Palladium-Catalyzed Amination of Unprotected Five-Membered Heterocyclic Bromides

Mingjuan Su, Naoyuki Hoshiya, and Stephen L. Buchwald

Department of Chemistry, Massachusetts Institute of Technology

77 Massachusetts Ave, Cambridge, MA 02139

Supporting Information

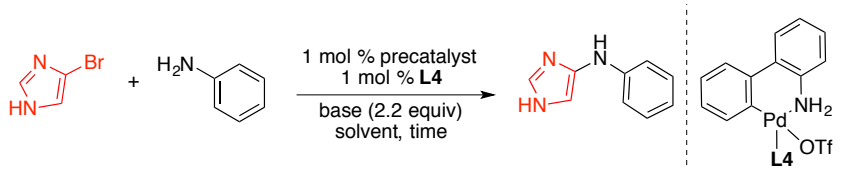
General Procedures

All reactions were carried out under an argon atmosphere. Lithium bis(trimethylsilyl)amide solution (1.0 M in THF) was purchased from Aldrich Chemical Co. in Sure/Seal™ bottles and was used as received. Heteroaryl halides and amines were purchased from Aldrich Chemical Co., Alfa Aesar, Acros, Combi-Blocks, Oakwood or Frontier Scientific and were used without further purification. All reactions were set-up in the air outside of the glovebox. Precatalysts,[1] **L3**,[2] and **L4**[3] were prepared by literature procedures.

Reactions were monitored by ^{1}H NMR, LCMS and thin-layer chromatography (TLC) carried out on 0.25 mm E. Merck silica gel plates (60F-254) or 0.20 mm Aluminum oxide/TLC cards (with fluorescent indicator 254 nm) using UV light and Ninhydrin or Iodine stains. Flash silica gel chromatography was performed using Silicycle SiliaFlashP60 (230-400 mesh) silica gel or EMD Millipore (80-325 Mesh) alumina. All compounds were characterized by ^{1}H NMR, ^{13}C NMR, ^{19}F NMR, and IR spectroscopy. Copies of the ^{1}H NMR, ^{13}C NMR, and ^{19}F NMR spectra can be found at the end of the Supporting Information. Nuclear Magnetic Resonance spectra were recorded on a Varian 300 and Bruker 400 MHz instrument. All ^{1}H NMR experiments are reported in δ units, parts per million (ppm), and were measured relative to the signals for residual methylene chloride (5.32 ppm), methanol-d_4 (3.31 ppm), dimethylsulfoxide-d_6 (2.50 ppm) or acetone-d_6 (2.05 ppm) in the deuterated solvent. All ^{13}C NMR spectra are reported in ppm relative to deuteromethylene chloride (53.84 ppm), methanol-d_4 (49.00 ppm) or dimethylsulfoxide-d_6 (39.52 ppm) or acetone-d_6 (29.84 ppm and 206.26 ppm) and all were obtained with ^{1}H decoupling. ^{19}F NMR spectra were calibrated using $CFCl_3$ as an external reference (0 ppm). All IR spectra were taken on a Thermo Scientific Nicolet iS5 FT-IR spectrometer (iD5 ATR). Melting points were obtained on a Mel-Temp II capillary melting point apparatus. Elemental analyses were performed by Atlantic Microlabs Inc., Norcross, GA. ESI-MS spectra were recorded on a Bruker Daltonics APEXIV 4.7 Tesla Fourier transform ion cyclotron resonance mass spectrometer (FT-ICR-MS). The pure compounds are estimated to be ≥ 95% pure as determined by ^{1}H NMR.

Optimization Table

Table S1. Optimization of reaction conditions for the amination of 4-bromo-1*H*-imidazole



entry	base	solvent	temp. (°C)	time (h)	^{1}H NMR yield [%][b]
1[a]	LHMDS	THF	100	20	65
2	LHMDS	THF	100	20	82
3	LHMDS	THF	90	20	82
4	KHMDS	THF	90	20	25
5	NaHMDS	THF	90	20	43
6	LiO*t*Bu	THF	90	20	6
7	KO*t*Bu	THF	90	20	-
8	NaO*t*Bu	THF	90	20	16
9	K_3PO_4	THF	90	20	-
10	Cs_2CO_3	THF	90	20	-
11	K_2CO_3	THF	90	20	-
12	LHMDS	Toluene	90	20	-
13	LHMDS	CPME	90	20	28
14	LHMDS	Dioxane	90	20	-
15	LHMDS	*t*BuOH	90	20	-
16	LHMDS	THF	90	6	78
17	LHMDS	THF	80	6	79
18	LHMDS	THF	70	6	88
19	LHMDS	THF	60	6	90
20	LHMDS	THF	50	6	90

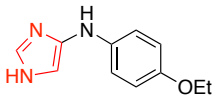
(a) Palladacyclic triflate precatalyst analogues (exhibit similar reactivity as the methanesulfonate precatalyst) were used in the current optimization studies.[1b] (b) Pd_2dba_3 and ligand were premixed in THF at 100 °C for 3 min. (c) ^{1}H NMR in methanol-d_4 with 1,3,5-trimethoxybenzene as internal standard.

Substrate Synthesis

General Procedure: Pd-Catalyzed Amination of Heterocyclic Bromides

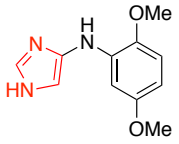
To an oven-dried re-sealable screw-cap test tube, equipped with a magnetic stir bar, was added precatalyst **P4** (1.0 mol %), *t*BuBrettPhos (1.0 mol %, Pd:L = 1:1), heteroaryl halide (1.0 mmol, 1.0 equiv), amine (if it is a solid) (1.2 mmol, 1.2 equiv). The vial was sealed with a teflon screw-cap, evacuated and backfilled with argon (this process was repeated a total of 3 times). Under argon, amine (if it is a liquid) (1.2 mmol, 1.2 equiv) was added followed by LHMDS (1M in THF) (2.2 mL, 2.2 equiv) via syringe. The argon source was removed and the sealed test tube was placed into a pre-heated 50 °C oil bath with vigorous stirring. After stirring for 6 h at 50 °C, the vessel was cooled to room temperature, then quenched by the careful addition of 1M HCl (4 mL), diluted with EtOAc and poured into saturated aqueous $NaHCO_3$. After extracting with 3 portions of EtOAc and 1 portion of CH_2Cl_2, the combined organic layers were dried over Na_2SO_4, concentrated in vacuo and purified via flash column chromatography.

***N*-(4-ethoxyphenyl)-1*H*-imidazol-4-amine (Table 1, entry 1a)**



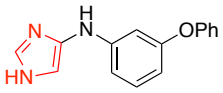
Following the general procedure, a mixture of **P4** (8.6 mg, 1.0 mol %), **L4** (4.9 mg, 1.0 mol %), 4-bromo-1*H*-imidazole (147 mg, 1.0 mmol), 4-ethoxyaniline (129 μL, 1.2 mmol), LHMDS (2.2 mL, 2.2 mmol) (1M in THF) was heated to 50 °C for 6 h. The crude product was purified via flash alumina chromatography (MeOH/CH_2Cl_2, 1:49) to provide the title compound as grey solid (154 mg, 76%), mp 131-132 °C. ^{1}H NMR (400 MHz, methanol-d_4) δ 7.45-7.44 (m, 1H), 6.79 (q, J = 8.8, 9.2 Hz, 4H), 6.69 (m, 1H), 3.94 (q, J = 6.8 Hz, 2H), 1.33 (t, J = 7.2, 6.8 Hz, 3H); ^{13}C NMR (100 MHz, methanol-d_4) δ 153.6, 142.8, 141.2, 133.4, 117.2, 116.7, 105.0, 65.2, 15.5; IR (film) ν_{max} 3296, 2893, 1579, 1571, 1509, 1475, 1450, 1409, 1392, 1317, 1300, 1317, 1250, 1218, 1174, 1116, 1087, 1049, 999, 941, 920, 838, 826, 782, 720, 679, 634, 614, 604, 600 cm^{-1}; Anal. Calcd. For $C_{11}H_{13}N_3O$: C, 65.01; H, 6.45. Found: C, 64.72; H, 6.31.

***N*-(2,5-dimethoxyphenyl)-1*H*-imidazol-4-amine (Table 1, entry 1b)**



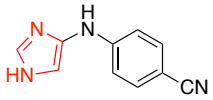
Following the general procedure, a mixture of **P4** (17.1 mg, 2.0 mol %), **L4** (9.7 mg, 2.0 mol %), 4-bromo-1*H*-imidazole (147 mg, 1.0 mmol), 2,5-dimethoxyaniline (184 mg, 1.2 mmol), LHMDS (2.2 mL, 2.2 mmol) (1M in THF) was heated to 80 °C for 6 h. The crude product was purified via flash alumina chromatography (MeOH/CH_2Cl_2, 1:24) to provide the title compound as blue oil (175 mg, 80%). ^{1}H NMR (400 MHz, CD_2Cl_2) δ 10.81 (br-s, 1H), 7.39 (s, 1H), 6.76-6.74 (m, 2H), 6.65 (d, J = 3.2 Hz, 1H), 6.36 (s, 1H), 6.26 (dd, J = 2.8, 3.2 Hz, 1H), 3.81 (s, 3H), 3.70 (s, 3H); ^{13}C NMR (100 MHz, CD_2Cl_2) δ 155.1, 142.0, 140.7, 136.2, 132.9, 103.8, 101.4, 100.7, 56.7, 55.9; IR (film) ν_{max} 3116, 2832, 1706, 1602, 1575, 1513, 1451, 1423, 1361, 1284, 1220, 1177, 1163, 1129, 1087, 1044, 1023, 997, 951, 819, 781, 710, 619 cm^{-1}; HRMS-ESI (*m/z*) [M + H]$^+$ calcd for $C_{11}H_{13}N_3O_2$: 220.1081; Found, 220.1083.

***N*-(3-phenoxyphenyl)-1*H*-imidazol-4-amine (Table 1, entry 1c)**



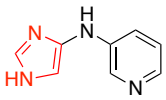
Following the general procedure, a mixture of **P4** (17.1 mg, 2.0 mol %), **L4** (9.7 mg, 2.0 mol %), 4-bromo-1*H*-imidazole (147 mg, 1.0 mmol), 3-phenoxyaniline (223 mg, 1.2 mmol), LHMDS (2.2 mL, 2.2 mmol) (1M in THF) was heated to 80 °C for 6 h. The crude product was purified via flash alumina chromatography (MeOH/CH_2Cl_2, 1:24) to provide the title compound as brown solid (218 mg, 87%), mp 59-60 °C. ^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.34-7.29 (m, 3H), 7.15 (t, J = 8.0 Hz, 1H), 7.08 (t, J = 7.2 Hz, 1H), 7.02-7.00 (m, 2H), 6.68-6.60 (m, 3H), 6.42 (dd, J = 2.0 Hz, 1H); ^{13}C NMR (100 MHz, CD_2Cl_2) δ 158.7, 157.6, 147.4, 140.2, 132.8, 130.7, 130.1, 123.5, 119.2, 109.8, 109.3, 105.1, 104.6; IR (film) ν_{max} 3064, 2887, 2358, 1717, 1699, 1695, 1645, 1585, 1575, 1559, 1557, 1554, 1541, 1538, 1484, 1456, 1436, 1419, 1257, 1213, 1160, 1143, 1072, 1022, 1001, 961, 821, 746, 667, 629, 618, 614 cm^{-1}; HRMS-ESI (*m/z*) [M + H]$^+$ calcd for $C_{15}H_{13}N_3O$: 252.1131; Found, 252.1139.

***N*-(4-cyanophenyl)-1*H*-imidazol-4-amine (Table 1, entry 1d)**



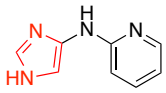
Following the general procedure, a mixture of **P4** (17.1 mg, 2.0 mol %), **L4** (9.7 mg, 2.0 mol %), 4-bromo-1*H*-imidazole (147 mg, 1.0 mmol), 4-cyanoaniline (142 mg, 1.2 mmol), LHMDS (2.2 mL, 2.2 mmol) (1M in THF) was heated to 80 °C for 12 h. The crude product was purified via trituration with EtOAc to provide the title compound as dark brown solid (141 mg, 77%), mp 256-257 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.96 (s, 1H), 8.82 (s, 1H), 7.52-7.49 (m, 3H), 7.08 (d, J = 8.8 Hz, 2H), 6.86 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 149.9, 139.9, 133.9, 133.2, 121.1, 114.1, 103.7, 97.9; IR (film) ν_{max} 3378, 3016, 2208, 1602, 1575, 1549, 1486, 1462, 1342, 1267, 1252, 1171, 1151, 1131, 1089, 1006, 992, 933, 842, 814, 727, 688, cm^{-1}; HRMS-ESI (*m/z*) [M + H]$^+$ calcd for $C_{10}H_8N_4$: 185.0822; Found, 185.0828.

***N*-(pyridin-3-yl)-1*H*-imidazol-4-amine (Table 1, entry 1e)**



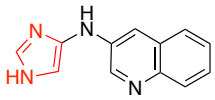
Following the general procedure, a mixture of **P4** (17.1 mg, 2.0 mol %), **L4** (9.7 mg, 2.0 mol %), 4-bromo-1*H*-imidazole (147 mg, 1.0 mmol), 3-aminopyridine (113 mg, 1.2 mmol), LHMDS (2.2 mL, 2.2 mmol) (1M in THF) was heated to 50 °C for 6 h. The crude product was purified via flash alumina chromatography (MeOH/CH_2Cl_2, 1:19) to provide the title compound as pale pink solid (120 mg, 75%), mp 154-155 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.91 (br-s, 1H), 8.32 (d, J = 2.4 Hz, 1H), 8.25 (s, 1H), 7.86 (dd, J = 1.6, 1.2 Hz, 1H), 7.50 (d, J = 1.2 Hz, 1H), 7.41-7.38 (m, 1H), 7.13-7.10 (m, 1H), 6.80 (d, J = 1.2 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 141.9, 140.3, 138.1, 136.6, 132.3, 123.6, 119.2, 101.6; IR (film) ν_{max} 3250, 3048, 2865, 2675, 1604, 1556, 1484, 1412, 1333, 1297, 1246, 1227, 1185, 1131, 1103, 1050, 1023, 994, 924, 871, 818, 776, 693, 620, 606 cm^{-1}; Anal. Calcd. For $C_8H_8N_4$: C, 59.99; H, 5.03. Found: C, 59.77; H, 5.24.

***N*-(pyridin-2-yl) -1*H*-imidazol-4-amine (Table 1, entry 1f)**



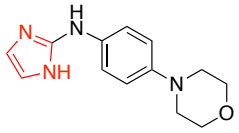
Following the general procedure, a mixture of **P4** (17.1 mg, 2.0 mol %), **L4** (9.7 mg, 2.0 mol %), 4-bromo-1*H*-imidazole (147 mg, 1.0 mmol), 2-aminopyridine (132 mg, 1.4 mmol), LHMDS (2.2 mL, 2.2 mmol) (1M in THF) was heated to 50 °C for 6 h. The crude product was purified via flash alumina chromatography (MeOH/CH_2Cl_2, 1:19) to provide the title compound as grey solid (134 mg, 84%), mp 139-140 °C. ^{1}H NMR (400 MHz, methanol-d_4) δ 8.05-8.04 (m, 1H), 7.49-7.41 (m, 2H), 7.09 (s, 1H), 6.73 (d, J = 8.4 Hz, 1H), 6.64-6.60 (m, 1H); ^{13}C NMR (100 MHz, methanol-d_4) δ 158.0, 148.3, 139.0, 138.8, 133.2, 114.9, 110.1, 106.9; IR (film) ν_{max} 3061, 2852, 2641, 1575, 1501, 1475, 1441, 1251, 1227, 1081, 1047, 1002, 863, 822, 730, 679, 667, 624, 609, 607, 600 cm^{-1}; HRMS-ESI (*m/z*) $[M + H]^+$ calcd for $C_8H_8N_4$: 161.0822; Found, 161.0816.

***N*-(quinolin-3-yl)-1*H*-imidazol-4-amine (Table 1, entry 1g)**



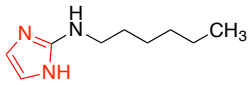
Following the general procedure, a mixture of **P4** (17.1 mg, 2.0 mol %), **L4** (9.7 mg, 1.0 mol %), 4-bromo-1*H*-imidazole (147 mg, 1.0 mmol), 3-aminoquinoline (173 mg, 1.2 mmol), LHMDS (2.2 mL, 2.2 mmol) (1M in THF) was heated to 50 °C for 6 h. The crude product was purified via flash alumina chromatography (MeOH/CH_2Cl_2, 1:19) to provide the title compound as green solid (176 mg, 84%), mp 227-228 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.02 (s, 1H), 8.81-8.76 (m, 2H), 7.84 (d, J = 7.6 Hz, 1H), 7.75-7.73 (m, 2H), 7.60 (s, 1H), 7.43-7.35 (m, 2H), 7.02 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 144.0, 141.5, 140.6, 138.7, 132.4, 129.4, 128.5, 126.7, 126.3, 124.6, 110.7, 100.9; IR (film) ν_{max} 3257, 3050, 2856, 2685, 1599, 1573, 1486, 1419, 1402, 1371, 1304, 1259, 1220, 1191, 1146, 1102, 1018, 994, 936, 926, 877, 853, 819, 802, 771, 735, 700, 623, 603 cm^{-1}; Anal. Calcd. For $C_{12}H_{10}N_4$: C, 68.56; H, 4.79. Found: C, 68.64; H, 4.80.

***N*-(4-morpholinophenyl)-1*H*-imidazol-2-amine (Table 1, entry 1h)**



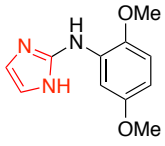
Following the general procedure, a mixture of **P4** (8.6 mg, 1.0 mol %), **L4** (4.9 mg, 1.0 mol %), 2-bromo-1*H*-imidazole (147 mg, 1.0 mmol), 4-morpholinoaniline (214 mg, 1.2 mmol), LHMDS (2.2 mL, 2.2 mmol) (1M in THF) was heated to 50 °C for 6 h. The crude product was purified via flash alumina chromatography (MeOH/CH_2Cl_2, 1:49) to provide the title compound as brown solid (222 mg, 91%), mp 215-216 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.57 (br-s, 1H), 8.32 (s, 1H), 7.31 (d, J = 8.8 Hz, 2H), 6.83 (d, J = 8.8 Hz, 2H), 6.64 (s, 2H), 3.72 (t, J = 4.4, 5.2 Hz, 4H), 2.96 (t, J = 4.8 Hz, 4H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 145.7, 144.5, 136.0, 116.6, 116.4, 66.3, 49.9; IR (film) ν_{max} 3363, 3039, 2944, 2851, 2812, 2752, 1602, 1538, 1514, 1459, 1449, 1425, 1412, 1383, 1338, 1303, 1270, 1251, 1230, 1173, 1163, 1114, 1100, 1091, 1065, 1053, 1028, 1013, 1005, 926, 907, 858, 830, 783, 749, 727, 712, 702, 629, 618, 609, 606, 604, 602 cm^{-1}; Anal. Calcd. For $C_{13}H_{16}N_4O$: C, 63.91; H, 6.60. Found: C, 63.77; H, 6.77.

***N*-hexyl-1*H*-imidazol-2-amine (Table 1, entry 1i)**



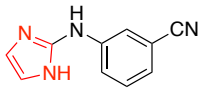
Following the general procedure, a mixture of **P4** (8.6 mg, 1.0 mol %), **L4** (4.9 mg, 1.0 mol %), 2-bromo-1*H*-imidazole (147 mg, 1.0 mmol), n-hexylamine (159 µL, 1.2 mmol), LHMDS (2.2 mL, 2.2 mmol) (1M in THF) was heated to 50 °C for 6 h. The crude product was purified via flash alumina chromatography (MeOH/CH_2Cl_2, 1:99) to provide the title compound as red-brown solid (137 mg, 82%), mp 68-69 °C. ^{1}H NMR (400 MHz, CD_2Cl_2) δ 10.95 (br-s, 1H), 6.61 (s, 2H), 4.75 (br-s, 1H), 3.23 (t, J = 7.2 Hz, 2H), 1.56-1.51 (m, 2H), 1.34-1.28 (m, 6H), 0.90-0.87 (m, 3H); ^{13}C NMR (100 MHz, CD_2Cl_2) δ 152.2, 117.8, 44.7, 32.0, 30.5, 27.0, 23.0, 14.2; IR (film) ν_{max} 3352, 3049, 2950, 2926, 2850, 1603, 1524, 1479, 1466, 1454, 1362, 1336, 1287, 1273, 1197, 1166, 1154, 1122, 1098, 1081, 1041, 996, 984, 899, 846, 728, 697 cm^{-1}; Anal. Calcd. For $C_{13}H_{16}N_4O$: C, 64.63; H, 10.25. Found: C, 64.46; H, 10.13.

***N*-(2,5-dimethoxyphenyl)-1*H*-imidazol-2-amine (Table 1, entry 1j)**



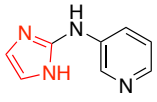
Following the general procedure, a mixture of **P4** (17.1 mg, 2.0 mol %), **L4** (9.7 mg, 2.0 mol %), 2-bromo-1*H*-imidazole (147 mg, 1.0 mmol), 2,5-dimethoxyaniline (184 mg, 1.2 mmol), LHMDS (2.2 mL, 2.2 mmol) (1M in THF) was heated to 80 °C for 6 h. The crude product was purified via flash alumina chromatography (MeOH/CH_2Cl_2, 1:99) to provide the title compound as pale grey solid (195 mg, 89%), mp 161-162 °C. ^{1}H NMR (400 MHz, acetone-d_6) δ 10.22 (br-s, 1H), 8.24 (d, J = 2.8 Hz, 1H), 7.64 (br-s, 1H), 6.90 (d, J = 8.8 Hz, 1H), 6.74 (s, 2H), 6.32 (dd, J = 3.2 Hz, 1H), 3.79 (s, 3H), 3.71 (s, 3H); ^{13}C NMR (100 MHz, acetone-d_6) δ 155.3, 146.2, 142.0, 133.2, 111.4, 103.7, 103.4, 56.6, 55.6; IR (film) ν_{max} 3371, 2931, 2836, 1618, 1572, 1544, 1498, 1466, 1454, 1419, 1363, 1298, 1244, 1212, 1200, 1176, 1169, 1112, 1087, 1041, 960, 924, 833, 734, 706, 691, 610 cm^{-1}; Anal. Calcd. For $C_{11}H_{13}N_3O_2$: C, 60.26; H, 5.98. Found: C, 60.26; H, 6.04.

***N*-(3-cyanophenyl)-1*H*-imidazol-2-amine (Table 1, entry 1k)**



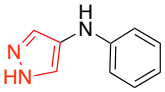
Following the general procedure, a mixture of **P4** (17.1 mg, 2.0 mol %), **L4** (9.7 mg, 2.0 mol %), 2-bromo-1*H*-imidazole (147 mg, 1.0 mmol), 3-cyanoaniline (142 mg, 1.2 mmol), LHMDS (2.2 mL, 2.2 mmol) (1M in THF) was heated to 80 °C for 6 h. The crude product was purified via flash alumina chromatography (MeOH/CH_2Cl_2, 1:49) to provide the title compound as pale yellow solid (169 mg, 92%), mp 170-171 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.93 (s, 1H), 9.15 (s, 1H), 8.02-8.01 (m, 1H), 7.63-7.60 (m, 1H), 7.38 (t, J = 8.0 Hz, 1H), 7.19-7.17 (t, J = 1.2 Hz, 1H), 6.75 (s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 143.8, 143.4, 130.0, 122.1, 119.9, 119.3, 117.4, 111.5; IR (film) ν_{max} 3333, 3060, 2781, 2233, 1641, 1595, 1538, 1516, 1486, 1459, 1364, 1331, 1309, 1257, 1170, 1156, 1094, 1008, 985, 873, 831, 810, 791, 776, 743, 697, 648, 601 cm^{-1}; Anal. Calcd. For $C_{10}H_8N_4$: C, 65.21; H, 4.38. Found: C, 65.19; H, 4.45.

***N*-(3-cyanophenyl)-1*H*-imidazol-2-amine (Table 1, entry 1l)**



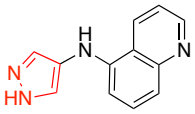
Following the general procedure, a mixture of **P4** (17.1 mg, 2.0 mol %), **L4** (9.7 mg, 2.0 mol %), 2-bromo-1*H*-imidazole (147 mg, 1.0 mmol), 3-aminopyridine (113 mg, 1.2 mmol), LHMDS (2.2 mL, 2.2 mmol) (1M in THF) was heated to 50 °C for 6 h. The crude product was purified via flash alumina chromatography (MeOH/CH_2Cl_2, 1:19) to provide the title compound as brown solid (136 mg, 85%), mp 169-170 °C. ^{1}H NMR (400 MHz, methanol-d_4) δ 8.36 (d, J = 2.8 Hz, 1H), 7.99 (dd, J = 1.2 Hz, 1H), 9.58 (dq, J = 1.2 Hz, 1H), 7.28-7.24 (m, 1H), 6.80 (s, 2H); ^{13}C NMR (100 MHz, methanol-d_4) δ 155.2, 151.8, 151.1, 148.2, 135.4, 134.0, 130.2 (br); IR (film) ν_{max} 3262, 3050, 2843, 1620, 1590, 1545, 1481, 1443, 1411, 1356, 1317, 1284, 1256, 1239, 1188, 1160, 1128, 1105, 1084, 1050, 1023, 996, 917, 867, 830, 803, 753, 685, 640, 623, 610, 605, 603 cm^{-1}; Anal. Calcd. $C_8H_8N_4$: C, 59.99; H, 5.03. Found: C, 59.73; H, 5.09.

***N*-phenyl-1*H*-pyrazol-4-amine (Table 2, entry 2a)** (CAS: 916734-78-6)



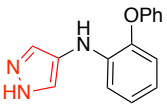
Following the general procedure, a mixture of **P4** (8.6 mg, 1.0 mol %), **L4** (4.9 mg, 1.0 mol %), 4-bromo-1*H*-pyrazole (147 mg, 1.0 mmol), aniline (110 μL, 1.2 mmol), LHMDS (2.2 mL, 2.2 mmol) (1M in THF) was heated to 50 °C for 6 h. The crude product was purified via flash silica gel chromatography (MeOH/CH_2Cl_2, 1:49) to provide the title compound as an off-white solid (152 mg, 96%), mp 111-112 °C. ^{1}H NMR (400 MHz, CD_2Cl_2) δ 11.45 (br-s, 1H), 7.57 (s, 2H), 7.21-7.16 (m, 2H), 6.80-6.74 (m, 3H), 5.27 (br-s, 1H); ^{13}C NMR (100 MHz, CD_2Cl_2) δ 147.2, 129.6, 125.1, 118.9, 113.9; IR (film) ν_{max} 3381, 3122, 2952, 1599, 1579, 1538, 1495, 1373, 1347, 1327, 1246, 1134, 1003, 942, 848, 745, 691, 652, 626, 612 cm^{-1}. Anal. Calcd. For $C_9H_9N_3$: C, 67.90; H, 5.70. Found: C, 67.45; H, 5.44.

***N*-(quinolin-5-yl)-1*H*-pyrazol-4-amine (Table 2, entry 2b)**



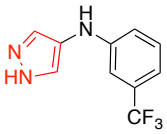
Following the general procedure, a mixture of **P4** (8.6 mg, 1.0 mol %), **L4** (4.9 mg, 1.0 mol %), 4-bromo-1*H*-pyrazole (147 mg, 1.0 mmol), 5-aminoquinoline (173 mg, 1.2 mmol), LHMDS (2.2 mL, 2.2 mmol) (1M in THF) was heated to 50 °C for 6 h. The crude product was purified via flash silica gel chromatography (MeOH/CH_2Cl_2, 1:19) to provide the title compound as an orange solid (170 mg, 81%), mp 255-256 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.80 (s, 1H), 8.84-8.76 (m, 2H), 8.00 (s, 1H), 7.69-7.43 (m, 4H), 7.31 (d, J = 8.4 Hz, 1H), 6.80 (d, J = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 150.0, 149.0, 143.6, 134.6, 130.3, 130.2, 123.5, 122.4, 119.4, 118.1, 117.5, 105.2; IR (film) ν_{max} 3116, 3078, 2904, 2842, 1586, 1520, 1495, 1463, 1404, 1370, 1362, 1348, 1324, 1293, 1273, 1204, 1148, 1135, 1089, 1065, 1023, 1003, 975, 953, 933, 894, 877, 865, 829, 808, 792, 766, 740, 736, 627, 617 cm^{-1}. Anal. Calcd. For $C_{12}H_{10}N_4$: C, 68.56; H, 4.79. Found: C, 68.32; H, 4.70.

***N*-(2-phenoxyphenyl)-1*H*-pyrazol-4-amine (Table 2, entry 2c)**



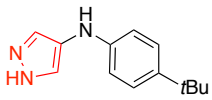
Following the general procedure, a mixture of **P4** (8.6 mg, 1.0 mol %), **L4** (4.9 mg, 1.0 mol %), 4-bromo-1*H*-pyrazole (147 mg, 1.0 mmol), 2-phenoxyaniline (223 mg, 1.2 mmol), LHMDS (2.2 mL, 2.2 mmol) (1M in THF) was heated to 50 °C for 6 h. The crude product was purified via flash silica gel chromatography (MeOH/CH_2Cl_2, 1:19) to provide the title compound as a brown solid (238 mg, 95%), mp 101-102 °C. ^{1}H NMR (400 MHz, CD_2Cl_2) δ 10.85 (br-s, 1H), 7.56 (s, 2H), 7.37-7.32 (m, 2H), 7.12-7.08 (m, 1H), 7.05-6.99 (m, 3H), 6.95-6.93 (m, 1H), 6.90-6.87 (m, 1H), 6.74-6.69 (m, 1H), 5.71 (s, 1H); ^{13}C NMR (100 MHz, CD_2Cl_2) δ 158.0, 143.6, 139.6, 130.3, 129.7, 125.3, 124.5, 123.5, 120.0, 118.7, 118.0, 113.4; IR (film) ν_{max} 3130, 2944, 1607, 1581, 1550, 1512, 1488, 1472, 1454, 1383, 1355, 1331, 1292, 1243, 1208, 1180, 1159, 1104, 1073, 953, 927, 894, 878, 834, 786, 743, 690, 646, 619, 610, 604 cm^{-1}. Anal. Calcd. For $C_{15}H_{13}N_3O$: C, 71.70; H, 5.21. Found: C, 71.51; H, 5.06.

***N*-(3-trifluoromethylphenyl)-1*H*-pyrazol-4-amine (Table 2, entry 2d)**



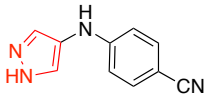
Following the general procedure, a mixture of **P4** (8.6 mg, 1.0 mol %), **L4** (4.9 mg, 1.0 mol %), 4-bromo-1*H*-pyrazole (147 mg, 1.0 mmol), 3-aminobenzotrifluoride (150 μL, 1.2 mmol), LHMDS (2.2 mL, 2.2 mmol) (1M in THF) was heated to 50 °C for 6 h. The crude product was purified via flash silica gel chromatography (MeOH/CH_2Cl_2, 1:24) to provide the title compound as brown oil (222 mg, 98%). ^{1}H NMR (400 MHz, CD_2Cl_2) δ 11.68 (br-s, 1H), 7.62 (s, 2H), 7.31-7.27 (m, 1H), 7.02-6.99 (m, 2H), 6.96-6.93 (m, 1H), 5.53 (s, 1H); ^{13}C NMR (100 MHz, CD_2Cl_2) δ 148.0, 131.8 (q, J = 63 Hz), 130.2, 124.8 (q, J = 541 Hz), 124.0, 117.0, 115.1 (q, J = 7.0 Hz), 110.0 (q, J = 8.0 Hz); ^{19}F NMR (282 MHz, CD_2Cl_2) -63.5; IR (film) ν_{max} 3412, 3182, 2960, 1615, 1584, 1475, 1439, 1333, 1272, 1247, 1161, 1115, 1097, 1067, 1004, 995, 954, 942, 921, 904, 863, 783, 754, 712, 696, 670, 658, 626 cm^{-1}. Anal. Calcd. For $C_{10}H_8F_3N_4$: C, 52.87; H, 3.55. Found: C, 52.72; H, 3.71.

***N*-(4-*tert*-butylphenyl)-1*H*-pyrazol-4-amine (Table 2, entry 2e)**



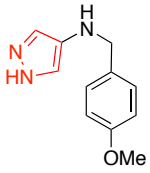
Following the general procedure, a mixture of **P4** (8.6 mg, 1.0 mol %), **L4** (4.9 mg, 1.0 mol %), 4-bromo-1*H*-pyrazole (147 mg, 1.0 mmol), 4-*tert*-butylaniline (192 µL, 1.2 mmol), LHMDS (2.2 mL, 2.2 mmol) (1M in THF) was heated to 50 °C for 6 h. The crude product was purified via flash silica gel chromatography ($MeOH/CH_2Cl_2$, 1:49) to provide the title compound as pale brown solid (204 mg, 95%), mp 154-155 °C. ^1H NMR (400 MHz, methanol-d_4) δ 7.48 (s, 1H), 7.17 (d, J = 8.4 Hz, 2H), 6.74 (d, J = 8.4 Hz, 2H), 1.25 (s, 1H); ^{13}C NMR (100 MHz, methanol-d_4) δ 146.0, 142.0, 127.6, 126.9, 114.6, 34.8, 32.2; IR (film) ν_{max} 3110, 2949, 2864, 2506, 2431, 1611, 1566, 1512, 1358, 1293, 1189, 1007, 869, 820, 657, 604 cm^{-1}. Anal. Calcd. For $C_{13}H_{17}N_3$: C, 72.52; H, 7.96. Found: C, 72.53; H, 7.84.

***N*-(4-cyanophenyl)-1*H*-pyrazol-4-amine (Table 2, entry 2f)**



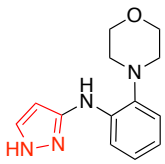
Following the general procedure, a mixture of **P4** (17.1 mg, 2.0 mol %), **L1** (9.7 mg, 2.0 mol %), 4-bromo-1*H*-pyrazole (147 mg, 1.0 mmol), 4-aminobenzonitrile (142 mg, 1.2 mmol), LHMDS (2.2 mL, 2.2 mmol) (1M in THF) was heated to 80 °C for 12 h. The crude product was purified via flash silica gel chromatography ($MeOH/CH_2Cl_2$, 1:24) to provide the title compound as brown solid (163 mg, 89%), mp 174-175 °C. ^1H NMR (400 MHz, acetone-d_6) δ 12.13 (s, 1H), 7.64 (s, 2H), 7.55 (s, 1H), 7.49-7.45 (m, 2H), 6.91-6.87 (m, 2H); ^{13}C NMR (100 MHz, acetone-d_6) δ 152.1, 134.8, 134.3, 123.3, 121.2, 120.6, 113.8, 99.7; IR (film) ν_{max} 3256, 3124, 3078, 2982, 2215, 1600, 1573, 1528, 1505, 1360, 1271, 1171, 1136, 1001, 934, 853, 822, 764, 725, 648, 606 cm^{-1}. Anal. Calcd. For $C_{13}H_{17}N_3$: C, 65.21; H, 4.38. Found: C, 64.95; H, 4.28.

