

Supporting Information for

# Exploring Homogeneous Conditions for Mild Buchwald-Hartwig Amination in Batch and Flow

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## 1 General experimental details

Unless otherwise indicated, reagents were obtained from Sigma Aldrich, Fisher Scientific or Combi-Blocks and used as received. Column chromatography was performed using Silicycle F60 40-63  $\mu\text{m}$  silica gel. Analytical thin layer chromatography (TLC) was conducted using aluminum-backed EMD Millipore Silica Gel 60. Visualization of developed plates was performed under UV light (254 nm) and/or using  $\text{KMnO}_4$ , ninhydrin or  $\text{I}_2$  stains.

## 1.1 Instrumentation and flow reactor details

$^1\text{H}$  NMR and  $^{13}\text{C}$  NMR were recorded on a Bruker AVANCE 400 MHz spectrometer and referenced to residual solvent signals. Data for  $^1\text{H}$  NMR are reported as follows: chemical shift ( $\delta$  ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constant (Hz), integration. Yields for optimization and HTE studies were determined by NMR or GC analysis of the crude reaction mixture using 1,3,5-trimethoxybenzene as an internal standard. IR spectra were collected on a Thermo Scientific Nicolet 6700 FTIR equipped with a diamond ATR crystal (ThermoScientific) and are reported in terms of frequency of absorption ( $\text{cm}^{-1}$ ). GC analysis were conducted on an Agilent Technologies 7890B GC with  $30\text{ m} \times 0.25\text{ mm}$  HP-5 column. Accurate mass data were obtained from an Agilent 5977A GC/MS using MassWorks 4.0 from CERNO bioscience. Unless otherwise indicated, continuous flow experiments were performed using 1.0 mm inner diameter PFA tubing reactor coils heated in silicone oil baths. Either Nexsus 6000 (from Chemyx) or NE-300 syringe pumps (from New Era Pump Systems Inc.) were installed with 5 or 10 mL Hamilton Gastight glass syringes for reagents and 10 mL HSW Norm-Ject plastic syringes for quench streams when necessary. PEEK fittings, tee mixers, and back-pressure regulators were purchased from Upchurch Scientific. The determination of enantiomeric excess was performed by chiral phase HPLC analysis using an Agilent 1200 Series instrument and Diacel ChiralPak columns.

## 2 General Procedures

### 2.1 General procedure for HTE analysis

HTE was performed using five different 96 well plates equipped with  $8 \times 40\text{ mm}$  glass vials. Metals, ligands, bases, and other additives were added to individual vials on the bench, provided they were air-stable solids. A magnetic stir bar was added to each vial and the plate was brought into a nitrogen-filled glovebox. Inside the glovebox, stock solutions were prepared for the amine and aryl halide coupling partners with the appropriate reaction solvent. Other additives, including air sensitive and/or liquid metals, ligands, and bases, were similarly diluted in the appropriate solvent. These stock solutions were dosed into the corresponding reaction vials and any extra solvent necessary was added to give 0.33 mL volume at 0.1 M final concentration. The plate was then sealed, heated, and stirred at the desired temperature for 18 hours in an aluminum heating block. Upon cooling, the plate was opened and a solution of either 1,3,5-trimethoxybenzene or

dodecane was added to each vial as internal standard. Then contents of each vial were passed through a multi-well filtration plate filled with silica gel, eluting with acetonitrile. The filtrates were diluted to an appropriate concentration and then analyzed by GC-MS. The effectiveness of each reaction was monitored by integration of the product peak relative to the internal standard.

## **2.2 General procedure for determining the crude yield of each reaction in HTE**

To estimate the yield of each reaction, GC analysis of available molecules which were structurally similar to expected HTE products were performed. Relative response factor, in comparison to the response factor for an equal molar amount of either dodecane or 1,3,5-trimethoxybenzene, was calculated. The resultant data was used to approximate a yield, as well as starting material recovery, for each of the HTE reactions.

### **2.2.1 HTE results and statistics**

A total of 480 experiments were performed, composed of each possible combination of two different solvents (S1, S2), 6 different aryl(pseudo)halide electrophiles (E1 - E6), 4 amine nucleophiles (N1 - N4), and 10 different ligands (L1 - L10) as varied parameters.  $\text{Pd}_2(\text{dba})_3$  as Pd source, DBU as base, and 100°C reaction temperature were fixed across all reactions (Scheme S1). In total, 35 different reactions showed detectable amounts of the desired product by GC-MS (Figure S1). The relative success for each different aryl halide, nucleophile, ligand, and solvent were tabulated.

Scheme S1 Exploring Buchwald-Hartwig aminations using high throughput experimentation

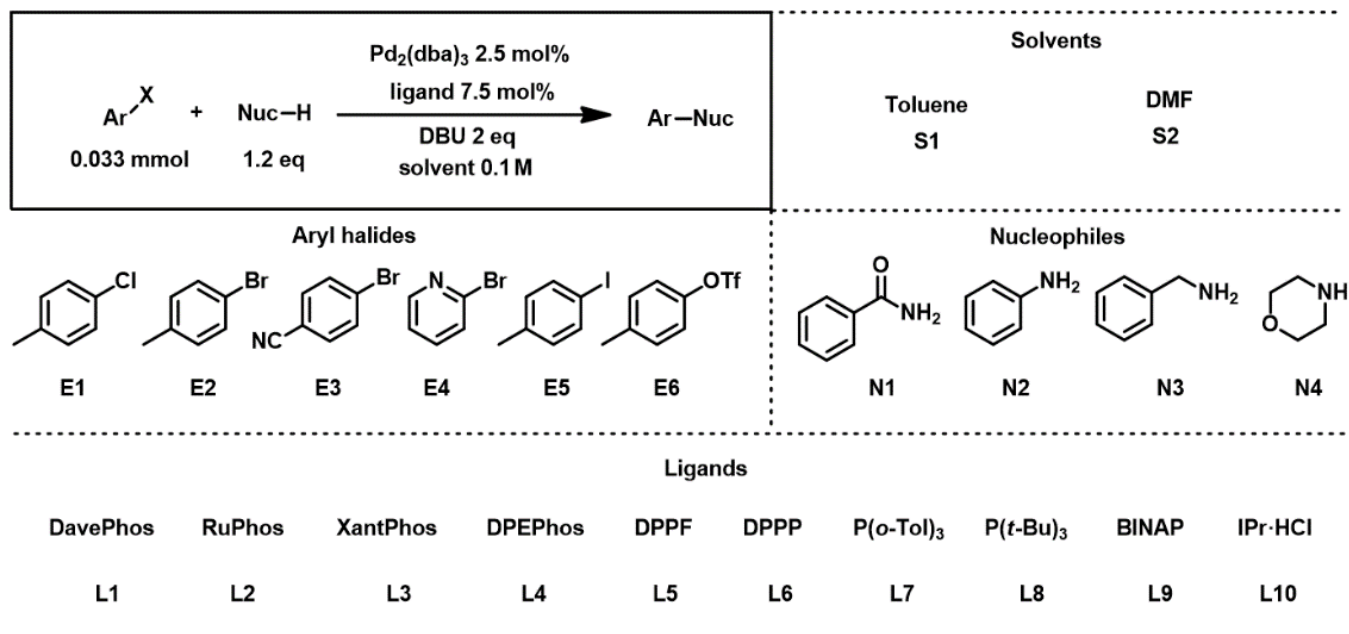
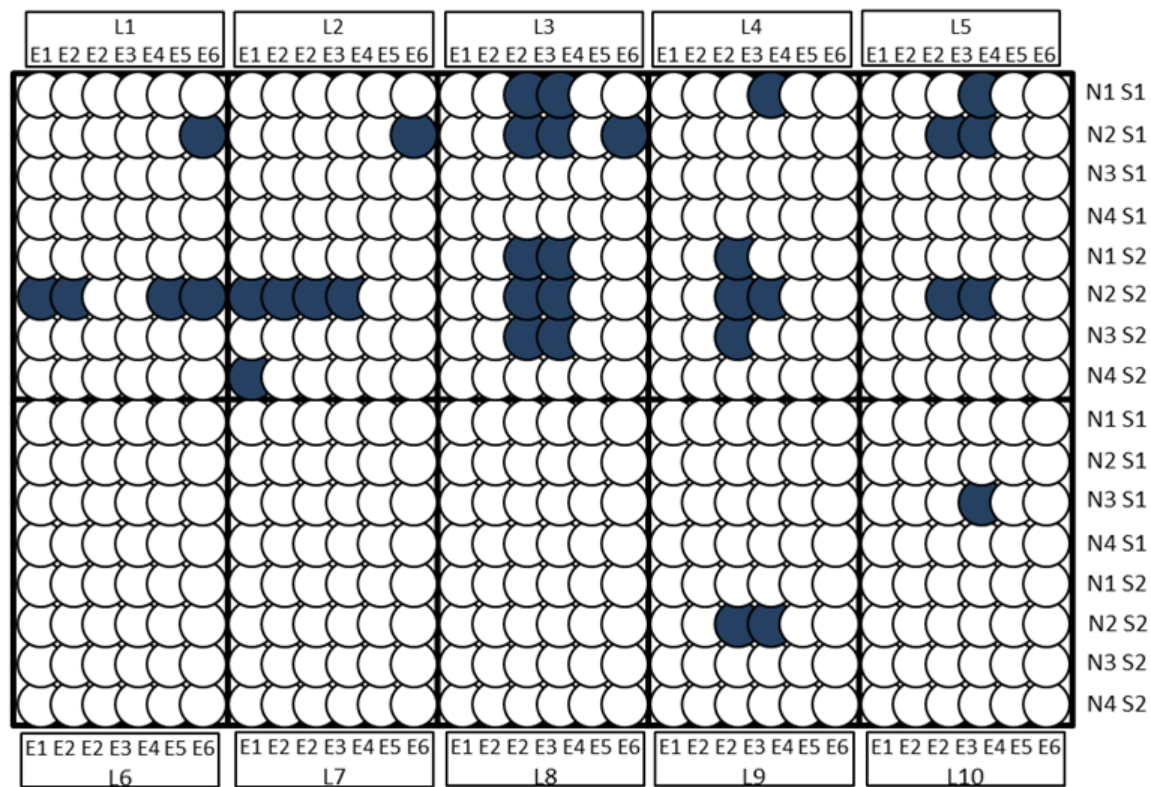


Figure S1 Heat map for the aminations in HTE



### Aryl (pseudo) halides:

Among the six different aryl halides studied, the fewest hits were observed using 4-chlorotoluene (E1), and the most with 2-bromopyridine (E4) (Table S1). In general, electron-poor substrates are more effective in the presence of DBU as a weak base.

**Table S1** Statistic analysis for the HTE results based on aryl (pseudo) halides

Aryl halide	# successful rxns	Avg estimated yield in successful rxns	Avg estimated yield in all reactions
E1	3	2.3%	0.09%
E2	2	2.5%	0.06%
E3	12	41%	6.15%
E4	13	10%	1.63%
E5	1	2%	0.03%
E6	4	7%	0.35%

### Nucleophiles:

Among the four different amine sources which were used across the HTE plates, aniline and benzamide showed the best result based on number of successful reactions and average of the estimated yield respectably. However, benzylamine and morpholine gave fewer hits and average yields in estimated conversions (Table S2).

**Table S2** Statistic analysis for the HTE results based on nucleophiles

Nucleophiles	# successful rxns	Avg estimated yield in successful rxns	Avg estimated yield in all reactions
N1	7	39%	2.28%
N2	23	15%	2.88%
N3	4	14%	0.47%
N4	1	2%	0.02%

### Solvents:

Two different solvents were used in our studies, one polar (DMF) and one non-polar (Toluene). DMF gave more hits across the HTE plates (Table S3).

**Table S3 Statistic analysis for the HTE results based on ligands**

Solvents	# successful rxns	Avg estimated yield in successful rxns	Avg estimated yield in all reactions
Toluene	12	16%	0.79%
DMF	23	21%	1.98%

### Ligands:

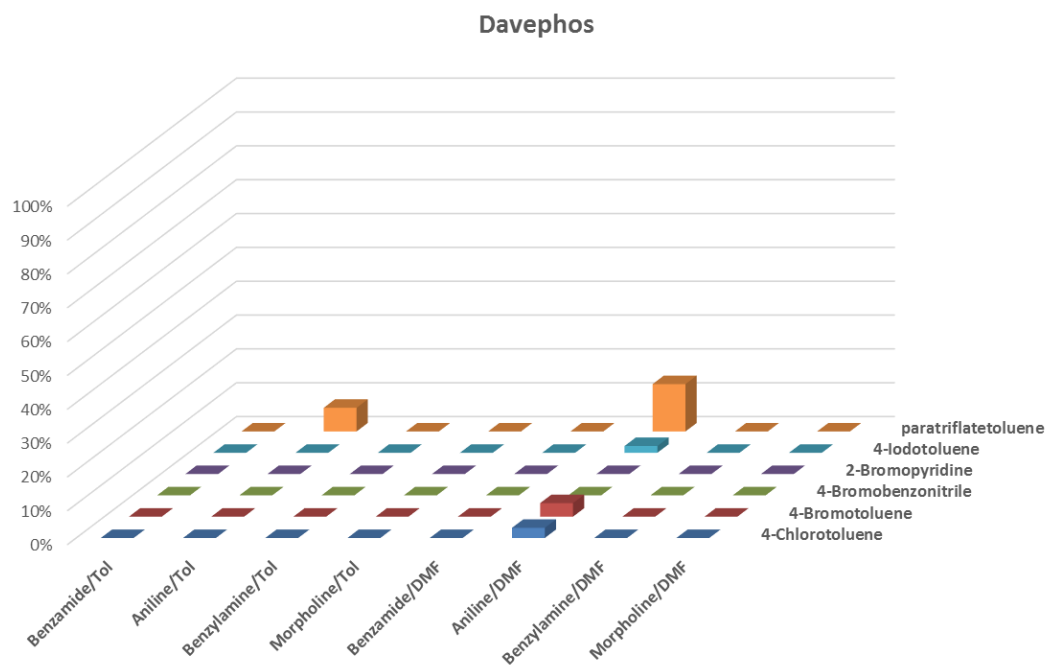
Ten different commercially available ligands were used in our studies. Xantphos was found to perform the best of all ligands tested. DPPP, P(o-Tol)<sub>3</sub>, P(t-Bu)<sub>3</sub> did not show any hits (Table S4).

**Table S4 Statistic analysis for the HTE results based on ligands**

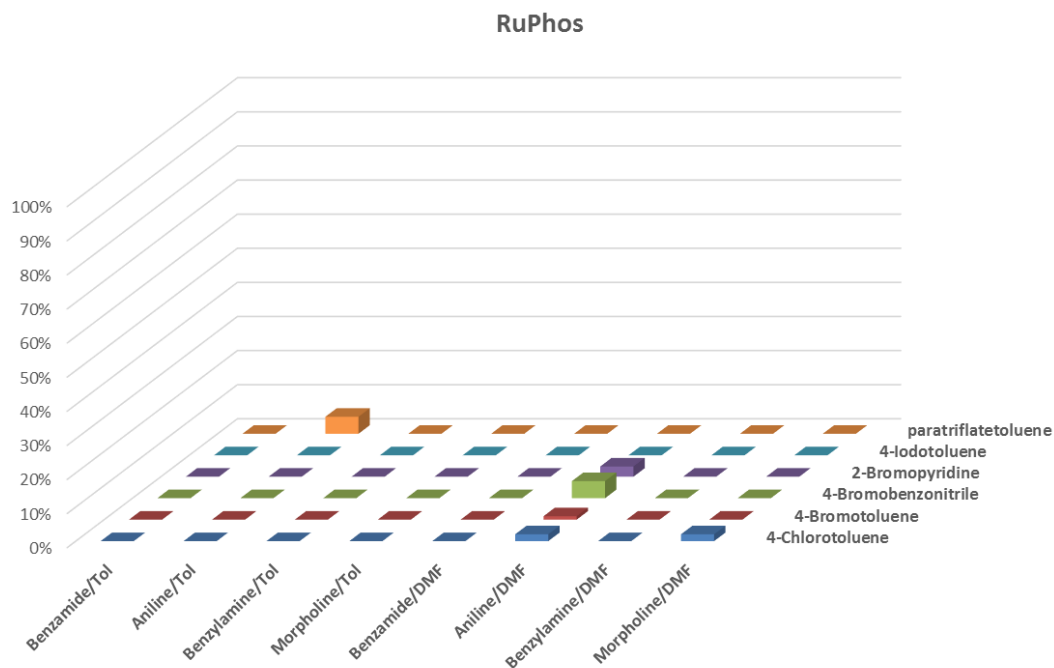
Ligand	# successful rxns	Avg estimated yield in successful rxns	Avg estimated yield in all reactions
DavePhos (L1)	5	6%	0.63%
RuPhos (L2)	6	3%	0.38%
XantPhos (L3)	11	38%	8.69%
DPEPhos (L4)	5	23%	2.44%
DPPF (L5)	5	14%	1.50%
DPPP (L6)	0	0%	0.00%
P(o-Tol) <sub>3</sub> (L7)	0	0%	0.00%
P(t-Bu) <sub>3</sub> (L8)	0	0%	0.00%
BINAP (L9)	2	3.5%	0.15%
IPr·HCl (L10)	1	2%	0.04%

The approximate yields for all 480 experiments classified by using ten different ligands:

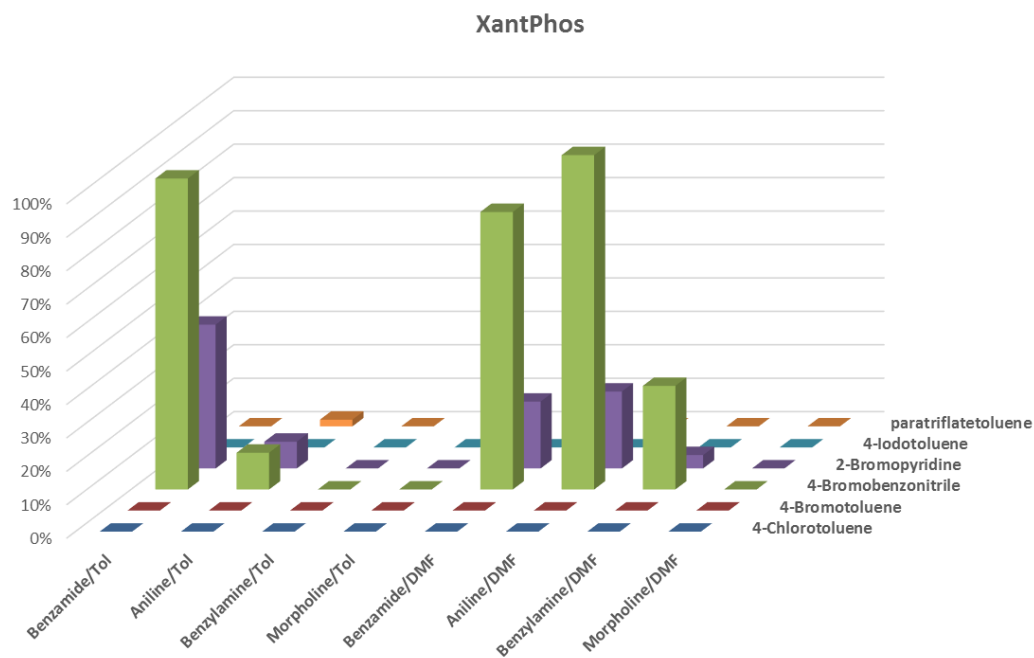
**Figure S2 Estimated yields for reactions in the presence of DavePhos as ligand.**



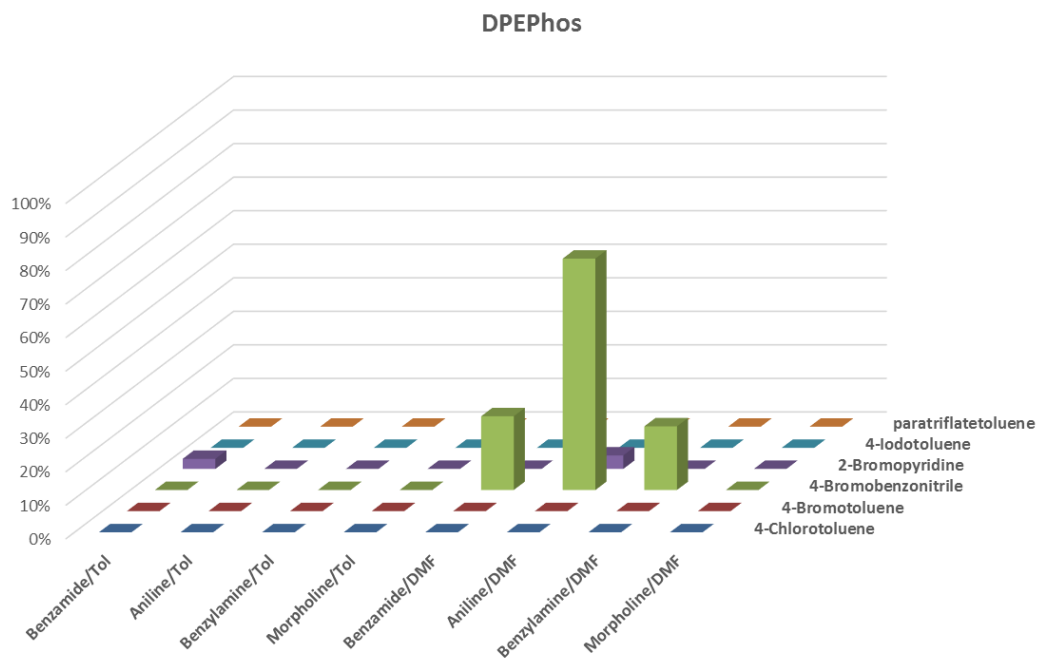
**Figure S3 Estimated yields for reactions in the presence of RuPhos as ligand.**



**Figure S4 Estimated yields for reactions in the presence of XantPhos as ligand.**

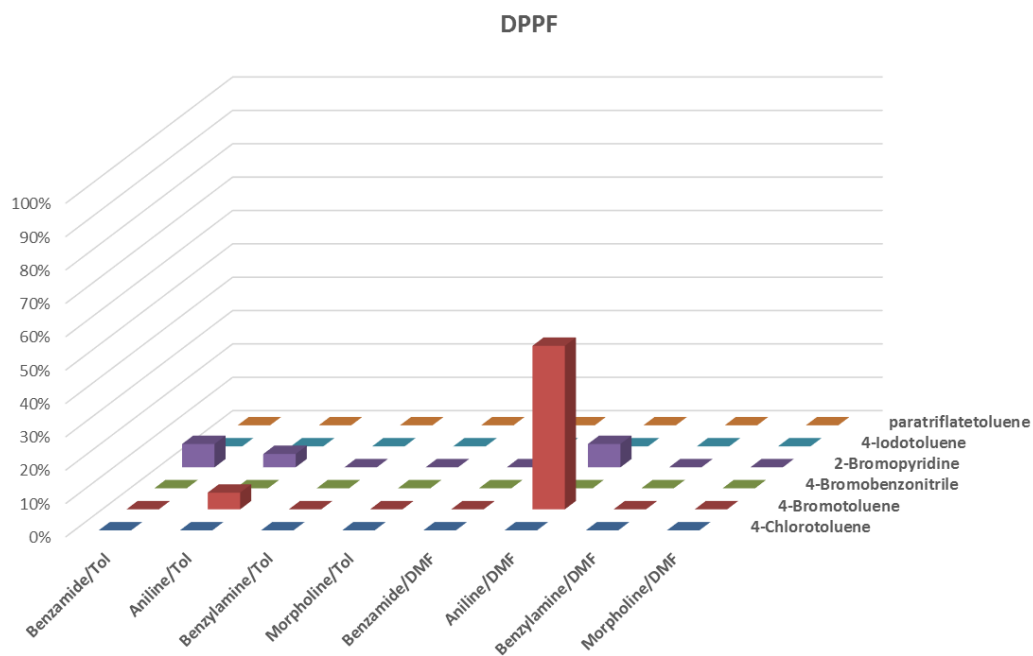


**Figure S5 Estimated yields for reactions in the presence of DPEPhos as ligand.**

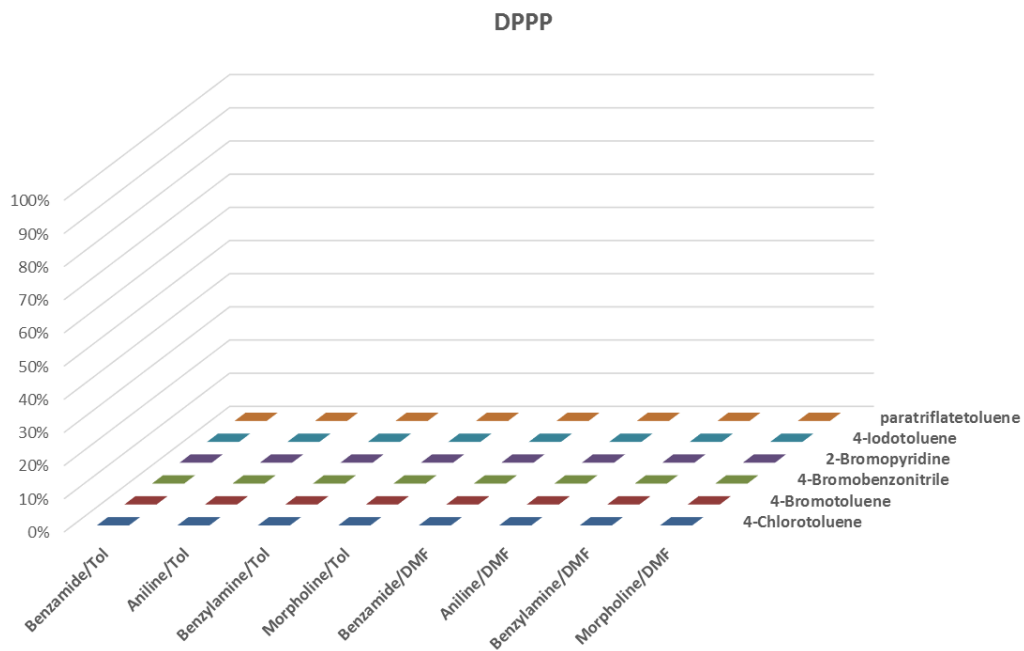




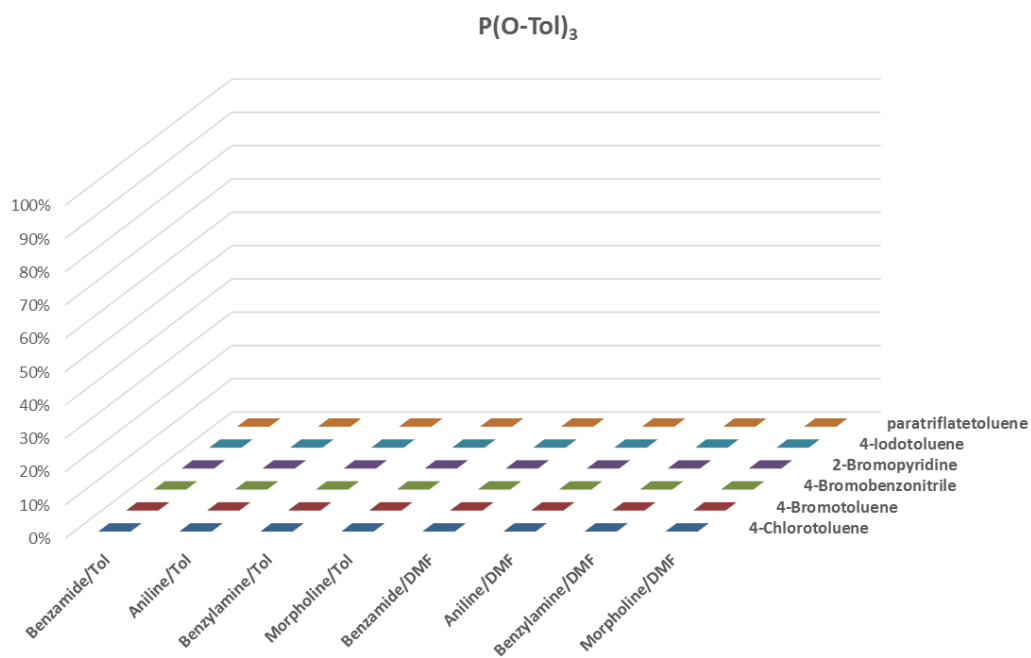
**Figure S6 Estimated yields for reactions in the presence of DPPF as ligand.**



