

Supporting Information
for
**Palladium-catalyzed picolinamide-directed iodination of
remote *ortho*-C–H bonds of arenes: Synthesis of
tetrahydroquinolines**

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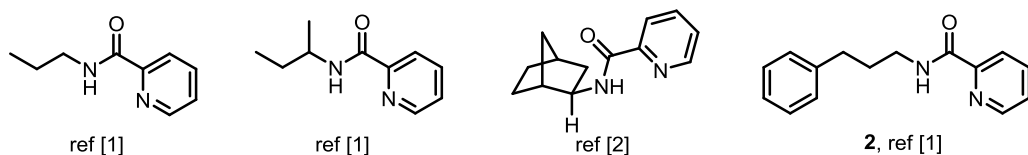
Detailed synthetic procedures and characterizations of all new compounds

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1. Reagents: All commercial materials were used as received unless otherwise noted. Anhydrous solvents were obtained from a JC Meyer solvent dispensing system and used without further purification. Flash chromatography was performed using 230–400 mesh SiliaFlash 60[®] silica gel (Silicycle Inc.). The following reagents were used as received: Pd(OAc)₂ (98%, Aldrich), silver carbonate (99%, Aldrich), iodine (Alfa, 99.8%), iodosobenzene diacetate (Alfa, 98%), dibenzylphosphate (Acros, 98%), copper iodide (Aldrich, 99.999%), cesium acetate (Acros, 99%), *N*-iodosuccinimide (Matrix Scientific, 97%), HBF₄•Et₂O (Aldrich), trifluoroacetic acid (Alfa, 99.5%), and α,α,α -trifluorotoluene (Aldrich, 99%).

2. Instruments: NMR spectra were recorded on a Bruker AV-3-HD-500 instrument and calibrated using residual solvent peaks as internal reference. Multiplicities are recorded as: s = singlet, d = doublet, t = triplet, dd = doublet of doublets, td = triplet of doublets, br s = broad singlet, m = multiplet. High resolution ESI mass experiments were operated on a Waters LCT Premier instrument.

3. Preparation of picolinamide substrates



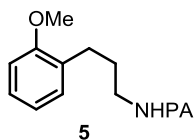
Scheme S1. List of all substrates used in this study.

All known compounds were prepared following the reported procedure and spectral data are consistent with those reported in the literature.^{1,2}

4. General procedure for the preparation of γ -arylpropylamine substrates via γ C–H arylation.

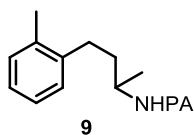
Conditions A for substrates 9, 12, 18, 21: A mixture of picolinamide substrate (1.0 equiv), Pd(OAc)₂ (0.1 equiv), Ag₂CO₃ (1.5 equiv), aryl iodide (2.0 equiv), and (BnO)₂PO₂H (0.2 equiv) in *t*-AmylOH (0.2M) in a 4 mL glass vial (purged with Ar, sealed with PTFE cap) was heated at 110 °C for 24 hours. The reaction mixture was cooled to rt, and filtered through a pad of celite. The filtrate was concentrated in vacuo and the resulting residue was purified by silica gel flash chromatography to give the arylated product.

Conditions B for substrates 5, 15: A mixture of picolinamide substrate (1.0 equiv), Pd(OAc)₂ (0.1 equiv), AgOAc (1.5 equiv), and aryl iodide (5.0 equiv) in a 10 mL glass vial (purged with Ar, sealed with PTFE cap) was heated at 150 °C for 12 hours.³ The reaction mixture was cooled to rt, before ethyl acetate was added, and then the mixture was filtered through a pad of celite. The filtrate was concentrated in vacuo and the resulting residue was purified by silica gel flash chromatography to give the arylated product.

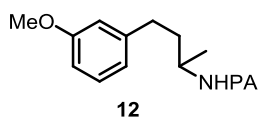


Compound **5** was isolated in 36% yield as a colorless oil. ¹H NMR (400 MHz, CDCl₃) δ 8.56 (d, J = 4.5 Hz, 1H), 8.28 (s, 1H), 8.22 (d, J = 5.7 Hz, 1H), 7.85 (td, J = 7.7, 1.6 Hz, 1H), 7.44-7.39 (m, 1H), 7.21-7.15 (m, 1H), 6.91-6.84 (m, 1H), 3.85 (s, 3H), 3.49 (q, J = 6.7 Hz, 2H), 2.74 (t, J =

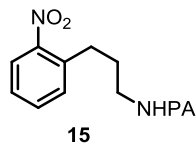
7.2 Hz, 2H), 1.96-1.89 (m, 2H); ^{13}C NMR (126 MHz, CDCl_3) δ 163.87, 157.06, 149.81, 147.67, 136.90, 129.62, 129.32, 126.92, 125.65, 121.73, 120.21, 109.89, 54.83, 38.38, 29.52, 26.94.



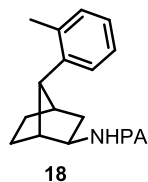
Compound **9** was prepared in 81% yield as a colorless oil using arylation conditions **A**. ^1H NMR (500 MHz, CDCl_3) δ 8.55 (d, $J = 4.1$ Hz, 1H), 8.23 (d, $J = 7.8$ Hz, 1H), 7.98 (d, $J = 7.9$ Hz, 1H), 7.85 (td, $J = 7.7, 1.6$ Hz, 1H), 7.42 (m, 1H), 7.19-7.05 (m, 4H), 4.35-4.24 (m, 1H), 2.77-2.62 (m, 2H), 2.30 (s, 3H), 1.92-1.79 (m, 2H), 1.34 (d, $J = 6.6$ Hz, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 163.71, 150.14, 148.03, 140.07, 137.49, 135.86, 130.28, 128.79, 126.16, 126.11, 126.08, 122.33, 45.52, 37.69, 30.01, 21.18, 19.35; HRMS: calculated for $\text{C}_{17}\text{H}_{20}\text{N}_2\text{O}$ [$\text{M}+\text{H}^+$]: 269.1649, found: 269.1652.



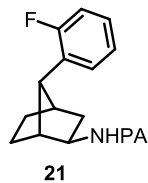
Compound **12** was prepared in 81% yield as a colorless oil using arylation conditions **A**. ^1H NMR (500 MHz, CDCl_3) δ 8.52 (d, $J = 4.2$ Hz, 1H), 8.20 (d, $J = 7.8$ Hz, 1H), 7.93 (d, $J = 8.3$ Hz, 1H), 7.82 (td, $J = 7.7, 1.6$ Hz, 1H), 7.39 (ddd, $J = 7.4, 4.8, 0.9$ Hz, 1H), 7.16 (t, $J = 7.8$ Hz, 1H), 6.78 (d, $J = 7.5$ Hz, 1H), 6.74 (s, 1H), 6.69 (dd, $J = 8.2, 2.0$ Hz, 1H), 4.33-4.15 (m, 1H), 3.76 (s, 3H), 2.68 (t, $J = 8.0$ Hz, 2H), 1.99-1.79 (m, 2H), 1.29 (d, $J = 6.6$ Hz, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 163.61, 159.67, 150.06, 147.96, 143.43, 137.39, 129.36, 126.09, 122.23, 120.76, 114.05, 111.27, 55.12, 45.16, 38.66, 32.65, 21.15; HRMS: calculated for $\text{C}_{17}\text{H}_{20}\text{N}_2\text{O}_2$ [$\text{M}+\text{H}^+$]: 285.1598, found: 285.1604.



Compound **15** was prepared in 28% yield as a colorless oil using arylation conditions **B**. ^1H NMR (500 MHz, CDCl_3) δ 8.52 (d, $J = 4.2$ Hz, 1H), 8.18 (s, 1H), 8.17 (d, $J = 7.8$ Hz, 1H), 7.88 (dd, $J = 8.1, 0.8$ Hz, 1H), 7.82 (td, $J = 7.7, 1.6$ Hz, 1H), 7.49 (td, $J = 7.6, 1.1$ Hz, 1H), 7.44-7.38 (m, 1H), 7.37 (d, $J = 7.7$ Hz, 1H), 7.34-7.28 (m, 1H), 3.54 (m, 2H), 3.03-2.92 (m, 2H), 2.00 (m, 2H); ^{13}C NMR (126 MHz, CDCl_3) δ 164.48, 149.87, 149.28, 148.10, 137.45, 136.63, 133.15, 132.09, 127.27, 126.22, 124.88, 122.23, 39.10, 30.62, 30.61; HRMS: calculated for $\text{C}_{15}\text{H}_{15}\text{N}_3\text{O}_3$ [$\text{M}+\text{H}^+$]: 286.1186, found: 286.1188.

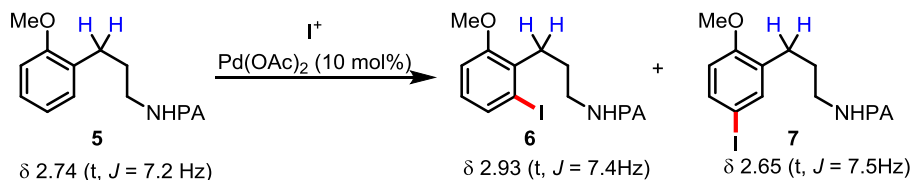


Compound **18** was prepared in 60% yield white solid using arylation conditions **A**. ^1H NMR (400 MHz, CDCl_3) δ 8.13 (d, $J = 4.2$ Hz, 1H), 7.99 (d, $J = 7.8$ Hz, 1H), 7.67 (t, $J = 7.4$ Hz, 1H), 7.36-7.30 (m, 2H), 7.27-7.13 (m, 3H), 7.09-7.07 (m, 1H), 4.14 (td, $J = 9.0, 3.2$ Hz, 1H), 2.98 (s, 1H), 2.80-2.78 (m, 2H), 2.30 (s, 3H), 2.10-1.98 (m, 2H), 1.93-1.85 (m, 1H), 1.76-1.70 (m, 1H), 1.52-1.46 (m, 1H), 1.37-1.31 (m, 1H); ^{13}C NMR (101 MHz, CDCl_3) δ 162.74, 149.78, 147.47, 138.53, 137.47, 136.84, 131.01, 127.41, 126.25, 126.17, 125.52, 121.52, 52.85, 52.23, 46.33, 38.56, 38.31, 28.91, 27.68, 20.74; HRMS Calcd for $\text{C}_{20}\text{H}_{22}\text{N}_2\text{O}$ [$\text{M}+\text{H}^+$]: 307.1805; Found: 307.1809.



Compound **21** was prepared in 94% yield as a white solid using arylation conditions **A**. ^1H NMR (400 MHz, CDCl_3) δ 8.16 (dd, $J = 4.7, 0.6$ Hz, 1H), 8.03 (d, $J = 7.8$ Hz, 1H), 7.72 (td, $J = 7.8, 1.5$ Hz, 1H), 7.40-7.25 (m, 3H), 7.24-7.19 (m, 1H), 7.12 (t, $J = 7.5$ Hz, 1H), 6.99-6.89 (m, 1H), 4.11 (td, $J = 8.8, 3.8$ Hz, 1H), 3.00 (s, 1H), 2.92 (s, 1H), 2.84 (t, $J = 3.8$ Hz, 1H), 2.04-1.99 (m, 1H), 1.94–1.80 (m, 2H), 1.78-1.70 (m, 1H), 1.54-1.45 (m, 1H), 1.40-1.29 (m, 1H); ^{13}C NMR (101 MHz, CDCl_3) δ 163.13, 162.90, 160.68, 149.90, 147.52, 137.06, 129.62, 129.57, 127.97, 127.88, 127.71, 127.56, 125.71, 124.42, 124.39, 121.79, 116.08, 115.85, 52.86, 48.51, 46.66, 46.63, 38.31, 37.88, 28.50, 27.86; HRMS Calcd for $\text{C}_{19}\text{H}_{19}\text{FN}_2\text{O}$ [$\text{M}+\text{H}^+$]: 311.1554, Found: 311.1556.

5. Reaction optimization in Table 1

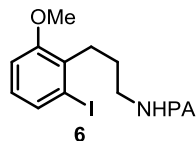


Scheme S2

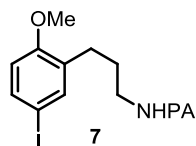
Reactions were carried out in a 10 mL sealed vial at a 0.2 mmol scale according to the condition in **Table 1**. After 24 hours, the reaction mixtures were cooled to room temperature and water was added. The mixture was extracted with ethyl acetate for three times. The combined organic layer was washed with water and brine, dried over Na_2SO_4 , filtered and concentrated in vacuo. The resulting residue was dissolved in 1 mL of deuterated chloroform for ^1H NMR analysis. Dibromomethane (34.8 mg, 0.2 mmol, 1 equiv, a singlet peak around 4.95 ppm was set as 1.00) was added as internal standard. Yields of compounds **6**, **7** were determined based on the following method:

Yield of **6** = integration of peak (δ 2.93, triplet) \times 100%

Yield of **7** = integration of peak (δ 2.65, triplet) \times 100%

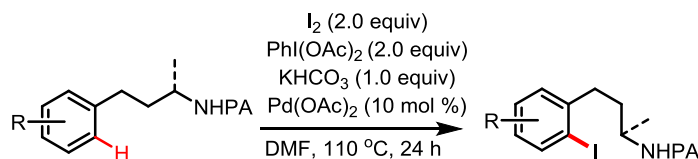


^1H NMR (400 MHz, CDCl_3) δ 8.56 (d, $J = 4.1$ Hz, 1H), 8.35 (s, 1H), 8.21 (d, $J = 7.8$ Hz, 1H), 7.84 (td, $J = 7.7, 1.6$ Hz, 1H), 7.43-7.41 (m, 2H), 6.89-6.81 (m, 2H), 3.84 (s, 3H), 3.49 (q, $J = 6.6$ Hz, 2H), 2.93 (t, $J = 7.4$ Hz, 2H), 1.90-1.83 (m, 2H); ^{13}C NMR (101 MHz, CDCl_3) δ 164.33, 157.53, 152.20, 150.35, 148.13, 147.68, 137.42, 132.97, 131.73, 128.68, 126.10, 122.32, 110.42, 102.02, 100.08, 55.86, 38.71, 31.91, 28.54; HRMS Calcd for $\text{C}_{16}\text{H}_{17}\text{IN}_2\text{O}_2$ [$\text{M}+\text{H}^+$]: 397.0407, Found: 397.0410.



^1H NMR (400 MHz, CDCl_3) δ 8.54 (d, $J = 4.5$ Hz, 1H), 8.22 (s, 1H), 8.18 (d, $J = 7.8$ Hz, 1H), 7.84-7.81 (m, 1H), 7.44-7.39 (m, 3H), 6.59 (d, $J = 8.2$ Hz, 1H), 3.80 (s, 3H), 3.45 (m, 2H), 2.65 (t, $J = 7.5$ Hz, 2H), 1.92-1.85 (m, 2H); ^{13}C NMR (101 MHz, CDCl_3) δ 164.28, 157.44, 150.12, 148.07, 138.44, 137.38, 136.01, 132.76, 126.10, 122.22, 112.63, 82.96, 55.48, 38.79, 29.73, 27.14; HRMS Calcd for $\text{C}_{16}\text{H}_{17}\text{IN}_2\text{O}_2$ [$\text{M}+\text{H}^+$]: 397.0407, Found: 397.0411.

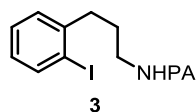
6. Preparation of iodinated compounds via Pd-catalyzed ϵ C–H iodination



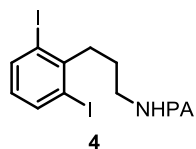
Scheme S3

A mixture of picolinamide substrate (0.2 mol, 1.0 equiv), $\text{Pd}(\text{OAc})_2$ (4.5 mg, 0.02 mol, 0.1 equiv), I_2 (101.6 mg, 0.4 mol, 2.0 equiv), $\text{PhI}(\text{OAc})_2$ (129 mg, 0.4 mol, 2.0 equiv), and KHCO_3

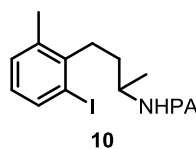
(20 mg, 0.2 mol, 1.0 equiv) in DMF 4 mL in a 10 mL glass vial (purged with Ar, sealed with PTFE cap) was heated at 110 °C for 24 hours. Then the reactions mixture was cooled to room temperature and water was added. The mixture was extracted with ethyl acetate for three times. The combined organic layer was washed with water and brine, dried over Na₂SO₄, filtered and concentrated in vacuo. The resulting residue was purified by silica gel flash chromatography to give the iodinated product.



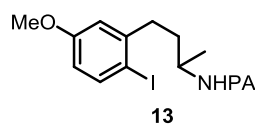
Compound **3** was isolated in 47% yield as a colorless oil. Compound **3** has been previously reported and its spectra are consistent with those from the literature.¹



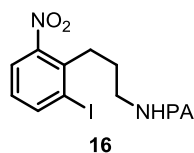
Compound **4** was isolated in 25% yield as a white solid. ¹H NMR (500 MHz, CDCl₃) δ 8.54 (d, *J* = 3.3 Hz, 1H), 8.25 (s, 1H), 8.22 (d, *J* = 7.7 Hz, 1H), 7.85 (t, *J* = 7.4 Hz, 1H), 7.79 (d, *J* = 7.8 Hz, 2H), 7.47-7.37 (m, 1H), 6.49 (t, *J* = 7.8 Hz, 1H), 3.64 (q, *J* = 6.6 Hz, 2H), 3.23-3.09 (m, 2H), 1.95-1.82 (m, 2H); ¹³C NMR (126 MHz, CDCl₃) δ 164.50, 150.10, 148.15, 145.39, 140.24, 137.50, 129.64, 126.22, 122.38, 99.10, 44.50, 39.21, 28.42; HRMS: calculated for C₁₅H₁₄I₂N₂O [M+H⁺]: 492.9268, found: 492.9281.



Compound **10** was isolated in 75% yield as a colorless oil. ^1H NMR (500 MHz, CDCl_3) δ 8.54 (d, $J = 4.1$ Hz, 1H), 8.22 (d, $J = 7.8$ Hz, 1H), 8.08 (d, $J = 8.2$ Hz, 1H), 7.84 (td, $J = 7.7$, 1.5 Hz, 1H), 7.64 (d, $J = 7.8$ Hz, 1H), 7.41 (m, 1H), 7.07 (d, $J = 7.4$ Hz, 1H), 6.74 (t, $J = 7.7$ Hz, 1H), 4.40-4.28 (m, 1H), 2.93-2.81 (m, 2H), 2.36 (s, 3H), 1.83-1.69 (m, 2H), 1.37 (d, $J = 6.6$ Hz, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 163.82, 150.13, 148.08, 142.46, 137.66, 137.46, 137.32, 130.62, 127.83, 126.16, 122.33, 101.93, 45.70, 35.67, 35.06, 21.10, 21.02; HRMS: calculated for $\text{C}_{17}\text{H}_{19}\text{IN}_2\text{O}$ [$\text{M}+\text{H}^+$]: 395.0615; found: 395.0614.

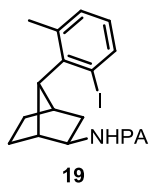


Compound **13** was isolated in 68% yield as a colorless oil. ^1H NMR (500 MHz, CDCl_3) δ 8.54 (d, $J = 4.3$ Hz, 1H), 8.21 (d, $J = 7.7$ Hz, 1H), 8.00 (d, $J = 8.0$ Hz, 1H), 7.84 (t, $J = 7.2$ Hz, 1H), 7.62 (d, $J = 8.6$ Hz, 1H), 7.42 (dd, $J = 6.6$, 5.2 Hz, 1H), 6.82 (d, $J = 2.7$ Hz, 1H), 6.47 (dd, $J = 8.6$, 2.7 Hz, 1H), 4.37-4.20 (m, 1H), 3.75 (s, 3H), 2.88-2.66 (m, 2H), 1.85 (m, 2H), 1.33 (d, $J = 6.6$ Hz, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 163.76, 160.16, 150.15, 148.07, 145.43, 139.94, 137.48, 126.18, 122.35, 115.47, 114.10, 88.91, 55.43, 45.20, 37.84, 37.55, 21.22; HRMS: calculated for $\text{C}_{17}\text{H}_{19}\text{IN}_2\text{O}_2$ [$\text{M}+\text{H}^+$]: 411.0564, found: 411.0564.

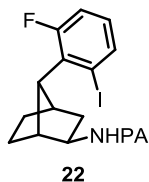


Compound **16** was isolated in 68% yield as a colorless oil. ^1H NMR (500 MHz, CDCl_3) δ 8.55 (d, $J = 4.2$ Hz, 1H), 8.24 (s, 1H), 8.21 (d, $J = 7.8$ Hz, 1H), 8.05 (d, $J = 7.8$ Hz, 1H), 7.85 (td, $J = 7.7$, 1.5 Hz, 1H), 7.73 (d, $J = 8.0$ Hz, 1H), 7.42 (dd, $J = 6.6$, 4.9 Hz, 1H), 7.04 (t, $J = 8.0$ Hz, 1H), 3.64 (q, $J = 6.6$ Hz, 2H), 3.04-2.94 (m, 2H), 2.11-1.97 (m, 2H); ^{13}C NMR (126 MHz, CDCl_3) δ

164.56, 150.38, 149.99, 148.16, 144.03, 137.92, 137.51, 128.58, 126.25, 124.54, 122.37, 102.96, 39.29, 35.39, 29.30; HRMS: calculated for C₁₅H₁₄IN₃O₃ [M+H⁺]: 412.0153; found: 412.0153.



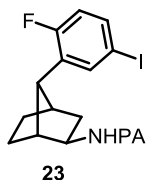
Compound **19** was isolated in 56% yield as a colorless oil. ¹H NMR (400 MHz, CDCl₃) δ 8.16 (d, *J* = 4.1 Hz, 1H), 7.99 (d, *J* = 7.8 Hz, 1H), 7.71 (d, *J* = 7.0 Hz, 1H), 7.70 (td, *J* = 7.7, 1.6 Hz, 1H), 7.27-7.24 (m, 2H), 7.09 (s, 1H), 6.75 (t, *J* = 7.3 Hz, 1H), 4.06 (td, *J* = 8.8, 3.0 Hz, 1H), 3.27 (s, 1H), 3.18 (s, 1H) 2.99 (s, 1H), 2.56 (s, 3H), 2.16-1.89 (m, 3H), 1.80-1.77 (m, 1H), 1.42-1.37 (m, 2H); ¹³C NMR (101 MHz, CDCl₃) δ 162.89, 149.86, 147.46, 139.42, 136.99, 133.51, 127.19, 125.68, 121.70, 60.21, 52.22, 49.65, 41.22, 38.70, 30.65, 25.22, 23.14.



