Synthesis, Anti-Cancer Activity, and Molecular Docking of New Halogenated Spiro[pyrrolidine-thiazolo-oxindoles] Derivatives

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Materials and Methods

General: All the chemicals were purchased from Aldrich, Sigma-Aldrich, Fluka etc, and were used without further purification, unless otherwise stated. All melting points were measured on a Gallenkamp melting point apparatus in open glass capillaries and are uncorrected. IR Spectra were measured as KBr pellets on a Nicolet 6700 FT-IR spectrophotometer. The NMR spectra were recorded on Agilent Technologies, Premium Shielded 400 NMR spectrometer. ^{1}H-NMR (400 MHz), and ^{13}C-NMR (100 MHz) were obtained in DMSO-d_6. Chemical shifts (δ) are referred in terms of *ppm* and *J* -coupling constants are given in *Hz*. Mass spectra were recorded on a Jeol of JMS-600 H JEOL equipment. Elemental analyses were carried out on a Perkin Elmer 2400 Elemental Analyzer; CHN mode.

General procedure (GP1): Dienones **1a-o** (0.5 mmol,) 5,7-dibromoIsatin (152 mg, 0.5 mmol) and thioproline (100 mg, 0.75mmol) were dissolved in 20 mL of dry MeOH in a 50 mL round bottom flask. The reaction mixture was then heated for 1.5 – 2 hours at 60 - 65 ^{o}C. After the reaction was completed as monitored by TLC, the crude material was subjected to column chromatography using ethyl acetate/*n*-hexane (2:3) to give the desired compound **5a-n.** Spectrometric data and NMR spectra of the synthesized compounds are presented below.

1. 5,7-dibromo-6'-cinnamoyl-7'-phenyl-3',6',7',7a'-tetrahydro-1'*H*-spiro[indoline-3,5'-pyrrolo[1,2-c]thiazol]-2-one **(5a)**

Yield 284 mg (0.46 mmol, 93%); m.p. 94-96 ^{o}C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.11 (s, 1H, NH), 7.68 (d, *J* = 1.8, 1H, Ar-H), 7.62 (d, *J* = 1.8, 1H, Ar-H), 7.49 (ddt, *J* = 13.4, 6.5, 1.7, 4H, Ar-H), 7.40 – 7.29 (m, 5H, Ar-H), 7.26 – 7.20 (m, 1H, Ar-H), 7.18 (d, *J* = 16.1, 1H, CH=CH), 6.47 (d, *J* = 16.1, 1H, CH=CH), 4.30 (d, *J* = 12.2, 1H, CH-CO), 4.03 (ddd, *J* = 9.3, 6.6, 2.7, 1H, N-CH), 3.77 (dd, *J* = 12.2, 9.3, 1H, S-CH-CH), 3.72 (d, *J* = 10.8, 1H, S-CH), 3.42 (d, *J* = 10.7, 1H, CH-CH-CH), 3.05 (dd, *J* = 11.5, 2.7, 1H, S-CH-CH), 2.99 (dd, *J* = 11.5, 6.6, 1H, S-CH); ^{13}C NMR (100 MHz, DMSO-d_6) δ 194.7, 178.5, 144.0, 141.7, 139.4, 134.9, 134.3, 131.4, 130.1, 129.3, 129.2, 129.0, 128.5, 127.7, 127.4, 125.1, 113.7, 103.6, 75.4, 75.1, 64.7, 54.3, 50.7, 36.2; IR (KBr, cm^{-1}) ν_{max} = 3195, 3063,

2920, 1727, 1603, 1493, 1450, 1293, 1155, 1071, 977, 859, 746, 690, 558; [Anal. Calcd. for $C_{28}H_{22}Br_2N_2O_2S$: C, 55.10; H, 3.63; N, 4.59; Found: C, 55.43; H, 3.71; N, 4.38]; LC/MS (ESI, *m*/*z*): [M+], found 608.0, $C_{28}H_{22}Br_2N_2O_2S$ for 607.98.

2. (*E*)-5,7-dibromo-7'-(p-tolyl)-6'-(3-(p-tolyl)acryloyl)-3',6',7',7a'-tetrahydro-1'*H*-spiro[indoline-3,5'-pyrrolo[1,2-c]thiazol]-2-one (**5b**)

Yield 281 mg (0.45 mmol, 89.1%); m.p. 98-100 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.10 (s, 1H, NH), 7.68 (d, *J* = 1.8, 1H, Ar-H), 7.60 (d, *J* = 1.8, 1H, Ar-H), 7.41 – 7.33 (m, 4H, Ar-H), 7.19 – 7.08 (m, 5H, Ar-H & , CH=CH), 6.42 (d, *J* = 16.0, 1H, CH=CH), 4.24 (d, *J* = 12.3, 1H, CH-CO), 4.00 (ddd, *J* = 9.3, 6.5, 2.7, 1H, N-CH), 3.72 (dd, *J* = 11.6, 9.0, 2H, S-CH), 3.40 (d, *J* = 10.7, 1H, CH-CH-CH), 3.02 (dd, *J* = 11.5, 2.7, 1H, S-CH-CH), 2.96 (dd, *J* = 11.5, 6.5, 1H, S-CH), 2.82 (s, 3H, CH_3), 2.22 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ 194.5, 178.6, 144.0, 141.7, 141.5, 136.8, 136.2, 134.9, 131.6, 130.1, 130.0, 129.8, 129.0, 128.3, 127.4, 124.1, 113.7, 103.6, 75.4, 75.1, 64.7, 54.4, 50.4, 36.2, 21.5, 21.0; IR (KBr, cm^{-1}) ν_{max} = 3241, 3023, 2918, 1730, 1599, 1469, 1329, 1178, 1117, 811, 750; [Anal. Calcd. for $C_{30}H_{26}Br_2N_2O_2S$: C, 56.44; H, 4.10; N, 4.39; Found: C, 56.72; H, 3.95; N, 4.21]; LC/MS (ESI, *m*/*z*): [M+], found 636.1, $C_{30}H_{26}Br_2N_2O_2S$ for 636.01.

3. (*E*)-5,7-dibromo-7'-(4-chlorophenyl)-6'-(3-(4-chlorophenyl)acryloyl)-3',6',7',7a'-tetrahydro-1'*H*-spiro[indoline-3,5'-pyrrolo[1,2-c]thiazol]-2-one (**5c)**

Yield 293 mg (0.43 mmol, 86%); m.p. 99-101 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.11 (s, 1H, NH), 7.69 (d, *J* = 1.8 Hz, 1H, Ar-H), 7.61 (d, *J* = 1.8 Hz, 1H, Ar-H), 7.59 – 7.44 (m, 4H, Ar-H), 7.47 – 7.31 (m, 4H, Ar-H), 7.15 (d, *J* = 16.0, 1H, CH=CH), 6.49 (d, *J* = 16.1, 1H, CH=CH), 4.27 (d, *J* = 12.2, 1H, CH-CO), 4.01 (ddd, *J* = 9.3, 6.5, 2.7, 1H, N-CH), 3.79 (dd, *J* = 12.2, 9.2, 1H, S-CH), 3.71 (d, *J* = 10.7, 1H, S-CH), 3.42 (d, *J* = 10.7, 1H, CH-CH-CH), 3.08 – 2.92 (m, 2H, S-CH); ^{13}C NMR (100 MHz, DMSO-d_6) δ 194.6, 178.4, 142.6, 141.7, 138.3, 135.9, 135.0, 133.2, 132.3, 130.7, 130.5, 130.1, 129.4, 129.1, 127.2, 125.6, 113.8, 103.7, 75.0, 75.1, 64.8, 54.3, 49.8, 36.1; IR (KBr, cm^{-1}) ν_{max}= 3239, 3057, 2920, 1728, 1612, 1489, 1468, 1327, 1177, 1089, 1012, 819, 749; [Anal. Calcd. for $C_{28}H_{20}Br_2Cl_2N_2O_2S$: C, 49.51; H, 2.97; N, 4.12; Found: C, 49.29; H, 3.09; N, 3.91]; LC/MS (ESI, *m*/*z*): [M+], found 676.0, $C_{28}H_{20}Br_2Cl_2N_2O_2S$ for 675.90.

4. (*E*)-5,7-dibromo-7'-(2,4-dichlorophenyl)-6'-(3-(2,4-dichlorophenyl)acryloyl)-3',6',7',7a'-tetrahydro-1'*H*-spiro[indoline-3,5'-pyrrolo[1,2-c]thiazol]-2-one (**5d)**

Yield 270 mg (0.36 mmol, 72%); m.p. 97-98 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.18 (s, 1H, NH), 7.71 (d, *J* = 8.6, 1H, Ar-H), 7.69 – 7.60 (m, 3H, Ar-H), 7.53 (d, *J* = 8.6, 1H, Ar-H), 7.48 (d, *J* = 1.9, 1H, Ar-H), 7.43 (ddd, *J* = 12.6, 8.5, 2.2, 2H, Ar-H), 7.13 (d, *J* = 16.1, 1H, Ar-H, CH=CH), 6.45 (d, *J* = 16.0, 1H, CH=CH), 4.43 (d, *J* = 11.5, 1H, CH-CO), 4.20 (dd, *J* = 11.5, 9.1, 1H, S-CH), 4.04 (ddd, *J* = 9.2, 6.2, 2.7, 1H, N-CH), 3.71 (d, *J* = 10.8, 1H, S-CH), 3.47 (d, *J* = 10.8, 1H, CH-CH-CH), 3.92 – 3.03 (m, 2H, S-CH); ^{13}C NMR (100 MHz, DMSO-d_6) δ 194.4, 178.2, 141.9, 137.0, 136.3, 135.6, 135.4, 135.3, 135.0, 132.9, 131.1, 130.0, 129.9, 129.6, 129.5, 128.4, 128.0, 127.1, 113.8, 104.0, 74.9, 74.6, 65.0, 54.5, 45.6, 35.8; IR (KBr, cm^{-1}) ν_{max} = 3399, 3069, 2926, 2781, 1730, 1606, 1581, 1456, 1382, 1301, 1227, 1158, 1101, 1048, 1024, 1001, 860, 818, 761, 677, 557; [Anal. Calcd. for $C_{28}H_{20}Br_2Cl_4N_2O_2S$: C, 44.95; H, 2.43; N, 3.74; Found: C, 45.15; H, 2.67; N, 3.98]; LC/MS (ESI, *m*/*z*): [M+], found 744.00, $C_{28}H_{20}Br_2Cl_4N_2O_2S$ for 743.82.

5. (*E*)-5,7-dibromo-7'-(3-fluorophenyl)-6'-(3-(3-fluorophenyl)acryloyl)-3',6',7',7a'-tetrahydro-1'*H*-spiro[indoline-3,5'-pyrrolo[1,2-c]thiazol]-2-one (**5e)**

Yield 270 mg (0.41 mmol, 83%); m.p. 81-82 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.11 (s, 1H, NH), 7.71 (dd, *J* = 1.8, 0.6, 1H, Ar-H), 7.62 (d, *J* = 1.8, 1H, Ar-H), 7.46 – 7.28 (m, 6H, Ar-H), 7.22 (tdd, J = 8.1, 2.6, 1.0, 1H, Ar-H), 7.17 (d, J = 16.1, 1H, CH=CH), 7.12 – 7.01 (m, 1H, Ar-H), 6.55 (d, *J* = 16.1, 1H, CH=CH), 4.30 (d, *J* = 12.2, 1H, CH-CO), 4.03 (td, *J* = 6.8, 3.3, 1H, N-CH), 3.84 (dd, *J* = 12.3, 9.4, 1H, S-CH), 3.71 (d, *J* = 10.8, 1H, S-CH), 3.43 (d, *J* = 10.7, 1H, CH-CH-CH), 3.08 (dd, *J* = 11.5, 2.6, 1H, S-CH), 3.00 (dd, *J* = 11.5, 6.7, 1H, S-CH); ^{13}C NMR (100 MHz, DMSO-d_6) δ 194.8, 178.3, 164.0, 161.5, 142.5 (d, *J* = 2.8 Hz), 141.7, 136.9, 136.8, 135.0, 131.3 (d, *J* = 8.4 Hz), 131.1 (d, *J* = 8.3 Hz), 130.1, 127.2, 126.2, 125.6 (d, *J* = 2.6 Hz), 124.5 (d, *J* = 2.7 Hz), 118.1, 117.9, 115.6, 115.4, 115.0, 114.8, 114.6, 114.4, 113.7, 103.7, 75.1, 75.0, 64.7, 54.3, 45.0 (d, *J* = 1.6 Hz), 36.1; IR (KBr, cm^{-1}) ν_{max}= 3072, 2924, 1730, 1607, 1581, 1485, 1448, 1267, 1231, 1147, 1071, 975, 864, 778, 686, 557, 515; [Anal.

Calcd. for $C_{28}H_{20}Br_2F_2N_2O_2S$: C, 52.03; H, 3.12; N, 4.33; Found: C, 52.21; H, 3.29; N, 4.42]; LC/MS (ESI, *m*/*z*): [M+], found 644.01, $C_{28}H_{20}Br_2F_2N_2O_2S$ for 643.96.

6. (*E*)-5,7-dibromo-7'-(4-bromophenyl)-6'-(3-(4-bromophenyl)acryloyl)-3',6',7',7a'-tetrahydro-1'*H*-spiro[indoline-3,5'-pyrrolo[1,2-c]thiazol]-2-one (**5f)**

Yield 284 mg (0.37 mmol, 74%); m.p. 120-122 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.12 (s, 1H, NH), 7.70 (d, *J* = 1.8, 1H, Ar-H), 7.63 (d, *J* = 1.8, 1H, Ar-H), 7.60 – 7.55 (m, 2H, Ar-H), 7.52 (d, *J* = 1.4, 4H, Ar-H), 7.48 – 7.42 (m, 2H, Ar-H), 7.15 (d, *J* = 16.1, 1H, CH=CH), 6.52 (d, *J* = 16.1, 1H, CH=CH), 4.28 (d, *J* = 12.2, 1H, CH-CO), 4.03 (ddd, *J* = 9.3, 6.5, 2.7, 1H, N-CH), 3.80 (dd, *J* = 12.2, 9.3, 1H, S-CH-CH), 3.73 (d, *J* = 10.8, 1H, S-CH), 3.44 (d, *J* = 10.7, 1H, CH-CH-CH), 3.09 – 2.96 (m, 2H, S-CH$_2$); ^{13}C NMR (100 MHz, DMSO-d_6) δ 194.6, 178.4, 142.7, 141.7, 138.7, 135.0, 133.6, 132.3, 132.0, 130.9, 130.9, 130.1, 127.2, 125.6, 124.8, 120.9, 113.8, 103.7, 75.1, 75.0, 64.8, 54.3, 49.9, 36.1; IR (KBr, cm^{-1}) ν_{max} = 3211, 3027, 2916, 1732, 1680, 1604, 1455, 1328, 1294, 1225, 1149, 1118, 1063, 1002, 856, 816, 727, 617, 569, 511; [Anal. Calcd. for $C_{28}H_{20}Br_4N_2O_2S$: C, 43.78; H, 2.62; N, 3.65; Found: C, 44.02; H, 2.44; N, 3.91]; LC/MS (ESI, *m*/*z*): [M+], found 663.90, $C_{28}H_{20}Br_4N_2O_2S$ for 663.80.

7. (*E*)-5,7-dibromo-7'-(3-nitrophenyl)-6'-(3-(3-nitrophenyl)acryloyl)-3',6',7',7a'-tetrahydro-1'*H*-spiro[indoline-3,5'-pyrrolo[1,2-c]thiazol]-2-one (**5g)**

Yield 245 mg (0.35 mmol, 70%); m.p. 203-205 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.12 (s, 1H, NH), 8.46 (t, *J* = 2.0, 1H, Ar-H), 8.30 (t, *J* = 2.0, 1H, Ar-H), 8.20 (ddd, *J* = 8.2, 2.3, 1.0, 1H, Ar-H), 8.10 (ddd, *J* = 8.2, 2.3, 0.9, 1H, Ar-H), 8.05 (dd, *J* = 8.0, 1.5, 1H, Ar-H), 7.94 (dd, *J* = 8.2, 1.7, 1H, Ar-H), 7.77 (d, *J* = 1.8, 1H, Ar-H), 7.67 – 7.61 (m, 3H, Ar-H), 7.27 (d, *J* = 16.2, 1H, CH=CH), 6.67 (d, *J* = 16.2, 1H, CH=CH), 4.43 (d, *J* = 11.8, 1H, CH-CO), 4.12 – 4.01 (m, 2H, N-CH & S-CH), 3.73 (d, *J* = 10.8, 1H, S-CH), 3.45 (d, *J* = 10.7, 1H, CH-CH-CH), 3.12 (dd, *J* = 11.5, 2.5, 1H, S-CH), 3.04 – 2.95 (m, 1H, S-CH); ^{13}C NMR (100 MHz, DMSO-d_6) δ 194.9, 178.2, 148.7, 148.5, 141.7, 141.6, 141.5, 136.1, 135.4, 135.1, 134.6, 130.9, 130.7, 130.1, 127.3, 127.1, 125.4, 123.8, 123.5, 122.8, 113.9, 103.7, 75.0, 75.1, 66.0, 54.2, 49.6, 36.0; IR (KBr, cm^{-1}) ν_{max} = 3082, 2929, 1783, 1611, 1528, 1455, 1351, 1218, 1160, 1094, 928, 869, 811, 733, 685, 559; [Anal. Calcd. for $C_{28}H_{20}Br_2Cl_4N_2O_2S$: C, 44.95; H, 2.43; N, 3.74; Found: C, 45.15; H, 2.67; N, 3.98]; LC/MS (ESI, *m*/*z*): [M+], found 744.00, $C_{28}H_{20}Br_2Cl_4N_2O_2S$ for 743.82.

