

Transition-metal-free oxidative C-H etherification of acylanilines with alcohols through a radical pathway

Xiaobo Xu,^{a,b} Zhengzhou Chu,^a and Chengcai Xia^{b*}

^a Shanghai Synmedia Chemical Co., Ltd, Shanghai 201201 (China).

^b Pharmacy College, Shandong First Medical University & Shandong Academy of Medical Sciences, Taian 271000 (China).

E-mail: xiachc@163.com

Supporting Information

Table of contents

| | |
|--|----|
| 1. General Information | 2 |
| 2. Characterization of the products | 3 |
| 3. Copies of ¹ H, ¹³ C and ¹⁹ F NMR Spectra | 12 |

General Information

All commercial reagents were used as received. All products were isolated by short chromatography on a silica gel (200-300 mesh) column using petroleum ether (60-90°C) and ethyl acetate. ^1H and ^{13}C NMR spectra were recorded on a Bruker Advance DRX-500 spectrometer at ambient temperature with CDCl_3 as solvent and tetramethylsilane (TMS) as the internal standard. All chemical shift values are quoted in ppm and coupling constants quoted in Hz. Compounds for HRMS were analyzed by positive mode electrospray ionization (ESI) using Agilent 6530 QTOF mass spectrometer.

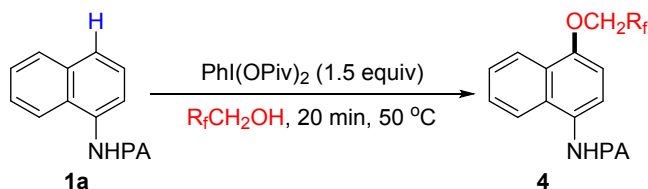
General experimental procedure for synthesis of products 2 or 3

Amide **1** (0.2 mmol), $\text{PhI}(\text{OPiv})_2$ (1.5 equiv) and alcohol (8.0 equiv) were combined in a 10 mL tube. The mixture was then stirred at 50 °C for 20 min. After the conversion was completed as indicated by TLC, the mixture was diluted with water and extracted with EA. The collected organic solvent was then evaporated under reduced pressure. The residue was purified directly by flash column chromatography (EA/PE, 1:10) to give the products **2** or **3**.

General experimental procedure for gram-scale synthesis of product 2a

Amide **1a** (5.0 mmol), $\text{PhI}(\text{OPiv})_2$ (1.5 equiv) and alcohol (8.0 equiv) were combined in a 25 mL tube. The mixture was then stirred at 50 °C for 20 min. After the conversion was completed as indicated by TLC, the mixture was diluted with water and extracted with EA. The collected organic solvent was then evaporated under reduced pressure. The residue was purified directly by flash column chromatography (EA/PE, 1:10) to give the product **2a**.

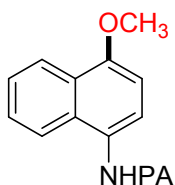
General experimental procedure for the reaction of 1a with mono-, di-, and tri-fluoroethanol



Amide **1a** (0.2 mmol), $\text{PhI}(\text{OPiv})_2$ (1.5 equiv) and fluoroethanol (8.0 equiv) were combined in a 10 mL tube. The mixture was then stirred at 50 °C for 20 min. After the conversion was completed as indicated by TLC, the mixture was diluted with water and extracted with EA. The collected organic solvent was then evaporated under reduced pressure. The residue was purified directly by flash column chromatography (EA/PE, 1:10) to give the product **4**.

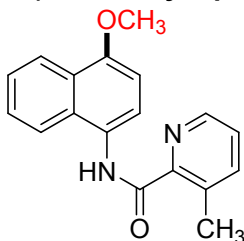
1. Characterization of the products

N-(4-methoxynaphthalen-1-yl)picolinamide (**2a**)



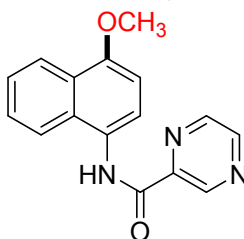
Products **2a** was obtained as a yellow solid, 69% yield, m.p. 110-111 °C. ¹H NMR (500 MHz, CDCl₃) δ 10.44 (s, 1H), 8.68 (d, *J* = 4.4 Hz, 1H), 8.35 (d, *J* = 7.8 Hz, 1H), 8.32 (d, *J* = 8.3 Hz, 1H), 8.11 (d, *J* = 8.3 Hz, 1H), 8.00 (d, *J* = 8.4 Hz, 1H), 7.94 (td, *J* = 7.7, 1.5 Hz, 1H), 7.58 (t, *J* = 7.6 Hz, 1H), 7.51 (dd, *J* = 9.5, 5.6 Hz, 2H), 6.86 (d, *J* = 8.3 Hz, 1H), 4.02 (s, 3H); ¹³C NMR (126 MHz, CDCl₃) δ 161.3, 152.2, 149.1, 146.9, 136.9, 127.2, 125.9, 125.4, 124.9, 124.4, 124.3, 121.7, 121.6, 119.8, 119.3, 102.6, 54.7. HRMS (ESI): Calculated for C₁₇H₁₄N₂O₂⁺: 279.1128 [M+H]⁺, Found: 279.1126.

N-(4-methoxynaphthalen-1-yl)-3-methylpicolinamide (**2b**)



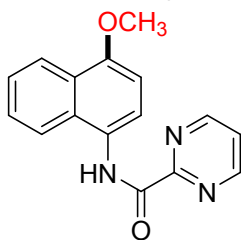
Products **2b** was obtained as a yellow solid, 67% yield, m.p. 120-121 °C. ¹H NMR (500 MHz, CDCl₃) δ 10.59 (s, 1H), 8.51 (d, *J* = 4.0 Hz, 1H), 8.31 (d, *J* = 8.0 Hz, 1H), 8.04 (d, *J* = 8.3 Hz, 1H), 7.99 (d, *J* = 8.4 Hz, 1H), 7.66 (d, *J* = 7.7 Hz, 1H), 7.58 – 7.54 (m, 1H), 7.50 (t, *J* = 7.4 Hz, 1H), 7.37 (dd, *J* = 7.6, 4.6 Hz, 1H), 6.85 (d, *J* = 8.3 Hz, 1H), 4.01 (s, 3H), 2.82 (s, 3H); ¹³C NMR (126 MHz, CDCl₃) δ 164.1, 153.1, 147.1, 145.4, 141.4, 136.2, 128.5, 126.8, 126.0, 125.6, 125.3, 122.7, 121.0, 120.4, 103.6, 55.7, 20.8. HRMS (ESI): Calculated for C₁₈H₁₆N₂O₂⁺: 293.1285 [M+H]⁺, Found: 293.1289.

N-(4-methoxynaphthalen-1-yl)pyrazine-2-carboxamide (**2c**)



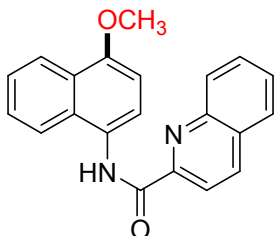
Products **2c** was obtained as a yellow solid, 62% yield, m.p. 124-125 °C. ¹H NMR (500 MHz, CDCl₃) δ 10.02 (s, 1H), 9.53 (s, 1H), 8.81 (s, 1H), 8.62 (s, 1H), 8.31 (d, *J* = 8.3 Hz, 1H), 8.06 (d, *J* = 8.3 Hz, 1H), 7.91 (d, *J* = 8.3 Hz, 1H), 7.57 (t, *J* = 7.5 Hz, 1H), 7.52 – 7.48 (m, 1H), 6.84 (d, *J* = 8.3 Hz, 1H), 4.00 (s, 3H); ¹³C NMR (126 MHz, CDCl₃) δ 161.2, 153.6, 147.5, 144.8, 144.7, 142.6, 128.1, 127.1, 125.9, 125.5, 124.6, 122.9, 120.7, 120.5, 103.5, 55.7. HRMS (ESI): Calculated for C₁₆H₁₃N₃O₂⁺: 280.1081 [M+H]⁺, Found: 280.1072.

***N*-(4-methoxynaphthalen-1-yl)pyrimidine-2-carboxamide (2d)**



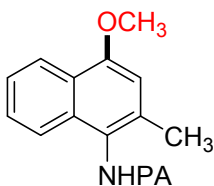
Products **2d** was obtained as a yellow solid, 34% yield, m.p. 132-133 °C. ¹H NMR (500 MHz, CDCl₃) δ 10.63 (s, 1H), 8.98 (d, *J* = 4.8 Hz, 2H), 8.47 (d, *J* = 7.5 Hz, 1H), 8.04 (d, *J* = 8.4 Hz, 1H), 7.72 (d, *J* = 8.2 Hz, 1H), 7.55 (ddd, *J* = 26.3, 12.9, 5.9 Hz, 4H), 4.09 (s, 3H); ¹³C NMR (126 MHz, CDCl₃) δ 159.8, 157.7, 145.6, 134.0, 131.9, 128.9, 126.3, 126.0, 126.0, 125.4, 122.7, 120.1, 118.9, 102.7, 53.9. HRMS (ESI): Calculated for C₁₆H₁₃N₃O₂⁺: 280.1081 [M+H]⁺, Found: 280.1087.

***N*-(4-methoxynaphthalen-1-yl)quinoline-2-carboxamide (2e)**



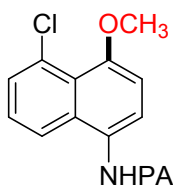
Products **2e** was obtained as a yellow solid, 70% yield, m.p. 179-180 °C. ¹H NMR (500 MHz, CDCl₃) δ 10.64 (s, 1H), 8.46 (d, *J* = 8.4 Hz, 1H), 8.40 (d, *J* = 8.5 Hz, 1H), 8.36 (d, *J* = 8.3 Hz, 1H), 8.26 (d, *J* = 8.5 Hz, 1H), 8.16 (d, *J* = 8.3 Hz, 1H), 8.09 (d, *J* = 8.4 Hz, 1H), 7.94 (d, *J* = 8.2 Hz, 1H), 7.84 (dd, *J* = 11.2, 4.1 Hz, 1H), 7.69 – 7.66 (m, 1H), 7.65 – 7.61 (m, 1H), 7.55 (t, *J* = 7.2 Hz, 1H), 6.91 (d, *J* = 8.3 Hz, 1H), 4.05 (s, 3H); ¹³C NMR (126 MHz, CDCl₃) δ 161.7, 152.3, 149.0, 145.4, 136.8, 129.3, 128.8, 128.5, 127.3, 127.1, 126.8, 125.9, 125.1, 124.4, 124.3, 121.8, 119.8, 119.4, 117.9, 102.6, 54.7. HRMS (ESI): Calculated for C₂₁H₁₆N₂O₂⁺: 329.1285 [M+H]⁺, Found: 329.1280.

***N*-(4-methoxy-2-methylnaphthalen-1-yl)picolinamide (2f)**



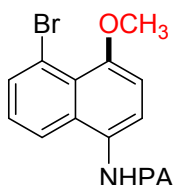
Products **2f** was obtained as a yellow solid, 70% yield, m.p. 159-160 °C. ¹H NMR (500 MHz, CDCl₃) δ 8.93 (s, 1H), 8.57 (ddd, *J* = 4.8, 1.5, 0.8 Hz, 1H), 8.10 (dd, *J* = 7.8, 1.0 Hz, 1H), 7.93 (dd, *J* = 7.8, 0.8 Hz, 1H), 7.75 (td, *J* = 7.7, 1.7 Hz, 1H), 7.64 (dd, *J* = 7.8, 0.7 Hz, 1H), 7.53 (ddd, *J* = 8.8, 7.6, 1.4 Hz, 1H), 7.45 – 7.40 (m, 2H), 6.57 (s, 1H), 2.89 (s, 3H), 2.00 (s, 3H); ¹³C NMR (126 MHz, CDCl₃) δ 183.6, 161.9, 153.8, 149.1, 148.3, 141.0, 137.5, 133.3, 132.6, 131.6, 129.1, 126.7, 126.0, 125.9, 122.1, 83.4, 50.1, 17.3. HRMS (ESI): Calculated for C₁₈H₁₆N₂O₂⁺: 293.1285 [M+H]⁺, Found: 293.1284.

***N*-(5-chloro-4-methoxynaphthalen-1-yl)picolinamide (2g)**



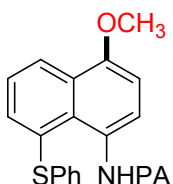
Products **2g** was obtained as a yellow solid, 57% yield, m.p. 162-163 °C. ¹H NMR (500 MHz, CDCl₃) δ 10.76 (s, 1H), 8.42 (d, *J* = 7.5 Hz, 1H), 8.37 (d, *J* = 7.8 Hz, 1H), 8.10 (d, *J* = 8.4 Hz, 1H), 7.94 (t, *J* = 7.7 Hz, 1H), 7.90 (d, *J* = 8.0 Hz, 1H), 7.71 (d, *J* = 8.2 Hz, 1H), 7.61 – 7.57 (m, 1H), 7.55 – 7.50 (m, 2H), 3.95 (s, 3H); ¹³C NMR (126 MHz, CDCl₃) δ 164.1, 153.1, 147.1, 145.4, 141.4, 136.2, 128.5, 126.8, 126.0, 125.6, 125.3, 125.0, 122.7, 121.0, 120.4, 103.6, 55.7. HRMS (ESI): Calculated for C₁₇H₁₃ClN₂O₂⁺: 313.0739 [M+H]⁺, Found: 313.0736.

***N*-(5-bromo-4-methoxynaphthalen-1-yl)picolinamid (2h)**



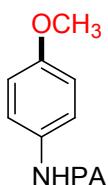
Products **2h** was obtained as a yellow solid, 60% yield, m.p. 171-172 °C. ¹H NMR (500 MHz, CDCl₃) δ 10.69 (s, 1H), 8.35 (d, *J* = 7.5 Hz, 1H), 8.30 (d, *J* = 7.8 Hz, 1H), 8.03 (d, *J* = 8.4 Hz, 1H), 7.87 (t, *J* = 7.7 Hz, 1H), 7.83 (d, *J* = 8.0 Hz, 1H), 7.64 (d, *J* = 8.2 Hz, 1H), 7.53 (dd, *J* = 10.5, 4.7 Hz, 1H), 7.46 (td, *J* = 7.0, 4.7 Hz, 2H), 3.89 (s, 3H); ¹³C NMR (126 MHz, CDCl₃) δ 164.5, 153.5, 147.5, 145.8, 141.8, 136.6, 128.9, 127.2, 126.4, 126.0, 125.7, 125.4, 123.1, 121.4, 120.8, 104.0, 56.1. HRMS (ESI): Calculated for C₁₇H₁₃BrN₂O₂⁺: 357.0233 [M+H]⁺, Found: 357.0237.

***N*-(4-methoxy-8-(phenylthio)naphthalen-1-yl)picolinamide (2i)**



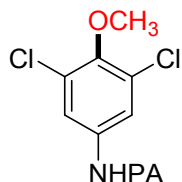
Products **2i** was obtained as a yellow solid, 72% yield, m.p. 178-179 °C. ¹H NMR (500 MHz, CDCl₃) δ 9.20 (s, 1H), 8.32 (dd, *J* = 8.4, 1.0 Hz, 1H), 8.11 (d, *J* = 4.1 Hz, 1H), 7.98 (d, *J* = 7.7 Hz, 1H), 7.87 (d, *J* = 8.3 Hz, 1H), 7.69 – 7.64 (m, 1H), 7.41 (dd, *J* = 8.3, 7.2 Hz, 1H), 7.25 (dd, *J* = 17.5, 9.2 Hz, 4H), 7.04 (t, *J* = 7.7 Hz, 2H), 6.84 (dd, *J* = 16.3, 8.0 Hz, 2H), 3.98 (s, 3H); ¹³C NMR (126 MHz, CDCl₃) δ 161.1, 152.8, 148.9, 146.3, 142.1, 136.5, 135.9, 130.0, 127.9, 126.9, 126.0, 125.7, 125.4, 124.6, 124.3, 123.3, 123.0, 121.2, 120.8, 102.9, 54.8. HRMS (ESI): Calculated for C₂₃H₁₈N₂O₂S⁺: 387.1162 [M+H]⁺, Found: 387.1167.

***N*-(4-methoxyphenyl)picolinamide (2j)**



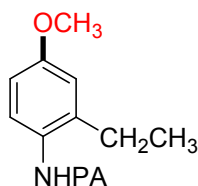
Products **2j** was obtained as a yellow solid, 50% yield, m.p. 105-106 °C. ¹H NMR (500 MHz, CDCl₃) δ 9.98 (s, 1H), 8.60 (d, *J* = 4.1 Hz, 1H), 8.30 (d, *J* = 7.5 Hz, 1H), 7.92 (t, *J* = 7.3 Hz, 1H), 7.70 (d, *J* = 8.9 Hz, 2H), 7.48 (dd, *J* = 6.9, 4.8 Hz, 1H), 6.91 (d, *J* = 8.8 Hz, 2H), 3.80 (s, 3H); ¹³C NMR (126 MHz, CDCl₃) δ 160.4, 155.4, 148.7, 146.6, 137.1, 129.9, 125.4, 121.6, 120.3, 113.2, 54.5. HRMS (ESI): Calculated for C₁₃H₁₂N₂O₂⁺: 229.0972 [M+H]⁺, Found: 229.0969.

***N*-(3,5-dichloro-4-methoxyphenyl)picolinamide (2k)**



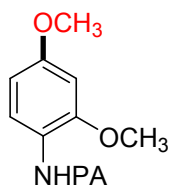
Products **2k** was obtained as a yellow solid, 43% yield, m.p. 137-138 °C. ¹H NMR (500 MHz, CDCl₃) δ 9.34 (s, 1H), 8.62 (d, *J* = 4.4 Hz, 1H), 8.28 (d, *J* = 7.8 Hz, 1H), 7.89 (td, *J* = 7.7, 1.6 Hz, 1H), 7.50 – 7.47 (m, 1H), 6.67 (s, 2H), 3.79 (s, 3H); ¹³C NMR (126 MHz, CDCl₃) δ 161.9, 153.6, 148.8, 148.3, 138.8, 138.6, 137.6, 126.8, 122.1, 112.9, 49.9. HRMS (ESI): Calculated for C₁₃H₁₀Cl₂N₂O₂⁺: 297.0192 [M+H]⁺, Found: 297.0198.

***N*-(2-ethyl-4-methoxyphenyl)picolinamide (2l)**



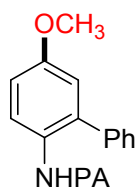
Products **2l** was obtained as a yellow solid, 51% yield, m.p. 128-129 °C. ¹H NMR (500 MHz, CDCl₃) δ 9.87 (s, 1H), 8.55 (d, *J* = 4.5 Hz, 1H), 8.23 (d, *J* = 7.8 Hz, 1H), 7.98 – 7.94 (m, 1H), 7.83 (td, *J* = 7.7, 1.6 Hz, 1H), 7.40 (ddd, *J* = 7.5, 4.8, 1.0 Hz, 1H), 6.74 (dd, *J* = 4.6, 2.0 Hz, 2H), 3.75 (s, 3H), 2.66 (q, *J* = 7.6 Hz, 2H), 1.22 (t, *J* = 7.6 Hz, 3H); ¹³C NMR (126 MHz, CDCl₃) δ 161.0, 156.0, 149.2, 147.1, 136.6, 135.8, 127.3, 125.3, 122.9, 121.3, 113.6, 110.2, 54.4, 23.7, 12.9. HRMS (ESI): Calculated for C₁₅H₁₆N₂O₂⁺: 257.1285 [M+H]⁺, Found: 257.1289.

***N*-(2,4-dimethoxyphenyl)picolinamide (2m)**



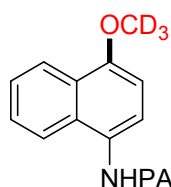
Products **2m** was obtained as a yellow solid, 57% yield, m.p. 125-126 °C. ¹H NMR (500 MHz, CDCl₃) δ 10.58 (s, 1H), 8.64 (d, *J* = 4.3 Hz, 1H), 8.34 (d, *J* = 3.0 Hz, 1H), 8.26 (d, *J* = 7.8 Hz, 1H), 7.88 (td, *J* = 7.7, 1.6 Hz, 1H), 7.45 (ddd, *J* = 7.5, 4.8, 1.0 Hz, 1H), 6.83 (d, *J* = 8.9 Hz, 1H), 6.61 (dd, *J* = 8.9, 3.0 Hz, 1H), 3.91 (s, 3H), 3.81 (s, 3H); ¹³C NMR (126 MHz, CDCl₃) δ 162.1, 153.9, 150.3, 148.2, 143.1, 137.6, 128.2, 126.3, 122.3, 111.0, 109.1, 105.8, 56.4, 55.8. HRMS (ESI): Calculated for C₁₄H₁₄N₂O₃⁺: 259.1077 [M+H]⁺, Found: 259.1079.

***N*-(5-methoxy-[1,1'-biphenyl]-2-yl)picolinamide (2n)**



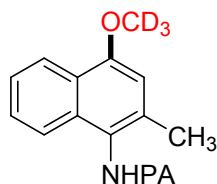
Products **2n** was obtained as a yellow solid, m.p. 131-132 °C. ¹H NMR (500 MHz, CDCl₃) δ 8.63 (s, 1H), 8.39 (d, *J* = 3.8 Hz, 1H), 7.97 (d, *J* = 7.7 Hz, 1H), 7.72 (t, *J* = 6.5 Hz, 3H), 7.33 (s, 4H), 6.96 (d, *J* = 10.0 Hz, 1H), 6.68 (s, 1H), 6.51 (d, *J* = 10.1 Hz, 1H), 3.32 (s, 3H); ¹³C NMR (126 MHz, CDCl₃) δ 185.7, 162.4, 152.8, 148.9, 148.1, 145.1, 137.4, 135.3, 130.4, 129.9, 129.8, 128.6, 128.0, 126.5, 122.0, 82.6, 50.8. HRMS (ESI): Calculated for C₁₉H₁₆N₂O₂⁺: 305.1285 [M+H]⁺, Found: 305.1289.

***N*-(4-(methoxy-d3)naphthalen-1-yl)picolinamide (2o)**



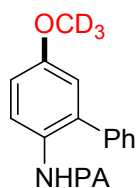
Products **2o** was obtained as a yellow solid, 70% yield, m.p. 112-113 °C. ¹H NMR (500 MHz, CDCl₃) δ 10.41 (s, 1H), 8.66 (d, *J* = 4.5 Hz, 1H), 8.32 (dd, *J* = 7.3, 6.1 Hz, 2H), 8.12 (d, *J* = 8.3 Hz, 1H), 7.99 (d, *J* = 8.4 Hz, 1H), 7.90 (td, *J* = 7.7, 1.6 Hz, 1H), 7.59 – 7.55 (m, 1H), 7.52 – 7.46 (m, 2H), 6.85 (d, *J* = 8.3 Hz, 1H); ¹³C NMR (126 MHz, CDCl₃) δ 161.4, 152.2, 149.2, 147.1, 136.7, 127.2, 125.8, 125.4, 124.9, 124.3, 124.3, 121.7, 121.4, 119.7, 119.2, 102.5. HRMS (ESI): Calculated for C₁₇H₁₁D₃N₂O₂⁺: 282.1317 [M+H]⁺, Found: 282.1315.

***N*-(4-(methoxy-d3)-2-methylnaphthalen-1-yl)picolinamide (2p)**



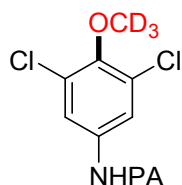
Products **2p** was obtained as a yellow solid, 68% yield, m.p. 152-153 °C. ¹H NMR (500 MHz, CDCl₃) δ 8.89 (s, 1H), 8.53 (d, *J* = 4.6 Hz, 1H), 8.06 (dd, *J* = 7.8, 1.1 Hz, 1H), 7.90 (d, *J* = 7.8 Hz, 1H), 7.72 (td, *J* = 7.7, 1.6 Hz, 1H), 7.60 (d, *J* = 7.8 Hz, 1H), 7.50 (td, *J* = 7.7, 1.3 Hz, 1H), 7.41 – 7.36 (m, 2H), 6.53 (d, *J* = 1.3 Hz, 1H), 1.96 (s, 3H); ¹³C NMR (126 MHz, CDCl₃) δ 183.6, 161.8, 153.8, 149.0, 148.2, 141.0, 137.4, 133.2, 132.6, 131.5, 129.0, 126.6, 126.0, 125.9, 122.0, 83.2, 17.2. HRMS (ESI): Calculated for C₁₈H₁₃D₃N₂O₂⁺: 296.1473 [M+H]⁺, Found: 296.1477.