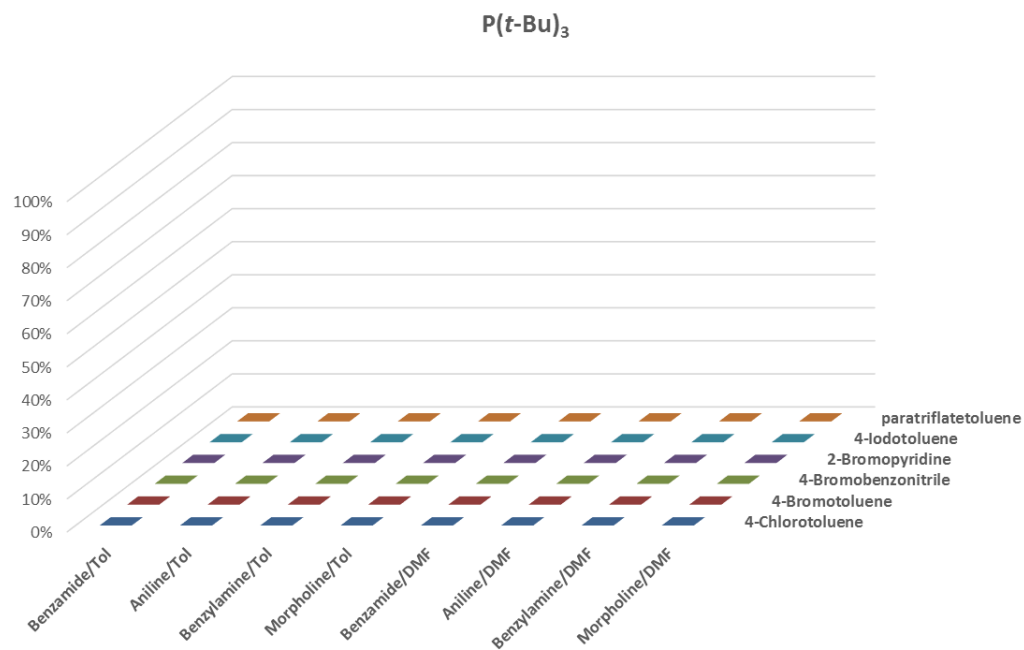
**Figure S7 Estimated yields for reactions in the presence of DPPP as ligand.**



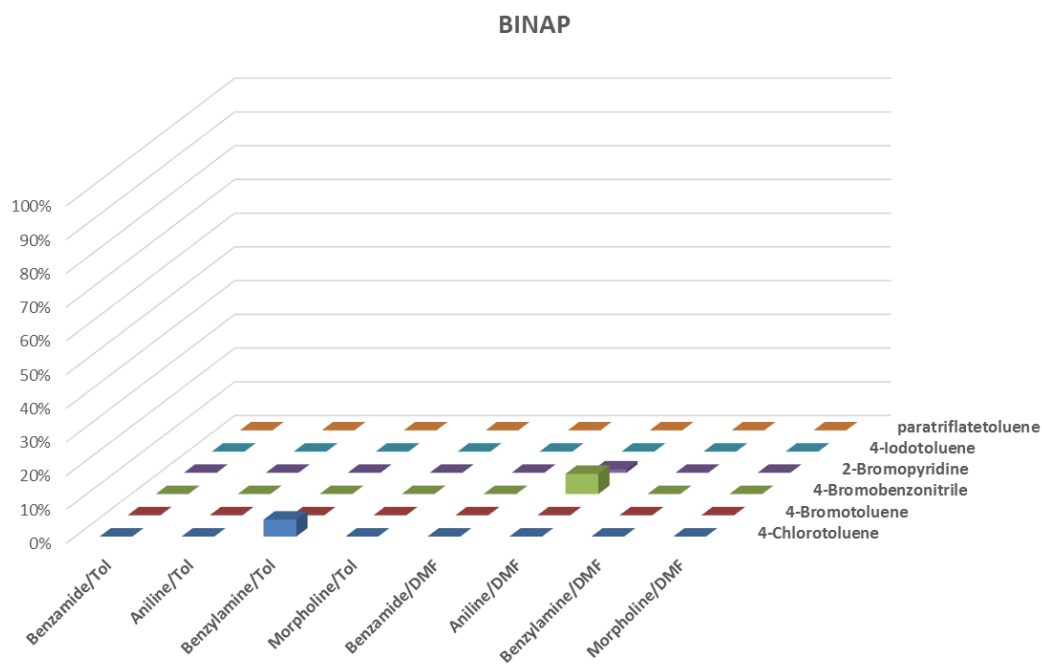
**Figure S8 Estimated yields for reactions in the presence of  $P(o\text{-tol})_3$  as ligand.**



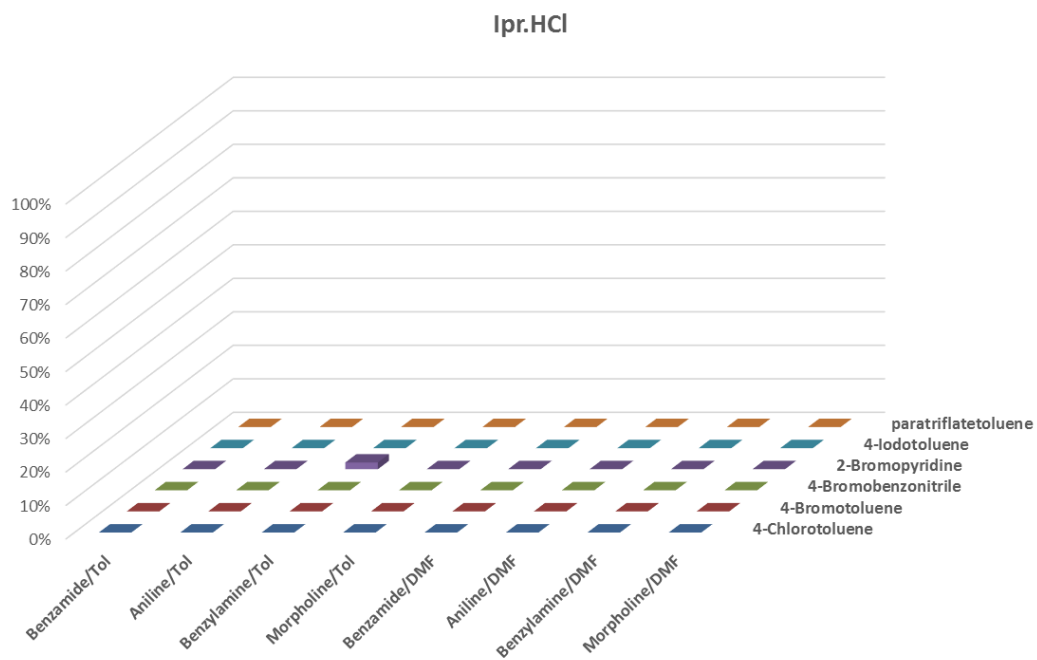
**Figure S9 Estimated yields for reactions in the presence of  $P(t\text{-Bu})_3$  as ligand.**



**Figure S10 Estimated yields for reactions in the presence of BINAP as ligand.**



**Figure S11 Estimated yields for reactions in the presence of IPr.HCl as ligand.**



### 2.3 General Procedure A for aminations with amides and electron-poor aryl halides in batch

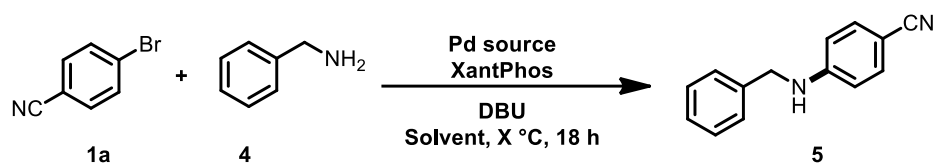
The procedure used for the data in Scheme 4 is as follows. To an 8 mL screw-capped reaction vial equipped with a magnetic stir bar, [Pd(cinnamyl)Cl]<sub>2</sub> (1.6 mg, 1.5 mol%), XantPhos (7 mg, 6 mol%), 4-Chlorobenzonitrile (27.5 mg, 0.2 mmol) and benzamide (48.4 mg, 0.4 mmol) were added. Then, inside the glovebox, DBU (60  $\mu$ l, 0.4 mmol) was added, and the reaction was diluted to ~2 mL (0.1 M) with Toluene (for other examples, all the liquids were added inside the glove box). The vial was capped, removed from the glove box, and placed in an oil bath pre-heated to 100 °C. After stirring for 18 hours, the reaction vial was removed from the oil bath and cooled down to room temperature. 1,3,5-trimethoxybenzene was added as an internal standard prior to filtering the reaction over a short pad of silica gel, washing with MeCN. The filtrate was diluted to an appropriate concentration and analyzed by GC-MS and <sup>1</sup>H-NMR to determine the yield. The reactions for the scope table were isolated by column chromatography.

### 2.4 General Procedure B for amination using benzylamine and aryl halide on batch

To an 8 mL screw-capped reaction vial equipped with a magnetic stir bar, [Pd(cinnamyl)Cl]<sub>2</sub> (2.6 mg, 2.5 mol%), XantPhos (8.6 mg, 7.5 mol%), and 4-bromobenzonitrile (36.4 mg, 0.2 mmol) were added. Then, inside the glovebox, benzylamine (44  $\mu$ l, 0.4 mmol) and DBU (60  $\mu$ l, 0.4 mmol) were added, and the reaction was diluted to ~0.6 mL (0.33 M) with DMSO. The vial was capped, removed from the glove box, and placed in an oil bath pre-heated to 100 °C. After stirring for 18 hours, the reaction vial was removed from the oil bath and cooled down to room temperature. 1,3,5-trimethoxybenzene was added as an internal standard prior to filtering the reaction over a short pad of silica gel, washing with MeCN. The filtrate was diluted to an appropriate concentration and analyzed by GC-MS and <sup>1</sup>H-NMR to determine the yield. The reactions for the scope table were isolated by column chromatography.

## 2.4.1 Optimization of amination with aniline and aryl triflates

Table S5 Optimization of Buchwald-Hartwig amination with benzylamine and aryl halide



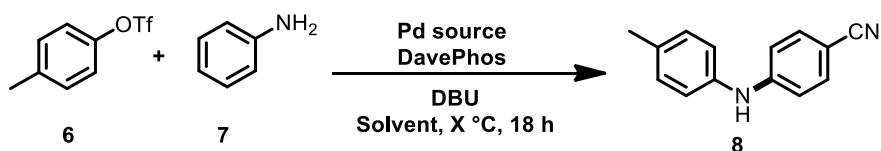
Entry	<b>4</b> (eq)	DBU (eq)	Catalys, Ligand (mol %)	Solvent Conc. (M)	T (°C)	Yield (%)
<b>1</b>	1.2	2	Pd <sub>2</sub> (dba) <sub>3</sub> 2.5, XantPhos 7.5	DMF (0.1M)	100	20
<b>2</b>	1.2	2	Pd(OAc) <sub>2</sub> 5, XantPhos 7.5	DMF (0.1M)	100	3
<b>3</b>	1.2	2	[Pd(Allyl)Cl] <sub>2</sub> 2.5, XantPhos 7.5	DMF (0.1M)	100	24
<b>4</b>	1.2	2	[Pd(Cinnamyl)Cl] <sub>2</sub> 2.5, XantPhos 7.5	DMF (0.1M)	100	30
<b>5</b>	1.2	2	[Pd(Cinnamyl)Cl] <sub>2</sub> 2.5, XantPhos 7.5	DMF (0.33M)	100	18
<b>6</b>	1.2	4	[Pd(Cinnamyl)Cl] <sub>2</sub> 2.5, XantPhos 7.5	DMF (0.1M)	100	8
<b>7</b>	2	2	[Pd(Cinnamyl)Cl] <sub>2</sub> 2.5, XantPhos 10	DMF (0.1M)	100	19
<b>8</b>	1.2	2	[Pd(Cinnamyl)Cl] <sub>2</sub> 2.5, XantPhos 7.5	DMSO (0.1M)	100	47
<b>9</b>	2	2	[Pd(Cinnamyl)Cl] <sub>2</sub> 2.5, XantPhos 7.5	DMSO (0.33M)	100	75

## 2.5 General Procedure C for amination using aniline and aryl triflates in batch

To an 8 mL screw-capped reaction vial equipped with a magnetic stir bar, [Pd(allyl)Cl]<sub>2</sub> (1.8 mg, 2.5 mol%) and DavePhos (8 mg, 10 mol%) were added. Then, inside the glovebox, aniline (40 µl, 0.2 mmol), *p*-tolyl methanesulfonate (36 µl, 0.2 mmol), and DBU (60 µl, 0.4 mmol) were added, and the reaction was diluted to ~0.6 mL (0.33 M) with DMF. The vial was capped, removed from the glove box, and placed in an oil bath pre-heated to 120 °C. After stirring for 18 hours, the reaction vial was removed from the oil bath and cooled down to room temperature. 1,3,5-trimethoxybenzene was added as an internal standard prior to filtering the reaction over a short pad of silica gel, washing with MeCN. The filtrate was diluted to an appropriate concentration and analyzed by GC-MS and <sup>1</sup>H-NMR to determine the yield. The reactions for the scope table were isolated by column chromatography.

## 2.5.1 Optimization of amination with aniline and aryl triflates

Table S6 Optimization of Buchwald-Hartwig amination with aniline and aryl triflates



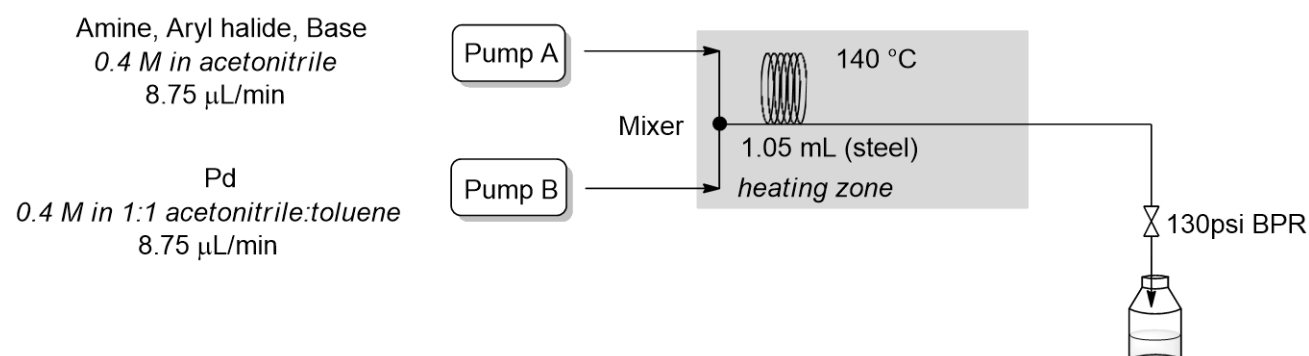
Entry	7 (eq)	DBU (eq)	Catalyst, Ligand (mol%)	Solvent Conc. (M)	T (°C)	Yield (%)
1	1.2	2	Pd <sub>2</sub> (dba) <sub>3</sub> 2.5, DavePhos 7.5	DMF (0.1)	100	trace
2	1.2	2	Pd(OAc) <sub>2</sub> 5, DavePhos 7.5	DMF (0.1)	100	trace
3	1.2	2	[Pd(Cinnamyl)Cl] <sub>2</sub> 2.5, DavePhos 7.5	DMF (0.1)	100	trace
4	1.2	2	[Pd(allyl)Cl] <sub>2</sub> 2.5, DavePhos 7.5	DMF (0.1)	100	10
5	1.2	2	[Pd(allyl)Cl] <sub>2</sub> 2.5, DavePhos 7.5	DMF (0.1)	120	45
6	1.2	2	[Pd(allyl)Cl] <sub>2</sub> 2.5, DavePhos 7.5	DMF (0.33)	100	38
7	1.2	2	[Pd(allyl)Cl] <sub>2</sub> 2.5, DavePhos 7.5	MeCN (0.1)	100	29
8	1.2	2	[Pd(allyl)Cl] <sub>2</sub> 2.5, DavePhos 7.5	Dioxane (0.1)	100	22
9	2	2	[Pd(allyl)Cl] <sub>2</sub> 2.5, DavePhos 7.5	DMF (0.1)	100	56
10	2	2	[Pd(allyl)Cl] <sub>2</sub> 2.5, DavePhos 7.5	DMF (0.33)	120	61
11	2	2	[Pd(allyl)Cl] <sub>2</sub> 2.5, DavePhos 10	DMF (0.33)	120	85

## 2.6 General Procedure D for Buchwald-Hartwig amination in flow

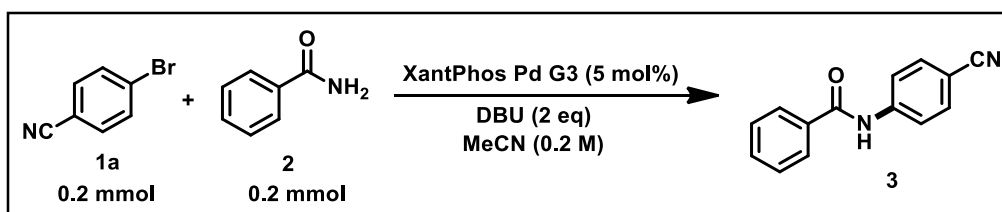
The procedure used for the data in Scheme 5 is provided below. In the glovebox, halide (1.2 mmol), amine/amide (1.2 mmol) and DBU (2.4 mmol) were combined in a 6 mL screw cap vial and made up to 3.00 mL with acetonitrile to give a 0.4M solution of halide, which was subsequently loaded into an 8 mL stainless steel syringe. In the glovebox, palladium pre-catalyst (0.06 mmol) was made up to 3.00 mL in a 6 mL screw cap vial with a 1:1 mixture of acetonitrile and toluene and loaded into a second 8 mL stainless steel syringe. The syringes were then attached in the glovebox to the steel continuous flow reactor depicted in Figure S1, which was subsequently shipped out of the glovebox. Syringes were loaded into Nexus 6000 pumps, and the reactor coil was submerged in an oil bath pre-heated to 140 °C. Both pumps were simultaneously set to deliver the syringe

contents at 8.75  $\mu\text{L}/\text{min}$  through a 1.05 mL stainless steel coil, with a 130 psi back pressure regulator set at the outlet. The first 3 hours (3 residence volumes) of effluent was discarded to reach steady state, followed by collection of effluent for the specified amount of time. Unless otherwise specified, solvent was evaporated, and the resulting material was dissolved in DCM (30 mL). The resulting solution was mixed and separated with saturated NaCl (30 mL), followed by 2 more washes of the aqueous layer with DCM ( $2 \times 30$  mL). The combined organic extracts were dried over  $\text{Na}_2\text{SO}_4$ , and the solvent was evaporated. Product was purified via silica gel column chromatography, dried again with  $\text{Na}_2\text{SO}_4$ , solvent was evaporated, and the product was dried under high vacuum.

**Figure S1** Schematic of flow reactor used for Buchwald-Hartwig reactions.



### Rational for 140 °C Reaction Temperature

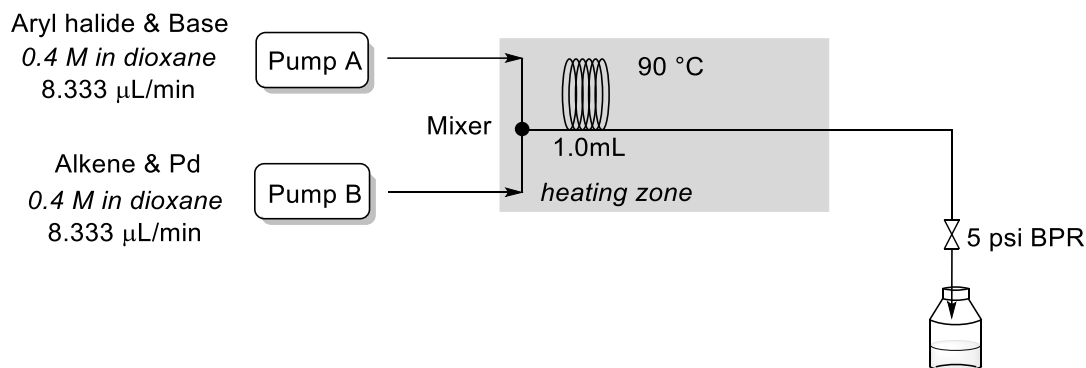


T (°C)	Reaction Time	NMR Yield
100	18 hr	95%
100	1 hr	22%
120	4 hr	96%
120	1 hr	34%
140	1 hr	88%

## 2.7 General Procedure E for Mizoroki-Heck reaction in flow

The procedure used for the data in Scheme 5 is provided below. In the glovebox, halide (1.2 mmol) and tributylamine (3.6 mmol) were combined in a 6 mL screw cap vial and made up to 3.00 mL with 1,4-dioxane to give a 0.4 M solution of halide, which was subsequently loaded into a 5 mL Hamilton Gastight syringe. In the glovebox, olefin (1.8 mmol) and palladium pre-catalyst (0.036 mmol) were combined in a 6 mL screw cap vial, made up to 3.00 mL with 1,4-dioxane, and loaded into a second 5 mL Hamilton Gastight syringe. The syringes were then attached in the glovebox to the PFA tubing continuous flow reactor depicted in Figure S2, which was subsequently shipped out of the glovebox. Syringes were loaded into Nexus 6000 pumps, and the reactor coil was submerged in an oil bath pre-heated to 90 °C. Both pumps were simultaneously set to deliver the syringe contents at 8.333  $\mu\text{L}/\text{min}$  through a 1 mL PFA coil of 0.5 mm i.d., with a 5 psi back pressure regulator set at the outlet. The first 3 hours (3 residence volumes) of effluent was discarded to reach steady state, followed by collection of effluent for the specified amount of time. Unless otherwise specified, solvent was evaporated, and the resulting material was dissolved in DCM (30 mL). The resultant solution was mixed and separated with 1M HCl (30 mL), followed by 2 more washes of the aqueous layer with DCM ( $2 \times 30$  mL). The combined organic extracts were washed with saturated NaCl solution (30 mL), dried over  $\text{Na}_2\text{SO}_4$ , and the solvent was evaporated. Product was purified via silica gel column chromatography, dried again with  $\text{Na}_2\text{SO}_4$ , solvent was evaporated, and the product was dried under high vacuum.

**Figure S2** Schematic of flow reactor used for Heck reactions.



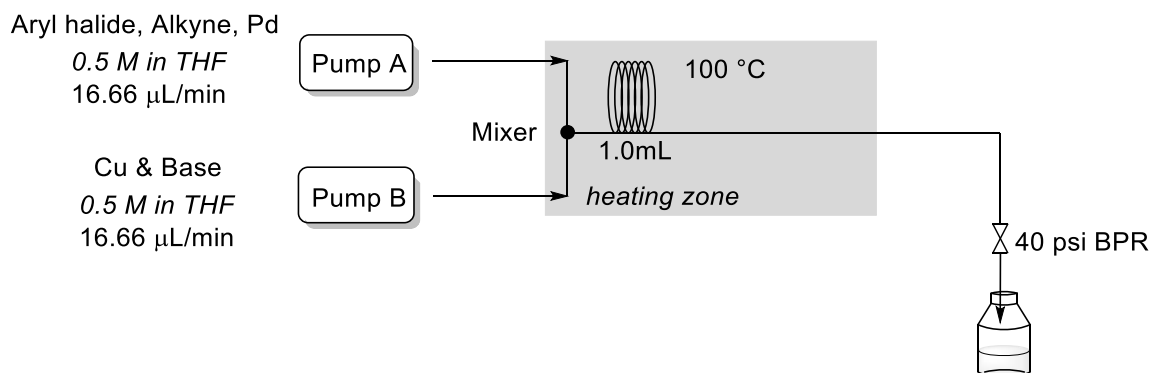
## 2.8 General Procedure F for Sonogashira coupling in flow

The procedure used for the data in Scheme 5 is provided below. In the glovebox, organohalide (1.5 mmol) and alkyne (2.25 mmol) and Tetrakis(triphenylphosphine)palladium(0) (0.03 mmol) were



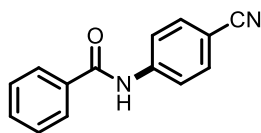
combined in a 6 mL screw cap vial and diluted to 3.00 mL with THF to give a 0.5 M solution of organohalide, which was subsequently loaded into a 10 mL Hamilton Gastight syringe. In a separate 6 mL vial, copper iodide (0.03 mmol) and tributylamine (4.5 mmol) were combined, diluted to 3.00 mL with THF, and loaded into a second 10 mL Hamilton Gastight syringe. The syringes were then attached in the glovebox to the PFA continuous flow reactor depicted in Figure S3, which was subsequently shipped out of the glovebox. Syringes were loaded into Nexus 6000 pumps, and the reactor coil was submerged in an oil bath pre-heated to 100 °C. Both pumps were simultaneously set to deliver the syringe contents at 16.66  $\mu\text{L}/\text{min}$  through a 1 mL PFA coil of 0.5 mm i.d., with a 40 psi back pressure regulator set at the outlet. The first 1.5 hours (3 residence volumes) of effluent was discarded to reach steady state, followed by collection of effluent for the specified amount of time. Unless otherwise specified, solvent was evaporated, and the resulting material was dissolved in DCM (30 mL). The resultant solution was mixed and separated with 1M HCl (30 mL), followed by 2 more washes of the aqueous layer with DCM ( $2 \times 30 \text{ mL}$ ). The combined organic extracts were washed with saturated NaCl solution (30 mL), dried over  $\text{Na}_2\text{SO}_4$ , and the solvent was evaporated. Product was purified via silica gel column chromatography, dried again with  $\text{Na}_2\text{SO}_4$ , solvent was evaporated, and the product was dried under high vacuum.

**Figure S3** Schematic of flow reactor used for Sonogashira reactions.



### 3 Characterization data for products formed in batch reactions

#### N-(4-cyanophenyl)benzamide (3)

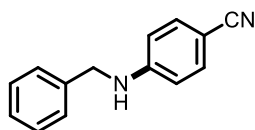


**X= Cl**, General Procedure A was followed using benzamide (48.4 mg) and 4-chlorobenzonitrile (27.6 mg). Column chromatography (1:2 EtOAc in hexanes) yielded the pure product as a white crystal (38 mg, 85% yield). Characterization data is in agreement with the literature.<sup>1</sup> <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 8.04 (s, 1H), 7.90-7.85 (d, J = 7.2 Hz, 2H), 7.82-7.77 (d, J = 8.8 Hz, 2H), 7.68-7.63 (d, J = 8.8 Hz, 2H), 7.63-7.57 (t, J = 7.4 Hz, 1H), 7.55-7.48 (t, J = 7.2 Hz, 2H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ 166.0, 142.1, 134.3, 133.5, 132.7, 129.2, 127.2, 120.0, 118.9, 107.6.

**X= Br**, General Procedure A was followed using benzamide (48.4 mg) and 4-bromobenzonitrile (36.4 mg). Column chromatography (1:2 EtOAc in hexanes) yielded the pure product as a white crystal (40 mg, 91% yield). Characterization data is in agreement with the literature.<sup>1</sup> <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 8.01 (s, 1H), 7.91-7.84 (d, J = 7.2 Hz, 2H), 7.83-7.77 (d, J = 8.8 Hz, 2H), 7.69-7.64 (d, J = 8.8 Hz, 2H), 7.63-7.57 (t, J = 7.4 Hz, 1H), 7.55-7.48 (t, J = 7.2 Hz, 2H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ 166.0, 142.1, 134.3, 133.5, 132.7, 129.2, 127.3, 120.1, 118.9, 107.6.

**X= I**, General Procedure A was followed using benzamide (48.4 mg) and 4-iodobenzonitrile (46 mg). Column chromatography (1:2 EtOAc in hexanes) yielded the pure product as a white crystal (31 mg, 70% yield). Characterization data is in agreement with the literature.<sup>1</sup> <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 7.97 (s, 1H), 7.92-7.84 (d, J = 6.9 Hz, 2H), 7.84-7.76 (d, J = 8.8 Hz, 2H), 7.70-7.64 (d, J = 8.8 Hz, 2H), 7.63-7.57 (t, J = 7.4 Hz, 1H), 7.56-7.49 (t, J = 7.2 Hz, 2H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ 166.0, 142.2, 134.3, 133.5, 132.7, 129.2, 127.2, 120.1, 119.0, 107.6.

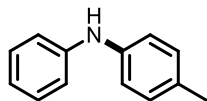
#### 4-(benzylamino)benzonitrile (5)



General Procedure B was followed. Column chromatography (8:1 Ether in MeOH) yielded the pure product as a white solid (29 mg, 70% yield). Characterization data is in agreement with the

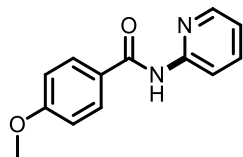
literature.<sup>2</sup> <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 7.44-7.40 (d, J = 7.9 Hz, 2H), 7.40-7.28 (m, 5H), 6.61-6.57 (d, J = 8.0 Hz, 2H), 4.59 (s, 1H), 4.38 (s, 2H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ 151.2, 137.9, 133.9, 129.0, 127.9, 127.5, 120.5, 112.6, 99.3, 47.7.

