Supporting Information

Microwave–Assisted Ullmann C–S Bond Formation: Synthesis of the P38α MAPK Clinical Candidate VX–745

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General Procedures. Commercially available reagents were used without further purification; solvents were dried by standard procedures. Light petroleum refers to the fraction with bp 40-60 °C and ether refers to diethyl ether. Flash chromatography was carried out using Merck Kieselgel 60 H silica or Matrex silica 60. Analytical thin layer chromatography was carried out using aluminium-backed plates coated with Merck Kieselgel 60 GF_{254} that were visualised under UV light (at 254 and/or 360 nm). Microwave irradiation experiments were performed using a self-tunable CEM Discover focused monomodal microwave synthesiser at the given temperature, measured using the instrument's in-built IR sensor, by varying the irradiation power (initial power given in parentheses). Infra-red (IR) spectra were recorded in the range 4000-600 cm^{-1} using KBr disks for solid samples and thin films between NaCl plates for liquid samples or as a nujol mull and are reported in cm^{-1}. Nuclear magnetic resonance (NMR) spectra were recorded in $CDCl_3$ at 25 °C unless stated otherwise and were reported in ppm; *J* values were recorded in Hz and multiplicities were expressed by the usual conventions. Low-resolution mass spectra (MS) were determined using atmospheric pressure chemical ionization (APcI) unless otherwise stated. ES refers to electrospray ionization, CI refers to chemical ionization (ammonia) and EI refers to electron ionization. *In vacuo* refers to evaporation at reduced pressure using a rotary evaporator and diaphragm pump, followed by the removal of trace volatiles using a vacuum (oil) pump.

Experimental Procedures for Table 1

4-Nitrophenyl phenyl sulfide (4b) (Table 1 entry 2). A solution of 4-nitroiodobenzene (**3b**) (249 mg, 1.0 mmol), PhSH (107 mg, 0.1 mL, 1.0 mmol), $Pd(OAc)_2$ (5.6 mg, 0.025 mmol), Xantphos^{TM} (29 mg, 0.05 mmol), LiCl (5.6 mg, 0.025 mmol) and *i*Pr_2NEt (258 mg, 2 mmol) in dry dioxane (2 mL) was irradiated at 100 °C for 3 x 30 min in a pressure-rated glass tube (10 mL) using a CEM Discover microwave synthesiser by moderating the initial power (150 W). The reaction mixture was cooled to rt, partitioned between water and Et_2O and the aqueous layer further extracted with Et_2O. The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated in vacuo. Purification by column chromatography on SiO_2, eluting with light petroleum–CH_2Cl_2 (3:1), gave **4b** (24 mg, 11%) as a yellow solid, mp 52 °C (lit.[1] mp 50–55 °C) (found: $M^{\cdot+}$, 231.0347. $C_{12}H_9NO_2S$ [*M*] requires 231.0354); ^{1}H NMR (400 MHz; d_6–DMSO) δ 8.15, 7.29 (4H, AA'XX', J_{AX} 9), 7.62–7.58 (2H, m), 7.55 (3H); ^{13}C NMR (100 MHz, d_6–DMSO) 148.6 (C), 145.3 (C), 134.8 (C), 130.4 (CH), 130.1 (CH), 129.7 (CH), 126.6 (CH), 124.1 (CH); MS (EI) *m/z* (rel. intensity) 231 ($M^{\cdot+}$, 100), 201 (33), 184 (79), 152 (14).

4-Nitrophenyl phenyl sulfide (4b) (Table 1 entry 3). A solution of 4-nitroiodobenzene (**3b**) (284 mg, 1.1 mmol), PhSH (275 mg, 2.5 mmol), $Pd(PPh_3)_4$ (66 mg, 0.057 mmol) and NaO*t*Bu (438 mg, 4.6 mmol) in IPA (3 mL) was irradiated at 100 °C for 1 h in a pressure-rated glass tube (10 mL) using a CEM Discover microwave synthesiser by moderating the initial power (150 W). The reaction mixture was cooled to rt and evaporated *in vacuo*. The residue was partitioned between water and hexane and the organic layer was washed successively with water and brine, dried and evaporated in vacuo to give **4b** (30 mg, 12%) as a yellow solid.

Phenyl disulfide (5) (Table 1 entries 4 and 5). A solution of bromobenzene (**3a**) (157 mg, 1.0 mmol), PhSH (132 mg, 1.2 mmol) and CsOH (336 mg, 2.0 mmol) in DMSO (3 mL) was irradiated at 120 °C for 5–10 min in a pressure-rated glass tube (10 mL) using a CEM Discover microwave synthesiser by moderating the initial power (200–250 W). The reaction mixture was cooled to rt and partitioned between saturated aqueous NH_4Cl and Et_2O. The aqueous layer was further extracted with Et_2O and the combined ethereal extracts were washed successively with saturated aqueous NH_4Cl and brine, dried ($MgSO_4$) and evaporated in vacuo to give the *title compound* as a yellow solid, mp 61 °C (lit.[2] mp 61–63 °C); ^{1}H NMR (400 MHz; d_6–DMSO) δ 7.53 (4H, d, *J* 8), 7.38 (4H, app t, *J* 8), 7.30 (2H, t, *J* 8); ^{13}C NMR (100 MHz; d_6–DMSO) 136.2 (C), 129.9 (CH), 128 (CH), 127.6 (CH); MS (EI) *m/z* (rel. intensity) 218 ($M^{\cdot+}$, 95%), 185 (15), 154 (20), 109 (100).

Phenyl sulfide (4a) (Table 1 entry 6). A solution of bromobenzene (**3a**) (157 mg, 1.0 mmol), PhSH (132 mg, 1.2 mmol) and CsOH (336 mg, 2.0 mmol) in dry DMSO (3 mL) was irradiated at 100 °C for 10 min in a pressure-rated glass tube (10 mL) using a CEM Discover microwave synthesiser by moderating the initial power (200 W). The reaction mixture was cooled to rt and partitioned between saturated aqueous NH_4Cl and Et_2O. The aqueous layer was further extracted with Et_2O and the combined ethereal extracts were washed successively with saturated aqueous NH_4Cl and brine, dried ($MgSO_4$) and evaporated in vacuo to give the *title compound* (28 mg, 15%) as a yellow oil (found: $M^{\cdot+}$, 186.0510. $C_{12}H_{11}S$ [*M*] requires 186.0503); ^{1}H NMR (400 MHz, d_6–DMSO) δ 7.53 (4H, d, *J* 8), 7.38 (4H, app t, *J* 8), 7.30 (2H, t, *J* 8); ^{13}C NMR (100 MHz, d_6–DMSO) 136.2 (C), 130 (CH), 128.1 (CH), 127.6 (CH); MS (EI) *m/z* (rel. intensity) 186 ($M^{\cdot+}$, 100), 171 (10).

4-Nitrophenyl phenyl sulfide (4b) (Table 1 entry 7). A solution of 4-nitroiodobenzene (249 mg, 1.0 mmol), PhSH (0.12 mL, 1.2 mmol) and CsOH (336 mg, 2.0 mmol) in dry DMSO (3 mL) was irradiated at 120 °C for 10 min in a pressure-rated glass tube (10 mL) using a CEM Discover microwave synthesiser by moderating the initial power (150 W). After cooling the reaction mixture in a flow of compressed air, it was filtered and evaporated in vacuo. Purification by column chromatography on SiO_2, eluting with light petroleum–CH_2Cl_2 (3:1), gave the *title compound* (25 mg, 11%) as a yellow solid, mp 50 °C (lit.[1] mp 50–55 °C), with identical physical and spectroscopic properties.

4-Nitrophenyl phenyl sulfide (4b) (Table 1 entry 10). According to the typical experimental procedure (see main text), a solution of 4-nitroiodobenzene (162 mg, 0.65 mmol), PhSH (0.05 mL, 0.50 mmol), PEPPSI-*i*Pr (7 mg, 0.01 mmol), LiCl (4.5 mg, 0.1 mmol) and NaO*t*Bu (72 mg, 0.75 mmol) in dry PhMe (2 mL) was irradiated at 120 °C for 3 x 1 h in a pressure-rated glass tube (10 mL) using a CEM Discover microwave synthesiser by moderating the initial power (150 W). After cooling in a flow of compressed air, the reaction mixture was filtered and evaporated in vacuo. Purification by column chromatography on SiO_2, eluting with light petroleum–CH_2Cl_2 (3:1), gave the *title compound* (86 mg, 74%) as a yellow solid, mp 53 °C (lit.[1] mp 50–55 °C), with identical physical and spectroscopic properties.

4-Nitrophenyl phenyl sulfide (4b) (Table 1 entry 11). A solution of 4-nitroiodobenzene (162 mg, 0.65 mmol), PhSH (0.05 mL, 0.50 mmol), PEPPSI-*i*Pr (7 mg, 0.01 mmol), LiCl (4.5 mg, 0.1 mmol) and K_2CO_3 (138 mg, 1 mmol) in dry dioxane (2 mL) was irradiated at 120 °C for 3 x 1 h in a pressure-rated glass tube (10 mL) using a CEM Discover microwave synthesiser by moderating the initial power (150 W). After cooling in a flow of compressed air, the reaction mixture was partioned between H_2O and Et_2O and the aqueous layer further extracted

with Et_2O. The combined ethereal extracts were washed with brine, dried ($MgSO_4$) and evaporated *in vacuo*. Purification by column chromatography on SiO_2, eluting with light petroleum–CH_2Cl_2 (3:1), gave the *title compound* (51 mg, 44%) as a yellow solid, mp 52 °C (lit.[1] mp 50–55 °C), with identical physical and spectroscopic properties.

4-Nitrophenyl phenyl sulfide (4b) (Table 1 entry 12). A solution of 4-nitroiodobenzene (162 mg, 0.65 mmol), PhSH (0.05 mL, 0.50 mmol), PEPPSI-*i*Pr (7 mg, 0.01 mmol), LiCl (4.5 mg, 0.1 mmol) and NaO*t*Bu (72 mg, 0.75 mmol) in dry dioxane (2 mL) was irradiated at 120 °C for 3 x 1 h in a pressure-rated glass tube (10 mL) using a CEM Discover microwave synthesiser by moderating the initial power (150 W). After cooling in a flow of compressed air, the reaction mixture was partioned between H_2O and Et_2O and the aqueous layer further extracted with Et_2O. The combined ethereal extracts were washed with brine, dried ($MgSO_4$) and evaporated *in vacuo*. Purification by column chromatography on SiO_2, eluting with light petroleum–CH_2Cl_2 (3:1), gave the *title compound* (52 mg, 45%) as a yellow solid, mp 52 °C (lit.[1] mp 50–55 °C), with identical physical and spectroscopic properties.

4-Nitrophenyl phenyl sulfide (4b) (Table 1 entry 15). A solution of 4-nitroiodobenzene (249 mg, 1.0 mmol), PhSH (0.10 mL, 1.0 mmol) and NaO*t*Bu (144 mg, 1.5 mmol) in dry PhMe (2 mL) was irradiated at 120 °C for 90 min, then 2 x 1 h, in a pressure-rated glass tube (10 mL) using a CEM Discover microwave synthesiser by moderating the initial power (150 W). After cooling in a flow of compressed air, the reaction mixture was filtered and evaporated *in vacuo*. Purification by column chromatography on SiO_2, eluting with light petroleum–CH_2Cl_2 (3:1), gave the *title compound* (108 mg, 47%) as a yellow solid, mp 54 °C (lit.[1] mp 50–55 °C), with identical physical and spectroscopic properties.

4-Nitrophenyl phenyl sulfide (4b) (Table 1 entry 16). According to the typical experimental procedure (see main text), a solution of 4-nitroiodobenzene (162 mg, 0.65 mmol), PhSH (0.05 mL, 0.50 mmol), LiCl (4.5 mg, 0.1 mmol) and NaO*t*Bu (72 mg, 0.75 mmol) in dry PhMe (2 mL) was irradiated at 120 °C for 3 x 1 h in a pressure–rated glass tube (10 mL) using a CEM Discover microwave synthesiser by moderating the initial power (150 W). After cooling in a flow of compressed air, the reaction mixture was partioned between H_2O and Et_2O and the aqueous layer further extracted with Et_2O. The combined ethereal extracts were washed with brine, dried ($MgSO_4$) and evaporated *in*

vacuo. Purification by column chromatography on SiO_2, eluting with light petroleum–CH_2Cl_2 (3:1), gave the *title compound* (93 mg, 80%) as a yellow solid, mp 52 °C (lit.[1] mp 50–55 °C), with identical physical and spectroscopic properties.