***N*-(4-methoxybenzyl)-1*H*-pyrazol-4-amine (Table 2, entry 2g)**



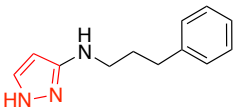
Following the general procedure, a mixture of **P4** (17.1 mg, 2.0 mol %), **L4** (9.7 mg, 2.0 mol %), 4-bromo-1*H*-pyrazole (147 mg, 1.0 mmol), 4-methoxybenzylamine (157 µL, 1.2 mmol), LHMDS (2.2 mL, 2.2 mmol) (1M in THF) was heated to 80 °C for 6 h. The crude product was purified via flash silica gel chromatography ($MeOH/CH_2Cl_2$, 3:97) to provide the title compound as pale yellow solid (152 mg, 75%), mp 150-151 °C. ^1H NMR (400 MHz, methanol-d_4) δ 7.28 (d, J = 8.8 Hz, 2H), 7.18 (s, 2H), 6.86 (d, J = 8.8 Hz, 2H), 4.04 (s, 2H), 3.76 (s, 3H); ^{13}C NMR (100 MHz, methanol-d_4) δ 160.5, 134.3, 133.0, 130.4, 114.9, 55.8, 53.0; IR (film) ν_{max} 3331, 3182, 3115, 2957, 2839, 1611, 1585, 1510, 1464, 1441, 1390, 1341, 1315, 1301, 1243, 1172, 1129, 1108, 1090, 1052, 1028, 943, 825, 774, 611 cm^{-1}. HRMS-ESI (*m/z*) $[M + H]^+$ calcd for $C_{11}H_{13}N_3O$: 204.1131; Found, 204.1128.

***N*-(methylfuran-2-yl)-1*H*-pyrazol-3-amine (Table 2, entry 2h)**



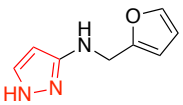
Following the general procedure, a mixture of **P4** (17.1 mg, 2.0 mol %), **L4** (9.7 mg, 2.0 mol %), 3-bromo-1*H*-pyrazole (147 mg, 1.0 mmol), 2-morpholinoaniline (214 mg, 1.2 mmol), LHMDS (2.2 mL, 2.2 mmol) (1M in THF) was heated to 80 °C for 6 h. The crude product was purified via flash silica gel chromatography ($MeOH/CH_2Cl_2$, 1:49) to provide the title compound as a brown solid (222 mg, 91%), mp 45-46 °C. ^1H NMR (400 MHz, CD_2Cl_2) δ 11.00 (br-s, 1H), 7.58 (dd, J = 1.2 Hz, 1H), 7.39 (d, J = 2.4 Hz, 1H), 7.18 (br-s, 1H), 7.15 (dd, J = 1.2, 1.6 Hz, 1H), 7.08-7.04 (m, 1H), 6.85 (dt, J = 1.6 Hz, 1H), 6.07 (d, J = 2.4 Hz, 1H), 3.84 (t, J = 4.4, 4.8 Hz, 4H), 2.90 (t, J = 4.8 Hz, 4H); ^{13}C NMR (100 MHz, CD_2Cl_2) δ 151.5, 139.7, 139.1, 130.3, 125.7, 120.8, 119.6, 114.1, 95.4, 67.9, 52.7; IR (film) ν_{max} 3184, 2959, 2825, 1589, 1547, 1506, 1484, 1456, 1372, 1297, 1257, 1229, 1200, 1160, 1113, 1068, 1053, 993, 953, 928, 914, 855, 840, 740, 708, 676, 646 cm^{-1}. HRMS-ESI (*m/z*) $[M + H]^+$ calcd for $C_{13}H_{16}N_4O$: 245.1397; Found, 245.1386.

***N*-(methylfuran-2-yl)-1*H*-pyrazol-3-amine (Table 2, entry 2i)**



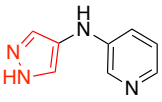
Following the general procedure, a mixture of **P4** (8.6 mg, 1.0 mol %), **L4** (4.9 mg, 1.0 mol %), 3-bromo-1*H*-pyrazole (147 mg, 1.0 mmol), 3-phenyl-1-propylamine (172 µL, 1.2 mmol), LHMDS (2.2 mL, 2.2 mmol) (1M in THF) was heated to 50 °C for 6 h. The crude product was purified via flash silica gel chromatography ($MeOH/CH_2Cl_2$, 3:97) to provide the title compound as an orange oil (173 mg, 86%). ^1H NMR (400 MHz, CD_2Cl_2) δ 7.38-7.34 (m, 3H), 7.28-7.25 (m, 3H), 5.63 (d, J = 2.4 Hz, 1H), 3.23 (t, J = 7.2 Hz, 2H), 2.75 (t, J = 7.6, 8.0 Hz, 2H), 1.96 (s, J = 7.6 Hz, 2H); ^{13}C NMR (100 MHz, CD_2Cl_2) δ 156.8, 142.4, 131.7, 128.8, 128.7, 126.1, 90.4, 45.3, 33.6, 32.0; IR (film) ν_{max} 3170, 3024, 2934, 2858, 1594, 1555, 1495, 1453, 1372, 1278, 1105, 1030, 985, 953, 926, 740, 698 cm^{-1}. HRMS-ESI (*m/z*) $[M + H]^+$ calcd for $C_{12}H_{15}N_3$: 202.1339; Found, 202.1336.

***N*-(methylfuran-2-yl)-1*H*-pyrazol-3-amine (Table 2, entry 2j)**



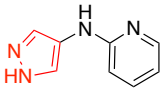
Following the general procedure, a mixture of **P4** (17.1 mg, 2.0 mol %), **L4** (9.7 mg, 2.0 mol %), 3-bromo-1*H*-pyrazole (147 mg, 1.0 mmol), 2-aminomethylfuran (106 µL, 1.2 mmol), LHMDS (2.2 mL, 2.2 mmol) (1M in THF) was heated to 80 °C for 6 h. The crude product was purified via flash silica gel chromatography ($MeOH/CH_2Cl_2$, 3:97) to provide the title compound as an orange oil (133 mg, 82%). ^1H NMR (400 MHz, CD_2Cl_2) δ 7.38 (dd, J = 0.8 Hz, 1H), 7.31 (d, J = 2.4 Hz, 1H), 6.34 (dd, J = 2.0 Hz, 1H), 6.24 (dd, J = 0.8 Hz, 1H), 5.66 (d, J = 2.4 Hz, 1H), 4.33 (s, 2H); ^{13}C NMR (100 MHz, CD_2Cl_2) δ 156.4, 153.9, 142.1, 131.1, 110.6, 107.1, 91.1, 42.6; IR (film) ν_{max} 3179, 2941, 1553, 1503, 1342, 1270, 1182, 1145, 1099, 1073, 1042, 1011, 917, 884, 730 cm^{-1}. HRMS-ESI (*m/z*) $[M + H]^+$ calcd for $C_{11}H_{13}N_3O$: 164.0818; Found, 164.0814.

***N*-(pyridin-3-yl)-1*H*-pyrazol-4-amine (Table 2, entry 2k)**



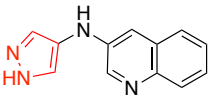
Following the general procedure, a mixture of **P4** (18.2 mg, 2.0 mol %), **L4** (9.7 mg, 2.0 mol %), 4-bromo-1*H*-pyrazole (147 mg, 1.0 mmol), 3-aminopyridine (113 mg, 1.2 mmol), LHMDS (2.2 mL, 2.2 mmol) (1M in THF) was heated to 80 °C for 6 h. The crude product was purified via flash silica gel chromatography ($MeOH/CH_2Cl_2$, 1:19) to provide the title compound as pale yellow powder (155 mg, 97%), mp 126-127 °C. ^1H NMR (400 MHz, DMSO-d_6) δ 12.69 (br-s, 1H), 9.13 (s, 1H), 7.85-7.59 (m, 4H), 7.12-7.07 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 143.3, 137.9, 135.9, 133.0, 123.8, 123.4, 120.7, 118.2; IR (film) ν_{max} 3262, 3123, 3019, 2933, 1616, 1580, 1557, 1484, 1429, 1377, 1335, 1279, 1248, 1186, 1068, 1046, 1023, 1002, 952, 930, 884, 865, 842, 777, 694 cm^{-1}; Anal. Calcd. For $C_8H_8N_4$: C, 59.99; H, 5.03. Found: C, 59.85; H, 5.17.

***N*-(pyridin-2-yl)-1*H*-pyrazol-4-amine (Table 2, entry 2l)**



Following the general procedure, a mixture of **P4** (17.1 mg, 2.0 mol %), **L4** (9.7 mg, 2.0 mol %), 4-bromo-1*H*-pyrazole (147 mg, 1.0 mmol), 2-aminopyridine (132 mg, 1.4 mmol), LHMDS (2.2 mL, 2.2 mmol) (1M in THF) was heated to 80 °C for 6 h. The crude product was purified via flash chromatography ($MeOH/CH_2Cl_2$, 1:19) to provide the title compound as yellow powder (150 mg, 94%), mp 173-174 °C. ^1H NMR (400 MHz, DMSO-d_6) δ 12.46 (s, 1H), 8.71 (s, 1H), 8.10-8.08 (m, 1H), 7.73 (br-s, 2H), 7.48-7.44 (m, 1H) 6.67-6.58 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 156.0, 147.5, 136.9, 123.4, 112.6, 108.9; IR (film) ν_{max} 3249, 3136, 3064, 3028, 2941, 1616, 1597, 1579, 1535, 1505, 1419, 1377, 1362, 1333, 1313, 1282, 1240, 1156, 1134, 1107, 1050, 1010, 989, 932, 855, 766, 738, 660, 631 cm^{-1}; Anal. Calcd. For $C_8H_8N_4$: C, 59.99; H, 5.03. Found: C, 59.80; H, 5.05.

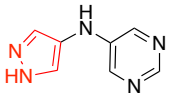
***N*-(quinolin-3-yl)-1*H*-pyrazol-4-amine (Table 2, entry 2m)**



Following the general procedure, a mixture of **P4** (17.1 mg, 2.0 mol %), **L4** (9.7 mg, 2.0 mol %), 4-bromo-1*H*-pyrazole (147 mg, 1.0 mmol), 3-aminoquinoline (173 mg, 1.2 mmol), LHMDS (2.2 mL, 2.2 mmol) (1M in THF) was heated to 80 °C for 6 h. The crude product was purified via flash silica gel chromatography ($MeOH/CH_2Cl_2$, 1:19) to

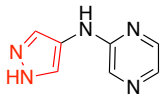
provide the title compound as a yellow solid (199 mg, 95%), mp 184-185 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.74 (s, 1H), 8.59 (d, J = 2.4 Hz, 1H), 8.22 (s, 1H), 7.87-7.79 (m, 2H), 7.72-7.69 (m, 1H), 7.53 (s, 1H), 7.43-7.33 (m, 3H) (d, J = 1.6 Hz, 1H), 7.53-7.31 (m, 9H), 5.19 (s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 143.5, 141.4, 140.4, 132.9, 129.4, 128.5, 126.7, 126.2, 124.5, 123.4, 120.3, 109.4; IR (film) ν_{max} 3308, 3130, 3050, 2889, 1616, 1604, 1583, 1559, 1535, 1489, 1474, 1464, 1423, 1395, 1365, 1331, 1293, 1282, 1245, 1229, 1213, 1145, 1118, 1069, 1022, 1003, 987, 949, 936, 914, 871, 844, 824, 798, 778, 772, 742 cm^{-1}; Anal. Calcd. For $C_{12}H_{10}N_4$: C, 68.56; H, 4.79. Found: C, 68.31; H, 4.79.

_N_-(pyrimidin-5-yl)-1_H_-pyrazol-4-amine (Table 2, entry 2n)



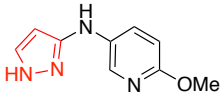
Following the general procedure, a mixture of **P4** (17.1 mg, 2.0 mol %), **L4** (9.7 mg, 2.0 mol %), 4-bromo-1*H*-pyrazole (147 mg, 1.0 mmol), 5-aminopyrimidine (114 mg, 1.2 mmol), LHMDS (2.2 mL, 2.2 mmol) (1M in THF) was heated to 80 °C for 6 h. The crude product was purified via flash silica gel chromatography (MeOH/CH_2Cl_2, 1:19) to provide the title compound as a pale yellow solid (136 mg, 85%), mp 233-234 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.76 (br-s, 1H), 8.47 (s, 1H), 8.27 (s, 2H), 7.98 (s, 1H), 7.82 (s, 1H), 7.48 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 147.6, 141.1, 140.7, 133.3, 122.2, 121.1; IR (film) ν_{max} 3167, 3124, 3003, 2903, 1606, 1578, 1553, 1482, 1444, 1419, 1373, 1336, 1294, 1204, 1135, 1123, 1063, 1001, 951, 930, 872, 845, 772, 714, 675, 625, 601 cm^{-1}; Anal. Calcd. For $C_7H_7N_5$: C, 52.17; H, 4.38. Found: C, 52.10; H, 4.49.

_N_-(pyrazin-2-yl)-1_H_-pyrazol-4-amine (Table 2, entry 2o)



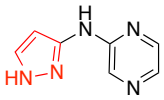
Following the general procedure, a mixture of **P4** (17.1 mg, 2.0 mol %), **L4** (9.7 mg, 2.0 mol %), 4-bromo-1*H*-pyrazole (147 mg, 1.0 mmol), aminopyrazine (114 mg, 1.2 mmol), LHMDS (2.2 mL, 2.2 mmol) (1M in THF) was heated to 80 °C for 16 h. The crude product was purified via flash silica gel chromatography (MeOH/CH_2Cl_2, 1:19) to provide the title compound as yellow powder (143 mg, 89%), mp 142-143 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.56 (br-s, 1H), 9.30 (s, 1H), 8.10-8.8.05 (m, 2H), 7.77-7.76 (m, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 152.2, 141.5, 133.9, 131.9, 122.2; IR (film) ν_{max} 3297, 3155, 3077, 2926, 1623, 1616, 1599, 1538, 1516, 1506, 1456, 1419, 1384, 1362, 1311, 1274, 1213, 1175, 1149, 1073, 1053, 1015, 1004, 939, 890, 859, 822, 763, 684, 646, 610 cm^{-1}; HRMS-ESI (*m/z*) $[M + H]^+$ calcd for $C_7H_7N_5$: 162.0774; Found, 162.0770.

_N_-(2-methoxypyridin-3-yl)- 1_H_-pyrazol-3-amine (Table 2, entry 2p)



Following the general procedure, a mixture of **P4** (17.1 mg, 2.0 mol %), **L4** (9.7 mg, 2.0 mol %), 3-bromo-1*H*-pyrazole (147 mg, 1.0 mmol), 3-amino-2-methoxypyridine (121 µL, 1.2 mmol), LHMDS (2.2 mL, 2.2 mmol) (1M in THF) was heated to 80 °C for 6 h. The crude product was purified via flash silica gel chromatography (MeOH/CH_2Cl_2, 1:24) to provide the title compound as a pale brown solid (176 mg, 93%), mp 137-138 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.92 (s, 1H), 8.26-8.22 (m, 2H), 7.76 (d, J = 6.4 Hz, 1H), 7.53 (s, 1H), 6.68 (d, J = 8.8 Hz, 1H), 5.75 (d, J = 1.6 Hz, 1H), 3.76 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 156.6, 151.7, 135.4, 132.5, 128.8, 127.2, 109.8, 92.6, 52.8; IR (film) ν_{max} 3364, 3267, 3013, 2988, 2942, 1620, 1547, 1484, 1460, 1454, 1433, 1397, 1356, 1299, 1266, 1253, 1234, 1185, 1172, 1119, 1025, 1010, 999, 921, 833, 803, 764, 739, 667, 634, 608 cm^{-1}; Anal. Calcd. For $C_9H_{10}N_4$: C, 56.83; H, 5.30. Found: C, 56.42; H, 5.27.

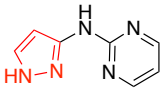
_N_-(pyrazin-2-yl)- 1_H_-pyrazol-3-amine (Table 2, entry 2q)



Following the general procedure, a mixture of **P4** (34.2 mg, 4.0 mol %), **L4** (19.4 mg, 4.0 mol %), 3-bromo-1*H*-pyrazole (147 mg, 1.0 mmol), aminopyrazine (134 mg, 1.4 mmol), LHMDS (2.2 mL, 2.2 mmol) (1M in THF) was heated to 80 °C for 16 h. The crude product was purified via flash silica gel chromatography (MeOH/CH_2Cl_2, 1:24) to provide the title compound as a orange solid (153 mg, 95%), mp 171-172 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.24 (s, 1H), 9.70 (s, 1H), 8.54 (s, 1H), 8.08 (q, J = 1.6 Hz, 1H), 7.88 (d, J = 2.8 Hz, 1H), 7.61 (s, 1H), 6.42 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 151.8, 148.6, 141.6, 133.7, 133.4, 128.7, 95.1; IR (film) ν_{max} 3270, 3156,

3007, 2954, 2885, 1621, 1526, 1487, 1471, 1394, 1344, 1297, 1265, 1193, 1169, 1139, 1093, 1053, 997, 923, 891, 816, 744, 681, 667, 624, 614 cm^{-1}; Anal. Calcd. For $C_9H_{10}N_4$: C, 52.17; H, 4.38. Found: C, 52.26; H, 4.41.

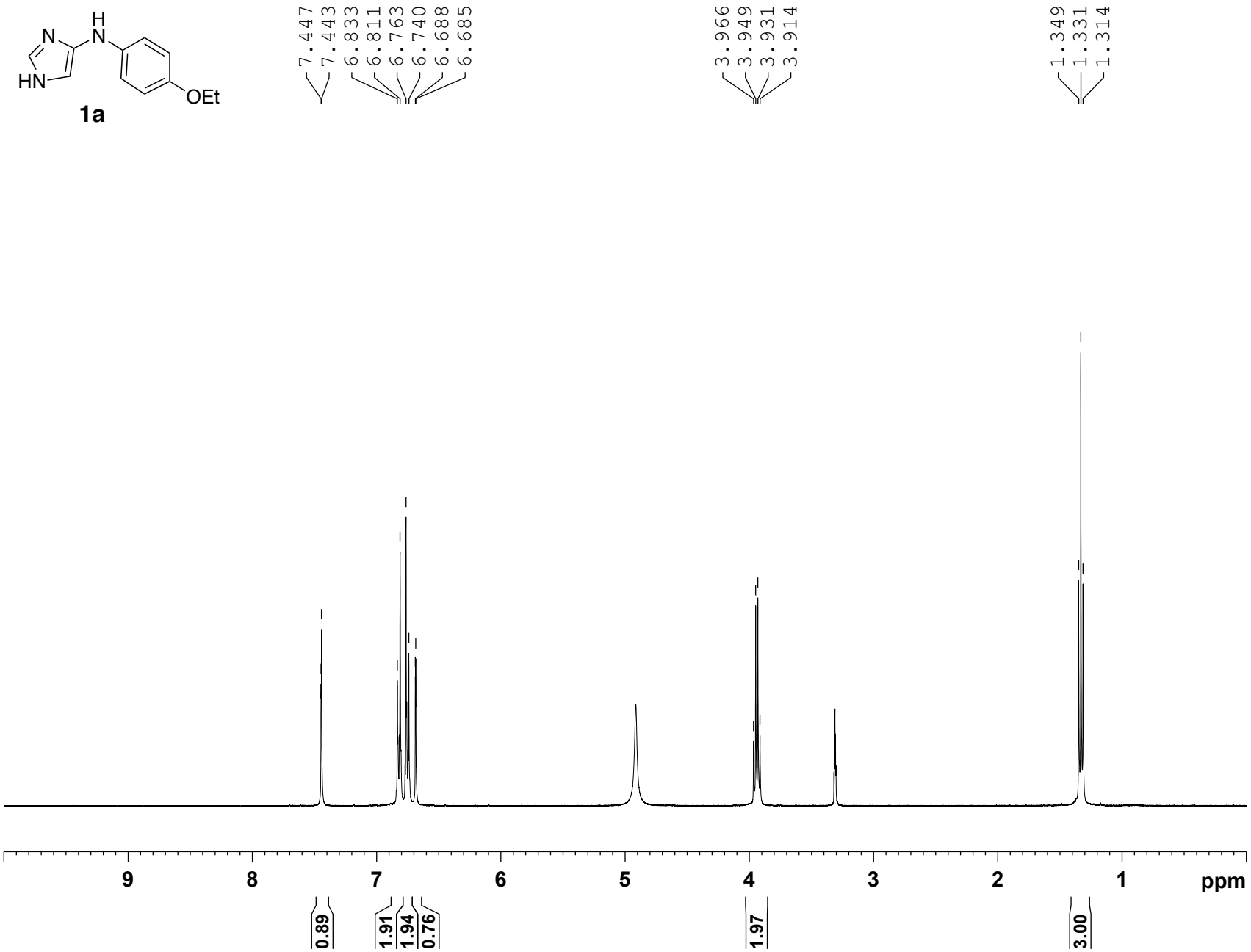
_N_-(pyrimidin-2-yl)-1_H_-pyrazol-3-amine (Table 2, entry 2r)



Following the general procedure, a mixture of **P4** (34.2 mg, 4.0 mol %), **L4** (19.4 mg, 4.0 mol %), 3-bromo-1*H*-pyrazole (147 mg, 1.0 mmol), 2-aminopyrimidine (134 mg, 1.4 mmol), LHMDS (2.2 mL, 2.2 mmol) (1M in THF) was heated to 80 °C for 16 h. The crude product was purified via flash silica gel chromatography ($MeOH/CH_2Cl_2$, 1:24) to provide the title compound as a pale orange solid (151 mg, 94%), mp 201-202 °C. ^1H NMR (400 MHz, DMSO-d_6) δ 12.25 (s, 1H), 9.91 (s, 1H), 8.46-8.44 (m, 1H), 7.56 (s, 1H), 6.78 (t, J = 4.8 Hz, 1H), 6.55 (br-s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 159.7, 158.1, 147.9, 128.7, 111.9, 95.9; IR (film) ν_{max} 3243, 3139, 3003, 2944, 2857, 1603, 1587, 1554, 1495, 1447, 1414, 1354, 1295, 1251, 1170, 1090, 1056, 1006, 987, 926, 899, 872, 796, 749, 690, 654, 636 cm^{-1}; Anal. Calcd. For $C_9H_{10}N_4$: C, 52.17; H, 4.38. Found: C, 52.21; H, 4.42.

