Supporting Information

One-Pot Synthesis of Highly-Substituted *N*-Fused Heteroaromatic Bicycles from Azole Aldehydes

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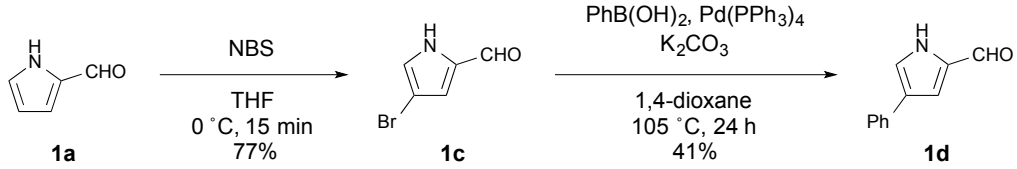
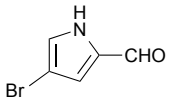
1 Experimental Section

1.1 General Information

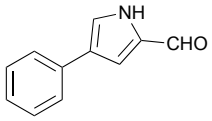
Reactions requiring anhydrous conditions were conducted under an inert atmosphere of argon using anhydrous solvents. DCM and toluene were distilled over CaH_2. Et_2O and THF were distilled over Na and benzophenone. All reactions were monitored by analytical thin-layer chromatography (TLC) using indicated solvent systems on Analtech Uniplate Silica Gel TLC plates (250 microns). All NMR spectra were recorded on either Bruker Avance 400 MHz or 300 MHz spectrometers as indicated. Chemical shifts (δ) are quoted in parts per million (ppm) and referenced to the following residual solvent signals: 1H δ = 7.26 ($CDCl_3$), 2.50 (DMSO-d_6), 3.31 (MeOD), 2.05 (acetone-d_6); ^{13}C δ = 77.0 ($CDCl_3$), 39.43 (DMSO-d_6), 49.05 (MeOD), 29.84 (acetone-d_6). Coupling constants (*J*) are given in Hz. All IR data were obtained on Triethylphosphine, fumaronitrile, pyrrole-2-carboxaldehyde (**1a**), 3,5-dimethylpyrrole-2-carboxaldehyde (**1b**), 5-Formyl-2,4-dimethyl-1*H*-pyrrole-3-carboxylic acid, 4-imidazolecarboxaldehyde (**1i**), 4-methyl-5-imidazolecarboxaldehyde (**1j**), 2-methyl-1*H*-imidazole-4-carboxaldehyde (**1k**), 5-chloro-2-phenyl-1*H*-imidazole-4-carboxaldehyde (**1l**), imidazole-2-carboxaldehyde (**1m**), and 4,5-dimethyl-1*H*-imidazole-5-carbaldehyde (**1n**) were obtained from Sigma-Aldrich.

1.2 Preparation of Aldehydes



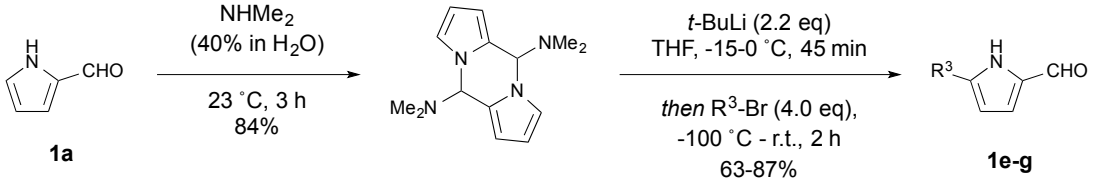


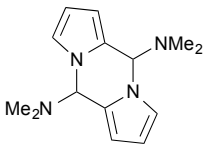
4-Bromo-1*H*-pyrrole-2-carbaldehyde (1c).[1] To a stirred solution of pyrrole–2-carboxaldehyde (100 mg, 1.05 mmol) in THF (1.1 mL) at 0 °C was added *N*-bromosuccinimide (187 mg, 1.05 mmol) as a single portion. The reaction mixture was stirred for 15 min at 0 °C before the solvent was removed *in vacuo*. The crude mixture was suspended in water, the suspension was filtered, and the filtrand was washed with water. Crystallization of the filtrand from hot ethanol and water afforded the desired 4-bromopyrrole–2-carbaldehyde as a tan solid (183 mg, 0.80 mmol, 77%). Spectral data matched literature values.[1] ^{1}H-NMR (400 MHz; acetone-d_6): δ 11.57–11.28 (s, 1H), 9.52 (s, 1H), 7.30 (d, *J* = 2.5 Hz, 1H), 7.05 (d, *J* = 2.5 Hz, 1H).



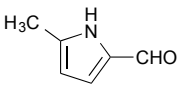
4-Phenyl-1*H*-pyrrole-2-carbaldehyde (1d).[2] The 4-bromopyrrole-2-carbaldehyde (250 mg, 1.44 mmol), phenyl boronic acid (210 mg, 1.72 mmol), and potassium carbonate (477 mg, 3.45 mmol) were suspended in dioxane (13 mmol), and the suspension was degassed with argon. Tetrakis(triphenylphosphine)palladium (83 mg, 5 mol%) was added, and the suspension was degassed again with argon and heated to 105 °C for 24 h. The reaction mixture was concentrated to dryness, and the residue was taken up in 20 mL EtOAc and 20 mL water. The mixture was extracted with EtOAc (3 × 20 mL), and the combined organic extracts were washed with brine, dried over sodium sulfate, and concentrated *in*

vacuo. Purification by flash chromatography (12→20% acetone/petroleum ether) afforded the desired 4-phenylpyrrole–2-carboxaldehyde as a white solid (101 mg, 0.59 mmol, 41%) as well as re-isolated starting material (98 mg, 0.56 mmol, 39%). Spectral data matched literature values.[2] ^{1}H-NMR (400 MHz; acetone-d_6): δ 9.59 (s, 1H), 7.68–7.64 (m, 3H), 7.38–7.34 (m, 3H), 7.23–7.19 (m, 1H).

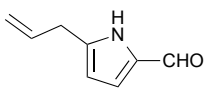




Pyrrole-2-carbaldehyde dimethylamine dimer.[3] A solution of pyrrole-2-carboxaldehyde 3.0 g, 31.55 mmol) in dimethylamine (6.3 mL, 40% in H_2O) was stirred at room temperature for 3 h. The precipitated solid was collected by filtration and dried in *vacuo*. The crude solid was recrystallized from hot EtOAc and hexanes to afford the dimer as a light pink solid (3.26 g, 13.3 mmol, 84%). Spectral data matched literature values.[3]

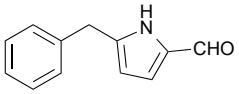


5-Methyl-1*H*-pyrrole-2-carbaldehyde (1e).[3] A 1.7 M solution of *t*-BuLi in pentane (1.06 mL, 1.80 mmol) was added dropwise to a stirred solution of the pyrrole-2-carbaldehyde dimethylamine dimer (200 mg, 0.82 mmol) in anhydrous THF at –15 °C. The reaction mixture was stirred for 15 min at this temperature and then for 30 min at 0 °C by which time it had become deep violet in color. The reaction mixture was cooled to –100 °C and MeI (204 μL, 3.27 mmol) was added in one portion. The reaction mixture was allowed to warm to –30 °C over 1.5 h and then 23 °C for 1 h. Water (20 mL) and saturated aqueous sodium bicarbonate (20 mL) were added and the mixture was heated to 80 °C for 15 h. The mixture was poured into a concentrated sodium bicarbonate solution and extracted with DCM (3 × 20 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated. Purification by flash chromatography (20% acetone in petroleum ether) afforded 5-methylpyrrole–2-carbaldehyde as an off-white solid (156 mg, 1.43 mmol, 87%). Spectral data matched literature values.[3] ^{1}H-NMR (400 MHz; acetone-d_6): δ 10.86 (s, 1H), 9.37 (s, 1H), 6.87 (s, 1H), 6.03 (s, 1H), 2.33 (s, 3H).

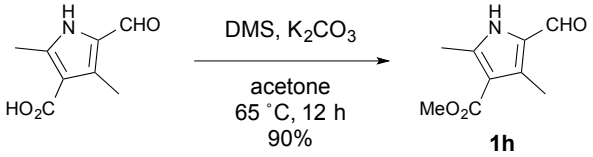


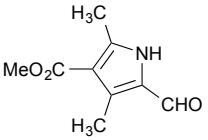
5-Allyl-1*H*-pyrrole-2-carbaldehyde (1f).[3] A 1.7 M solution of *t*-BuLi in pentane (1.06 mL, 1.80 mmol) was added dropwise to a stirred solution of the pyrrole-2-carbaldehyde dimethylamine dimer (200 mg, 0.82 mmol) in anhydrous THF at –15 °C. The reaction mixture was stirred for 15 min at this temperature and then for 30 min at 0 °C by which time it had become deep violet In color. The reaction mixture was cooled to –100 °C and allyl bromide (283 μL, 3.27 mmol) was added in one portion. The reaction mixture was allowed to warm to –30 °C over 1.5 h and then 23 °C for 1 h. Water (20 mL) and saturated aqueous sodium bicarbonate (20 mL) were added and the mixture was heated to 80 °C for 15 h. The mixture was poured into a concentrated sodium bicarbonate solution and extracted with DCM (3 × 20 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated. Crystallization from EtOAc and

hexanes afforded 5-allylpyrrole–2-carbaldehyde as an off-white solid (140 mg, 1.04 mmol, 63%). ^{1}H-NMR (400 MHz; acetone-d_6): δ 10.92 (s, 1H), 9.41 (s, 1H), 6.91 (s, 1H), 6.09 (s, 1H), 5.99 (ddt, *J* = 17.0, 10.1, 6.7 Hz, 1H), 5.14 (d, *J* = 17.0 Hz, 1H), 5.07 (d, *J* = 10.1 Hz, 1H), 3.48 (d, *J* = 6.7 Hz, 2H).



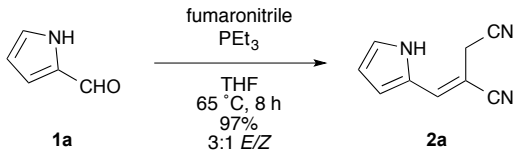
5-Benzyl-1*H*-pyrrole-2-carbaldehyde (1g). A 1.7 M solution of *t*-BuLi in pentane (1.06 mL, 1.80 mmol) was added dropwise to a stirred solution of the pyrrole-2-carbaldehyde dimethylamine dimer (200 mg, 0.82 mmol) in anhydrous THF at -15 °C. The reaction mixture was stirred for 15 min at this temperature and then for 30 min at 0 °C by which time it had become deep violet In color. The reaction mixture was cooled to -100 °C and BnBr (390 μL, 3.27 mmol) was added in one portion. The reaction mixture was allowed to warm to -30 °C over 1.5 h and then 23 °C for 1 h. Water (20 mL) and saturated aqueous sodium bicarbonate (20 mL) were added and the mixture was heated to 80 °C for 15 h. The mixture was poured into a concentrated sodium bicarbonate solution and extracted with DCM (3 × 20 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated. Crystallization from EtOAc and hexanes afforded 5-benzylpyrrole-2-carbaldehyde as an off-white solid (208 mg, 1.12 mmol, 69%). ^{1}H-NMR (400 MHz; acetone-d_6): δ 10.99 (s, 1H), 9.41 (s, 1H), 7.31–7.21 (m, 5H), 6.90 (d, *J* = 1.7 Hz, 1H), 6.07 (d, *J* = 1.7 Hz, 1H); ^{13}C-NMR (101 MHz, acetone-d_6): δ 178.61, 141.72, 140.04, 133.75, 129.50, 129.32, 127.22, 122.03, 110.46, 34.42; HRMS (FAB) calcd for $C_{12}H_{11}NO$ [M]+, 185.0841; found, 185.0840; [M+H]+, 186.0919; found, 186.0914.

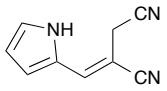




Methyl 5-formyl-2,4-dimethyl-1*H*-pyrrole-3-carboxylate (1h). To a stirring solution of 5-formyl–2,4-dimethylpyrrole–3-carboxylic acid (100 mg, 0.60 mmol) in acetone (6.0 mL) was added potassium carbonate (91 mg, 0.66 mmol) followed by dimethyl sulfate (60 μL, 0.63 mmol). The reaction mixture was stirred at 23 °C for 12 h, then filtered over Celite. The filter pad was washed with EtOAc and the filtrate was concentrated. Crystallization from hot EtOAc and hexanes afforded the desired product as a white solid (98 mg, 0.54 mmol, 90%). ^{1}H-NMR (400 MHz; acetone-d_6): δ 11.06 (s, 1H), 9.68 (s, 1H), 3.78 (s, 3H), 2.54 (s, 3H), 2.52 (s, 3H); ^{13}C-NMR (101 MHz, acetone-d_6): δ 177.97, 165.80, 143.32, 134.47, 129.54, 114.13, 50.85, 13.89, 10.61; HRMS (FAB) calcd for $C_9H_{11}NO_3$ [M]+, 181.0739; found, 181.0739; [M+H]+, 182.0817; found, 182.0818.

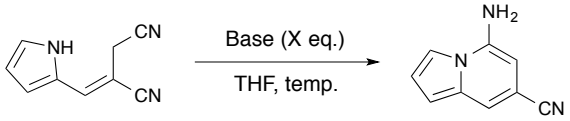
1.3 Preparation of Alkene 2a





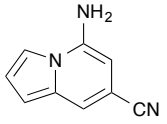
(*E*)-2-((1*H*-pyrrol-2-yl)methylene)succinonitrile (2a). To a stirring solution of pyrrole-2-carboxaldehyde (100 mg, 1.05 mmol) in THF (4.2 mL) at room temperature was added fumaronitrile (103 mg, 1.31 mmol) followed by triethylphosphine (186 μL, 1.26 mmol) dropwise. The reaction mixture was stirred at 65 ˚C for 8 h, then quenched with saturated $NaHCO_3$ (15 mL) and extracted with EtOAc (3 × 10 mL). The combined organic extracts were washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. Purification by flash chromatography (20% acetone in petroleum ether) afforded a 3:1 mixture of *E* and *Z* isomers as a white solid (161 mg, 1.02 mmol, 97%). Recrystallization from hot EtOAc and hexanes gave 116 mg (70%) of pure *E*-isomer. mp 148-149 °C; ^{1}H-NMR (400 MHz; acetone-d_6): δ 10.76 (s, 1H), 7.39 (s, 1H), 7.20 (m, 1H), 6.75 (m, 1H), 6.39 (m, 1H), 3.83 (s, 2H); ^{13}C-NMR (101 MHz, acetone-d_6): δ 137.17 (CH), 126.95 (C), 124.65 (CH), 120.47 (C), 116.73 (C), 115.97 (CH), 112.60 (CH), 94.97 (C), 19.80 (CH_2); HRMS (FAB) calcd for $C_9H_7N_3$ [M]+, 157.0640; found, 157.0640.

1.4 Optimizing Conditions for Annulation of 2a to Indolizine 3a



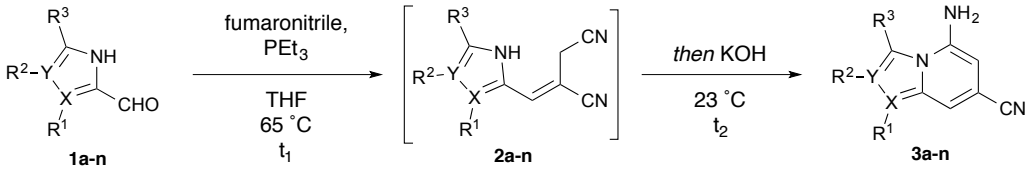
2a **3a**

General Procedure. To a stirring solution of alkene **2a** (50 mg, 0.32 mmol) in THF (3.2 mL) was added the base as a single portion. The mixture was stirred at the temperature indicated until conversion was complete as determined by TLC. The reaction was quenched with saturated NH_4Cl (10 mL) and extracted with EtOAc (3 × 10 mL). The combined organic extracts were washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. Purification by crystallization from hot EtOAc and hexanes afforded the indolizine **3a**. See Table 1 in the manuscript for specific information regarding temperature, base identity, number of base equivalents, reactions times, and yields.



5-Aminoindolizine-7-carbonitrile (3a). mp 219-200 °C; ^{1}H-NMR (400 MHz; acetone-d_6): δ 7.63 (d, *J* = 1.7 Hz, 1H), 7.44 (s, 1H), 6.96 (t, *J* = 3.2 Hz, 1H), 6.69 (d, *J* = 3.2 Hz, 1H), 6.06 (s, 2H), 5.95 (d, *J* = 1.7 Hz, 1H); ^{13}C-NMR (101 MHz, acetone-d_6): δ 142.05 (C), 133.18 (C), 120.43 (C), 116.24 (CH), 115.07 (CH), 111.15 (CH), 104.18 (CH), 102.18 (C), 87.93 (CH); IR (cm^{-1}) 3427, 3335, 3029, 2217, 1651, 1629, 1538; HRMS (EI) calcd for $C_9H_7N_3$ [M]+, 157.0640; found, 157.0641.

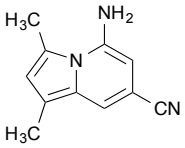
1.5 One-Pot Wittig/Annulation Sequence



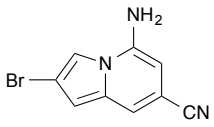
entry	aldehyde	X	Y	R^1	R^2	R^3	t_1 (h)	t_2 (h)	product	yield (%)[a]
1	1a	-C-	-C-	-H	-H	-H	8	0.5	3a	74
2	1b	-C-	-C-	$-CH_3$	-H	$-CH_3$	8	1	3b	73
3	1c	-C-	-C-	-H	-Br	-H	8	0.5	3c	67
4	1d	-C-	-C-	-H	-Ph	-H	8	0.5	3d	72
5	1e	-C-	-C-	-H	-H	$-CH_3$	8	1	3e	74
6	1f	-C-	-C-	-H	-H	$-CH_2CH{=}CH_2$	8	1	3f	72
7	1g	-C-	-C-	-H	-H	$-CH_2Ph$	8	1	3g	72
8	1h	-C-	-C-	$-CH_3$	$-CO_2Me$	$-CH_3$	10	2	3h	65
9	1i	-C-	-N-	-H	--	-H	3	9	3i	72
10	1j	-C-	-N-	$-CH_3$	--	-H	5	9	3j	65
11	1k	-C-	-N-	-H	--	$-CH_3$	4	10	3k	71
12	1l	-C-	-N-	-Cl	--	-Ph	5	16	3l	69
13	1m	-N-	-C-	--	-H	-H	3	12	3m	72
14	1n	-N-	-C-	--	$-CH_3$	$-CH_3$	5	14	3n	73

[a]Isolated yield.

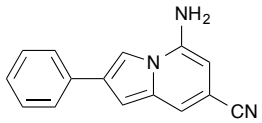
General Procedure. To a stirring 0.25 M solution of the aldehyde (1.0 equiv.) in anhydrous THF at room temperature was added fumaronitrile (1.25 equiv.) followed by triethylphosphine (1.20 equiv.) dropwise. The reaction mixture was heated to 65 °C. The reaction was monitored by TLC for disappearance of starting material (3-10 h), then allowed to cool to room temperature. KOH (0.40 equiv.) was added as a single portion, and the reaction mixture was stirred for the time described (0.5-16 h) at room temperature. The reaction was quenched with saturated NH_4Cl and extracted with EtOAc (×3). The combined organic extracts were washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. Purification by either flash chromatography (eluted with ~20% acetone in petroleum ether for the indolizines, ~40% acetone in petroleum ether for the imidazopyridines) or crystallization afforded the desired cyclized products.



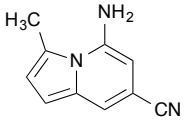
5-amino-1,3-dimethylindolizine-7-carbonitrile (03b). 73% yield; mp 156-158 °C; ^{1}H-NMR (300 MHz; acetone-d_6): δ 7.25 (d, *J* = 1.6 Hz, 1H), 6.42 (s, 1H), 5.68 (d, *J* = 1.6 Hz, 1H), 5.42 (s, 2H), 2.96 (s, 3H), 2.26 (s, 3H); ^{13}C-NMR (101 MHz, acetone-d_6): δ 144.65 (C), 131.99 (C), 123.79 (C), 120.61 (C), 119.44 (CH), 115.98 (CH), 112.77 (C), 98.97 (C), 89.53 (CH), 16.01 (CH_3), 10.52 (CH_3); IR (cm^{-1}) 3429, 3347, 3083, 2917, 2203, 1636, 1607, 1558; HRMS (FAB) calcd for $C_{11}H_{11}N_3$ [M]+, 185.0953; found, 185.0955.



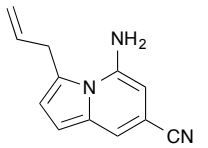
5-Amino-2-bromoindolizine-7-carbonitrile (3c). 67% yield; mp 202-203 °C; ^{1}H-NMR (400 MHz; acetone-d_6): δ 7.74 (s, 1H), 7.41 (s, 1H), 6.77 (s, 1H), 6.19 (s, 2H), 6.04 (s, 1H); ^{13}C-NMR (101 MHz, acetone-d_6): δ 141.61 (C), 133.65 (C), 119.84 (C), 113.51 (CH), 110.96 (CH), 105.85 (C), 105.81 (CH), 104.07 (C), 88.97 (CH); IR (cm^{-1}) 3438, 3342, 3145, 2221, 1632, 1541, 1322; HRMS (FAB) calcd for $C_9H_6(^{79}Br)N_3$ [M]+, 234.9745; found, 234.9741; $C_9H_6(^{81}Br)N_3$ [M]+, 236.9725; found, 236.9737.



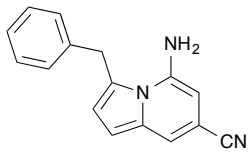
5-Amino-2-phenylindolizine-7-carbonitrile (3d). 72% yield; mp 230-232 °C; ^{1}H-NMR (400 MHz; acetone-d_6): δ 8.07 (s, 1H), 7.77 (d, *J* = 7.4 Hz, 2H), 7.44–7.40 (m, 3H), 7.28 (t, *J* = 7.4 Hz, 1H), 7.06 (s, 1H), 6.13 (s, 2H), 5.99 (s, 1H); ^{13}C-NMR (101 MHz, acetone-d_6): δ 142.01 (C), 135.58 (C), 134.14 (C), 131.92 (C), 129.73 (CH), 127.86 (CH), 126.87 (CH), 120.31 (C), 114.73 (CH), 108.16 (CH), 102.95 (C), 101.36 (CH), 88.48 (CH); IR (cm^{-1}) 3429, 3336, 3139, 2217, 1603, 1495; HRMS (FAB) calcd for $C_{15}H_{11}N_3$ [M]+, 233.0953; found, 233.0955.



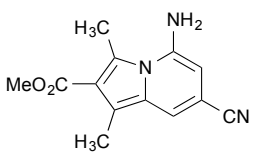
5-Amino-3-methylindolizine-7-carbonitrile (3e). 74% yield; mp 134-135 °C; ^{1}H-NMR (400 MHz; acetone-d_6): δ 7.31 (s, 1H), 6.57 (d, *J* = 3.9 Hz, 1H), 6.50 (d, *J* = 3.9 Hz, 1H), 5.77 (s, 1H), 5.53 (s, 2H), 3.00 (s, 3H); ^{13}C-NMR (101 MHz, acetone-d_6): δ 144.91 (C), 134.75 (C), 124.74 (C), 120.29 (C), 117.97 (CH), 117.48 (CH), 103.76 (CH), 100.68 (C), 90.08 (CH), 16.23 (CH_3); IR (cm^{-1}) 3414, 3343, 2208, 1634, 1542, 1472; HRMS (FAB) calcd for $C_{10}H_9N_3$ [M]+, 171.0797; found, 171.0794.