4-Nitrophenyl phenyl sulfide (4b) (Table 1 entry 17). A solution of 4-nitroiodobenzene (249 mg, 1.0 mmol), PhSH (0.11 mL, 1.1 mmol), CuI (19 mg, 0.10 mmol), neocuproine (20 mg, 0.10 mmol) and NaO*t*Bu (144 mg, 1.5 mmol) in dry PhMe (3 mL) was irradiated at 80 °C in a pressure-rated glass tube (10 mL) for 3 x 1 h by moderating the initial power (150 W). After cooling in a flow of compressed air, the reaction mixture was filtered and evaporated *in vacuo*. Purification by column chromatography on SiO_2, eluting with light petroleum–CH_2Cl_2 (3:1), gave the *title compound* (142 mg, 61%) as a yellow solid, mp 48 °C (lit.[1] mp 50–55 °C), with identical physical and spectroscopic properties.

4-(Phenylthio)anisole (4c) (Table 1 entry 23). A solution of 4-iodoanisole (234 mg, 1.0 mmol), PhSH (0.11 mL, 1.1 mmol), CuI (19 mg, 0.10 mmol), neocuproine (20 mg, 0.10 mmol) and NaO*t*Bu (144 mg, 1.5 mmol) in dry PhMe (3 mL) was irradiated at 80 °C for 2 x 1 h in a pressure-rated glass tube (10 mL) using a CEM Discover microwave synthesiser by moderating the initial power (150 W). After cooling in a flow of compressed air, the reaction mixture was filtered and evaporated *in vacuo*. Purification by column chromatography on SiO_2, eluting with light petroleum–EtOAc (3:1), gave the *title compound* (89 mg, 41%) as a yellow oil (found: $M^{\cdot+}$, 216.0614. $C_{13}H_{12}OS$ [*M*] requires 216.0609); ^{1}H NMR (400 MHz, d_6-DMSO) δ 7.42, 7.01 (4H, AA'XX', J_{AX} 9), 7.30 (2H, m), 7.19 (1H, app tt, *J* 7, 1), 7.05 (2H, m), 3.78 (3H, s); ^{13}C NMR (125 MHz; d_6–DMSO) 158.8 (C), 137.6 (C), 134.3 (CH), 127.9 (CH), 127.3 (CH), 124.7 (C), 123.4 (CH), 114 (CH), 54.4 (Me); MS (EI) *m/z* (rel. intensity) 216 ($M^{\cdot+}$, 100%), 201 (55).

4-(Phenylthio)anisole (4c) (Table 1 entry 29). According to the typical experimental procedure (see main text), a solution of 4-iodoanisole (117 mg, 0.5 mmol), PhSH (55 mg, 0.05 mL, 0.5 mmol), CuI (5 mg, 25 μmol), (±)-*trans*-cyclohexane-1,2-diol (116 mg, 1.0 mmol), K_2CO_3 (138 mg, 1.0 mmol) in 2-propanol (2 mL) was irradiated at 120 °C for 3 x 1 h in a pressure-rated glass tube (10 mL) using a CEM Discover microwave synthesiser by moderating the initial power (150 W). After cooling in a flow of compressed air, the reaction mixture was filtered and evaporated *in vacuo*. Purification by column chromatography on silica gel, eluting with hexane–CH_2Cl_2 (3:1), gave the *title compound* (103 mg, 95%) as a yellow oil (found: $M^{\cdot+}$, 216.0607. $C_{13}H_{12}OS$ [*M*] requires 216.0609), with identical spectroscopic properties.

Experimental Procedures for Table 2

2-(Phenylthio)pyridine (7a) (Table 2 entry 1). According to the typical experimental procedure (see main text), a solution of 2-iodopyridine (192 mg, 1.0 mmol), PhSH (118 mg, 1.1 mmol), neocuproine (21 mg, 0.10 mmol) and NaO*t*Bu (144 mg, 1.5 mmol) in dry PhMe (2 mL) was irradiated at 120 °C for 3 x 1 h in a pressure-rated glass tube (10 mL) using a CEM Discover microwave synthesiser by moderating the initial power (150 W). After cooling in a flow of compressed air, the reaction mixture was filtered and evaporated in vacuo. Purification by column chromatography on SiO_2, eluting with light petroleum–CH_2Cl_2 (1:1), gave the *title compound* (142 mg, 76%) as a pale yellow oil (found: $M^{\cdot+}$, 187.0454. $C_{11}H_9NS$ [*M*] requires 187.0456); ^{1}H NMR (400 MHz, d_6–DMSO) δ 8.40 (1H, ddd, *J* 4.8, 2, 1), 7.65 (1H, ddd, *J* 8, 7.5, 2), 7.59 (2H, m), 7.51–7.48 (3H), 7.15 (1H, ddd, *J* 7.5, 4.8, 1), 6.94 (1H, app dt, *J* 8, 1); ^{13}C NMR (100 MHz; d_6–DMSO) 159.8 (C), 149.6 (CH), 137.4 (CH), 134.6 (C), 130.2 (CH), 129.8 (CH), 129.2 (CH), 121.1 (CH), 120.5 (CH); MS (EI) *m/z* (rel. intensity) 187 ($M^{\cdot+}$, 25%).

2-(Phenylthio)pyridine (7a) (Table 2 entry 2). A solution of 2-iodopyridine (192 mg, 1.0 mmol), PhSH (107 mg, 0.10 mL, 1.0 mmol), PEPPSI-*i*Pr (13 mg, 0.02 mmol) and NaO*t*Bu (144 mg, 1.5 mmol) in dry PhMe (2 mL) was irradiated at 120 °C for 3 x 1 h in a pressure-rated glass tube (10 mL) using a CEM Discover microwave synthesiser by moderating the initial power (150 W). After cooling in a flow of compressed air, the reaction mixture was filtered and evaporated in vacuo. Purification by column chromatography on SiO_2, eluting with light petroleum–CH_2Cl_2 (1:1), gave the *title compound* (119 mg, 64%) as a pale yellow oil, with identical physical and spectroscopic properties.

2-(Phenylthio)pyridine (7a) (Table 2 entry 3). According to the typical experimental procedure (see main text), a solution of 2-iodopyridine (192 mg, 1.0 mmol), PhSH (107 mg, 0.10 mL, 1.0 mmol), PEPPSI-*i*Pr (13 mg, 0.02 mmol), LiCl (9 mg, 20 mol%) and NaO*t*Bu (144 mg, 1.5 mmol) in dry PhMe (2 mL) was irradiated at 120 °C for 3 x 1 h in a pressure-rated glass tube (10 mL) using a CEM Discover microwave synthesiser by moderating the initial power (150 W). After cooling in a flow of compressed air, the reaction mixture was filtered and evaporated in vacuo. Purification by column chromatography on SiO_2, eluting with light petroleum–CH_2Cl_2 (1:1), gave the *title compound* (165 mg, 88%) as a pale yellow oil, with identical physical and spectroscopic properties.

2-(Phenylthio)pyridine (7a) (Table 2 entry 5). According to the typical experimental procedure (see main text), a solution of 2-iodopyridine (192 mg, 1.0 mmol), PhSH (107 mg, 0.10 mL, 1.0 mmol), CuI (19 mg, 0.10 mmol), neocuproine (20 mg, 0.10 mmol) and NaO*t*Bu (144 mg, 1.5 mmol) in dry PhMe (2 mL) was irradiated at 120 °C for 3 x 1 h in a pressure-rated glass tube (10 mL) using a CEM Discover microwave synthesiser by moderating the initial power (150 W). After cooling in a flow of compressed air, the reaction mixture was filtered and evaporated in vacuo. Purification by column chromatography on SiO_2, eluting with light petroleum–CH_2Cl_2 (1:1), gave the *title compound* (180 mg, 96%) as a pale yellow oil, with identical physical and spectroscopic properties.

2-(Phenylthio)pyridine (7a) (Table 2 entry 6). According to the typical experimental procedure (see main text), a solution of 2-iodopyridine (96 mg, 0.5 mmol), PhSH (55 mg, 0.05 mL, 0.5 mmol), CuI (5 mg, 25 μmol), (±)–*trans*–cyclohexane–1,2–diol (0.12 g, 1.0 mmol) and K_2CO_3 (0.14 g, 1.0 mmol) in 2-propanol (2 mL) was irradiated at 120 °C for 3 x 1 h in a pressure-rated glass tube (10 mL) using a CEM Discover microwave synthesiser by moderating the initial power (150 W). After cooling in a flow of compressed air, the reaction mixture was filtered and evaporated *in vacuo*. Purification by column chromatography on SiO_2, eluting with light petroleum–CH_2Cl_2 (1:1), gave the *title compound* (85 mg, 91%) as a pale yellow oil, with identical physical and spectroscopic properties.

3,6-Bis(phenylthio)pyridazine (7c) (Table 2 entry 7). According to the typical experimental procedure (see main text), a solution of 3,6-dichloropyridazine (**2**) (149 mg, 1.0 mmol), PhSH (107 mg, 0.10 mL, 1.0 mmol), PEPPSI-*i*Pr (13 mg, 0.02 mmol), LiCl (9 mg, 20 mol%) and NaO*t*Bu (144 mg, 1.5 mmol) in dry PhMe (2 mL) was irradiated at 120 °C for 3 x 1 h in a pressure-rated glass tube (10 mL) using a CEM Discover microwave synthesiser by moderating the initial power (150 W). After cooling in a flow of compressed air, the reaction mixture was filtered and evaporated in vacuo. Purification by column chromatography on SiO_2, eluting with light petroleum–CH_2Cl_2 (1:1), gave the *title compound*[3] (124 mg, 42%) as a brown oil (found: $M^{\cdot+}$, 296.0453. $C_{16}H_{12}N_2S_2$ [*M*] requires 296.0442) which was not purified further; ^{1}H NMR (400 MHz, d_6–DMSO) δ 7.61–7.58 (4H, m), 7.51–7.48 (6H), 7.19 (2H, s); ^{13}C NMR (125 MHz; d_6–DMSO) 161.3 (C), 134.5 (C), 129.9 (CH), 129.6 (CH), 128.7 (CH), 126.4 (CH); MS (EI) *m/z* (rel. intensity) 296 ($M^{\cdot+}$, 30%), 109 (22).

3,6-Bis(phenylthio)pyridazine (7c) (Table 2 entry 8). According to the typical experimental procedure (see main text), a solution of 3,6-dichloropyridazine (**2**) (149 mg, 1.0 mmol), PhSH (107 mg, 0.10 mL, 1.0 mmol), CuI (19 mg, 0.10 mmol), neocuproine (20 mg, 0.10 mmol)

and NaO*t*Bu (144 mg, 1.5 mmol) in dry PhMe (2 mL) was irradiated at 120 °C for 3 x 1 h in a pressure-rated glass tube (10 mL) using a CEM Discover microwave synthesiser by moderating the initial power (150 W). After cooling in a flow of compressed air, the reaction mixture was filtered and evaporated in vacuo. Purification by column chromatography on SiO_2, eluting with light petroleum–CH_2Cl_2 (1:1), gave the *title compound* (190 mg, 75%) as a brown oil, with identical physical and spectroscopic properties.

3,6-Bis(phenylthio)pyridazine (7c) (Table 2 entry 9). A solution of 3,6-dichloropyridazine (**2**) (149 mg, 1.0 mmol), PhSH (107 mg, 0.10 mL, 1.0 mmol) and NaO*t*Bu (144 mg, 1.5 mmol) in dry PhMe (2 mL) was irradiated at 120 °C for 3 x 1 h in a pressure-rated glass tube (10 mL) using a CEM Discover microwave synthesiser by moderating the initial power (150 W). After cooling in a flow of compressed air, the reaction mixture was filtered and evaporated in vacuo. Purification by column chromatography on SiO_2, eluting with light petroleum–CH_2Cl_2 (1:1), gave the *title compound* (140 mg, 47%) as a brown oil, with identical physical and spectroscopic properties.