#### 4-methyl-N-phenylaniline (8)



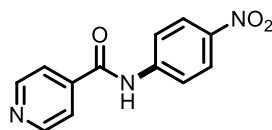
General Procedure C was followed. Column chromatography (1:10 EtOAc in hexanes) yielded the pure product as a white crystal (31.2 mg, 85% yield). Characterization data is in agreement with the literature.<sup>3</sup> <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 7.28–7.21 (t, J = 8.2 Hz, 2H), 7.12-7.07 (d, J = 7.8 Hz, 2H), 7.04-6.99 (m, 4H), 6.92-6.85 (t, J = 7.2 Hz, 1H), 5.60 (s, 1H), 2.31 (s, 1H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ 144.1, 140.4, 131.1, 130.0, 129.4, 120.4, 119.0, 117.0, 20.8.

#### 4-methoxy-N-(pyridin-2-yl)benzamide (9)



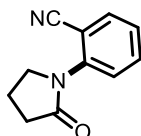
General Procedure A was followed using 4-methoxybenzamide (60.5 mg) and 2-bromopyridine (19.1 μl). Column chromatography (1:3 EtOAc in hexanes) yielded the pure product as a yellow solid (34.0 mg, 75% yield). Characterization data is in agreement with the literature.<sup>4</sup> <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 8.76 (s, 1H), 8.45-8.40 (d, J = 8.4 Hz, 1H), 8.32-8.27 (m, 1H), 7.96-7.90 (dt, J = 8.9 Hz, 2.8 Hz, 2H), 7.82-7.75 (m, 1H), 7.12-7.05 (m, 1H), 7.02-6.95 (dt, J = 8.8 Hz, 3.1 Hz, 2H), 3.88 (s, 3H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ 165.3, 163.1, 151.8, 147.2, 139.1, 129.4, 126.4, 119.8, 114.5, 114.2, 55.7.

#### N-(4-nitrophenyl)isonicotinamide (10)



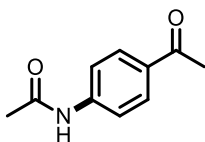
General Procedure A was followed using 4-nicotinamide (48.8 mg) and 1-chloro-4-nitrobenzene (31.5 mg). Column chromatography (8:1 EtOAc in hexanes) yielded the pure product as a yellow powder (46.6 mg, 96% yield). Characterization data is in agreement with the literature.<sup>5</sup> <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  8.90-8.82 (d, J = 5.6 Hz, 2H), 8.33-8.26 (d, J = 9.3 Hz, 2H), 8.07 (s, 1H), 7.89-7.83 (d, J = 9.2 Hz, 2H), 7.75-7.70 (d, J = 6.0 Hz, 2H). <sup>13</sup>C NMR (100 MHz, DMSO-d<sub>6</sub>):  $\delta$  164.8, 150.3, 144.8, 142.9, 141.3, 124.8, 121.7, 120.1.

### 2-(2-oxopyrrolidin-1-yl)benzonitrile (11)



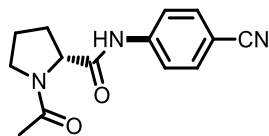
General Procedure A was followed using 2-pyrrolidinone (30  $\mu$ l) and 2-iodobenzonitrile (45.8 mg). Column chromatography (1:1 EtOAc in DCM) yielded the pure product as a yellow solid (34.8 mg, 93% yield). MP: 97 °C. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  7.74-7.67 (dd, J = 7.9 Hz, 1.5 Hz, 1H), 7.67-7.60 (td, J = 7.9 Hz, 1.6 Hz, 2H), 7.47-7.40 (d, J = 8.0 Hz, 1H), 7.40-7.34 (td, J = 7.7 Hz, 1.1 Hz, 1H), 3.99-3.90 (t, J = 6.9 Hz, 2H), 2.67-2.58 (t, J = 8.2 Hz, 2H), 2.32-2.21 (m, 2H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$  174.9, 141.9, 133.9, 133.8, 127.4, 127.2, 116.9, 110.5, 50.3, 31.4, 19.3. IR  $\nu$  (cm<sup>-1</sup>) 2985, 2952, 2923, 2894, 2852, 2228, 1690, 1593, 1491, 1453, 1401, 1312, 1273, 1117. Accurate mass (EI): m/z calcd for C<sub>11</sub>H<sub>10</sub>N<sub>2</sub>O: 186.0788. Found 186.0878, Spectral accuracy = 99.7%.

### N-(4-acetylphenyl)acetamide (12)



General Procedure A was followed using acetamide (23.6 mg) and 4-bromoacetophenone (39.8 mg). Column chromatography (2:1 EtOAc in hexanes) yielded the pure product as a cream solid (28.1 mg, 79% yield). Characterization data is in agreement with the literature.<sup>6</sup> <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  7.96-7.92 (dt, J = 8.7 Hz, 2.0 Hz, 2H), 7.67-7.55 (d, J = 8.9 Hz, 2H), 7.38 (s, 1H), 2.58 (s, 3H), 2.22 (s, 3H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$  197.0, 168.6, 142.3, 133.0, 129.9, 118.9, 26.5, 24.9.

**(R)-1-acetyl-N-(4-cyanophenyl) pyrrolidine-2-carboxamide (13)**

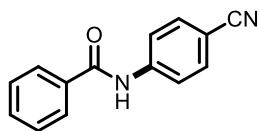


General Procedure A was followed using N-acetyl-L-prolinamide (62.5 mg) and 4-bromobenzonitrile (36.4 mg). The reaction was stopped after 2 hrs instead of 18 hrs. Column chromatography (8:1 Ether in MeOH) yielded the pure product as a white solid (47.6 mg, 92% yield). MP: 225 °C.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  10.23 (s, 1H), 7.61-7.56 (d,  $J$  = 8.9 Hz, 2H), 7.53-7.48 (d,  $J$  = 9.2 Hz, 2H), 4.80-4.75 (d,  $J$  = 7.4 Hz, 1H), 3.65-3.57 (m, 1H), 3.53-3.44 (m, 1H), 2.60-2.48 (m, 1H), 2.17 (m, 3H), 2.15-1.99 (m, 2H), 1.93-1.83 (m, 1H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  172.1, 169.6, 142.5, 133.2, 119.7, 119.1, 106.7, 60.1, 48.8, 26.9, 25.2, 22.7. IR  $\nu$  ( $\text{cm}^{-1}$ ) 3254, 3181, 3094, 3040, 2881, 2222, 1709, 1623, 1599, 1535, 1508, 1452, 1359, 1306, 1252, 1176, 1001. Accurate mass (EI):  $m/z$  calcd for  $\text{C}_{14}\text{H}_{15}\text{N}_2\text{O}$ : 257.1159. Found 257.1167, Spectral accuracy = 99.2%. HPLC: IA chiral column, 10% iPrOH in hexanes, 1.0 mL/min, 254 nm,  $t_{\text{R1}}$ (minor) = 26.8 min,  $t_{\text{R2}}$ (major) = 35.4 min.

**4 Characterization data for products formed in flow reactions**

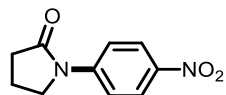
**4.1 Buchwald-Hartwig aminations in flow**

**N-(4-cyanophenyl)benzamide (14)**



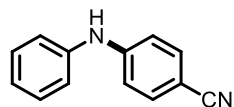
General Procedure D was followed for the reaction of 4-bromobenzonitrile and benzamide using 8 mL stainless steel syringes. Column chromatography (20% acetone in hexanes) yielded the product as an off white solid (76.5 min collection time, 50.3 mg, 85% yield). Characterization data is in agreement with the literature.<sup>7</sup>  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  8.01 (br, 1H), 7.90-7.85 (m, 2H), 7.83-7.77 (m, 2H), 7.68-7.64 (m, 2H), 7.60 (tt,  $J$  = 7.4, 2.1, 1H), 7.54-7.49 (m, 2H).  $^{13}\text{C}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  165.8, 142.0, 134.1, 133.4, 132.5, 129.0, 127.1, 119.9, 188.8, 107.5.

### 1-(4-nitrophenyl)pyrrolidin-2-one (15)



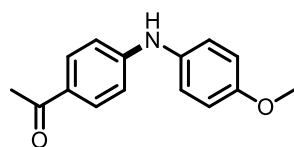
General Procedure D was followed for the reaction of 4-chloronitrobenzene and 2-pyrrolidone using 8 mL stainless steel syringes. Column chromatography (20% acetone in hexanes) yielded the product as an orange solid (67.0 min collection time, 42.6 mg, 88% yield). Characterization data is in agreement with the literature.<sup>8</sup> <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 8.26-8.20 (m, 2H), 7.86 – 7.81 (m, 2H), 3.92 (t, J = 7.0, 2H), 2.67 (t, J = 8.3, 2H), 2.28-2.18 (m, 2H) <sup>13</sup>C NMR (400 MHz, CDCl<sub>3</sub>): δ 174.9, 144.9, 143.4, 124.7, 118.7, 48.5, 32.8, 17.8.

### 4-(phenylamino)benzonitrile (16)



General Procedure D was followed for the reaction of 4-bromobenzonitrile and aniline using 8 ml stainless steel syringes. Column chromatography (15% ethyl acetate in hexanes) yielded the product as a pale orange solid (104.5 min collection time, 57.4 mg, 81% yield). Characterization data is in agreement with the literature.<sup>9</sup> <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 7.50-7.46 (m, 2H), 7.39-7.33 (m, 2H), 7.19-7.09 (m, 2H), 7.00-7.95 (m, 2H), 6.05 (br, 1H). <sup>13</sup>C NMR (400 MHz, CDCl<sub>3</sub>): δ 148.0, 140.0, 133.8, 129.7, 124.0, 121.3, 119.9, 114.9, 101.6.

### 1-(4-((4-methoxyphenyl)amino)phenyl)ethanone (17)

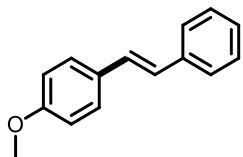


General Procedure D was followed for the reaction of 4-bromoacetophenone and 4-methoxyaniline using 8mL stainless steel syringes. Column chromatography (0-35% acetone in hexanes, 5% increase/50 mL) yielded the product as a pale yellow solid (92.8 min collection time, 61.0 mg, 78% yield). Characterization data is in agreement with the literature.<sup>10</sup> <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 7.85-7.80 (m, 2H), 7.16-7.11 (m, 2H), 6.94-6.88 (m, 2H), 6.84-6.79 (m, 2H), 5.98

(s, 1H), 3.82 (s, 3H), 2.51 (s, 3H).  $^{13}\text{C}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  196.3, 156.7, 150.1, 133.2, 130.7, 128.2, 124.6, 114.8, 113.1, 55.6, 26.1.

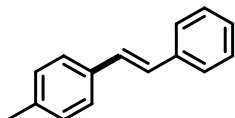
## 4.2 Mizoroki-Heck couplings in flow

### 1-methoxy-4-styryl-benzene (18)



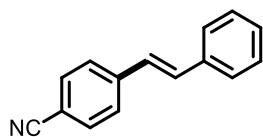
General Procedure E was followed for the reaction of 4-iodoanisole and styrene using 5 mL Hamilton Gastight syringes. Column chromatography (7.5% EtOAc in hexanes) yielded the product as a white solid (105.6 min collection time, 66.4 mg, 90% yield). Characterization data is in agreement with the literature.<sup>11</sup>  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ), E isomer:  $\delta$  7.52-7.44 (m, 4H), 7.38-7.32 (m, 2H), 7.27-7.22 (m, 1H), 7.08 (d,  $J$  = 16.3 Hz, 1H), 6.98 (d,  $J$  = 16.3 Hz, 1H), 6.94-6.89 (m, 2H), 6.84 (s, 3H).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ), terminal olefin: 7.31-7.27 (m, 2H), 6.89-6.85 (m, 2H), 5.41 (d,  $J$  = 2.1 Hz, 1H), 5.37 (d,  $J$  = 2.2 Hz, 1H), 3.83 (s, 3H). Other resonances are obscured by the resonances of the E isomer.  $^{13}\text{C}$  NMR (400 MHz,  $\text{CDCl}_3$ ), E isomer:  $\delta$  159.4, 137.8, 130.3, 129.5, 128.8, 128.5, 128.4, 128.3, 127.9, 127.3, 126.8, 126.4, 114.3, 55.5.

### 1-methyl-4-styrylbenzene (19)



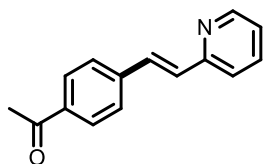
General Procedure E was followed for the reaction of 4-iodotoluene and styrene using 5 mL Hamilton Gastight syringes. Column chromatography (pure hexanes) yielded the product as a white solid (89.0 min collection time, 46.6 mg, 81% yield). Characterization data is in agreement with the literature.<sup>12</sup>  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ), E isomer:  $\delta$  7.54-7.49 (m, 2H), 7.45-7.41 (m, 2H), 7.39-7.34 (m, 2H), 7.29-7.23 (m, 1H), 7.21-7.16 (m, 2H), 7.10-7.08 (m, 2H).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ), terminal olefin:  $\delta$  5.45 (d,  $J$  = 1.2, 1H), 5.44 (d,  $J$  = 1.2, 1H). Other resonances are obscured by the resonances of the E isomer.  $^{13}\text{C}$  NMR (400 MHz,  $\text{CDCl}_3$ ), E isomer:  $\delta$  137.7, 134.7, 129.5, 128.79, 128.76, 127.8, 127.5, 126.57, 126.53, 21.4.

### 1-cyano-4-styryl-benzene (20)



General Procedure E was followed for the reaction of 4-iodobenzonitrile and styrene using 10 mL Hamilton Gastight syringes. Column chromatography (15% EtOAc in hexanes) yielded the product as a white solid (113.9 min collection time, 74.7 mg, 96% yield). Characterization data is in agreement with the literature.<sup>13</sup> <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>), E isomer:  $\delta$  7.66-7.51 (m, 6H), 7.42-7.37 (m, 2H), 7.35-7.30 (m, 1H), 7.22 (d,  $J$  = 16.3, 1H), 7.09 (d,  $J$  = 16.3, 1H). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>), terminal olefin:  $\delta$  5.59 (d,  $J$  = 0.6, 1H), 5.54 (d,  $J$  = 0.6, 1H). Other resonances are obscured by the resonances of the E isomer. <sup>13</sup>C NMR (400 MHz, CDCl<sub>3</sub>), E isomer:  $\delta$  142.0, 136.4, 132.60, 132.53, 129.0, 128.8, 127.04, 126.99, 126.8, 119.1, 110.7.

### (E)-1-(4-(2-(pyridin-2-yl)vinyl)phenyl)ethanone (21)

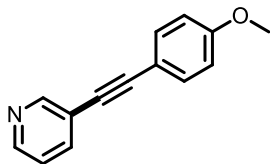


General Procedure E was followed, with one change, for the reaction of 4-bromoacetophenone and 2-vinylpyridine using 10 mL Hamilton Gastight syringes. The crude product was only separated with saturated NaCl solution, not with HCl. Column chromatography (20% MeCN in toluene) yielded the product as a pale-yellow solid (73.6 min collection time, 52.4 mg, 96% yield). Only the linear E isomer was observed. Characterization data is in agreement with the literature.<sup>14</sup> <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  8.63 (d,  $J$  = 4.1, 1H), 7.98-7.94 (m, 2H), 7.71-7.63 (m, 4H), 7.42-7.38 (m, 2H), 7.27 (d,  $J$  = 16.1, 1H), 7.18 (ddd,  $J$  = 7.5, 4.8, 1.0, 1H), 2.61 (s, 3H). <sup>13</sup>C NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  197.6, 155.1, 149.9, 141.4, 136.8, 136.6, 131.6, 130.6, 129.0, 127.3, 122.78, 122.76, 26.7.



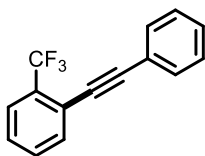
### 4.3 Sonogashira couplings in flow

#### 1-methoxy-4-(3'-pyridinylethynyl)-benzene (22)



General Procedure F was followed, with one change, for the reaction of 3-iodopyridine and 4-ethynylanisole using 10 mL Hamilton Gastight syringes. The crude product was only separated with saturated NaCl solution, not with HCl. Column chromatography (0-30% acetone in hexanes, 5% increase/50 mL) yielded the product as a white solid (40.6 min collection time, 70.8 mg, 83% yield). Characterization data is in agreement with the literature.<sup>15</sup> <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 8.75 (s, 1H), 8.52 (d, J = 3.5, 1H), 7.78 (dt, J = 7.9, 1.9, 1H), 7.51-7.46 (m, 2H), 7.27 (dd, J = 7.8, 4.8, 1H), 6.92-6.87 (m, 2H), 3.84 (s, 3H). <sup>13</sup>C NMR (400 MHz, CDCl<sub>3</sub>): δ 160.1, 152.0, 148.1, 138.3, 133.2, 123.1, 120.9, 114.6, 114.1, 92.8, 84.7, 55.3.

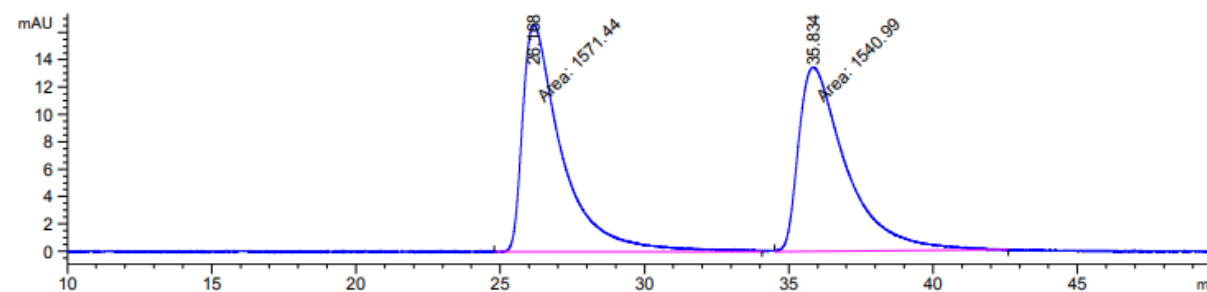
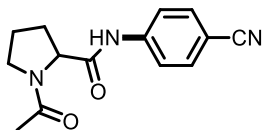
#### 1-(2-phenylethynyl)-3-(trifluoromethyl)benzene (23)



General Procedure F was followed for the reaction of 3-iodobenzotrifluoride and phenylacetylene using 10 mL Hamilton Gastight syringes. Column chromatography (0-4% acetone in hexanes, 1% increase/100 mL) yielded the product as a white solid (51.5 min collection time, 103 mg, 97% yield). Characterization data is in agreement with the literature.<sup>16</sup> <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 7.81 (s, 1H), 7.70 (d, J = 7.7, 1H), 7.61-7.53 (m, 3H), 7.48 (t, J = 7.8, 1H), 7.41-7.35 (m, 2H). <sup>13</sup>C NMR (400 MHz, CDCl<sub>3</sub>): δ 134.66, 134.65, 131.7, 128.9, 128.8, 128.45, 128.42, 128.38, 128.35, 124.81, 124.78, 124.74, 124.70, 124.3, 122.6, 90.9, 87.8.

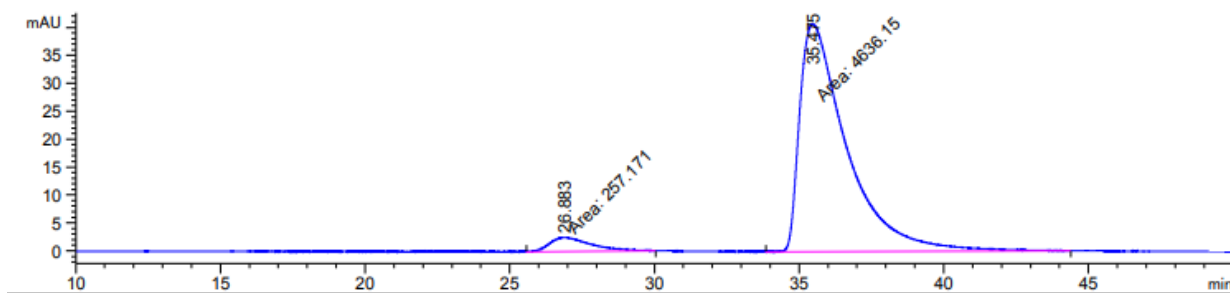
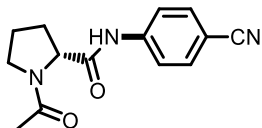
## 5 HPLC chromatograms

### (±)-1-acetyl-N-(4-cyanophenyl)pyrrolidine-2-carboxamide



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	26.164	MM	1.5675	1073.96204	11.41869	50.0594
2	35.829	MM	1.9385	1071.41418	9.21154	49.9406

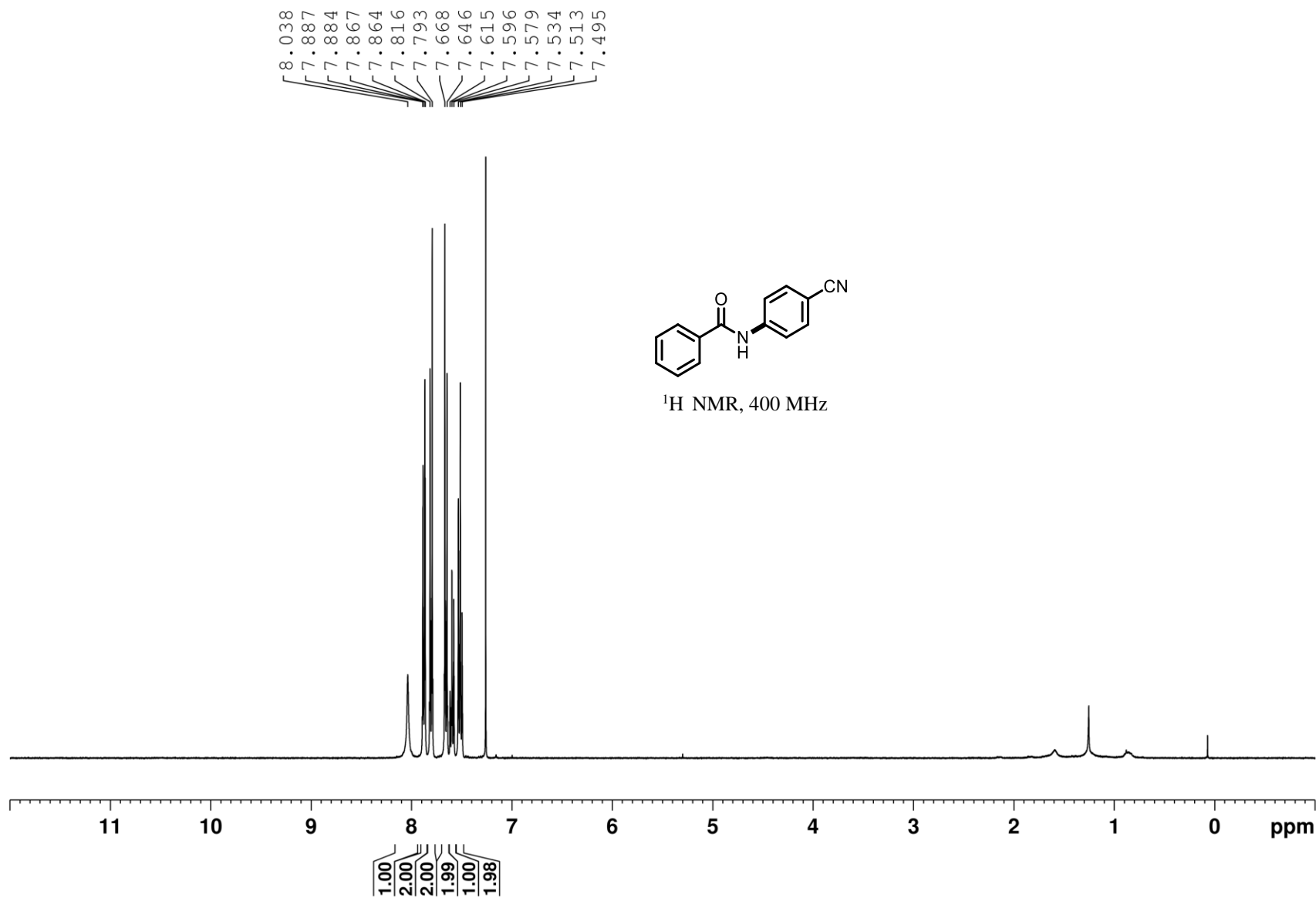
### (R)-1-acetyl-N-(4-cyanophenyl)pyrrolidine-2-carboxamide (13)

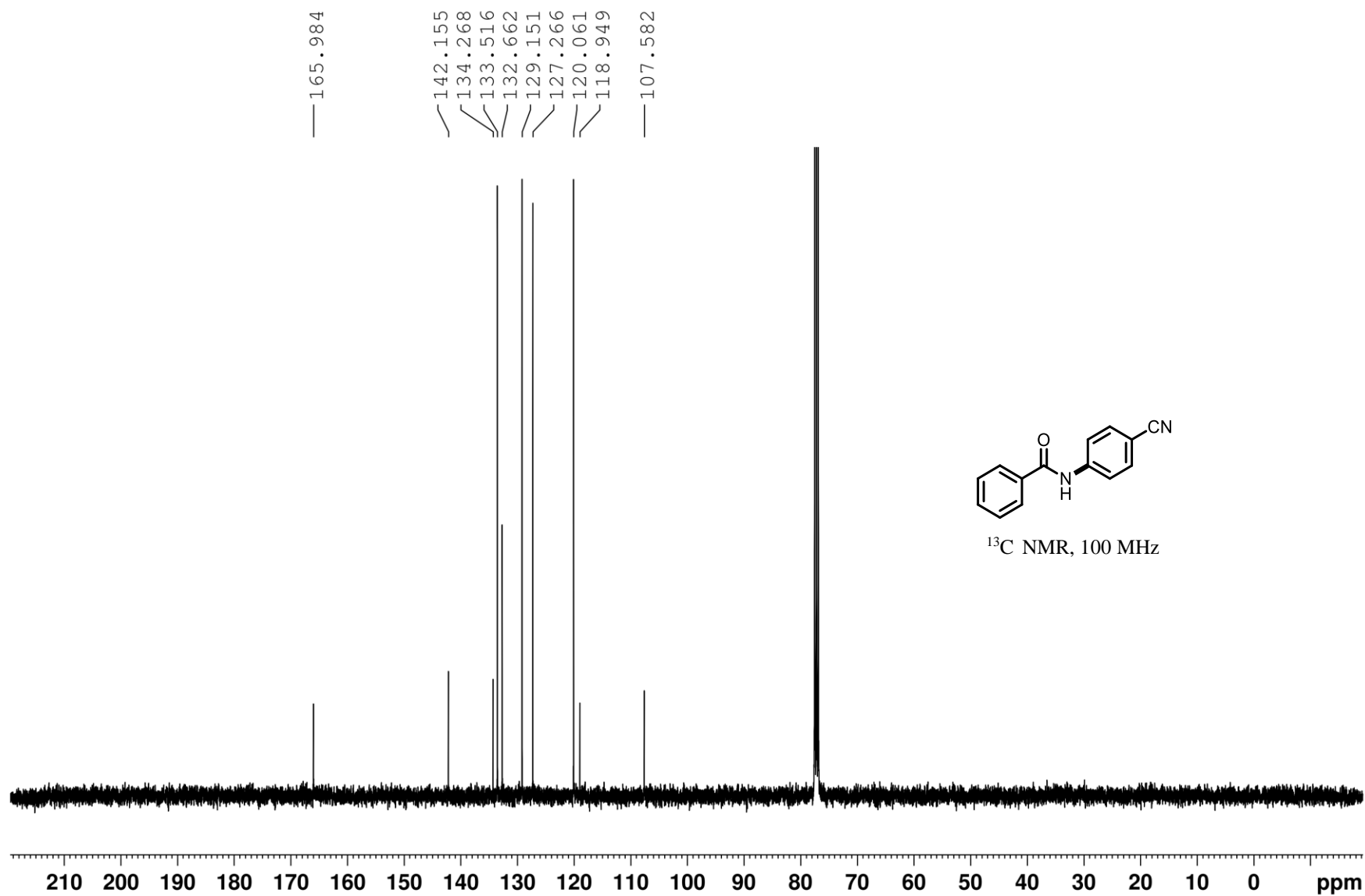


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	26.877	MM	1.7592	185.89343	1.76117	5.6299
2	35.476	MM	1.8633	3116.01001	27.87178	94.3701