3-Allyl-5-aminoindolizine-7-carbonitrile (3f). 72% yield; R_f = 0.30 (25% acetone/petroleum ether); ^{1}H-NMR (400 MHz; acetone-d_6): δ 7.39 (s, 1H), 6.69 (d, *J* = 4.0 Hz, 1H), 6.60 (d, *J* = 4.0 Hz, 1H), 6.23 (ddt, *J* = 17.0, 10.5, 5.7 Hz, 1H), 5.86 (s, 1H), 5.45 (s, 2H), 5.20 (dd, *J* = 10.5, 1.1 Hz, 1H), 4.98 (dd, *J* = 17.0, 1.1 Hz, 1H), 4.17 (d, *J* = 5.7 Hz, 2H); ^{13}C-NMR (101 MHz, acetone-d_6): δ 144.48 (C), 139.11 (CH_2), 135.20 (C), 126.57 (C), 120.15 (C), 118.19 (CH), 117.51 (CH), 117.28 (CH), 104.10 (CH), 101.06 (C), 90.84 (CH), 34.25 (CH_2); IR (cm^{-1}) 3399, 3331, 2208, 1633, 1540, 1440; HRMS (FAB) calcd for $C_{12}H_{11}N_3$ [M]+, 197.0953; found, 197.0960.

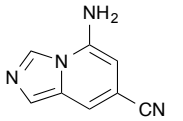


5-Amino-3-benzylindolizine-7-carbonitrile (3g). 72% yield; mp 121-122 °C; ^{1}H-NMR (400 MHz; acetone-d_6): δ 7.39 (s, 1H), 7.32 (t, *J* = 7.5 Hz, 2H), 7.23 (t, *J* = 7.3 Hz, 1H), 7.14 (d, *J* = 7.6 Hz, 2H), 6.61 (s, 2H), 5.79 (s, 1H), 5.27 (br. s, 2H), 4.77 (s, 2H); ^{13}C-NMR (101 MHz, acetone-d_6): δ 144.47 (C), 141.47 (C), 135.42 (C), 129.70 (CH), 129.15 (CH), 127.42 (CH), 127.25 (C), 120.08 (C), 119.42 (CH), 117.58 (CH), 104.11 (CH), 101.22 (C), 90.95 (CH), 35.87 (CH_2); IR (cm^{-1}) 3413, 3343, 2210, 1635, 1540, 1472; HRMS (FAB) calcd for $C_{16}H_{13}N_3$ [M]+, 247.1110; found, 247.1108.

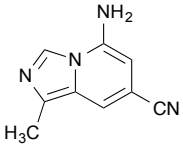


Methyl 5-amino-7-cyano-1,3-dimethylindolizine-2-carboxylate (3h). 65% yield; R_f = 0.30 (25% acetone/petroleum ether); ^{1}H-NMR (400 MHz; acetone-

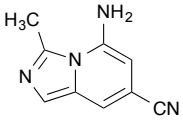
d_6): δ 7.42 (s, 1H), 5.80 (s, 1H), 5.62 (br. s, 2H), 3.88 (s, 3H), 3.26 (s, 3H), 2.44 (s, 3H); ^{13}C-NMR (101 MHz, acetone-d_6): δ 166.74 (C), 145.41 (C), 131.46 (C), 128.62 (C), 119.93 (C), 119.57 (C), 116.97 (CH), 114.72 (C), 101.27 (C), 91.39 (CH), 51.41 (CH_3), 14.20 (CH_3), 10.83 (CH_3); IR (cm^{-1}) 3428, 3335, 3139, 2983, 2217, 1738, 1628, 1537, 1220; HRMS (FAB) calcd for $C_{13}H_{13}N_3O_2$ [M]+, 243.1008; found, 243.1007.



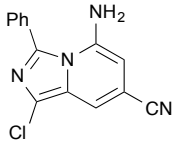
5-aminoimidazo[1,5-a]pyridine-7-carbonitrile (3i). 72% yield; mp 226-227 °C; ^{1}H-NMR (300 MHz; acetone-d_6): δ 8.47 (s, 1H), 7.61 (s, 1H), 7.58 (d, *J* = 1.3 Hz, 1H), 6.40 (s, 2H), 5.93 (d, *J* = 1.3 Hz, 1H); ^{13}C-NMR (101 MHz, acetone-d_6): δ 140.79 (C), 130.80 (C), 126.83 (C), 124.46 (CH), 119.60 (C), 114.00 (CH), 105.13 (CH), 88.64 (CH); IR (cm^{-1}) 3401, 3136, 2222, 1659, 1544, 1118; HRMS (FAB) calcd for $C_8H_6N_4$ [M]+, 159.0671; found, 159.0669.



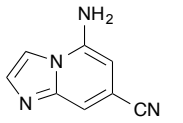
5-amino-1-methylimidazo[1,5-a]pyridine-7-carbonitrile (3j). 65% yield; mp 233-234 °C; ^{1}H-NMR (400 MHz; MeOD): δ 8.30 (s, 1H), 7.38 (s, 1H), 5.75 (s, 1H), 2.47 (s, 3H); ^{13}C-NMR (100 MHz, MeOD): δ 141.22 (C), 132.51 (C), 127.72 (C), 125.40 (CH), 120.12 (C), 113.82 (CH), 104.49 (C), 88.51 (CH), 12.37 (CH_3); IR (cm^{-1}) 3398, 3331, 2209, 1633, 1541, 1441; HRMS (FAB) calcd for $C_9H_8N_4$ [M]+, 172.0749; found, 172.0744.



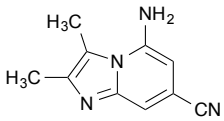
5-amino-3-methylimidazo[1,5-a]pyridine-7-carbonitrile (3k). 71% yield; mp 214-215 °C; ^{1}H-NMR (400 MHz; MeOD): δ 8.30 (s, 1H), 7.38 (s, 1H), 5.75 (s, 1H), 2.47 (s, 3H); ^{13}C-NMR (100 MHz, MeOD): δ 141.22 (C), 132.51 (C), 127.72 (C), 125.40 (CH), 120.12 (C), 113.82 (CH), 104.49 (C), 88.51 (C), 12.37 (CH_3); IR (cm^{-1}) 3437, 3340, 2221, 1645, 1539, 1431; HRMS (FAB) calcd for $C_9H_9N_4$ [M+H]+, 173.0828; found, 173.0828.



5-amino-1-chloro-3-phenylimidazo[1,5-a]pyridine-7-carbonitrile (3l). 69% yield; mp 201-202 °C; ^{1}H-NMR (400 MHz; acetone-d_6): δ 8.04 (d, *J* = 6.8 Hz, 2H), 7.53-7.48 (m, 4H), 7.24 (s, 1H), 4.63-4.45 (m, 2H); ^{13}C-NMR (101 MHz, DMSO-d_6): δ 146.75 (C), 133.45 (C), 131.82 (C), 129.71 (CH), 128.90 (CH), 128.56 (CH), 125.50 (CH), 122.06 (C), 119.21 (C), 117.11 (C), 99.07 (C), 18.44 (CH_2); IR (cm^{-1}) 3190, 2207, 1621, 1479; HRMS (FAB) calcd for $C_{14}H_9{}^{35}ClN_4$ [M]+, 269.0594; found, 269.0587; $C_{14}H_9{}^{37}ClN_4$ [M]+, 271.0565; found, 271.0566.



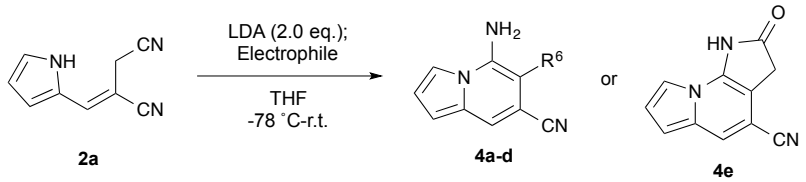
5-aminoimidazo[1,2-a]pyridine-7-carbonitrile (3m). 72% yield; R_f = 0.35 (40% acetone/petroleum ether); ^{1}H-NMR (400 MHz; acetone-d_6): δ 7.98 (s, 1H), 7.75 (d, *J* = 1.4 Hz, 1H), 7.43 (s, 1H), 6.52 (s, 1H), 6.24 (d, *J* = 1.4 Hz, 1H); ^{13}C-NMR (101 MHz, MeOD): δ 144.74 (C), 143.53 (C), 133.74 (CH), 117.93 (C), 110.24 (C), 109.22 (CH), 107.97 (CH), 90.10 (CH); IR (cm^{-1}) 3382, 3152, 2233, 1664, 1544, 1494; HRMS (EI) calcd for $C_8H_6N_4$ [M+H]+, 159.0671; found, 159.0667.



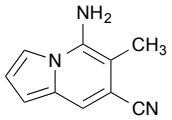
5-amino-2,3-dimethylimidazo[1,2-a]pyridine-7-carbonitrile (3n). 73% yield; mp 220-221 °C; ^{1}H-NMR (400 MHz; MeOD): δ 7.09 (s, 1H), 6.01 (s, 1H), 2.80

(s, 3H), 2.31 (s, 3H); ^{13}C-NMR (101 MHz, MeOD): δ 146.83 (C), 145.52 (C), 142.59 (C), 119.31 (C), 110.87 (CH), 110.82 (C), 109.74 (C), 93.60 (CH), 12.91 (CH_3), 11.54 (CH_3); IR (cm^{-1}) 3443, 2226, 1656, 1532, 1381; HRMS (FAB) calcd for $C_{10}H_{10}N_4$ [M+H]+, 187.0984; found, 187.0985.

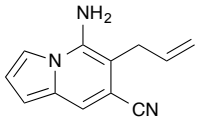
1.6 One-Pot Alkylation/Cyclization Sequence of 2a to Indolizines 4a-e



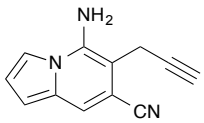
General Procedure. To a stirring solution of alkene **2a** (100 mg, 0.63 mmol) in THF (6.3 mL) at -78 °C was added freshly prepared 1.0 M LDA (1.27 mL, 1.27 mmol) dropwise. The mixture was allowed to stir at -78 °C for 45 min before slow addition of the electrophile (1.0 equiv). The reaction mixture was stirred at -78 °C for 1.5 h, then allowed to warm to room temperature over 10 minutes. The reaction was quenched with saturated NH_4Cl (15 mL) and the crude mixture was extracted with EtOAc (3 × 15 mL). The combined organic extracts were washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. Purification by flash chromatography (eluted with ~20% acetone in petroleum ether) or crystallization from hot EtOAc and hexanes afforded the desired indolizines.



5-amino-6-methylindolizine-7-carbonitrile (4a). 87% yield; R_f = 0.30 (20% acetone/petroleum ether); ^{1}H-NMR (400 MHz; acetone-d_6): δ 7.62-7.62 (m, 1H), 7.47 (s, 1H), 6.92 (dd, *J* = 4.0, 2.8 Hz, 1H), 6.63 (dd, *J* = 4.0, 1.1 Hz, 1H), 5.78 (s, 2H), 2.34 (s, 3H); ^{13}C-NMR (101 MHz, acetone-d_6): δ 132.75 (C), 129.17 (C), 127.60 (C), 126.49 (CH), 121.21 (CH), 116.63 (CH), 114.07 (C), 105.65 (CH), 103.57 (C), 14.91 (CH_3); IR (cm^{-1}) 3368, 3326, 2213, 1651, 1529, 1319; HRMS (FAB) calcd for $C_{10}H_9N_3$ [M]+, 171.0797; found, 171.0794.

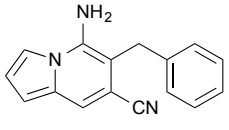


6-allyl-5-aminoindolizine-7-carbonitrile (4b). 98% yield; R_f = 0.30 (20% acetone/petroleum ether); ^{1}H-NMR (400 MHz; acetone-d_6): δ 7.66-7.65 (m, 1H), 7.52 (s, 1H), 6.94 (t, *J* = 3.7 Hz, 1H), 6.66 (d, *J* = 3.7 Hz, 1H), 6.02-5.92 (m, 1H), 5.80 (s, 2H), 5.09 (d, *J* = 17.2 Hz, 1H), 5.04 (d, *J* = 10.0 Hz, 1H), 3.55 (d, *J* = 5.9 Hz, 2H); ^{13}C-NMR (100 MHz, acetone-d_6): δ 138.90 (C), 135.75 (CH), 132.33 (C), 119.63 (C), 116.25 (CH), 115.93 (CH), 115.74 (CH), 111.10 (CH), 104.61 (C), 103.85 (CH), 96.08 (C), 32.62 (CH_2); IR (cm^{-1}) 3399, 3331, 2208, 1634, 1540, 1440; HRMS (FAB) calcd for $C_{12}H_{11}N_3$ [M]+, 197.0953; found, 197.0958.

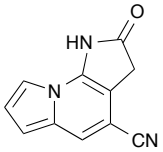


5-amino-6-(prop-2-yn-1-yl)indolizine-7-carbonitrile (4c). 94% yield; R_f = 0.30 (20% acetone/petroleum ether); ^{1}H-NMR (400 MHz; acetone-d_6): δ 7.70 (m, 1H), 7.53 (s, 1H), 6.96 (t, *J* = 3.7 Hz, 1H), 6.68 (d, *J* = 3.7 Hz, 1H), 6.01 (s, 2H), 3.72 (d, *J* = 2.6 Hz, 2H), 2.52 (t, *J* = 2.6 Hz, 1H); ^{13}C-NMR (101 MHz, acetone-d_6): δ 139.08 (C), 132.31 (C), 119.27 (C), 116.52 (CH), 116.00 (CH), 111.48 (CH), 104.29 (CH), 103.87 (C),

93.88 (C), 81.32 (C), 71.01 (CH), 18.26 (CH_2); IR (cm^{-1}) 3428, 3336, 3309, 2216, 1629, 1536, 1323; HRMS (FAB) calcd for $C_{12}H_9N_3$ [M]+, 195.0796; found, 197.0795.



5-amino-6-benzylindolizine-7-carbonitrile (4d). 98% yield; R_f = 0.25 (20% acetone/petroleum ether); ^{1}H-NMR (400 MHz; acetone-d_6): δ 7.68 (m, 1H), 7.56 (s, 1H), 7.27 (d, J = 4.3 Hz, 4H), 7.18 (q, J = 4.3 Hz, 1H), 6.96 (t, J = 3.7 Hz, 1H), 6.69 (d, J = 3.7 Hz, 1H), 5.86 (s, 2H), 4.20 (s, 2H); ^{13}C-NMR (101 MHz, acetone-d_6): δ 140.43, 139.32, 132.38, 129.22, 128.90, 127.01, 119.87, 116.37, 116.13, 111.35, 105.00, 104.04, 97.52, 34.01; IR (cm^{-1}) 3340, 2216, 1698, 1639, 1538; HRMS (FAB) calcd for $C_{16}H_{13}N_3$ [M]+, 247.1110; found, 247.1099.



2-oxo-2,3-dihydro-1H-pyrrolo[2,3-e]indolizine-4-carbonitrile (4e). 90% yield; R_f = 0.30 (25% acetone/petroleum ether); ^{1}H-NMR (300 MHz; acetone-d_6): δ 10.62 (s, 1H), 7.73 (s, 1H), 7.65 (dd, J = 1.7, 0.7 Hz, 1H), 7.04 (dd, J = 4.1, 2.7 Hz, 1H), 6.83 (dd, J = 4.1, 0.7 Hz, 1H); ^{13}C-NMR (101 MHz, acetone-d_6): δ 175.53 (C), 137.22 (C), 133.31 (C), 118.43 (CH), 118.19 (C), 117.61 (CH), 111.62 (CH), 105.33 (CH), 98.82 (C), 98.51 (C), 36.07 (CH_2); IR (cm^{-1}) 3336, 3231, 2217, 1640, 1539, 1380; HRMS (FAB) calcd for $C_{11}H_7N_3O$ [M]+, 197.0589; found, 197.0595.

2 NMR Spectra

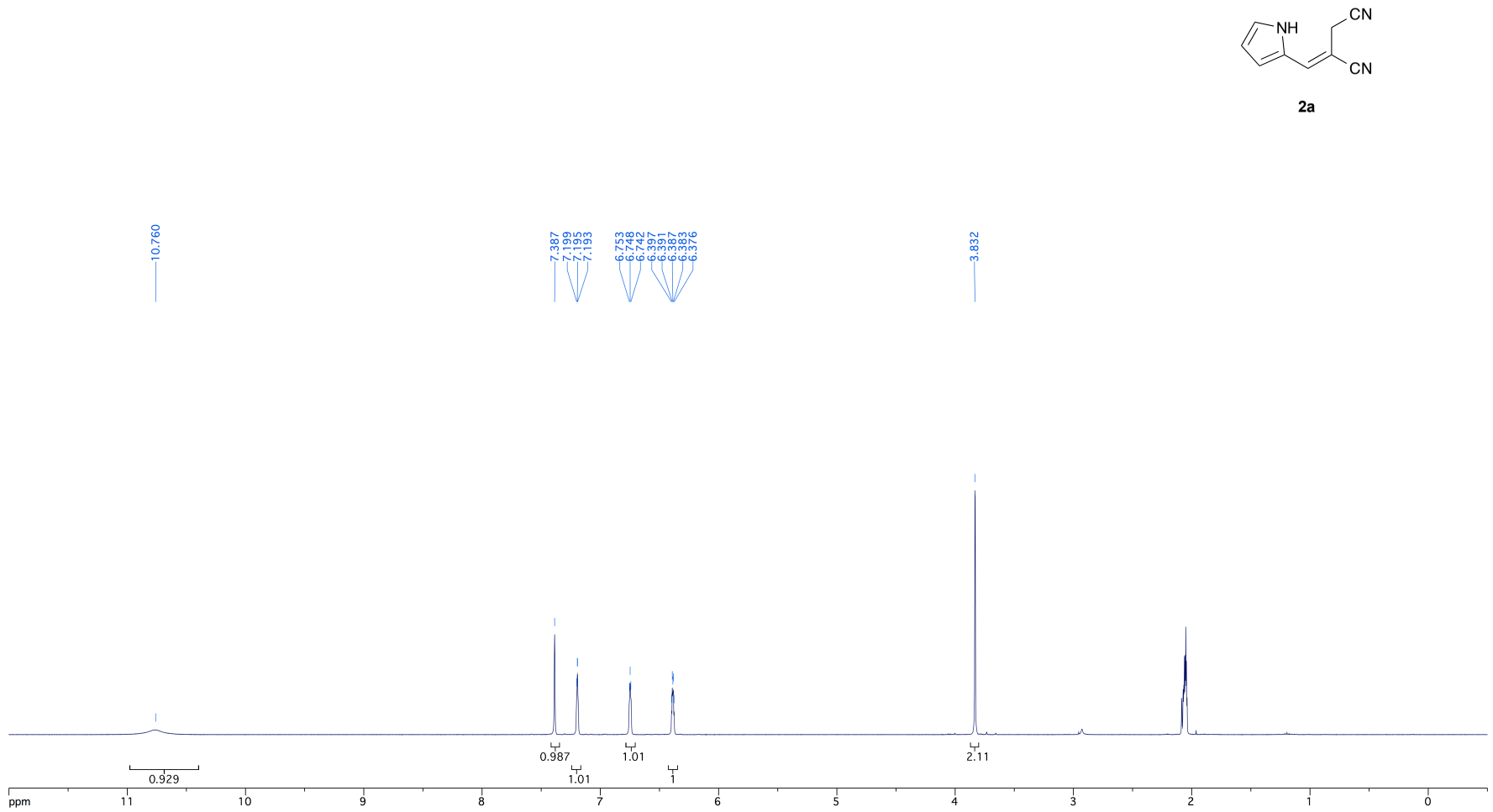


Figure 1 ^{1}H-NMR spectrum for compound 2a (Acetone-d_6, 400 MHz)

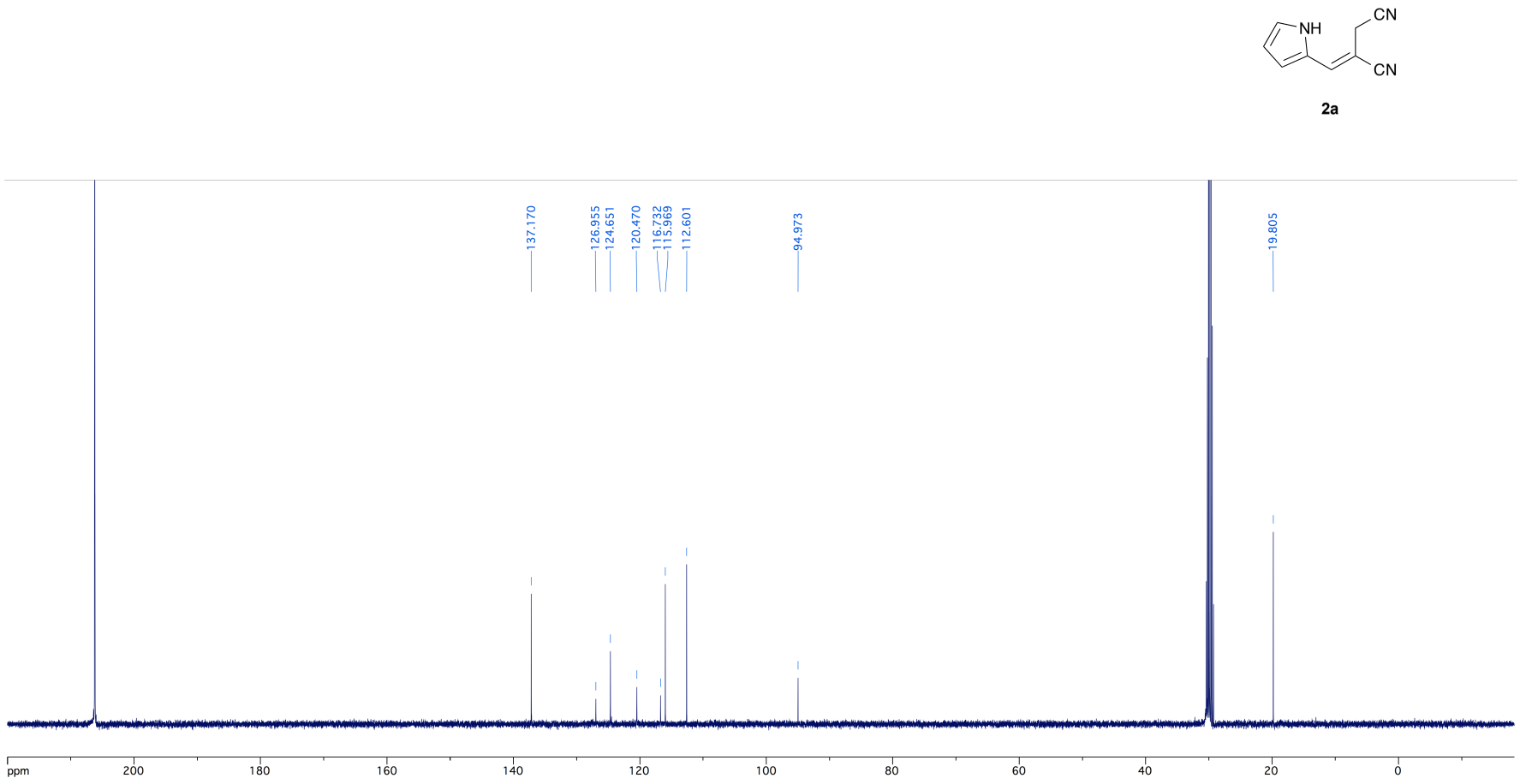


Figure 2 ^{13}C-NMR spectrum for compound 2a (Acetone-d_6, 100 MHz)

