

Electronic Supplementary Information

A facile approach to the synthesis of structurally diverse 6,8a-dihydropyrido[2,3-d]pyrimidine derivatives via a three-component domino reaction

Yuvaraj Dommaraju,^{a,b} Shruti Bora,^a and Dipak Prajapati^{a,b*}

^aMedicinal Chemistry Division, CSIR-North-East Institute of Science and Technology, Jorhat, Assam
785006, India.

^bAcademy of Scientific and Innovative Research, New Delhi, India

E-mail: dr_dprijapati2003@yahoo.co.uk

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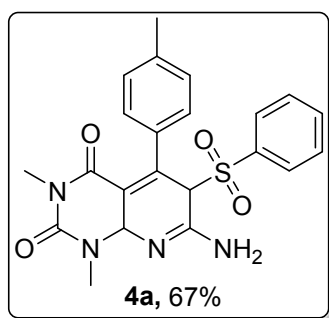
General information

All the commercially available reagents were used as received. Melting points are uncorrected. IR Spectra were recorded on a SHIMADZU FTIR-8400 instrument. NMR spectra were recorded on Avance DPX 300 MHz FT-NMR spectrometer and Avance DPX 500 MHz FT-NMR using tetramethylsilane (TMS) as an internal standard. Mass spectra were recorded on ESQUIRE 3000 Mass spectrometer. All the experiments were monitored by thin layer chromatography (TLC). TLC was performed on pre-coated silica gel plates (Merck). After elution, plate was visualized under UV illumination at 254 nm for UV active materials. Further visualization was achieved by staining KMnO₄ warming in a hot air oven.

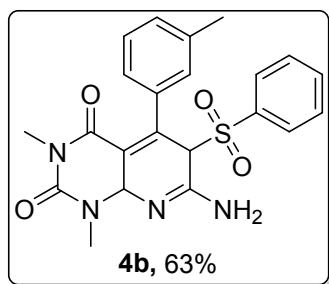
Experimental Data

General procedure for the synthesis of 6,8a-dihydropyrido[2,3-*d*]pyrimidine derivatives (4a-4w): In a 50 mL round bottom flask a mixture of 6-aminouracil **1** (1 mmol), alkylsulfonyl acetonitrile **2** (1 mmol), and aromatic aldehyde **3** (1 mmol), and 8 mL of ethanol was heated under reflux in the presence of 30 mol% of NEt₃ till the completion of the reaction as indicated by TLC. After completion of the reaction, the reaction mixture was cooled to room temperature. The formed solids were collected and washed with a little cold ethanol to give the pure product (**4a-4w**).

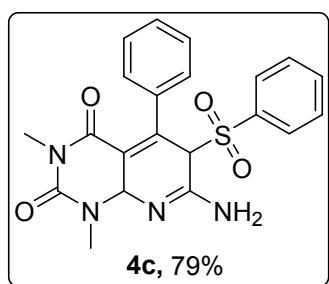
Characterization of the Products



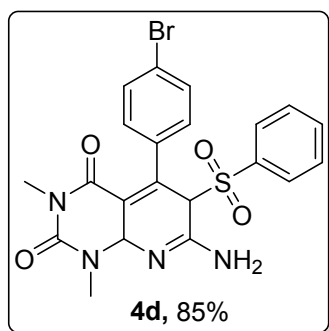
7-amino-1,3-dimethyl-6-(phenylsulfonyl)-5-(*p*-tolyl)-6,8a-dihydropyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (4a): White solid (yield 67%); mp: 281.2-282.2 °C; IR (KBr, ν / cm⁻¹): 3397, 2932, 2816, 2730, 1610, 1507, 1486, 1446, 1385, 1352, 1320, 1281, 1249, 1213, 1174, 1138, 1080, 927, 810, 758, 708; ¹H NMR (300 MHz, DMSO) δ 8.71 (s, 1H), 8.34 (s, 1H), 7.71 – 7.61 (m, 3H), 7.51 (t, $J = 7.7$ Hz, 2H), 7.09 (d, $J = 7.9$ Hz, 2H), 6.92 (d, $J = 7.9$ Hz, 2H), 4.51 (s, 1H), 4.34 (s, 1H), 3.02 (s, 6H), 2.23 (s, 3H); ¹³C NMR (75 MHz, DMSO) δ 161.09, 159.01, 153.42, 151.42, 137.39, 137.10, 136.53, 134.68, 129.92, 129.08, 128.99, 127.06, 88.01, 68.15, 36.35, 29.51, 27.59, 21.00; MS (LCMS, m/z) 439.1 [M]⁺; Anal. Calcd. For C₂₂H₂₂N₄O₄S: C, 60.26; H, 5.06; N, 12.78. Found C, 60.21; H, 5.07; N, 12.79.



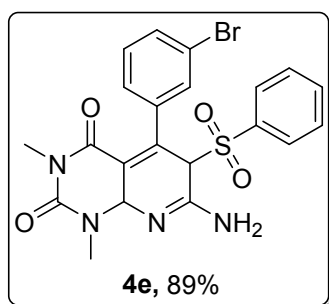
7-amino-1,3-dimethyl-6-(phenylsulfonyl)-5-(*m*-tolyl)-6,8a-dihydropyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (4b): White solid (yield 63%); mp: 284.6-285.6 °C; IR (KBr, ν/cm^{-1}): 3359, 3208, 3090, 2952, 2921, 2759, 2364, 1686, 1662, 1623, 1552, 1473, 1414, 1366, 1322, 1280, 1245, 1201, 1179, 1160, 1138, 1082, 1040, 987, 922, 883, 852, 804, 781, 760; ^1H NMR (300 MHz, DMSO) δ 8.72 (s, 1H), 8.31 (s, 1H), 7.66 (dd, $J = 13.7, 7.3$ Hz, 3H), 7.51 (t, $J = 7.7$ Hz, 2H), 7.17 (t, $J = 7.6$ Hz, 1H), 7.05 (d, $J = 7.5$ Hz, 1H), 6.88 – 6.77 (m, 2H), 4.51 (s, 1H), 4.34 (s, 1H), 3.02 (s, 6H), 2.25 (s, 3H); ^{13}C NMR (75 MHz, DMSO) δ 161.09, 158.99, 153.49, 151.43, 140.45, 138.57, 136.51, 134.70, 129.30, 129.08, 129.01, 128.54, 127.75, 124.21, 87.81, 68.13, 36.68, 29.52, 27.60, 21.48; MS (LCMS, m/z) 439.2 $[\text{M}]^+$; Anal. Calcd. For $\text{C}_{22}\text{H}_{22}\text{N}_4\text{O}_4\text{S}$: C, 60.26; H, 5.06; N, 12.78. Found C, 60.23; H, 5.06; N, 12.76.



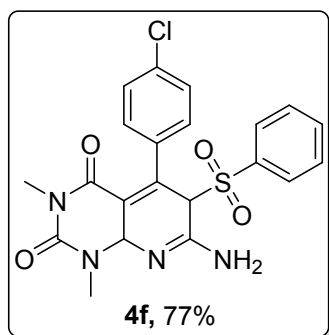
7-amino-1,3-dimethyl-5-phenyl-6-(phenylsulfonyl)-6,8a-dihydropyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (4c): White solid (yield 79%); mp: 306.1-307.1 °C; IR (KBr, ν/cm^{-1}): 3379, 3201, 2931, 1677, 1661, 1633, 1619, 1569, 1477, 1447, 1415, 1393, 1354, 1323, 1310, 1286, 1249, 1212, 1184, 1137, 1082, 1038, 943, 892, 857, 777, 758, 709; ^1H NMR (300 MHz, DMSO) δ 8.75 (s, 1H), 8.36 (s, 1H), 7.66 (d, $J = 7.1$ Hz, 3H), 7.53 (d, $J = 7.4$ Hz, 2H), 7.35 – 7.21 (m, 3H), 7.06 (d, $J = 7.3$ Hz, 2H), 4.57 (s, 1H), 4.39 (s, 1H), 3.04 (s, 6H); ^{13}C NMR (75 MHz, DMSO) δ 161.13, 159.02, 153.53, 151.43, 140.46, 136.52, 134.71, 129.41, 129.11, 129.02, 127.88, 127.20, 87.86, 68.03, 36.73, 29.53, 27.62; MS (LCMS, m/z) 425.1 $[\text{M}]^+$; Anal. Calcd. For $\text{C}_{21}\text{H}_{20}\text{N}_4\text{O}_4\text{S}$: C, 59.42; H, 4.75; N, 13.20; Found C, 59.40; H, 4.76; N, 13.22.



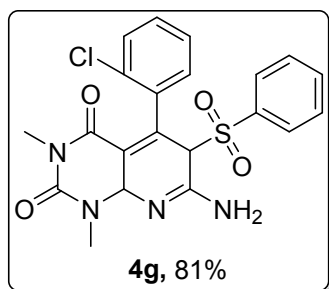
7-amino-5-(4-bromophenyl)-1,3-dimethyl-6-(phenylsulfonyl)-6,8a-dihydropyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (4d): White solid (yield 85%); mp: 282.0-283.0 °C; IR (KBr, ν/cm^{-1}): 3385, 392, 3064, 2921, 1776, 1686, 1659, 1621, 1560, 1484, 1447, 1416, 1367, 1321, 1282, 1247, 1209, 1173, 1139, 1081, 1035, 985, 939, 894, 857, 808, 776, 755, 727; ^1H NMR (300 MHz, DMSO) δ 8.78 (s, 1H), 8.35 (s, 1H), 7.65 (d, $J = 7.9$ Hz, 3H), 7.51 (t, $J = 8.2$ Hz, 4H), 7.01 (d, $J = 8.3$ Hz, 2H), 4.53 (s, 1H), 4.39 (s, 1H), 3.02 (s, 3H), 3.01 (s, 3H); ^{13}C NMR (75 MHz, DMSO) δ 161.08, 158.91, 153.60, 151.39, 139.75, 136.39, 134.78, 132.31, 129.51, 129.11, 129.04, 121.04, 87.38, 67.67, 36.29, 29.53, 27.62; MS (LCMS, m/z) 504.3 [M]⁺; Anal. Calcd. For C₂₁H₁₉BrN₄O₄S: C, 50.11; H, 3.80; N, 11.13. Found C, 50.09; H, 3.81; N, 11.12.



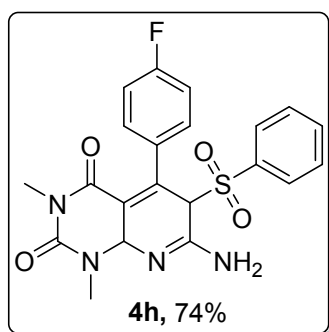
7-amino-5-(3-bromophenyl)-1,3-dimethyl-6-(phenylsulfonyl)-6,8a-dihydropyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (4e): White solid (yield 89%); mp: 272.1-273.1 °C; IR (KBr, ν/cm^{-1}): 3398, 3328, 3288, 3234, 3050, 2937, 1679, 1660, 1619, 1555, 1475, 1442, 1393, 1362, 1322, 1278, 1234, 1173, 1146, 1082, 1030, 998, 936, 889, 782, 772, 758, 735; ^1H NMR (300 MHz, DMSO) δ 8.82 (s, 1H), 8.33 (s, 1H), 7.73 – 7.60 (m, 3H), 7.56 – 7.43 (m, 3H), 7.28 (t, $J = 7.8$ Hz, 1H), 7.19 (s, 1H), 7.08 (d, $J = 7.7$ Hz, 1H), 4.55 (s, 1H), 4.43 (s, 1H), 3.03 (s, 3H), 3.01 (s, 3H); ^{13}C NMR (75 MHz, DMSO) δ 161.11, 158.96, 153.69, 151.40, 143.18, 136.40, 134.79, 131.68, 130.92, 129.80, 129.12, 129.07, 126.45, 122.58, 87.21, 67.57, 36.49, 29.56, 27.64; MS (LCMS, m/z) 504.3 [M]⁺; Anal. Calcd. For C₂₁H₁₉BrN₄O₄S: C, 50.11; H, 3.80; N, 11.13. Found C, 50.10; H, 3.82; N, 11.11.



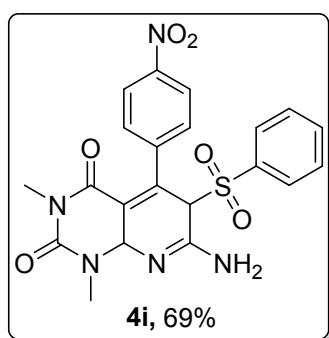
7-amino-5-(4-chlorophenyl)-1,3-dimethyl-6-(phenylsulfonyl)-6,8a-dihydropyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (4f): White solid (yield 77%); mp: 290.8-291.8 °C; IR (KBr, ν/cm^{-1}): 3638, 3534, 3454, 3374, 3227, 2931, 1682, 1668, 1615, 1555, 1486, 1447, 1422, 1396, 1352, 1325, 1280, 1251, 1214, 1174, 1140, 1081, 1035, 1016, 899, 863, 840, 779, 757, 730; ^1H NMR (300 MHz, DMSO) δ 8.78 (s, 1H), 8.35 (s, 1H), 7.65 (d, $J = 7.9$ Hz, 3H), 7.51 (t, $J = 7.7$ Hz, 2H), 7.36 (d, $J = 8.4$ Hz, 2H), 7.07 (d, $J = 8.4$ Hz, 2H), 4.55 (s, 1H), 4.39 (s, 1H), 3.02 (s, 3H), 3.01 (s, 3H); ^{13}C NMR (75 MHz, DMSO) δ 161.09, 158.93, 153.59, 151.40, 139.32, 136.40, 134.77, 132.55, 129.38, 129.15, 129.11, 129.04, 87.45, 67.73, 36.21, 29.53, 27.62; MS (LCMS, m/z) 460.1 [M]⁺; Anal. Calcd. For $\text{C}_{21}\text{H}_{19}\text{ClN}_4\text{O}_4\text{S}$: C, 54.96; H, 4.17; N, 12.21. Found C, 54.98; H, 4.16; N, 12.19.



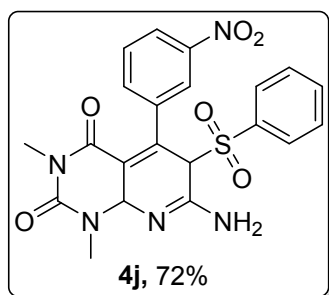
7-amino-5-(2-chlorophenyl)-1,3-dimethyl-6-(phenylsulfonyl)-6,8a-dihydropyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (4g): White solid (yield 81%); mp: 288.5-289.5 °C; IR (KBr, ν/cm^{-1}): 3399, 3356, 3231, 2948, 2810, 1632, 1595, 1499, 1450, 1384, 1352, 1302, 1213, 1078, 1005, 789, 761; ^1H NMR (300 MHz, DMSO) δ 8.71 (s, 1H), 8.33 (s, 1H), 7.72 – 7.65 (m, 3H), 7.56 – 7.49 (m, 3H), 7.29 (t, $J = 7.5$ Hz, 1H), 7.19 (t, $J = 7.4$ Hz, 1H), 6.79 (d, $J = 7.6$ Hz, 1H), 4.97 (s, 1H), 4.36 (s, 1H), 3.04 (s, 6H); ^1H NMR (300 MHz, DMSO + 2 drops D_2O (Deuterium exchange)) δ 7.72 – 7.65 (m, 3H), 7.56 – 7.49 (m, 3H), 7.29 (t, $J = 7.3$ Hz, 1H), 7.18 (t, $J = 7.1$ Hz, 1H), 6.77 (d, $J = 7.4$ Hz, 1H), 4.97 (s, 1H), 4.37 (s, 1H), 3.04 (s, 6H); ^{13}C NMR (75 MHz, DMSO) δ 160.93, 159.02, 154.65, 151.53, 136.75, 136.34, 134.77, 132.83, 130.48, 129.89, 129.26, 129.09, 129.06, 128.13, 86.78, 66.00, 34.05, 29.61, 27.64; MS (LCMS, m/z) 460.1 [M]⁺; Anal. Calcd. For $\text{C}_{21}\text{H}_{19}\text{ClN}_4\text{O}_4\text{S}$: C, 54.96; H, 4.17; N, 12.21. Found C, 54.94; H, 4.18; N, 12.17.



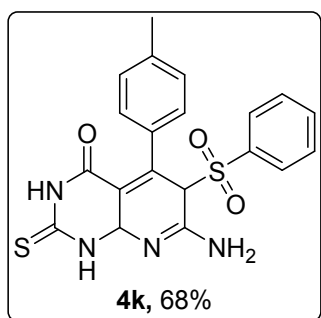
7-amino-5-(4-fluorophenyl)-1,3-dimethyl-6-(phenylsulfonyl)-6,8a-dihydropyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (4h): White solid (yield 74%); mp: 304.5-305.5 °C; IR (KBr, ν/cm^{-1}): 3375, 3202, 2936, 1678, 1662, 1633, 1573, 1509, 1486, 1457, 1447, 1417, 1385, 1351, 1325, 1307, 1289, 1250, 1228, 1212, 1178, 1161, 1139, 1081, 1035, 932, 895, 861, 837, 804, 789, 758; ^1H NMR (300 MHz, DMSO) δ 8.76 (s, 1H), 8.35 (s, 1H), 7.65 (d, $J = 7.7$ Hz, 3H), 7.51 (t, $J = 7.7$ Hz, 2H), 7.16 – 7.06 (m, 4H), 4.56 (s, 1H), 4.39 (s, 1H), 3.03 (s, 3H), 3.02 (s, 3H); ^{13}C NMR (75 MHz, DMSO) δ 161.11, 158.96, 153.51, 151.42, 136.48, 134.73, 129.27, 129.16, 129.10, 129.02, 116.30, 116.02, 87.83, 67.96, 36.06, 29.51, 27.60; MS (LCMS, m/z) 443.1 [M]⁺; Anal. Calcd. For C₂₁H₁₉FN₄O₄S: C, 57.01; H, 4.33; N, 12.66. Found C, 56.95; H, 4.36; N, 12.64.



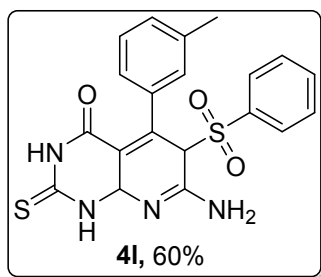
7-amino-5-(4-nitrophenyl)-1,3-dimethyl-6-(phenylsulfonyl)-6,8a-dihydropyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (4i): Yellow solid (yield 69%); mp: 277.7-278.7 °C; IR (KBr, ν/cm^{-1}): 3466, 3376, 3218, 2933, 2805, 1682, 1607, 1558, 1526, 1486, 1447, 1385, 1352, 1279, 1250, 1219, 1170, 1139, 1079, 1030, 895, 861, 843, 775, 753, 728; ^1H NMR (300 MHz, DMSO) δ 8.85 (s, 1H), 8.37 (s, 1H), 8.17 (d, $J = 8.7$ Hz, 2H), 7.67 (d, $J = 7.9$ Hz, 3H), 7.53 (t, $J = 7.7$ Hz, 2H), 7.35 (d, $J = 8.6$ Hz, 2H), 4.68 (s, 1H), 4.49 (s, 1H), 3.03 (s, 3H), 3.02 (s, 3H); ^{13}C NMR (75 MHz, DMSO) δ 161.09, 158.89, 153.81, 151.39, 147.87, 147.35, 136.30, 134.87, 129.15, 129.09, 128.75, 124.62, 86.83, 67.19, 36.74, 29.54, 27.62; MS (LCMS, m/z) 470.1 [M]⁺; Anal. Calcd. For C₂₁H₁₉N₅O₆S: C, 53.73; H, 4.08; N, 14.92. Found C, 53.70; H, 4.07; N, 14.95.



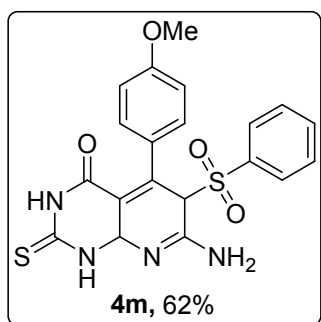
7-amino-5-(3-nitrophenyl)-1,3-dimethyl-6-(phenylsulfonyl)-6,8a-dihydropyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (4j): Yellow solid (yield 72%); mp: 281.4-282.4 °C; IR (KBr, ν/cm^{-1}): 3376, 3328, 3182, 2931, 1683, 1664, 1622, 1558, 1539, 1488, 1413, 1347, 1326, 1285, 1248, 1216, 1177, 1149, 1139, 1081, 1033, 990, 948, 918, 899, 854, 819, 781, 756, 727; ^1H NMR (300 MHz, DMSO) δ 8.90 (s, 1H), 8.35 (s, 1H), 8.13 (d, $J = 7.8$ Hz, 1H), 7.85 (s, 1H), 7.72 – 7.50 (m, 7H), 4.70 (s, 1H), 4.55 (s, 1H), 3.03 (s, 3H), 3.02 (s, 3H); ^{13}C NMR (75 MHz, DMSO) δ 161.12, 158.98, 153.81, 151.38, 148.58, 142.58, 136.35, 134.87, 134.19, 131.14, 129.11, 123.09, 121.78, 86.95, 67.19, 36.49, 29.56, 27.64; MS (LCMS, m/z) 470.1 [M] $^+$; Anal. Calcd. For $\text{C}_{21}\text{H}_{19}\text{N}_5\text{O}_6\text{S}$: C, 53.73; H, 4.08; N, 14.92. Found C, 53.71; H, 4.08; N, 14.91.



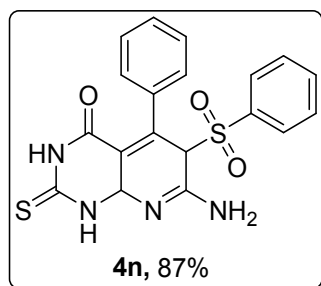
7-amino-6-(phenylsulfonyl)-2-thioxo-5-(*p*-tolyl)-2,3,6,8a-tetrahydropyrido[2,3-*d*]pyrimidin-4(1*H*)-one (4k): Pale yellow solid (yield 68%); mp: 306.1-307.1 °C; IR (KBr, ν/cm^{-1}): 3375, 3207, 2937, 2815, 1678, 1662, 1632, 1574, 1509, 1485, 1458, 1415, 1385, 1352, 1325, 1289, 1251, 1228, 1213, 1178, 1161, 1139, 1100, 1082, 1036, 932, 895, 861, 805, 789, 758, 723; ^1H NMR (300 MHz, DMSO) δ 11.94 (s, 1H), 11.75 (s, 1H), 8.65 (s, 1H), 8.15 (s, 1H), 7.83 – 7.71 (m, 3H), 7.59 (t, $J = 7.6$ Hz, 2H), 7.09 (d, $J = 7.7$ Hz, 2H), 6.83 (d, $J = 7.8$ Hz, 2H), 4.33 (s, 1H), 4.31 (s, 1H), 2.22 (s, 3H); ^{13}C NMR (75 MHz, DMSO) δ 174.71, 160.80, 159.15, 154.85, 137.27, 137.02, 136.38, 134.96, 130.03, 129.63, 129.04, 126.88, 92.26, 67.61, 35.06, 21.01; MS (LCMS, m/z) 427.1 [M] $^+$; Anal. Calcd. For $\text{C}_{20}\text{H}_{18}\text{N}_4\text{O}_3\text{S}_2$: C, 56.32; H, 4.25; N, 13.14. Found C, 56.30; H, 4.26; N, 13.11.



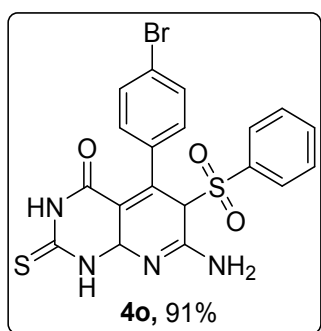
7-amino-6-(phenylsulfonyl)-2-thioxo-5-(*m*-tolyl)-2,3,6,8a-tetrahydropyrido[2,3-*d*]pyrimidin-4(1*H*)-one (4l): Pale yellow solid (yield 60%); mp: 316.2-317.2 °C; IR (KBr, ν/cm^{-1}): 3437, 3313, 3109, 2919, 1641, 1606, 1574, 1524, 1445, 1343, 1306, 1272, 1242, 1221, 1196, 1145, 1080, 998, 967, 851, 809, 776, 748; ^1H NMR (300 MHz, DMSO) δ 11.95 (s, 1H), 11.75 (s, 1H), 8.67 (s, 1H), 8.14 (s, 1H), 7.78 (dd, $J = 12.5, 7.4$ Hz, 3H), 7.60 (t, $J = 7.6$ Hz, 2H), 7.17 (t, $J = 7.5$ Hz, 1H), 7.05 (d, $J = 7.4$ Hz, 1H), 6.80 – 6.70 (m, 2H), 4.36 (s, 1H), 4.33 (s, 1H), 2.23 (s, 3H); ^{13}C NMR (75 MHz, DMSO) δ 174.74, 160.83, 159.19, 154.95, 140.08, 138.71, 136.36, 134.97, 129.64, 129.44, 129.07, 128.70, 127.52, 124.05, 92.12, 67.60, 35.39, 21.49; MS (LCMS, m/z) 427.1 [M]⁺; Anal. Calcd. For $\text{C}_{20}\text{H}_{18}\text{N}_4\text{O}_3\text{S}_2$: C, 56.32; H, 4.25; N, 13.14. Found C, 56.29; H, 4.25; N, 13.13.



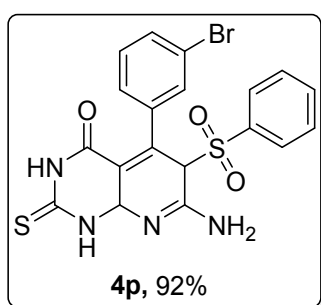
7-amino-5-(4-methoxyphenyl)-6-(phenylsulfonyl)-2-thioxo-2,3,6,8a-tetrahydropyrido[2,3-*d*]pyrimidin-4(1*H*)-one (4m): Pale yellow solid (yield 62%); mp: 304.3-305.3 °C; IR (KBr, ν/cm^{-1}): 3305, 3196, 3125, 2918, 2346, 1962, 1909, 1668, 1648, 1607, 1568, 1547, 1513, 1459, 1445, 1413, 1330, 1270, 1242, 1199, 1178, 1140, 1082, 1045, 1012, 971, 916, 875, 847, 820, 789, 743, 721; ^1H NMR (300 MHz, DMSO) δ 11.92 (s, 1H), 11.75 (s, 1H), 8.67 (s, 1H), 8.18 (s, 1H), 7.88 – 7.71 (m, 3H), 7.59 (t, $J = 7.6$ Hz, 2H), 6.86 (s, 4H), 4.34 (s, 1H), 4.31 (s, 1H), 3.68 (s, 3H); MS (LCMS, m/z) 443.1 [M]⁺; Anal. Calcd. For $\text{C}_{20}\text{H}_{18}\text{N}_4\text{O}_4\text{S}_2$: C, 54.29; H, 4.10; N, 12.66. Found C, 54.27; H, 4.12; N, 12.68.



