

Supporting Information

Synthesis of Benzisoxazoles by the [3 + 2] Cycloaddition of *in situ* Generated Nitrile Oxides and Arynes

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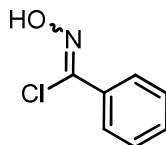
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General Information. The ^1H and ^{13}C NMR spectra were recorded at 300 and 75.5 MHz or 400 and 100 MHz respectively. Thin layer chromatography was performed using 60 mesh silica gel plates, and visualization was effected by short wavelength UV light (254 nm). All melting points are uncorrected. All high resolution mass spectra were recorded using EI at 70 eV. All reagents were used directly as obtained commercially, unless otherwise noted.

General procedure for synthesis of the starting chlorooximes.

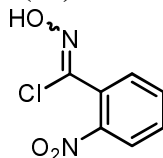
A mixture of the aldehyde (7.0 mmol), hydroxylamine hydrochloride (9.1 mmol) and Na_2CO_3 (4.6 mmol) in 20 ml of water was refluxed for 2 h. After the reaction mixture was allowed to cool down to room temperature, it was extracted with dichloromethane (2×25 ml), and the organic fractions were combined and concentrated under reduced pressure. The residue was dissolved in 25 ml of chloroform (in some cases where there was poor solubility, an additional 3 ml of methanol were necessary) and a drop of pyridine was added. After 5 min, *N*-chlorosuccinimide (7.0 mmol) was added portionwise to the stirring reaction mixture. After the reaction was complete (4 h to 1 d, monitored by TLC), the solvent was removed under reduced pressure. The residue was purified by flash chromatography on silica gel using hexanes/EtOAc as the eluent to afford the desired chlorooximes.

***N*-Hydroxybenzimidoyl chloride (2a)**



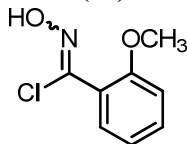
This compound was obtained as a brown solid from commercially available *syn*-benzaldehyde in a 96% yield: mp 48-49 °C (lit.¹ 50 °C); ^1H NMR (400 MHz, CDCl_3) δ 7.40-7.46 (m, 3H), 7.85 (d, $J = 8.0$ Hz, 2H), 8.28 (s, 1H). The ^1H NMR spectral data are in good agreement with the literature data.¹

***N*-Hydroxy-2-nitrobenzimidoyl chloride (2b)**



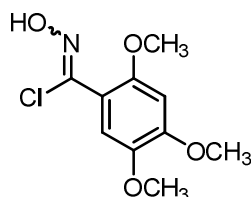
This compound was obtained as a white solid in a 99% yield: mp 96-98 °C (lit.¹ 95-98 °C); ^1H NMR (400 MHz, CDCl_3) δ 7.59 (m, 2H), 7.66 (t, $J = 7.4$ Hz, 1H), 7.93 (d, $J = 7.6$ Hz, 1H).

***N*-Hydroxy-2-methoxybenzimidoyl chloride (2c)**



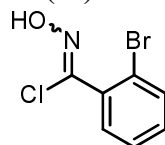
This compound was obtained as a pale yellow solid in a 92% yield: mp 105-108 °C (lit.² 110.5-112 °C); ^1H NMR (300 MHz, CDCl_3) δ 3.92 (s, 3H), 6.97-7.05 (m, 2H), 7.42 (t, $J = 7.8$ Hz, 1H), 7.59 (d, $J = 7.8$ Hz, 1H), 9.46 (s, 1H); HRMS (EI) calcd for $\text{C}_8\text{H}_8\text{ClNO}_2$ 185.02435, found 185.02476. The ^1H NMR spectral data are in good agreement with the literature data.³

***N*-Hydroxy-2,4,5-trimethoxybenzimidoyl chloride (2d)**



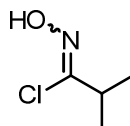
This compound was obtained as a fine light brown solid in a 79% yield: mp 128-130 °C; ^1H NMR (400 MHz, CDCl_3) δ 3.87 (s, 3H), 3.89 (s, 3H), 3.93 (s, 3H), 6.56 (s, 1H), 7.28 (s, 1H), 9.48 (s, 1H).

***N*-Hydroxy-2-bromobenzimidoyl chloride (2e)**



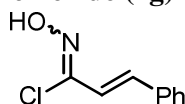
This compound was obtained as a pale yellow solid in an 81% yield: mp 59-60 °C (lit.⁴ 68-69 °C); ^1H NMR (300 MHz, CDCl_3) δ 7.29 (t, J = 7.5 Hz, 1H), 7.36 (t, J = 7.5 Hz, 1H), 7.44 (d, J = 7.6 Hz, 1H), 7.63 (d, J = 7.8 Hz, 1H), 8.59 (s, 1H).

***N*-Hydroxyisobutyrimidoyl chloride (2f)**



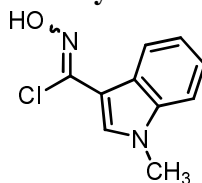
This compound was obtained as a colorless liquid in an 85% yield: ^1H NMR (400 MHz, CDCl_3) δ 1.19 (d, J = 6.8 Hz, 6H), 2.81 (m, 1H), 8.82 (s, 1H).

(2*Z*)-*N*-Hydroxy-3-phenylacrylimidoyl chloride (2g)



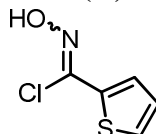
This compound was obtained as a bright yellow amorphous solid in an 80% yield: ^1H NMR (400 MHz, CDCl_3) δ 6.87 (d, J = 15.6 Hz, 1H), 7.29-7.50 (m, 6H), 8.39 (s, 1H).

***N*-Hydroxy-1-methyl-1*H*-indole-3-carbimidoyl chloride (2h)**



This compound was obtained as a dark red amorphous solid in a 55% yield: ^1H NMR (400 MHz, CDCl_3) δ 3.72 (s, 3H), 7.15 (m, 1H), 7.27 (m, 2H), 7.46 (s, 1H), 8.08 (d, J = 8.0 Hz, 1H), 8.87 (s, 1H).

***N*-Hydroxythiophene-2-carbimidoyl chloride (2i)**

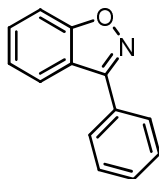


This compound was obtained as a brown amorphous solid in a 56% yield: ^1H NMR (400 MHz, CDCl_3) δ 7.04 (dd, J = 5.1, 3.9 Hz, 1H), 7.37 (d, J = 5.1 Hz, 1H), 7.52 (d, J = 3.9 Hz, 1H), 9.95 (s, 1H).

General procedure for synthesis of the benzisoxazoles.

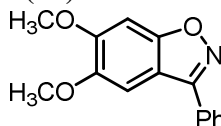
A solution of the appropriate chlorooxime (0.25 mmol) in 3 mL of acetonitrile was added by syringe pump to a stirring mixture of the silylaryl triflate (0.50 mmol) and CsF (1.50 mmol) in 3 mL of acetonitrile over the course of 2.5 h. After the addition was complete, the reaction mixture was allowed to stir for an additional 6 h at room temperature. Then the solvent was evaporated, 15 mL of dichloromethane was added to the residue, and the reaction mixture was poured into 15 mL of water in a separatory funnel. After shaking the layers, the organic fraction was separated and the aqueous layer was extracted with dichloromethane (2×10 mL). All organic fractions were combined and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using hexanes/EtOAc as the eluent to afford the desired benzisoxazoles.

3-Phenylbenzisoxazole (3a)



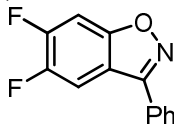
This compound was obtained as a pale brown solid in a 90% yield: mp 81-82 °C (lit.⁵ 80-82 °C); ¹H NMR (400 MHz, CDCl₃) δ 7.39 (t, J = 7.4 Hz, 1H), 7.56-7.67 (m, 5H), 7.93-7.99 (m, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 110.4, 120.7, 122.4, 124.1, 128.3, 129.2, 129.3, 130.0, 130.4, 157.5, 164.1; HRMS (EI) calcd for C₁₃H₉NO 195.06841, found 195.06868. The ¹H and ¹³C NMR spectral data are in good agreement with the literature data.⁶

5,6-Dimethoxy-3-phenylbenzisoxazole (3b)



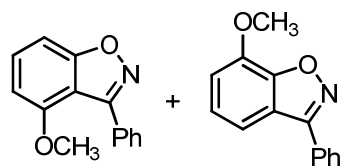
This compound was obtained as a pale white solid in a 65% yield: mp 100-101 °C; ¹H NMR (400 MHz, CDCl₃) δ 3.95 (s, 3H), 3.99 (s, 3H), 7.10 (s, 1H), 7.17 (s, 1H), 7.54 (m, 3H), 7.90 (d, J = 7.6 Hz, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 56.6, 56.7, 92.8, 101.3, 112.2, 128.1, 129.3, 129.4, 130.2, 147.9, 152.9, 157.3, 160.4; HRMS (EI) calcd for C₁₅H₁₃NO₃ 255.08954, found 255.09010.

5,6-Difluoro-3-phenylbenzisoxazole (3c)



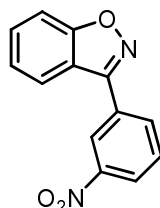
This compound was obtained as a light yellow solid in a 36% yield: mp 82-85 °C; ¹H NMR (400 MHz, CDCl₃) δ 7.48 (dd, J = 6.5, 8.2 Hz, 1H), 7.58 (m, 3H), 7.69 (t, J = 8.2 Hz, 1H), 7.88 (m, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 99.3 (d, J = 22.3 Hz), 108.8 (d, J = 20.8 Hz), 115.9 (d, J = 7.7 Hz), 128.1, 128.2, 129.5, 130.9, 148.9 (dd, J = 244.8, 15.0 Hz), 152.8 (dd, J = 254.0, 16.2 Hz), 157.7, 159.7 (d, J = 10.8 Hz); HRMS (EI) calcd for C₁₃H₇F₂NO 231.04957, found 231.05013.

Mixture of 4-methoxy-3-phenylbenzisoxazole and 7-methoxy-3-phenylbenzisoxazole (~1.8:1 ratio) (3d and 3e)



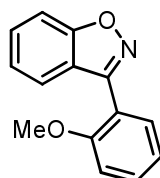
This mixture was obtained as a pale brown oil in a 74% yield: ^1H NMR (400 MHz, CDCl_3) δ 3.87 (s, $1.8 \times 3\text{H}$), 4.06 (s, $1.0 \times 3\text{H}$), 6.67 (d, $J = 7.9$ Hz, $1.8 \times 1\text{H}$), 7.00 (d, $J = 7.8$ Hz, $1 \times 1\text{H}$), 7.20 (d, $J = 8.3$ Hz, $1.8 \times 1\text{H}$), 7.27 (t, $J = 7.9$ Hz, $1 \times 1\text{H}$), 7.44-7.58 (m, $2.8 \times 4\text{H}$), 7.93 (m, $2.8 \times 2\text{H}$); ^{13}C NMR (100 MHz, CDCl_3) δ 55.8, 56.6, 102.9, 103.7, 110.1, 113.8, 115.5, 122.5, 125.2, 128.3, 128.7, 129.1, 129.3, 129.9, 130.3, 130.4, 131.6, 133.8, 144.9, 154.6, 155.0, 157.7, 158.1, 166.0; HRMS (EI) calcd for $\text{C}_{14}\text{H}_{11}\text{NO}_2$ 225.07897, found 225.07942.

3-(3-Nitrophenyl)benzoxazole (3f)



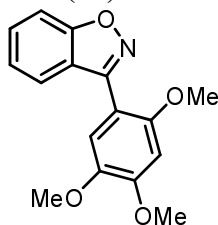
This compound was obtained as colorless pale needles in a 54% yield: mp 169-171 °C (lit.⁷ 176 °C); ^1H NMR (400 MHz, CDCl_3) δ 7.46 (t, $J = 7.4$ Hz, 1H), 7.68 (m, 2H), 7.77 (t, $J = 8.0$ Hz, 1H), 7.96 (d, $J = 8.0$ Hz, 1H), 8.34 (d, $J = 7.7$ Hz, 1H), 8.40 (d, $J = 8.2$ Hz, 1H), 8.85 (s, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 110.7, 119.9, 121.8, 123.1, 124.8, 125.1, 130.5, 131.0, 134.0, 148.9, 155.5, 164.4; HRMS (EI) calcd for $\text{C}_{13}\text{H}_8\text{N}_2\text{O}_3$ 240.05349, found 240.05389.