8. (*E*)-5,7-dibromo-7'-(4-methoxyphenyl)-6'-(3-(4-methoxyphenyl)acryloyl)-3',6',7',7a'-tetrahydro-1'*H*-spiro[indoline-3,5'-pyrrolo[1,2-c]thiazol]-2-one (**5h)**

Yield 305 mg (0.46 mmol, 91%); m.p. 112-114 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.06 (s, 1H, NH), 7.68 (dd, *J* = 1.8, 0.6, 1H, Ar-H), 7.61 (d, *J* = 1.8, 1H, Ar-H), 7.49 – 7.38 (m, 4H, Ar-H), 7.14 (d, *J* = 16.0, 1H, Ar-H), 6.89 (dd, *J* = 11.3, 8.8, 4H Ar-H & CH=CH), 6.35 (d, *J* = 16.0, 1H, CH=CH), 4.19 (d, *J* = 12.3, 1H, CH-CO), 3.99 (ddd, *J* = 9.3, 6.4, 2.8, 1H, N-CH), 3.76 (s, 3H, OCH$_3$), 3.77 – 3.68 (m, 2H S-CH & S-CH-CH), 3.69 (s, 3H, , OCH$_3$), 3.40 (d, *J* = 10.7, 1H, CH-CH-CH), 3.05 – 2.95 (m, 2H, , S-CH); ^{13}C NMR (101 MHz, DMSO-d_6) δ 194.4, 178.6, 162.0, 158.8, 143.9, 134.8, 131.1, 131.0, 130.2, 129.5, 127.5, 126.8, 122.8, 114.9, 114.6, 113.6, 103.5, 75.4, 75.1, 64.6, 55.8, 55.5, 54.4, 50.1, 36.2; IR (KBr, cm^{-1}) ν_{max} = 3202, 3072, 2925, 2837, 1727, 1679, 1593, 1509, 1452, 1298, 1247, 1164, 1027, 981, 861, 825, 559, 523; [Anal. Calcd. for $C_{30}H_{26}Br_2N_2O_4S$: C, 53.75; H, 3.91; N, 4.18; Found: C, 53.52; H, 4.05; N, 4.33]; LC/MS (ESI, *m*/*z*): [M+], found 668.10, $C_{30}H_{26}Br_2N_2O_4S$ for 668.00.

9. (*E*)-5,7-dibromo-7'-(naphthalen-2-yl)-6'-(3-(naphthalen-2-yl)acryloyl)-3',6',7',7a'-tetrahydro-1'*H*-spiro[indoline-3,5'-pyrrolo[1,2-c]thiazol]-2-one (**5i)**

Yield 266 mg (0.41 mmol, 82.0%); m.p. 92-93 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.25 (s, 1H, NH), 8.54 (d, *J* = 8.7, 1H, Ar-H), 7.99 – 7.92 (m, 4H, Ar-H), 7.92 – 7.86 (m, 2H, Ar-H), 7.84 (d, *J* = 8.2, 1H, Ar-H), 7.74 (d, *J* = 1.9, 1H, Ar-H), 7.70 (ddd, *J* = 8.5, 6.8, 1.5, 1H, Ar-H), 7.66 (d, *J* = 1.8, 1H, , Ar-H), 7.55 (dddd, *J* = 18.2, 7.4, 3.4, 1.4, 5H, , Ar-H & CH=CH), 7.46 – 7.40 (m, 1H, Ar-H), 6.39 (d, *J* = 15.9, 1H, CH=CH), 4.81 (d, *J* = 11.5, 1H, CH-CO), 4.68 (dd, *J* = 11.6, 8.6 Hz, 1H, N-CH), 4.24 (s, 1H, S-CH), 3.79 (d, *J* = 10.5 Hz, 1H, S-CH), 3.54 (d, *J* = 10.4, 1H, CH-CH-CH), 2.96 (dd, *J* = 8.7, 4.9, 2H, S-CH); ^{13}C NMR (100 MHz, DMSO-d_6) δ 194.9, 178.8, 141.8, 140.6, 135.9, 135.2, 134.2, 133.6, 132.1, 131.5, 131.3, 131.2, 129.9, 129.4, 129.1, 128.0, 127.9, 127.8, 127.7, 127.0, 126.8, 126.3, 126.3, 126.0, 126.0, 125.9, 123.6, 123.6, 114.0, 103.9, 79.6, 76.5, 75.0, 65.7, 54.0, 36.6; IR (KBr, cm^{-1}) ν_{max} = 3370, 3054, 2924, 1726, 1660, 1601, 1511, 1451, 1397, 1348, 1299, 1228, 1156, 971, 860, 771, 687, 555, 487;

[Anal. Calcd. for $C_{36}H_{26}Br_2N_2O_2S$: C, 60.86; H, 3.69; N, 3.94; Found: C, 61.03; H, 3.52; N, 4.16]; LC/MS (ESI, *m*/*z*): [M+], found 708.00, $C_{36}H_{26}Br_2N_2O_2S$ for 708.01.

10. (*E*)-5,7-dibromo-7'-(thiophen-2-yl)-6'-(3-(thiophen-2-yl)acryloyl)-3',6',7',7a'-tetrahydro-1'*H*-spiro[indoline-3,5'-pyrrolo[1,2-c]thiazol]-2-one (**5j)**

Yield 270 mg (0.44 mmol, 87%); m.p. 83-85 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.14 (s, 1H, NH), 7.72 (dt, *J* = 5.1, 1.0, 1H, , Ar-H), 7.63 (q, *J* = 1.9, 2H, Ar-H), 7.44 (dd, *J* = 4.0, 1.2, 1H, Ar-H), 7.42 – 7.40 (m, 1H, Ar-H), 7.40 – 7.36 (m, 1H, Ar-H), 7.18 (dd, *J* = 3.5, 1.2, 1H, Ar-H), 7.09 (dd, *J* = 5.0, 3.7, 1H, Ar-H), 6.98 (dd, *J* = 5.1, 3.5, 1H, CH=CH), 6.20 (d, *J* = 15.7, 1H, CH=CH), 4.14 – 3.94 (m, 3H, CH-CO, N-CH & S-CH), 3.71 (d, *J* = 10.8, 1H, S-CH), 3.41 (d, *J* = 10.8, 1H, CH-CH-CH), 3.14 (dd, *J* = 11.6, 1.8, 1H, S-CH), 3.07 (ddd, *J* = 11.7, 4.4, 1.8, 1H, S-CH); ^{13}C NMR (100 MHz, DMSO-d_6) δ 193.5, 178.3, 142.2, 141.7, 139.1, 137.0, 135.0, 134.0, 131.5, 130.0, 129.3, 127.7, 127.1, 126.2, 125.3, 122.9, 113.7, 103.7, 75.4, 75.1, 65.5, 54.4, 45.9, 36.3; IR (KBr, cm^{-1}) ν_{max} = 3186, 3079, 2920, 1725, 1678, 1652, 1581, 1453, 1363, 1297, 1228, 1153, 1041, 965, 855, 699, 583, 559; [Anal. Calcd. for $C_{24}H_{18}Br_2N_2O_2S_3$: C, 46.31; H, 2.91; N, 4.50; Found: C, 46.47; H, 3.01; N, 4.63]; LC/MS (ESI, *m*/*z*): [M+], found 620.00, $C_{24}H_{18}Br_2N_2O_2S_3$ for 619.89.

11. (*E*)-5,7-dibromo-7'-(furan-2-yl)-6'-(3-(furan-2-yl)acryloyl)-3',6',7',7a'-tetrahydro-1'*H*-spiro[indoline-3,5'-pyrrolo[1,2-c]thiazol]-2-one (**5k)**

Yield 271 mg (0.46 mmol, 92%); m.p. 171-173 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.15 (s, 1H, NH), 7.84 (d, *J* = 1.8, 1H, Ar-H), 7.65 (d, *J* = 1.8, 1H, Ar-H), 7.60 (dd, *J* = 1.9, 0.9, 1H, Ar-H), 7.56 (d, *J* = 1.9, 1H, Ar-H), 7.05 (d, *J* = 15.7, 1H, CH=CH), 6.93 (d, *J* = 3.5, 1H, Ar-H), 6.61 (dd, *J* = 3.4, 1.8, 1H, Ar-H), 6.44 – 6.40 (m, 1H, Ar-H), 6.39 (dd, *J* = 3.2, 1.8, 1H, Ar-H), 6.21 (d, *J* = 15.7, 1H, CH=CH), 4.18 (d, *J* = 12.2, 1H, CH-CO), 4.05 (ddd, *J* = 9.1, 6.7, 2.4, 1H, N-CH), 3.85 (dd, *J* = 12.2, 9.2, 1H, S-CH), 3.71 (d, *J* = 10.9, 1H, S-CH), 3.41 (d, *J* = 10.9, 1H, CH-CH-CH), 3.17 (dd, *J* = 11.6, 2.5, 1H, S-CH), 3.10 (dd, *J* = 11.6, 6.7, 1H, S-CH); ^{13}C NMR (100 MHz, DMSO-d_6) δ 193.4, 178.2, 152.4, 150.5, 147.12, 143.0, 141.7, 135.0, 130.4, 130.0, 127.1, 121.0, 118.7, 113.7, 111.0, 107.5, 103.7, 74.9, 72.5, 62.2, 54.5, 44.3, 36.6; IR (KBr, cm^{-1}) ν_{max} = 3119, 2922, 2856, 1728, 1601, 1550, 1453, 1382, 1302, 1226, 1155, 1071, 1013, 970, 926, 872, 819, 737, 685, 592, 557; [Anal. Calcd. for $C_{24}H_{18}Br_2N_2O_4S$: C, 48.83; H, 3.07; N, 4.75; Found: C, 49.09; H, 3.15; N, 4.86]; LC/MS (ESI, *m*/*z*): [M+], found 588.01, $C_{24}H_{18}Br_2N_2O_4S$ for 587.94.

12. (*E*)-5,7-dibromo-7'-(3-bromophenyl)-6'-(3-(3-bromophenyl)acryloyl)-3',6',7',7a'-tetrahydro-1'*H*-spiro[indoline-3,5'-pyrrolo[1,2-c]thiazol]-2-one (**5l)**

Yield 272 mg (0.35 mmol, 71.0%); m.p. 88-90 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.11 (s, 1H, NH), 7.79 (t, *J* = 1.9, 1H, Ar-H), 7.71 (d, *J* = 1.8, 2H, Ar-H), 7.62 (d, *J* = 1.8, 1H, Ar-H), 7.59 – 7.53 (m, 2H, Ar-H), 7.49 (dt, *J* = 7.9, 1.3, 1H, Ar-H), 7.43 (ddd, *J* = 8.0, 2.0, 1.0, 1H, Ar-H), 7.30 (td, *J* = 7.8, 4.1, 2H, Ar-H), 7.13 (d, *J* = 16.1, 1H, CH=CH), 6.55 (d, *J* = 16.1, 1H, CH=CH), 4.29 (d, *J* = 12.2, 1H, CH-CO), 4.03 (ddd, *J* = 9.2, 6.6, 2.6, 1H, N-CH), 3.83 (dd, *J* = 12.2, 9.2, 1H, S-CH), 3.71 (d, *J* = 10.8, 1H, S-CH), 3.42 (d, *J* = 10.7, 1H, CH-CH-CH), 3.07 (dd, *J* = 11.5, 2.6, 1H, S-CH), 2.99 (dd, *J* = 11.5, 6.7, 1H, S-CH); ^{13}C NMR (100 MHz, DMSO-d_6) δ 194.8, 178.3, 142.3, 142.2, 141.7, 136.8, 135.0, 133.8, 131.6, 131.4, 131.3, 131.3, 130.6, 130.1, 127.9, 127.4, 127.2, 126.2, 122.7, 122.5, 113.8, 103.7, 75.2, 75.0, 64.8, 54.2, 49.8, 36.0; IR (KBr, cm^{-1}) ν_{max} = 3390, 3206, 3067, 2921, 1730, 1661, 1604, 1565, 1452, 1305, 1157, 1070, 980, 863, 775, 735, 683, 560; [Anal. Calcd. for $C_{28}H_{20}Br_4N_2O_2S$: C, 43.78; H, 2.62; N, 3.65; Found: C, 43.66; H, 2.52; N, 3.86]; LC/MS (ESI, *m*/*z*): [M+], found 663.81, $C_{28}H_{20}Br_4N_2O_2S$ for 663.80.

13. (*E*)-5,7-dibromo-7'-(4-fluorophenyl)-6'-(3-(4-fluorophenyl)acryloyl)-3',6',7',7a'-tetrahydro-1'*H*-spiro[indoline-3,5'-pyrrolo[1,2-c]thiazol]-2-one (**5m)**

Yield 274 mg (0.42 mmol, 85%); m.p. 95-97 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.11 (s, 1H, NH), 7.70 (dd, *J* = 1.9, 0.6, 1H, Ar-H), 7.63 (d, *J* = 1.8, 1H, Ar-H), 7.61 – 7.53 (m, 4H, Ar-H), 7.26 – 7.11 (m, 5H, Ar-H & CH=CH), 6.46 (d, *J* = 16.2, 1H, CH=CH), 4.28 (d, *J* = 12.2, 1H, CH-CO), 4.03 (ddd, *J* = 9.4, 6.6, 2.7, 1H, N-CH), 3.81 (dd, *J* = 12.2, 9.3, 1H, S-CH), 3.73 (d, *J* = 10.8, 1H, S-CH), 3.44 (d, *J* = 10.7, 1H, CH-CH-CH), 3.10 – 2.96 (m, 2H, S-CH); ^{13}C NMR (100 MHz, DMSO-d_6) δ 194.6, 178.4, 142.8, 141.7, 135.5, 135.4, 135.0, 131.5, 131.4, 130.5, 130.4, 130.1, 127.3, 125.0, 124.9, 116.5, 116.3, 116.0, 115.8, 113.7, 103.6, 79.6, 75.3, 75.0, 64.8, 54.3, 49.8,

36.1; IR (KBr, cm^{-1}) ν_{max}= 3647, 3268, 3071, 3005, 2923, 2856, 1732, 1680, 1597, 1453, 1324, 1292, 1225, 1153, 1029, 985, 862, 828, 798, 672, 558, 510; [Anal. Calcd. for $C_{28}H_{20}Br_2F_2N_2O_2S$: C, 52.03; H, 3.12; N, 4.33; Found: C, 52.13; H, 3.25; N, 4.47]; LC/MS (ESI, *m*/*z*): [M+], found 644.10, $C_{28}H_{20}Br_2F_2N_2O_2S$ for 643.96.

14. ((*E*)-5,7-dibromo-7'-(4-(trifluoromethyl)phenyl)-6'-(3-(4-(trifluoromethyl)phenyl) acryloyl)-3',6',7',7a'-tetrahydro-1'*H*-spiro[indoline-3,5'-pyrrolo[1,2-c]thiazol]-2-one (**5n)**

Yield 286 mg (0.41 mmol, 77%); m.p. 128-130 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.14 (s, 1H, NH), 7.82 (s, 1H, Ar-H), 7.72 (dd, *J* = 5.2, 2.4, 6H, Ar-H), 7.65 (d, *J* = 1.8, 2H, Ar-H), 7.49 (s, 1H, Ar-H), 7.23 (d, *J* = 16.1, 1H, CH=CH), 6.60 (d, *J* = 16.1, 1H, CH=CH), 4.41 (d, *J* = 12.1, 1H CH-CO), 4.15 – 4.06 (m, 2H CH_2), 3.93 (dd, *J* = 12.1, 9.3, 1H, CH), 3.74 (d, *J* = 10.8, 1H, CH), 3.10 (dd, *J* = 11.5, 2.6, 1H, CH_2), 3.02 (dd, *J* = 11.5, 6.7, 1H, CH_2); ^{13}C NMR (100 MHz, DMSO-d_6) δ 194.8, 178.3, 144.1, 142.1, 141.7, 141.4, 138.3, 135.1, 130.0, 129.9, 129.6, 129.6, 129.4, 129.4, 129.3, 127.3, 127.1, 126.2, 126.1, 126.1, 126.0, 126.0, 126.0, 113.8, 103.8, 75.1, 75.0, 64.9, 54.2, 50.1, 36.1; IR (KBr, cm^{-1}) ν_{max}= 3645, 3269, 3072, 3007, 2924, 2859, 1731, 1683, 1598, 1451, 1325, 1291, 1222, 1154, 1022, 987, 861, 826, 795, 677, 561; [Anal. Calcd. for $C_{30}H_{20}Br_2F_6N_2O_2S$: C, 48.28; H, 2.70; N, 3.75; Found: C, 48.41; H, 2.83; N, 3.58]; LC/MS (ESI, *m*/*z*): [M+], found 744.00, $C_{30}H_{20}Br_2F_6N_2O_2S$ for 743.95.

Anticancer activity

Cell lines and drugs

The cytotoxic activity of the new synthesized compounds was tested against different mammalian cancer cells, breast cancer (MCF-7), colorectal cancer (HCT-116), and hepatocellular carcinoma (HepG-2). The cell lines were obtained from American Type Culture Collection (ATCC). The cells were cultivated at 37 °C and 5% CO_2 in DMEM (Lonza) medium supplemented with 10% fetal bovine serum (Lonza), 100 IU/mL penicillin and 100 µg/mL streptomycin (Lonza). *Cis*platin was used as a positive control and was obtained from Sigma-Aldrich. The synthesized compounds were solubilized in DMSO and stored at -20 °C. 0.5% crystal violet was used in the initial screening. The viability of the cells were determined by using MTT reagent.

Cytotoxicity assay

The cells were seeded in 96-well plate and serial dilutions of tested compounds or cisplatin was added after overnight incubation of the cells at 37 °C and 5% CO_2. DMSO was used as a negative control (0.1 %). After that, MTT (5 mg/mL PBS) was added after 48 hours of incubation. The formazan crystals were solubilized by acidified SDS solution. The absorbance was recorded at 570 nm by Biotech ELx-800™ plate reader. The viability assay was performed 3 times and standard deviation was determined (±). IC_{50} was calculated as the concentration that cause 50% inhibition for cell growth. Selectivity index was calculated as reported.

Shape alignment and ROCS

Basic method to represent shape and color features in ROCS is using ROCs application Open Eye scientific software [1]. Final compounds were selected as query molecules. Compounds library was adopted as the database file. Both query and database files were energy minimized by Omega applications. ROCS runs were employed by personal PC in very fast using vROCS interface. vROCS was employed to run and analyze/visualize the results. ROCS application searched the database with the query to find molecules with similar shape and colors. Compounds conformers were scored based upon the Gaussian overlap to the query.