7-amino-5-phenyl-6-(phenylsulfonyl)-2-thioxo-2,3,6,8a-tetrahydropyrido[2,3-*d*]pyrimidin-4(1*H*)-one (4n): Pale yellow solid (yield 87%); mp: 323.1-324.1 °C; IR (KBr, ν/cm^{-1}): 3396, 3091, 2933, 1641, 1607, 1577, 1524, 1465, 1445, 1347, 1302, 1225, 1186, 1151, 1080, 972, 872, 833, 797, 753, 700; ^1H NMR (300 MHz, DMSO) δ 11.97 (s, 1H), 11.77 (s, 1H), 8.68 (s, 1H), 8.17 (s, 1H), 7.79 (t, $J = 8.1$ Hz, 3H), 7.60 (t, $J = 7.6$ Hz, 2H), 7.28 (dd, $J = 16.1, 8.8$ Hz, 3H), 6.96 (d, $J = 7.5$ Hz, 2H), 4.39 (s, 1H), 4.37 (s, 1H); ^{13}C NMR (75 MHz, DMSO) δ 174.77, 160.84, 159.17, 154.96, 140.07, 136.35, 135.01, 129.67, 129.54, 129.07, 128.04, 127.00, 92.12, 67.47, 35.44; MS (LCMS, m/z) 413.1 $[\text{M}]^+$; Anal. Calcd. For $\text{C}_{19}\text{H}_{16}\text{N}_4\text{O}_3\text{S}_2$: C, 55.33; H, 3.91; N, 13.58. Found C, 55.31; H, 3.93; N, 13.57.

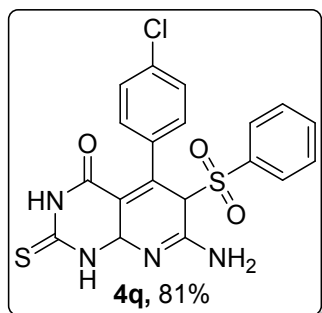


7-amino-5-(4-bromophenyl)-6-(phenylsulfonyl)-2-thioxo-2,3,6,8a-tetrahydropyrido[2,3-*d*]pyrimidin-4(1*H*)-one (4o): Pale yellow solid (yield 91%); mp: 303.8-304.8 °C; IR (KBr, ν/cm^{-1}): 3402, 3310, 3099, 2919, 2857, 2374, 2365, 2338, 1641, 1612, 1557, 1538, 1520, 1485, 1461, 1443, 1345, 1305, 1218, 1196, 1158, 1139, 1075, 1009, 974, 869, 834, 810, 777, 751, 705; ^1H NMR (300 MHz, DMSO) δ 11.94 (s, 1H), 11.75 (s, 1H), 8.68 (s, 1H), 8.14 (s, 1H), 7.78 (dd, $J = 15.3, 7.4$ Hz, 3H), 7.59 (t, $J = 7.7$ Hz, 2H), 7.50 (d, $J = 8.3$ Hz, 2H), 6.93 (d, $J = 8.3$ Hz, 2H), 4.38 (s, 1H), 4.35 (s, 1H); MS (LCMS, m/z) 492.0 $[\text{M}]^+$; Anal. Calcd. For $\text{C}_{19}\text{H}_{15}\text{BrN}_4\text{O}_3\text{S}_2$: C, 46.44; H, 3.08; N, 11.40. Found C, 46.41; H, 3.11; N, 11.42.

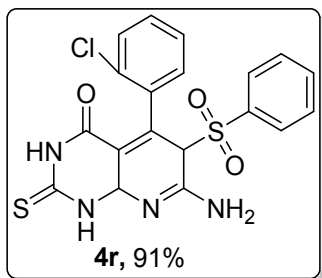


7-amino-5-(3-bromophenyl)-6-(phenylsulfonyl)-2-thioxo-2,3,6,8a-tetrahydropyrido[2,3-*d*]pyrimidin-4(1*H*)-one (4p): Pale yellow solid (yield 92%); mp: 301.7-302.7 °C; IR (KBr, ν/cm^{-1}): 3411, 3305, 3178, 3102, 2917, 1638, 1604, 1570, 1521, 1444, 1340, 1306, 1271, 1223, 1142, 1188, 1079, 997, 964, 882, 859, 834, 805, 772, 752; ^1H NMR (300 MHz, DMSO) δ 11.99 (s, 1H), 11.81 (s, 1H), 8.75 (s, 1H), 8.15 (s, 1H), 7.78 (dd, $J = 13.7, 7.4$ Hz, 3H), 7.60 (t, $J = 7.5$ Hz, 2H), 7.47 (d, $J = 7.7$ Hz, 1H), 7.28 (t, $J = 7.8$ Hz, 1H), 7.10 (s, 1H), 6.99 (d, $J = 7.5$ Hz, 1H), 4.44 (s, 1H), 4.37 (s, 1H); ^{13}C NMR (75 MHz, DMSO) δ 174.90, 160.79, 159.20, 155.06, 142.72, 136.26, 135.06, 131.81, 131.05, 129.67, 129.10, 126.20, 122.64, 91.49, 67.02.

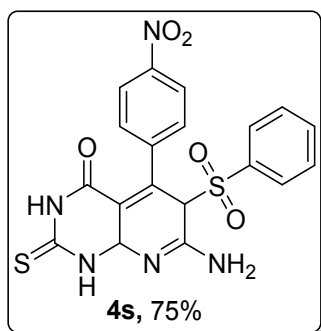
35.13; MS (LCMS, m/z) 492.0 $[M]^+$; Anal. Calcd. For $C_{19}H_{15}BrN_4O_3S_2$: C, 46.44; H, 3.08; N, 11.40. Found C, 46.43; H, 3.10; N, 11.41.



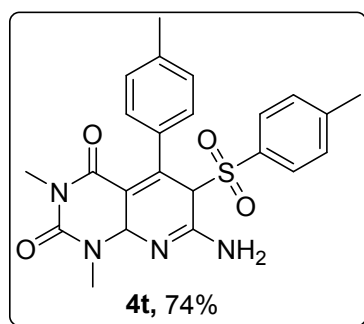
7-amino-5-(4-chlorophenyl)-6-(phenylsulfonyl)-2-thioxo-2,3,6,8a-tetrahydropyrido[2,3-*d*]pyrimidin-4(1*H*)-one (4p): Pale yellow solid (yield 81%); mp: 305.3-306.3 °C; IR (KBr, ν / cm^{-1}): 3401, 3305, 3114, 2916, 1639, 1610, 1561, 1538, 1519, 1492, 1462, 1446, 1347, 1306, 1276, 1227, 1201, 1150, 1140, 1094, 1081, 1014, 975, 872, 847, 818, 752; 1H NMR (300 MHz, DMSO) δ 11.98 (s, 1H), 11.79 (s, 1H), 8.72 (s, 1H), 8.17 (s, 1H), 7.78 (dd, $J = 9.9, 8.3$ Hz, 3H), 7.59 (t, $J = 7.7$ Hz, 2H), 7.37 (d, $J = 8.3$ Hz, 2H), 7.00 (d, $J = 6.9$ Hz, 2H), 4.40 (s, 1H), 4.38 (s, 1H); ^{13}C NMR (75 MHz, DMSO) δ 174.85, 160.80, 159.16, 154.99, 138.92, 136.25, 135.03, 132.70, 129.66, 129.51, 129.07, 128.98, 91.74, 67.23, 34.92; MS (LCMS, m/z) 448.0 $[M]^+$; Anal. Calcd. For $C_{19}H_{15}ClN_4O_3S_2$: C, 51.06; H, 3.38; N, 12.54. Found C, 51.01; H, 3.39; N, 12.56.



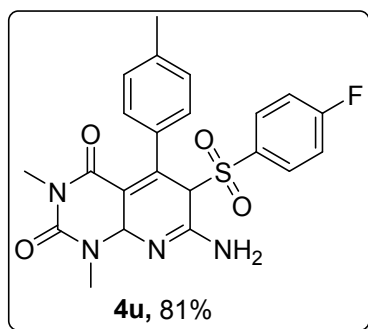
7-amino-5-(2-chlorophenyl)-6-(phenylsulfonyl)-2-thioxo-2,3,6,8a-tetrahydropyrido[2,3-*d*]pyrimidin-4(1*H*)-one (4q): Pale yellow solid (yield 91%); mp: 246.5-247.5 °C; IR (KBr, ν / cm^{-1}): 3437, 3301, 3059, 2943, 2345, 1967, 1897, 1644, 1614, 1570, 1527, 1467, 1445, 1363, 1322, 1274, 1253, 1200, 1182, 1142, 1077, 1050, 1038, 997, 975, 927, 887, 815, 798, 775, 757, 721; 1H NMR (300 MHz, DMSO) δ 12.07 (s, 1H), 11.84 (s, 1H), 8.63 (s, 1H), 8.14 (s, 1H), 7.79 (d, $J = 7.5$ Hz, 3H), 7.63 (t, $J = 7.5$ Hz, 2H), 7.45 (d, $J = 7.4$ Hz, 1H), 7.34 – 7.19 (m, 2H), 6.79 (d, $J = 7.1$ Hz, 1H), 4.77 (s, 1H), 4.35 (s, 1H); MS (LCMS, m/z) 448.0 $[M]^+$; Anal. Calcd. For $C_{19}H_{15}ClN_4O_3S_2$: C, 51.06; H, 3.38; N, 12.54. Found C, 51.07; H, 3.38; N, 12.54.



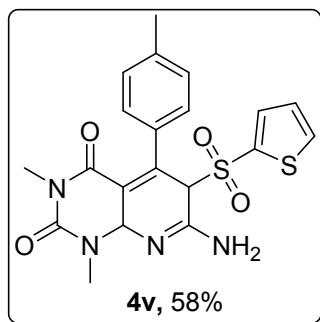
7-amino-5-(4-nitrophenyl)-6-(phenylsulfonyl)-2-thioxo-2,3,6,8a-tetrahydropyrido[2,3-*d*]pyrimidin-4(1*H*)-one (4s): Yellow solid (yield 75%); mp: 289.2-290.2 °C; IR (KBr, ν/cm^{-1}): 3597, 3526, 3190, 3043, 2925, 2852, 1635, 1606, 1575, 1519, 1459, 1445, 1415, 1352, 1321, 1306, 1228, 1158, 1141, 1084, 979, 892, 857, 750; ^1H NMR (300 MHz, DMSO) δ 12.02 (s, 1H), 11.83 (s, 1H), 8.78 (s, 1H), 8.19 (s, 2H), 8.16 (s, 1H), 7.79 (dd, $J = 12.8, 7.2$ Hz, 3H), 7.60 (t, $J = 7.2$ Hz, 2H), 7.28 (d, $J = 7.8$ Hz, 2H), 4.52 (s, 1H), 4.49 (s, 1H); ^{13}C NMR (75 MHz, DMSO) δ 175.00, 160.76, 159.10, 155.17, 147.42, 136.14, 135.13, 129.70, 129.10, 128.63, 124.76, 91.03, 66.72, 35.40; MS (LCMS, m/z) 458.1 $[\text{M}]^+$; Anal. Calcd. For $\text{C}_{19}\text{H}_{15}\text{N}_5\text{O}_5\text{S}_2$: C, 49.88; H, 3.31; N, 15.31. Found C, 49.90; H, 3.32; N, 15.29.



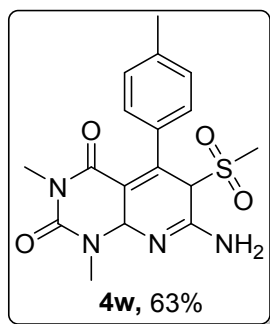
7-amino-2-thioxo-5-(*p*-tolyl)-6-tosyl-2,3,6,8a-tetrahydropyrido[2,3-*d*]pyrimidin-4(1*H*)-one (4t): White solid (yield 74%); mp: 317.0-318.0 °C; IR (KBr, ν/cm^{-1}): 3377, 3323, 3178, 3029, 2936, 2760, 2366, 1929, 1683, 1662, 1627, 1595, 1560, 1463, 1414, 1367, 1341, 1320, 1284, 1248, 1218, 1207, 1179, 1134, 1082, 1033, 956, 946, 898, 860, 817, 809, 782, 761, 725; ^1H NMR (500 MHz, DMSO) δ 8.66 (s, 1H), 8.31 (s, 1H), 7.50 (d, $J = 8.2$ Hz, 2H), 7.32 (d, $J = 8.1$ Hz, 2H), 7.09 (d, $J = 8.0$ Hz, 2H), 6.90 (d, $J = 8.0$ Hz, 2H), 4.45 (s, 1H), 4.26 (s, 1H), 3.04 (s, 3H), 3.03 (s, 3H), 2.32 (s, 3H), 2.23 (s, 3H); ^{13}C NMR (126 MHz, DMSO) δ 161.01, 158.99, 153.24, 151.44, 145.97, 137.34, 136.96, 133.28, 129.79, 129.24, 128.92, 126.92, 87.83, 67.91, 36.25, 29.34, 27.50, 21.40, 20.88; MS (LCMS, m/z) 441.1 $[\text{M}]^+$; Anal. Calcd. For $\text{C}_{21}\text{H}_{20}\text{N}_4\text{O}_3\text{S}_2$: C, 57.26; H, 4.58; N, 12.72. Found C, 57.28; H, 4.59; N, 12.74.



7-amino-6-((4-fluorophenyl)sulfonyl)-2-thioxo-5-(*p*-tolyl)-2,3,6,8a-tetrahydropyrido[2,3-*d*]pyrimidin-4(1*H*)-one (4u): White solid (yield 81%); mp: 292.0-293.0 °C; IR (KBr, ν/cm^{-1}): 3517, 3374, 3201, 3101, 2979, 2931, 2419, 2297, 1682, 1666, 1618, 1588, 1556, 1475, 1422, 1401, 1367, 1328, 1280, 1244, 1211, 1172, 1158, 1138, 1083, 1057, 982, 951, 898, 860, 844, 797, 762, 746, 727; ^1H NMR (500 MHz, DMSO) δ 8.74 (s, 1H), 8.35 (s, 1H), 7.70 (dd, $J = 8.2, 5.0$ Hz, 2H), 7.39 (t, $J = 8.4$ Hz, 2H), 7.09 (d, $J = 7.6$ Hz, 2H), 6.92 (d, $J = 7.8$ Hz, 2H), 4.48 (s, 1H), 4.34 (s, 1H), 3.08 (s, 3H), 3.04 (s, 3H), 2.23 (s, 3H); ^{13}C NMR (126 MHz, DMSO) δ 167.01, 164.99, 160.95, 158.89, 153.34, 151.37, 137.07, 132.73, 132.23, 132.15, 129.82, 126.94, 116.33, 116.15, 87.76, 67.90, 56.39, 36.19, 29.42, 27.52, 20.87, 18.85; MS (LCMS, m/z) 445.1 [M]⁺; Anal. Calcd. For C₂₀H₁₇FN₄O₃S₂: C, 54.04; H, 3.86; N, 12.60. Found C, 54.02; H, 3.85; N, 12.61.



7-amino-1,3-dimethyl-6-(thiophen-2-ylsulfonyl)-5-(*p*-tolyl)-6,8a-dihydropyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (4v): White solid (yield 58%); mp: 276.3-277.3 °C; IR (KBrKBr, ν/cm^{-1}): 3485, 3372, 3344, 3221, 3097, 2942, 2923, 2414, 2366, 2348, 1910, 1684, 1659, 1549, 1474, 1414, 1397, 1365, 1342, 1283, 1242, 1216, 1175, 1133, 1077, 1018, 983, 934, 891, 853, 798, 760, 748, 727; ^1H NMR (500 MHz, DMSO) δ 8.71 (s, 1H), 8.28 (s, 1H), 8.09 (dd, $J = 5.1, 3.9$ Hz, 1H), 7.54 (d, $J = 3.8$ Hz, 1H), 7.16 (d, $J = 4.9$ Hz, 1H), 7.10 (t, $J = 7.1$ Hz, 2H), 6.91 (dd, $J = 7.0, 3.5$ Hz, 2H), 4.48 (s, 1H), 4.38 (s, 1H), 3.19 (s, 3H), 3.04 (s, 3H), 2.23 (s, 3H); ^{13}C NMR (126 MHz, DMSO) δ 161.00, 158.43, 153.47, 151.58, 137.36, 137.29, 137.03, 136.44, 136.37, 129.84, 128.31, 126.93, 87.68, 68.46, 56.39, 36.52, 29.53, 27.53, 20.88, 18.86; MS (LCMS, m/z) 445.1 [M]⁺; Anal. Calcd. For C₂₀H₂₀N₄O₄S₂: C, 54.04; H, 4.54; N, 12.60. Found C, 54.02; H, 4.55; N, 12.64.



7-amino-1,3-dimethyl-6-(methylsulfonyl)-5-(*p*-tolyl)-6,8a-dihydropyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (4w): White solid (yield 63%); mp: 289.2-290.2 °C; IR (KBr, ν/cm^{-1}): 3414, 3341, 3320, 3188, 3031, 3005, 2976, 2961, 2924, 2750, 2357, 2346, 1903, 1698, 1655, 1618, 1544, 1511, 1482, 1416, 1364, 1316, 1279, 1244, 1207, 1170, 1140, 1102, 1082, 1055, 1025, 985, 963, 954, 888, 856, 799, 770, 757, 728; ^1H NMR (500 MHz, DMSO) δ 8.66 (s, 1H), 8.19 (s, 1H), 7.12 (d, $J = 7.9$ Hz, 2H), 7.02 (d, $J = 8.0$ Hz, 2H), 4.64 (s, 1H), 4.20 (s, 1H), 3.48 (s, 3H), 3.13 (s, 3H), 3.10 (s, 3H), 2.25 (s, 3H); ^{13}C NMR (126 MHz, DMSO) δ 161.09, 158.99, 154.23, 152.04, 137.61, 136.91, 129.73, 127.09, 88.15, 65.42, 40.93, 34.64, 29.82, 27.72, 20.90; MS (LCMS, m/z) 377.1 $[\text{M}]^+$; Anal. Calcd. For $\text{C}_{26}\text{H}_{23}\text{NO}_4$: C, 54.24; H, 5.36; N, 14.88. Found C, 54.26; H, 5.35; N, 14.86.