3-(2-Methoxyphenyl)benzoxazole (3g)



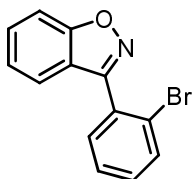
This compound was obtained as a colorless oil in a 93% yield: ^1H NMR (400 MHz, CDCl_3) δ 3.86 (s, 3H), 7.11 (m, 2H), 7.31 (d, $J = 7.4$ Hz, 1H), 7.53 (m, 2H), 7.66 (m, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 55.8, 110.0, 111.6, 117.9, 121.2, 122.1, 123.4, 123.7, 129.7, 131.5, 131.8, 156.7, 157.7, 163.4; HRMS (EI) calcd for $\text{C}_{14}\text{H}_{11}\text{NO}_2$ 225.07897, found 225.07942.

3-(2,4,5-Trimethoxyphenyl)benzoxazole (3h)



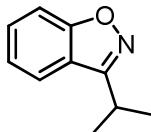
This compound was obtained as a dark oil in an 81% yield: ^1H NMR (400 MHz, CDCl_3) δ 3.82 (s, 3H), 3.89 (s, 3H), 3.98 (s, 3H), 6.69 (s, 1H), 7.22 (s, 1H), 7.29 (t, $J = 7.4$ Hz, 1H), 7.53 (t, $J = 7.7$ Hz, 1H), 7.59 (d, $J = 8.4$ Hz, 1H), 7.74 (d, $J = 8.0$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 56.4, 56.7, 56.7, 98.0, 109.0, 109.9, 114.3, 122.0, 123.3, 123.9, 129.6, 143.6, 151.8, 152.5, 156.5, 163.5; HRMS (EI) calcd for $\text{C}_{16}\text{H}_{15}\text{NO}_4$ 285.10010, found 285.10041.

3-(2-Bromophenyl)benzoxazole (3i)



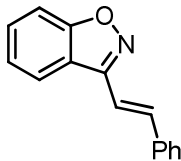
This compound was obtained as a pale yellow oil in a 93% yield: ^1H NMR (400 MHz, CDCl_3) δ 7.34 (t, $J = 7.3$ Hz, 1H), 7.41 (t, $J = 7.7$ Hz, 1H), 7.48 (t, $J = 7.2$ Hz, 1H), 7.53-7.69 (m, 4H), 7.78 (d, $J = 7.9$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 110.3, 121.4, 123.1, 123.8, 127.8, 130.1, 130.2, 131.6, 132.2, 133.8, 158.2, 163.4; HRMS (EI) calcd for $\text{C}_{13}\text{H}_8\text{BrNO}$ 272.97892, found 272.97966.

3-Isopropylbenzisoxazole (3j)



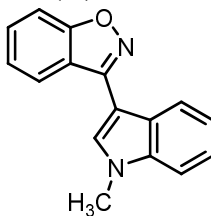
This compound was obtained as a dark oil in an 82% yield: ^1H NMR (400 MHz, CDCl_3) δ 1.50 (d, $J = 7.0$ Hz, 6H), 3.41 (m, 1H), 7.29 (m, 1H), 7.54 (m, 2H), 7.72 (d, $J = 7.9$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 21.3, 27.1, 110.2, 121.0, 121.8, 123.1, 129.7, 163.3, 163.3; HRMS (EI) calcd for $\text{C}_{10}\text{H}_{11}\text{NO}$ 161.08406, found 161.08453.

(E)-3-Styrylbenzisoxazole (3k)



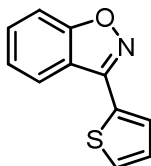
This compound was obtained as dark crystals in a 70% yield: mp 75-77 °C; ^1H NMR (400 MHz, CDCl_3) δ 7.36-7.46 (m, 5H), 7.55-7.70 (m, 5H), 8.00 (d, $J = 8.0$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 110.4, 115.9, 117.6, 120.5, 122.1, 127.3, 129.1, 129.4, 130.0, 136.1, 137.0, 155.6, 163.8; HRMS (EI) calcd for $\text{C}_{15}\text{H}_{11}\text{NO}$ 221.08406, found 221.08460.

3-(1-Methyl-1H-indol-3-yl)benzisoxazole (3l)



This compound was obtained as yellow crystals in a 61% yield: mp 156-157 °C; ^1H NMR (400 MHz, CDCl_3) δ 3.88 (s, 3H), 7.28-7.41 (m, 4H), 7.57 (t, $J = 7.7$ Hz, 1H), 7.63 (d, $J = 8.4$ Hz, 1H), 7.73 (s, 1H), 7.92 (d, $J = 8.0$ Hz, 1H), 8.37 (d, $J = 7.1$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 33.5, 104.4, 109.7, 110.2, 115.5, 121.3, 122.3, 122.5, 123.2, 123.4, 126.2, 129.3, 129.7, 137.3, 153.2, 163.0; HRMS (EI) calcd for $\text{C}_{16}\text{H}_{12}\text{N}_2\text{O}$ 248.09496, found 248.09553.

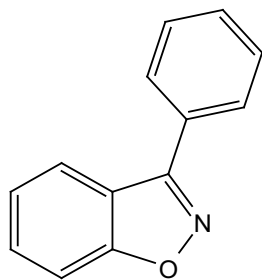
3-(2-Thiophenyl)benzisoxazole (3m)



This compound was obtained as a dark oil in a 54% yield: ^1H NMR (400 MHz, CDCl_3) δ 7.25 (m, 1H), 7.41 (t, $J = 7.3$ Hz, 1H), 7.55 (d, $J = 5.1$ Hz, 1H), 7.62 (m, 2H), 7.82 (d, $J = 3.6$ Hz, 1H), 8.00 (d, $J = 8.0$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 110.4, 115.5, 120.2, 122.2, 128.1, 128.2, 128.4, 130.2, 152.5, 163.9; HRMS (EI) calcd for $\text{C}_{11}\text{H}_7\text{NOS}$ 201.02483, found 201.02520.

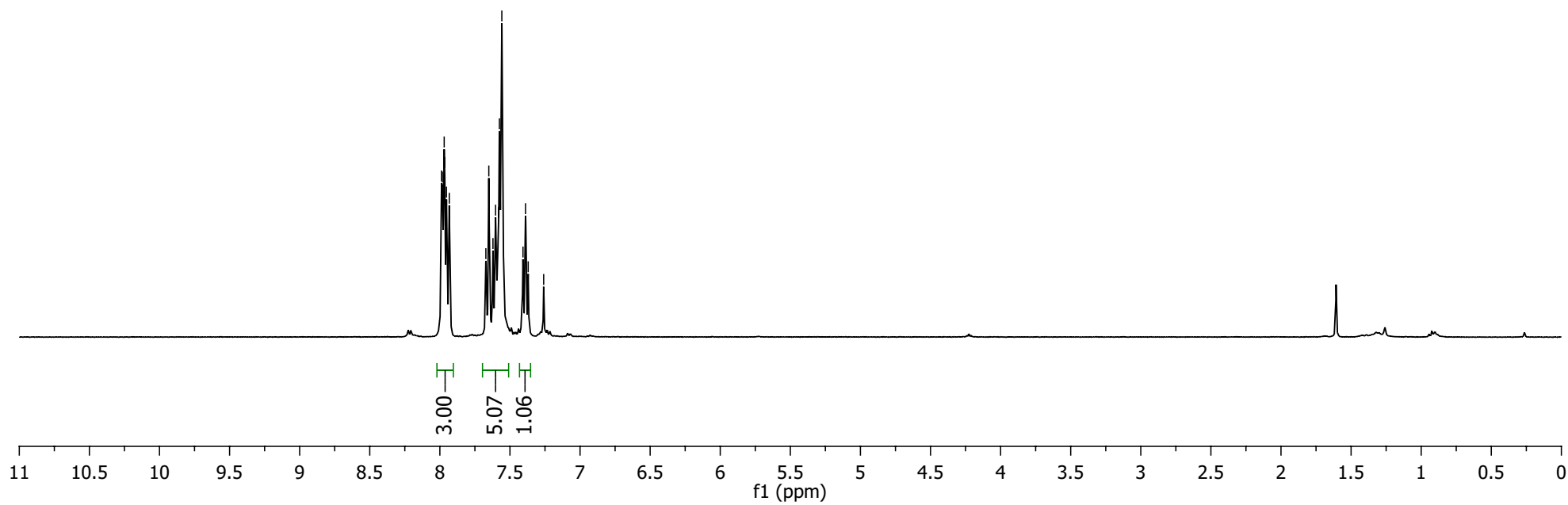
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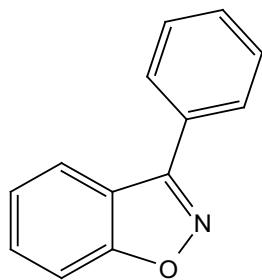
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3a

7.99
7.98
7.97
7.97
7.95
7.93
7.67
7.65
7.62
7.60
7.58
7.58
7.56
7.41
7.39
7.37
7.26





