

Supporting Information
Monodentate Transient Directing Group Enabled
Pd-Catalyzed *Ortho*-C–H Methoxylation and Chlorination
of Benzaldehydes

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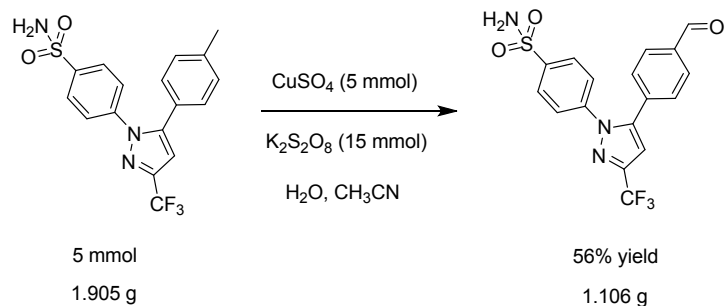
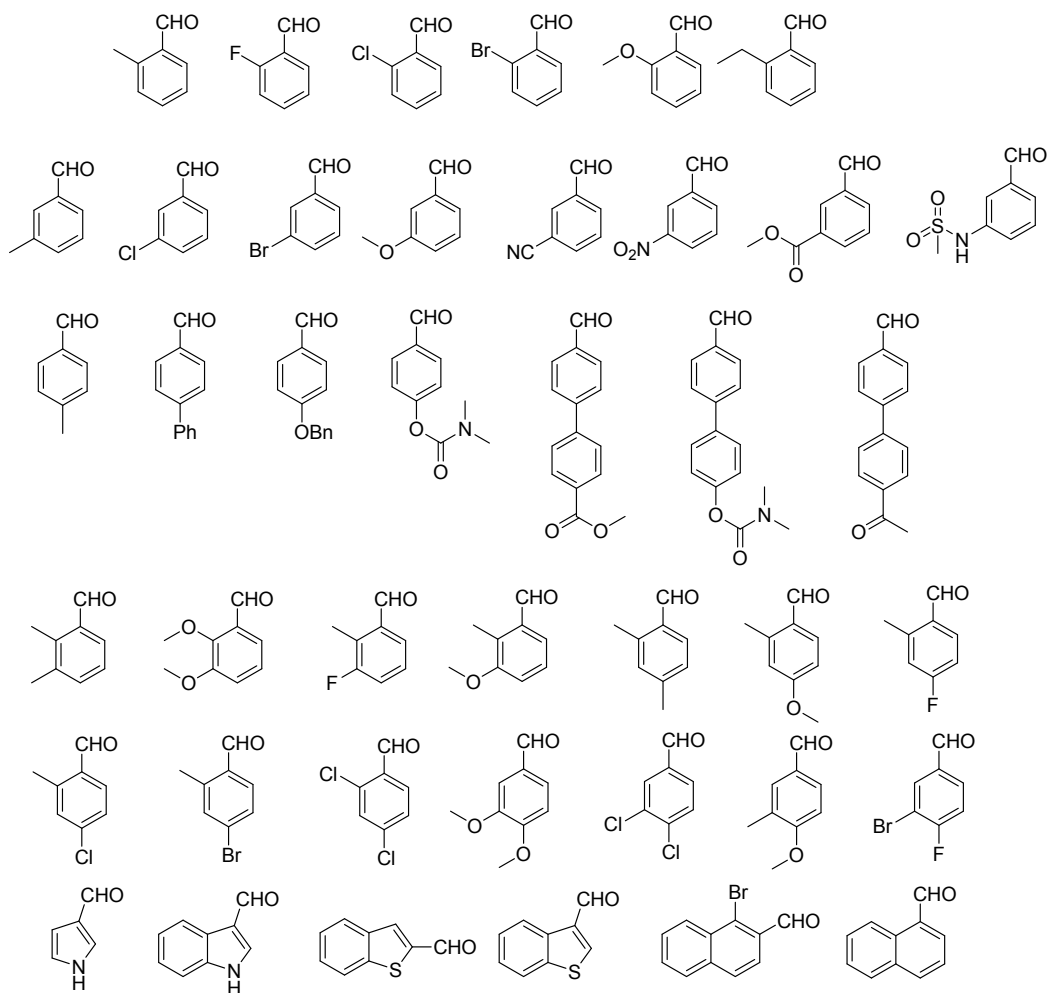
1. General Information

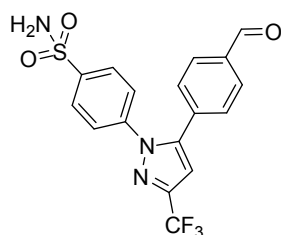
Aldehydes and transient directing groups were obtained from the commercial sources or synthesized following literature procedures. Pd(OAc)₂ was obtained from Strem. Solvents were obtained from Sigma-Aldrich, Alfa-Aesar, Oakwood, and Acros and used directly without further purification. Analytical thin layer chromatography was performed on 0.25 mm silica gel 60-F254. Visualization was carried out with UV light. ¹H NMR was recorded on Bruker instrument (400, and 500MHz). Chemical shifts were quoted in parts per million (ppm) referenced to 0.0 ppm for tetramethylsilane. The following abbreviations (or combinations thereof) were used to explain multiplicities: s = singlet, d = doublet, t = triplet, q =quartet, m = multiplet, br = broad. Coupling constants, *J*, were reported in Hertz unit (Hz). ¹³C NMR spectra were recorded on Bruker instrument (101, and 126MHz), and were fully decoupled by broad band proton decoupling. Chemical shifts were reported in ppm referenced to either the center line of a triplet at 77.0 ppm of chloroform-*d* or referenced to the center line of a septet at 39.52 ppm of DMSO-*d*₆. High-resolution mass spectra (HRMS) were recorded on an Agilent Mass spectrometer using ESI-TOF (electrospray ionization-time of flight).

2. Experimental Section

2.1 Preparation of Substrates

- List of substrates





4-(5-(4-formylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl)benzenesulfonamide

1.150 g (5 mmol) of copper sulfate pentahydrate and 4.055 g (15 mmol) of potassium persulfate were dissolved in 40 ml of water to obtain a blue mixed solution. Then, the mixed solution is heated to 65 °C; then, 1.905 g (5 mmol) of celecoxib was dissolved in 20 ml of acetonitrile solvent and added to the mixed solution to obtain a light green solution. Heating the light green solution to reflux for 45 min; Track the reaction by TLC. After completion of the reaction, water and dichloromethane were added to the reaction mixture, and extracted with CH₂Cl₂ for 3 times. The combined organic layers were dried over anhydrous Na₂SO₄, and concentrated in vacuo. The crude residue was purified by column chromatography on silica gel to afford the desired product as a white solid (1.106 g, 56%).

¹H NMR (500 MHz, DMSO) δ 10.00 (s, 1H), 7.93 (d, *J* = 7.1 Hz, 2H), 7.92 (d, *J* = 6.7 Hz, 2H), 7.58 (s, 2H), 7.56 (s, 1H), 7.54 (d, *J* = 4.4 Hz, 2H), 7.52 (s, 1H), 7.29 (s, 1H).

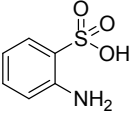
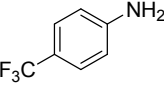
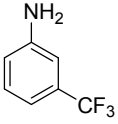
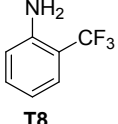
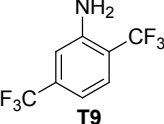
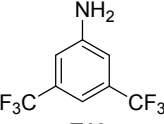
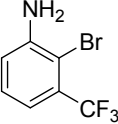
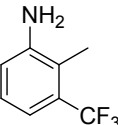
¹³C NMR (126 MHz, DMSO) δ 193.37, 144.46, 144.26, 143.02 (q, *J* = 38.1 Hz), 141.29, 136.47, 133.96, 130.21, 129.94, 127.40, 126.48, 121.40 (q, *J* = 269.4 Hz), 107.49.

HRMS (ESI): *m/z* calculated for C₁₇H₁₃F₃N₃O₃S⁺[M+H]⁺ 396.0630, found 396.0637.

2.2 Optimization of Conditions for Benzaldehyde Methoxylation

Table S1 Screening of Transient DG

| Entry | Transient DG | Yield (%) |
|-------|--------------|-----------|
| 1 | T1 | N.R. |
| 2 | T2 | N.R. |
| 3 | T3 | N.R. |
| 4 | T4 | N.R. |

| | | |
|----|---|-----------|
| 5 |  T5 | N.R. |
| 6 |  T6 | 45 |
| 7 |  T7 | 63 |
| 8 |  T8 | 41 |
| 9 |  T9 | 53 |
| 10 |  T10 | 51 |
| 11 |  T11 | 46 |
| 12 |  T12 | 36 |

Reaction conditions: substrate (0.4 mmol, 1.0 equiv.), MeOH (20.0 equiv.), Pd(OAc)₂ (10 mol%), Transient DG (40 mol%), K₂S₂O₈ (2.0 equiv.), DCE (4.0 mL), 60 °C, 24 h. Isolated yields.

Table S2 Screening of Solvent



| Entry | Solution | Yield (%) |
|----------|--|-----------|
| 1 | MeOH as Solvent | 35 |
| 2 | MeOH:Toluene = 1:1 | 34 |
| 3 | MeOH:DCE = 1:1 | 41 |
| 4 | MeOH:DCM = 1:1 | 43 |
| 5 | MeOH (20.0 equiv.) DCE as solvent | 63 |
| 6 | MeOH (20.0 equiv.) DCM as solvent | 67 |
| 7 | MeOH (10.0 equiv.) DCM as solvent | 58 |
| 8 | MeOH (30.0 equiv.) DCM as solvent | 64 |

Reaction conditions: substrate (0.4 mmol, 1.0 equiv.), Pd(OAc)₂ (10 mol%), **T7** (40 mol%), K₂S₂O₈ (2.0 equiv.), solution (4.0 mL), 60 °C, 24 h. Isolated yields.

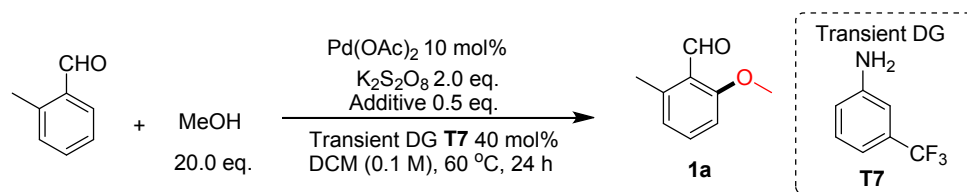
Table S3 Screening of Oxidant



| Entry | Oxidant (2.0 equiv.) | Yield (%) |
|----------|--|-----------|
| 1 | Na ₂ S ₂ O ₈ | 49 |
| 2 | PhI(OAc) ₂ | trace |
| 3 | Cu(OAc) ₂ | N.R. |
| 4 | AgTFA | N.R. |
| 5 | Ag ₂ CO ₃ | N.R. |
| 6 | AgNTf ₂ | N.R. |
| 7 | / | N.R. |
| 8 | K₂S₂O₈ | 67 |

Reaction conditions: substrate (0.4 mmol, 1.0 equiv.), MeOH (20.0 equiv.), Pd(OAc)₂ (10 mol%), **T7** (40 mol%), oxidant (2.0 equiv.), DCM (4.0 mL), 60 °C, 24 h. Isolated yields.

