

# Methods for the Direct Synthesis of Benzoxazoles from Halogenated Nitriles in Alcoholic Solvents

Roy P. Lester and Jason E. Camp\*

*School of Chemistry, University of Nottingham, Nottingham NG7 2RD, U.K.*

*jason.camp@nottingham.ac.uk*

## Supporting Information

### Contents

I.	General experimental information .....	S2
II.	Synthesis of trichlorobenzoxazoles 2a-l .....	S2
III.	Synthesis of dichlorobenzoxazoles 3a, e, i, j, l .....	S7
IV.	References .....	S10
V.	<sup>1</sup> H, <sup>13</sup> C{ <sup>1</sup> H} and <sup>19</sup> F{ <sup>1</sup> H} NMR spectra .....	S11

## I. General Experimental Information

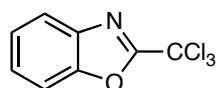
Unless otherwise stated, all commercially available reagents and solvents were used without further purification. THF and DCM were dried over sodium/benzophenone and calcium hydride respectively, and purified by distillation prior to use. Toluene was dried by distillation. All anhydrous experiments were carried out in flame-dried glassware. The solvents used for flash column chromatography were technical grade. For purification procedures using column chromatography, silica gel (60-120) mesh was used. Thin layer chromatography was carried out using Merck Kieselgel silica gel 60 F254 plates (0.2 mm) and visualisation was achieved using UV light followed by dipping in a potassium permanganate solution and heating.  $^1\text{H}$  NMR and  $^{13}\text{C}$  NMR were recorded on a JEOL 270 Mhz spectrometer at ambient temperature using  $\text{CDCl}_3$  (7.27 ppm). Chemical shift values are expressed as parts per million (ppm) and coupling constants and are expressed in Hertz, followed by multiplicity indicated as s: singlet, d: doublet, t: triplet, q: quartet or combination, br.s broad singlet or m: multiplet. Solution IR spectra were recorded on a Perkin Elmer 1600 series FTIR-spectrophotometer. Microwave reactions were run in a Biotage Initiator 2.0 microwave and the reaction temperature was monitored by IR. Mass spectra were determined using a Bruker MicroTOF mass spectrometer.

## II. Synthesis of trichlorobenzoxazoles 2a-l

General procedure 1: To a stirred suspension of  $\text{PtCl}_4$  (10 mol %) and 2-aminophenol (1 equiv.) in *n*-hexane (1 M) at rt was added trichloroacetonitrile (2.2 equiv.). The resultant mixture was stirred at 80 °C for 19 h. The solvent was removed under reduced pressure and the residue was purified by flash column chromatography on silica gel (3% ethyl acetate in petroleum ether) to afford the benzoxazole.

General procedure 2: To a solution of 2-aminophenol (1 equiv.) in methanol (1M) at rt was added trichloroacetonitrile (1.1 equiv.). The resultant mixture was stirred at 40 °C for 19 h. The solvent was removed under reduced pressure and the residue was purified by flash column chromatography on silica gel (3% ethyl acetate in petroleum ether) to afford the trichlorobenzoxazole.

### 2-(Trichloromethyl)benzo[*d*]oxazole (**2a**)<sup>1</sup>



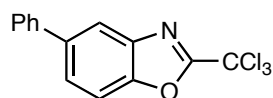
**2a**

General procedure 1:  $\text{PtCl}_4$  (18 mg, 0.05 mmol), 2-aminophenol (**1a**, 58 mg, 0.53 mmol), trichloroacetonitrile (117  $\mu\text{L}$ , 1.17 mmol) in *n*-hexane (0.53 mL), afforded 2-(trichloromethyl)benzo[*d*]oxazole (**2a**, 102 mg, 82% yield) as a white solid.

General procedure 2: 2-Aminophenol (**1a**, 233 mg, 2.14 mmol), trichloroacetonitrile (236  $\mu\text{L}$ , 2.35 mmol) in methanol (2.14 mL), afforded 2-(trichloromethyl)benzo[*d*]oxazole (**2a**, 499 mg, 99% yield) as a white solid.

mp 60 – 62 °C (lit 61 °C); IR (CHCl<sub>3</sub>)  $\nu(\text{cm}^{-1})$  3011, 1617; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta_{\text{H}}$  7.89 - 7.86 (1H, m), 7.67 - 7.64 (1H, m), 7.55 - 7.44 (2H, m); <sup>13</sup>C{<sup>1</sup>H} NMR (75 MHz, CDCl<sub>3</sub>)  $\delta_{\text{C}}$  160.1, 151.5, 139.9, 127.5, 125.7, 121.8, 111.5, 86.0; HRMS (ESI)  $m/z$ : calculated for [M+H]<sup>+</sup>, C<sub>8</sub>H<sub>4</sub>Cl<sub>3</sub>NO<sup>+</sup>, 235.9432 found: 235.9430

### 5-Phenyl-2-(trichloromethyl)benzo[d]oxazole (2b)



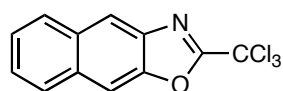
**2b**

General procedure 1: PtCl<sub>4</sub> (20 mg, 0.06 mmol), 2-amino-4-phenylphenol (**1b**, 110 mg, 0.59 mmol), trichloroacetonitrile (130  $\mu\text{L}$ , 1.30 mmol) in *n*-hexane (0.6 mL), afforded 5-phenyl-2-(trichloromethyl)benzo[d]oxazole (**2b**, 35 mg, 20% yield) as a white solid.

General procedure 2: 2-Amino-4-phenylphenol (**1b**, 104 mg, 0.56 mmol), trichloroacetonitrile (62  $\mu\text{L}$ , 0.62 mmol) in methanol (0.6 mL), afforded 5-phenyl-2-(trichloromethyl)benzo[d]oxazole (**2b**, 159 mg, 91% yield) as a white solid.

mp 113 – 115 °C; IR (CHCl<sub>3</sub>)  $\nu(\text{cm}^{-1})$  3011, 1602; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta_{\text{H}}$  8.06 (1H, s), 7.76 - 7.38 (7H, m); <sup>13</sup>C{<sup>1</sup>H} NMR (75 MHz, CDCl<sub>3</sub>)  $\delta_{\text{C}}$  160.6, 151.0, 140.5, 140.3, 139.8, 129.0, 127.7, 127.5, 127.2, 120.0, 111.5, 86.0; HRMS (ESI)  $m/z$ : calculated for [M+Na]<sup>+</sup>, C<sub>14</sub>H<sub>8</sub>Cl<sub>3</sub>NONa<sup>+</sup>, 333.9564 found: 333.9570.

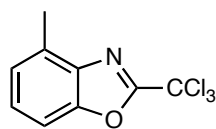
### 2-(Trichloromethyl)naphtho[2,3-*d*]oxazole (2c)



**2c**

General procedure 2: 3-Amino-2-naphthol (**1c**, 108 mg, 0.7 mmol), trichloroacetonitrile (75  $\mu\text{L}$ , 0.75 mmol) in methanol (0.7 mL), afforded 2-(trichloromethyl)naphtho[2,3-*d*]oxazole (**2c**, 147 mg, 76% yield). mp 148 – 150 °C; IR (CHCl<sub>3</sub>)  $\nu(\text{cm}^{-1})$  3011, 1639; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta_{\text{H}}$  8.30 (1H, s), 8.06 - 7.92 (3H, m), 7.60 - 7.48 (2H, m); <sup>13</sup>C{<sup>1</sup>H} NMR (75 MHz, CDCl<sub>3</sub>)  $\delta_{\text{C}}$  161.7, 149.9, 139.2, 132.5, 131.54, 128.7, 127.9, 126.5, 125.3, 119.8, 107.4, 86.0; HRMS (ESI)  $m/z$ : calculated for [M+H]<sup>+</sup>, C<sub>12</sub>H<sub>7</sub>Cl<sub>3</sub>NO<sup>+</sup>, 285.9588 found: 285.9599

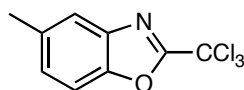
#### 4-Methyl-2-(trichloromethyl)benzo[d]oxazole (**2d**)<sup>2</sup>



**2d**

General procedure 2: 2-Amino-3-methylphenol (**1d**, 109 mg, 0.88 mmol), trichloroacetonitrile (97  $\mu$ L, 0.97 mmol) in methanol (0.9 mL), afforded 4-methyl-2-(trichloromethyl)benzo[d]oxazole (**2d**, 192 mg, 82% yield) as a white solid. mp 63 – 64 °C (lit. mp 68 °C); IR (CHCl<sub>3</sub>)  $\nu$ (cm<sup>-1</sup>) 3011, 1625; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$ <sub>H</sub> 7.44 (1H, d, *J* = 8.3 Hz), 7.37 (1H, dd, *J* = 7.4, 8.3 Hz), 7.23 (1H, d, *J* = 7.4 Hz), 2.68 (3H, s); <sup>13</sup>C{<sup>1</sup>H} NMR (75 MHz, CDCl<sub>3</sub>)  $\delta$ <sub>c</sub> 159.2, 151.3, 139.3, 132.5, 127.1, 126.0, 108.5, 86.2, 16.4; HRMS (ESI) *m/z*: calculated for [M+H]<sup>+</sup>, C<sub>9</sub>H<sub>7</sub>Cl<sub>3</sub>NO<sup>+</sup>, 249.9588 found: 249.9589.

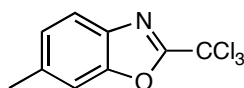
#### 5-Methyl-2-(trichloromethyl)benzo[d]oxazole (**2e**)<sup>3</sup>



**2e**

General procedure 2: 2-Amino-4-methylphenol (**1e**, 154 mg, 1.25 mmol), trichloroacetonitrile (138  $\mu$ L, 1.38 mmol) in methanol (1.3 mL), afforded 5-methyl-2-(trichloromethyl)benzo[d]oxazole (**2e**, 258 mg, 83% yield). mp 55 – 56 °C (lit. mp 58 °C); IR (CHCl<sub>3</sub>)  $\nu$ (cm<sup>-1</sup>) 3011, 1612; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$ <sub>H</sub> 7.55 (1H, s), 7.41 (1H, d, *J* = 8.5 Hz), 7.20 (1H, dd, *J* = 8.5, 1.1 Hz), 2.43 (3H, s); <sup>13</sup>C{<sup>1</sup>H} NMR (75 MHz, CDCl<sub>3</sub>)  $\delta$ <sub>c</sub> 159.9, 149.6, 139.9, 135.6, 128.5, 121.2, 110.6, 86.0, 21.6; HRMS (ESI) *m/z*: calculated for [M+H]<sup>+</sup>, C<sub>9</sub>H<sub>7</sub>Cl<sub>3</sub>NO<sup>+</sup>, 249.9588 found: 249.9589.

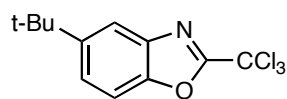
#### 6-Methyl-2-(trichloromethyl)benzo[d]oxazole (**2f**)<sup>2</sup>



**2f**

General procedure 2: 2-Amino-5-methylphenol (**1f**, 172 mg, 1.40 mmol), trichloroacetonitrile (154  $\mu$ L, 1.54 mmol), methanol (1.7 mL), afforded 6-methyl-2-(trichloromethyl)benzo[d]oxazole (**2f**, 284 mg, 81% yield). mp 64 – 66 °C (lit. mp 69 °C); IR (CHCl<sub>3</sub>)  $\nu$ (cm<sup>-1</sup>) 3011, 1618; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$ <sub>H</sub> 7.71 (1H, d, *J* = 8.3 Hz), 7.44 – 7.42 (1H, m), 7.29 – 7.24 (1H, m), 2.53 (3H, s); <sup>13</sup>C{<sup>1</sup>H} NMR (75 MHz, CDCl<sub>3</sub>)  $\delta$ <sub>c</sub> 159.5, 151.8, 138.3, 137.7, 127.0, 121.0, 111.4, 86.1, 21.9; HRMS (ESI) *m/z*: calculated for [M+H]<sup>+</sup>, C<sub>9</sub>H<sub>7</sub>Cl<sub>3</sub>NO<sup>+</sup>, 249.9588 found: 249.9589.

### 5-(*tert*-Butyl)-2-(trichloromethyl)benzo[*d*]oxazole (**2g**)



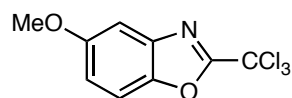
**2g**

General procedure 1: PtCl<sub>4</sub> (27 mg, 0.08 mmol), 2-amino-4-*tert*-butylphenol (**1g**, 132 mg, 0.80 mmol), trichloroacetonitrile (176 μL, 1.76 mmol) in *n*-hexane (0.8 mL), afforded 5-(*tert*-butyl)-2-(trichloromethyl)benzo[*d*]oxazole (**2g**, 60 mg, 26% yield) as a light brown solid.

General procedure 2: 2-Amino-4-*tert*-butylphenol (**1g**, 123 mg, 0.75 mmol), trichloroacetonitrile (82 μL, 82 mmol) in methanol (0.8 mL), afforded 5-(*tert*-butyl)-2-(trichloromethyl)benzo[*d*]oxazole (**2g**, 176 mg, 80% yield) as a light brown solid.

mp 39 – 41 °C; IR (CHCl<sub>3</sub>) ν(cm<sup>-1</sup>) 3011, 2967, 1602; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ<sub>H</sub> 7.86 (1H, t, *J* = 1.3 Hz), 7.56 - 7.52 (2H, m), 1.37 (9H, s); <sup>13</sup>C{<sup>1</sup>H} NMR (75 MHz, CDCl<sub>3</sub>) δ<sub>C</sub> 160.1, 149.5, 149.4, 139.8, 125.4, 118.0, 110.6, 86.1, 35.1, 31.7; HRMS (ESI) *m/z*: calculated for [M+H]<sup>+</sup>, C<sub>12</sub>H<sub>13</sub>Cl<sub>3</sub>NO<sup>+</sup>, 292.0058 found: 292.0061.

### 5-Methoxy-2-(trichloromethyl)benzo[*d*]oxazole (**2h**)



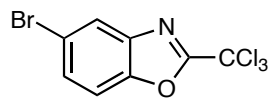
**2h**

General procedure 1: PtCl<sub>4</sub> (23 mg, 0.07 mmol), 2-amino-4-methoxyphenol (**1h**, 95 mg, 0.68 mmol), trichloroacetonitrile (150 μL, 1.5 mmol) in *n*-hexane (0.7 mL), afforded 5-methoxy-2-(trichloromethyl)benzo[*d*]oxazole (**2h**, 49 mg, 27% yield) as an orange solid.

General procedure 2: 2-Amino-4-methoxyphenol (**1h**, 89 mg, 0.6 mmol), trichloroacetonitrile (71 μL, 0.7 mmol), methanol (0.6 mL). afforded 5-methoxy-2-(trichloromethyl)benzo[*d*]oxazole (**2h**, 169 mg, 99% yield) as an orange solid.

mp 52 – 54 °C; IR (CHCl<sub>3</sub>) ν(cm<sup>-1</sup>) 3011, 2962, 1614; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ<sub>H</sub> 7.51 (1H, d, *J* = 9.0 Hz), 7.29 (1H, d, *J* = 2.5 Hz), 7.09 (1H, dd, *J* = 9.0, 2.5 Hz), 3.87 (3H, s); <sup>13</sup>C{<sup>1</sup>H} NMR (75 MHz, CDCl<sub>3</sub>) δ<sub>C</sub> 160.6, 158.1, 146.1, 140.7, 116.8, 111.7, 103.7, 86.0, 56.0; HRMS (ESI) *m/z*: calculated for [M+H]<sup>+</sup>, C<sub>9</sub>H<sub>7</sub>Cl<sub>3</sub>NO<sub>2</sub>, 265.9537 found: 265.9529.

### 5-Bromo-2-(trichloromethyl)benzo[d]oxazole (**2i**)



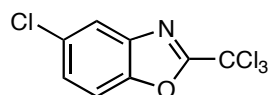
**2i**

General procedure 1: PtCl<sub>4</sub> (20 mg, 0.06 mmol), 2-amino-4-bromophenol (**1i**, 111 mg, 0.58 mmol), trichloroacetonitrile (128 μL, 1.28 mmol) in *n*-hexane (0.6 mL), afforded 5-bromo-2-(trichloromethyl)benzo[d]oxazole (**2i**, 96 mg, 52% yield) as a grey solid.

General procedure 2: 2-amino-4-bromophenol (**1i**, 157 mg, 0.8 mmol), trichloroacetonitrile (92 μL, 0.9 mmol) in methanol (0.8 mL), afforded 5-bromo-2-(trichloromethyl)benzo[d]oxazole (**2i**, 229 mg, 90% yield) as a grey solid.

mp 72 – 74 °C; IR (CHCl<sub>3</sub>)  $\nu(\text{cm}^{-1})$  3011, 1606; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta_{\text{H}}$  8.00 (1H, d, *J* = 1.8 Hz), 7.63 (1H, dd, *J* = 8.8, 1.8 Hz), 7.50 (1H, d, *J* = 8.8 Hz); <sup>13</sup>C{<sup>1</sup>H} NMR (75 MHz, CDCl<sub>3</sub>)  $\delta_{\text{C}}$  161.1, 150.4, 141.3, 130.7, 124.7, 118.5, 112.8, 85.6; HRMS (ESI) *m/z*: calculated for [M+H]<sup>+</sup>, C<sub>8</sub>H<sub>4</sub>BrCl<sub>3</sub>NO, 313.8537 found: 313.8539.

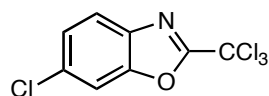
### 5-Chloro-2-(trichloromethyl)benzo[d]oxazole (**2j**)<sup>3</sup>



**2j**

General procedure 2: 2-amino-4-chlorophenol (**1j**, 163 mg, 1.14 mmol), trichloroacetonitrile (125 μL, 1.25 mmol) in methanol (1.1 mL), afforded 5-chloro-2-(trichloromethyl)benzo[d]oxazole (**2j**, 250 mg, 81% yield) as a grey solid. m.p. 82 – 84 °C (lit. mp 84 °C); IR (CHCl<sub>3</sub>)  $\nu(\text{cm}^{-1})$  3011, 1605; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta_{\text{H}}$  7.77 (1H, d, *J* = 2.0 Hz), 7.52 (1H, d, *J* = 8.8 Hz), 7.40 (1H, dd, *J* = 8.8, 2.0 Hz); <sup>13</sup>C{<sup>1</sup>H} NMR (75 MHz, CDCl<sub>3</sub>)  $\delta_{\text{C}}$  161.0, 149.8, 140.7, 131.2, 127.8, 121.4, 112.1, 85.5; HRMS (ESI) *m/z*: calculated for [M+H]<sup>+</sup>, C<sub>8</sub>H<sub>4</sub>Cl<sub>4</sub>NO<sup>+</sup>, 271.9012 found: 271.9023.

### 6-Chloro-2-(trichloromethyl)benzo[d]oxazole (**2k**)



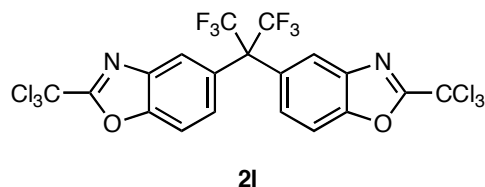
**2k**

General procedure 1: PtCl<sub>4</sub> (21 mg, 0.06 mmol), 2-amino-5-chlorophenol (**1k**, 90 mg, 0.62 mmol), trichloroacetonitrile (137 μL, 1.36 mmol) in *n*-hexane (0.6 mL), afforded 6-chloro-2-(trichloromethyl)benzo[*d*]oxazole (**2k**, 110 mg, 65% yield) as a brown/grey solid.

General procedure 2: 2-Amino-5-chlorophenol (**1k**, 170 mg, 1.18 mmol), trichloroacetonitrile (130 μL, 1.3 mmol) in methanol (1.2 mL), afforded 6-chloro-2-(trichloromethyl)benzo[*d*]oxazole (**2k**, 262 mg, 82% yield) as a brown/grey solid.

mp 78 – 80 °C; IR (CHCl<sub>3</sub>) ν(cm<sup>-1</sup>) 3011, 1606; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ<sub>H</sub> 7.74 (1H, d, *J* = 8.8 Hz), 7.62 (1H, d, *J* = 2.3 Hz), 7.4 (1H, dd, *J* = 8.8, 2.3 Hz); <sup>13</sup>C{<sup>1</sup>H} NMR (75 MHz, CDCl<sub>3</sub>) δ<sub>C</sub> 160.4, 151.5, 138.5, 133.2, 126.5, 122.2, 112.0, 85.6; HRMS (ESI) *m/z*: calculated for [M+H]<sup>+</sup>, C<sub>8</sub>H<sub>4</sub>Cl<sub>4</sub>NO<sup>+</sup>, 271.9012 found: 271.9018

### 5,5'-(Perfluoropropane-2,2-diyl)bis(2-(trichloromethyl)benzo[*d*]oxazole) (**2l**)



To a solution of 2,2-bis(3-amino-4-hydroxyphenyl)hexafluoropropane (**1l**, 79 mg, 0.22 mmol) in methanol (0.2 mL, 1M) at rt was added trichloroacetonitrile (48 μL, 0.5 mmol). The resultant mixture was stirred at 40 °C for 19 h. The solvent was removed under reduced pressure and the residue was purified by flash column chromatography on silica gel (3% ethyl acetate in petroleum ether) to afford 5,5'-(perfluoropropane-2,2-diyl)bis(2-(trichloromethyl)benzo[*d*]oxazole) (**2l**, 94 mg, 69% yield) as a brown solid. mp 150 – 154 °C; IR (CHCl<sub>3</sub>) ν(cm<sup>-1</sup>) 3011, 1619; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ<sub>H</sub> 8.03 (2H, s), 7.66 (2H, d, *J* = 8.9 Hz), 7.50 (2H, d, *J* = 8.9 Hz); <sup>13</sup>C{<sup>1</sup>H} NMR (75 MHz, CDCl<sub>3</sub>) δ<sub>C</sub> 161.4, 151.5, 140.0, 131.3, 129.5, 125.4, 124.2, 122.5, 111.5, 85.6, 64.8 (1C, t, *J* = 26.0 Hz); <sup>19</sup>F{<sup>1</sup>H} NMR (282 MHz, CDCl<sub>3</sub>) 63.7; HRMS (ESI) *m/z*: calculated for [M+H]<sup>+</sup>, C<sub>19</sub>H<sub>7</sub>Cl<sub>6</sub>F<sub>6</sub>N<sub>2</sub>O<sub>2</sub><sup>+</sup>, 620.8508 found: 620.8512.

