

Aqueous MW eco-friendly protocol for amino group protection.

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General:

All chemicals and solvents were purchased from common commercial sources and were used as received without any further purification. All reactions were monitored by TLC on silica Merck 60 F254 percolated aluminum plates and were developed by spraying with ninhydrin solution when possible or with a GC-MS Shimadzu workstation, constituted by a GC 2010 (provided of a 30 m-QUADREX 007–5MS capillary column, operating in “splitless” mode, 1 ml min⁻¹ flow of He as carrier gas) and a 2010 quadrupole mass-detector. All reactions were carried out in the a Syntos 3000 Microwave oven (Anton-Paar) with rotor 4×24MG5. Proton nuclear magnetic resonance (¹H-NMR) spectra were recorded on a Brücker spectrometer at 300 MHz. Chemical shifts are reported in δ units (ppm) with TMS as reference (δ 0.00). All coupling constants (*J*) are reported in Hertz. Multiplicity is indicated by one or more of the following: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet). Carbon nuclear magnetic resonance (¹³C-NMR) spectra were recorded on a Brücker at 300 MHz. Chemical shifts are reported in δ units (ppm) relative to CDCl₃ (δ 77.0). Melting points were obtained on a Kofler apparatus.

General Procedure to determine the substrate scope

To a stirred solution of tosyl chloride, fmoc chloride, boc anidride and acetyl chloride (2.2 mmol), in H₂O (3 mL) was added the N-nucleophile (2.0 mmol) and conducted in MW. The reaction mixture until TLC indicated consumption of the starting material. The reaction mixture presents a organic precipitate. The same, repeatedly washed with water is subsequently dried.

***N*-Benzyl-*p*-toluenesulfonamide (1a):** yellow solid obtained in 90 % yield (mp 115.1-115.9 °C); ¹H-NMR (300 MHz, CDCl₃): δ = 7.76 (d, 2H, *J* = 8.24, CH_{ar}), 7.24 -7.32 (m, 4H, CH_{ar}), 7.17 – 7.21, (m, 2H, CH_{ar}), 4.76 (t, 1H, NH, *J* = 6.15), 4.11 (d, 2 H, CH₂, *J* = 6.22), 2.44 (s, 3H, CH₃). ¹³C-NMR (75 MHz, CDCl₃): 21.85, 47.59, 114.34, 127.52, 128.20, 129.01, 136.07, 137.26, 136.64, 143.84.

***N*-(9-Fluorenylmethoxycarbonyl) benzylamine (1b):** Colorless solid obtained in 98 % yield. ¹H-NMR (300 MHz, CDCl₃): δ = 7.58-7.79 (m, 4H, CH_{ar}), 7.25-7.46 (m, 5H, CH_{ar}), 4.51 (dd, 2H, CH₂), 4.21-4.39 (m, 2 H, CH₂). ¹³C-NMR (75 MHz, CDCl₃): 46.20, 47.32, 66.71, 79.74, 125.00, 127.05, 127.39, 127.55, 127.69, 127.27, 128.73, 141.33, 142.42, 143.93, 156.43.

***N*-(tert-Butoxycarbonyl) benzylamine (1c):** white solid obtained in 98% yield (mp 55-57 °C); ¹H-NMR (300 MHz, CDCl₃): δ = 7.25-7.35 (m, 5H, CH_{ar}), 4.31 (d, *J*= 5.49, 2H), 1.46 (s, 9H) ¹³C-NMR (75 MHz, CDCl₃): 46.20, 47.32, 66.71, 79.74, 125.00, 127.05, 127.39, 127.55, 127.69, 127.27, 128.73, 141.33, 142.42, 143.93, 156.43.

***N*-benzylacetamide (1d):** yellow flake solid obtained in 98% yield (mp 60-62°C). Spectroscopic data compared to those of the pure product.

***N*-phenyl-*p*-toluenesulfonamide (2a):** white solid obtained in 98 % yield (mp 101.5-102.2 °C); ¹H-NMR (300 MHz, CDCl₃): 7.67 (d, J= 7.5 Hz, 2H, CHar), 7.08-7.32 (m, 5H, H-Ar), 7.11 (d, J= 7.5 Hz, 2H, CHar), 2.38 (s, 3H, CH₃), 1.74, (s, 1H, NH). ¹³C-NMR (75 MHz, CDCl₃): 21.5, 111.1, 121.1, 125.7, 126.0, 129.5, 136.7, 143.1. 149.6.

***N*-(9-fluorenylmethoxycarbonyl) aniline (2b):** Brown solid obtained in 92 % yield; ¹H-NMR (300 MHz, CDCl₃) δ = 7.79 (d, 2H, CHar, J=7.4 Hz), 7.63 (d, 2H, CHar, J=7.0 Hz), 7.43-7.05 (m, 8H, CHar), 6.63 (br s, 1H), 4.56 (d, 2H, J=6.4 Hz), 4.28 (t, 1H, J=6.4 Hz). ¹³C-NMR (75 MHz, CDCl₃) δ: 47.1, 66.8, 118.81, 120.0, 123.6, 124.9, 127.1, 127.8, 129.1, 137.7, 141.4, 143.8, 153.4.

***N*-(tert-Butoxycarbonyl) aniline (2c):** White solid obtained in 94 % yield (mp 133-137 °C); ¹H-NMR (300 MHz, CDCl₃) ¹H-NMR (300 MHz, CDCl₃): δ = 7.38-7.25 (m, 4 H), 1.52 (s, 9H), 7.25 (tt, 1H, Ar, J= 7.27; J= 1.38), 6.49 (s, 1H, NH), ¹³C-NMR (75 MHz, CDCl₃): 28.69, 80.83, 118.89, 123.38, 129.31, 138.69, 153.99.

***N*-Acetyl aniline (2d):** White solid obtained in 98 % yield (114-116 °C). Spectroscopic data compared to those of the pure product.

***N*-toluidine *p*-toluenesulfonamide (3a):** Colorless oil obtained in 98 % yield. Spectroscopic data compared to those of the pure product.

***N*-(9-Fluorenylmethoxycarbonyl)-toluidine (3b):** colorless solid obtained in 90 % yield (mp 195-197 °C). ¹H-NMR (300 MHz, CDCl₃) δ= 7.79-7.77 (m, 2H, CH_{ar}), 7.63-7.61 (m, 2H, CH_{ar}), 7.44-7.26 (m, 6H, CH_{ar}), 7.11-7.09 (m, 2H, CH_{ar}), 7.08-6.90 (m, 4H, CH_{ar}), 4.53 (m, 2H), 4.27 (br, 1H, NH), 2.30 (s, 3H), ¹³C-NMR (75 MHz, CDCl₃) δ = 20.76, 47.17, 66.74, 120.03, 127.11, 127.16, 129.55, 141.86, 143.8.

***N*-(tert-Butoxycarbonyl)-toluidine (3c):** brown solid obtained in 98 % yield (mp 34–36 °C); ¹H-NMR (300 MHz, CDCl₃): δ = 7.22-7.26 (m, 2H, CH_{ar}), 7.08 (d, J= 8.25, 2H, CH_{ar}), 6.56 (s, 1H, NH), 2.29 (s, 3H), 1.50 (s, 9H); ¹³C-NMR (75 MHz, CDCl₃): 28.69, 80.64, 119.03, 129.78, 132.87, 136.06, 153.23

***N*-Acetyl-toluidine (3d):** off white to brown flake solid obtained in 97 % yield (mp 34–36 °C).

***N*-(*p*-nitro-aniline) *p*-toluenesulfonamide (4a):** yellow flake solid obtained in 85 % yield (mp 190-191 °C). Spectroscopic data compared to those of the pure product.

***N*-(9-fluorenylmethoxycarbonyl) *p*-nitro-aniline (4b):** yellow solid obtained in 80 % yield. ¹H-NMR (300 MHz, CDCl₃): δ = 8.14-8.17 (m, 2H, CHar), 7.19-7.79 (m, 10H, CHar), 4.53 – 4.63 (m, 1H, CH), 4.26 (t, 2 H, CH₂, J = 6.05). ¹³C-NMR (75 MHz, CDCl₃): 46.20, 47.32, 66.71, 79.74, 125.00, 127.05, 127.39, 127.55, 127.69, 127.27, 128.73,

141.33, 142.42, 143.93, 156.43.

***N*-(*tert*-Butoxycarbonyl) *p*-nitro-aniline (4c)** yellow flake oil obtained in 98 % yield. Spectroscopic data compared to those of the pure product. ***N*-*p*-nitro-aniline acetamide (4d)**: Solid, yellow obtained in 96% yield (mp 214-216 °C). Spectroscopic data compared to those of the pure product.

***N*-*p*-nitro-aniline-*p*-toluenesulfonamide (5a)** white solid obtained in 98% yield (mp 181-183°C). Spectroscopic data compared to those reported in the literature.²⁰

***N*-(9-fluorenylmethoxycarbonyl) *p*-methoxybenzylamine (5b)**: yellow solid obtained in 95 % yield (mp). ¹H NMR (300 MHz, CDCl₃) δ: 7.77 (d, 2H, J=7.0 Hz), 7.59 (d, 2H, J=5.8 Hz), 7.51-7.19 (m, 6H), 6.87 (d, 2H, J=6.9 Hz), 4.45 (d, 2H, J=5.5 Hz), 4.45-4.22 (m, 5 H) 3.80 (s, 3H). ¹³C-NMR (75 MHz, CDCl₃) δ: 44.6, 47.3, 55.3, 66.6, 114.1, 120.0, 125.0, 127.0, 127.7, 128.9, 130.5, 141.3, 143.9, 156.3, 159.1

***N*-(*tert*-Butoxycarbonyl) *p*-methoxybenzylamine (5c)**: colourless oil 98. ¹H-NMR (300 MHz, CDCl₃) δ = 7.26-7.19 (m, 2H, CHar), 6.87- 6.84 (m, 2H, CHar), 4.25-4.23 (m, 2 H, CH₂), 3.79 (s, 3H), 1.47 (s, 9H), ¹³C-NMR (75 MHz, CDCl₃): 28.76, 44.52, 55.64, 79.74, 114.34, 129.19, 131.36, 156.18, 159.25.

***p*-methoxybenzyl acetamide (5d)**: yellow oil obtained in 97 % yield. Spectroscopic data compared to those of the pure product.