Reference:

1. VIDA, version 4.1.2; OpenEye Scientific Software, Santa Fe, NM (USA); http://www.eyesopen.com.

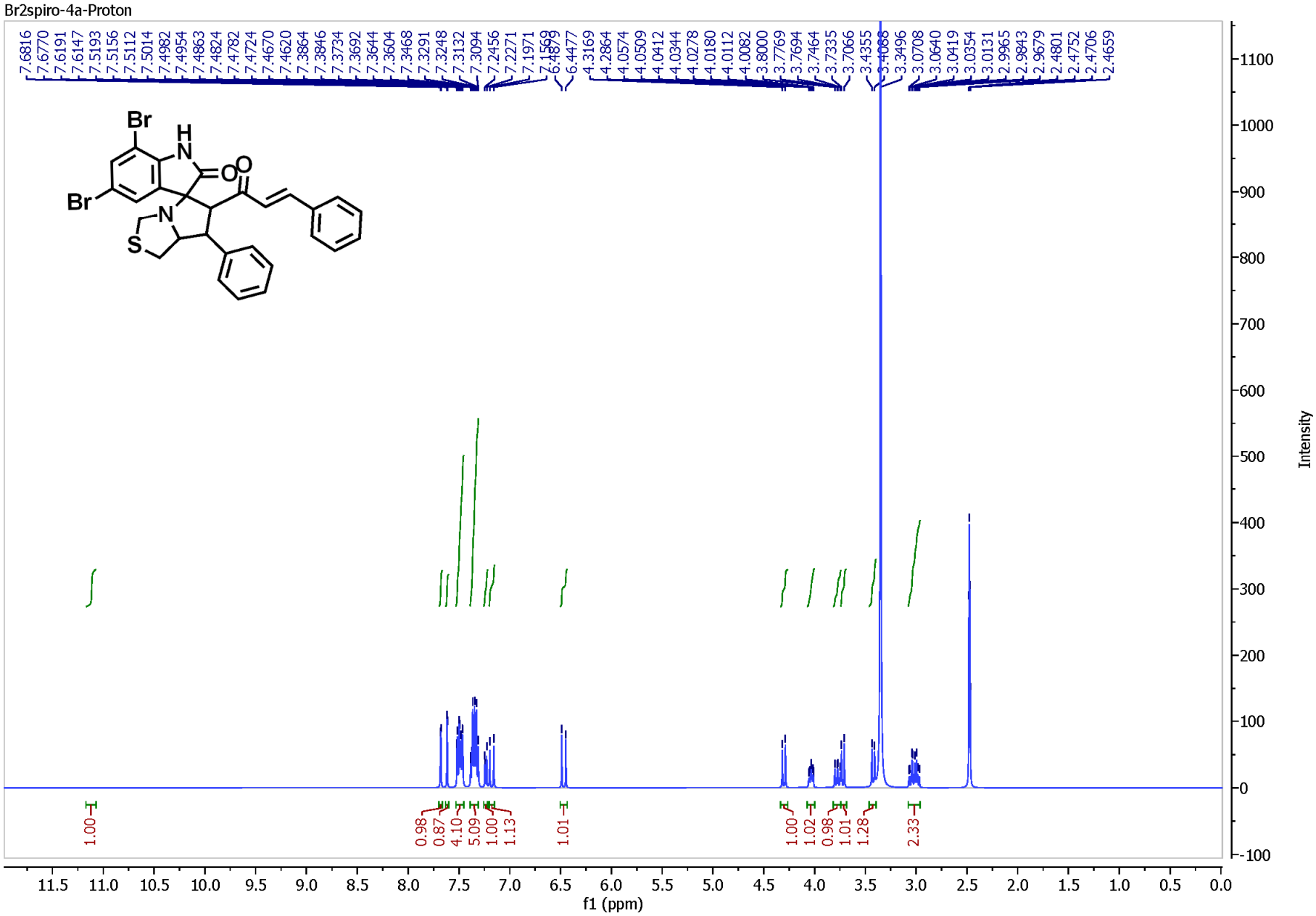

Figure S1. ^{1}H NMR spectrum of compound **5a** (400 MHz, DMSO-d_6)

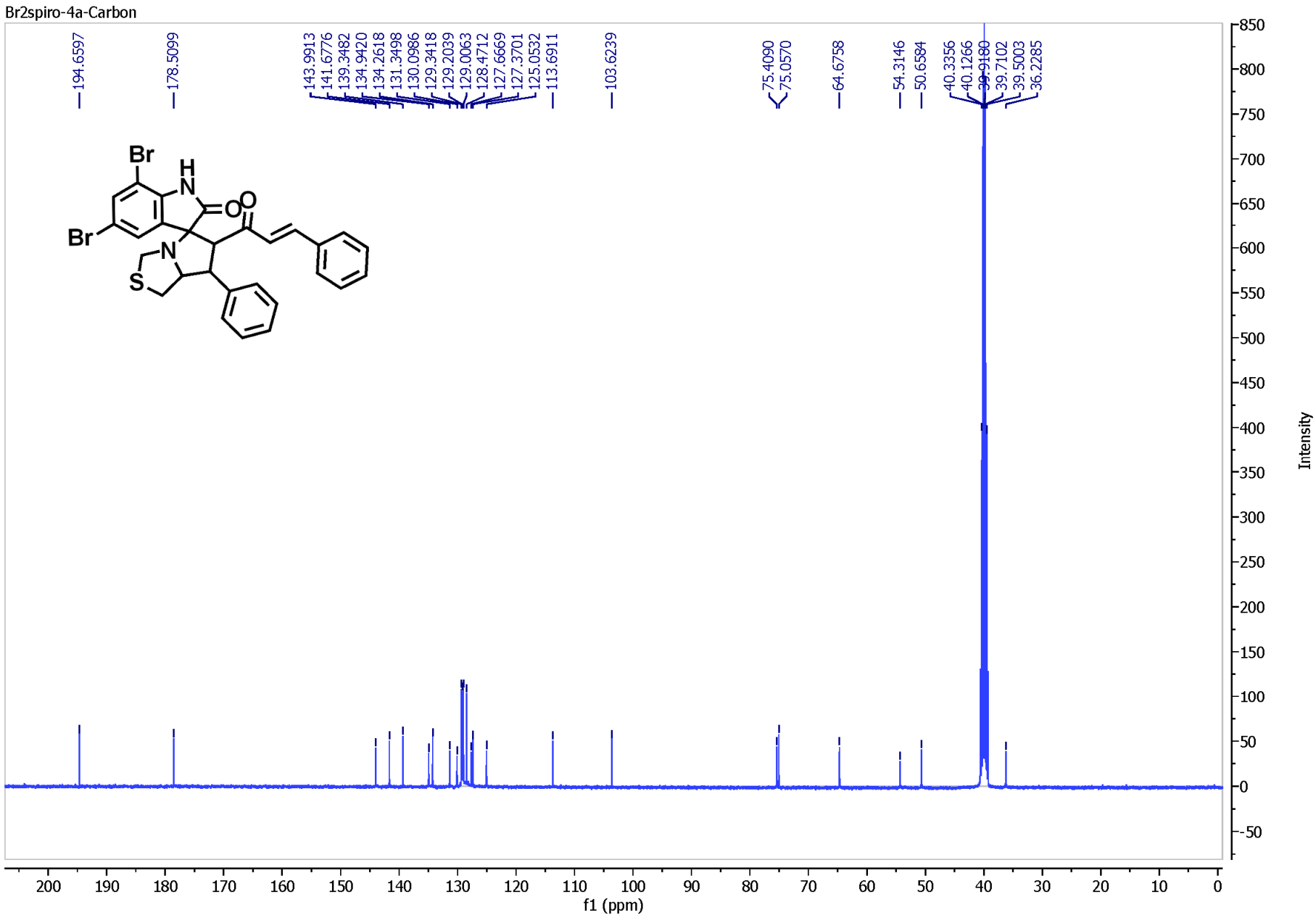

Figure S2. ^{13}C NMR spectrum of compound **5a** (100 MHz, DMSO-d_6)

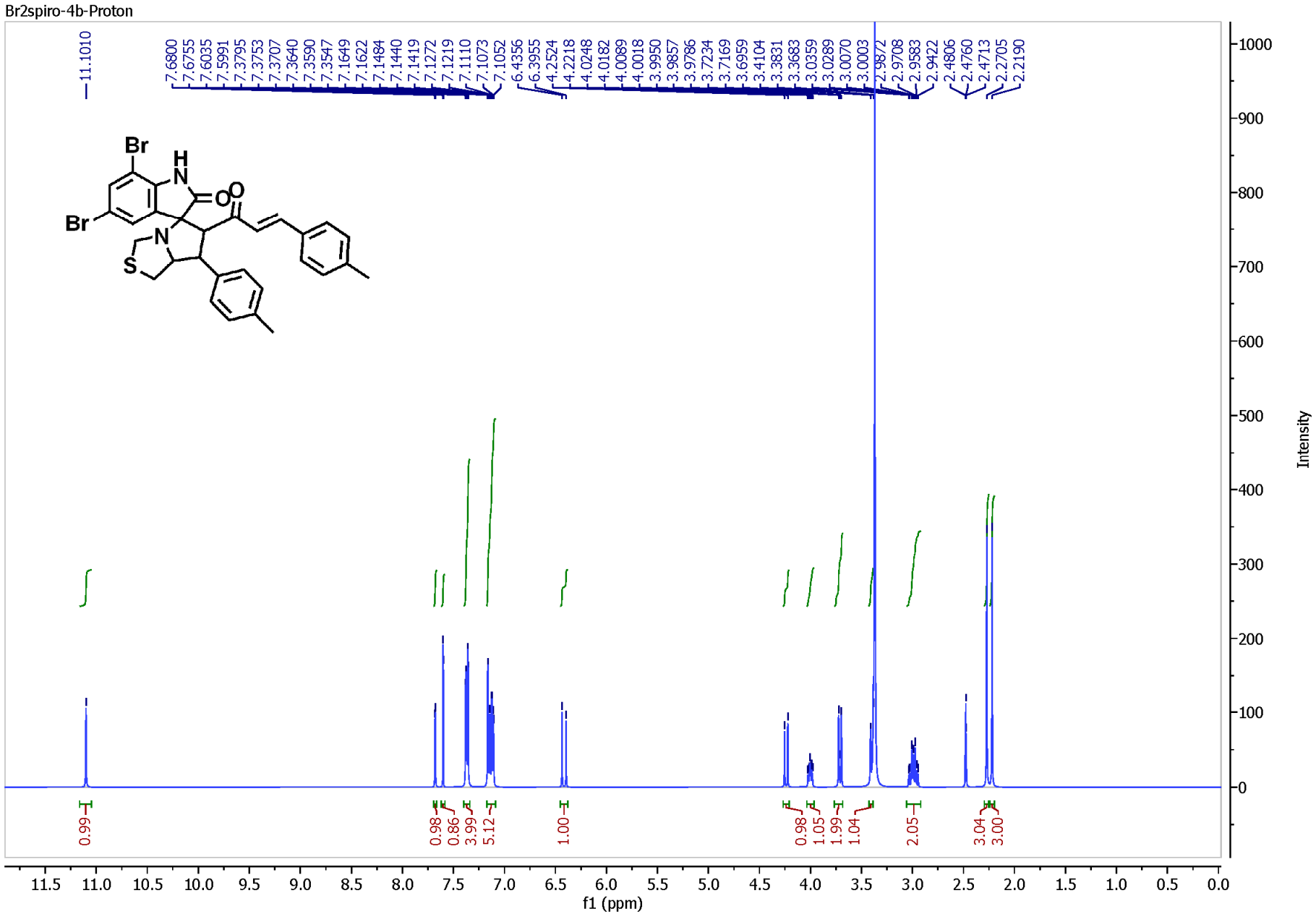

Figure S3. ^{1}H NMR spectrum of compound **5b** (400 MHz, DMSO-d_6)

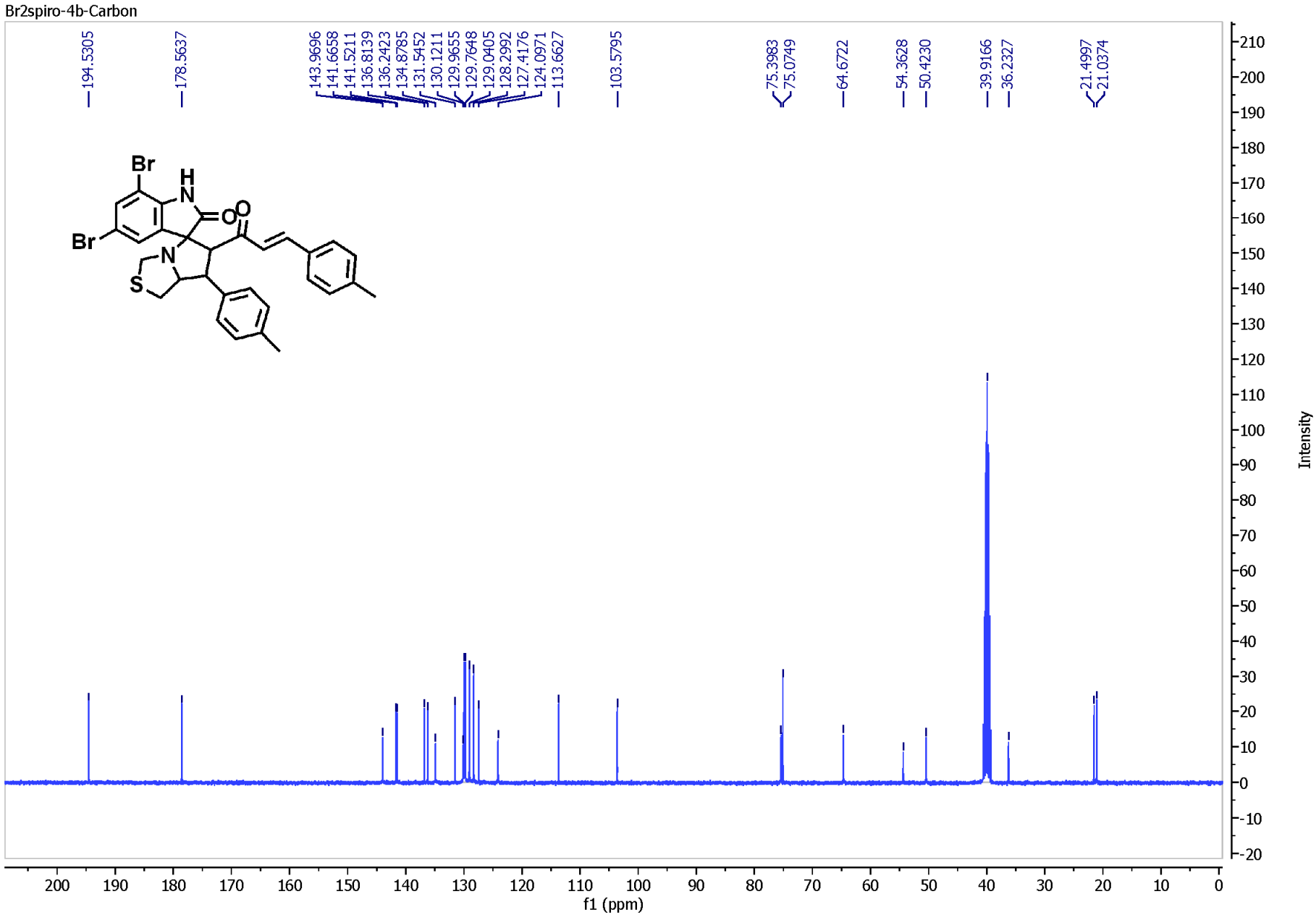

Figure S4. ^{13}C NMR spectrum of compound **5b** (100 MHz, DMSO-*d*$_6$)

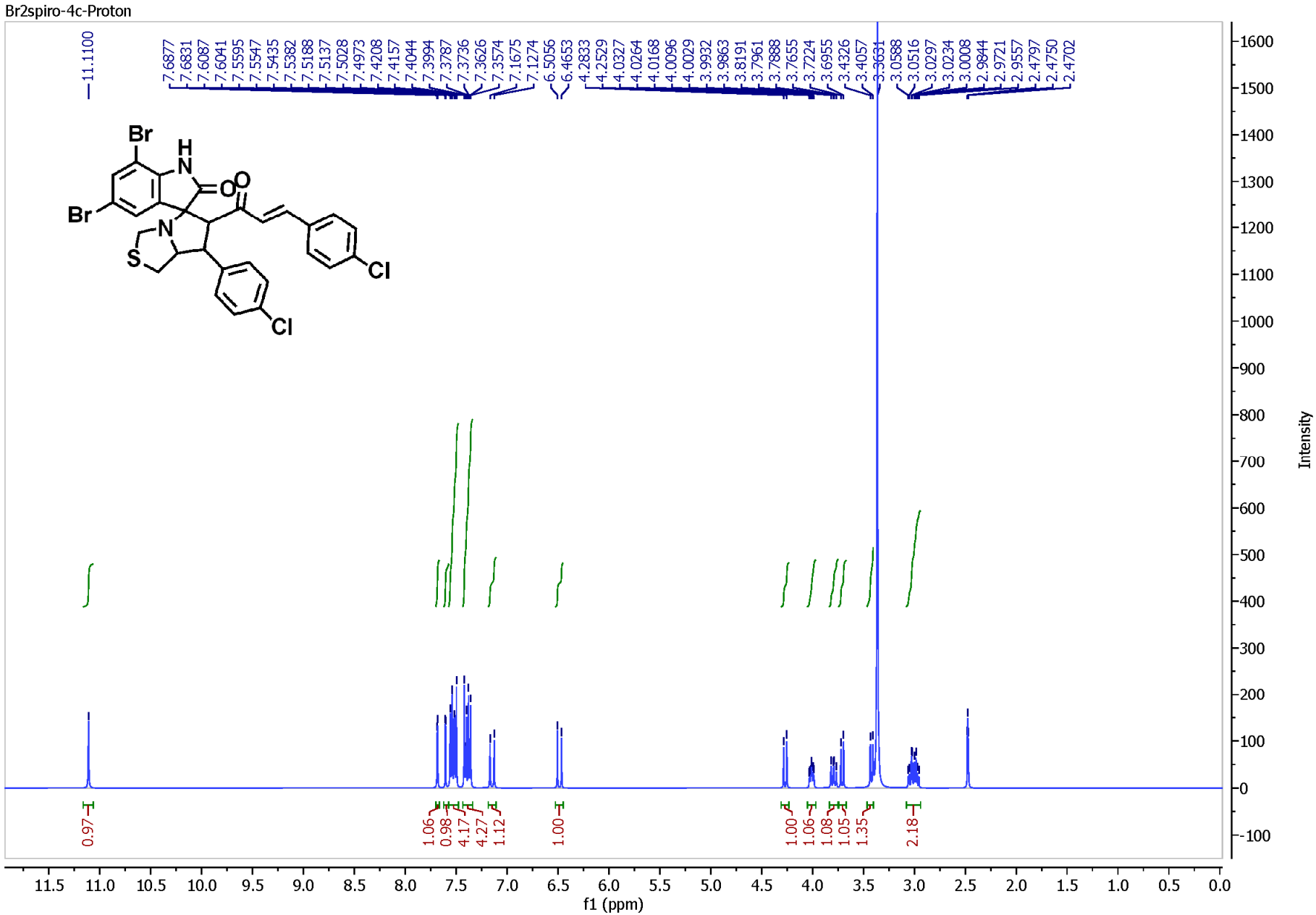

Figure S5. ^{1}H NMR spectrum of compound **5c** (400 MHz, DMSO-d_6)

