

Supporting information

Continuous-Flow Synthesis of Thioureas Enabled by Aqueous Polysulfide Solution

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Table S1. Batch results for compounds **4**, **11–14**, **16**, **26** and **29–36** from reference 1.

Product ^a	Yield [%] ^b	Product ^a	Yield [%] ^b
 4 (0.5 h)	91 ^c	 31 (0.5 h)	84 ^e
 11 (1 h)	92 ^c	 32 (0.5 h)	74 ^e
 12 (2 h)	62 ^c	 33 (0.5 h)	74 ^e
 13 (0.5 h)	67 ^c	 34 (1 h)	81 ^e
 14 (0.5 h)	72 ^c	 35 (1 h)	76 ^e
 16 (1 h)	50 ^c	 36 (1 h)	77 ^e
 26 (0.5 h)	89 ^d		
 29 (2 h)	81 ^d		
 30 (2 h)	89 ^d		

^aReaction time in parentheses. ^bIsolated yields. ^cReaction conditions: isocyanide (0.5 mmol), polysulfide solution (1.0 M amidine/0.4 M S₈, 2.5 mL), 60 °C, water. ^dReaction conditions: isocyanide (0.50 mmol), amine (0.75 mmol), polysulfide solution (1.0 M PMDTA/0.4 M S₈, 2.5 mL), 60 °C, water. ^eReaction conditions: same as the previous conditions at 80 °C.

All of the compounds except **15**, **27** and **28** are known in the literature, and if not indicated otherwise, have been characterized in reference 1.

General procedure for the synthesis of formamides:

To formic acid (1.66 mL, 44 mmol) at 0 °C acetic anhydride (3.40 mL, 36 mmol) was added, then the mixture was heated up to 60 °C for 2 h. After cooling to 0 °C the reaction mixture was diluted with tetrahydrofuran (15 mL) and the solution of the amine (10 mmol) in tetrahydrofuran (15 mL) was added carefully. After the complete consumption of the amine followed by TLC, the volatiles were evaporated and flash column chromatography was applied if necessary providing the formamides 89%-quantitative yield.

N-(6-bromopyridin-3-yl)formamide (S1): Pale yellow crystals (2.01 g, quant.), m.p. 158–159 °C (acetic acid–formic acid); ¹H-NMR: (500 MHz, DMSO-*d*₆, mixture of E/Z isomers) δ 10.41 ((two signals: 10.52 (bs), 10.29 (d, *J* = 10.2 Hz)), 1H), 8.71 ((two signals: 8.81 (d, *J* = 10.8 Hz), 8.60 (d, *J* = 2.3 Hz)), 1H), 8.33 ((two signals: 8.37 (s), 8.29 (s)), 1H), 7.79 ((two signals: 7.97 (dd, *J* = 8.6 Hz, *J* = 2.5 Hz), 7.60 (m)), 1H), 7.60–7.58 (m, 1H) ppm.

N-(quinolin-3-yl)formamide (S2): Compound have been characterized in ref.² The observed ¹H NMR spectrum was consistent with the previously reported data (although the solvent was MeOD); White solid (1.54 g, 89%), m.p. 160–161 °C (acetic acid–formic acid, ref.² chloroform–methanol 159.5–160.5 °C); ¹H-NMR: (500 MHz, DMSO-*d*₆, mixture of E/Z isomers, ref.²) δ 10.57 ((two signals: 10.66 (bs), 10.48 (bs)), 1H), 8.94 ((two signals: 8.96 (bs), 8.92 (d, *J* = 2.5 Hz)), 1H), 8.76 ((two signals: 8.82 (d, *J* = 2.4 Hz), 8.70 (d, *J* = 2.3 Hz)), 1H), 8.31 ((two signals: 8.46 (s), 8.15 (d, *J* = 2.1 Hz)), 1H), 7.97–7.87 (m, 2H), 7.67–7.56 (m, 2H) ppm.

N-(2-(1H-indol-3-yl)ethyl)formamide (S3): Compound have been characterized in ref.³ The observed ¹H NMR spectrum was consistent with the previously reported data; Yellow oil (1.86 g, 99%); ¹H-NMR: (500 MHz, CDCl₃, mixture of E/Z isomers, ref. ³) δ 8.35 (bs, 1H), 7.95 ((two signals: 8.06 (bs), 7.84 (d, *J* = 12.0 Hz)), 1H), 7.57 ((two signals: 7.59 (d, *J* = 7.9 Hz), 7.55 (d, *J* = 7.9 Hz)), 1H), 7.36 (d, *J* = 8.2 Hz, 1H), 7.21 (t, *J* = 8.0 Hz, 1H), 7.14–7.11 (m, 1H), 6.99 ((two signals: 7.01 (bs), 6.97 (bs)), 1H), 5.85 ((two signals: 5.95 (bs), 5.75 (bs)), 1H), 3.56 ((two signals: 3.63 (q, *J* = 6.5 Hz), 3.48 (q, *J* = 6.4 Hz)), 2H), 3.00–2.93 (m, 2H) ppm.

General procedure for the synthesis of isocyanides 5, 6 and 8:

To a solution of the formamide (5 mmol) in tetrahydrofuran (10 mL) and triethylamine (5.58 mL, 40 mmol) was added phosphoryl chloride (0.93 mL, 10 mmol) dropwise at 0 °C. The resulted mixture was stirred at either room temperature (isocyanide 5 and 8) or reflux temperature (isocyanide 6) until the consumption of the formamide followed by TLC. Afterwards, aqueous sodium hydrogencarbonate (15 mL) was added slowly under ice cooling, then the reaction mixture was extracted with dichloromethane (2 × 15 mL) and the organic layer was washed with brine (15 mL). Evaporation of the solvent followed by purification by flash column chromatography in hexane-ethyl acetate on aluminium oxide provided the isocyanide 5, 6 and 8 in 54–59% yield.

2-Bromo-5-isocyanopyridine (5): White crystals (490 mg, 54%), m.p. 113–114 °C (decomp., hexane-ethyl acetate); ¹H-NMR: (500 MHz, CDCl₃) δ 8.45 (d, *J* = 1.3 Hz, 1H), 7.58–7.53 (m, 2H) ppm.

3-Isocyanquinoline (6): Compound have been characterized in ref.⁴ The observed ¹H NMR spectrum was consistent with the previously reported data; Pale yellow crystals (455 mg, 59%), m.p. 83–84 °C (hexane-dichloromethane); ¹H-NMR: (500 MHz, DMSO-*d*₆, ref.⁴) δ 8.90 (d, *J* = 2.3 Hz, 1H), 8.19 (d, *J* = 1.9 Hz, 1H), 8.15 (d, *J* = 8.5 Hz, 1H), 7.86–7.80 (m, 2H), 7.66 (td, *J*₁ = 7.6 Hz, *J*₂ = 1.0 Hz, 1H) ppm.

3-(2-Isocianoethyl)-1H-indole (8): Pale yellow crystals (502 mg, 59%), m.p. 70–71 °C (hexane-ethyl acetate); ¹H-NMR: (500 MHz, CDCl₃) δ 8.17 (bs, 1H), 7.59 (d, *J* = 7.8 Hz, 1H), 7.39 (d, *J* = 8.2 Hz, 1H), 7.26 (td, *J*₁ = 7.6 Hz, *J*₂ = 0.9 Hz, 1H), 7.19 (td, *J*₁ = 7.5 Hz, *J*₂ = 0.9 Hz, 1H), 7.11 (d, *J* = 2.3 Hz, 1H), 3.67 (t, *J* = 7.0 Hz, 1H), 3.17 (t, *J* = 6.9 Hz, 1H) ppm.

(2-Isocianoethyl)benzene (7): Compound have been characterized in ref.⁵ The observed ¹H NMR spectrum was consistent with the previously reported data (only the coupling constants are different); To formic acid (1.66 mL, 44 mmol) at 0 °C acetic anhydride (3.40 mL, 36 mmol) was added, then the mixture was heated up to 60 °C for 2 h. After cooling to 0 °C the reaction mixture was diluted with tetrahydrofuran (15 mL) and the solution of the amine (10 mmol) in tetrahydrofuran (15 mL) was added carefully. After the complete consumption of the amine followed by TLC, the volatiles were evaporated. The crude product was dissolved in tetrahydrofuran (20 mL) and triethylamine (11.2 mL, 80 mmol), then phosphoryl chloride (1.86 mL, 20 mmol) was added dropwise at 0 °C. The resulted mixture was stirred at room temperature until the consumption of the formamide followed by TLC. Afterwards, aqueous sodium hydrogencarbonate (30 mL) was added slowly under ice cooling, then the reaction mixture was extracted with dichloromethane (2×30 mL) and the organic layer was washed with brine (30 mL). Evaporation of the solvent followed by purification by flash column chromatography in hexane-ethyl acetate on aluminium oxide provided the isocyanide 7 in 65% yield (850 mg). Yellow oil; ¹H-NMR: (500 MHz, CDCl₃, ref. ⁵) δ 7.36–7.23 (m, 5H), 3.61 (t, *J* = 7.1 Hz, 2H), 2.99 (t, *J* = 7.1 Hz, 2H) ppm.

1-(2,6-Dimethylphenyl)-3-(3-(2-oxoazepan-1-yl)propyl)thiourea (4): White solid, m.p. 163–164 °C (water); ¹H-NMR: (500 MHz, CDCl₃) δ 7.25 (bs, 1H), 7.21–7.14 (m, 3H), 6.38 (bs, 1H), 3.57 (t, 2H, *J* = 6.0 Hz), 3.29–3.27 (m, 4H), 2.41–2.38 (m, 2H), 2.27 (s, 6H), 1.77–1.60 (m, 8H) ppm.

1-(2,6-Dimethylphenyl)-3-(3-(2-oxopyrrolidin-1-yl)propyl)thiourea (11): White solid, m.p. 154–155 °C (water); ¹H-NMR: (500 MHz, CDCl₃) δ 7.27 (bs, 1H), 7.22–7.14 (m, 3H), 6.32 (bs, 1H), 3.54 (bs, 2H), 3.35 (t, 2H, *J* = 7.0 Hz), 3.18 (bs, 2H), 2.32–2.24 (m, 2H), 2.27 (s, 6H), 2.01–1.95 (m, 2H), 1.79–1.76 (m, 2H) ppm.

1-(2,6-Dimethylphenyl)-3-(3-(2-oxotetrahydropyrimidin-1(2H)-yl)propyl)thiourea (12): White solid, m.p. 142–143 °C (water); ¹H-NMR: (500 MHz, CDCl₃) δ 7.27 (bs, 1H), 7.18–7.11 (m, 3H), 6.67 (bs, 1H), 4.50 (bs, 1H), 3.59–3.56 (m, 2H), 3.20–3.18 (m, 6H), 2.25 (s, 6H), 1.88–1.86 (m, 2H), 1.73 (p, 2H, *J* = 6.1 Hz) ppm.

1-(6-Bromopyridin-3-yl)-3-(3-(2-oxoazepan-1-yl)propyl)thiourea (13): White solid, m.p. 182–183 °C (water); ¹H-NMR: (500 MHz, DMSO-*d*₆) δ 9.77 (bs, 1H), 8.40 (d, *J* = 2.7 Hz, 1H), 8.01 (bs, 1H), 7.94 (d, *J* = 6.9 Hz, 1H), 7.56 (d, *J* = 8.6 Hz, 1H), 3.36–3.30 (m, 6H), 2.42 (t, *J* = 5.6 Hz, 2H), 1.72–1.54 (m, 8H) ppm.

1-(3-(2-Oxazepan-1-yl)propyl)-3-(quinolin-3-yl)thiourea (14): Beige crystals, m.p. 134–135 °C (water); ¹H-NMR: (500 MHz, CDCl₃) δ 9.18 (bs, 1H), 8.82 (s, 1H), 8.37 (s, 1H), 7.96 (d, *J* = 8.4 Hz, 1H), 7.85 (bs, 1H), 7.71 (d, *J* = 8.1 Hz, 1H), 7.55 (t, *J* = 7.9 Hz, 1H), 7.43 (d, *J* = 7.7 Hz, 1H), 3.62 (d, *J* = 5.4 Hz, 2H), 3.36 (t, *J* = 6.1 Hz, 2H), 3.26 (t, *J* = 4.5 Hz, 2H), 2.39 (t, *J* = 5.4 Hz, 2H), 1.77 (p, *J* = 6.1 Hz, 2H), 1.64 (d, *J* = 5.2 Hz, 2H), 1.55 (d, *J* = 4.4 Hz, 4H) ppm.

1-(3-(2-Oxazepan-1-yl)propyl)-3-phenethylthiourea (15): Off white solid 83 °C (water); ¹H-NMR: (500 MHz, CDCl₃) δ 7.45 (bs, 1H), 7.31–7.20 (m, 5H), 5.88 (s, 1H), 3.65–3.58 (m, 4H), 3.41 (t, *J* = 5.9 Hz, 2H), 3.34 (t, *J* = 5.0 Hz, 2H), 2.91 (t, *J* = 7.0 Hz, 2H), 2.54 (t, *J* = 5.9 Hz, 2H), 1.76–1.65 (m, 8H) ppm; ¹³C-NMR: (125 MHz, CDCl₃) δ 172.6, 133.5, 124.0, 123.9, 121.9, 45.0, 40.4, 39.6, 36.1, 32.4, 30.3, 25.1, 23.6, 21.8, 18.7 ppm; HRMS (ESI/Q-TOF) *m/z*: [M+H]⁺ Calcd. for C₁₈H₂₈N₃OS 334.1947; found 334.1965.

1-(2-(1H-Indol-3-yl)ethyl)-3-(3-(2-oxazepan-1-yl)propyl)thiourea (16): Yellow gum; ¹H-NMR: (500 MHz, CDCl₃) δ 8.63 (bs, 1H), 7.56 (d, *J* = 7.9 Hz, 1H), 7.33 (d, *J* = 8.1 Hz, 1H), 7.15 (t, *J* = 7.2 Hz, 1H), 7.07 (t, *J* = 7.8 Hz, 1H), 6.97 (d, *J* = 1.6 Hz, 1H), 6.13 (bs, 1H), 3.68 (bs, 2H), 3.51 (bs, 2H), 3.34–3.32 (m, 4H), 3.00 (t, *J* = 6.6 Hz, 2H), 2.48 (t, *J* = 5.5 Hz, 2H), 1.70–1.59 (m, 8H) ppm.

1-Benzyl-3-(2,6-dimethylphenyl)thiourea (26): White solid 106–107 °C (water); ¹H-NMR: (500 MHz, CDCl₃) δ 7.53 (bs, 1H), 7.33–7.26 (m, 5H), 7.20–7.12 (m, 3H), 5.64 (bs, 1H), 4.87 (d, *J* = 5.3 Hz, 2H), 2.28 (s, 6H) ppm.

1-Benzyl-3-(quinolin-3-yl)thiourea (27): Off white solid 147–148 °C (water); ¹H-NMR: (500 MHz, CDCl₃) δ 8.73 (d, *J* = 2.5 Hz, 1H), 8.34 (bs, 1H), 8.07 (d, *J* = 1.8 Hz, 1H), 7.99 (d, *J* = 8.5 Hz, 1H), 7.70–7.65 (m, 2H), 7.52 (d, *J* = 7.8 Hz, 1H), 7.32–7.25 (m, 5H), 6.69 (bs, 1H), 4.87 (*J* = 4.9 Hz, 2H) ppm; ¹³C-NMR: (125 MHz, CDCl₃) δ 181.6, 172.5, 146.9, 131.6, 130.2, 129.8, 128.8, 127.9, 127.8, 127.7, 127.2, 123.8, 49.0 ppm; HRMS (ESI/Q-TOF) *m/z*: [M + H]⁺ Calcd. for C₁₇H₁₆N₃S 294.1059; found 294.1067.

