

Continuous Flow Photochemistry as an Enabling Synthetic Technology: Synthesis of Substituted-6(5*H*)-Phenanthridinones for use as Poly(ADP-ribose) Polymerase Inhibitors

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Supplemental Information

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1. General information

^1H and ^{13}C NMR spectra were obtained using a 400MHz Bruker NMR spectrometer at 400 and 100 MHz, respectively. TMS or CDCl_3 were used as an internal NMR standard for spectral shifts unless otherwise specified. Anhydrous acetone was used as purchased from VWR and all other reagents were used as purchased without further purification.

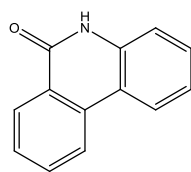
2. Experimental section

2.1 General procedure for the continuous-flow photochemical synthesis of phenanthridinone(s) and derivatives

A solution of starting material (corresponding 2-chloroanilide (benzamide) derivative) (0.1 mmol, 0.005 mmol/mL) in acetone (2mL) was passed continuously through the Vapourtec® UV-150 photochemical flow reactor using a Vapourtec® R2+/R4 flow chemistry system at a rate of 0.200 mL/min (reacting time 50min). The UV-150 reactor uses a medium-pressure pure Hg lamp (lamp power 75%, approximately 112.5 watts), a 10mL FEP reactor coil, and a filter (type 1, quartz, whole-wavelength range). The temperature was set and maintained at 60°C using the Vapourtec R4 reactor module, and the UV reactor coil flow stream was passed through an 8 bar back pressure regulator, with the Vapourtec R2+ pressure limit set at 12 bar. The reaction stream of crude product was collected into a round-bottom flask which was covered by aluminum foil. Solvent acetone was removed by a rotary vacuum and the residue was loaded on silica gel and purified by column chromatography (Teledyne Isco CombiFlash Rf®) using 10% ethyl acetate in hexanes. The purified product was dried under vacuum and weighed.

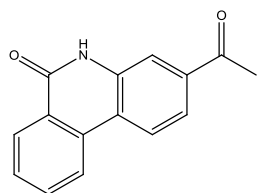
2.2 Characterization of phenanthridinone and derivatives

Phenanthridin-6(5H)-one (entry 1)



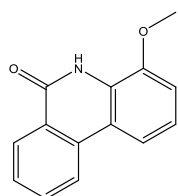
2-Chloro-*N*-phenylbenzamide was treated according to the general procedure as starting material. Purification by CombiFlash® Rf afforded the title compound (19.4 mg, 99%) as a pale yellow crystalline solid. $R_f = 0.22$ (40% Ethyl acetate/hexane). ^1H NMR (400 MHz, DMSO) δ 11.71 (s, 1H), 8.51 (d, $J = 8.1$ Hz, 1H), 8.39 (d, $J = 7.9$ Hz, 1H), 8.33 (dd, $J = 7.9, 1.2$ Hz, 1H), 7.91 – 7.82 (m, 1H), 7.65 (t, $J = 7.3$ Hz, 1H), 7.53 – 7.46 (m, 1H), 7.39 – 7.35 (m, 1H), 7.30 – 7.23 (m, 1H). ^{13}C NMR (100 MHz, DMSO) δ 161.27, 137.03, 134.72, 133.27, 130.03, 128.39, 127.93, 126.15, 123.72, 123.09, 122.73, 118.02, 116.57. $\text{C}_{13}\text{H}_9\text{NO}$ (ESI+, $M+1$) = 196.10.

3-Acetylphenanthridin-6(5H)-one (entry 2)



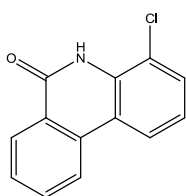
2-Chloro-*N*-(3-chloro-4-methylphenyl)benzamide was treated according to the general procedure as starting material. Major product was separated and purified by CombiFlash® Rf, affording the title compound (17.9 mg 76%) as pale yellow crystalline solid. R_f = 0.48 (40% Ethyl acetate/ Hexane) ^1H NMR (400 MHz, DMSO) δ 11.86 (s, 1H), 8.59 (d, J = 8.1 Hz, 1H), 8.54 (d, J = 8.4 Hz, 1H), 8.35 (dd, J = 7.9, 1.1 Hz, 1H), 7.94 – 7.88 (m, 2H), 7.82 (dd, J = 8.4, 1.7 Hz, 1H), 7.73 (t, J = 7.2 Hz, 1H), 2.64 (s, 3H). ^{13}C NMR (100 MHz, DMSO) δ 197.70, 161.23, 137.50, 137.00, 133.78, 133.53, 129.59, 128.05, 126.83, 124.24, 123.97, 122.26, 121.81, 116.23, 27.30. $\text{C}_{15}\text{H}_{11}\text{NO}_2$ (ESI+, $M+1$) = 238.15.

2-Methoxyphenanthridin-6(5H)-one (entry 3)



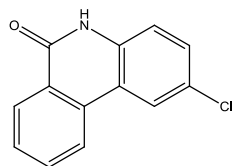
2-Chloro-*N*-(2-methoxyphenyl)benzamide was treated according to the general procedure as starting material. Major product was separated and purified by CombiFlash® Rf affording the title compound (18.1 mg, 80%) as a off-white solid. R_f = 0.25 (40% Ethyl acetate/hexane). ^1H NMR (400 MHz, DMSO) δ 10.61 (s, 1H, NH), 8.49 (d, J = 8.2 Hz, 1H), 8.35 (dd, J = 7.9, 1.1 Hz, 1H), 7.98 (d, J = 8.0 Hz, 1H), 7.89 – 7.83 (m, 1H), 7.65 (dd, J = 11.1, 3.9 Hz, 1H), 7.24 (t, J = 8.0 Hz, 1H), 7.17 (d, J = 7.3 Hz, 1H), 3.94 (s, 3H). ^{13}C NMR (100 MHz, DMSO) δ 160.81, 146.72, 134.73, 133.38, 128.53, 128.05, 126.61, 126.30, 123.51, 122.67, 118.52, 115.39, 110.95, 56.54. $\text{C}_{14}\text{H}_{11}\text{NO}_2$ (ESI+, $M+1$) = 226.10.

4-Chlorophenanthridin-6(5H)-one (entry 4)



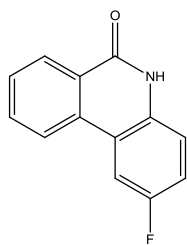
2-chloro-*N*-(2-chlorophenyl)benzamide was treated according to the general procedure as starting material. Major product was separated and purified by CombiFlash® Rf, affording the title compound (17 mg, 74%) as off-white solid. R_f = 0.11 (40% Ethyl acetate/hexane). ^1H NMR (400 MHz, DMSO) δ 10.82 (s, 1H), 8.56 (d, J = 8.2 Hz, 1H), 8.44 (d, J = 8.0 Hz, 1H), 8.36 (dd, J = 8.0, 1.1 Hz, 1H), 7.94 – 7.88 (m, 1H), 7.74 – 7.68 (m, 1H), 7.66 (dd, J = 7.8, 1.1 Hz, 1H), 7.30 (t, J = 8.0 Hz, 1H). ^{13}C NMR (100 MHz, DMSO) δ 161.27, 134.11, 133.84, 133.31, 130.26, 129.25, 128.10, 126.01, 123.62, 123.33, 122.99, 120.06, 119.75. $\text{C}_{13}\text{H}_8\text{NOCl}$ (ESI+, $M+1$) = 230.10.

2-Chlorophenanthridin-6(5H)-one (entry 5)



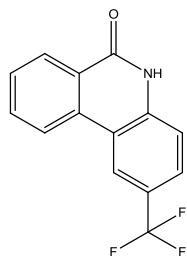
2-Chloro-*N*-(4-chlorophenyl)benzamide was treated according to the general procedure as starting material. Major product was separated and purified by CombiFlash® Rf affording the title compound (21.3 mg, 93%) as a yellow crystalline solid. R_f = 0.31 (40% Ethyl acetate/ Hexane) ^1H NMR (400 MHz, DMSO) δ 11.82 (s, 1H), 8.57 (d, J = 8.1 Hz, 1H), 8.48 (d, J = 2.2 Hz, 1H), 8.32 (dd, J = 7.9, 1.2 Hz, 1H), 7.90 – 7.83 (m, 1H), 7.69 (t, J = 7.5 Hz, 1H), 7.54 (dd, J = 8.7, 2.2 Hz, 1H), 7.37 (d, J = 8.7 Hz, 1H). ^{13}C NMR (100 MHz, DMSO) δ 161.08, 135.80, 133.65, 133.43, 129.89, 129.11, 127.92, 127.03, 126.27, 123.59, 123.33, 119.61, 118.35. $\text{C}_{13}\text{H}_8\text{NOCl}$ (ESI+, $M+1$) = 230.10.

2-Fluorophenanthridin-6(5H)-one (entry 6)



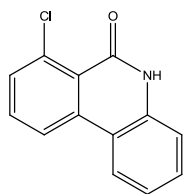
2-Chloro-*N*-(4-fluorophenyl)benzamide was treated according to the general procedure as starting material. Major product was separated and purified by CombiFlash® Rf affording the title compound (17 mg 80%) as off-white solid. R_f = 0.26 (40% Ethyl acetate/ Hexane) ^1H NMR (400 MHz, DMSO) δ 11.76 (s, 1H, NH), 8.52 (d, J = 8.1 Hz, 1H), 8.33 (d, J = 7.9 Hz, 1H), 8.28 (d, J = 10.3 Hz, 1H), 7.86 (t, J = 7.6 Hz, 1H), 7.68 (t, J = 7.5 Hz, 1H), 7.38 (m, 2H). ^{13}C NMR (100 MHz, DMSO) δ 160.99, 158.31 (d, J = 233 Hz), 134.05 (d, J = 3 Hz), 133.62, 133.31, 129.05, 127.94, 126.29, 123.68, 119.31 (d, J = 8.4 Hz), 118.23 (d, J = 8.5 Hz), 117.66 (d, J = 24.2 Hz), 109.65 (d, J = 24.0 Hz). $\text{C}_{13}\text{H}_8\text{NOF}$ (ESI+, $M+1$) = 214.10.

2-(Trifluoromethyl)phenanthridin-6(5H)-one (entry 7)



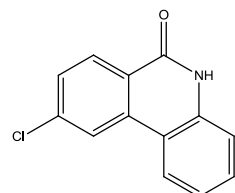
2-Chloro-*N*-(4-(trifluoromethyl)phenyl)benzamide was treated according to the general procedure as starting material. Major compound was separated and purified by CombiFlash® Rf affording the title compound (23mg, 86%). R_f = 0.39 (40% Ethyl acetate/ Hexane) ^1H NMR (400 MHz, DMSO) δ 12.03 (s, 1H, NH), 8.74 (s, 1H), 8.69 (d, J = 8.1 Hz, 1H), 8.34 (dd, J = 7.9, 1.0 Hz, 1H), 7.93 – 7.86 (m, 1H), 7.82 (dd, J = 8.6, 1.4 Hz, 1H), 7.72 (t, J = 7.5 Hz, 1H), 7.53 (d, J = 8.5 Hz, 1H). ^{13}C NMR (100 MHz, DMSO) δ 161.47, 139.77, 133.80, 133.64, 129.35, 127.96, 126.44 (q, J = 3.6 Hz), 126.34, 125.00 (q, J = 270 Hz), 123.75, 123.25 (q, J = 32.5 Hz), 121.39 (q, J = 3.8 Hz), 118.17, 117.42. $\text{C}_{14}\text{H}_8\text{NOF}_3$ (ESI+, $M+1$) = 264.15.

7-Chlorophenanthridin-6(5H)-one (entry 8)



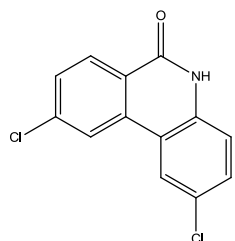
2,6-Dichloro-*N*-phenylbenzamide was treated according to the general procedure as starting material. Major Product was purified by CombiFlash® Rf, re-dissolved in 1 mL methanol and dried, affording the title compound (15.1 mg, 67%) as yellowish white solid. $R_f = 0.32$ (40% Ethyl acetate/ Hexane) ^1H NMR (400 MHz, DMSO) δ 11.67 (s, 1H), 8.51 (dd, $J = 8.4, 1.0$ Hz, 1H), 8.35 (t, $J = 6.2$ Hz, 1H), 7.76 (t, $J = 8.0$ Hz, 1H), 7.65 (dd, $J = 7.8, 1.0$ Hz, 1H), 7.53 – 7.47 (m, 1H), 7.33 (dd, $J = 8.2, 1.0$ Hz, 1H), 7.24 (ddd, $J = 8.3, 7.2, 1.2$ Hz, 1H). ^{13}C NMR (100 MHz, DMSO) δ 159.54, 138.02, 137.19, 134.98, 133.28, 131.69, 130.72, 124.30, 122.71, 122.58, 122.36, 117.31, 116.07. $\text{C}_{13}\text{H}_8\text{NOCl}$ (ESI+, $M+1$) = 230.15.

9-Chlorophenanthridin-6(5H)-one (entry 9)



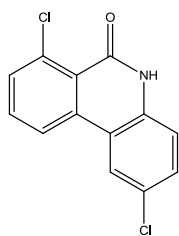
2,4-Dichloro-*N*-phenylbenzamide was treated according to the general procedure as starting material. Major Product was purified by CombiFlash® Rf, re-dissolved in 1 mL methanol and dried, affording the title compound (19 mg, 85%) as yellowish white solid. $R_f = 0.33$ (40% Ethyl acetate/ Hexane). ^1H NMR (400 MHz, DMSO) δ 11.80 (s, 1H), 8.62 (d, $J = 1.7$ Hz, 1H), 8.45 (d, $J = 8.0$ Hz, 1H), 8.30 (d, $J = 8.5$ Hz, 1H), 7.68 (dd, $J = 8.5, 1.8$ Hz, 1H), 7.53 (t, $J = 7.3$ Hz, 1H), 7.37 (d, $J = 7.9$ Hz, 1H), 7.27 (t, $J = 7.3$ Hz, 1H). ^{13}C NMR (100 MHz, DMSO) δ 160.64, 138.74, 137.49, 136.56, 130.81, 130.18, 128.56, 124.83, 124.29, 122.89, 122.86, 117.07, 116.65. $\text{C}_{13}\text{H}_8\text{NOCl}$ (ESI+, $M+1$) = 230.05.

2,9-dichlorophenanthridin-6(5H)-one (entry 10)



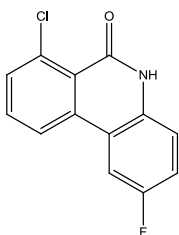
2,4-Dichloro-*N*-(4-chlorophenyl)benzamide was treated according to the general procedure as starting material. Major Product was separated and purified by CombiFlash® Rf, affording the title compound (19 mg, 83%) $R_f = 0.35$ (40% Ethyl acetate/ Hexane). ^1H NMR (400 MHz, DMSO) δ 11.89 (s, 1H), 8.70 (d, $J = 1.9$ Hz, 1H), 8.56 (d, $J = 2.2$ Hz, 1H), 8.29 (dd, $J = 8.4, 4.5$ Hz, 1H), 7.70 (dd, $J = 8.5, 1.9$ Hz, 1H), 7.56 (dd, $J = 8.7, 2.2$ Hz, 1H), 7.35 (d, $J = 8.7$ Hz, 1H). ^{13}C NMR (100 MHz, DMSO) δ 160.46, 138.94, 136.25, 135.47, 130.62, 130.09, 129.22, 127.24, 124.95, 123.88, 123.41, 118.61, 118.39. $\text{C}_{13}\text{H}_7\text{NOCl}_2$ (ESI+, $M+1$) = 264.05.

2,7-dichlorophenanthridin-6(5H)-one (entry 11)



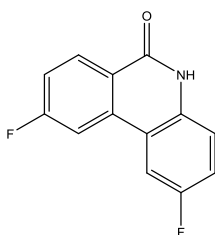
2,6-Dichloro-*N*-(4-chlorophenyl)benzamide was treated according to the general procedure as starting material. Major Product was separated and purified by CombiFlash® Rf, re-dissolved in 1 mL methanol and dried, affording the title compound (17 mg, 74%) as a white solid. $R_f = 0.39$ (40% Ethyl acetate/ Hexane). ^1H NMR (400 MHz, DMSO) δ 11.77 (s, 1H), 8.56 (dd, $J = 8.3, 0.9$ Hz, 1H), 8.45 (d, $J = 2.2$ Hz, 1H), 7.76 (t, $J = 8.0$ Hz, 1H), 7.71 – 7.66 (m, 1H), 7.57 – 7.51 (m, 1H), 7.32 (d, $J = 8.7$ Hz, 1H). ^{13}C NMR (100 MHz, DMSO) δ 159.35, 136.92, 135.97, 135.01, 133.42, 132.37, 130.58, 126.97, 123.85, 123.08, 122.51, 118.87, 117.86. $\text{C}_{13}\text{H}_7\text{NOCl}_2$ (ESI+, $M+1$) = 264.10.

7-chloro-2-fluorophenanthridin-6(5H)-one (entry 12)



2,6-dichloro-*N*-(4-fluorophenyl)benzamide was treated according to the general procedure as starting material. Major product was separated and purified by CombiFlash® Rf, re-dissolved in 1 mL methanol and dried, affording the title compound (15.5 mg, 67%) as white solid. $R_f = 0.42$ (40% Ethyl acetate/ Hexane). ^1H NMR (400 MHz, DMSO) δ 11.70 (s, 1H), 8.55 – 8.48 (m, 1H), 8.25 (dd, $J = 10.7, 2.5$ Hz, 1H), 7.77 (t, $J = 8.0$ Hz, 1H), 7.69 (dd, $J = 7.8, 1.0$ Hz, 1H), 7.44 – 7.30 (m, 2H). ^{13}C NMR (100 MHz, DMSO) δ 159.27, 158.18 (d, $J = 236$ Hz), 137.28 (d, $J = 3$ Hz), 135.03, 133.83, 133.31, 132.32, 123.19, 122.53, 118.53 (d, $J = 8.7$ Hz), 118.45 (d, $J = 24.2$ Hz), 117.77 (d, $J = 8.4$ Hz), 110.18 (d, $J = 24.0$ Hz). $\text{C}_{13}\text{H}_7\text{NOClF}$ (ESI+, $M+1$) = 248.15.

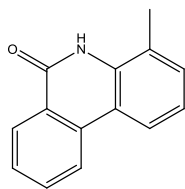
2,9-Difluorophenanthridin-6(5H)-one (entry 13)



2-chloro-4-fluoro-*N*-(4-fluorophenyl)benzamide was treated according to the general procedure as starting material. Major product was separated and purified by CombiFlash® Rf, re-dissolved in 1 mL methanol and dried, affording the title compound (18.8 mg, 84%) as white solid. $R_f = 0.40$ (40% Ethyl acetate/ Hexane). ^1H NMR (400 MHz, DMSO) δ 11.78 (s, 1H, NH), 8.41 – 8.33 (m, 1H), 8.36 (s, 1H), 8.29 (dd, $J = 10.4, 2.3$ Hz, 1H), 7.51 (td, $J = 8.6, 2.3$ Hz, 1H), 7.45 – 7.34 (m, 2H). ^{13}C NMR (100 MHz, DMSO) δ 165.53 (d, $J = 247$ Hz), 160.32, 158.17 (d, $J = 236$ Hz), 136.95 (d, $J = 10.1$ Hz), 134.11, 131.36 (d, $J = 10.2$ Hz), 123.14, 118.69 (d, $J =$

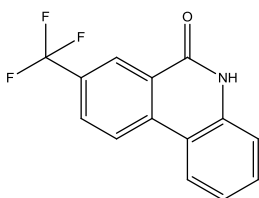
8.3Hz), 118.47 (d, $J = 24.0$ Hz), 118.33 (d, $J = 8.3$ Hz), 117.09 (d, $J = 23.8$ Hz), 110.23 (d, $J = 24.0$ Hz), 109.77 (d, $J = 24.1$ Hz). $C_{13}H_7NOF_2$ (ESI+, $M+1$) = 232.10.