Table S4 Screening of Additive

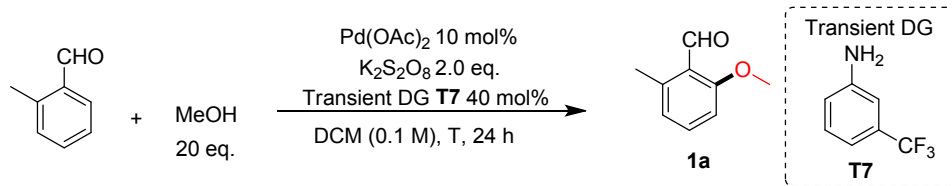


| Entry | Additive (0.5 equiv.) | Yield (%) |
|----------|-----------------------|-----------|
| 1 | 3-methylbenzoic acid | 55 |
| 2 | AcOH | 46 |
| 3 | MsOH | 52 |
| 4 | TfOH | 47 |
| 5 | / | 67 |

Reaction conditions: substrate (0.4 mmol, 1.0 equiv.), MeOH (20.0 equiv.), Pd(OAc)₂ (10 mol%), **T7** (40 mol%), K₂S₂O₈ (2.0 equiv.), additive (0.5 equiv.) DCM (4.0 mL), 60 °C, 24 h.

Isolated yields.

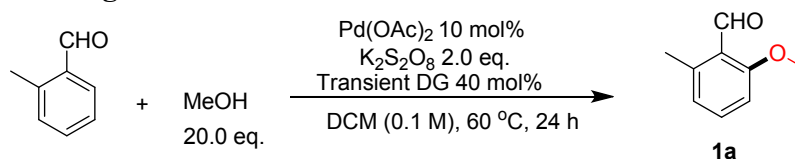
Table S5 Screening Temperature

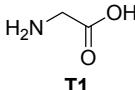
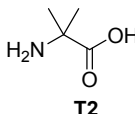
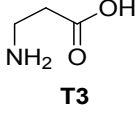
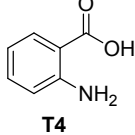
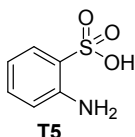


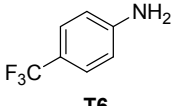
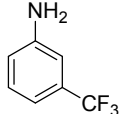
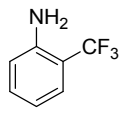
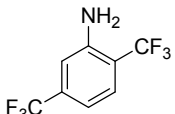
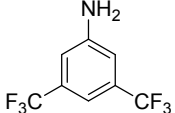
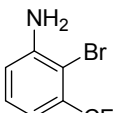
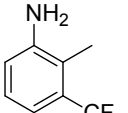
| Entry | T (°C) | Yield (%) |
|----------|-----------|-----------|
| 1 | 25 | 10 |
| 2 | 30 | 17 |
| 3 | 40 | 37 |
| 4 | 50 | 48 |
| 5 | 60 | 67 |
| 6 | 70 | 65 |
| 7 | 80 | 62 |

Reaction conditions: substrate (0.4 mmol, 1.0 equiv.), MeOH (20.0 equiv.), Pd(OAc)₂ (10 mol%), **T7** (40 mol%), K₂S₂O₈ (2.0 equiv.), DCM (4.0 mL), T °C, 24 h. Isolated yields.

Table S6 Screening of Transient DG When DCM as Solution



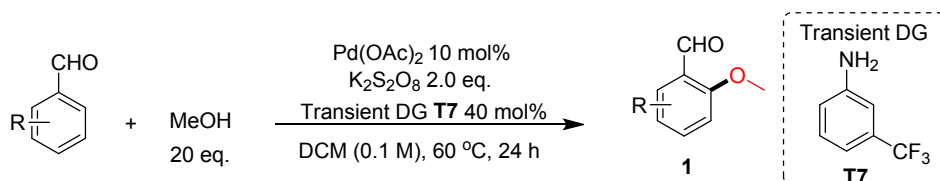
| Entry | Transient DG | Yield (%) |
|-------|--|-----------|
| 1 |  T1 | N.R. |
| 2 |  T2 | N.R. |
| 3 |  T3 | N.R. |
| 4 |  T4 | N.R. |
| 5 |  T5 | N.R. |

| | | |
|----|---|----|
| 6 |  <p style="text-align: center;">T6</p> | 50 |
| 7 |  <p style="text-align: center;">T7</p> | 67 |
| 8 |  <p style="text-align: center;">T8</p> | 45 |
| 9 |  <p style="text-align: center;">T9</p> | 59 |
| 10 |  <p style="text-align: center;">T10</p> | 55 |
| 11 |  <p style="text-align: center;">T11</p> | 52 |
| 12 |  <p style="text-align: center;">T12</p> | 40 |

Reaction conditions: substrate (0.4 mmol, 1.0 equiv.), MeOH (20.0 equiv.), Pd(OAc)₂ (10 mol%), Transient DG (40 mol%), K₂S₂O₈ (2.0 equiv.), DCM (4.0 mL), 60 °C, 24 h. Isolated yields.

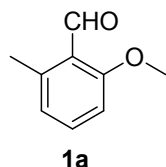
2.3 General Procedure for the *ortho*-C(sp²)-H Methoxylation of Benzaldehydes

General Procedure A (GP A)



A sealed tube with magnetic stir bar was charged with benzaldehyde (0.4 mmol), Pd(OAc)₂,

(0.04 mmol, 9.0 mg), $K_2S_2O_8$ (0.8 mmol, 216.0 mg) in air, followed by CH_2Cl_2 (4.0 mL), alcohols (8.0 mmol) and **T7** (0.16 mmol, 25.8 mg). The reaction mixture was stirred at 60 °C for 24 hours. Upon completion, the reaction mixture was cooled to room temperature and filtered through a sand funnel. Next the reaction mixture was quenched by sat. $NaHCO_3$ (aq) (10 mL), and extracted with CH_2Cl_2 for 3 times. The combined organic layers were washed with water (15 mL), dried over anhydrous Na_2SO_4 , and concentrated *in vacuo*. The crude residue was purified by column chromatography on silica gel using petroleum ether/EtOAc as eluent to afford the desired products.



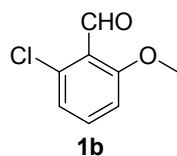
2-methoxy-6-methylbenzaldehyde

The compound **1a** was prepared according to **GP A** in 0.4 mmol scale to give white solid in 67% yield (40.2 mg). Purified by column chromatography (Petroleum ether/EtOAc = 10:1).

1H NMR (500 MHz, $CDCl_3$) δ 10.63 (s, 1H), 7.37 (t, $J = 8.0$ Hz, 1H), 6.82 (d, $J = 8.4$ Hz, 1H), 6.79 (d, $J = 7.6$ Hz, 1H), 3.88 (s, 3H), 2.56 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 192.32, 163.17, 142.03, 134.43, 124.09, 123.36, 109.05, 55.77, 21.44.

HRMS (ESI): m/z calculated for $C_9H_{11}O_2^+[M+H]^+$ 151.0759, found 151.0753.



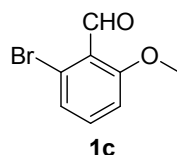
2-chloro-6-methoxybenzaldehyde

The compound **1b** was prepared according to **GP A** in 0.4 mmol scale to give red solid in 46% yield (31.3 mg). Purified by column chromatography (Petroleum ether/EtOAc = 10:1).

1H NMR (500 MHz, $CDCl_3$) δ 10.51 (s, 1H), 7.40 (t, $J = 8.1$ Hz, 1H), 7.03 (d, $J = 8.0$ Hz, 1H), 6.91 (d, $J = 8.4$ Hz, 1H), 3.92 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 189.22, 162.02, 136.60, 134.61, 123.13, 122.34, 110.34, 56.27.

HRMS (ESI): m/z calculated for $C_8H_8ClO_2^+[M+H]^+$ 171.0213, found 171.0218.



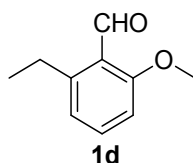
2-bromo-6-methoxybenzaldehyde

The compound **1c** was prepared according to **GP A** in 0.4 mmol scale to give light yellow solid in 48% yield (41.1 mg). Purified by column chromatography (Petroleum ether/EtOAc = 10:1).

^1H NMR (500 MHz, CDCl_3) δ 10.41 (s, 1H), 7.32 (t, $J = 8.2$ Hz, 1H), 7.24 (d, $J = 7.9$ Hz, 1H), 6.95 (d, $J = 8.3$ Hz, 1H), 3.91 (s, 3H).

^{13}C NMR (126 MHz, CDCl_3) δ 190.41, 161.95, 134.76, 126.50, 124.92, 123.50, 111.04, 56.23.

HRMS (ESI): m/z calculated for $\text{C}_8\text{H}_8\text{BrO}_2^+[\text{M}+\text{H}]^+$ 214.9708, found 214.9701.



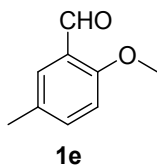
2-ethyl-6-methoxybenzaldehyde

The compound **1d** was prepared according to **GP A** in 0.4 mmol scale to give yellow oil in 63% yield (41.3 mg). Purified by column chromatography (Petroleum ether/EtOAc = 10:1).

^1H NMR (500 MHz, CDCl_3) δ 10.62 (s, 1H), 7.41 (t, $J = 8.0$ Hz, 1H), 6.84 (d, $J = 5.5$ Hz, 1H), 6.83 (d, $J = 7.7$ Hz, 1H), 3.89 (s, 3H), 2.97 (q, $J = 7.5$ Hz, 2H), 1.19 (t, $J = 7.5$ Hz, 3H).

^{13}C NMR (126 MHz, CDCl_3) δ 192.17, 163.18, 148.21, 134.62, 122.94, 122.50, 109.03, 55.79, 26.96, 15.50.

HRMS (ESI): m/z calculated for $\text{C}_{10}\text{H}_{13}\text{O}_2^+[\text{M}+\text{H}]^+$ 165.0916, found 165.0911.