References

1. (a) Bruno, N. C.; Tudge, M. T.; Buchwald, S. L. *Chem. Sci.* **2013**, *4*, 916. (b) Bruno, N. C.; Buchwald, S. L. *Org. Lett.* **2013**, *15*, 2876.
2. Su, M.; Buchwald, S. L. *Angew. Chem. Int. Ed.* **2012**, *51*, 4710.
3. Fors, B. F.; Dooleweerdt, K.; Zeng, Q.; Buchwald, S. L. *Tetrahedron* **2009**, *65*, 6576.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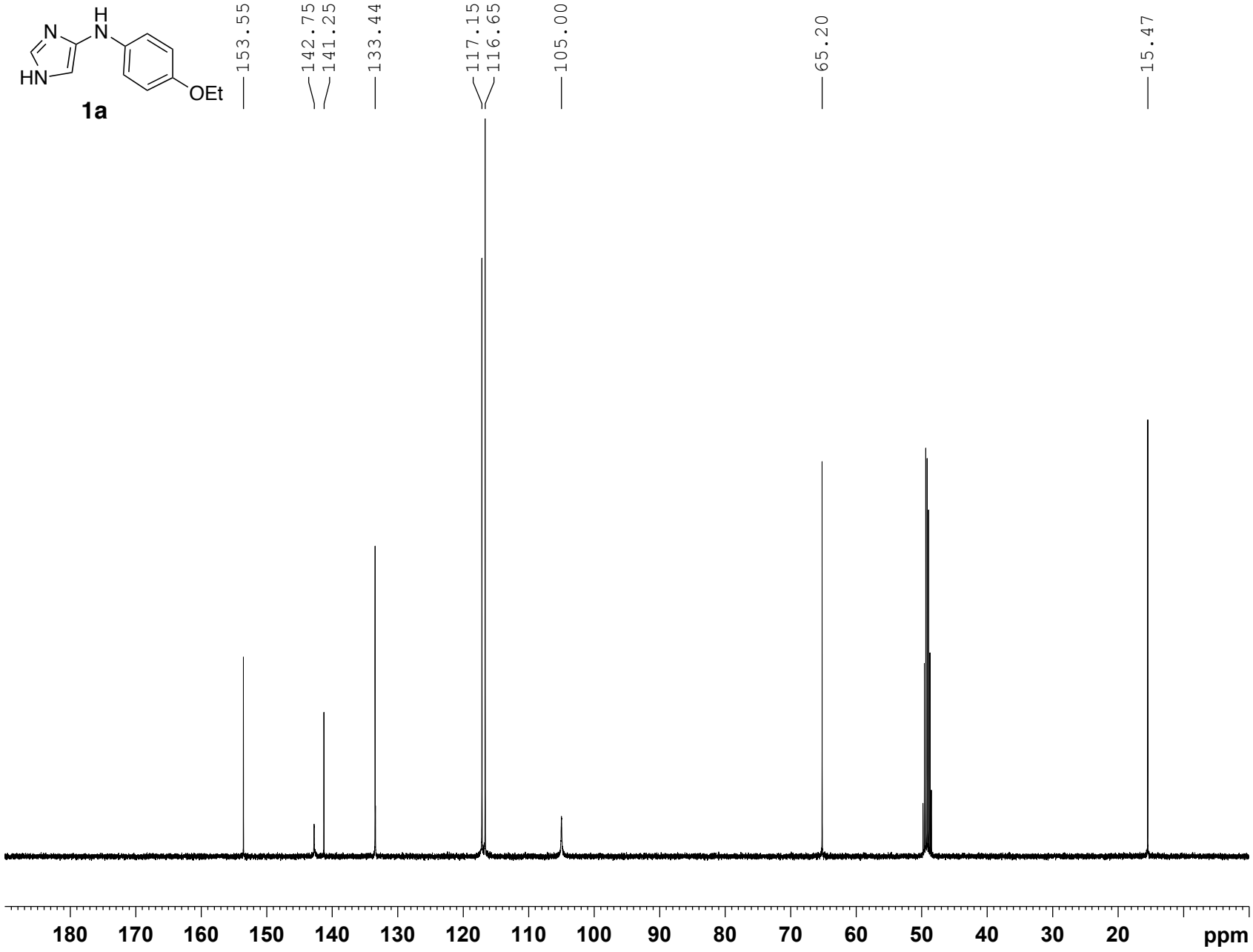
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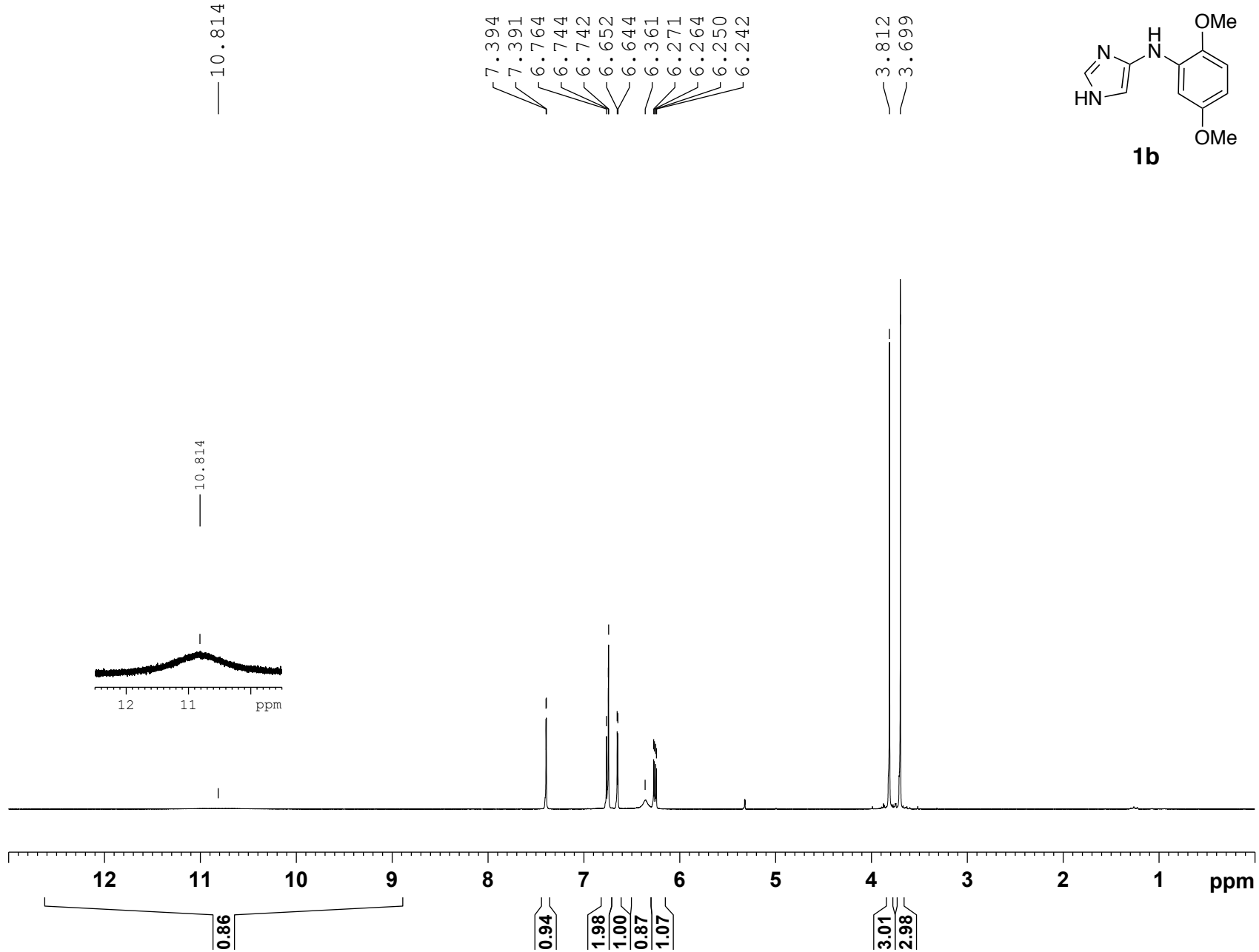
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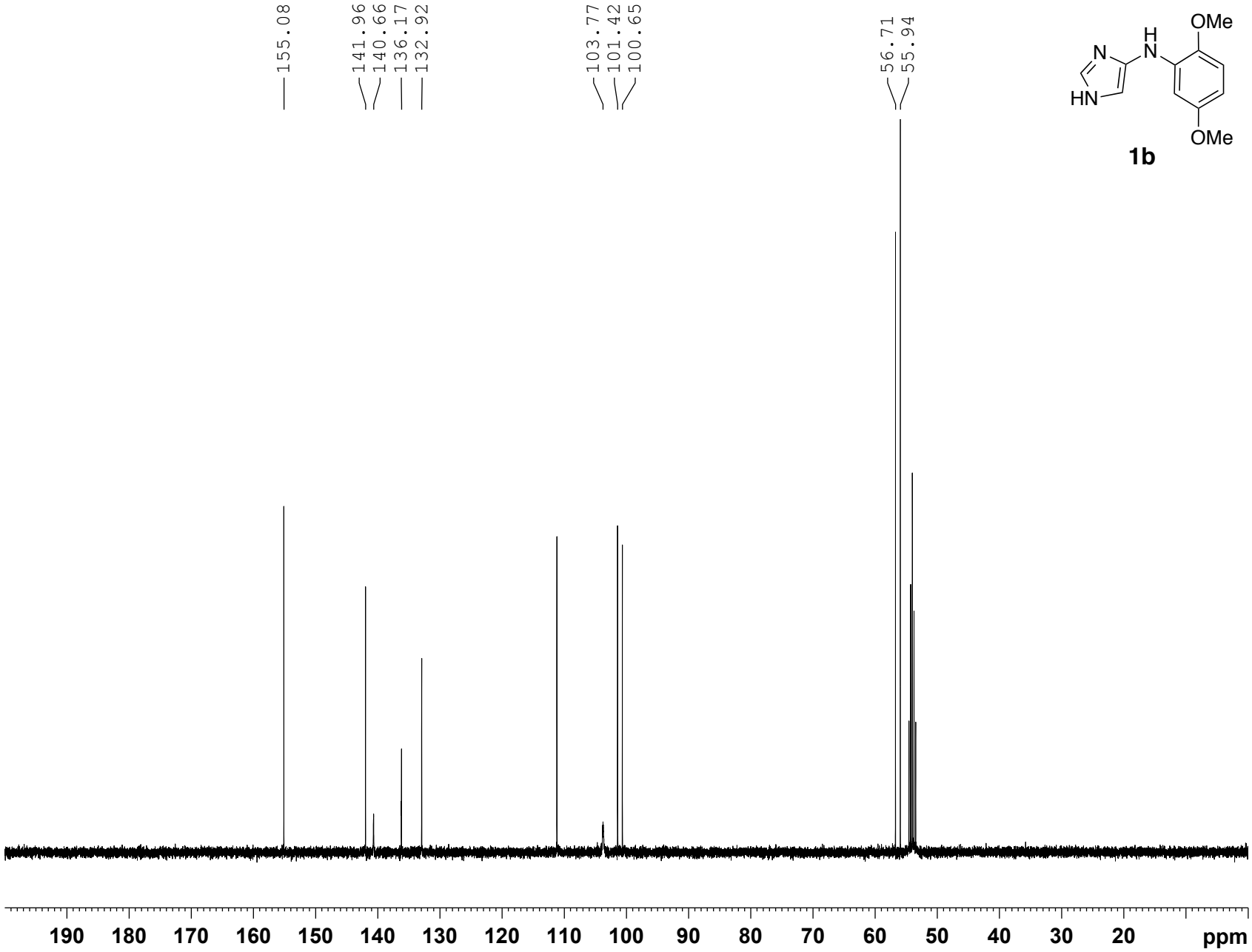
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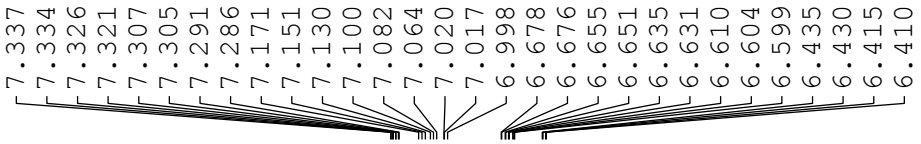
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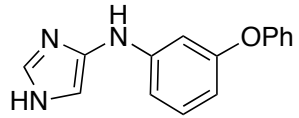
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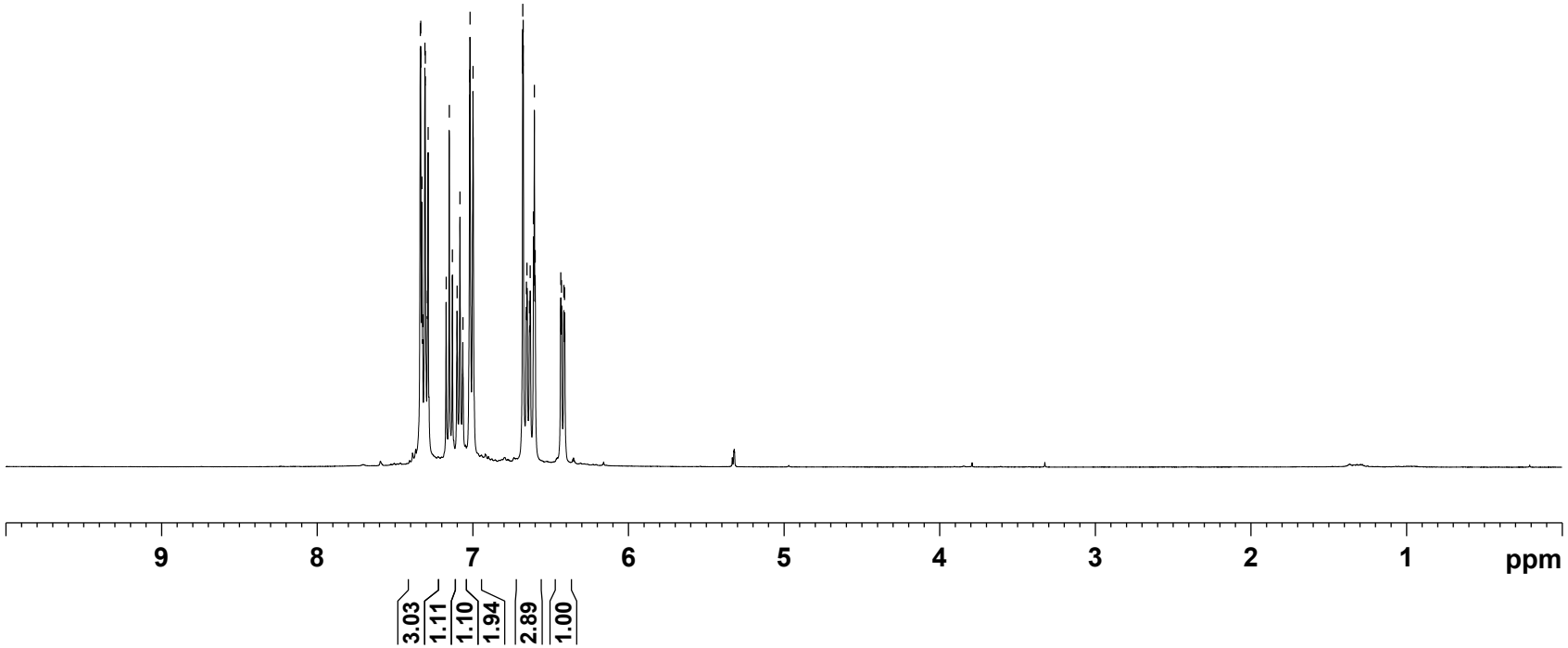
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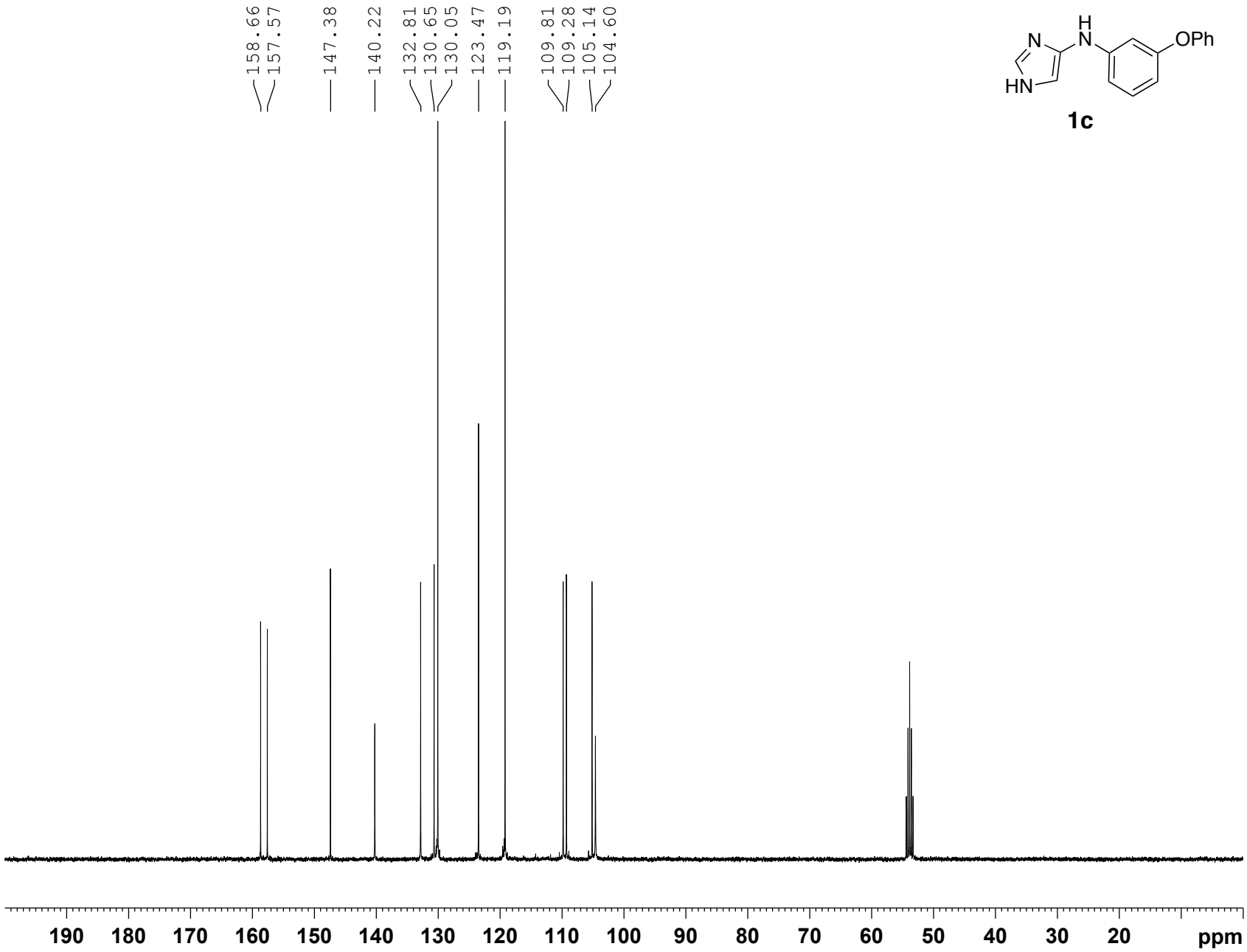
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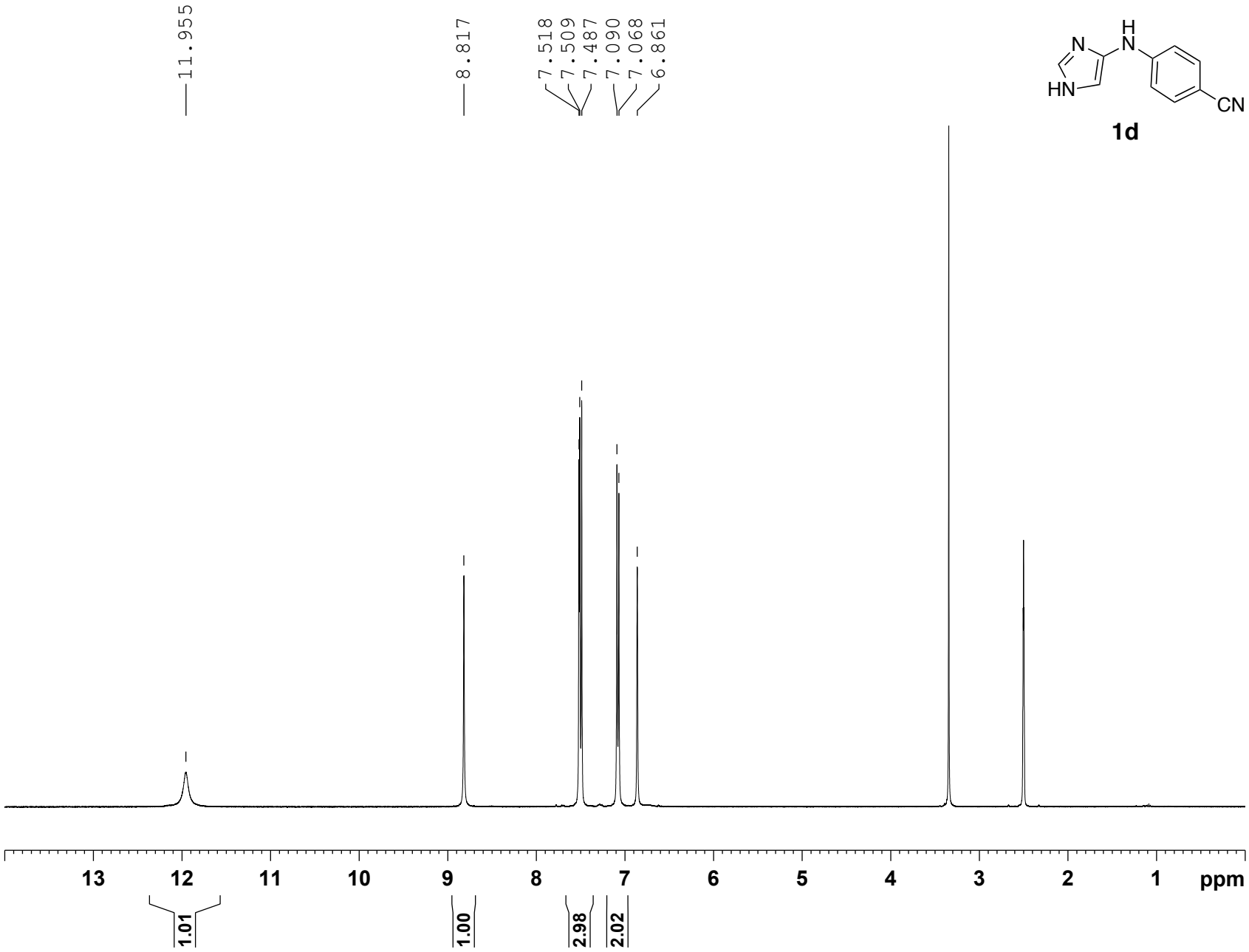
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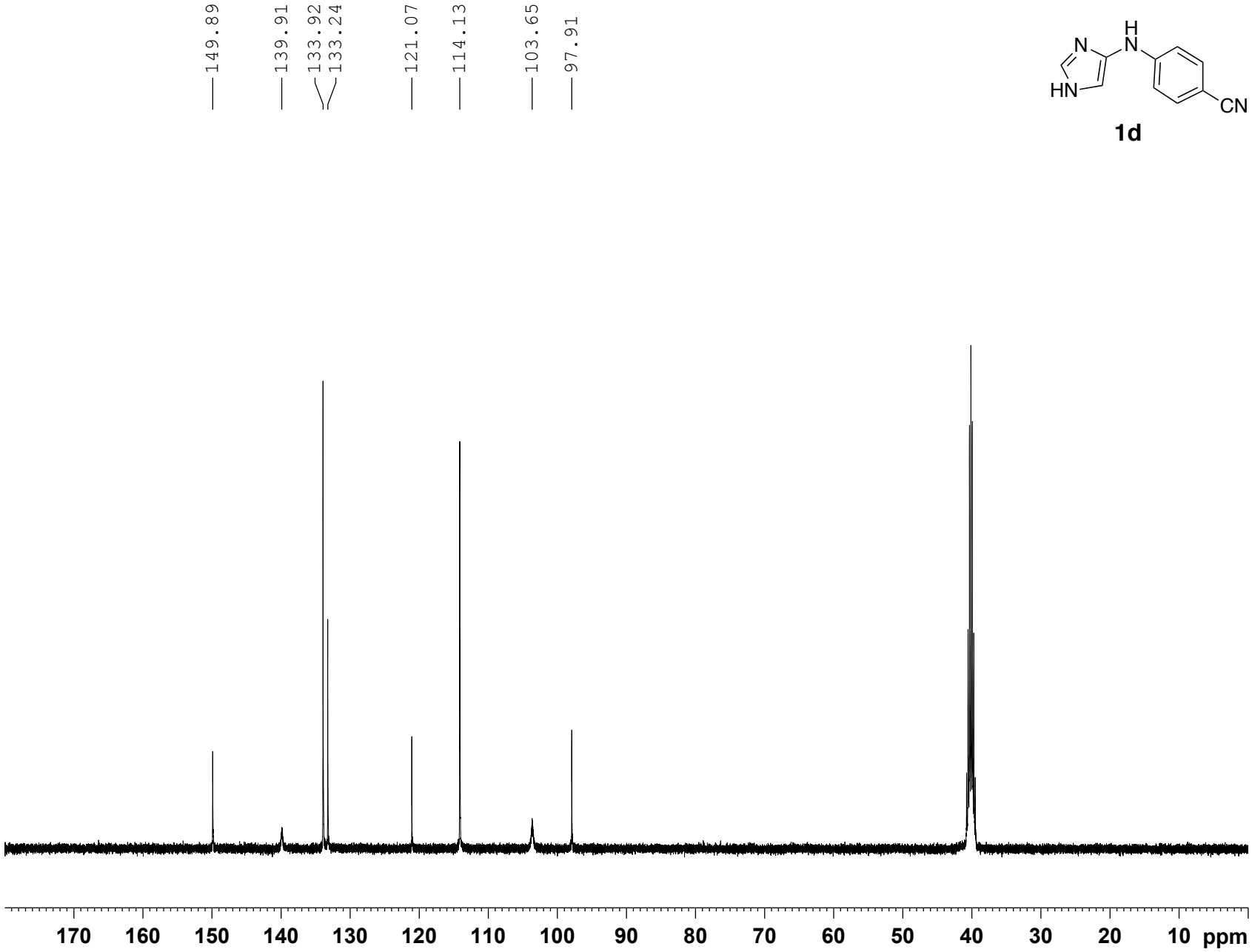
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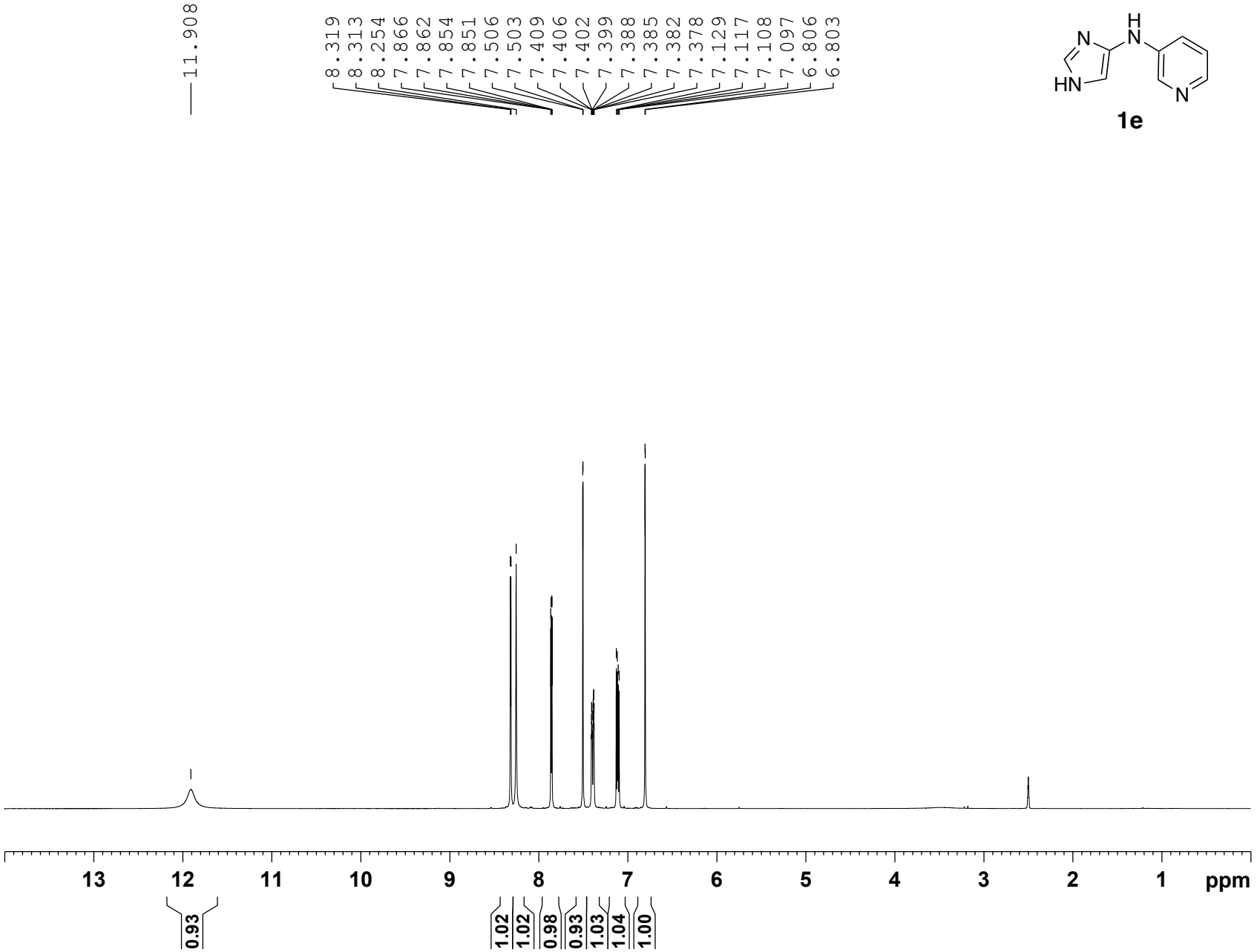
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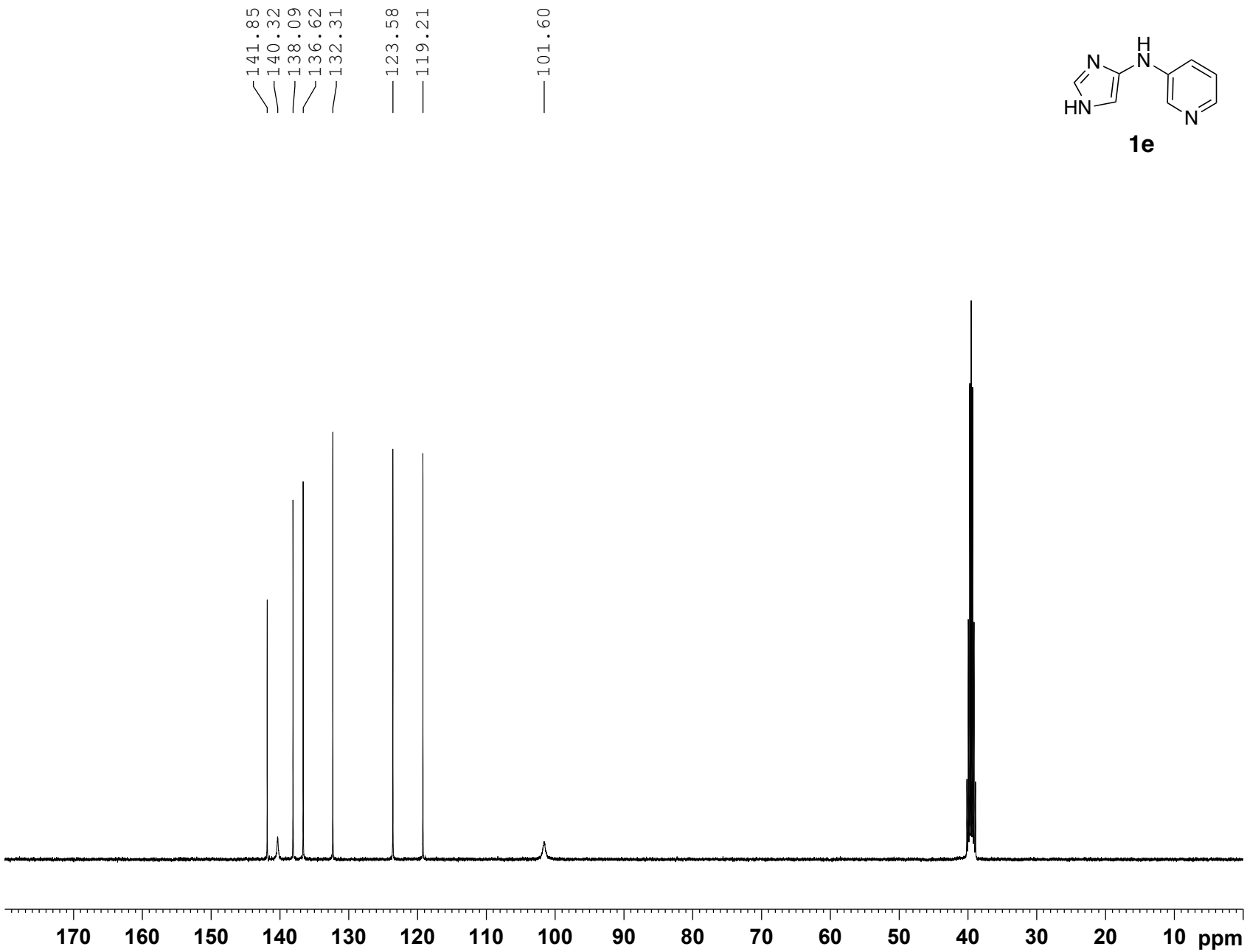
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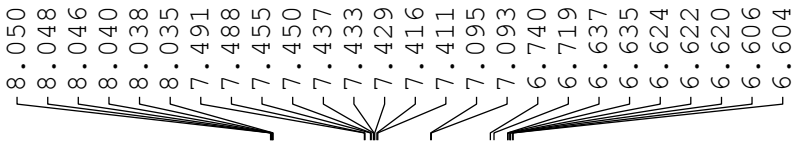
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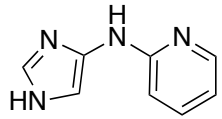
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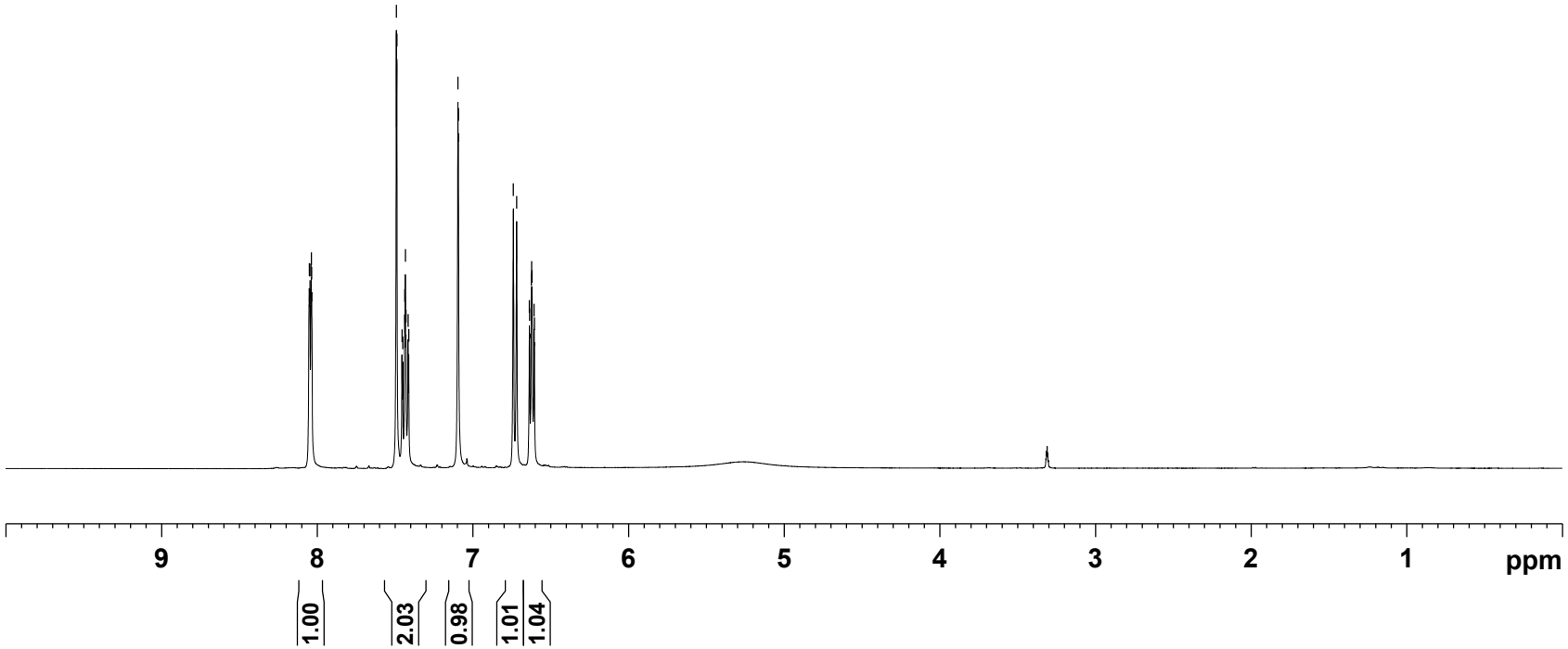
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3
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ppm
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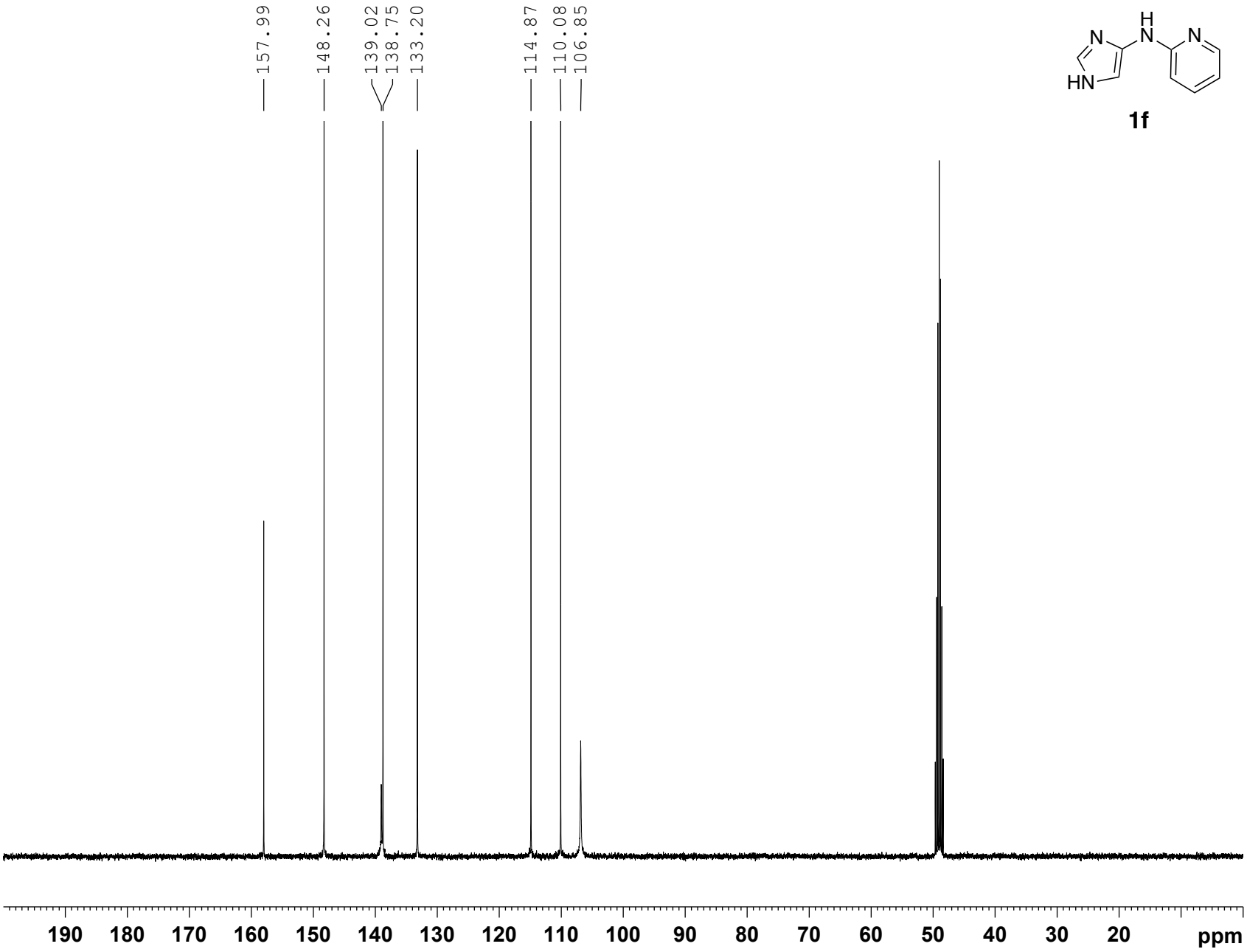
2.03
0.98
1.01
1.04


157.99
148.26
139.02
138.75
133.20
114.87
110.08
106.85
190
180
170
160
150
140
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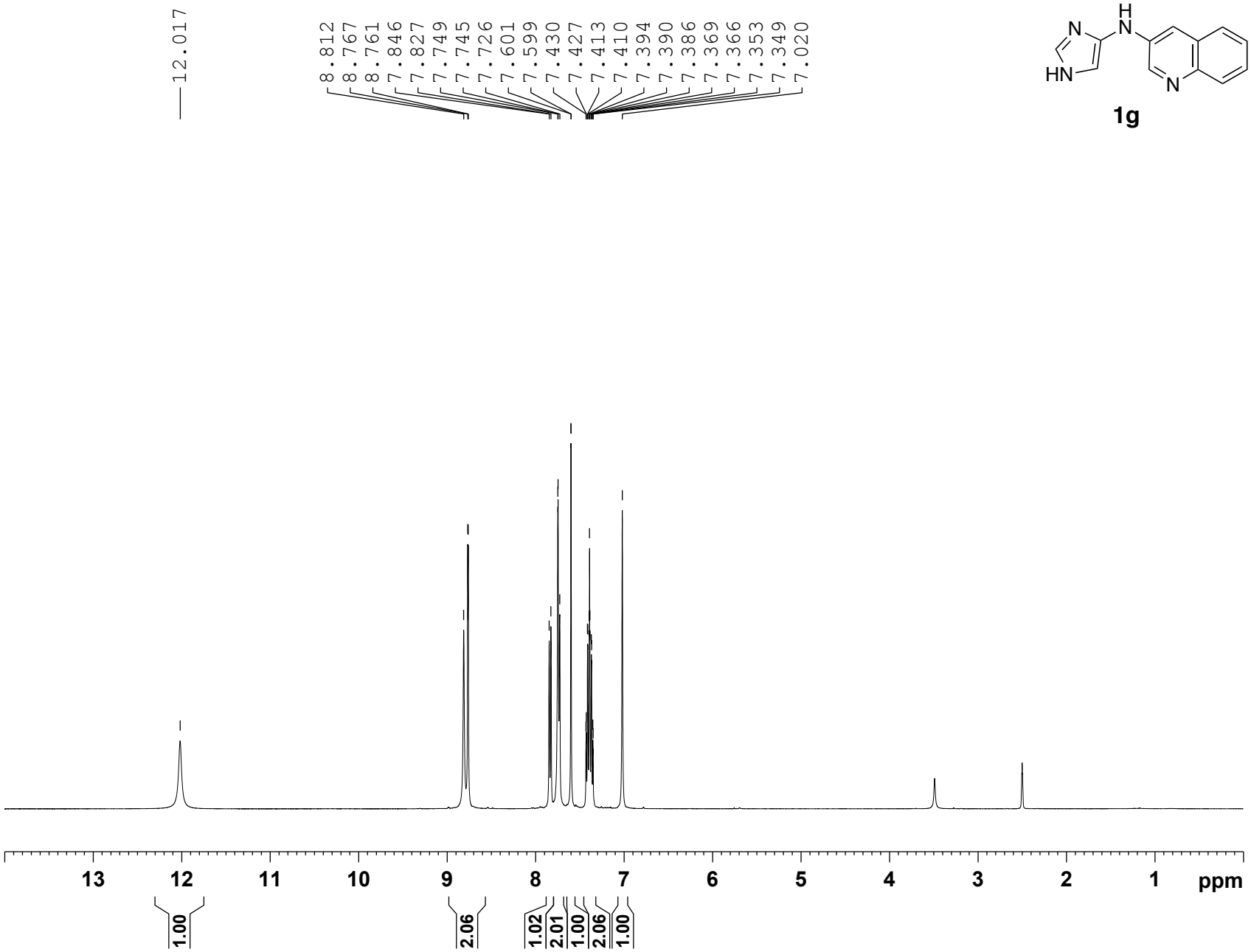
100
90
80
70
60
50
40
30
20
ppm