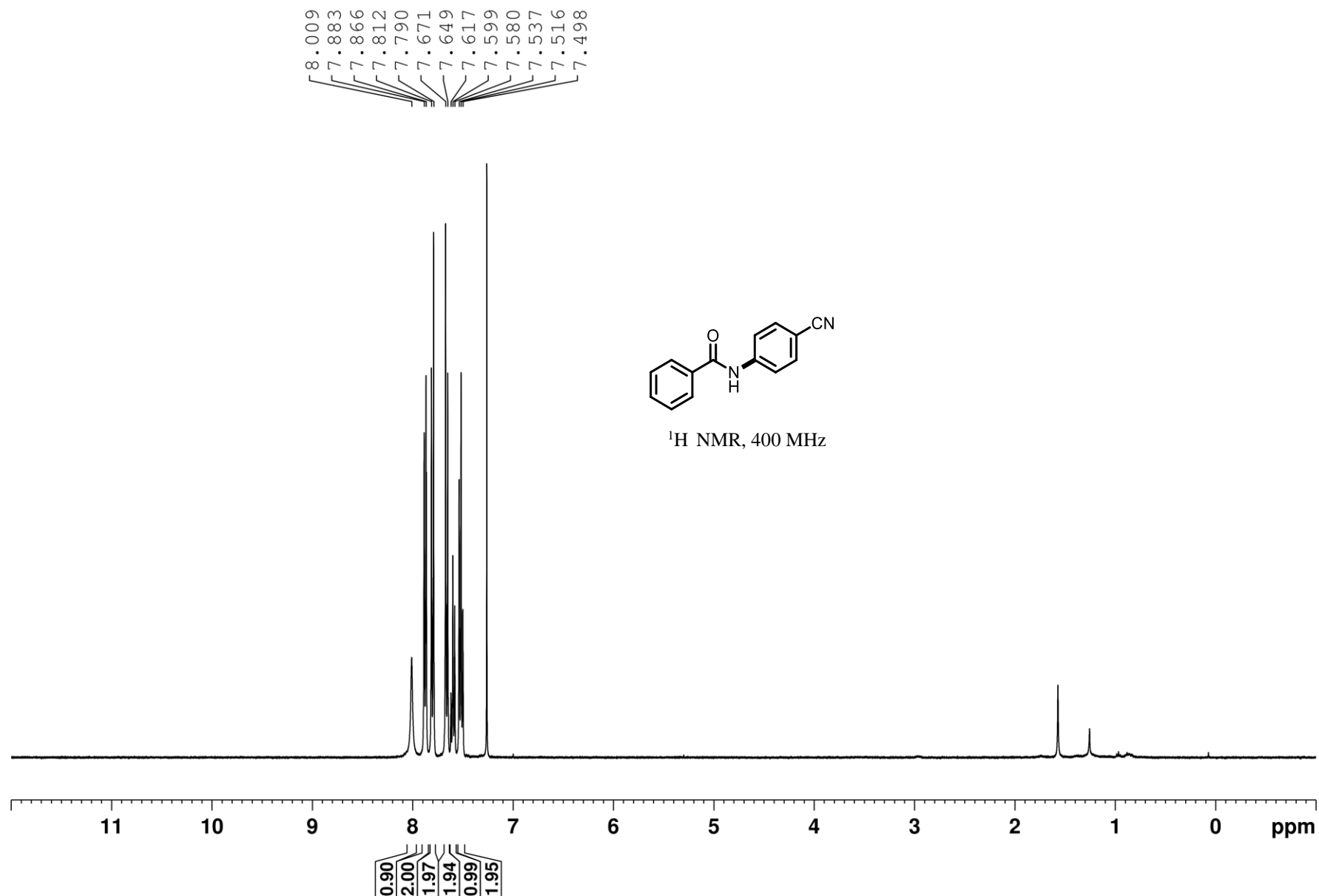
## 6 NMR Spectra

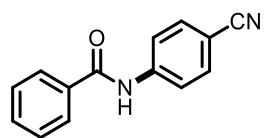
### N-(4-cyanophenyl)benzamide (3), X= Cl



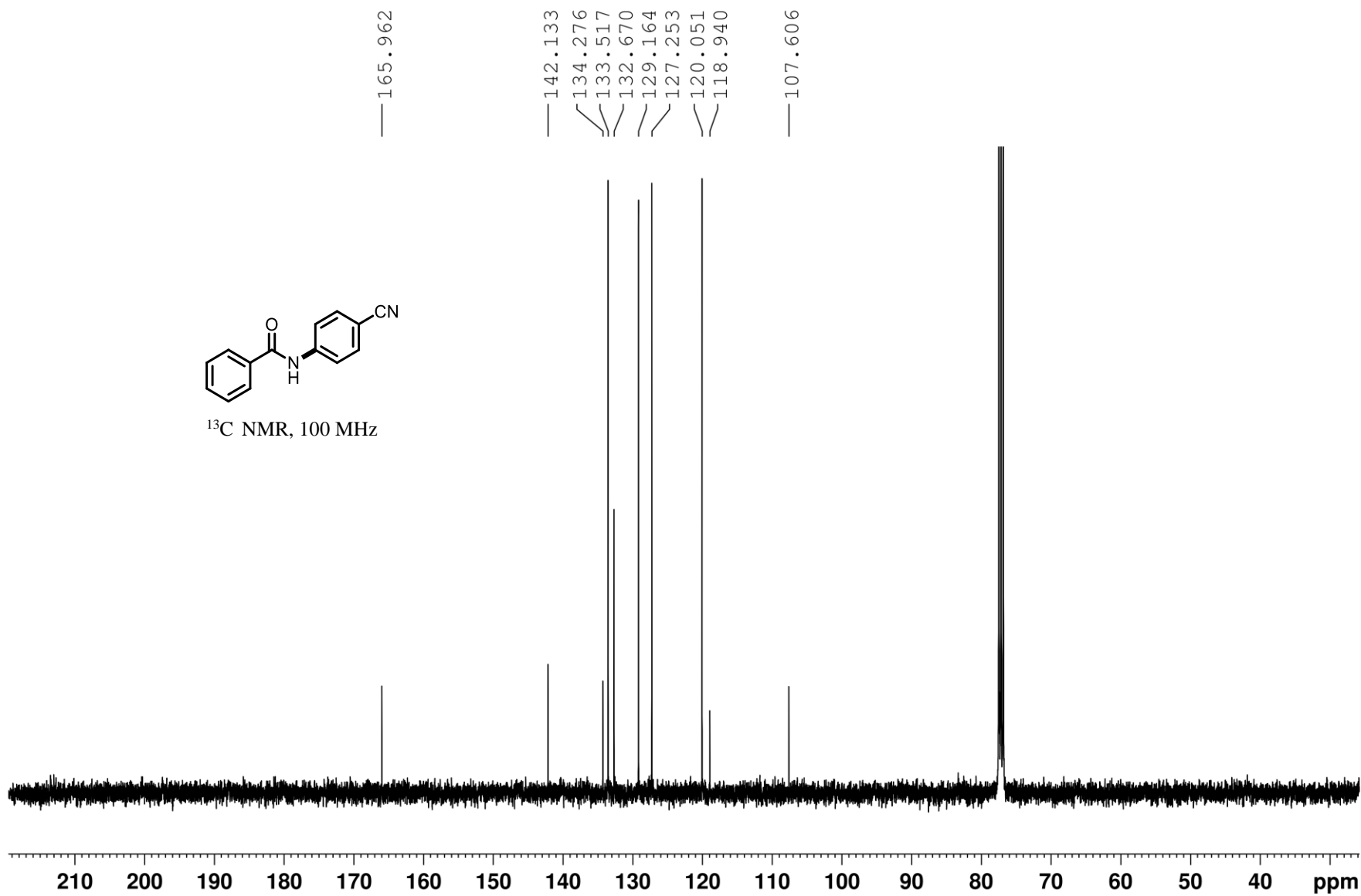


**N-(4-cyanophenyl)benzamide (3), X= Br**

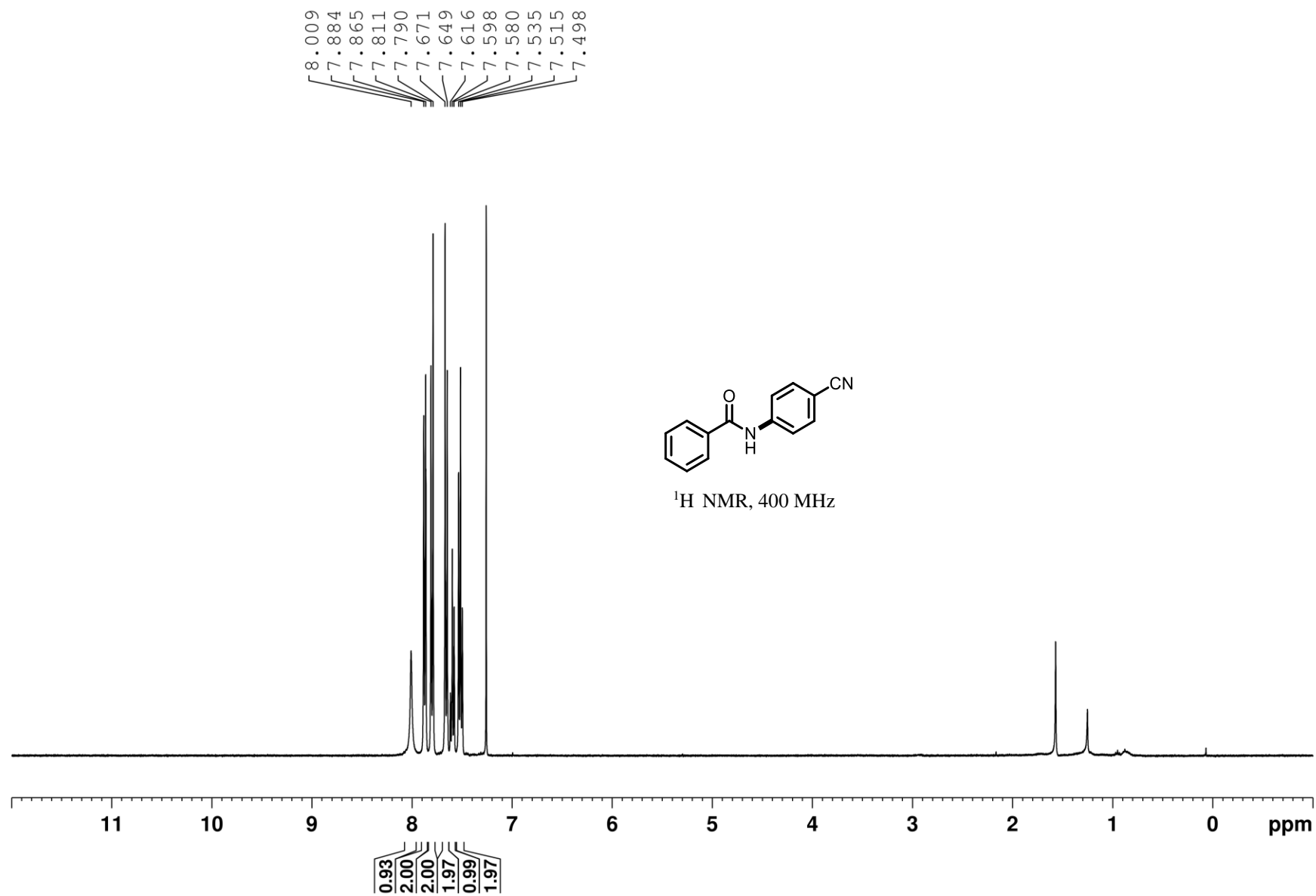


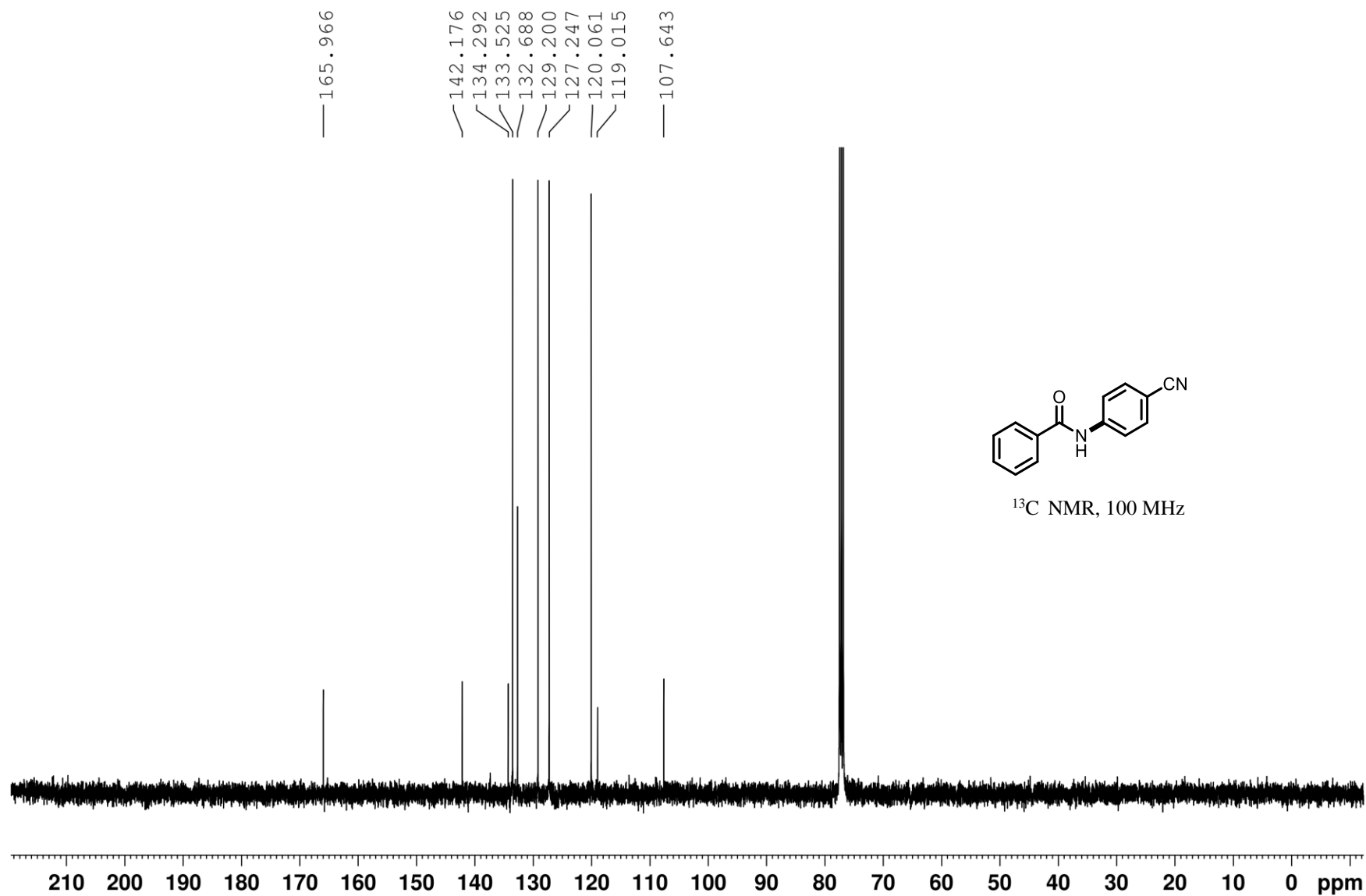


$^{13}\text{C}$  NMR, 100 MHz



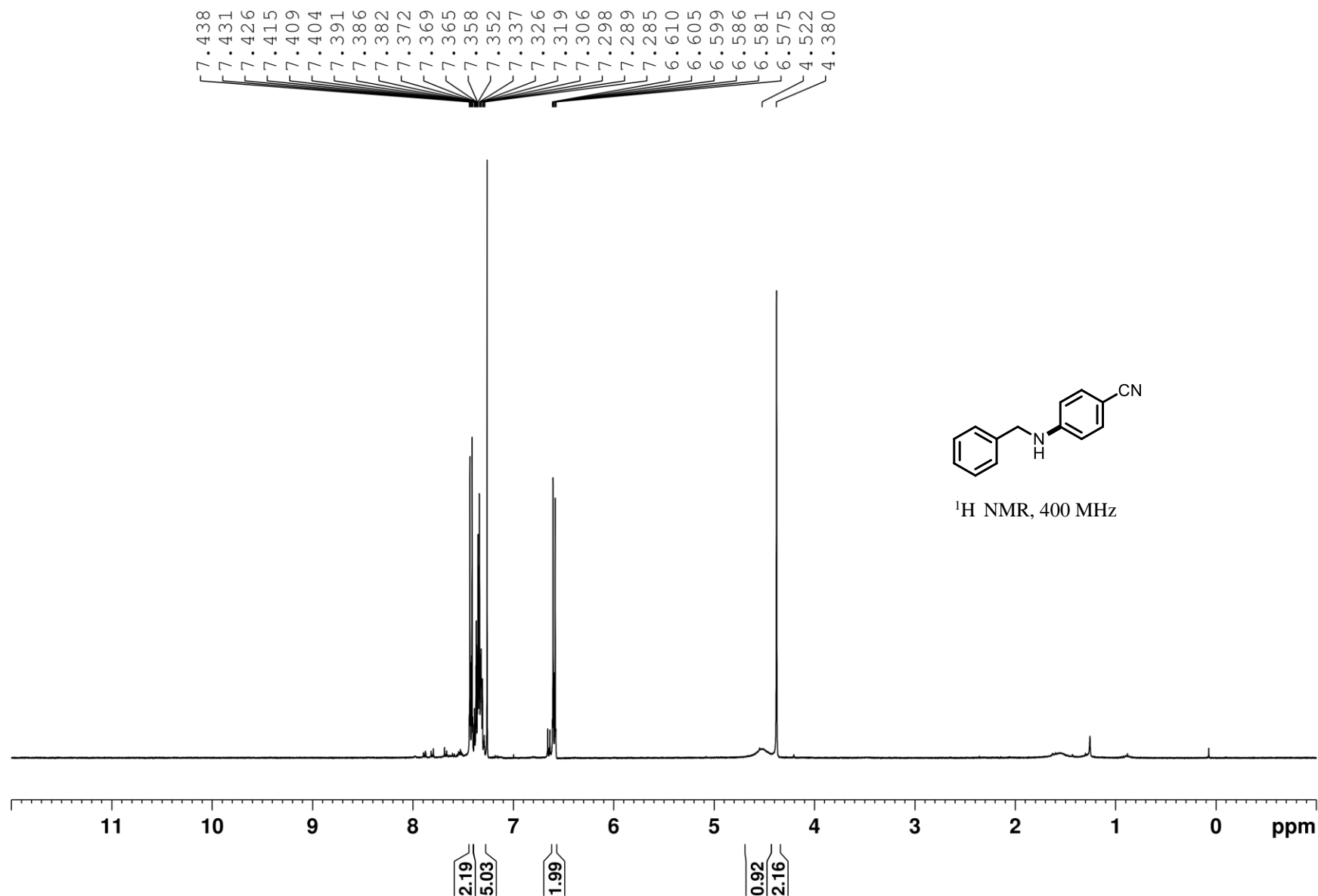
**N-(4-cyanophenyl)benzamide (3), X= I**

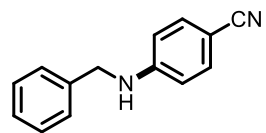




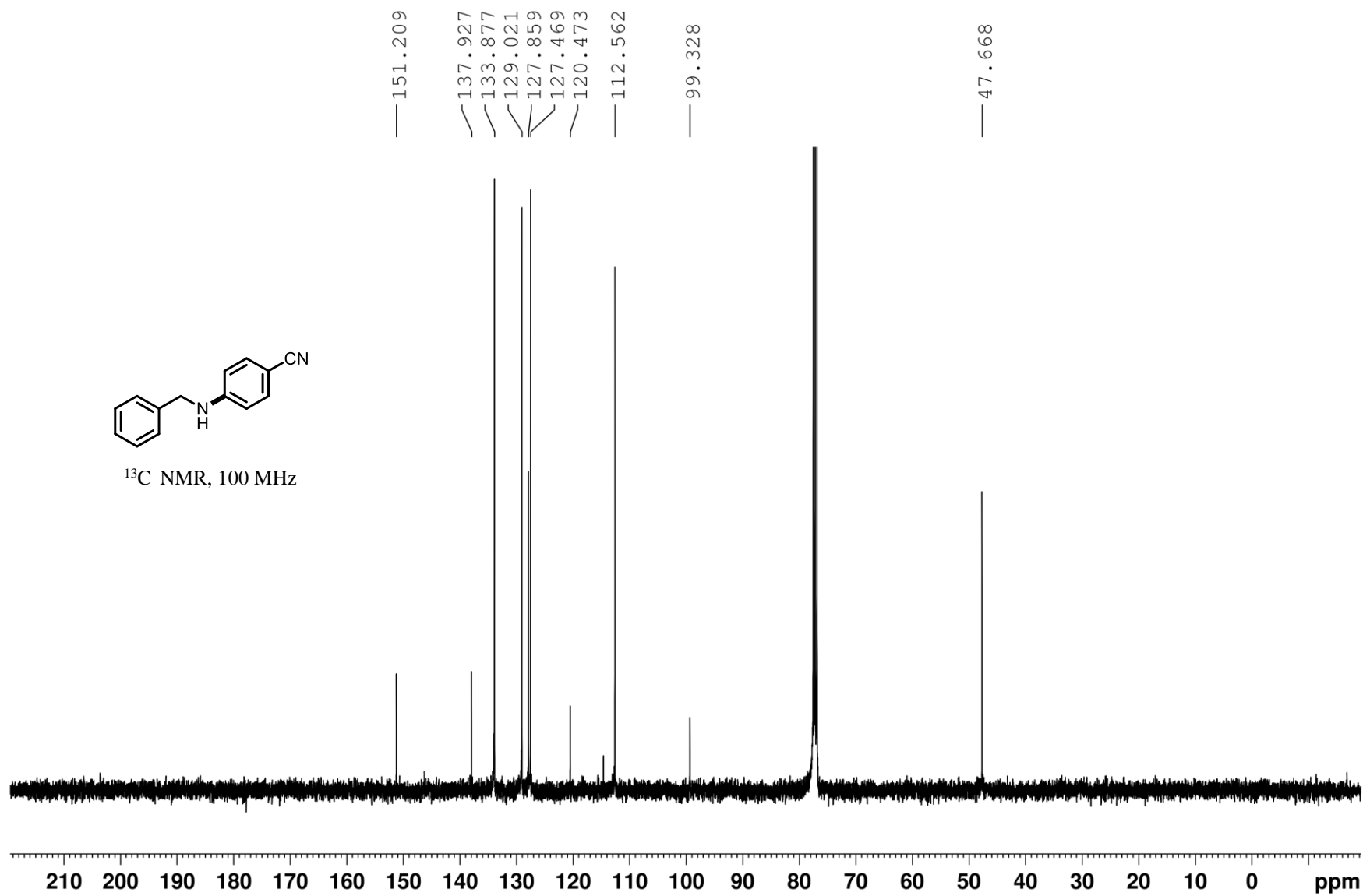


4-(benzylamino)benzonitrile (5)