Experimental Procedures for Table 3

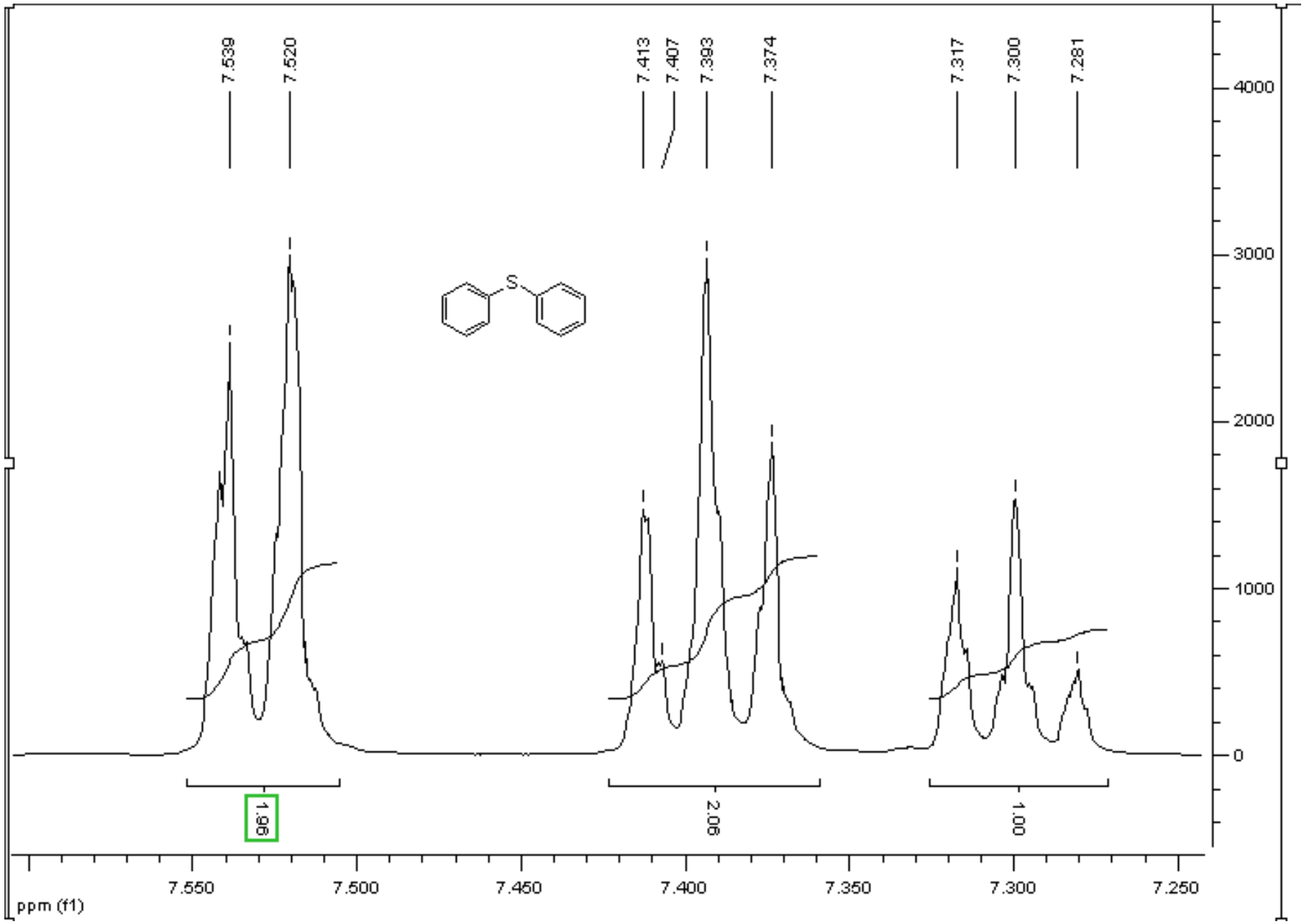
6–Chloro–α–(2,6–dichlorophenyl)–3–pyridazineacetonitrile (9). In a repeat of the literature procedure,[19a] a solution of (2,6–dichlorophenyl)acetonitrile (**8**) (2.0 g, 10.8 mmol) in anhydrous THF (20 mL) was added to a suspension of NaH (0.50 g, 12.9 mmol) in THF (20 mL) at room temperature. After 15 min, a solution of 3,6–dichloropyridazine (**2**) (1.6 g, 10.8 mmol) in dry THF (10 mL) was added dropwise and the solution was stirred for a further 30 min. The mixture was partitioned between saturated aqueous NH_4Cl solution (20 mL) and EtOAc (20 mL). The aqueous layer was further extracted with EtOAc (2 × 20 mL) and the combined organic extracts were washed with brine (20 mL), dried (Na_2SO_4) and evaporated *in vacuo* to give a red oil. Purification by column chromatography on SiO_2, eluting with EtOAc–hexane (1:1), and recrystallization (EtOH) gave the *title compound* (1.0 g, 32%) as orange needles, mp 122–124 °C (lit.[19a] mp 124–131 °C) with identical spectroscopic properties.

α–(2,6–Dichlorophenyl)–6–[(2,4–difluorophenyl)thio]–3–pyridazineacetonitrile (10) (Table 3, entry 11). 6–Chloro–α–(2,6–dichlorophenyl)–3–pyridazineacetonitrile (**9**) (120 mg, 0.4 mmol) was added to a stirred solution of CuI (8 mg, 40 μmol) in dioxane (5 mL) at room temperature. A solution of NEt_3 (67 μL, 0.5 mmol) and 2,4–difluorothiophenol (46 μL, 0.4 mmol) in dioxane (5 mL) was added by

syringe and the solution heated to 90 °C in an oil bath for 16 h. After this time the reaction mixture was allowed to cool and evaporated *in vacuo*. The residue was partitioned between H_2O (10 mL) and EtOAc (10 mL) and the aqueous layer was further extracted with EtOAc (2 × 10 mL). The combined organic extracts were washed successively with aqueous NaOH (1M, 10 mL) and brine (10 mL), dried (Na_2SO_4) and evaporated *in vacuo* to give an orange solid. Purification by column chromatography on SiO_2, eluting with EtOAc–hexane (1:1), gave the *title compound* (133 mg, 82%) as an orange solid, mp 134–136 °C (Found: MH^+, 407.9940. $C_{18}H_{10}{}^{35}Cl_2F_2N_3S$ [*MH*] requires 407.9941), with identical spectroscopic properties.

α–(2,6–Dichlorophenyl)–6–[(2,4–difluorophenyl)thio]–3–pyridazineacetonitrile (10) (Table 3, entry 12). 6–Chloro–α–(2,6–dichlorophenyl)–3–pyridazineacetonitrile (**9**) (120 mg, 0.4 mmol) was added to a solution of CuI (8 mg, 40 μmol), NEt_3 (67 μL, 0.5 mmol) and 2,4–difluorothiophenol (46 μL, 0.4 mmol) in dioxane (2 mL). The solution was irradiated at 120 °C for 3 x 1 h in a pressure-rated glass tube (10 mL) using a CEM Discover microwave synthesiser by moderating the initial power (100 W). After cooling in a flow of compressed air, the reaction mixture was filtered and evaporated *in vacuo*. Purification by column chromatography on SiO_2, eluting with EtOAc–hexane (1:1), gave the *title compound* (90 mg, 55%) as an orange solid with identical physical and spectroscopic properties.