***N*-(5-(methoxy-d3)-[1,1'-biphenyl]-2-yl)picolinamide (2q)**



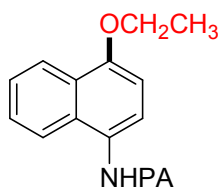
Products **2q** was obtained as a yellow solid, 48% yield, m.p. 127-128 °C. ¹H NMR (500 MHz, CDCl₃) δ 8.64 (s, 1H), 8.42 (d, *J* = 4.2 Hz, 1H), 8.01 (s, 1H), 7.78 – 7.72 (m, 3H), 7.36 (d, *J* = 2.1 Hz, 4H), 6.98 (d, *J* = 10.1 Hz, 1H), 6.70 (s, 1H), 6.53 (d, *J* = 10.1 Hz, 1H); ¹³C NMR (126 MHz, CDCl₃) δ 185.7, 162.4, 152.8, 149.0, 148.1, 145.1, 137.4, 135.3, 130.4, 129.9, 129.8, 128.6, 128.0, 126.5, 122.0, 82.5. HRMS (ESI): Calculated for C₁₉H₁₃D₃N₂O₂⁺: 308.1473 [M+H]⁺, Found: 308.1478.

***N*-(3,4-dichloro-4-(methoxy-d3)phenyl)picolinamide (2r)**



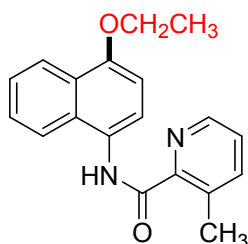
Products **2r** was obtained as a yellow solid, 41% yield, m.p. 130-131 °C. ¹H NMR (500 MHz, CDCl₃) δ 9.38 (s, 1H), 8.63 (d, *J* = 4.0 Hz, 1H), 8.30 (d, *J* = 7.7 Hz, 1H), 7.92 (t, *J* = 7.6 Hz, 1H), 7.52 – 7.48 (m, 1H), 6.67 (s, 2H); ¹³C NMR (126 MHz, CDCl₃) δ 161.6, 157.3, 148.7, 146.9, 136.7, 136.7, 135.8, 125.4, 121.7, 112.4. HRMS (ESI): Calculated for C₁₃H₇D₃Cl₂N₂O₂⁺: 300.0381 [M+H]⁺, Found: 300.0387.

***N*-(4-ethoxynaphthalen-1-yl)picolinamide (3a)**



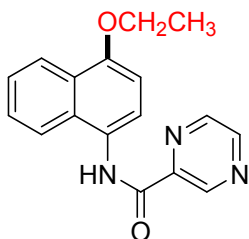
Products **3a** was obtained as a yellow solid, 66% yield, m.p. 123-124 °C. ¹H NMR (500 MHz, CDCl₃) δ 10.43 (s, 1H), 8.69 (d, *J* = 4.2 Hz, 1H), 8.36 (dd, *J* = 12.1, 8.1 Hz, 2H), 8.11 (d, *J* = 8.3 Hz, 1H), 8.00 (d, *J* = 8.4 Hz, 1H), 7.93 (td, *J* = 7.7, 1.6 Hz, 1H), 7.59 (ddd, *J* = 8.3, 6.9, 1.2 Hz, 1H), 7.54 – 7.49 (m, 2H), 6.87 (d, *J* = 8.3 Hz, 1H), 4.24 (q, *J* = 7.0 Hz, 2H), 1.56 (t, *J* = 7.0 Hz, 3H); ¹³C NMR (126 MHz, CDCl₃) δ 162.5, 152.6, 150.3, 148.1, 137.7, 128.2, 126.8, 126.4, 126.1, 125.3, 125.1, 122.9, 122.5, 120.7, 120.3, 104.5, 64.0, 14.9. HRMS (ESI): Calculated for C₁₈H₁₆N₂O₂⁺: 293.1285 [M+H]⁺, Found: 293.1283.

***N*-(4-ethoxynaphthalen-1-yl)-3-methylpicolinamide (3b)**



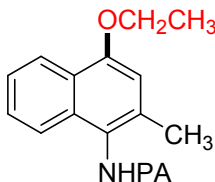
Products **3b** was obtained as a yellow solid, 64% yield, m.p. 128-129 °C. ¹H NMR (500 MHz, CDCl₃) δ 10.59 (s, 1H), 8.50 (d, *J* = 3.9 Hz, 1H), 8.35 (d, *J* = 8.2 Hz, 1H), 8.03 (d, *J* = 8.3 Hz, 1H), 7.98 (d, *J* = 8.4 Hz, 1H), 7.65 (d, *J* = 7.6 Hz, 1H), 7.57 – 7.53 (m, 1H), 7.51 – 7.47 (m, 1H), 7.37 (dd, *J* = 7.7, 4.6 Hz, 1H), 6.84 (d, *J* = 8.3 Hz, 1H), 4.22 (q, *J* = 6.9 Hz, 2H), 2.82 (s, 3H), 1.54 (t, *J* = 7.0 Hz, 3H); ¹³C NMR (126 MHz, CDCl₃) δ 164.0, 152.5, 147.2, 145.3, 141.4, 136.2, 128.5, 126.7, 126.1, 126.0, 125.5, 125.2, 122.8, 121.0, 120.4, 104.5, 64.0, 20.8, 14.9. HRMS (ESI): Calculated for C₁₉H₁₈N₂O₂⁺: 307.1441 [M+H]⁺, Found: 307.1449.

***N*-(4-ethoxynaphthalen-1-yl)pyrazine-2-carboxamide (3c)**



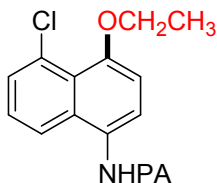
Products **3c** was obtained as a yellow solid, 60% yield, m.p. 138-139 °C. ¹H NMR (500 MHz, CDCl₃) δ 10.04 (s, 1H), 9.56 (s, 1H), 8.84 (s, 1H), 8.66 (s, 1H), 8.38 (d, *J* = 8.6 Hz, 1H), 8.07 (d, *J* = 8.3 Hz, 1H), 7.93 (d, *J* = 8.4 Hz, 1H), 7.58 (dd, *J* = 11.3, 4.1 Hz, 1H), 7.53 (d, *J* = 7.3 Hz, 1H), 6.86 (d, *J* = 8.3 Hz, 1H), 4.24 (q, *J* = 7.0 Hz, 2H), 1.56 (t, *J* = 7.0 Hz, 3H); ¹³C NMR (126 MHz, CDCl₃) δ 161.2, 153.0, 147.5, 144.8, 144.7, 142.5, 128.1, 127.0, 126.1, 125.4, 124.4, 123.1, 120.8, 120.4, 104.3, 64.0, 14.8. HRMS (ESI): Calculated for C₁₇H₁₅N₃O₂⁺: 294.1237 [M+H]⁺, Found: 294.1237.

***N*-(4-ethoxy-2-methylnaphthalen-1-yl)picolinamide (3d)**



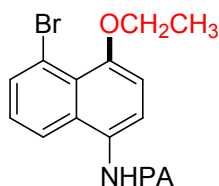
Products **3d** was obtained as a yellow solid, 67% yield, m.p. 147-148 °C. ¹H NMR (500 MHz, CDCl₃) δ 9.75 (s, 1H), 8.69 (d, *J* = 4.3 Hz, 1H), 8.34 (d, *J* = 7.7 Hz, 1H), 8.29 (d, *J* = 8.2 Hz, 1H), 7.94 (t, *J* = 7.1 Hz, 1H), 7.85 (d, *J* = 8.3 Hz, 1H), 7.53 (dd, *J* = 7.0, 5.0 Hz, 1H), 7.48 (t, *J* = 7.1 Hz, 1H), 7.42 (t, *J* = 7.3 Hz, 1H), 6.74 (s, 1H), 4.23 (q, *J* = 6.9 Hz, 2H), 2.45 (s, 3H), 1.56 (t, *J* = 6.9 Hz, 3H); ¹³C NMR (126 MHz, CDCl₃) δ 163.2, 154.0, 149.9, 148.1, 137.7, 133.5, 131.5, 127.0, 126.5, 125.0, 124.5, 122.8, 122.4, 122.2, 122.1, 107.4, 63.9, 19.2, 14.8. HRMS (ESI): Calculated for C₁₉H₁₈N₂O₂⁺: 307.1441 [M+H]⁺, Found: 307.1444.

***N*-(5-chloro-4-ethoxynaphthalen-1-yl)picolinamide (3e)**



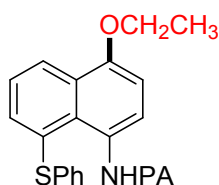
Products **3e** was obtained as a yellow solid, 52% yield, m.p. 167-168 °C. ¹H NMR (500 MHz, CDCl₃) δ 10.74 (s, 1H), 8.40 (d, *J* = 7.5 Hz, 1H), 8.35 (d, *J* = 7.8 Hz, 1H), 8.08 (d, *J* = 8.4 Hz, 1H), 7.94 – 7.89 (m, 1H), 7.88 (d, *J* = 8.0 Hz, 1H), 7.69 (d, *J* = 8.2 Hz, 1H), 7.59 – 7.55 (m, 1H), 7.51 (td, *J* = 7.0, 4.7 Hz, 2H); 4.20 (q, *J* = 6.9 Hz, 2H), 1.55 (t, *J* = 6.9 Hz, 3H); ¹³C NMR (126 MHz, CDCl₃) δ 163.1, 152.1, 146.1, 144.4, 140.4, 135.2, 127.5, 125.8, 125.0, 124.6, 124.3, 124.0, 121.7, 120.0, 119.4, 102.6, 63.8, 14.8. HRMS (ESI): Calculated for C₁₈H₁₅ClN₂O₂⁺: 327.0895 [M+H]⁺, Found: 327.0898.

***N*-(5-bromo-4-ethoxynaphthalen-1-yl)picolinamide (3f)**



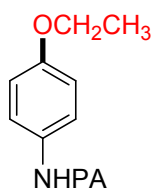
Products **3f** was obtained as a yellow solid, 59% yield, m.p. 175-176 °C. ¹H NMR (500 MHz, CDCl₃) δ 10.70 (s, 1H), 8.36 (d, *J* = 7.5 Hz, 1H), 8.30 (d, *J* = 7.8 Hz, 1H), 8.04 (d, *J* = 8.4 Hz, 1H), 7.87 (t, *J* = 7.7 Hz, 1H), 7.84 (d, *J* = 8.0 Hz, 1H), 7.65 (d, *J* = 8.2 Hz, 1H), 7.55 – 7.51 (m, 1H), 7.48 – 7.43 (m, 2H), 4.16 (q, *J* = 7.0 Hz, 2H), 1.55 (t, *J* = 7.0 Hz, 3H); ¹³C NMR (126 MHz, CDCl₃) δ 163.2, 152.3, 146.3, 144.5, 140.5, 135.3, 127.6, 125.9, 125.1, 124.8, 124.5, 124.1, 121.8, 120.2, 119.5, 102.7, 64.3, 15.1. HRMS (ESI): Calculated for C₁₈H₁₅BrN₂O₂⁺: 371.0390 [M+H]⁺, Found: 371.0394.

***N*-(4-ethoxy-8-(phenylthio)naphthalen-1-yl)picolinamide (3g)**



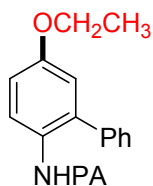
Products **3g** was obtained as a yellow solid, 70% yield, m.p. 181-182 °C. ¹H NMR (500 MHz, CDCl₃) δ 9.29 (s, 1H), 8.38 (dd, *J* = 8.5, 1.1 Hz, 1H), 8.18 (d, *J* = 4.4 Hz, 1H), 8.04 (d, *J* = 7.8 Hz, 1H), 7.92 (d, *J* = 8.3 Hz, 1H), 7.74 (td, *J* = 7.7, 1.6 Hz, 1H), 7.47 (dd, *J* = 8.3, 7.1 Hz, 1H), 7.35 – 7.30 (m, 4H), 7.09 (t, *J* = 7.7 Hz, 2H), 6.91 (t, *J* = 8.4 Hz, 2H), 4.18 (q, *J* = 7.0 Hz, 2H), 1.51 (t, *J* = 6.9 Hz, 3H); ¹³C NMR (126 MHz, CDCl₃) δ 160.9, 152.8, 148.8, 146.1, 142.1, 136.5, 136.0, 130.0, 128.0, 126.9, 126.0, 125.7, 125.3, 124.6, 124.3, 123.3, 123.1, 121.3, 120.9, 102.9, 61.7, 14.7. HRMS (ESI): Calculated for C₂₄H₂₀N₂O₂S⁺: 401.1318 [M+H]⁺, Found: 401.1322.

***N*-(4-ethoxyphenyl)picolinamide (3h)**



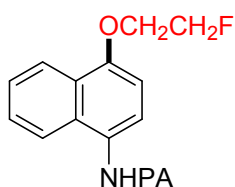
Products **3h** was obtained as a yellow solid, 45% yield, m.p. 112-113 °C. ¹H NMR (500 MHz, CDCl₃) δ 9.92 (s, 1H), 8.54 (d, *J* = 4.1 Hz, 1H), 8.24 (d, *J* = 7.5 Hz, 1H), 7.86 (t, *J* = 7.3 Hz, 1H), 7.64 (d, *J* = 8.9 Hz, 2H), 7.43 (dd, *J* = 6.9, 4.8 Hz, 1H), 6.85 (d, *J* = 8.8 Hz, 2H), 4.24 (q, *J* = 6.9 Hz, 2H), 1.57 (t, *J* = 6.8 Hz, 3H); ¹³C NMR (126 MHz, CDCl₃) δ 160.4, 155.4, 148.7, 146.6, 137.1, 130.0, 125.4, 121.6, 120.3, 113.2, 63.4, 15.1. HRMS (ESI): Calculated for C₁₄H₁₄N₂O₂⁺: 243.1128 [M+H]⁺, Found: 243.1133.

***N*-(5-ethoxy-[1,1'-biphenyl]-2-yl)picolinamide (3i)**



Products **3i** was obtained as a yellow solid, 48% yield, m.p. 135-136 °C. ^1H NMR (500 MHz, CDCl_3) δ 8.56 (s, 1H), 8.34 (d, $J = 4.2$ Hz, 1H), 7.92 (d, $J = 7.7$ Hz, 1H), 7.67 (dd, $J = 9.1, 6.1$ Hz, 3H), 7.28 (d, $J = 2.1$ Hz, 4H), 6.90 (d, $J = 10.1$ Hz, 1H), 6.62 (s, 1H), 6.45 (d, $J = 10.1$ Hz, 1H), 4.19 (q, $J = 7.1$ Hz, 2H), 1.53 (t, $J = 7.0$ Hz, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 185.6, 162.4, 152.7, 148.9, 148.0, 145.1, 137.3, 135.2, 130.4, 129.9, 129.8, 128.6, 127.9, 126.5, 121.9, 82.4, 62.5, 14.3. HRMS (ESI): Calculated for $\text{C}_{20}\text{H}_{18}\text{N}_2\text{O}_2^+$: 319.1441 $[\text{M}+\text{H}]^+$, Found: 319.1445.

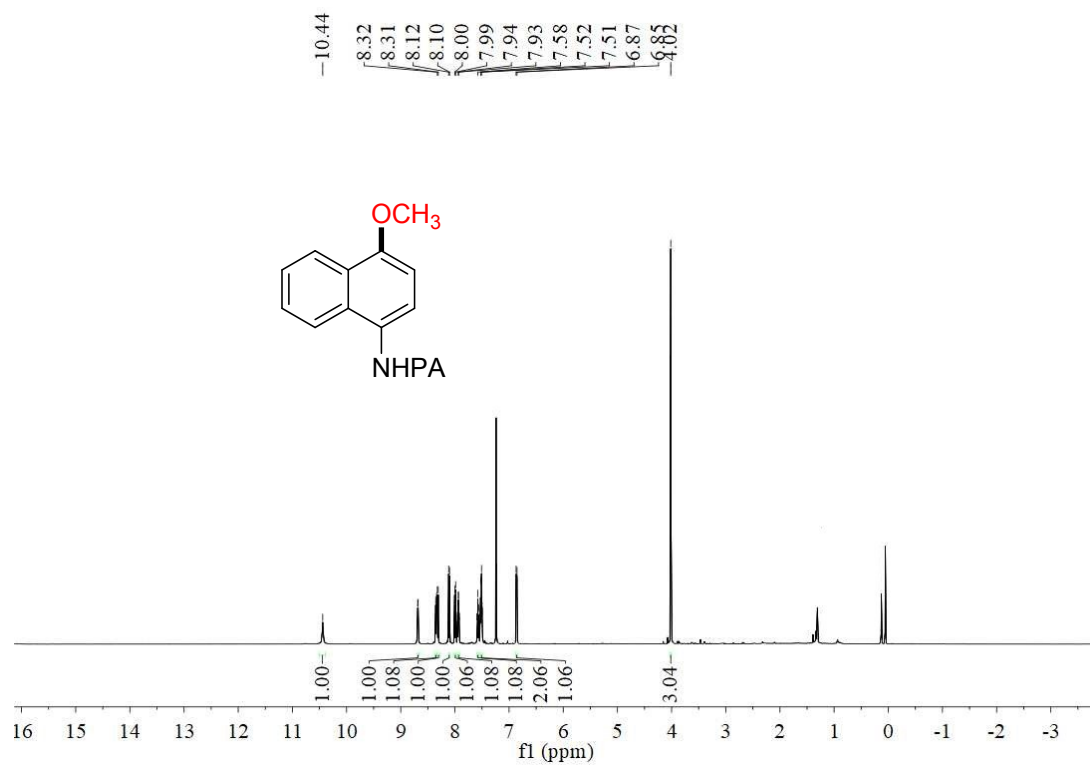
***N*-(4-(2-fluoroethoxy)naphthalen-1-yl)picolinamide (4a)**



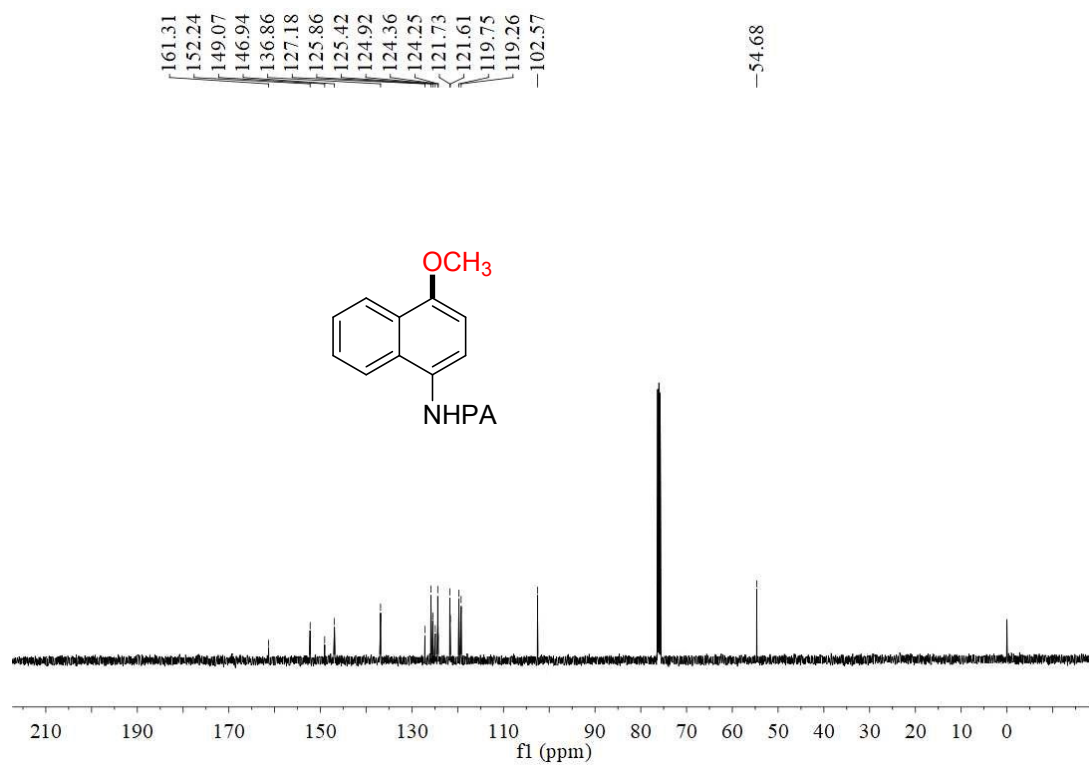
Products **4a** was obtained as a yellow solid, 25% yield, m.p. 119-120 °C. ^1H NMR (500 MHz, CDCl_3) δ 10.48 (s, 1H), 8.70 (d, $J = 4.1$ Hz, 1H), 8.40 (d, $J = 7.8$ Hz, 1H), 8.35 (d, $J = 7.8$ Hz, 1H), 8.16 (d, $J = 8.3$ Hz, 1H), 8.03 (d, $J = 8.4$ Hz, 1H), 7.94 (td, $J = 7.7, 1.7$ Hz, 1H), 7.61 (t, $J = 8.3$ Hz, 1H), 7.57 – 7.51 (m, 2H), 6.88 (d, $J = 8.3$ Hz, 1H), 4.98 – 4.85 (m, 2H), 4.47 – 4.39 (m, 2H); ^{13}C NMR (126 MHz, CDCl_3) δ 162.46, 151.90, 150.16, 148.16, 137.72, 128.13, 127.04, 126.46, 126.06, 125.99, 125.60, 122.88, 122.49, 120.67, 119.75, 104.91, 80.00 (d, $J = 171.4$ Hz), 67.74 (d, $J = 21.4$ Hz); ^{19}F NMR (471 MHz, CDCl_3) δ -224.16. HRMS (ESI): Calculated for $\text{C}_{18}\text{H}_{15}\text{FN}_2\text{O}_2^+$: 311.1191 $[\text{M}+\text{H}]^+$, Found: 311.1196.

