 3.19 min. LC-MS (ESI): *m/z* calcd for $C_{12}H_{12}FNO_5$ $(M+H)^+$ 270.08, found 270.1.

4-((Carboxy(3,4-difluorophenyl)methyl)amino)-4-oxobutanoic acid (5). White solid. Yield: 83% (7.15 g); mp. 145.5–146.4ºC; TLC: R_f = 0.28 (S_4); UPLC (purity 100%): t_R = 3.33 min. LC-MS (ESI): *m/z* calcd for $C_{12}H_{11}F_2NO_5$ $(M+H)^+$ 288.07, found 288.1.

Intermediate monocarboxylic acids 7–10, and 51

2-(2,5-Dioxopyrrolidin-1-yl)-3-phenylpropanoic acid (7). White solid. Yield: 94% (4.64 g); mp. 123.2–124.7ºC; TLC: R_f = 0.71 (S_4); UPLC (purity 100%): t_R = 3.62 min. LC-MS (ESI): *m/z* calcd for $C_{13}H_{13}NO_4$ $(M+H)^+$ 248.09, found 248.1. ^{1}H NMR (300 MHz, DMSO-D_6) δ 2.30–2.77 (m, 4H, imide), 3.21–3.59 (m, 2H Ar-C<u>H</u>$_2$-), 4.84–5.14 (m, 1H, -C<u>H</u>-COOH), 7.00–7.40 (m, 4H, ArH), 13.23 (br. s, 1H, COO<u>H</u>).

2-(2,5-Dioxopyrrolidin-1-yl)-2-(3-fluorophenyl)acetic acid (8). White solid. Yield: 92% (4.62 g); mp. 151.8–152.4ºC; TLC: R_f = 0.21 (S_4); UPLC (purity 98.3%): t_R = 3.70 min. LC-MS (ESI): *m/z* calcd for $C_{12}H_{10}FNO_4$ $(M+H)^+$ 252.06, found 252.1. ^{1}H NMR (300 MHz, DMSO-D_6) δ 2.75 (s, 4H, imide), 5.79 (s, 1H, -C<u>H</u>-COOH), 6.91–7.15 (m, 1H, ArH), 7.18–7.49 (m, 3H, ArH), 13.21 (br. s, 1H, COO<u>H</u>).

2-(2,5-Dioxopyrrolidin-1-yl)-2-(4-fluorophenyl)acetic acid (9). White solid. Yield: 88% (4.42 g); mp. 200.2–201.9ºC; TLC: R_f = 0.25 (S_4); UPLC (purity 98.1%): t_R = 3.69 min. LC-MS (ESI): *m/z* calcd for $C_{12}H_{10}FNO_4$ $(M-H)^+$ 252.06, found 252.1. ^{1}H NMR (300 MHz, DMSO-D_6) δ 2.74 (s, 4H, imide), 5.80 (s, 1H, -C<u>H</u>-COOH), 7.04 (t, 2H, *J*=8.8 Hz, ArH), 7.40–7.62 (m, 2H, ArH), 13.22 (br. s, 1H, COO<u>H</u>).

2-(3,4-Difluorophenyl)-2-(2,5-dioxopyrrolidin-1-yl)acetic acid (10). White solid. Yield: 91% (4.90 g); mp. 159.5–160.3ºC; TLC: R_f = 0.35 (S_4); UPLC (purity 100%): t_R = 4.07 min. LC-MS (ESI): *m/z* calcd for $C_{12}H_9F_2NO_2$ $(M-H)^+$ 268.05, found 268. ^{1}H NMR (300 MHz, DMSO-D_6) δ 2.75 (s, 4H, imide), 5.77 (s, 1H -C<u>H</u>-COOH), 7.12–7.29 (m, 2H, ArH), 7.44 (ddd, 1H, *J*=11.7, 7.8, 2.0 Hz, ArH), 13.23 (br. s, 1H, COO<u>H</u>).

4-(2,5-Dioxopyrrolidin-1-yl)benzoic acid (51). White solid. Yield: 76% (3.33 g); mp. 231–232.5ºC; TLC: R_f = 0.60 (S_4); UPLC (purity 95.2%): t_R = 2.54 min. LC-MS (ESI): *m/z* calcd for $C_{11}H_9NO_4$ $(M+H)^+$ 220.06, found 220.1. ^{1}H NMR (300 MHz, DMSO-D_6) δ 2.75–2.93 (m, 4H, imide), 7.37–7.49 (m, 2H, ArH), 8.07–8.17 (m, 2H, ArH), 13.07 (br. s, 1H, COOH).

Final compounds 12–49, 52 and 53

1-(2-(4-(2-Chlorophenyl)piperazin-1-yl)-2-oxo-1-phenylethyl)pyrrolidine-2,5-dione (12). White solid. Yield: 80% (1.97 g); mp. 189.5–191.2ºC; TLC: R_f = 0.38 (S_2); UPLC (purity 100%): t_R = 6.65 min. LC-MS (ESI): *m/z* calcd for $C_{22}H_{22}ClN_3O_3$ $(M+H)^+$ 412.13, found 412.3. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.54–2.78 (m, 5H; 4H, imide, 1H, piperazine), 2.79–2.90 (m, 1H, piperazine), 2.92–3.13 (m, 2H, piperazine), 3.18–3.31 (m, 1H, piperazine), 3.32–3.44 (m, 1H, piperazine), 3.73–3.86 (m, 1H, piperazine), 3.88–3.99 (m, 1H, piperazine), 6.12 (s, 1H, CHCO), 6.86–7.03 (m, 2H, ArH), 7.19 (td, 1H, *J*=7.7, 1.5 Hz, ArH), 7.27–7.51 (m, 6H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 28.0, 42.8, 46.2, 50.8, 50.9, 56.8, 120.5, 124.3, 127.7, 128.6, 128.8, 129.8, 130.7, 133.0, 148.4, 165.0, 176.3. Anal. calcd for $C_{22}H_{22}ClN_3O_3$ (411.88): C: 64.15, H: 5.38, N: 10.20; Found C: 64.13, H: 5.39, N: 10.19.

1-(2-(4-(3-Chlorophenyl)piperazin-1-yl)-2-oxo-1-phenylethyl)pyrrolidine-2,5-dione (13). White solid. Yield: 81% (2.00 g); mp. 128.1–129ºC; TLC: R_f = 0.51 (S_1); UPLC (purity 100%): t_R = 6.72 min. LC-MS (ESI): *m/z* calcd for $C_{22}H_{22}ClN_3O_3$ $(M+H)^+$ 412.13, found 412.2. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.58–2.73 (m, 4H, imide), 3.00 (br. s, 1H, piperazine), 3.27–3.53 (m, 3H, piperazine), 3.54–3.86 (m, 2H, piperazine), 4.17 (br. s, 2H, piperazine), 6.02 (s, 1H, CHCO), 7.27–7.40 (m, 7H, ArH), 7.51–7.63 (m, 2H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 28.0, 40.0, 43.3, 53.3, 53.7, 56.5, 118.9, 120.8, 128.9, 129.1, 129.3, 129.6, 131.4, 132.1, 135.9, 143.8, 165.5, 176.7. Anal. calcd for $C_{22}H_{22}ClN_3O_3$ (411.89): C: 64.15, H: 5.38, N: 10.20; Found C: 64.16, H: 5.40, N: 10.17.

1-(2-(4-(4-Chlorophenyl)piperazin-1-yl)-2-oxo-1-phenylethyl)pyrrolidine-2,5-dione (14). White solid. Yield: 83% (2.05 g); mp. 162.8–163.5ºC; TLC: R_f = 0.44 (S_2); UPLC (purity 100%): t_R = 6.67 min. LC-MS (ESI): *m/z* calcd for $C_{22}H_{22}ClN_3O_3$ $(M+H)^+$ 412.13, found 412.4. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.59–2.78 (m, 5H; 4H, imide, 1H, piperazine), 2.94–3.08 (m, 2H, piperazine), 3.14–3.37 (m, 3H, piperazine), 3.61–3.76 (m, 1H, piperazine), 3.90–4.03 (m, 1H, piperazine), 6.11 (s, 1H, CHCO), 6.69–6.78 (m, 2H, ArH), 7.13–7.21 (m, 2H, ArH), 7.29–7.47 (m, 5H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 28.0, 42.3, 45.6, 48.9, 49.1, 56.7, 117.8, 125.5, 128.7, 128.9, 129.1, 129.8, 132.9, 149.3, 165.0, 176.3. Anal. calcd for $C_{22}H_{22}ClN_3O_3$ (411.89): C: 64.15, H: 5.38, N: 10.20; Found C: 64.20, H: 5.36, N: 10.30.

1-(2-(4-(2-Fluorophenyl)piperazin-1-yl)-2-oxo-1-phenylethyl)pyrrolidine-2,5-dione (15). White solid. Yield: 69% (1.64g); mp. 211.2–212.5ºC; TLC: R_f = 0.46 (S_2); UPLC (purity 100%): t_R = 6.10 min LC-MS (ESI): *m/z* calcd for $C_{22}H_{22}FN_3O_3$ $(M+H)^+$ 396.16, found 396.4. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.53–2.78 (m, 5H; 4H imide, 1H, piperazine), 2.85–2.92 (m, 1H, piperazine), 2.97–3.17 (m, 2H, piperazine), 3.21–3.44 (m, 2H, piperazine), 3.68–3.84 (m, 1H, piperazine), 3.87–4.01 (m, 1H, piperazine), 6.12 (s, 1H, CHCO), 6.79–6.88 (m, 1H, ArH), 6.89–7.07 (m, 3H, ArH), 7.28–7.48 (m, 5H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 28.0, 42.6, 46.0, 50.1, 56.7, 116.2 (d, *J*=20.7 Hz), 119.1, 123.2 (d, *J*=8.1 Hz), 124.5, 128.6, 128.8, 129.8, 133.0, 139.3 (d, *J*=8.1 Hz), 154.0, 157.3, 165.0, 176.3; ^{19}F NMR (282 MHz, $CDCl_3$) δ -123.00 (br. s, 1F). Anal. calcd for $C_{22}H_{22}FN_3O_3$ (395.43): C: 66.82, H: 5.61, N: 10.63; Found C: 66.78, H: 5.59, N: 10.65.

1-(2-(4-(3-Fluorophenyl)piperazin-1-yl)-2-oxo-1-phenylethyl)pyrrolidine-2,5-dione (16). White solid. Yield: 77% (1.92 g); mp. 182.1–183.5ºC; TLC: R_f = 0.42 (S_1); UPLC (purity 98.45%): t_R = 6.18 min. LC-MS (ESI): *m/z* calcd for $C_{22}H_{22}FN_3O_3$ $(M+H)^+$ 396.16, found 396.5. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.51–2.66 (m, 4H, imide), 2.72–2.87 (m, 1H, piperazine), 3.03–3.57 (m, 5H, piperazine), 3.94(br. s, 2H, piperazine), 5.99 (s, 1H, C<u>H</u>CO), 6.72 (t, 1H, *J*=8.1, 1.5 Hz, ArH), 6.82–7.00 (m, 1H, ArH), 7.15–7.33 (m, 7H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 27.9, 40.9, 44.2, 48.2, 48.4, 48.7, 49.0, 49.3, 51.0, 51.3, 56.5, 106.0 (d, *J*=25.4 Hz), 110.0, 111.7, 114.1, 128.7, 129.0, 129.5, 130.9, 131.0, 132.2, 161.6, 165.5, 176.8. ^{19}F NMR (282 MHz, $CDCl_3$) δ -109.91 (br. s, 1F). Anal. calcd for $C_{22}H_{22}FN_3O_3$ (395.43): C: 66.82, H: 5.61, N: 10.63; Found C: 66.88, H: 5.65, N: 10.61.

1-(2-(4-(4-Fluorophenyl)piperazin-1-yl)-2-oxo-1-phenylethyl)pyrrolidine-2,5-dione (17). White solid. Yield: 76% (1.80 g); mp. 141.2–142.5ºC; TLC: R_f = 0.43 (S_2); UPLC (purity 100%): t_R = 5.93 min. LC-MS (ESI): *m/z* calcd for $C_{22}H_{22}FN_3O_3$ $(M+H)^+$ 396.16, found 396.4. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.54–2.78 (m, 5H; 4H, imide, 1H, piperazine), 2.84–3.07 (m, 2H, piperazine), 3.08–3.41 (m, 3H, piperazine), 3.63–3.77 (m, 1H, piperazine), 3.90–4.03 (m, 1H, piperazine), 6.11 (s, 1H, C<u>H</u>CO), 6.74–6.83 (m, 2H, ArH), 6.88–6.98 (m, 2H, ArH), 7.28–7.47 (m, 5H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 28.0, 42.5, 45.8, 49.9, 50.2, 56.7, 115.7 (d, *J*=21.9 Hz), 118.5 (d, *J*=8.1 Hz), 128.6, 128.9, 129.8, 132.9, 147.4, 156.0, 159.2, 165.0, 176.3; ^{19}F NMR (282 MHz, $CDCl_3$) δ -123.21 (br. s, 1F). Anal. calcd for $C_{22}H_{22}FN_3O_3$ (395.43): C: 66.82, H: 5.61, N: 10.63; Found C: 66.79, H: 5.62, N: 10.59.

1-(2-Oxo-1-phenyl-2-(4-(o-tolyl)piperazin-1-yl)ethyl)pyrrolidine-2,5-dione (18). White solid. Yield: 75% (1.76 g); mp. 187.2–188.1ºC; TLC: R_f = 0.41 (S_2); UPLC (purity 100%): t_R = 6.72 min LC-MS (ESI): *m/z* calcd for $C_{23}H_{25}N_3O_3$ $(M+H)^+$ 392.19, found 392.3. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.25 (s, 3H, -C<u>H</u>$_3$), 2.44–2.56 (m, 1H, piperazine), 2.59–2.78 (m, 5H; 4H, imide, 1H, piperazine), 2.79–2.98 (m, 2H, piperazine), 3.16–3.42 (m, 2H, piperazine), 3.70–3.98 (m, 2H, piperazine), 6.14 (s, 1H, C<u>H</u>CO), 6.90 (d, 1H, *J*=7.8 Hz, ArH), 6.94–7.02 (m, 1H, ArH), 7.10–7.19 (m, 2H, ArH), 7.30–7.50 (m, 5H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.7, 28.1, 43.1, 46.4, 51.3, 51.5, 56.8, 119.1, 123.8, 126.7, 128.6, 128.8, 129.9, 131.1, 132.6, 133.0, 150.6, 165.0, 176.4. Anal. calcd for $C_{23}H_{25}N_3O_3$ (391.47): C: 70.57, H: 6.44, N: 10.73; Found C: 70.55, H: 6.45, N: 10.79.

1-(2-Oxo-1-phenyl-2-(4-(m-tolyl)piperazin-1-yl)ethyl)pyrrolidine-2,5-dione (19). White solid. Yield: 86% (2.02 g); mp. 188.7–192.1ºC; TLC: R_f = 0.45 (S_2); UPLC (purity 98.92%): t_R = 6.40 min. LC-MS (ESI): *m/z* calcd for $C_{23}H_{25}N_3O_3$ $(M+H)^+$ 392.19, found 392.1. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.36 (s, 3H, -C<u>H</u>$_3$), 2.57–2.78 (m, 5H; 4H, imide, 1H, piperazine), 2.91–3.54 (m, 3H, piperazine), 3.63–4.55 (m, 4H, piperazine), 6.06 (s, 1H, C<u>H</u>CO), 7.22 (d, 1H, *J*=7.5 Hz, ArH), 7.27–7.62 (m, 8H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.4, 28.1, 39.7, 43.0, 54.1, 54.6, 56.5, 117.9, 121.7, 128.9, 129.3, 129.7, 130.2, 130.8, 132.3, 141.0, 141.8, 165.4, 176.3. Anal. calcd for $C_{23}H_{25}N_3O_3$ (391.47): C: 70.57, H: 6.44, N: 10.73; Found C: 70.60, H: 6.48, N: 10.71.

1-(2-Oxo-1-phenyl-2-(4-(p-tolyl)piperazin-1-yl)ethyl)pyrrolidine-2,5-dione (20). White solid. Yield: 77% (1.81 g); mp. 140.2–141.8ºC; TLC: R_f = 0,28 (S_2); UPLC (purity 100%): t_R = 6.22 min. LC-MS (ESI): *m/z* calcd for $C_{23}H_{25}N_3O_3$ $(M+H)^+$ 392.19, found 391.9. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.26 (s, 3H, -CH_3), 2.57–2.81 (m, 5H; 4H, imide, 1H, piperazine), 2.88–3.10 (m, 2H, piperazine), 3.12–3.42 (m, 3H, piperazine), 3.63–3.77 (m, 1H, piperazine), 3.90–4.05 (m, 1H, piperazine), 6.12 (s, 1H, C<u>H</u>CO), 6.72–6.79 (m, 2H, ArH), 7.05 (d, 2H, *J*=8.2 Hz, ArH), 7.28–7.48 (m, 5H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.4, 28.0, 42.5, 45.8, 49.5, 49.7, 56.8, 116.9, 128.6, 128.8, 129.7, 129.9, 130.2, 133.0, 148.6, 164.9, 176.3. . Anal. calcd for $C_{23}H_{25}N_3O_3$ (391.47): C: 70.57, H: 6.44, N: 10.73; Found C: 70.51, H: 6.40, N: 10.77.

1-(2-Oxo-1-phenyl-2-(4-(2-(trifluoromethyl)phenyl)piperazin-1-yl)ethyl)pyrrolidine-2,5-dione (21). White solid. Yield: 69% (1.84 g); mp. 167.1–168.7ºC; TLC: R_f = 0.25 (S_2); UPLC (purity 100%): t_R = 7.08 min. LC-MS (ESI): *m/z* calcd for $C_{23}H_{22}F_3N_3O_3$ $(M+H)^+$ 446.16, found 446.2. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.44–2.55 (m, 1H, piperazine), 2.59–2.79 (m, 5H; 4H, imide, 1H, piperazine), 2.82–2.98 (m, 2H, piperazine), 3.15–3.22 (m, 1H, piperazine), 3.29–3.42 (m, 1H, piperazine), 3.83 (br. s, 2H, piperazine), 6.12 (s, 1H, C<u>H</u>CO), 7.19–7.27 (m, 2H, ArH), 7.29–7.54 (m, 6H, ArH), 7.60 (d, 1H, *J*=8.1 Hz, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 28.0, 43.0, 46.4, 52.9, 56.8, 123.8 (q, *J*=272.9 Hz), 124.0, 125.5, 127.2 (q, *J*=5.7 Hz), 128.6, 128.8, 129.8, 132.8, 133.0, 151.4, 165.0, 176.3; ^{19}F NMR (282 MHz, $CDCl_3$) δ -60.46 (s, 3F). Anal. calcd for $C_{23}H_{22}F_3N_3O_3$ (445.44): C: 62.02, H: 4.98, N: 9.43; Found C: 62.08, H: 4.97, N: 9.46.

1-(2-Oxo-1-phenyl-2-(4-(3-(trifluoromethyl)phenyl)piperazin-1-yl)ethyl)pyrrolidine-2,5-dione (22). White solid. Yield: 82% (2.19 g); mp. 150.3–151.4ºC; TLC: R_f = 0.34 (S_1); UPLC (purity 100%): t_R = 6.99 min. LC-MS (ESI): *m/z* calcd for $C_{23}H_{22}F_3N_3O_3$ $(M+H)^+$ 446.16, found 446.2. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.60–2.86 (m, 5H; 4H, imide, 1H, piperazine), 3.00–3.20 (m, 2H, piperazine), 3.23–3.44 (m, 3H, piperazine), 3.62–3.76 (m, 1H, piperazine), 3.93–4.06 (m, 1H, piperazine), 6.12 (s, 1H, C<u>H</u>CO), 6.94–7.04 (m, 2H, ArH), 7.09 (d, 1H, *J*=7.7 Hz, ArH), 7.28–7.51 (m, 6H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 28.0, 42.2, 45.6, 48.4, 48.6, 56.8, 112.7 (q, *J*=4.6 Hz), 116.7 (q, *J*=4.6 Hz), 119.2, 123.4 (q, *J*=271.8 Hz), 128.7, 128.9, 129.7, 129.8, 131.5 (q, *J*=31.8 Hz), 132.9, 150.8, 165.1, 176.3; ^{19}F NMR (282 MHz, $CDCl_3$) δ -62.77 (br. s, 3F). Anal. calcd for $C_{23}H_{22}F_3N_3O_3$ (445.44): C: 62.02, H: 4.98, N: 9.43; Found C: 62.05, H: 5.00, N: 9.40.

1-(2-Oxo-1-phenyl-2-(4-(4-(trifluoromethyl)phenyl)piperazin-1-yl)ethyl)pyrrolidine-2,5-dione (23). White solid. Yield: 62% (1.66 g); mp. 173.2–174.3ºC; TLC: R_f = 0.49 (S_2); UPLC (purity 100%): t_R = 6.99 min. LC-MS (ESI): *m/z* calcd for $C_{23}H_{22}F_3N_3O_3$ $(M+H)^+$ 446.16, found 446.2. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.61–2.85 (m, 5H; 4H, imide, 1H, piperazine), 3.04–3.43 (m, 5H, piperazine), 3.63–3.77 (m, 1H, piperazine), 3.91–4.05 (m, 1H, piperazine), 6.12 (s, 1H, C<u>H</u>CO), 6.83 (d, 2H, *J*=8.6 Hz, ArH), 7.30–7.40 (m, 3H, ArH), 7.40–7.50 (m, 4H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 28.0, 42.1, 45.4, 47.6, 47.9, 56.8, 115.0, 124.5 (q, *J*=270.6 Hz), 126.5 (q, *J*=4.6 Hz), 128.7, 128.8, 128.9, 129.8, 132.8, 152.7, 165.1, 176.3; ^{19}F NMR (282 MHz, $CDCl_3$) δ -61.5 (s, 3F). Anal. calcd for $C_{23}H_{22}F_3N_3O_3$ (445.44): C: 62.02, H: 4.98, N: 9.43; Found C: 62.08, H: 4.96, N: 9.50.

1-(2-(4-(3-Methoxyphenyl)piperazin-1-yl)-2-oxo-1-phenylethyl)pyrrolidine-2,5-dione (24). White solid. Yield: 73% (1.78 g); mp. 161.4–162.7ºC; TLC: R_f = 0.36 (S_2); UPLC (purity 100%): t_R = 5.87 min. LC-MS (ESI): *m/z* calcd for $C_{23}H_{25}N_3O_4$ $(M+H)^+$ 408.18, found 408.2. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.63–2.75 (m, 5H; 4H, imide, 1H, piperazine), 2.92–3.11 (m, 3H, piperazine), 3.19–3.33 (m, 2H, piperazine), 3.61–3.72 (m, 1H, piperazine), 3.73 (s, 3H, OCH_3), 3.87–4.00 (m, 1H, piperazine), 6.09 (s, 1H, C<u>H</u>CO), 6.34 (t, 1H, *J*=2.3 Hz, ArH), 6.38–6.45 (m, 2H, ArH), 7.12 (t, 1H, *J*=8.2 Hz, ArH), 7.27–7.44 (m, 5H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 28.0, 42.4, 45.7, 48.8, 49.0, 55.2, 56.7, 103.1, 105.3, 109.2, 128.6, 128.9, 129.8, 129.9, 132.8, 152.0, 160.5, 165.1, 176.5. Anal. calcd for $C_{23}H_{25}N_3O_4$ (407.47): C: 67.80, H: 6.18, N: 10.31; Found C: 67.85, H: 6.20, N: 10.29.

1-(2-Oxo-1-phenyl-2-(4-(3-(trifluoromethoxy)phenyl)piperazin-1-yl)ethyl)pyrrolidine-2,5-dione (25). White solid. Yield: 89% (2.46 g); mp. 100.3–101.6ºC; TLC: R_f = 0.42 (S_2); UPLC (purity 100%): t_R = 7.13 min. LC-MS (ESI): *m/z* calcd for $C_{23}H_{22}F_3N_3O_4$ $(M+H)^+$ 462.16, found 462.2. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.63–2.79 (m, 5H; 4H, imide, 1H, piperazine), 3.00–3.16 (m, 2H, piperazine), 3.22–3.39 (m, 3H, piperazine), 3.93–4.05 (m, 1H, piperazine), 3.63–3.75 (m, 1H, piperazine), 6.12 (s, 1H, C<u>H</u>CO), 6.62 (s, 1H, ArH), 6.66–6.78 (m, 2H, ArH), 7.16–7.28 (m, 1H, ArH), 7.32–7.48 (m, 5H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 28.0, 42.2, 45.5, 48.3, 48.5, 56.8, 108.8, 112.1, 114.2, 120,4 (q, *J*=256.8 Hz), 128.7, 128.9, 129.8, 130.2,

132.8, 150.2, 151.9, 165.1, 176.3. Anal. calcd for $C_{23}H_{22}F_3N_3O_4$ (461.44): C: 59.87, H: 4.81, N: 9.11; Found C: 59.85, H: 4.79, N: 9.15.

1-(2-(4-(3-(Methylthio)phenyl)piperazin-1-yl)-2-oxo-1-phenylethyl)pyrrolidine-2,5-dione (26). White solid. Yield: 72% (1.82 g); m.p. 88.1–89.2 °C; TLC: R_f = 0.69 (S_3); UPLC (purity 98.55%): t_R = 6.60 min. LC-MS (ESI): *m/z* calcd for $C_{23}H_{25}N_3O_3S$ $(M+H)^+$ 424.16, found 424.1. ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.43 (s, 3H, CH_3), 2.64–2.75 (m, 5H; 4H, imide, 1H, piperazine), 2.97–3.11 (m, 2H, piperazine), 3.22–3.33 (m, 3H, piperazine), 3.63–3.71 (m, 1H, piperazine), 3.98 (ddd, 1H, *J*=13.17, 5.73, 3.44 Hz, piperazine), 6.11 (s, 1H, C<u>H</u>CO), 6.60 (dd, 1H, *J*=8.31, 2.00 Hz, ArH), 6.71 (t, 1H, *J*=2.00 Hz, ArH), 6.75 (d, 1H, *J*=7.66 Hz, ArH), 7.14 (t, 1H, *J*=8.02 Hz, ArH), 7.32–7.36 (m, 3H, ArH), 7.42 (d, 2H, *J*=6.87 Hz, ArH). ^{13}C NMR (126 MHz, $CDCl_3$) δ 15.9, 28.1, 42.5, 45.8, 48.9, 49.1, 56.9, 113.6, 114.9, 118.6, 128.8, 129.0, 129.6, 129.9, 133.0, 139.6, 151.1, 165.1, 176.4. Anal. calcd for $C_{23}H_{25}N_3O_3S$ (423.53): C: 65.23, H: 5.95, N: 9.92; Found C: 65.38, H: 5.87, N: 9.98.

1-(2-Oxo-1-phenyl-2-(4-(3-((trifluoromethyl)thio)phenyl)piperazin-1-yl)ethyl)pyrrolidine-2,5-dione (27). White solid. Yield: 64% (1.83 g); m.p. 97.8–99.2 °C; TLC: R_f = 0.48 (S_3); UPLC (purity 100%): t_R = 7.55 min. LC-MS (ESI): *m/z* calcd for $C_{23}H_{22}F_3N_3O_3S$ $(M+H)^+$ 478.13, found 478.1. ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.64–2.78 (m, 5H; 4H, imide, 1H, piperazine), 3.01–3.07 (m, 1H, piperazine), 3.09–3.15 (m, 1H, piperazine), 3.24–3.32 (m, 2H, piperazine), 3.34 (dd, 1H, *J*= 7.7, 3.2 Hz, piperazine), 3.62–3.75 (m, 1H, piperazine), 3.99 (ddd, 1H, *J*= 13.2, 5.7, 3.4 Hz, piperazine), 6.11 (s, 1H, C<u>H</u>CO), 6.92 (dd, 1H, *J*= 8.0, 2.3 Hz, ArH), 7.06 (s, 1H, ArH), 7.12 (d, 1H, *J*= 7.4 Hz, ArH), 7.24–7.29 (m, 1H, ArH), 7.33–7.38 (m, 3H, ArH), 7.43 (d, 2H, *J*= 6.8 Hz, ArH). ^{13}C NMR (126 MHz, $CDCl_3$) δ 28.1, 45.6, 48.4, 48.7, 56.9, 118.5, 123.7, 125.3, 127.8, 128.5, 129.4 (d, *J*= 141.2 Hz), 129.6 (d, *J*= 137.0 Hz), 130.9, 132.9, 151.4, 165.2, 176.4. Anal. calcd for $C_{23}H_{22}F_3N_3O_3S$ (477.50): C: 57.85, H: 4.64, N: 8.80; Found C: 57.72, H: 4.72, N: 8.73.

1-(2-(4-(3-(Difluoromethyl)phenyl)piperazin-1-yl)-2-oxo-1-phenylethyl)pyrrolidine-2,5-dione (28). White solid. Yield: 83% (2.13g); m.p. 156.4–157.6 °C; TLC: R_f = 0.55 (S_2); UPLC (purity 100%): t_R = 6.36 min. LC-MS (ESI): *m/z* calcd for $C_{23}H_{23}F_2N_3O_3$ $(M+H)^+$ 428.17, found 428.2. ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.68–2.74 (m, 4H, imide), 3.01–3.17 (m, 3H, piperazine), 3.23–3.40 (m, 3H, piperazine), 3.65–3.74 (m, 1H, piperazine), 4.01 (ddd, 1H, *J*=13.17, 5.73, 2.86 Hz, piperazine), 6.12 (s, 1H, C<u>H</u>CO), 6.55 (t, 1H, *J*=56.42 Hz, C<u>H</u>F_2), 6.90–6.94 (m, 2H, ArH), 6.98 (d, 1H, *J*=7.45 Hz, ArH), 7.28–7.38 (m, 4H, ArH), 7.42–7.45 (m, 2H, ArH). ^{13}C NMR (126 MHz, $CDCl_3$) δ 28.1, 42.4, 45.7, 48.8 (d, *J*=29.6 Hz), 56.9, 113.1, 116.2 (d, *J*=341.0 Hz), 118.6, 129.4 (d, *J*=143.1 Hz), 129.4 (d, *J*=86.3 Hz), 133.0, 151.0, 162.3, 165.2, 176.4. Anal. calcd for $C_{23}H_{23}F_2N_3O_3$ (427.45): C: 64.63, H: 5.42, N: 9.83; Found C: 64.51, H: 5.28, N: 9.71.

1-(2-(4-(3-Aminophenyl)piperazin-1-yl)-2-oxo-1-phenylethyl)pyrrolidine-2,5-dione (29). White solid. Yield: 65% (1.53 g); mp. 122.1–123.6ºC; TLC: R_f = 0.48 (S_3); UPLC (purity 98.75%): t_R = 3.32min. LC-MS (ESI): *m/z* calcd for $C_{22}H_{24}N_4O_3$ $(M+H)^+$ 393.19, found 393.2. ^{1}H NMR (300 MHz, 300 MHz, $CDCl_3$) δ 2.56–2.81 (m, 5H; 4H, imide, 1H, piperazine), 2.94–3.10 (m, 3H, piperazine), 3.17–3.36 (m, 3H, piperazine), 3.52–3.72 (m, 1H, piperazine), 5.88 (br. s, 2H, NH_2), 6.04–6.12 (m, 1H, C<u>H</u>CO), 6.23 (dt, 1H, *J* =1.9, 8.3 Hz, ArH), 7.01 (t, 1H, *J*=8.0 Hz, ArH), 7.10 (t, 1H, *J*=8.1 Hz, ArH), 7.31–7.69 (m, 6H, ArH). ^{13}C NMR (75 MHz, $CDCl_3$) δ 28.0, 28.2, 31.0, 42.4, 45.8, 48.6, 48.9, 49.1, 56.8, 59.3, 103.3, 107.1, 107.7, 112.6, 128.6, 128.7, 128.8, 128.9, 129.5, 129.7, 129.8, 129.9, 130.0, 132.9, 133.7, 147.4, 151.3, 151.9, 164.7, 165.0, 176.3, 176.5. Anal. calcd for $C_{22}H_{24}N_4O_3$ (392.45): C: 67.33, H: 6.16, N: 14.28; Found C: 67.30, H: 6.15, N: 14.31.

1-(2-(4-(3-Isopropylphenyl)piperazin-1-yl)-2-oxo-1-phenylethyl)pyrrolidine-2,5-dione (30). White solid. Yield: 72% (1.81g); mp. 149.4–151.2ºC; TLC: R_f = 0.46 (S_2); UPLC (purity 100%): t_R = 7.19 min. LC-MS (ESI): *m/z* calcd for $C_{25}H_{29}N_3O_3$ $(M+H)^+$ 420.22, found 420.3. ^{1}H NMR (300 MHz, 300 MHz, $CDCl_3$) δ 1.09–1.35 (m, 6H, CH($C\underline{H}_3$)$_2$), 2.15 (s, 4H, imide), 2.52–4.10 (m, 9H; 1H, C$\underline{H}$(CH_3)$_2$; 8H, piperazine), 6.12 (s, 1H, C$\underline{H}$CO), 6.57–8.15 (m, 9H, ArH). ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.6, 22.7, 24.0, 28.1, 29.7, 30.5, 30.9, 33.9, 42.9, 46.3, 50.8, 51.1, 51.3, 56.7, 118.0, 118.7, 122.2, 125.8, 127.1, 128.7, 128.8, 129.2, 129.5, 129.8, 129.8, 130.4, 132.9, 148.8, 165.2, 176.5, 207.2. Anal. calcd for $C_{25}H_{29}N_3O_3$ (419.53): C: 71.57, H: 6.97, N: 10.02; Found C: 71.60, H: 6.99, N: 10.04.

1-(2-(4-(3-(*tert*-Butyl)phenyl)piperazin-1-yl)-2-oxo-1-phenylethyl)pyrrolidine-2,5-dione (31). White solid. Yield: 64% (1.66 g); mp. 158.2–160.7ºC; TLC: R_f = 0.42 (S_1); UPLC (purity 97.92%): t_R = 7.63 min. LC-MS (ESI): *m/z* calcd for $C_{26}H_{31}N_3O_3$ $(M+H)^+$ 434.24, found 434.2. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.24–1.35 (m, 9H, C($C\underline{H}_3$)$_3$), 2.71 (s, 4H, imide), 2.87–4.58 (m, 8H, piperazine), 6.08 (s, 1H, C$\underline{H}$CO), 7.29–7.56 (m, 8H, ArH), 7.79 (br. s, 1H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 28.1, 31.1, 35.2, 39.9, 43.2, 54.5, 56.5, 117.6, 118.1, 129.0, 129.3, 129.8, 130.1, 154.5, 165.3, 176.4. Anal. calcd for $C_{26}H_{31}N_3O_3$ (433.55): C: 72.03, H: 7.21, N: 9.69; Found C: 72.10, H: 7.20, N: 9.63.

1-(2-(4-([1,1'-Biphenyl]-3-yl)piperazin-1-yl)-2-oxo-1-phenylethyl)pyrrolidine-2,5-dione (32). White solid. Yield: 82% (2.23 g); mp. 114.1–115.4ºC; TLC: R_f = 0.4 (S_3); UPLC (purity 100%): t_R = 7.40 min. LC-MS (ESI): *m/z* calcd for $C_{28}H_{27}N_3O_3$ $(M+H)^+$ 454.20, found 454.5. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.56–2.81 (m, 5H; 4H, imide, 1H, piperazine), 3.00–3.21 (m, 2H, piperazine), 3.23–3.56 (m, 3H, piperazine), 3.65–3.79 (m, 1H, piperazine), 3.94–4.11 (m, 1H, piperazine), 6.14 (s, 1H, C$\underline{H}$CO), 6.83 (dd, 1H, *J* = 8.1, 2.0 Hz, ArH), 7.00–7.17 (m, 2H, ArH), 7.27–7.62 (m, 11H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 28.1, 42.5, 45.8, 49.0, 49.2, 56.8, 115.4, 115.6, 119.7, 127.2, 127.4, 128.7, 128.8, 129.6, 129.9, 132.9, 141.4, 142.5, 151.1, 165.0, 176.4. Anal. calcd for $C_{28}H_{27}N_3O_3$ (453.54): C: 74.15, H: 6.00, N: 9.27; Found C: 74.12, H: 6.03, N: 9.25.

1-(2-(4-(3-(Benzyloxy)phenyl)piperazin-1-yl)-2-oxo-1-phenylethyl)pyrrolidine-2,5-dione (33). White solid. Yield: 64% (1.86 g); mp. 94.1–95.6ºC; TLC: R_f = 0.49 (S_2); UPLC (purity 100%): t_R = 7.43 min. LC-MS (ESI): *m/z* calcd for $C_{29}H_{29}N_3O_4$ $(M+H)^+$ 484.21, found 484.2. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.59–2.88 (m, 5H; 4H, imide, 1H, piperazine), 3.03–3.22 (m, 2H, piperazine), 3.25–3.55(m, 3H, piperazine), 3.62–3.75 (m, 1H, piperazine), 3.90–4.08 (m, 1H, piperazine), 5.12 (s, 2H, -C$\underline{H}_2$-O-), 6.14 (s, 1H, C$\underline{H}$CO), 6.81–6.90 (m, 1H, ArH), 7.19–7.24 (m, 2H, ArH), 7.26–7.63 (m, 11H, ArH). Anal. calcd for $C_{29}H_{29}N_3O_4$ (483.56): C: 72.03, H: 6.05, N: 8.69; Found C: 72.05, H: 6.07, N: 8.66.

1-(1-(3-Fluorophenyl)-2-oxo-2-(4-(3-(trifluoromethyl)phenyl)piperazin-1-yl)ethyl)pyrrolidine-2,5-dione (34). White solid. Yield: 81% (2.25 g); mp. 134.7–136.1ºC; TLC: R_f = 0.62 (S_3); UPLC (purity 100%): t_R = 7.09 min. LC-MS (ESI): *m/z* calcd for $C_{23}H_{21}F_4N_3O_3$ $(M+H)^+$ 464.15, found 464.0. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.58–2.83 (m, 5H; 4H, imide, 1H, piperazine), 3.00–3.20 (m, 2H, piperazine), 3.22–3.44 (m, 3H, piperazine), 3.64–3.80 (m, 1H, piperazine), 3.90–4.04 (m, 1H, piperazine), 6.09 (s, 1H C$\underline{H}$CO), 6.93–7.15 (m, 5H, ArH), 7.29–7.38 (m, 1H, ArH), 7.39–7.48 (m, 2H, ArH). ^{13}C NMR (75 MHz, $CDCl_3$) δ 28.0, 28.1, 42.3, 45.6, 48.5, 48.6, 56.0, 112.7 (q, *J*=3.4 Hz), 115.6, 115.9, 116.8 (q, *J*=3.4 Hz), 119.3, 124.1 (q, *J*=271.8 Hz), 128.7 (d, *J*=3.4 Hz), 129.7, 131.5 (q, *J*=32.2 Hz), 131.7, 132.8, 150.7, 161.1, 164.4, 164.9, 176.3. ^{19}F NMR (282 MHz, $CDCl_3$) δ -111.83 - -111.78 (m, 1F), -62.78 (br. s, 3F). Anal. calcd for $C_{23}H_{21}F_4N_3O_3$ (463.43): C: 59.61, H: 4.57, N: 9.07; Found C: 59.58, H: 4.55, N: 9.05.

1-(1-(4-Fluorophenyl)-2-oxo-2-(4-(3-(trifluoromethyl)phenyl)piperazin-1-yl)ethyl)pyrrolidine-2,5-dione (35).White solid. Yield: 73% (2.03 g); mp. 88.8–90.7ºC; TLC: R_f = 0.63 (S_3); UPLC (purity 100%): t_R = 7.07 min. LC-MS (ESI): *m/z* calcd for $C_{23}H_{21}F_4N_3O_3$ $(M+H)^+$ 464.15, found 464.1. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.61–2.89 (m, 5H; 4H, imide, 1H, piperazine), 3.02–3.46 (m, 5H, piperazine), 3.67–3.80 (m, 1H, piperazine), 3.88–4.04 (m, 1H, piperazine), 6.09 (s, 1H C<u>H</u>CO), 6.94–7.27 (m, 6H, ArH), 7.29–7.40 (m, 2H, ArH). ^{13}C NMR (75 MHz, $CDCl_3$) δ 28.0, 42.3, 45.6, 48.5, 48.6, 56.0, 112.7 (q, *J*=3.4 Hz), 115.9, 116.2, 116.7 (q, *J*=3.4 Hz), 117.0, 119.3, 124.1 (q, *J*=272.9 Hz), 125.5 (d, *J*=3.4 Hz), 129.7, 130.2, 130.3, 131.5 (q, *J*=31.1 Hz), 135.1 (d, *J*=6.91 Hz), 150.7, 160.9, 164.2, 164.5, 176.23. ^{19}F NMR (282 MHz, $CDCl_3$) δ -111.73 - -111.65 (m, 1F), -62.77 (br. s, 3F). Anal. calcd for $C_{23}H_{21}F_4N_3O_3$ (463.43): C: 59.61, H: 4.57, N: 9.07; Found C: 59.61, H: 4.60, N: 9.09.

1-(1-(3,4-Difluorophenyl)-2-oxo-2-(4-(3-(trifluoromethyl)phenyl)piperazin-1-yl)ethyl)pyrrolidine-2,5-dione (36). White solid. Yield: 85% (2.45 g); mp. 145.6–146.7ºC; TLC: R_f = 0.63 (S_3); UPLC (purity 100%): t_R = 7.24 min. LC-MS (ESI): *m/z* calcd for $C_{23}H_{20}F_5N_3O_3$ $(M+H)^+$ 482.15, found 482.1. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.68–2.93 (m, 5H; 4H, imide, 1H, piperazine), 3.03–3.47 (m, 5H, piperazine), 3.68–3.82 (m, 1H, piperazine), 3.85–4.00 (m, 1H, piperazine), 6.04 (s, 1H, C<u>H</u>CO), 6.94–7.07 (m, 2H, ArH), 7.09–7.22 (m, 3H, ArH), 7.25–7.43 (m, 2H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 28.0, 42.4, 45.6, 48.6, 55.5, 112.8 (q, *J*=3.5 Hz), 116.9 (q, *J*=3.5 Hz), 117.4, 117.7, 118.7, 119.0, 119.2, 119.3, 122.3, 125.9, 126.2 (dd, *J*=5.8, 3.5 Hz), 129.5, 129.8, 129.9, 131.6 (q, *J*=32.2 Hz), 148.6 (dd, *J*=31.1, 15.0 Hz) 150.7, 152.0 (dd, *J*=32.8, 14.4 Hz), 164.3, 176.2.^{19}F NMR (282 MHz, $CDCl_3$) δ -136.47 - -135.80 (m, 2F) -62.77 (br. s, 3F). Anal. calcd for $C_{23}H_{20}F_5N_3O_3$ (481.42): C: 57.38, H: 4.19, N: 8.73; Found C: 57.40, H: 4.17, N: 8.71.

1-(1-Oxo-3-phenyl-1-(4-phenylpiperazin-1-yl)propan-2-yl)pyrrolidine-2,5-dione (37). White solid. Yield: 87% (2.04 g); mp. 121.7–123.2ºC; TLC: R_f = 0.62 (S_3); UPLC (purity 100%): t_R = 6.19 min. LC-MS (ESI): *m/z* calcd for $C_{23}H_{25}N_3O_3$ $(M+H)^+$ 392.19, found 392.4. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.49–2.61 (m, 4H, imide), 2.95–3.20 (m, 4H, piperazine), 3.31–3.89 (m, 6H, piperazine, -C<u>H</u>$_2$-), 5.19 (dd, 1H, *J*=10.3, 6.2 Hz, C<u>H</u>CO), 6.83–6.96 (m, 3H, ArH), 7.13–7.33 (m, 7H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 27.8, 34.2, 42.5, 45.4, 49.3, 49.6, 52.9, 116.6, 120.7, 127.1, 128.6, 129.1, 129.3, 136.7, 150.7, 166.4, 176.5. Anal. calcd for $C_{23}H_{25}N_3O_3$ (391.46): C: 70.57, H: 6.44, N: 10.73; Found C: 70.60, H: 6.42, N: 10.71.

1-(1-(4-(3-Chlorophenyl)piperazin-1-yl)-1-oxo-3-phenylpropan-2-yl)pyrrolidine-2,5-dione (38). White solid. Yield: 87% (2.21 g); mp. 114.3–116.2ºC; TLC: R_f = 0.8 (S_3); UPLC (purity 100%): t_R = 6.95 min. LC-MS (ESI): *m/z* calcd for $C_{23}H_{24}ClN_3O_3$ $(M+H)^+$ 426.15, found 426.3. ^{1}H NMR (300 MHz, $CDCl_3$) 2.49–2.64 (m, 4H, imide), 2.95–3.21 (m, 4H, piperazine), 3.30–3.86 (m, 6H; 4H, piperazine, 2H, -C<u>H</u>$_2$-), 5.17 (dd, 1H, *J*=10.0, 6.2 Hz, C<u>H</u>CO), 6.73 (ddd, 1H, *J*=8.3, 2.2, 0.9 Hz, ArH), 6.79–6.88 (m, 2H, ArH), 7.06–7.35 (m, 6H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 27.8, 34.2, 42.2, 45.2, 48.7, 49.0, 52.9, 114.4, 116.3, 120.2, 127.1, 128.6, 129.1, 130.2, 135.0, 136.6, 151.7, 166.4, 176.5. Anal. calcd for $C_{23}H_{24}ClN_3O_3$ (425.91): C: 64.86, H: 5.68, N: 9.87; Found C: 64.83, H: 5.70, N: 9.86.

1-(1-Oxo-3-phenyl-1-(4-(m-tolyl)piperazin-1-yl)propan-2-yl)pyrrolidine-2,5-dione (39). White solid. Yield: 75% (1.82 g); 123.8–125.1ºC; TLC: R_f = 0.65 (S_3); UPLC (purity 100%): t_R = 6.62 min. LC-MS (ESI): *m/z* calcd for $C_{24}H_{27}N_3O_3$ $(M+H)^+$ 406.2, found 406.3. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.31 (s, 3H, CH_3), 2.46–2.65 (m, 4H, imide), 2.97–3.19 (m, 4H, piperazine), 3.30–3.86 (m, 6H; 4H, piperazine; 2H, -C<u>H</u>$_2$-), 5.19 (dd, 1H, *J*=10.2, 6.0 Hz, C<u>H</u>CO), 6.65–6.76 (m, 3H, ArH), 7.11–7.32 (m, 6H, ArH). ^{13}C NMR (75 MHz, $CDCl_3$) δ 27.8, 34.2, 42.5, 45.4, 49.4, 49.7, 53.0, 115.5, 115.7, 119.7, 127.1, 127.2, 127.4, 128.6, 128.7, 129.1, 129.6, 136.7, 141.4, 142.5, 151.1, 166.4, 176.5 Anal. calcd for $C_{24}H_{27}N_3O_3$ (405.49): C: 71.09, H: 6.71, N: 10.36; Found C: 71.12, H: 6.73, N: 10.40.

1-(1-Oxo-3-phenyl-1-(4-(3-(trifluoromethyl)phenyl)piperazin-1-yl)propan-2-yl)pyrrolidine-2,5-dione (40). White solid. Yield: 84% (2.31 g); mp. 126.1–127.2ºC; TLC: R_f = 0.72 (S_3); UPLC (purity 100%): t_R = 7.19 min. LC-MS (ESI): *m/z* calcd for $C_{24}H_{24}F_3N_3O_3$ $(M+H)^+$ 460.18, found 460.3. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.44–2.64 (m, 4H, imide), 3.00–3.24 (m, 4H, piperazine), 3.32–3.89 (m, 6H; 4H, piperazine, 2H, C<u>H</u>$_2$-ArH), 5.18 (dd, 1H, *J*=10.0, 6.2 Hz, C<u>H</u>CO), 6.94–7.42 (m, 9H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 27.8, 34.2, 42.2, 45.2, 48.7, 49.0, 52.9, 112.7 (q, *J*=3.4 Hz), 116.8 (q, *J*=3.4 Hz), 124.1 (q, *J*=271.8 Hz), 127.1, 128.6, 129.1, 129.7, 131.5 (q, *J*=32.2 Hz), 136.6, 150.8, 166,5, 176.5; ^{19}F NMR (282 MHz, $CDCl_3$) δ -62.76 (br. s, 3F). Anal. calcd for $C_{24}H_{24}F_3N_3O_3$ (459.47): C: 62.74, H: 5.27, N: 9.15; Found C: 62.72, H: 5.25, N: 9.13.

1-(1-Oxo-3-phenyl-1-(4-(3-(trifluoromethoxy)phenyl)piperazin-1-yl)propan-2-yl)pyrrolidine-2,5-dione (41). White solid. Yield: 83% (2.36 g); mp. 104.4–105.5ºC; TLC: R_f = 0.71 (S_3); UPLC (purity 100%): t_R = 7.37 min. LC-MS (ESI): *m/z* calcd for $C_{24}H_{24}F_3N_3O_4$ $(M+H)^+$ 476.17, found 476.3. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.41–2.73 (m, 4H, imide), 2.94–3.22 (m, 4H, piperazine), 3.31–3.86 (m, 6H; 4H, piperazine, 2H, -C<u>H</u>$_2$-), 5.18 (dd, 1H, *J*=10.0, 6.2 Hz, C<u>H</u>CO), 6.62–6.85 (m, 3H, ArH), 7.11–7.36 (m, 6H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 27.8, 34.2, 42.2, 45.2, 48.6, 48.9, 52.9, 108.8, 112.2, 114,2, 120.4 (q, *J*=256.8 Hz), 127.1, 128.6, 129.1, 130.2, 136.6, 150.2, 151.9, 166.5, 176.5; ^{19}F NMR (282 MHz, $CDCl_3$) δ -57.6 (br. s, 3F). Anal. calcd for $C_{24}H_{24}F_3N_3O_4$ (475.47): C: 60.63, H: 5.09, N: 8.84; Found C: 60.61, H: 5.08, N: 8.82.

1-(2-(4-(2,3-Dichlorophenyl)piperazin-1-yl)-2-oxo-1-phenylethyl)pyrrolidine-2,5-dione (42). White solid. Yield: 81% (2.17 g); mp.164.2–165.8ºC; TLC: R_f = 0.33 (S_2); UPLC (purity 100%): t_R = 7.24 min. LC-MS (ESI): *m/z* calcd for $C_{22}H_{21}Cl_2N_3O_3$ $(M+H)^+$ 446.10, found 446.4. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.54–2.89 (m, 6H; 4H, imide, 2H, piperazine), 2.91–3.11 (m, 2H, piperazine), 3.19–3.30 (m, 1H, piperazine), 3.32–3.45 (m, 1H, piperazine), 3.75–3.99 (m, 2H, piperazine), 6.12 (s, 1H, C<u>H</u>CO), 6.84 (dd, 1H, *J*=7.5, 2.0 Hz, ArH), 7.07–7.20 (m, 2H, ArH), 7.27–7.48 (m, 5H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 28.0, 42.7, 46.1, 50.9, 51.0, 56.8, 118.7, 125.2, 127.5, 127.7, 128.6, 128.8, 129.8, 132.9, 134.2, 150.3, 165.1, 176.3. Anal. calcd for $C_{22}H_{21}Cl_2N_3O_3$ (446.33): C: 59.20, H: 4.74, N: 9.41; Found C: 59.15, H: 4.75, N: 9.50.

1-(2-(4-(3,4-Dichlorophenyl)piperazin-1-yl)-2-oxo-1-phenylethyl)pyrrolidine-2,5-dione (43). White solid. Yield: 79% (2.11 g); mp. 177.1–177.8ºC; TLC: R_f = 0.33 (S_2); UPLC (purity 100%): t_R = 7.19 min. LC-MS (ESI): *m/z* calcd for $C_{22}H_{21}Cl_2N_3O_3$ $(M+H)^+$ 446.10, found 446.3. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.59–2.81 (m, 5H; 4H, imide, 1H, piperazine), 2.89–3.13 (m, 2H, piperazine), 3.15–3.40 (m, 3H, piperazine), 3.60–3.73 (m, 1H, piperazine), 3.91–4.04 (m, 1H, piperazine), 6.10 (s, 1H, C<u>H</u>CO), 6.64 (dd, 1H, *J*=8.9, 2.9 Hz, ArH), 6.86 (d, 1H, *J*=2.9 Hz, ArH), 7.23 (s, 1H, ArH), 7.29–7.46 (m, 5H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 28.0, 42.1, 45.4, 48.4, 48.6, 56.7, 115.8, 117.8, 123.1, 128.7, 129.0, 129.8, 130.6, 132.8, 132.9, 150.0, 165.1, 176.3. Anal. calcd for $C_{22}H_{21}Cl_2N_3O_3$ (446.33): C: 59.20, H: 4.74, N: 9.41; Found C: 59.16, H: 4.70, N: 9.51.

1-(2-(4-(3,5-dichlorophenyl)piperazin-1-yl)-2-oxo-1-phenylethyl)pyrrolidine-2,5-dione (44). White solid. Yield: 77% (2.06 g); m.p. 163.8–165.2°C; TLC: R_f = 0.42 (S_2); UPLC (purity 100%): t_R = 7.58 min. LC-MS (ESI): *m/z* calcd for $C_{22}H_{21}Cl_2N_3O_3$ $(M+H)^+$ 446.10, found 446.1. ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.63–2.78 (m, 5H; 4H, imide, 1H, piperazine), 2.98–3.13 (m, 2H, piperazine), 3.20–3.36 (m, 3H, piperazine), 3.59–3.68 (m, 1H, piperazine), 3.97–4.00 (m, 1H, piperazine), 6.09 (s, 1H, C<u>H</u>CO), 6.64 (d, *J*=1.7 Hz, 2H, ArH), 6.80 (t, *J*=1.7 Hz, 1H, ArH), 7.33–7.38 (m, 3H, ArH), 7.42 (d, *J*=6.7 Hz, 2H, ArH). ^{13}C NMR (126 MHz, $CDCl_3$) δ 28.1, 42.2, 45.4, 48.0, 48.2, 56.9, 114.4, 119.8, 128.8, 129.1, 129.9, 132.9, 135.6, 152.1, 165.2, 176.4. Anal. calcd for $C_{22}H_{21}Cl_2N_3O_3$ (446.33) C, 59.20; H, 4.74; N, 9.41; Found C: 59.33, H: 4.59, N: 9.28.

1-(2-(4-(3,5-bis(trifluoromethyl)phenyl)piperazin-1-yl)-2-oxo-1-phenylethyl)pyrrolidine-2,5-dione (45). White solid. Yield: 69% (2.12 g); m.p. 228.1–229.4 °C; TLC: R_f = 0.47 (S_3); UPLC (purity 100%): t_R = 6.57 min. LC-MS (ESI): *m/z* calcd for $C_{24}H_{21}F_6N_3O_3$ $(M+H)^+$ 514.10, found 514.4. ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.64–2.79 (m, 4H, imide), 3.04–3.15 (m, 3H, piperazine), 3.26–3.42 (m, 3H, piperazine), 3.65–3.74 (m, 1H, piperazine), 3.99–4.07 (m, 1H, piperazine), 6.12 (s, 1H, C<u>H</u>CO), 7.15 (s, 2H, ArH), 7.34–7.38 (m, 4H, ArH), 7.43–7.45 (m, 2H, ArH). ^{13}C NMR (126 MHz, $CDCl_3$) δ 28.1, 42.1, 45.4, 48.0 (d, *J*=27.2 Hz), 56.9, 113.0 (d, *J*=3.6 Hz), 115.2, 123.4 (q, *J*=272.4 Hz), 128.9, 129.2, 129.9, 132.6 (q, *J*=32.6 Hz), 132.8, 151.2, 165.3, 176.4. Anal. calcd for $C_{24}H_{21}F_6N_3O_3$ (513.44) C, 56.14; H, 4.12; N, 8.18; Found C: 56.31, H: 4.25, N: 8.11.

1-(2-(4-(3,5-bis((trifluoromethyl)thio)phenyl)piperazin-1-yl)-2-oxo-1-phenylethyl)pyrrolidine-2,5-dione (46). White solid. Yield: 64% (2.21 g); m.p. 232.1–233.6 °C; TLC: R_f = 0.51 (S_3); UPLC (purity 100%): t_R = 6.50 min. LC-MS (ESI): *m/z* calcd for $C_{24}H_{21}F_6N_3O_3S_2$ $(M+H)^+$ 578.21 found 578.2. ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.65–2.75 (m, 4H, imide), 3.10–3.32 (m, 4H, piperazine), 3.56–3.75 (m, 3H, piperazine), 3.89–4.03 (m, 1H, piperazine), 6.12 (s, 1H, C<u>H</u>CO), 6.64–6.58 (m, 2H, ArH), 6.93–7.12 (m, 2H, ArH), 7.28–7.57 (m, 4H, ArH). ^{13}C NMR (126 MHz, $CDCl_3$) δ 28.2, 42.2, 45.4, 48.3 (d, *J*=27.1 Hz), 56.8, 113.0 (d, *J*=3.5 Hz), 115.2, 124.6 (q, *J*=271.4 Hz), 128.7, 129.2, 129.8, 132.7, 132.9, 151.9, 165.1, 176.5. Anal. calcd for $C_{24}H_{21}F_6N_3O_3S_2$ (577.56) C, 49.91; H, 3.67; N, 7.28; Found C: 49.64, H: 3.72, N: 7.35.

1-(2-(4-(3-chloro-5-(trifluoromethyl)phenyl)piperazin-1-yl)-2-oxo-1-phenylethyl)pyrrolidine-2,5-dione (47). White solid. Yield: 69% (1.98 g); mp. 214.8–215.5ºC; TLC: R_f = 0.43 (S_3); UPLC (purity 100%): t_R = 7.71 min. LC-MS (ESI): *m/z* calcd for $C_{23}H_{21}ClF_3N_3O_3$ $(M+H)^+$ 480.12, found 480.2. ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.66–2.76 (m, 5H; 4H, imide, 1H, piperazine), 3.04–3.20 (m, 2H, piperazine), 3.24–3.39 (m, 3H, piperazine), 3.62–3.71 (m, 1H, piperazine), 3.96–4.06 (m, 1H, piperazine), 6.10 (s, 1H, C<u>H</u>CO), 6.86–6.93 (m, 2H, ArH), 7.04 (s, 1H, ArH), 7.33–7.38 (m, 3H, ArH), 7.43 (d, 2H, *J*=6.75 Hz, ArH). ^{13}C NMR (126 MHz, $CDCl_3$) δ 28.1, 42.2, 45.4, 47.9, 48.2, 56.9, 110.8 (d, *J*=4.2 Hz), 116.5 (d, *J*=3.6 Hz), 118.7, 123.4 (q, *J*=273.2 Hz), 128.8, 129.1, 129.9, 132.8 (d, *J*=32.6 Hz), 132.9, 135.8, 151.7, 165.2, 176.4.

1-(2-Oxo-1-phenyl-2-(4-(3-(trifluoromethyl)phenyl)piperidin-1-yl)ethyl)pyrrolidine-2,5-dione (48). White solid. Yield: 85% (2,26 g); mp. 100.1–101.5ºC; TLC: R_f = 0.45 (S_3); UPLC (purity 100%): t_R = 7.24 min. LC-MS (ESI): *m/z* calcd for $C_{24}H_{23}F_3N_2O_3$ $(M+H)^+$ 445.17, found 445.1. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.24–2.04 (m, 3H, piperidin), 2.64–2.80 (m, 8H; 4H, imide, 4H, piperidin), 2.98–3.13 (m, 1H, piperidin), 3.63 (t, *J*=14.4 Hz, 1H, piperidin), 4.71–4.95 (m, 1H, piperidin) 6.14 (d, 1H, *J*=9.4 Hz, C<u>H</u>CO), 7.31–7.54 (m, 9H, ArH); Anal. calcd for $C_{24}H_{23}F_3N_2O_3$ (444.45): C: 64.86, H: 5.22, N: 6.30; Found C: 64.77, H: 5.19, N: 6.45.

1-(2-Oxo-1-phenyl-2-(4-(3-(trifluoromethyl)phenyl)-1,4-diazepan-1-yl)ethyl)pyrrolidine-2,5-dione (49). White solid. Yield: 83% (2,28 g); mp. 80.5–81.2ºC; TLC: R_f = 0.50 (S_3); UPLC (purity 100%): t_R = 7.04 min. LC-MS (ESI): *m/z* calcd for $C_{24}H_{24}F_3N_3O_3$ $(M+H)^+$ 460.18, found 460.2. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.06–2.13 (m, 1H, 1,4-diazepane), 2.63–2.75 (m, 4H, imide), 3.17–3.30 (m, 2H, 1,4-diazepane), 3.32–3.62 (m, 5H, 1,4-diazepane), 3.73–3.90 (m, 2H, 1,4-diazepane), 5.93–6.18 (m, 1H, C<u>H</u>CO), 6.74–6.84 (m, 1H, ArH), 6.93 (t, 1H, *J*=7.0 Hz, ArH), 7.19–7.35 (m, 5H, ArH), 7.39–7.44 (m, 2H, ArH). Anal. calcd for $C_{24}H_{24}F_3N_3O_3$ (459.47): C, 62.74; H, 5.27; N, 9.15; Found C: 62.77, H: 5.35, N: 9.04.

1-(3-(4-(3-(Trifluoromethyl)phenyl)piperazine-1-carbonyl)phenyl)pyrrolidine-2,5-dione (52). White solid. Yield: 60% (1.55 g); mp. 126.9–128.5ºC; TLC: R_f = 0.31 (S_2); UPLC (purity 100%): t_R = 6.27 min. LC-MS (ESI): *m/z* calcd for $C_{22}H_{20}F_3N_3O_3$ $(M+H)^+$ 432.15, found 432.2. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.88 (s, 4H, imide), 3.24 (br. s, 4H, piperazine), 3.50–4.05 (m, 4H, piperazine), 6.99–7.18 (m, 3H, ArH), 7.30–7.46 (m, 3H, ArH), 7.47–7.59 (m, 2H, ArH); ^{19}F NMR (282 MHz, $CDCl_3$) δ -62.70 (br. s, 3F). Anal. calcd for $C_{22}H_{20}F_3N_3O_3$ (431.42): C: 61.25, H: 4.67, N: 9.74; Found C: 61.24, H: 4.65, N: 9.76.

1-(4-(4-(3-(Trifluoromethyl)phenyl)piperazine-1-carbonyl)phenyl)pyrrolidine-2,5-dione (53). White solid. Yield: 82% (2.12 g); mp. 196.0–197.5ºC; TLC: R_f = 0.47 (S_2); UPLC (purity 99.40%): t_R = 6.34 min. LC-MS (ESI): *m/z* calcd for $C_{22}H_{20}F_3N_3O_3$ $(M+H)^+$ 432.15, found 432.1. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.83–2.93 (m, 4H, imide), 3.03–3.38 (m, 4H, piperazine), 3.49–4.05 (m, 4H, piperazine), 7.01–7.19 (m, 3H, ArH), 7.31–7.45 (m, 3H, ArH), 7.49–7.59 (m, 2H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 28.4, 49.2, 112.8 (q, *J*=3.4 Hz), 116.8 (q, *J*=3.4 Hz), 119.5, 124.1 (q, *J*=272.9 Hz), 126.5, 128.0, 129.7, 131.5 (q, *J*=31.1 Hz), 133.3, 135.4, 151.0, 169.3, 175.8; ^{19}F NMR (282 MHz, $CDCl_3$) δ -62.72 (s, 3F). Anal. calcd for $C_{22}H_{20}F_3N_3O_3$ (431.42): C: 61.25, H: 4.67, N: 9.74; Found C: 61.27, H: 4.69, N: 9.75.

Table S1. Anticonvulsant activity–MES and 6 Hz (32 mA) tests in mice *i.p.* (dose of 100 mg/kg) – compounds **11**–**47**

Compd	n	R	R^1	R^2	MES test		6 Hz (32 mA) test	
					Pretreatment times (h)[a]		Pretreatment time (h)[a]	
					0.5	2.0	0.5	2.0
11	0	H	H	-	**4/4**	0/4	**3/4**	0/4
12	0	H	2-Cl	-	0/4	**1/4**	-	-
13	0	H	3-Cl	-	**3/4**	0/4	**4/4**	**3/4**
14	0	H	4-Cl	-	0/4	0/4	-	-
15	0	H	2-F	-	0/4	0/4	-	-
16	0	H	3-F	-	**2/4**	0/4	-	-
17	0	H	4-F	-	0/4	**1/4**	-	-
18	0	H	2-CH_3	-	0/4	0/4	-	-
19	0	H	3-CH_3	-	**3/4**	**3/4**	**4/4**	**1/4**
20	0	H	4-CH_3	-	**3/4**	**2/4**	**1/4**	0/4
21	0	H	2-CF_3	-	0/4	0/4	-	-
22	0	H	3-CF_3	-	**4/4**	**4/4**	**4/4**	**2/4**
23	0	H	4-CF_3	-	**3/4**	**2/4**	**3/4**	**2/4**
24	0	H	3-OCH_3	-	**1/4**	**1/4**	-	-
25	0	H	3-OCF_3	-	**4/4**	**4/4**	**4/4**	**1/4**
26	0	H	3-SCH_3	-	**1/4**	**1/4**	-	-
27	0	H	3-SCF_3	-	**4/4**	**4/4**	**4/4**	**2/4**
28	0	H	3-CHF_2	-	**3/4**	**2/4**	**3/4**	**2/4**
29	0	H	3-NH_2	-	0/4	0/4	-	-
30	0	H	$CH(CH_3)_2$	-	**1/4**	**1/4**	-	-
31	0	H	$C(CH3)_3$	-	**2/4**	0/4	-	-
32	0	H	C_6H_5	-	**4/4**	**3/4**	**4/4**	**1/4**
33	0	H	$OCH_2C_6H_5$	-	**1/4**	0/4	-	-
34	0	3-F	3-CF_3	-	**1/4**	**1/4**	-	-
35	0	4-F	3-CF_3	-	**4/4**	**1/4**	**3/4**	0/4
36	0	3,4-F	3-CF_3	-	**1/4**	**1/4**	-	-
37	1	H	H	-	**2/4**	0/4	-	-
38	1	H	3-Cl	-	**2/4**	0/4	-	-
39	1	H	3-CH_3	-	**2/4**	0/4	-	-
40	1	H	3-CF_3	-	**2/4**	**1/4**	-	-
41	1	H	3-OCF_3	-	**2/4**	0/4	-	-
42	-	-	2-Cl	3-Cl	0/4	0/4	-	-
43	-	-	3-Cl	3-Cl	0/4	0/4	-	-
44	-	-	3-Cl	5-Cl	**4/4**	**3/4**	**4/4**	**2/4**
45	-	-	3-CF_3	5-CF_3	**1/4**	**1/4**	-	-
46	-	-	3-SCF_3	5-SCF_3	**1/4**	**1/4**	-	-
47	-	-	3-Cl	5-CF_3	**1/4**	**1/4**	-	-

Ratios where at least one animal was protected have been highlighted in bold for easier data interpretation.
[a] Data indicate: number of mice protected / number of mice tested. The animals were examined at two pretreatment times–0.5 and 2 h. A dash indicates-not tested.

Table S2. Anticonvulsant activity–PTZ test in mice *i.p.* (dose of 100 mg/kg)

Compd	n	R	R^1	R^2	PTZ test	
					Pretreatment times (h)[a]	
					0.5	2.0
11	0	H	H	-	**3/4**	**1/4**
13	0	H	3-Cl	-	**3/4**	**2/4**
19	0	H	3-CH_3	-	**3/4**	**1/4**
22	0	H	3-CF_3	-	**4/4**	**3/4**
23	0	H	4-CF_3	-	**1/4**	**1/4**
25	0	H	3-OCF_3	-	**2/4**	**2/4**
27	0	H	3-SCF_3	-	0/4	0/4
28	0	H	3-CHF_2	-	**3/4**	**1/4**
32	0	H	C_6H_5	-	**2/4**	**2/4**
35	0	4-F	3-CF_3	-	**1/4**	**1/4**
44	-	-	3-Cl	5-Cl	**3/4**	**1/4**

Ratios where at least one animal was protected have been highlighted in bold for easier data interpretation.
[a] Data indicate: number of mice protected / number of mice tested. The animals were examined at two pretreatment times–0.5 and 2 h.

Table S3. Anticonvulsant activity in mice *i.p.* (dose of 100 mg/kg) – compounds **48**, **49**, **52**, and **53**

Cmpd	X	m	MES test		6 Hz (32 mA) test		PTZ test	
			Pretreatment times (h)[a]		Pretreatment time (h)[a]		Pretreatment times (h)[a]	
			0.5	2.0	0.5	2.0	0.5	2.0
48	C	1	**3/4**	**1/4**	**3/4**	**1/4**	**1/4**	0/4
49	N	2	0/4	0/4	-	-	-	-
52	-	-	**2/4**	0/4	-	-	-	-
53	-	-	**1/4**	0/4	-	-	-	-

Ratios where at least one animal was protected have been highlighted in bold for easier data interpretation.
[a] Data indicate: number of mice protected / number of mice tested. The animals were examined at two pretreatment times–0.5 and 2 h. A dash indicates-not tested.