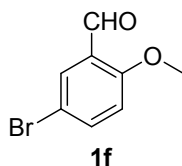
2-methoxy-5-methylbenzaldehyde

The compound **1e** was prepared according to **GP A** in 0.4 mmol scale to give white solid in 47% yield (28.2 mg). Purified by column chromatography (Petroleum ether/EtOAc = 10:1).

^1H NMR (500 MHz, CDCl_3) δ 10.44 (s, 1H), 7.63 (s, 1H), 7.35 (d, $J = 8.4$ Hz, 1H), 6.89 (d, $J = 8.5$ Hz, 1H), 3.90 (s, 3H), 2.31 (s, 3H).

^{13}C NMR (126 MHz, CDCl_3) δ 190.01, 160.00, 136.57, 130.06, 128.60, 124.52, 111.63, 20.23.

HRMS (ESI): m/z calculated for $\text{C}_9\text{H}_{11}\text{O}_2^+[\text{M}+\text{H}]^+$ 151.0759, found 151.0752.



5-bromo-2-methoxybenzaldehyde

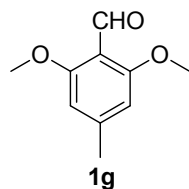
The compound **1f** was prepared according to **GP A** in 0.4 mmol scale to give light yellow solid in 30% yield (25.7 mg). Purified by column chromatography (Petroleum ether/EtOAc = 10:1).

^1H NMR (500 MHz, CDCl_3) δ 10.38 (s, 1H), 7.92 (s, 1H), 7.63 (d, $J = 8.8$ Hz, 1H), 6.89 (d, J

= 8.8 Hz, 1H), 3.92 (s, 3H).

^{13}C NMR (126 MHz, CDCl_3) δ 188.34, 160.74, 138.27, 131.10, 126.13, 113.71, 113.49, 55.98.

HRMS (ESI): m/z calculated for $\text{C}_8\text{H}_8\text{BrO}_2^+[\text{M}+\text{H}]^+$ 214.9708, found 214.9714.



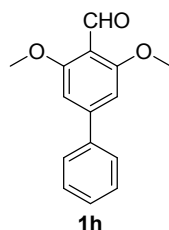
2,6-dimethoxy-4-methylbenzaldehyde

The compound **1g** was prepared according to **GP A** in 0.4 mmol scale to give white solid in 27% yield (19.4 mg). Purified by column chromatography (Petroleum ether/EtOAc = 10:1).

^1H NMR (500 MHz, CDCl_3) δ 10.44 (s, 1H), 6.38 (s, 2H), 3.88 (s, 6H), 2.37 (s, 3H).

^{13}C NMR (126 MHz, CDCl_3) δ 188.96, 162.26, 147.55, 112.14, 104.70, 55.97, 22.89.

HRMS (ESI): m/z calculated for $\text{C}_{10}\text{H}_{13}\text{O}_3^+[\text{M}+\text{H}]^+$ 181.0865, found 181.0861.



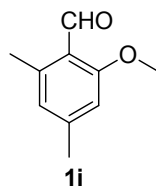
3,5-dimethoxy-[1,1'-biphenyl]-4-carbaldehyde

The compound **1h** was prepared according to **GP A** in 0.4 mmol scale to give white solid in 31% yield (30.0 mg). Purified by column chromatography (Petroleum ether/EtOAc = 5:1).

^1H NMR (400 MHz, CDCl_3) δ 10.53 (s, 1H), 7.60 (d, $J = 7.1$ Hz, 2H), 7.53 – 7.38 (m, 3H), 6.76 (s, 2H), 3.96 (s, 6H).

^{13}C NMR (126 MHz, CDCl_3) δ 189.05, 162.42, 149.21, 140.46, 128.95, 128.72, 127.24, 113.11, 103.04, 56.15.

HRMS (ESI): m/z calculated for $\text{C}_{15}\text{H}_{15}\text{O}_3^+[\text{M}+\text{H}]^+$ 243.1021, found 243.1027.



2-methoxy-4,6-dimethylbenzaldehyde

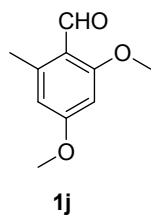
The compound **1i** was prepared according to **GP A** in 0.4 mmol scale to give light yellow solid in 65% yield (42.6 mg). Purified by column chromatography (Petroleum ether/EtOAc = 10:1).

^1H NMR (500 MHz, CDCl_3) δ 10.57 (s, 1H), 6.63 (s, 1H), 6.61 (s, 1H), 3.87 (s, 3H), 2.53 (s, 3H), 2.34 (s, 3H).

^{13}C NMR (126 MHz, CDCl_3) δ 191.75, 163.35, 145.68, 142.00, 125.02, 120.99, 109.76, 55.70,

22.15, 21.49.

HRMS (ESI): m/z calculated for $C_{10}H_{13}O_2^+[M+H]^+$ 165.0916, found 165.0923.

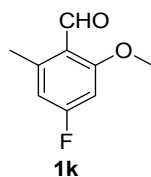


2,4-dimethoxy-6-methylbenzaldehyde

The compound **1j** was prepared according to **GP A** in 0.4 mmol scale to give light yellow oil in 60% yield (43.2 mg). Purified by column chromatography (Petroleum ether/EtOAc = 10:1). 1H NMR (500 MHz, $CDCl_3$) δ 10.47 (s, 1H), 6.31 (s, 2H), 3.87 (s, 3H), 3.85 (s, 3H), 2.57 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 190.48, 165.17, 164.42, 144.68, 117.39, 108.78, 95.78, 55.75, 55.41, 22.27.

HRMS (ESI): m/z calculated for $C_{10}H_{13}O_3^+[M+H]^+$ 181.0865, found 181.0859.



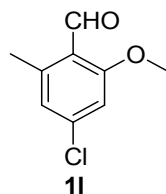
4-fluoro-2-methoxy-6-methylbenzaldehyde

The compound **1k** was prepared according to **GP A** in 0.4 mmol scale to give light yellow solid in 40% yield (26.9 mg). Purified by column chromatography (Petroleum ether/EtOAc = 10:1).

1H NMR (500 MHz, $CDCl_3$) δ 10.53 (s, 1H), 6.56-6.50 (m, 2H), 3.89 (s, 3H), 2.57 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 190.67, 166.11 (d, $J = 245.4$ Hz), 165.05 (d, $J = 2.0$ Hz), 145.27 (d, $J = 11.0$ Hz), 120.02, 110.95 (d, $J = 27.3$ Hz), 97.23 (d, $J = 25.3$ Hz), 56.07, 21.89.

HRMS (ESI): m/z calculated for $C_9H_{10}FO_2^+[M+H]^+$ 169.0665, found 169.0669.



4-chloro-2-methoxy-6-methylbenzaldehyde

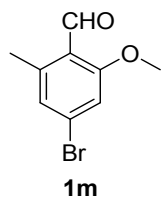
The compound **1l** was prepared according to **GP A** in 0.4 mmol scale to give light yellow solid in 35% yield (25.8 mg). Purified by column chromatography (Petroleum ether/EtOAc = 10:1).

1H NMR (500 MHz, $CDCl_3$) δ 10.55 (s, 1H), 6.83 (s, 1H), 6.82 (s, 1H), 3.90 (s, 3H), 2.55 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 191.15, 163.54, 143.61, 140.10, 124.18, 121.76, 109.83, 56.09,

21.43.

HRMS (ESI): m/z calculated for $C_9H_{10}ClO_2^+[M+H]^+$ 185.0369, found 185.0361.



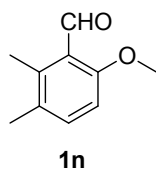
4-bromo-2-methoxy-6-methylbenzaldehyde

The compound **1m** was prepared according to **GP A** in 0.4 mmol scale to give light yellow solid in 26% yield (23.7 mg). Purified by column chromatography (Petroleum ether/EtOAc = 10:1).

1H NMR (500 MHz, $CDCl_3$) δ 10.55 (s, 1H), 6.99 (s, 2H), 3.90 (s, 3H), 2.54 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 191.33, 163.28, 143.59, 128.72, 127.16, 122.12, 112.81, 56.12, 21.29.

HRMS (ESI): m/z calculated for $C_9H_{10}BrO_2^+[M+H]^+$ 228.9864, found 228.9869.



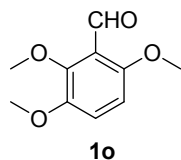
6-methoxy-2,3-dimethylbenzaldehyde

The compound **1n** was prepared according to **GP A** in 0.4 mmol scale to give light yellow solid in 75% yield (49.2 mg). Purified by column chromatography (Petroleum ether/EtOAc = 10:1).

1H NMR (500 MHz, $CDCl_3$) δ 10.63 (s, 1H), 7.27 (d, $J = 10.6$ Hz, 1H), 6.73 (d, $J = 8.5$ Hz, 1H), 3.86 (s, 3H), 2.47 (s, 3H), 2.24 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 193.31, 161.36, 139.77, 135.70, 129.88, 123.87, 108.41, 55.75, 19.56, 16.23.

HRMS (ESI): m/z calculated for $C_{10}H_{13}O_2^+[M+H]^+$ 165.0916, found 165.0911.



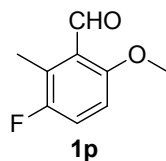
2,3,6-trimethoxybenzaldehyde

The compound **1o** was prepared according to **GP A** in 0.4 mmol scale to give light yellow oil in 50% yield (39.2 mg). Purified by column chromatography (Petroleum ether/EtOAc = 10:1).

1H NMR (500 MHz, $CDCl_3$) δ 10.44 (s, 1H), 7.08 (d, $J = 9.1$ Hz, 1H), 6.64 (d, $J = 9.1$ Hz, 1H), 3.91 (s, 3H), 3.84 (s, 6H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 189.76, 154.94, 152.16, 146.85, 119.76, 119.24, 106.43, 62.04, 56.80, 56.24.

HRMS (ESI): m/z calculated for $C_{10}H_{13}O_4^+[M+H]^+$ 197.0814, found 197.0817.



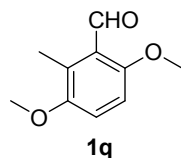
3-fluoro-6-methoxy-2-methylbenzaldehyde

The compound **1p** was prepared according to **GP A** in 0.4 mmol scale to give light yellow solid in 52% yield (34.9 mg). Purified by column chromatography (Petroleum ether/EtOAc = 10:1).

^1H NMR (500 MHz, CDCl_3) δ 10.57 (s, 1H), 7.21-7.15 (m, 1H), 6.81-6.75 (m, 1H), 3.88 (s, 3H), 2.47 (s, 3H).