4-Methylphenanthridin-6(5H)-one (entry 14)



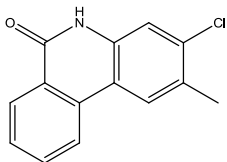
2-Chloro-*N*-(2-methylphenyl)benzamide was treated according to the general procedure as starting material. Major product was separated and purified by CombiFlash® Rf affording the title compound (4.4 mg, 21%) as a pale yellow crystalline solid $R_f = 0.37$ (40% Ethyl acetate/ Hexane) 1H NMR (400 MHz, DMSO) δ 10.72 (s, 1H, NH), 8.52 (d, $J = 8.2$ Hz, 1H), 8.35 (dd, $J = 7.9, 1.2$ Hz, 1H), 8.27 (d, $J = 8.0$ Hz, 1H), 7.89 – 7.81 (m, 1H), 7.65 (dd, $J = 11.1, 3.9$ Hz, 1H), 7.36 (d, $J = 7.2$ Hz, 1H), 7.19 (t, $J = 7.7$ Hz, 1H), 2.48 (s, 3H). ^{13}C NMR (100 MHz, DMSO) δ 161.66, 135.24, 135.00, 133.42, 131.48, 128.33, 127.93, 125.82, 124.65, 123.29, 122.46, 121.62, 118.02, 18.14. $C_{14}H_{11}NO$ (ESI+, $M+1$) = 210.15.

8-(Trifluoromethyl)phenanthridin-6(5H)-one (entry 15)



2-Chloro-*N*-phenyl-5-(trifluoromethyl)benzamide was treated according to the general procedure as starting material. Major product was purified by CombiFlash Rf®, re-dissolved in 1 mL methanol and dried, affording the title compound (6.7mg, 26%) as yellow crystalline solid. $R_f = 0.38$ (40% Ethyl acetate/ Hexane). 1H NMR (400 MHz, DMSO) δ 12.00 (s, 1H), 8.76 (d, $J = 8.6$ Hz, 1H), 8.56 (s, 1H), 8.49 (d, $J = 7.9$ Hz, 1H), 8.17 (dd, $J = 8.5, 2.0$ Hz, 1H), 7.63 – 7.54 (m, 1H), 7.44 – 7.38 (m, 1H), 7.36 – 7.29 (m, 1H). ^{13}C NMR (100 MHz, DMSO) δ 160.45, 138.09, 137.75, 131.46, 129.20 (q, $J = 3.3$ Hz), 128.57, 128.41 (q, $J = 32.6$ Hz), 126.31, 125.80, 124.88 (q, $J = 4.1$ Hz), 124.40 (q, $J = 279$ Hz), 123.18, 117.01, 116.88. $C_{14}H_8NOF_3$ (ESI+, $M+1$) = 264.10.

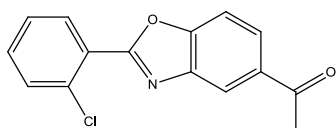
3-Chloro-2-methylphenanthridin-6(5H)-one (entry 16)



2-Chloro-*N*-(3-chloro-4-methylphenyl)benzamide was treated according to the general procedure as starting material. Purification by CombiFlash® Rf afforded the title compound (3.2 mg, 13%) as a white crystalline solid. $R_f = 0.45$ (40% Ethyl acetate/ Hexane). 1H NMR (400 MHz, DMSO) δ 11.69 (s, 1H), 8.49 (d, $J = 8.1$ Hz, 1H), 8.40 (s, 1H), 8.30 (dd, $J = 8.0, 1.1$ Hz, 1H), 7.89 – 7.83

(m, 1H), 7.69 – 7.61 (m, 1H), 7.38 (s, 1H), 2.42 (s, 3H). ^{13}C NMR (100 MHz, DMSO) δ 161.14, 136.09, 134.67, 134.00, 133.38, 129.49, 128.63, 127.98, 126.07, 125.99, 123.25, 117.12, 116.07, 19.68. $\text{C}_{14}\text{H}_{10}\text{NOCl}$ (ESI+, M+1) = 244.10.

1-(2-(2-Chlorophenyl)benzo[d]oxazol-5-yl)ethanone



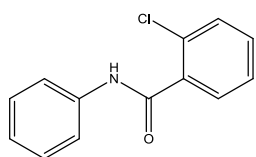
N-(5-acetyl-2-bromophenyl)-2-chlorobenzamide treated according to the general procedure as starting material. Major Product was purified by CombiFlash® Rf affording the title compound (17 mg, 63%) as a yellowish white crystalline solid. R_f = 0.47 (40% Ethyl acetate/ Hexane) ^1H NMR (400 MHz, DMSO) δ 8.50 (d, J = 1.5 Hz, 1H), 8.18 (dd, J = 7.7, 1.7 Hz, 1H), 8.09 (dd, J = 8.6, 1.7 Hz, 1H), 7.94 (d, J = 8.6 Hz, 1H), 7.74 (dd, J = 8.0, 1.1 Hz, 1H), 7.67 (td, J = 7.7, 1.7 Hz, 1H), 7.60 (td, J = 7.5, 1.2 Hz, 1H). ^{13}C NMR (100 MHz, DMSO) δ 197.57, 161.99, 153.31, 141.72, 134.75, 133.74, 132.78, 132.50, 131.85, 128.30, 126.72, 125.44, 121.54, 111.69, 27.47. $\text{C}_{15}\text{H}_{10}\text{NO}_2\text{Cl}$ (ESI+, M+1) = 272.10.

2.3 General procedure of the preparation of benzamide substrates (2-chloroanilides)

A round-bottom flask with magnetic stir-bar was cleaned and oven-dried. The corresponding acyl chloride (1.1 equiv.) and aniline (1 equiv.) were dissolved in tetrahydrofuran (THF) (5mL per 1mmol reagent) respectively to make two solutions, one of acyl chloride and one of the aniline. The solution of aniline was introduced to the flask and stirred in ice bath at 0°C for 5 minutes. Triethylamine (1 equiv.) was added to the solution of aniline followed by addition of the solution of acyl chloride drop by drop at 0°C. The resulting reaction mixture was stirred at r.t. for overnight after removing the ice bath. The resulting product was filtered twice to remove the solid which was washed by THF. THF was then removed from the solution of crude product by vacuum and the residue was loaded on silica gel, separated and purified by column chromatography (CombiFlash® Rf). The purified product was then dried under vacuum.

2.4 Characterization of benzamide (2-chloroanilides) substrates

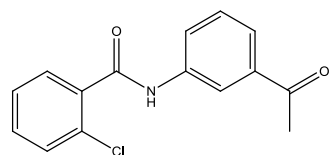
2-Chloro-*N*-phenylbenzamide



Aniline (93.2 mg, 1 mmol) and 2-chlorobenzoyl chloride (195 mg, 1.11 mmol) were treated according to the general procedure. Purification by CombiFlash® Rf afforded the title compound (230 mg, 99%) as a white

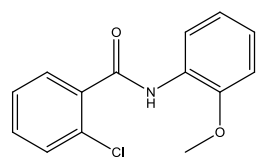
crystalline solid. $R_f=0.61$ (40% Ethyl acetate/hexane). ^1H NMR (400 MHz, CDCl_3) δ 8.68 (s, 1H), 7.63 (d, $J = 7.7$ Hz, 2H), 7.47 (dd, $J = 7.6, 1.4$ Hz, 1H), 7.34-7.26 (m, 4H), 7.20 (dt, $J=7.4, 1.6$ Hz, 1H), 7.13 (t, $J=7.2$ Hz, 1H). ^{13}C NMR (100 MHz, CDCl_3) δ 164.52, 137.56, 135.21, 131.72, 130.63, 130.39, 130.35, 129.15, 127.32, 124.89, 120.15.

***N*-(3-acetylphenyl)-2-chlorobenzamide**



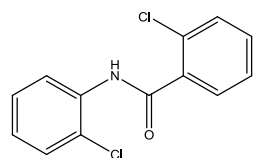
3'-Aminoacetophenone (135 mg, 1 mmol) and 2-chlorobenzoyl (194 mg, 1.1 mmol) were treated according to the general procedure. Purification by CombiFlash® Rf afforded the title compound (251 mmg, 92%). $R_f=0.44$. ^1H NMR (400 MHz, DMSO) δ 10.73 (s, 1H), 8.34 (s, 1H), 7.96 (d, $J = 8.1$ Hz, 1H), 7.74 (d, $J = 7.8$ Hz, 1H), 7.61 (ddd, $J = 11.2, 7.6, 1.5$ Hz, 2H), 7.57 – 7.45 (m, 3H), 2.59 (s, 3H). ^{13}C NMR (100 MHz, DMSO) δ 198.09, 165.65, 139.74, 137.85, 137.15, 131.73, 130.38, 130.17, 129.73, 129.42, 127.77, 124.48, 124.36, 119.22, 27.24.

2-Chloro-*N*-(2-methoxyphenyl)benzamide



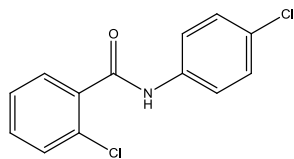
2-Methoxy-benzenamine (123 mg, 1 mmol) and 2-chlorobenzoyl chloride (193 mg, 1.1 mmol) were treated according to the general procedure. Purification by CombiFlash® Rf afforded the title compound (253 mg, 97%) as a white crystalline solid. $R_f=0.68$ (40% Ethyl acetate/hexane). ^1H NMR (400 MHz, DMSO) δ 9.63 (s, 1H), 7.93 (d, $J = 7.9$ Hz, 1H), 7.59-7.43(m, 4H), 7.17 (t, 1H), 7.09 (d, $J = 7.7$ Hz, 1H), 6.98 (t, $J = 7.5$ Hz, 1H), 3.82 (s, 3H). ^{13}C NMR (100 MHz, CDCl_3) δ 165.32, 138.84, 138.29, 134.55, 132.23, 129.45, 128.99, 127.19, 126.06, 121.77, 90.22.

2-chloro-*N*-(2-chlorophenyl)benzamide



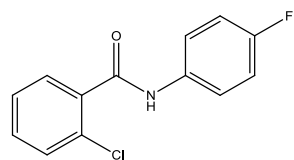
2-Chloroaniline (128 mg, 1 mmol) and 2-chlorobenzoyl chloride (194 mg, 1.1 mmol) were treated according to the general procedure. Purification by CombiFlash® Rf afforded the title compound (265 mg, 99%) as a off-white solid. $R_f=0.77$ (40% Ethyl acetate/hexane). ^1H NMR (400 MHz, CDCl_3) δ 8.60 (d, $J = 8.1$ Hz, 1H), 8.52 (s, 1H), 7.84 (dd, $J = 7.4, 1.5$ Hz, 1H), 7.55 – 7.40 (m, 4H), 7.37 (t, $J = 7.8$ Hz, 1H), 7.13 (td, $J = 7.8, 1.5$ Hz, 1H). ^{13}C NMR (100 MHz, CDCl_3) δ 164.35, 134.77, 134.54, 132.02, 130.79, 130.61, 129.18, 127.84, 127.37, 125.13, 123.18, 121.82.

2-Chloro-*N*-(4-chlorophenyl)benzamide



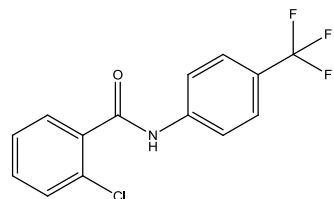
4-Chloroaniline (127.6 mg, 1 mmol) and 2-chlorobenzoyl chloride (193 mg, 1.1 mmol) were treated according to the general procedure. Purification by CombiFlash® Rf afforded the title compound (231 mg, 99%) as a white crystalline solid. R_f =0.64 (40% Ethyl acetate/hexane). ^1H NMR (400MHz, DMSO): δ 10.66 (s, 1H), 7.76 (d, J =8.8Hz, 2H), 7.61-7.45 (m, 4H), 7.42 (d, J =8.8Hz, 2H). ^{13}C NMR (100 MHz, DMSO) δ 165.47, 138.33, 137.17, 131.71, 130.36, 130.15, 129.40, 129.19, 127.88, 127.77, 121.55.

2-Chloro-*N*-(4-fluorophenyl)benzamide



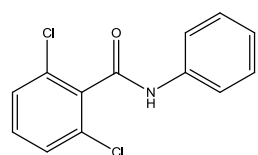
4-Fluoroaniline (111 mg, 1 mmol) and 2-chlorobenzoyl chloride (202mg, 1.2 mmol) were treated according to the general procedure. Purification by CombiFlash® Rf afforded the title compound (213mg, 99%) as white crystalline solid. R_f =0.64 (40% Ethyl acetate/hexane). ^1H NMR (400 MHz, CDCl_3) δ 7.97 (s, 1H), 7.76 (dd, J = 7.4, 1.7 Hz, 1H), 7.66 – 7.58 (m, 2H), 7.50 – 7.36 (m, 3H), 7.13 – 7.05 (m, 2H). ^{13}C NMR (100 MHz, CDCl_3) δ 164.49, 159.72 (d, J = 242 Hz), 134.92, 132.53 (d, J = 2.8 Hz), 131.83, 130.60, 130.42, 130.40, 127.36, 122.03 (d, J = 8.0 Hz), 115.82 (d, J = 22.6 Hz).

2-Chloro-*N*-(4-(trifluoromethyl)phenyl)benzamide



4-(Trifluoromethyl)aniline (161 mg, 1 mmol) and 2-chlorobenzoyl chloride (201mg, 1.1 mmol) were treated according to the general procedure. Purification by CombiFlash® Rf afforded the title compound (272 mg, 91%) as a white crystalline solid. R_f = 0.60 (40% Ethyl acetate/hexane). ^1H NMR (400 MHz, CDCl_3) δ 8.15 (s, 1H), 7.79 (t, J = 7.2 Hz, 3H), 7.65 (d, J = 8.5 Hz, 2H), 7.51 – 7.37 (m, 3H). ^{13}C NMR (100 MHz, CDCl_3) δ 164.67, 140.55, 134.57, 132.14, 130.59, 130.52, 130.50, 127.46, 126.44 (q, 3.8 Hz), 126.63 (q, J = 32.3 Hz), 124.03 (q, J = 269 Hz), 119.73.

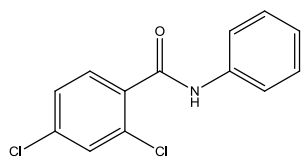
2,6-Dichloro-*N*-phenylbenzamide



Aniline (95.8 mg, 1.03 mmol) and 2,6-dichlorobenzoyl chloride (210 mg, 1 mmol) were treated according to the general procedure. Purification by

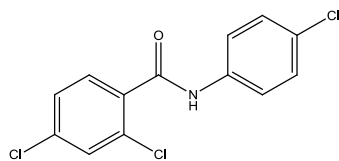
CombiFlash[®] Rf afforded the title compound (255 mg, 96%). $R_f = 0.57$ (40% Ethyl acetate/hexane). ^1H NMR (400 MHz, CDCl_3) δ 7.65 (d, $J = 7.6$ Hz, 2H), 7.53 (s, 1H), 7.44 – 7.36 (m, 4H), 7.32 (dd, $J = 9.3, 6.5$ Hz, 1H), 7.22 (dd, $J = 9.1, 5.8$ Hz, 1H). ^{13}C NMR (100 MHz, CDCl_3) δ 162.47, 137.17, 135.89, 132.44, 130.98, 129.19, 128.19, 125.22, 120.35.

2,4-Dichloro-*N*-phenylbenzamide



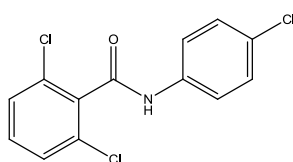
Aniline (96.7 mg, 1.04 mmol) and 2,4-dichlorobenzoyl chloride (209 mg, 1 mmol) were treated according to the general procedure. Purification by CombiFlash[®] Rf afforded the title compound (231 mg, 87%) as a yellow crystalline solid. $R_f = 0.71$ (40% Ethyl acetate/hexane). ^1H NMR (400 MHz, CDCl_3) δ 7.98 (s, 1H), 7.72 (d, $J = 8.3$ Hz, 1H), 7.65 (d, $J = 7.9$ Hz, 2H), 7.49 (d, $J = 1.4$ Hz, 1H), 7.45 – 7.35 (m, 3H), 7.21 (t, $J = 7.4$ Hz, 1H). ^{13}C NMR (100 MHz, CDCl_3) δ 163.49, 137.33, 137.26, 133.52, 131.47, 130.21, 129.20, 127.76, 125.10, 120.21.

2,4-Dichloro-*N*-(4-chlorophenyl)benzamide



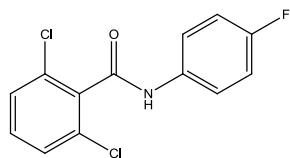
4-Chloroaniline (127.7 mg 1 mmol) and 2,4-dichlorobenzoyl chloride (213 mg, 1 mmol) were treated according to the general procedure. Purification by CombiFlash[®] Rf afforded the title compound (290 mg, 97%) as a white crystalline solid. $R_f = 0.72$ (40% Ethyl acetate/hexane). ^1H NMR (400 MHz, DMSO) δ 10.70 (s, 1H), 7.79 (d, $J = 1.5$ Hz, 1H), 7.74 (d, $J = 8.7$ Hz, 2H), 7.66 (d, $J = 8.2$ Hz, 1H), 7.57 (dd, $J = 8.2, 1.4$ Hz, 1H), 7.43 (d, $J = 8.7$ Hz, 2H). ^{13}C NMR (100 MHz, DMSO) δ 164.55, 138.14, 135.96, 135.47, 131.69, 130.83, 129.71, 129.24, 128.04, 127.98, 121.58.

2,6-Dichloro-*N*-(4-chlorophenyl)benzamide



4-Chloroaniline (127.8 mg 1mmol), and 2,6-dichlorobenzoyl chloride (209 mg, 1 mmol) were treated according to the general procedure. Purification by CombiFlash[®] Rf afforded the title compound (254 mg 85%) as a white crystalline solid. $R_f = 0.58$ (40% Ethyl acetate/hexane). ^1H NMR (400 MHz, DMSO) δ 10.91 (s, 1H), 7.76 – 7.70 (m, 2H), 7.63 – 7.57 (m, 2H), 7.55 – 7.49 (m, 1H), 7.47 – 7.41 (m, 2H). ^{13}C NMR (100 MHz, DMSO) δ 162.60, 137.92, 136.56, 132.02, 131.62, 129.36, 128.76, 128.23, 121.52.

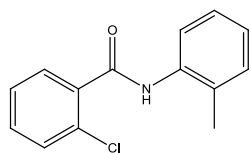
2,6-Dichloro-*N*-(4-fluorophenyl)benzamide [edit](#)



4-Fluoroaniline (115mg, 1mmol) and 2,6-dichlorobenzoyl chloride (216mg, 1mmol) were treated according to the general procedure. Purification by CombiFlash® Rf afforded the title compound (282 mg, 96%) as a white crystalline solid. R_f = 0.59 (40% Ethyl acetate/hexane).

^1H NMR (400 MHz, MeOD) δ 7.72 – 7.66 (m, 2H), 7.47 (m, 3H), 7.17 – 7.10 (m, 2H). ^{13}C NMR (100 MHz, MeOD) δ 163.71, 159.69 (d, J = 241 Hz), 136.10, 134.20 (d, J = 2.8 Hz), 131.90, 130.96, 127.92, 121.91 (d, J = 7.9 Hz), 115.09 (d, J = 22.5 Hz).

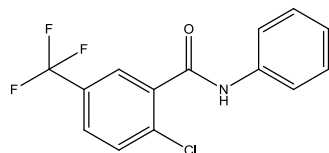
2-Chloro-*N*-(2-methylphenyl)benzamide



o-Toluidine (108 mg, 1 mmol) and 2-chlorobenzoyl (202 mg, 1.15 mmol) were treated according to the general procedure. Purification by CombiFlash® Rf afforded the title compound (241 mg, 99%). R_f = 0.61. ^1H NMR (400 MHz, CDCl_3) δ 8.04 (d, J = 8.0 Hz, 1H), 7.86 (dd, J = 7.3, 2.0 Hz, 1H), 7.84 (s, 1H, NH), 7.51 – 7.40 (m, 3H), 7.33 – 7.25 (m, 2H), 7.16 (t, J = 7.1 Hz, 1H), 2.38 (s, 3H).

^{13}C NMR (100 MHz, DMSO) δ 165.57, 137.55, 136.23, 133.46, 131.40, 130.87, 130.37, 130.10, 129.45, 127.69, 126.47, 126.43, 126.42, 18.47.

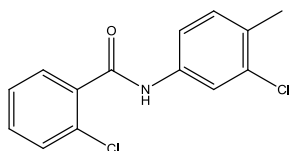
2-Chloro-*N*-phenyl-5-(trifluoromethyl)benzamide [edit](#)



Aniline (96.4 mg 1.04 mmol) and 2-chloro-5-(trifluoromethyl)benzoyl chloride (243 mg 1 mmol) were treated according to the general procedure. Purification by CombiFlash® Rf afforded the title compound (290 mg, 97%) as brown crystalline solid. R_f = 0.72 (40% Ethyl acetate/hexane).

^1H NMR (400 MHz, CDCl_3) δ 8.04 (d, J = 1.5 Hz, 1H), 7.94 (s, 1H), 7.71 – 7.59 (m, 4H), 7.42 (t, J = 7.9 Hz, 2H), 7.23 (t, J = 7.4 Hz, 1H). ^{13}C NMR (100 MHz, CDCl_3) δ 163.06, 137.11, 135.94, 134.44, 131.10, 130.00 (q, J = 34.1 Hz), 129.25, 128.27 (q, J = 3.6 Hz), 127.50 (q, 3.8 Hz), 125.32, 123.22 (q, J = 271 Hz), 120.28.