Table S4. The detailed data form *sc*PTZ seizure test for compounds **11**, **13**, **19**, and **22**

Compd	Dose (mg/kg)	Number of seizure episodes	Number of deaths/total	Mortality (%)	Protection (%)
Vehicle	-	20	5/10	50	-
11	60	11	0/6	0	100
	80	5	2/6	33.3	66.7
	120	2*	2/6	33.3	66.7
13	40	6	1/6	16.7	83.3
	60	3	0/6	0	100
	80	1*	0/6	0	100
19	40	6	2/6	33.3	66.7
	60	3	2/6	33.3	66.7
	80	6	1/6	16.7	83.3
22	30	6	1/6	16.7	83.3
	60	8	1/6	16.7	83.3
	80	4	0/6	0	100
vehicle	-	14	3/6	50.0	-
ETX	120	5	0/6	0	100
	150	3	0/6	0	100
	180	1*	0/6	0	100
VPA	200	4	1/6	16.7	83.3
	250	2*	0	0	100
	300	1*	0	0	100

The tested compounds and valproic acid (VPA) were administered *i.p.* 30 min and ethosuximide (ETX) 15 min before the *sc*PTZ test. ETX and VPA were used as positive control (reference drugs). *$p<0.05$ *vs* control group (Fisher's exact test).

Table S5. Binding/functional profile for anticonvulsant active (**27**, **44**) vs. inactive (**26**) compounds

Binding studies	Source	% Inhibition of control specific binding[a] (concentration μM)		
Compd		**26**	**27**	**44**
Na^+ channel (site 2)	rat cerebral cortex	**24.8** (100) **-3.7** (10)	**85.8** (100) **25.1** (10)	**45.8** (100) **2.2** (10)
Functional studies		% Inhibition of control agonist response[a] (concentration μM)		
TRPV1 (VR1) *(h)* (antagonist effect)	human recombinant (CHO cells)	**2.5** (100)	**75.3** (100)	**68.3** (100)
$Cav_{1.2}$ (L-type) *(h)* calcium ion channel cell based antagonist calcium flux assay	human recombinant (HEK-293 cells)	**38.0** (10)	**107.0** (10)	**97.0** (10)

[a] **Results showing activity higher than 50% are considered to represent significant effects of the test compounds**; results showing an inhibition between 25% and 50% are indicative of weak effect; results showing an inhibition lower than 25% are not considered significant and mostly attributable to variability of the signal around the control level. Binding or functional studies were performed commercially in Cerep Laboratories (Poitiers, France).

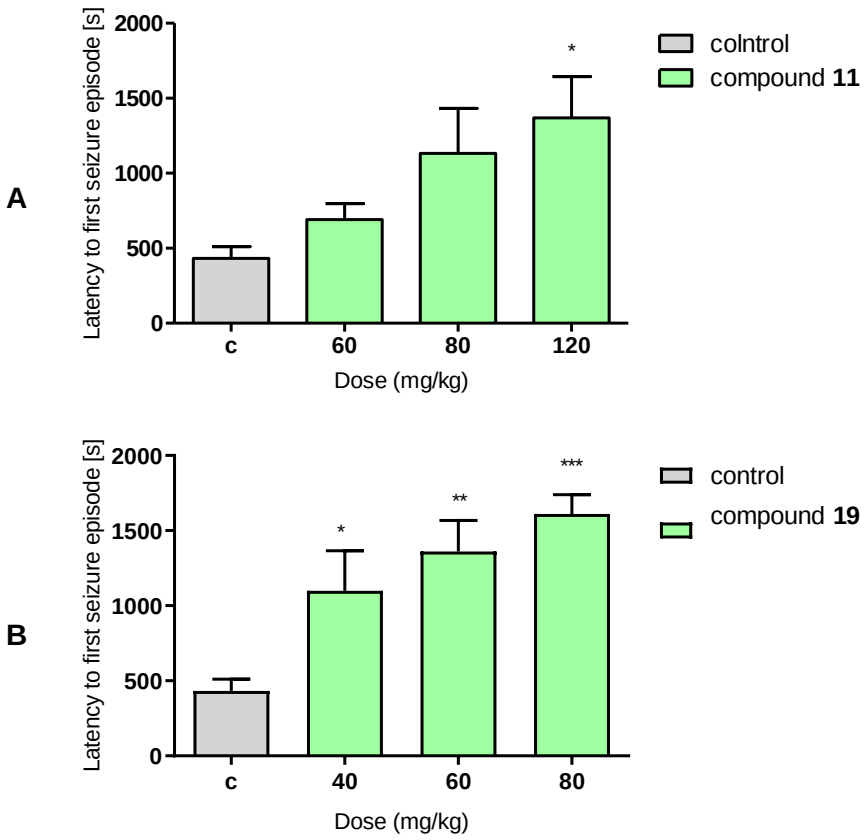

Figure S1 A and **B.** Anticonvulsant activity of compounds **11** and **19** in the *sc*PTZ test. Each value represents the mean ± SEM obtained from 6–10 mice. Statistical analysis: one-way analysis of variance (ANOVA), followed by Dunnett's *post hoc* test. The compounds were administered *i.p.* 0.5 h before the test. Significant difference compared to the control group: *p < 0.05, **p < 0.01, ***p < 0.001.

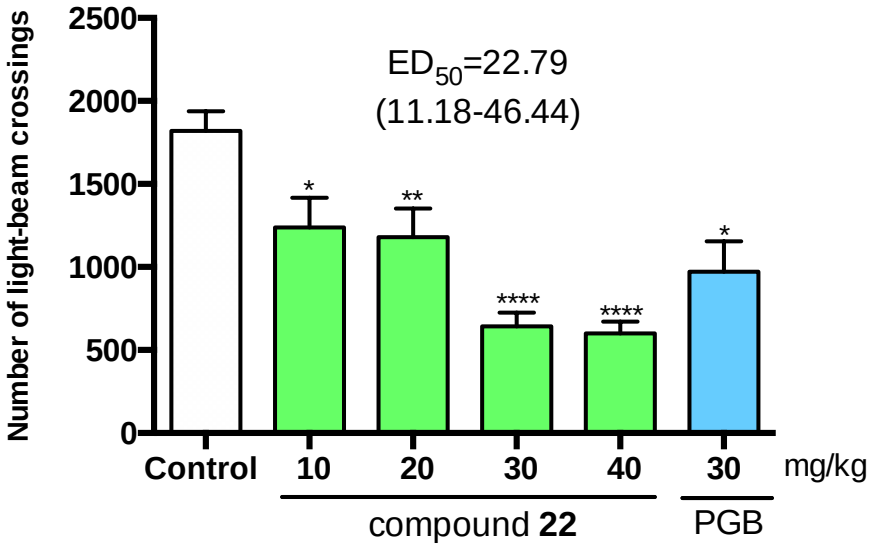

Figure S2. The influence of compound **22** and PGB on spontaneous activity of mice. Results are shown as number of light beam crossings in 30 min period after *i.p.* injection of the test compound. Each value represents the mean ± S.E.M. for 8-10 animals. Statistical analysis: one-way ANOVA followed by *post hoc* Dunnett's test. Statistical significance compared to vehicle-treated animals (Tween): *$p < 0.05$, **$p<0,01$, ****$p < 0.0001$.

The mean number of light-beam crossings in the vehicle-treated animals was $1.82 \pm 0.12 \times 10^3$ measured during the whole 30-min-long period of observation. The values were significantly decreased in animals treated with test compound at doses 10, 20, 30 and 40 mg/kg by 31.94% ($p < 0.05$), 35.18% ($p < 0.01$), 64.64% ($p < 0.0001$) and 66.93% ($p < 0.0001$), respectively. The ED_{50} value obtained in this test was 22.7 mg/kg, it was approximately 1.8-fold higher than the ED_{50} value obtained in the late phase of the formalin test. The administration of PGB at the dose of 30 mg/kg also resulted in a significant decrease in number of light beam crossings by 45.78% ($p < 0.05$).

Compound I.D.		IC_{50} (M)	K_B (M)	nH	Test Concentration	% Inhibition of Control Agonist Response 1st	2nd	Mean
TRPV1 (VR1) *(h)* (antagonist effect)								
100041240-1	KA-104	4.4E-05 M	5.8E-06 M	n/a	3.0E-08 M	-2.9	-5.5	-4.2
					1.0E-07 M	0.8	-11.5	-5.4
					3.0E-07 M	0.4	-9.3	-4.4
					1.0E-06 M	-10.4	-23.6	-17.0
					3.0E-06 M	-19.1	-36.8	-28.0
					1.0E-05 M	-3.7	3.3	-0.2
					3.0E-05 M	15.4	20.2	17.8
					1.0E-04 M	80.9	97.9	89.4

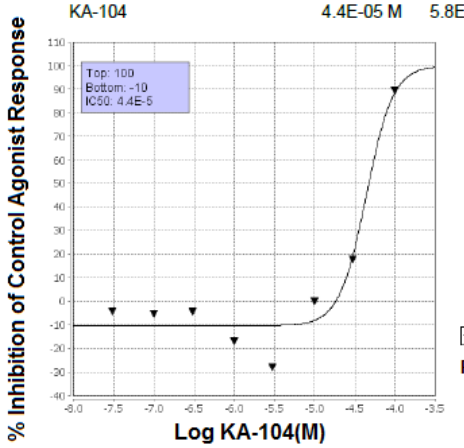

Figure 1. KA-104 on TRPV1 (VR1) *(h)* (antagonist effect)

Figure S3. TRPV1 antagonism - IC_{50} determination and K_B value for compound **22** (studies were performed in Cerep Laboratories (Poitiers, France).

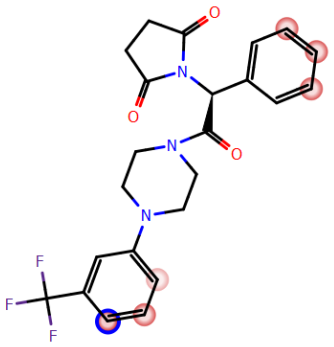

Figure S4. The *in silico* prediction of the most probably sites of metabolism of **22** by using MetaSite 5.1.1 software. The darker red color of the marked functional group indicates its higher probability to be involved in the metabolism pathway. The blue circle marked the site involved in metabolism with the highest probability (100%).

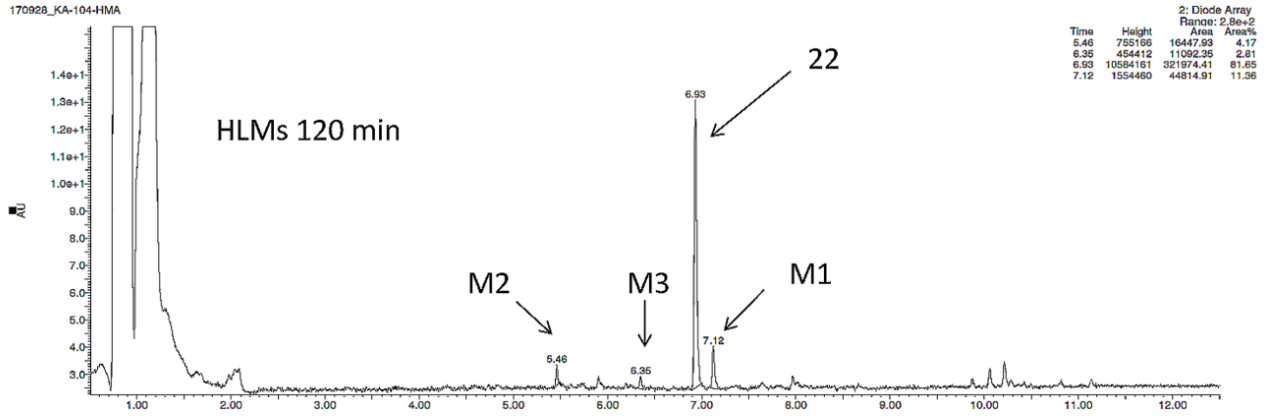

Figure S5. The UPLC spectrum after 120 min reaction of **22** with HLMs. Three metabolites (**M1**–**M3**) were observed. Around 20% of **22** was metabolized with HLMs.

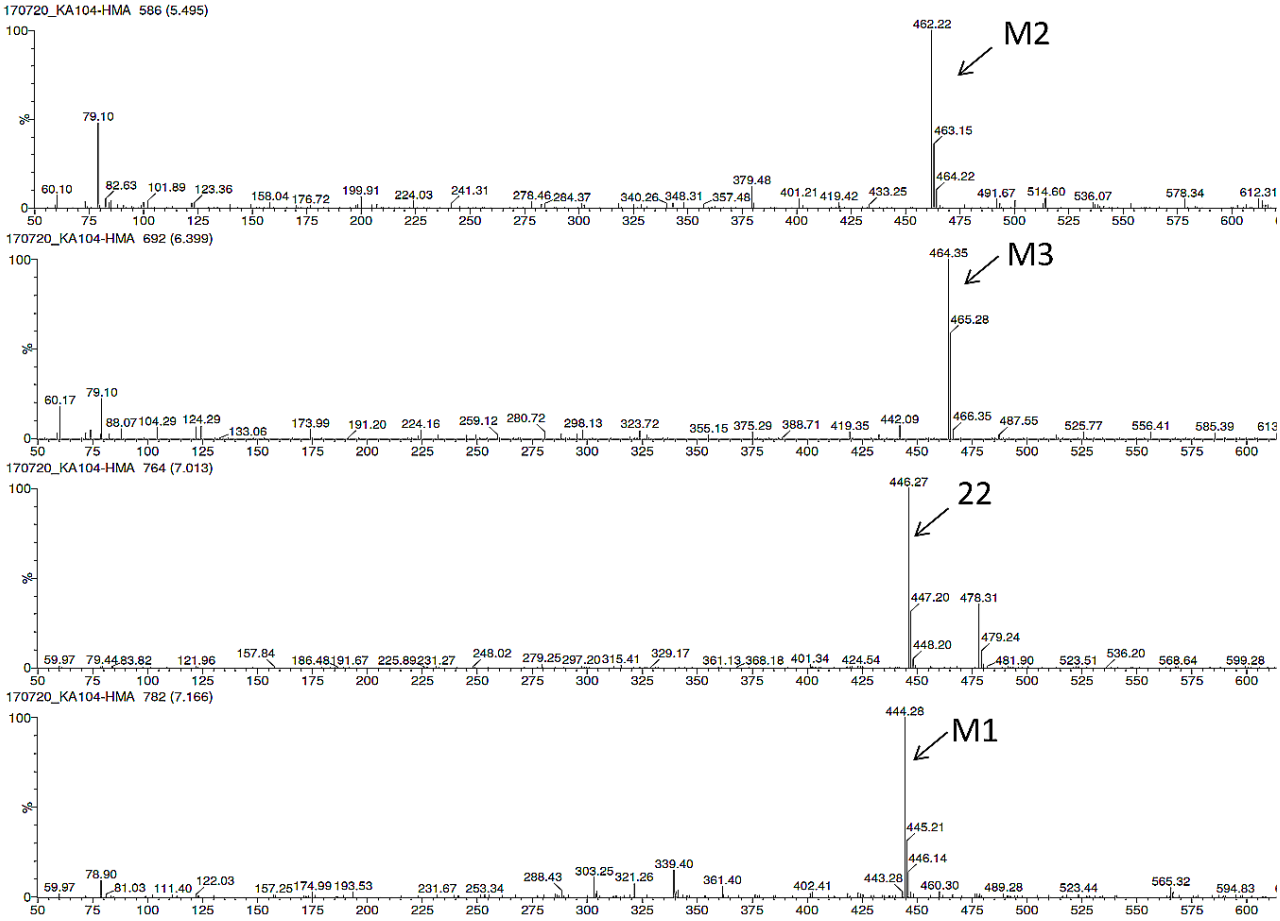

Figure S6. MS spectra of compound **22** and its metabolites **M1**–**M3** obtained after incubation with HLMs.

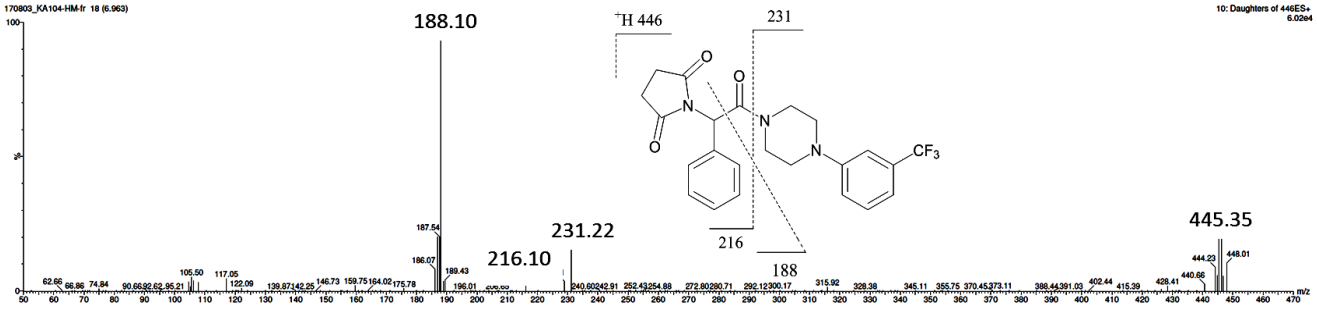

Figure S7. The MS fragmentation analysis of **22**.

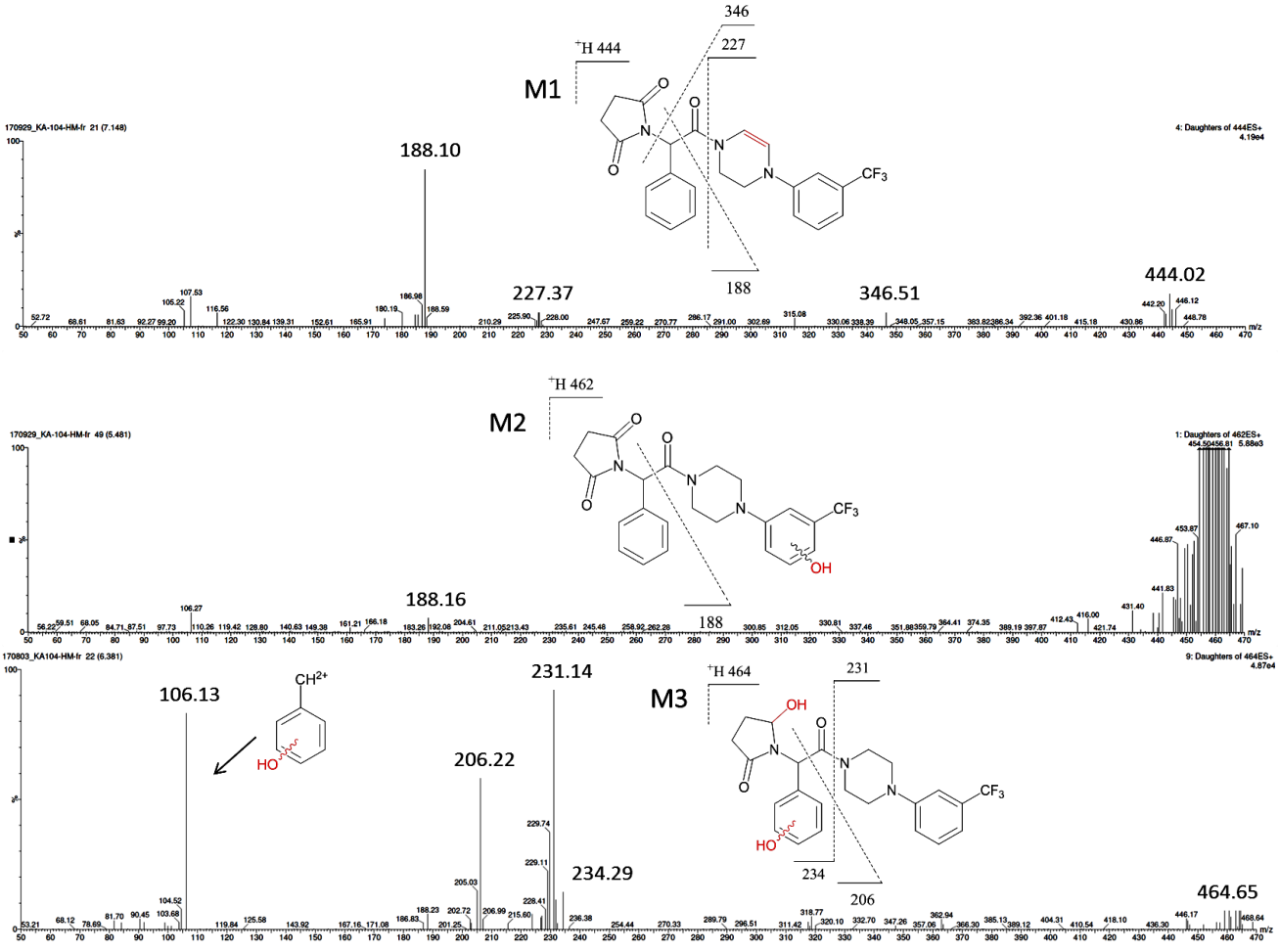

Figure S8. The most probably structures of metabolites **M1**–**M3** based on the MetaSite metabolites' prediction and MS fragmentation analysis.

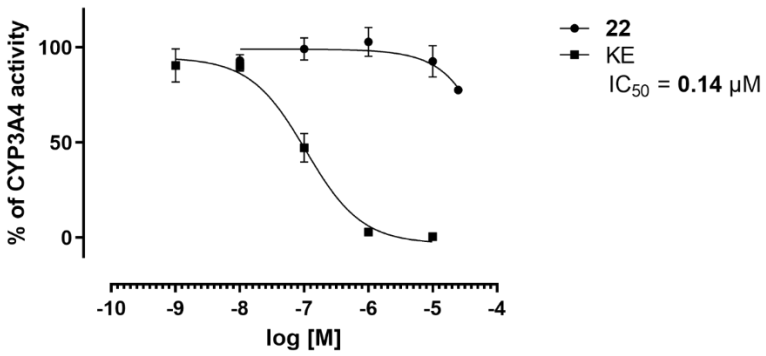

Figure S9. The influence of **22** and the reference inhibitor ketoconazole (KE) on CYP3A4 activity.

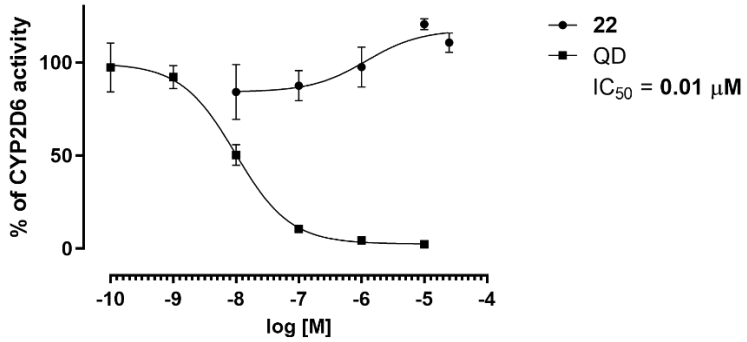

Figure S10. The influence of **22** and the reference inhibitor quinidine (QD) on CYP2D6 activity.

In vitro ADME-Tox studies - materials and methods

Chemicals

The reference compounds used during *in vitro* study, as follows: doxorubicin (DX), caffeine (CFN), carbonyl cyanide 3-chlorophenylhydrazone (CCCP), ketoconazole (KE), norfloxacin (NFX), quinidine (QD) were provided by Sigma-Aldrich (St. Louis, MO, USA).

Metabolic stability

Human liver microsomes (HLMs) were purchased form Sigma-Aldrich (St. Louis, MO, USA). The NADPH Regeneration System was purchased from Promega (Madison, WI, USA). All experiments were performed as described before.[1,2] For determination of the half-life ($t_{1/2}$) and intrinsic clearance (CL_{int}) parameters the four independent reactions with **22** (50 μM) were performed and terminated by the addition of cold methanol containing internal standard (IS) at different points: 5, 15, 30, 45 min. The $t_{1/2}$ and CL_{int} values were calculated using Eq. 1, 2, and 3, according to Obach et al.[3] For the metabolic pathways determination the reactions were terminated after 120 min.

$$t_{1/2} = \frac{ln\,2}{-k} \qquad \textbf{(Eq. 1)}$$

(Eq. 2)

$$CL_{int\ (mouse\ )} = \frac{0.693}{in\ vitro\ t_{1/2}} \times \frac{ml\ incubation}{mg\ microsomes} \times \frac{50\ mg\ microsomes}{gm\ liver} \times \frac{140\ gm\ liver}{kg\ b.w.}$$

$$CL_{int\ (human\ )} = \frac{0.693}{in\ vitro\ t_{1/2}} \times \frac{ml\ incubation}{mg\ microsomes} \times \frac{45\ mg\ microsomes}{gm\ liver} \times \frac{20\ gm\ liver}{kg\ b.w.}$$

Influence on CYP3A4 and CYP2D6 activity

The luminescent CYP3A4 P450-Glo™ and CYP2D6 P450-Glo ™ assays and protocols were provided by Promega (Madison, WI, USA). All experiments were performed as described before.[4] Each compound was tested in triplicate at the final concentrations similar for both CYP3A4 and CYP2D6 assays in range from 0.025 to 25 μM. The IC_{50} values of the reference compounds ketoconazole and quinidine were estimated previously.[5] The luminescent signal was measured by using a microplate reader EnSpire (PerkinElmer, Waltham, MA USA).

Radioligand binding/functional assays

Binding studies were performed commercially in Cerep Laboratories (Poitiers, France) using testing procedures described elsewhere:

Binding studies	Ref.
Na^+ channel (site 2)	6
L-type Ca^{2+} (dihydropyridine site, antagonist radioligand)	7
L-type Ca^{2+} (diltiazem site, antagonist radioligand)	8
L-type Ca^{2+} (verapamil site, antagonist radioligand)	9
NMDA (antagonist radioligand)	10
Na^+ channel (site 1)	11
N-type Ca^{2+} (antagonist radioligand)	12
GABA transporter (antagonist radioligand)	13
Potassium channel (hERG)	14
Functional studies	
TRPV1 (VR1) *(h)* (antagonist effect)	15
$Cav_{1.2}$ (L-type) *(h)* calcium ion channel cell based antagonist calcium flux assay	16,17

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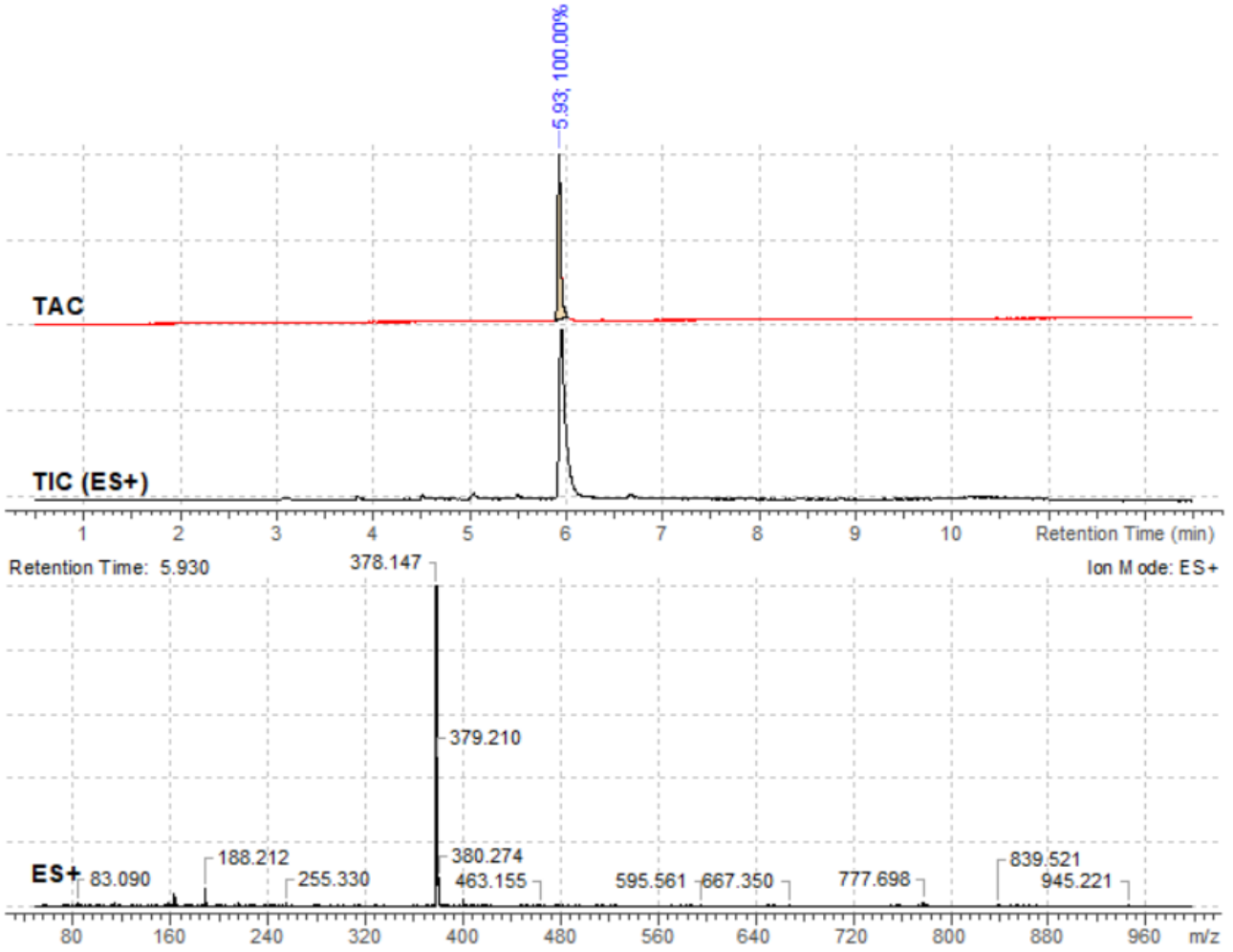
UPLC/MS traces for target compounds

1-(2-Oxo-1-phenyl-2-(4-phenylpiperazin-1-yl)ethyl)pyrrolidine-2,5-dione (11)



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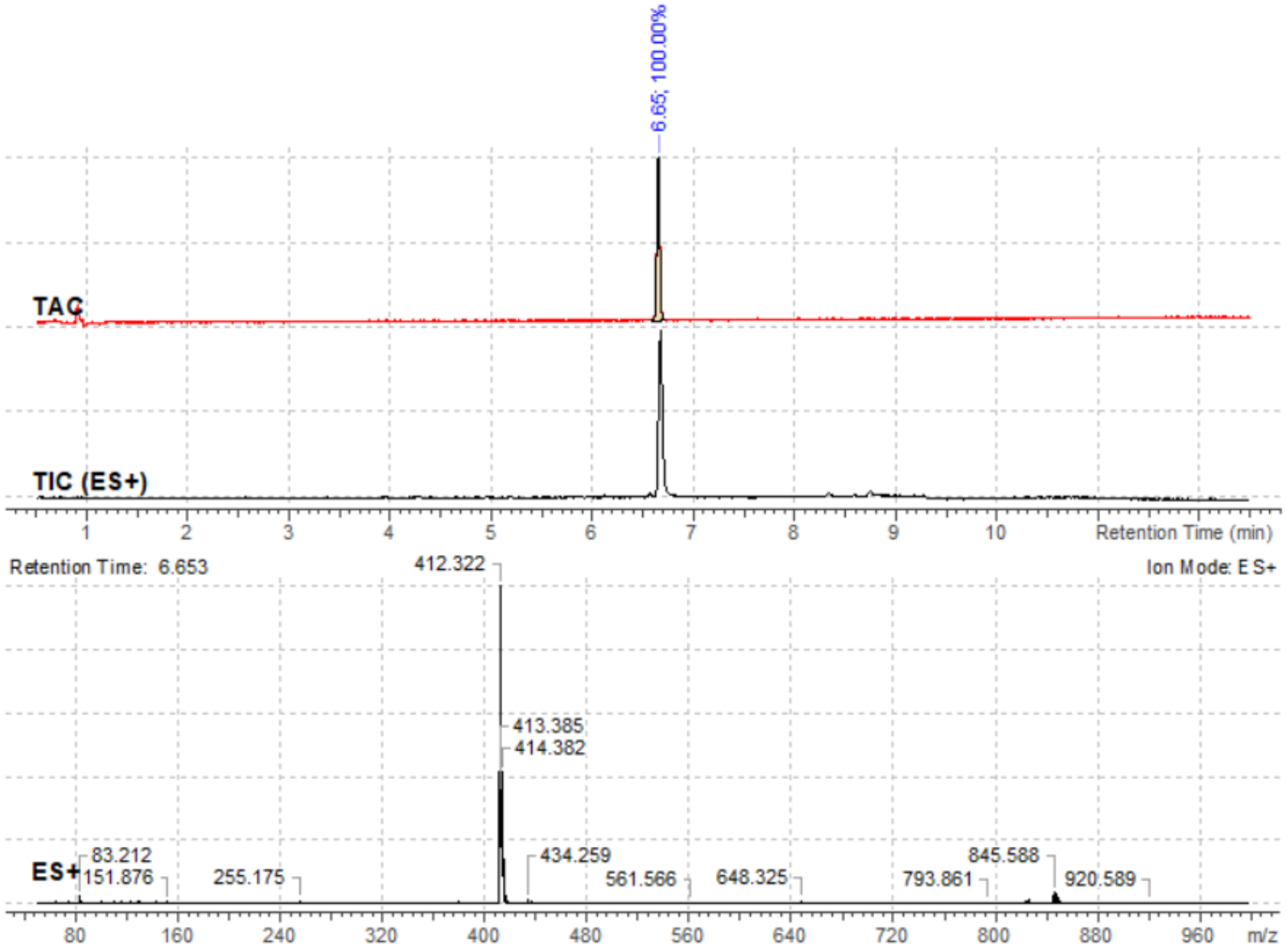

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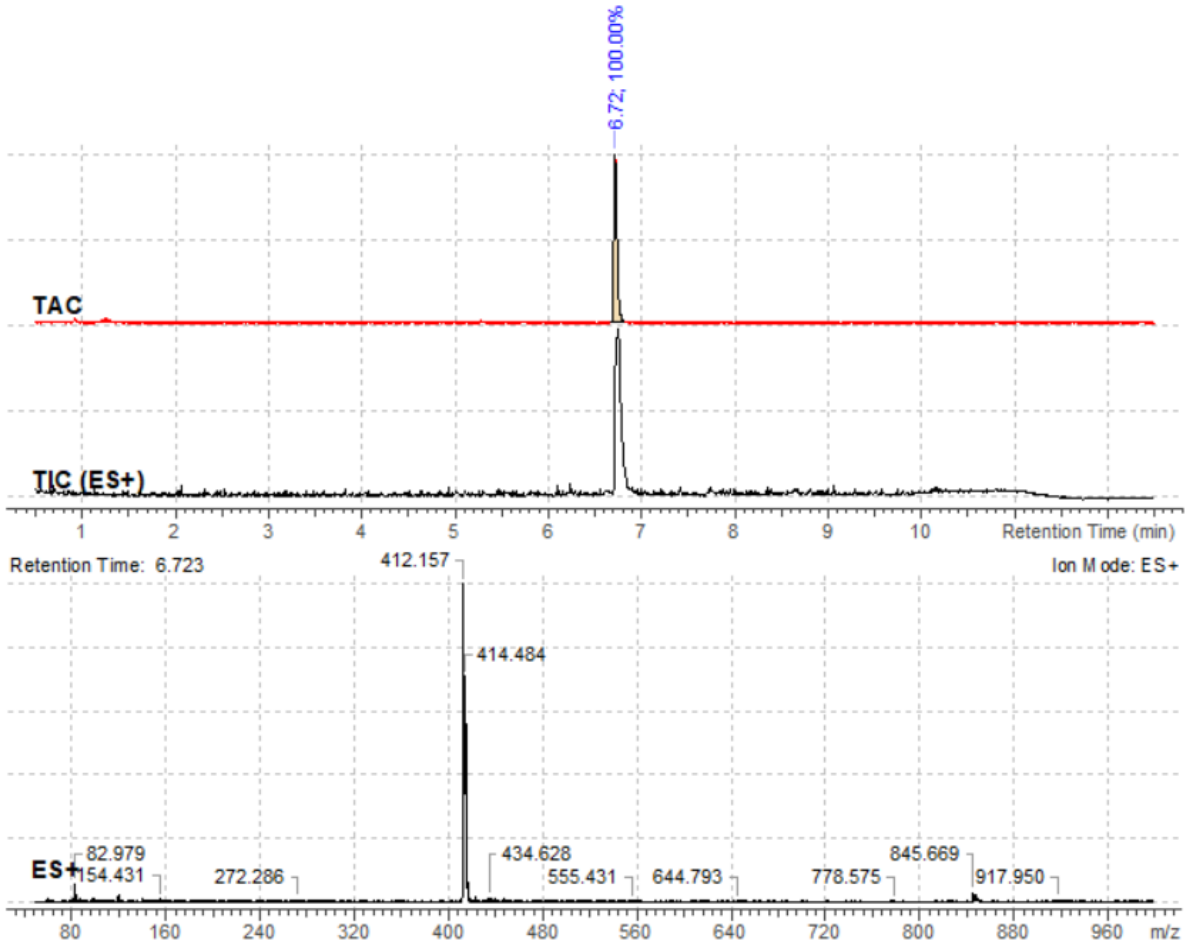

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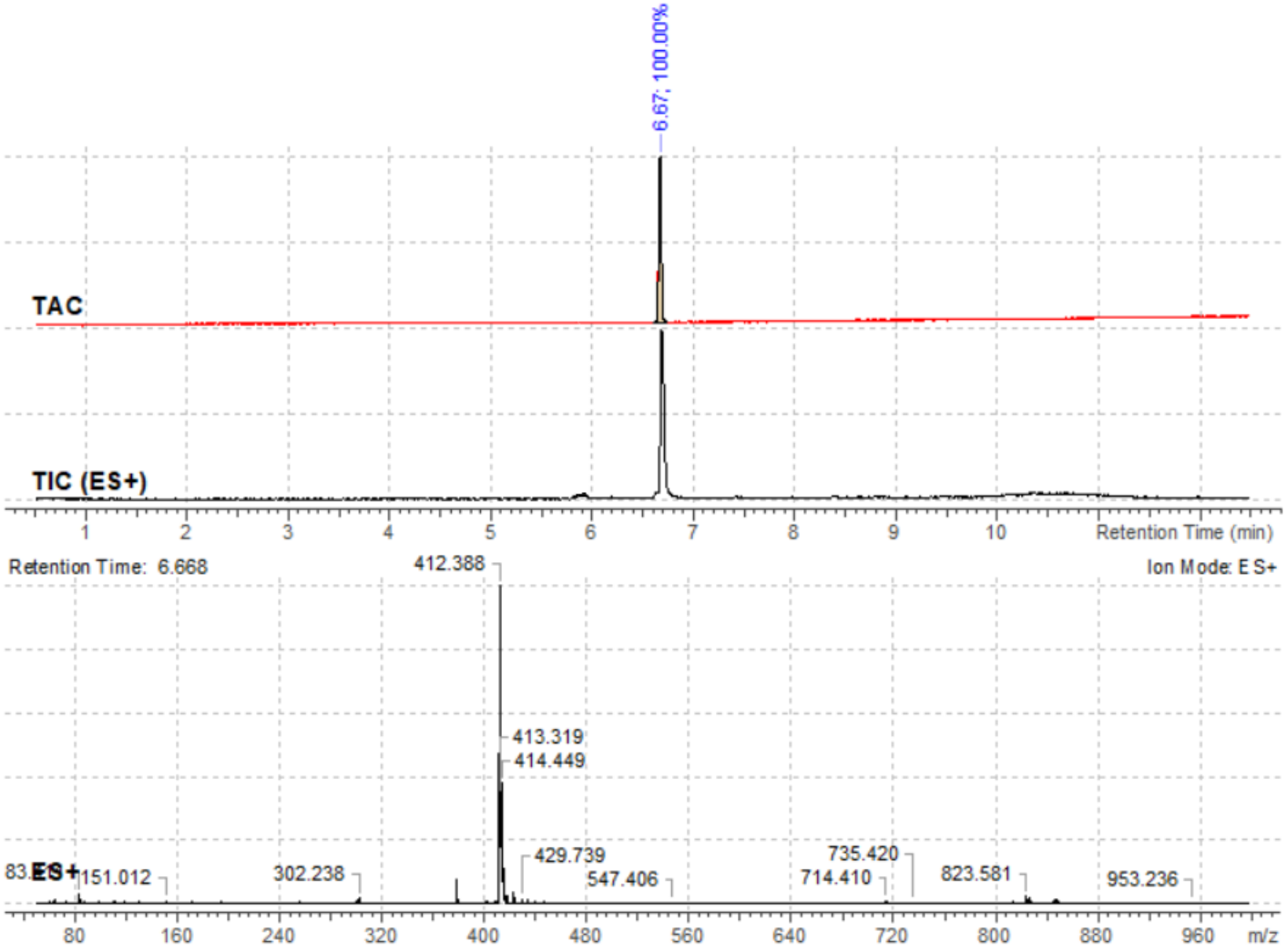

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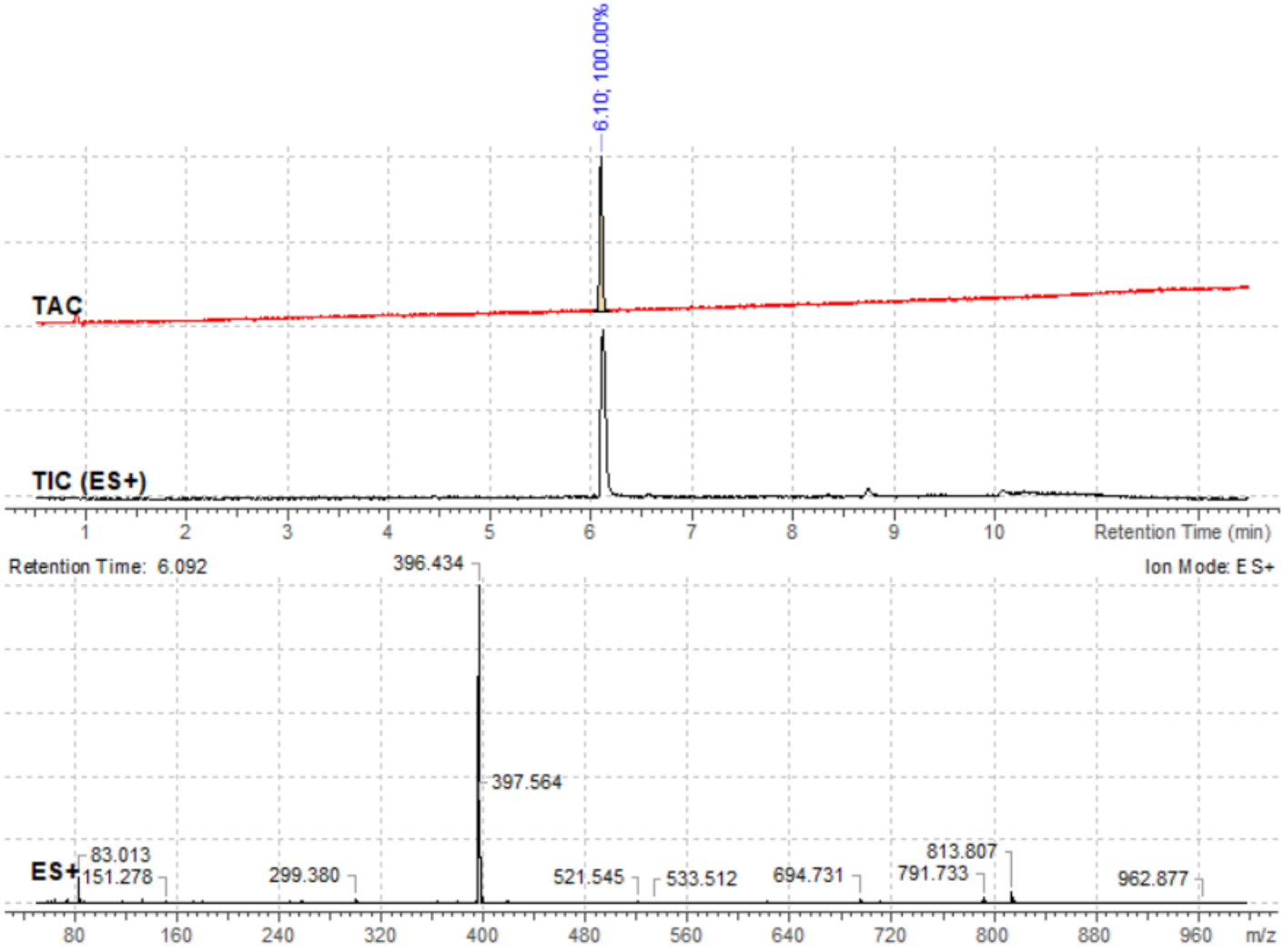

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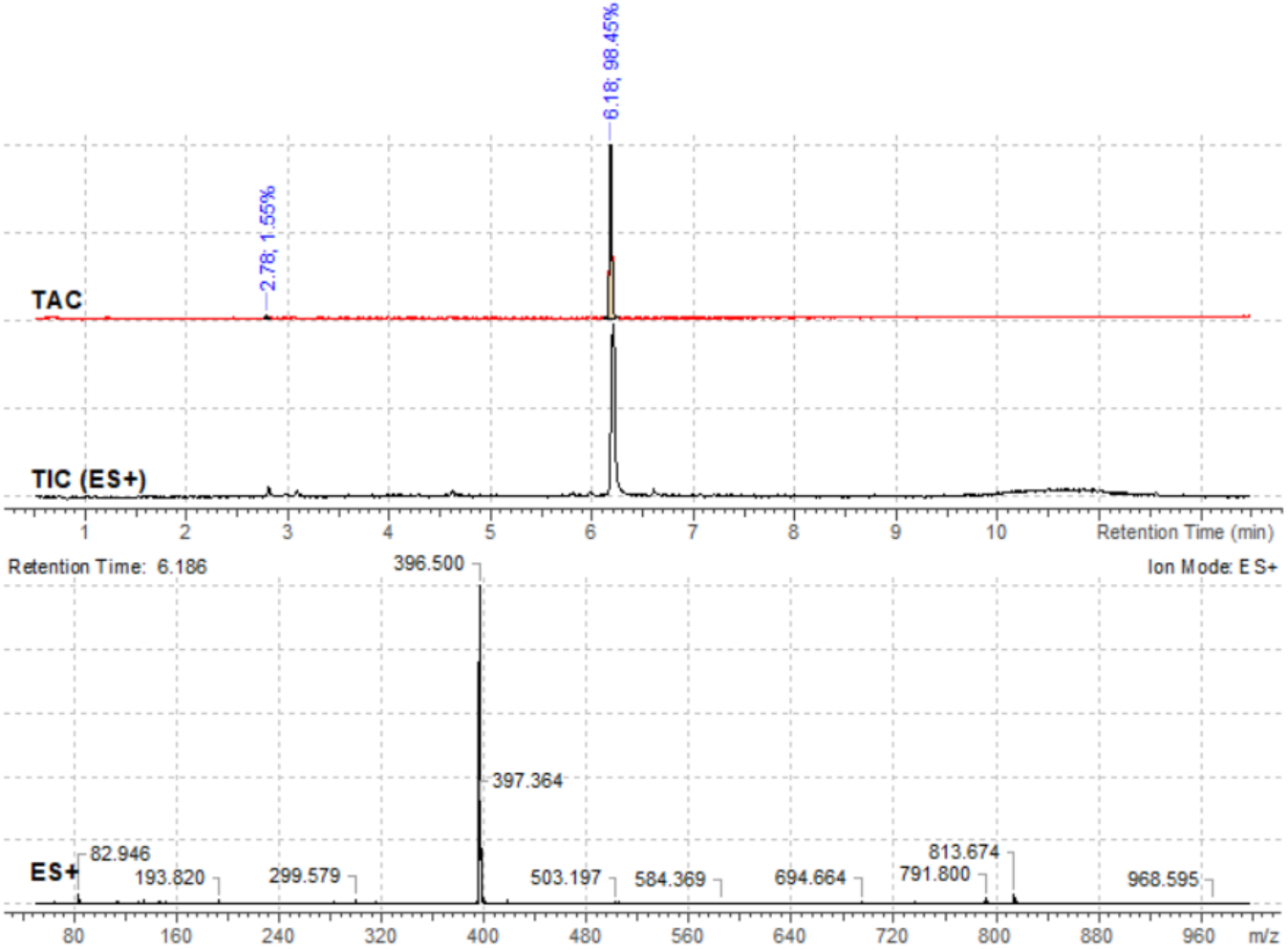

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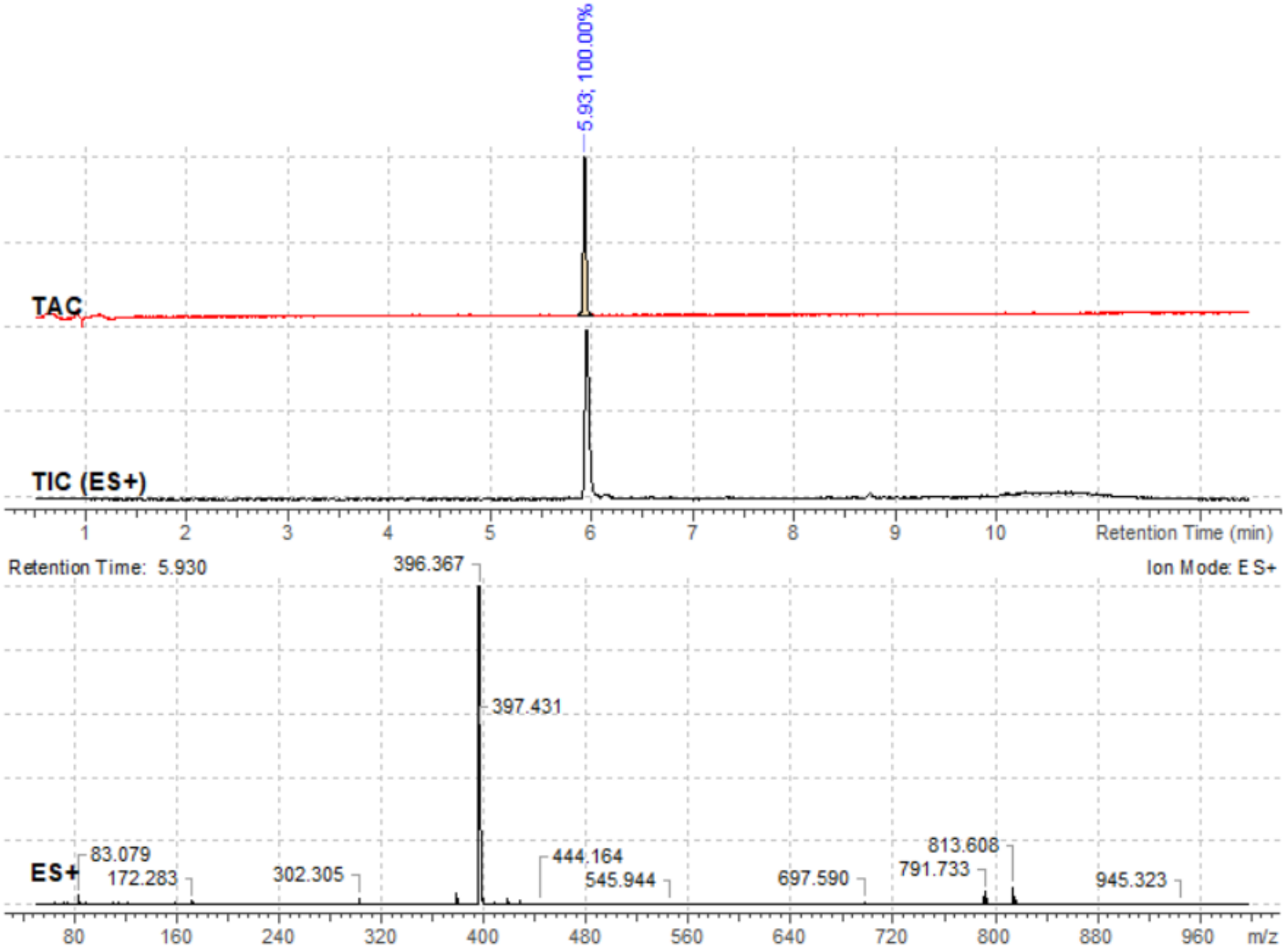

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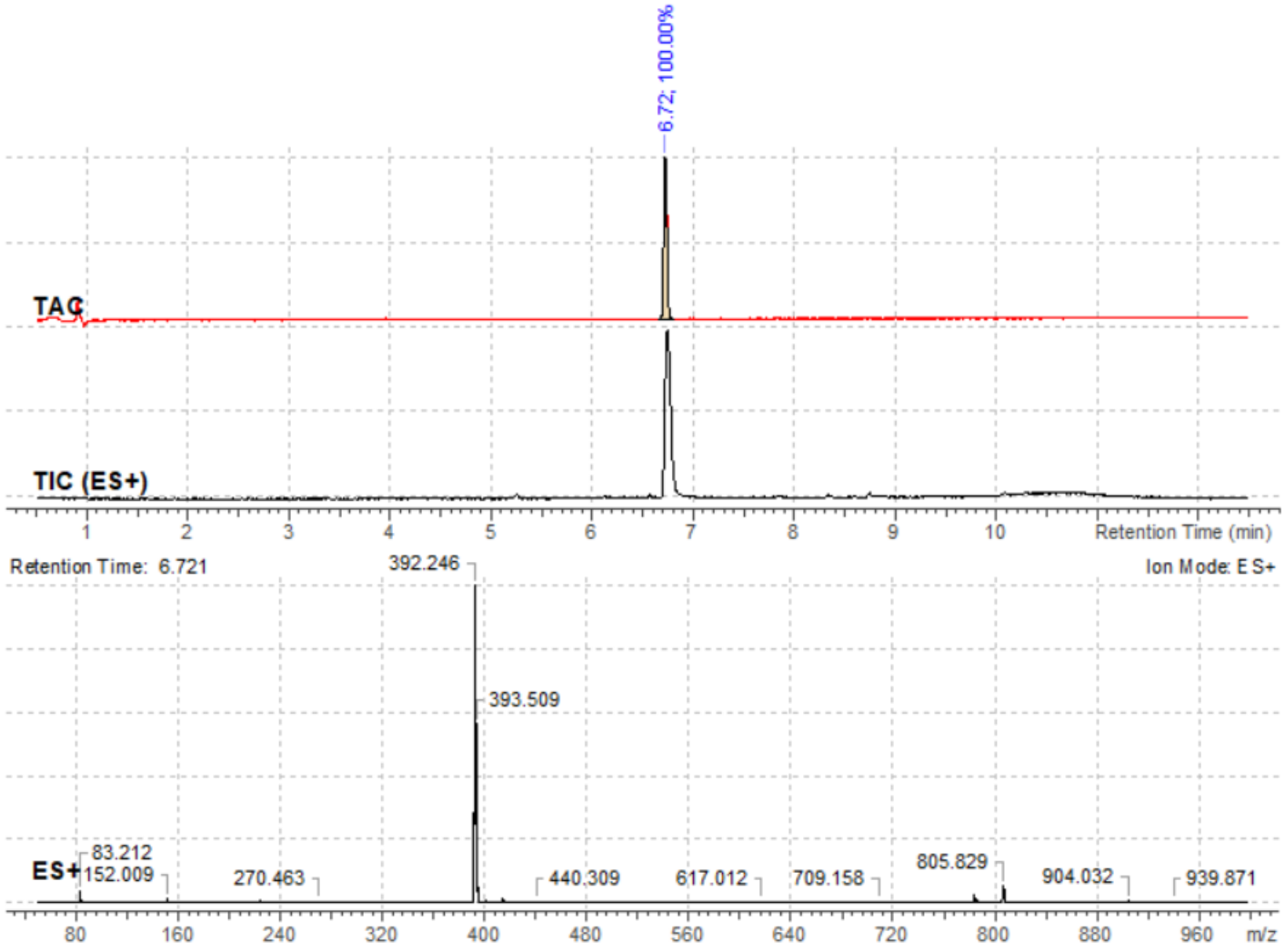

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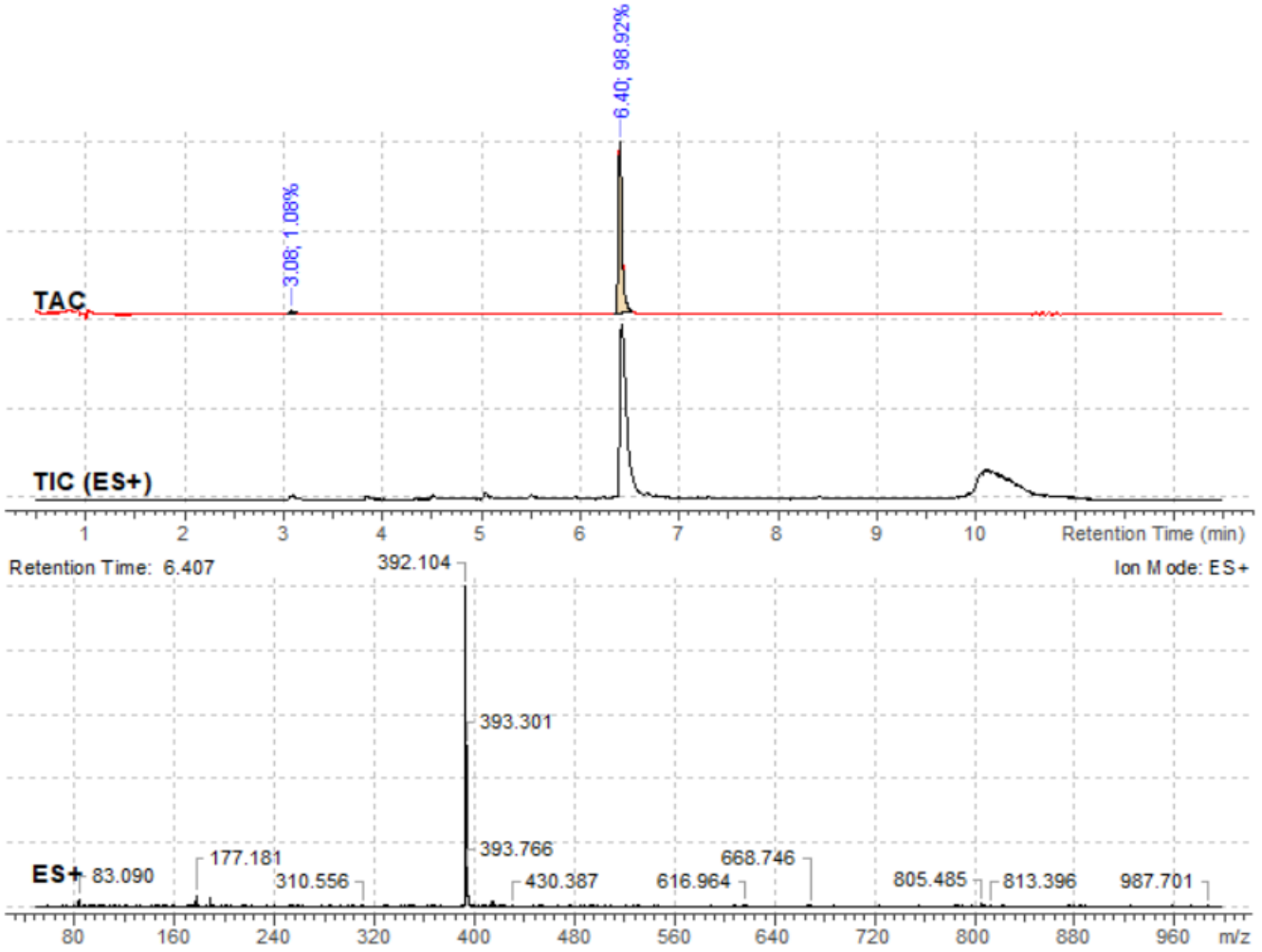

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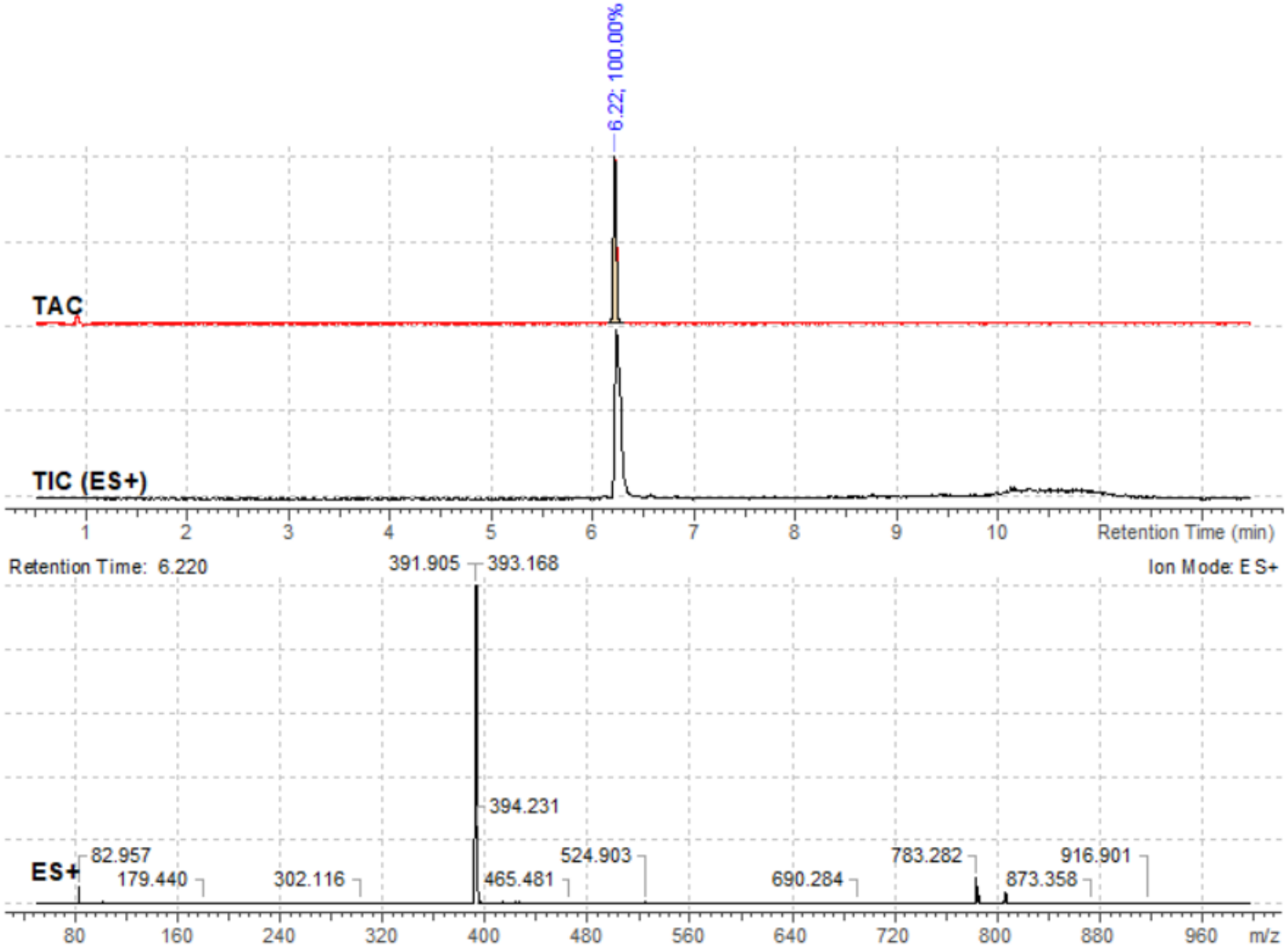

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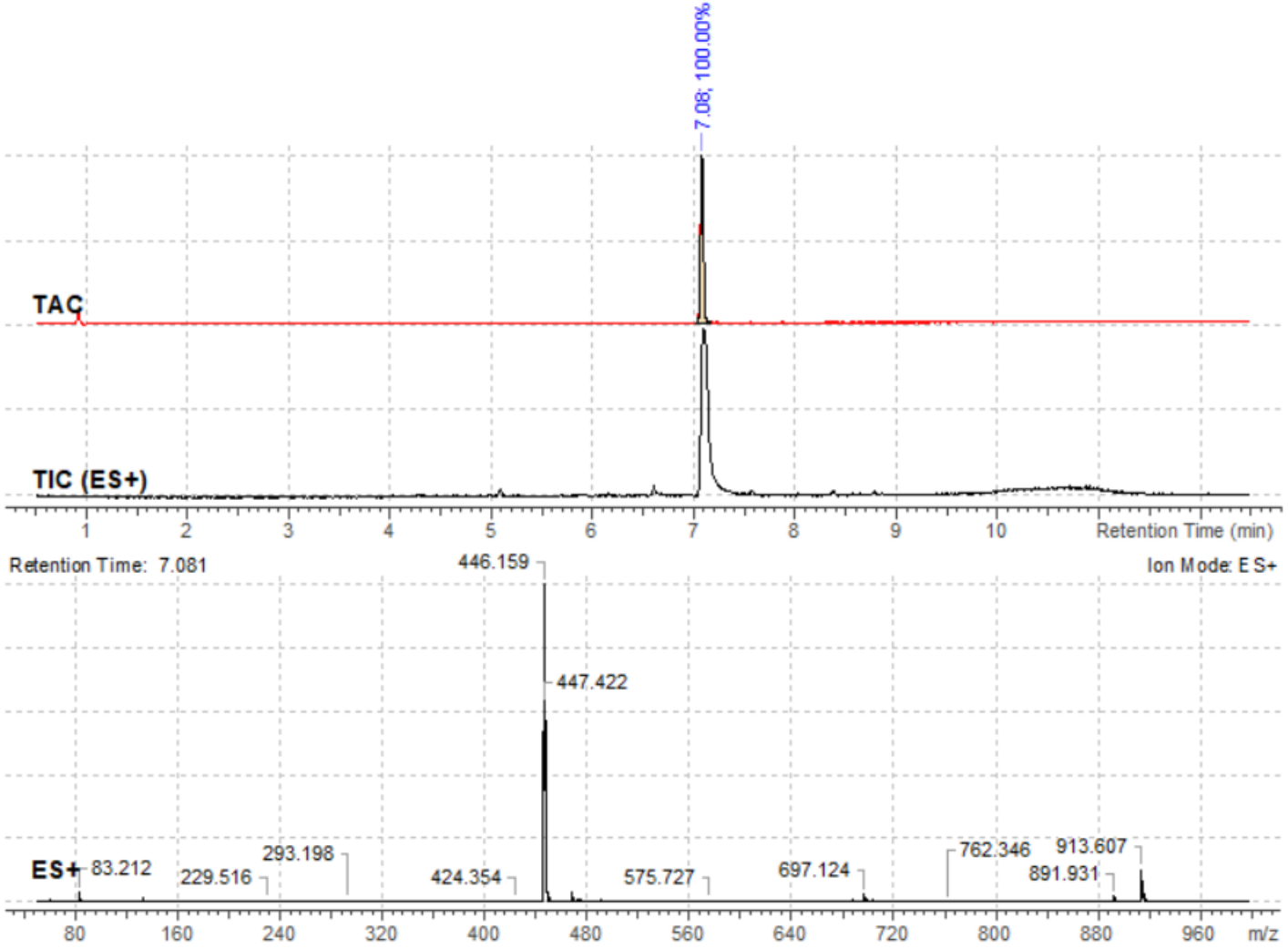

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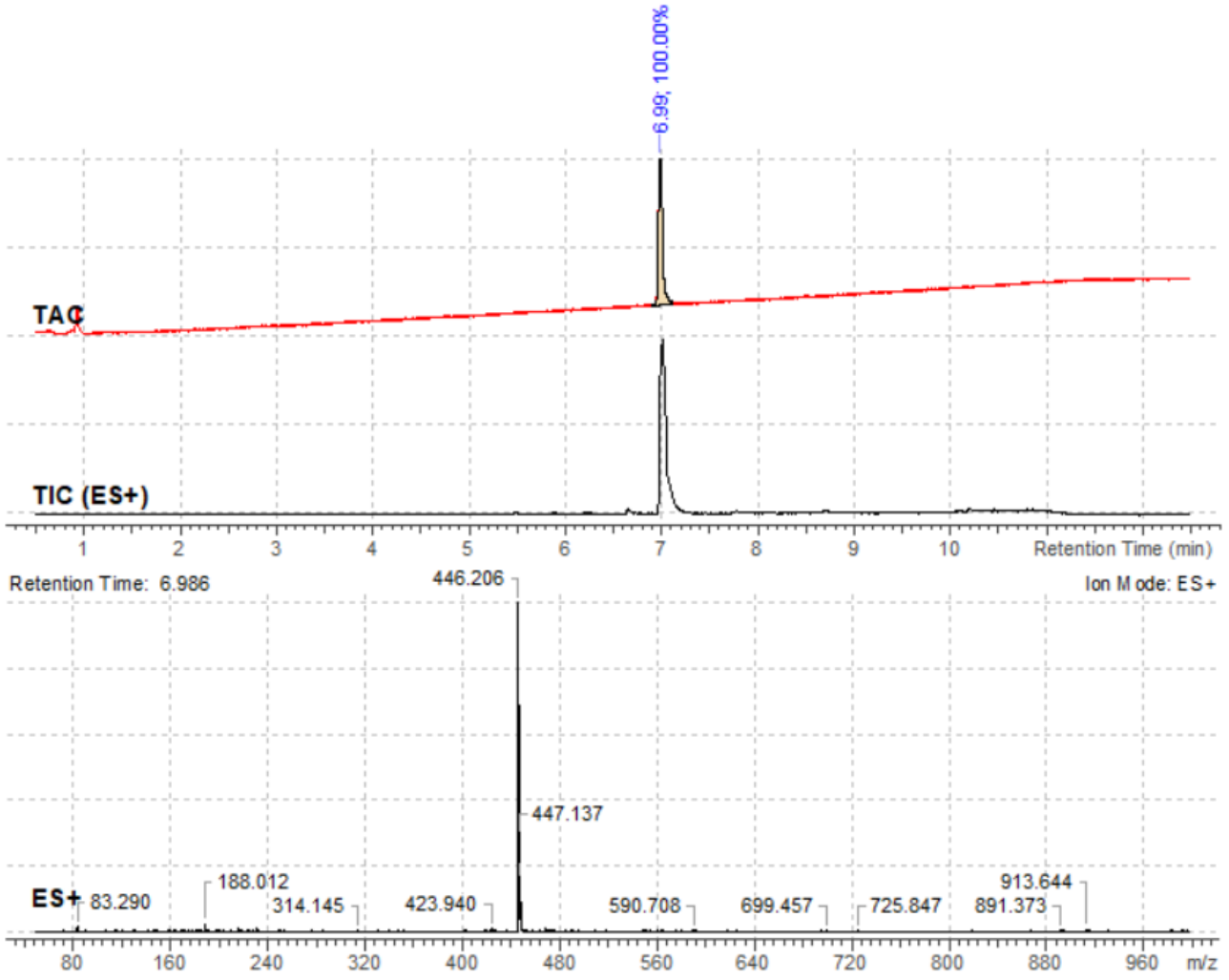