^{13}C NMR (126 MHz, CDCl_3) δ 191.96 (d, $J = 2.1$ Hz), 159.14 (d, $J = 1.8$ Hz), 155.42 (d, $J = 238.0$ Hz), 127.90 (d, $J = 18.0$ Hz), 124.10 (d, $J = 3.3$ Hz), 120.64 (d, $J = 26.1$ Hz), 109.49 (d, $J = 8.2$ Hz), 56.18, 11.51 (d, $J = 6.0$ Hz).

HRMS (ESI): m/z calculated for $\text{C}_9\text{H}_9\text{FO}_2^+[\text{M}+\text{H}]^+$ 169.0665, found 169.0662.



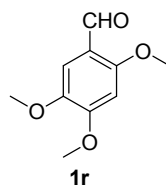
3,6-dimethoxy-2-methylbenzaldehyde

The compound **1q** was prepared according to **GP A** in 0.4 mmol scale to give light yellow solid in 70% yield (50.4 mg). Purified by column chromatography (Petroleum ether/EtOAc = 10:1).

^1H NMR (400 MHz, CDCl_3) δ 10.60 (s, 1H), 7.01 (d, $J = 9.0$ Hz, 1H), 6.77 (d, $J = 9.0$ Hz, 1H), 3.84 (s, 3H), 3.79 (s, 3H), 2.45 (s, 3H).

^{13}C NMR (126 MHz, CDCl_3) δ 192.97, 156.97, 151.96, 130.38, 124.50, 116.86, 108.85, 56.57, 56.11, 12.18.

HRMS (ESI): m/z calculated for $\text{C}_{10}\text{H}_{13}\text{O}_3^+[\text{M}+\text{H}]^+$ 181.0865, found 181.0864.



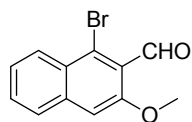
2,4,5-trimethoxybenzaldehyde

The compound **1r** was prepared according to **GP A** in 0.4 mmol scale to give white solid in 33% yield (25.9 mg). Purified by column chromatography (Petroleum ether/EtOAc = 5:1).

^1H NMR (500 MHz, CDCl_3) δ 10.31 (s, 1H), 7.32 (s, 1H), 6.49 (s, 1H), 3.97 (s, 3H), 3.92 (s, 3H), 3.87 (s, 3H).

^{13}C NMR (126 MHz, CDCl_3) δ 188.01, 158.64, 155.80, 143.62, 117.40, 109.09, 96.00, 56.32, 56.24, 56.20.

HRMS (ESI): m/z calculated for $\text{C}_{10}\text{H}_{13}\text{O}_4^+[\text{M}+\text{H}]^+$ 197.0814, found 197.0806.



1s

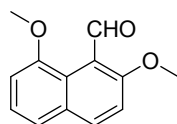
1-bromo-3-methoxy-2-naphthaldehyde

The compound **1s** was prepared according to **GP A** in 0.4 mmol scale to give white solid in 46% yield (48.6 mg). Purified by column chromatography (Petroleum ether/EtOAc = 5:1).

^1H NMR (400 MHz, CDCl_3) δ 10.55 (s, 1H), 8.36 (d, $J = 8.4$ Hz, 1H), 7.71 (d, $J = 8.0$ Hz, 1H), 7.56 (t, $J = 7.3$ Hz, 1H), 7.49 (t, $J = 7.5$ Hz, 1H), 7.18 (s, 1H), 3.98 (s, 3H).

^{13}C NMR (126 MHz, CDCl_3) δ 191.64, 156.51, 136.38, 129.39, 128.18, 127.57, 127.13, 127.05, 125.93, 125.85, 106.58, 56.09.

HRMS (ESI): m/z calculated for $\text{C}_{12}\text{H}_{10}\text{BrO}_2^+[\text{M}+\text{H}]^+$ 264.9864, found 264.98671.



1t

2,8-dimethoxy-1-naphthaldehyde

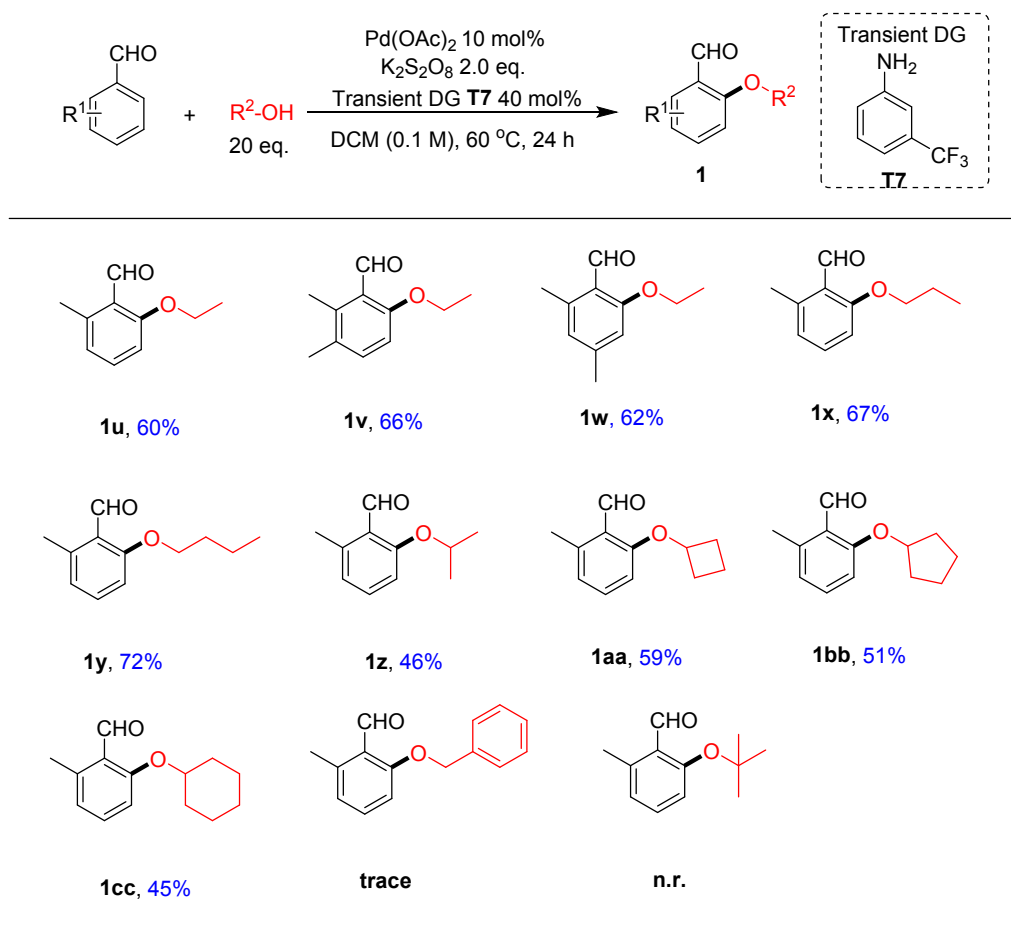
The compound **1t** was prepared according to **GP A** in 0.4 mmol scale to give red oil in 52% yield (44.9 mg). Purified by column chromatography (Petroleum ether/EtOAc = 5:1).

^1H NMR (400 MHz, CDCl_3) δ 10.74 (s, 1H), 7.84 (d, $J = 9.0$ Hz, 1H), 7.39 (d, $J = 8.1$ Hz, 1H), 7.31-7.26 (m, 2H), 6.84 (d, $J = 7.5$ Hz, 1H), 3.91 (s, 3H), 3.91 (s, 3H).

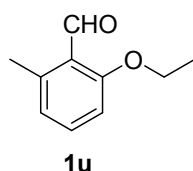
^{13}C NMR (126 MHz, CDCl_3) δ 194.92, 154.80, 154.55, 131.79, 130.01, 124.39, 123.96, 121.86, 120.98, 114.10, 106.52, 56.98, 55.87.

HRMS (ESI): m/z calculated for $\text{C}_{13}\text{H}_{13}\text{O}_3^+[\text{M}+\text{H}]^+$ 217.0865, found 217.0861.

Table S7 Alkoxylation of Benzaldehyde with Different Alcohols



^aReaction conditions: benzaldehyde (0.4 mmol, 1.0 equiv), alcohols (20.0 equiv), Pd(OAc)₂ (10 mol%), **T7** (40 mol%), K₂S₂O₈ (2.0 equiv), DCM (4.0 mL) at 60 °C for 24 h. Isolated yields for all.



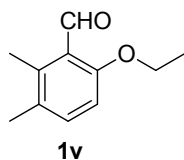
2-ethoxy-6-methylbenzaldehyde

The compound **1u** was prepared according to **GP A** in 0.4 mmol scale to give yellow oil in 60% yield (39.4 mg). Purified by column chromatography (Petroleum ether/EtOAc = 100:1).

¹H NMR (500 MHz, CDCl₃) δ 10.68 (s, 1H), 7.35 (t, *J* = 8.0 Hz, 1H), 6.82 (d, *J* = 8.4 Hz, 1H), 6.79 (d, *J* = 7.6 Hz, 1H), 4.12 (q, *J* = 7.0 Hz, 2H), 2.57 (s, 3H), 1.46 (t, *J* = 7.0 Hz, 3H).

¹³C NMR (126 MHz, CDCl₃) δ 192.63, 162.68, 141.94, 134.37, 123.91, 123.39, 109.95, 64.31, 21.50, 14.70.

HRMS (ESI): *m/z* calculated for C₁₀H₁₃O₂⁺[M+H]⁺ 165.0916, found 165.0921.



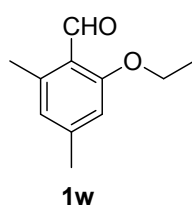
6-ethoxy-2,3-dimethylbenzaldehyde

The compound **1v** was prepared according to **GP A** in 0.4 mmol scale to give yellow oil in 66% yield (47.0 mg). Purified by column chromatography (Petroleum ether/EtOAc = 100:1).

¹H NMR (500 MHz, CDCl₃) δ 10.68 (s, 1H), 7.27 (d, *J* = 8.6 Hz, 1H), 6.74 (d, *J* = 8.5 Hz, 1H), 4.10 (q, *J* = 7.0 Hz, 2H), 2.50 (s, 3H), 2.26 (s, 3H), 1.46 (t, *J* = 7.0 Hz, 3H).

¹³C NMR (126 MHz, CDCl₃) δ 193.57, 160.88, 139.64, 135.70, 129.71, 123.93, 109.43, 64.30, 19.55, 16.22, 14.72.

HRMS (ESI): *m/z* calculated for C₁₁H₁₅O₂⁺[M+H]⁺ 179.1072, found 179.1066.



