Synthesis in water and antimicrobial activity of 5-trichloromethyl-4,5-dihydroisoxazoles

Alex F. C. Flores[a], *Luciana A. Piovesan*[a], *Alynne A. Souto*[a], *Marano A. Pereira*[b], *Marcos A. P. Martins*[a], *Tatiane L. Balliano*[b], *Givanildo S. da Silva*[b]

[a]NUQUIMHE - Departamento de Química, Universidade Federal de Santa Maria
97105 900, Santa Maria, RS, Brazil

[b]LabCriMM Instituto de Química e Biotecnologia - Universidade Federal de Alagoas
57072-970, Maceió, AL, Brazil

Supplementary Information

^{1}H and ^{13}C NMR data and spectra for 5-trichloromethyl-5-hydroxy-4,5-dihydroisoxazoles (**2**) and 1H and 13C NMR data 5-trichloromethylisoxazoles (**3**) are presented. The ^{1}H and ^{13}C spectra were recorded at 298 K on a Bruker DPX 400 spectrometer (^{1}H at 400.13 MHz, ^{13}C at 100.63 MHz) with a digital resolution of ± 0.01 ppm. All chemical shifts are expressed in ppm, and ^{1}H and ^{13}C are reported with respect to internal TMS. 0.1 M $CDCl_3$ solutions were used. Also show the X-ray diffraction data for 5-trichloromethyl-5-hydroxy-3-propyl-4,5-dihydroisoxazole (**2d**) and 5-trichloromethyl-5-hydroxy-3,4-hexamethylene-4,5-dihydroisoxazole (**2o**). Biological assays were used to screen 5-trichloromethyl-5-hydroxy-4,5-dihydroisoxazole (**2**) for the antibacterial activity.

Data for **2a**: Yield 85%, m.p.: 141–142°C/ Lit. 143–144°C [1]; ^{1}H NMR (200 MHz, DMSO-d6): 3.29 (dd, 1H, *J* 18.5 Hz, *J* 1.6 Hz, H4), 3.74 (dd, 1H, *J* 18.5 Hz, *J* 1.6 Hz, H4'), 7.11 (br, 1H, OH), 7.48 (t, 1H, J 1.6 Hz, H3); ^{13}C NMR (50 MHz, DMSO-d6): 148.8 (C3), 46.3 (C4), 110.5 (C5), 102.3 (CCl_3); MS (70 eV): m/z 204 (M+, 25), 187 (40), 117 (20), 86 (100); Anal. Calcd. for $C_4H_4Cl_3NO_2$: C, 23.5; H, 2.0; N, 6.9; found C, 23.7; H, 2.1; N, 7.0.

2b: Yield 89%, m.p.: 127–128°C/ Lit. 127°C [2]; ^{1}H NMR (200 MHz, DMSO-d6): 2.04 (s, 3H,Me), 3.23 (d, 1H, J 18.8 Hz, H4), 3.76 (d, 1H, J 18.8 Hz, H4'), 6.98 (s, 1H, OH); ^{13}C NMR (50 MHz, DMSO-d6): 156.7 (C3), 47.9 (C4), 111.1 (C5), 101.9 (CCl_3), 12.3 (Me); MS

(70 eV): m/z 218 (M+, 40), 201 (60), 117 (14), 101 (58), 58 (100); Anal. Calcd. for $C_5H_6Cl_3NO_2$: C, 27.5; H, 2.8; N, 6.4; found C, 27.7; H, 2.9; N, 6.4.

2c: Yield 96%, m.p.: 121–122°C/ Lit 121–122°C [2]; ^{1}H NMR (200 MHz, DMSO-d6): 1.16 (t, 3H, *J* 7.4 Hz, Me), 2.41 (q, 2H, *J* 7.4 Hz, -CH_2-), 3.23 (d, 1H, J 18.6 Hz, H4), 3.71 (d, 1H, J 18.6 Hz, H4'); ^{13}C NMR (50 MHz, DMSO-d6): δ 161.7 (C3), 47.1 (C4), 111.7 (C5), 102.7 (CCl_3), 21.6 (-CH_2-), 10.9 (Me); MS (70 eV): m/z 232 (M+, 25), 215 (27), 117 (100), 71 (61); Anal. Calcd. for $C_6H_8Cl_3NO_2$: C, 31.0; H, 3.5; N, 6.0; found C, 31.2; H, 3.6; N, 6.0.

2d: Yield 93%, m.p.: 140–141°C/ Lit. 140°C[27]; ^{1}H NMR (200 MHz, DMSO-d6): 0.96 (t, 3H, *J* 7.6 Me), 1.65 (sx, 2H, *J* 7.2 Hz, -CH_2-), 2.4 (t, 2H, *J* 7.2, -CH_2-), 3.24 (dt, 1H, *J* 18 Hz, *J* 0.8 Hz, H4), 3.69 (dt, 1H, *J* 18 Hz, *J* 0.8 Hz, H4'); ^{13}C NMR (50 MHz, DMSO-d6): δ 160.5 (C3), 47.2 (C4), 111.5 (C5), 102.7 (CCl_3), 29.8 (-CH_2-), 20 (-CH_2-), 13.7 (Me); MS (70 eV): *m/z* 246 (M^+, 20), 229 (23), 117 (72), 85 (100); Anal. Calcd. for $C_7H_{10}Cl_3NO_2$: C, 34.1; H, 4.1; N, 5.7; found C, 34.3; H, 4.2; N, 5.7.

2e: Yield 91%, m.p.: 139–140°C/ Lit. 139–140°C [3]; ^{1}H NMR (200 MHz, DMSO-d6): 1.2 (d, 6H, *J* 6.8 Me), 2.75 (sp, 1H, J 6.8 Hz, CH), 3.28 (dd, 1H, *J* 18.6 Hz, *J* 0.8 Hz, H4), 3.69 (dt, 1H, *J* 18.6 Hz, *J* 0.8 Hz, H4'); ^{13}C NMR (50 MHz, DMSO-d6): 164.9 (C3), 45.3 (C4), 111.6 (C5), 102.8 (CCl_3), 29.8 (CH), 20.1 (Me); MS (70 eV): m/z 246 (M+, 10), 229 (13), 117 (100), 85 (40); Anal. Calcd. for $C_7H_{10}Cl_3NO_2$: C, 34.1; H, 4.1; N, 5.7; found C, 34.3; H, 4.2; N, 5.7.

2f: Yield 89%, m.p.: 165°C/ Lit. 164–165°C [3]; ^{1}H NMR (200 MHz, DMSO-d6): 0.82 (m, 2H, cis to CH), 0.91 (dm, 2H, trans to CH), 1.78 (m, 1H, CH), 3.07 (d, 1H, *J* 18.5 Hz, H4), 3.55 (d, 1H, *J* 18.5 Hz, H4'); ^{13}C NMR (50 MHz, DMSO-d6): 162.5 (C3), 45.3 (C4), 111.6 (C5), 102.6 (CCl3), 9.45 (CH), 6.4, 6.1 (-CH_2-); MS (70 eV): m/z 244 (M+, 50), 227 (18), 117 (72), 83 (68); Anal. Calcd. for $C_7H_8Cl_3NO_2$: C, 34.4; H, 3.3; N, 5.7; found C, 34.5; H, 3.4; N, 5.7.

2g: Yield 96%, m.p.: 156°C/ Lit. 152–154°C [3]; ^{1}H NMR (200 MHz, DMSO-d6): 0.97 (d, 6H, J 6.6, Me), 2.05 (m, 1H, CH), 2.27 (d, 2H, J 7.0, CH_2), 3.22 (d, 1H, J 18.5 Hz, H4), 3.69

(d, ^{1}H, J 18.5 Hz, H4'); ^{13}C NMR (50 MHz, DMSO-d6): δ 160 (C3), 47.5 (C4), 111.6 (C5), 102.8 (CCl_3), 36.8 (CH_2), 26.7 (CH), 22.5, 22.6 (Me); MS (70 eV): m/z 260 (M+, 30), 243 (35), 143 (72), 117 (16), 100 (31), 57 (100); Anal. Calcd. for $C_8H_{12}Cl_3NO_2$: C, 36.9; H, 4.6; N, 5.4; found C, 37.0; H, 4.6; N, 5.4.

2h: Yield 91%, m.p.: 169°C/ Lit. 170–171°C [3]; ^{1}H NMR (200 MHz, DMSO-d6): 1.22 (s, 9H, Me), 3.30 (d, 1H, *J* 18.5 Hz, H4), 3.73 (d, 1H, *J* 18.5 Hz, H4'); ^{13}C NMR (50 MHz, DMSO-d6): 166.9 (C3), 44.4 (C4), 111.6 (C5), 102.4 (CCl_3), 33.6 (Cq), 26.7 (Me); MS (70 eV): m/z 259 (M+, 10), 243 (11), 143 (15), 117 (10), 57 (100); Anal. Calcd. for $C_8H_{12}Cl_3NO_2$: C, 36.9; H, 4.6; N, 5.4; found C, 37.0; H, 4.6; N, 5.4.

2i: Yield 87%, m.p.: 90–91°C/ Lit. 88–92°C [4]; ^{1}H NMR (200 MHz, DMSO-d6): 3.41 (d, 1H, J 18.9 Hz, H4), 3.86 (d, 1H, J 18.9 Hz, H4'), 4.5 (s, 2H, -CH2-); ^{13}C NMR (50 MHz, DMSO-d6): δ 157.3 (C3), 44.7 (C4), 112.9 (C5), 102.0 (CCl_3), 37.9 (-CH_2-); MS (70 eV): m/z 297 (M+, 10), 280 (10), 233 (25), 177 (100), 117 (43); Anal. Calcd. for $C_5H_5BrCl_3NO_2$: C, 20.2; H, 1.7; N, 4.7; found C, 20.5; H, 1.9; N, 4.7.

2j: Yield 90%, m.p.: 84–85°C/ Lit. 85–86°C [4]; ^{1}H NMR (200 MHz, DMSO-d6): 3.60 (d, 1H, J 18.9 Hz, H4), 4.05 (d, 1H, J 18.9 Hz, H4'), 6.9 (s, 1H, CH); ^{13}C NMR (50 MHz, DMSO-d6): δ 158.6 (C3), 42.6 (C4), 113.7 (C5), 101.4 (CCl_3), 30.8 (CH); MS (70 eV): m/z 373 (M+, 5), 356 (8), 256 (17), 211 (100), 173 (23), 117 (53); Anal. Calcd. for $C_5H_4Br_2Cl_3NO_2$: C, 20.2; H, 1.7; N, 4.7; found C, 20.5; H, 1.9; N, 4.7.

2m: Yield 95%, m.p.: 106–107°C; ^{1}H NMR (200 MHz, DMSO-d6): 1.35 (d, 3H, J 7.5 Hz, Me), 3.9 (qd, 1H, J 7.5 Hz, 1,2 Hz, H4), 7.38 (d, 1H, J 1.2 Hz, H3); ^{13}C NMR (50 MHz, DMSO-d6): δ 152.8 (C3), 48.8 (C4), 109.1 (C5), 102,7 (CCl_3), 11.2 (Me); MS (70 eV): m/z 219 (M+, 19), 201 (17), 117 (100), 55 (90); Anal. Calcd. for $C_5H_6Cl_3NO_2$: C, 27.5; H, 2.8; N, 6.4; found C, 27.7; H, 2.9; N, 6.4.

2n: Yield 95%; m.p.: 148–150°C/ Lit. 150°C [5]; ^{1}H NMR (200 MHz, $CDCl_3$) 1.22–2.61 (m, 8H, -CH2-), 3.51 (dd, *J* 12 Hz, 6 Hz, H4); ^{13}C NMR (50 MHz, $CDCl_3$) 161.6 (C3), 53.4 (C4), 110.2 (C5), 103.5 (CCl3), 27.6, 25.8, 25.7, 24 (-CH2-). MS (EI, 70 eV): m/z (%): 259 (M+,

29), 242 (100), 224 (44), 189 (37), 117 (39), 95 (61). Anal. Calcd. for $C_8H_{10}Cl_3NO_2$: C, 37.17; H, 3.90, N, 5.42; found: C, 37.20; H, 3.90; N, 5.50.

2o: Yield 90%; m.p.: 121°C/ Lit. 118–120°C [5]; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.58–1.67 (m, 5H, -CH_2-), 1.77–1.82 (m, 3H, -CH_2-), 1.9–1.97 (m, 1H, -CH_2-), 2.1–2.15 (m, 1H, -CH_2-), 2.44–2.5 (m, 1H, -CH_2-), 2.67–2.72 (m, 1H, -CH_2-), 3.7 (dd, *J* 7.2 Hz, 4.0 Hz, H4); ^{13}C NMR (50 MHz, $CDCl_3$) δ 164.2 (C3), 54.1 (C4), 110.2 (C5), 102.6 (CCl_3), 26.3, 26.0, 25.8, 25.6, 25.3, 24.7 (-CH_2-). MS (EI, 70 eV): *m/z* (%): 273 (M^+, 29), 256 (35), 238 (49), 203 (45), 117 (57), 107 (35), 95 (100). Anal. Calcd. for $C_{10}H_{14}Cl_3NO_2$: C, 41.49; H, 4.92, N, 4.89; found: C, 41.5; H, 5.1; N, 4.60.

2p: Yield 87%; m.p.: 141–142°C/ Lit. 140–142°C [5]; ^{1}H NMR (400 MHz, $CDCl_3$) 1.14 (t, 3H, J 7.4 Hz, Me), 1.31 (d, 3H, J 7.4 Hz, Me), 2.30 (m, 2H, -CH2-), 3.72 (q, 1H, J 7.4 Hz, H4); ^{13}C NMR (50 MHz, $CDCl_3$) 165.0 (C3), 49.9 (C4), 110.9 (C5), 103.8 (CCl3), 20.4 (-CH2-), 12.0 (Me-4), 10.5 (Me). MS (EI, 70 eV): m/z (%): 247 (M+, 29), 230 (60), 212 (59), 176 (64), 130 (100), 117 (39), 72 (41). Anal. Calcd. for $C_7H_{10}Cl_3NO_2$: C, 34.11; H, 4.09, N, 5.68; found: C, 34.0; H, 4.0; N, 5.70.

2q: Yield 97%; m.p.: 156°C/ Lit. 155–158°C [5]; ^{1}H NMR (200 MHz, $CDCl_3$) 1.30 (d, 3H, J 7.4 Hz, Me), 4.10 (q, 1H, J 7.4 Hz, H4), 7.30 (m, 3H, Ph), 7.51 (m, 2H, Ph); ^{13}C NMR (50 MHz, $CDCl_3$) 162.0 (C3), 47.3 (C4), 110.8 (C5), 102.2 (CCl3), 127, 127.8, 128.8, 130.2 (Ph). MS (EI, 70 eV): m/z (%): 281 (M+, 29), 263 (100), 246 (29), 211 (54), 120 (37), 117 (39), 76 (41). Anal. Calcd. for $C_{10}H_8Cl_3NO_2$: C, 44.85; H, 3.42, N, 4.76; found: C, 45.0; H, 3.5; N, 4.70.

Data for **3a**: Yield 93%, yellow oil/ Lit. 24–26°C [1]; 1H NMR (200 MHz, $CDCl_3$): δ 6.98 (d, 1H, J 2.0 Hz, H4), 8.61 (d, 1H, J 2.0 Hz, H3); ^{13}C NMR (50 MHz, $CDCl_3$): δ 152 (C3), 104.6 (C4), 168.5 (C5), 85.2 (CCl_3); MS (70 eV): m/z 187 (M+, 100), 152 (46), 117 (65), 40 (79); Anal. Calcd. for $C_4H_2Cl_3NO$: C, 25.8; H, 1.08; N, 7.5; found C, 26.0; H, 1.0; N, 7.5.

3b: Yield 92%, m.p.: yellow oil/ Lit. oil [5]; ^{1}H NMR (200 MHz, $CDCl_3$): 2.78 (s, 3H,Me), 7.25 (s, 1H, H4); ^{13}C NMR (50 MHz, CDCl3): δ 161.4 (C3), 105.7 (C4), 168.7 (C5), 85.5 (CCl_3), 11.4 (Me); MS (70 eV): m/z 201 (M+, 100), 166 (30), 131 (45), 117 (30), 56 (70); Anal. Calcd. for $C_5H_4Cl_3NO$: C, 29.92; H, 2.0; N, 6.99; found C, 30.0; H, 2.0; N, 7.0.

3c: Yield 95%, yellow oil; ^{1}H NMR (200 MHz, $CDCl_3$): 1.28 (t, 3H, *J* 7.6 Hz, Me), 2.73 (q, 2H, *J* 7.6 Hz, -CH2-), 6.87 (s, 1H, H4); ^{13}C NMR (50 MHz, DMSO-D6): δ 166.5 (C3), 104.5 (C4), 168.7 (C5), 85.6 (CCl3), 20.1 (-CH2-), 12.7 (Me); MS (70 eV): m/z 214 (M+, 95), 179 (77), 143 (100), 117 (45), 71 (80); Anal. Calcd. for $C_6H_6Cl_3NO$: C, 33.6; H, 2.82; N, 6.53; found C, 33.5; H, 3.0; N, 6.5.