Compound **22** was isolated in 53% yield as a white solid and the yield of **22** was improved to 85% when 1.0 equiv of Na₂CO₃ was used instead of KHCO₃. ¹H NMR (500 MHz, CDCl₃) δ 8.13 (d, *J* = 4.0 Hz, 1H), 8.01 (d, *J* = 7.8 Hz, 1H), 7.71 (td, *J* = 7.7, 1.6 Hz, 1H), 7.64 (d, *J* = 7.7 Hz, 1H), 7.39 (d, *J* = 5.5 Hz, 1H), 7.32-7.19 (m, 1H), 7.04 (dd, *J* = 11.4, 8.7 Hz, 1H), 6.84 (td, *J* = 7.9, 5.5 Hz, 1H), 4.05 (dd, *J* = 14.0, 6.0 Hz, 1H), 3.30 (d, *J* = 4.5 Hz, 1H), 2.98 (s, 1H), 2.88 (s, 1H), 2.08 (m, 2H), 1.95-1.80 (m, 1H), 1.80-1.61 (m, 1H), 1.45-1.31 (m, 2H); ¹³C NMR (126 MHz, CDCl₃) δ 162.81, 160.60, 158.60, 149.80, 147.37, 137.12, 136.89, 136.87, 129.87, 129.75, 128.84, 128.77, 125.71, 121.77, 117.65, 117.44, 102.56, 102.52, 56.76, 56.73, 52.71, 47.92, 40.48, 40.40, 39.06, 39.00, 29.99, 25.49; HRMS: calculated for C₁₉H₁₈FIN₂O [M+H⁺]: 437.0521; found: 437.0516.

7. Preparation of iodinated compounds via directed electrophilic aromatic iodination

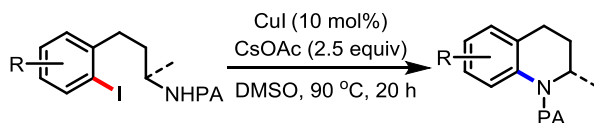
Directed electrophilic aromatic iodination reactions were carried out following the literature protocol¹: Picolinamide substrate (0.2 mmol, 1 equiv) and NIS (49.5 mg, 0.22 mmol, 1.1 equiv) were dissolved in anhydrous CH₂Cl₂ (27 mL) and cooled to 0 °C under Ar. TFA (3 mL) and HBF₄·Et₂O (0.11 mL, 0.8 mmol, 4 equiv) were added, and the reaction mixture was stirred at 0 °C for 4 hours. Solvents were then removed in vacuo or with stream of N₂. The residue was redissolved in CH₂Cl₂ (15 mL), washed with aq NaHCO₃, aq Na₂S₂O₃, brine, dried over anhydrous Na₂SO₄, and concentrated in vacuo. The resulting residue was purified by silica gel flash chromatography to give the iodinated products. Yields of *ortho*-iodinated products were obtained using ¹H NMR with 1,1,2,2-tetrachloroethane standard for substrates **2**, **9**, **12**, **15**, and **18**.



Compound **23** was isolated via silica gel flash chromatography in 90% yield as a white solid. ¹H NMR (500 MHz, CDCl₃) δ 8.26 (d, *J* = 4.2 Hz, 1H), 8.03 (d, *J* = 7.8 Hz, 1H), 7.72 (td, *J* = 7.7, 1.5 Hz, 1H), 7.61 (d, *J* = 6.0 Hz, 1H), 7.51-7.44 (m, 1H), 7.34 (d, *J* = 7.5 Hz, 1H), 7.29 (dd, *J* = 6.7, 4.9 Hz, 1H), 6.66 (dd, *J* = 10.3, 8.7 Hz, 1H), 4.05 (td, *J* = 8.5, 3.7 Hz, 1H), 2.92 (s, 1H), 2.90 (s, 1H), 2.79 (s, 1H), 2.00 (dd, *J* = 13.5, 8.7 Hz, 1H), 1.82 (m, 1H), 1.78-1.63 (m, 2H), 1.52-1.39 (m, 1H), 1.39-1.28 (m, 1H); ¹³C NMR (126 MHz, CDCl₃) δ 162.89, 162.62, 160.65, 149.65, 147.66, 138.43, 138.39, 137.08, 136.80, 136.74, 130.69, 130.57, 125.80, 121.70, 118.21,

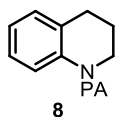
118.02, 87.51, 87.48, 52.84, 48.36, 46.39, 46.36, 38.03, 37.86, 37.85, 28.46, 27.50; HRMS: calculated for C₁₉H₁₈FIN₂O [M+H⁺]: 437.0521; found: 437.0520.

8. Preparation of tetrahydroquinolines via Cu-catalyzed cyclization⁴

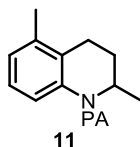


Scheme S4

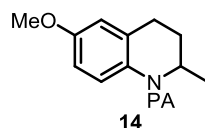
A mixture of *ortho*-iodinated compound (0.2 mmol, 1.0 equiv), copper iodide (3.8 mg, 0.02 mmol, 0.1 equiv), and CsOAc (96 mg, 0.5 mmol, 2.5 equiv) in DMSO (2 mL) was heated at 90 °C under Ar for 20 hours. The reaction mixture was cooled to rt, diluted with EtOAc, washed with water and brine. The organic phase was dried over anhydrous Na₂SO₄, filtered and the filtration was concentrated in vacuo. The resulting residue was purified by silica gel flash chromatography to give the cyclized product.



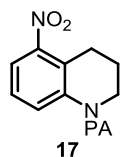
Compound **8** was isolated in 93% yield as a white solid. Compound **8** has been previously reported and its spectra are consistent with those from the literature.¹



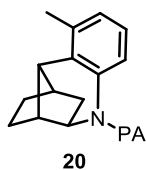
Compound **11** was isolated in 96% yield as a colorless oil. ^1H NMR (500 MHz, CDCl_3) δ 8.43 (d, $J = 1.8$ Hz, 1H), 7.55 (s, 1H), 7.26 (s, 1H), 7.16 (s, 1H), 6.82 (d, $J = 7.3$ Hz, 1H), 6.69 (s, 1H), 6.40 (s, 1H), 4.83 (s, 1H), 2.72 (m, 1H), 2.65-2.47 (m, 1H), 2.32 (m, 1H), 2.22 (s, 3H), 1.58 (m, 1H), 1.19 (d, $J = 6.6$ Hz, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 167.85, 155.05, 148.83, 136.64, 136.31, 135.54, 130.31, 126.38, 125.02, 124.00, 123.95, 123.26, 48.46, 30.56, 21.74, 19.2, 18.36; HRMS: calculated for $\text{C}_{17}\text{H}_{18}\text{N}_2\text{O}$ $[\text{M}+\text{H}^+]$: 267.1492; found: 267.1495.



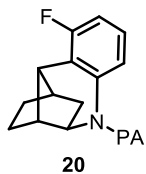
Compound **14** was isolated in 94% yield as a pale yellow oil. ^1H NMR (500 MHz, CDCl_3) δ 8.50 (s, 1H), 7.60 (s, 1H), 7.21 (s, 2H), 6.69 (s, 1H), 6.34 (s, 2H), 4.90 (s, 1H), 3.72 (s, 3H), 2.73 (m, 2H), 2.43 (s, 1H), 1.49 (s, 1H), 1.25 (d, $J = 6.4$ Hz, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 167.49, 157.00, 155.13, 148.99, 136.56, 127.13, 124.11, 123.40, 112.88, 111.47, 55.43, 49.34, 32.31, 26.45, 19.87; HRMS: calculated for $\text{C}_{17}\text{H}_{18}\text{N}_2\text{O}_2$ $[\text{M}+\text{H}^+]$: 283.1441; found: 283.1442.



Compound **17** was isolated in 47% yield as a yellow solid. ^1H NMR (500 MHz, CDCl_3) δ 8.48 (s, 1H), 7.79 (t, $J = 7.4$ Hz, 1H), 7.68 (d, $J = 7.6$ Hz, 1H), 7.63 (d, $J = 8.1$ Hz, 1H), 7.38-7.29 (m, 1H), 7.14 (s, 1H), 7.08 (s, 1H), 3.94 (t, $J = 6.0$ Hz, 2H), 3.14 (t, $J = 6.6$ Hz, 2H), 2.06 (m, 2H); ^{13}C NMR (126 MHz, CDCl_3) δ 168.75, 153.76, 149.48, 148.78, 140.83, 137.28, 129.69, 125.85, 125.18, 124.40, 120.79, 44.98, 23.78, 23.30; HRMS: calculated for $\text{C}_{15}\text{H}_{13}\text{N}_3\text{O}_3$ $[\text{M}+\text{H}^+]$: 284.1030; found: 284.1030.

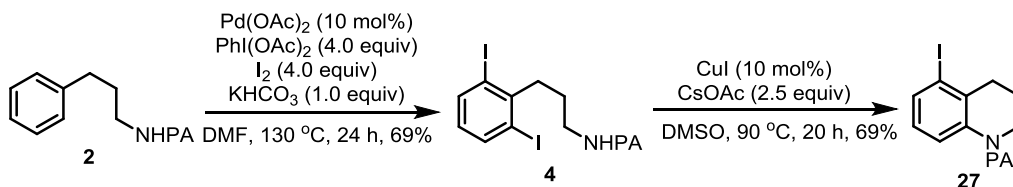


Compound **20** was isolated in 85% yield as an off white solid. ^1H NMR (500 MHz, CDCl_3) δ 8.59 (s, 1H), 7.77 (s, 1H), 7.57 (s, 1H), 7.32 (s, 1H), 6.87 (s, 2H), 2.91 (s, 1H), 2.42 (s, 1H), 2.31 (m, 4H), 1.93-1.71 (m, 2H), 1.72-1.58 (m, 1H), 1.53 (dd, $J = 13.5, 7.3$ Hz, 2H); ^{13}C NMR (126 MHz, CDCl_3) δ 167.44, 155.51, 148.97, 137.09, 136.04, 135.91, 129.63, 126.06, 125.73, 124.47, 123.68, 121.58, 46.97, 44.67, 39.78, 34.46, 29.81, 29.19, 24.89, 19.58; HRMS: calculated for $\text{C}_{20}\text{H}_{20}\text{N}_2\text{O}$ [$\text{M}+\text{H}^+$]: 305.1649; found: 305.1650.

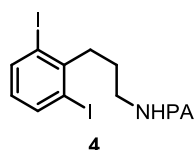


Compound **24** was isolated in 78% yield as a colorless oil. ^1H NMR (400 MHz, CDCl_3) δ 8.59 (d, $J = 4.0$ Hz, 1H), 7.81-7.77 (m, 1H), 7.62 (d, $J = 7.6$ Hz, 1H), 7.35 (dd, $J = 6.9, 5.1$ Hz, 1H), 7.01 (s, 1H), 6.74 (t, $J = 8.6$ Hz, 1H), 4.42-4.38 (m, 1H), 3.08 (s, 1H), 2.50 (s, 1H), 2.27 (s, 1H), 1.84-1.79 (m, 2H), 1.57-1.63 (m, 1H), 1.56-1.52 (m, 1H), 1.26-1.21 (m, 2H); ^{13}C NMR (101 MHz, CDCl_3) δ 167.72, 161.40, 158.99, 154.98, 148.95, 137.64, 137.19, 126.79, 124.75, 123.77, 119.02, 118.82, 118.71, 118.68, 110.52, 110.30, 45.51, 42.71, 38.82, 34.77, 29.15, 24.64; HRMS Calcd for $\text{C}_{19}\text{H}_{17}\text{FN}_2\text{O}$ [$\text{M}+\text{H}^+$]: 309.1398, Found: 309.1402.

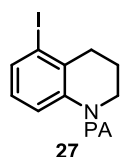
9. Preparation of iodinated THQs



Scheme S5

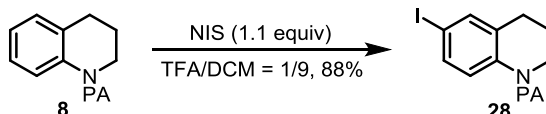


Compound **2** (48 mg, 0.2 mmol, 1.0 equiv), $\text{PhI}(\text{OAc})_2$ (260 mg, 0.8 mmol, 4.0 equiv), I_2 (200 mg, 0.8 mmol, 4.0 equiv), $\text{Pd}(\text{OAc})_2$ (4.5 mg, 0.02 mmol, 0.1 equiv), and KHCO_3 (20 mg, 0.2 mmol, 1.0 equiv) were dissolved in anhydrous DMF (6 mL, 0.03 M) in a 10 mL vial. 4 Å molecular sieves (200 mg) was added and the reaction vial was purged with Ar and sealed with a PTFE cap. The mixture was stirred at 25 °C for 1 h, then heated to 130 °C for 24 h. The reaction mixture was cooled to room temperature, diluted with EtOAc, then washed with aq $\text{Na}_2\text{S}_2\text{O}_3$ (sat.), H_2O , and brine. The organic layer was dried over anhydrous Na_2SO_4 , filtered, and concentrated in vacuo. The resulting residue was purified by silica gel flash chromatography to give **4** in 69% yield as a white solid.



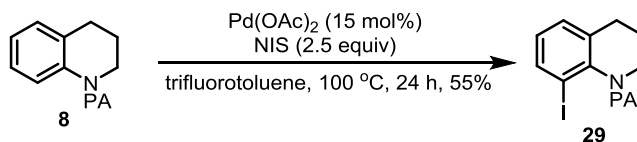
Compound **27** was obtained from compound **4** using the standard Cu-catalyzed cross coupling protocol in 69% yield as a white solid. ^1H NMR (500 MHz, CDCl_3) δ 8.50 (s, 1H), 7.74 (t, $J =$

7.2 Hz, 1H), 7.56 (s, 2H), 7.39-7.27 (m, 1H), 7.15-6.70 (m, 1H), 6.62 (s, 1H), 3.89 (s, 2H), 2.85 (t, $J = 6.6$ Hz, 2H), 2.24-1.85 (m, 2H); ^{13}C NMR (126 MHz, CDCl_3) δ 168.24, 154.39, 148.84, 139.78, 137.03, 135.60, 133.47, 127.04, 125.37, 124.77, 124.08, 101.42, 44.72, 33.65, 24.56; HRMS: calculated for $\text{C}_{15}\text{H}_{13}\text{IN}_2\text{O}$ [$\text{M}+\text{H}^+$]: 365.0145, found: 365.0150.



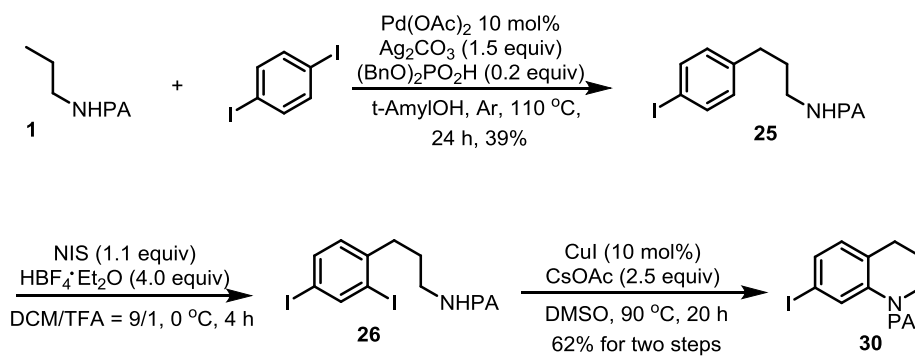
Scheme S6

Compound **28** was prepared from compound **8** using the NIS-mediated $\text{S}_{\text{E}}\text{Ar}$ iodination protocol: Picolinamide substrate **8** (47.6 mg, 0.2 mmol, 1 equiv) and NIS (49.5 mg, 0.22 mmol, 1.1 equiv) were dissolved in a mixture of anhydrous CH_2Cl_2 (27 mL) and TFA (3 mL) at room temperature. After 16 hours, solvents were removed in vacuo or with a stream of N_2 . The residue was redissolved in CH_2Cl_2 (15 mL), washed with aq NaHCO_3 , aq $\text{Na}_2\text{S}_2\text{O}_3$, brine, dried over anhydrous Na_2SO_4 , and concentrated in vacuo. The resulting residue was purified by silica gel flash chromatography to give the iodinated products in 88% yield as a yellow solid. ^1H NMR (500 MHz, CDCl_3) δ 8.49 (s, 1H), 7.73 (t, $J = 7.4$ Hz, 1H), 7.55 (d, $J = 7.2$ Hz, 1H), 7.47 (s, 1H), 7.33-7.27 (m, 1H), 7.19 (s, 1H), 6.94-6.17 (m, 1H), 3.88 (s, 2H), 2.80 (t, $J = 6.6$ Hz, 2H), 2.09-1.94 (m, 2H); ^{13}C NMR (126 MHz, CDCl_3) δ 168.31, 154.35, 148.87, 137.51, 137.02, 134.67, 126.53, 124.78, 123.98, 88.85, 26.71, 23.57; HRMS: calculated for $\text{C}_{15}\text{H}_{13}\text{IN}_2\text{O}$ [$\text{M}+\text{H}^+$]: 365.0145; found: 365.0146.

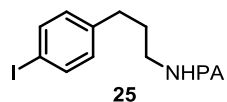


Scheme S7

Compound **8** (48 mg, 0.2 mmol, 1.0 equiv), NIS (113 mg, 0.5 mmol, 2.5 equiv), and Pd(OAc)₂ (6.5 mg, 0.03 mmol, 0.015 equiv) were dissolved in α,α,α -trifluorotoluene (2 mL, 0.1 M) in a 10 mL vial. The vial was purged with Ar, sealed with a PTFE cap, and heated to 100 °C. After 24 h, the reaction was cooled to room temperature, filtered through a pad of celite and eluted with EtOAc. The filtrate was washed with aq Na₂S₂O₃ (sat.), dried over anhydrous Na₂SO₄, and concentrated in vacuo. The resulting residue was purified by silica gel flash chromatography to give **29** as a white solid (40 mg, 55%). The NMR spectrum of **29** at room temperature in CDCl₃ represents a 2:1 mixture of rotamers. ¹H NMR (500 MHz, CDCl₃) δ 8.72 (s, 1H), 8.06 (d, J = 3.8 Hz, 2H), 7.93-7.80 (m, 4H), 7.77 (d, J = 7.9 Hz, 1H), 7.66 (t, J = 7.2 Hz, 2H), 7.46-7.34 (m, 3H), 7.24-7.08 (m, 6H), 6.90 (t, J = 7.7 Hz, 1H), 6.82 (t, J = 7.7 Hz, 2H), 4.78 (m, 2H), 4.25-4.13 (m, 1H), 3.54-3.41 (m, 1H), 3.21-3.06 (m, 2H), 2.90-2.72 (m, 6H), 2.47-2.32 (m, 2H), 2.17-2.03 (m, 1H), 1.87-1.64 (m, 3H); ¹³C NMR (126 MHz, CDCl₃) δ 168.48, 167.54, 154.31, 153.92, 148.91, 147.10, 143.54, 141.59, 138.79, 138.23, 137.76, 137.19, 137.06, 136.62, 136.00, 128.52, 127.83, 127.72, 127.43, 125.86, 125.31, 124.73, 96.30, 94.76, 47.00, 42.69, 27.76, 26.62, 25.02, 24.54; HRMS: calculated for C₁₅H₁₃IN₂O [M+H⁺]: 365.0145, found: 365.0145.

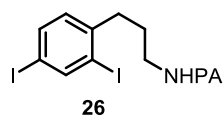


Scheme S8

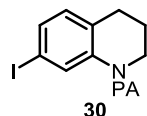


Compound **25** was isolated in 39% yield as a pale yellow oil using C-H arylation conditions **A**.

^1H NMR (500 MHz, CDCl_3) δ 8.54 (d, $J = 4.3$ Hz, 1H), 8.19 (d, $J = 7.8$ Hz, 1H), 8.07 (s, 1H), 7.84 (td, $J = 7.7, 1.6$ Hz, 1H), 7.59 (d, $J = 8.2$ Hz, 2H), 7.42 (m, 1H), 6.96 (d, $J = 8.2$ Hz, 2H), 3.50 (m, 2H), 2.73-2.60 (m, 2H), 2.00-1.89 (m, 2H); ^{13}C NMR (126 MHz, CDCl_3) δ 164.43, 150.01, 148.16, 141.23, 137.59, 137.50, 130.65, 126.26, 122.30, 91.13, 39.00, 32.95, 31.20; HRMS: calculated for $\text{C}_{15}\text{H}_{16}\text{IN}_2\text{O}$ [$\text{M}+\text{H}^+$]: 367.0302, found: 367.0305.



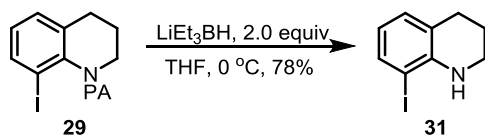
Compound **26** was prepared via the standard directed electrophilic aromatic iodination protocol, and was applied directly to the next step.



Compound **30** was isolated in 62% yield (over 2 steps) as a colorless oil via the standard cross coupling protocol. ^1H NMR (500 MHz, CDCl_3) δ 8.51 (s, 1H), 7.77 (t, $J = 7.5$ Hz, 1H), 7.58 (d, J

= 7.0 Hz, 1H), 7.40-7.27 (m, 2H), 7.24-6.93 (m, 1H), 6.86 (d, $J = 8.0$ Hz, 1H), 3.88 (t, $J = 5.6$ Hz, 2H), 2.80 (t, $J = 6.6$ Hz, 2H), 2.12-1.95 (m, 2H); ^{13}C NMR (126 MHz, CDCl_3) δ 168.38, 154.29, 148.82, 139.98, 137.05, 133.56, 133.55, 130.31, 124.88, 124.04, 89.49, 44.97, 26.79, 23.59; HRMS: calculated for $\text{C}_{15}\text{H}_{13}\text{IN}_2\text{O}$ [$\text{M}+\text{H}^+$]: 365.0145, found: 365.0147.

10. Removal of PA group



Scheme S9

Compound **29** (0.3 mmol, 70 mg, 1.0 equiv) was dissolved in anhydrous THF (2 mL) in an oven-dried 10 mL vial at 0 °C, and LiEt_3BH (0.6 mL of 1 M solution in THF) was added. The mixture was stirred at 0 °C for 4 h, then aq NH_4Cl (sat.) followed by 1 M NaOH (aq) was added. The mixture was extracted with CH_2Cl_2 , the combined organic layers were dried with anhydrous Na_2SO_4 and concentrated in vacuo. The resulting residue was purified by silica gel flash chromatography (2% ether in hexanes) to give **31** as a pale yellow oil in 78% yield. ^1H NMR (500 MHz, CDCl_3) δ 7.47 (d, $J = 7.8$ Hz, 1H), 6.91 (d, $J = 7.2$ Hz, 1H), 6.34 (t, $J = 7.6$ Hz, 1H), 4.30 (bs, 1H), 3.49-3.31 (m, 2H), 2.75 (t, $J = 6.3$ Hz, 2H), 2.00-1.82 (m, 2H); ^{13}C NMR (126 MHz, CDCl_3) δ 144.10, 136.72, 129.59, 122.49, 118.10, 84.67, 42.68, 27.84, 21.98; HRMS: calculated for $\text{C}_9\text{H}_{10}\text{IN}$ [$\text{M}+\text{H}^+$]: 259.9931, found: 259.9932.