NMR Spectra of the Products

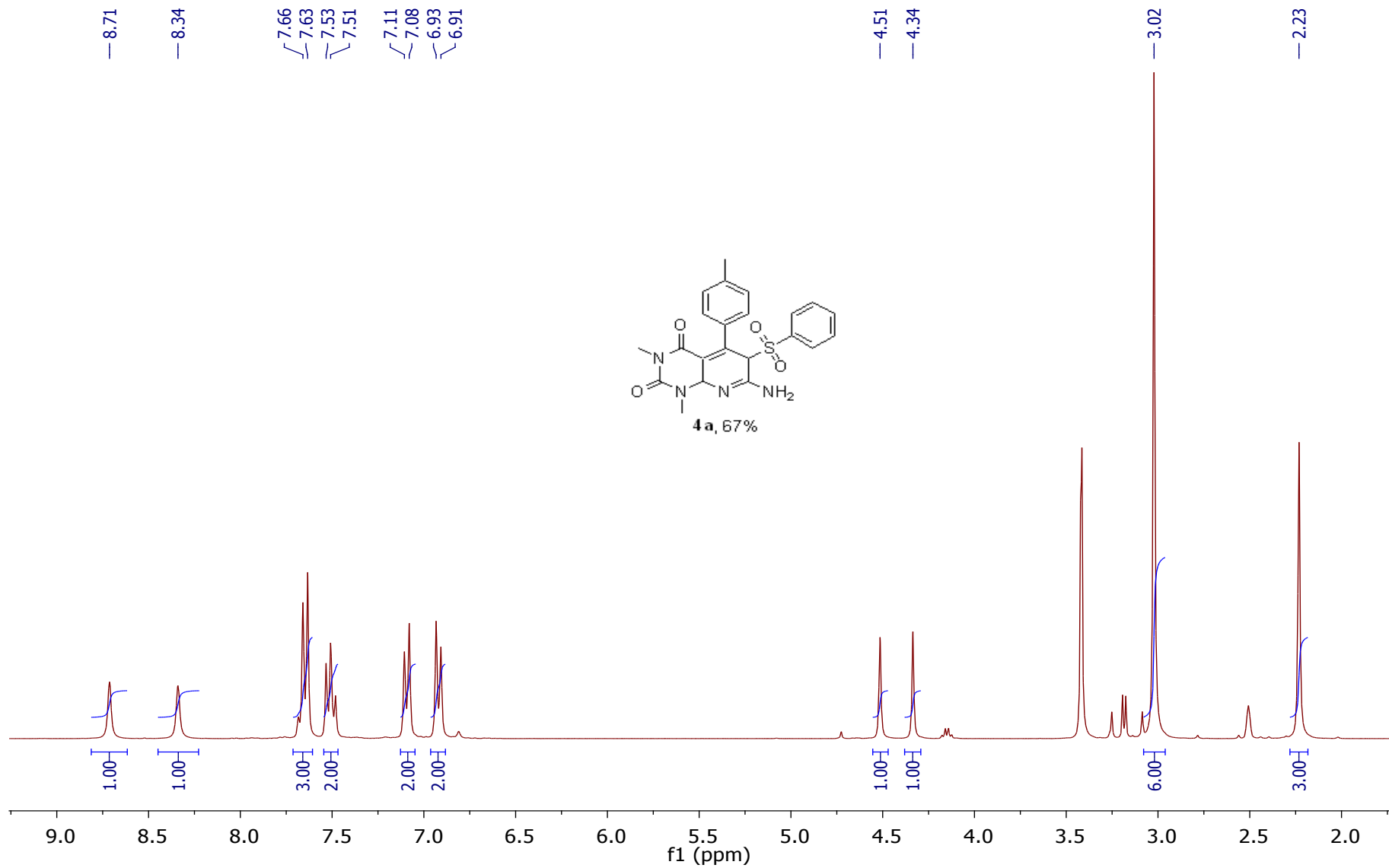


Fig S-1: ¹H NMR Spectrum of Product **4a**

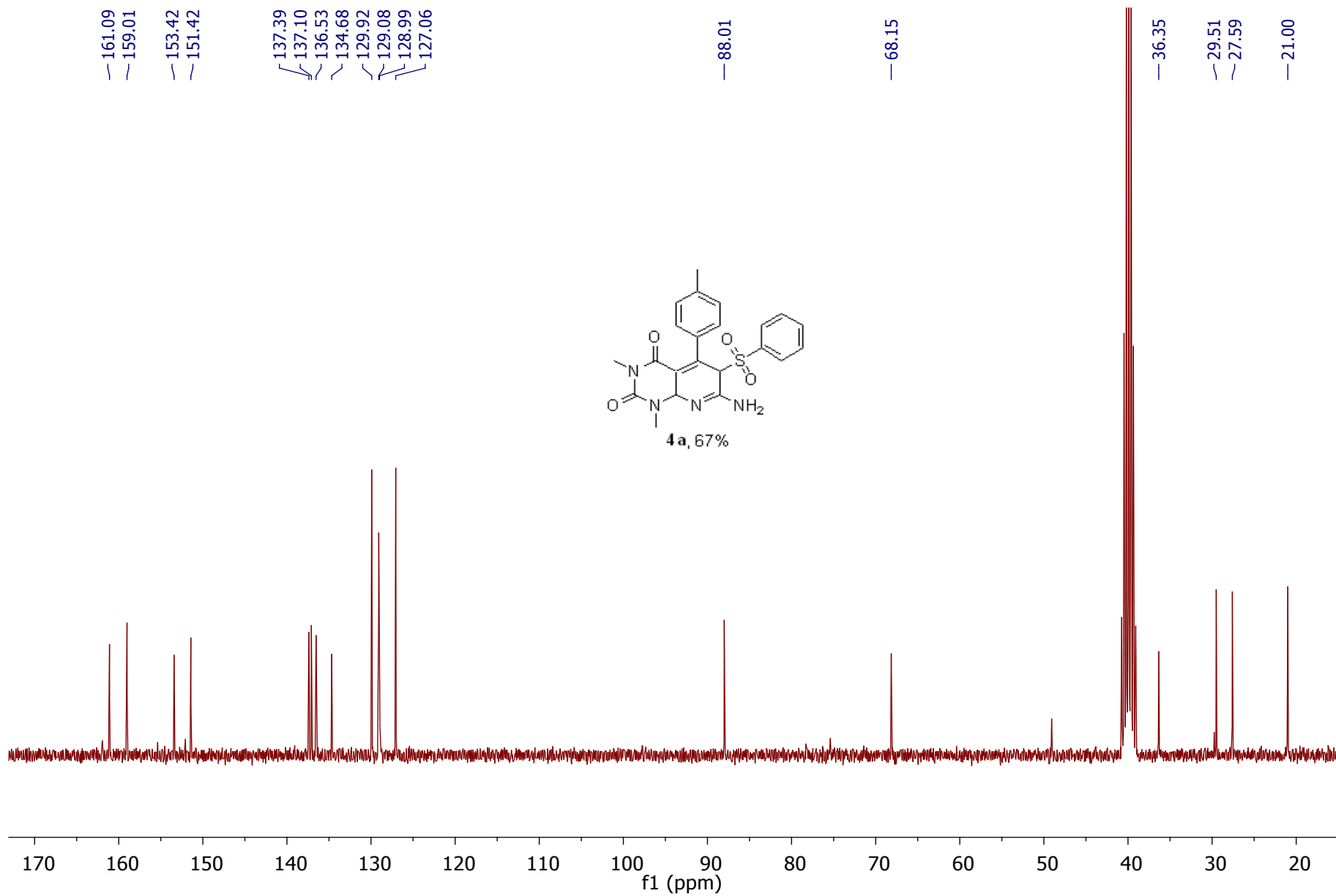


Fig S-2: ¹³C NMR Spectrum of Product 4a

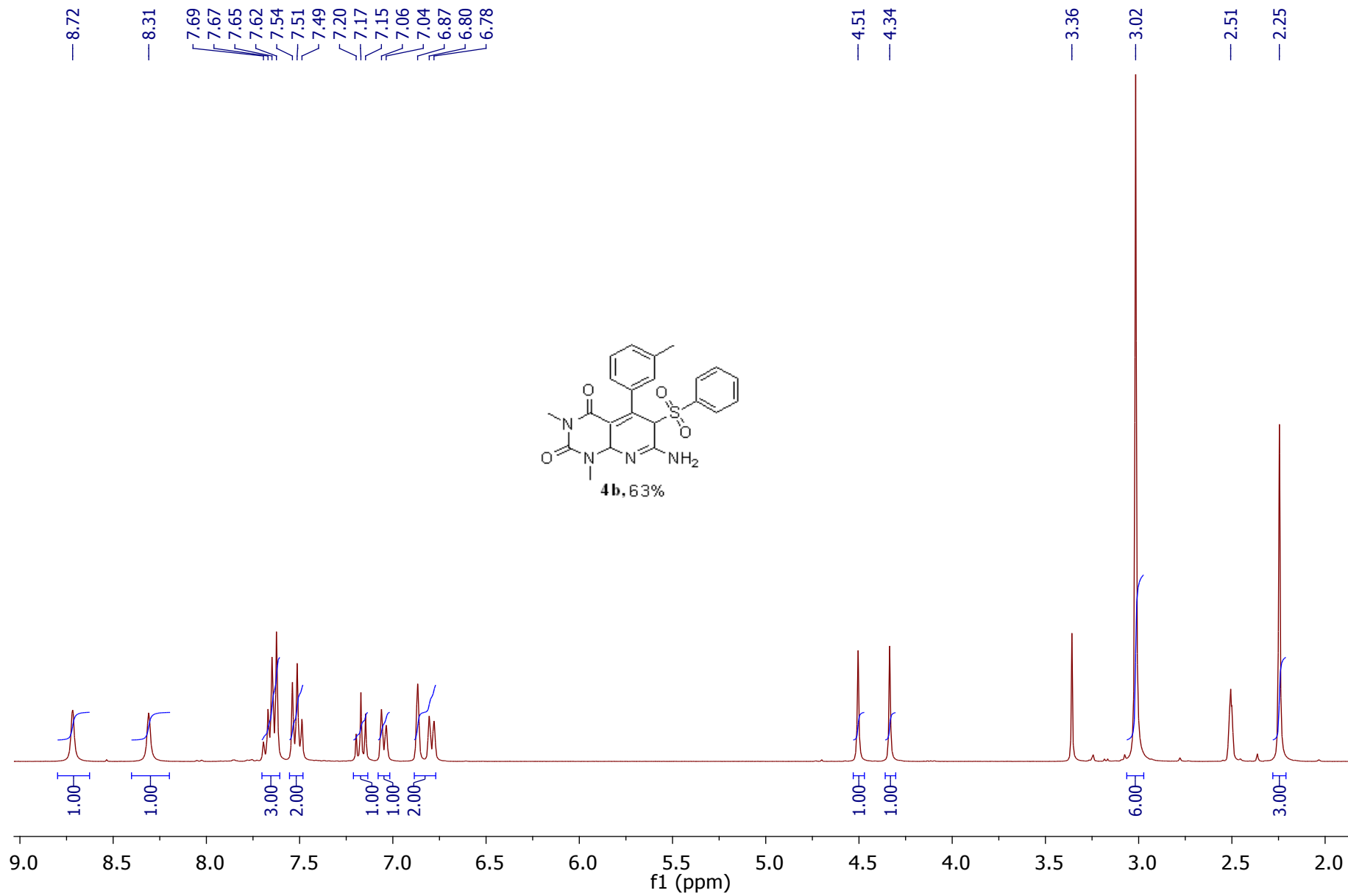


Fig S-3: ¹H NMR Spectrum of Product **4b**

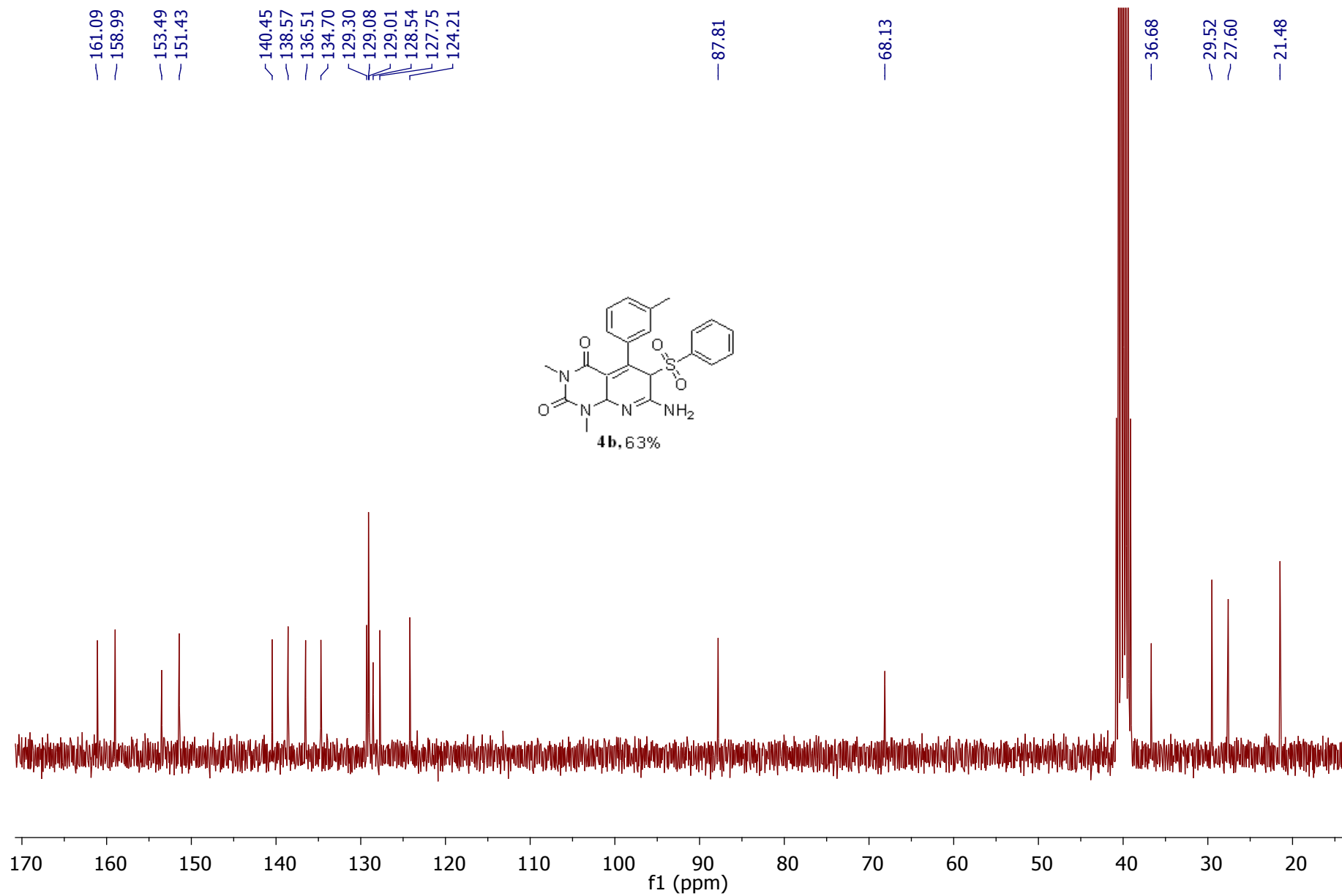


Fig S-4: ¹³C NMR Spectrum of Product **4b**

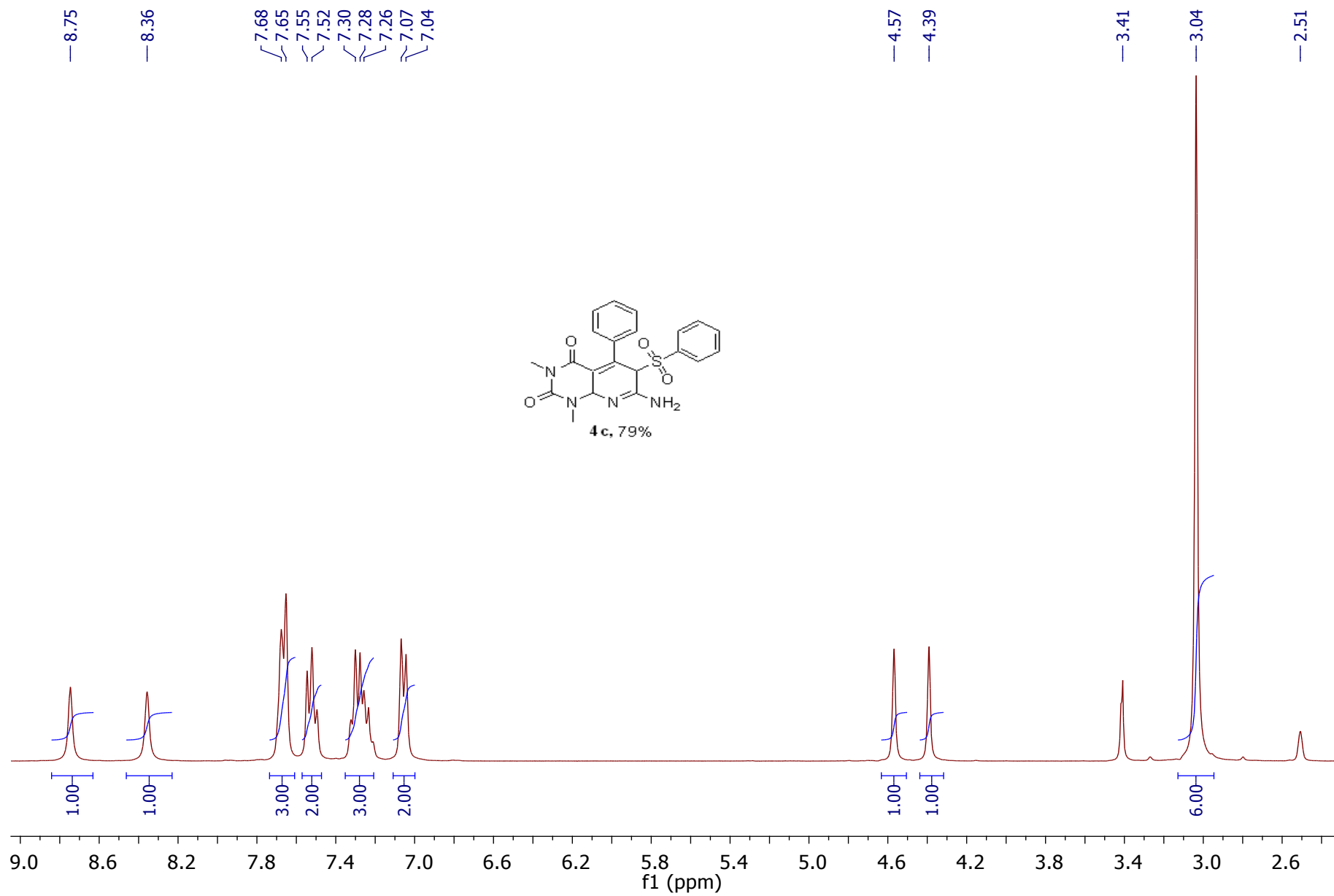


Fig S-5: ^1H NMR Spectrum of Product **4c**

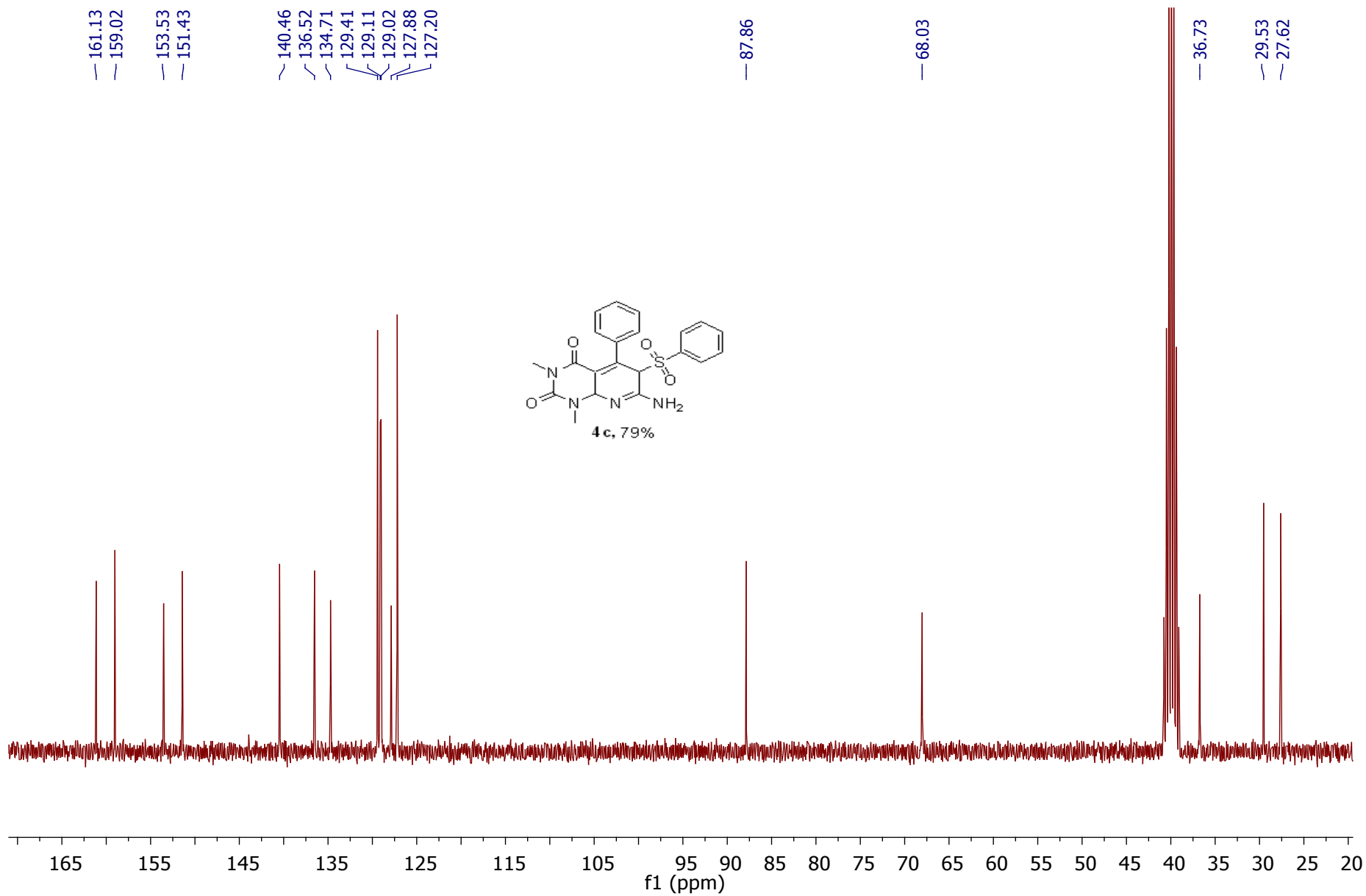


Fig S-6: ¹³C NMR Spectrum of Product 4c

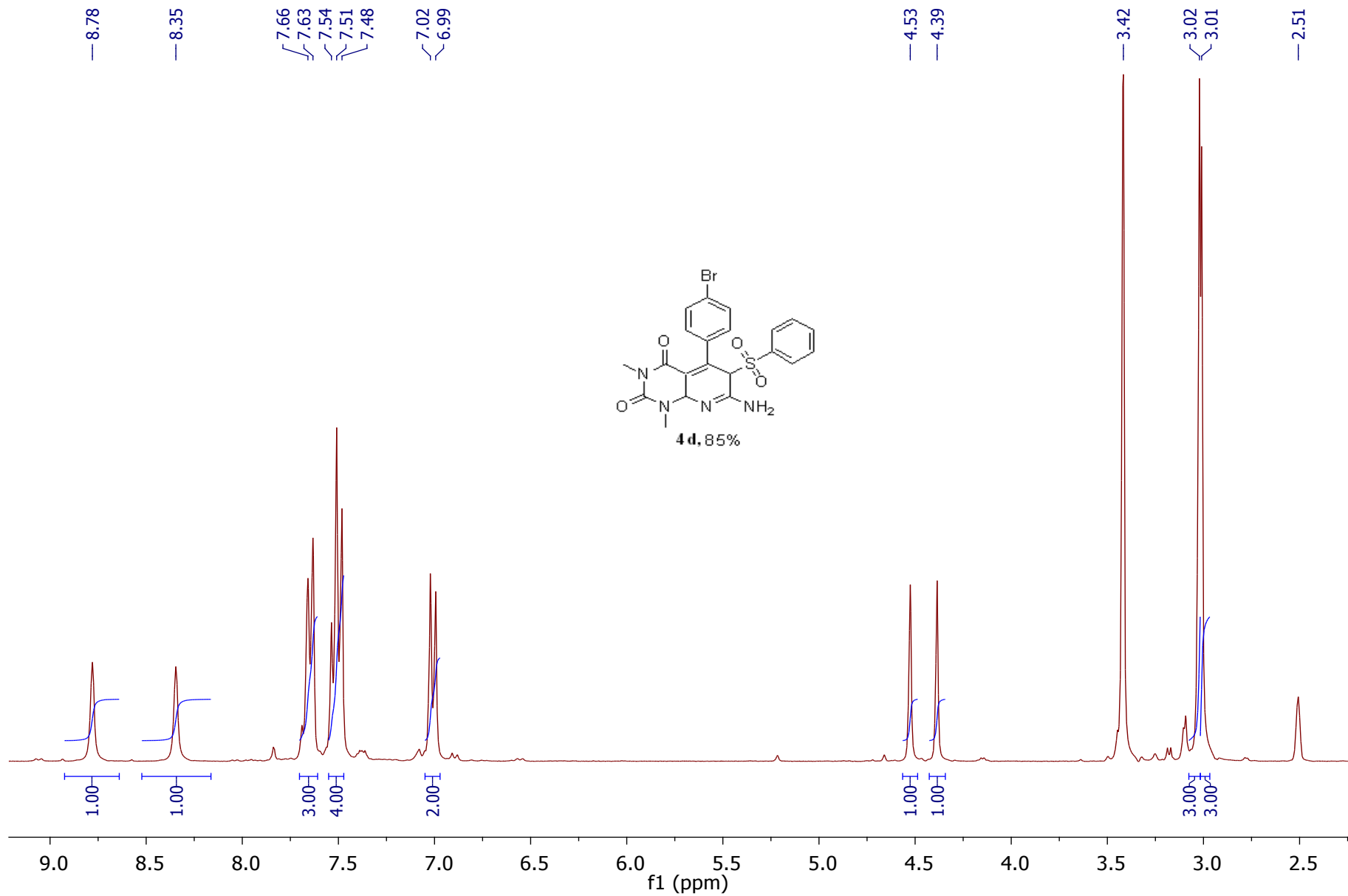


Fig S-7: ¹H NMR Spectrum of Product **4d**

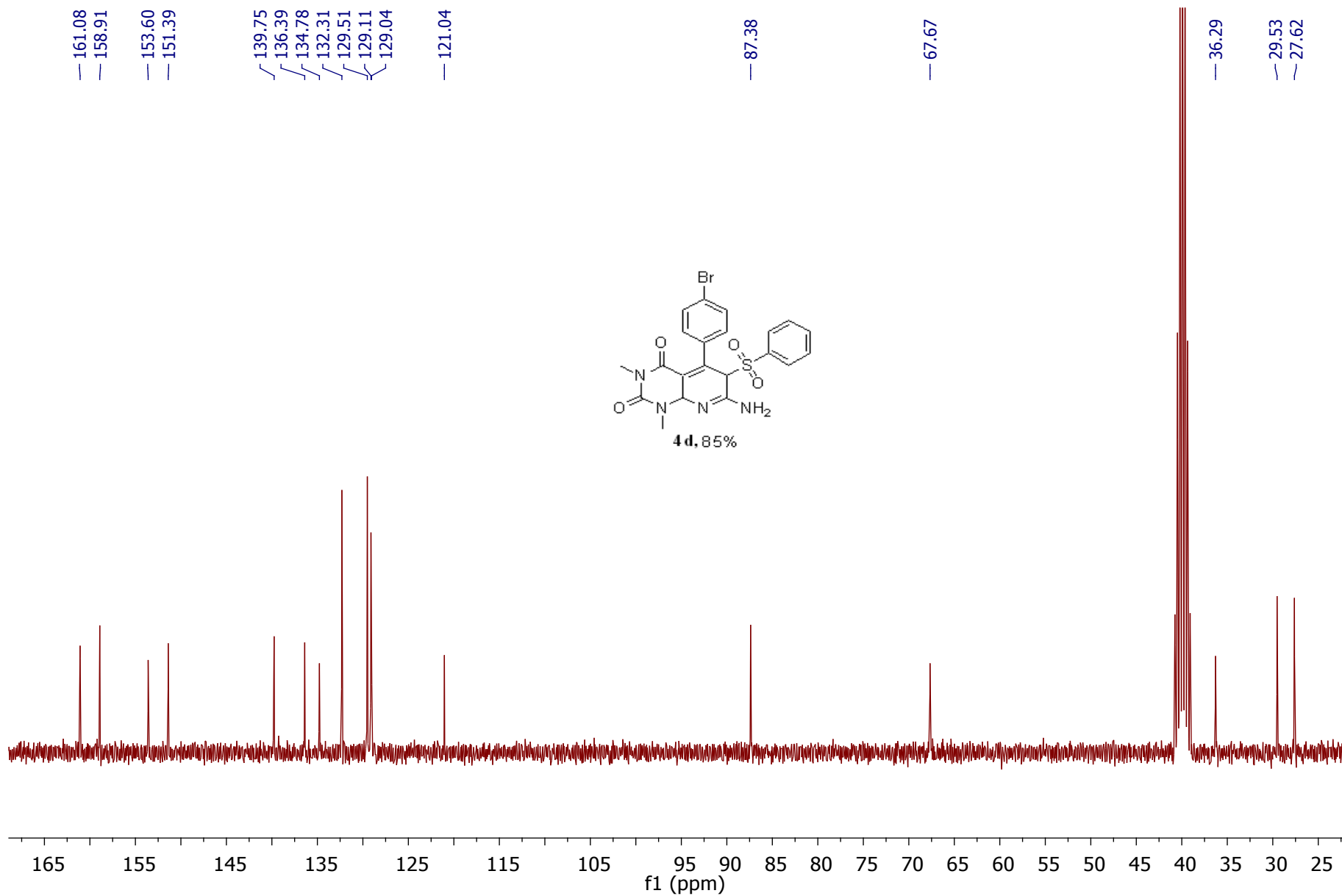