H
N
N
N
HN

1f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8.767
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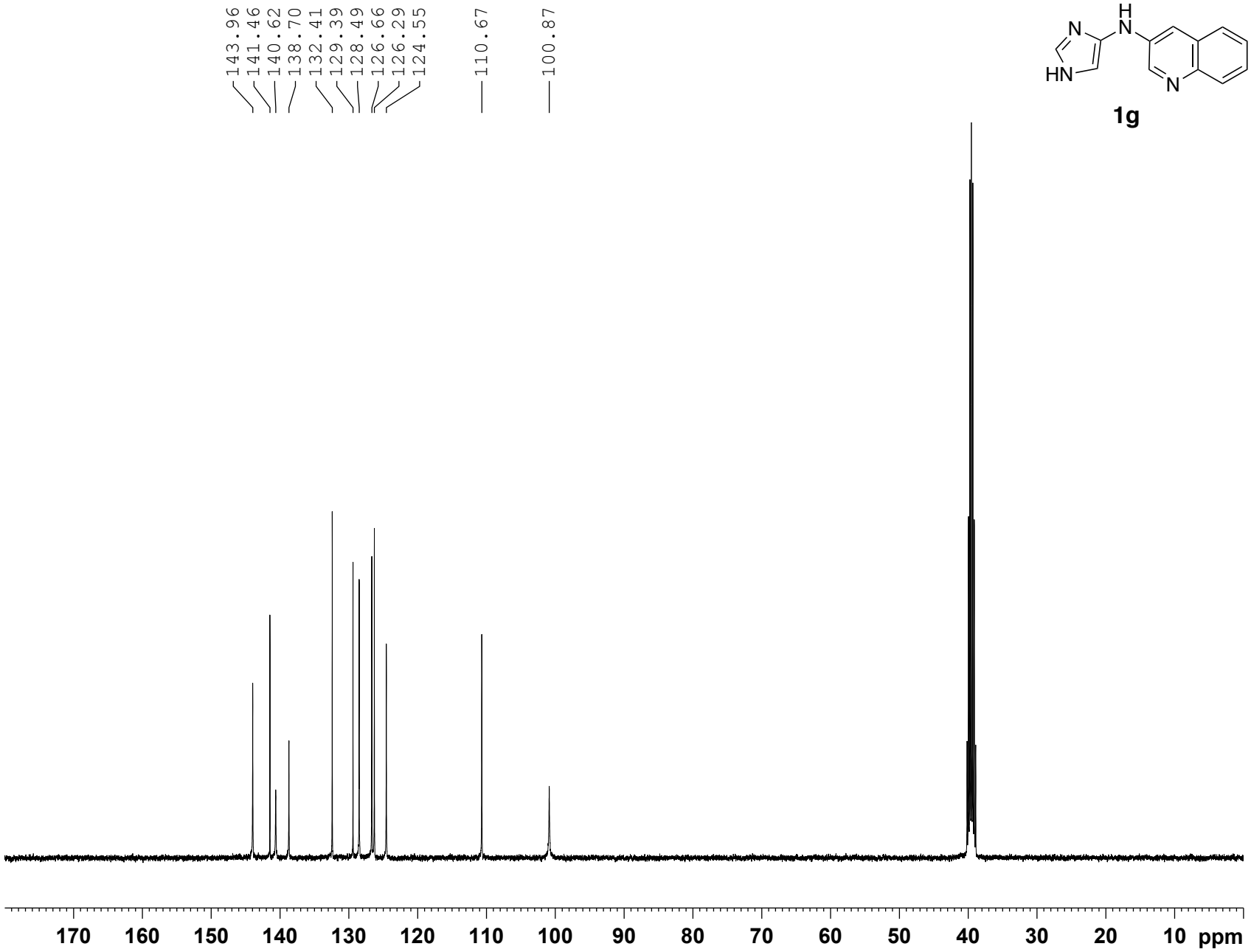
7.846
7.827
7.749
7.745
7.726
7.601
7.599
7.430
7.427
7.413
7.410
7.394
7.390
7.386
7.369
7.366
7.353
7.349
7.020
HN
N
H
N
N
1g
13
12
11
10
9
8
7
6
5
4
3
2
1
ppm
1.00
2.06
1.02
2.01
1.00
2.06
1.00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141.46
140.62
138.70
132.41
129.39
128.49
126.66
126.29
124.55
110.67
100.87
H
N
N
HN
N
1g
170
160
150
140
130
120
110
100
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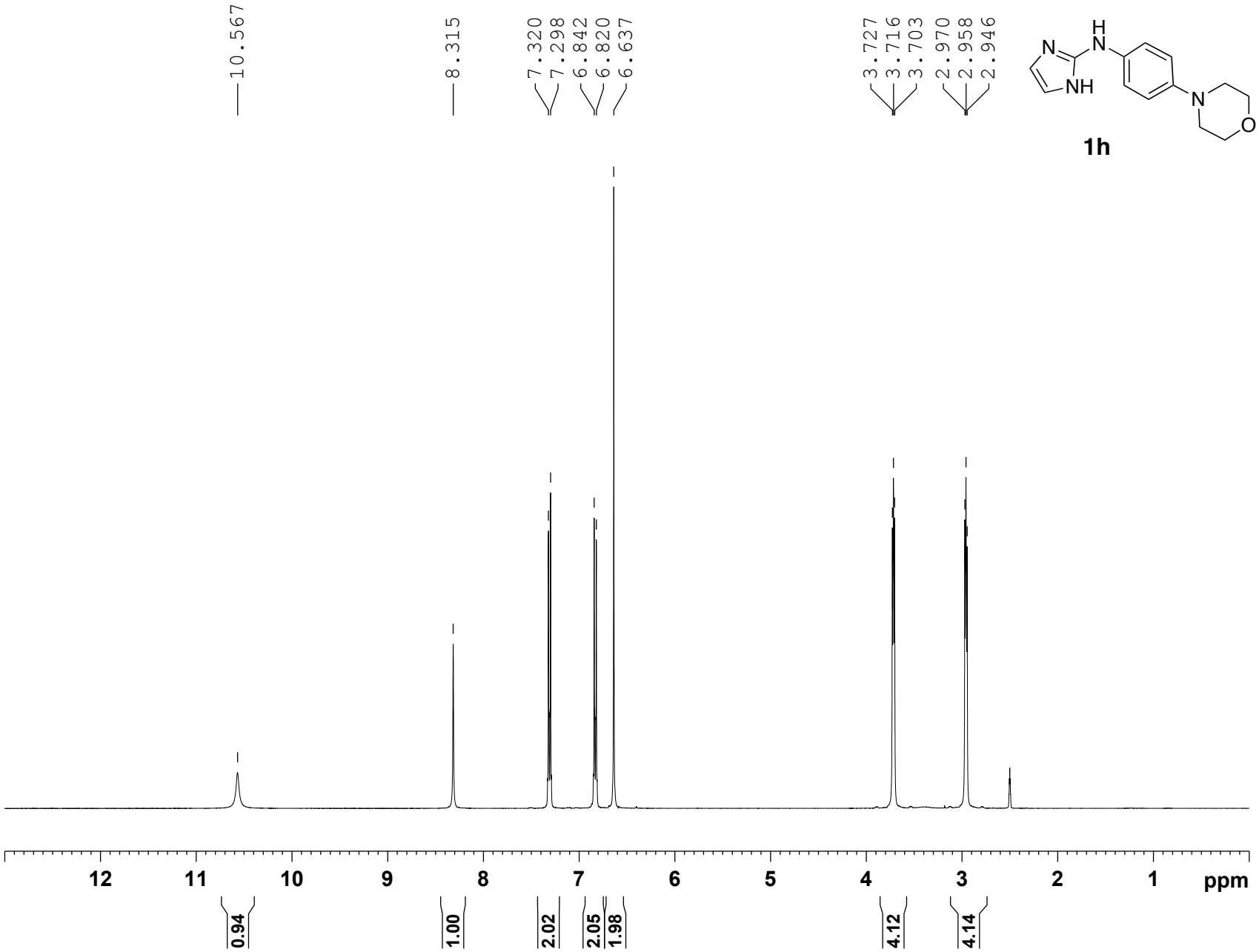
80
70
60
50
40
30
20
10
ppm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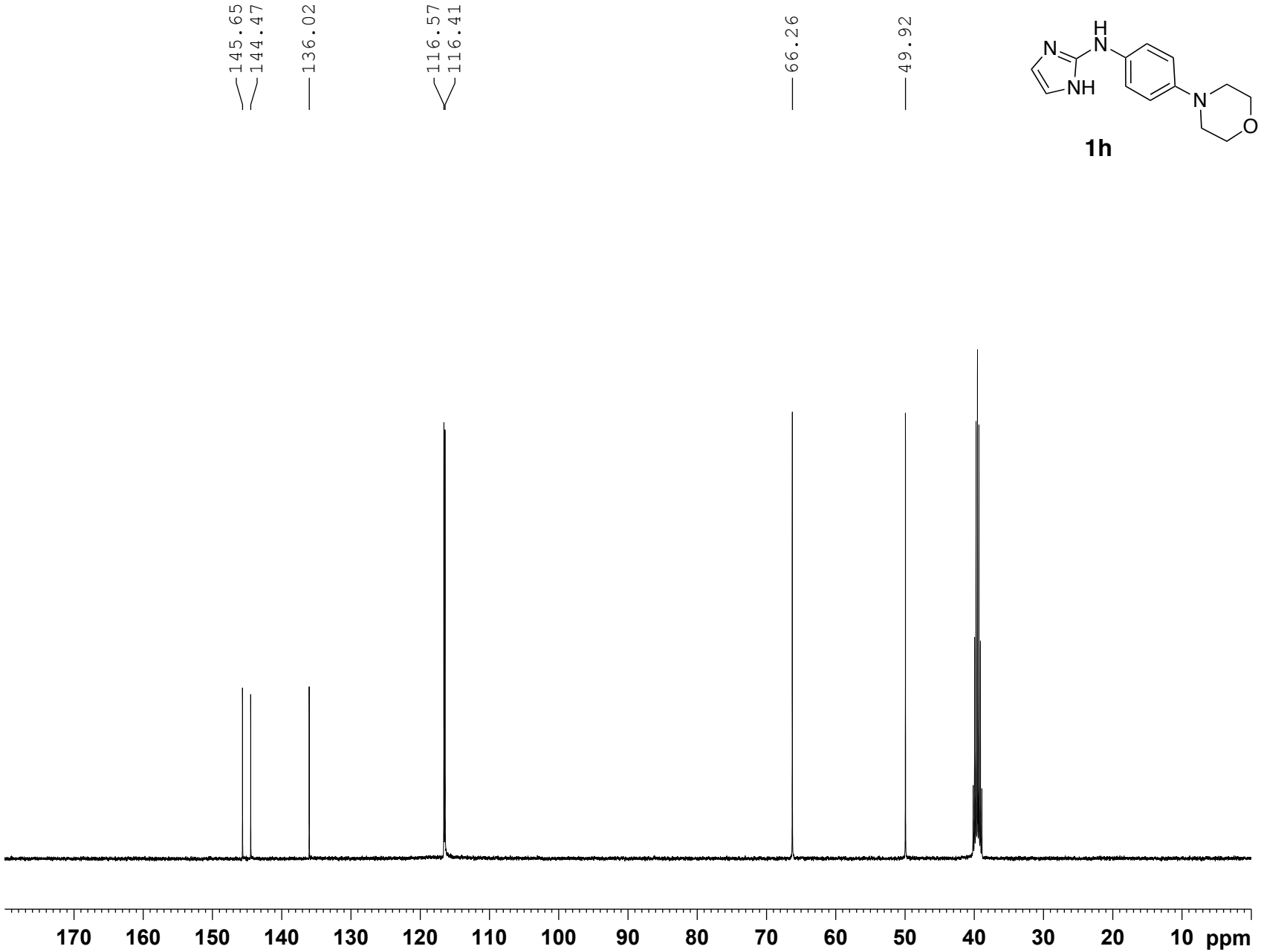
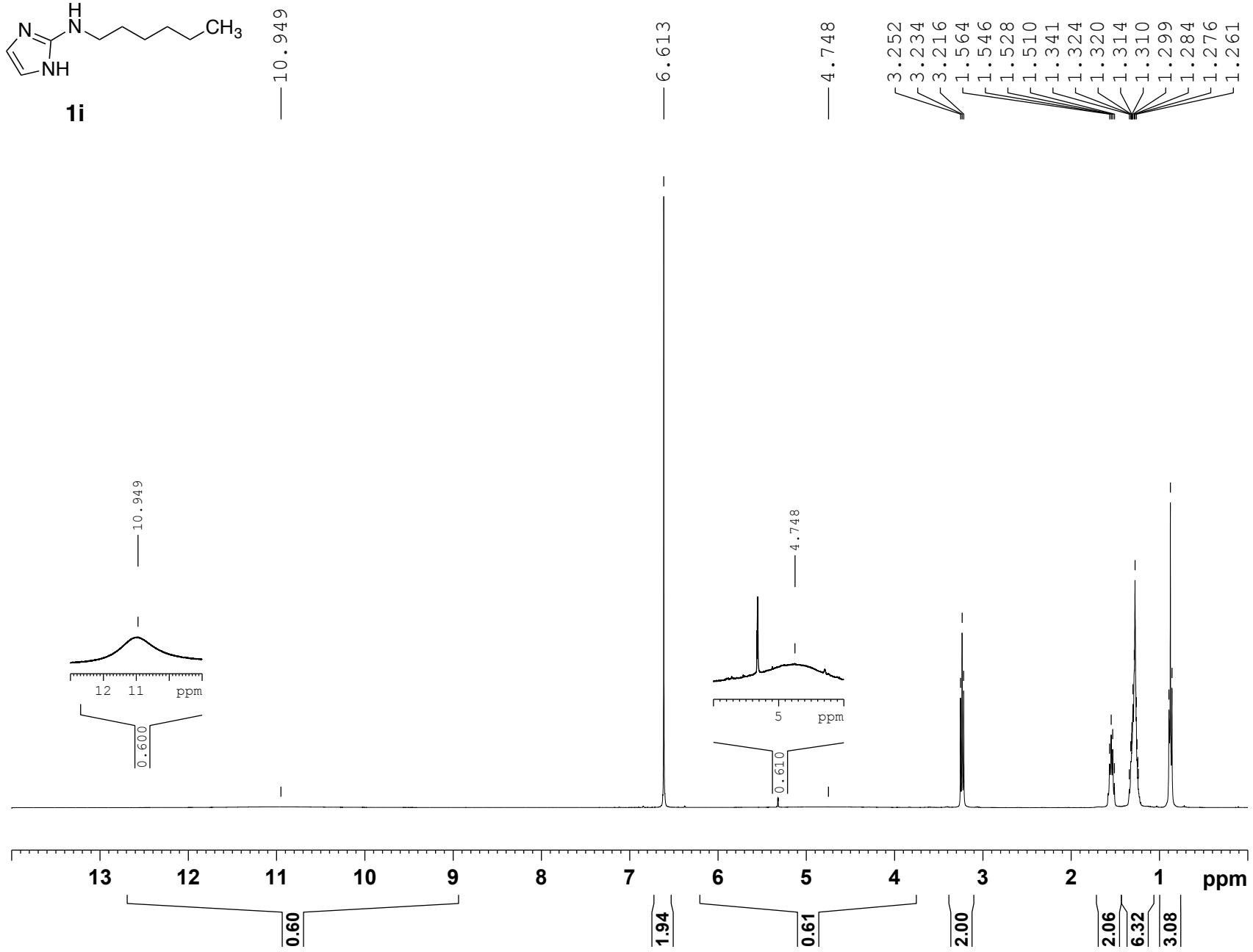
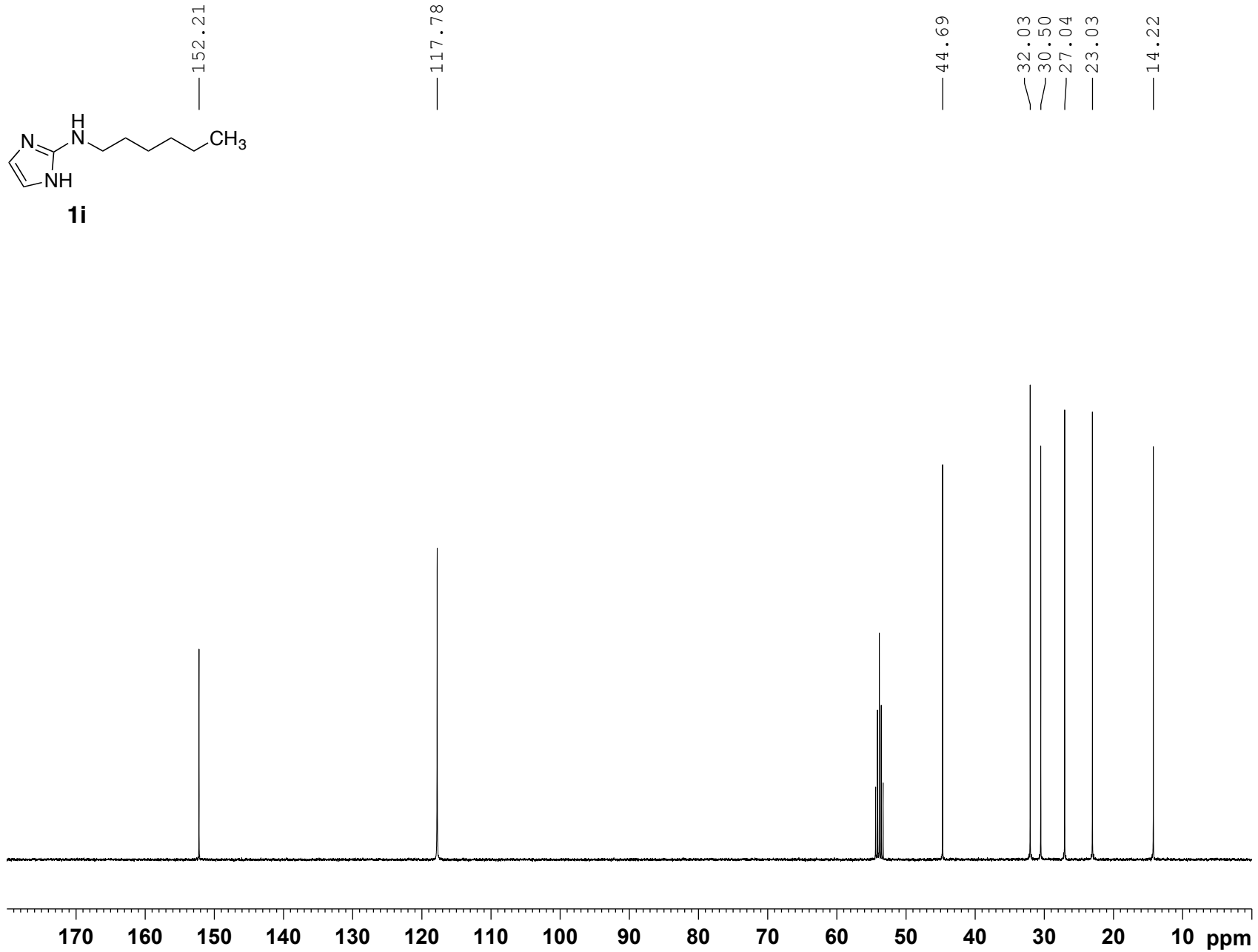
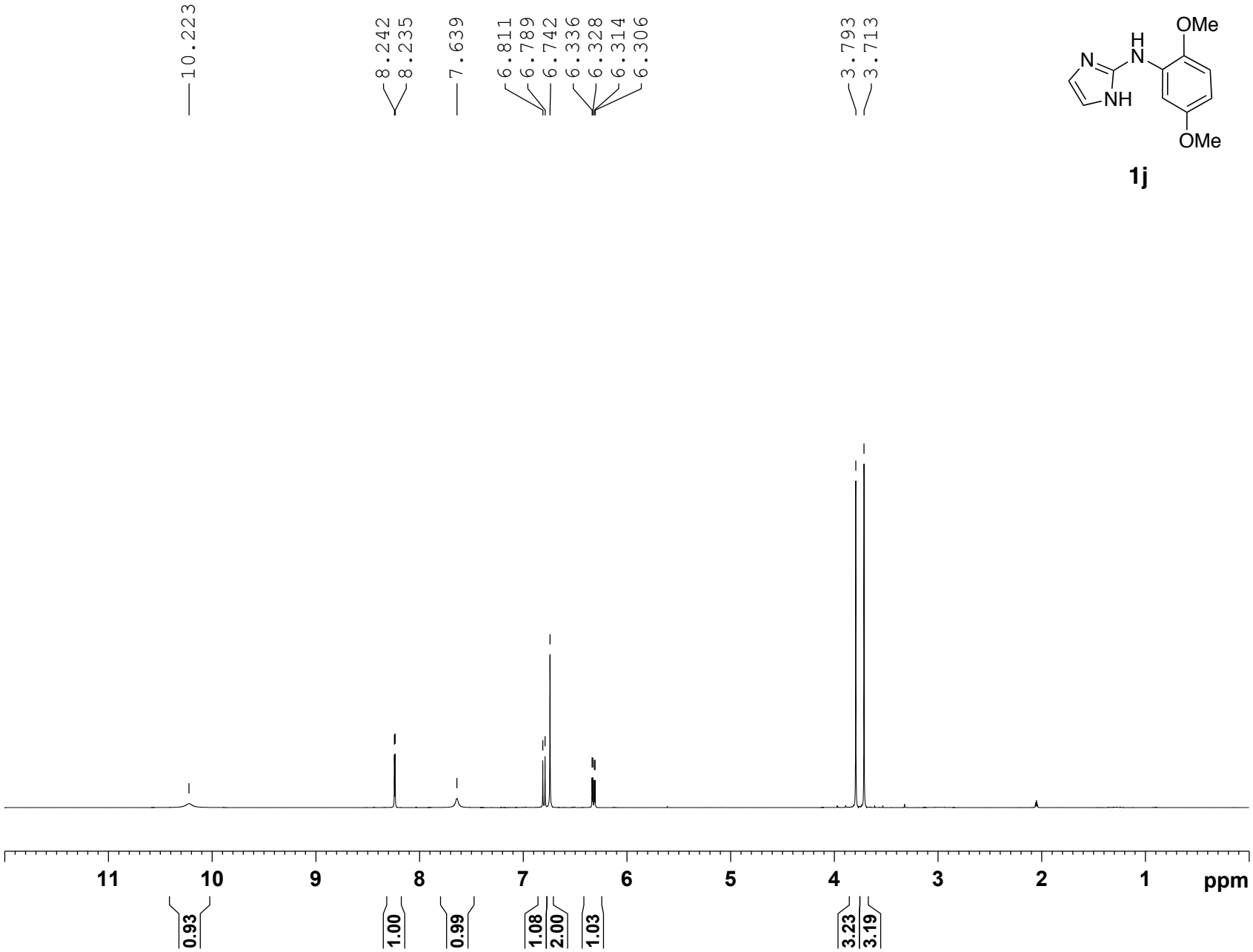
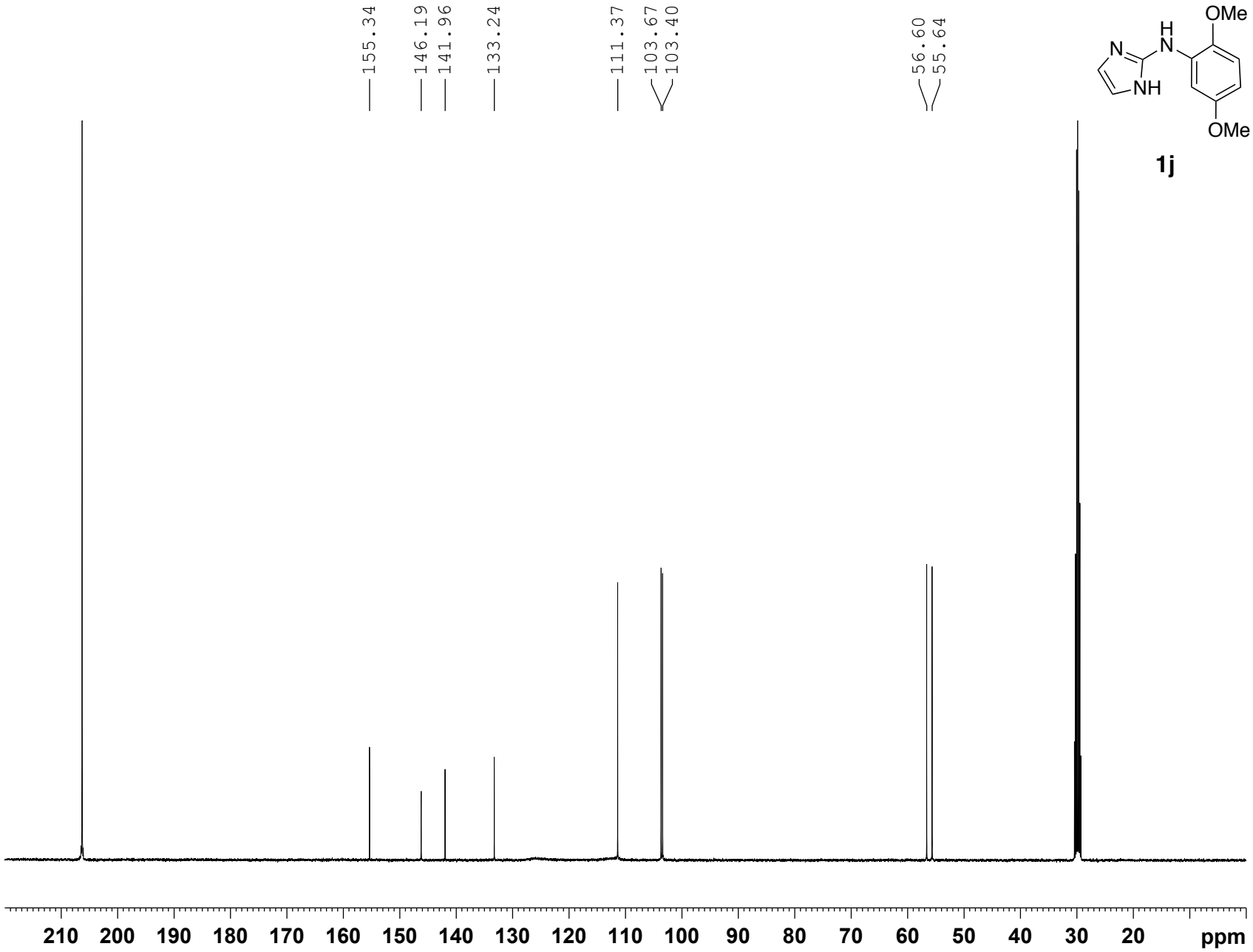
7.320
7.298
6.842
6.820
6.637
3.727
3.716
3.703
2.970
2.958
2.946
1h
12
11
10
9
8
7
6
5
4
3
2
1
ppm
0.94
1.00
2.02
2.05
1.98
4.12
4.14

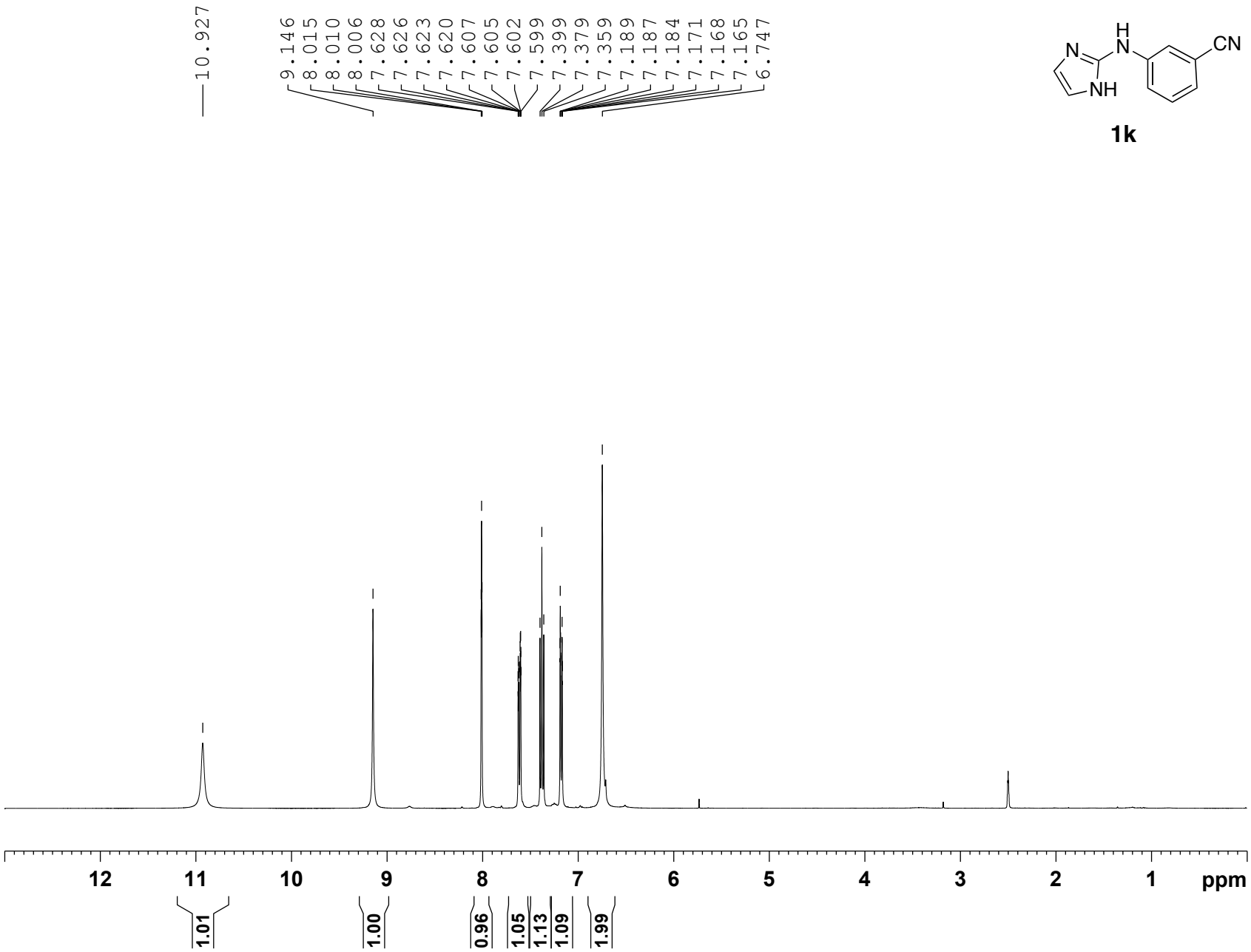

145.65
144.47
136.02
116.57
116.41
66.26
49.92
H
N
N
NH
N
O
1h
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

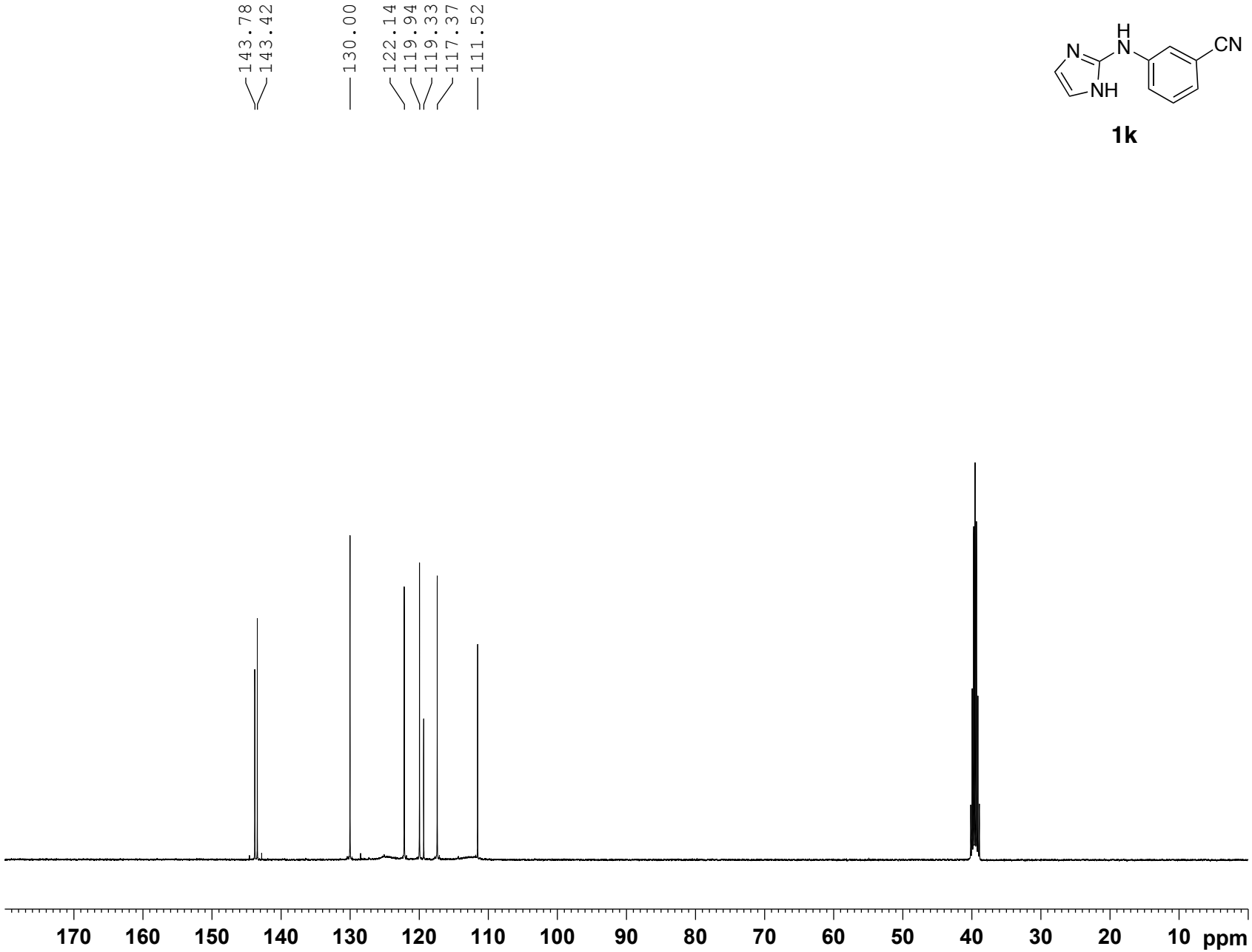

1i
10.949
6.613
4.748
3.252
3.234
3.216
1.564
1.546
1.528
1.510
1.341
1.324
1.320
1.314
1.310
1.299
1.284
1.276
1.261
12 11 ppm
0.600
5 ppm
0.610
13 12 11 10 9 8 7 6 5 4 3 2 1 ppm
0.60
1.94
0.61
2.00
2.06
6.32
3.08

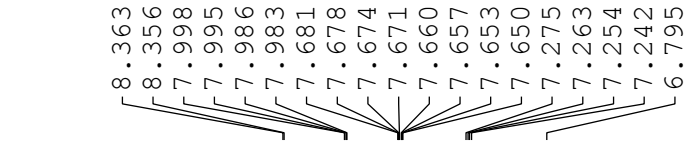

152.21
117.78
44.69
32.03
30.50
27.04
23.03
14.22
H
N
N
NH
CH3
1i
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

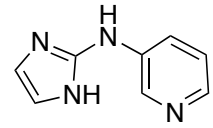

10.223
8.242
8.235
7.639
6.811
6.789
6.742
6.336
6.328
6.314
6.306
3.793
3.713
OMe
H
N
N
NH
OMe
1j
11
10
9
8
7
6
5
4
3
2
1
ppm
0.93
1.00
0.99
1.08
2.00
1.03
3.23
3.19


155.34
146.19
141.96
133.24
111.37
103.67
103.40
56.60
55.64
OMe
H
N
N
NH
OMe
1j
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm

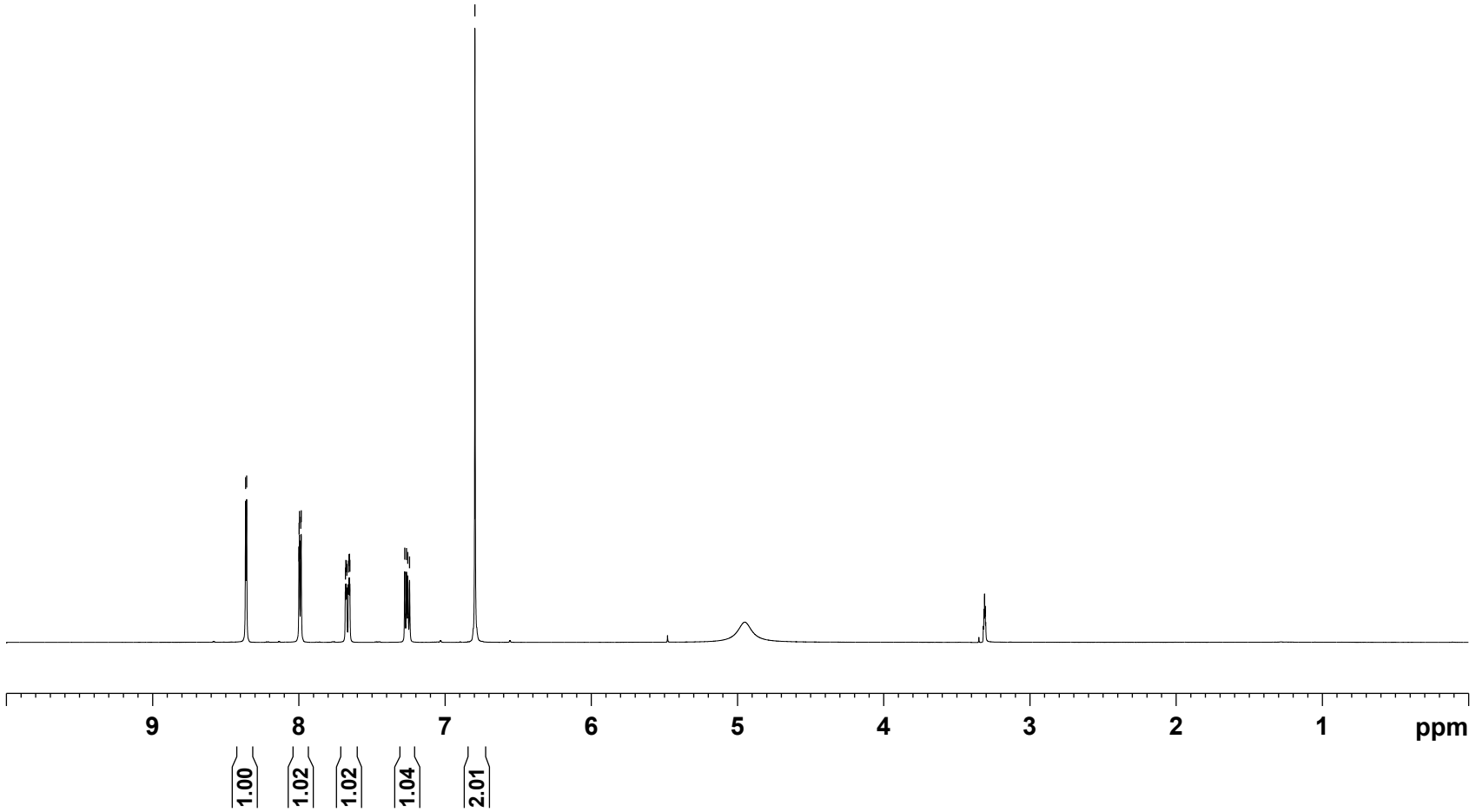

10.927
9.146
8.015
8.010
8.006
7.628
7.626
7.623
7.620
7.607
7.605
7.602
7.599
7.399
7.379
7.359
7.189
7.187
7.184
7.171
7.168
7.165
6.747
H
N
N
NH
CN
1k
12
11
10
9
8
7
6
5
4
3
2
1
ppm
1.01
1.00
0.96
1.05
1.13
1.09
1.99