11. Crystallographic data of 23

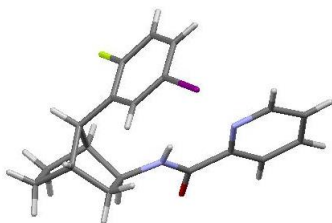


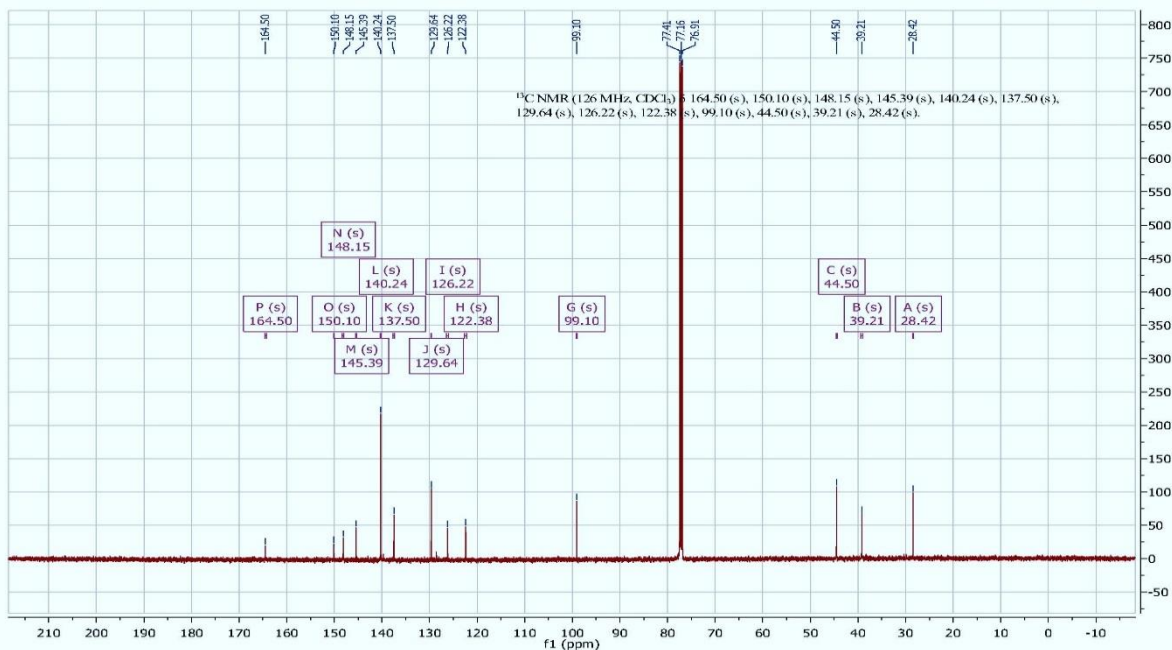
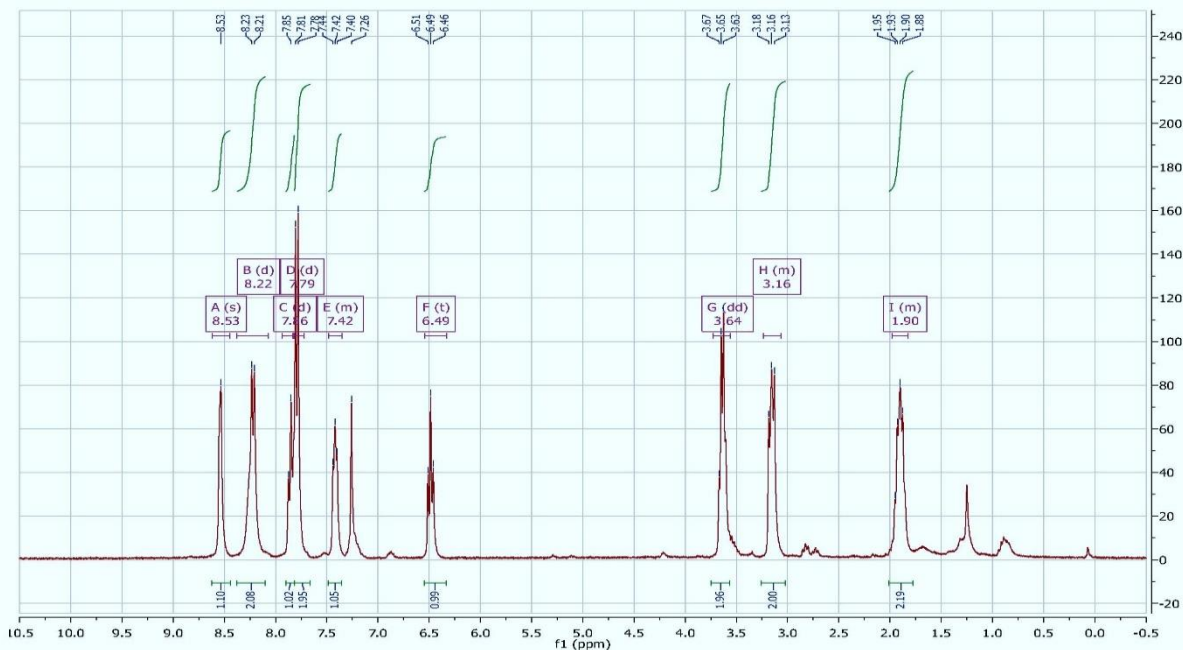
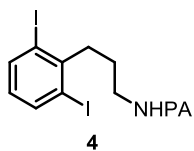
Figure S1. ORTEP view of compound **23**

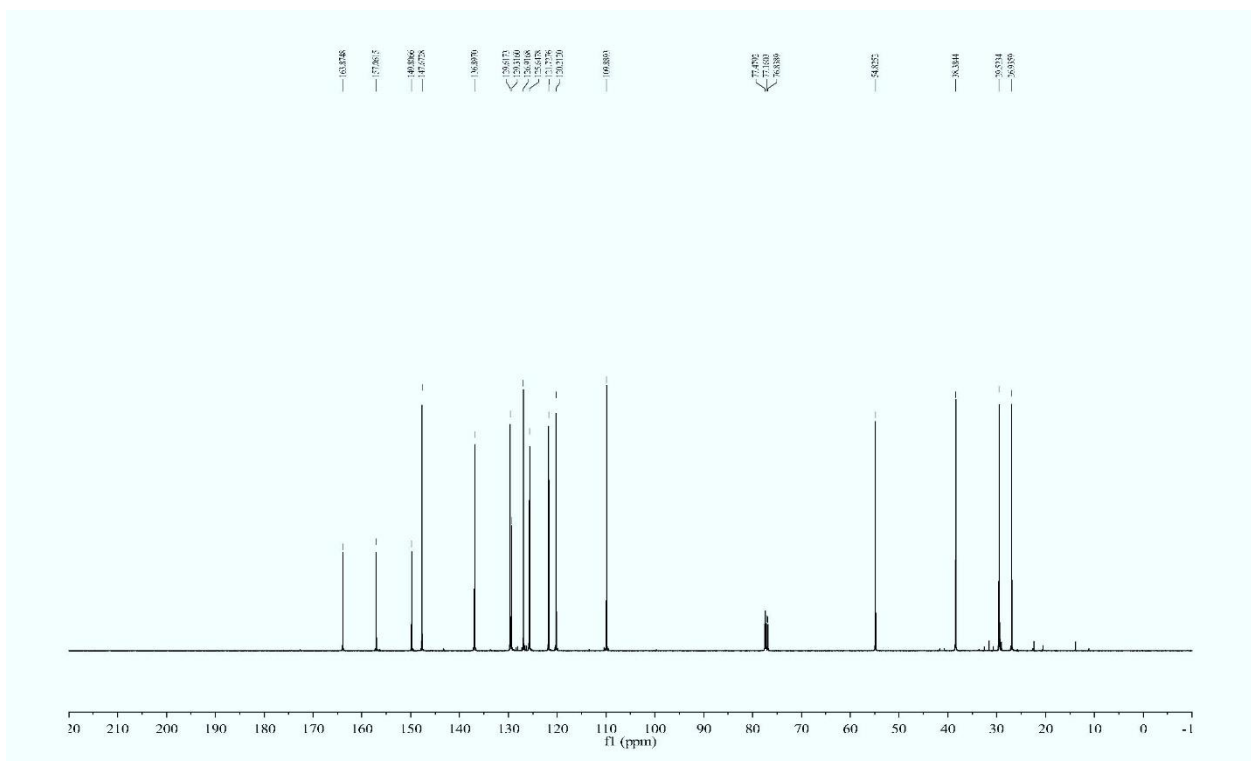
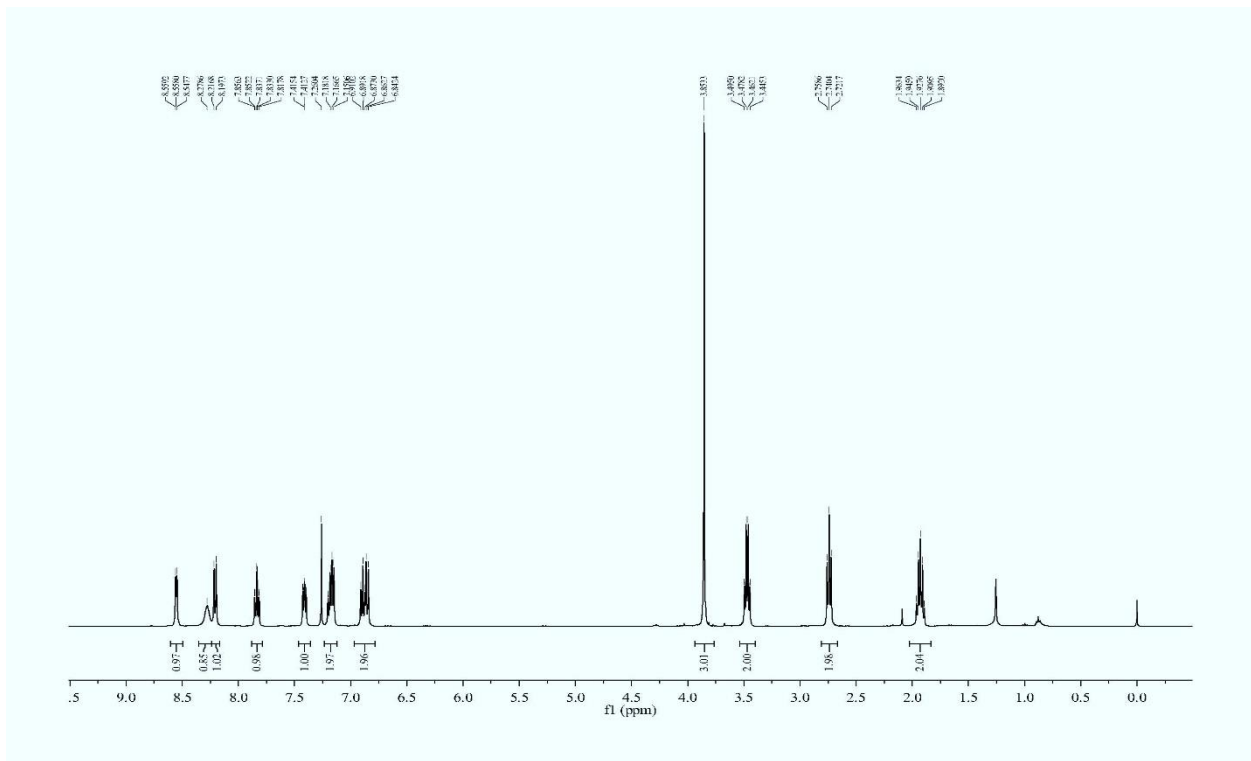
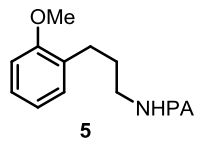
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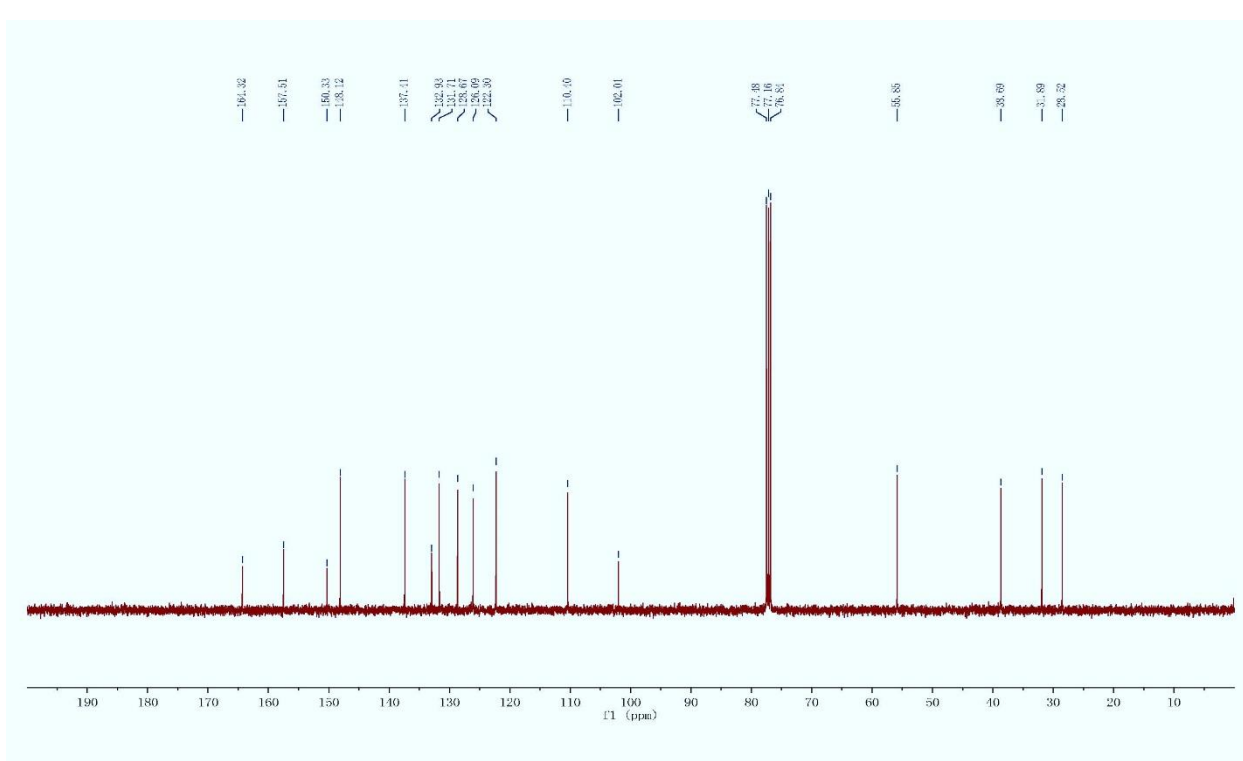
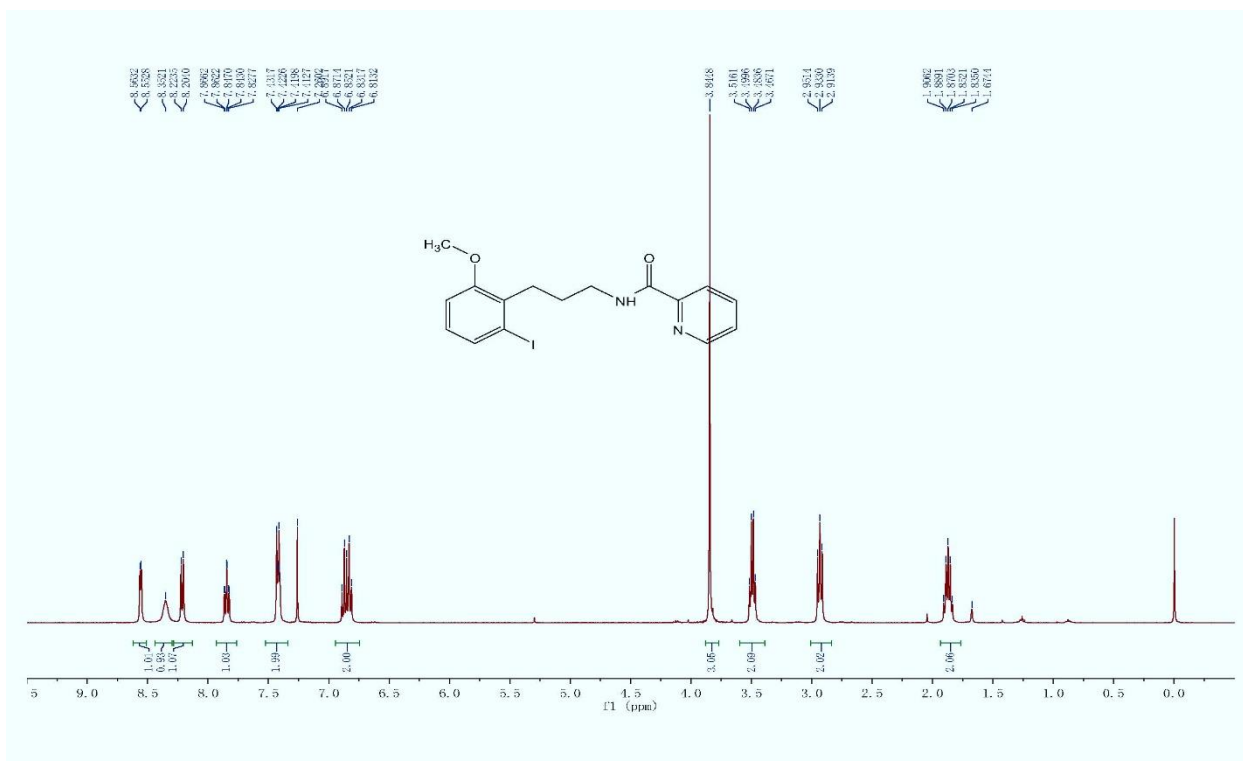
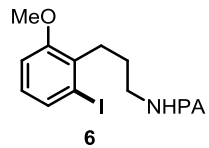
12. References