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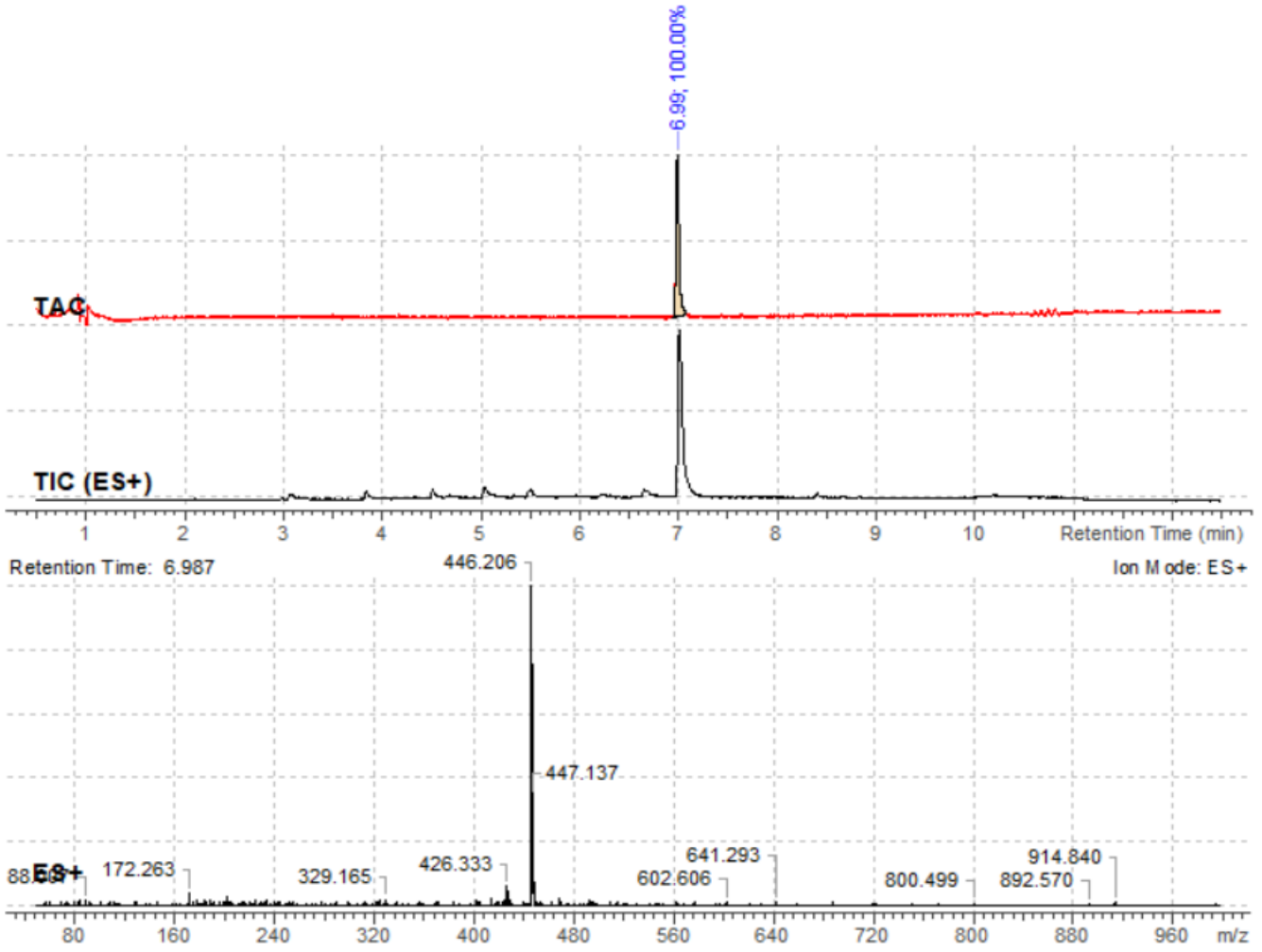
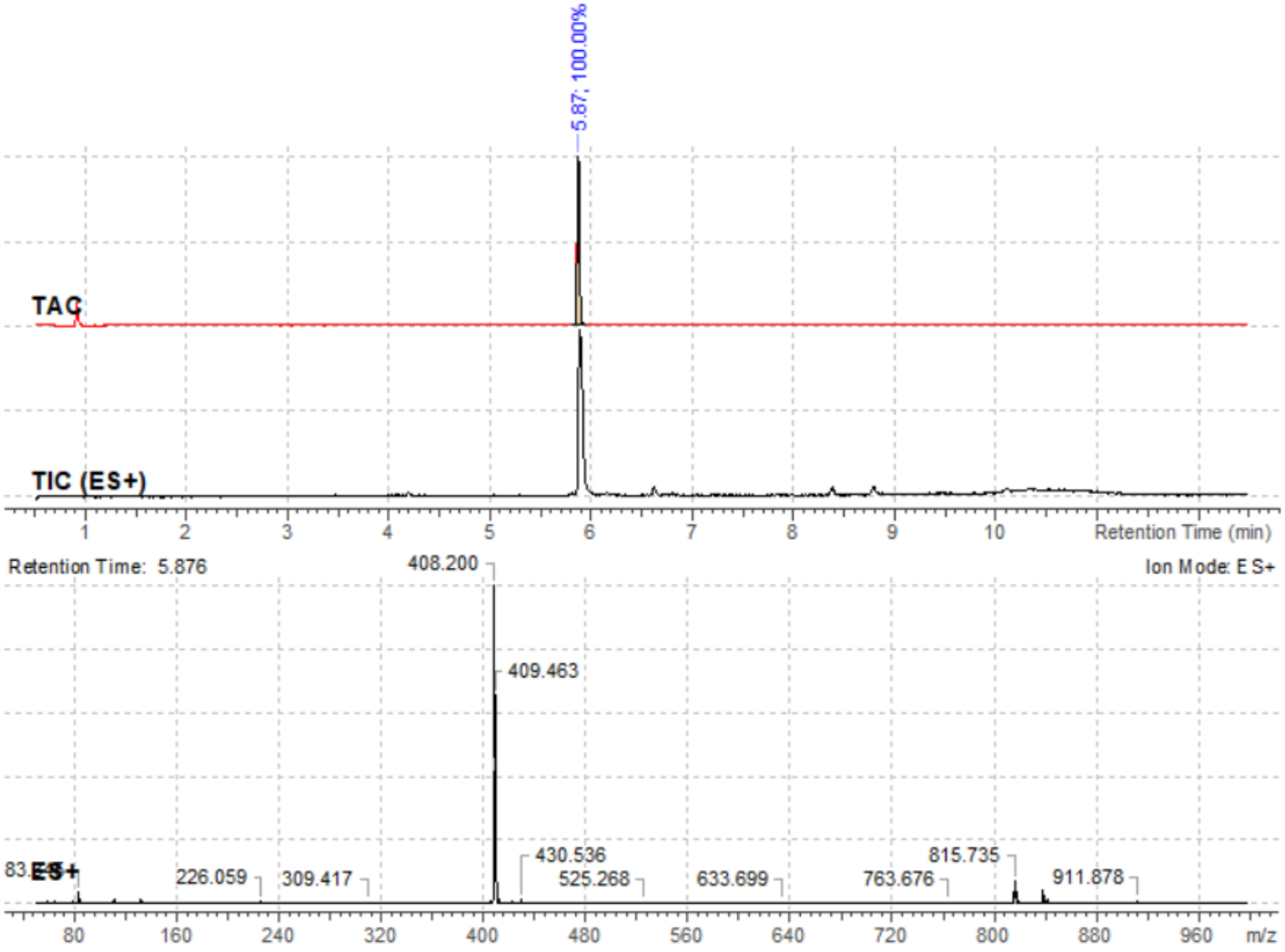
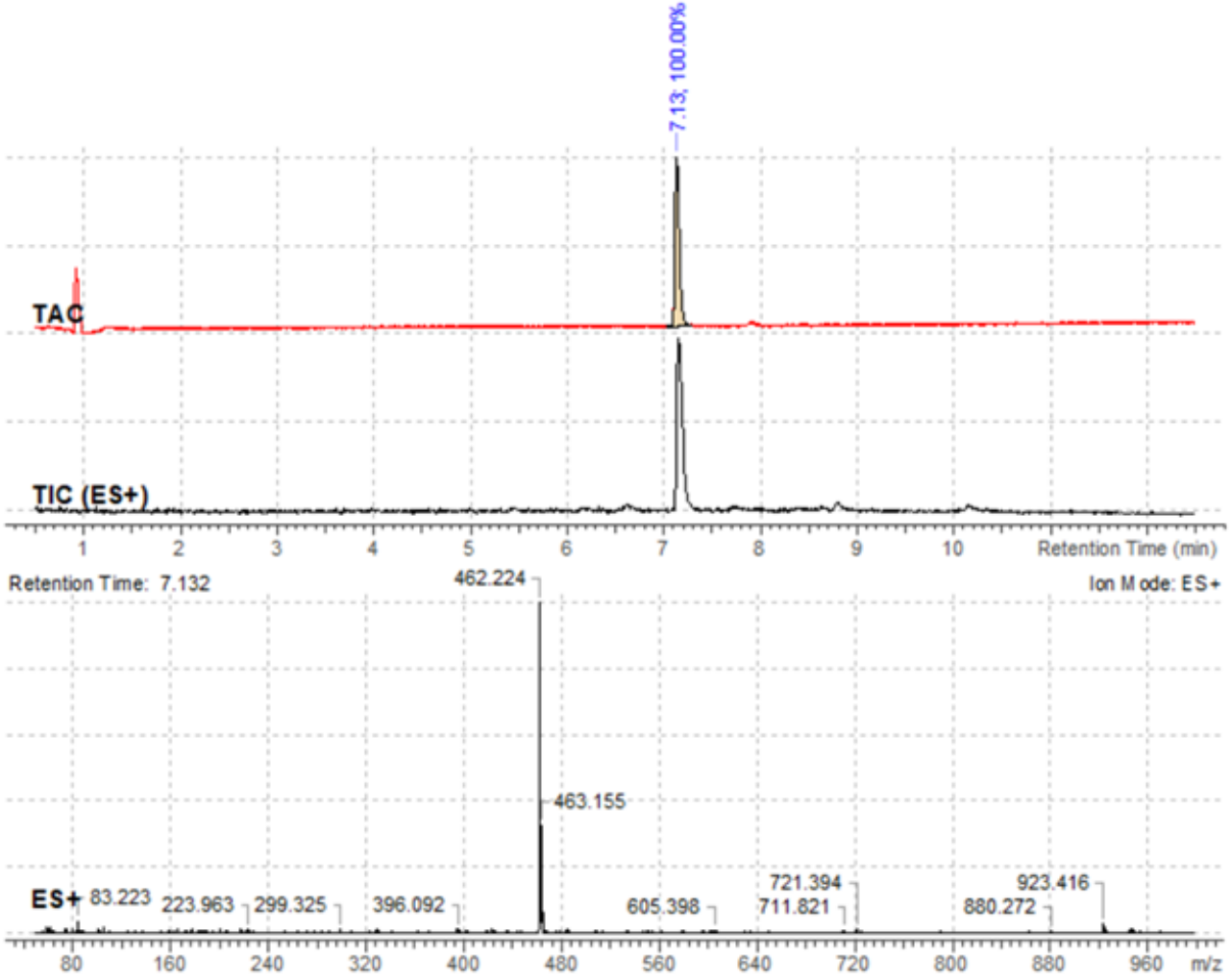


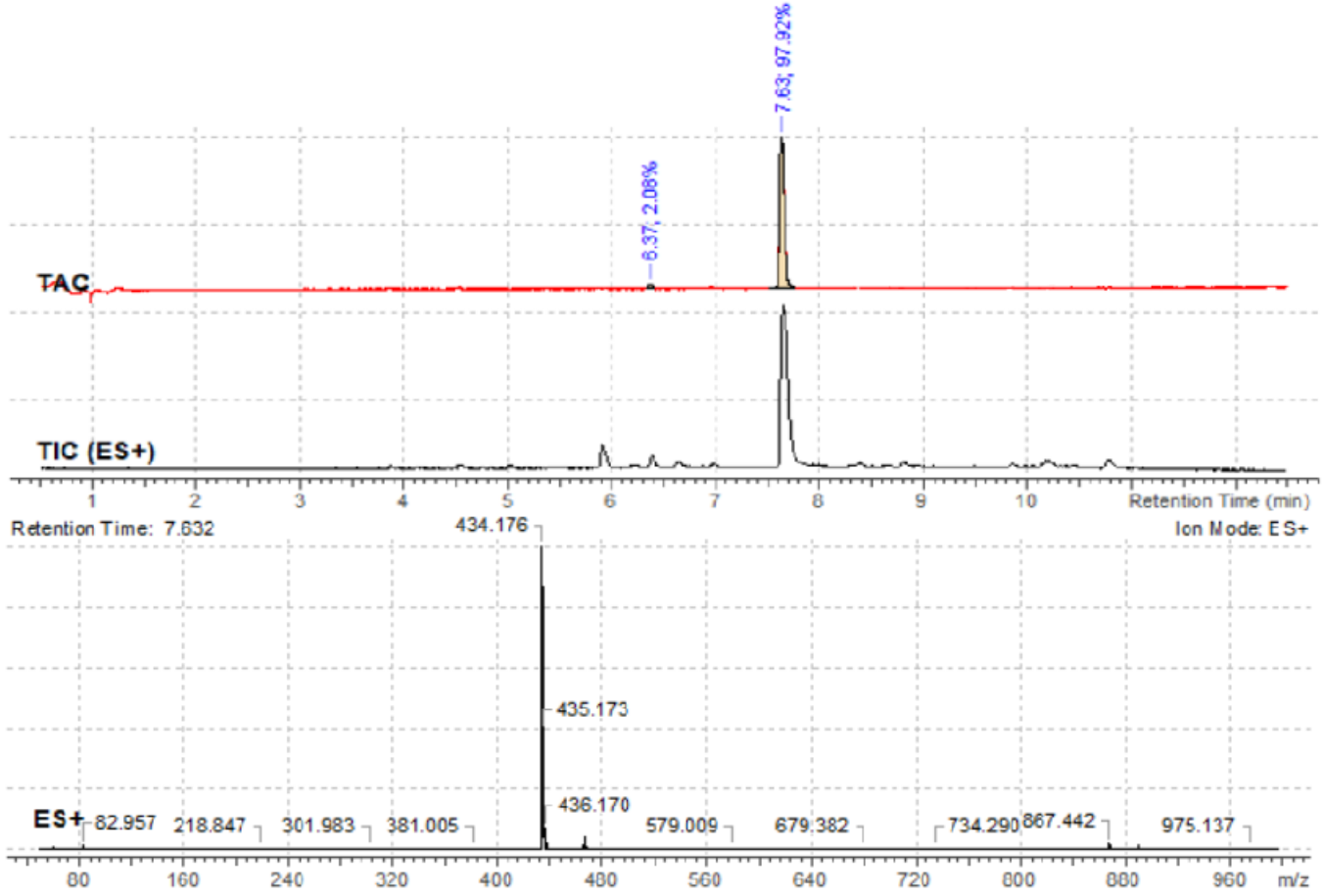
1-(2-(4-(3-Methoxyphenyl)piperazin-1-yl)-2-oxo-1-phenylethyl)pyrrolidine-2,5-dione (24).



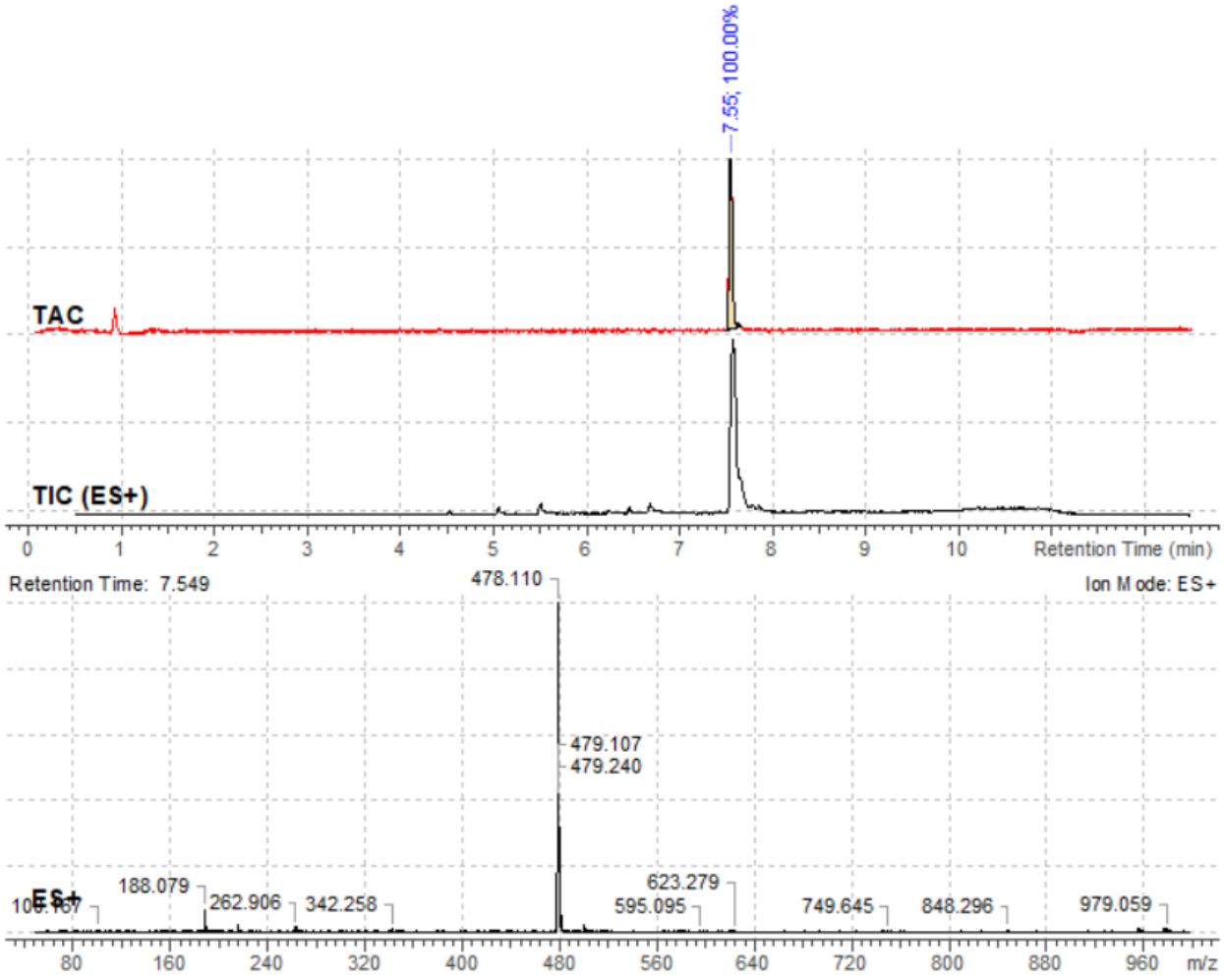
1-(2-Oxo-1-phenyl-2-(4-(3-(trifluoromethoxy)phenyl)piperazin-1-yl)ethyl)pyrrolidine-2,5-dione (25)



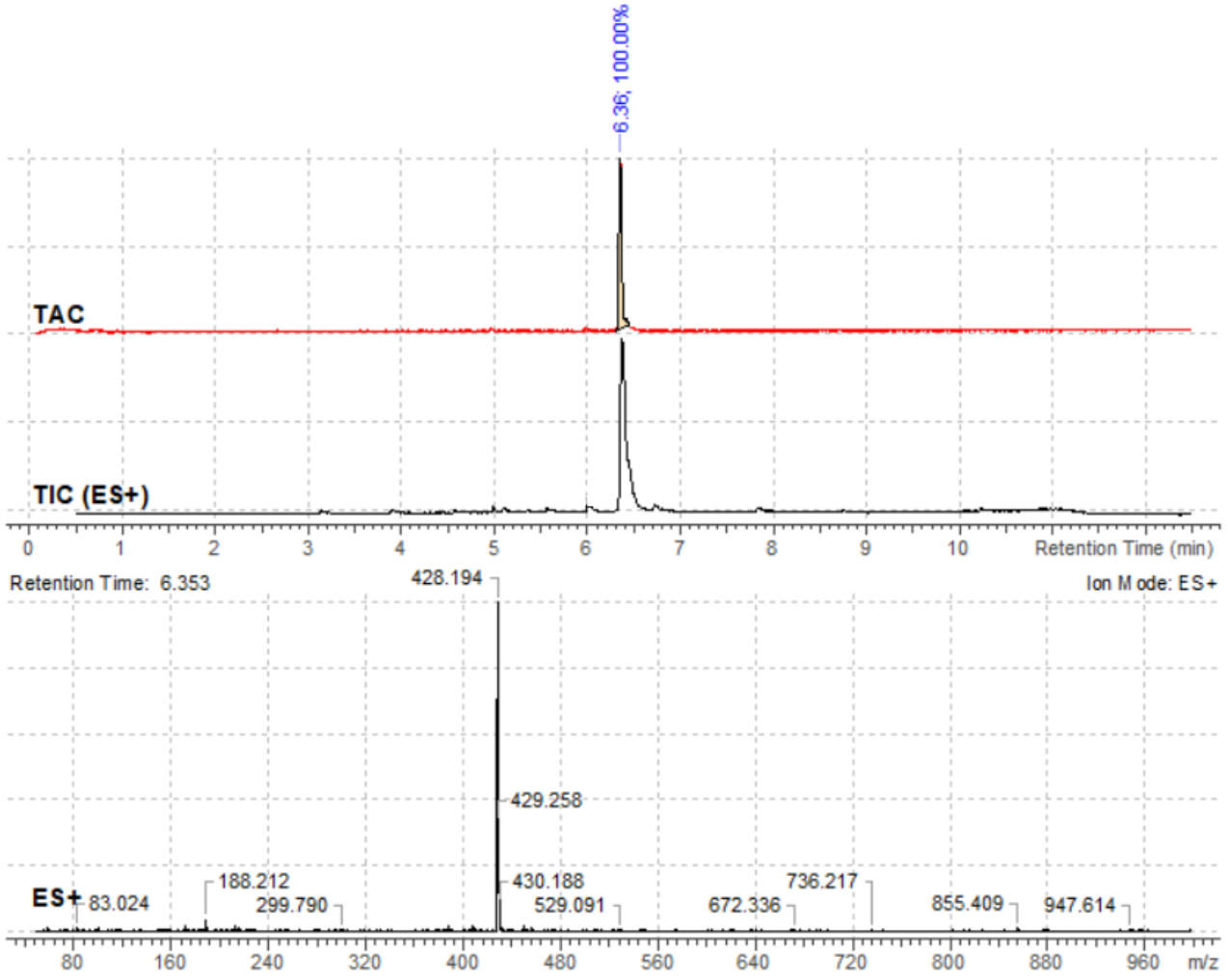
1-(2-(4-(3-(Methylthio)phenyl)piperazin-1-yl)-2-oxo-1-phenylethyl)pyrrolidine-2,5-dione (26).



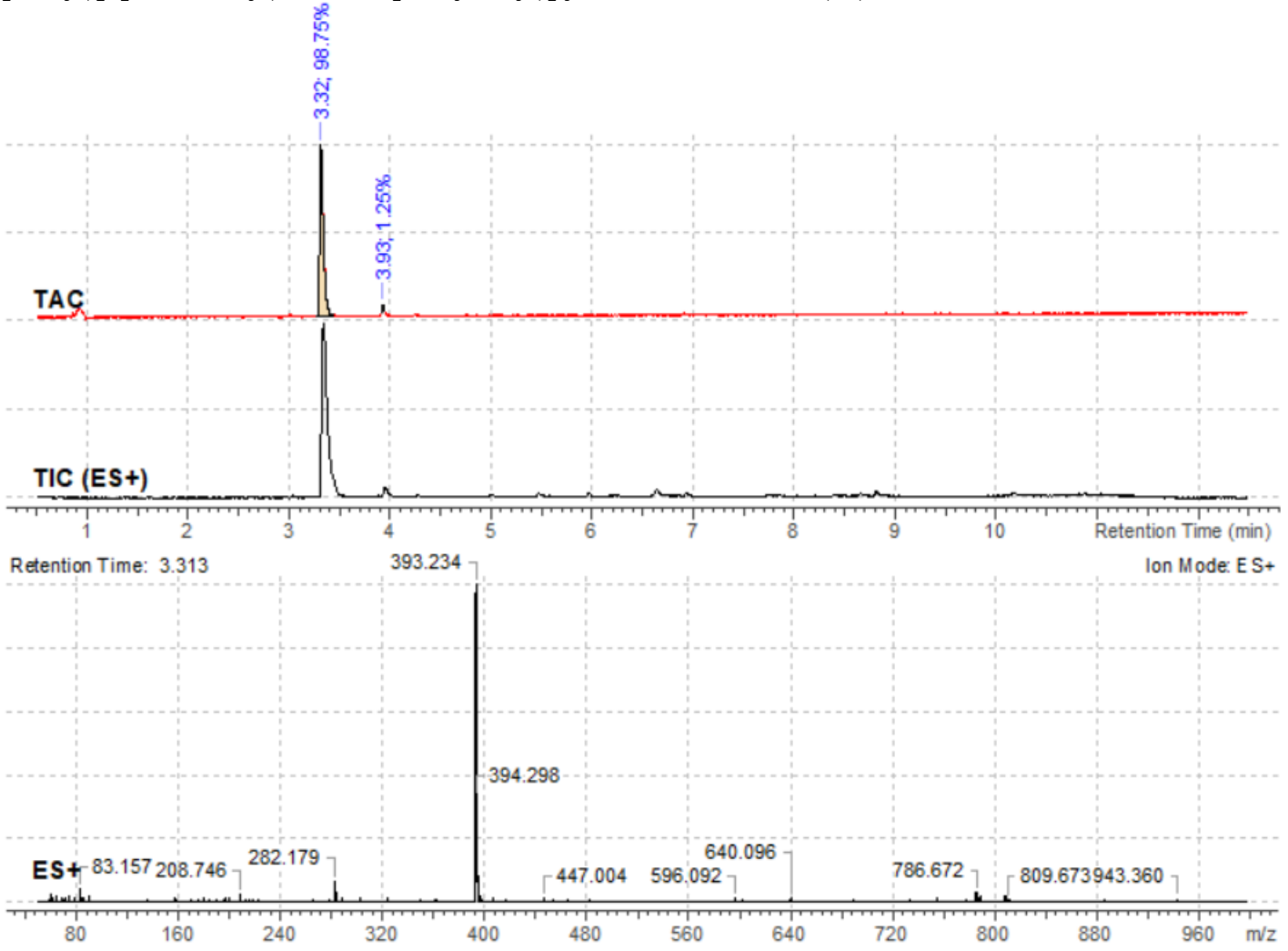
1-(2-Oxo-1-phenyl-2-(4-(3-((trifluoromethyl)thio)phenyl)piperazin-1-yl)ethyl)pyrrolidine-2,5-dione (27)



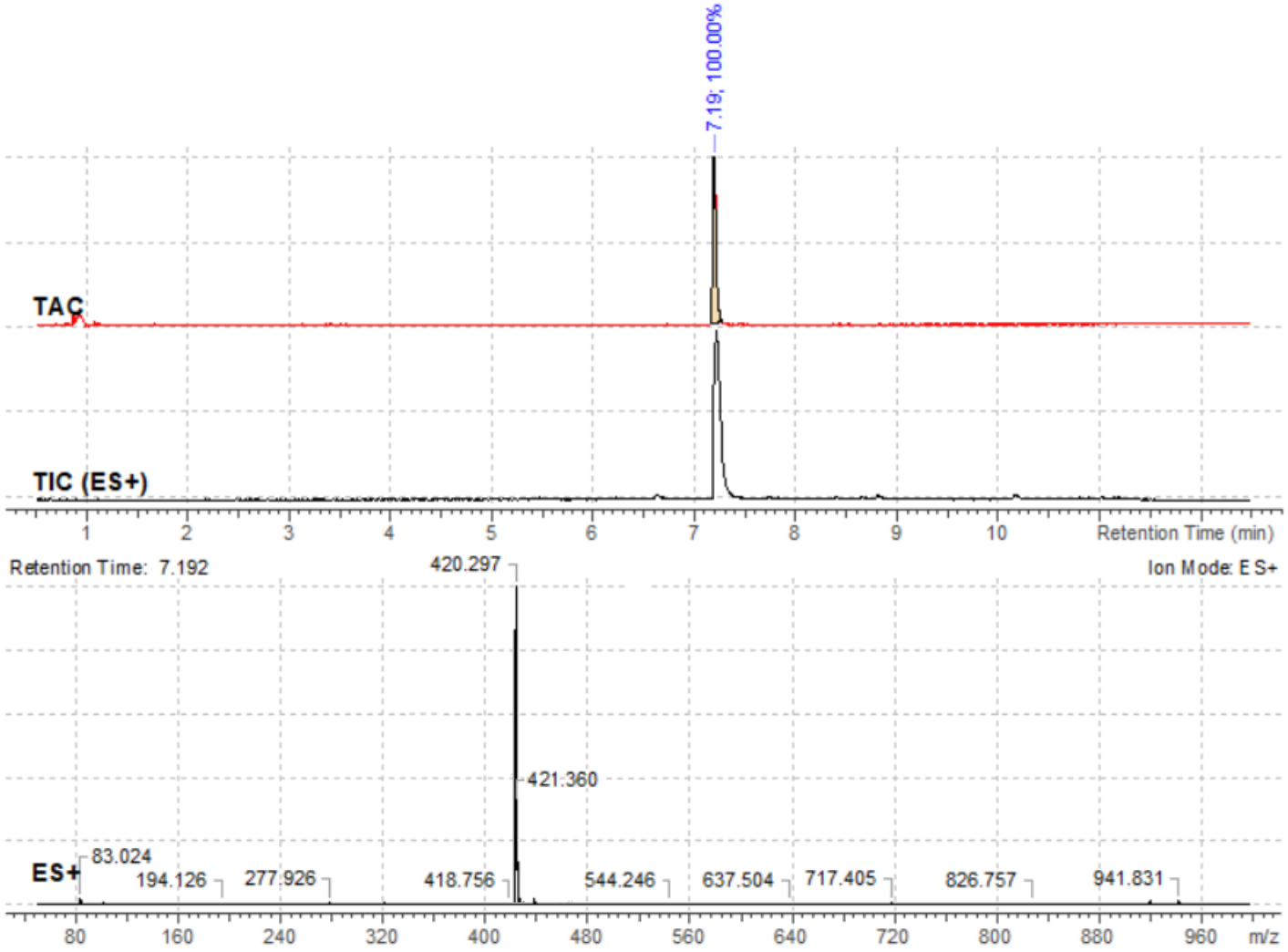
1-(2-(4-(3-(Difluoromethyl)phenyl)piperazin-1-yl)-2-oxo-1-phenylethyl)pyrrolidine-2,5-dione (28)



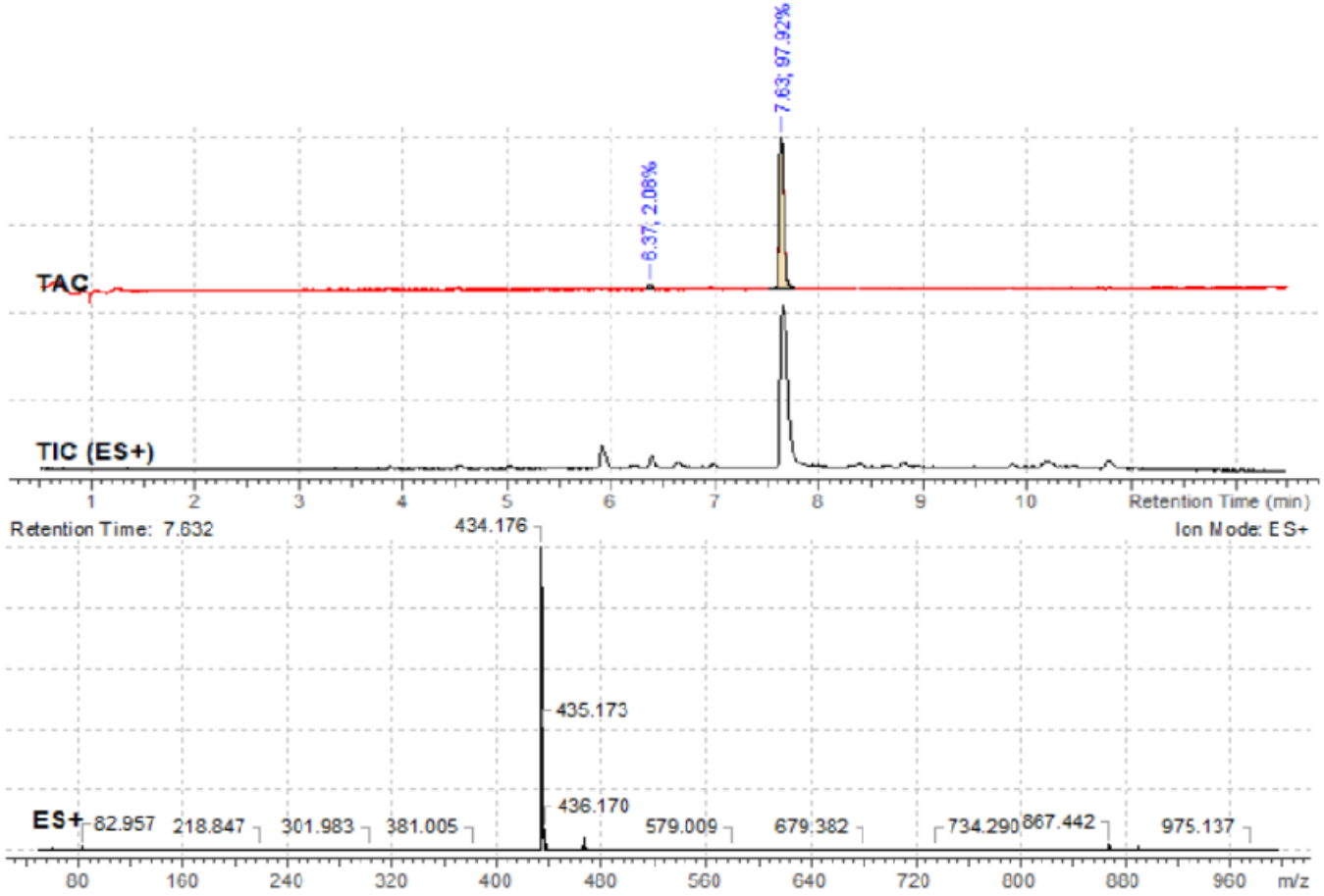
1-(2-(4-(3-Aminophenyl)piperazin-1-yl)-2-oxo-1-phenylethyl)pyrrolidine-2,5-dione (29).



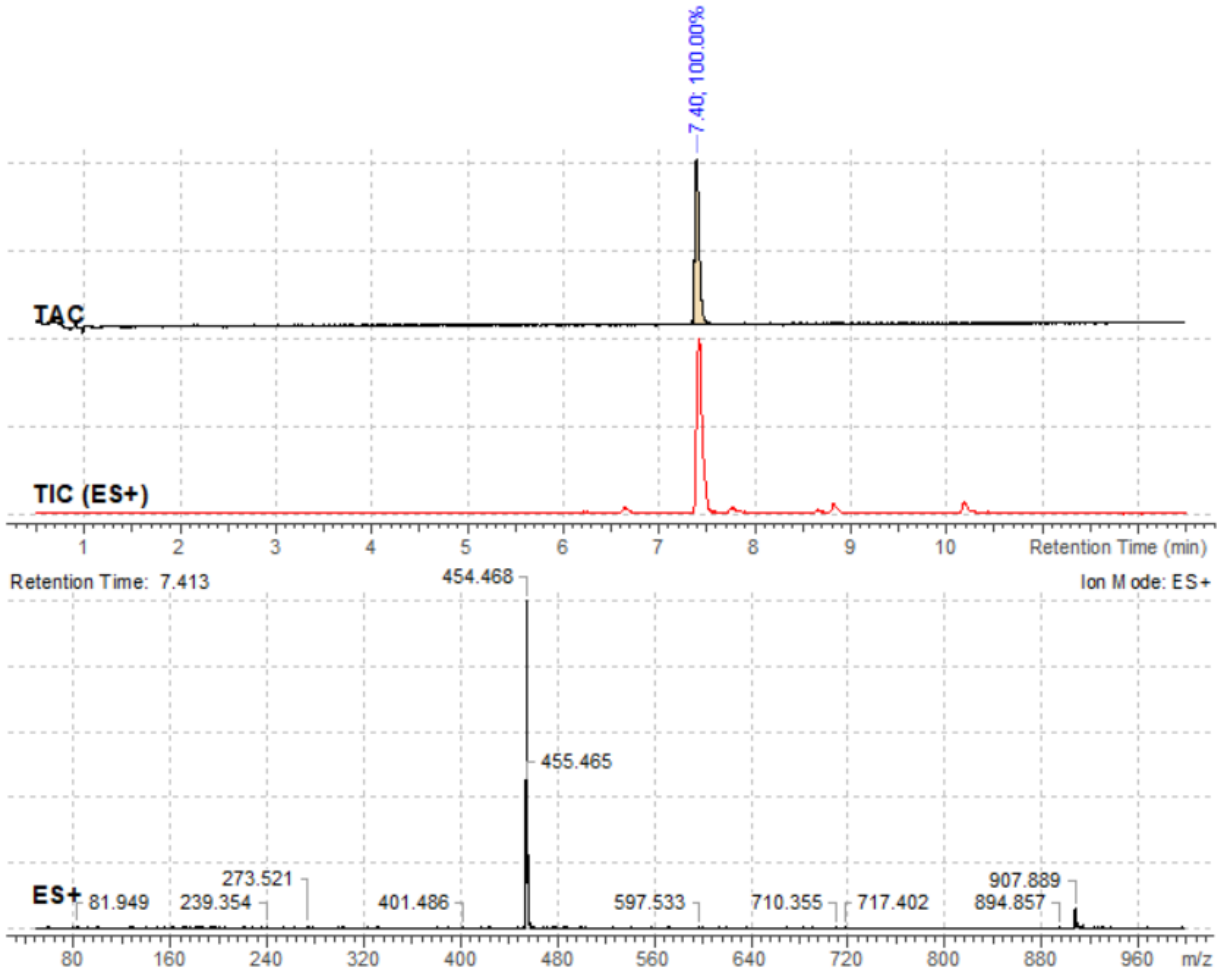
1-(2-(4-(3-Isopropylphenyl)piperazin-1-yl)-2-oxo-1-phenylethyl)pyrrolidine-2,5-dione (30).



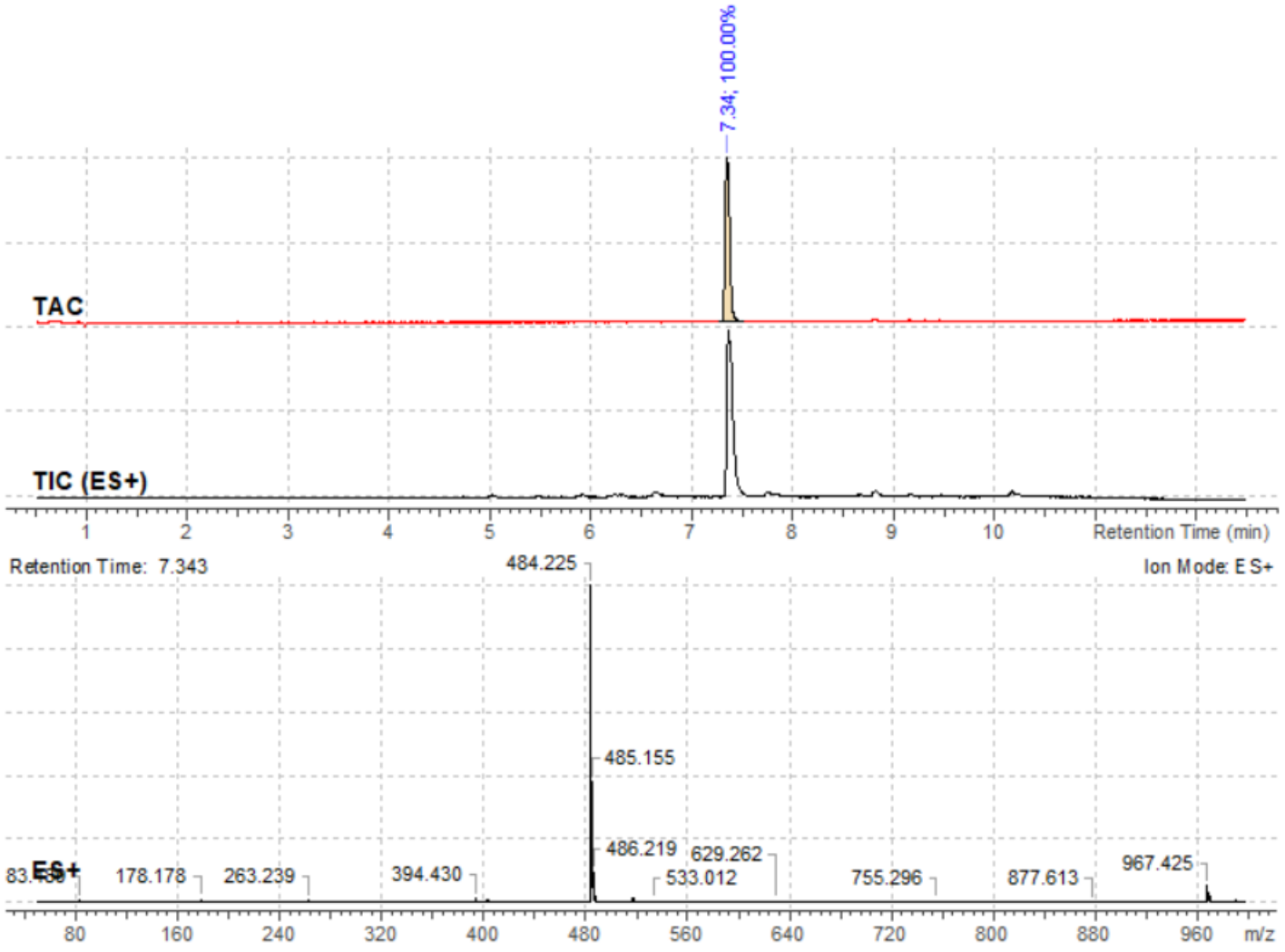
1-(2-(4-(3-(*tert*-Butyl)phenyl)piperazin-1-yl)-2-oxo-1-phenylethyl)pyrrolidine-2,5-dione (31).



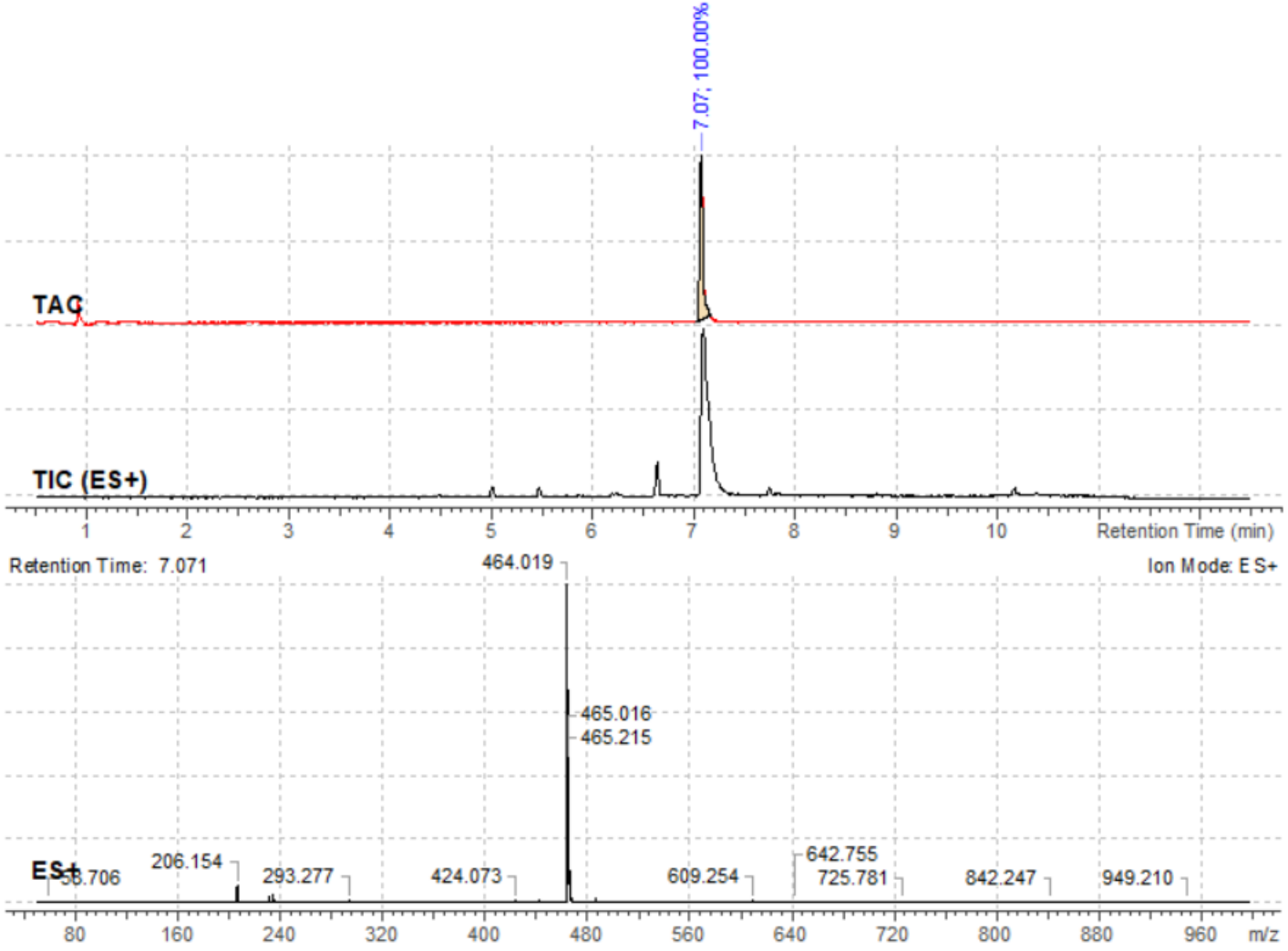
1-(2-(4-([1,1'-Biphenyl]-3-yl)piperazin-1-yl)-2-oxo-1-phenylethyl)pyrrolidine-2,5-dione (32)



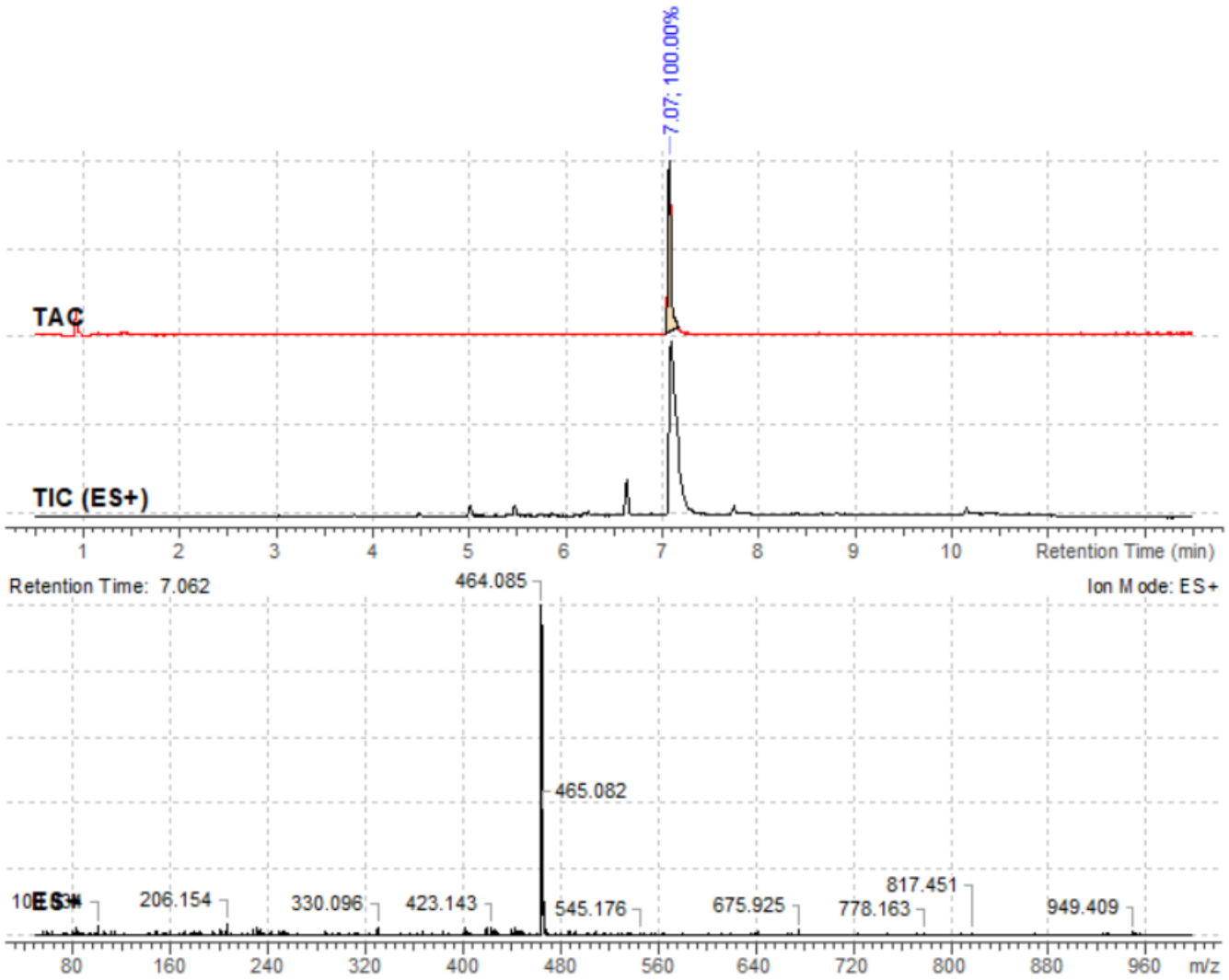
1-(2-(4-(3-(Benzyloxy)phenyl)piperazin-1-yl)-2-oxo-1-phenylethyl)pyrrolidine-2,5-dione (33).



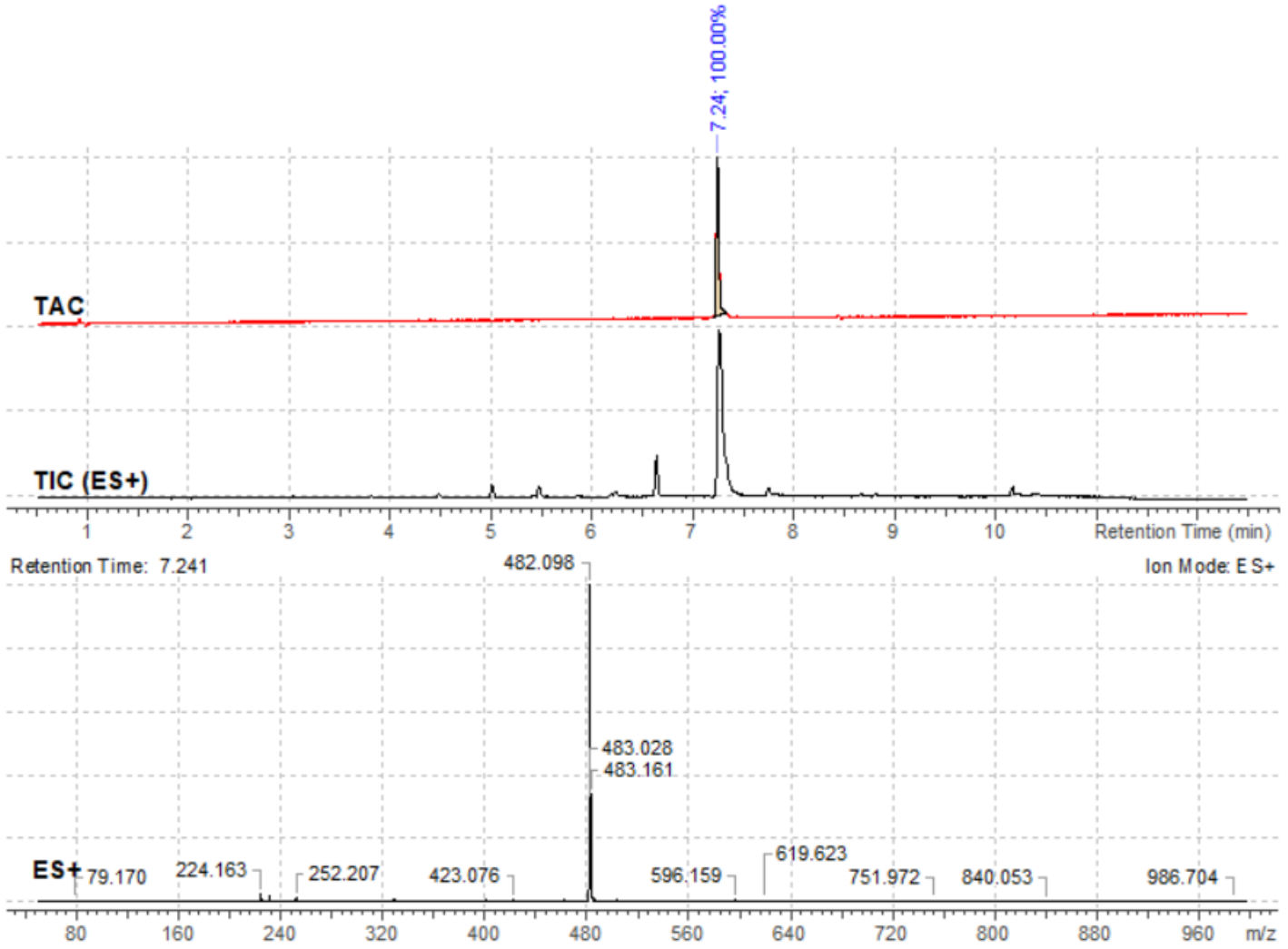
1-(1-(3-Fluorophenyl)-2-oxo-2-(4-(3-(trifluoromethyl)phenyl)piperazin-1-yl)ethyl)pyrrolidine-2,5-dione (34).



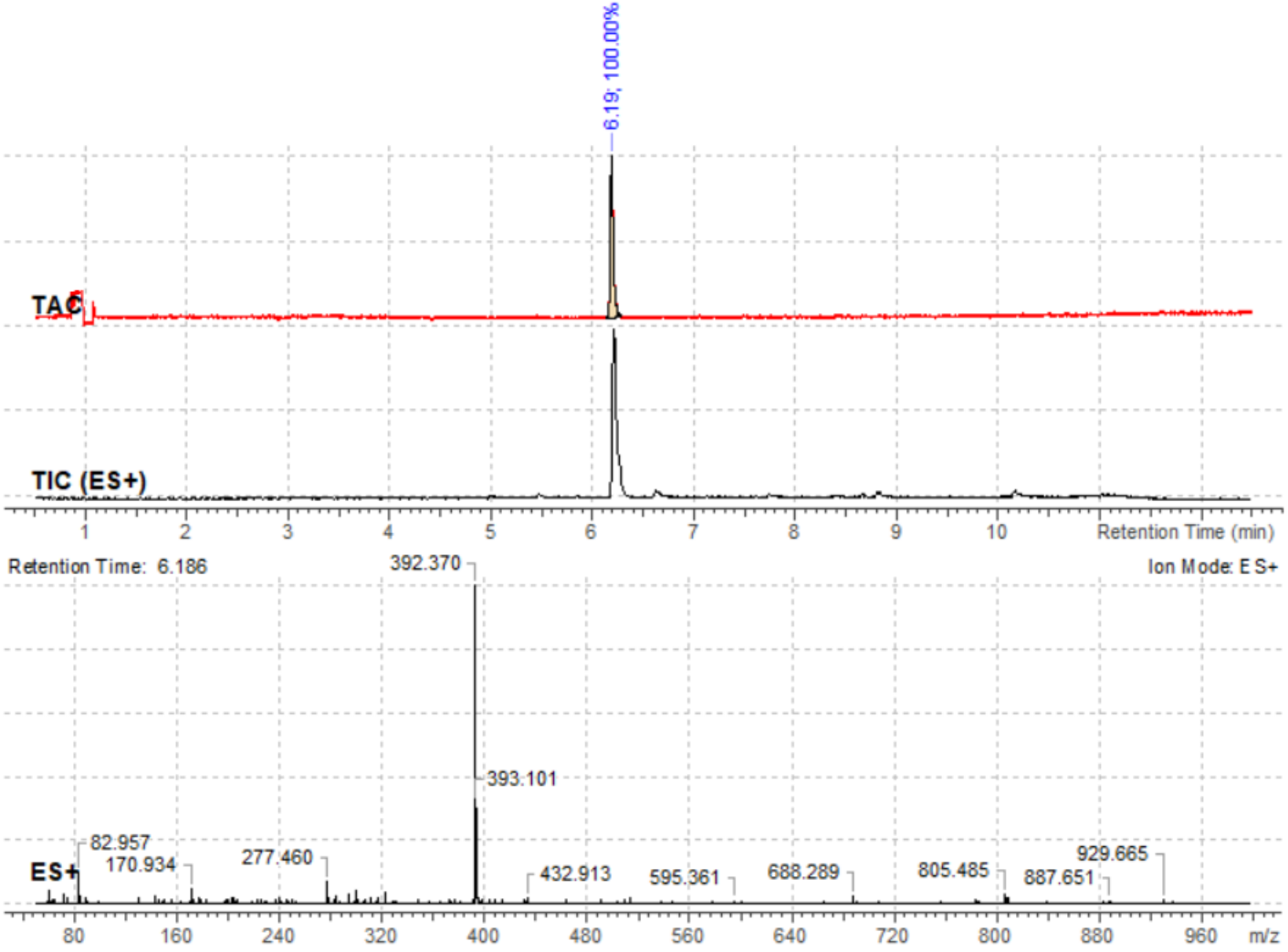
1-(1-(4-Fluorophenyl)-2-oxo-2-(4-(3-(trifluoromethyl)phenyl)piperazin-1-yl)ethyl)pyrrolidine-2,5-dione (35)



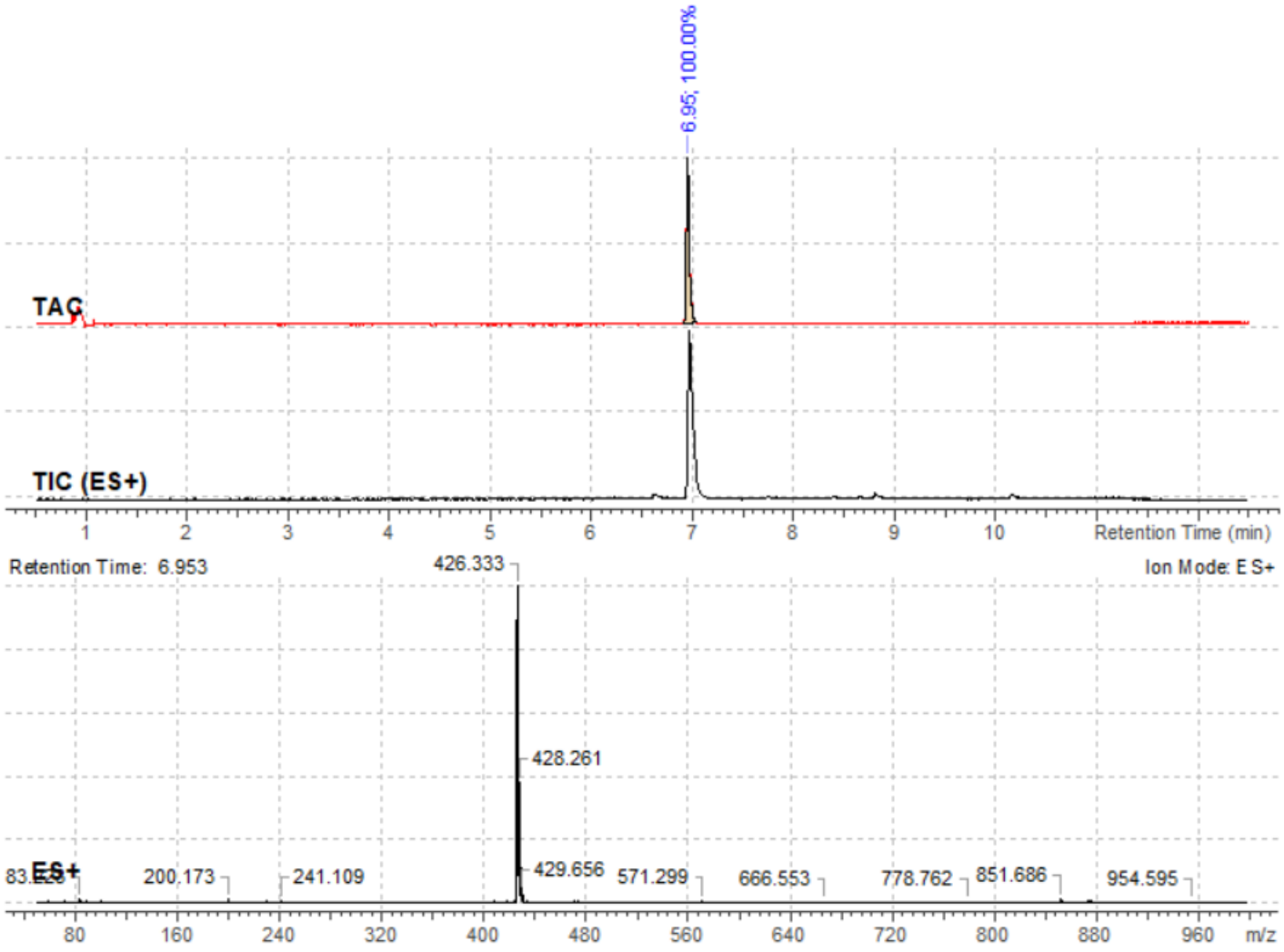
1-(1-(3,4-Difluorophenyl)-2-oxo-2-(4-(3-(trifluoromethyl)phenyl)piperazin-1-yl)ethyl)pyrrolidine-2,5-dione (36).



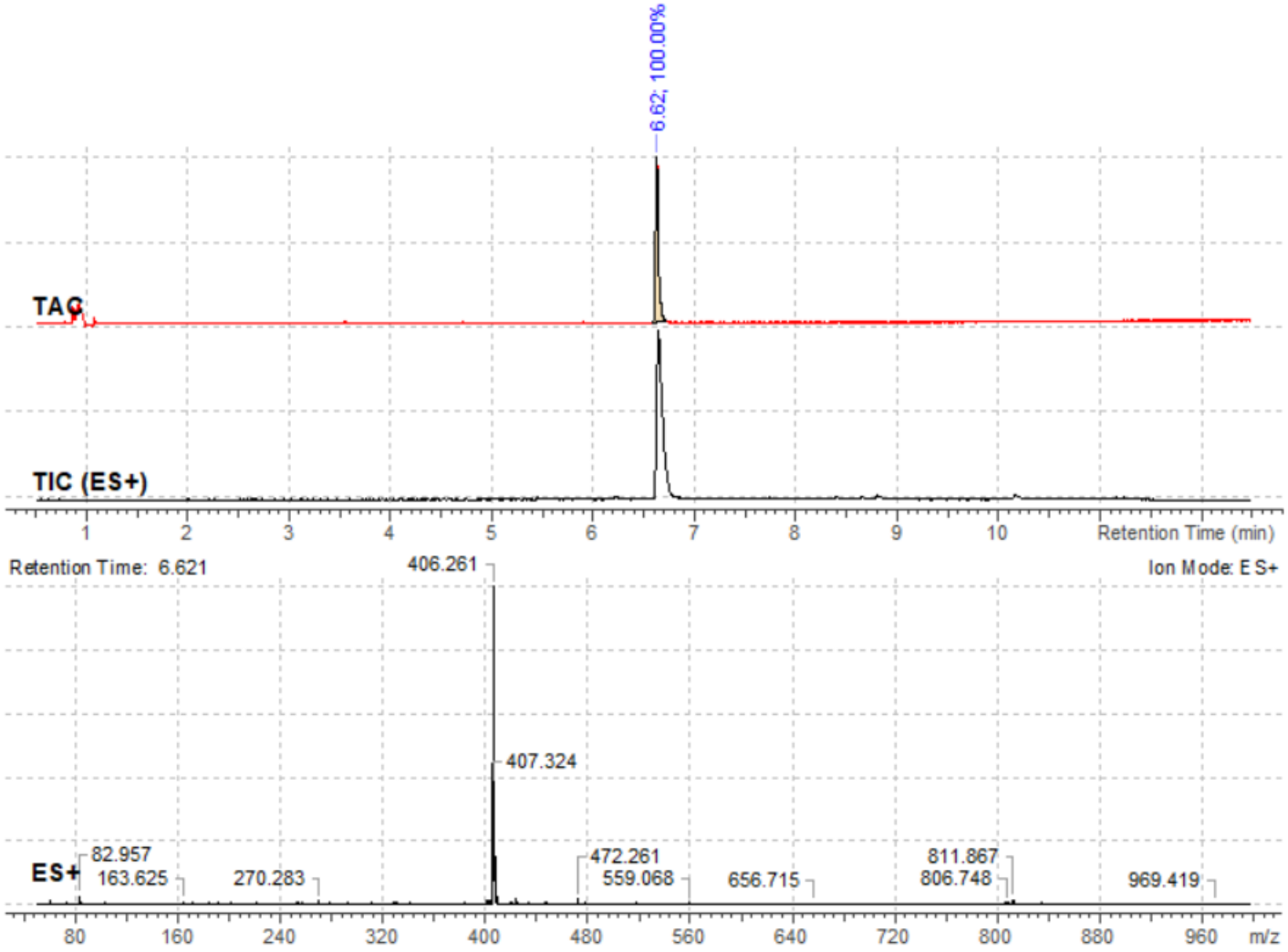
1-(1-Oxo-3-phenyl-1-(4-phenylpiperazin-1-yl)propan-2-yl)pyrrolidine-2,5-dione (37).



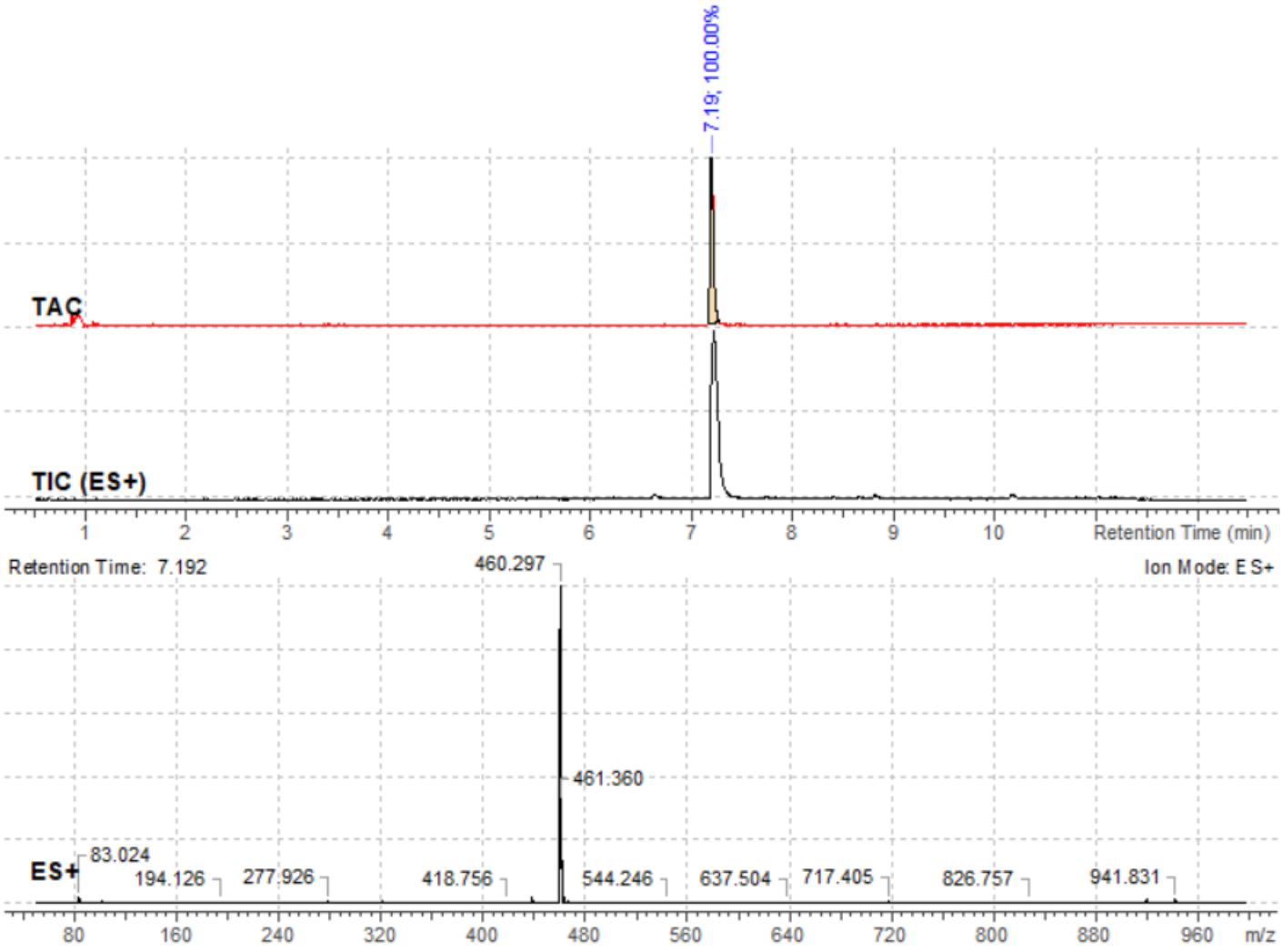
1-(1-(4-(3-Chlorophenyl)piperazin-1-yl)-1-oxo-3-phenylpropan-2-yl)pyrrolidine-2,5-dione (38).