3a

— 164.05

— 157.46

130.43

129.97

129.33

129.15

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— 124.07

122.41

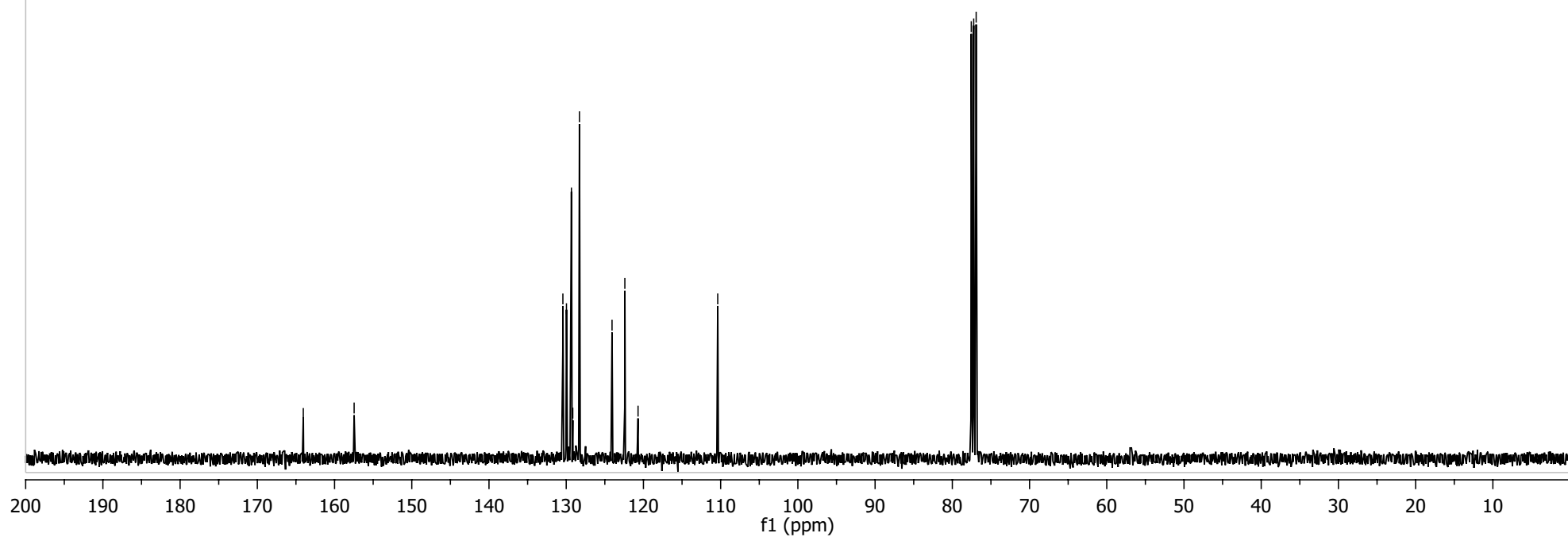
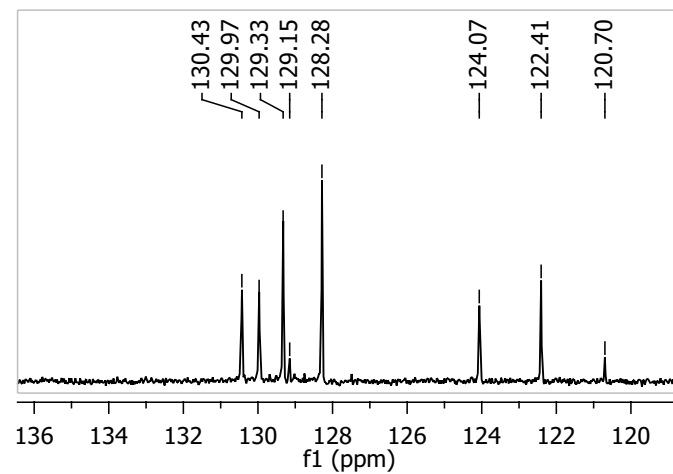
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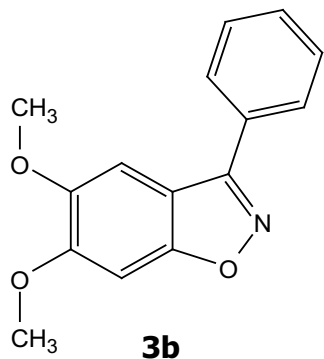
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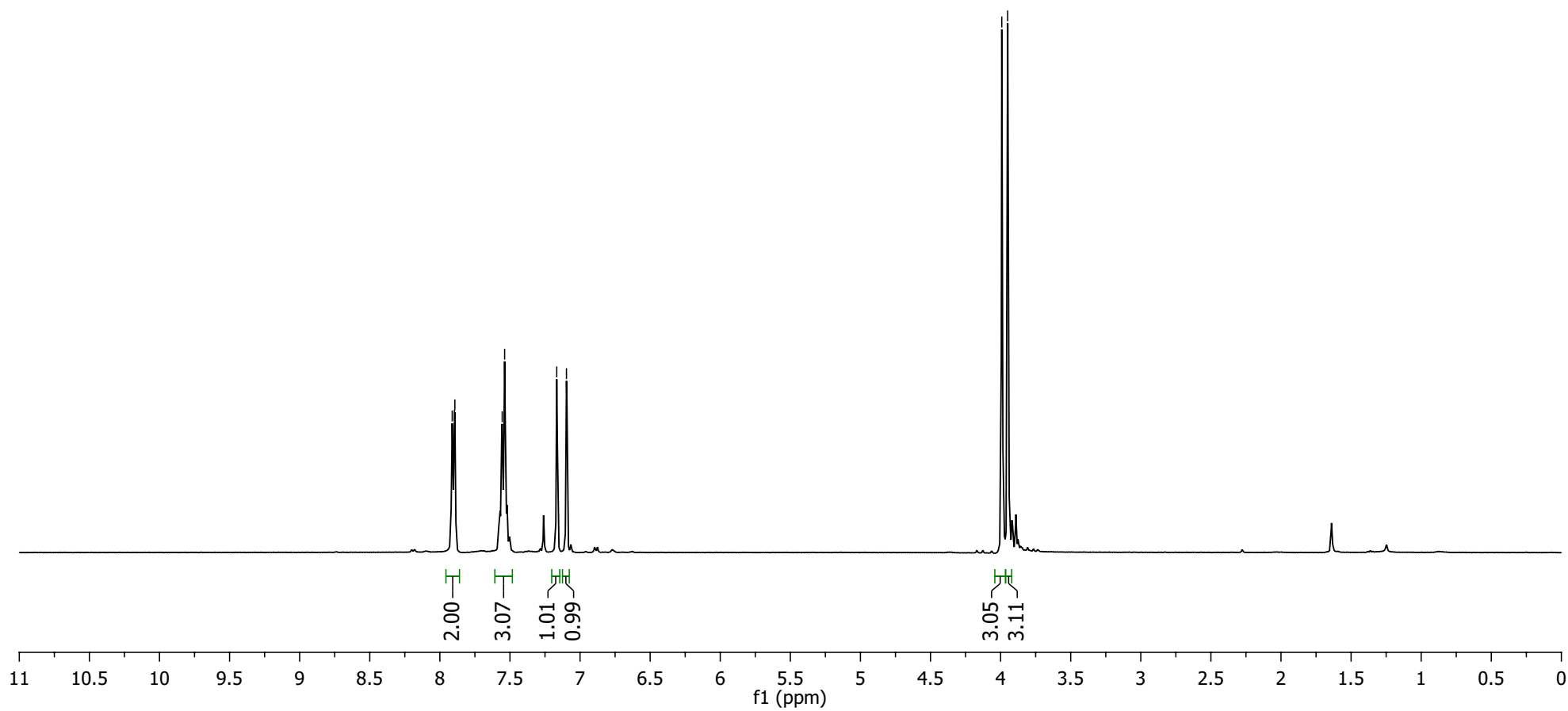
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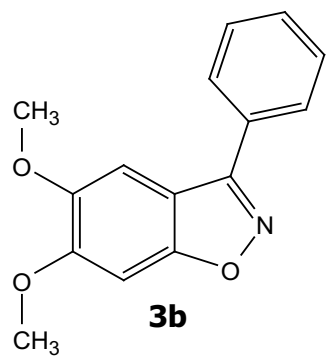




7.91
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— 160.39
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— 147.90

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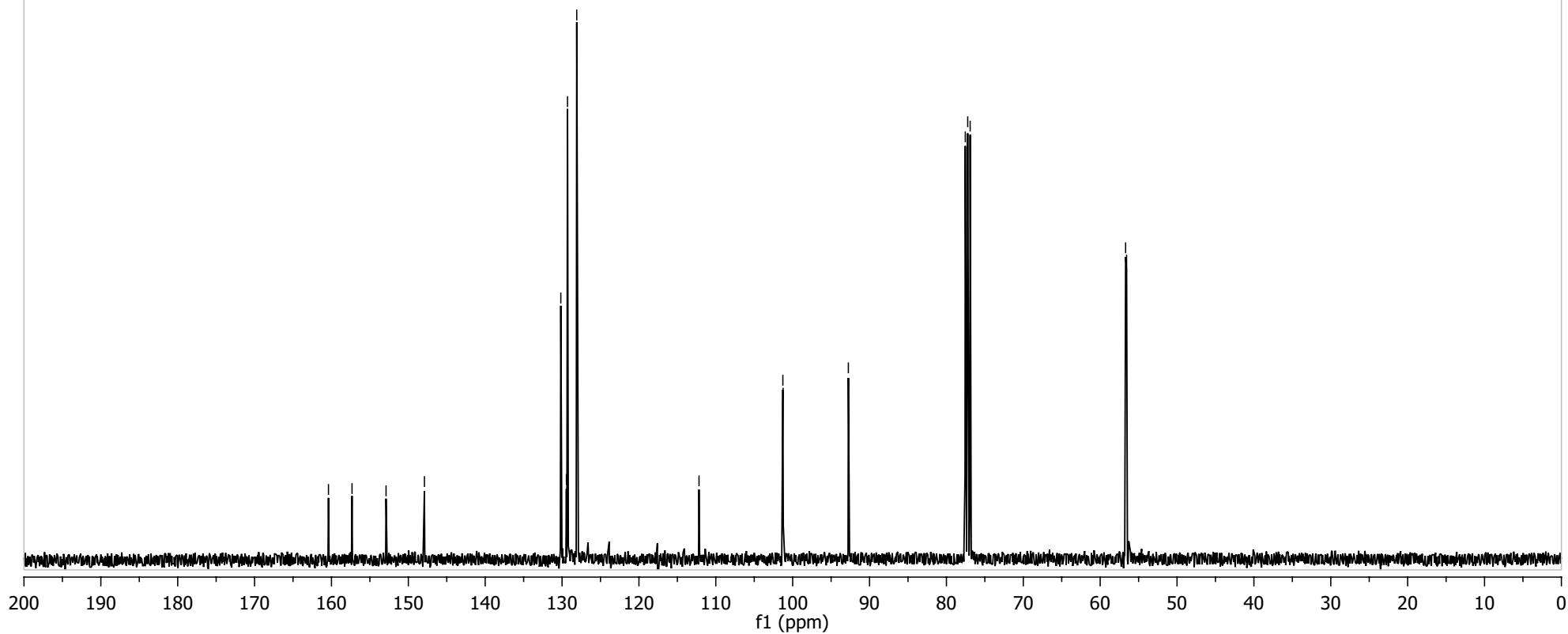
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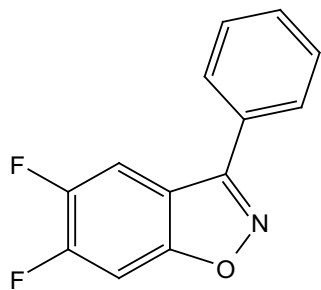
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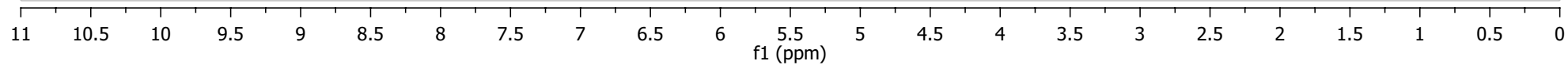