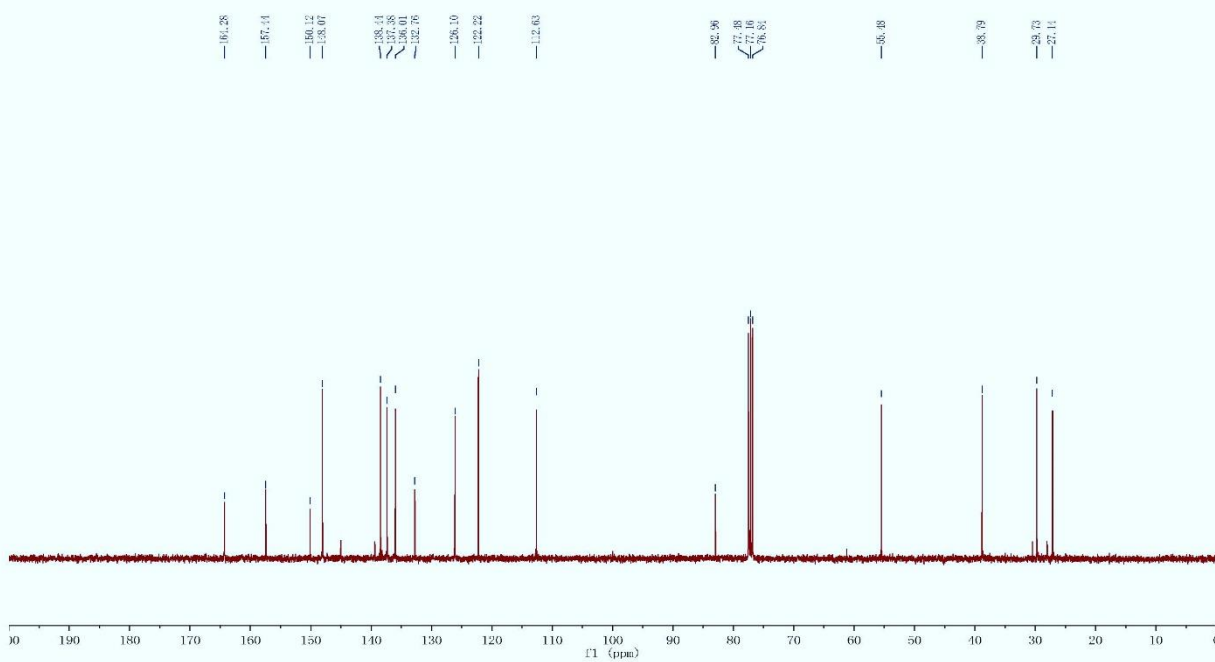
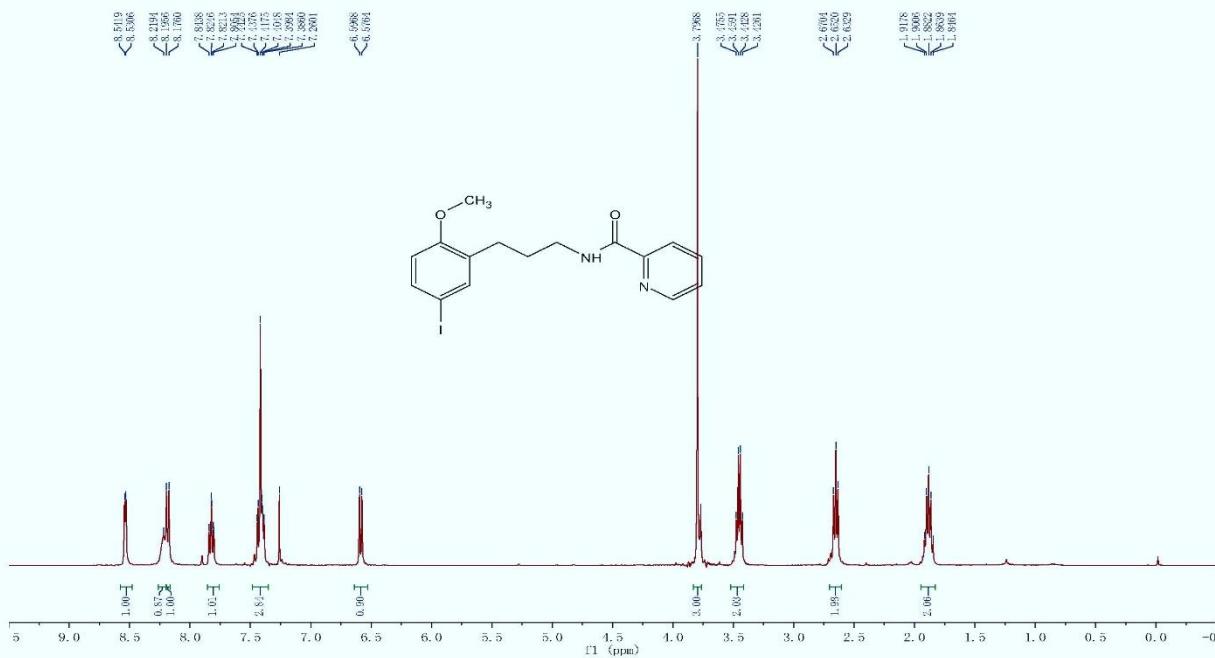
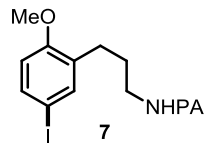
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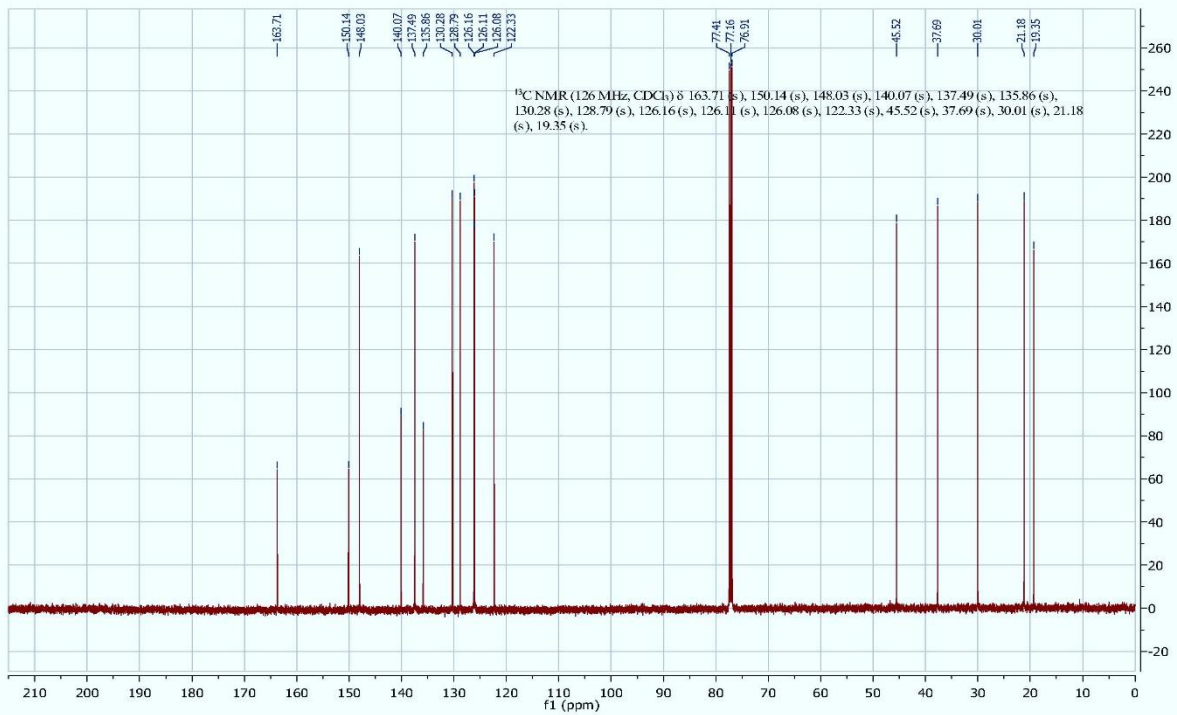
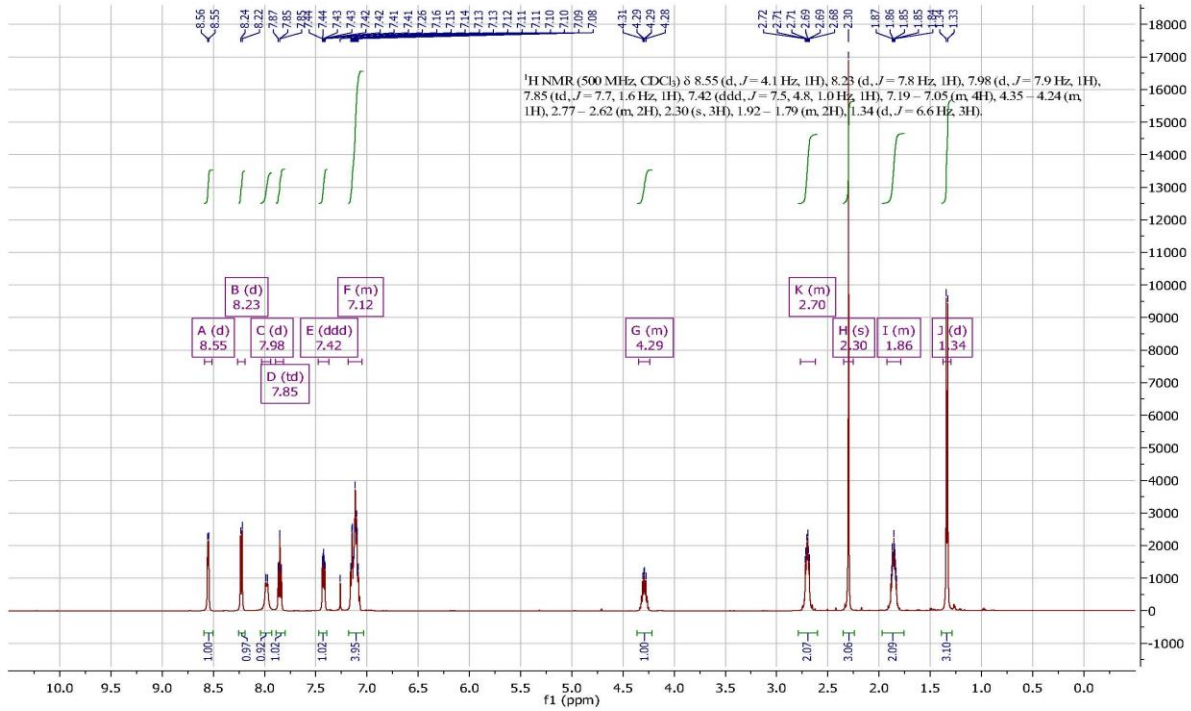
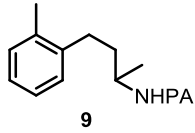
13. Spectra

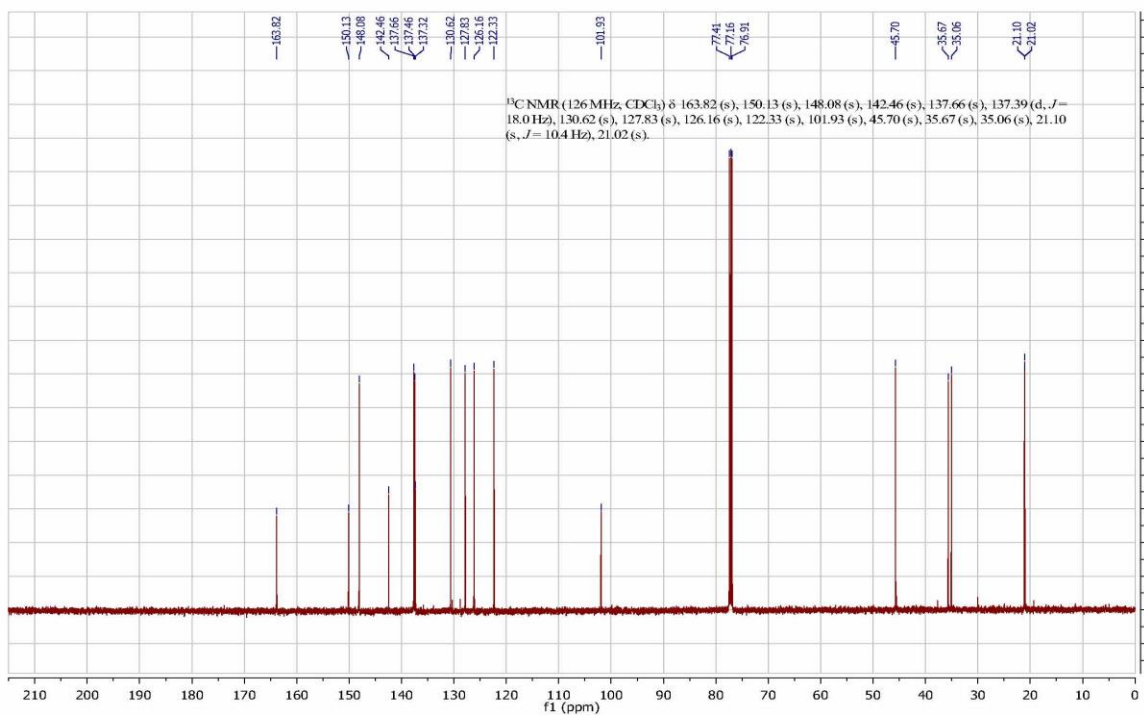
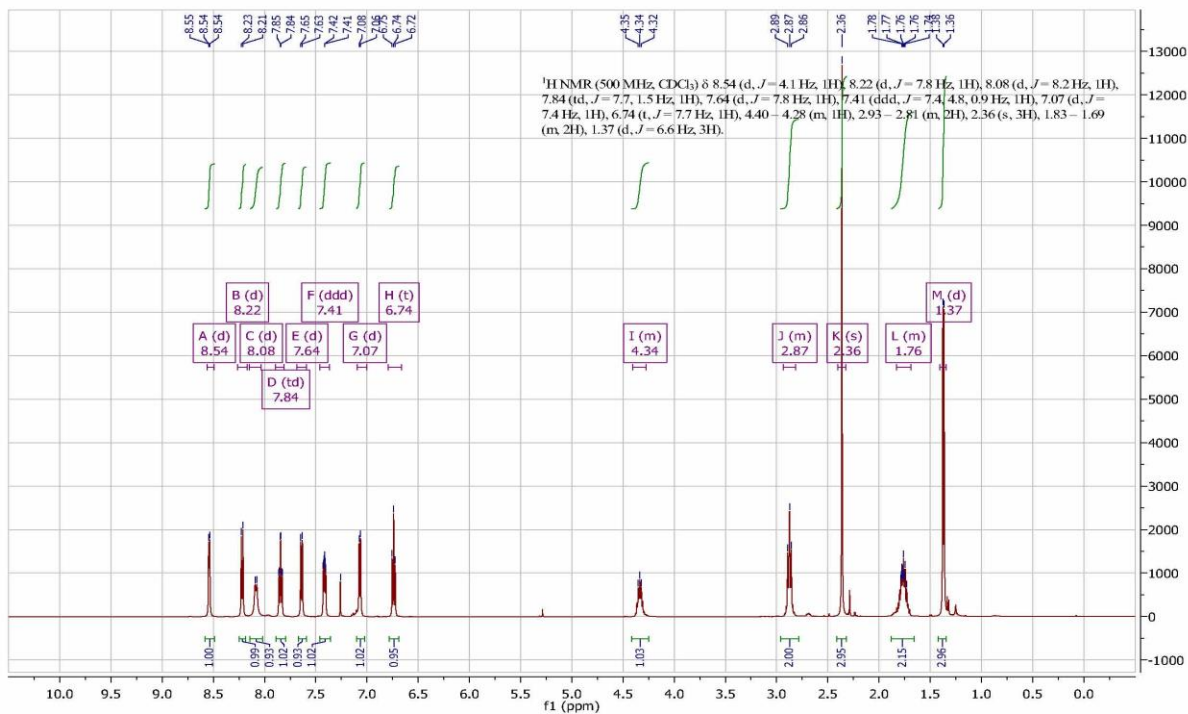
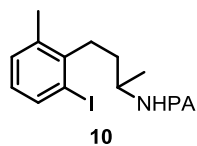


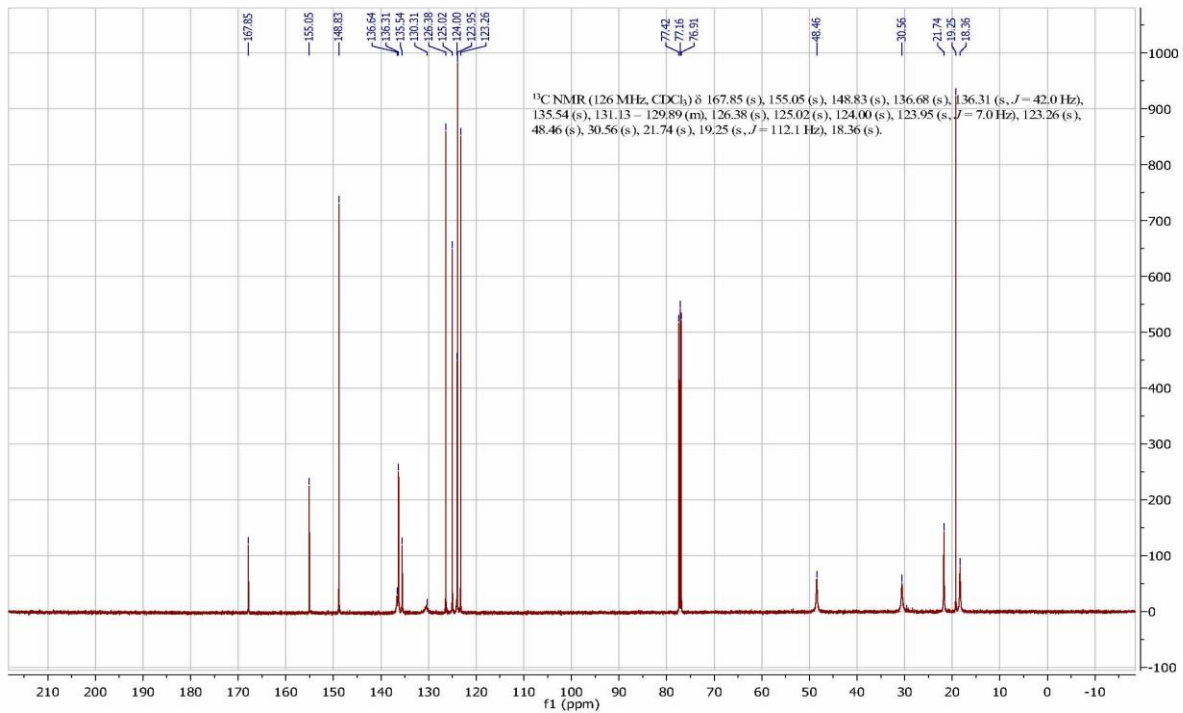
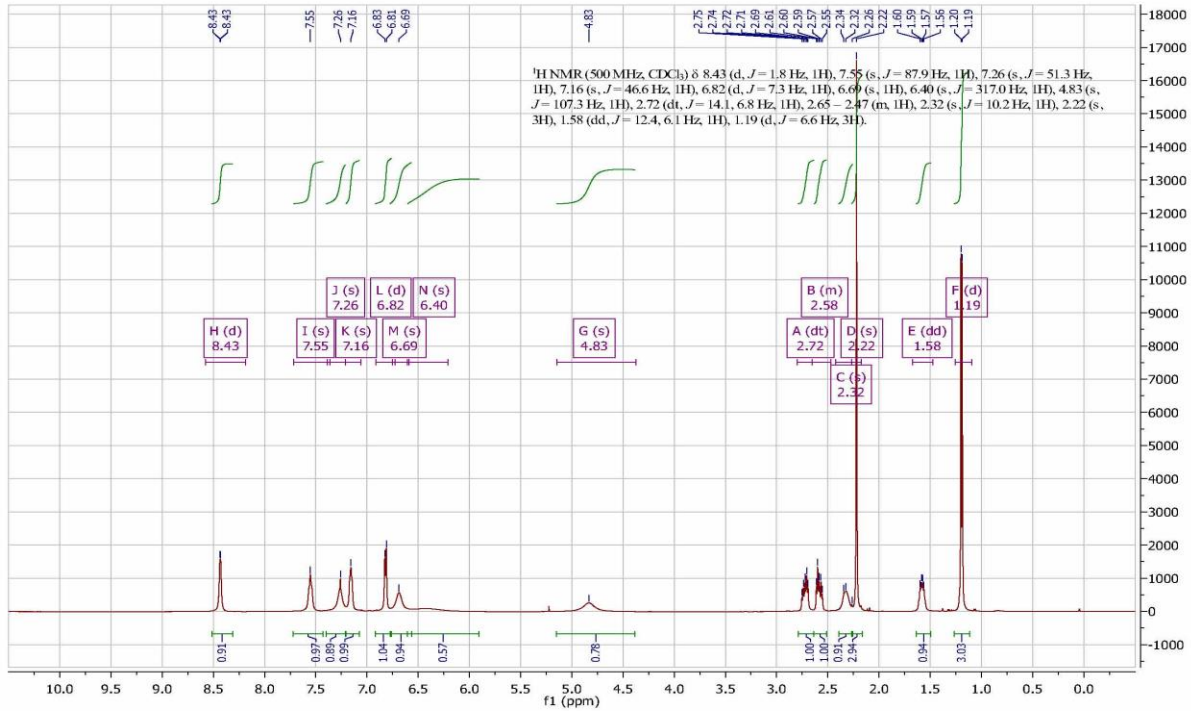
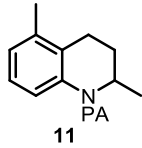


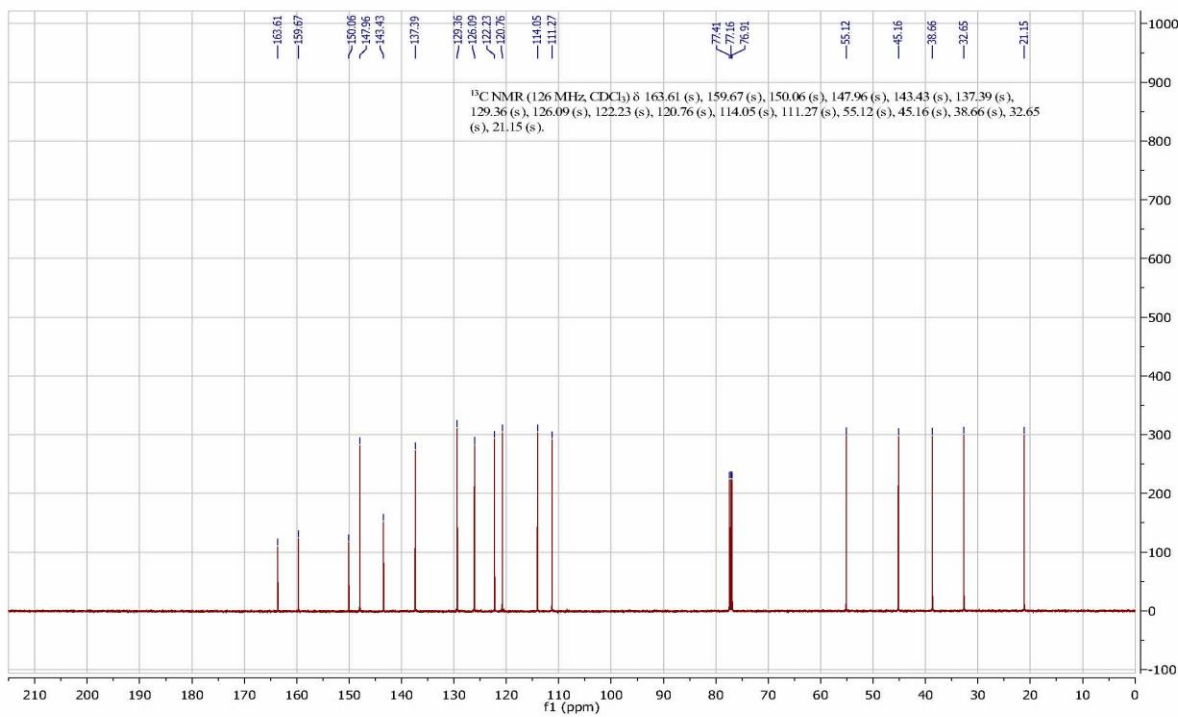
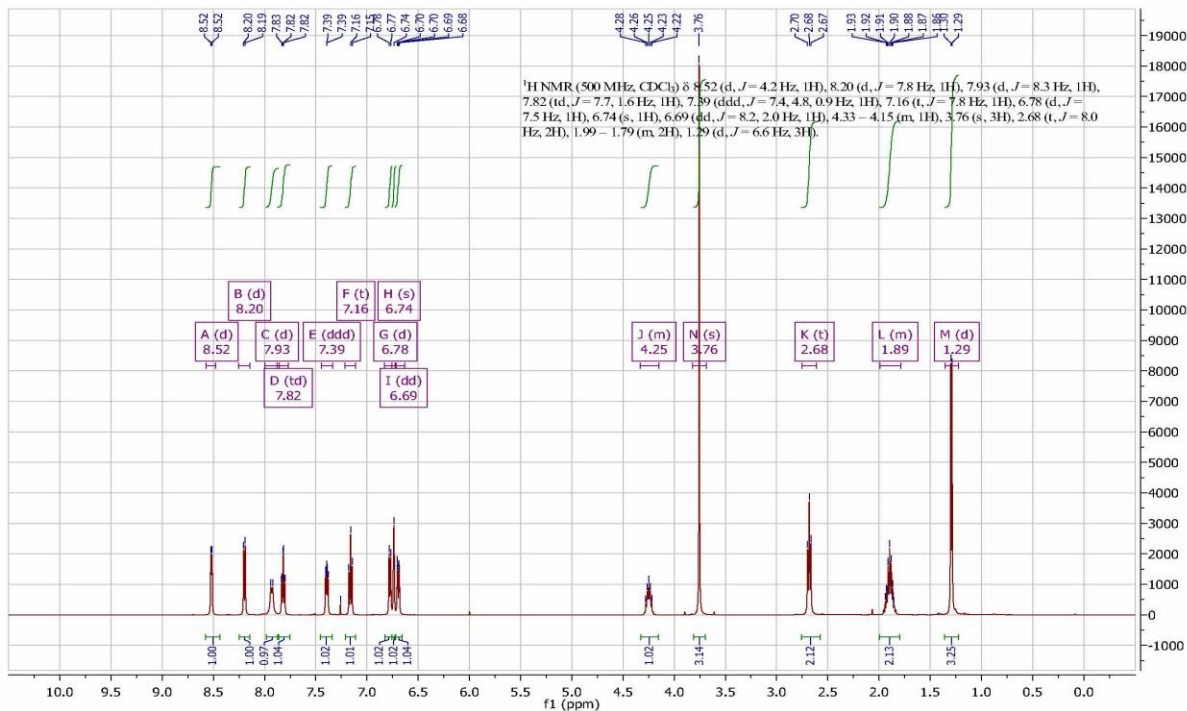
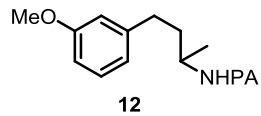