Fig S-8: ¹³C NMR Spectrum of Product 4d

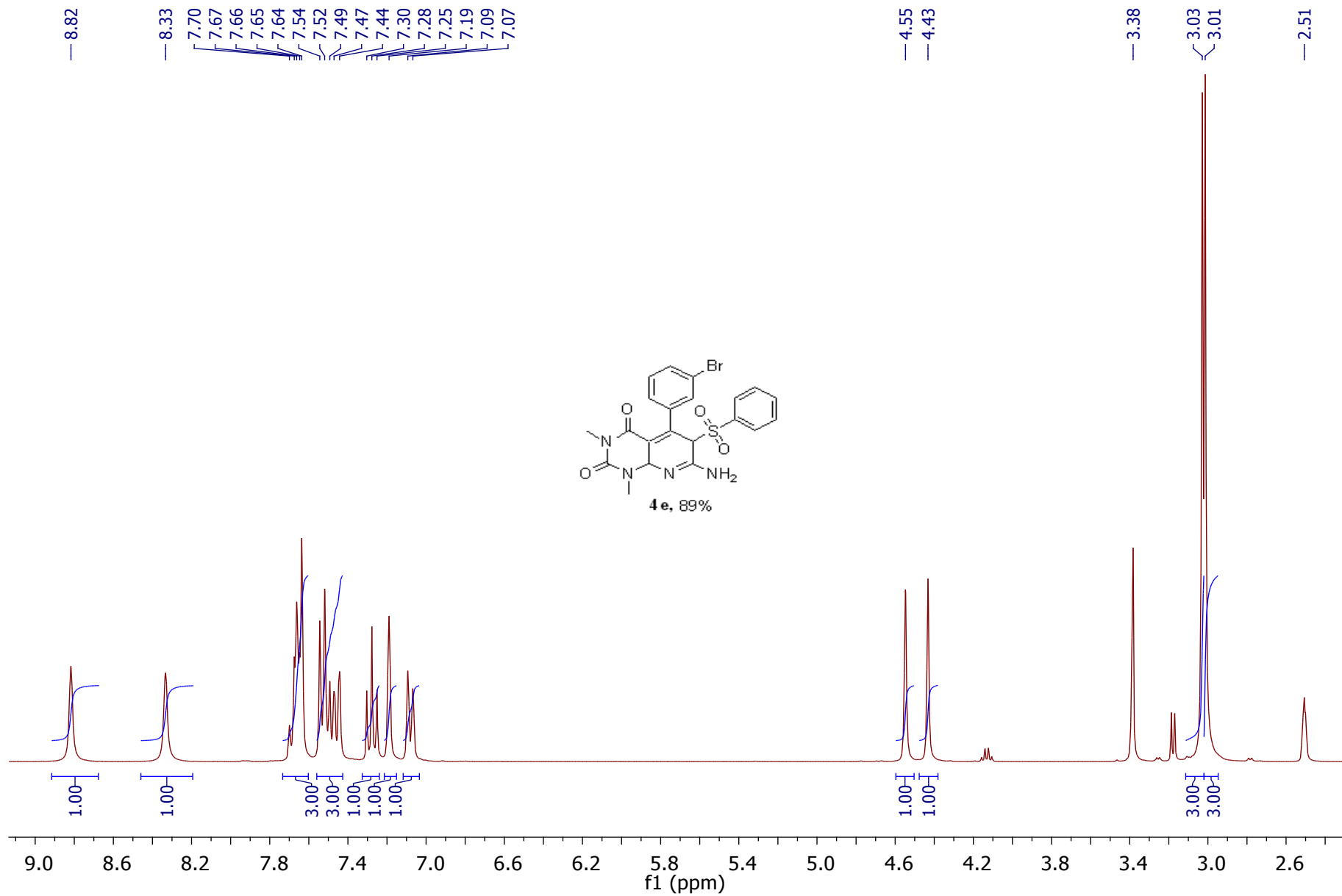


Fig S-9: ¹H NMR Spectrum of Product 4e

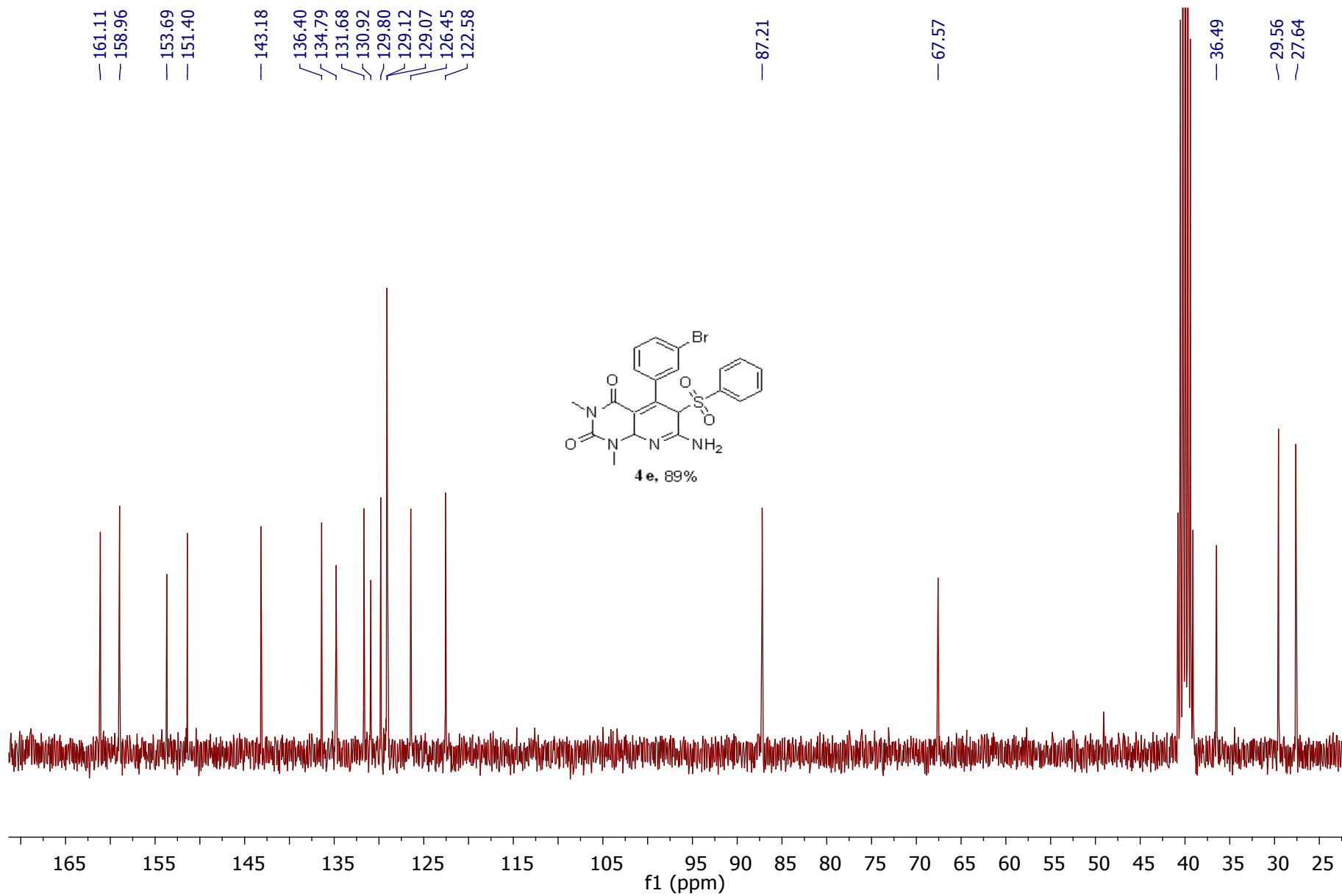


Fig S-10: ¹³C NMR Spectrum of Product 4e

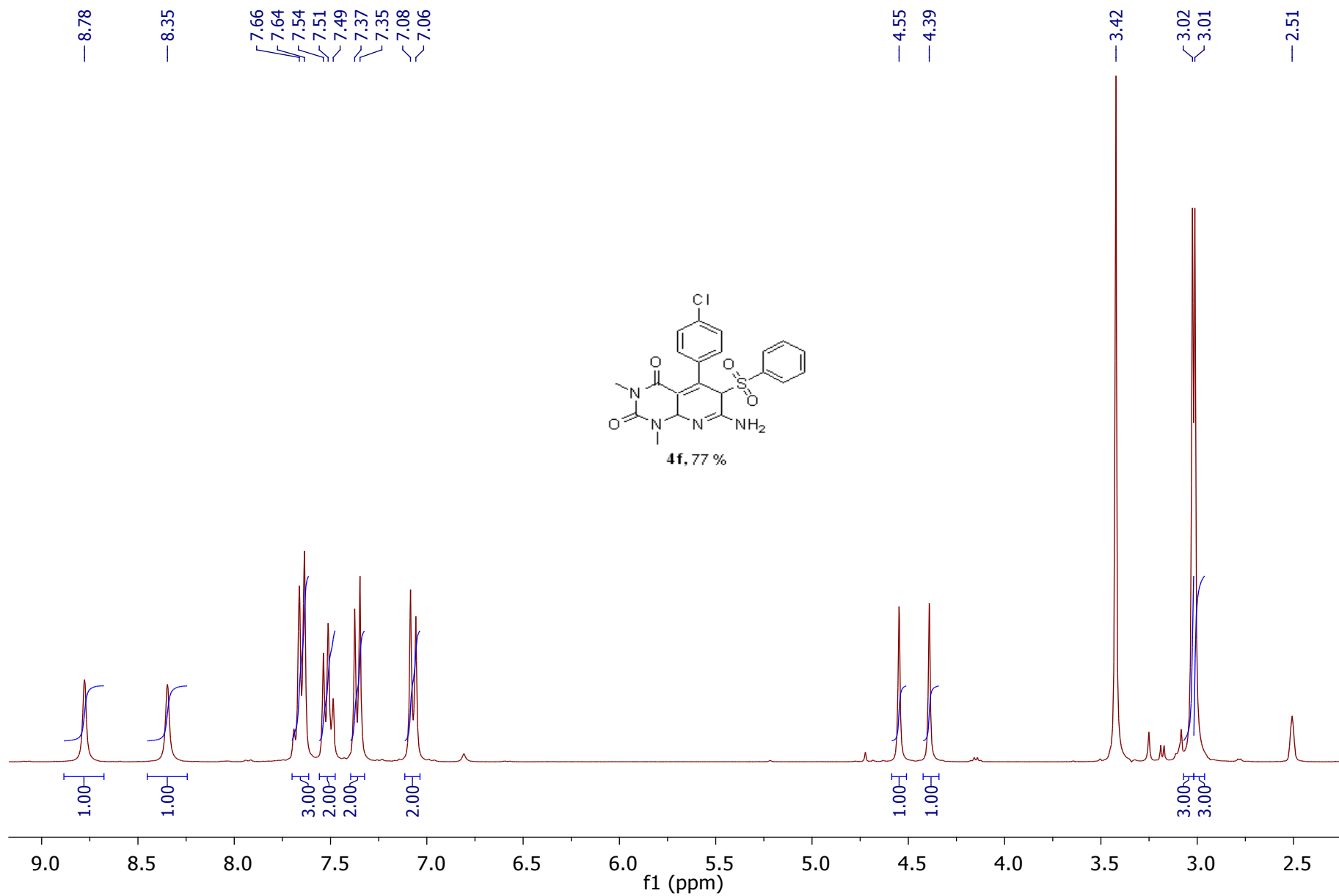


Fig S-11: ¹H NMR Spectrum of Product 4f

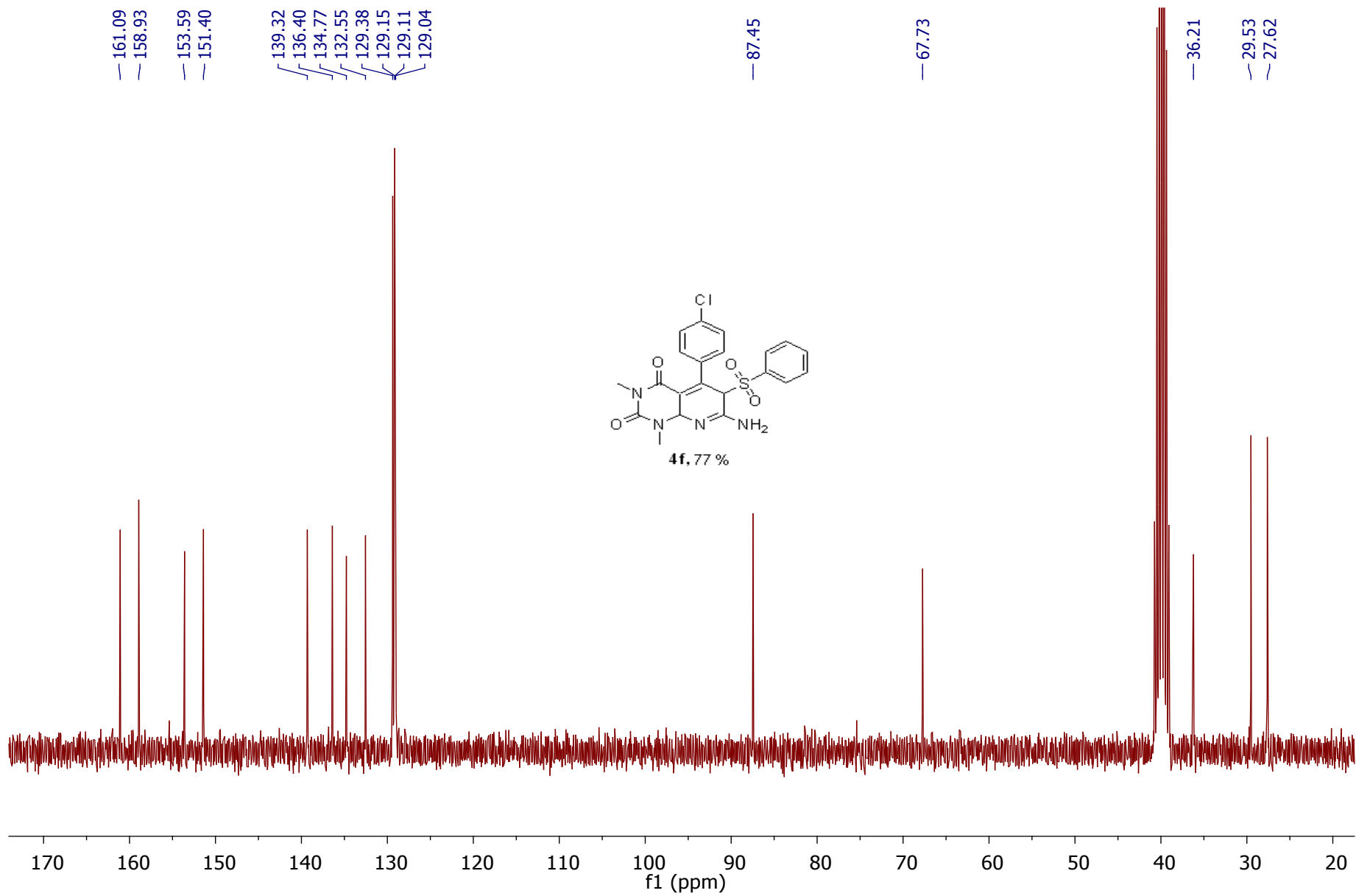


Fig S-12: ¹³C NMR Spectrum of Product 4f

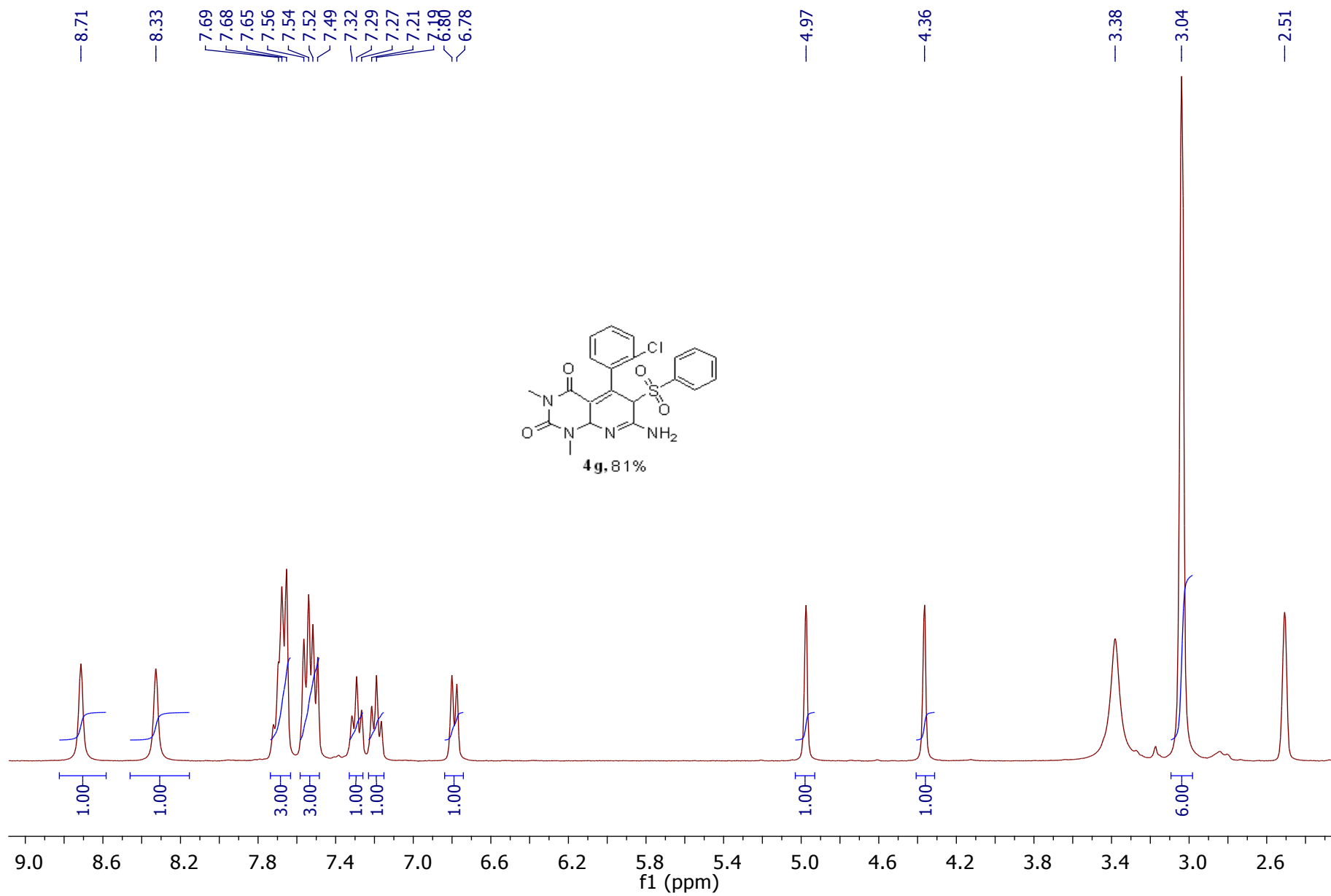


Fig S-13: ¹H NMR Spectrum of Product **4g**

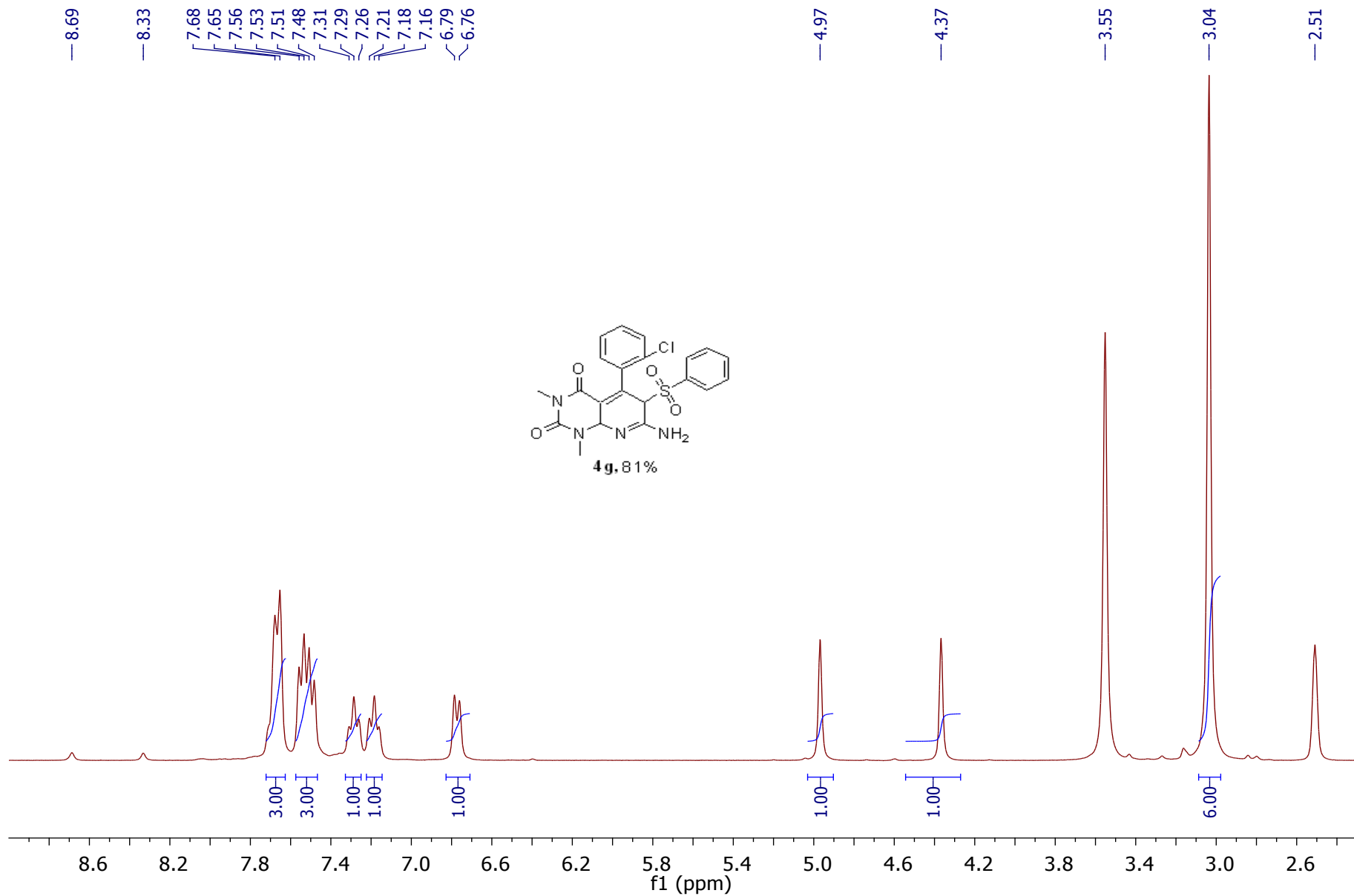


Fig S-14: ^1H NMR (Deuterium exchange) Spectrum of Product **4g**

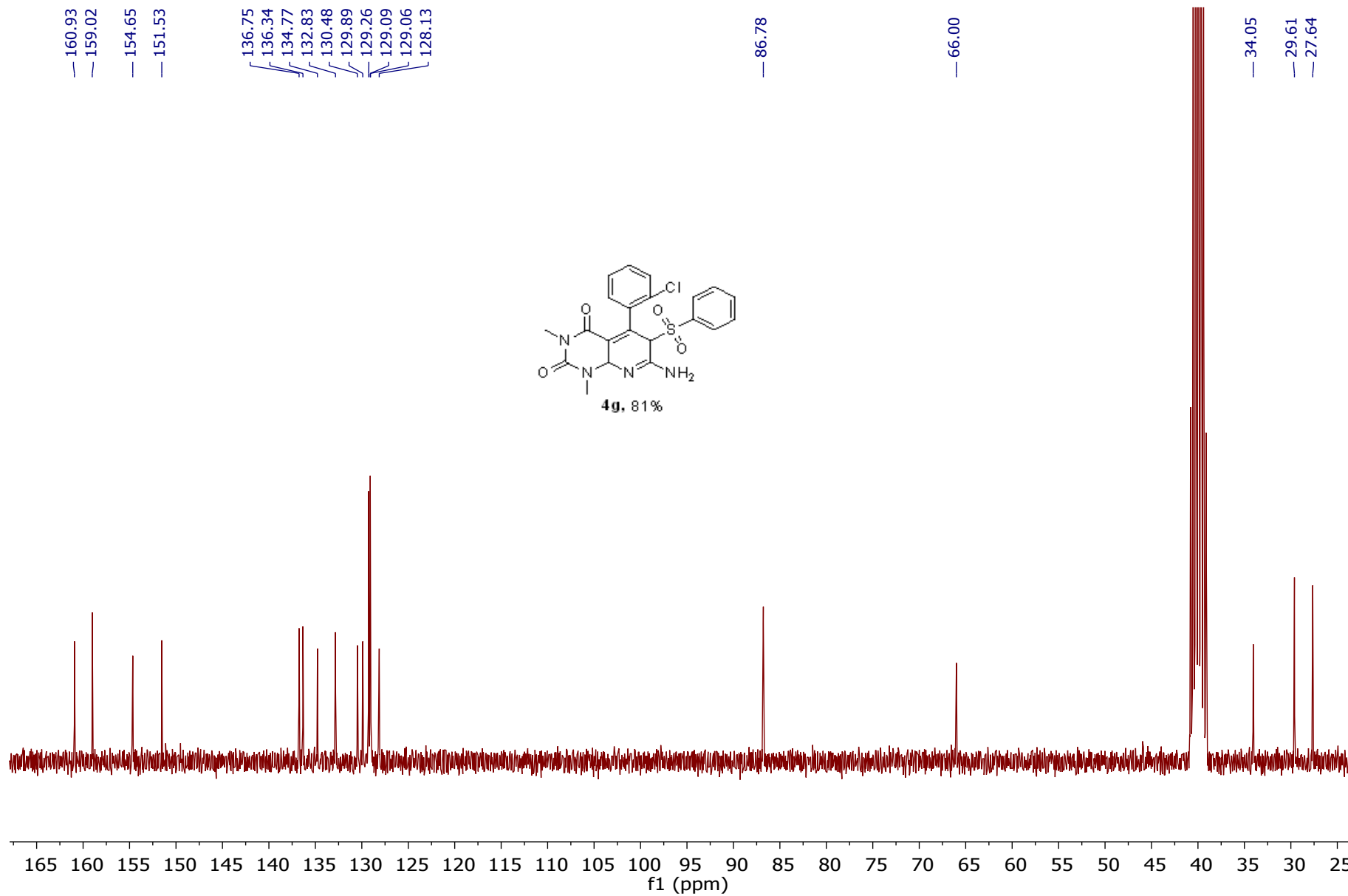


Fig S-15: ¹³C NMR Spectrum of Product 4g