2. Copies of ^1H and ^{13}C NMR Spectra

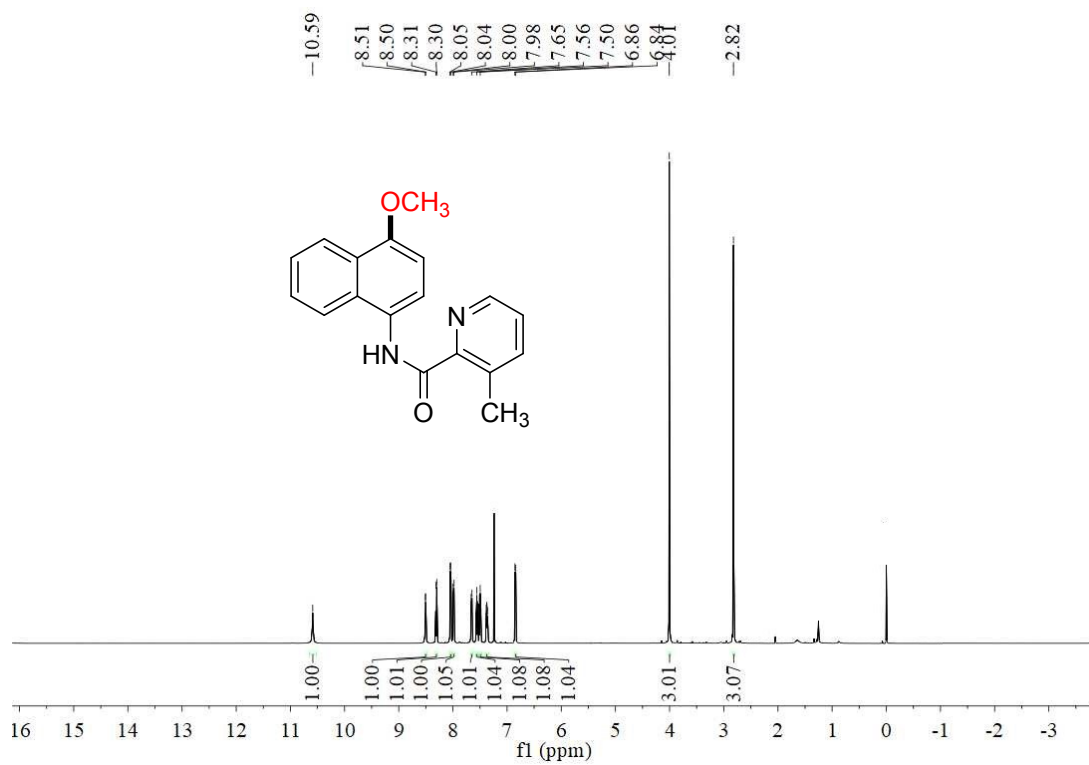
2a ^1H NMR



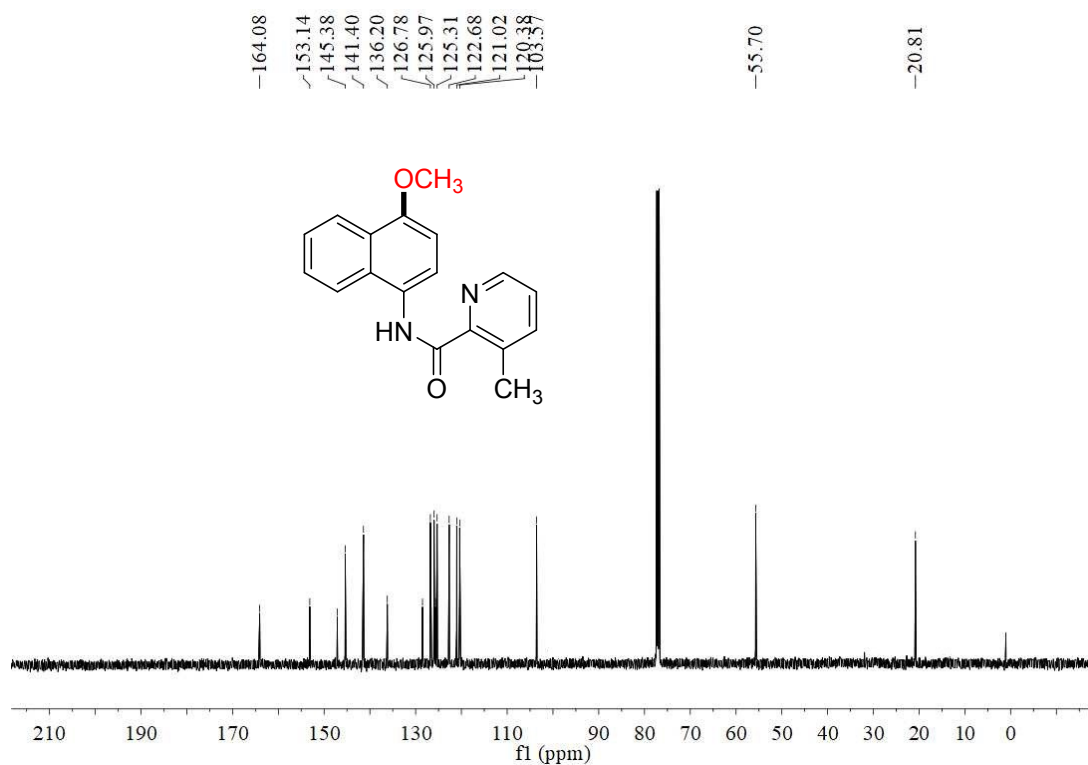
2a ^{13}C NMR



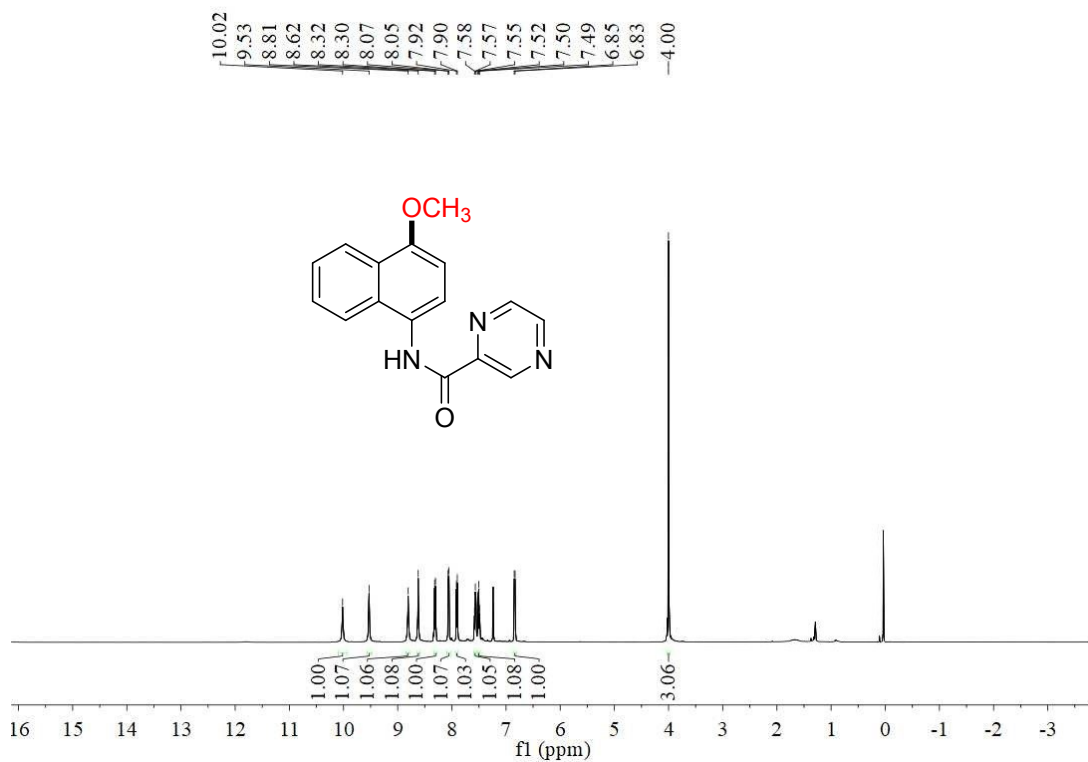
2b ¹H NMR



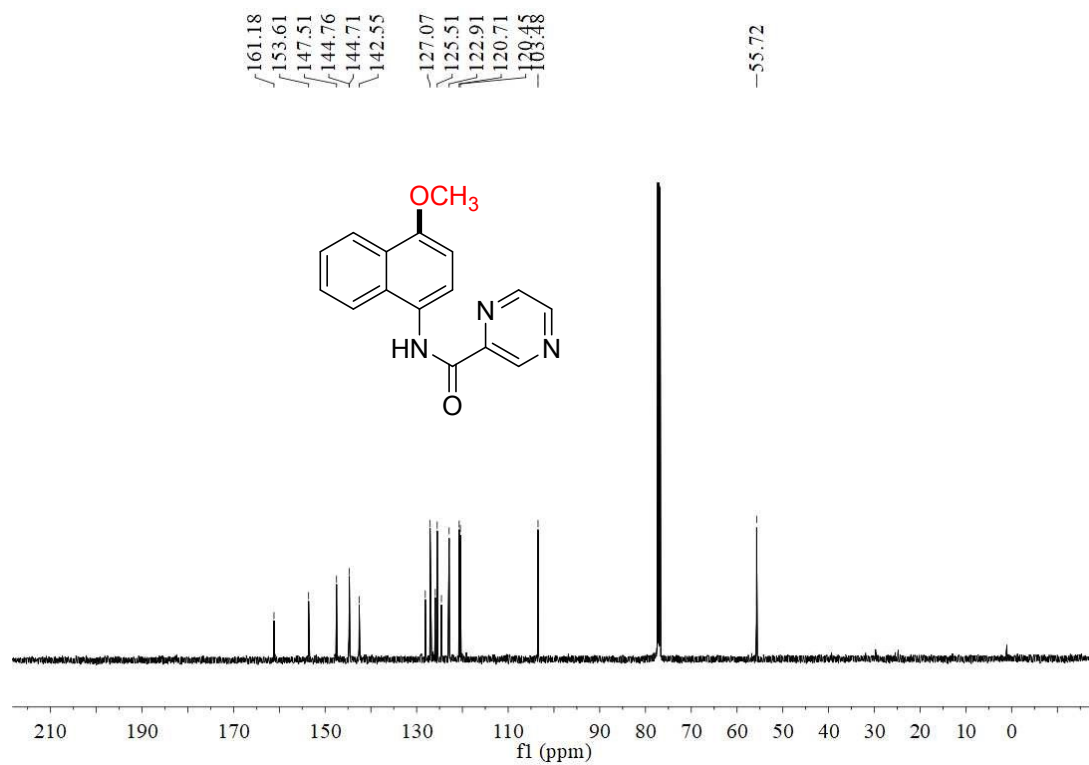
2b ¹³C NMR



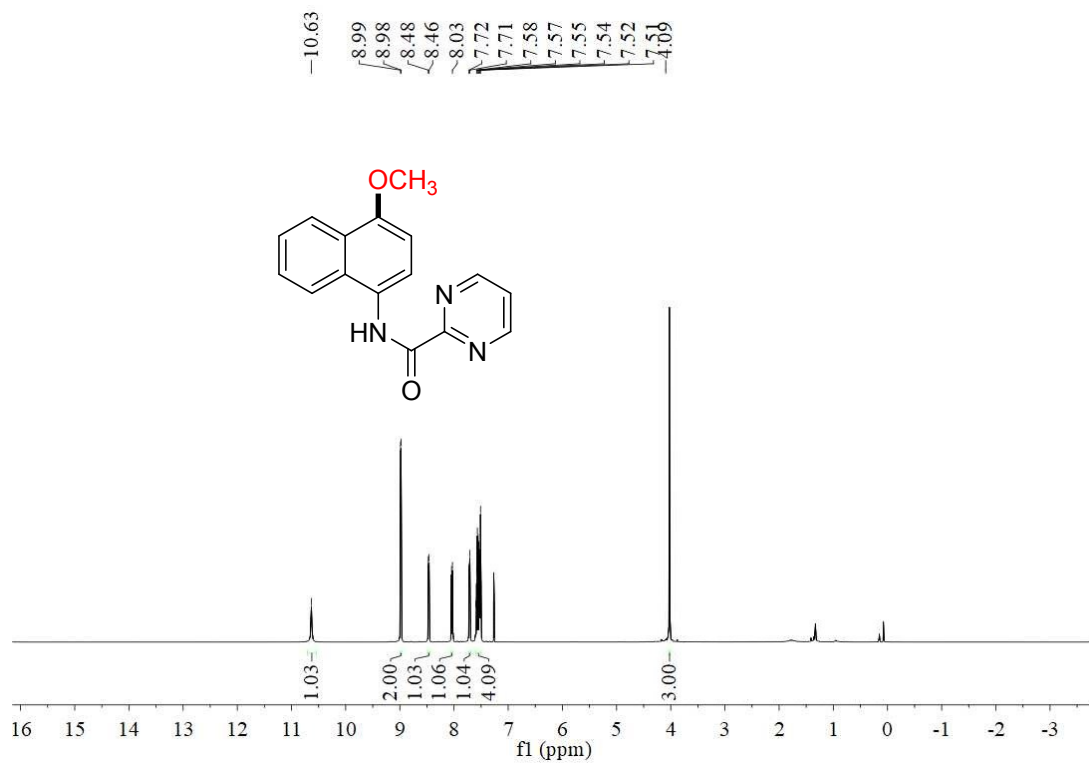
2c ¹H NMR



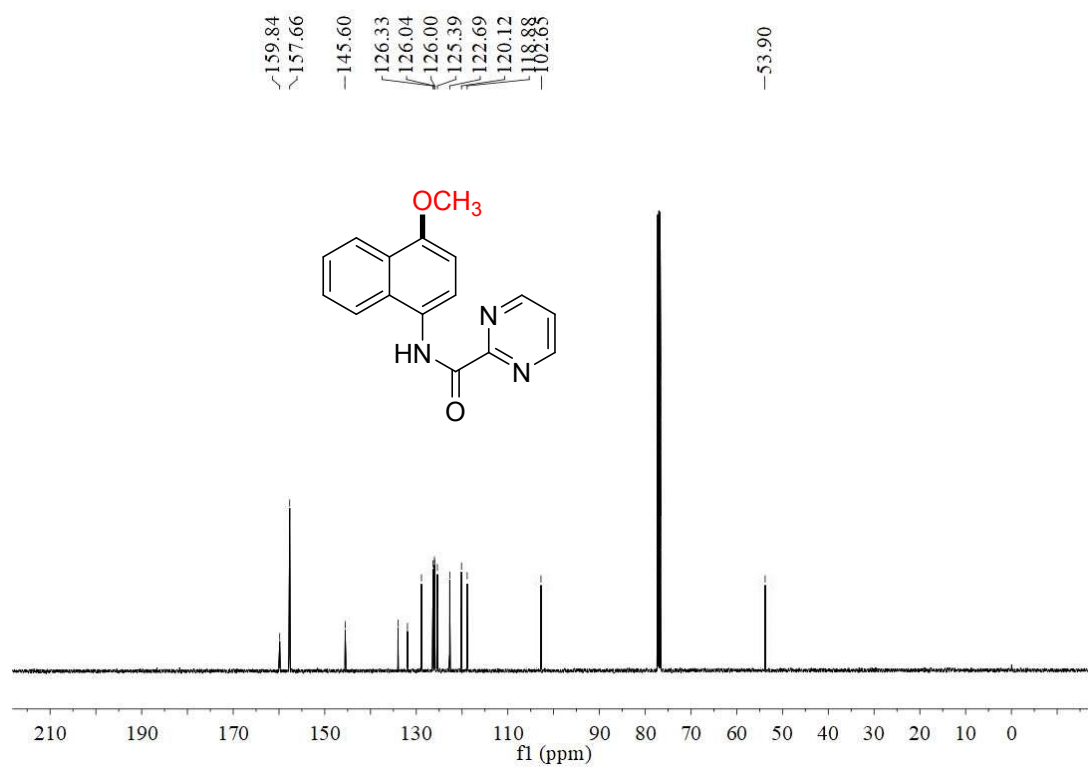
2c ¹³C NMR



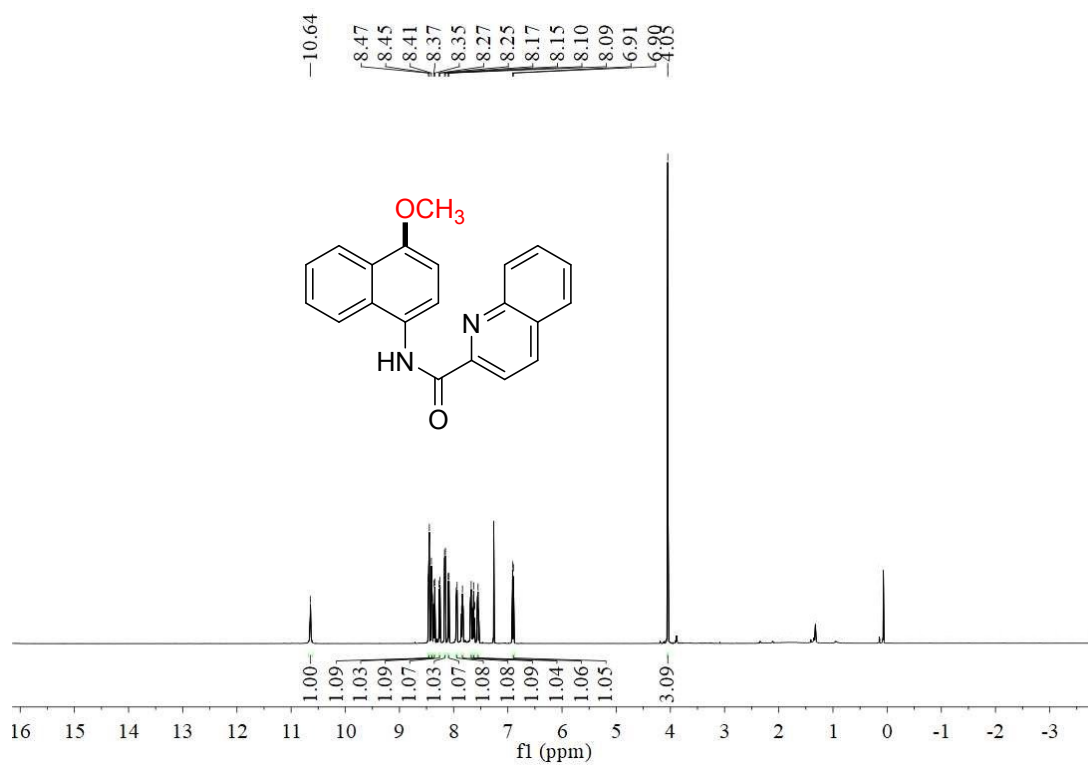
2d ¹H NMR



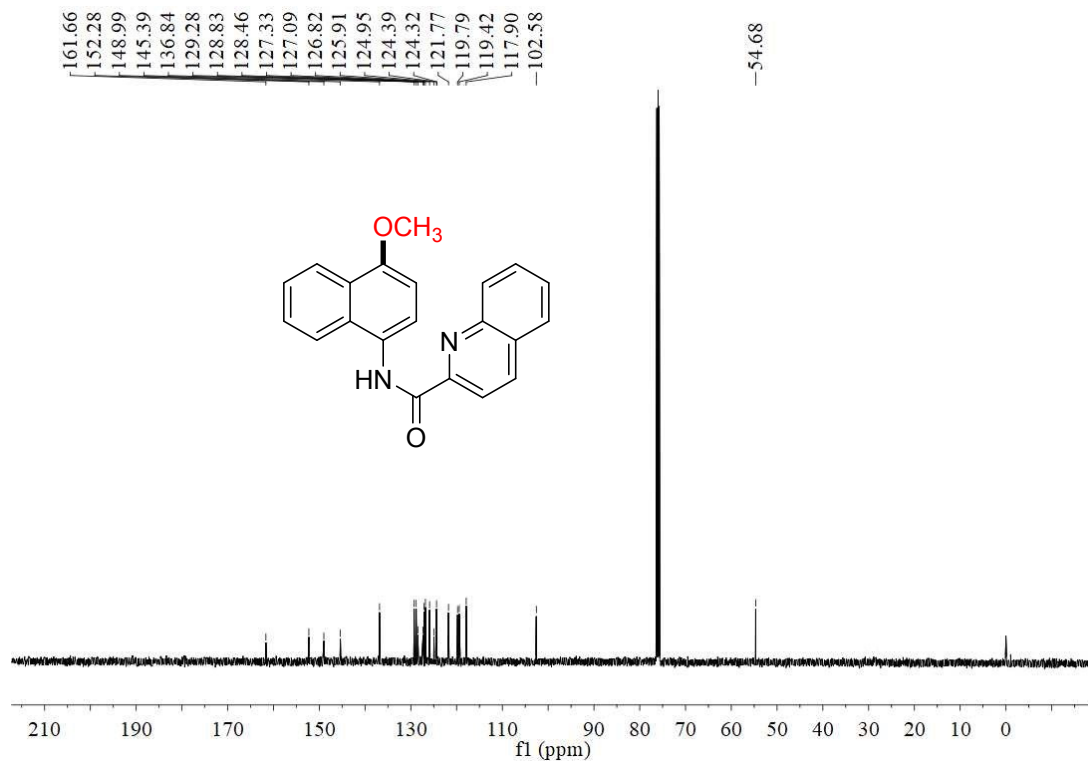
2d ¹³C NMR



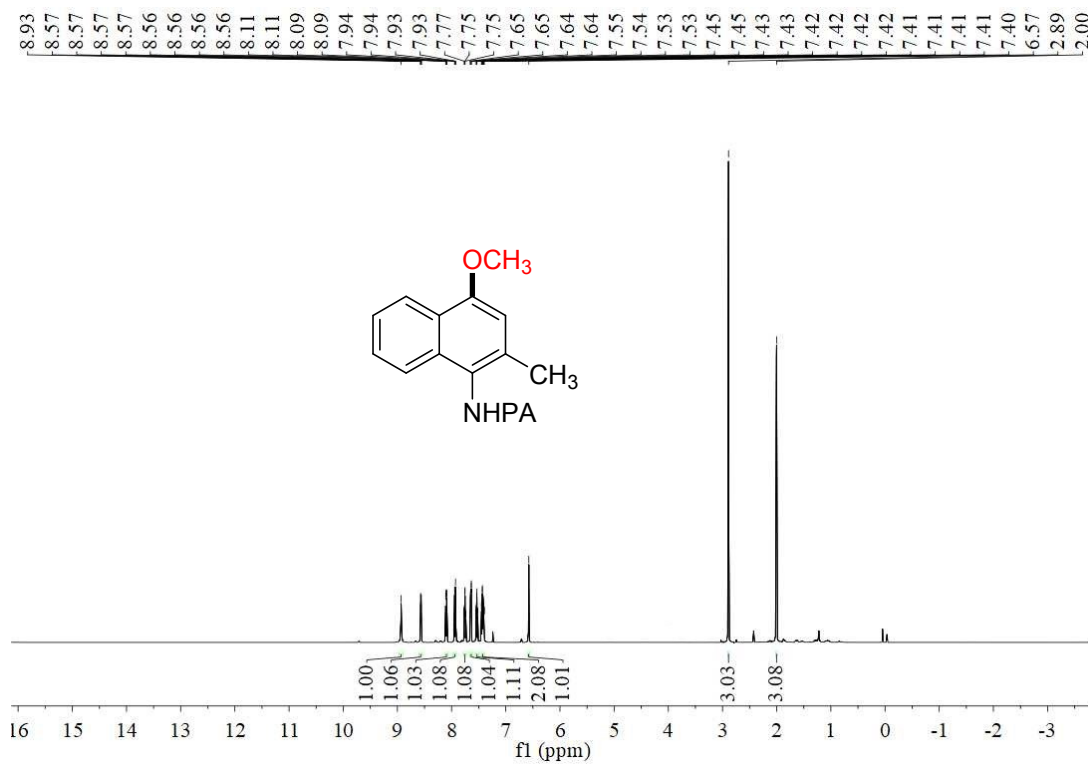