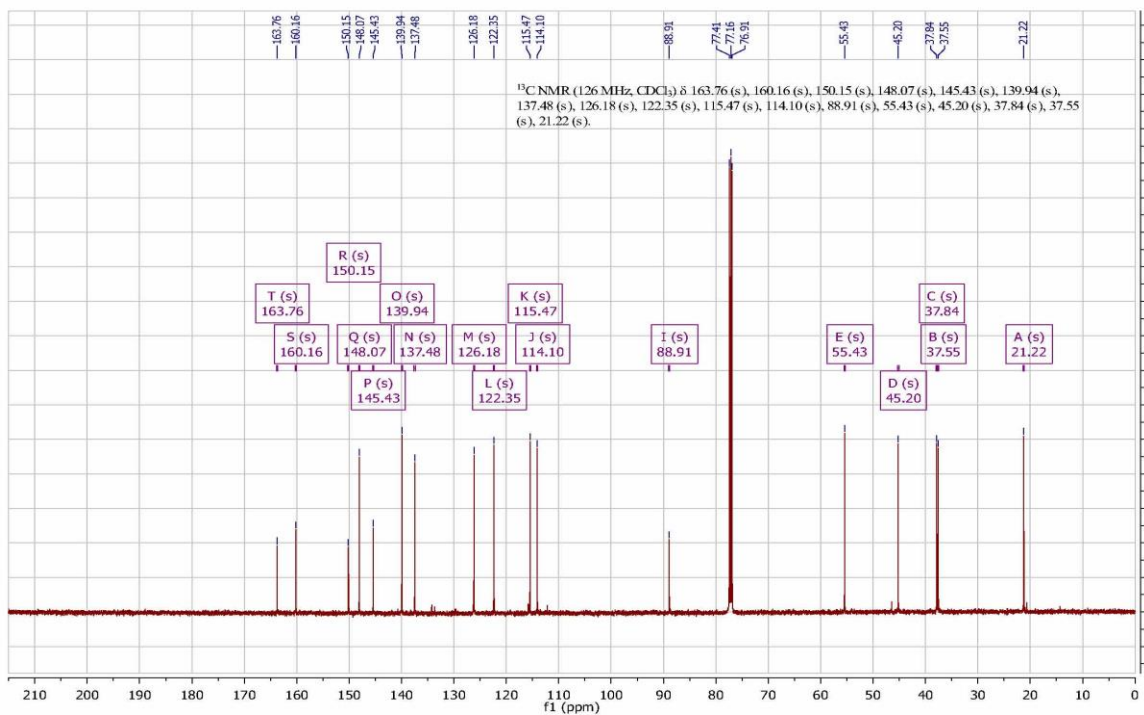
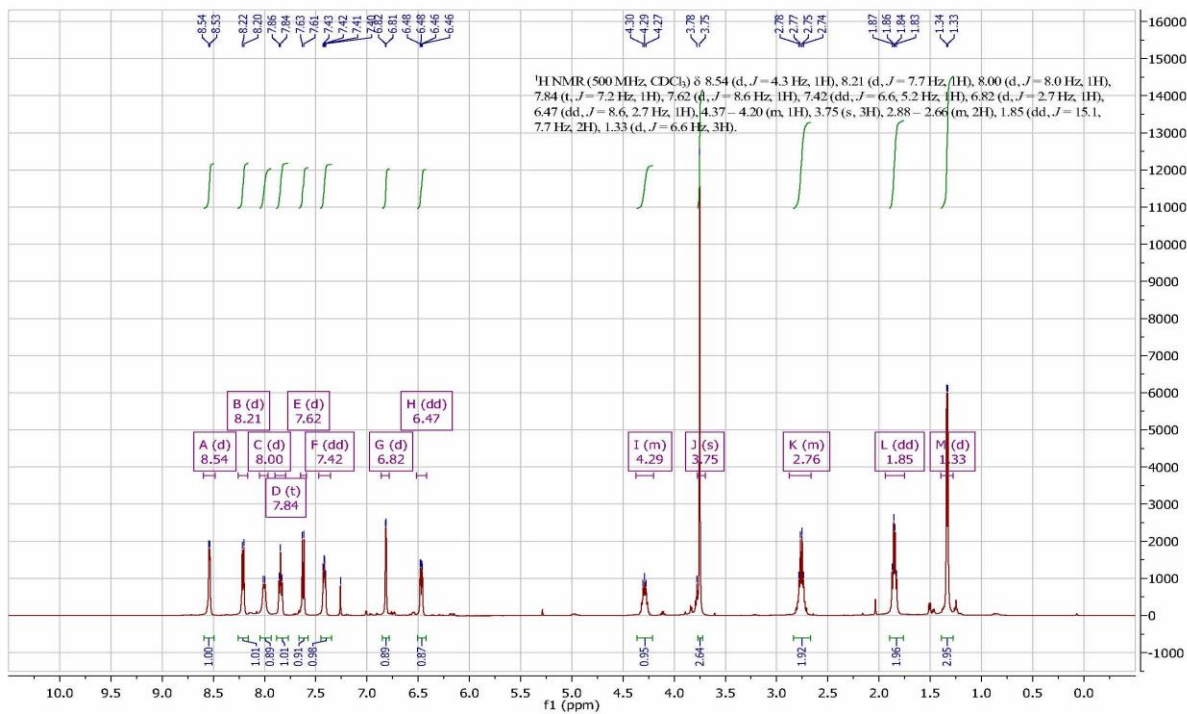
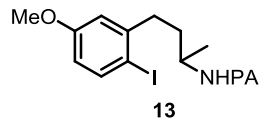


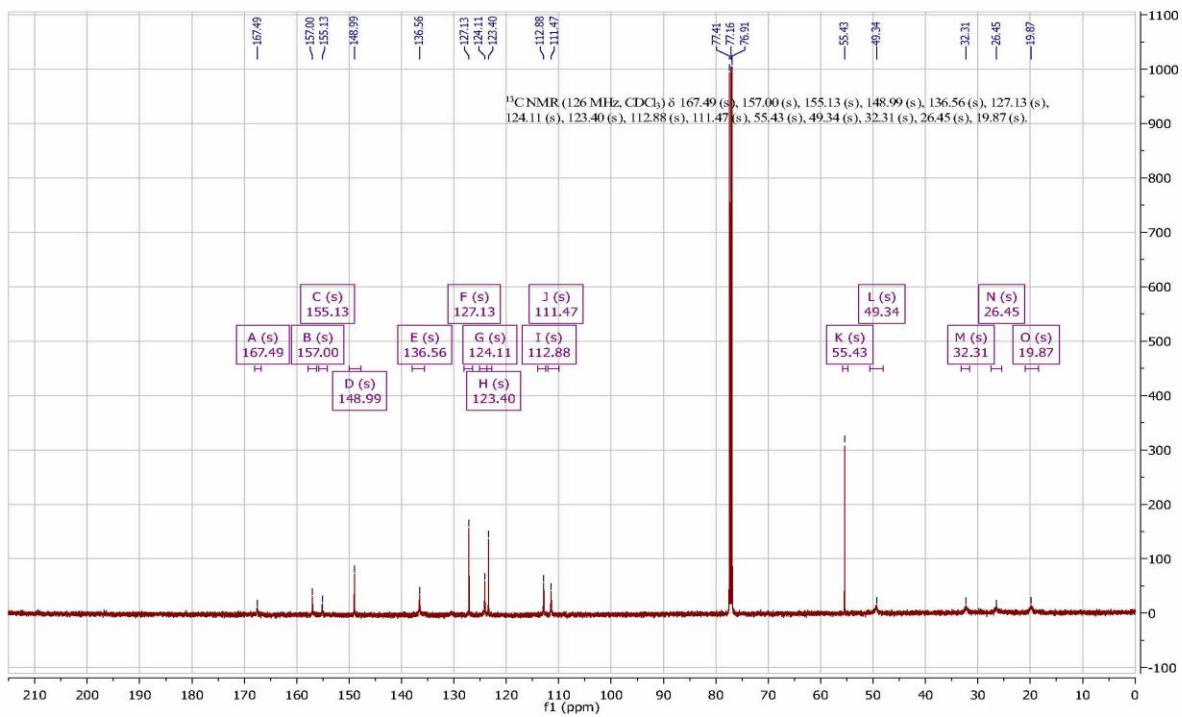
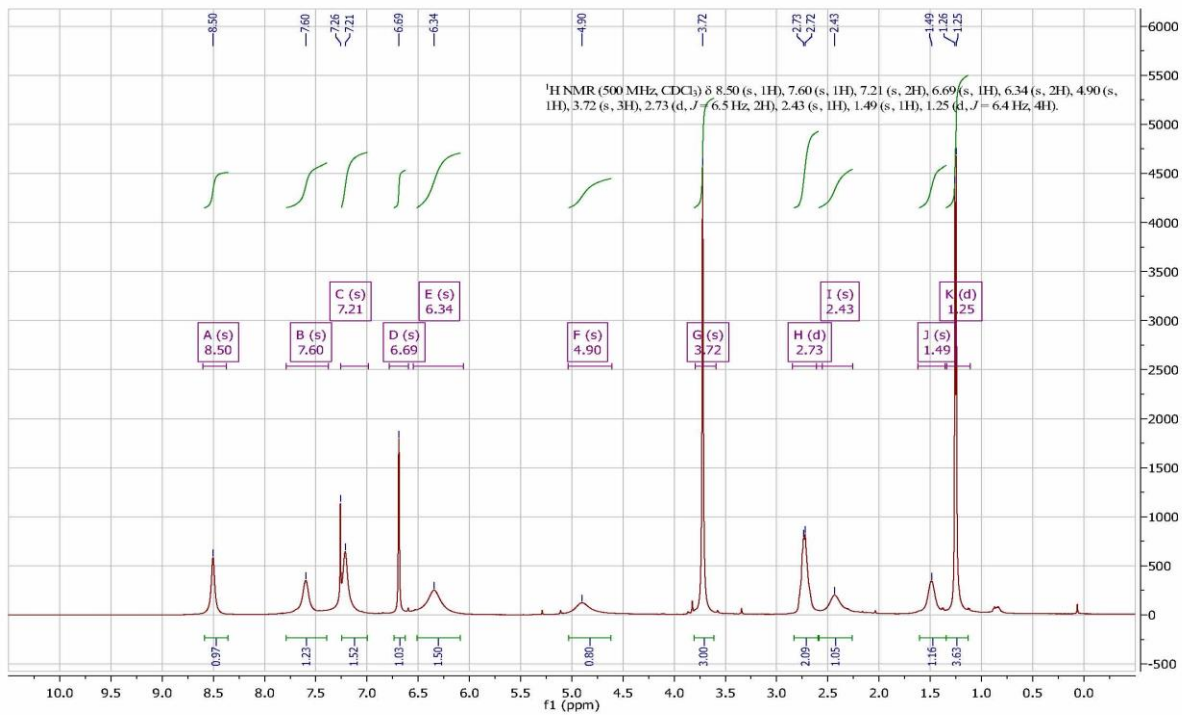
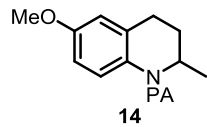


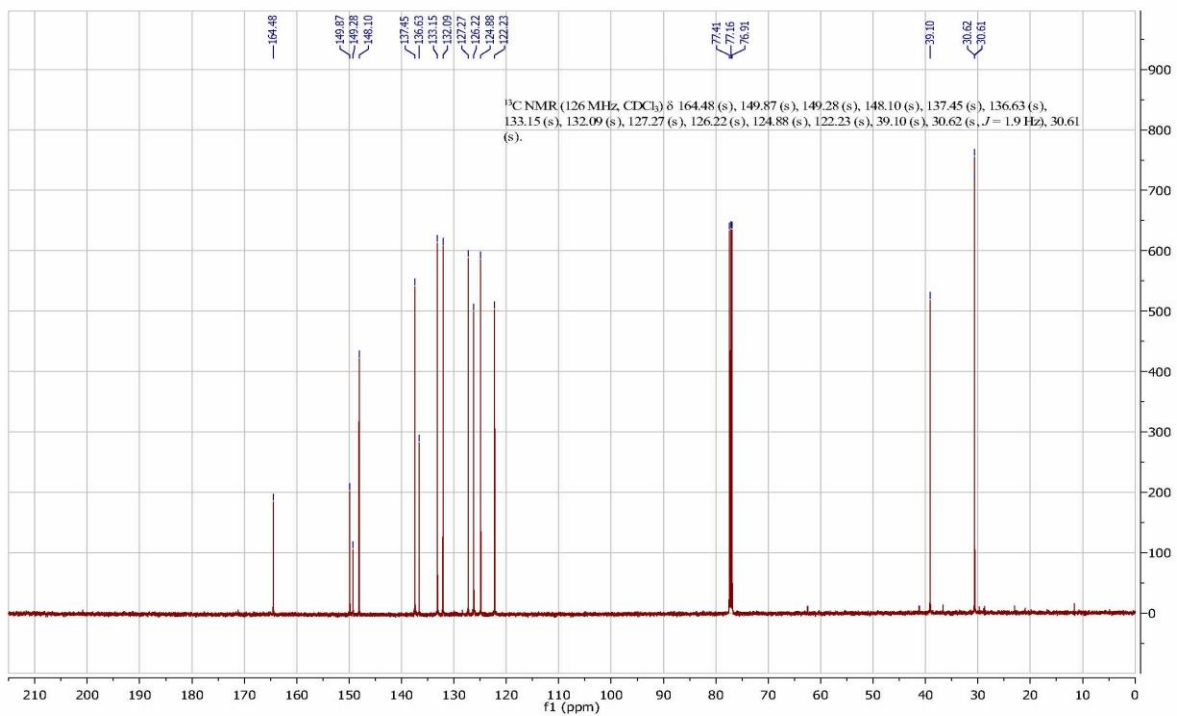
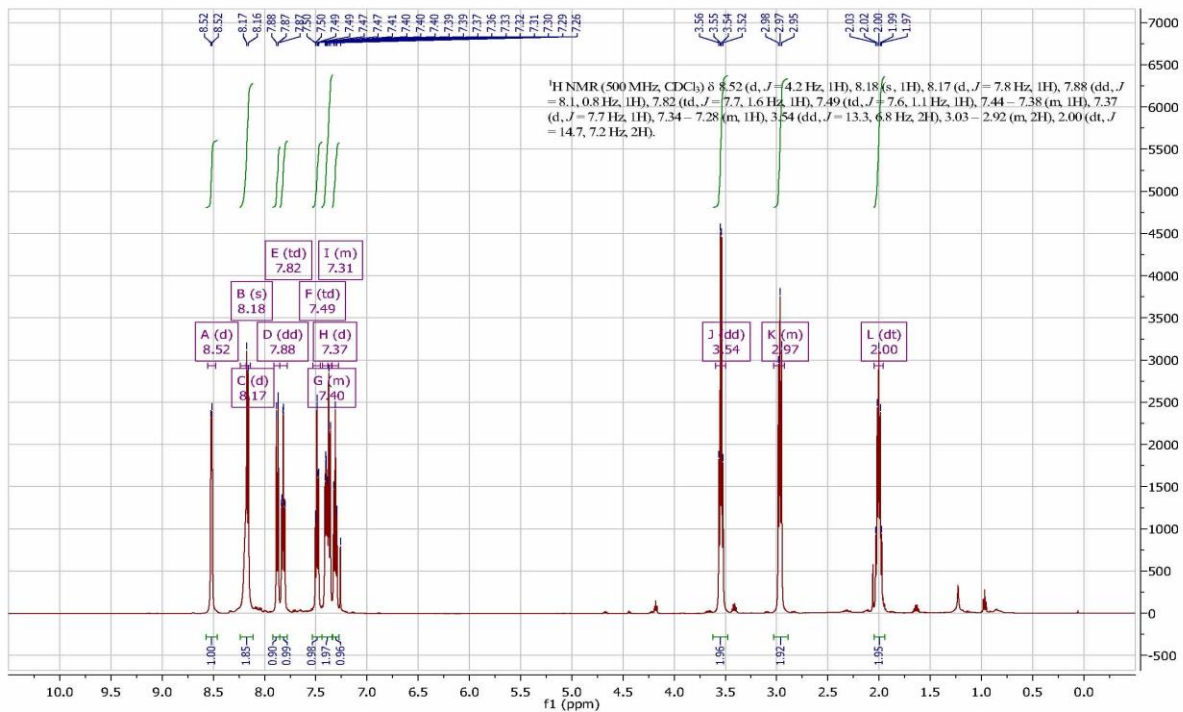
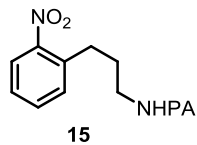


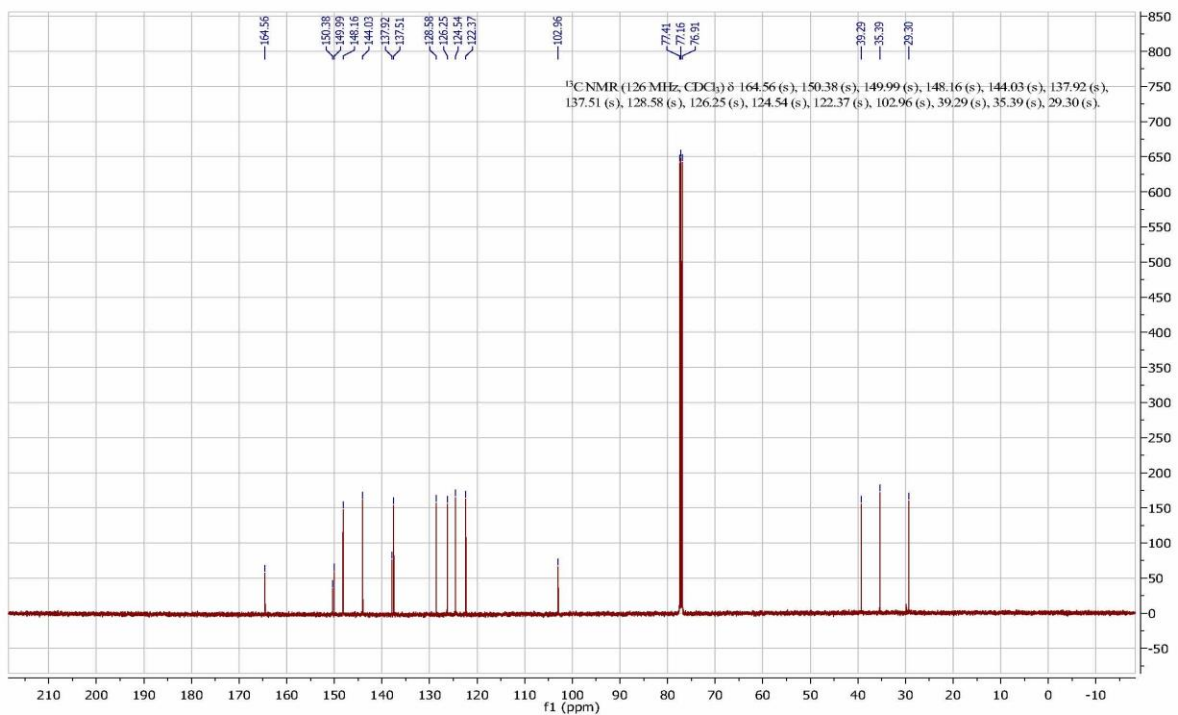
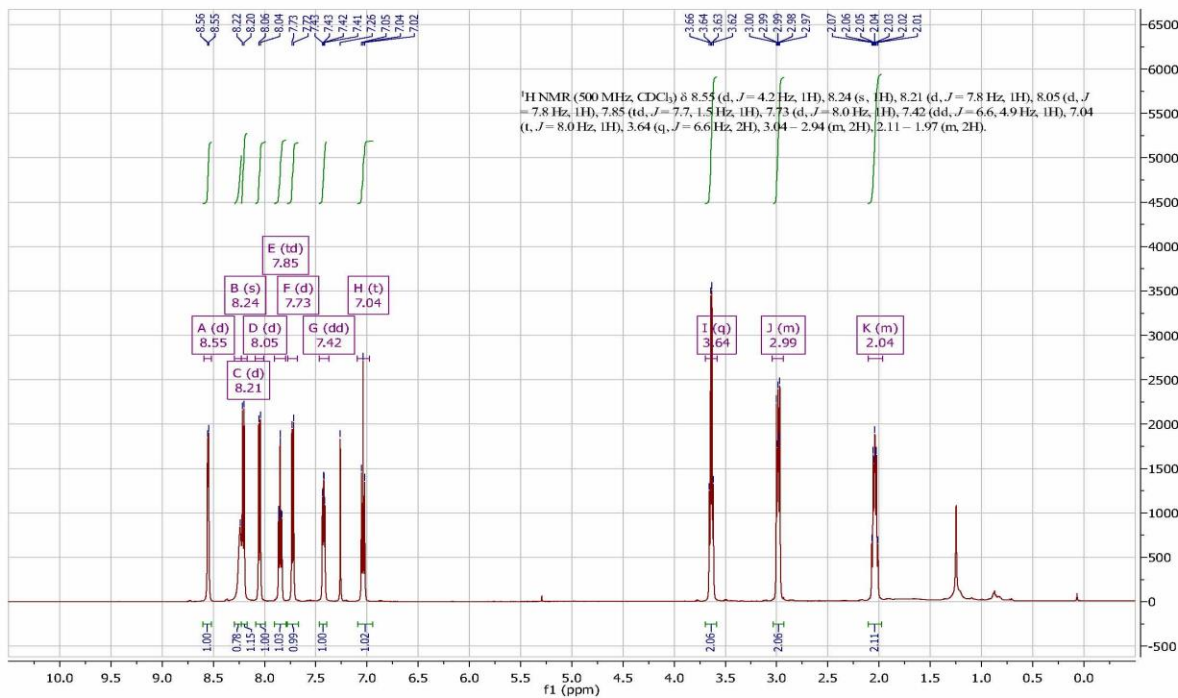
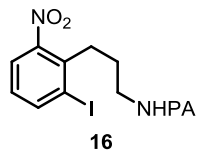