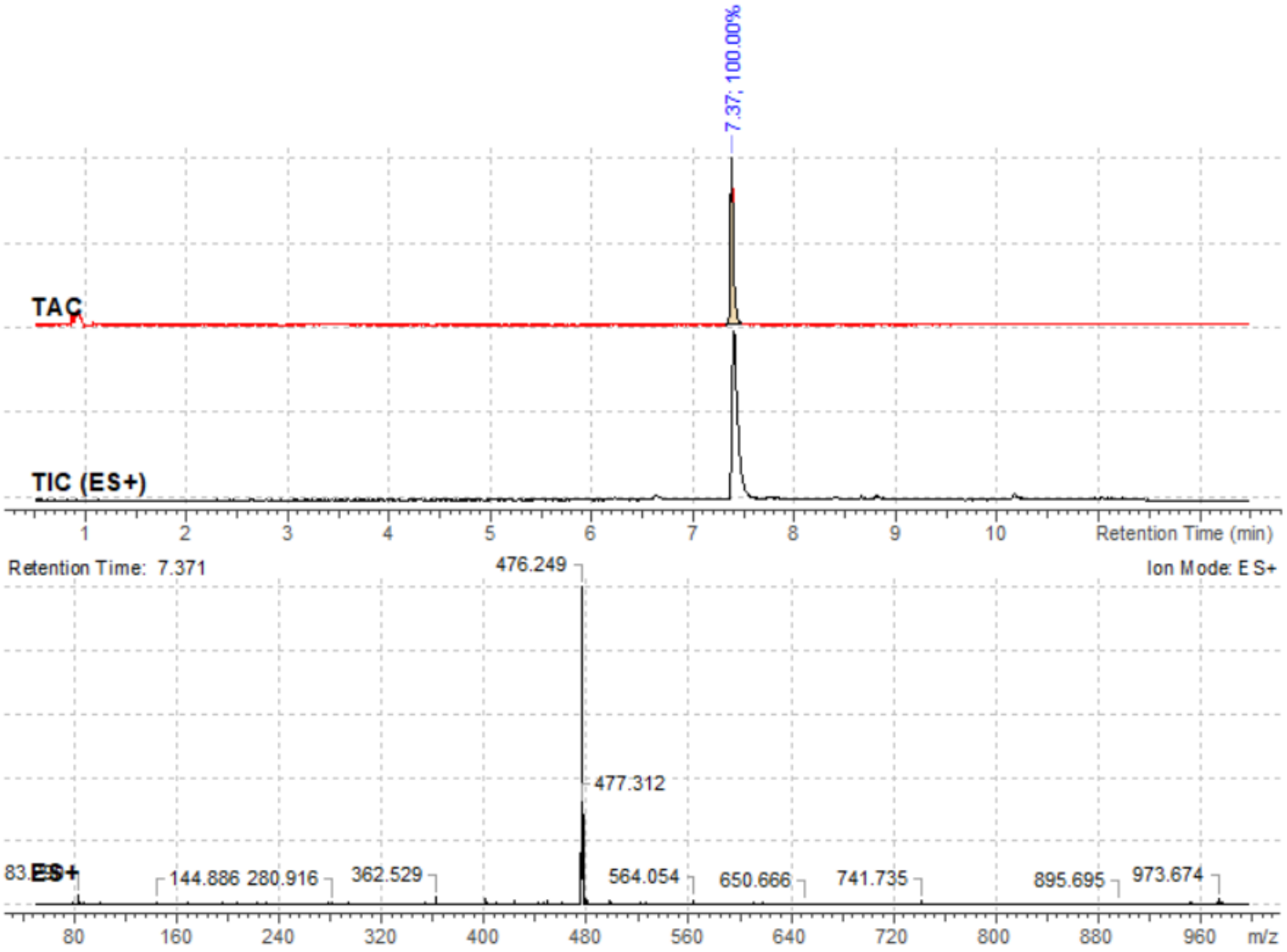
1-(1-Oxo-3-phenyl-1-(4-(m-tolyl)piperazin-1-yl)propan-2-yl)pyrrolidine-2,5-dione (39).



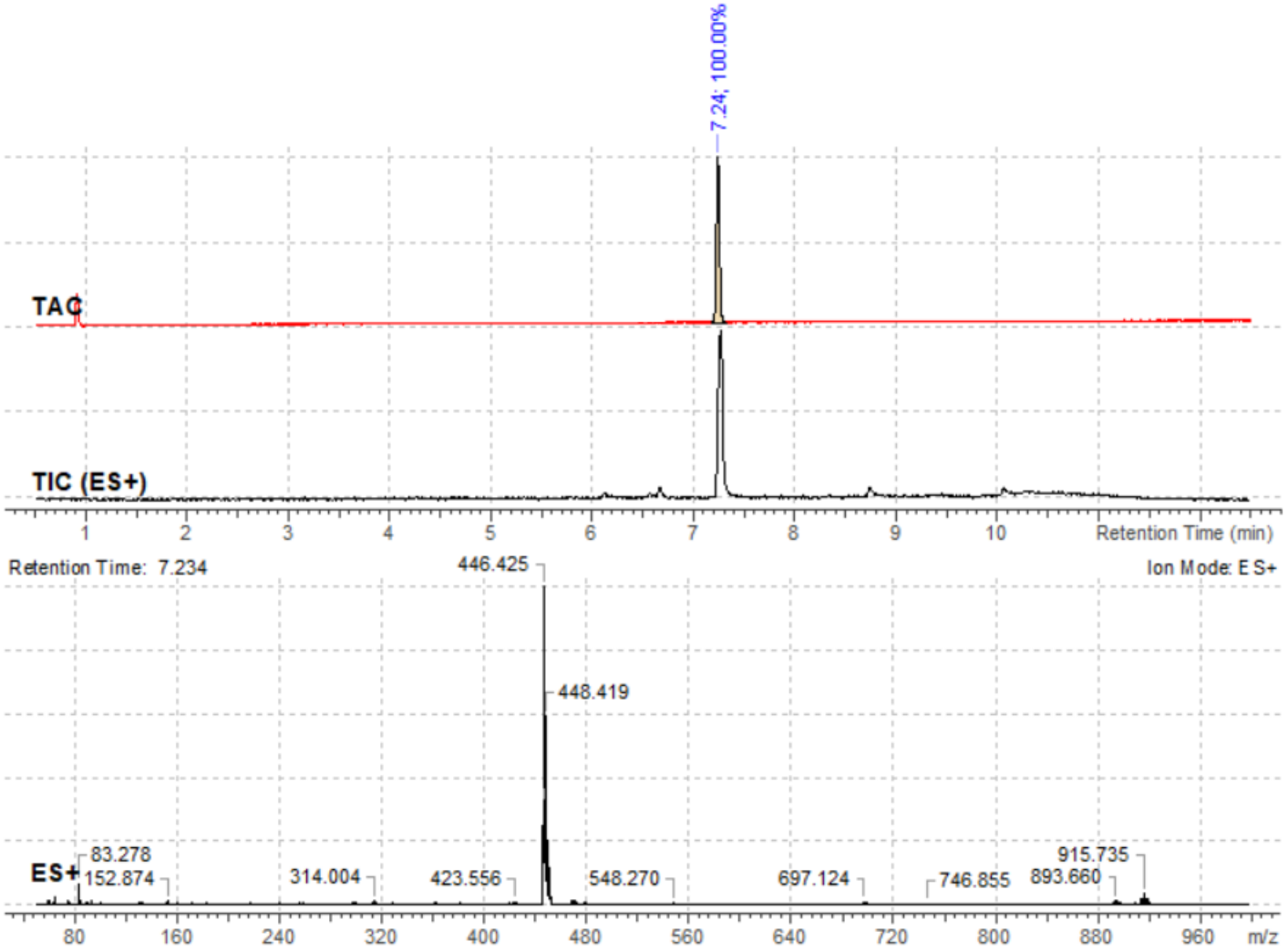
1-(1-Oxo-3-phenyl-1-(4-(3-(trifluoromethyl)phenyl)piperazin-1-yl)propan-2-yl)pyrrolidine-2,5-dione (40).



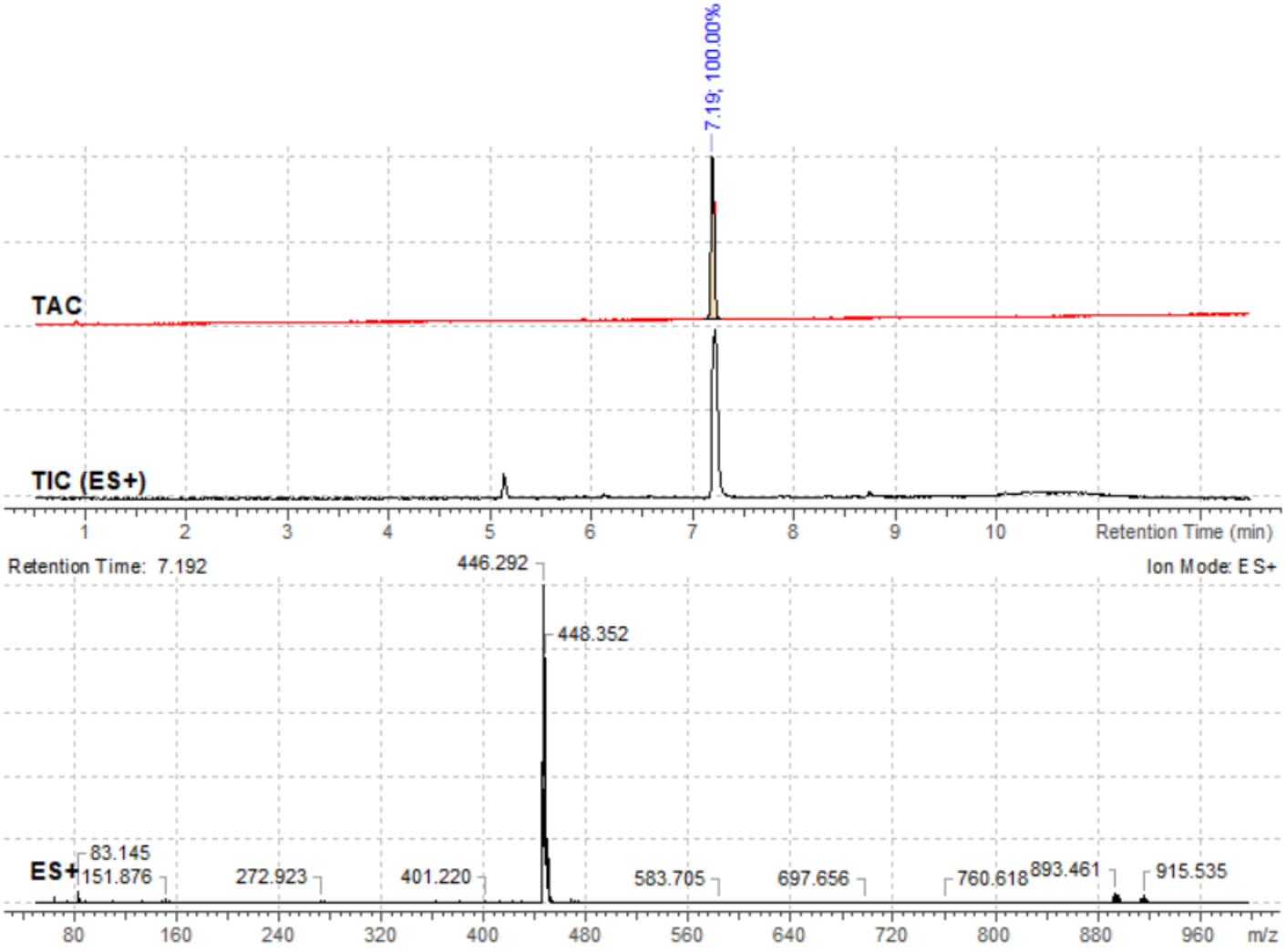
1-(1-Oxo-3-phenyl-1-(4-(3-(trifluoromethoxy)phenyl)piperazin-1-yl)propan-2-yl)pyrrolidine-2,5-dione (41).



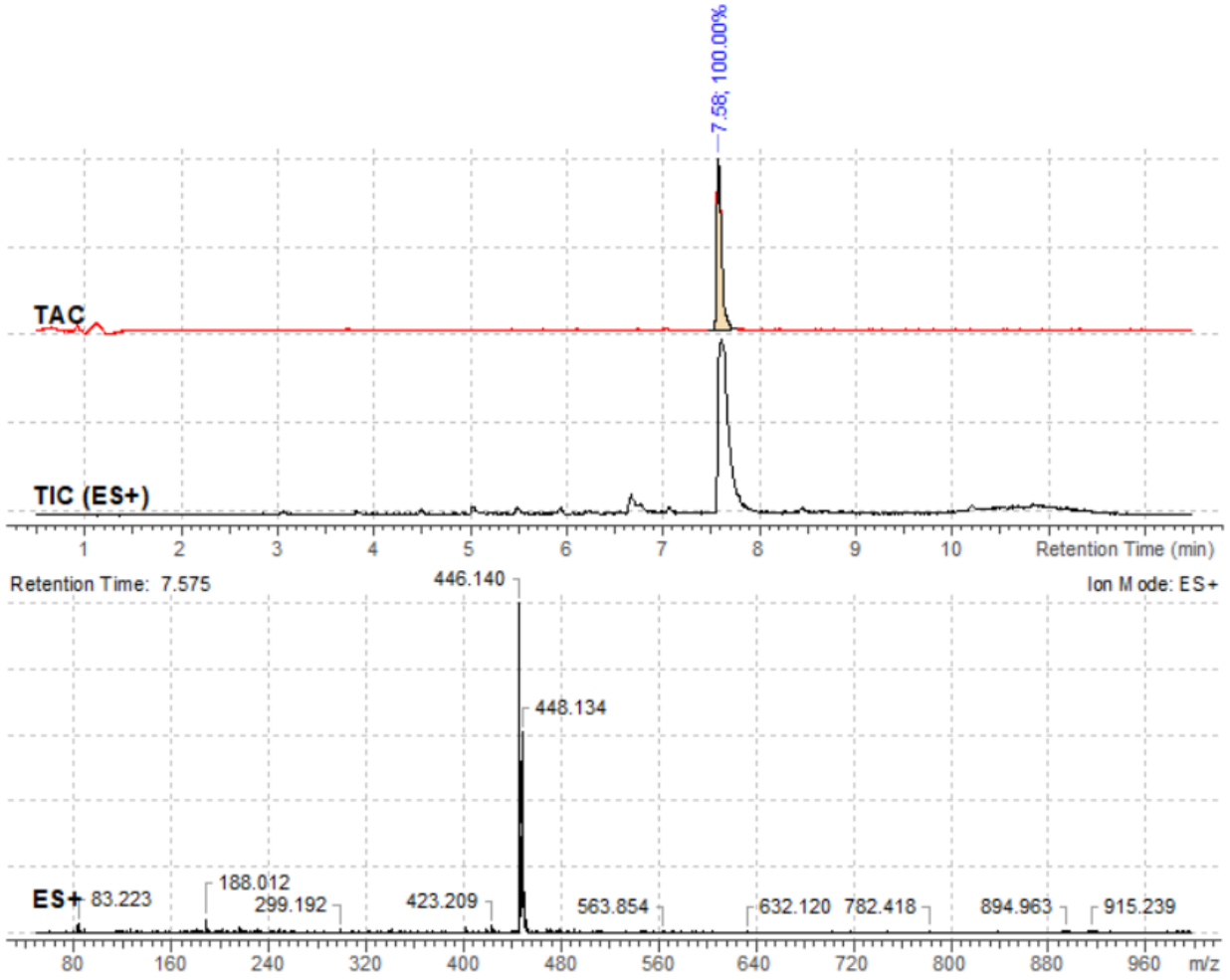
1-(2-(4-(2,3-Dichlorophenyl)piperazin-1-yl)-2-oxo-1-phenylethyl)pyrrolidine-2,5-dione (42).



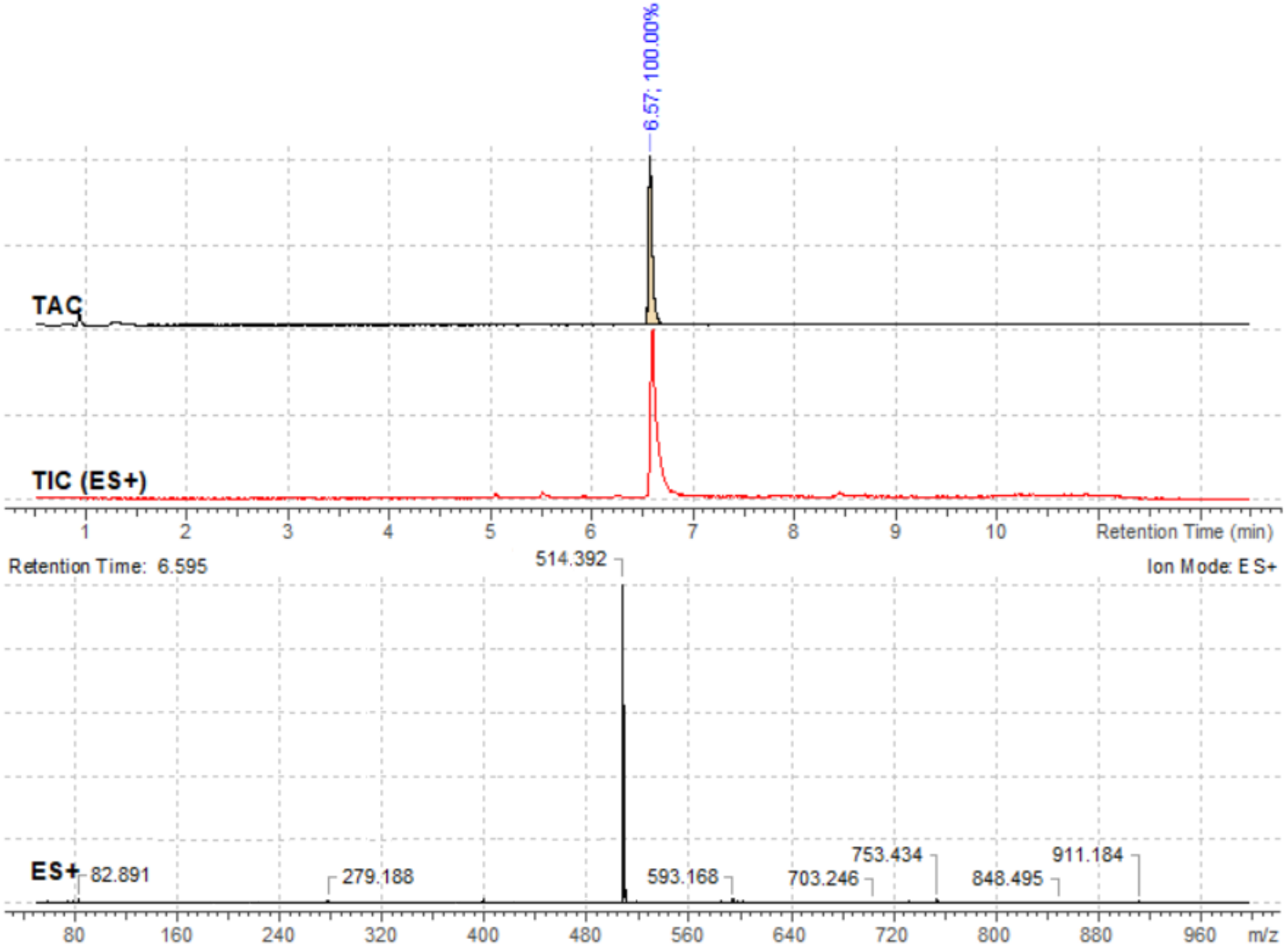
1-(2-(4-(3,4-Dichlorophenyl)piperazin-1-yl)-2-oxo-1-phenylethyl)pyrrolidine-2,5-dione (43).



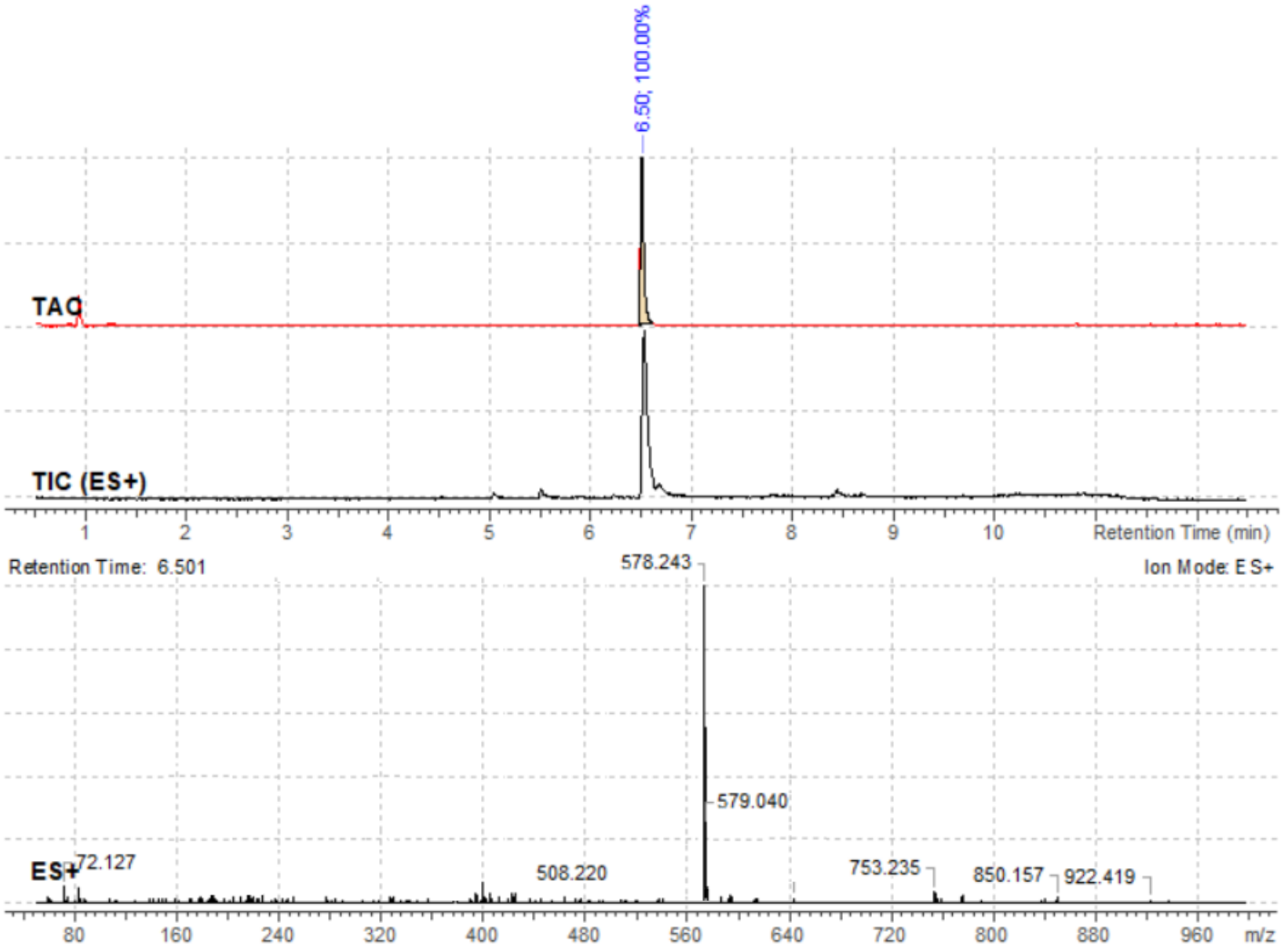
1-(2-(4-(3,5-Dichlorophenyl)piperazin-1-yl)-2-oxo-1-phenylethyl)pyrrolidine-2,5-dione (44)



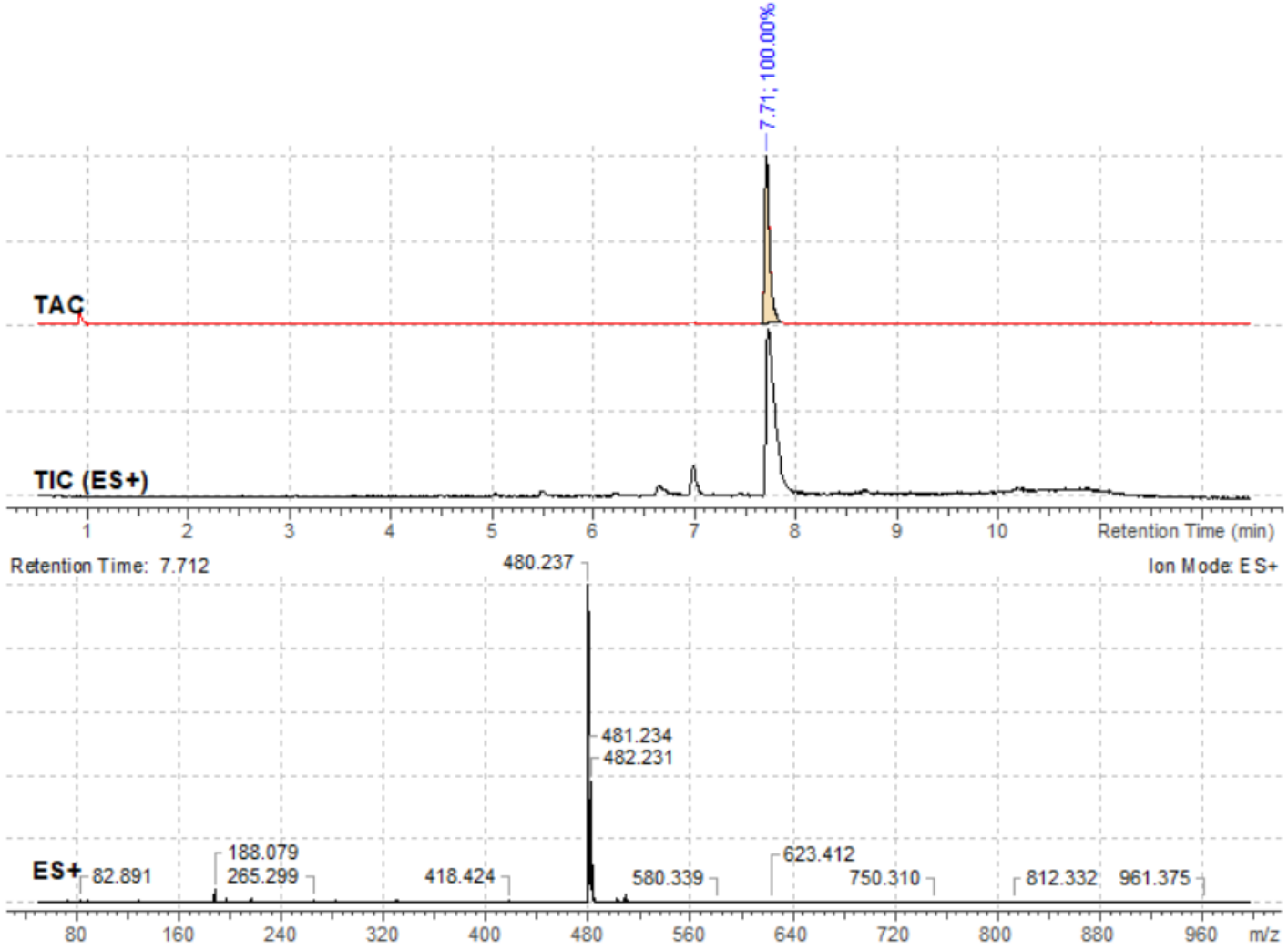
1-(2-(4-(3,5-bis(trifluoromethyl)phenyl)piperazin-1-yl)-2-oxo-1-phenylethyl)pyrrolidine-2,5-dione (45).



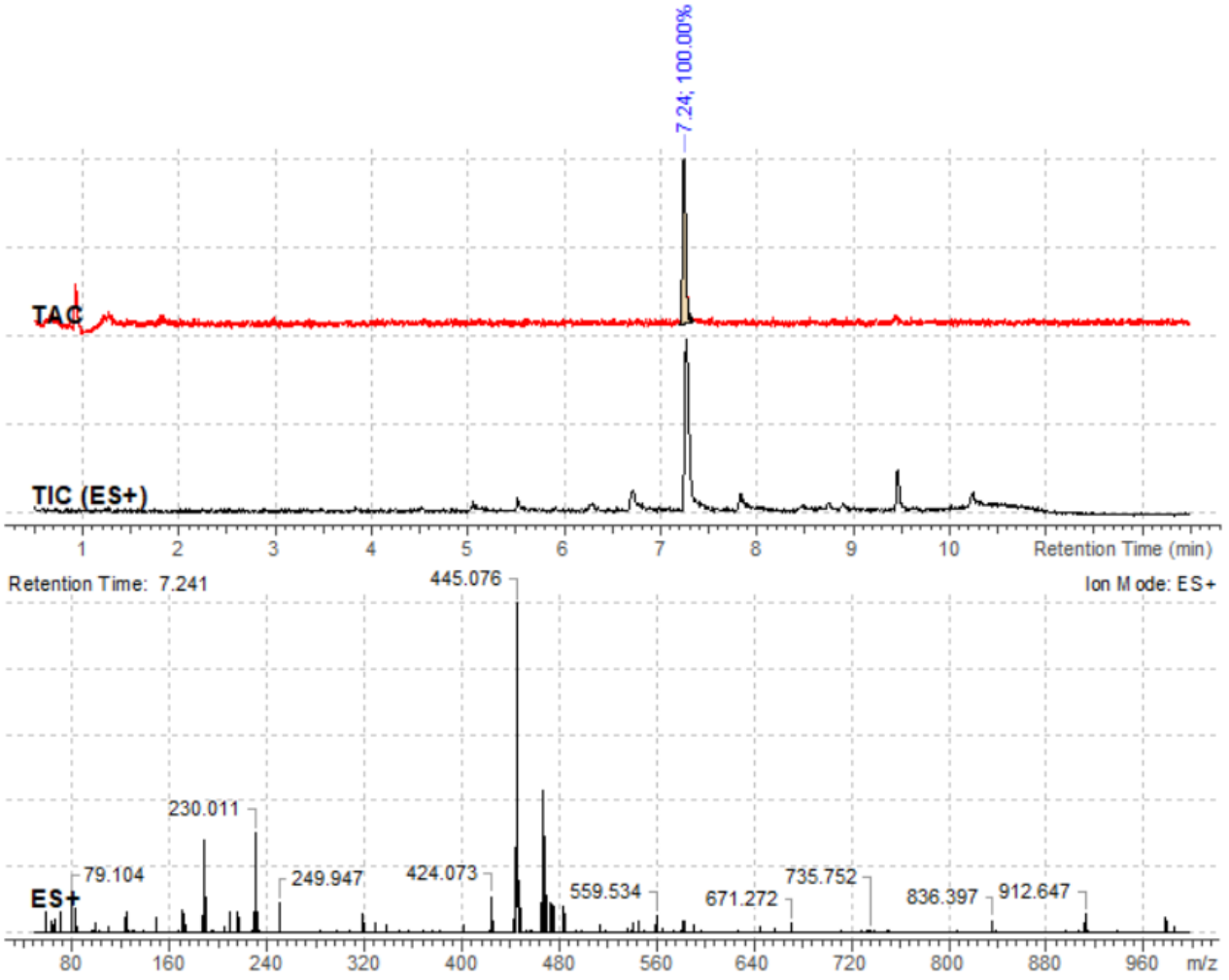
1-(2-(4-(3,5-bis((trifluoromethyl)thio)phenyl)piperazin-1-yl)-2-oxo-1-phenylethyl)pyrrolidine-2,5-dione (46).



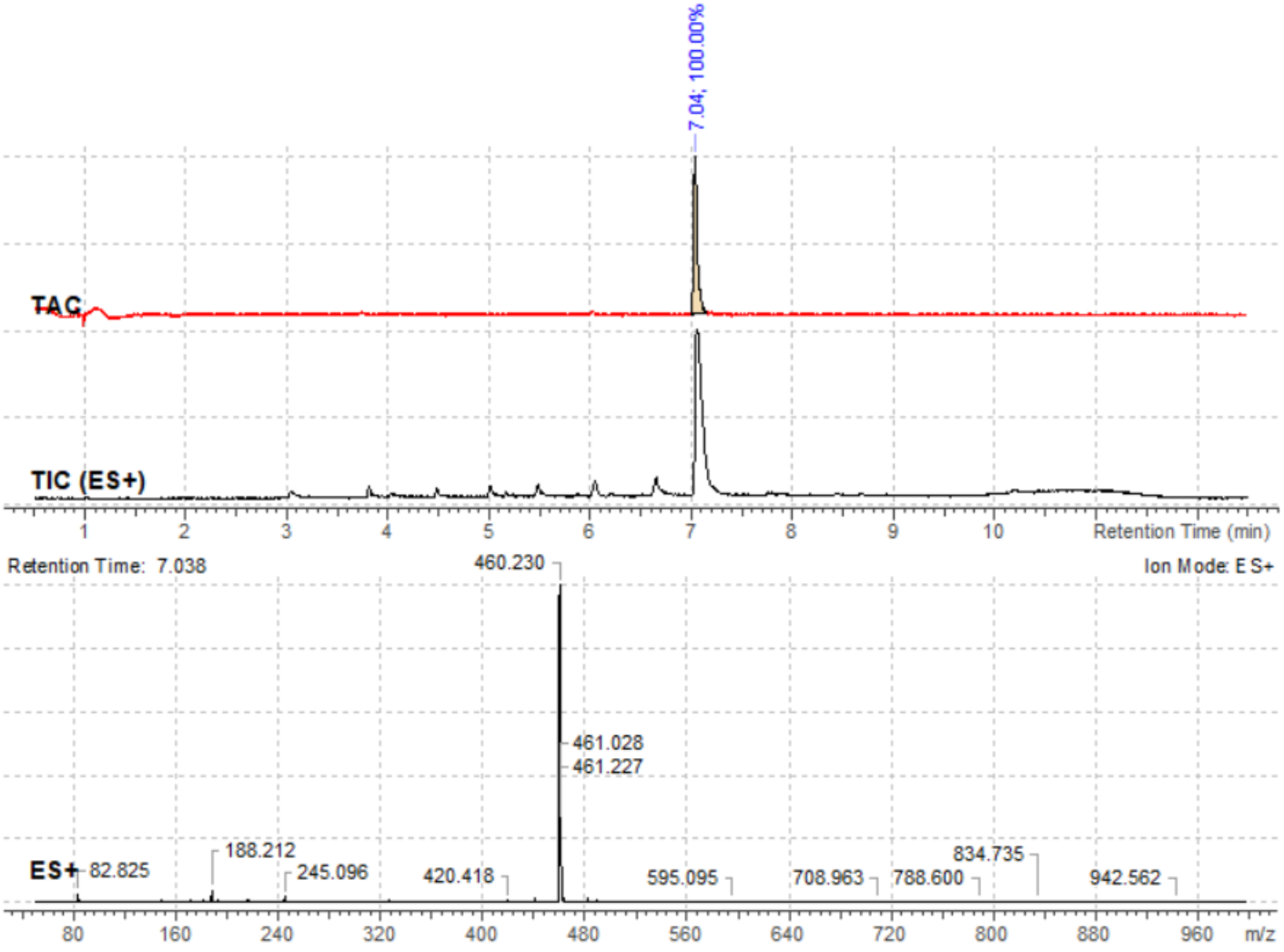
1-(2-(4-(3-chloro-5-(trifluoromethyl)phenyl)piperazin-1-yl)-2-oxo-1-phenylethyl)pyrrolidine-2,5-dione (47).



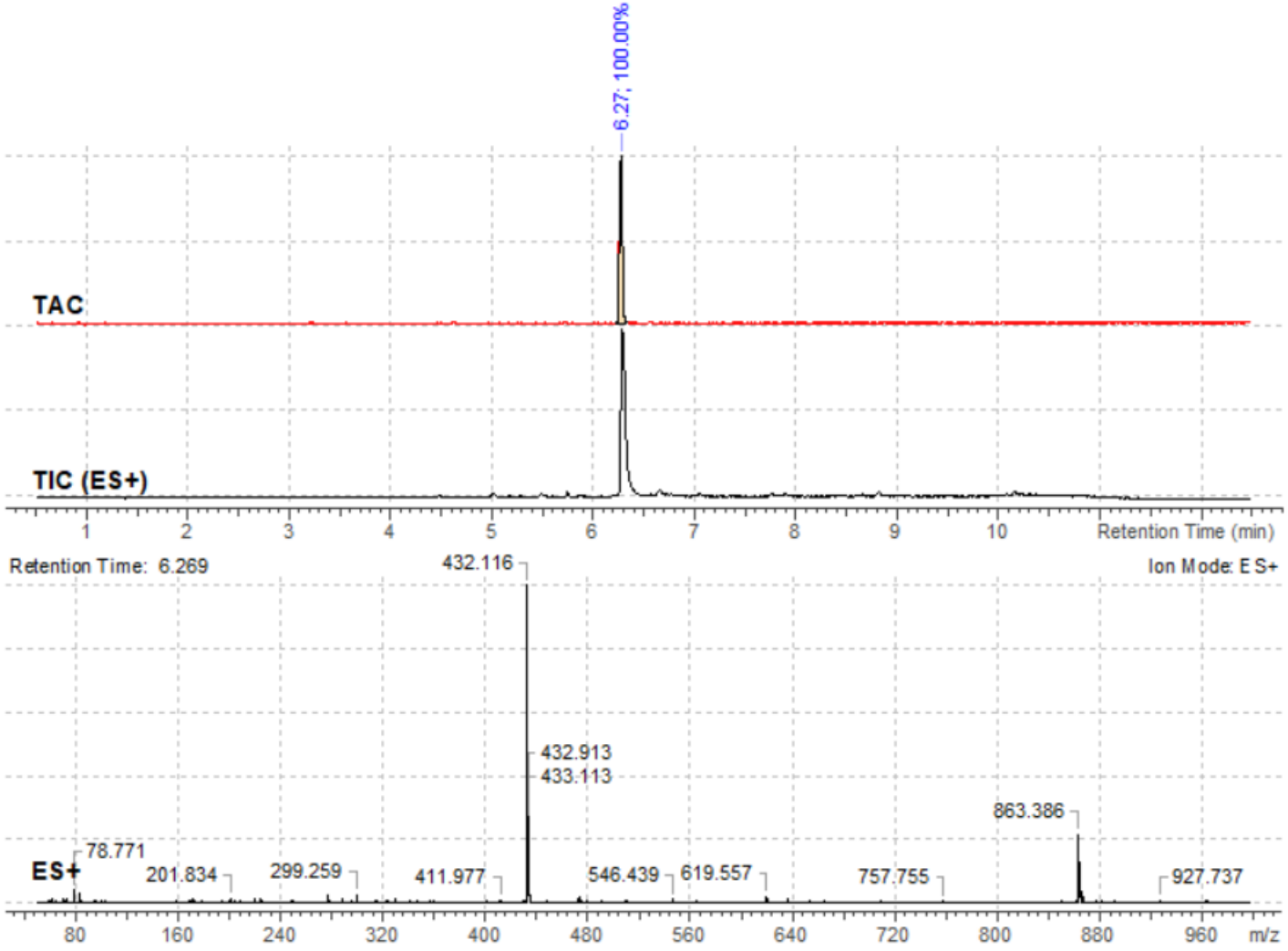
1-(2-Oxo-1-phenyl-2-(4-(3-(trifluoromethyl)phenyl)piperidin-1-yl)ethyl)pyrrolidine-2,5-dione (48)



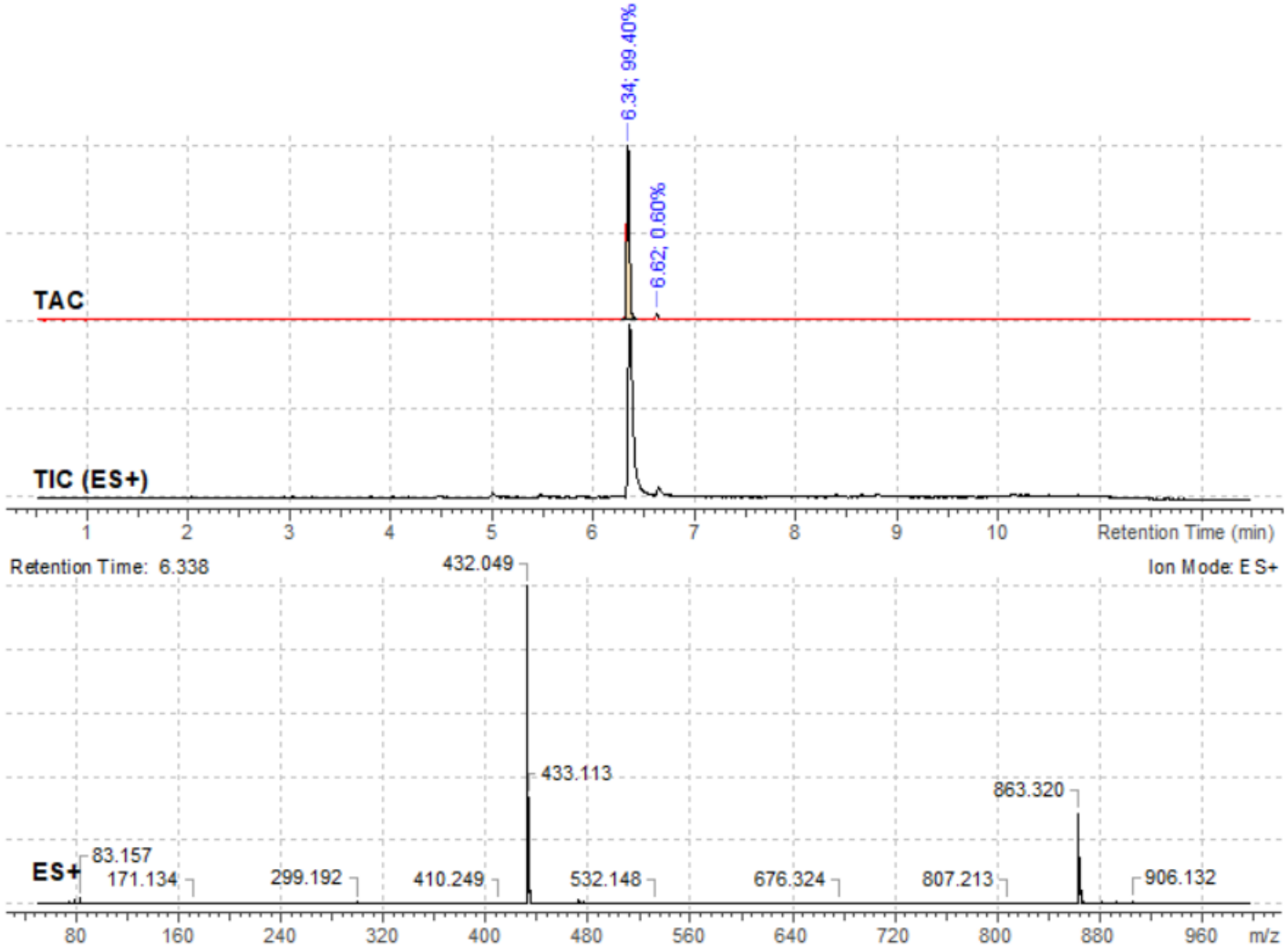
1-(2-Oxo-1-phenyl-2-(4-(3-(trifluoromethyl)phenyl)-1,4-diazepan-1-yl)ethyl)pyrrolidine-2,5-dione (49).



1-(3-(4-(3-(Trifluoromethyl)phenyl)piperazine-1-carbonyl)phenyl)pyrrolidine-2,5-dione (52).

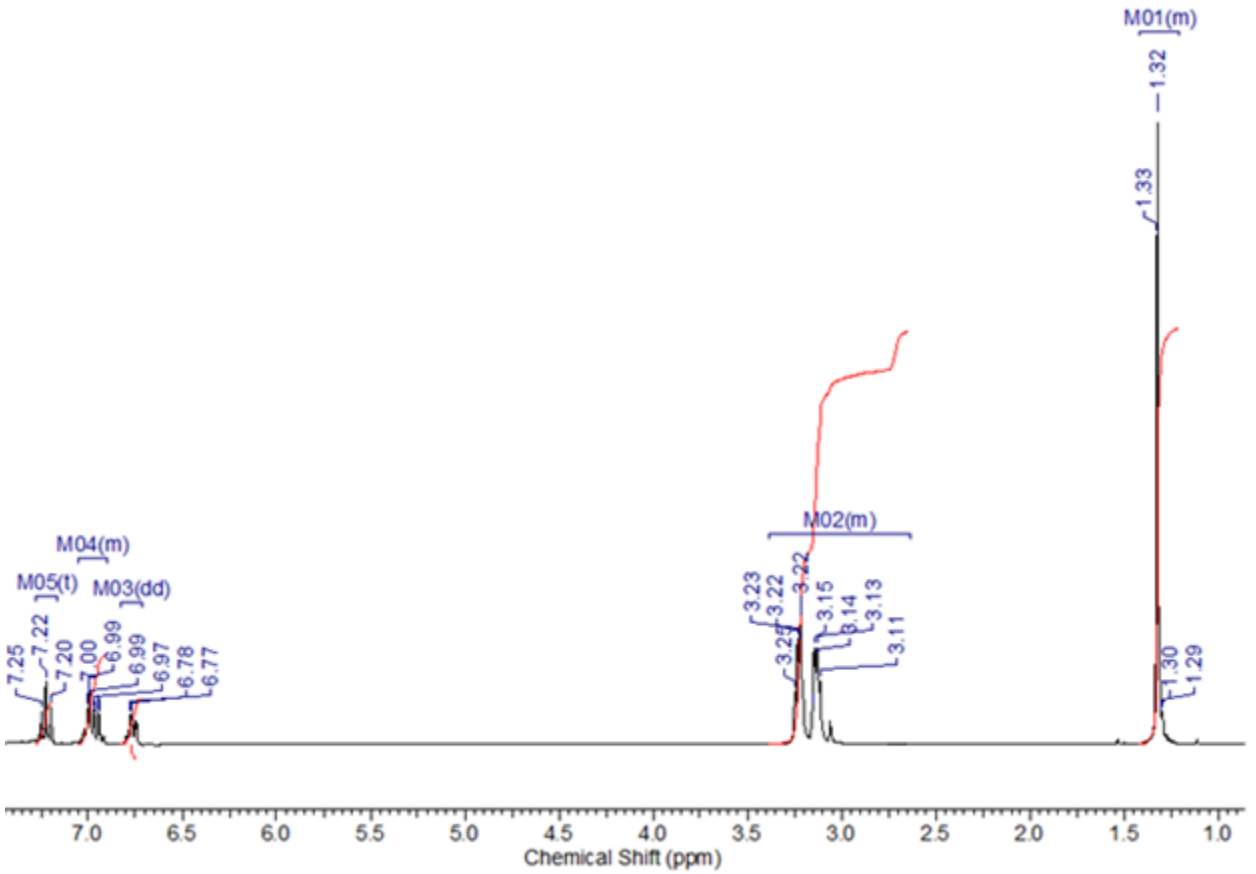


1-(4-(4-(3-(Trifluoromethyl)phenyl)piperazine-1-carbonyl)phenyl)pyrrolidine-2,5-dione (53).

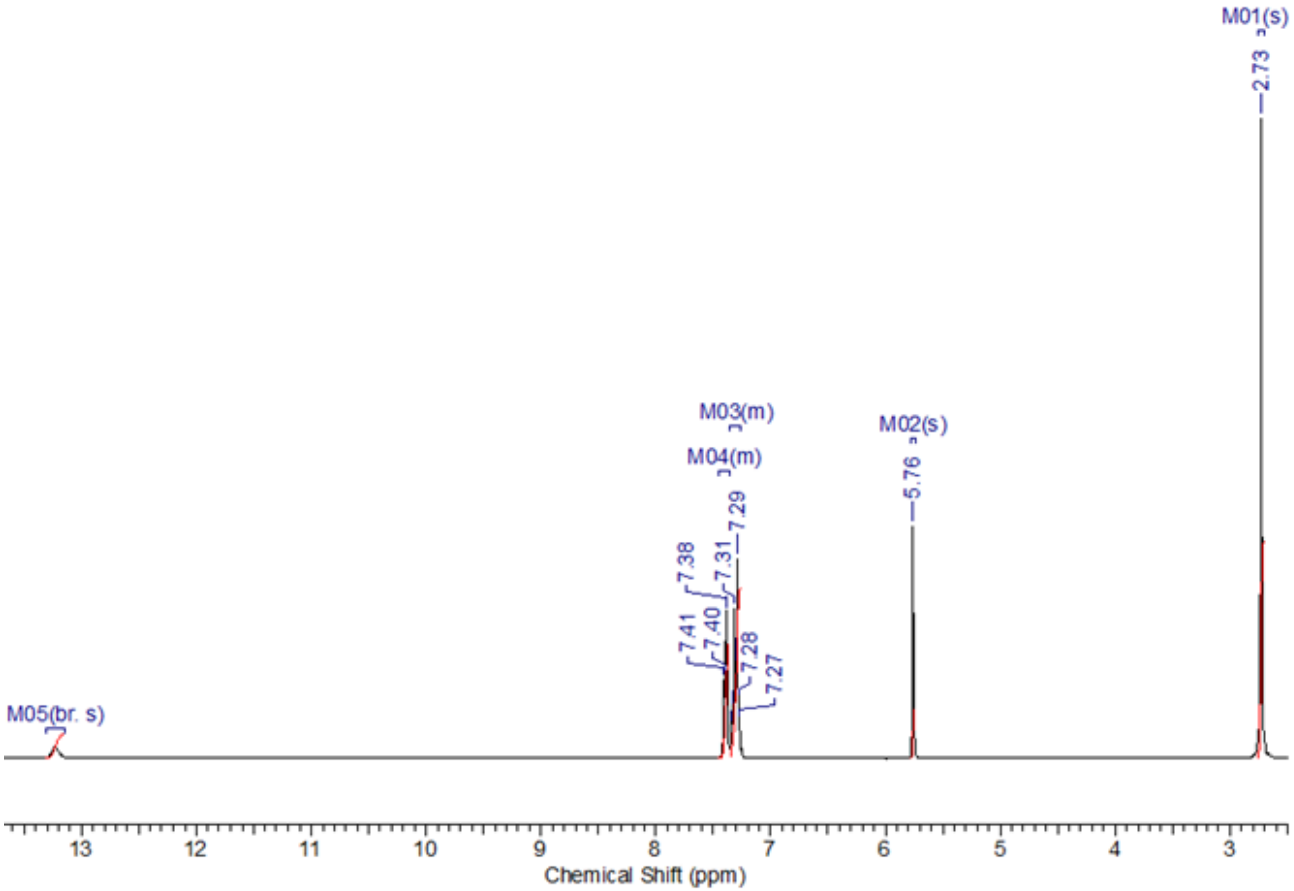


^{1}H NMR, ^{13}C NMR, ^{19}F NMR spectra for selected starting amines, intermediates and final compounds

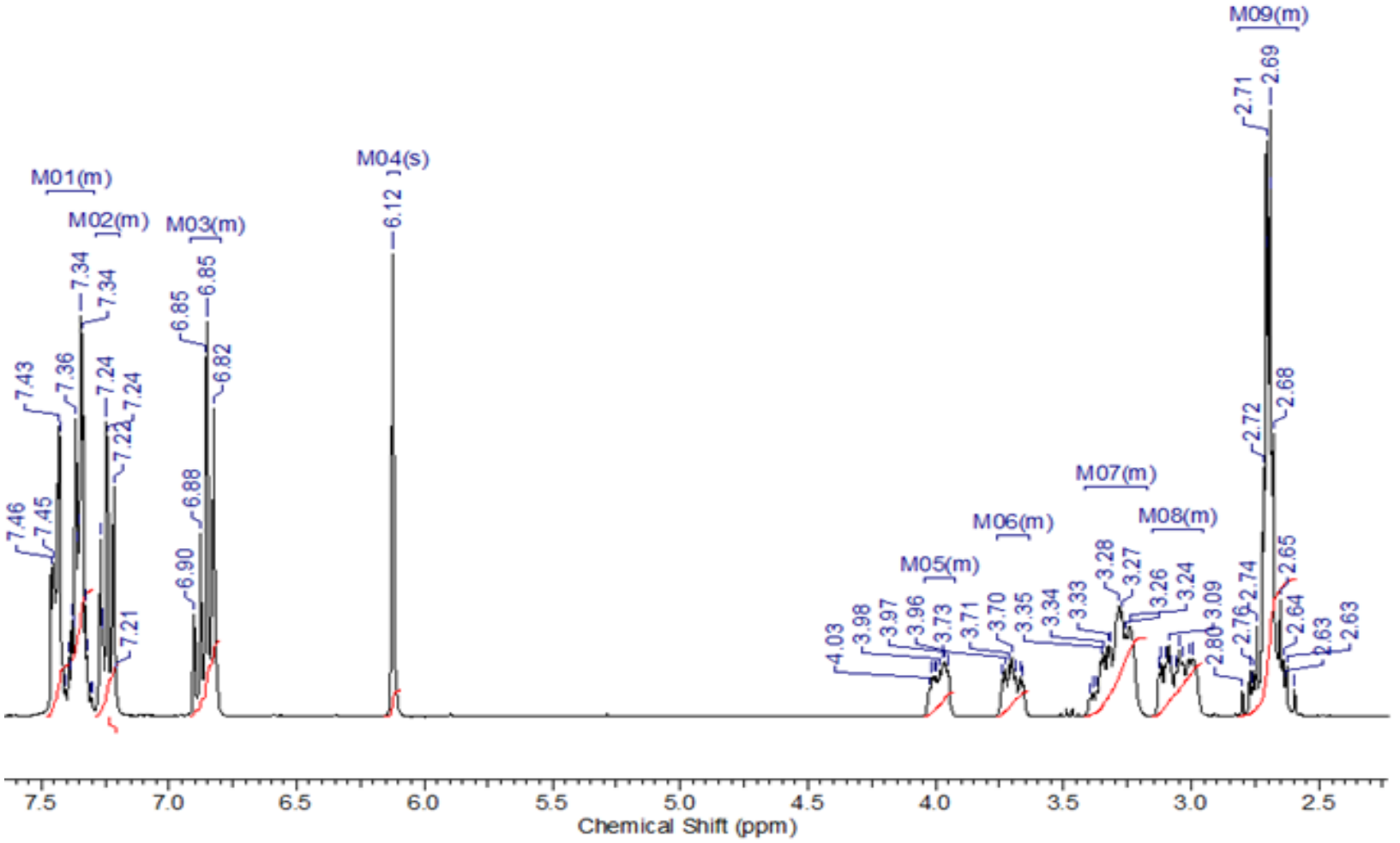
1-(3-(*Tert*-butyl)phenyl)piperazine (A14) - ^{1}H NMR



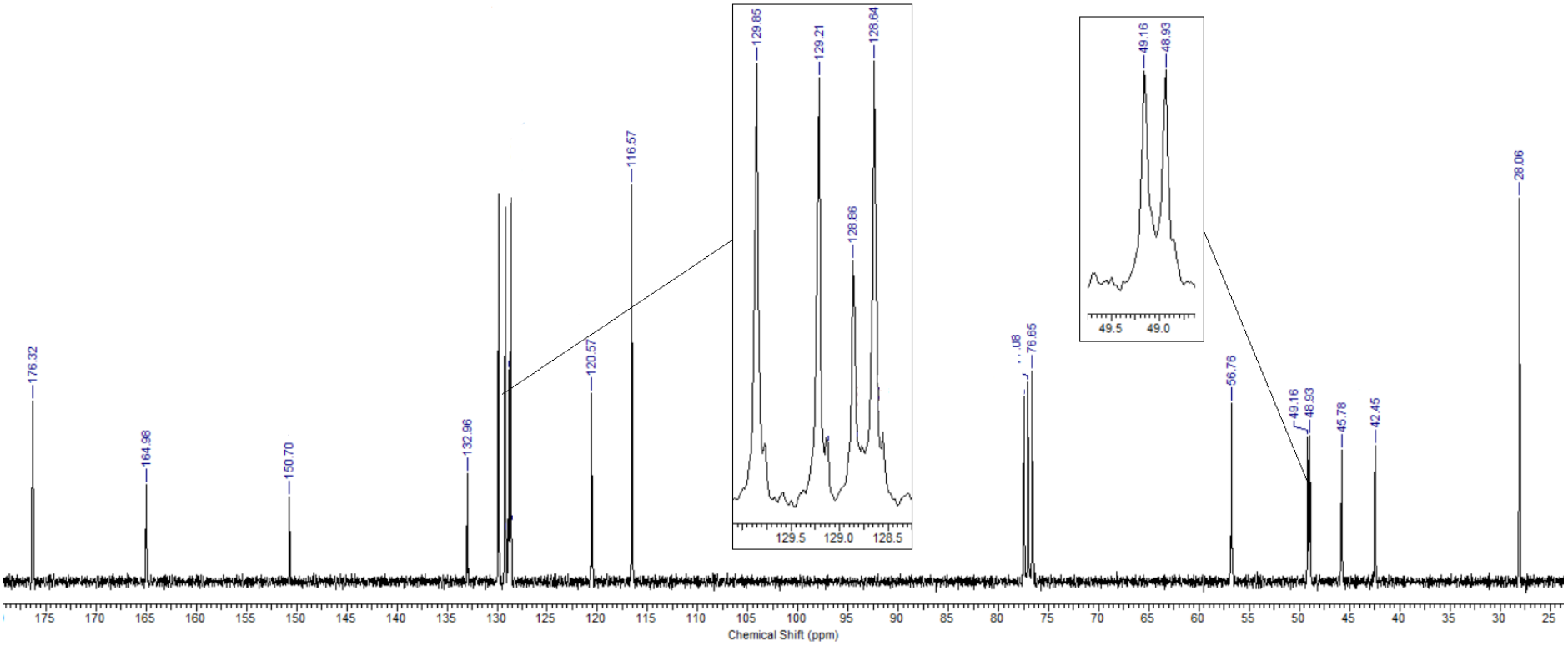
2-(2,5-dioxopyrrolidin-1-yl)-2-phenylacetic acid (6) - ^{1}H NMR



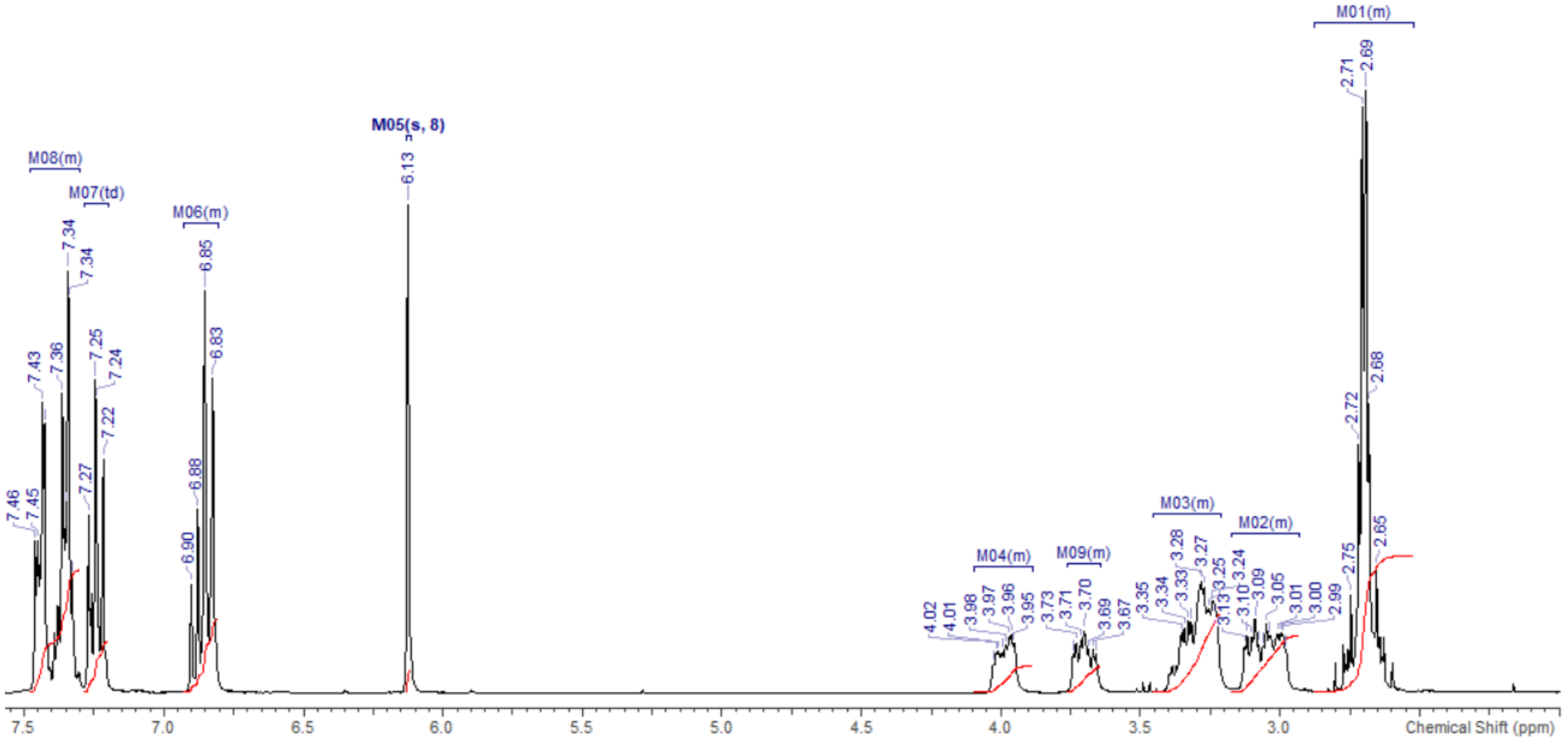
1-(2-Oxo-1-phenyl-2-(4-phenylpiperazin-1-yl)ethyl)pyrrolidine-2,5-dione (11) - ^{1}H NMR



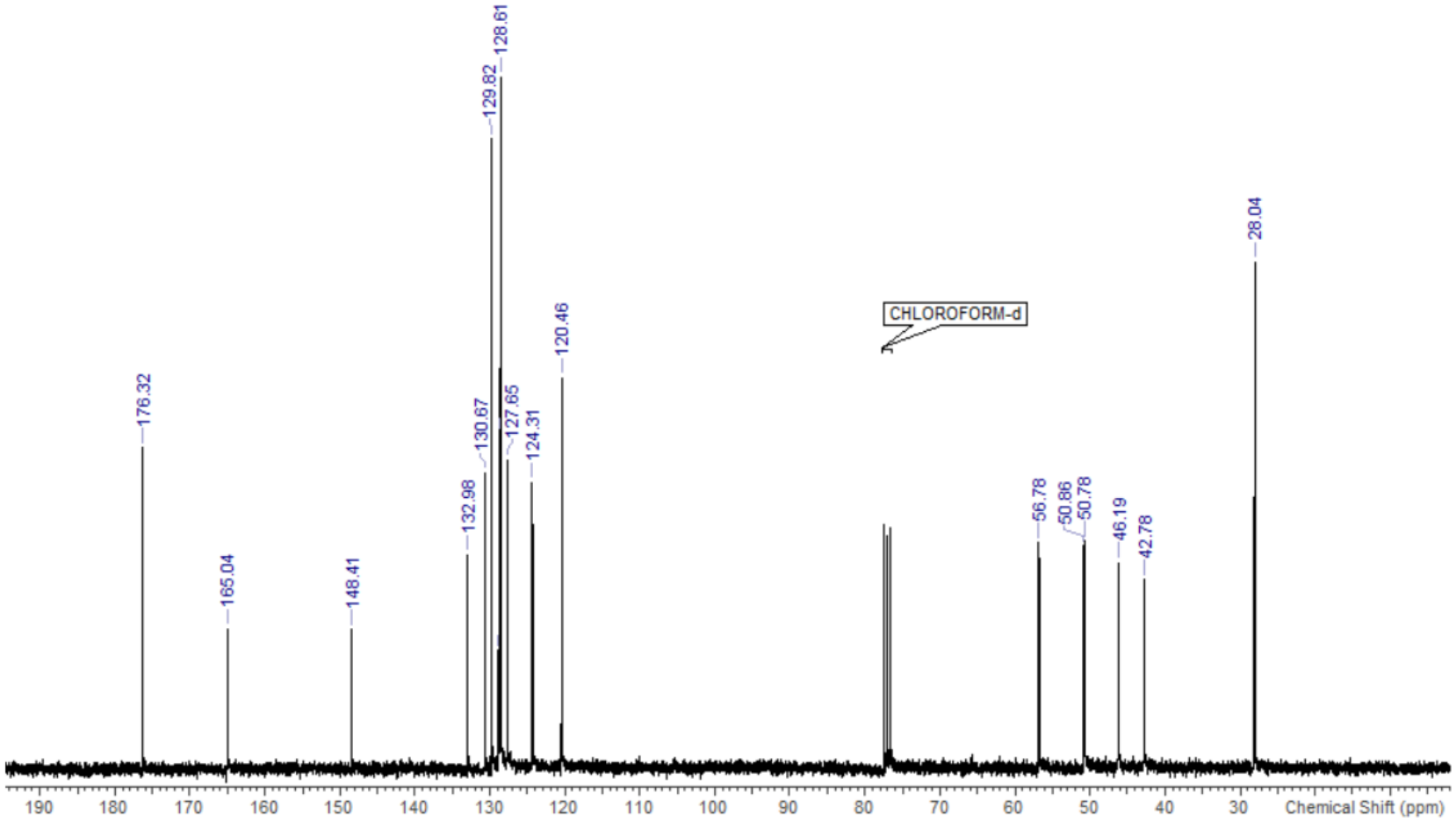
1-(2-Oxo-1-phenyl-2-(4-phenylpiperazin-1-yl)ethyl)pyrrolidine-2,5-dione (11) – ^{13}C NMR