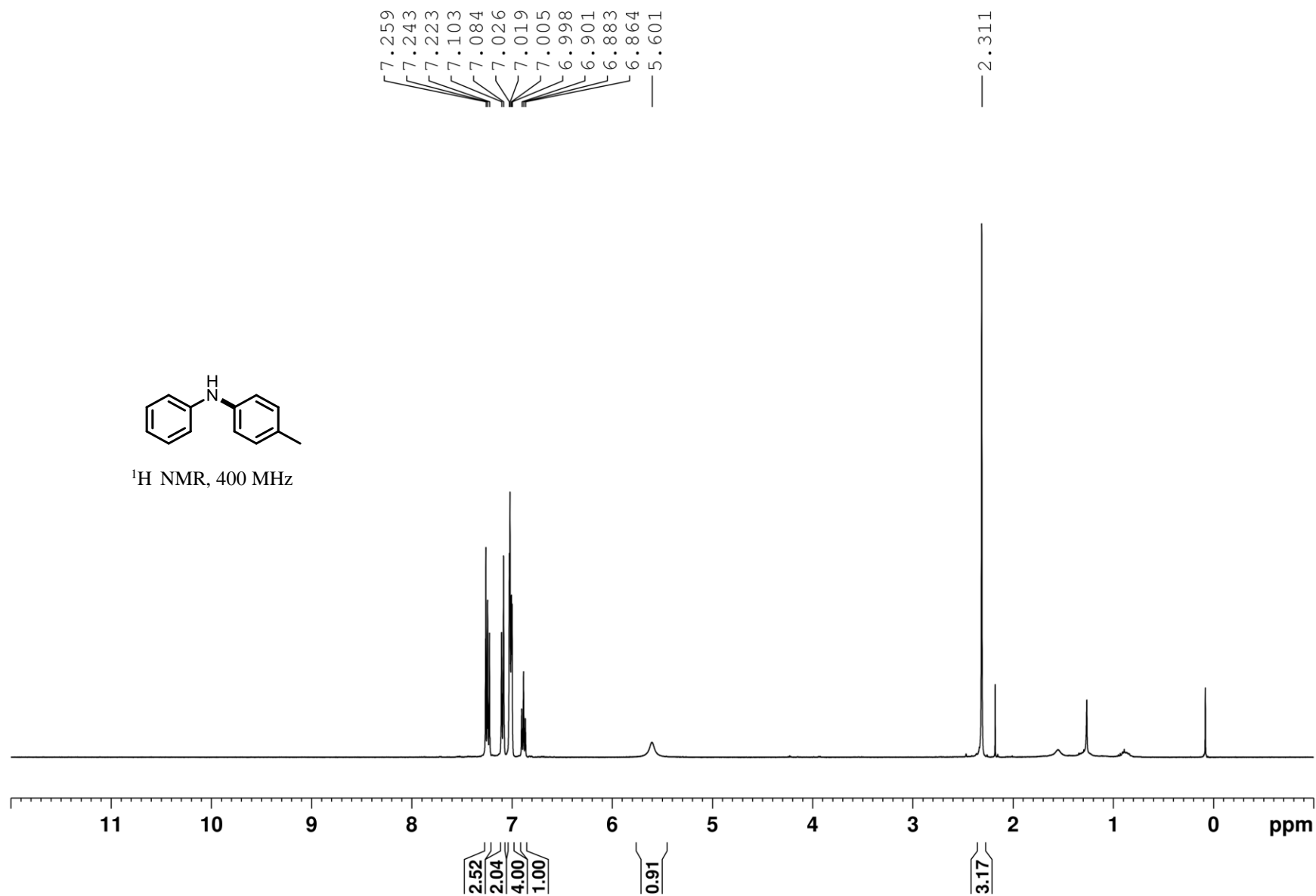


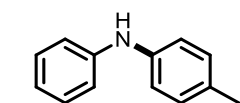


$^{13}\text{C}$  NMR, 100 MHz

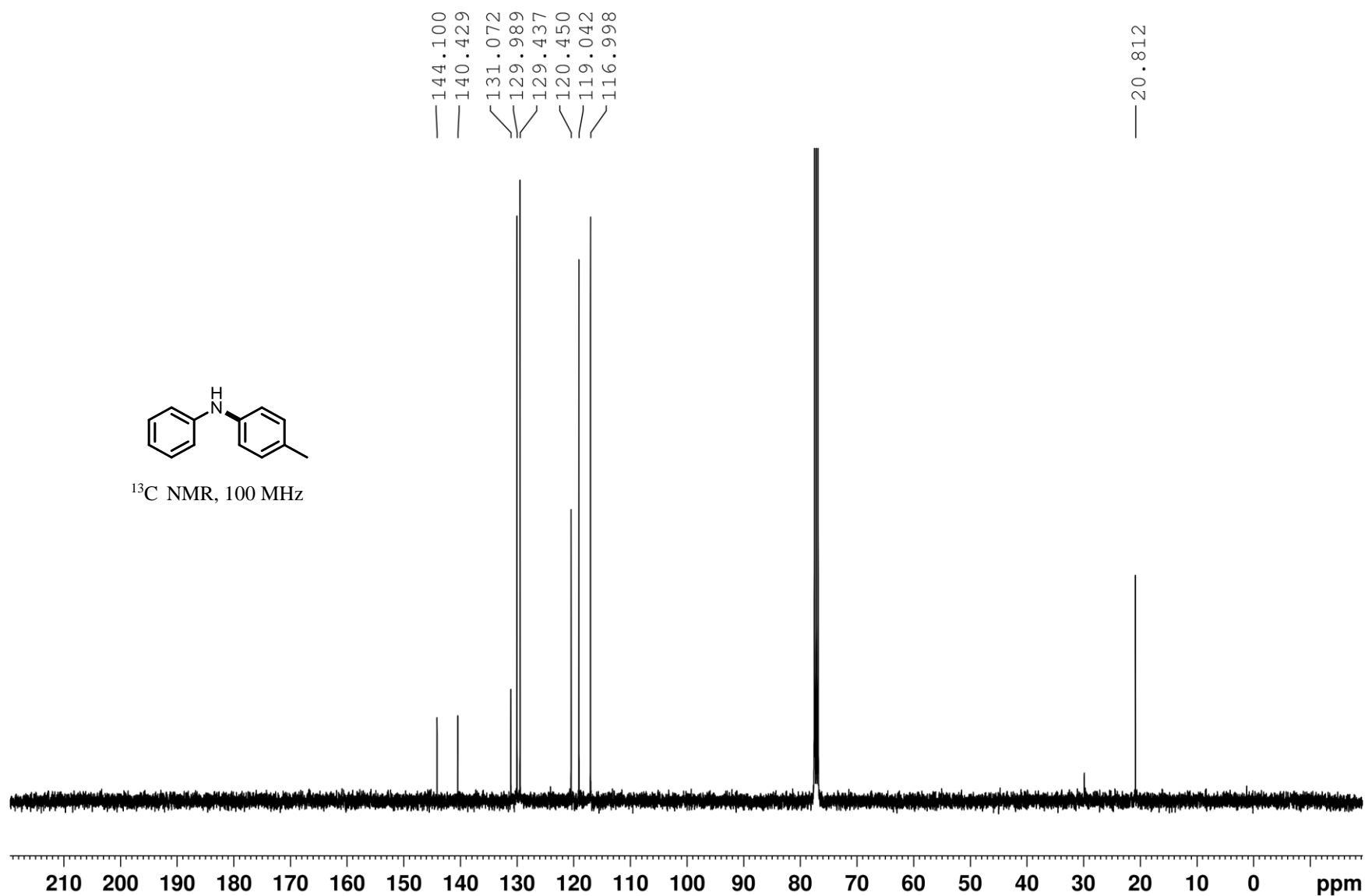


**4-methyl-N-phenylaniline (8)**

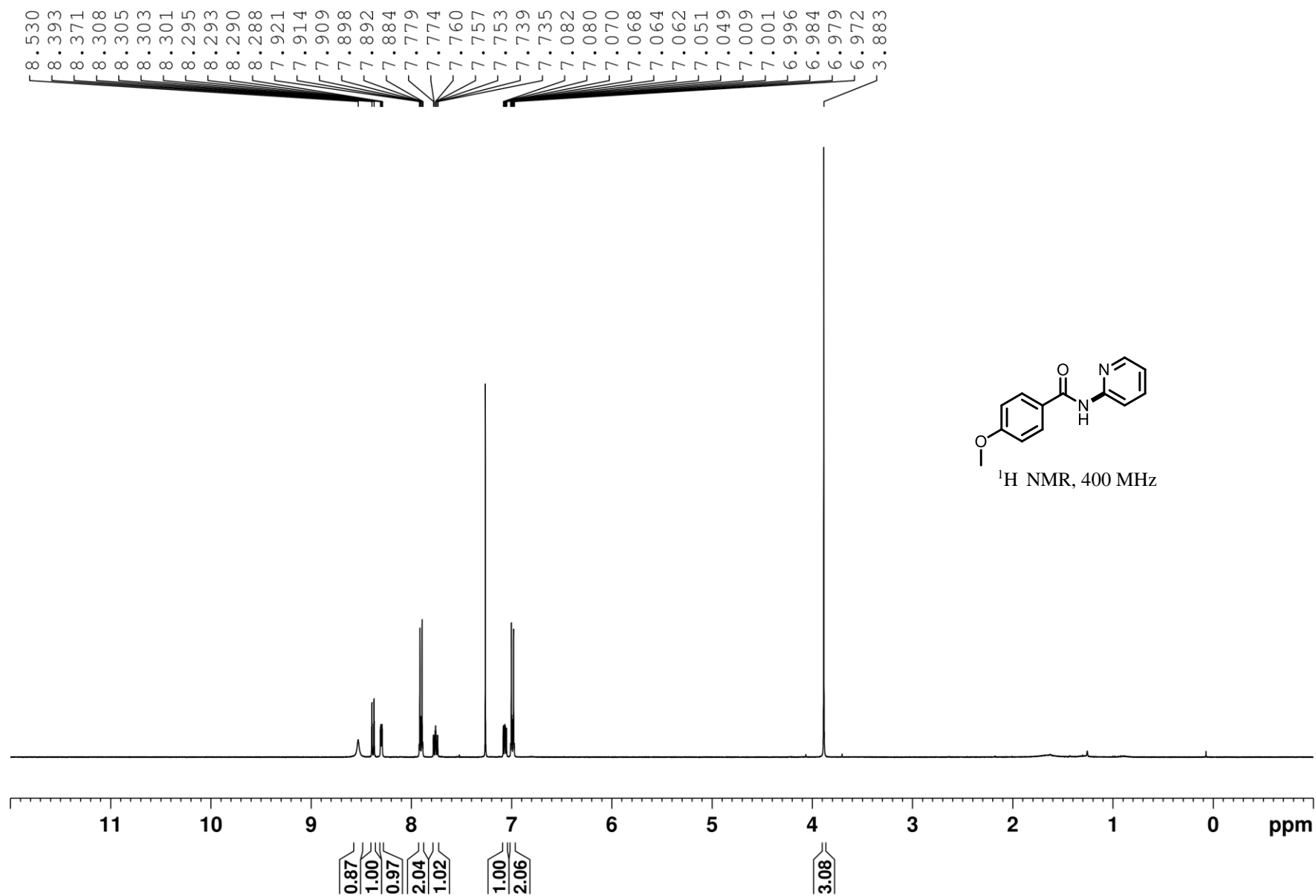


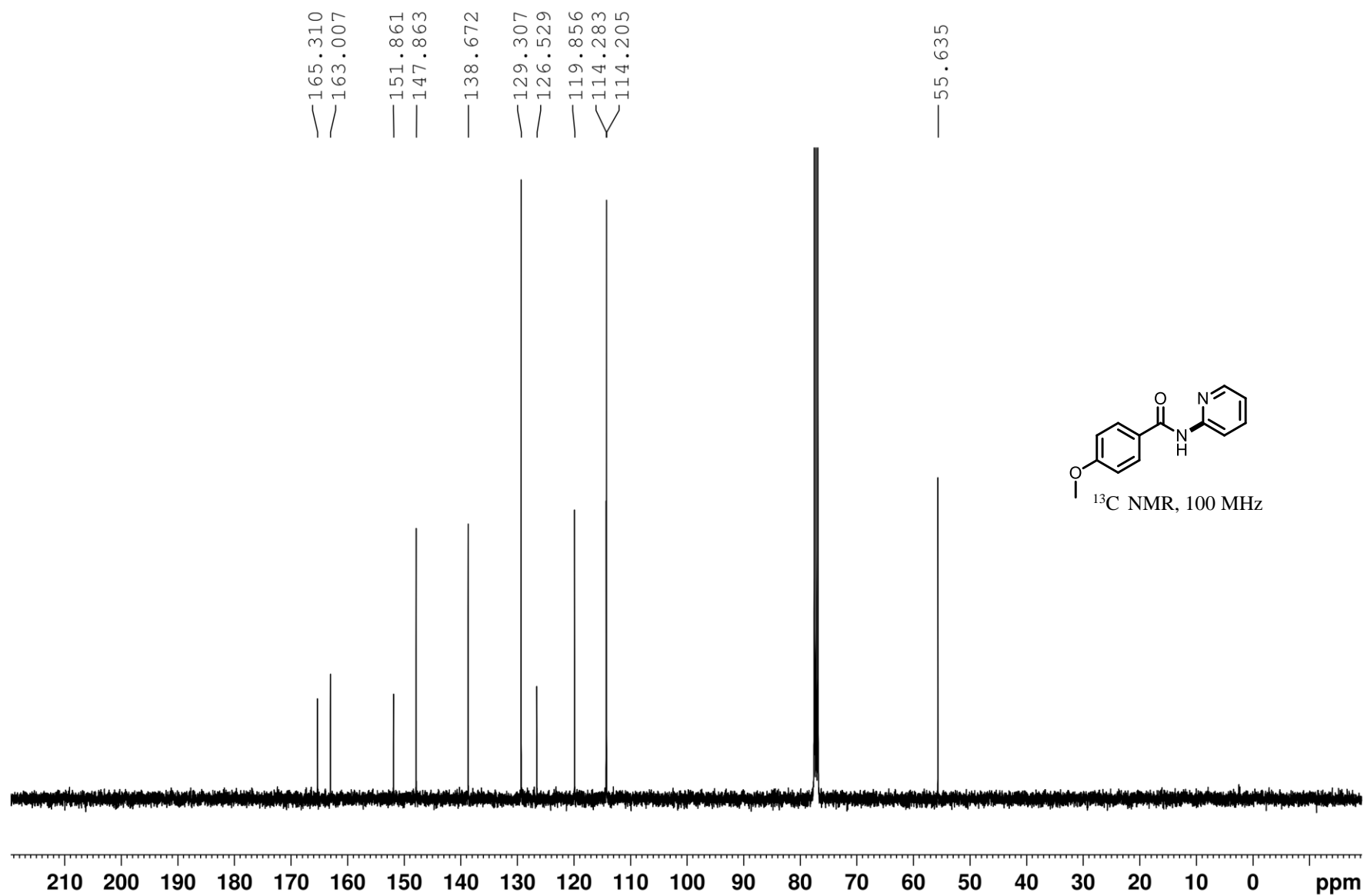


$^{13}\text{C}$  NMR, 100 MHz

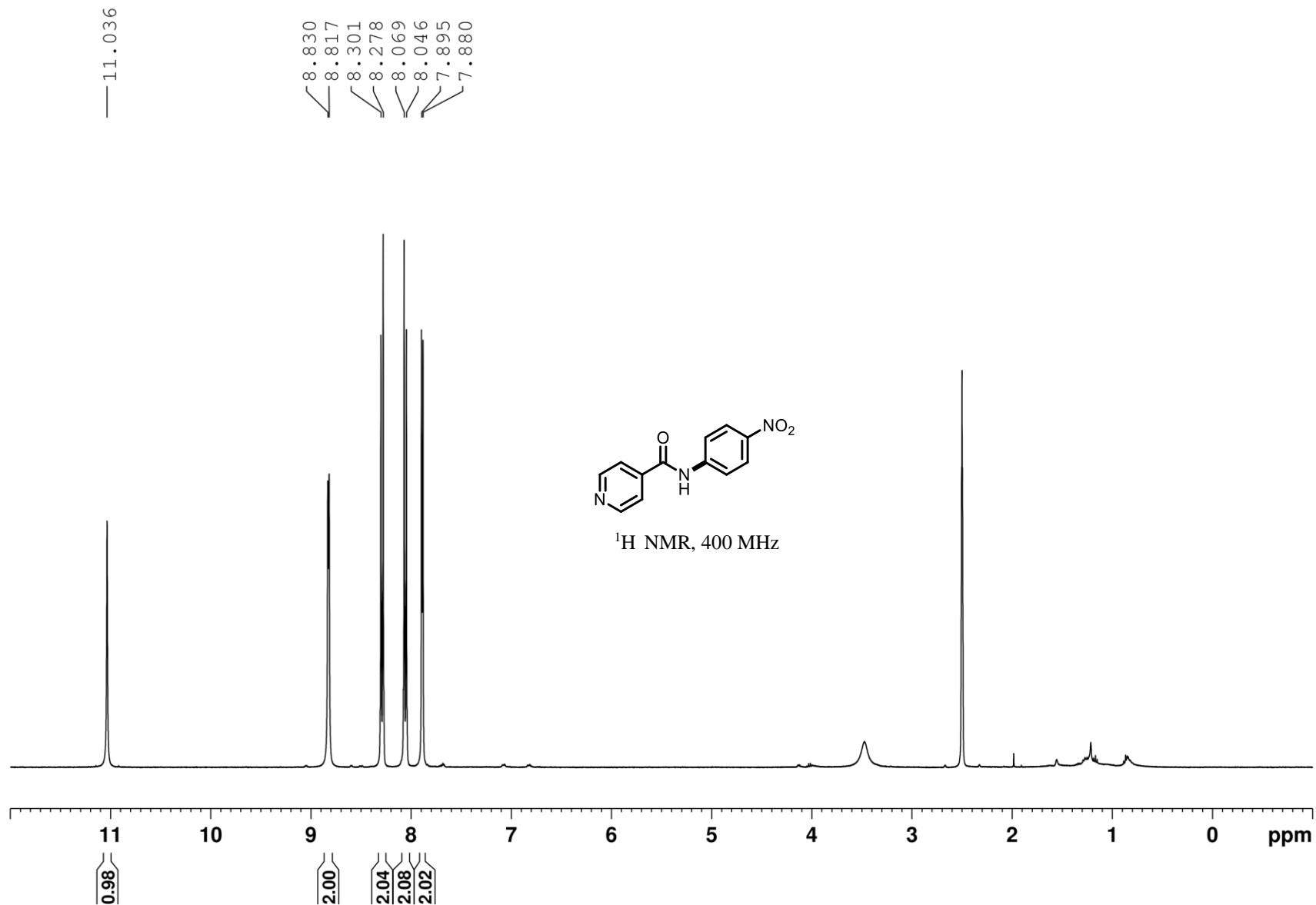


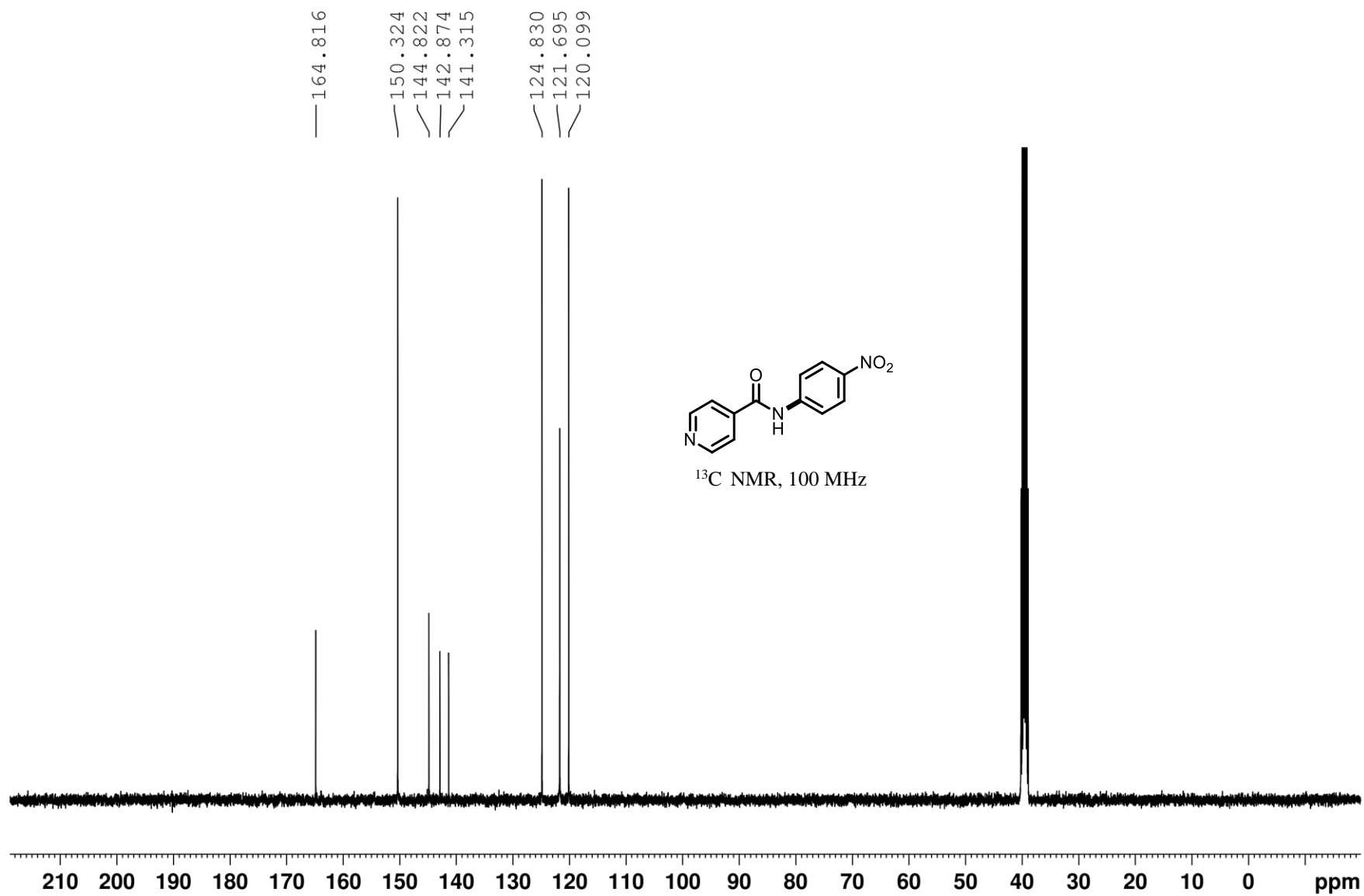
**4-methoxy-N-(pyridin-2-yl)benzamide (9)**





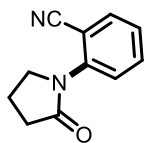
**N-(4-nitrophenyl)isonicotinamide (10)**