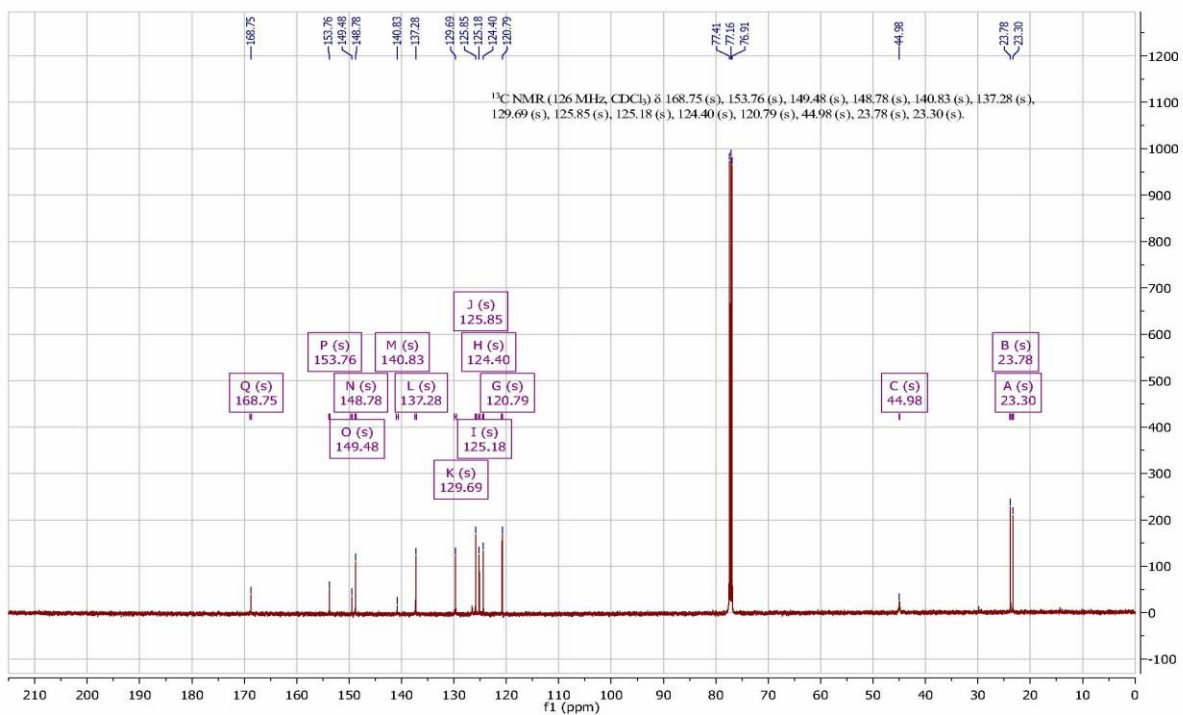
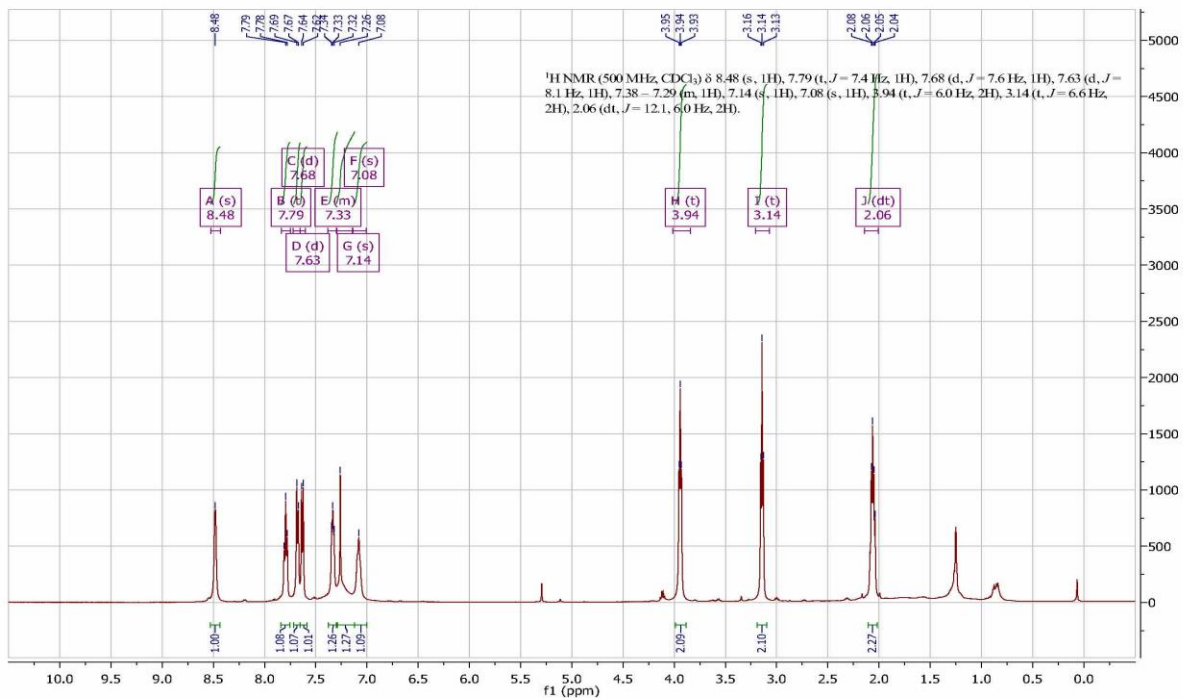
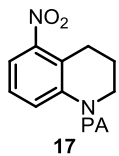


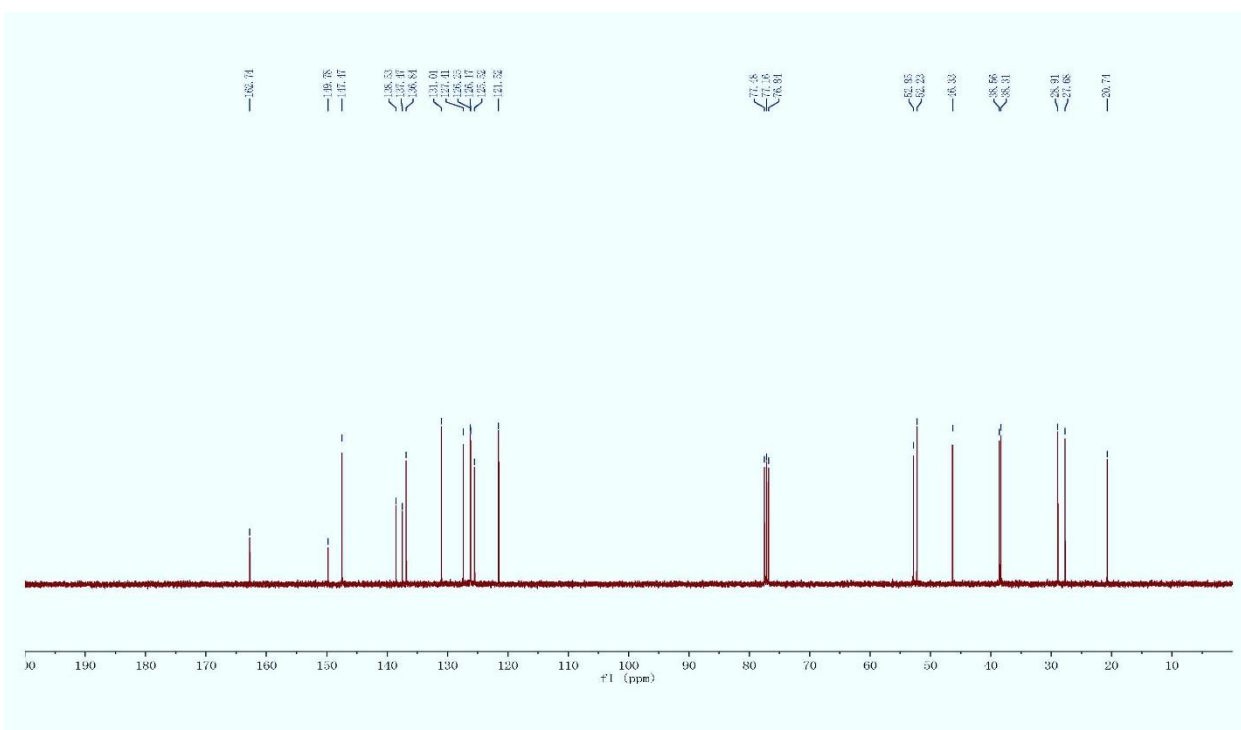
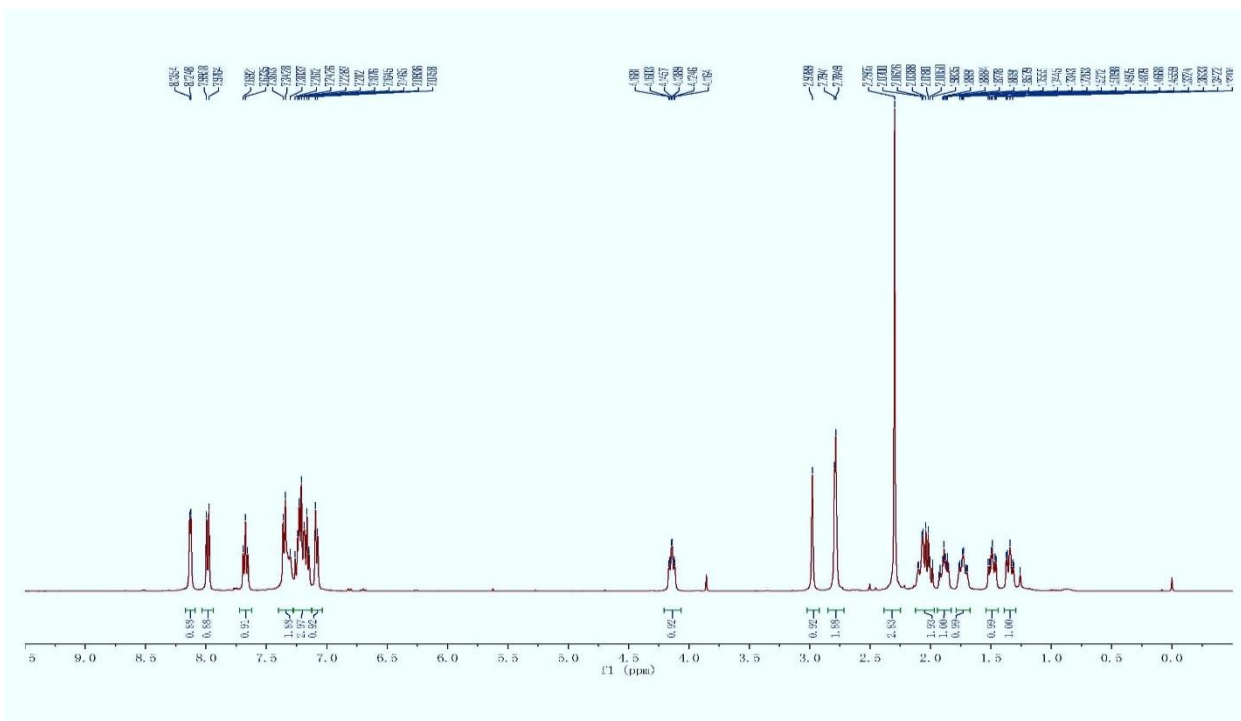
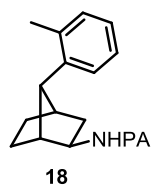


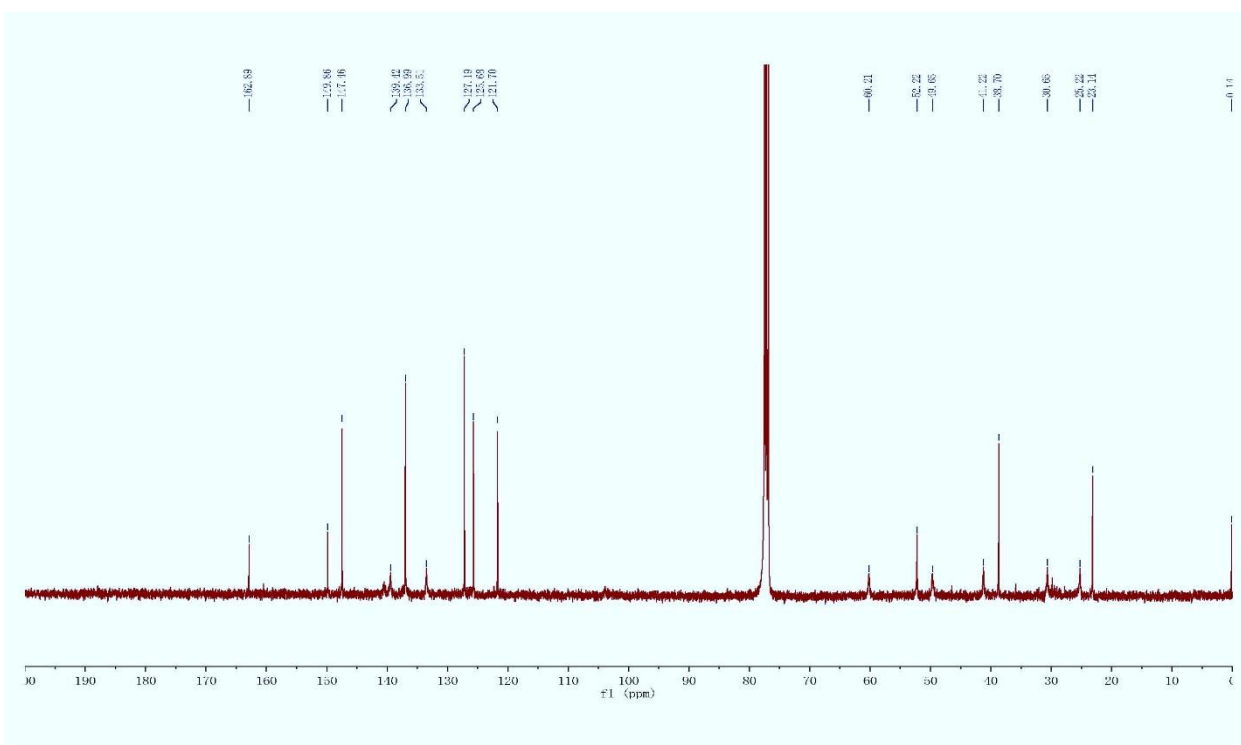
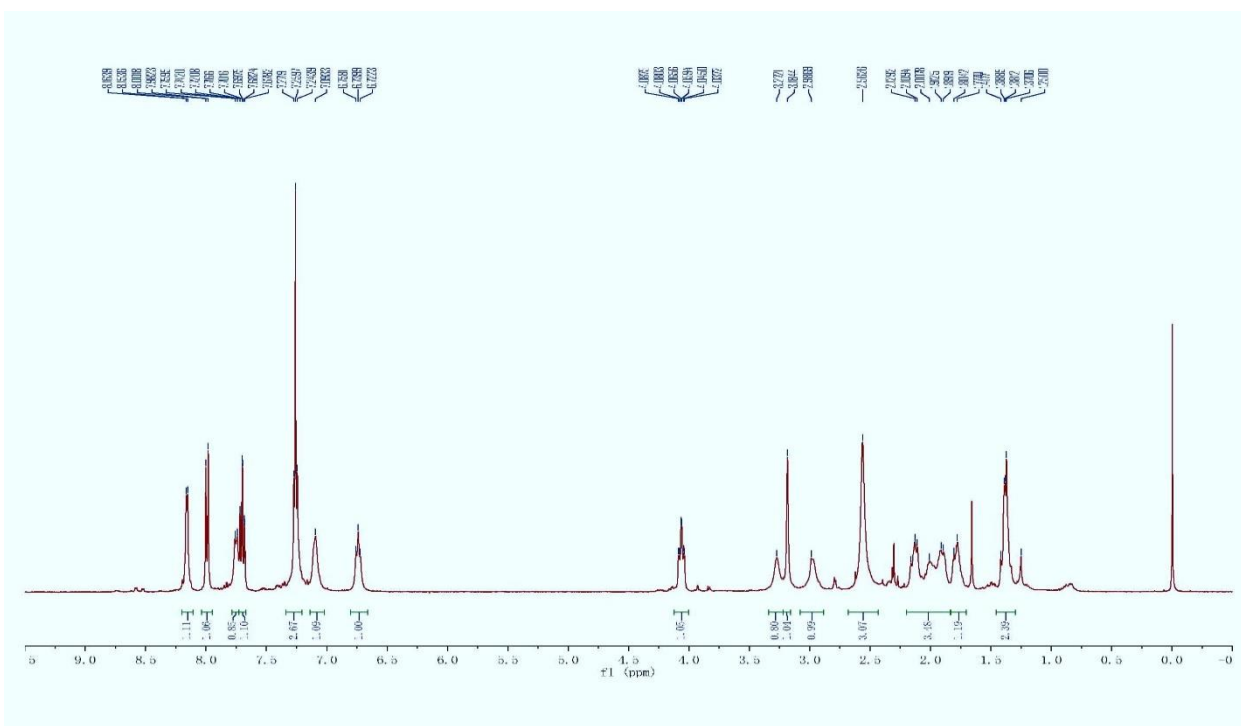
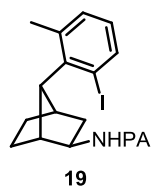


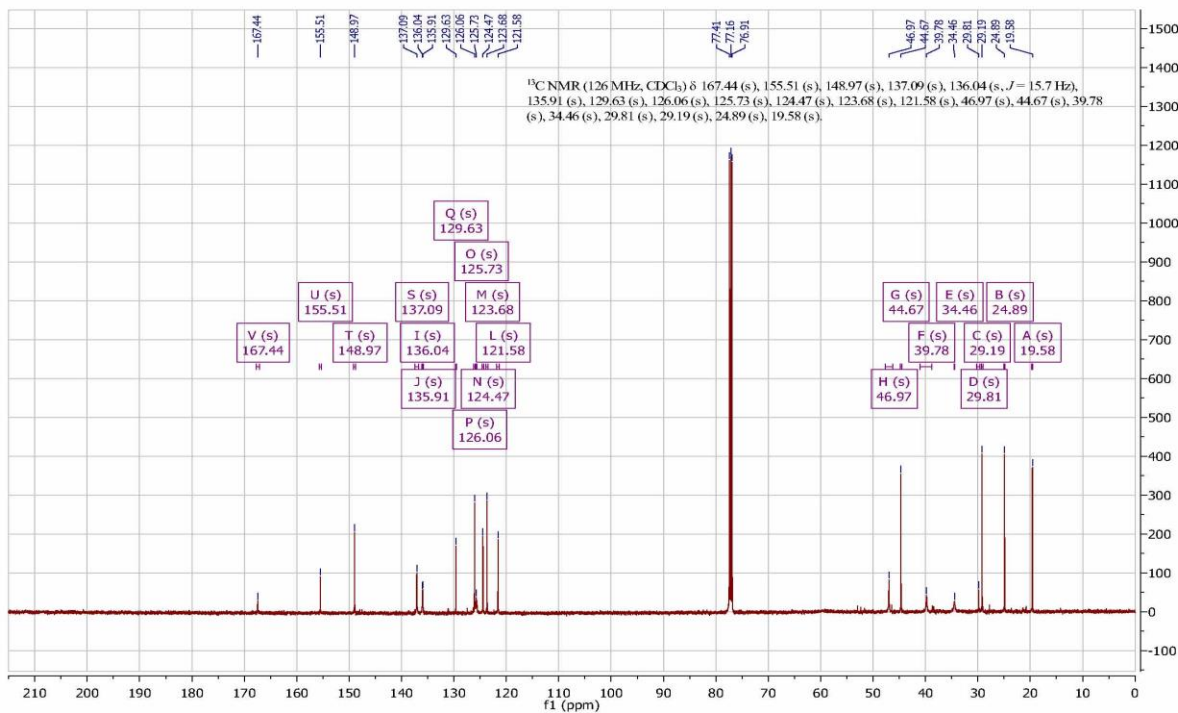
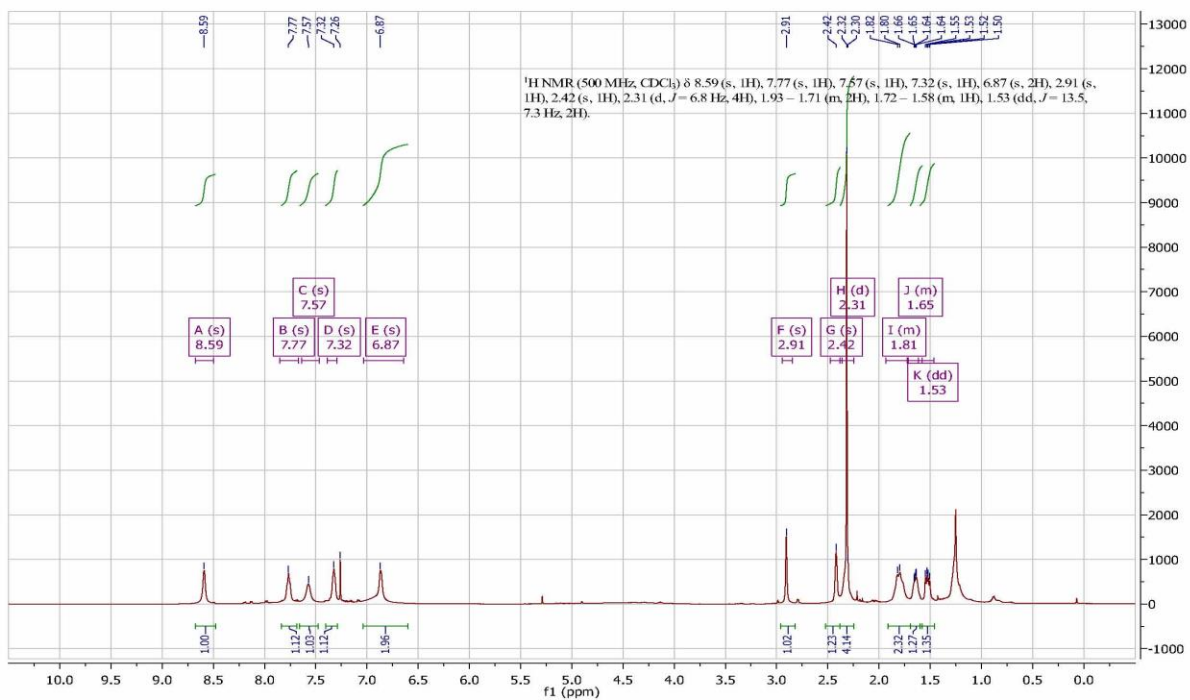
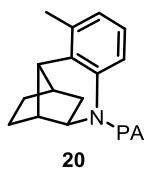


