

Regioselective synthesis, structural diversification and cytotoxic activity of (thiazol-4-yl)furoxans

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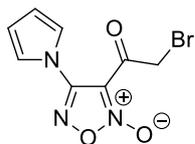
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General remarks

^1H and ^{13}C NMR spectra were recorded on a Bruker AM-300 (300.13 and 75.47 MHz, respectively) and Bruker AC-200 (200.13 and 50.32 MHz, respectively) spectrometers and referenced to residual solvent peak. The chemical shifts are reported in ppm (δ); multiplicities are indicated by s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet) and br (broad). Coupling constants, J , are reported in Hertz. The IR spectra were recorded on a Bruker “Alpha” spectrometer in the range 400-4000 cm^{-1} (resolution 2 cm^{-1}) as pellets with KBr or as a thin layer. The melting points were determined on Stuart SMP20 apparatus and are uncorrected. Analytical thin-layer chromatography (TLC) was carried out on Merck 25 TLC silica gel 60 F₂₅₄ aluminum sheets. The visualization of the TLC plates was accomplished with a UV light. Flash chromatography was performed on silica gel 60 A (0.060-0.200 mm, Acros Organics). High resolution mass spectra were recorded on a Bruker microTOF spectrometer with electrospray ionization (ESI). 4-Amino-3-(bromoacetyl)furoxan **1a** [S1] and compound **4a** [S2] were prepared according to the published procedures.

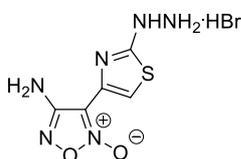
Characteristics of the synthesized compounds



3-Bromoacetyl-4-(1H-pyrrol-1-yl)furoxan 1c.

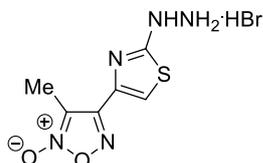
2,5-Dimethoxytetrahydrofuran (1.40 g, 10.6 mmol) was added to a solution of 4-amino-3-(bromoacetyl)furoxan **1a** (2.22 g, 10 mmol) in AcOH (20 mL). The mixture was stirred at 78–80 °C for 2 h (TLC monitoring) and AcOH was evaporated under reduced pressure. The residue was purified by flash chromatography (eluent CHCl₃-CCl₄, 1:3).

White solid, yield 2.10 g (77%), mp 57–58 °C, *R_f* 0.85 (CHCl₃). IR (KBr): 3144, 2999, 2946, 1705, 1593, 1539, 1475, 1337, 1226, 1111, 960, 831, 733 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ: 7.28 (br. s, 2H, CH pyrrole), 6.43 (br. s, 2H, CH pyrrole), 4.49 (s, 2H, CH₂); ¹³C NMR (75.5 MHz, CDCl₃) δ: 180.0, 151.2, 121.6, 121.3, 112.8, 112.4, 109.7, 32.0. Calcd for C₈H₆BrN₃O₃ (%): C 35.32, H 2.22, N 15.45. Found C 35.45, H 2.36, N 15.29.



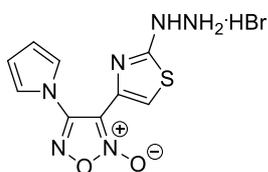
4-Amino-3-(2-hydrazinylthiazol-4-yl)furoxan hydrobromide 2a.

Yield 0.84 g (95%), yellow solid, mp 175–180 °C. IR (KBr), ν, cm⁻¹: 3407, 3296, 2967, 1611, 1542, 1178, 1072, 998, 820, 754. ¹³C NMR, δ, ppm: 167.7, 155.9, 134.1, 113.4, 106.1. Calcd. for C₅H₇BrN₆O₂S (%): C 20.35; H 2.39; N 28.48. Found: C 20.45; H 2.28; N 28.60.



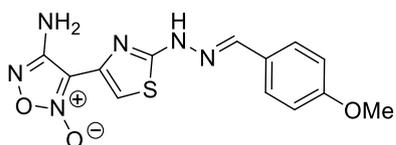
4-(2-Hydrazinylthiazol-4-yl)-3-methylfuroxan hydrobromide 2b.

Yield 0.81 g (92%), yellow solid, mp 155–160 °C. IR (KBr), ν, cm⁻¹: 3317, 3165, 3099, 1665, 1598, 1461, 1374, 1110, 1038, 852. ¹³C NMR, δ, ppm: 169.5, 152.3, 137.0, 113.9, 112.6, 9.1. Calcd. for C₆H₈BrN₅O₂S (%): C 24.50; H 2.74; N 23.81. Found: C 24.39; H 2.84; N 23.77.



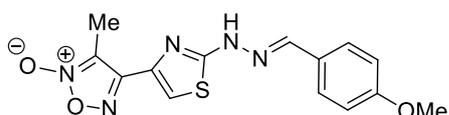
3-(2-Hydrazinylthiazol-4-yl)-4-(pyrrol-1-yl)furoxan hydrobromide 2c.

Yield 0.87 g (84%), yellow solid, mp 115–120 °C. IR (KBr), ν, cm⁻¹: 3274, 2972, 1610, 1545, 1533, 1464, 1426, 1353, 1102, 794. Calcd. for C₉H₉BrN₆O₂S (%): C 31.32; H 2.63; N 24.35. Found: C 31.40; H 2.74; N 24.47. NMR spectra for this compound could not be recorded due to its fast decomposition in DMSO-d₆ and insolubility in other *d*-solvents (CDCl₃, acetone-d₆, CD₃CN).



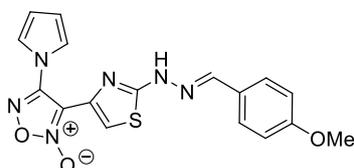
4-Amino-3-[2-[2-(4-methoxybenzylidene)hydrazino]thiazol-4-yl]furoxan 3a.

Beige solid, yield 0.55 g (83%), mp 203-204 °C (EtOH), R_f 0.43 (CHCl₃-EtOAc, 3:1). IR (KBr): 3422, 3321, 1607, 1575, 1559, 1510, 1246, 1168, 1030, 828 cm⁻¹; ¹H NMR (300 MHz, DMSO-d₆) δ: 12.11 (s, 1H, NH), 7.99 (s, 1H, CH thiazole), 7.68 (s, 1H, N=CH), 7.59 (d, 2H, Ar, ³J 8.6), 6.98 (d, 2H, Ar, ³J 8.6), 6.69 (s, 2H, NH₂), 3.78 (s, 3H, OMe); ¹³C NMR (75.5 MHz, DMSO-d₆) δ: 169.7, 161.0, 156.3, 143.2, 135.3, 128.5, 127.0, 114.8, 110.4, 106.3, 55.7; HRMS (ESI) m/z for C₁₃H₁₃N₆O₃S (M+H)⁺: calcd 333.0764, found 333.0759.



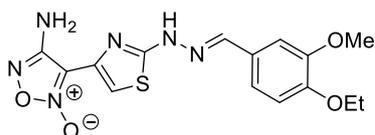
4-{2-[2-(4-Methoxybenzylidene)hydrazino]thiazol-4-yl}-3-methylfuroxan 3b.

Yellow solid, yield 0.52 g (79%), mp 207-208 °C (EtOH), R_f 0.65 (CHCl₃-EtOAc, 3:1). IR (KBr): 3423, 1607, 1587, 1512, 1244, 1172, 1033, 830 cm⁻¹; ¹H NMR (300 MHz, DMSO-d₆) δ: 12.16 (br s, 1H exchangeable proton, NH), 8.00 (s, 1H, CH thiazole), 7.59 (d, 2H, Ar, ³J 8.6), 7.57 (s, 1H, N=CH), 6.98 (d, 2H, Ar, ³J 8.6), 3.78 (s, 3H, OCH₃), 2.37 (s, 3H, CH₃); ¹³C NMR (75.5 MHz, DMSO-d₆) δ: 169.8, 160.9, 153.1, 142.8, 138.4, 128.4, 127.2, 114.8, 113.1, 112.1, 55.7, 9.5; HRMS (ESI) m/z for C₁₄H₁₄N₅O₃S (M+H)⁺: calcd 332.0811, found 332.0812.



3-{2-[2-(4-Methoxybenzylidene)hydrazino]thiazol-4-yl}-4-(1H-pyrrol-1-yl)furoxan 3c.

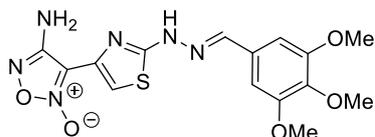
Grey solid, yield 0.63 g (83%), mp 211-212 °C (EtOH), R_f 0.43 (CHCl₃-EtOAc, 3:1). IR (KBr): 3268, 1609, 1570, 1537, 1512, 1438, 1247, 1111, 1021, 746 cm⁻¹; ¹H NMR (300 MHz, DMSO-d₆) δ: 12.11 (s, 1H, NH), 8.00 (s, 1H, CH thiazole), 7.64 (s, 1H, N=CH), 7.59 (d, 2H, Ar, ³J 8.2), 7.37 (s, 2H, CH pyrrole), 6.99 (d, 2H, Ar, ³J 8.2), 6.38 (s, 2H, CH pyrrole), 3.79 (s, 3H, CH₃); ¹³C NMR (75.5 MHz, DMSO-d₆) δ: 168.9, 160.4, 151.5, 142.5, 132.6, 127.9, 126.7, 121.6, 114.3, 113.8, 111.5, 108.4, 55.2; HRMS (ESI) m/z for C₁₇H₁₅N₆O₃S (M+H)⁺: calcd 383.0921, found 383.0925.



4-Amino-3-[2-[2-(4-ethoxy-3-methoxybenzylidene)hydrazino]thiazol-4-yl]furoxan 3d.

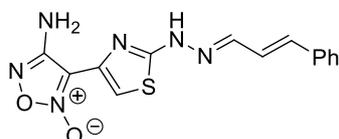
Beige solid, yield 0.48 g (64%), mp 204-206 °C (EtOH), R_f 0.55 (CHCl₃-EtOAc, 3:1). IR (KBr): 3366, 3273, 1600, 1576, 1511, 1439, 1266, 1120, 1031, 742 cm⁻¹; ¹H NMR (300 MHz, DMSO-d₆) δ: 12.15 (s, 1H, NH), 8.00 (s, 1H, CH thiazole), 7.72 (s, 1H, N=CH), 7.29 (s, 1H, Ar), 7.18 (d, 1H, Ar, ³J 8.0), 6.99 (d, 1H, Ar, ³J 8.0), 6.73 (s, 2H, NH₂), 4.06 (q, 2H, OCH₂, ³J 6.7), 3.83

(s, 3H, MeO), 1.35 (t, 3H, CH₃, ³J 6.7); ¹³C NMR (75.5 MHz, DMSO-d₆) δ: 169.2, 155.8, 149.6, 149.1, 142.9, 134.9, 126.7, 120.6, 112.5, 109.9, 108.6, 105.7, 63.7, 55.3, 14.6; HRMS (ESI) *m/z* for C₁₅H₁₇N₆O₄S (M+H)⁺: calcd 377.1027, found 377.1033.



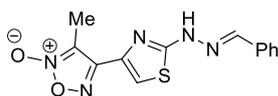
4-Amino-3-{2-[2-(3,4,5-trimethoxybenzylidene)hydrazino]thiazol-4-yl}furoxan 3e.

Grey-purple solid, yield 0.65 g (83%), mp 209-211 °C (EtOH), *R_f* 0.32 (CHCl₃-EtOAc, 3:1). IR (KBr): 3467, 3300, 3206, 1602, 1581, 1504, 1437, 1329, 1231, 1122, 1003 cm⁻¹; ¹H NMR (300 MHz, DMSO-d₆) δ: 12.26 (s, 1H, NH), 7.99 (s, 1H, CH thiazole), 7.72 (s, 1H, N=CH), 7.00 (s, 2H, Ar), 6.72 (s, 2H, NH₂), 3.84 (s, 6H, 2 x OMe), 3.72 (s, 3H, OMe); ¹³C NMR (75.5 MHz, DMSO-d₆) δ: 169.1, 155.8, 153.2, 142.5, 139.0, 134.9, 129.5, 110.1, 105.8, 103.8, 60.1, 55.8; HRMS (ESI) *m/z* for C₁₅H₁₇N₆O₅S (M+H)⁺: calcd 393.0975, found 393.0978.



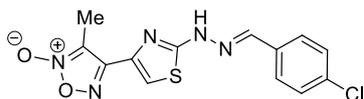
4-Amino-3-{2-[2-(3-phenylprop-2-en-1-ylidene)hydrazino]thiazol-4-yl}furoxan 3f.

Yellowish solid, yield 0.54 g (82%), mp 235-236 °C (EtOH), a mixture of *E* and *Z*-isomers, *R_f* 0.15 (CHCl₃). IR (KBr): 3448, 3321, 1602, 1571, 1438, 1138, 1062, 966, 750 cm⁻¹; ¹H NMR (300 MHz, DMSO-d₆) δ: 12.15 and 11.85 (both br s, 1H, NH), 7.88 (s, 1H, CH thiazole), 7.71-7.57 (m, 3H), 7.45-7.24 (m, 3H), 7.09-6.97 (m, 2H), 6.77 and 6.68. (both s, 2H, NH₂); ¹³C NMR (75.5 MHz, DMSO-d₆) δ: 168.6, 155.7, 145.3, 141.91, 140.0, 137.7, 135.9, 135.8, 134.8, 129.3, 128.8, 128.7, 128.5, 127.4, 126.9, 124.8, 118.0, 110.4, 110.1, 105.7; HRMS (ESI) *m/z* for C₁₄H₁₂N₆O₂S (M+H)⁺: calcd 329.0815, found 329.0825.



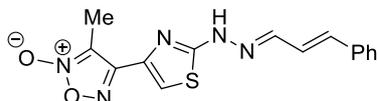
4-[2-(2-Benzylidenehydrazino)thiazol-4-yl]-3-methylfuroxan 3g.

Beige solid, yield 0.73 g (81%), mp 202-203 °C (EtOH), R_f 0.35 (CHCl₃-EtOAc, 10:1). IR (KBr): 3407, 1612, 1560, 1522, 1283, 1194, 1058, 836 cm⁻¹; ¹H NMR (300 MHz, DMSO-d₆) δ: 12.38 (br s, 1H exchangeable proton, NH), 8.06 (s, 1H, CH thiazole), 7.68-7.65 (m, 3H, Ph and CH hydrazone), 7.46-7.39 (m, 3H, Ph), 2.38 (s, 3H, Me). ¹³C NMR (75.5 MHz, DMSO-d₆) δ: 168.8, 152.6, 143.4, 139.0, 129.4, 128.9, 128.2, 115.4, 113.3, 110.9, 9.6; HRMS (ESI) m/z for C₁₃H₁₁N₅O₂S (M+H)⁺: calcd 302.0707, found 302.0710.



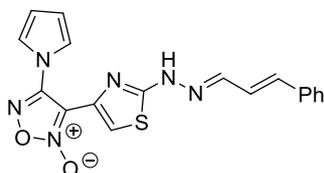
4-{2-[2-(4-Chlorobenzylidene)hydrazino]thiazol-4-yl}-3-methylfuroxan 3h.

Yellowish solid, yield 0.39 g (58%), mp 230-231 °C (EtOH), R_f 0.15 (CHCl₃). IR (KBr): 3449, 3082, 1598, 1582, 1509, 1468, 1165, 1054, 829 cm⁻¹; ¹H NMR (300 MHz, DMSO-d₆) δ: 12.42 (br s, 1H, NH), 8.03 (s, 1H, CH thiazole), 7.67 (d, 2H, Ar, ³J 8.2), 7.65 (s, 1H, N=CH), 7.47 (d, 2H, Ar, ³J 8.2), 2.37 (s, 3H, CH₃); ¹³C NMR (75.5 MHz, DMSO-d₆) δ: 169.6, 153.1, 141.5, 138.5, 134.4, 133.5, 129.4, 128.5, 113.0, 112.6, 9.5. HRMS (ESI) m/z for C₁₃H₁₁³⁵ClN₅O₂S (M+H)⁺: calcd 336.0316, found 336.0321.



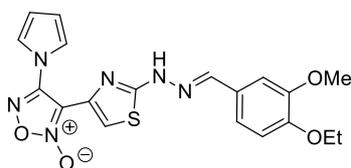
3-Methyl-4-{2-[2-(3-phenylprop-2-en-1-ylidene)hydrazino]thiazol-4-yl}furoxan 3i.

Yellowish solid, yield 0.57 g (85%), mp 206-207 °C (EtOH), R_f 0.15 (CHCl₃). IR (KBr): 3205, 1601, 1573, 1476, 1428, 1373, 1123, 1048, 964, 826, 749 cm⁻¹; ¹H NMR (300 MHz, DMSO-d₆) δ: 12.24 (br s, 1H, NH), 7.89 (s, 1H, CH thiazole), 7.63-7.59 (m, 2H, CH=CH), 7.56 (s, 1H, N=CH), 7.38-7.28 (m, 3H, Ph), 6.95 (br s, 2H, Ph), 2.36 (s, 3H, CH₃); ¹³C NMR (75.5 MHz, DMSO-d₆) δ: 168.7, 152.5, 144.9, 137.9, 137.3, 136.0, 128.7, 128.5, 126.9, 124.9, 112.4, 111.7, 8.9; HRMS (ESI) m/z for C₁₅H₁₄N₅O₂S (M+H)⁺: calcd 328.0862, found 328.0865.