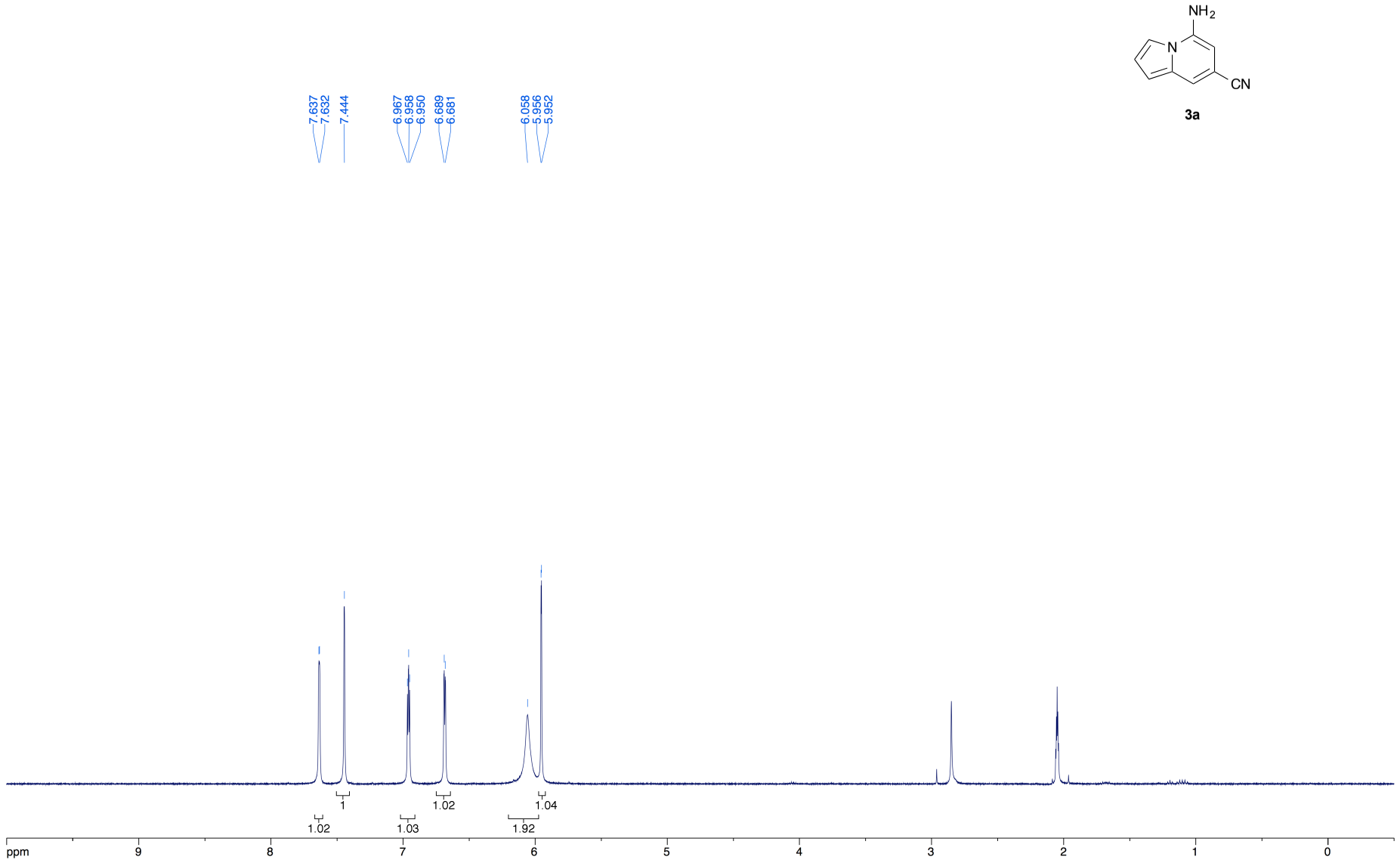


Figure 3 ^{1}H-NMR spectrum for compound 3a (Acetone-d_6, 400 MHz)

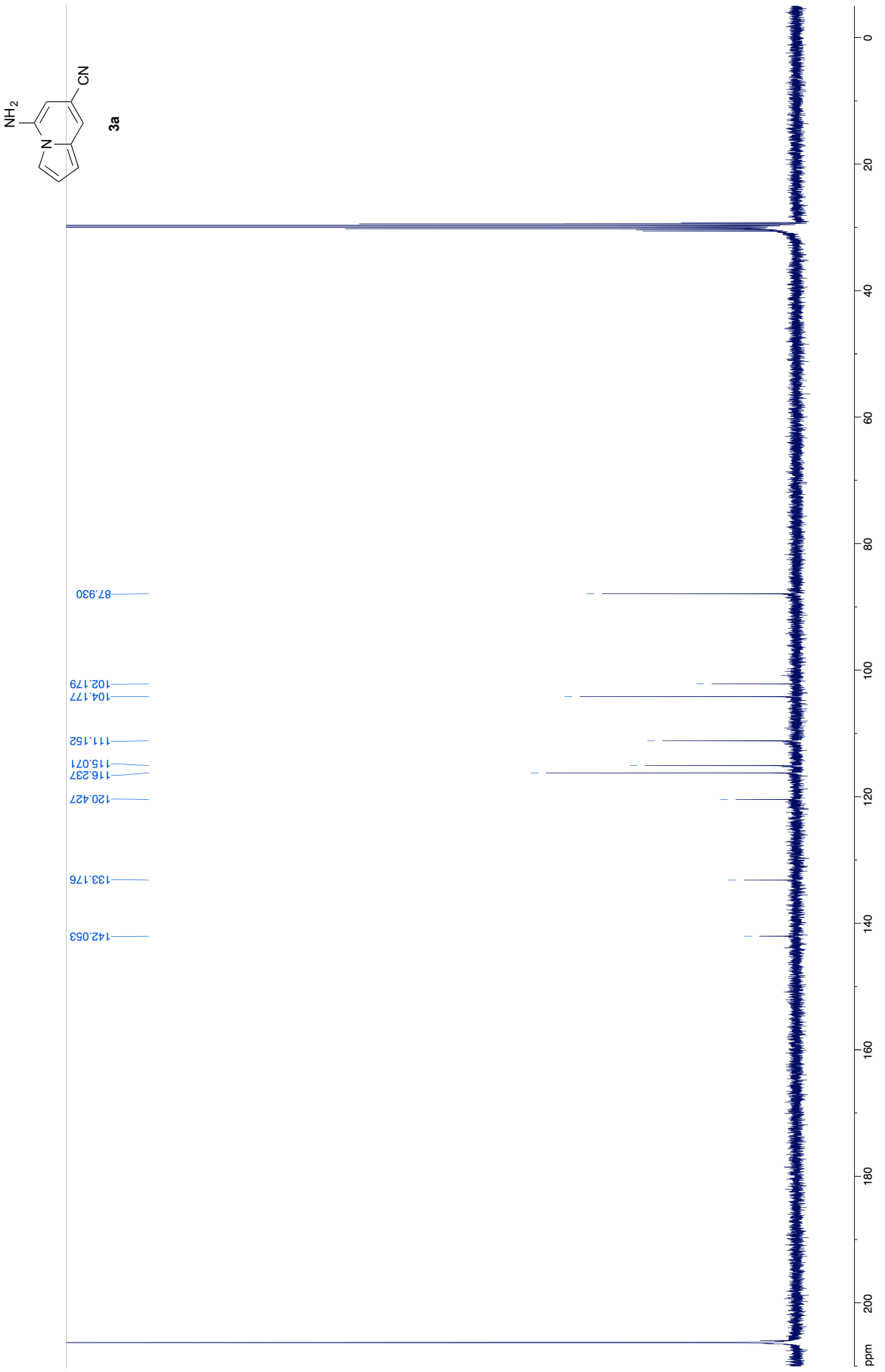


Figure 4 ^{13}C-NMR spectrum for compound 3a (Acetone-d$_6$, 100 MHz)

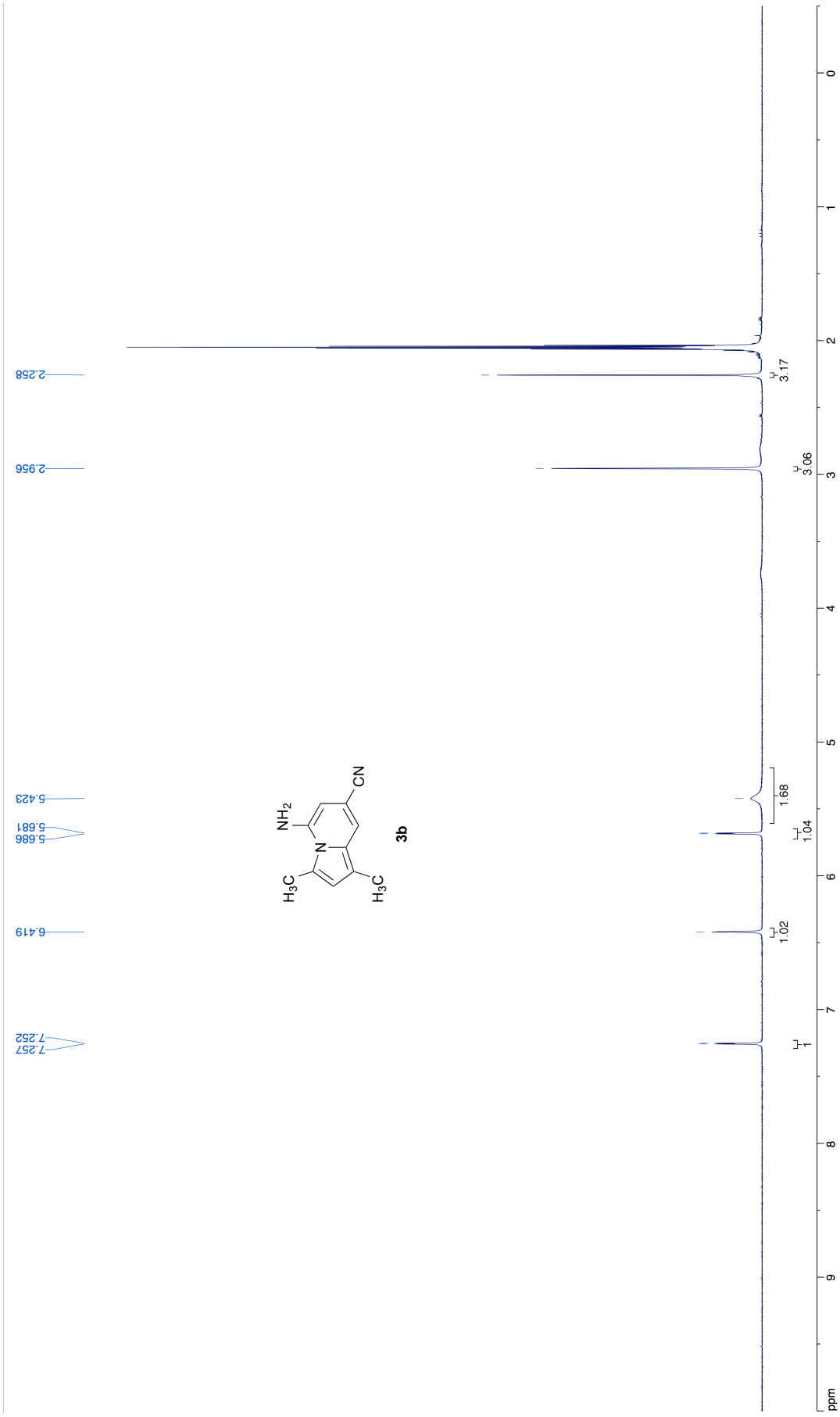


Figure S ^{1}H-NMR spectrum for compound 3b (Acetone-d_6, 400 MHz)

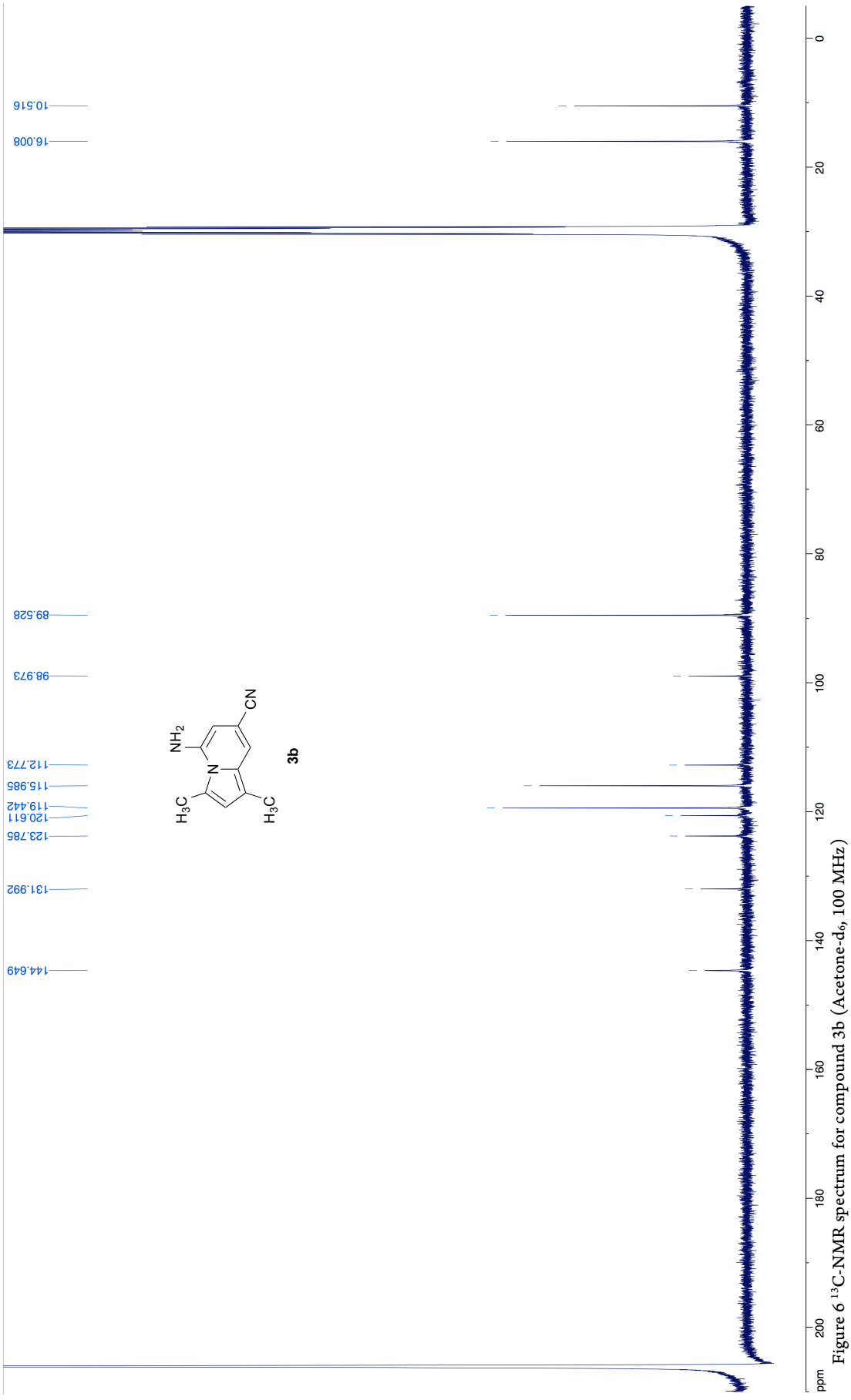


Figure 6 ^{13}C-NMR spectrum for compound 3b (Acetone-d_6, 100 MHz)

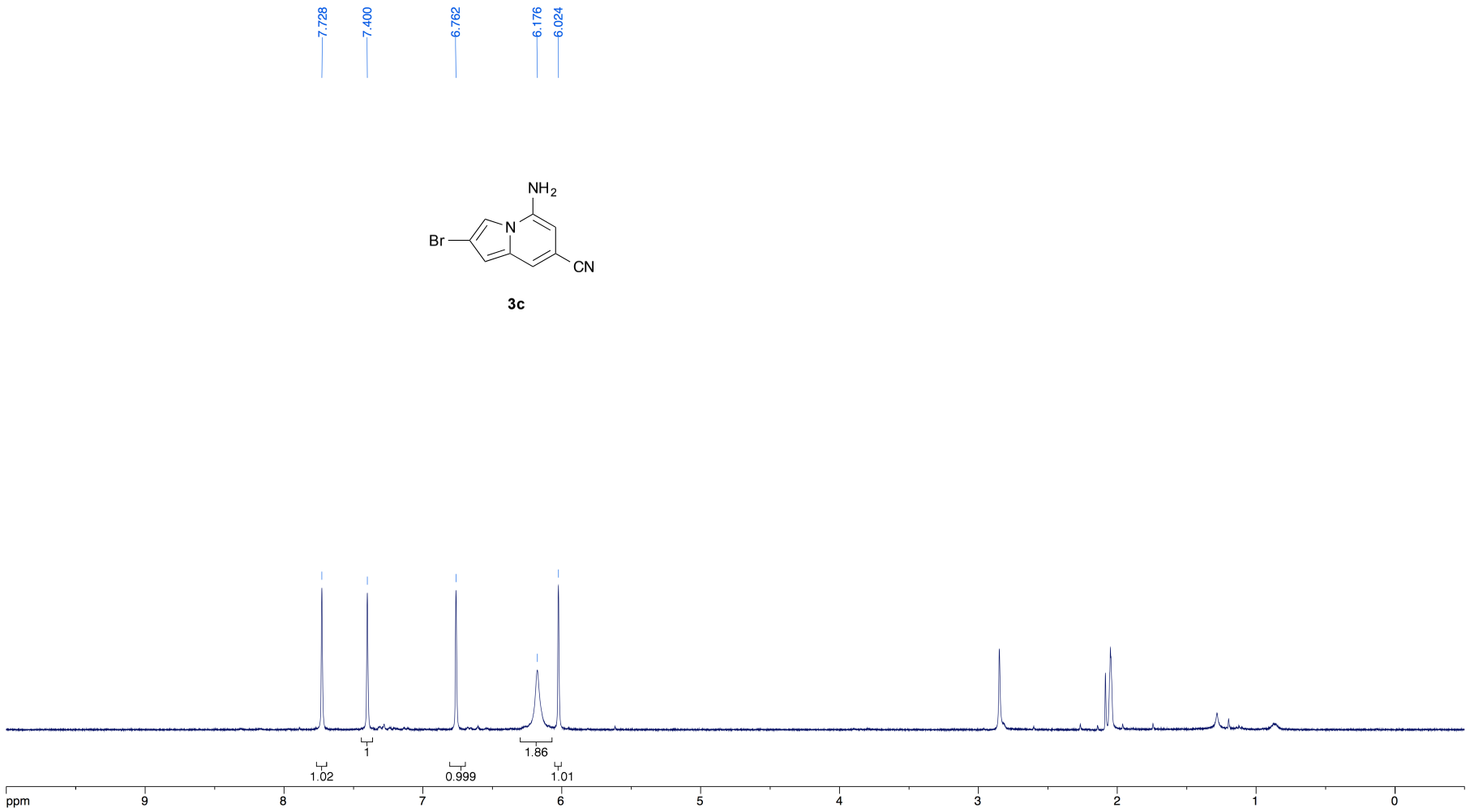


Figure 7 ^{1}H-NMR spectrum for compound 3c (Acetone-d_6, 400 MHz)

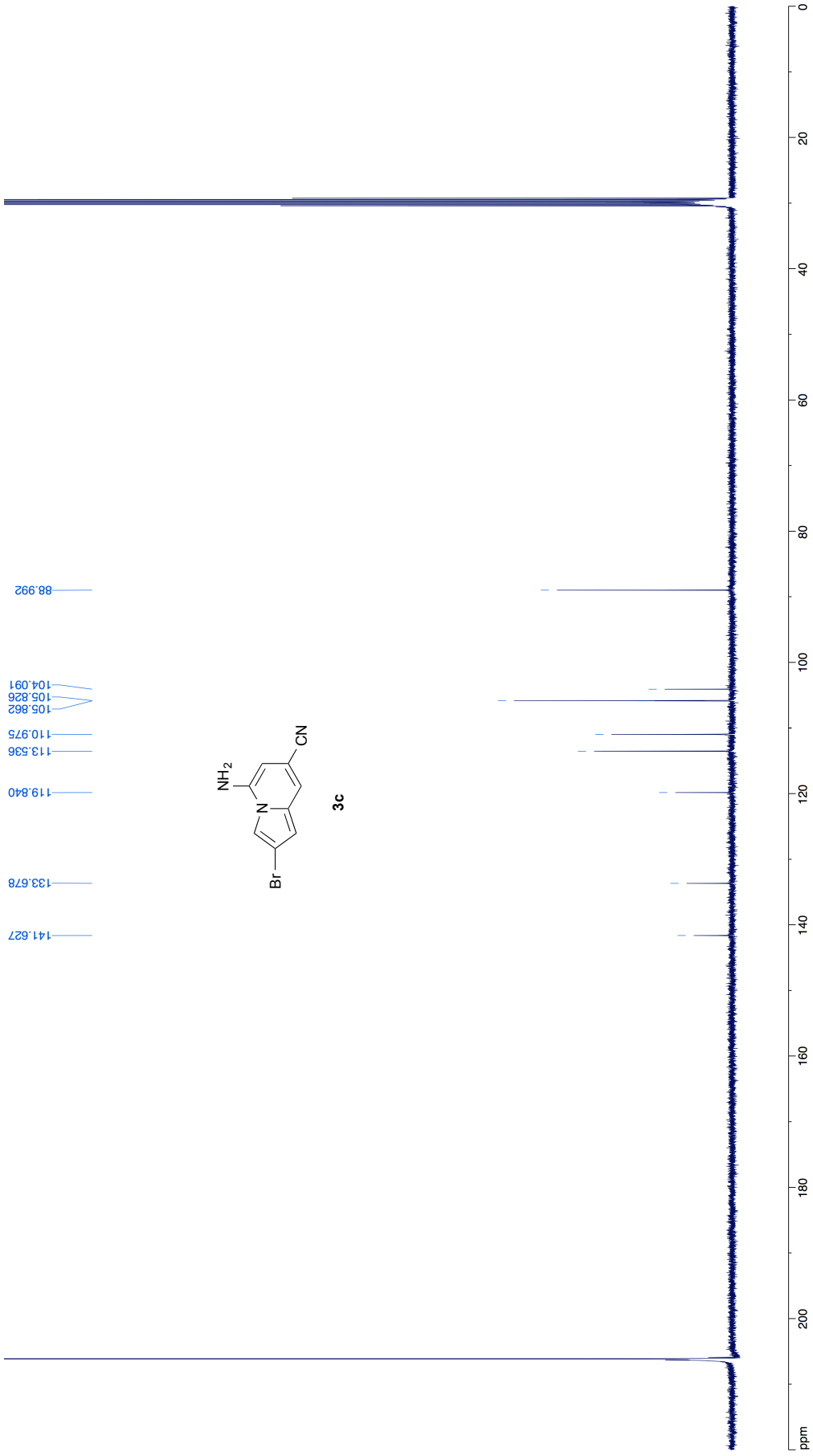


Figure 8 ^{13}C-NMR spectrum for compound 3c (Acetone-d$_6$, 100 MHz)

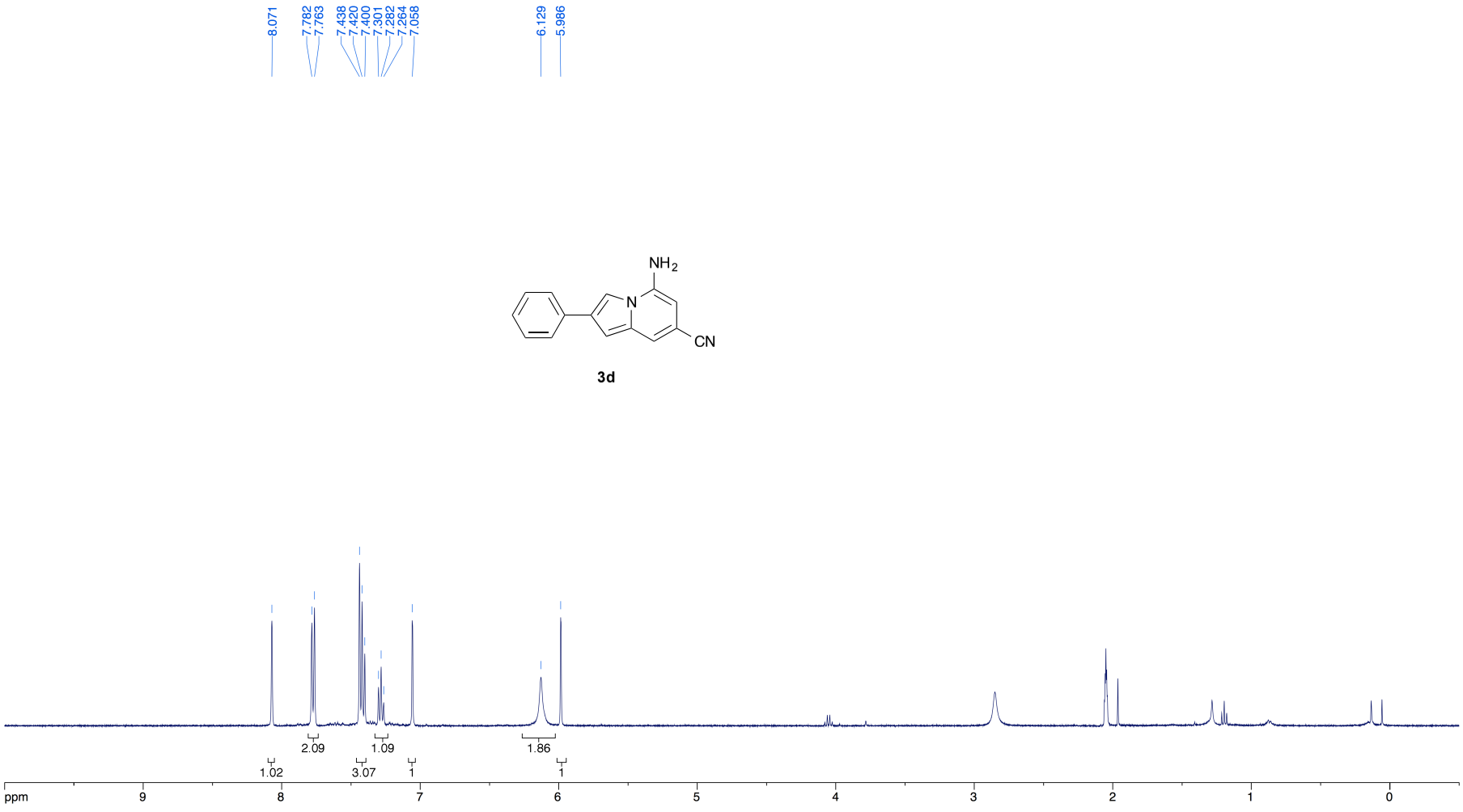


Figure 9 ^{1}H-NMR spectrum for compound 3d (Acetone-d_6, 400 MHz)