***N*-Octyl *p*-toluenesulfonamide (6a)**: yellow oil obtained in 83 % yield. ¹H-NMR (300 MHz, CDCl₃) δ = 7.73 (d, J= 7.4 Hz, 2H, CHar), 7.31 (d, J= 7.4 Hz, 2H, CHar), 3.17-3.15 (m, 2H, NCH₂), 2.40 (s, 3H, CH₃), 1.56-1.53 (m, 2H, CH₂), 1.37- 1.20 (m, 10 H, 5 CH₂) ,0.90- 1.00 (m, 3 H, CH₃),. ¹³C-NMR (75 MHz, CDCl₃): 14.38, 22.83, 24.53, 43.53, 27.11, 29.48, 29.61, 31.23, 41.50, 127.28, 128.97, 136.37, 141.74.

***N*-(9-fluorenylmethoxycarbonyl) Octylamine (6b)**: Pale yellow solid obtained in 95% yield (mp 91-93°C). ¹H-NMR (300 MHz, CDCl₃): δ = 7.80-7.19 (m, 8H, CH_{ar}), 4.50-4.32 (m, 2H, CH₂O), 4.32-4.20 (m, 1 H, CH), 3.19 (dd, 2H, NCH₂, J = 12.9, J = 6.66), 1.58–1.40 (m, 2H, CH₂), 1.38-1.05- (m, 10 H, 5 CH₂), 0.90-0.70 (m, 3 H, CH₃). ¹³C-NMR (75 MHz, CDCl₃): 14.42, 22.97, 44.52, 27.07, 29.54, 29.57, 32.12, 41.44, 47.65, 66.80, 120.28, 125.36, 127.34, 127.97, 141.66, 144.37, 156.75.

***N*-(*tert*-Butoxycarbonyl) Octylamine (6c)**: Colourless oil obtained in 91% yield. Spectroscopic data compared to those reported in the literature.²¹

***N*-Octyl acetamide (6d)**: Colorless oil obtained in 97% yield. Spectroscopic data compared to those of the pure product.

***p*-toluenesulfonamide phenylalanine (7a):** White solid obtained in 98 % yield (mp 165- 166 °C). Spectroscopic data compared to those of the pure product.

***N*-(9-fluorenylmethoxycarbonyl)-phenylalanine (7b):** white solid obtained in 92 % yield (mp 180-187 °C). Spectroscopic data compared to those of the pure product.

***N*-(*tert*-Butoxycarbonyl)-phenylalanine (7c):** white solid obtained in 94 % yield (mp 85- 87 °C). Spectroscopic data compared to those of the pure product.

***N*-Acetil-phenylalanine (7d):** white solid obtained in 97 % yield (mp 171-173 °C). Spectroscopic data compared to those of the pure product.

***p*-toluenesulfonamide phenylalanine methyl ester (8a):** white solid obtained in 94% yield. ¹H-NMR (CDCl₃, 300 MHz) δ 7.63 (d, J=8.25 Hz, 2H), 7.28-7.20 (M, 5H), 7.05 (dd, J=5.42, 2.02 Hz, 2H), 5.08 (d, 1H, NH, J = 9.06), 4.20 (dt, J= 9.06, J = 5.90, Hz, 2H), 3.48 (s, 3H, CH₃), 3.02 (d, 2H, J = 5.90), 2.40 (s, 3H, CH₃); ¹³C-NMR (CDCl₃, 75 MHz) δ= 21.84, 39.70, 52.68, 56.93, 127.50, 127.57, 128.90, 129.72, 129.92, 135.25, 136.94, 143.92, 171.56.

***N*-(9-fluorenylmethoxycarbonyl)-phenylalanine methyl ester (8b):** white solid obtained in 92% yield . ¹H-NMR (CDCl₃, 300 MHz) d 7.76 (d, J=7.5 Hz, 2H), 7.56 (t, J=6.7 Hz, 2H), 7.40 (td, J=7.5, 0.6 Hz, 2H), 7.33–7.27 (m, 5H), 7.08 (d, J=6.5 Hz, 2H), 5.26 (d, J=8.1 Hz, 1H), 4.67 (m, 1H), 4.44 (dd, J=10.6, 7.1 Hz, 1H), 4.34 (dd, J=10.6, 6.9 Hz, 1H), 4.20 (t, J=7.0 Hz, 1H), 3.73 (s, 3H), 3.11 (m, 2H); ¹³C-NMR (CDCl₃, 75 MHz) δ= 38.4, 47.3, 52.6, 54.9, 67.1, 120.2, 125.3, 127.3, 127.4, 127.9, 128.8, 129.5, 135.9, 141.5, 144.0, 155.7, 172.1.

***N*-(*tert*-Butoxycarbonyl)-phenylalanine methyl ester (8 c):** white solid obtained in 96% yield. (mp 36-40 °C). Spectroscopic data compared to those of the pure product.

***N*-Acetil-phenylalanine methyl esther (8d):** colorless oil obtained in 95% yield. Spectroscopic data compared to those of the pure product.

***p*-toluenesulfonamide alanine (9a):** white solid obtained in 96% (mp 132-137 °C). Spectroscopic data compared to those of the pure product.

***N*-(9-fluorenylmethoxycarbonyl)-alanine (9b):** white solid obtained in 96% (mp 147-153 °C). Spectroscopic data compared to those of the pure product.

***N*-(*tert*-Butoxycarbonyl)- alanine (9c):** white solid obtained in 96% (mp 79-83 °C). Spectroscopic data compared to those of the pure product.

***N*-Acetil-alanine (9d):** white solid obtained in 96 % yield. (mp 126-128 °C). Spectroscopic data compared to those of the pure product.

***p*-toluenesulfonamide alanine methyl ester (10a):** white solid obtained in 98% yield (mp 101-103 °C). Spectroscopic data compared to those reported in the literature.²²

***N*-(9-fluorenylmethoxycarbonyl)-alanine methyl ester (10b):** white solid obtained in 92% yield (mp 110–112 °C). Spectroscopic data compared to those of the pure product.

***N*-(*tert*-Butoxycarbonyl)-alanine methyl ester (10c):** colorless oil obtained in 93% yield. Spectroscopic data compared to those reported in the literature.²³

***N*-Acetil-alanine methyl ester (10 d):** colorless oil obtained in 97% yield. Spectroscopic data compared to those of the pure product.

***p*-toluenesulfonamide isoleucine (11a):** white solid obtained in 86% yield (mp 140-145 °C). Spectroscopic data compared to those of the pure product.

***N*-(9-fluorenylmethoxycarbonyl)-isoleucine (11b):** white solid obtained in 80% yield (mp 145-147 °C). Spectroscopic data compared to those of the pure product.

***N*-(*tert*-Butoxycarbonyl)-isoleucine (11c)** white solid obtained in 85% yield (mp 66-69 °C). Spectroscopic data compared to those of the pure product.

***N*-Acetil-isoleucine (11d)** white solid obtained in 87% yield (mp 132-147 °C). Spectroscopic data compared to those of the pure product.

***p*-toluenesulfonamide isoleucine methyl ester (12a):** white solid obtained in 98% yield (mp 84–86 °C). Spectroscopic data compared to those reported in the literature.²⁴

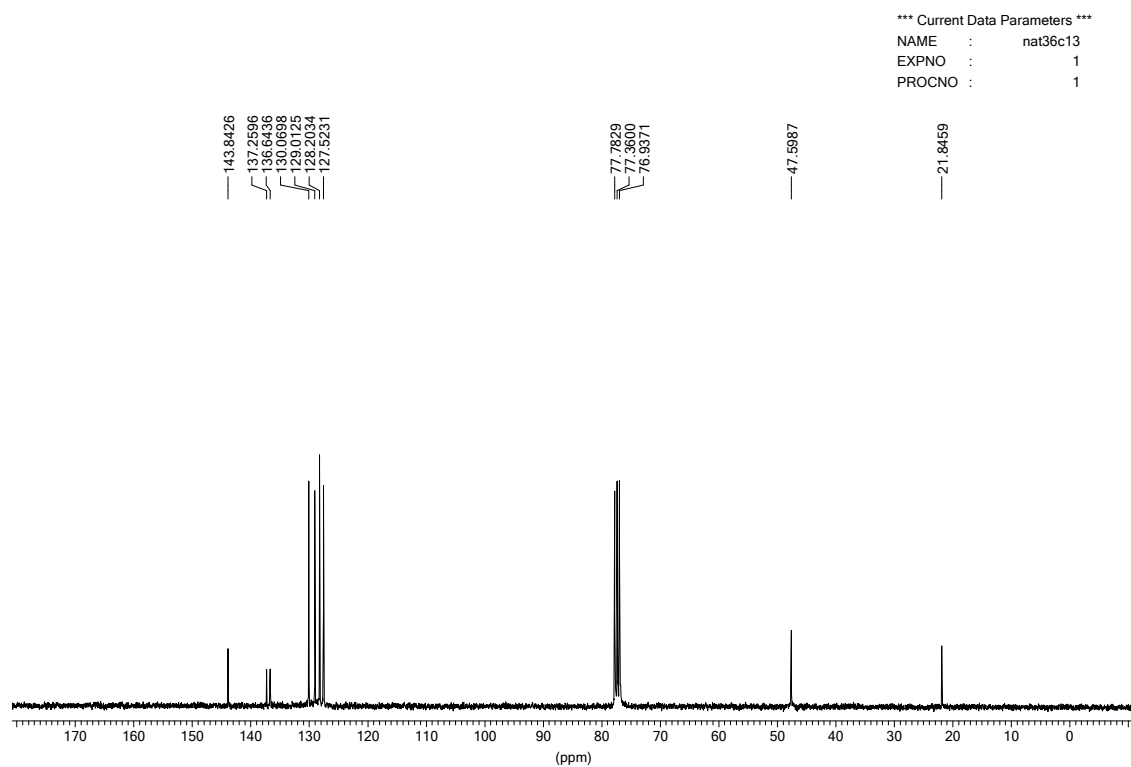
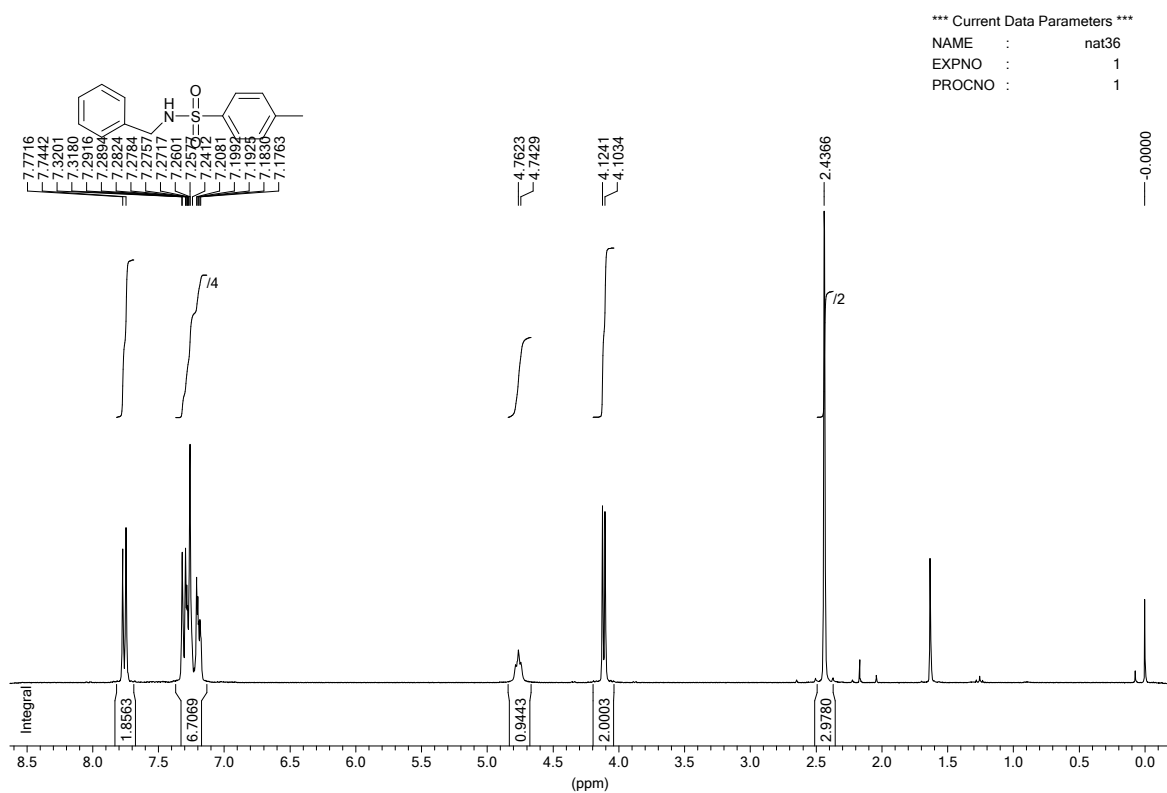
***N*-(9-fluorenylmethoxycarbonyl) isoleucine methyl ester (12b):** white solid obtained in 93% yield (mp 140-143 °C). Spectroscopic data compared to those of the pure product.