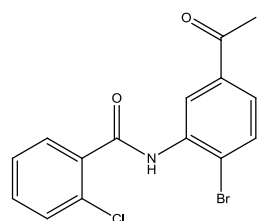
2-Chloro-*N*-(3-chloro-4-methylphenyl)benzamide



3-Chloro-4-methyl-benzenamine (142 mg, 1 mmol) and 2-chlorobenzoyl chloride (193 mg, 1.1 mmol) were treated according to the general procedure. Purification by CombiFlash® Rf afforded the title compound

(280 mg, 99%) as a white crystalline solid. $R_f=0.65$ (40% Ethyl acetate/hexane). ^1H NMR (400MHz, DMSO): δ 10.62 (s, 1H), 7.91 (s, 1H), 7.61-7.57(m, 2H), 7.55-7.45 (m, 3H), 7.33 (d, J = 8.5 Hz, 1H), 2.30 (s, 3H). ^{13}C NMR (100 MHz, DMSO) δ 165.46, 138.48, 137.12, 133.50, 131.72, 130.98, 130.37, 130.16, 129.40, 127.77, 119.91, 118.64, 19.47.

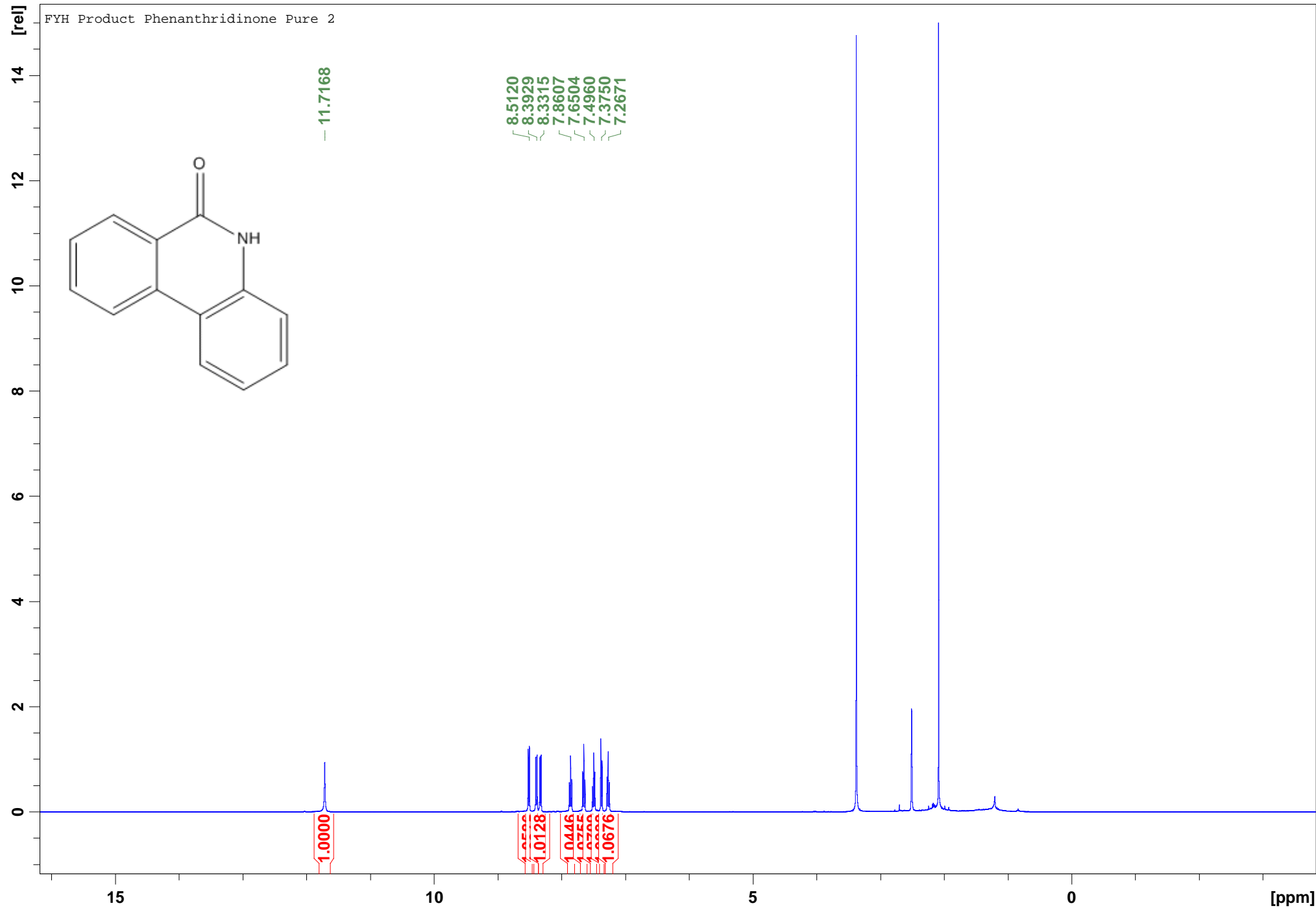
***N*-(3-acetylphenyl)-2-chloro-benzamide**



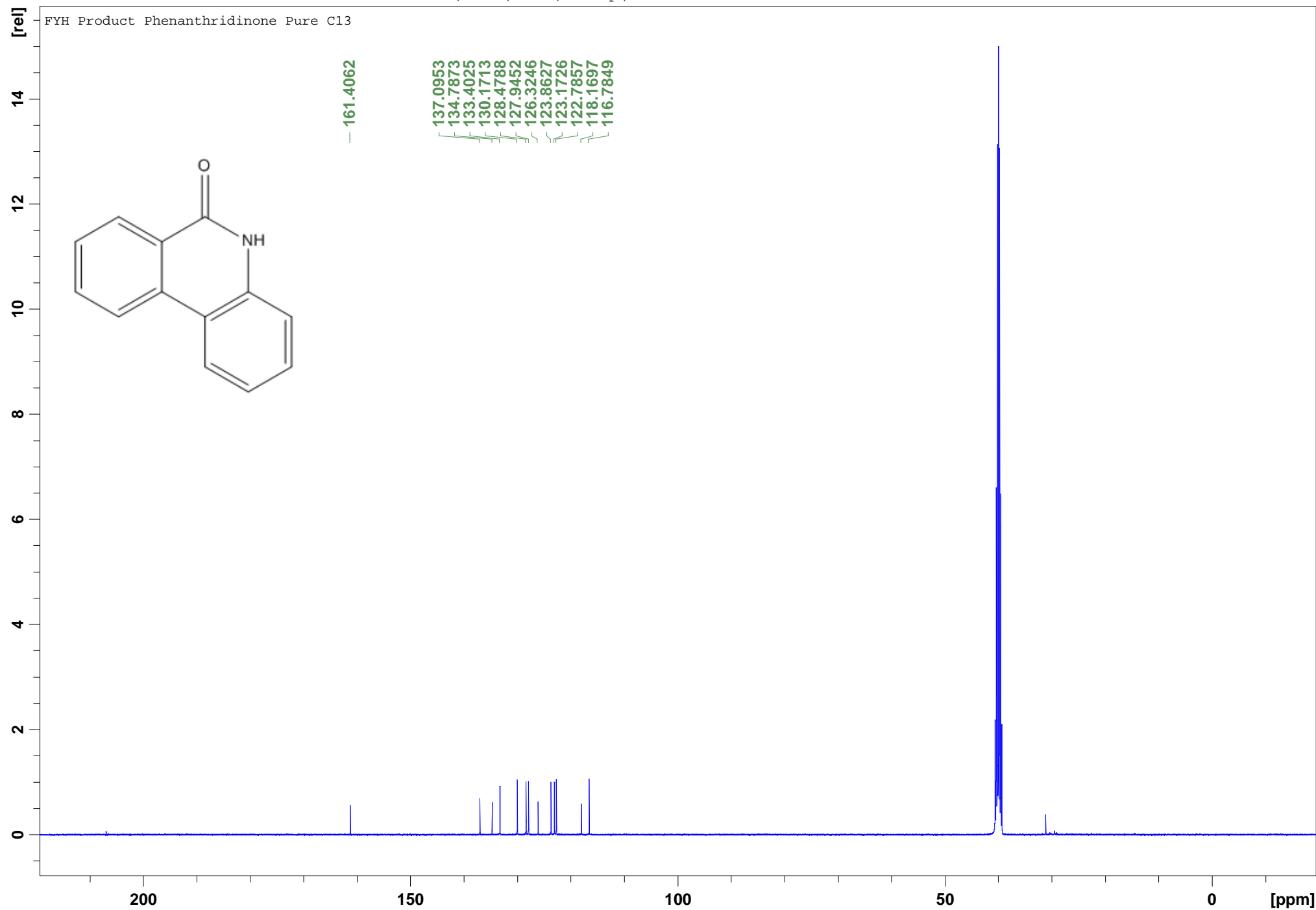
3'-Amino-4'-bromoacetophenone (214 mg, 1 mmol) and 2-chlorobenzoyl (193 mg, 1.1 mmol) were treated according to the general procedure. Purification by CombiFlash[®] Rf afforded the title compound (349 mg, 99%). $R_f=0.58$. ^1H NMR (400 MHz, CDCl_3) δ 9.19 (s, 1H), 8.59 (s, 1H), 7.86 (d, J = 8 Hz, 1H), 7.72 (d, J = 8.4 Hz, 1H), 7.67 (dd, J = 8.4, 2.0 Hz, 1H), 7.56 - 7.42 (m, 3H), 2.68 (s, 3H). ^{13}C NMR (100 MHz, CDCl_3) δ 197.23, 137.22, 136.05, 134.34, 132.80, 132.32, 130.79, 130.73, 127.49, 124.71, 122.08, 119.19, 118.75, 114.64, 26.77.

2.5 General procedure for the two-step (table 2) continuous-flow photochemical synthesis of phenanthridinone(s) and derivatives

The corresponding acyl chloride was dissolved in acetone (0.05 mmol/mL); and the appropriate aniline was dissolved in acetone as well (0.05 mmol/mL), and each placed/injected into the respective sample loops (2mL, A/B) of the Vapourtec[®] R2+/R4 system equipped with a stainless steel heating coil reactor (Vapourtec[®] HT Reactor, 10 mL) and photochemical coil reactor (Vapourtec[®] UV-150 ,10 mL). The chloride solution and the aniline solution were injected/flowed through the reactors respectively at a flow rate of 0.100 mL/min/each, and pumped into the heating coil reactor first (Temperature: 60 °C) and then the UV coil reactor (Lamp power 75% (~ 112.5 watts), whole-wavelength range, temperature: 60 °C). The pressure limit of the whole system was 12 Bar. The crude product was collected in a round bottom flask covered by aluminum foil and then preabsorbed onto silica gel, and solvent acetone removed by vacuum. The silica gel residue was loaded into an empty purification cartridge and the product was then separated and purified by column chromatography (CombiFlash[®] Rf, hexane/ethyl acetate). The solvent hexane/ethyl acetate was removed by vacuum and the product was dried under vacuum. All reactions provided products as described for the single step photochemical cyclization. Please see above entries for data.