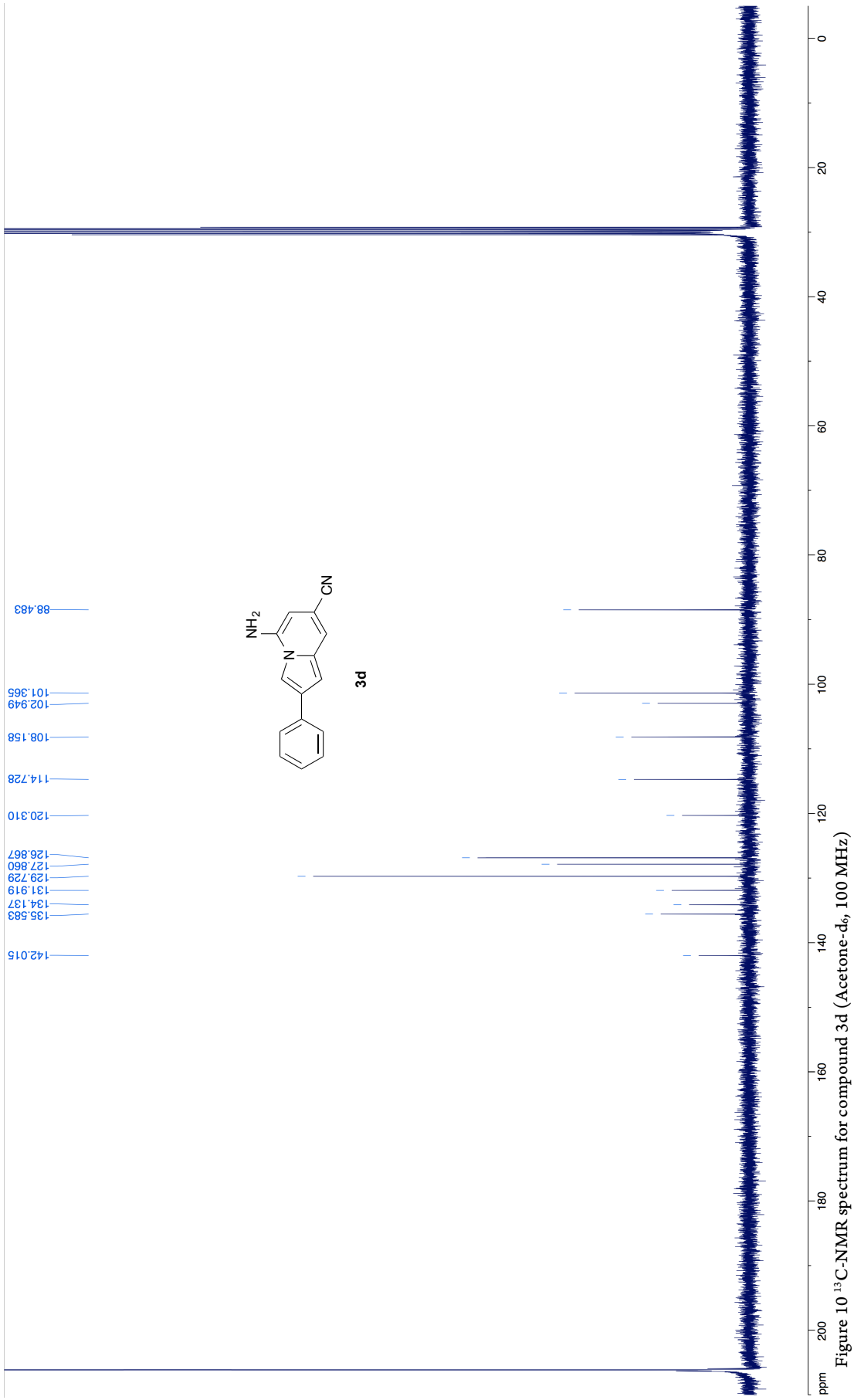


Figure 10 ^{13}C-NMR spectrum for compound 3d (Acetone-d_6, 100 MHz)

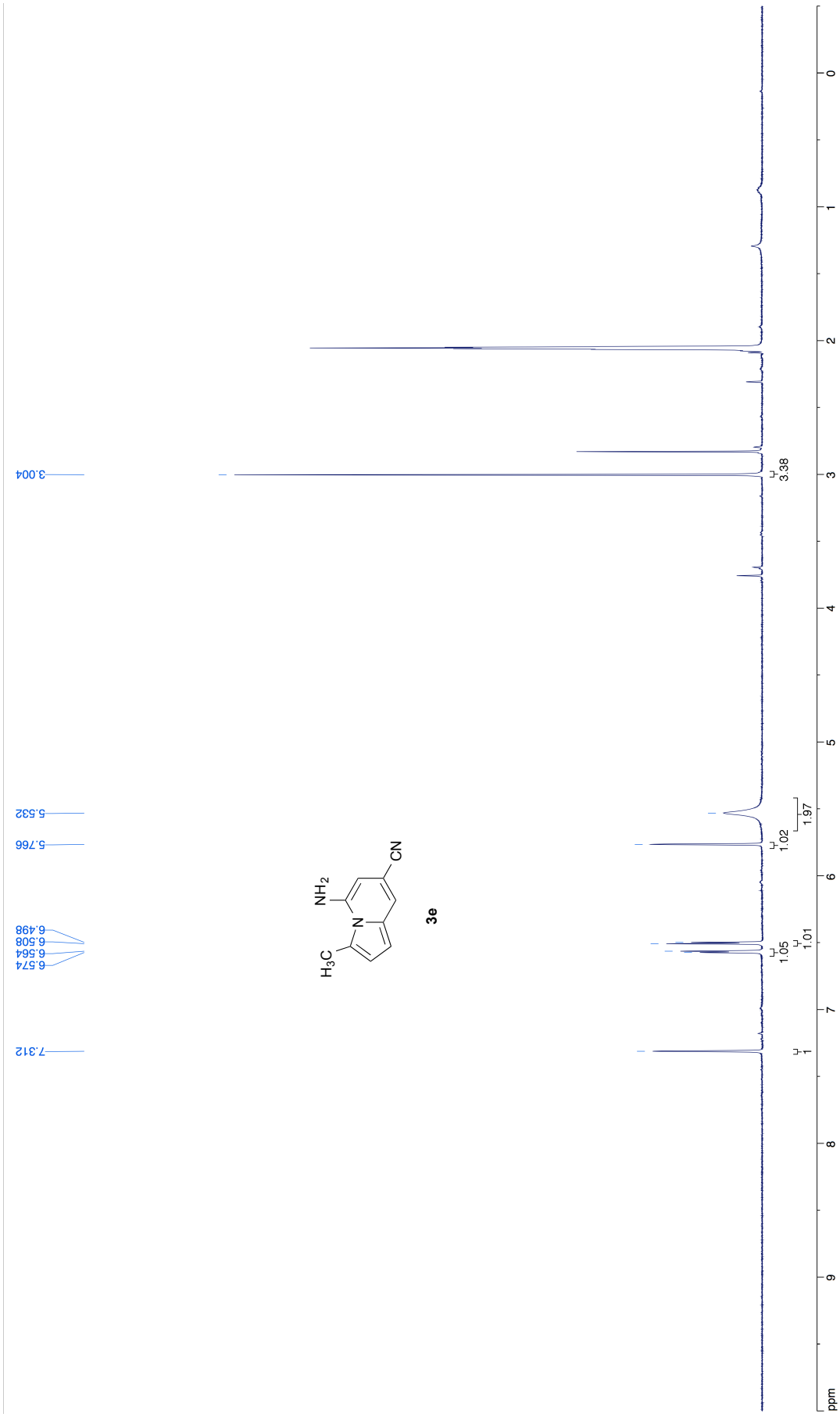


Figure 11 ^{1}H-NMR spectrum for compound 3e (Acetone-d_6, 400 MHz)

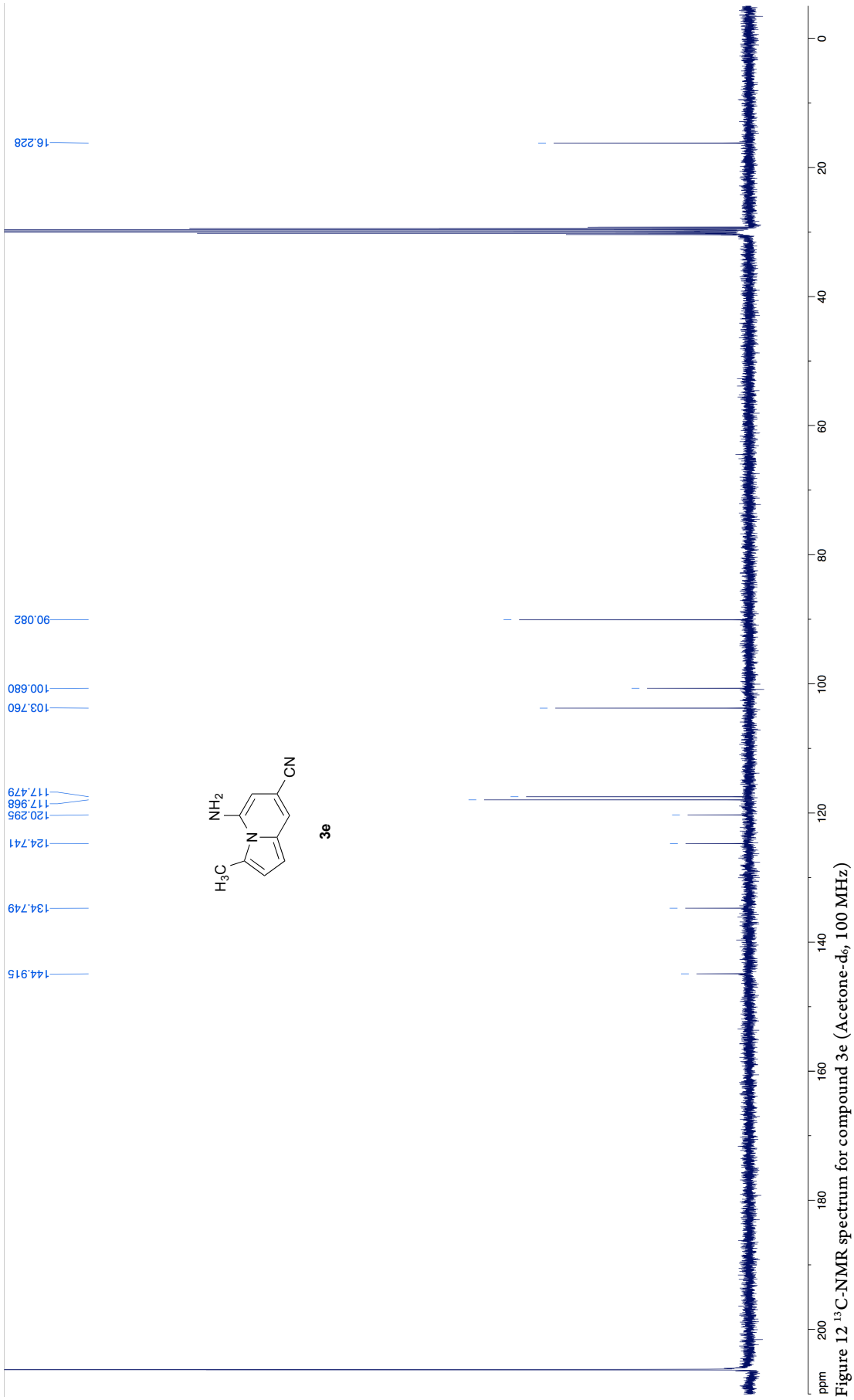


Figure 12 ^{13}C-NMR spectrum for compound 3e (Acetone-d_6, 100 MHz)

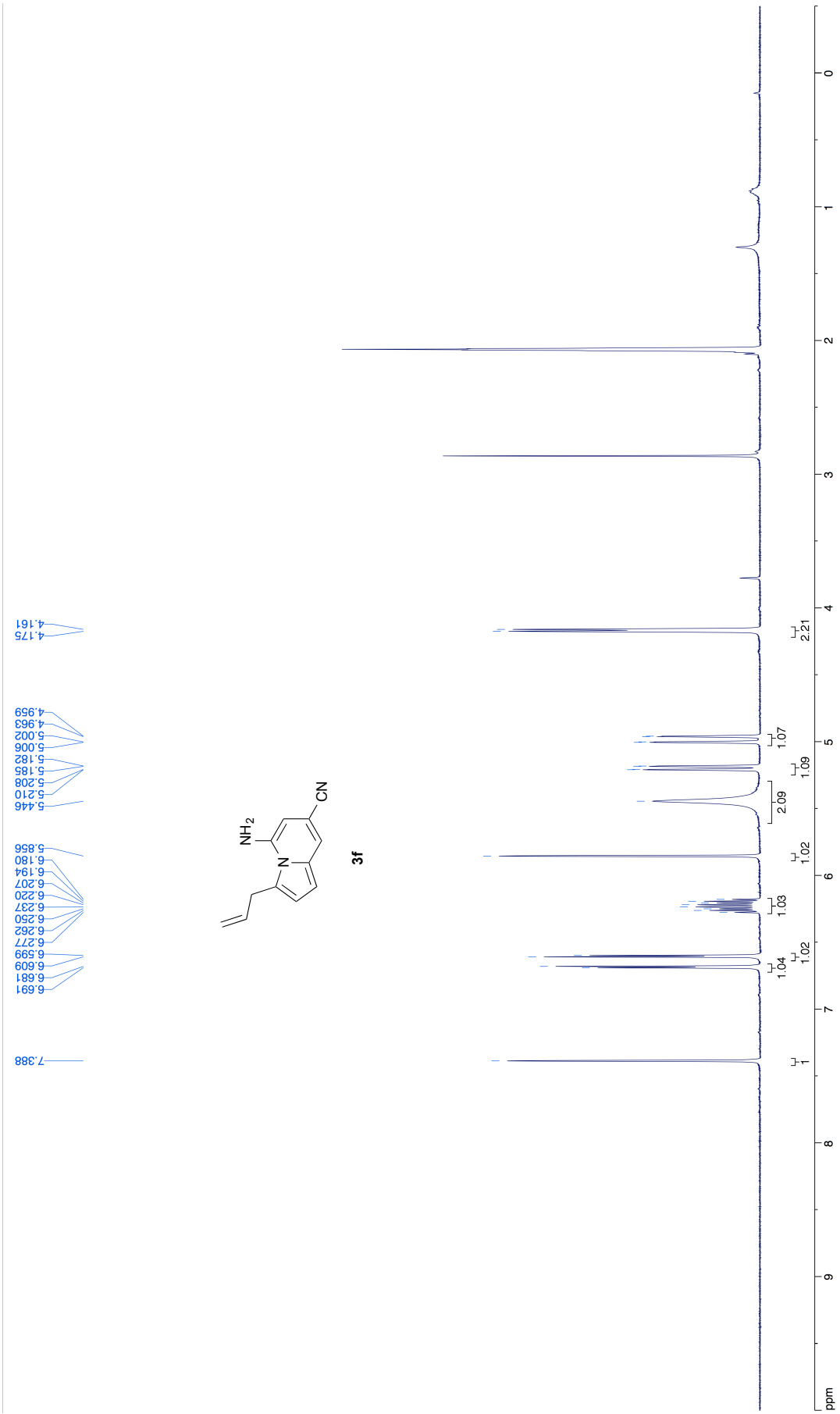


Figure 13 ^{1}H-NMR spectrum for compound 3f (Acetone-d$_6$, 400 MHz)

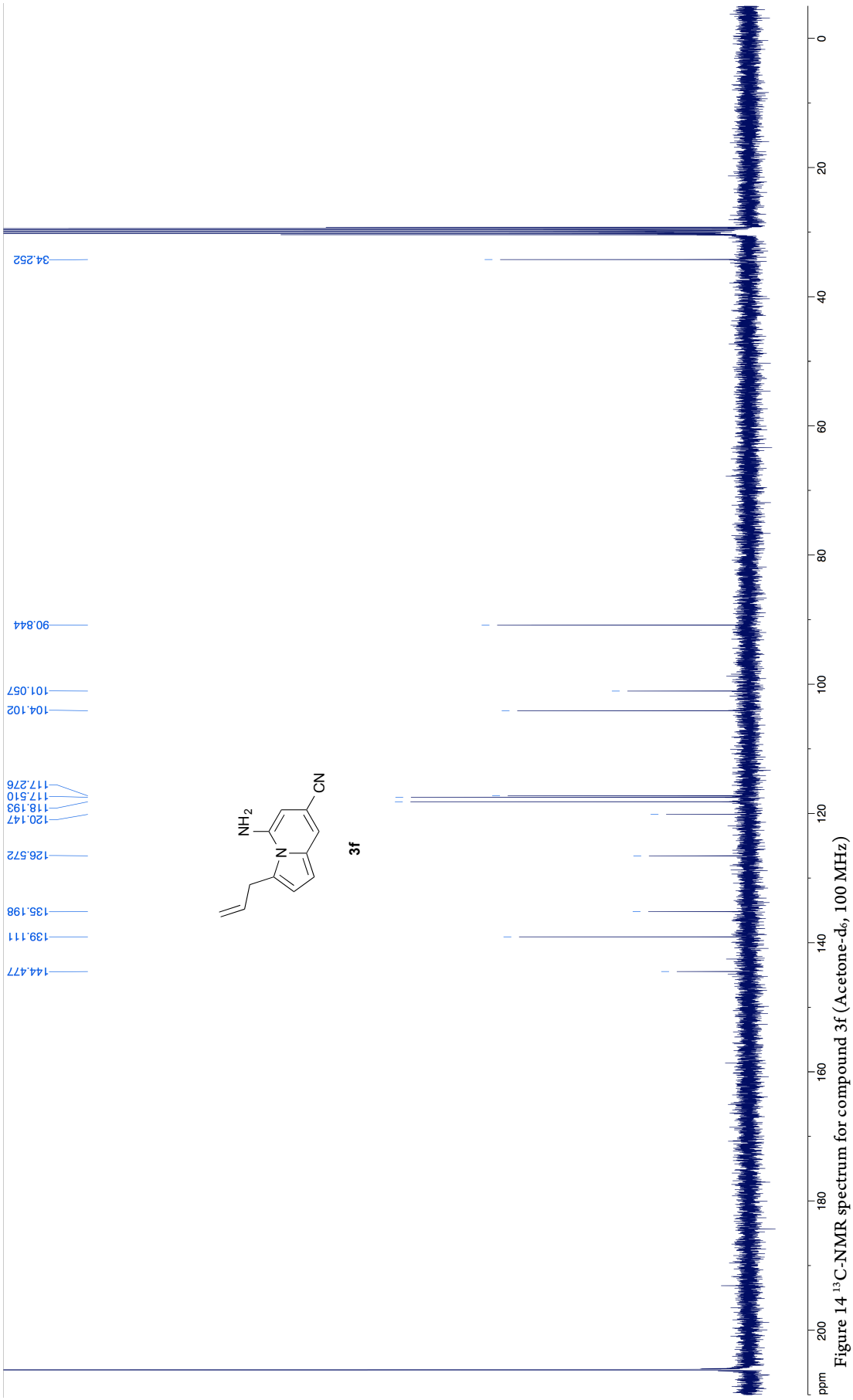


Figure 14 ^{13}C-NMR spectrum for compound 3f (Acetone-d_6, 100 MHz)

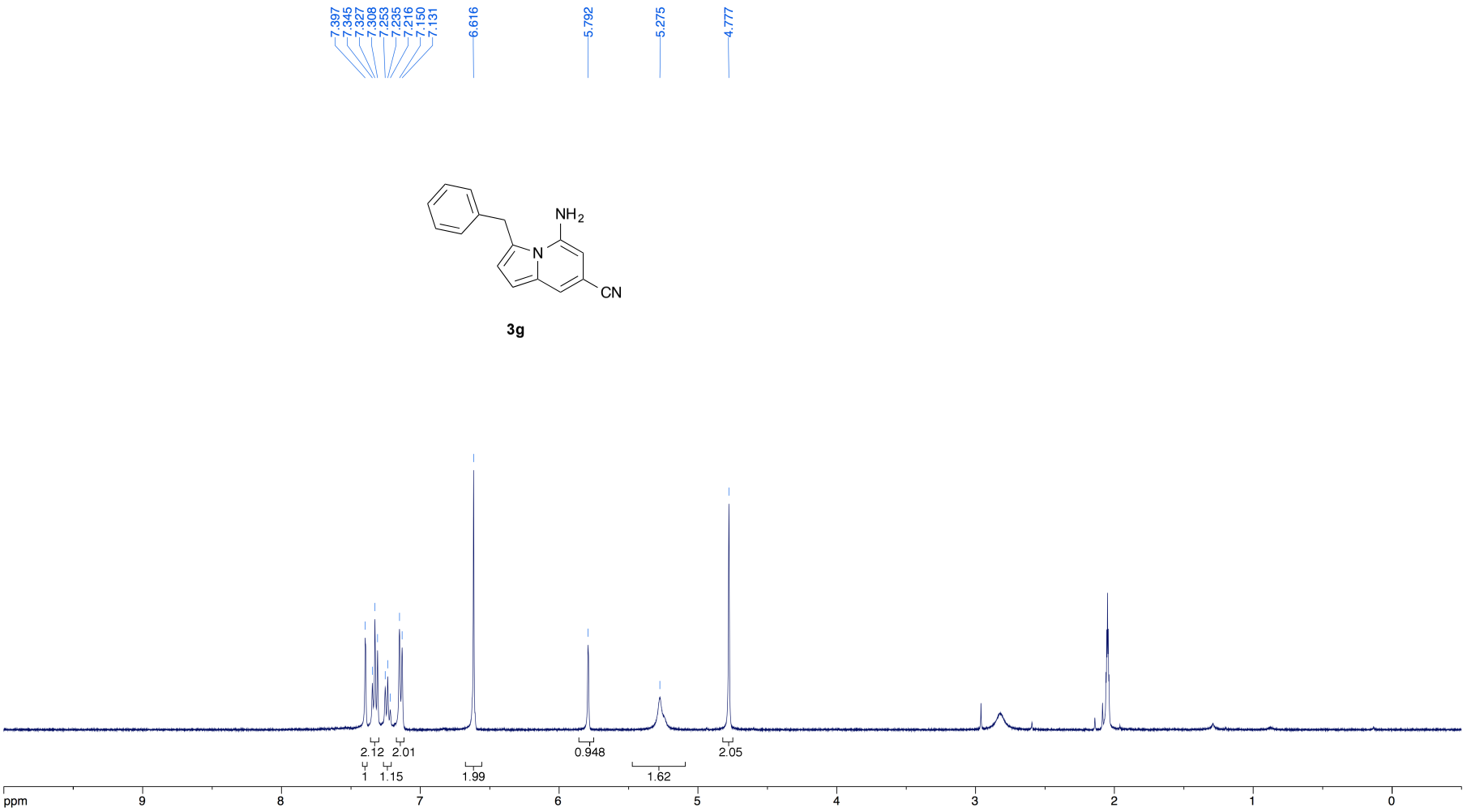


Figure 15 ^{1}H-NMR spectrum for compound 3g (Acetone-d_6, 400 MHz)