2e ¹H NMR



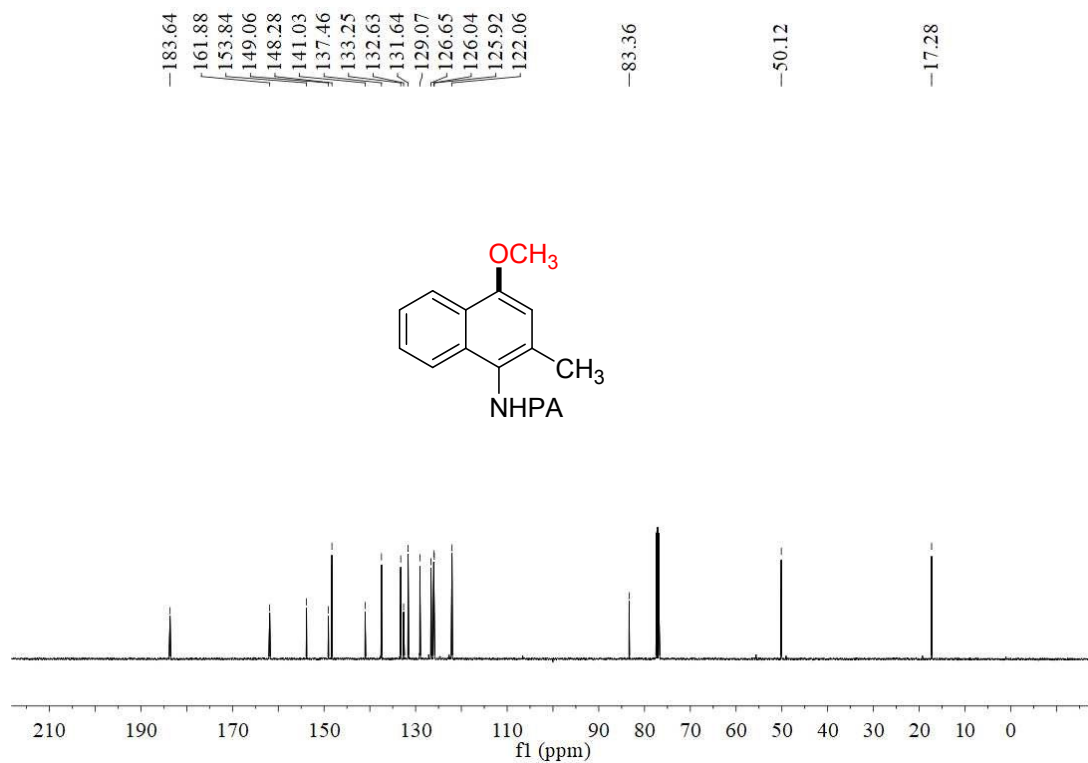
2e ¹³C NMR



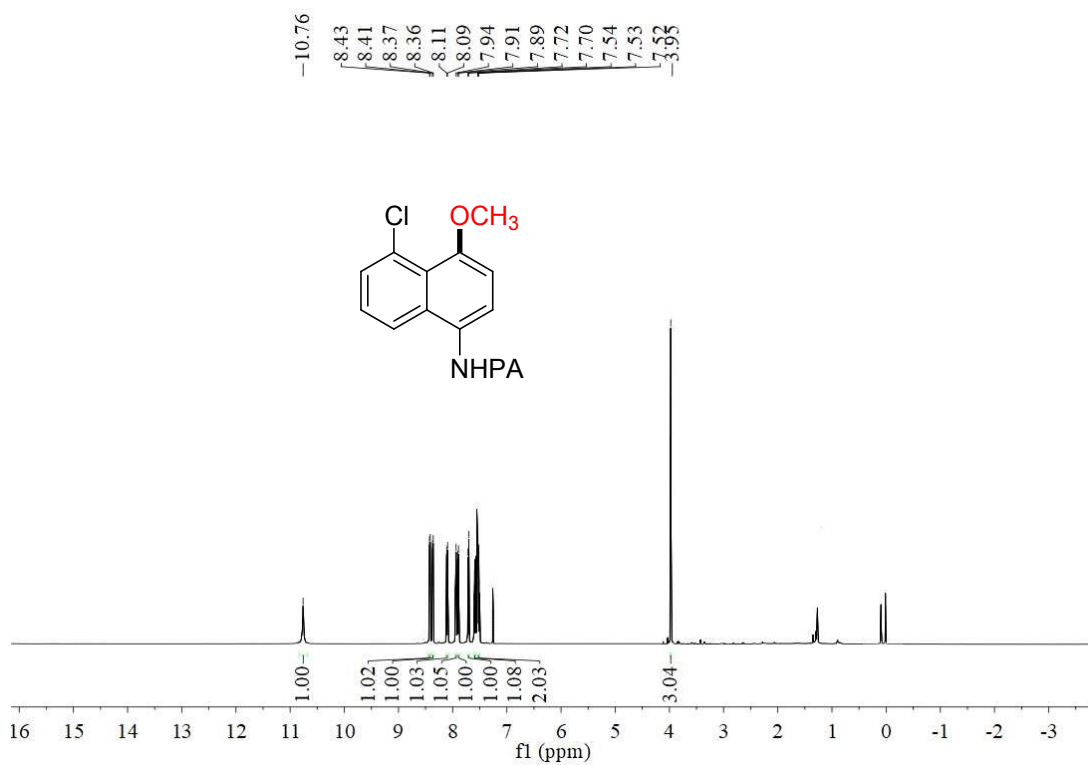
2f ¹H NMR



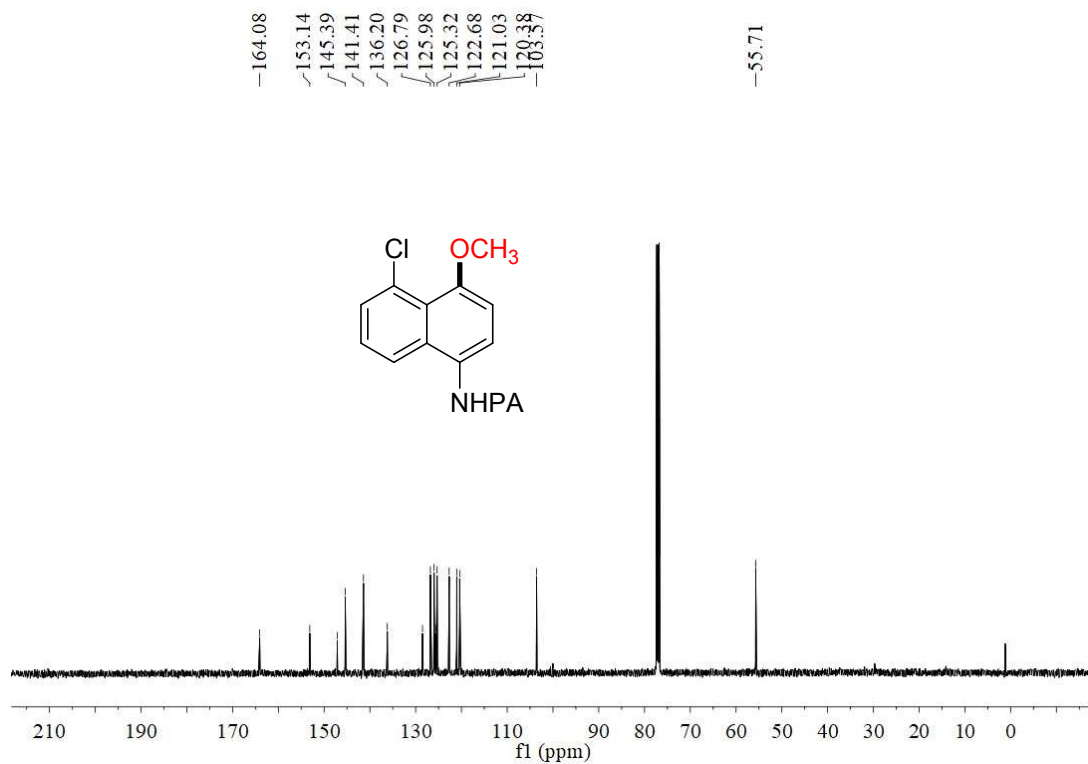
2f ^{13}C NMR



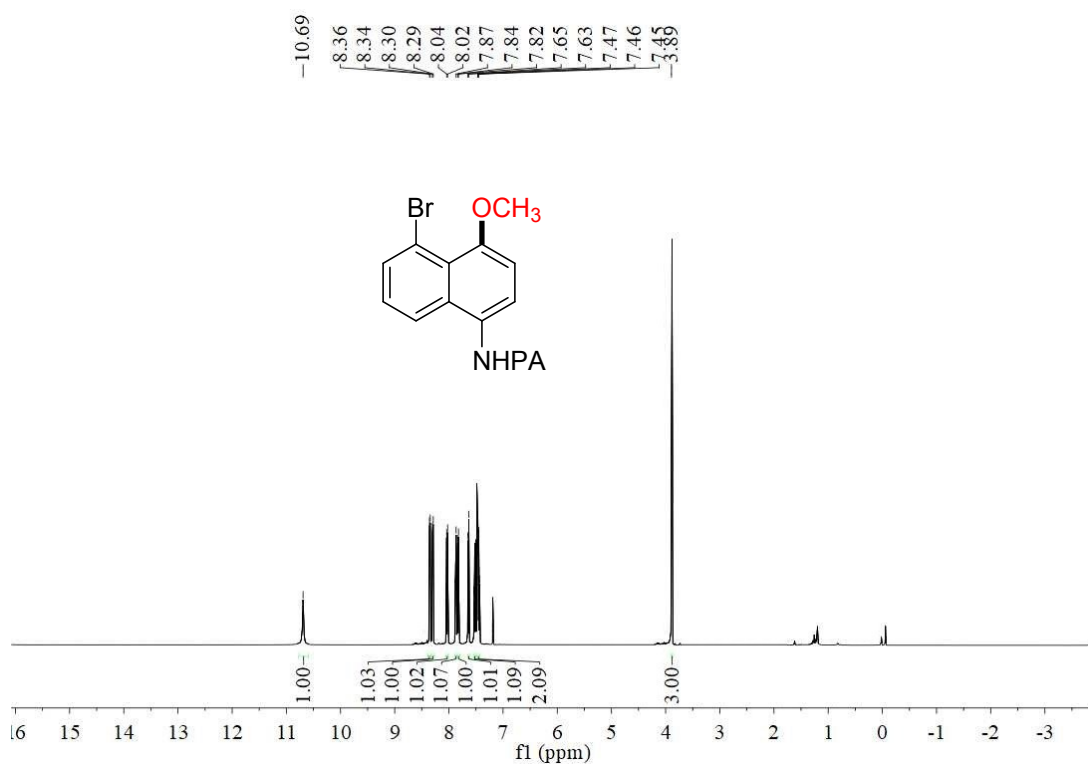
2g ^1H NMR



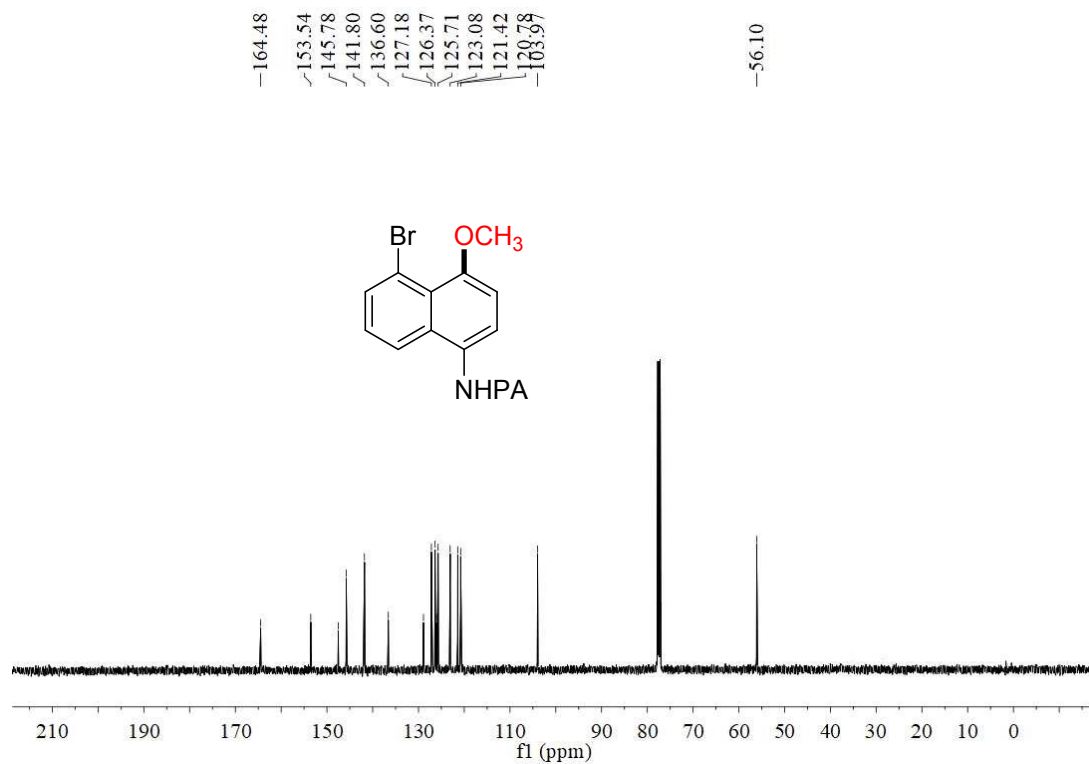
2g ¹³C NMR



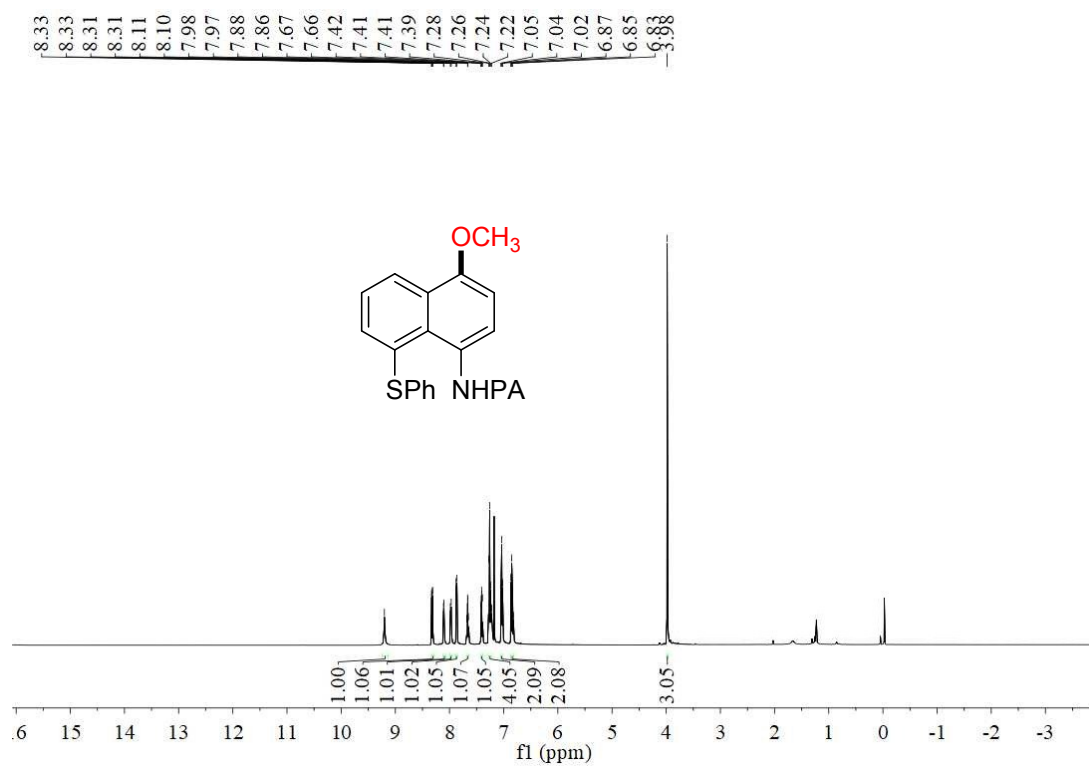
2h ¹H NMR



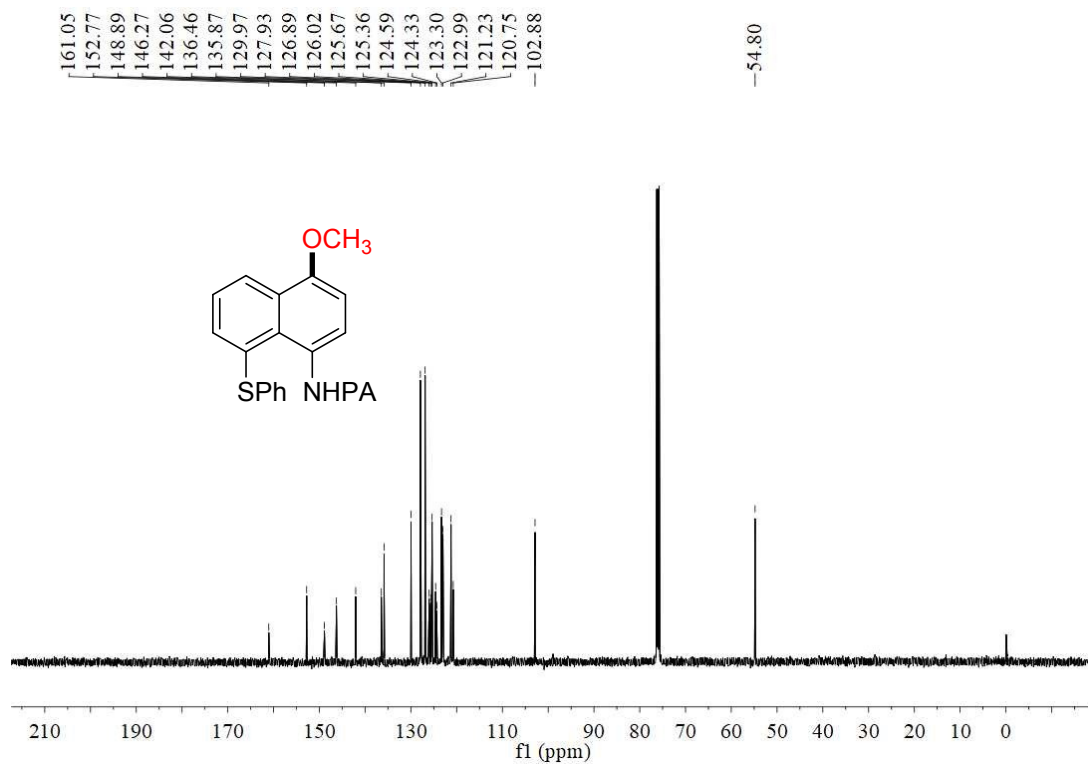
2h ¹³C NMR



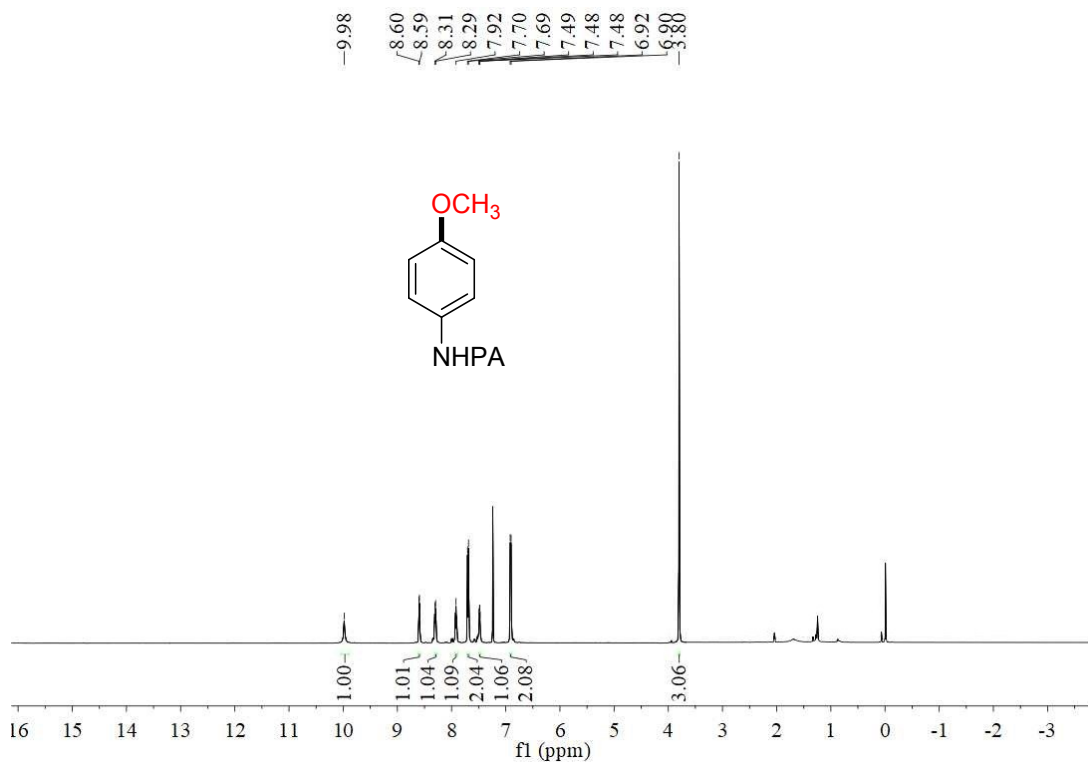
2i ¹H NMR



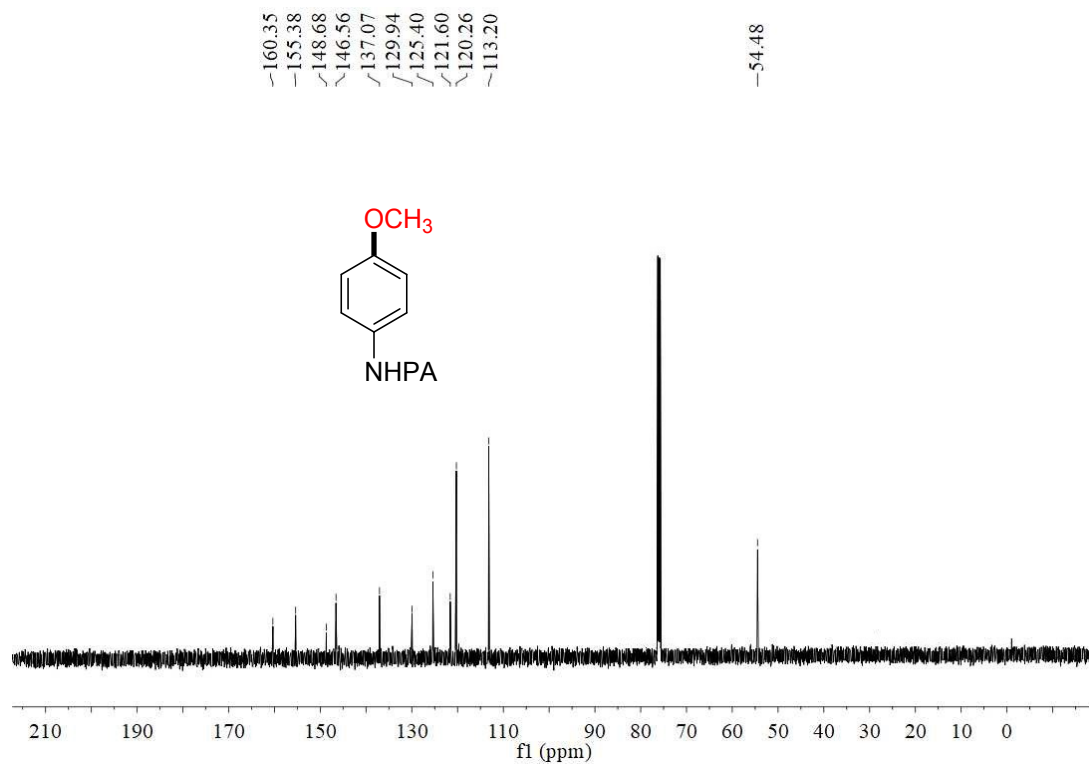
2i ¹³C NMR



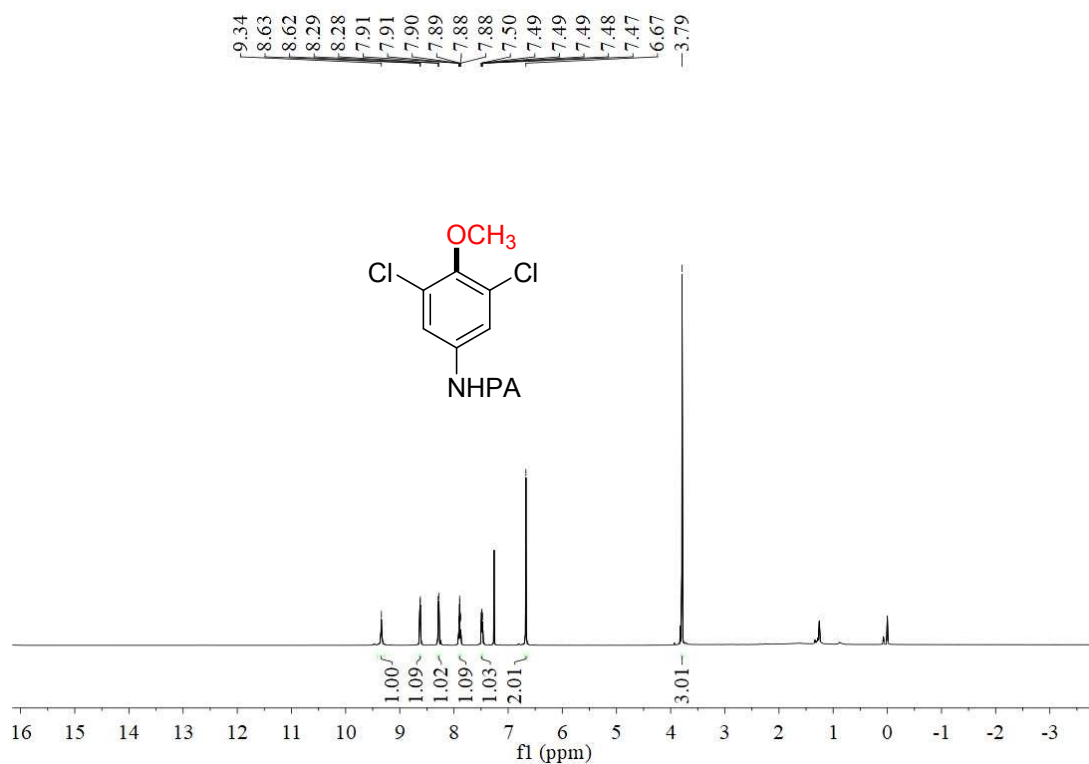