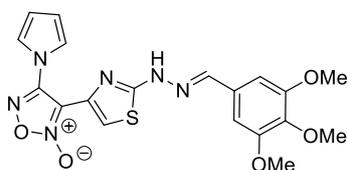


3-{2-[2-(3-Phenylprop-2-en-1-ylidene)hydrazino]thiazol-4-yl}-4-(1H-pyrrol-1-yl)furoxan 3j.

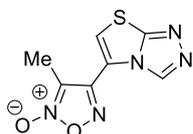
Grey solid, yield 0.46 g (61%), mp 178-180 °C (EtOH), a mixture of *E* and *Z*-isomers, R_f 0.25 (CHCl₃). IR (KBr): 3423, 1624, 1560, 1364, 1113, 970, 749, 691 cm⁻¹; ¹H NMR (300 MHz, DMSO-d₆) δ: 12.45 and 12.15 (both br s 1H, NH), 7.89 and 7.84 (both s, 1H, CH thiazole), 7.64-7.57 (m, 2H), 7.43-7.31 (m, 5H), 7.09-6.95 (m, 3H), 6.58-6.35 (m, 2H); ¹³C NMR (75.5 MHz, CDCl₃) δ: 145.2, 138.4, 136.0, 130.9, 128.8, 128.7, 127.4, 127.0, 126.7, 124.4, 121.5, 120.6, 112.5, 111.7. HRMS (ESI) m/z for C₁₈H₁₅N₆O₂S (M+H)⁺: calcd 379.0971, found 379.0978.



3-{2-[2-(4-Ethoxy-3-methoxybenzylidene)hydrazino]thiazol-4-yl}-4-(1H-pyrrol-1-yl)furoxan **3k**. Grey solid, yield 0.60 g (70%), mp 193-194 °C (EtOH), R_f 0.16 (CHCl₃). IR (KBr): 3285, 1597, 1554, 1536, 1511, 1268, 1238, 1107, 735 cm⁻¹; ¹H NMR (300 MHz, DMSO-d₆) δ: 12.13 (s, 1H, NH), 7.98 (s, 1H, CH thiazole), 7.65 (s, 1H, N=CH), 7.37 (s, 2H, CH pyrrole), 7.25 (s, 1H, Ar), 7.14 (d, 1H, Ar, ³J 8.1), 6.97 (d, 1H, Ar, ³J 8.1), 6.38 (s, 2H, CH pyrrole), 4.04 (q, 2H, OCH₂, ³J 6.9), 3.80 (s, 3H, MeO), 1.33 (t, 3H, CH₃, ³J 6.9); ¹³C NMR (75.5 MHz, DMSO-d₆) δ: 168.9, 151.5, 149.5, 149.1, 142.6, 132.6, 126.8, 121.6, 120.4, 113.8, 112.6, 111.4, 108.6, 108.4, 63.7, 55.3, 14.6. HRMS (ESI) m/z for C₁₉H₁₉N₆O₄S (M+H)⁺: calcd 427.1183, found 427.1180.



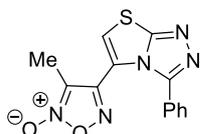
3-{2-[2-(3,4,5-Trimethoxybenzylidene)hydrazino]thiazol-4-yl}-4-(1H-pyrrol-1-yl)furoxan **3l**. Grey solid, yield 0.51 g (58%), mp 208-209 °C (EtOH), R_f 0.22 (CHCl₃). IR (KBr): 3132, 1580, 1537, 1504, 1456, 1413, 1329, 1234, 1126, 1002, 735 cm⁻¹; ¹H NMR (300 MHz, DMSO-d₆) δ: 12.26 (s, 1H, NH), 7.97 (s, 1H, CH thiazole), 7.67 (s, 1H, N=CH), 7.36 (s, 2H, CH pyrrole), 6.96 (s, 2H, Ar), 6.38 (s, 2H, CH pyrrole), 3.82 (s, 6H, 2 x MeO), 3.69 (s, 3H, MeO); ¹³C NMR (75.5 MHz, DMSO-d₆) δ: 168.9, 153.1, 151.5, 142.3, 132.6, 129.6, 121.6, 114.1, 111.5, 108.6, 103.7, 60.1, 55.8; HRMS (ESI) m/z for C₁₉H₁₉N₆O₅S (M+H)⁺: calcd 443.1132, found 443.1134.



3-Methyl-4-(thiazolo[2,3-c][1,2,4]triazol-5-yl)furoxan **4a**.

CF₃COOH (1 mL) was added to a magnetically stirred suspension of 4-(2-hydrazinylthiazol-4-yl)-3-methylfuroxan hydrobromide **2b** (0.59 g, 2 mmol) in trimethyl orthoformate (4 mL). In 10 min the reaction mixture became homogeneous and green. After standing for 12 h a precipitate was formed. It was filtered off, washed with water and dried in air.

Brown solid, yield 0.13 g (29%), mp 248-250 °C, R_f 0.24 (CHCl₃-EtOAc, 3:2). IR (KBr): 3163, 3077, 1612, 1594, 1496, 1468, 1368, 1198, 1173, 1036, 855, 814 cm⁻¹; ¹H NMR (300 MHz, DMSO-d₆) δ: 9.33 (s, 1H, CH triazole), 8.28 (s, 1H, CH thiazole), 2.40 (s, 3H, CH₃); ¹³C NMR (75.5 MHz, DMSO-d₆) δ: 155.7, 148.2, 137.0, 123.7, 116.6, 111.7, 8.8; HRMS (ESI) m/z for C₇H₆N₅O₂S (M+H)⁺: calcd 224.0237, found 224.0245.

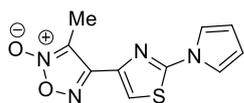


3-Methyl-4-(thiazolo[2,3-c][1,2,4](4-phenyltriazol-5-yl)furoxan **4b**.

PhI(OAc)₂ (0.386 g, 1.2 mmol) was added to a magnetically stirred suspension of hydrazone **3g** (0.301 g, 1.0 mmol) in MeCN (3 mL). The mixture was stirred at room temperature for 2 h until

the consumption of initial hydrazone (TLC monitoring, eluent CHCl₃-EtOAc, 10:1). The solvent was evaporated and the residue was triturated with Et₂O (5 mL). The solid formed was filtered off, washed consecutively with Et₂O (2x5 mL), PhH (3x5 mL) and ⁱPrOH (3 mL) and dried in air.

Beige solid, yield 0.153 g (51%), mp 170-172 °C, R_f 0.20 (CHCl₃-EtOAc, 10:1). IR (KBr): 1633, 1608, 1464, 1387, 1022, 804 cm⁻¹; ¹H NMR (300 MHz, DMSO-d₆) δ: 8.15 (s, 1H, CH thiazole), 7.49 (br s, 5H, Ph), 2.49 (s, 3H, CH₃); ¹³C NMR (75.5 MHz, DMSO-d₆) δ: 157.6, 148.2, 147.2, 130.2, 129.0, 128.1, 126.1, 124.9, 115.7, 113.0, 7.4. HRMS (ESI) *m/z* for C₁₃H₁₀N₅O₂S (M+H)⁺: calcd 300.0550, found 300.0549.



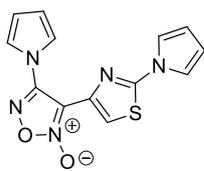
3-Methyl-4-[2-(1H-pyrrol-1-yl)thiazol-4-yl]furoxan 6a.

White solid, yield 2.01 g (81%), mp 111-112 °C, R_f 0.59 (CHCl₃). IR (KBr): 3123, 3101, 1604, 1560, 1526, 1482, 1465, 1374, 1173, 1032, 817, 731 cm⁻¹; ¹H NMR (300 MHz, DMSO-d₆) δ: 8.12 (s, 1H, CH thiazole), 7.50 (s, 2H, CH pyrrole), 6.36 (s, 2H, CH pyrrole), 2.39 (s, 3H, CH₃); ¹³C NMR (75.5 MHz, DMSO-d₆) δ: 161.2, 151.9, 138.3, 119.8, 117.3, 112.5, 112.4, 8.9. HRMS (ESI) *m/z* for C₁₀H₈N₄O₂S (M+H)⁺: calcd 249.0440, found 249.0435.



3-(2-Aminothiazol-4-yl)-4-(1H-pyrrol-1-yl)furoxan 6b.

White solid, yield 0.60 g (80%), mp 134-135 °C, R_f 0.73 (CHCl₃-EtOAc, 3:1). IR (KBr): 3414, 3141, 1631, 1613, 1562, 1539, 1469, 1098, 790, 737 cm⁻¹; ¹H NMR (300 MHz, DMSO-d₆) δ: 7.42-7.28 (m, 5H, Het), 6.36 (s, 2H, NH₂); ¹³C NMR (75.5 MHz, DMSO-d₆) δ: 169.3, 152.0, 132.1, 122.0, 112.6, 112.0, 108.8; HRMS (ESI) *m/z* for C₉H₇N₅O₂S (M+H)⁺: calcd 250.0393, found 250.0399.



3-[2-(1H-Pyrrol-4-yl)thiazol-4-yl]-4-(1H-pyrrol-1-yl)furoxan 6c.

Grey solid, yield 0.42 g (70%), mp 156-157 °C, R_f 0,18 (CCl₄). IR (KBr): 3165, 3126, 1599, 1537, 1526, 1432, 1105, 1071, 796, 727 cm⁻¹; ¹H NMR (300 MHz, DMSO-d₆) δ: 8.24 (s, 1H, CH thiazole), 7.33 (s, 4H, CH pyrrole), 6.40 (s, 2H, CH pyrrole), 6.34 (s, 2H, CH pyrrole); ¹³C NMR (75.5 MHz, DMSO-d₆) δ: 160.8, 151.7, 133.3, 122.3, 119.7, 118.8, 112.6, 110.9, 108.9. HRMS (ESI) *m/z* for C₁₃H₉N₅O₂S (M+H)⁺: calcd 300.0550, found 300.0554.

Cytotoxicity in vitro

The IC₅₀ values of the synthesized compounds against cells were determined by the MTT method [S3]. A549 and HCT116 cells were seeded at 1.0×10^4 cells/200 μ L in 96-well plates and incubated at 37 °C in a humidified atmosphere with 5% CO₂. After 24 h of pre-incubation, the various concentrations of the tested compounds (100-1.56 μ M) were added into each well, and these cells were incubated under similar conditions for 72 h. All compounds were dissolved in DMSO. The final DMSO concentration in each well did not exceed 1% and was not toxic for the cells. The wells with a specific cell culture containing 1% DMSO solution in the medium were monitored as control. After incubation, 20 mM MTT reagent (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide), at a final concentration of 5 mg/mL, was added into each well, and the cells were incubated for another 2 h. The medium was removed and 100 μ L DMSO was added to each well. The optical density was measured at 544 nm minus background absorption at 620 nm using the Victor3 (Perkin Elmer) microplate reader. Concentrations (IC₅₀) were calculated according to the dose-dependent inhibition curves with GraphPad Prism 7 software. The experiments were carried out in triplicate.

Table S1. Cytotoxicity results of thiazolylfuroxans derivatives **3-6**

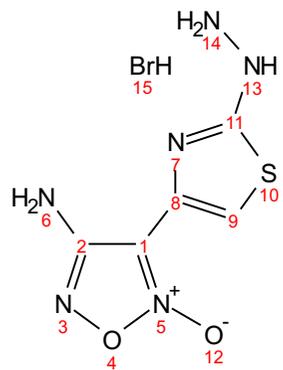
Compound	IC ₅₀ , μ M	
	A549	HCT116
3a	257.84 \pm 12.65	799.84 \pm 11.56
3b	- ^a	- ^a
3c	90.11 \pm 10.13	193.04 \pm 8.27
3d	676.06 \pm 34.76	- ^a
3e	137.54 \pm 3.94	261.78 \pm 8.52
3f	524.43 \pm 13.36	- ^a
3i	96.29 \pm 1.57	247.62 \pm 10.21
3j	36.04 \pm 1.01	70.74 \pm 3.59
3k	- ^a	- ^a
3l	259.09 \pm 20.67	759.46 \pm 22.44
4a	- ^a	- ^a
4b	365.43 \pm 26.33	880.46 \pm 42.70
5a	456.90 \pm 24.14	341.07 \pm 3.94
5b	237.61 \pm 3.08	542.19 \pm 21.58
5c	271.38 \pm 15.49	682.56 \pm 44.31
6a	- ^a	- ^a
6b	130.35 \pm 1.37	442.42 \pm 19.07
6c	547.37 \pm 17.06	908.73 \pm 21.49
Camptothecin	2.71 \pm 0.09	2.99 \pm 0.24

^a no effect

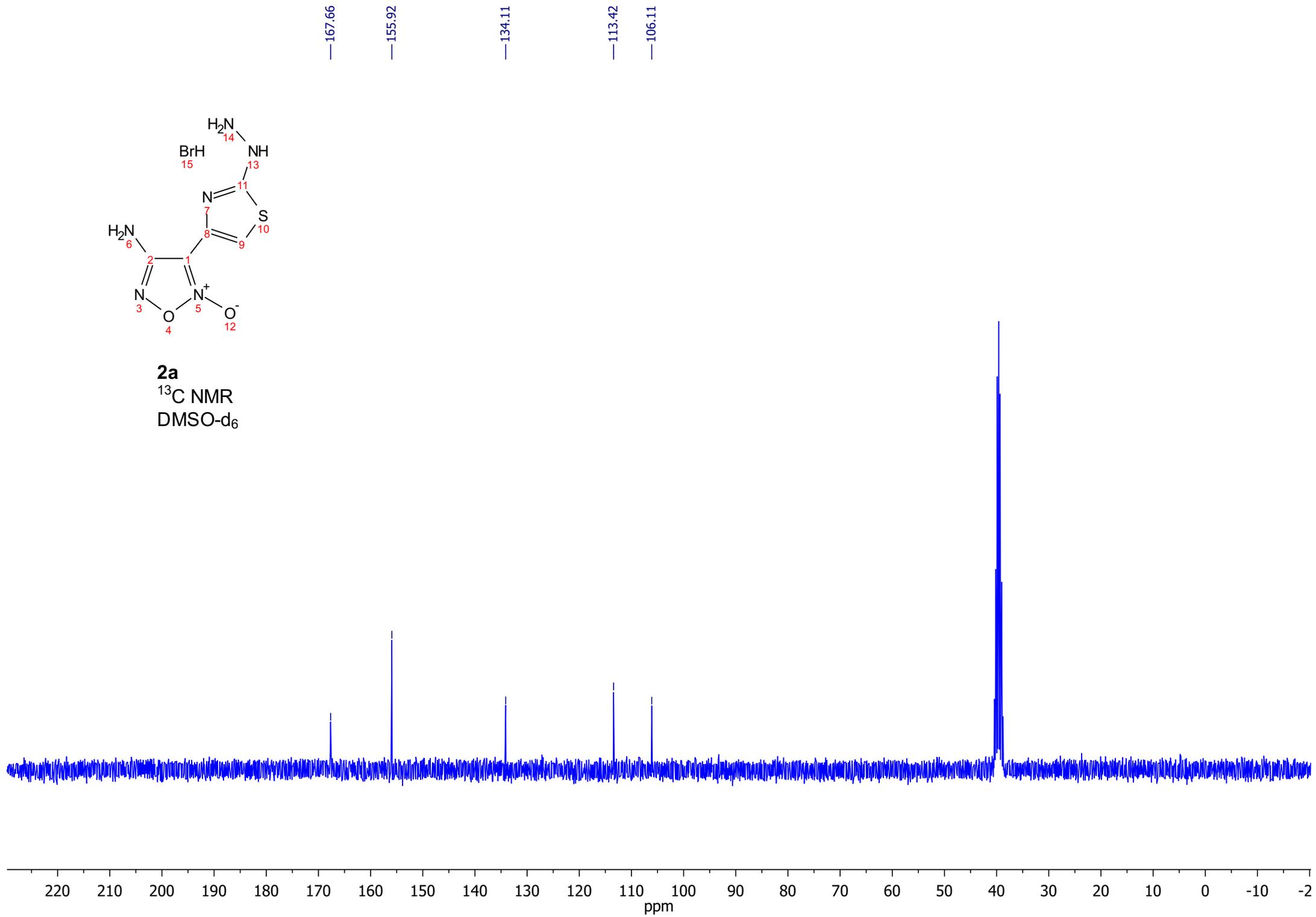
References

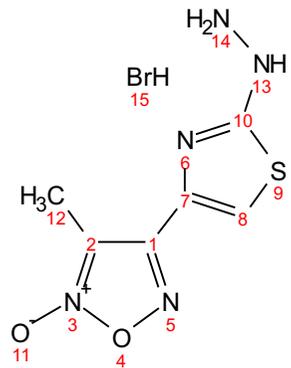
- [S1] A. B. Sheremetev, A. S. Kulikov and L. I. Khmel'nitskii, *Russ. Chem. Bull.*, 1993, **42**, 708 (*Izv. Akad. Nauk, Ser. Khim.*, 1993, 744).
- [S2] A. S. Kulikov and N. N. Makhova, *Russ. Chem. Bull.*, 1998, **47**, 139 (*Izv. Akad. Nauk, Ser. Khim.*, 1998, 137).
- [S3] T. Mosmann, *J. Immunol. Methods*, 1983, **65**, 55.