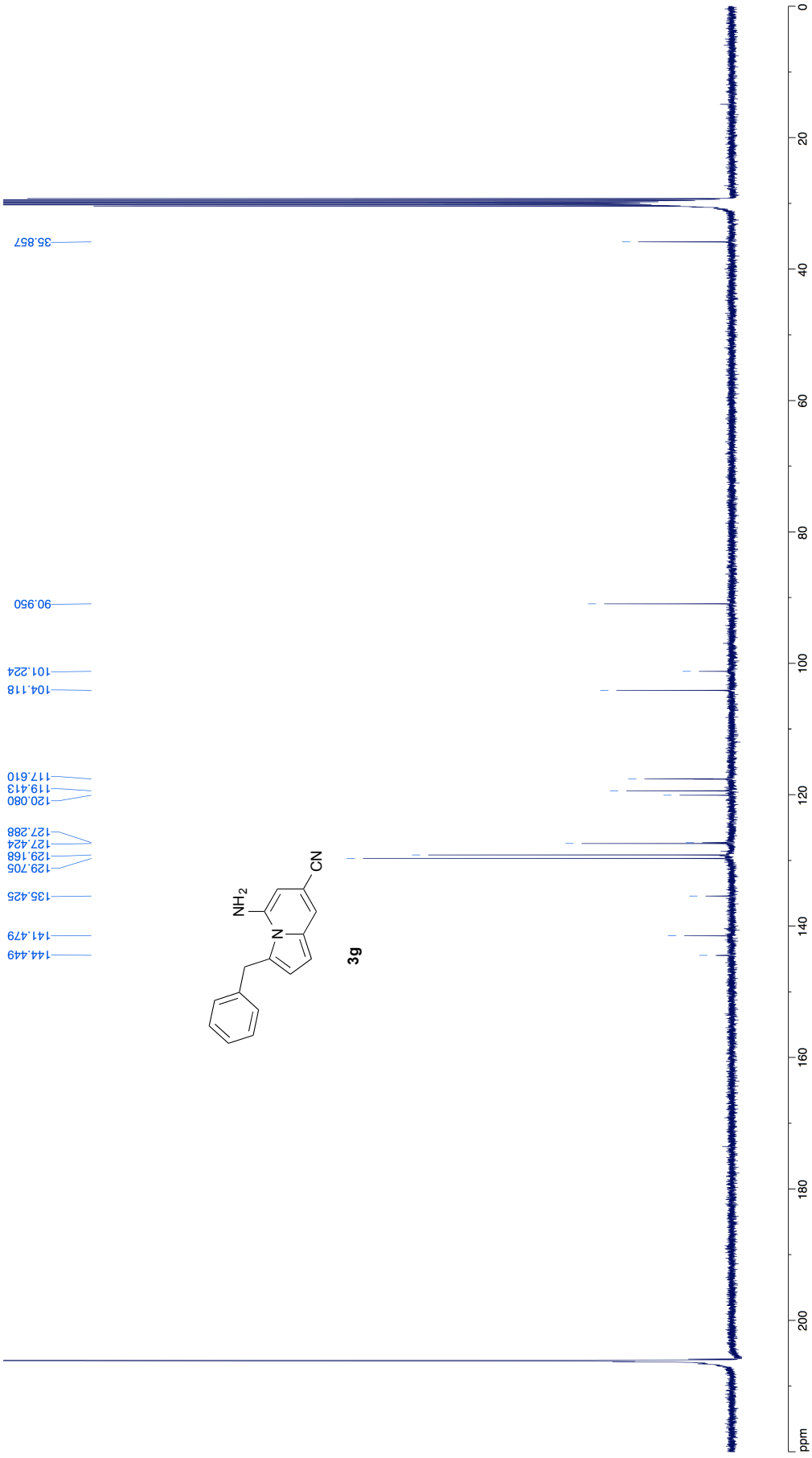


Figure 16 ^{13}C-NMR spectrum for compound 3g (Acetone-d_6, 100 MHz)

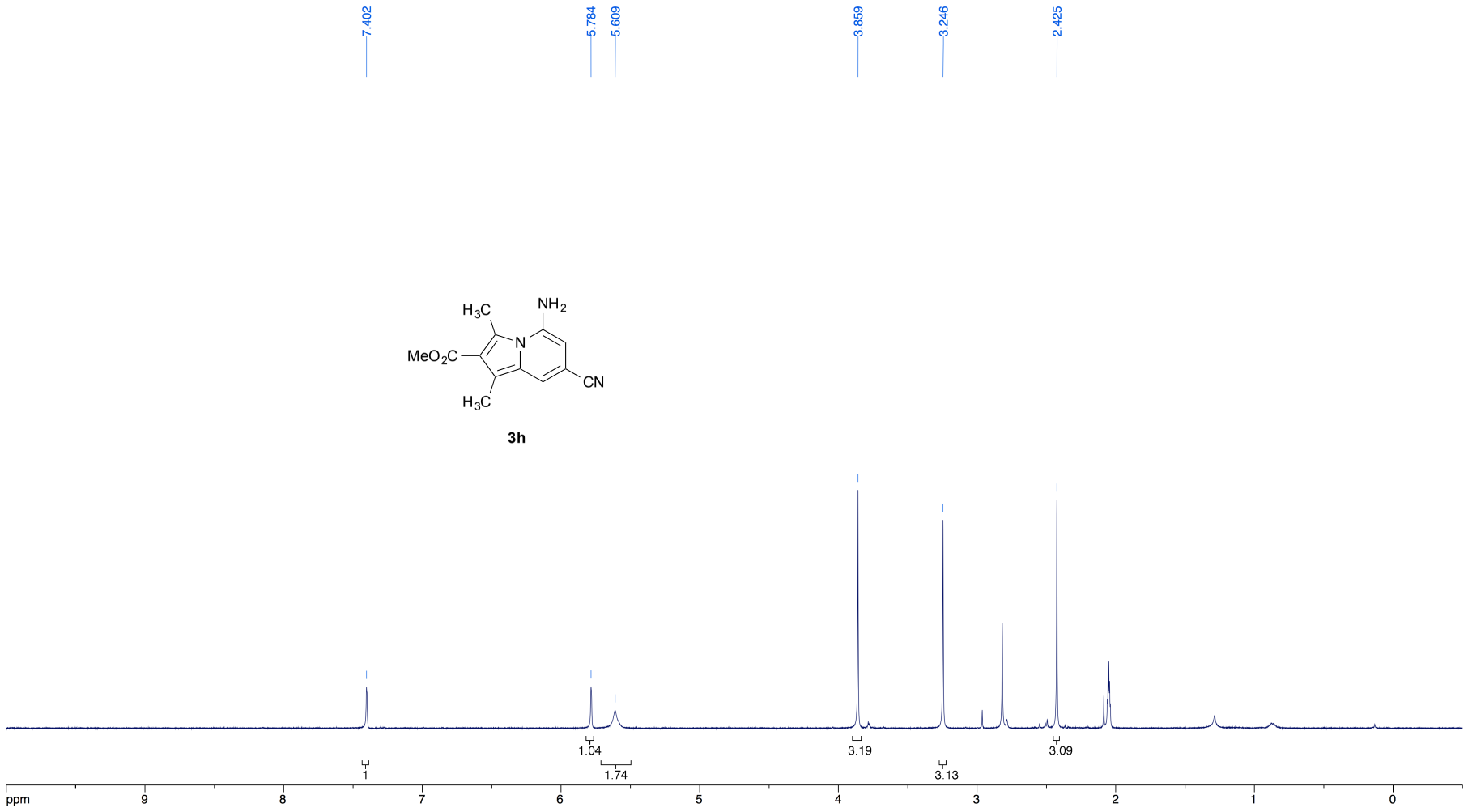


Figure 17 ^{1}H-NMR spectrum for compound 3h (Acetone-d_6, 400 MHz)

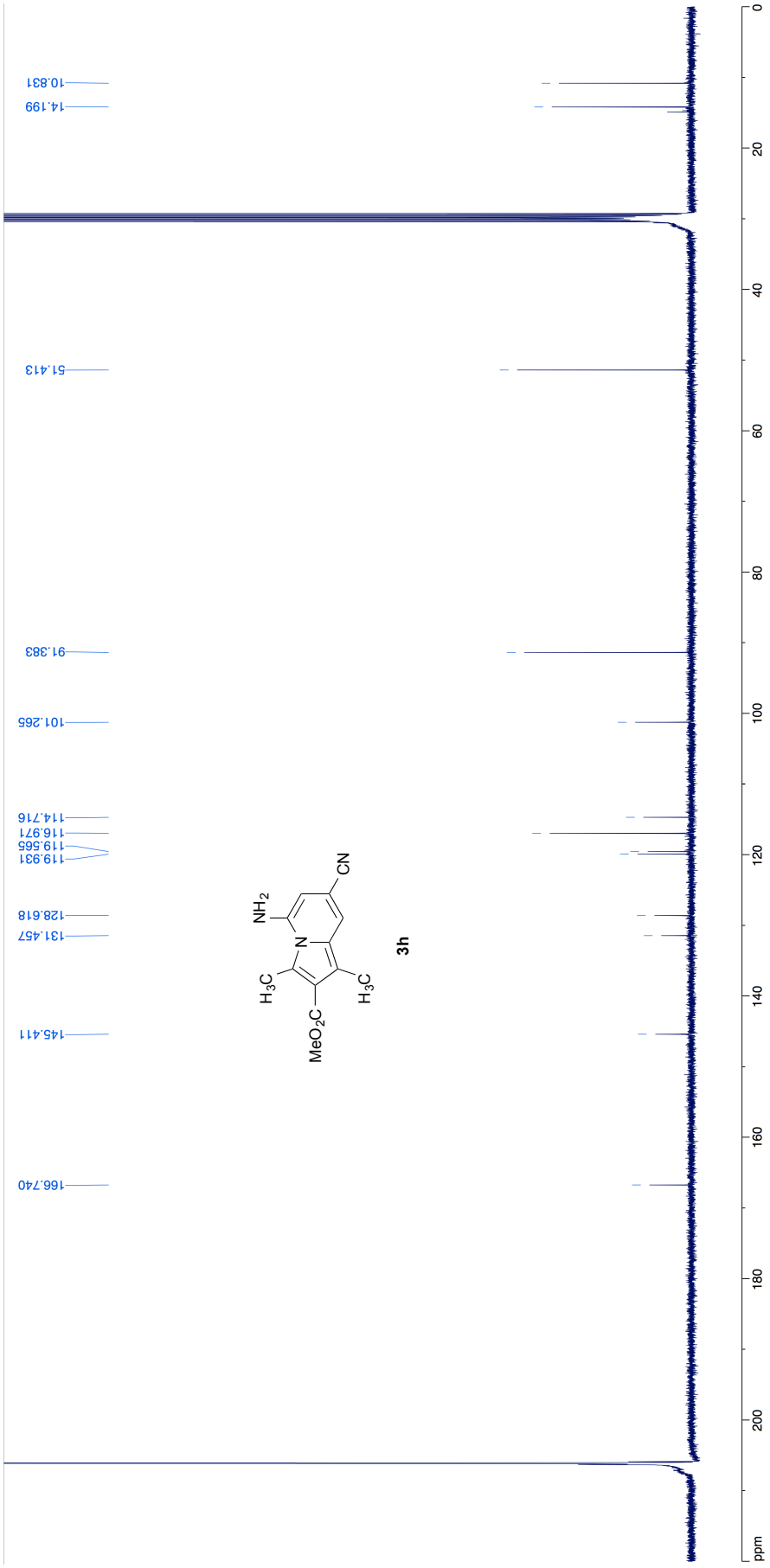


Figure 18 ^{13}C-NMR spectrum for compound 3h (Acetone-d$_6$, 100 MHz)

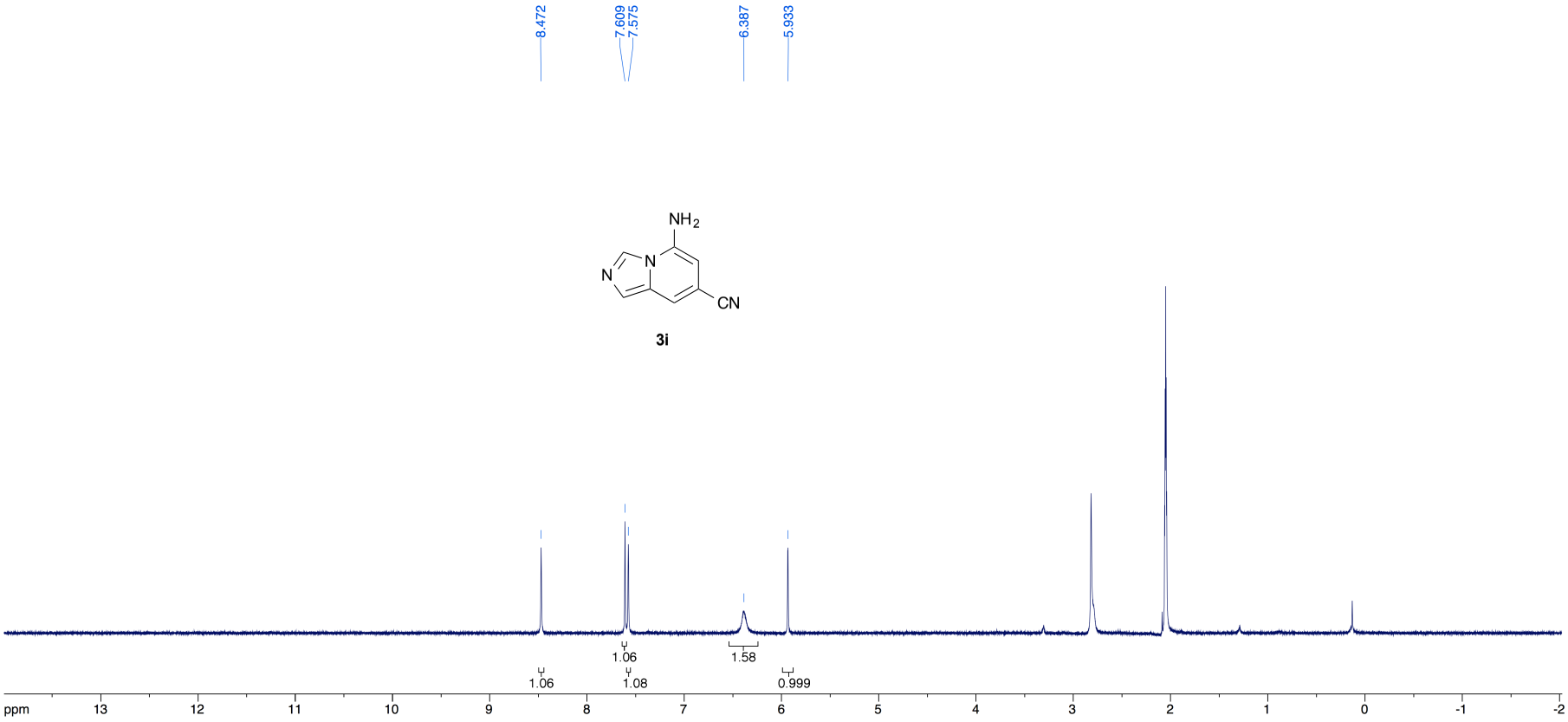


Figure 19 ^{1}H-NMR spectrum for compound 3i (Acetone-d_6, 400 MHz)

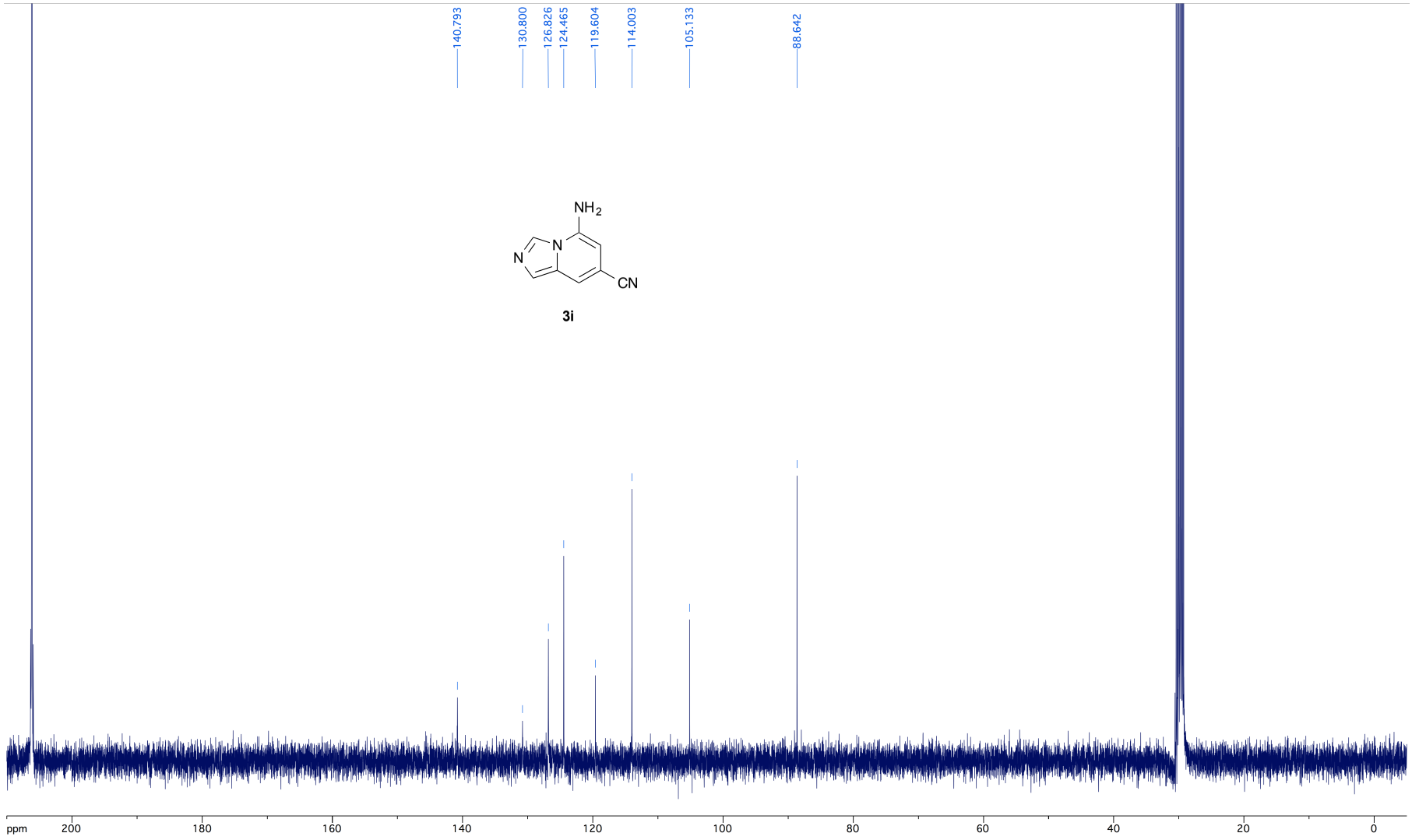


Figure 20 ^{13}C-NMR spectrum for compound 3i (Acetone-d_6, 100 MHz)

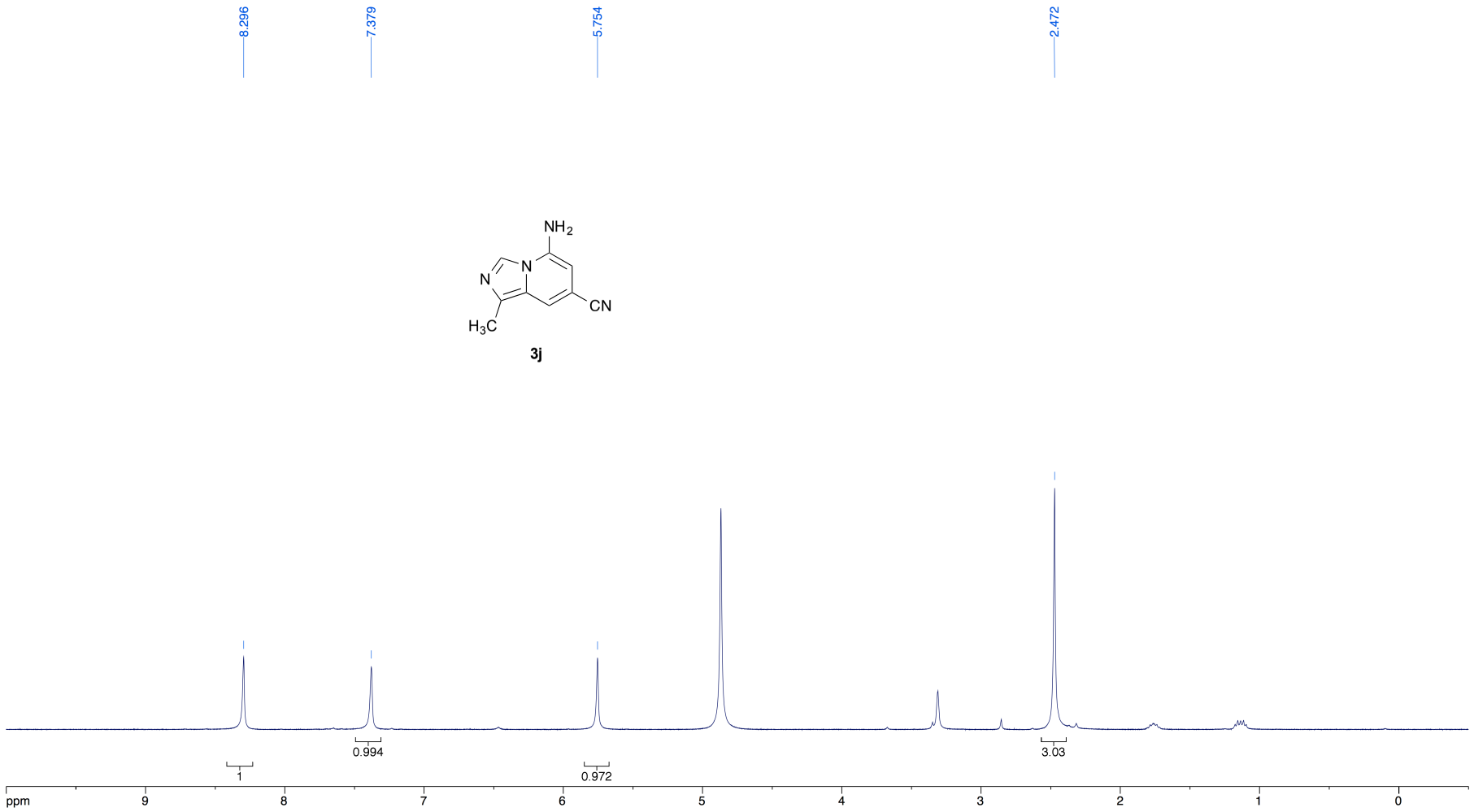


Figure 21 ^{1}H-NMR spectrum for compound 3j (Acetone-d_6, 400 MHz)