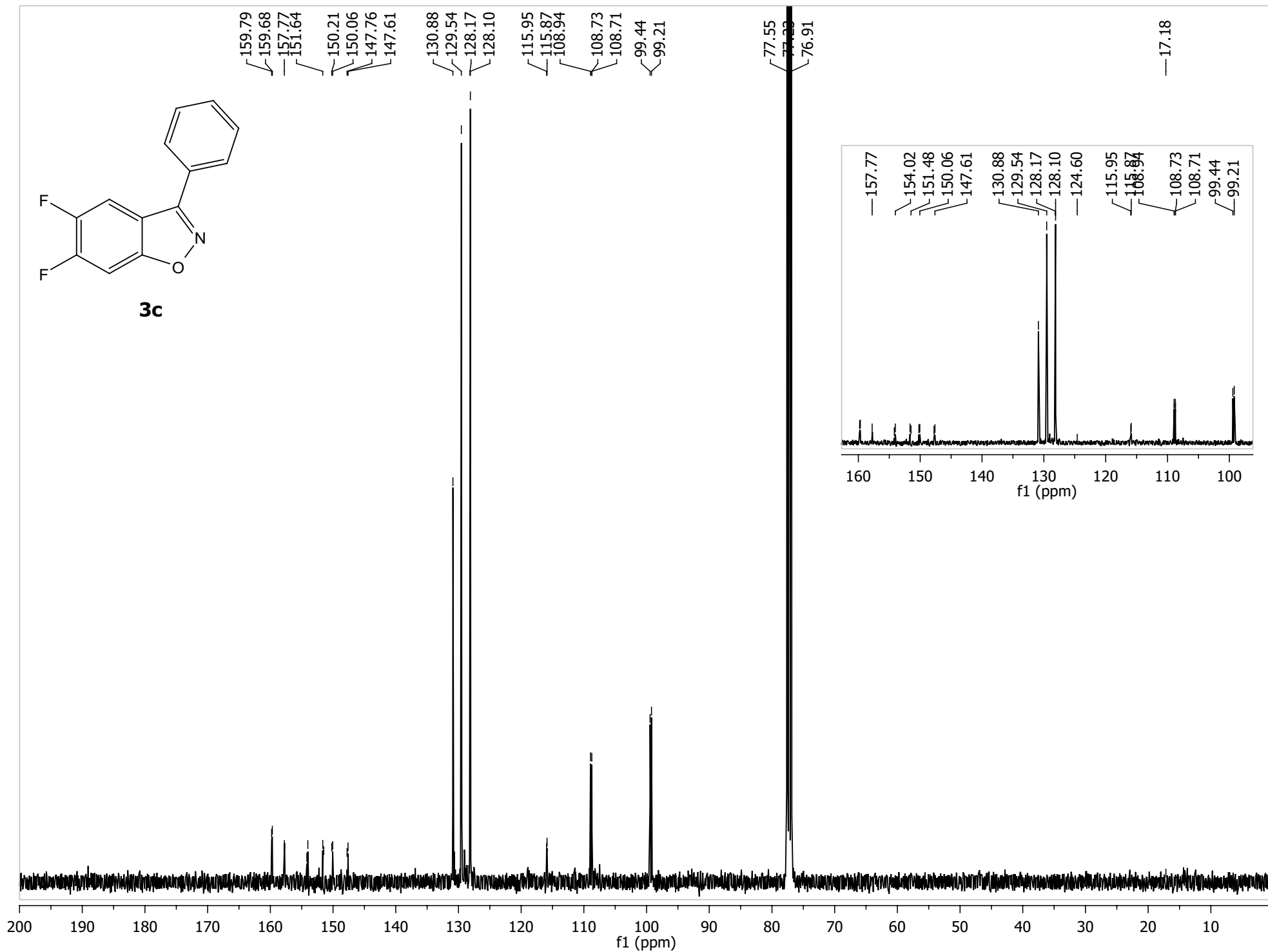


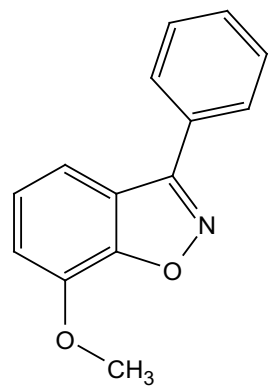
3c

7.88
7.88
7.57
7.48
7.26

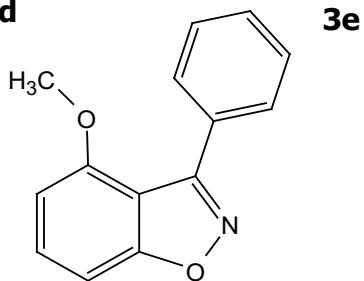
2.06
1.00
3.27
0.96







3d

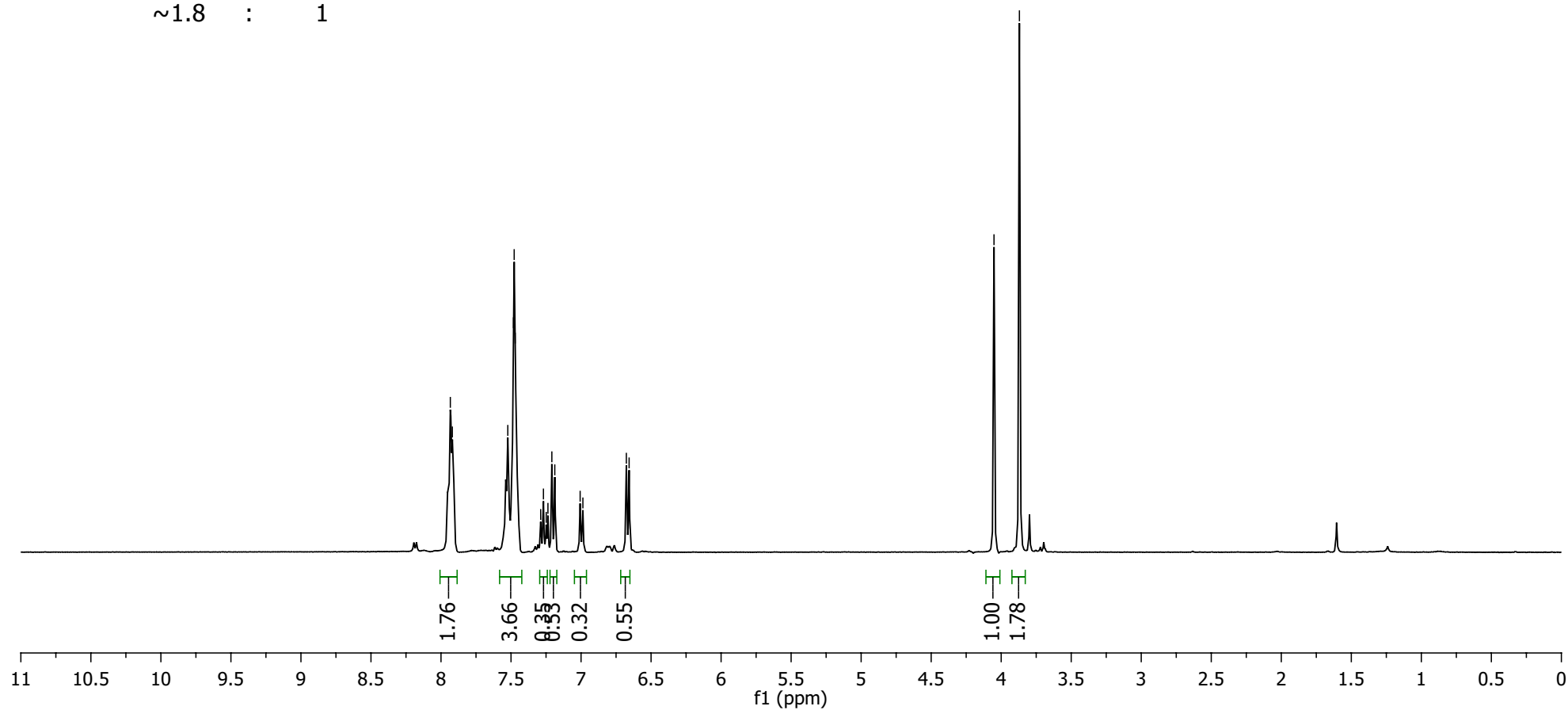


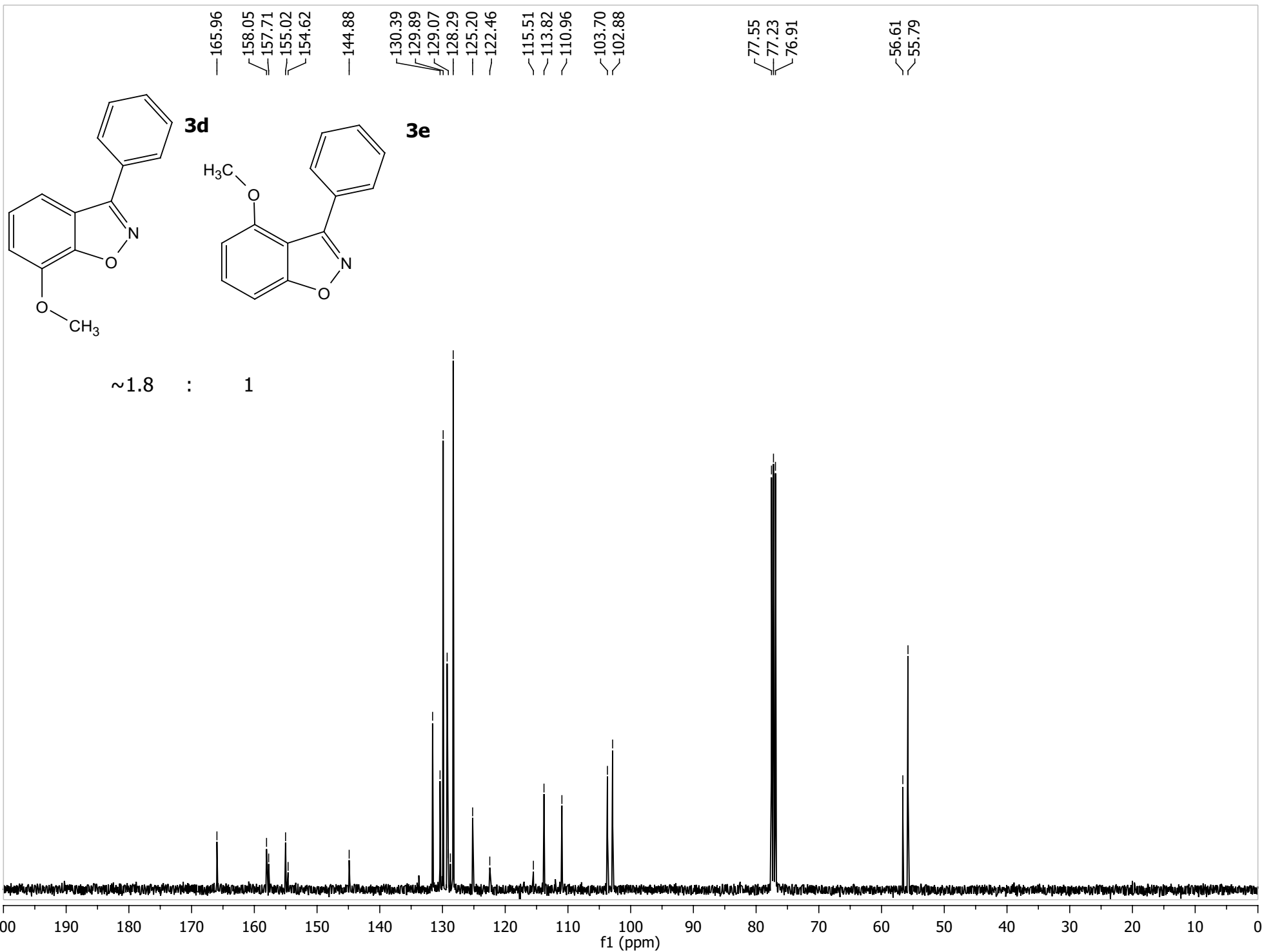
3e

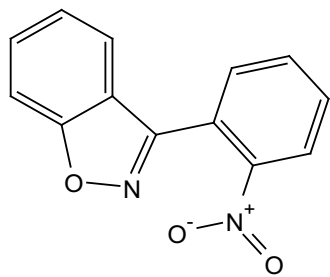
~1.8 : 1

7.93
7.92
7.48
7.47
7.19
6.99
6.68
6.66

4.05
3.87