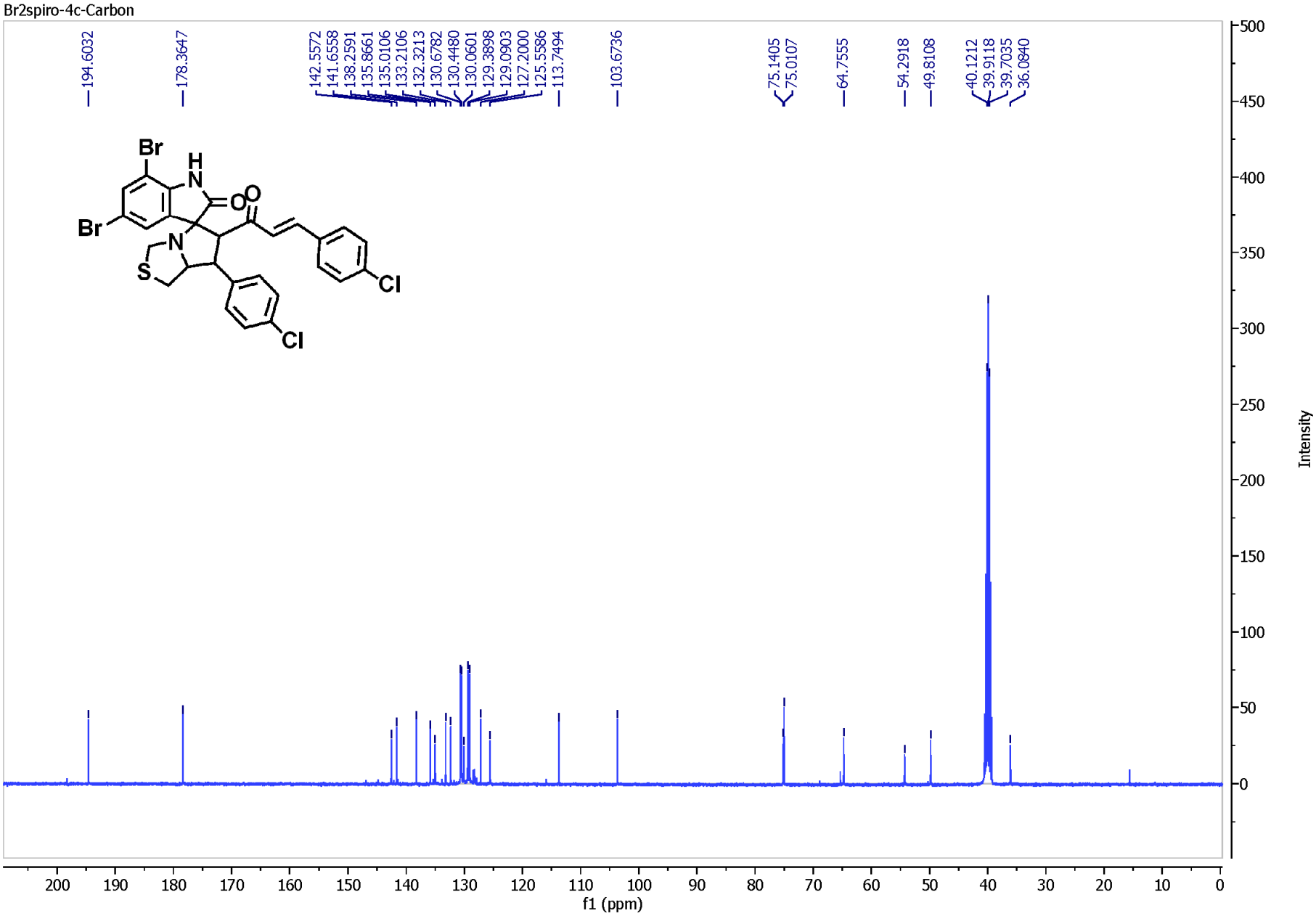

Figure S6. ^{13}C NMR spectrum of compound **5c** (100 MHz, DMSO-d_6)

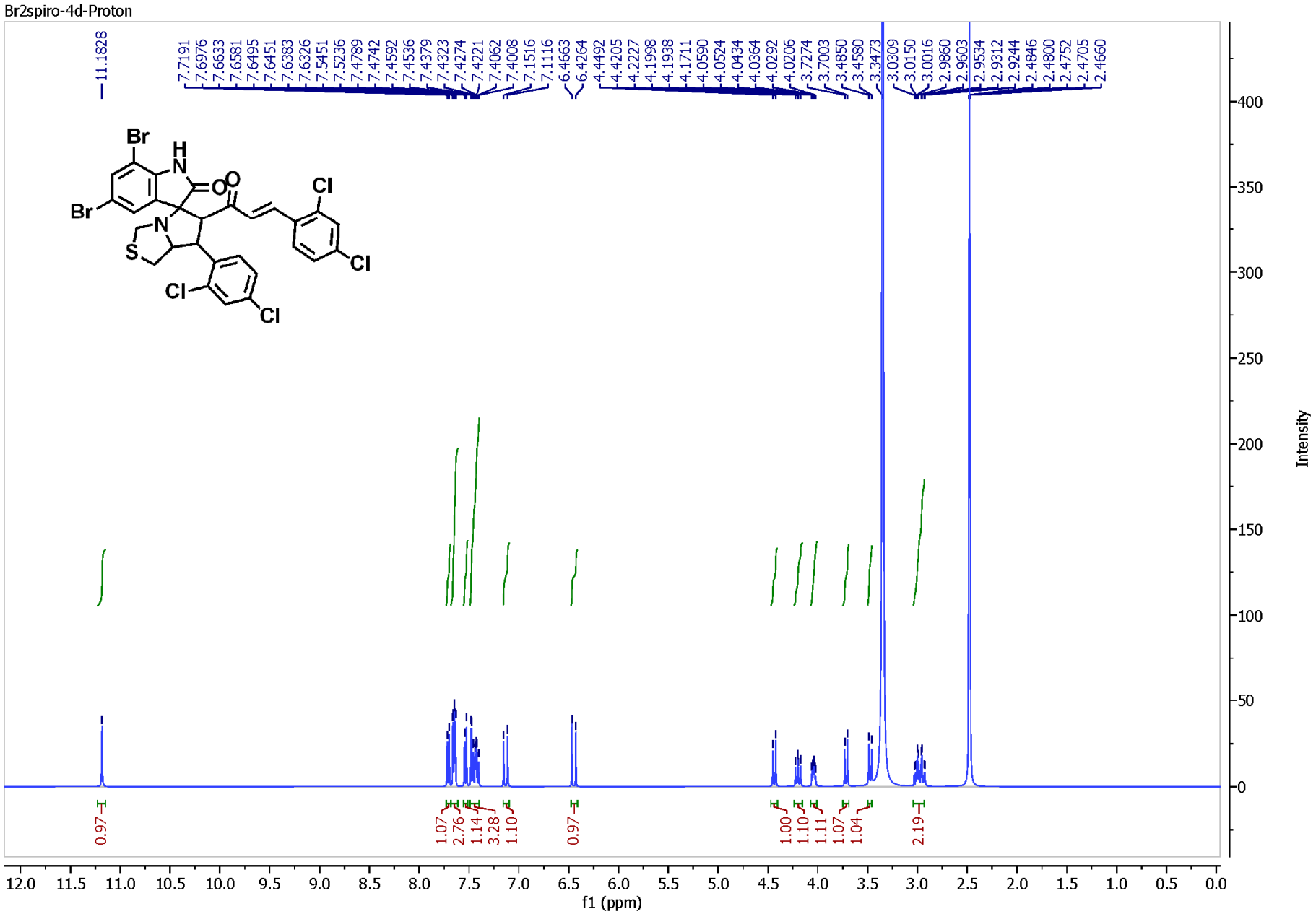

Figure S7. ^{1}H NMR spectrum of compound **5d** (400 MHz, DMSO-d_6)

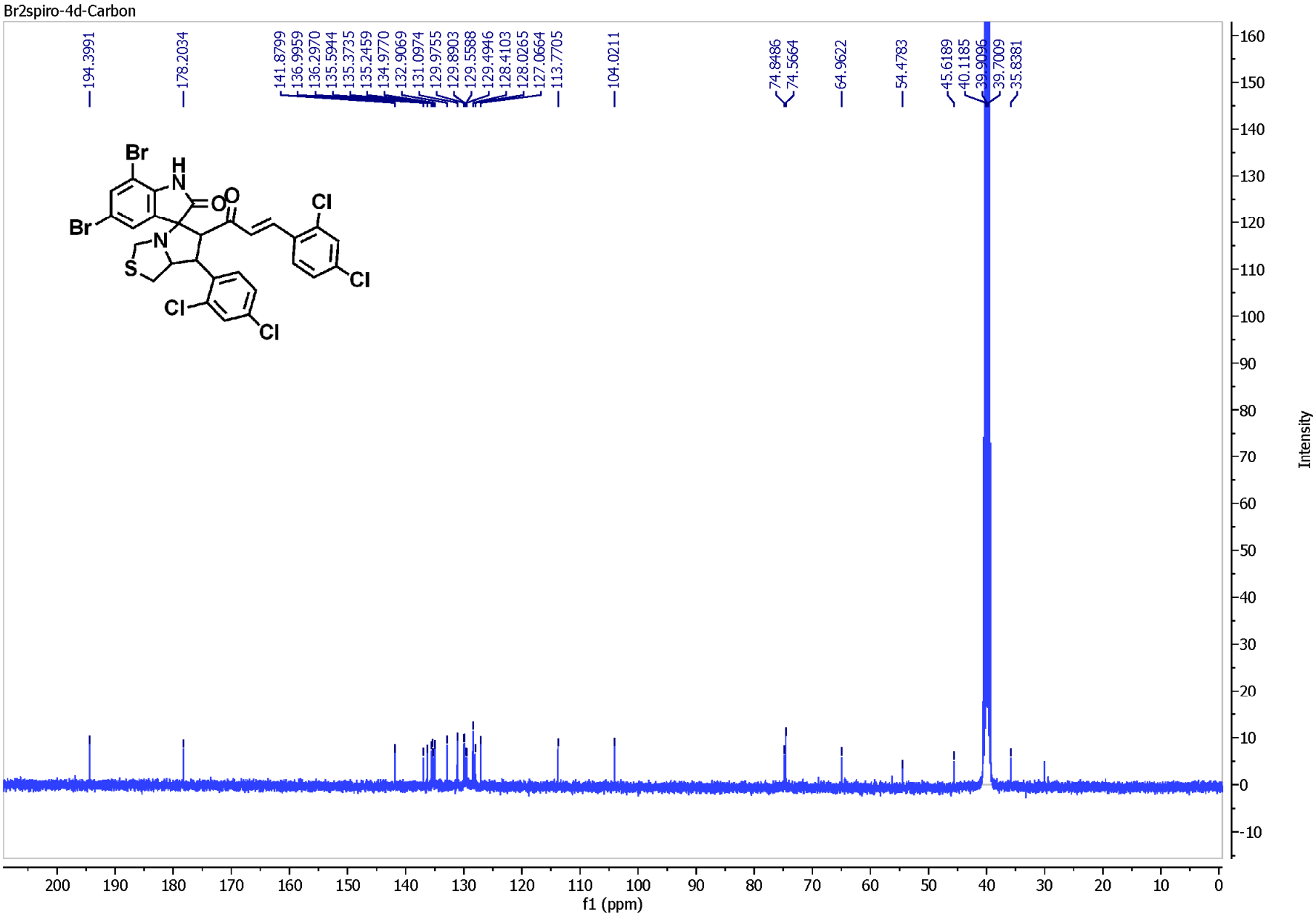

Figure S8. ^{13}C NMR spectrum of compound **5d** (100 MHz, DMSO-*d*$_6$)

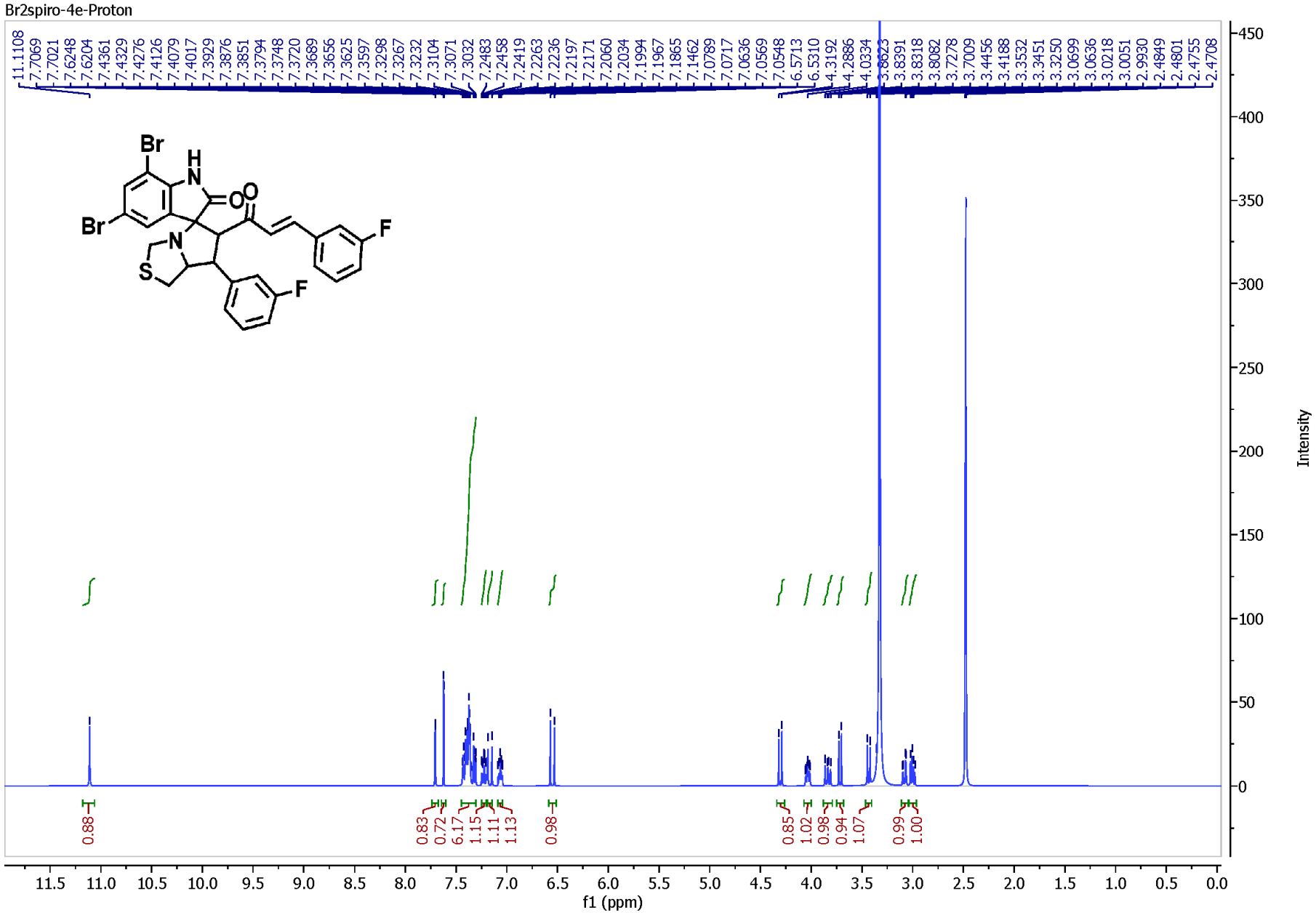

Figure S9. ^{1}H NMR spectrum of compound **5e** (400 MHz, DMSO-d_6)