1-Benzyl-3-phenethylthiourea (28): Compound have been characterized in ref.^{6,7} The observed ¹H NMR spectrum was consistent with the previously reported data; Off white solid 101–102 °C (water; ref.⁶ 118–120 °C, ethanol); ¹H-NMR: (500 MHz, CDCl₃, ref.⁷) δ 7.34–7.27 (m, 5H), 7.24–7.20 (m, 3H), 7.14–7.13 (m, 2H), 6.10 (bs, 1H), 5.74 (bs, 1H), 4.50 (m, 2H), 3.73 (m, 2H), 2.87 (t, *J* = 6.9 Hz, 2H) ppm; HRMS (ESI/Q-TOF) *m/z*: [M + H]⁺ Calcd. for C₁₆H₁₉N₂S 271.1263; found 271.1265.

1-Benzyl-3-cyclohexylthiourea (29): Compound have been characterized in ref.^{8,9} The observed ¹H NMR spectrum was consistent with the previously reported data; Beige solid, m.p. 108–109 °C (water; ref.⁸ 89–90 °C); ¹H-NMR: (500 MHz, CDCl₃, ref.⁹) δ 7.34–7.30 (m, 5H), 6.16 (bs, 1H), 5.79 (bs, 1H), 4.62 (bs, 2H), 3.85 (bs, 1H), 1.95–1.93 (m, 2H), 1.65–1.56 (m, 3H), 1.34–1.13 (m, 5H) ppm.

1-Benzyl-3-(*tert*-butyl)thiourea (30): Compound have been characterized in ref.¹⁰ The observed ¹H NMR spectrum was consistent with the previously reported data; White solid, m.p. 93–94 °C (water; ref.¹⁰ 94 °C); ¹H-NMR: (500 MHz, CDCl₃, mixture of E/Z isomers, ref.¹⁰) δ 7.38–7.30 (m, 5H), 6.01 (bs, 1H), 5.86 (bs, 1H), 4.78–4.77 (m, 2H), 1.39 (s, 9H) ppm.

(S)-1-(2,6-Dimethylphenyl)-3-(1-phenylethyl)thiourea (31): White solid, m.p. 117–118 °C (water); ¹H-NMR: (500 MHz, CDCl₃, mixture of E/Z isomers) δ 7.56 (bs, 1H), 7.30–7.11 (m, 8H), 5.75 (bs, 1H), 5.48 (bs, 1H), 2.24 ((two signals: 2.30 (s), 2.17 (s)) 3H), 1.48 ((two signals: 1.48 (s), 1.47 (s)) 3H) ppm.

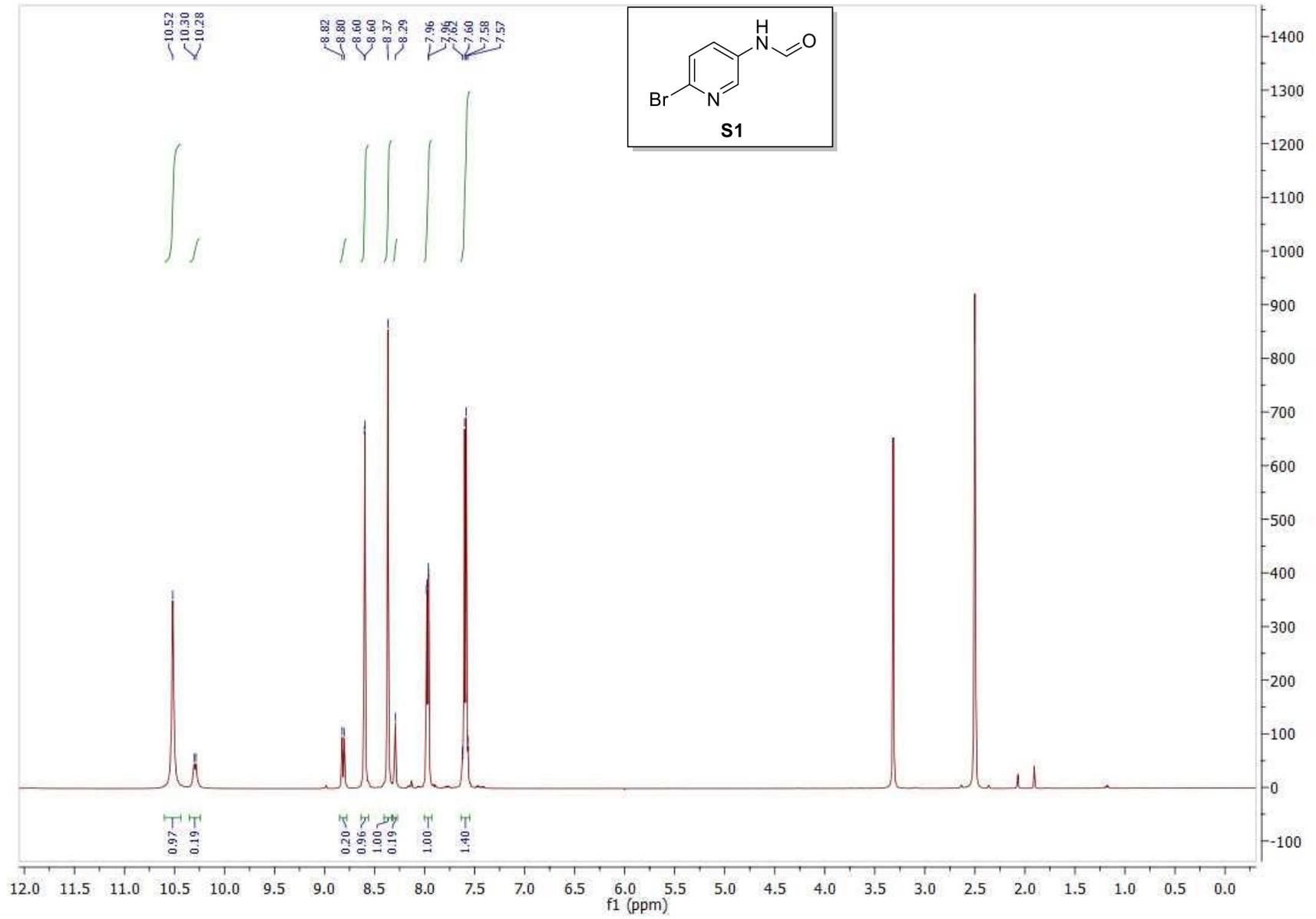
N-(2,6-Dimethylphenyl)morpholine-4-carbothioamide (32): Compound have been characterized in ref.¹¹ The observed ¹H NMR spectrum was consistent with the previously reported data (although the solvent was DMSO-*d*₆); White solid, m.p. 163–164 °C (water; ref.¹¹ 138–140 °C); ¹H-NMR: (500 MHz, CDCl₃, ref.¹¹) δ 7.15–7.08 (m, 3H), 6.84 (bs, 1H), 3.84 (t, *J* = 4.4 Hz, 2H), 3.73 (t, *J* = 5.1 Hz, 2H), 2.25 (s, 6H) ppm.

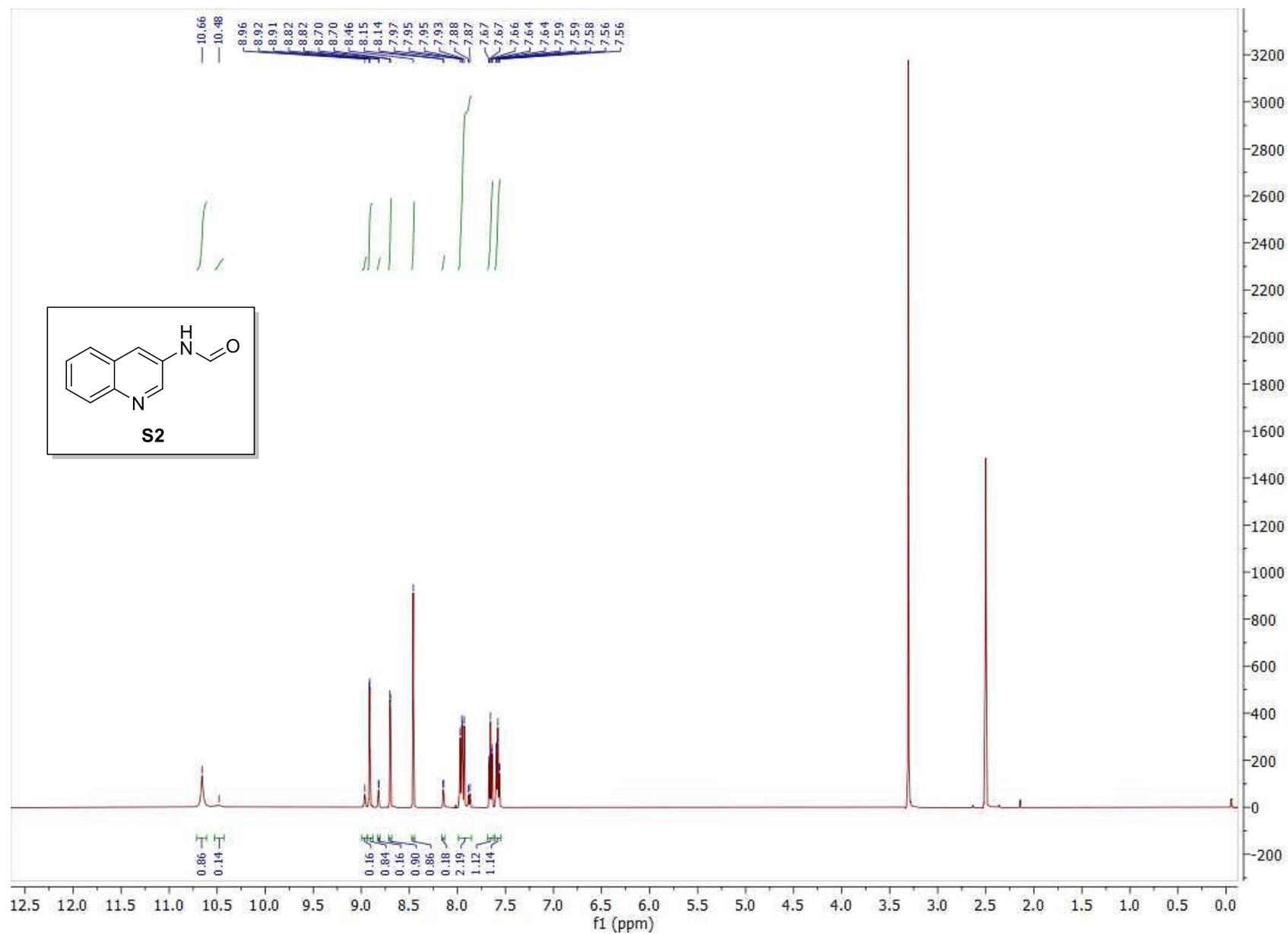
1-(2,6-Dimethylphenyl)-3-phenylthiourea (33): Compound have been characterized in ref.^{12,13} The observed ¹H NMR spectrum was consistent with the previously reported data; White solid, m.p. 170–171 °C (water; ref.¹² 203–205 °C); ¹H-NMR: (500 MHz, DMSO-*d*₆, ref.¹³) δ 9.87 (bs, 1H), 8.98 (bs, 1H), 7.52–7.09 (m, 8H), 2.22 (s, 6H) ppm.

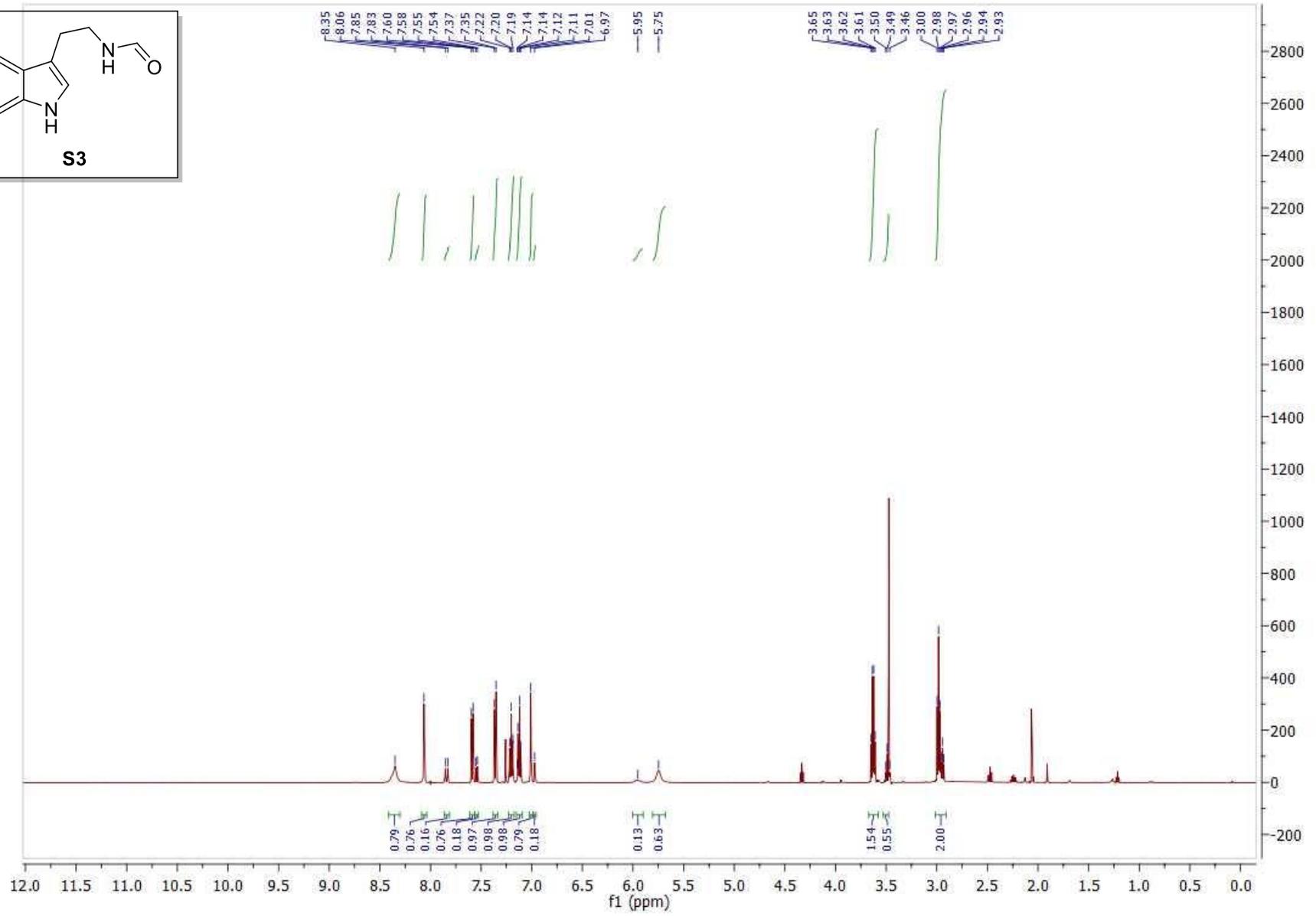
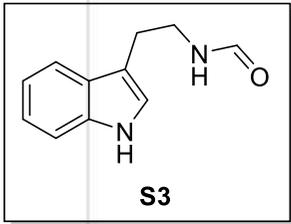
1-(2,6-Dimethylphenyl)-3-(*p*-tolyl)thiourea (34): White solid, m.p. 156–157 °C (water); ¹H-NMR: (500 MHz, DMSO-*d*₆) δ 9.75 (bs, 1H), 8.84 (bs, 1H), 7.34–7.08 (m, 7H), 2.28 (s, 3H), 2.21 (s, 6H) ppm; ¹³C-NMR: (125 MHz, DMSO-*d*₆) δ 180.2, 137.2 (bs), 136.8, 136.3, 133.7, 129.2 (bs), 128.8, 128.1, 127.6 (bs), 126.7 (bs), 123.9, 123.6 (bs), 20.5, 18.1 ppm; HRMS (ESI/Q-TOF) *m/z*: [M + H]⁺ Calcd. for C₁₆H₁₉N₂S 271.1263; found 217.1268.