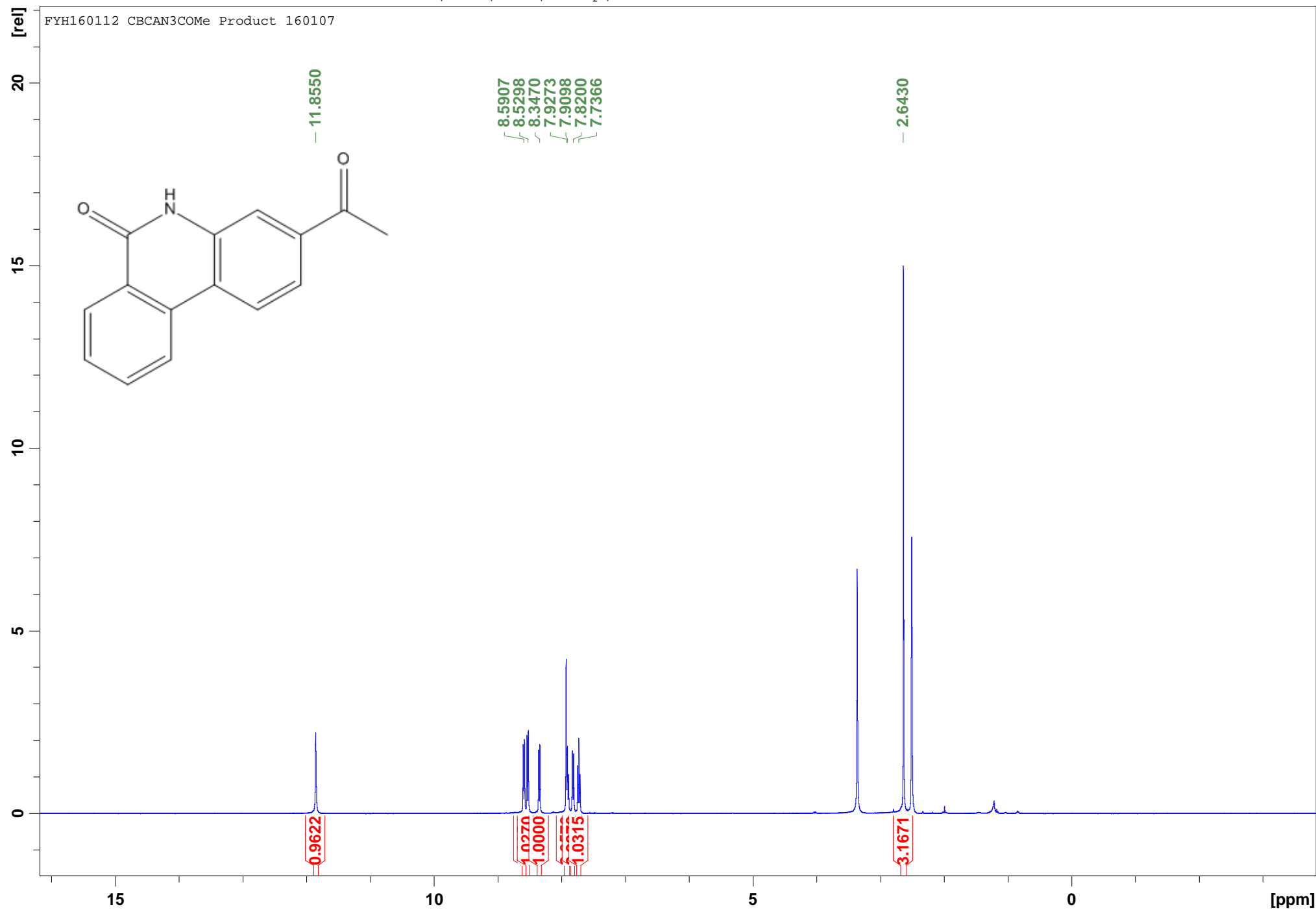


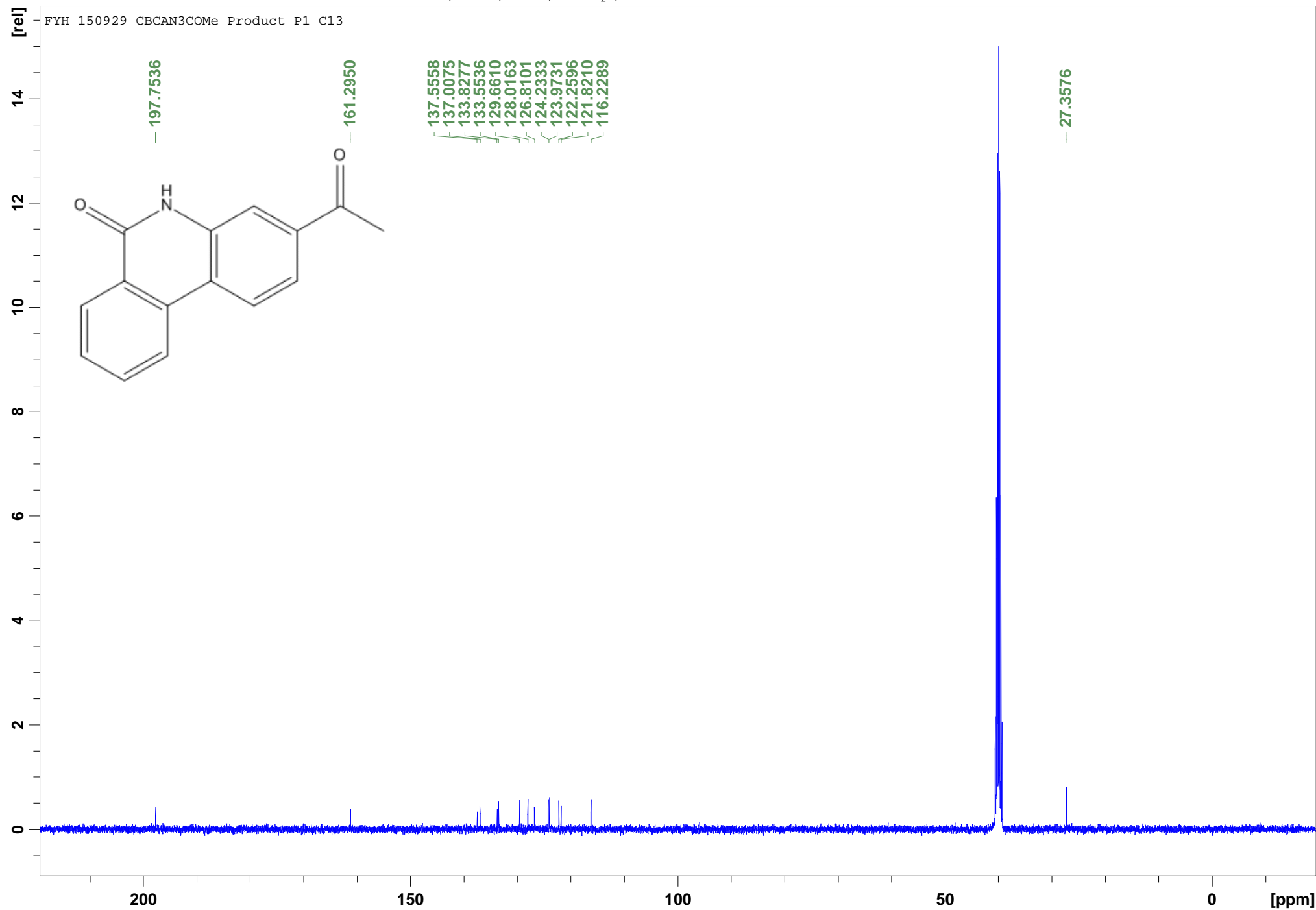
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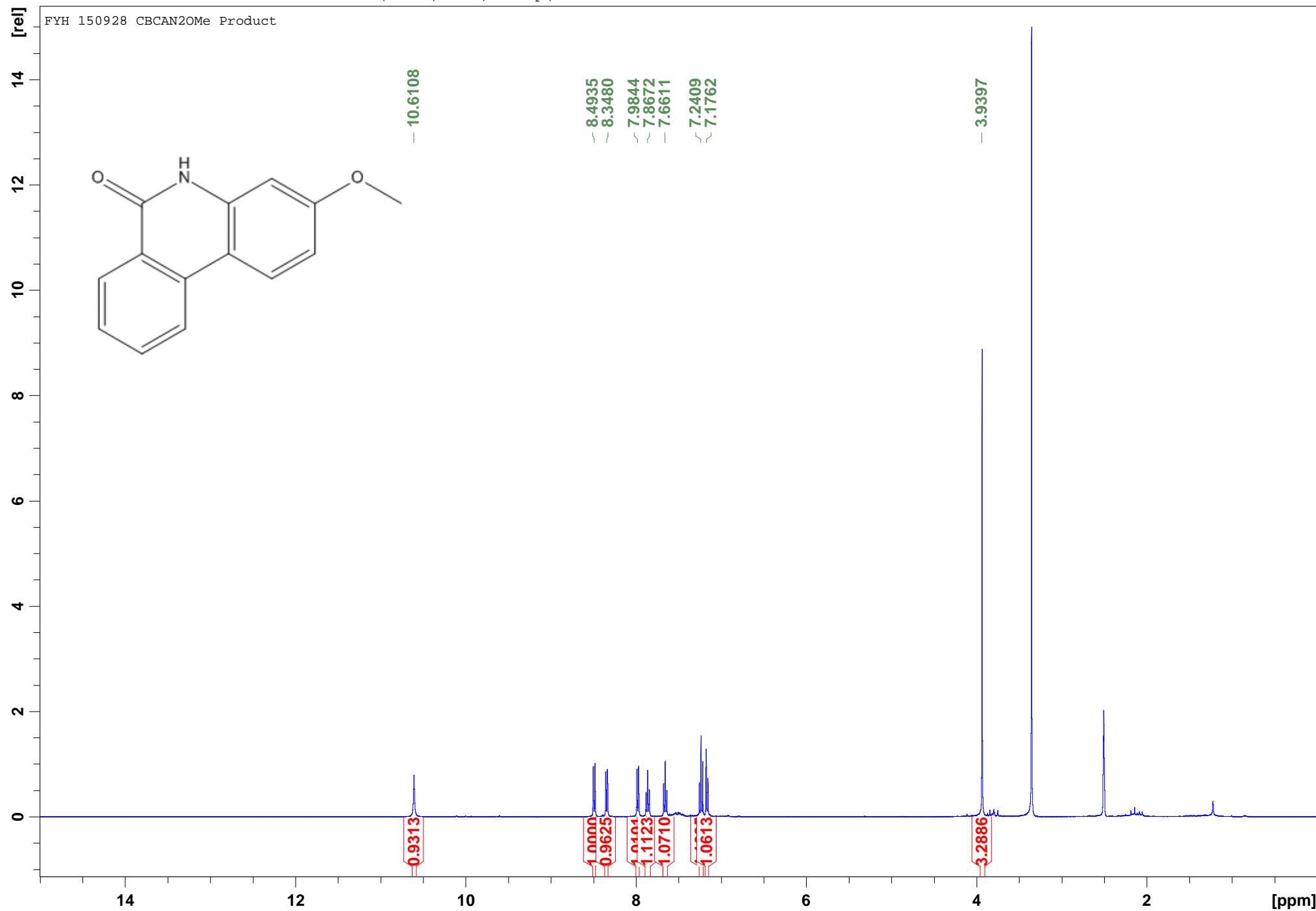
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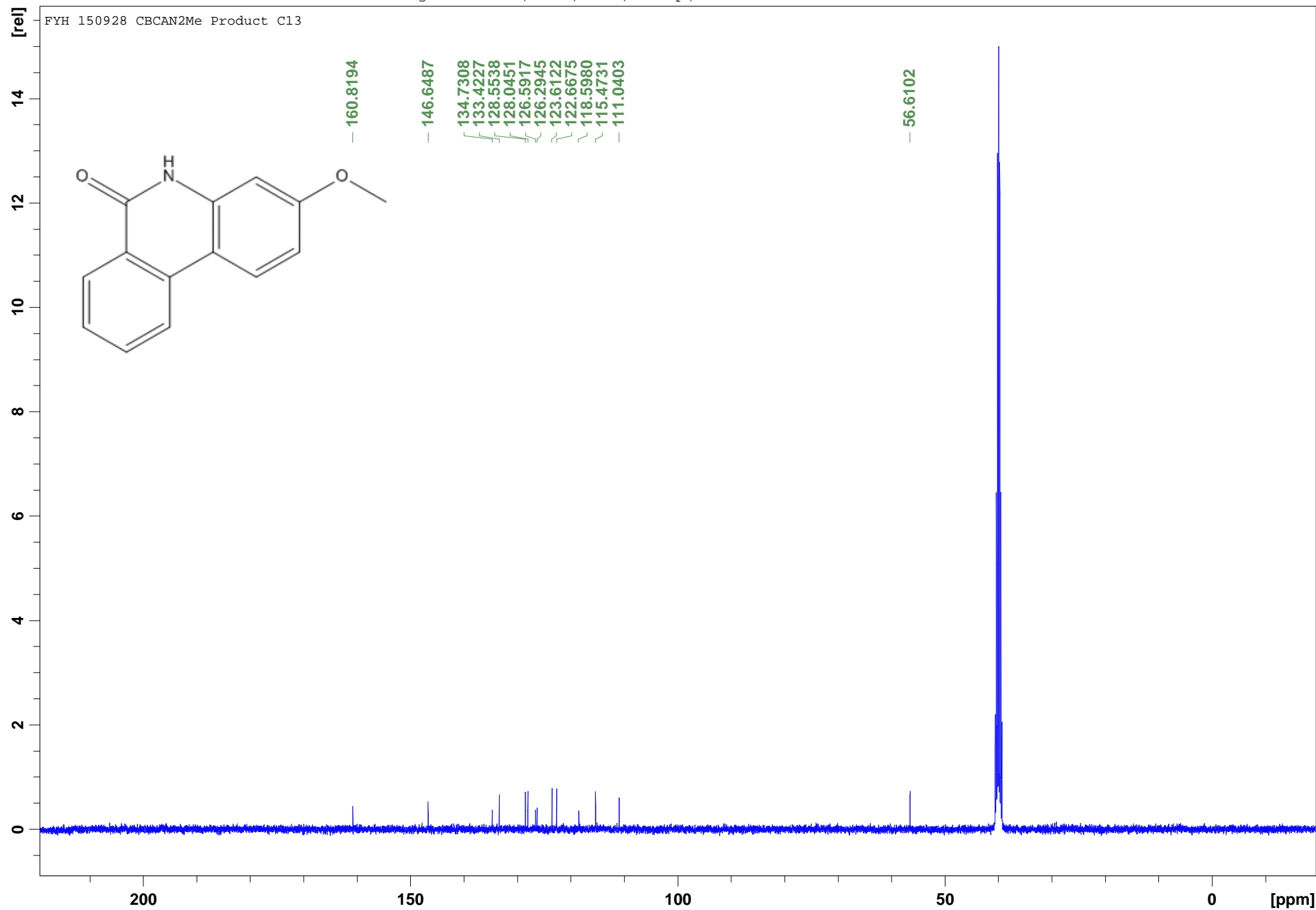
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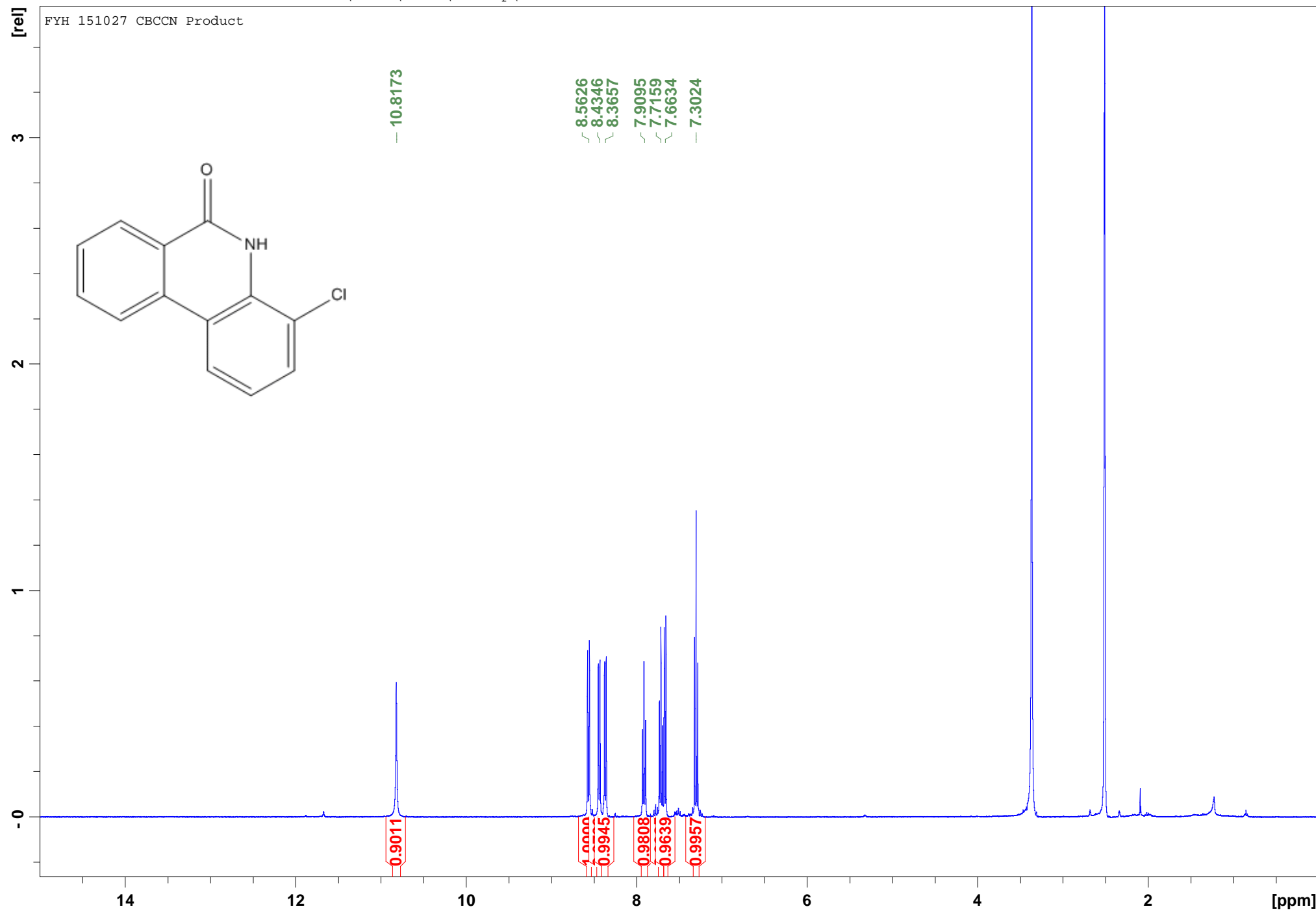


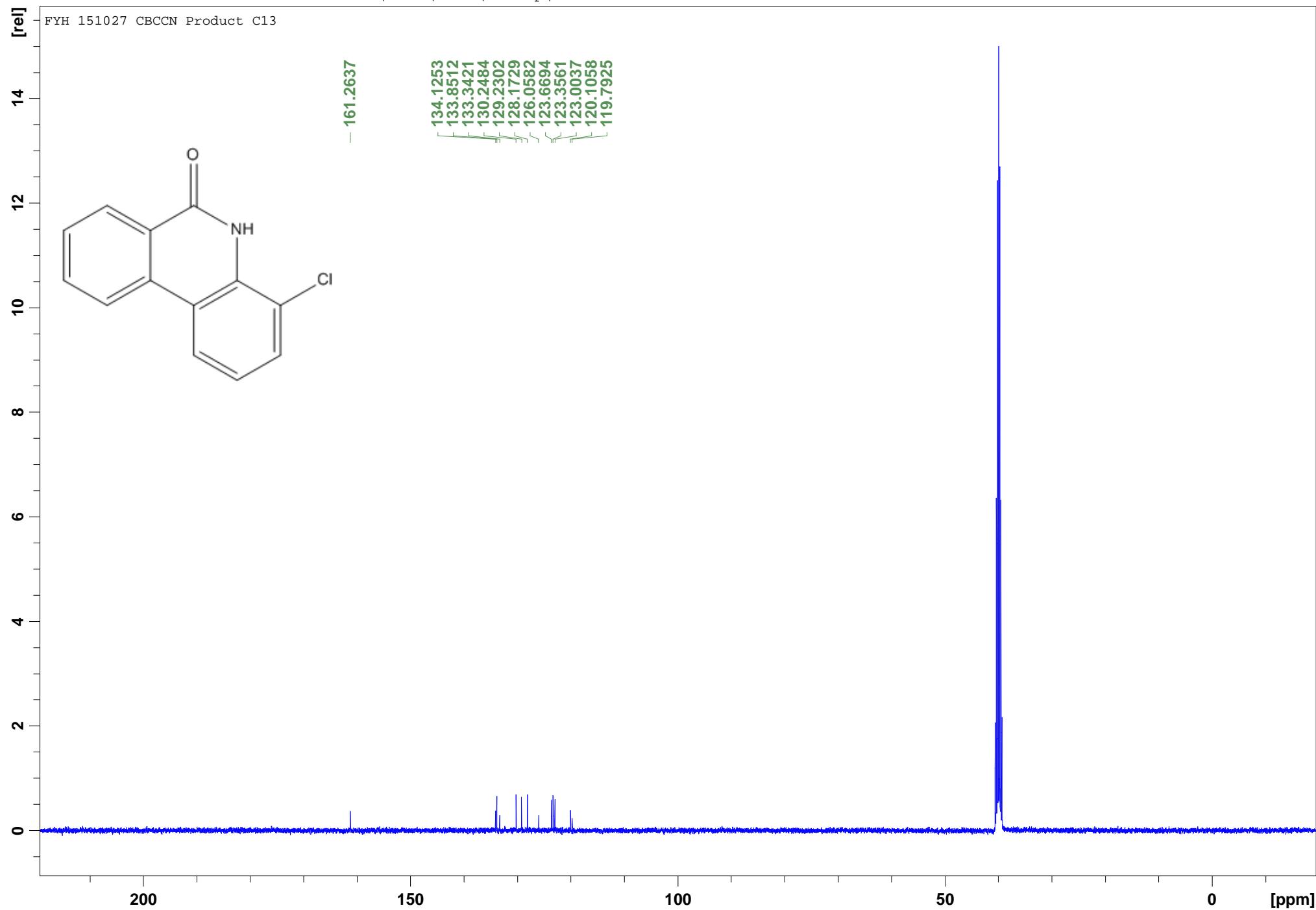
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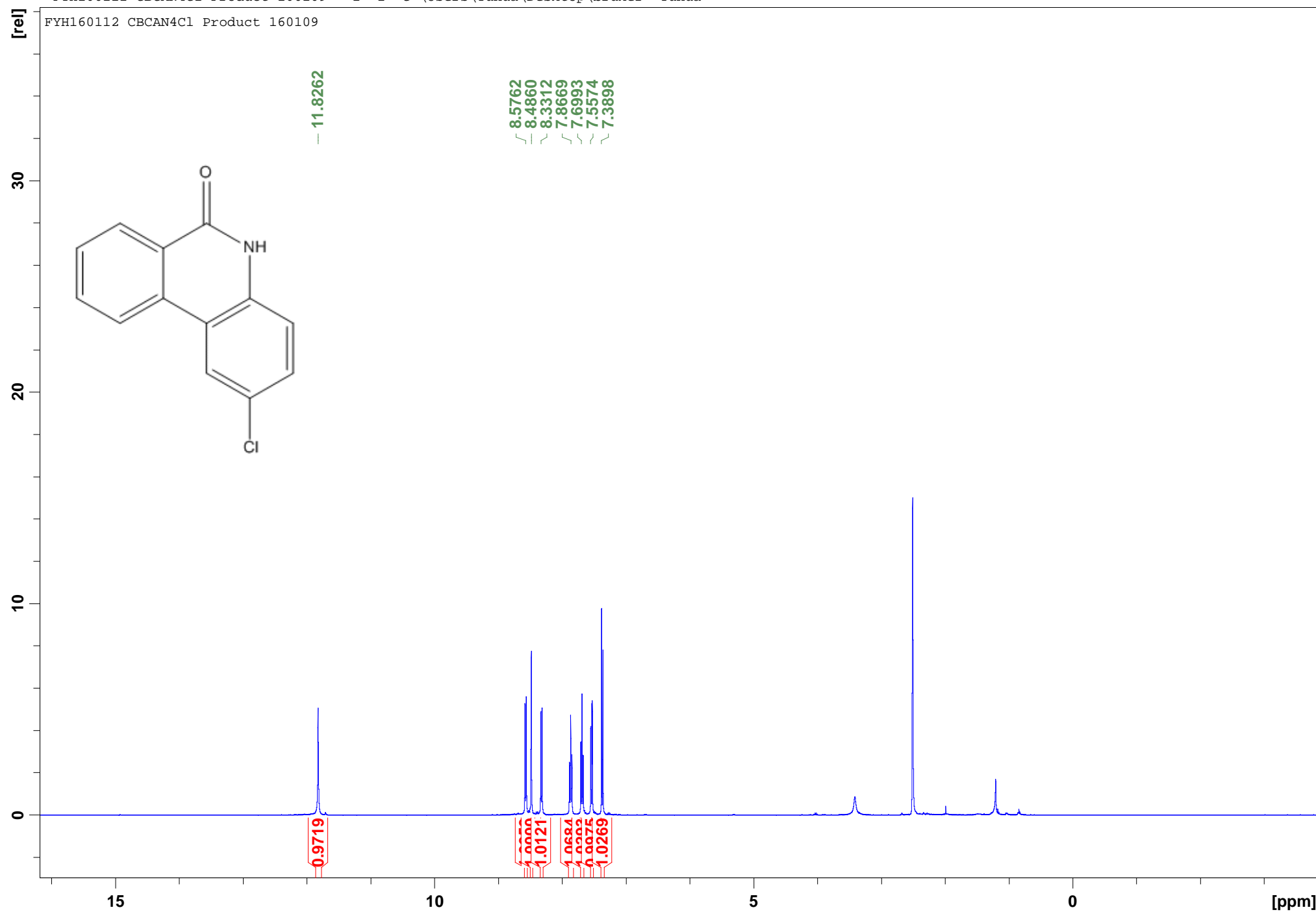
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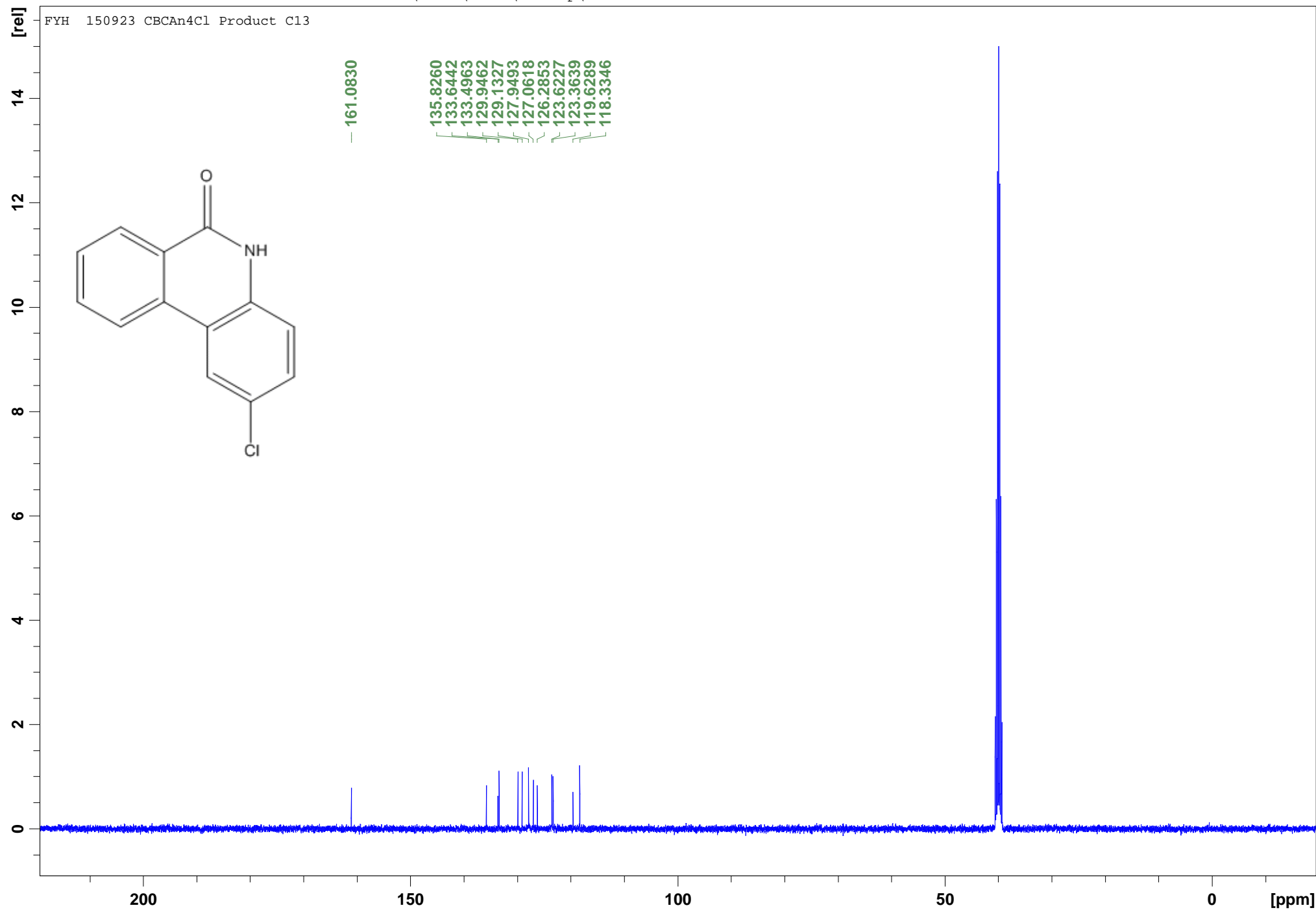
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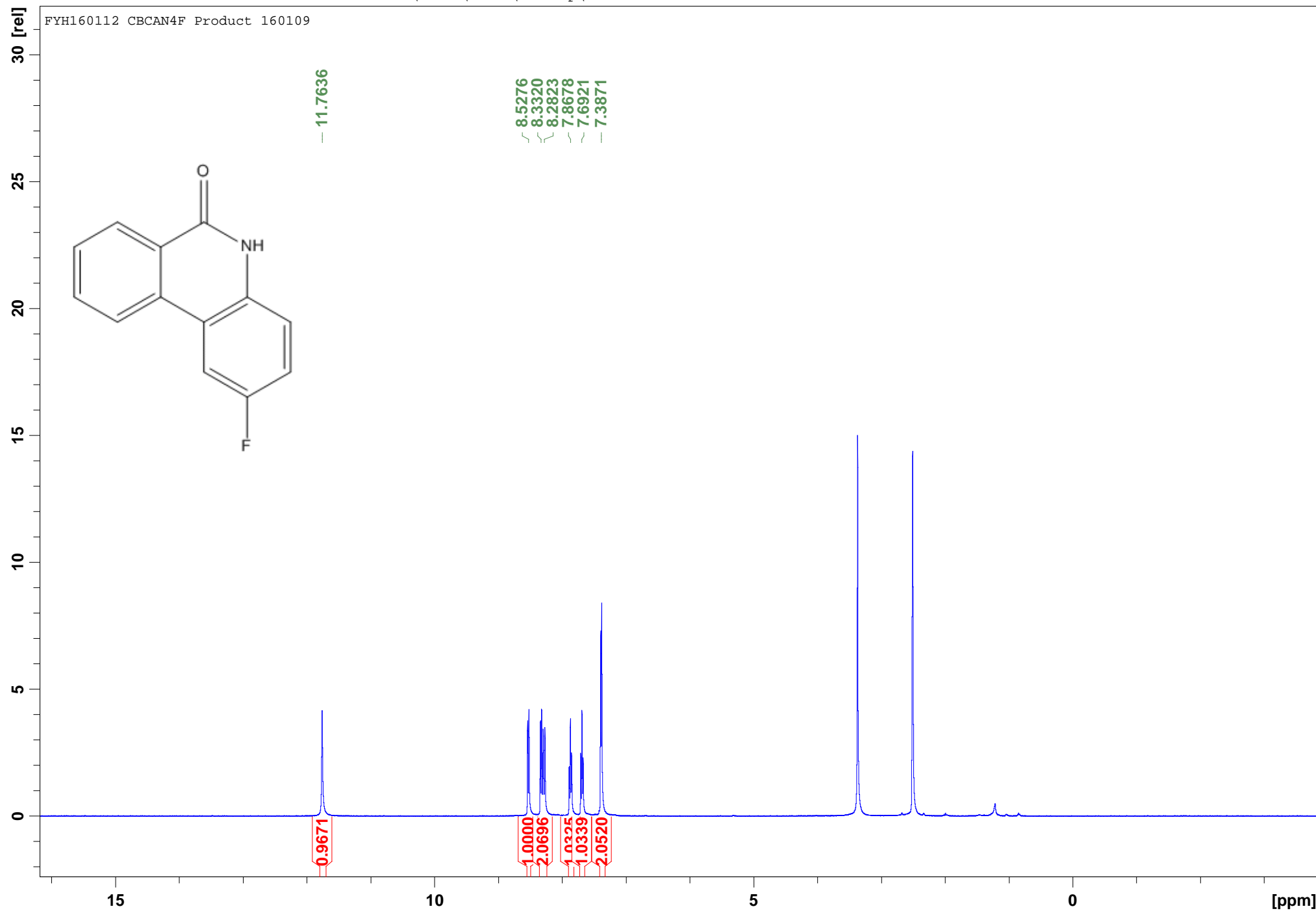