***N*-(*tert*-Butoxycarbonyl)-isoleucine methyl ester (12c):** white solid obtained in 97% yield (mp 68-72°C). Spectroscopic data compared to those of the pure product.

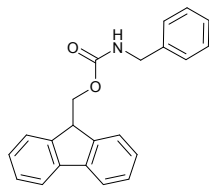
***N*-Acetil-isoleucine methyl ester (12d):** colorless oil obtained in 95% yield. Spectroscopic data compared to those of the pure product.

^1H , and ^{13}C spectra of compounds

1a

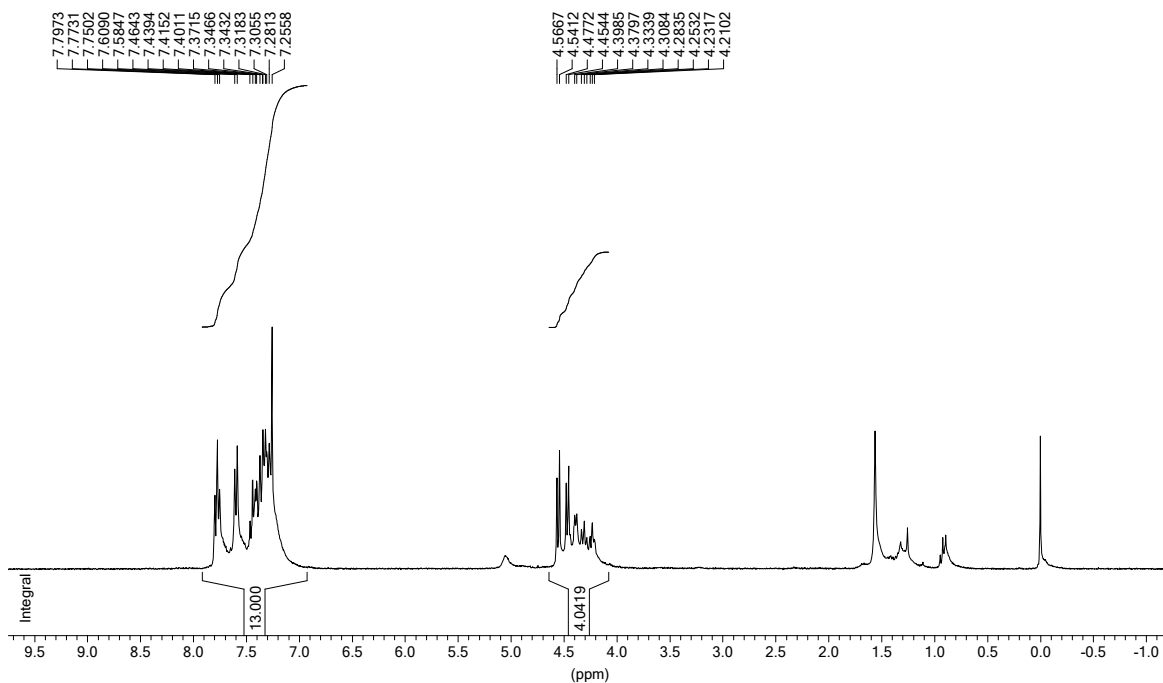


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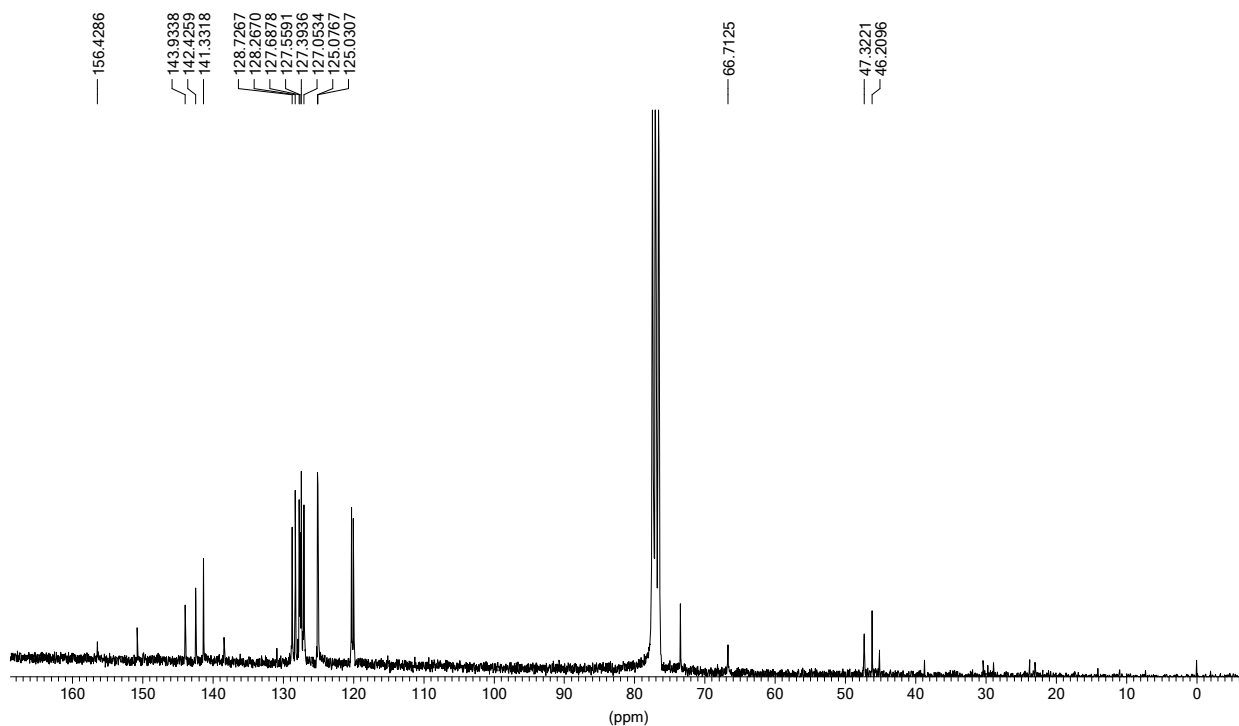
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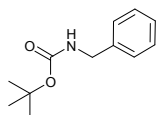


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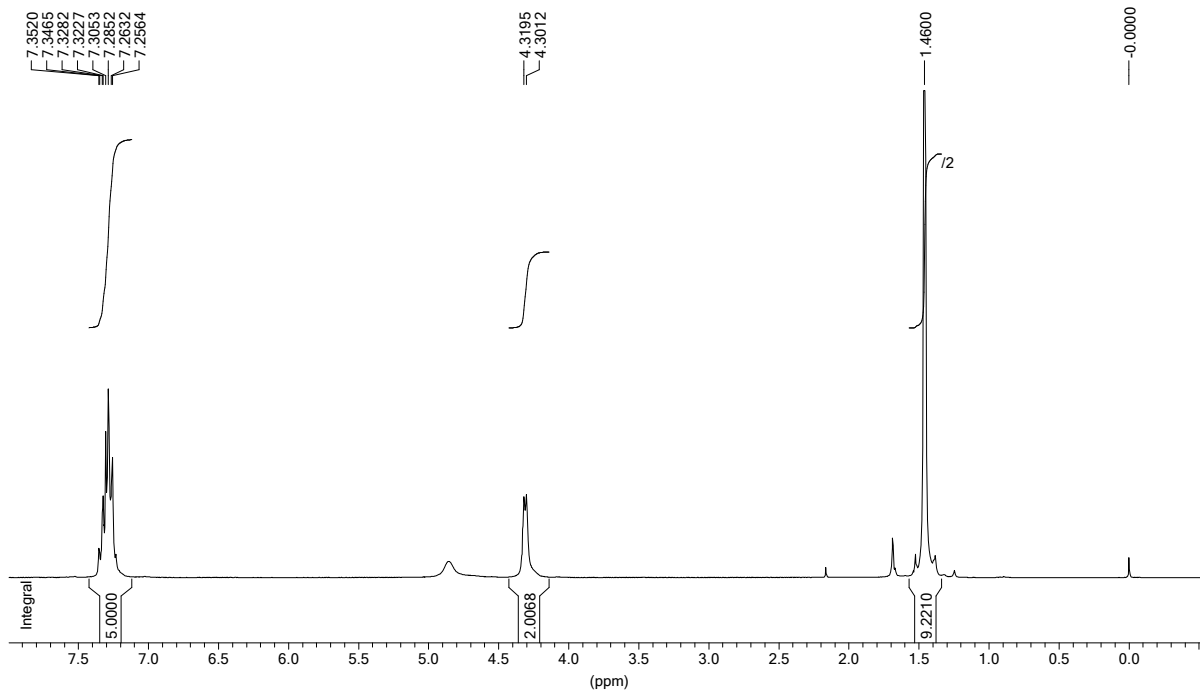