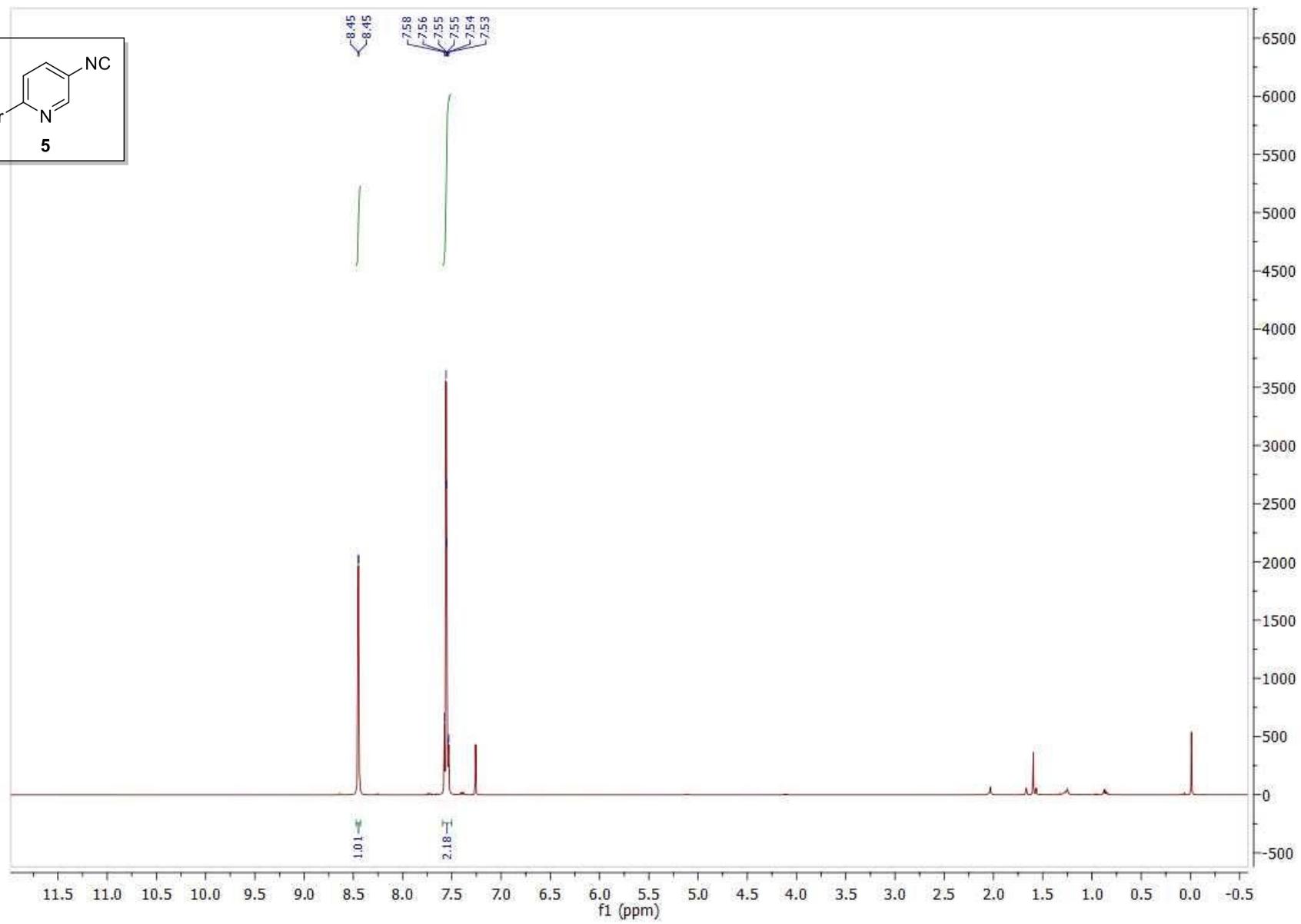
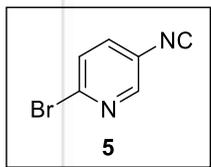
1-(4-Chlorophenyl)-3-(2,6-dimethylphenyl)thiourea (35): Off white solid 136–137 °C (water); ¹H-NMR: (500 MHz, DMSO-*d*₆) δ 9.93 (bs, 1H), 9.02 (bs, 1H), 7.55–7.27 (m, 4H), 7.09–7.06 (m, 3H), 2.20 (s, 6H) ppm; ¹³C-NMR: (125 MHz, DMSO-*d*₆) δ 180.3, 138.3, 136.3, 128.5 (bs), 128.3, 127.7 (bs), 126.8 (bs), 125.3, 124.7 (bs), 18.0 ppm; HRMS (ESI/Q-TOF) *m/z*: [M + H]⁺ Calcd. for C₁₅H₁₆ClN₂S 291.0717; found 291.0725.

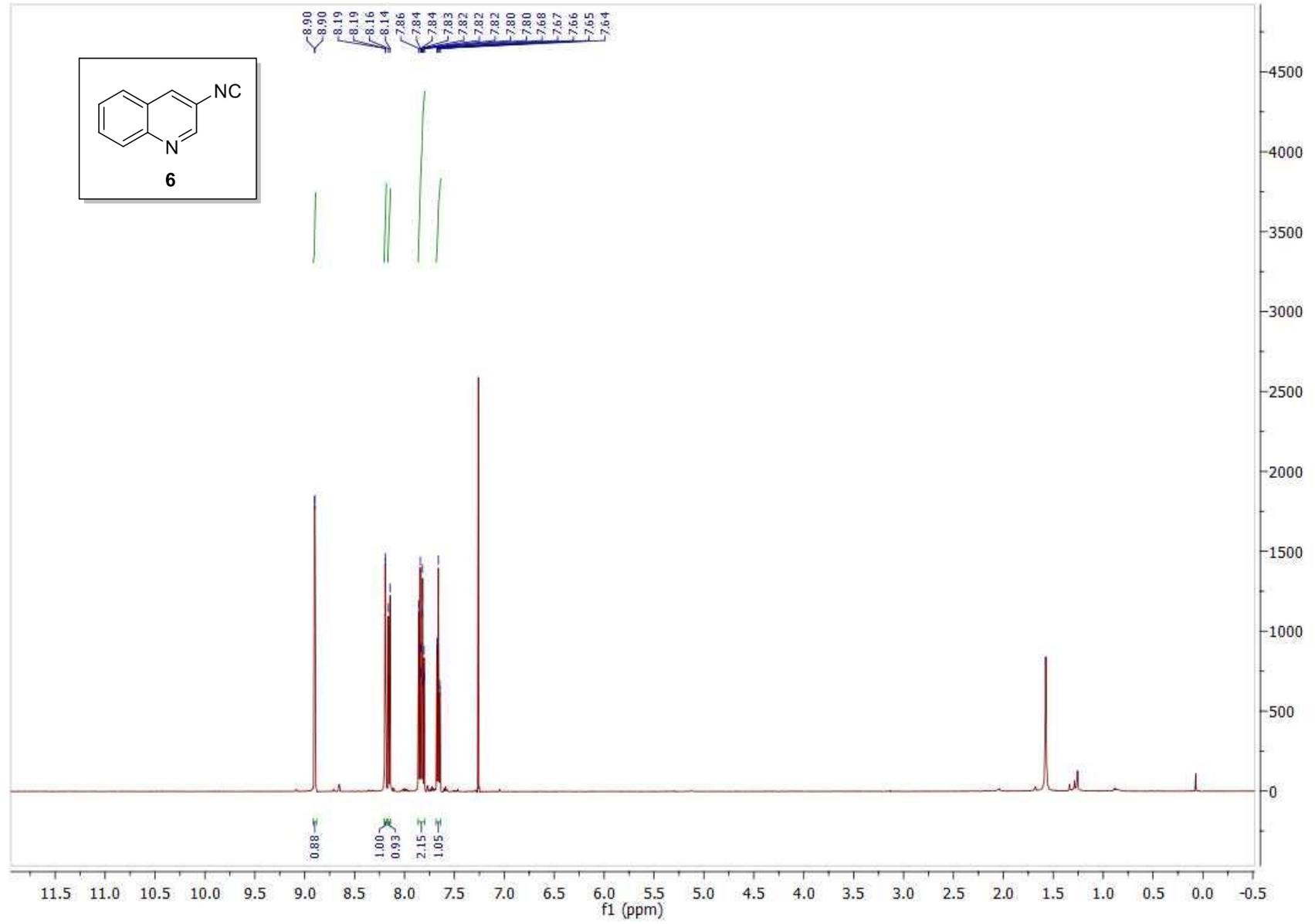
1-(4-Bromophenyl)-3-(2,6-dimethylphenyl)thiourea (36): Off white solid 128–129 °C (water); ¹H-NMR: (500 MHz, DMSO-*d*₆) δ 9.91 (bs, 1H), 9.04 (bs, 1H), 7.52–7.45 (m, 5H), 7.09 (m, 3H), 2.21 (s, 3H) ppm.

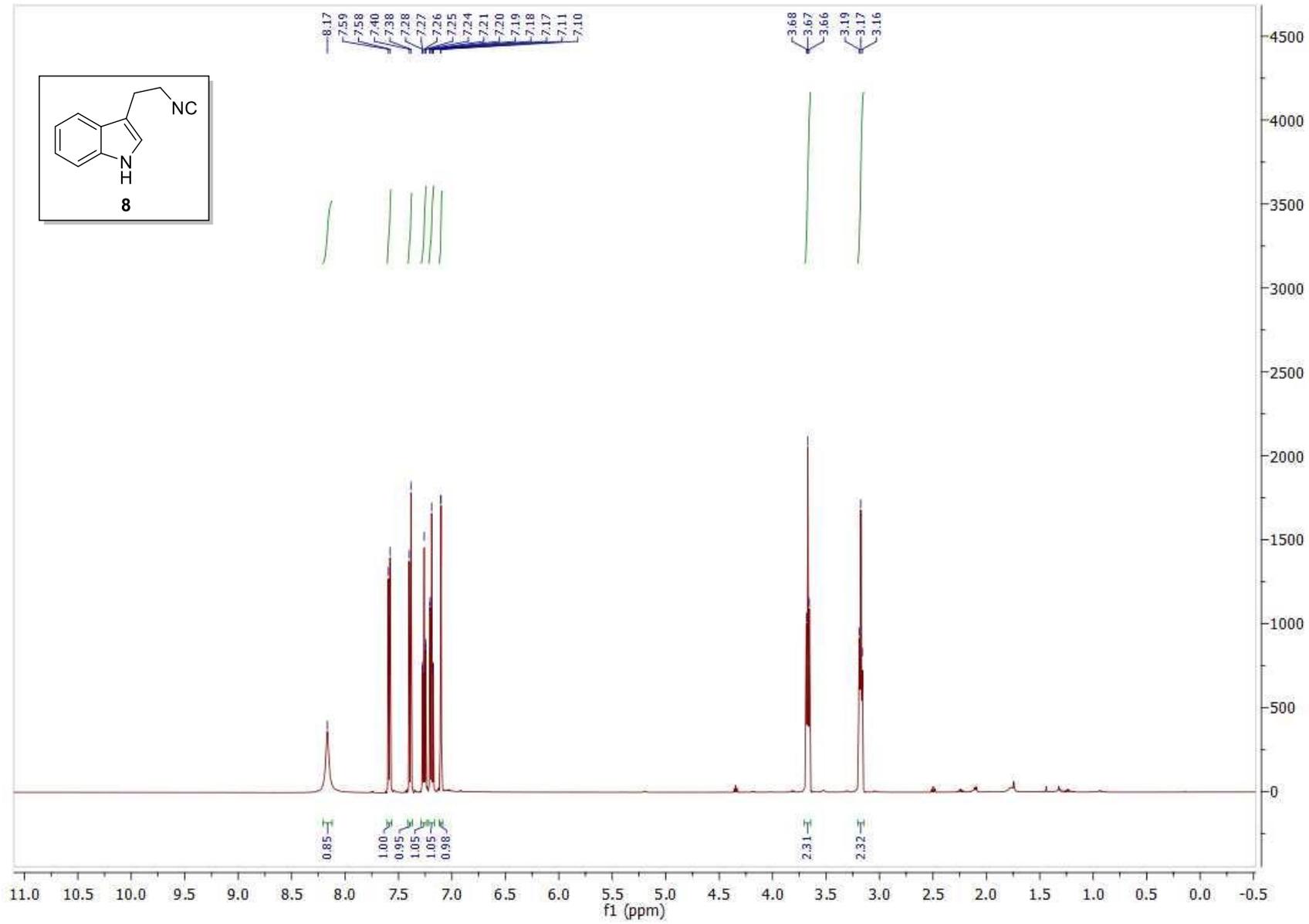
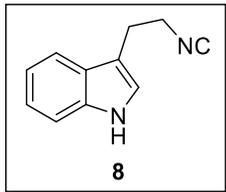


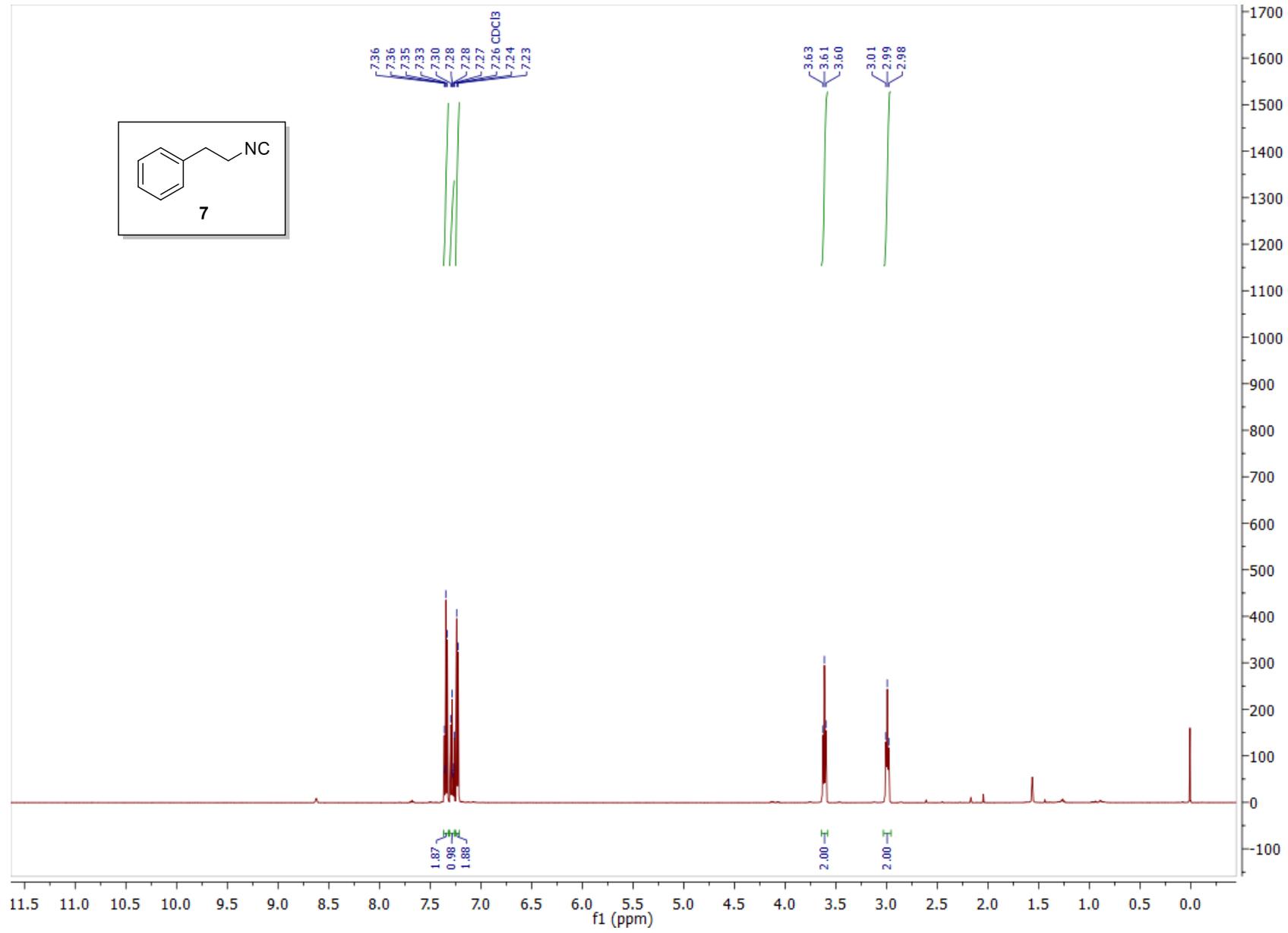
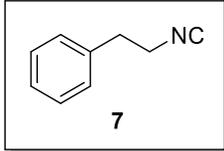