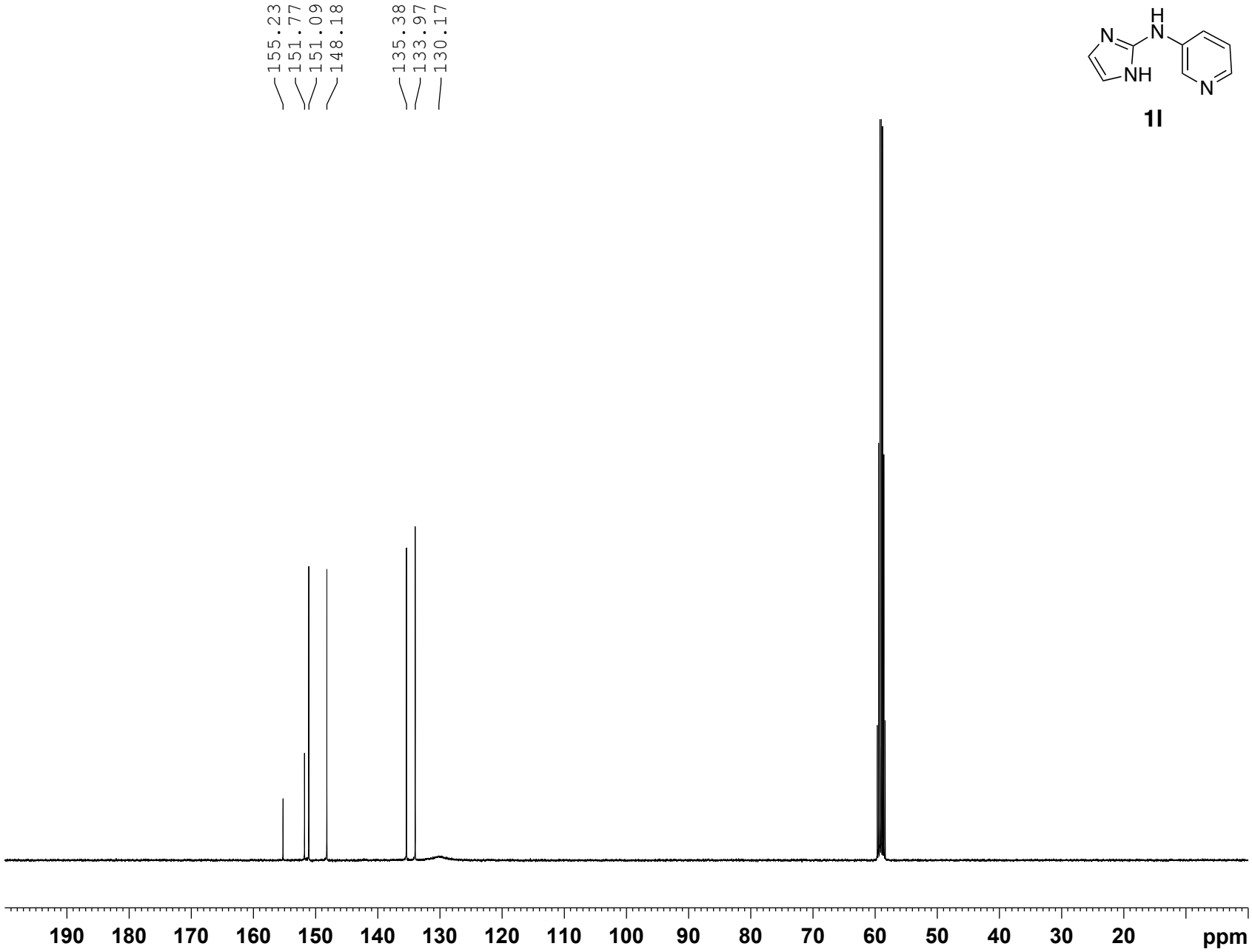

143.78
143.42
130.00
122.14
119.94
119.33
117.37
111.52
H
N
N
NH
CN
1k
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

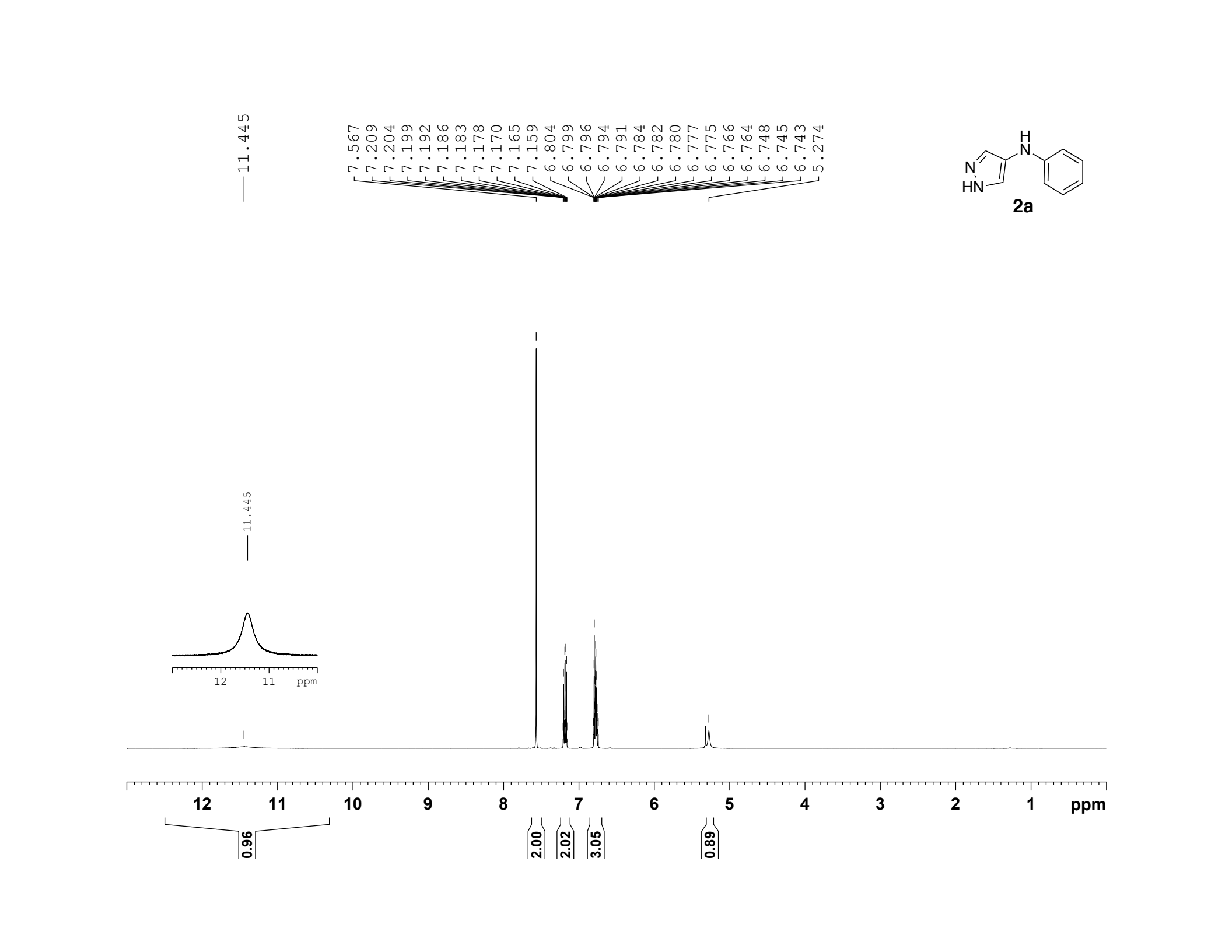

8.363
8.356
7.998
7.995
7.986
7.983
7.681
7.678
7.674
7.671
7.660
7.657
7.653
7.650
7.275
7.263
7.254
7.242
6.795

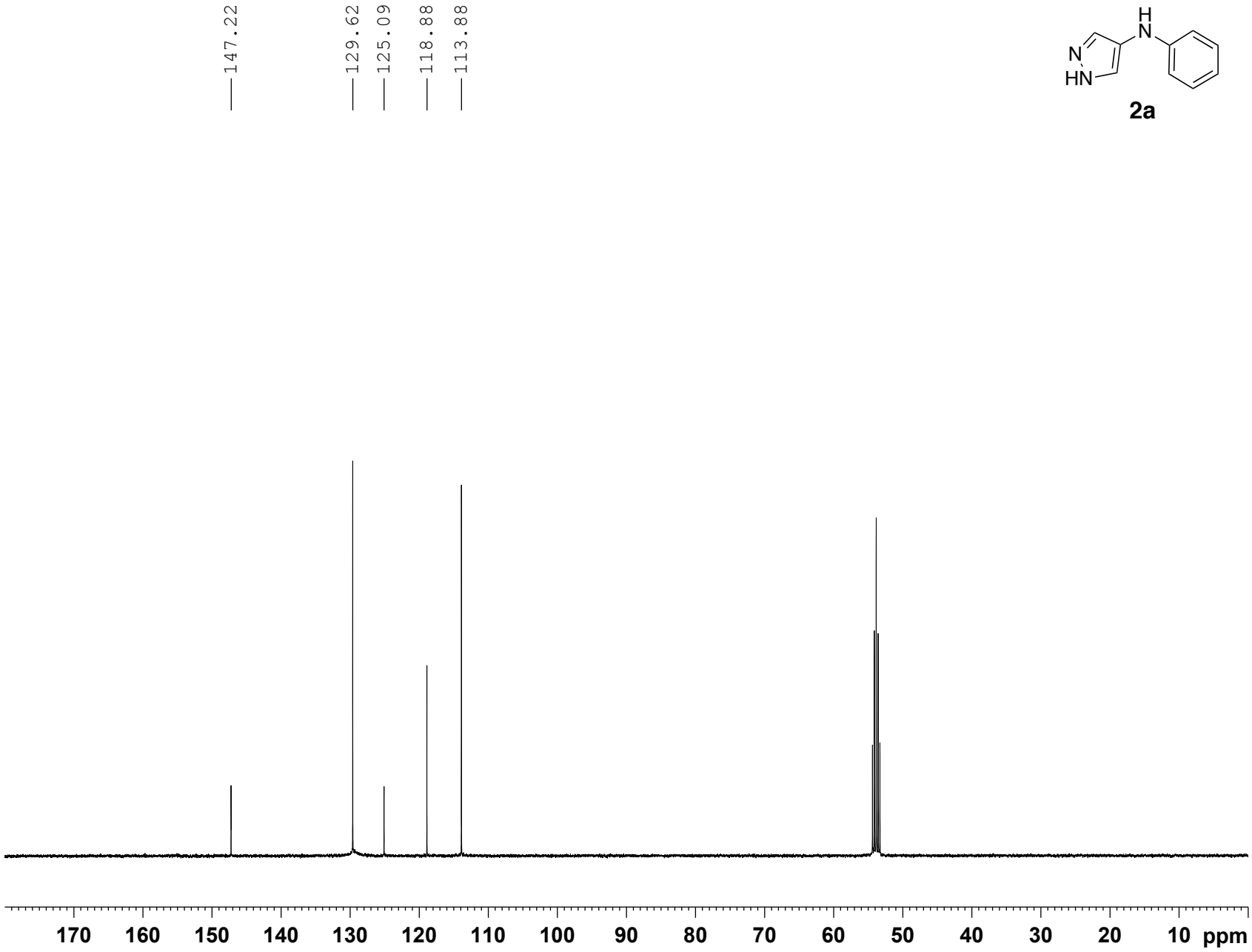

H
N
N
NH
N

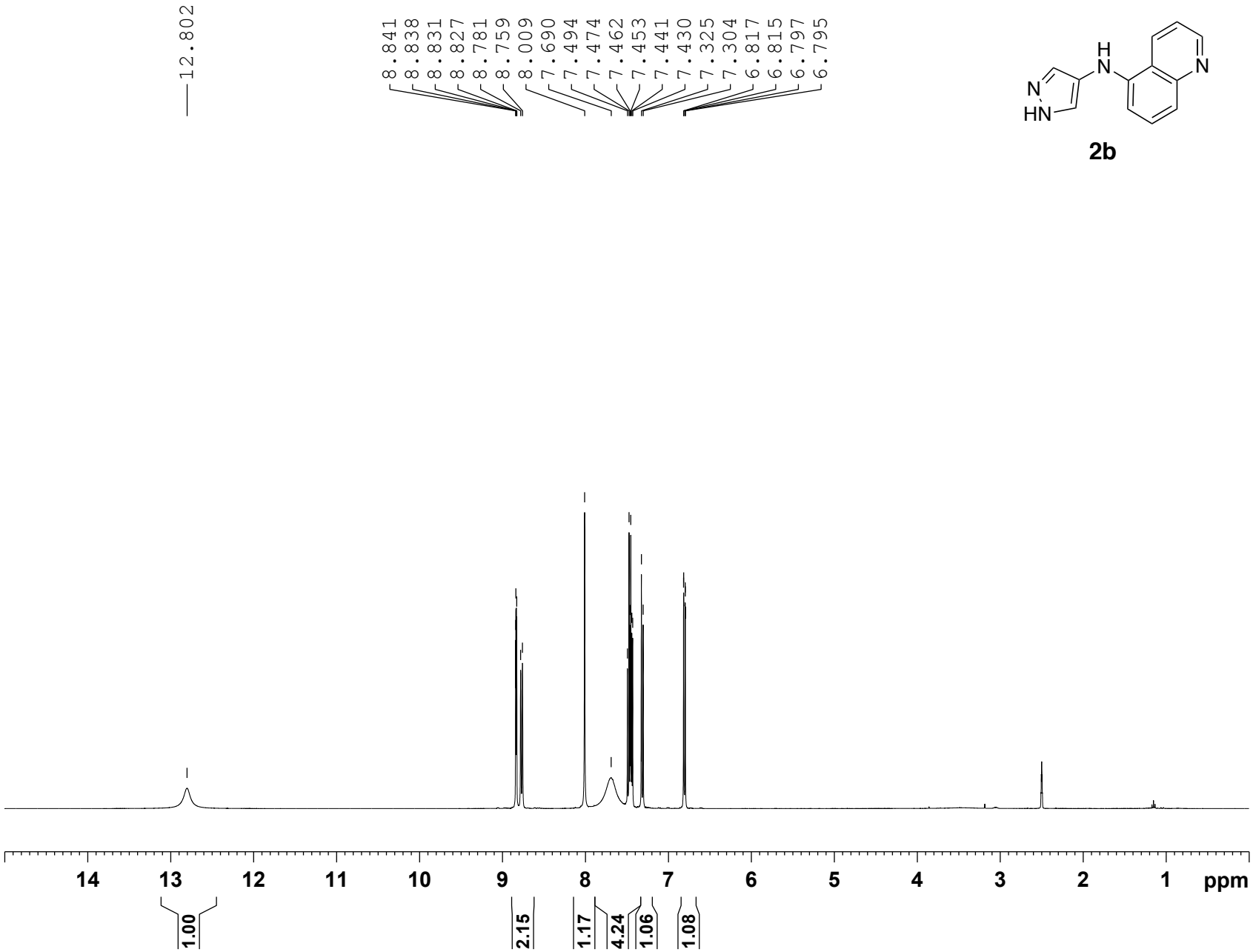
1l


9
8
7
6
5
4
3
2
1
ppm
1.00
1.02
1.02
1.04
2.01


155.23
151.77
151.09
148.18
135.38
133.97
130.17
H
N
N
NH
N
1l
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm


11.445
7.567
7.209
7.204
7.199
7.192
7.186
7.183
7.178
7.170
7.165
7.159
6.804
6.799
6.796
6.794
6.791
6.784
6.782
6.780
6.777
6.775
6.766
6.764
6.748
6.745
6.743
5.274
H
N
N
HN
2a
11.445
12
11
ppm
12
11
10
9
8
7
6
5
4
3
2
1
ppm
0.96
2.00
2.02
3.05
0.89


147.22
129.62
125.09
118.88
113.88
H
N
N
HN
2a
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm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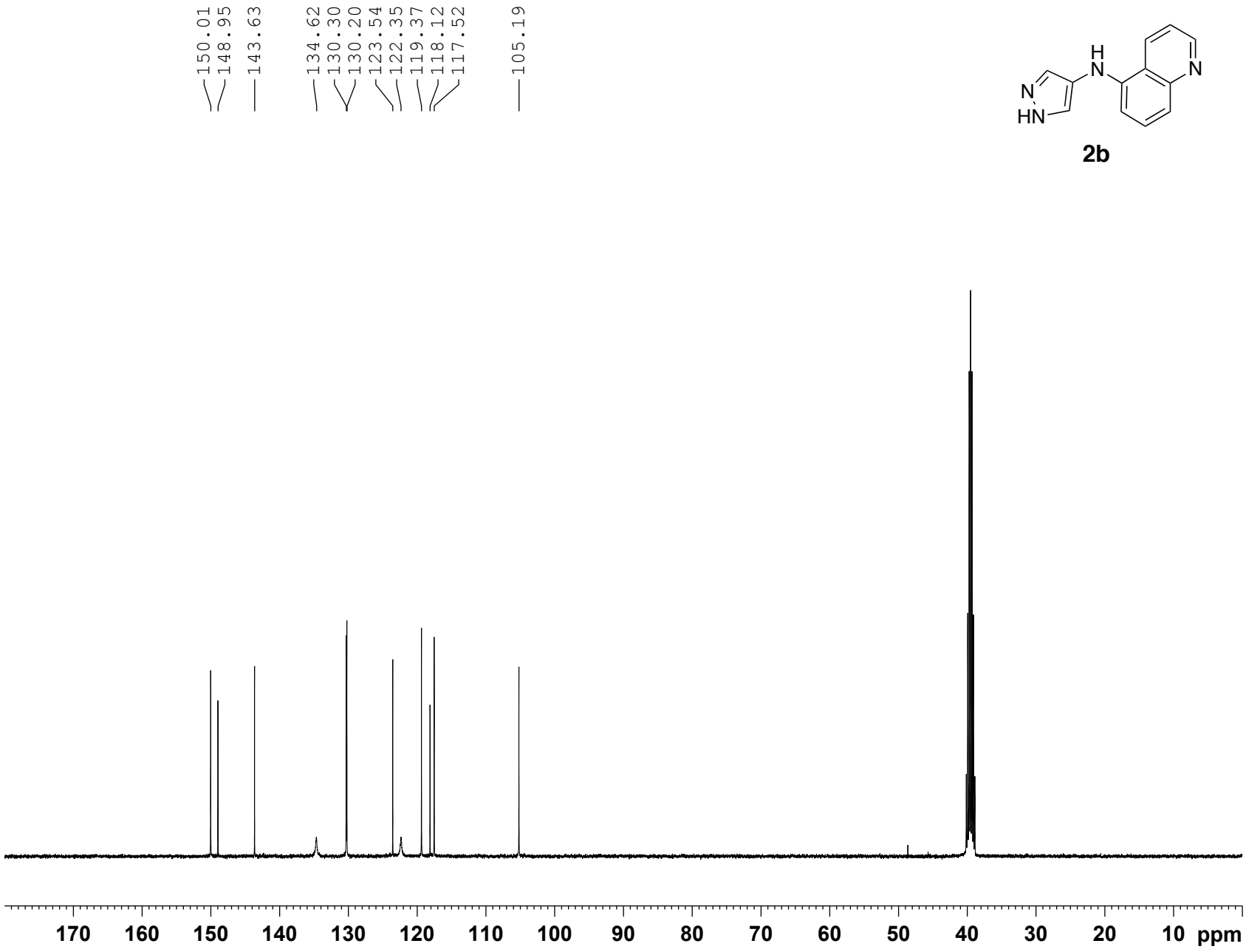
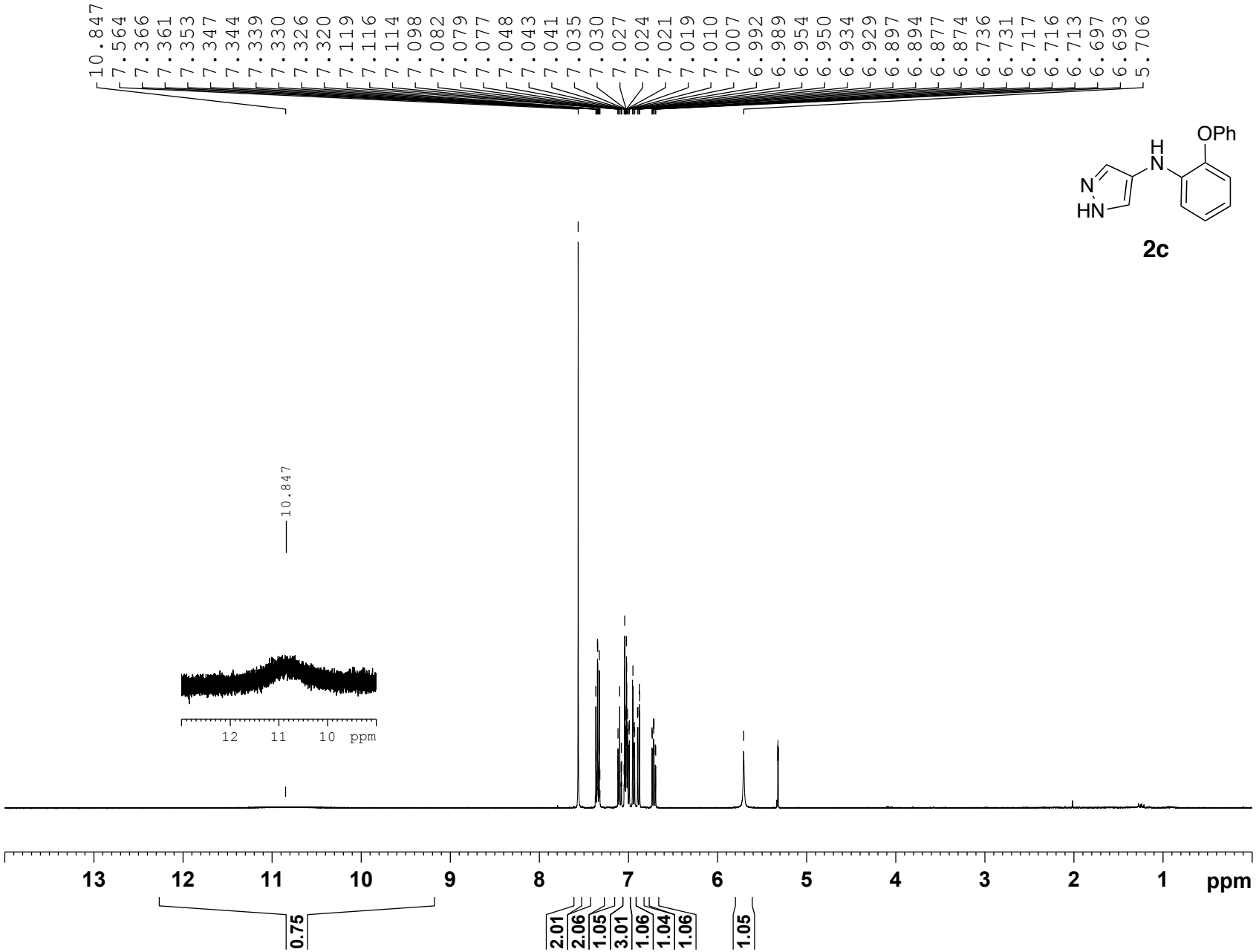
8.838
8.831
8.827
8.781
8.759
8.009
7.690
7.494
7.474
7.462
7.453
7.441
7.430
7.325
7.304
6.817
6.815
6.797
6.795
H
N
N
N
HN
2b
14
13
12
11
10
9
8
7
6
5
4
3
2
1
ppm
1.00
2.15
1.17
4.24
1.06
1.08


150.01
148.95
143.63
134.62
130.30
130.20
123.54
122.35
119.37
118.12
117.52
105.19
H
N
N
N
HN
2b
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm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7.366
7.361
7.353
7.347
7.344
7.339
7.330
7.326
7.320
7.119
7.116
7.114
7.098
7.082
7.079
7.077
7.048
7.043
7.041
7.035
7.030
7.027
7.024
7.021
7.019
7.010
7.007
6.992
6.989
6.954
6.950
6.934
6.929
6.897
6.894
6.877
6.874
6.736
6.731
6.717
6.716
6.713
6.697
6.693
5.706
OPh
H
N
N
HN
2c
10.847
12
11
10 ppm
13
12
11
10
9
8
7
6
5
4
3
2
1
ppm
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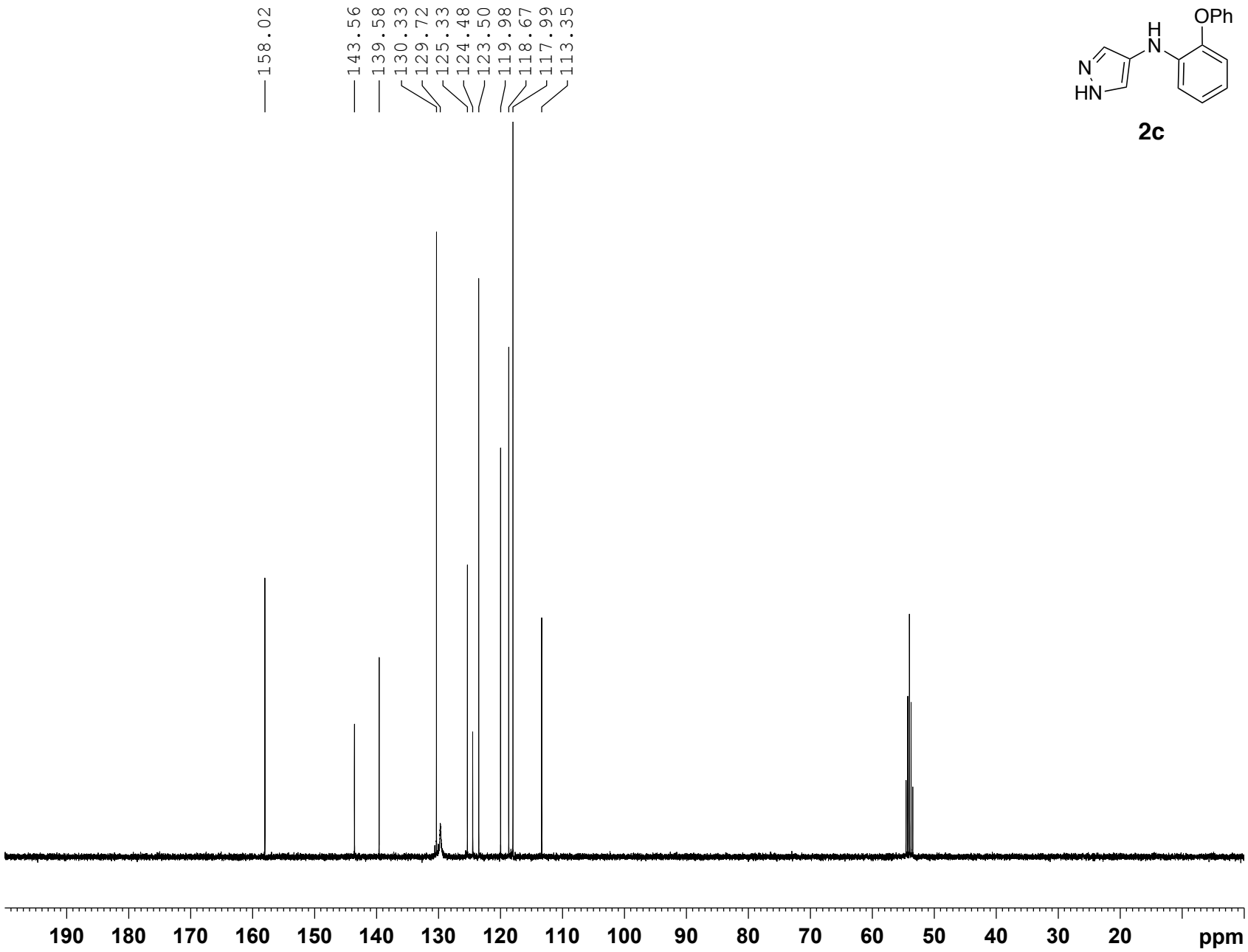
2.06
1.05
3.01
1.06
1.04
1.06
1.05


158.02
143.56
139.58
130.33
129.72
125.33
124.48
123.50
119.98
118.67
117.99
113.35
OPh
H
N
N
HN
2c
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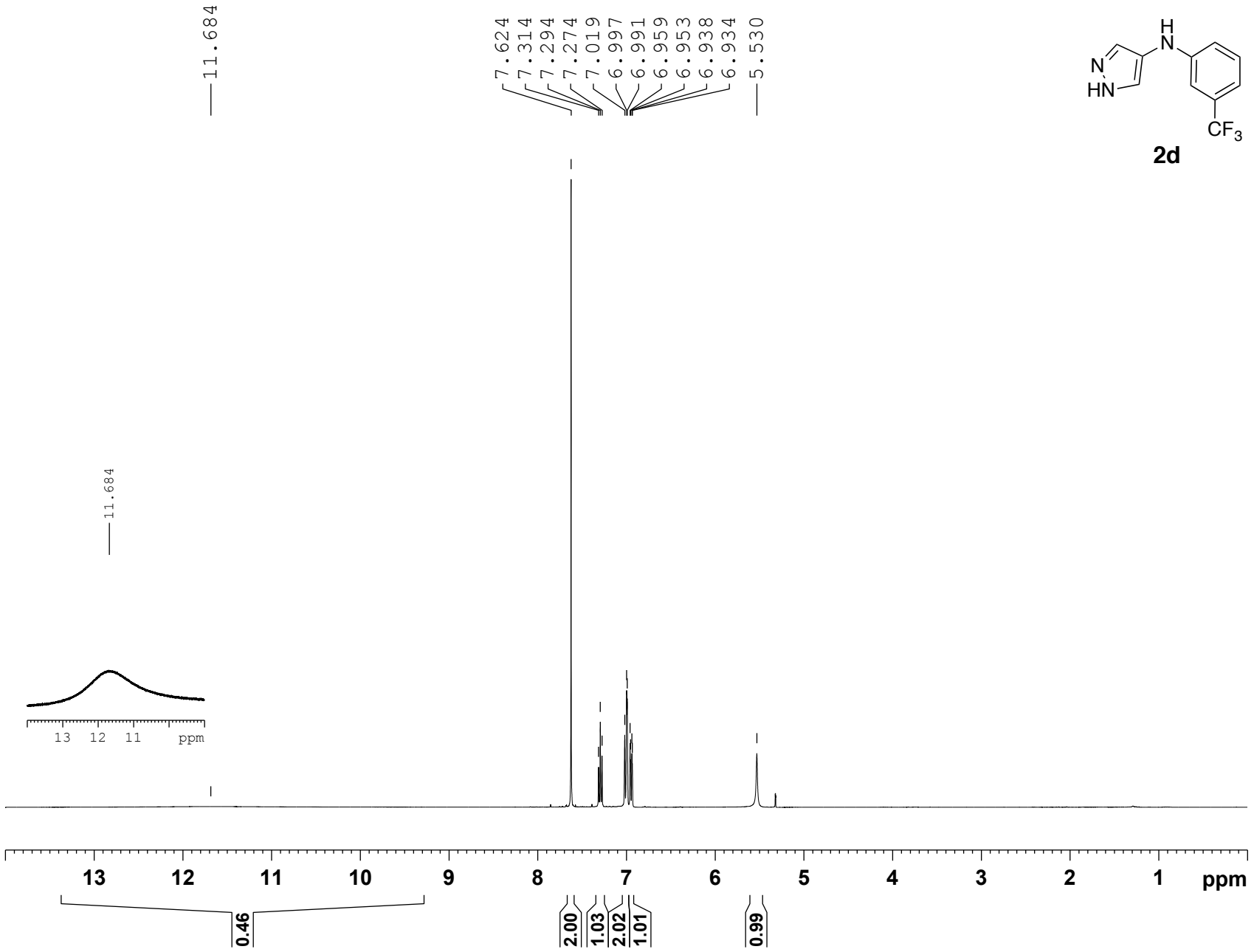
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm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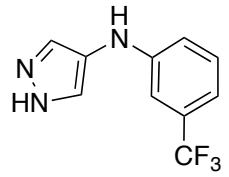
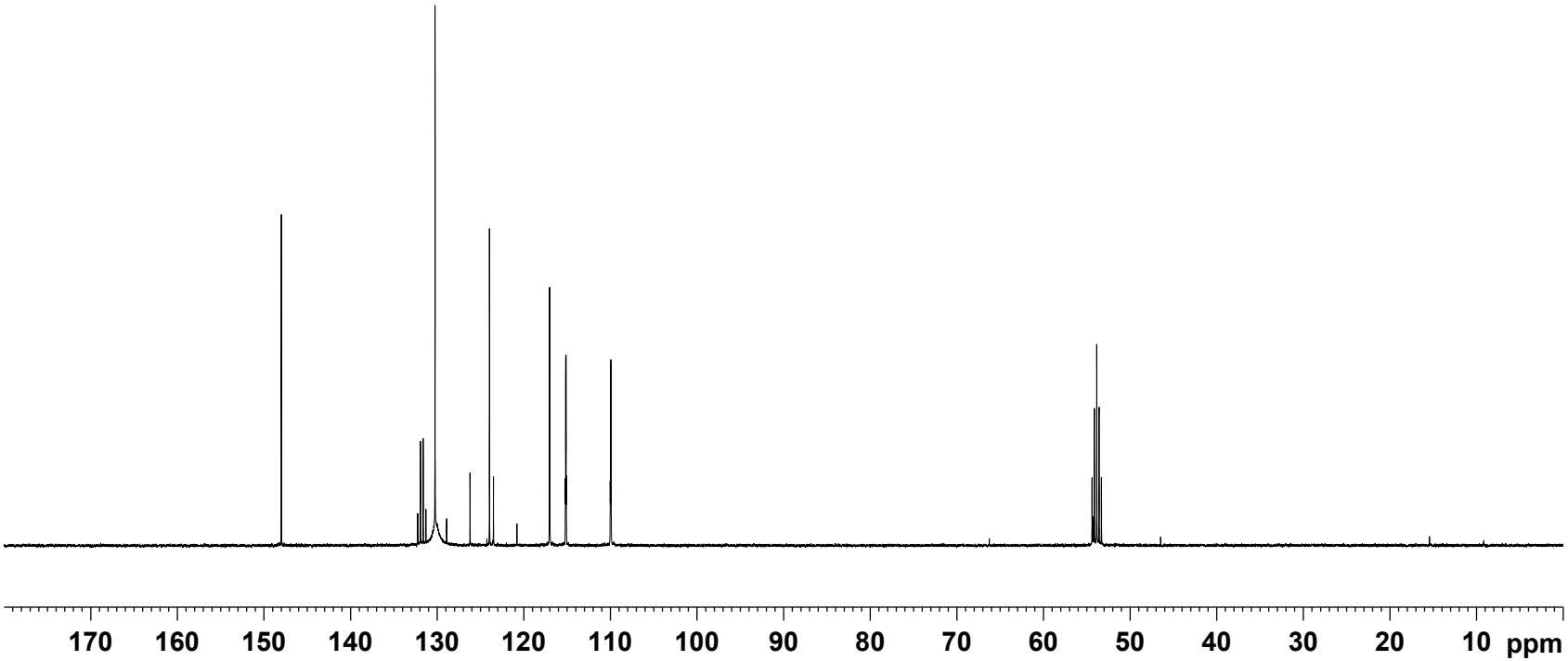
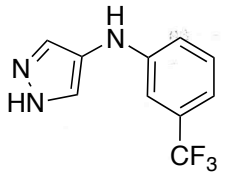
7.624
7.314
7.294
7.274
7.019
6.997
6.991
6.959
6.953
6.938
6.934
5.530
H
N
N
HN
CF3
2d
11.684
13 12 11 ppm
13 12 11 10 9 8 7 6 5 4 3 2 1 ppm
0.46
2.00
1.03
2.02
1.01
0.99

147.97
132.24
131.92
131.61
131.29
130.24
128.90
126.20
123.95
123.49
120.79
117.02
117.01
115.19
115.15
115.12
115.08
110.02
109.98
109.94
109.90