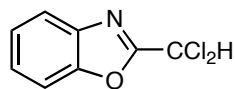
### III. Synthesis of dichlorobenzoxazoles **3a**, **e**, **i**, **j**, **l**

General procedure 3: To a stirred suspension of PtCl<sub>4</sub> (10 mol %) and 2-aminophenol (1 equiv.) in *n*-hexane (1 M) at rt was added dichloroacetonitrile (2.2 equiv.). The resultant mixture was stirred at 80 °C for 19 h. The resultant mixture was stirred at 80 °C for 19 h. The solvent was removed under reduced pressure and the residue was purified by flash column chromatography on silica gel (3% ethyl acetate in petroleum ether) to afford the dichlorobenzoxazole.

General procedure 4: To a solution of 2-aminophenol (1.05 equiv.) in methanol (1M) at rt was added dichloroacetonitrile (1 equiv.). The resultant mixture was stirred at 40 °C for 19 h. The solvent was removed

under reduced pressure and the residue was purified by flash column chromatography on silica gel (3% ethyl acetate in petroleum ether) to afford the dichlorobenzoxazole.

### 2-(Dichloromethyl)benzo[*d*]oxazole (**3a**)<sup>4</sup>



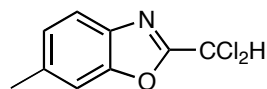
**3a**

General procedure 3: PtCl<sub>4</sub> (22 mg, 0.07 mmol), 2-aminophenol (**1a**, 71 mg, 0.53 mmol), dichloroacetonitrile (47  $\mu$ L, 0.59 mmol) in *n*-hexane (0.65 mL), afforded 2-(dichloromethyl)benzo[*d*]oxazole (**3a**, 40 mg, 31% yield) as a white solid.

General procedure 4: 2-Aminophenol (**1a**, 500 mg, 4.58 mmol), dichloroacetonitrile (331  $\mu$ L, 4.12 mmol) in methanol (4.1 mL), afforded 2-(dichloromethyl)benzo[*d*]oxazole (**3a**, 690 mg, 83% yield) as a white solid.

mp 68 – 70 °C; IR (CHCl<sub>3</sub>)  $\nu$ (cm<sup>-1</sup>) 3011, 1613; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$ <sub>H</sub> 7.81 - 7.75 (1H, m), 7.61 - 7.57 (1H, m), 7.46 - 7.35 (2H, m), 6.89 (1H, s); <sup>13</sup>C{<sup>1</sup>H} NMR (75 MHz, CDCl<sub>3</sub>)  $\delta$ <sub>C</sub> 159.5, 151.0, 140.0, 126.7, 125.2, 121.1, 111.2, 61.0; HRMS (ESI) *m/z*: calculated for [M+H]<sup>+</sup>, C<sub>8</sub>H<sub>6</sub>Cl<sub>2</sub>NO<sup>+</sup>, 201.9821 found: 201.9839.

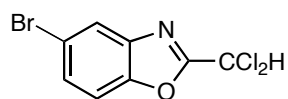
### 6-Methyl-2-(dichloromethyl)benzo[*d*]oxazole (**3e**)<sup>4</sup>



**3e**

General procedure 4: 4-Methyl-2-aminophenol (**1e**, 140 mg, 1.14 mmol), dichloroacetonitrile (87  $\mu$ L, 1.08 mmol) in methanol (1.08 mL). afforded 6-methyl-2-(dichloromethyl)benzo[*d*]oxazole (**3e**, 136 mg, 58% yield) as a brown/grey solid. mp 62 – 64 °C; IR (CHCl<sub>3</sub>)  $\nu$ (cm<sup>-1</sup>) 3011, 1609; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$ <sub>H</sub> 7.64 (1H, d, *J* = 8.3 Hz), 7.38 (1H, s), 7.20 (1H, d, *J* = 8.3 Hz), 6.86 (1H, s), 2.50 (3H, s); <sup>13</sup>C{<sup>1</sup>H} NMR (75 MHz, CDCl<sub>3</sub>)  $\delta$ <sub>C</sub> 159.0, 151.3, 137.8, 137.6, 126.6, 120.5, 111.3, 61.1, 21.9; HRMS (ESI) *m/z*: calculated for [M+H]<sup>+</sup>, C<sub>9</sub>H<sub>8</sub>Cl<sub>2</sub>NO<sup>+</sup>, 215.9978, found: 215.9998.

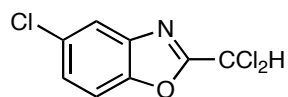
### 5-Bromo-2-(dichloromethyl)benzo[d]oxazole (**3i**)



**3i**

General procedure 4: 4-Bromo-2-aminophenol (**1i**, 113 mg, 0.79 mmol), dichloroacetonitrile (60  $\mu$ L, 0.75 mmol) in methanol (0.8 mL), afforded 5-bromo-2-(dichloromethyl)benzo[d]oxazole (**3i**, 130 mg, 74% yield) as a yellow solid. mp 54 – 56  $^{\circ}$ C; IR (CHCl<sub>3</sub>)  $\nu$ (cm<sup>-1</sup>) 3009, 1607; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$ <sub>H</sub> 7.92 (1H, s), 7.58 - 7.47 (2H, m), 6.85 (1H, s); <sup>13</sup>C {<sup>1</sup>H} NMR (75 MHz, CDCl<sub>3</sub>)  $\delta$ <sub>c</sub> 160.6, 149.9, 141.5, 130.0, 124.1, 118.1, 112.5, 60.6; HRMS (ESI)  $m/z$ : calculated for [M+H]<sup>+</sup>, C<sub>8</sub>H<sub>4</sub>BrCl<sub>2</sub>NONa, 301.8746, found: 301.8730.

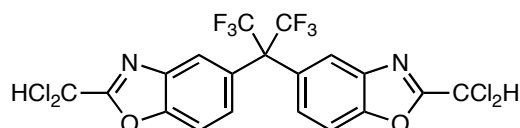
### 5-Chloro-2-(dichloromethyl)benzo[d]oxazole (**3j**)



**3j**

General procedure 4: 4-Chloro-2-aminophenol (**1j**, 113 mg, 0.79 mmol), dichloroacetonitrile (60  $\mu$ L, 0.75 mmol) in methanol (0.8 mL), afforded 5-chloro-2-(dichloromethyl)benzo[d]oxazole (**3j**, 130 mg, 74% yield) as a white solid. mp 68 – 70  $^{\circ}$ C; IR (CHCl<sub>3</sub>)  $\nu$ (cm<sup>-1</sup>) 3011, 1605; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$ <sub>H</sub> 7.77 (1H, d,  $J$  = 2.0 Hz), 7.54 (1H, d,  $J$  = 8.8 Hz), 7.42 (1H, dd,  $J$  = 8.8, 2.0 Hz), 6.85 (1H, s); <sup>13</sup>C {<sup>1</sup>H} NMR (75 MHz, CDCl<sub>3</sub>)  $\delta$ <sub>c</sub> 160.9, 149.5, 141.1, 130.9, 127.3, 121.1, 112.1, 60.7.; HRMS (ESI)  $m/z$ : calculated for [M+H]<sup>+</sup>, C<sub>8</sub>H<sub>5</sub>Cl<sub>3</sub>NO<sup>+</sup>, 235.9432, found: 235.9450.

### 5,5'-(Perfluoropropane-2,2-diyl)bis(2-(dichloromethyl)benzo[d]oxazole) (**3l**)

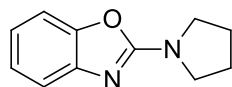


**3l**

To a solution of 2,2-bis(3-amino-4-hydroxyphenyl)hexafluoropropane (**1l**, 114 mg, 0.31 mmol) in methanol (0.3 mL, 1M) at rt was added dichloroacetonitrile (100  $\mu$ L, 1.25 mmol, 4 equiv.). The resultant mixture was stirred at 40  $^{\circ}$ C for 19 h. The solvent was removed under reduced pressure and the residue was purified by flash column chromatography on silica gel (3% ethyl acetate in petroleum ether) to afford 5,5'-(perfluoropropane-2,2-diyl)bis(2-(dichloromethyl)benzo[d]oxazole) (**3l**, 118 mg, 69% yield) as a brown solid. mp 55 – 58  $^{\circ}$ C; IR (CHCl<sub>3</sub>)  $\nu$ (cm<sup>-1</sup>) 3008, 1621; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$ <sub>H</sub> 7.95 (1H, s), 7.64 (1H, d,  $J$  = 9.0 Hz), 7.45 (1H, d,

$J = 9.0$  Hz), 6.87 (1H, s);  $^{13}\text{C}\{^1\text{H}\}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{c}}$  161.0, 151.0, 140.2, 130.9, 129.0, 123.7, 111.3, 60.7;  $^{19}\text{F}\{^1\text{H}\}$  NMR (282 MHz,  $\text{CDCl}_3$ ) 63.7; HRMS (ESI)  $m/z$ : calculated for  $[\text{M}+\text{H}]^+$ ,  $\text{C}_{19}\text{H}_9\text{Cl}_4\text{F}_6\text{N}_2\text{O}_2^+$ , 552.9288, found: 552.9330.

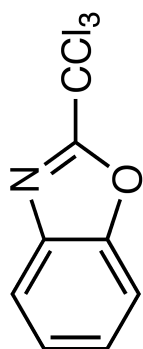
#### 2-(Pyrrolidin-1-yl)benzo[*d*]oxazole (**4**)<sup>5</sup>



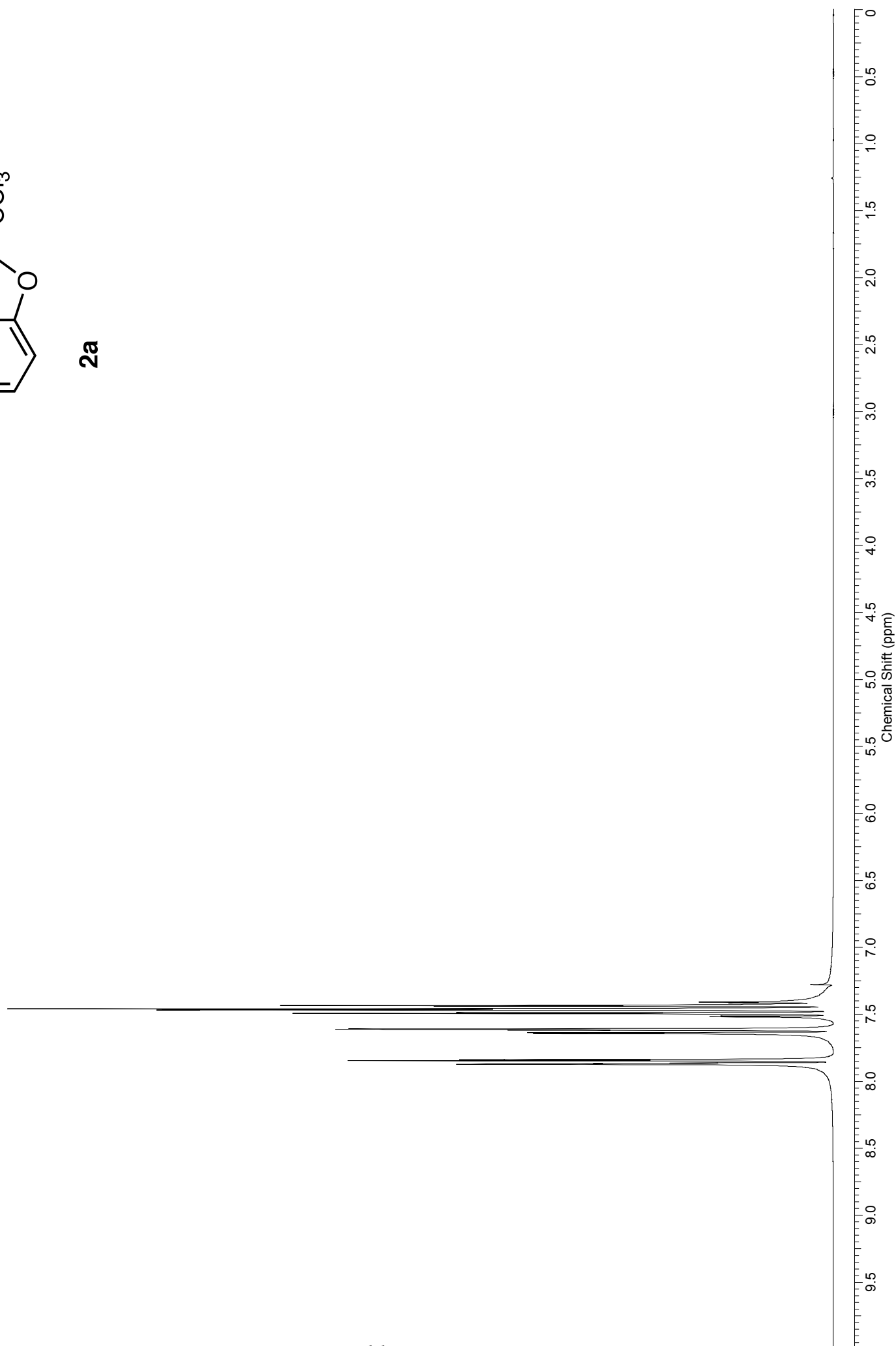
To a solution of 2-(trichloromethyl)benzo[*d*]oxazole (**2a**, 116 mg, 0.49 mmol) in tetrahydrofuran (0.75 mL, 0.7 M) at rt was added pyrrolidine (61  $\mu\text{L}$ , 0.74 mmol). The resultant mixture was stirred at 70 °C for 24 h. The solvent was removed under reduced pressure and the residue was purified by flash column chromatography on silica gel (20% ethyl acetate in petroleum ether) to afford 2-(pyrrolidin-1-yl)benzo[*d*]oxazole (**4**, 51 mg, 55% yield) as a yellow solid. mp 133 – 135 °C (lit. mp 136 – 137 °C); IR ( $\text{CHCl}_3$ )  $\nu(\text{cm}^{-1})$  3011, 2978, 1647;  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{H}}$  7.36 (1H, dq,  $J = 7.8, 0.5$  Hz), 7.26 (1H, dq,  $J = 7.8, 0.5$  Hz), 7.15 (1H, td,  $J = 7.7, 1.2$  Hz), 6.99 (1H, td,  $J = 7.7, 1.2$  Hz), 3.69 - 3.62 (4H, m), 2.07-2.01 (4H, m);  $^{13}\text{C}\{^1\text{H}\}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{c}}$  160.9, 148.9, 143.5, 123.6, 119.9, 115.8, 108.4, 47.2, 25.4; HRMS (ESI)  $m/z$ : calculated for  $[\text{M}+\text{H}]^+$ ,  $\text{C}_{11}\text{H}_{13}\text{N}_2\text{O}^+$ , 189.1023, found: 189.1030.

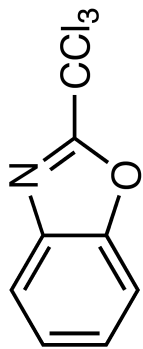
#### IV. References

- (1) Verhaeghe, P.; Rathelot, P.; Gellis, A.; Rault, S.; Vanelle, P. *Tetrahedron* **2006**, *62*, 8173–8176.
- (2) Clifford, D. P.; Edwards, R. V.; Hewson, R. T. *J. Agric. Food. Chem.* **1981**, *29*, 640–643.
- (3) Holan, G.; Samuel, E. L.; Ennis, B. C.; Hinde, R. W. *J. Chem. Soc.* **1967**, 20–25.
- (4) Gauss, W.; Heitzer, H. *Liebigs Ann. Chem.* **1970**, *733*, 59–69.
- (5) Manolikakes, G.; Gavryushin, A.; Knochel, P. *J. Org. Chem.* **2008**, *73*, 1429–1434.