Copies of NMR spectra

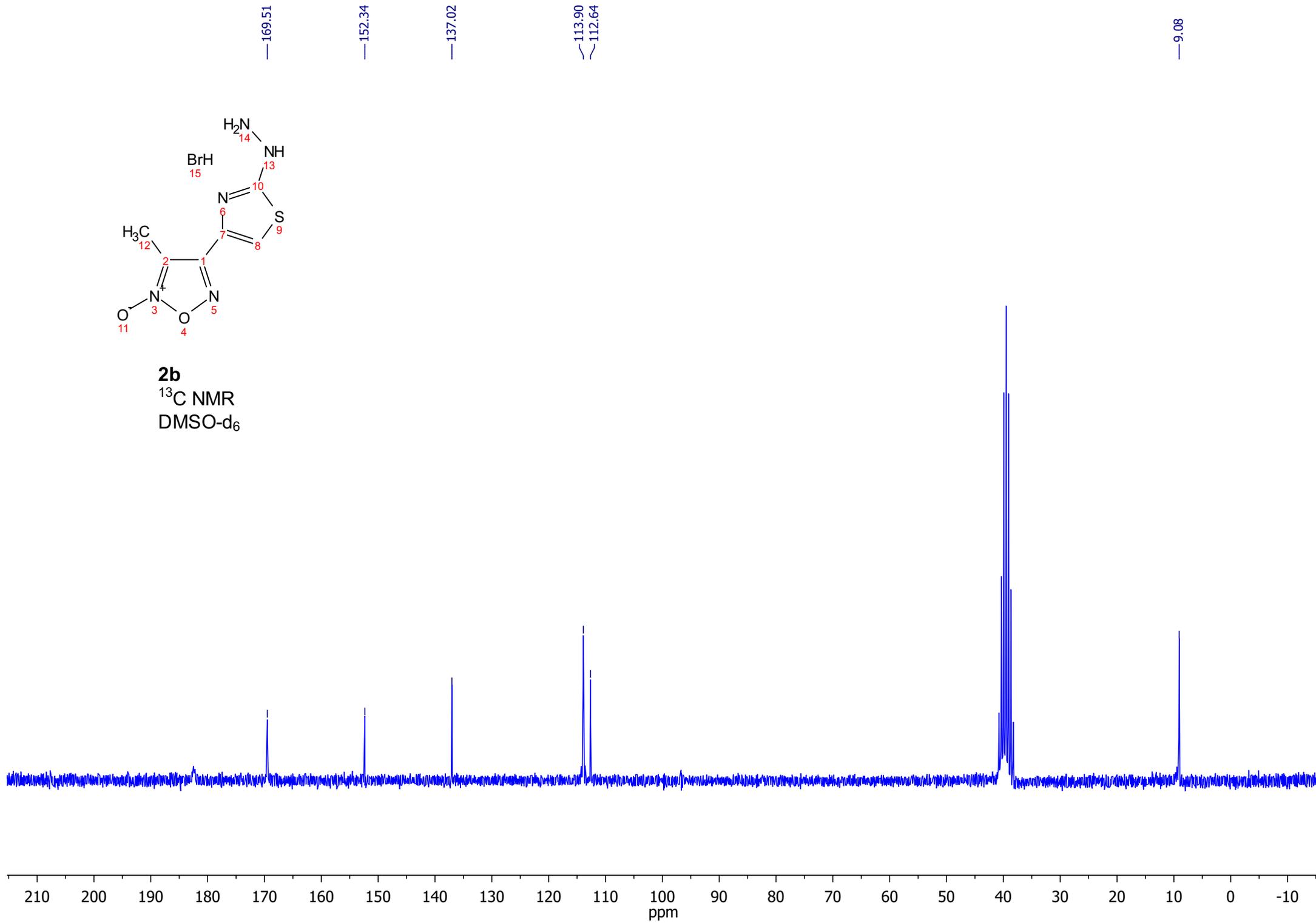


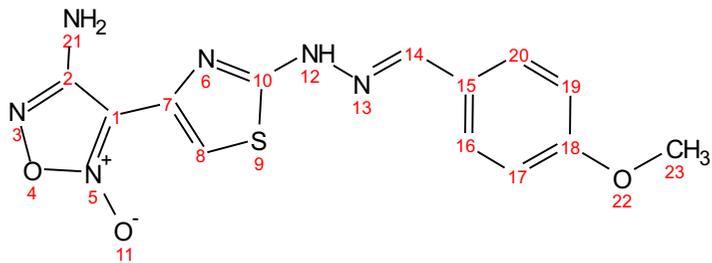
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DMSO-d₆



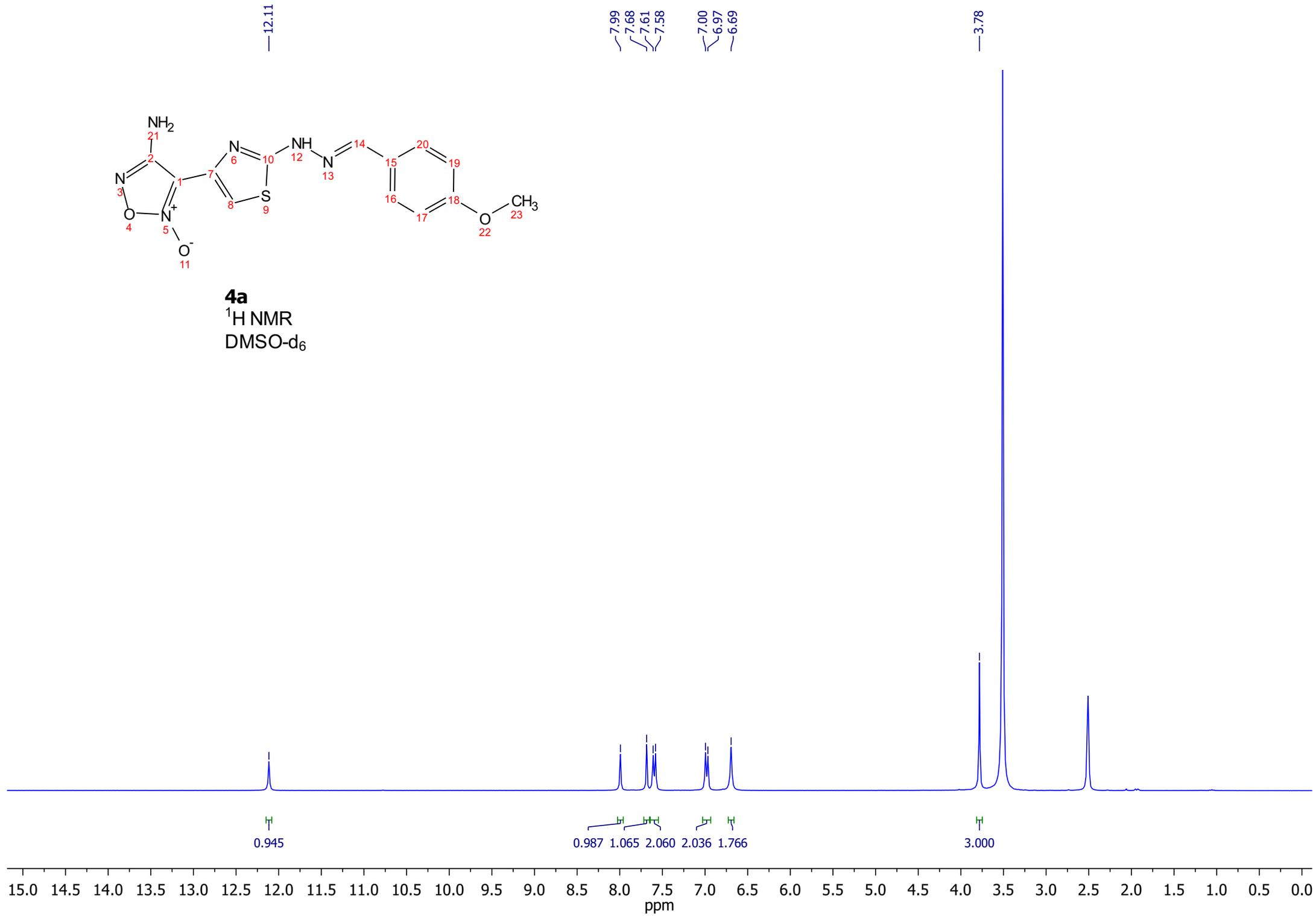


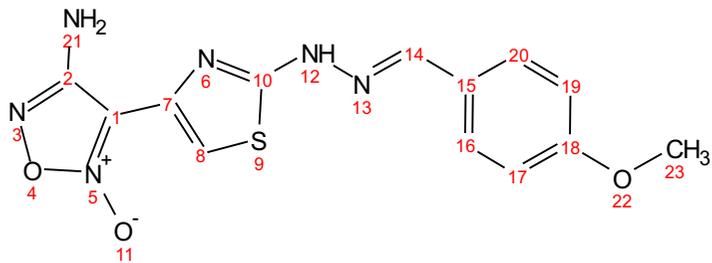
2b
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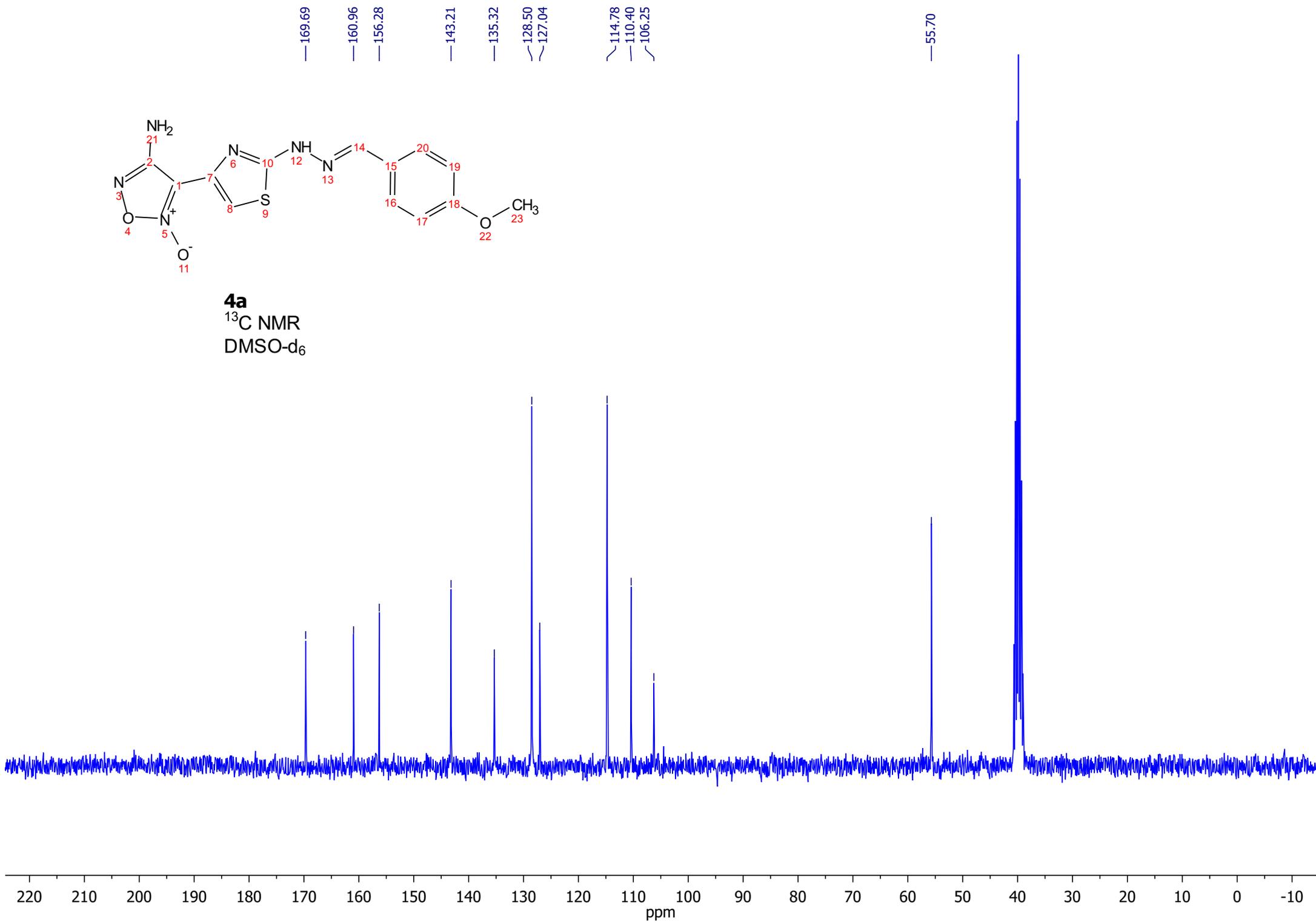