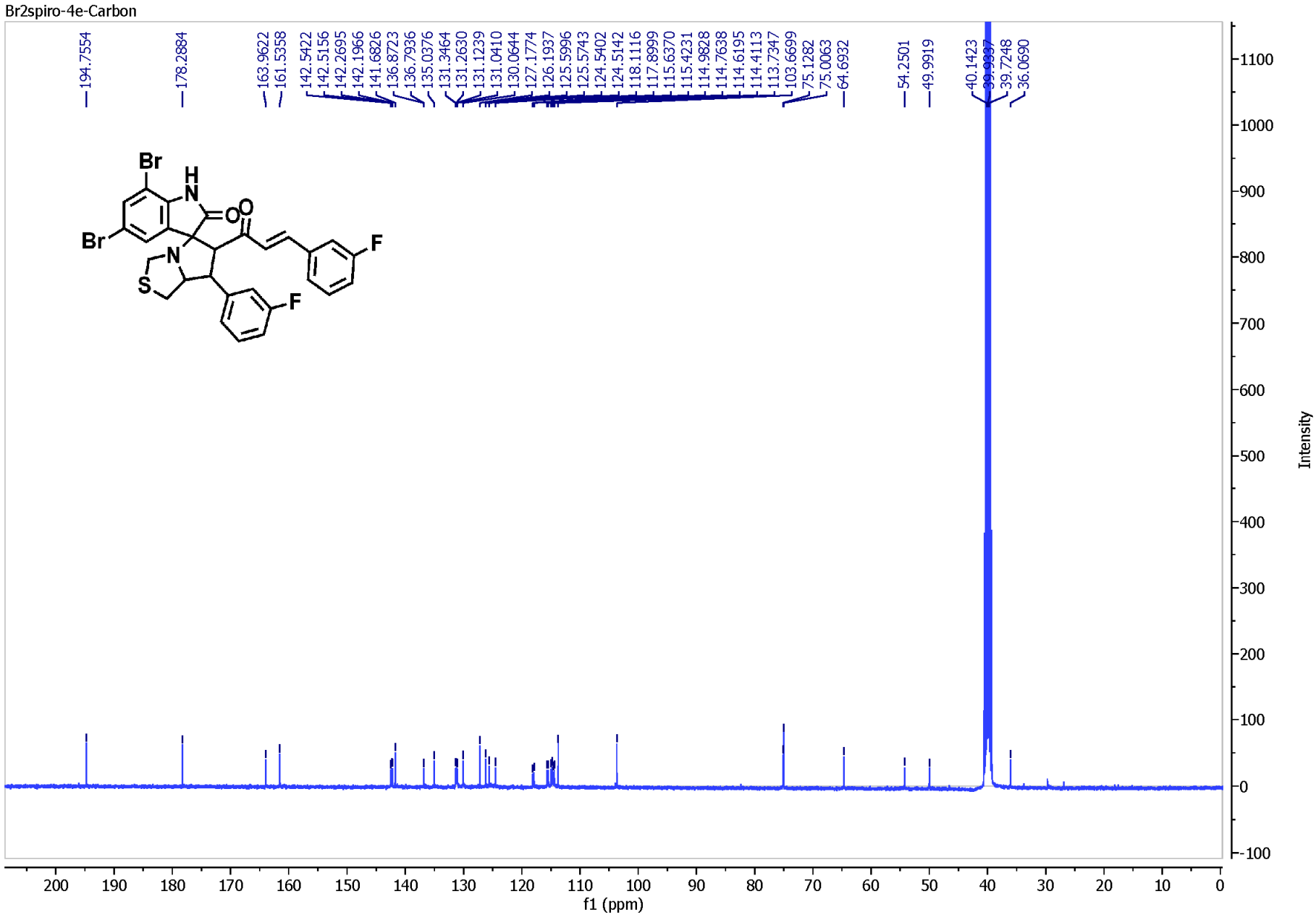

Figure S10. ^{13}C NMR spectrum of compound **5e** (100 MHz, DMSO-d_6)

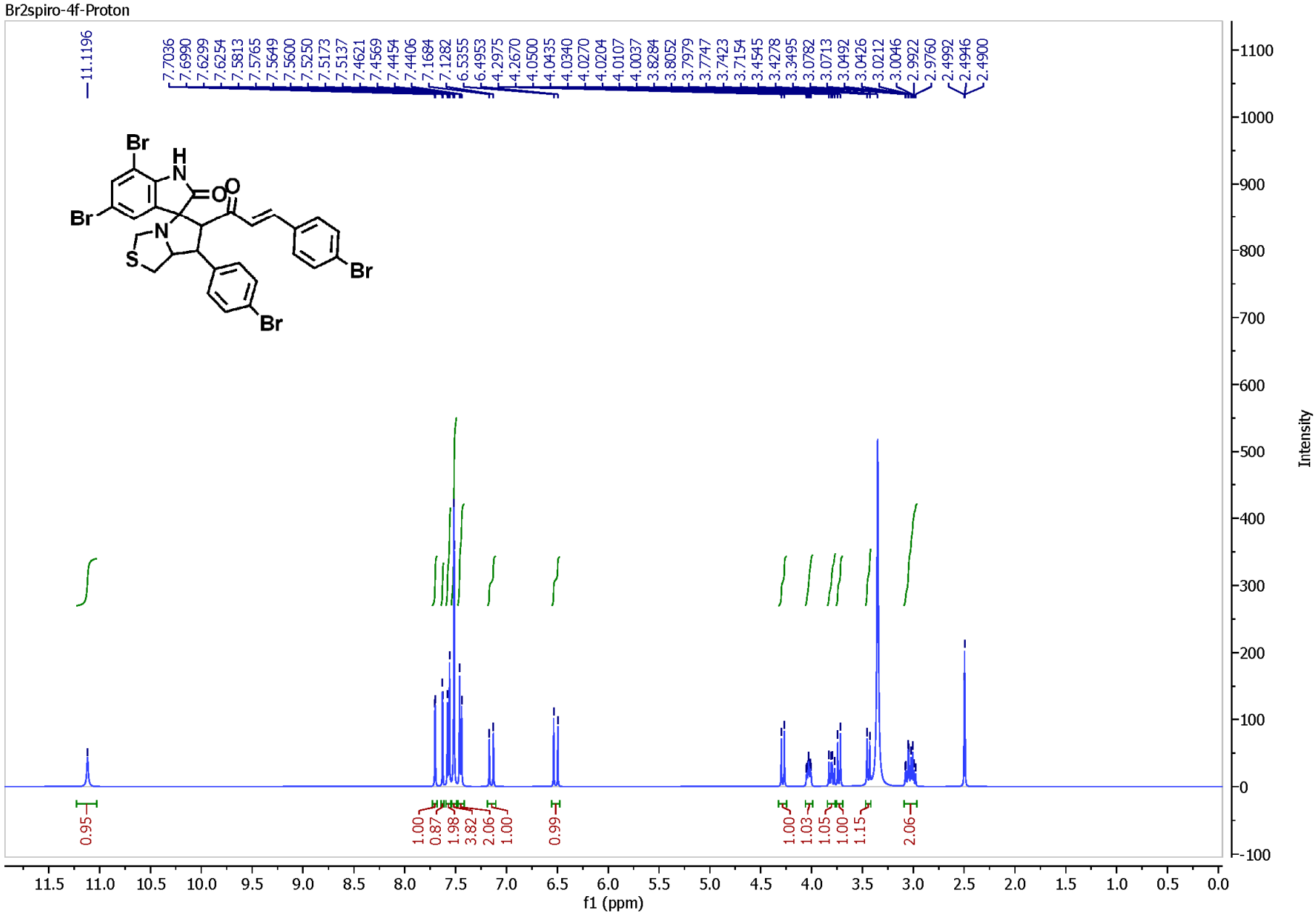

Figure S11. ^{1}H NMR spectrum of compound **5f** (400 MHz, DMSO-d_6)

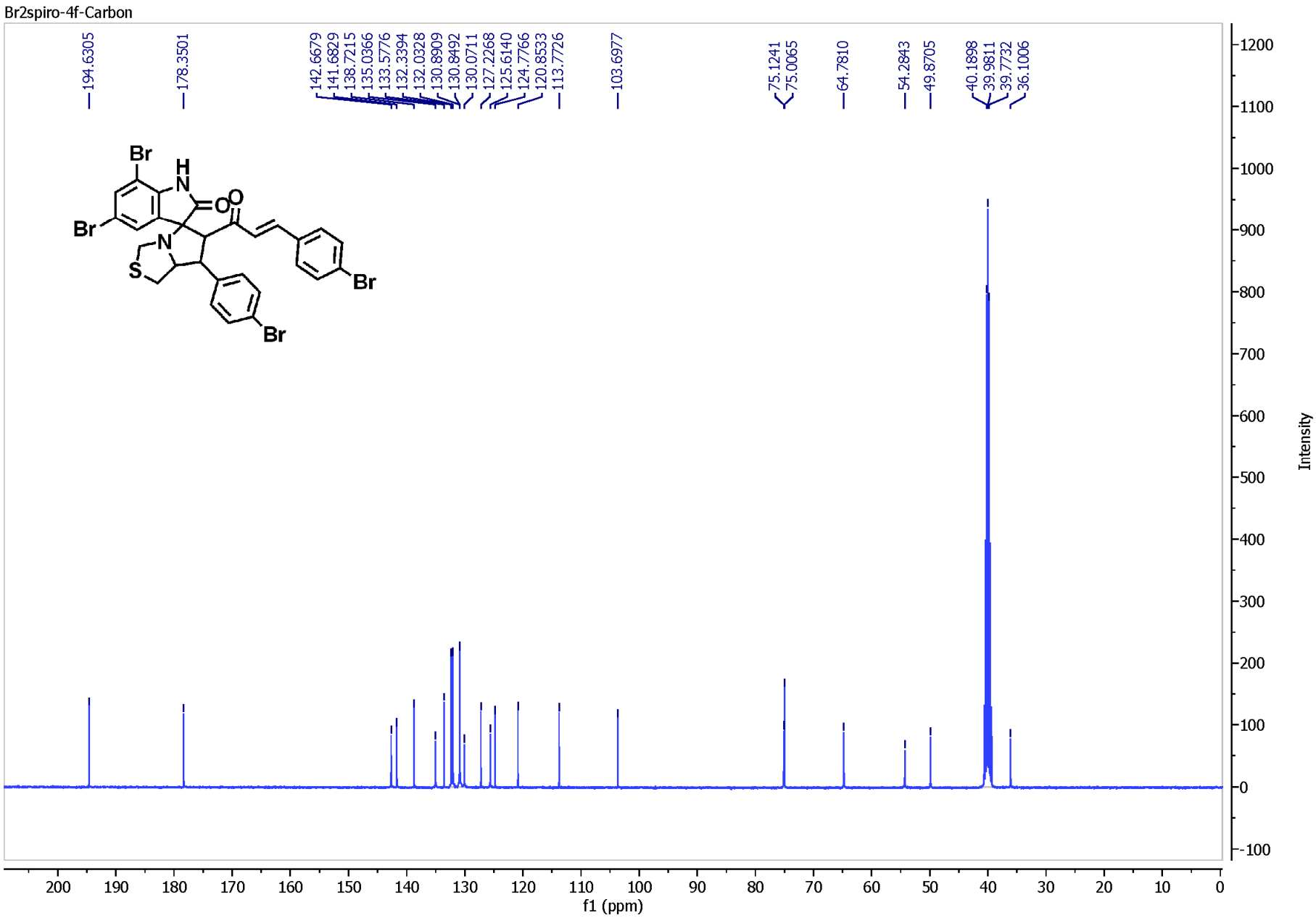

Figure S12. ^{13}C NMR spectrum of compound **5f** (100 MHz, DMSO-d_6)

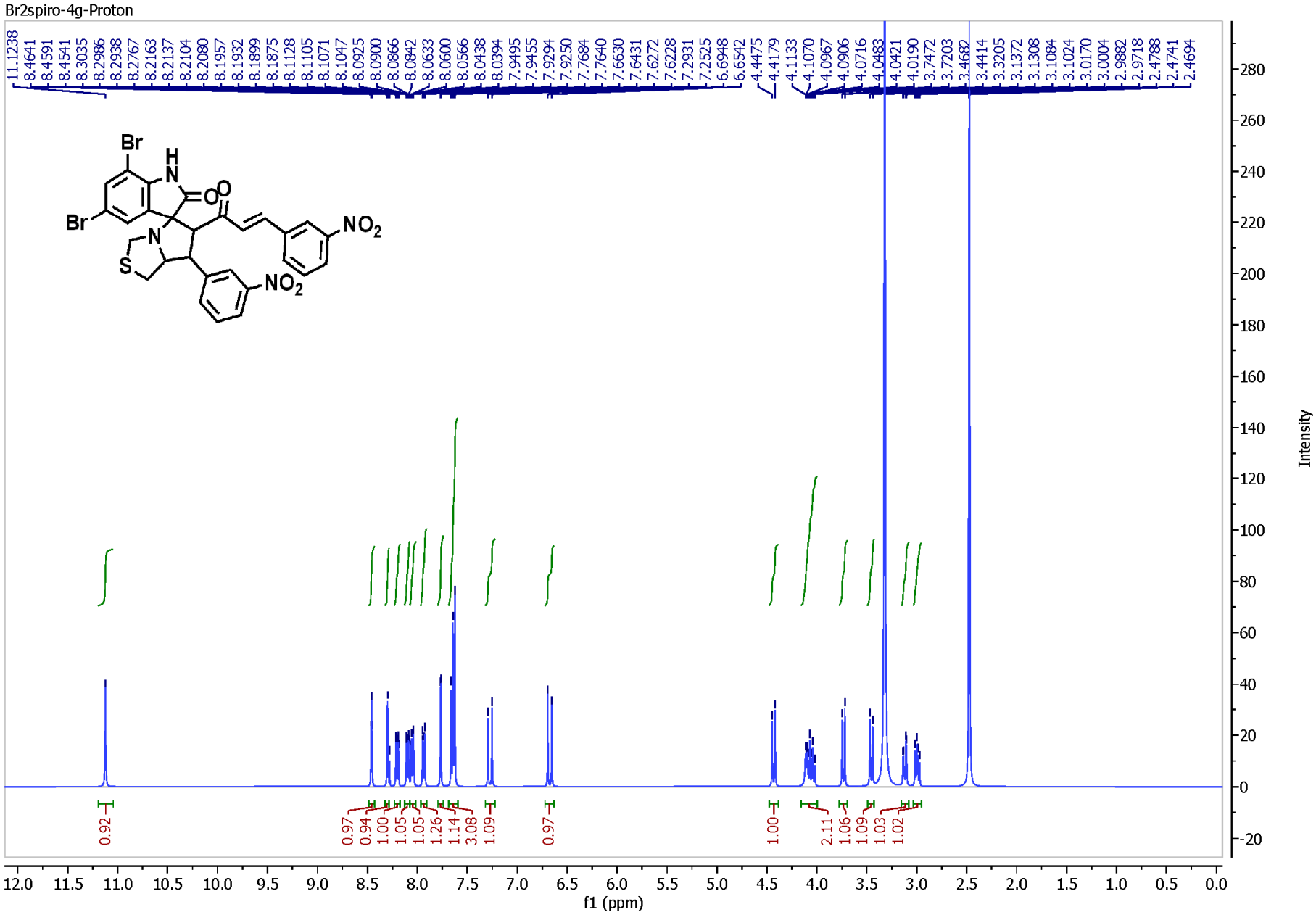

Figure S13. [1]H NMR spectrum of compound **5g** (400 MHz, DMSO-d_6)

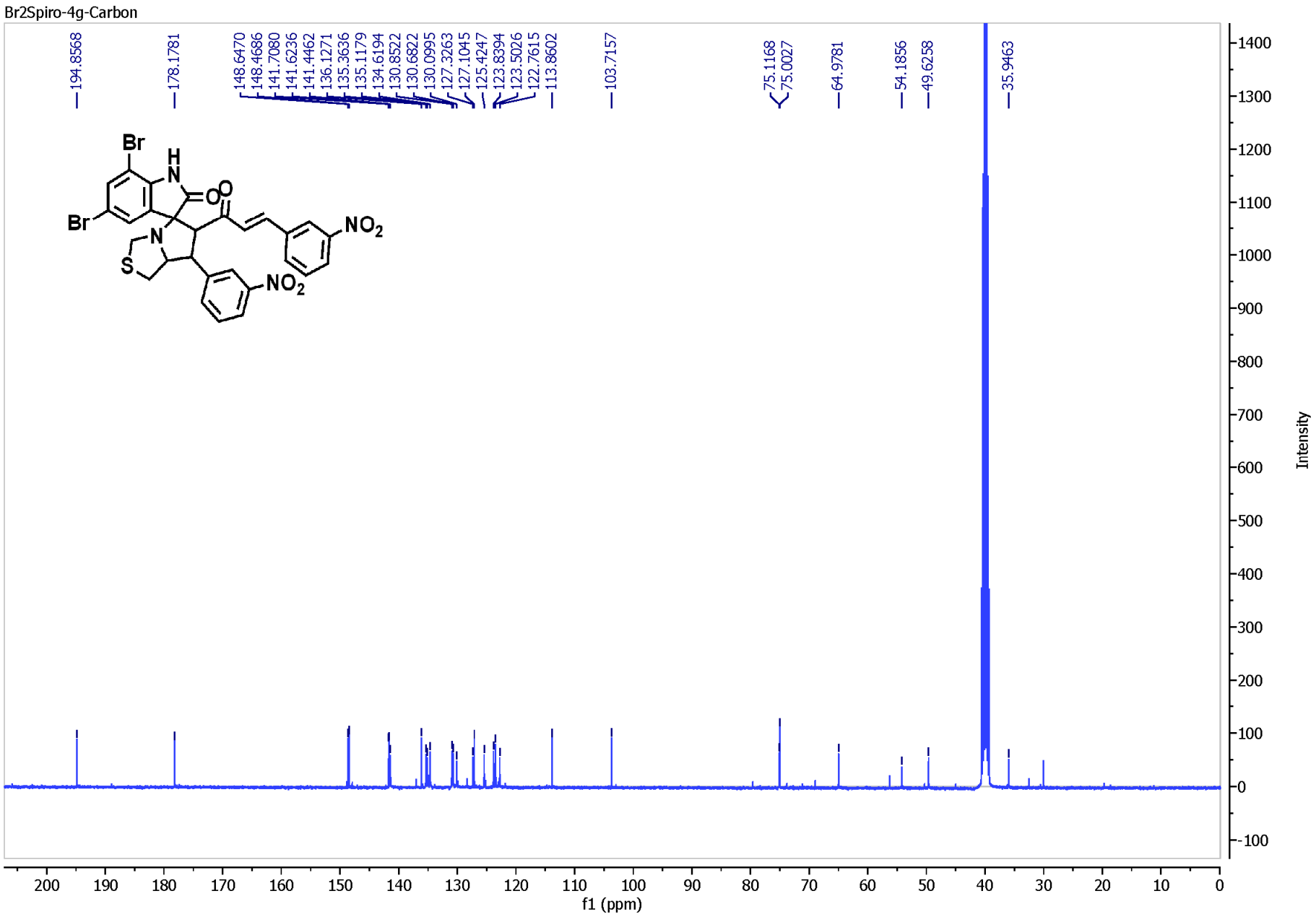

Figure S14. ^{13}C NMR spectrum of compound **5g** (100 MHz, DMSO-d_6)

