From Lossen Transposition to Solventless Medicinal Mechanochemistry

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GENERAL METHODS AND MATERIALS

Commercially available reagents were purchased from Acros, Aldrich, Strem Chemicals, Alfa-Aesar, TCI Europe and used as received. All reactions were monitored by thin-layer chromatography (TLC) performed on glass-backed silica gel 60 F254, 0.2 mm plates (Merck), and compounds were visualized under UV light (254 nm) or using cerium ammonium molybdate solution with subsequent heating. The eluents were technical grade. A Spex 8000M Mixer/Mill®, ball-milling apparatus was used for all reactions. The reagents were milled using a zirconia grinding jar (45 mL; product number 8005) equipped with balls (d = 5 mm) of the same material. ^{1}H and ^{13}C liquid NMR spectra were recorded on a Varian 500 MHz and Bruker Avance III HD 600 MHz NMR spectrometer at 298 K and were calibrated using trimethylsylane (TMS). Proton chemical shifts are expressed in parts per million (ppm, δ scale) and are referred to the residual hydrogen in the solvent ($CHCl_3$, 7.27 ppm or DMSO 2.54 ppm). Data are represented as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet and/or multiple resonances, br s = broad singlet), coupling constant (*J*) in Hertz (*Hz*) and integration. Carbon chemical shifts are expressed in parts per million (ppm, δ scale) and are referenced to the carbon resonances of the NMR solvent ($CDCl_3$, δ 77.0 ppm or δ DMSO-d_6 δ 39.5 ppm). Deuterated NMR solvents were obtained from Aldrich. High-resolution mass spectra (HRMS) were recorded using an Electrospray Ionisation (ESI) spectrometer. Analysis of reaction mixture was determined by GC-MS (GC Agilent 6850, MS Agilent 5973) and equipped with HP5 universal capillary column (30 m length and 0.20 mm diameter, 0.11 film thickness) and a flame ionization detector (FID). GC oven temperature was programmed from 80 °C to 250 °C at the rate of 10 °C/min. He gas was used as a carrier gas. Temperatures of injection port and FID were kept constant at 300 °C. Retention times of different compounds were determined by injecting pure compound under identical conditions. Melting points were determined in an open capillary on a Büchi melting point apparatus and are uncorrect. Chiral HPLC analysis were determined by chiral stationary phase HPLC in a PerkinElmer Flexatm chromatograph using a column 5 mm, 4.6 x 250 mm (for racemization studies) coupled to a Perkin–Elmer UV-VIS detector (λ = 220 nm). HPLC grade solvents were used for HPLC analysis. All the experiments were carried out in duplicate to ensure reproducibility of the experimental data. Yields refer to pure isolated materials.

GENERAL EXPERIMENTAL PROCEDURES

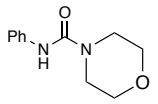
GENERAL PROCEDURE FOR THE PREPARATION OF UREAS 1-18.
Hydroxamic acid (1.0 mmol) and 1,1′-carbonyldiimidazole (CDI), (1.1 mmol) were transferred into a zirconia grinding jar (45 mL) equipped with 40 balls (d = 5.0 mm) of the same material. The jar was shaken at 14.6 *Hz* for 15 minutes in a Spex 8000M Mixer/Mill. Then, the amine (1.1 mmol) was added to the reaction jar and the mixture was milled for 1 hour. Upon completion of the ball milling process, monitored by TLC (Heptane/AcOEt 7:3 v/v) and GC, the resulting off-white waxy solid was triturated twice (10 mL) with a 15 % citric acid aqueous solution to remove the imidazole and any unreacted amine. The precipitated solid was filtered off and dried *in vacuo* over P_2O_5 overnight using a desiccator, to give the corresponding ureas **1-18**.

GENERAL PROCEDURE FOR THE PREPARATION OF HYDANTOINS 19, 21 and 27-46.
Hydroxamic acid (1.0 mmol) and 1,1′-carbonyldiimidazole (CDI) (1.1 mmol) were transferred into a zirconia grinding jar (45 mL) equipped with 40 balls (d = 5.0 mm) of the same material. The jar was shaken at 14.6 *Hz* for 15 minutes in a Spex 8000M Mixer/Mill. Then, the amino ester hydrochloride derivative (1.1 mmol) and K_2CO_3 (1.1 mmol) were added to the jar and the mixture was grinded for further for 3.5 hours. Upon completion of the ball milling process, monitored by TLC (Heptane/AcOEt 7:3 v/v) and GC, the resulting white waxy solid was repeatedly triturated with a 15 % citric acid aqueous solution (10 mL) and then deionized water (10 mL). The precipitate was

collected by filtration and dried in desiccator *in vacuo* overnight over P_2O_5 to afford the corresponding 3,5-disubstituted hydantoins **19**, **21**, **27-46**.

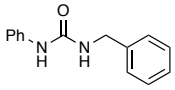
GENERAL PROCEDURE FOR THE PREPARATION OF THE CYCLIC CARBONATE A. Heptyl hydroxamate (1.0 mmol) and 1,1′-carbonyldiimidazole (CDI) (1.1 mmol) were transferred into a zirconia grinding jar (45 mL) equipped with 40 balls (d = 5.0 mm) of the same material. The jar was shaken at 14.6 *Hz* for 15 minutes in a Spex 8000M Mixer/Mill. Then, the crude mixture was directly analysed by NMR, revealing the formation of the dioxazole intermediate (cyclic carbonate) **A** as a colourless waxy solid (170 mg, 92 % yield).

SPECTRAL DATA FOR UREAS 1-18.



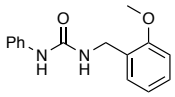
1

***N*-Phenylmorpholine-4-carboxamide (1)**, CAS [2645-36-5]. White solid, (188 mg, 91 % yield). M.p.: 158–159 °C (*Lit.*:[1] 159–160 °C); IR (KBr) ν (cm^{-1}): 3273, 2859, 1596, 1447, 1247, 1117, 749, 690; ^{1}H NMR (500 MHz, DMSO-d_6) δ (ppm): 8.50 (s, 1H), 7.46 (d, J = 7.7 *Hz*, 2H), 7.24 (t, J = 7.9 *Hz*, 2H), 6.94 (t, J = 7.3 *Hz*, 1H), 3.64–3.59 (t, J = 5.0 *Hz*, 4H), 3.45–3.40 (m, J = 5.0 *Hz*, 4H); ^{13}C NMR (126 MHz, DMSO-d_6) δ (ppm): 155.1, 140.3, 128.2, 121.8, 119.6, 65.9, 44.1. Spectroscopic data are in agreement with those reported earlier in the literature.[1]



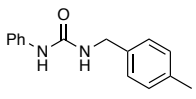
2

1-Benzyl-3-phenylurea (2), CAS [1467-21-6]. Off-white solid, (208 mg, 92 % yield). M.p.: 165–166 °C (*Lit.*:[2] 164–165 °C); IR (KBr) ν (cm^{-1}): 3226, 2970, 2832, 1669, 1628, 1557; ^{1}H NMR (600 MHz, DMSO-d_6) δ (ppm): 8.53 (s, 1H), 7.41 (d, J = 7.7 *Hz*, 2H), 7.37–7.32 (m, 2H), 7.31 (d, J = 6.9 *Hz*, 2H), 7.24 (dt, J = 15.8 and 7.7 *Hz*, 3H), 6.90 (t, J = 7.3 *Hz*, 1H), 6.60 (t, J = 6.0 *Hz*, 1H), 4.31 (d, J = 5.9 Hz, 2H); ^{13}C NMR (126 MHz, DMSO-d_6) δ (ppm): 155.2, 140.4, 140.3, 128.6, 128.3, 127.1, 126.7, 121.0, 117.7, 42.7. Spectroscopic data are in agreement with those reported earlier in the literature.[2]



3

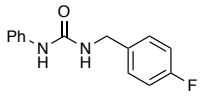
1-(2-methoxybenzyl)-3-phenylurea (3), CAS [610276-66-9]. Off-white solid, (241 mg, 94 % yield). M.p.: 139–140 °C (*Lit.*:[3] 139-141 °C); IR (KBr) ν (cm^{-1}): 3312, 3193, 3101, 1639, 1597, 1565, 1497, 1240, 751; ^{1}H NMR (600 MHz, DMSO-d_6) δ (ppm): 8.56 (s, 1H), 7.38 (d, J = 8.0 *Hz*, 2H), 7.28–7.18 (m, 4H), 7.00 (dd, J = 8.2 and 2.6 *Hz*, 1H), 6.95–6.86 (m, 2H), 6.45–6.39 (m, 1H), 4.25 (d, J = 5.9 *Hz*, 2H), 3.83 (t, J = 2.0 *Hz*, 3H). ^{13}C NMR (151 MHz, DMSO-d_6) δ (ppm): 157.3, 155.6, 141.0, 129.1, 128.6, 128.5, 128.1, 121.5, 120.6, 118.0, 111.0, 55.8, 38.6. HRMS ESI-(+) calcd. for $C_{15}H_{17}N_2O$ $[M+H]^+$ 257.1290, found 257.1288.



4

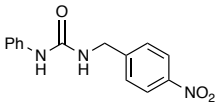
1-(4-Methylbenzyl)-3-phenylurea (4), CAS [35305-46-5]. Off-white solid, (224 mg, 93 % yield). M.p.: 177–178 °C (*Lit.*:[4] 176-177 °C); IR (KBr) ν (cm^{-1}): 3359, 2911, 2867, 1649, 1511, 1249, 1119, 1005, 757; ^{1}H NMR (600 MHz, DMSO-d_6) δ (ppm): 8.50 (s, 1H), 7.43–7.38 (m, 2H), 7.25–7.17 (m, 4H), 7.14 (d, J = 7.9 *Hz*, 2H), 6.90 (tt J = 7.3 and 1.2 *Hz*, 1H), 6.54 (t, J = 5.9 *Hz*, 1H), 4.25 (d, J = 5.9 *Hz*, 2H), 2.28 (s, 3H); ^{13}C NMR (151 MHz, DMSO-d_6) δ (ppm):

155.6, 140.9, 137.7, 136.2, 129.3, 129.1, 127.6, 121.5, 118.1, 42.9, 21.1. Spectroscopic data are in agreement with those reported earlier in the literature.[5]



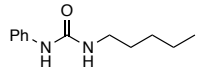
5

1-(4-Fluorobenzyl)-3-phenylurea (5), CAS [541545-68-0]. White solid, (222 mg, 91 % yield). M.p.: 155–156 °C; IR (KBr) ν (cm^{-1}): 2963, 2931, 1622, 1589, 1509, 1231, 1162, 1064, 817; ^{1}H NMR (500 MHz, DMSO-d_6) δ (ppm): 8.51 (s, 1H), 7.41–7.35 (m, 2H), 7.35–7.29 (m, 2H), 7.24–7.17 (m, 2H), 7.17–7.09 (m, 2H), 6.88 (tt, J = 7.3 and 1.2 *Hz*, 1H), 6.58 (t, J = 6.0 *Hz*, 1H), 4.26 (d, J = 6.0 *Hz*, 2H); ^{19}F NMR (565 MHz, DMSO-d_6) δ (ppm): -116.34; ^{13}C NMR (126 MHz, DMSO-d_6) δ (ppm): 161.1 (d, $J_{C\text{-}F}$ =242.1 *Hz*), 155.2, 140.4, 136.6, 129.1 (d, $J_{C\text{-}F}$ =7.9 *Hz*), 128.6, 121.1, 117.7, 114.9 (d, $J_{C\text{-}F}$ =21.2 *Hz*), 42.0; HRMS ESI-(+) calcd for $C_{14}H_{13}FN_2ONa$ $[M+Na]^+$ 267.0910; found 267.0907.



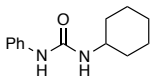
6

1-(4-Nitrobenzyl)-3-phenylurea (6), CAS [1366179-97-6]. Pale-yellow solid, (250 mg, 92 % yield). M.p.: 196–197 °C (*Lit.*:[4] 195–198 °C); IR (KBr) ν (cm^{-1}): 3420, 3095, 2857, 1659, 1509, 1236, 1144, 1002, 795, 740; ^{1}H NMR (500 MHz, DMSO-d_6) δ (ppm): 8.74 (s, 1H), 8.21 (d, J = 8.5 *Hz*, 2H), 7.57 (d, J = 8.5 *Hz*, 2H), 7.41 (d, J = 8.1 *Hz*, 2H), 7.23 (t, J = 7.8 *Hz*, 2H), 6.91 (t, J = 7.4 *Hz*, 1H), 6.85 (t, J = 6.2 *Hz*, 1H), 4.44 (d, J = 6.0 *Hz*, 2H). ^{13}C NMR (126 MHz, DMSO-d_6) δ (ppm): 155.3, 148.9, 146.4, 140.3, 128.6, 127.9, 123.5, 121.2, 117.8, 42.3. Spectroscopic data are in agreement with those reported earlier in the literature.[4]



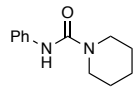
7

1-Pentyl-3-phenylurea (7), CAS [91907-79-8]. Off-white solid, (196 mg, 95 % yield); M.p.: 90–91 °C (*Lit.*:[6] 91–92 °C); IR (KBr) ν (cm^{-1}): 3324; 2927; 1637; 1560; 1234, 759; ^{1}H NMR (500 MHz, DMSO-d_6) δ (ppm): 8.33 (s, 1H), 7.38–7.32 (m, 2H), 7.18 (t, J = 7.9 *Hz*, 2H), 6.85 (tt, J = 7.3 and 1.2 Hz, 1H), 6.07 (t, J = 5.4 *Hz*, 1H), 3.05 (td, J = 7.0, 5.4 *Hz*, 2H), 1.41 (p, J = 7.0 *Hz*, 2H), 1.35–1.20 (m, 4H), 0.86 (t, J = 7.0 *Hz*, 3H); ^{13}C NMR (151 MHz, DMSO-d_6) δ (ppm): 155.7, 141.1, 129.1, 121.3, 117.9, 39.4, 29.9, 29.1, 22.4, 14.4. Spectroscopic data are in agreement with those reported earlier in the literature.[6]



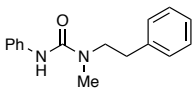
8

1-Cyclohexyl-3-phenylurea (8). CAS [886-59-9]. White solid, (199 mg, 91 % yield). M.p.: 167–168 °C (*Lit.*:[7] 168 °C); IR (KBr) ν (cm^{-1}): 3324, 3101, 3054, 3020, 2931, 2855, 1629, 1581, 1569, 1497, 1444, 1310, 1240, 715; ^{1}H NMR (500 MHz, DMSO-d_6) δ (ppm): 8.23 (s, 1H), 7.37–7.31 (m, 2H), 7.22–7.14 (m, 2H), 6.85 (tt, J = 7.3 and 1.2 *Hz*, 1H), 6.01 (d, J = 7.8 *Hz*, 1H), 3.46-3.44 (m, 1H), 1.81-1.76 (m, 2H), 1.66-1.62 (m, 2H), 1.52 (1.54-1.50, 1H), 1.35–1.23 (m, 2H), 1.22–1.08 (m, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ (ppm): 154.4, 140.5, 128.6, 120.8, 117.4, 47.5, 32.9, 25.2, 24.3. Spectroscopic data are in agreement with those reported earlier in the literature.[7]



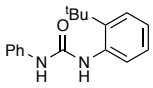
9

***N*-phenylpiperidine-1-carboxamide (9).** CAS [2645-36-5]. Off-white solid, (184 mg, 90 % yield). M.p.: 170–171 °C (*Lit.*:[8] 169–171 °C); IR (KBr) ν (cm^{-1}): 3286, 2921, 2853, 1630, 1593, 1530, 1431; ^{1}H NMR (600 MHz, DMSO-d_6) δ (ppm): 8.44 (s, 1H), 7.46 (d, J = 8.0 *Hz*, 2H), 7.21 (t, J = 8.0 *Hz*, 2H), 6.91 (t, J = 7.3 *Hz*, 1H), 3.51–3.33 (m, 4H), 1.57 (d, J = 5.9 *Hz*, 2H), 1.49 (q, J = 5.9 and 5.3 *Hz*, 4H); ^{13}C NMR (151 MHz, DMSO-d_6) δ (ppm): 155.4, 141.3, 128.7, 121.9, 120.0, 45.1, 25.9, 24.6. Spectroscopic data are in agreement with those reported earlier in the literature.[8]



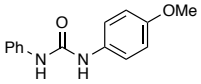
10

1-Methyl-1-phenethyl-3-phenylurea (10). CAS [73355-73-4]. White solid, (221 mg, 87 % yield). M.p.: 115–116 °C; IR (KBr) ν (cm^{-1}): 3297, 3121, 3042, 2971, 2950, 2875, 1652, 1595, 1537, 1441, 1372, 1296, 1244, 1172, 762; ^{1}H NMR (600 MHz, DMSO-d_6) δ (ppm): 8.18 (s, 1H), 7.45 (d, J = 7.2 *Hz*, 2H), 7.33–7.18 (m, 7H), 6.93 (tt, J = 7.3 and 1.2 *Hz*, 1H), 3.57–3.52 (m, 2H), 2.93 (s, 3H), 2.84–2.79 (m, 2H). ^{13}C NMR (151 MHz, DMSO-d_6) δ (ppm): 155.2, 140.6, 139.3, 128.7, 128.3, 128.1, 126.1, 121.6, 119.8, 49.8, 34.62, 33.59. HRMS ESI-(+) calcd. for $C_{16}H_{19}N_2O$ $[M+H]^+$ 255.1497, found 255.1495.



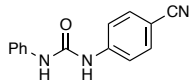
11

1-(2-(*Tert*-butyl)phenyl)-3-phenylurea (11). CAS [862891-84-7]. White solid, (220 mg, 82 % yield). M.p.: 207–208 °C (*Lit.*:[9] 208 °C); IR (KBr) ν (cm^{-1}): 3280, 3254, 3161, 3132, 3122, 3074, 2938, 2905, 1691, 1631, 1462, 1362, 1274, 1185, 761; ^{1}H NMR (600 MHz, DMSO-d_6) δ (ppm): 9.01 (s, 1H), 7.53 (s, 1H), 7.48–7.44 (m, 2H), 7.37 (dd, J = 7.9 and 1.6 *Hz*, 1H), 7.30–7.25 (m, 3H), 7.20 (td, J = 7.5 and 1.6 *Hz*, 1H), 7.15 (td, J = 7.6 and 1.6 *Hz*, 1H), 6.96–6.93 (m, 1H), 1.38 (s, 9H); ^{13}C NMR (151 MHz, DMSO-d_6) δ (ppm): 153.5, 144.2, 140.2, 135.9, 130.1, 128.7, 126.1, 126.0, 125.4, 121.4, 117.8, 34.5, 30.5. Spectroscopic data are in agreement with those reported earlier in the literature.[9]



12

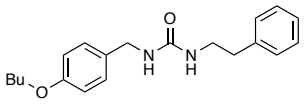
1-(4-Methoxyphenyl)-3-phenylurea (12). CAS [3746-53-0]. Pale yellow solid, (213 mg, 88 % yield). M.p.: 159–160 °C (*Lit.*:[4] 158–160 °C); IR (KBr) ν (cm^{-1}): 3411, 2855, 1644, 1505, 1248, 1149, 1025, 754; ^{1}H NMR (600 MHz, DMSO-d_6) δ (ppm): 8.56 (s, 1H), 8.45 (s, 1H), 7.44 (d, J = 7.3 *Hz*, 2H), 7.35 (d, J = 9.0 *Hz*, 2H), 7.30–7.24 (m, 2H), 6.95 (t, J = 7.3 *Hz*, 1H), 6.87 (d, J = 9.0 *Hz*, 2H), 3.72 (s, 3H); ^{13}C NMR (151 MHz, DMSO-d_6) δ (ppm): 154.4, 152.7, 139.9, 132.7, 128.7, 121.6, 120.0, 118.1, 114.0, 55.2. Spectroscopic data are in agreement with those reported earlier in the literature.[10]



13

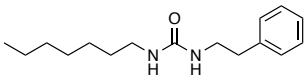
1-(4-Cyanophenyl)-3-phenylurea (13). CAS [107676-58-4]. Off-white solid, (188 mg, 79 % yield). M.p.: 169–170 °C (*Lit.*:[11] 170–172 °C); IR (KBr) ν (cm^{-1}): 3414, 2856, 1644, 1510, 1245, 1147, 1020, 758; ^{1}H NMR (600 MHz, DMSO-d_6) δ (ppm): 9.21 (s, 1H), 8.87 (s, 1H), 7.73 (d, J = 8.6 *Hz*, 2H), 7.64 (dd, J = 8.6 and 1.4 *Hz*, 2H), 7.47 (d, J = 8.1 *Hz*, 2H), 7.30 (t, J = 7.7 *Hz*, 2H), 7.01 (t, J = 7.3 *Hz*, 1H); ^{13}C NMR (151 MHz, DMSO-d_6) δ (ppm): 152.1, 144.3, 139.2, 133.28, 128.8, 122.4, 119.3, 118.6, 118.0, 103.2.

Spectroscopic data are in agreement with those reported earlier in the literature.[11]



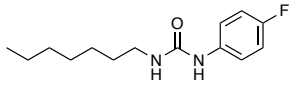
14

1-(4-Butoxybenzyl)-3-phenethylurea (14). CAS [1023257-54-6]. White solid, (278 mg, 85 % yield). M.p.: 105–106°C; IR (KBr) ν (cm^{-1}): 3366, 3321, 3119, 2968, 2917, 1631, 1568, 1450, 1362, 1245, 1029, 771; ^{1}H NMR (600 MHz, DMSO-d_6) δ (ppm): 7.36–7.24 (m, 2H), 7.20 (dd, J = 6.8 and 5.1 *Hz*, 3H), 7.13 (d, J = 8.6 *Hz*, 2H), 6.90–6.82 (d, J = 8.6 *Hz*, 2H), 6.26 (t, J = 5.8 *Hz*, 1H), 5.87 (t, J = 5.7 *Hz*, 1H), 4.11 (d, J = 5.9 *Hz*, 2H), 3.94 (t, J = 6.5 *Hz*, 2H), 3.27–3.22 (m, 2H), 2.69 (t, J = 7.2 *Hz*, 2H), 1.72–1.64 (m, 2H), 1.46-1.40 (m, 2H), 0.93 (t, J = 7.4 *Hz*, 3H); ^{13}C NMR (151 MHz, DMSO-d_6) δ (ppm): 171.7, 158.4, 157.9, 140.2, 133.2, 129.1, 128.8, 126.4, 114.6, 67.6, 42.8, 41.4, 36.6, 31.2, 19.2, 14.2. HRMS ESI-(+) calcd. for $C_{20}H_{27}N_2O_2$ $[M+H]^+$ 327.2072, found 327.2069.



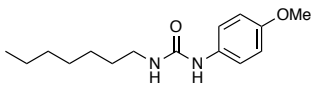
15

1-Heptyl-3-phenethylurea (15). Off-white solid, (250 mg, 95 % yield). M.p.: 124–125 °C; IR (KBr) ν (cm^{-1}): 3361, 3320, 3181, 3119, 3029, 2961, 2923, 1635, 1569, 1450, 1283, 1210, 1149, 737; ^{1}H NMR (600 MHz, DMSO-d_6) δ (ppm): 11.26 (s, 1H), 7.73 (s, 1H), 7.29 (t, J = 7.5 *Hz*, 2H), 7.23–7.18 (m, 3H), 3.24 (q, J = 6.9 *Hz*, 2H), 2.73 (t, J = 7.3 *Hz*, 2H), 2.05 (t, J = 7.3 *Hz*, 2H), 1.55–1.46 (m, 2H), 1.28–1.21 (m, 8H), 0.86 (t, J = 7.0 *Hz*, 3H); ^{13}C NMR (151 MHz, DMSO-d_6) δ (ppm): 154.9, 139.0, 128.6, 128.3, 126.1, 42.1, 35.2, 31.9, 31.1, 28.4, 28.3, 24.7, 22.0, 13.9. HRMS ESI-(+) calcd. for $C_{16}H_{27}N_2O$ $[M+H]^+$ 263.2123, found 263.2121.



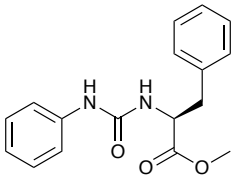
16

1-(4-Fluorophenyl)-3-heptylurea, **(16).** Off-white solid, (202 mg, 80 % yield). M.p.: 107–108 °C; IR (KBr) ν (cm^{-1}): 3327, 3315, 3191, 3057, 3031, 1637, 1599, 1560, 1495, 1312, 1244, 1045; 752; ^{1}H NMR (600 MHz, DMSO-d_6) δ (ppm): 8.39 (s, 1H), 7.41–7.35 (m, 2H), 7.08–7.01 (m, 2H), 6.07 (t, J = 5.7 *Hz*, 1H), 3.08-3.04 (m, 2H), 1.42 (t, J = 7.0 *Hz*, 2H), 1.33–1.22 (m, 8H), 0.90–0.83 (m, 3H); ^{13}C NMR (151 MHz, DMSO-d_6) δ (ppm): 156.8 (d, $J_{C\text{-}F}$ = 236.8 *Hz*), 155.2, 137.0 (d, $J_{C\text{-}F}$ = 2.4 *Hz*), 119.1 (d, $J_{C\text{-}F}$ = 7.5 *Hz*), 115.0 (d, $J_{C\text{-}F}$ = 22.1 *Hz*), 39.1, 31.2, 29.7, 28.4, 26.3, 22.0, 13.9. ^{19}F NMR (565 MHz, DMSO-d_6) δ (ppm): -122.81. HRMS ESI-(+) calcd. for $C_{14}H_{22}FN_2O$ $[M+H]^+$ 253.1716, found 253.1715.



17

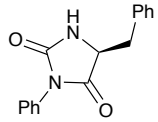
1-Heptyl-3-(4-methoxyphenyl)urea (17). White solid, (254 mg, 96% yield). M.p.: 190–191 °C; IR (KBr) ν (cm^{-1}): 3325, 3318, 3275, 3105, 3056, 2961, 2869, 1655, 1601, 1563, 1502, 1321, 1235, 1025, 751; ^{1}H NMR (600 MHz, DMSO-d_6) δ (ppm): 11.49 (s, 1H), 9.96 (s, 1H), 7.35 (d, J = 9.1 *Hz*, 2H), 6.90 (d, J = 9.0 *Hz*, 2H), 3.72 (s, 3H), 2.12 (t, J = 7.4 *Hz*, 2H), 1.54 (t, J = 7.2 *Hz*, 2H), 1.32–1.23 (m, 8H), 0.87 (t, J = 7.0 *Hz*, 3H); ^{13}C NMR (151 MHz, DMSO-d_6) δ (ppm): 155.2, 152.4, 131.2, 119.9, 114.1, 55.2, 40.06, 31.9, 31.1, 28.3, 24.7, 22.0, 13.9. HRMS ESI-(+) calcd. for $C_{15}H_{24}N_2NaO_2$ $[M+Na]^+$ 287.1735, found 287.1736.



18

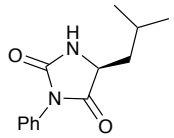
Methyl (phenylcarbamoyl)-*L*-phenylalaninate (18). CAS [104060-47-1]. White solid, (283 mg, 95 % yield). M.p.: 85–86 °C (*Lit.*:[12] 81–82 °C); IR (KBr) ν (cm^{-1}): 3345, 2359, 1747, 1653, 1557, 1494, 1445, 1219; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.30–7.16 (m, 7H), 7.13–7.07 (m, 2H), 7.07–7.00 (m, 2H), 5.66 (d, J = 7.9 *Hz*, 1H), 4.83 (dt, J = 8.0 and 6.1 *Hz*, 1H), 3.70 (s, 3H), 3.12 (dd, J = 13.9 and 5.8 *Hz*, 1H), 3.02 (dd, J = 13.8 and 6.4 *Hz*, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm): 173.5, 155.5, 138.6, 136.3, 129.3, 129.1, 128.6, 127.1, 123.5, 120.6, 54.2, 52.3, 38.4. Spectroscopic data are in agreement with those reported earlier in the literature.[13]

SPECTRAL DATA FOR 3,5-DISUBSTITUTED HYDANTOINS 19, 21, 27-46 AND CYCLIC CARBONATE A.



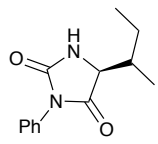
19

(*S*)-5-Benzyl-3-phenylimidazolidine-2,4-dione (19). CAS [215670-78-3]. White solid, (240 mg, 90% yield, *e.r.* 90:10 in favour of the *L*-isomer). M.p.: 157–158 °C (*Lit.*:[14] 159–161 °C); IR (KBr) ν (cm^{-1}): 3244, 3112, 1771, 1713, 1603, 1501, 1425, 1344; ^{1}H NMR (600 MHz, DMSO-d_6) δ (ppm): 8.57 (s, 1H), 7.45 (dd, J = 8.5 and 7.0 *Hz*, 2H), 7.41–7.34 (m, 3H), 7.33–7.25 (m, 3H), 7.10–6.97 (m, 2H), 4.72–4.55 (m, 1H), 3.22–3.01 (m, 2H); ^{13}C NMR (151 MHz, DMSO-d_6) δ (ppm): 172.5, 155.3, 135.0, 131.9, 129.8, 128.7, 128.1, 127.7, 126.9, 126.5, 57.0, 36.6. The enantiomeric ratio (*e.r.)* of the final compound was determined by chiral HPLC analyses using a Phenomenex Lux 5u Cellulose-1 column [*n*-hexane/*i*-PrOH (95:5 v/v); flow rate 1.25 mL min^{-1}]: t = 12.2 min, detection: λ = 220 nm.[14] Spectroscopic data are in agreement with those reported earlier in the literature.[14]



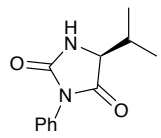
27

(*S*)-5-isobutyl-3-phenylimidazolidine-2,4-dione (27). CAS [88576-98-1]. White solid, (204 mg, 88 % yield). M.p.: 119–120 °C; IR (KBr) ν (cm^{-1}): 3260, 3115, 1775, 1725, 1495, 1432, 1399, 766. ^{1}H NMR (500 MHz, DMSO-d_6) δ (ppm): 8.55 (s, 1H), 7.45 (t, J = 7.7 *Hz*, 2H), 7.39–7.35 (m, 1H), 7.35–7.29 (m, 2H), 4.22 (ddd, J = 9.1, 4.5 and 1.4 *Hz*, 1H), 1.88-1.84 (m, 1H), 1.66–1.50 (m, 2H), 0.92 (dd, J = 6.6 and 1.4 *Hz*, 6H); ^{13}C NMR (151 MHz, DMSO-d_6) δ (ppm): 173.7, 155.6, 132.2, 128.7, 127.7, 126.6, 54.8, 40.6, 24.1, 23.0, 21.5. Spectroscopic data are in agreement with those reported earlier in the literature.[15]



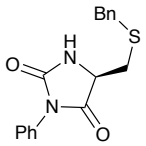
28

(*S*)-5-[(*S*)-*sec*-butyl]-3-phenylimidazolidine-2,4-dione (28). CAS [947596-21-6]. White solid, (197 mg, 85 % yield). M.p.: 106–107 °C; IR (KBr) ν (cm^{-1}): 3264, 3120, 2857, 1774, 1728, 1505, 1493, 1175, 758; ^{1}H NMR (600 MHz, DMSO-d_6) δ (ppm): 8.39 (d, J = 9.4 *Hz*, 1H), 7.48 (td, J = 7.9 and 1.6 *Hz*, 2H), 7.39 (td, J = 7.3 and 1.5 *Hz*, 1H), 7.33 (dt, J = 7.6 and 1.5 *Hz*, 2H), 4.24 (dd, J = 3.1 and 1.4 *Hz*, 1H), 1.96–1.87 (m, 1H), 1.56–1.43 (m, 1H), 1.38–1.25 (m, 1H), 1.01 (d, J = 7.0 *Hz*, 1H), 0.94 (t, J = 21.3 and 7.4 *Hz*, 2H), 0.91 (t, J = 21.3 and 7.4 *Hz*, 1H), 0.86 (d, J = 6.8 *Hz*, 2H); ^{13}C NMR (151 MHz, DMSO-d_6) δ (ppm): 172.8, 155.8, 131.9, 128.4, 127.4, 126.2, 59.5, 36.1, 25.2, 14.7, 11.3. HRMS ESI-(+) calcd. for $C_{13}H_{17}N_2O_2$ $[M+H]^+$ 233.1290, found 233.1287.