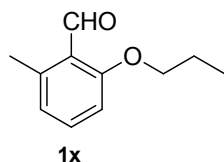
2-ethoxy-4,6-dimethylbenzaldehyde

The compound **1w** was prepared according to **GP A** in 0.4 mmol scale to give white solid in 62% yield (44.1 mg). Purified by column chromatography (Petroleum ether/EtOAc = 100:1).

¹H NMR (500 MHz, CDCl₃) δ 10.61 (s, 1H), 6.62 (s, 1H), 6.60 (s, 1H), 4.10 (q, *J* = 7.0 Hz, 2H), 2.54 (s, 3H), 2.33 (s, 3H), 1.44 (t, *J* = 7.0 Hz, 3H).

¹³C NMR (126 MHz, CDCl₃) δ 192.09, 162.90, 145.58, 141.91, 124.87, 121.03, 110.67, 64.24, 22.13, 21.55, 14.72.

HRMS (ESI): *m/z* calculated for C₁₁H₁₅O₂⁺[M+H]⁺ 179.1072, found 179.1067.



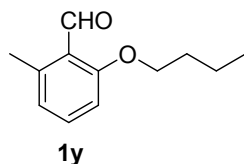
2-methyl-6-propoxybenzaldehyde

The compound **1x** was prepared according to **GP A** in 0.4 mmol scale to give yellow oil in 67% yield (47.7 mg). Purified by column chromatography (Petroleum ether/EtOAc = 100:1).

¹H NMR (500 MHz, CDCl₃) δ 10.69 (s, 1H), 7.35 (t, *J* = 7.9 Hz, 1H), 6.82 (d, *J* = 8.4 Hz, 1H), 6.78 (d, *J* = 7.5 Hz, 1H), 4.01 (t, *J* = 6.3 Hz, 2H), 2.57 (s, 3H), 1.91 – 1.81 (m, 2H), 1.06 (t, *J* = 7.4 Hz, 3H).

¹³C NMR (126 MHz, CDCl₃) δ 192.54, 162.86, 141.95, 134.40, 123.85, 123.44, 109.93, 70.18, 22.53, 21.52, 10.62.

HRMS (ESI): *m/z* calculated for C₁₁H₁₅O₂⁺[M+H]⁺ 179.1072, found 179.1078.



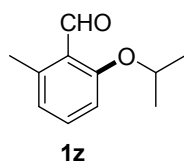
2-butoxy-6-methylbenzaldehyde

The compound **1y** was prepared according to **GP A** in 0.4 mmol scale to give yellow oil in 72% yield (55.3 mg). Purified by column chromatography (Petroleum ether/EtOAc = 100:1).

¹H NMR (500 MHz, CDCl₃) δ 10.68 (s, 1H), 7.35 (t, *J* = 8.0 Hz, 1H), 6.82 (d, *J* = 8.4 Hz, 1H), 6.78 (d, *J* = 7.6 Hz, 1H), 4.05 (t, *J* = 6.3 Hz, 2H), 2.57 (s, 3H), 1.85 – 1.77 (m, 2H), 1.55-1.48 (m, 2H), 0.98 (t, *J* = 7.4 Hz, 3H).

¹³C NMR (126 MHz, CDCl₃) δ 192.56, 162.88, 141.95, 134.40, 123.84, 123.43, 109.91, 68.37, 31.20, 21.50, 19.32, 13.79.

HRMS (ESI): *m/z* calculated for C₁₂H₁₇O₂⁺[M+H]⁺ 193.1229, found 193.1225.



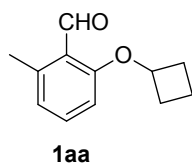
2-isopropoxy-6-methylbenzaldehyde

The compound **1z** was prepared according to **GP A** in 0.4 mmol scale to give white solid in 46% yield (32.8 mg). Purified by column chromatography (Petroleum ether/EtOAc = 100:1).

¹H NMR (500 MHz, CDCl₃) δ 10.65 (s, 1H), 7.34 (t, *J* = 8.0 Hz, 1H), 6.84 (d, *J* = 8.4 Hz, 1H), 6.77 (d, *J* = 7.6 Hz, 1H), 4.68 – 4.60 (m, 1H), 2.56 (s, 3H), 1.39 (s, 3H), 1.38 (s, 3H).

¹³C NMR (126 MHz, CDCl₃) δ 192.93, 161.86, 142.02, 134.23, 124.37, 123.78, 111.58, 71.28, 22.04, 21.53.

HRMS (ESI): *m/z* calculated for C₁₁H₁₅O₂⁺[M+H]⁺ 179.1072, found 179.1065.



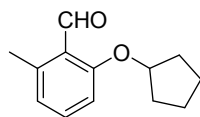
2-cyclobutoxy-6-methylbenzaldehyde

The compound **1aa** was prepared according to **GP A** in 0.4 mmol scale to give white solid in 59% yield (44.8 mg). Purified by column chromatography (Petroleum ether/EtOAc = 100:1).

¹H NMR (500 MHz, CDCl₃) δ 10.66 (s, 1H), 7.32 (t, *J* = 8.0 Hz, 1H), 6.77 (d, *J* = 7.6 Hz, 1H), 6.66 (d, *J* = 8.4 Hz, 1H), 4.71 (p, *J* = 7.1 Hz, 1H), 2.56 (s, 3H), 2.51 – 2.44 (m, 2H), 2.26 – 2.17 (m, 2H), 1.93-1.86 (m, 1H), 1.76 – 1.67 (m, 1H).

¹³C NMR (126 MHz, CDCl₃) δ 192.62, 161.35, 142.01, 134.31, 123.92, 123.38, 110.84, 72.26, 30.60, 21.51, 13.31.

HRMS (ESI): *m/z* calculated for C₁₂H₁₅O₂⁺[M+H]⁺ 191.1072, found 191.1078.



1bb

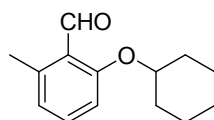
2-(cyclopentyloxy)-6-methylbenzaldehyde

The compound **1bb** was prepared according to **GP A** in 0.4 mmol scale to give yellow oil in 51% yield (41.6 mg). Purified by column chromatography (Petroleum ether/EtOAc = 100:1).

^1H NMR (500 MHz, CDCl_3) δ 10.61 (s, 1H), 7.34 (t, $J = 8.0$ Hz, 1H), 6.82 (d, $J = 8.4$ Hz, 1H), 6.76 (d, $J = 7.5$ Hz, 1H), 4.89 – 4.84 (m, 1H), 2.56 (s, 3H), 1.94 – 1.89 (m, 4H), 1.83 – 1.77 (m, 2H), 1.68 – 1.63 (m, 2H).

^{13}C NMR (126 MHz, CDCl_3) δ 192.83, 161.86, 141.99, 134.20, 123.94, 123.55, 111.28, 80.26, 32.87, 23.96, 21.54.

HRMS (ESI): m/z calculated for $\text{C}_{13}\text{H}_{17}\text{O}_2^+[\text{M}+\text{H}]^+$ 205.1229, found 205.1236.



1cc

2-(cyclohexyloxy)-6-methylbenzaldehyde

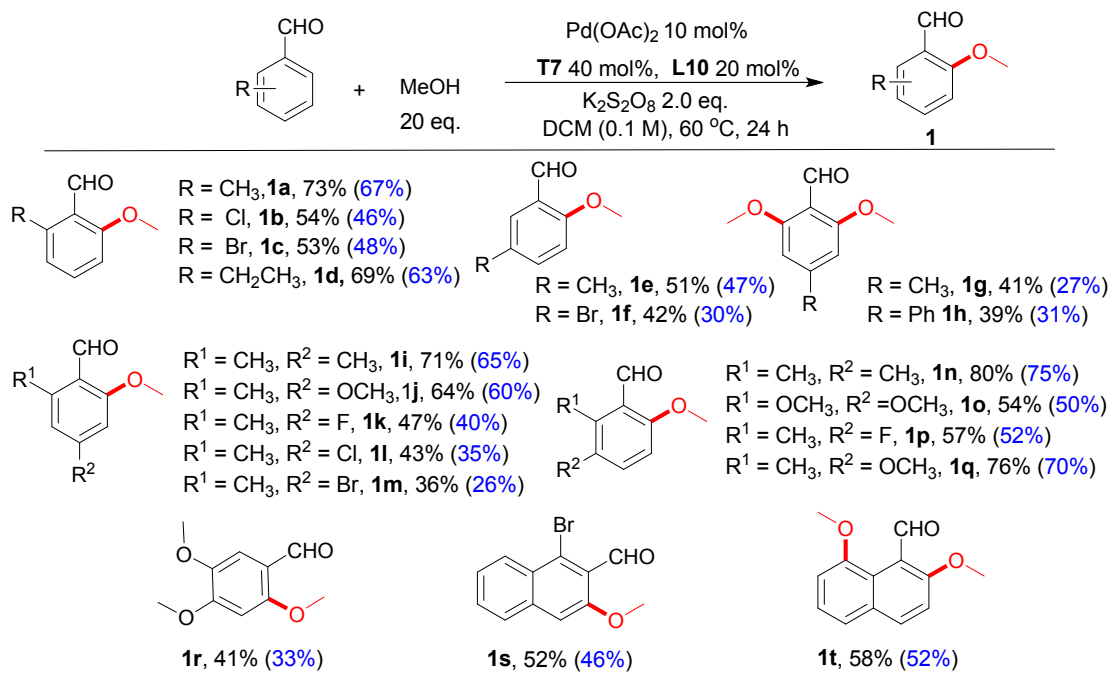
The compound **1cc** was prepared according to **GP A** in 0.4 mmol scale to give white solid in 45% yield (39.2 mg). Purified by column chromatography (Petroleum ether/EtOAc = 100:1).

^1H NMR (500 MHz, CDCl_3) δ 10.68 (s, 1H), 7.33 (t, $J = 8.0$ Hz, 1H), 6.84 (d, $J = 8.4$ Hz, 1H), 6.76 (d, $J = 7.5$ Hz, 1H), 4.42 – 4.36 (m, 1H), 2.56 (s, 3H), 1.99 – 1.92 (m, 2H), 1.80-1.77 (m, 2H), 1.64-1.62 (m, 2H), 1.48 – 1.33 (m, 4H).

^{13}C NMR (126 MHz, CDCl_3) δ 192.89, 161.77, 142.05, 134.21, 124.44, 123.72, 111.72, 76.16, 31.54, 25.51, 23.40, 21.54.

HRMS (ESI): m/z calculated for $\text{C}_{14}\text{H}_{19}\text{O}_2^+[\text{M}+\text{H}]^+$ 219.1385, found 219.1381.