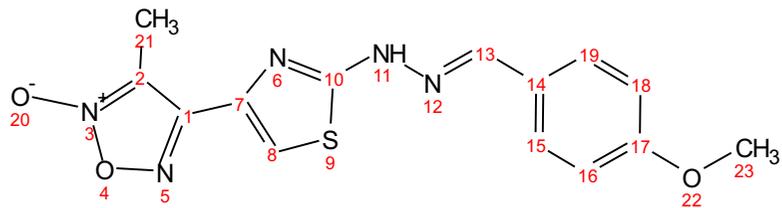
4a
¹H NMR
DMSO-d₆



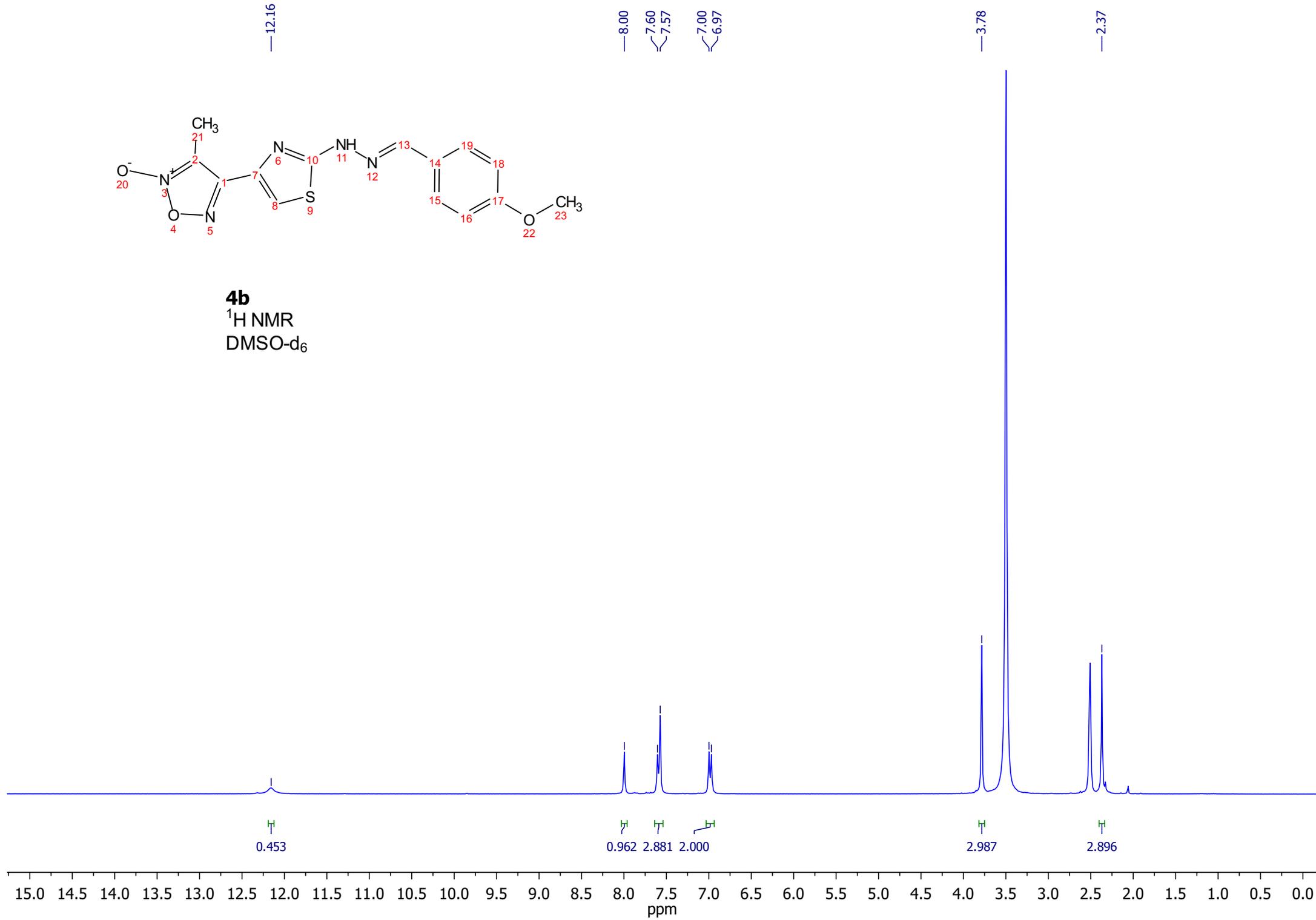


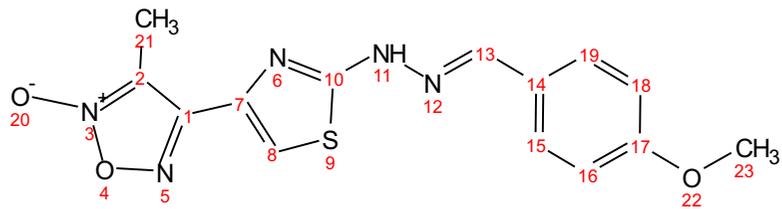
4a
¹³C NMR
DMSO-d₆



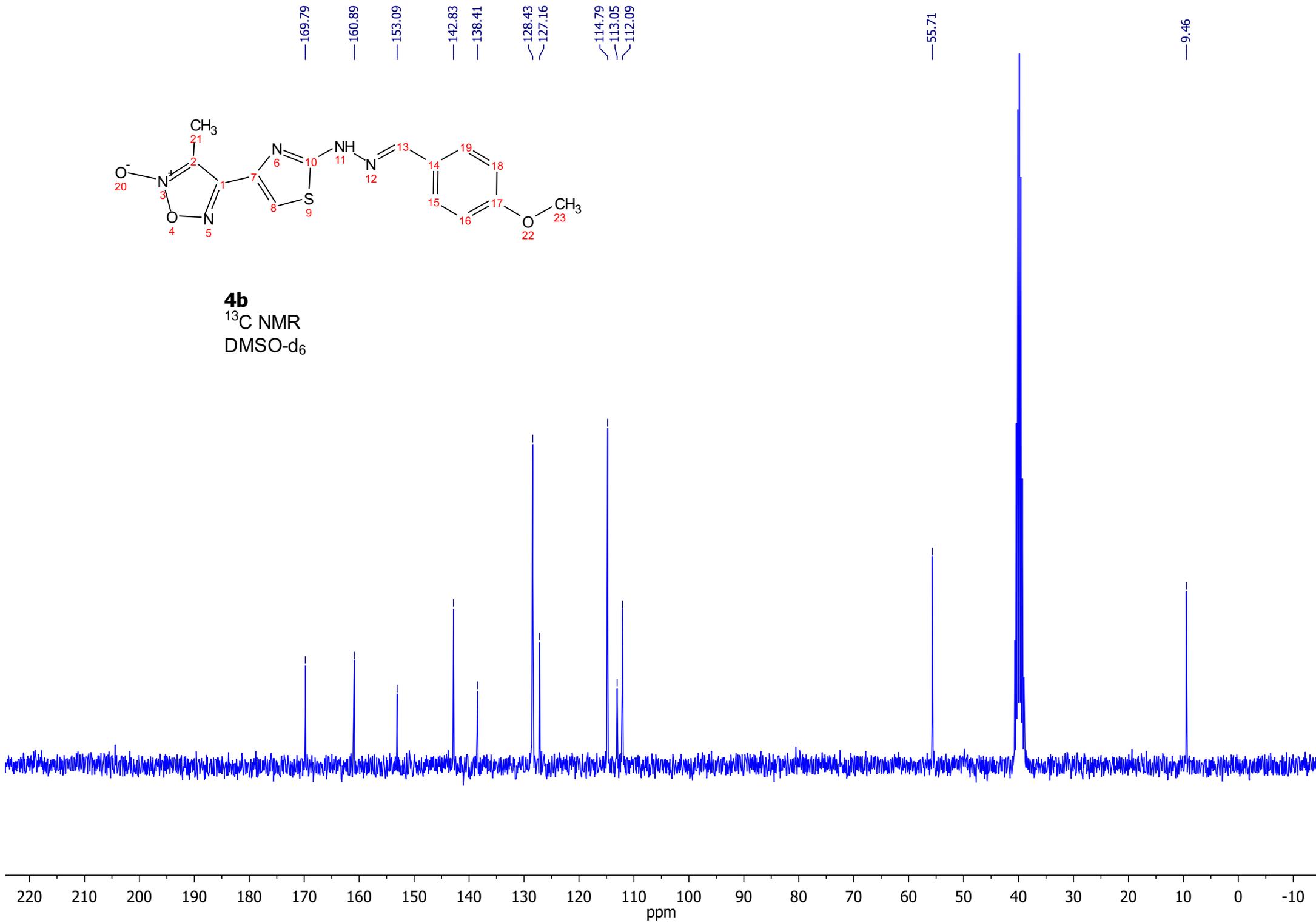


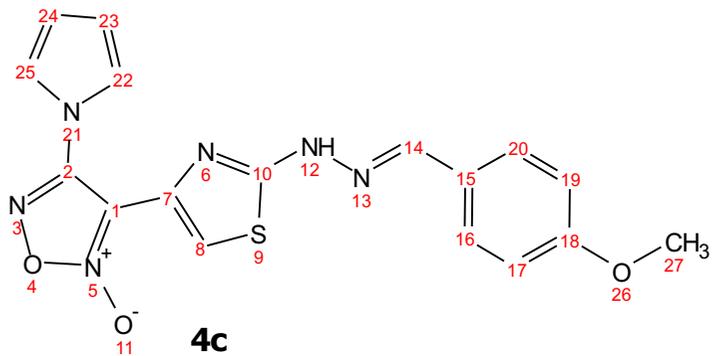
4b
¹H NMR
DMSO-d₆



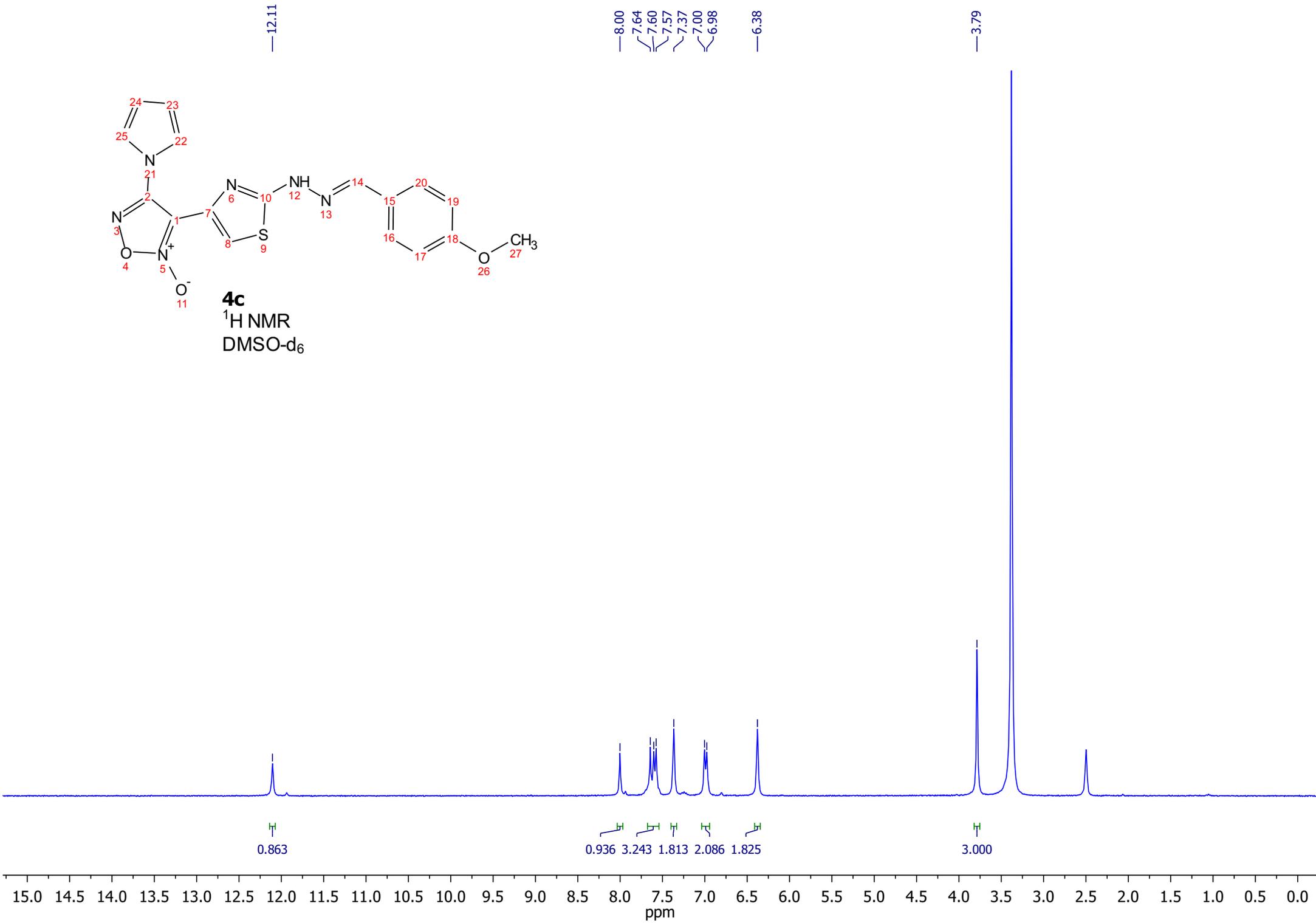


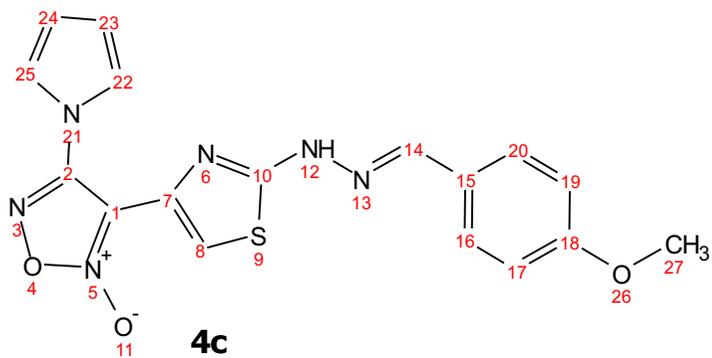
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¹³C NMR
DMSO-d₆



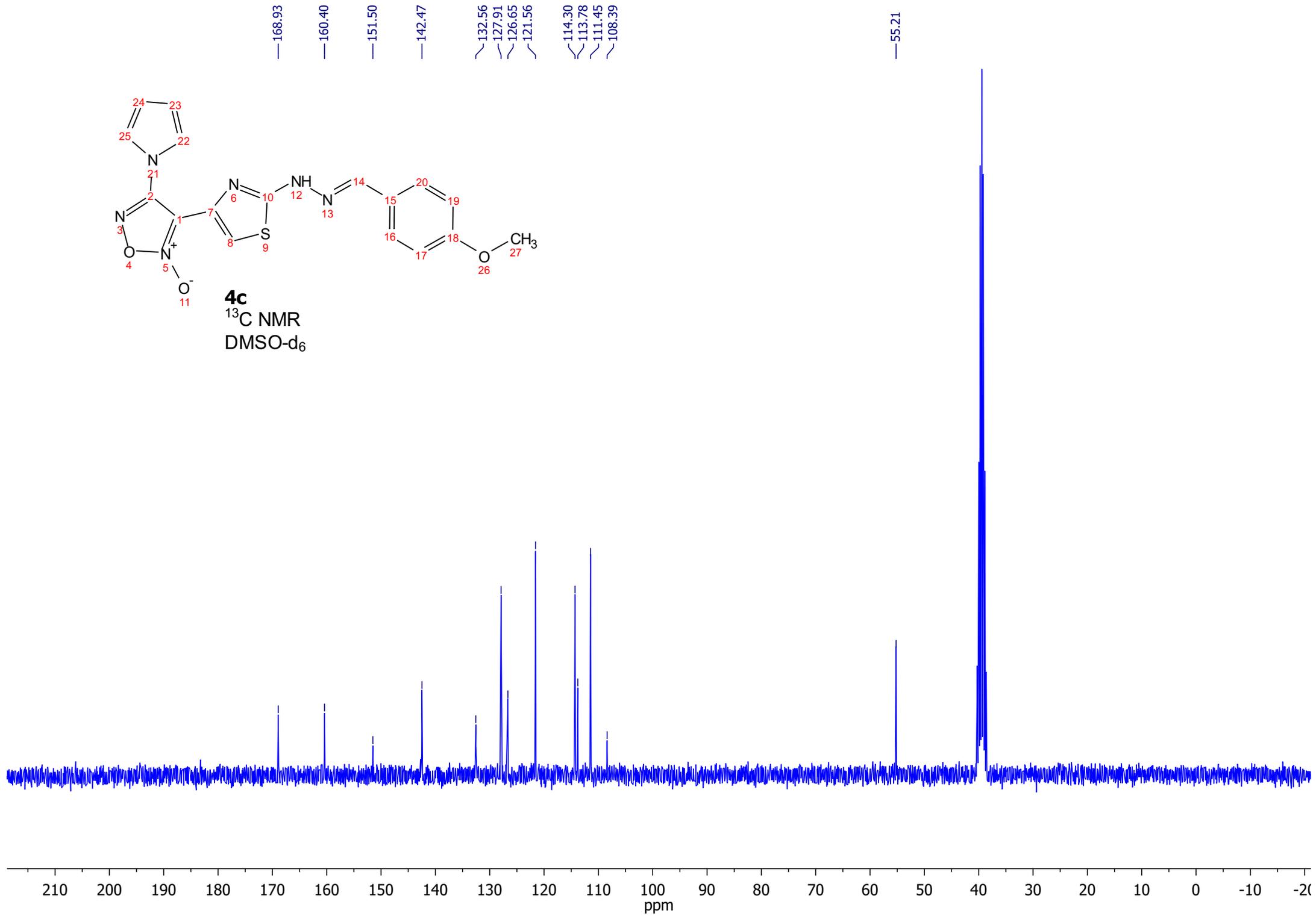


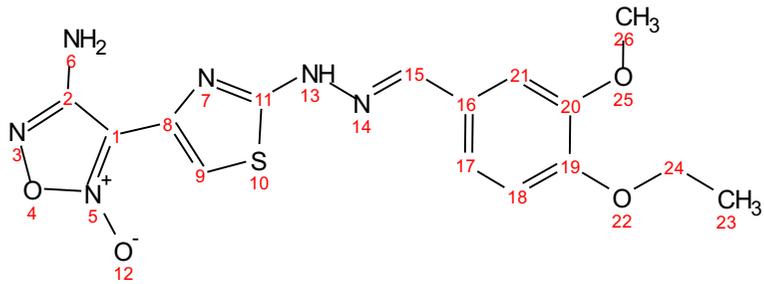
4c
¹H NMR
 DMSO-d₆





4c
¹³C NMR
DMSO-d₆





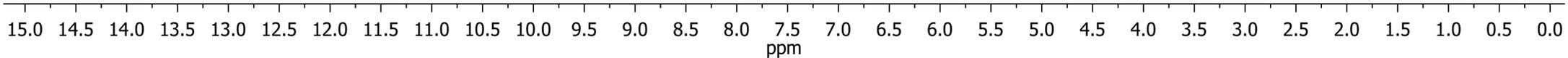
4d
¹H NMR
 DMSO-d₆

— 12.15

— 8.00
 — 7.72
 — 7.29
 — 7.20
 — 7.17
 — 7.01
 — 6.98
 — 6.73

— 4.09
 — 4.07
 — 4.05
 — 4.03
 — 3.83 H₂O

— 1.38
 — 1.35
 — 1.33

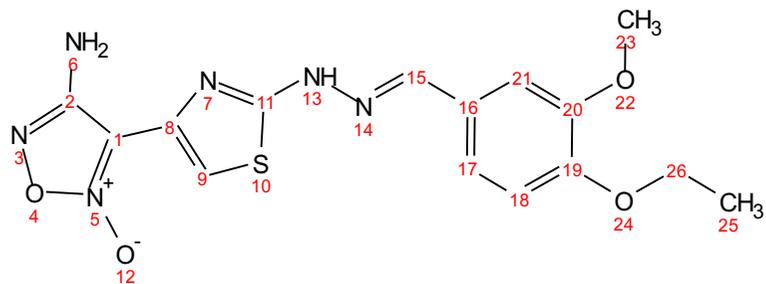


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0.921 0.691 0.975 1.088 1.055 1.660