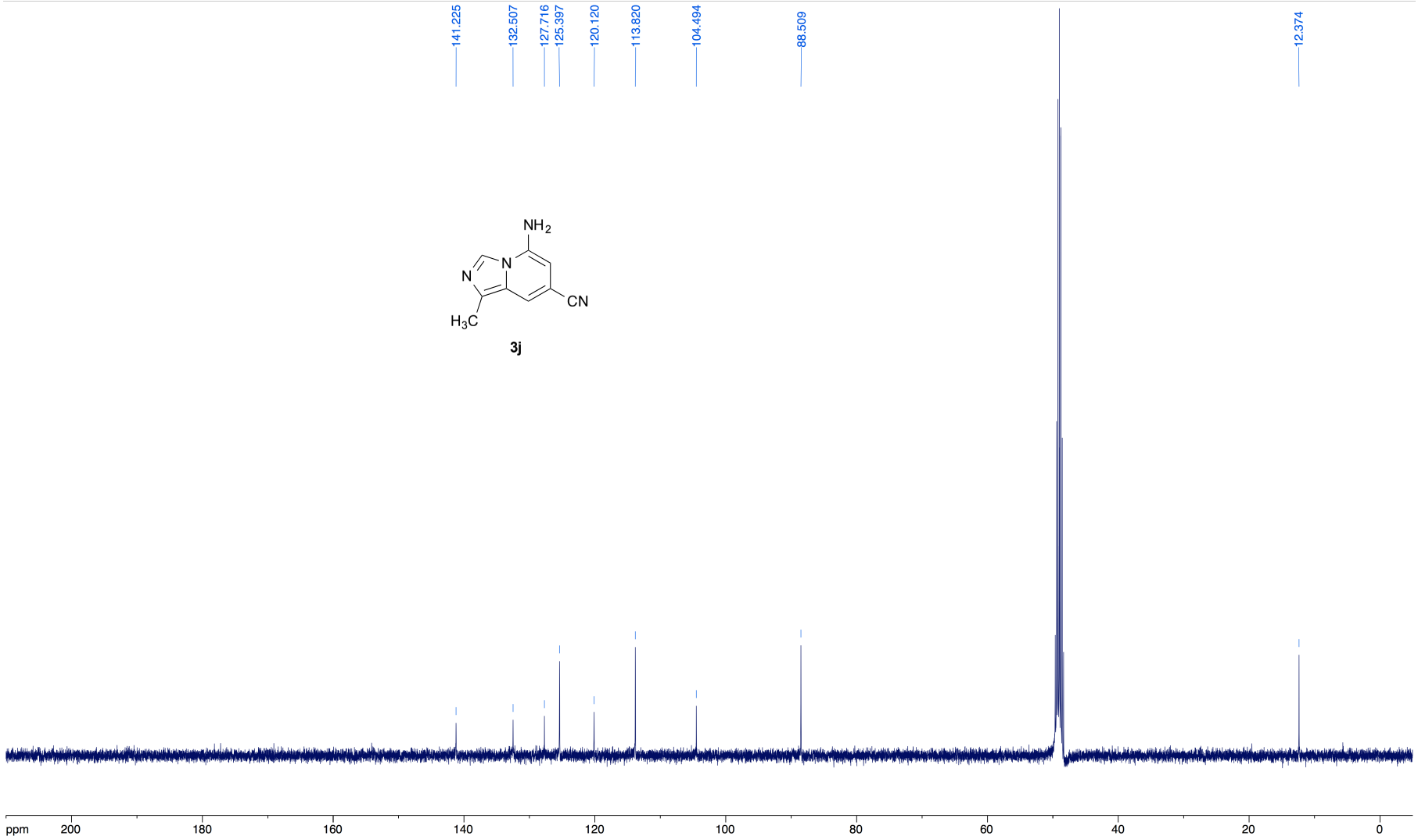


Figure 22 ^{13}C-NMR spectrum for compound 3j (Acetone-d_6, 100 MHz)

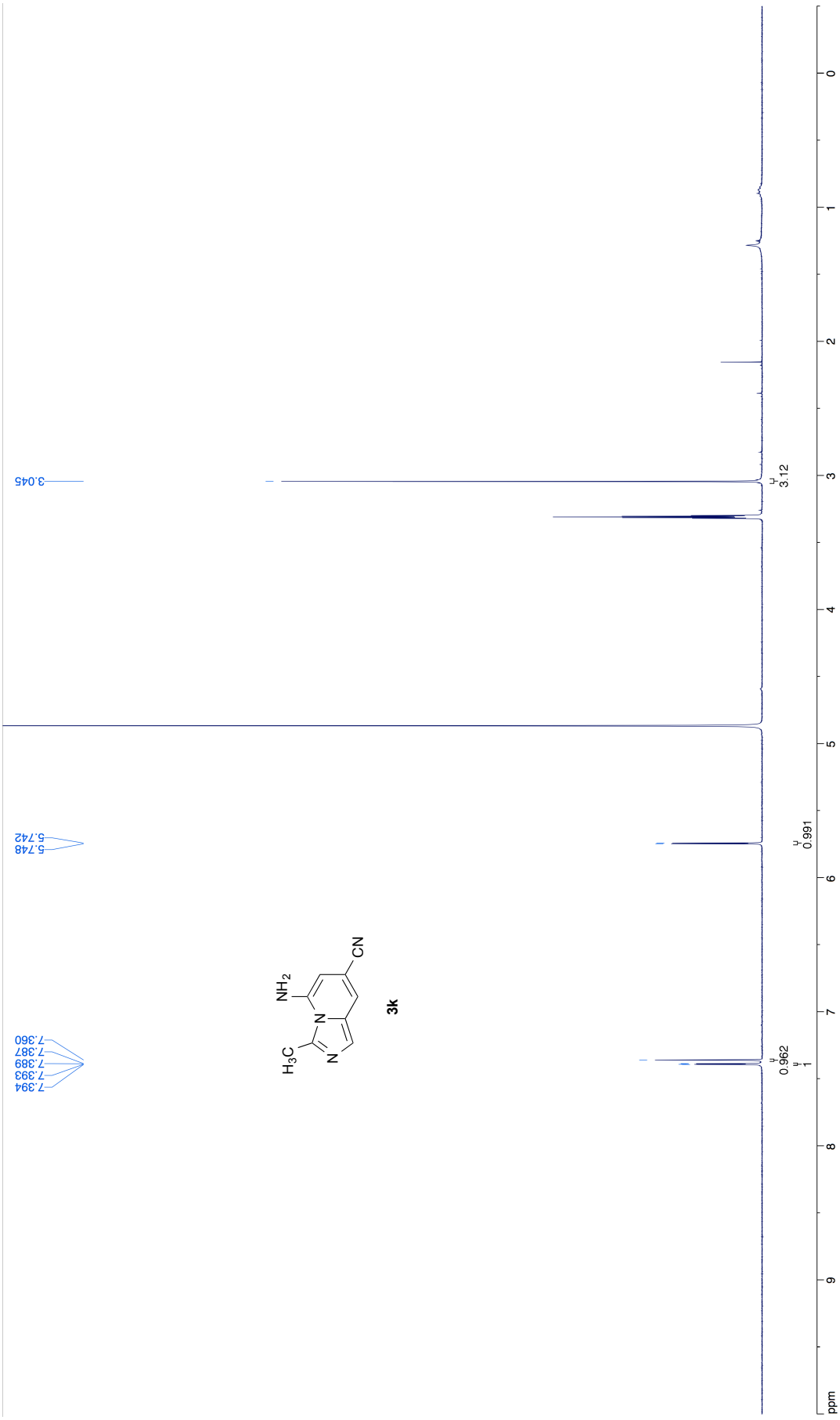


Figure 23 ^{1}H-NMR spectrum for compound 3k (MeOD, 400 MHz)

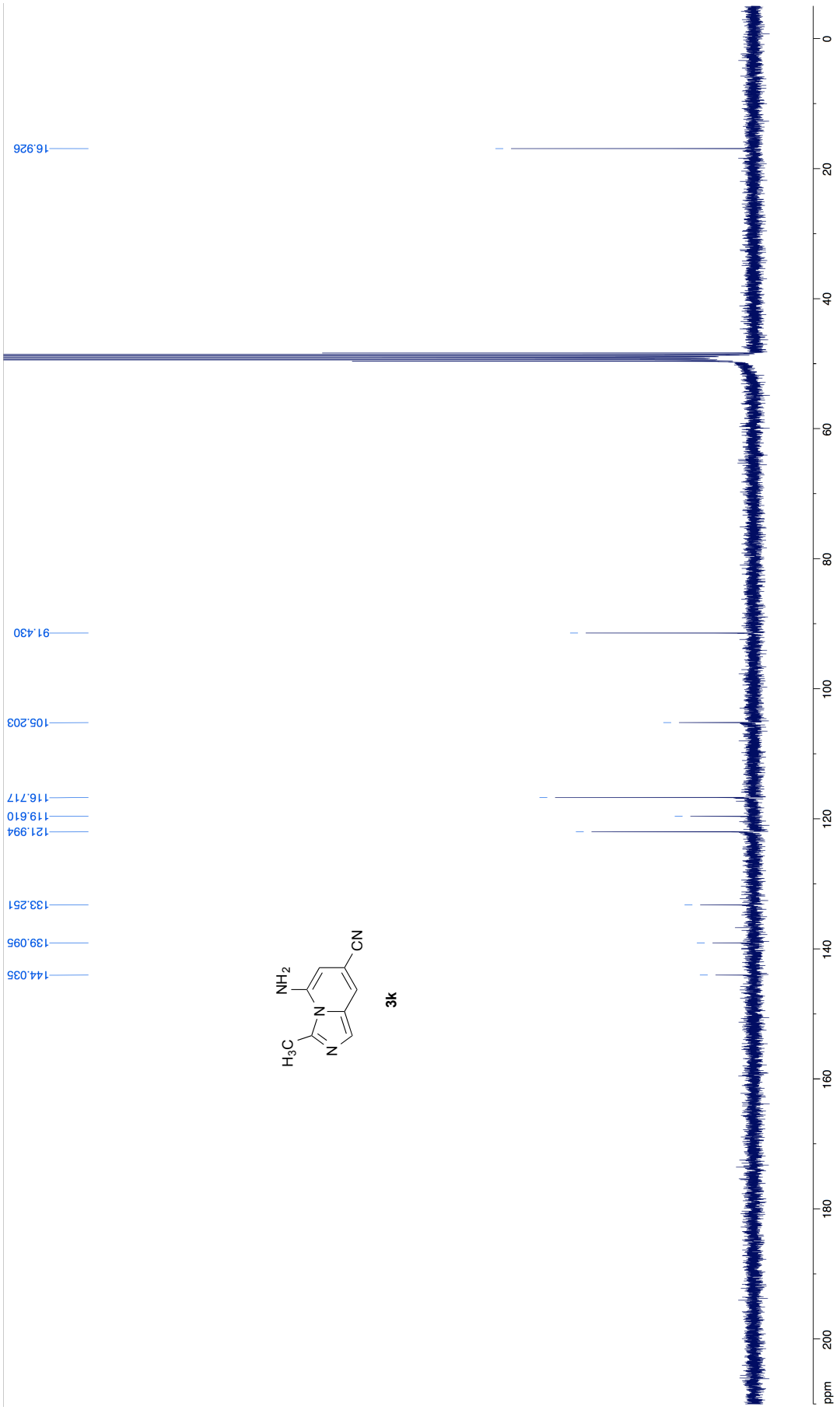


Figure 24 ^{13}C-NMR spectrum for compound 3k (MeOD, 100 MHz)

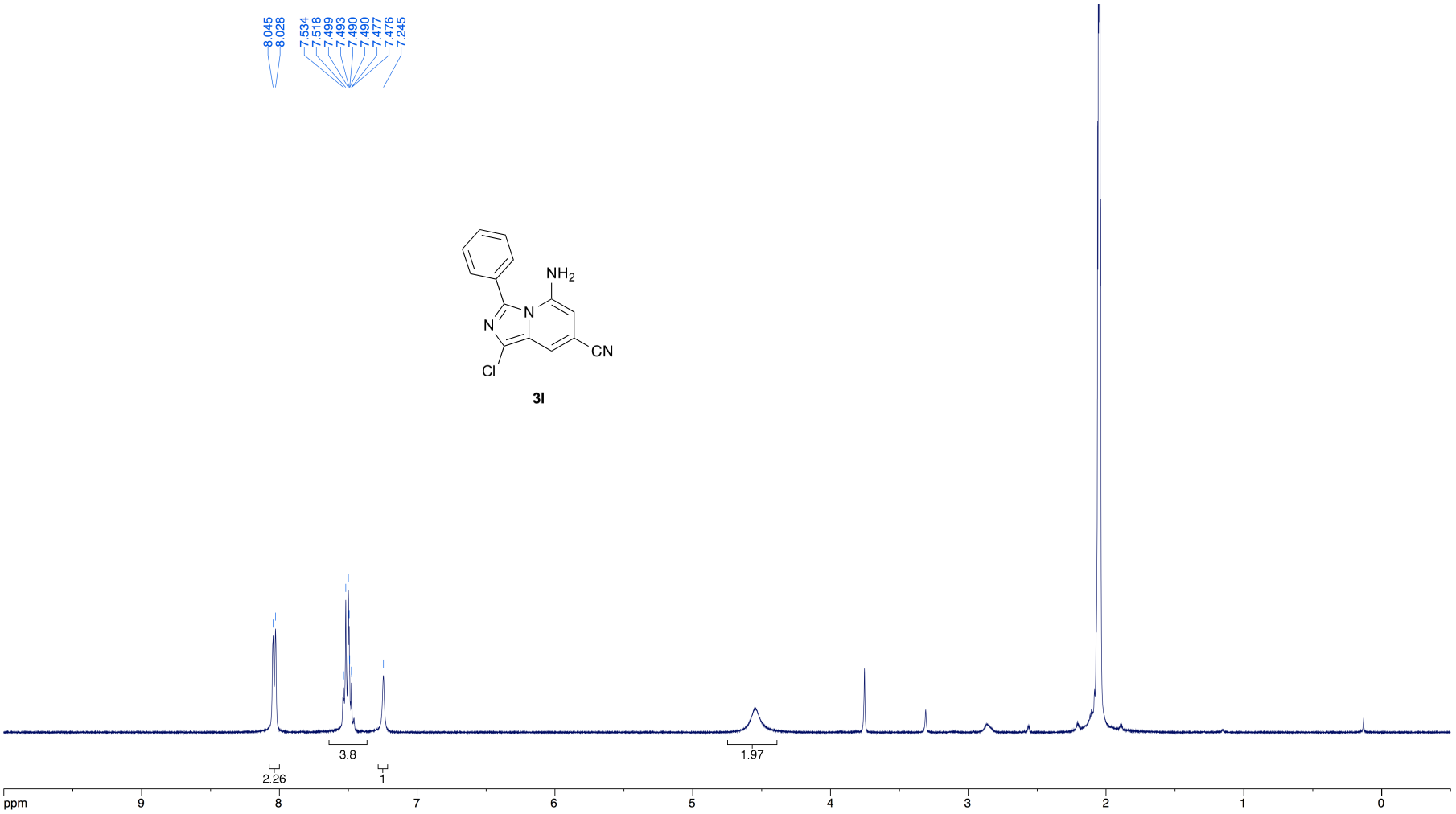


Figure 25 ^{1}H-NMR spectrum for compound 3l (Acetone-d_6, 400 MHz)

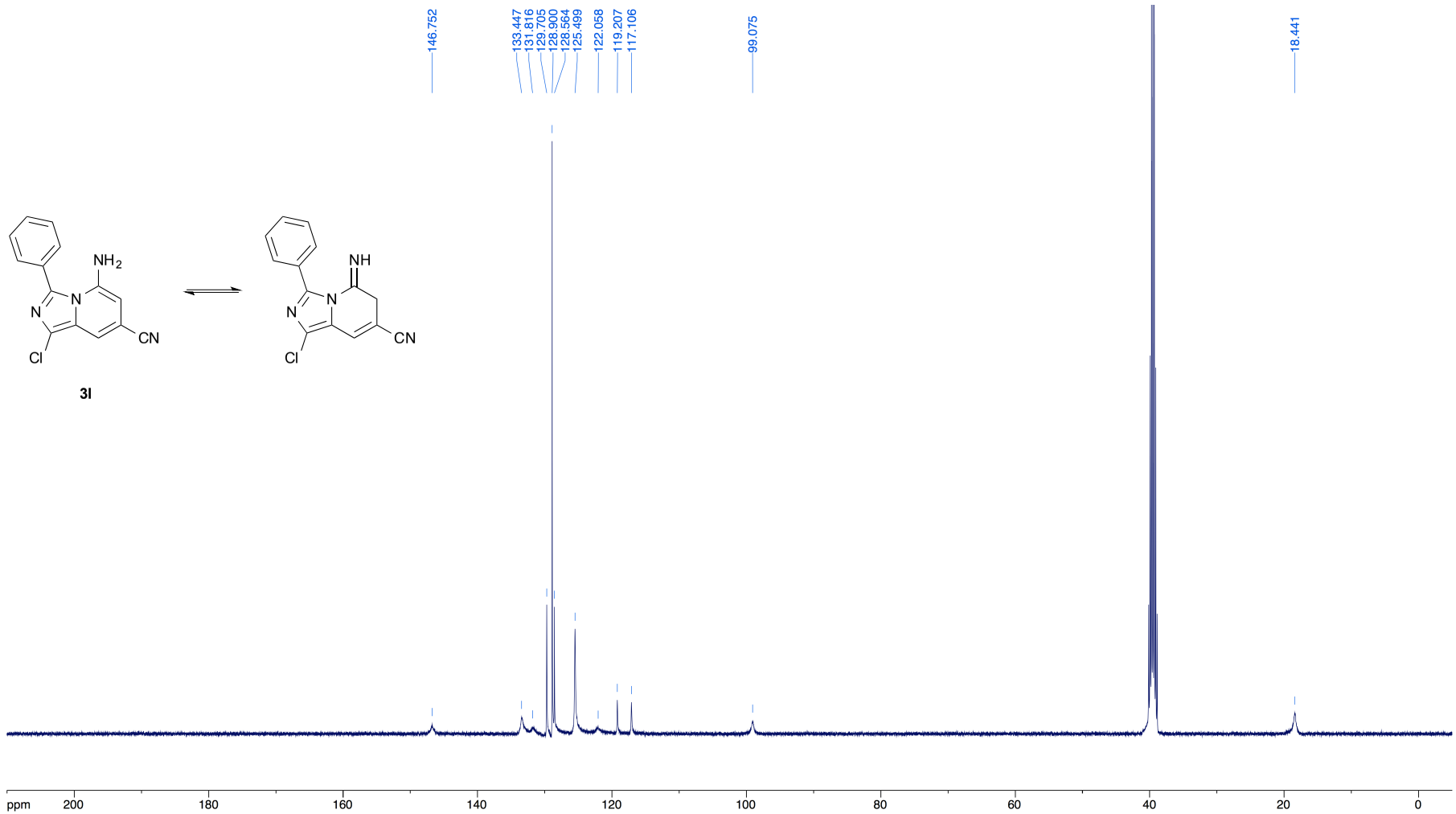


Figure 26 ^{13}C-NMR spectrum for compound 3l (DMSO-d_6, 100 MHz)

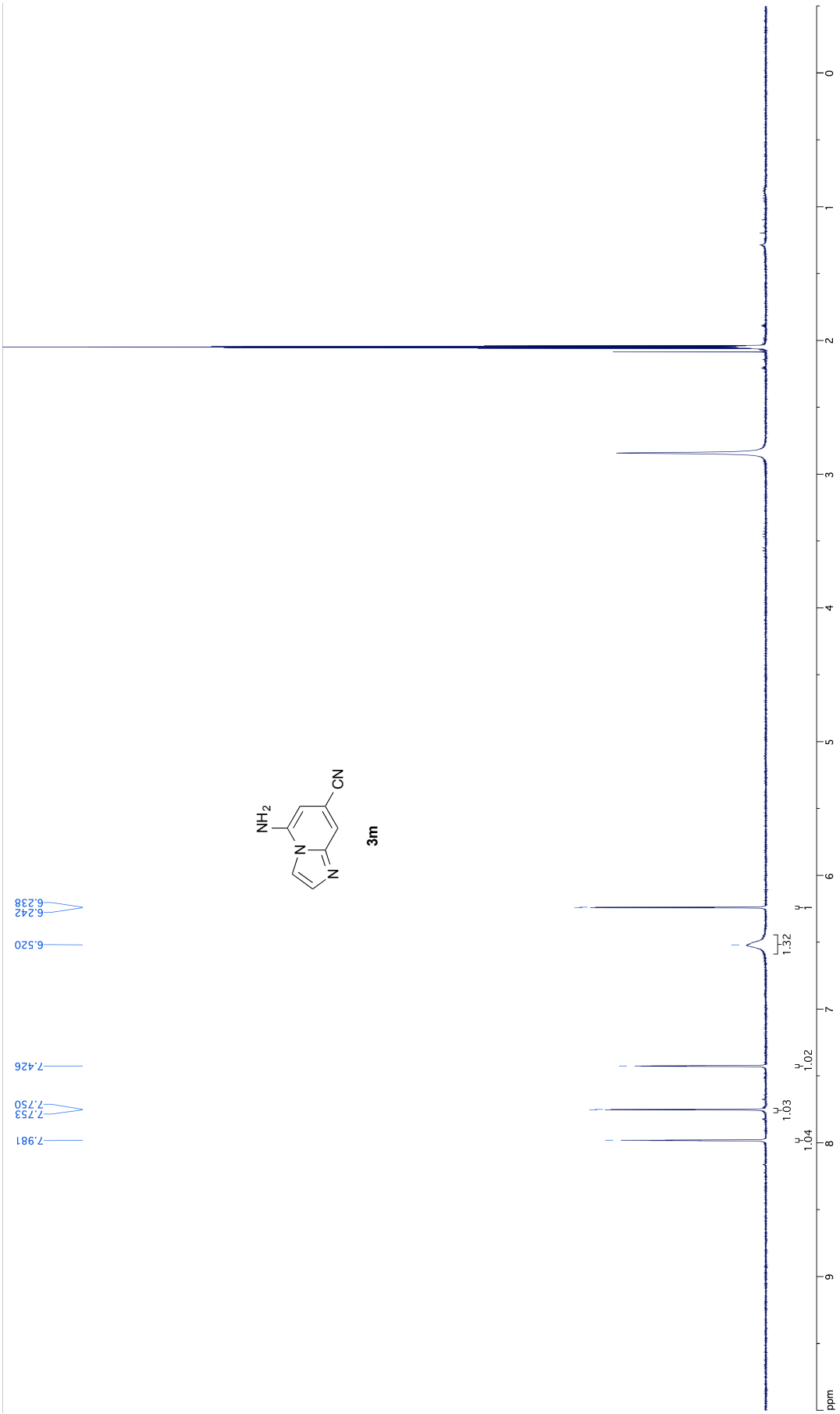


Figure 27 ^{1}H-NMR spectrum for compound 3m (Acetone-d_6, 400 MHz)