α–(2,6–Dichlorophenyl)–6–[(2,4–difluorophenyl)thio]–3–pyridazineacetonitrile (10) (Table 3, entry 15). 6–Chloro–α–(2,6–dichlorophenyl)–3–pyridazineacetonitrile (**9**) (150 mg, 0.5 mmol) was added to a stirred solution of (±)–*trans*–cyclohexane–1,2–diol (118 mg, 1.0 mmol), K_2CO_3 (140 mg, 1.0 mmol) and 2,4–difluorothiophenol (57 μL, 0.5 mmol), in propan–2–ol (3 mL). The solution was irradiated at 120 °C for 3 x 1 h in a pressure–rated glass tube (10 mL) using a CEM Discover microwave synthesiser by moderating the initial power (150 W). After cooling in a flow of compressed air, the reaction mixture was filtered on SiO_2, washing with MeOH, and evaporated *in vacuo*. Purification by column chromatography on SiO_2, gradient eluting with Et_2O–hexane (1:5 to 1:1), gave the *title compound* as an orange solid (190 mg, 92%), with identical physical and spectroscopic properties.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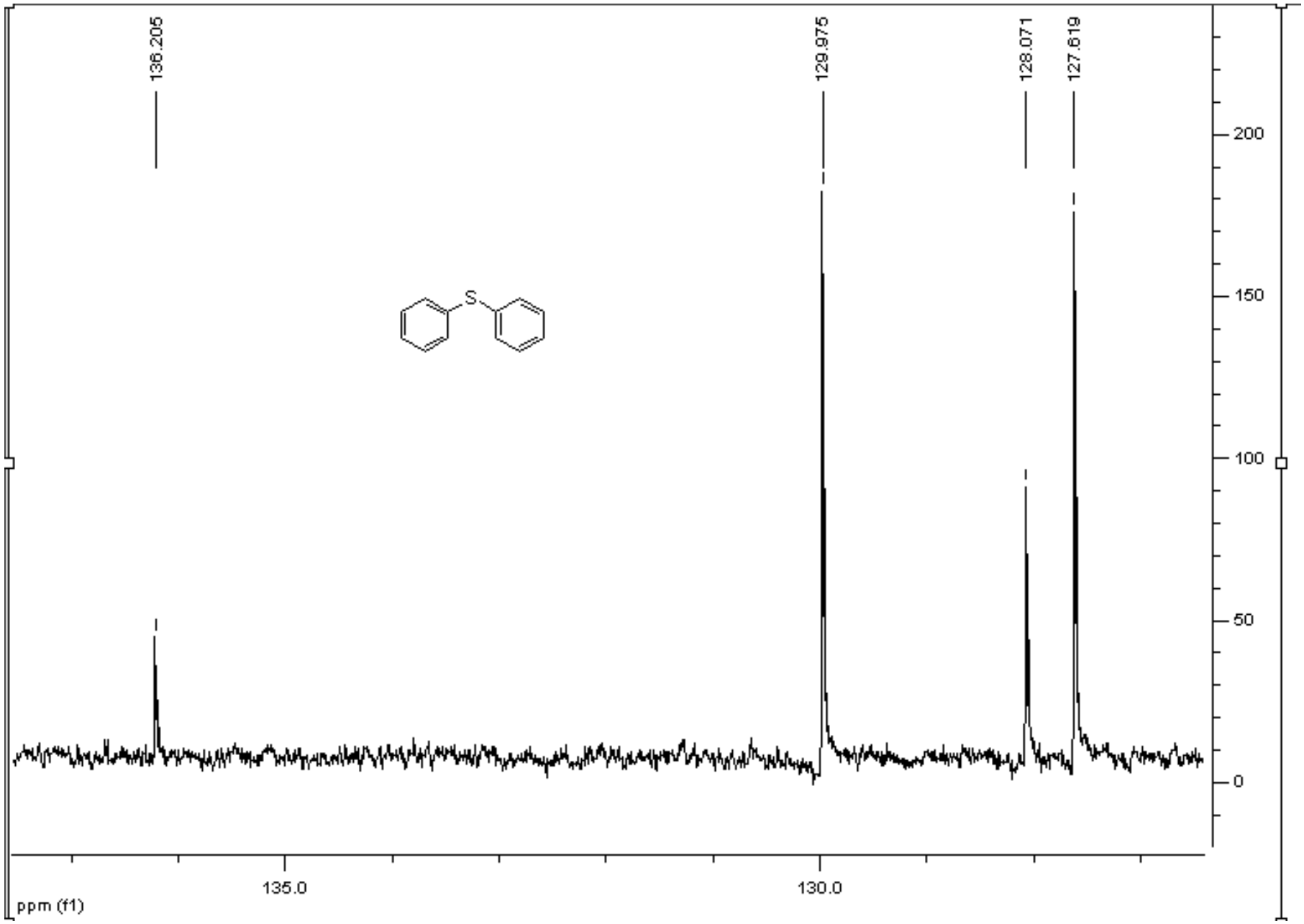
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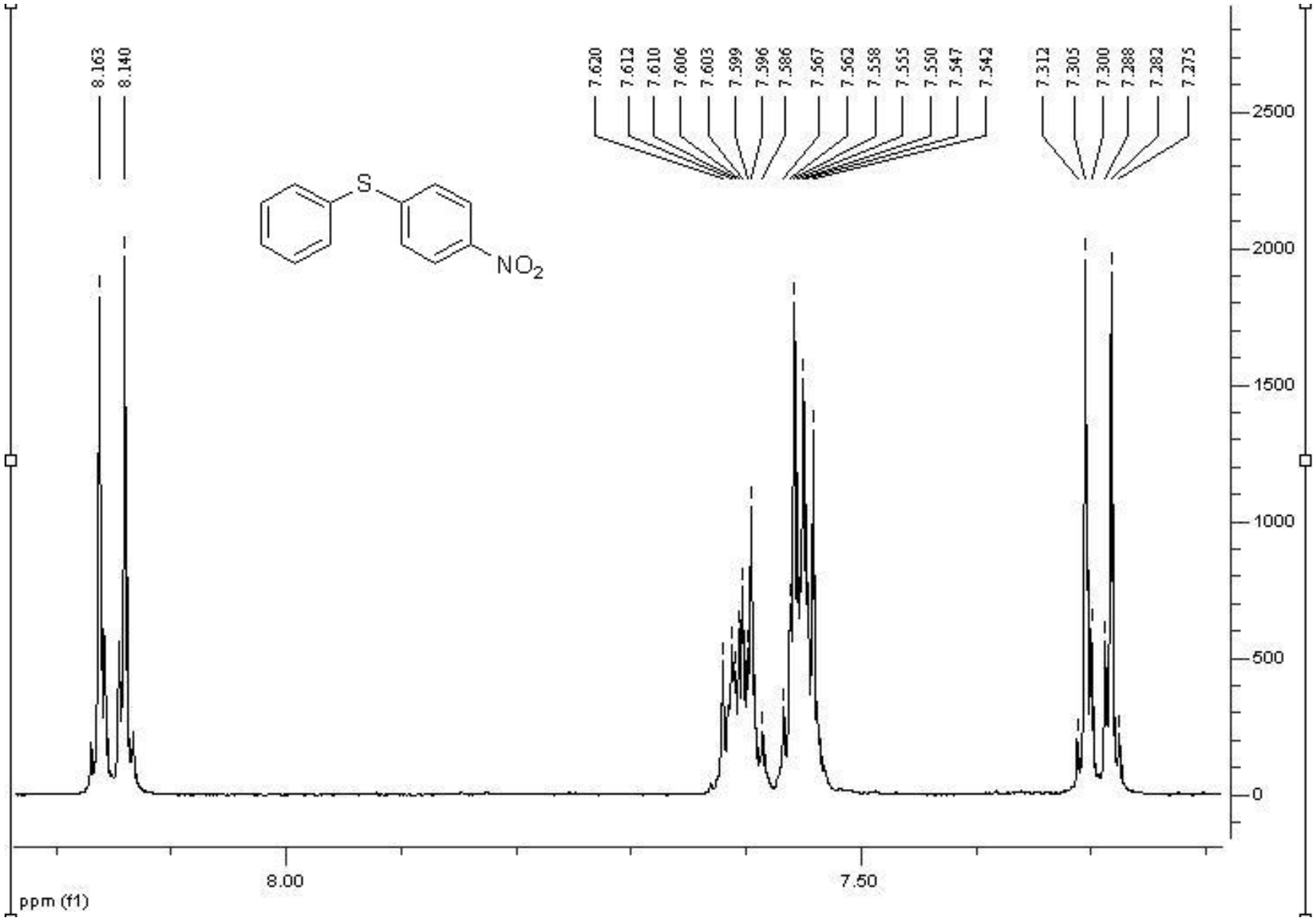
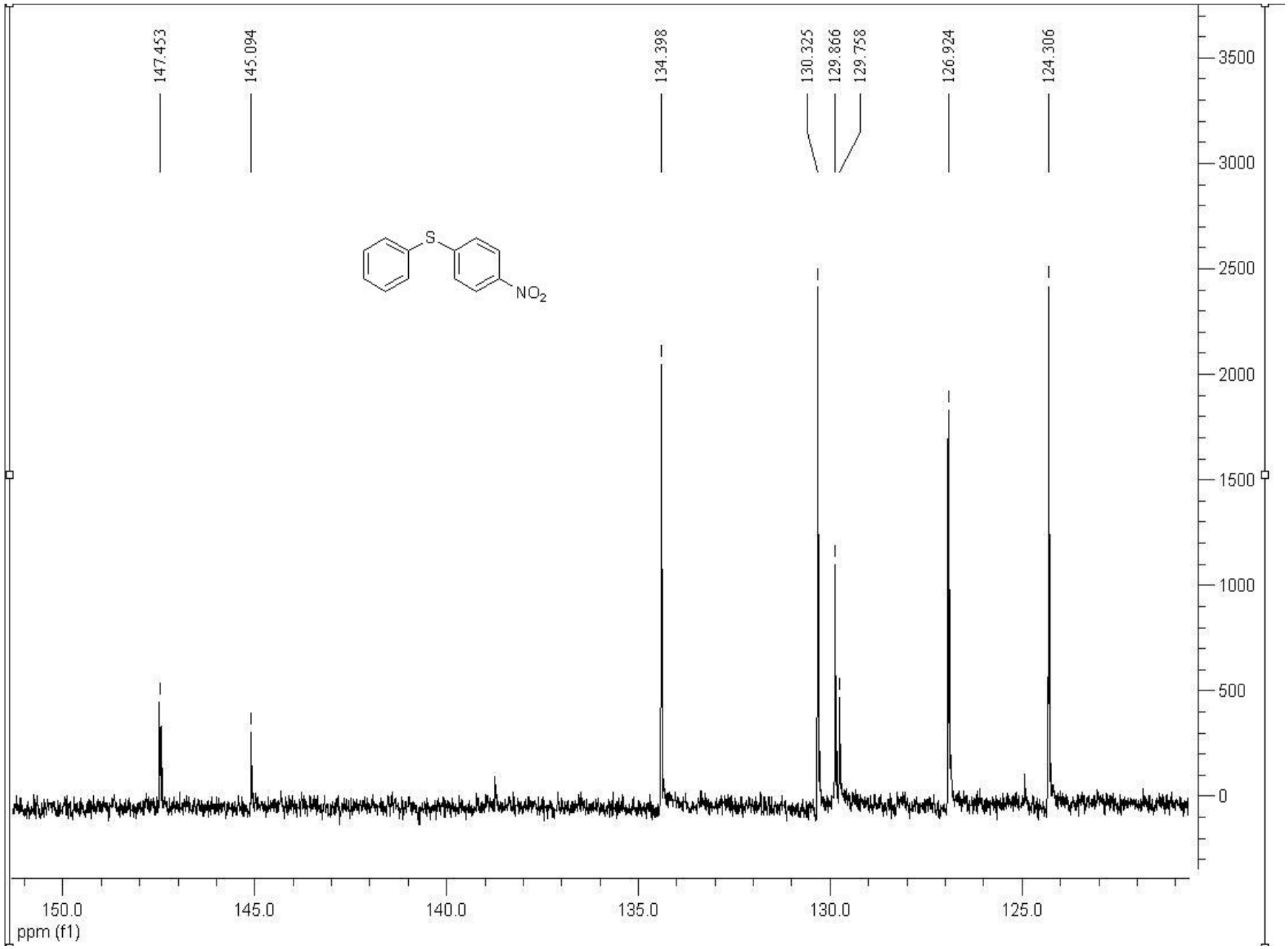
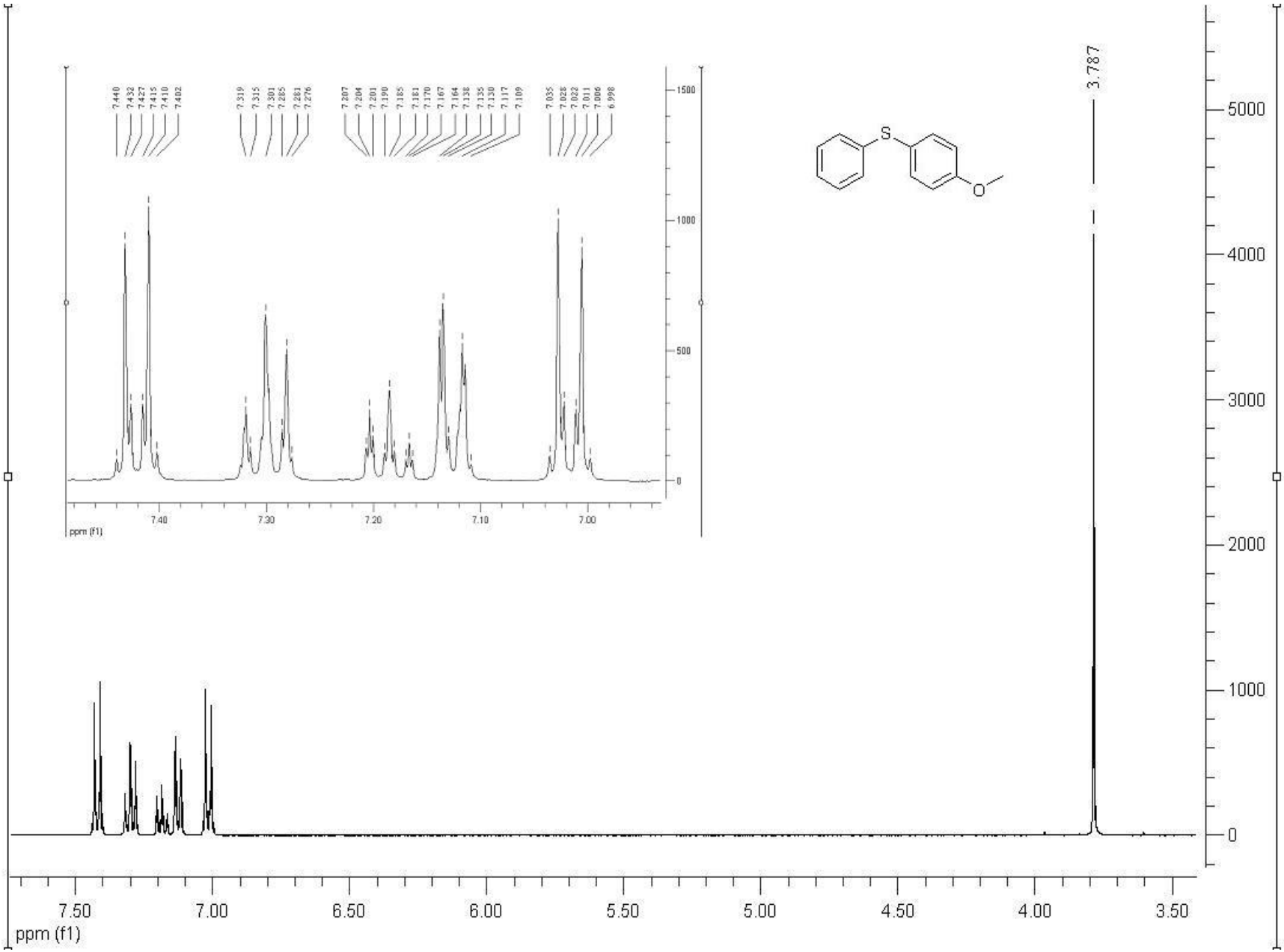
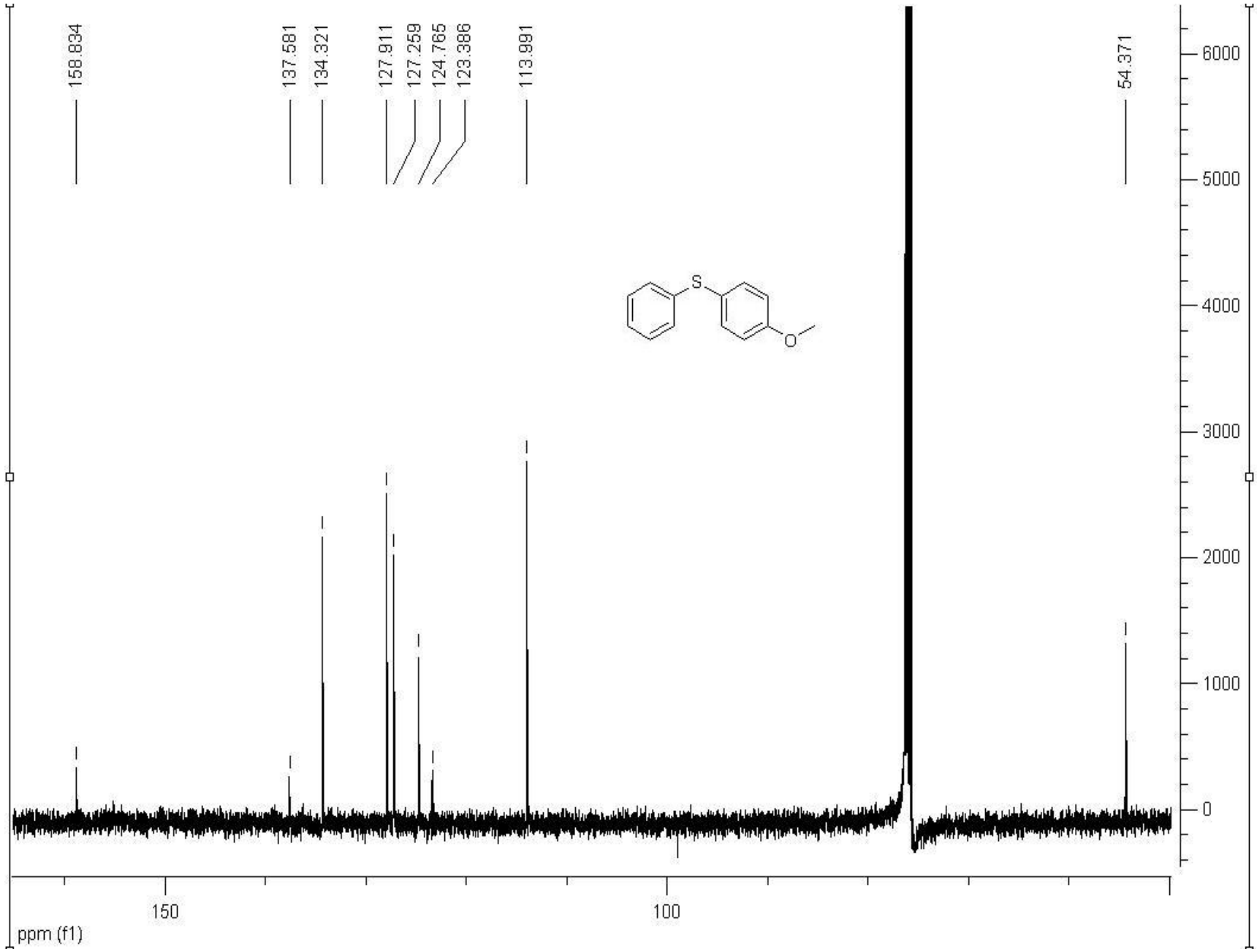
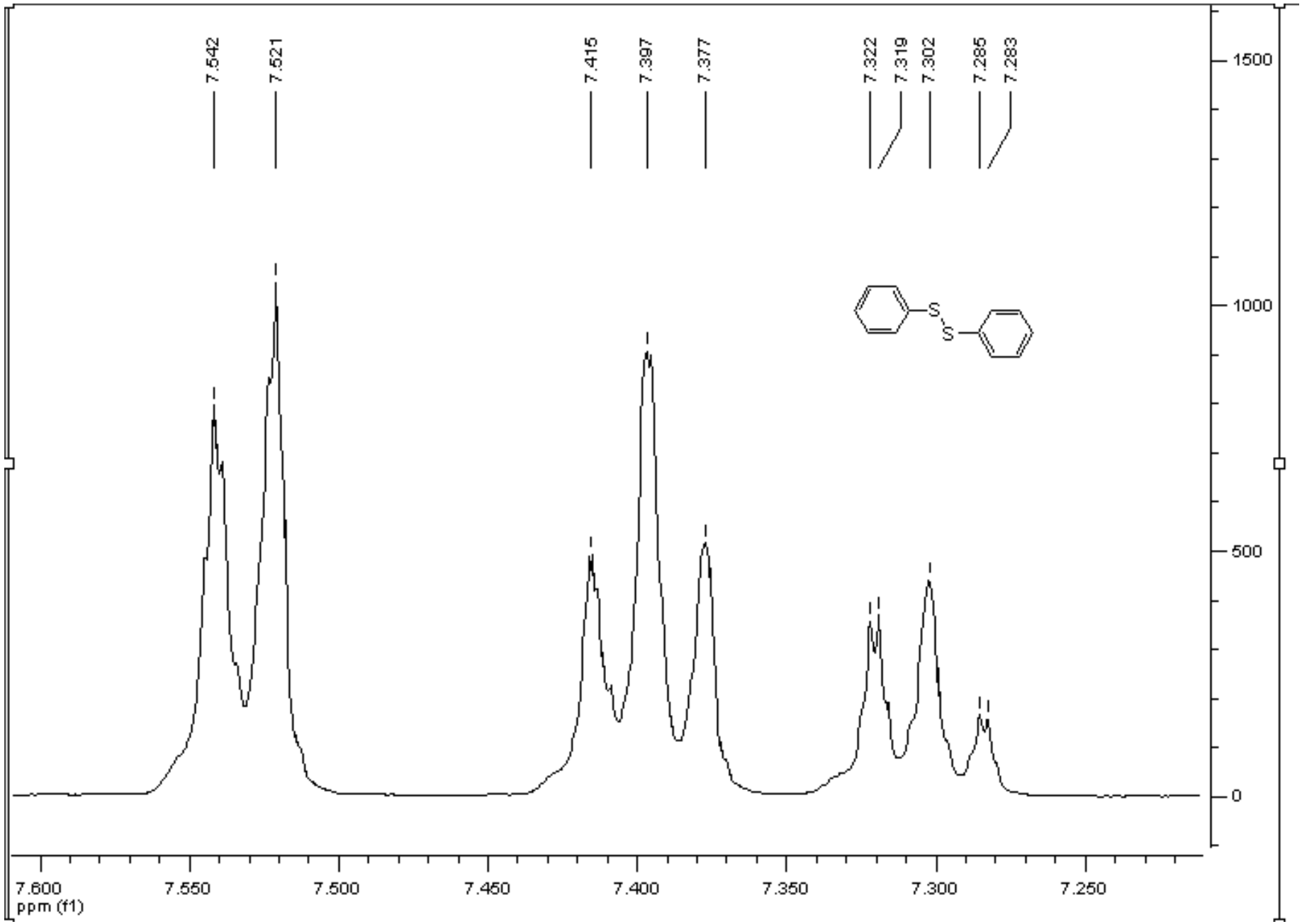
ppm (f1)