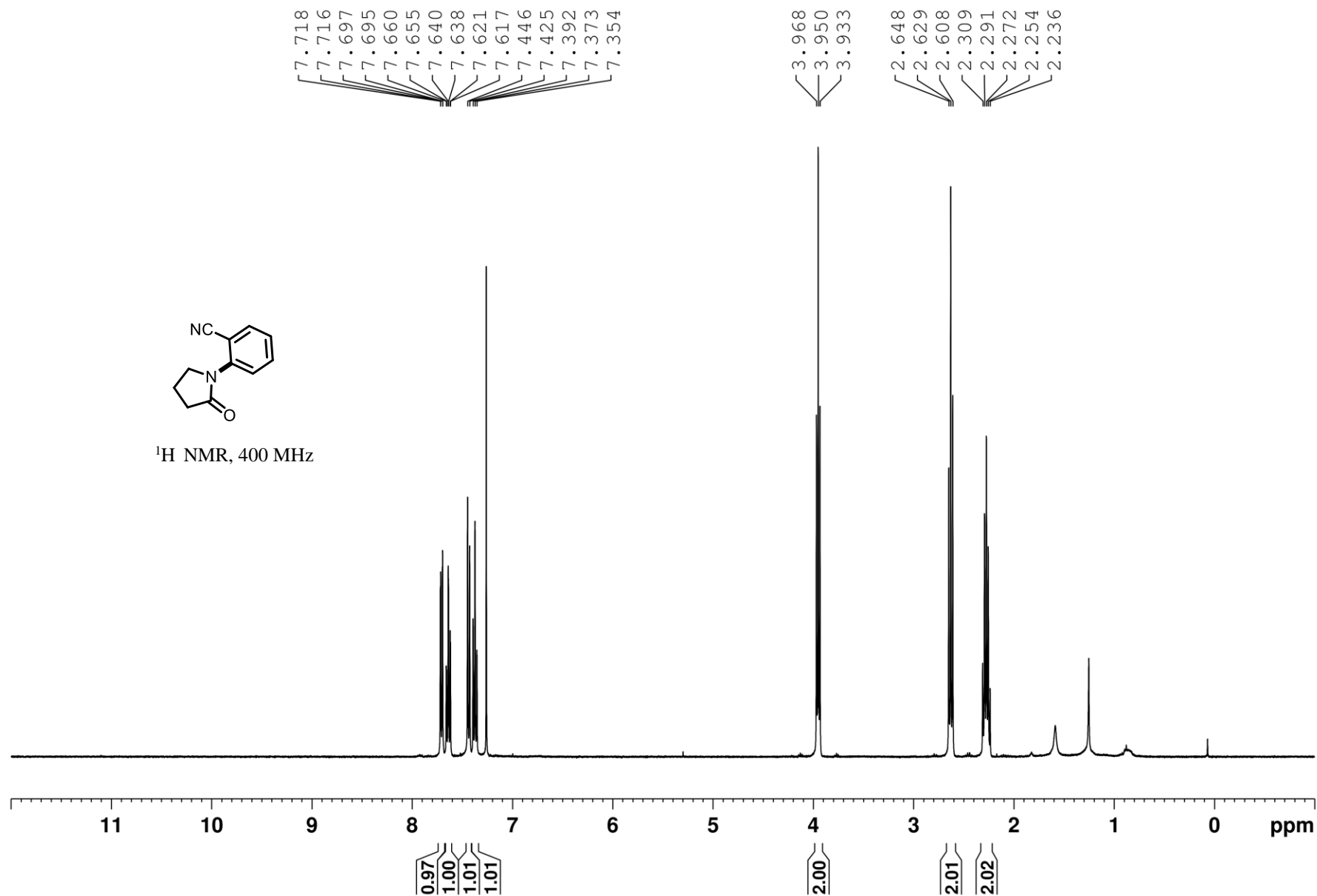


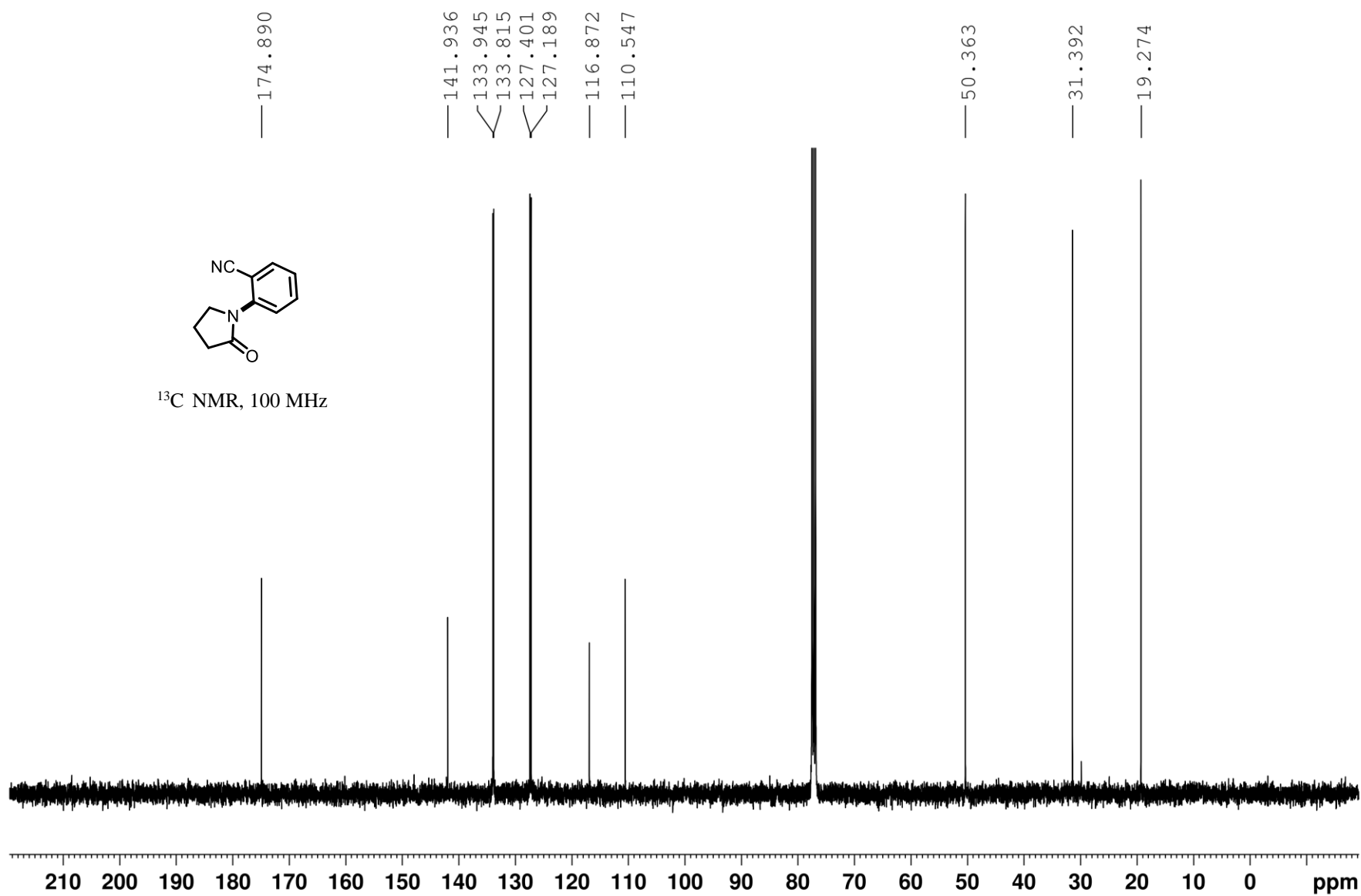


**2-(2-oxopyrrolidin-1-yl)benzonitrile (11)**

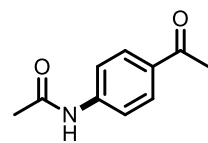


$^1\text{H}$  NMR, 400 MHz

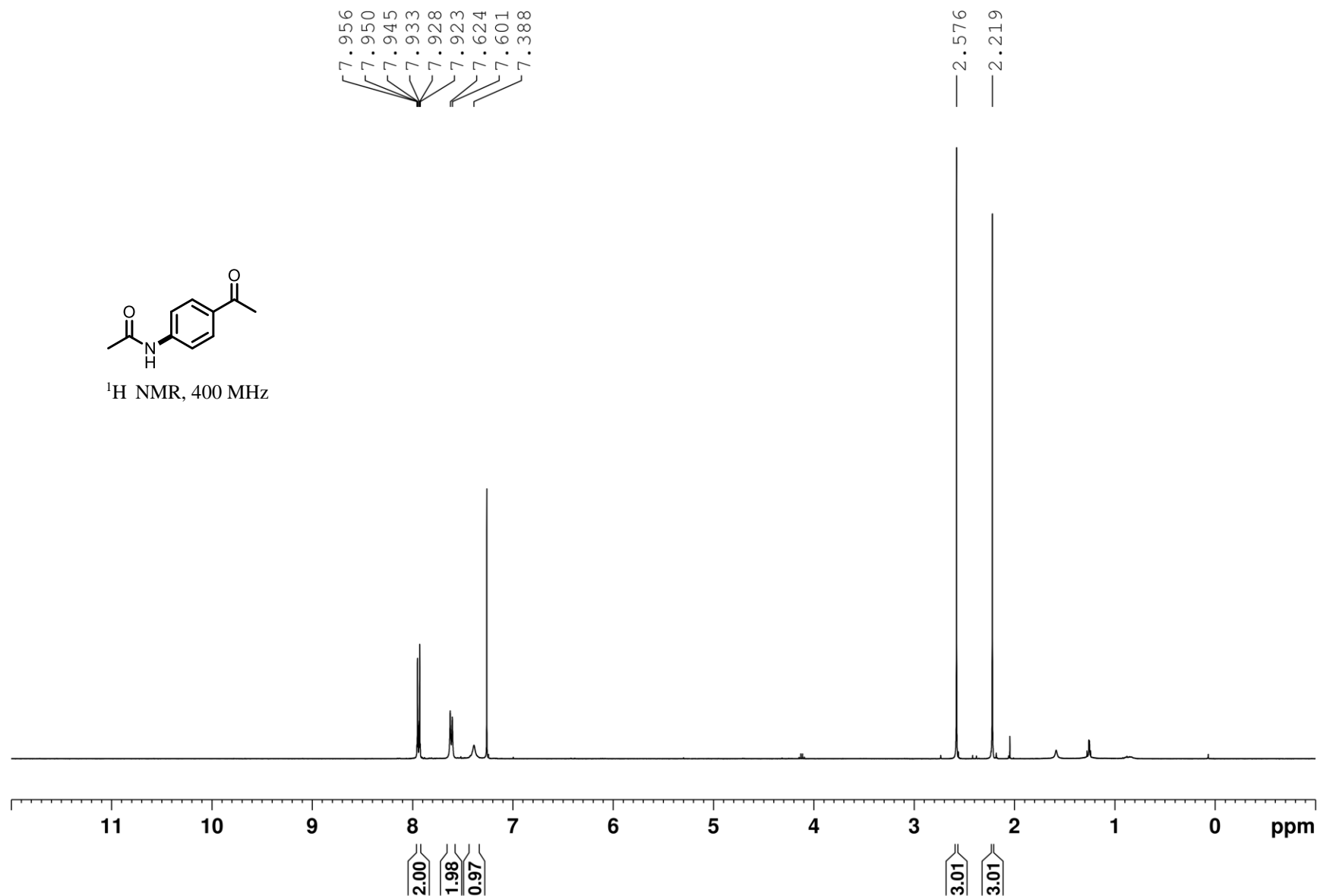


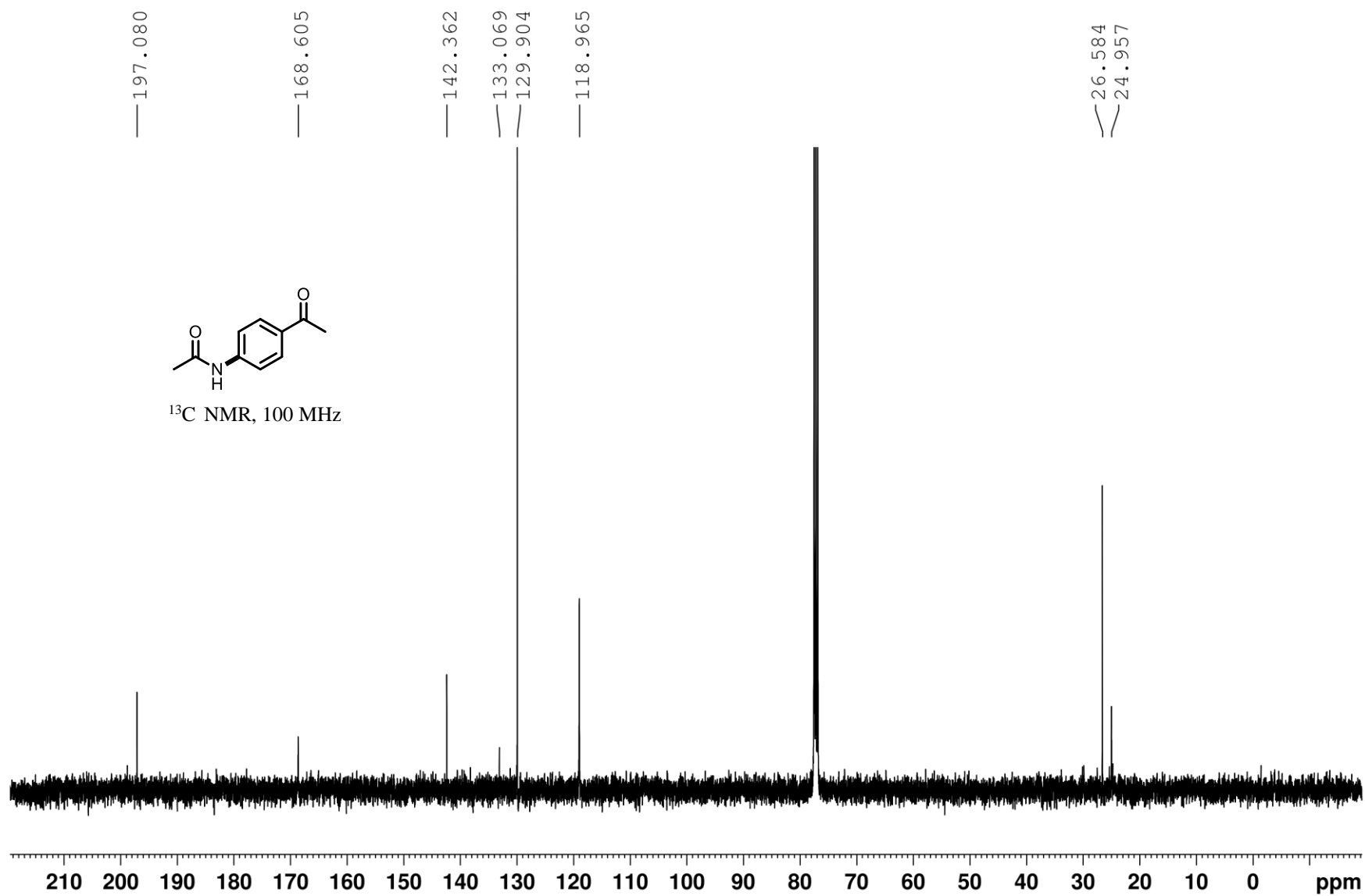


**N-(4-acetylphenyl)acetamide (12)**

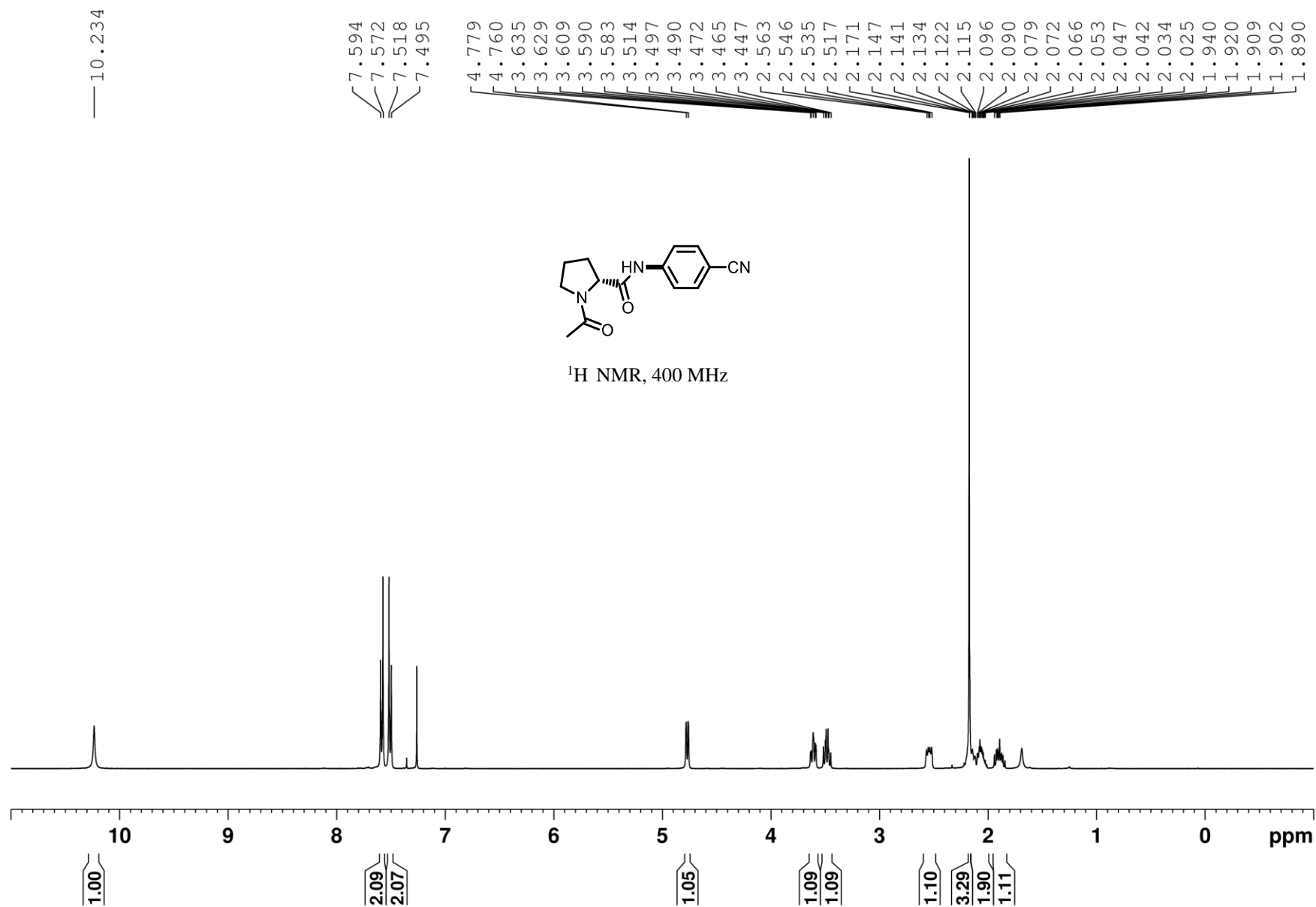


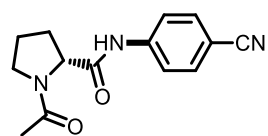
$^1\text{H}$  NMR, 400 MHz



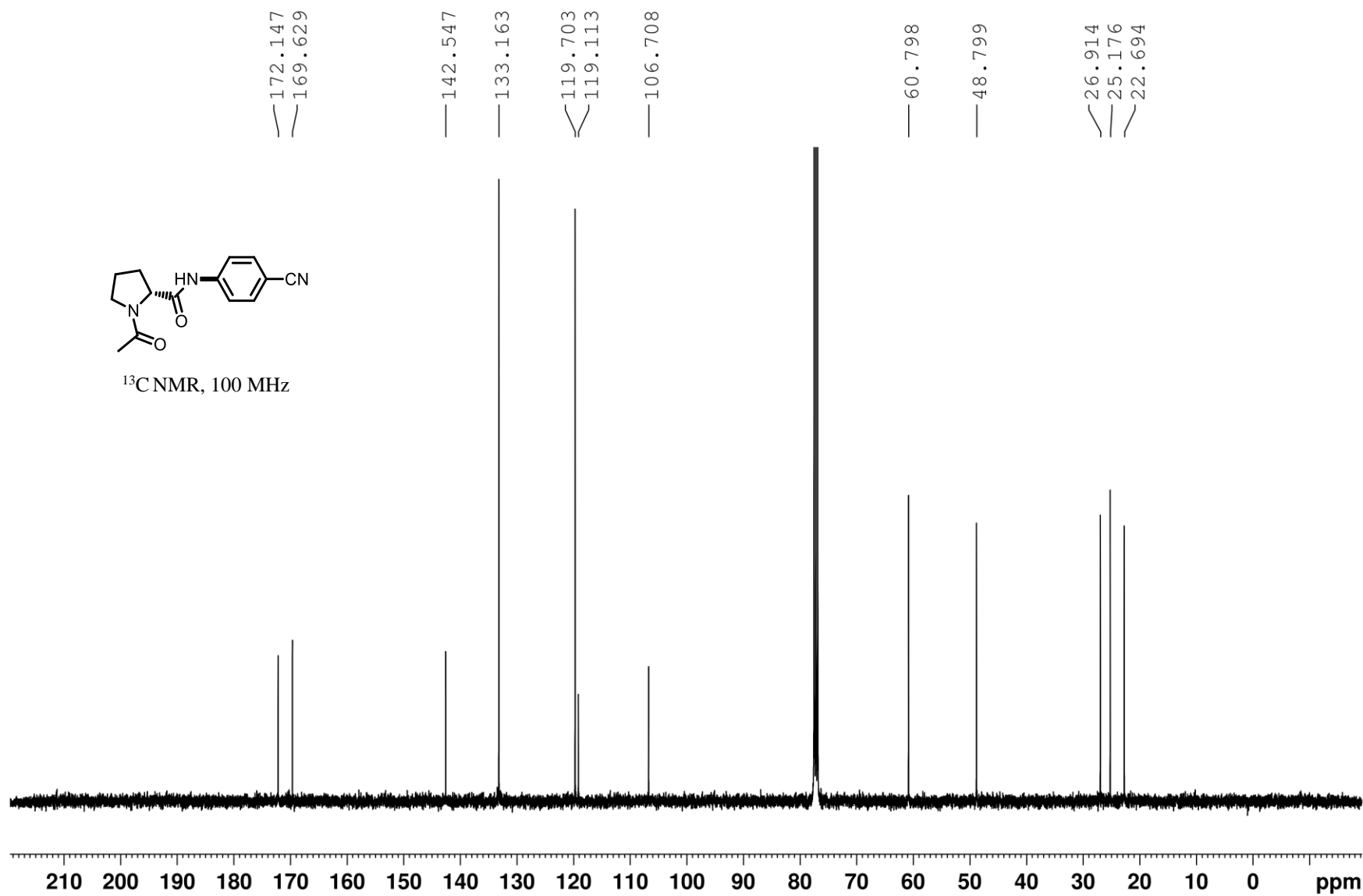


**(R)-1-acetyl-N-(4-cyanophenyl)pyrrolidine-2-carboxamide (13)**

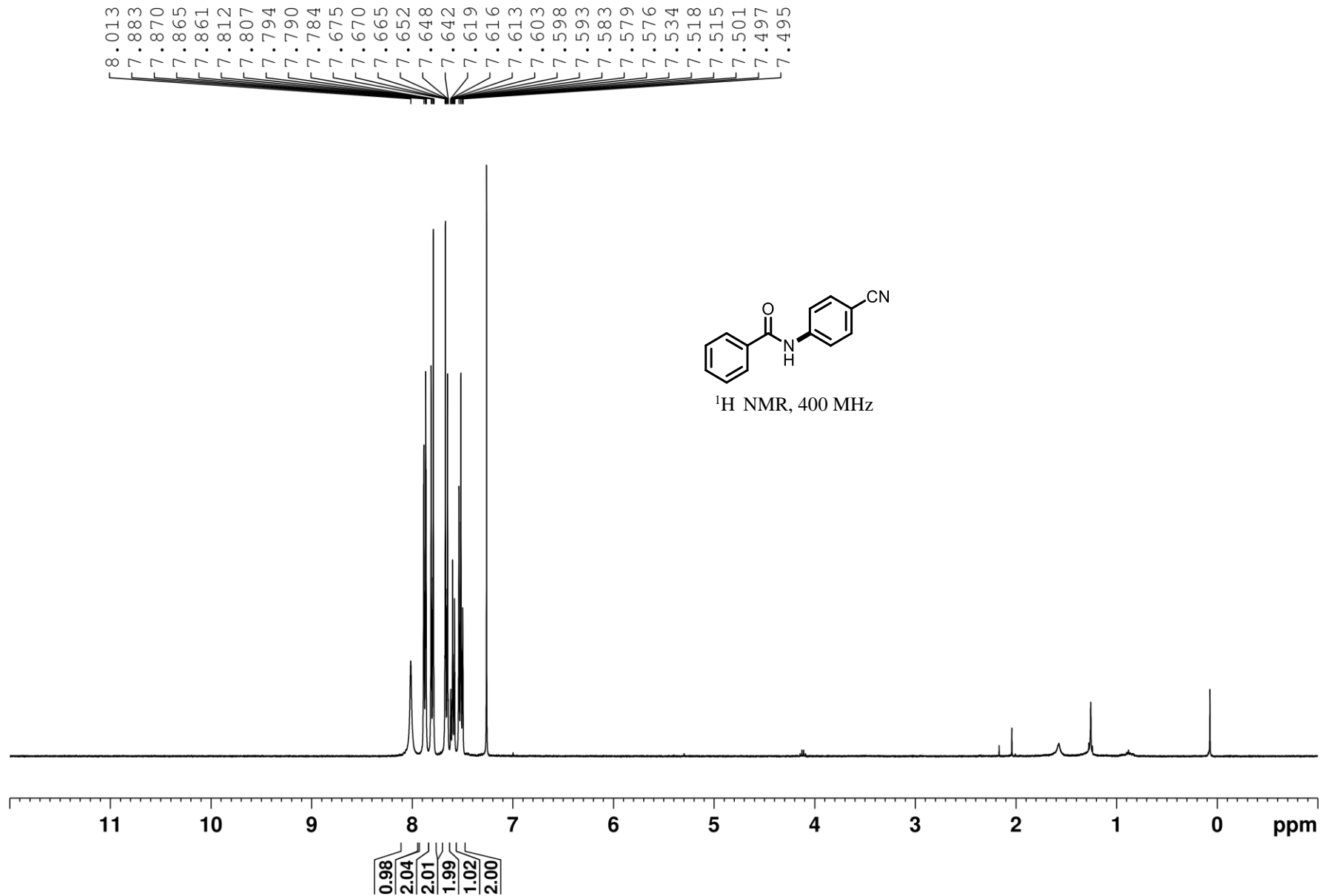


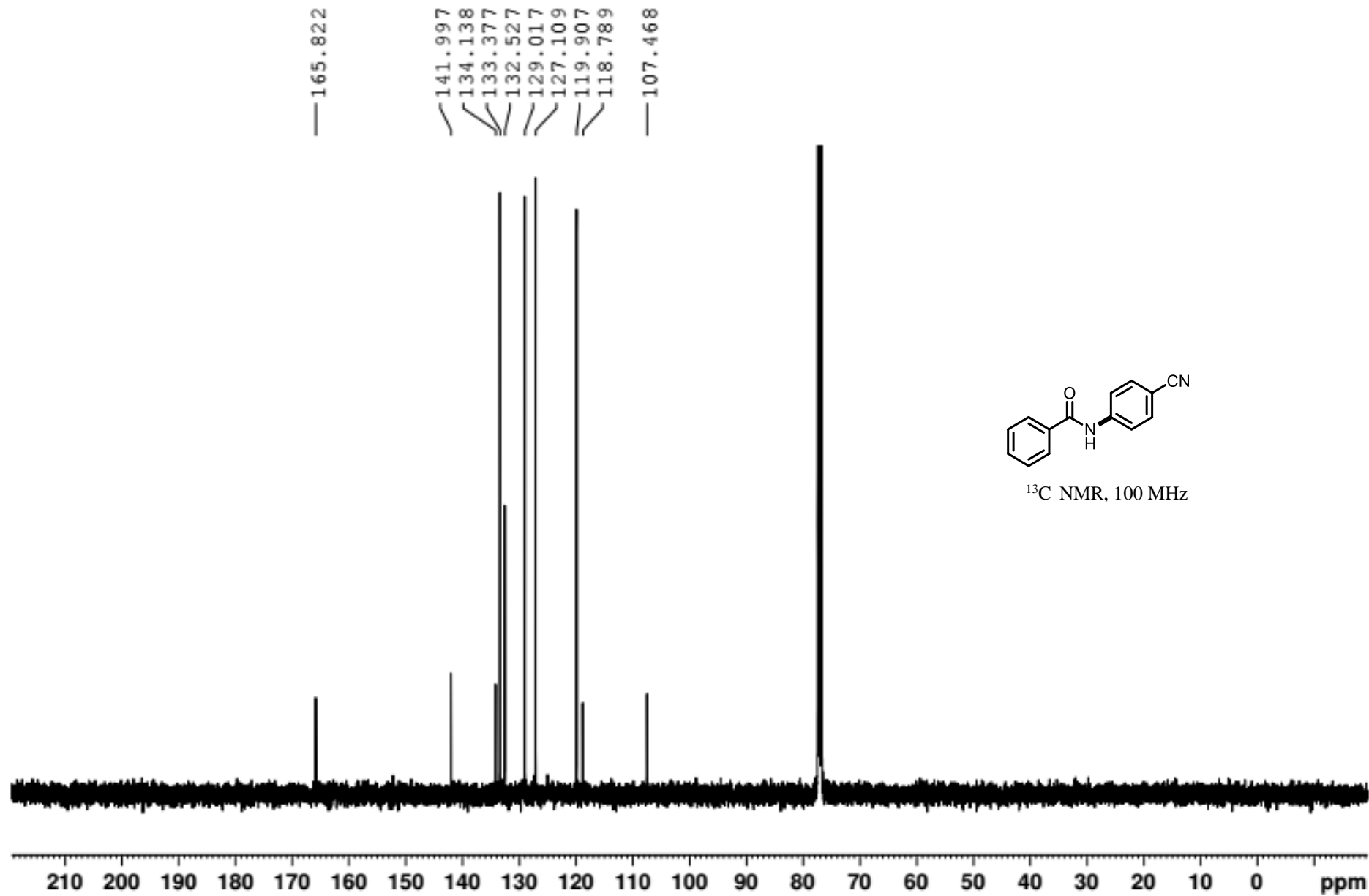


$^{13}\text{C}$  NMR, 100 MHz



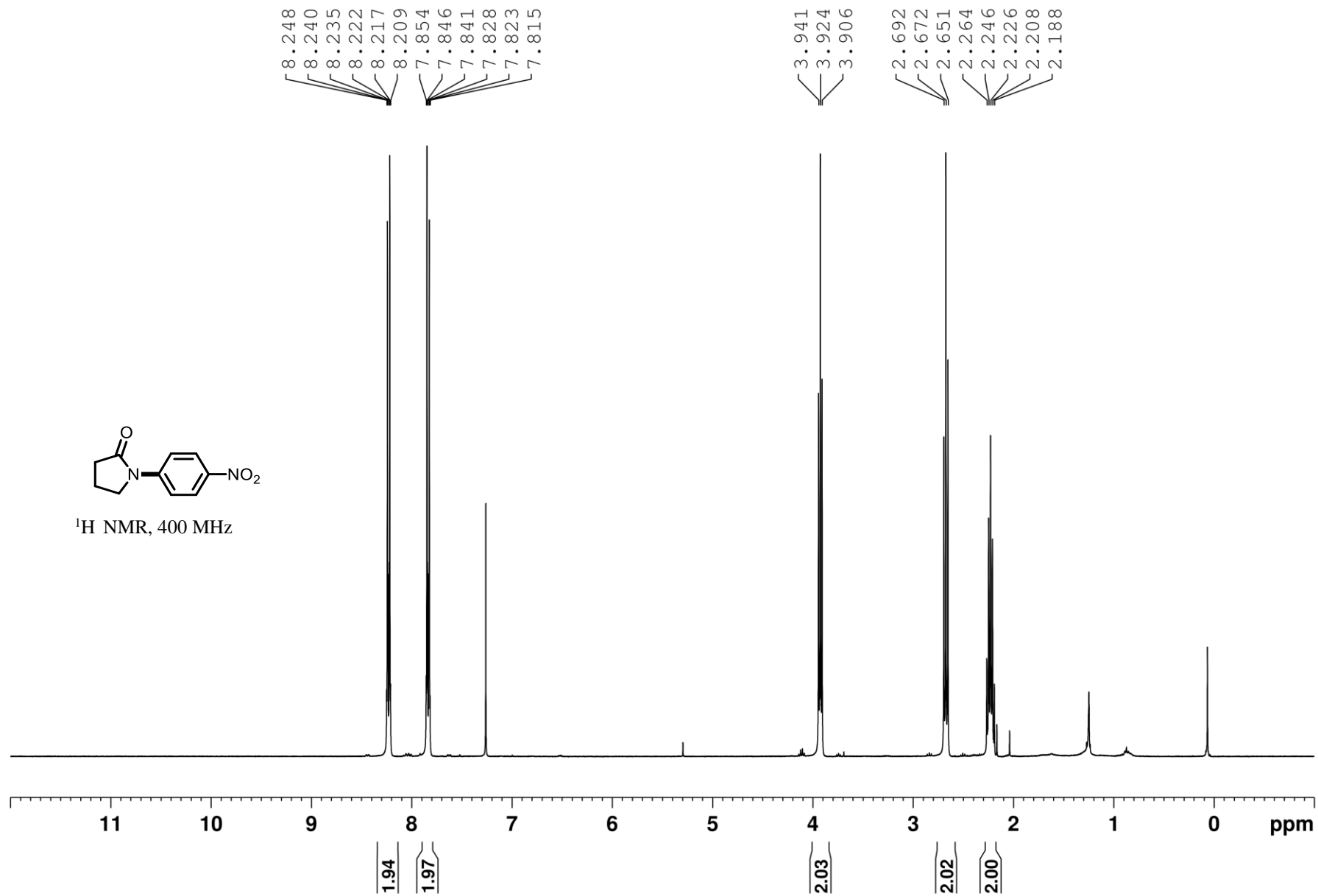