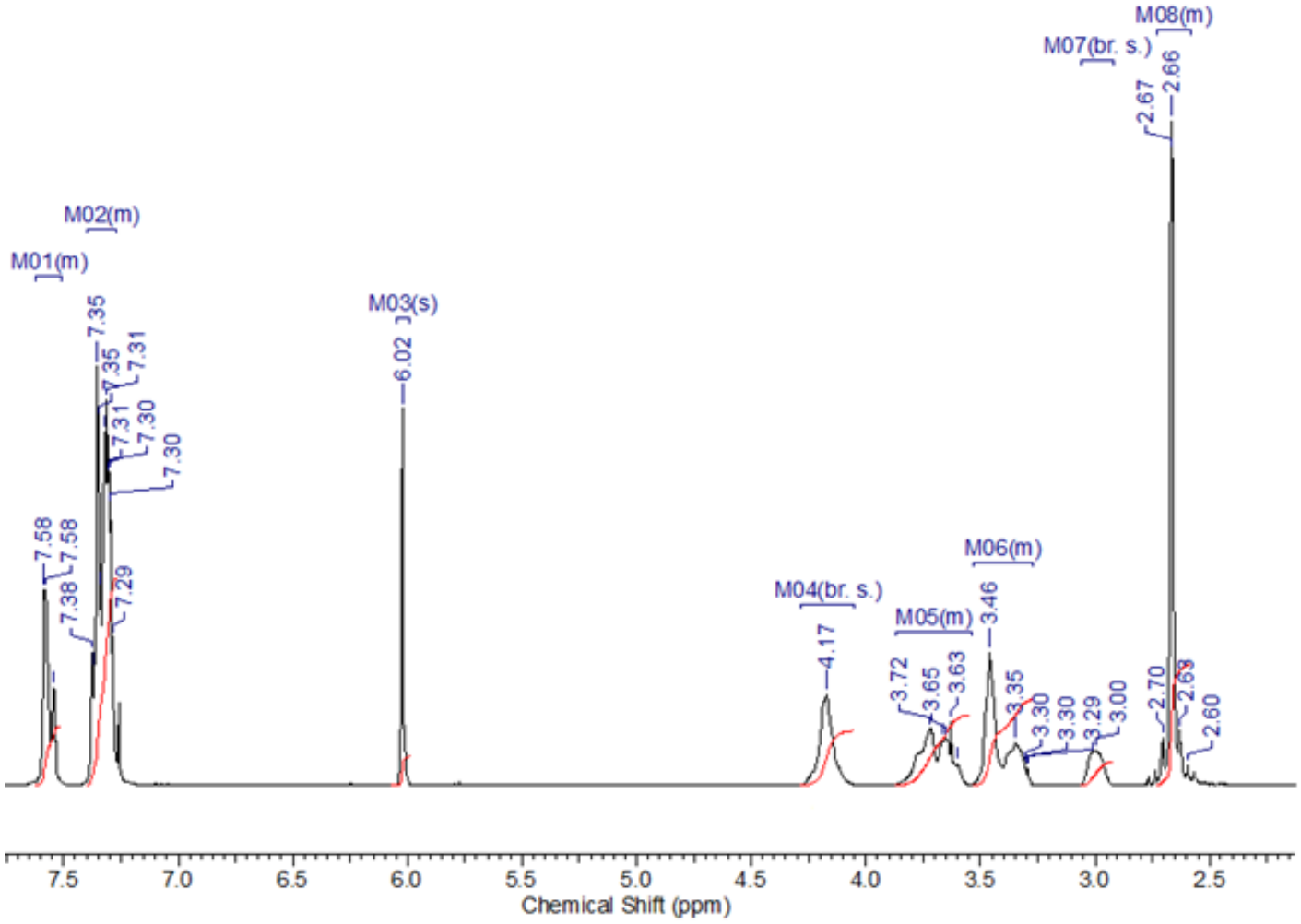
1-(2-(4-(2-Chlorophenyl)piperazin-1-yl)-2-oxo-1-phenylethyl)pyrrolidine-2,5-dione (12) - ^{1}H NMR



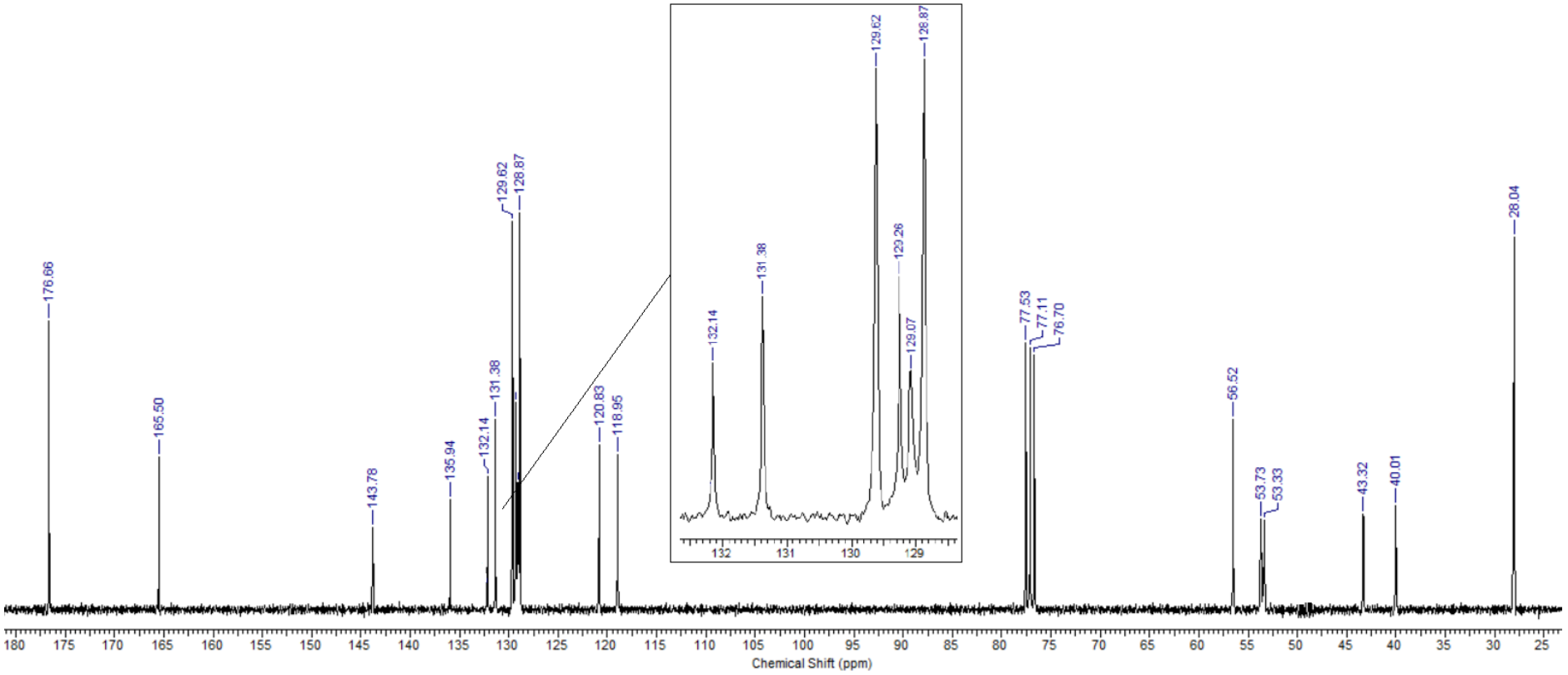
1-(2-(4-(2-Chlorophenyl)piperazin-1-yl)-2-oxo-1-phenylethyl)pyrrolidine-2,5-dione (12) – ^{13}C NMR



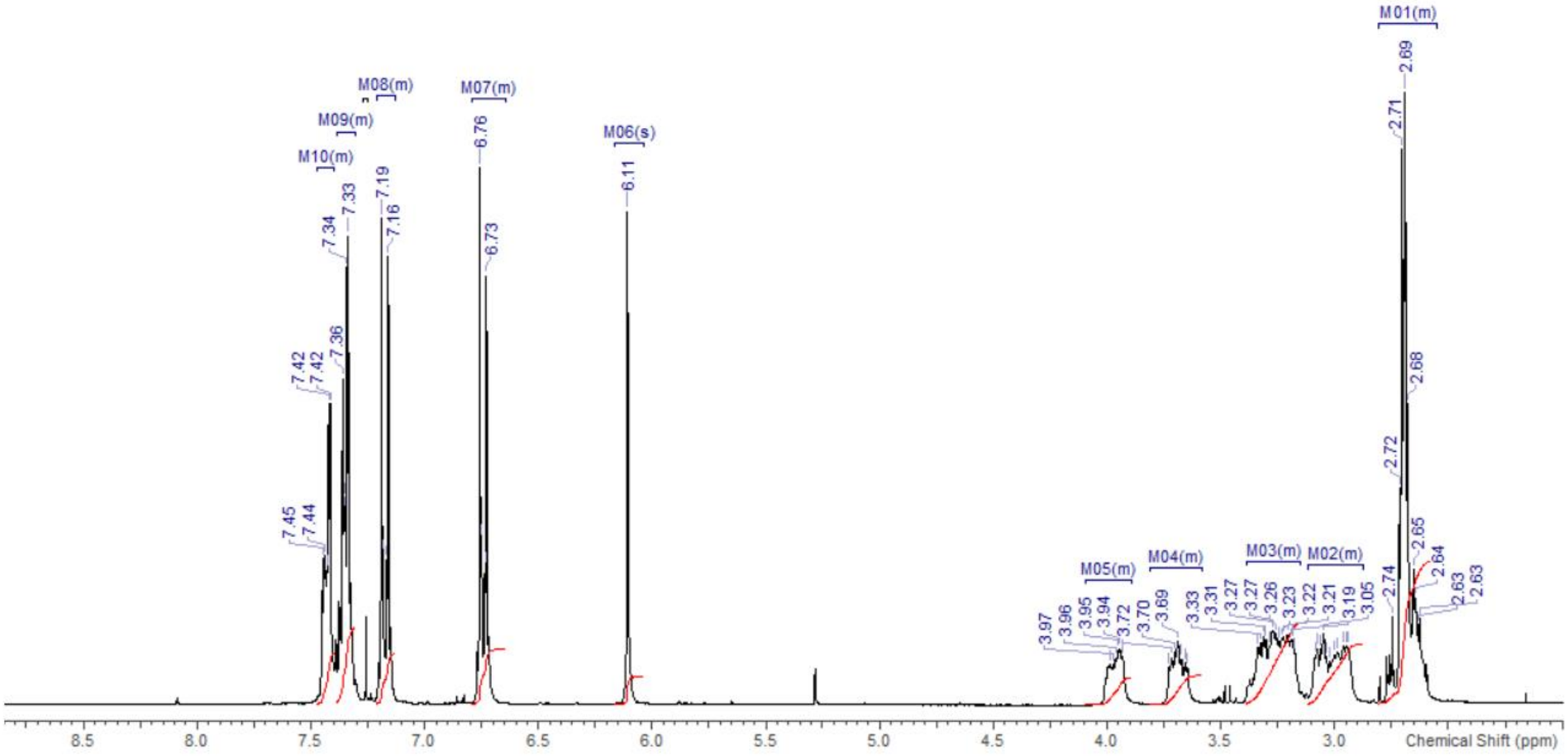
1-(2-(4-(3-Chlorophenyl)piperazin-1-yl)-2-oxo-1-phenylethyl)pyrrolidine-2,5-dione (13) - ^{1}H NMR



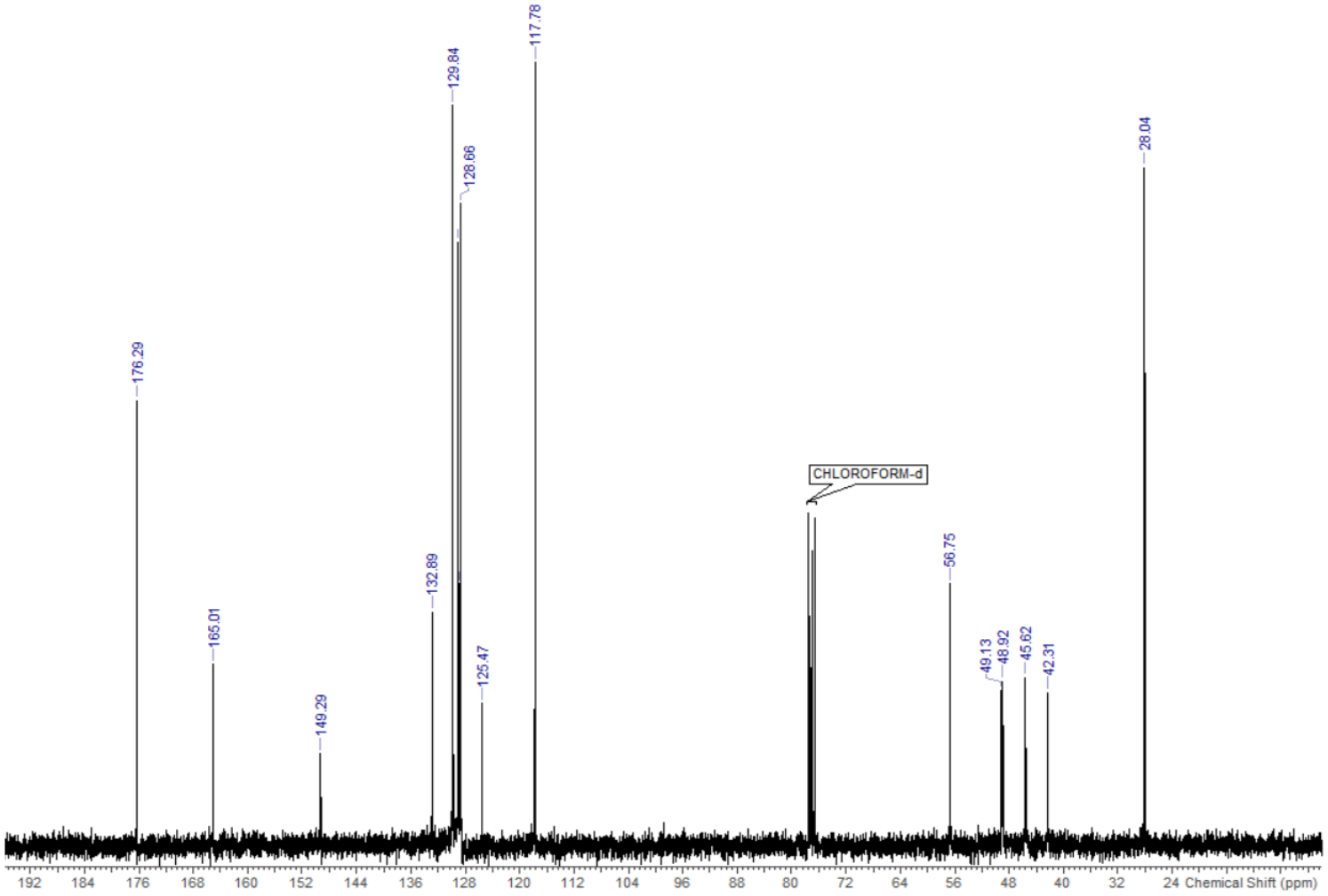
1-(2-(4-(3-Chlorophenyl)piperazin-1-yl)-2-oxo-1-phenylethyl)pyrrolidine-2,5-dione (13) - ^{13}C NMR



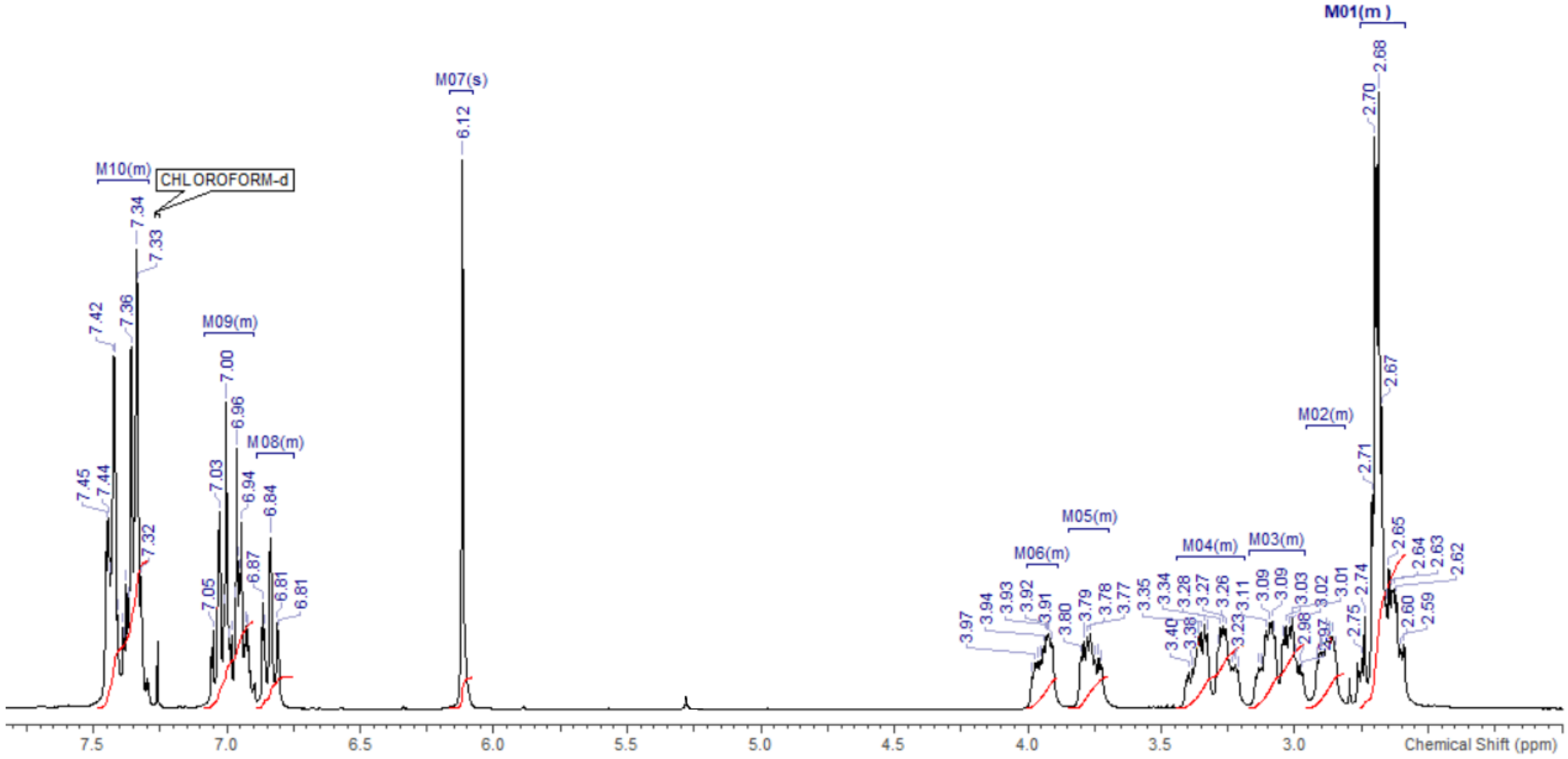
1-(2-(4-(4-Chlorophenyl)piperazin-1-yl)-2-oxo-1-phenylethyl)pyrrolidine-2,5-dione (14) - ^{1}H NMR



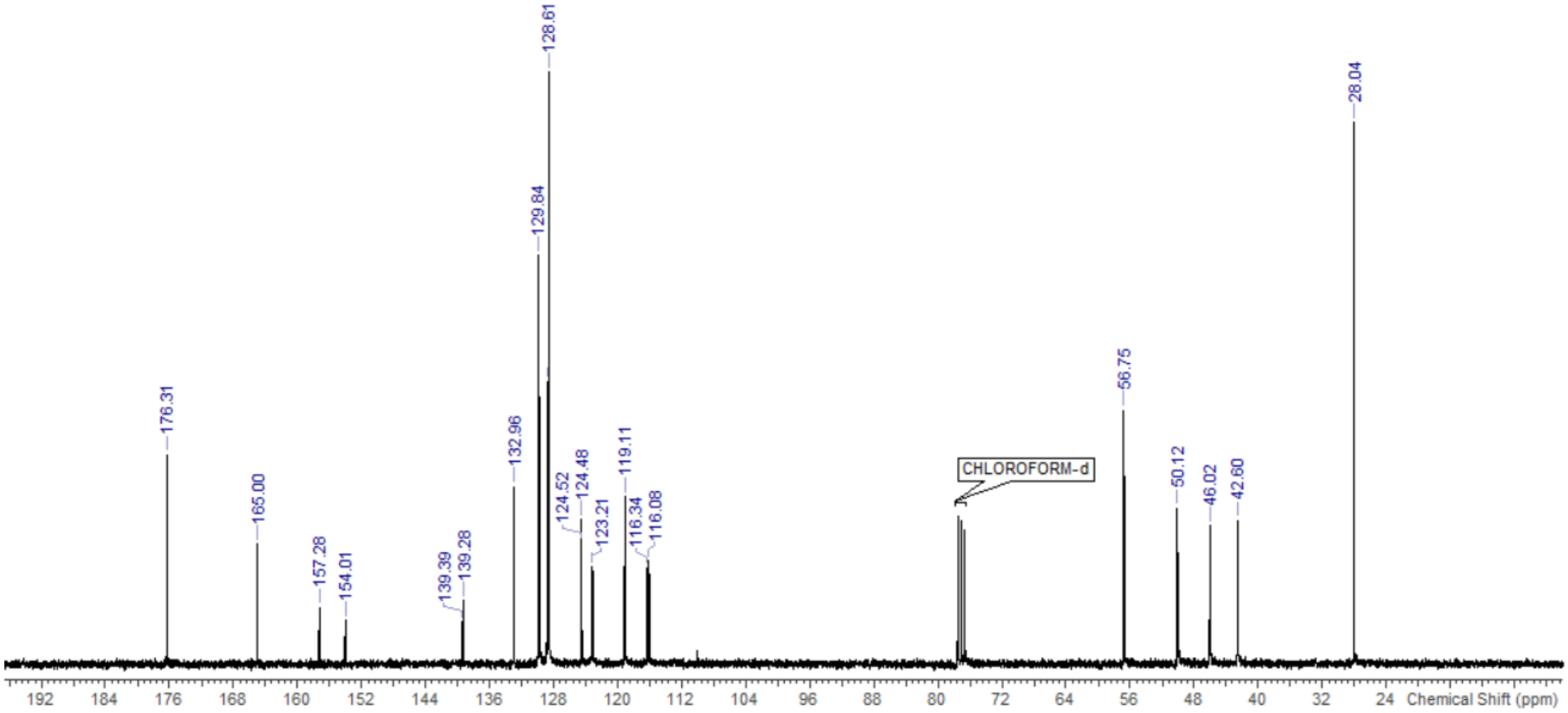
1-(2-(4-(4-Chlorophenyl)piperazin-1-yl)-2-oxo-1-phenylethyl)pyrrolidine-2,5-dione (14) – ^{13}C NMR



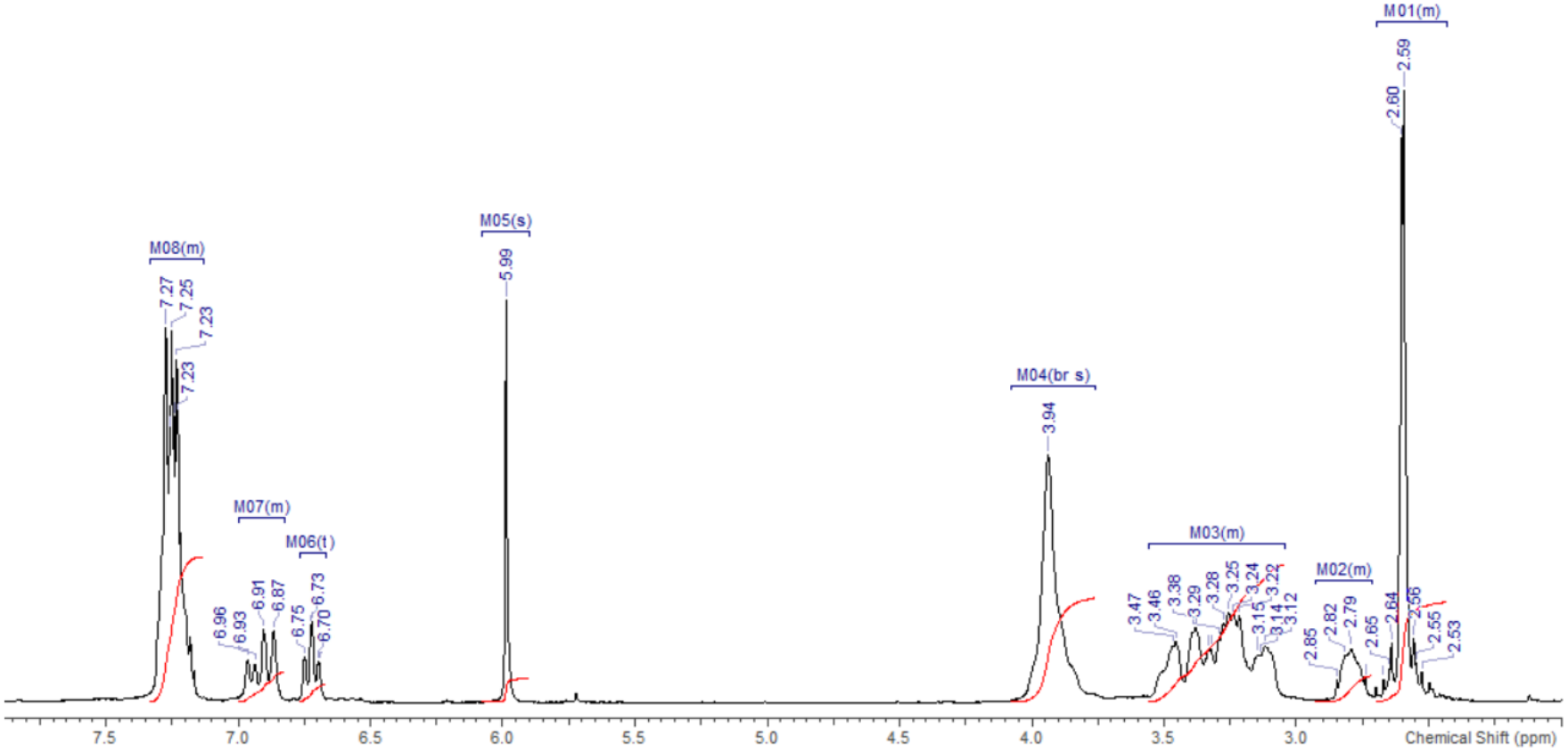
1-(2-(4-(2-Fluorophenyl)piperazin-1-yl)-2-oxo-1-phenylethyl)pyrrolidine-2,5-dione (15) - ^{1}H NMR



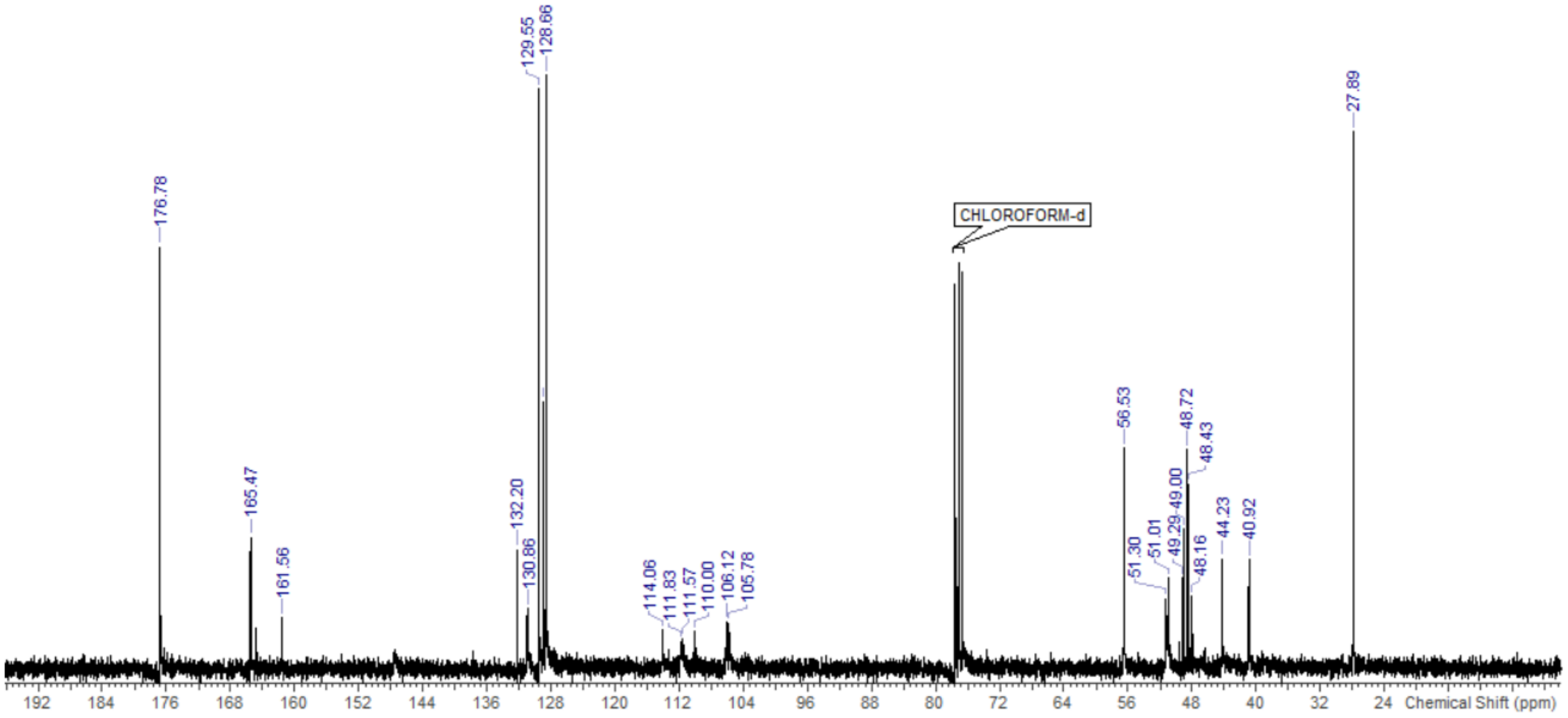
1-(2-(4-(2-Fluorophenyl)piperazin-1-yl)-2-oxo-1-phenylethyl)pyrrolidine-2,5-dione (15) – ^{13}C NMR



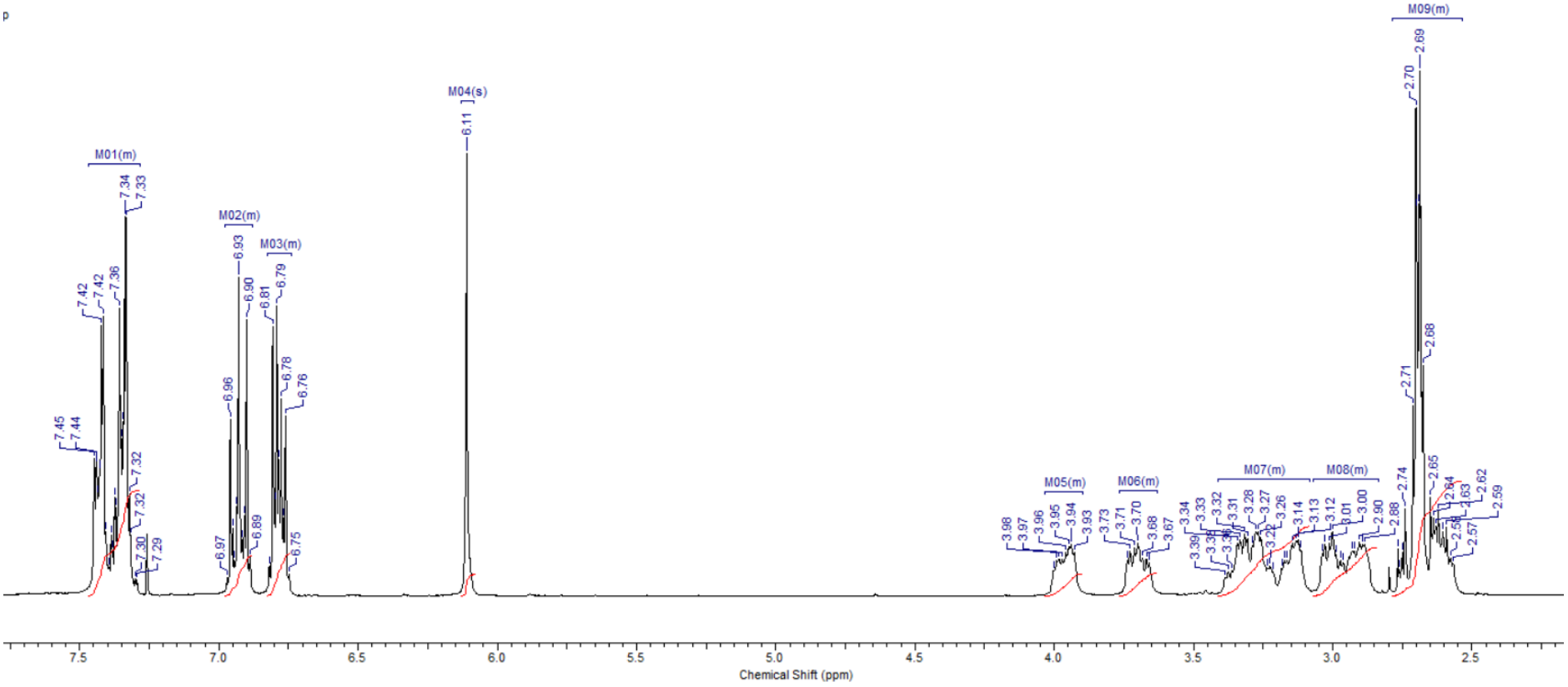
1-(2-(4-(3-Fluorophenyl)piperazin-1-yl)-2-oxo-1-phenylethyl)pyrrolidine-2,5-dione (16) - ^{1}H NMR



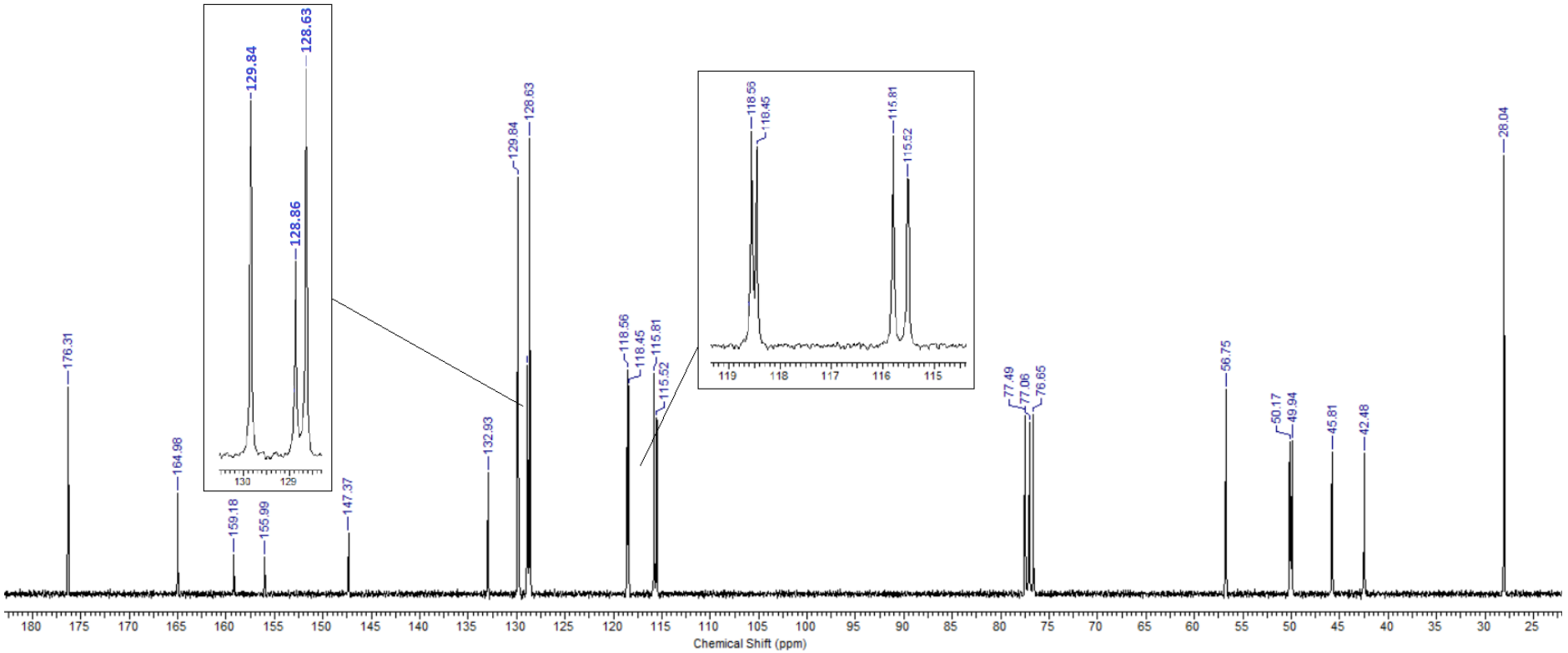
1-(2-(4-(3-Fluorophenyl)piperazin-1-yl)-2-oxo-1-phenylethyl)pyrrolidine-2,5-dione (16) – ^{13}C NMR



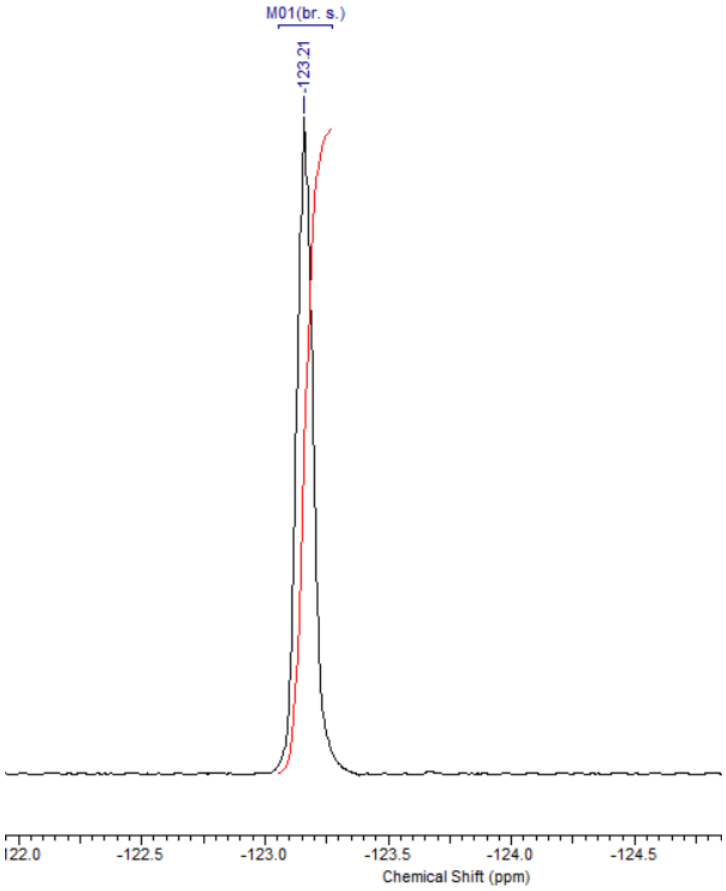
1-(2-(4-(4-Fluorophenyl)piperazin-1-yl)-2-oxo-1-phenylethyl)pyrrolidine-2,5-dione (17) - ^{1}H NMR



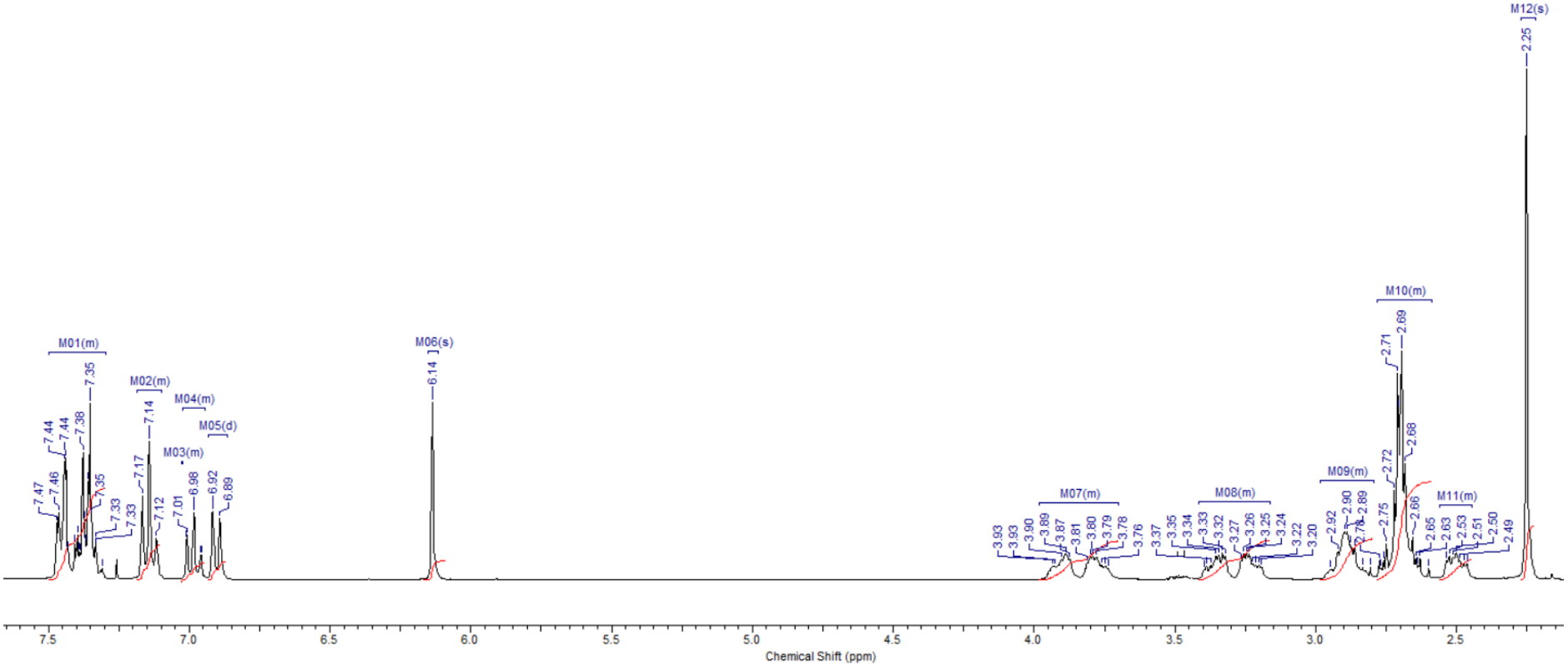
1-(2-(4-(4-Fluorophenyl)piperazin-1-yl)-2-oxo-1-phenylethyl)pyrrolidine-2,5-dione (17) - ^{13}C NMR



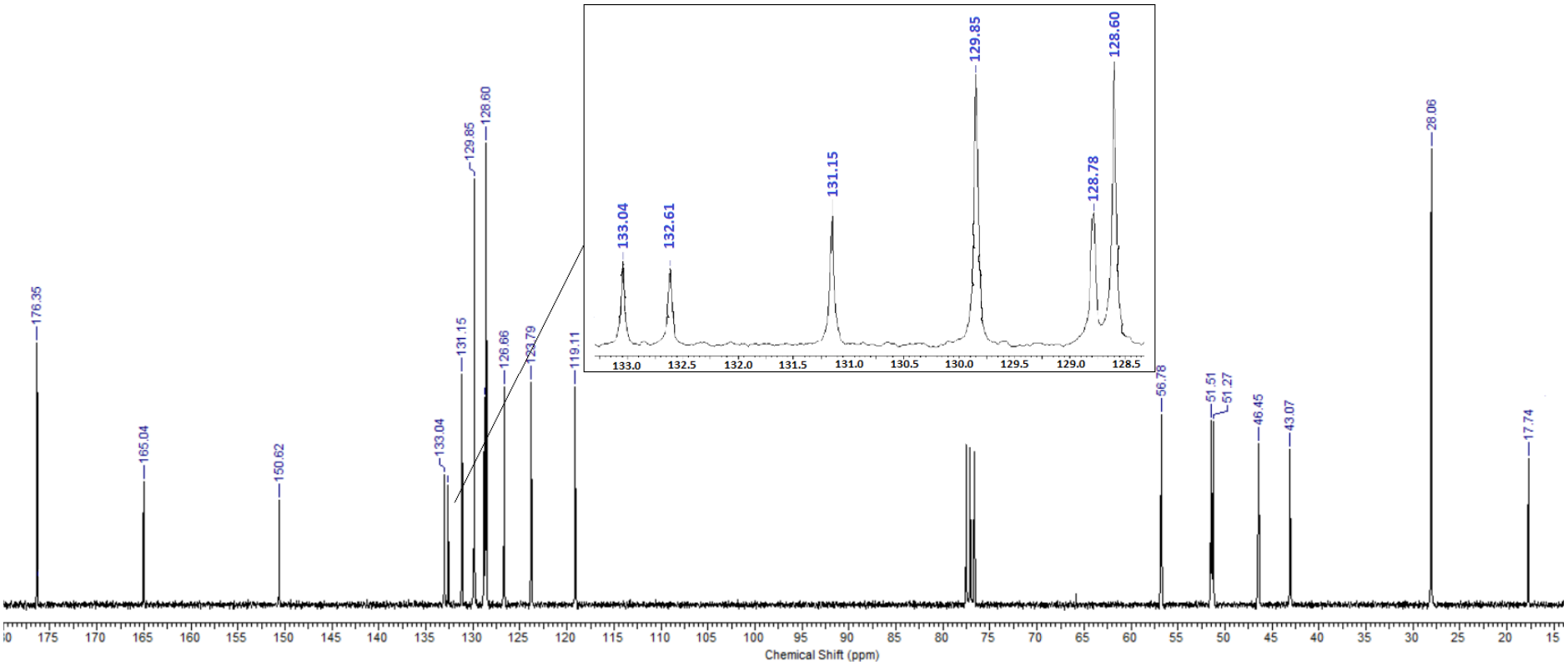
1-(2-(4-(4-Fluorophenyl)piperazin-1-yl)-2-oxo-1-phenylethyl)pyrrolidine-2,5-dione (17) - ^{18}F NMR



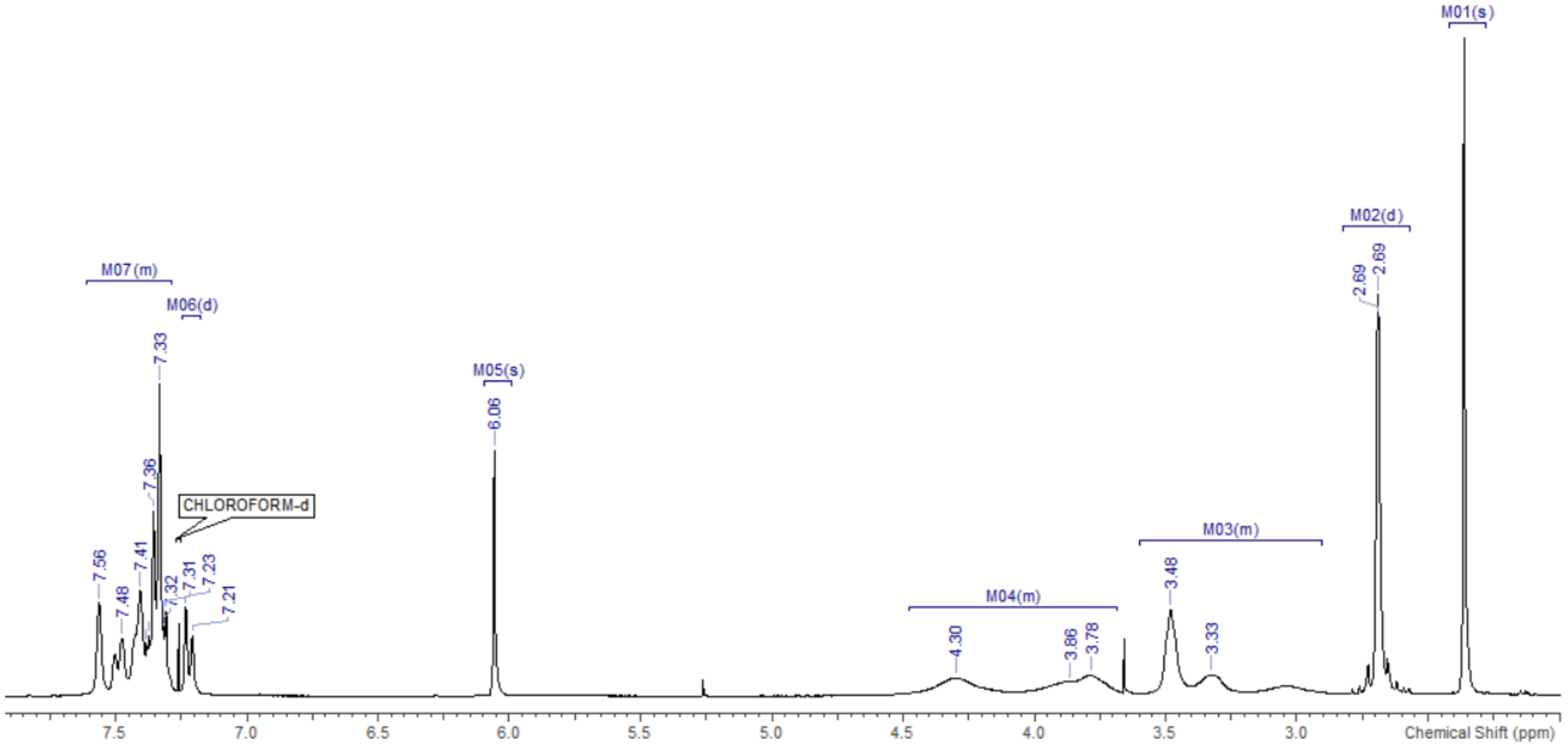
1-(2-Oxo-1-phenyl-2-(4-(o-tolyl)piperazin-1-yl)ethyl)pyrrolidine-2,5-dione (18) - ^{1}H NMR



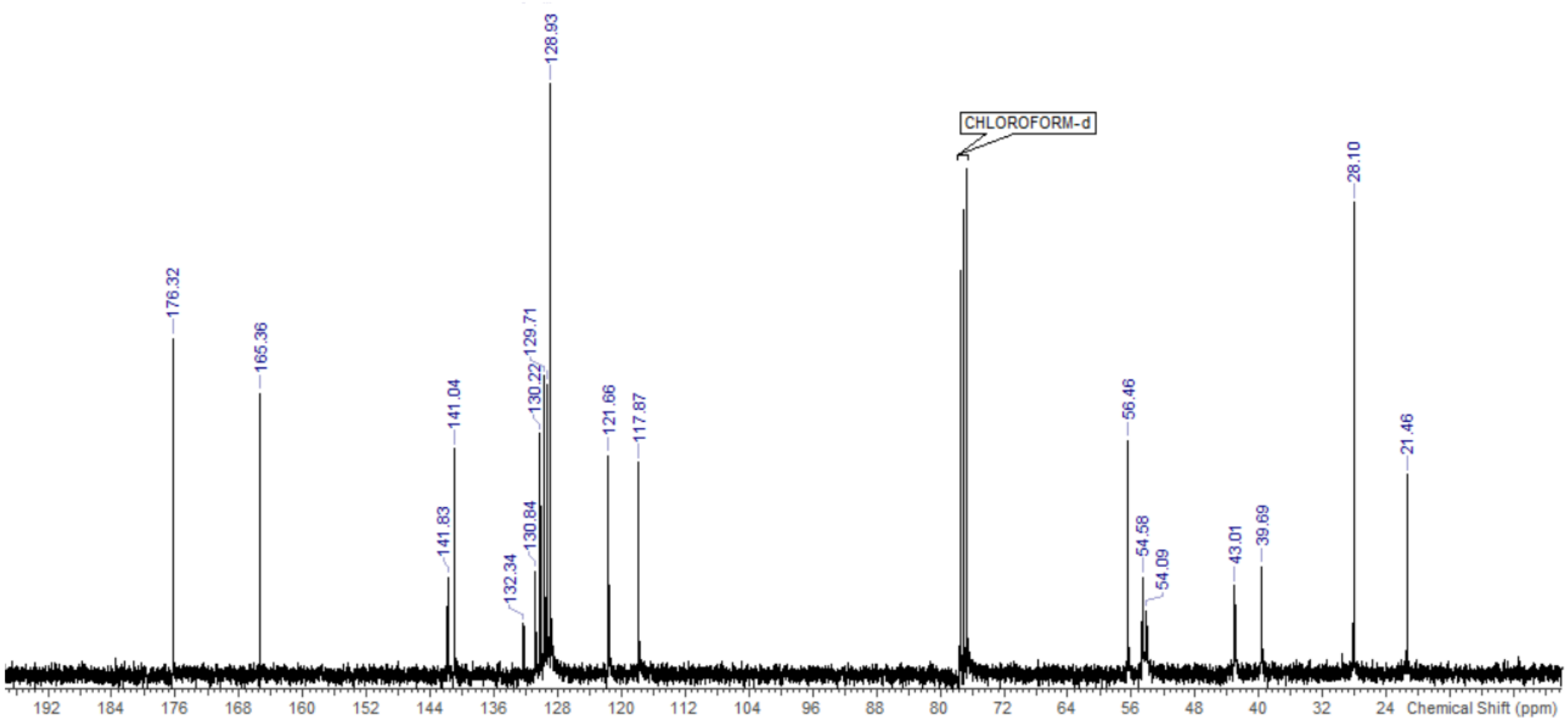
1-(2-Oxo-1-phenyl-2-(4-(o-tolyl)piperazin-1-yl)ethyl)pyrrolidine-2,5-dione (18) - ^{13}C NMR



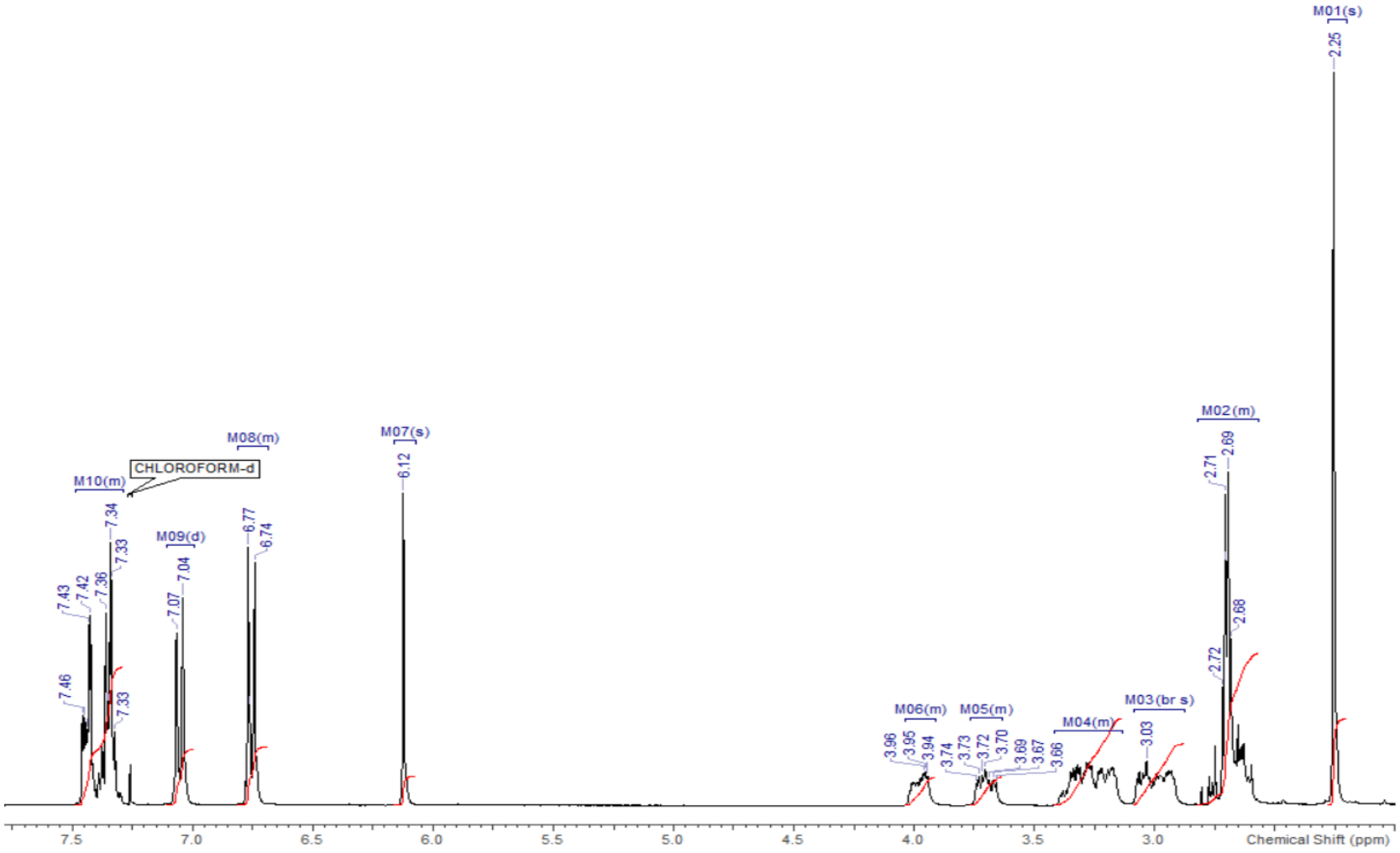
1-(2-Oxo-1-phenyl-2-(4-(m-tolyl)piperazin-1-yl)ethyl)pyrrolidine-2,5-dione (19) - ^{1}H NMR



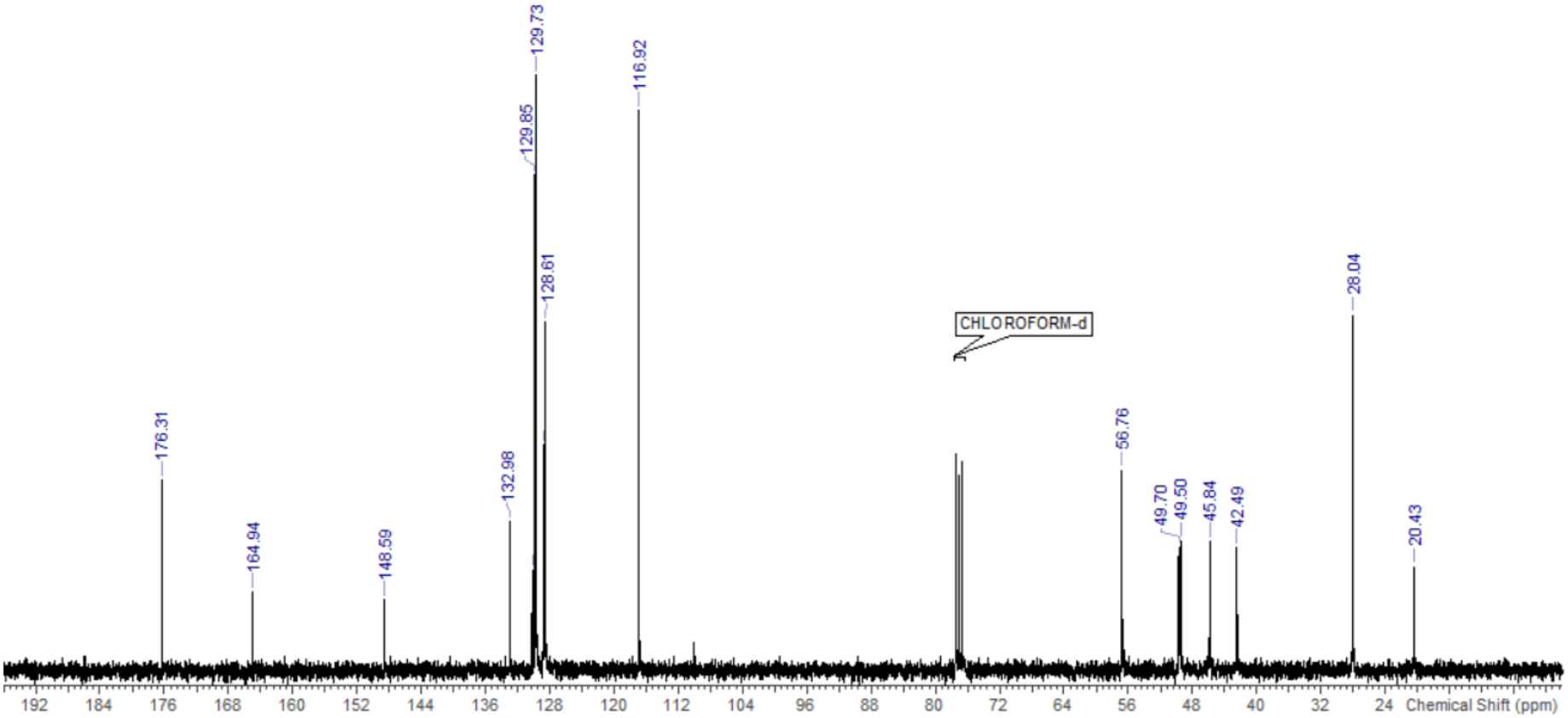
1-(2-Oxo-1-phenyl-2-(4-(m-tolyl)piperazin-1-yl)ethyl)pyrrolidine-2,5-dione (19) – ^{13}C NMR



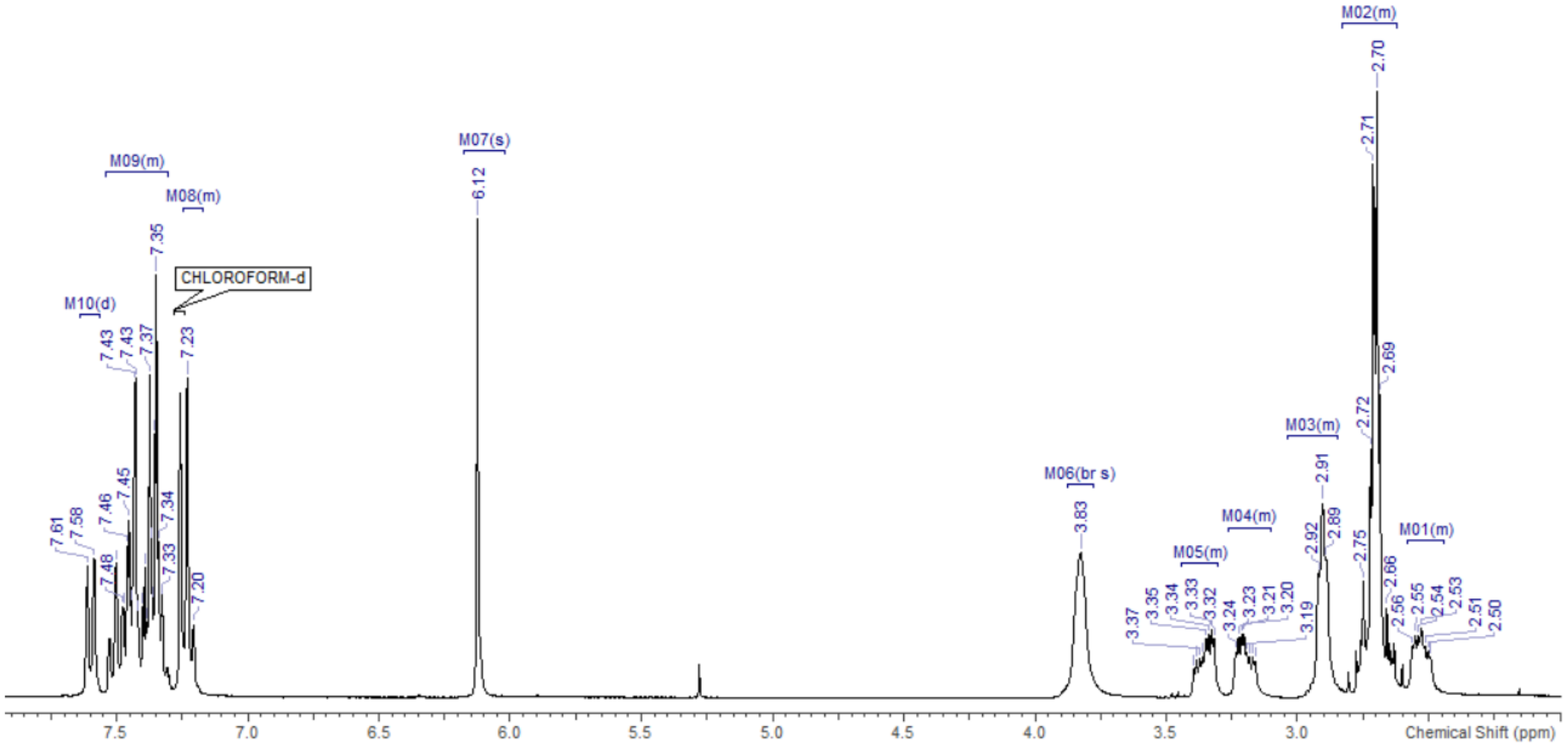
1-(2-Oxo-1-phenyl-2-(4-(p-tolyl)piperazin-1-yl)ethyl)pyrrolidine-2,5-dione (20) - ^{1}H NMR



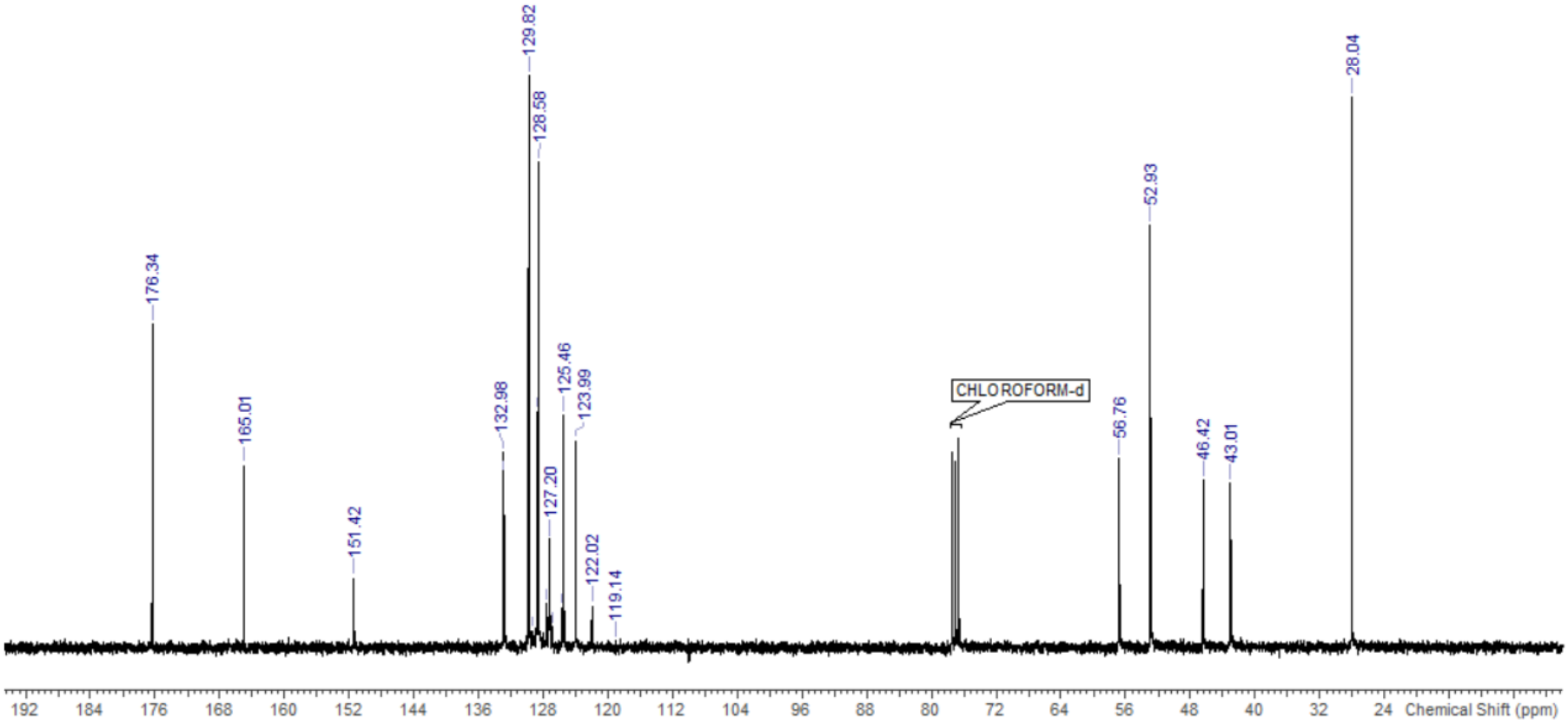
1-(2-Oxo-1-phenyl-2-(4-(p-tolyl)piperazin-1-yl)ethyl)pyrrolidine-2,5-dione (20) – ^{13}C NMR



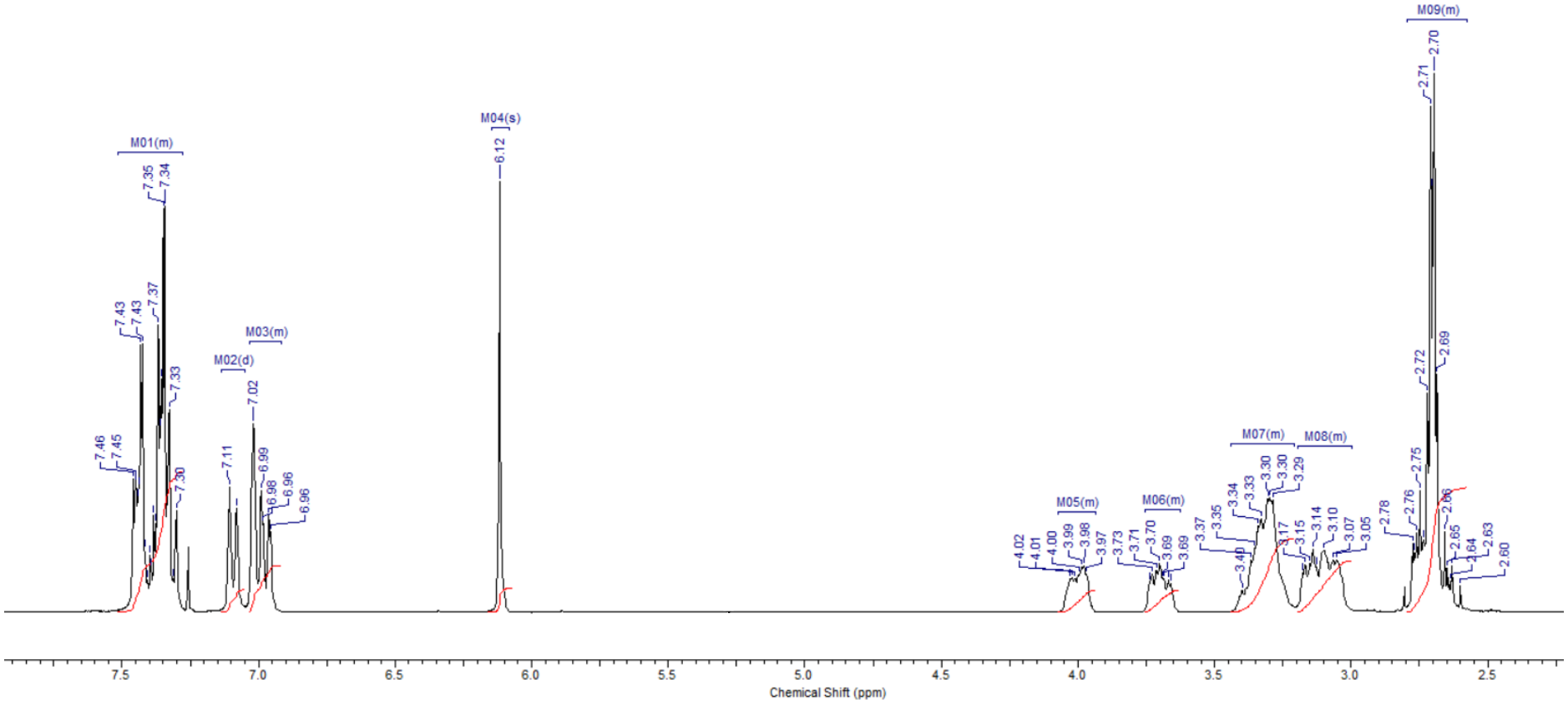
1-(2-Oxo-1-phenyl-2-(4-(2-(trifluoromethyl)phenyl)piperazin-1-yl)ethyl)pyrrolidine-2,5-dione (21) - ^{1}H NMR