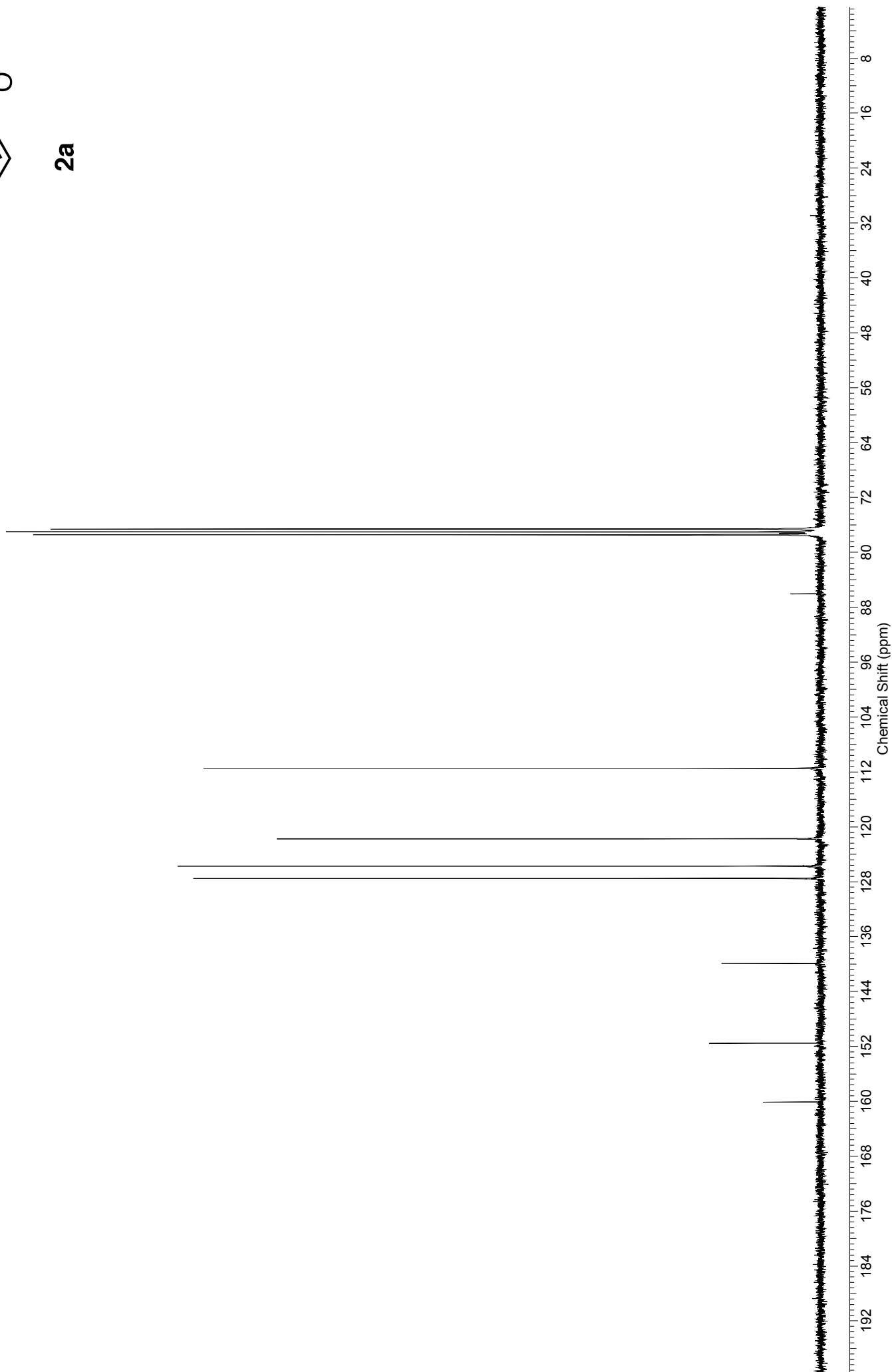


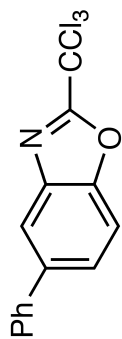
**2a**



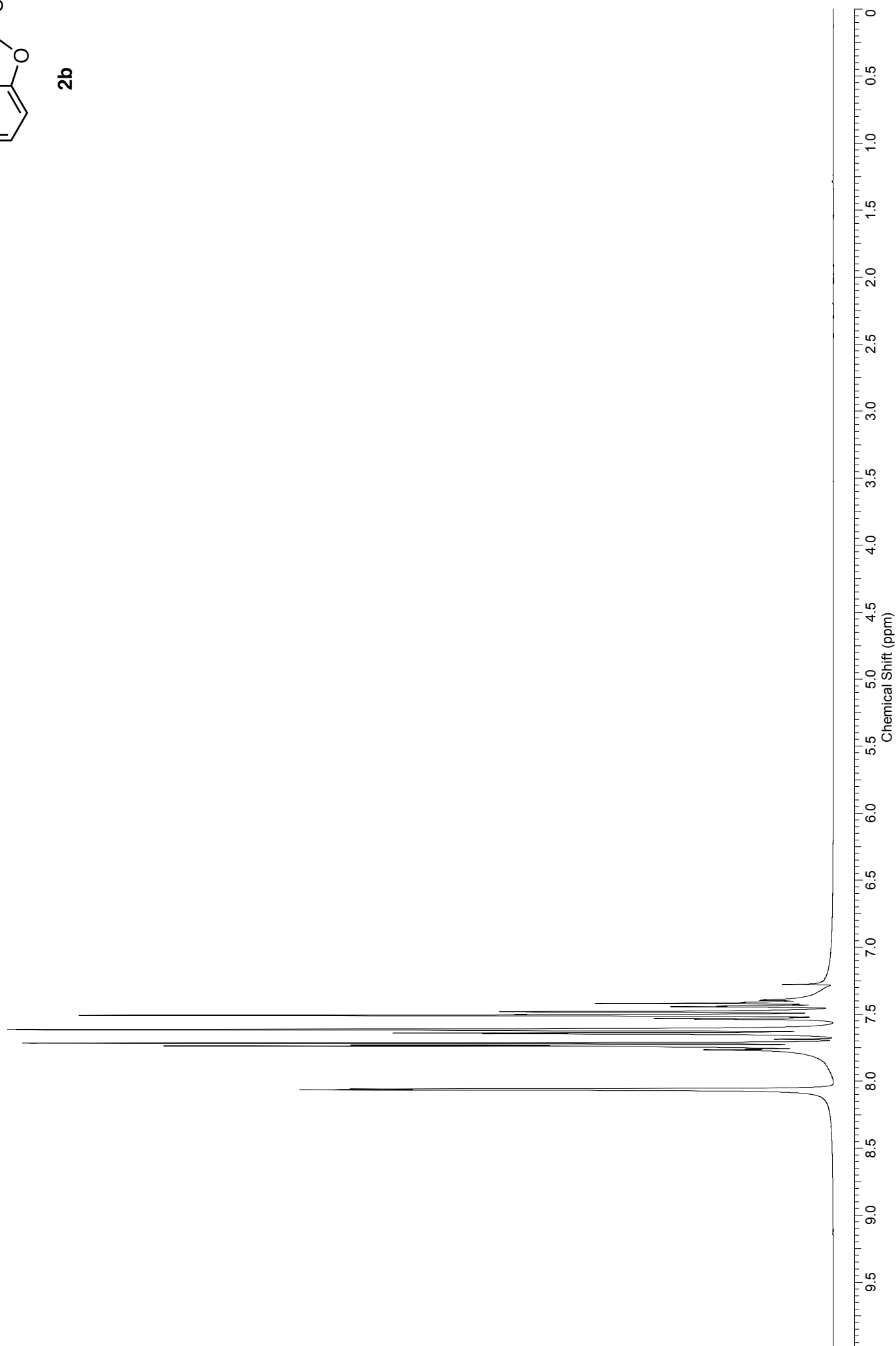


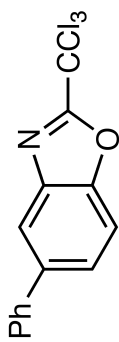
**2a**



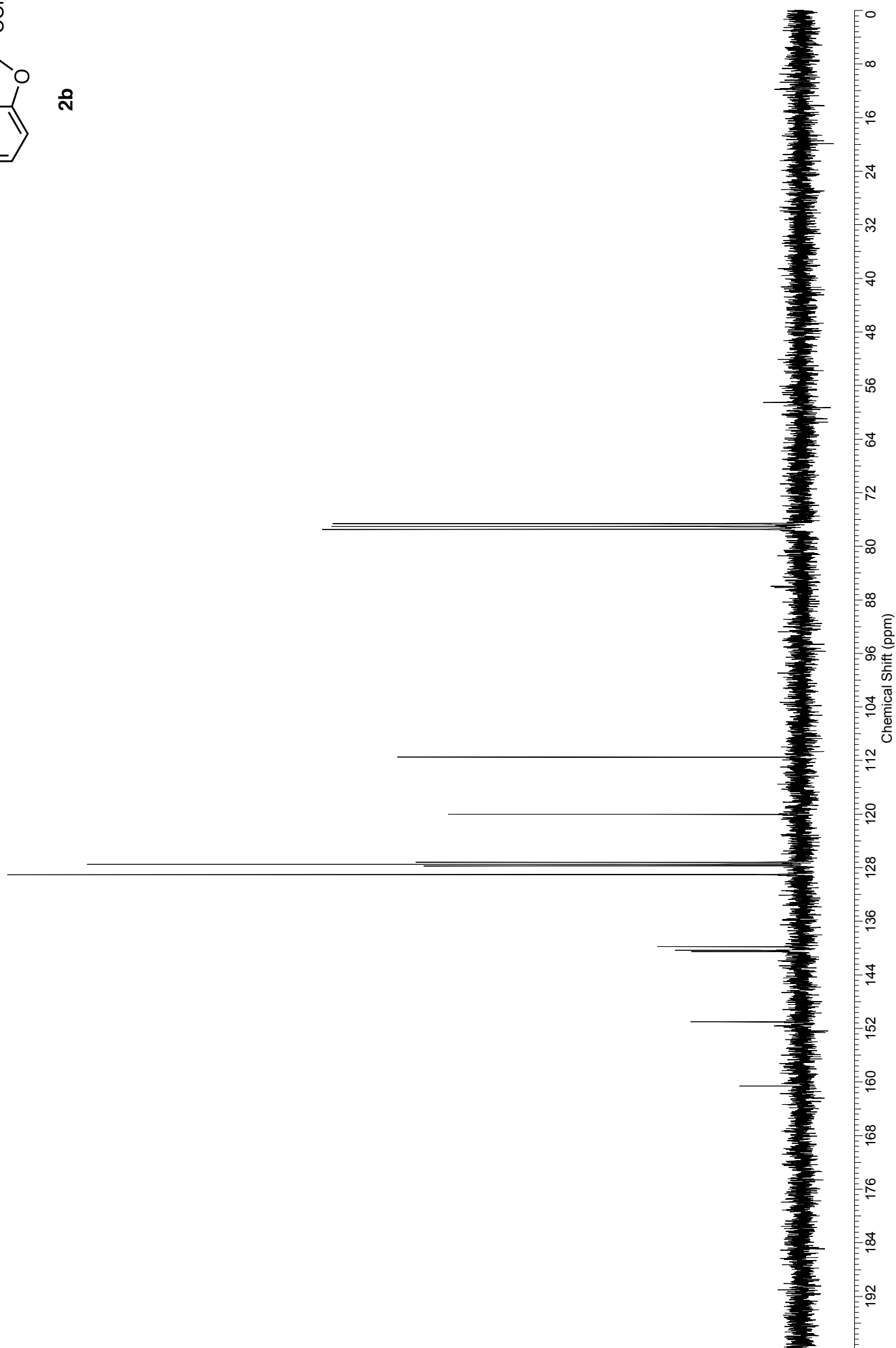


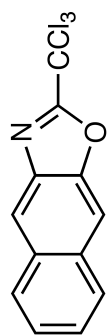
2b



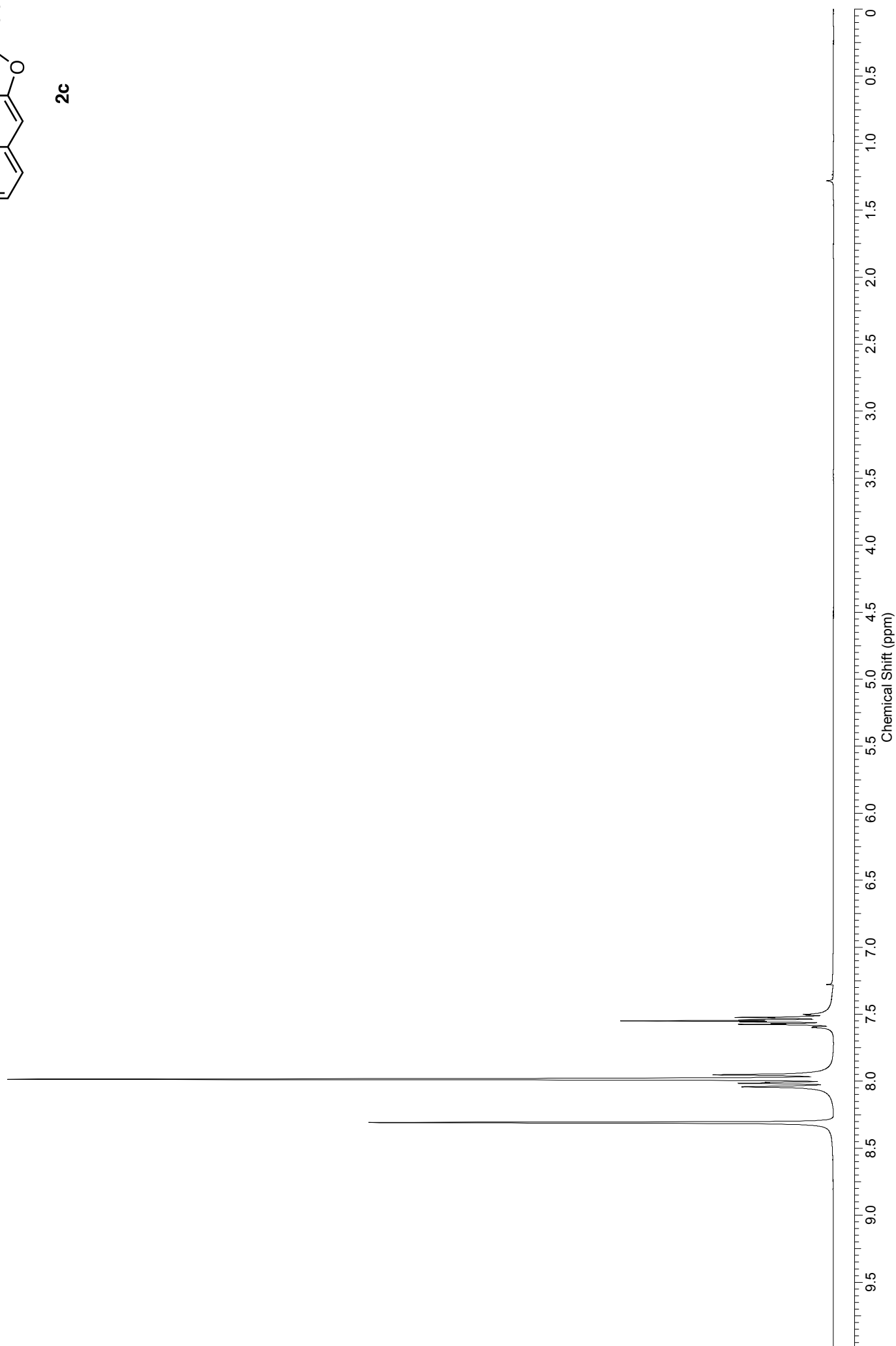


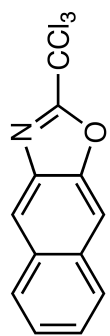
2b



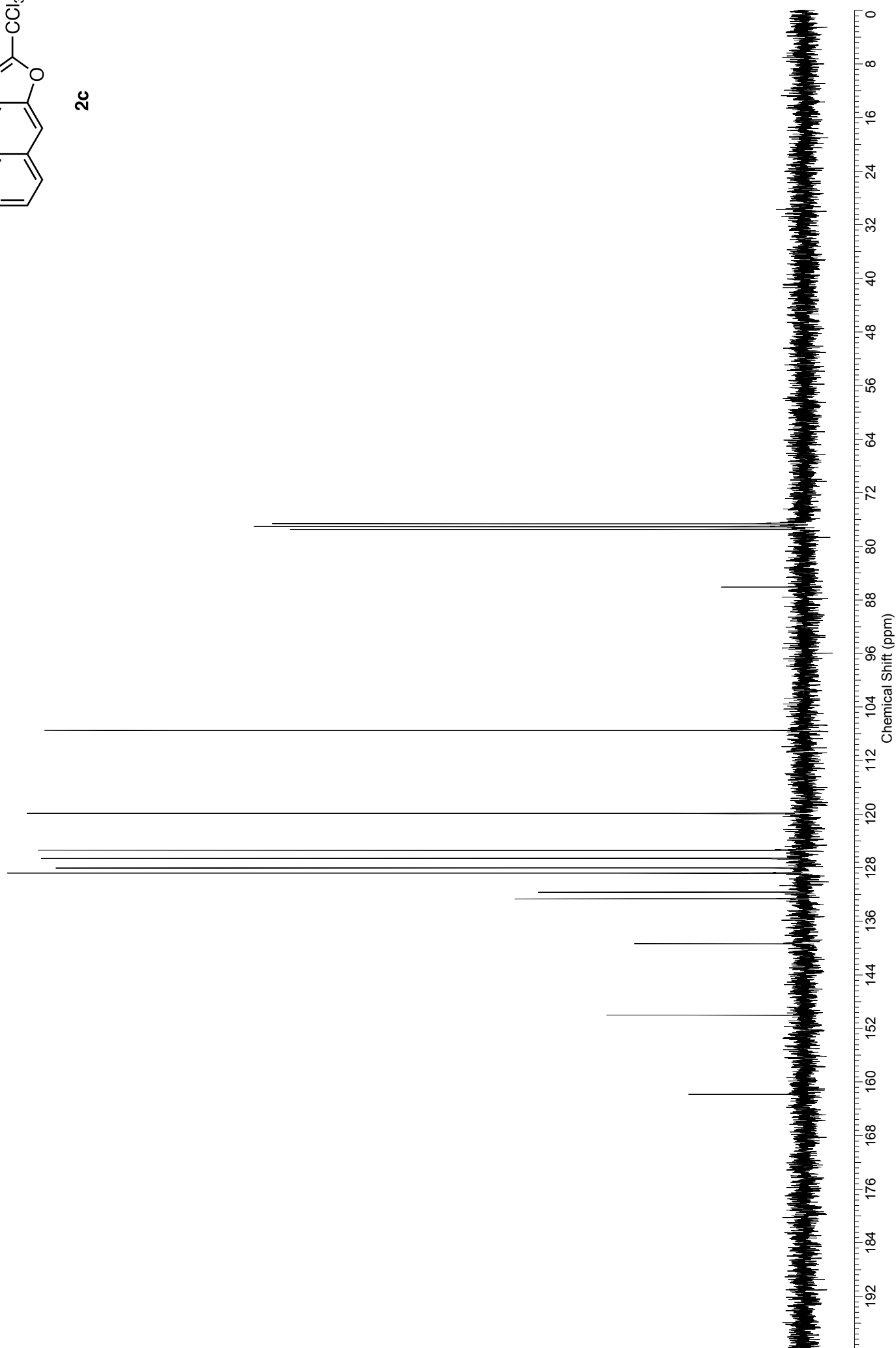


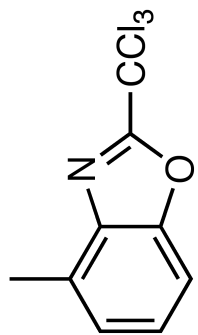
**2c**



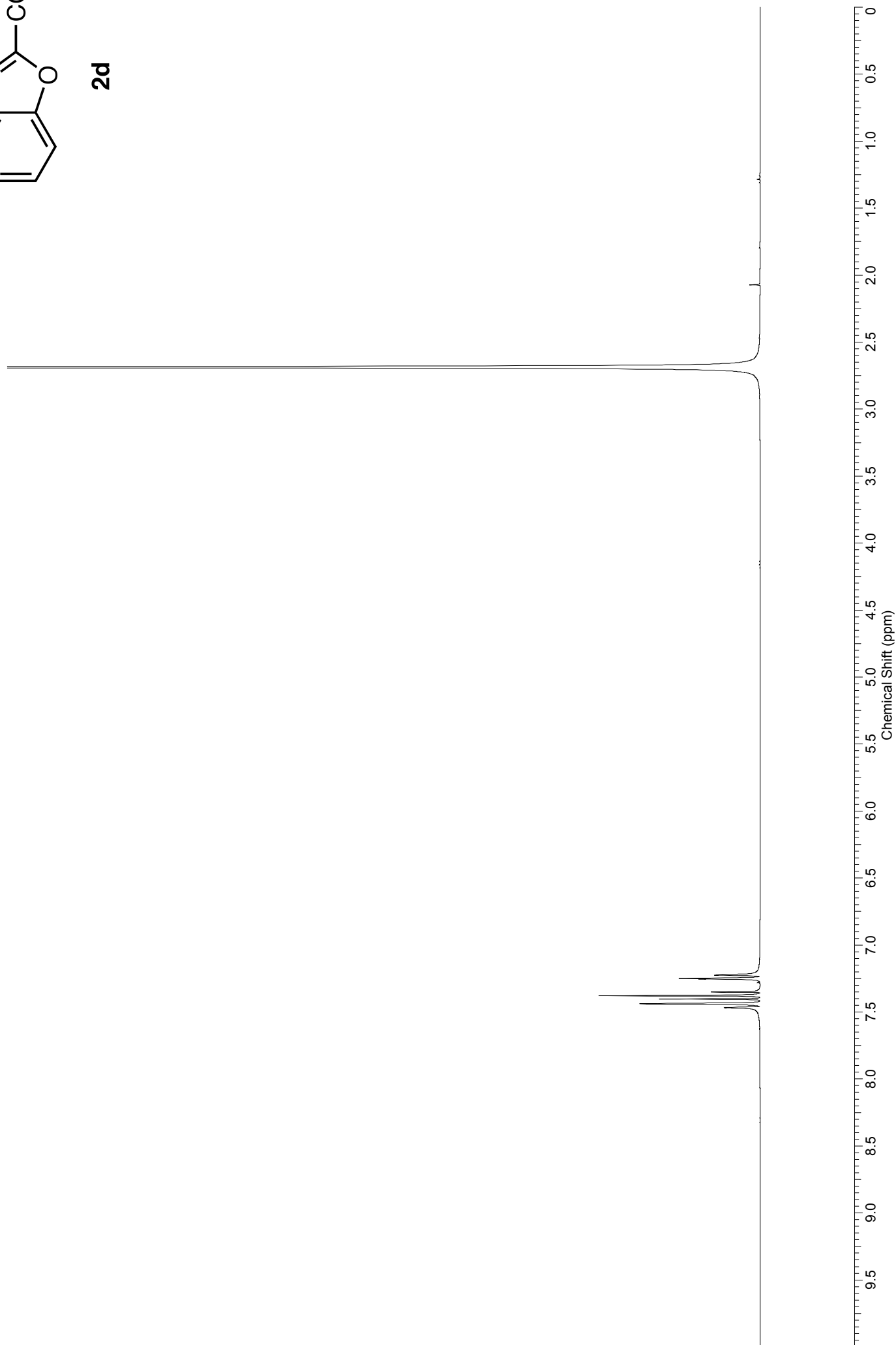