3e: Yield 92%, yellow oil; ^{1}H NMR (200 MHz, $CDCl_3$): 1.31 (d, 6H, *J* 7.2 Hz, Me), 3.08 (sp, 1H, *J* 7.2 Hz, CH), 6.93 (s, H, H4); ^{13}C NMR (50 MHz, $CDCl_3$): δ 170.5 (C3), 103.5 (C4), 168.7 (C5), 85.6 (CCl_3), 27.3 (CH), 21.5 (Me); MS (70 eV): m/z 229 (M+, 100), 194 (70), 158 (85), 117 (40), 75 (78); Anal. Calcd. for $C_7H_8Cl_3NO$: C, 36.79; H, 3.53; N, 6.13; found C, 36.5; H, 3.4; N, 6.1.

3f: Yield 95%, yellow oil; ^{1}H NMR (200 MHz, $CDCl_3$): 0.89–0.94 (m, 2H, -CH_2-), 1.05–1.13 (m, 2H, -CH_2-), 2.06 (m, 1H, CH), 6.72 (d, 1H, J 1.2 Hz, H4); ^{13}C NMR (50 MHz, $CDCl_3$): δ 167.8 (C3), 102.6 (C4), 168.6 (C5), 85.5 (CCl_3), 8.5 (-CH2-), 7.8 (CH); MS (70 eV): m/z 226 (M+, 95), 191 (27), 156 (40), 117 (55), 81 (54), 41 (100); Anal. Calcd. for $C_7H_6Cl_3NO$: C, 37.1; H, 2.67; N, 6.18; found C, 36.8; H, 2.5; N, 6.2.

3g: Yield 95%, yellow oil; ^{1}H NMR (200 MHz, $CDCl_3$): 1,01 (d, 6H, J 7.5 Me), 2.08 (m, 1H, *J* 7.5 Hz, CH), 2.64 (d, 2H, *J* 7.5, -CH−2-), 6.88 (s, 1H, H4); ^{13}C NMR (50 MHz, $CDCl_3$): 164.4 (C3), 105 (C4), 168.6 (C5), 85.5 (CCl_3), 35.2 (-CH2-), 28.2 (CH), 22.4 (Me); MS (70 eV): m/z 242 (M+, 90), 207 (43), 172 (72), 125 (25), 117 (40), 87 (100); Anal. Calcd. for $C_8H_{10}Cl_3NO$: C, 39.6; H, 4.16; N, 5.78; found C, 39.8; H, 4.2; N, 5.9.

3h: Yield 88%, yellow oil; ^{1}H NMR (200 MHz, $CDCl_3$): 1.35 (s, 9H,Me), 6.98 (s, 1H, H4); ^{13}C NMR (50 MHz, $CDCl_3$): δ 173.1 (C3), 103.2 (C4), 168.6 (C5), 85.5 (CCl_3), 33.0 (Cq), 29.3 (Me); MS (70 eV): m/z 242 (M+, 80), 207 (10), 185 (25), 172 (41), 125 (30), 117 (100),

57 (79); Anal. Calcd. for $C_8H_{10}Cl_3NO$: C, 39.6; H, 4.16; N, 5.79; found C, 39.8; H, 4.3; N, 5.5.

3i: Yield 89%, red oil/ B. p. Lit. 94–96°C/4 mBar [5]; ^{1}H NMR (200 MHz, $CDCl_3$): 4.94 (s, 2H, -CH_2Br), 7.22 (s, 1H, H4); ^{13}C NMR (50 MHz, $CDCl_3$): δ 162.4 (C3), 104.3 (C4), 169.4 (C5), 85.1 (CCl_3), 35.6 (CH_2Br); (Me); MS (70 eV): *m/z* 280 (M^+, 95), 245 (17), 210 (50), 200 (100), 186 (35), 165 (60), 117 (25), 95 (67); Anal. Calcd. for $C_5H_3BrCl_3NO$: C, 21.5; H, 1.08; N, 5.01; found C, 21.8; H, 1.0; N, 5.3.

3j: Yield 90%, m.p. 71°C/ Lit. 68–70°C [5]; ^{1}H NMR (400 MHz, $CDCl_3$): 7.23 (s, 1H, H4), 7.36 (s, 1H, $CHBr_2$); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.9 (C3), 104.3 (C4), 170.4 (C5), 84.6 (CCl_3), 27.0 ($CHBr_2$); MS (70 eV) *m/z* 359 (M^+, >5), 289 (75), 242 (30), 175 (56), 117 (100), 68 (72); Anal. Calcd. for $C_5H_2Br_2Cl_3NO$: C, 16.76; H, 0.56; N, 3.91; found C, 16.8; H, 0.6; N, 4.0.

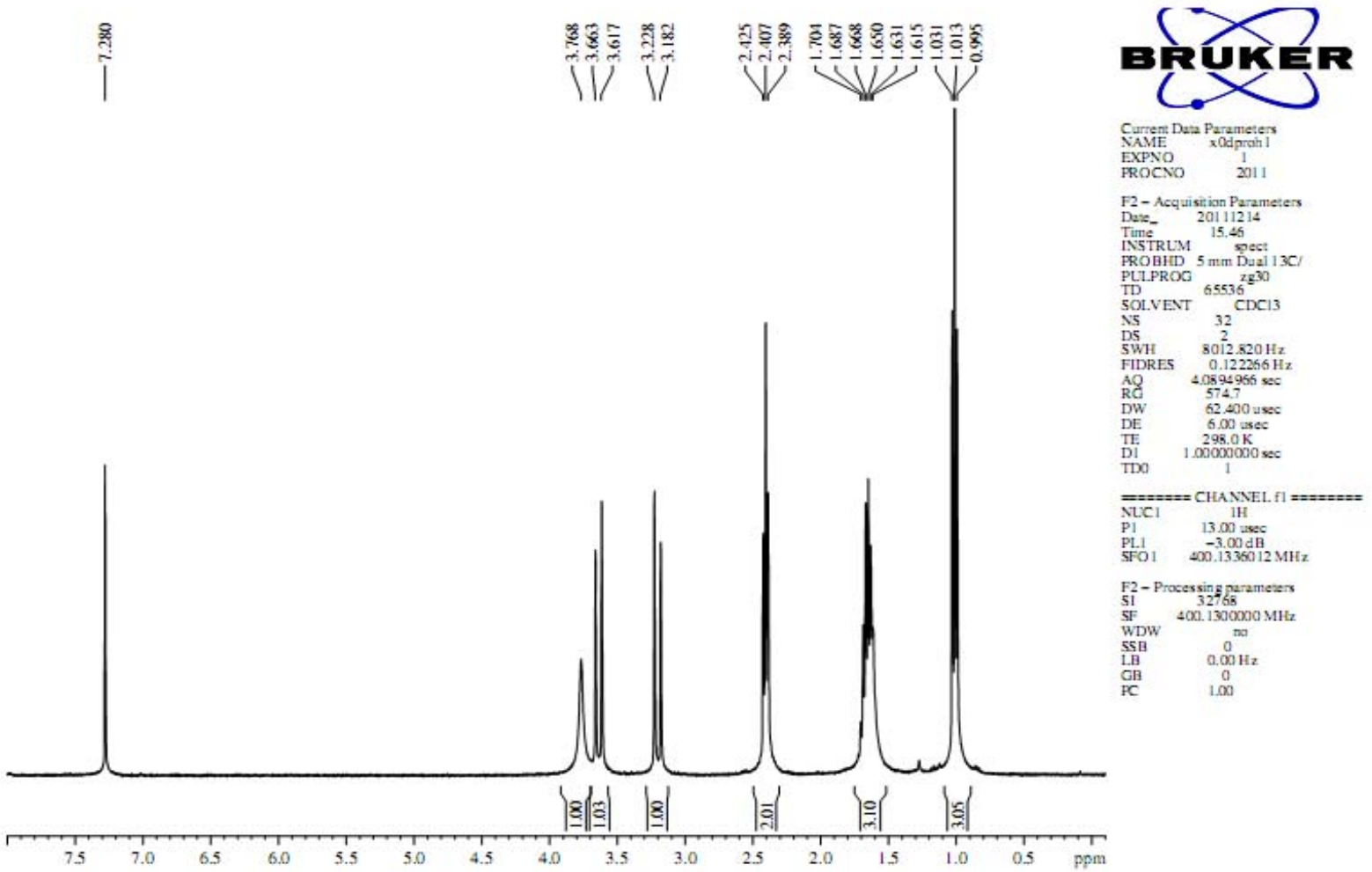


Figure S1: ^{1}H NMR spectrum of the 5-trichloromethyl-5-hydroxy-3-propyl-4,5-dihydroisoxazole (**2d**), $CDCl_3$.

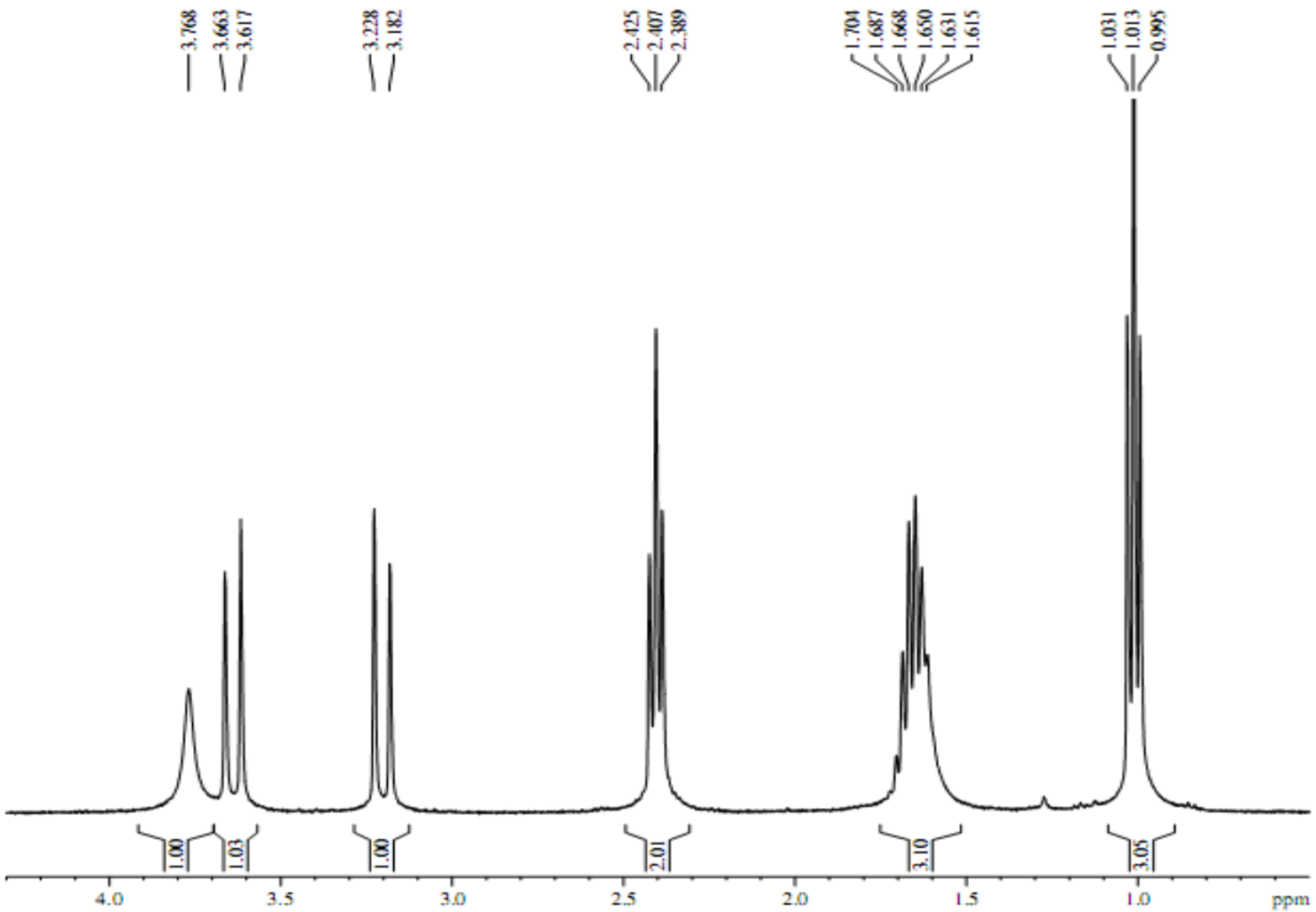


Figure S2: ^{1}H NMR spectrum of the 5-trichloromethyl-5-hydroxy-3-propyl-4,5-dihydroisoxazole (**2d**), $CDCl_3$.

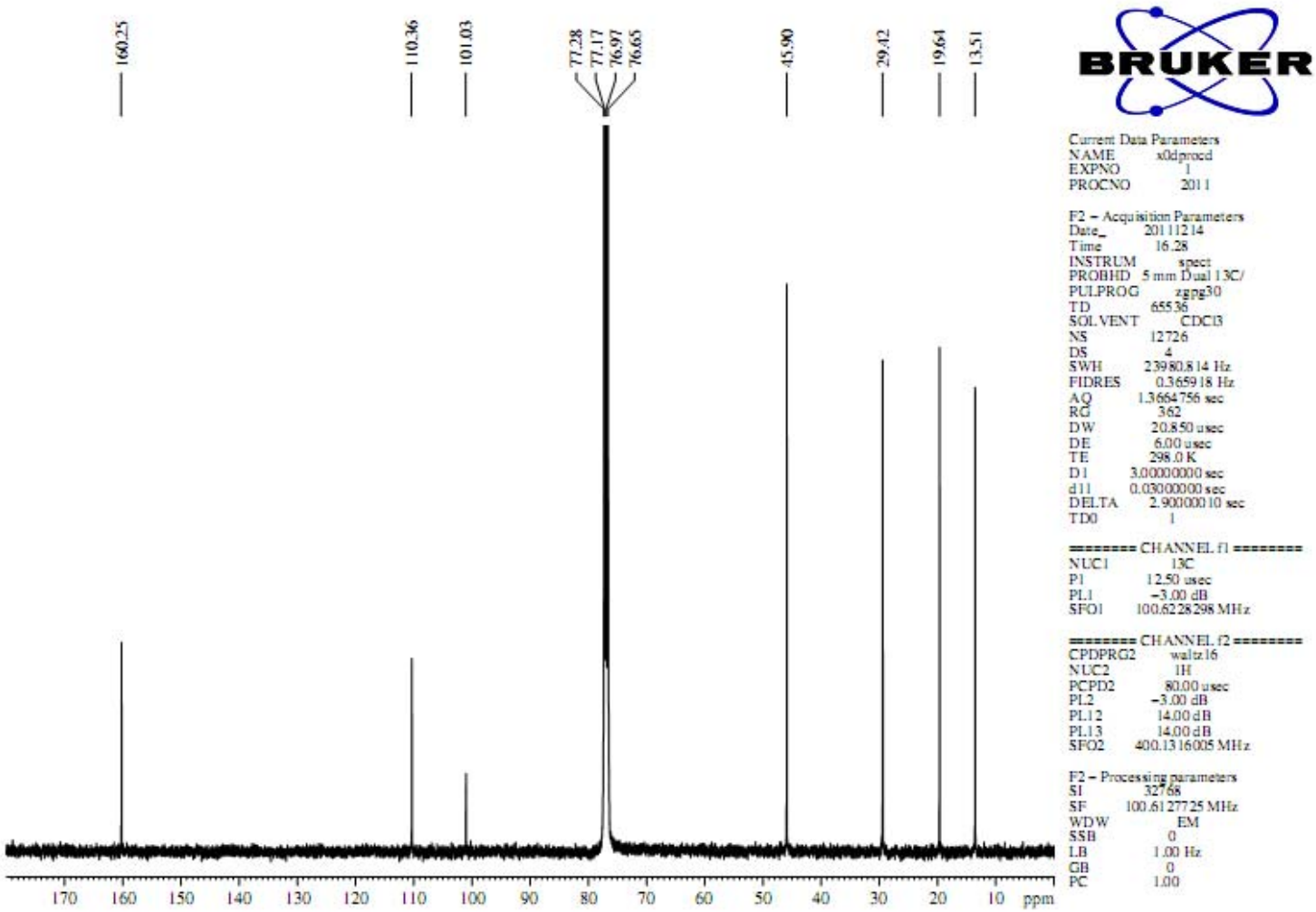


Figure S3: ^{13}C NMR spectrum of the 5-trichloromethyl-5-hydroxy-3-propyl-4,5-dihydroisoxazole (**2d**), $CDCl_3$.