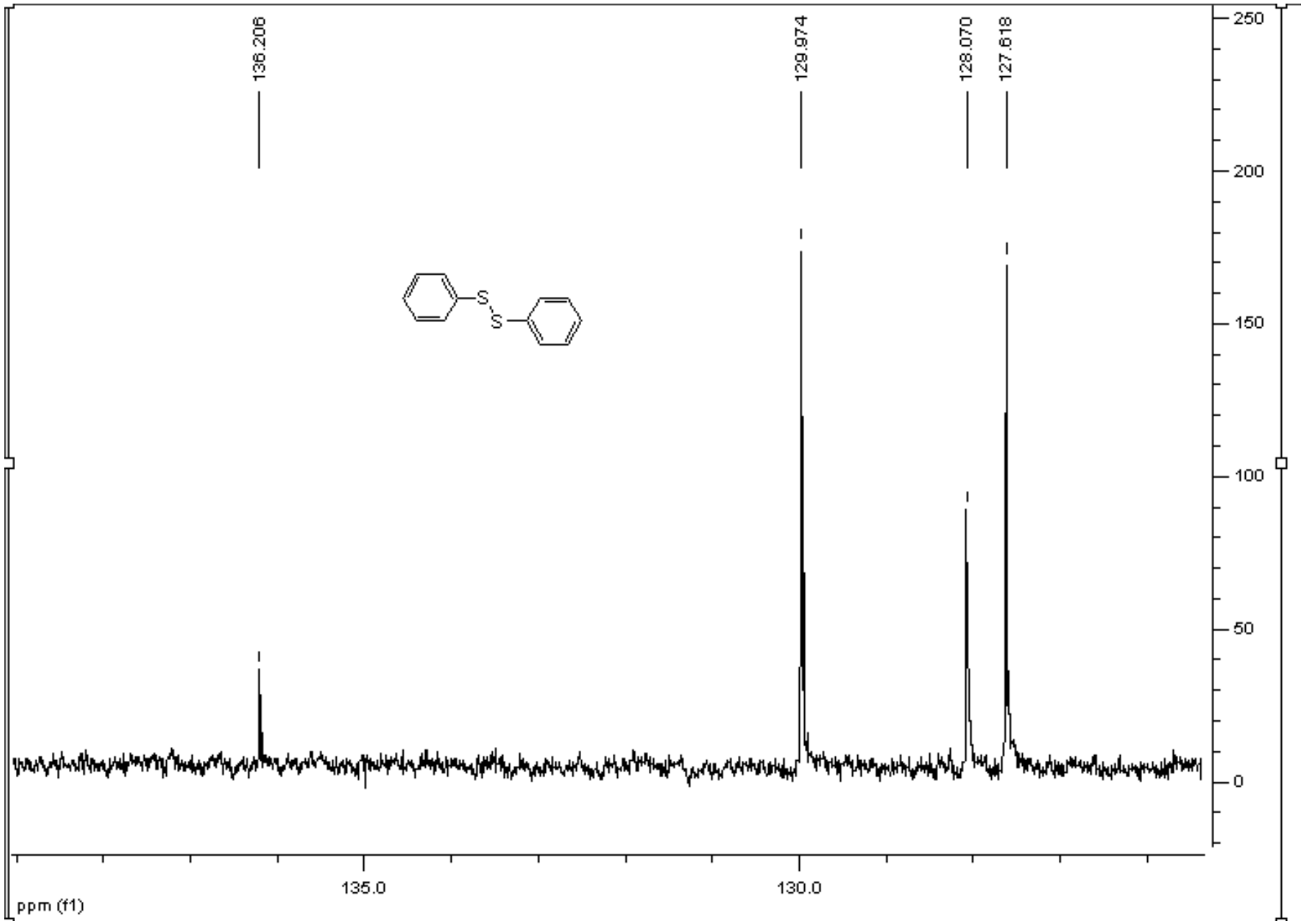

8.163
8.140
7.620
7.612
7.610
7.606
7.603
7.599
7.596
7.586
7.567
7.562
7.558
7.555
7.550
7.547
7.542
7.312
7.305
7.300
7.288
7.282
7.275
S
NO2
2500
2000
1500
1000
500
0
8.00
7.50
ppm (f1)

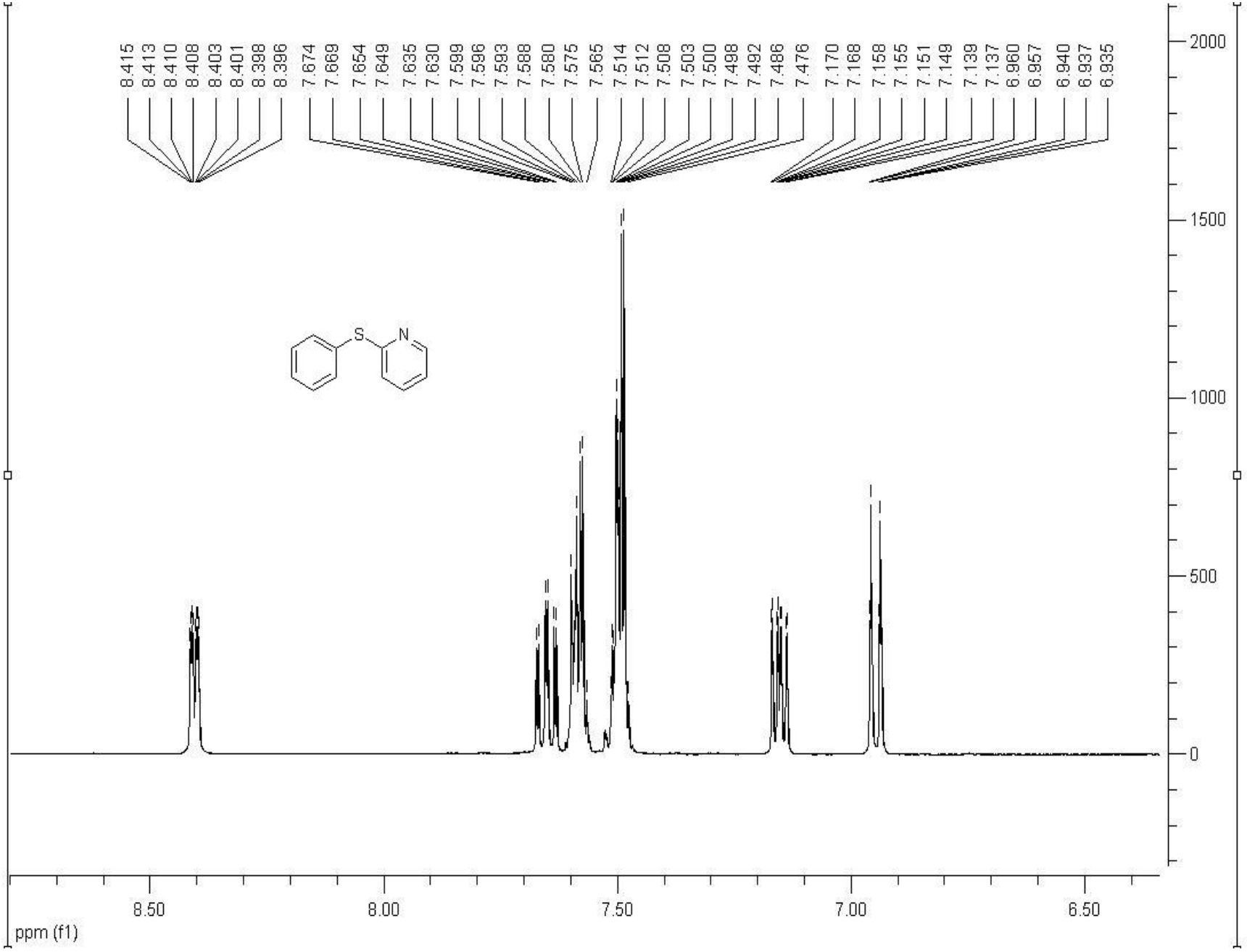

147.453
145.094
134.398
130.325
129.866
129.758
126.924
124.306
S
NO2
3500
3000
2500
2000
1500
1000
500
0
150.0
145.0
140.0
135.0
130.0
125.0
ppm (f1)