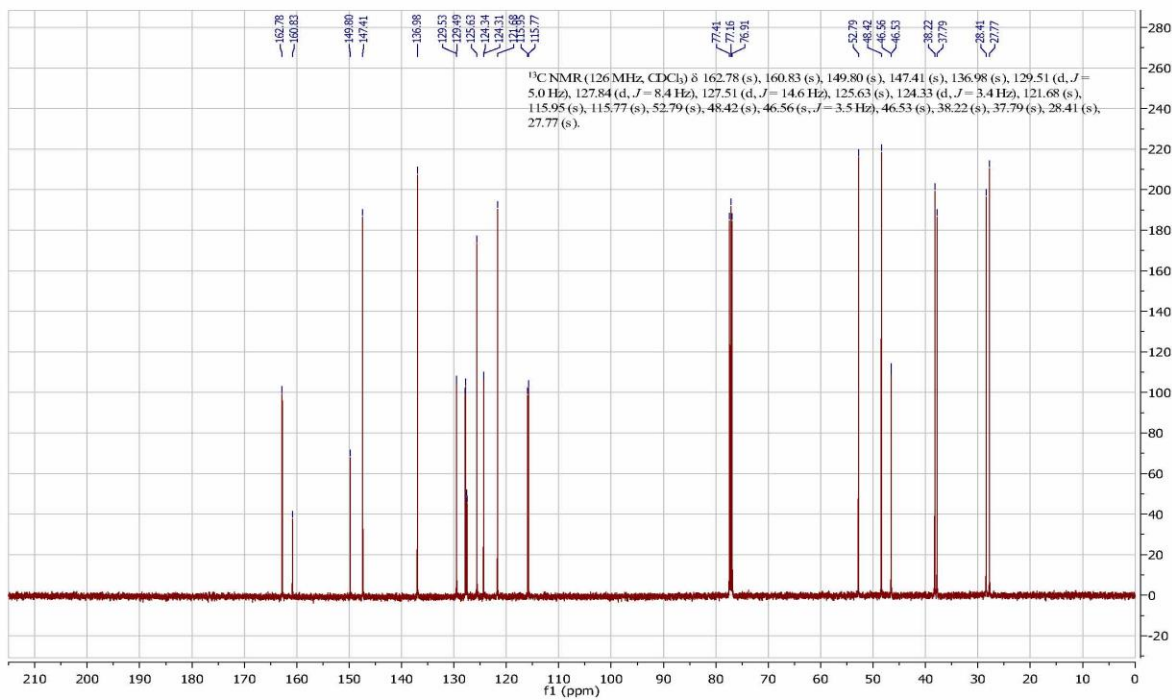
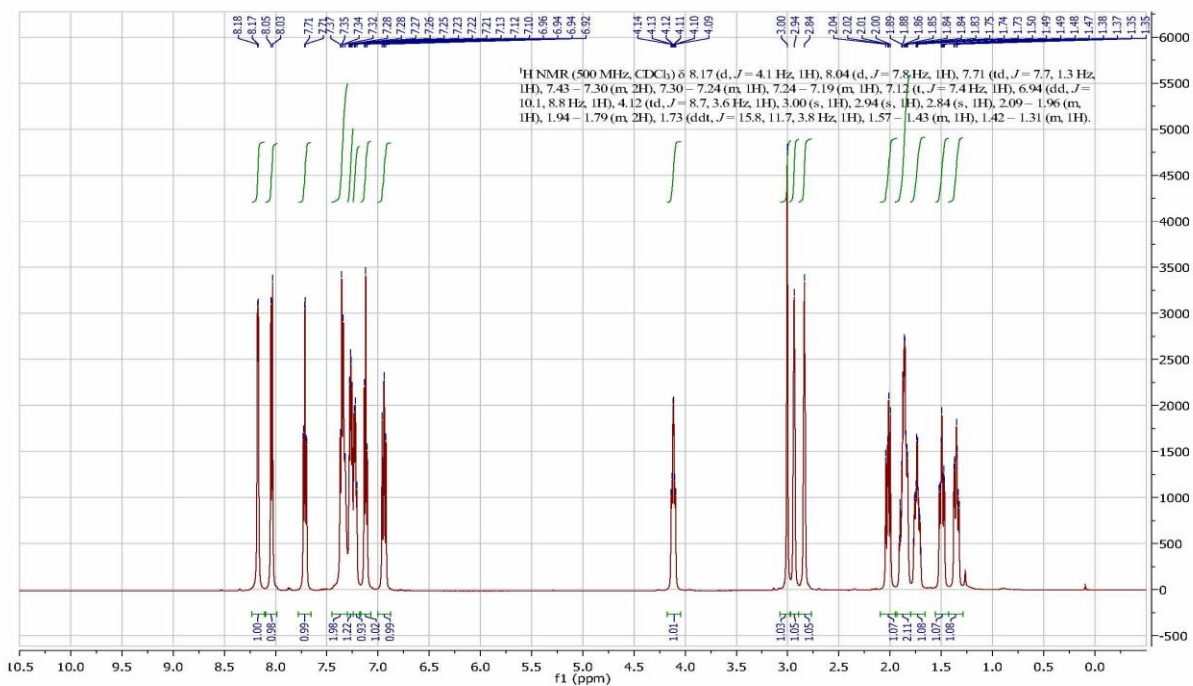
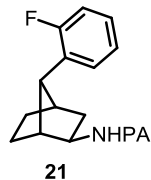


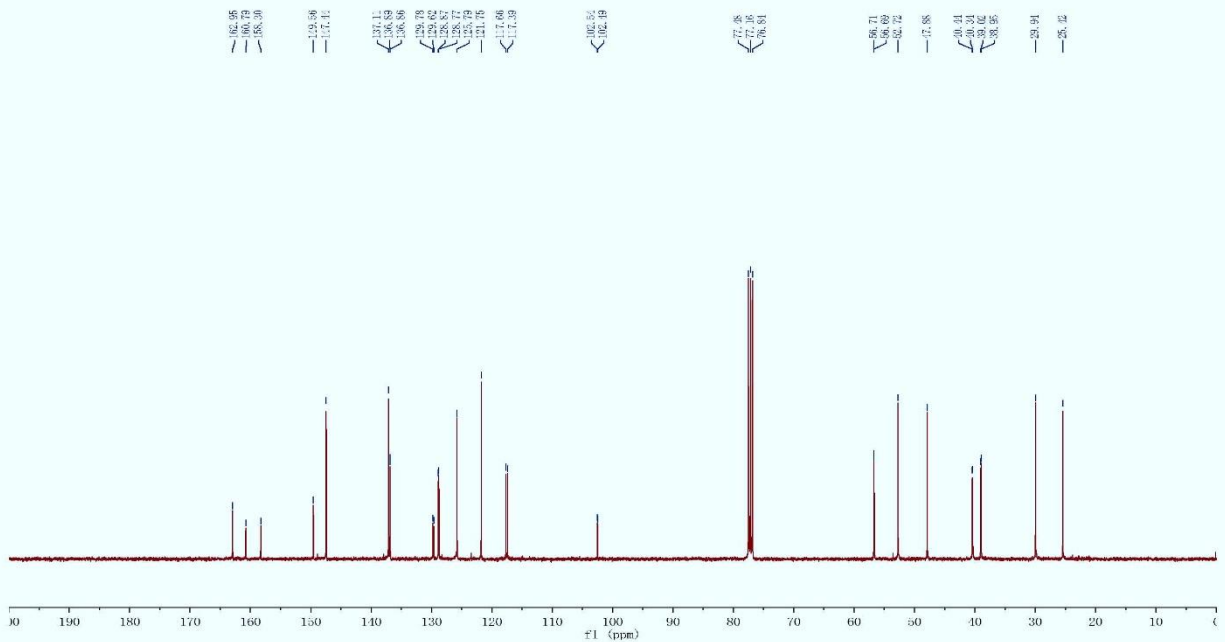
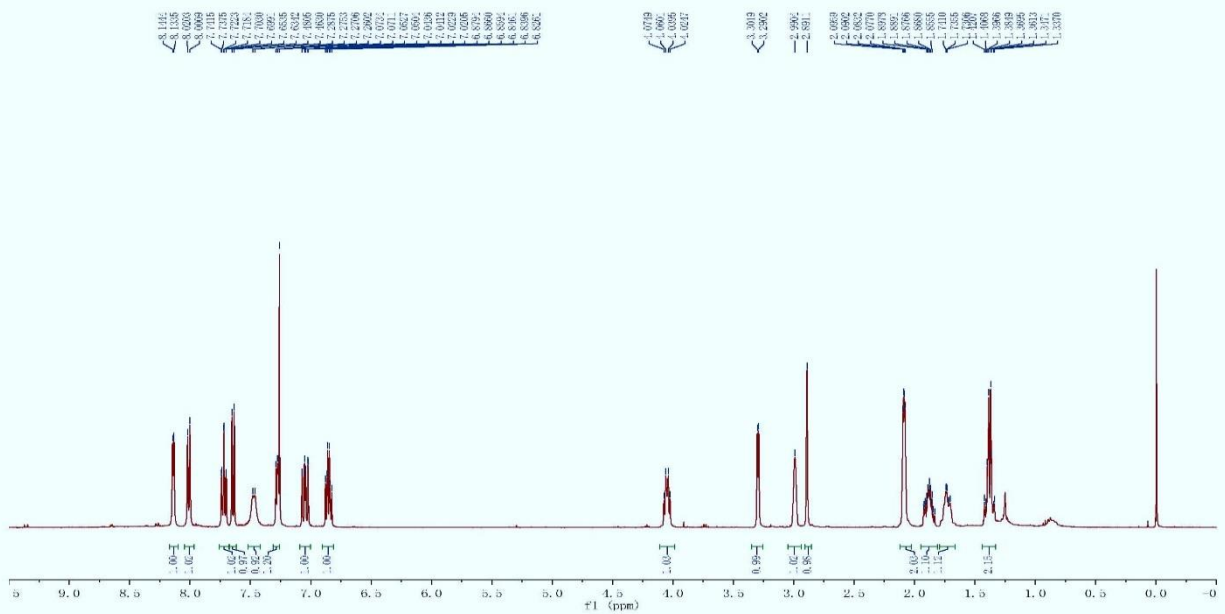
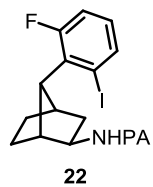


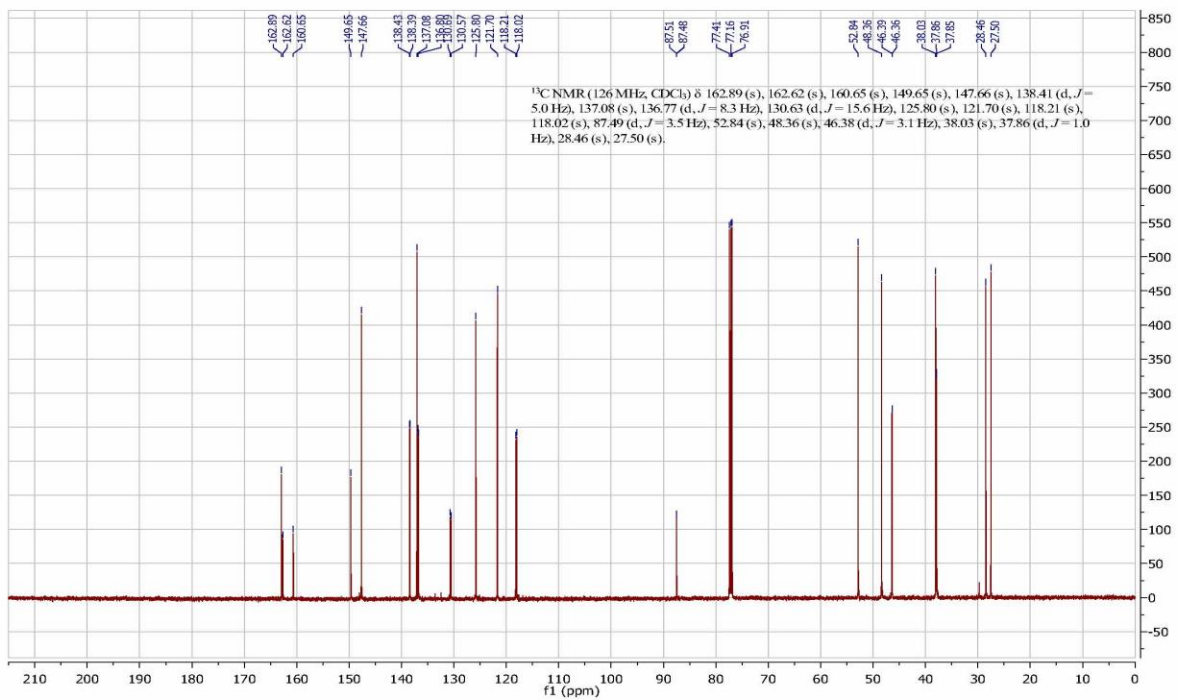
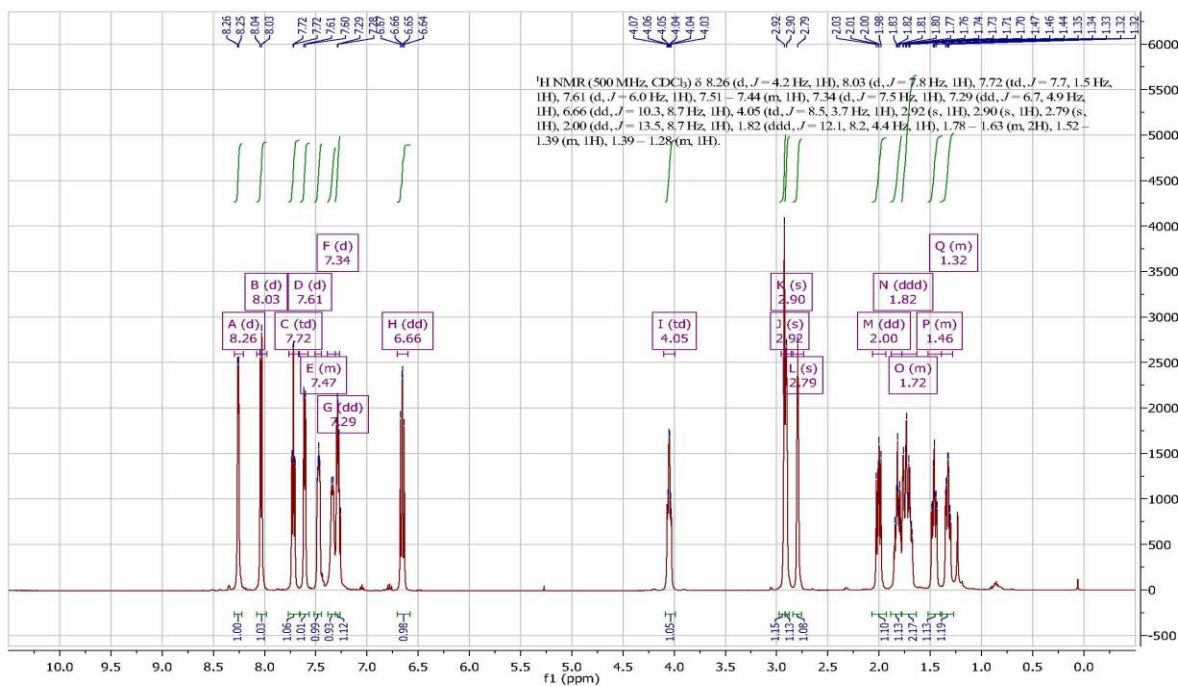
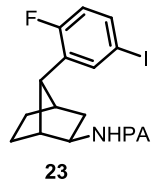


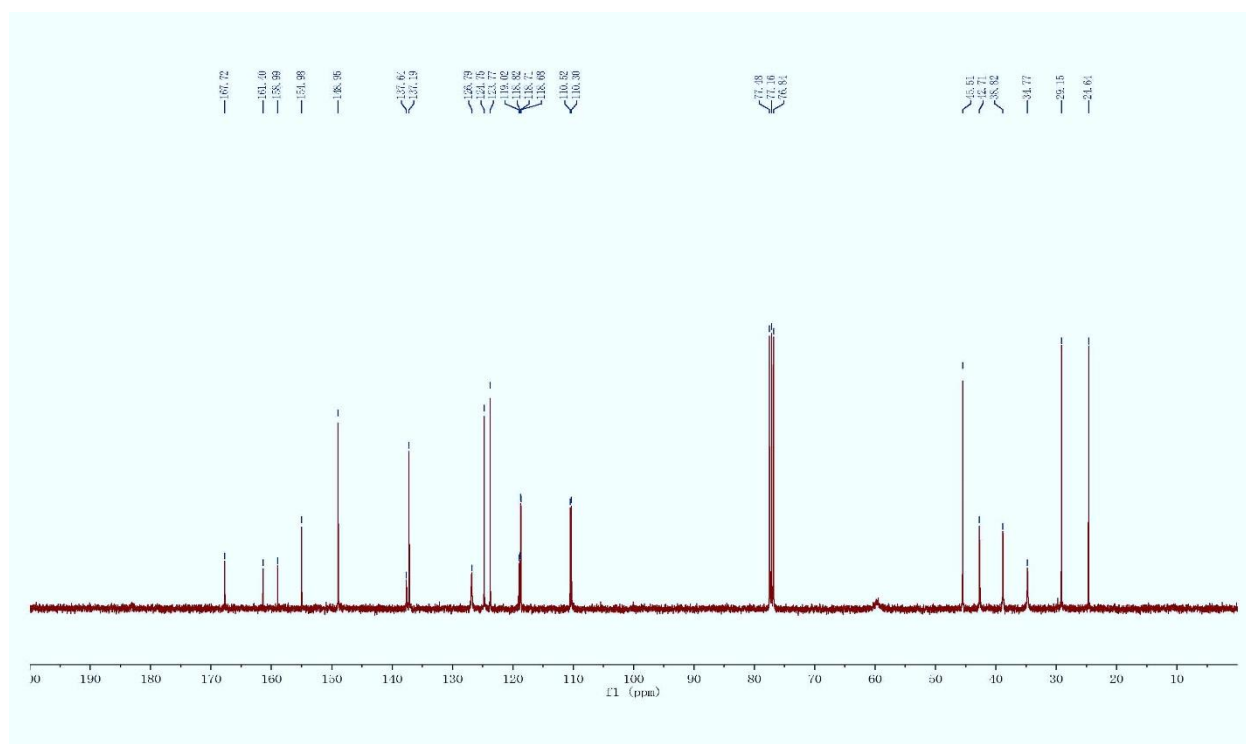
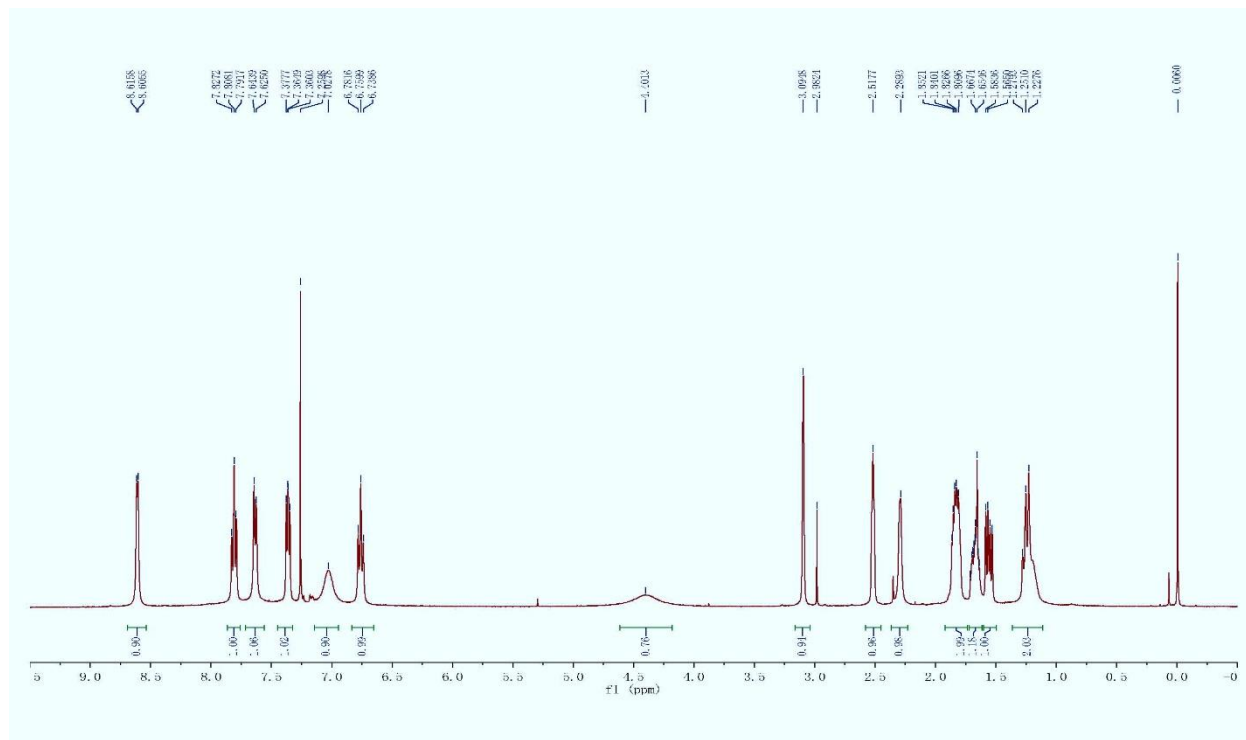
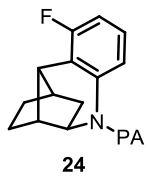


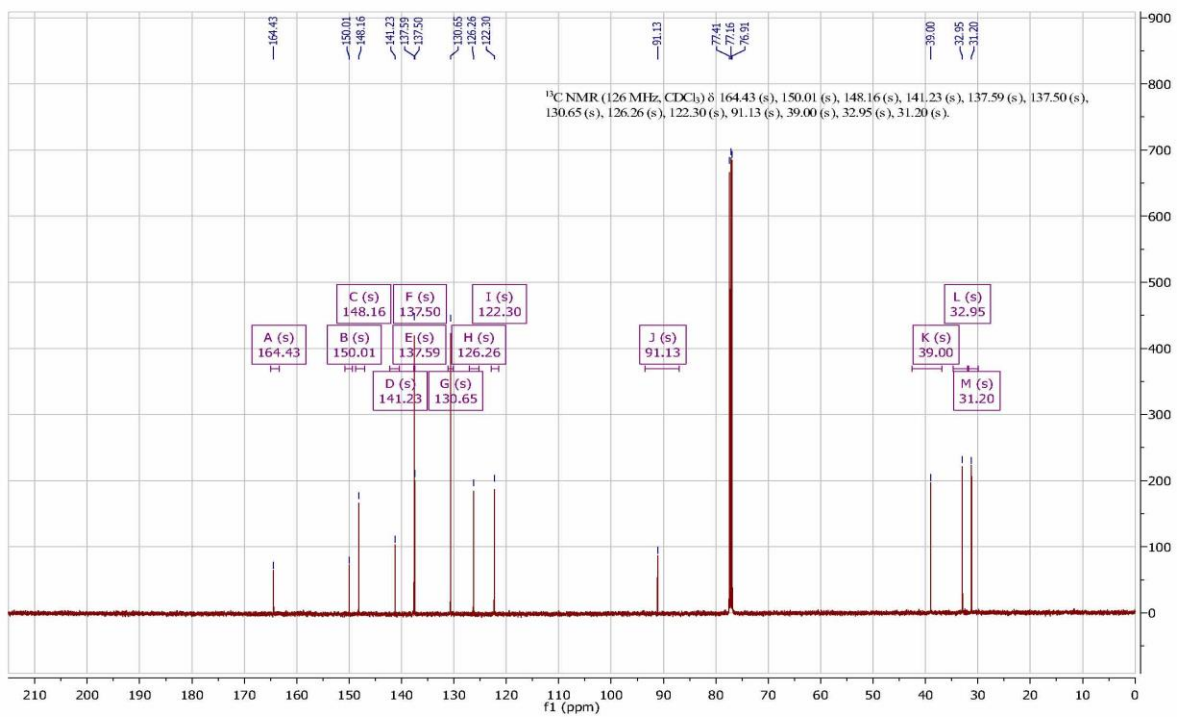
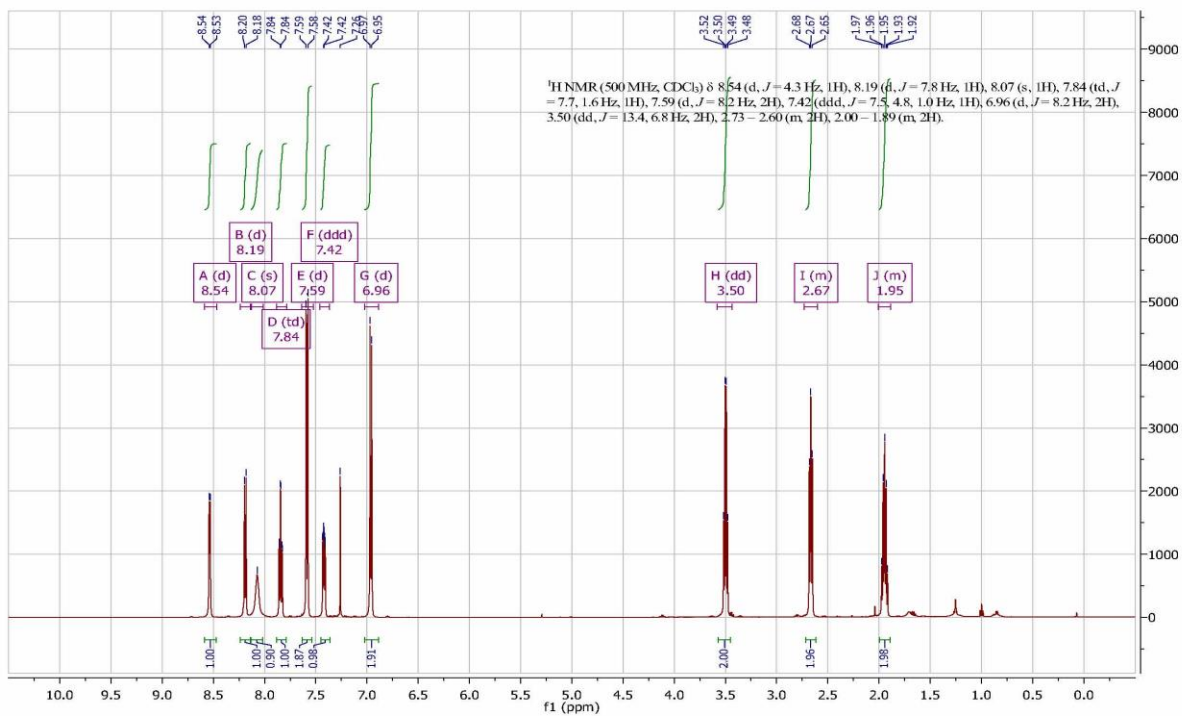
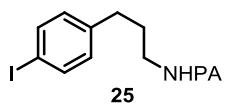