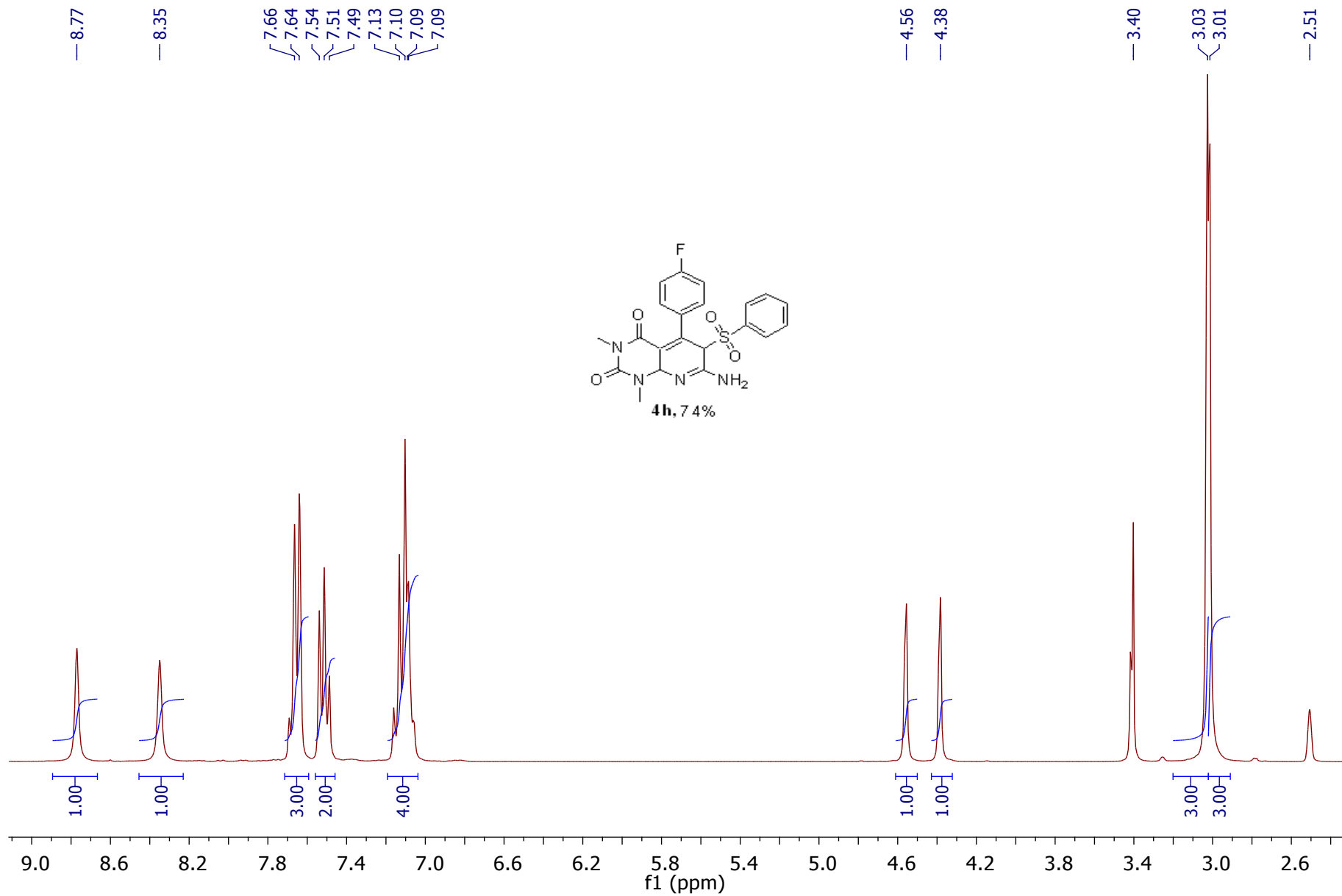


Fig S-16: ¹H NMR Spectrum of Product **4h**

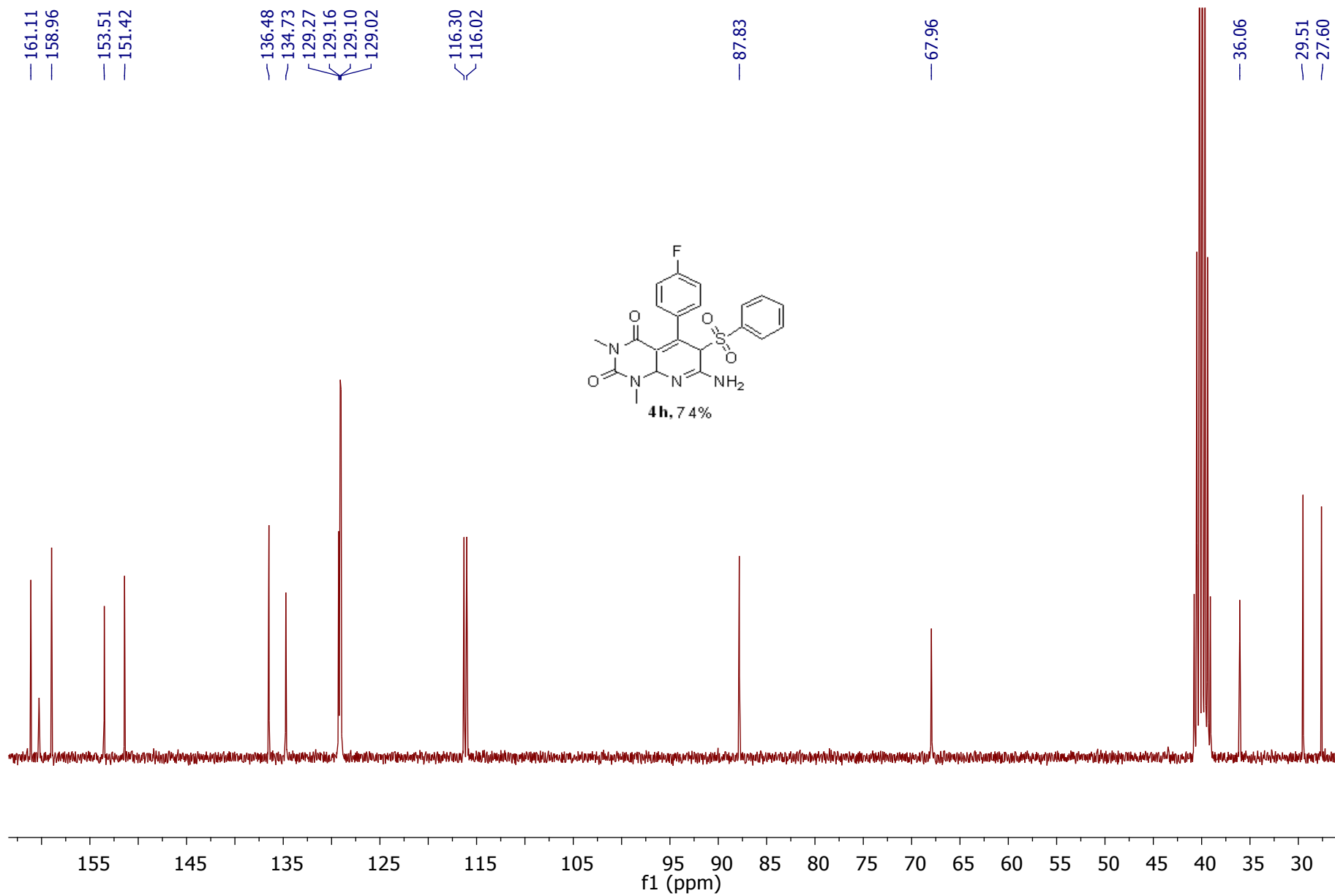


Fig S-17: ¹³C NMR Spectrum of Product **4h**

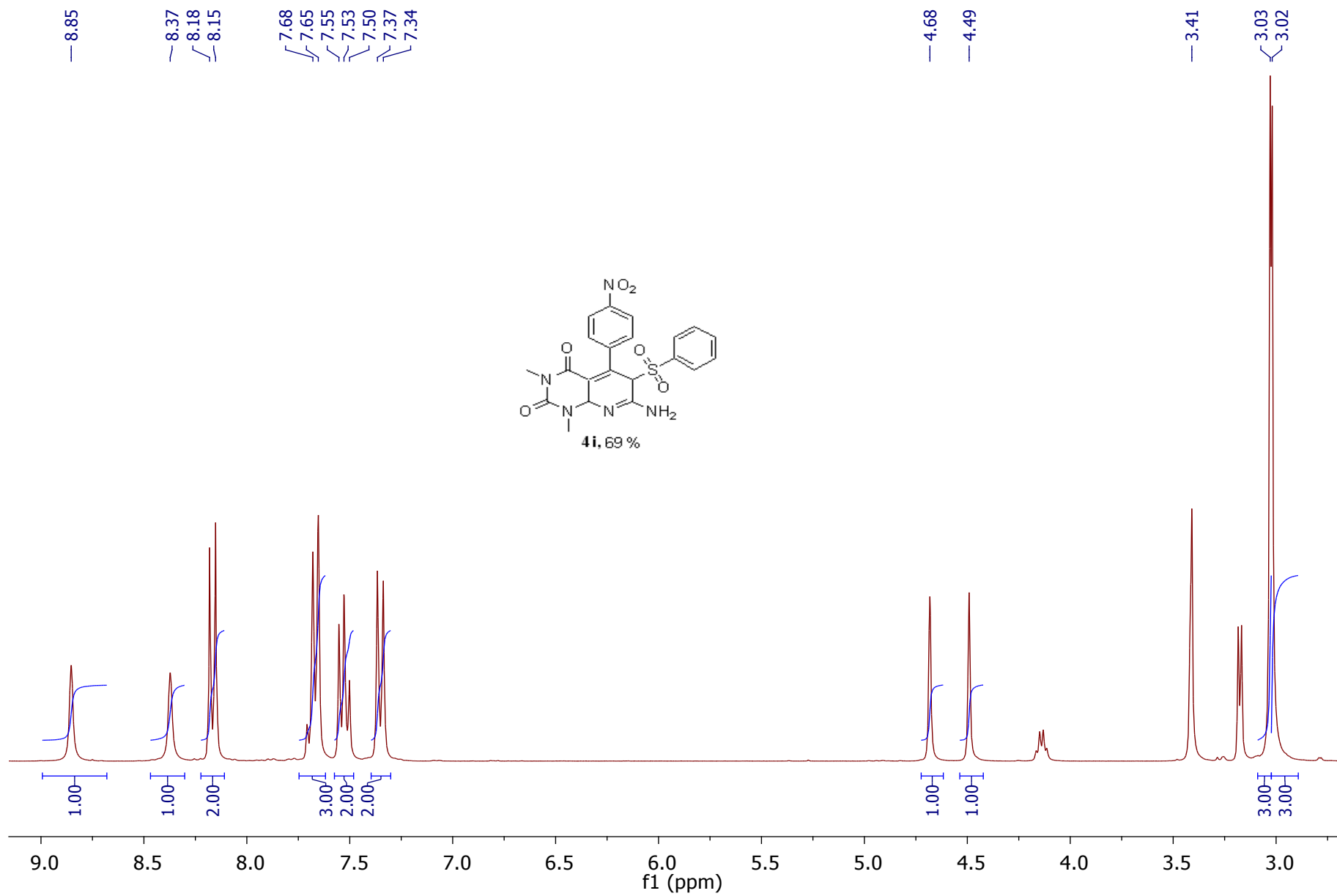


Fig S-18: ¹H NMR Spectrum of Product **4i**

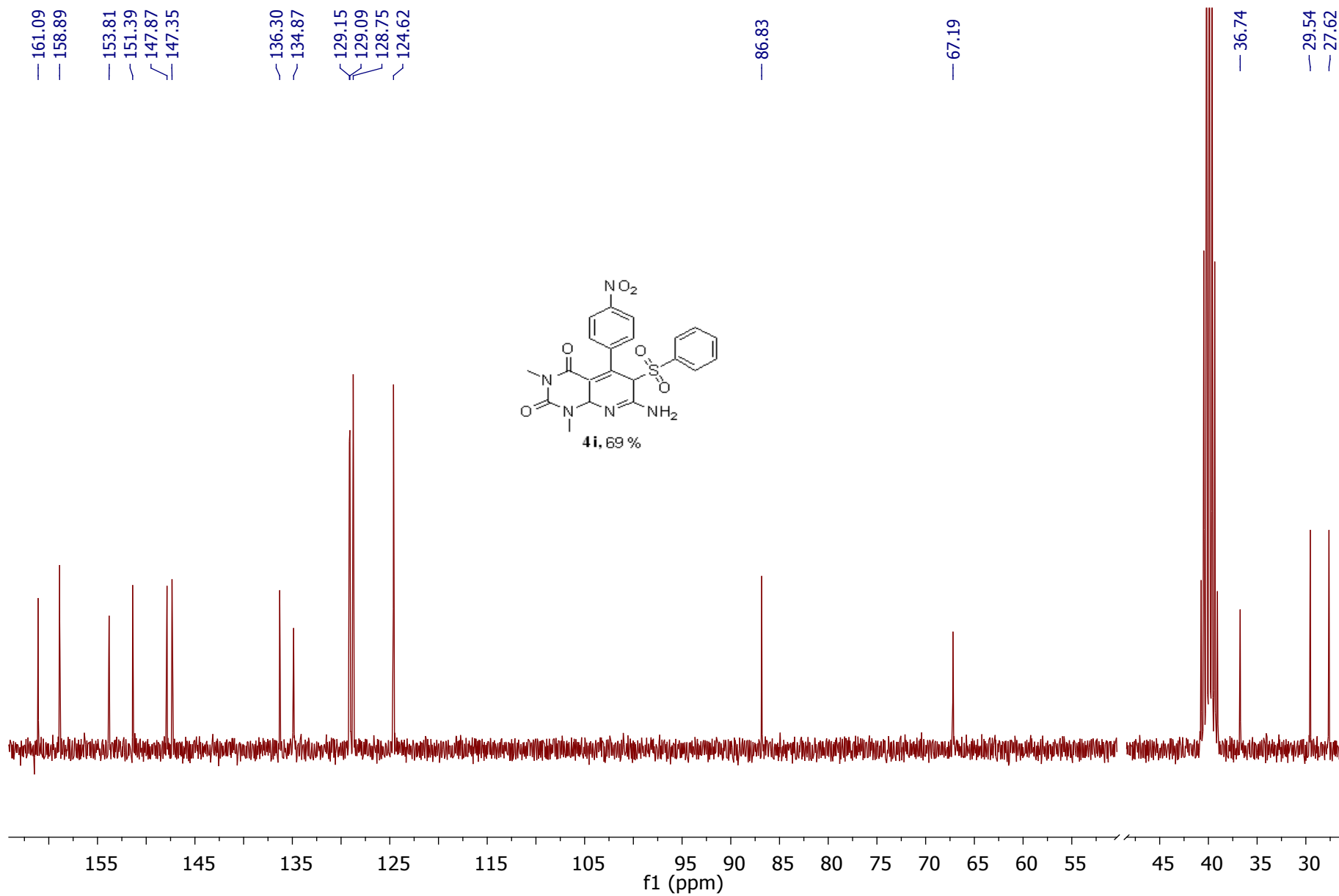


Fig S-19: ¹³C NMR Spectrum of Product 4i

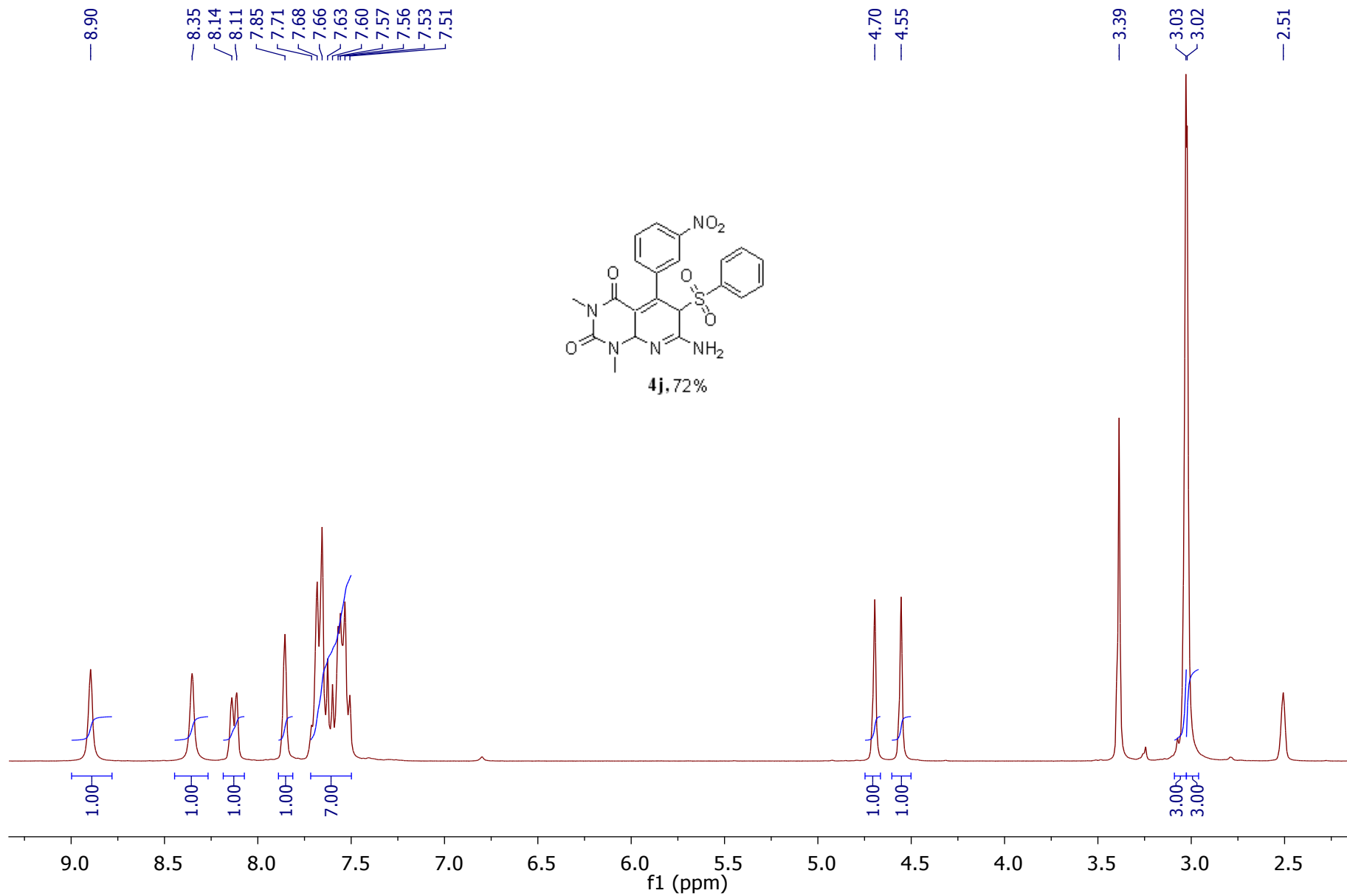


Fig S-20: ¹H NMR Spectrum of Product **4j**

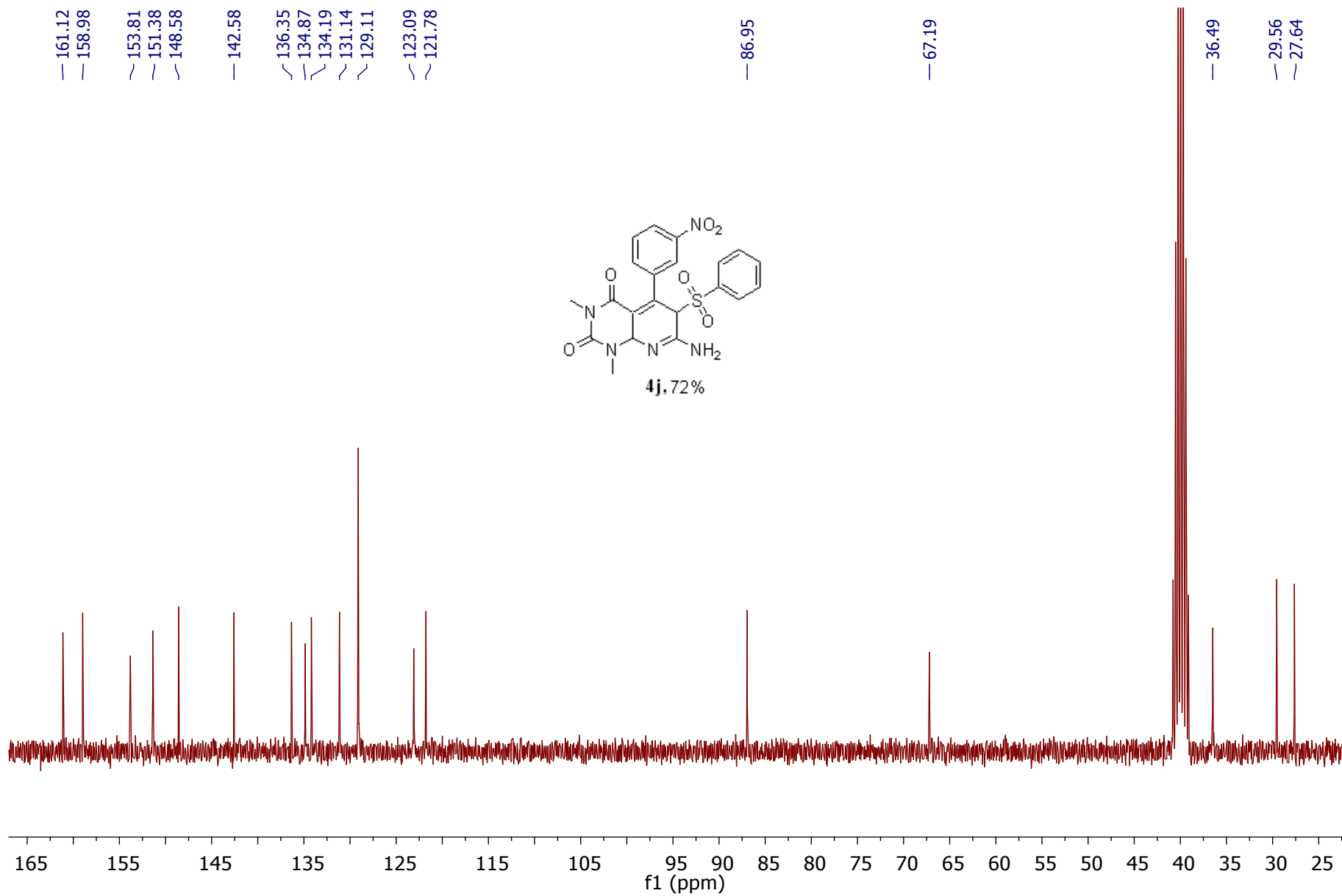


Fig S-21: ¹³C NMR Spectrum of Product 4j

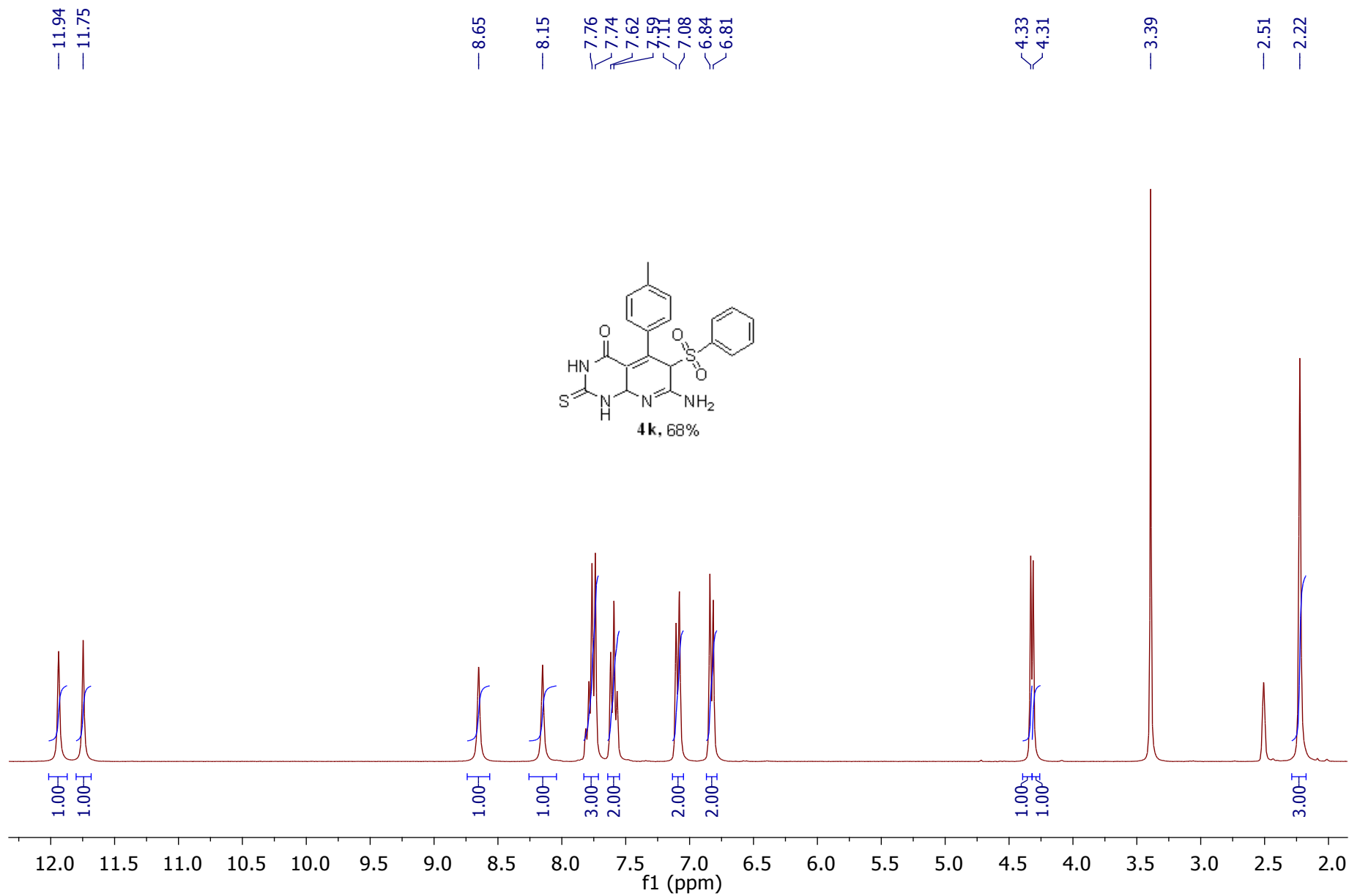


Fig S-22: ¹H NMR Spectrum of Product **4k**

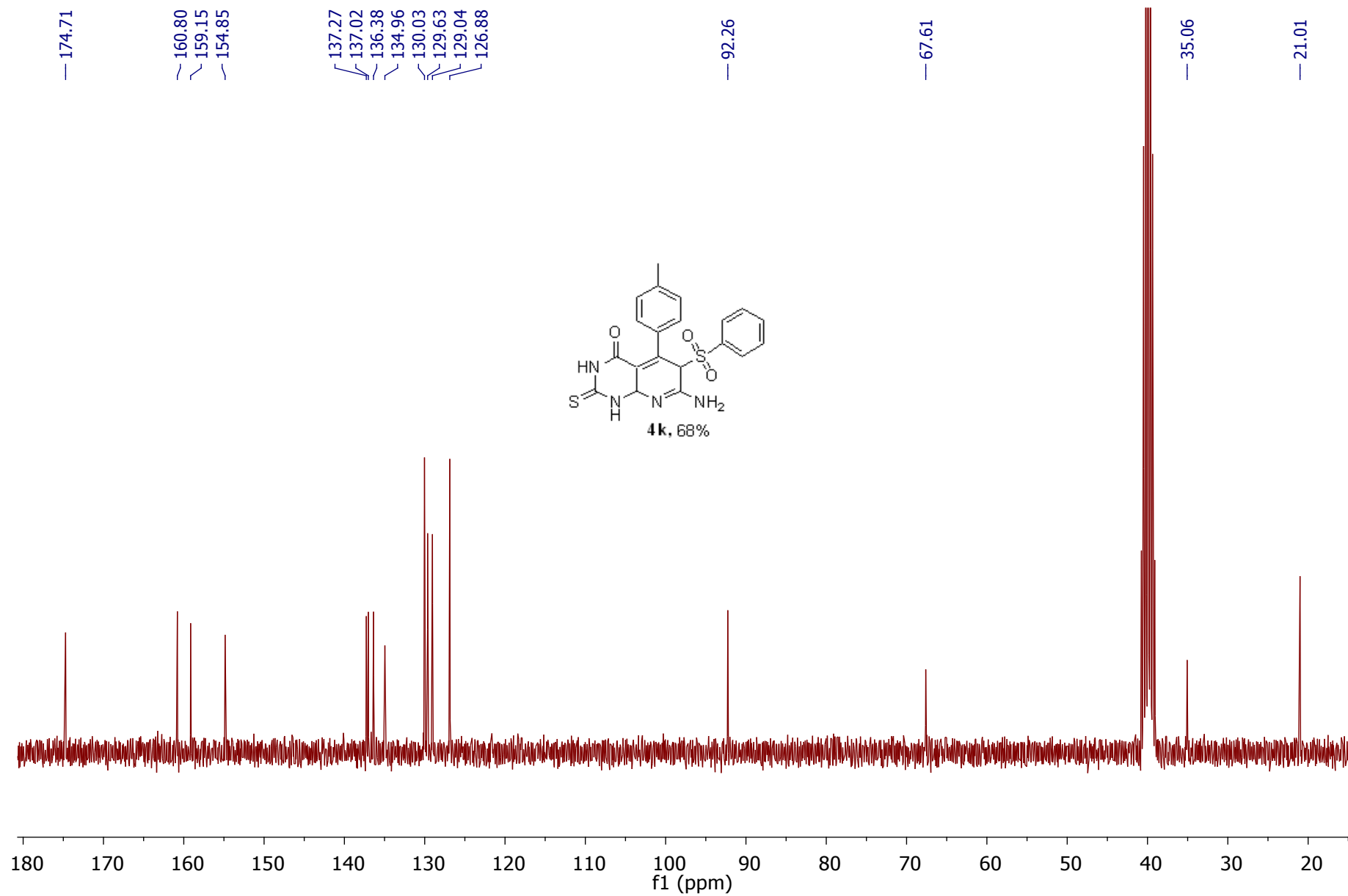