2j ¹H NMR



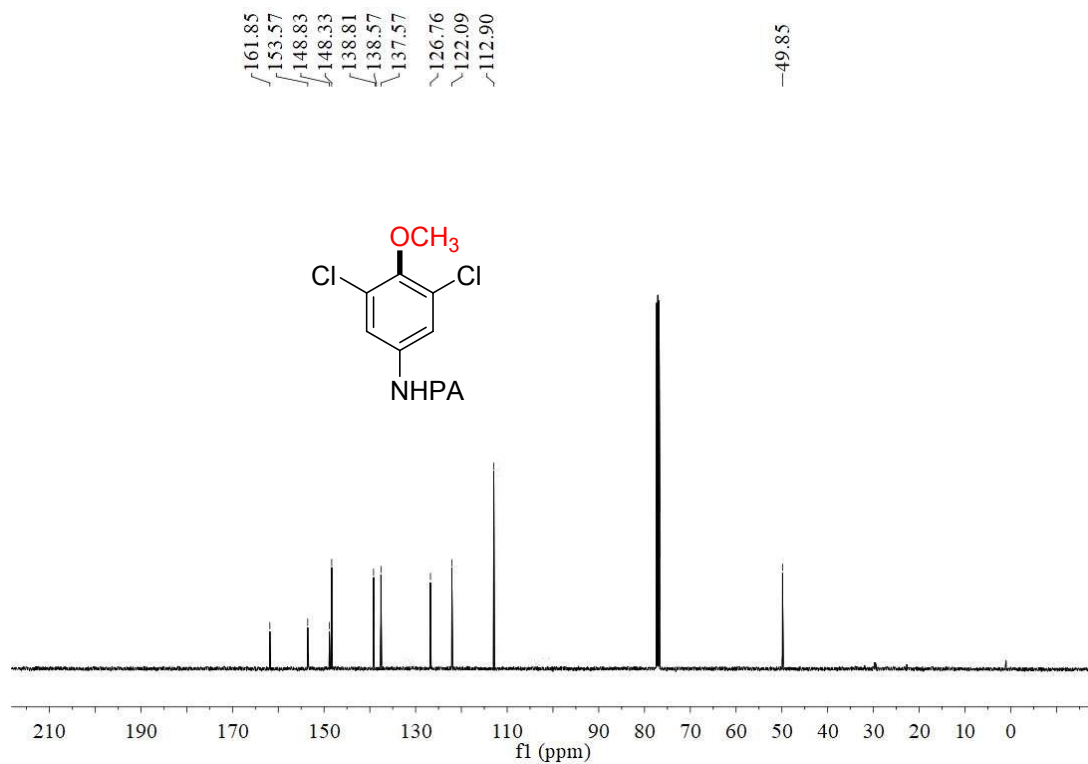
2j ¹³C NMR



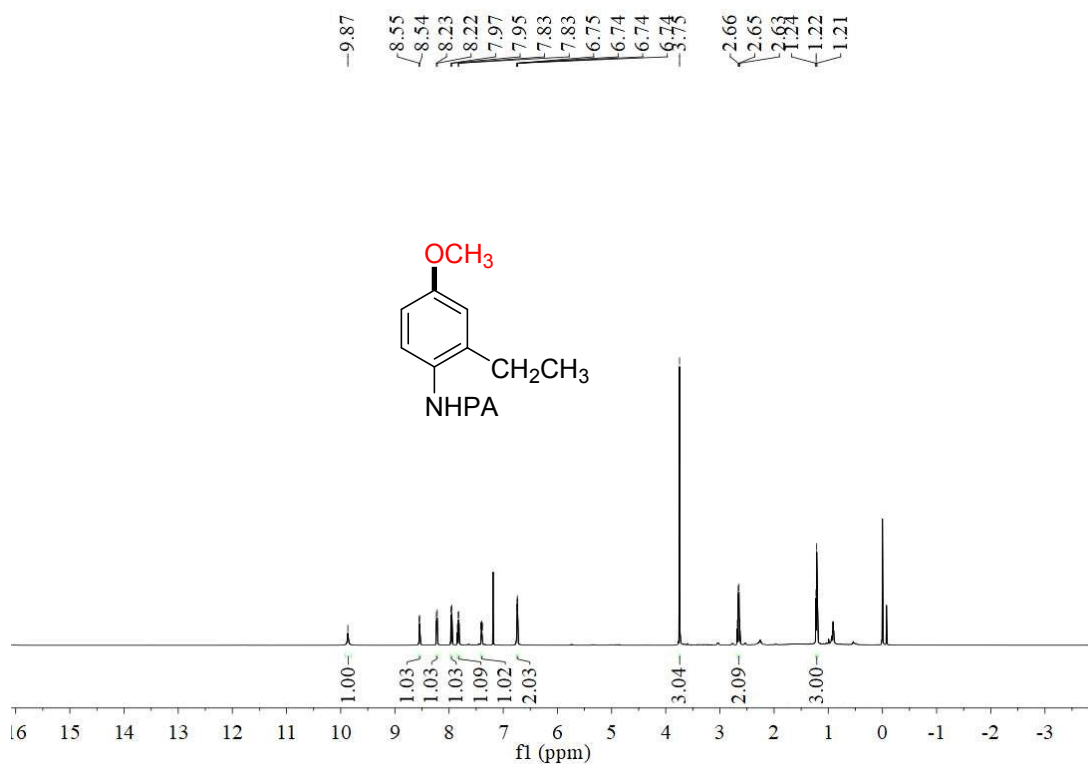
2k ¹H NMR



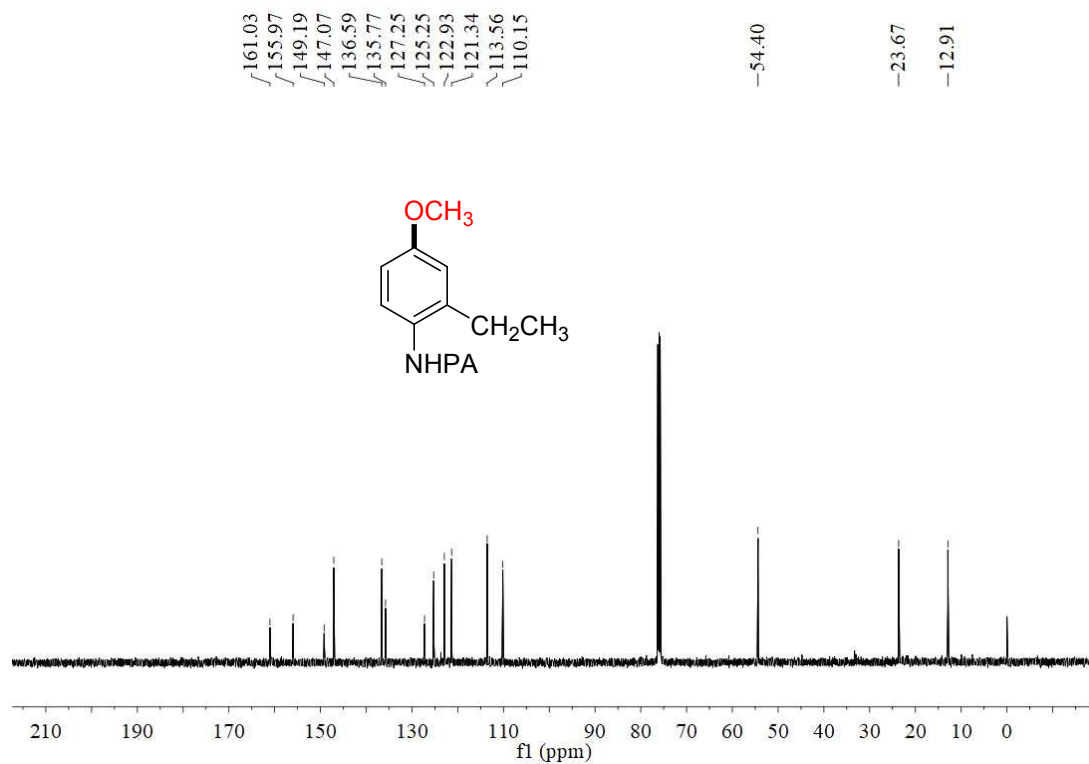
2k ¹³C NMR



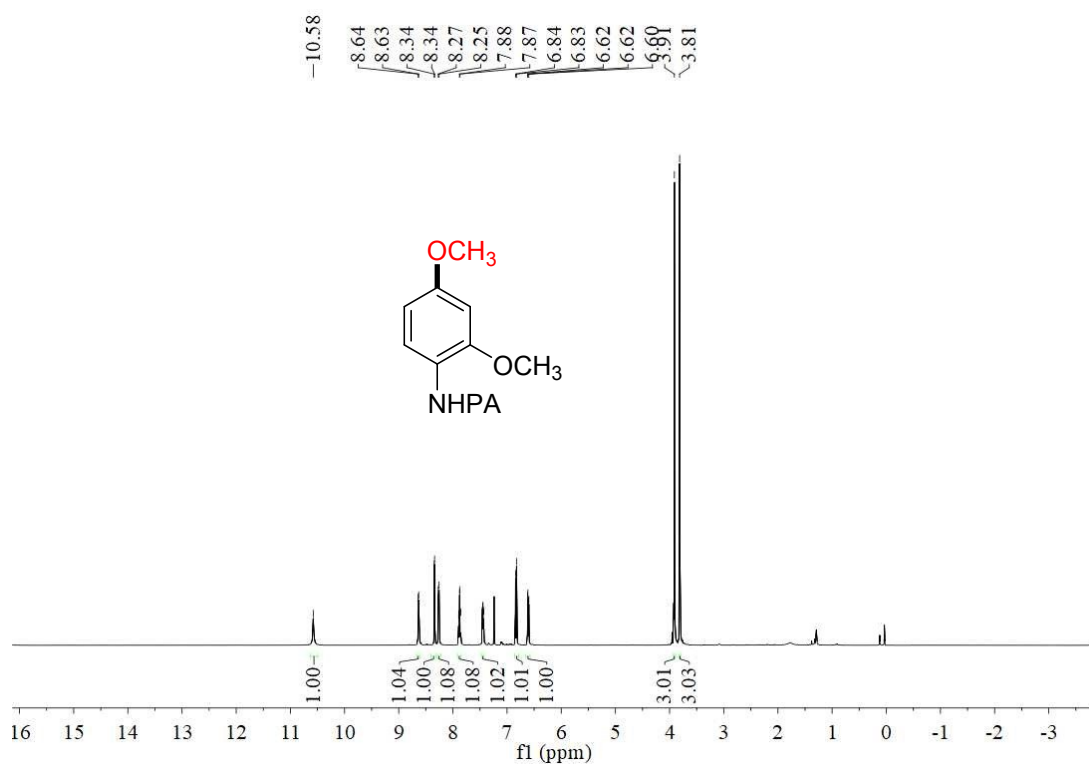
2l ¹H NMR



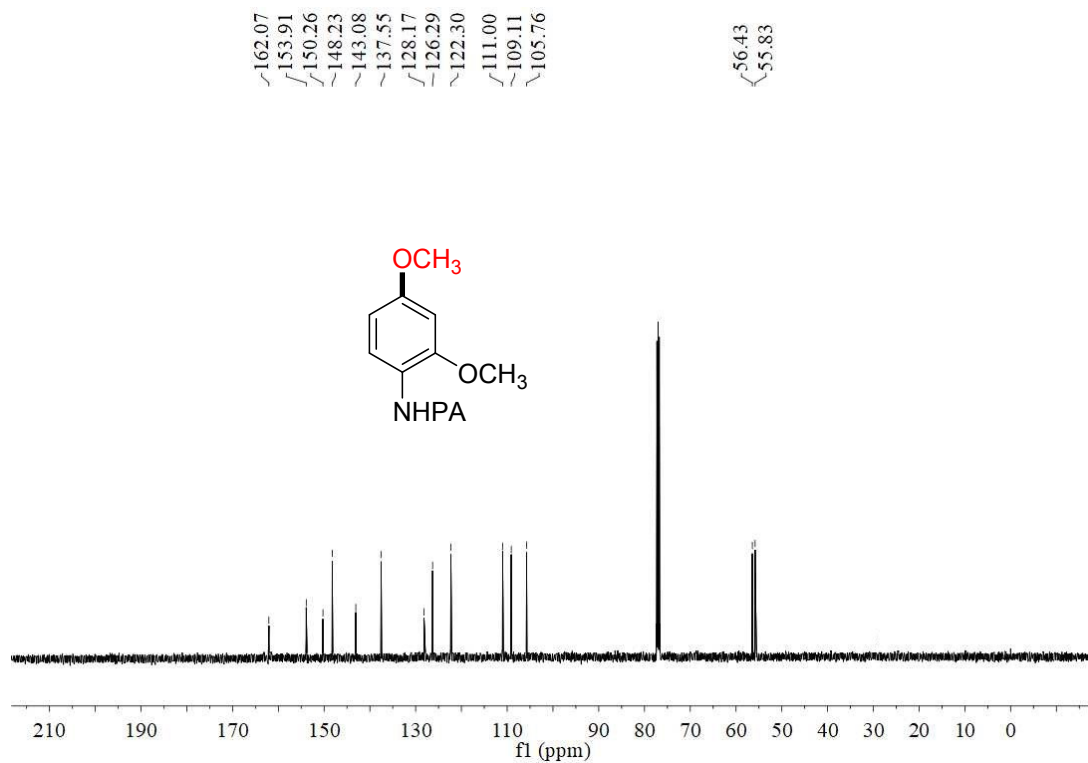
2l ¹³C NMR



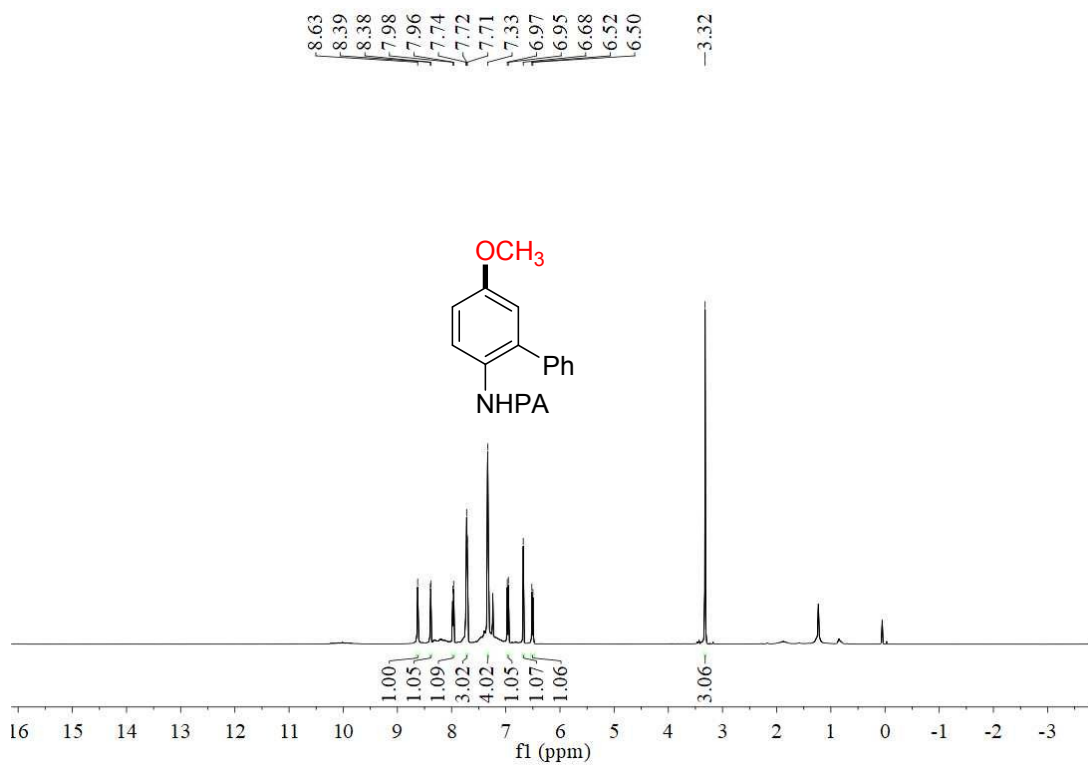
2m ¹H NMR



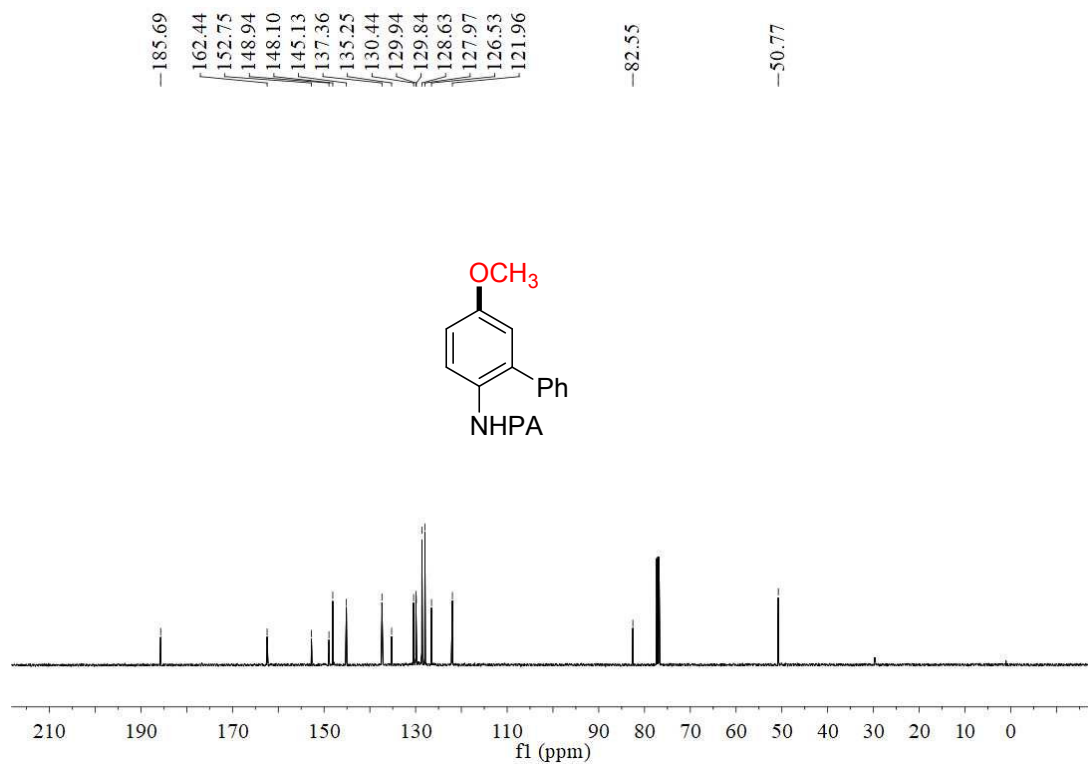
2m ¹³C NMR



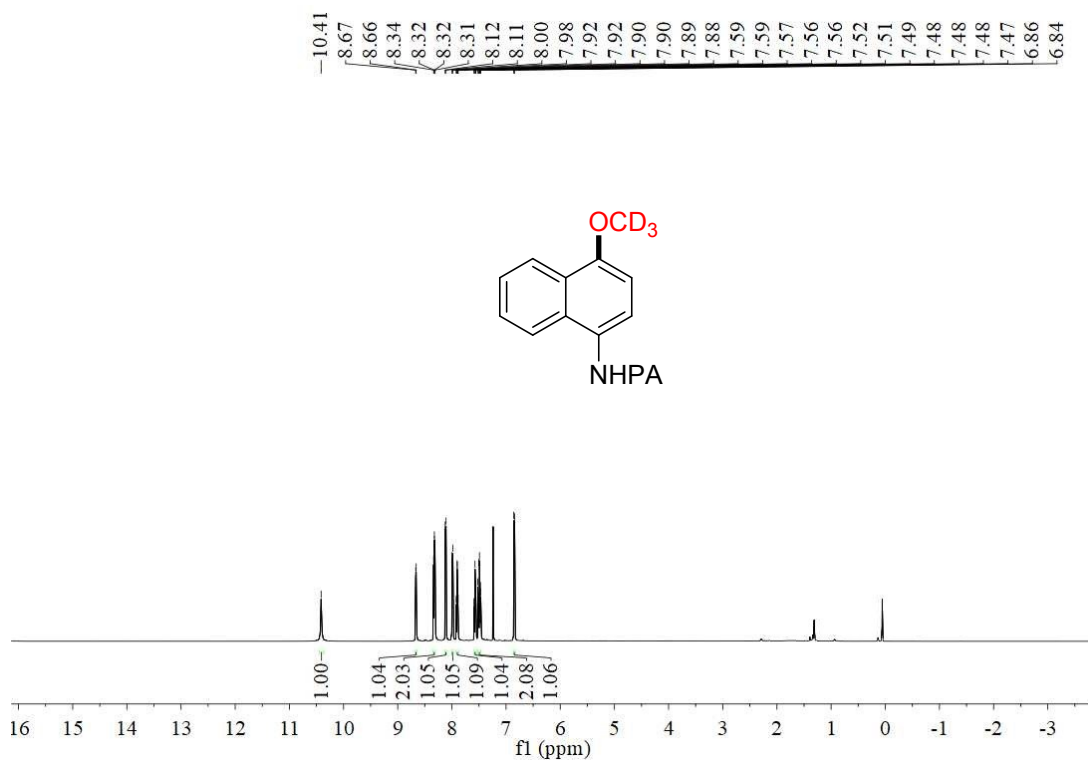
2n ¹H NMR



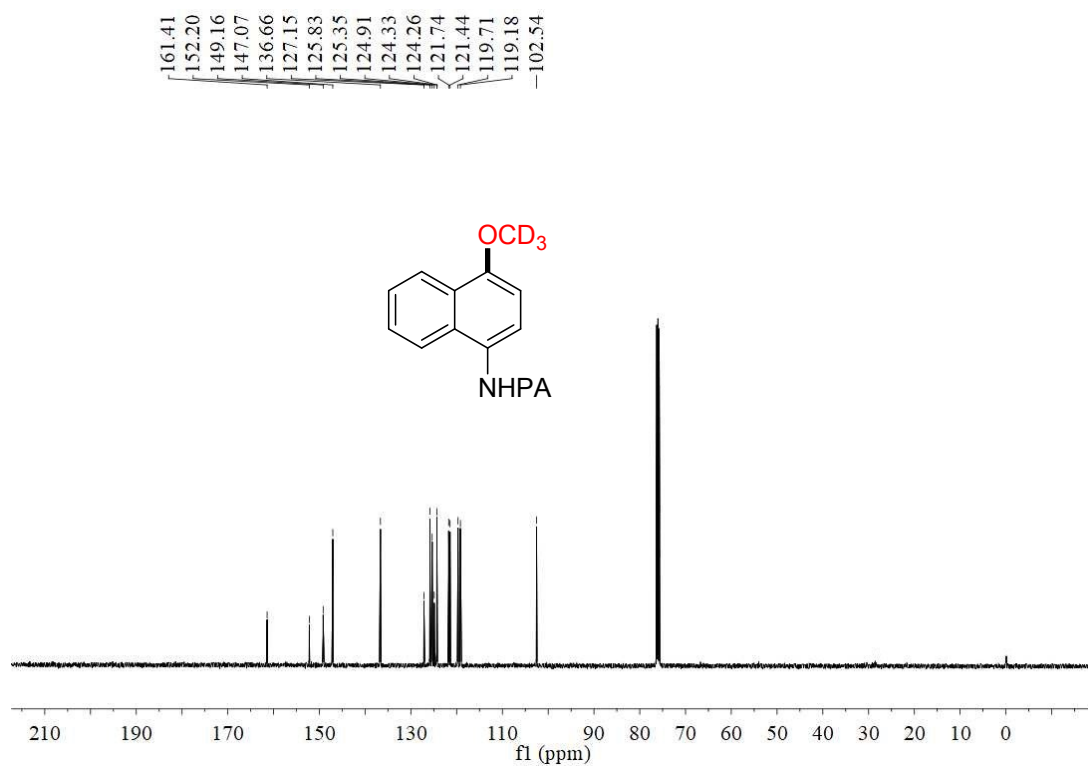
2n ^{13}C NMR