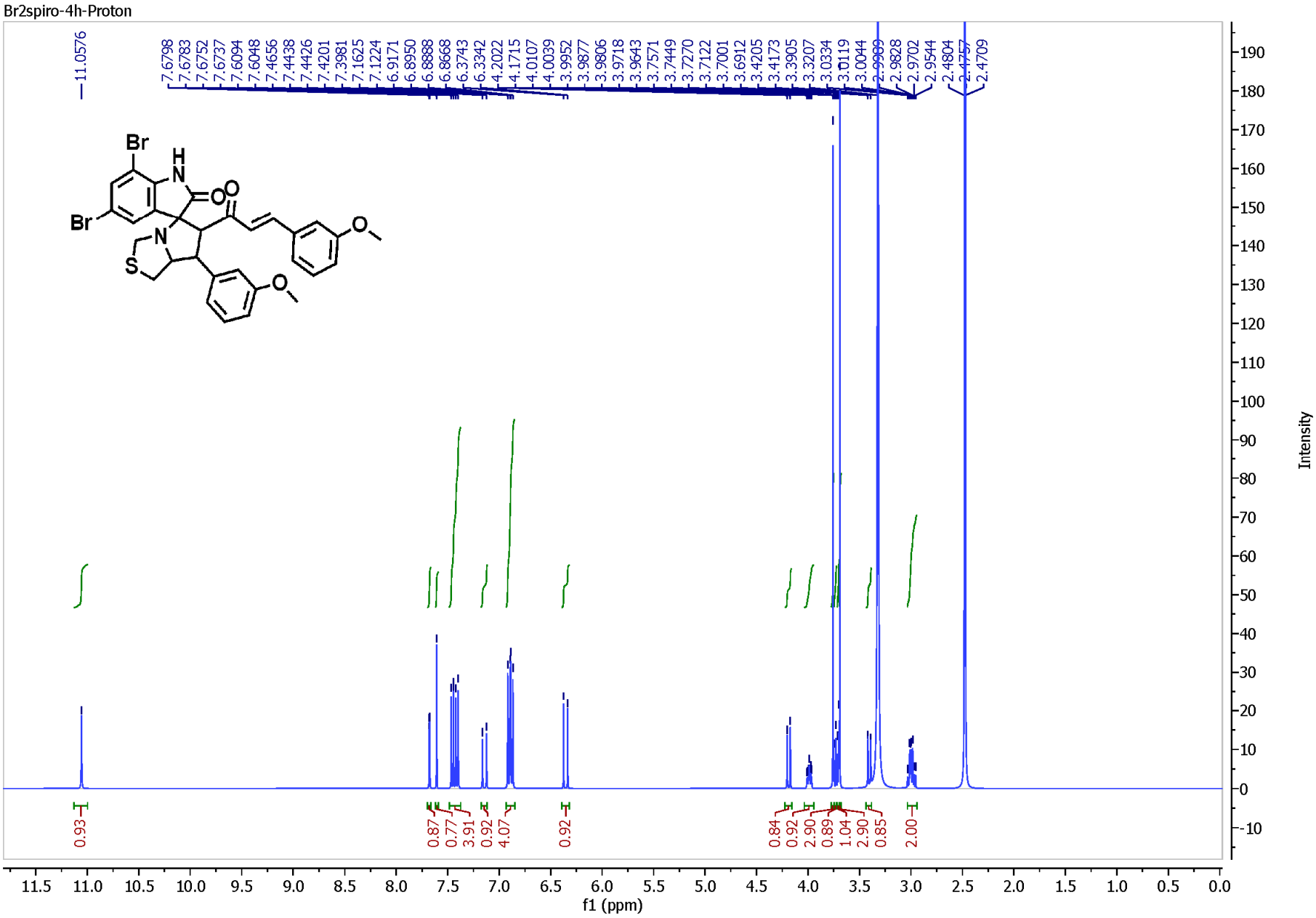

Figure S15. ^{1}H NMR spectrum of compound **5h** (400 MHz, DMSO-d_6)

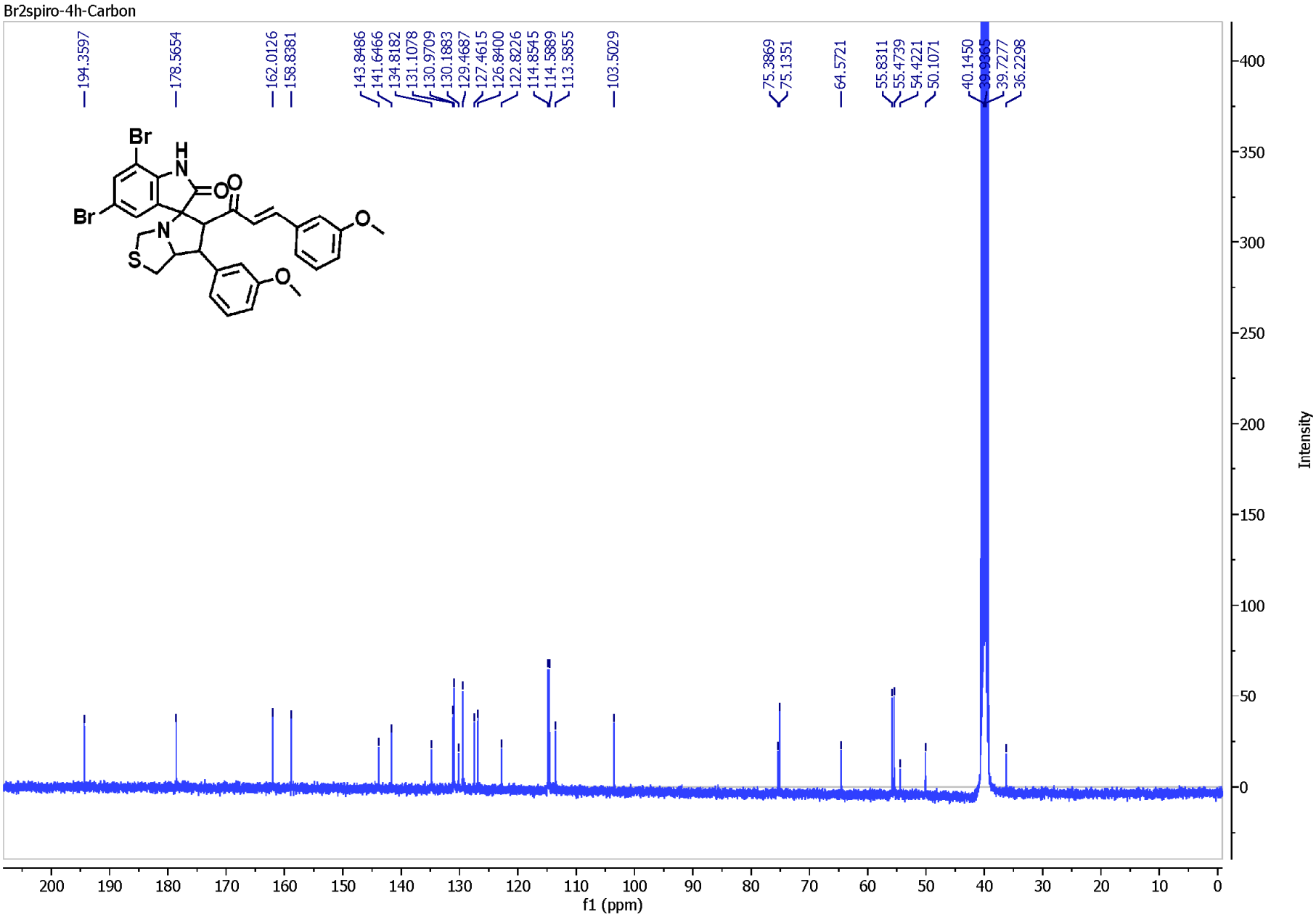

Figure S16. ^{13}C NMR spectrum of compound **5h** (100 MHz, DMSO-d_6)

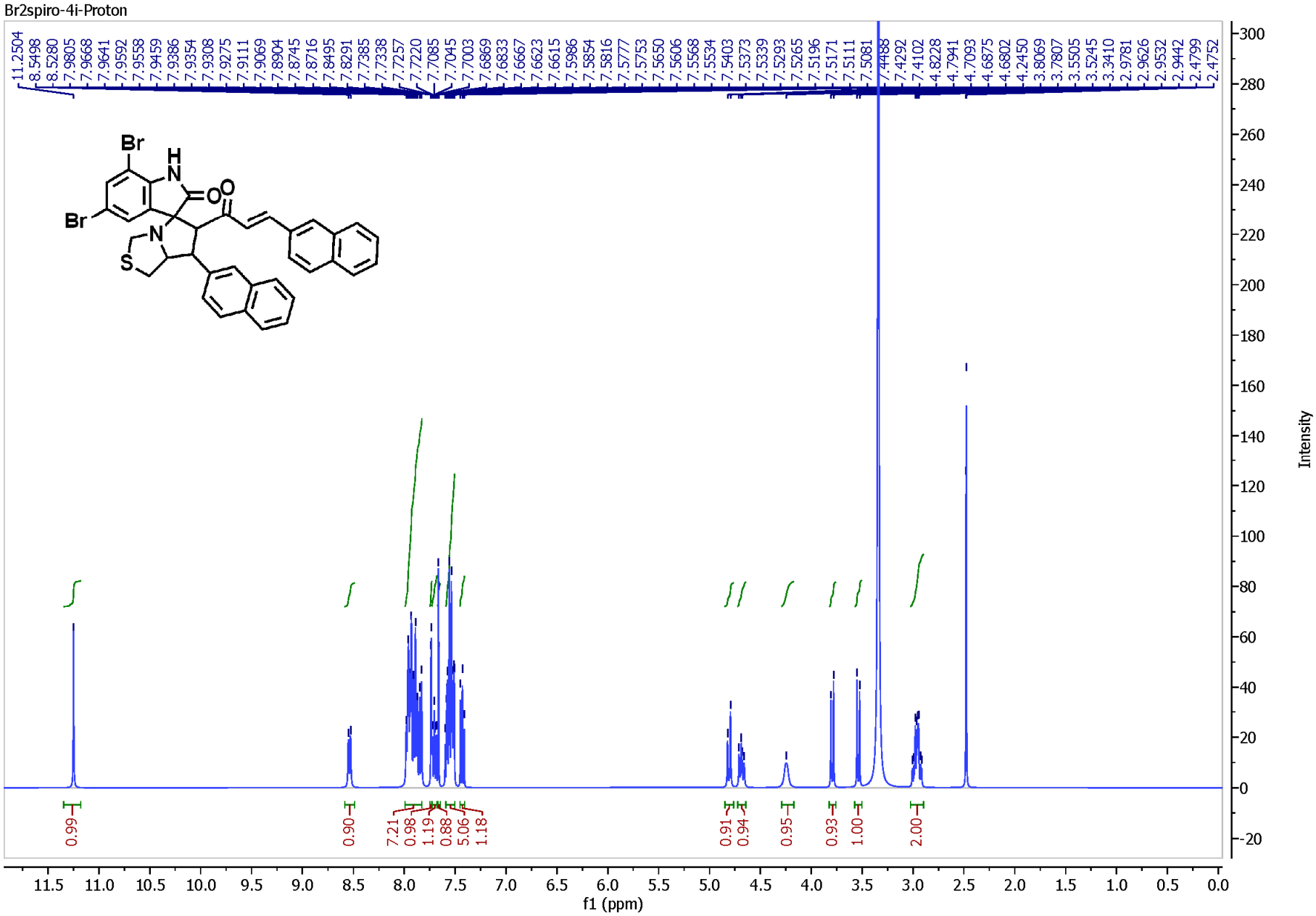

Figure S17. ^{1}H NMR spectrum of compound **5i** (400 MHz, DMSO-d_6)

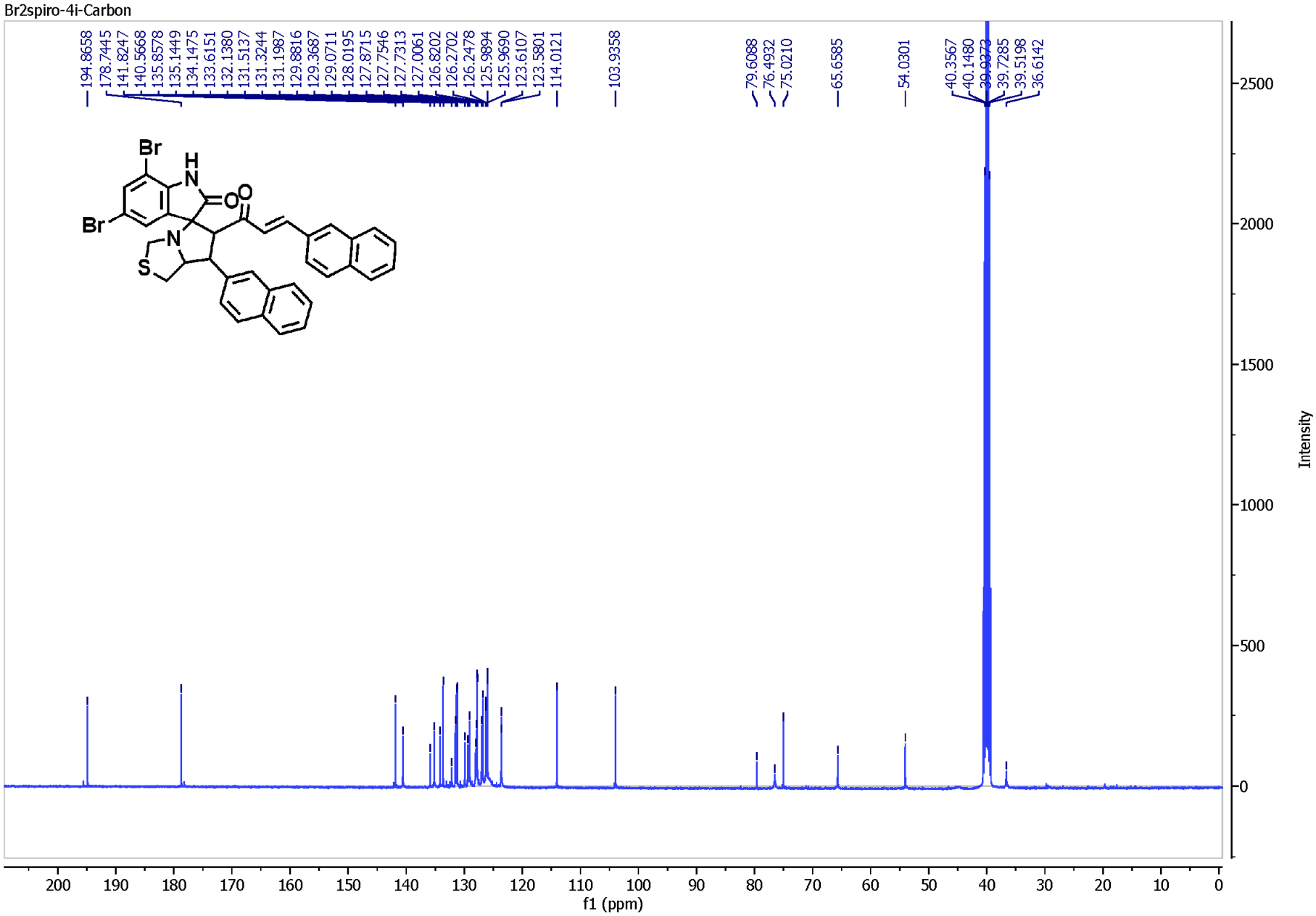

Figure S18. ^{13}C NMR spectrum of compound **5i** (100 MHz, DMSO-d_6)

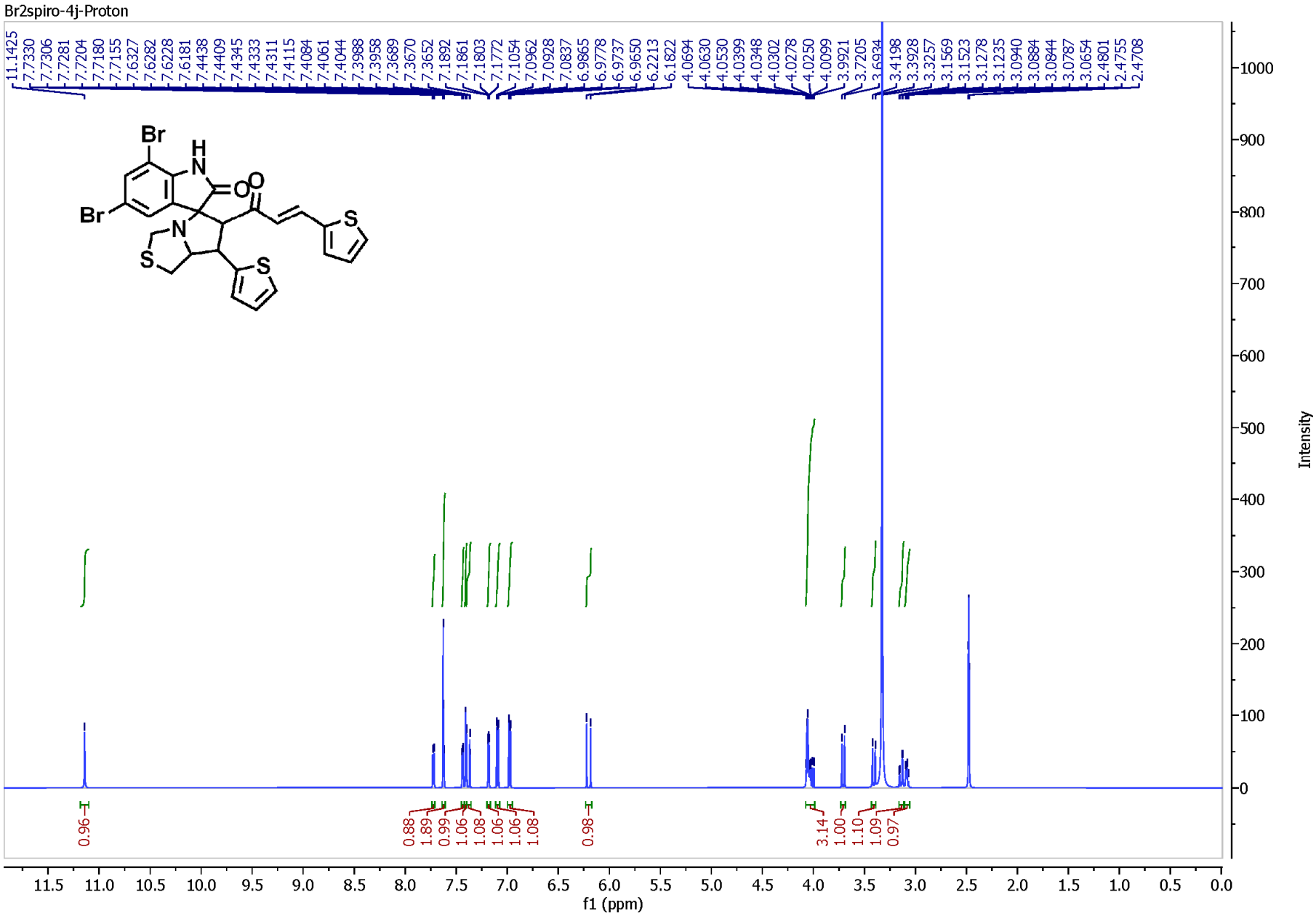

Figure S19. ^{1}H NMR spectrum of compound **5j** (400 MHz, DMSO-*d*$_6$)