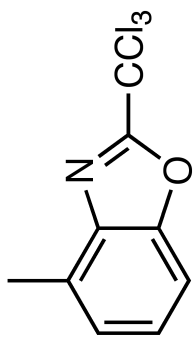
**2c**



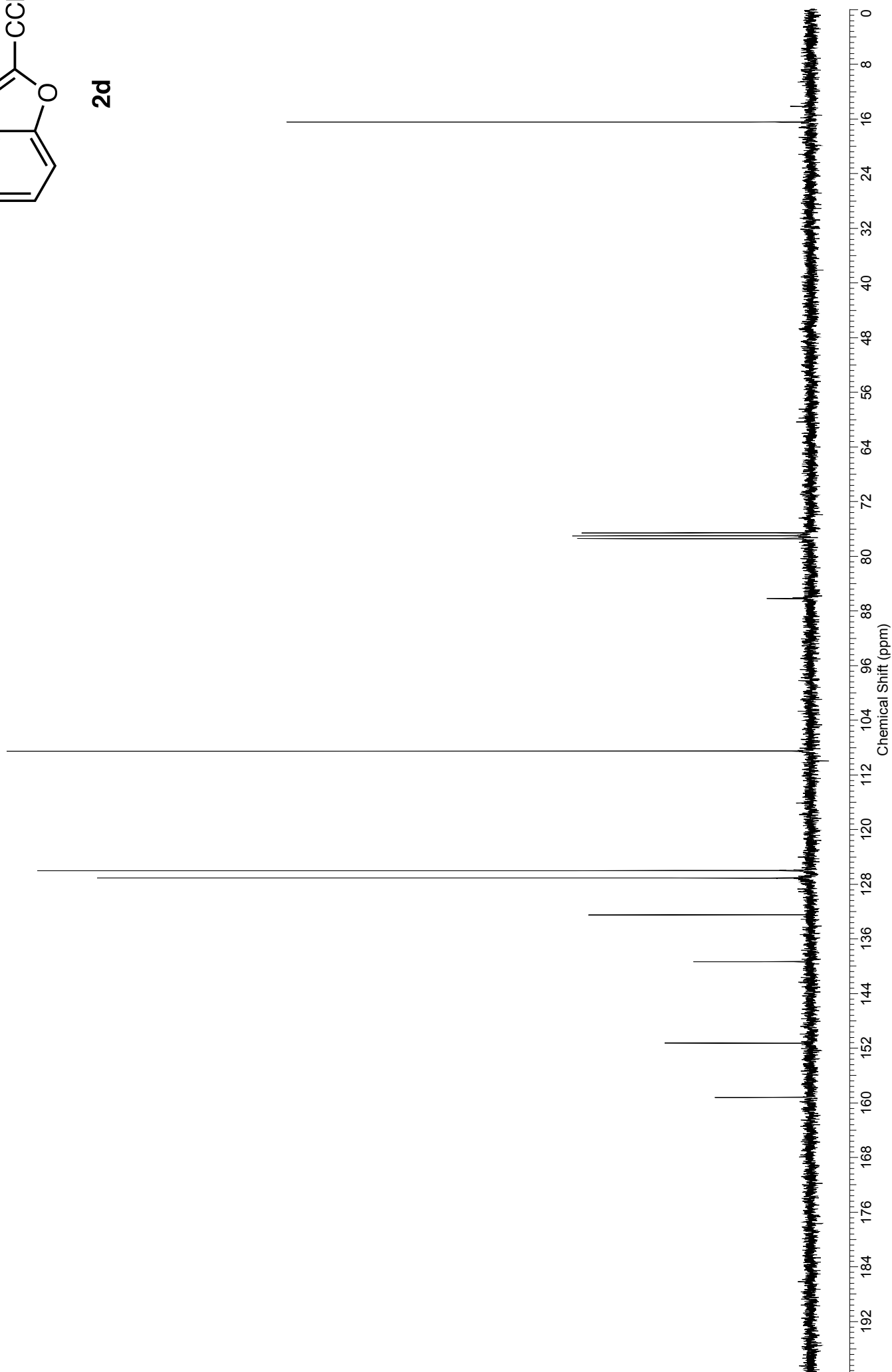


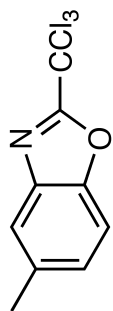
2d



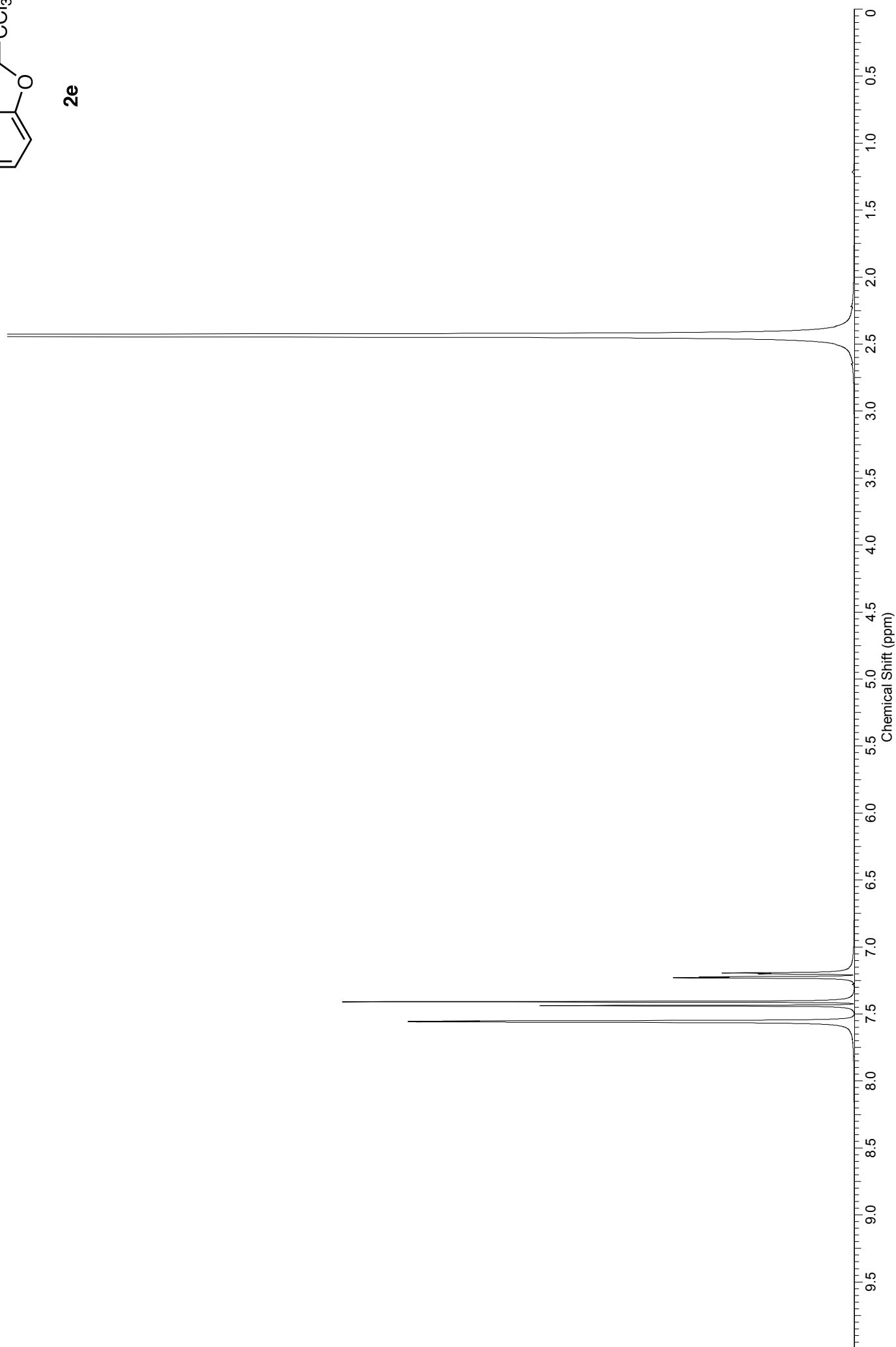


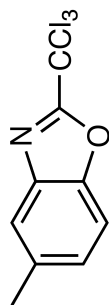
2d



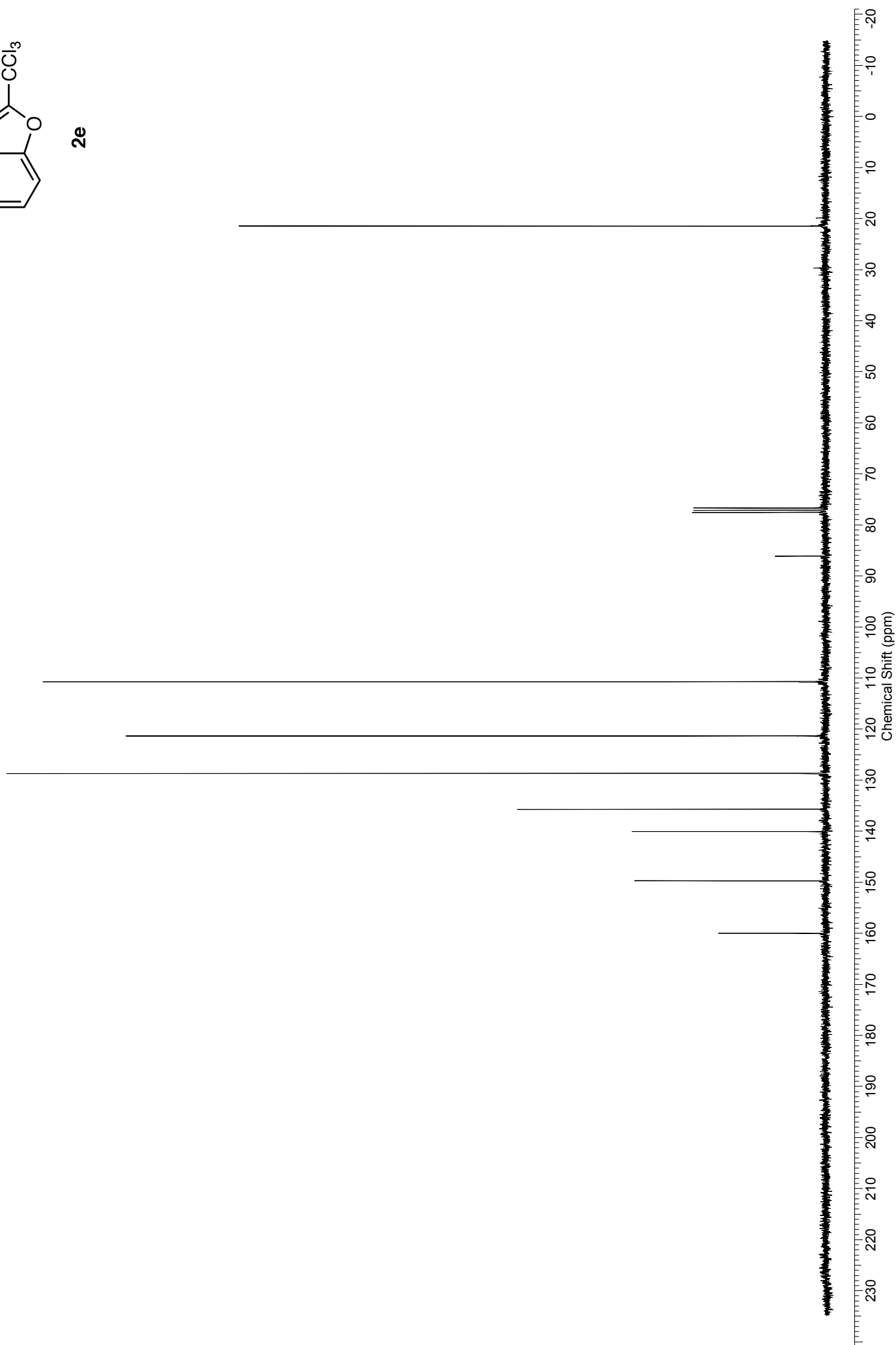


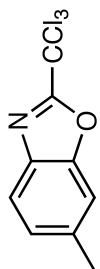
**2e**



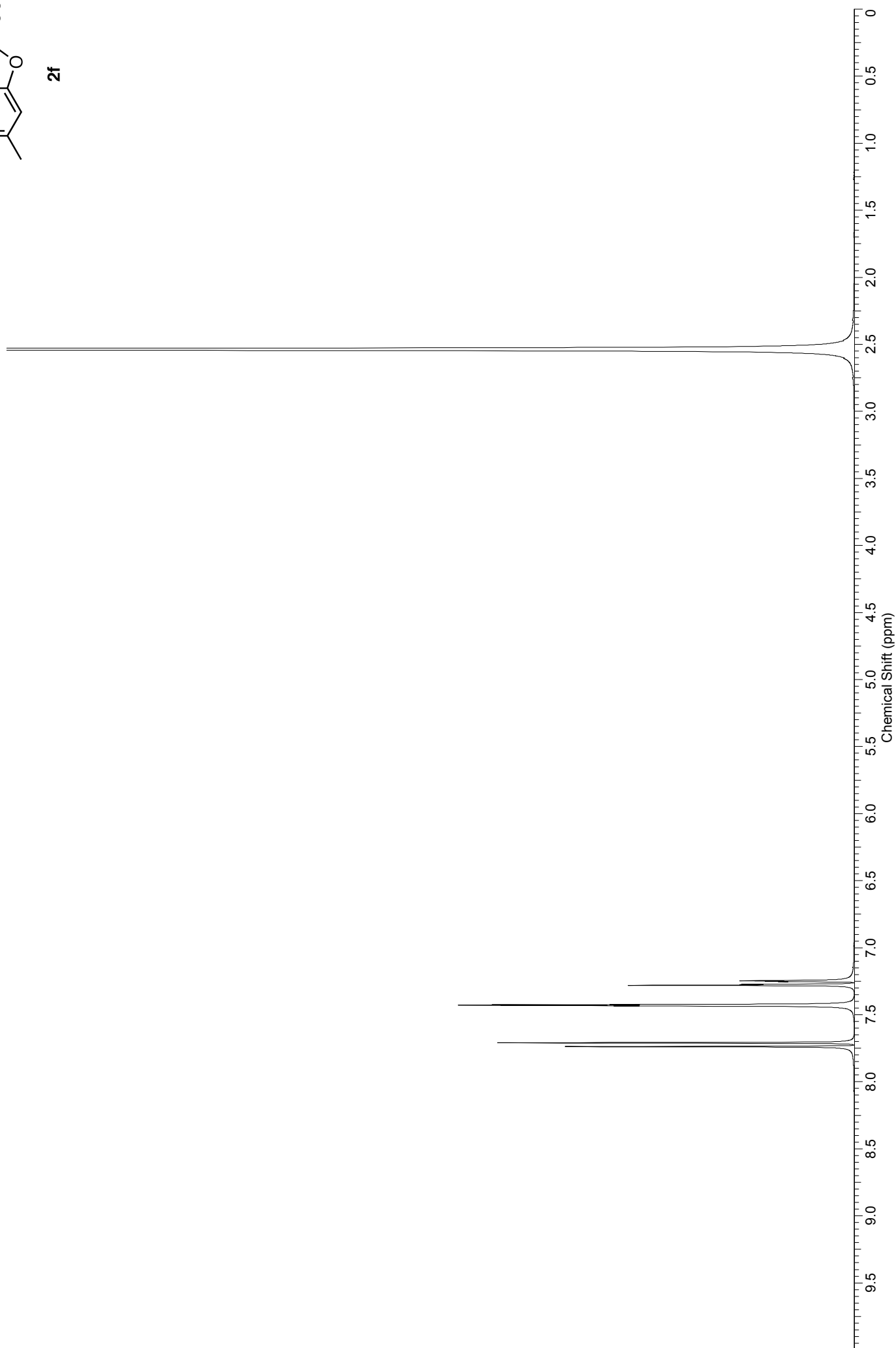


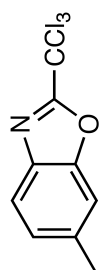
2e



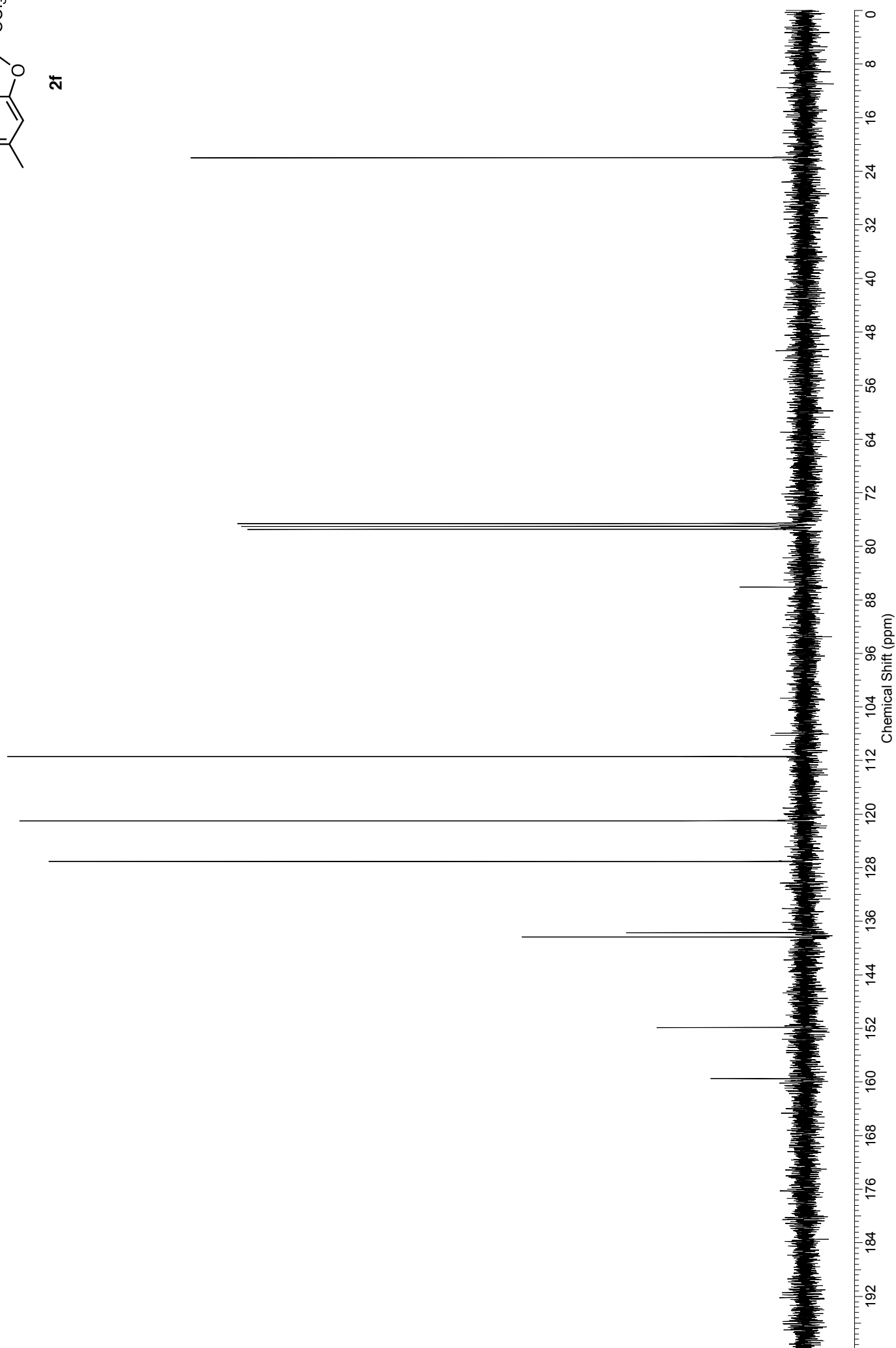


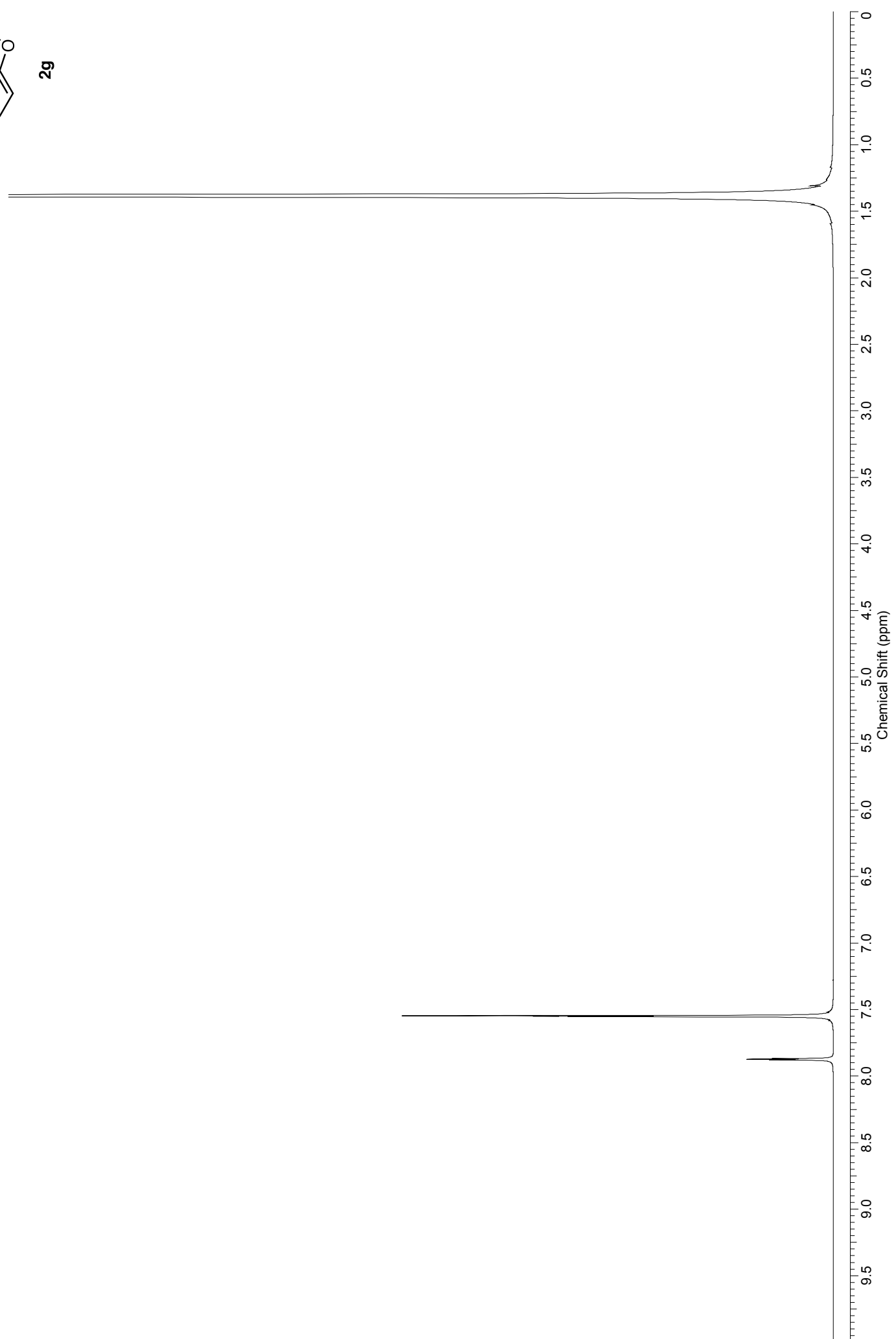
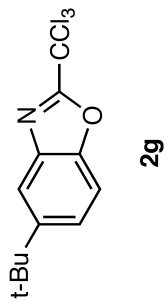
2f