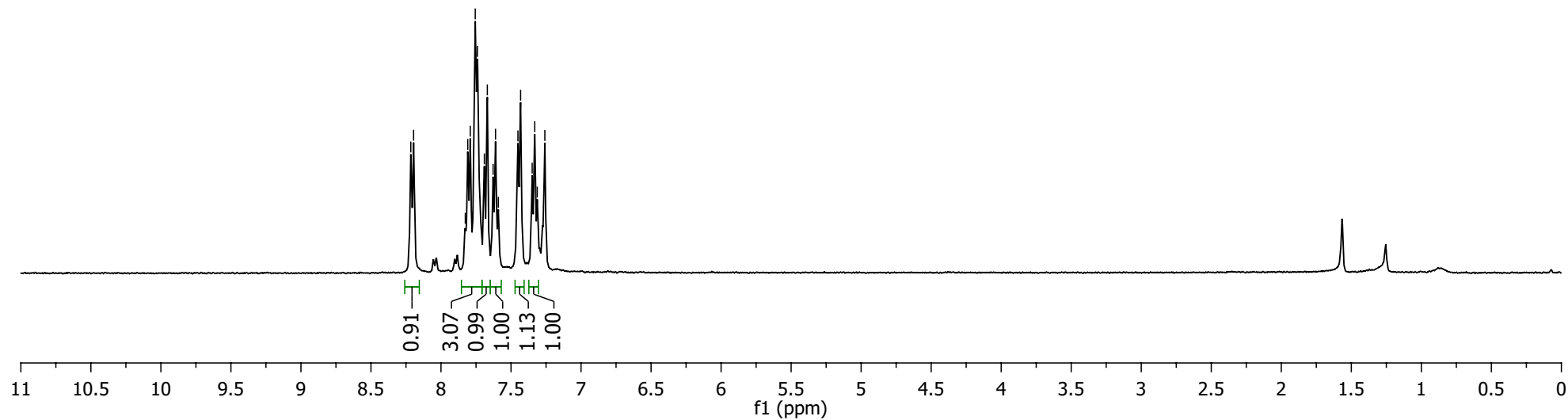


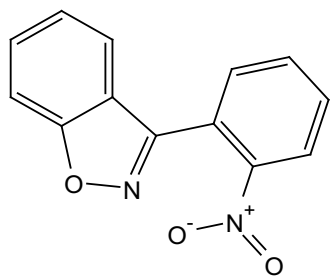




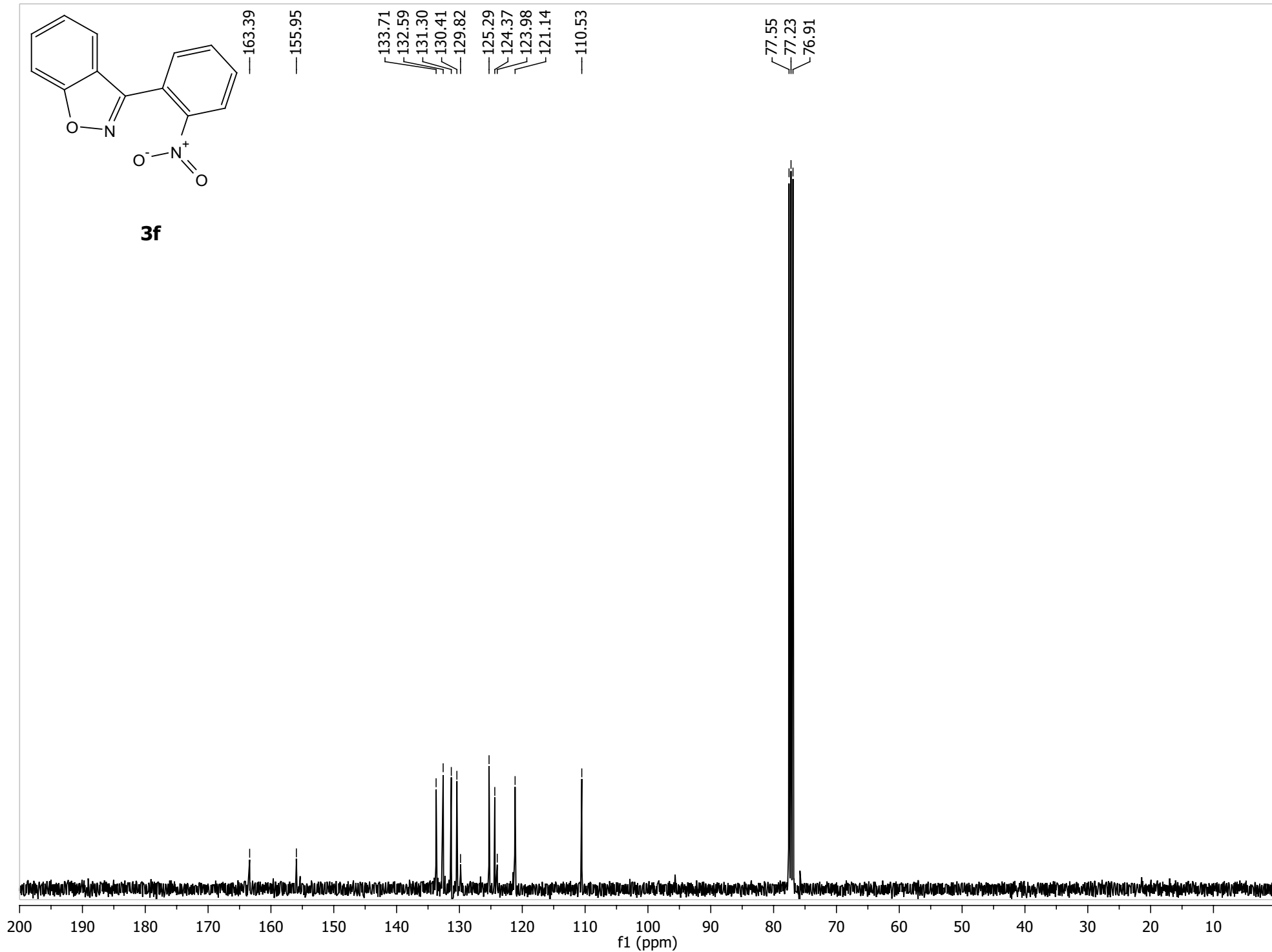
3f

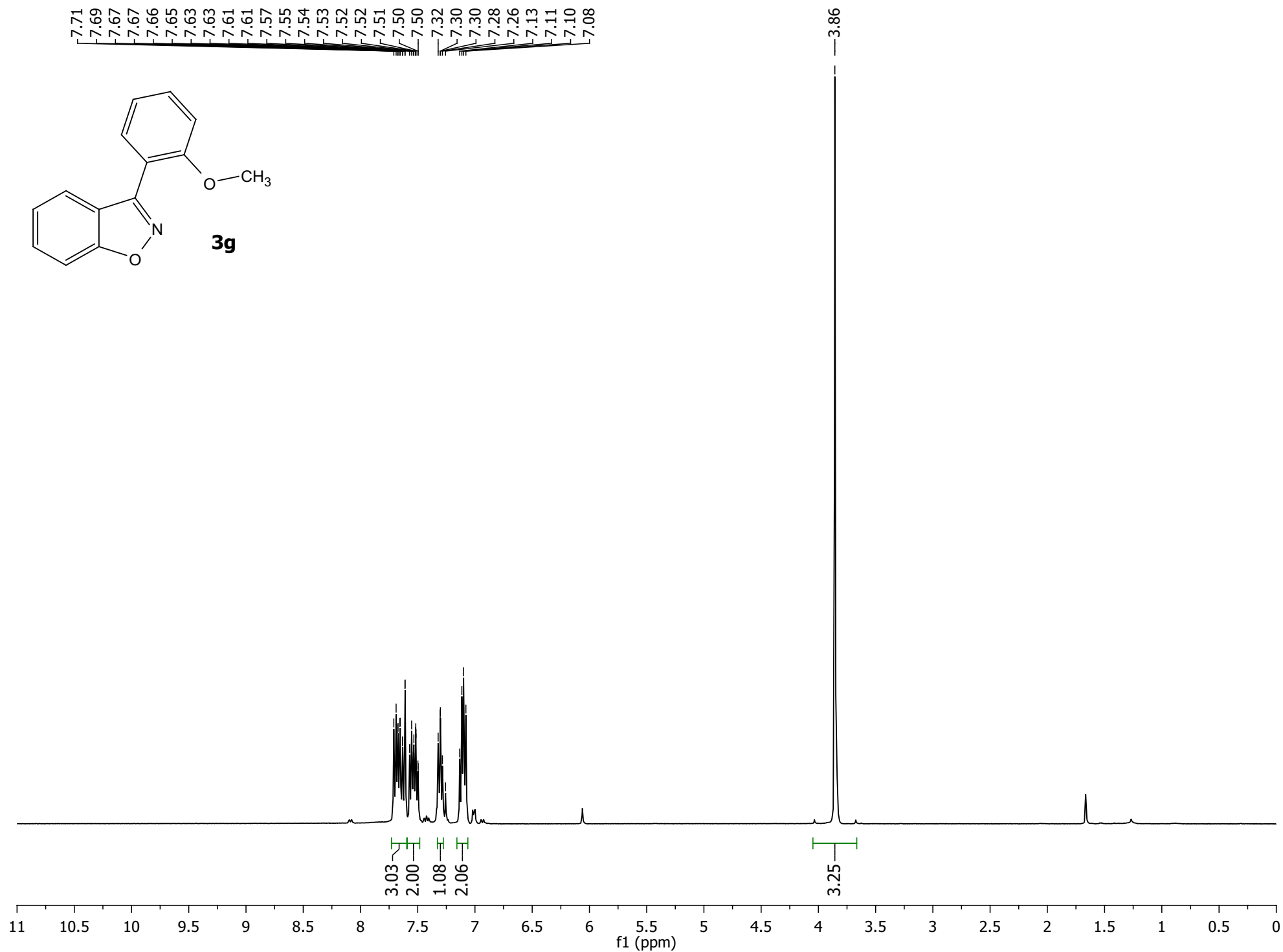
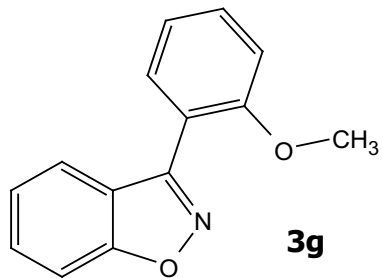
8.22
8.20
7.83
7.81
7.79
7.76
7.74
7.69
7.67
7.63
7.61
7.59
7.45
7.43
7.35
7.33
7.31
7.26

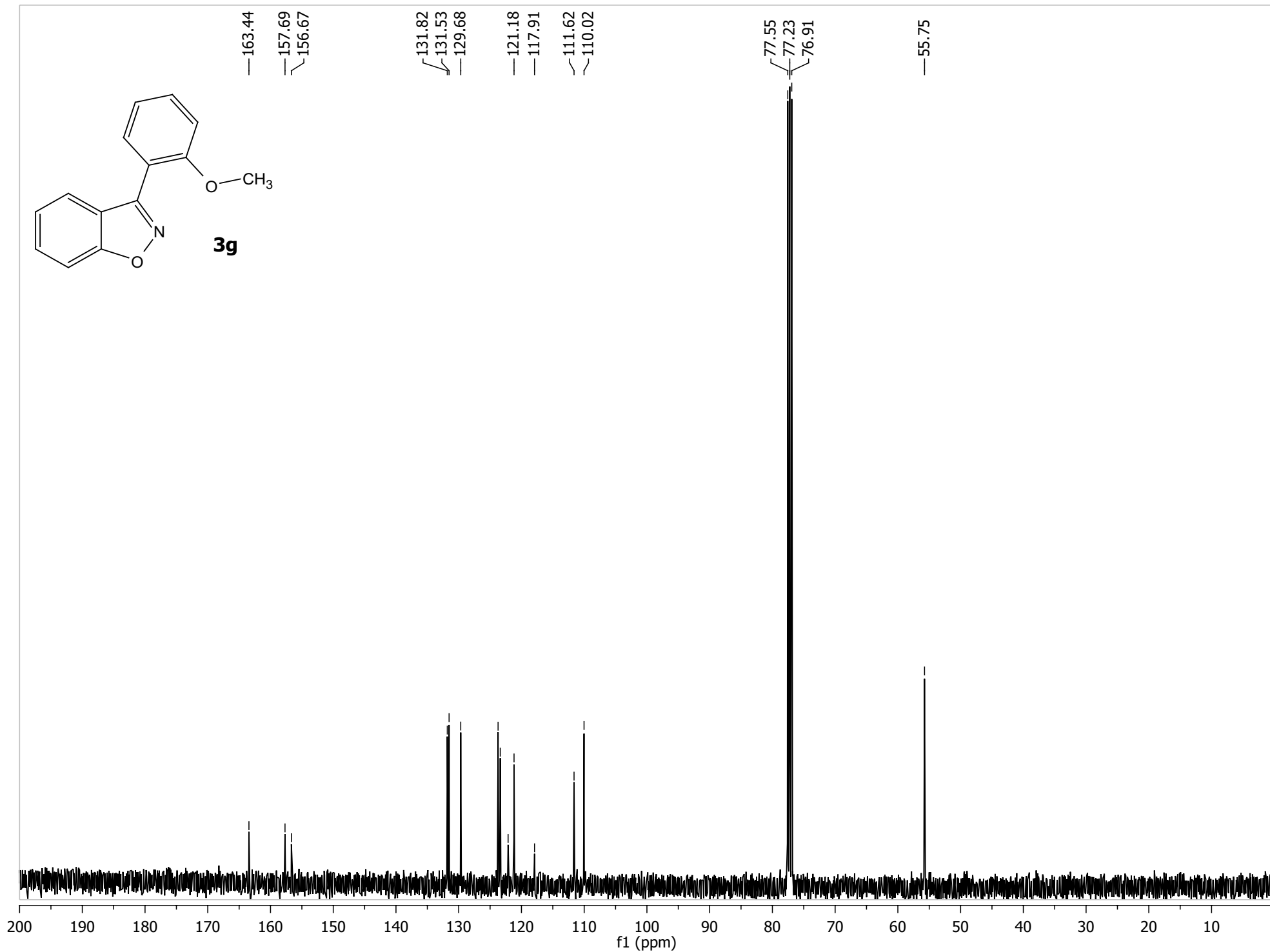
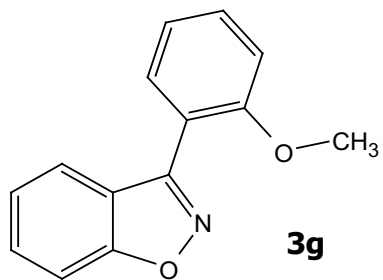