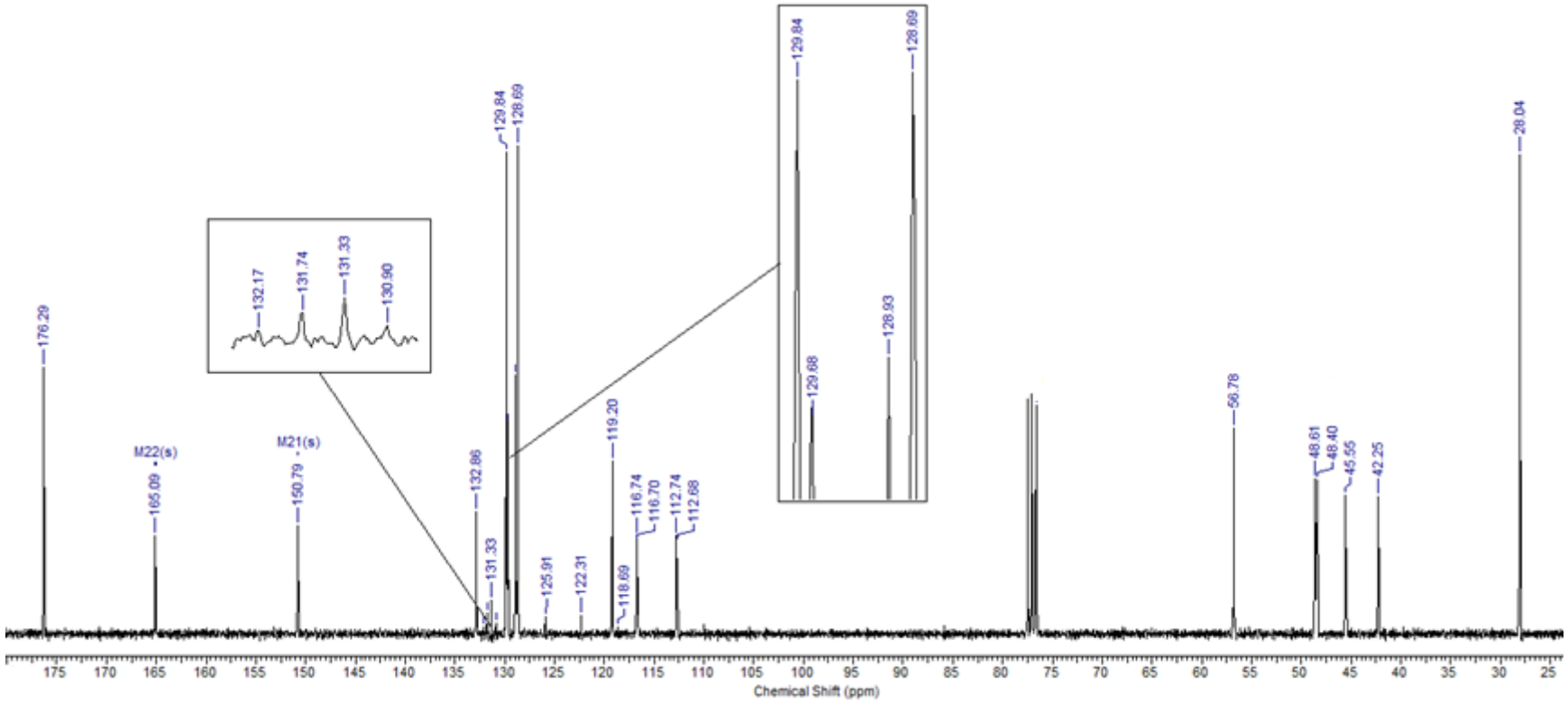
1-(2-Oxo-1-phenyl-2-(4-(2-(trifluoromethyl)phenyl)piperazin-1-yl)ethyl)pyrrolidine-2,5-dione (21) – ^{13}C NMR



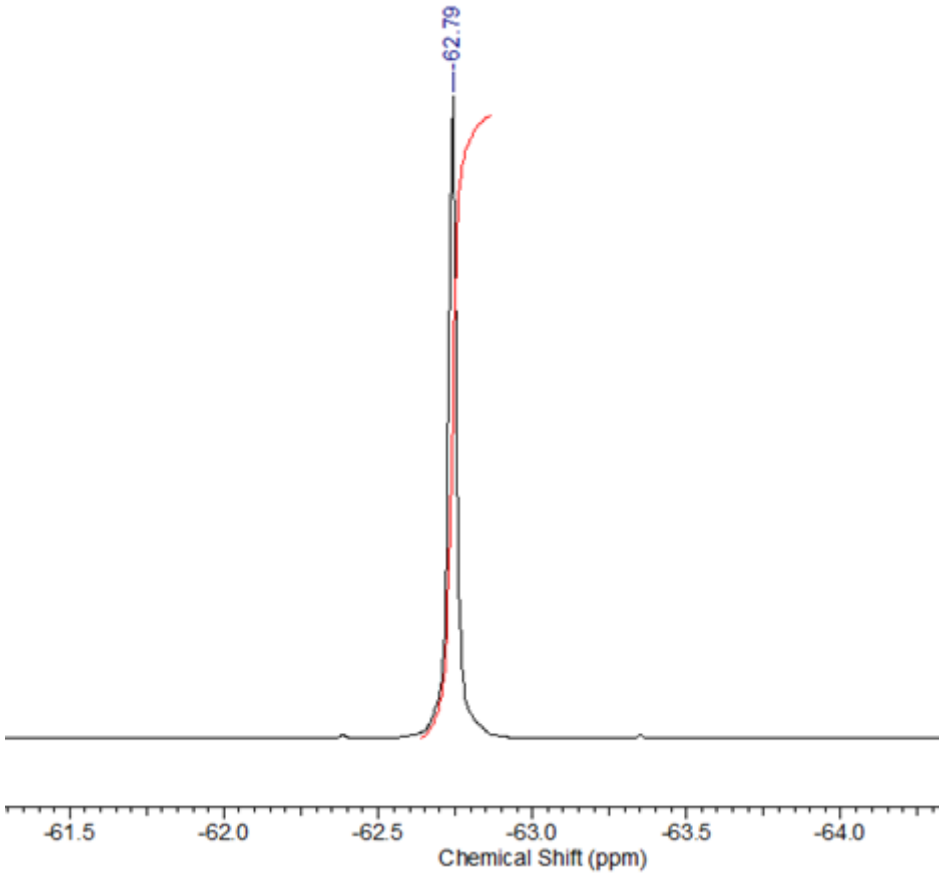
1-(2-Oxo-1-phenyl-2-(4-(3-(trifluoromethyl)phenyl)piperazin-1-yl)ethyl)pyrrolidine-2,5-dione (22) - ^{1}H NMR



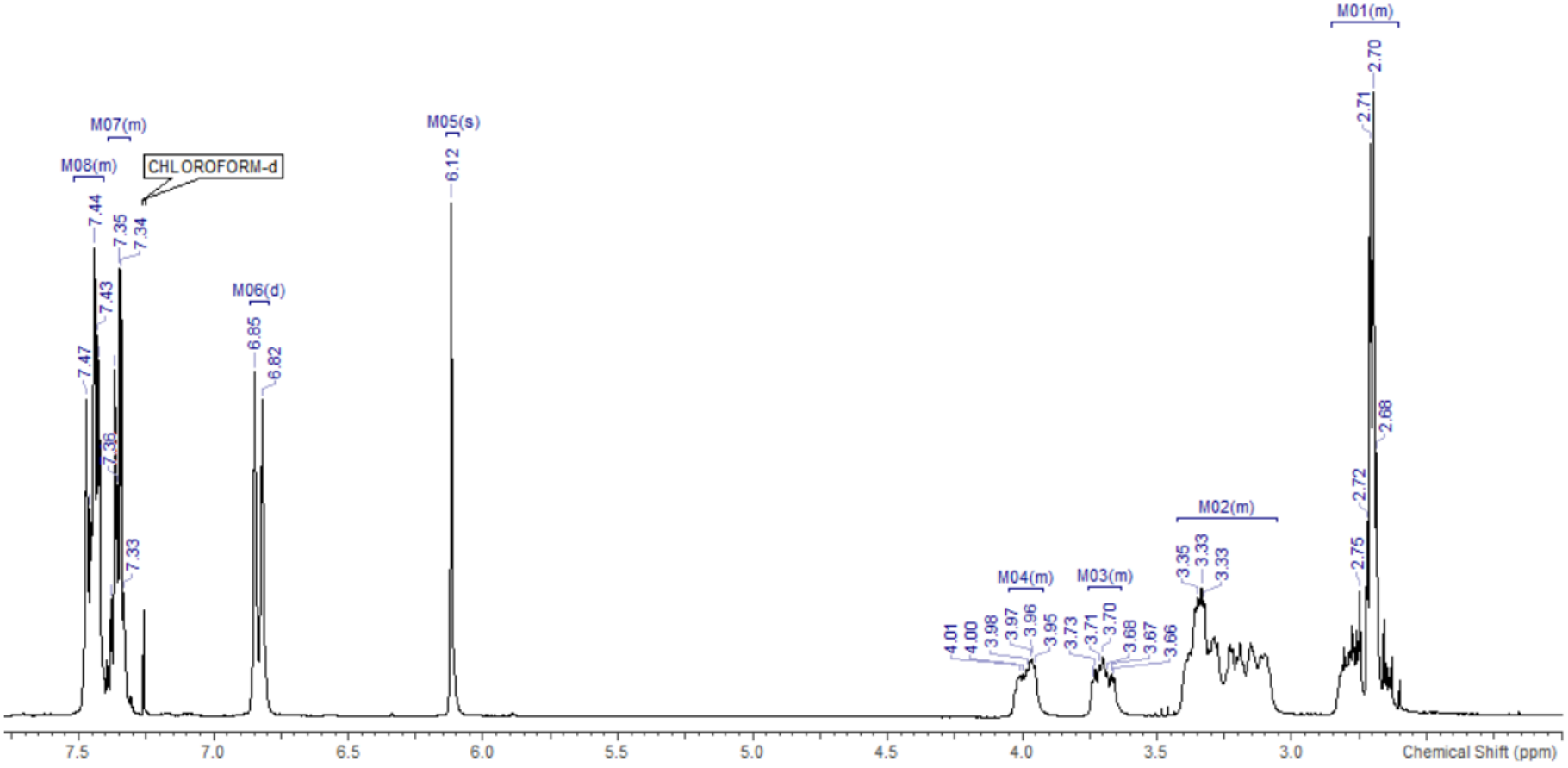
1-(2-Oxo-1-phenyl-2-(4-(3-(trifluoromethyl)phenyl)piperazin-1-yl)ethyl)pyrrolidine-2,5-dione (22) - ^{13}C NMR



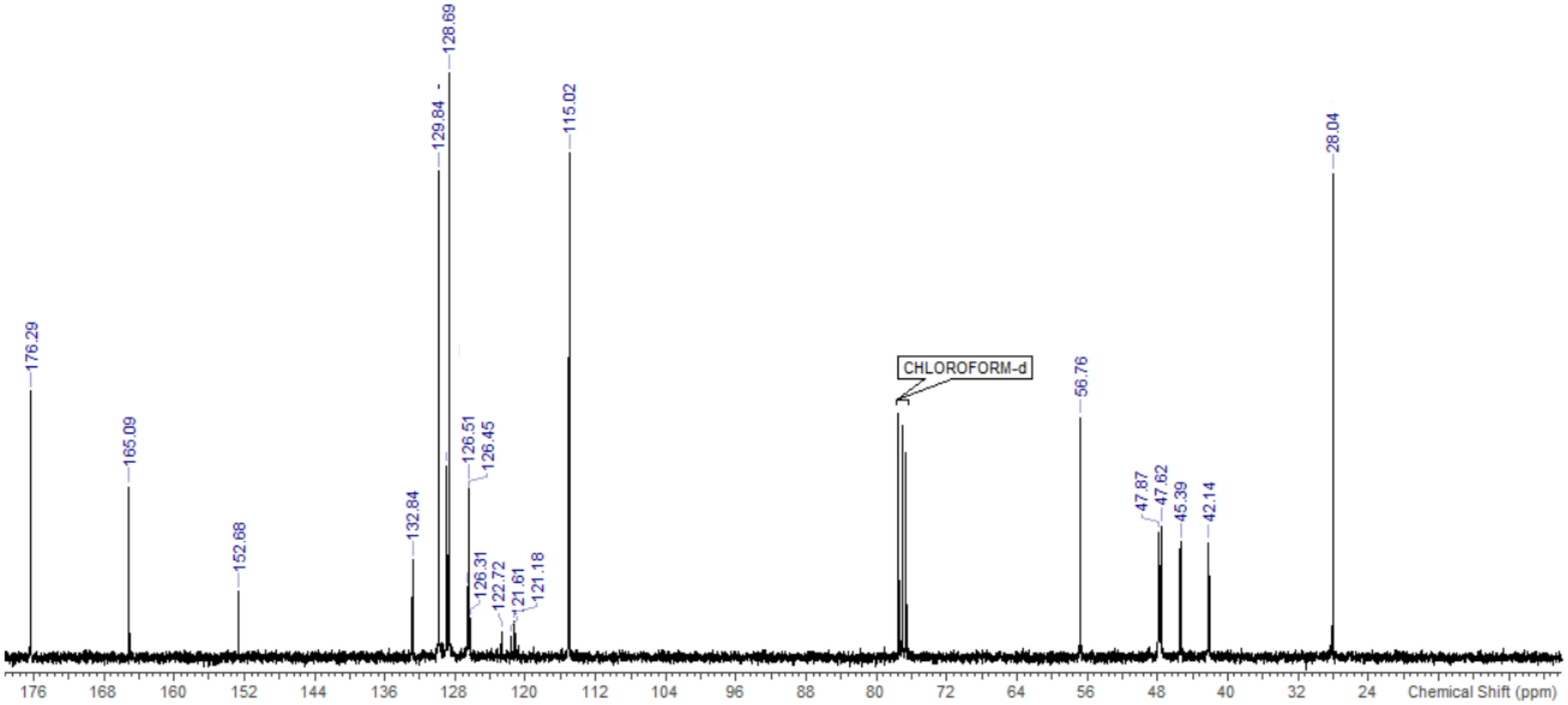
1-(2-Oxo-1-phenyl-2-(4-(3-(trifluoromethyl)phenyl)piperazin-1-yl)ethyl)pyrrolidine-2,5-dione (22) - ^{19}F NMR



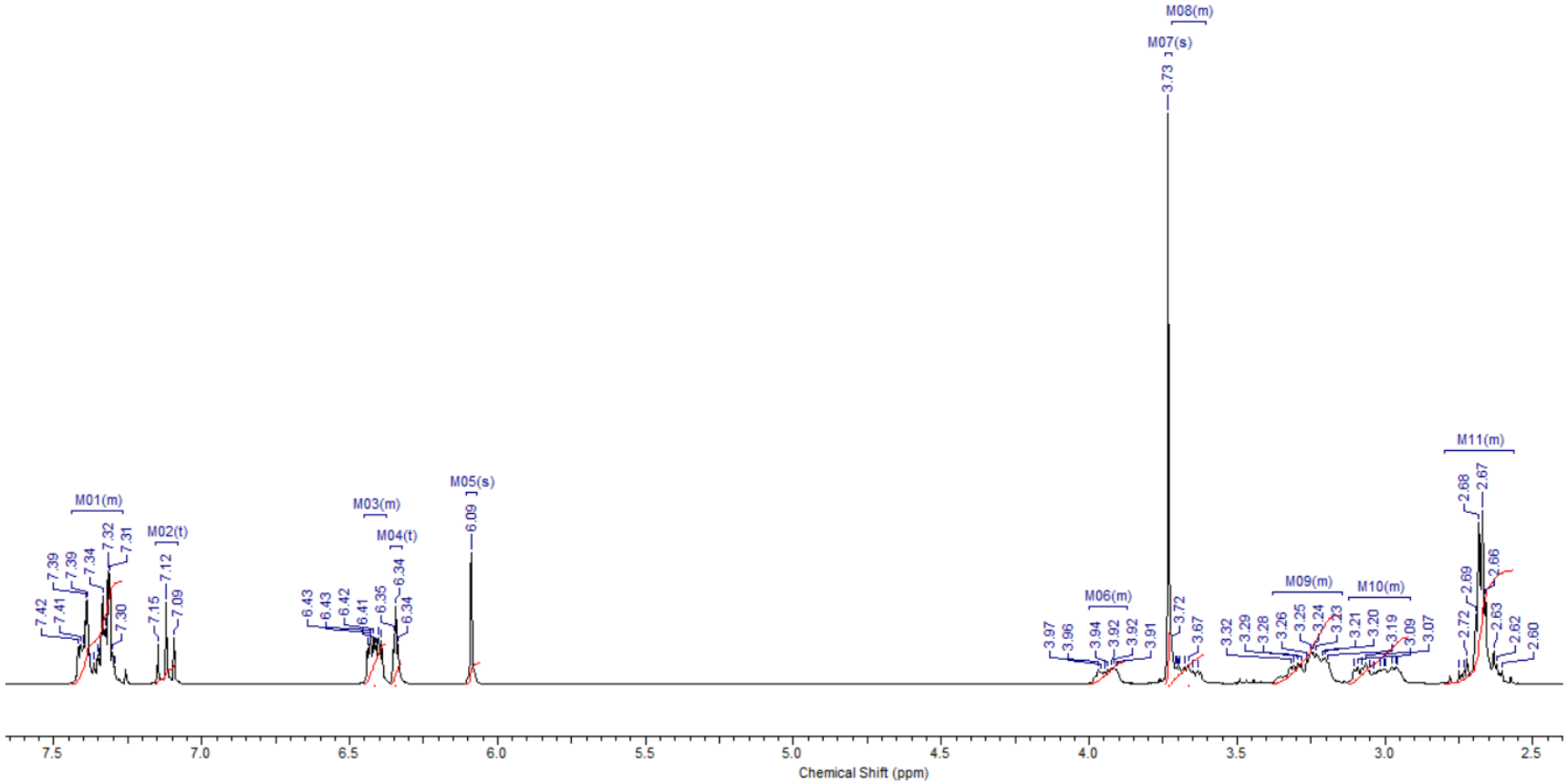
1-(2-Oxo-1-phenyl-2-(4-(4-(trifluoromethyl)phenyl)piperazin-1-yl)ethyl)pyrrolidine-2,5-dione (23) - ^{1}H NMR



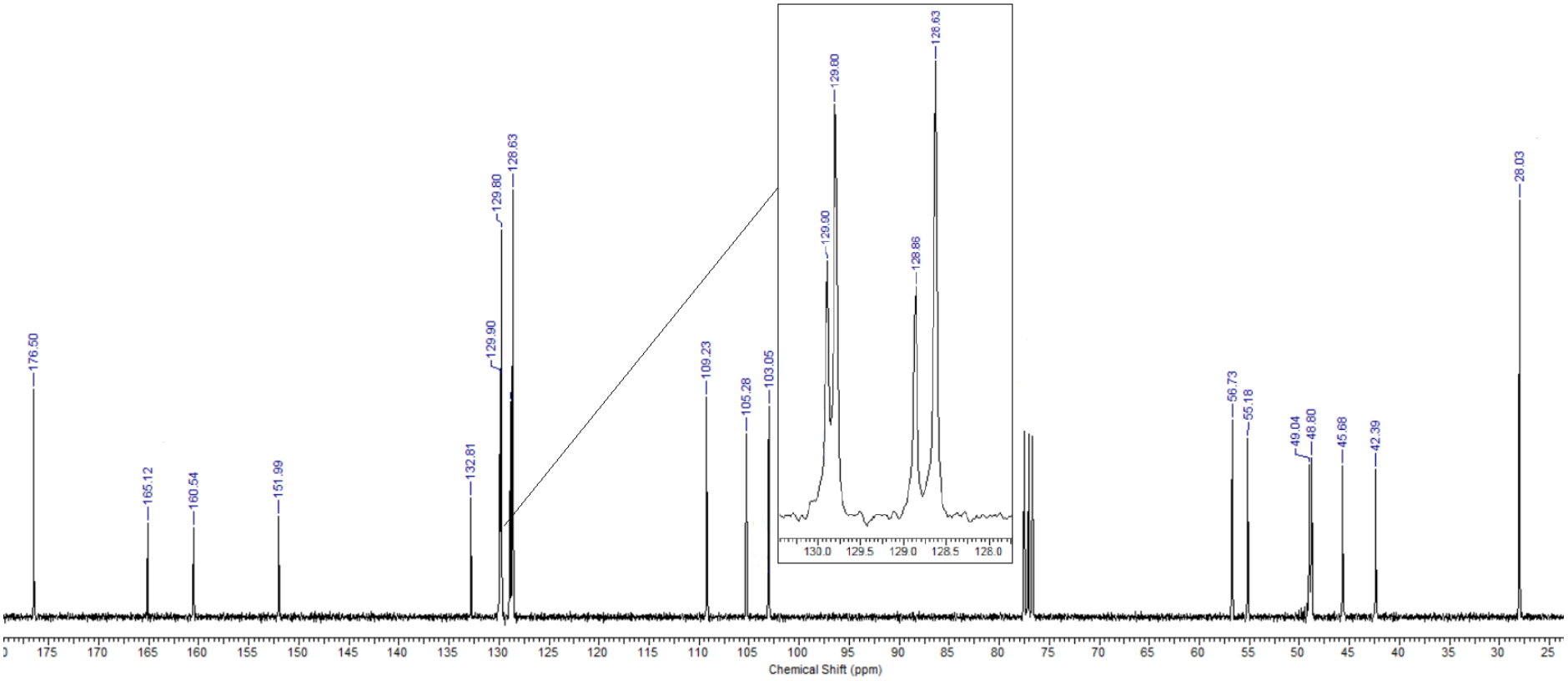
1-(2-Oxo-1-phenyl-2-(4-(4-(trifluoromethyl)phenyl)piperazin-1-yl)ethyl)pyrrolidine-2,5-dione (23) – ^{13}C NMR



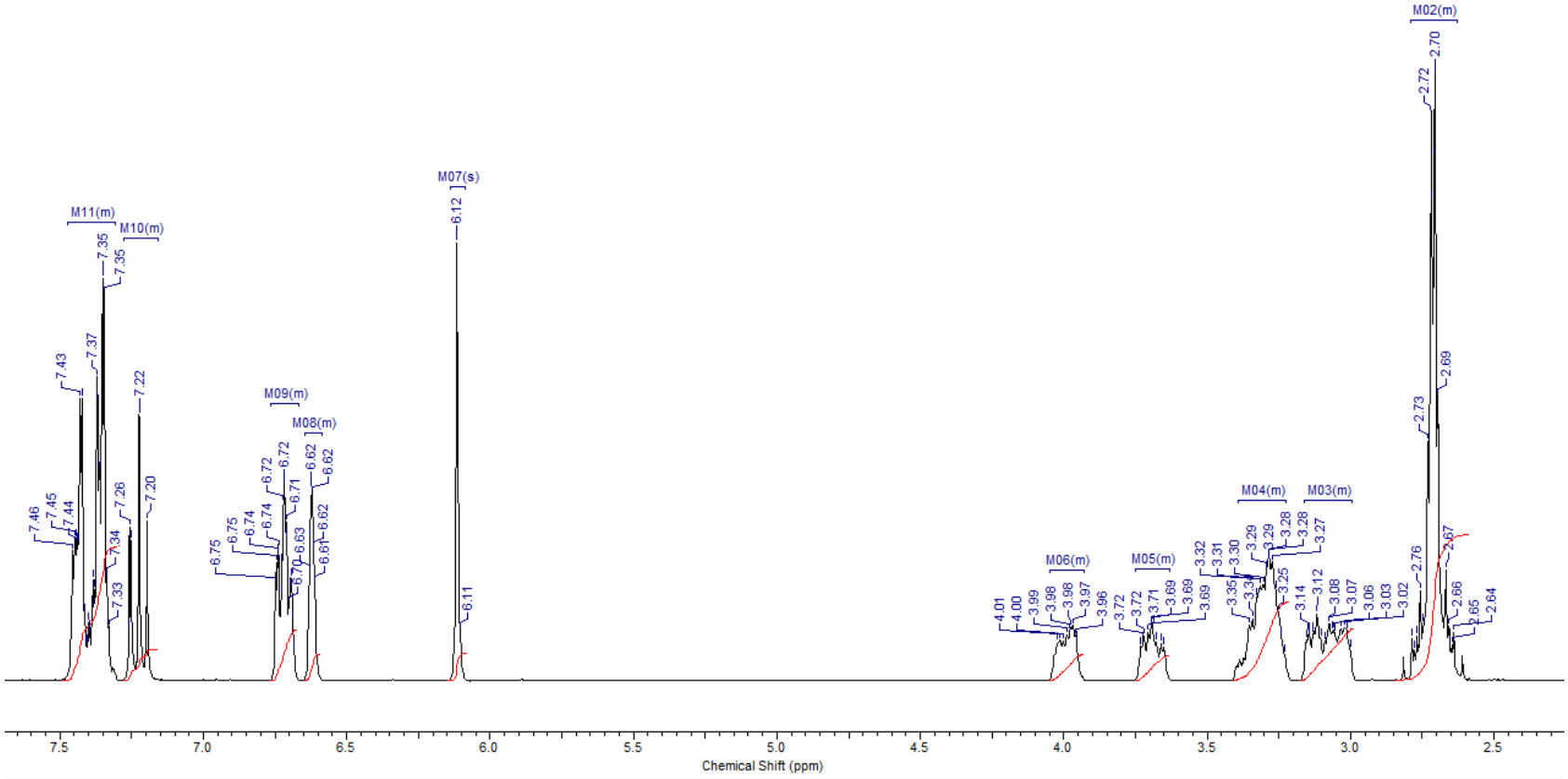
1-(2-(4-(3-Methoxyphenyl)piperazin-1-yl)-2-oxo-1-phenylethyl)pyrrolidine-2,5-dione (24) - ^{1}H NMR



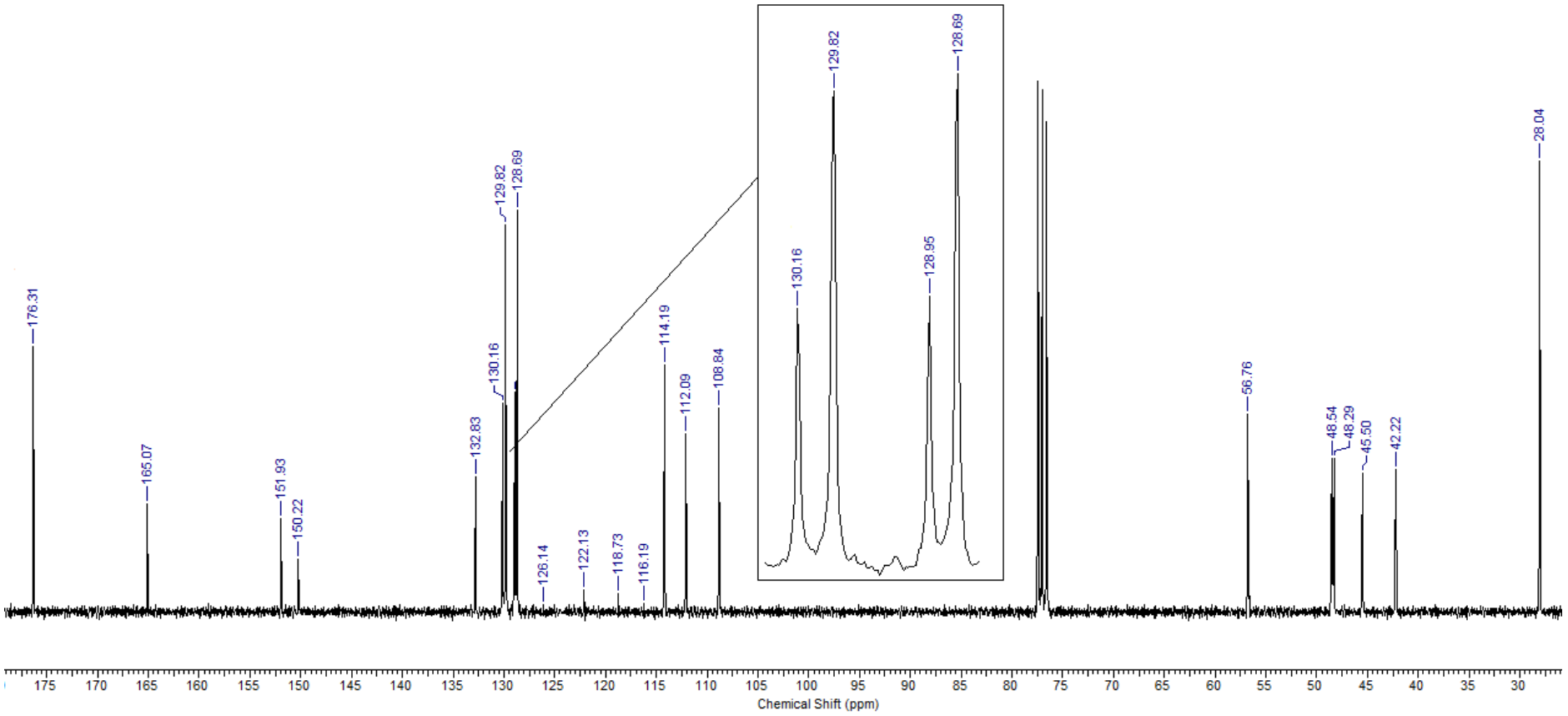
1-(2-(4-(3-Methoxyphenyl)piperazin-1-yl)-2-oxo-1-phenylethyl)pyrrolidine-2,5-dione (24) - ^{13}C NMR



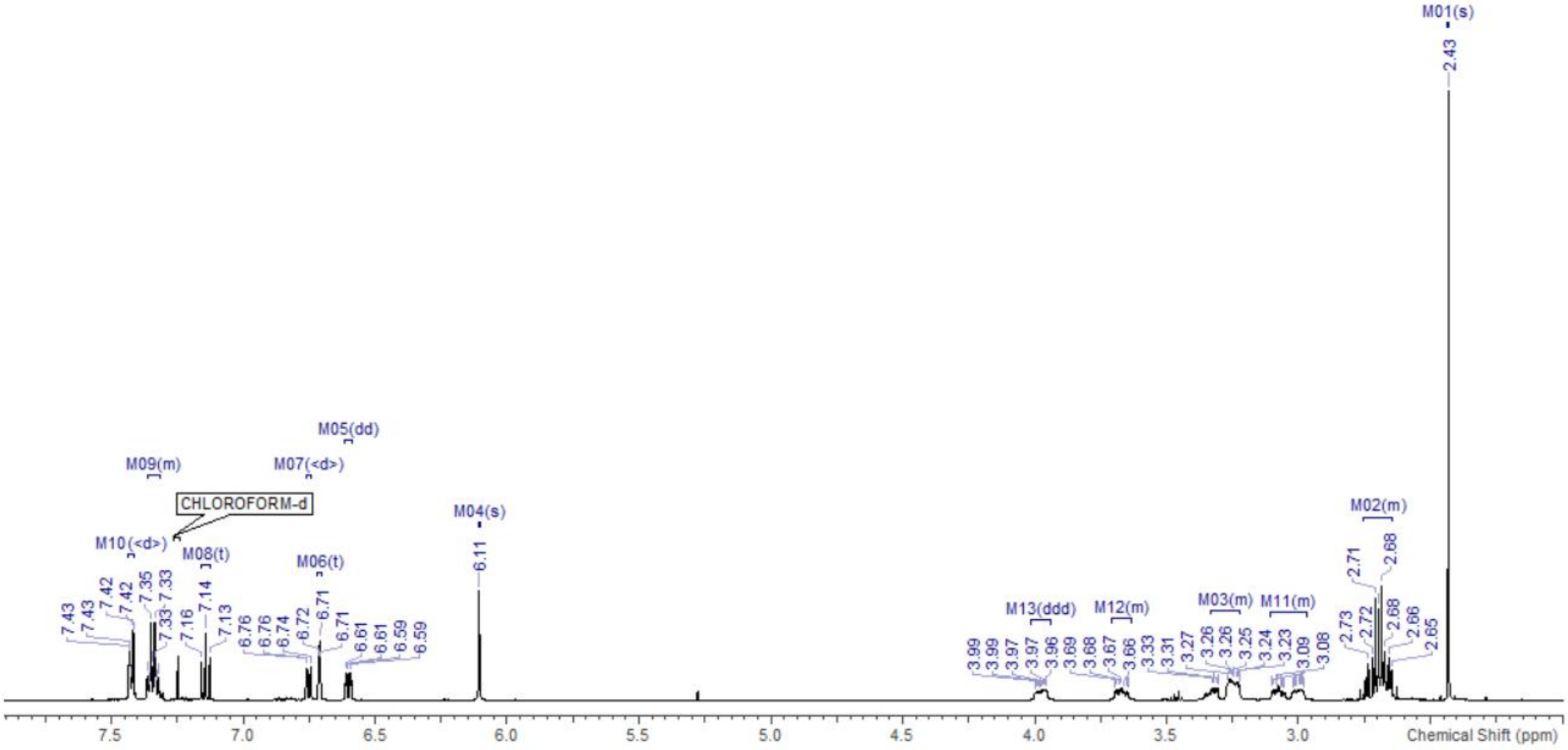
1-(2-Oxo-1-phenyl-2-(4-(3-(trifluoromethoxy)phenyl)piperazin-1-yl)ethyl)pyrrolidine-2,5-dione (25) - ^{1}H NMR



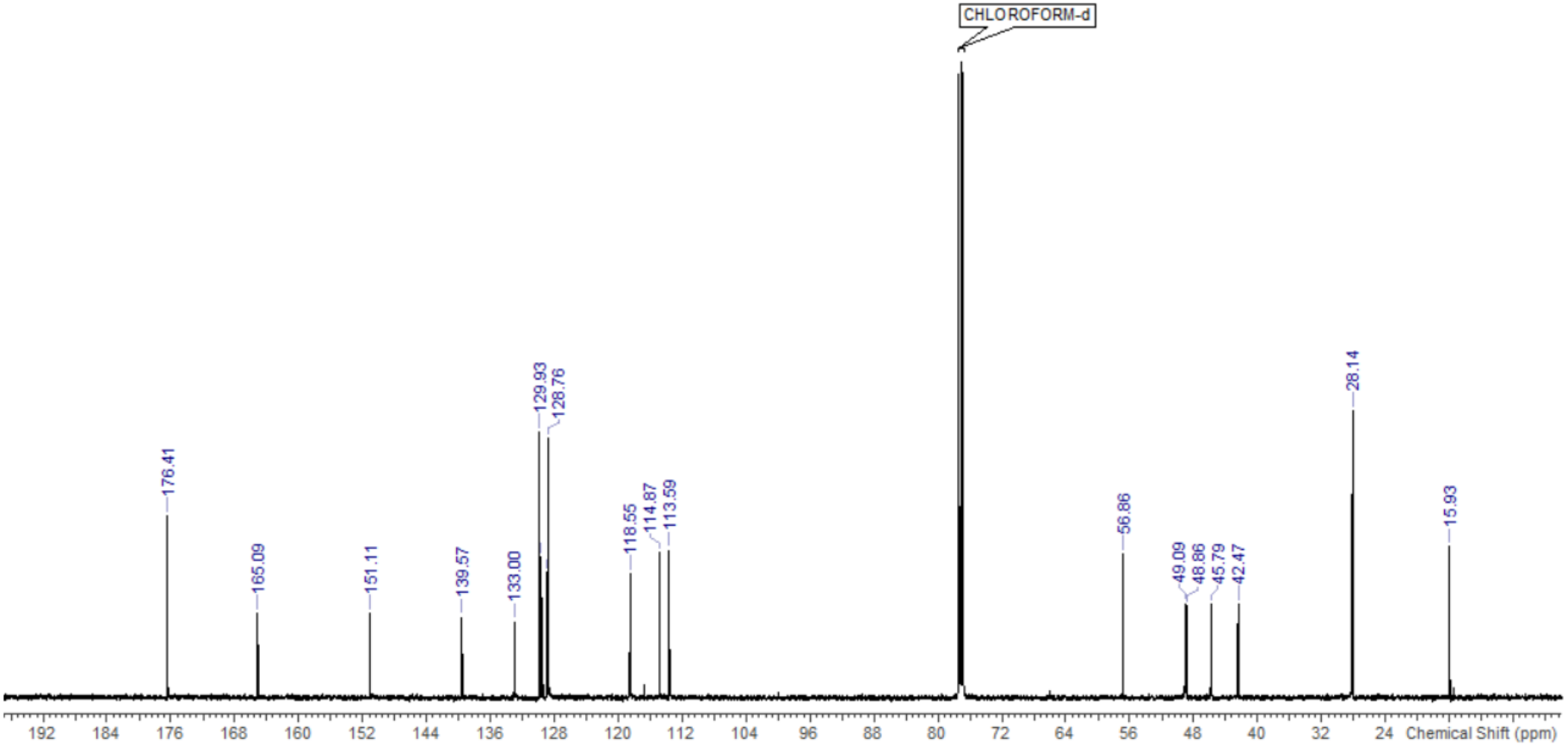
1-(2-Oxo-1-phenyl-2-(4-(3-(trifluoromethoxy)phenyl)piperazin-1-yl)ethyl)pyrrolidine-2,5-dione (25) – ^{13}C NMR



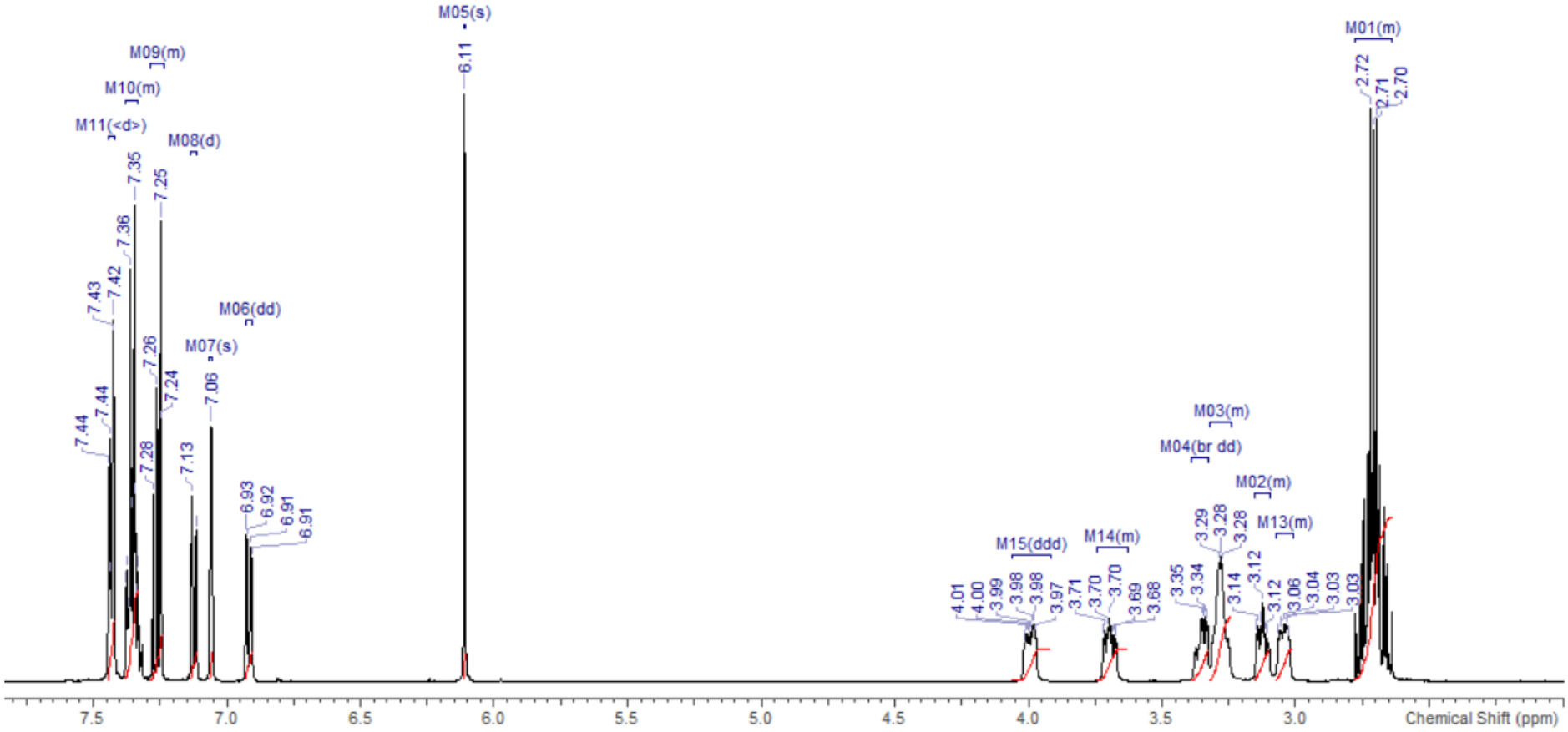
1-(2-(4-(3-(Methylthio)phenyl)piperazin-1-yl)-2-oxo-1-phenylethyl)pyrrolidine-2,5-dione (26) - ^{1}H NMR



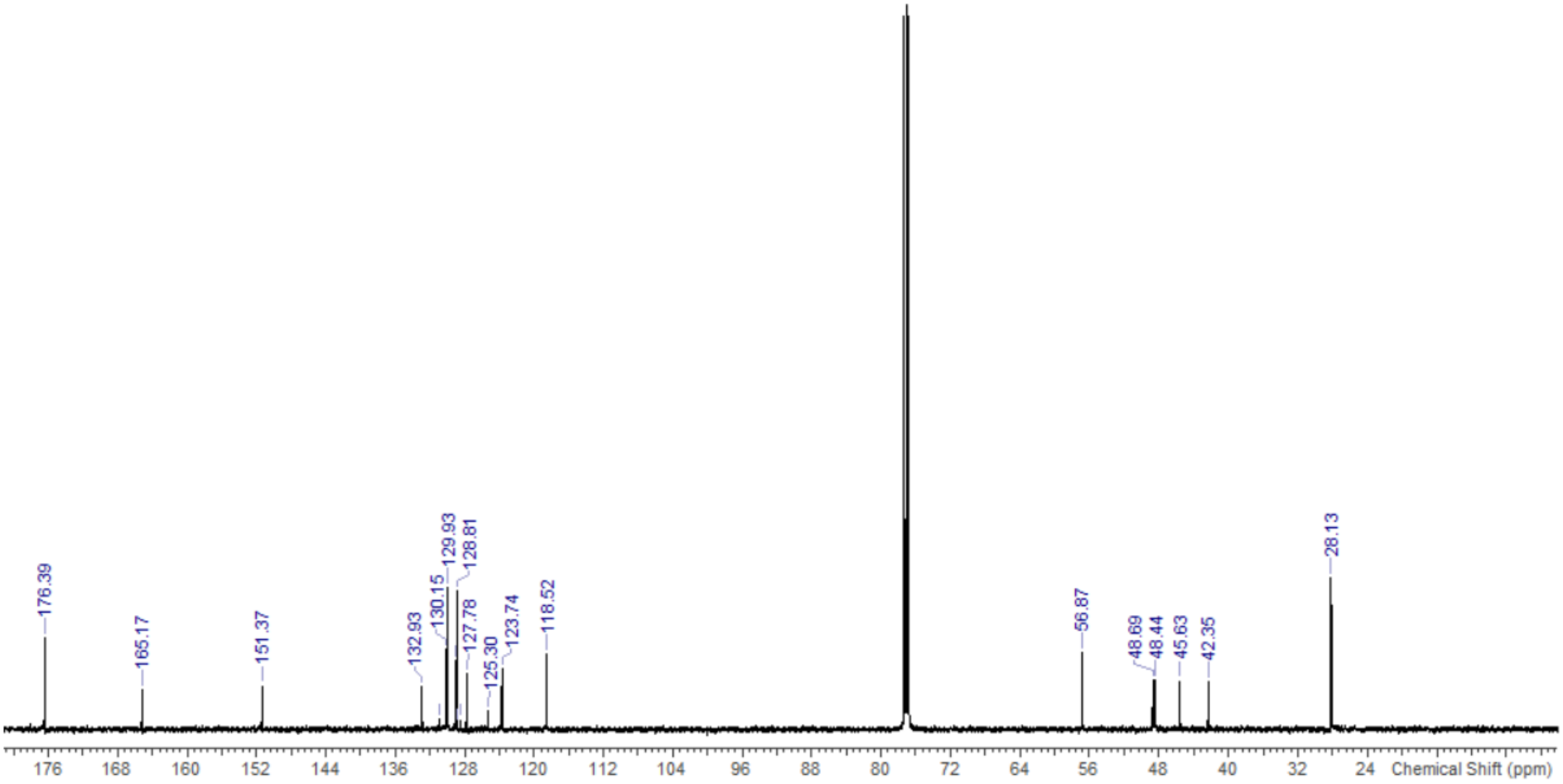
1-(2-(4-(3-(Methylthio)phenyl)piperazin-1-yl)-2-oxo-1-phenylethyl)pyrrolidine-2,5-dione (26) – ^{13}C NMR



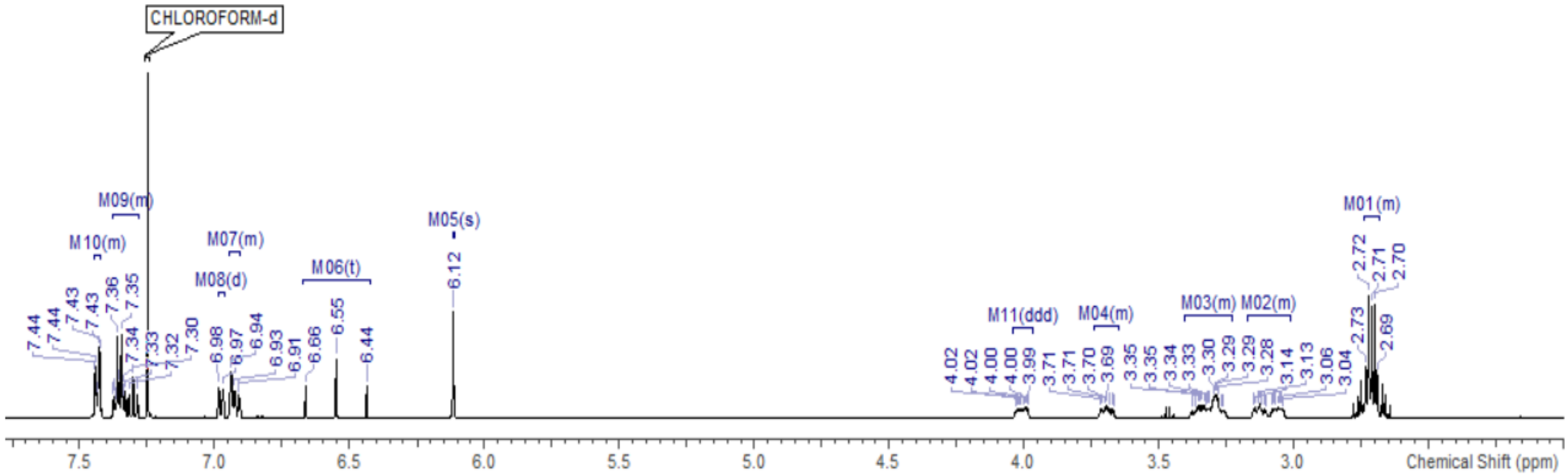
1-(2-Oxo-1-phenyl-2-(4-(3-((trifluoromethyl)thio)phenyl)piperazin-1-yl)ethyl)pyrrolidine-2,5-dione (27) - ^{1}H NMR



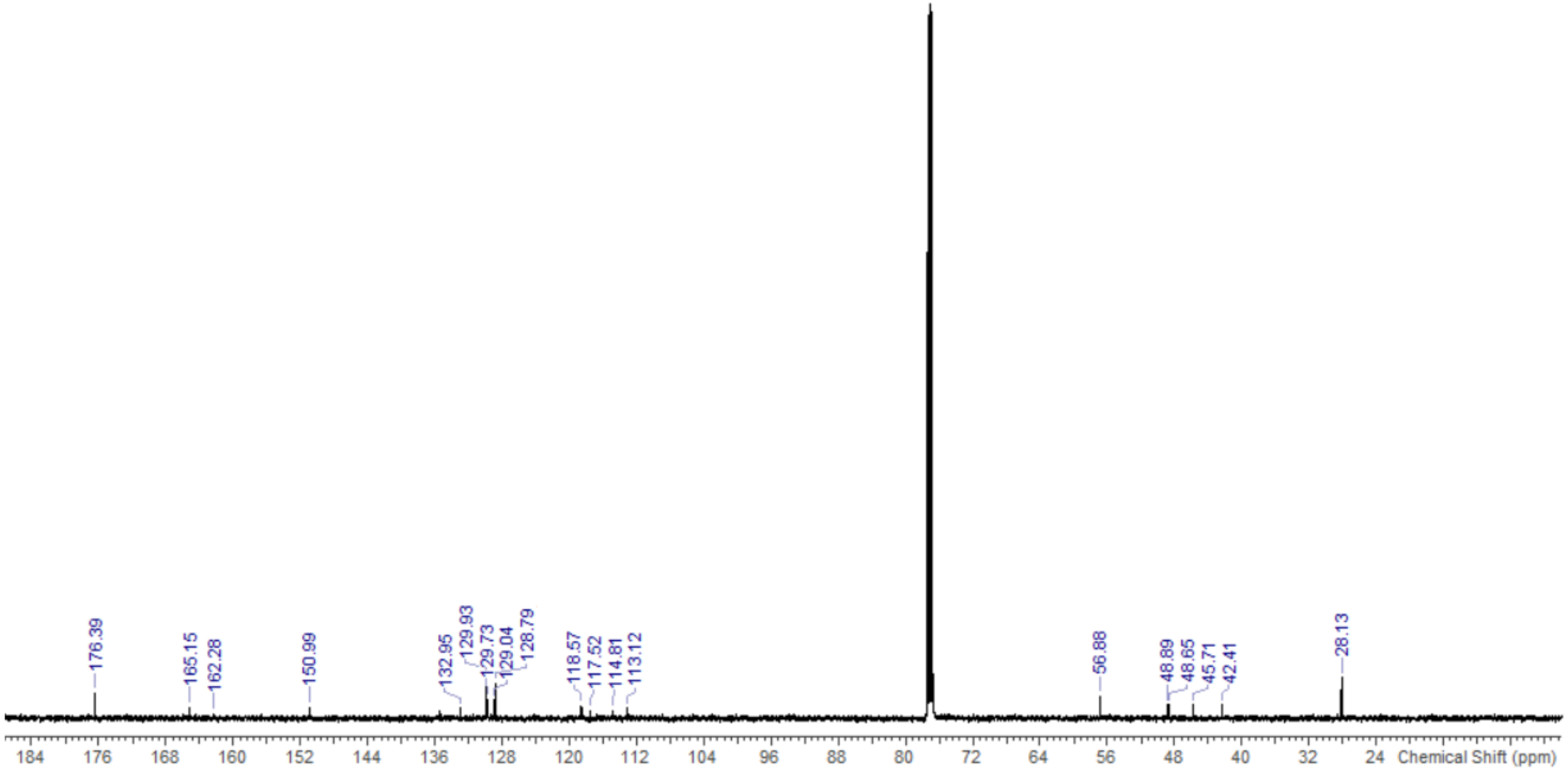
1-(2-Oxo-1-phenyl-2-(4-(3-((trifluoromethyl)thio)phenyl)piperazin-1-yl)ethyl)pyrrolidine-2,5-dione (27) – ^{13}C NMR



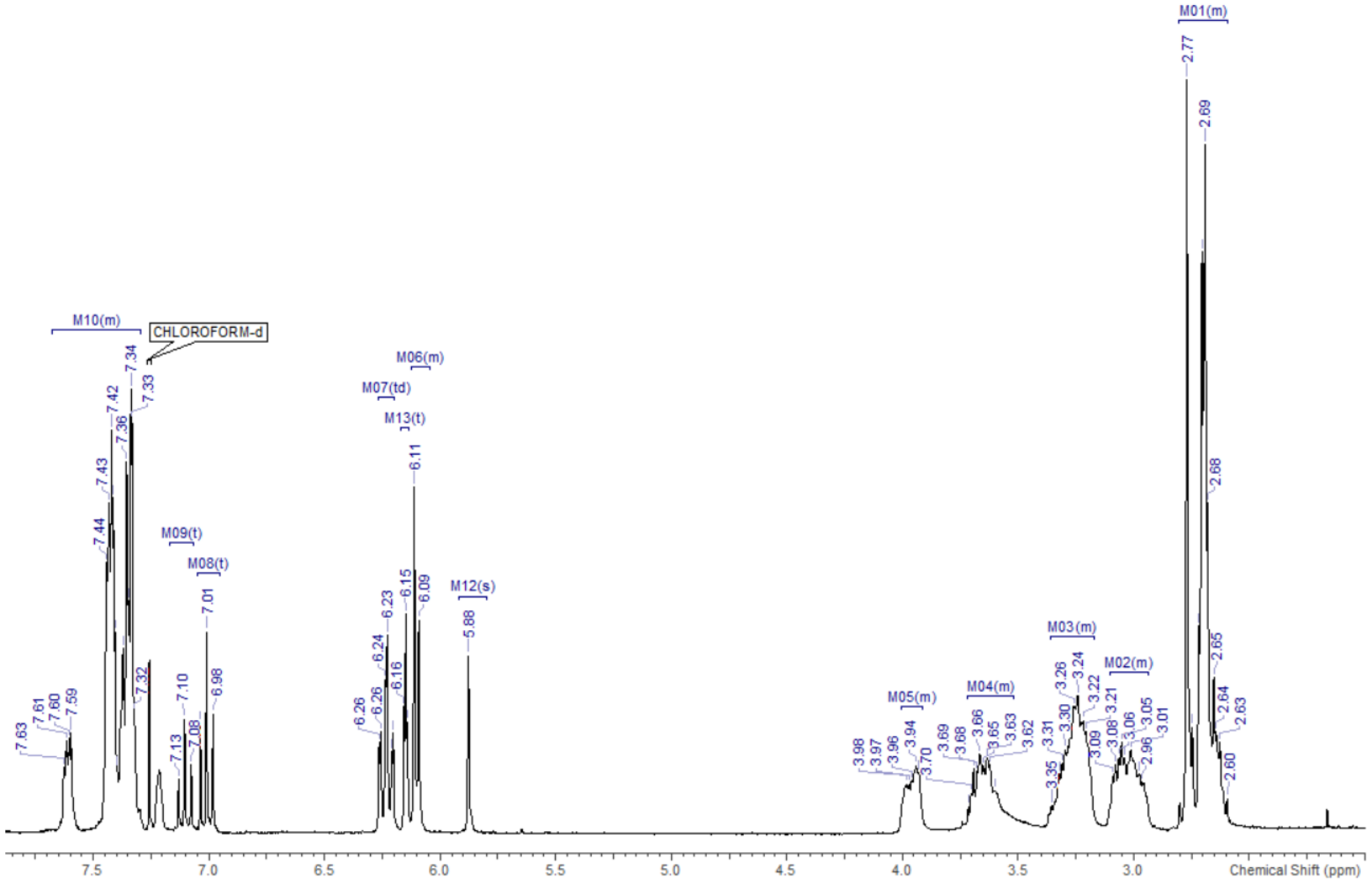
1-(2-(4-(3-(Difluoromethyl)phenyl)piperazin-1-yl)-2-oxo-1-phenylethyl)pyrrolidine-2,5-dione (28) - ^{1}H NMR



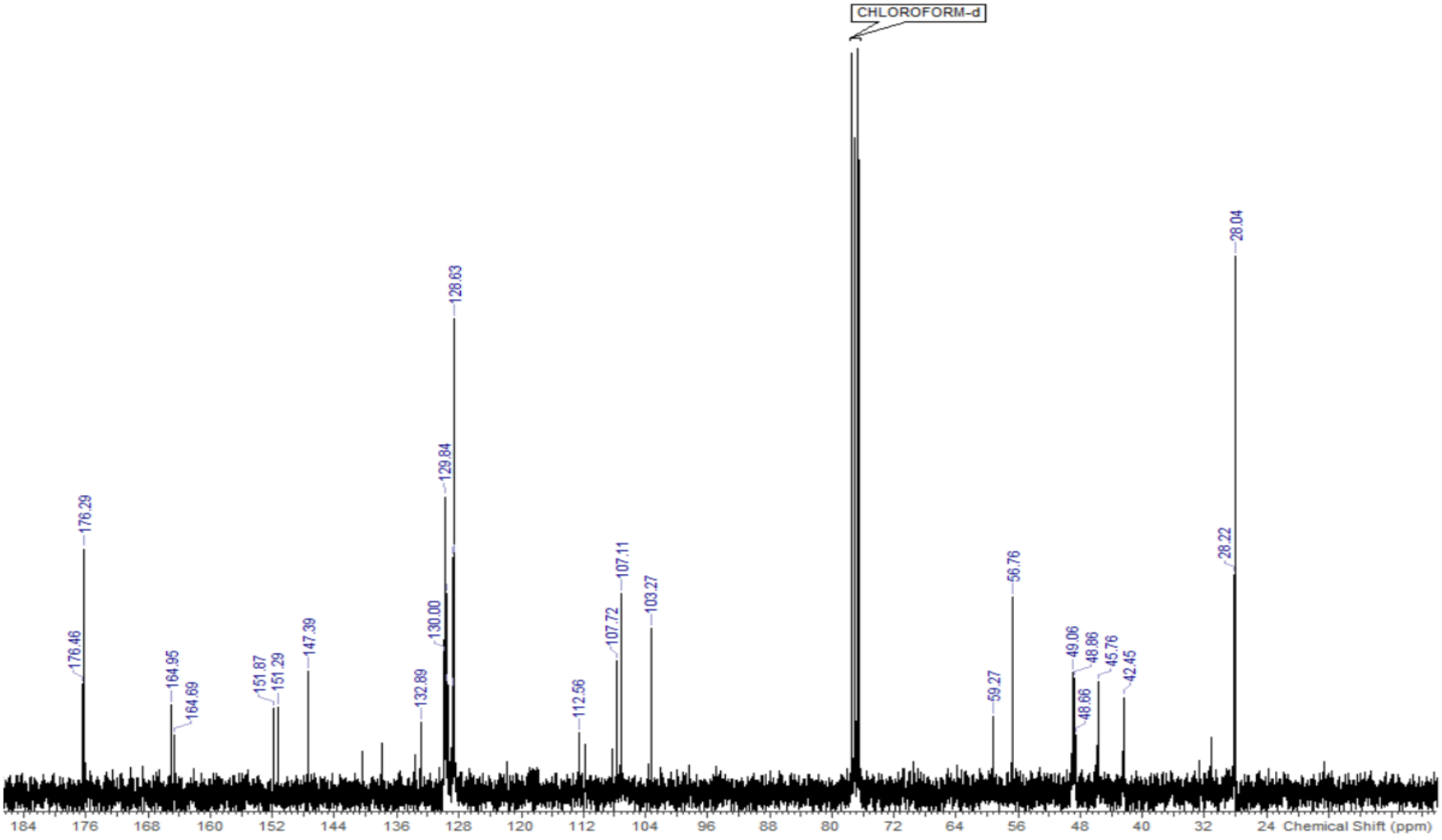
1-(2-(4-(3-(Difluoromethyl)phenyl)piperazin-1-yl)-2-oxo-1-phenylethyl)pyrrolidine-2,5-dione (28) – ^{13}C NMR



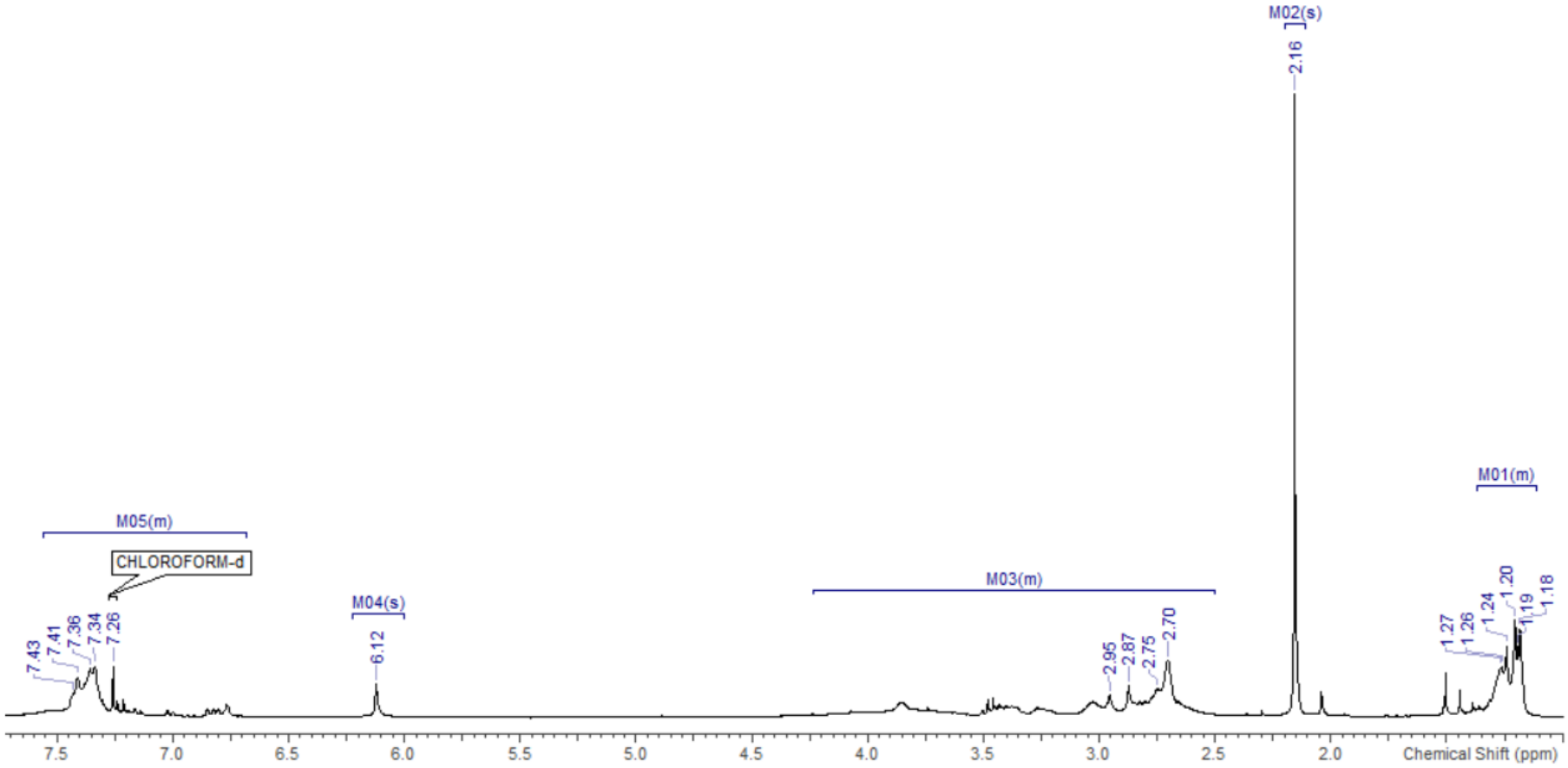
1-(2-(4-(3-Aminophenyl)piperazin-1-yl)-2-oxo-1-phenylethyl)pyrrolidine-2,5-dione (29) - ^{1}H NMR



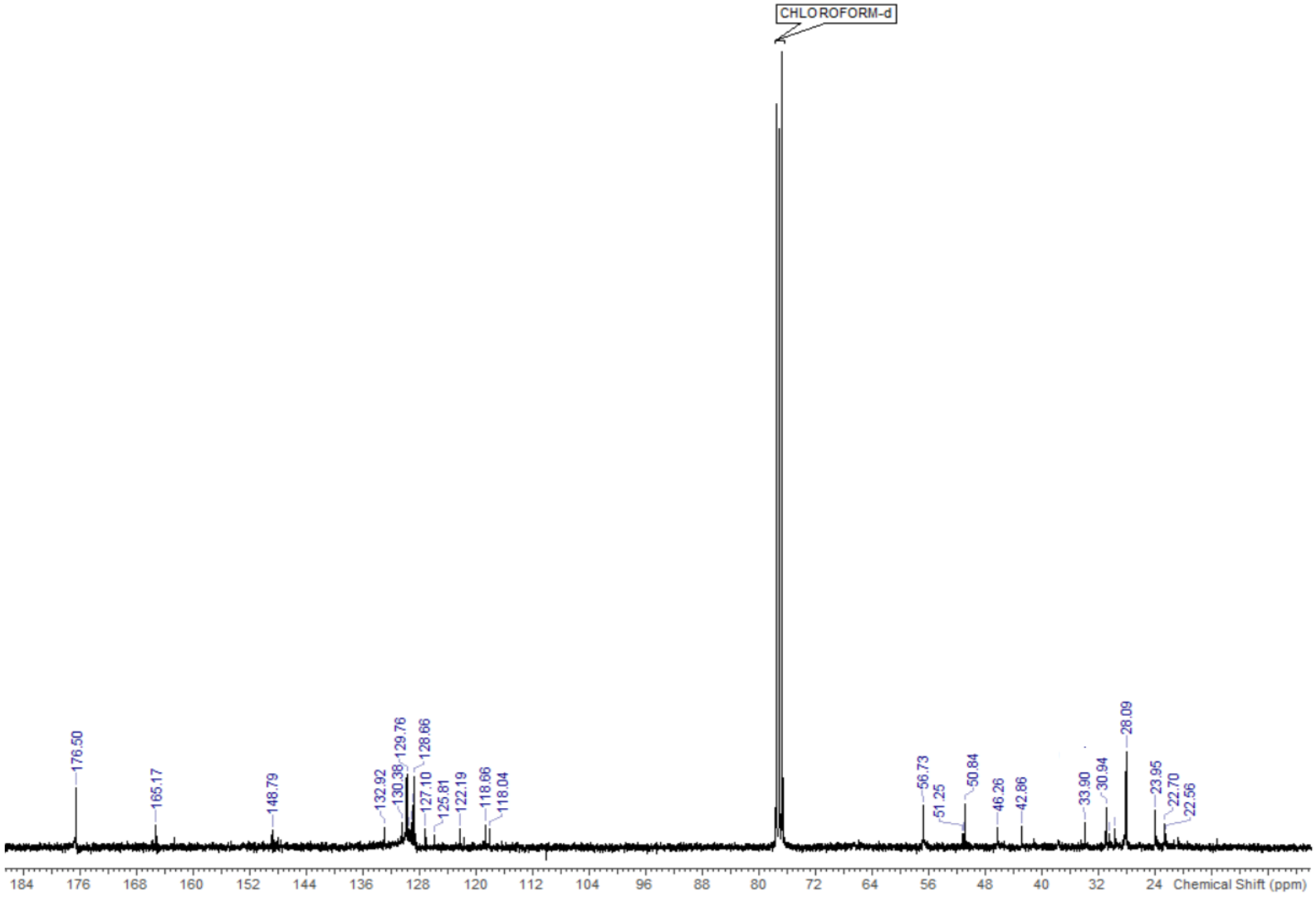
1-(2-(4-(3-Aminophenyl)piperazin-1-yl)-2-oxo-1-phenylethyl)pyrrolidine-2,5-dione (29) – ^{13}C NMR