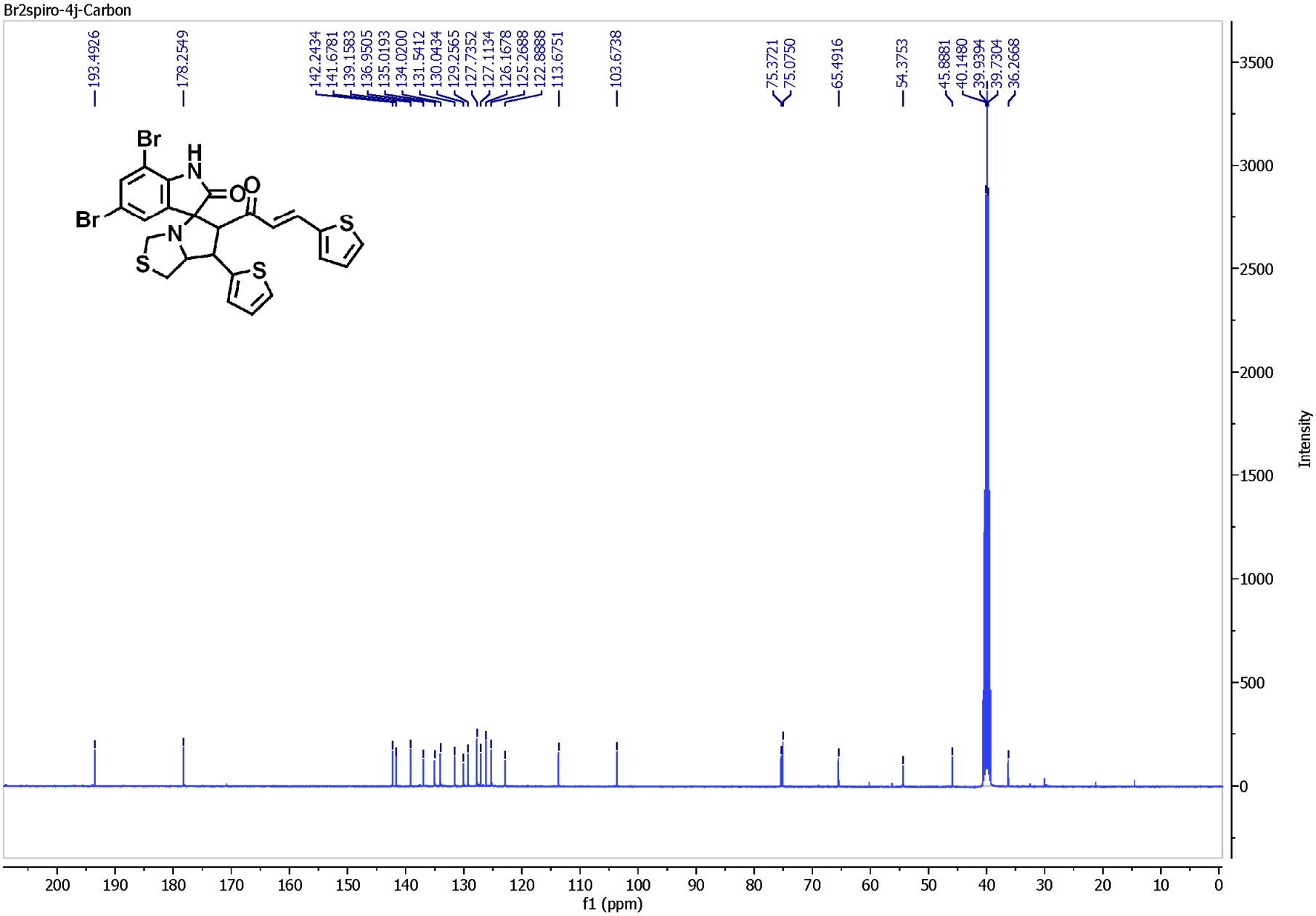

Figure S20. ^{13}C NMR spectrum of compound **5j** (100 MHz, DMSO-d_6)

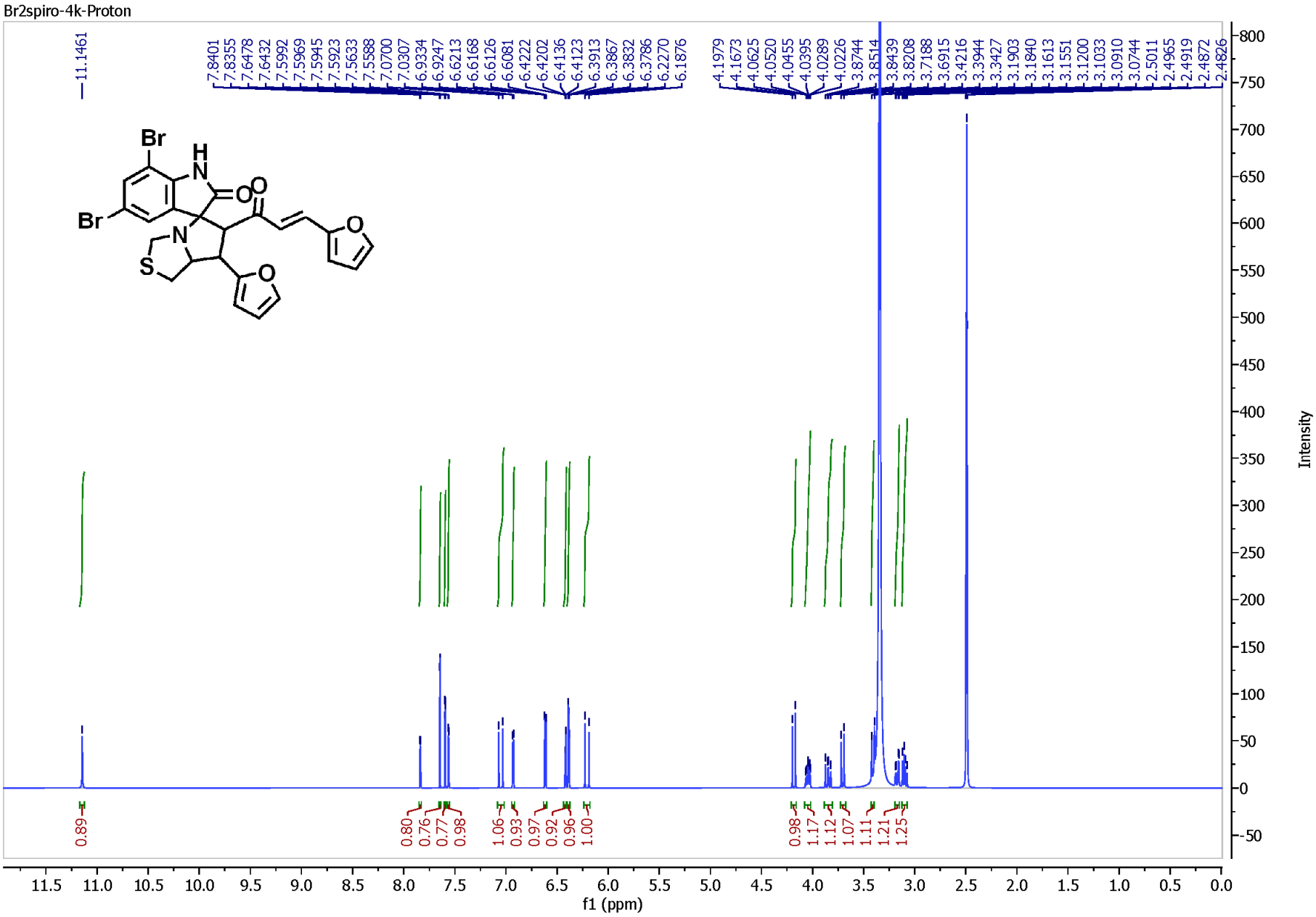

Figure S21. [1]H NMR spectrum of compound **5k** (400 MHz, DMSO-d_6)

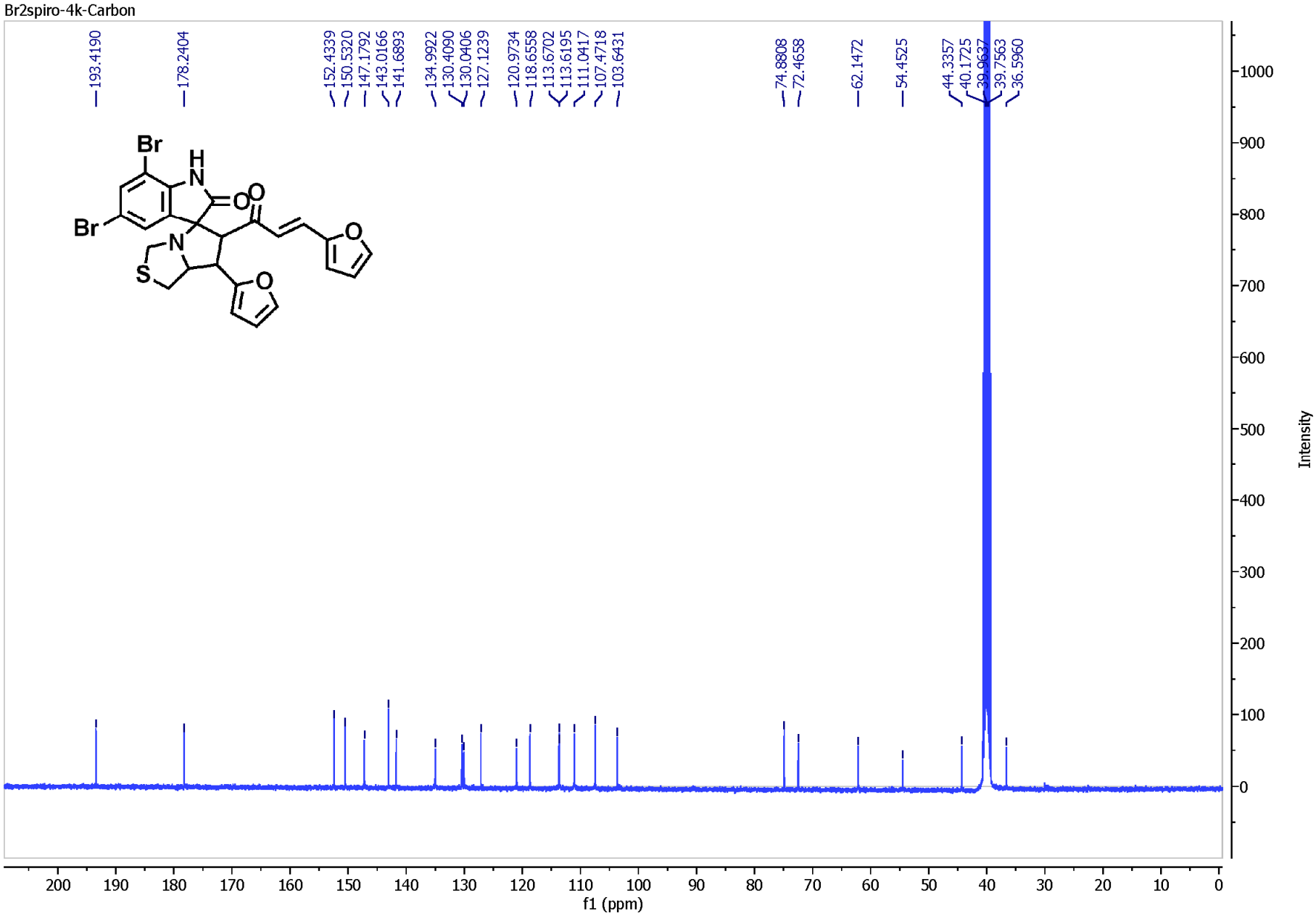

Figure S22. ^{13}C NMR spectrum of compound **5k** (100 MHz, DMSO-d_6)

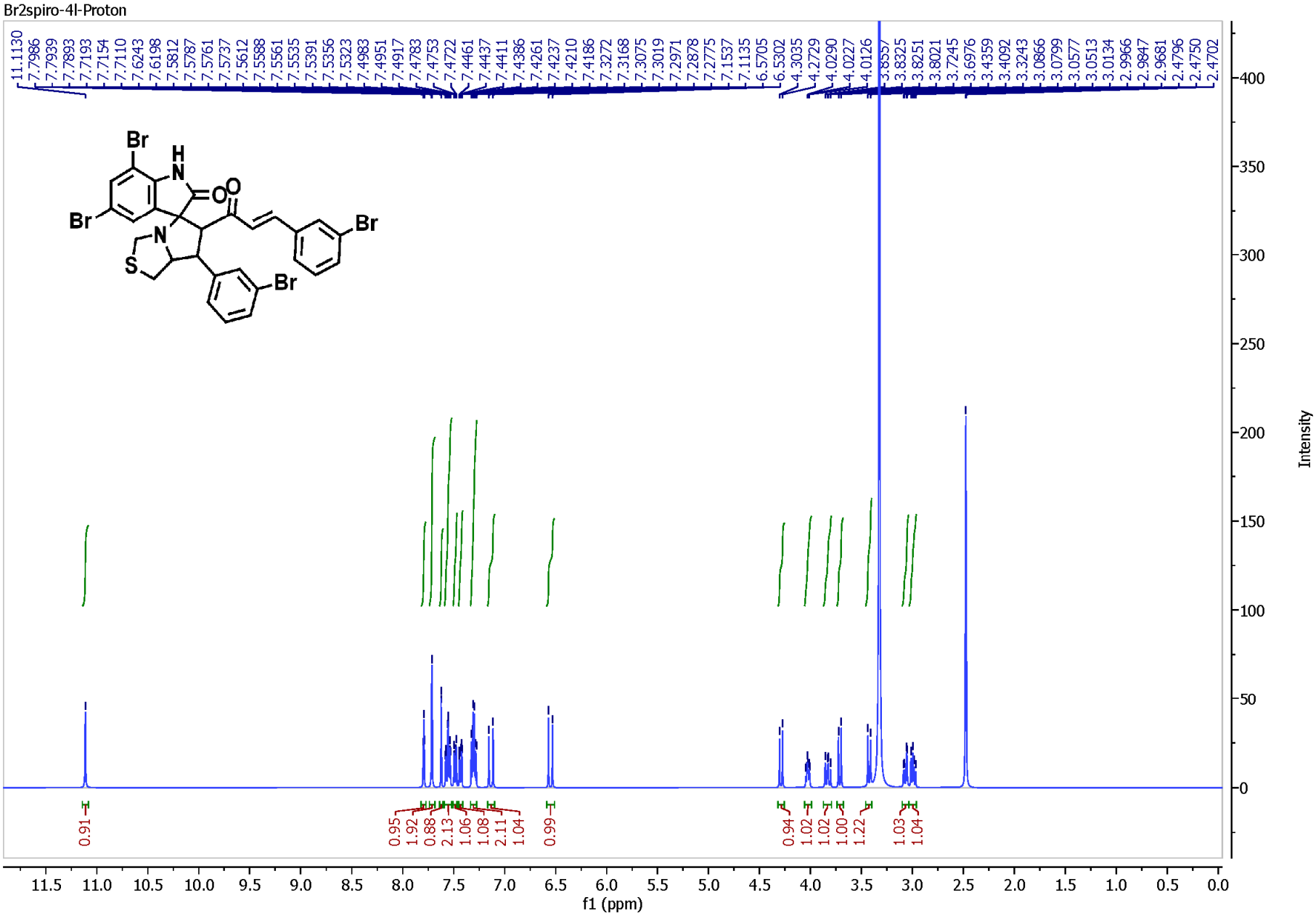

Figure S23. ^{1}H NMR spectrum of compound **5l** (400 MHz, DMSO-d_6)