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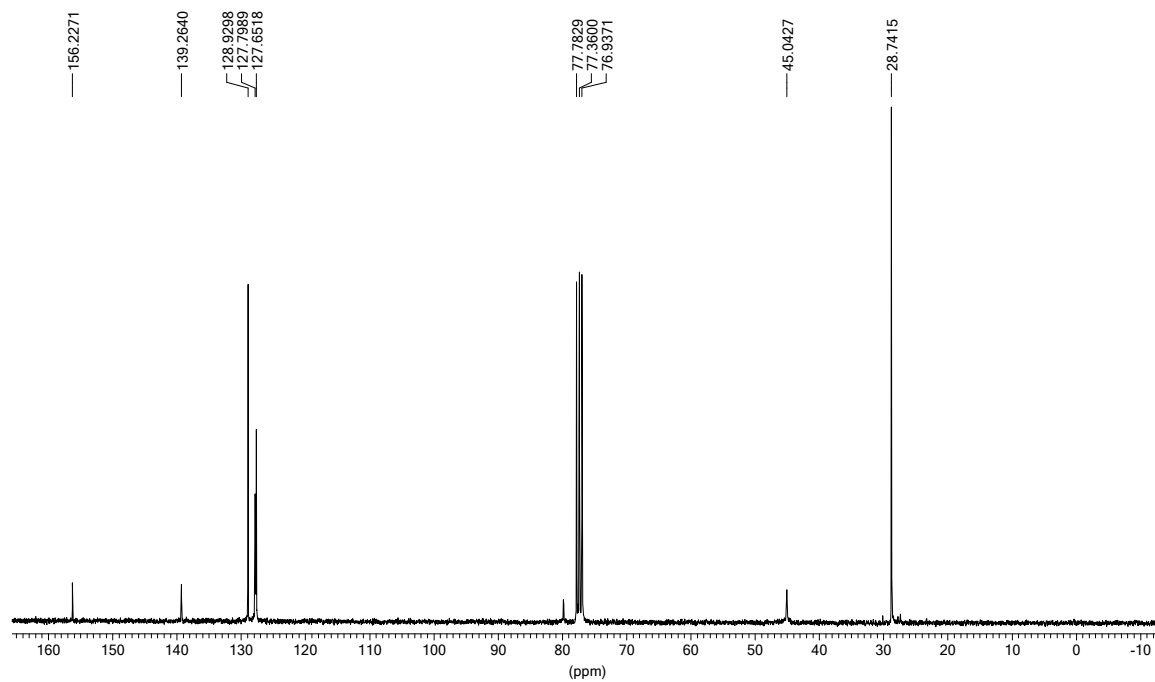
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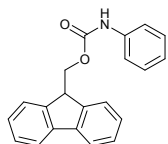


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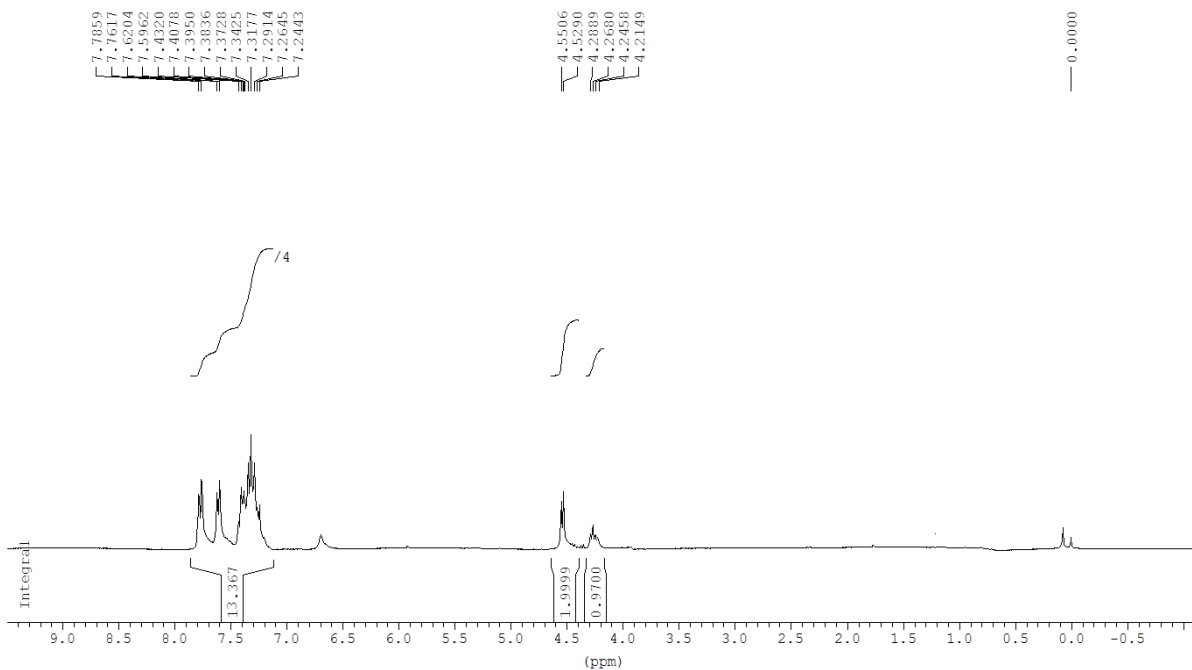
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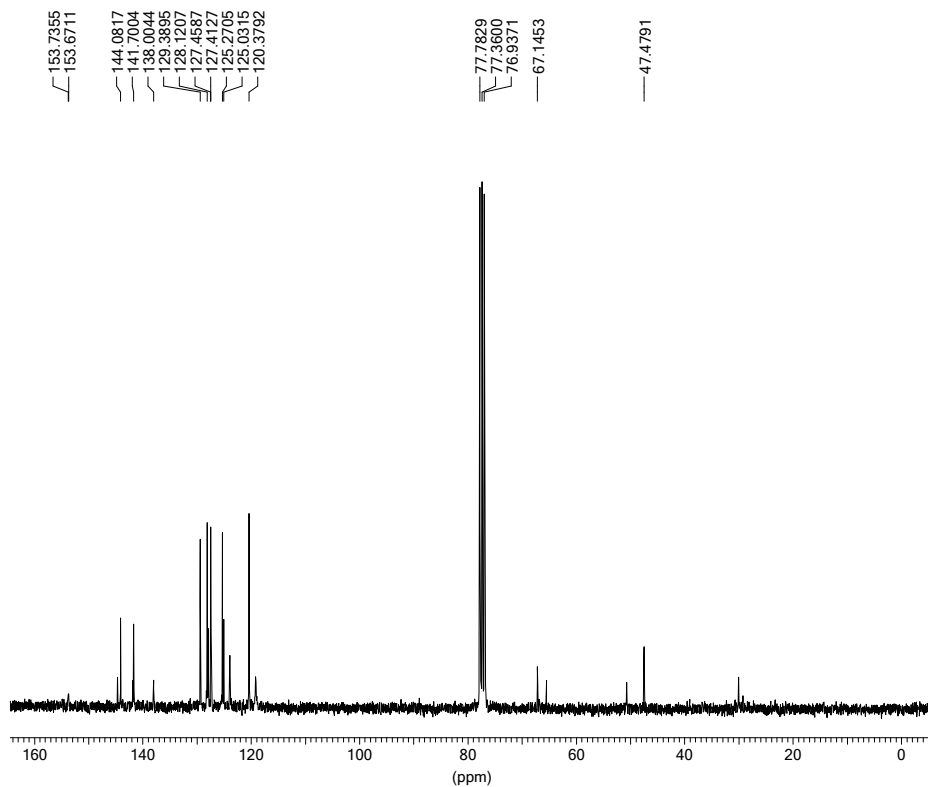
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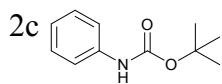