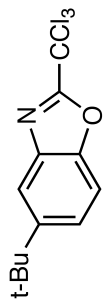




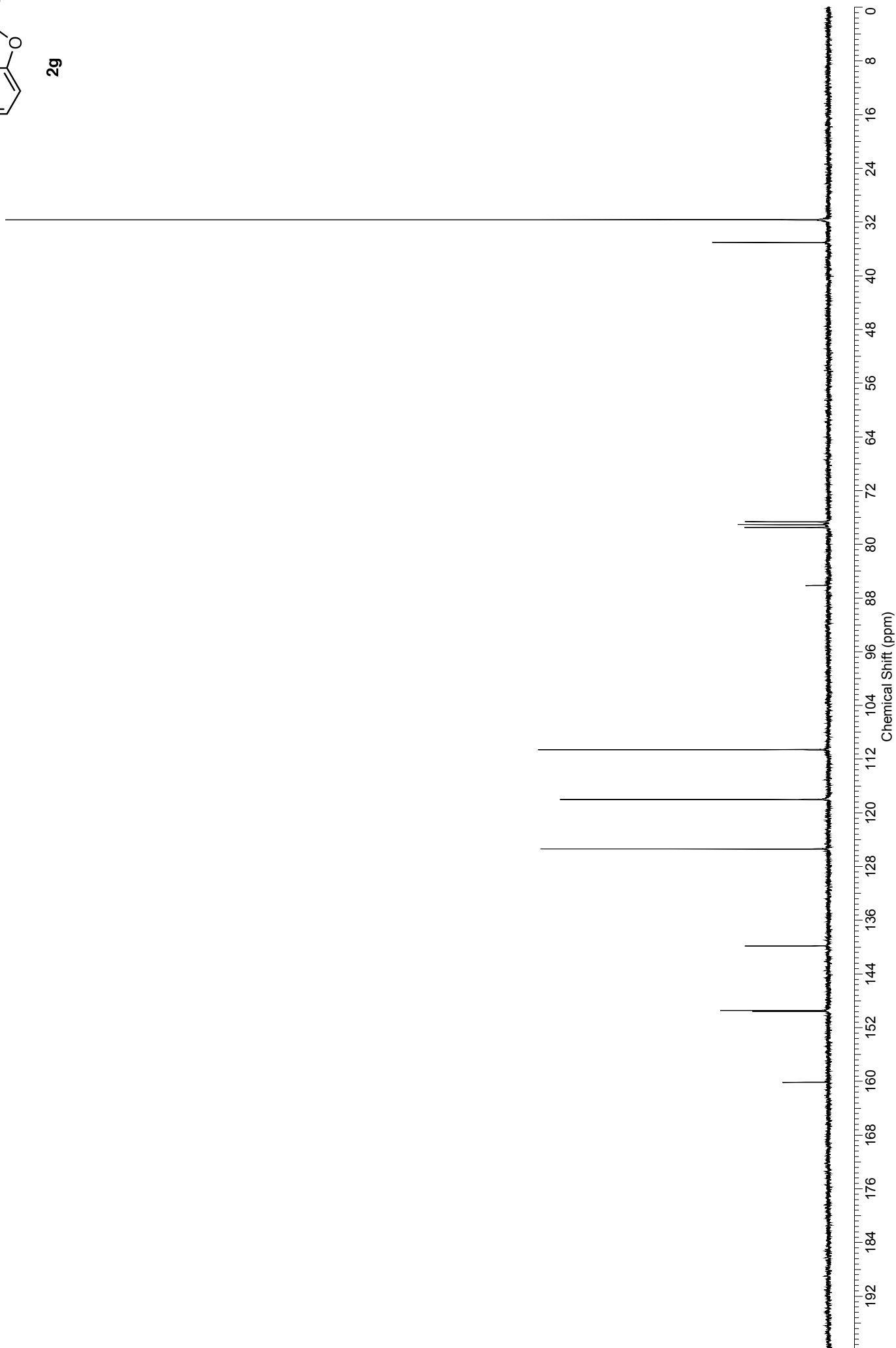
2f

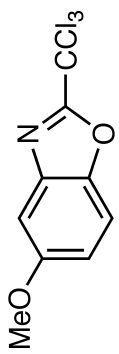




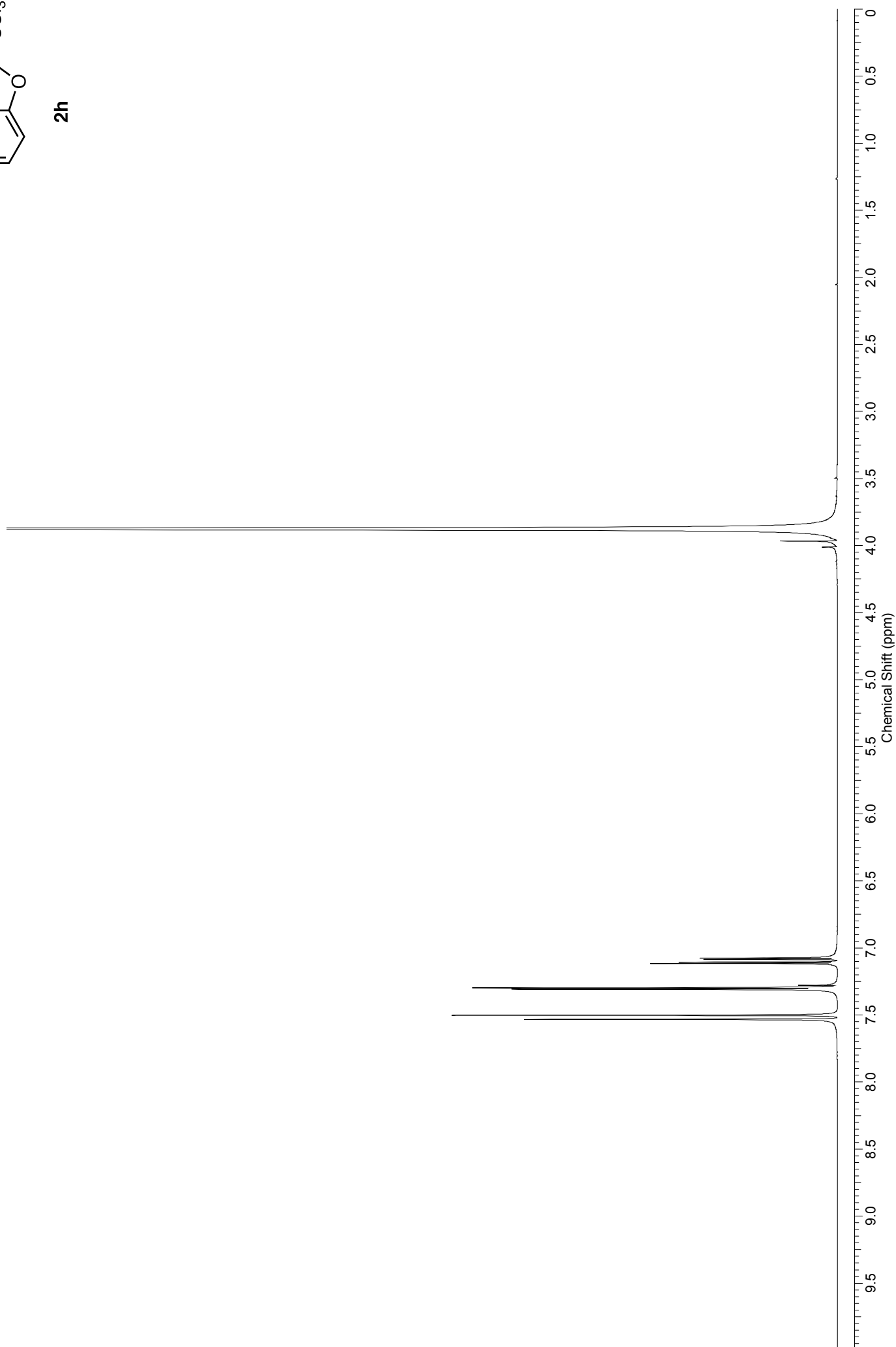


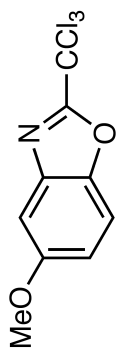
2g



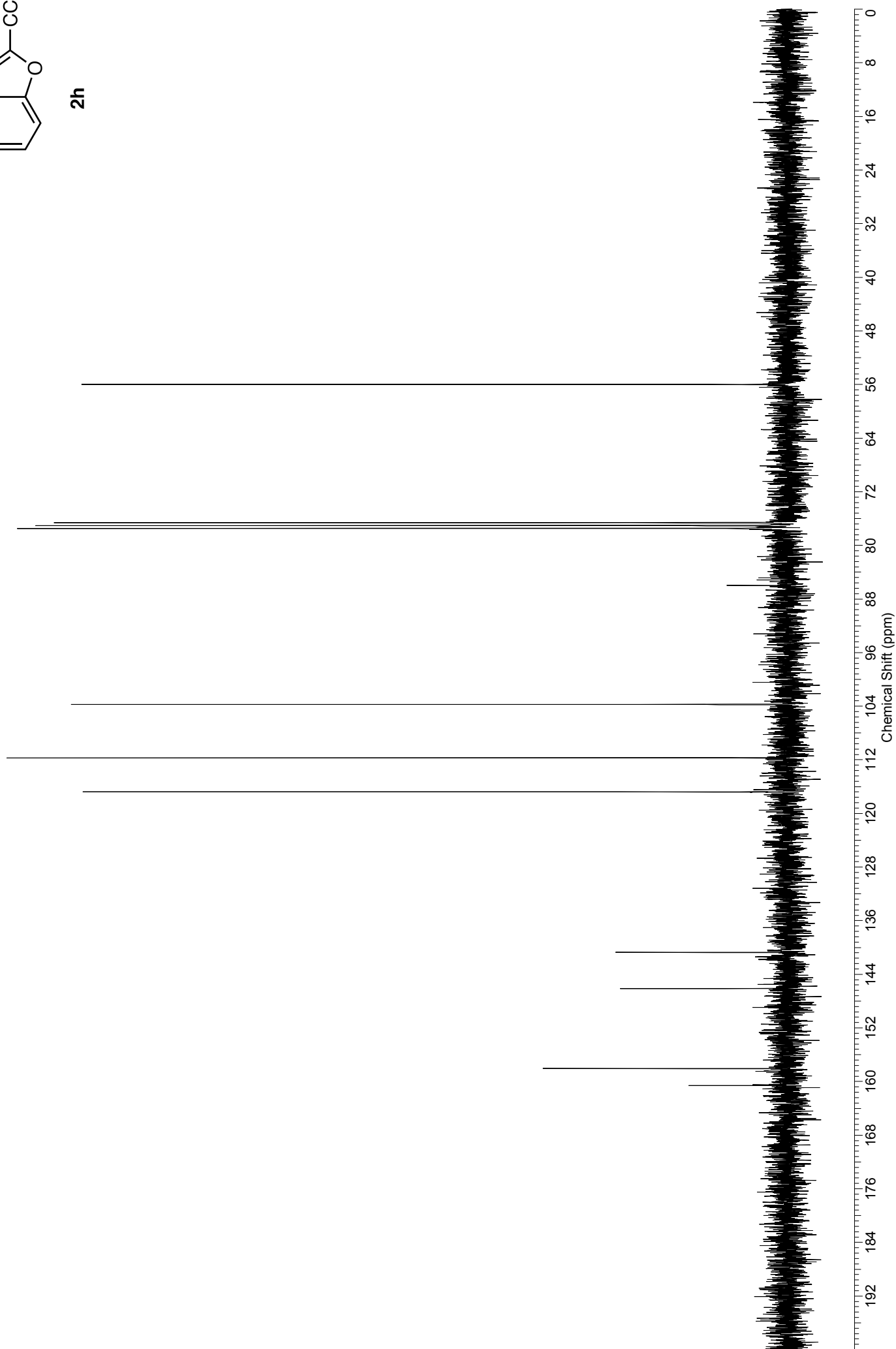


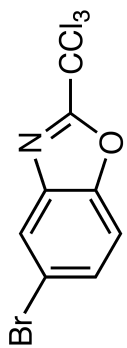
2h



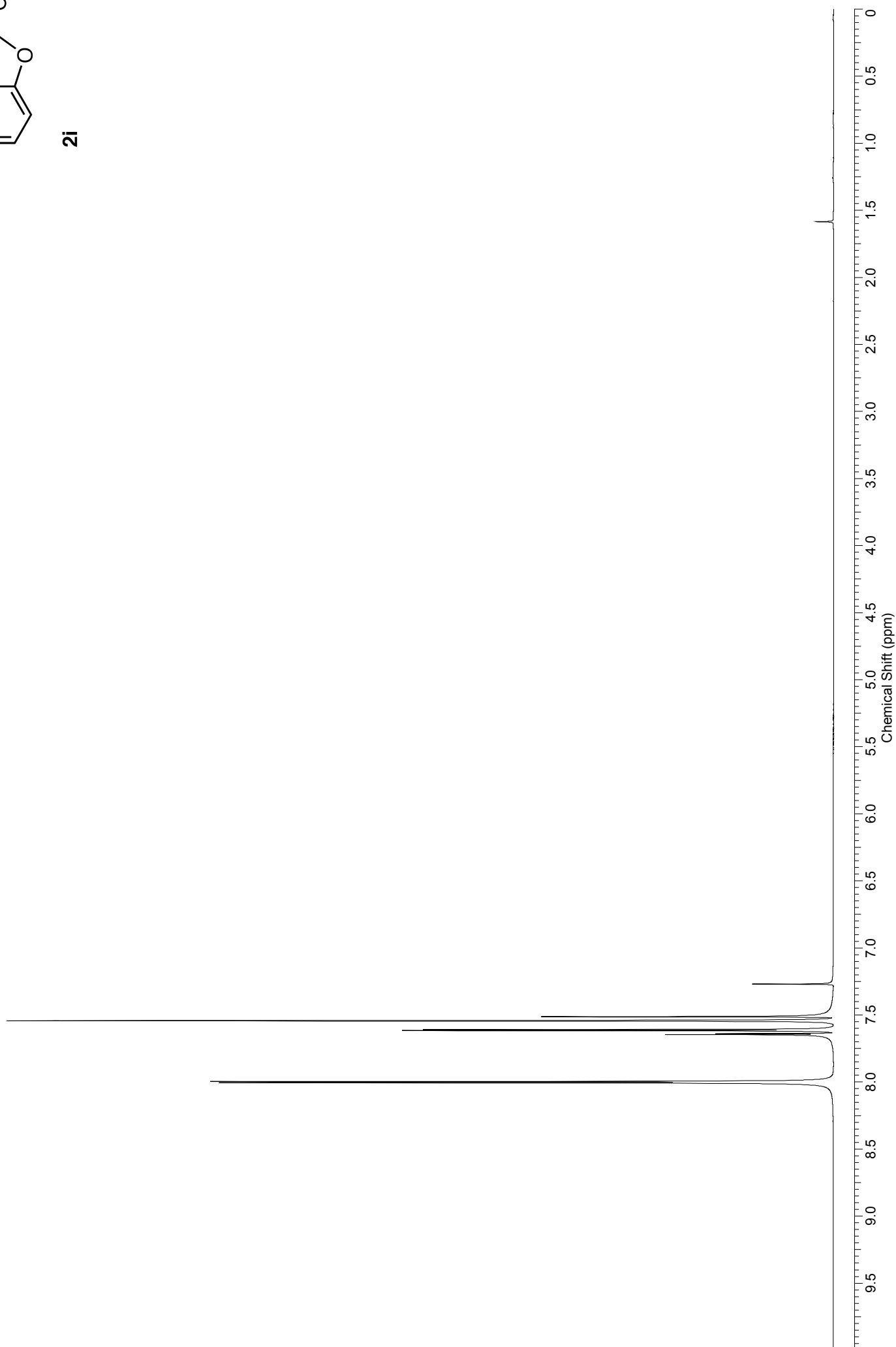


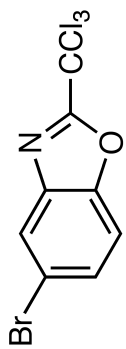
2h



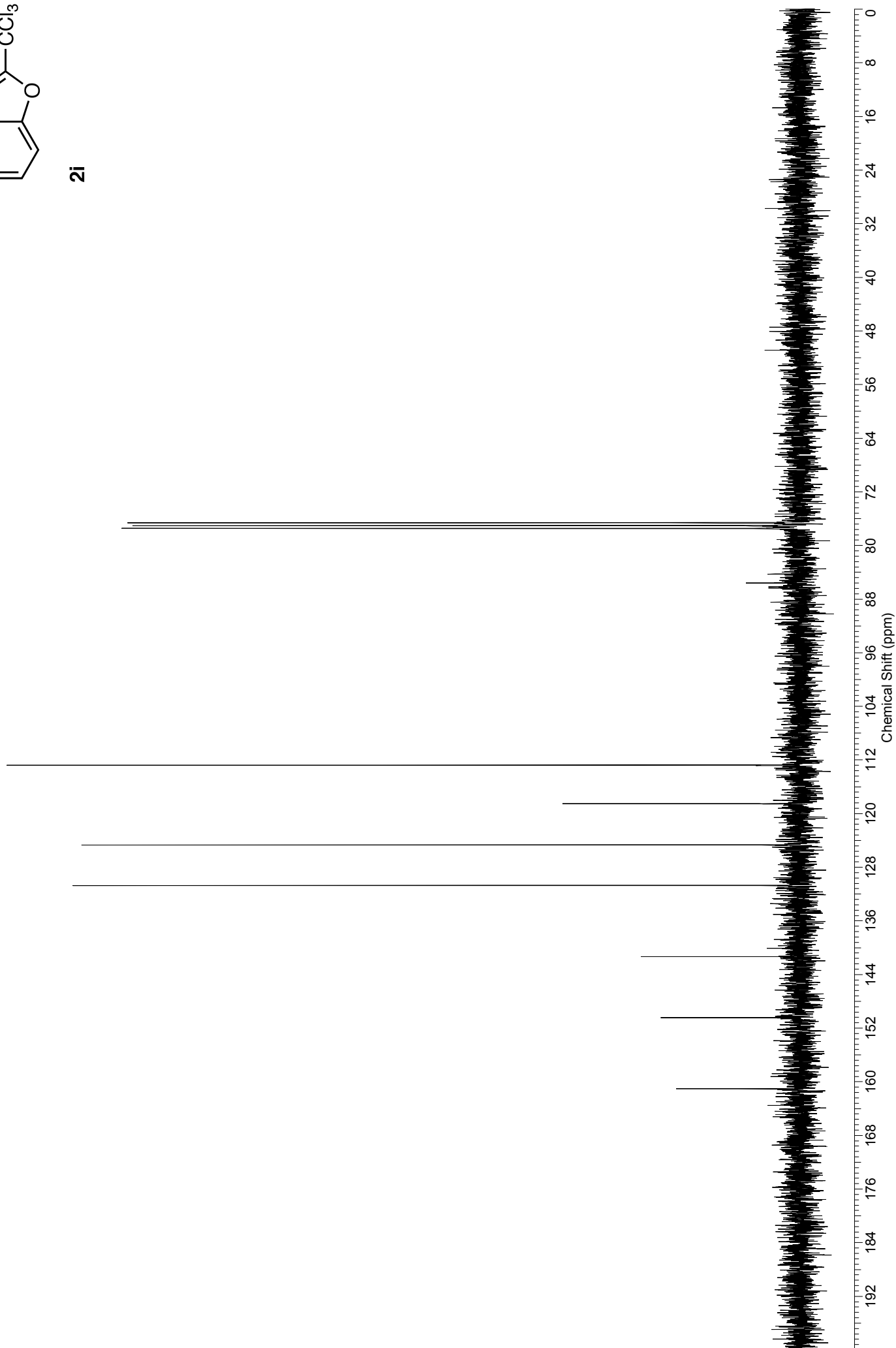


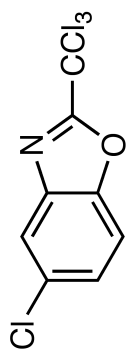
2i



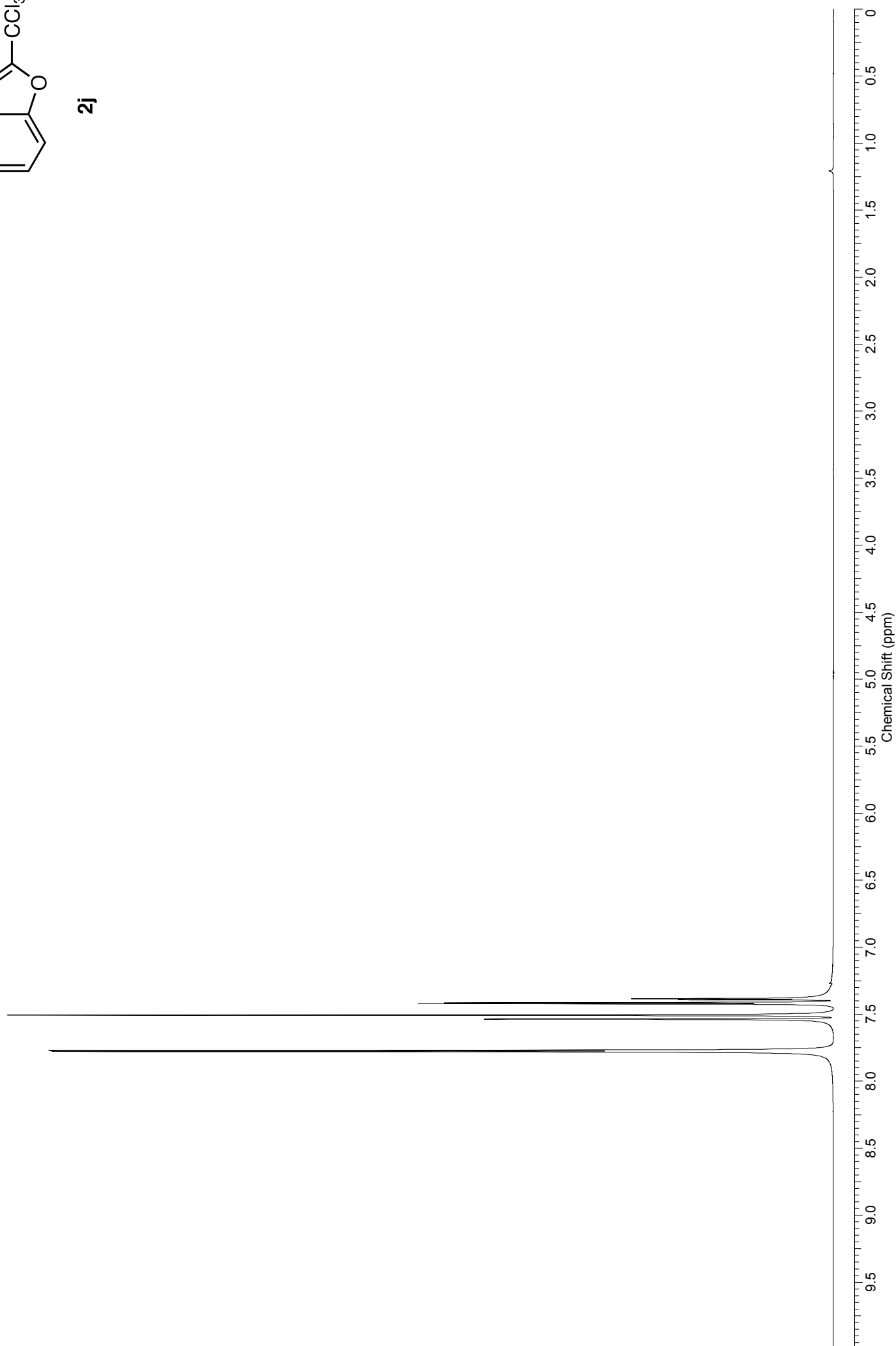