**N-(4-cyanophenyl)benzamide (14)**

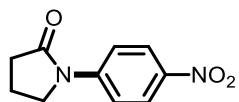




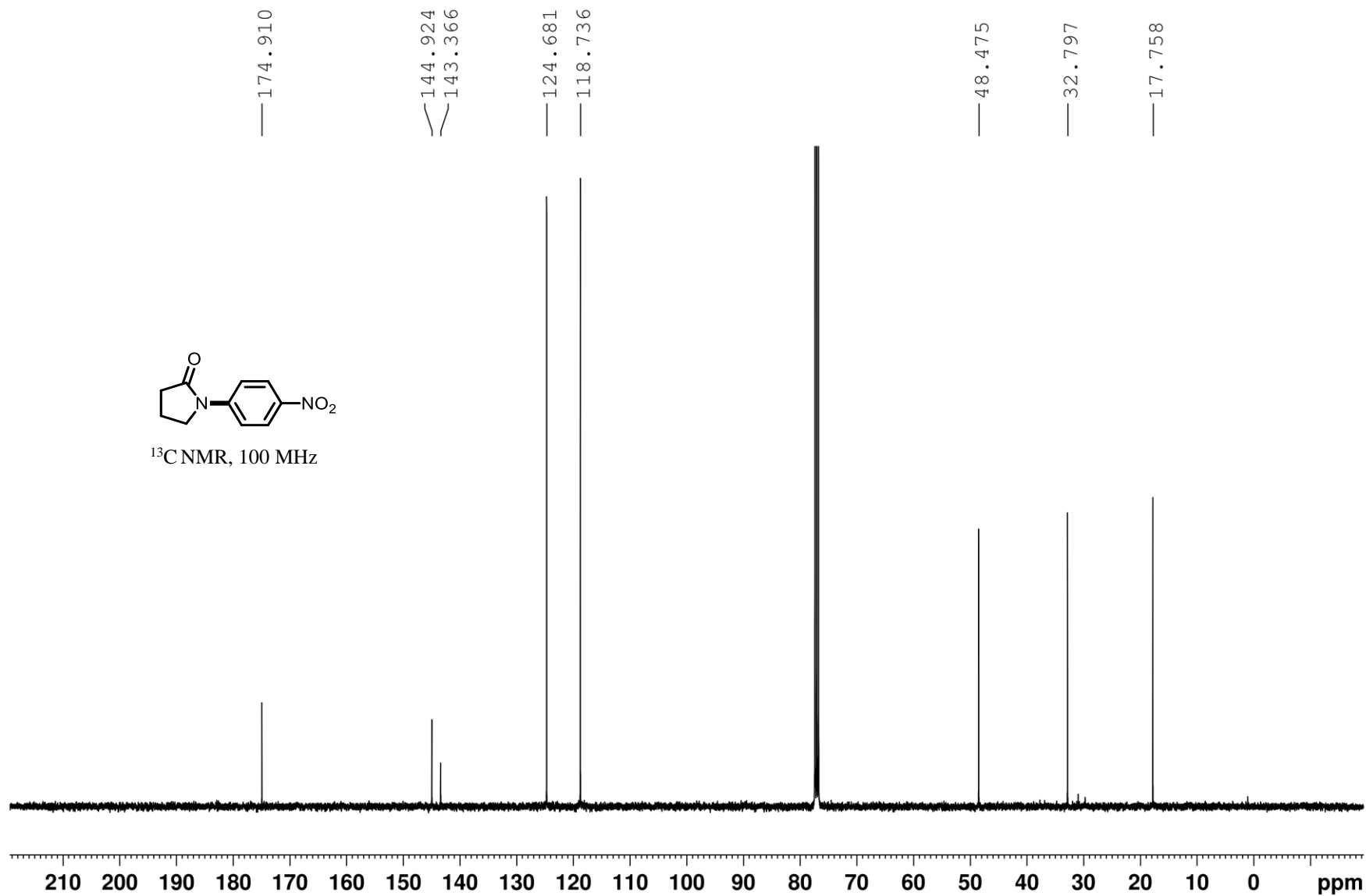


**1-(4-nitrophenyl)pyrrolidin-2-one (15)**

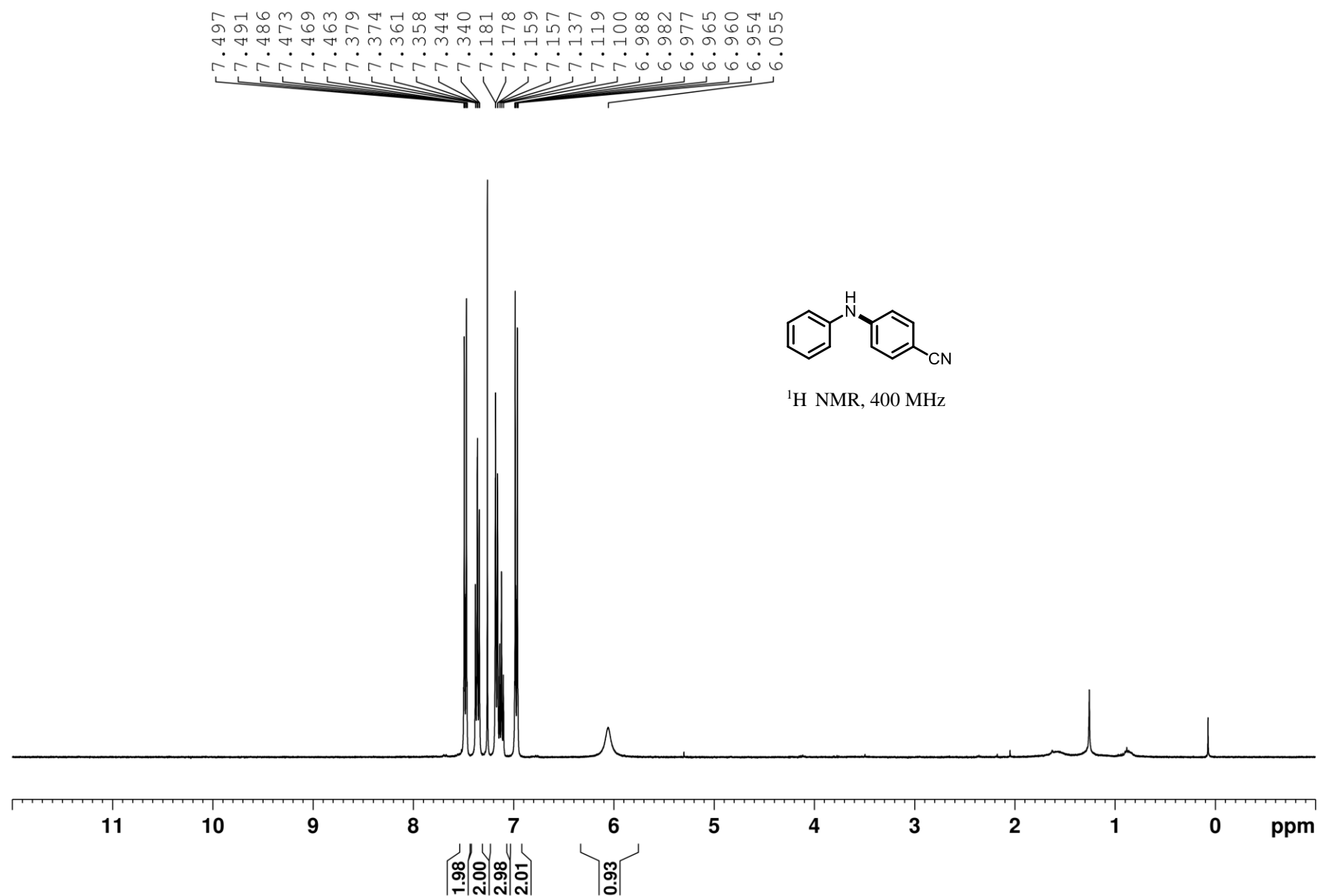


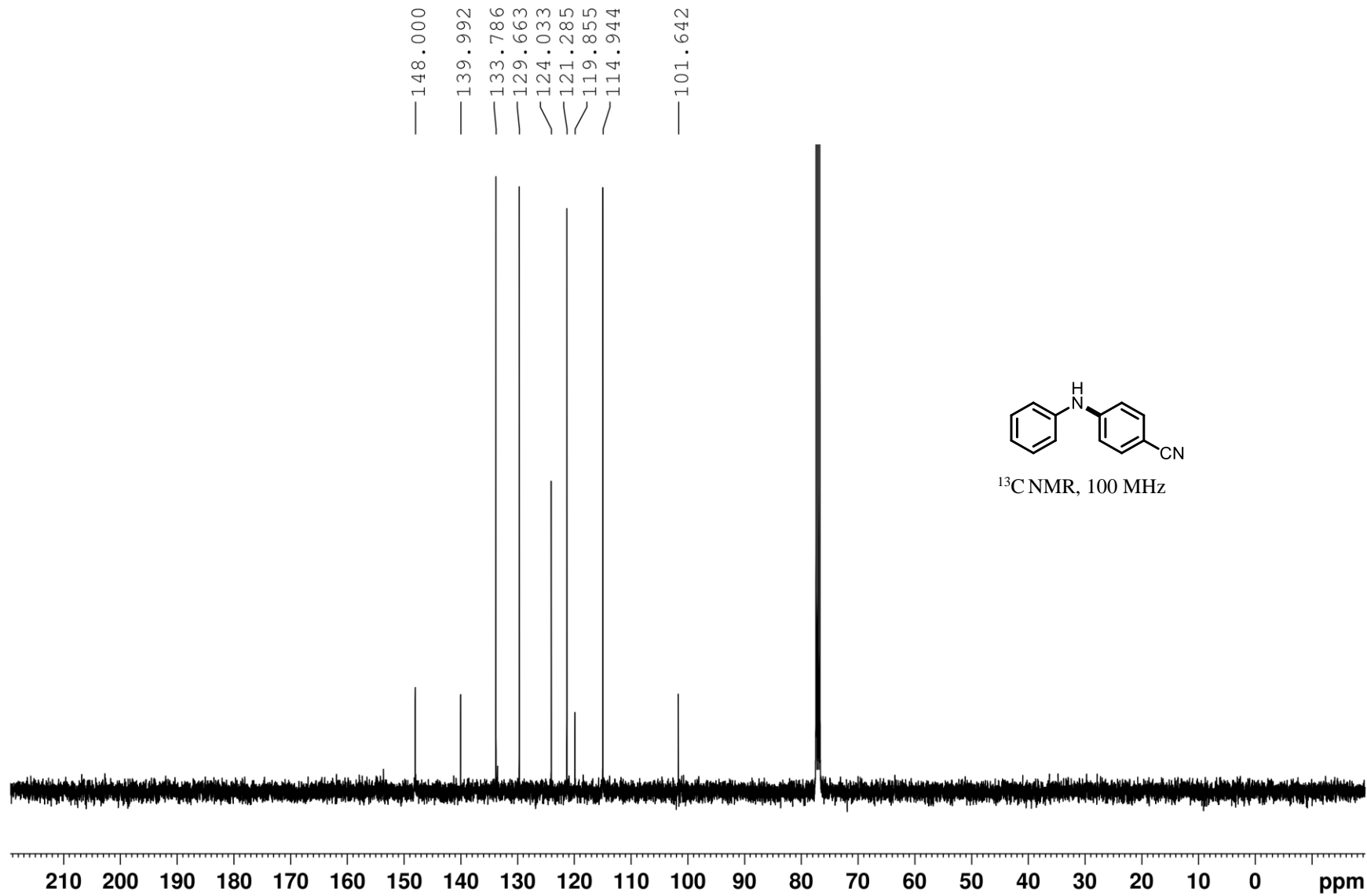


$^{13}\text{C}$  NMR, 100 MHz

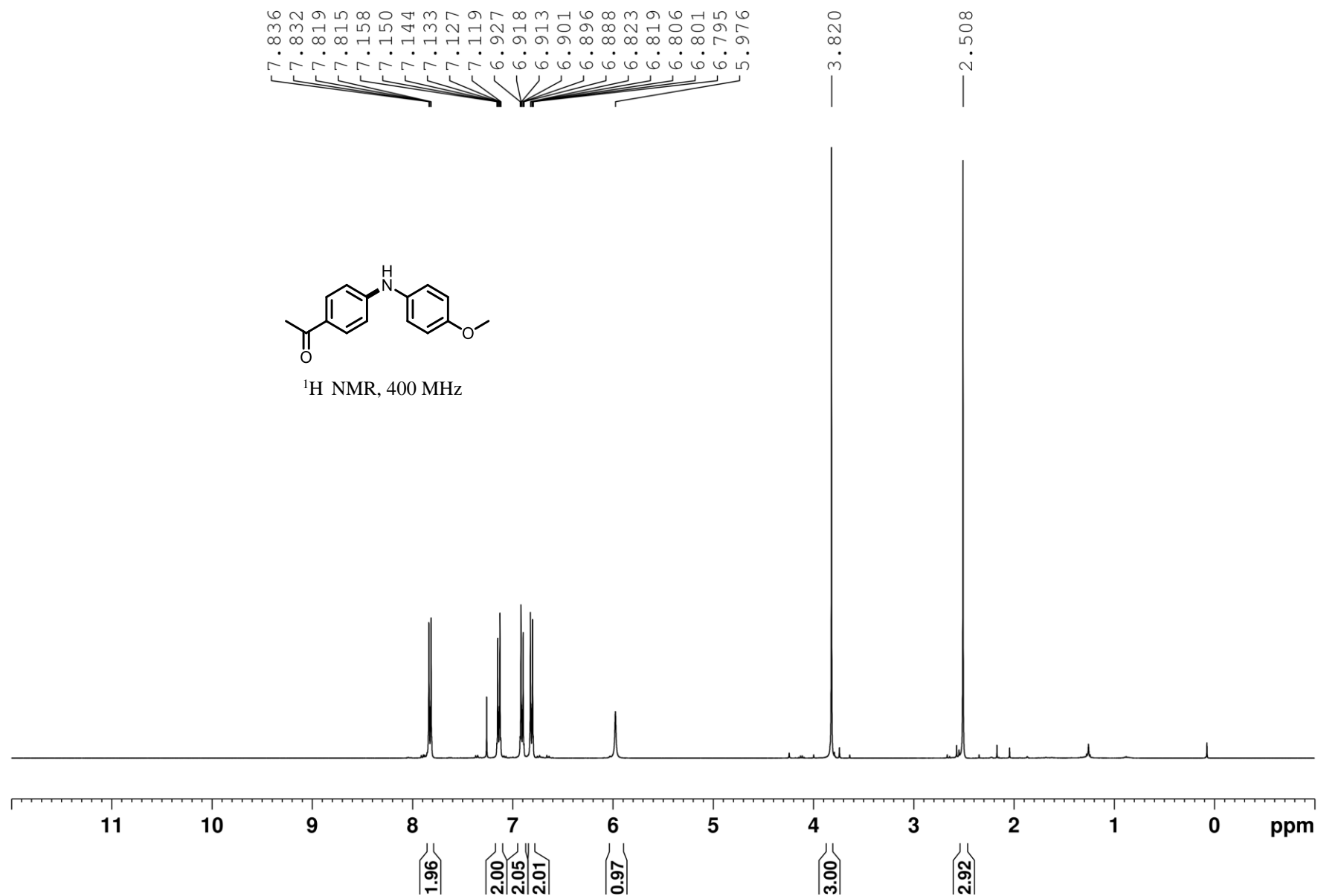


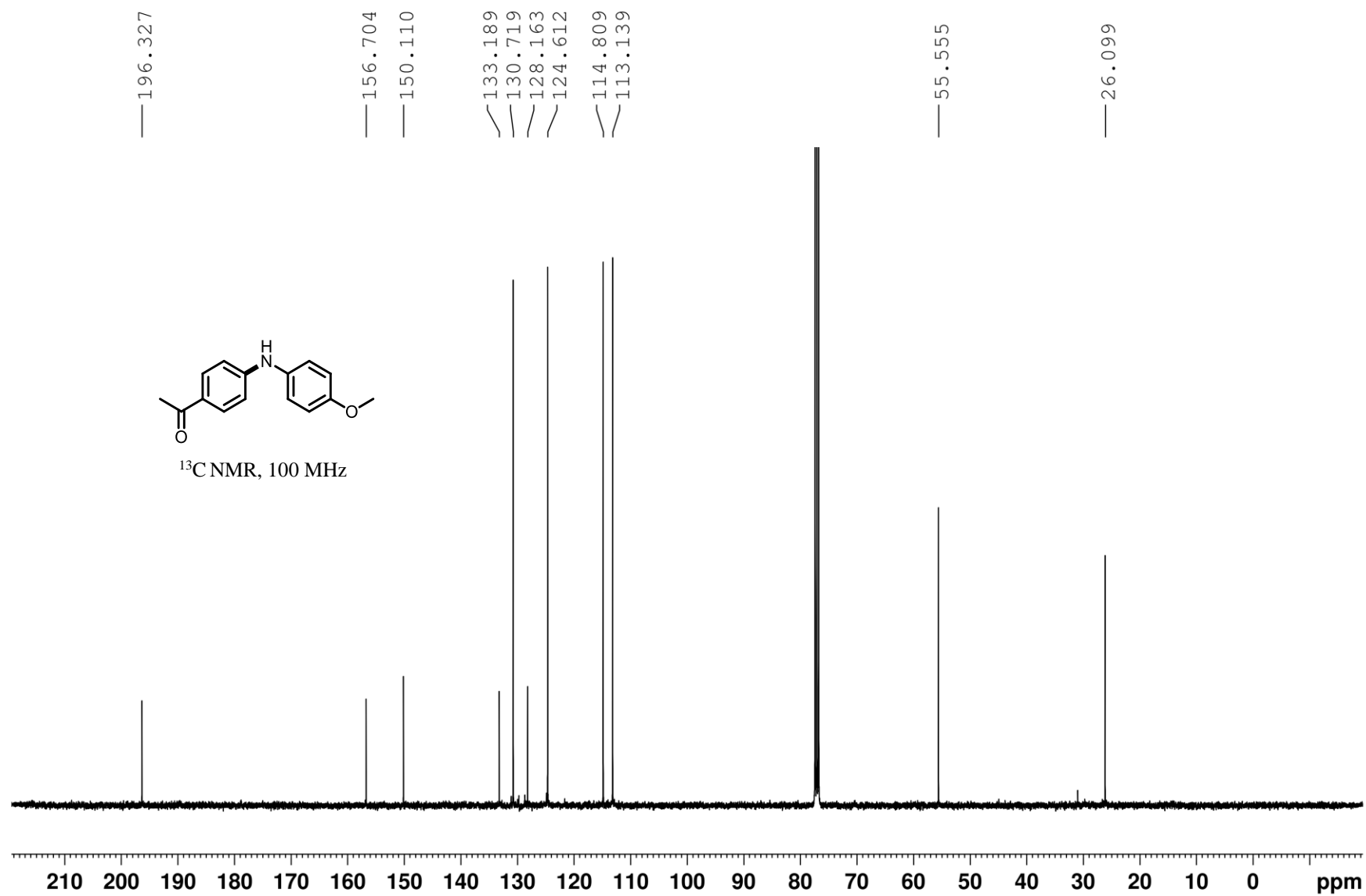
**4-(phenylamino)benzonitrile (16)**



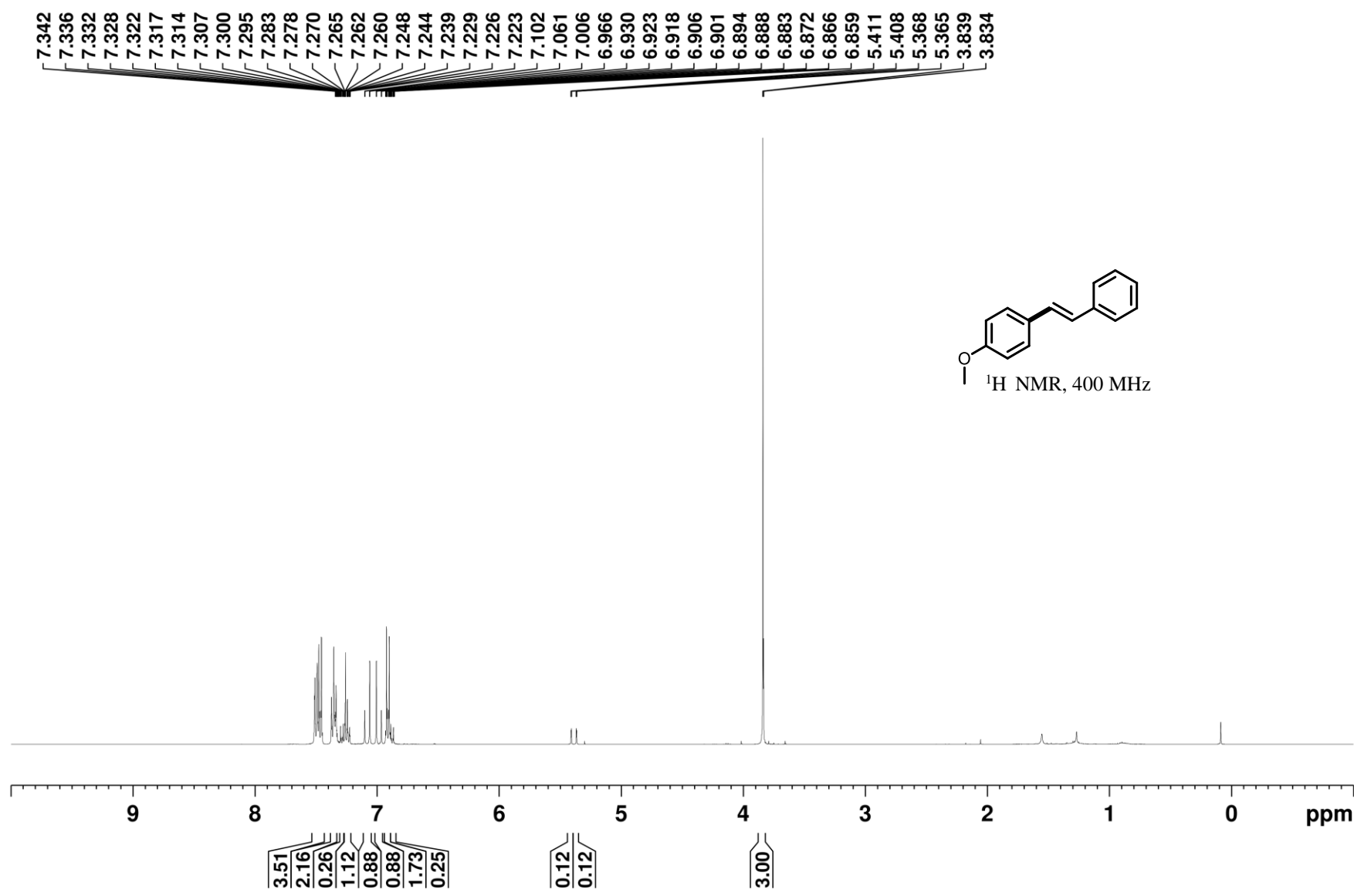


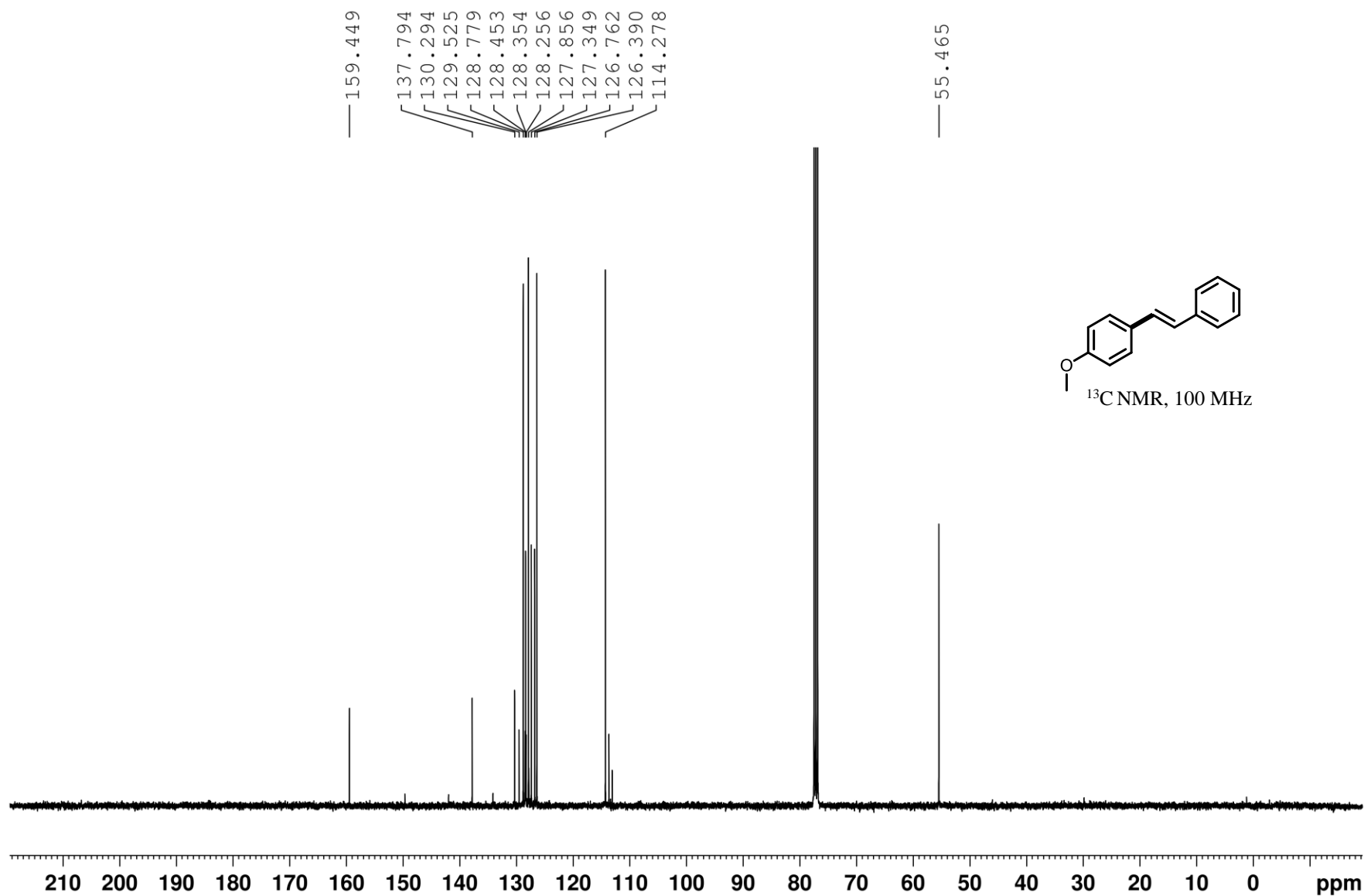
**1-(4-((4-methoxyphenyl)amino)phenyl)ethanone (17)**





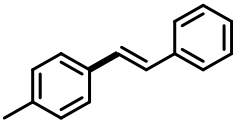
1-methoxy-4-styryl-benzene (18)



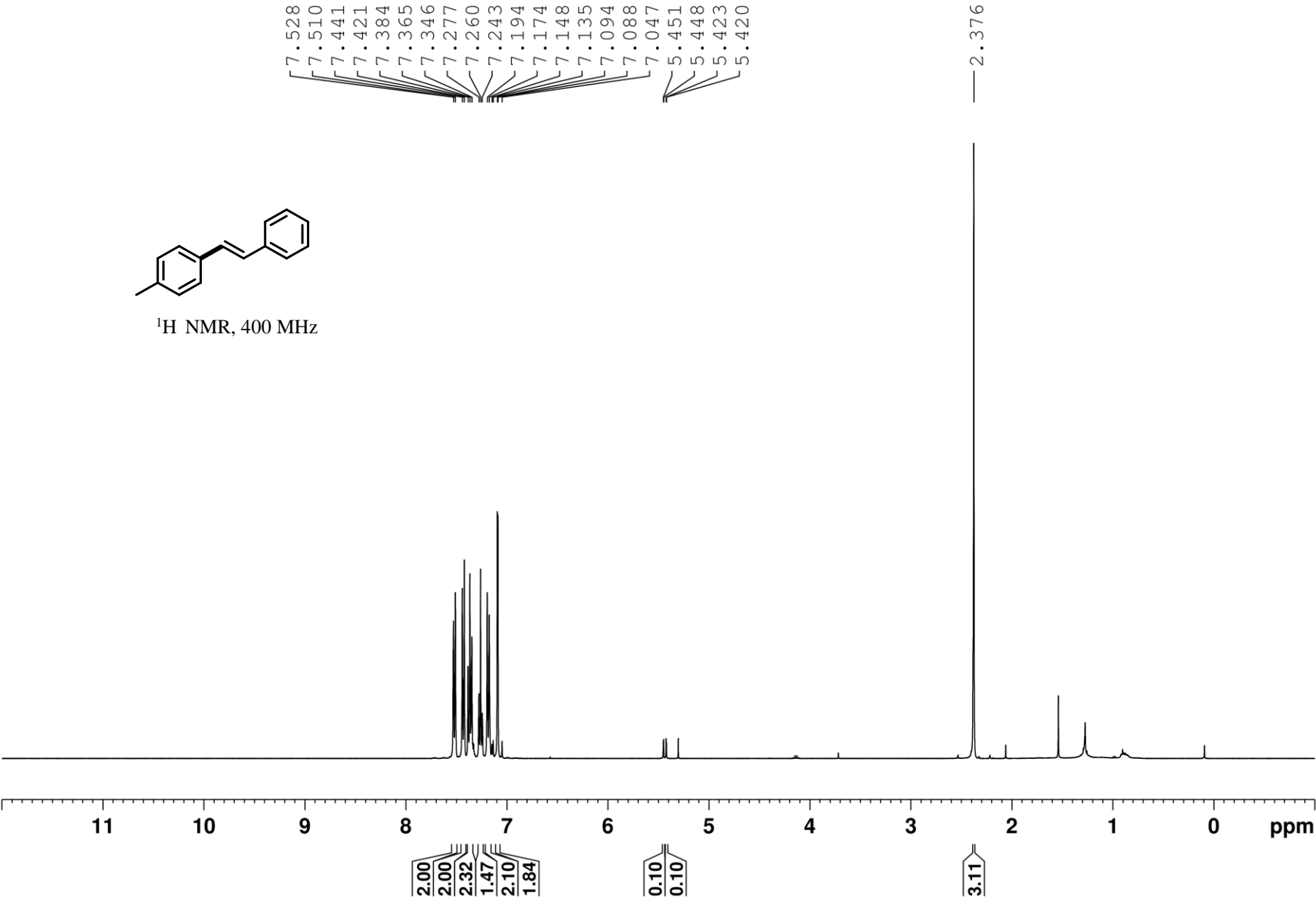


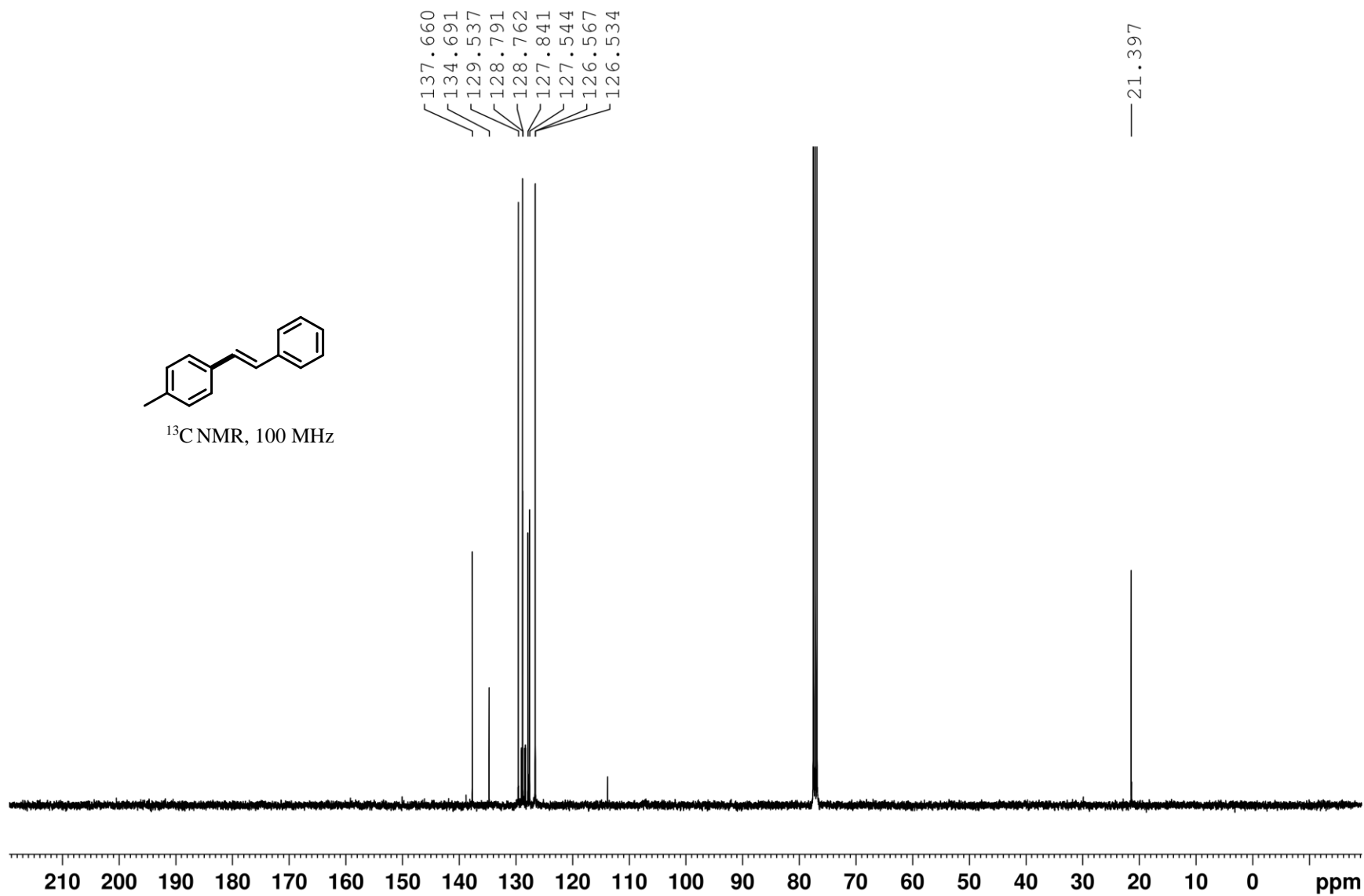


1-methyl-4-styryl-benzene (19)