Fig S-23: ¹³C NMR Spectrum of Product **4k**

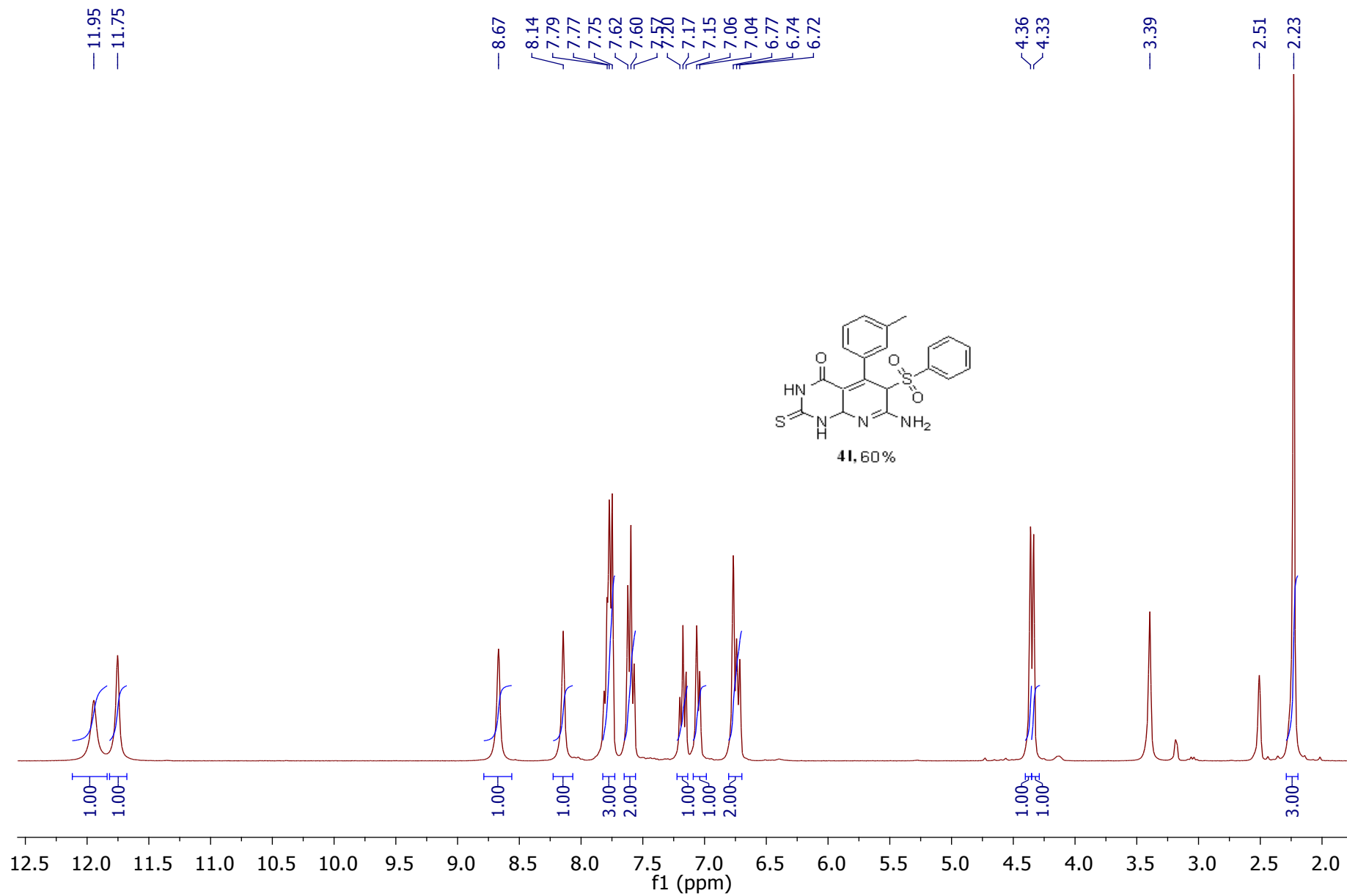


Fig S-24: ¹H NMR Spectrum of Product 4I

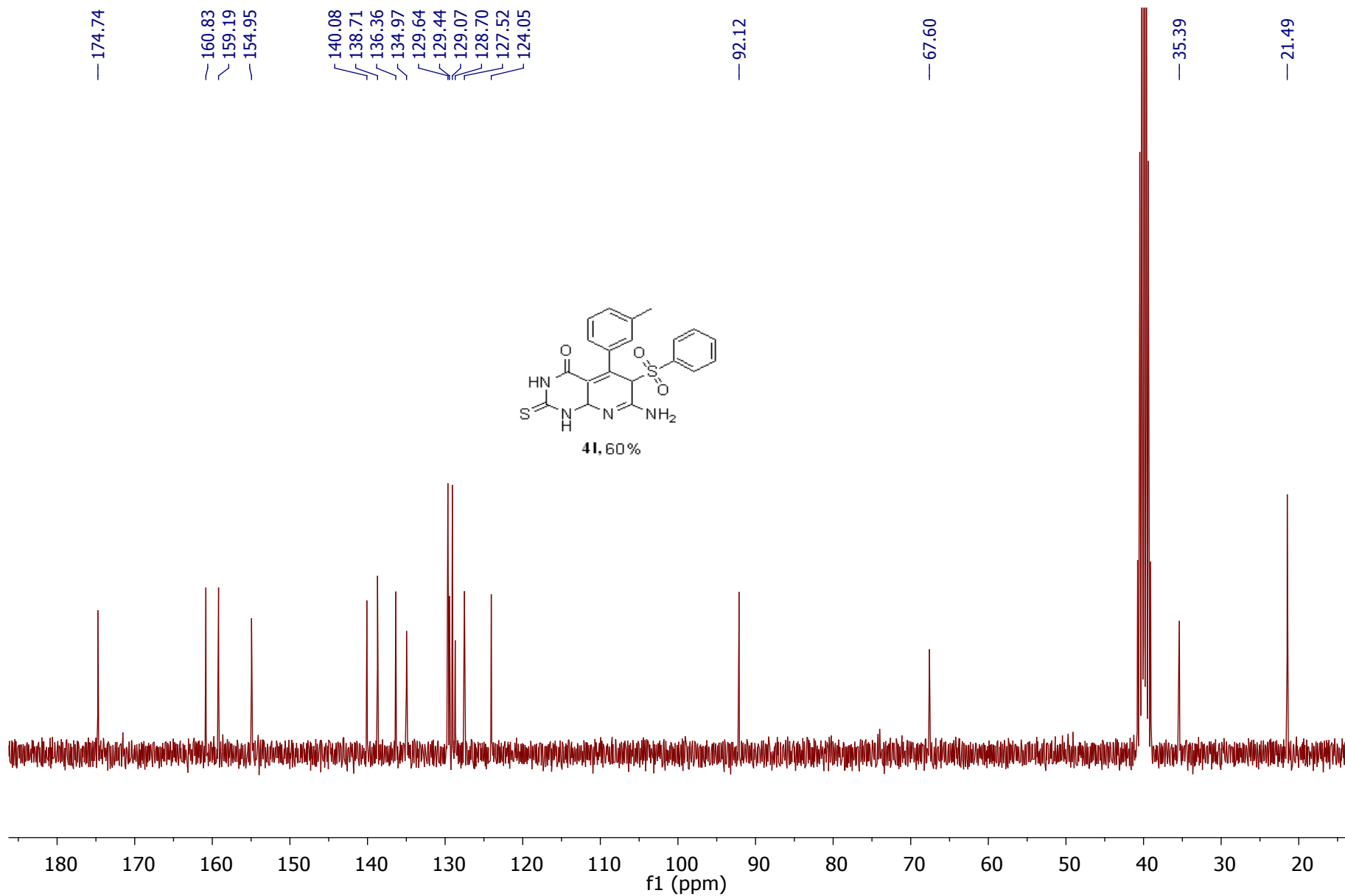


Fig S-25: ¹³C NMR Spectrum of Product 41

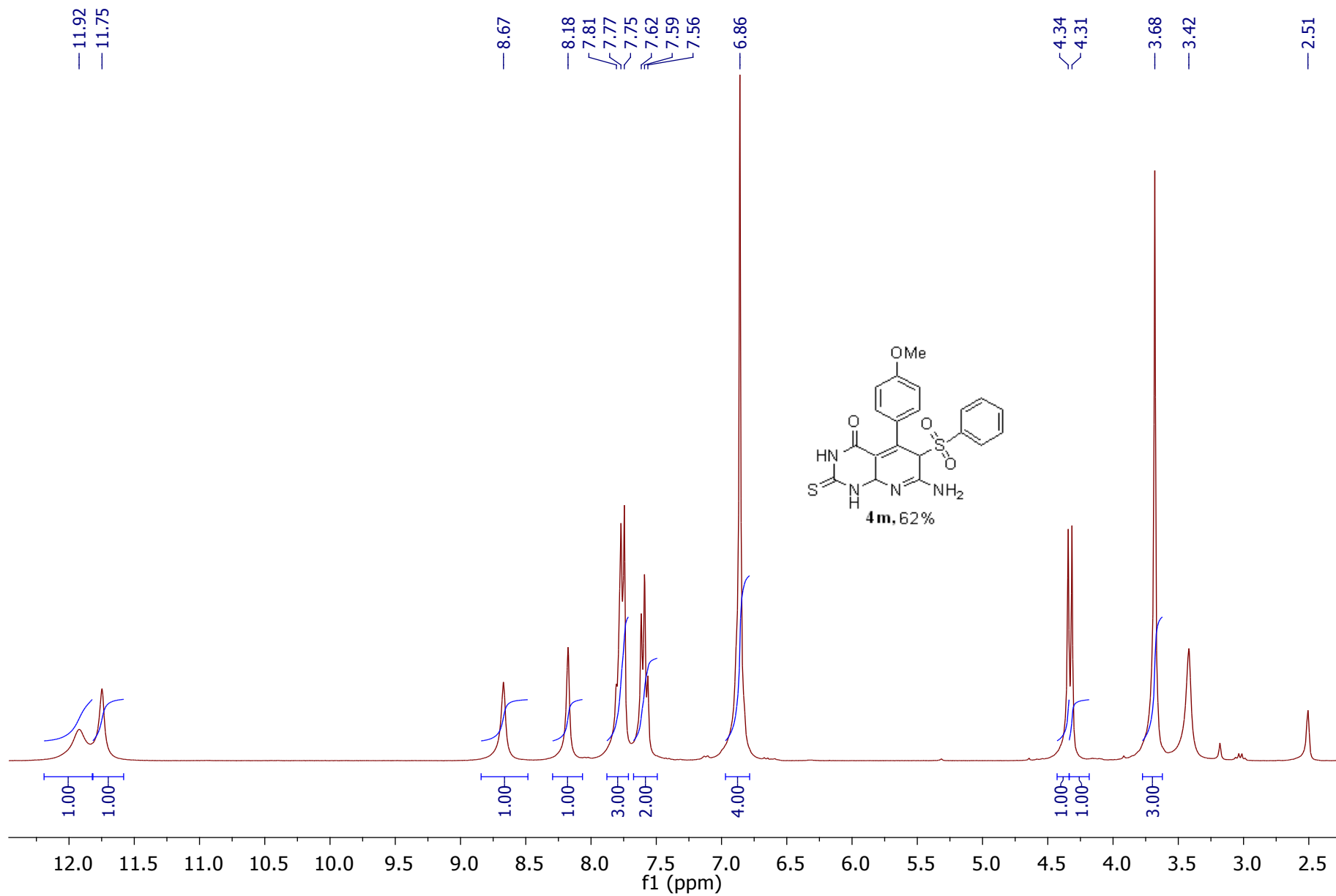


Fig S-26: ^1H NMR Spectrum of Product **4m**

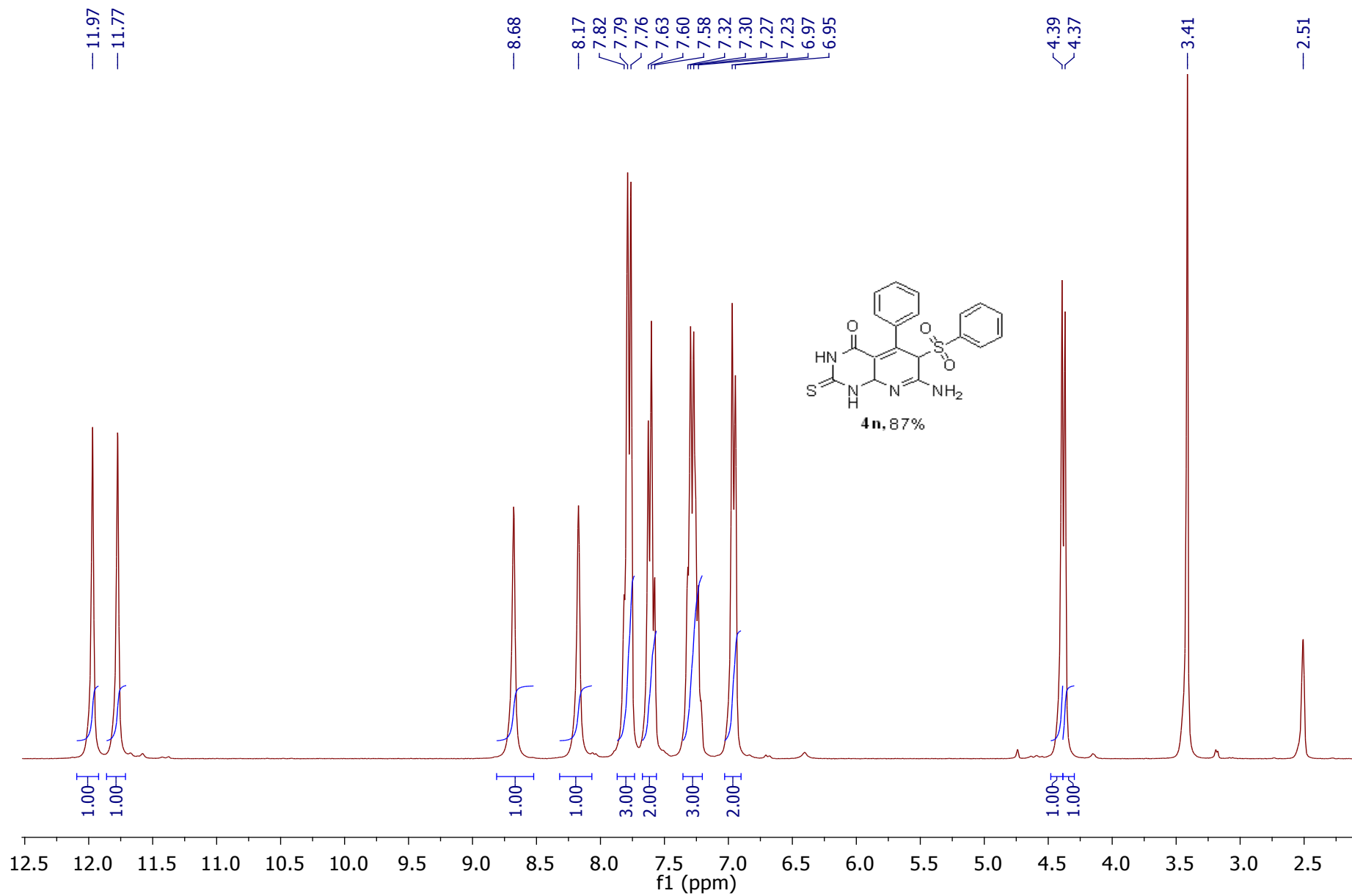


Fig S-27: ¹H NMR Spectrum of Product **4n**

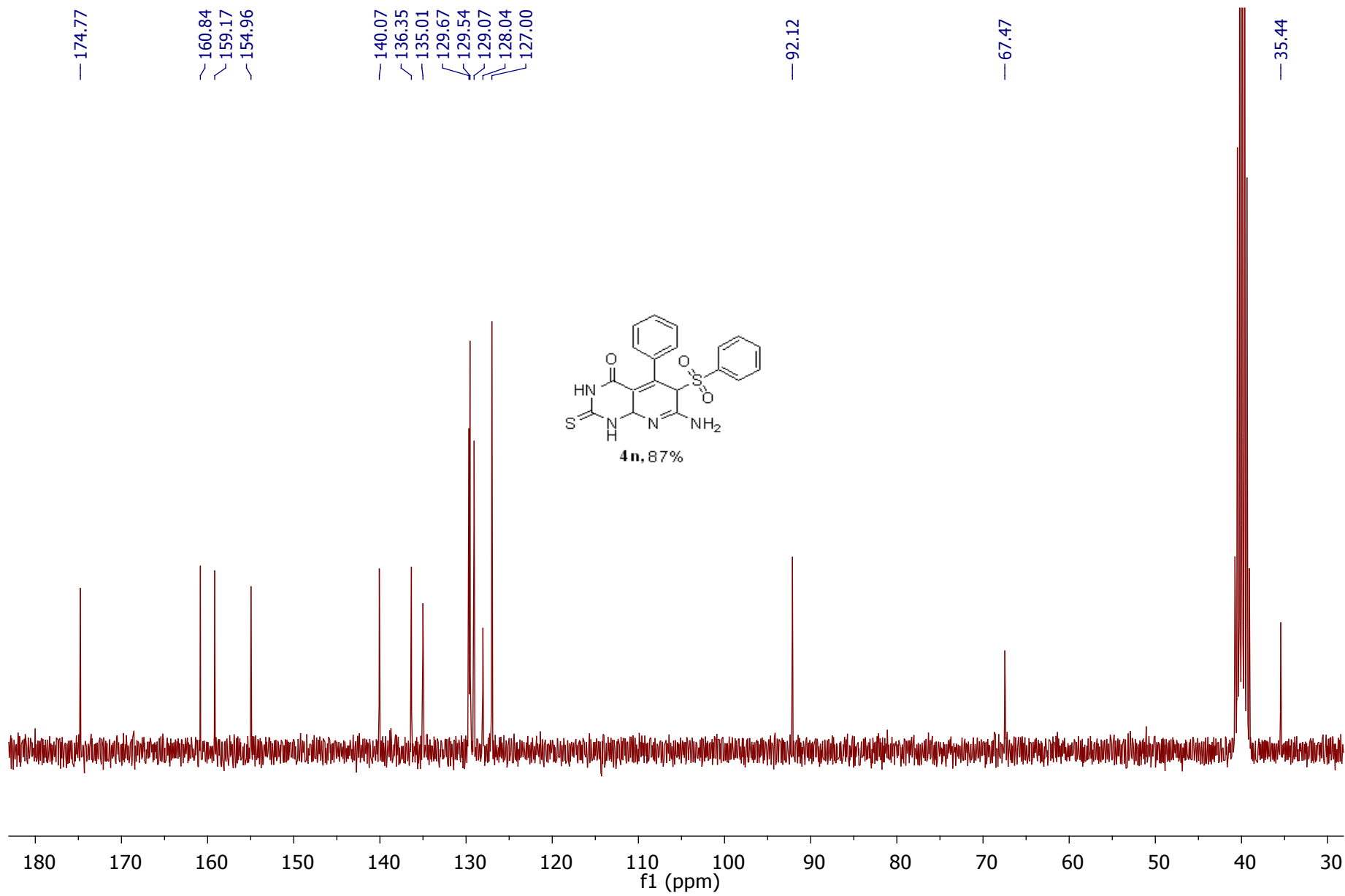


Fig S-28: ¹³C NMR Spectrum of Product **4n**

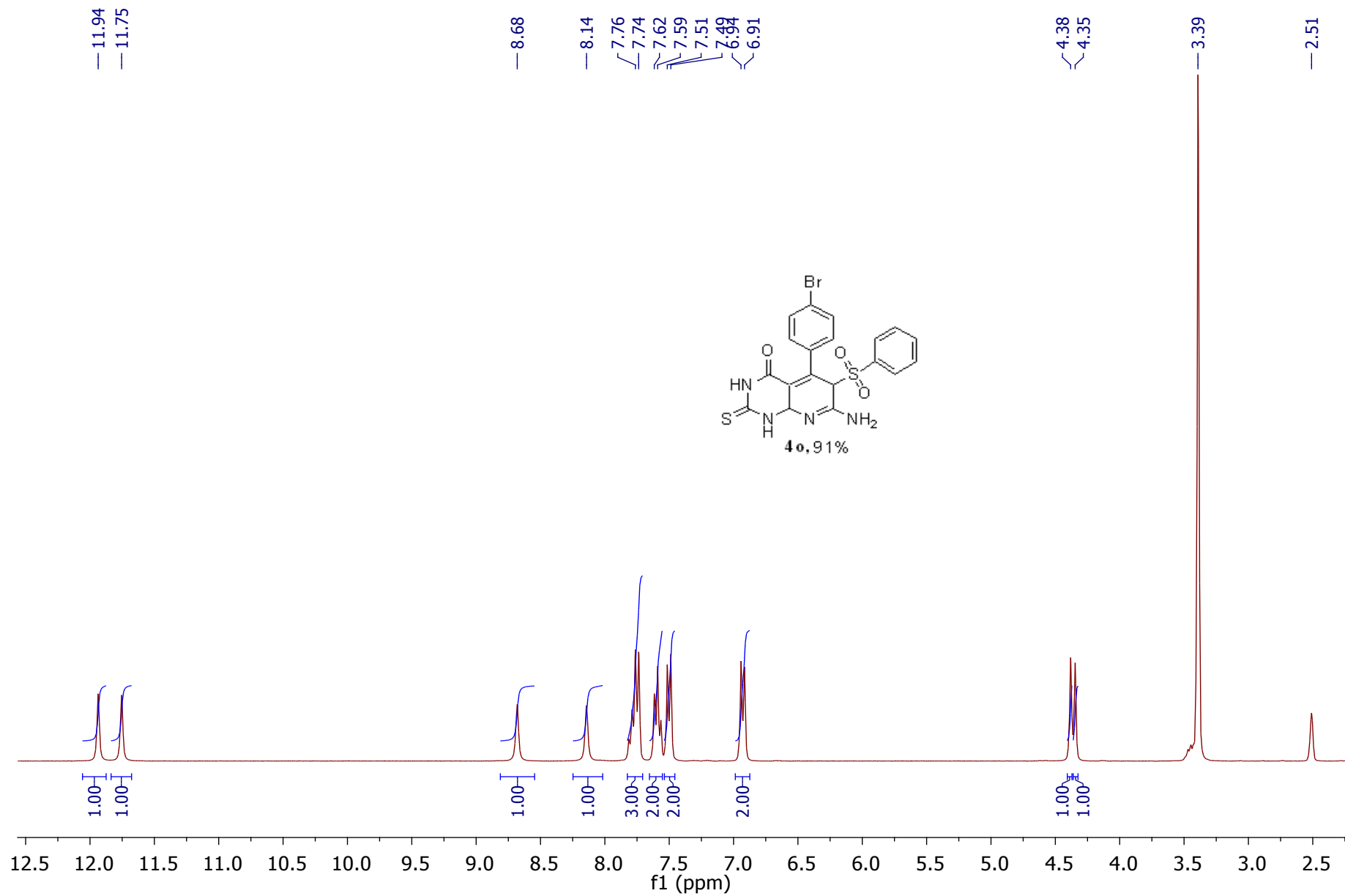


Fig S-29: ^1H NMR Spectrum of Product **4o**

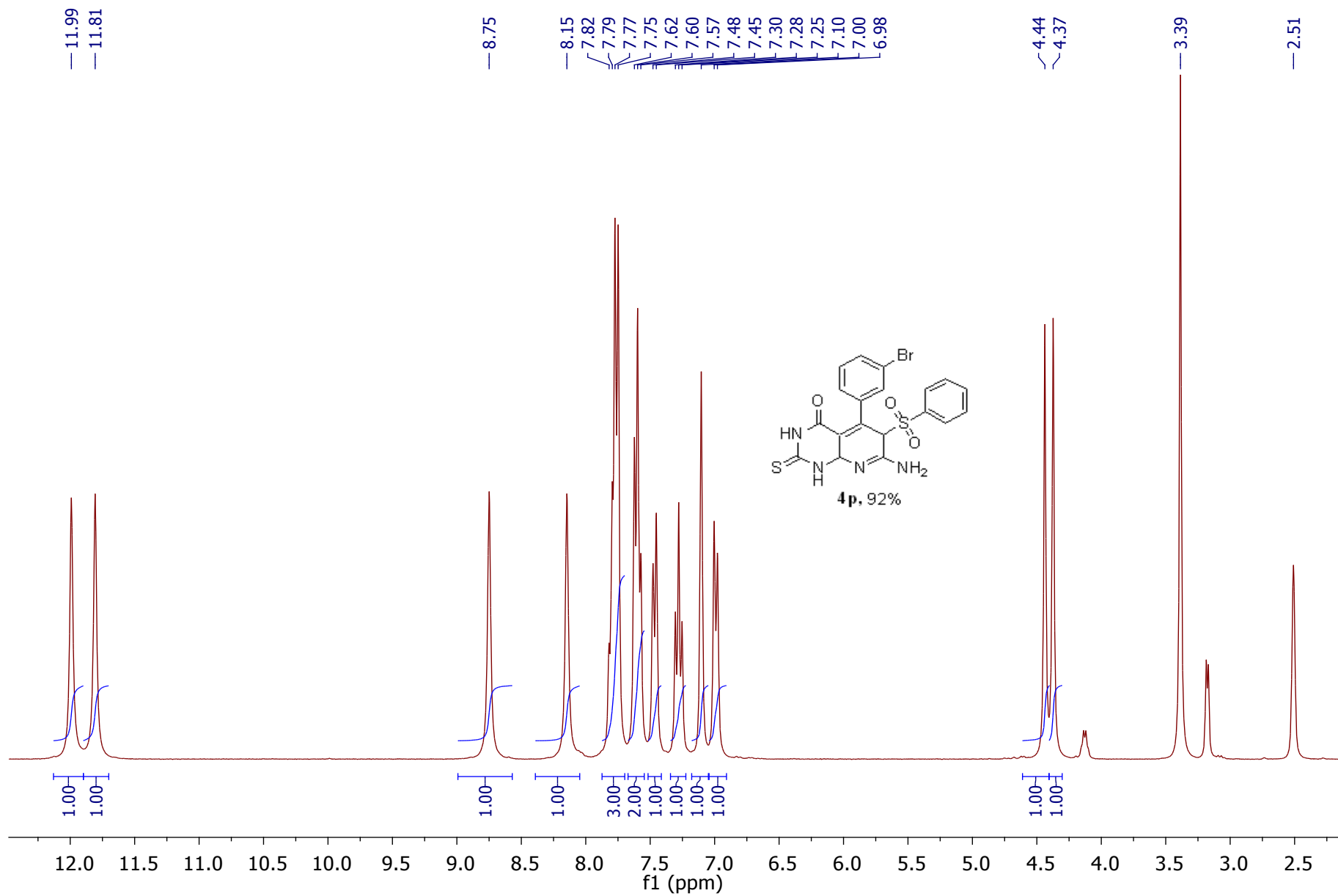


Fig S-30: ¹H NMR Spectrum of Product **4p**