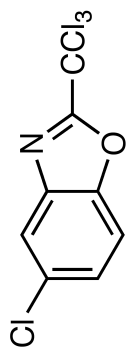
2i



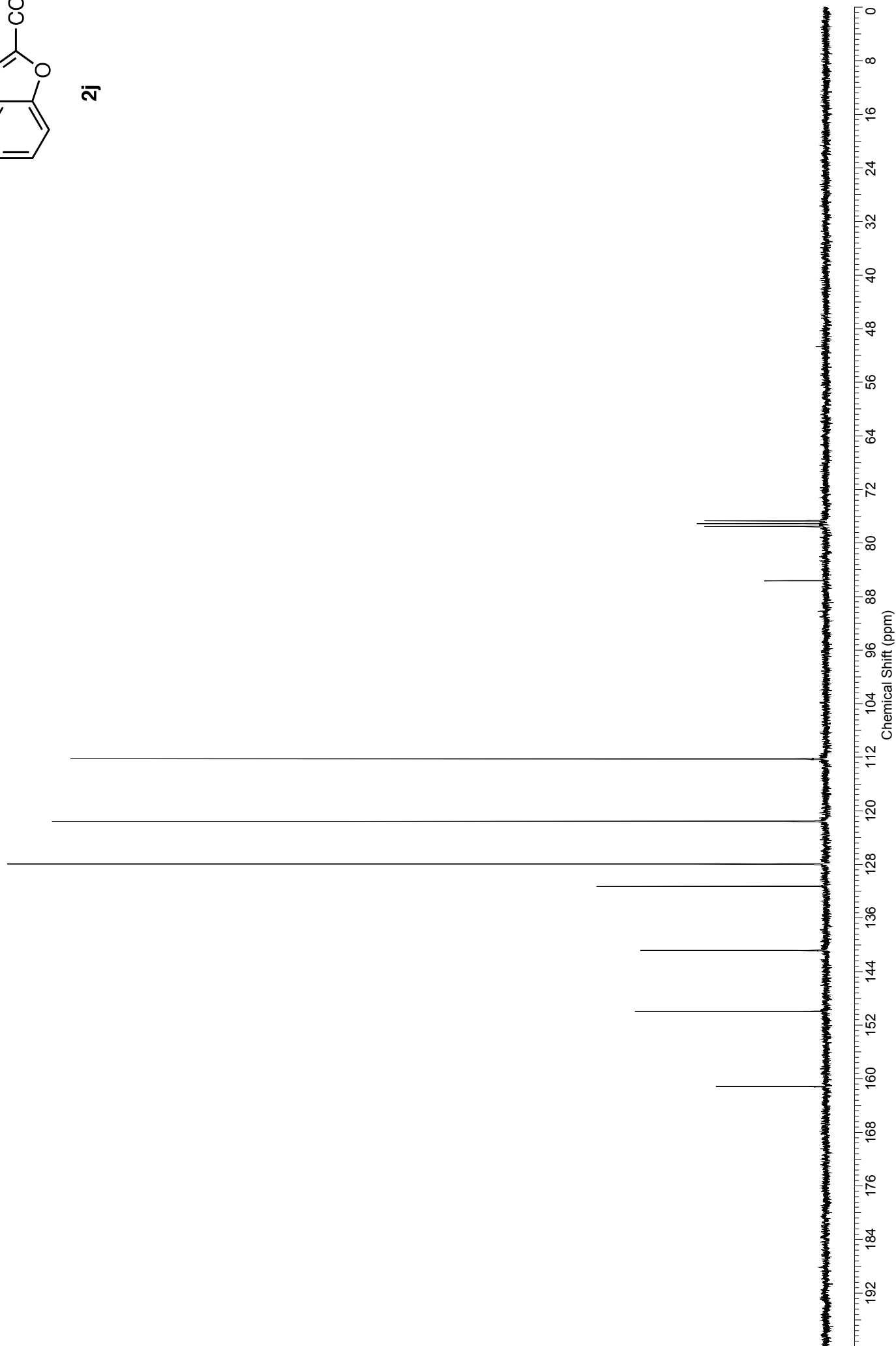


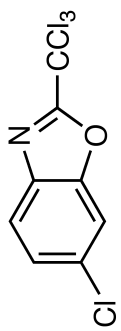
2j



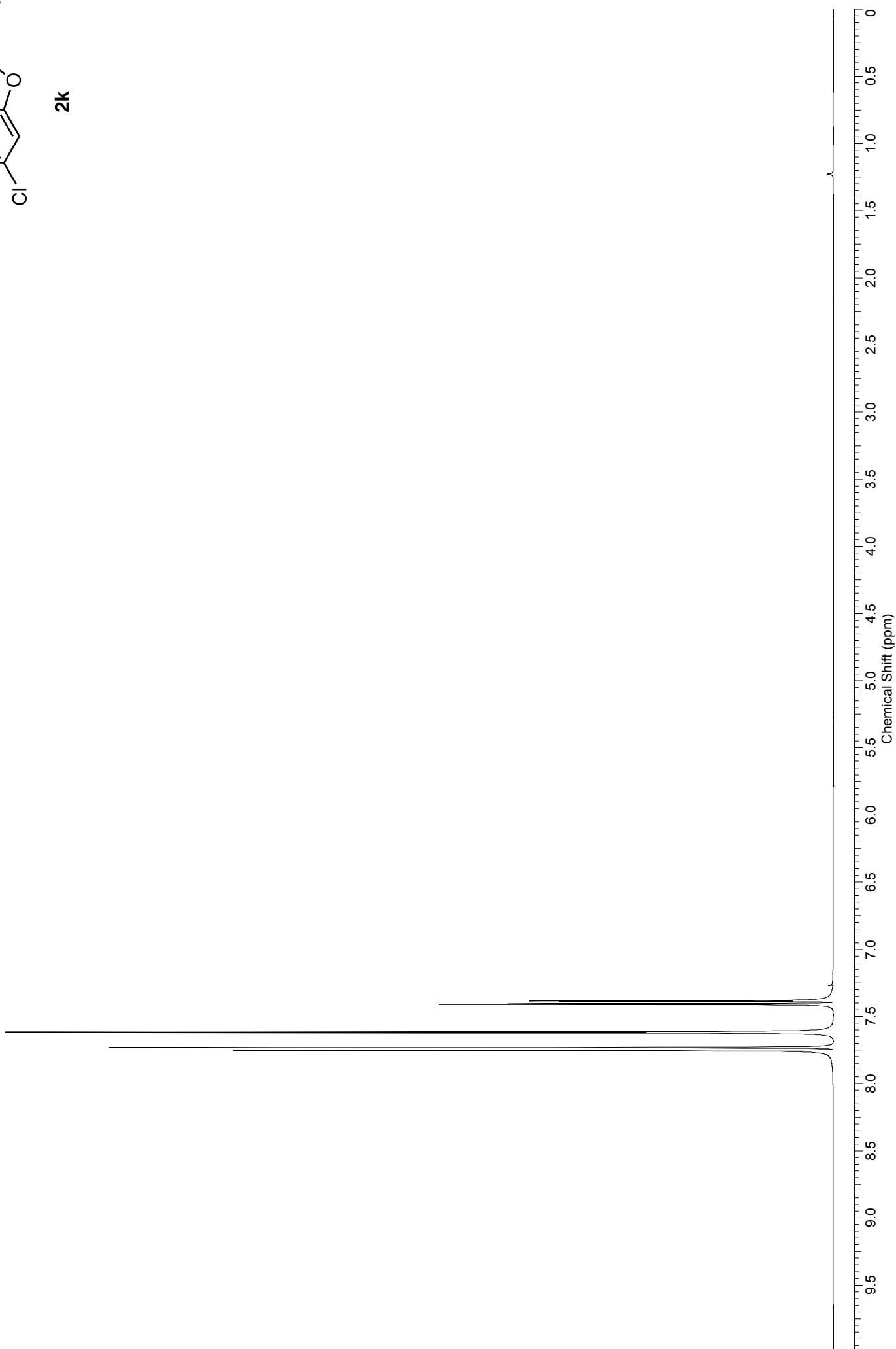


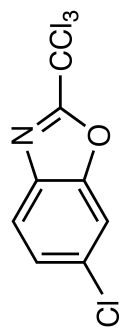
2j



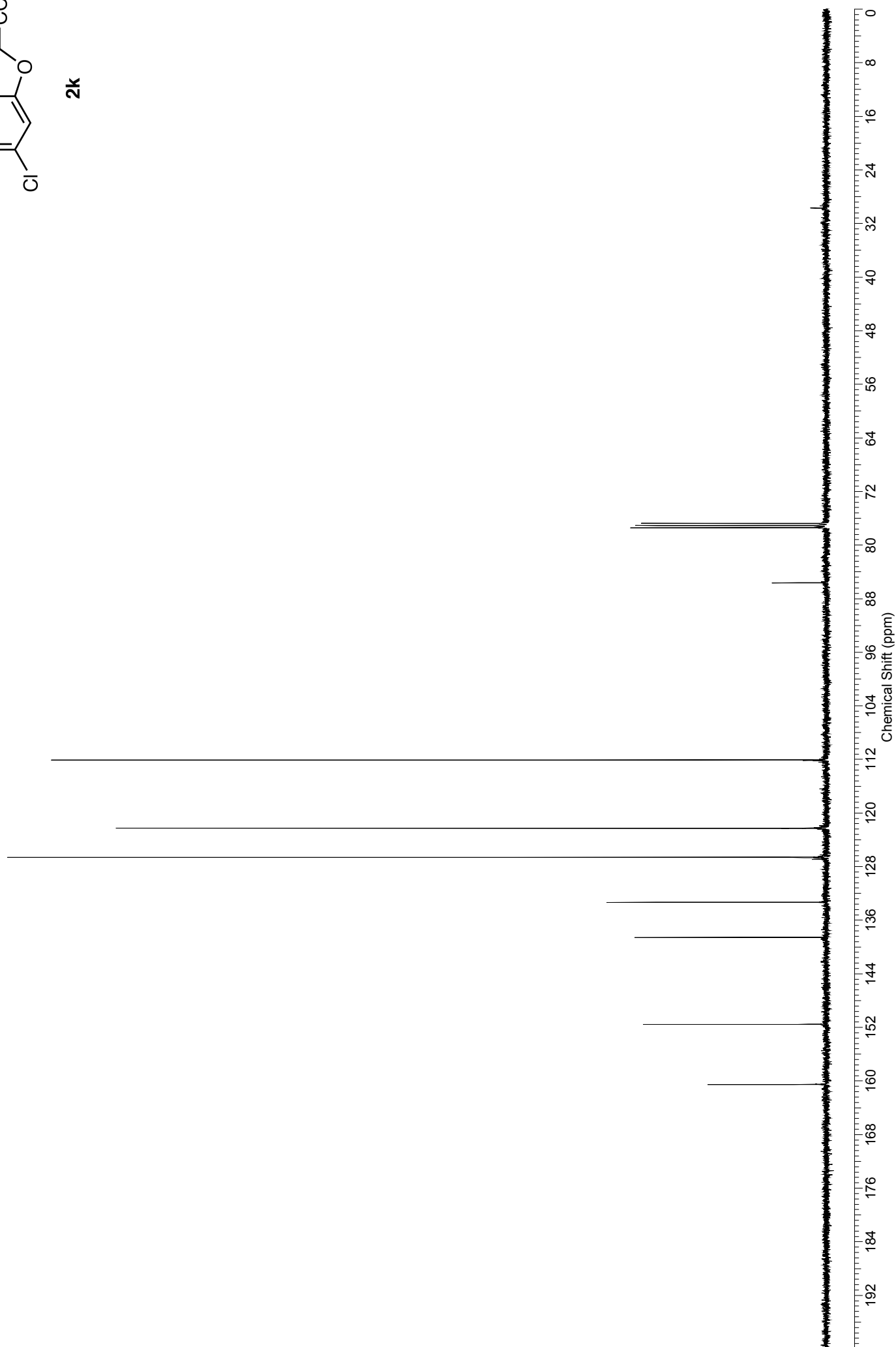


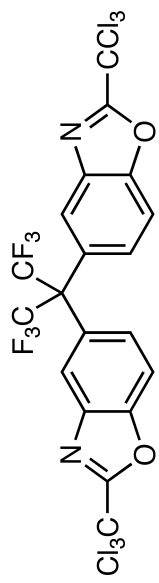
2k



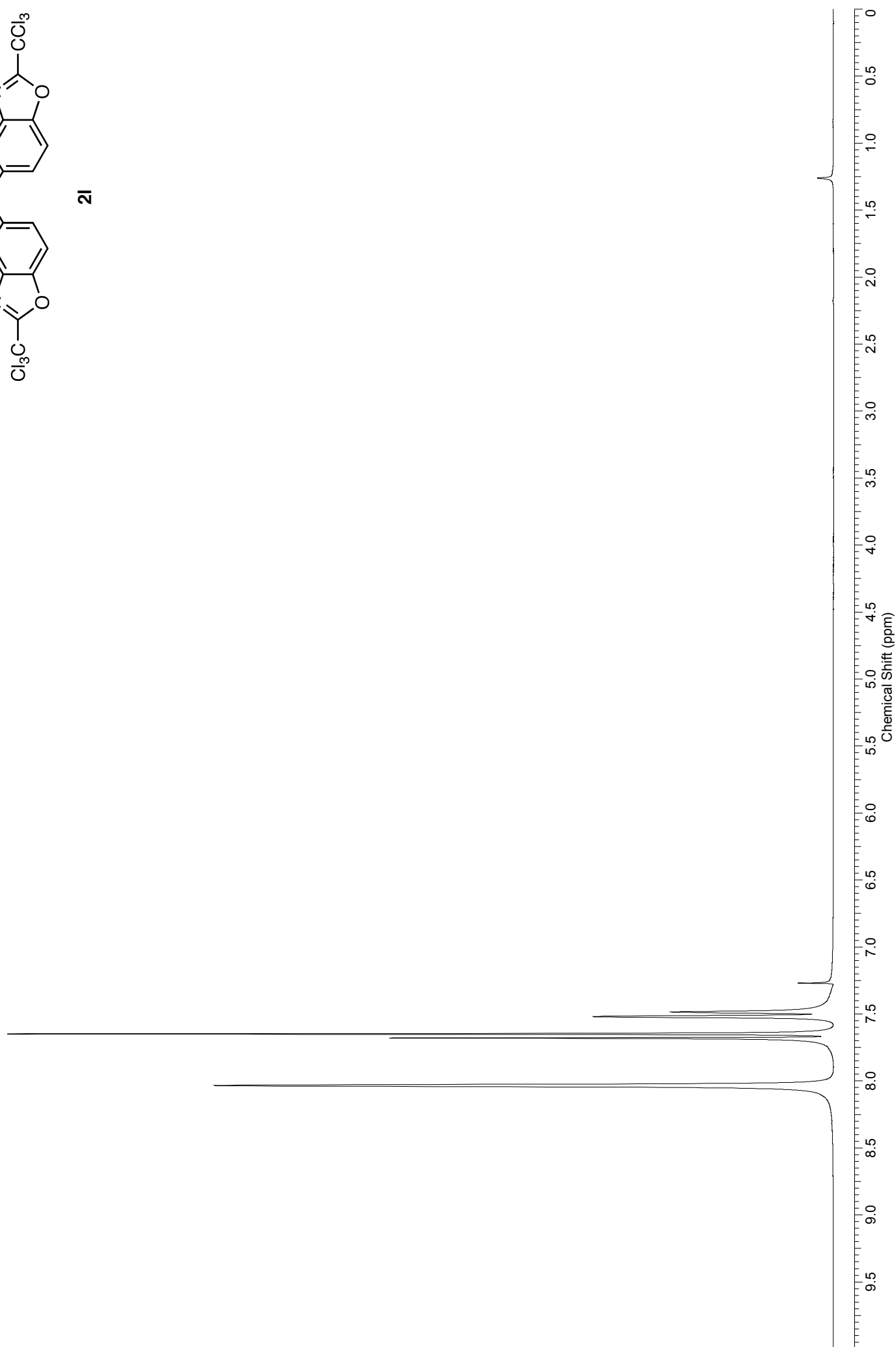


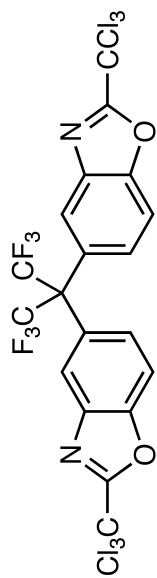
2k



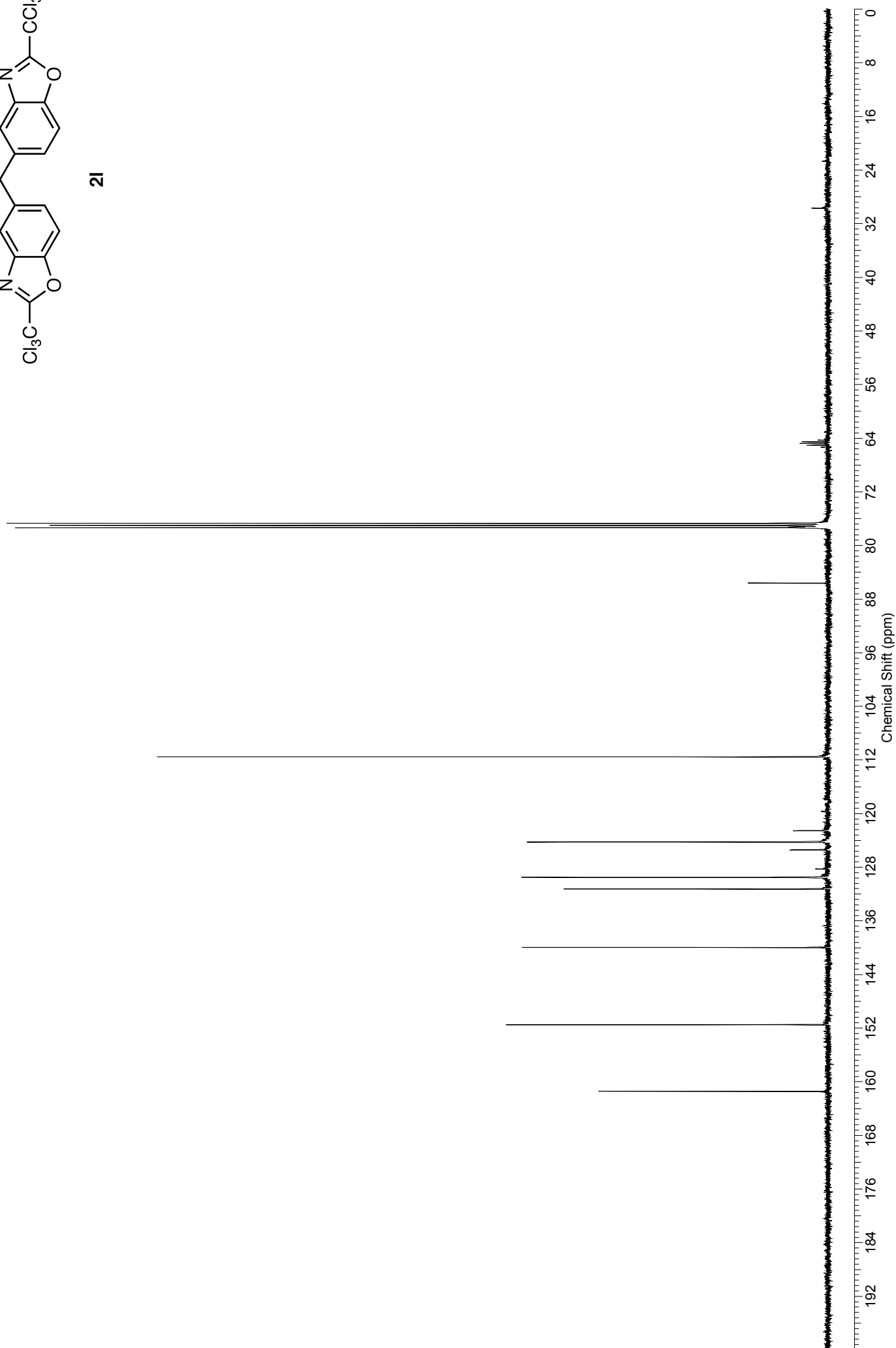


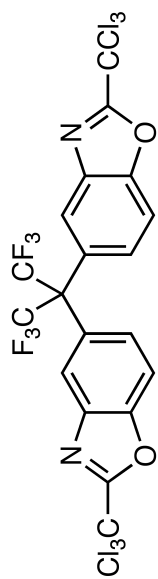
21



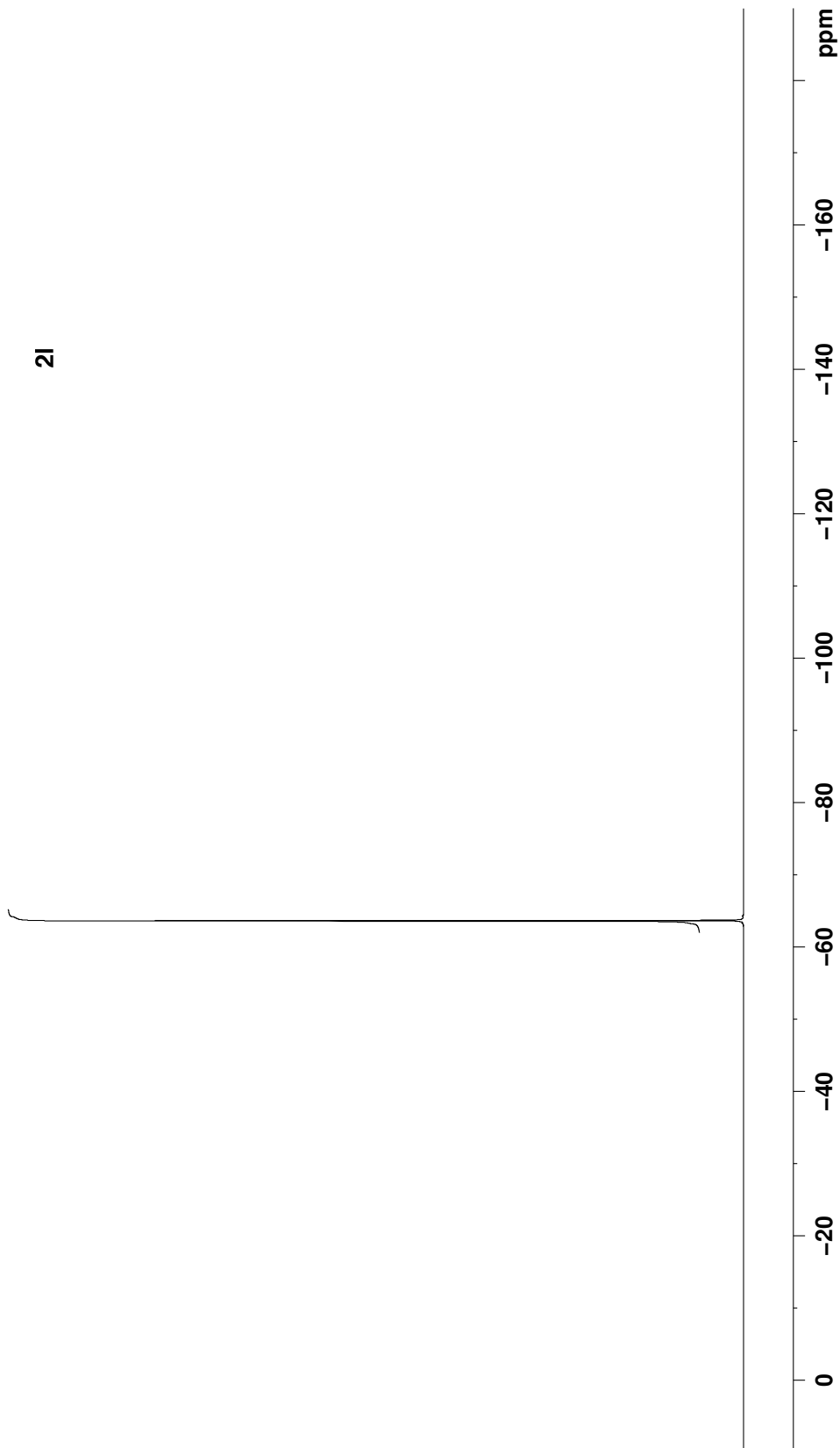


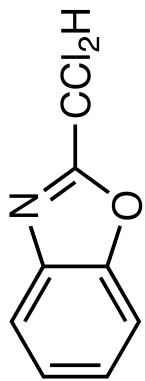