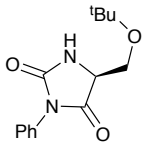
29

(*S*)-5-isopropyl-3-phenylimidazolidine-2,4-dione (29). CAS [65462-94-4]. White solid, (190 mg, 87% yield). M.p.: 129–130 °C (*Lit.*:[16] 128-130 °C); IR (KBr) ν (cm^{-1}): 3297, 1778, 1710, 1505, 1415, 1170, 800; ^{1}H NMR (600 MHz, DMSO-d_6) δ (ppm): 8.41 (s, 1H), 7.48 (t, J = 7.8 *Hz*, 2H), 7.42–7.36 (m, 1H), 7.35–7.30 (m, 2H), 4.13 (d, J = 3.6 *Hz*, 1H), 2.18-2.13 (m, 1H), 1.04 (d, J = 7.0 *Hz*, 3H), 0.92 (d, J = 6.8 *Hz*, 3H); ^{13}C NMR (151 MHz, DMSO-d_6) δ (ppm): 172.7, 156.0, 132.2, 128.7, 127.7, 126.6, 61.4, 30.0, 18.4, 16.0. Spectroscopic data are in agreement with those reported earlier in the literature.[15]



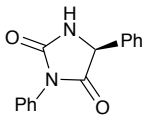
30

(*R*)-5-[(benzylthio)methyl]-3-phenylimidazolidine-2,4-dione (30). CAS [1653997-43-3]. White solid, (169 mg, 54 % yield). M.p.: 144–145 °C; IR (KBr) ν (cm^{-1}): 3233, 3099, 3066, 2911, 2850, 1765, 1715, 1597, 1505, 1431, 1401, 1250, 1186, 709; ^{1}H NMR (600 MHz, DMSO-d_6) δ (ppm): 8.50 (s, 1H), 7.49 (t, J = 7.8 *Hz*, 2H), 7.42–7.38 (m, 1H), 7.37–7.33 (m, 6H), 7.29–7.24 (m, 1H), 4.54 (t, J = 4.3 *Hz*, 1H), 3.85 (d, J = 1.9 *Hz*, 2H), 2.95–2.90 (m, 2H); ^{13}C NMR (151 MHz, DMSO-d_6) δ (ppm): 172.0, 155.6, 138.0, 132.1, 128.7, 128.6, 128.2, 127.6, 126.8, 126.3, 56.3, 36.1, 32.5. HRMS ESI-(+) calcd. for $C_{17}H_{17}N_2O_2S$ $[M+H]^+$ 313.1011, found 313.1012.



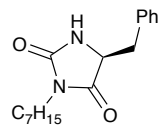
31

(*S*)-5-(*tert*-butoxymethyl)-3-phenylimidazolidine-2,4-dione (31). CAS [215656-25-0]. Off-white solid, (100 mg, 38 % yield). M.p.: 104–105 °C (Lit.:[17] 101–103 °C); IR (KBr) ν (cm^{-1}): 3329, 2968, 2920, 2854, 1785, 1706, 1595, 1497, 1418, 1360, 1340, 1280, 1240, 1181, 1105, 1080, 1014, 935, 819, 737; ^{1}H NMR (600 MHz, DMSO-d_6) δ (ppm): 8.28 (s, 1H), 7.51–7.45 (m, 2H), 7.41–7.35 (m, 1H), 7.33–7.28 (m, 2H), 4.30-4.29 (m, 1H), 3.69 (dd, J = 9.8 and 3.8 *Hz*, 1H), 3.63 (dd, J = 9.8 and 2.6 *Hz*, 1H), 1.15 (s, 9H); ^{13}C NMR (151 MHz, DMSO-d_6) δ (ppm): 171.7, 156.0, 132.3, 128.5, 127.4, 126.4, 72.7, 60.6, 57.4, 27.0. Spectroscopic data are in agreement with those reported earlier in the literature.[14,17]



32

(*S*)-3,5-diphenylimidazolidine-2,4-dione (32). CAS [2180158-21-6]. Off-white solid (139 mg, 55 % yield). M.p.: 178–179 °C; IR (KBr) ν (cm^{-1}): 3307, 1782, 1715, 1498, 1410, 1170, 715; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.47–7.32 (m, 10H), 6.21 (t, J = 10.5 *Hz*, 1H), 5.21 (s, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm): 170.9, 156.5, 134.3, 131.6, 129.4, 129.4, 129.3, 128.5, 126.7, 126.3, 60.7. Spectroscopic data are in agreement with those reported earlier in the literature.[15]

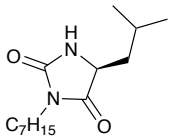


33

(*S*)-5-benzyl-3-heptylimidazolidine-2,4-dione (33). CAS [426258-94-8]. Off-white solid, (245 mg, 85 % yield). M.p.: 117–118 °C; IR (KBr) ν (cm^{-1}): 3248, 3214, 1774, 1710, 1489, 1423, 1340, 930, 822, 741; ^{1}H NMR (600 MHz, DMSO-d_6) δ (ppm): 8.08 (s, 1H), 7.25 (t, J = 7.3 *Hz*, 2H), 7.20 (t, J = 7.3 *Hz*, 1H), 7.17 (d, J = 7.1 *Hz*, 2H), 4.35 (t, J = 4.7 *Hz*, 1H), 3.20-3.15 (m, 2H), 2.99–2.95

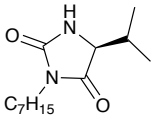
33

(m, 2H), 1.38–1.11 (m, 8H), 1.01– 0.91 (m, 2H), 0.87 (t, *J* = 7.3 *Hz*, 3H); ^{13}C NMR (151 MHz, DMSO-d_6) δ (ppm): 173.1, 156.4, 135.0, 129.5, 127.7, 126.4, 56.7, 37.2, 36.2, 30.8, 27.9, 27.0, 26.0, 21.7, 13.6. HRMS ESI-(+) calcd. for $C_{17}H_{25}N_2O_2$ $[M+H]^+$ 289.1916, found 289.1914.



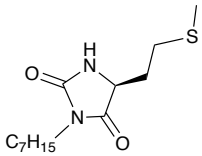
34

(*S*)-3-heptyl-5-isobutylimidazolidine-2,4-dione (34). White solid, (196 mg, 77 % yield). M.p.: 80–81 °C; IR (KBr) ν (cm^{-1}): 3225, 1767, 1714, 1680, 1497, 1354, 1241, 781; ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm): 5.93 (s, 1H), 4.00 (dd, *J* = 9.4 and 3.6 *Hz*, 1H), 3.48 (tt, *J* = 10.2 and 5.1 *Hz*, 2H), 1.83-1.79 (m, 2H), 1.63–1.58 (m, 2H), 1.55–1.46 (m, 1H), 1.35–1.22 (m, 8H), 0.97 (t, *J* = 6.7 *Hz*, 6H), 0.88 (t, *J* = 6.9 *Hz*, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ (ppm): 174.6, 157.9, 55.9, 41.27, 38.9, 31.8, 28.9, 28.2, 26.8, 25.4, 23.1, 22.7, 21.9, 14.1. HRMS ESI-(+) calcd. for $C_{14}H_{27}N_2O_2$ $[M+H]^+$ 255.2072, found 255.2073.



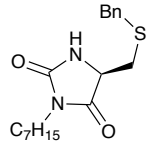
35

(*S*)-3-heptyl-5-isopropylimidazolidine-2,4-dione (35). White solid, (168 mg, 70 % yield). M.p.: 87–88 °C; IR (KBr) ν (cm^{-1}): 3237, 2933, 2873, 1761, 1711, 1684, 1435; 1357, 1239, 777. ^{1}H NMR (500 MHz, DMSO-d_6) δ (ppm): 8.14 (s, 1H), 3.91 (dd, *J* = 3.5 and 1.4 *Hz*, 1H), 3.34–3.28 (m, 2H), 2.01 (m, 1H), 1.48-1.45 (m, 2H), 1.25-1.20 (m, 8H), 0.92 (d, *J* = 7.0 *Hz*, 3H), 0.83 (t, *J* = 7.0 *Hz*, 3H), 0.76 (d, *J* = 7.0 *Hz*, 3H); ^{13}C NMR (126 MHz, DMSO-d_6) δ (ppm): 173.6, 157.2, 61.2, 37.3, 31.3, 29.5, 28.1, 27.4, 25.9, 21.9, 18.3, 15.67, 13.8. HRMS ESI-(+) calcd. for $C_{13}H_{25}N_2O_2$ $[M+H]^+$ 241.1916, found 241.1914.



36

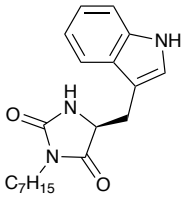
(*S*)-3-heptyl-5-[2-(methylthio)ethyl]imidazolidine-2,4-dione (36). Off-white solid, (180 mg, 66 % yield). M.p.: 68–69 °C; IR (KBr) ν (cm^{-1}): 3242, 2954, 2924, 2862, 1770, 1714, 1681, 1463, 1422, 1354, 1287, 1168; ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm): 5.79 (s, 1H), 4.15 (dd, *J* = 8.0, 4.2 Hz, 1H), 3.55-3.48 (m, 2H), 2.72-2.63 (m, 2H), 2.28-2.23 (m, 1H), 2.19–2.10 (m, 3H), 1.99-1.93 (m, 1H), 1.64 (t, *J* = 7.3 *Hz*, 2H), 1.38–1.29 (m, 8H), 0.91 (t, *J* = 6.8 *Hz*, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ (ppm): 173.6, 157.3, 56.3, 38.8, 31.6, 30.8, 30.4, 28.7, 27.9, 26.6, 22.5, 15.2, 13.9. HRMS ESI-(+) calcd. for $C_{13}H_{25}N_2O_2S$ $[M+H]^+$ 273.1637, found 273.1635.



37

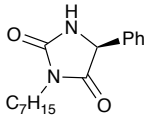
(*R*)-5-[(benzylthio)methyl]-3-heptylimidazolidine-2,4-dione (37). Off-white solid, (87 mg, 26 % yield). M.p.: 85–87 °C ; IR (KBr) ν (cm^{-1}): 3332, 3223, 3062, 3031, 2951, 2922, 2855, 2920, 1759, 1708, 1626, 1557, 1455, 1348, 1238, 718; ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm): 7.54–7.14 (m, 5H), 5.28 (s, 1H), 4.02 (dt, *J* = 8.4 and 4.2 *Hz*, 0.5 H), 3.80 (m, 1H), 3.75-3.74 (m, 0.5 H), 3.71–3.62 (m, 2H), 3.60-3.7 (m, 0.5H), 3.54-3.46 (m, 1H), 3.19-3.16 (m, 0.5 H), 3.04-3.00 (m, 0.5 H), 2.69-2.64 (m, 0.5H), 1.68–1.61 (m, 2 H), 1.39–1.26 (m, 8H), 0.91 (t, *J* = 7.3 and 6.6 *Hz*, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ (ppm): 172.2, 156.8, 137.5, 132.8, 128.8, 127.5, 56.6, 38.9, 37.0, 33.6, 31.6, 28.7, 27.9, 26.6, 22.5, 13.9.

HRMS ESI-(+) calcd. for $C_{18}H_{27}N_2O_2S$ $[M+H]^+$ 335.1793, found 335.1791.



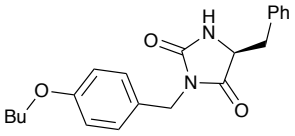
38

(*S*)-5-[(1*H*-indol-3-yl)methyl]-3-heptylimidazolidine-2,4-dione (38). White solid, (268 mg, 82 % yield). M.p.: 88–89 °C; IR (KBr): 3448, 3332, 2953, 2924, 2851, 1752, 1707, 1617, 1578, 1477, 1465, 1522, 1430, 875. 762 (cm^{-1}); ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm): 8.19 (s, 1H), 7.58 (d, J = 7.9 *Hz*, 1H), 7.31 (d, J = 8.0 *Hz*, 1H), 7.18 (t, J = 7.6 *Hz*, 1H), 7.10 (t, J = 7.5 *Hz*, 1H), 7.01-6.99 (m, 1H), 1.44 (d, J = 7.4 *Hz*, 1H), 1.41 (d, J = 7.4 *Hz*, 1H), 1.27–1.16 (m, 8H), 0.87 (t, J = 7.1 *Hz*, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ (ppm): 173.6, 157.5, 136.4, 127.1, 123.1, 122.5, 119.9, 118.6, 111.3, 109.6, 57.4, 38.3, 31.1, 28.2, 28.0, 27.5, 26.4, 22.5, 13.9. HRMS ESI-(+) calcd. for $C_{19}H_{26}N_3O_2$ $[M+H]^+$ 328.2025, found 328.2026.



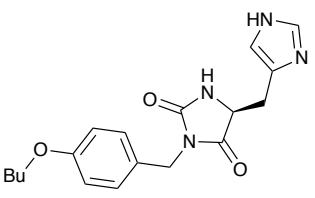
39

(*S*)-3-heptyl-5-phenylimidazolidine-2,4-dione (39). CAS [1786132-62-4]. White solid, (137 mg, 50 % yield). M.p.: 79–80 °C; IR (KBr) ν (cm^{-1}): 3318, 3060, 2952, 2926, 2855, 1727, 1694, 1651, 1574, 1519, 1417, 1347, 849, 756; ^{1}H NMR (600 MHz, DMSO-d_6) δ (ppm) 8.57 (s, 1H), 7.43–7.39 (m, 2H), 7.38–7.34 (m, 1H), 7.35–7.32 (m, 2H), 5.19 (bs, 1H), 3.44–3.34 (m, 2H), 1.57–1.50 (m, 2H), 1.28–1.18 (m, 8H), 0.86 (t, J = 7.0 *Hz*, 3H); ^{13}C NMR (151 MHz, DMSO-d_6) δ (ppm): 173.0, 157.4, 136.4, 129.1, 128.8, 127.2, 60.3, 38.3, 31.5, 28.5, 27.9, 26.4, 22.3, 14.3. HRMS ESI-(+) calcd. for $C_{16}H_{23}N_2O_2$ $[M+H]^+$ 275.1759, found 275.1761.



40

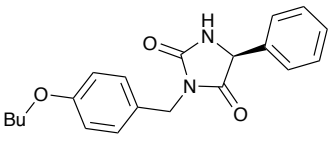
(*S*)-5-Benzyl-3-(4-butoxybenzyl)imidazolidine-2,4-dione (40). Off-white solid, (282 mg, 80 % yield). M.p.: 127–128 °C; IR (KBr) ν (cm^{-1}): 3229, 3096, 3062, 2955, 2931, 2871, 1766, 1708, 1612, 1511, 1498, 1450, 1293, 1247, 1109, 1107, 697; ^{1}H NMR (600 MHz, DMSO-d_6) δ (ppm): 8.22 (s, 1H), 7.28–7.24 (m, 3H), 7.19 (dd, J = 6.6 and 3.0 *Hz*, 2H), 6.87 (d, J = 8.6 *Hz*, 2H), 6.78 (d, J = 8.7 *Hz*, 2H), 4.47 (td, J = 4.9 and 1.3 *Hz*, 1H), 4.38 (d, J = 15.1 *Hz*, 1H), 4.30 (d, J = 15.1 *Hz*, 1H), 3.97 (t, J = 6.5 *Hz*, 2H), 3.03 (dd, J = 4.9 and 3.0 *Hz*, 2H), 1.76–1.68 (m, 2H), 1.47 (q, J = 7.4 *Hz*, 2H), 0.97 (t, J = 7.4 *Hz*, 3H); ^{13}C NMR (151 MHz, DMSO-d_6) δ (ppm): 173.0, 157.7, 156.1, 135.0, 129.5, 128.2, 128.2, 127.9, 126.5, 114.2, 67.1, 57.0, 40.2, 36.1, 30.6, 18.5, 13.4. HRMS ESI-(+) calcd. for $C_{21}H_{25}N_2O_3$ $[M+H]^+$ 353.1865, found 353.1862.



41

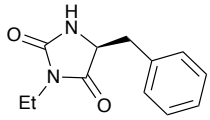
(*S*)-5-[(1*H*-imidazol-4-yl)methyl]-3-(4-butoxybenzyl)imidazolidine-2,4-dione (41). Off-white solid, (219 mg, 64 % yield). M.p.: 154–155 °C; IR (KBr) ν (cm^{-1}): 3268, 2933, 1708, 1513, 1451, 1246, 1164, 823; ^{1}H NMR (600 MHz, DMSO-d_6) δ (ppm): 7.49 (s, 1H), 7.00 (d, J = 8.6 *Hz*, 2H), 6.82 (d, J = 8.7 *Hz*, 2H), 6.78 (s, 1H), 4.43–4.33 (m, 2H), 4.30 (dd, J = 6.2 and 4.5 *Hz*, 1H), 3.41 (bs, 2H), 3.94 (d, J = 6.5 *Hz*, 2H), 2.97 (dd, J = 14.9 and 4.4 *Hz*, 1H), 2.83 (dd, J = 14.9 and 6.3 *Hz*, 1H), 1.69-1.66 (m, J = 7.7 and 6.5 *Hz*, 2H), 1.48–1.39 (m, 2H), 0.93 (t, J = 7.4 *Hz*, 3H); ^{13}C NMR (151 MHz, DMSO-d_6) δ (ppm): 173.4, 157.8, 156.5,

141.9, 134.9, 134.5, 128.3, 118.0, 114.2, 67.1, 56.4, 54.4, 51.1, 30.6, 18.5, 13.4. HRMS ESI-(+) calcd. for $C_{18}H_{23}N_4O_3$ $[M+H]^+$ 343.1770, found 343.1767.



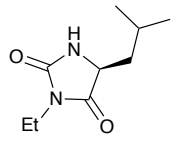
42

(*S*)-3-(4-Butoxybenzyl)-5-phenylimidazolidine-2,4-dione (42). White solid, (173 mg, 51 % yield). M.p 116–117 °C; IR (KBr) ν (cm^{-1}): 3431, 3338, 2957, 2935, 2873, 1716, 1654, 1602, 1559, 1513, 1468, 1486, 1387, 1345, 1303, 1246, 1175, 946, 737; ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm): 7.44–7.36 (m, 3H), 7.34 (t, J = 8.0 *Hz*, 4H), 6.85 (d, J = 8.7 *Hz*, 2H), 5.68 (s, 1H), 5.05 (s, 1H), 4.71–4.58 (m, 2H), 3.96 (t, J = 6.5 *Hz*, 2H), 1.81–1.72 (m, 2H), 1.54–1.45 (m, 2H), 0.99 (t, J = 7.4 *Hz*, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ (ppm): 171.7, 159.09, 157.2, 134.4, 130.2, 129.3, 129.3, 128.1, 126.7, 114.7, 67.8, 61.0, 42.2, 31.4, 19.4, 14.0. HRMS ESI-(+) calcd. for $C_{20}H_{23}N_2O_3$ $[M+H]^+$ 339.1708, found 339.1709.



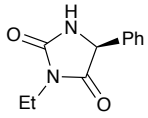
43

(*S*)-5-Benzyl-3-ethylimidazolidine-2,4-dione (43). CAS [880487-32-1]. White solid, (164 mg, 75 % yield). M.p.: 122–123 °C (*Lit.*:[17] 116–117 °C); IR (KBr) ν (cm^{-1}): 3288, 3065, 3065, 3033, 2979, 1760, 1697, 1651, 1454, 1428, 1340, 1179, 1068, 1008, 748; ^{1}H NMR (600 MHz, DMSO-d_6) δ (ppm): 8.19 (s, 1H), 7.26 (dd, J = 8.0 and 6.5 Hz, 2H), 7.21 (t, J = 7.3 *Hz*, 1H), 7.19–7.14 (m, 2H), 4.35 (t, J = 4.8 *Hz*, 1H), 3.24-3.15 (m, 2H), 2.96 (d, J = 4.8 *Hz*, 2H), 0.75 (t, J = 7.2 *Hz*, 3H); ^{13}C NMR (151 MHz, DMSO-d_6) δ (ppm): 173.2, 156.3, 135.1, 129.7, 128.0, 126.7, 56.8, 36.4, 32.2, 12.8. Spectroscopic data are in agreement with those reported earlier in the literature.[17]



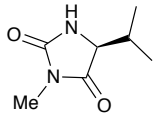
44

(*S*)-3-Ethyl-5-isobutylimidazolidine-2,4-dione (44). CAS [1841226-37-6]. White solid, (131 mg, 71 % yield). M.p.: 110–111 °C (*Lit.*:[17] 116–117 °C); IR (KBr) ν (cm^{-1}): 3247, 2962, 2940, 2877, 1761, 1713, 1537, 1459, 1323, 1218, 1094, 873, 756; ^{1}H NMR (500 MHz, DMSO-d_6) δ (ppm): 8.23 (s, 1H), 4.01 (ddd, J = 9.3, 4.4 and 1.4 Hz, 1H), 3.34 (qd, J = 7.1 and 2.1 *Hz*, 2H), 1.80-1.76 (m, 1H), 1.53-1.48 (m, 1H), 1.39-1.33 (m, 1H), 1.04 (t, J = 7.2 *Hz*, 3H), 0.87 (d, J = 6.6 *Hz*, 6H); ^{13}C NMR (126 MHz, DMSO-d_6) δ (ppm): 174.5, 156.6, 54.7, 40.6, 32.4, 24.0, 23.0, 21.5, 13.2; Spectroscopic data are in agreement with those reported earlier in the literature.[17]



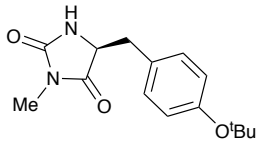
21

(*S*)-3-Ethyl-5-phenylimidazolidine-2,4-dione [Ethotoin, (21)] CAS [108739-43-1]. White solid, (107 mg, 52 % yield). M.p.: 85–87 °C (*Lit.*:[Error! Bookmark not defined.,17] 86–88 °C); IR (KBr) ν (cm^{-1}): 3322, 2985, 2945, 1764, 1690; 1455, 1423, 1344, 1287, 1210, 1180, 1077, 1003, 760; ^{1}H NMR (600 MHz, DMSO-d_6) δ (ppm): 8.67 (s, 1H), 7.42–7.39 (m, 2H), 7.37–7.34 (m, 1H), 7.33–7.30 (m, 2H), 5.19 (d, J = 1.4 *Hz*, 1H), 3.45-3.41 (m, 2H), 1.08 (t, J = 7.2 *Hz*, 3H); ^{13}C NMR (151 MHz, DMSO-d_6) δ (ppm): 172.3, 156.7, 135.8, 128.7, 128.3, 126.8, 59.7, 32.8, 13.2. Spectroscopic data are in agreement with those reported earlier in the literature. [14,17]



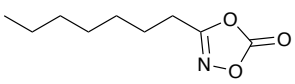
45

(*S*)-5-Isopropyl-3-methylimidazolidine-2,4-dione (45). CAS [71921-91-0].[17] White solid, (105 mg, 67 % yield). M.p.: 101–102 °C; IR (KBr) ν (cm^{-1}): 3345, 2991, 2965, 1765, 1705, 1463, 1035, 824, 762; ^{1}H NMR (600 MHz, DMSO-d_6) δ (ppm): 8.09 (s, 1H), 3.92 (dd, J = 3.8 and 1.3 *Hz*, 1H), 2.81 (s, 3H), 2.04-2.01 (m, 1H), 0.95 (d, J = 7.0 *Hz*, 3H), 0.79 (d, J = 6.8 *Hz*, 3H); ^{13}C NMR (151 MHz, DMSO-d_6) δ (ppm): 173.5, 157.2, 61.5, 29.5, 23.6, 18.2, 15.9. HRMS ESI-(+) calcd. for $C_7H_{13}N_2O_2$ $[M+H]^+$ 157.0977, found 157.0979.



46

(*S*)-5-[4-(*tert*-butoxy)benzyl]-3-methylimidazolidine-2,4-dione (46). Off-white solid, (202 mg, 73 % yield). M.p.: 158–159 °C; IR (KBr) ν (cm^{-1}): 3320, 2974, 1764, 1695, 1500, 1467, 1392, 1235, 1160, 1106, 964, 896, 754; ^{1}H NMR (600 MHz, DMSO-d_6) δ (ppm): 8.16 (s, 1H), 7.06 (d, J = 8.4 *Hz*, 2H), 6.85 (d, J = 8.4 *Hz*, 2H), 4.32-4.30 (m, 1H), 2.99–2.80 (m, 2H), 2.63 (s, 3H), 1.25 (s, 9H); ^{13}C NMR (151 MHz, DMSO-d_6) δ (ppm): 173.6, 156.7, 153.8, 130.0, 130.0, 123.3, 77.7, 57.4, 36.0, 28.5, 23.7. HRMS ESI-(+) calcd. for $C_{15}H_{21}N_2O_3$ $[M+H]^+$ 277.1552, found 277.1550.



A

3-Heptyl-1,4,2-dioxazol-5-one (A, Scheme 2). Colourless waxy solid, (170 mg, 92 % yield). IR (KBr) ν (cm^{-1}): 3346, 2931, 2858, 1828, 1639, 1467, 1429, 1359, 1321, 1237, 1152, 982, 762; ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm): 2.67–2.59 (m, 2H), 1.74 (p, J = 7.6 *Hz*, 2H), 1.45–1.39 (m, 2H), 1.38–1.26 (m, 6H), 0.91 (t, J = 6.9 *Hz*, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ (ppm): 166.7, 154.2, 31.5, 28.7, 28.6, 24.7, 24.5, 22.5, 14.0. HRMS ESI-(+) calcd. for $C_9H_{16}NO_3$ 186.1130 $[M+H]^+$, found 186.1131.

Table S1. Comparative Yields for non-symmetrical ureas **1-18** obtained by Mechanochemical Lossen Transposition *versus* Solution Synthesis.

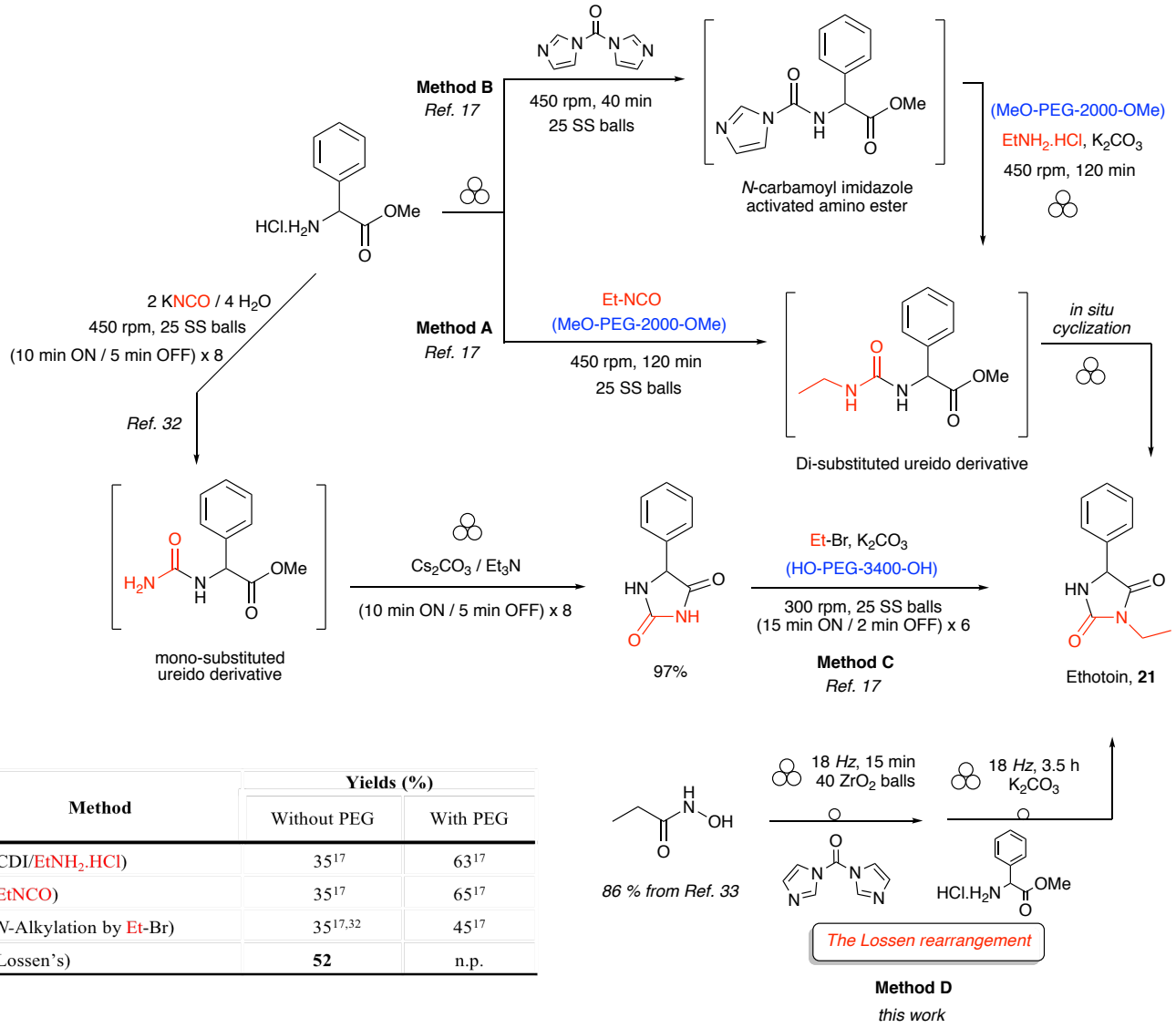
Compound	Method and Yields (%)		
	By Lossen rearrangement		From RNCO
	By Mechanochemistry	In solution	In solution
1	91	n.r.[a]	99[18]
2	92	96[19]	n.r.[a]
3	94	n.r.[a]	94[20]
4	93	n.r.[a]	88[20]
5	91	n.r.[a]	63[21]
6[c]	92	n.a.[b]	n.a.[a]
7[c]	95	n.a.[b]	n.a.[a]
8	91	85[19]	n.r.[a]
9	90	n.r.[a]	61[18]
10	87	n.r.[a]	88[22]
11	82	n.r.[a]	87[23]
12[c]	88	n.a.[b]	n.a.[a]
13[c]	79	n.a.[b]	n.a.[a]
14[c]	85	n.a.[b]	n.a.[a]
15[c]	95	n.a.[b]	n.a.[a]
16[c]	80	n.a.[b]	n.a.[a]
17[c]	96	n.a.[b]	n.a.[a]
18	95	n.r.[a]	70[13]

[a] n.r. = not reported; [b] n.a. = not available; [c] Unknown compound.