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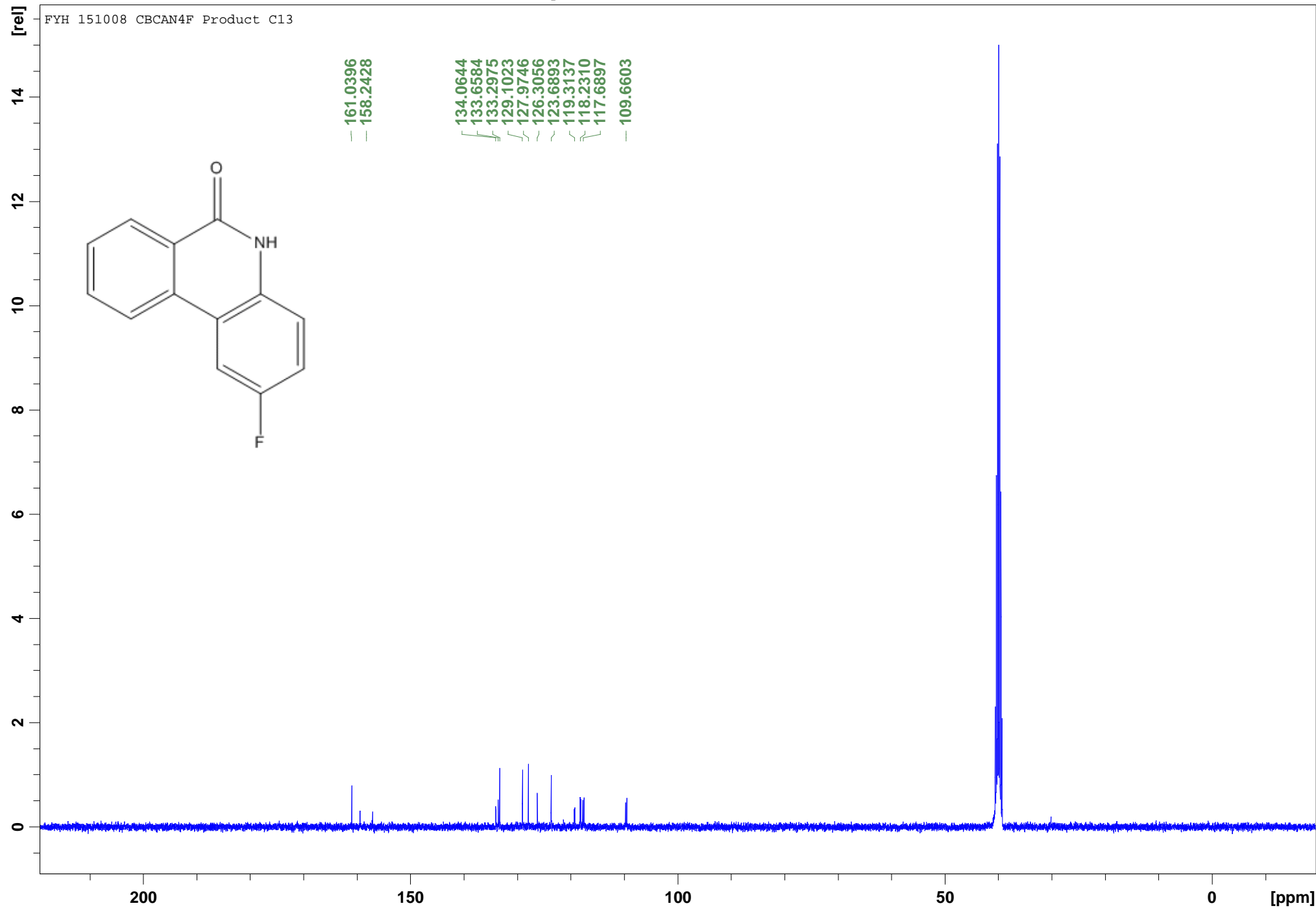
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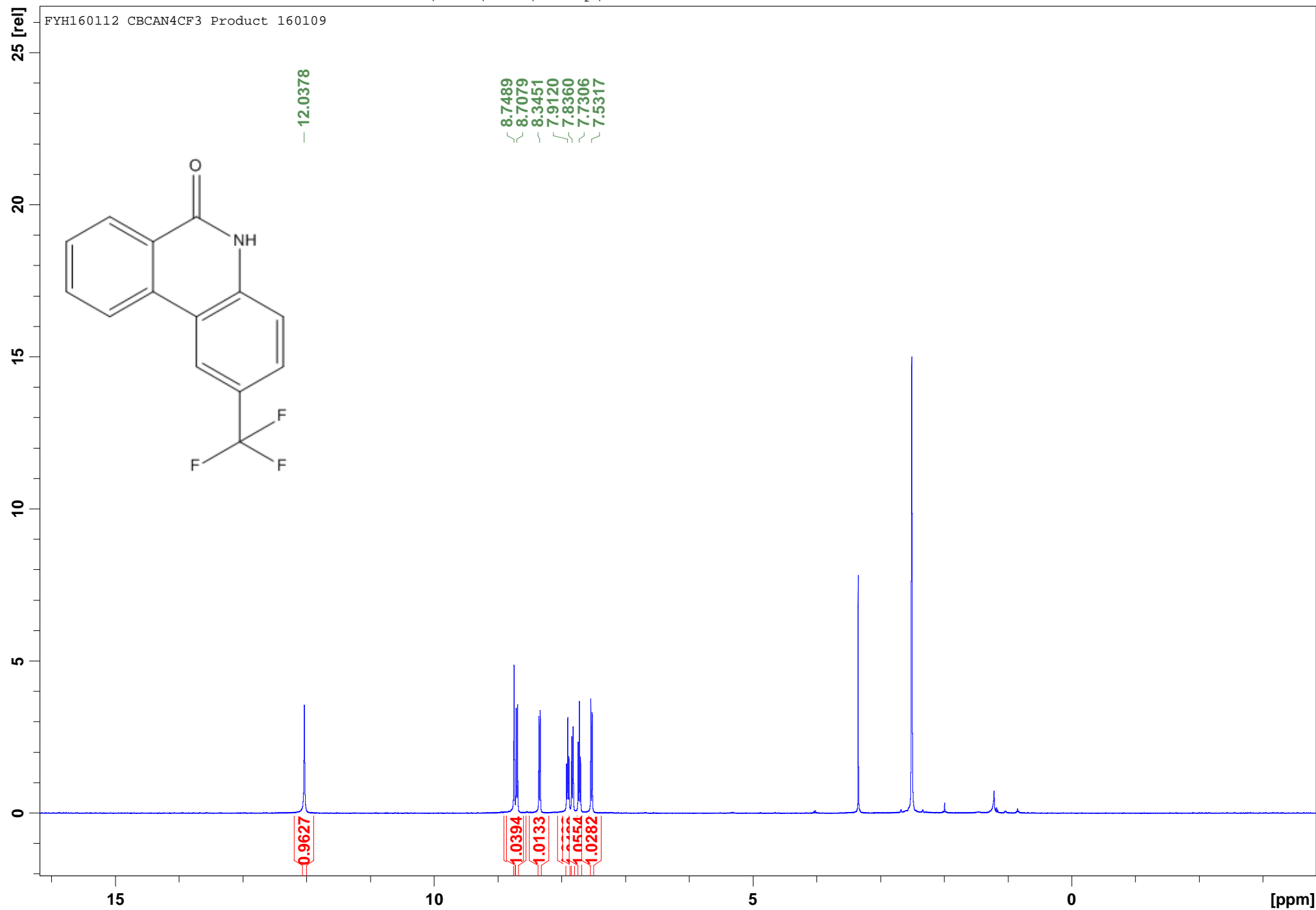


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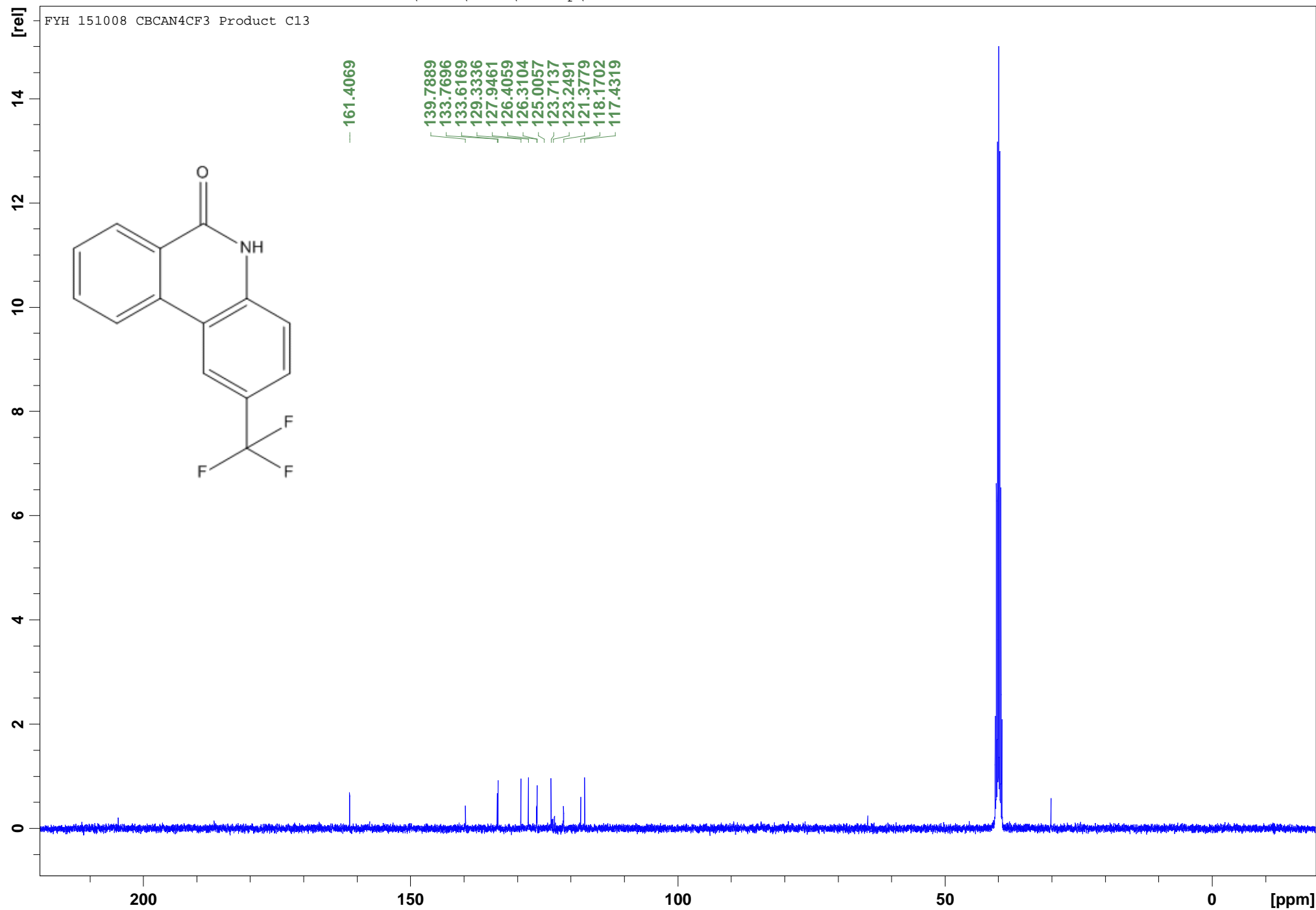


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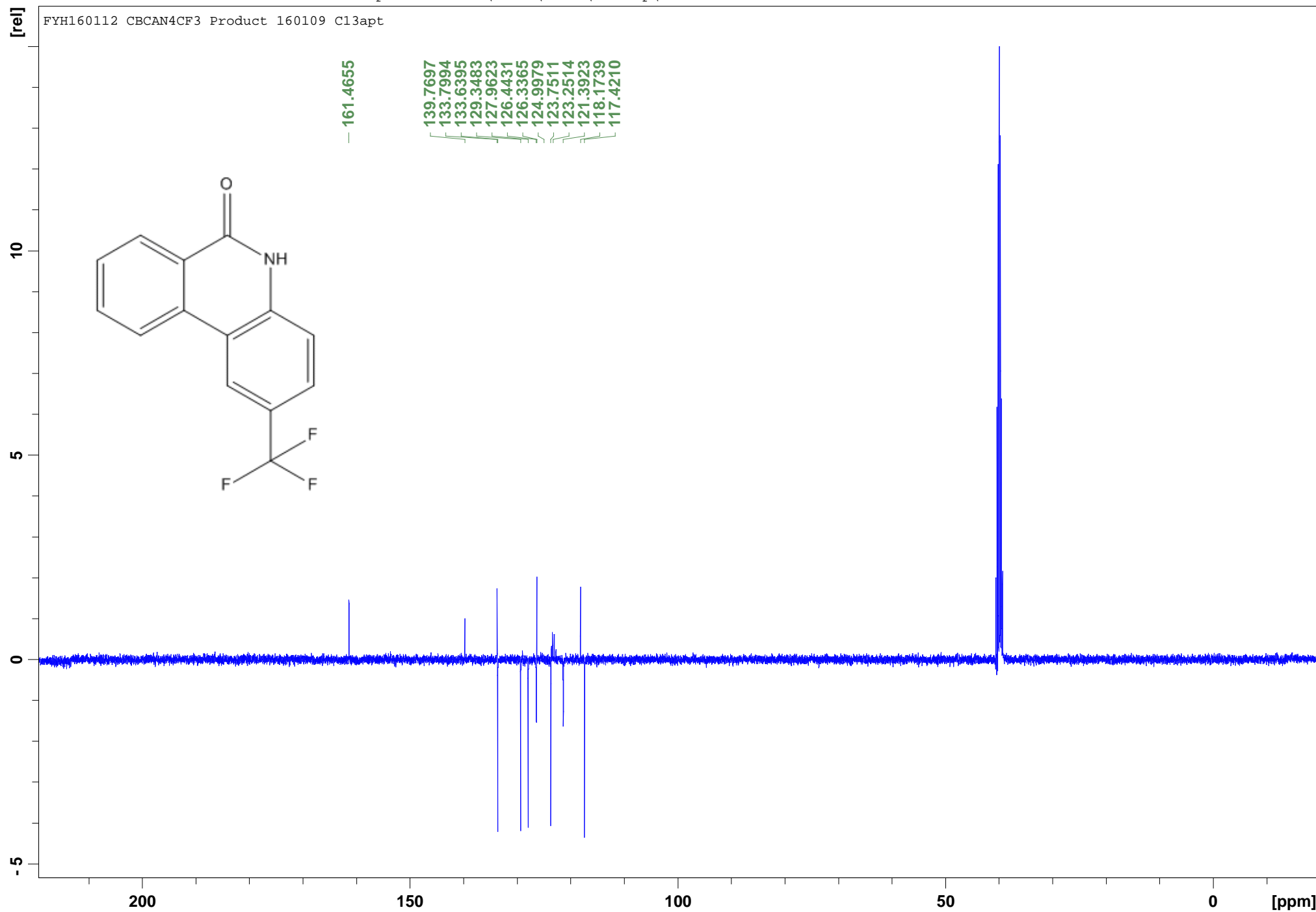