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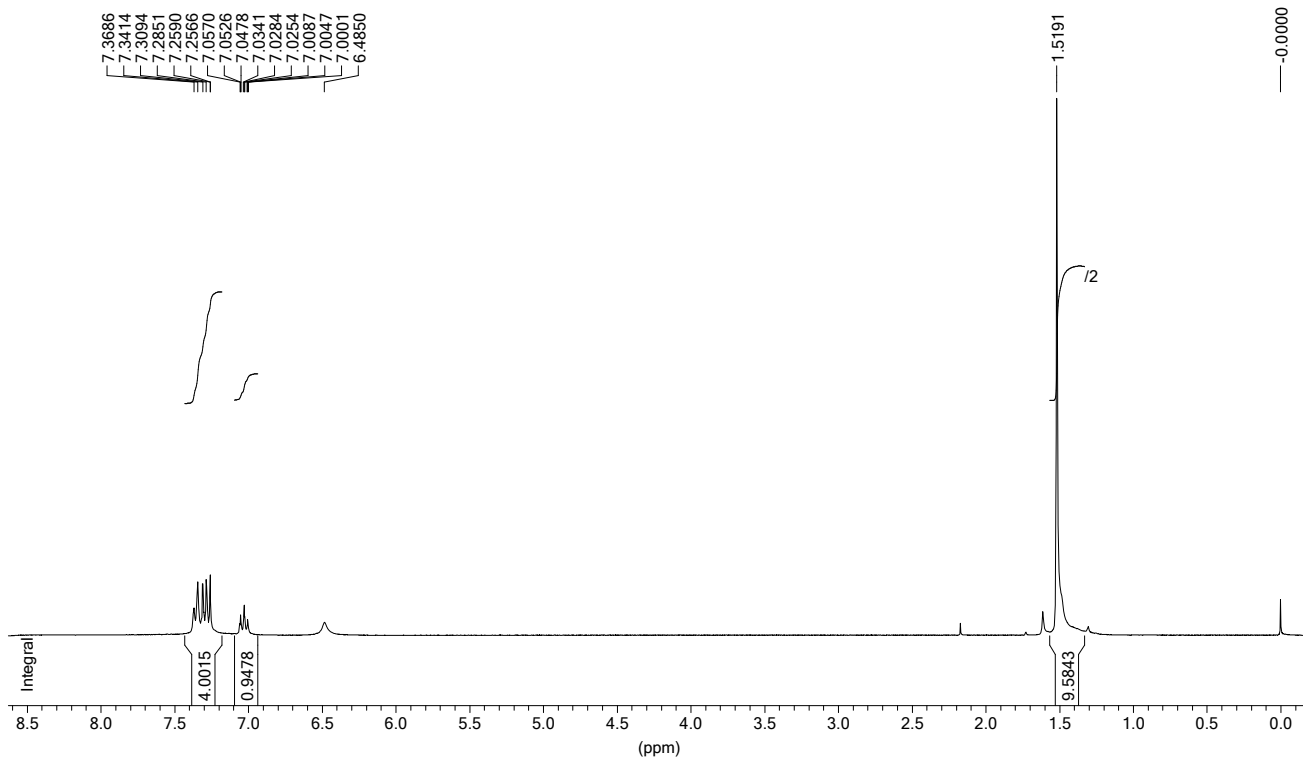
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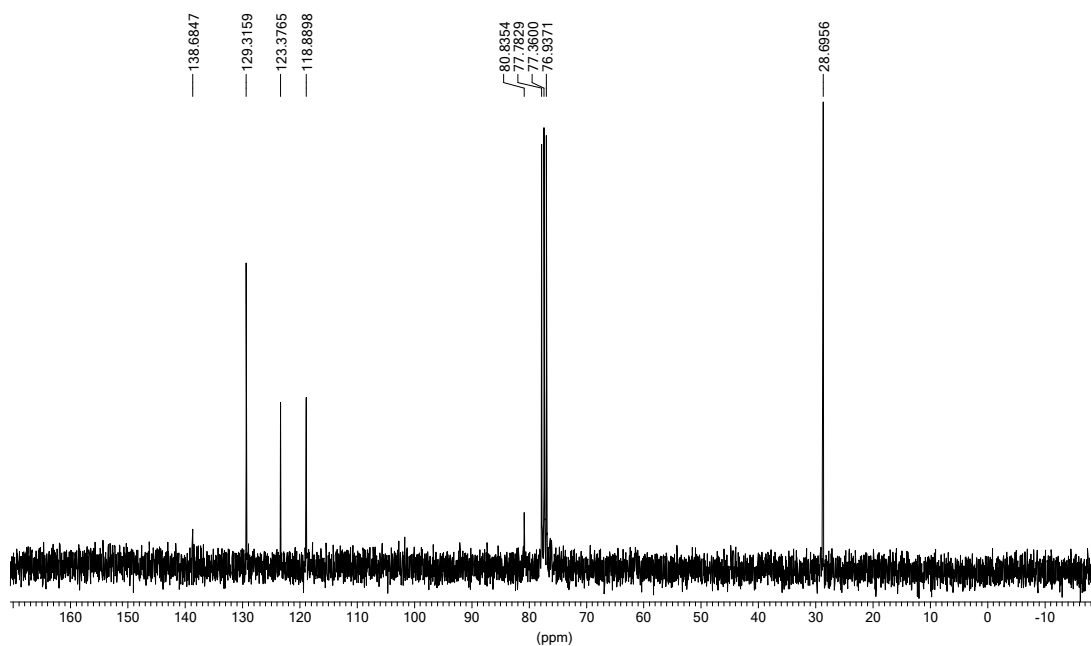
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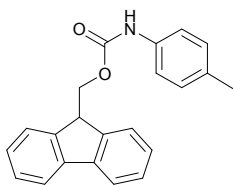


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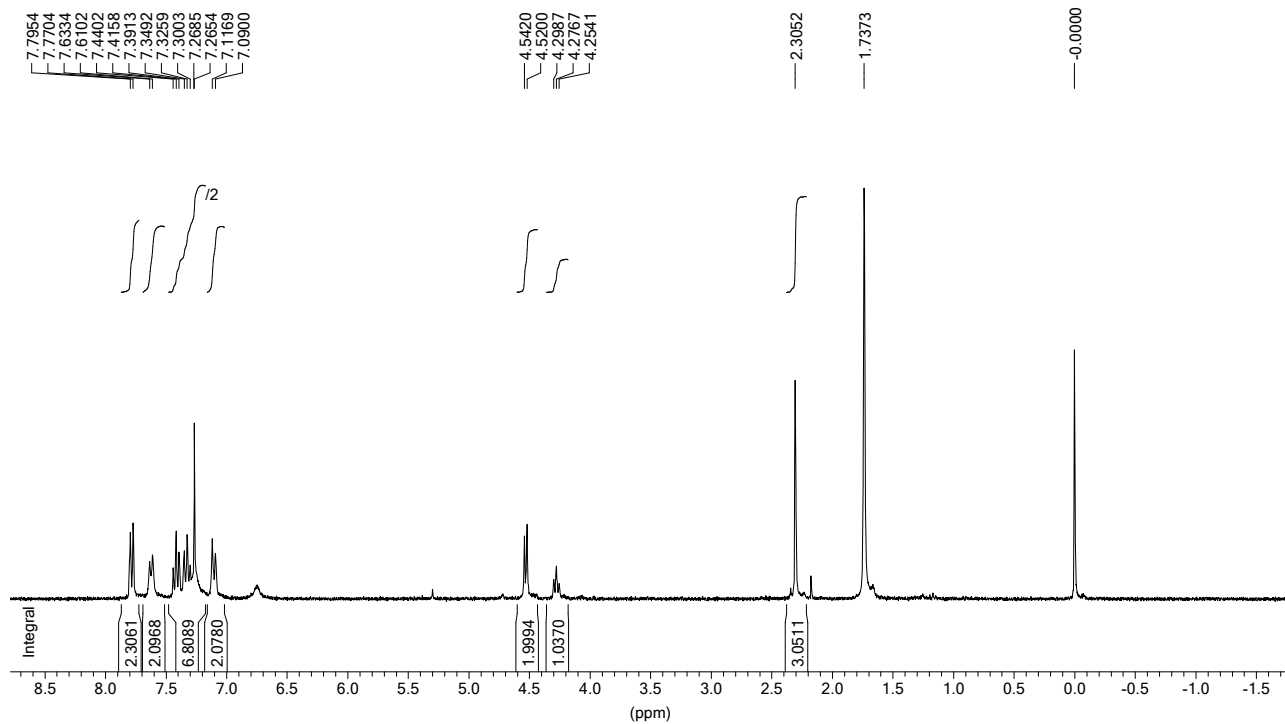


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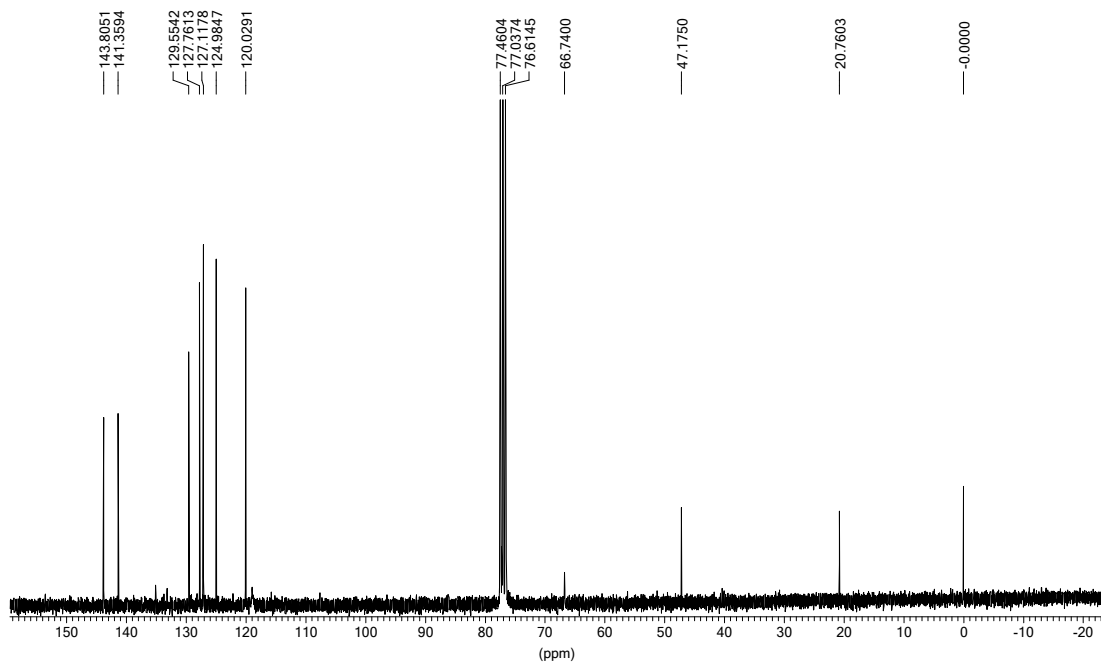
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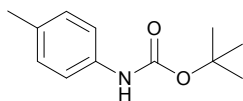