Table S2. Comparative Yields for 3,5-disubstituted hydantoins **19, 21, 27-46** obtained by Mechanochemical Lossen Transposition *versus* Solution Synthesis.

Compound	Method and Yields (%)			
	Mechanochemistry	In Solution	Other mechanochemical methods	
	Lossen rearrangement		With RNCO	With CDI/RNH_2
19	90	79,[14] 92[24]	n.r.[a]	0[17]
21	52	65[25]	35,[17] 65[17,b]	n.r.[a]
27	88	99[24]	n.a.[d]	
28	85	92[26]	84[17]	67[17]
29	87	80,[26] 65[16]	n.a.[d]	
30	54	64[27]	n.a.[d]	
31	38	99[24]	0[17]	n.r.[a]
32	55	n.r.[a,28]	n.a.[d]	
33	85	n.r.[a, 29]	n.a.[d]	
34[c]	77	n.a.[d]	n.a.[d]	
35[c]	70	n.a.[d]	n.a.[d]	
36[c]	66	n.a.[d]	n.a.[d]	
37[c]	26	n.a.[d]	n.a.[d]	
38[c]	82	n.a.[d]	n.a.[d]	
39[c]	50	n.a.[d]	n.a.[d]	
40[c]	80	n.a.[d]	n.a.[d]	
41[c]	64	n.a.[d]	n.a.[d]	
42[c]	51	n.a.[d]	n.a.[d]	
43	75	61[30]	75,[17] 70[a, 31]	84[17]
44	71	n.r.[a]	83[17]	61,[17] 73[a,31]
45	67	52[16]	n.a.[d]	
46[c]	73	n.a.[d]	n.a.[d]	

[a] n.r. = not reported; [b] Wet-grinding conditions using PEG additive; [c] Unknown compound; [d] n.a. = not available.



Method	Yields (%)	
	Without PEG	With PEG
A (CDI/$EtNH_2$.HCl)	35[17]	63[17]
B (EtNCO)	35[17]	65[17]
C (*N*-Alkylation by Et-Br)	35[17,32]	45[17]
D (Lossen's)	**52**	n.p.

Scheme S1. Comparative mechanochemical methods for Ethotoin **21** preparation. The 'rearrangement' reaction is represented using the curly arrow formalism firstly introduced by Liebig;[34] for mechanochemically activated reactions, the formalism recently proposed by Hanusa was used.[35]

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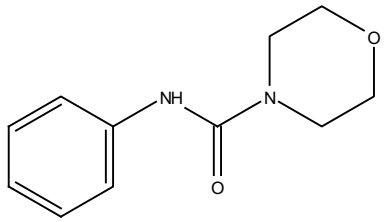
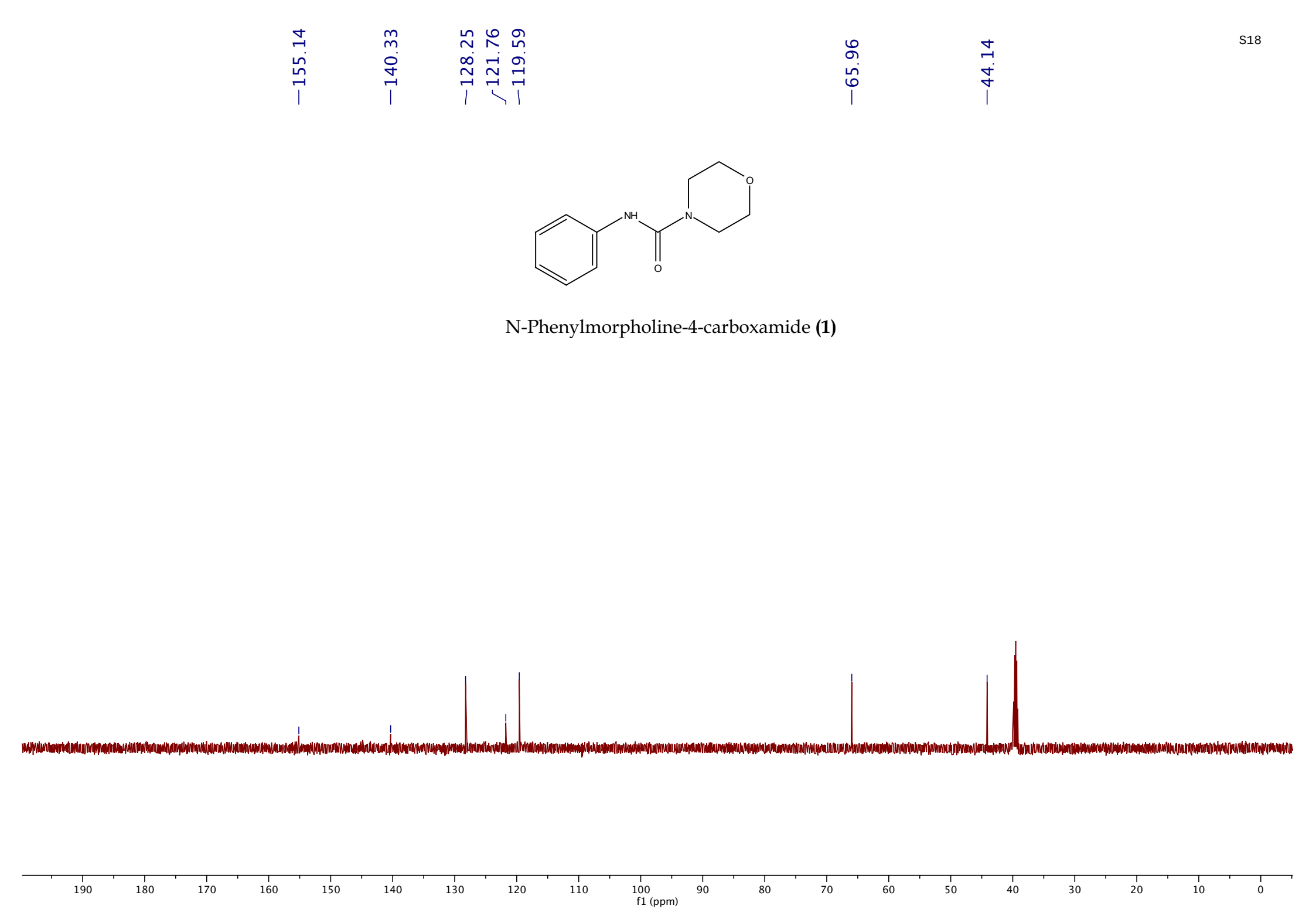
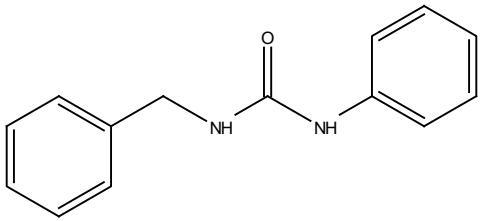


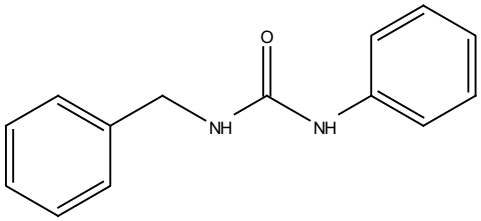
N-Phenylmorpholine-4-carboxamide (1)



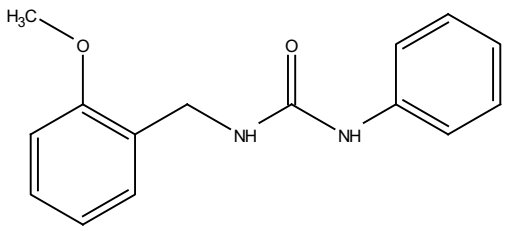
N-Phenylmorpholine-4-carboxamide **(1)**



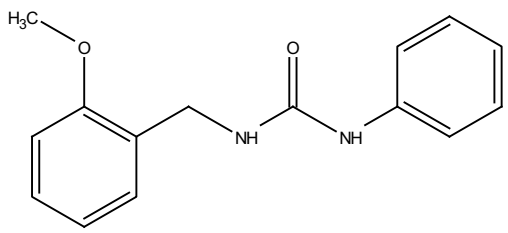
1-Benzyl-3-phenylurea **(2)**



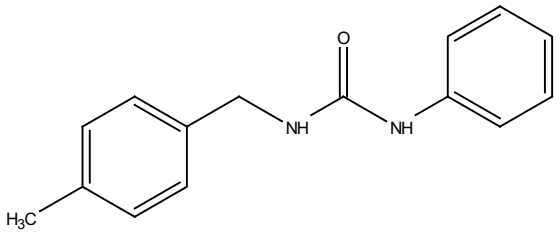
1-Benzyl-3-phenylurea (2)



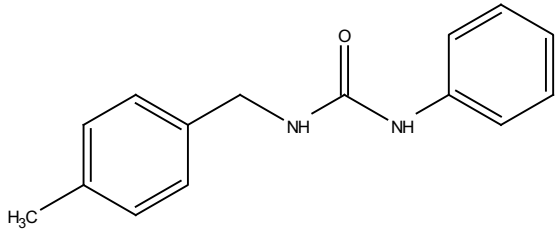
1-(2-methoxybenzyl)-3-phenylurea (3)



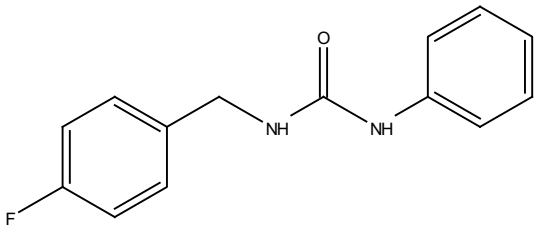
1-(2-methoxybenzyl)-3-phenylurea (3)



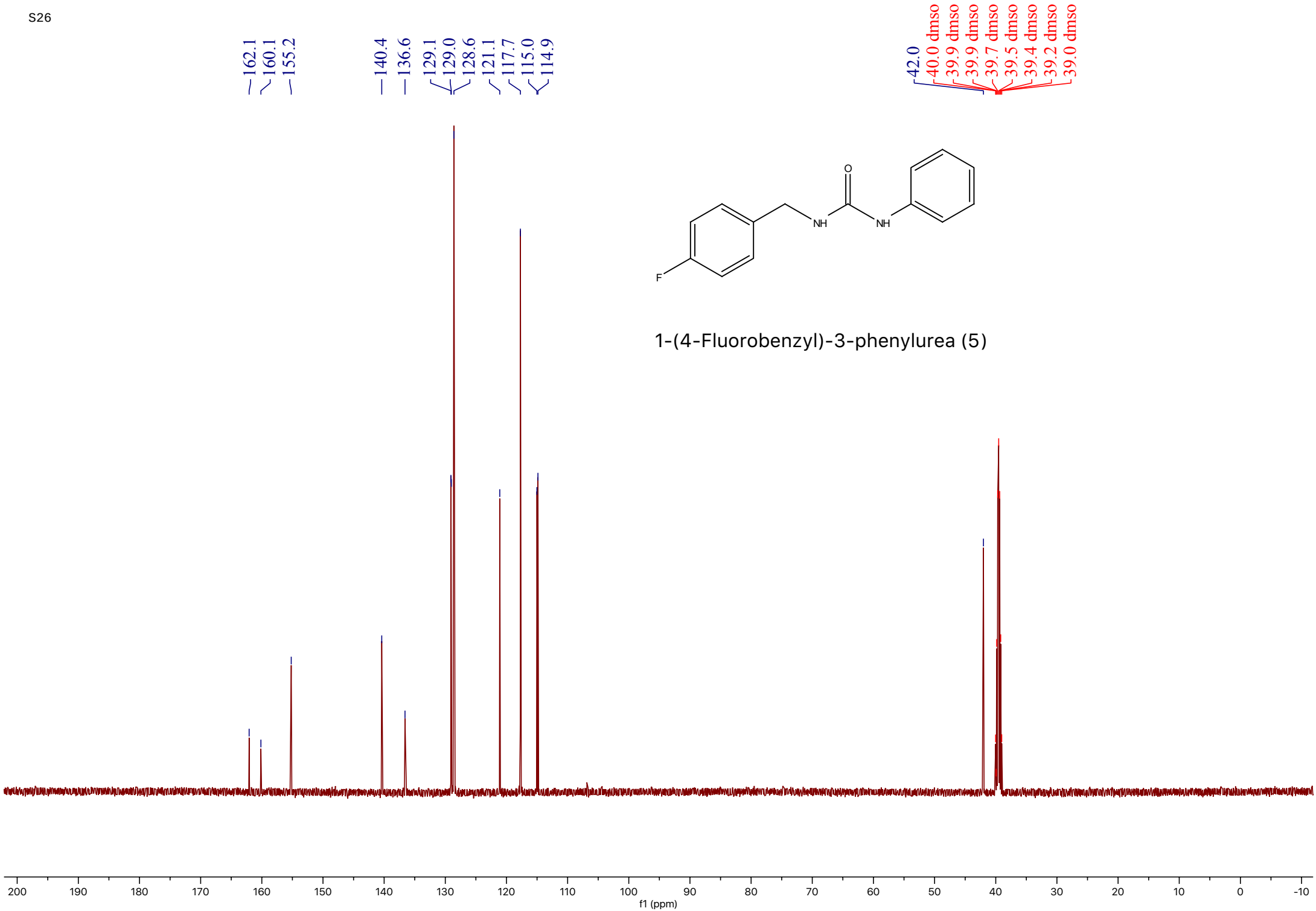
1-(4-Methylbenzyl)-3-phenylurea (4)

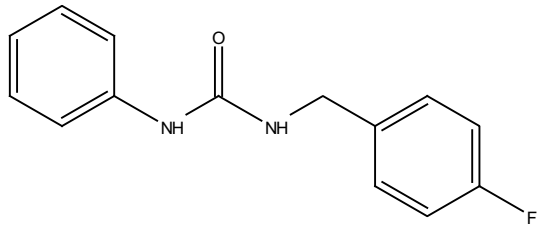


1-(4-Methylbenzyl)-3-phenylurea (4)

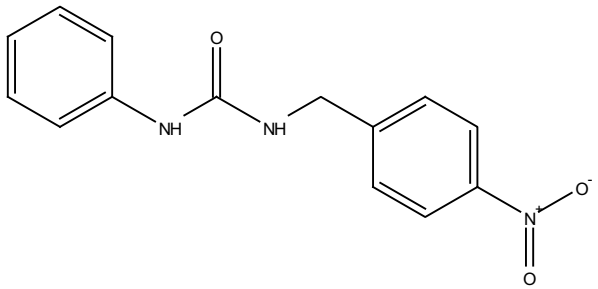


1-(4-Fluorobenzyl)-3-phenylurea (5)

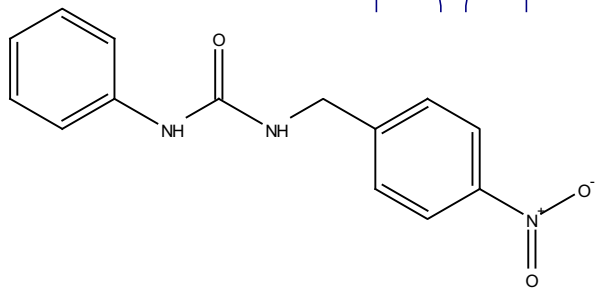

162.1
160.1
155.2
140.4
136.6
129.1
129.0
128.6
121.1
117.7
115.0
114.9
42.0
40.0 dmso
39.9 dmso
39.9 dmso
39.7 dmso
39.5 dmso
39.4 dmso
39.2 dmso
39.0 dmso
O
NH
NH
F
1-(4-Fluorobenzyl)-3-phenylurea (5)
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)



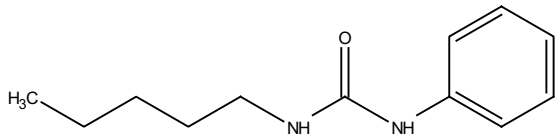
1-(4-Fluorobenzyl)-3-phenylurea (5)



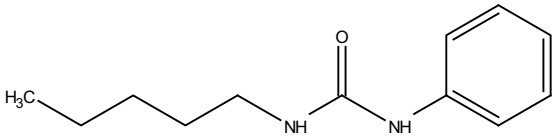
1-(4-Nitrobenzyl)-3-phenylurea (6)



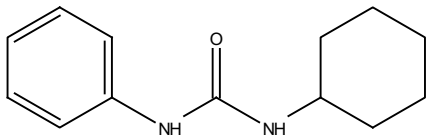
1-(4-Nitrobenzyl)-3-phenylurea (6)



1-Pentyl-3-phenylurea (7)



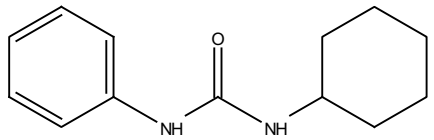
1-Pentyl-3-phenylurea (7)



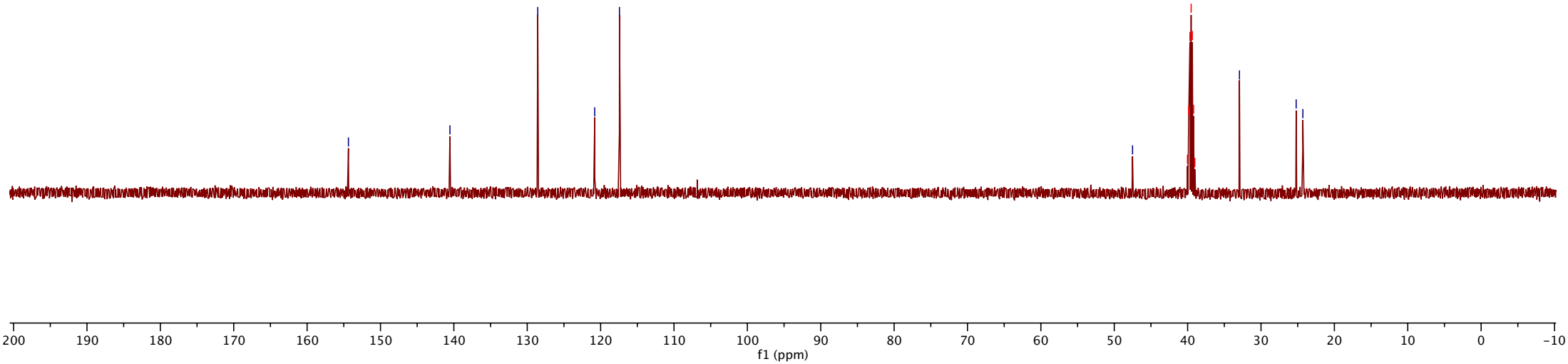
1-Cyclohexyl-3-phenylurea (8)

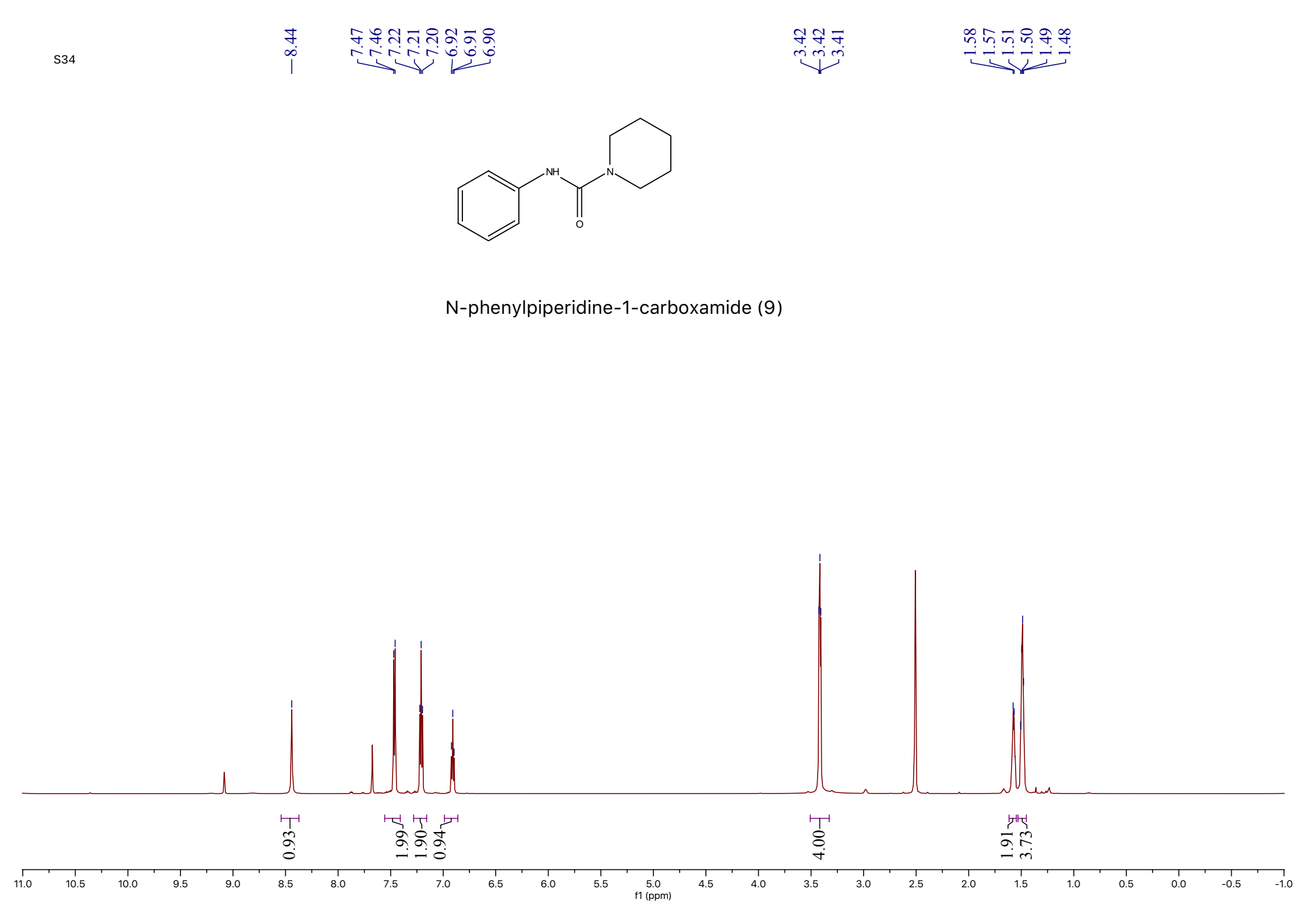
154.37
140.54
128.57
120.80
117.43

47.51
40.02 dmso
39.85 dmso
39.69 dmso
39.52 dmso
39.35 dmso
39.19 dmso
39.02 dmso
32.94
25.21
24.30

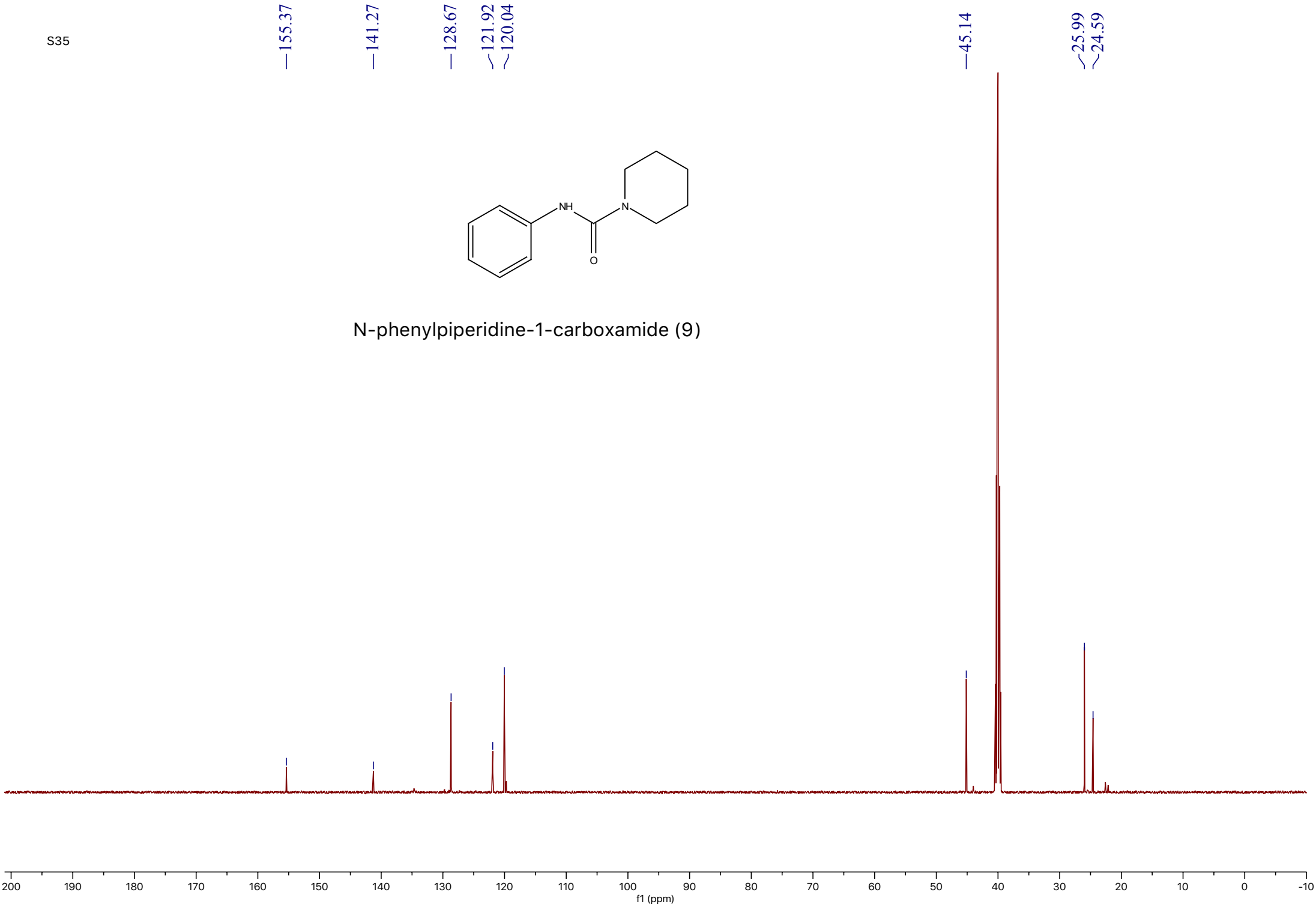


1-Cyclohexyl-3-phenylurea (8)

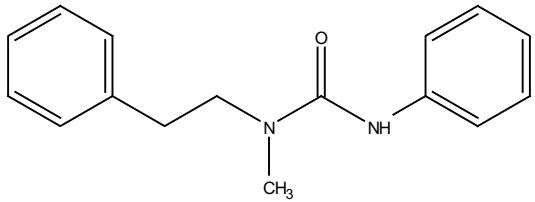




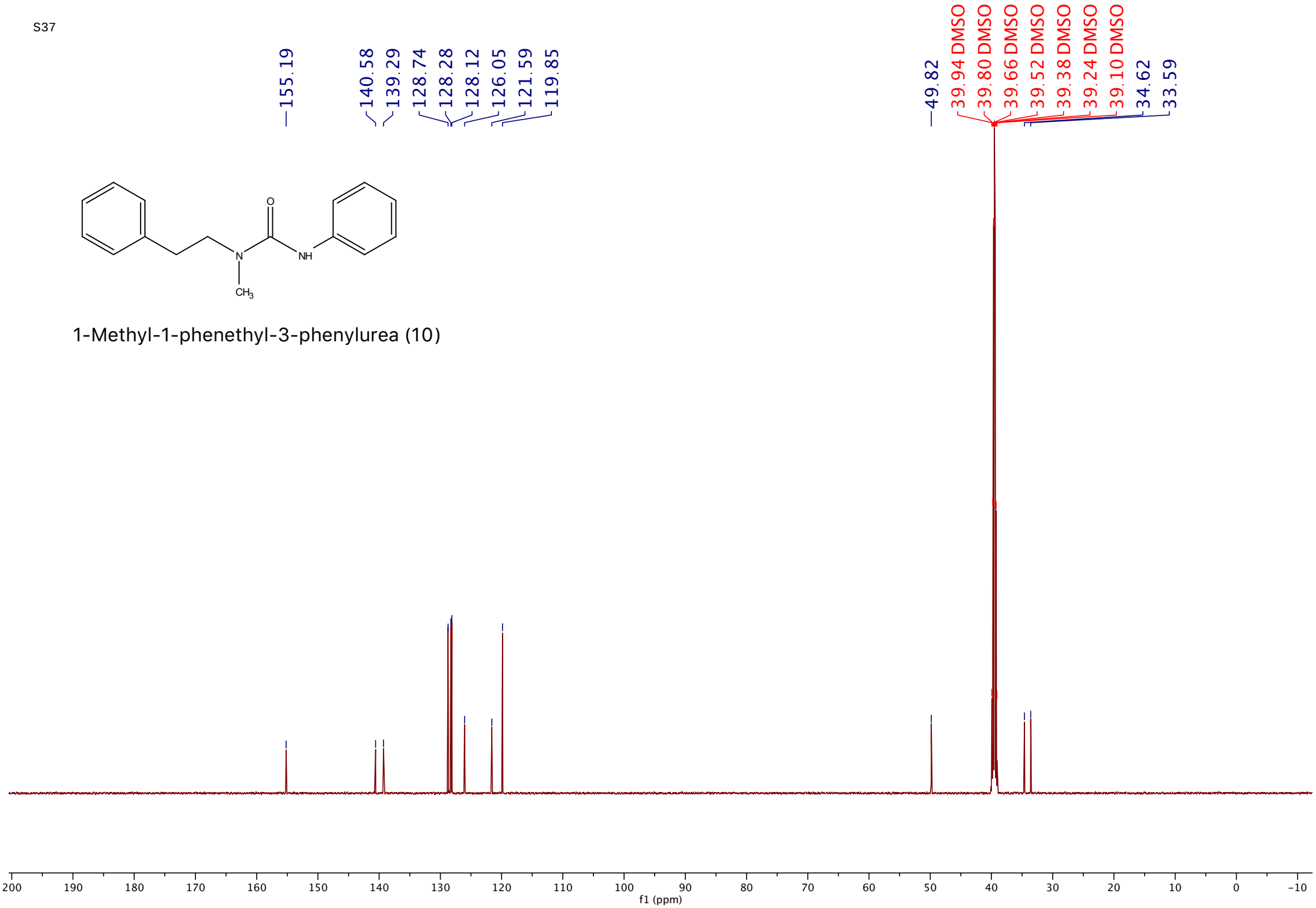
N-phenylpiperidine-1-carboxamide (9)