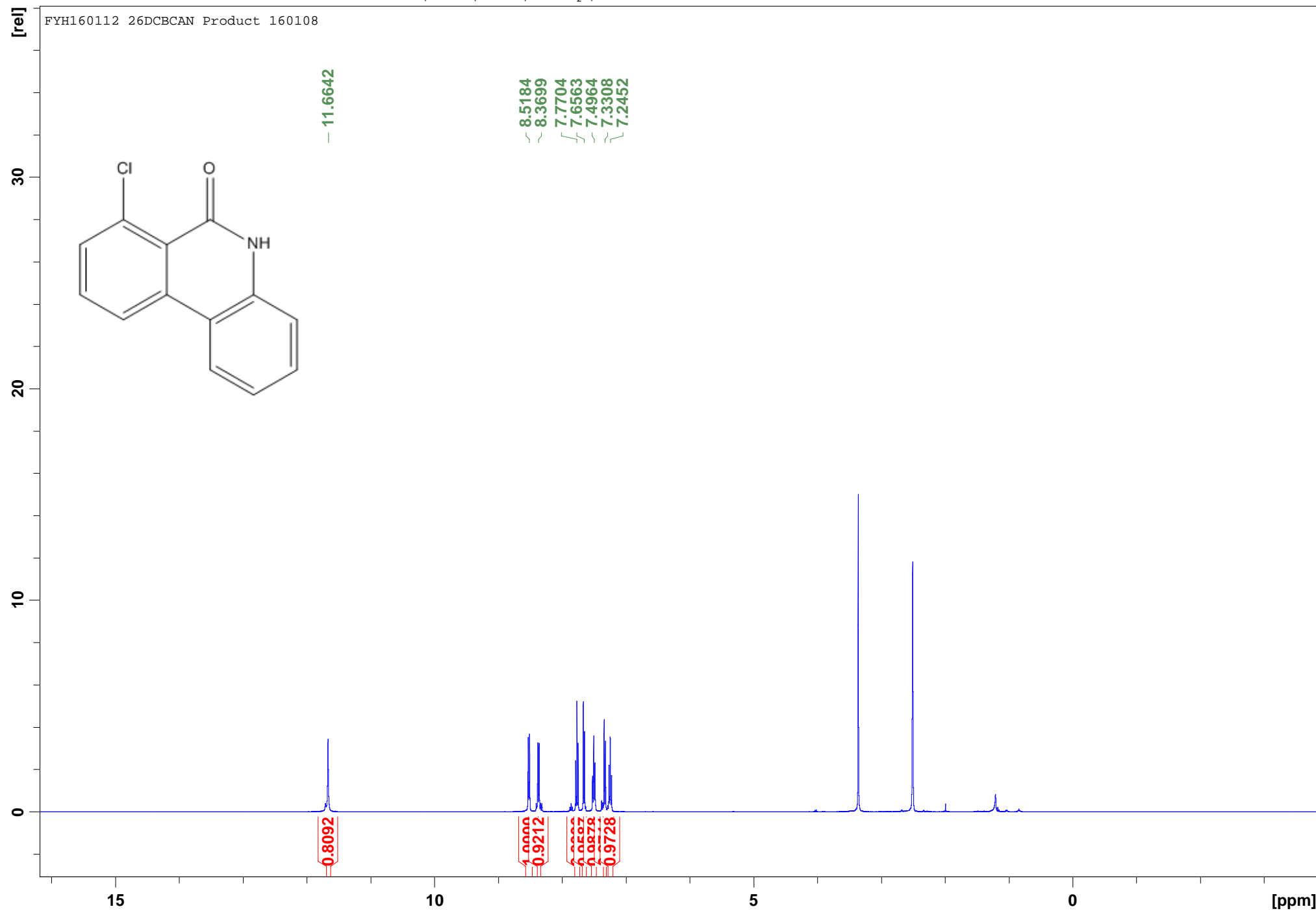
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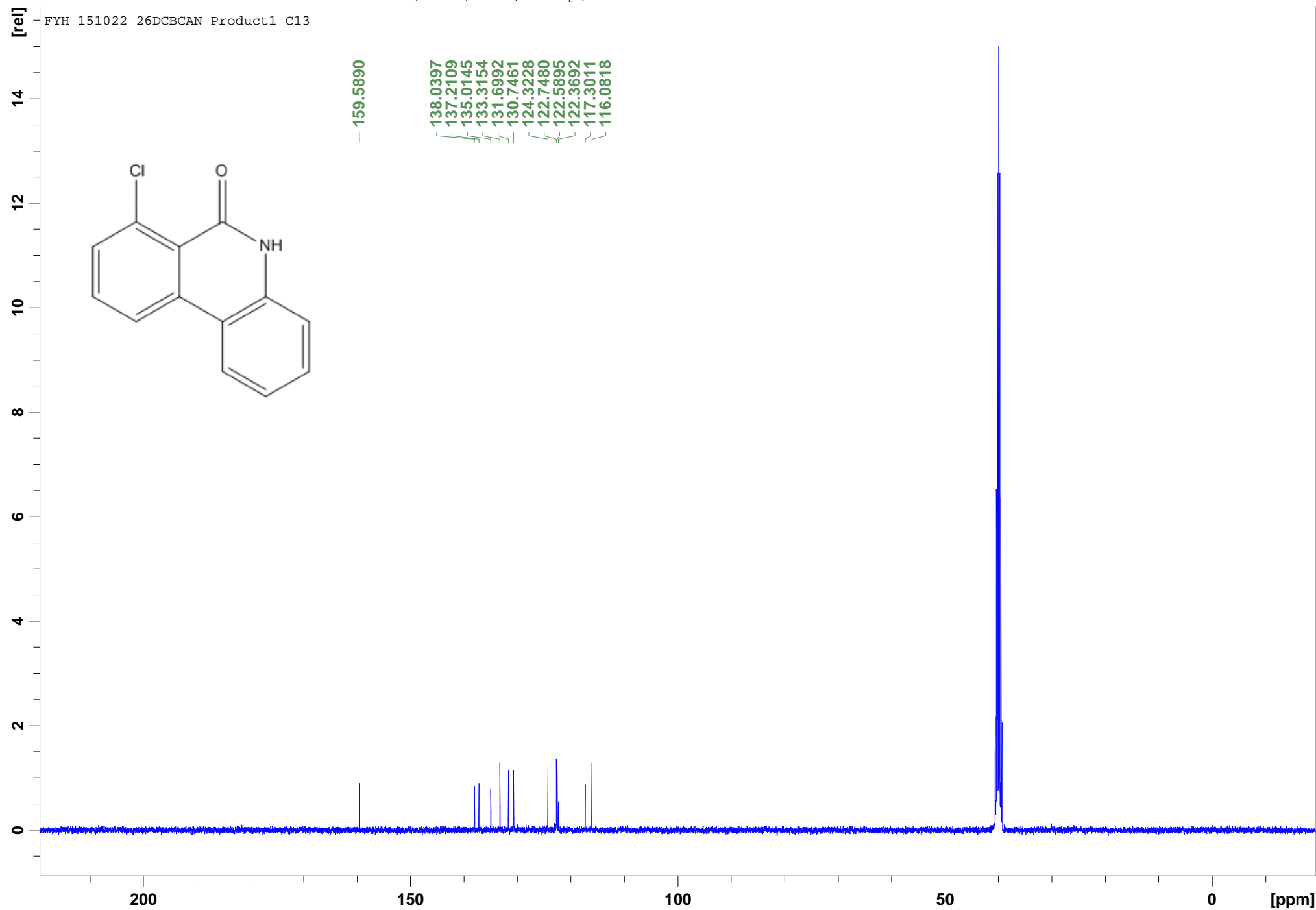
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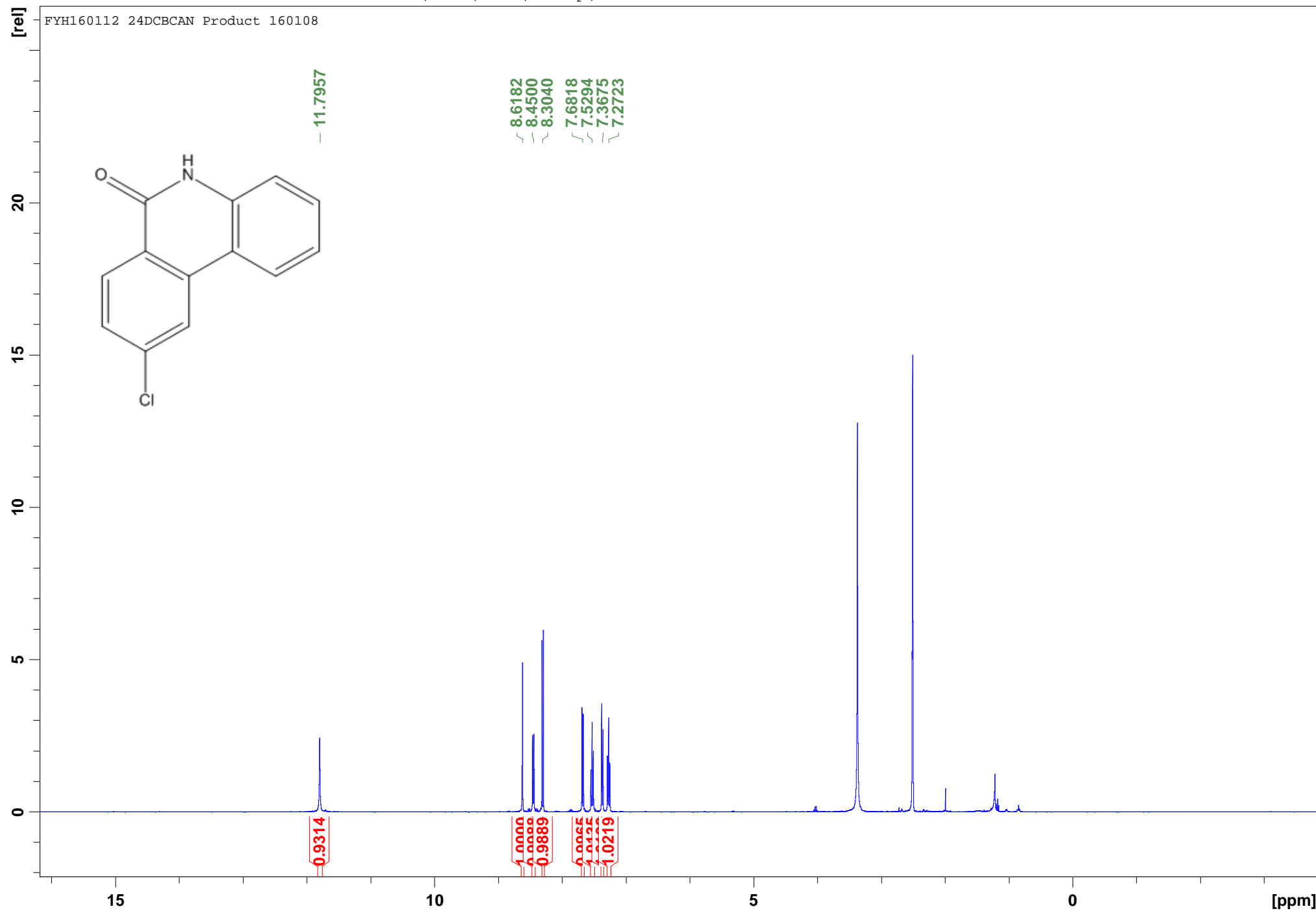
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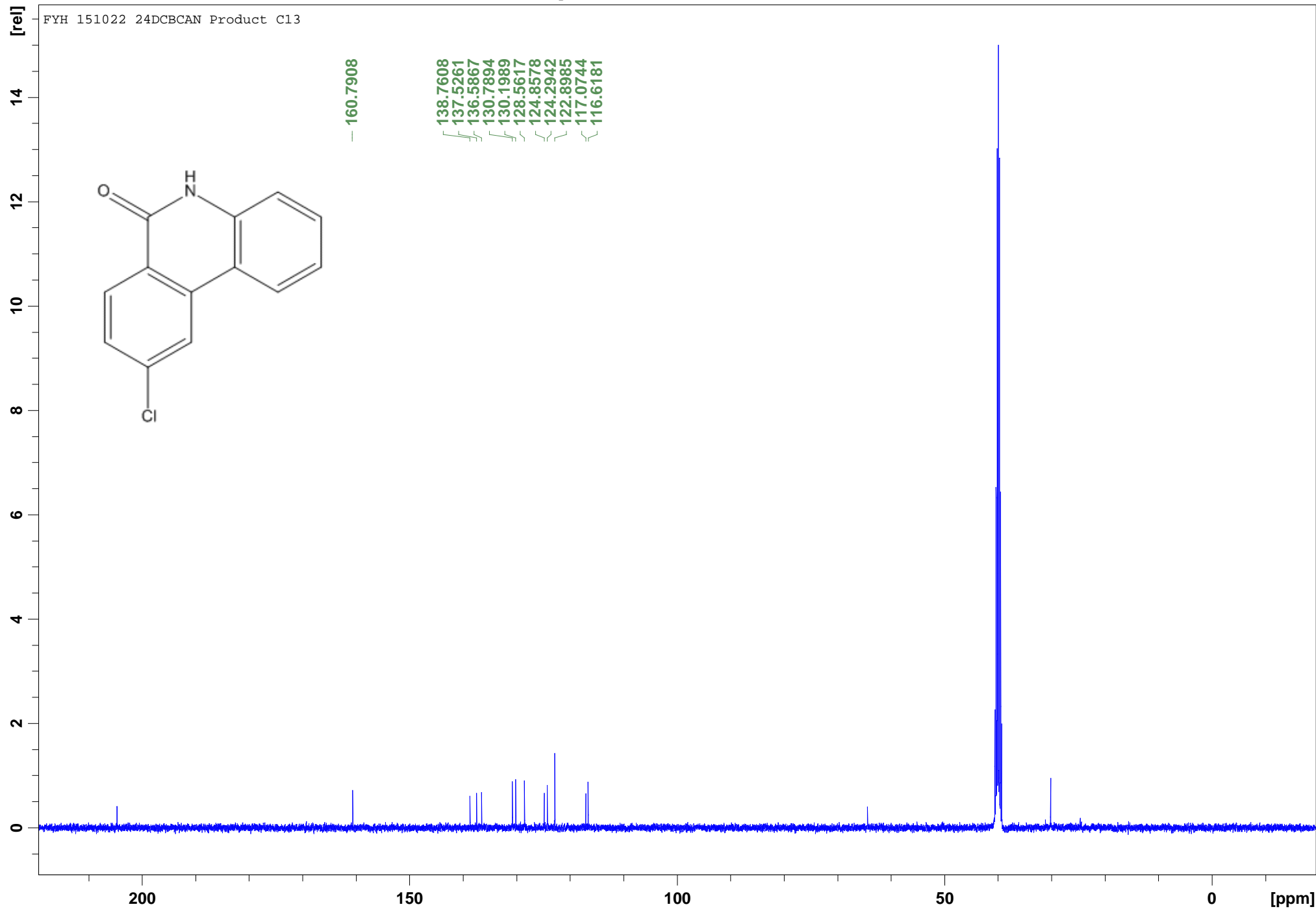




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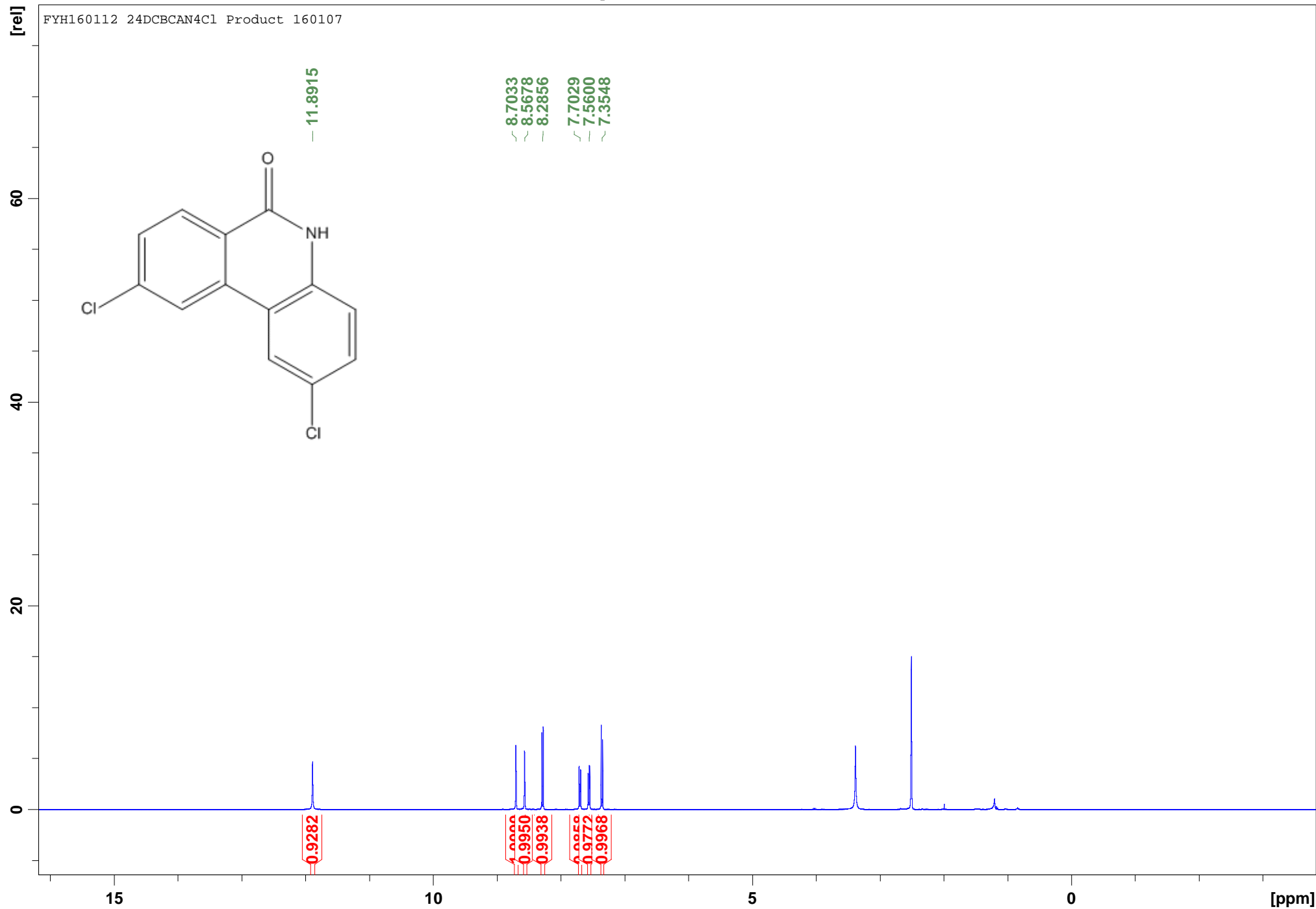