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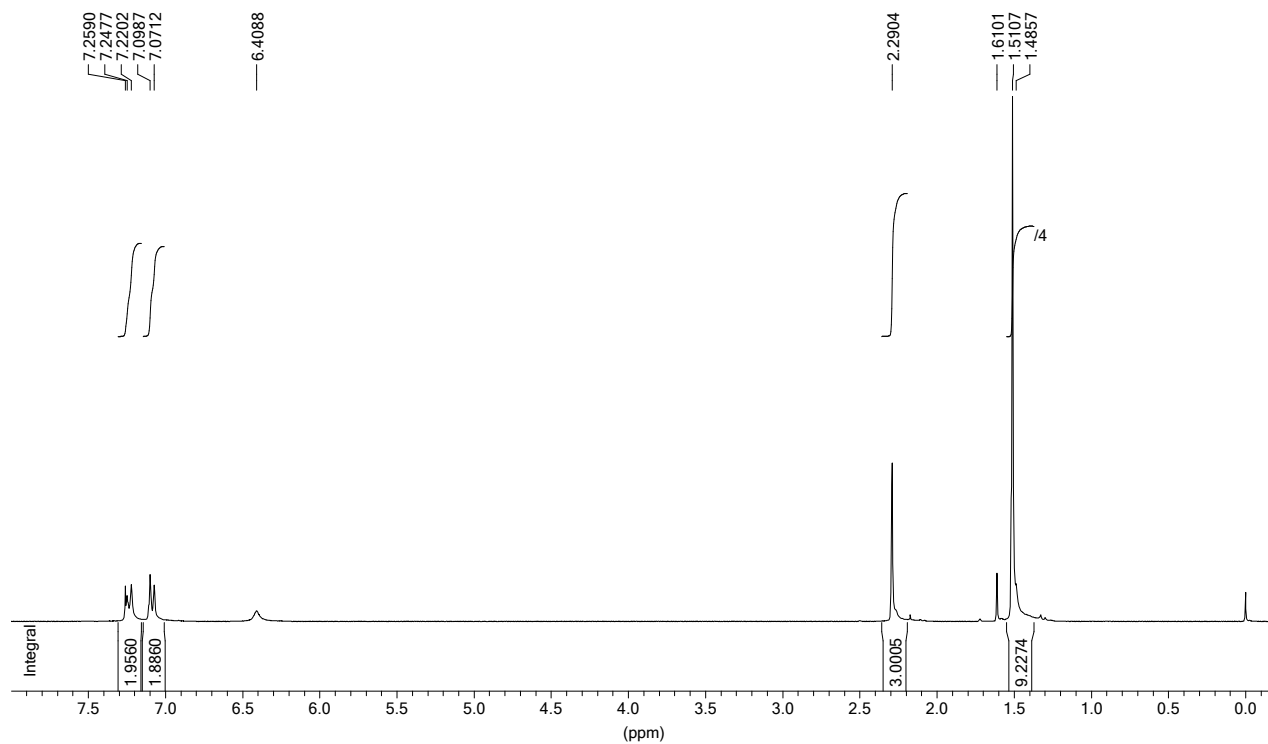


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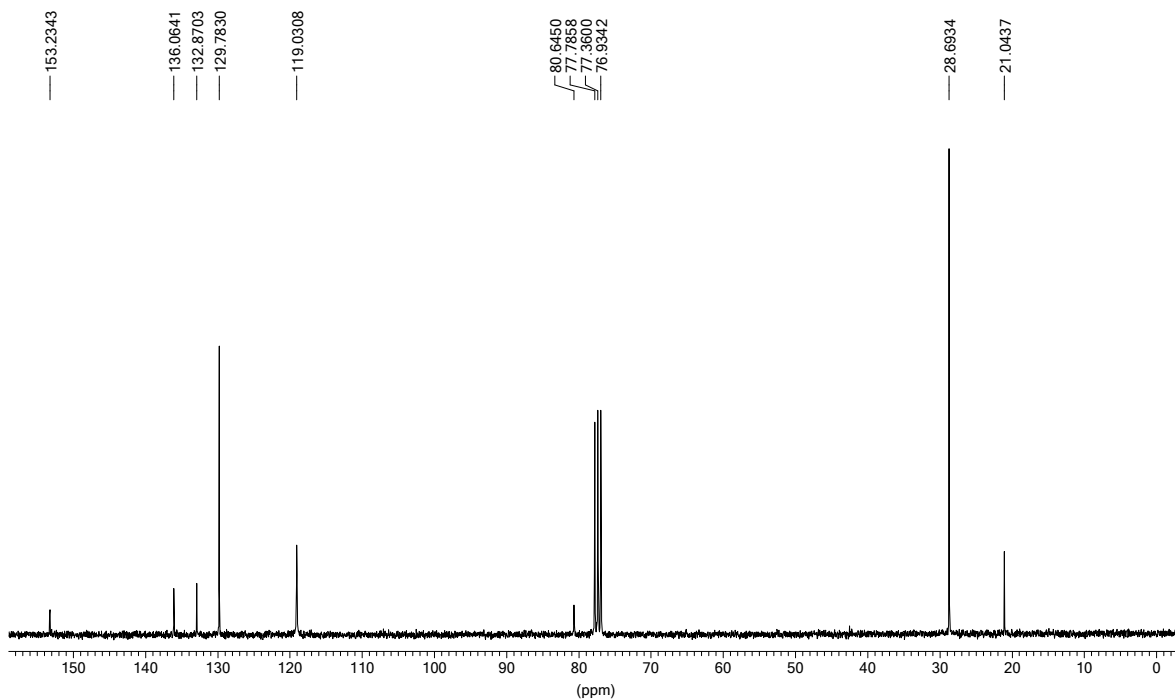
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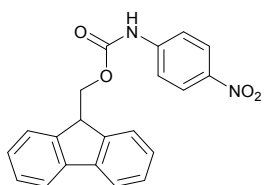


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4b



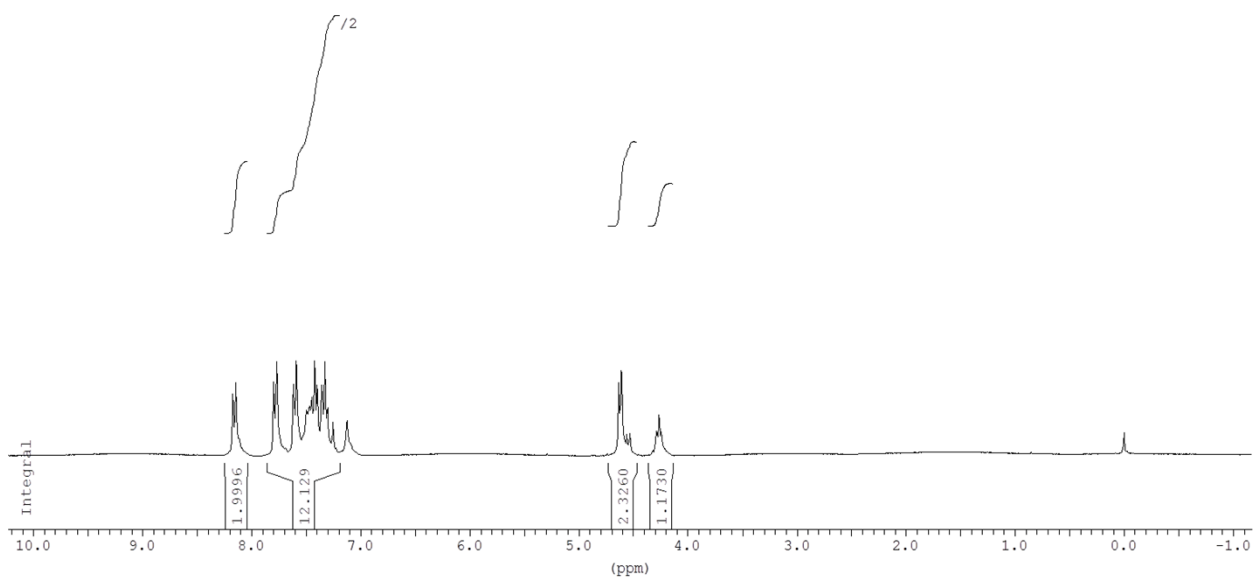
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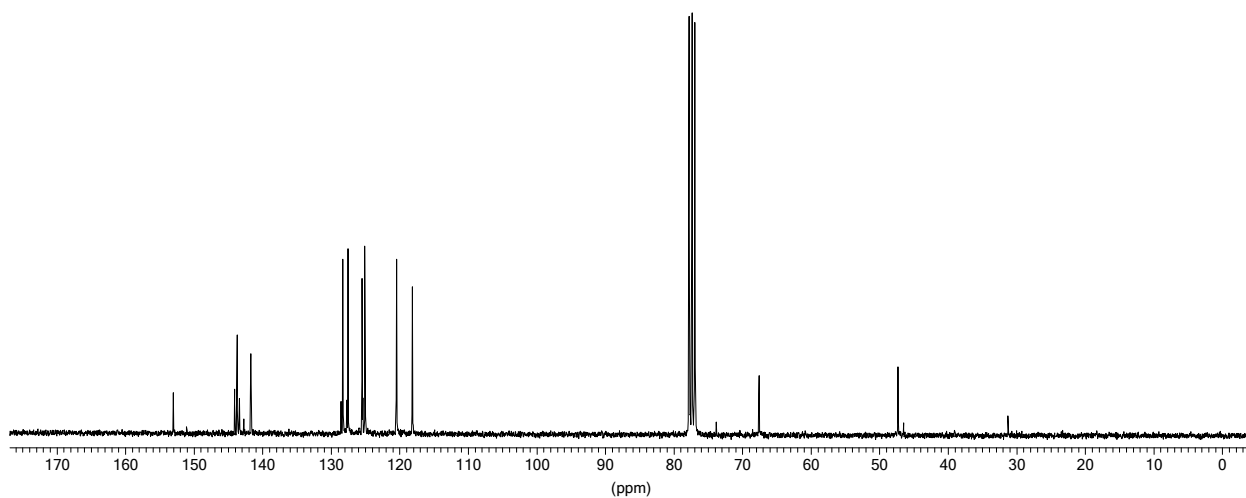