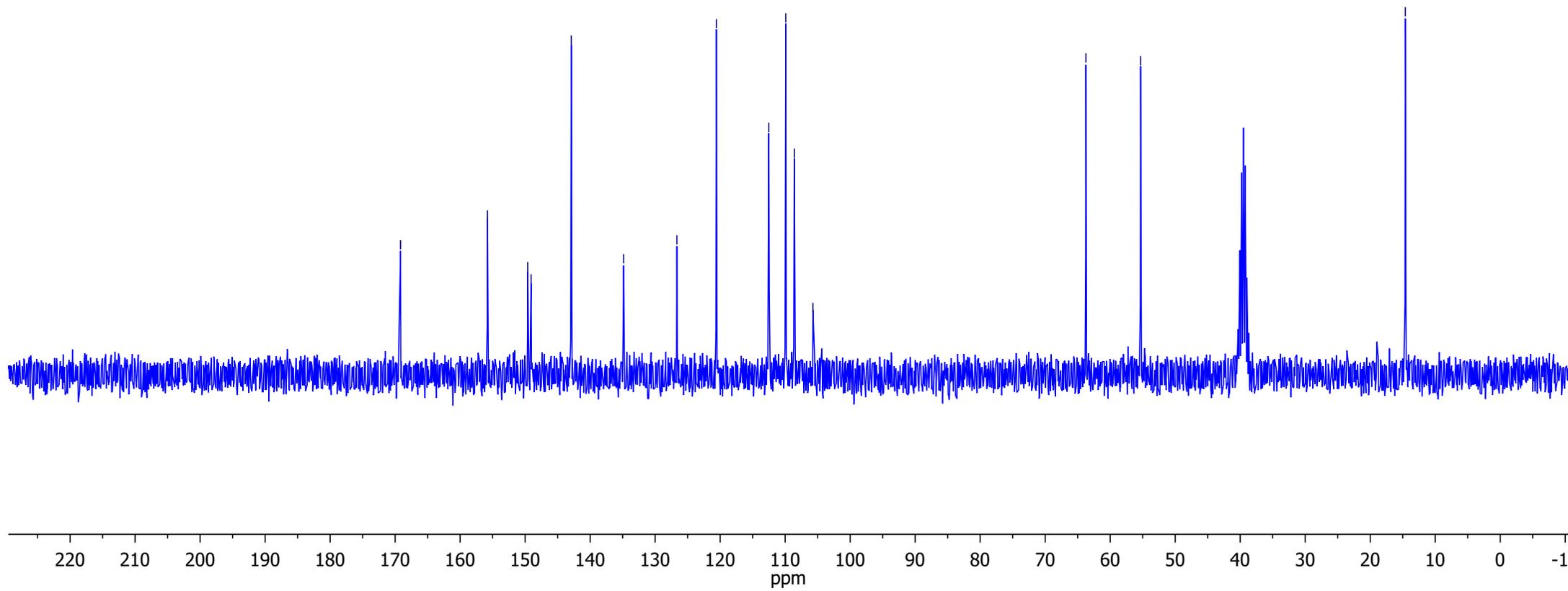
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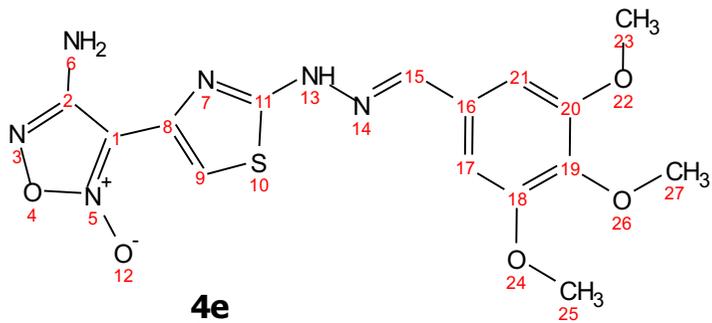
3.000



4d
¹³C NMR
DMSO-d₆

— 169.17
— 155.80
— 149.60
— 149.09
— 142.90
— 134.85
— 126.65
— 120.57
— 112.51
— 109.91
— 108.59
— 105.73
— 63.73
— 55.32
— 14.61





4e
¹H NMR
 DMSO-d₆

— 12.26

— 7.99

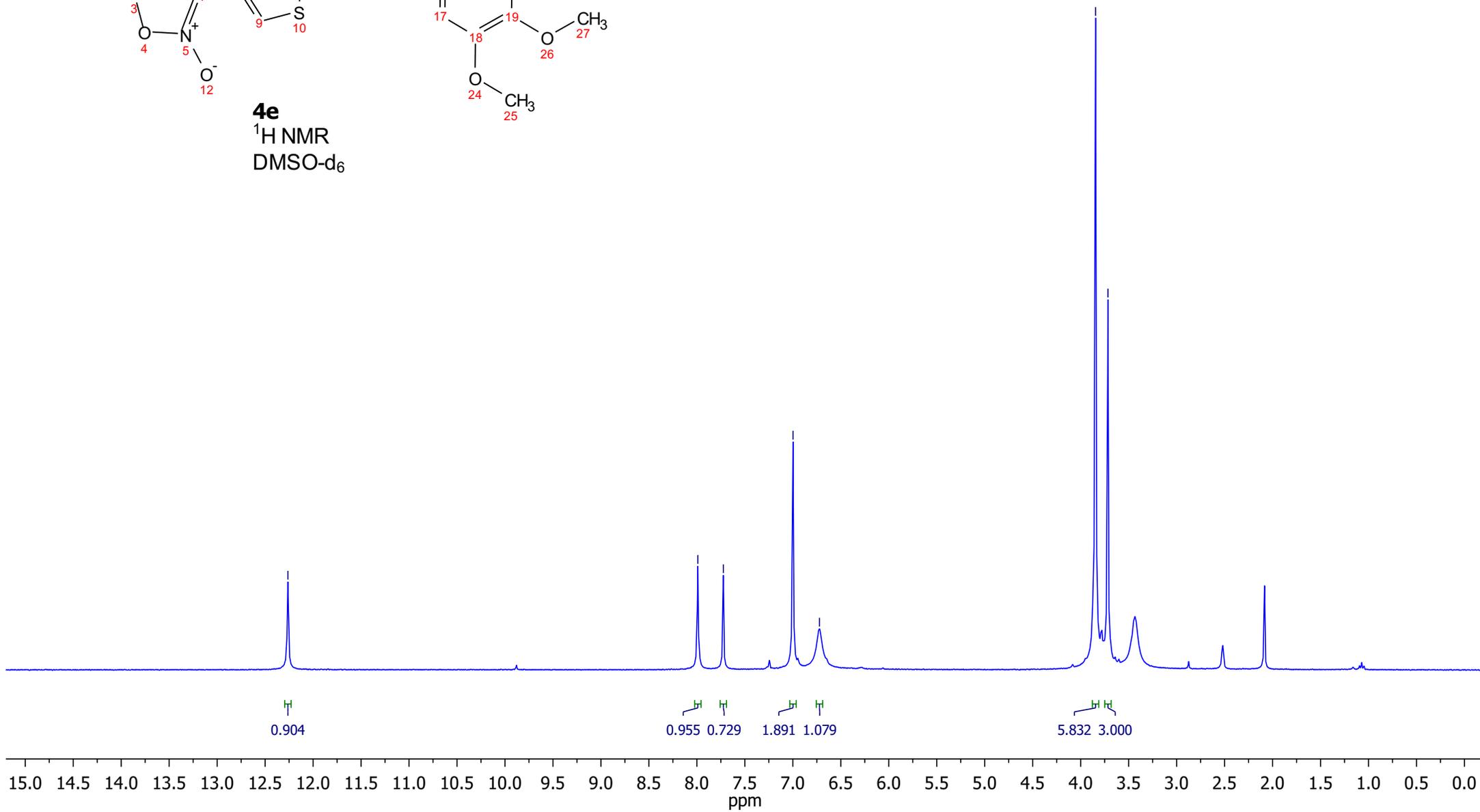
— 7.72

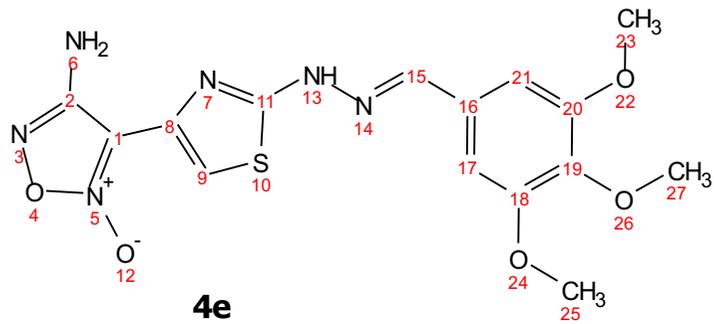
— 7.00

— 6.72

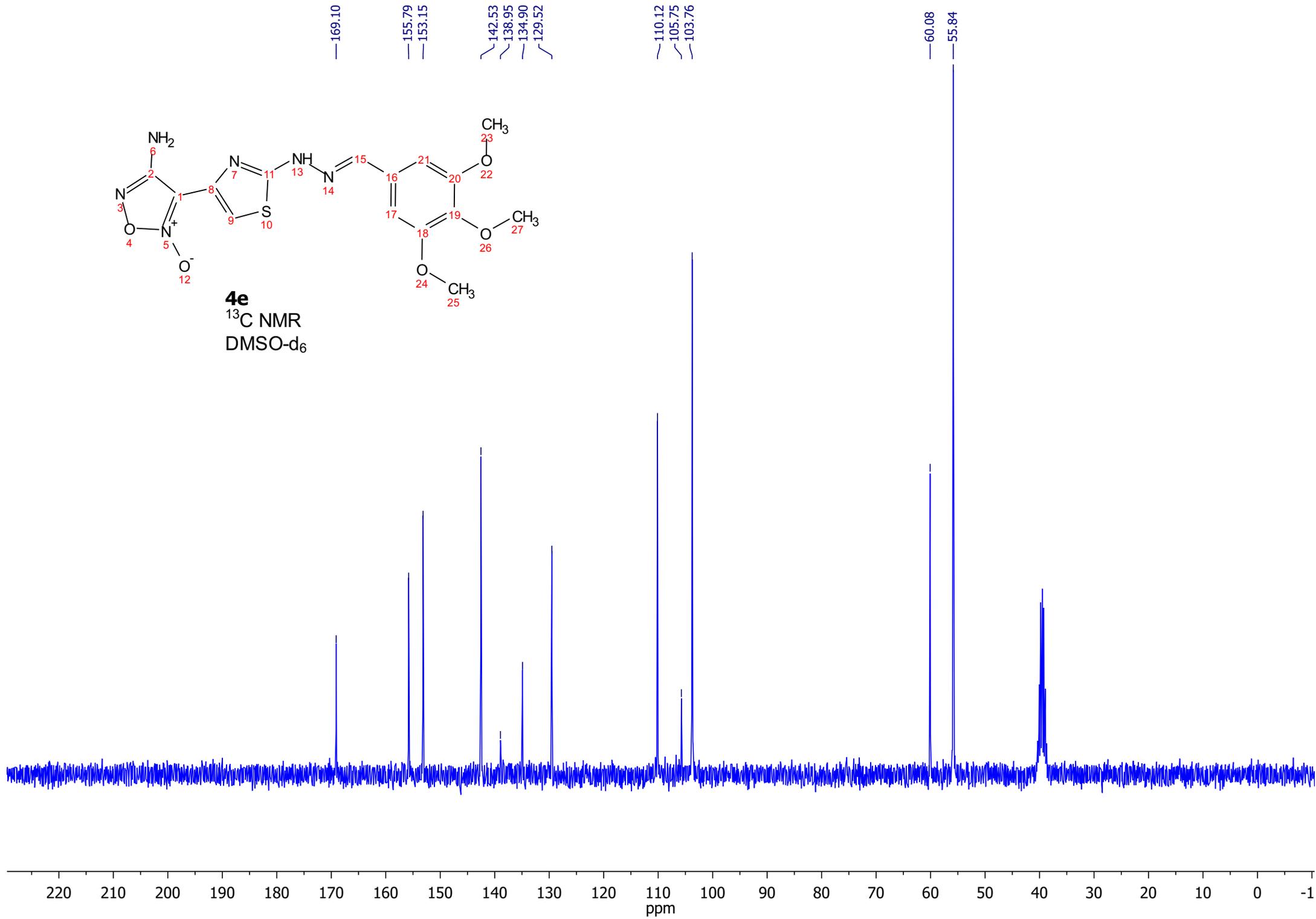
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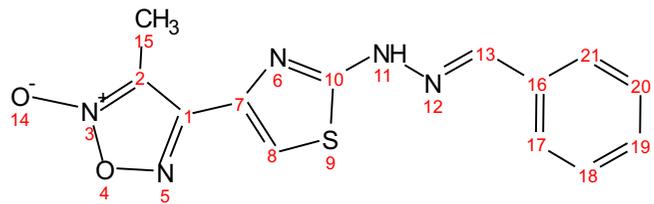
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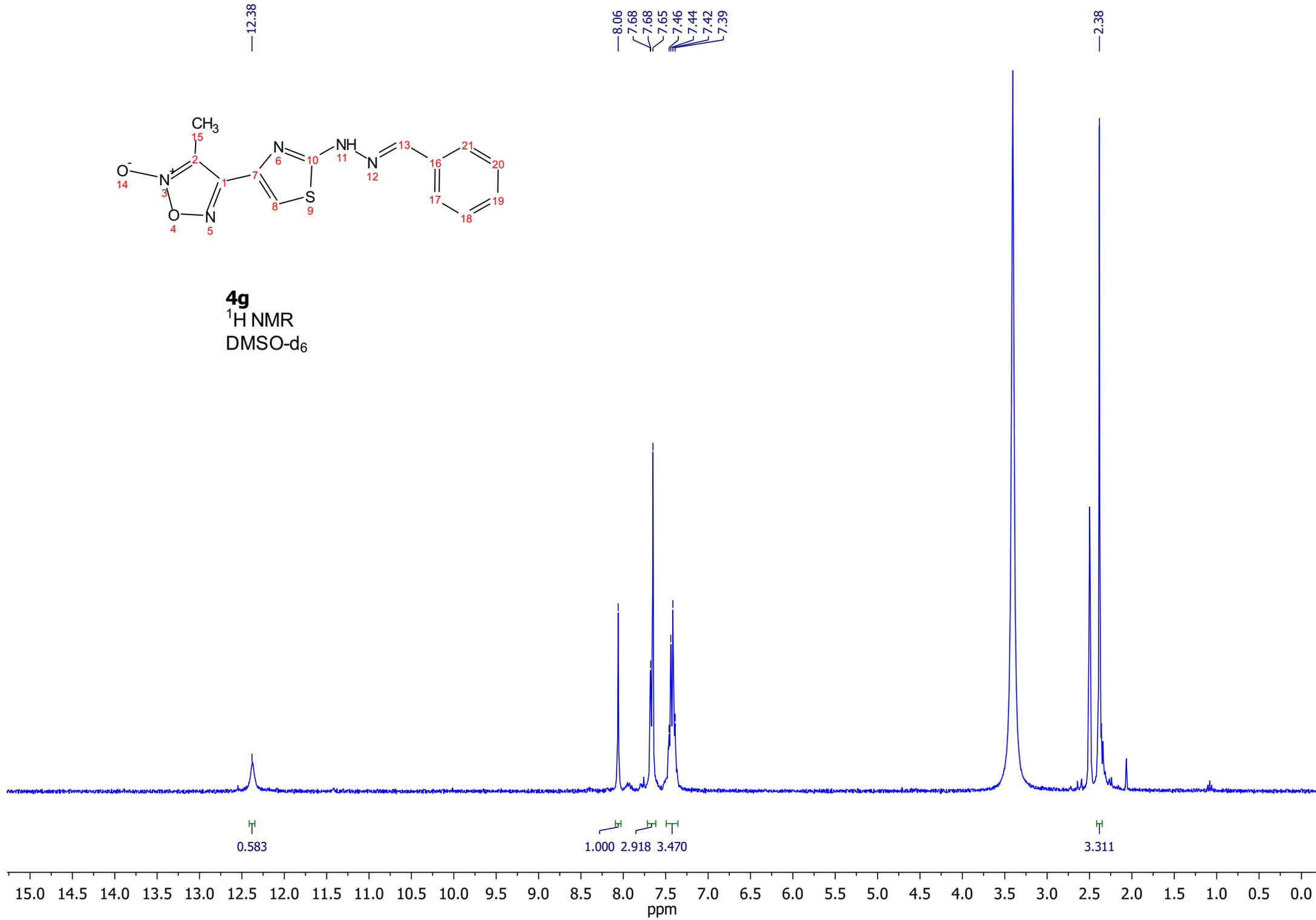