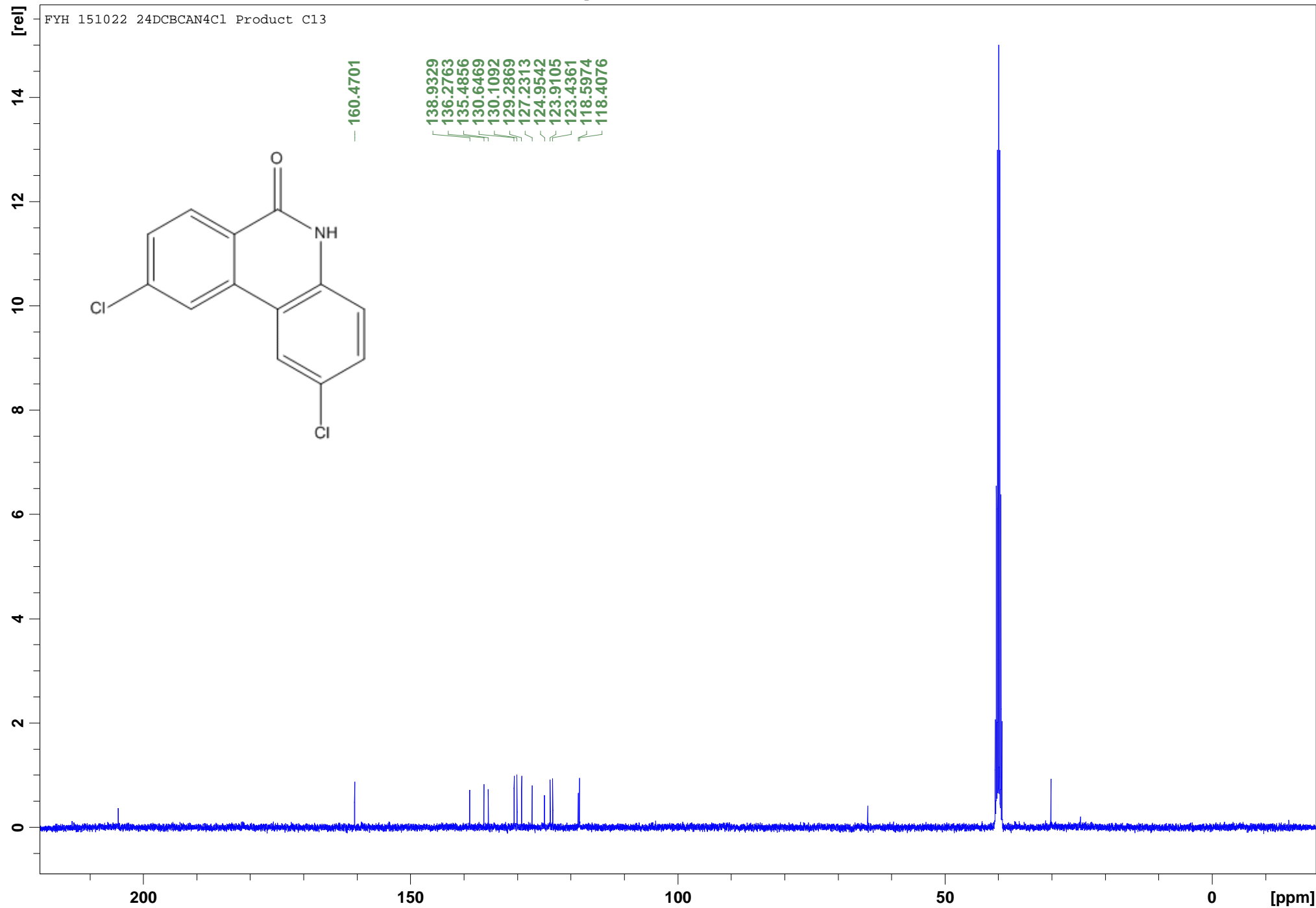


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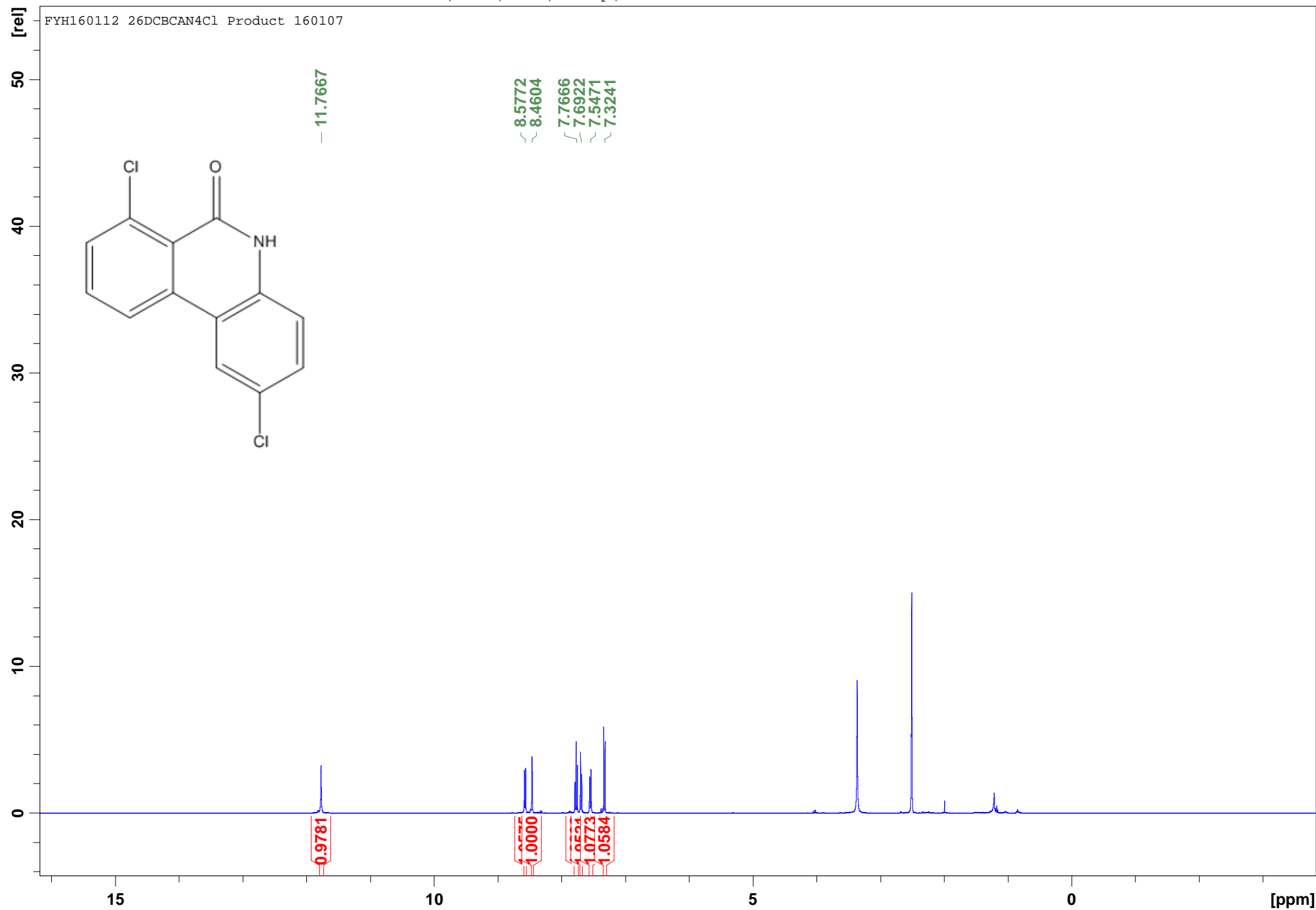


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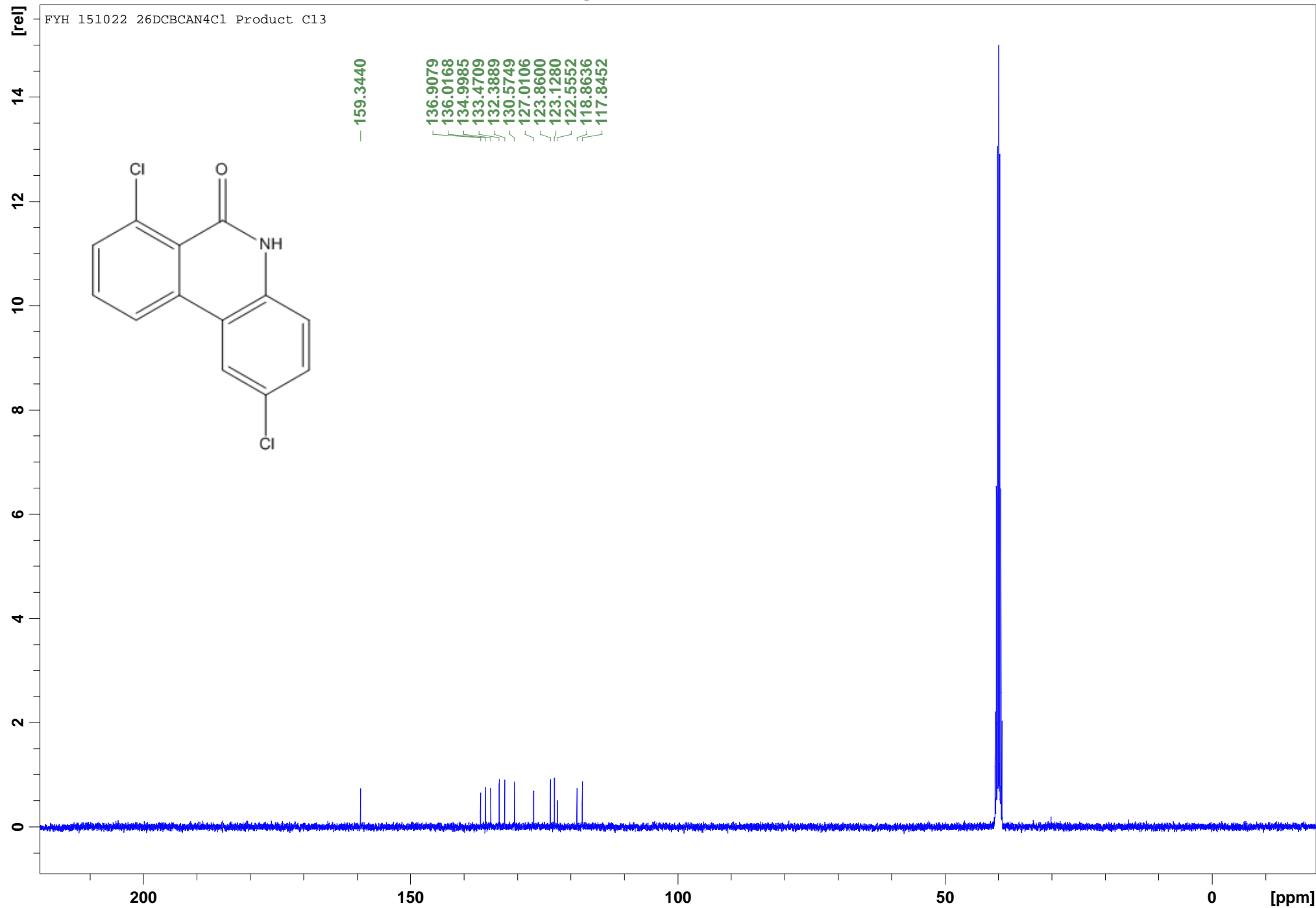


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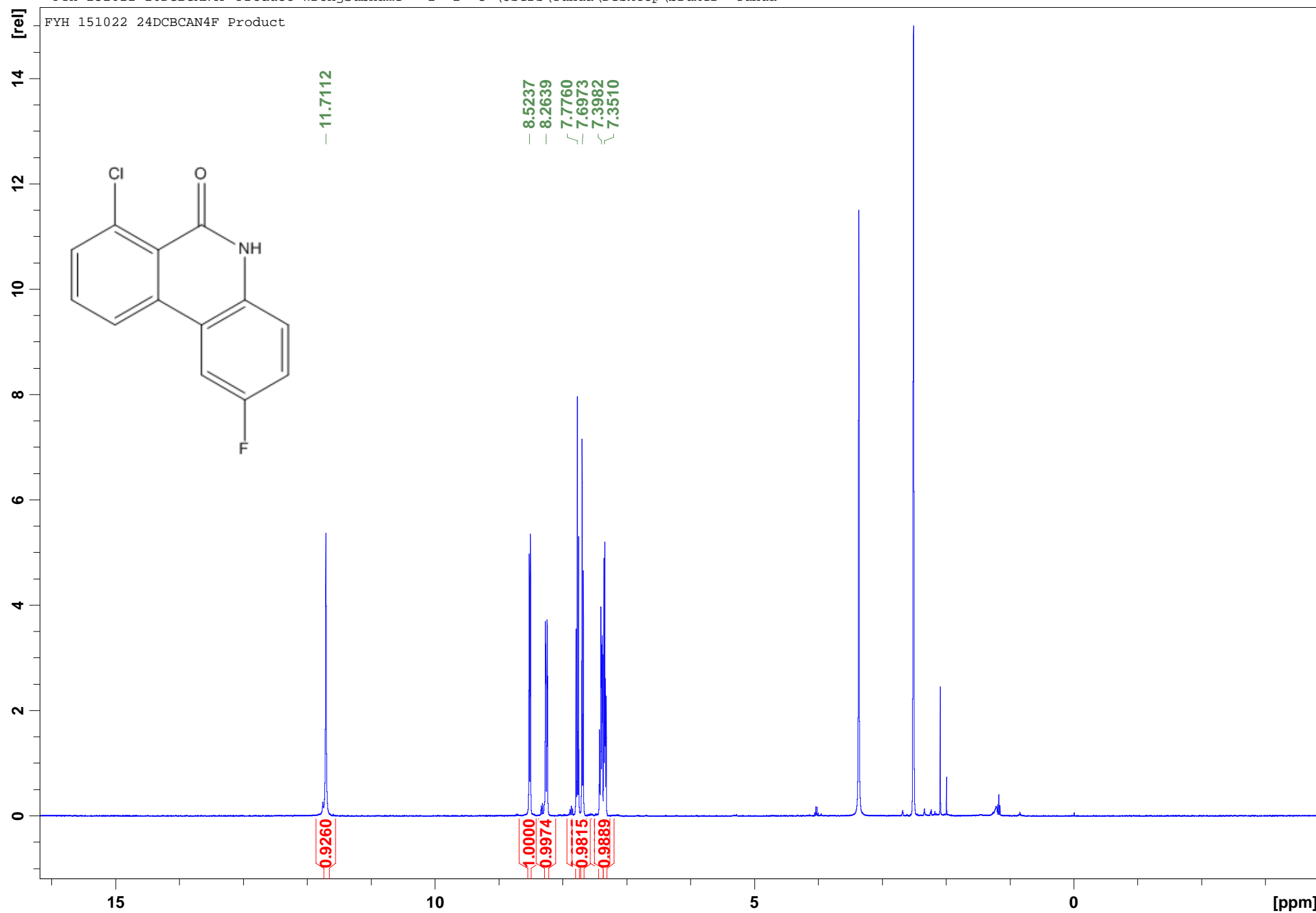
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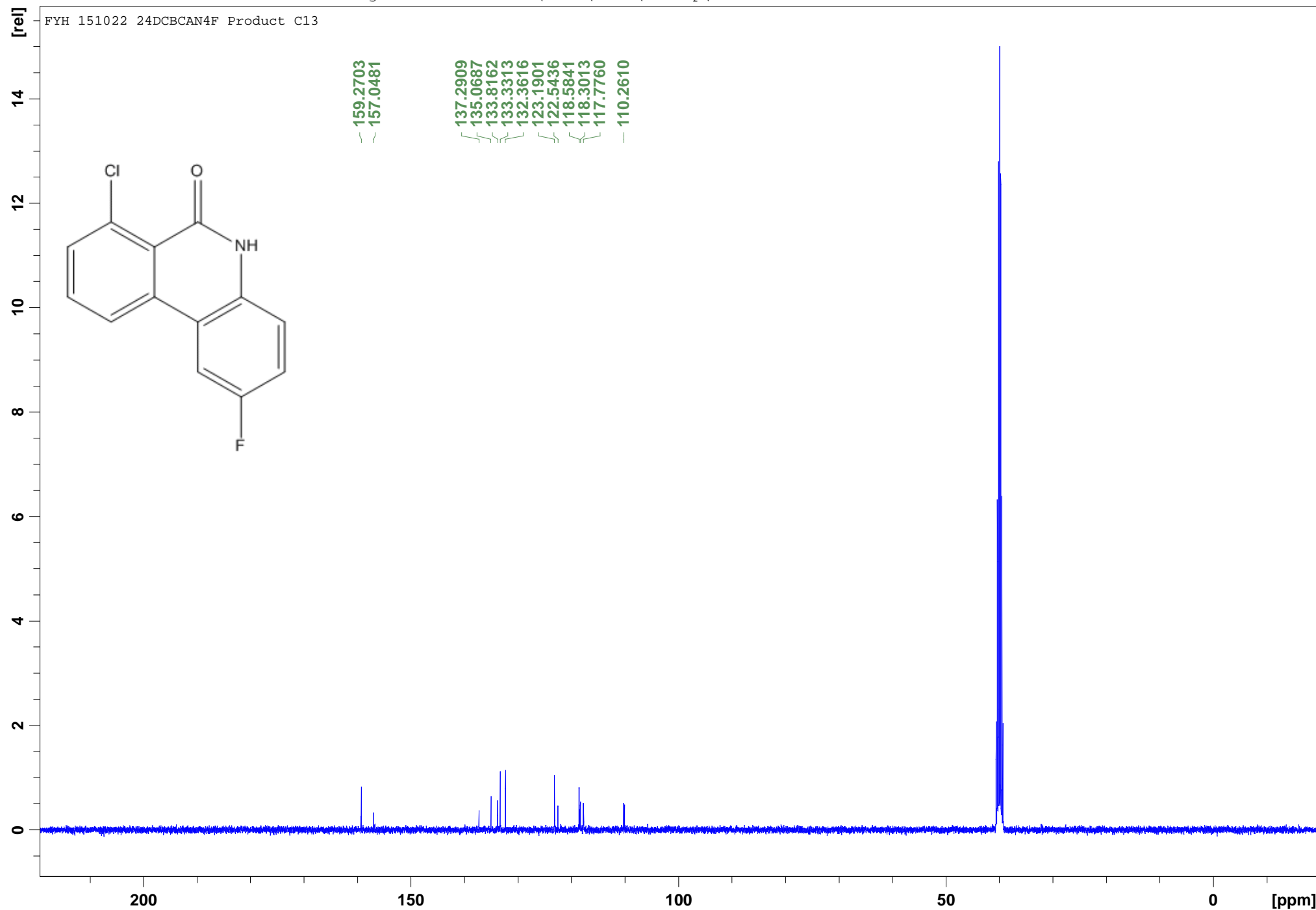