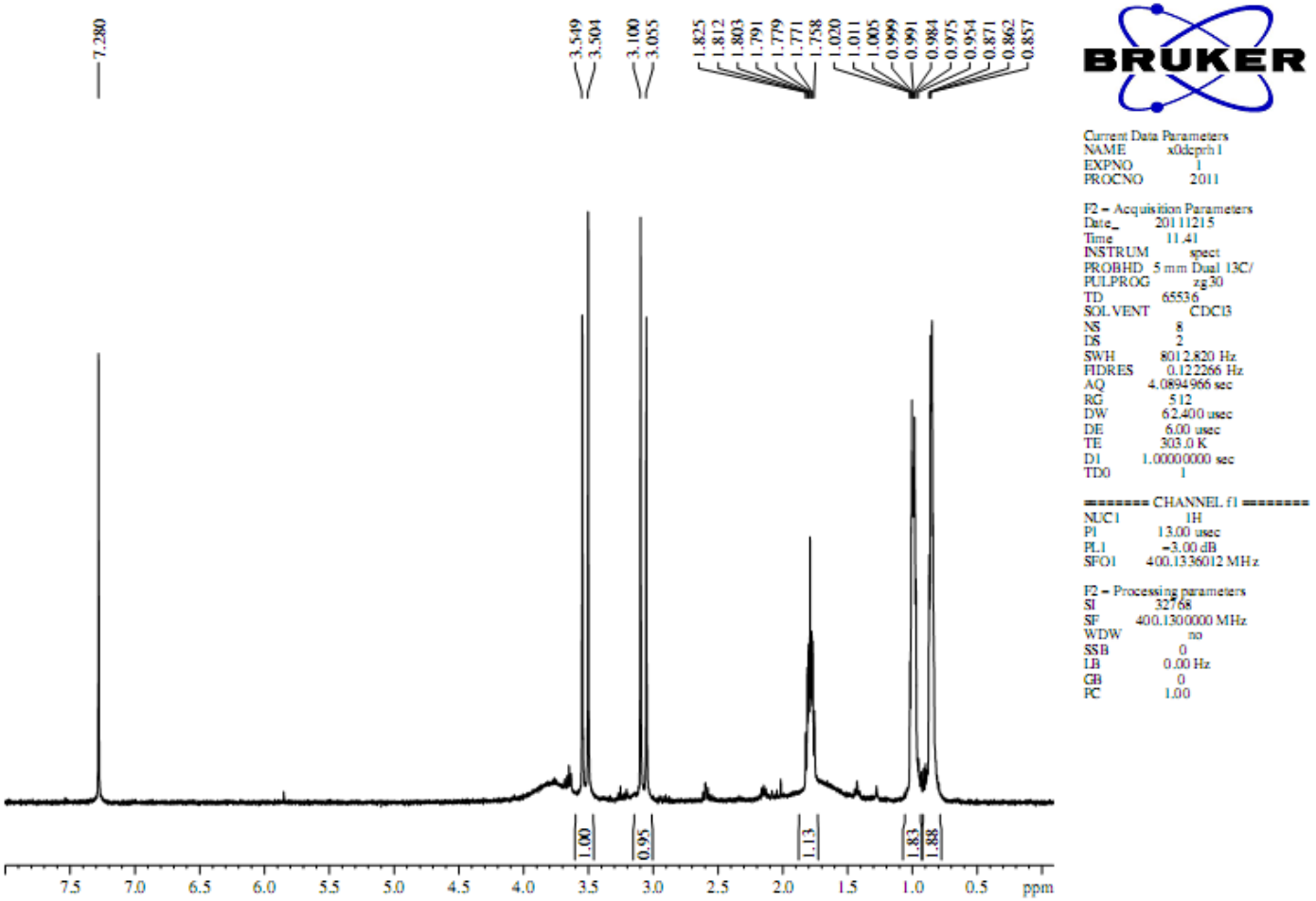


Figure S4: ^{1}H NMR spectrum of the 5-trichloromethyl-5-hydroxy-3-cyclopropyl-4,5-dihydroisoxazole (**2f**), $CDCl_3$.

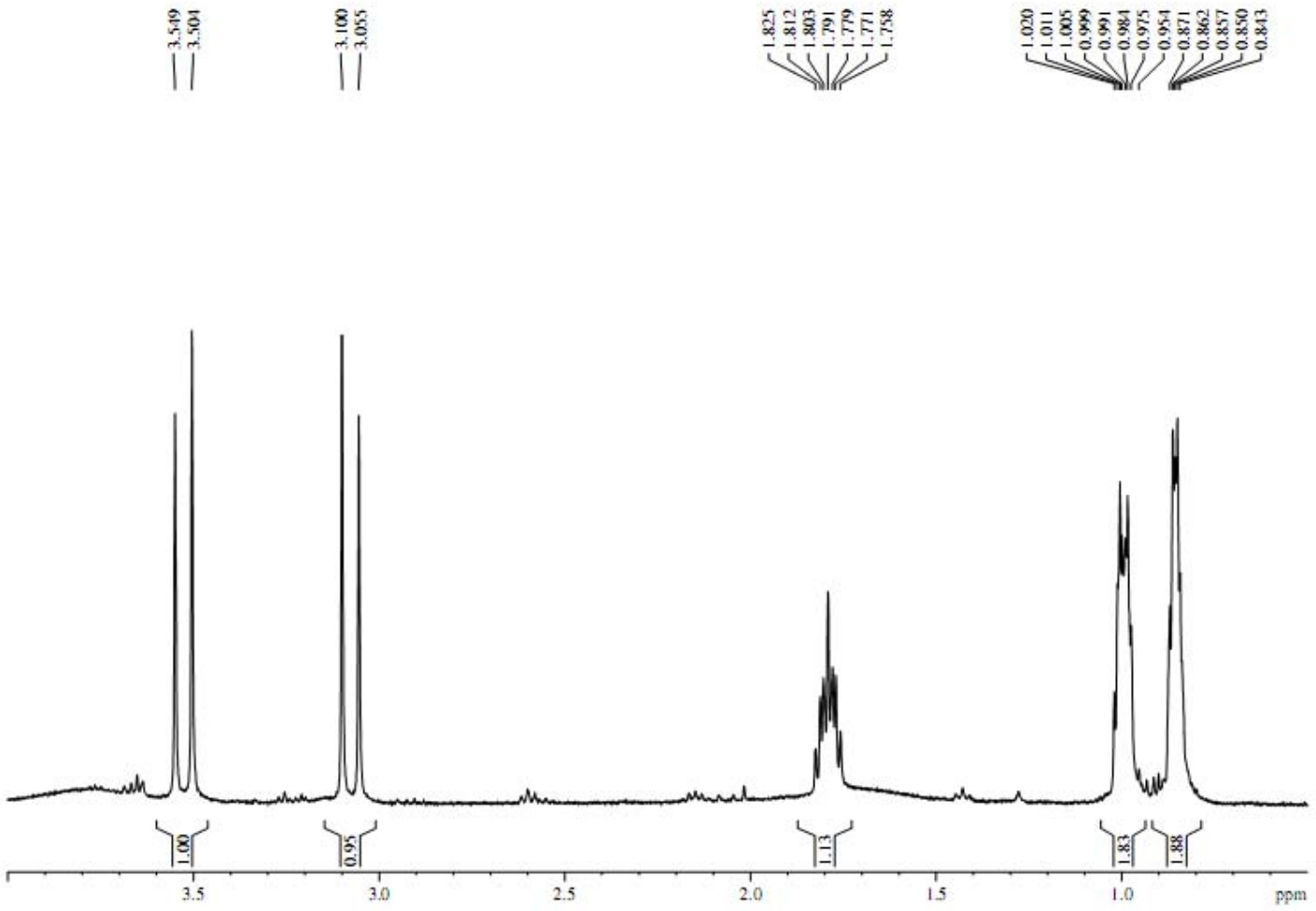


Figure S5: ^{1}H NMR spectrum of the 5-trichloromethyl-5-hydroxy-3-cyclopropyl-4,5-dihydroisoxazole (**2f**), $CDCl_3$.

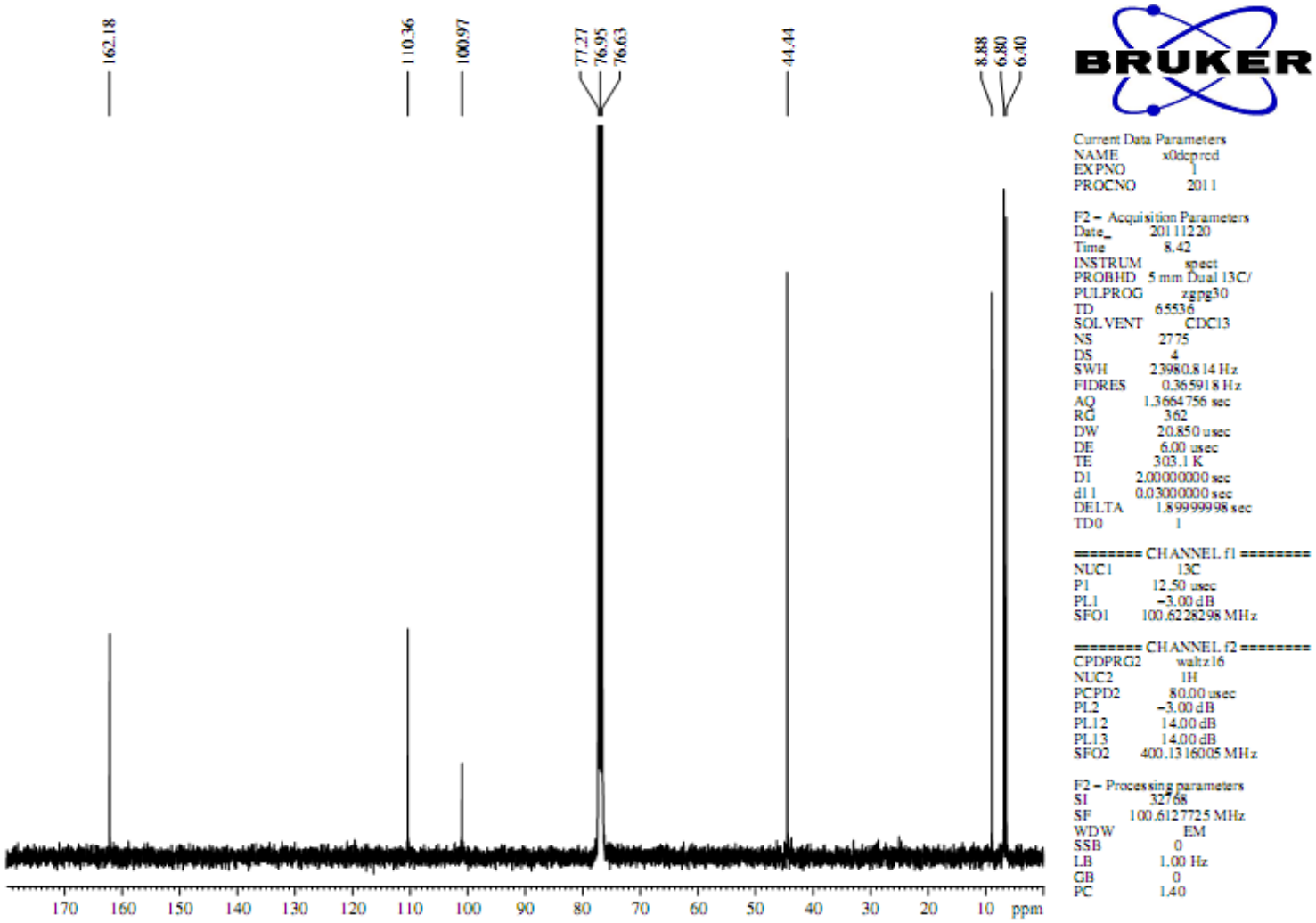


Figure S6: ^{13}C NMR spectrum of the 5-trichloromethyl-5-hydroxy-3-cyclopropyl-4,5-dihydroisoxazole (**2f**), $CDCl_3$.

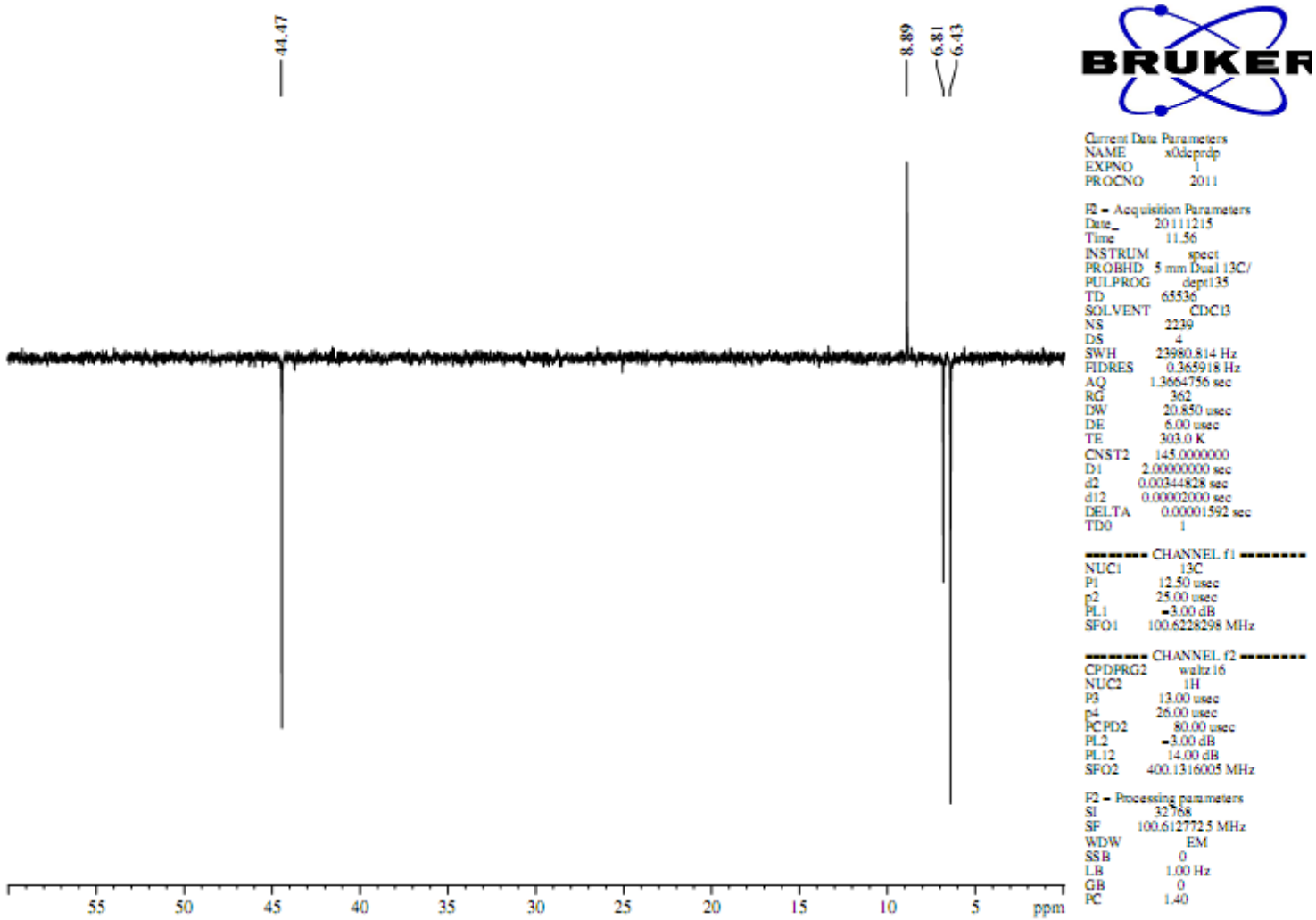


Figure S7: DEPT 135 ^{13}C NMR spectrum of the 5-trichloromethyl-5-hydroxy-3-cyclopropyl-4,5-dihydroisoxazole (**2f**), $CDCl_3$.