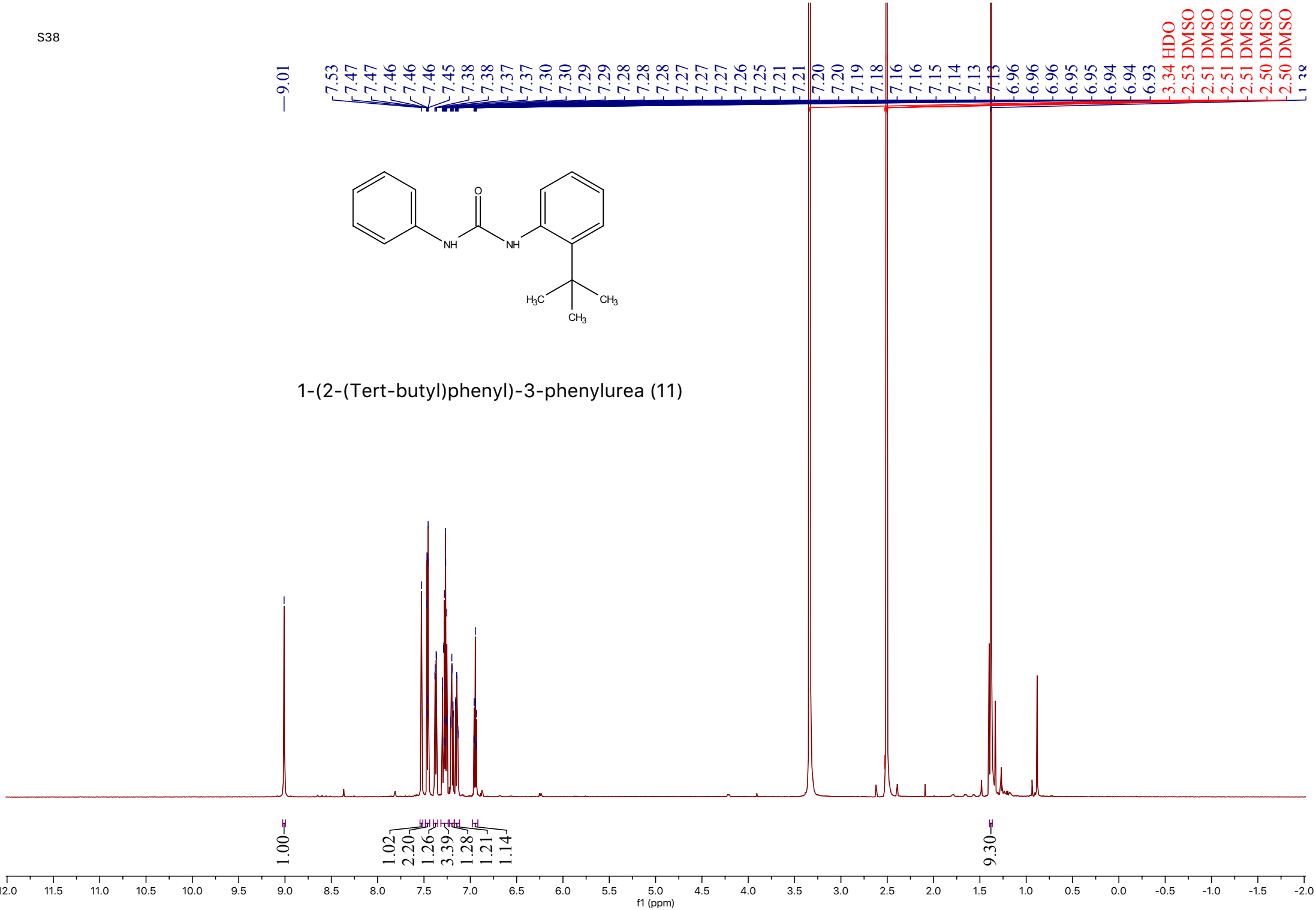
N-phenylpiperidine-1-carboxamide (9)

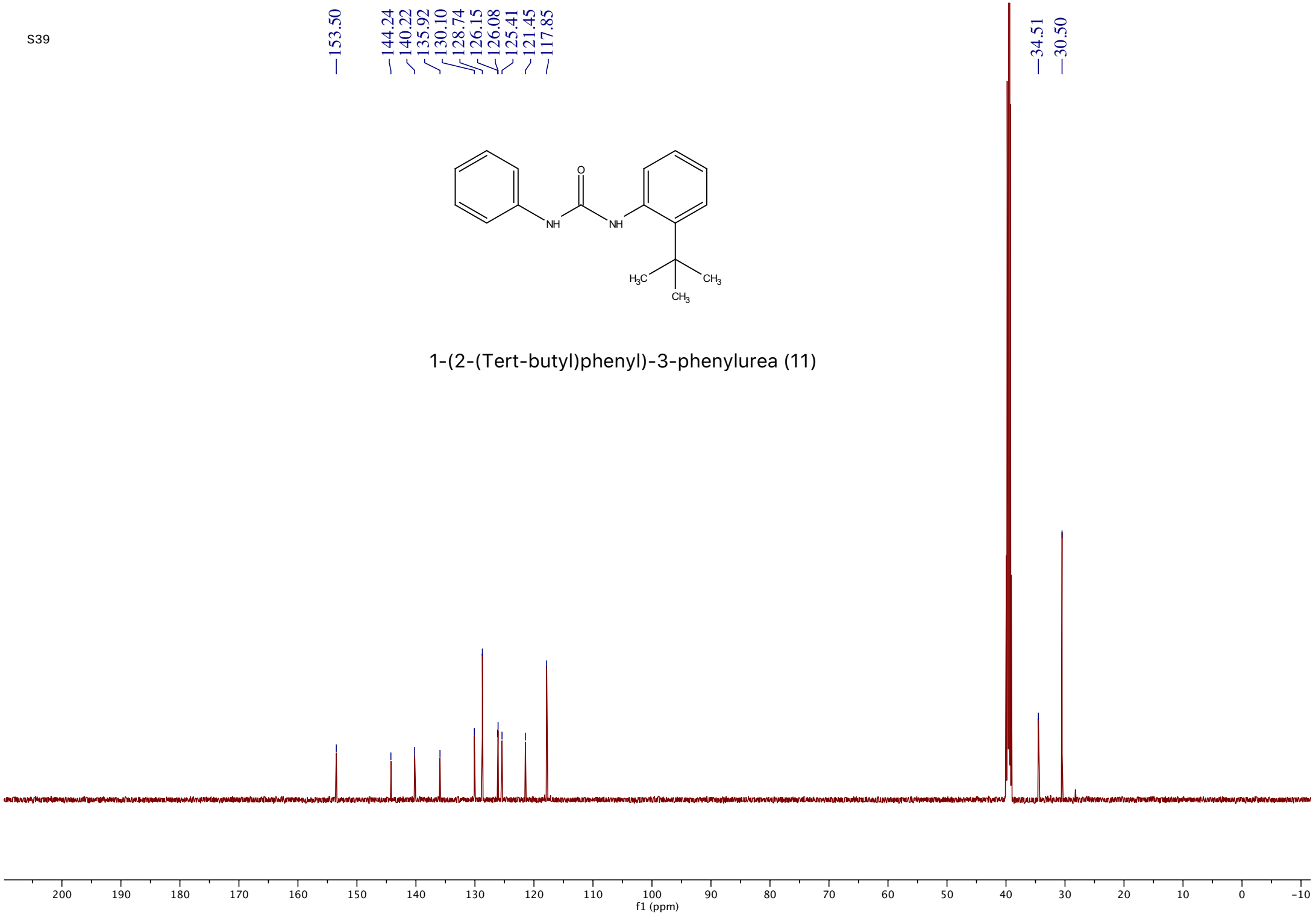


1-Methyl-1-phenethyl-3-phenylurea (10)

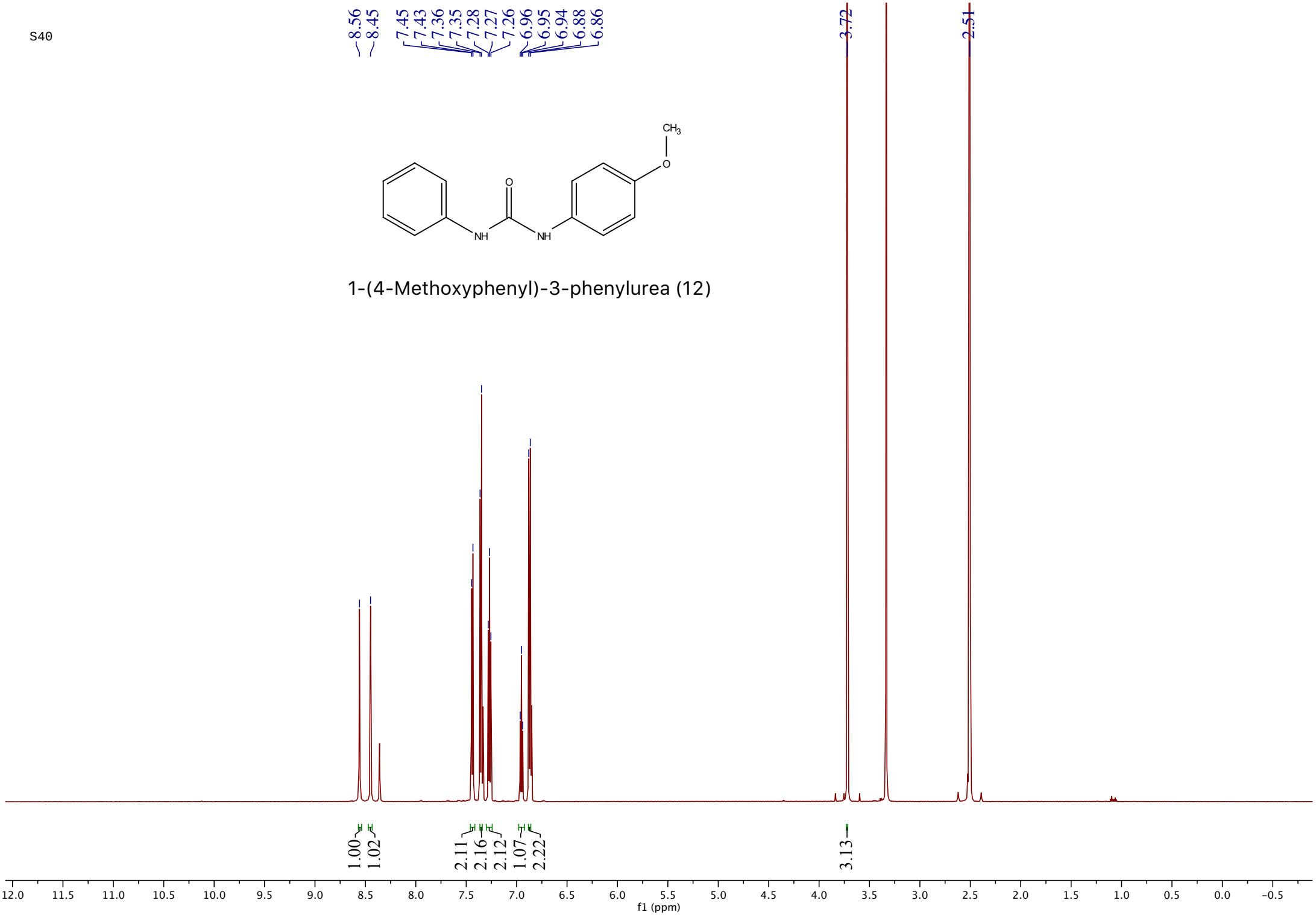


1-Methyl-1-phenethyl-3-phenylurea (10)

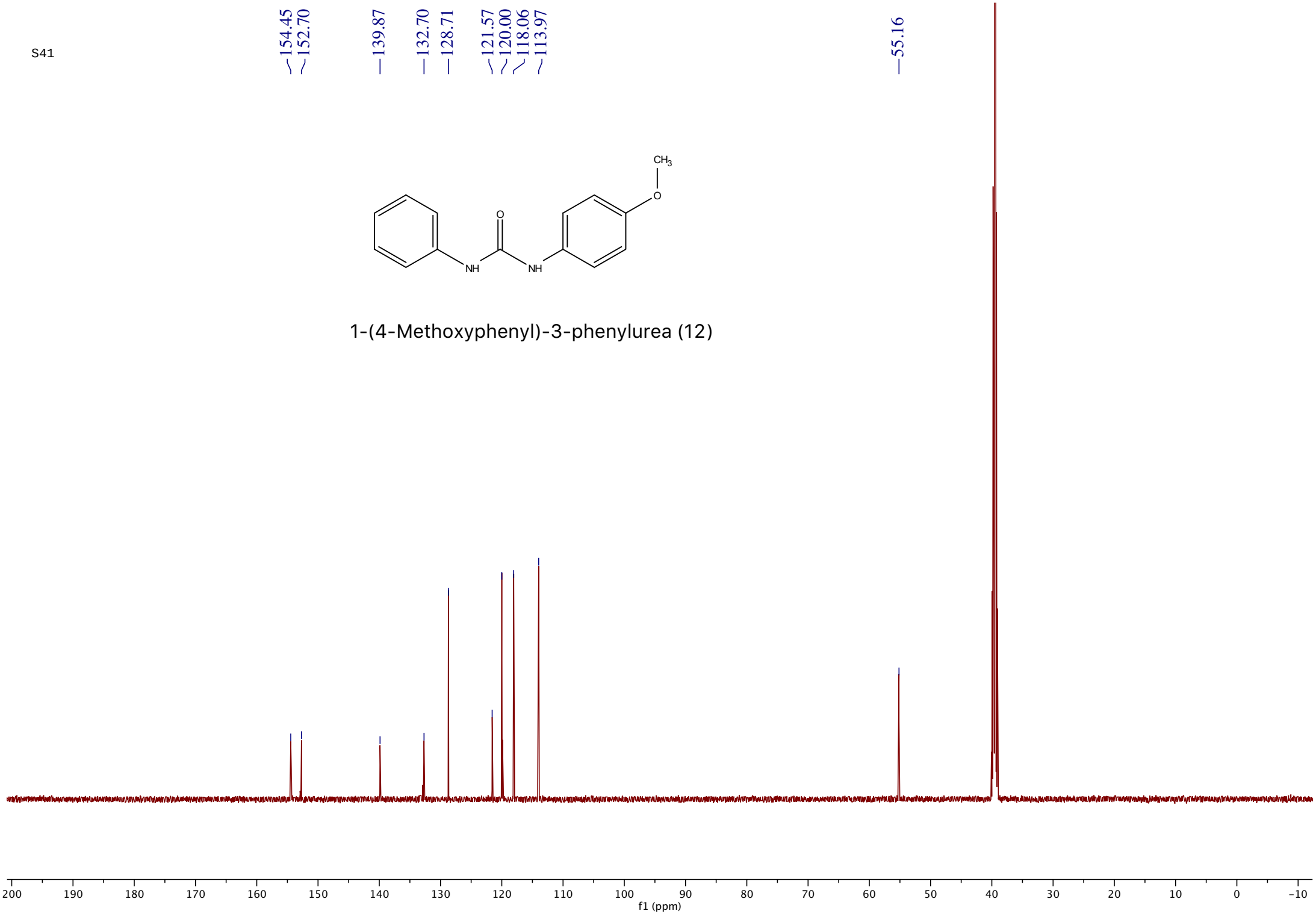

9.01
7.53
7.47
7.47
7.46
7.46
7.46
7.45
7.38
7.38
7.37
7.37
7.30
7.30
7.29
7.29
7.28
7.28
7.28
7.27
7.27
7.27
7.26
7.25
7.21
7.21
7.20
7.20
7.19
7.18
7.16
7.16
7.15
7.14
7.13
7.13
6.96
6.96
6.96
6.95
6.95
6.94
6.94
6.93
3.34 HDO
2.53 DMSO
2.51 DMSO
2.51 DMSO
2.51 DMSO
2.50 DMSO
2.50 DMSO
O
NH
NH
H3C
CH3
CH3
1-(2-(Tert-butyl)phenyl)-3-phenylurea (11)
1.00
1.02
2.20
1.26
3.39
1.28
1.21
1.14
9.30
12.0
11.5
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1.0
-1.5
-2.0
f1 (ppm)



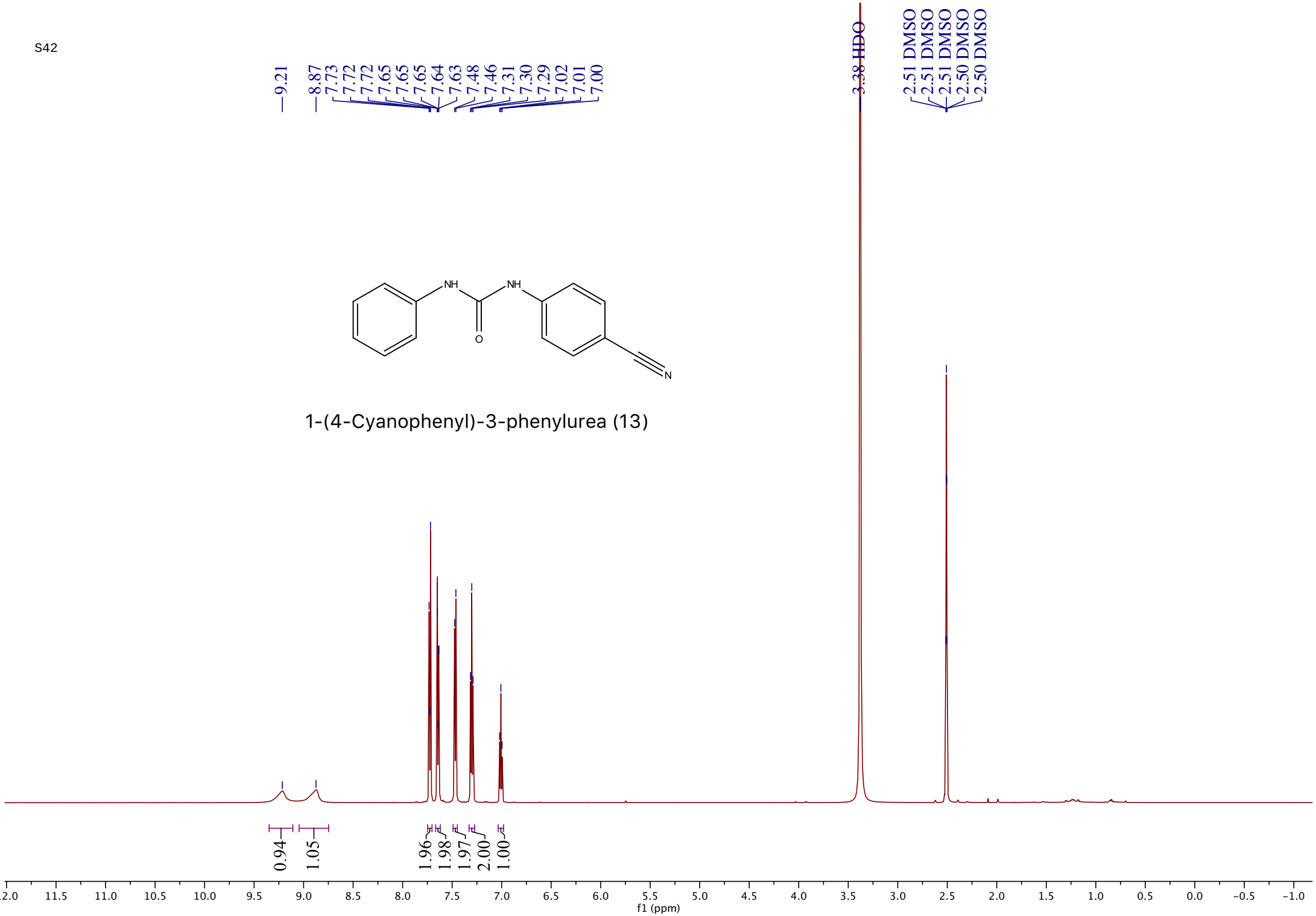
1-(2-(Tert-butyl)phenyl)-3-phenylurea (11)



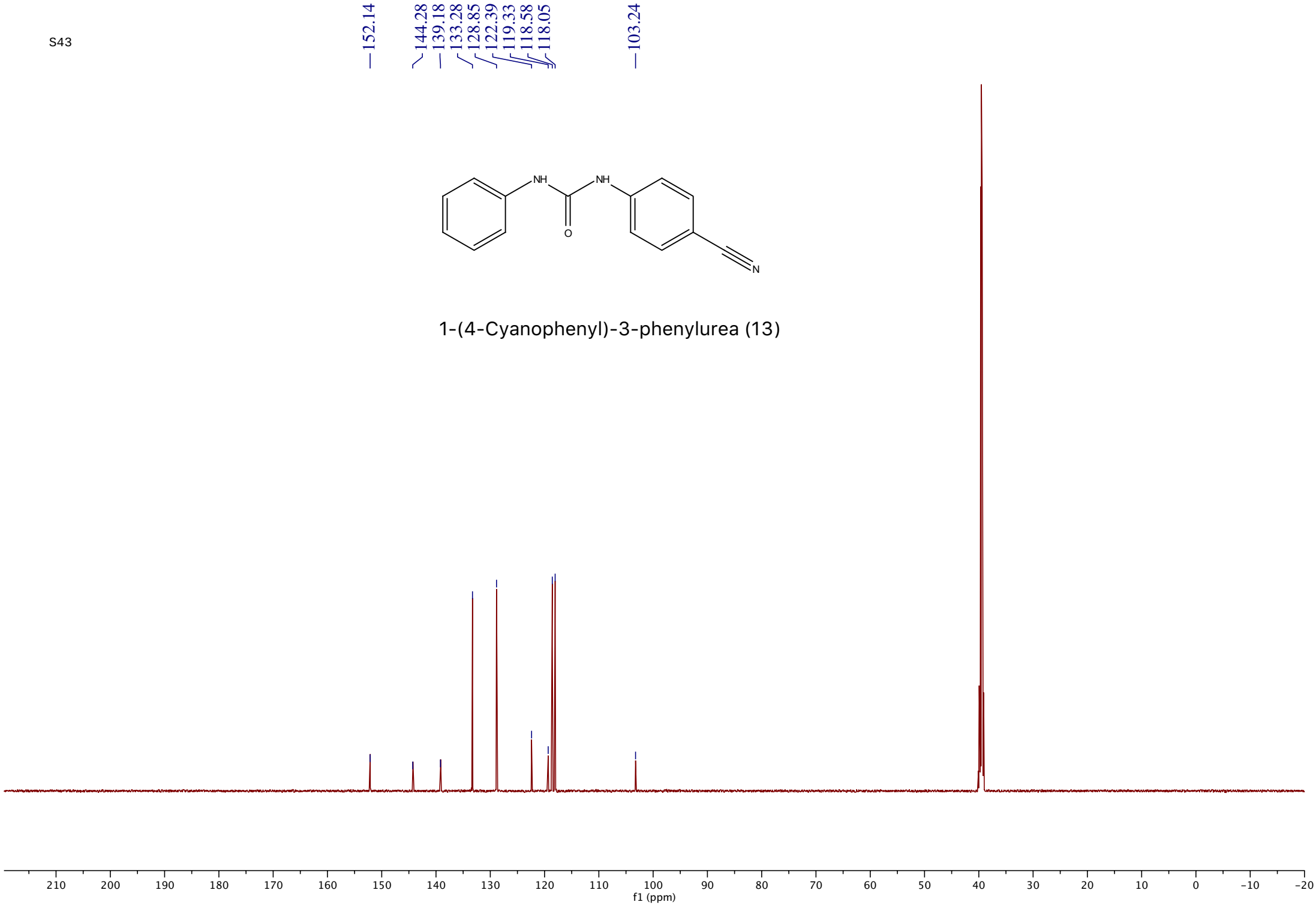
1-(4-Methoxyphenyl)-3-phenylurea (12)

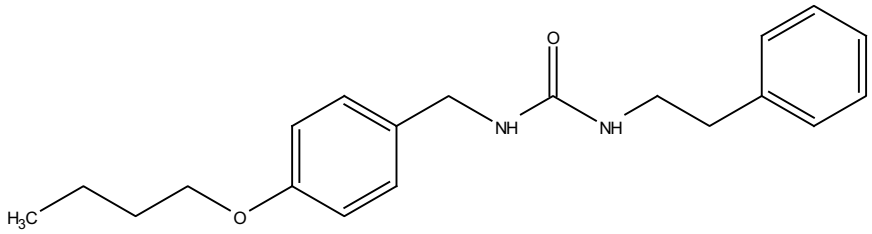


1-(4-Methoxyphenyl)-3-phenylurea (12)

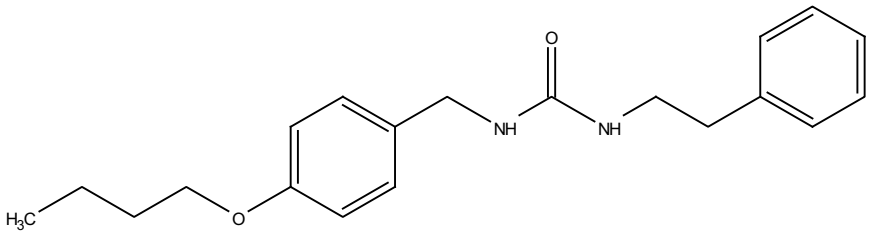


1-(4-Cyanophenyl)-3-phenylurea (13)

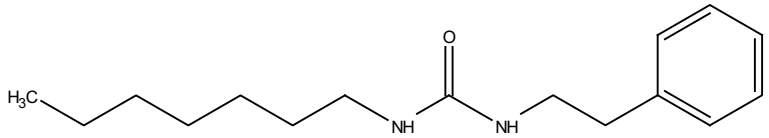

152.14
144.28
139.18
133.28
128.85
122.39
119.33
118.58
118.05
103.24
NH
NH
O
N
1-(4-Cyanophenyl)-3-phenylurea (13)
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
−10
−20
f1 (ppm)



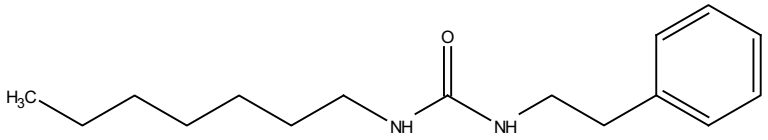
1-(4-Butoxybenzyl)-3-phenethylurea (14)



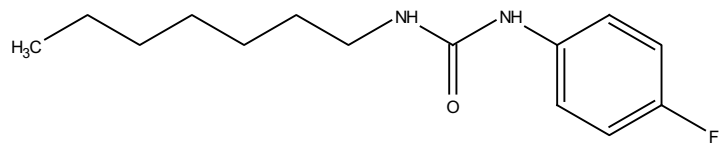
1-(4-Butoxybenzyl)-3-phenethylurea (14)



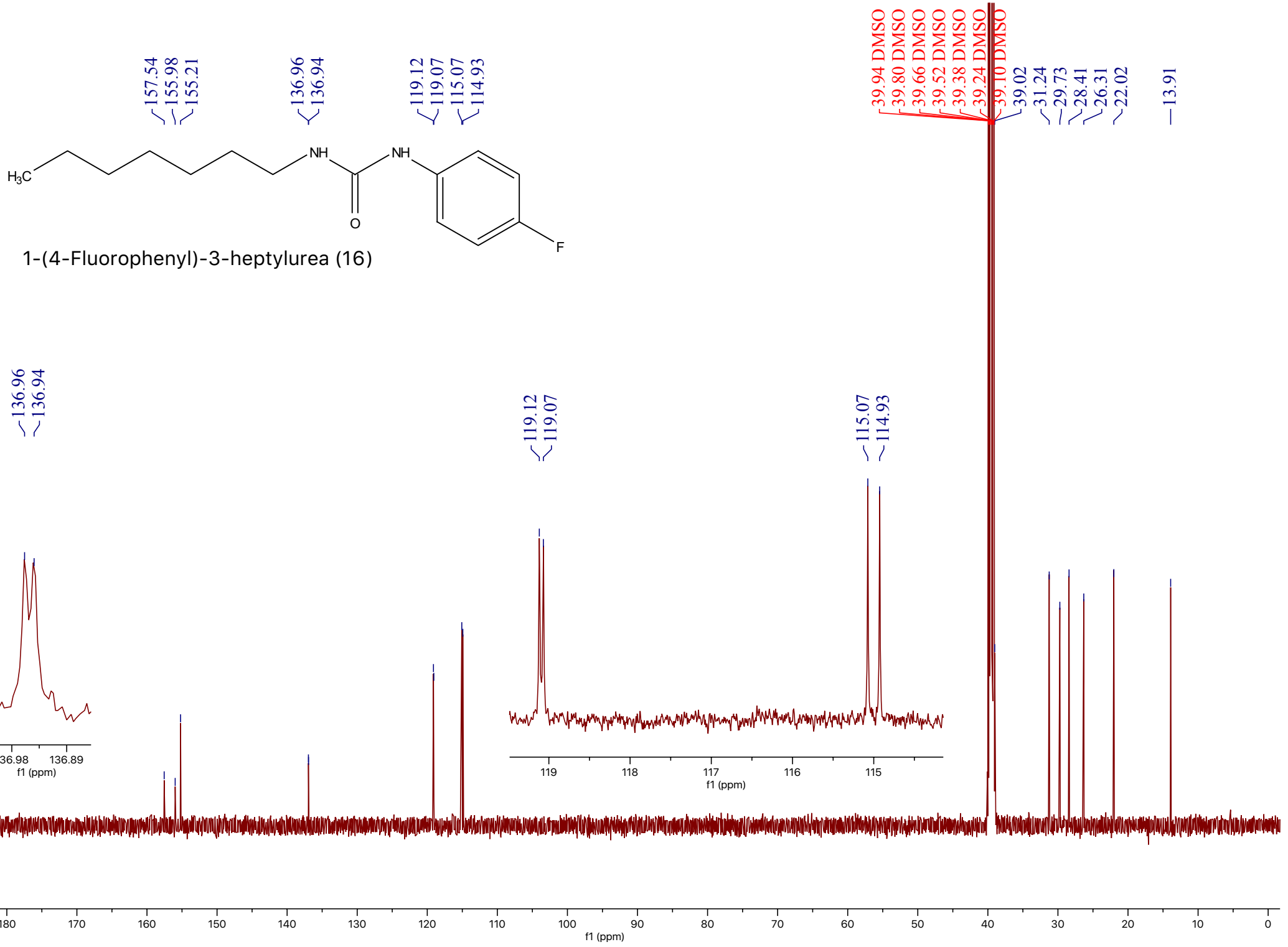
1-Heptyl-3-phenethylurea (15)

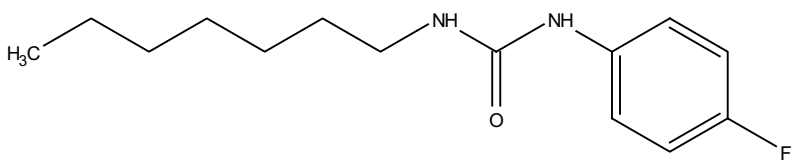


1-Heptyl-3-phenethylurea (15)