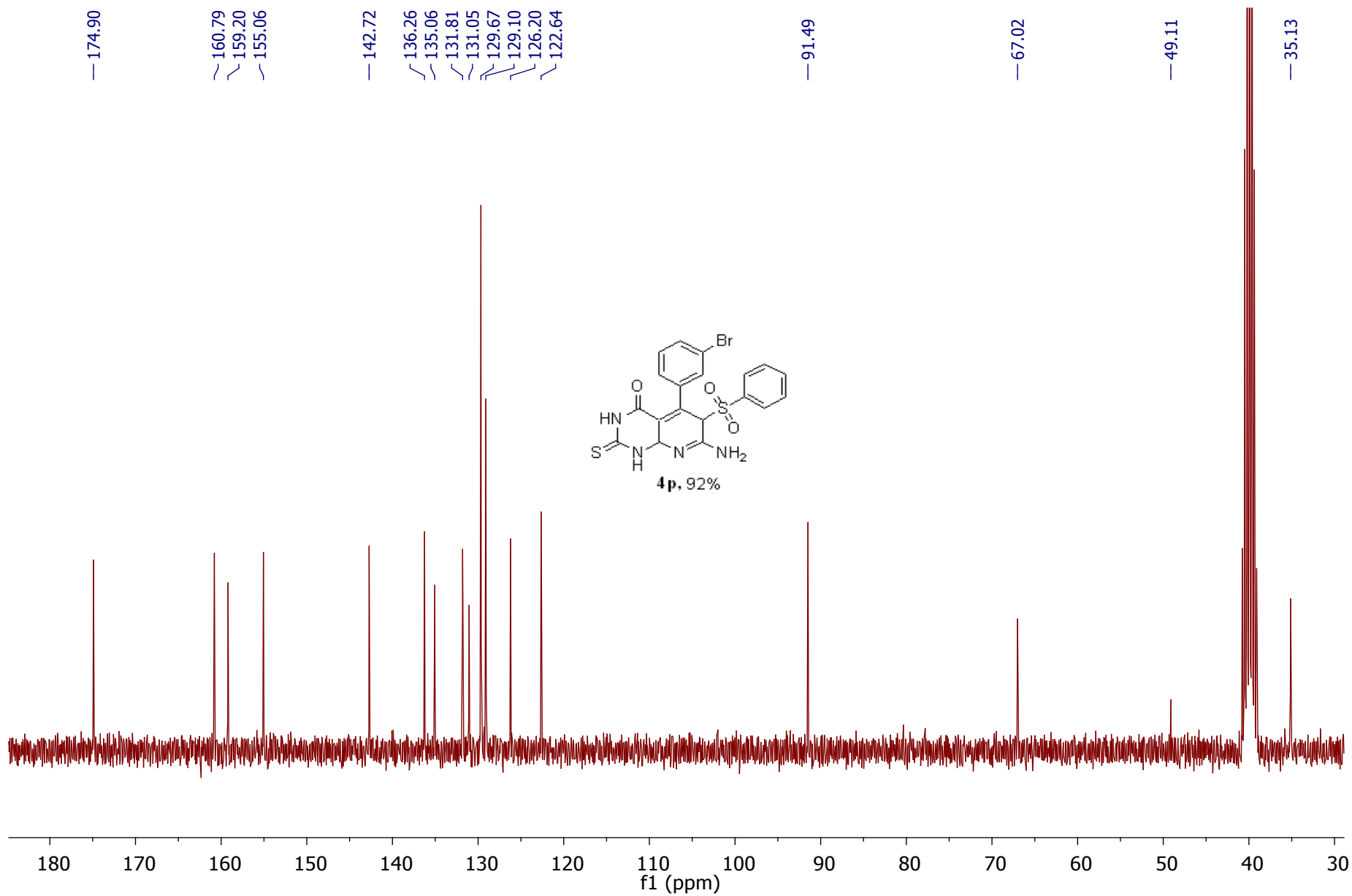


Fig S-31: ^{13}C NMR Spectrum of Product **4p**

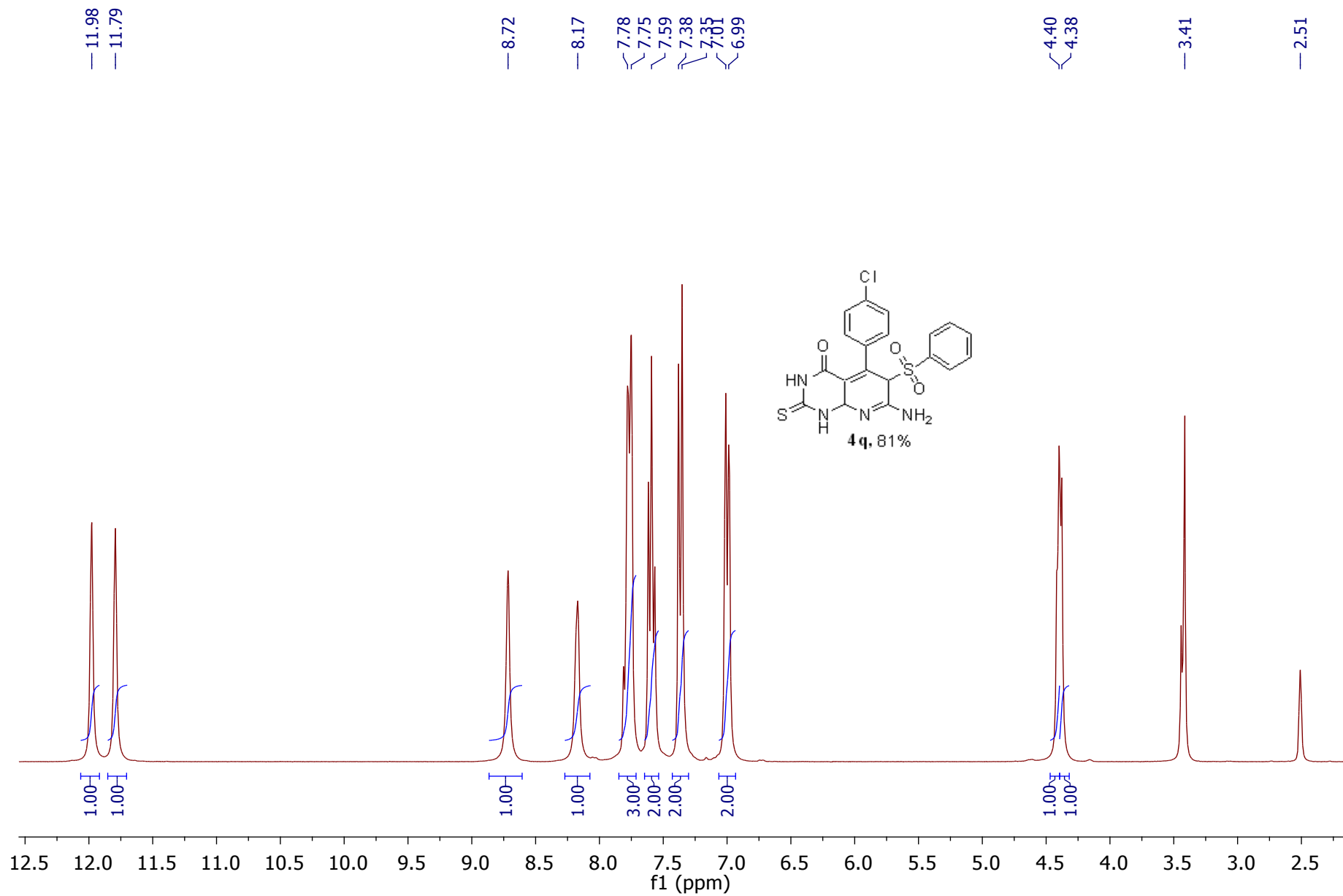


Fig S-32: ^1H NMR Spectrum of Product **4q**

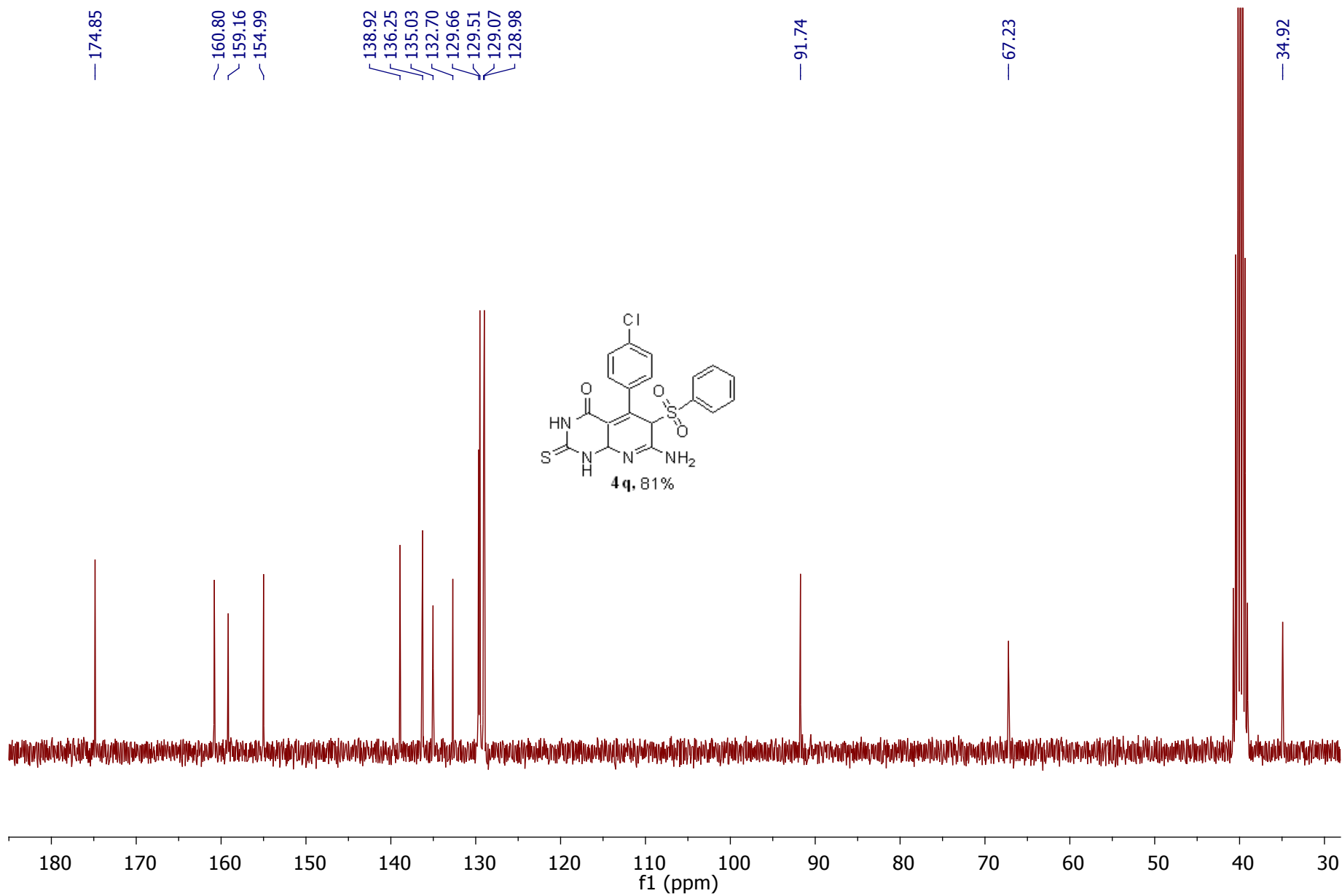


Fig S-33: ¹³C NMR Spectrum of Product **4q**

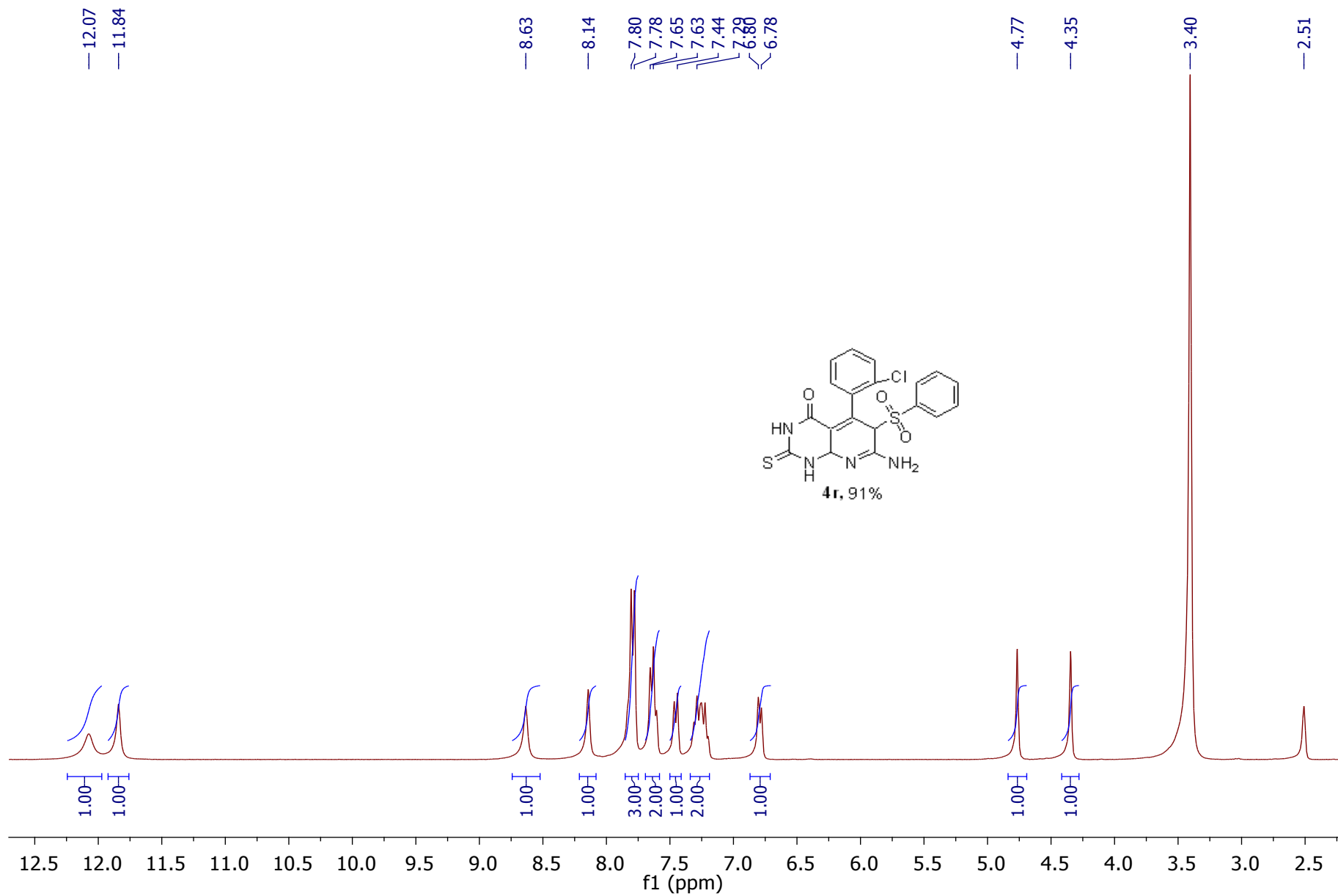


Fig S-34: ¹H NMR Spectrum of Product **4r**

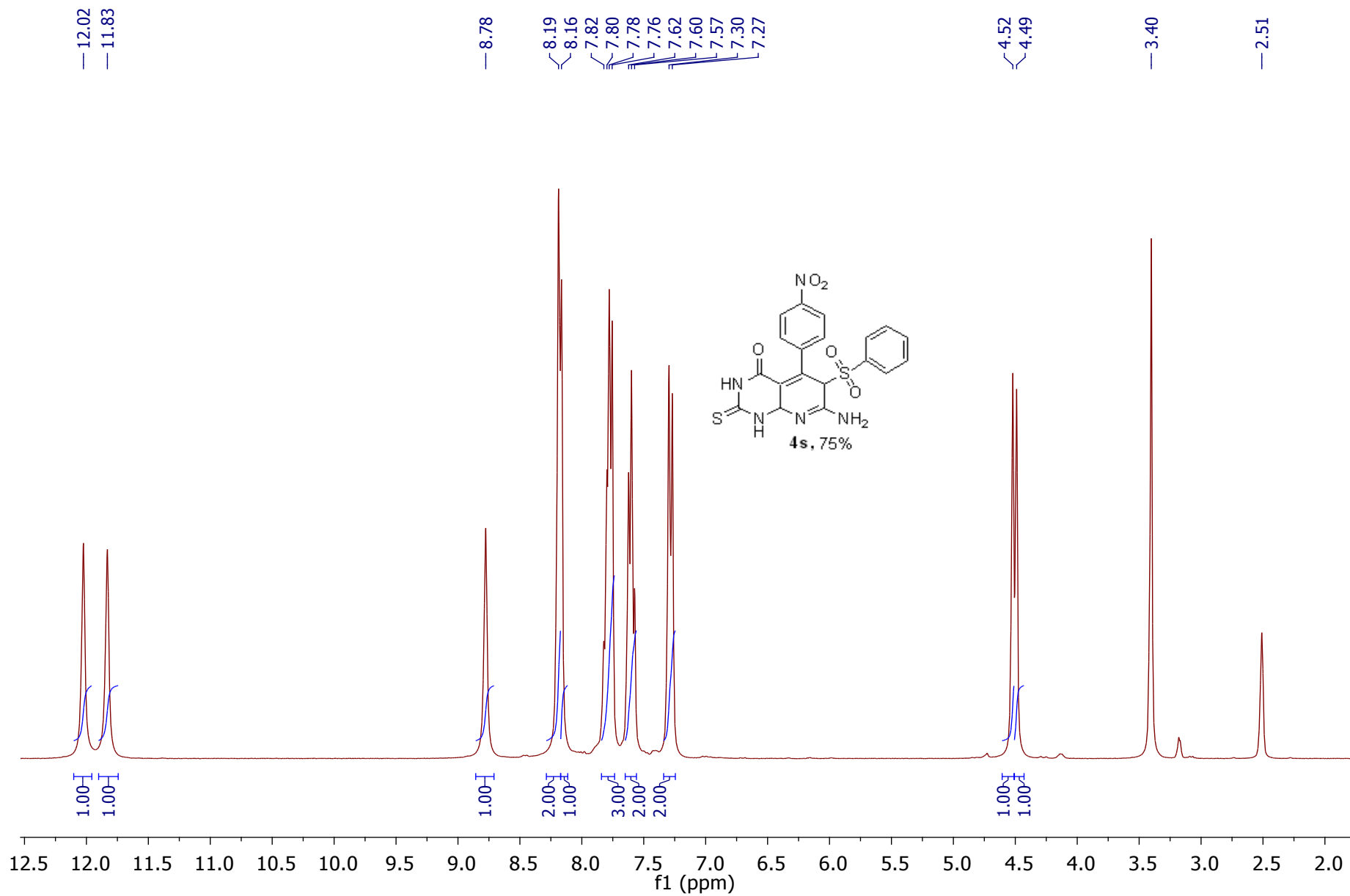


Fig S-35: ¹H NMR Spectrum of Product **4s**

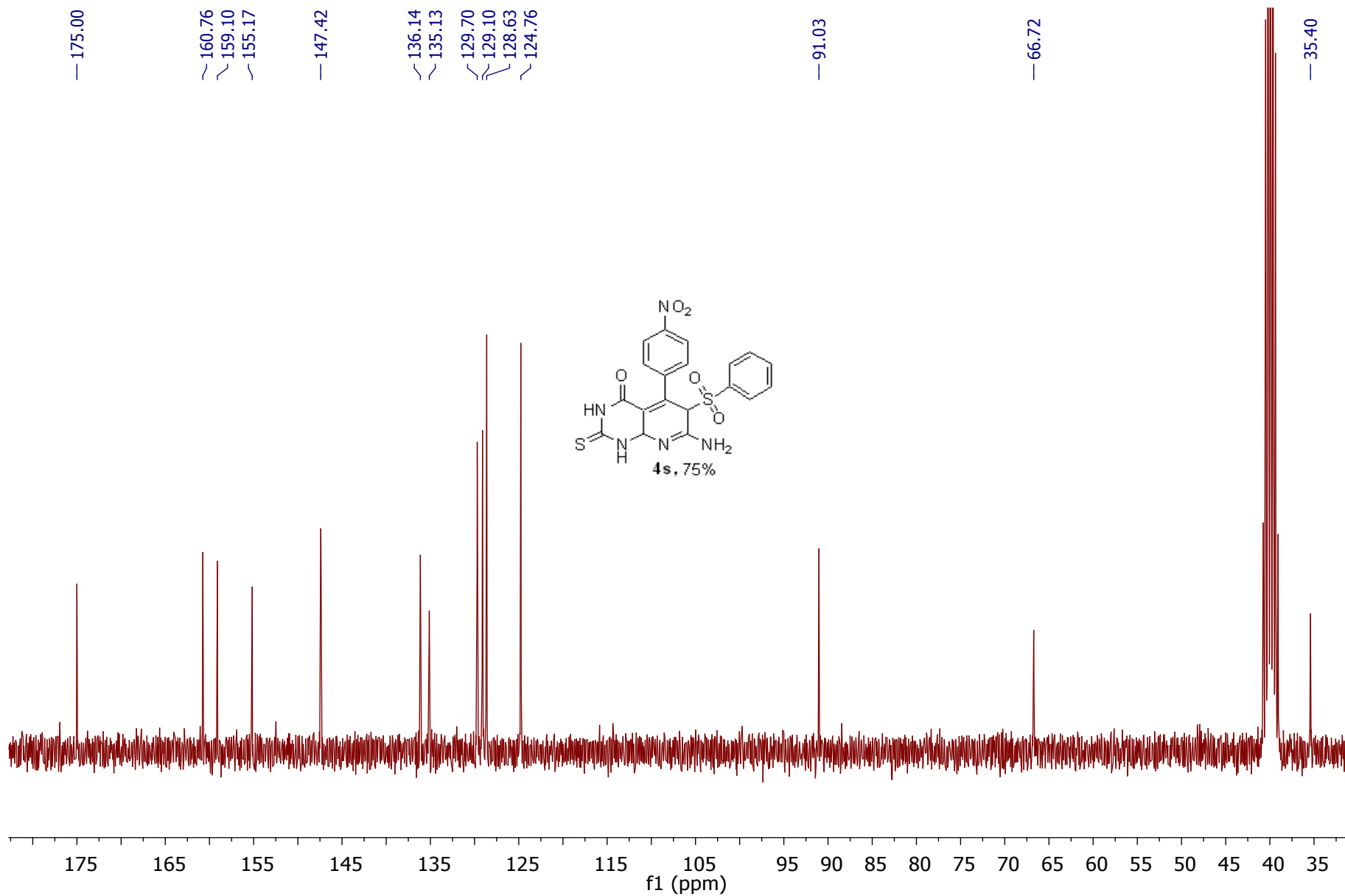


Fig S-36: ¹³C NMR Spectrum of Product 4s

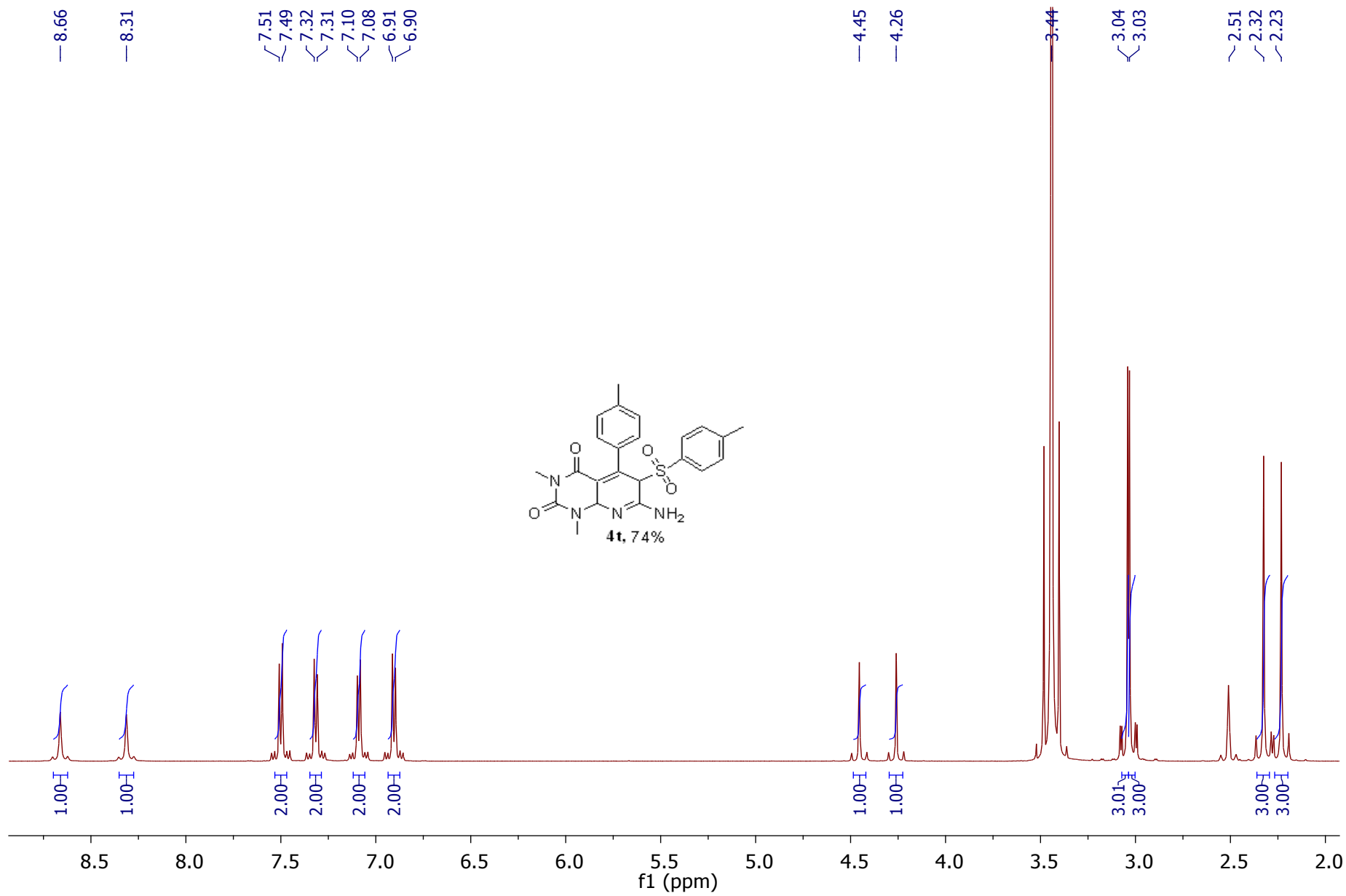


Fig S-37: ¹H NMR Spectrum of Product 4t

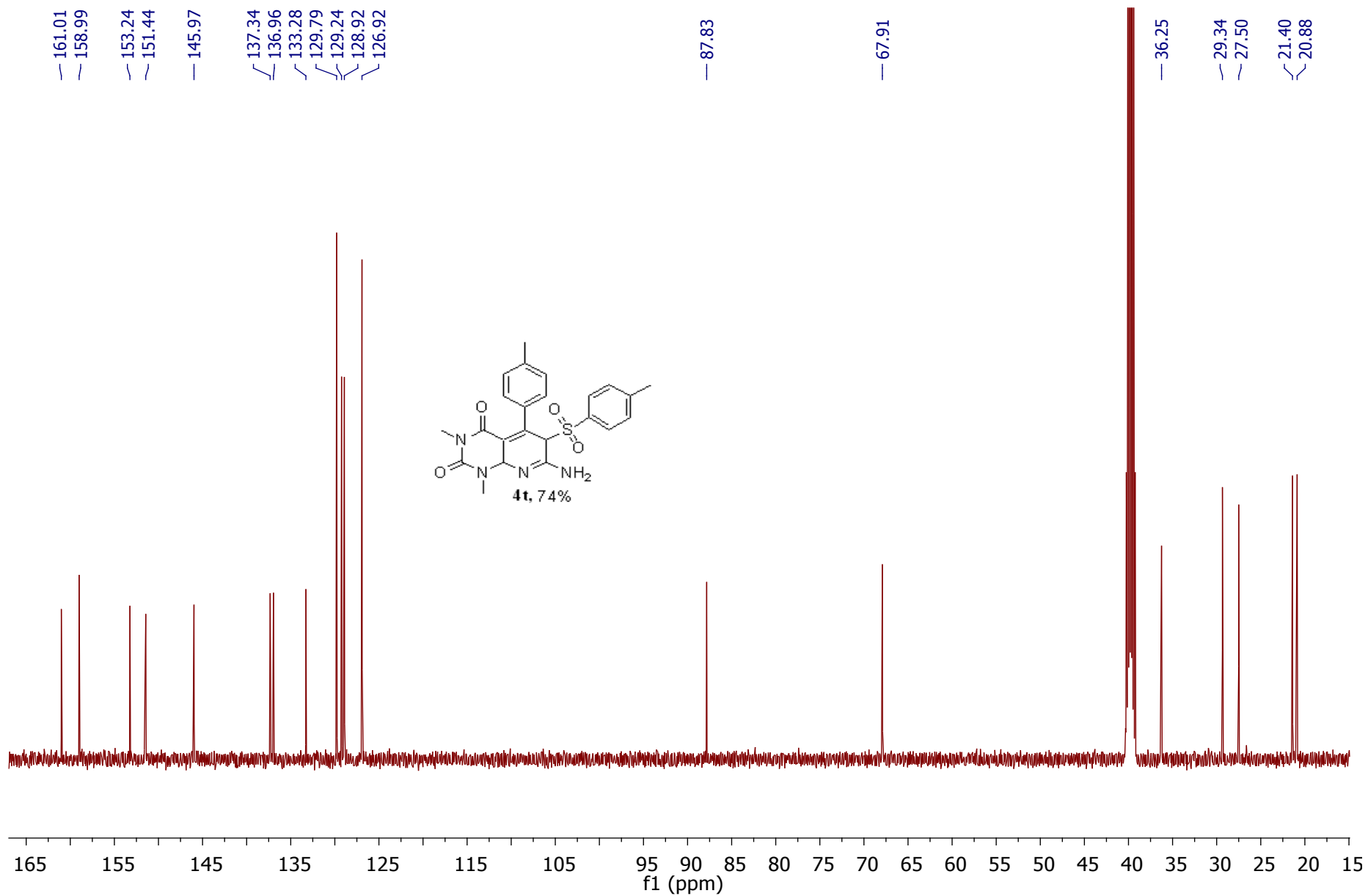