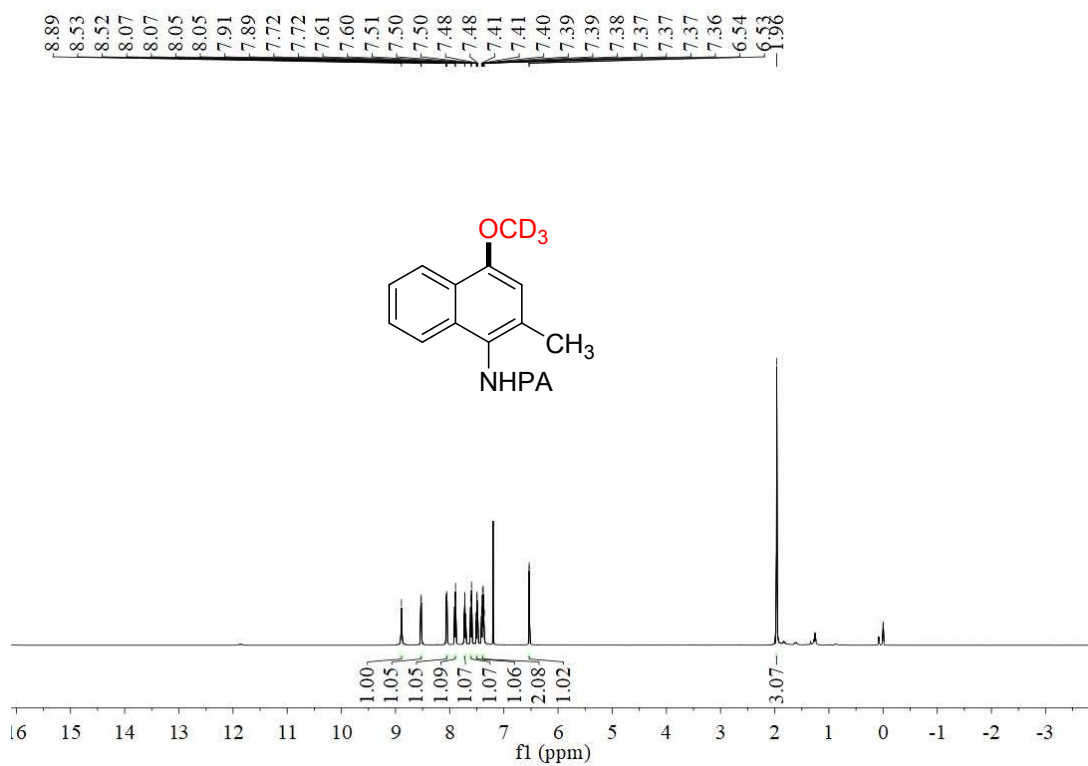
2o ^1H NMR



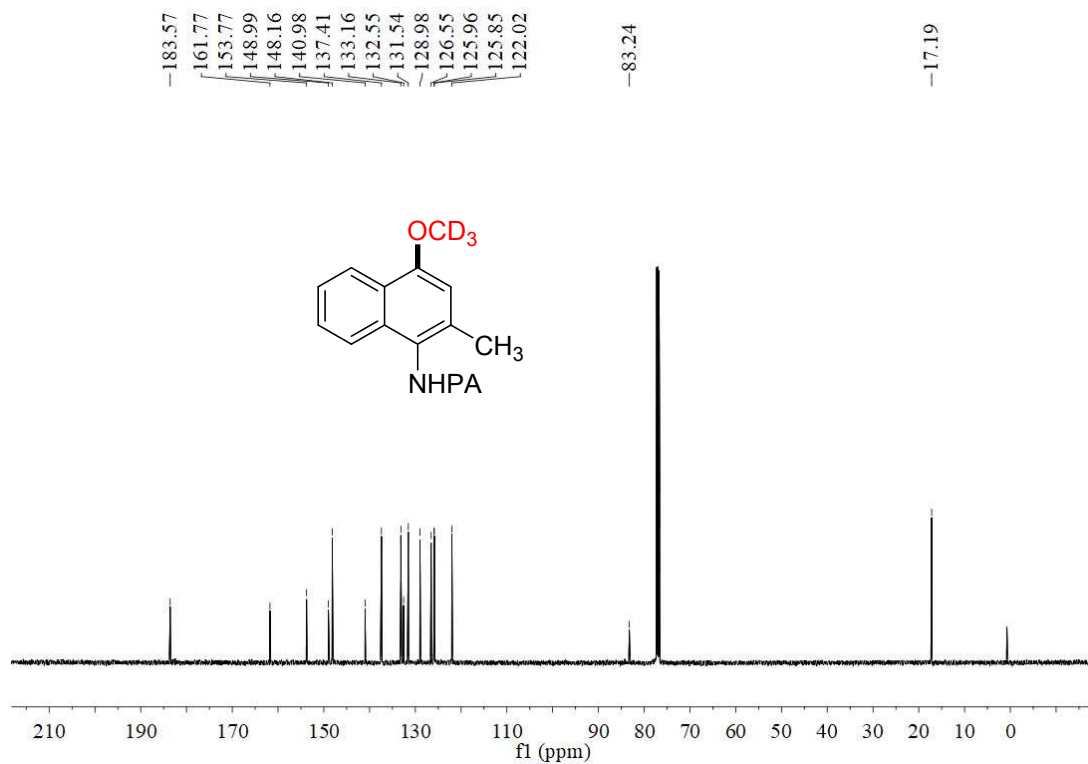
2o ¹³C NMR



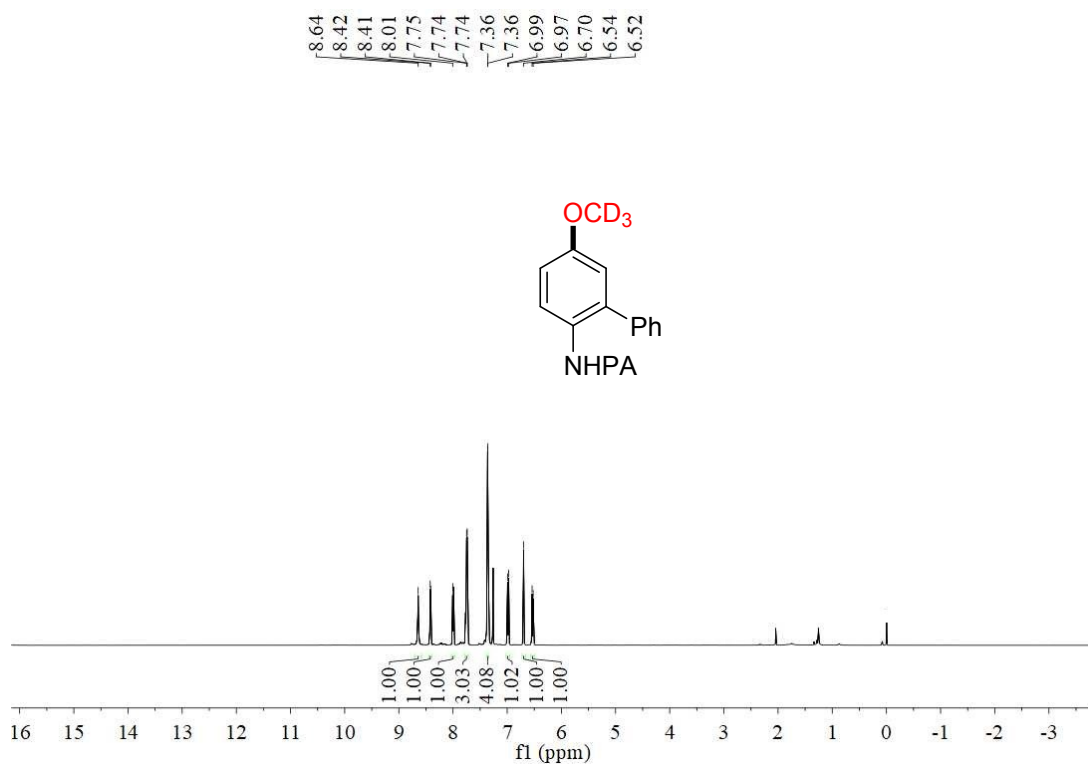
2p ¹H NMR



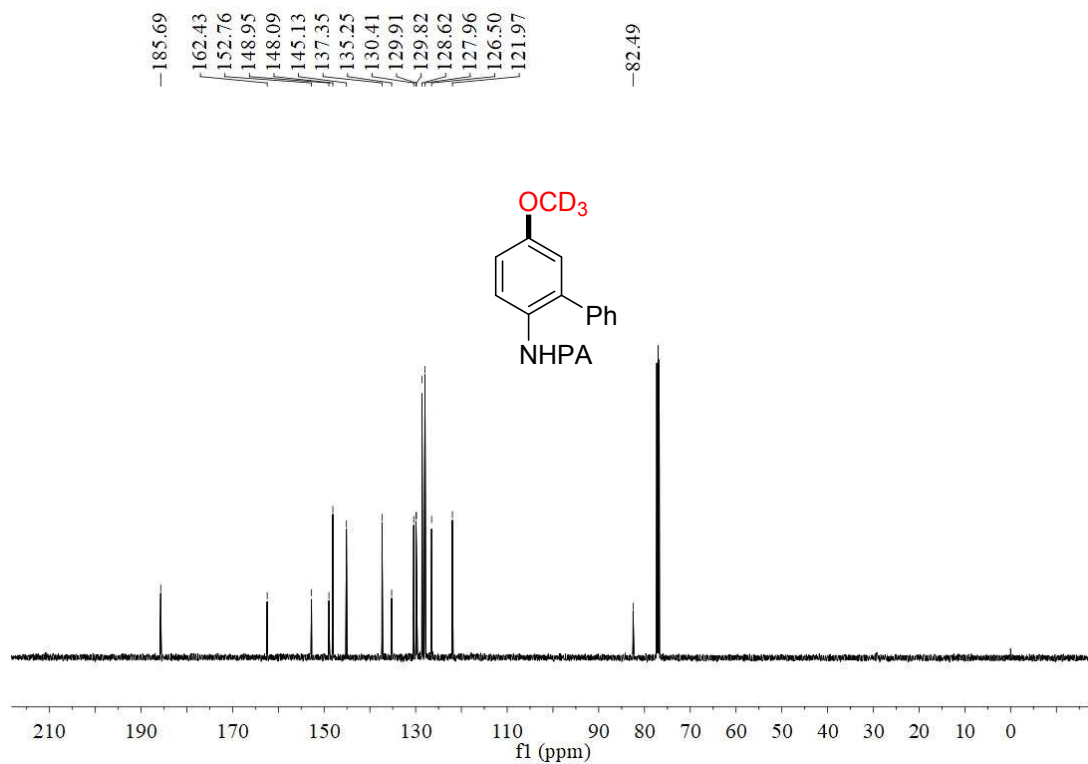
2p ¹³C NMR



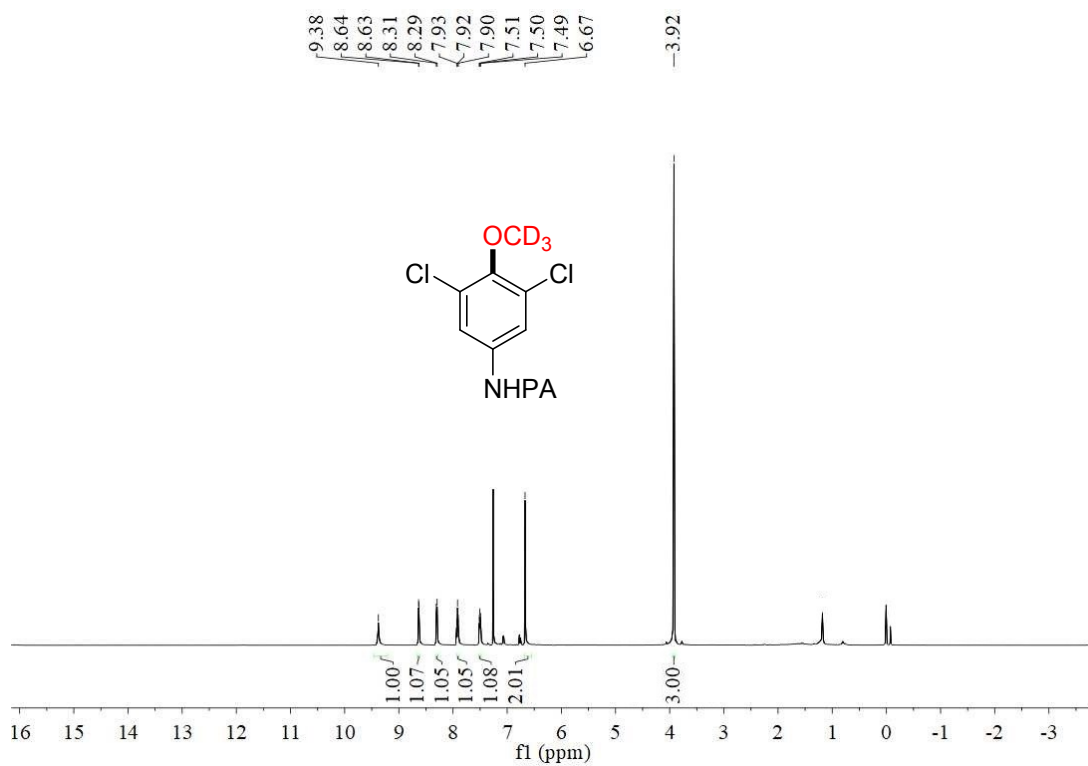
2q ¹H NMR



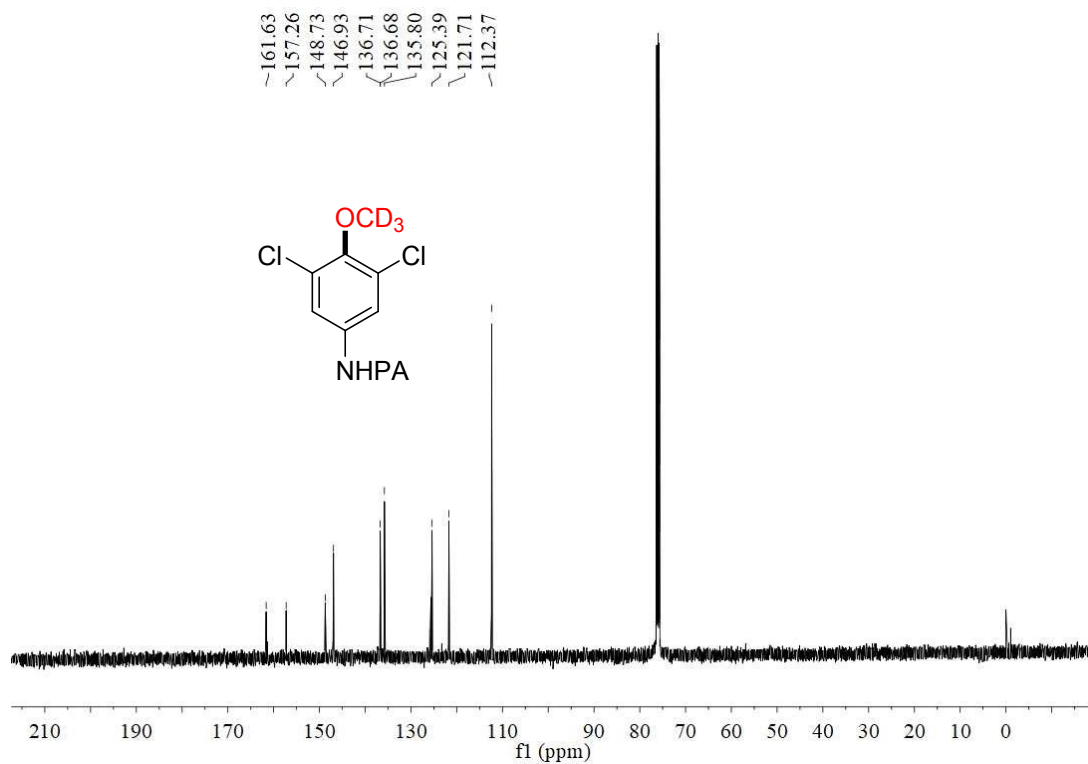
2q ^{13}C NMR



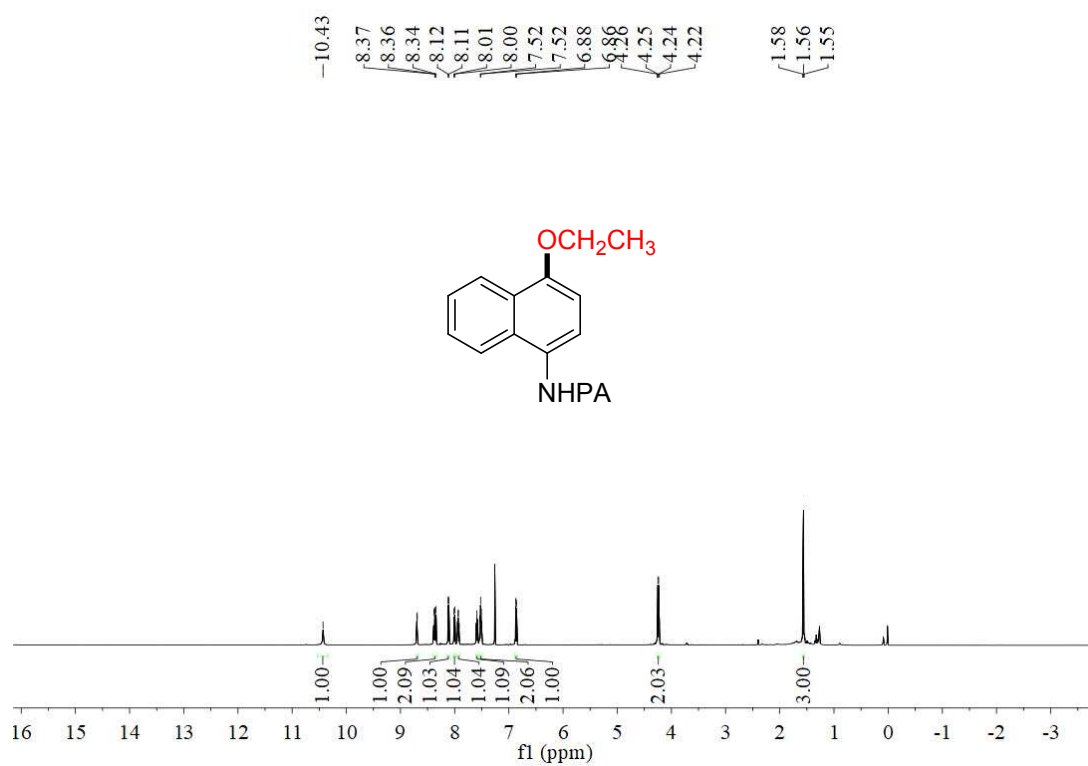
2r ^1H NMR



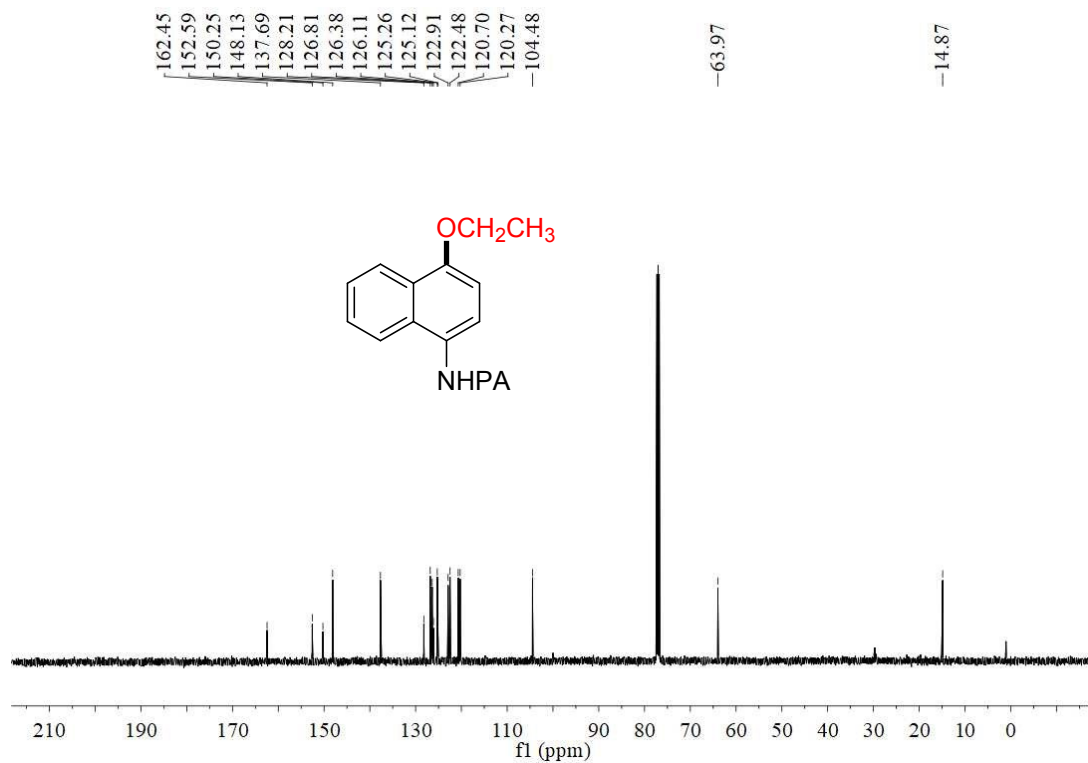
2r ¹³C NMR



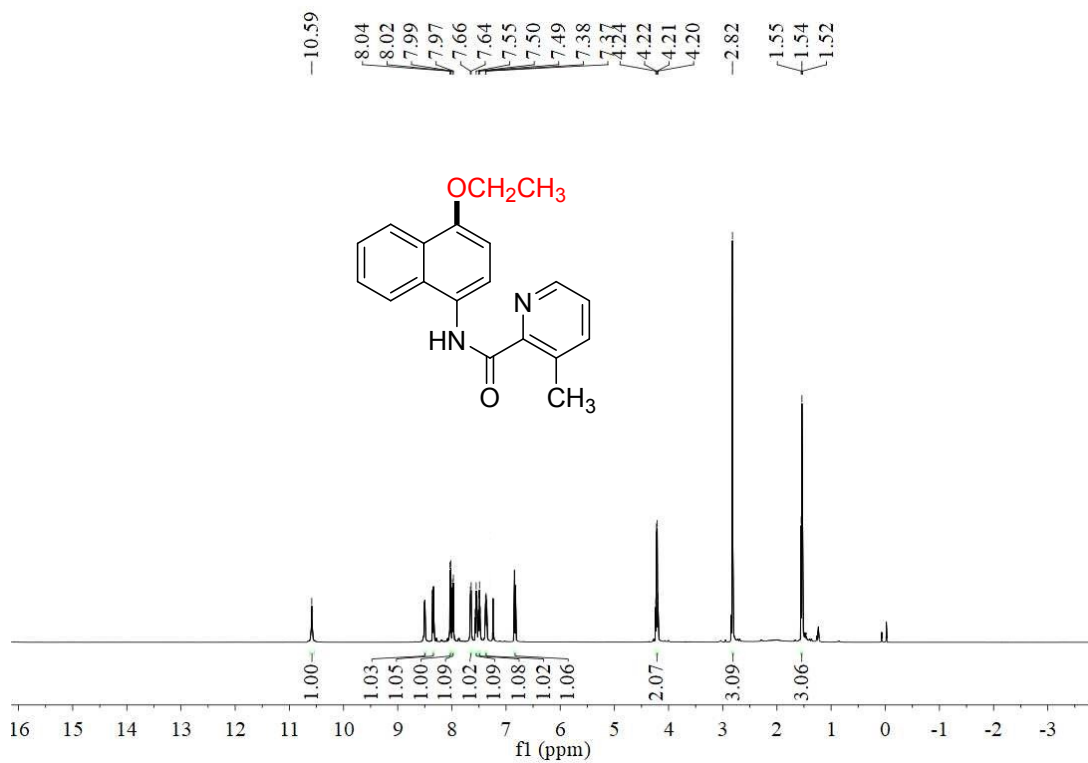
3a ¹H NMR



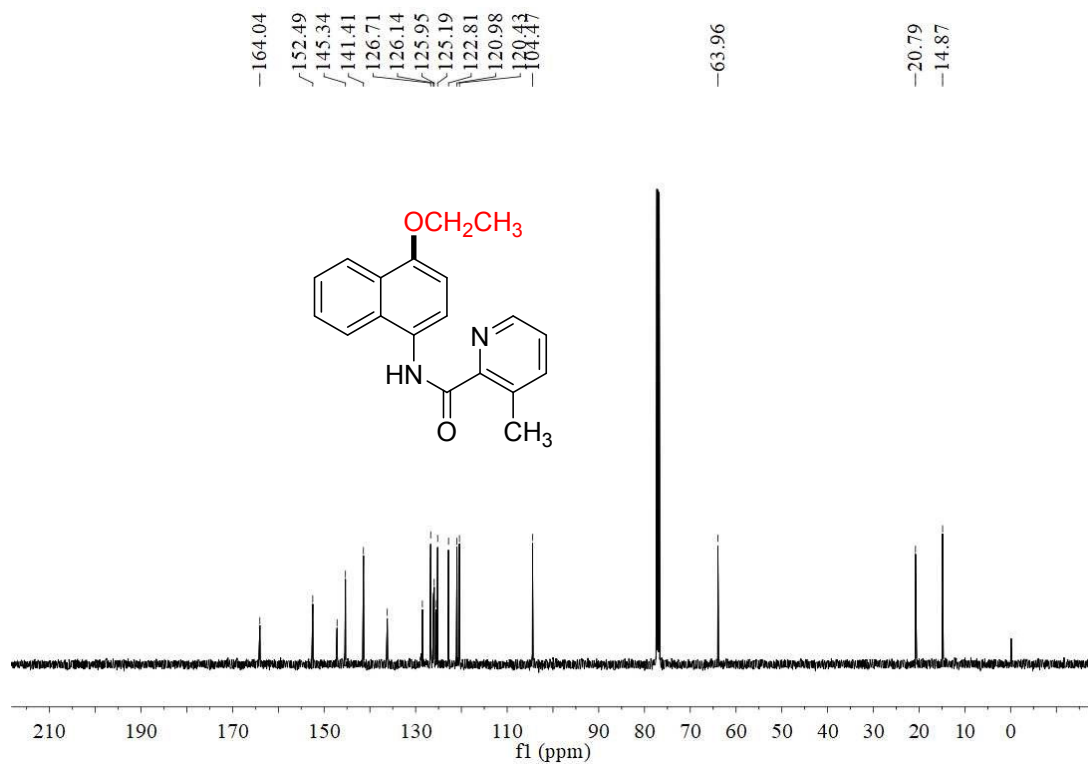