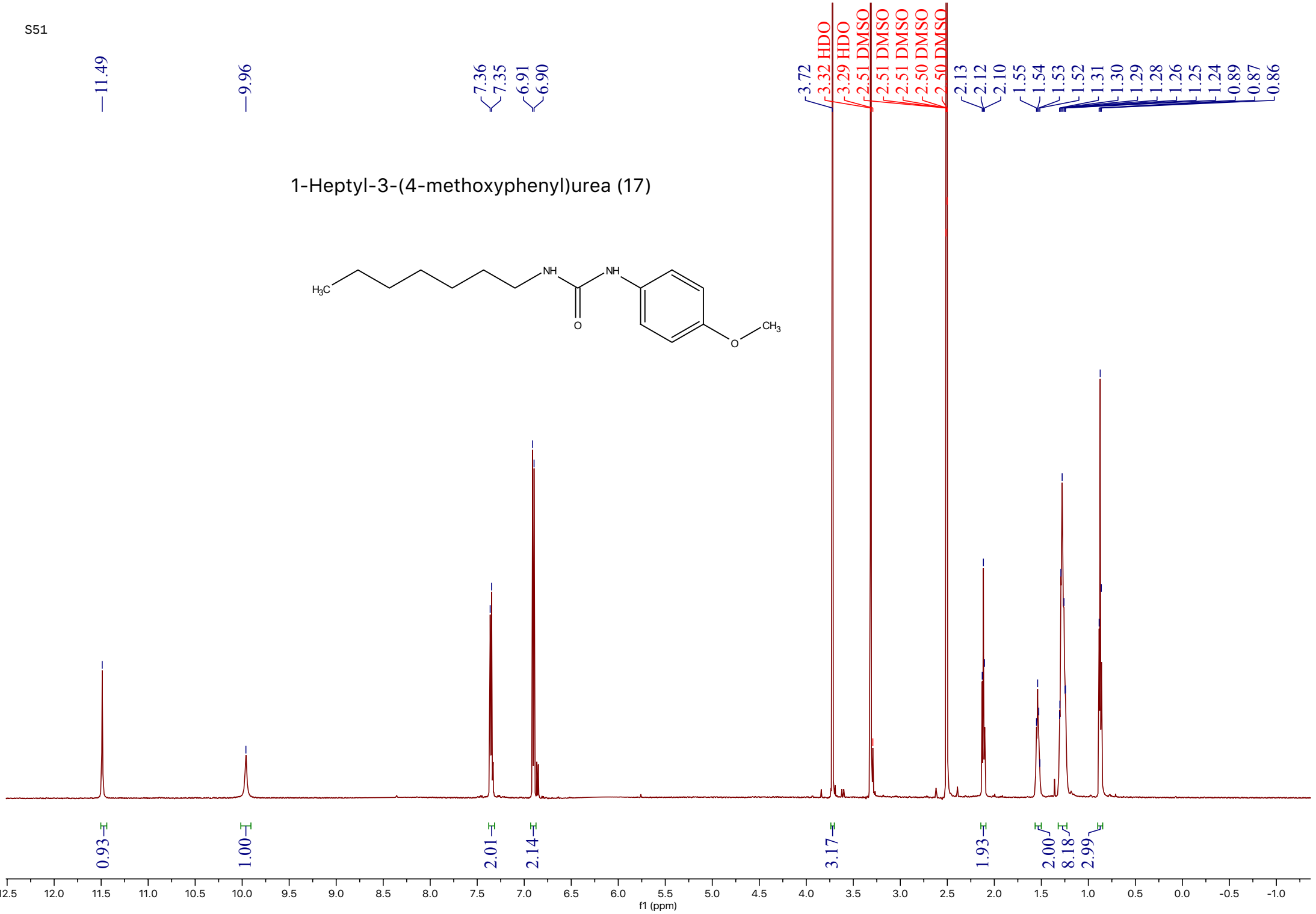


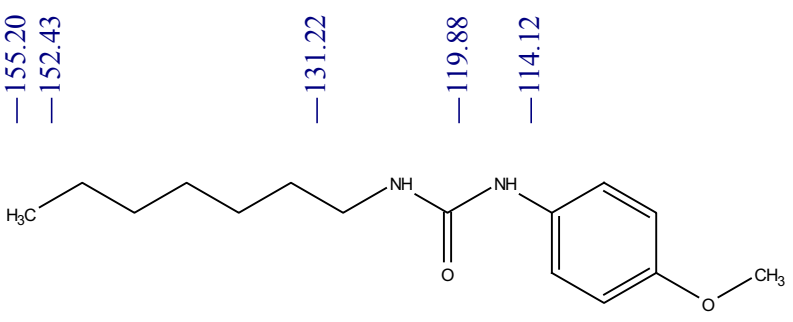
1-(4-Fluorophenyl)-3-heptylurea (16)


157.54
155.98
155.21
136.96
136.94
119.12
119.07
115.07
114.93
39.94 DMSO
39.80 DMSO
39.66 DMSO
39.52 DMSO
39.38 DMSO
39.24 DMSO
39.10 DMSO
39.02
31.24
29.73
28.41
26.31
22.02
13.91
H3C
NH
NH
O
F
1-(4-Fluorophenyl)-3-heptylurea (16)
136.98
136.89
f1 (ppm)
119
118
117
116
115
f1 (ppm)
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

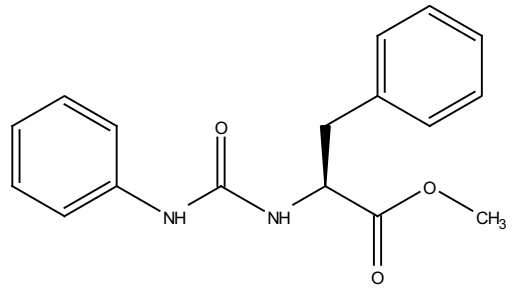


1-(4-Fluorophenyl)-3-heptylurea (16)


11.49
9.96
7.36
7.35
6.91
6.90
3.72
3.32 HDO
3.29 HDO
2.51 DMSO
2.51 DMSO
2.51 DMSO
2.50 DMSO
2.50 DMSO
2.13
2.12
2.10
1.55
1.54
1.53
1.52
1.31
1.30
1.29
1.28
1.26
1.25
1.24
0.89
0.87
0.86
1-Heptyl-3-(4-methoxyphenyl)urea (17)
H3C
NH
NH
O
O
CH3
0.93
1.00
2.01
2.14
3.17
1.93
2.00
8.18
2.99
f1 (ppm)

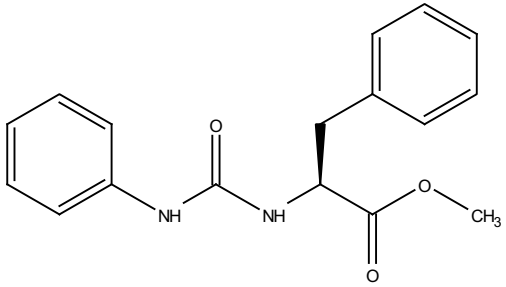


1-Heptyl-3-(4-methoxyphenyl)urea (17)

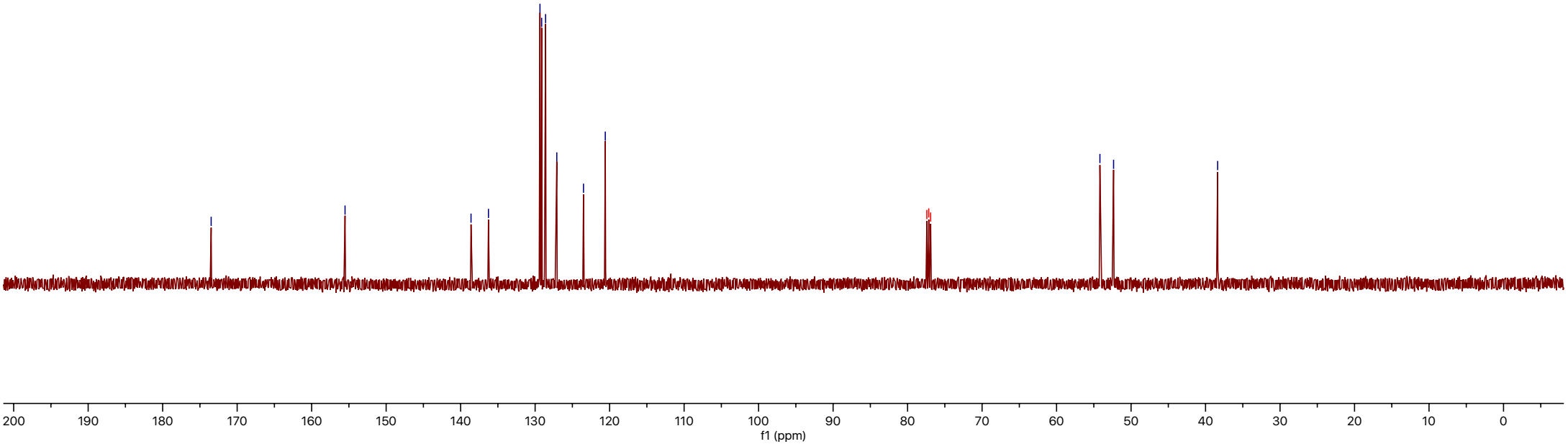


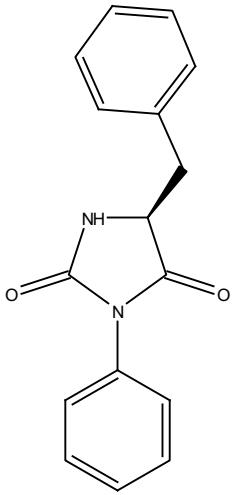
Methyl (phenylcarbamoyl)-L-phenylalaninate (18)

173.49
155.52
138.61
136.26
129.35
129.12
128.59
127.09
123.51
120.58
77.41 cdcl3
77.16 cdcl3
76.91 cdcl3
54.18
52.35
38.38

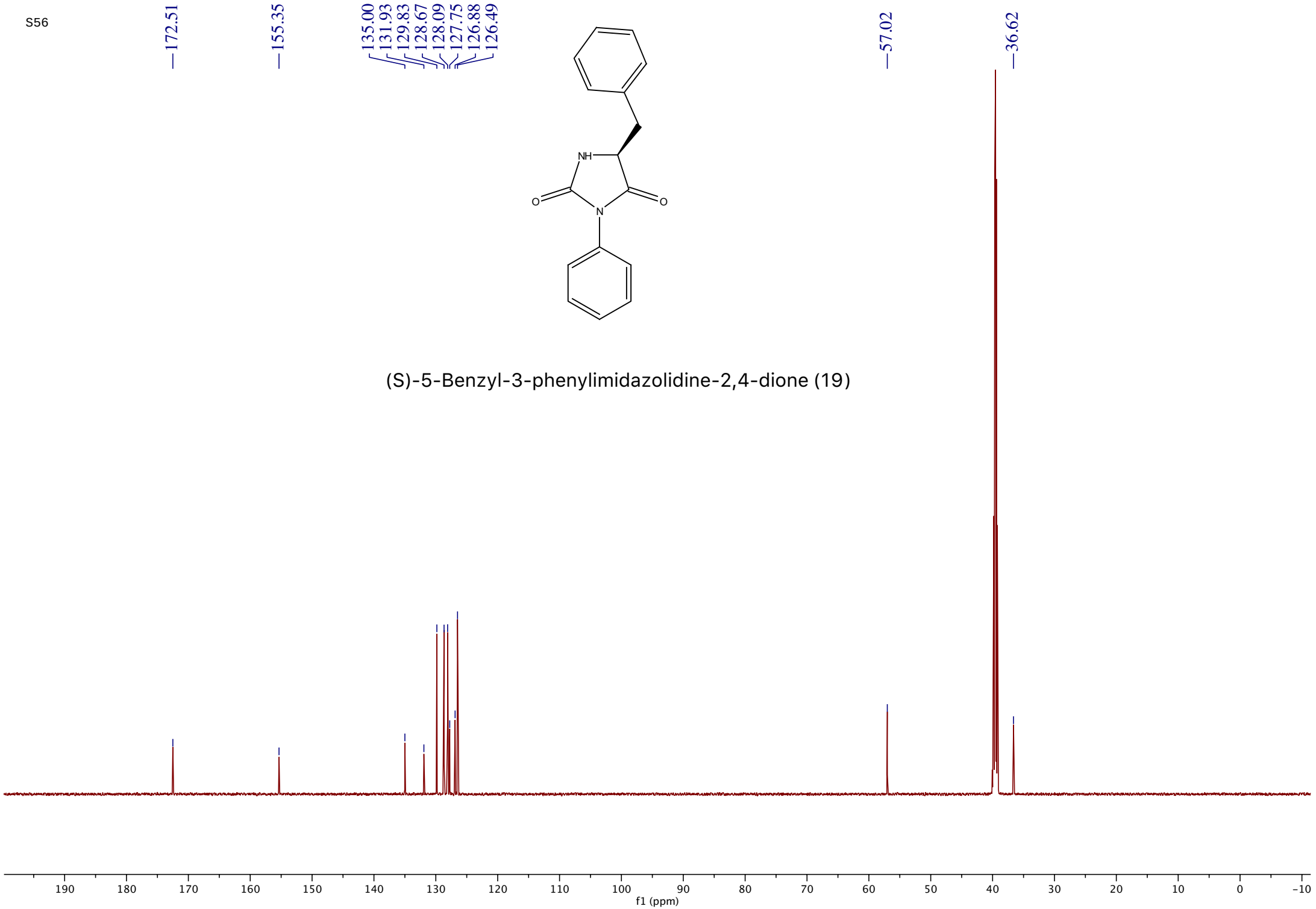


Methyl (phenylcarbamoyl)-L-phenylalaninate (18)

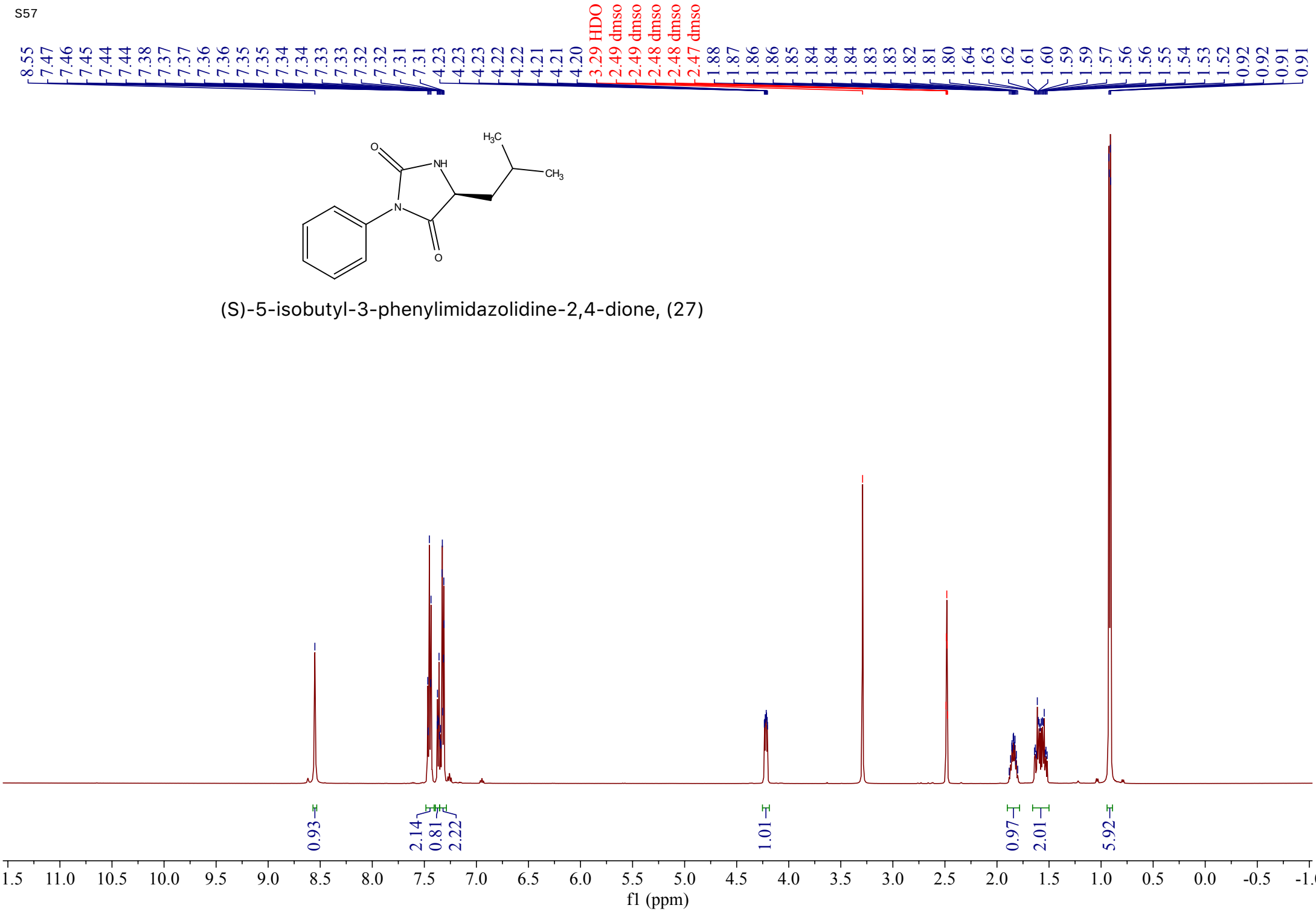


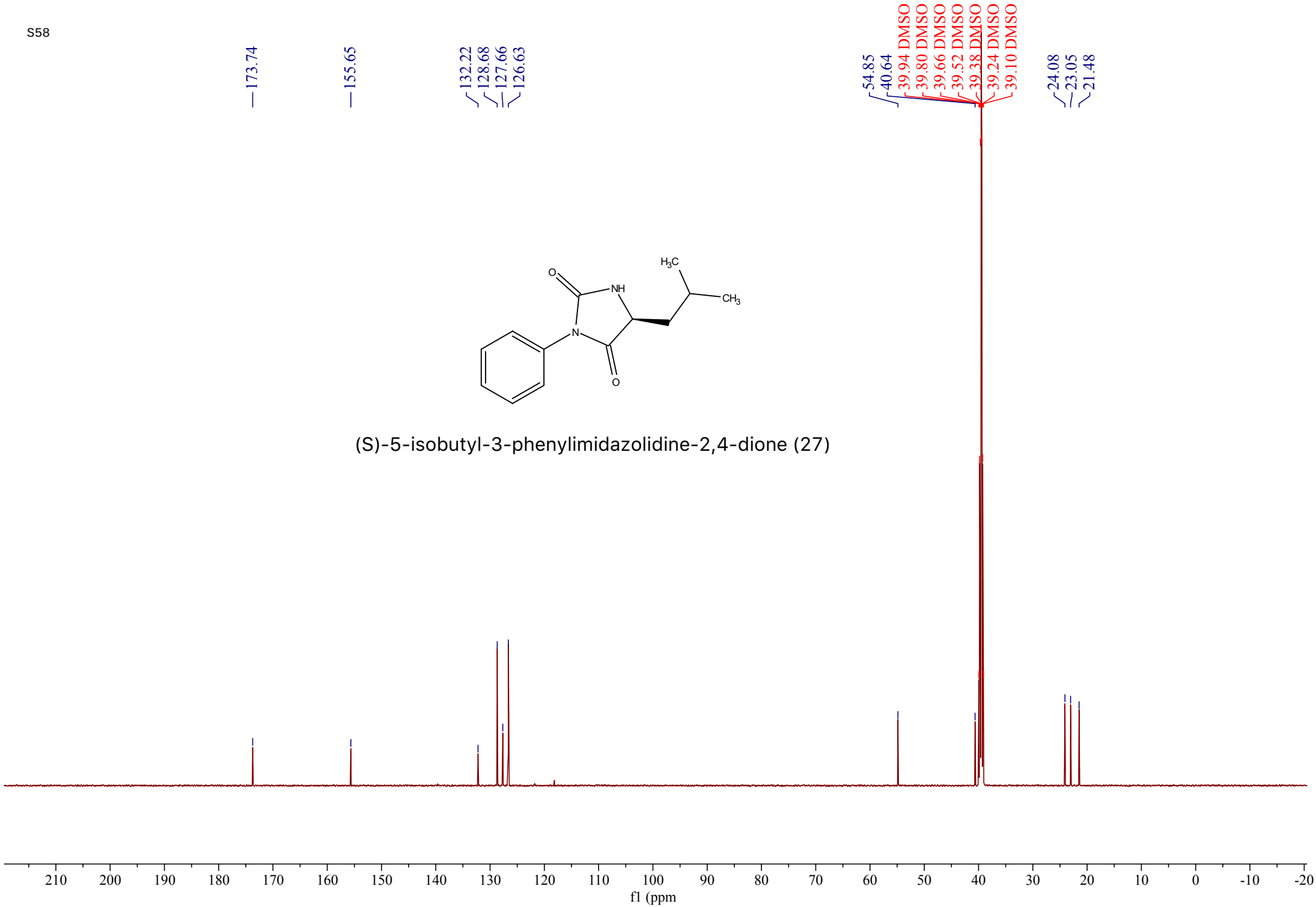


(*S*)-5-Benzyl-3-phenylimidazolidine-2,4-dione (19)

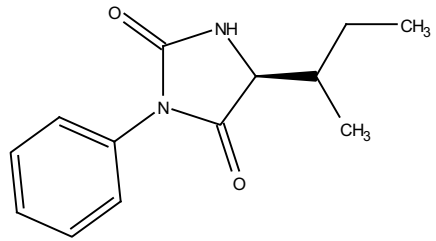


(S)-5-Benzyl-3-phenylimidazolidine-2,4-dione (19)


8.55 7.47 7.46 7.45 7.44 7.44 7.38 7.37 7.37 7.36 7.36 7.35 7.35 7.34 7.34 7.33 7.33 7.32 7.32 7.31 7.31
4.23 4.23 4.23 4.22 4.22 4.21 4.21 4.20
3.29 HDO
2.49 dmso 2.49 dmso 2.48 dmso 2.48 dmso 2.47 dmso
1.88 1.87 1.86 1.86 1.85 1.84 1.84 1.84 1.83 1.83 1.82 1.81 1.80
1.64 1.63 1.62 1.61 1.60 1.59 1.59 1.57 1.56 1.56 1.55 1.54 1.53 1.52
0.92 0.92 0.91 0.91
O
NH
N
O
H3C
CH3
(S)-5-isobutyl-3-phenylimidazolidine-2,4-dione, (27)
0.93
2.14
0.81
2.22
1.01
0.97
2.01
5.92
11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
f1 (ppm)

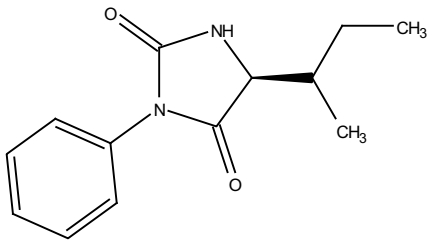


(S)-5-isobutyl-3-phenylimidazolidine-2,4-dione (27)

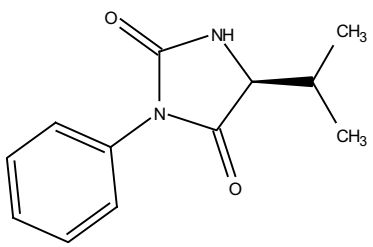


(S)-5-((S)-sec-butyl)-3-phenylimidazolidine-2,4-dione (28)

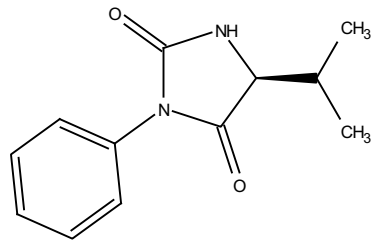
S60



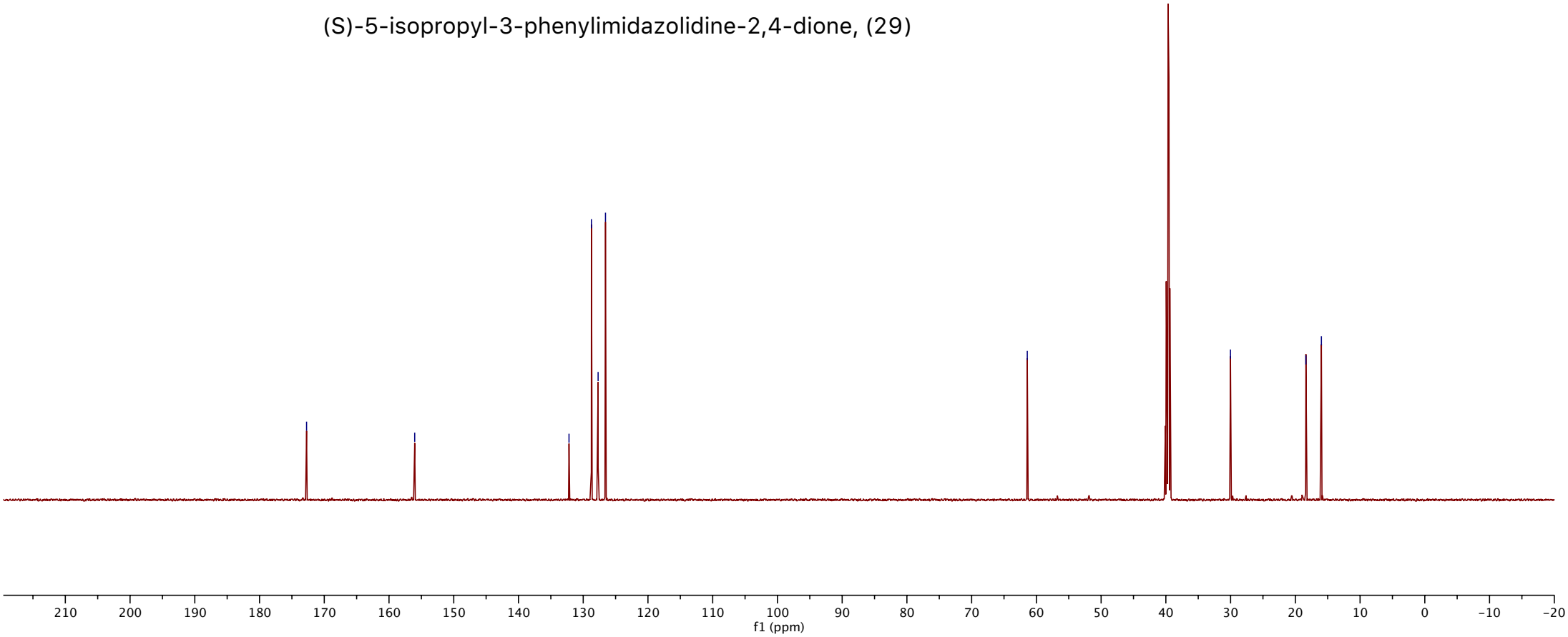
(S)-5-((S)-sec-butyl)-3-phenylimidazolidine-2,4-dione (28)

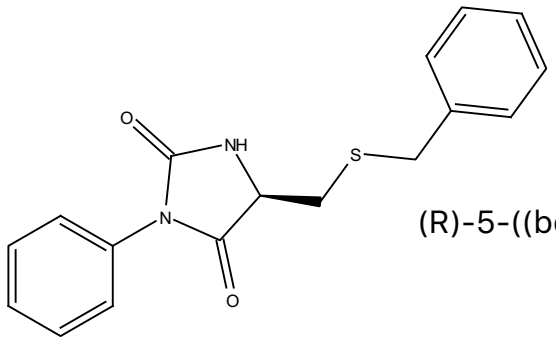


(S)-5-isopropyl-3-phenylimidazolidine-2,4-dione (29)

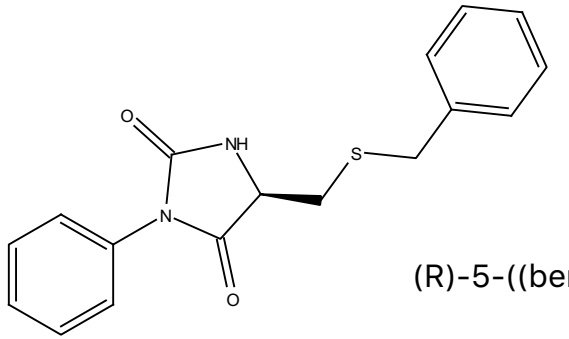


(S)-5-isopropyl-3-phenylimidazolidine-2,4-dione, (29)

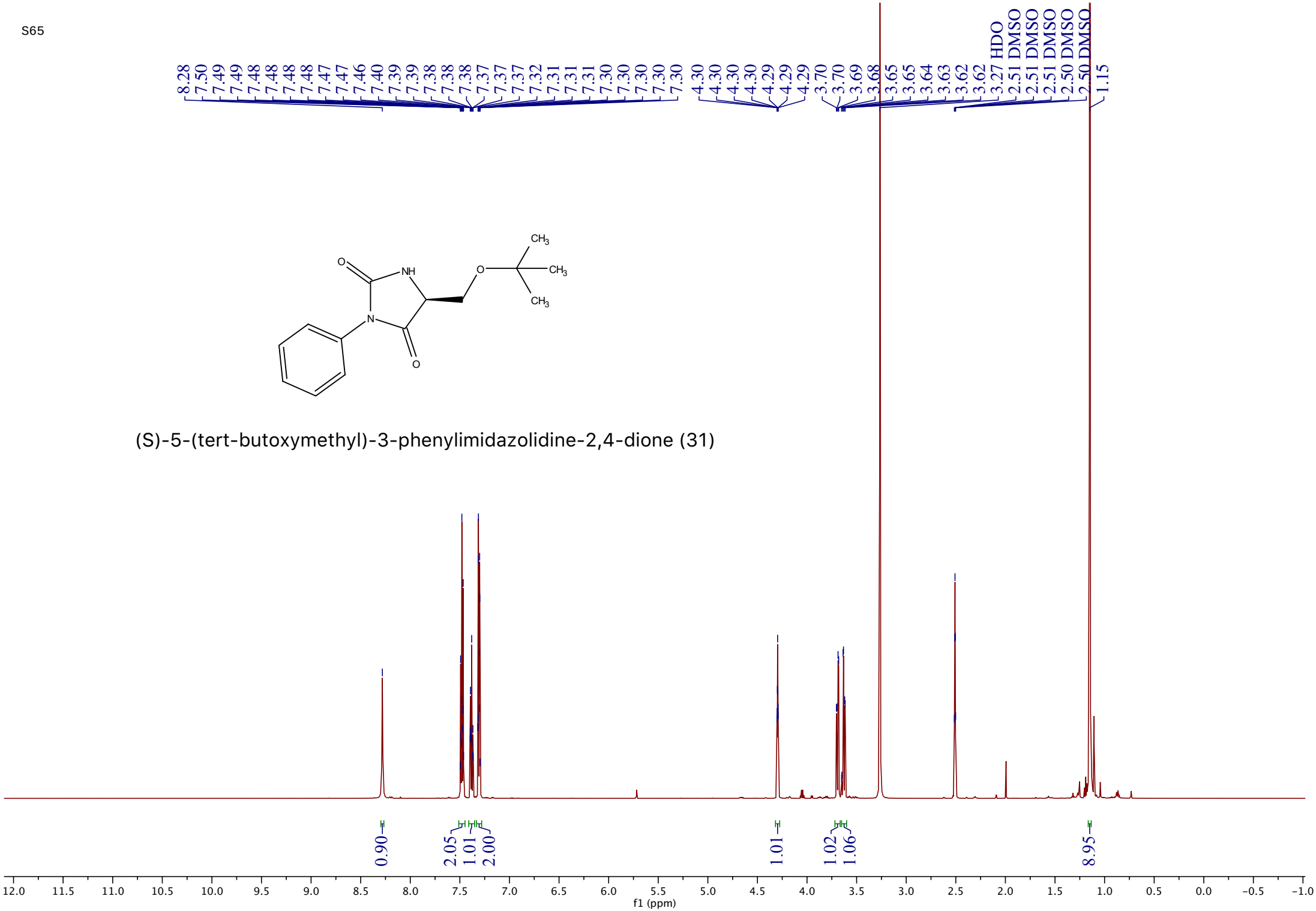




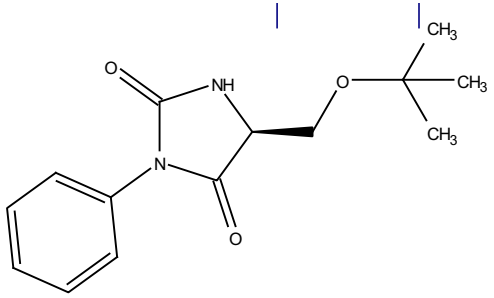
(R)-5-((benzylthio)methyl)-3-phenylimidazolidine-2,4-dione (30)