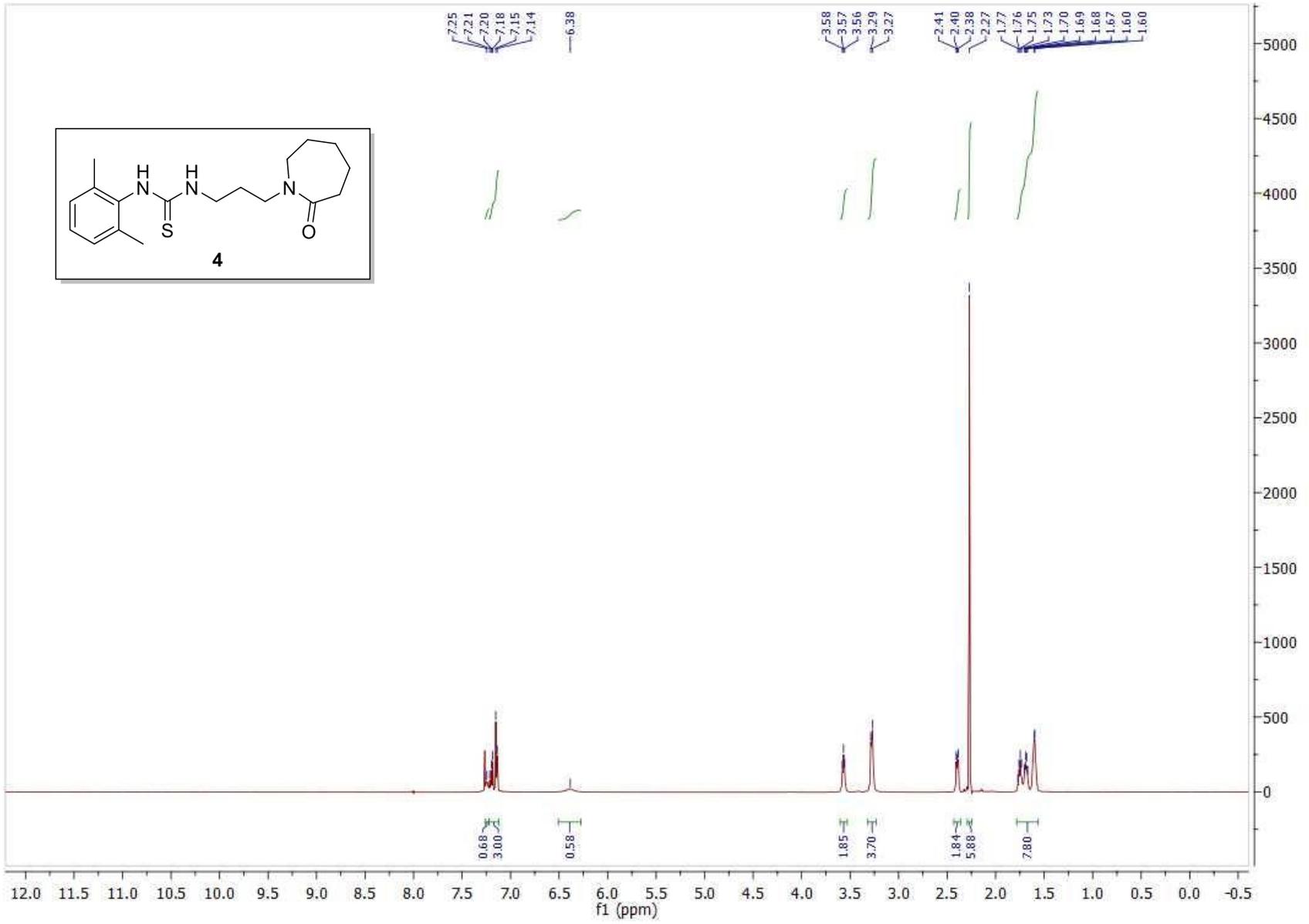
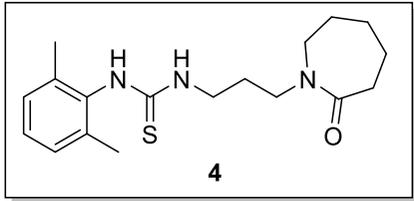


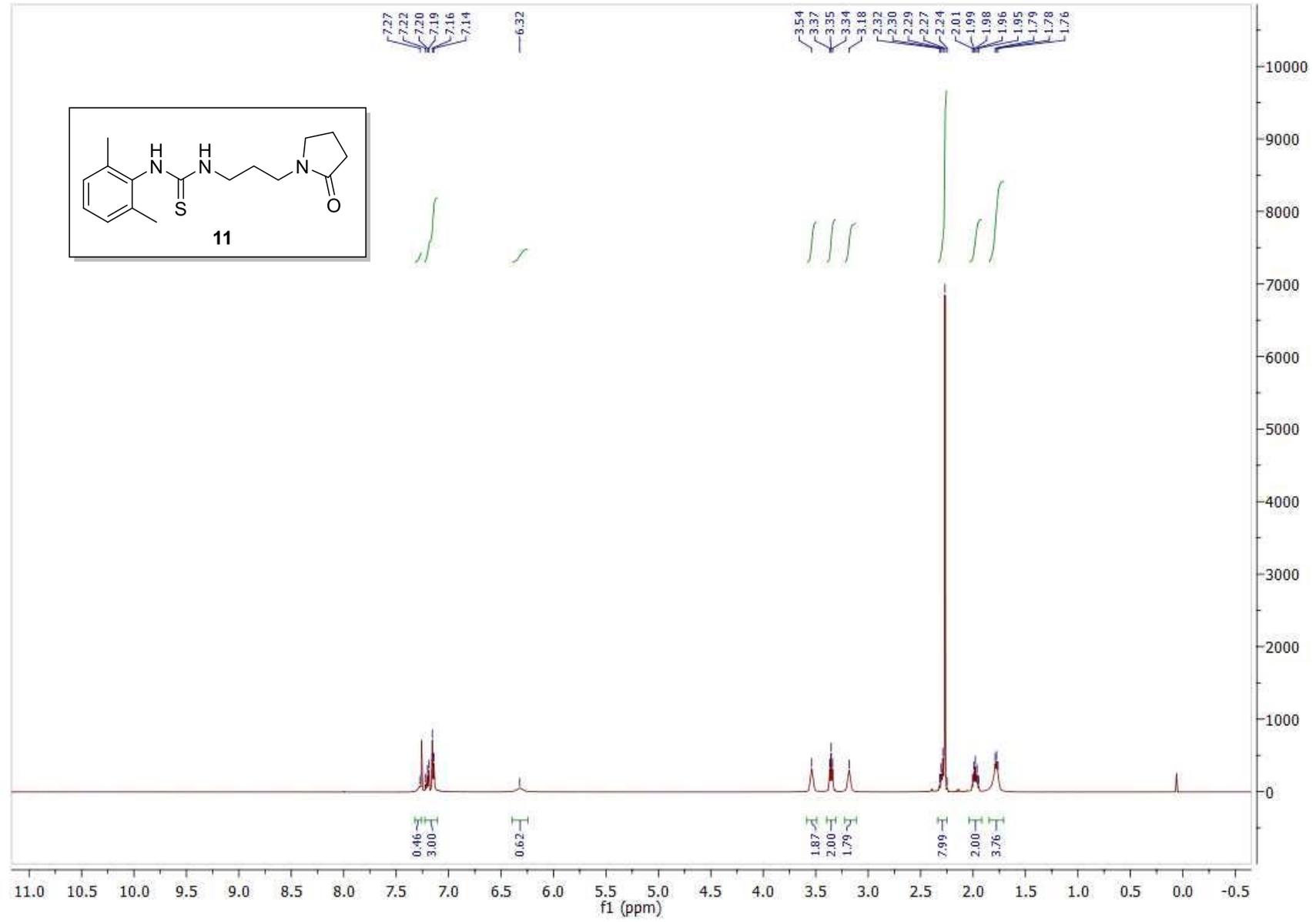


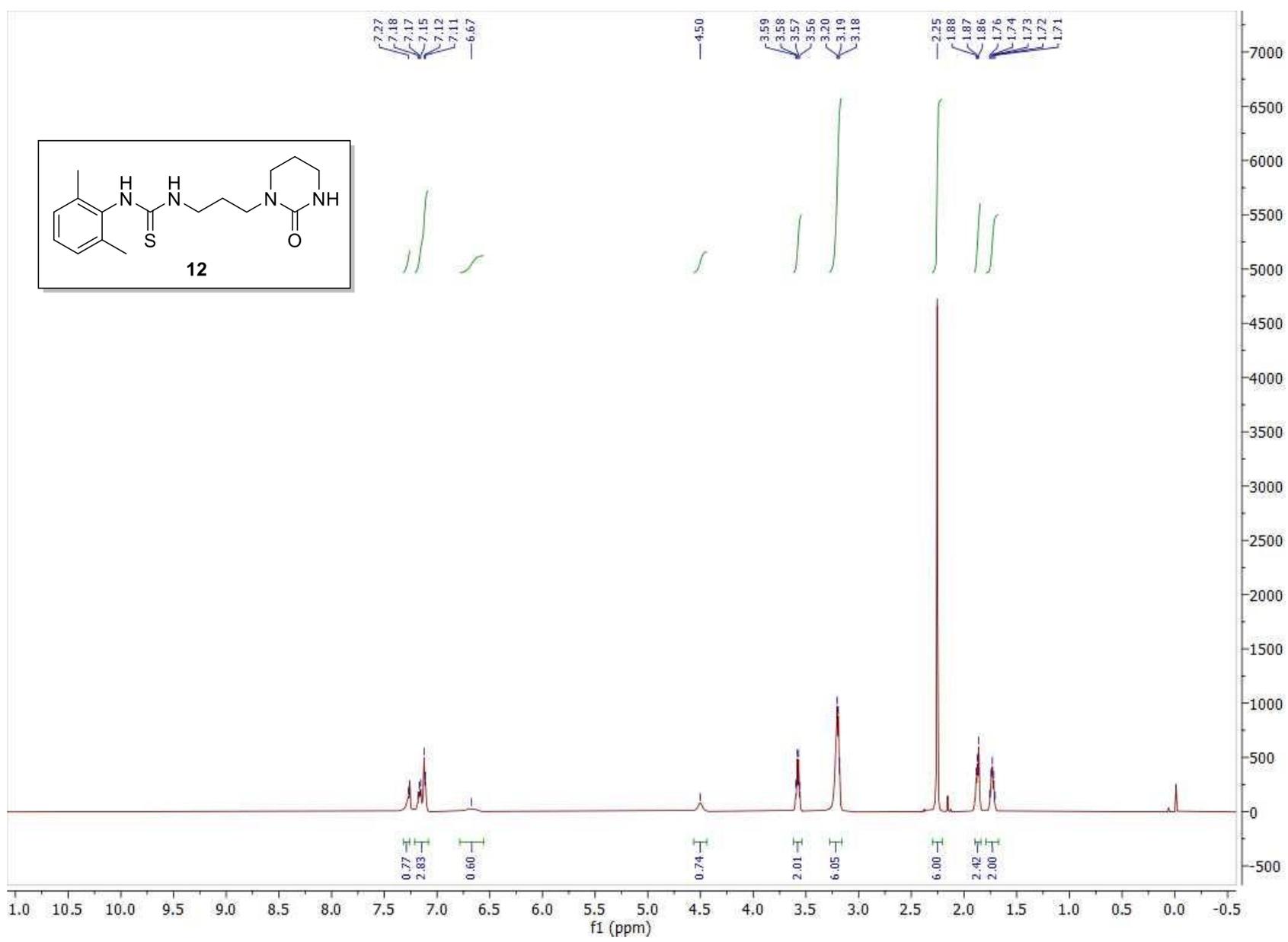


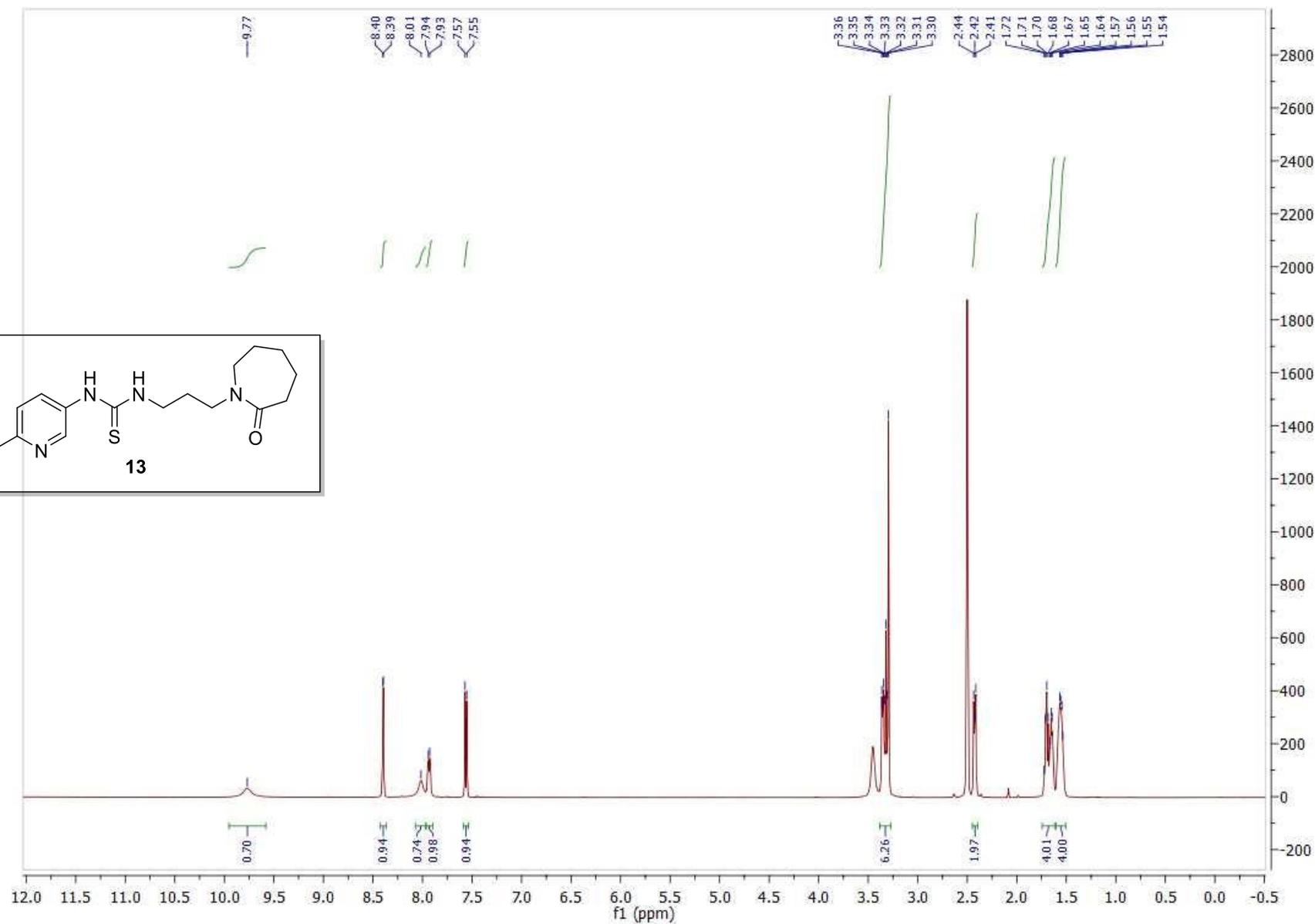
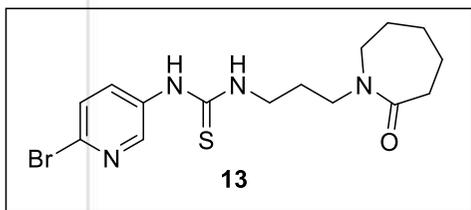