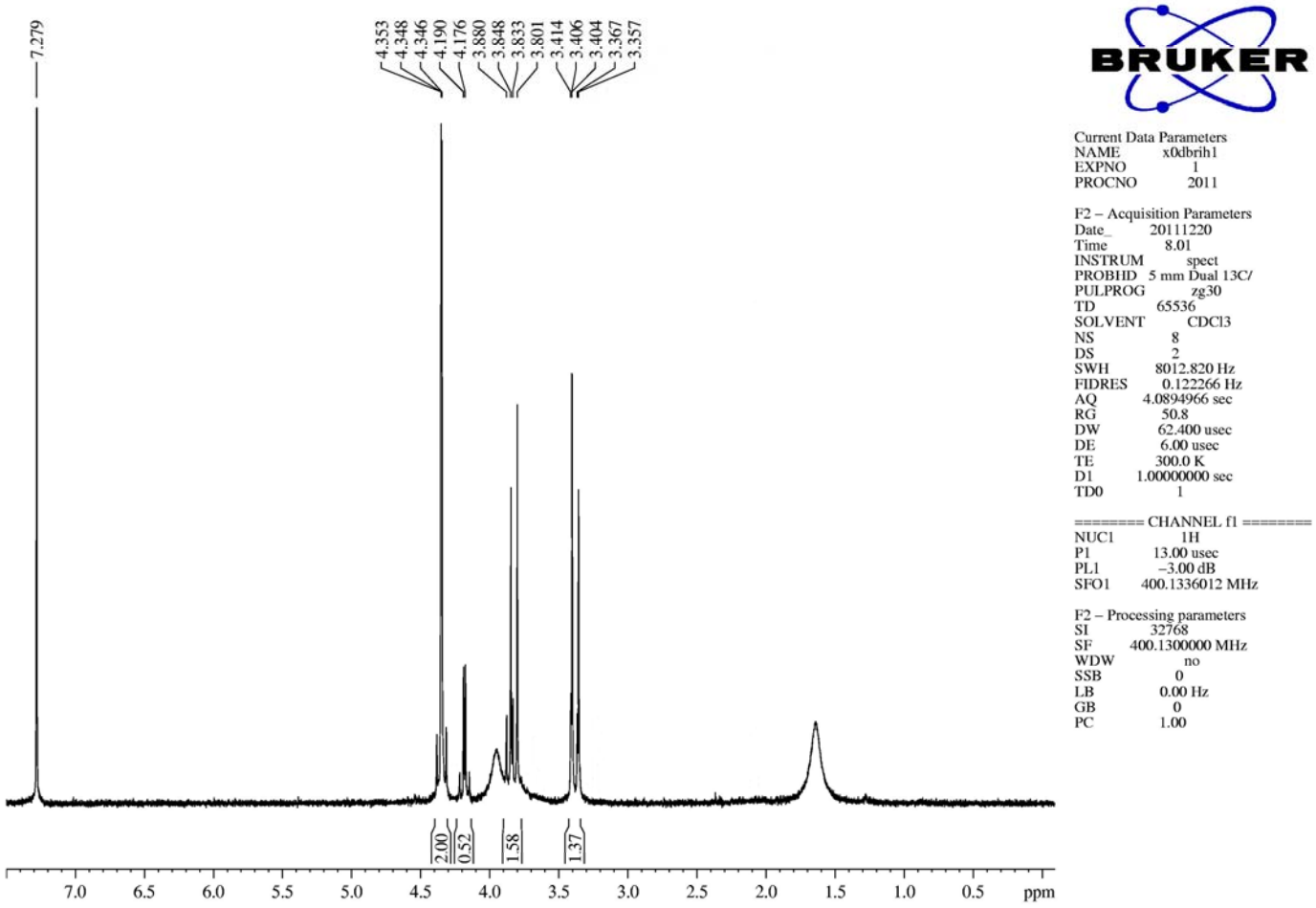


Figure S8: DEPT 135 ^{13}C NMR spectrum of the 3-bromomethyl-5-trichloromethyl-5-hydroxy-4,5-dihydroisoxazole (**2i**), $CDCl_3$.

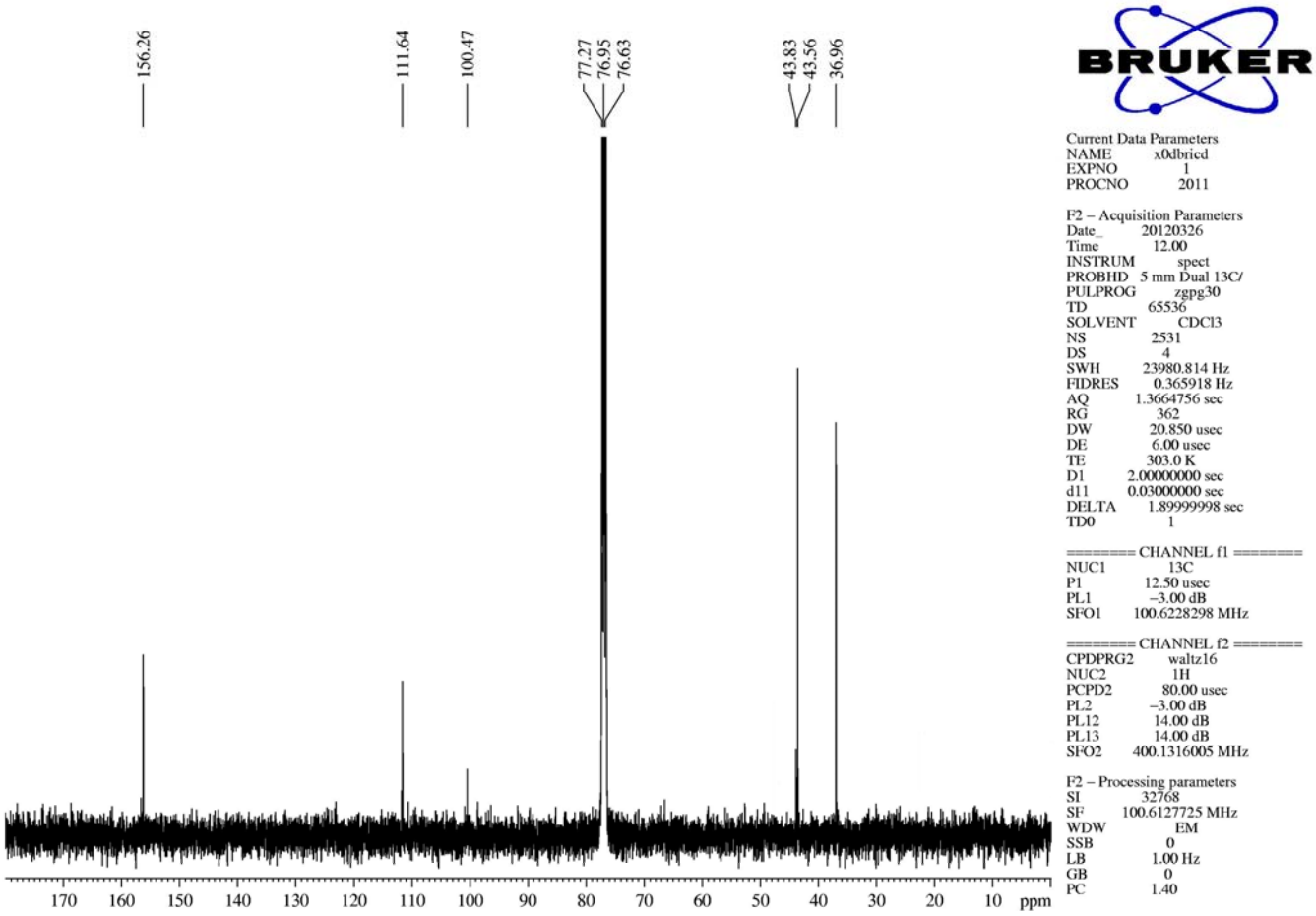


Figure S9: $^{13}C[H]$ NMR spectrum of the 3-bromomethyl-5-trichloromethyl-5-hydroxy-4,5-dihydroisoxazole (**2i**), $CDCl_3$.

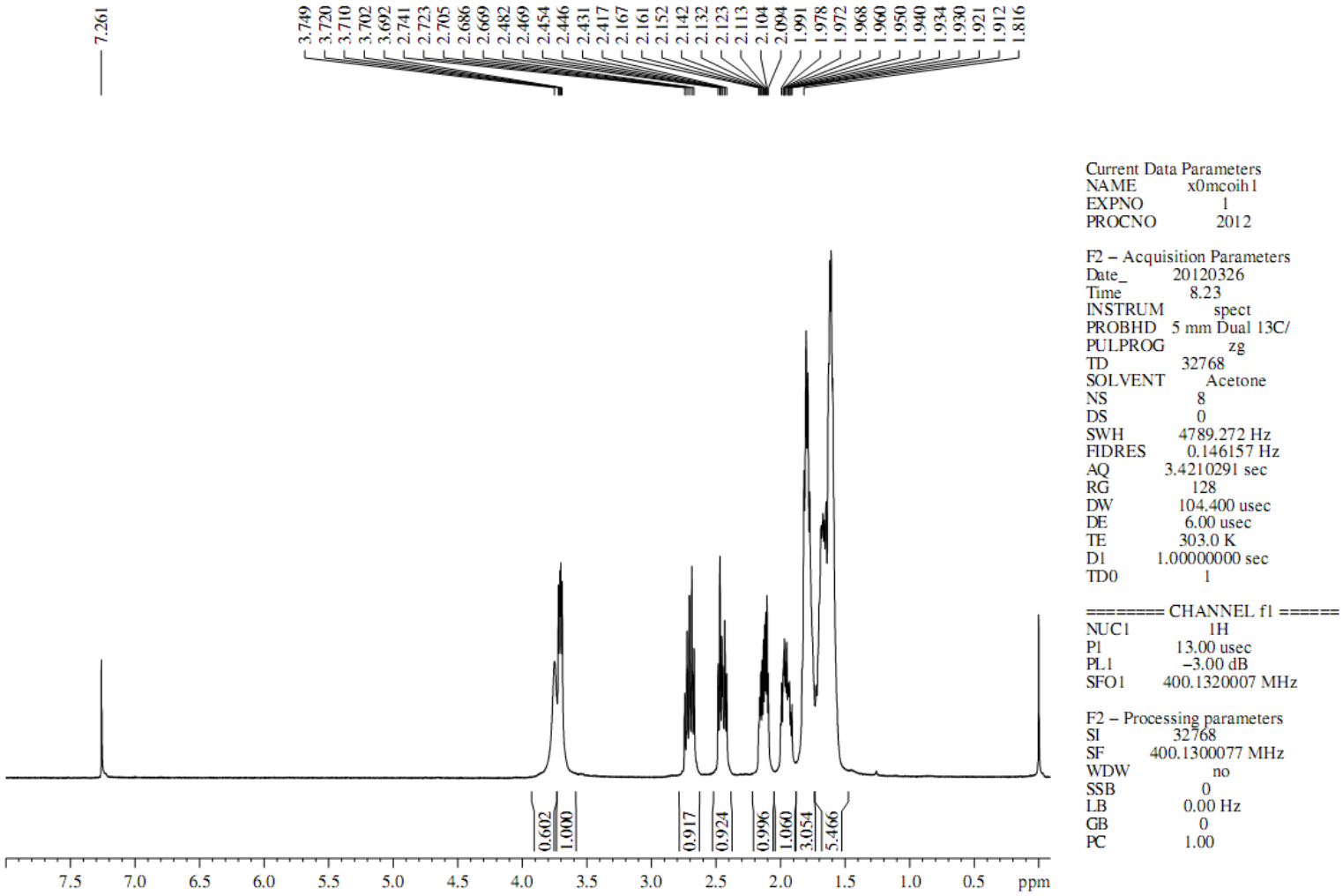


Figure S10: ^{1}H NMR spectrum of the 5-trichloromethyl-3,4-hexamethylene-5-hydroxy-4,5-dihydroisoxazole (**2o**), $CDCl_3$.

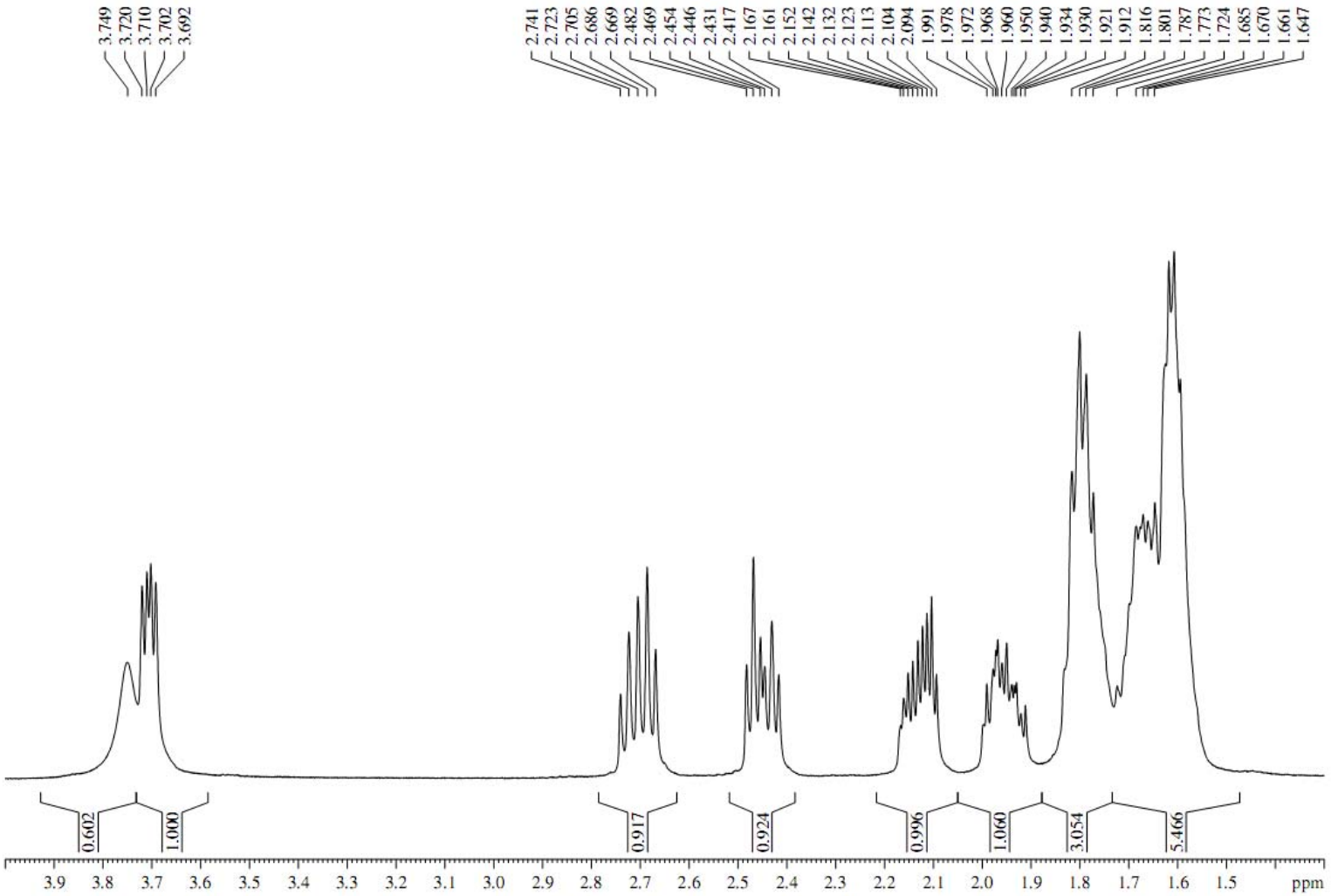


Figure S11: ^{1}H NMR spectrum of the 5-trichloromethyl-3,4-hexamethylene-5-hydroxy-4,5-dihydroisoxazole (**2o**), $CDCl_3$.