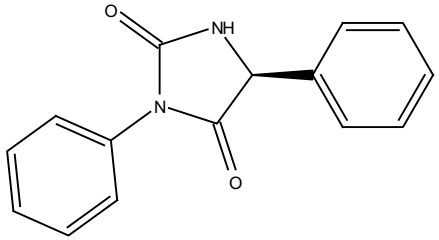
(R)-5-((benzylthio)methyl)-3-phenylimidazolidine-2,4-dione (30)



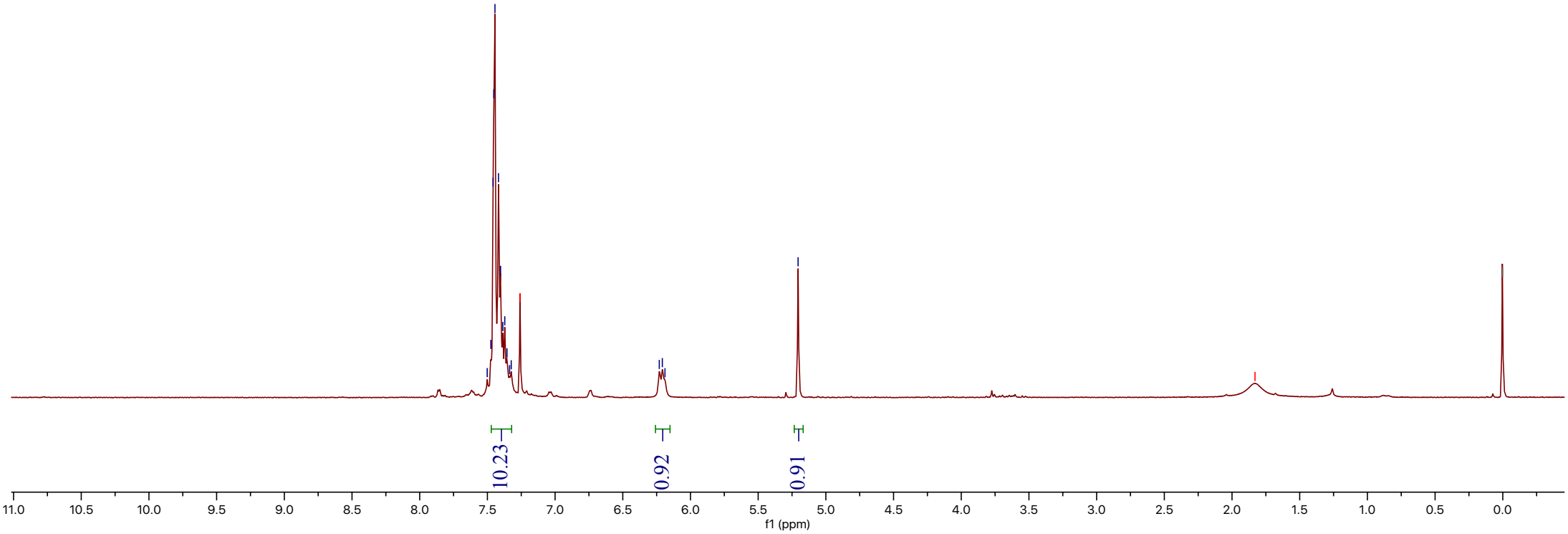
(S)-5-(tert-butoxymethyl)-3-phenylimidazolidine-2,4-dione (31)

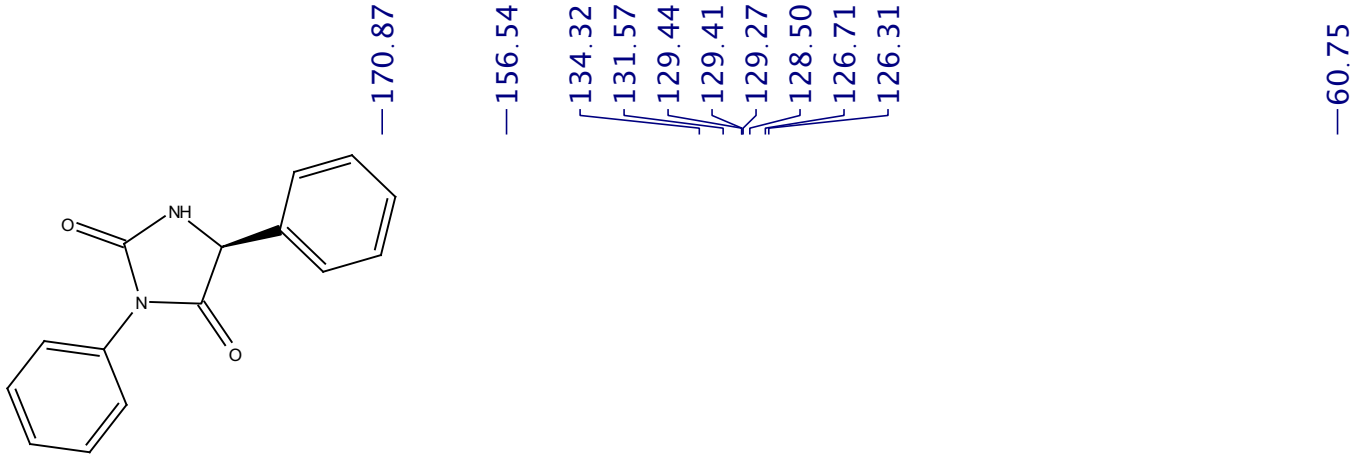


171.66
156.00
132.31
128.55
127.44
126.36
72.69
60.62
57.37
40.06 DMSO
39.94 DMSO
39.92 DMSO
39.80 DMSO
39.78 DMSO
39.66 DMSO
39.52 DMSO
39.38 DMSO
39.24 DMSO
39.10 DMSO
27.04

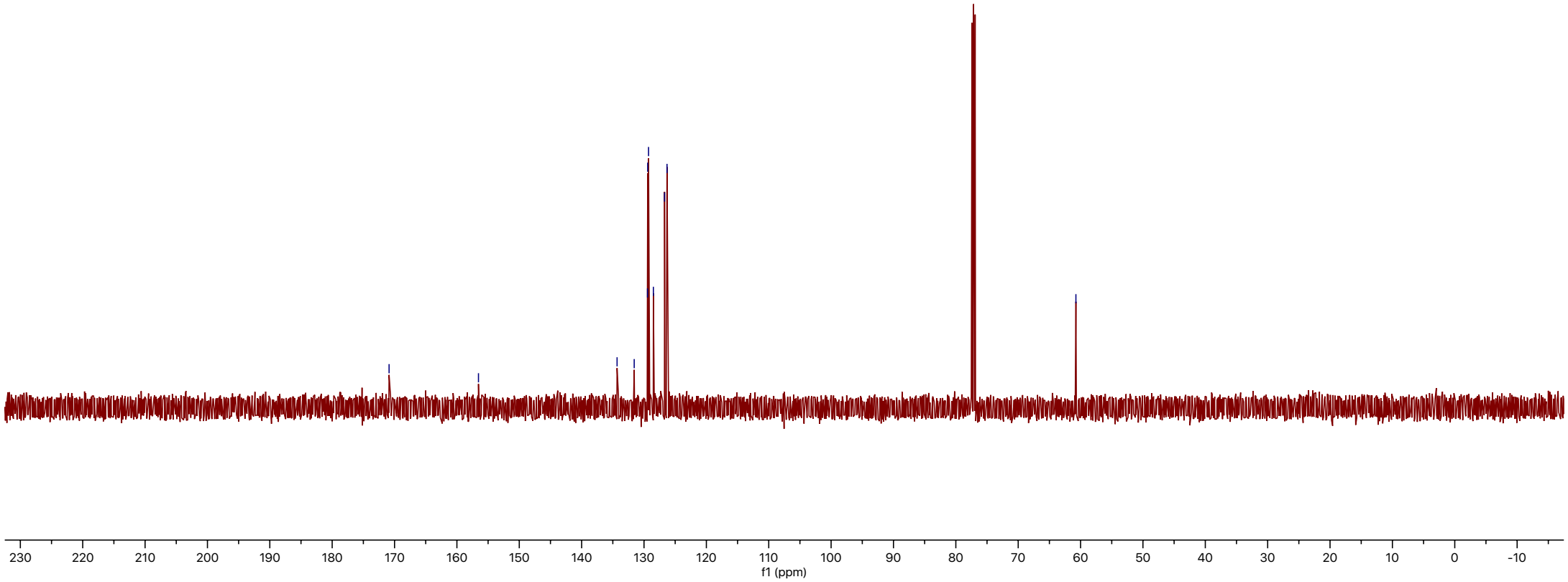


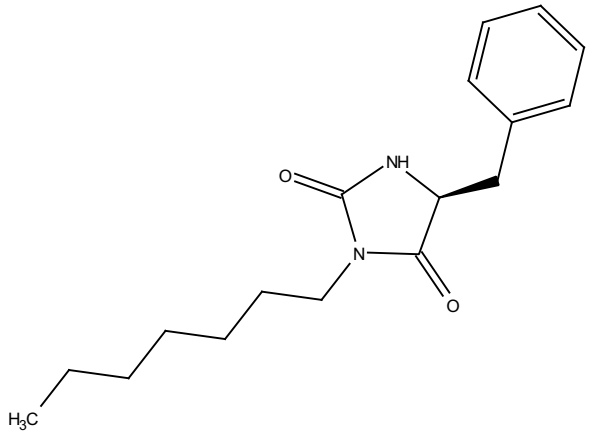
(S)-3,5-diphenylimidazolidine-2,4-dione (32)



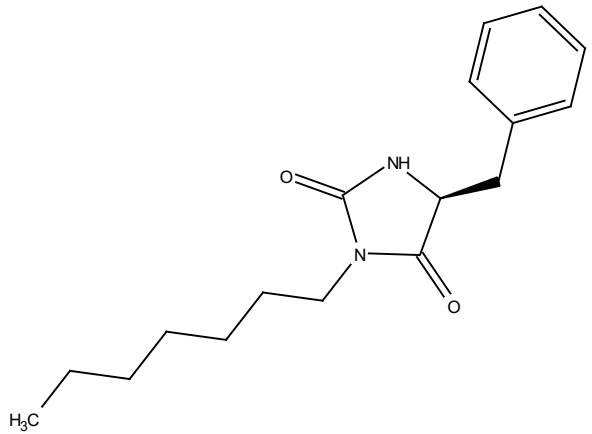


(S)-3,5-diphenylimidazolidine-2,4-dione (32)

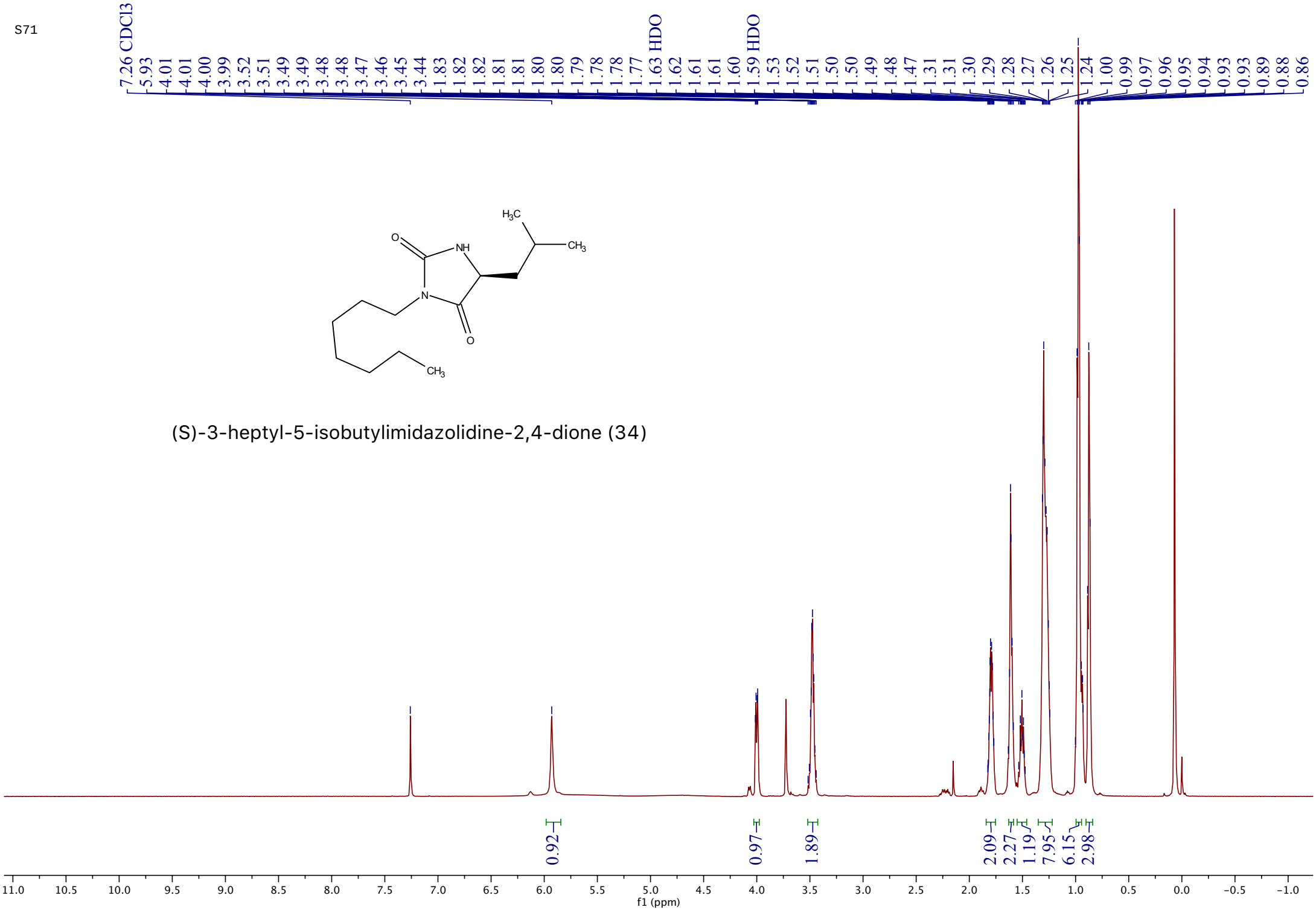



NH
O
N
O
H3C

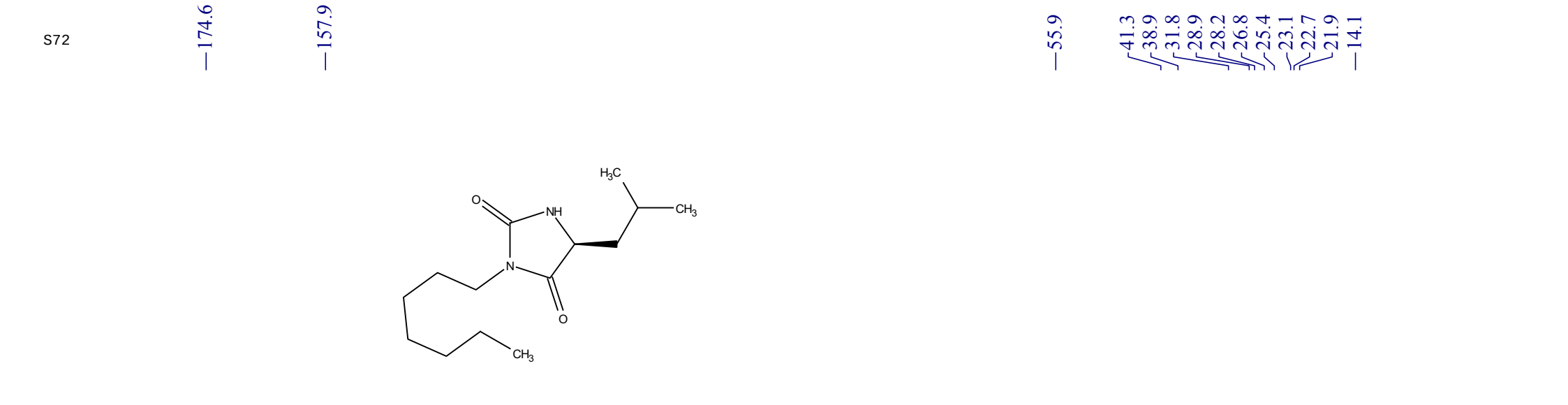
8.08
7.27
7.25
7.24
7.22
7.20
7.19
7.18
7.17
4.35
4.35
4.34
3.21
3.20
3.19
3.17
3.16
3.14
3.13
3.12
3.11
3.09
2.97
2.97
2.97
1.27
1.26
1.24
1.24
1.23
1.23
1.22
1.21
1.20
1.18
1.17
1.17
1.16
1.15
0.98
0.97
0.95
0.94
0.88
0.87
1.0
2.0
1.1
2.0
1.0
2.2
2.1
8.3
2.0
3.2
12.0
11.5
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1.0
f1 (ppm)



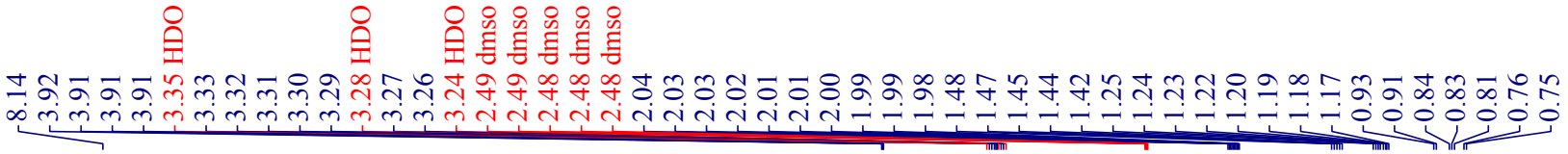
S)-5-benzyl-3-heptylimidazolidine-2,4-dione (33)

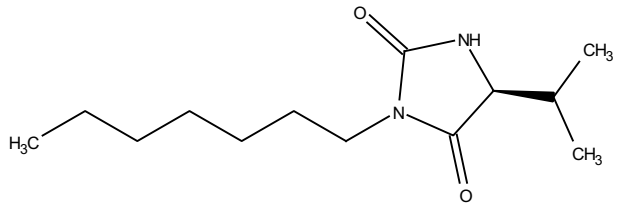


(S)-3-heptyl-5-isobutylimidazolidine-2,4-dione (34)

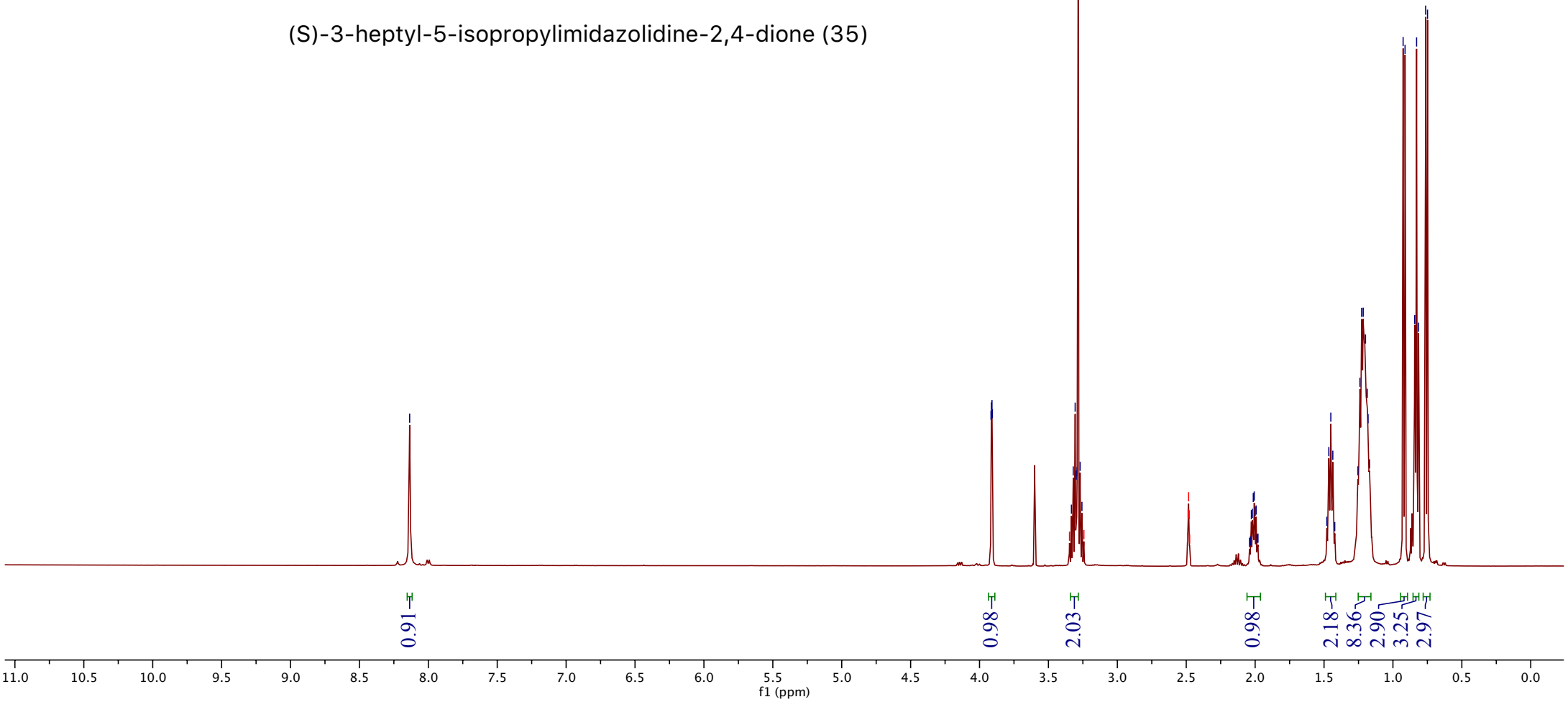


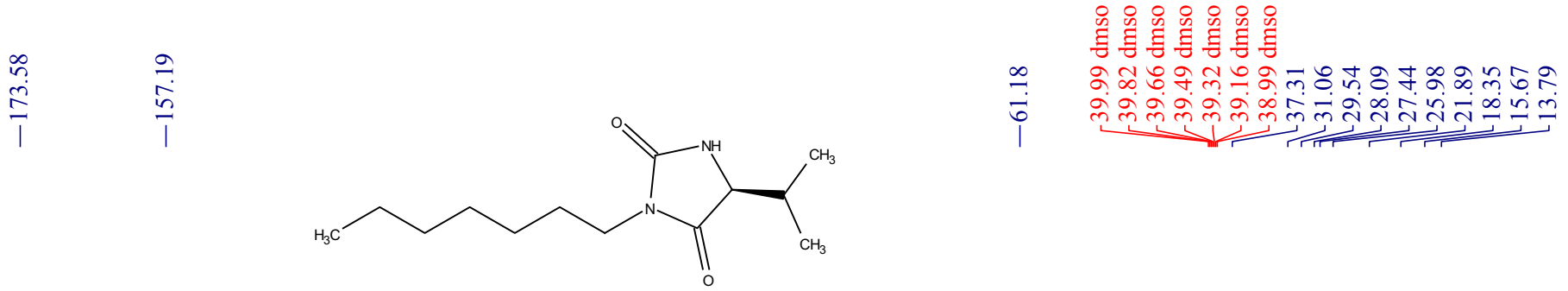
(S)-3-heptyl-5-isobutylimidazolidine-2,4-dione (34)



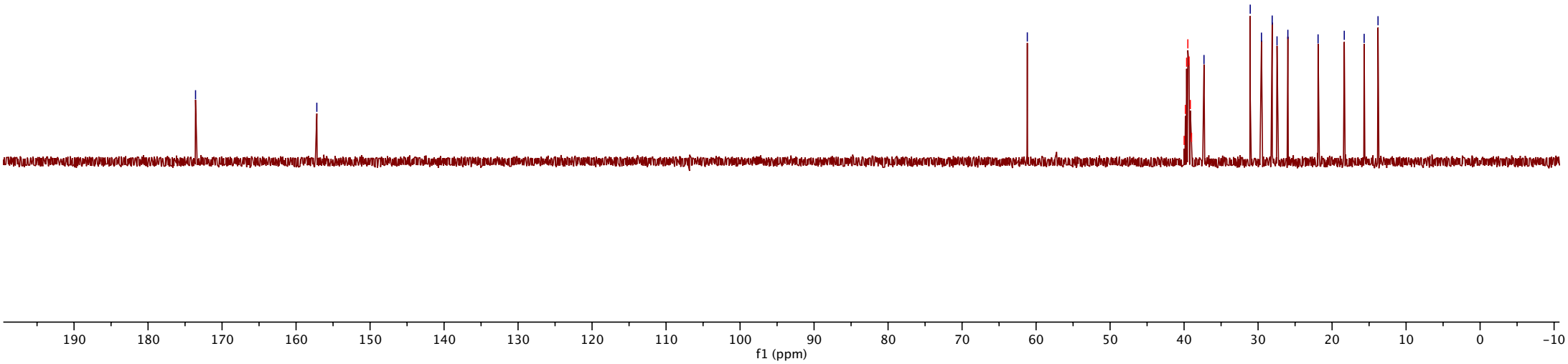


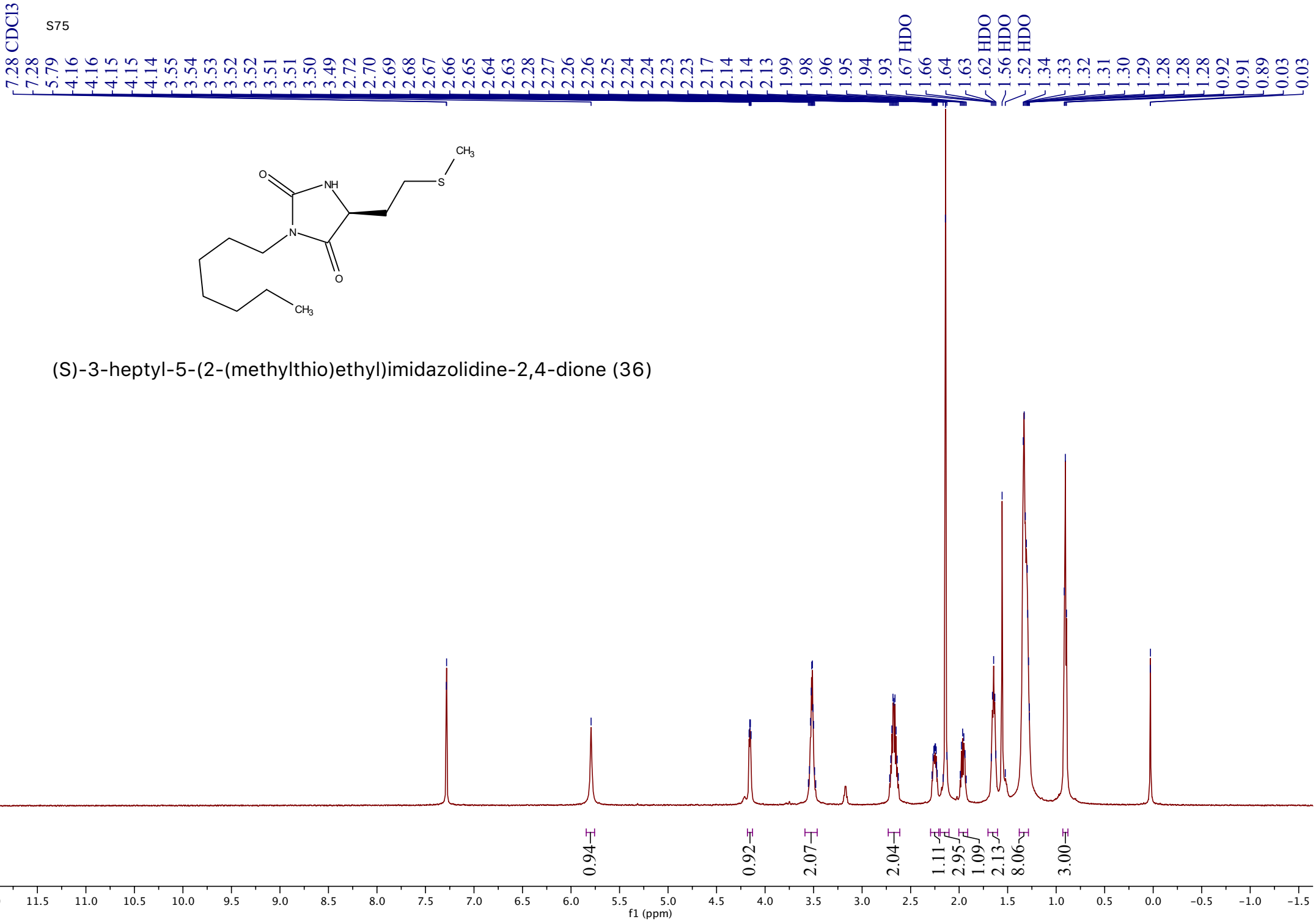
(S)-3-heptyl-5-isopropylimidazolidine-2,4-dione (35)



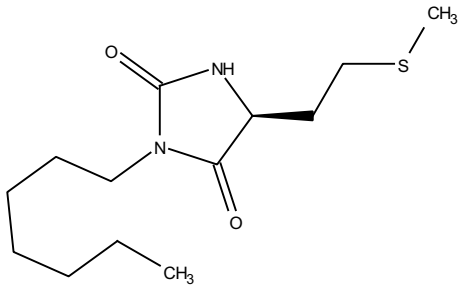


(S)-3-heptyl-5-isopropylimidazolidine-2,4-dione (35)

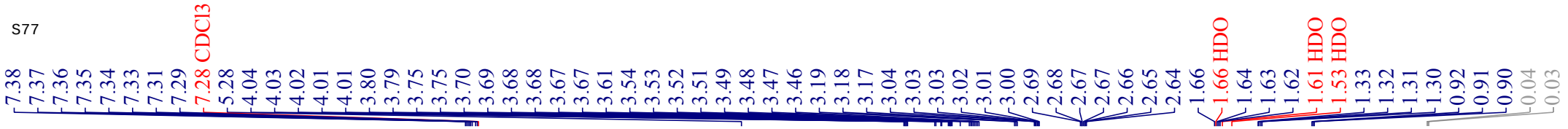


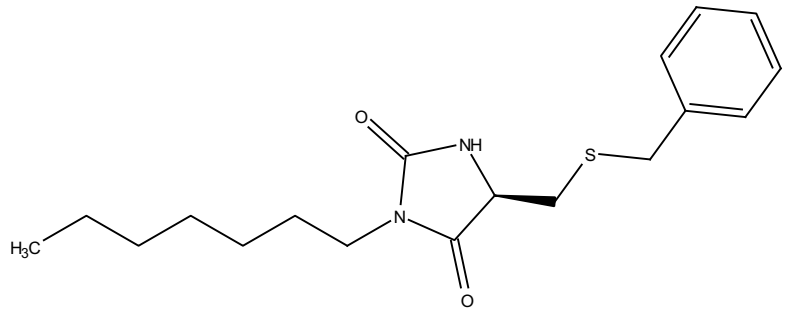


(S)-3-heptyl-5-(2-(methylthio)ethyl)imidazolidine-2,4-dione (36)