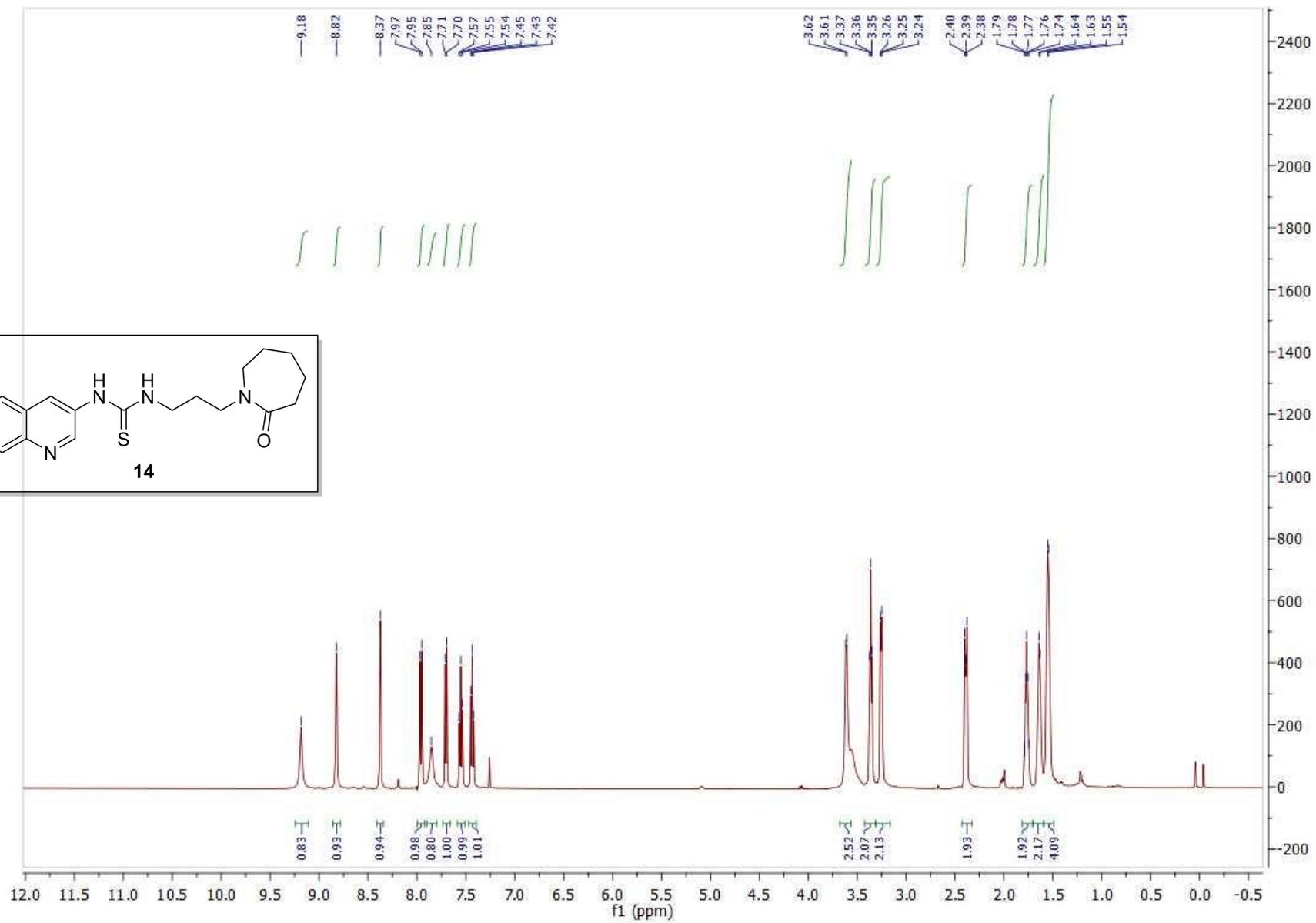
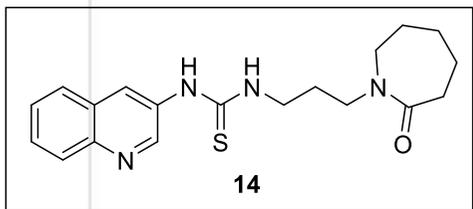


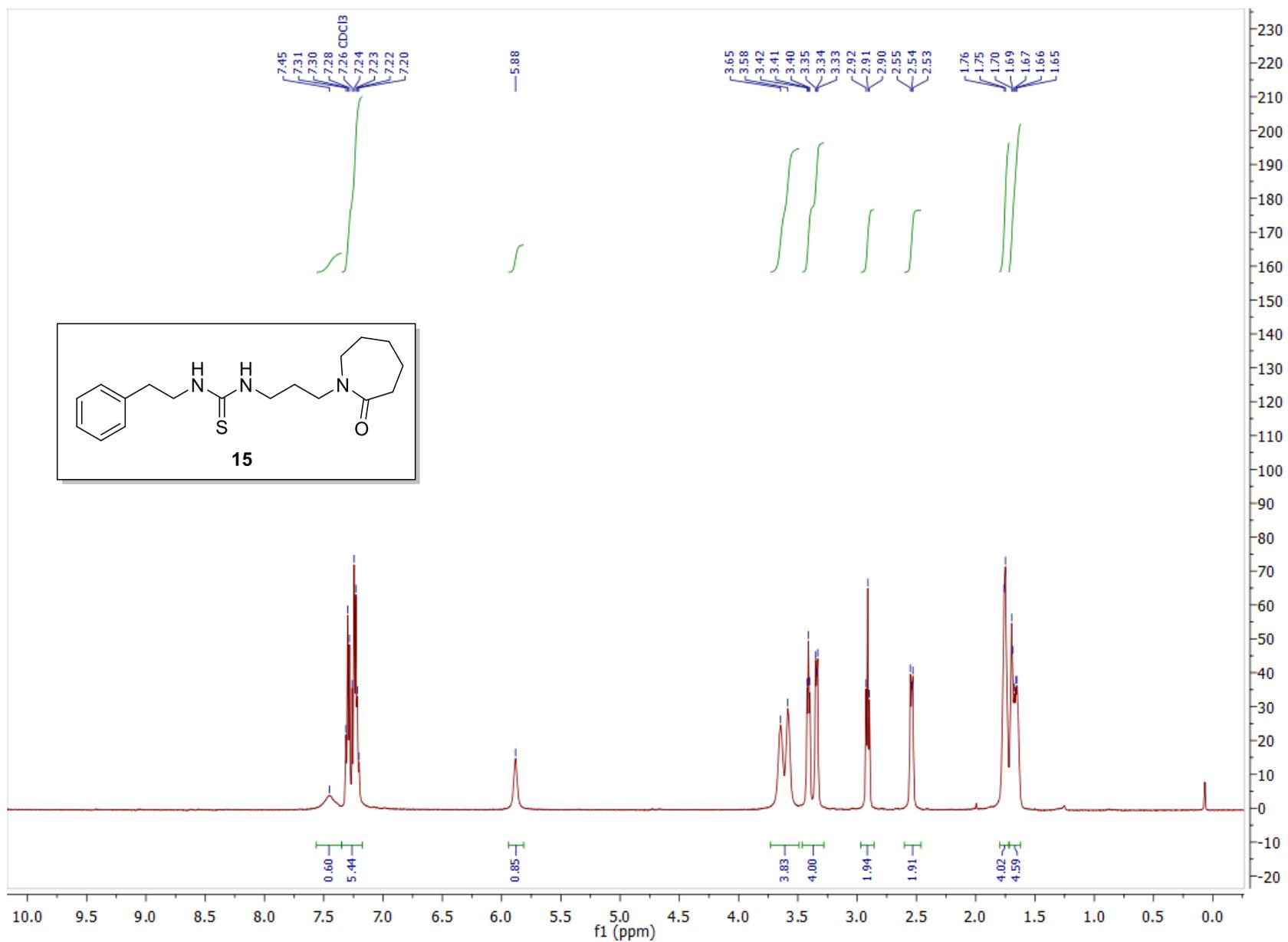


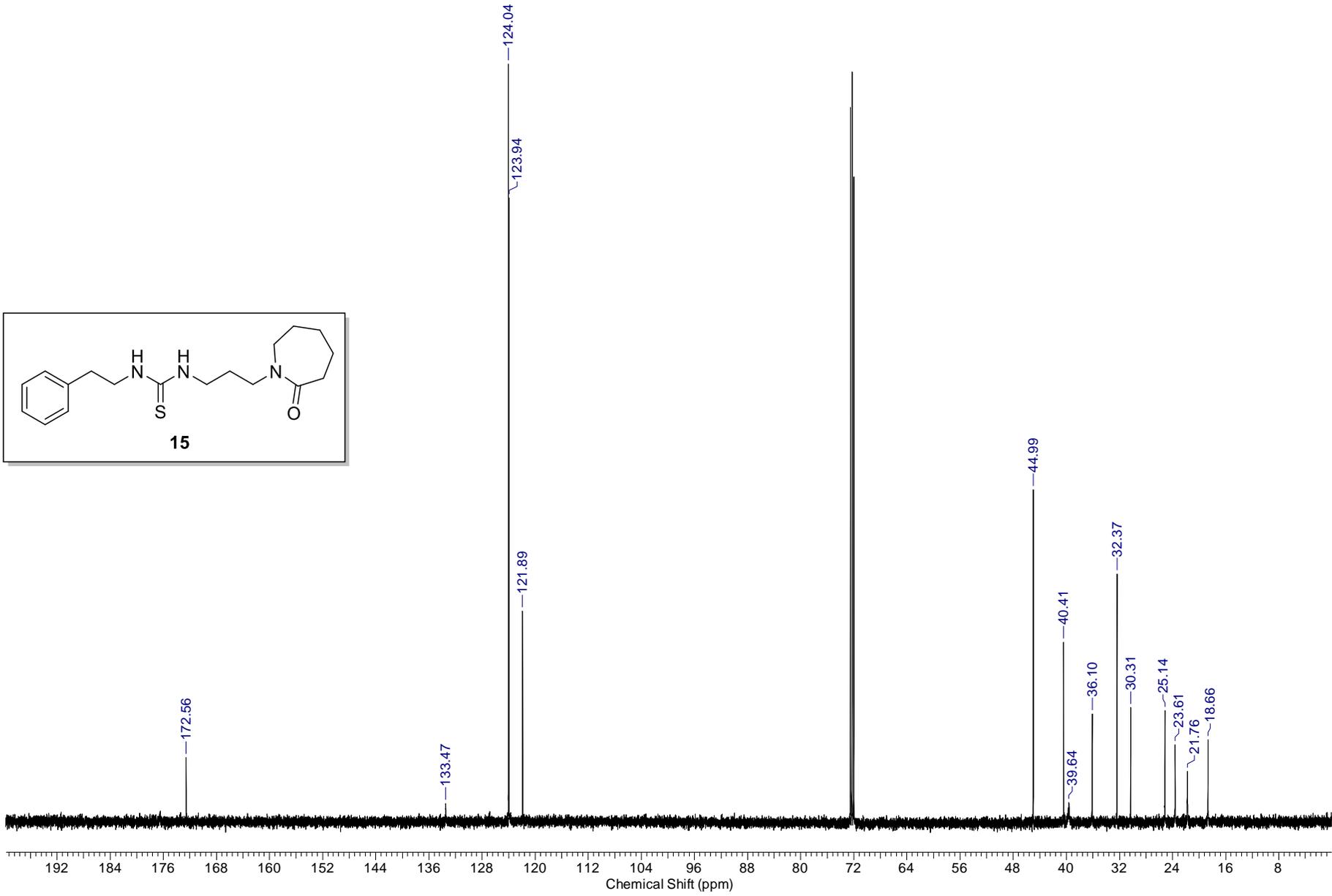
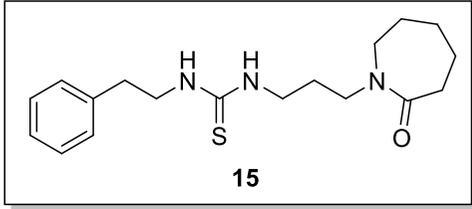


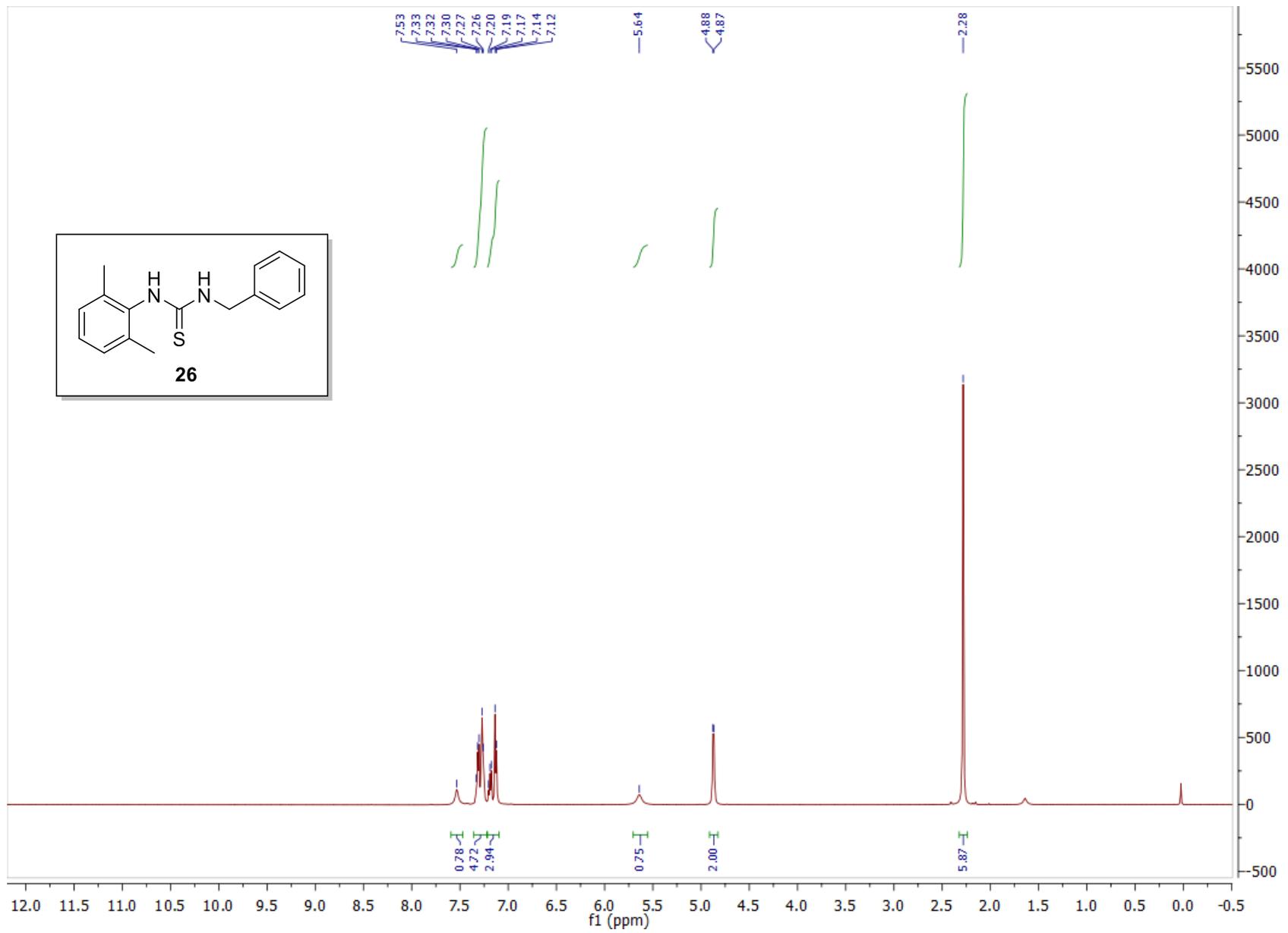
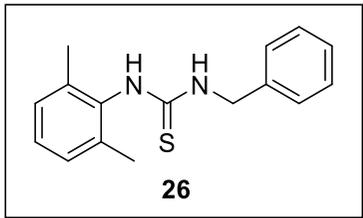