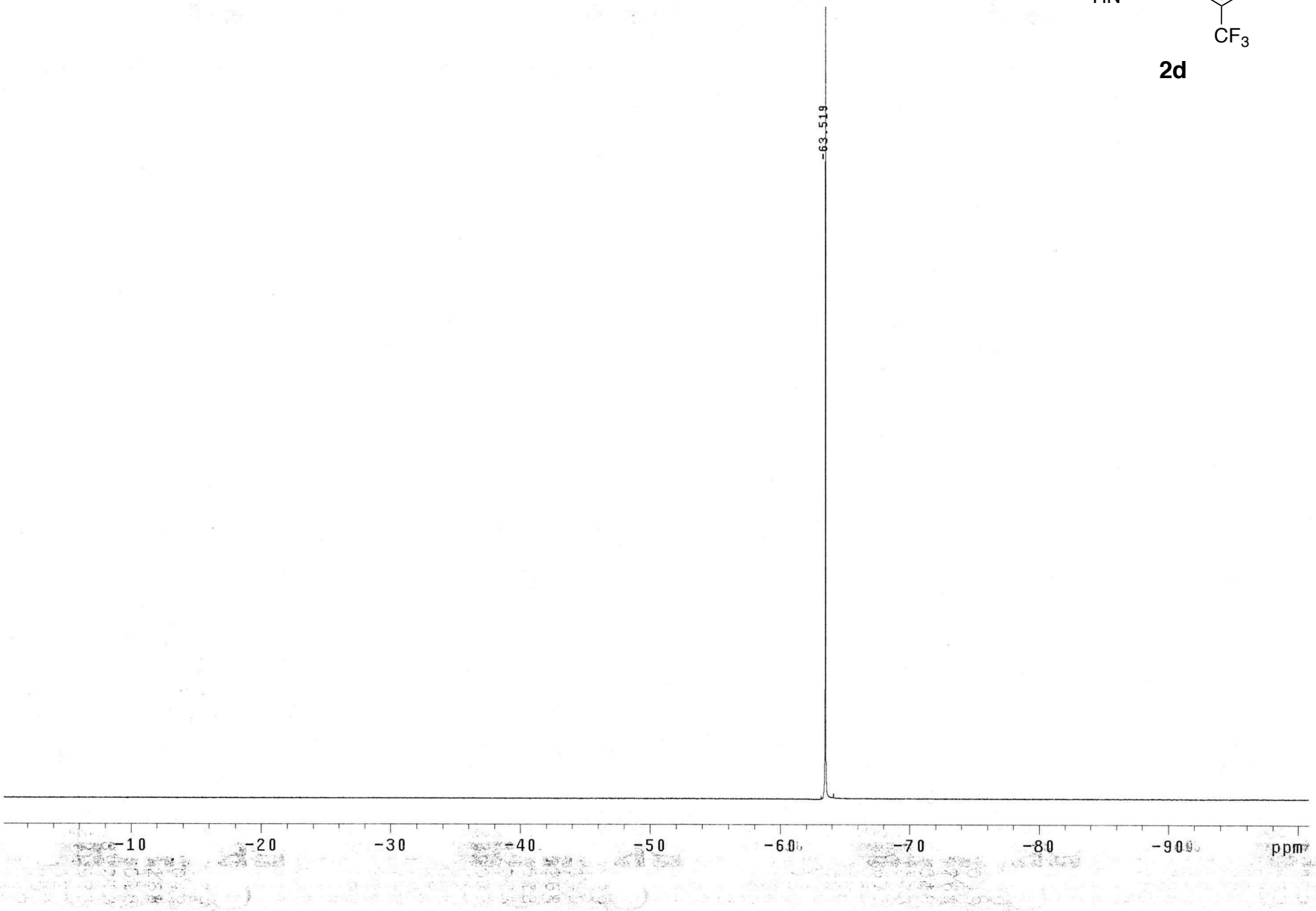


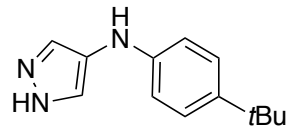
2d





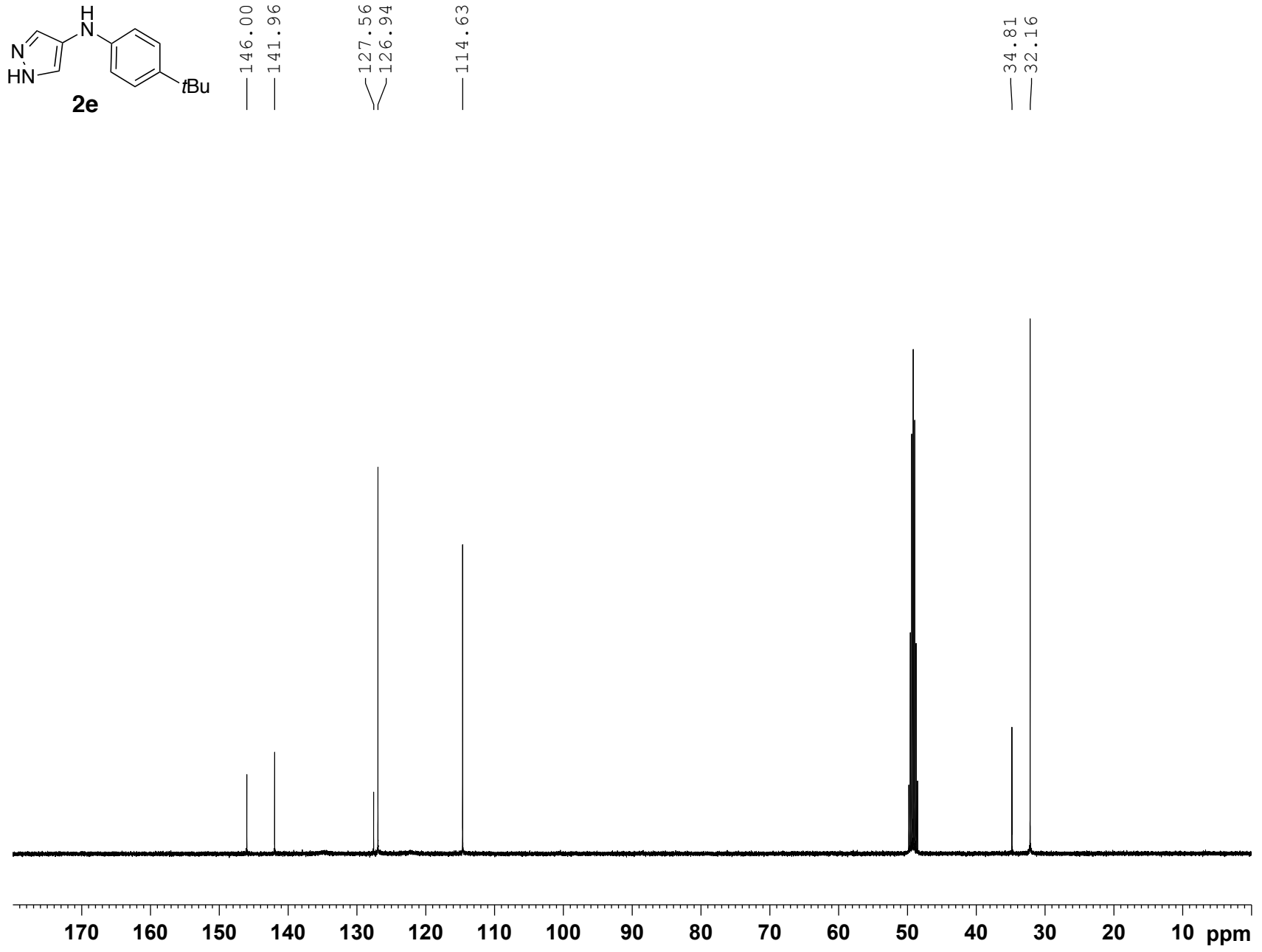
2d

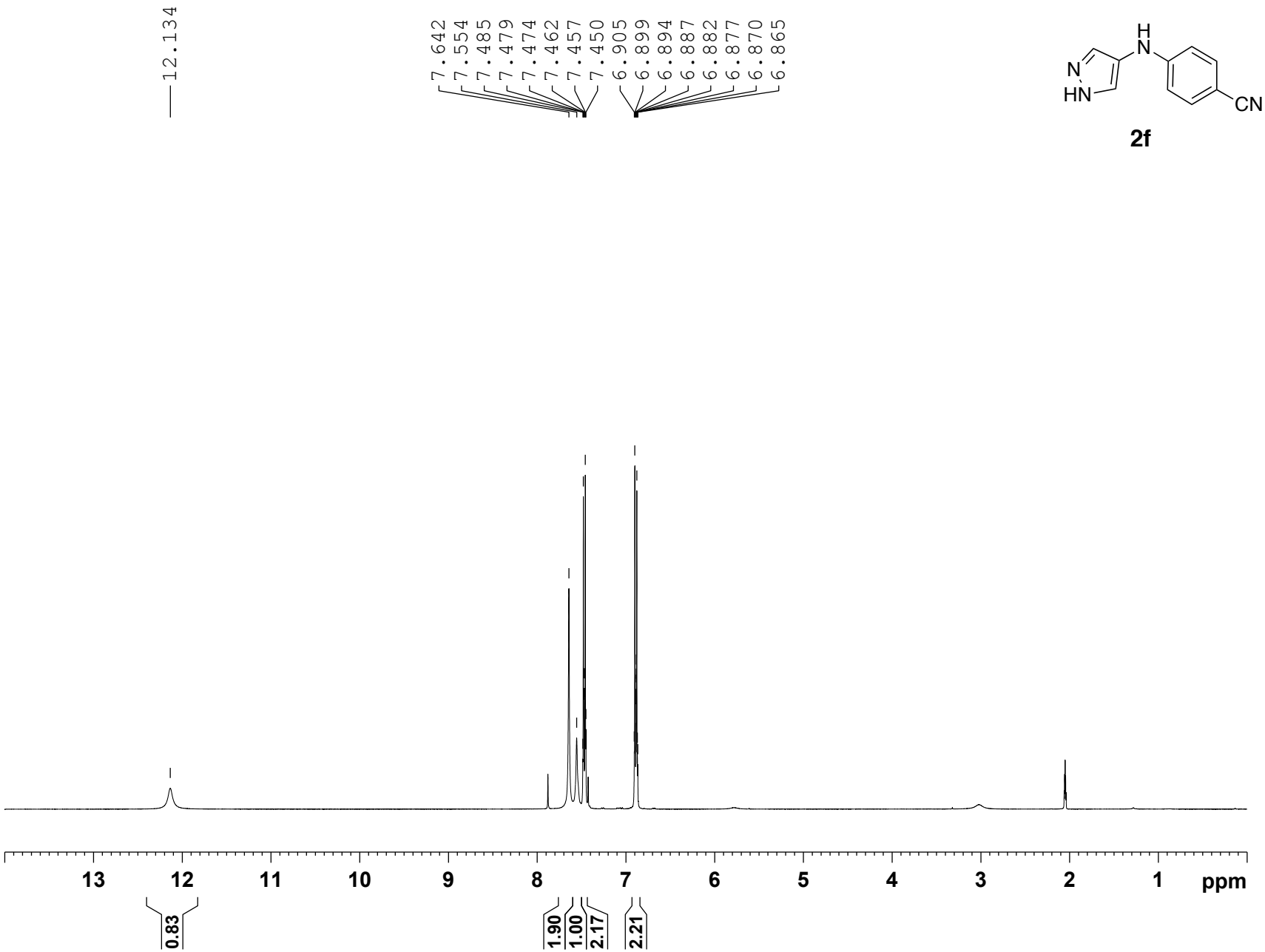


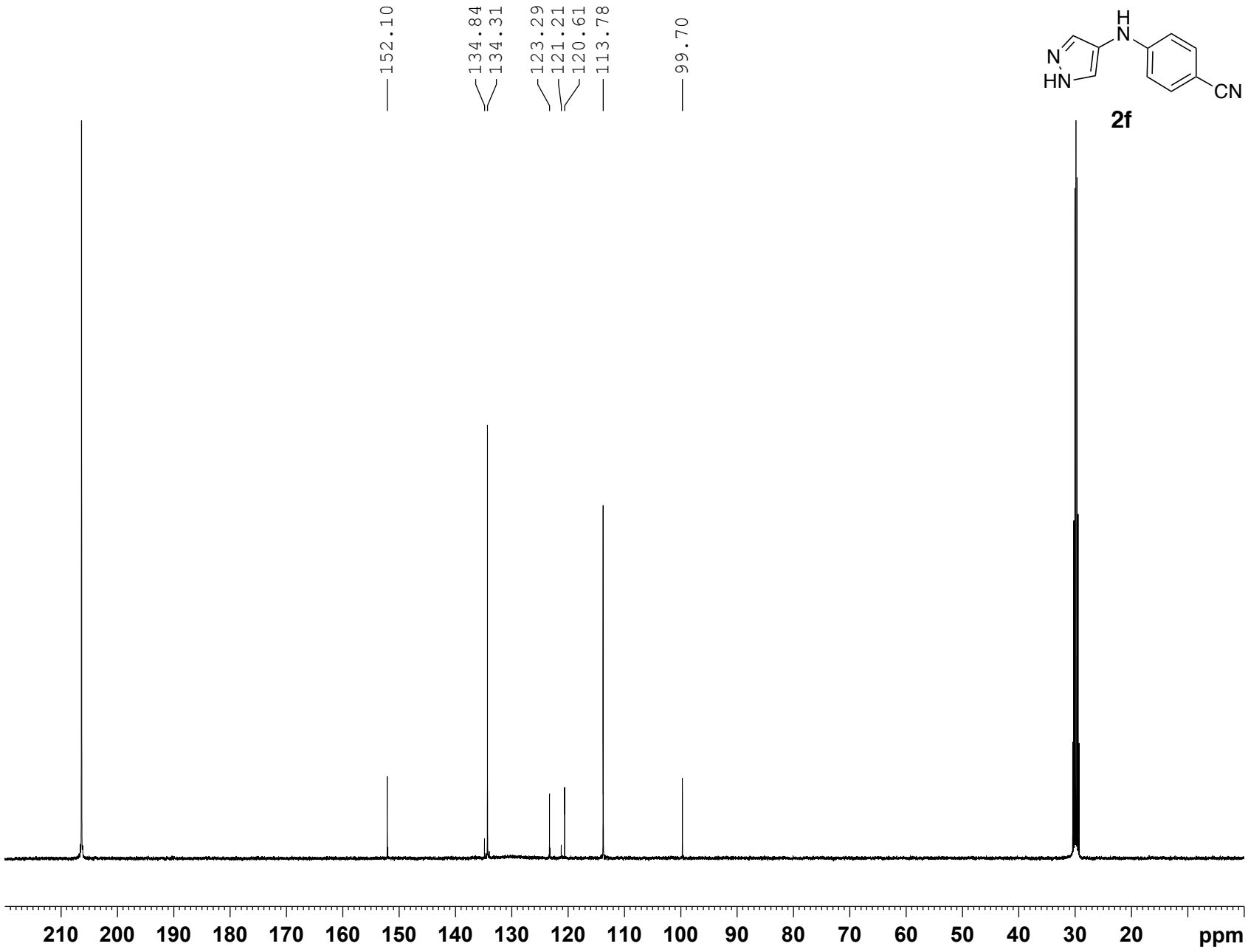

H
N
N
HN
tBu

2e

7.475
7.178
7.157
6.752
6.731
1.254
9
8
7
6
5
4
3
2
1
ppm
1.91
2.00
1.94
8.99


H
N
N
HN
tBu
2e
146.00
141.96
127.56
126.94
114.63
34.81
32.16
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm


12.134
7.642
7.554
7.485
7.479
7.474
7.462
7.457
7.450
6.905
6.899
6.894
6.887
6.882
6.877
6.870
6.865
H
N
N
HN
CN
2f
13
12
11
10
9
8
7
6
5
4
3
2
1
ppm
0.83
1.90
1.00
2.17
2.21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134.84
134.31
123.29
121.21
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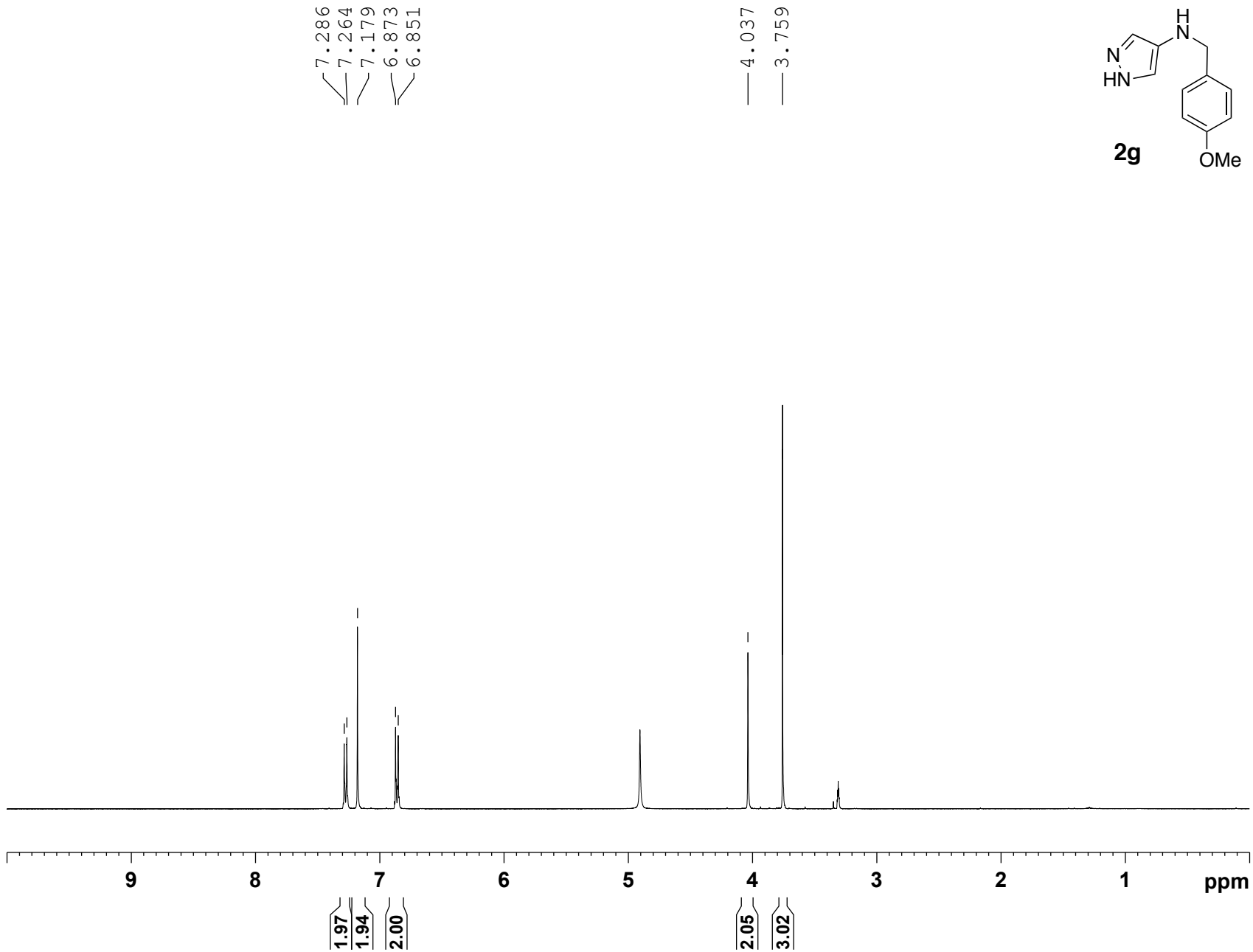
99.70
H
N
N
HN
CN
2f
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm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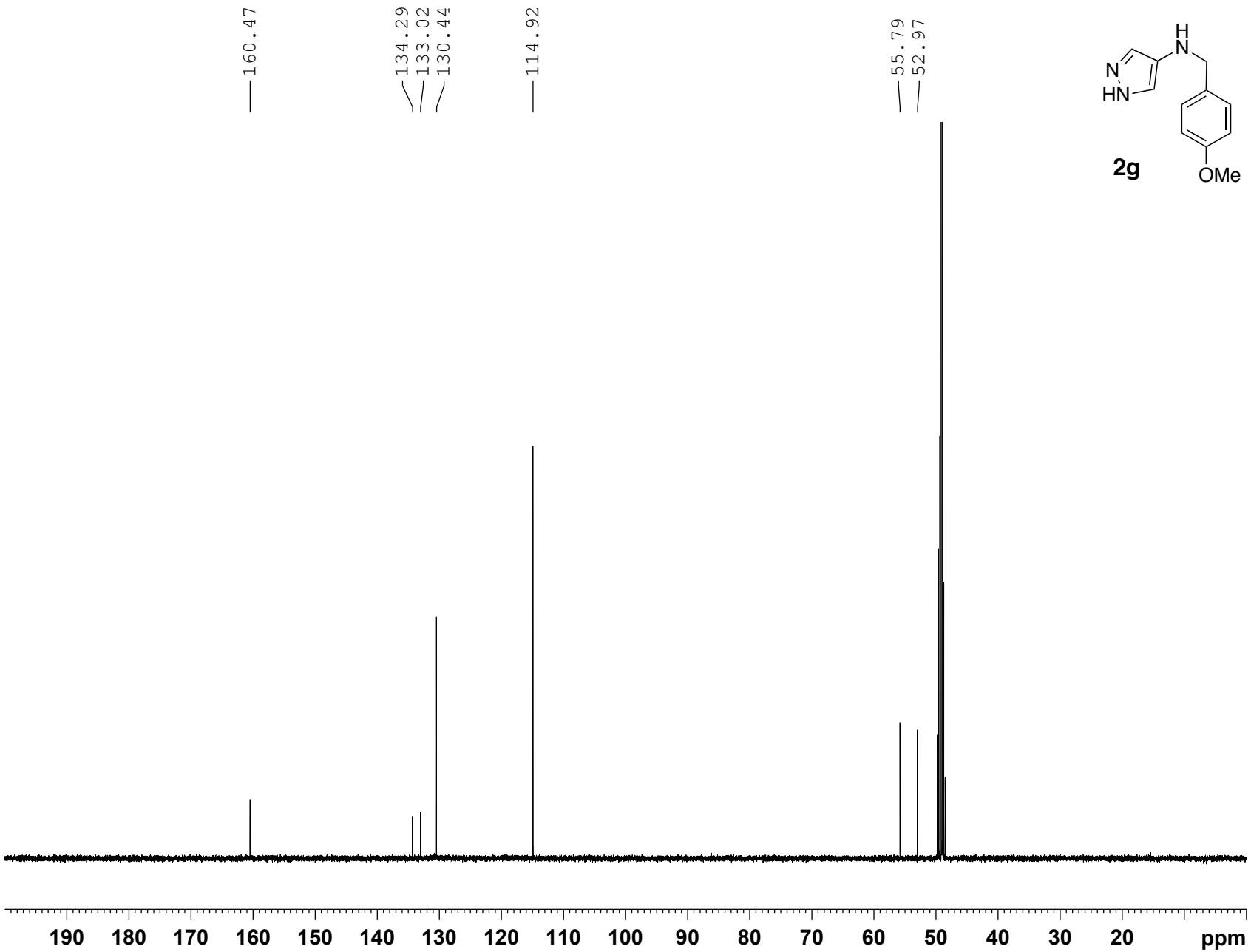
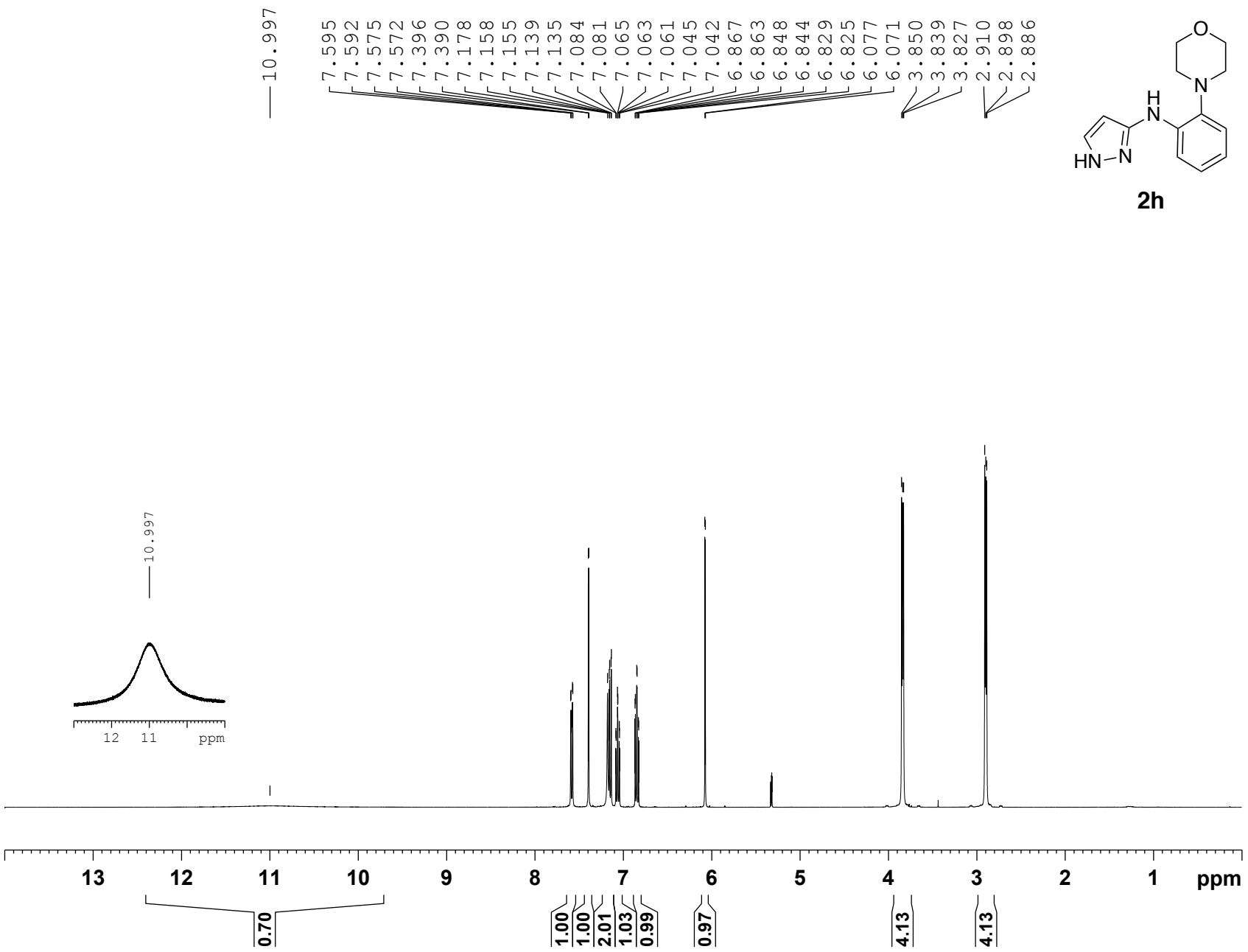
7.264
7.179
6.873
6.851
4.037
3.759
H
N
N
HN
2g
OMe
9
8
7
6
5
4
3
2
1
ppm
1.97
1.94
2.00
2.05
3.02


160.47
134.29
133.02
130.44
114.92
55.79
52.97
N
H
N
HN
2g
OMe
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm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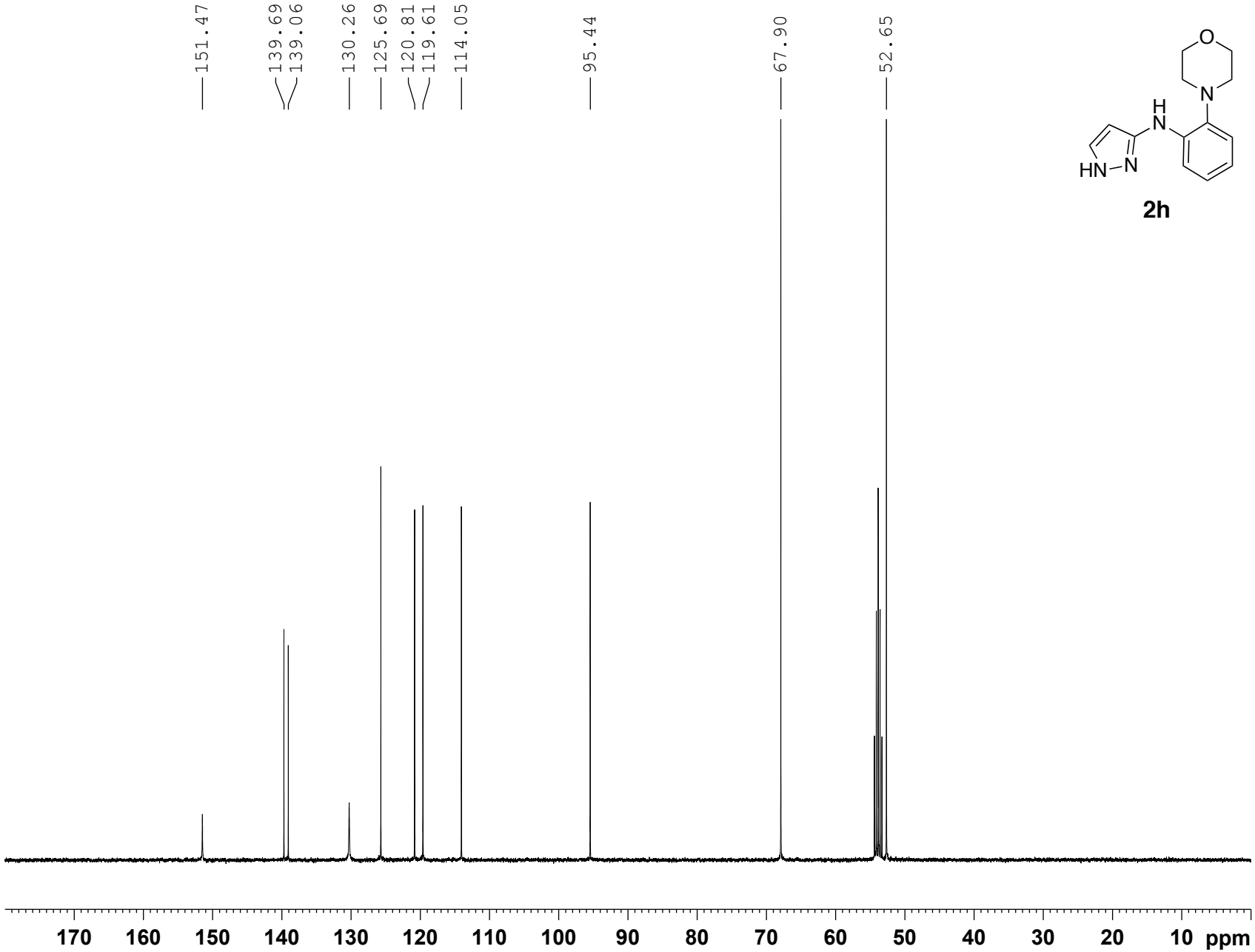
7.592
7.575
7.572
7.396
7.390
7.178
7.158
7.155
7.139
7.135
7.084
7.081
7.065
7.063
7.061
7.045
7.042
6.867
6.863
6.848
6.844
6.829
6.825
6.077
6.071
3.850
3.839
3.827
2.910
2.898
2.886
O
N
H
N
HN
N
2h
10.997
12
11
ppm
13
12
11
10
9
8
7
6
5
4
3
2
1
ppm
0.70
1.00
1.00
2.01
1.03
0.99
0.97
4.13
4.13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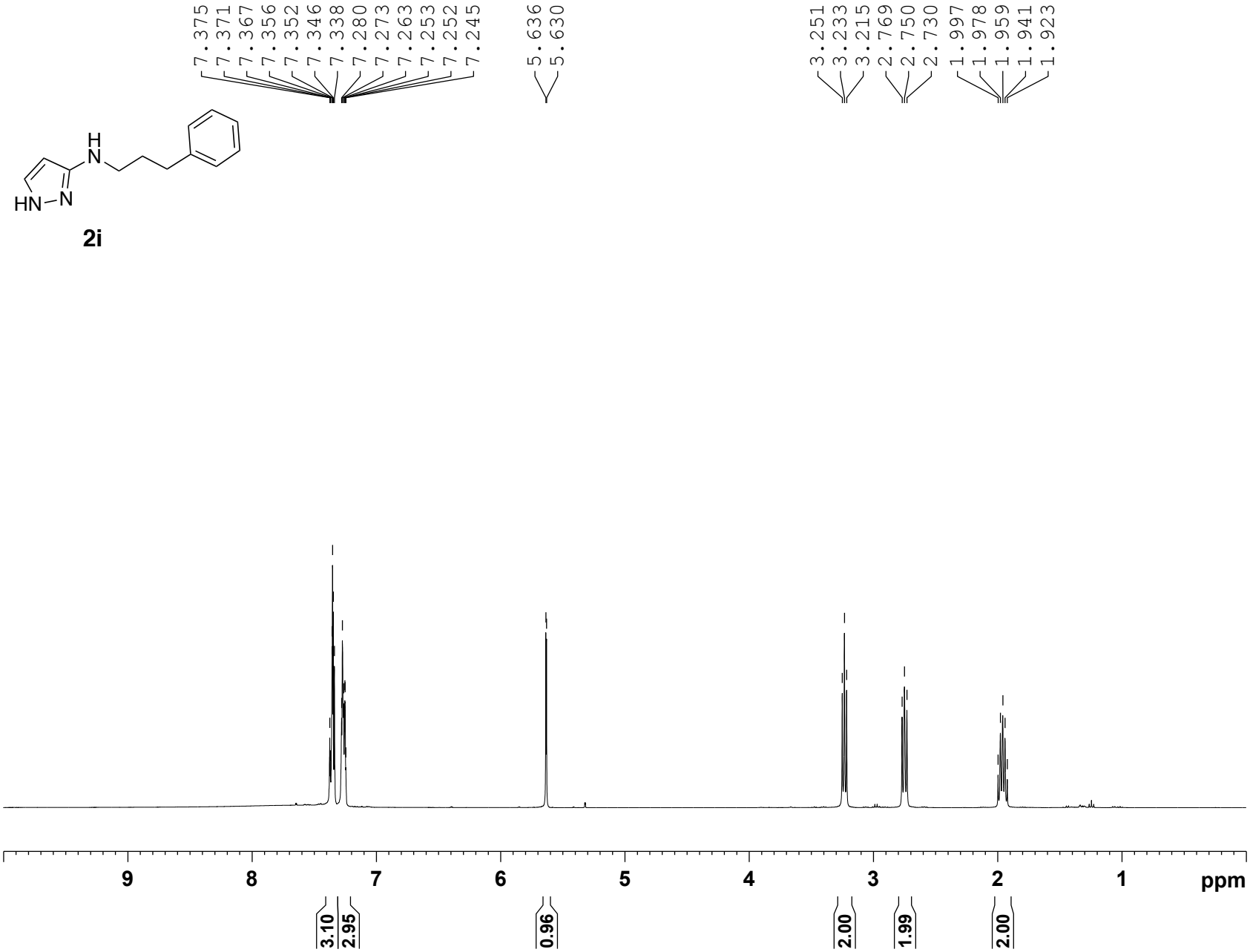
139.69
139.06
130.26
125.69
120.81
119.61
114.05
95.44
67.90
52.65
O
N
H
N
HN
N
2h
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm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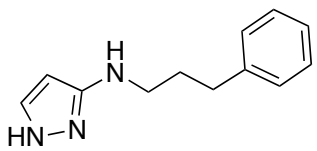
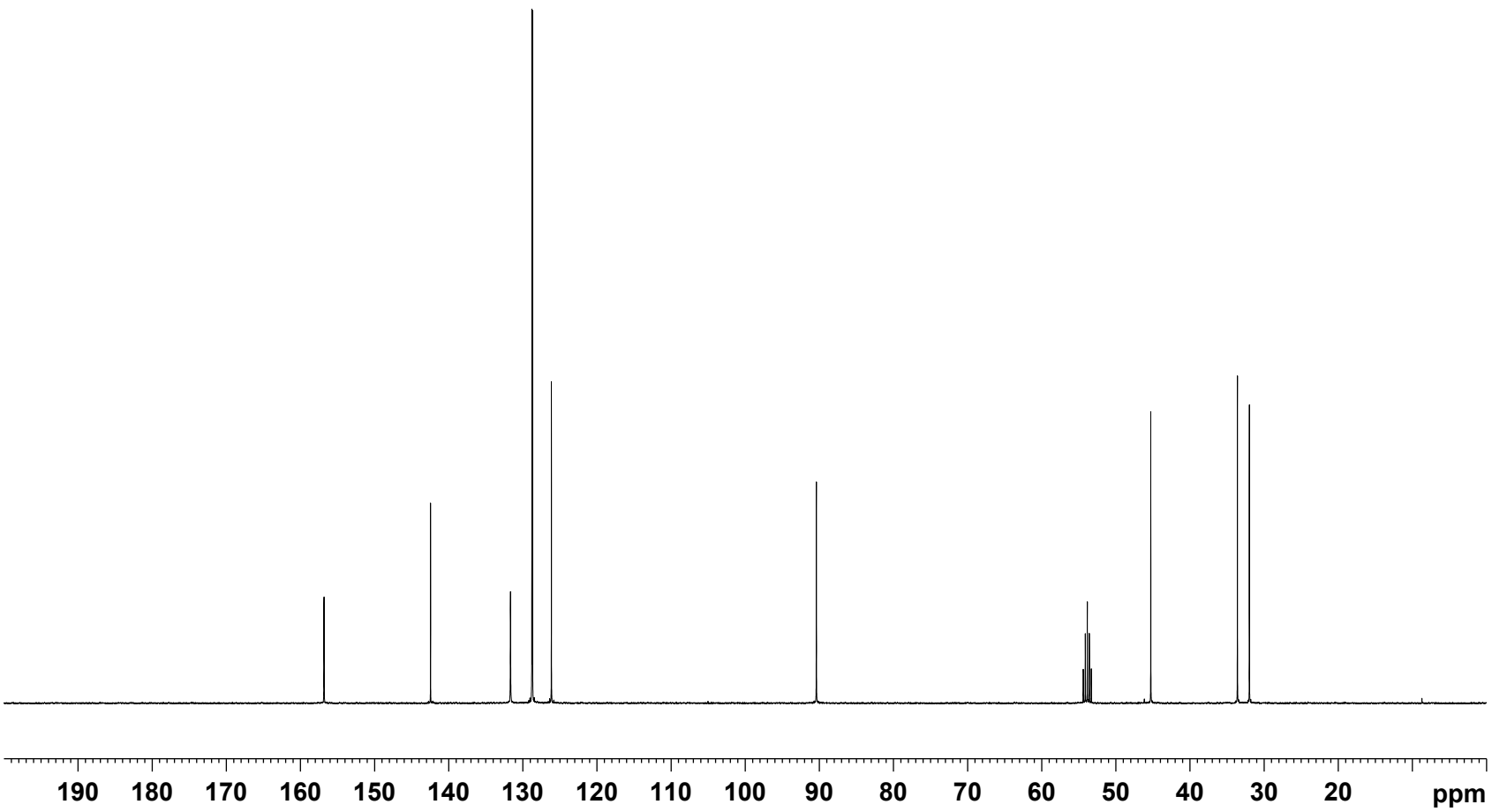
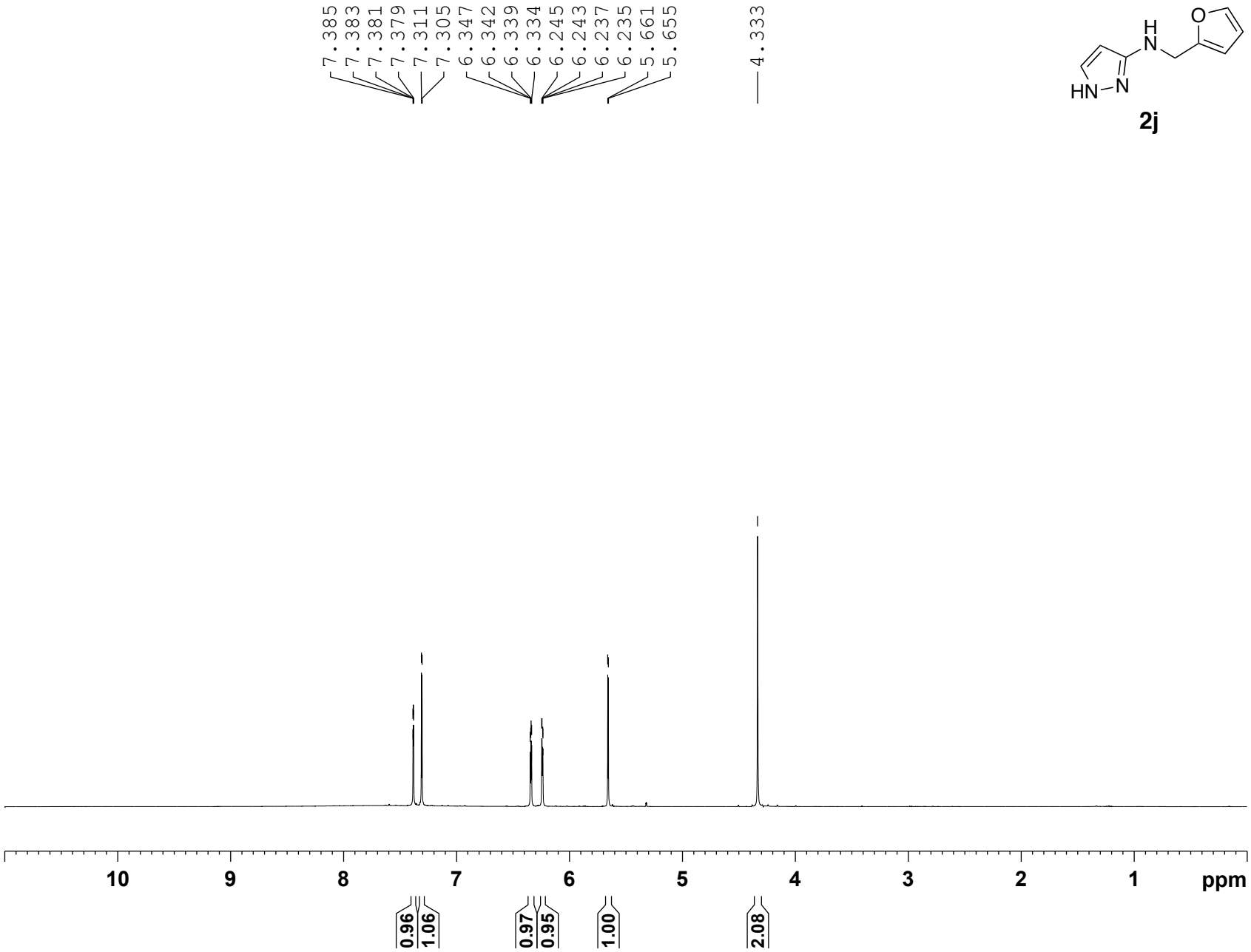
7.371
7.367
7.356
7.352
7.346
7.338
7.280
7.273
7.263
7.253
7.252
7.245
5.636
5.630
3.251
3.233
3.215
2.769
2.750
2.730
1.997
1.978
1.959
1.941
1.923
H
N
HN
N
2i
9
8
7
6
5
4
3
2
1
ppm
3.10
2.95
0.96
2.00
1.99
2.00