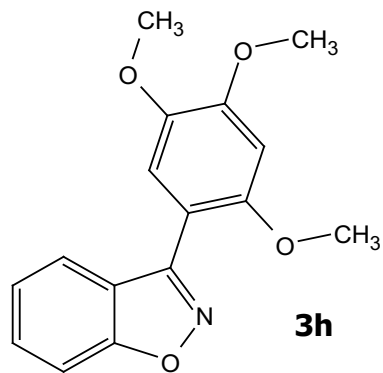


3f



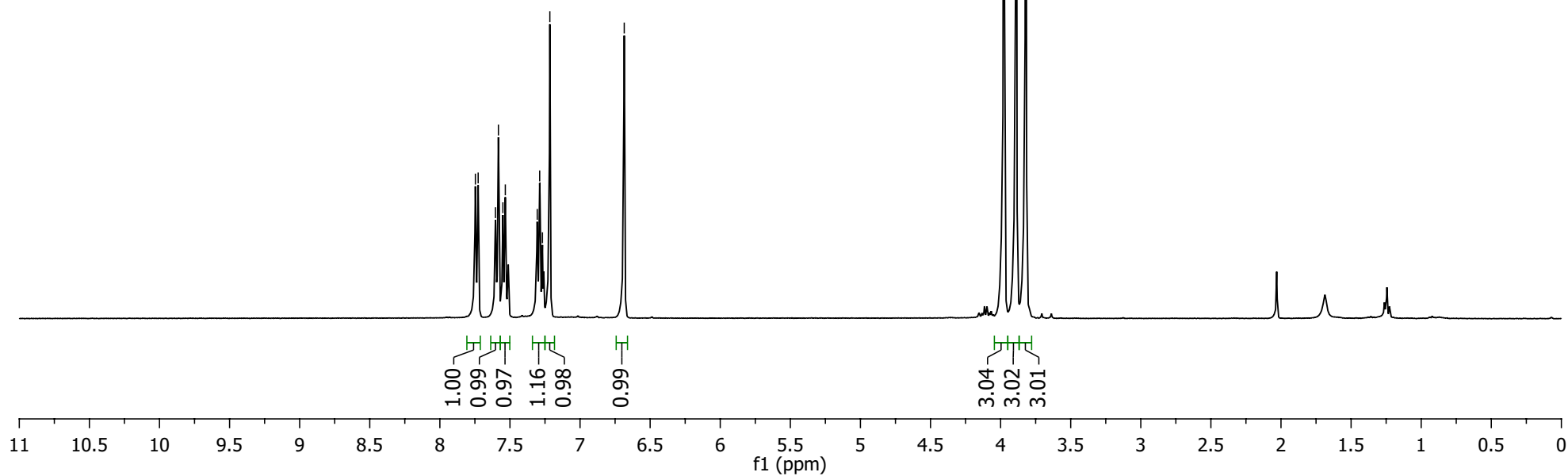


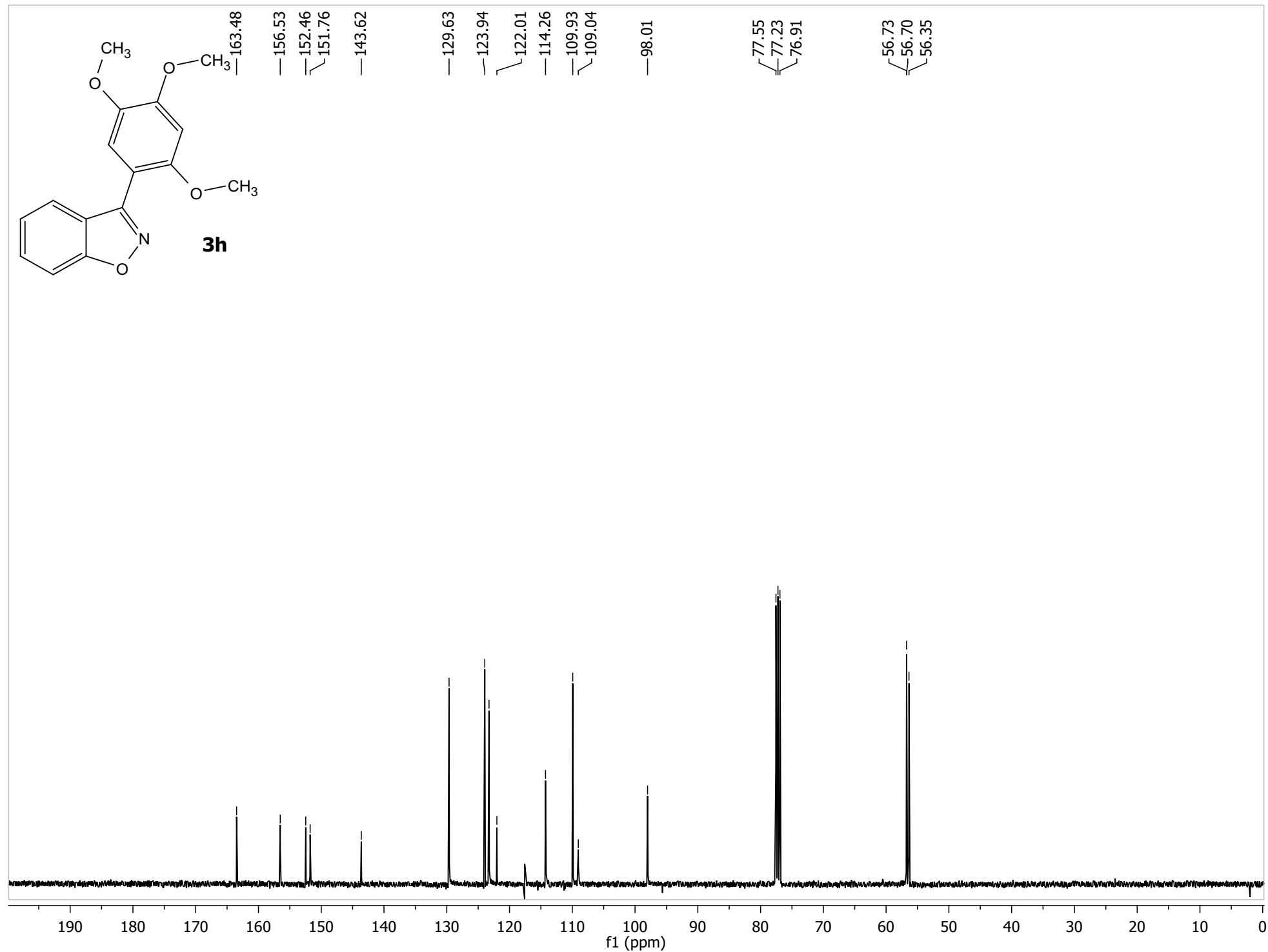
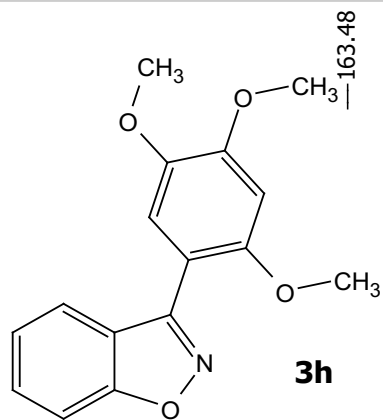


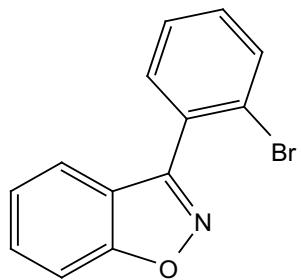


7.75
7.73
7.60
7.58
7.55
7.53
7.29
7.27
7.22
—6.68

3.98
3.89
3.82



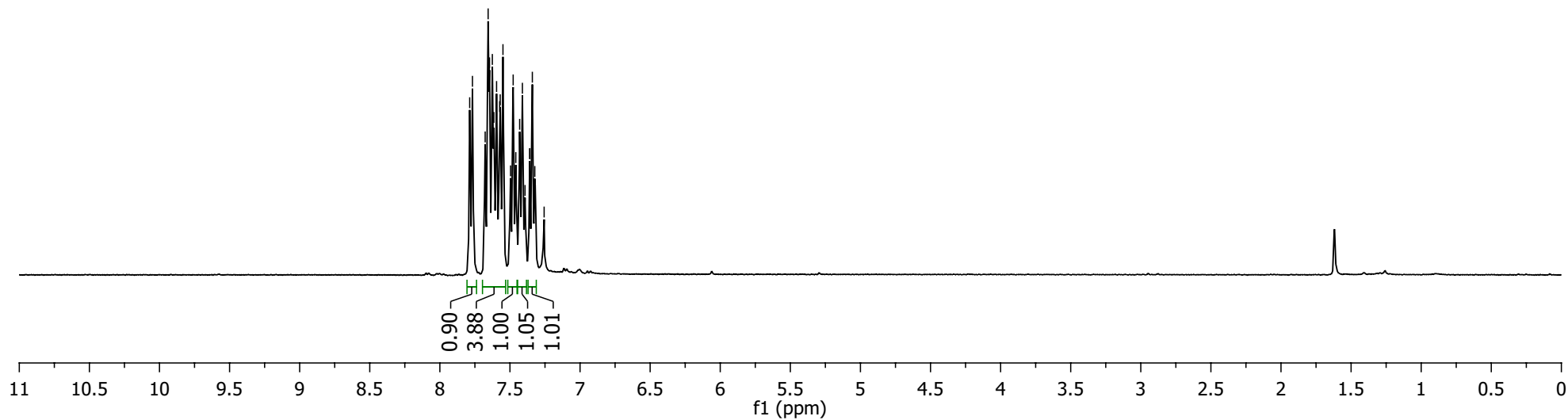
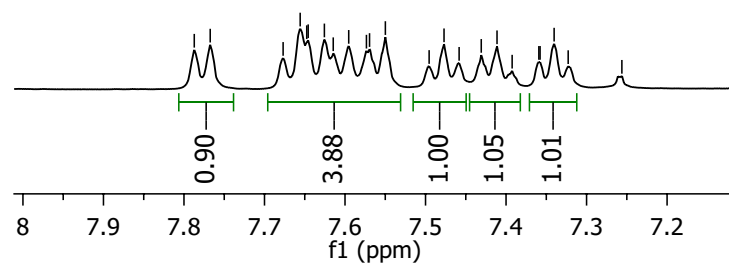


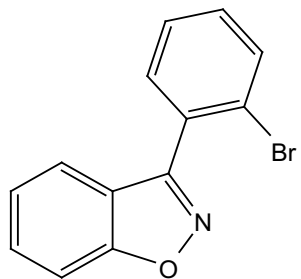


3i

7.79
7.77
7.68
7.66
7.65
7.65
7.63
7.61
7.60
7.57
7.57
7.55
7.50
7.48
7.46
7.43
7.41
7.39
7.36
7.36
7.34
7.32
7.26