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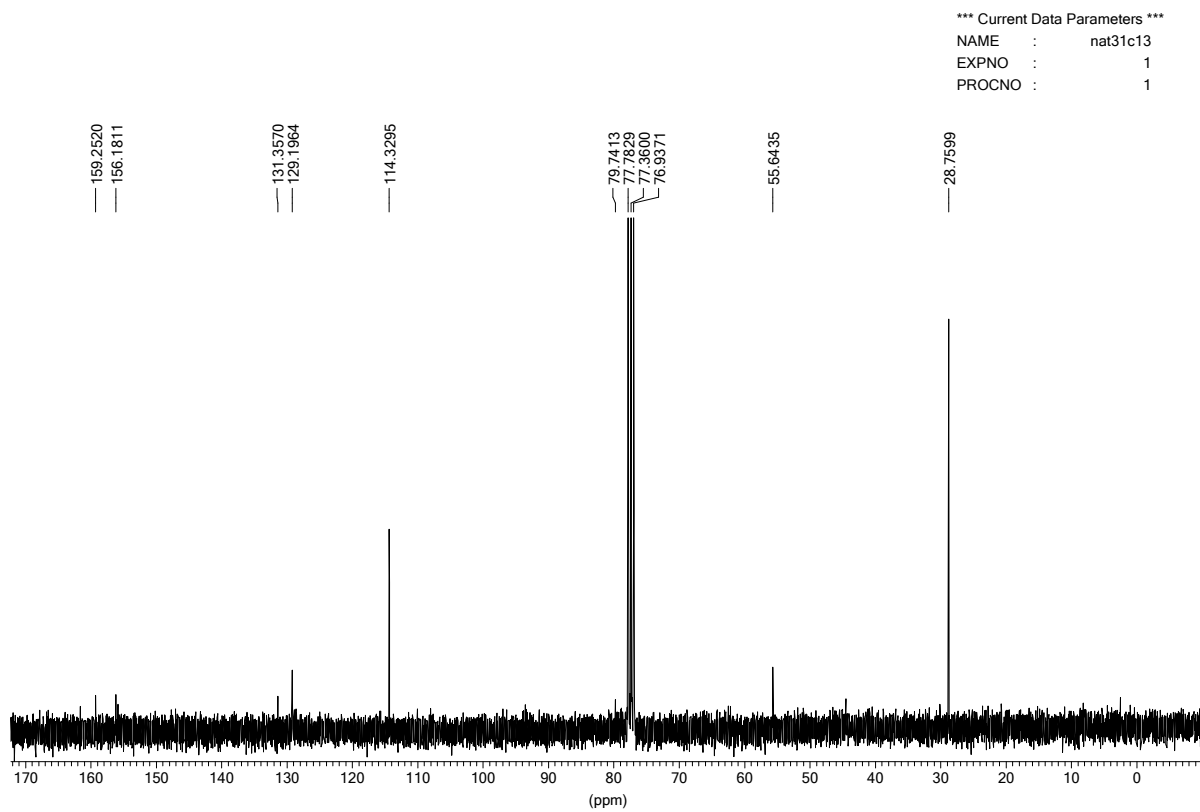
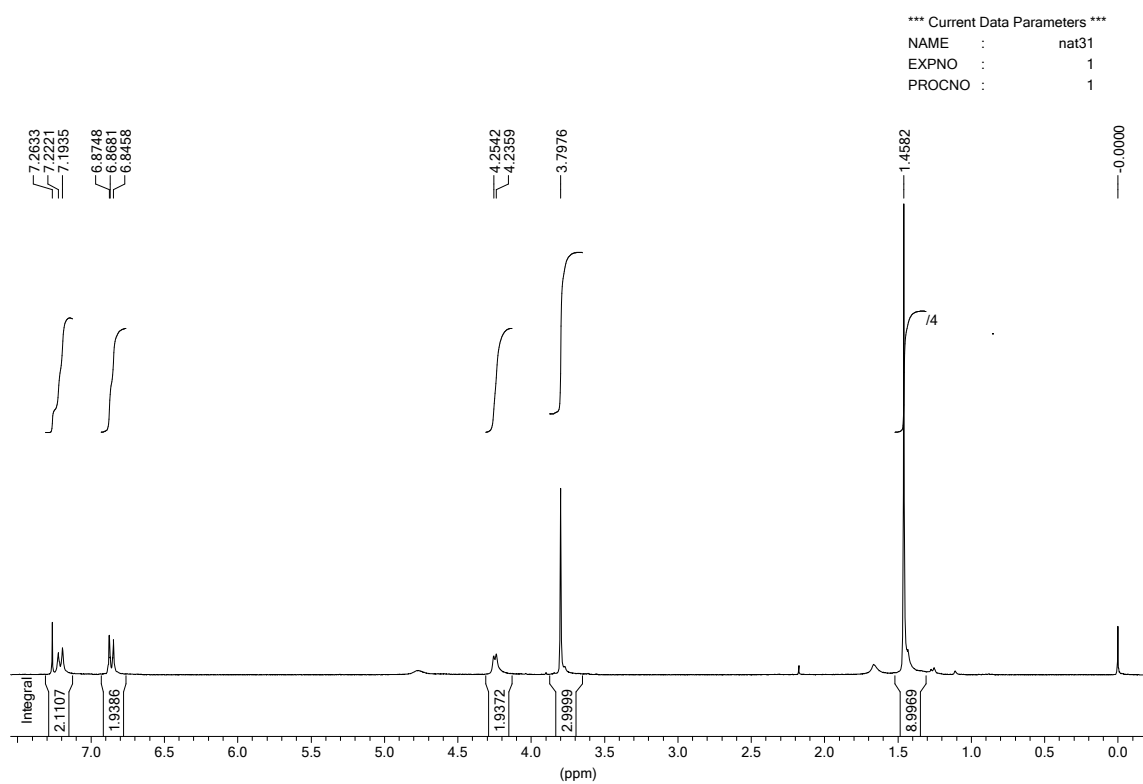
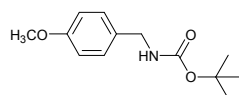
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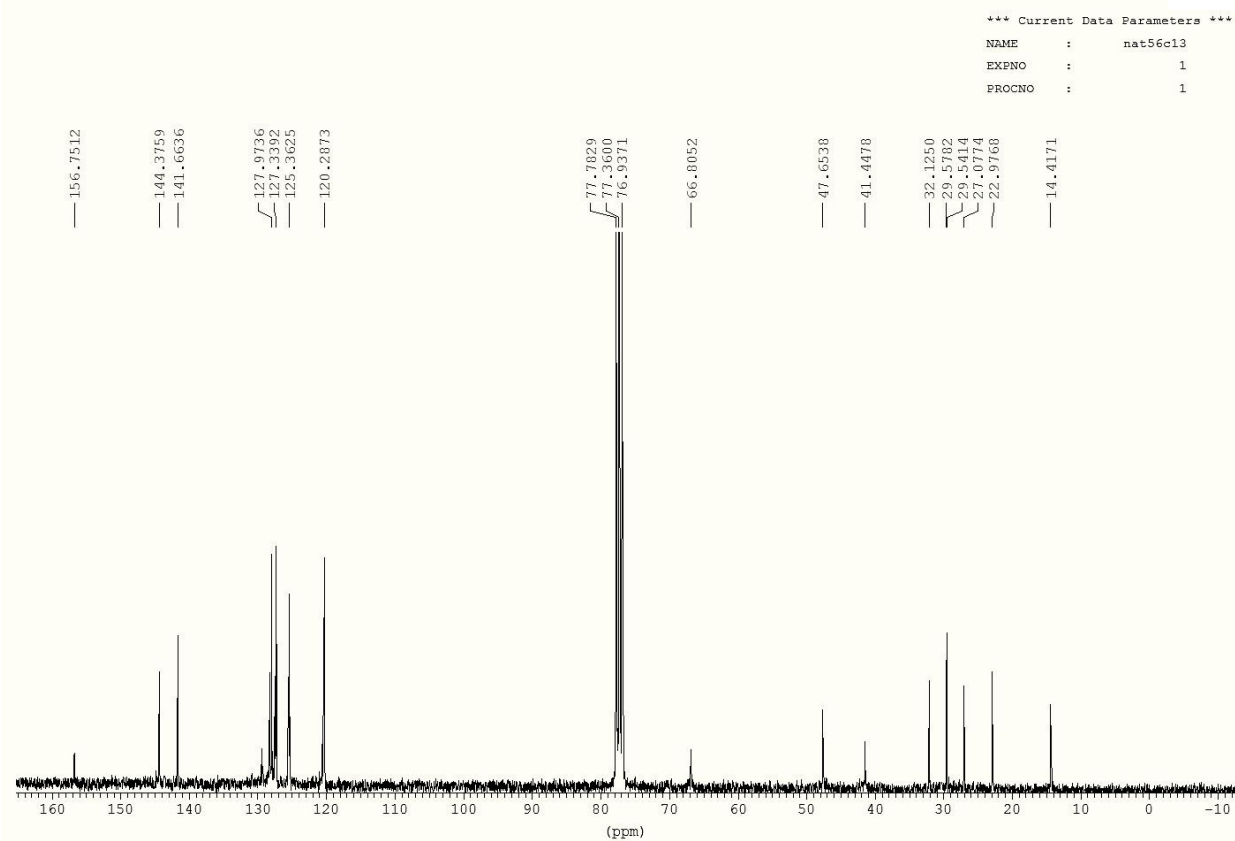
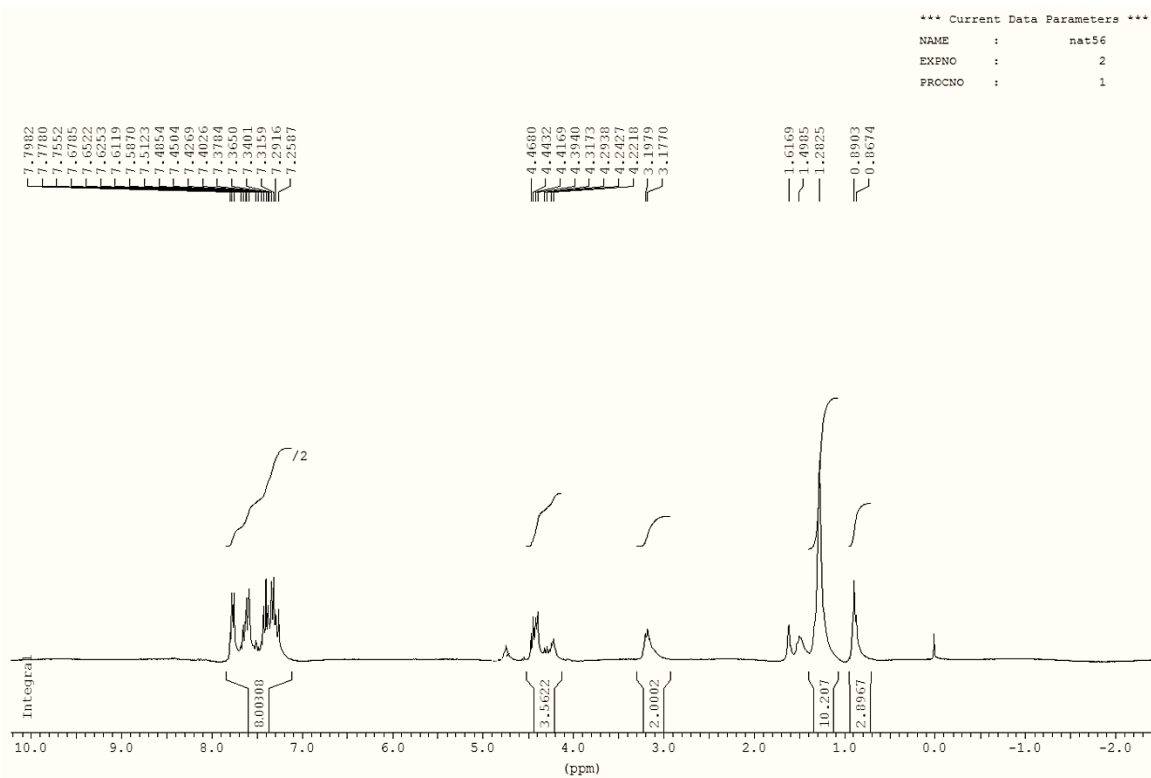
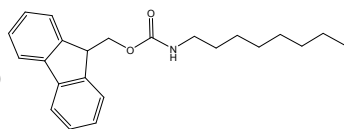
77.7829
77.3600
76.9371
67.5867
47.2953