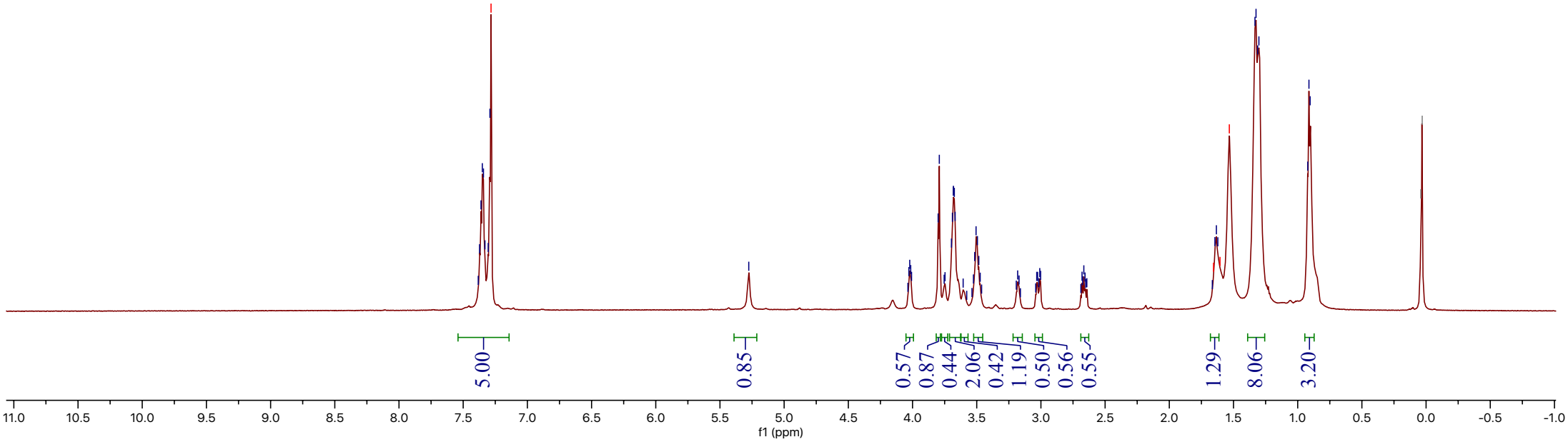


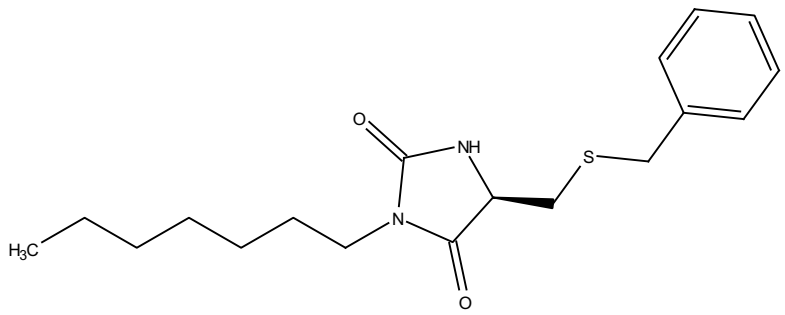
(S)-3-heptyl-5-(2-(methylthio)ethyl)imidazolidine-2,4-dione (36)



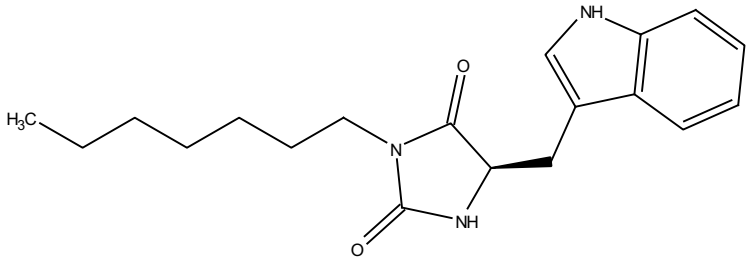


(R)-5-((benzylthio)methyl)-3-heptylimidazolidine-2,4-dione (37)

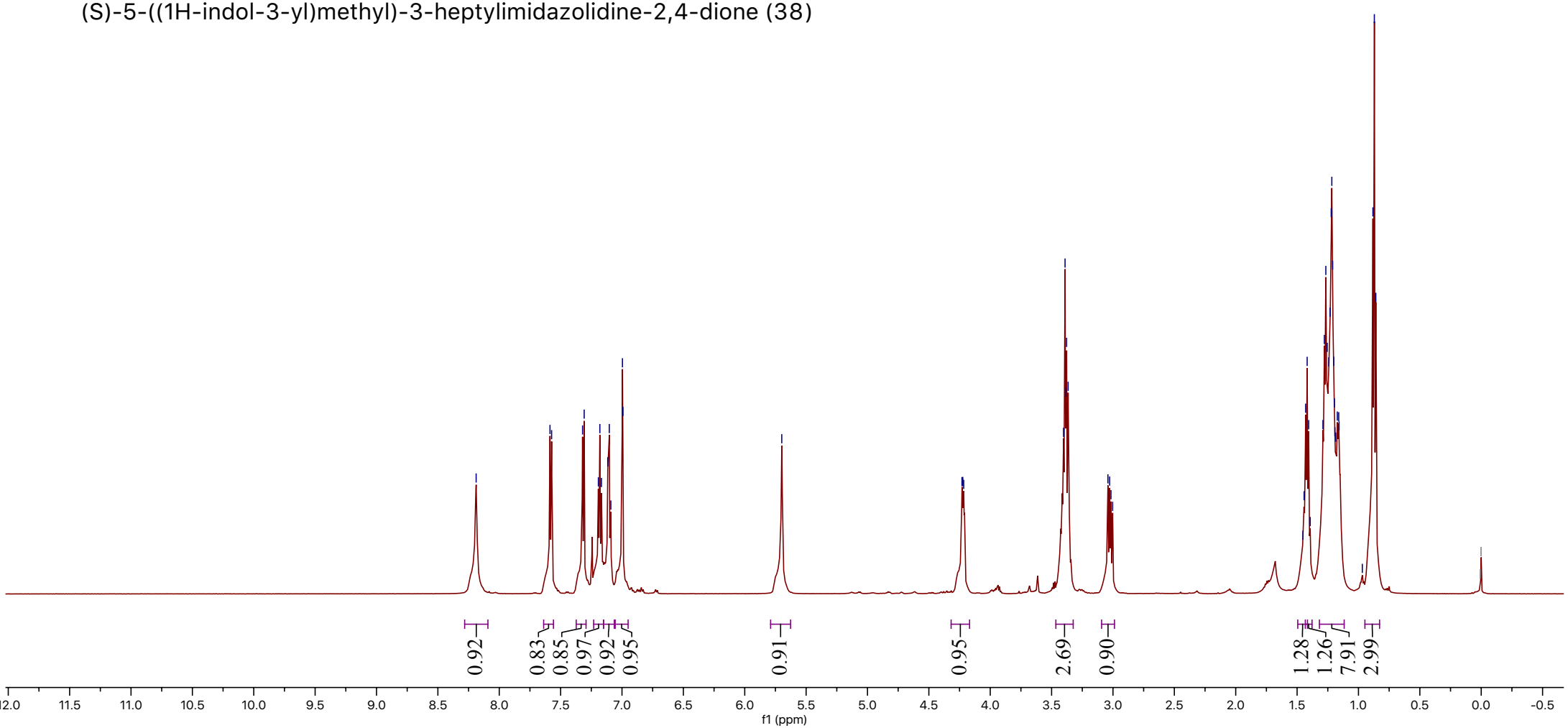


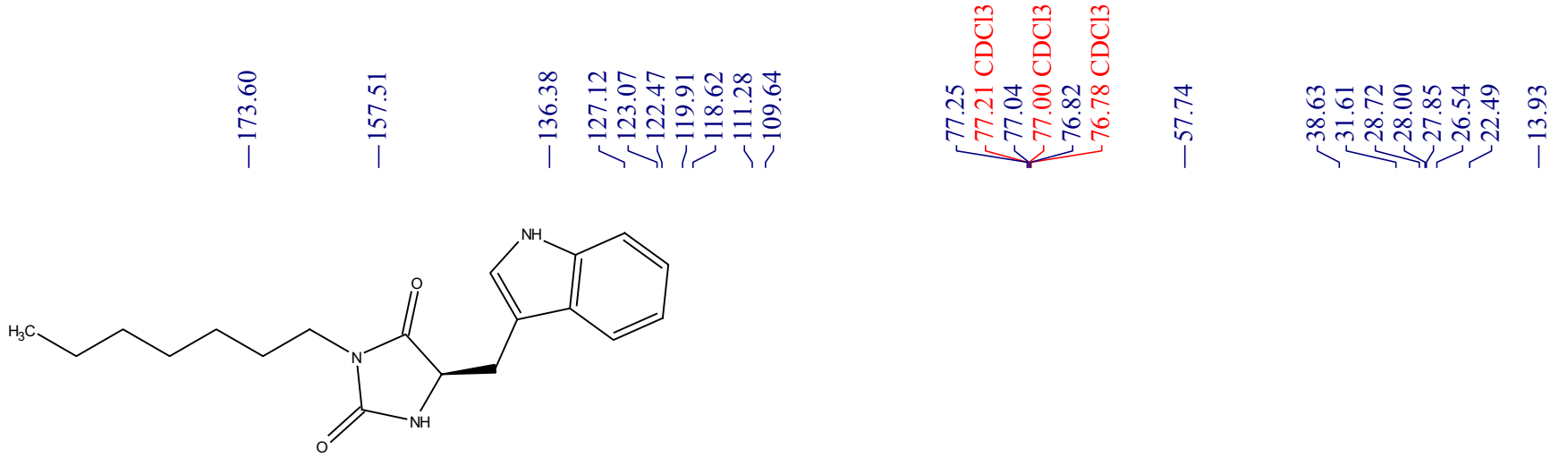


(R)-5-((benzylthio)methyl)-3-heptylimidazolidine-2,4-dione (37)

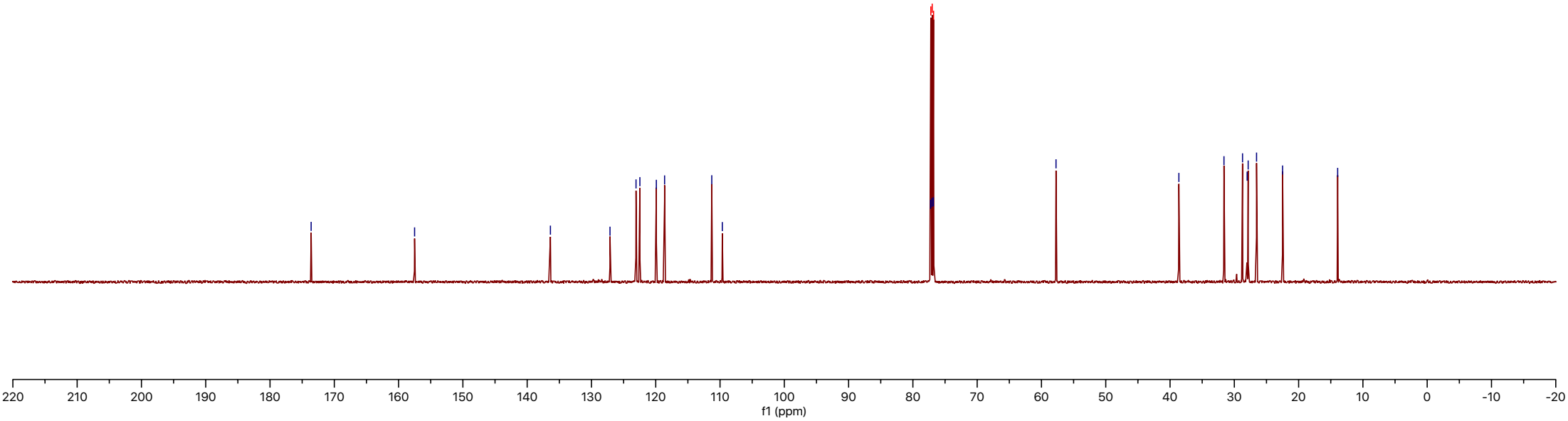


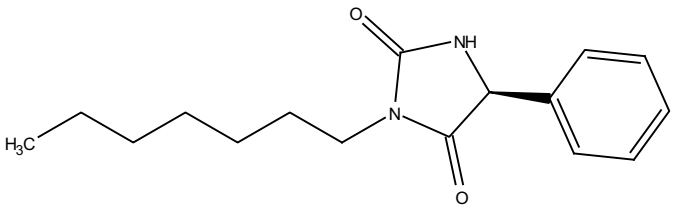
(S)-5-((1H-indol-3-yl)methyl)-3-heptylimidazolidine-2,4-dione (38)



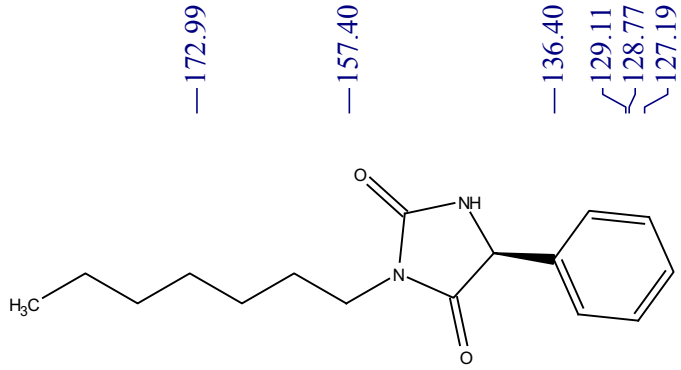


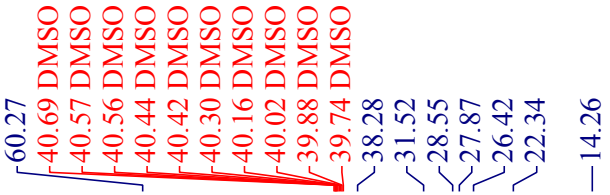
(S)-5-((1H-indol-3-yl)methyl)-3-heptylimidazolidine-2,4-dione (38)



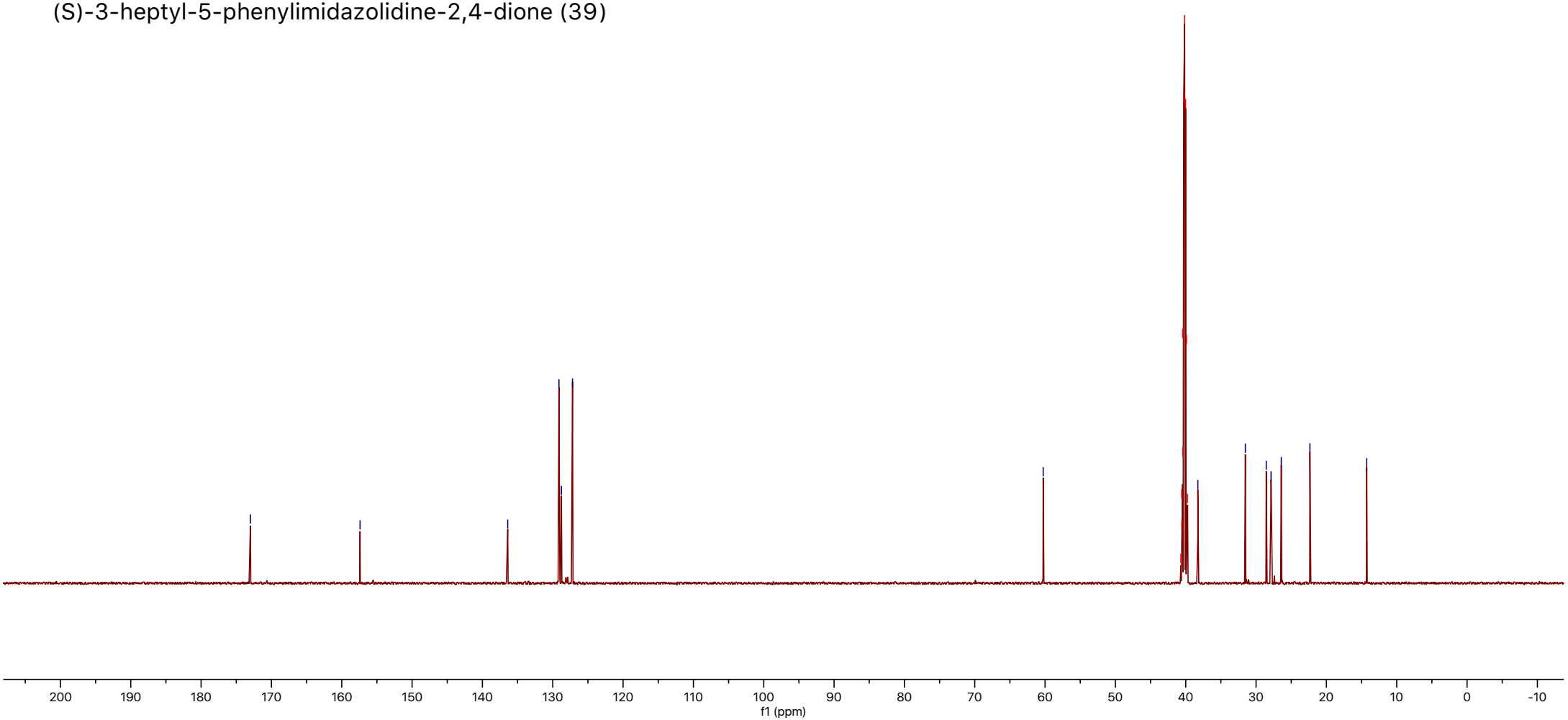


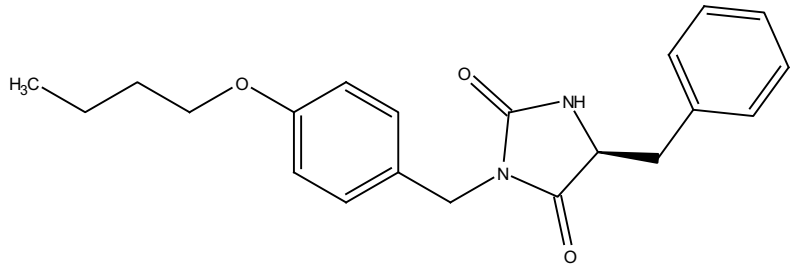
(*S*)-3-heptyl-5-phenylimidazolidine-2,4-dione (39)





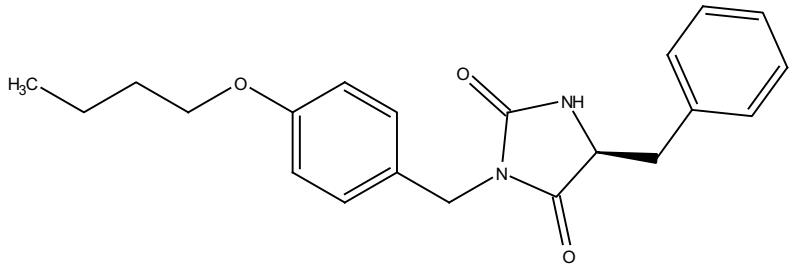
(S)-3-heptyl-5-phenylimidazolidine-2,4-dione (39)



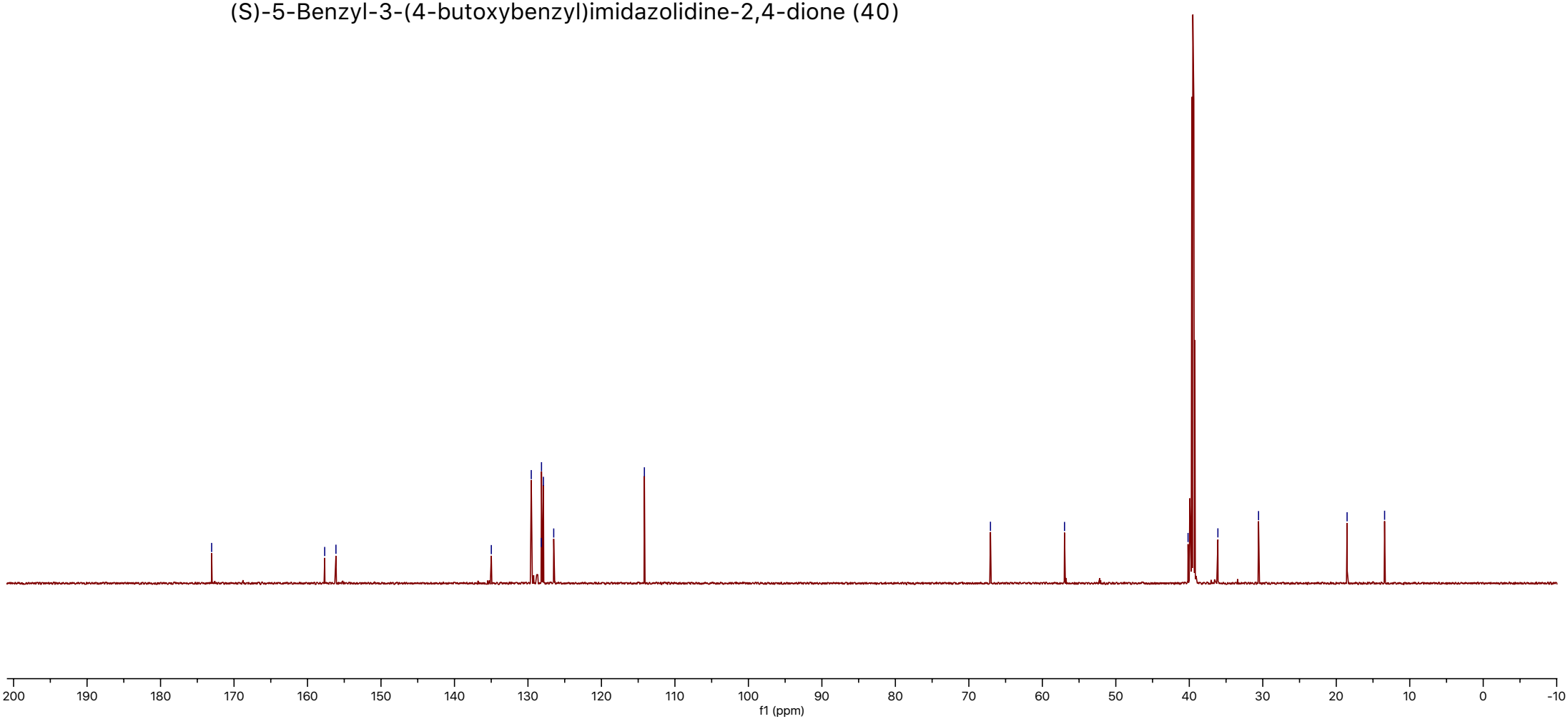


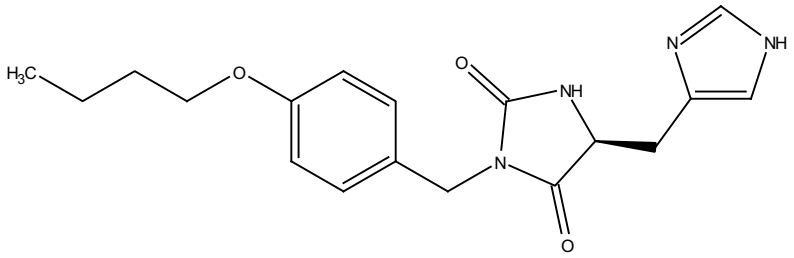
(S)-5-Benzyl-3-(4-butoxybenzyl)imidazolidine-2,4-dione (40)

173.05
157.66
156.13
134.99
129.55
128.18
128.16
127.89
126.49
114.16
67.06
56.98
40.17
36.11
30.58
18.53
13.42

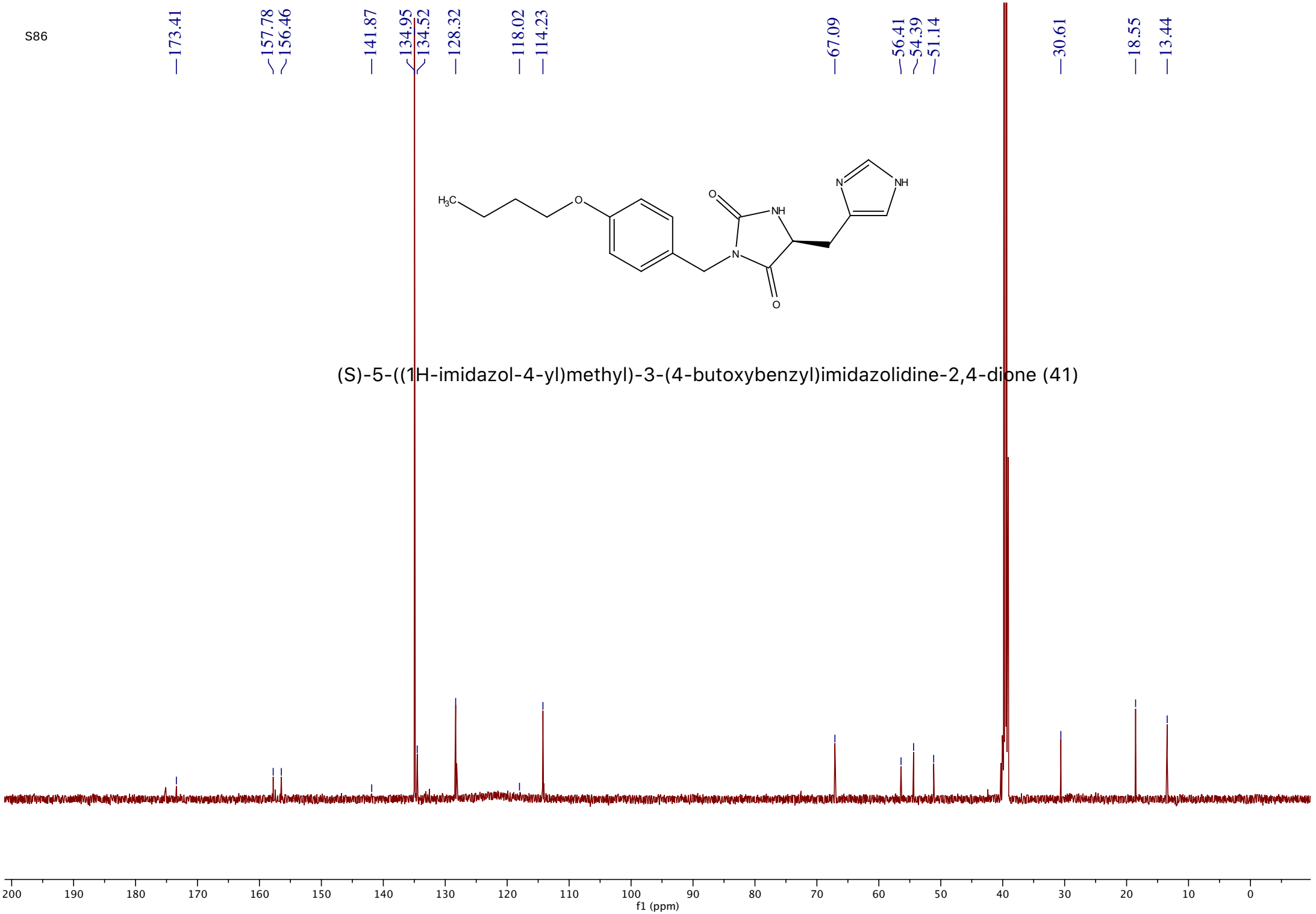


(S)-5-Benzyl-3-(4-butoxybenzyl)imidazolidine-2,4-dione (40)

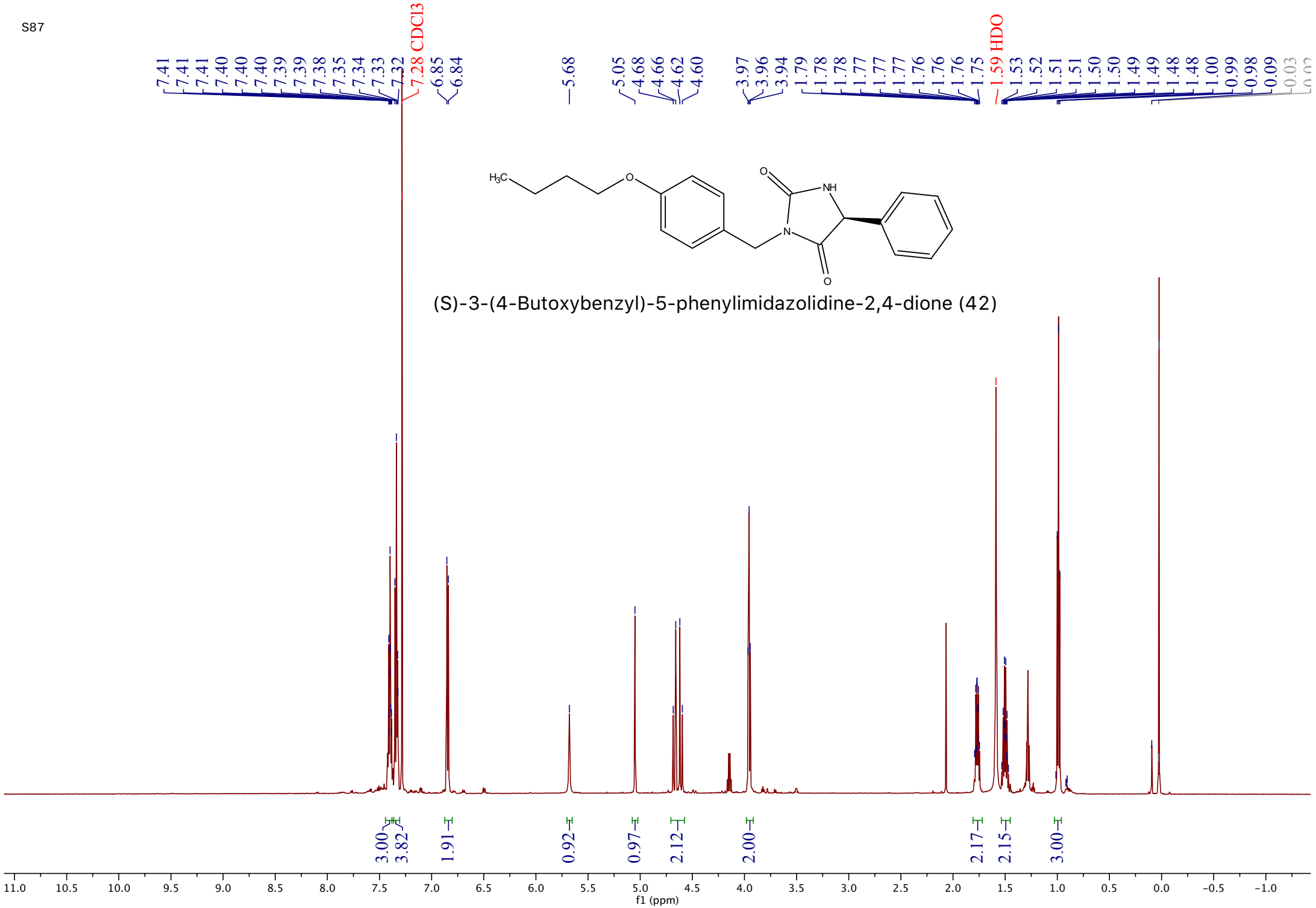


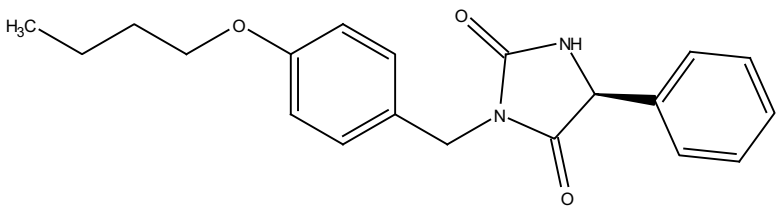


(S)-5-((1H-imidazol-4-yl)methyl)-3-(4-butoxybenzyl)imidazolidine-2,4-dione (41).