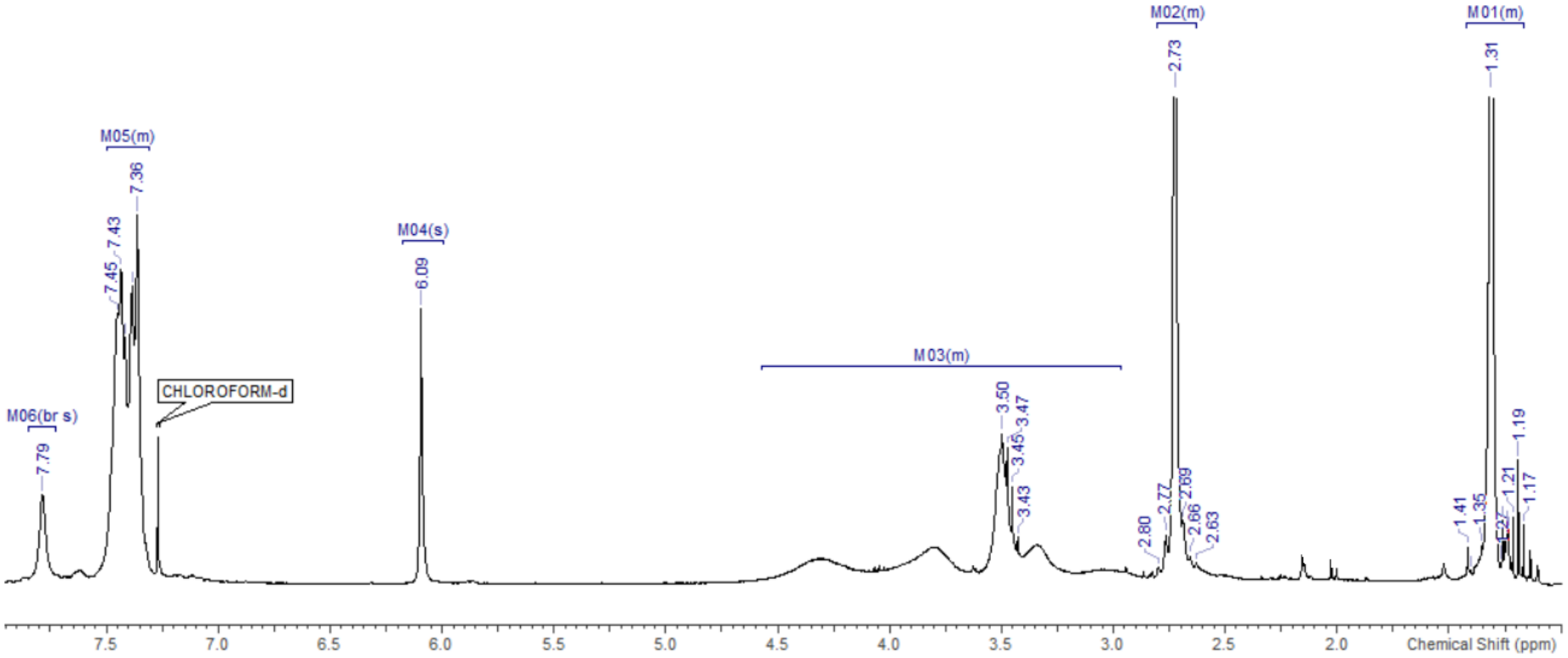
1-(2-(4-(3-Isopropylphenyl)piperazin-1-yl)-2-oxo-1-phenylethyl)pyrrolidine-2,5-dione (30) - ^{1}H NMR



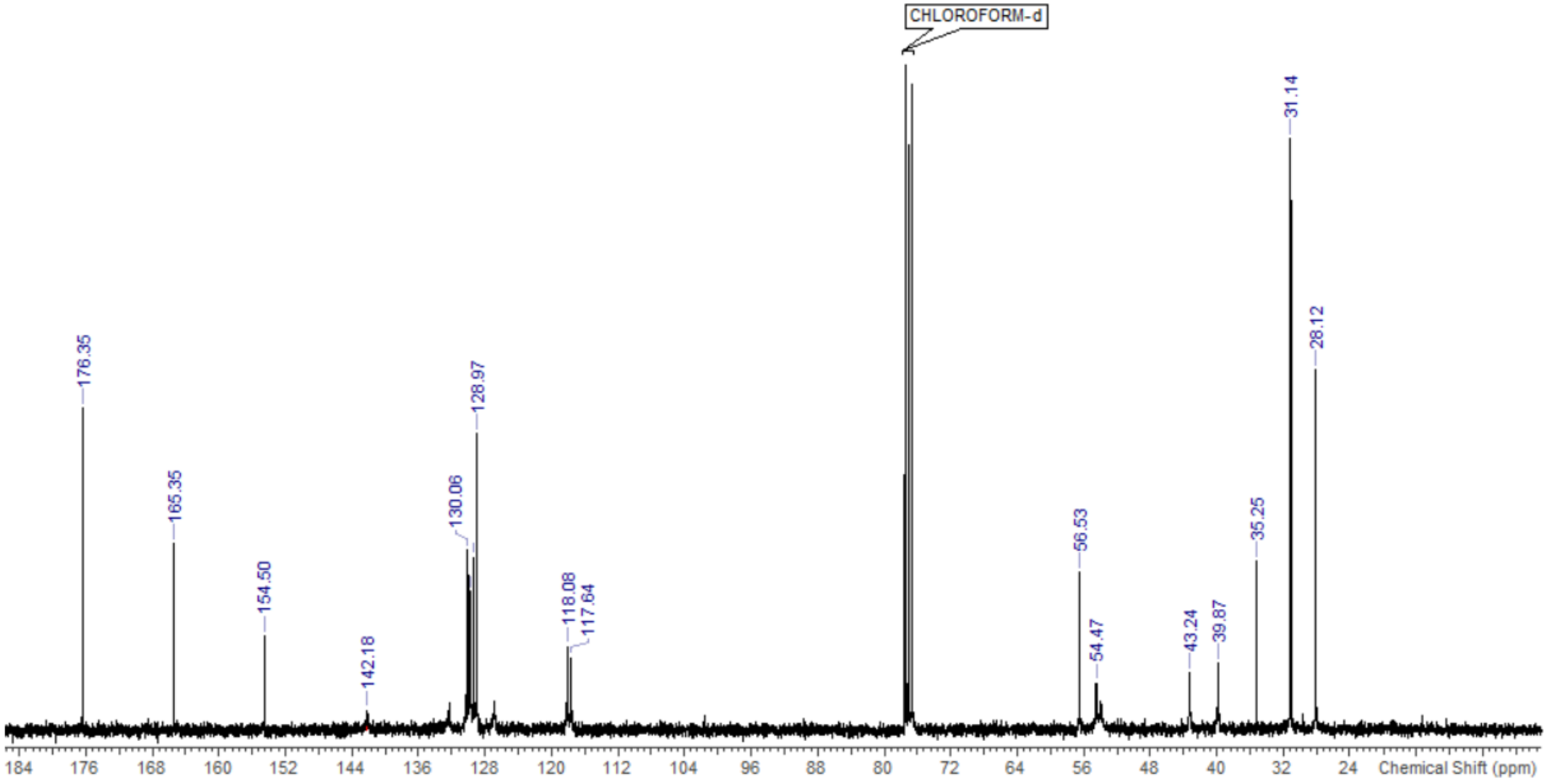
1-(2-(4-(3-Isopropylphenyl)piperazin-1-yl)-2-oxo-1-phenylethyl)pyrrolidine-2,5-dione (30) – ^{13}C NMR



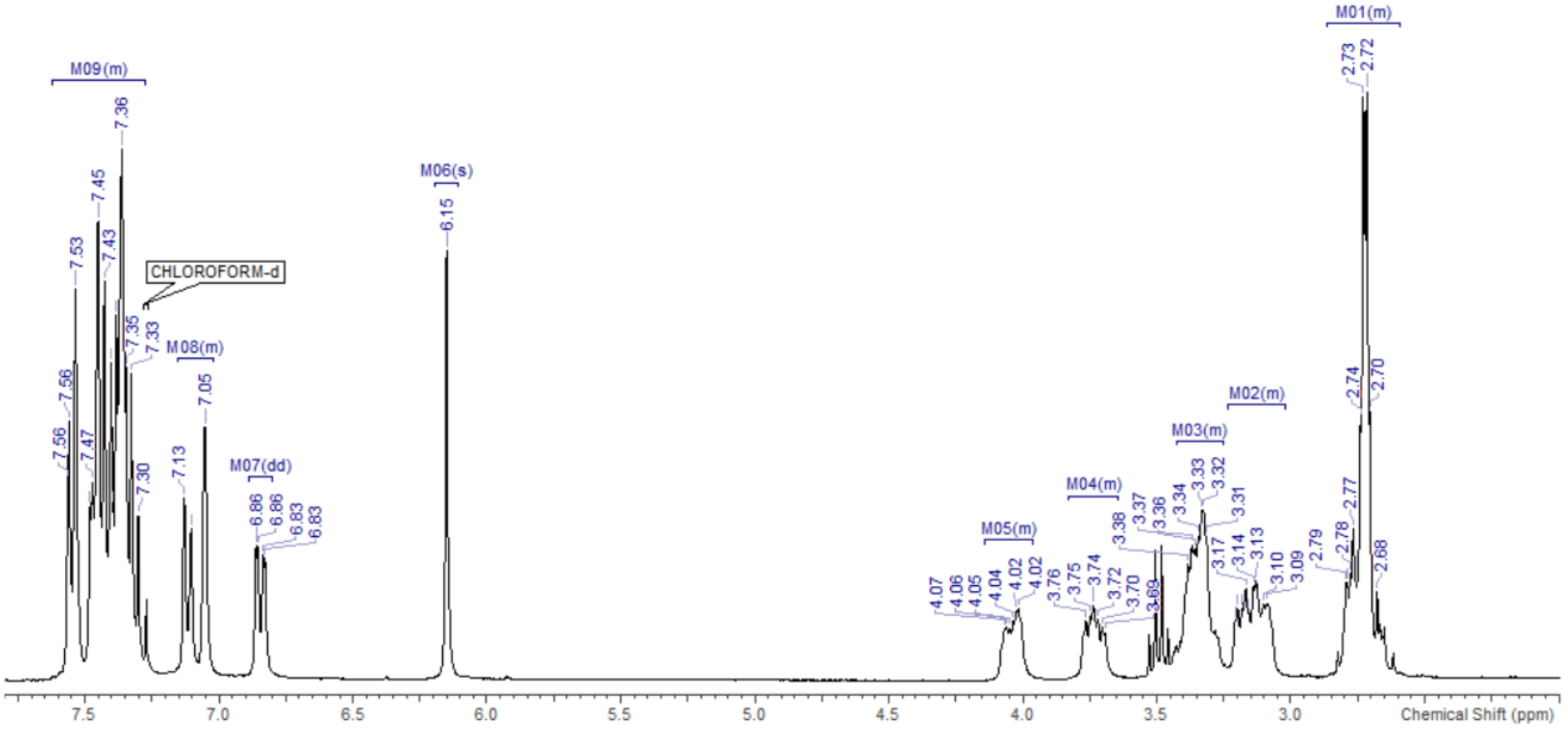
1-(2-(4-(3-(*tert*-Butyl)phenyl)piperazin-1-yl)-2-oxo-1-phenylethyl)pyrrolidine-2,5-dione (31) - ^{1}H NMR



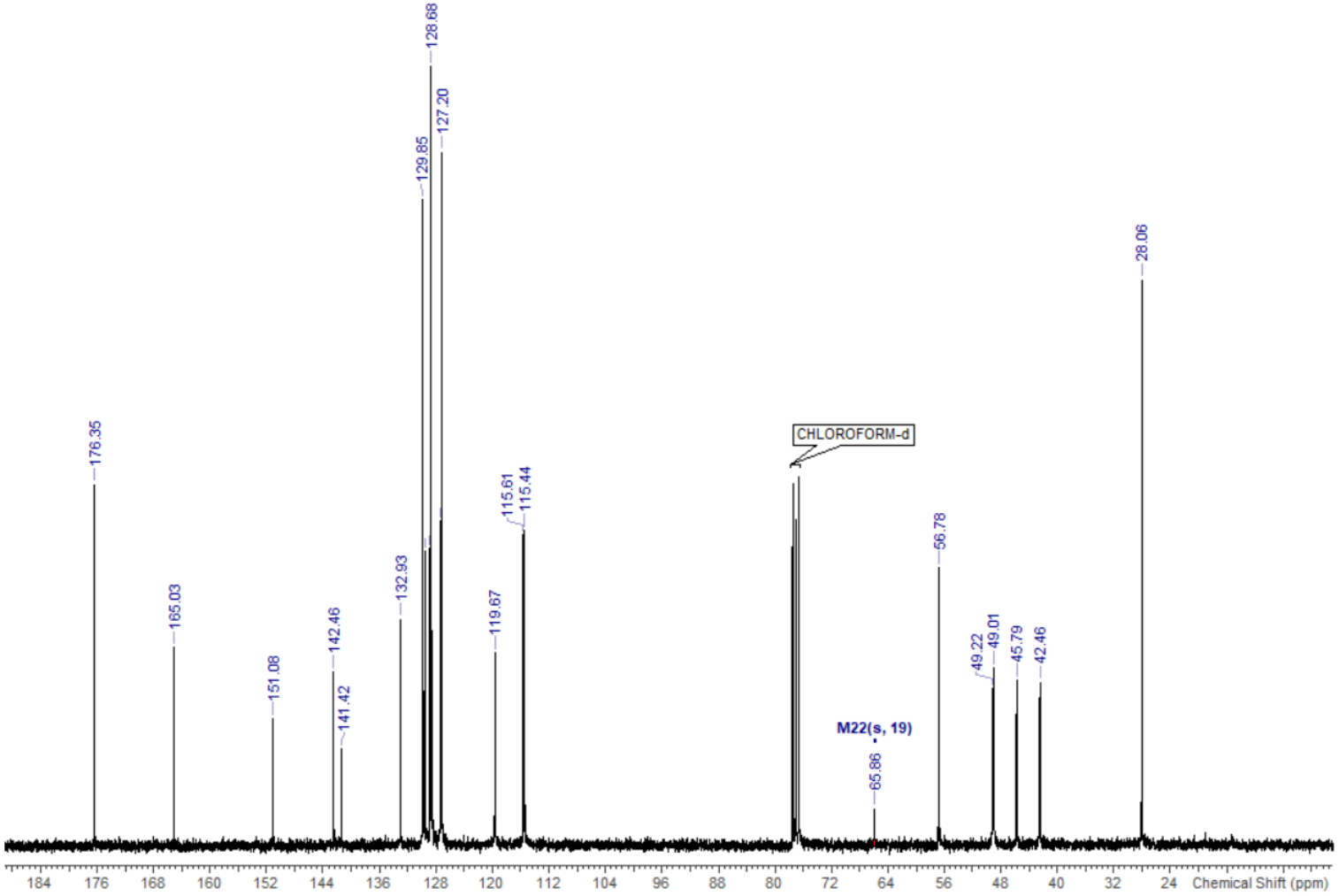
1-(2-(4-(3-(*tert*-Butyl)phenyl)piperazin-1-yl)-2-oxo-1-phenylethyl)pyrrolidine-2,5-dione (31) – ^{13}C NMR



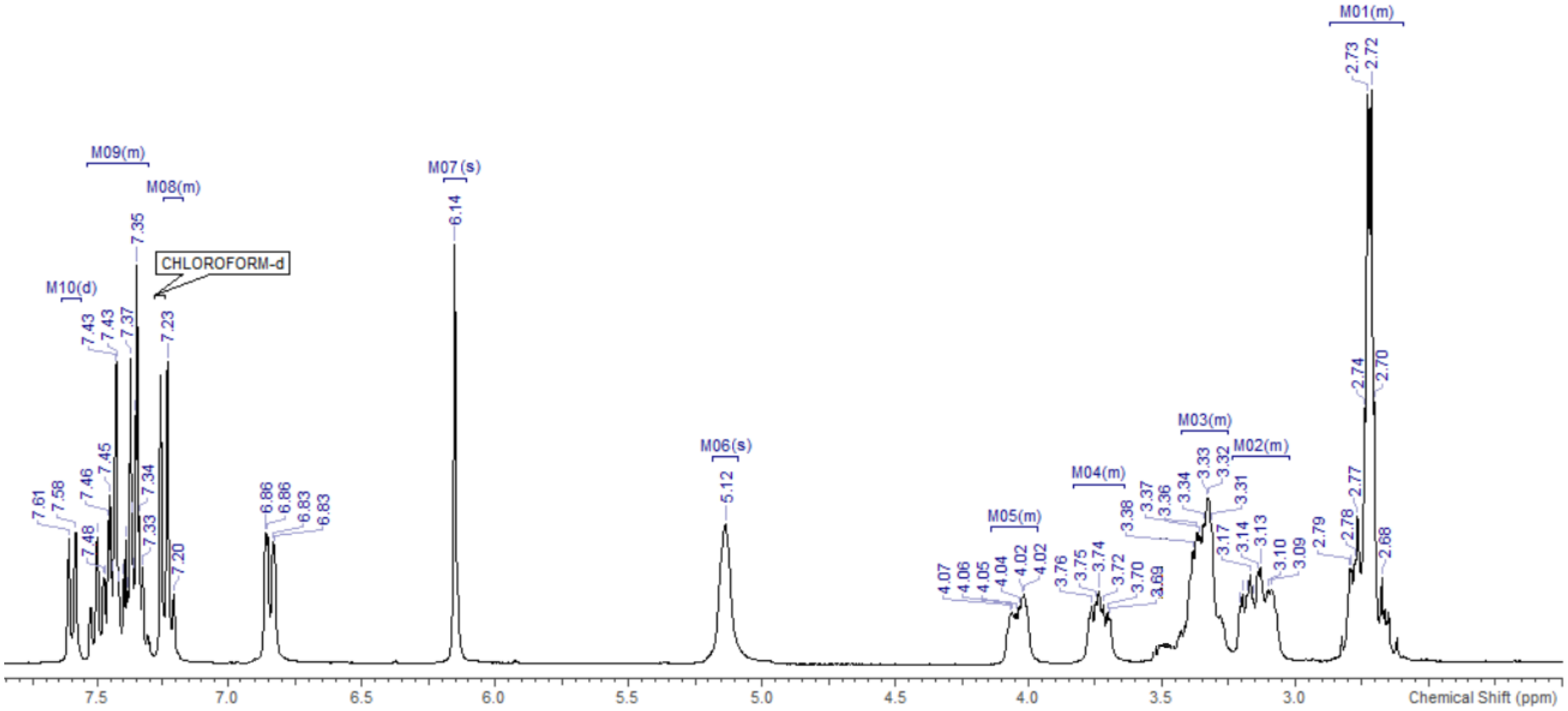
1-(2-(4-([1,1'-Biphenyl]-3-yl)piperazin-1-yl)-2-oxo-1-phenylethyl)pyrrolidine-2,5-dione (32) - ^{1}H NMR



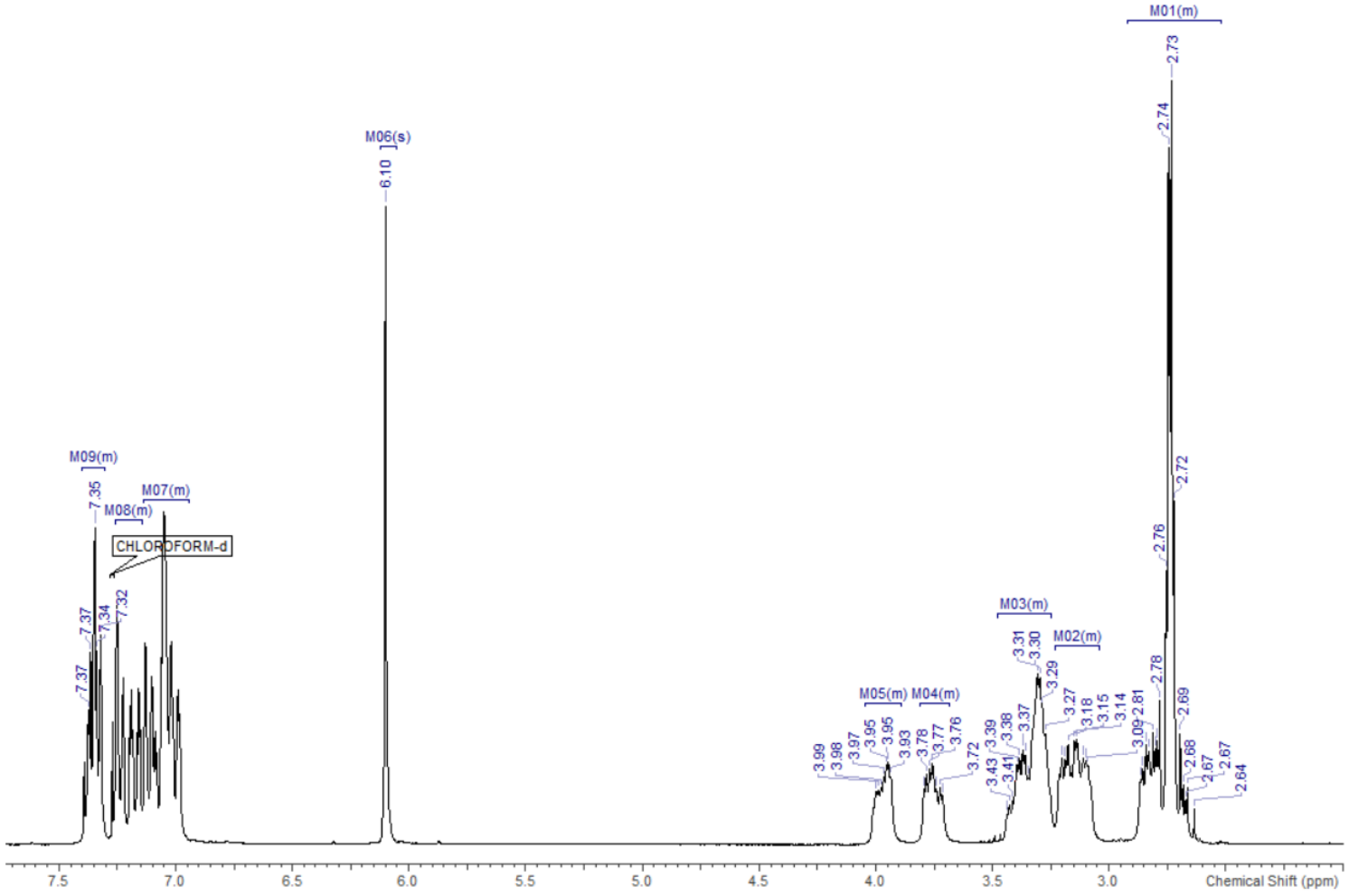
1-(2-(4-([1,1'-Biphenyl]-3-yl)piperazin-1-yl)-2-oxo-1-phenylethyl)pyrrolidine-2,5-dione (32) – ^{13}C NMR



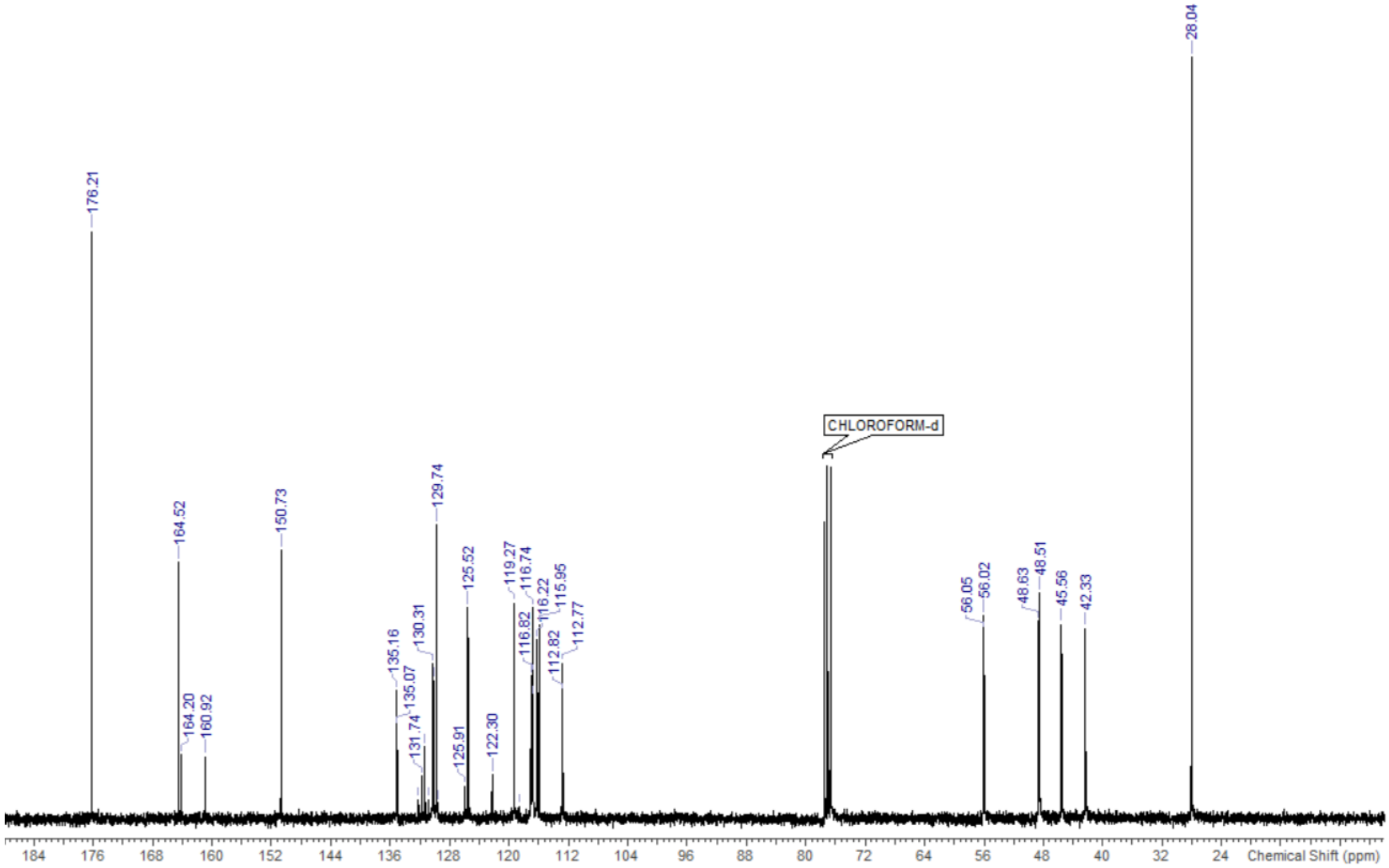
1-(2-(4-(3-(Benzyloxy)phenyl)piperazin-1-yl)-2-oxo-1-phenylethyl)pyrrolidine-2,5-dione (33) - ^{1}H NMR



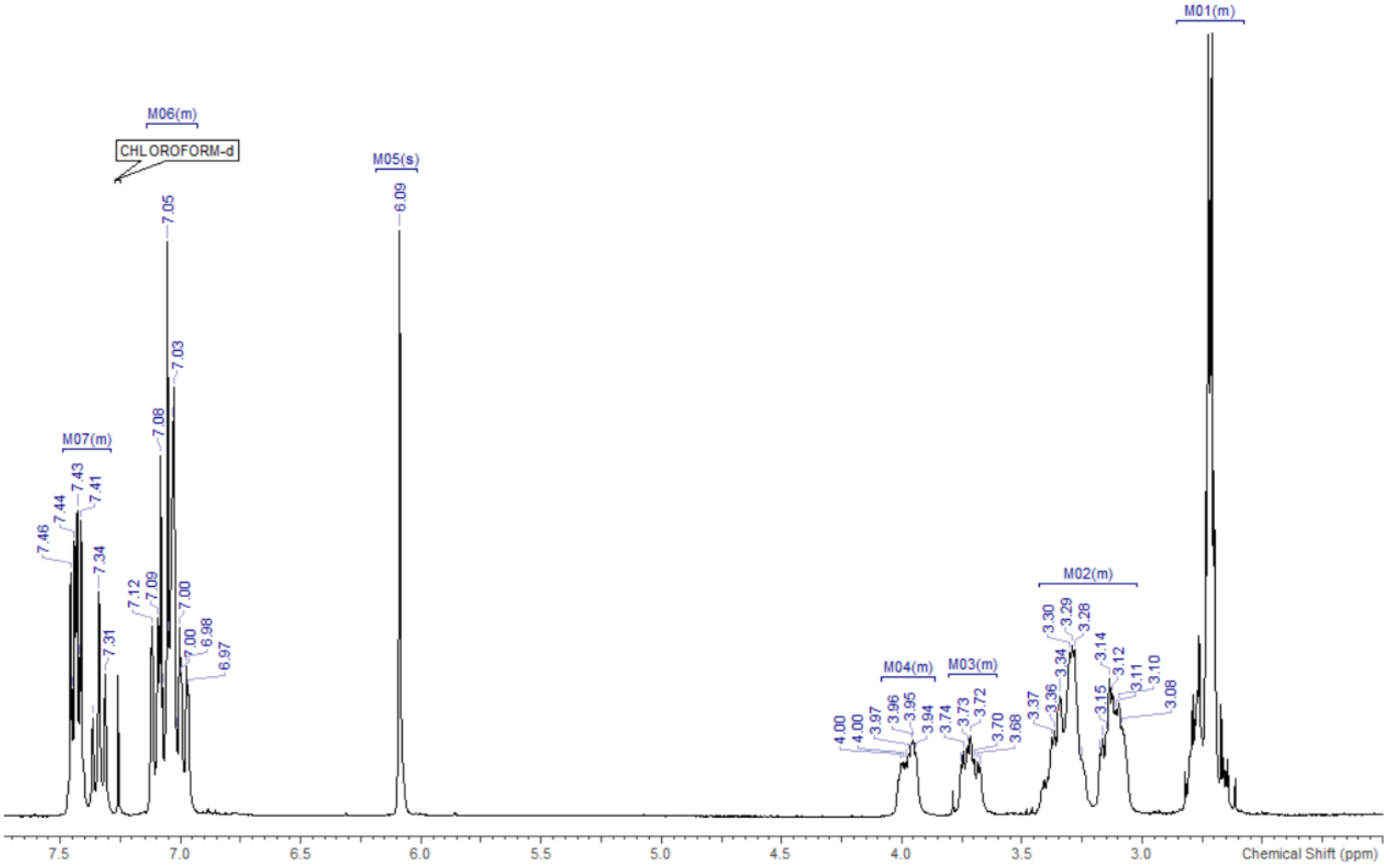
1-(1-(3-Fluorophenyl)-2-oxo-2-(4-(3-(trifluoromethyl)phenyl)piperazin-1-yl)ethyl)pyrrolidine-2,5-dione (34) - ^{1}H NMR



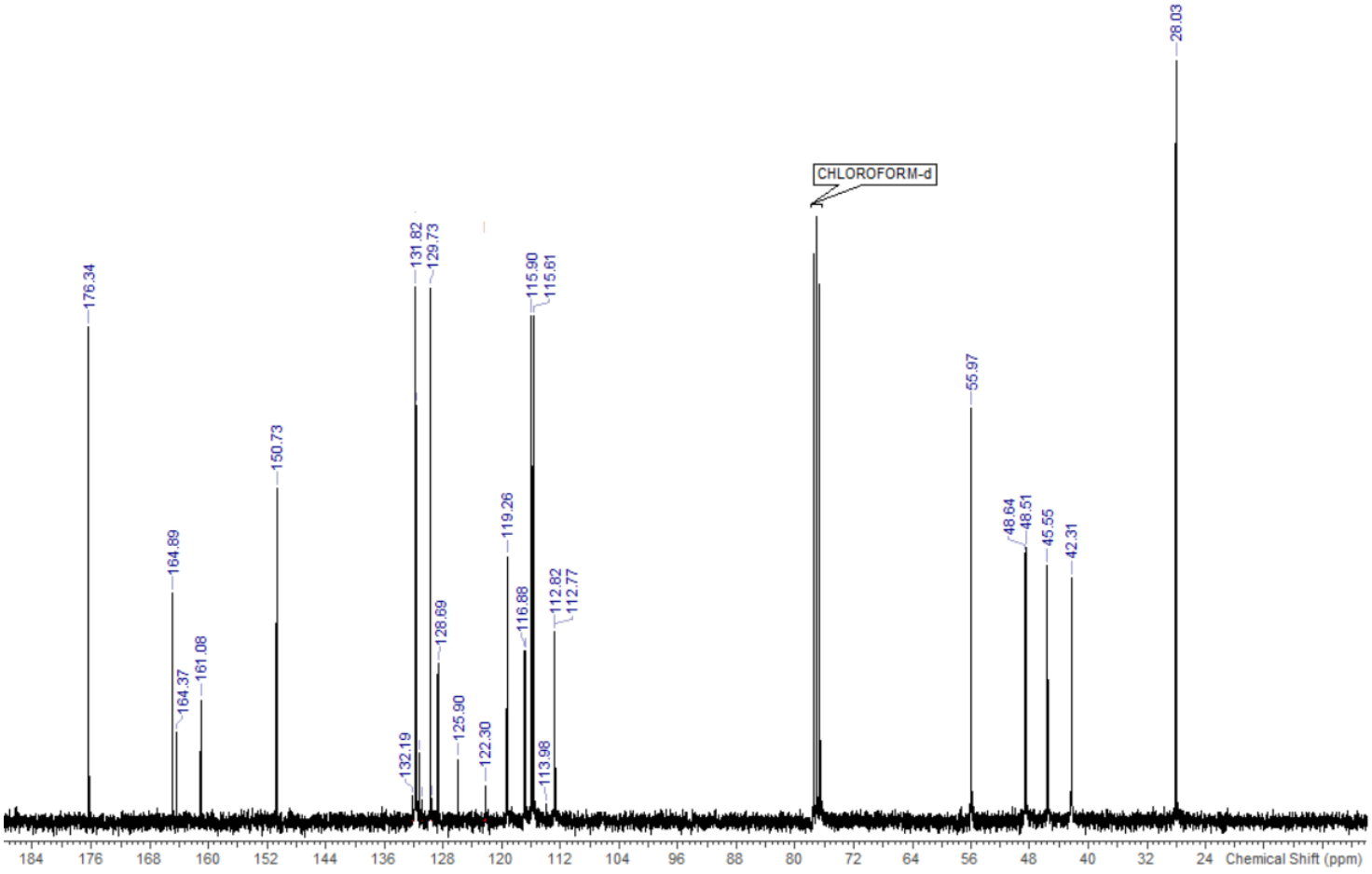
1-(1-(3-Fluorophenyl)-2-oxo-2-(4-(3-(trifluoromethyl)phenyl)piperazin-1-yl)ethyl)pyrrolidine-2,5-dione (34) – ^{13}C NMR



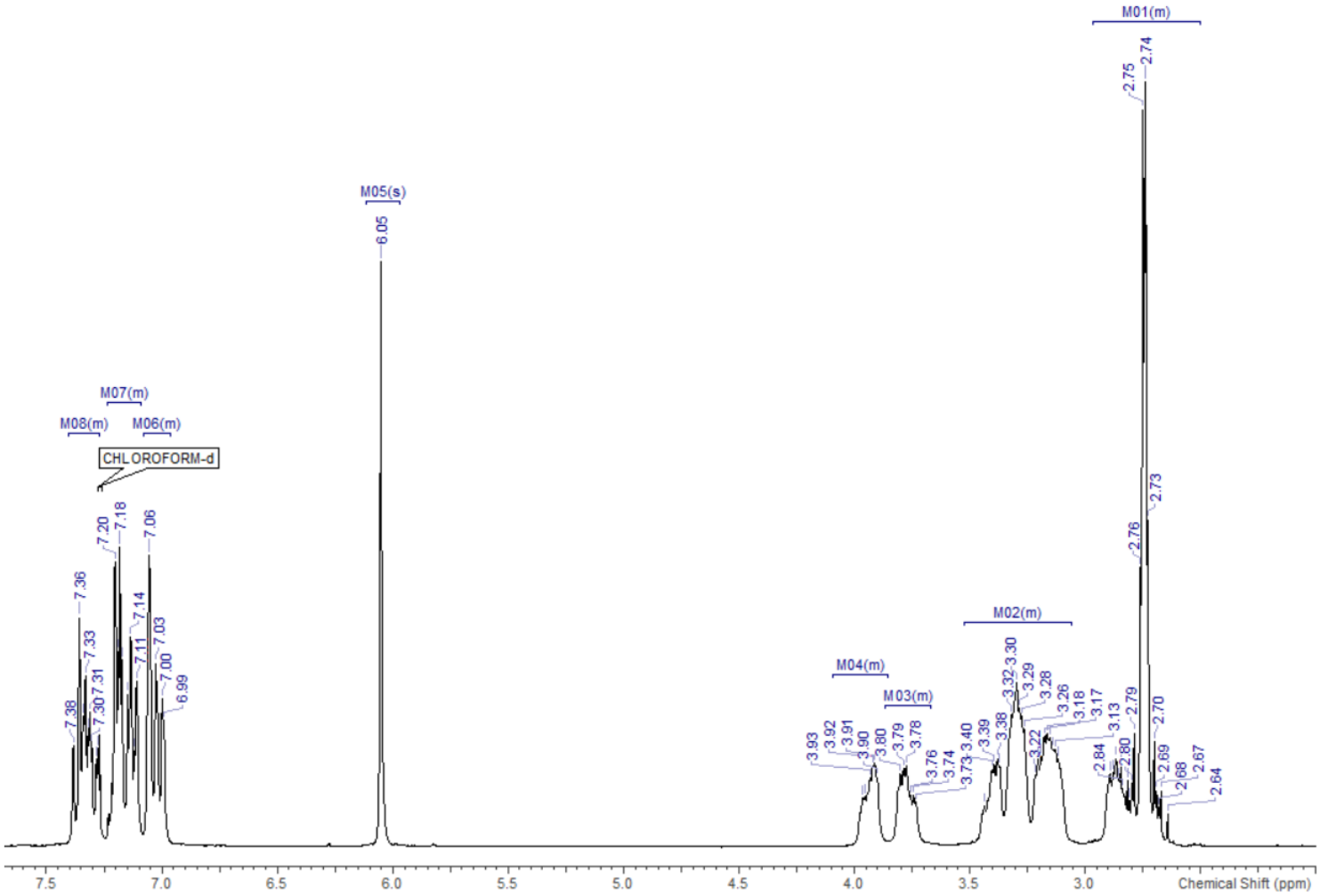
1-(1-(4-Fluorophenyl)-2-oxo-2-(4-(3-(trifluoromethyl)phenyl)piperazin-1-yl)ethyl)pyrrolidine-2,5-dione (35) - ^{1}H NMR



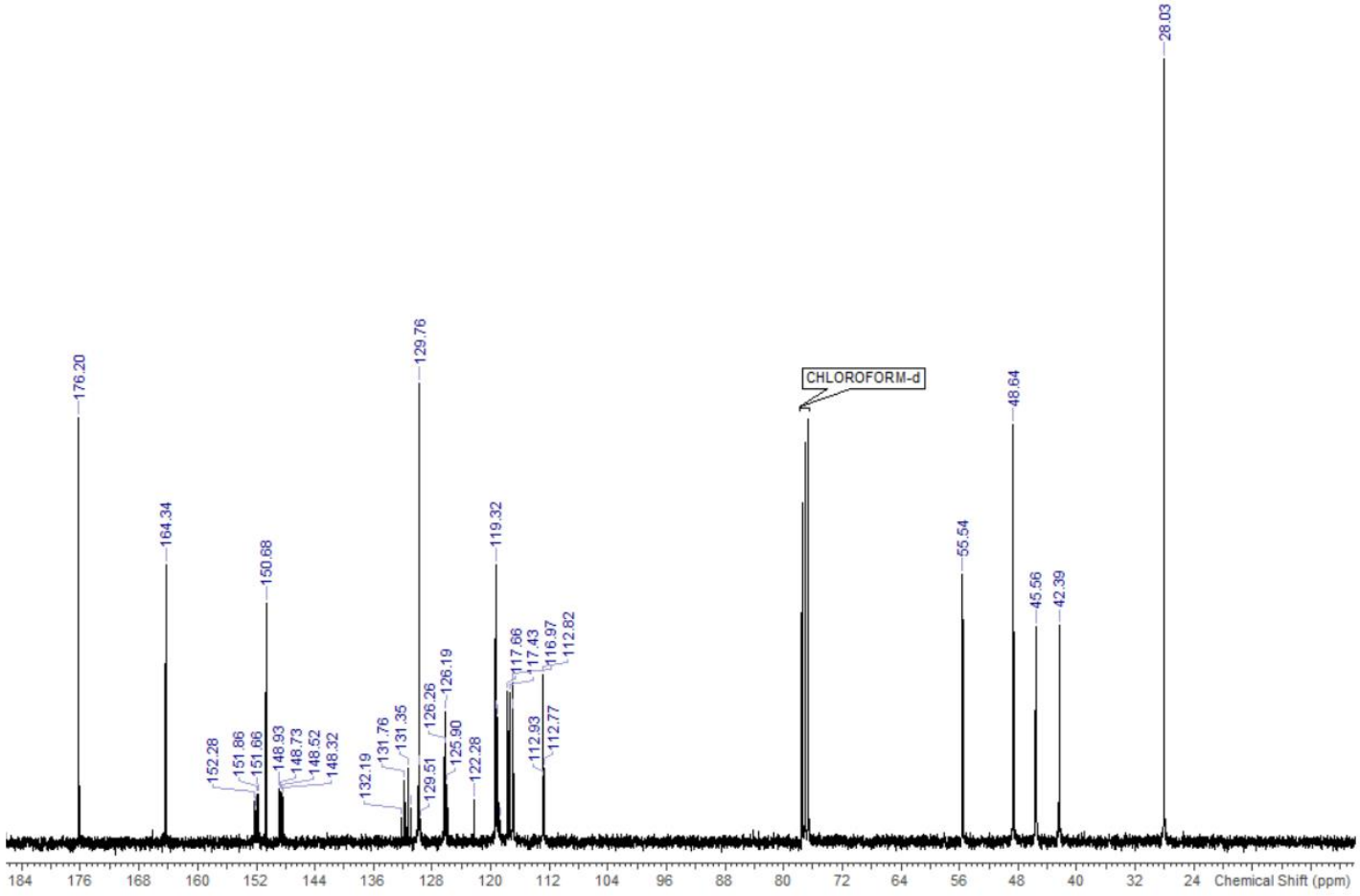
1-(1-(4-Fluorophenyl)-2-oxo-2-(4-(3-(trifluoromethyl)phenyl)piperazin-1-yl)ethyl)pyrrolidine-2,5-dione (35) – ^{13}C NMR



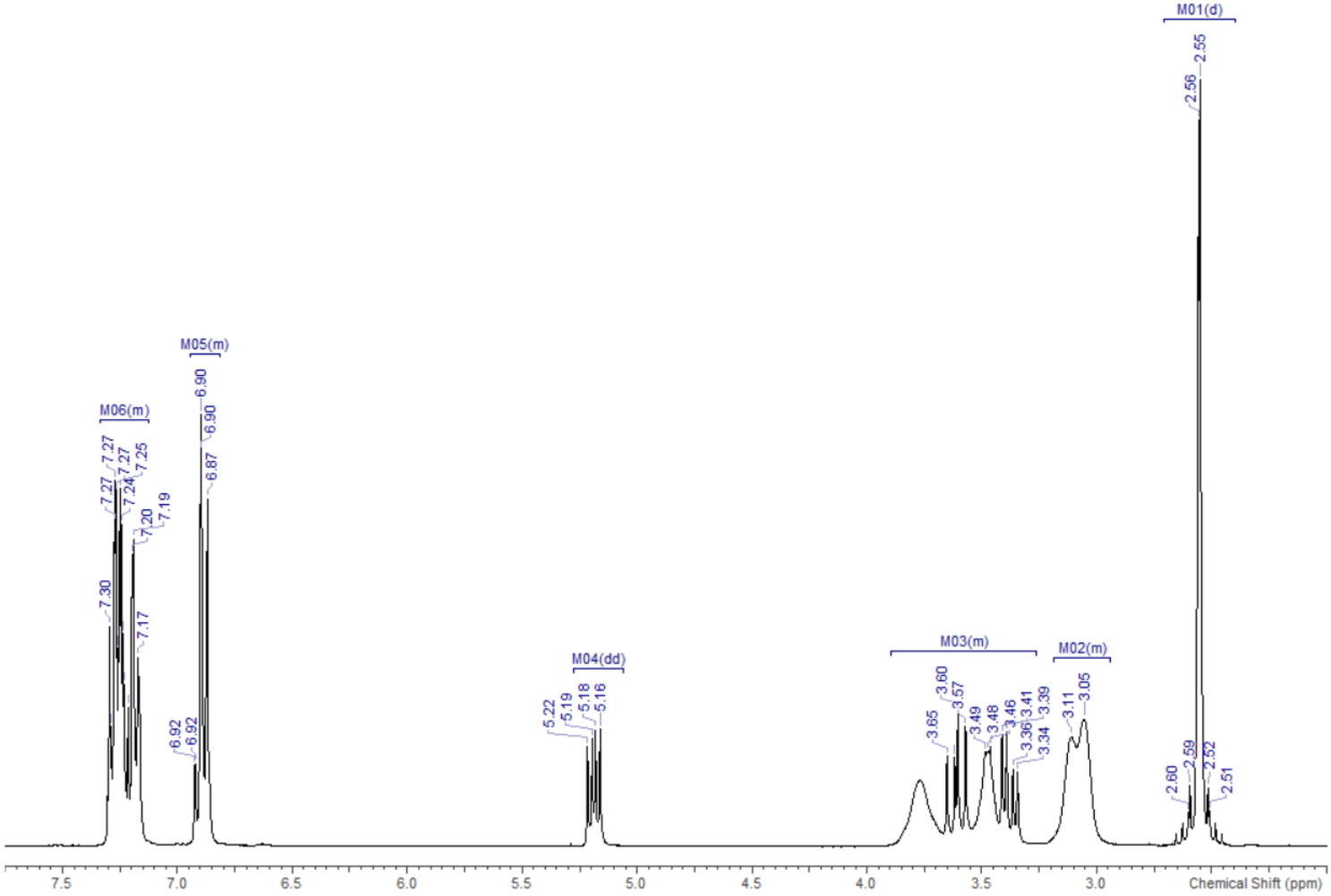
1-(1-(3,4-Difluorophenyl)-2-oxo-2-(4-(3-(trifluoromethyl)phenyl)piperazin-1-yl)ethyl)pyrrolidine-2,5-dione (36) - ^{1}H NMR



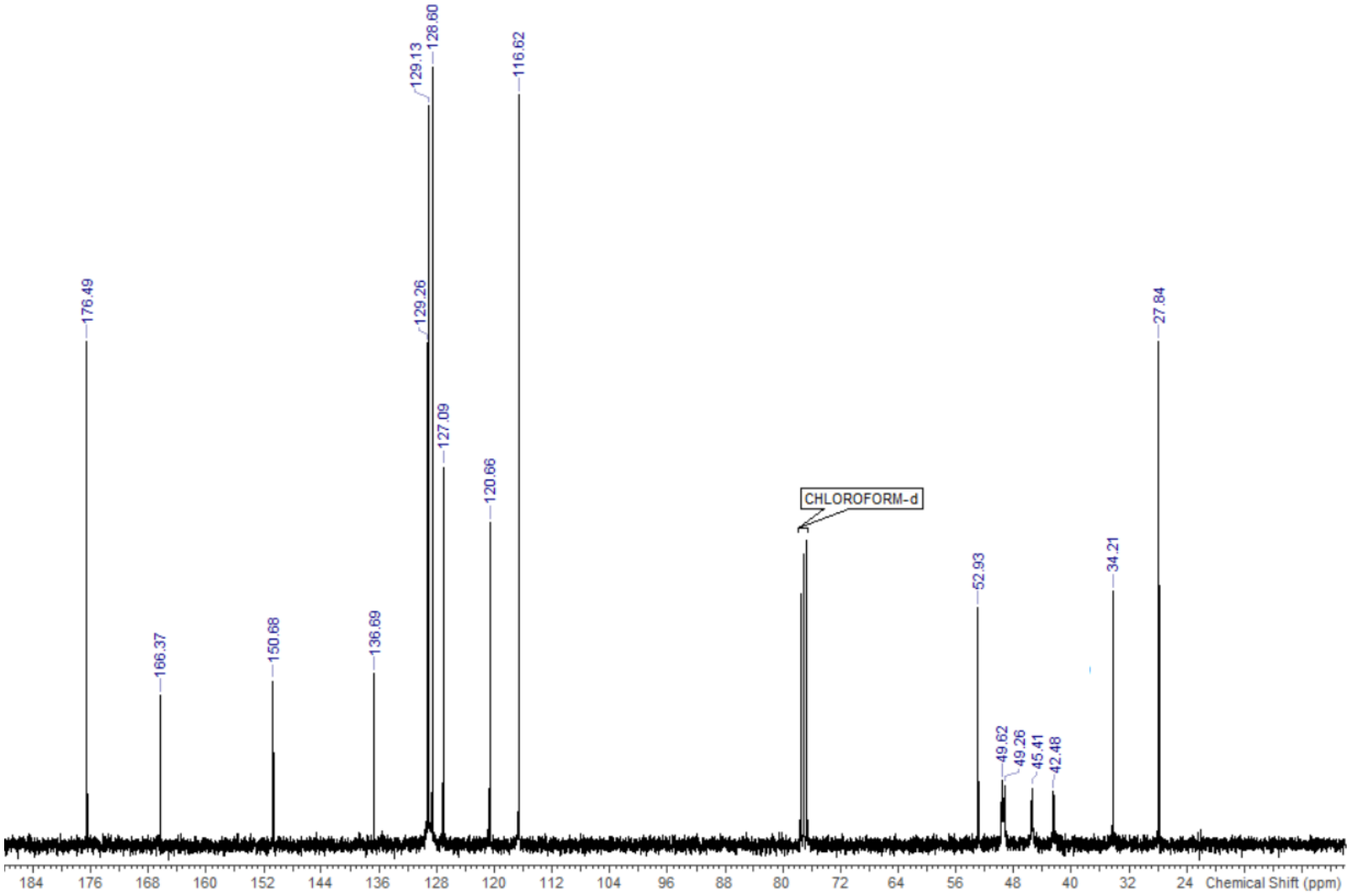
1-(1-(3,4-Difluorophenyl)-2-oxo-2-(4-(3-(trifluoromethyl)phenyl)piperazin-1-yl)ethyl)pyrrolidine-2,5-dione (36) – ^{13}C NMR



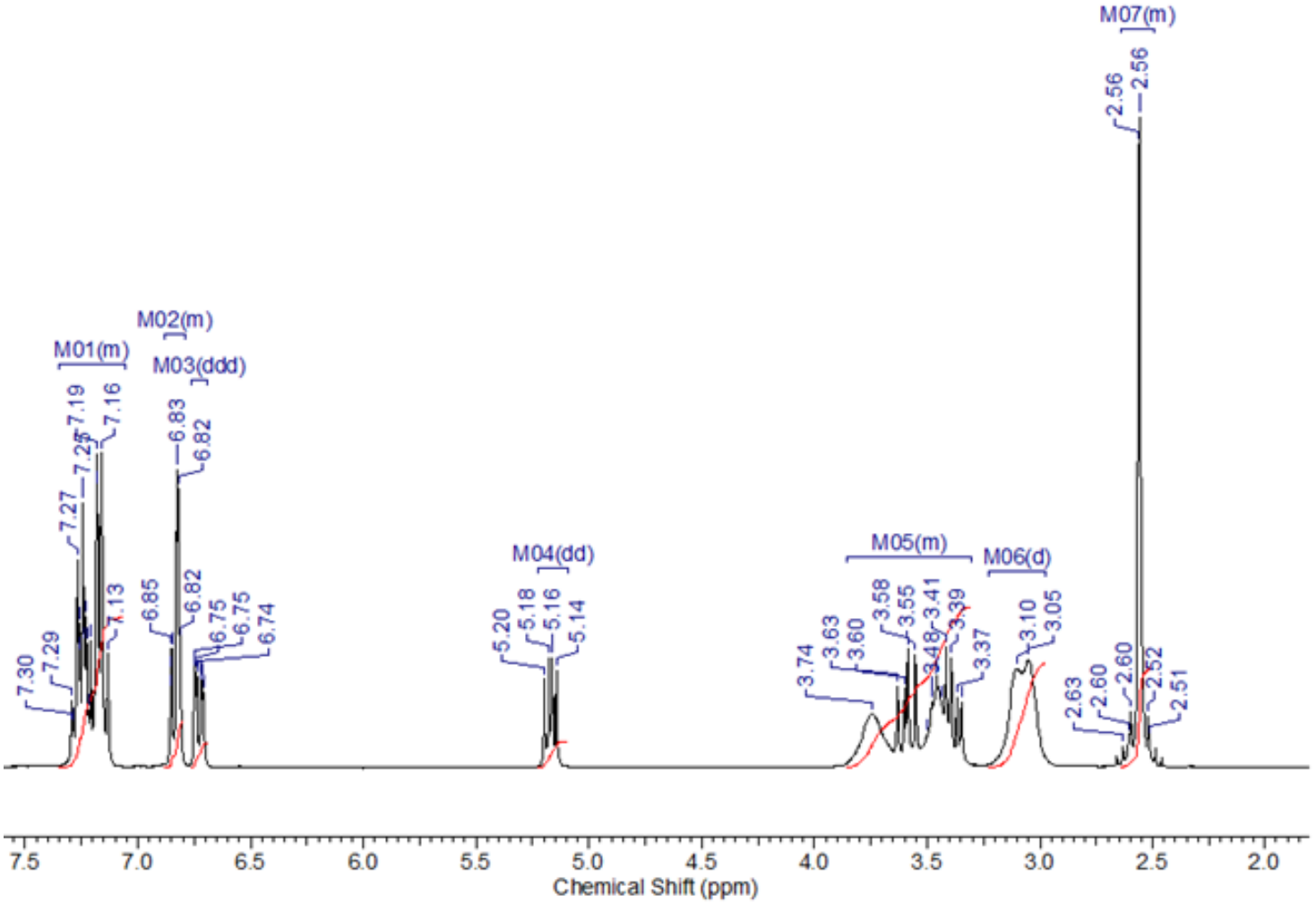
1-(1-Oxo-3-phenyl-1-(4-phenylpiperazin-1-yl)propan-2-yl)pyrrolidine-2,5-dione (37) - ^{1}H NMR



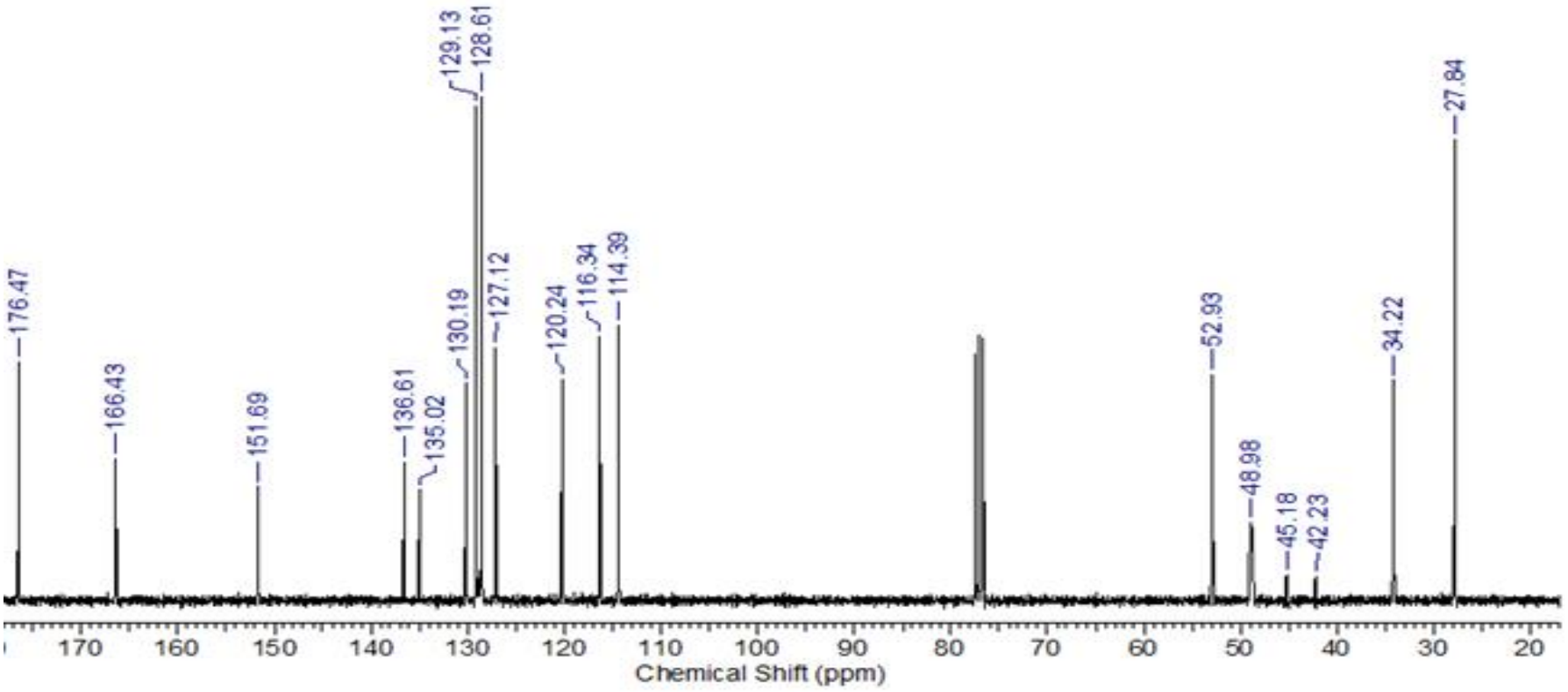
1-(1-Oxo-3-phenyl-1-(4-phenylpiperazin-1-yl)propan-2-yl)pyrrolidine-2,5-dione (37) – ^{13}C NMR



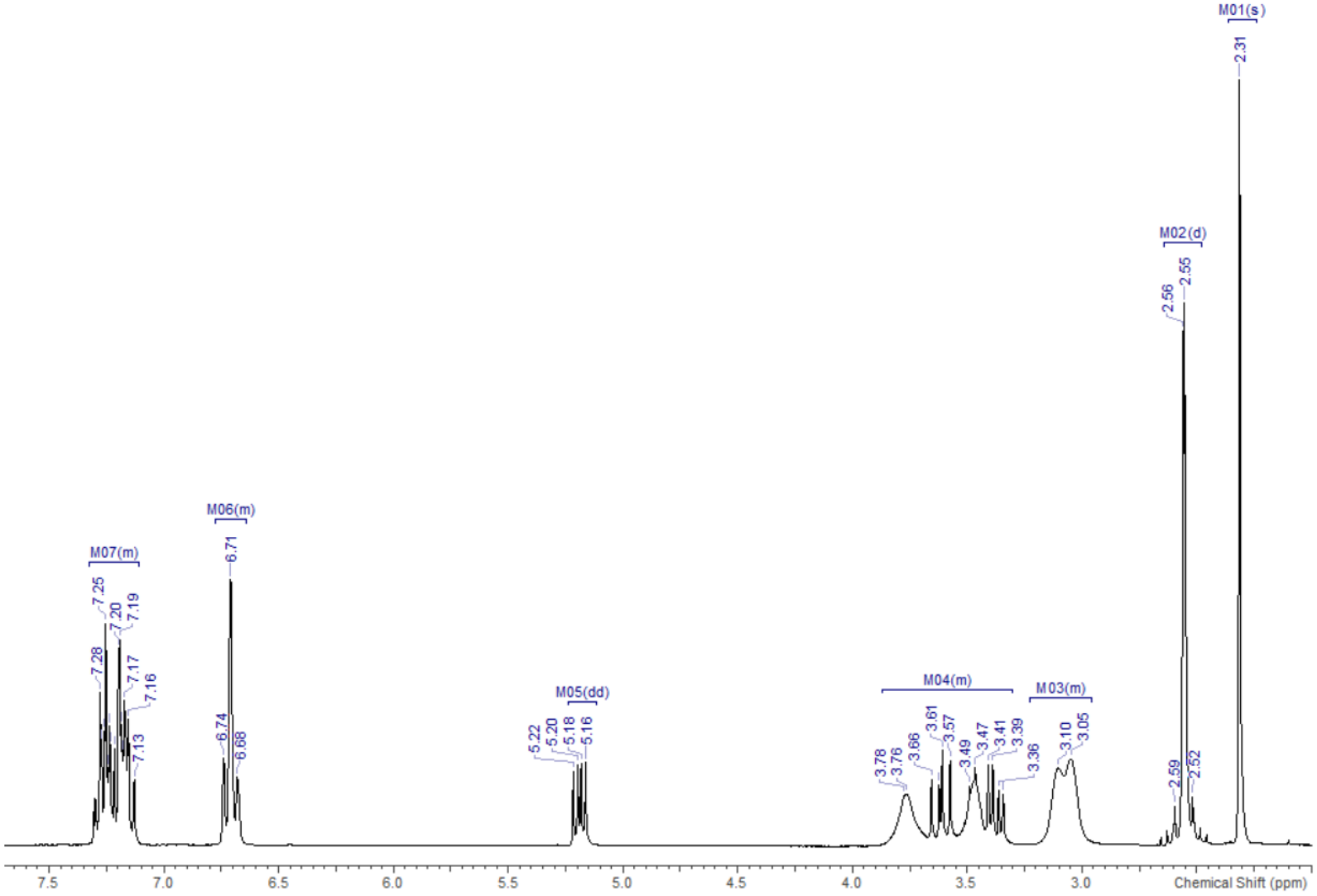
1-(1-(4-(3-Chlorophenyl)piperazin-1-yl)-1-oxo-3-phenylpropan-2-yl)pyrrolidine-2,5-dione (38) - ^{1}H NMR



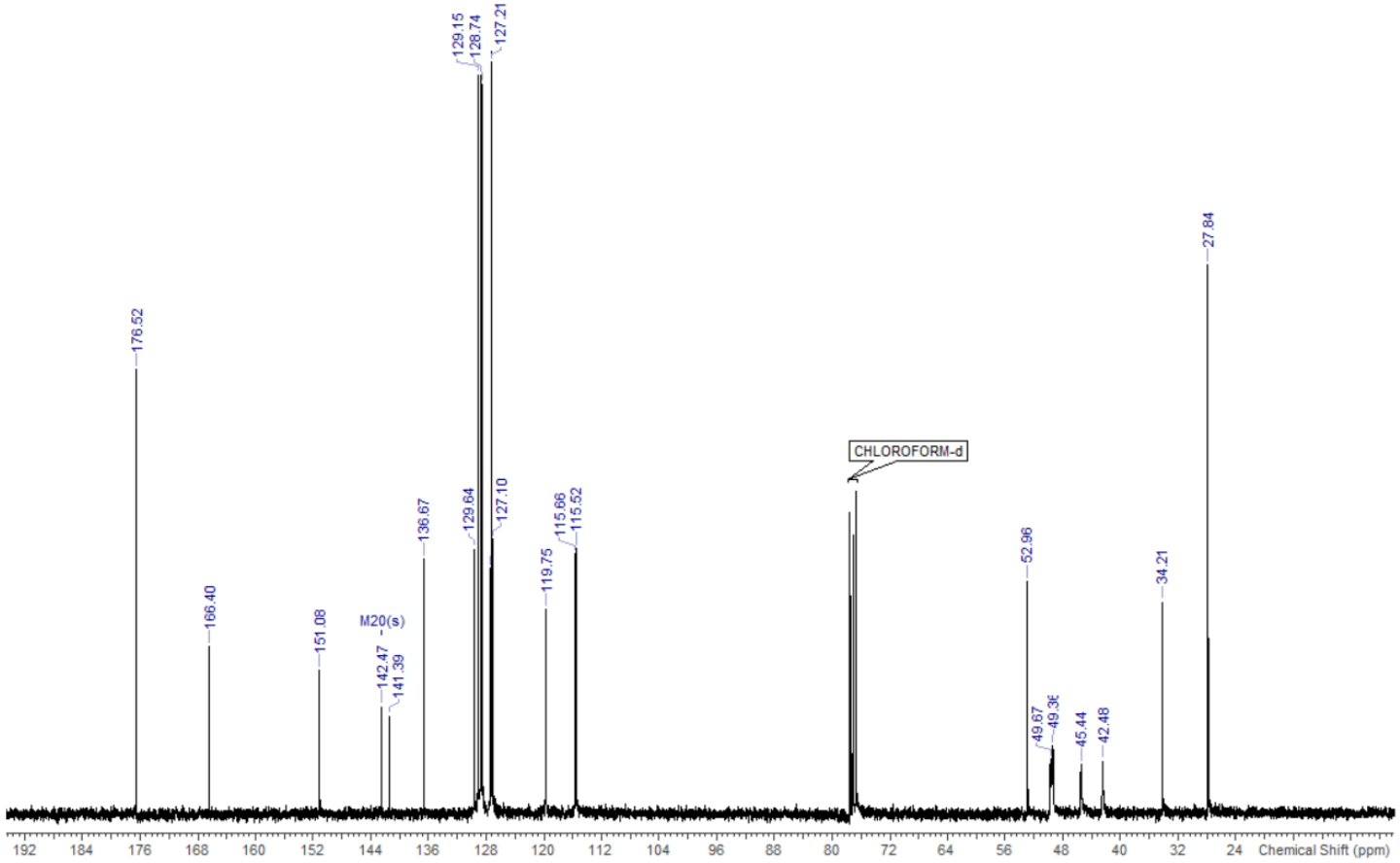
1-(1-(4-(3-Chlorophenyl)piperazin-1-yl)-1-oxo-3-phenylpropan-2-yl)pyrrolidine-2,5-dione (38) – ^{13}C NMR



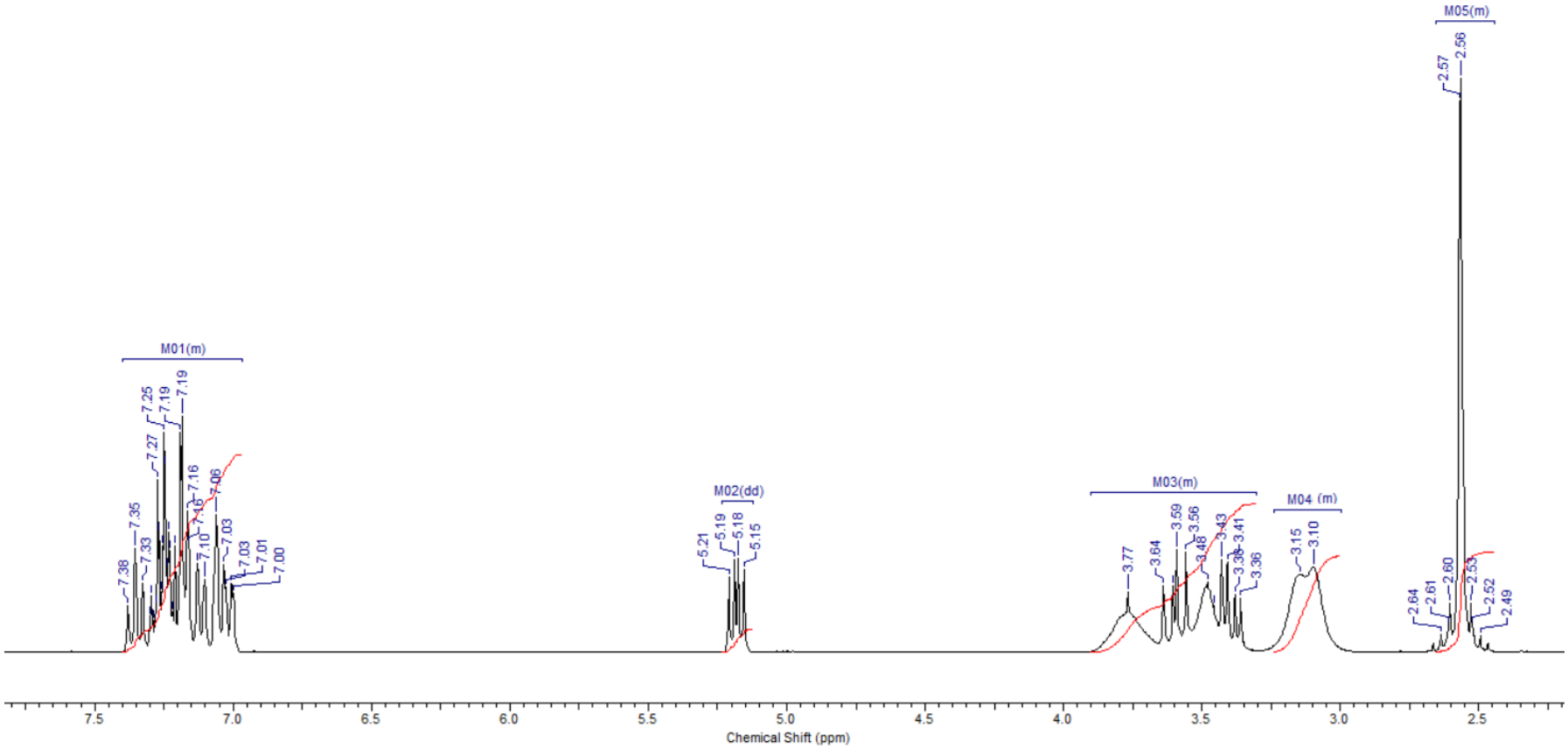
1-(1-Oxo-3-phenyl-1-(4-(m-tolyl)piperazin-1-yl)propan-2-yl)pyrrolidine-2,5-dione (39) - ^{1}H NMR