~7.79
~7.77
7.66
7.65
~7.61
~7.57
~7.55
~7.48
~7.43
~7.39
~7.36
~7.32
~7.26





3i

— 163.41

— 158.23

133.75

132.20

131.58

130.17

130.10

— 127.77

— 123.83

— 123.05

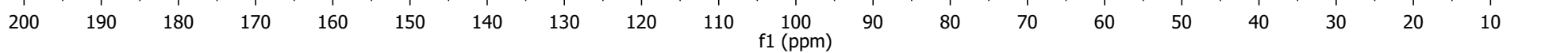
— 121.43

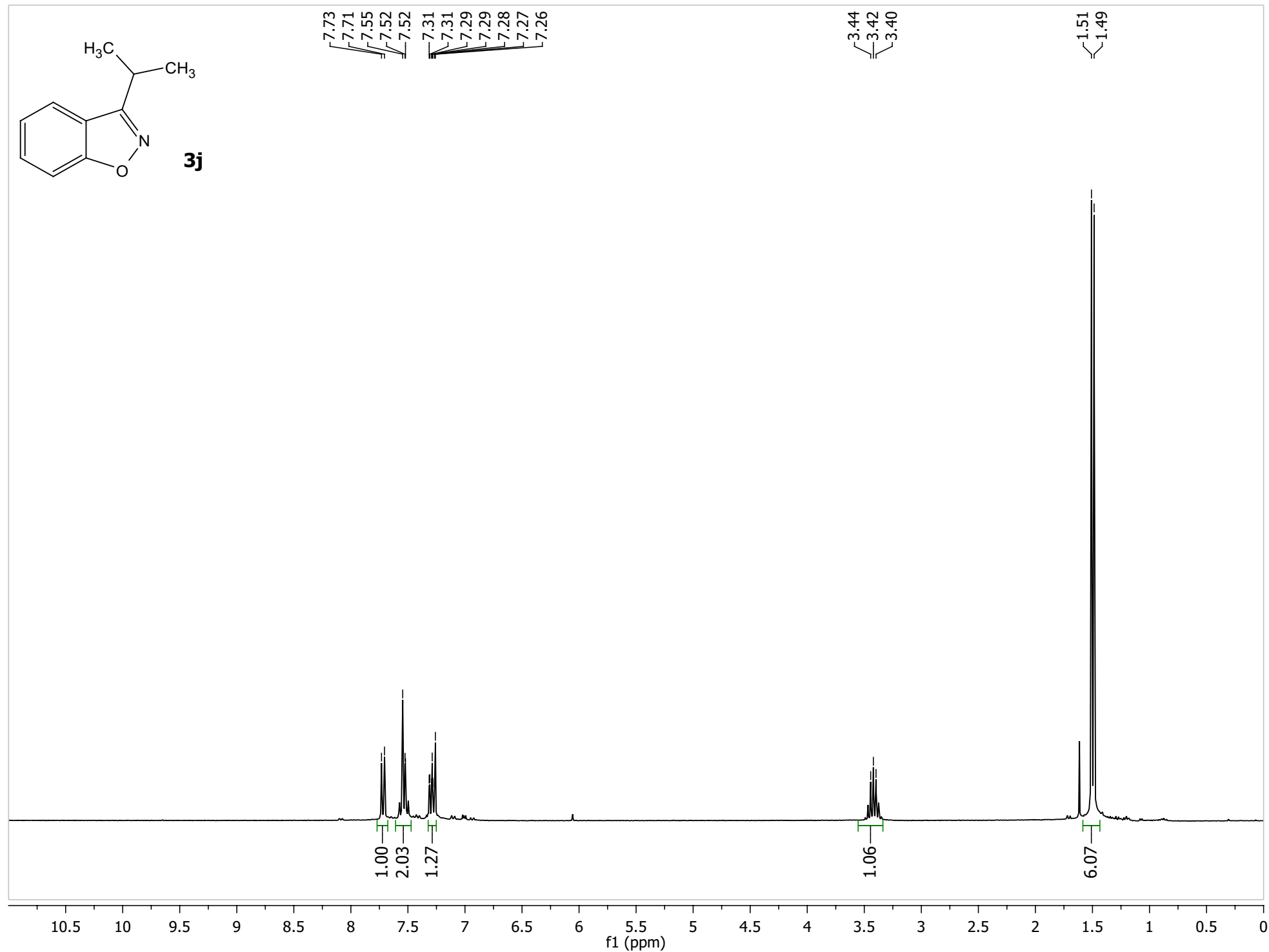
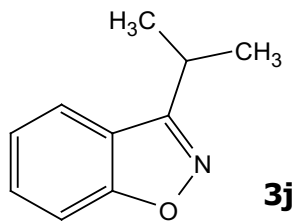
— 110.27