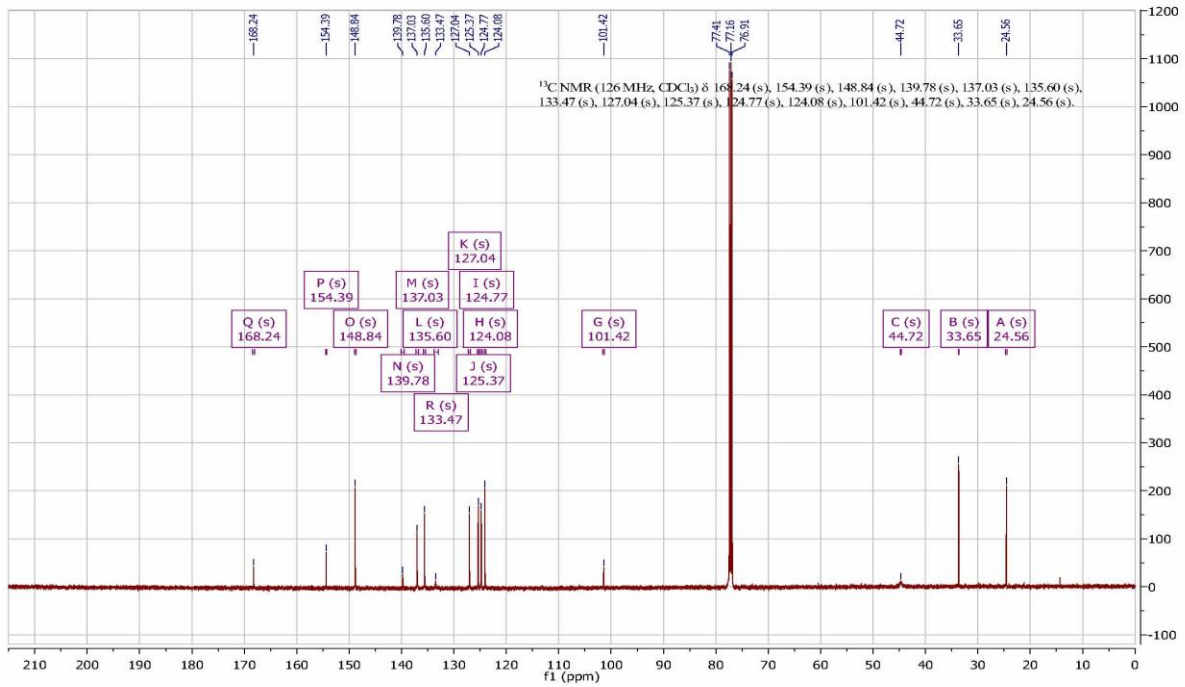
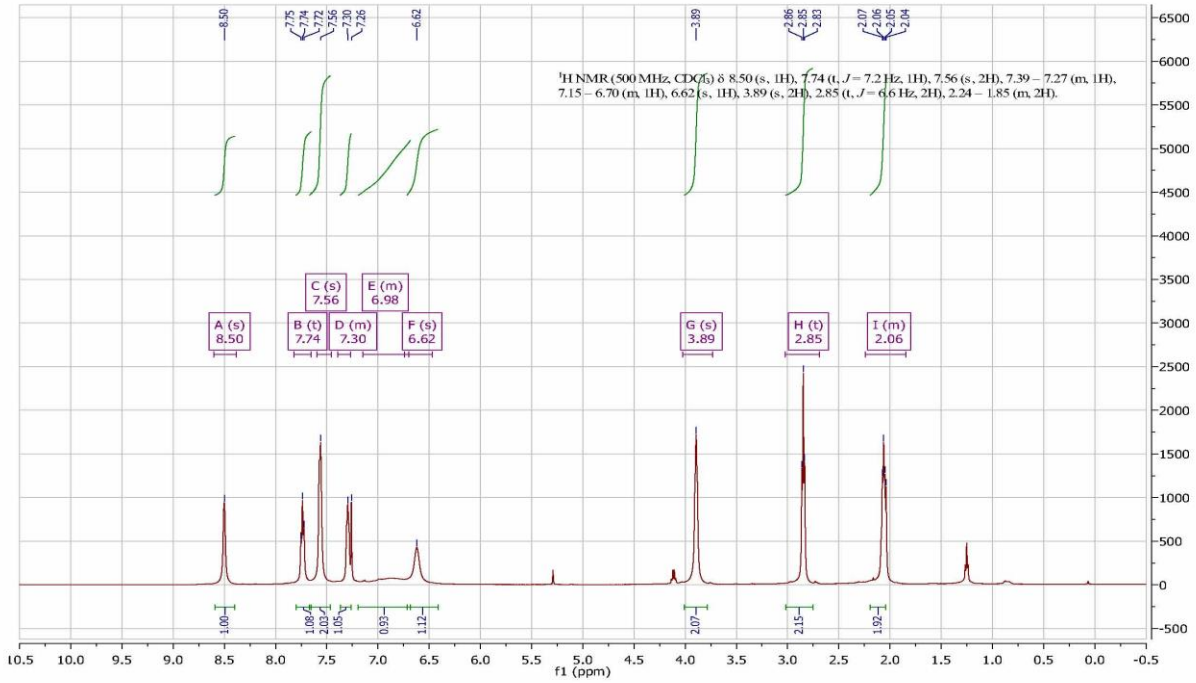
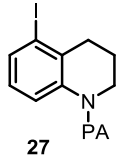


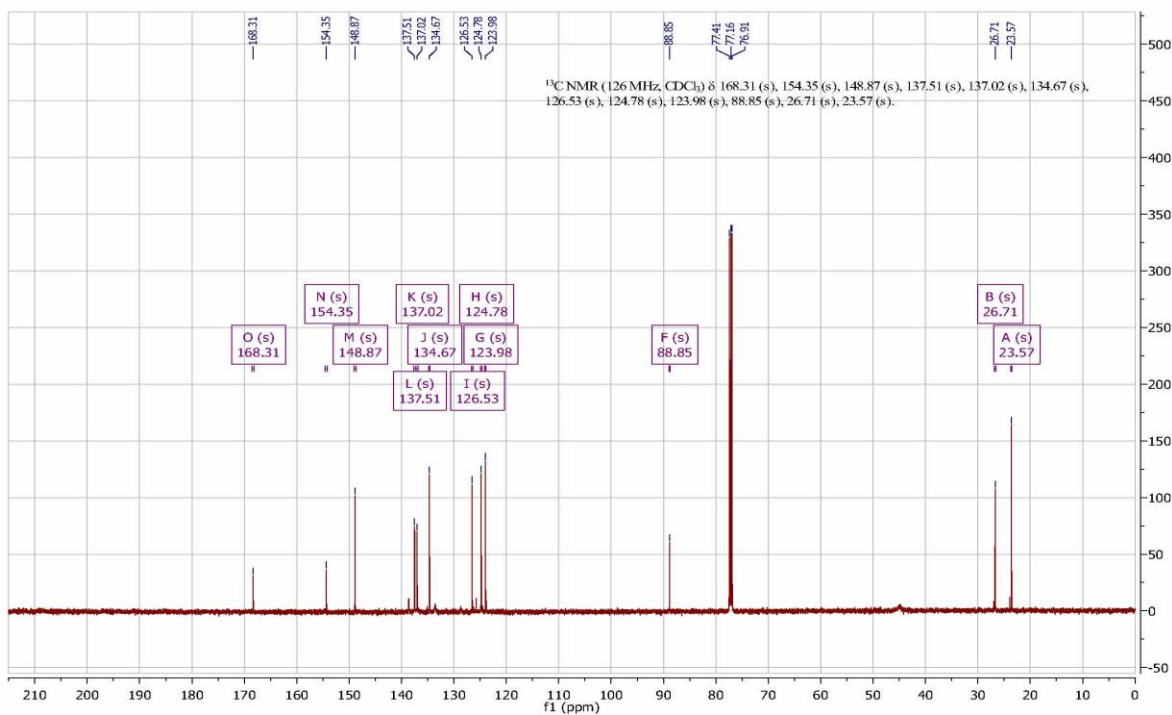
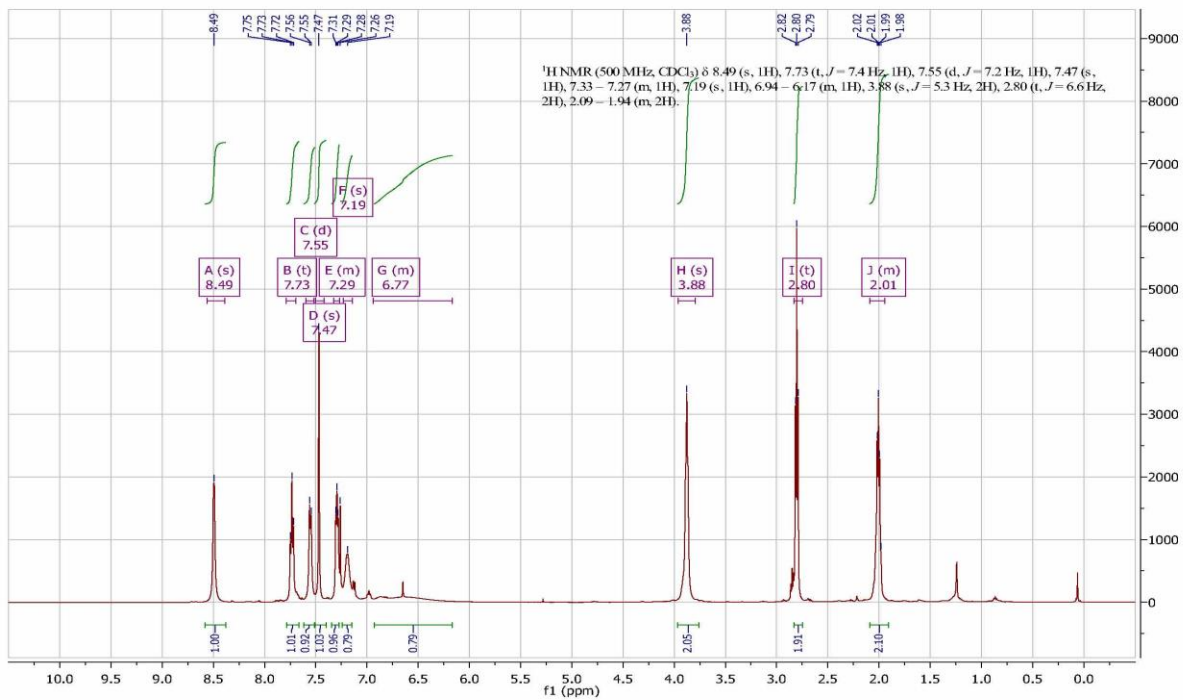
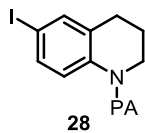


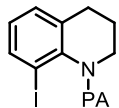




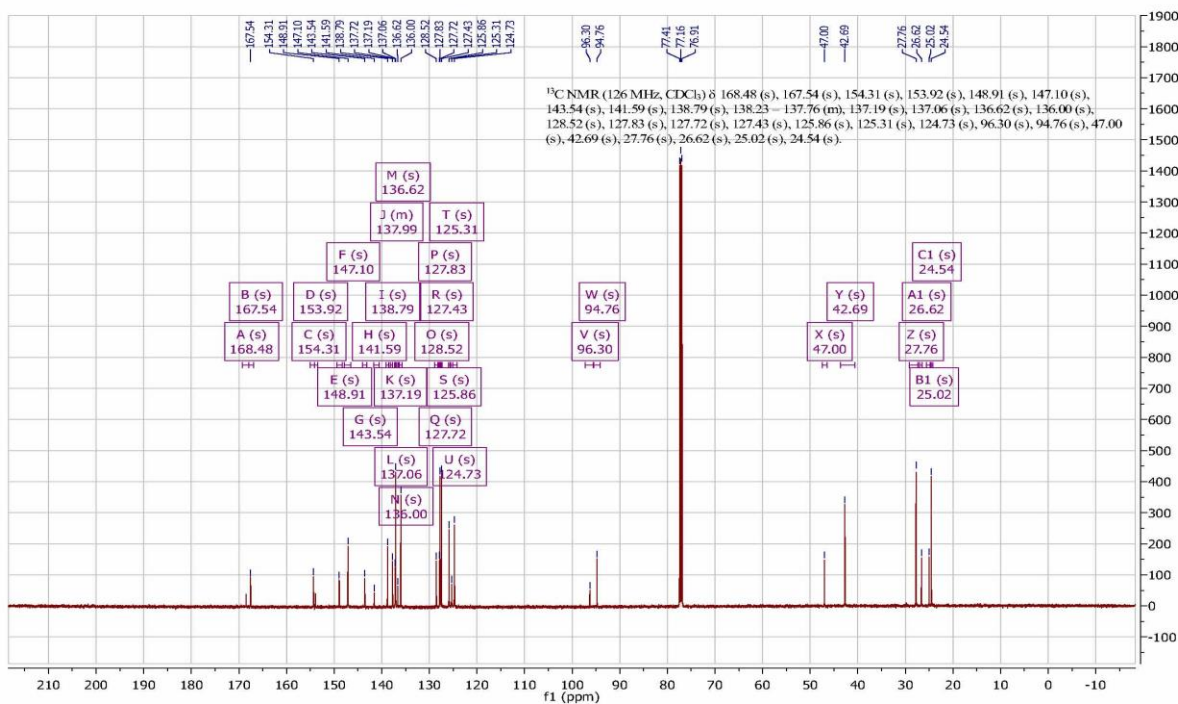
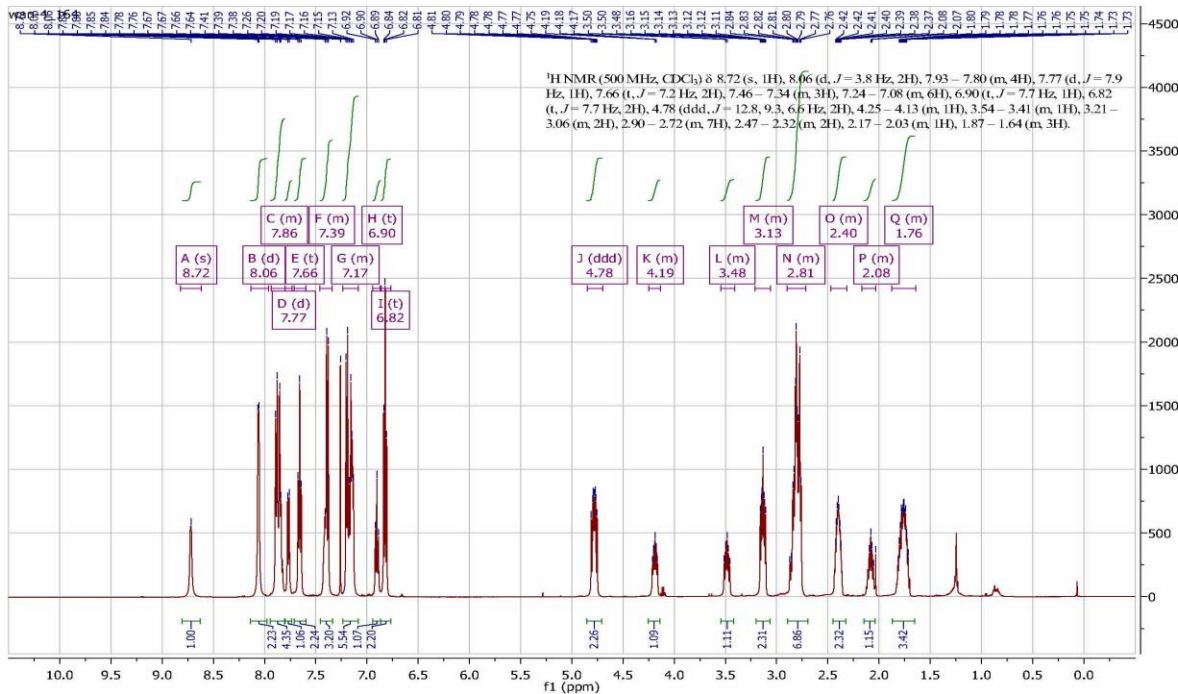


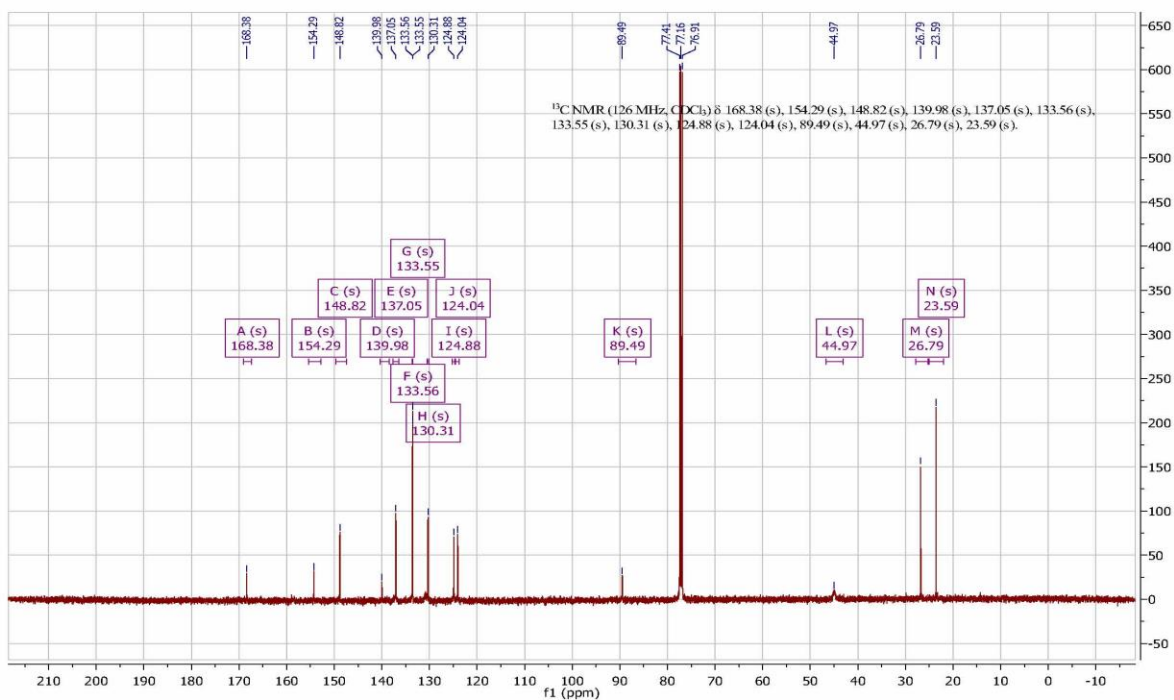
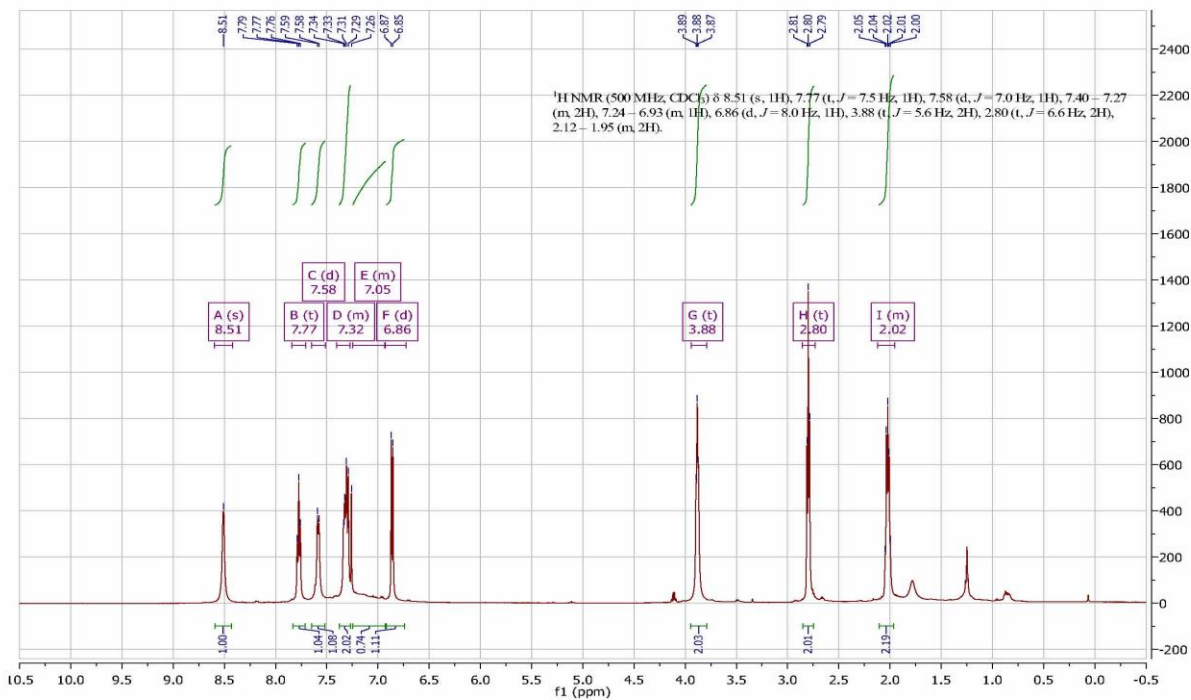
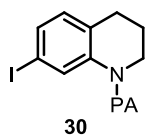


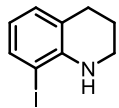




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