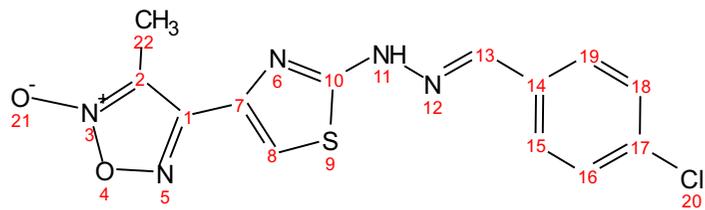
4e
 ^{13}C NMR
DMSO- d_6



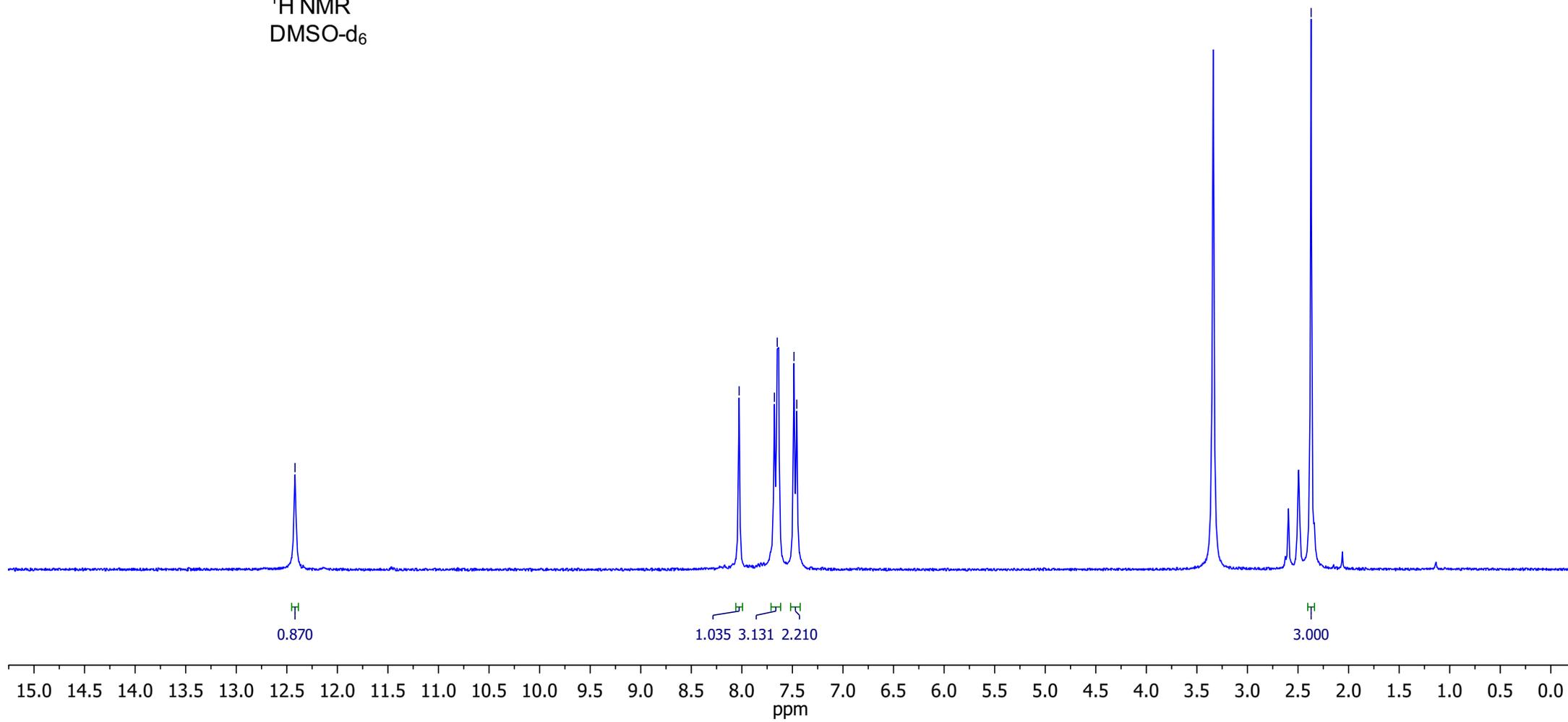


4g
¹H NMR
DMSO-d₆





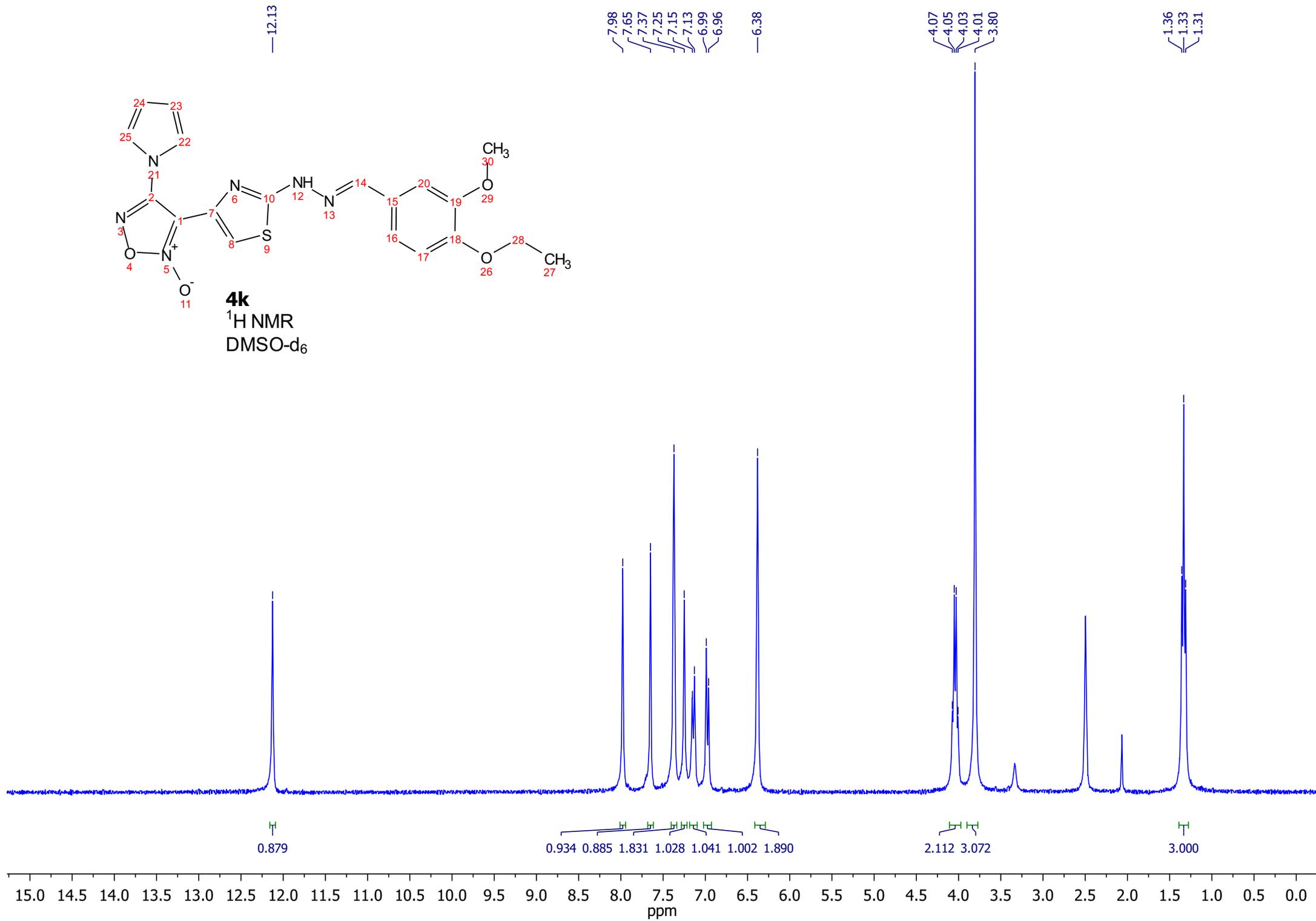
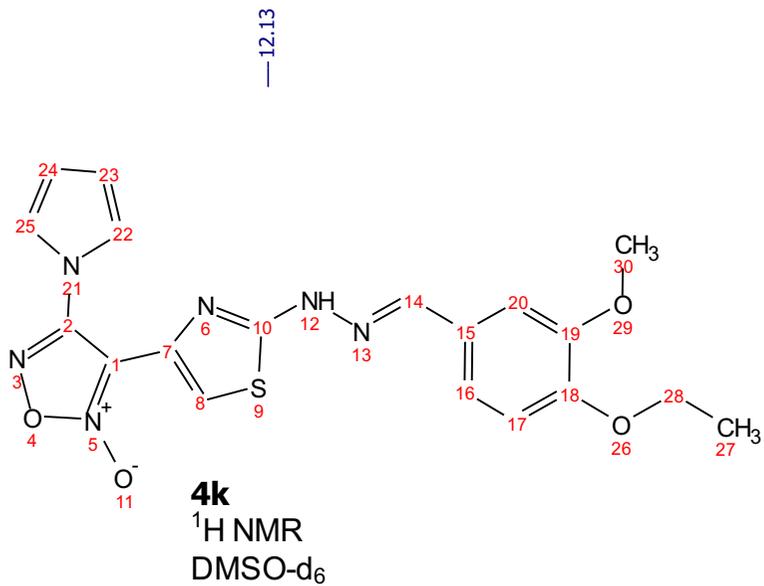
4h
¹H NMR
DMSO-d₆

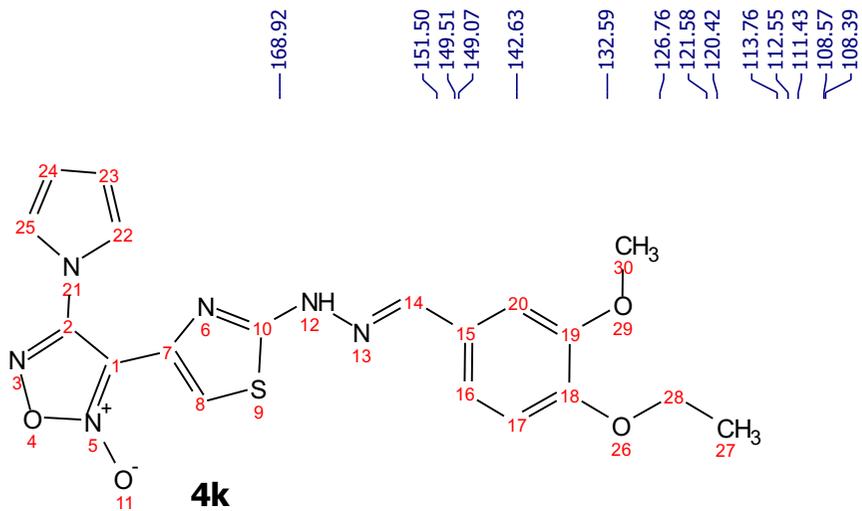


—12.42

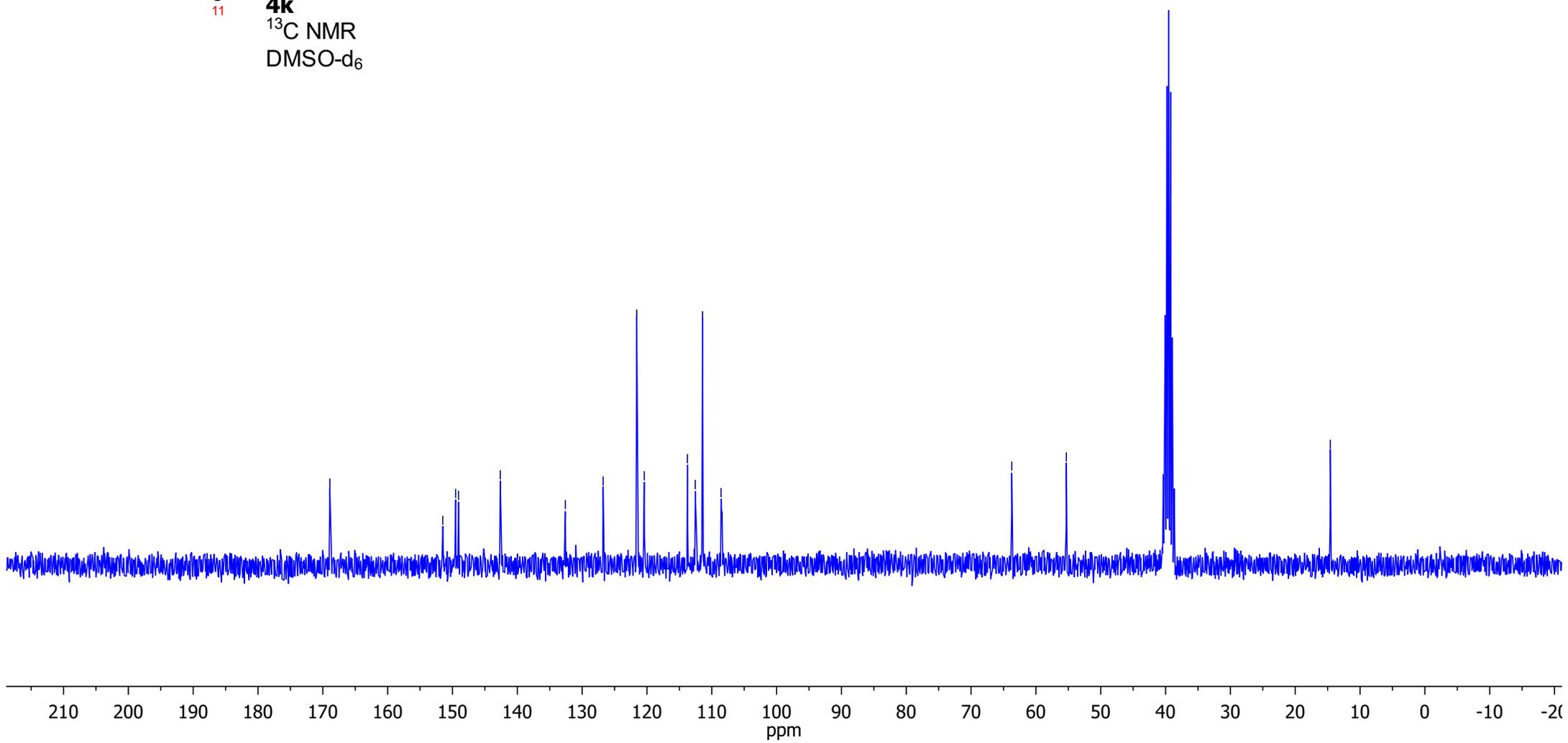
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7.65
7.48
7.46

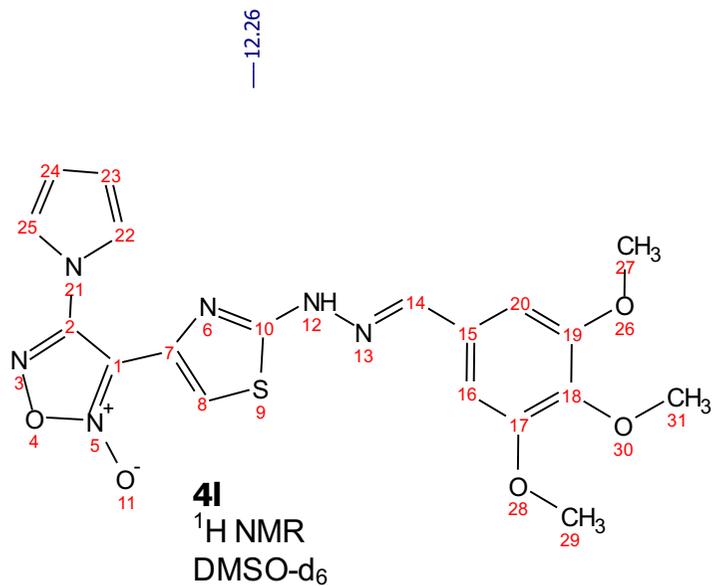
—3.37





4k
 ^{13}C NMR
 DMSO- d_6





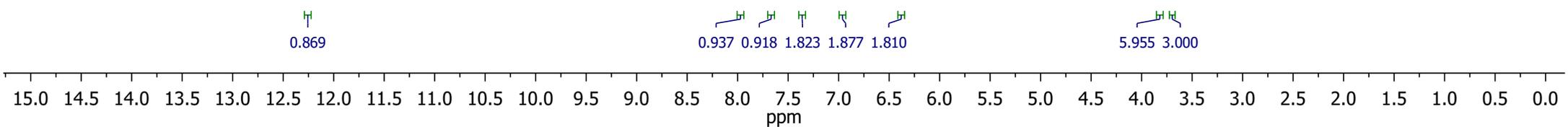
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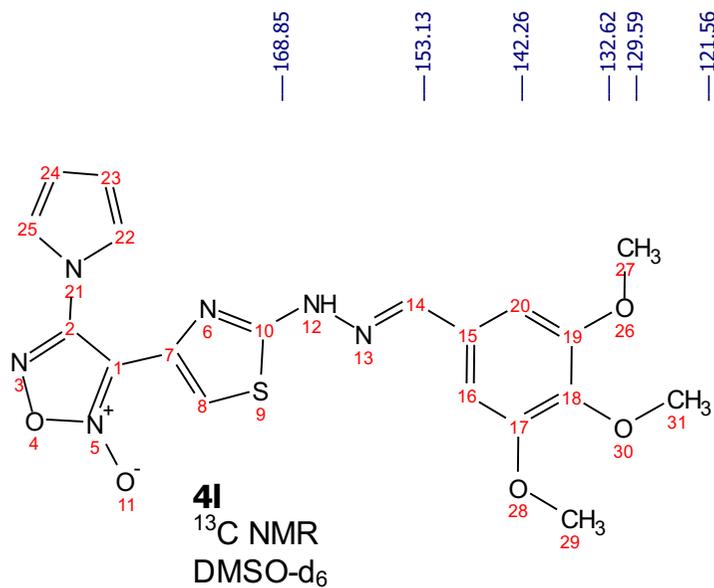
7.97
 7.67
 7.36