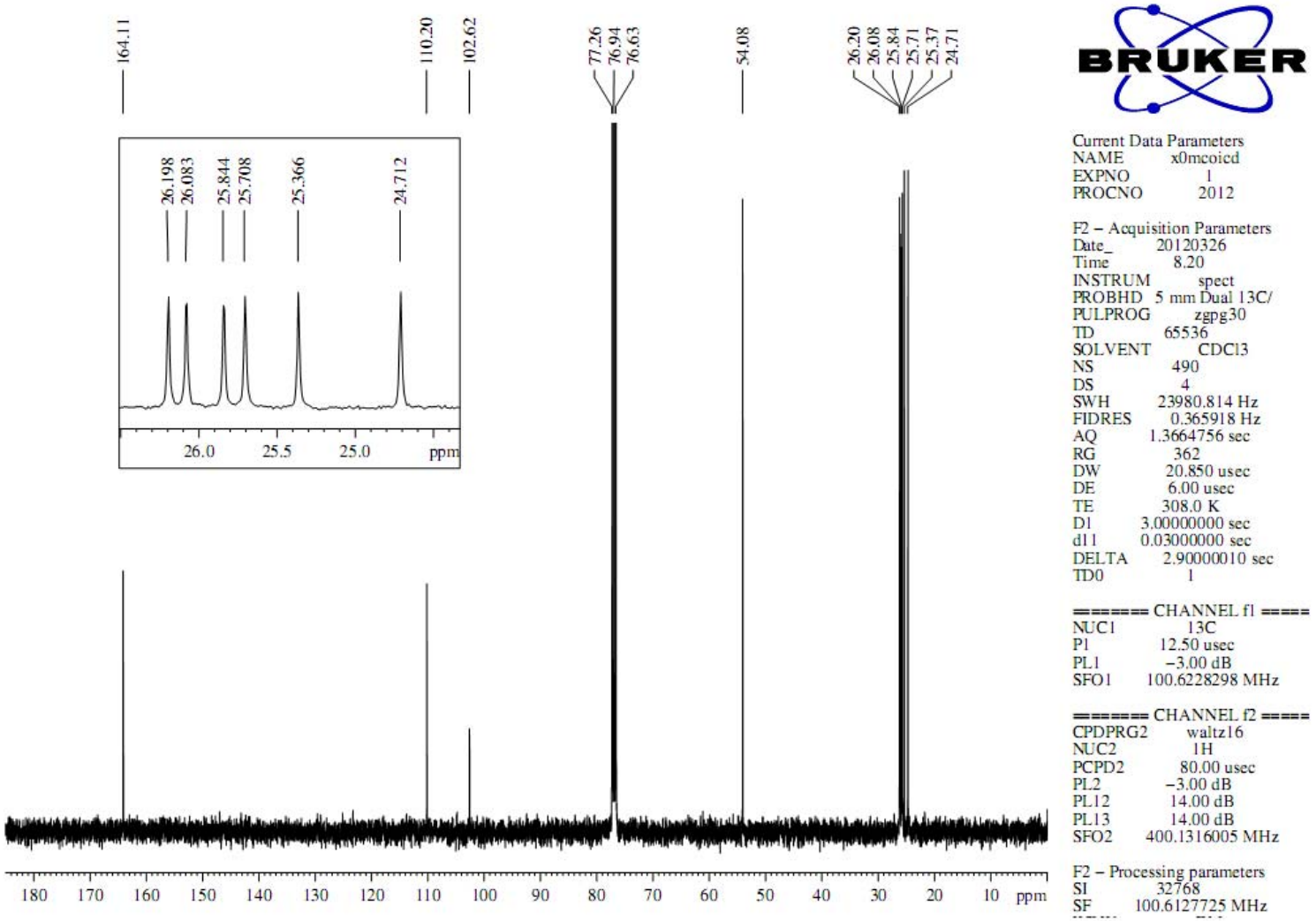


Figure S12: $^{13}C[H]$ NMR spectrum of the 5-trichloromethyl-3,4-hexamethylene-5-hydroxy-4,5-dihydroisoxazole (**2o**), $CDCl_3$.

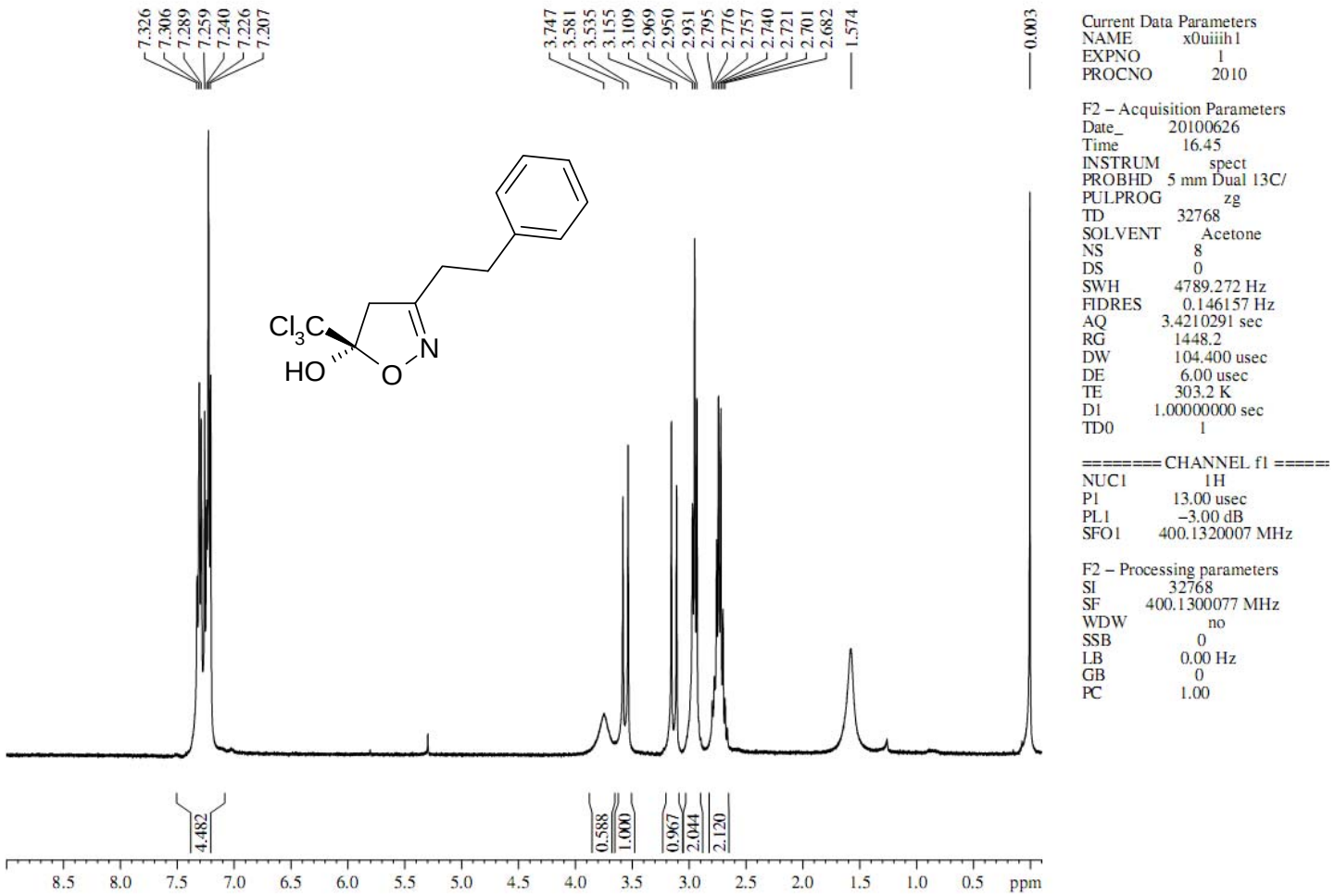


Figure S13: ^{1}H NMR spectrum of the 5-trichloromethyl-5-hydroxy-3-(2-phenylethyl)-4,5-dihydroisoxazole (**2k**), $CDCl_3$.

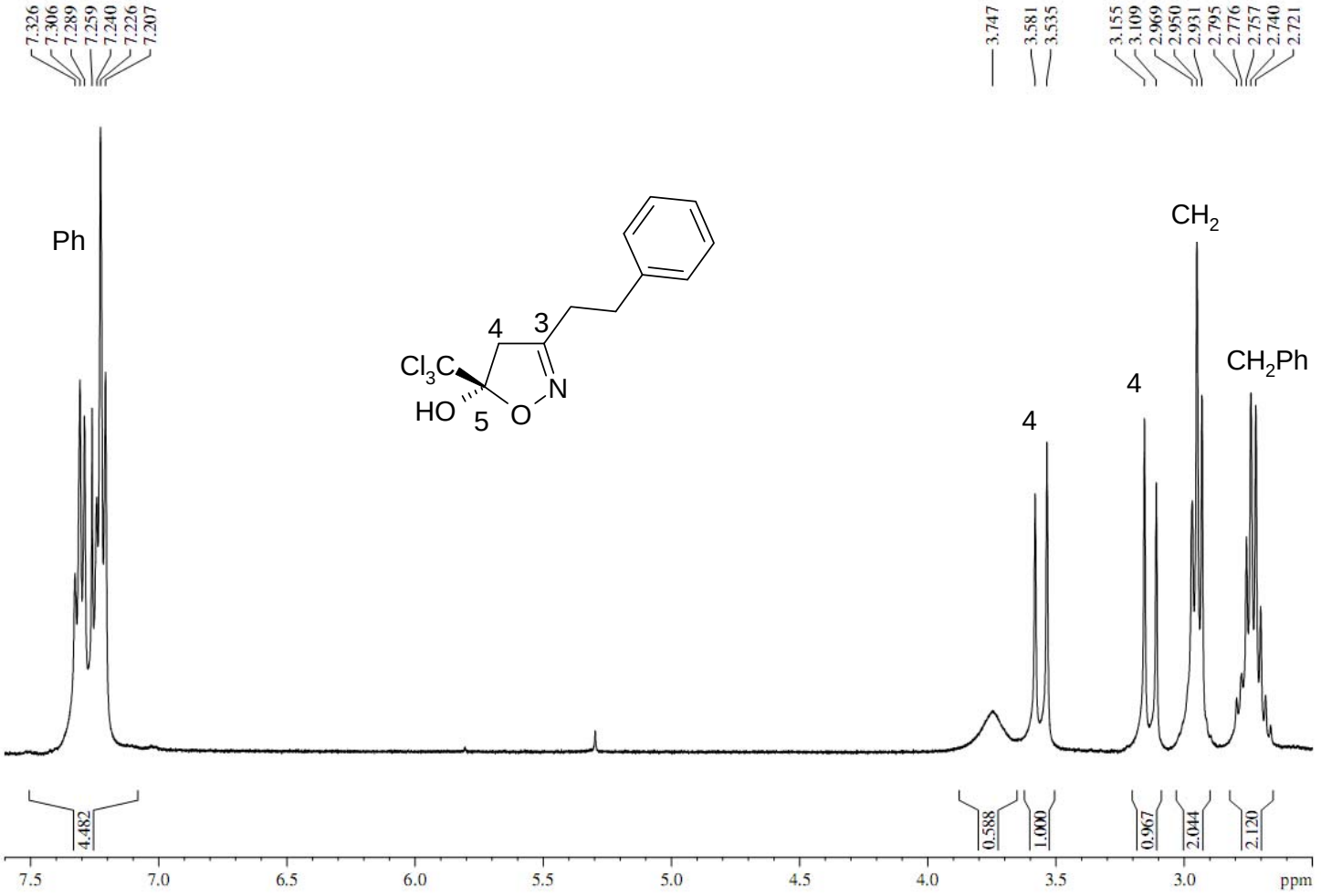
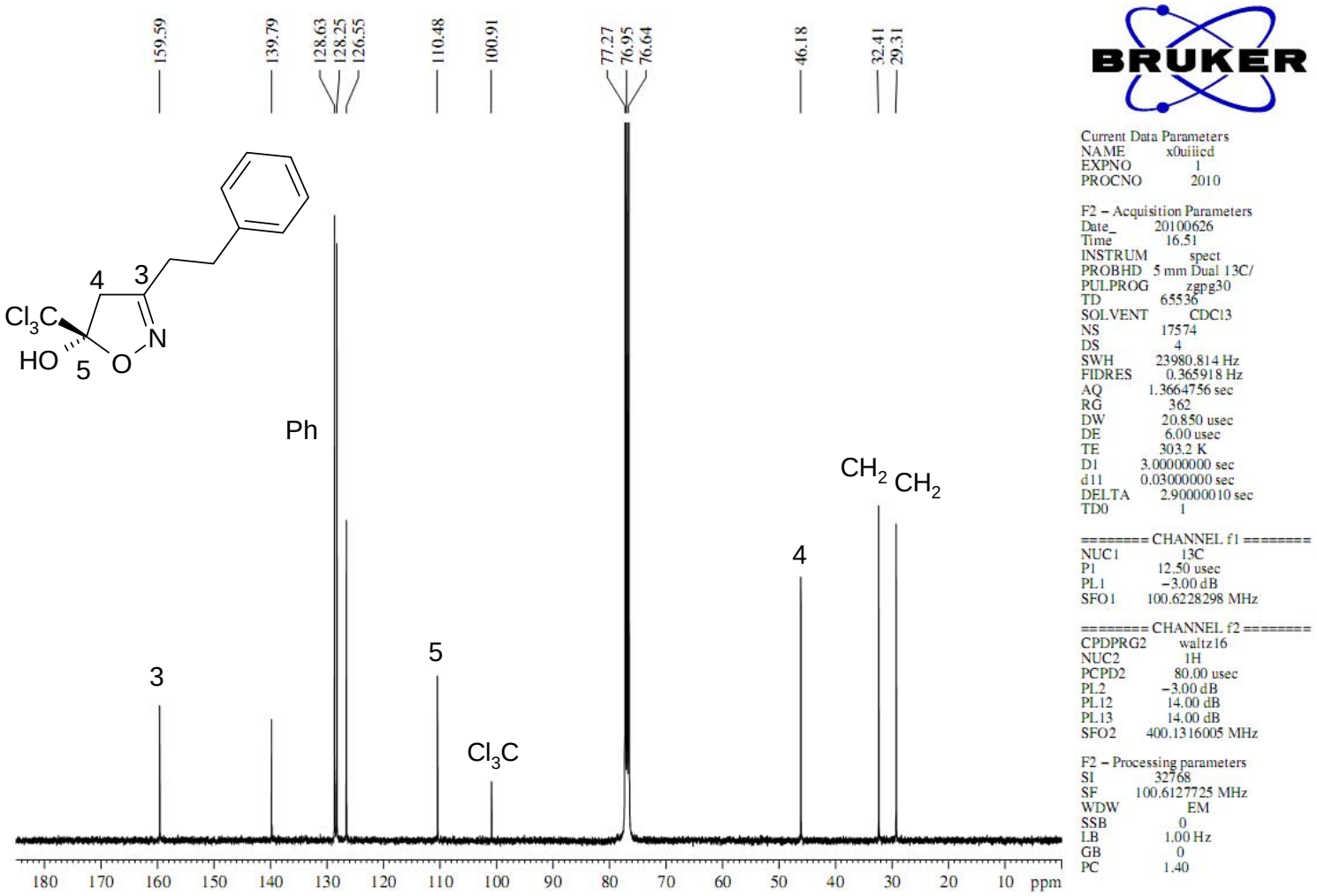


Figure S14: ^{1}H NMR spectrum of **2k** in $CDCl_3$, expanded between 2.5–7.6 ppm.



Current Data Parameters
NAME x0uiiicd
EXPNO 1
PROCNO 2010

F2 – Acquisition Parameters
Date_ 20100626
Time 16.51
INSTRUM spect
PROBHD 5 mm Dual 13C/
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 17574
DS 4
SWH 23980.814 Hz
FIDRES 0.365918 Hz
AQ 1.3664756 sec
RG 362
DW 20.850 usec
DE 6.00 usec
TE 303.2 K
D1 3.00000000 sec
d11 0.03000000 sec
DELTA 2.90000010 sec
TD0 1

======== CHANNEL f1 ========
NUC1 13C
P1 12.50 usec
PL1 −3.00 dB
SFO1 100.6228298 MHz

======== CHANNEL f2 ========
CPDPRG2 waltz16
NUC2 1H
PCPD2 80.00 usec
PL2 −3.00 dB
PL12 14.00 dB
PL13 14.00 dB
SFO2 400.1316005 MHz

F2 – Processing parameters
SI 32768
SF 100.6127725 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40

Figure S15: ^{13}C NMR spectrum of the 5-trichloromethyl-5-hydroxy-3-(2-phenylethyl)-4,5-dihydroisoxazole (**2k**), $CDCl_3$.