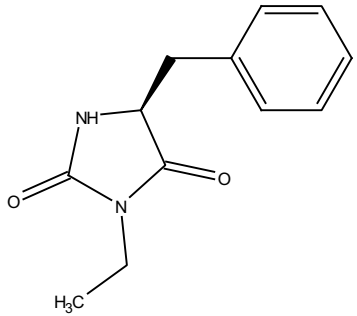


(S)-5-((1H-imidazol-4-yl)methyl)-3-(4-butoxybenzyl)imidazolidine-2,4-dione (41)

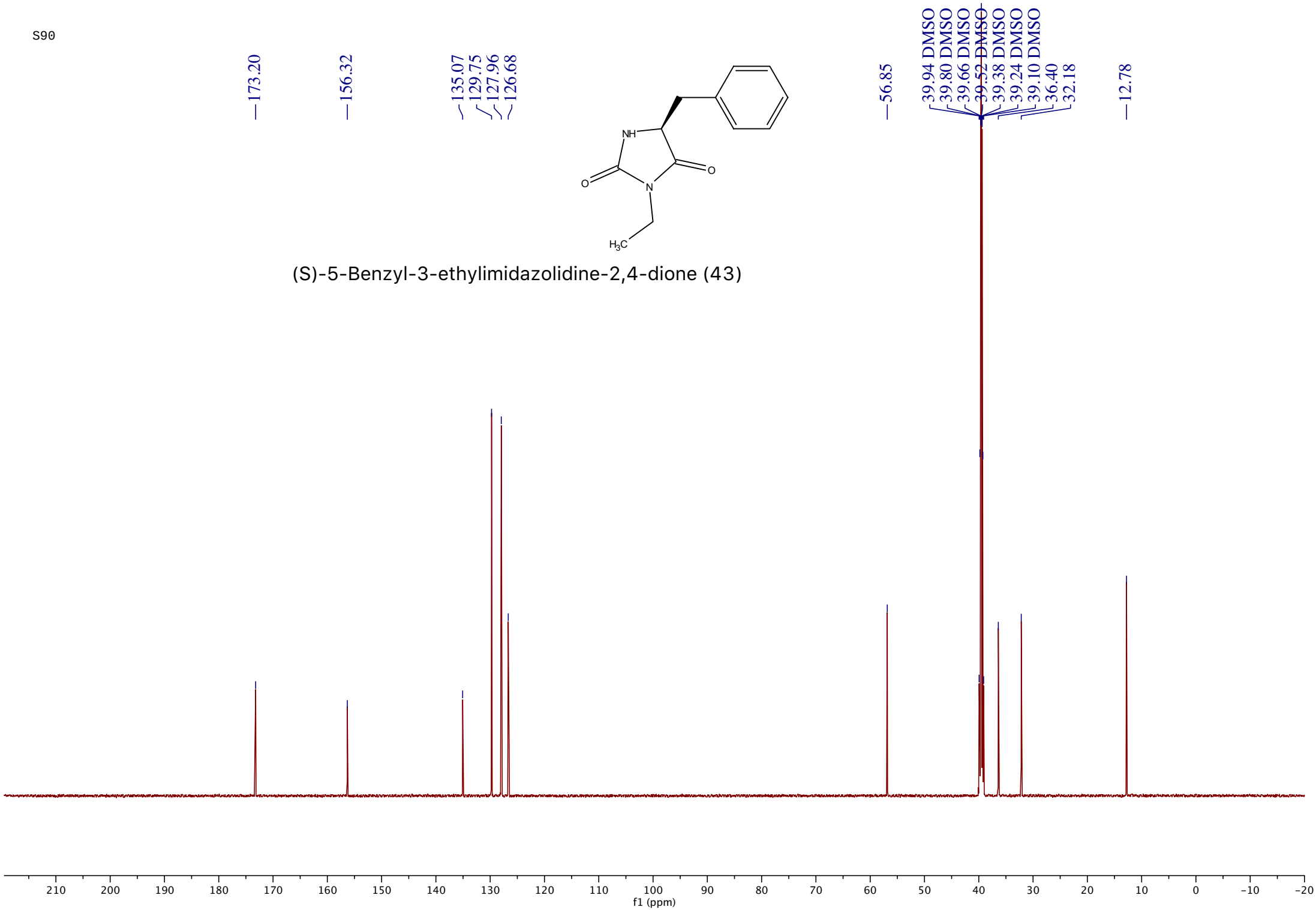

7.41
7.41
7.41
7.40
7.40
7.40
7.39
7.39
7.38
7.35
7.34
7.33
7.32
7.28 CDCl3
6.85
6.84
5.68
5.05
4.68
4.66
4.62
4.60
3.97
3.96
3.94
1.79
1.78
1.78
1.77
1.77
1.77
1.76
1.76
1.76
1.75
1.59 HDO
1.53
1.52
1.51
1.51
1.50
1.50
1.49
1.49
1.48
1.48
1.00
0.99
0.98
0.09
0.03
H3C
O
O
NH
N
O
O
(S)-3-(4-Butoxybenzyl)-5-phenylimidazolidine-2,4-dione (42)
3.00
3.82
1.91
0.92
0.97
2.12
2.00
2.17
2.15
3.00
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1.0
f1 (ppm)



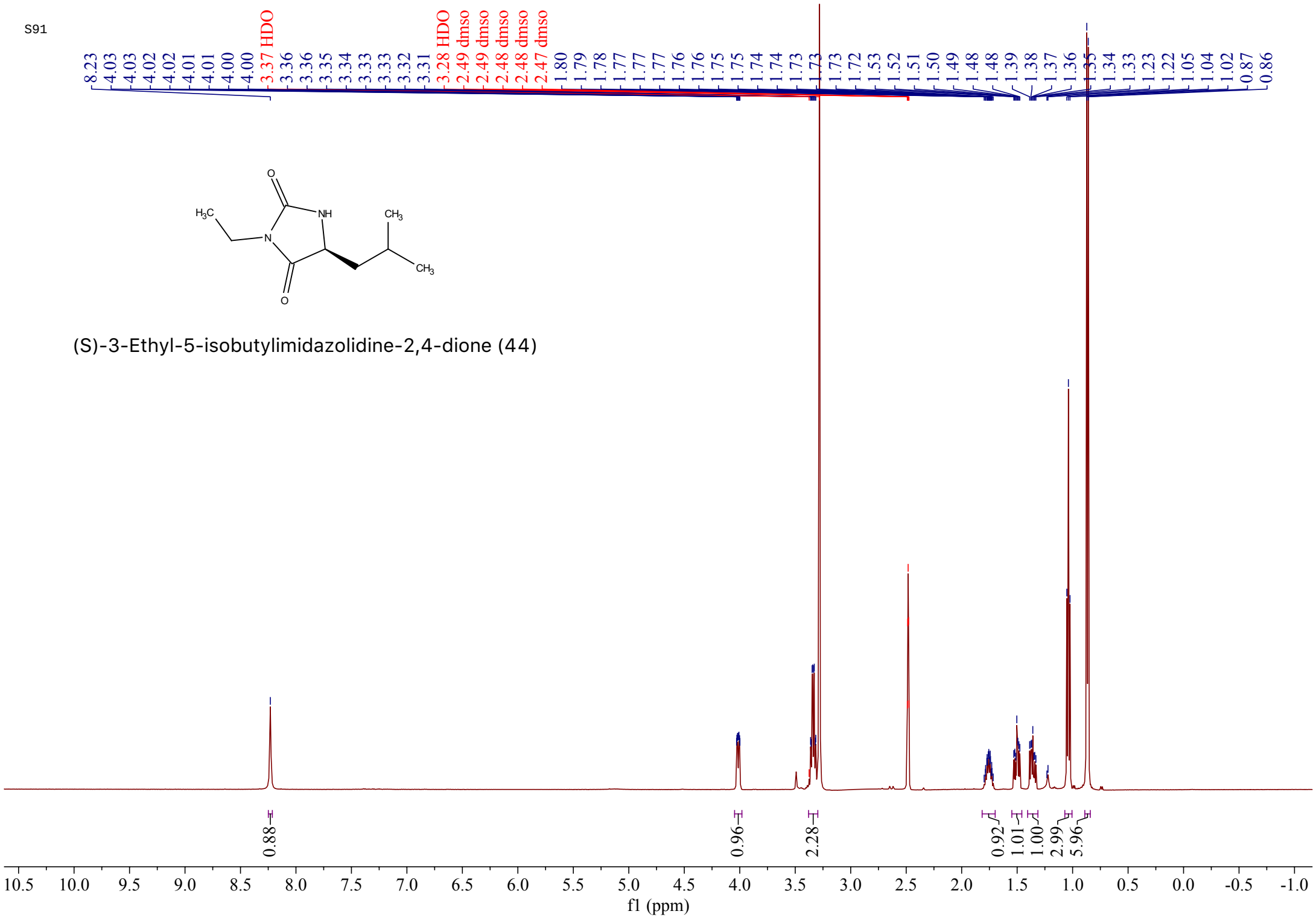
(S)-3-(4-Butoxybenzyl)-5-phenylimidazolidine-2,4-dione (42)



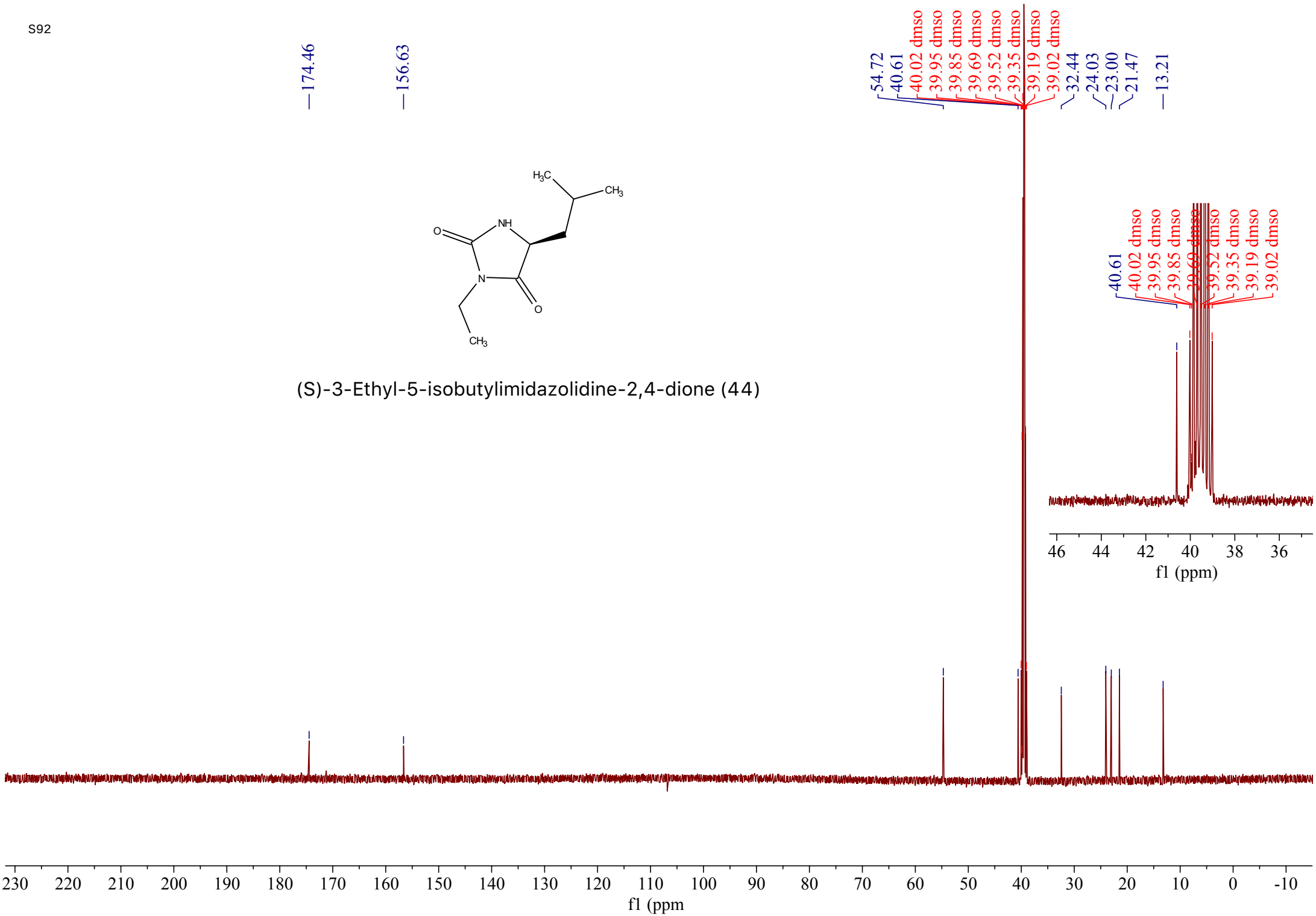
(S)-5-Benzyl-3-ethylimidazolidine-2,4-dione (43)



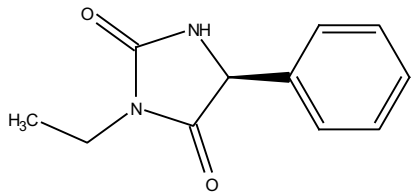
(S)-5-Benzyl-3-ethylimidazolidine-2,4-dione (43)



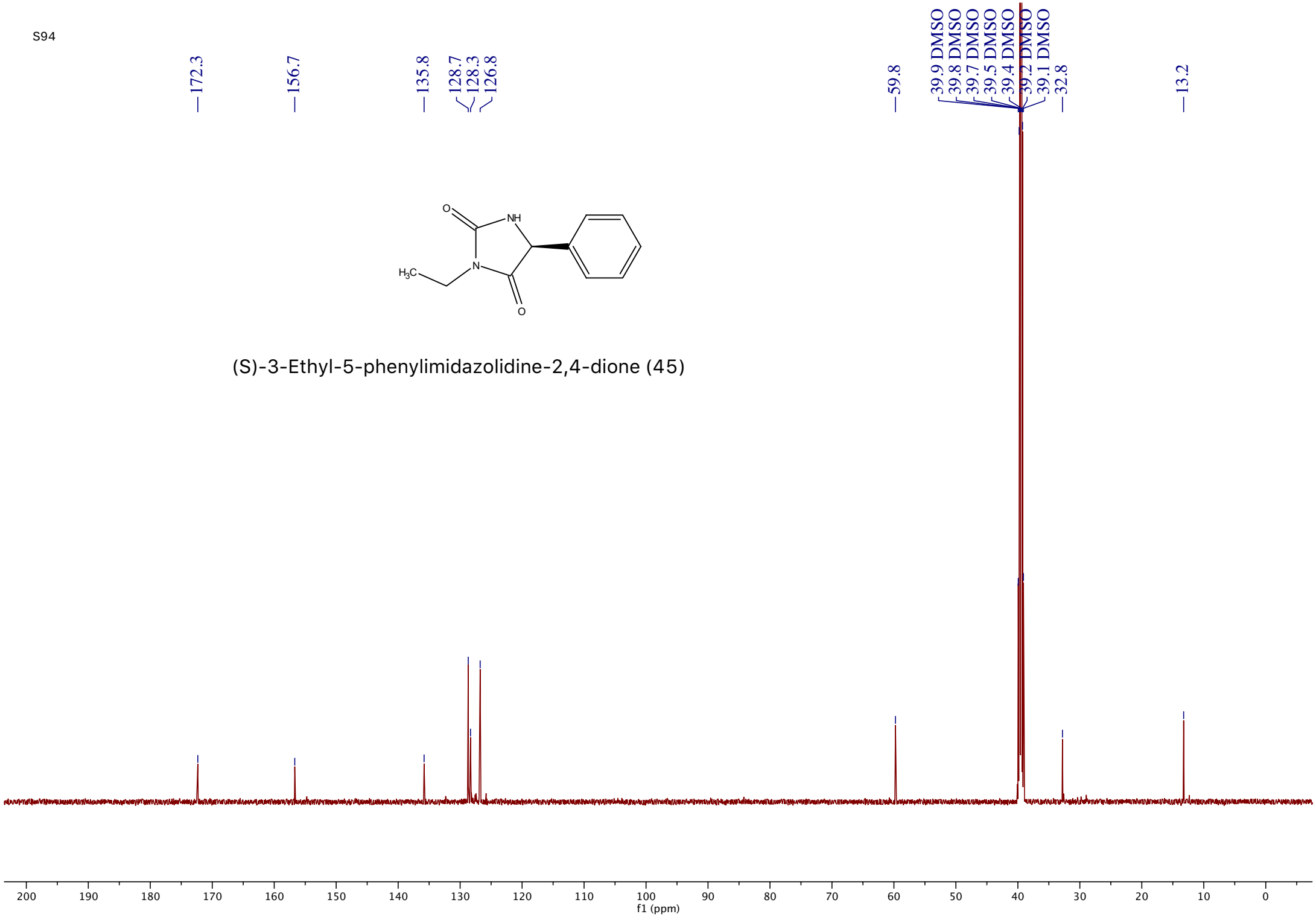
(S)-3-Ethyl-5-isobutylimidazolidine-2,4-dione (44)



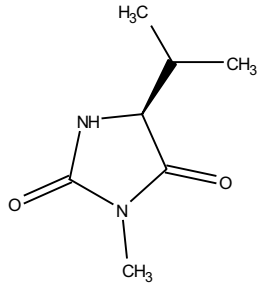
(S)-3-Ethyl-5-isobutylimidazolidine-2,4-dione (44)



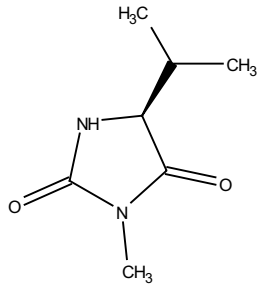
(S)-3-Ethyl-5-phenylimidazolidine-2,4-dione (45)



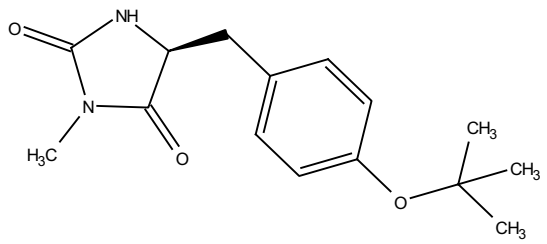
(S)-3-Ethyl-5-phenylimidazolidine-2,4-dione (45)



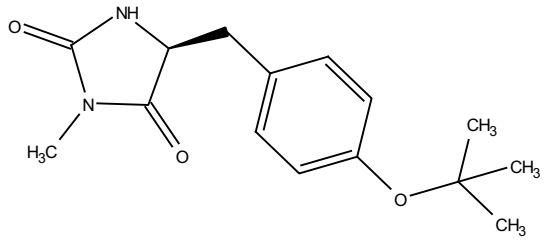
(S)-5-Isopropyl-3-methylimidazolidine-2,4-dione (46)



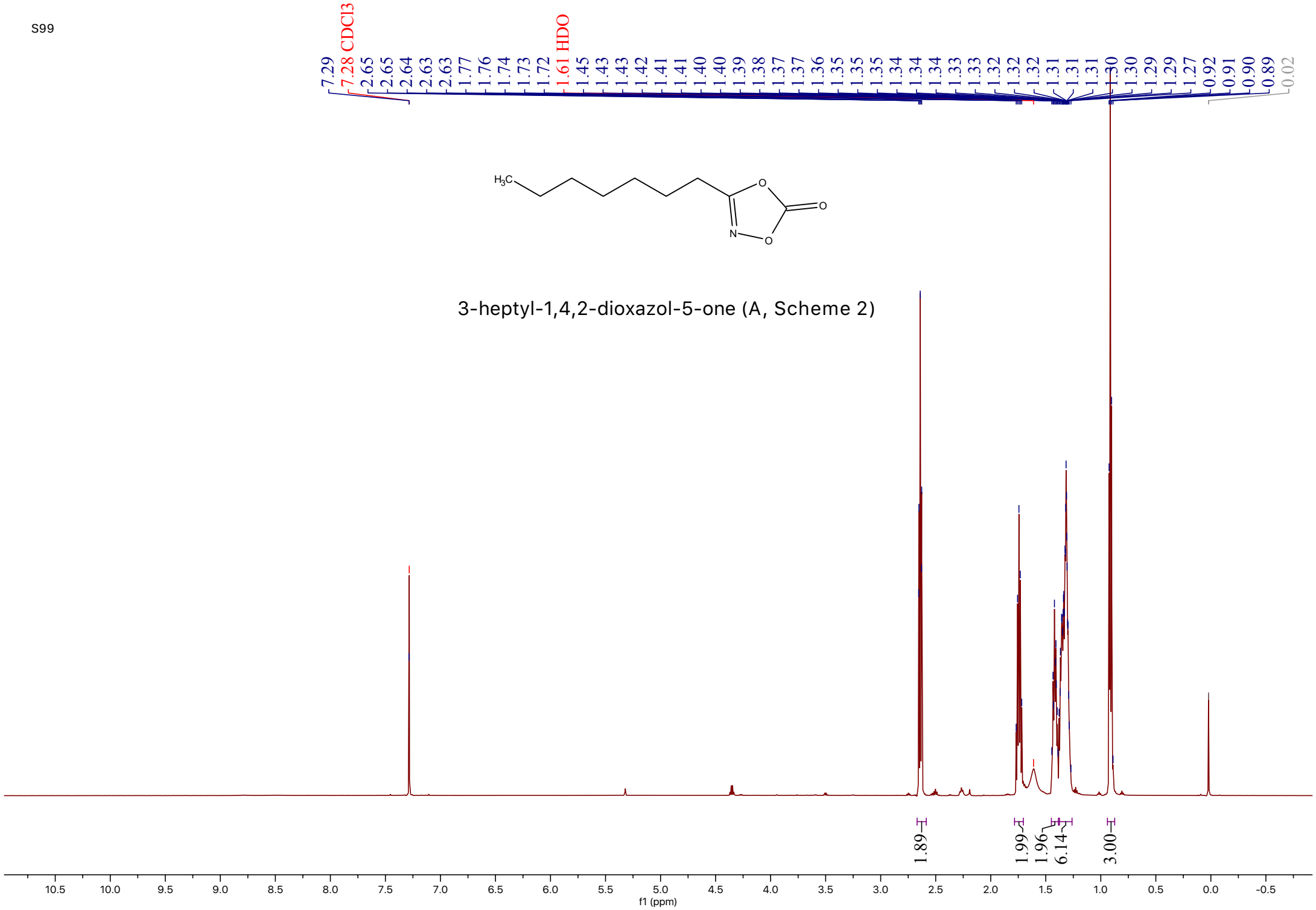
(S)-5-Isopropyl-3-methylimidazolidine-2,4-dione (46)



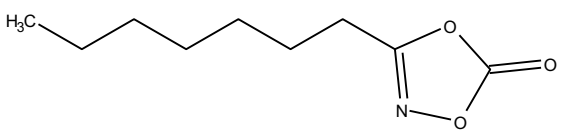
(S)-5-(4-(tert-butoxy)benzyl)-3-methylimidazolidine-2,4-dione (47)



(S)-5-(4-(tert-butoxy)benzyl)-3-methylimidazolidine-2,4-dione (47)


7.29
7.28 CDCl3
2.65
2.65
2.64
2.63
2.63
1.77
1.76
1.74
1.73
1.72
1.61 HDO
1.45
1.43
1.43
1.42
1.41
1.41
1.40
1.40
1.39
1.38
1.37
1.37
1.36
1.35
1.35
1.35
1.34
1.34
1.34
1.33
1.33
1.32
1.32
1.32
1.31
1.31
1.31
1.30
1.30
1.29
1.29
1.27
0.92
0.91
0.90
0.89
0.02
H3C
O
O
O
N
3-heptyl-1,4,2-dioxazol-5-one (A, Scheme 2)
1.89
1.99
1.96
6.14
3.00
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

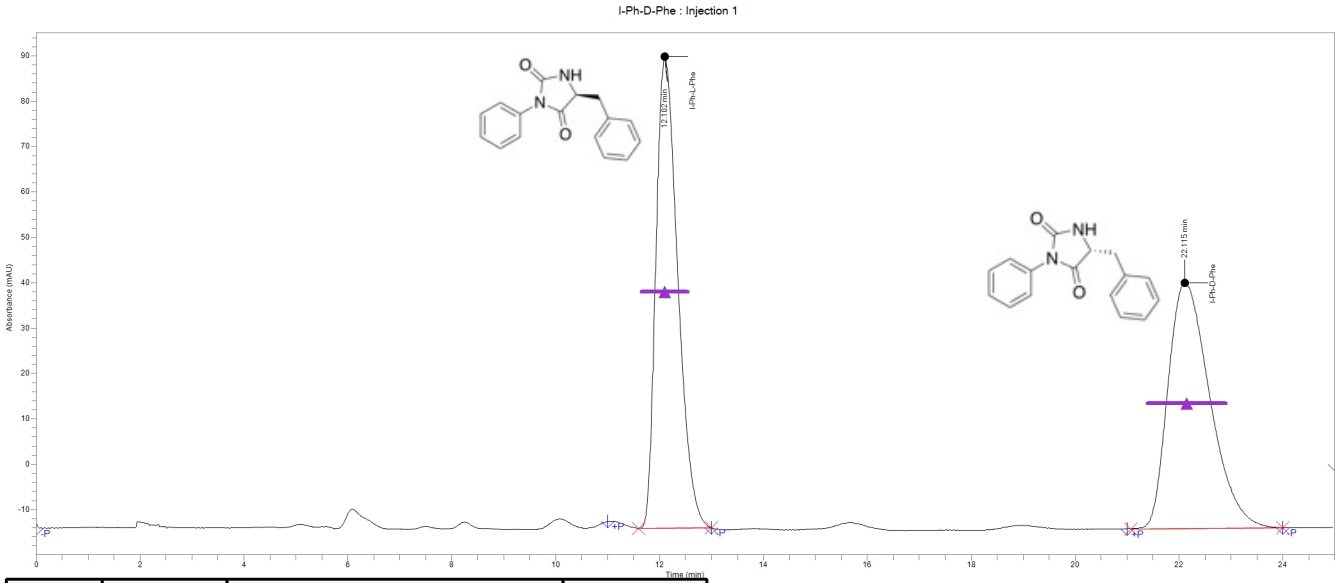
S100



3-heptyl-1,4,2-dioxazol-5-one (A, Scheme 2)

Sample Report - Single Channel

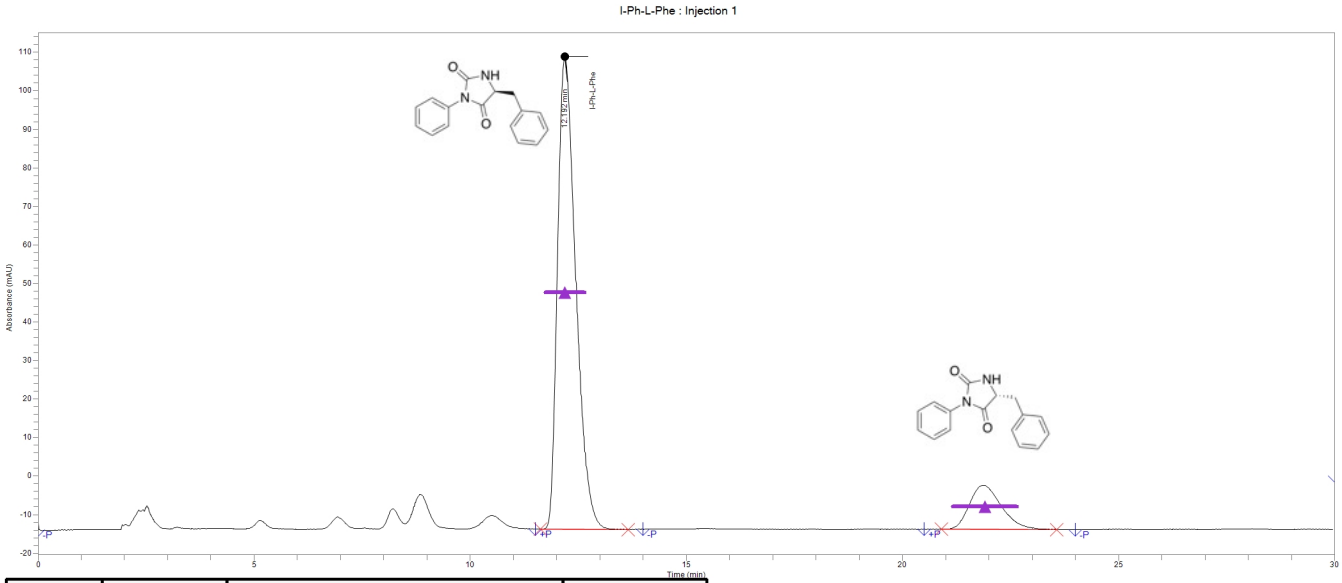
Sample Name	I-Ph-D/L-Phe		
Batch Group/Name	Hplc/FE_racemo		
Acquisition Method	I-Ph-D/L-Phe		
Processing Method	I-Ph-D/L-Phe		
Instrument Name	Flexar Pump	Channel Name	FXUVDet-2 1
Vial Number		Injection Number	1
Operator	hplc	Chromera Version	4.1.2.6410
Acquisition Date/Time	10/1/2018 7:02:45 PM		



Peak #	RT (min)	Component Name	Area %
1	12.102	I-Ph-L-Phe	50.04
2	22.115	I-Ph-D-Phe	49.96
Total			100.00

Sample Report - Single Channel

Sample Name	I-Ph-L-Phe		
Batch Group/Name	Hplc/FE_1 equiv K2CO3		
Acquisition Method	I-Ph-L-Phe		
Processing Method	I-Ph-L-Phe		
Instrument Name	Flexar Pump	Channel Name	FXUVDet-2 1
Vial Number		Injection Number	1
Operator	hplc	Chromera Version	4.1.2.6410
Acquisition Date/Time	10/1/2018 4:54:30 PM		



Peak #	RT (min)	Component Name	Area %
1	12.192	I-Ph-L-Phe	85.83
2	21.844	I-Ph-D-Phe	14.17
Total			100.00