21



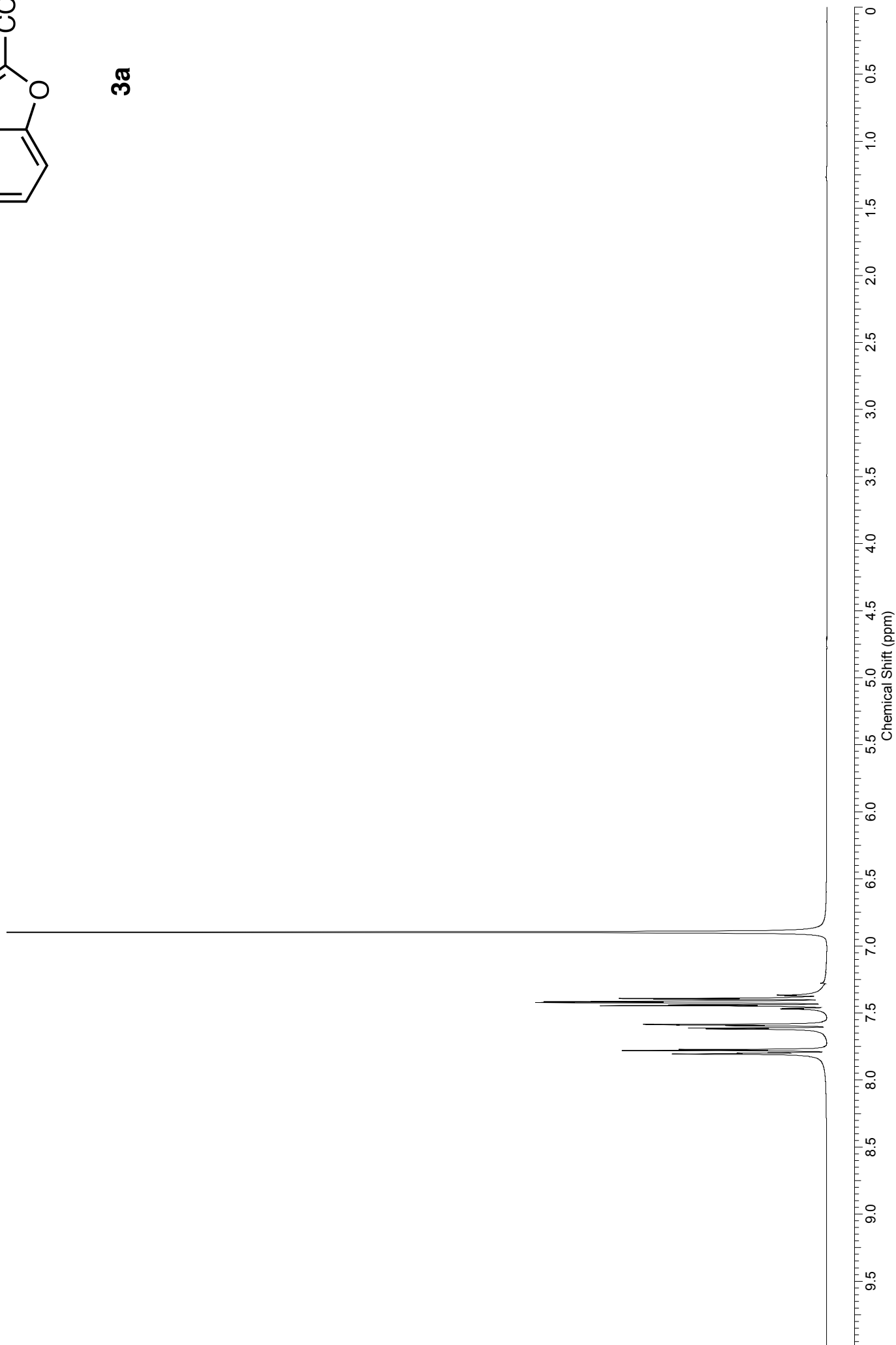


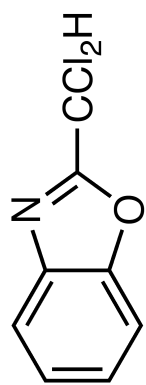
21



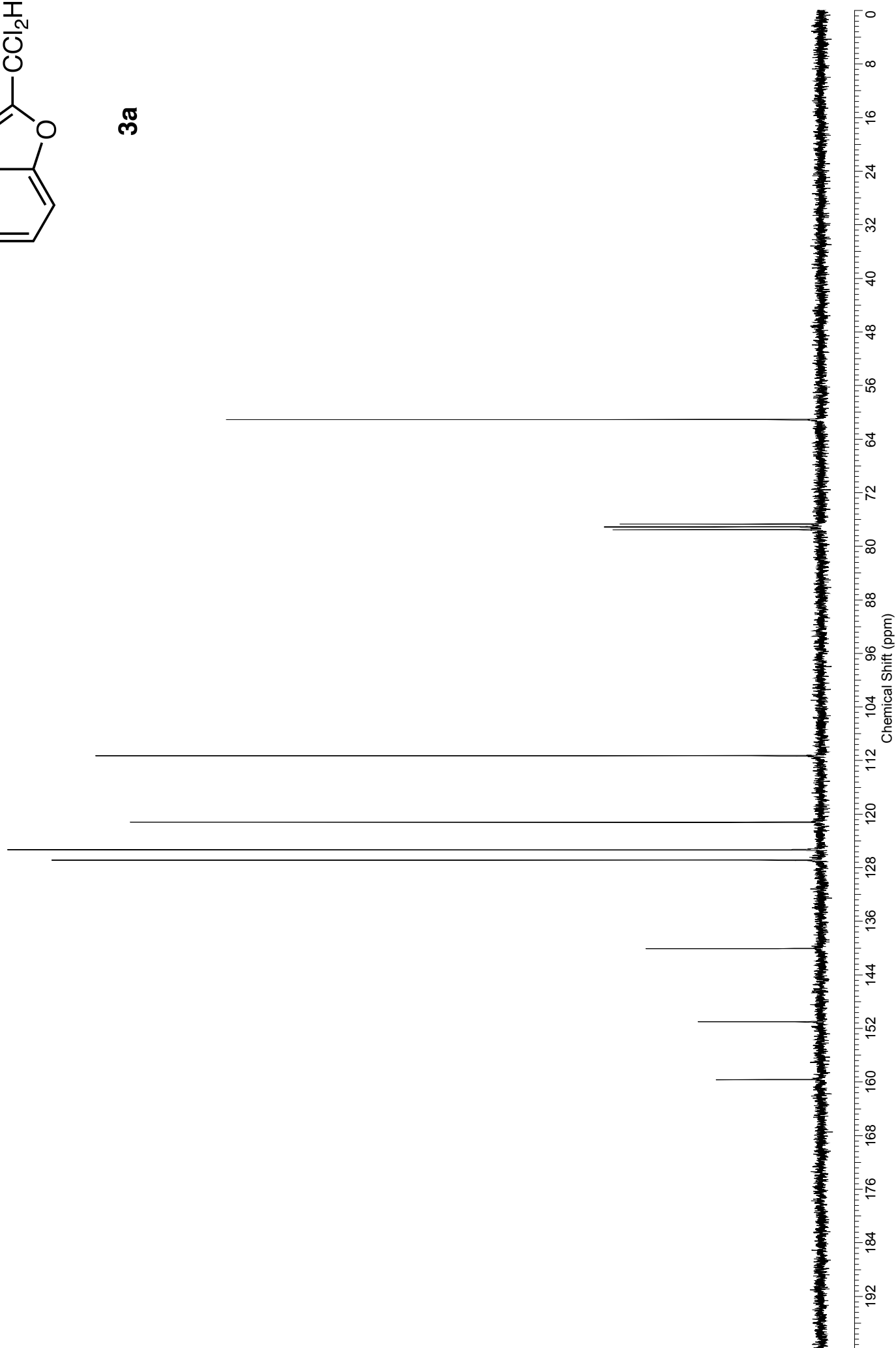


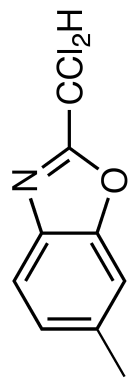
**3a**



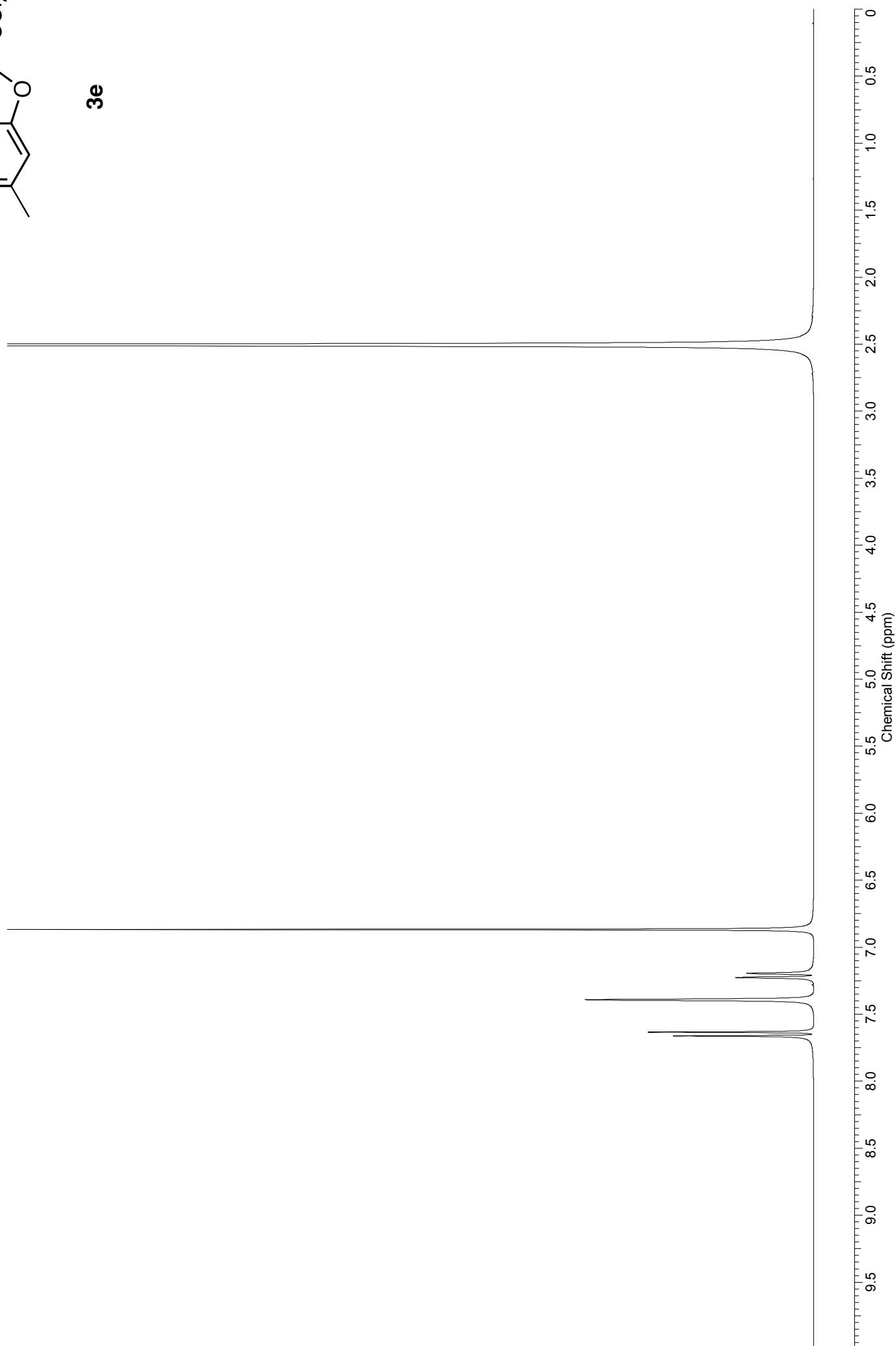


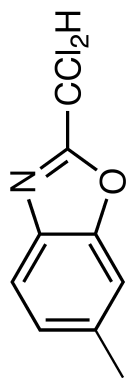
**3a**



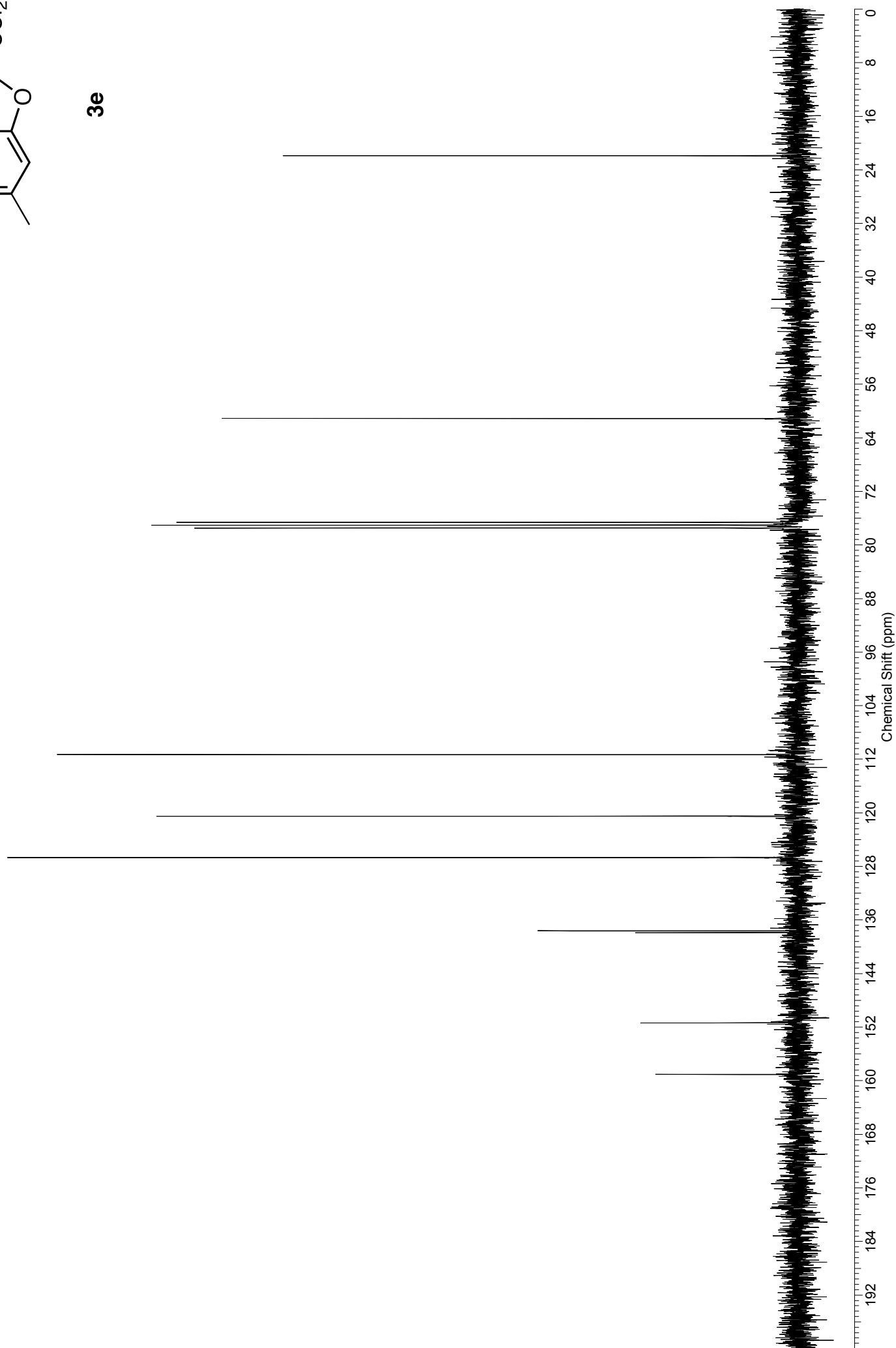


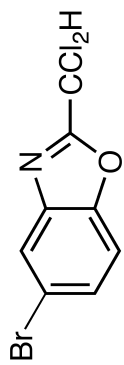
3e



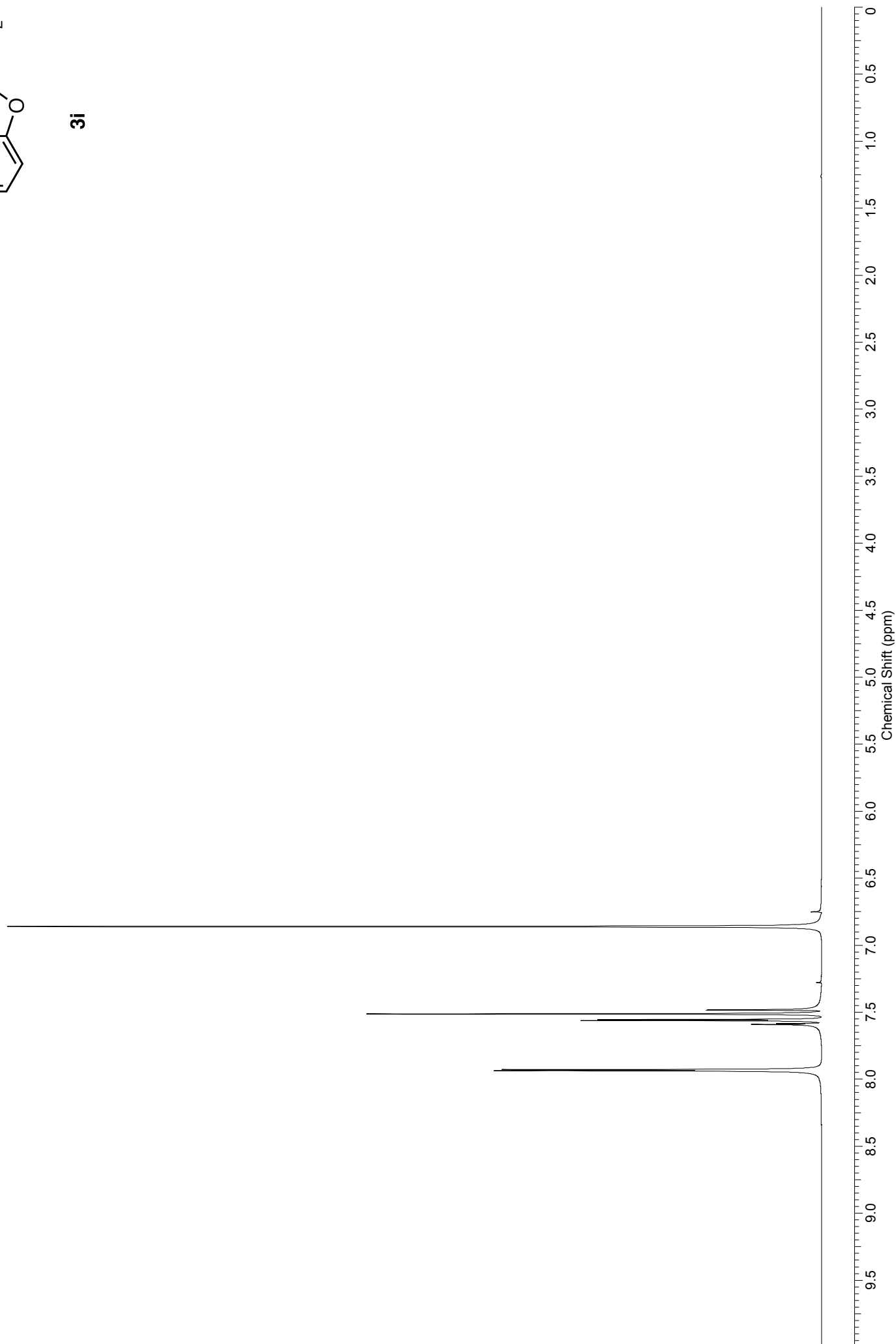


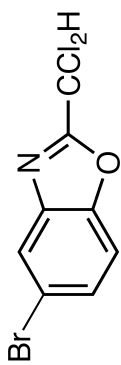
3e



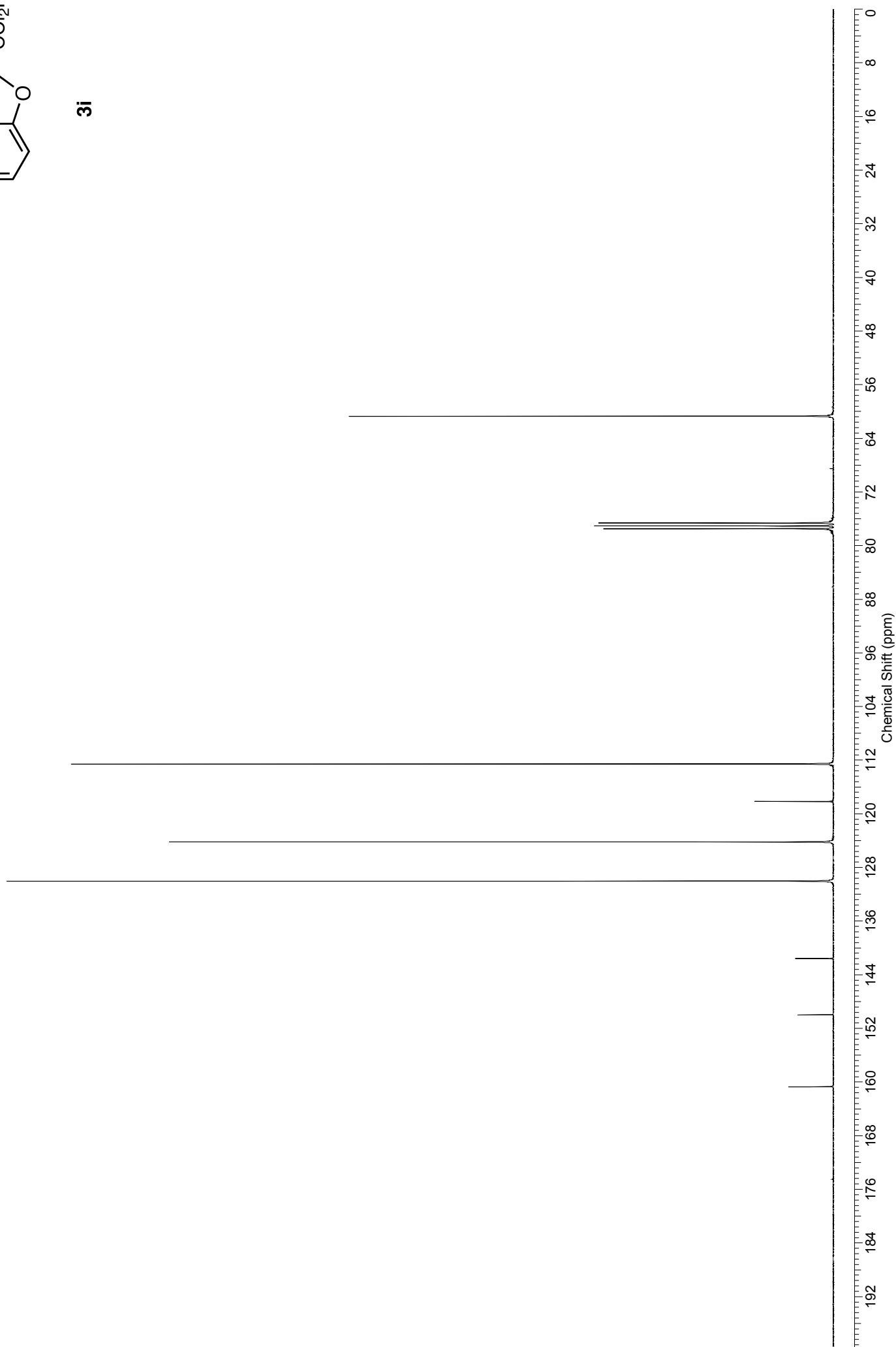


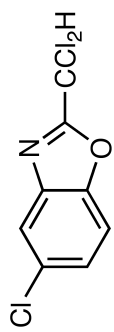