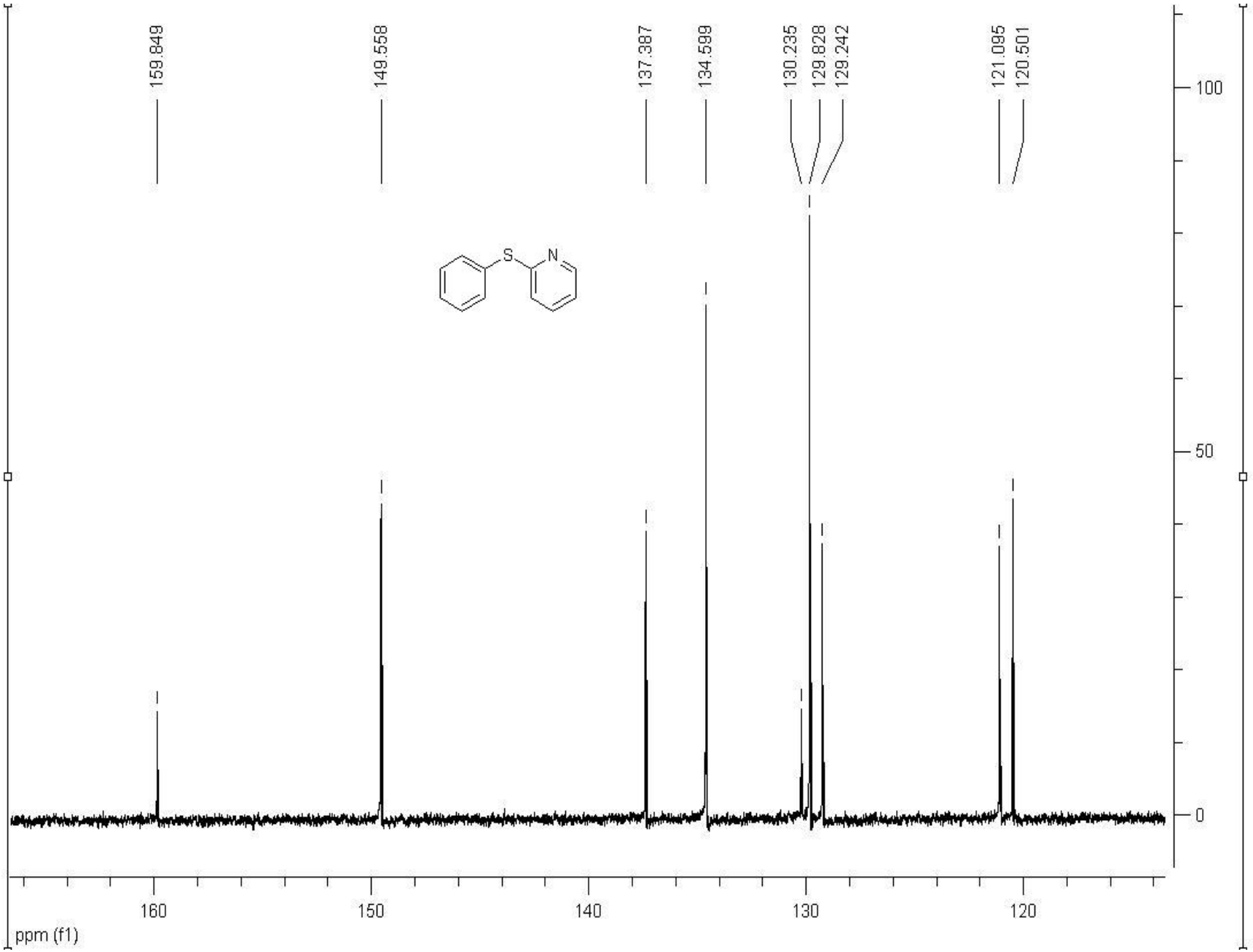

7.440
7.432
7.427
7.415
7.410
7.402
7.319
7.315
7.301
7.285
7.281
7.276
7.207
7.204
7.201
7.190
7.185
7.181
7.170
7.167
7.164
7.158
7.135
7.130
7.117
7.109
7.035
7.028
7.022
7.011
7.006
6.998
1500
1000
500
0
7.40
7.30
7.20
7.10
7.00
ppm (f1)
3.787
S
O
5000
4000
3000
2000
1000
0
7.50
7.00
6.50
6.00
5.50
5.00
4.50
4.00
3.50
ppm (f1)

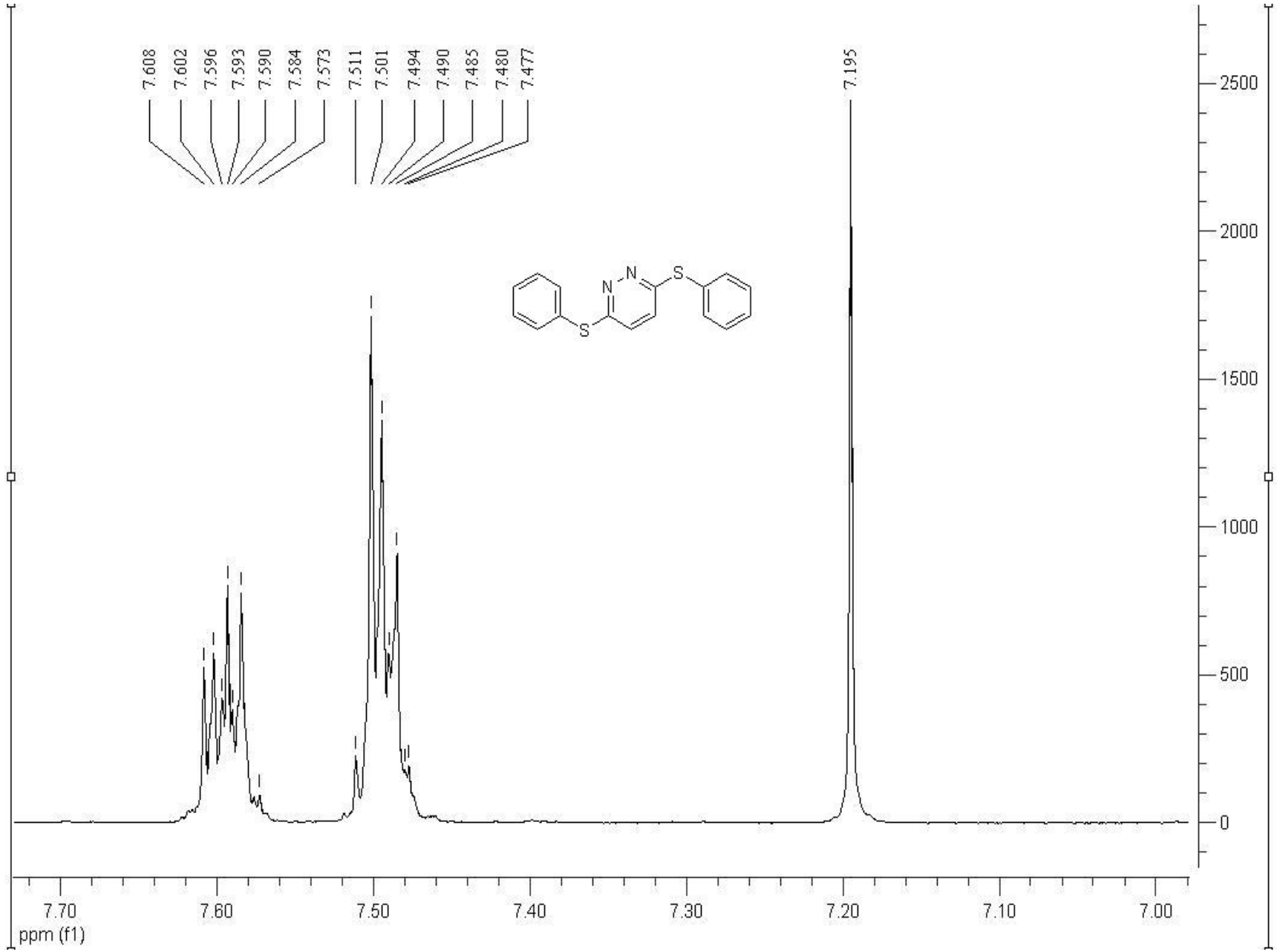

158.834
137.581
134.321
127.911
127.259
124.765
123.386
113.991
54.371
S
O
6000
5000
4000
3000
2000
1000
0
150
100
ppm (f1)

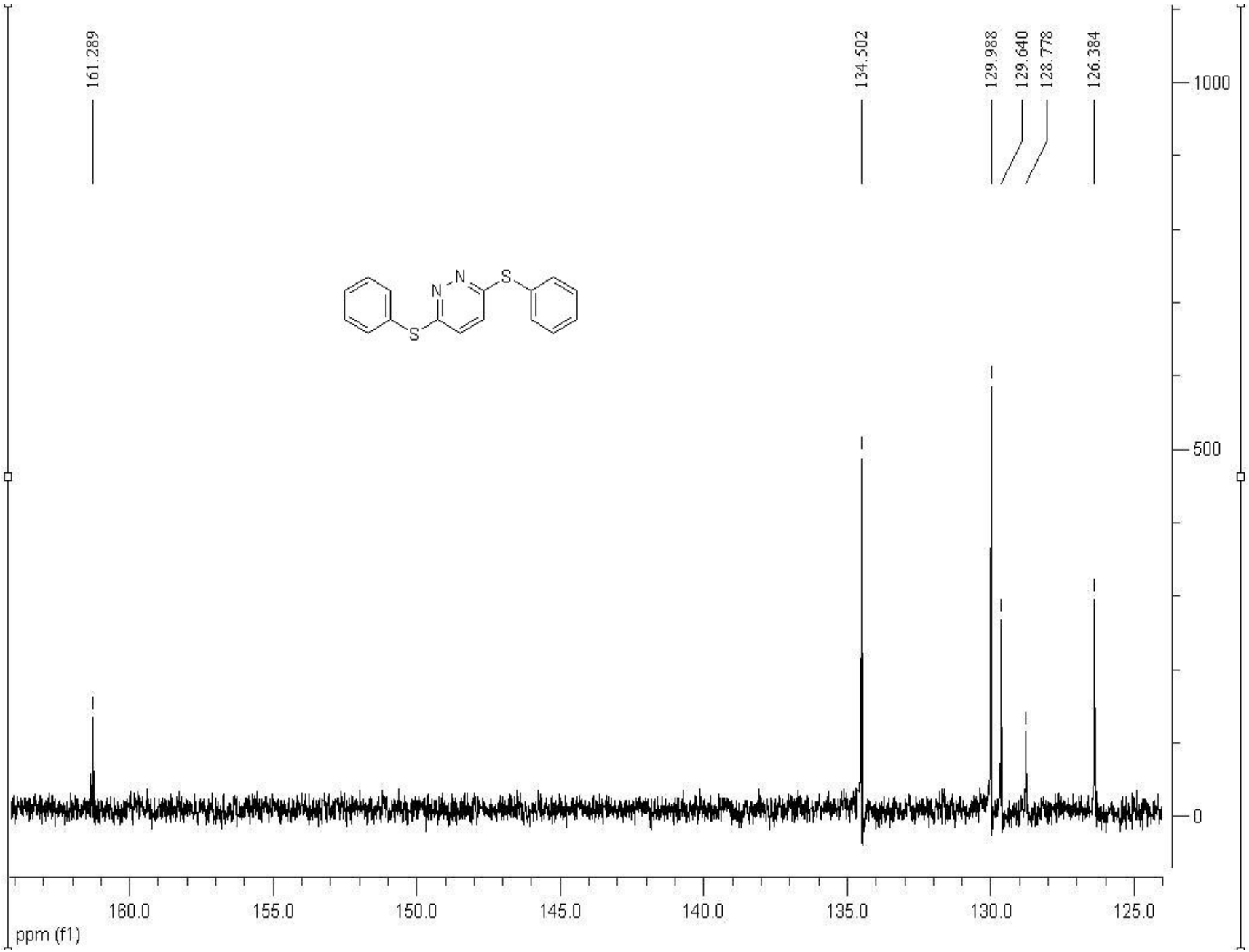

7.542
7.521
7.415
7.397
7.377
7.322
7.319
7.302
7.285
7.283
S
S
1500
1000
500
0
7.600
ppm (f1)
7.550
7.500
7.450
7.400
7.350
7.300
7.250