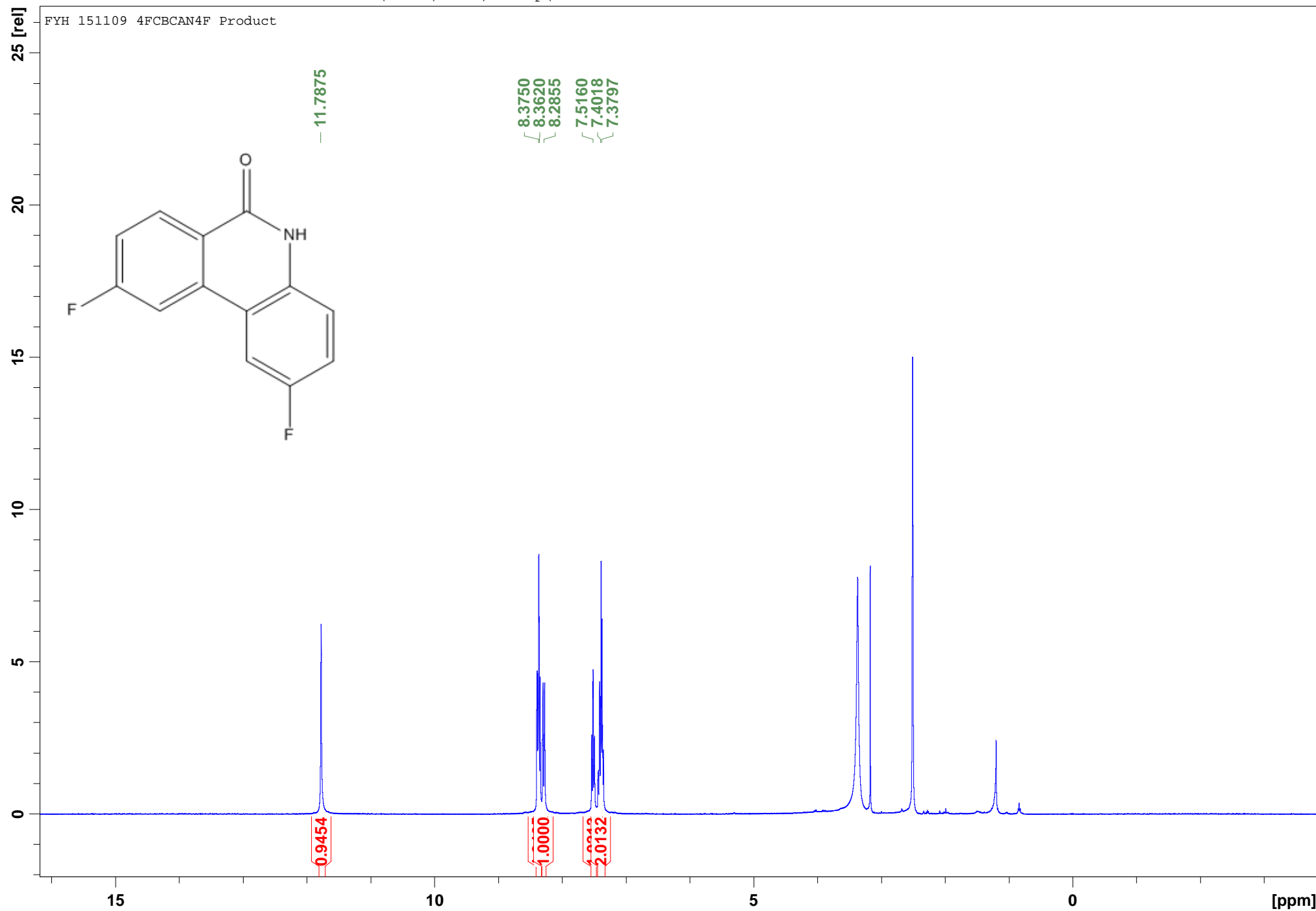
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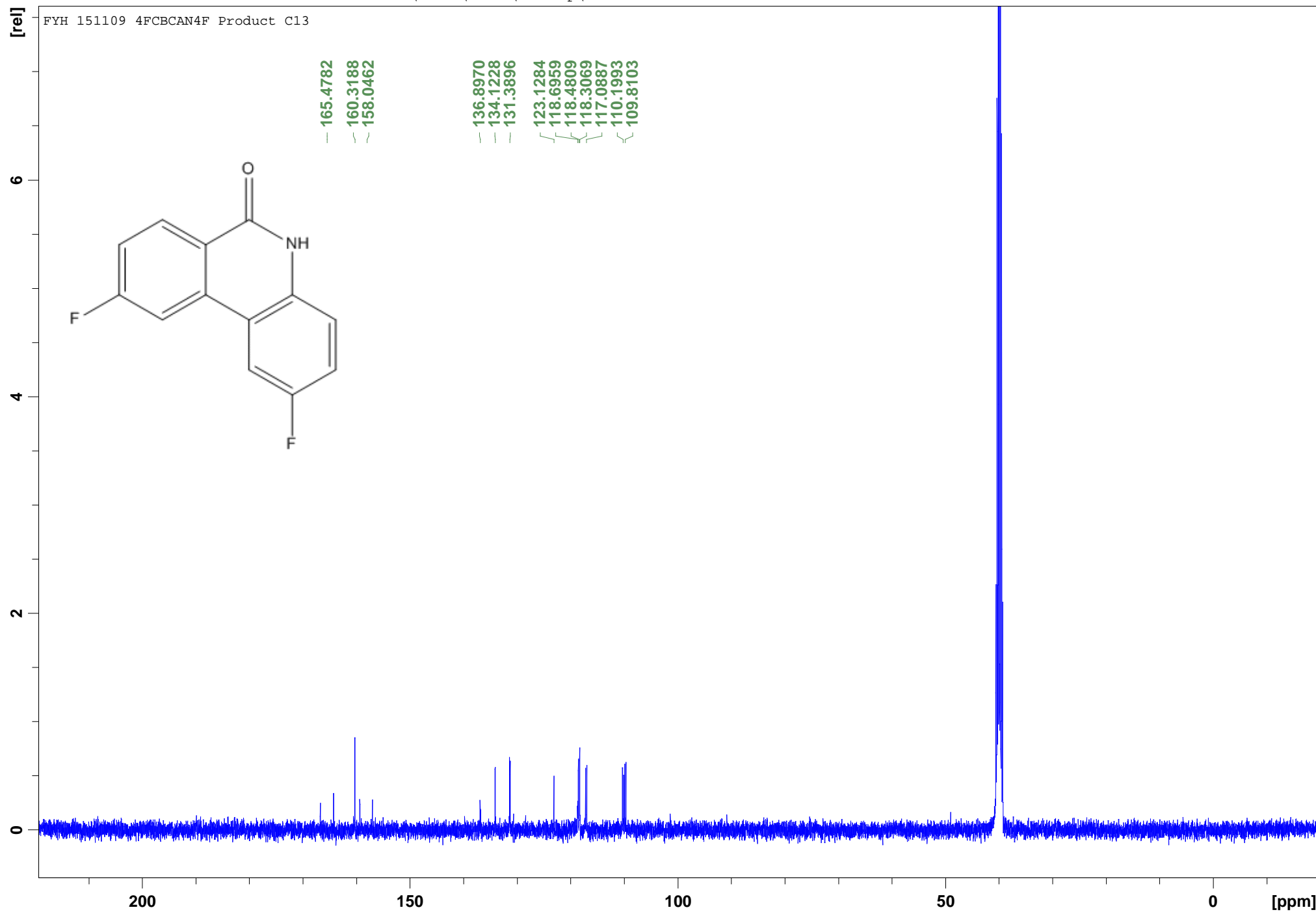
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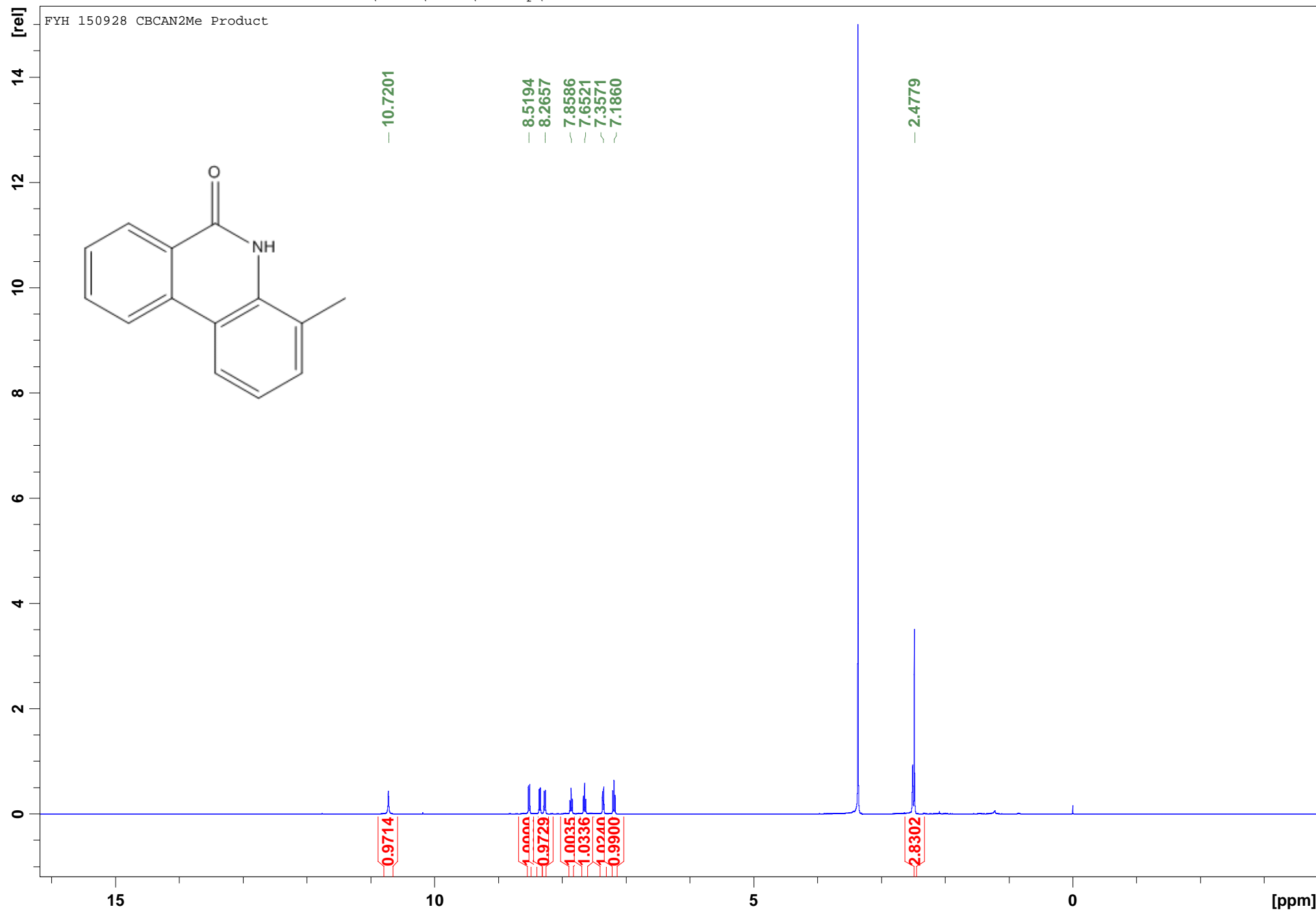
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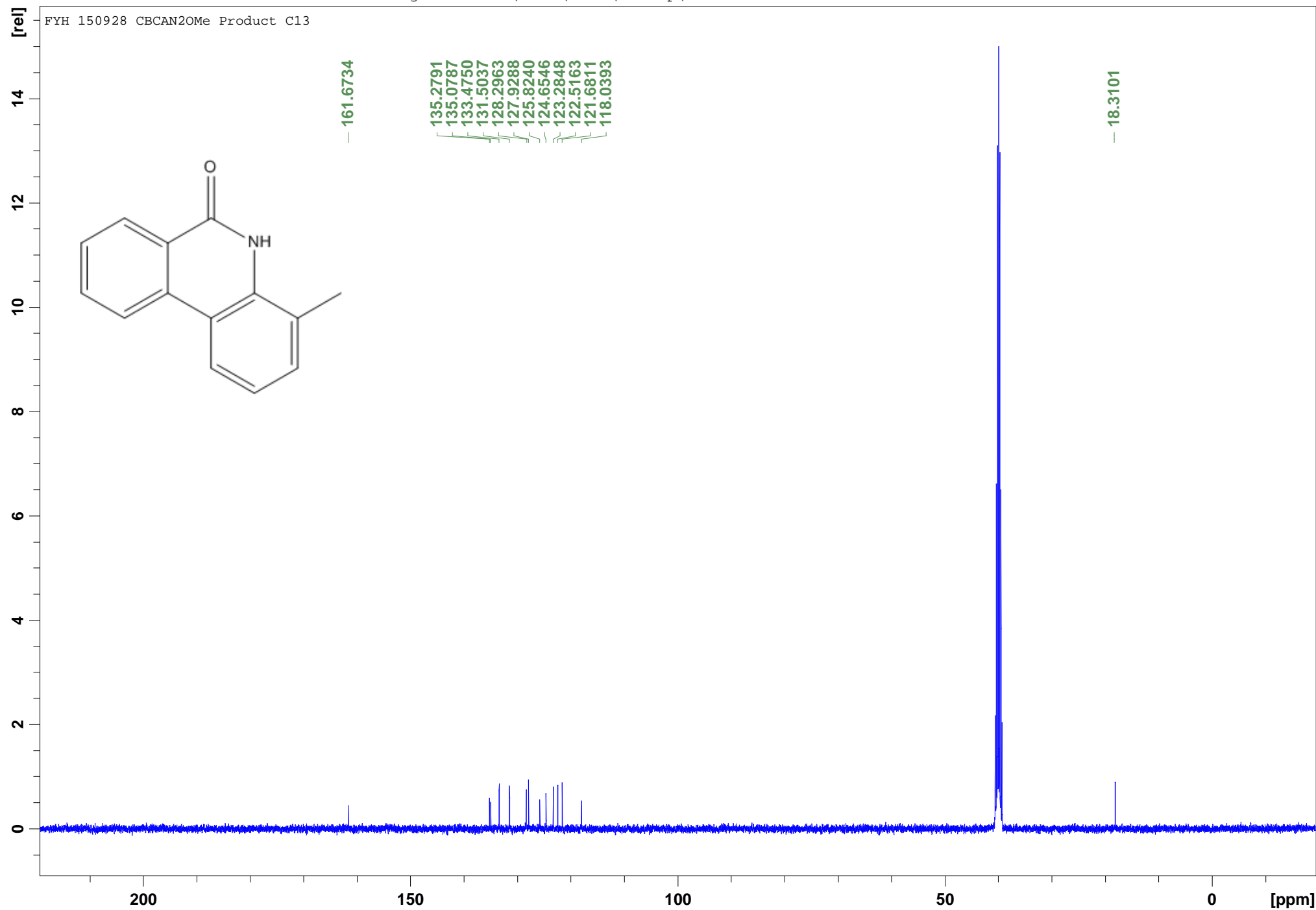
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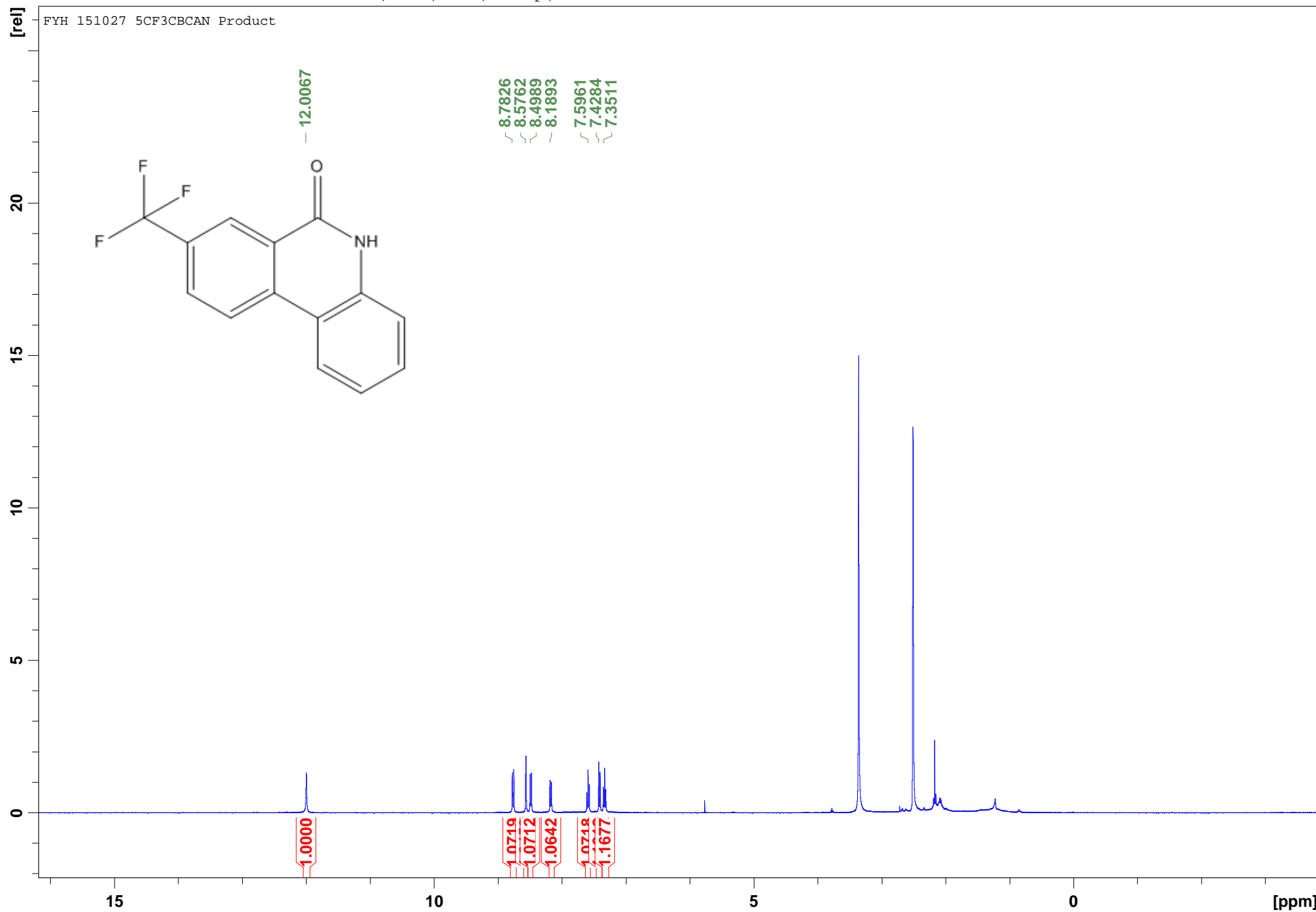


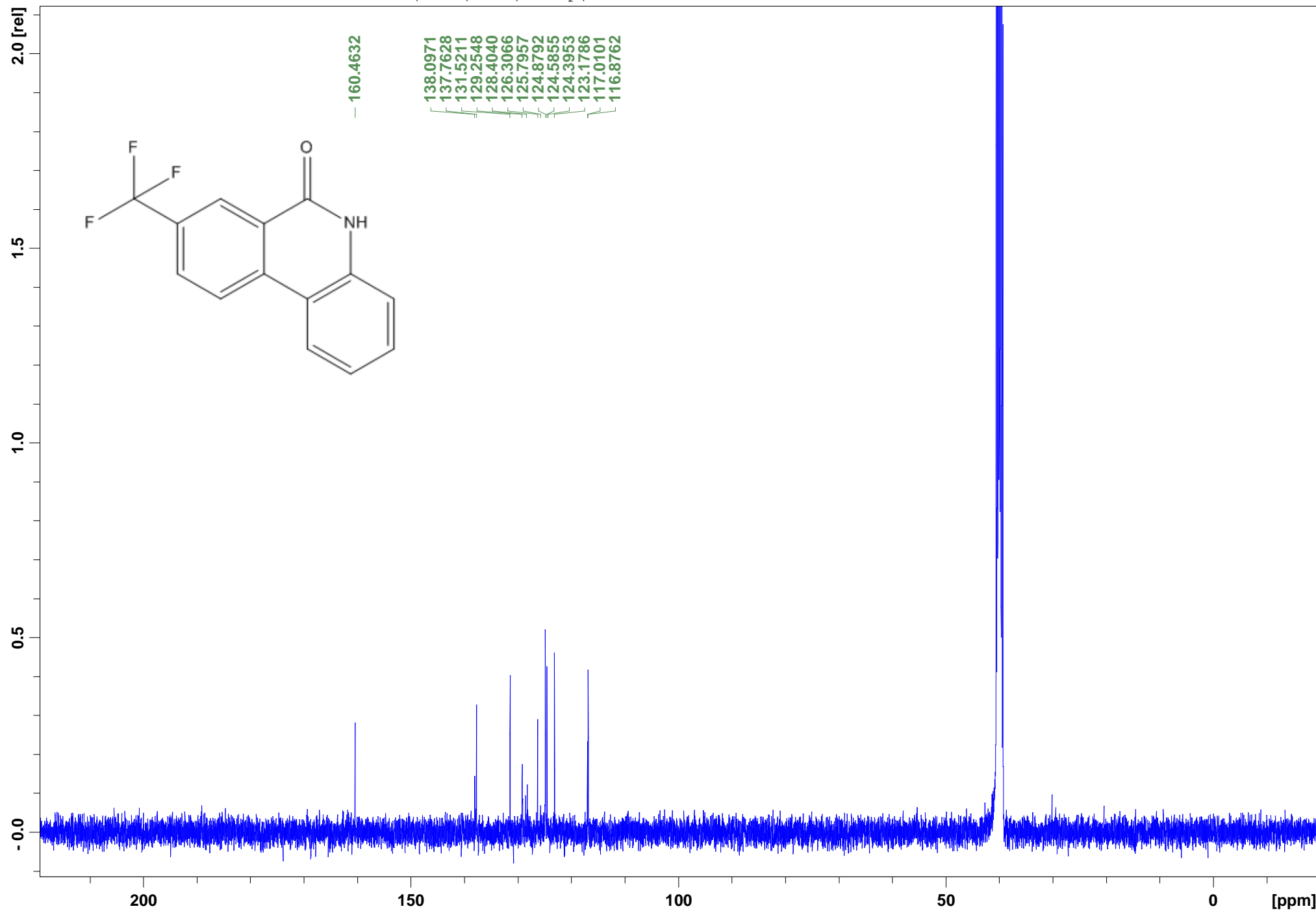


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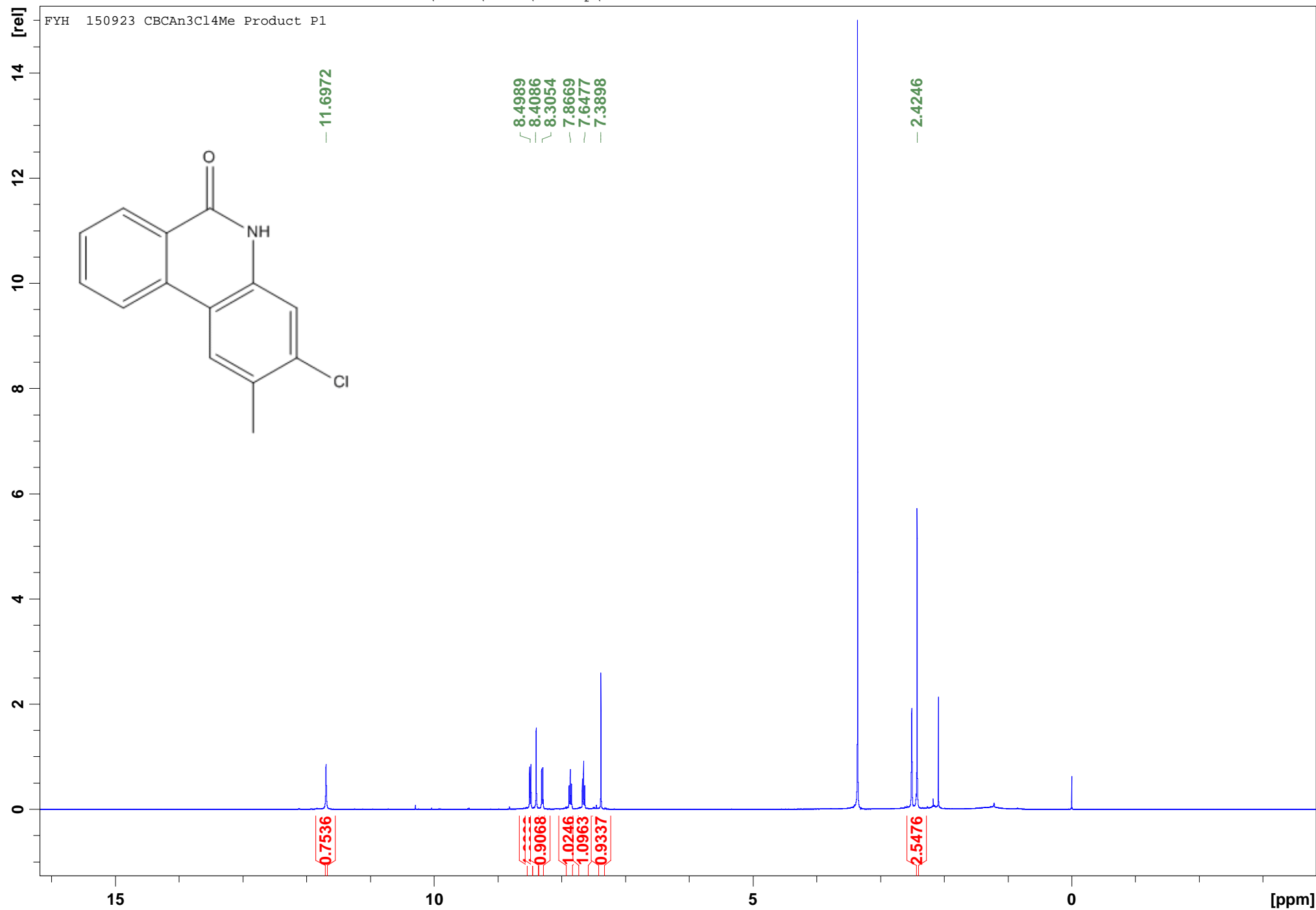






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FYH 150923 CBCAn3Cl4Me Product P1



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