3i



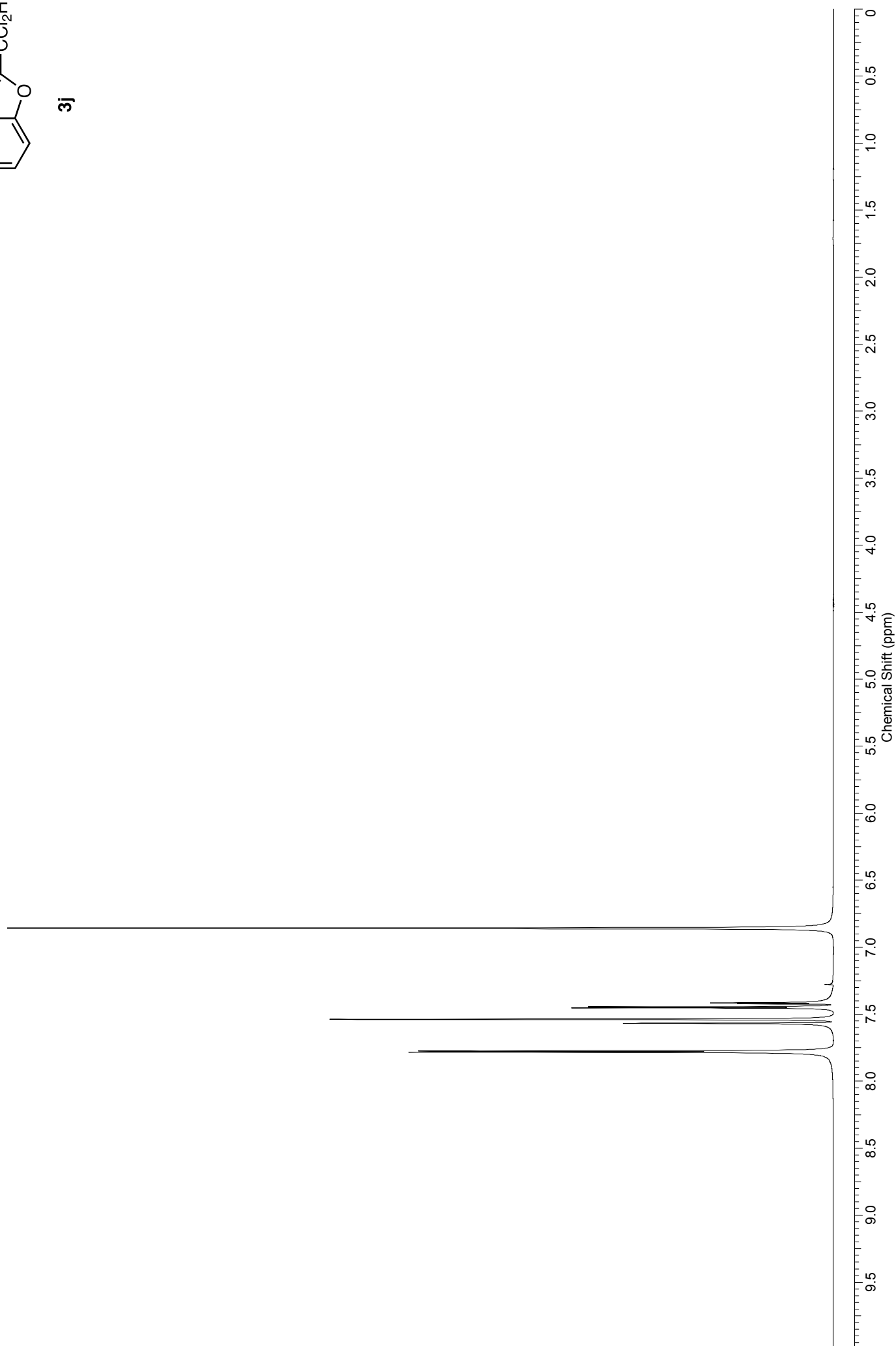


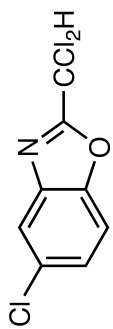
3i



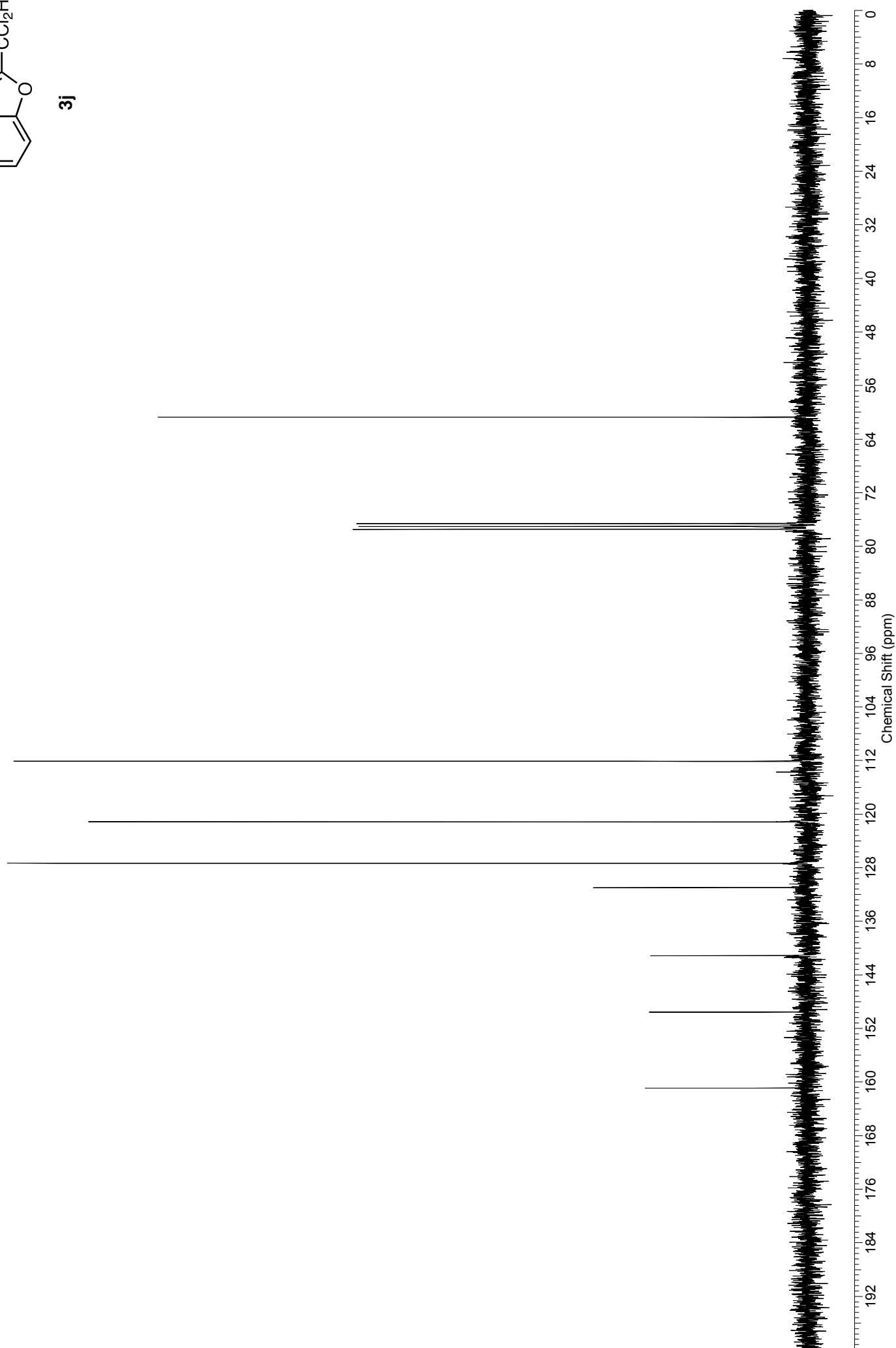


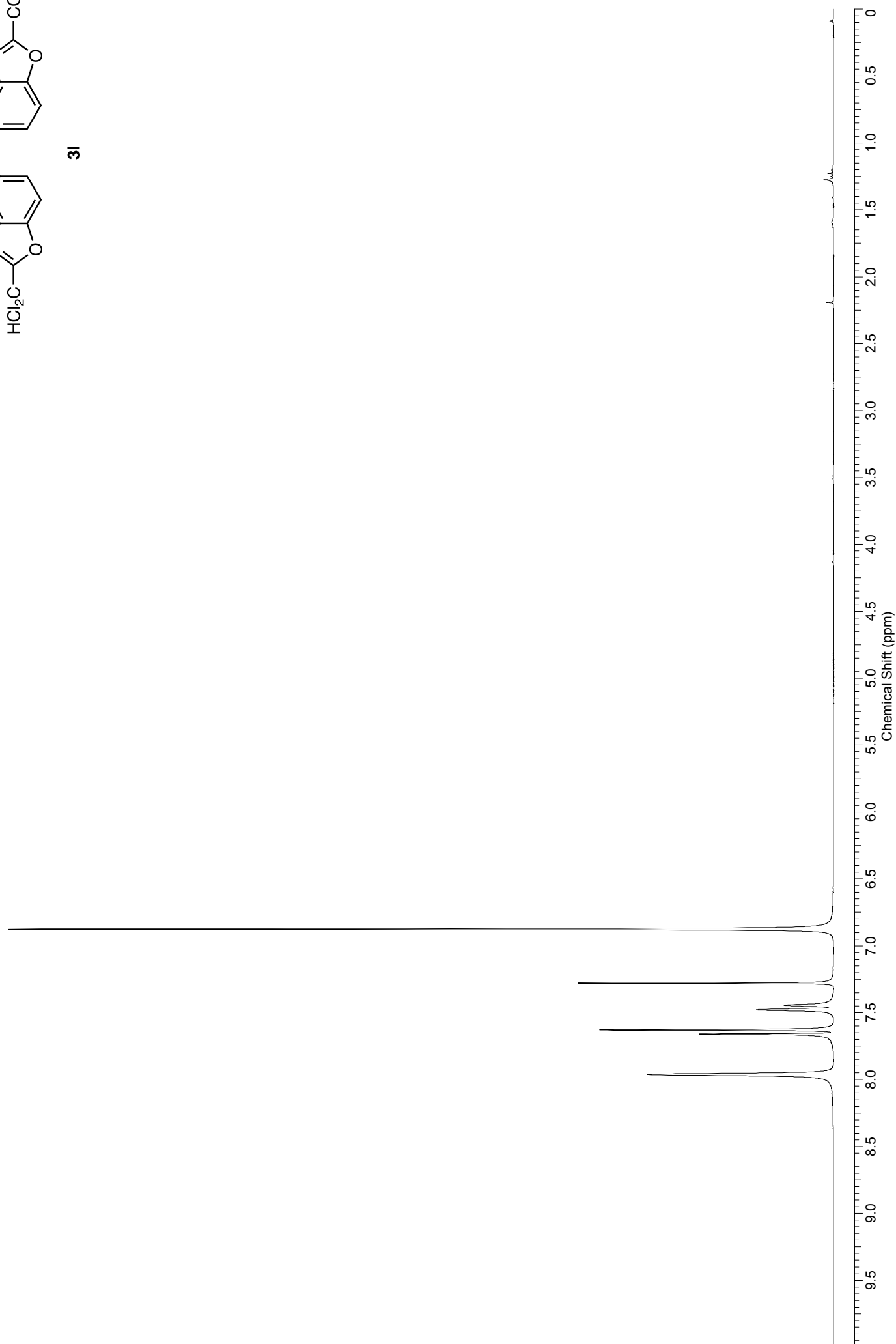
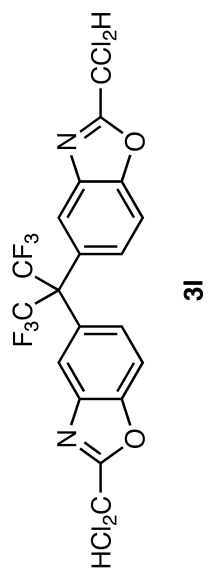
3j

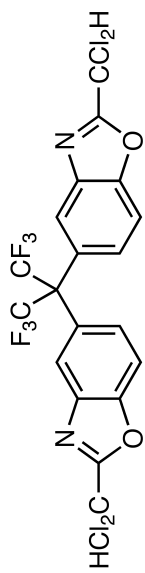




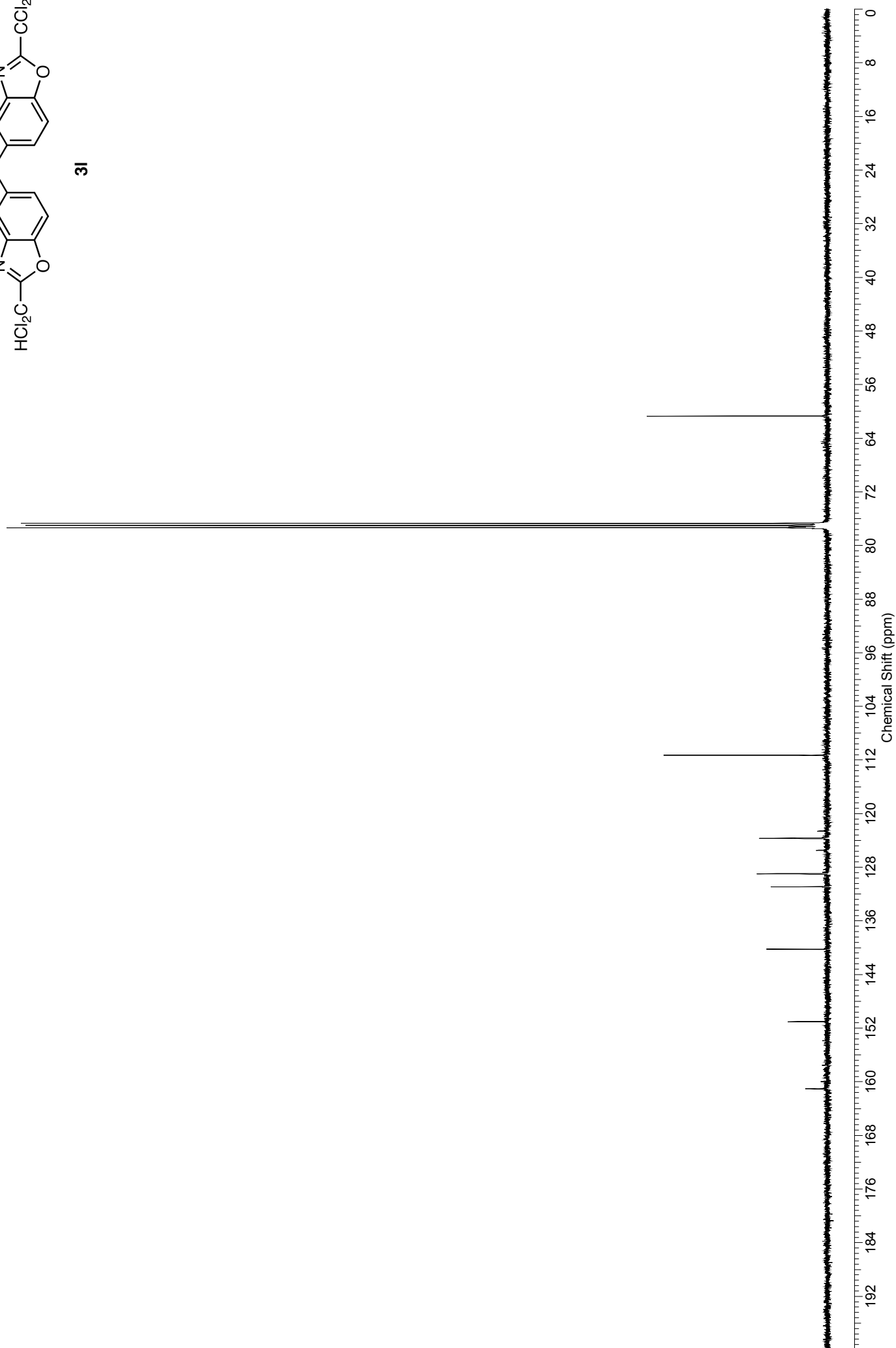
3j

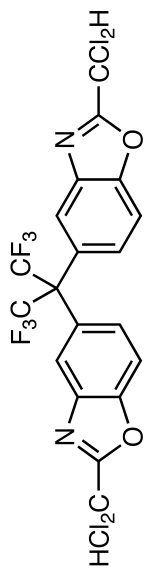




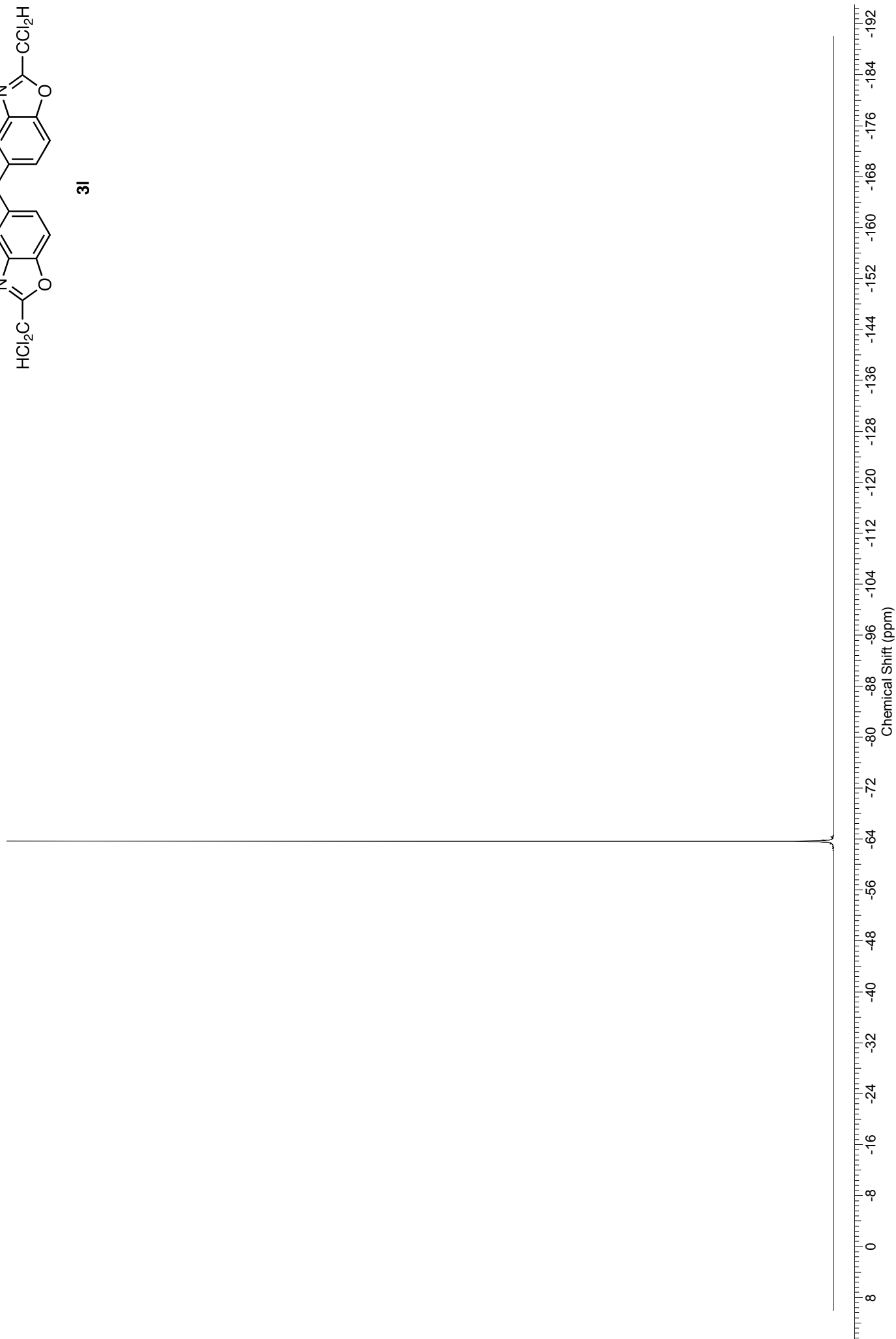


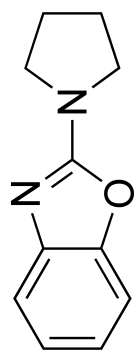
3I



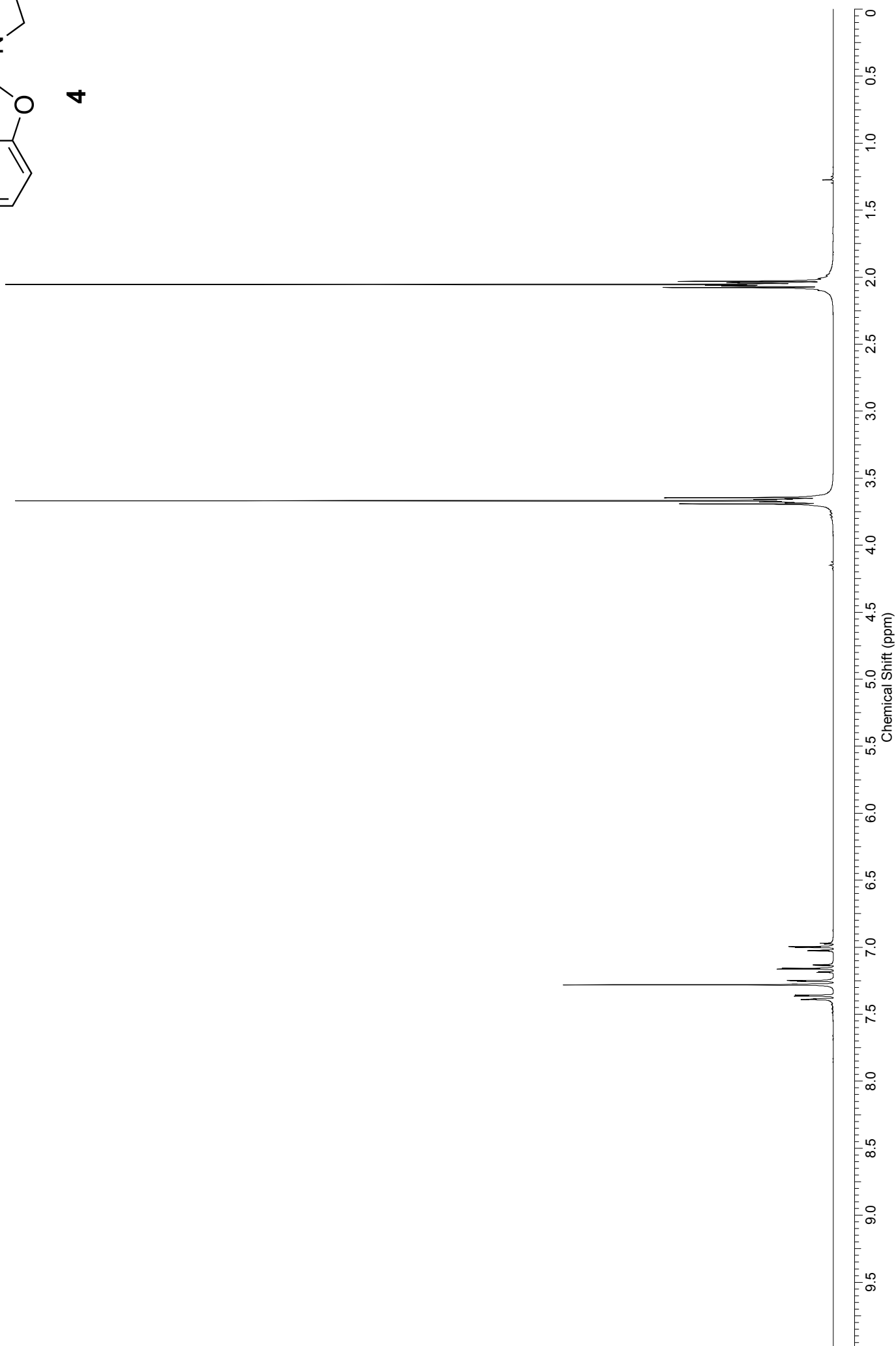


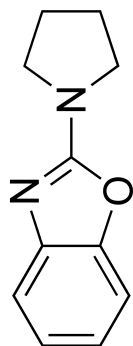
31





4





4