Table S8 *ortho*-Methoxylation of Benzaldehydes with L10 liand^a

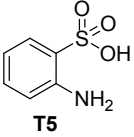
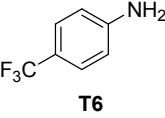
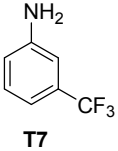
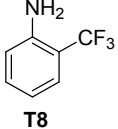
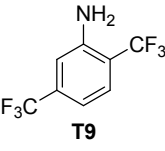
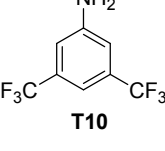
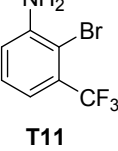
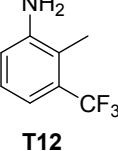


^aReaction conditions: substrate (0.4 mmol, 1.0 equiv), MeOH (20.0 equiv), Pd(OAc)₂ (10 mol%), **T7** (40 mol%), **L10** (20 mol%), K₂S₂O₈ (2.0 equiv), DCM (4.0 mL), 60 °C, 24 h. The yields in the brackets (blue) were obtained without **L10** at 60 °C for 24 h. Isolated yields for all.

2.4 Optimization of conditions for benzaldehyde chlorination

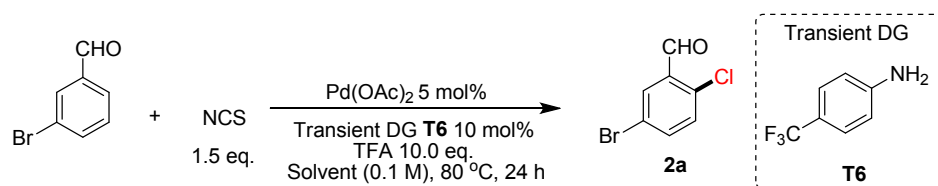
Table S9 Screening of Transient DG

| Entry | Transient DG | Yield (%) |
|-------|--------------|-----------|
| 1 | | 23 |
| 2 | | 28 |
| 3 | | trace |
| 4 | | 30 |

| | | |
|----|---|------|
| 5 |  T5 | N.R. |
| 6 |  T6 | 74 |
| 7 |  T7 | 66 |
| 8 |  T8 | 40 |
| 9 |  T9 | 33 |
| 10 |  T10 | 62 |
| 11 |  T11 | 58 |
| 12 |  T12 | 67 |

Reaction conditions: substrate (0.4 mmol, 1.0 equiv.), NCS (1.5 equiv.), Pd(OAc)₂ (5 mol%), Transient DG (10 mol%), TFA (10.0 equiv.), DCE (4.0 mL), 80 °C, 24 h. Isolated yields.

Table S10 Screening of Solvent



Entry

Solvent

Yield (%)

| | | |
|----------|--------------------|-----------|
| 1 | TFA | 71 |
| 2 | DCM | 63 |
| 3 | THF | 0 |
| 4 | CH ₃ CN | 0 |
| 5 | 1,4-dioxane | 0 |
| 6 | HFIP | 70 |
| 7 | PhCH ₃ | 8 |
| 8 | DCE | 74 |

Reaction conditions: substrate (0.4 mmol, 1.0 equiv.), NCS (1.5 equiv.), Pd(OAc)₂ (5 mol%), **T6** (10 mol%), TFA (10.0 equiv.), solvent (4.0 mL), 80 °C, 24 h. Isolated yields.

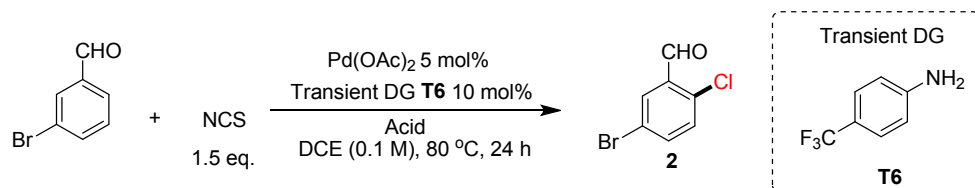
Table S11 Screening of Additive



| Entry | Additive (10 mol%) | Yield (%) |
|----------|--|-----------|
| 1 | K ₂ S ₂ O ₈ | 34 |
| 2 | AgTFA | 68 |
| 3 | Ag ₂ CO ₃ | 47 |
| 4 | Ag ₂ O | 53 |
| 5 | / | 74 |

Reaction conditions: substrate (0.4 mmol, 1.0 equiv.), NCS (1.5 equiv.), Pd(OAc)₂ (5 mol%), additive (10 mol%) **T6** (10 mol%), TFA (10.0 equiv.), DCE (4.0 mL), 80 °C, 24 h. Isolated yields.

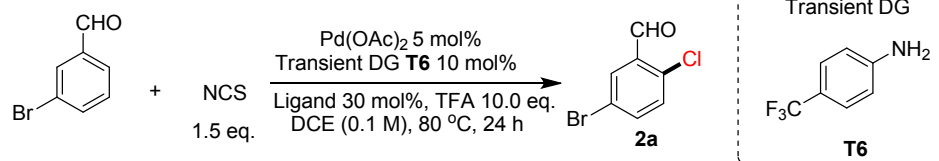
Table S12 Screening of Acid

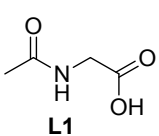
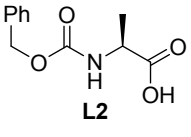
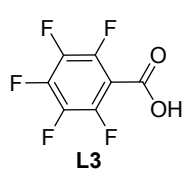
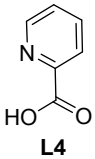
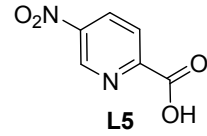
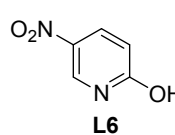
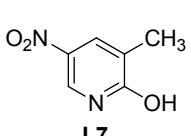
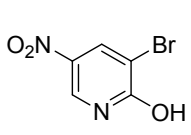
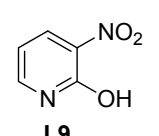


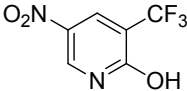
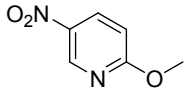
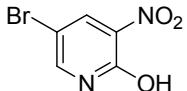
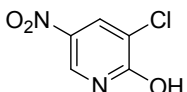
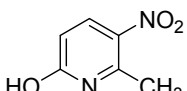
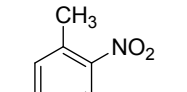
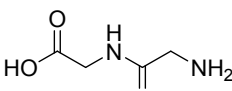
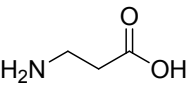
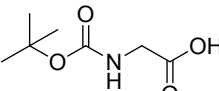
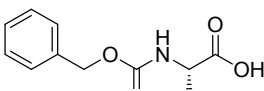
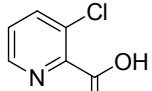
| Entry | Acid | Yield (%) |
|----------|--------------------------|-----------|
| 1 | / | 15 |
| 2 | AcOH (2.0 equiv.) | 37 |
| 3 | TfOH (2.0 equiv.) | 47 |
| 4 | MsOH (2.0 equiv.) | 45 |
| 5 | TFA (2.0 equiv.) | 55 |
| 6 | TFA (5.0 equiv.) | 67 |
| 7 | TFA (10.0 equiv.) | 74 |
| 8 | TFA (20.0 equiv.) | 72 |
| 9 | TFA (30.0 equiv.) | 71 |

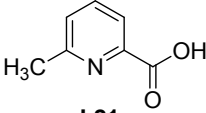
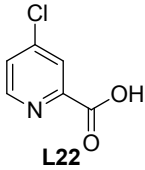
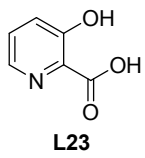
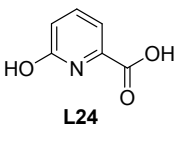
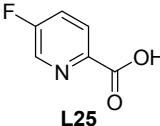
Reaction conditions: substrate (0.4 mmol, 1.0 equiv.), NCS (1.5 equiv.), Pd(OAc)₂ (5 mol%), **T6** (10 mol%), acid (x equiv.), DCE (4.0 mL), 80 °C, 24 h. Isolated yields.

Table S13 Screening of Ligand



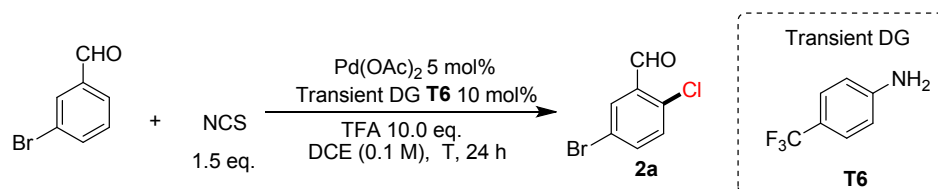
| Entry | Ligand | Yield (%) |
|-------|--|-----------|
| 1 |  <p>L1</p> | 77 |
| 2 |  <p>L2</p> | 70 |
| 3 |  <p>L3</p> | 78 |
| 4 |  <p>L4</p> | trace |
| 5 |  <p>L5</p> | trace |
| 6 |  <p>L6</p> | 84 |
| 7 |  <p>L7</p> | 74 |
| 8 |  <p>L8</p> | 78 |
| 9 |  <p>L9</p> | 87 |

| | | |
|----|---|-------|
| 10 |  <p>L10</p> | 94 |
| 11 |  <p>T11</p> | 20 |
| 12 |  <p>L12</p> | 80 |
| 13 |  <p>L13</p> | 78 |
| 14 |  <p>L14</p> | 76 |
| 15 |  <p>L15</p> | 75 |
| 16 |  <p>L16</p> | 76 |
| 17 |  <p>L17</p> | 73 |
| 18 |  <p>L18</p> | 71 |
| 19 |  <p>L19</p> | 72 |
| 20 |  <p>L20</p> | trace |

| | | |
|----|---|-------|
| 21 |  L21 | trace |
| 22 |  L22 | trace |
| 23 |  L23 | trace |
| 24 |  L24 | trace |
| 25 |  L25 | trace |

Reaction conditions: substrate (0.4 mmol, 1.0 equiv.), NCS (1.5 equiv.), Pd(OAc)₂ (5 mol%), **T6** (10 mol%), Ligand (30 mol%), DCE (4.0 mL), 80 °C, 24 h. Isolated yields.