2i

156.79
142.44
131.65
128.77
128.69
126.14
90.39
45.27
33.59
31.97

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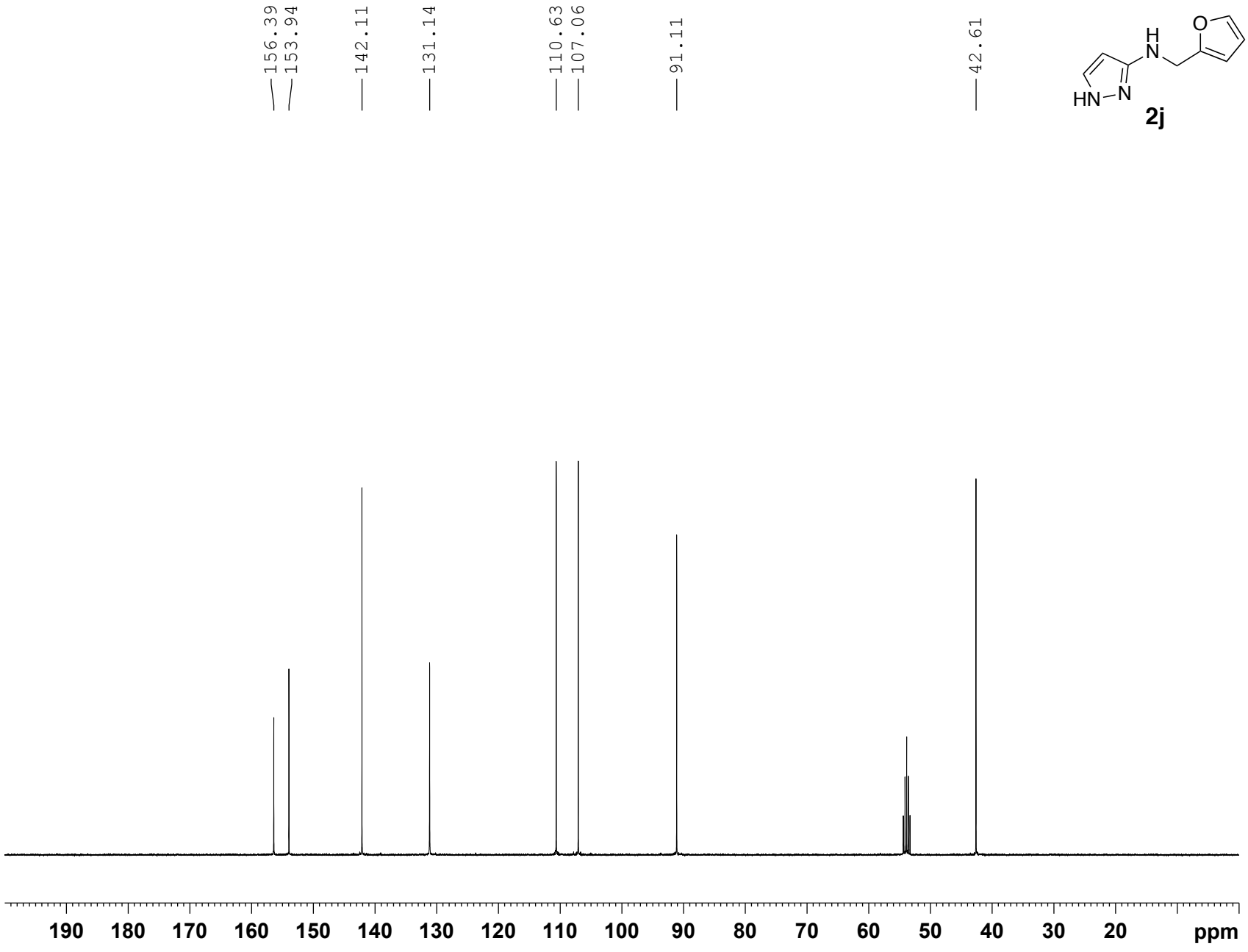
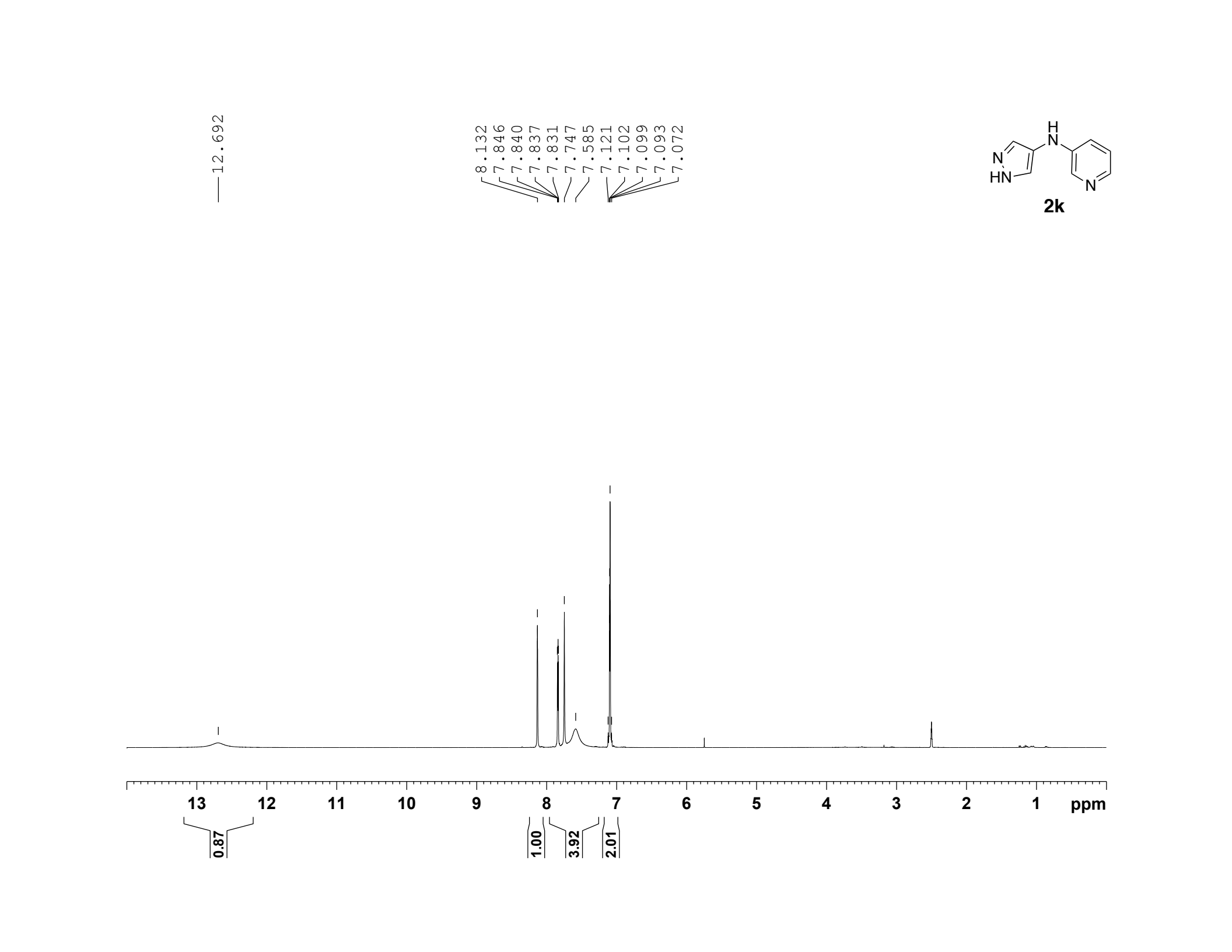
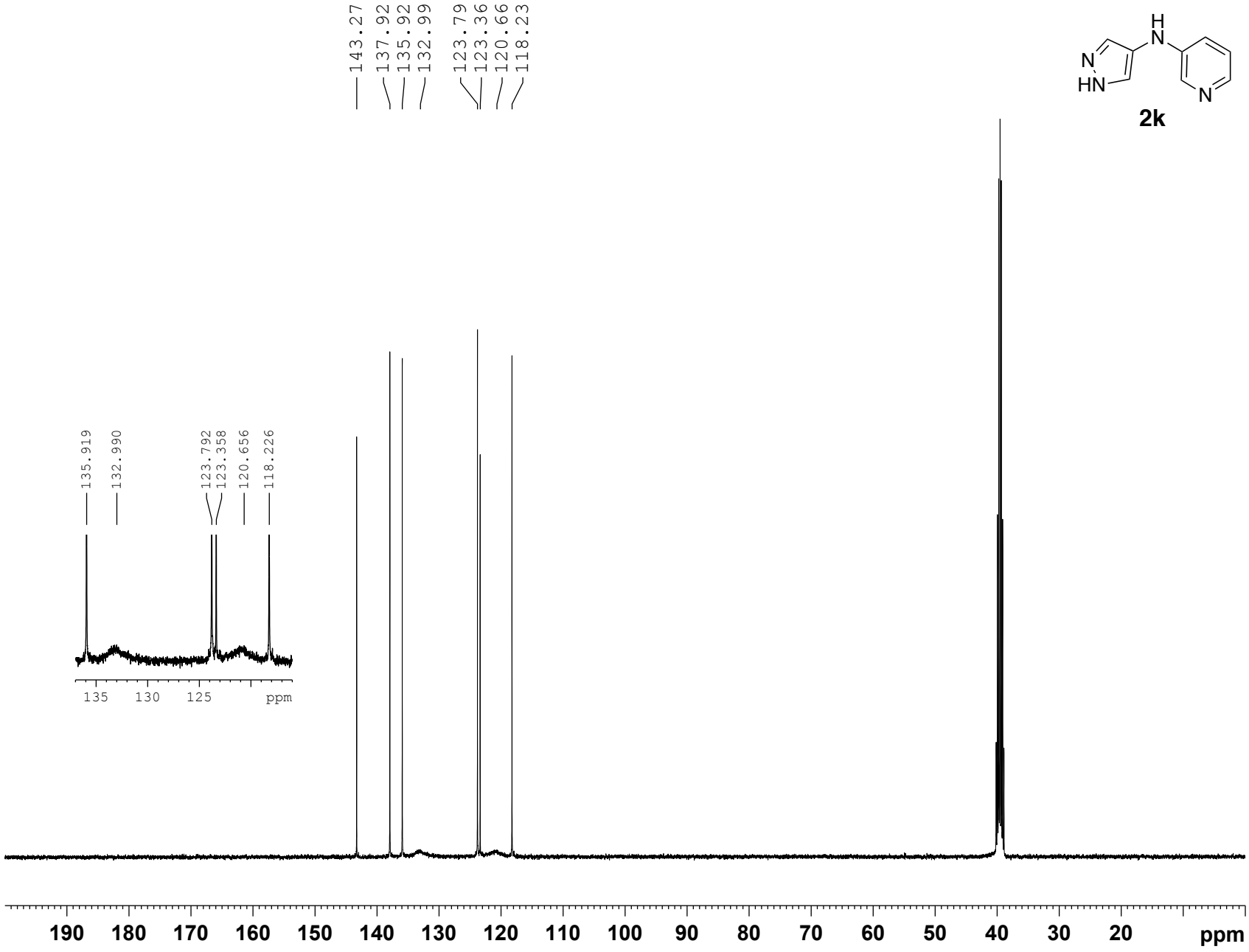
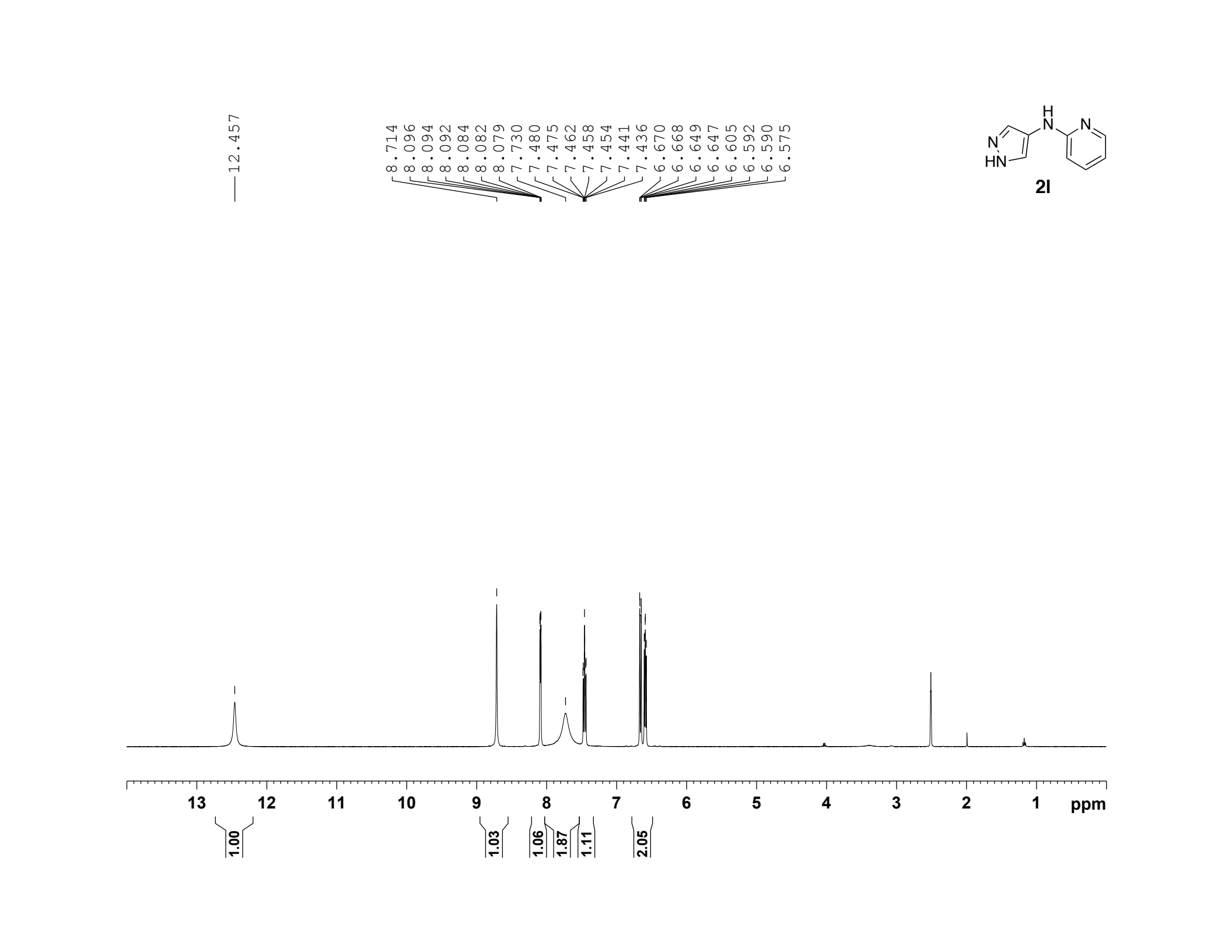
7.383
7.381
7.379
7.311
7.305
6.347
6.342
6.339
6.334
6.245
6.243
6.237
6.235
5.661
5.655
4.333
H
N
O
HN
N
2j
10
9
8
7
6
5
4
3
2
1
ppm
0.96
1.06
0.97
0.95
1.00
2.08


156.39
153.94
142.11
131.14
110.63
107.06
91.11
42.61
H
N
O
HN
N
2j
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm


12.692
8.132
7.846
7.840
7.837
7.831
7.747
7.585
7.121
7.102
7.099
7.093
7.072
H
N
N
HN
N
2k
13
12
11
10
9
8
7
6
5
4
3
2
1
ppm
0.87
1.00
3.92
2.01


143.27
137.92
135.92
132.99
123.79
123.36
120.66
118.23
H
N
N
HN
N
2k
135.919
132.990
123.792
123.358
120.656
118.226
135
130
125
ppm
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm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8.094
8.092
8.084
8.082
8.079
7.730
7.480
7.475
7.462
7.458
7.454
7.441
7.436
6.670
6.668
6.649
6.647
6.605
6.592
6.590
6.575
H
N
N
N
HN
2l
13
12
11
10
9
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4
3
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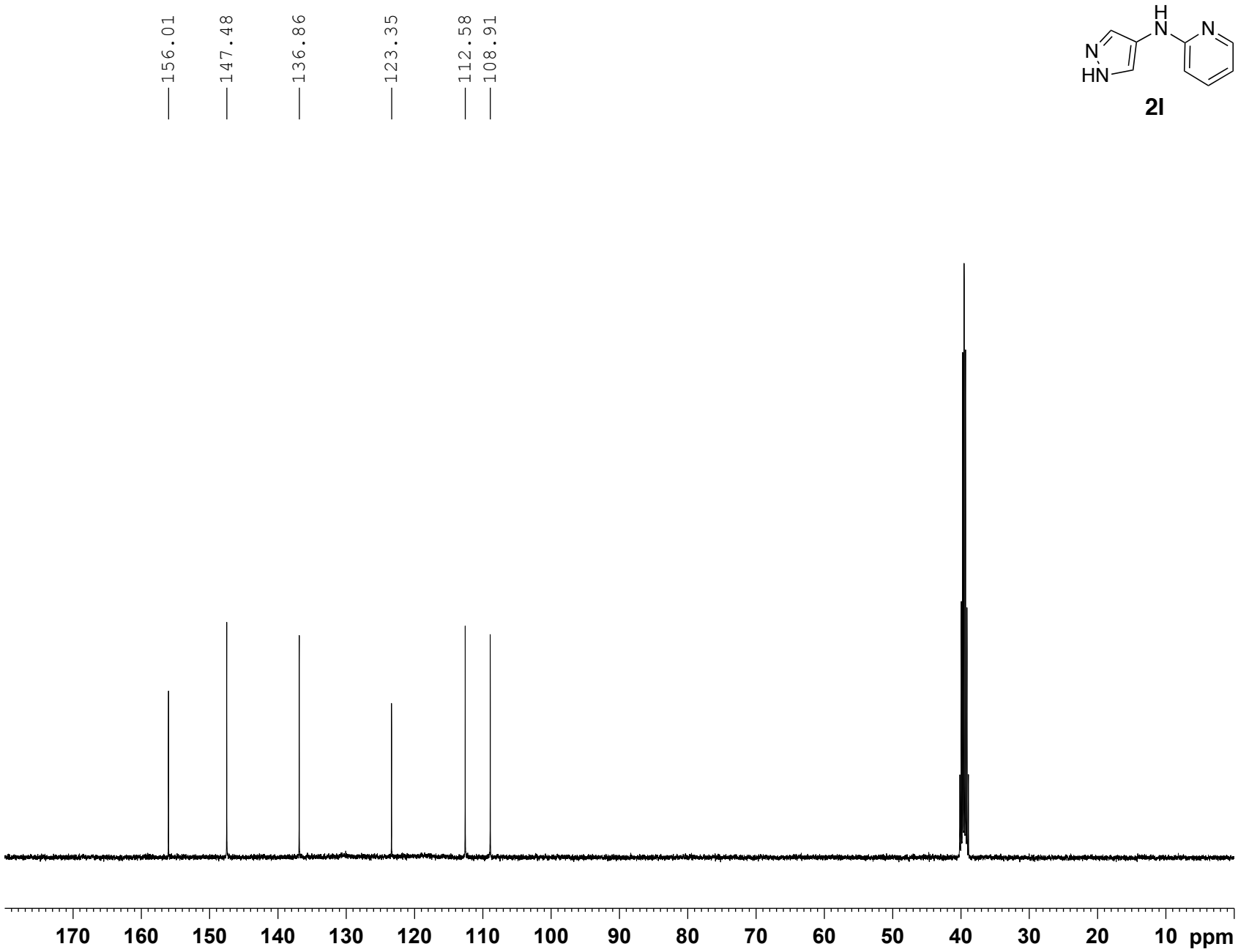
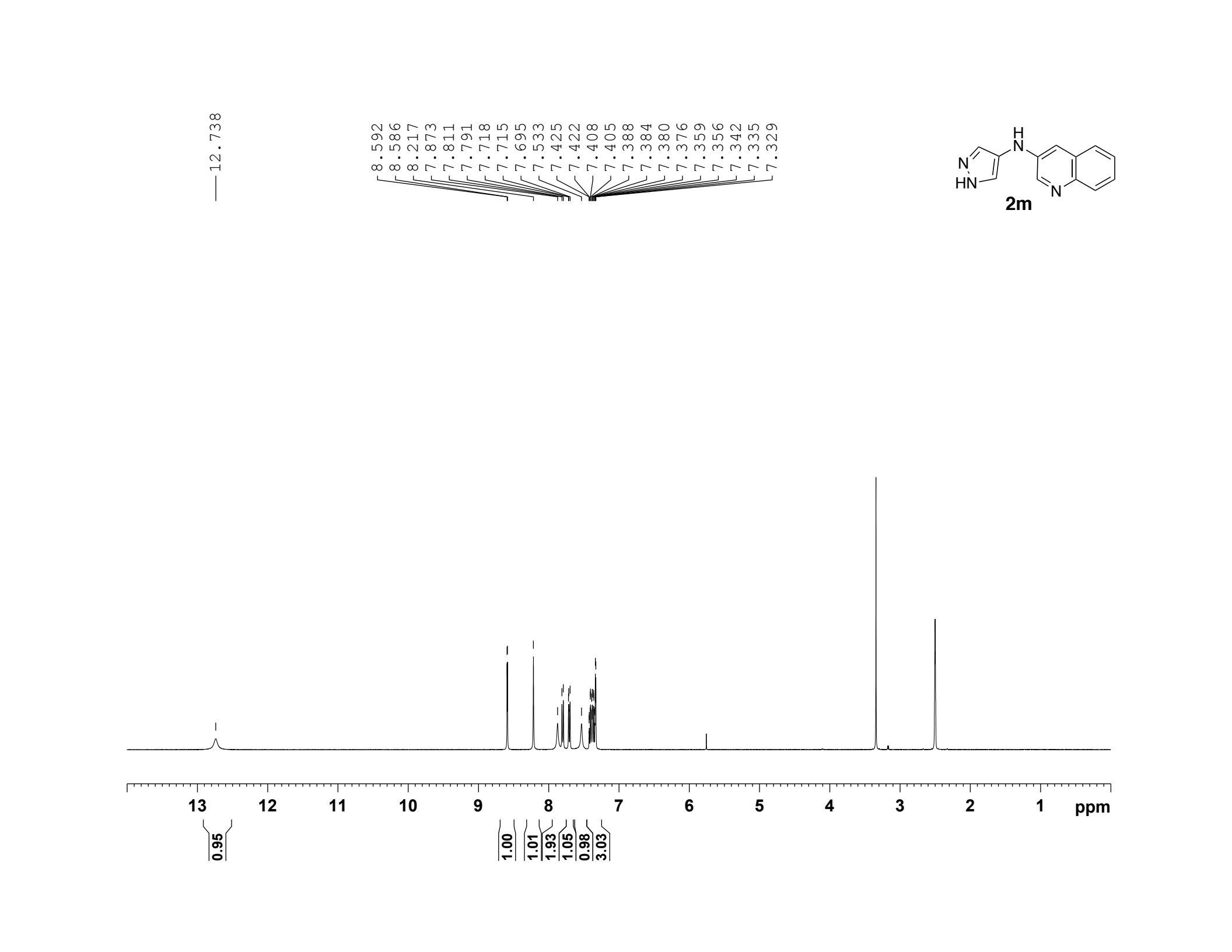
ppm
1.00
1.03
1.06
1.87
1.11
2.05


156.01
147.48
136.86
123.35
112.58
108.91
H
N
N
N
HN
2l
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm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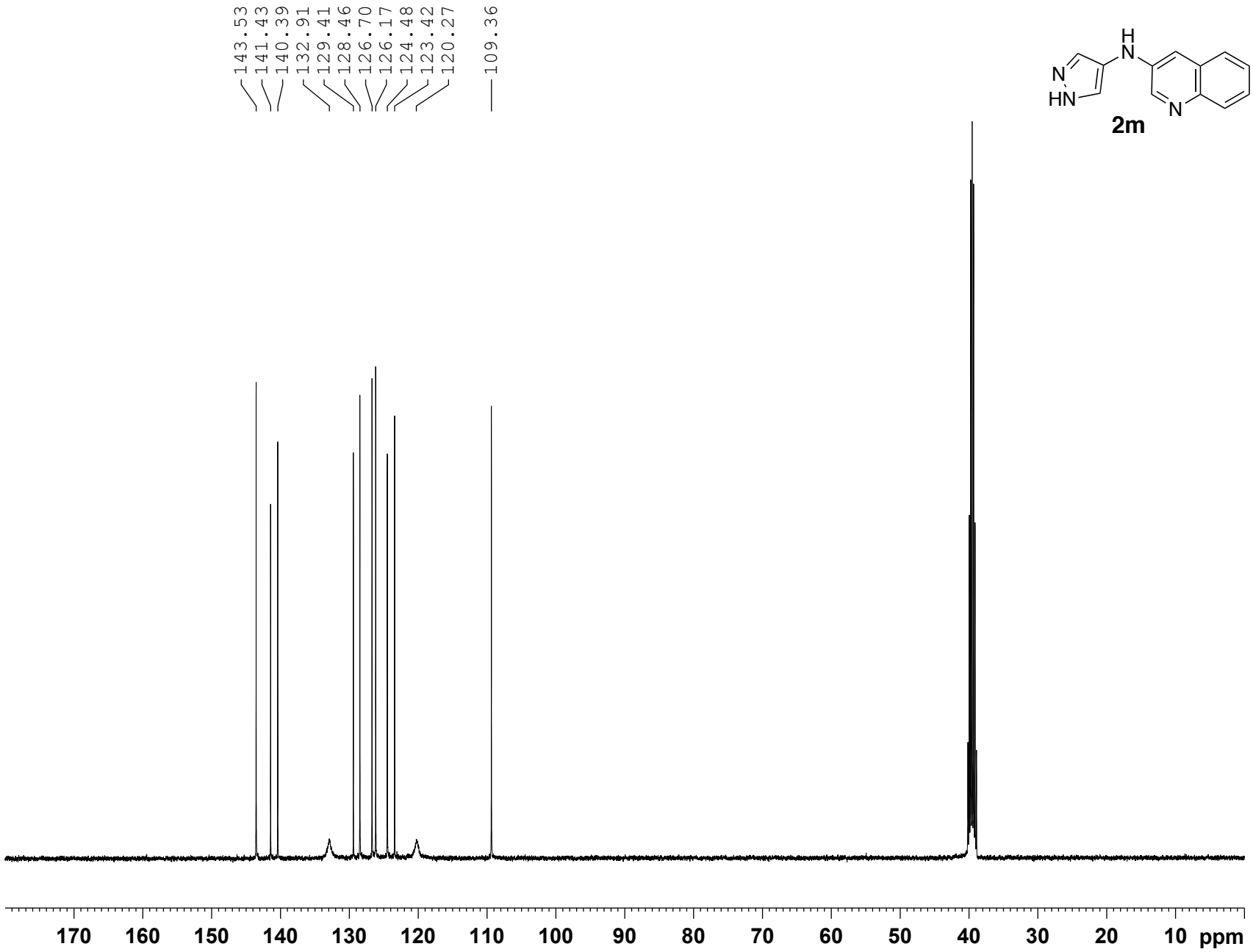
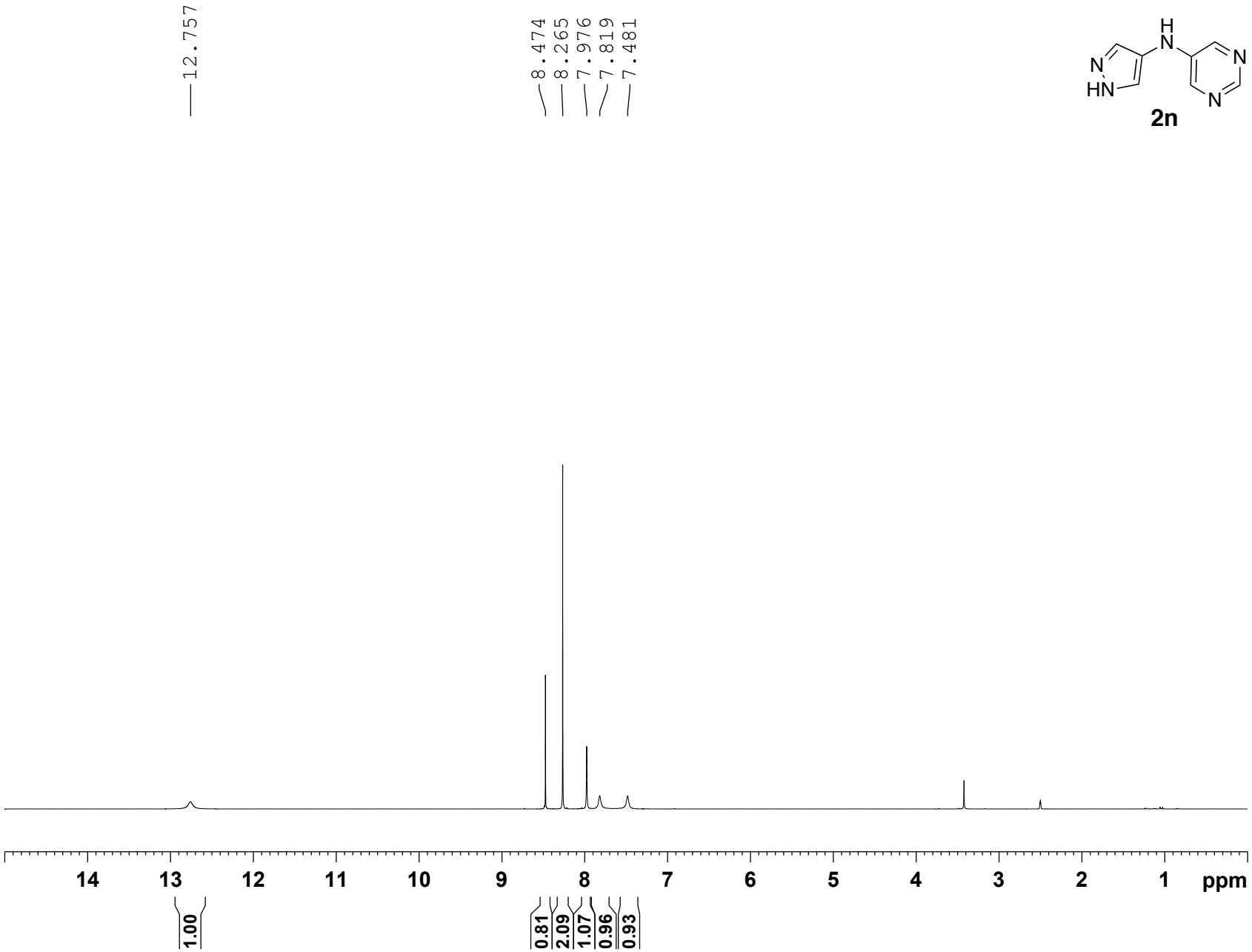
8.592
8.586
8.217
7.873
7.811
7.791
7.718
7.715
7.695
7.533
7.425
7.422
7.408
7.405
7.388
7.384
7.380
7.376
7.359
7.356
7.342
7.335
7.329
H
N
N
HN
N
2m
13
12
11
10
9
8
7
6
5
4
3
2
1
ppm
0.95
1.00
1.01
1.93
1.05
0.98
3.03