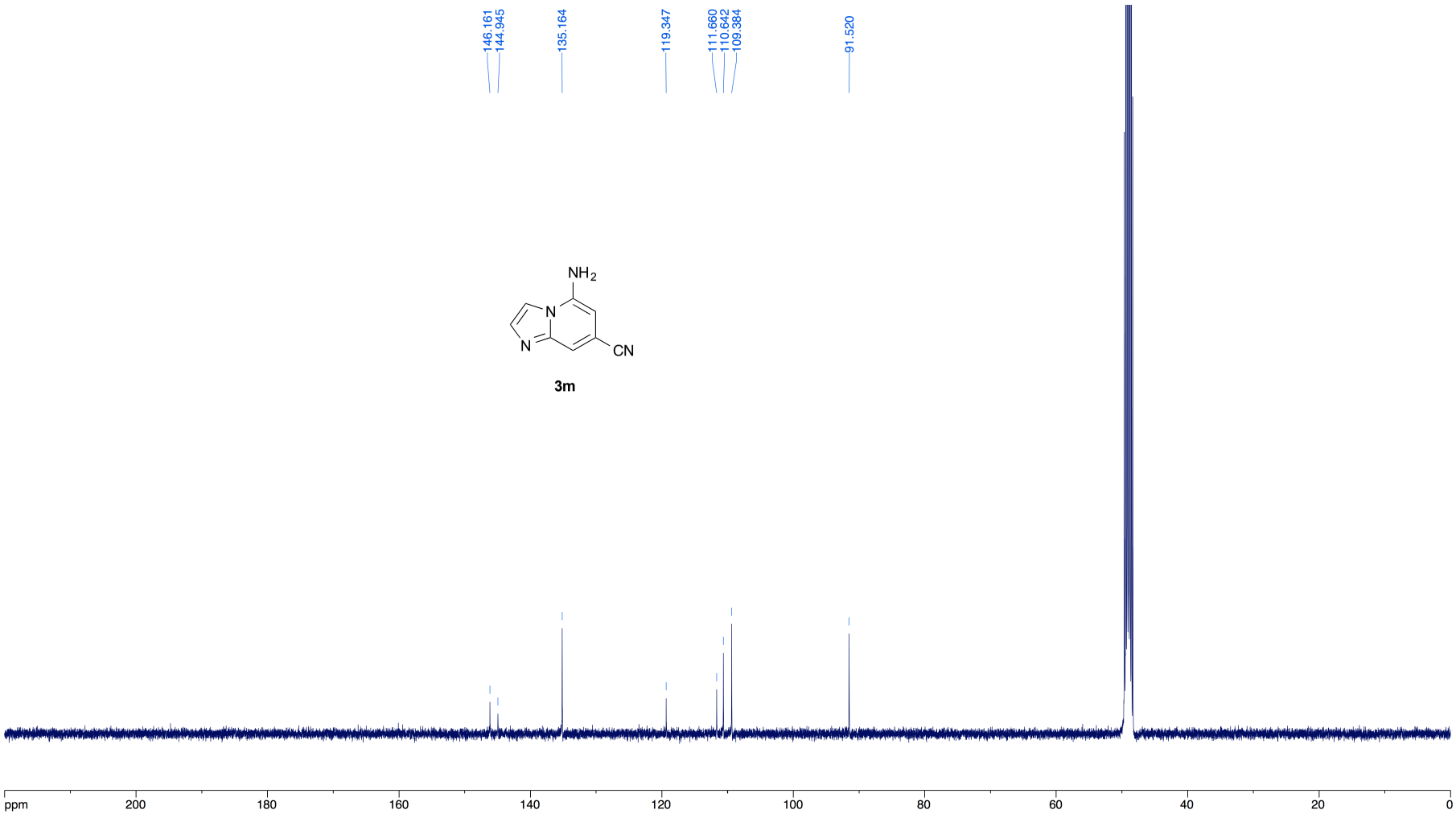


Figure 28 ^{13}C-NMR spectrum for compound 3m (Acetone-d_6, 100 MHz)

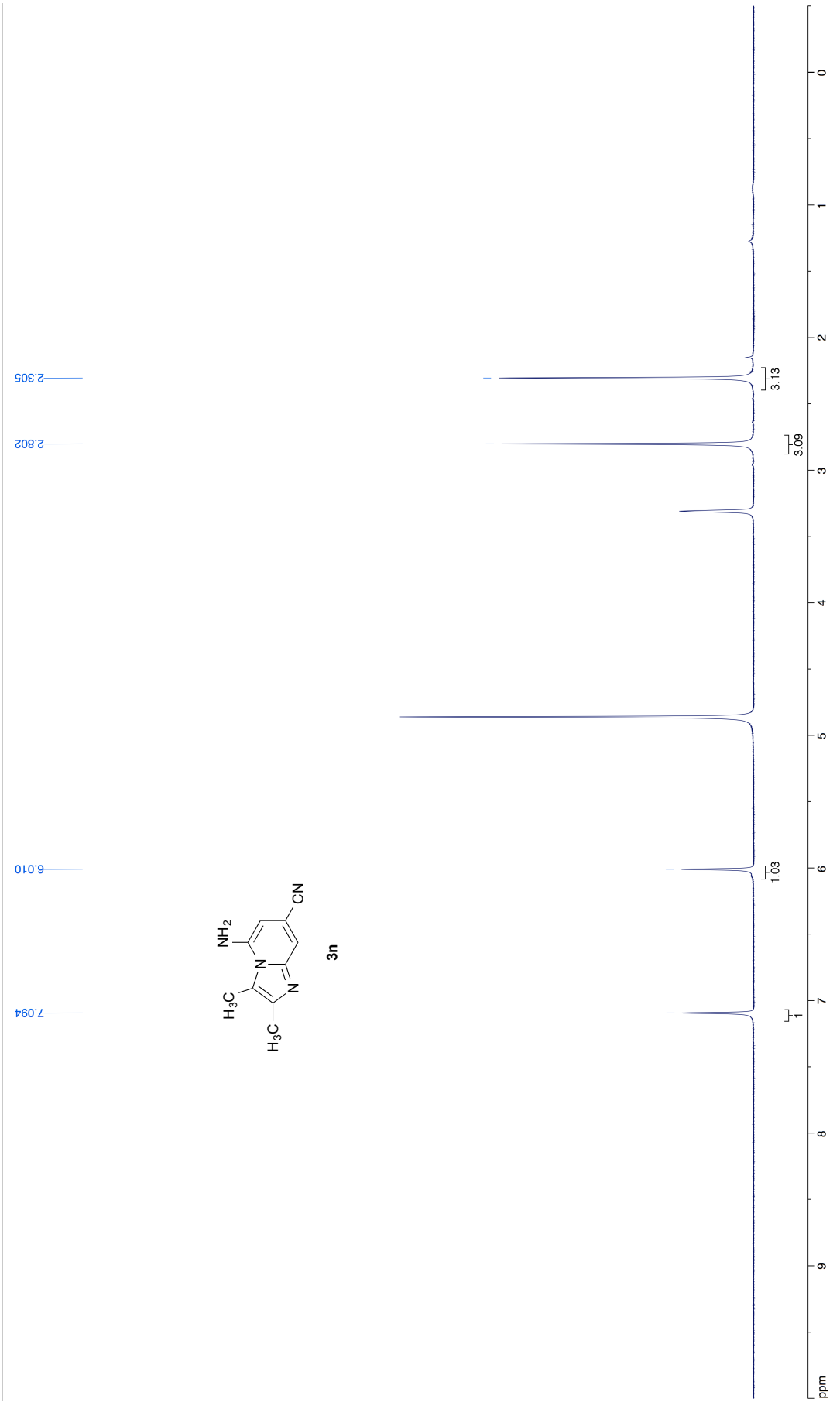


Figure 29 ^{1}H-NMR spectrum for compound 3n (MeOD, 400 MHz)

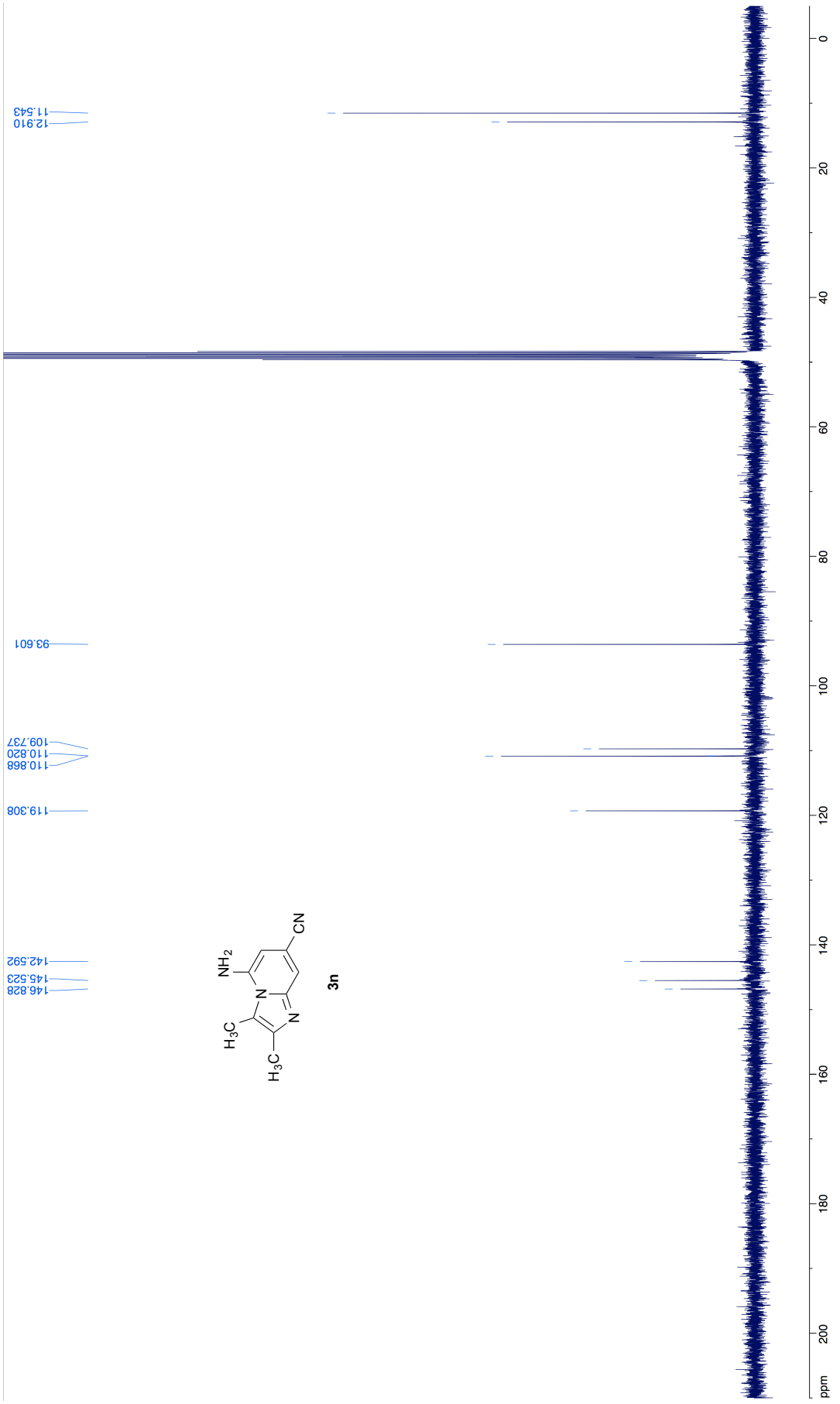


Figure 30 ^{13}C-NMR spectrum for compound 3n (MeOD, 100 MHz)

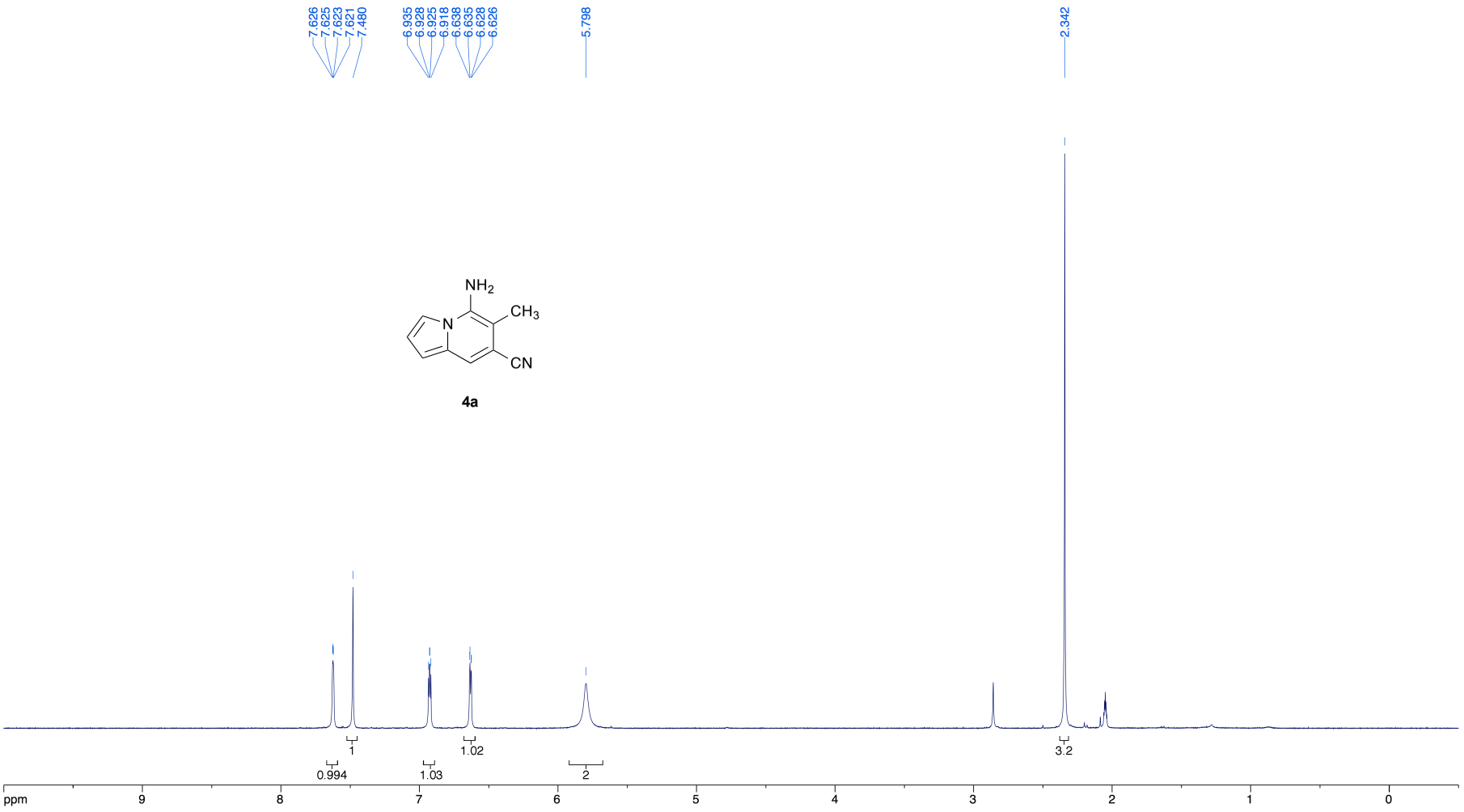


Figure 31 ^{1}H-NMR spectrum for compound 4a (Acetone-d_6, 400 MHz)

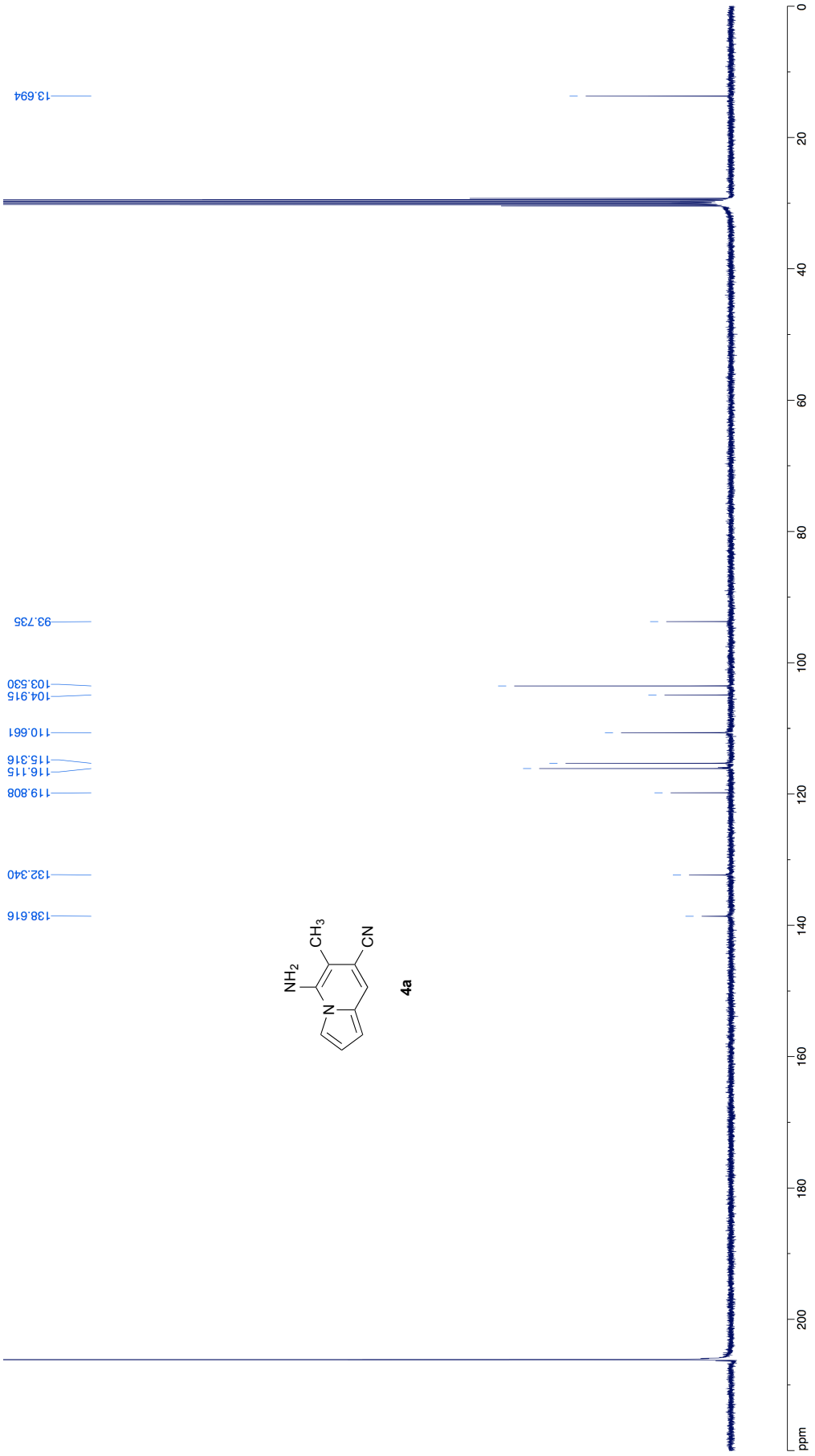


Figure 32 ^{13}C-NMR spectrum for compound 4a (Acetone-d_6, 100 MHz)

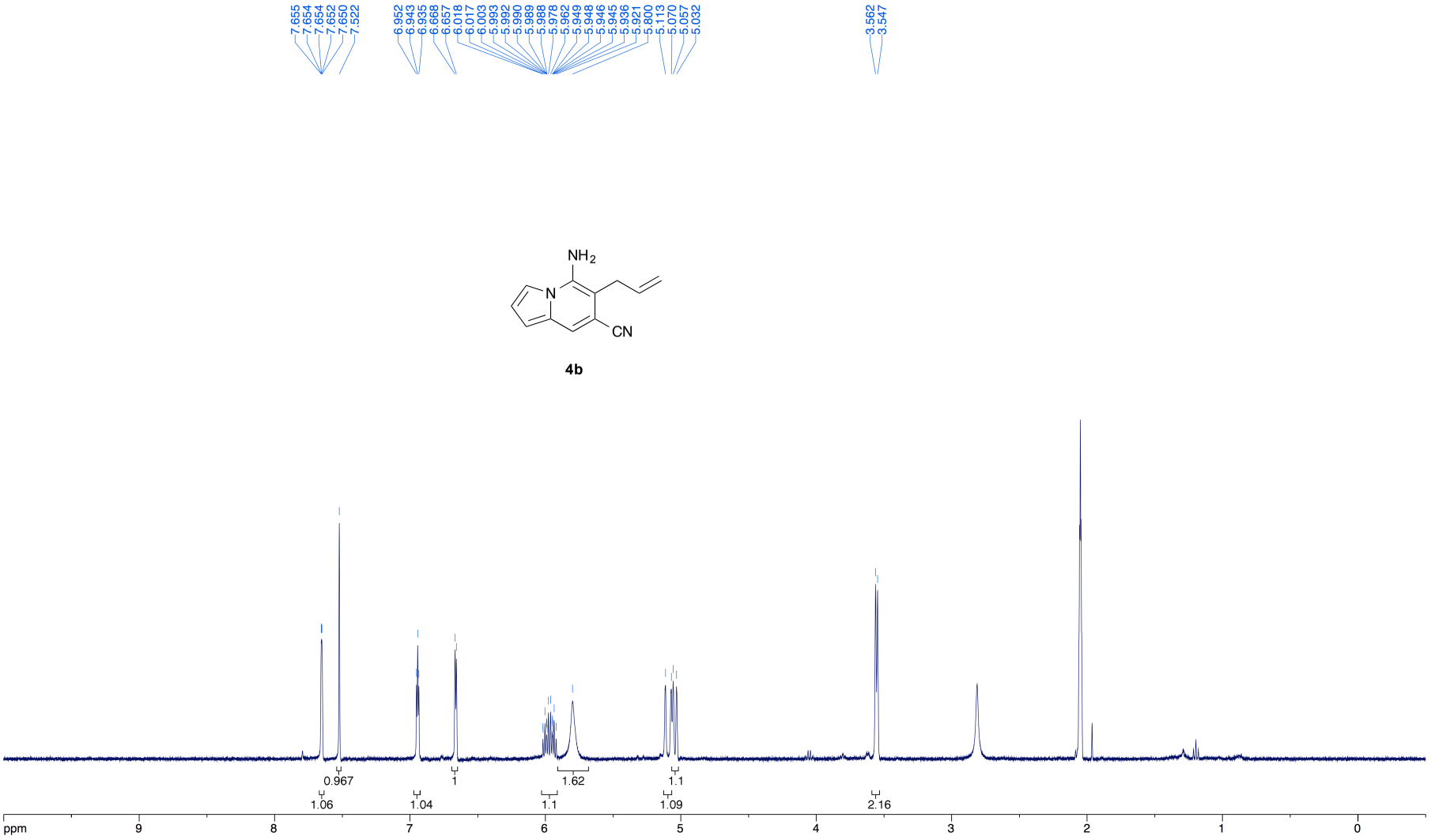


Figure 33 ^{1}H-NMR spectrum for compound 4b (Acetone-d_6, 400 MHz)

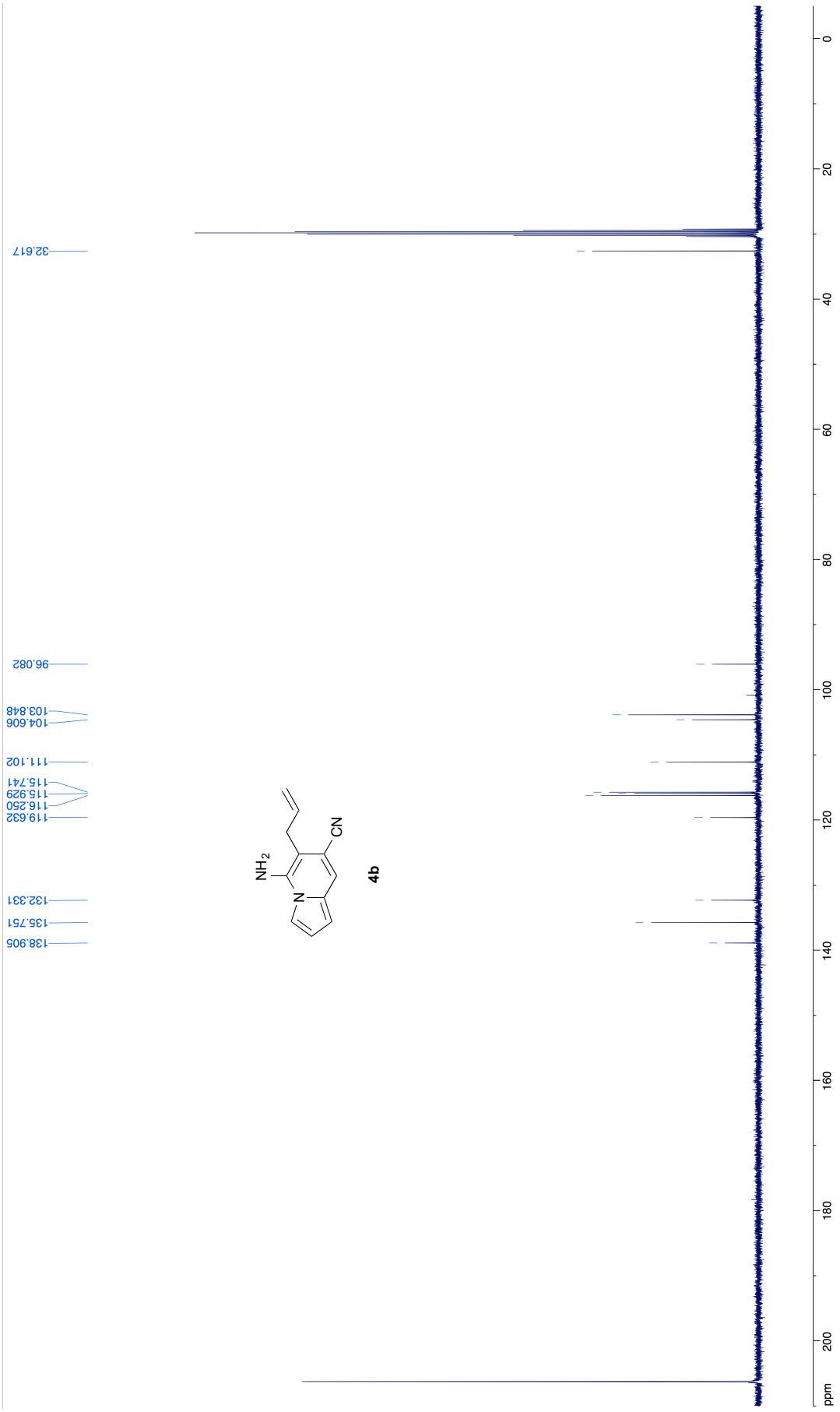


Figure 34 ^{13}C-NMR spectrum for compound 4b (Acetone-d_6, 100 MHz)