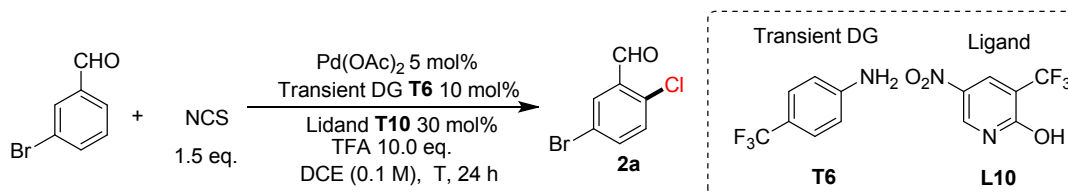
Table S14 Screening Temperature under Transient DG



| Entry | T (°C) | Yield (%) |
|----------|-----------|-----------|
| 1 | 40 | 32 |
| 2 | 50 | 44 |
| 3 | 60 | 53 |
| 4 | 70 | 65 |
| 5 | 80 | 74 |
| 6 | 90 | 71 |
| 7 | 100 | 70 |

Reaction conditions: substrate (0.4 mmol, 1.0 equiv.), NCS (1.5 equiv.), Pd(OAc)₂ (5 mol%), **T6** (10 mol%), TFA (10.0 equiv.), DCE (4.0 mL), T °C, 24 h. Isolated yields.

Table S15 Screening Temperature under both Transient DG and Ligand

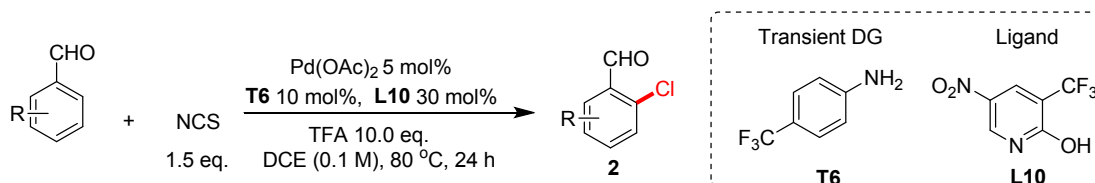


| Entry | T (°C) | Yield (%) |
|-------|--------|-----------|
| 1 | 40 | 61 |
| 2 | 50 | 73 |
| 3 | 60 | 82 |
| 4 | 70 | 86 |
| 5 | 80 | 94 |
| 6 | 90 | 92 |
| 7 | 100 | 91 |

Reaction conditions: substrate (0.4 mmol, 1.0 equiv.), NCS (1.5 equiv.), Pd(OAc)₂ (5 mol%), **T6** (10 mol%), **L10** (30 mol%), TFA (10.0 equiv.), DCE (4.0 mL), T °C, 24 h. Isolated yields.

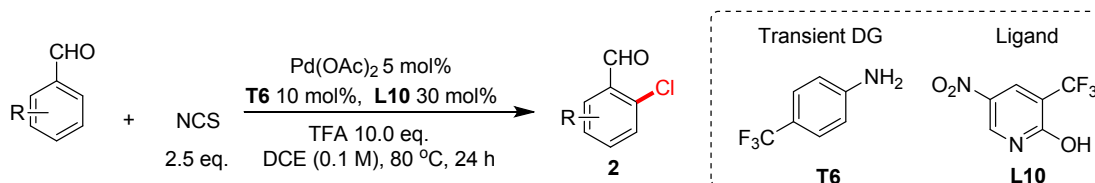
2.5 General Procedure for the *ortho*-C(sp²)-H Chlorination

General Procedure B (GP B)



A sealed tube with magnetic stir bar was charged with substrate (0.4 mmol), NCS (0.6 mmol, 79.8 mg), Pd(OAc)₂ (0.02 mmol, 4.5 mg), **L10** (0.12 mmol, 25.0 mg) in air, followed by DCE (4.0 mL), **T6** (0.04 mmol, 6.4 mg) and TFA (4.0 mmol, 456.0 mg). The reaction mixture was stirred at 80 °C for 24 hours. Upon completion, the reaction mixture was quenched by sat. NaHCO₃ (aq) (10 mL), and extracted with CH₂Cl₂ for 3 times. The combined organic layers were washed with water (15 mL), dried over anhydrous Na₂SO₄, and concentrated *in vacuo*. The crude residue was purified by column chromatography on silica gel using petroleum ether/EtOAc as eluent to afford the desired products.

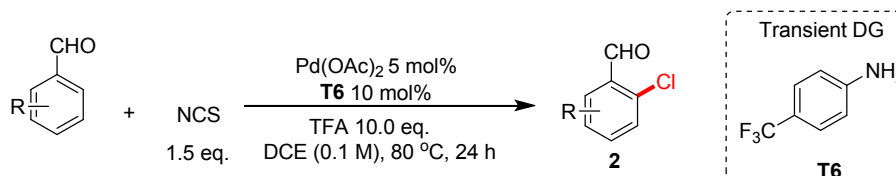
General Procedure C (GP C)



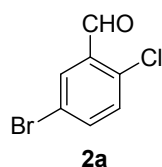
A sealed tube with magnetic stir bar was charged with substrate (0.4 mmol), NCS (1.0 mmol, 133.0 mg), Pd(OAc)₂ (0.02 mmol, 4.5 mg), **L10** (0.12 mmol, 25.0 mg) in air, followed by DCE (4.0 mL), **T6** (0.04 mmol, 6.4 mg) and TFA (4.0 mmol, 456.0 mg). The reaction

mixture was stirred at 80 °C for 24 hours. Upon completion, the reaction mixture was quenched by sat. NaHCO₃ (aq) (30 mL), and extracted with CH₂Cl₂ for 3 times. The combined organic layers were washed with water (50 mL), dried over anhydrous Na₂SO₄, and concentrated *in vacuo*. The crude residue was purified by column chromatography on silica gel using petroleum ether/EtOAc as eluent to afford the desired products.

General Procedure D (GP D)



A sealed tube with magnetic stir bar was charged with substrate (0.4 mmol), NCS (0.6 mmol, 79.8 mg), Pd(OAc)₂ (0.02 mmol, 4.5 mg) in air, followed by DCE (4.0 mL), **T6** (0.04 mmol, 6.4 mg) and TFA (4.0 mmol, 456.0 mg). The reaction mixture was stirred at 80 °C for 24 hours. Upon completion, the reaction mixture was quenched by sat. NaHCO₃ (aq) (10 mL), and extracted with CH₂Cl₂ for 3 times. The combined organic layers were washed with water (15 mL), dried over anhydrous Na₂SO₄, and concentrated *in vacuo*. The crude residue was purified by column chromatography on silica gel using petroleum ether/EtOAc as eluent to afford the desired products.



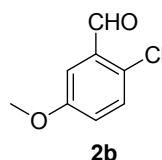
5-bromo-2-chlorobenzaldehyde

The compound **2a** was prepared according to **GP B** in 0.4 mmol scale to give white solid in 94% yield (81.9 mg), according to **GP D** in 0.4 mmol scale to give white solid in 74% yield (64.5 mg). Purified by column chromatography (Petroleum ether/EtOAc = 50:1).

¹H NMR (400 MHz, CDCl₃) δ 10.40 (s, 1H), 8.04 (d, *J* = 2.5 Hz, 1H), 7.64 (dd, *J* = 8.5, 2.5 Hz, 1H), 7.35 (d, *J* = 8.5 Hz, 1H).

¹³C NMR (101 MHz, CDCl₃) δ 188.35, 137.82, 136.63, 133.59, 132.17, 132.11, 121.40.

HRMS (ESI): *m/z* calculated for C₇H₅BrClO⁺[M+H]⁺ 218.9212, found 218.9217.



2-chloro-5-methoxybenzaldehyde

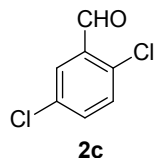
The compound **2b** was prepared according to **GP B** in 0.4 mmol scale to give white solid in 66% yield (44.9 mg), according to **GP D** in 0.4 mmol scale to give white solid in 59% yield (40.1 mg). Purified by column chromatography (Petroleum ether/EtOAc = 10:1).

¹H NMR (500 MHz, DMSO) δ 10.30 (s, 1H), 7.54 (d, *J* = 8.6 Hz, 1H), 7.35 (s, 1H), 7.30 (d, *J*

= 8.1 Hz, 1H), 3.83 (s, 3H).

^{13}C NMR (126 MHz, CDCl_3): δ 189.74, 158.68, 132.96, 131.45, 129.75, 122.85, 111.92, 55.79.

HRMS (ESI): m/z calculated for $\text{C}_8\text{H}_8\text{ClO}_2^+[\text{M}+\text{H}]^+$ 171.0213, found 171.0218.



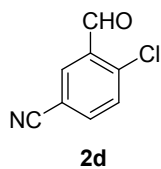
2,5-dichlorobenzaldehyde

The compound **2c** was prepared according to **GP B** in 0.4 mmol scale to give white solid in 94% yield (65.4 mg), according to **GP D** in 0.4 mmol scale to give white solid in 75% yield (52.2 mg). Purified by column chromatography (Petroleum ether/EtOAc = 50:1).

^1H NMR (400 MHz, CDCl_3) δ 10.42 (s, 1H), 7.89 (d, $J = 2.6$ Hz, 1H), 7.50 (dd, $J = 8.5, 2.6$ Hz, 1H), 7.41 (d, $J = 8.6$ Hz, 1H).

^{13}C NMR (101 MHz, CDCl_3): 188.46, 135.94, 134.92, 133.86, 133.37, 131.87, 129.15.

HRMS (ESI): m/z calculated for $\text{C}_7\text{H}_5\text{Cl}_2\text{O}^+[\text{M}+\text{H}]^+$ 174.9717, found 174.9711.



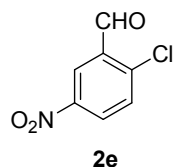
4-chloro-3-formylbenzonitrile

The compound **2d** was prepared according to **GP B** in 0.4 mmol scale to give white solid in 43% yield (28.4 mg), according to **GP D** in 0.4 mmol scale to give white solid in 20% yield (13.2 mg). Purified by column chromatography (Petroleum ether/EtOAc = 10:1).

^1H NMR (500 MHz, CDCl_3) δ 10.46 (s, 1H), 8.20 (d, $J = 2.0$ Hz, 1H), 7.79 (dd, $J = 8.3, 2.1$ Hz, 1H), 7.62 (d, $J = 8.3$ Hz, 1H).

^{13}C NMR (101 MHz, CDCl_3) δ 187.49, 142.19, 137.31, 133.20, 133.16, 131.91, 116.84, 112.09.

HRMS (ESI): m/z calculated for $\text{C}_8\text{H}_5\text{ClNO}^+[\text{M}+\text{H}]^+$ 166.0060, found 166.0064.



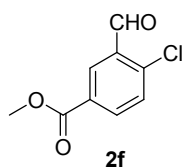
2-chloro-5-nitrobenzaldehyde

The compound **2e** was prepared according to **GP B** in 0.4 mmol scale to give white solid in 61% yield (45.1 mg), according to **GP D** in 0.4 mmol scale to give white solid in 38% yield (28.1 mg). Purified by column chromatography (Petroleum ether/EtOAc = 10:1).