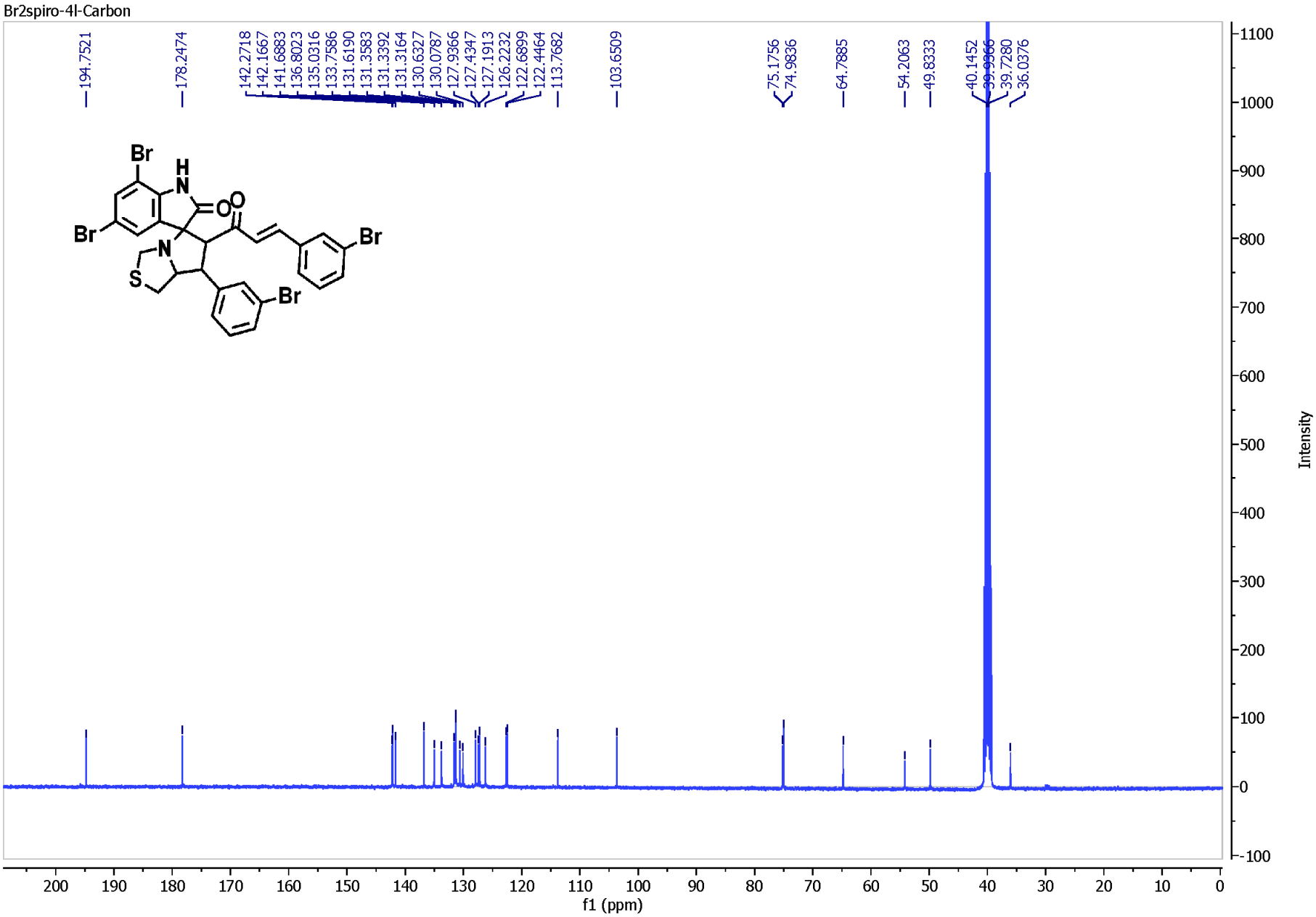

Figure S24. ^{13}C NMR spectrum of compound **5l** (100 MHz, DMSO-d_6)

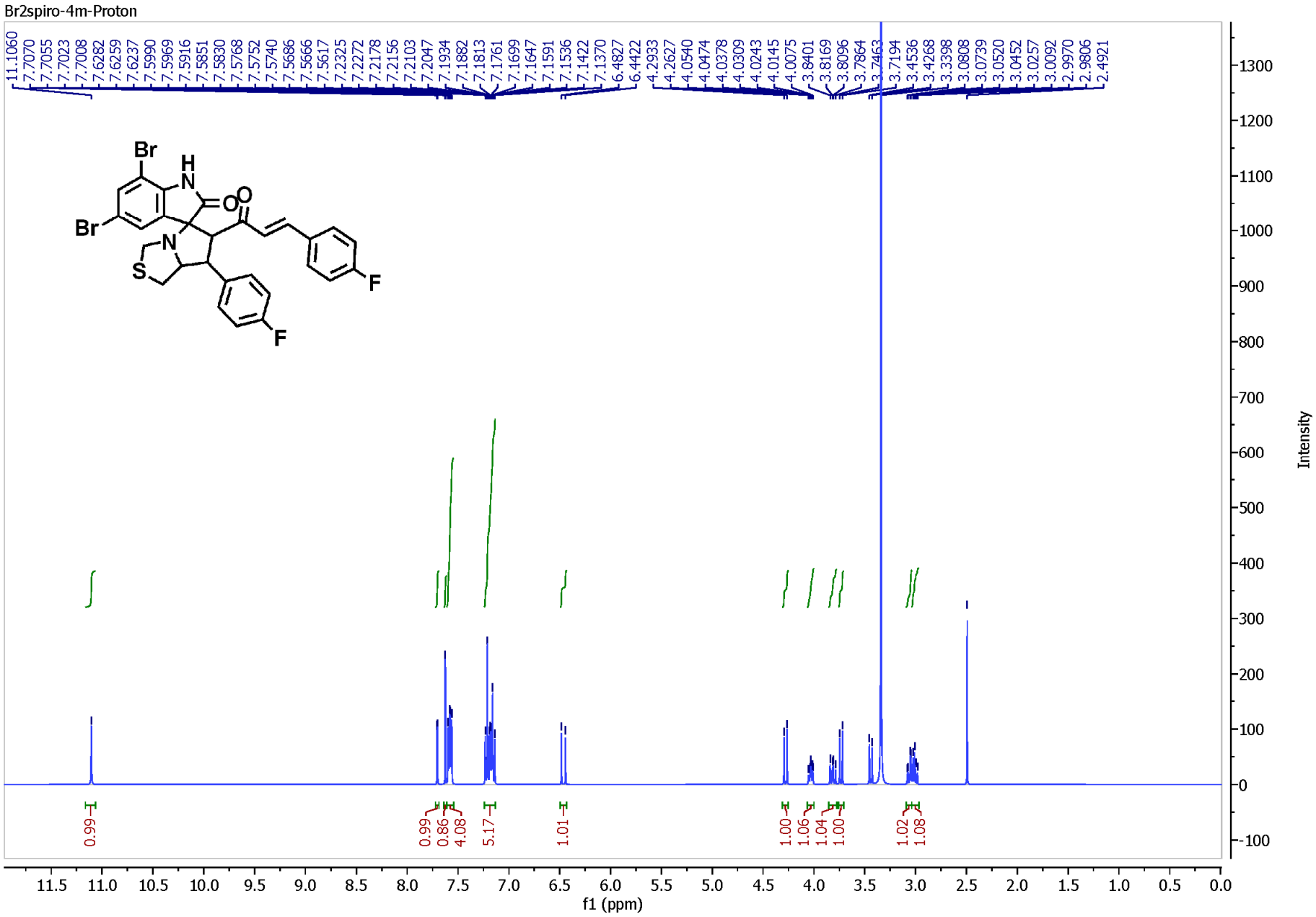

Figure S25. ^{1}H NMR spectrum of compound **5m** (400 MHz, DMSO-d_6)

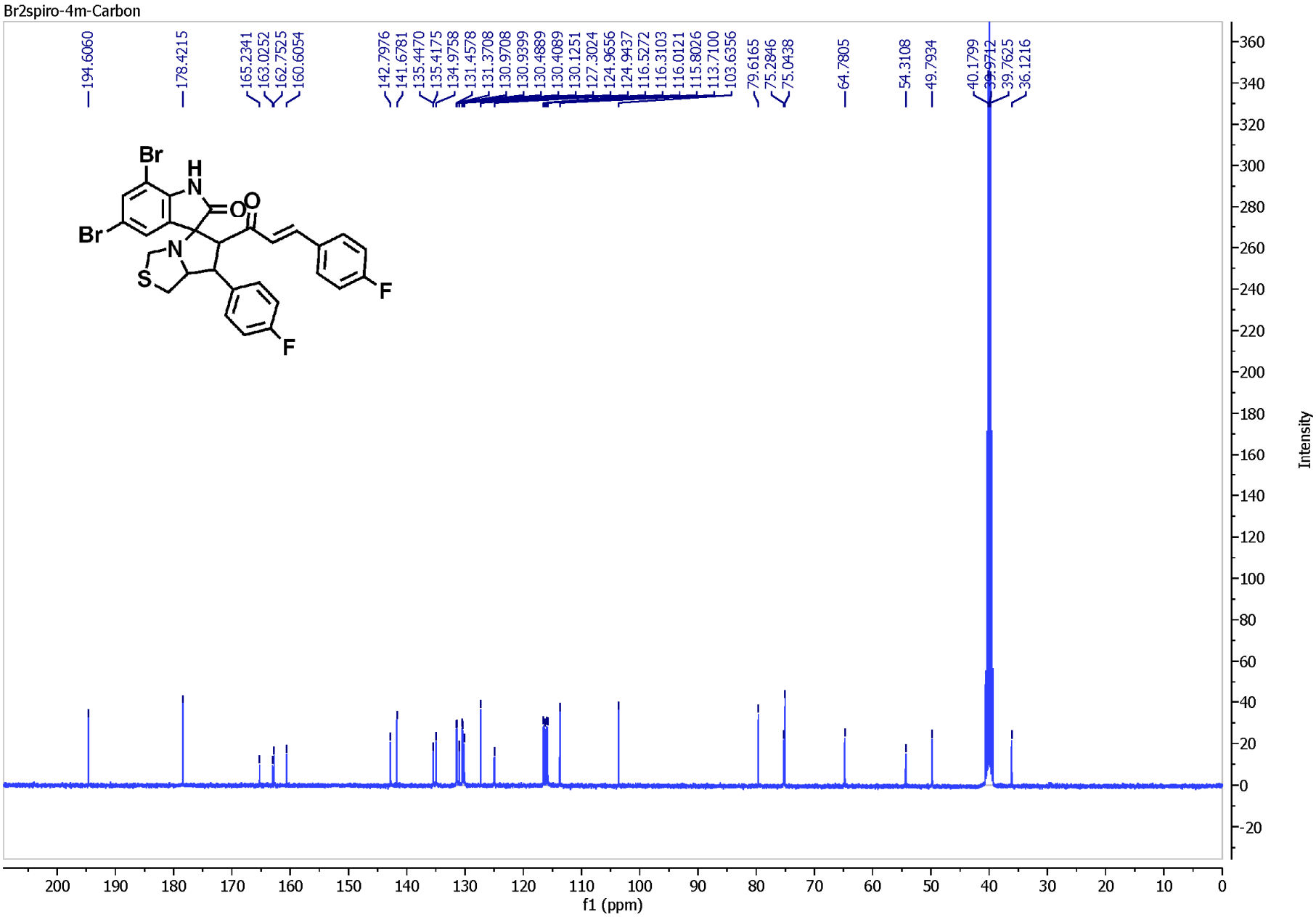

Figure S26. ^{13}C NMR spectrum of compound **5m** (100 MHz, DMSO-d_6)

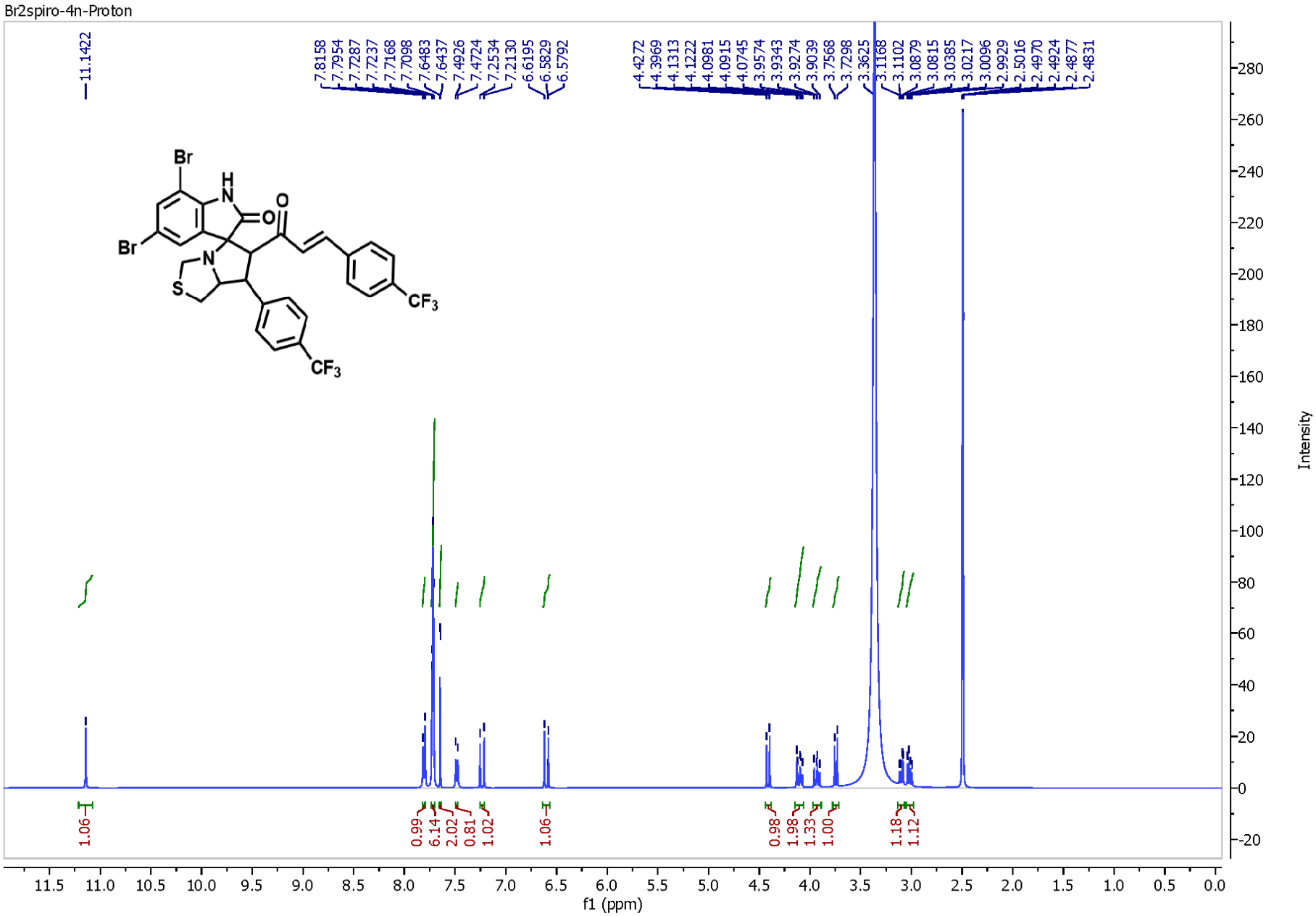

Figure S27. ^{1}H NMR spectrum of compound **5n** (400 MHz, DMSO-d_6)

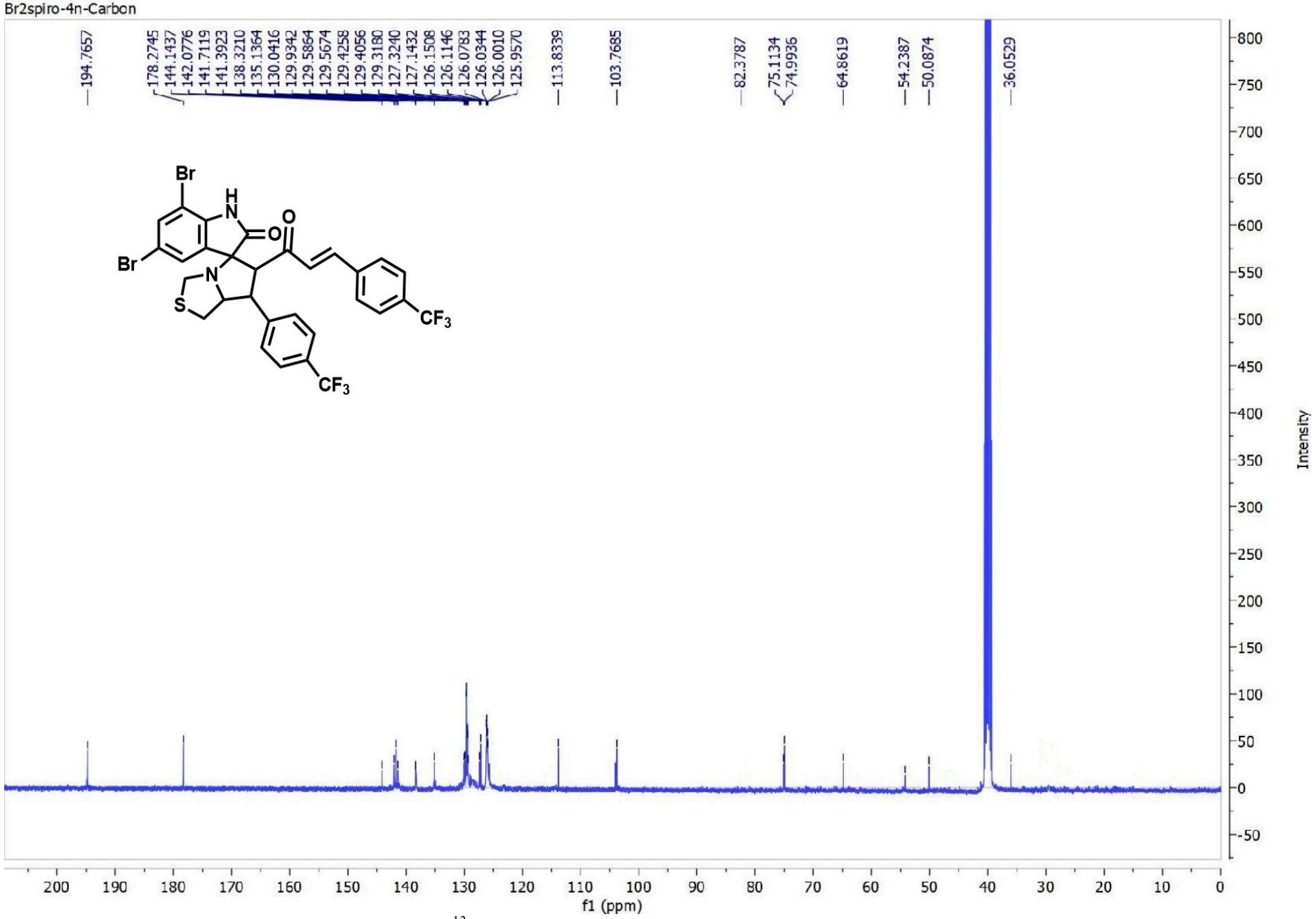

Figure S28. ^{13}C NMR spectrum of compound **5n** (100 MHz, DMSO-d_6)