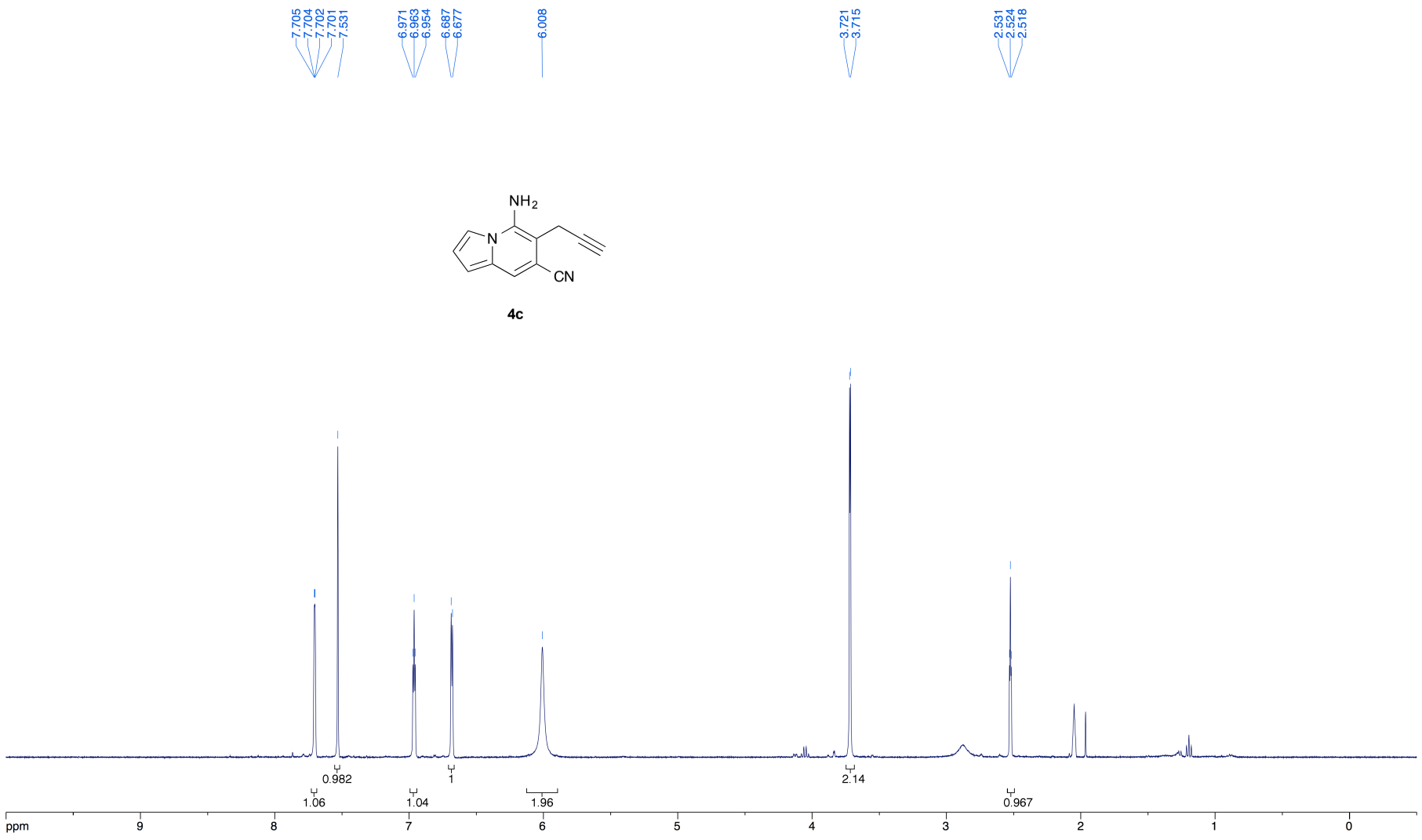


Figure 35 ^{1}H-NMR spectrum for compound 4c (Acetone-d_6, 400 MHz)

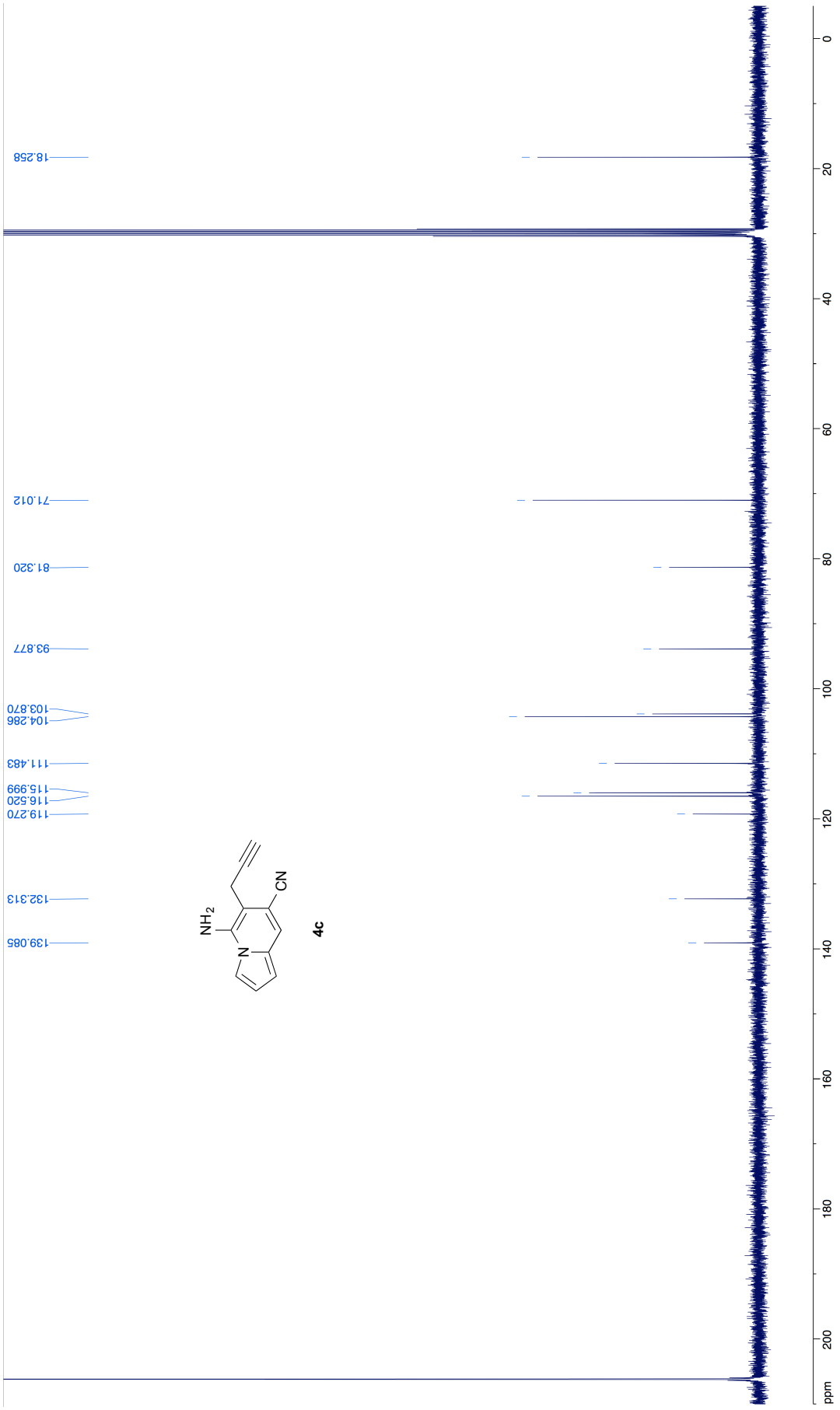


Figure 36 ^{13}C-NMR spectrum for compound 4c (Acetone-d_6, 100 MHz)

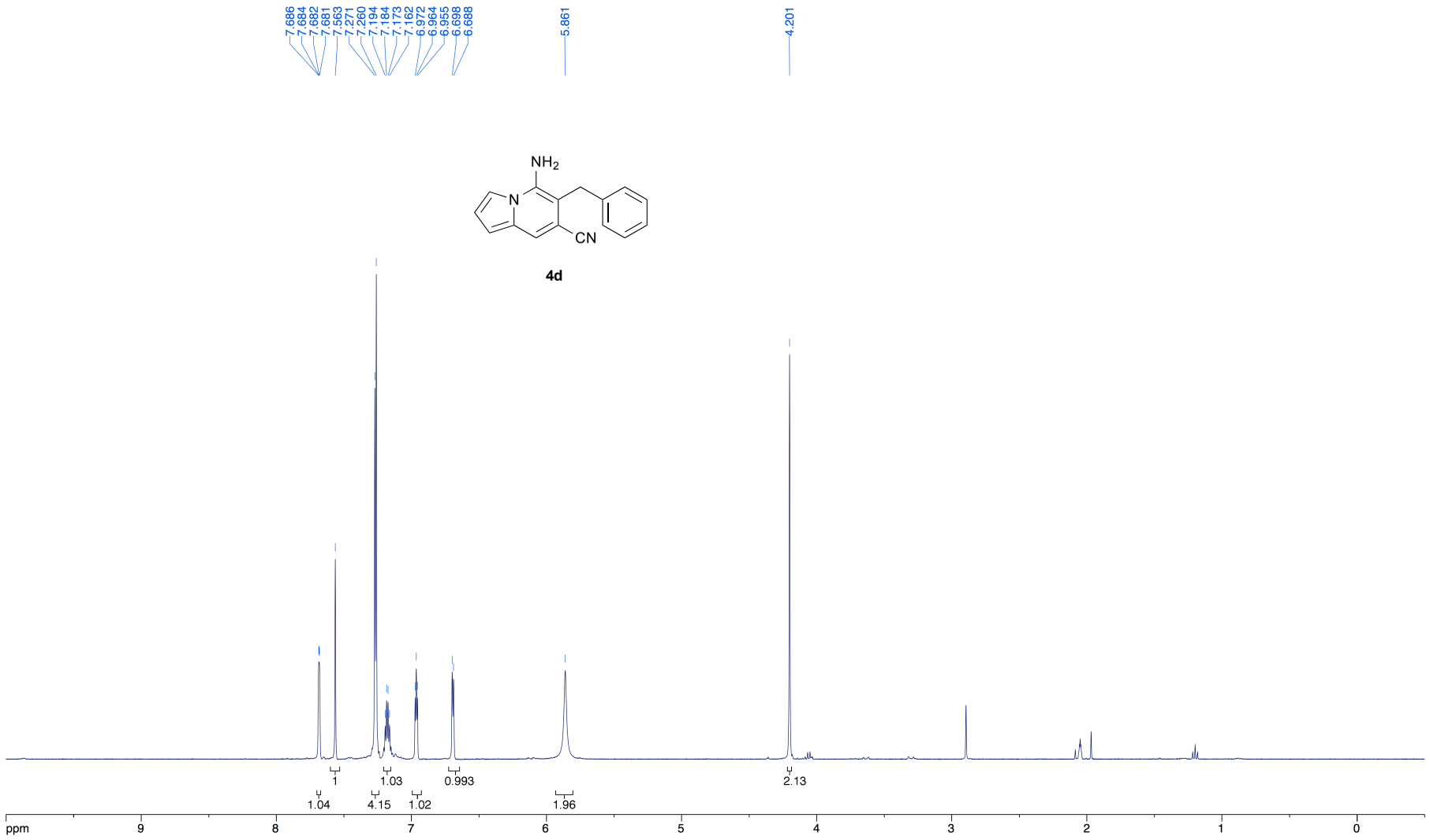


Figure 37 ^{1}H-NMR spectrum for compound 4d (Acetone-d_6, 400 MHz)

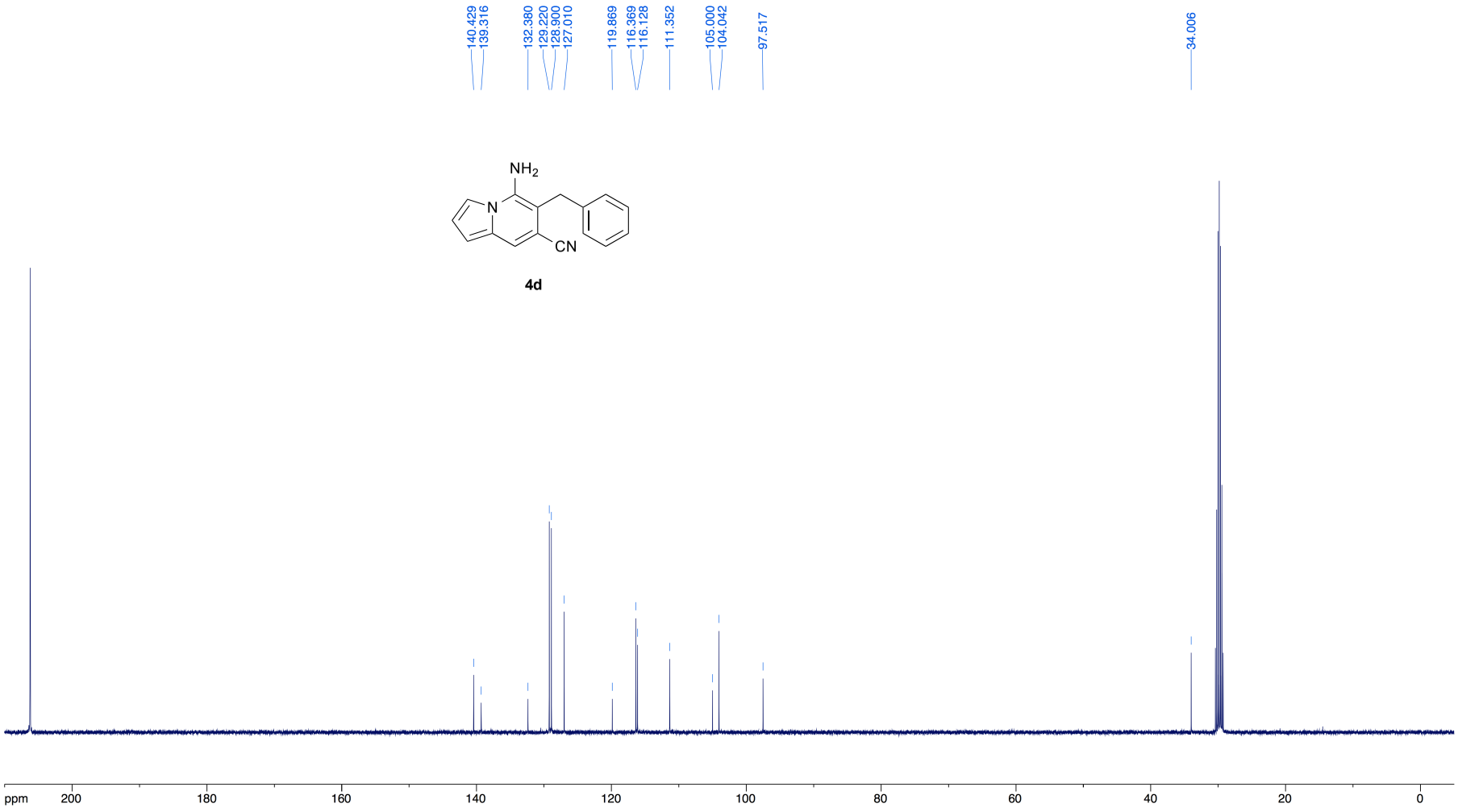


Figure 38 ^{13}C-NMR spectrum for compound 4d (Acetone-d_6, 100 MHz)

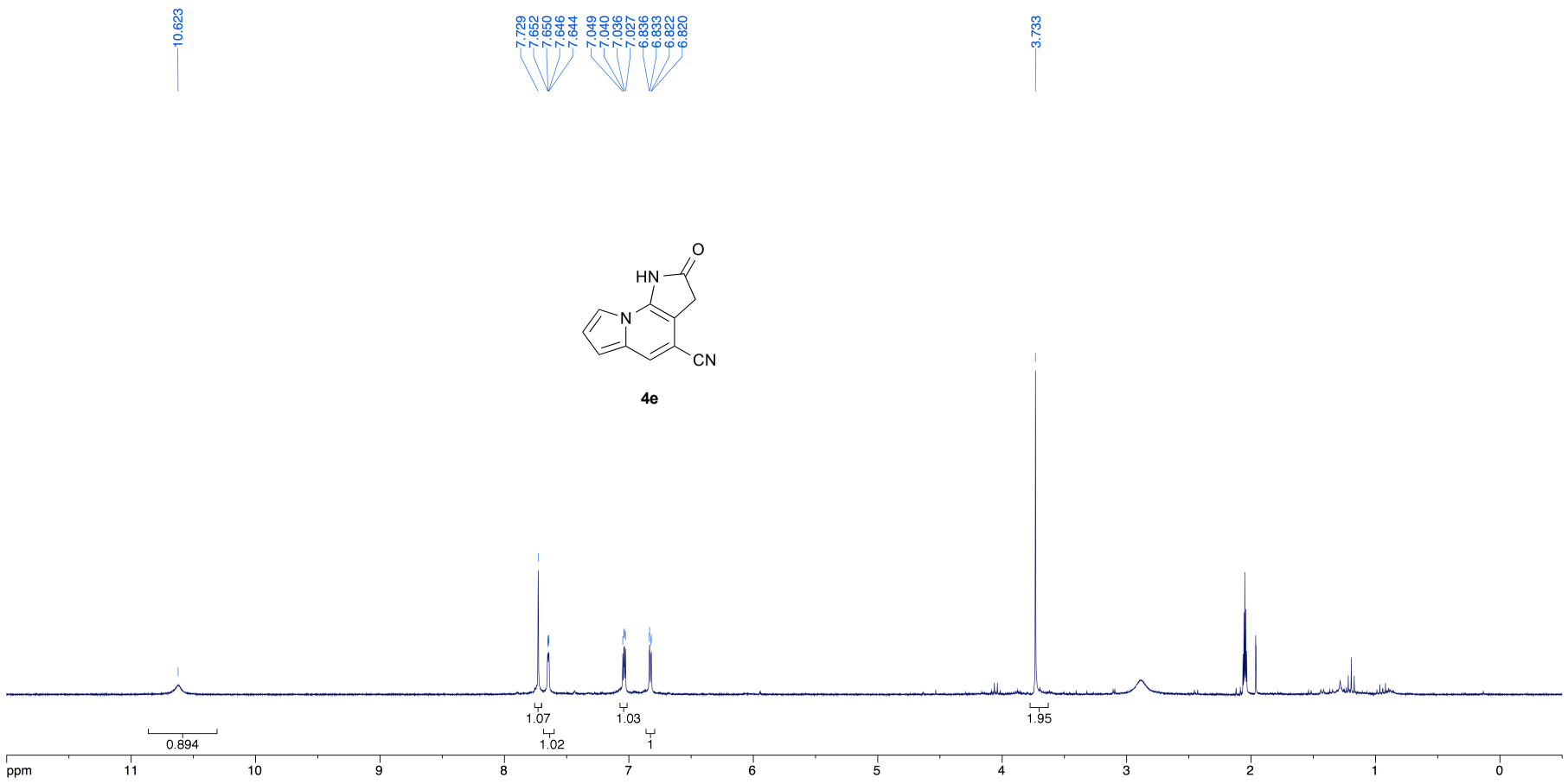


Figure 39 ^{1}H-NMR spectrum for compound 4e (Acetone-d_6, 400 MHz)

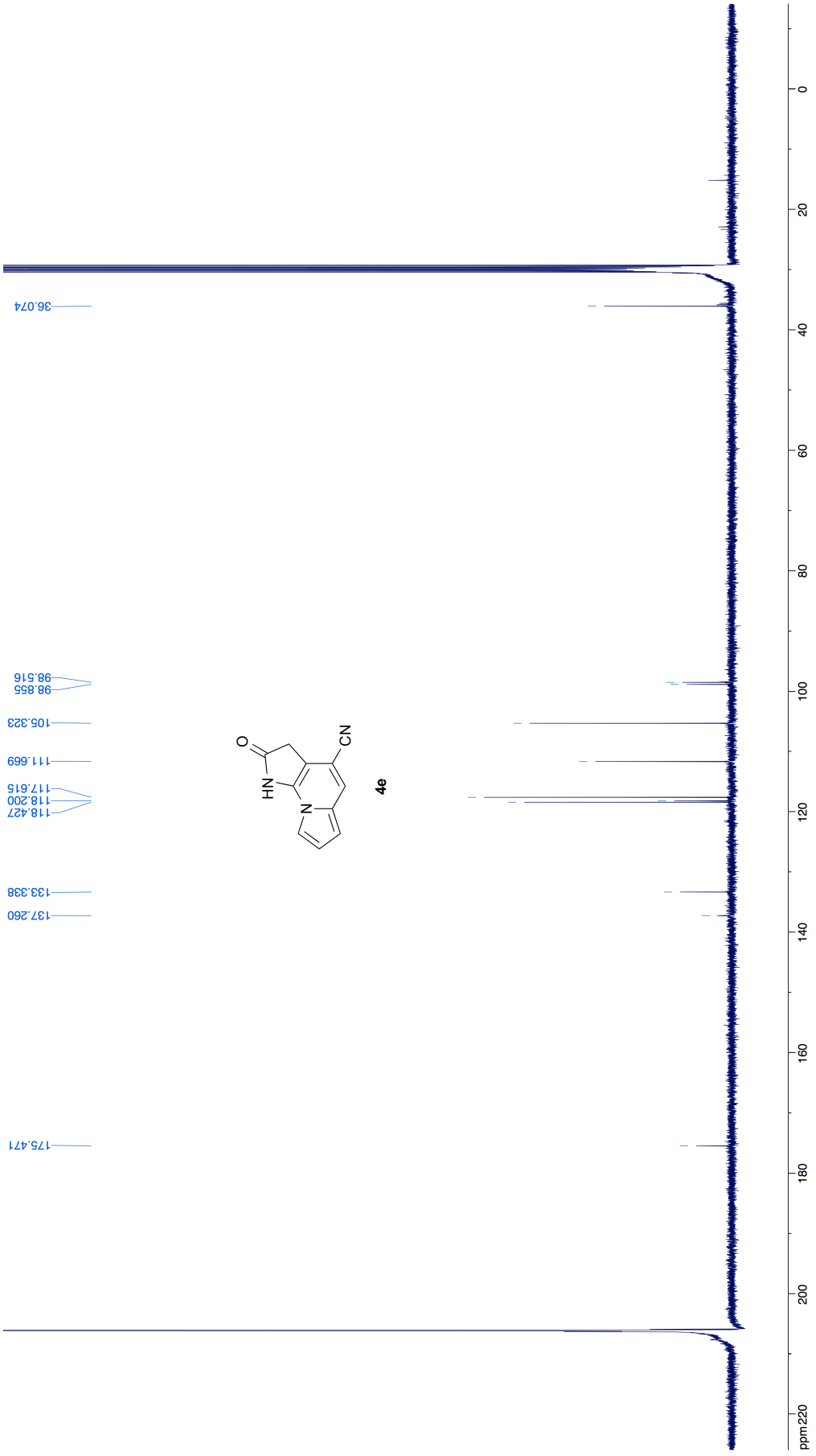


Figure 40 ^{13}C-NMR spectrum for compound 4e (Acetone-d_6, 100 MHz)

3 References

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2. Bergauer, M.; Gmeiner, P. *Synthesis* **2002**, *2*, 0274–0278.
3. Muchowski, J. M.; Hess, P. *Tetrahedron Letters* **1988**, *29*, 777–780.