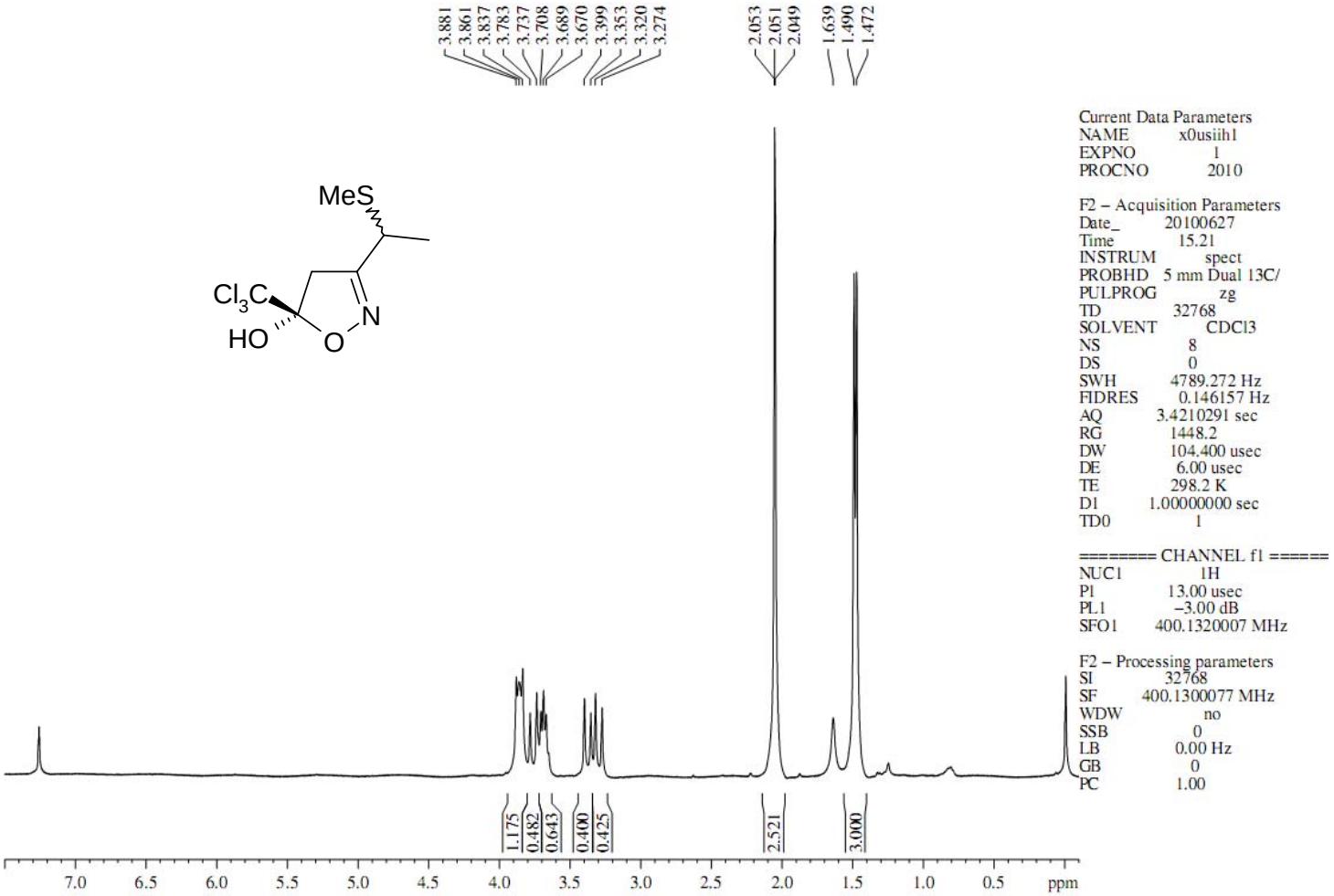


Figure S16: ^{1}H NMR spectrum of the 5-trichloromethyl-5-hydroxy-3-(1-thiomethylethyl)-4,5-dihydroisoxazole (**2l**), $CDCl_3$.

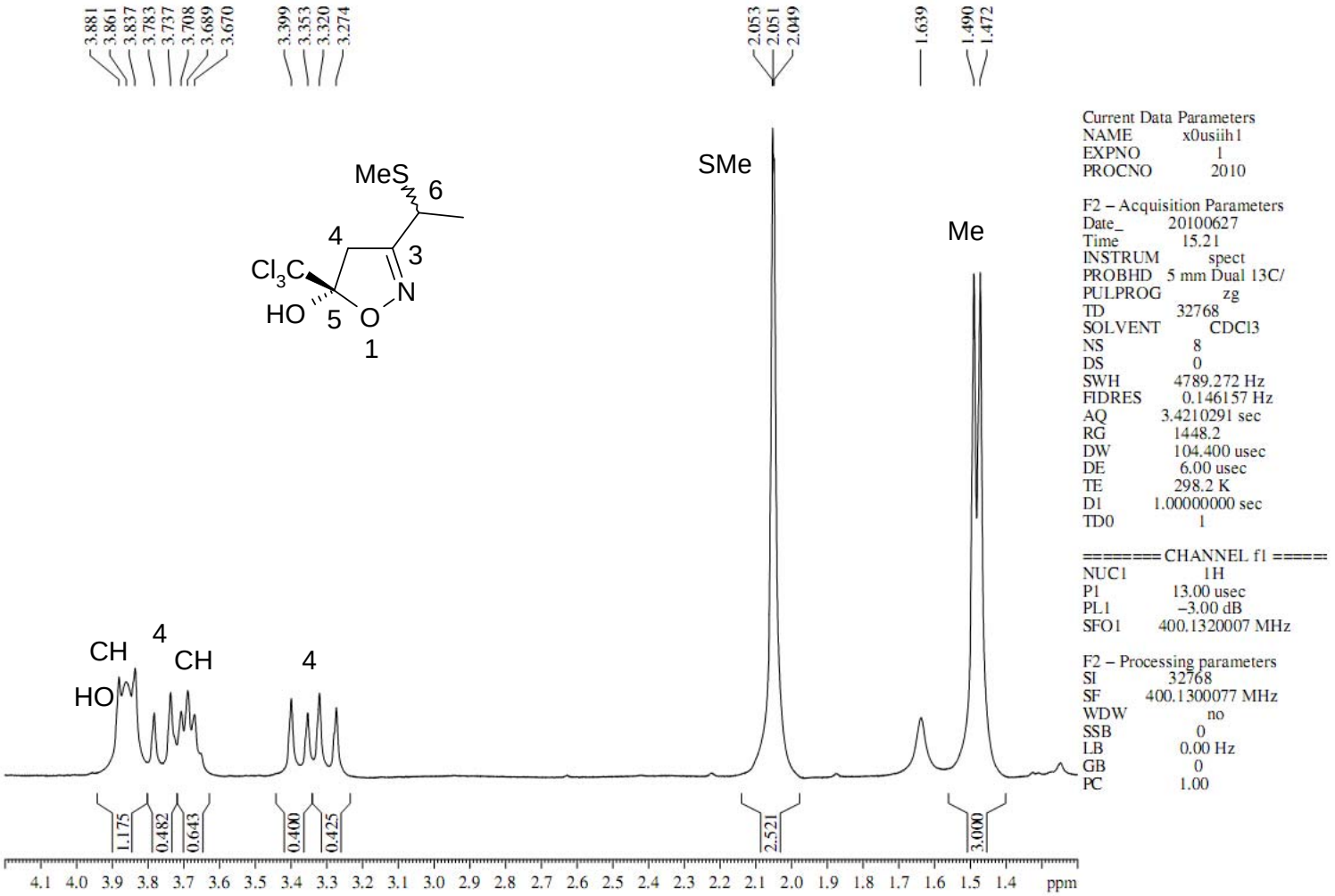


Figure S17: ^{13}C NMR spectrum of **2h** in $CDCl_3$, expanded between 1.2–4.2 ppm.

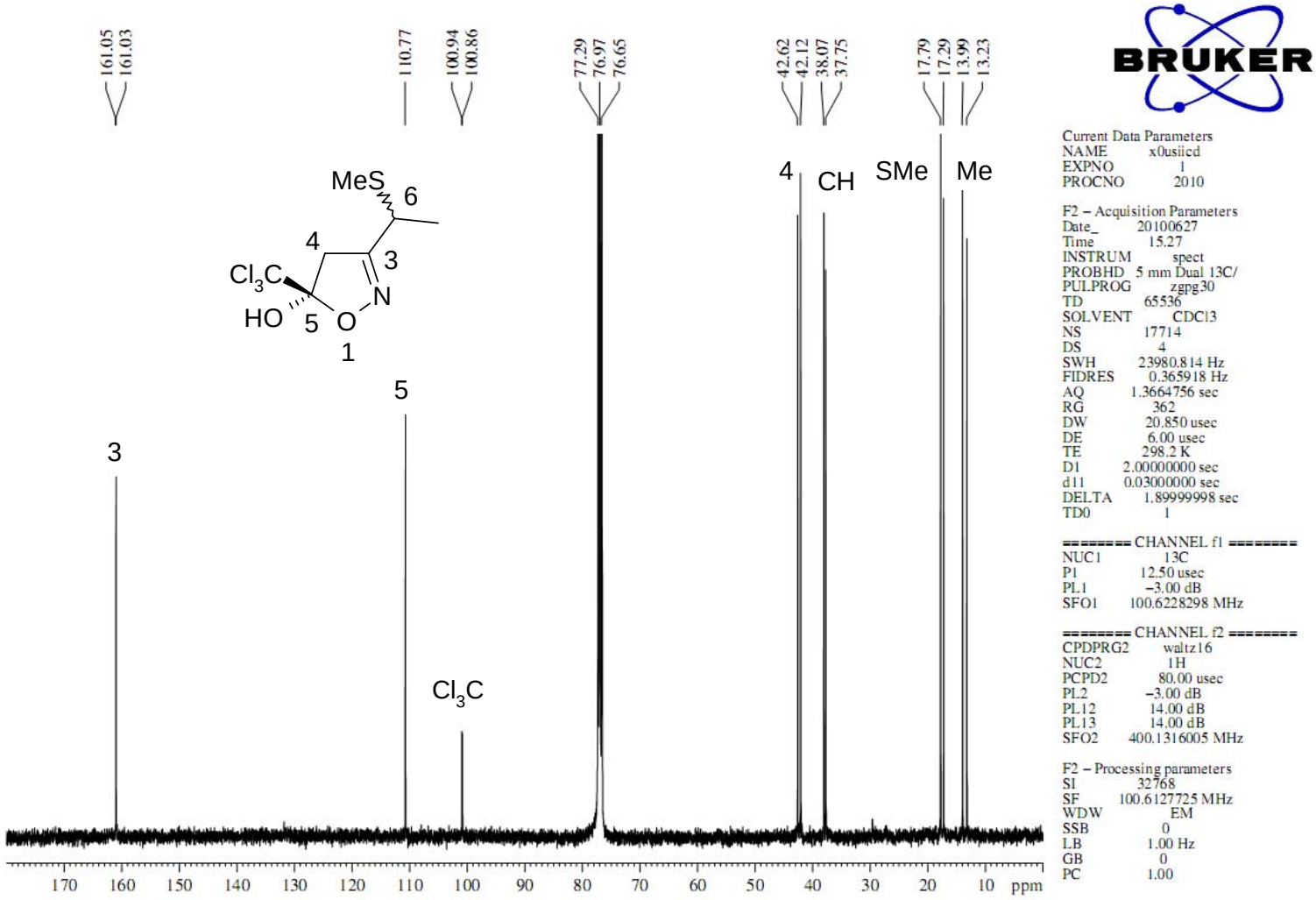


Figure S18: ^{13}C NMR spectrum of the 5-trichloromethyl-5-hydroxy-3-(1-thiomethylethyl)-4,5-dihydroisoxazole (**2l**), $CDCl_3$.

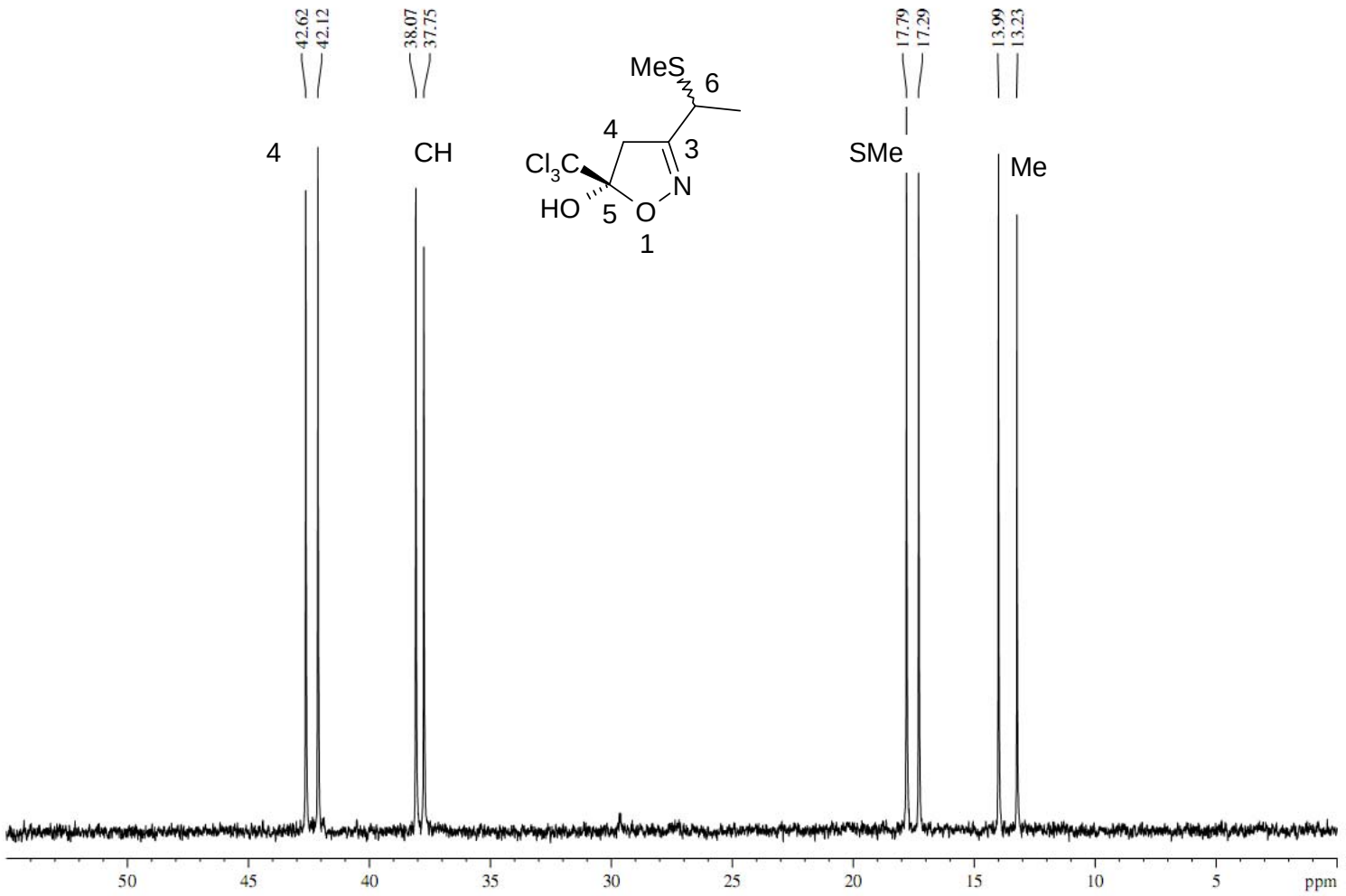


Figure S19: ^{13}C NMR spectrum of **2l** in $CDCl_3$, expanded between 0–55 ppm.

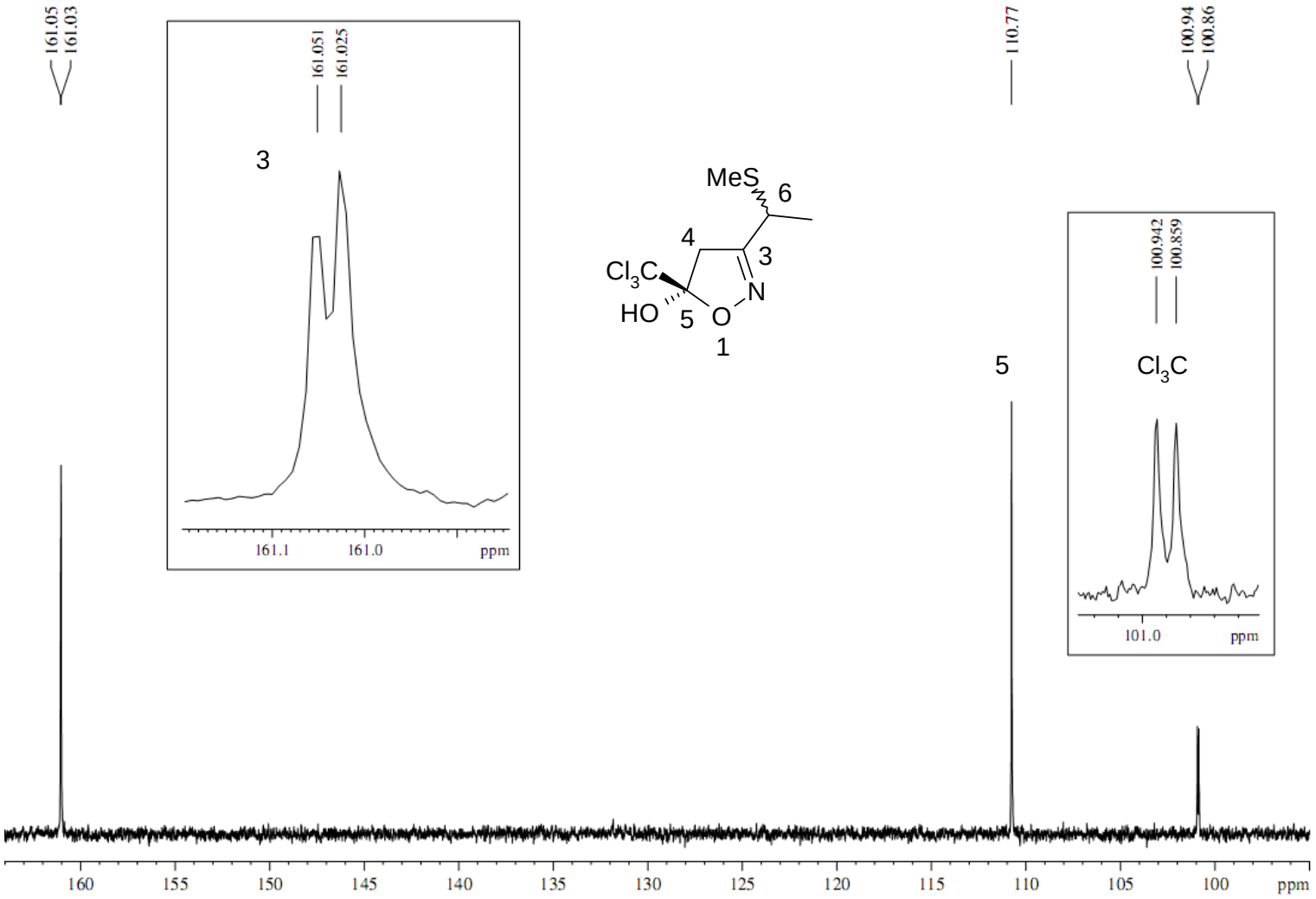


Figure S20: ^{13}C NMR spectrum of **2l** in $CDCl_3$, expanded between 95–164 ppm.