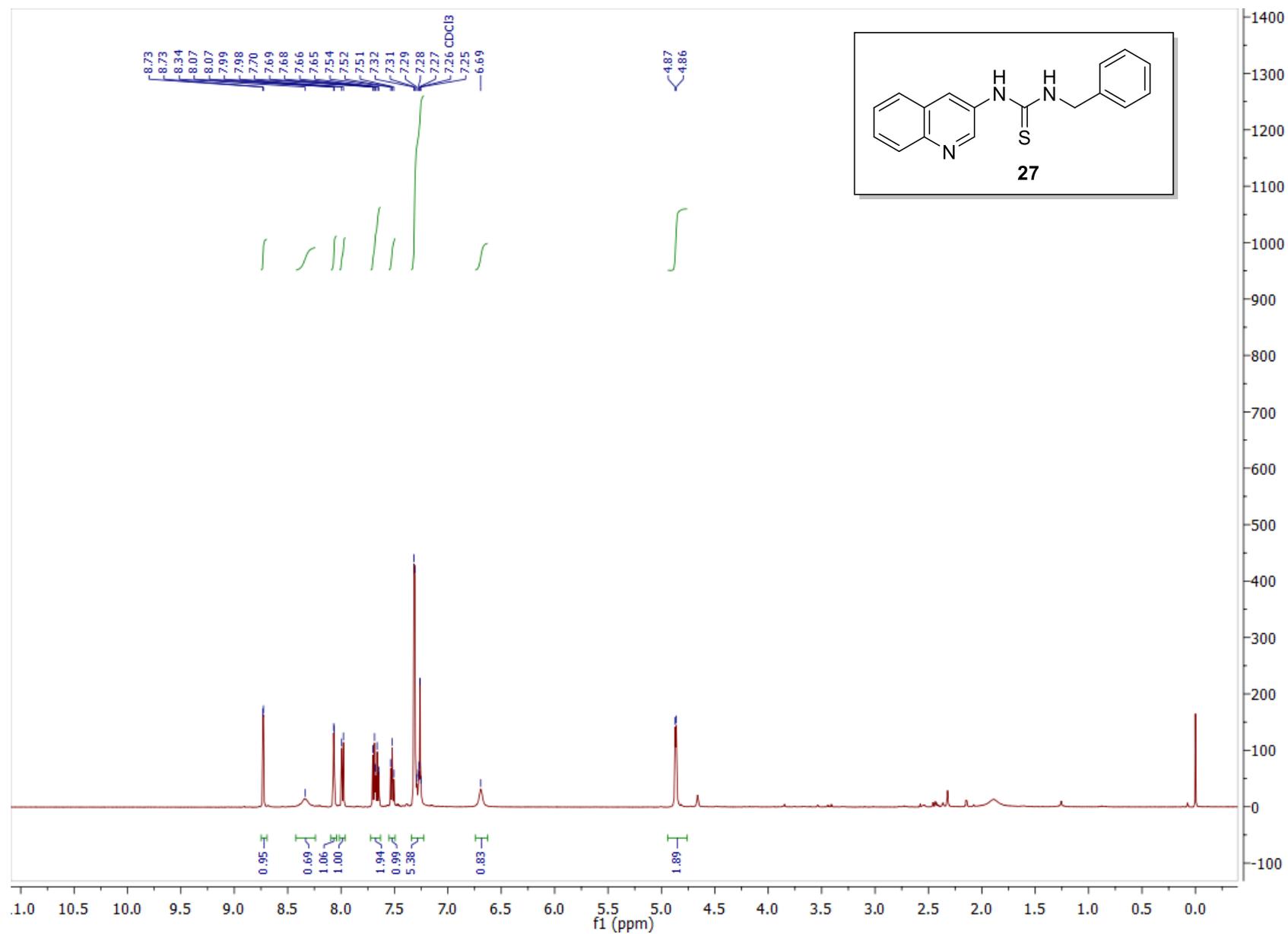


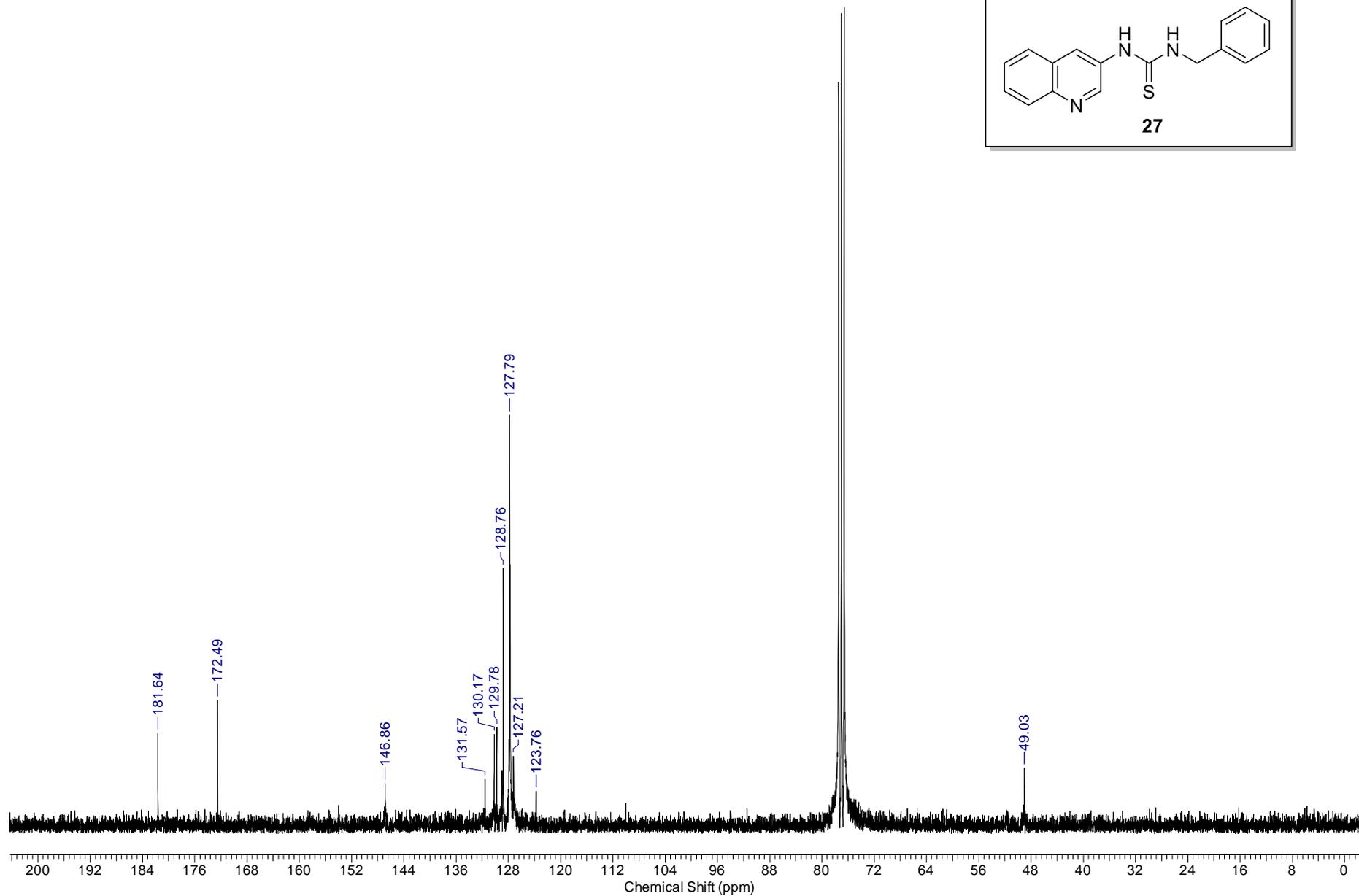
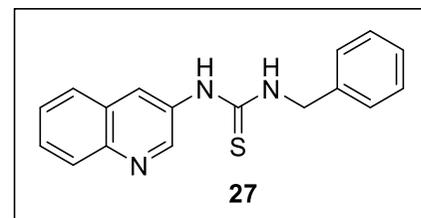


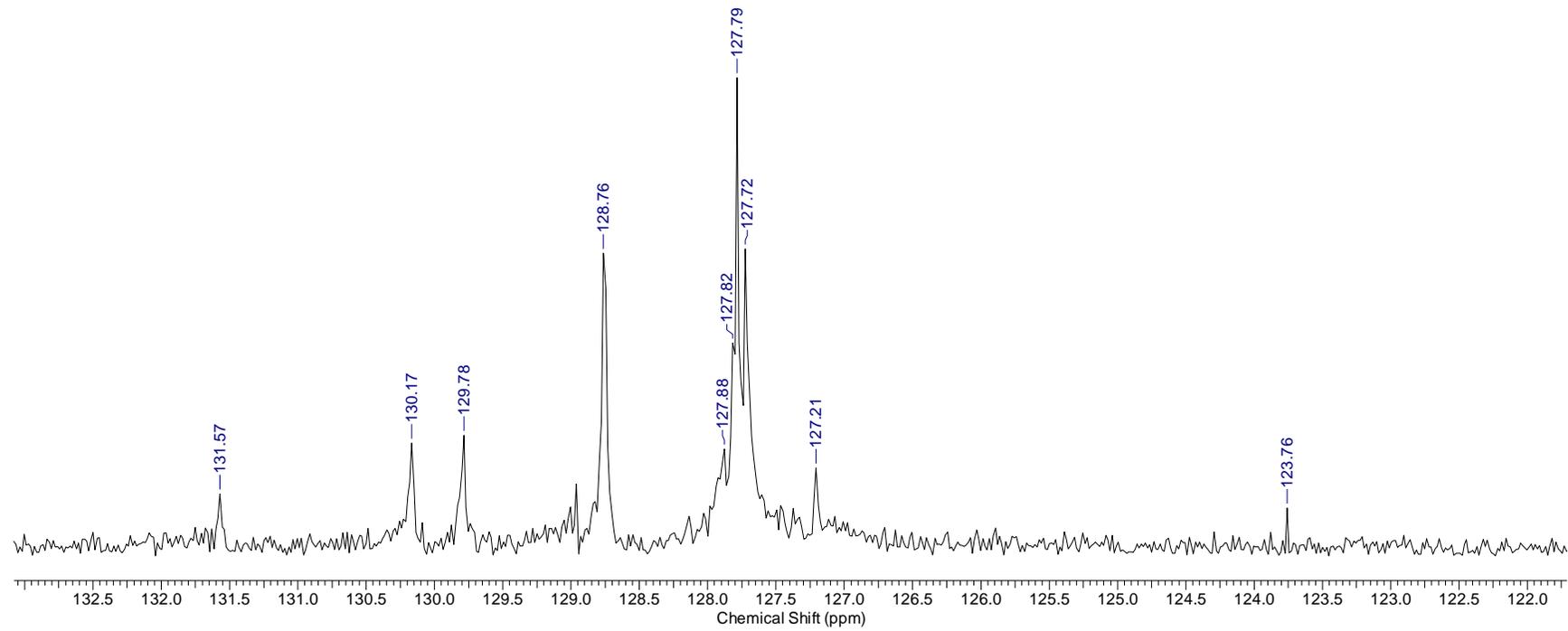
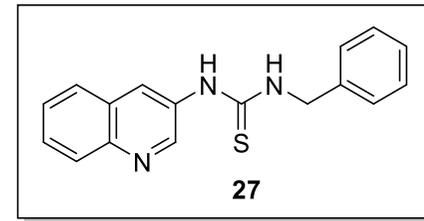