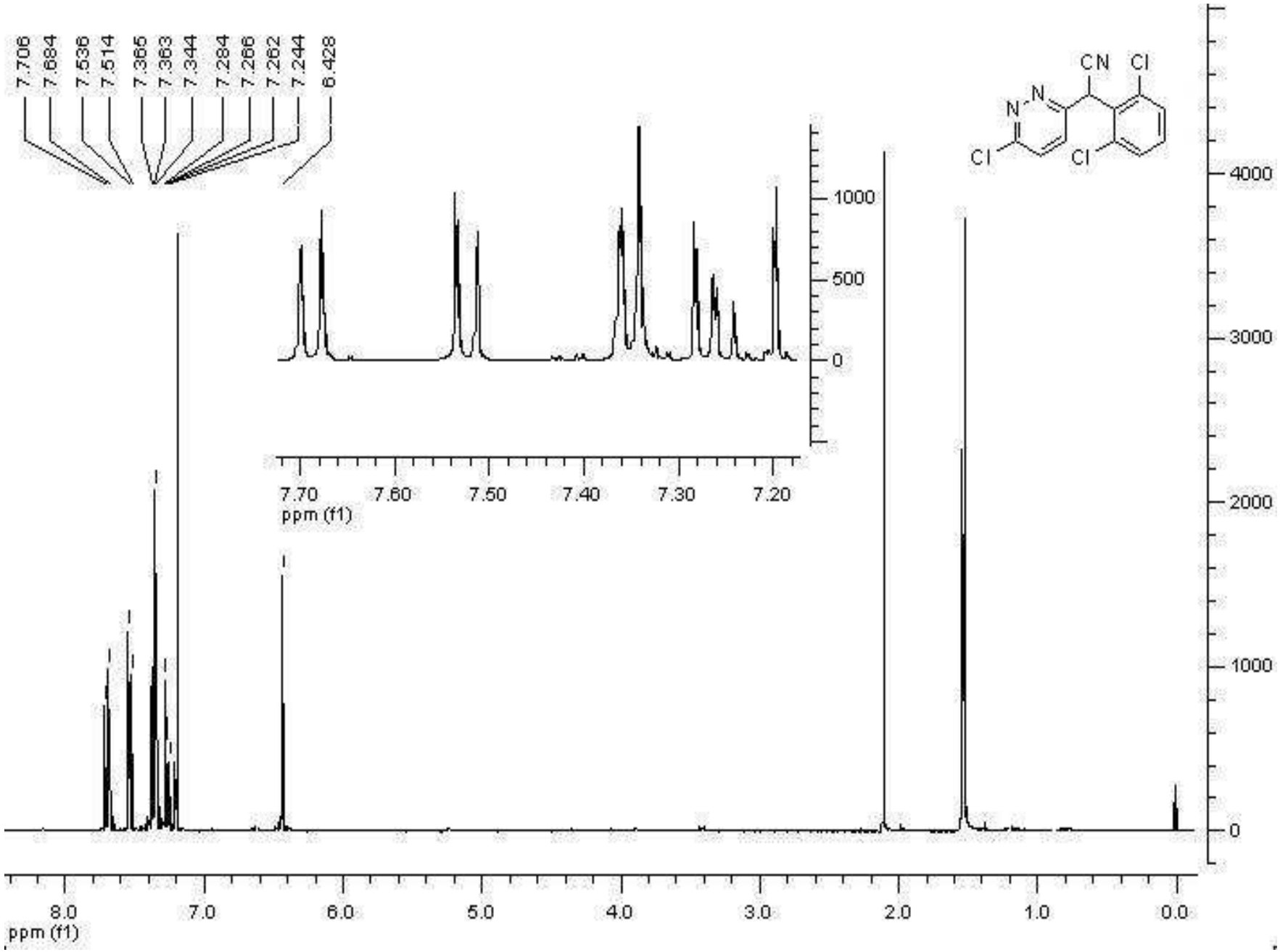

136.206
129.974
128.070
127.618
250
200
150
100
50
0
135.0
130.0
ppm (f1)

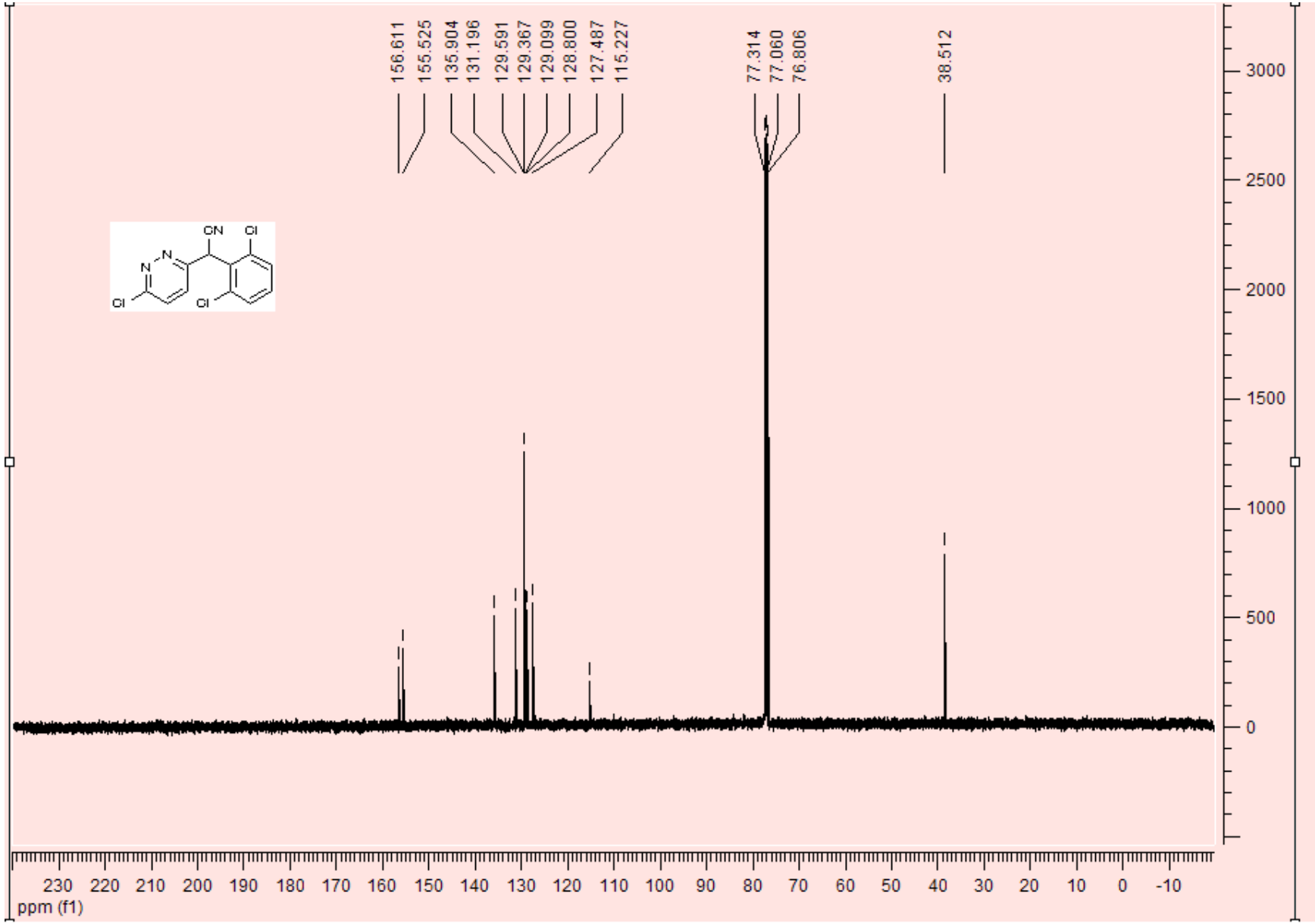

8.415
8.413
8.410
8.408
8.403
8.401
8.398
8.396
7.674
7.669
7.654
7.649
7.635
7.630
7.599
7.596
7.593
7.588
7.580
7.575
7.565
7.514
7.512
7.508
7.503
7.500
7.498
7.492
7.486
7.476
7.170
7.168
7.158
7.155
7.151
7.149
7.139
7.137
6.960
6.957
6.940
6.937
6.935
S
N
2000
1500
1000
500
0
8.50
8.00
7.50
7.00
6.50
ppm (f1)

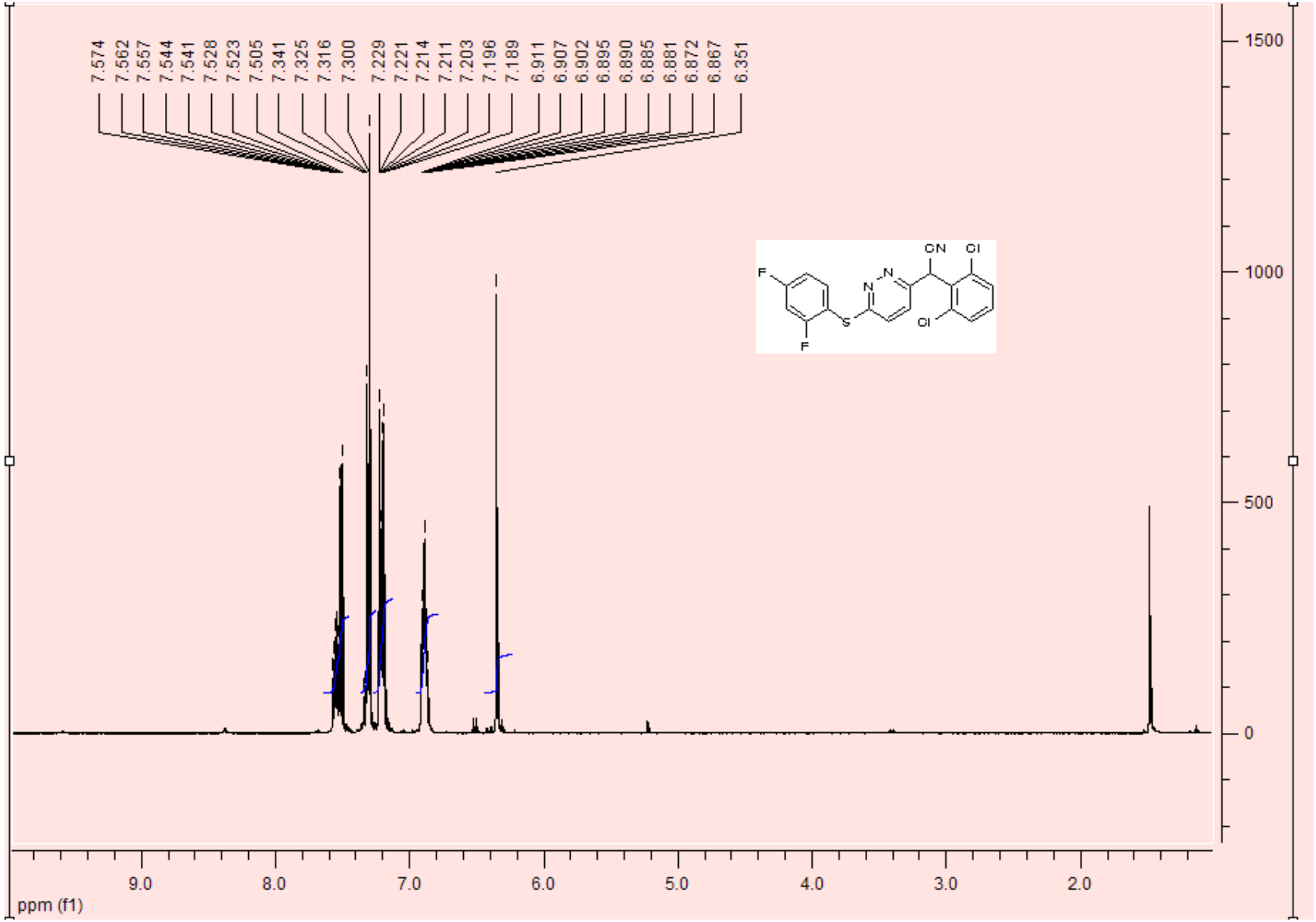

159.849
149.558
137.387
134.599
130.235
129.828
129.242
121.095
120.501
S
N
100
50
0
160
150
140
130
120
ppm (f1)