3a ¹³C NMR



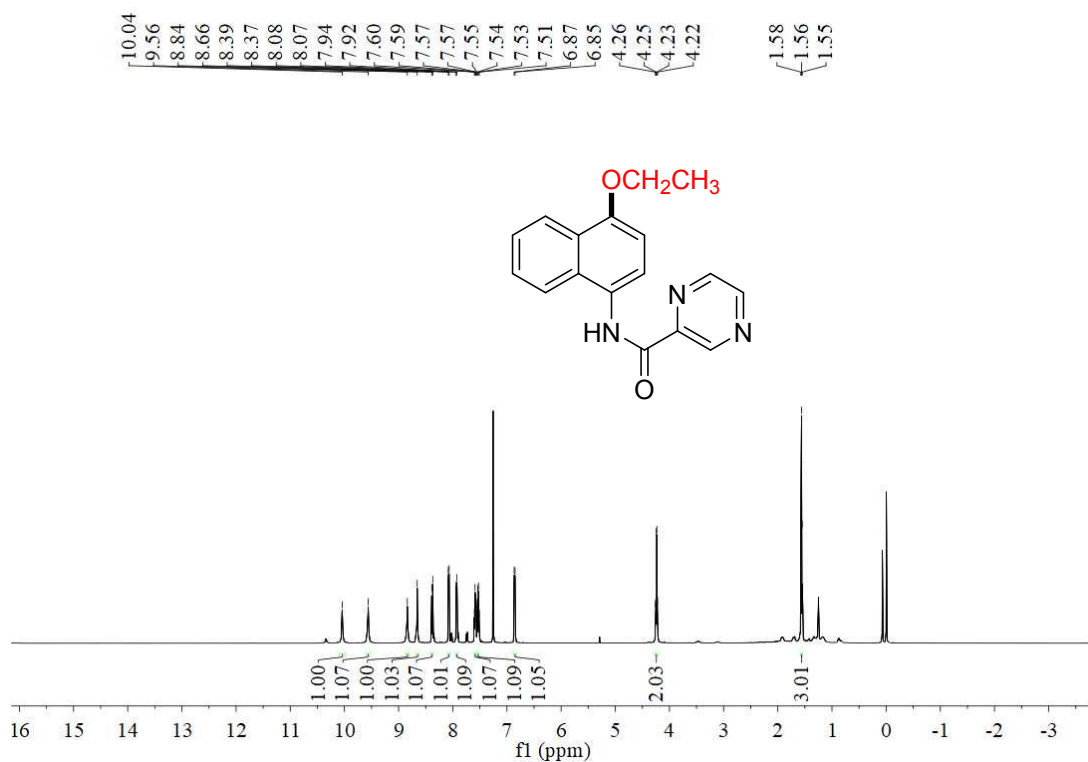
3b ¹H NMR



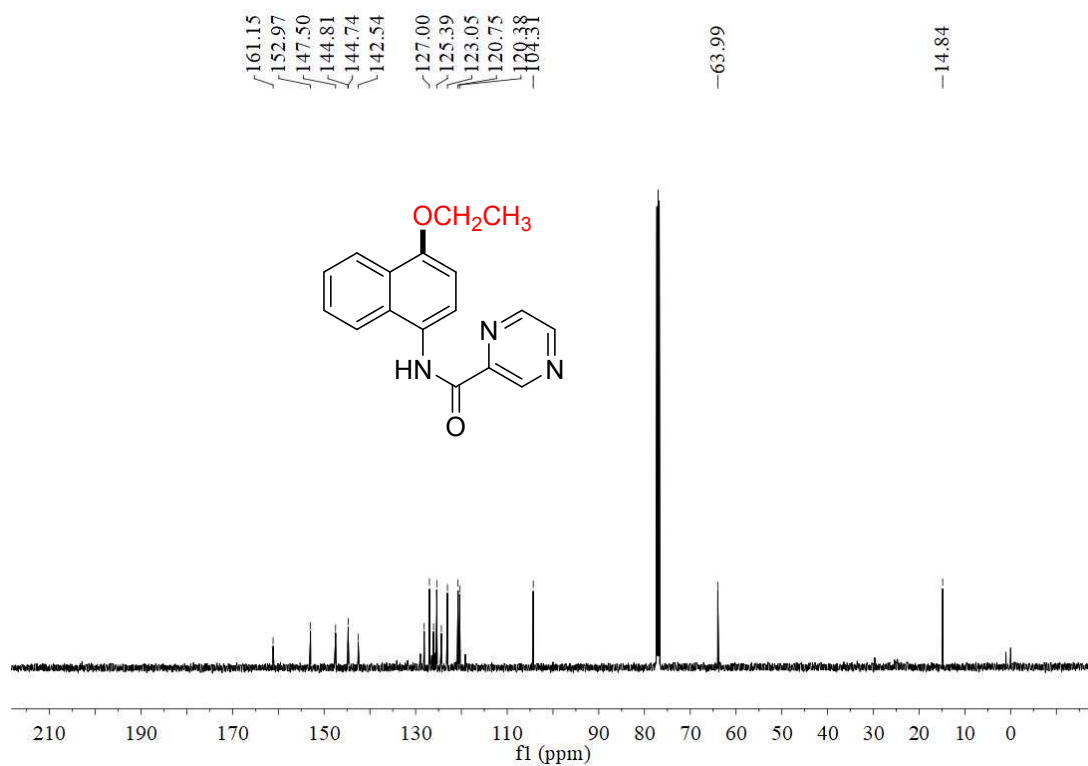
3b ¹³C NMR



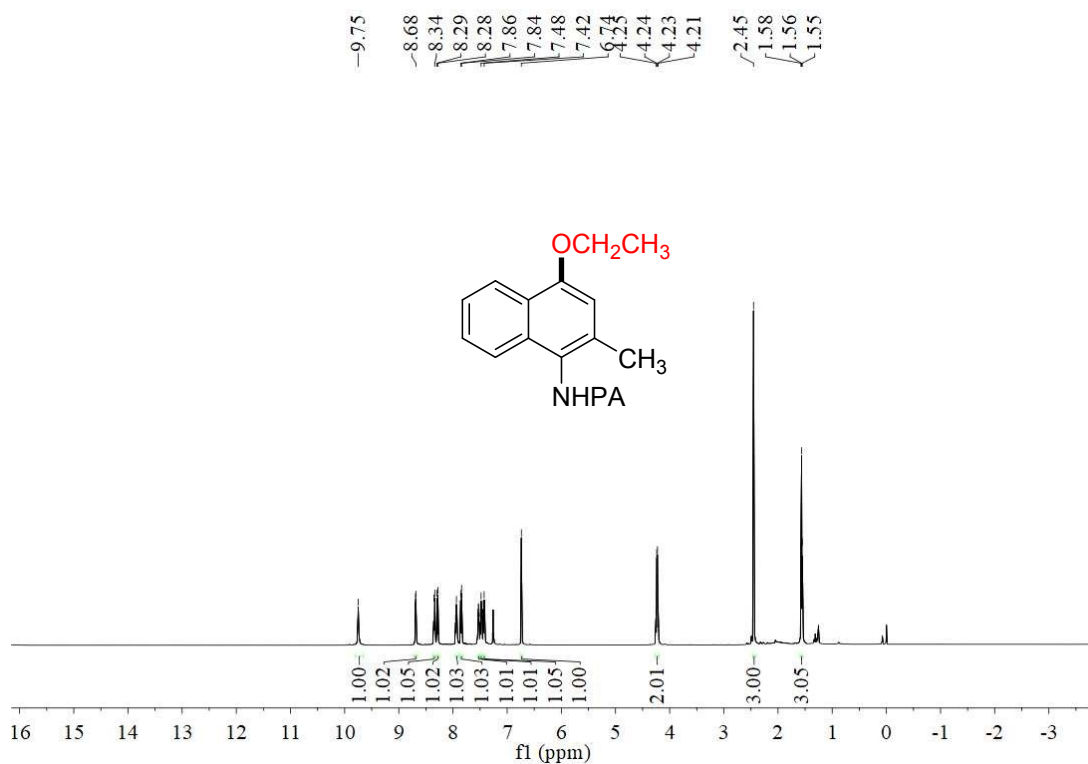
3c ¹H NMR



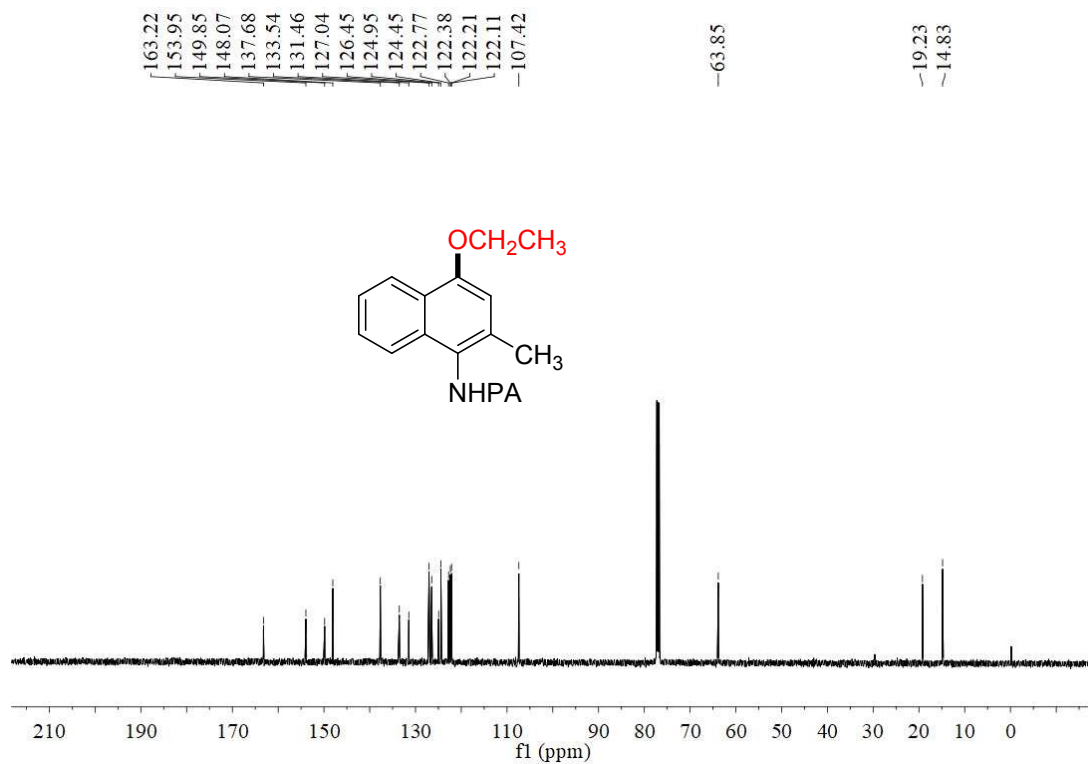
3c ¹³C NMR



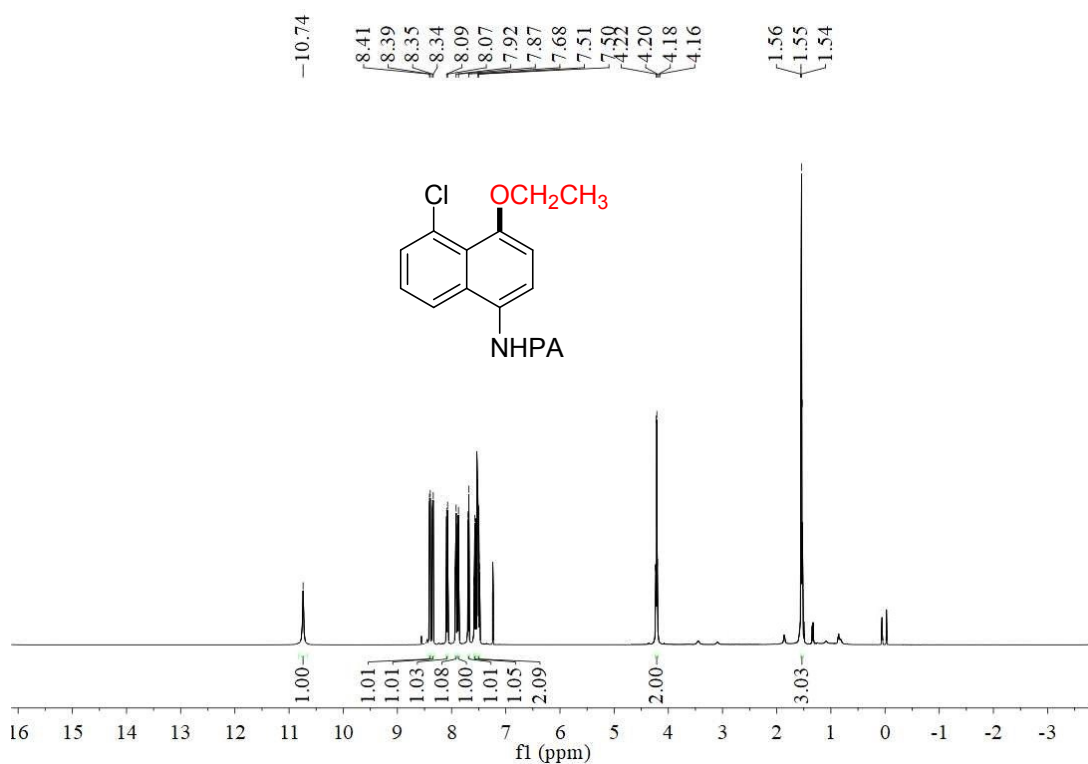
3d ¹H NMR



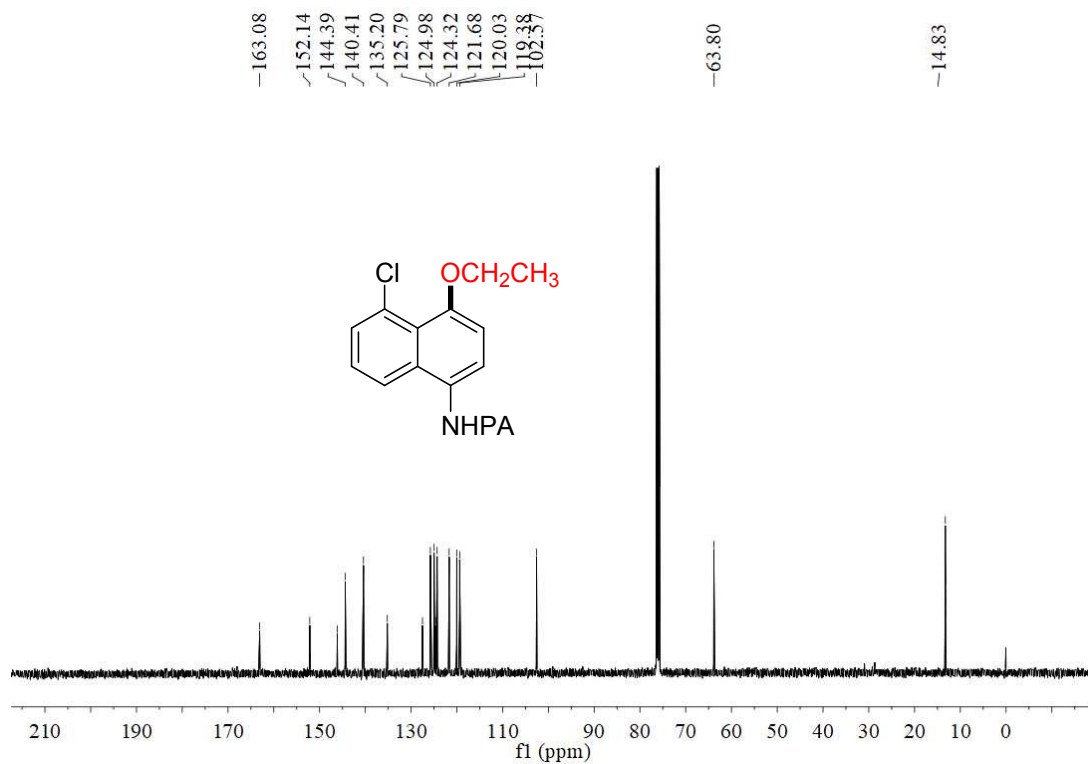
3d ¹³C NMR



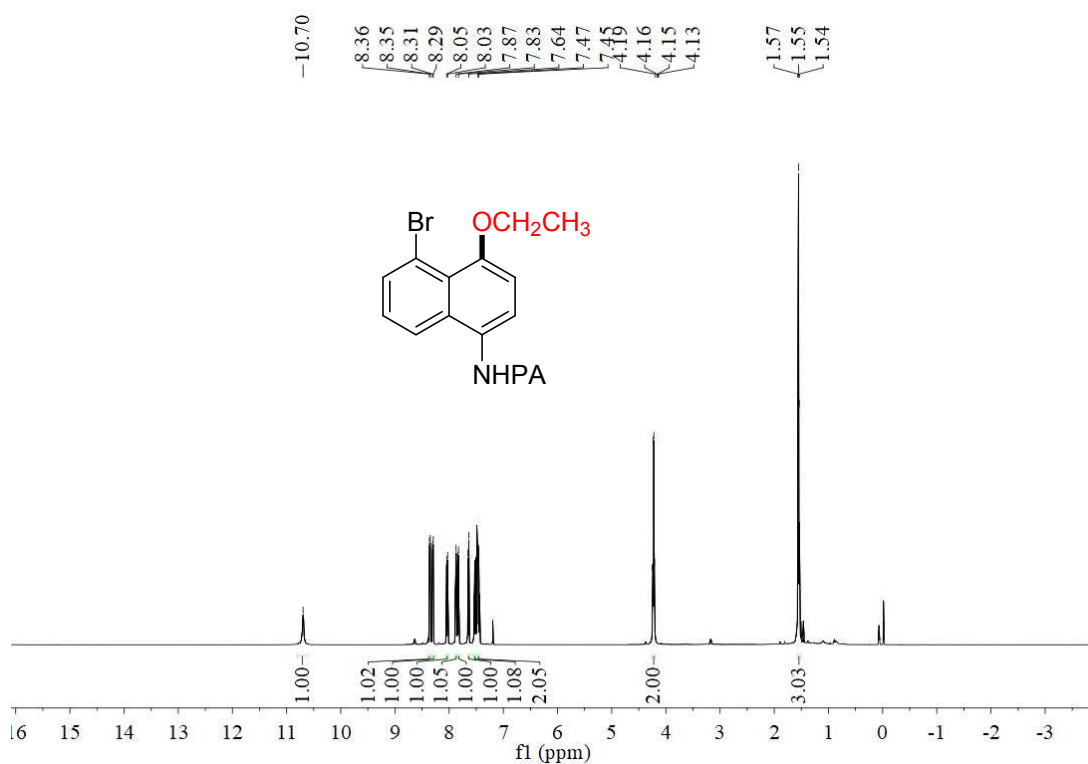
3e ¹H NMR



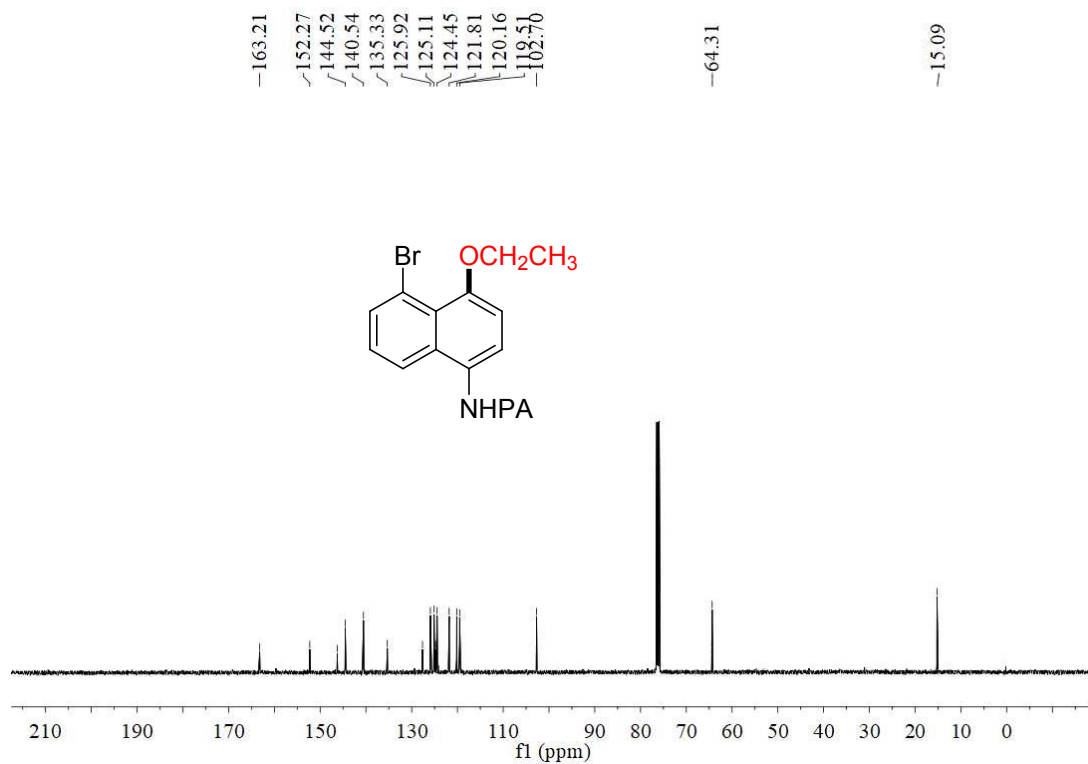
3e ¹³C NMR



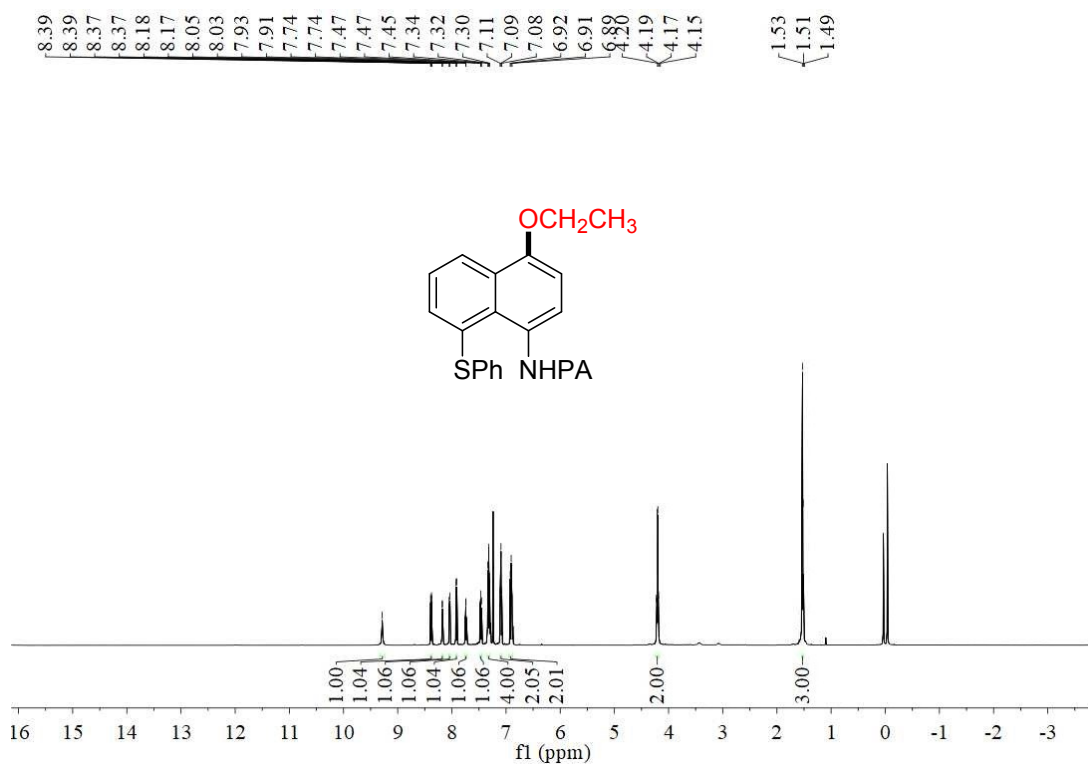
3f ¹H NMR



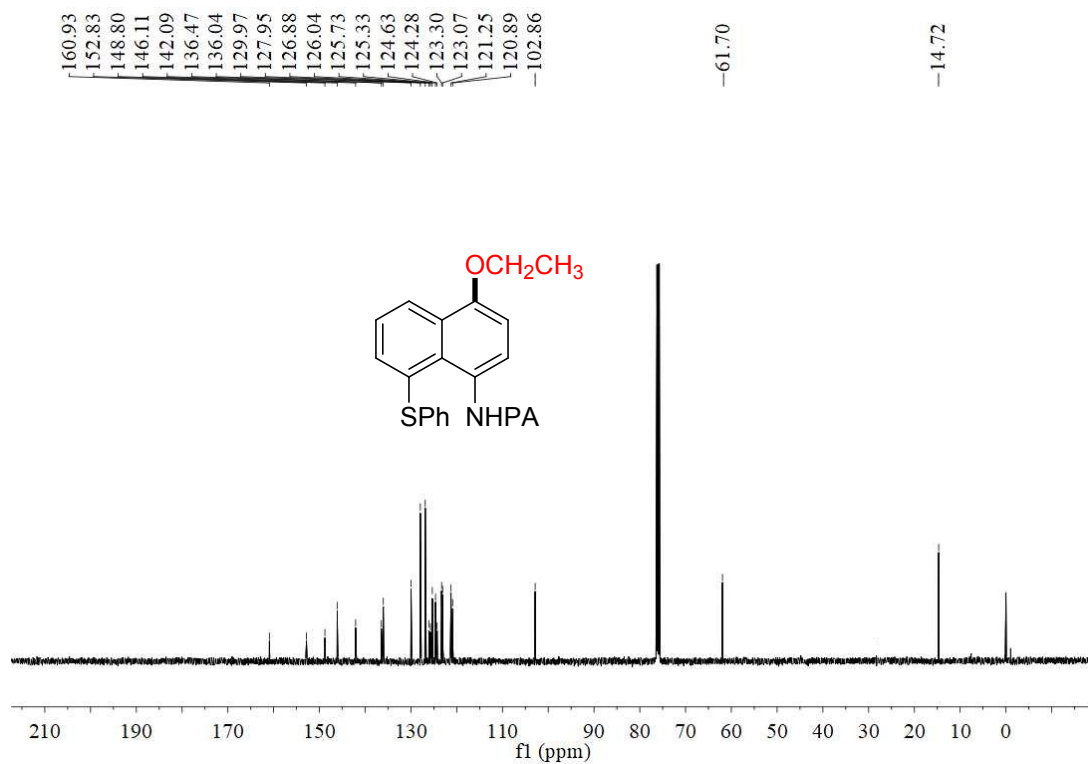