Table S1. Crystal data and structure refinement **2d**.

Identification code	**2d**
Empirical formula	C7 H10 Cl3 N O2
Formula weight	246.51
Temperature	293(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	P21/c
Unit cell dimensions	a = 10.304(2) Å α=90.000°
	b = 5.7322(1) Å β= 104.346(1)°
	c = 18.2694(3) Å γ= 90.000°
Volume	1045.44(3) Å3
Z	4
Density (calculated)	1.566 mg/m3
Absorption coefficient	0.844 mm-1
F(000)	504
Crystal size	0.12 × 0.26 × 0.28 mm3
Theta range for data collection	3.43 to 27.87°.
Index ranges	-13≤ h ≤13, -7 ≤ k ≤7, -22 ≤ l ≤23
Reflections collected	12664
Independent reflections	2363 [R(int) = 0.0630]
Completeness to theta = 27.86°	98.8%
Refinement method	Full-matrix least-squares on F2
Computing	COLLECT[6], HKL Denzo and Scalepack
	[7], SHELXS-97[8], SHELXL-97[8]
Max. and min. transmission	0.8493 and 0.8493
Refinement method	Full-matrix least-squares on F2
Data / restraints / parameters	2363 / 0 / 118
Goodness-of-fit on F2	1.085
Final R indices [I>2sigma(I)]	R1 = 0.0442, wR2 = 0.1080

Table S2. Atomic coordinates (x104) and equivalent isotropic displacement parameters ($Å^2x10^3$). U(eq) is defined as one-third of the trace of the orthogonalized Uij tensor **2d**.

Atom	x	y	z	U(eq)
Cl1	0.04414(5)	0.20679(0)	0.11113(3)	0.0494(2)
Cl2	0.09915(5)	-0.14027(0)	0.22805(3)	0.0471(2)
Cl3	0.18575(6)	-0.21529(0)	0.09190(3)	0.0523(2)
O1	0.38606(3)	-0.0626(3)	0.23161(7)	0.0390(4)
O2	0.34366(3)	0.2081(3)	0.13461(7)	0.0381(4)
N1	0.43514(5)	-0.0040(3)	0.30946(9)	0.0382(5)
C1	0.16277(7)	-0.0020(3)	0.15721(0)	0.0323(5)
C2	0.29751(6)	0.1203(3)	0.19352(9)	0.0290(5)
C3	0.38492(7)	0.1880(3)	0.32348(0)	0.0333(5)
C4	0.29040(18)	0.2928(3)	0.25629(0)	0.0316(5)
C5	0.4218(2)	0.2948(5)	0.40034(1)	0.0488(7)
C6	0.3015(3)	0.3419(5)	0.43243(3)	0.0580(9)
C7	0.2258(3)	0.1275(7)	0.44338(6)	0.0854(3)

Table S3. Bond lengths (Å) for **2d**.

Atom 1	Atom 2	Bond (Å)
Cl1	C1	1.7673(8)
C5	C6	1.521(4)
Cl2	C1	1.7774(9)
C6	C7	1.495(5)
Cl3	C1	1.7644(8)
C4	H4A	0.9700
O1	N1	1.427(2)
C4	H4B	0.9700
O1	C2	1.450(2)
C5	H5A	0.9700
O2	C2	1.375(2)

C5	H5B	0.9700
O2	H2O2	0.8500
C6	H6A	0.9700
N1	C3	1.268(2)
C6	H6B	0.9700
C1	C2	1.550(2)
C7	H7A	0.9600
C2	C4	1.528(2)
C7	H7B	0.9600
C3	C4	1.491(3)
C7	H7C	0.9600
C3	C5	1.492(3)

Table S4. Bond angles [°] for **2d**.

Atom 1	Atom 2	Atom 3	Angle (°)
N1	O1	C2	109.50(14)
C2	C4	H4A	111.00
C2	O2	H2O2	105.00
C2	C4	H4B	111.00
O1	N1	C3	110.14(5)
C3	C4	H4A	111.00
Cl1	C1	Cl3	110.05(0)
C3	C4	H4B	111.00
Cl1	C1	C2	109.85(2)
H4A	C4	H4B	109.00
Cl1	C1	Cl2	108.31(0)
C3	C5	H5A	109.00
Cl2	C1	C2	110.05(2)
C3	C5	H5B	109.00
Cl3	C1	C2	110.40(2)
C6	C5	H5A	109.00

Cl2	C1	Cl3	108.64(9)
C6	C5	H5B	109.00
O1	C2	O2	110.09(4)
H5A	C5	H5B	108.00
O1	C2	C1	105.71(4)
C5	C6	H6A	109.00
O2	C2	C1	106.14(3)
C5	C6	H6B	109.00
O2	C2	C4	116.16(5)
C7	C6	H6A	109.00
O1	C2	C4	104.54(3)
C7	C6	H6B	109.00
C1	C2	C4	114.34(4)
H6A	C6	H6B	108.00
N1	C3	C5	121.63(8)
C6	C7	H7A	110.00
C4	C3	C5	124.98(7)
C6	C7	H7B	109.00
N1	C3	C4	113.68(6)
C6	C7	H7C	109.00
C2	C4	C3	102.45(4)
H7A	C7	H7B	109.00
C3	C5	C6	113.25(8)
H7A	C7	H7C	109.00
C5	C6	C7	114.1(2)
H7B	C7	H7C	109.00

Table S5. Anisotropic displacement parameters. The anisotropic displacement factor exponent takes the following form: -2π2[h2a*2U11+…+2hka*b*U12] **2d**.

Atom	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
Cl1	0.0343(3)	0.0487(3)	0.0577(3)	0.0103(2)	-0.0028(2)	0.0027(2)
Cl2	0.0459(3)	0.0432(3)	0.0591(3)	0.0090(2)	0.0263(2)	-0.0037(2)
Cl3	0.0576(3)	0.0465(3)	0.0556(3)	-0.0212(3)	0.0194(3)	-0.0128(3)
O1	0.0362(7)	0.0415(8)	0.0383(7)	-0.0018(6)	0.0075(5)	0.0147(6)
O2	0.0372(7)	0.0478(8)	0.0308(7)	-0.0036(6)	0.0114(5)	-0.0134(6)
N1	0.0300(8)	0.0501(0)	0.0344(8)	0.0063(7)	0.0059(6)	0.0072(7)
C1	0.0317(9)	0.0286(9)	0.0386(0)	0.0008(7)	0.0103(7)	-0.0005(7)
C2	0.0252(8)	0.0316(9)	0.0304(9)	-0.0003(7)	0.0071(6)	0.0019(7)
C3	0.0251(8)	0.0458(1)	0.0310(9)	0.0007(8)	0.0091(7)	-0.0032(8)
C4	0.0311(9)	0.0315(9)	0.0327(9)	-0.0023(7)	0.0091(7)	0.0019(7)
C5	0.0442(1)	0.0701(6)	0.0345(0)	-0.0090(0)	0.0083(9)	-0.0146(1)
C6	0.0635(15)	0.0767(8)	0.0389(2)	-0.0154(1)	0.0192(0)	-0.0027(3)
C7	0.0790(9)	0.127(3)	0.0592(6)	-0.0133(7)	0.0368(4)	-0.039(2)

Table S6. Hydrogen coordinates (x10^4) and isotropic displacement parameters (Å^2 × 10^3) for **2d**.

Atom	x	y	z	U(iso)
H2O2	0.41275	0.28620	0.15500	0.0572
H4A	0.31954	0.44709	0.24539	0.0379
H4B	0.20038	0.30265	0.26335	0.0379
H5A	0.46842	0.44056	0.39784	0.0586
H5B	0.48301	0.19130	0.43419	0.0586
H6A	0.33196	0.42026	0.48060	0.0697
H6B	0.24100	0.44692	0.39856	0.0697
H7A	0.15108	0.17031	0.46304	0.1268
H7B	0.28387	0.02472	0.47815	0.1268

Table S7. Complete list of torsion angles [°] for **2d**.

Atom 1	Atom 2	Atom 3	Atom 4	Angle (°)
C2	O1	N1	C3	1.5(2)
N1	O1	C2	O2	122.45(5)
N1	O1	C2	C1	-123.74(4)
N1	O1	C2	C4	-2.94(8)
O1	N1	C3	C4	0.6(2)
O1	N1	C3	C5	-178.37(7)
Cl1	C1	C2	C4	64.11(6)
Cl1	C1	C2	O1	178.29(1)
Cl1	C1	C2	O2	-65.09(16)
Cl3	C1	C2	C4	-174.81(2)
Cl2	C1	C2	O1	59.37(5)
Cl3	C1	C2	O2	56.29(6)
Cl3	C1	C2	O1	-60.63(5)
Cl2	C1	C2	O2	176.08(2)
Cl2	C1	C2	C4	-55.02(7)
O1	C2	C4	C3	3.03(7)
O2	C2	C4	C3	-118.42(6)
C1	C2	C4	C3	117.91(6)
C5	C3	C4	C2	176.62(8)
N1	C3	C4	C2	-2.3(2)
N1	C3	C5	C6	-124.0(2)
C4	C3	C5	C6	57.4(3)
C3	C5	C6	C7	62.2(3)

Table S8. Crystal data and structure refinement for **2o.**

Identification code	**2o**
Empirical formula	$C_{10}H_{14}Cl_3NO_2$
Formula weight	286.59
Temperature	293 K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	C2/c
Unit cell dimensions	a = 24.6810(9) Å α = 90.000(0) b = 7.2280(2) Å β = 130.690(1) c = 18.7730(2) Å γ = 90.000(0)
Volume	2539.57(9) $Å^3$
Z	9
Density (calculated)	1.504 mg/m^3
Absorption coefficient	0,706
F(000)	1192
Crystal size	0.30 × 0.22 × 0.02 mm^3
Theta range for data collection	2.86 to 27.80°
Index ranges	$-32 \le h \le 30$, $-9 \le k \le 9$, $-22 \le l \le 24$
Reflections collected	11226
Independent reflections	2703
Completeness to theta = 27.86°	89.5%
Refinement method	Full-matrix least-squares on F^2
Computing	COLLECT[6], HKL Denzo and Scalepack [7], SHELXS-97[8], SHELXL-97[8]
Max. and min. transmission	0.8716/0.8716
Data/ restrains/ parameters	2703 / 0 / 145
Goodness-of-fit on F^2	1.049
Final R indices [I>2σ(I)]	R1 = 0.0513, wR2 = 0.1046
R índices (all data)	R1 = 0.0715, wR2 = 0.1140
Largest diff. Peak and hole	0.303 and -0.211 $e.Å^{-3}$

Table S9. Atomic coordinates ($x10^4$) and equivalent isotropic displacement parameters ($Å^2 \times 10^3$). U(eq) is defined as one-third of the trace of the orthogonalized U_{ij} tensor for **2o**.

Atom	x	y	z	U(eq)
Cl1	0.13540(4)	0.55614(11)	-0.07125(4)	0.0741(3)
Cl2	0.17345(4)	0.85705(10)	0.05398(5)	0.0706(3)
Cl3	0.07455(4)	0.57985(13)	0.01724(6)	0.0806(3)
O1	0.22468(9)	0.5547(2)	0.19676(11)	0.0519(5)
O2	0.19348(9)	0.3179(2)	0.09484(11)	0.0540(6)
N1	0.29434(12)	0.6306(3)	0.26528(13)	0.0530(7)
C1	0.15254(13)	0.6191(3)	0.03289(16)	0.0508(8)
C2	0.21524(12)	0.4989(3)	0.11609(15)	0.0425(7)
C3	0.28711(13)	0.5385(3)	0.14056(15)	0.0465(7)
C4	0.32814(13)	0.6233(3)	0.23573(17)	0.0508(8)
C5	0.3972(6)	0.7159(17)	0.2847(7)	0.061(3)
C6	0.4588(3)	0.5881(7)	0.3063(4)	0.0616(17)
C7	0.4709(8)	0.3939(15)	0.3564(9)	0.075(3)
C8	0.4359(6)	0.2177(16)	0.2911(7)	0.054(2)
C9	0.35545(14)	0.2335(4)	0.21975(19)	0.0612(9)
C10	0.32191(14)	0.3668(4)	0.13740(17)	0.0578(9)
C6A	0.4596(6)	0.517(2)	0.3734(8)	0.117(5)
C7A	0.4752(14)	0.410(4)	0.3317(16)	0.119(9)
C8A	0.4360(12)	0.264(3)	0.2919(17)	0.130(7)
C5A	0.4099(10)	0.677(2)	0.3116(10)	0.067(4)

Table S10. Bond lengths (Å) for **2o**.

Atom 1	**Atom 2**	**Bond Length (Å)**
Cl1	C1	1.769(3)
C9	C10	1.528(4)
Cl2	C1	1.765(2)
C3	H3	0.9800
Cl3	C1	1.771(4)

C5	H5A	0.9700
O1	N1	1.424(3)
C5	H5B	0.9700
O1	C2	1.432(3)
C5A	H5A1	0.9700
O2	C2	1.371(3)
C5A	H5A2	0.9700
O2	H2O2	0.9100
C6	H6A	0.9700
N1	C4	1.269(5)
C6	H6B	0.9700
C1	C2	1.561(3)
C6A	H6A1	0.9700
C2	C3	1.542(5)
C6A	H6A2	0.9700
C3	C10	1.532(4)
C7	H7A	0.9700
C3	C4	1.495(3)
C7	H7B	0.9700
C4	C5	1.468(15)
C7A	H7A2	0.9700
C4	C5A	1.58(2)
C7A	H7A1	0.9700
C5	C6	1.589(17)
C8	H8B	0.9700
C5A	C6A	1.53(2)
C8	H8A	0.9700
C6	C7	1.606(13)
C8A	H8A1	0.9700
C6A	C7A	1.32(4)
C8A	H8A2	0.9700
C7	C8	1.578(16)

C9	H9A	0.9700
C7A	C8A	1.29(4)
C9	H9B	0.9700
C8	C9	1.511(15)
C10	H10A	0.9700
C8A	C9	1.53(3)
C10	H10B	0.9700

Table S11. Bond angles [°] for **2o**.

Atom 1	**Atom 2**	**Atom 3**	**Angle**
N1	O1	C2	109.4(2)
C6A	C7A	C8A	115(3)
C2	O2	H2O2	114.00
C7	C8	C9	111.4(11)
O1	N1	C4	109.9(2)
C7A	C8A	C9	133(2)
Cl1	C1	Cl3	108.94(14)
C8A	C9	C10	109.9(10)
Cl1	C1	C2	109.2(2)
C8	C9	C10	118.5(6)
Cl2	C1	Cl3	108.70(17)
C3	C10	C9	114.8(3)
Cl2	C1	C2	111.33(17)
C2	C3	H3	109.00
Cl3	C1	C2	109.8(2)
C4	C3	H3	109.00
Cl1	C1	Cl2	108.84(15)
C10	C3	H3	109.00
O1	C2	C1	105.8(2)
C4	C5	H5A	109.00
O1	C2	C3	105.68(19)

C4	C5	H5B	108.00
O1	C2	O2	109.8(2)
C6	C5	H5A	109.00
O2	C2	C3	114.9(2)
C6	C5	H5B	109.00
C1	C2	C3	113.1(2)
H5A	C5	H5B	108.00
O2	C2	C1	107.2(2)
H5A1	C5A	H5A2	108.00
C2	C3	C4	100.6(3)
C6A	C5A	H5A2	109.00
C4	C3	C10	114.7(2)
C4	C5A	H5A1	108.00
C2	C3	C10	113.8(2)
C4	C5A	H5A2	109.00
N1	C4	C3	114.4(3)
C6A	C5A	H5A1	109.00
N1	C4	C5A	114.4(8)
C7	C6	H6A	108.00
C3	C4	C5	122.7(6)
C7	C6	H6B	108.00
C3	C4	C5A	130.5(8)
H6A	C6	H6B	108.00
N1	C4	C5	122.2(6)
C5	C6	H6B	108.00
C4	C5	C6	115.0(8)
C5	C6	H6A	108.00
C4	C5A	C6A	114.8(12)
C5A	C6A	H6A1	109.00
C5	C6	C7	116.1(11)
C5A	C6A	H6A2	109.00
C5A	C6A	C7A	113.1(16)

H6A1	C6A	H6A2	108.00
C6	C7	C8	116.9(9)
C7A	C6A	H6A2	109.00
C7A	C6A	H6A1	109.00
C7A	C8A	H8A2	104.00
C8	C7	H7A	108.00
C9	C8A	H8A1	104.00
C8	C7	H7B	108.00
C9	C8A	H8A2	104.00
C6	C7	H7B	108.00
C7A	C8A	H8A1	104.00
C6	C7	H7A	108.00
C10	C9	H9A	108.00
H7A	C7	H7B	107.00
C10	C9	H9B	108.00
H7A1	C7A	H7A2	107.00
H9A	C9	H9B	107.00
C8A	C7A	H7A2	108.00
C8	C9	H9B	108.00
C6A	C7A	H7A1	109.00
C8	C9	H9A	108.00
C6A	C7A	H7A2	109.00
C8A	C9	H9B	104.00
C8A	C7A	H7A1	108.00
C8A	C9	H9A	120.00
C7	C8	H8B	109.00
H10A	C10	H10B	108.00
C7	C8	H8A	109.00
C9	C10	H10B	109.00
C9	C8	H8A	109.00
C3	C10	H10A	109.00
C9	C8	H8B	109.00

C3	C10	H10B	109.00
H8A	C8	H8B	108.00
C9	C10	H10A	109.00
H8A1	C8A	H8A2	106.00

Table S12. Anisotropic displacement parameters. The anisotropic displacement factor exponent takes the following form: $-2\pi^2[h^2a^{*2}U_{11}+\ldots+2hka^*b^*U_{12}]$ for **2o**.