—6.96

—6.38

3.82
 3.69





— 168.85

— 153.13

— 142.26

— 132.62

— 129.59

— 121.56

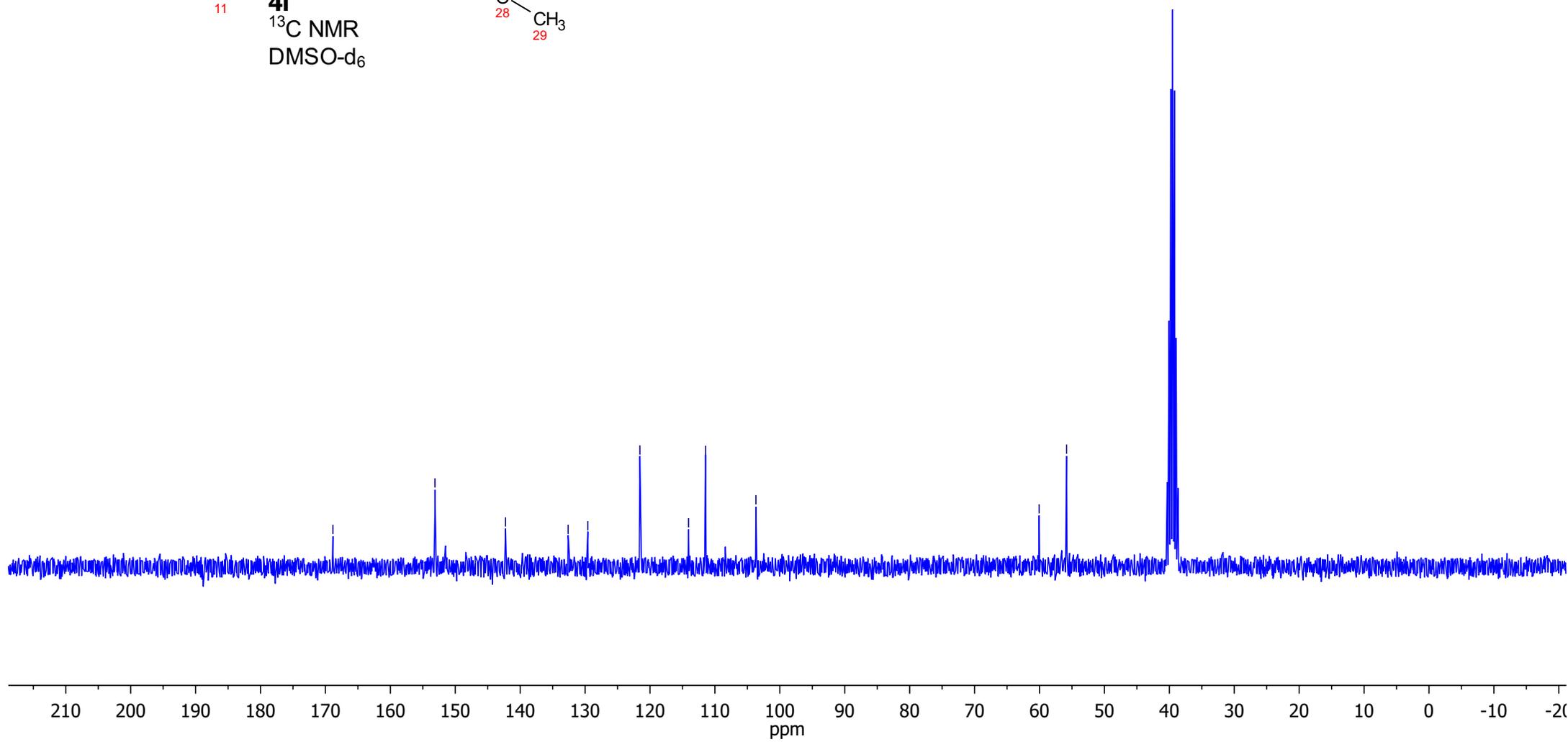
— 114.06

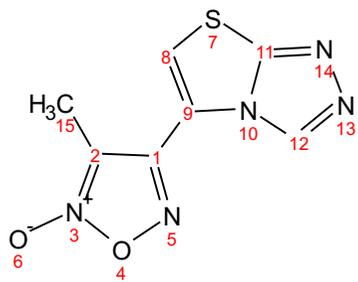
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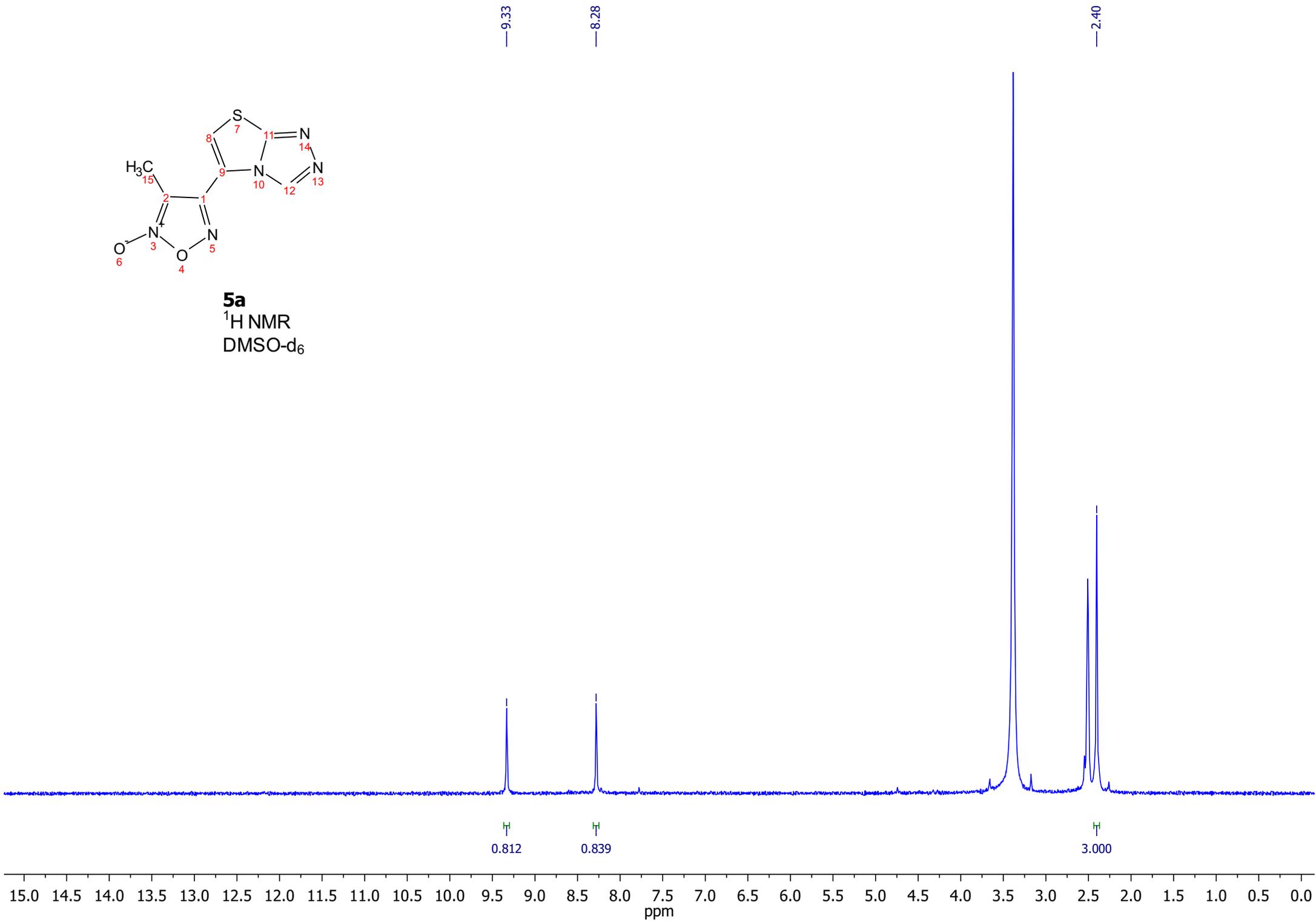
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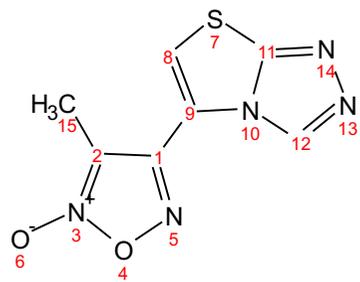
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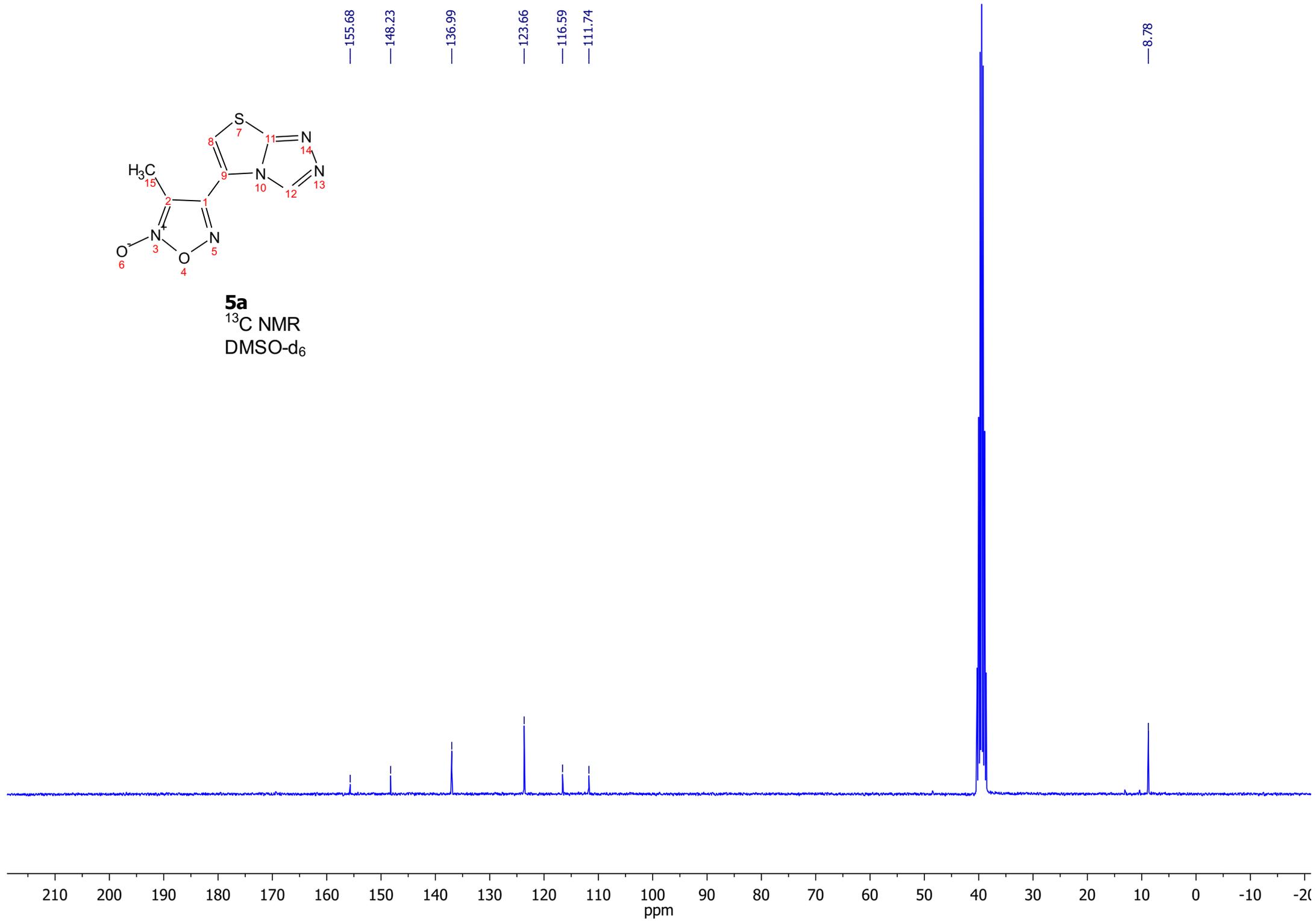