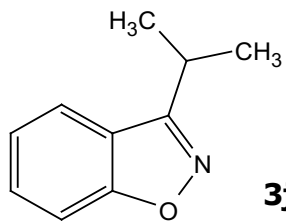
77.55

77.23

76.91







3j

163.34
163.28

129.71

123.12

121.83

121.03

110.21

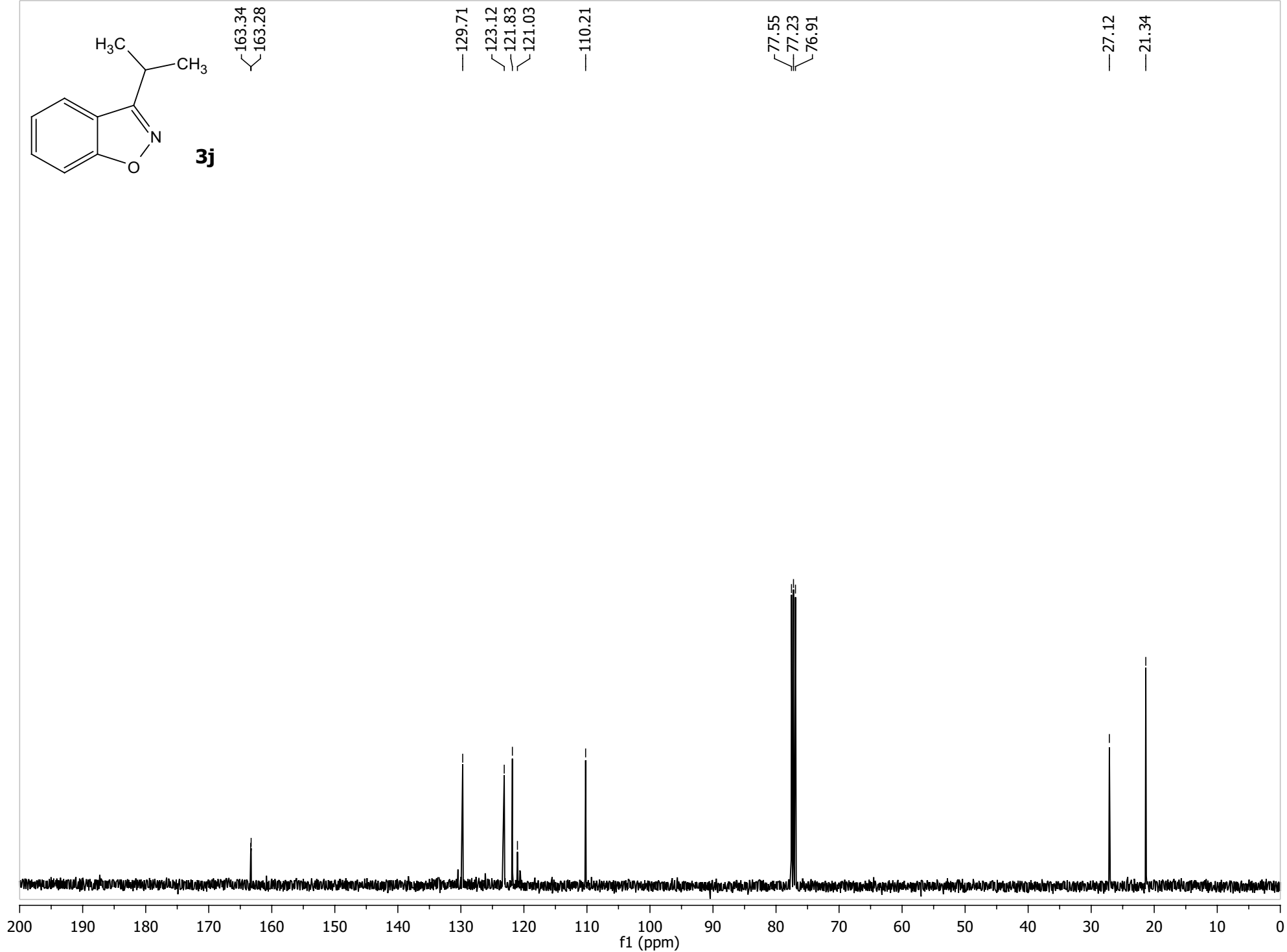
77.55

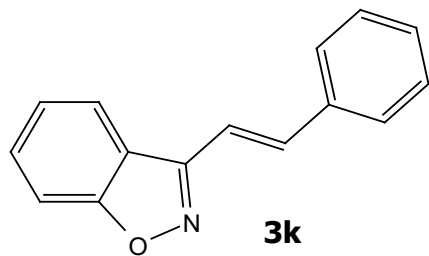
77.23

76.91

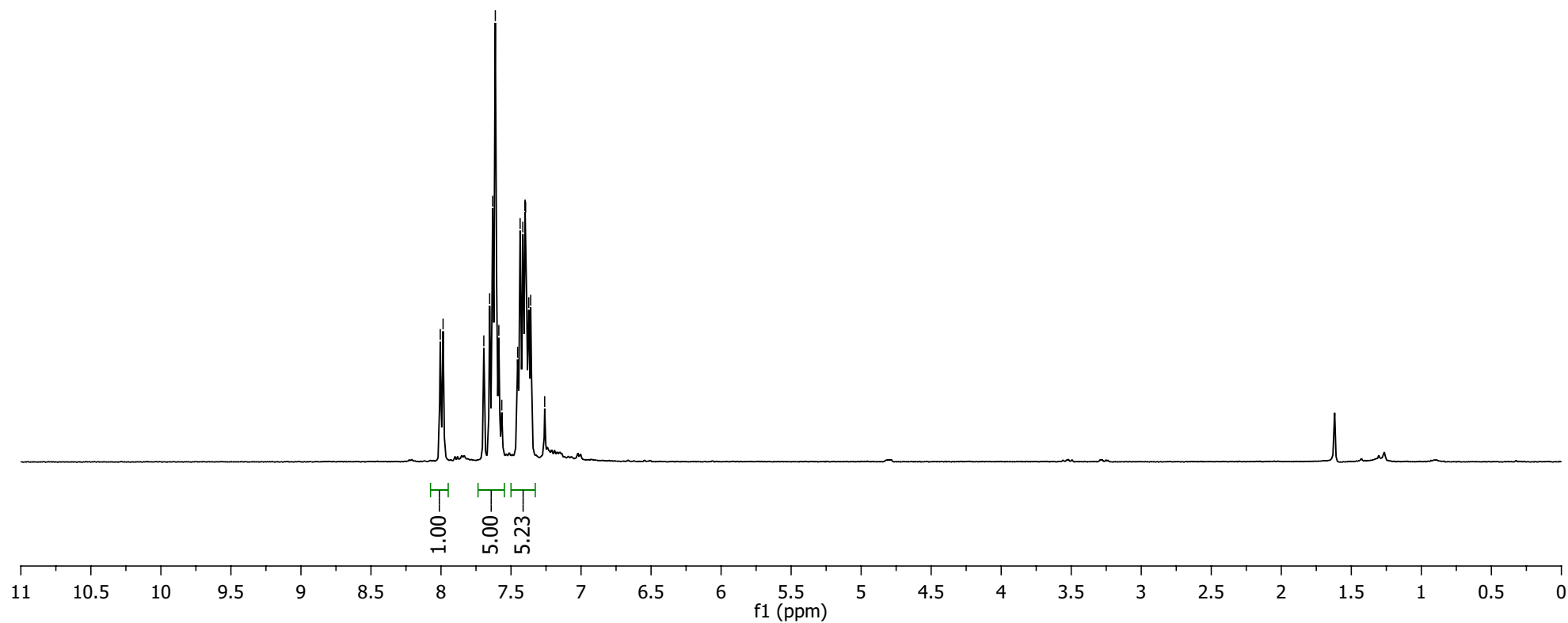
27.12

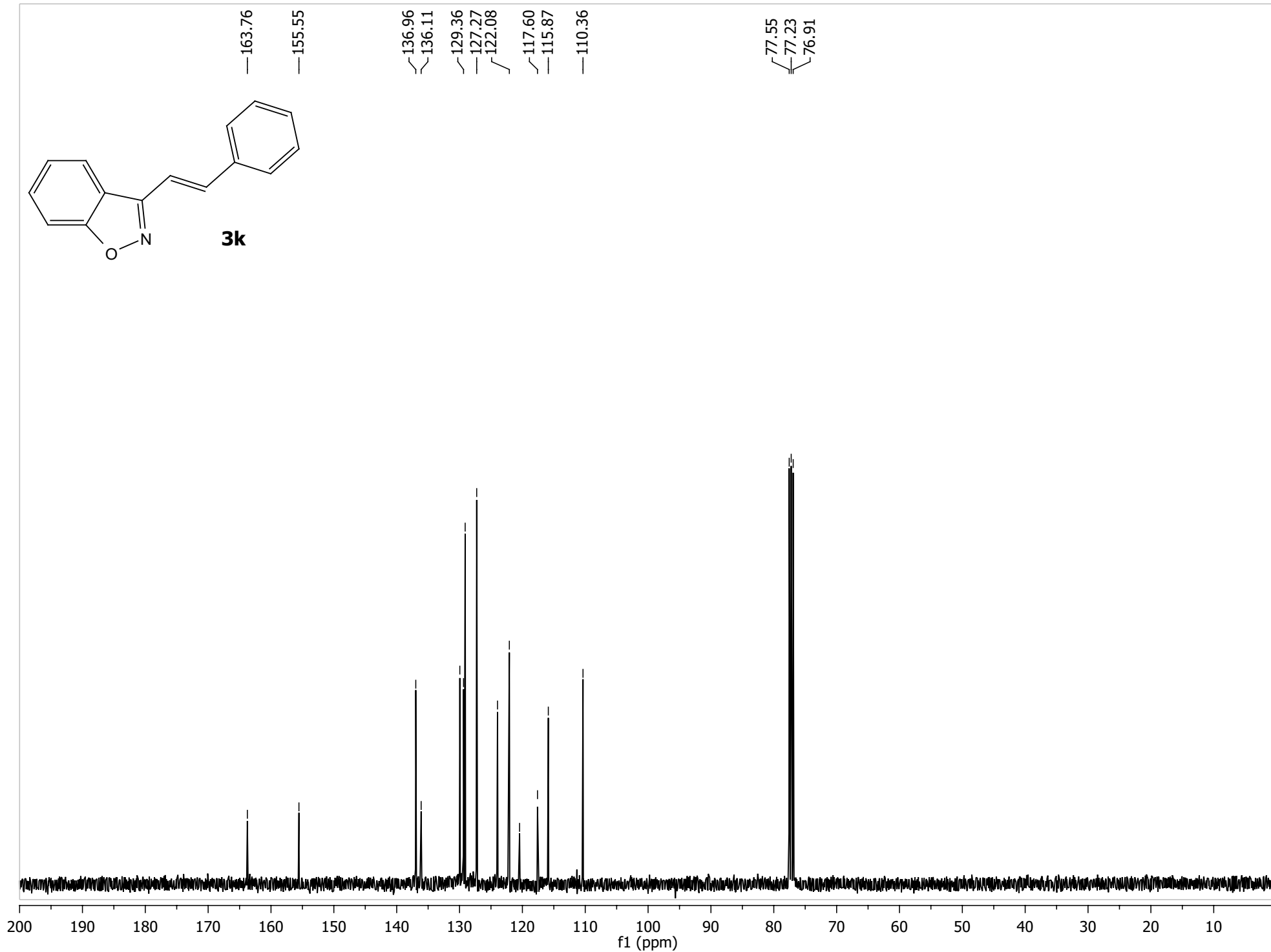
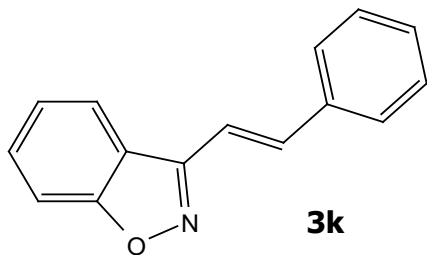
21.34

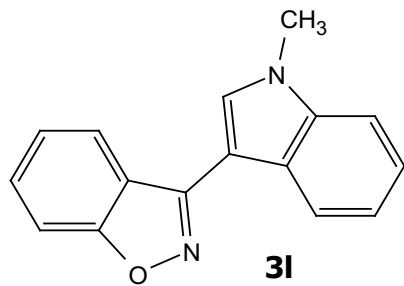




8.01
7.99
7.69
7.65
7.63
7.61
7.59
7.57
7.45
7.43
7.42
7.40
7.40
7.40
7.37
7.36
7.26

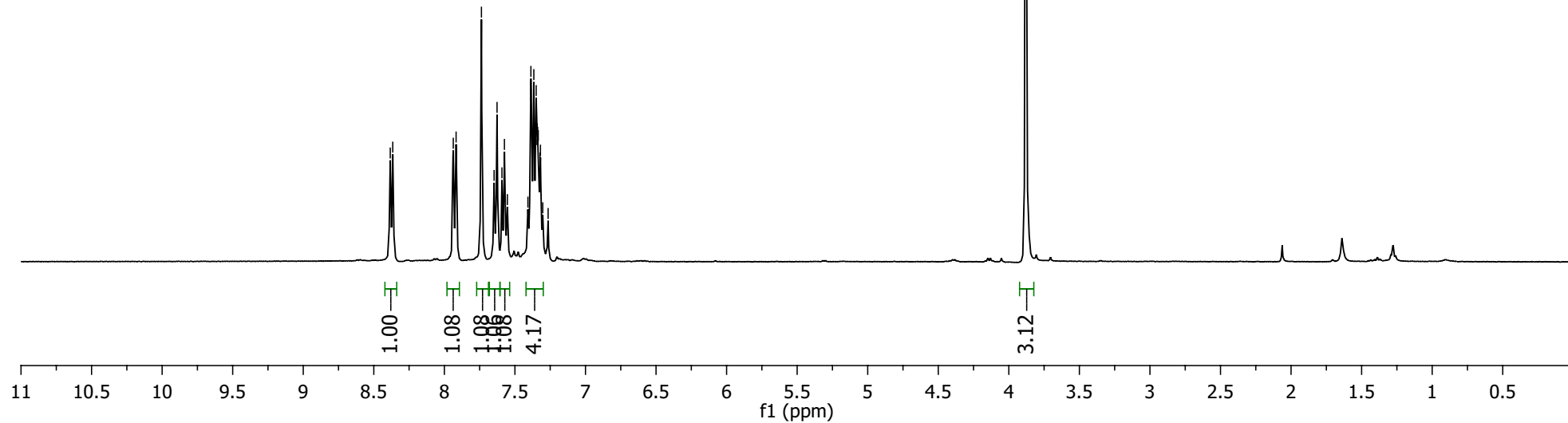


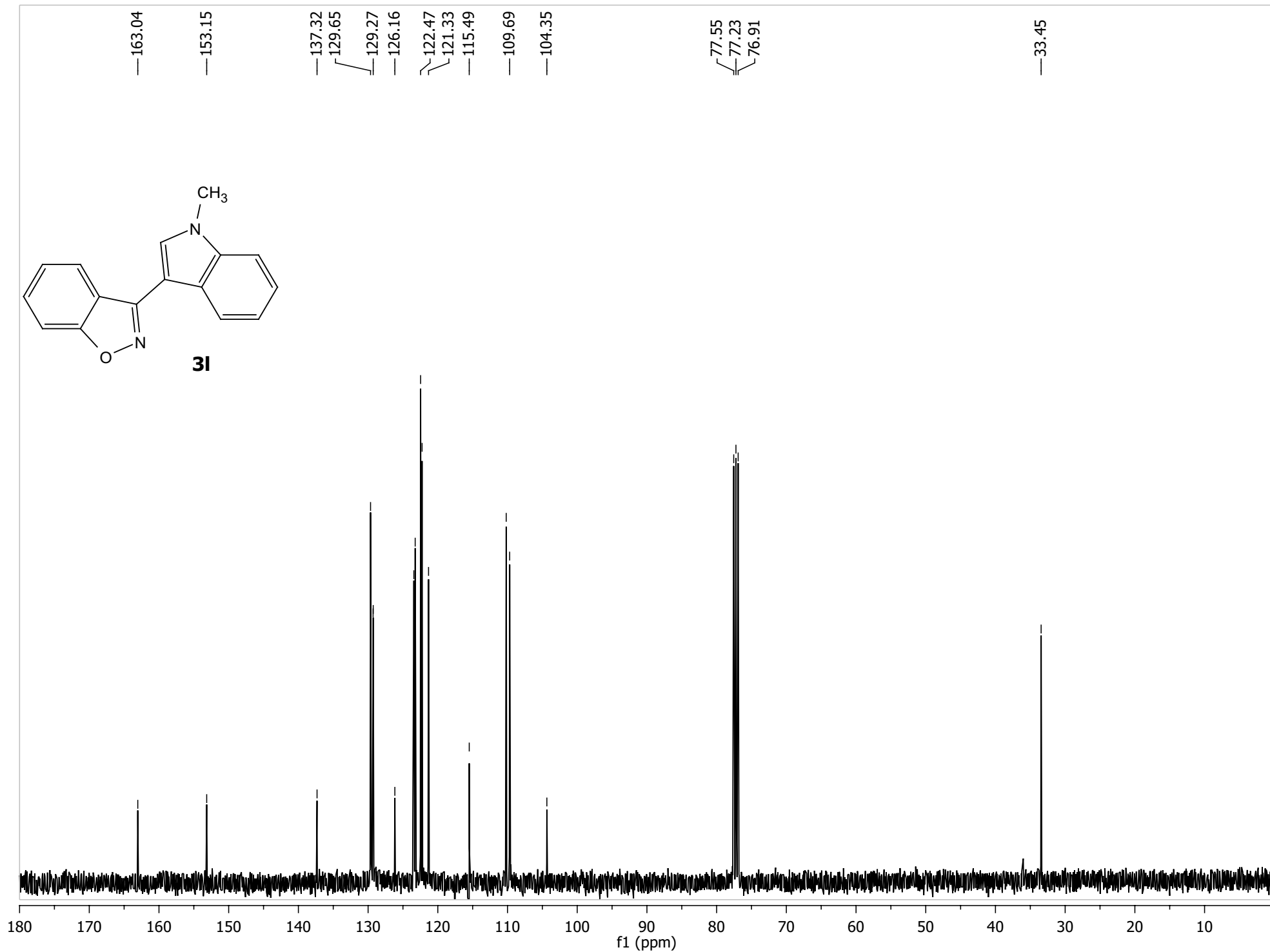
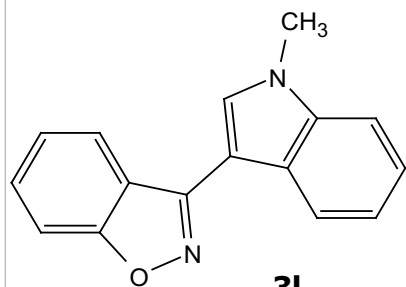


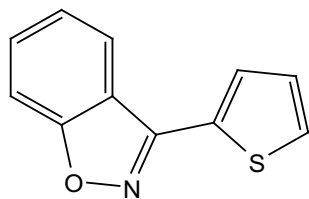


8.38
8.37
7.94
7.94
7.57
7.55
7.41
7.39
7.37
7.35
7.34
7.34
7.33
7.32
7.32
7.30
7.26

3.88

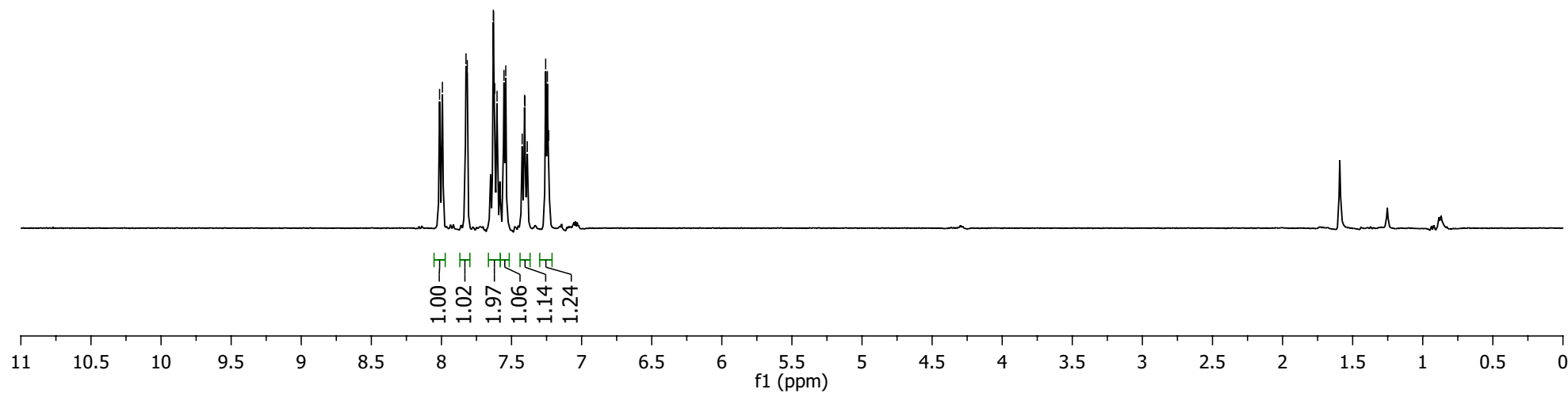


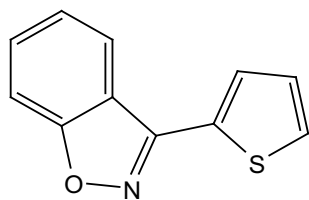




3m

8.01
7.99
7.82
7.63
7.63
7.62
7.60
7.55
7.54
7.42
7.41
7.40
7.39
7.26
7.24
7.23





3m

— 163.93

— 152.48

130.24

128.38

128.15

128.11

122.15

120.17

115.53

110.43

77.55

77.23

76.91