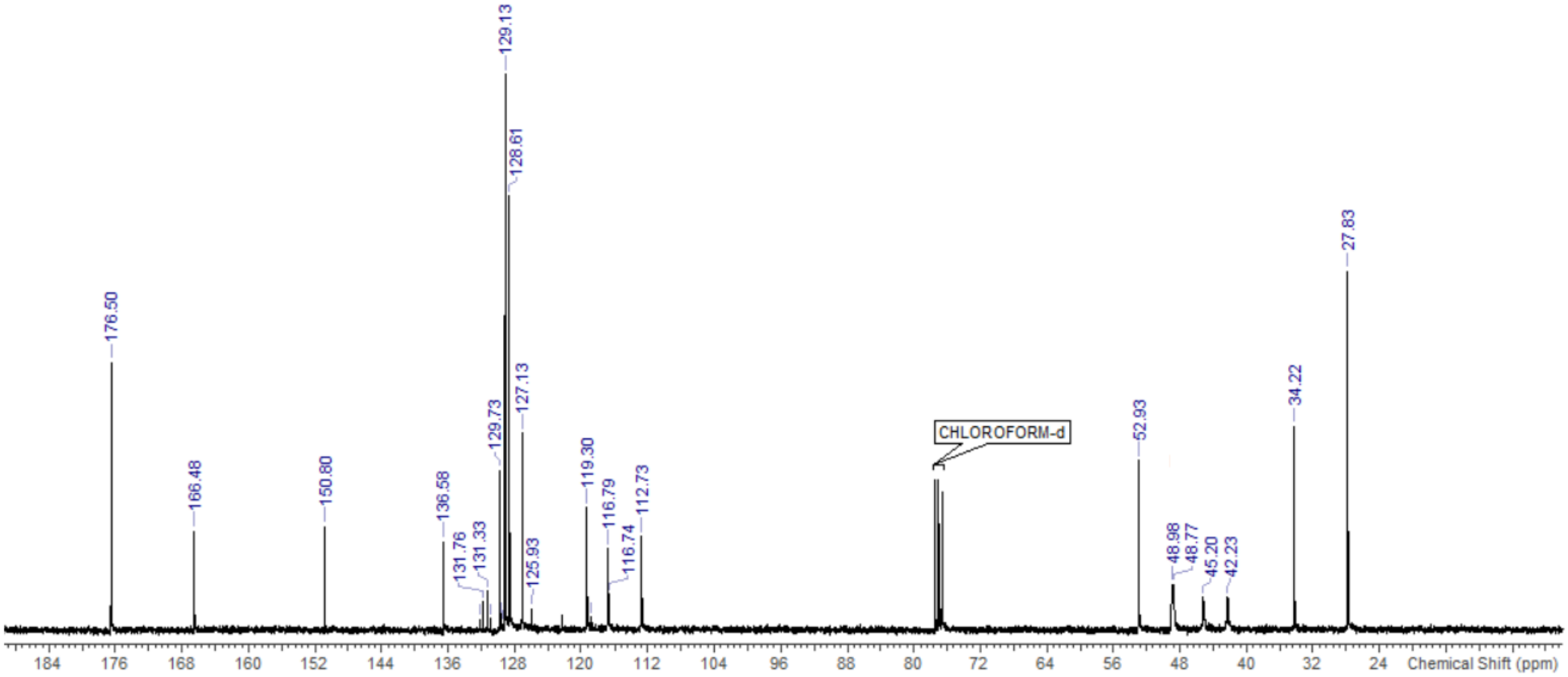
1-(1-Oxo-3-phenyl-1-(4-(m-tolyl)piperazin-1-yl)propan-2-yl)pyrrolidine-2,5-dione (39) – ^{13}C NMR



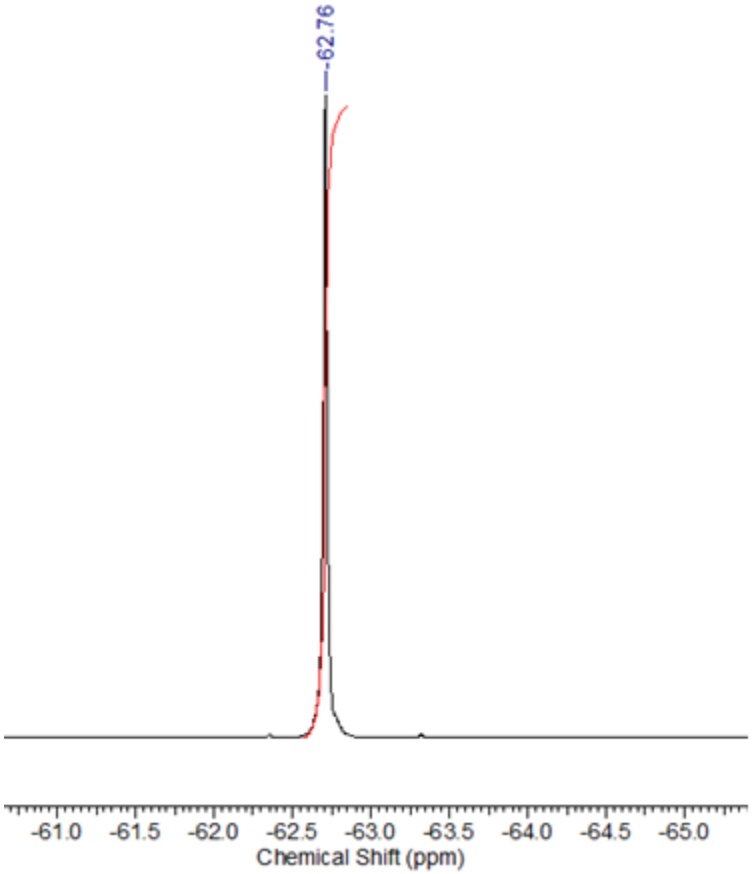
1-(1-Oxo-3-phenyl-1-(4-(3-(trifluoromethyl)phenyl)piperazin-1-yl)propan-2-yl)pyrrolidine-2,5-dione (40) - ^{1}H NMR



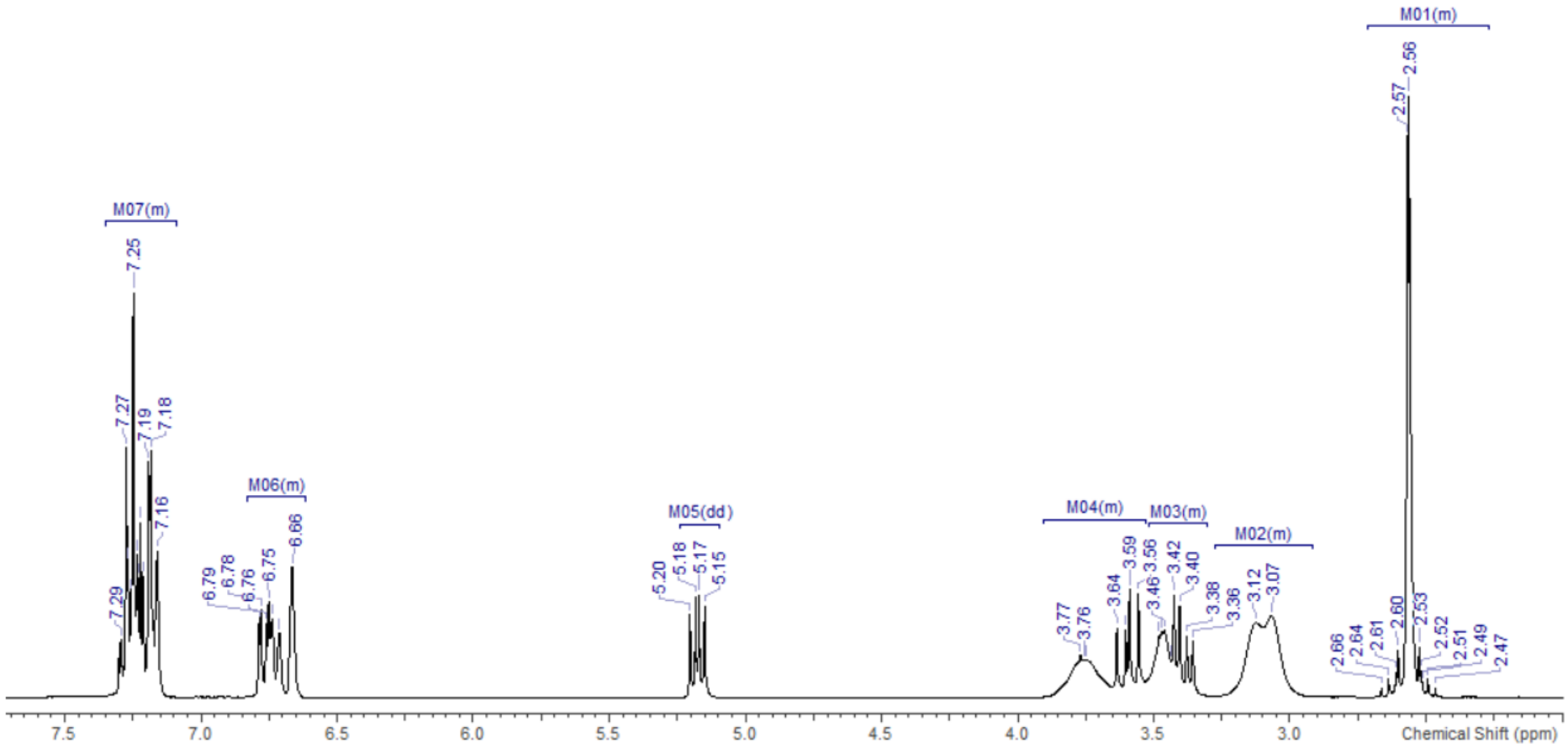
1-(1-Oxo-3-phenyl-1-(4-(3-(trifluoromethyl)phenyl)piperazin-1-yl)propan-2-yl)pyrrolidine-2,5-dione (40) – ^{13}C NMR



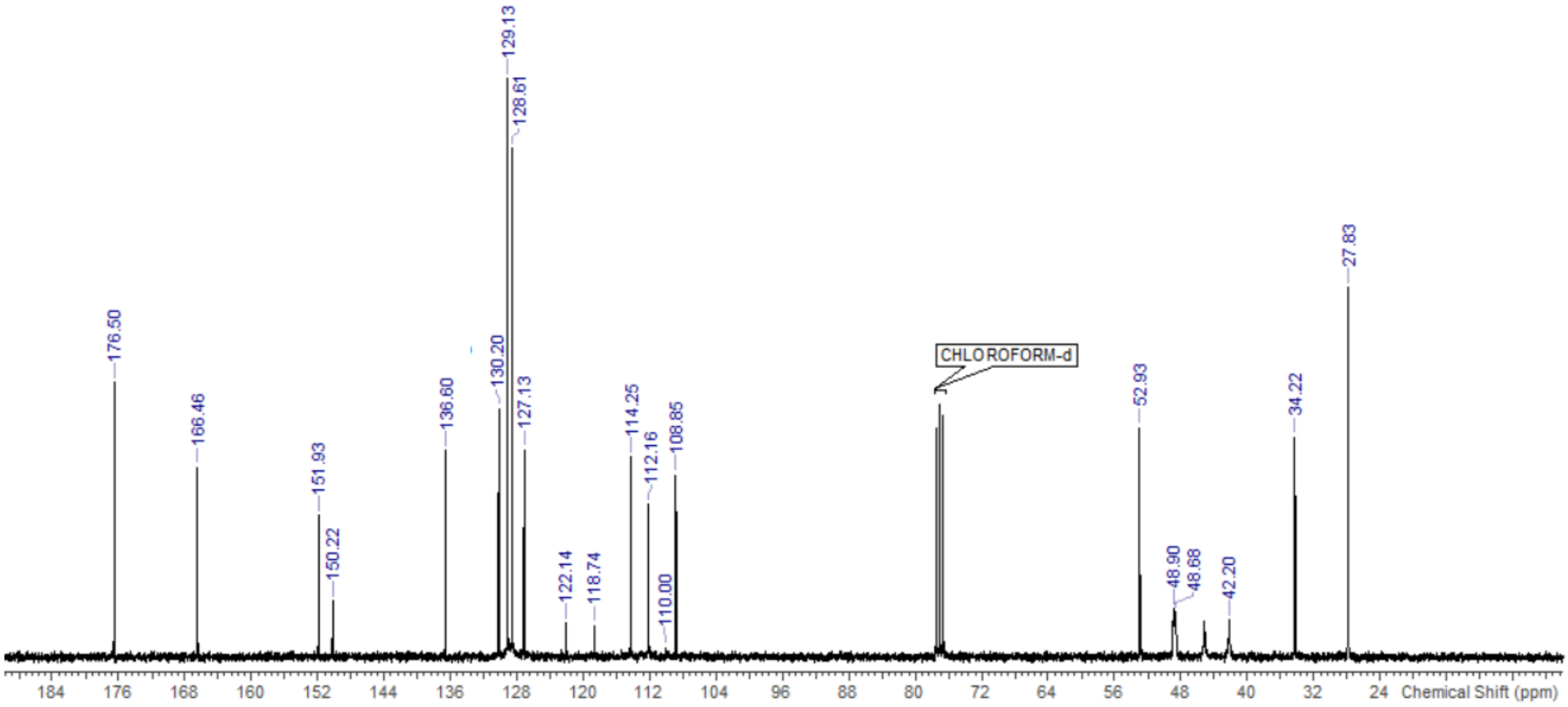
1-(1-Oxo-3-phenyl-1-(4-(3-(trifluoromethyl)phenyl)piperazin-1-yl)propan-2-yl)pyrrolidine-2,5-dione (40) – ^{19}F NMR



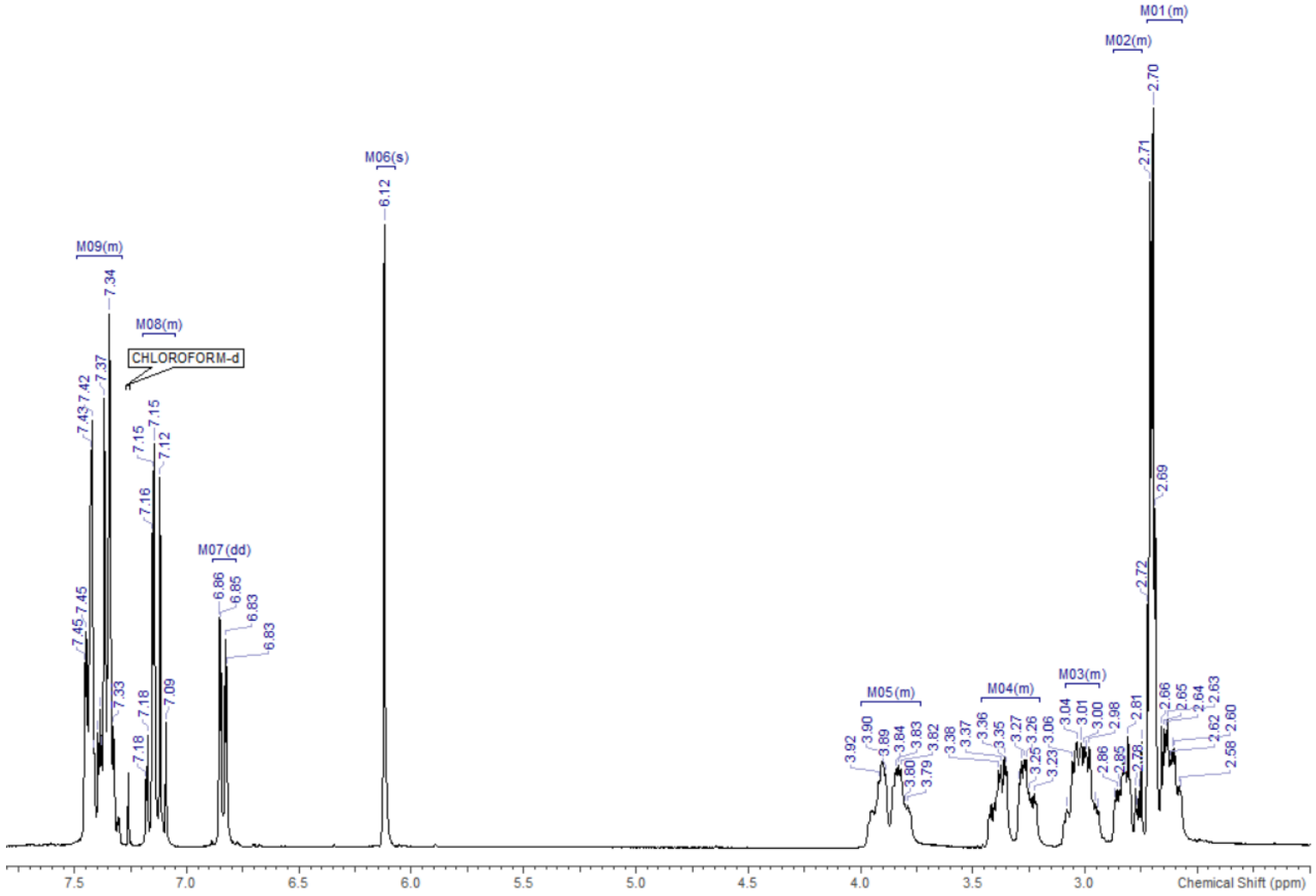
1-(1-Oxo-3-phenyl-1-(4-(3-(trifluoromethoxy)phenyl)piperazin-1-yl)propan-2-yl)pyrrolidine-2,5-dione (41) - ^{1}H NMR



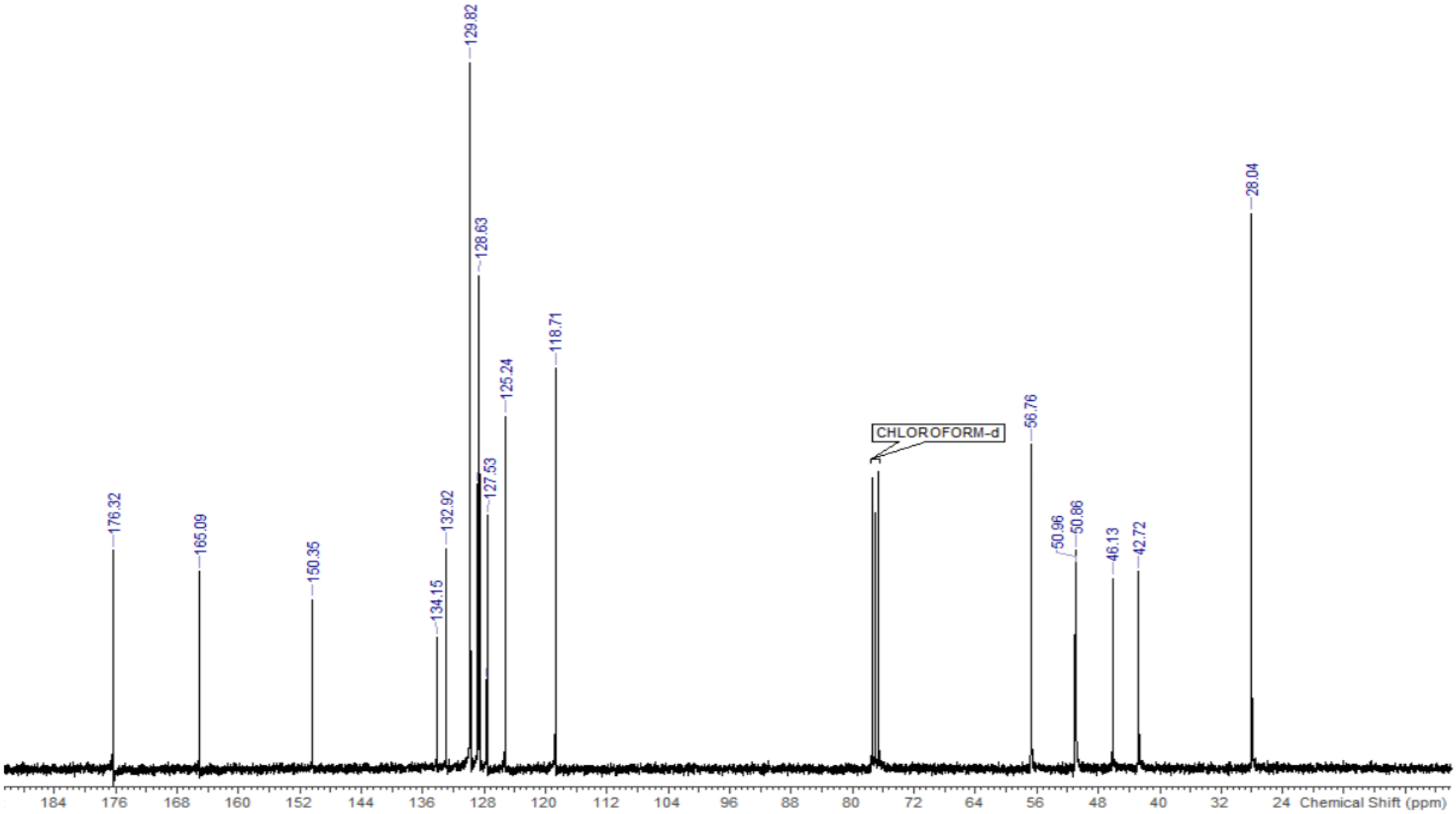
1-(1-Oxo-3-phenyl-1-(4-(3-(trifluoromethoxy)phenyl)piperazin-1-yl)propan-2-yl)pyrrolidine-2,5-dione (41) – ^{13}C NMR



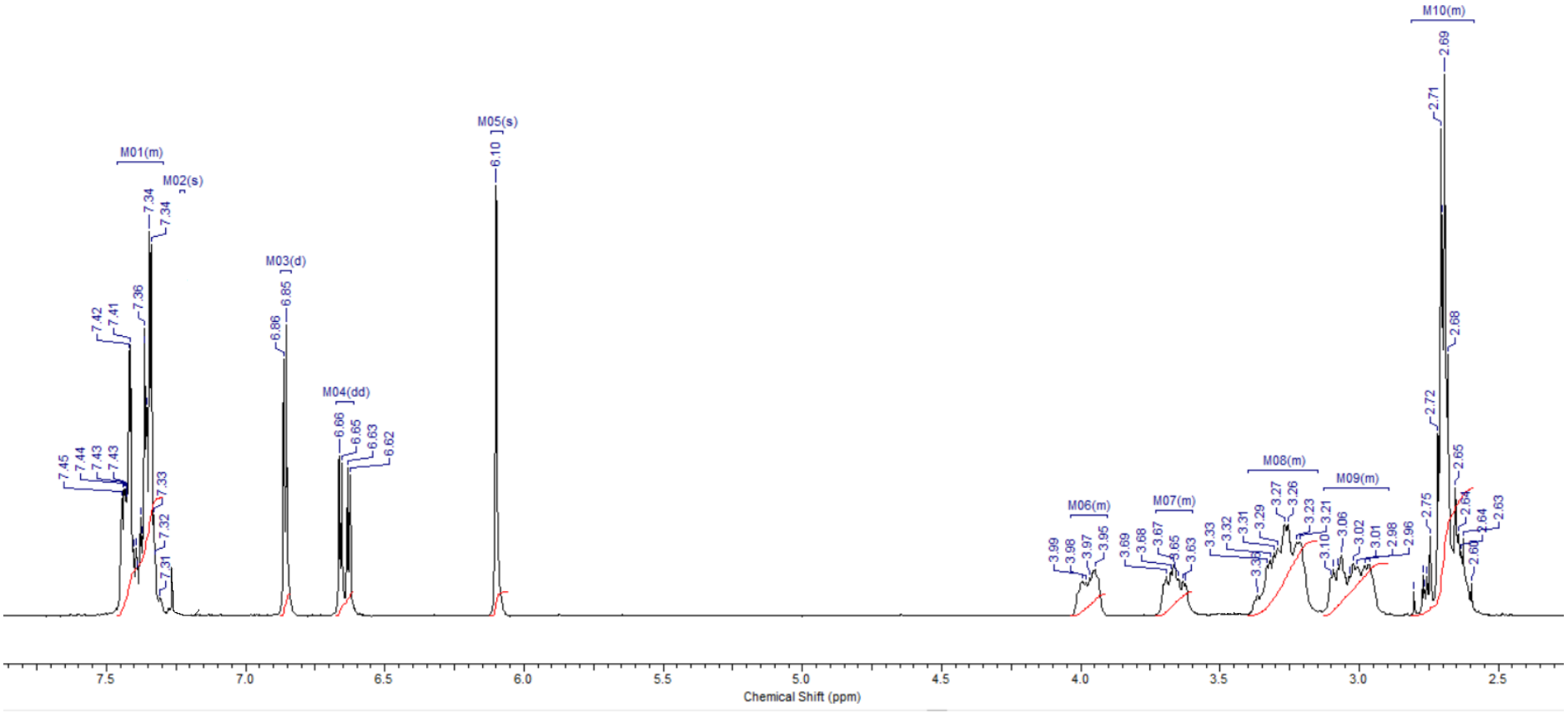
1-(2-(4-(2,3-Dichlorophenyl)piperazin-1-yl)-2-oxo-1-phenylethyl)pyrrolidine-2,5-dione (42) - ^{1}H NMR



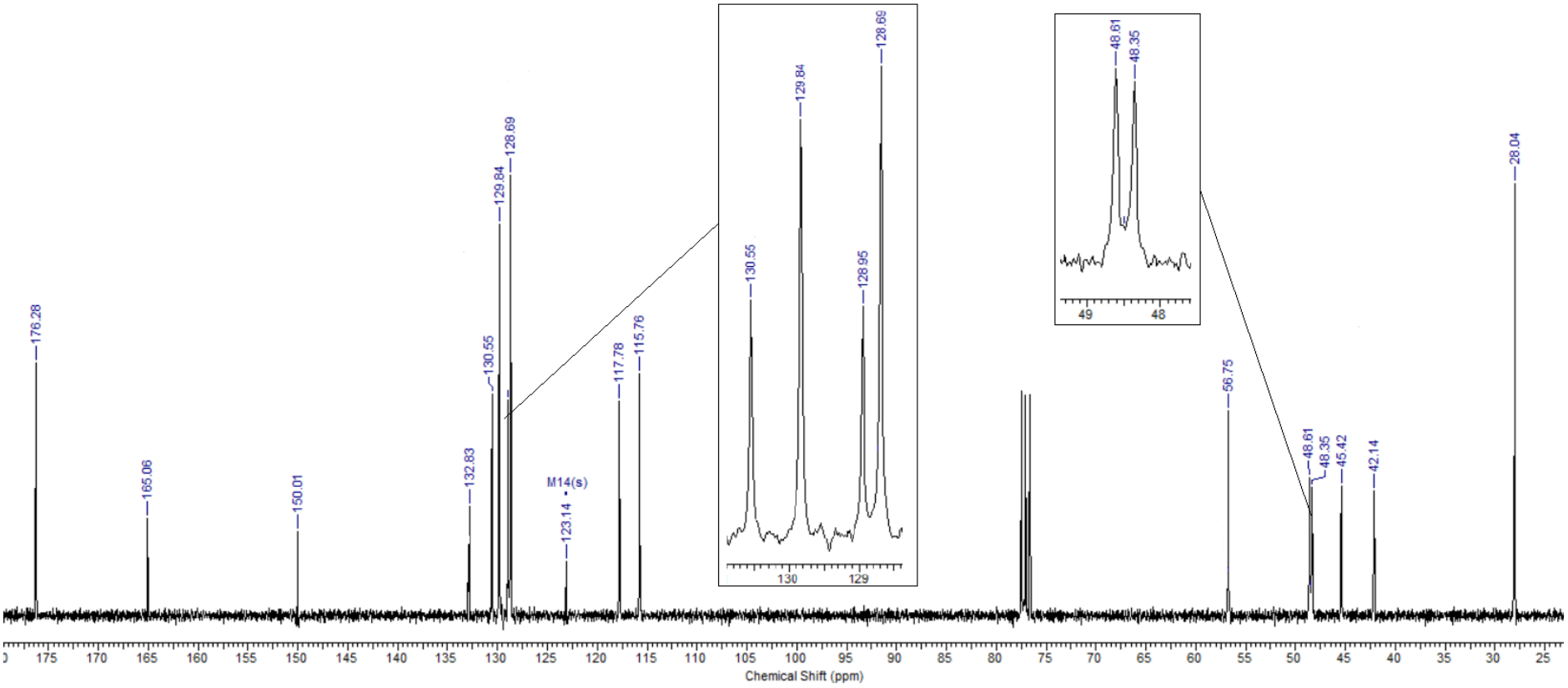
1-(2-(4-(2,3-Dichlorophenyl)piperazin-1-yl)-2-oxo-1-phenylethyl)pyrrolidine-2,5-dione (42) – ^{13}C NMR



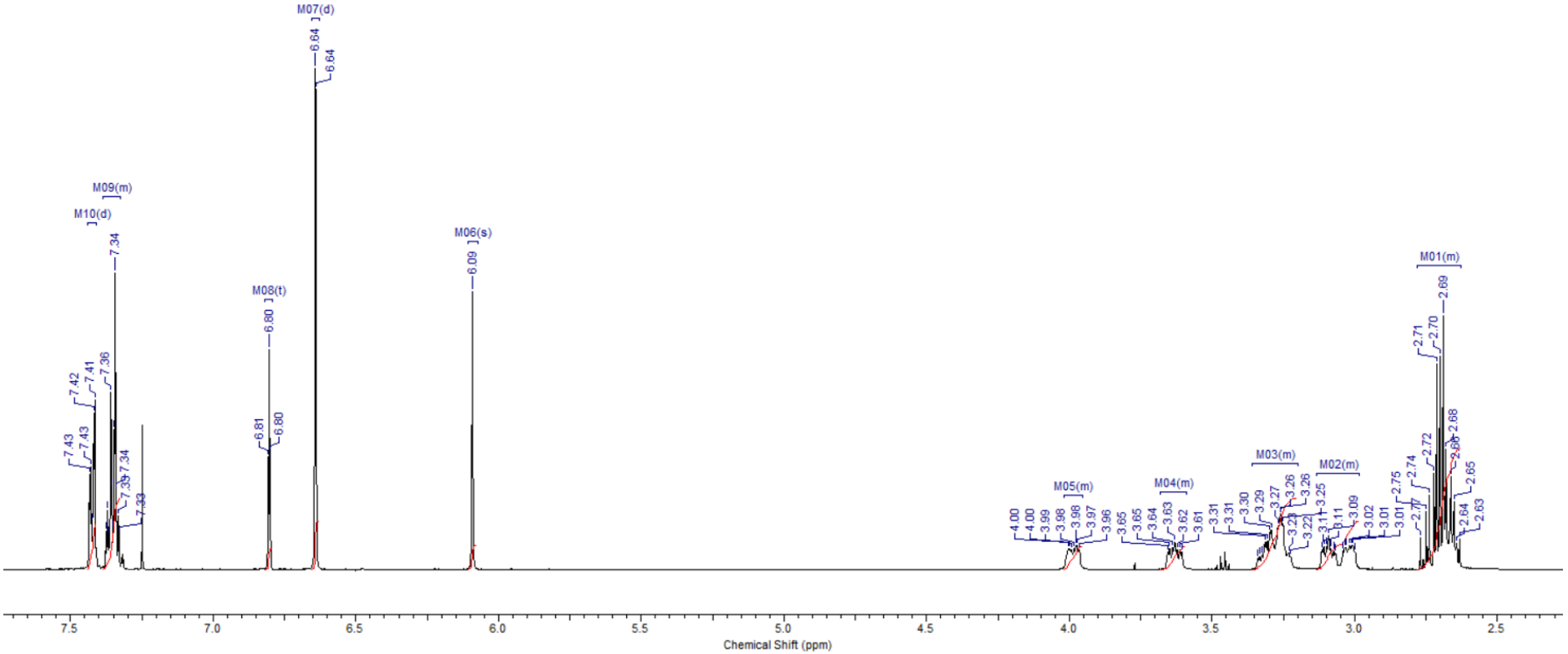
1-(2-(4-(3,4-Dichlorophenyl)piperazin-1-yl)-2-oxo-1-phenylethyl)pyrrolidine-2,5-dione (43) - ^{1}H NMR



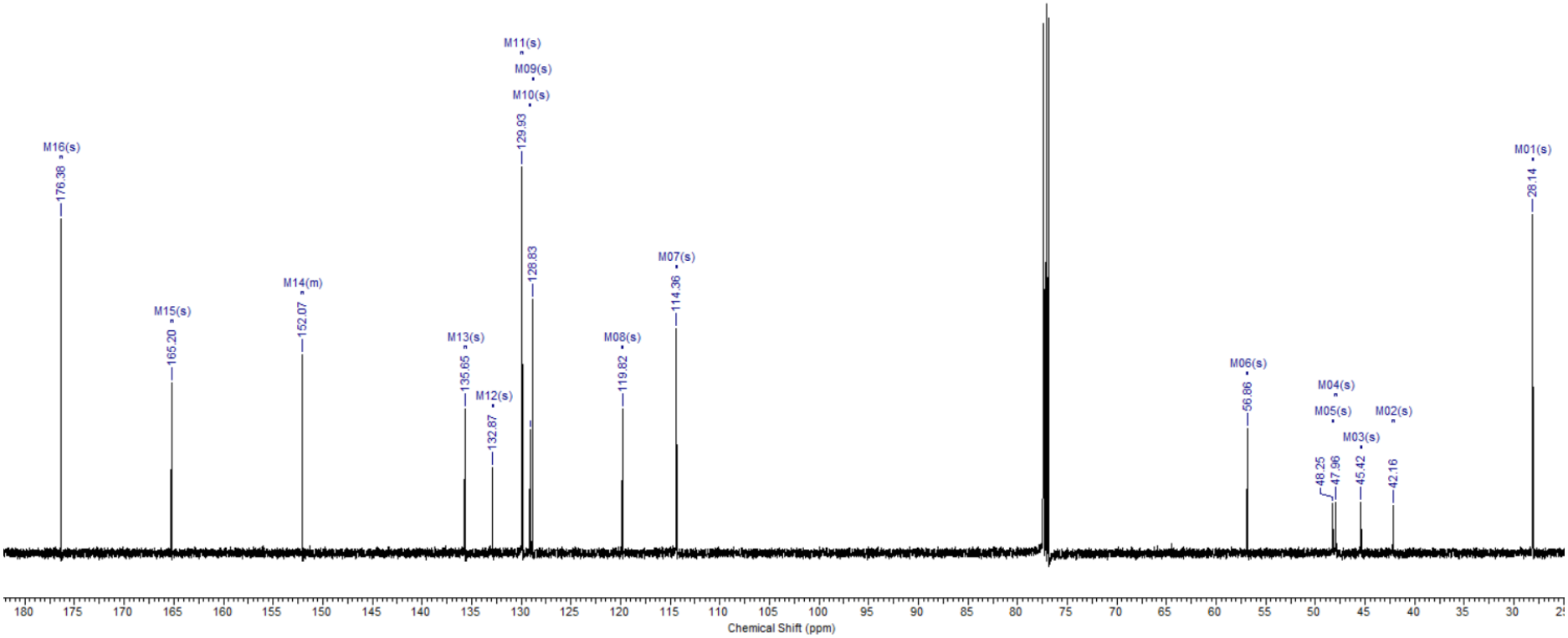
1-(2-(4-(3,4-Dichlorophenyl)piperazin-1-yl)-2-oxo-1-phenylethyl)pyrrolidine-2,5-dione (43) - ^{13}C NMR



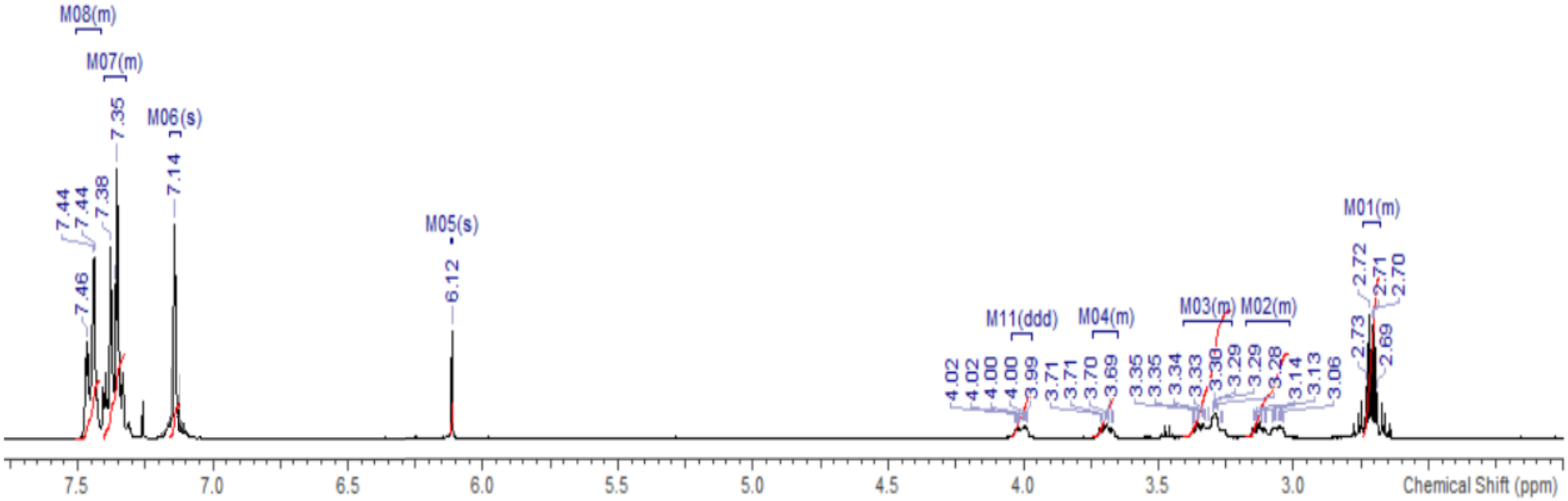
1-(2-(4-(3,5-Dichlorophenyl)piperazin-1-yl)-2-oxo-1-phenylethyl)pyrrolidine-2,5-dione (44) - ^{1}H NMR



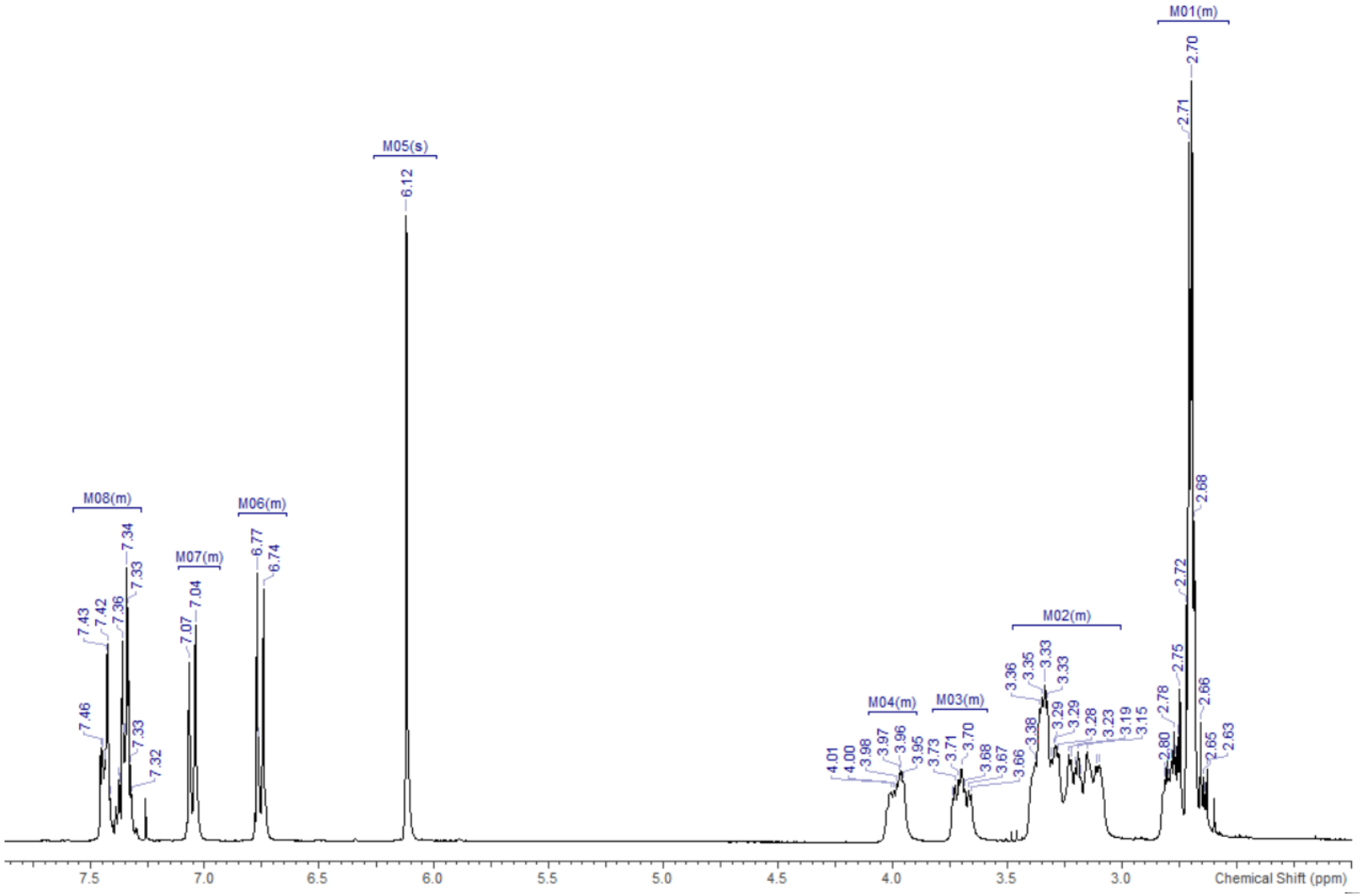
1-(2-(4-(3,5-Dichlorophenyl)piperazin-1-yl)-2-oxo-1-phenylethyl)pyrrolidine-2,5-dione (44) – ^{13}C NMR



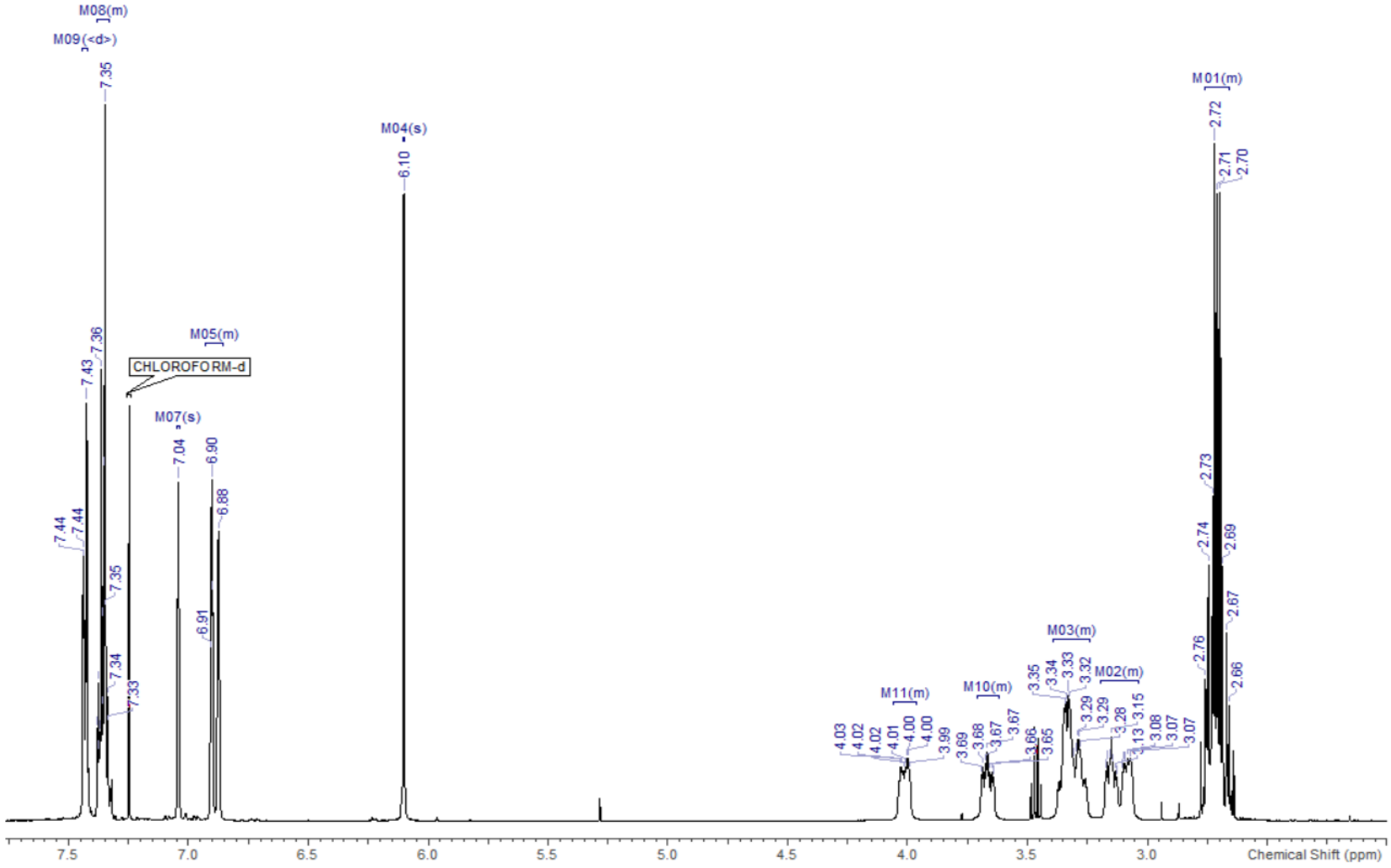
1-(2-(4-(3,5-bis(trifluoromethyl)phenyl)piperazin-1-yl)-2-oxo-1-phenylethyl)pyrrolidine-2,5-dione (45) - ^{1}H NMR



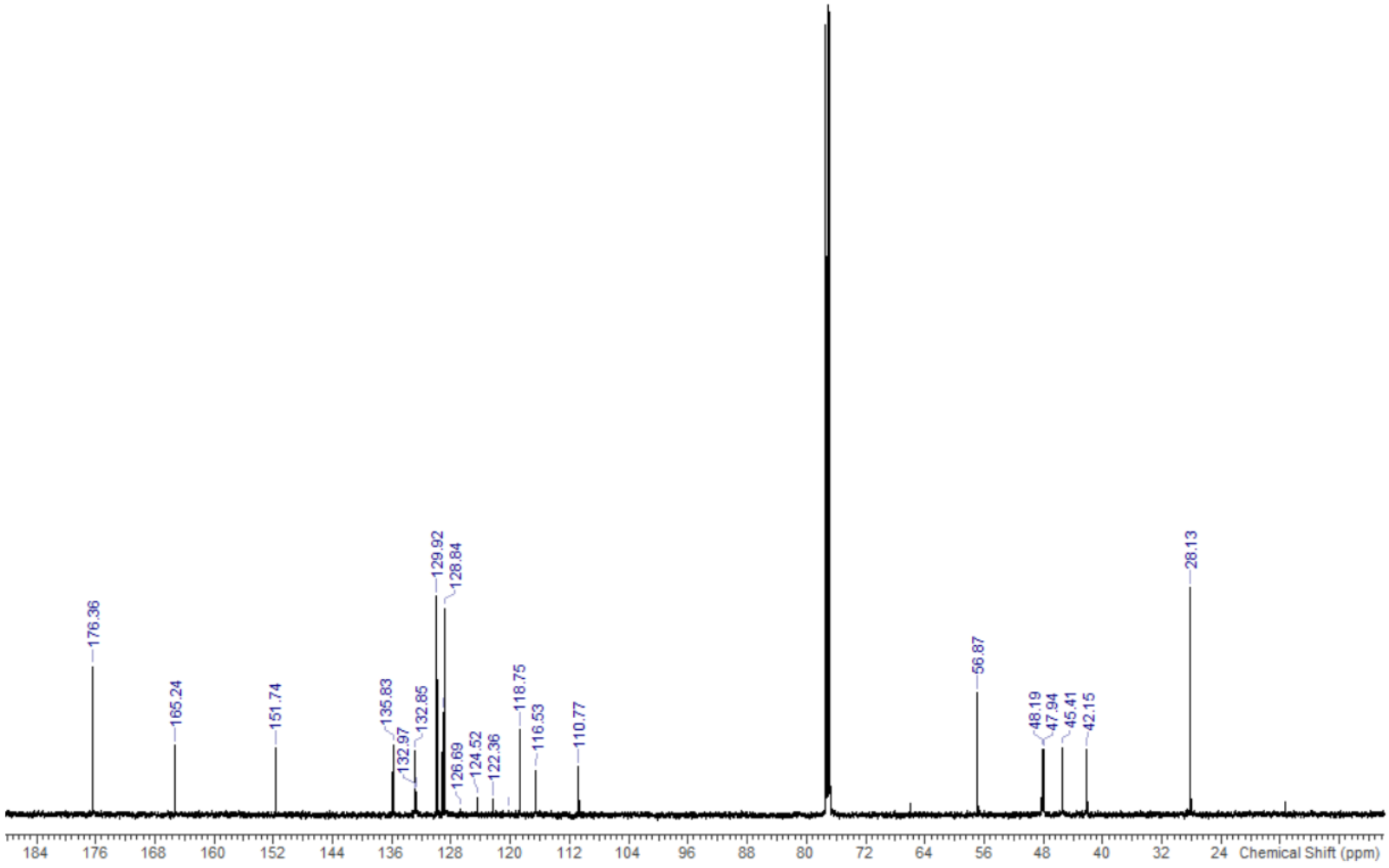
1-(2-(4-(3,5-bis((trifluoromethyl)thio)phenyl)piperazin-1-yl)-2-oxo-1-phenylethyl)pyrrolidine-2,5-dione (46) - ^{1}H NMR



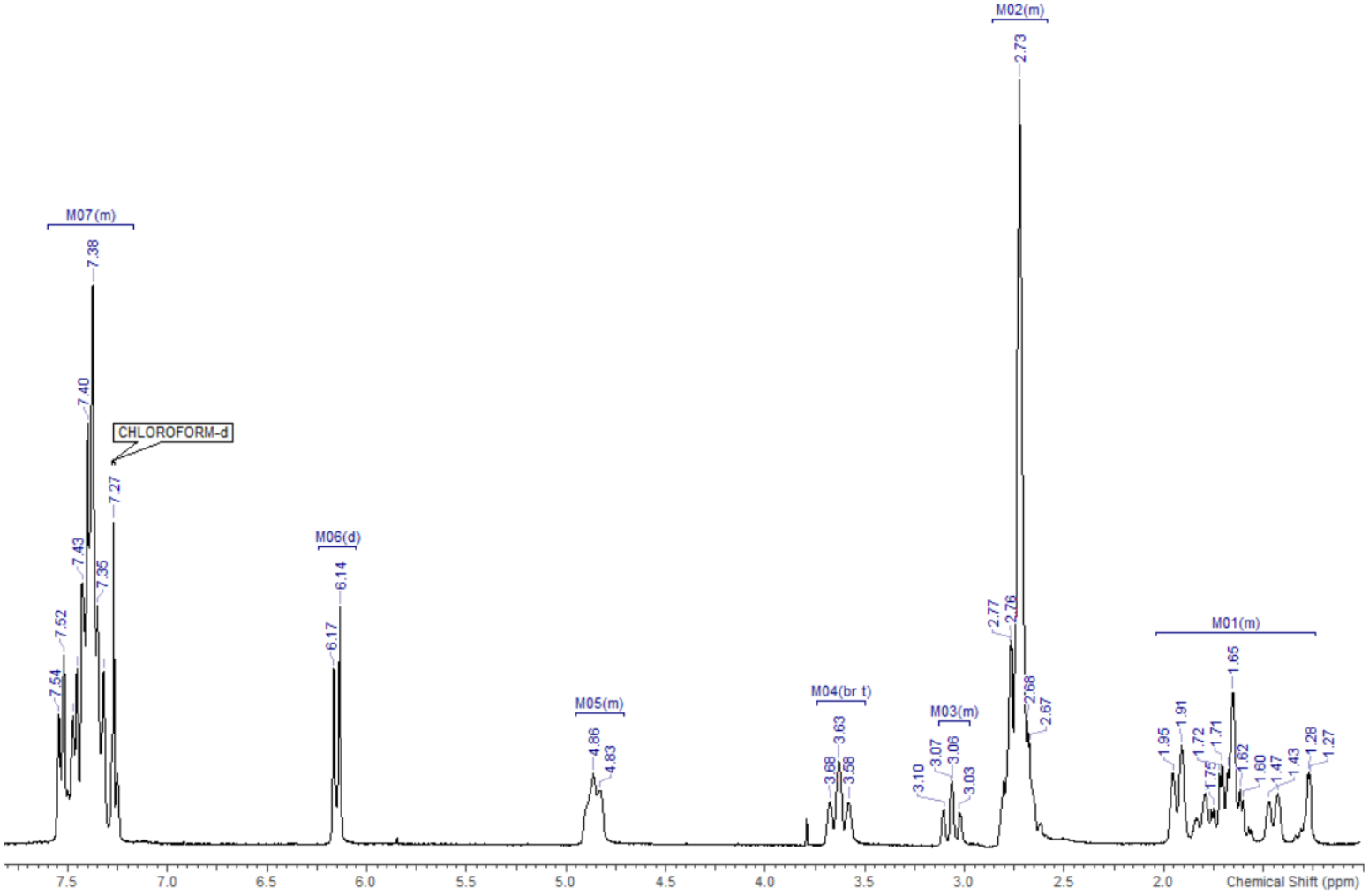
1-(2-(4-(3-chloro-5-(trifluoromethyl)phenyl)piperazin-1-yl)-2-oxo-1-phenylethyl)pyrrolidine-2,5-dione (47) - ^{1}H NMR



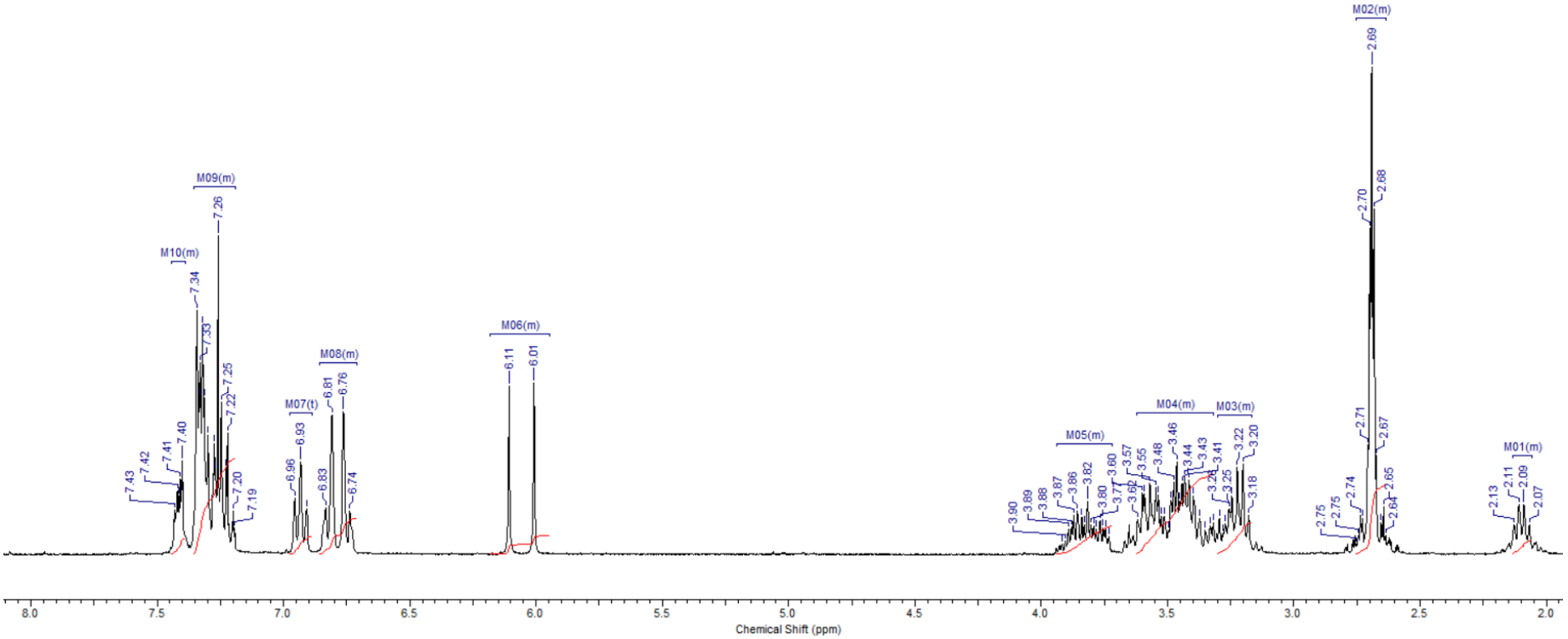
1-(2-(4-(3-chloro-5-(trifluoromethyl)phenyl)piperazin-1-yl)-2-oxo-1-phenylethyl)pyrrolidine-2,5-dione (47) - ^{13}C NMR



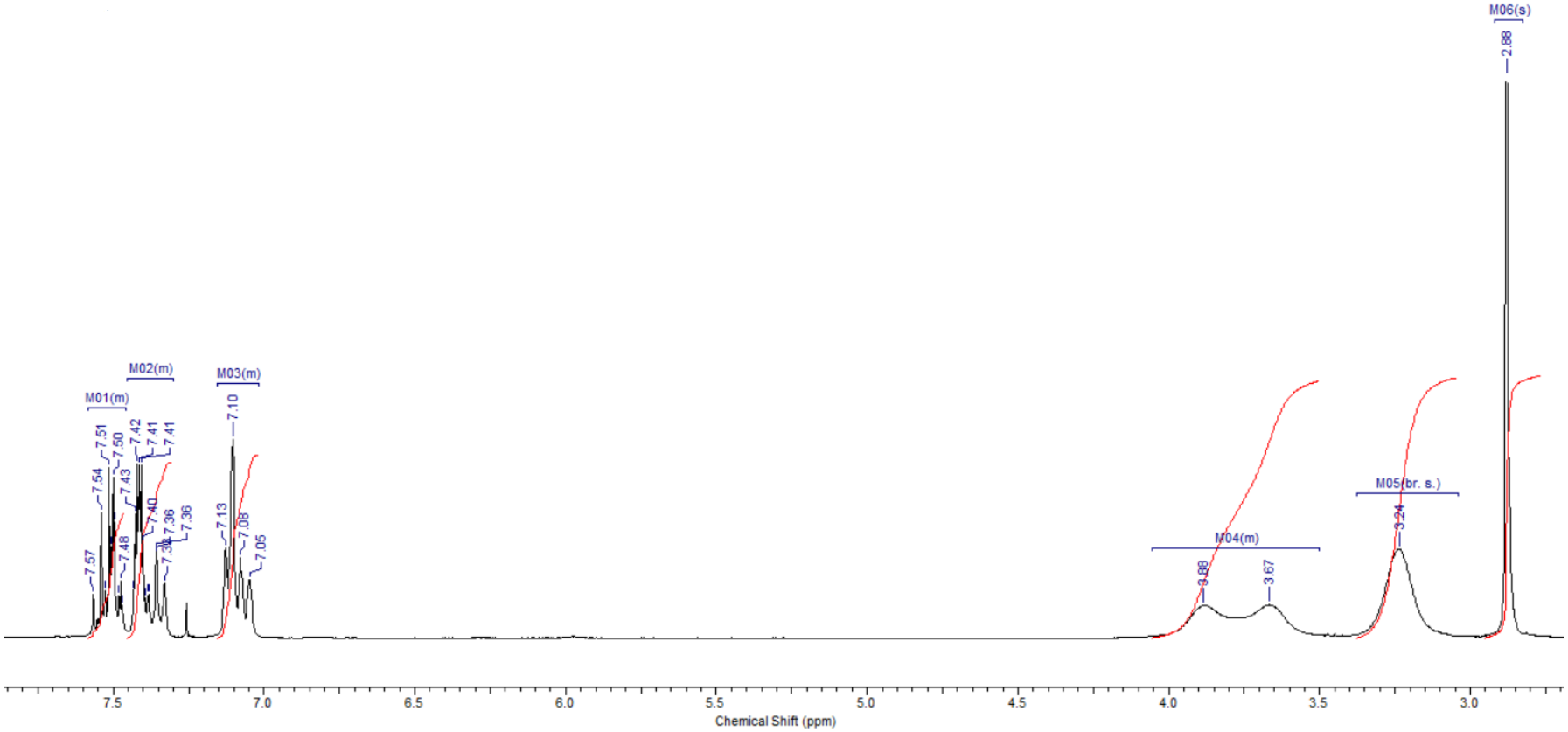
1-(2-Oxo-1-phenyl-2-(4-(3-(trifluoromethyl)phenyl)piperidin-1-yl)ethyl)pyrrolidine-2,5-dione (48) - ^{1}H NMR



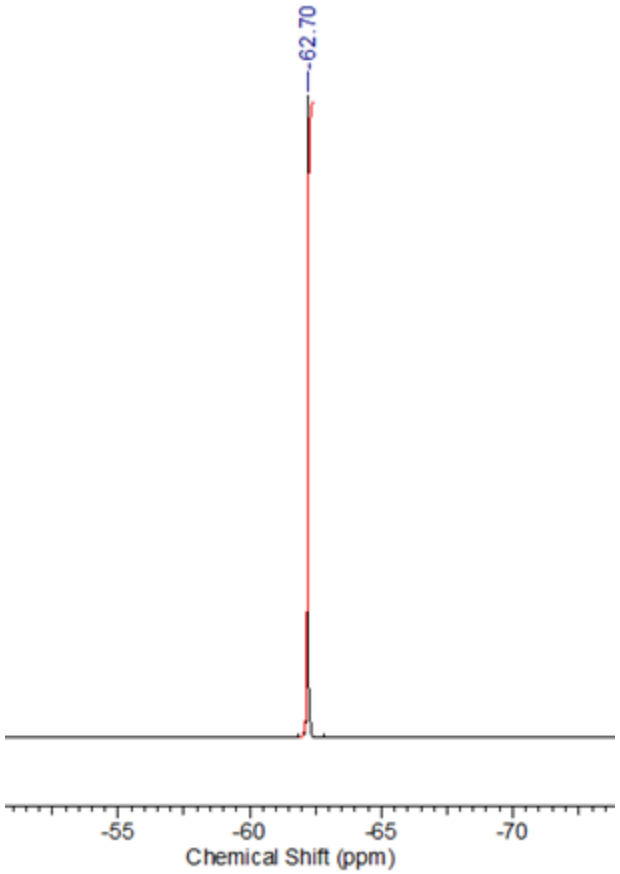
1-(2-Oxo-1-phenyl-2-(4-(3-(trifluoromethyl)phenyl)-1,4-diazepan-1-yl)ethyl)pyrrolidine-2,5-dione (49) - ^{1}H NMR



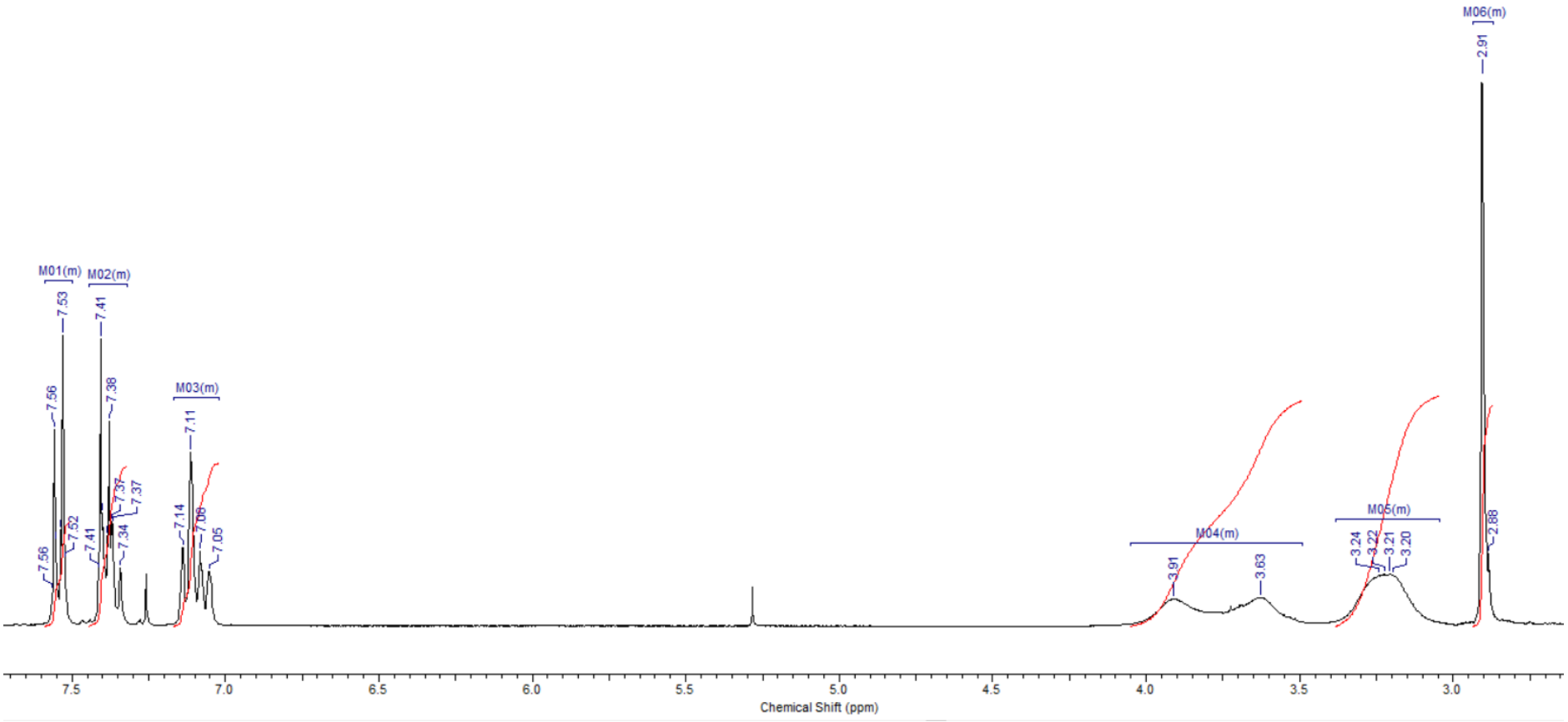
1-(3-(4-(3-(Trifluoromethyl)phenyl)piperazine-1-carbonyl)phenyl)pyrrolidine-2,5-dione (52)- ^{1}H NMR



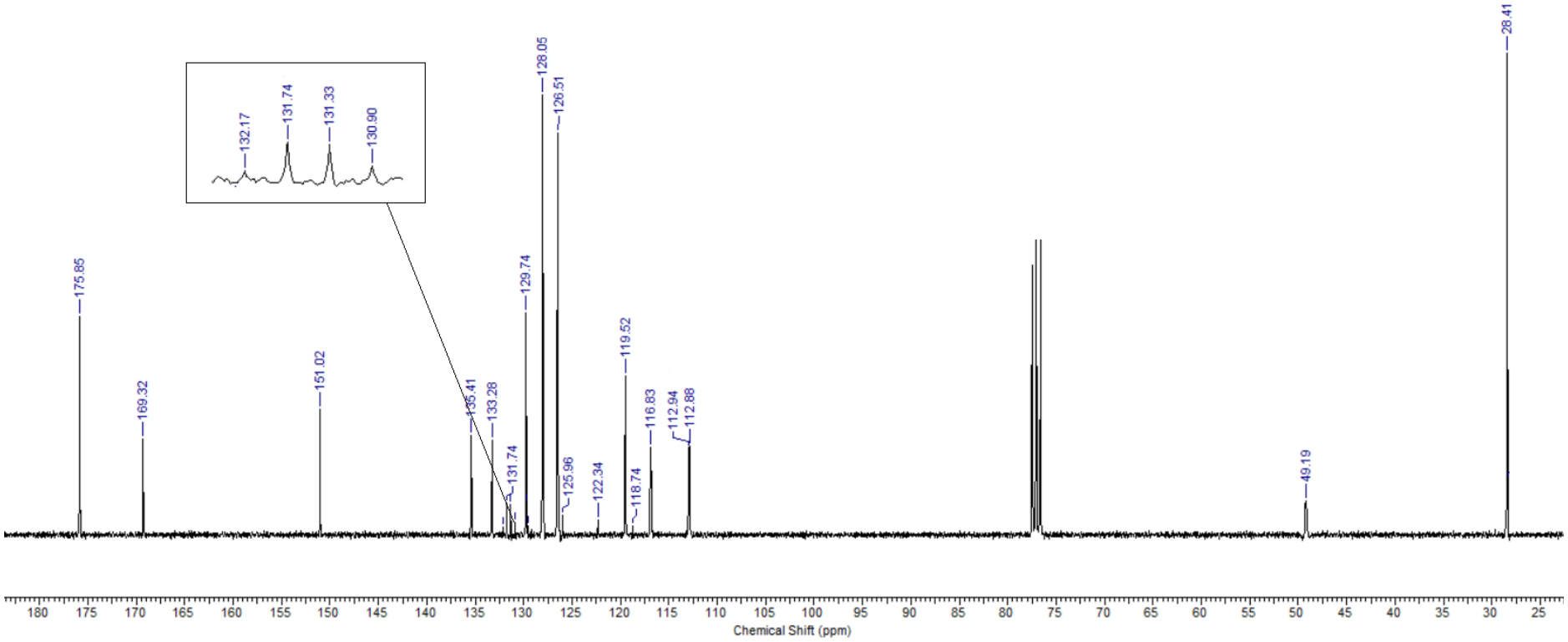
1-(3-(4-(3-(Trifluoromethyl)phenyl)piperazine-1-carbonyl)phenyl)pyrrolidine-2,5-dione (52)- ^{19}F NMR



1-(4-(4-(3-(Trifluoromethyl)phenyl)piperazine-1-carbonyl)phenyl)pyrrolidine-2,5-dione (53) - ^{1}H NMR



1-(4-(4-(3-(Trifluoromethyl)phenyl)piperazine-1-carbonyl)phenyl)pyrrolidine-2,5-dione (53) - ^{13}C NMR



1-(4-(4-(3-(Trifluoromethyl)phenyl)piperazine-1-carbonyl)phenyl)pyrrolidine-2,5-dione (53) - ^{19}F NMR