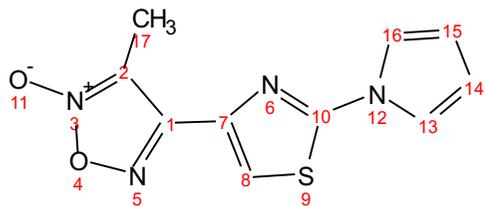
5a
¹H NMR
DMSO-d₆



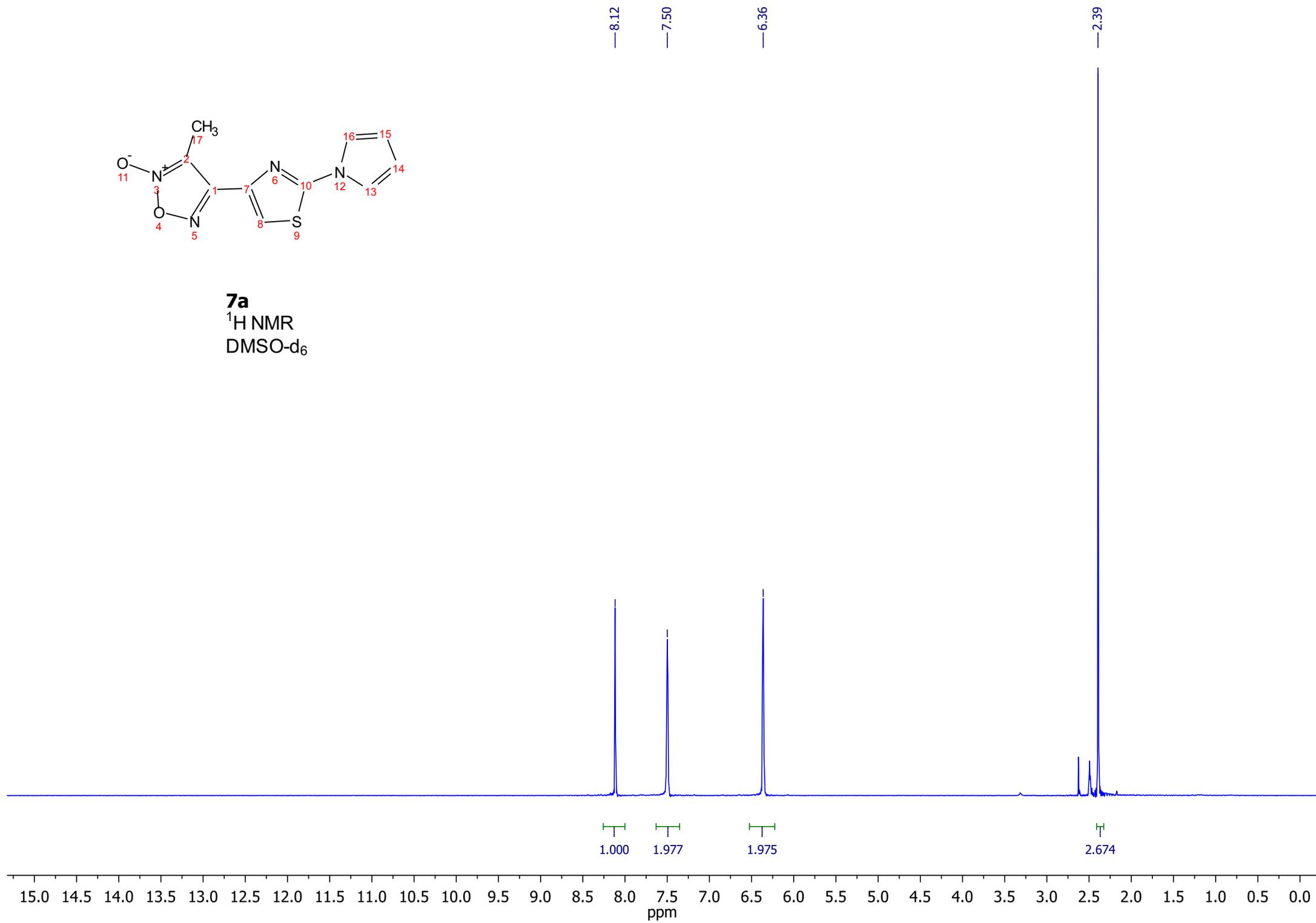


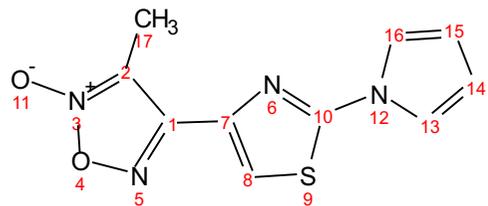
5a
¹³C NMR
DMSO-d₆



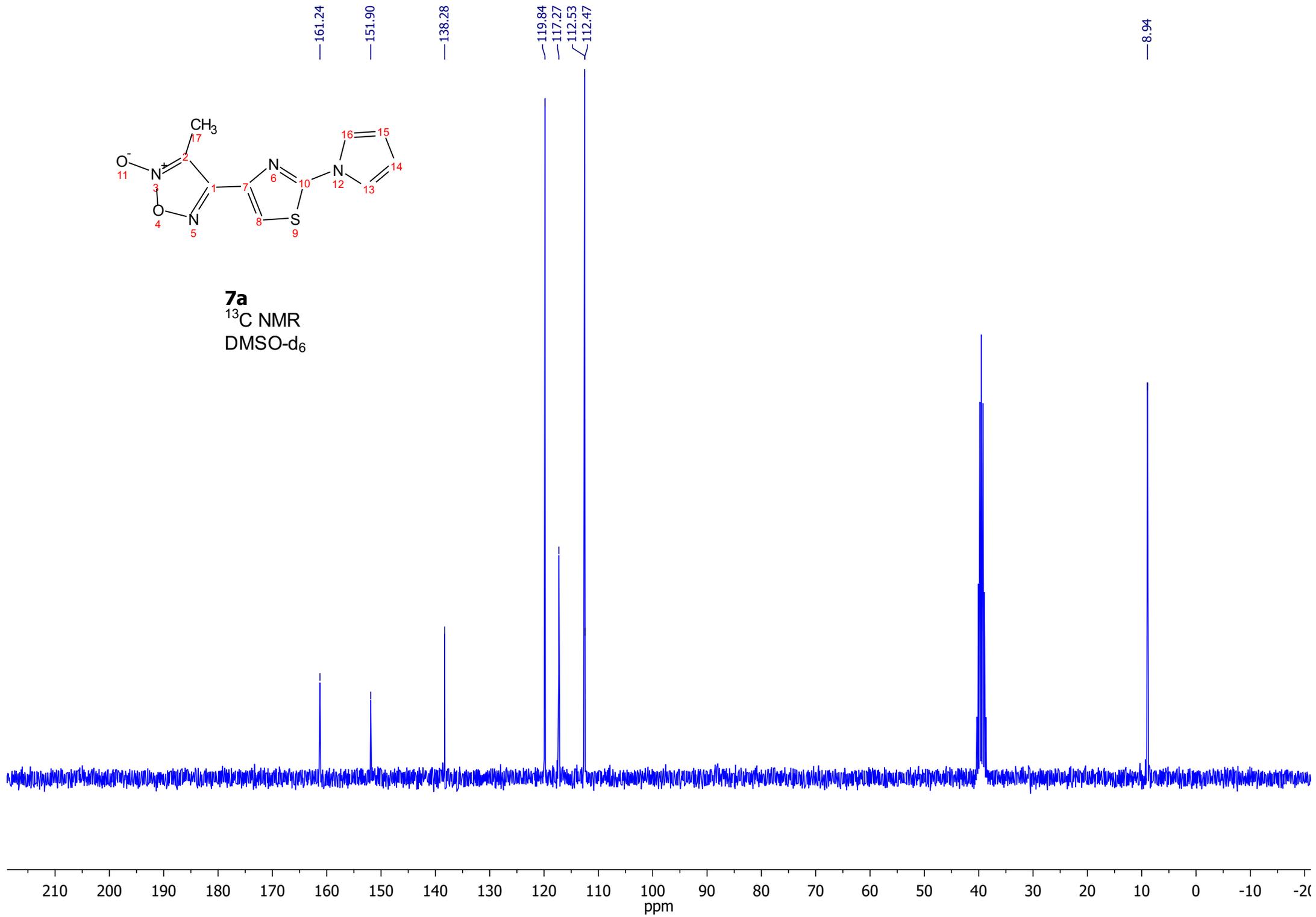


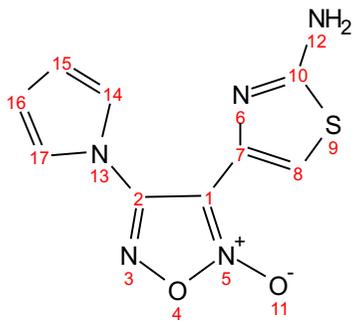
7a
¹H NMR
DMSO-d₆



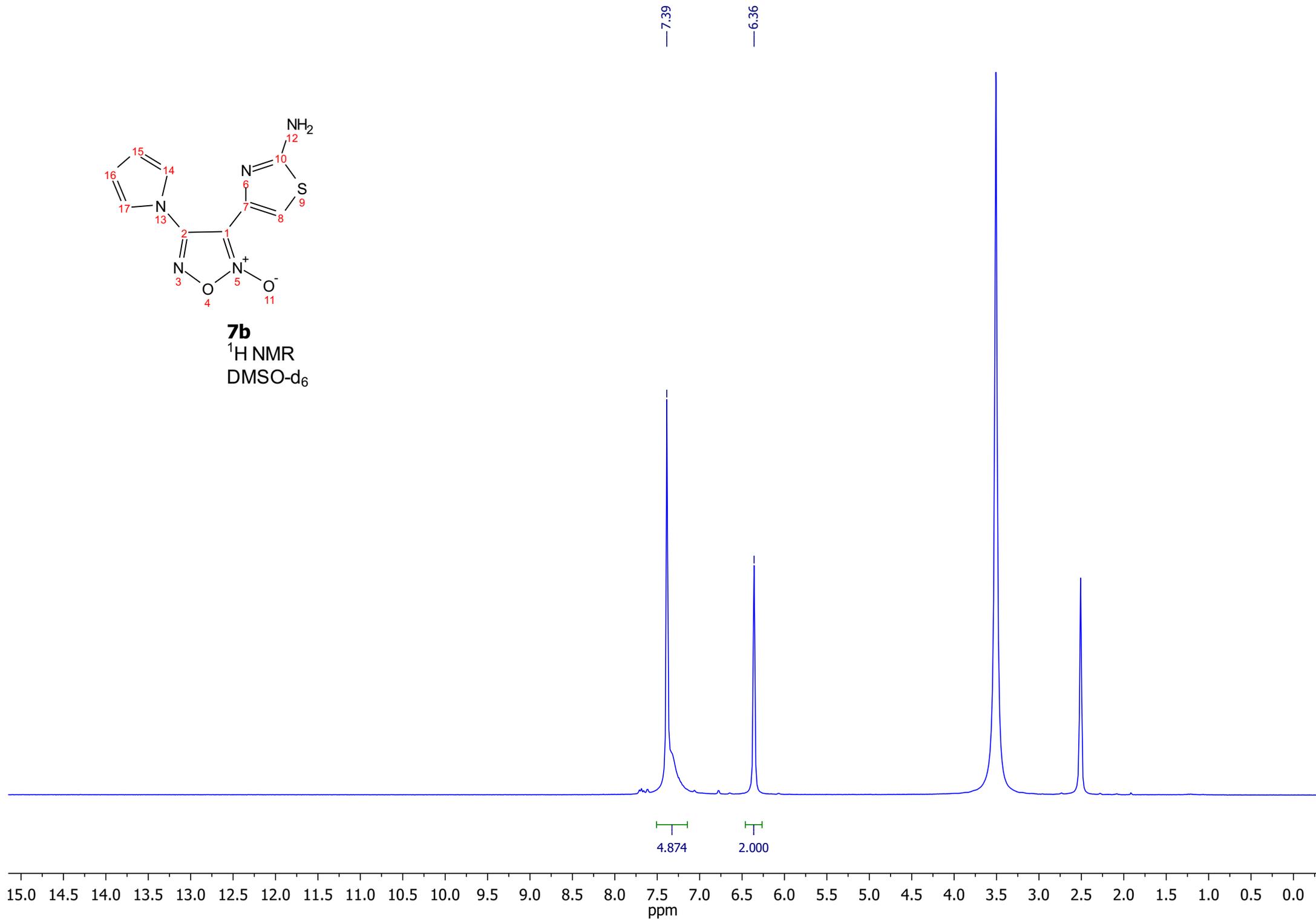


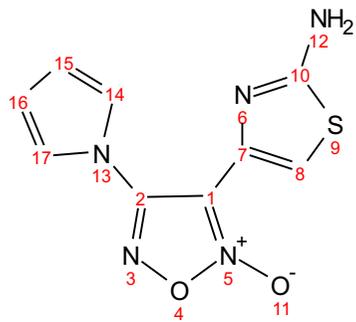
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¹³C NMR
DMSO-d₆



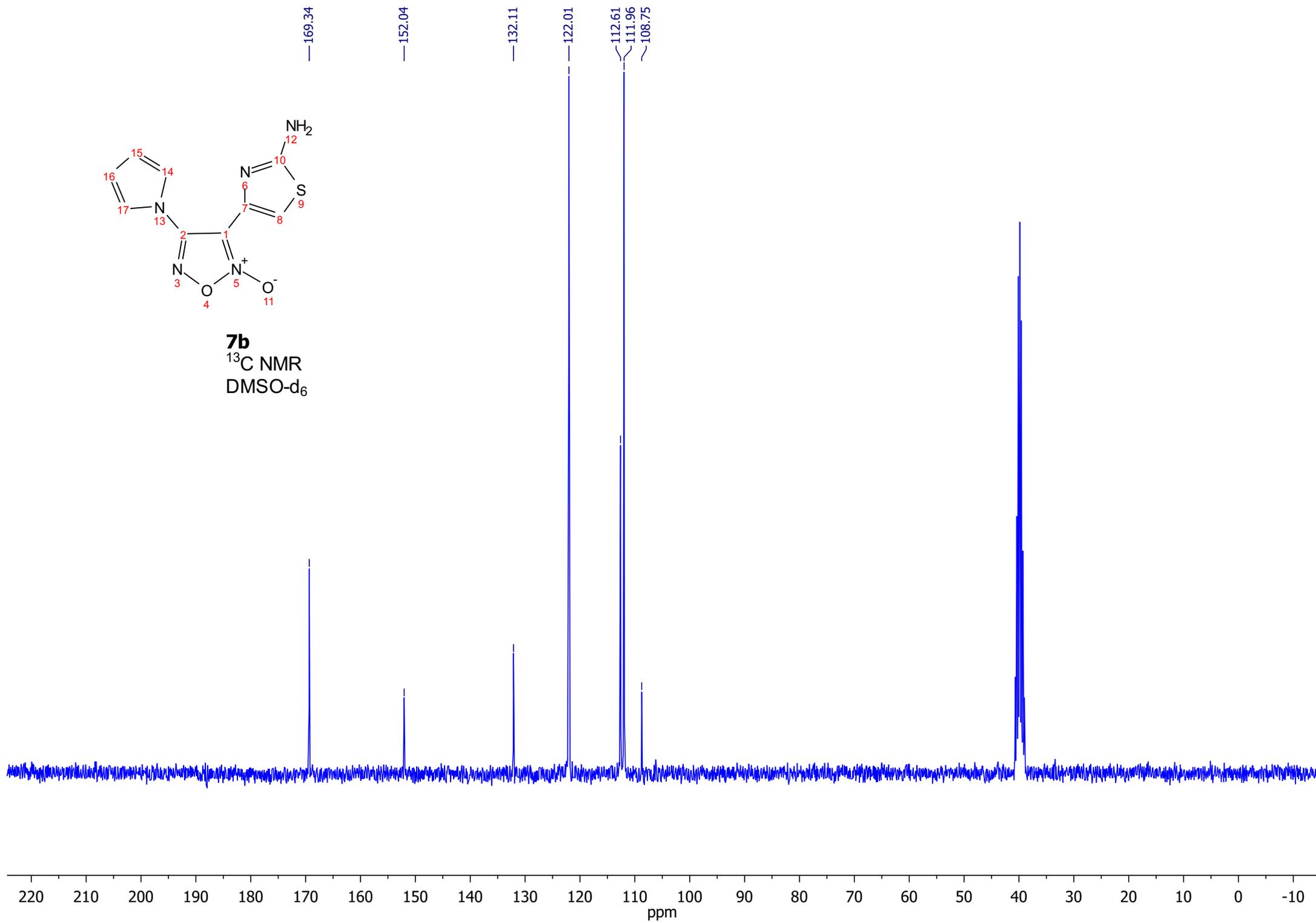


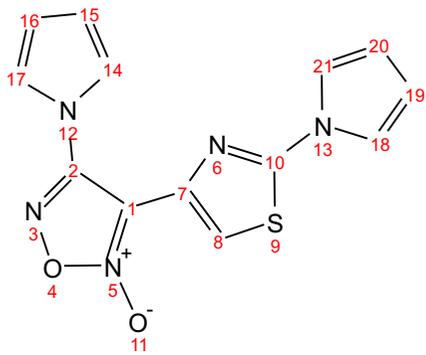
7b
 $^1\text{H NMR}$
DMSO- d_6



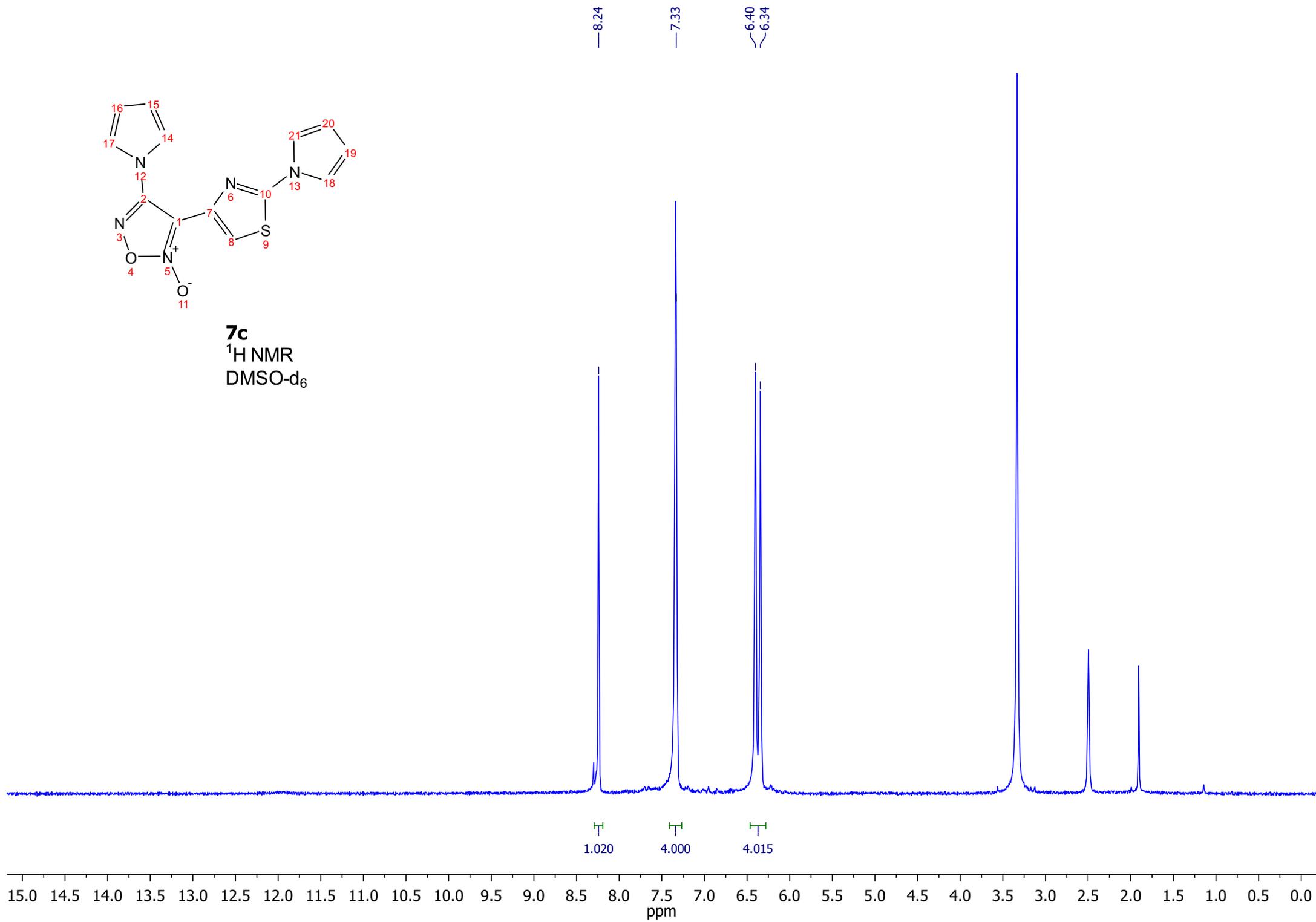


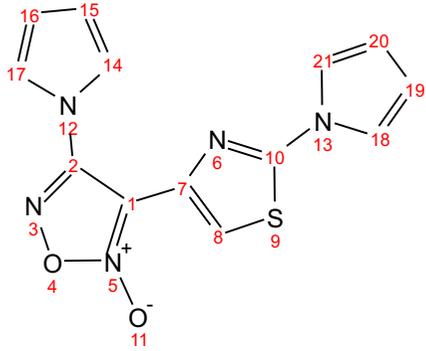
7b
¹³C NMR
DMSO-d₆





7c
¹H NMR
DMSO-d₆





7c
¹³C NMR
DMSO-d₆