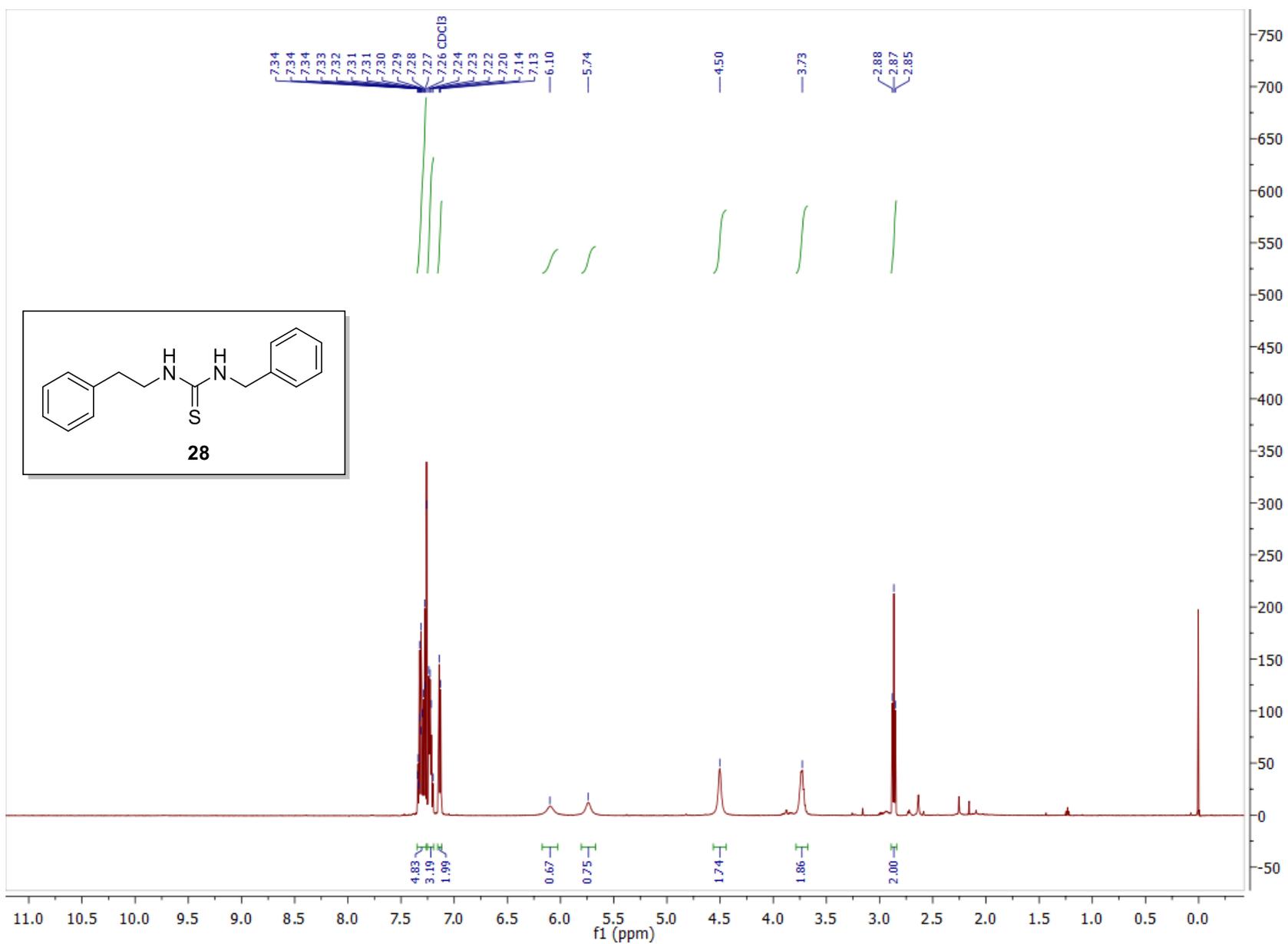


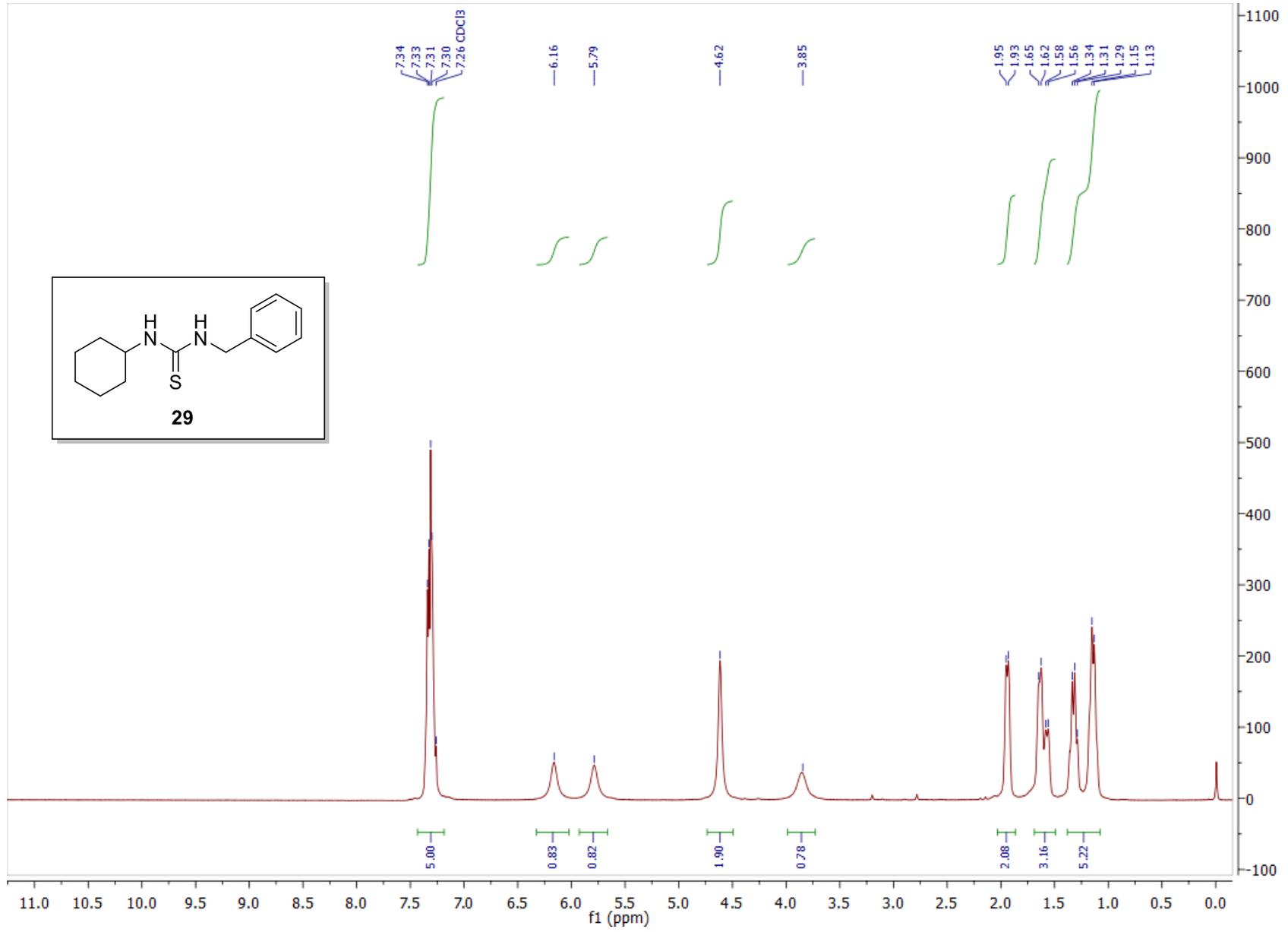
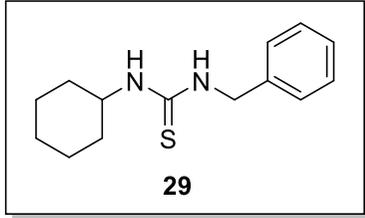


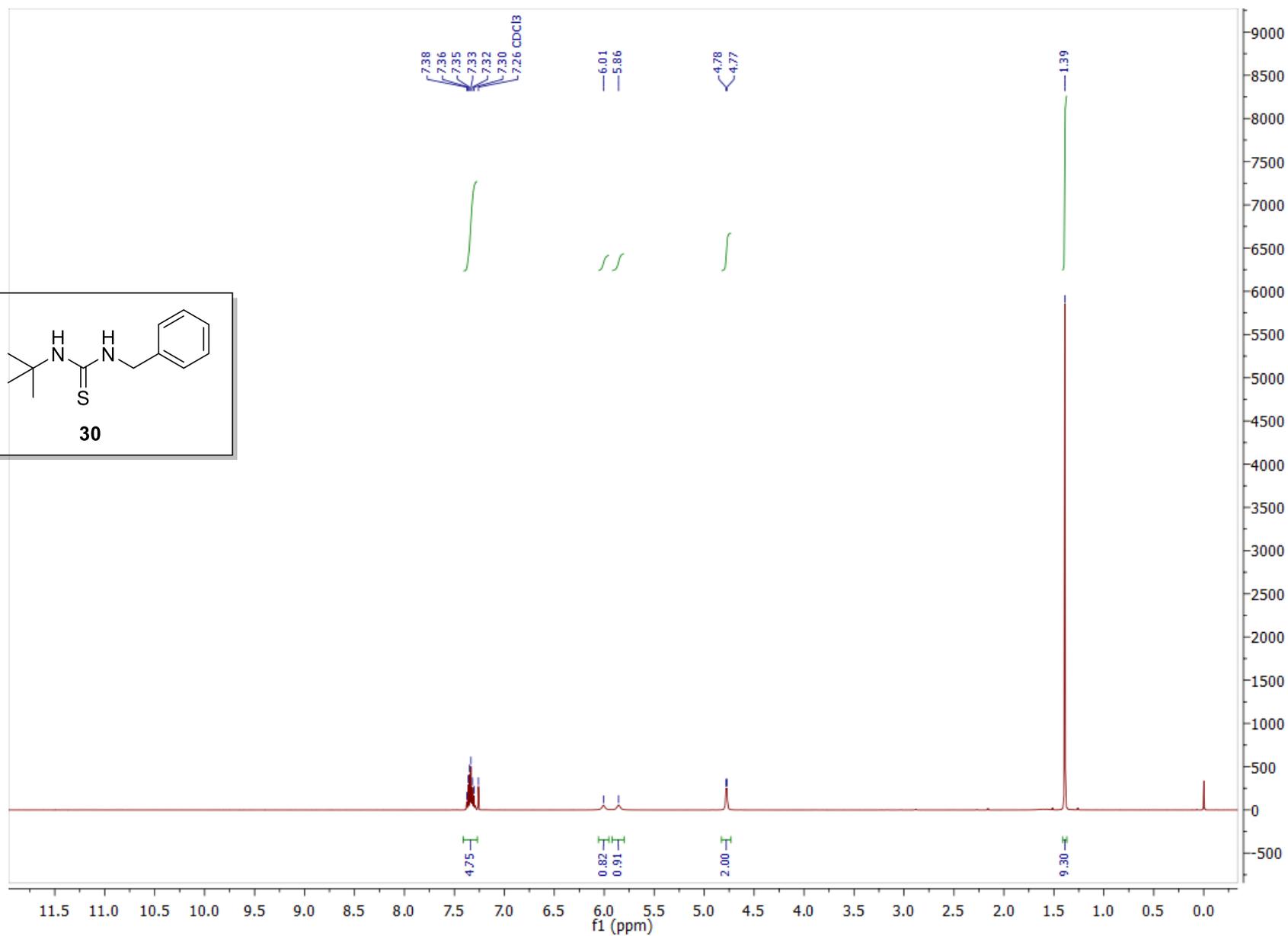
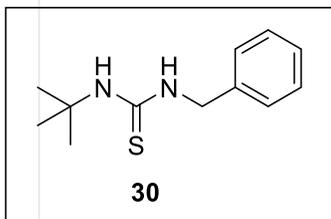


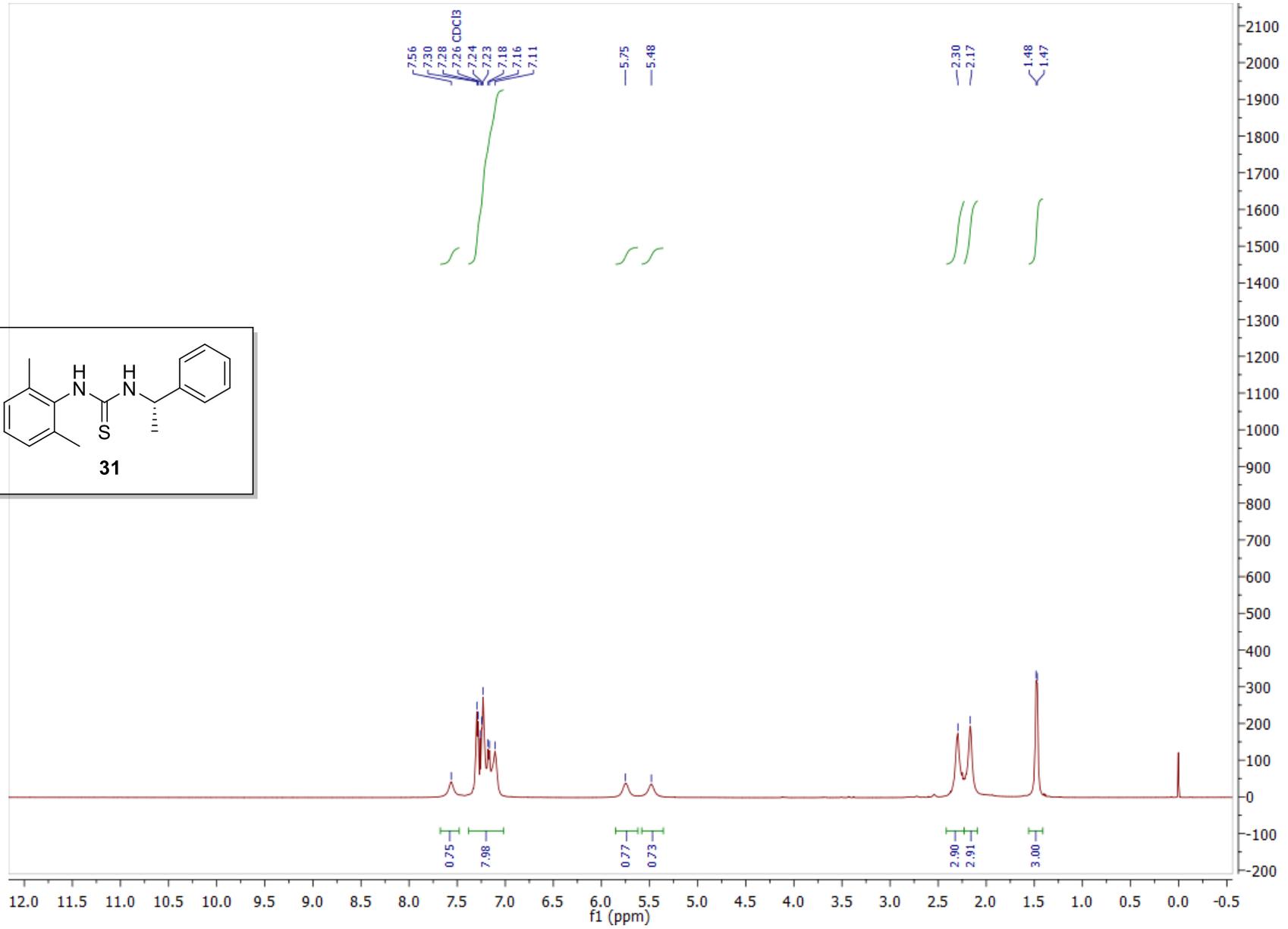
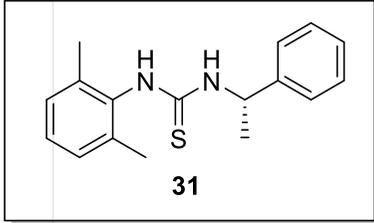


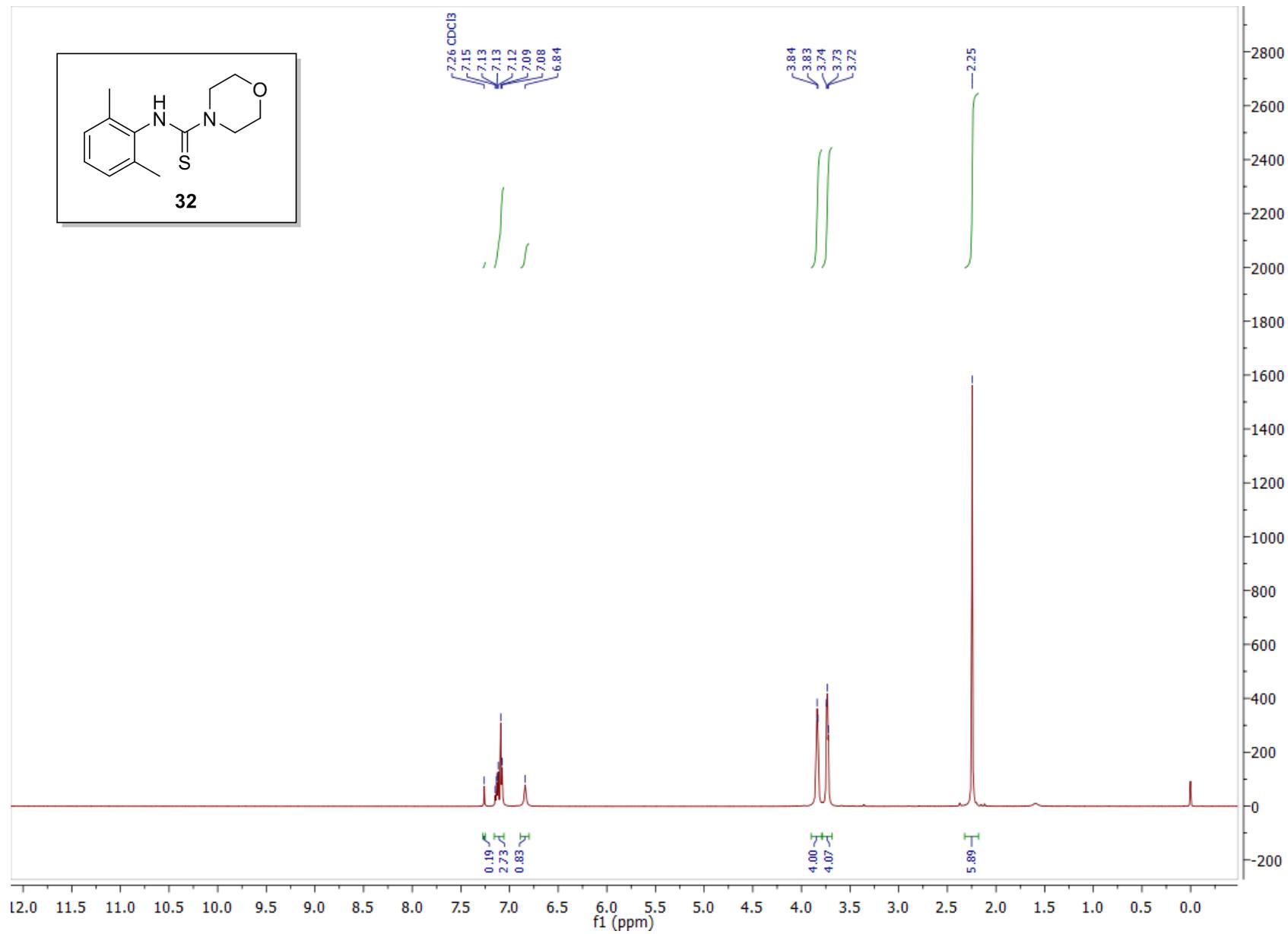
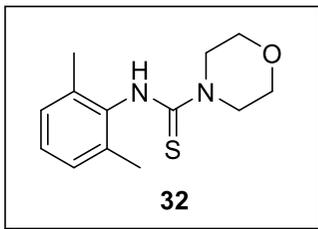