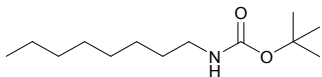
5c



6b

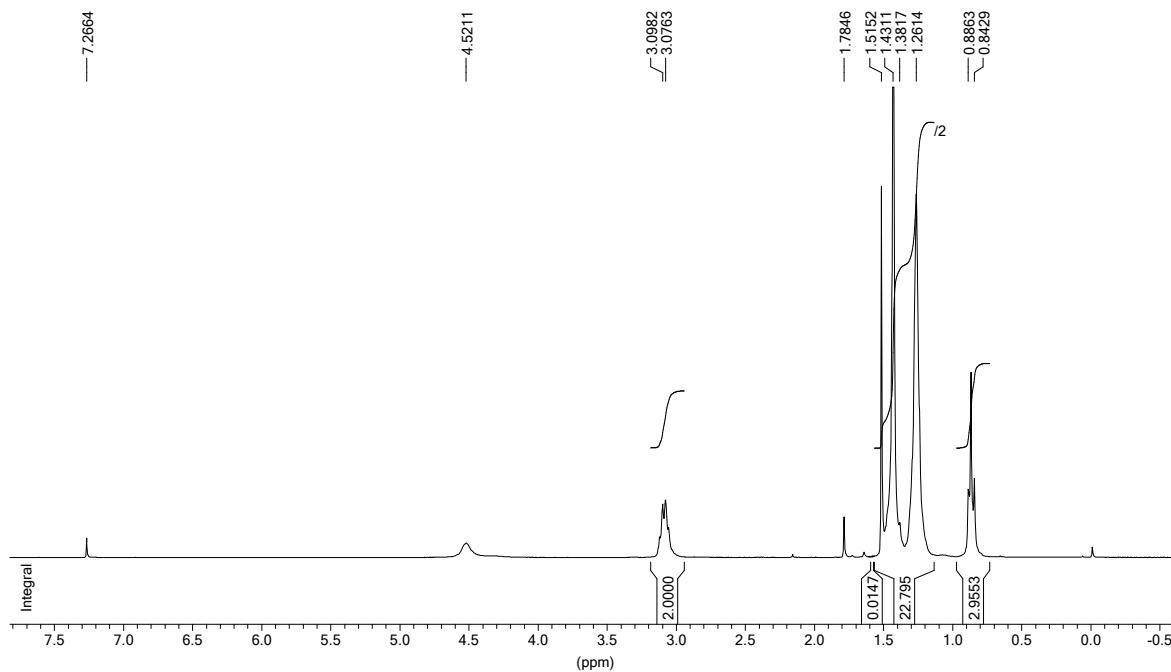


6c



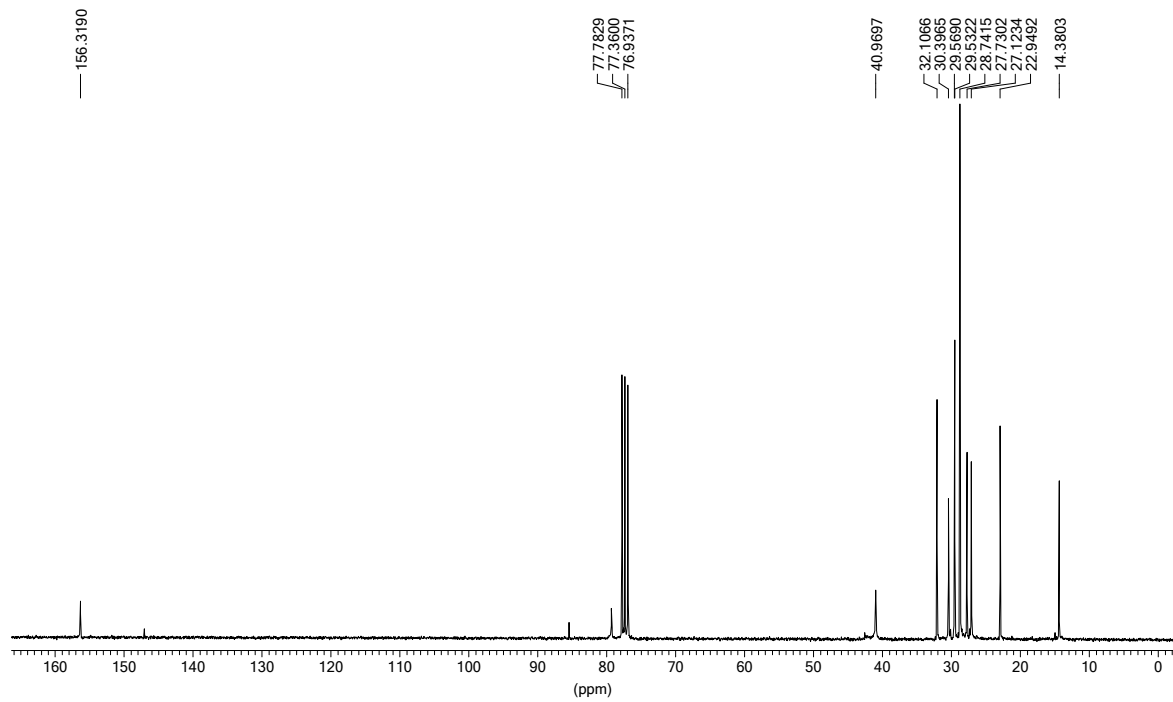
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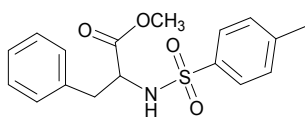
NAME : nat45
EXPNO : 1
PROCNO : 1



*** Current Data Parameters ***

NAME : nat45c13
EXPNO : 2
PROCNO : 1

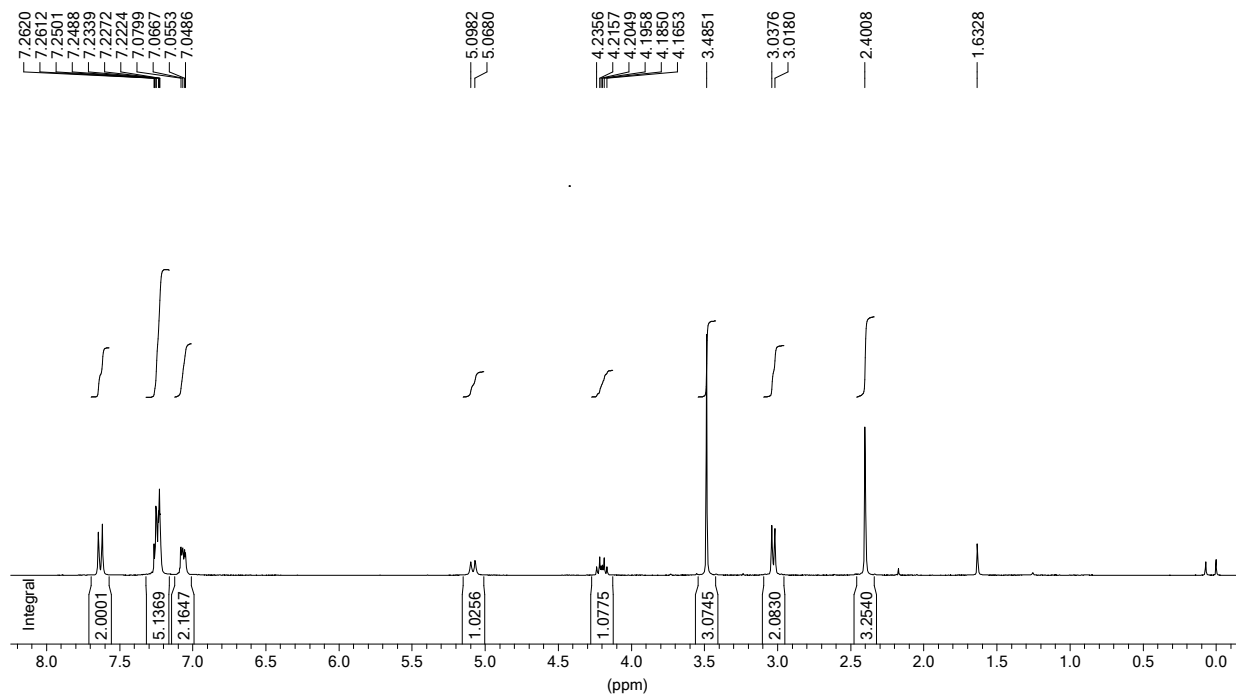




8a

*** Current Data Parameters ***

NAME : nat38
EXPNO : 1
PROCNO : 1



*** Current Data Parameters ***

NAME : nat38c13
EXPNO : 1
PROCNO : 1