Atom	**U^{11}**	**U^{22}**	**U^{33}**	**U^{23}**	**U^{13}**	**U^{12}**
C(1)	53(1)	51(2)	46(1)	2(1)	31(1)	-1(1)
C(2)	54(1)	41(1)	38(1)	2(1)	32(1)	1(1)
C(3)	56(1)	46(1)	45(1)	-4(1)	36(1)	-1(1)
C(4)	58(1)	36(1)	54(1)	4(1)	35(1)	2(1)
C(9)	66(2)	51(2)	64(2)	3(1)	42(1)	-3(1)
C(10)	61(2)	70(2)	49(1)	6(1)	39(1)	-6(1)
Cl(1)	94(1)	78(1)	42(1)	-2(1)	40(1)	-7(1)
Cl(2)	81(1)	45(1)	74(1)	-4(1)	45(1)	-9(1)
Cl(3)	55(1)	98(1)	83(1)	-5(1)	42(1)	-3(1)
N(1)	66(1)	40(1)	43(1)	7(1)	31(1)	3(1)
O(1)	64(1)	58(1)	44(1)	8(1)	39(1)	5(1)
O(2)	76(1)	42(1)	52(1)	5(1)	45(1)	9(1)
C(5)	55(5)	51(6)	52(5)	1(3)	25(5)	-1(4)
C(6)	50(3)	58(3)	75(3)	11(2)	40(2)	15(2)
C(7)	66(6)	61(5)	55(5)	1(3)	21(3)	-4(4)
C(8)	54(4)	46(4)	63(4)	2(3)	38(4)	-4(3)
C(6A)	69(7)	143(12)	80(7)	35(8)	23(5)	45(8)
C(5A)	47(6)	31(6)	59(8)	2(5)	7(6)	3(4)
C(7A)	57(7)	170(20)	87(15)	-13(12)	32(10)	15(8)
C(8A)	78(10)	78(14)	128(14)	-33(11)	20(10)	-24(9)

Table S13. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2 \times 10^3$).

Atom	x	y	z	U(eq)
H(3)	2798	3684	5970	56
H(9A)	3363	8888	6940	73
H(9B)	3393	7306	7530	73

H(10A)	3586	5933	6358	69
H(10B)	2860	6996	5795	69
H(2O2)	1952	7406	6393	81
H(5A)	3903	1802	7469	73
H(5B)	4128	2350	8436	73
H(6A)	4482	4368	7476	74
H(6B)	5032	3431	8460	74
H(7A)	4525	5951	8887	89
H(7B)	5219	6274	9038	89
H(8A)	4491	8915	8295	65
H(8B)	4542	7968	7588	65
H(6A1)	4373	5573	8910	140
H(6A2)	5036	4328	9305	140
H(5A1)	4150	2272	8517	79
H(5A2)	4251	2715	7795	79
H(7A1)	5247	6285	8781	141
H(7A2)	4708	5176	7846	141
H(8A1)	4536	7946	7640	156
H(8A2)	4516	8144	8441	156

Table S14. Complete list of torsion angles [°] for **2o**.

Atom 1	Atom 2	Atom 3	Atom 4	Angle
Cl(2)	C(1)	C(2)	O(2)	178.25(15)
Cl(1)	C(1)	C(2)	O(2)	61.5(2)
Cl(3)	C(1)	C(2)	O(2)	57.8(2)
Cl(2)	C(1)	C(2)	O(1)	61.1(2)
Cl(1)	C(1)	C(2)	O(1)	178.67(15)
Cl(3)	C(1)	C(2)	O(1)	59.3(2)
Cl(2)	C(1)	C(2)	C(3)	54.2(2)
Cl(1)	C(1)	C(2)	C(3)	66.1(2)
Cl(3)	C(1)	C(2)	C(3)	174.56(15)
O(2)	C(2)	C(3)	C(4)	123.57(19)

O(1)	C(2)	C(3)	C(4)	2.4(2)
C(1)	C(2)	C(3)	C(4)	113.0(2)
O(2)	C(2)	C(3)	C(10)	0.4(3)
O(1)	C(2)	C(3)	C(10)	120.8(2)
C(1)	C(2)	C(3)	C(10)	123.9(2)
C(10)	C(3)	C(4)	N(1)	120.7(2)
C(2)	C(3)	C(4)	N(1)	1.8(3)
C(10)	C(3)	C(4)	C(5)	68.2(6)
C(2)	C(3)	C(4)	C(5)	169.3(5)
C(10)	C(3)	C(4)	C(5A)	48.7(7)
C(2)	C(3)	C(4)	C(5A)	171.2(7)
C(8)	C(9)	C(10)	C(3)	110.0(5)
C(8A)	C(9)	C(10)	C(3)	99.7(9)
C(4)	C(3)	C(10)	C(9)	40.8(3)
C(2)	C(3)	C(10)	C(9)	74.3(3)
C(5)	C(4)	N(1)	O(1)	170.7(5)
C(3)	C(4)	N(1)	O(1)	0.4(3)
C(5A)	C(4)	N(1)	O(1)	171.6(6)
C(4)	N(1)	O(1)	C(2)	1.3(2)
O(2)	C(2)	O(1)	N(1)	126.76(18)
C(3)	C(2)	O(1)	N(1)	2.4(2)
C(1)	C(2)	O(1)	N(1)	117.86(19)
N(1)	C(4)	C(5)	C(6)	128.7(6)
C(3)	C(4)	C(5)	C(6)	60.9(7)
C(5A)	C(4)	C(5)	C(6)	61(4)
C(4)	C(5)	C(6)	C(7)	50.3(10)
C(5)	C(6)	C(7)	C(8)	98.9(11)
C(8A)	C(9)	C(8)	C(7)	24(5)
C(10)	C(9)	C(8)	C(7)	73.2(7)
C(6)	C(7)	C(8)	C(9)	62.3(11)
C(7A)	C(6A)	C(5A)	C(4)	80(2)
N(1)	C(4)	C(5A)	C(6A)	87.1(16)

C(5)	C(4)	C(5A)	C(6A)	152(6)
C(3)	C(4)	C(5A)	C(6A)	82.3(16)
C(5A)	C(6A)	C(7A)	C(8A)	96(3)
C(6A)	C(7A)	C(8A)	C(9)	53(4)
C(8)	C(9)	C(8A)	C(7A)	177(7)
C(10)	C(9)	C(8A)	C(7A)	48(3)

Biological assays

5-Trichloromethyl-4,5-dihydroisoxazole derivatives were screened for antibacterial activity, in accordance with the National Committee for Clinical Laboratory Standards (NCCLS) and for antifungal activity in accordance with Shadomy and Pfaller and the NCCLS.[1–3] The compounds were evaluated *in vitro* for antimicrobial activity against representative human pathogenic Gram-positive bacteria (*S. aureus*), Gram-negative bacteria (*E. coli* and *P. aeruginosa*), and a panel of fungi (*C. albicans*, *C. tropicalis*, *C. lusitaniae*, *C. neoformans* var. *gattii* serotype A, *C. neoformans* var. *gattii* serotype B, *C. neoformans* var. *gatti* serotype C, and *C. neoformans* serotype D).

Minimal inhibitory concentrations (MIC) were determined with a standard two-fold dilution method using broth medium, antibacterial activity was determined based on the NCCLS M7-A5 document, and antifungal activity was evaluated based on Shadomy and Pfaller and the NCCLS M27-A2 document. Test compounds were dissolved in DMSO at an initial concentration of 5000 μg/cm^3 and then were serially diluted in culture media (Müeller-Hinton broth for bacterial and Sabouraud broth for fungal assays).

Cultures of microorganisms were adjusted to 105 CFUs/cm^3 according to the McFarland scale. Antimicrobial assays were performed in triplicate and incubated at 35°C for 24 h for bacteria and *Candida* spp. and for 72 h for *Cryptococcus* spp. MIC was defined as the

compound concentration at which no macroscopic sign of microbial growth was detected. The interpretation of the results was based on fluconazole breakpoints for fungi and imipenem for bacterial pathogens, according to the M27-A2 and M7-A5 techniques. The minimal germicidal concentrations (MBC or MFC) were determined by subcultivating samples from cultures with apparent growth in Müeller-Hinton agar for bacteria or Sabouraud dextrose agar for fungi.

Table S15. The in vitro antibacterial activity of synthesized 5-trichloromethyl-4,5-dihydroisoxazole derivatives.

Compd.	*Staphylococcus aureus*		*Escherichia coli*		*Pseudomonas aerugionosa*	
	MIC	MBC	MIC	MBC	MIC	MBC
2a	312	> 625	312	> 625	312	> 625
2b	> 625	--	> 625	--	> 625	> 625
2c	> 625	--	> 625	--	> 625	> 625
2d	> 625	--	> 625	--	> 625	> 625
2e	> 625	--	> 625	--	> 625	> 625
2f	> 625	--	312	> 625	> 625	> 625
2g	--	--	--	--	--	--
2h	78	156	312	> 625	> 625	> 625
2i	156	312	156	312	> 625	> 625
2j	> 625	--	> 625	> 625	> 625	> 625
2k	> 625	--	> 625	--	> 625	> 625
2l	> 625	--	> 625	> 625	> 625	> 625
2m	> 625	--	> 625	--	> 625	--
2n	> 625	--	> 625	> 625	312	--
2o	156	> 625	> 625	--	> 625	--
I	0.06		0.06		2.0	

MIC, minimum inhibitory concentration (μg/cm^3); MFC, minimum fungicidal concentration (μg/cm^3);
I, imipenem; --, no activity

Table S16. The in vitro antifungal profile of synthesized 5-trichloromethyl-4,5-dihydroisoxazole derivatives.

Compd.	*Candida albicans*		*Candida tropicalis*		*Candida lusitaneae*		*Cryptococcus neoformans A*		*Cryptococcus neoformans B*		*Cryptococcus neoformans C*		*Cryptococcus neoformans D*	
	MIC	MFC	MIC	MFC	MIC	MFC	MIC	MFC	MIC	MFC	MIC	MFC	MIC	MFC
2a	> 625	> 625	> 625	> 625	> 625	> 625	312	> 625	312	> 625	156	312	312	> 625
2b	> 625	--	> 625	--	--	--	> 625	> 625	312	> 625	39	78	> 625	> 625
2c	> 625	--	> 625	--	> 625	> 625	> 625	--	> 625	> 625	39	> 625	> 625	> 625
2d	> 625	--	> 625	> 625	> 625	> 625	312	> 625	312	> 625	39	312	312	> 625
2e	312	> 625	> 625	--	312	> 625	312	> 625	312	> 625	39	156	312	> 625
2f	> 625	> 625	312	> 625	156	> 625	39	312	312	> 625	19	39	312	> 625
2g	312	> 625	> 625	--	312	> 625	39	312	312	> 625	39	78	312	> 625
2h	156	> 625	312	> 625	312	> 625	78	312	78	312	39	312	39	312
2j	312	> 625	312	--	312	> 625	78	312	312	> 625	39	156	312	≥ 625
2k	312	> 625	> 625	--	> 625	> 625	156	> 625	312	> 625	39	312	312	≥ 625
2l	312	> 625	> 625	> 625	> 625	> 625	156	> 625	312	> 625	39	> 625	156	≥ 625
2m	312	> 625	> 625	--	> 625	> 625	312	> 625	312	> 625	78	156	312	--
2n	> 625	--	> 625	--	> 625	--	156	> 625	156	--	156	312	> 625	--
2o	> 625	--	312	--	312	> 625	39	> 625	312	> 625	19	39	312	> 625
F	4.0		4.0		4.0		2.0		2.0		2.0		2.0	

MIC, minimum inhibitory concentration (μg/cm^3); MFC, minimum fungicidal concentration (μg/cm^3);
F, fluconazole; -- no activity

References

1. Spiegler, W.; Götz, N. Synthesis of Isoxazole-5-carboxylic acid. *Synthesis* **1986**, 69–70.

2. Martins, M. A. P.; Pereira, C. M. P.; Cunico, W.; Moura, S.; Rosa, F. A.; Peres, R. L.; Machado, P.; Bonacorso, H. G.; Zanatta, N. Ultrasound promoted synthesis of 5-hydroxy-5-trihalomethyl-4,5-dihydroisoxazoles and β-enamino trihalomethyl ketones in water. *Ultrasound Sonochem*. **2006**, *13*, 364–370.

3. Martins, M. A. P.; Beck, P. ; Cunico, W.; Pereira, C. M. P.; Sinhorin, A. P.; Blanco, R. F.; Peres, R.; Bonacorso, H. G.; Zanatta, N. Microwave assisted synthesis of 5-hydroxy-5-trichloromethyl-4,5-dihydroisoxazoles. *Tetrahedron Lett*. **2002**, *43*, 7005–7008.

4. Martins, M. A. P.; Sinhorin, A. P.; Rosa, A.; Flores, A. F. C.; Wastowski, A. D.; Pereira, C. M. P.; Flores, D. C.; Beck, P.; Freitag, R. A.; Brondani, S.; Cunico, W.; Bonacorso, H. G.; Zanatta, N. Regiospecific allylic mono- and dibromination of 4-methoxy-1,1,1-trihalo-3-alken-2-ones and 5-methoxy-1,1,1,2,2-pentafluoro-4-hexen-3-one and their applications to the synthesis of heterocycles. *Synthesis* **2002**, 2353–2358.

5. Martins, M. A. P.; Brondani, S.; Leidens, V. L.; Flores, D. C.; Moura, S.; Zanatta, N.; Hörner, M.; Flores, A. F. C. Synthesis and structure of new trichloromethyl-β-diketones-5-trichloromethylisoxazole and 5-isoxazolecarboxylic acid derivatives. Can J. Chem. **2005**, *83*, 1171–1177.

6. National Committee for Clinical Laboratory Standards, document M7-A5; National Committee for Clinical Laboratory Standards: Wayne, PA, 2002.

7. Shadomy, S.; Pfaller, M. In Manual of Clinical Microbiology; Balows, A., Hausler, W. J. Jr., Herrman, K. L., Isenberg, H. D., Shadomy, H. J., Eds; American Society of Microbiology: Washington, 1991; pp 1173–1183.

8. National Committee for Clinical Laboratory Standards, document M27-A2; National Committee for Clinical Laboratory Standards: Wayne, PA, 2002.

9. Farrugia, L. J. ORTEP-3 for *Windows*- a version of ORTEP-III with a Graphical User Interface. *J*. *Appl*. *Cryst*. **1997**, *30*, 565.

10. Enraf-Nonius COLLECT 1997–2000. Nonius B. V., Delft, The Netherlands.

11.Otwinowski, Z.; Minor, W. HKL *Denzo and Scalepack*. *In Methods in Enzymology*, edited by C.W. Carter, Jr. & R.M. Sweet pp. 307–326, New York, Academic Press 1997.

12.Sheldrick, G. M. SHELXS-97. Program for Crystal Structure Resolution. University of Göttingen, Göttingen, Germany, 1997.

13.Sheldrick, G. M. SHELXL-97. Program for Crystal Structures Analysis. University. of Göttingen, Göttingen, Germany, 1997.