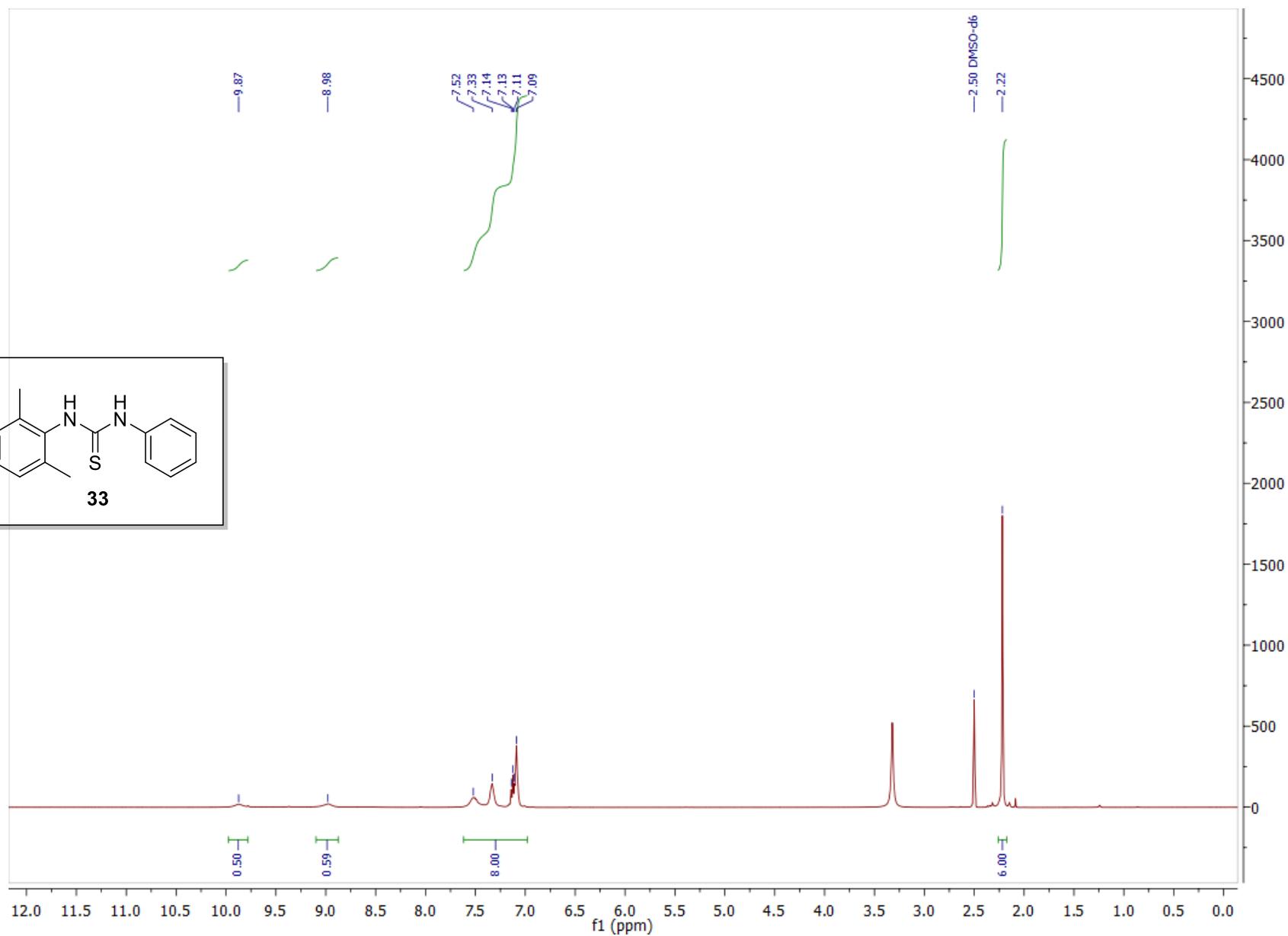
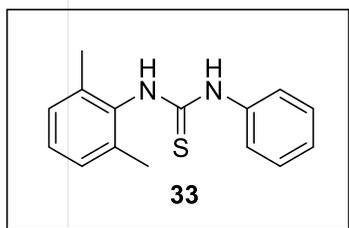


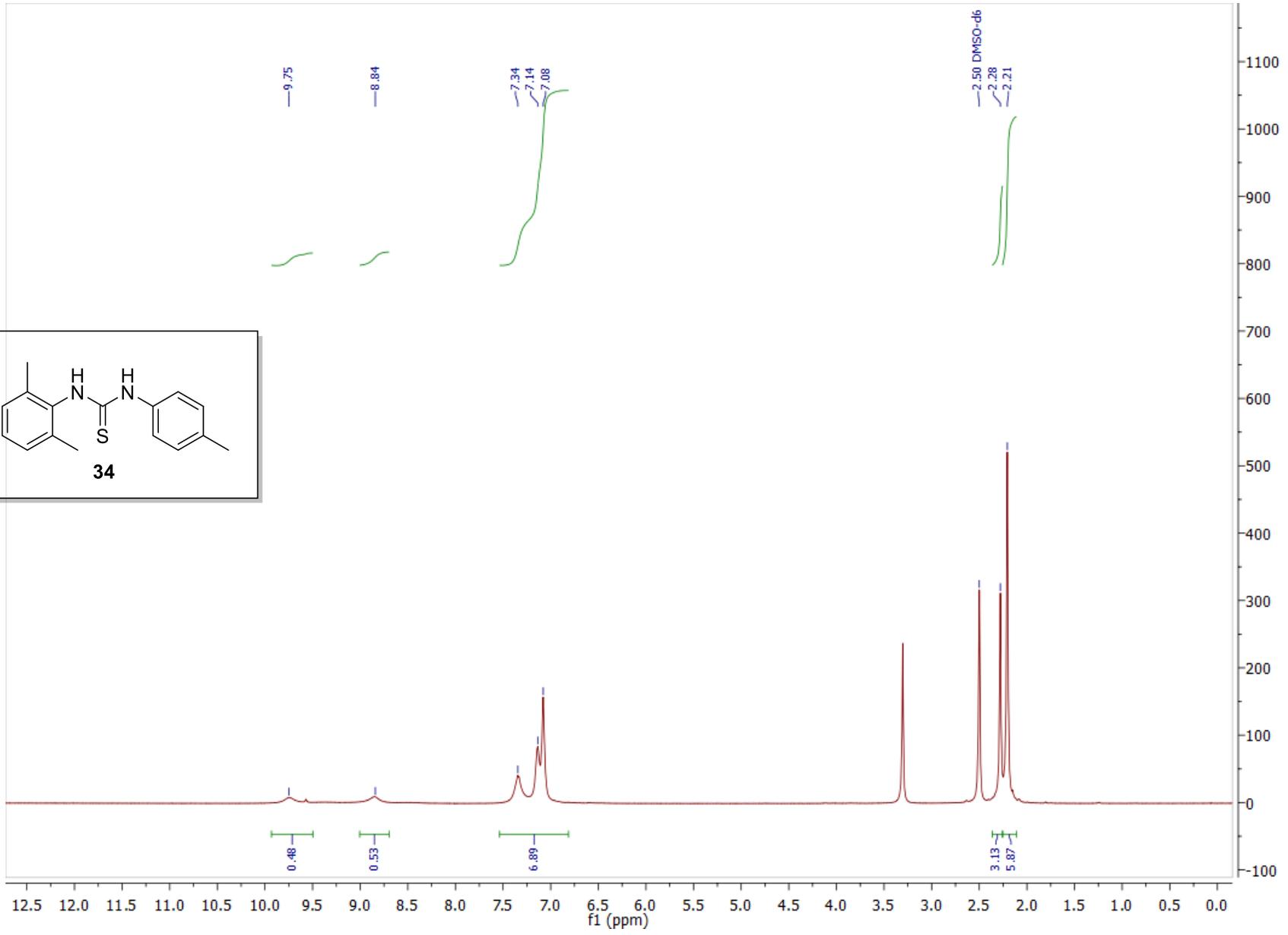
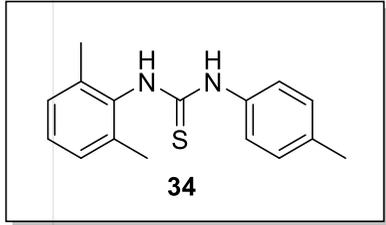


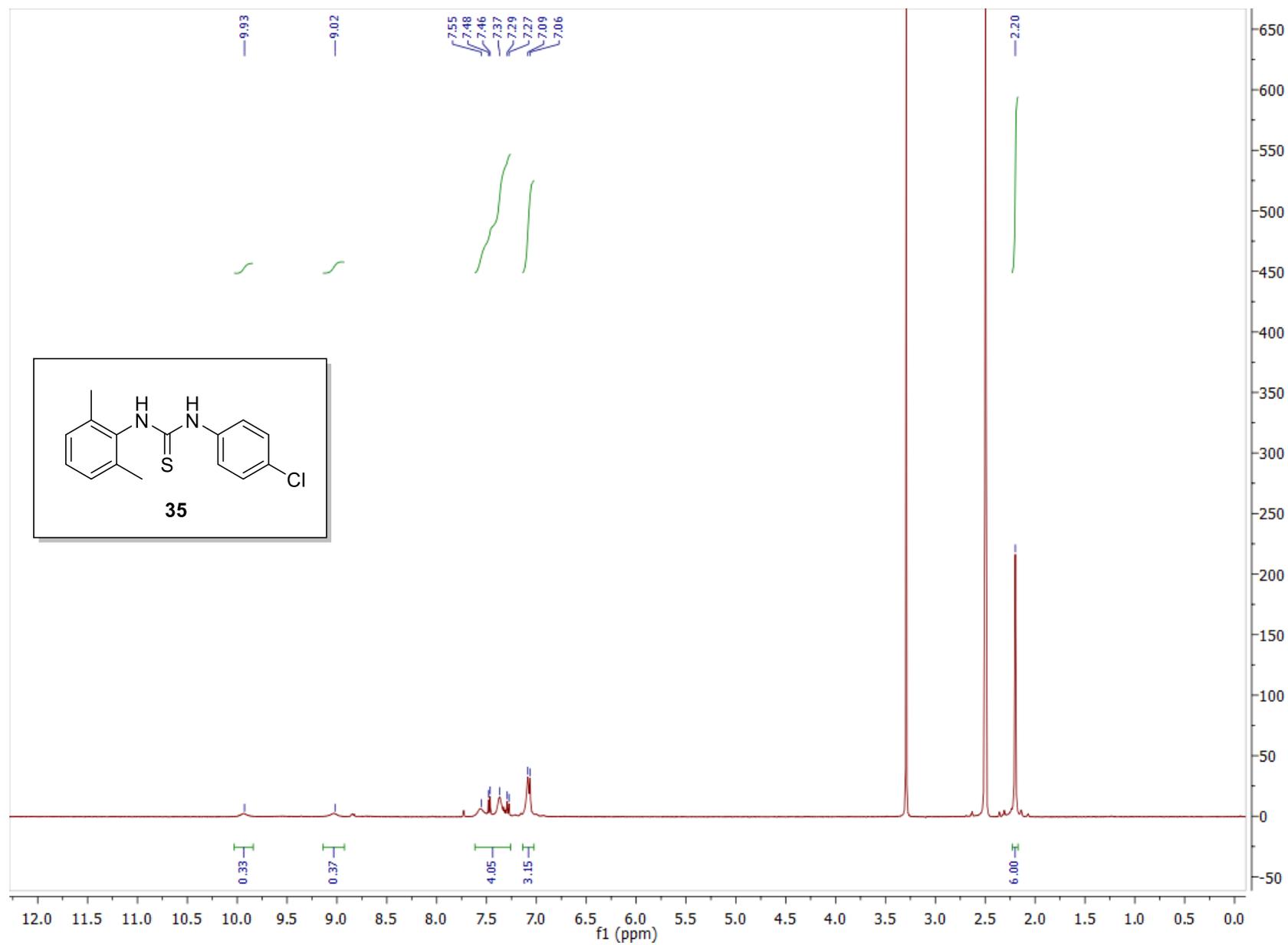


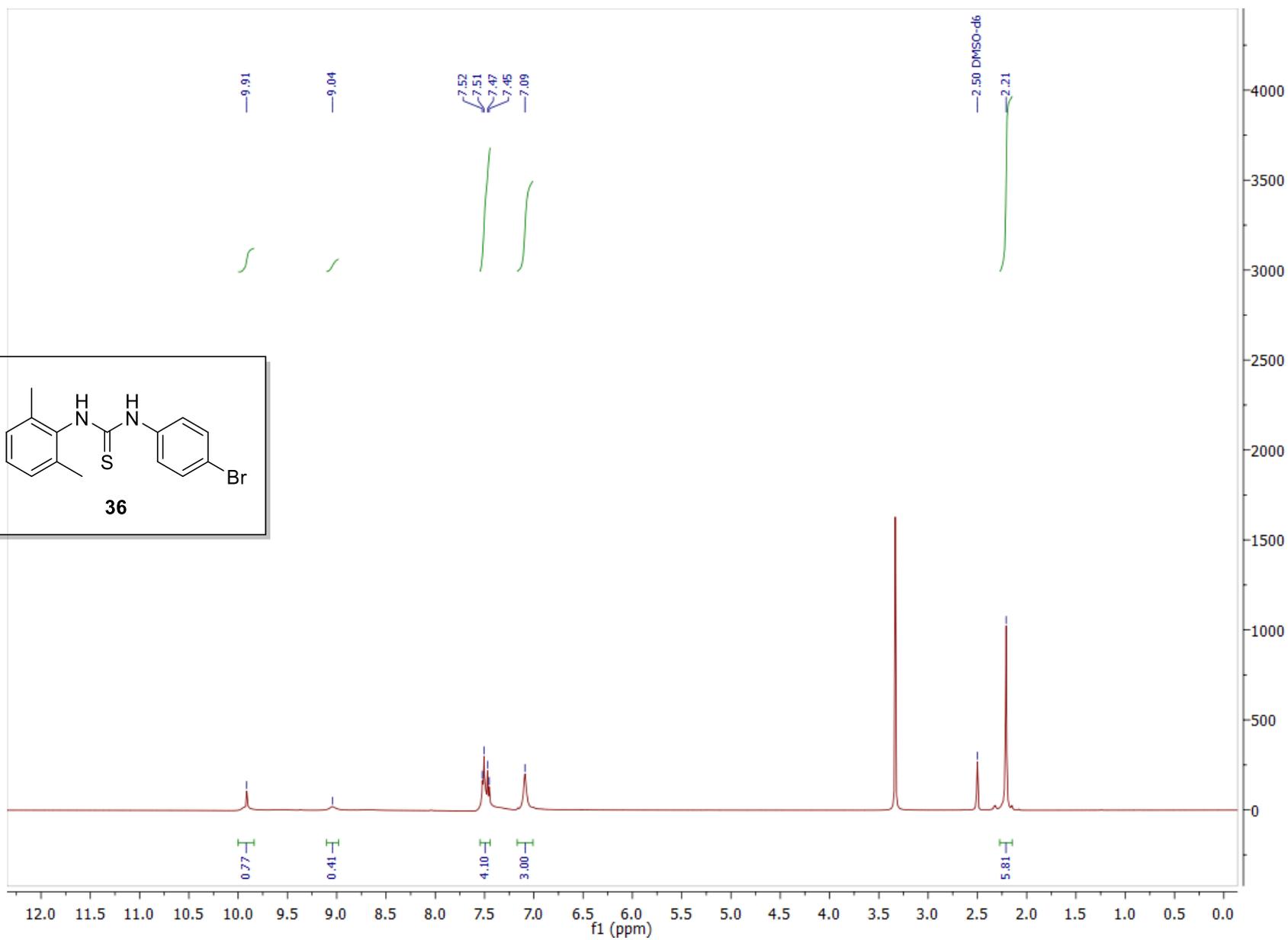
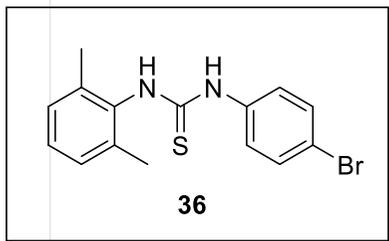












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