3f ^{13}C NMR



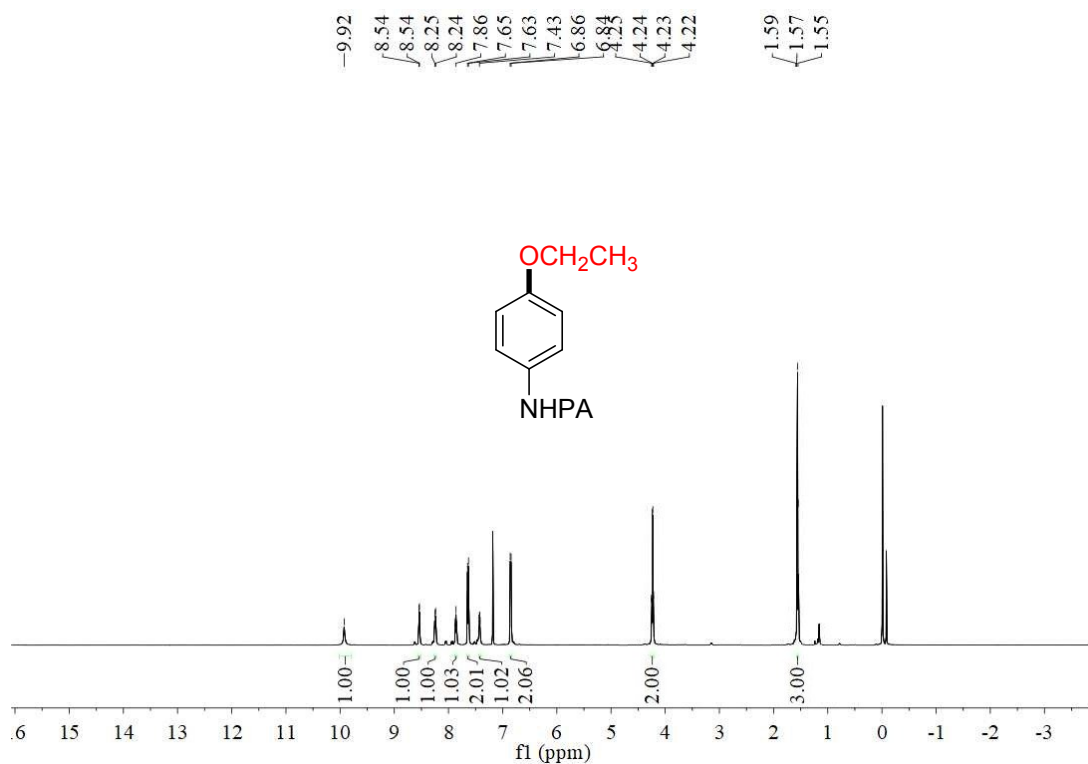
3g ^1H NMR



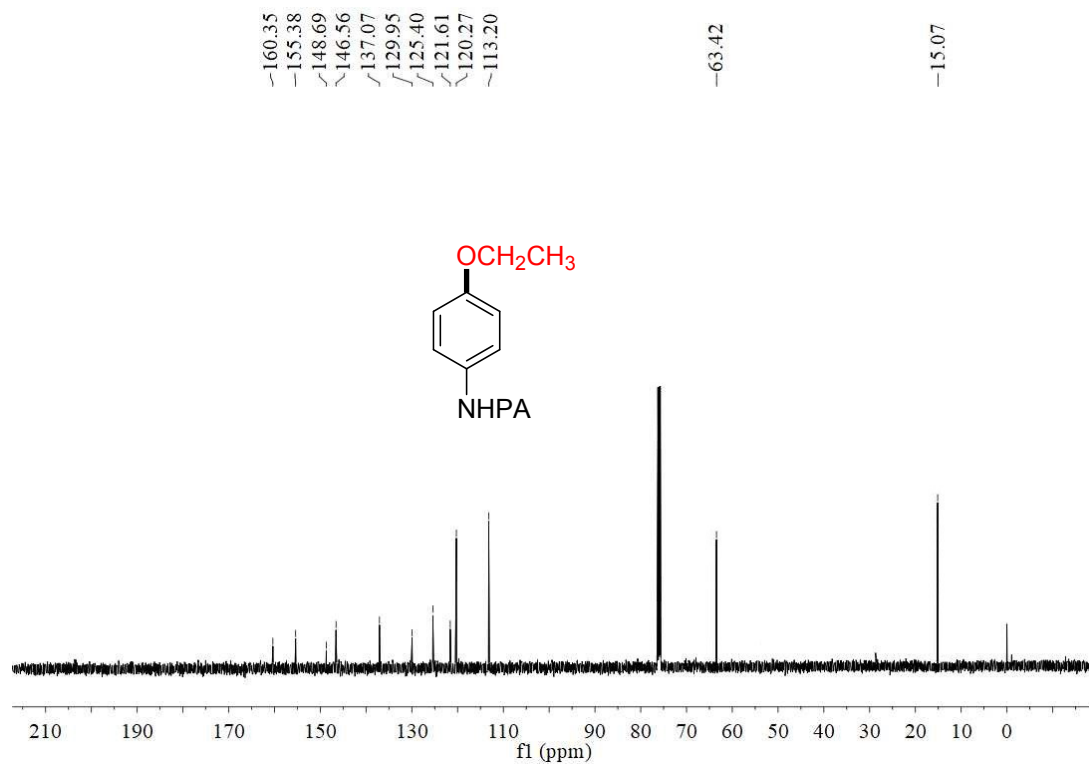
3g ^{13}C NMR



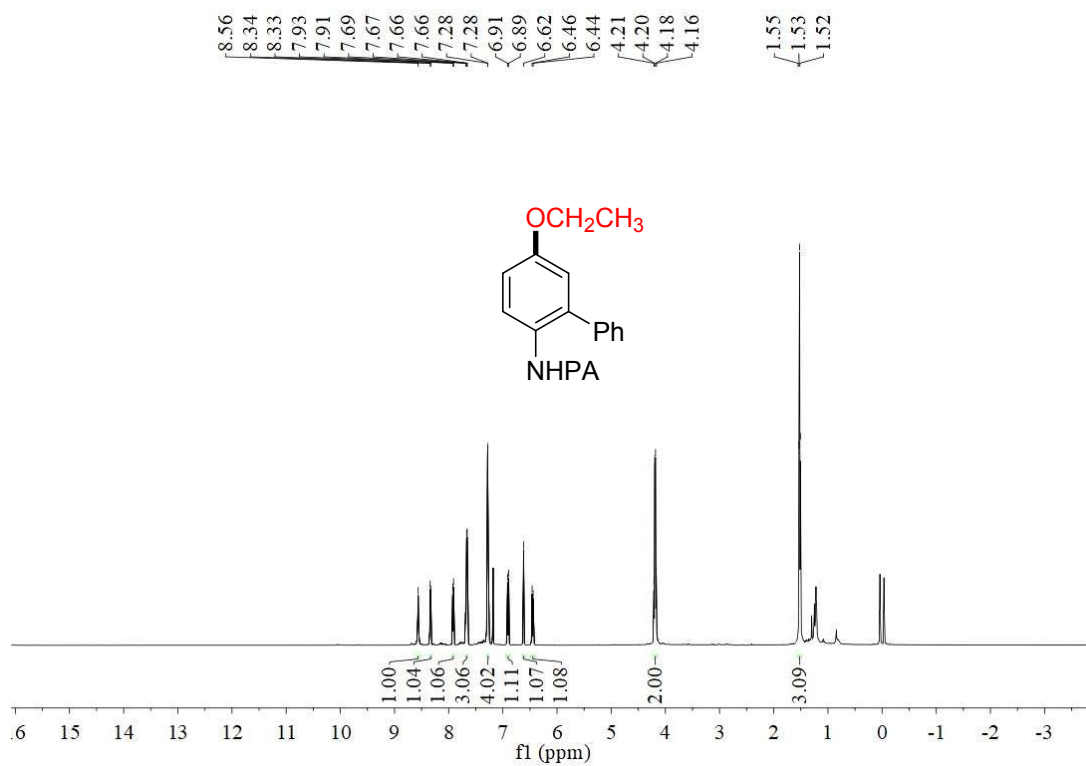
3h ^1H NMR



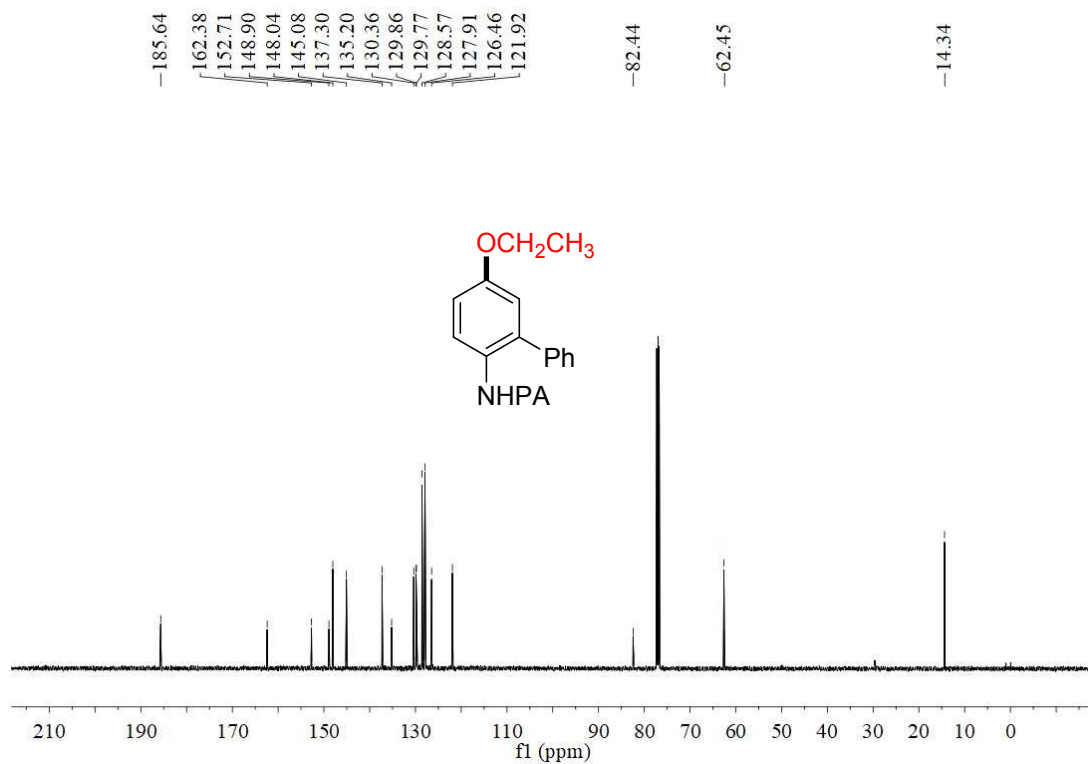
3h ¹³C NMR



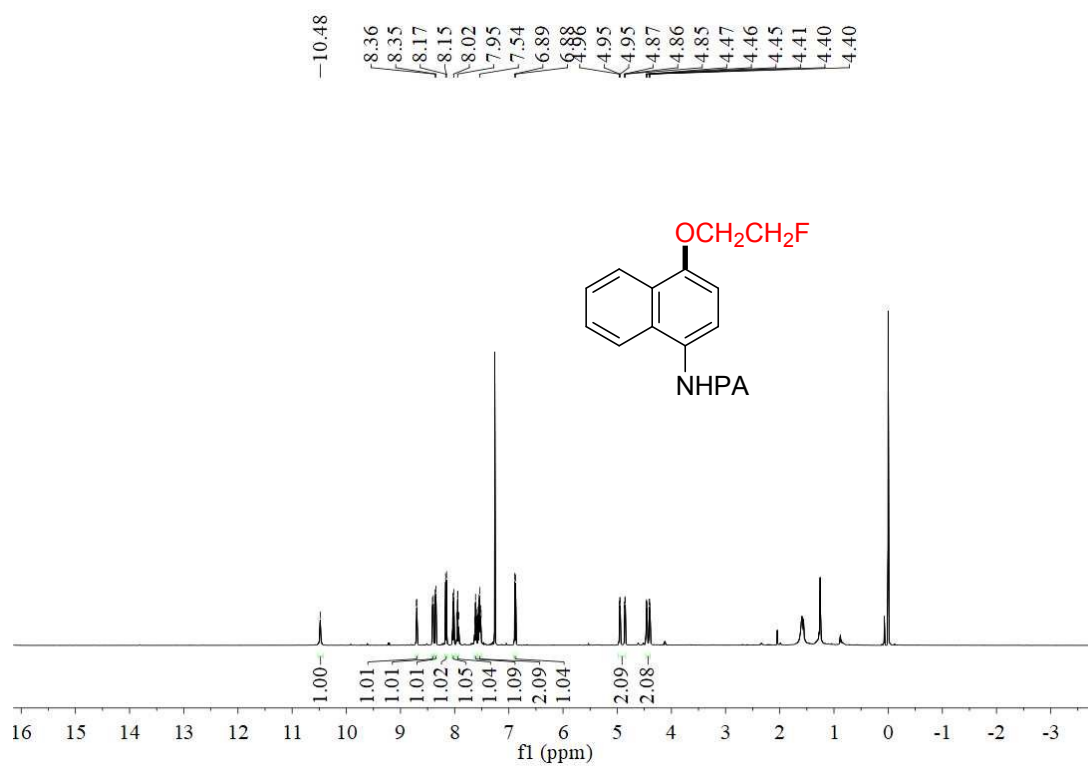
3i ¹H NMR



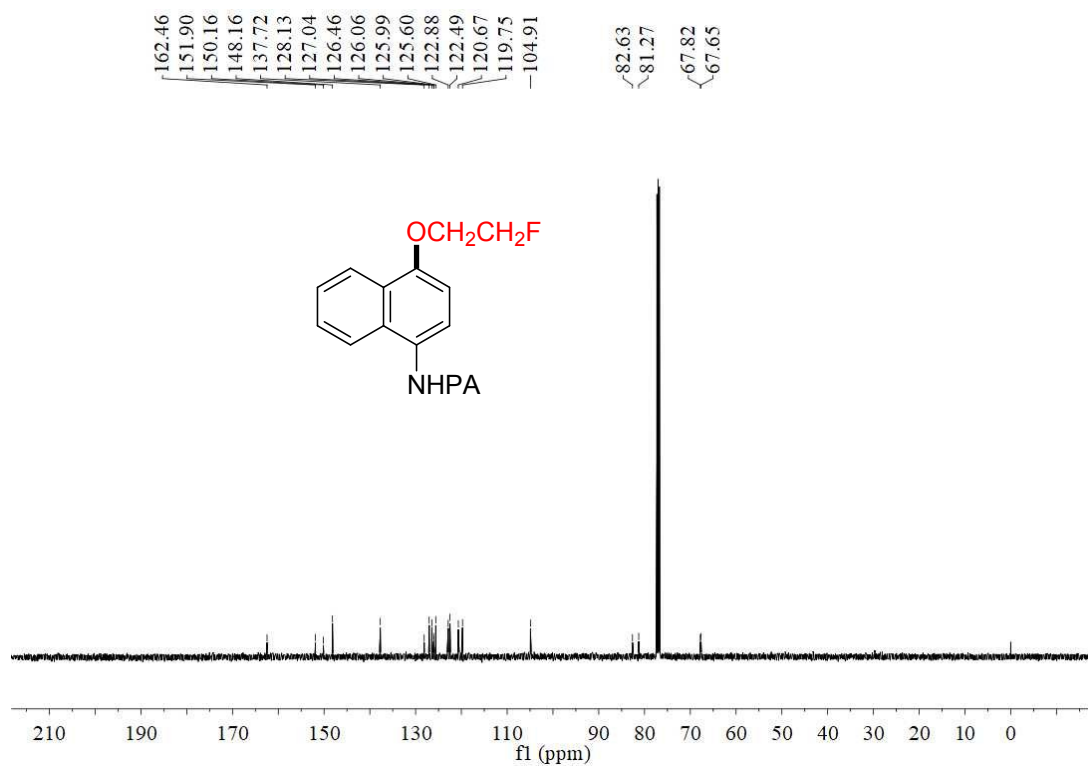
3i ^{13}C NMR



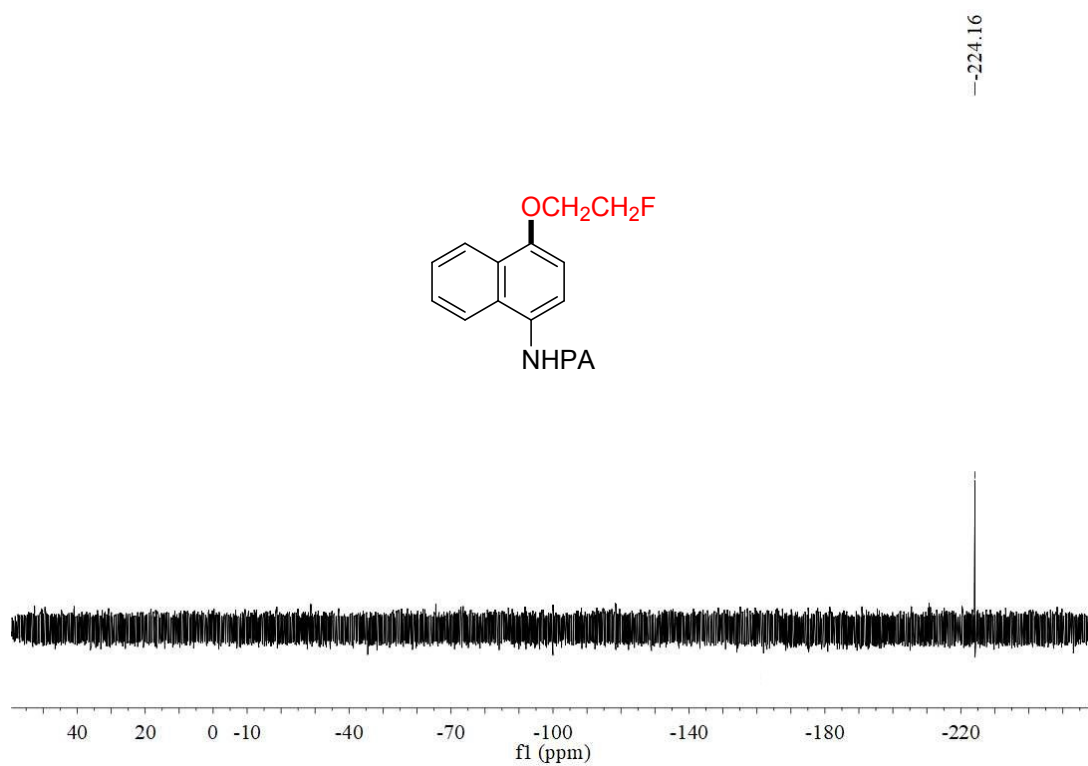
4a ^1H NMR



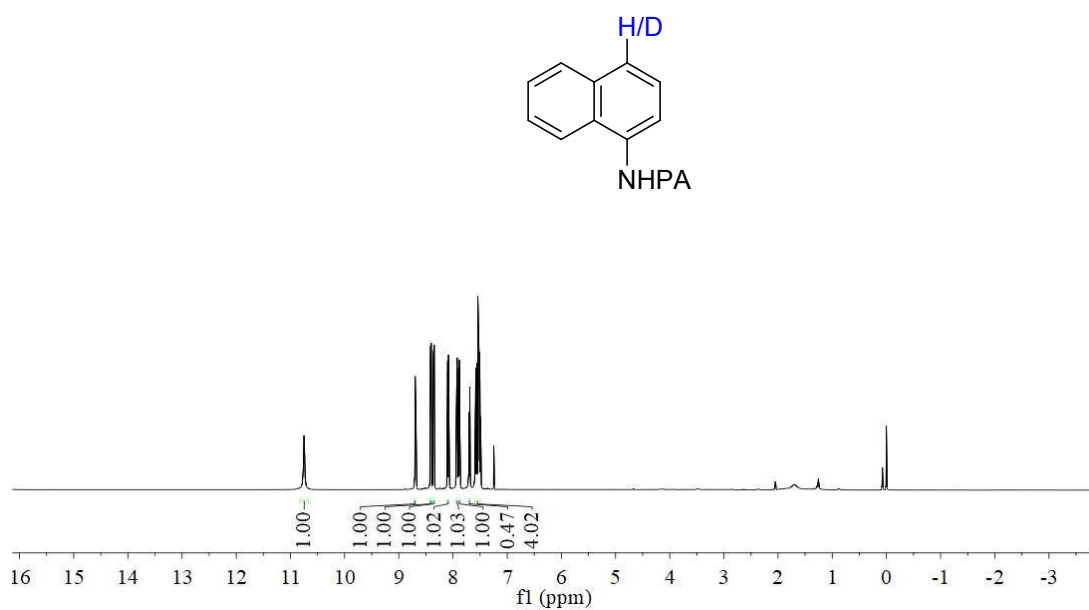
4a ¹³C NMR



4a ¹⁹F NMR



1a/1a-d ^1H NMR



2a/2o ^1H NMR