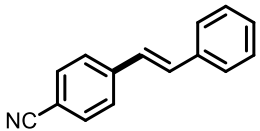


<sup>1</sup>H NMR, 400 MHz

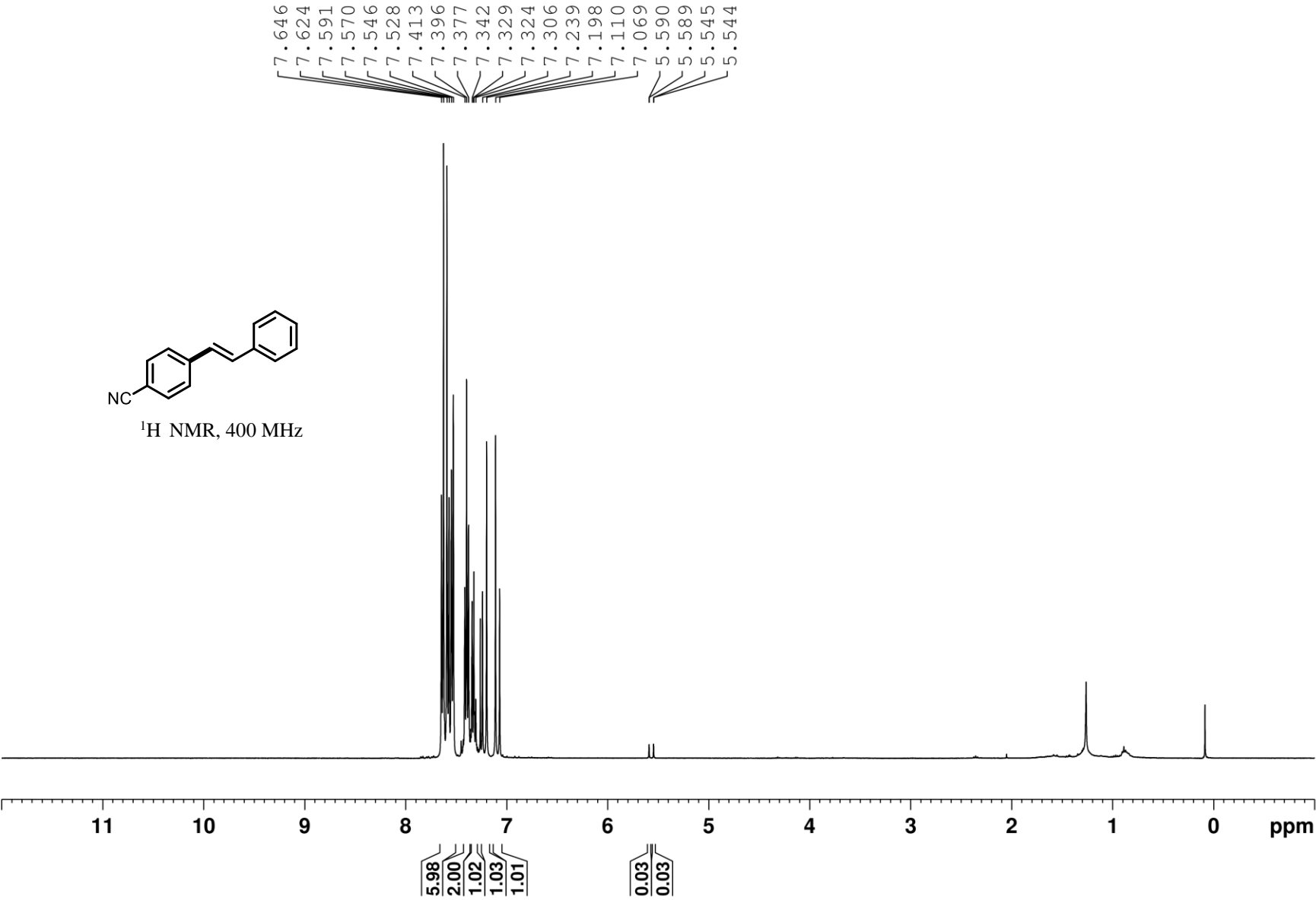


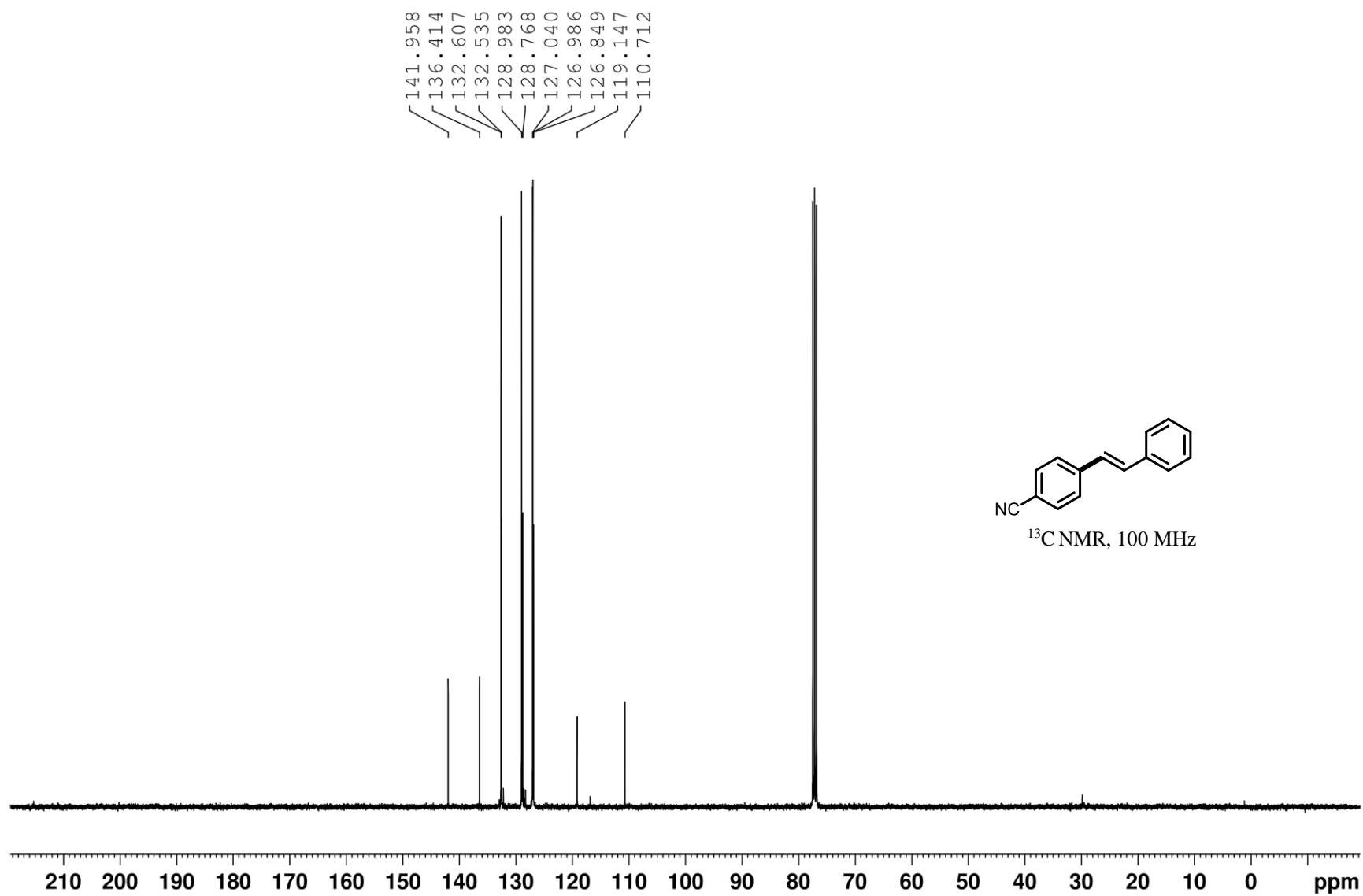


1-cyano-4-styryl-benzene (20)

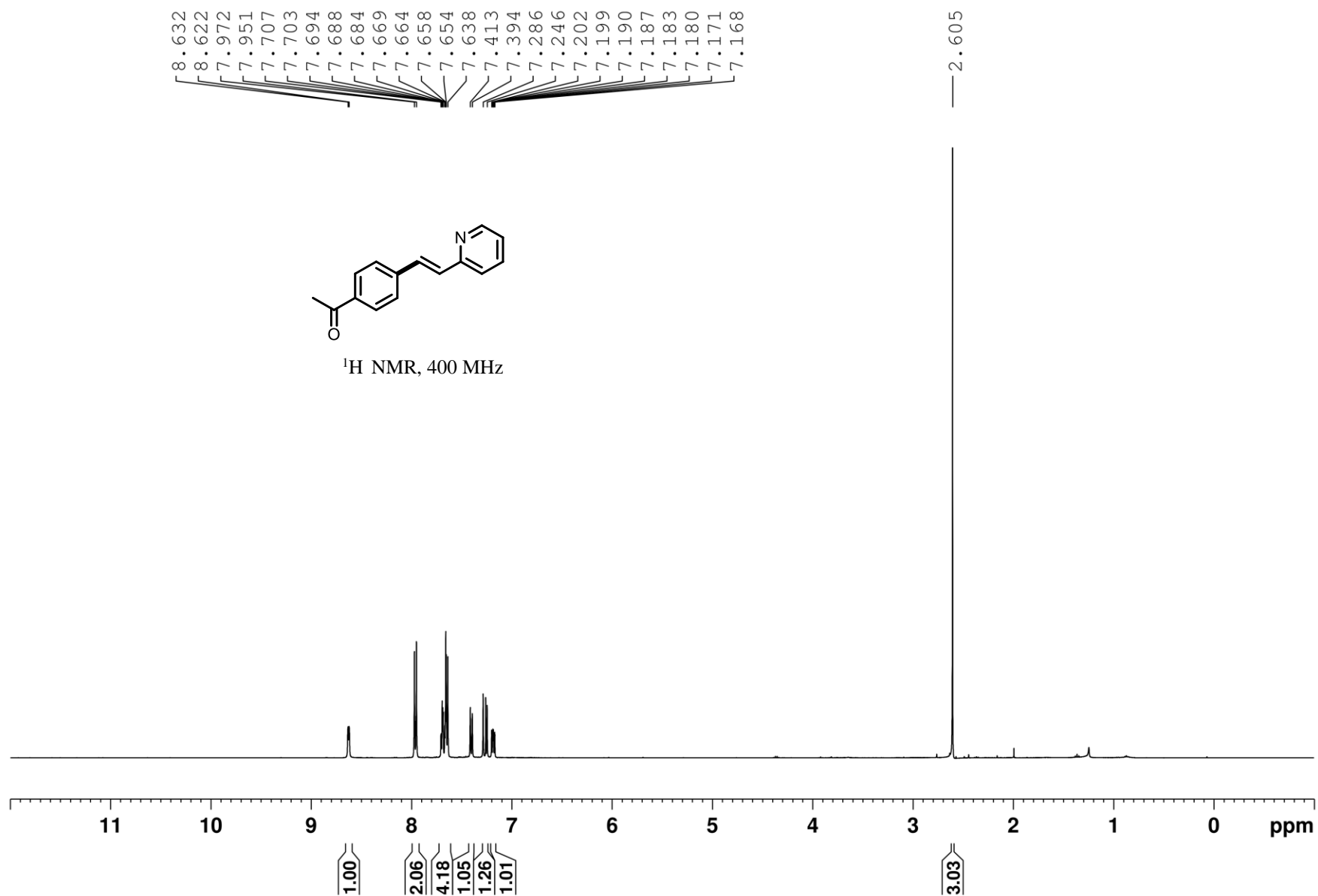


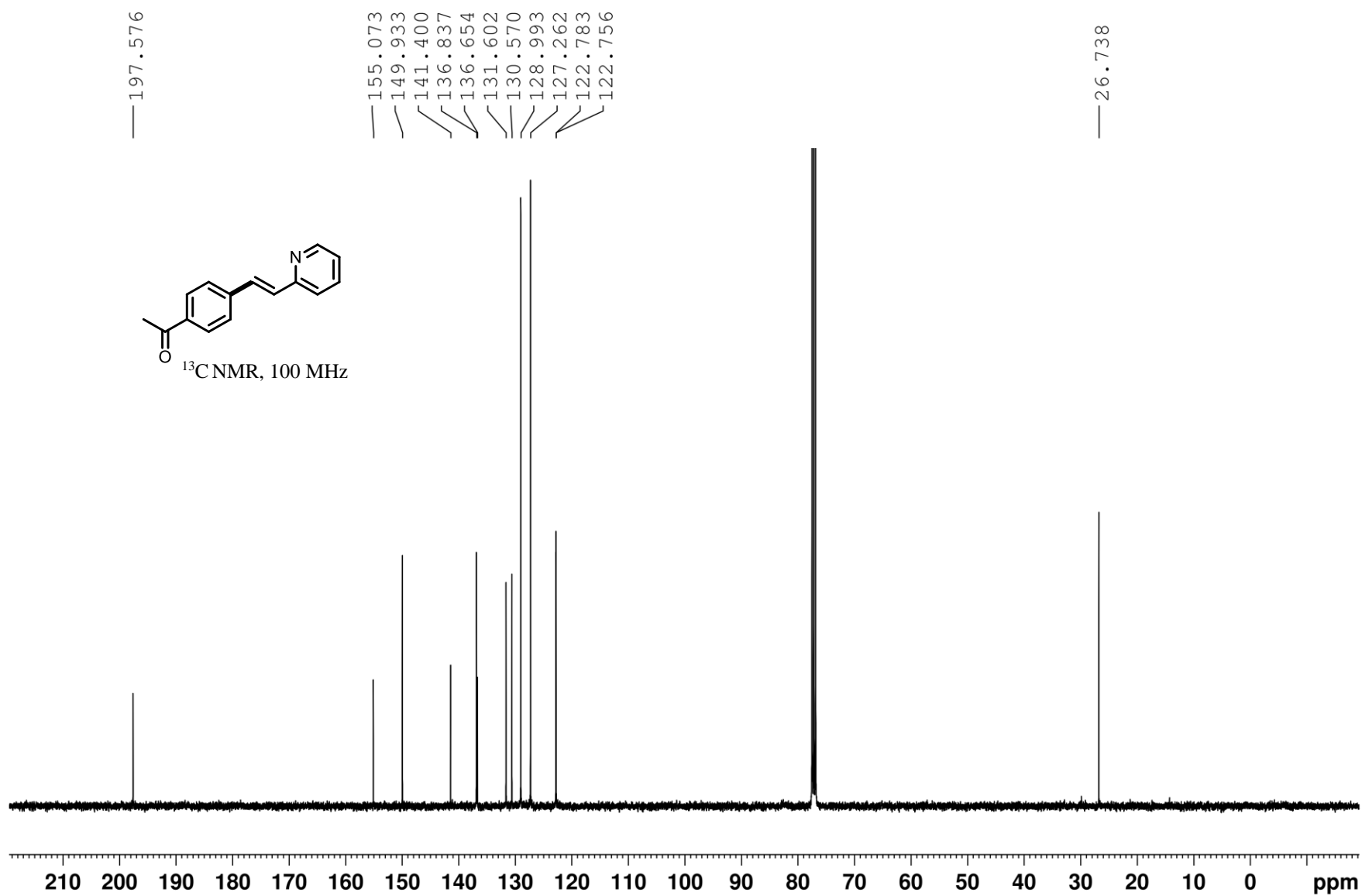
<sup>1</sup>H NMR, 400 MHz



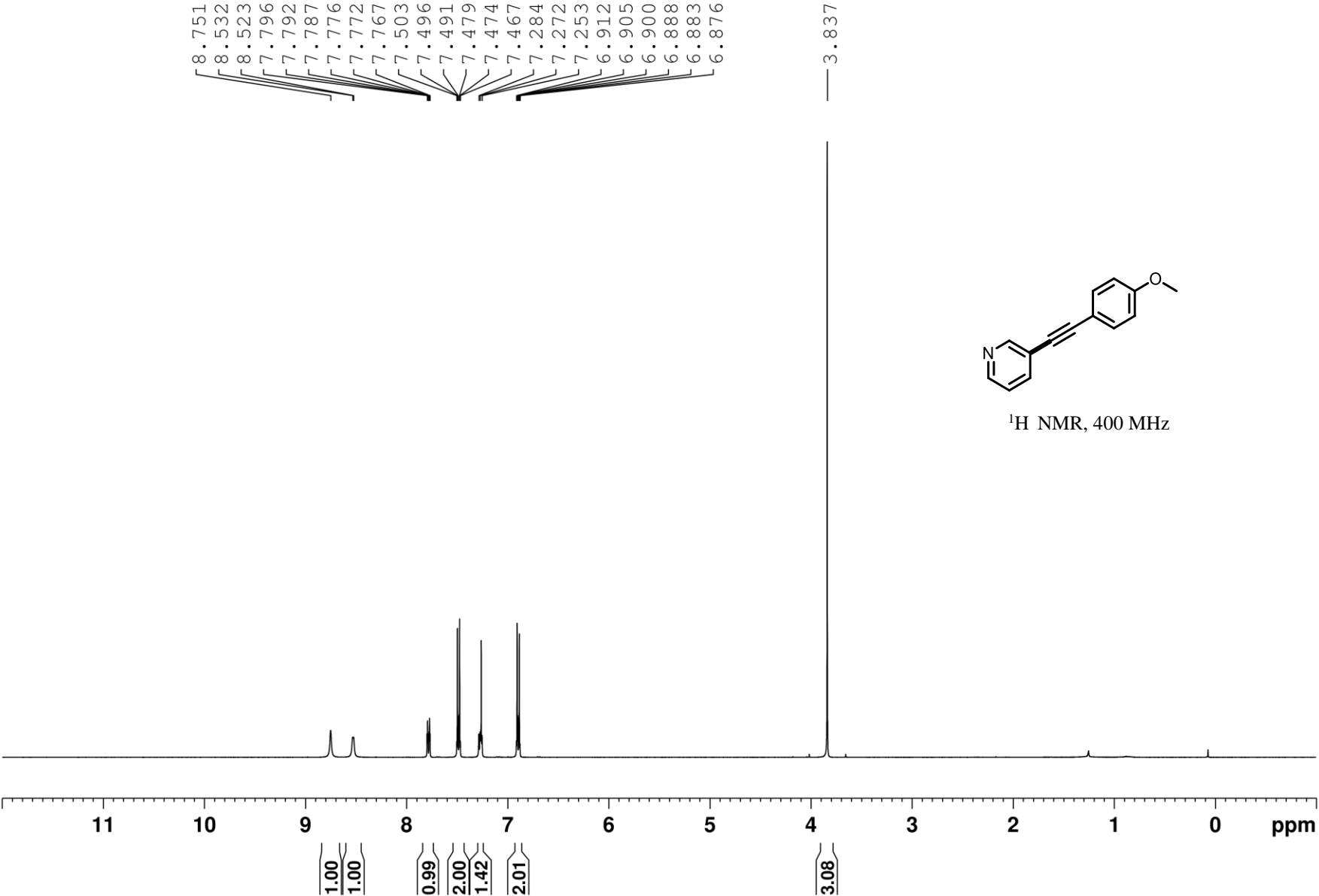


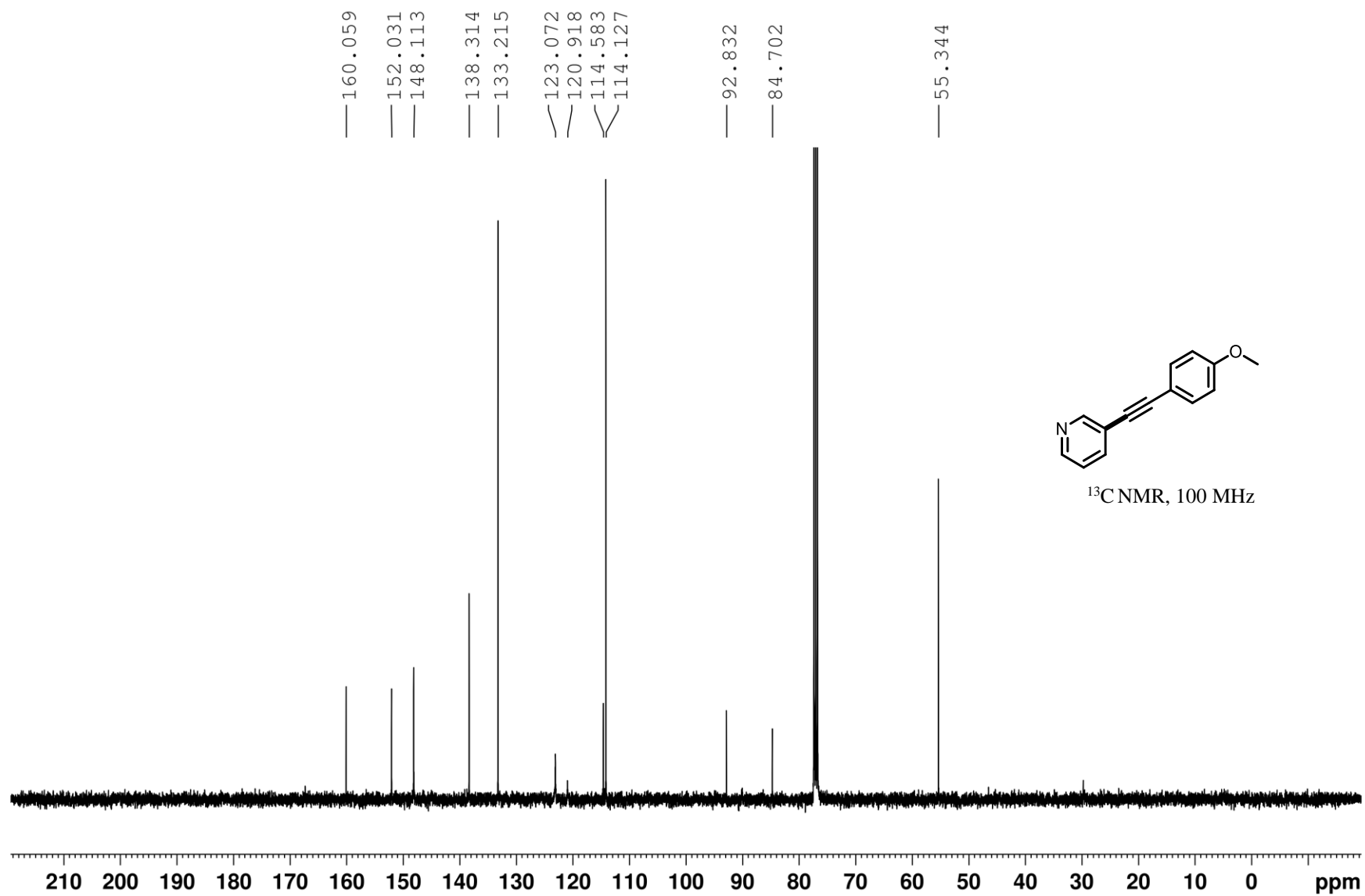
**(E)-1-(4-(2-(pyridin-2-yl)vinyl)phenyl)ethanone (21)**





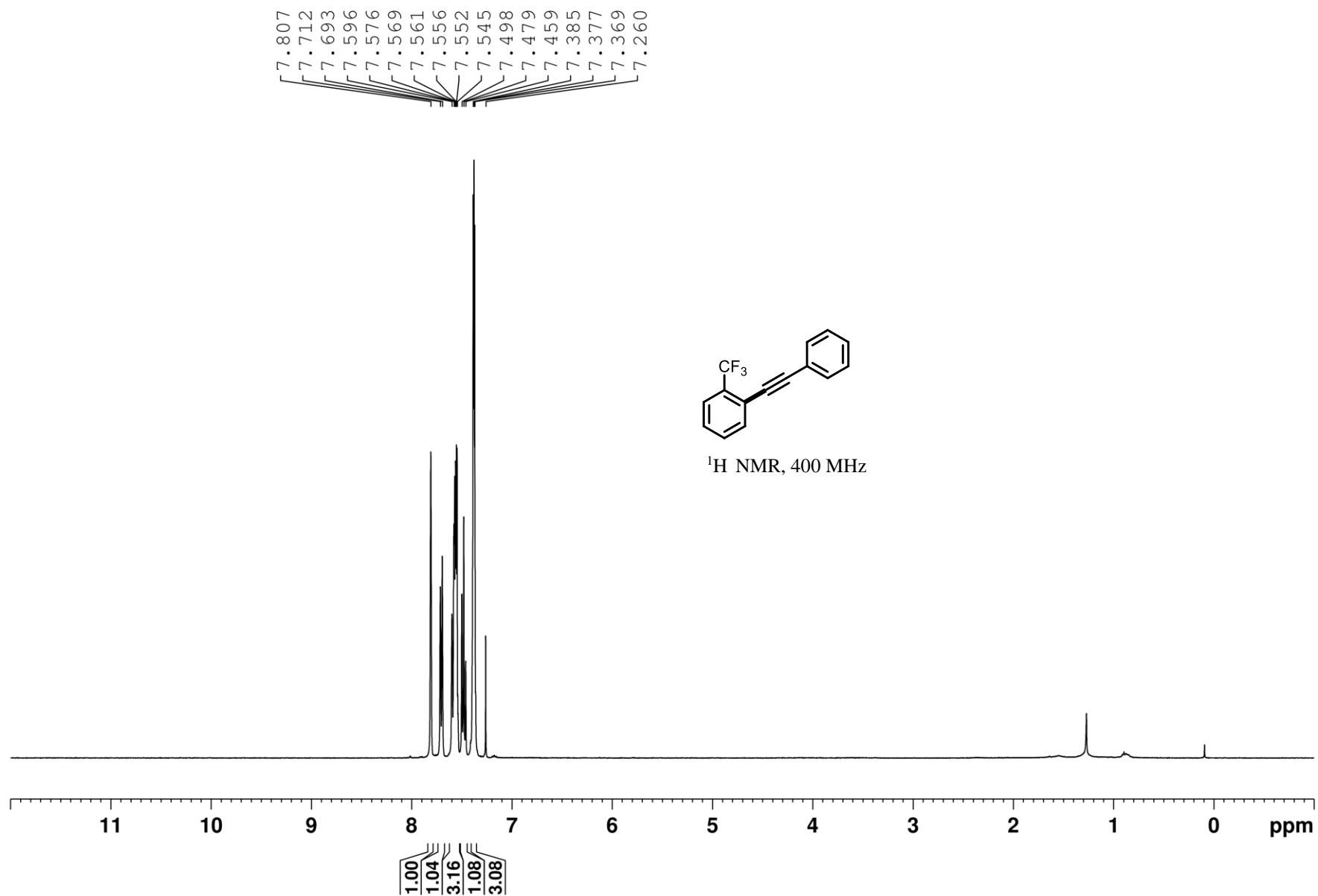
1-methoxy-4-(3'-pyridinylethynyl)-benzene (22)

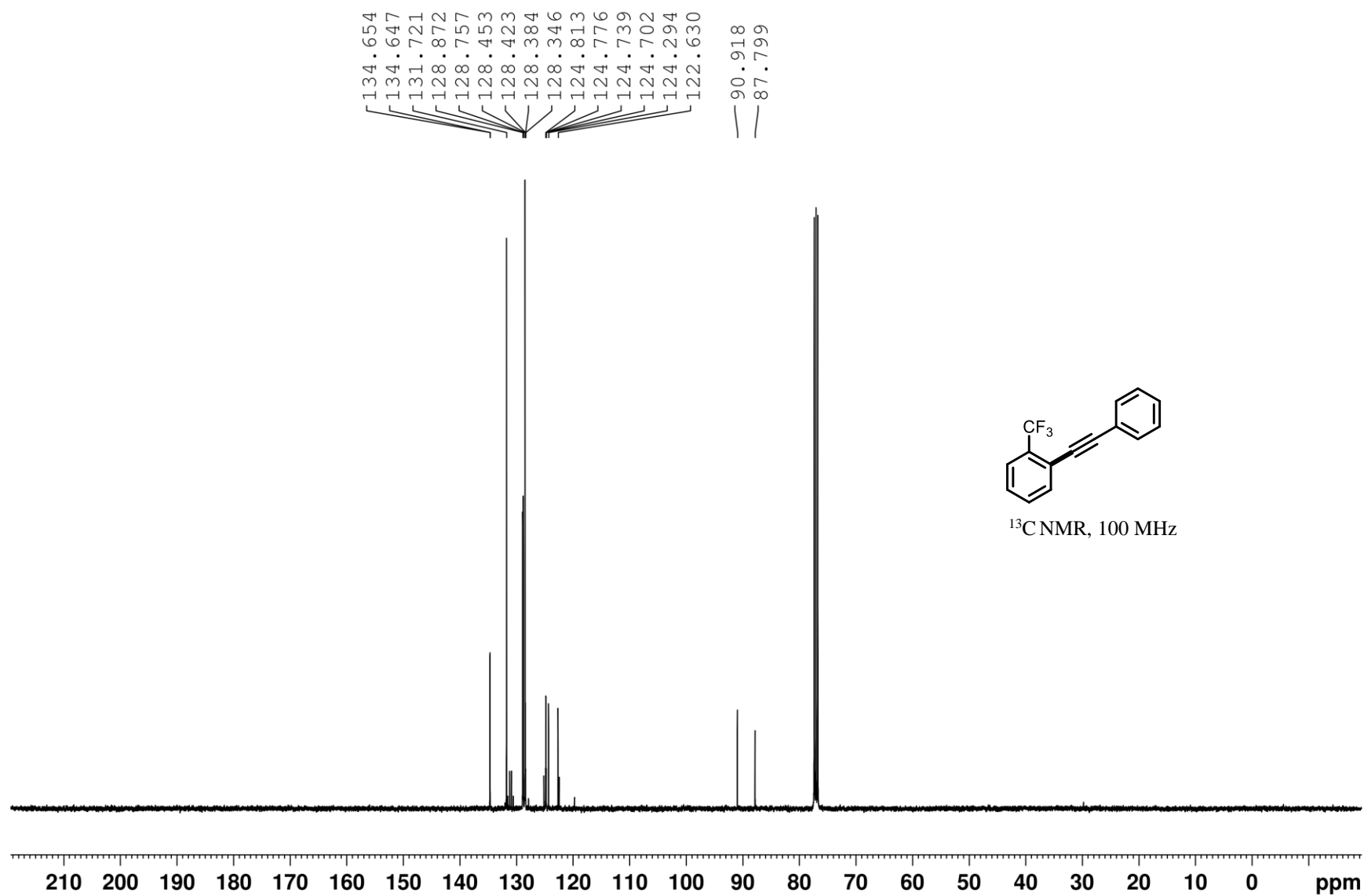






**1-(2-phenylethynyl)-3-(trifluoromethyl)benzene (23)**





## 7 References

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