Fig S-38: ^{13}C NMR Spectrum of Product **4t**

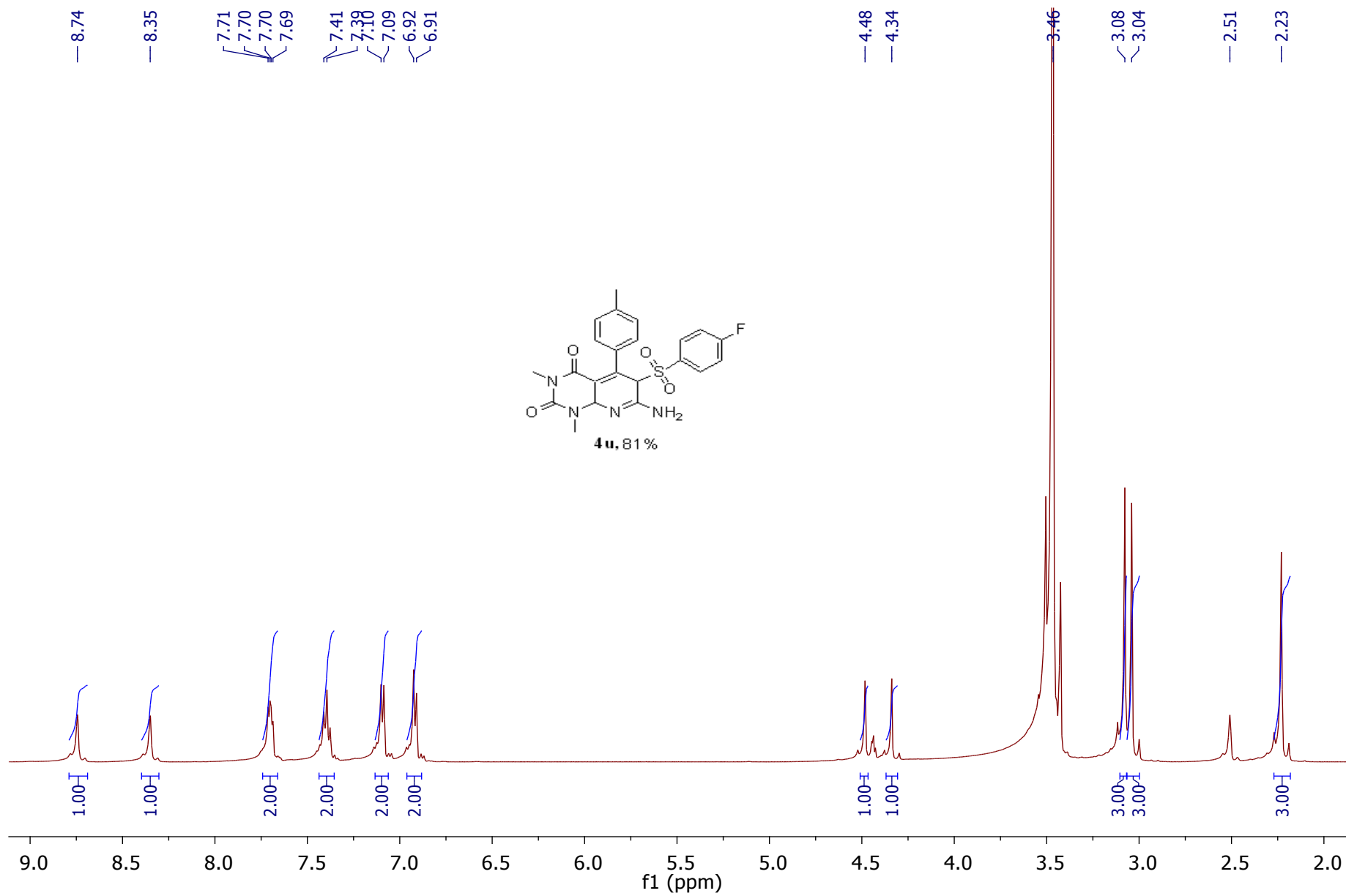


Fig S-39: ^1H NMR Spectrum of Product **4u**

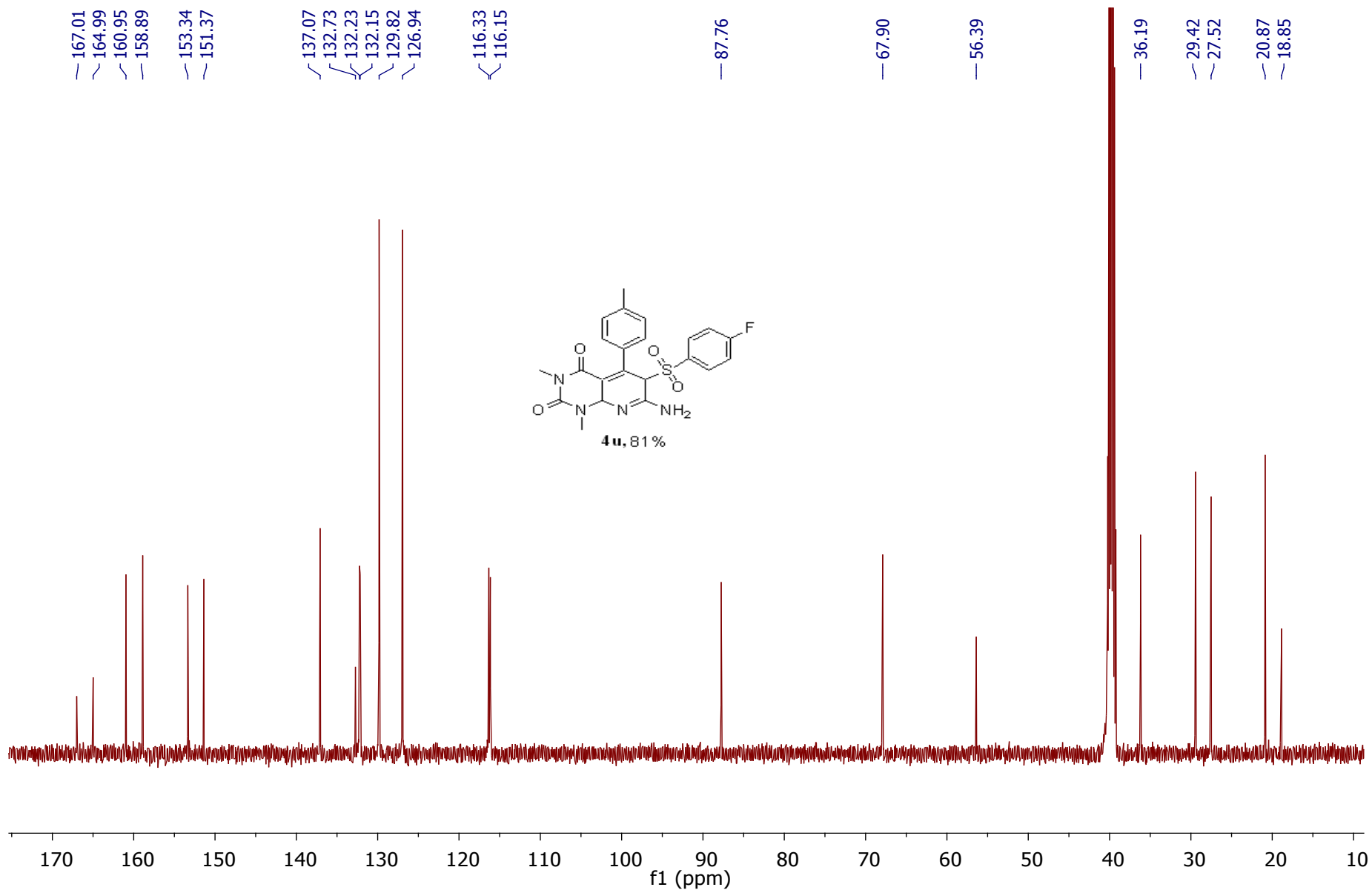


Fig S-40: ^{13}C NMR Spectrum of Product **4u**

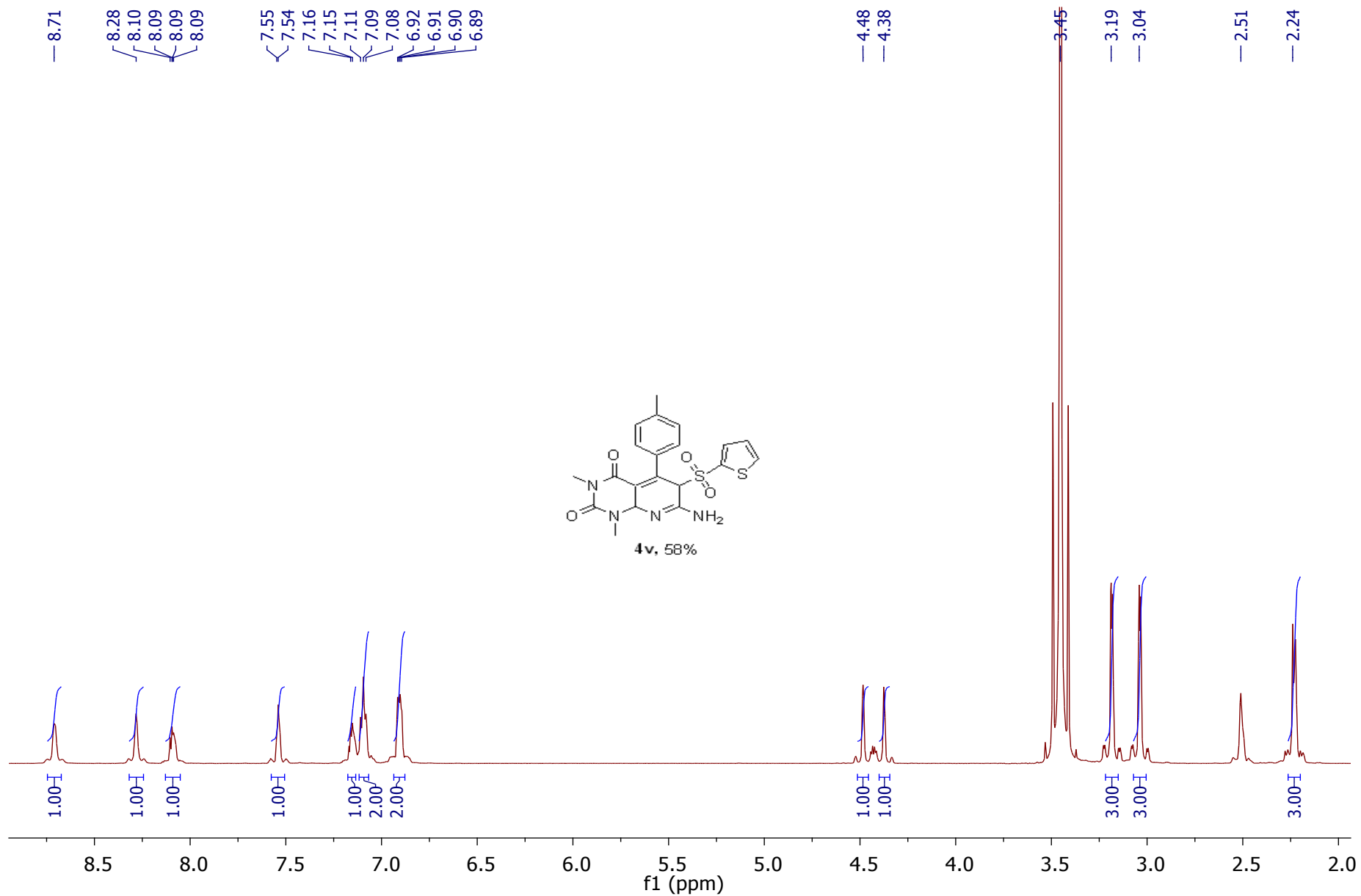


Fig S-41: ^1H NMR Spectrum of Product **4v**

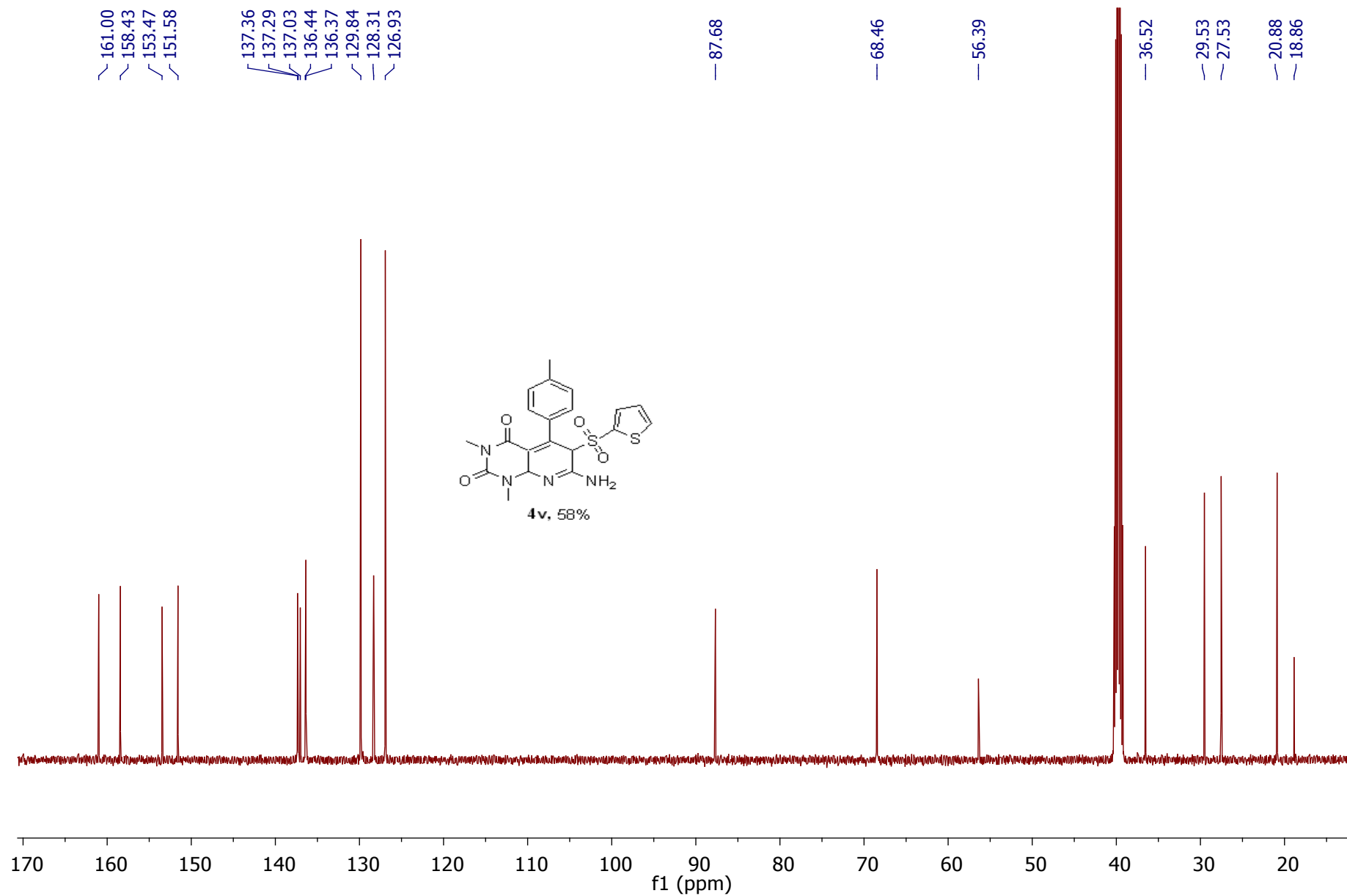


Fig S-42: ^{13}C NMR Spectrum of Product 4v

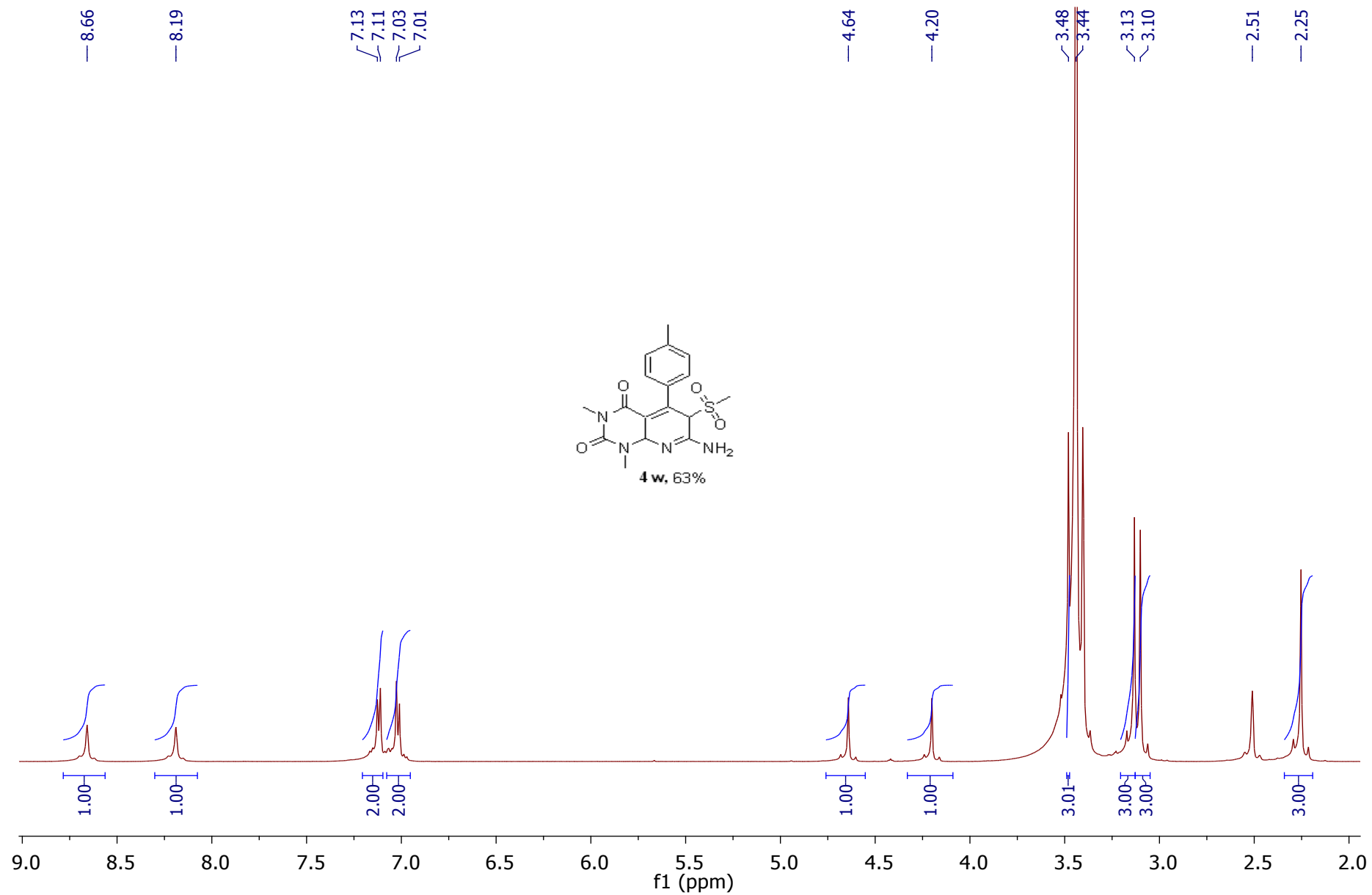


Fig S-43: ¹H NMR Spectrum of Product **4w**

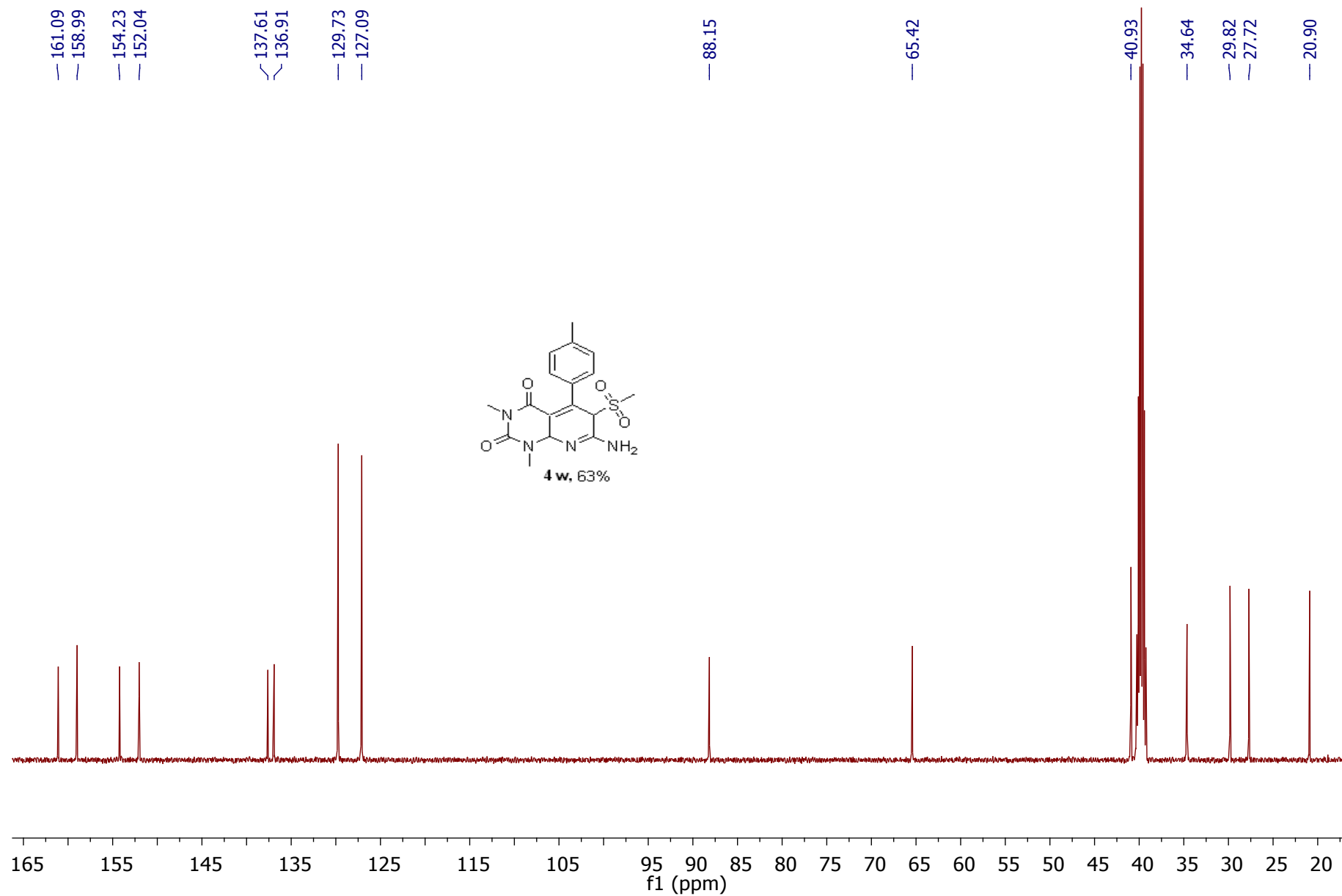


Fig S-44: ^{13}C NMR Spectrum of Product **4w**

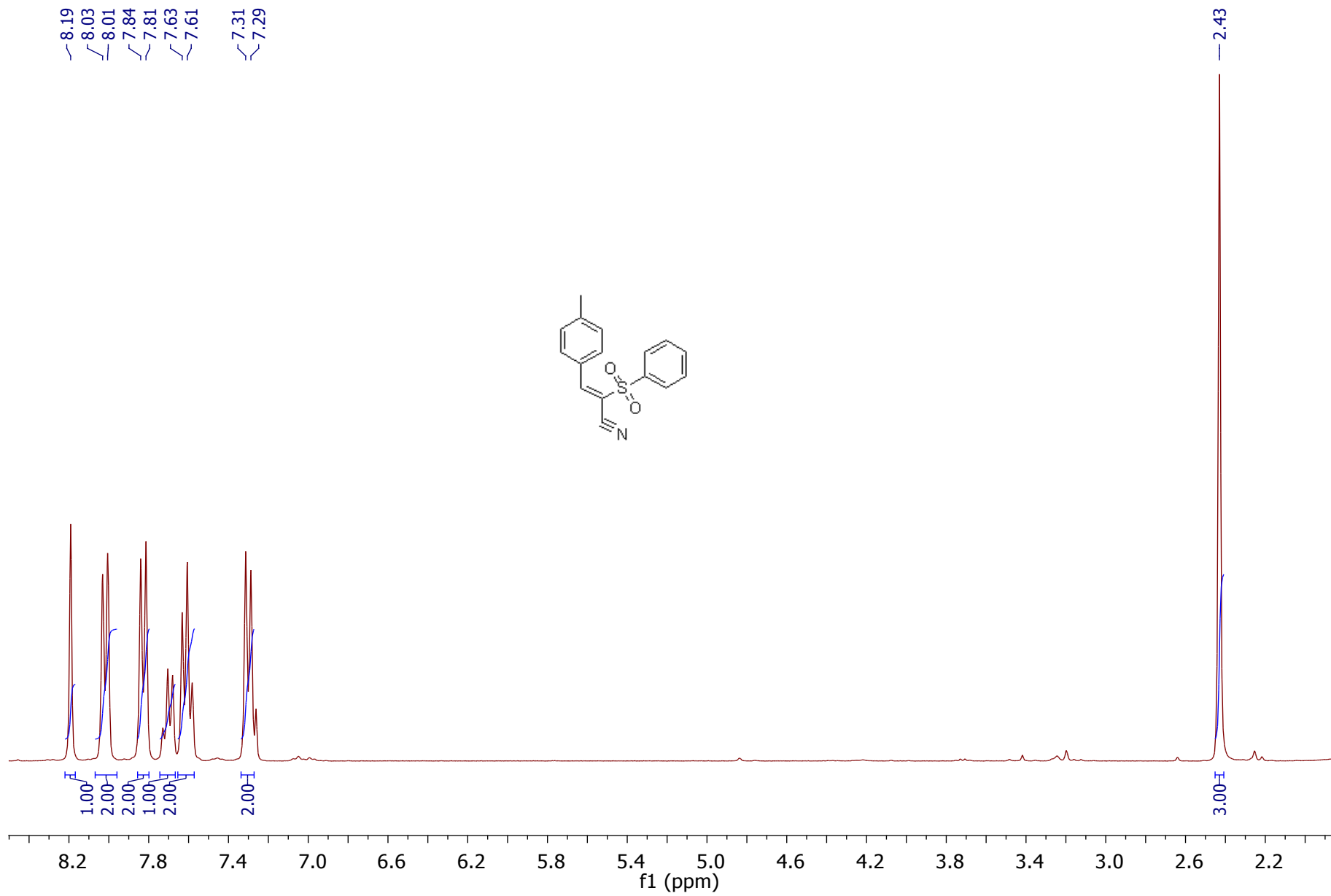


Fig S-45: ^1H NMR Spectrum of Knoevenagel Product A