143.53
141.43
140.39
132.91
129.41
128.46
126.70
126.17
124.48
123.42
120.27
109.36
H
N
N
HN
N
2m
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm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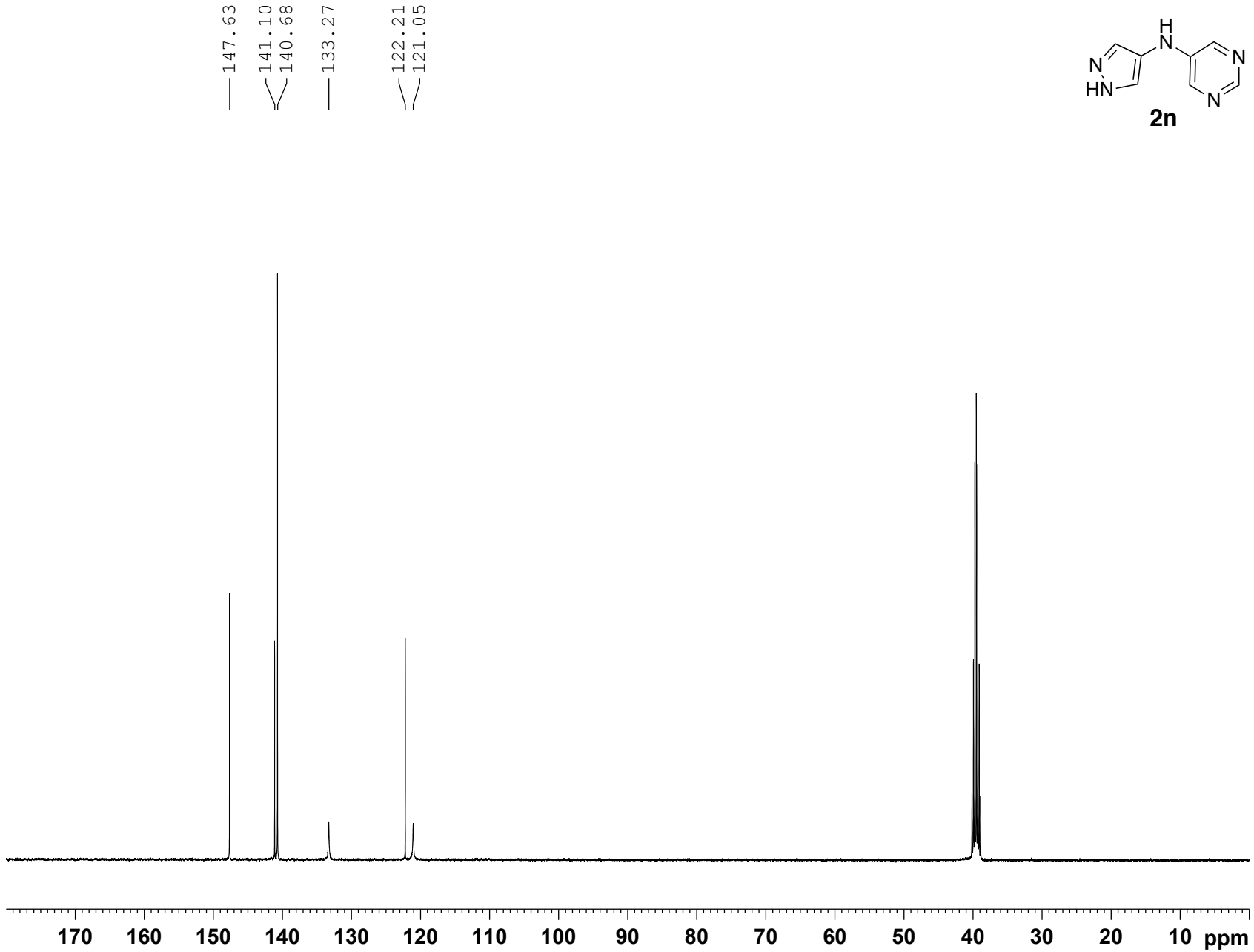
8.474
8.265
7.976
7.819
7.481
H
N
N
HN
N
N
2n
14
13
12
11
10
9
8
7
6
5
4
3
2
1
ppm
1.00
0.81
2.09
1.07
0.96
0.93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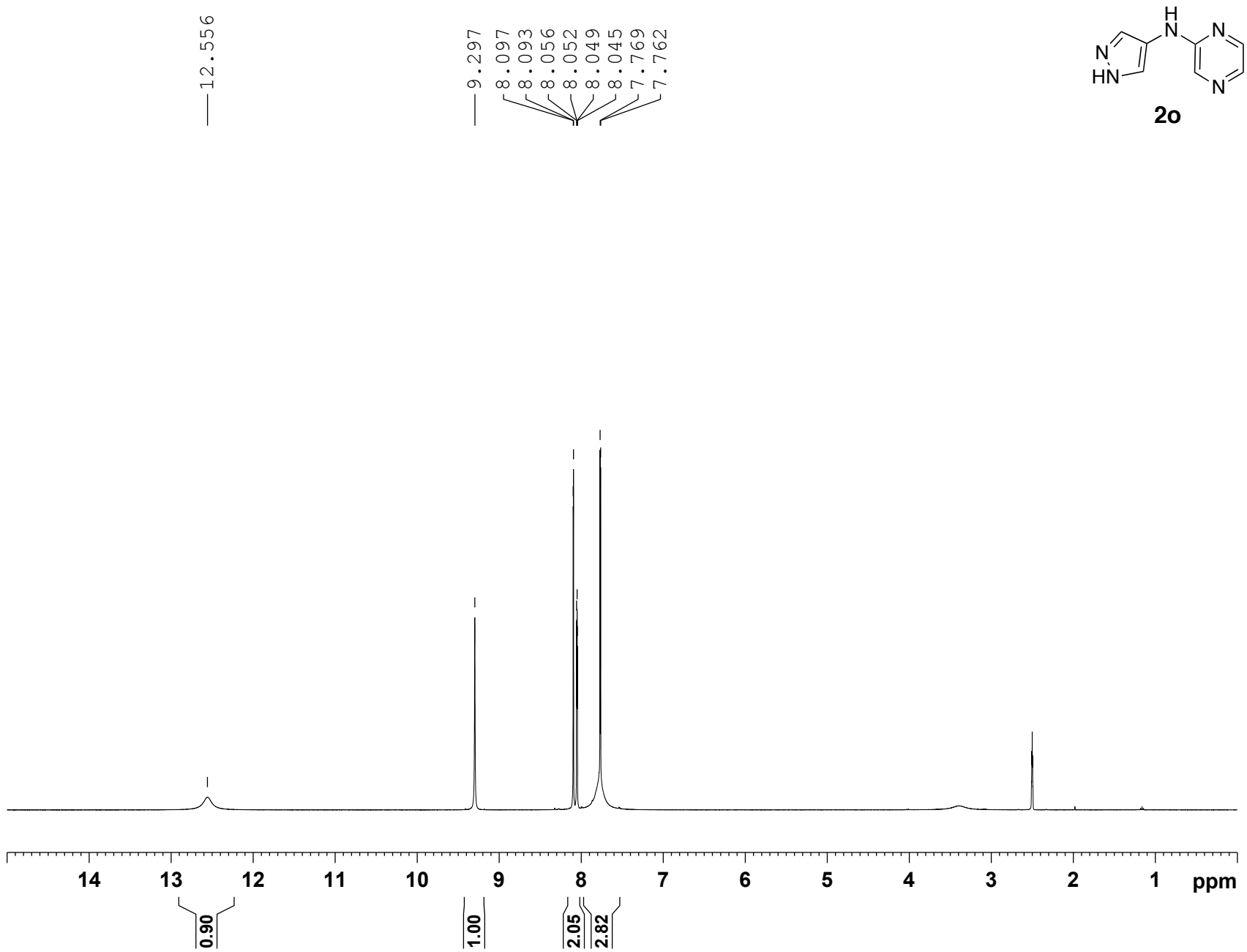
141.10
140.68
133.27
122.21
121.05
H
N
N
HN
N
N
2n
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm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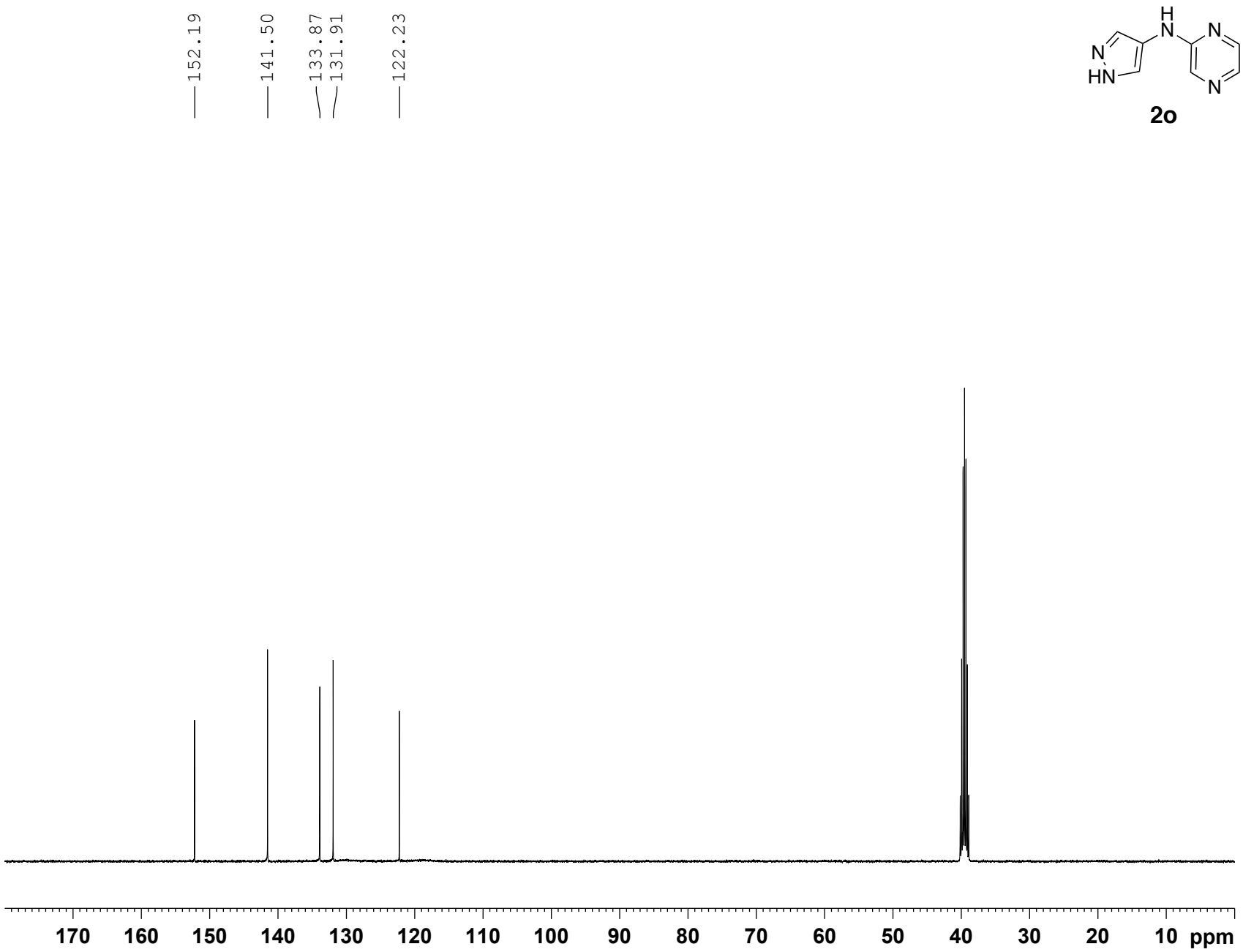
8.093
8.056
8.052
8.049
8.045
7.769
7.762
H
N
N
N
HN
N
2o
14
13
12
11
10
9
8
7
6
5
4
3
2
1
ppm
0.90
1.00
2.05
2.82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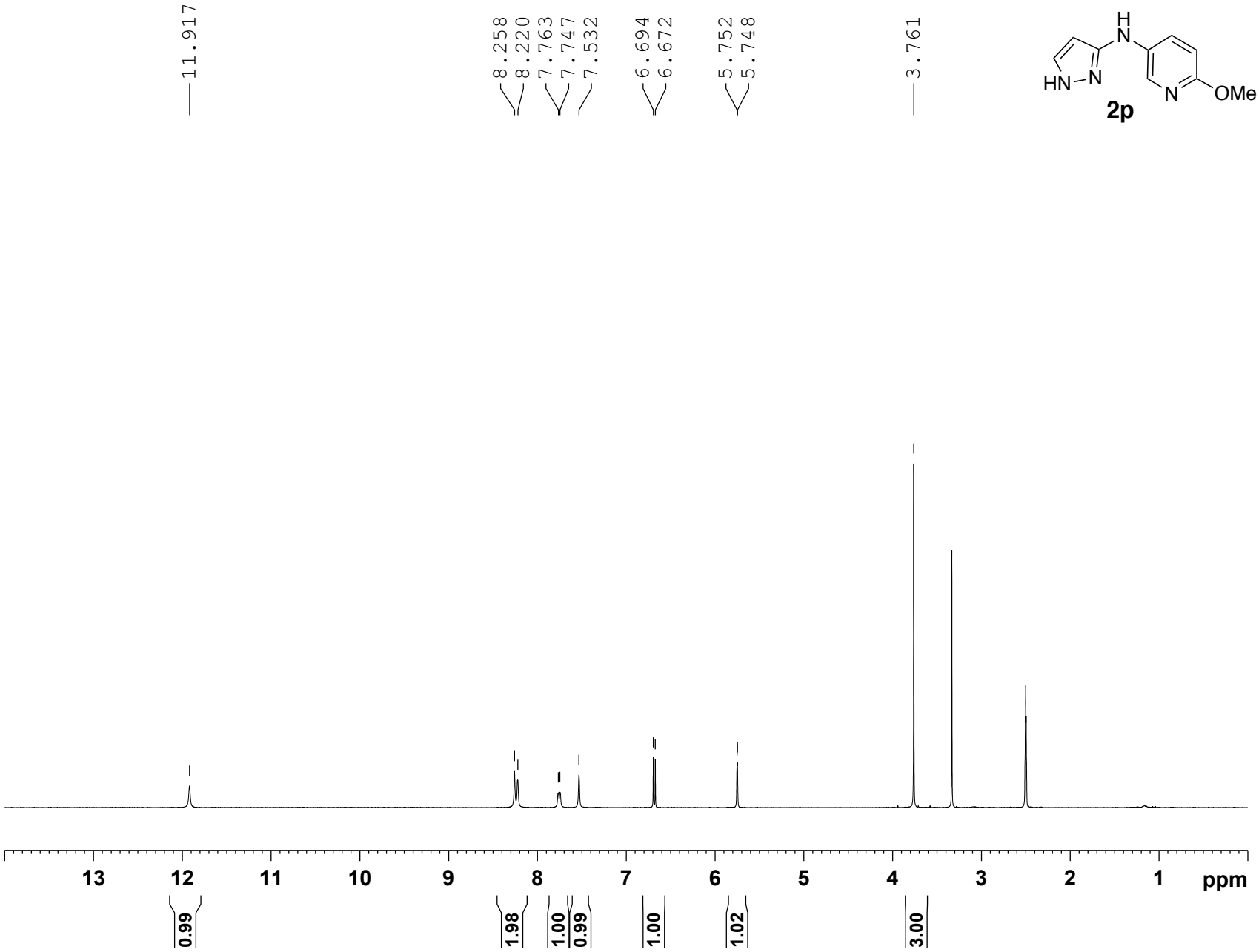
141.50
133.87
131.91
122.23
H
N
N
N
HN
N
2o
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm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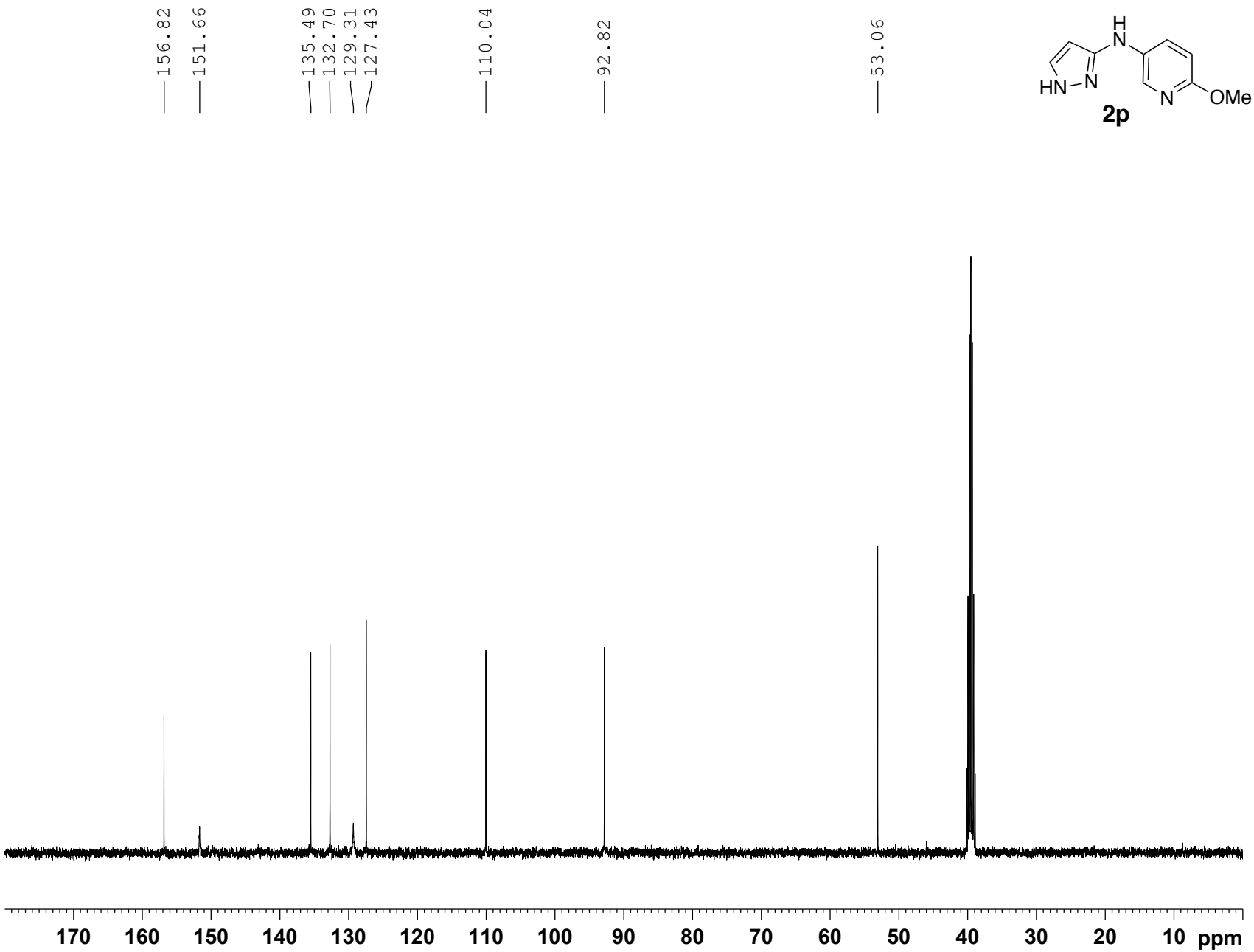
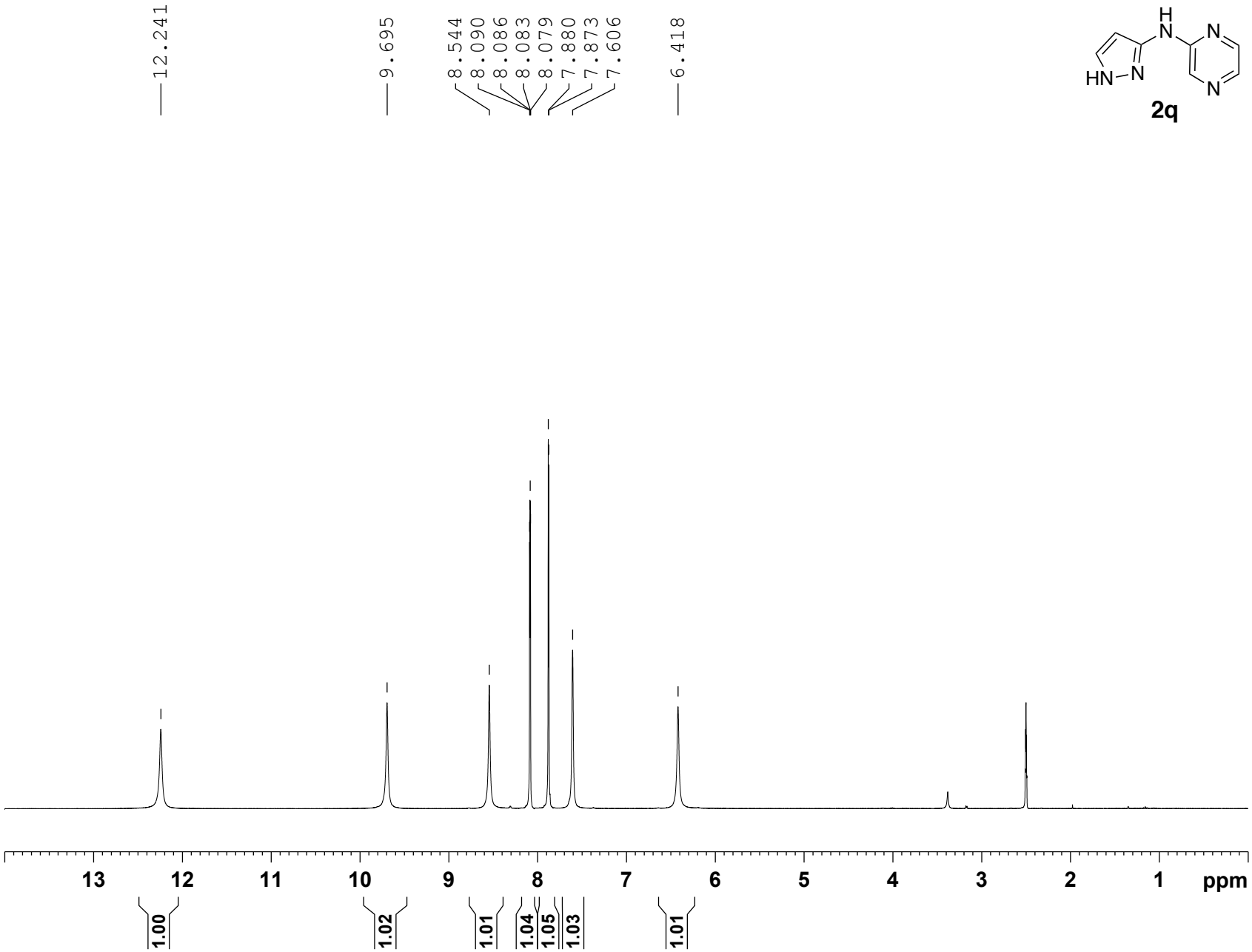
8.220
7.763
7.747
7.532
6.694
6.672
5.752
5.748
3.761
H
N
HN
N
N
OMe
2p
13
12
11
10
9
8
7
6
5
4
3
2
1
ppm
0.99
1.98
1.00
0.99
1.00
1.02
3.00


156.82
151.66
135.49
132.70
129.31
127.43
110.04
92.82
53.06
H
N
HN
N
N
OMe
2p
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm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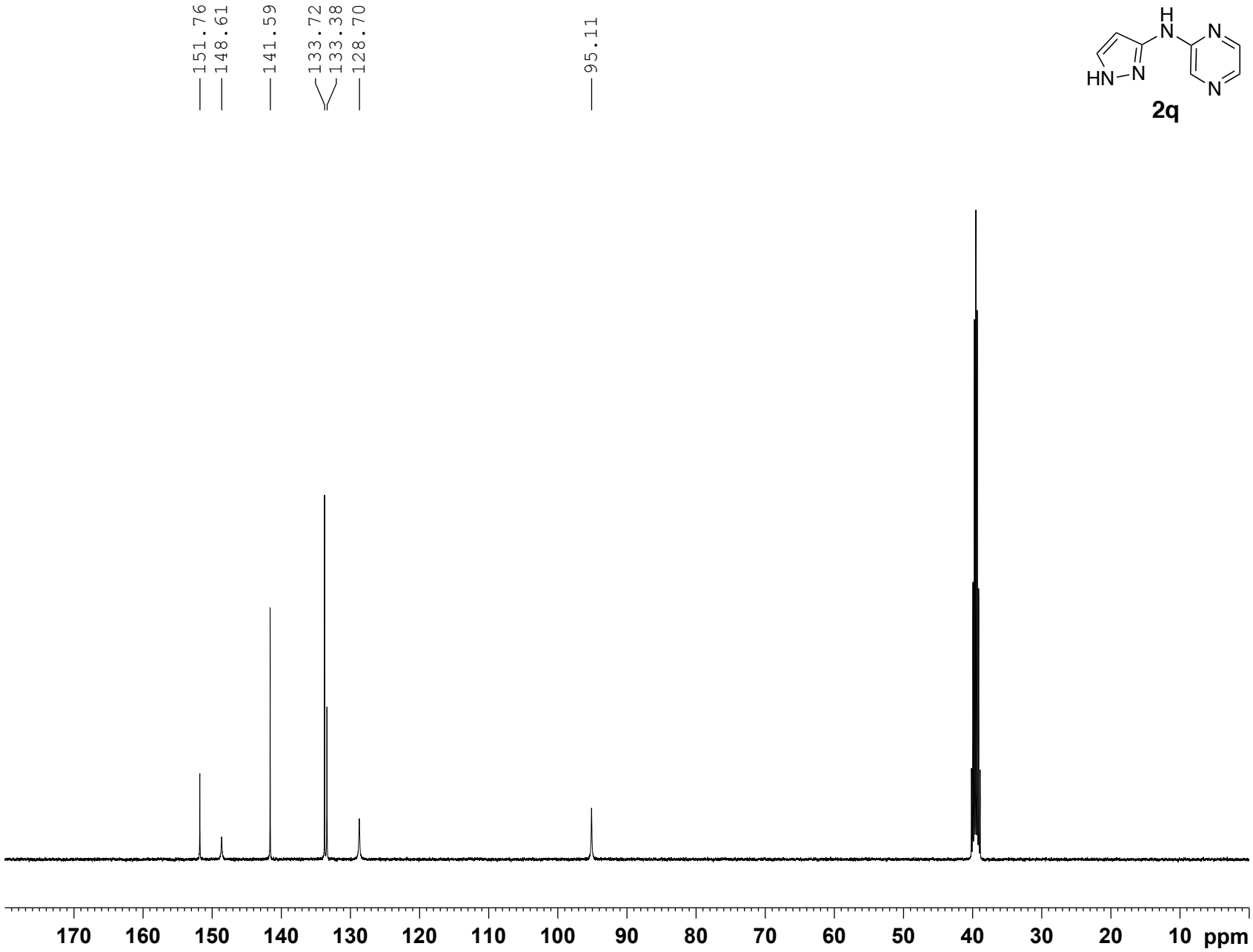
7.880
7.873
7.606
6.418
H
N
N
HN
N
N
2q
13
12
11
10
9
8
7
6
5
4
3
2
1
ppm
1.00
1.02
1.01
1.04
1.05
1.03
1.01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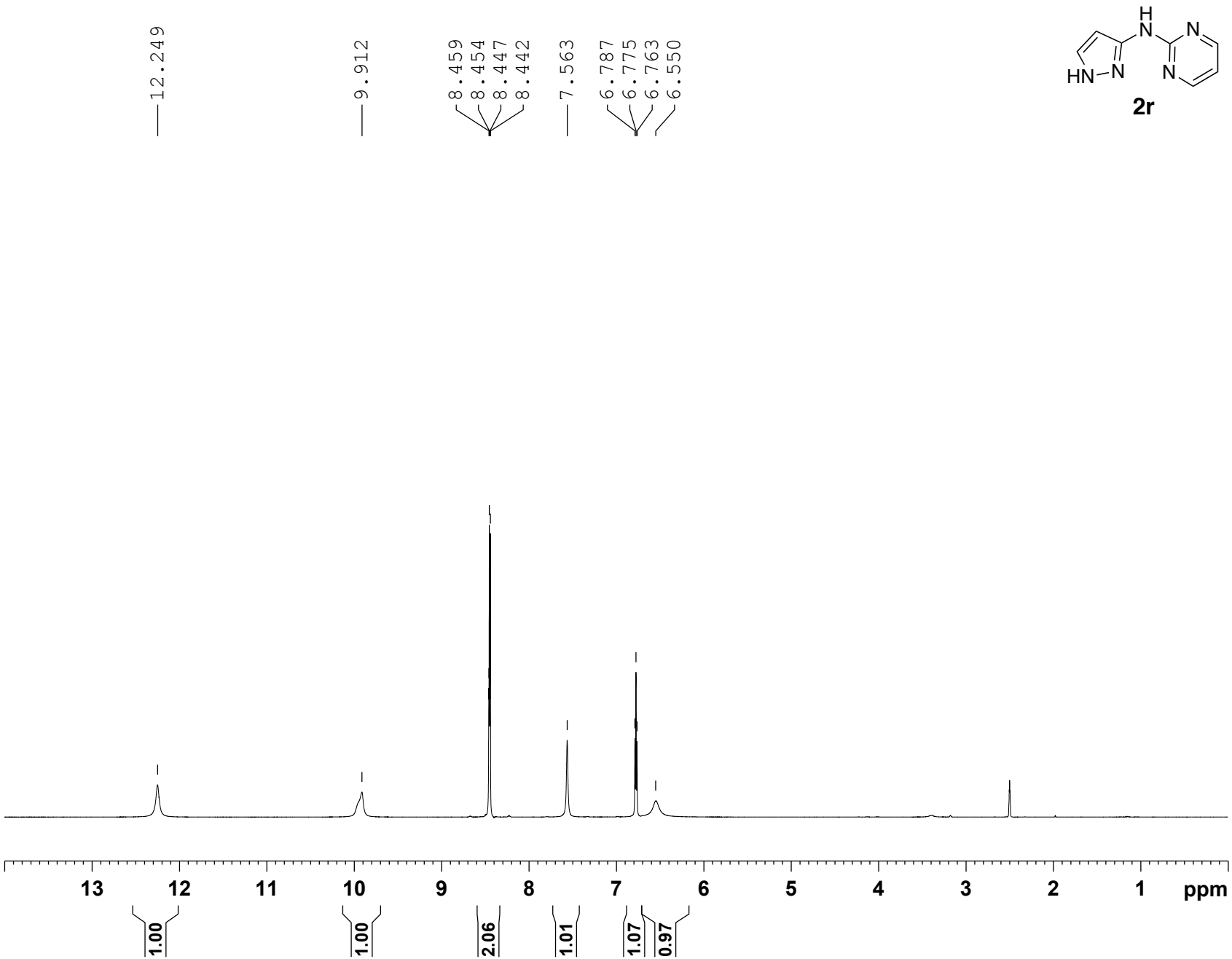
141.59
133.72
133.38
128.70
95.11
H
N
N
HN
N
N
2q
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm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8.447
8.442
7.563
6.787
6.775
6.763
6.550
HN
N
N
H
N
2r
13
12
11
10
9
8
7
6
5
4
3
2
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ppm
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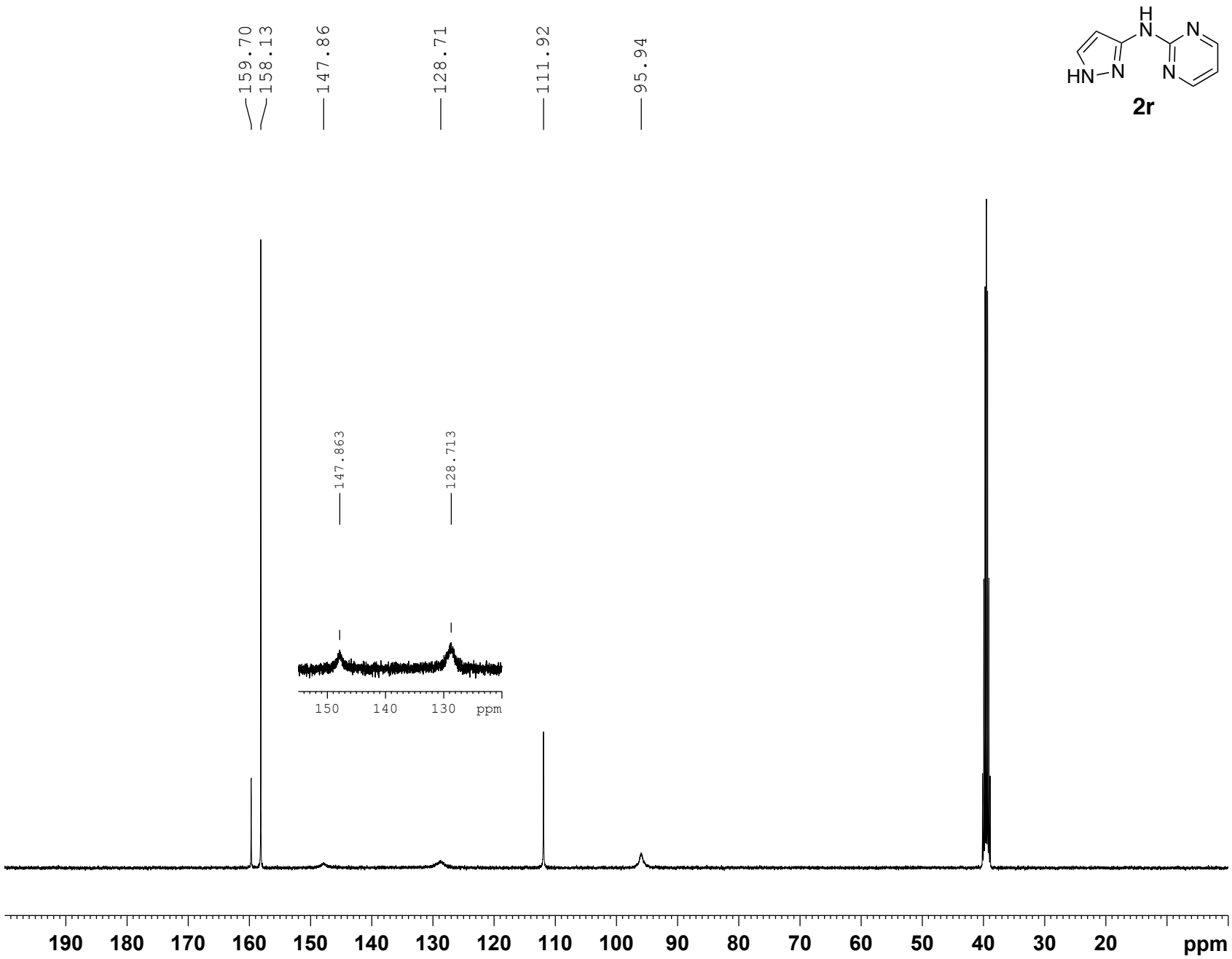
1.00
2.06
1.01
1.07
0.97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128.71
111.92
95.94
147.863
128.713
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140
130
ppm
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180
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140
130
120
110
100
90
80
70
60
50
40
30
20
ppm
H
N
N
HN
N
N
2r