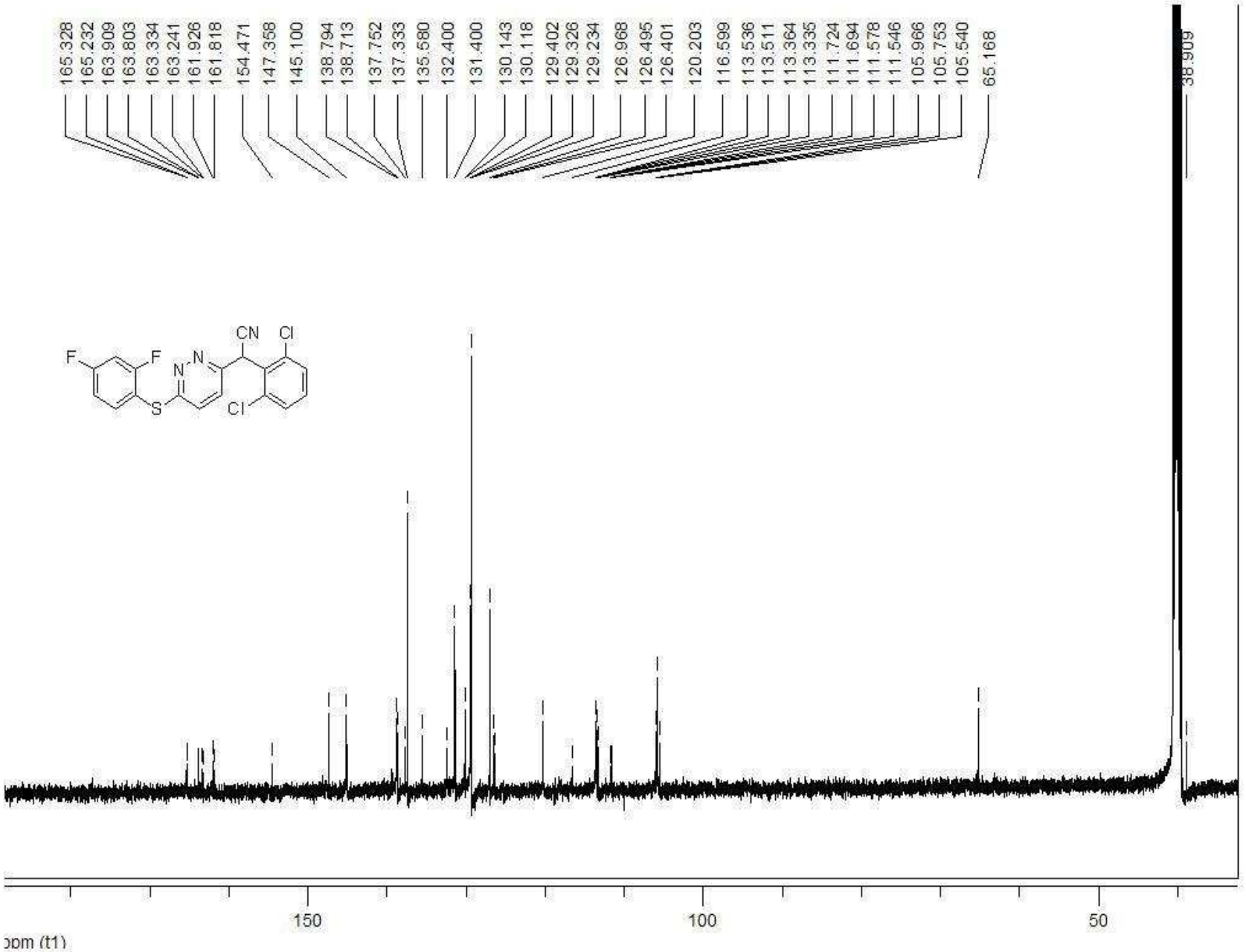

7.608
7.602
7.596
7.593
7.590
7.584
7.573
7.511
7.501
7.494
7.490
7.485
7.480
7.477
7.195
N
N
S
S
2500
2000
1500
1000
500
0
7.70
7.60
7.50
7.40
7.30
7.20
7.10
7.00
ppm (f1)

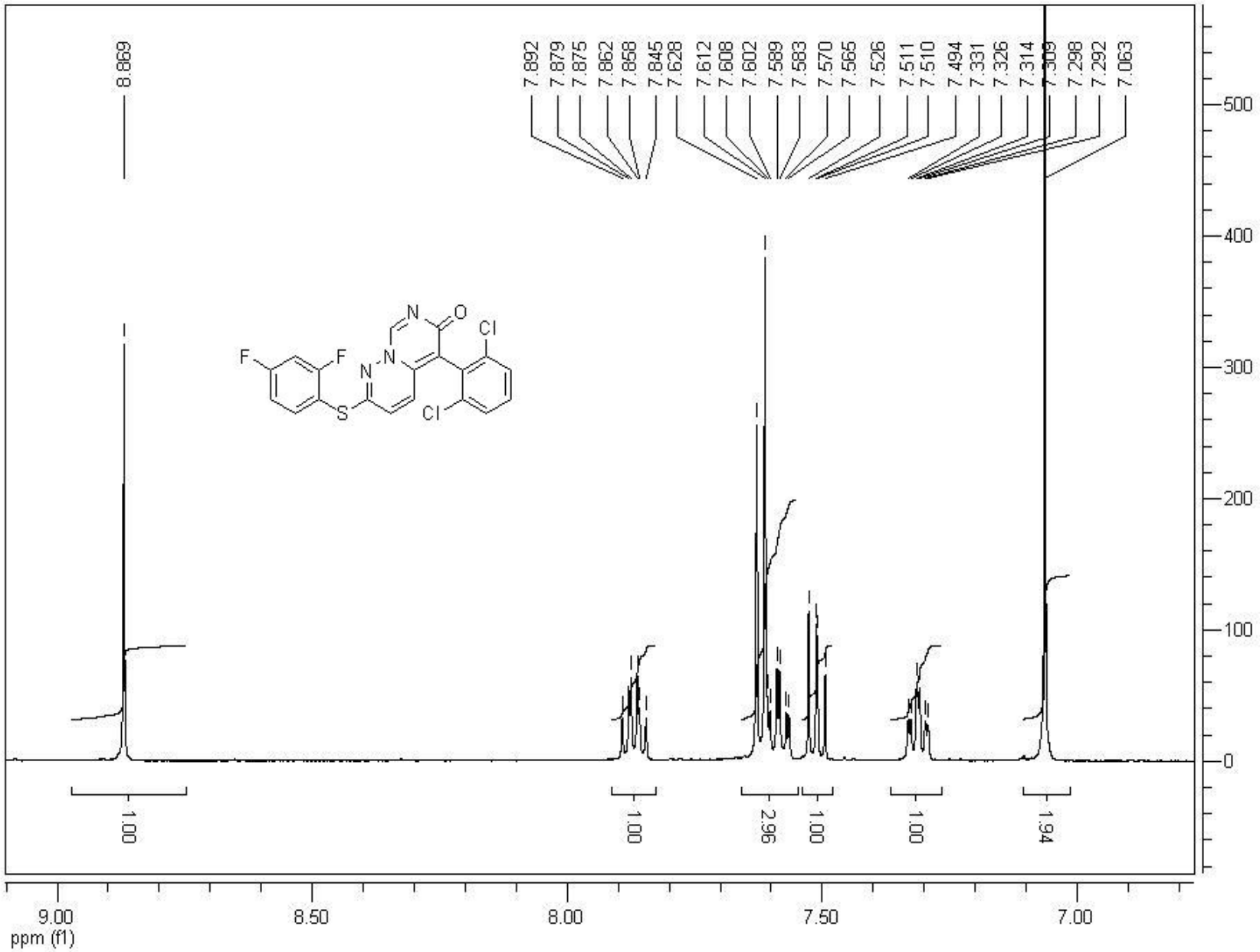

161.289
134.502
129.988
129.640
128.778
126.384
1000
500
0
160.0
155.0
150.0
145.0
140.0
135.0
130.0
125.0
ppm (f1)
N
N
S
S

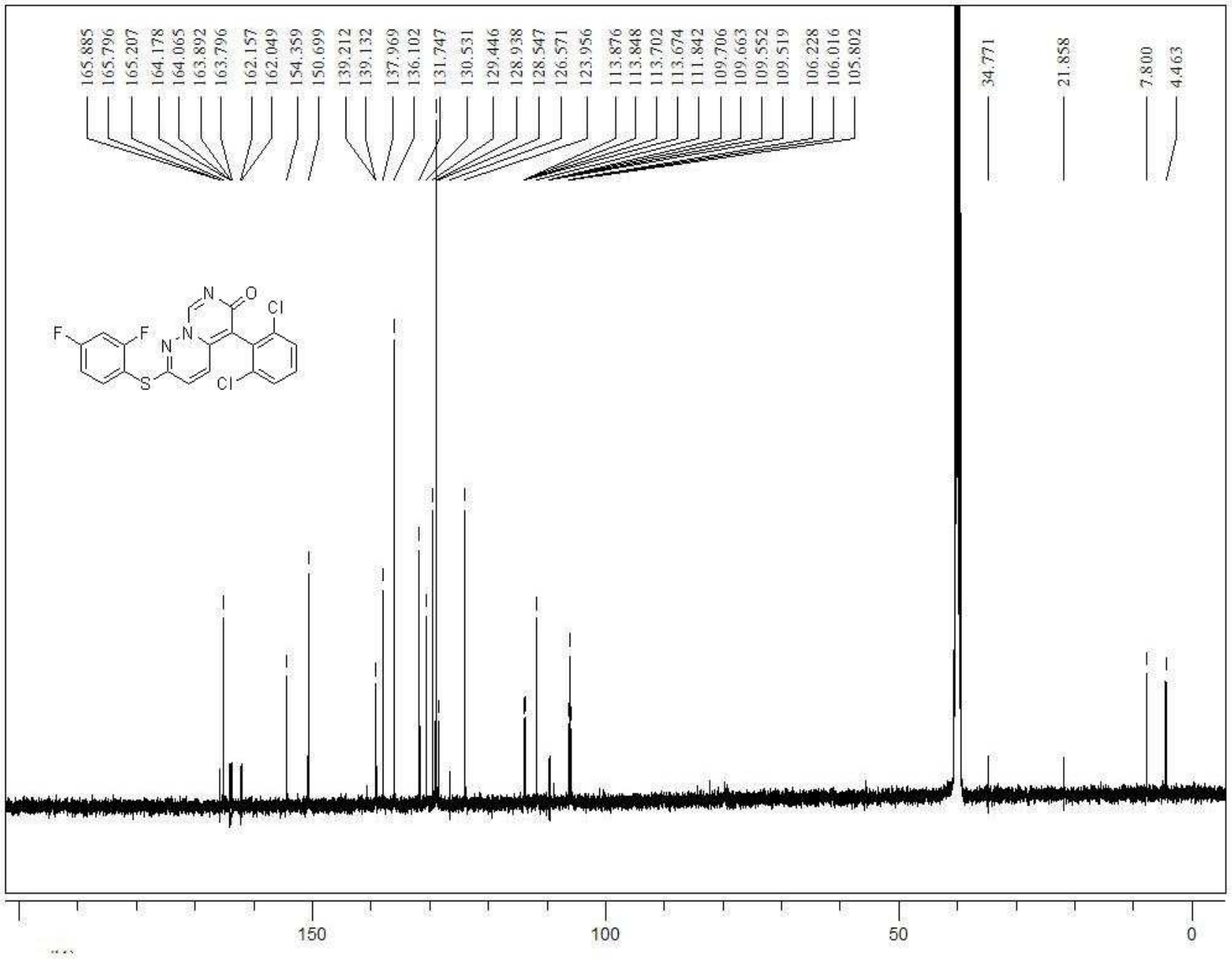

7.706
7.684
7.536
7.514
7.365
7.363
7.344
7.284
7.266
7.262
7.244
6.428
CN
Cl
N
N
Cl
Cl
1000
500
0
7.70
7.60
7.50
7.40
7.30
7.20
ppm (f1)
4000
3000
2000
1000
0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (f1)


156.611
155.525
135.904
131.196
129.591
129.367
129.099
128.800
127.487
115.227
77.314
77.060
76.806
38.512
CN
Cl
N
N
Cl
Cl
3000
2500
2000
1500
1000
500
0
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
ppm (f1)


7.574
7.562
7.557
7.544
7.541
7.528
7.523
7.505
7.341
7.325
7.316
7.300
7.229
7.221
7.214
7.211
7.203
7.196
7.189
6.911
6.907
6.902
6.895
6.890
6.885
6.881
6.872
6.867
6.351
CN
Cl
F
N
N
S
Cl
F
1500
1000
500
0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
ppm (f1)


165.328
165.232
163.909
163.803
163.334
163.241
161.926
161.818
154.471
147.358
145.100
138.794
138.713
137.752
137.333
135.580
132.400
131.400
130.143
130.118
129.402
129.326
129.234
126.968
126.495
126.401
120.203
116.599
113.536
113.511
113.364
113.335
111.724
111.694
111.578
111.546
105.966
105.753
105.540
65.168
38.909
CN
Cl
F
F
N
N
S
Cl
150
100
50
ppm (t1)


8.869
7.892
7.879
7.875
7.862
7.858
7.845
7.628
7.612
7.608
7.602
7.589
7.583
7.570
7.565
7.526
7.511
7.510
7.494
7.331
7.326
7.314
7.309
7.298
7.292
7.063
F
F
S
N
N
N
O
Cl
Cl
1.00
1.00
2.96
1.00
1.00
1.94
9.00
8.50
8.00
7.50
7.00
ppm (f1)
500
400
300
200
100
0


165.885
165.796
165.207
164.178
164.065
163.892
163.796
162.157
162.049
154.359
150.699
139.212
139.132
137.969
136.102
131.747
130.531
129.446
128.938
128.547
126.571
123.956
113.876
113.848
113.702
113.674
111.842
109.706
109.663
109.552
109.519
106.228
106.016
105.802
34.771
21.858
7.800
4.463
F
F
N
N
O
Cl
S
Cl
150
100
50
0

Additional references (other reference numbers refer to references and notes from the main article):

(1) Kornblum, N.; Cheng, L.; Kerber, R. C.; Kestner, M. M.; Newton, B. N.; Pinnick, H. W.; Smith, R. G.; Wade, P.A. *J. Org. Chem.* **1976**, *41*, 1560.

(2) Firouzabadi, H.; Mottghinejad, E.; Seddighi, M. *Synthesis* **1989**, 378.

(3) de Geest, D. J.; O'Keefe, B. J.; Steel, P. J. *J. Organomet. Chem.* **1999**, *579*, 97.