^1H NMR (500 MHz, CDCl_3) δ 10.48 (s, 1H), 8.73 (d, $J = 2.7$ Hz, 1H), 8.37 (dd, $J = 8.8, 2.8$ Hz, 1H), 7.69 (d, $J = 8.8$ Hz, 1H).

^{13}C NMR (126 MHz, CDCl_3) δ 187.33, 147.09, 143.56, 133.19, 132.04, 128.83, 124.49.

HRMS (ESI): m/z calculated for $\text{C}_7\text{H}_5\text{ClNO}_3^+[\text{M}+\text{H}]^+$ 185.9958, found 185.9952.



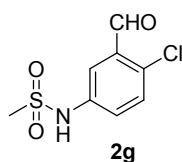
methyl 4-chloro-3-formylbenzoate

The compound **2f** was prepared according to **GP B** in 0.4 mmol scale to give white solid in 90% yield (71.3 mg), according to **GP D** in 0.4 mmol scale to give white solid in 65% yield (51.5 mg). Purified by column chromatography (Petroleum ether/EtOAc = 10:1).

^1H NMR (500 MHz, DMSO) δ 10.34 (s, 1H), 8.33 (s, 1H), 8.17 (d, $J = 8.3$ Hz, 1H), 7.78 (d, $J = 8.2$ Hz, 1H), 3.90 (s, 3H).

^{13}C NMR (126 MHz, DMSO): δ 189.62, 165.18, 141.08, 135.74, 132.77, 132.03, 130.63, 129.63, 53.12.

HRMS (ESI): m/z calculated for $\text{C}_9\text{H}_8\text{ClO}_3^+[\text{M}+\text{H}]^+$ 199.0162, found 199.0167.



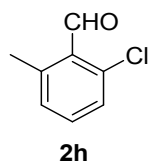
N-(4-chloro-3-formylphenyl)methanesulfonamide

The compound **2g** was prepared according to **GP B** in 0.4 mmol scale to give white solid in 86% yield (80.2 mg), according to **GP D** in 0.4 mmol scale to give white solid in 44% yield (41.0 mg). Purified by column chromatography (Petroleum ether/ CH_2Cl_2 /EtOAc = 4:4:1).

^1H NMR (500 MHz, CDCl_3) δ 10.45 (s, 1H), 7.82 (d, $J = 8.9$ Hz, 1H), 7.44 (d, $J = 8.9$ Hz, 1H), 7.03 (s, 1H), 3.04 (s, 3H).

^{13}C NMR (126 MHz, CDCl_3) δ 188.10, 134.01, 133.53, 131.01, 130.36, 126.29, 126.15, 40.47.

HRMS (ESI): m/z calculated for $\text{C}_8\text{H}_9\text{ClNO}_3\text{S}^+[\text{M}+\text{H}]^+$ 233.9992, found 233.9999.



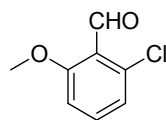
2-chloro-6-methylbenzaldehyde

The compound **2h** was prepared according to **GP B** in 0.4 mmol scale to give white solid in 95% yield (58.5 mg), according to **GP D** in 0.4 mmol scale to give white solid in 93% yield (57.3 mg). Purified by column chromatography (Petroleum ether/EtOAc = 50:1).

^1H NMR (500 MHz, CDCl_3) δ 10.65 (s, 1H), 7.35 (t, $J = 7.7$ Hz, 1H), 7.31 (d, $J = 7.8$ Hz, 1H), 7.16 (d, $J = 7.4$ Hz, 1H), 2.59 (s, 3H).

^{13}C NMR (126 MHz, CDCl_3) δ 172.38, 137.09, 132.62, 130.67, 130.64, 128.61, 127.03, 19.83.

HRMS (ESI): m/z calculated for $C_8H_8ClO^+[M+H]^+$ 155.0264, found 155.0269.



2i

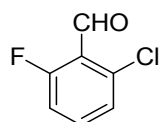
2-chloro-6-methoxybenzaldehyde

The compound **2i** was prepared according to **GP B** in 0.4 mmol scale to give white solid in 90% yield (61.2 mg), according to **GP D** in 0.4 mmol scale to give white solid in 90% yield (61.2 mg). Purified by column chromatography (Petroleum ether/EtOAc = 10:1).

1H NMR (400 MHz, $CDCl_3$) δ 10.51 (s, 1H), 7.41 (t, $J = 8.3$ Hz, 1H), 7.04 (d, $J = 8.0$ Hz, 1H), 6.91 (d, $J = 8.5$ Hz, 1H), 3.92 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 189.23, 162.04, 136.59, 134.62, 123.13, 122.33, 110.35, 56.27.

HRMS (ESI): m/z calculated for $C_8H_8ClO^+[M+H]^+$ 171.0213, found 171.0218.



2j

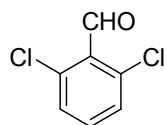
2-chloro-6-fluorobenzaldehyde

The compound **2j** was prepared according to **GP B** in 0.4 mmol scale to give white solid in 92% yield (58.1 mg), according to **GP D** in 0.4 mmol scale to give white solid in 84% yield (53.1 mg). Purified by column chromatography (Petroleum ether/EtOAc = 50:1).

1H NMR (500 MHz, $CDCl_3$) δ 10.46 (s, 1H), 7.52-7.45 (m, 1H), 7.28 (d, $J = 8.1$ Hz, 1H), 7.10 (t, $J = 9.3$ Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 187.01 (d, $J = 2.8$ Hz), 163.28 (d, $J = 265.9$ Hz), 137.14 (d, $J = 3.6$ Hz), 135.22 (d, $J = 10.7$ Hz), 126.81 (d, $J = 3.8$ Hz), 121.82 (d, $J = 9.6$ Hz), 115.68 (d, $J = 21.6$ Hz).

HRMS (ESI): m/z calculated for $C_7H_5ClFO^+[M+H]^+$ 159.0013, found 159.0008.



2k

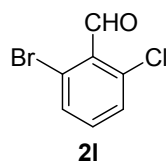
2,6-dichlorobenzaldehyde

The compound **2k** was prepared according to **GP B** in 0.4 mmol scale to give white solid in 92% yield (64.0 mg), according to **GP D** in 0.4 mmol scale to give white solid in 91% yield (63.3 mg). Purified by column chromatography (Petroleum ether/EtOAc = 50:1).

1H NMR (500 MHz, DMSO) δ 10.37 (s, 1H), 7.67-7.57 (m, 3H).

^{13}C NMR (126 MHz, DMSO) δ 190.01, 135.53, 135.08, 130.86, 130.46.

HRMS (ESI): m/z calculated for $C_7H_5Cl_2O^+[M+H]^+$ 174.9717, found 174.9711.



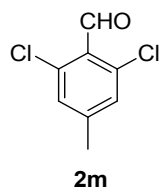
2-bromo-6-chlorobenzaldehyde

The compound **2l** was prepared according to **GP B** in 0.4 mmol scale to give white solid in 89% yield (77.6 mg), according to **GP D** in 0.4 mmol scale to give white solid in 85% yield (74.1 mg). Purified by column chromatography (Petroleum ether/EtOAc = 50:1)

$^1\text{H NMR}$ (500 MHz, DMSO) δ 10.25 (s, 1H), 7.77 (d, $J = 7.8$ Hz, 1H), 7.64 (d, $J = 7.9$ Hz, 1H), 7.53 (t, $J = 7.9$ Hz, 1H).

$^{13}\text{C NMR}$ (126 MHz, DMSO) δ 191.32, 135.22, 135.17, 133.58, 132.24, 130.96, 124.07.

HRMS (ESI): m/z calculated for $\text{C}_7\text{H}_5\text{BrClO}^+[\text{M}+\text{H}]^+$ 218.9212, found 218.9216.



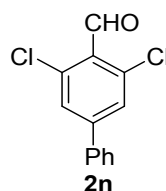
2,6-dichloro-4-methylbenzaldehyde

The compound **2m** was prepared according to **GP C** in 0.4 mmol scale to give white solid in 94% yield (70.7 mg). Purified by column chromatography (Petroleum ether/EtOAc = 50:1).

$^1\text{H NMR}$ (500 MHz, CDCl_3) δ 10.46 (s, 1H), 7.20 (s, 2H), 2.37 (s, 3H).

$^{13}\text{C NMR}$ (126 MHz, CDCl_3) δ 188.44, 145.38, 136.94, 130.44, 127.58, 21.18.

HRMS (ESI): m/z calculated for $\text{C}_8\text{H}_7\text{Cl}_2\text{O}^+[\text{M}+\text{H}]^+$ 188.9874, found 188.9869.



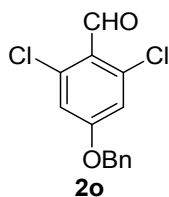
3,5-dichloro-[1,1'-biphenyl]-4-carbaldehyde

The compound **2n** was prepared according to **GP C** in 0.4 mmol scale to give white solid in 92% yield (92.0 mg). Purified by column chromatography (Petroleum ether/EtOAc = 50:1).

$^1\text{H NMR}$ (500 MHz, CDCl_3) δ 10.49 (s, 1H), 7.57 (s, 2H), 7.56-7.53 (m, 2H), 7.50-7.42 (m, 3H).

$^{13}\text{C NMR}$ (101 MHz, CDCl_3) δ 188.33, 146.83, 137.45, 136.90, 129.54, 129.28, 128.20, 128.11, 127.12.

HRMS (ESI): m/z calculated for $\text{C}_{13}\text{H}_9\text{Cl}_2\text{O}^+[\text{M}+\text{H}]^+$ 251.0030, found 251,0037.



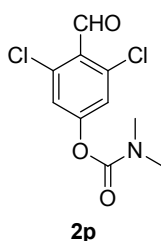
4-(benzyloxy)-2,6-dichlorobenzaldehyde

The compound **2o** was prepared according to **GP C** in 0.4 mmol scale to give white solid in 92% yield (103.0 mg). Purified by column chromatography (Petroleum ether/EtOAc = 20:1).

¹H NMR (500 MHz, CDCl₃) δ 10.40 (s, 1H), 7.43 – 7.38 (m, 5H), 6.98 (s, 2H), 5.10 (s, 2H).

¹³C NMR (101 MHz, CDCl₃) δ 187.57, 161.85, 139.04, 134.88, 128.87, 128.72, 127.62, 122.98, 116.47, 70.88.

HRMS (ESI): *m/z* calculated for C₁₄H₁₁Cl₂O₂⁺[M+H]⁺ 281.0136, found 281.0141.



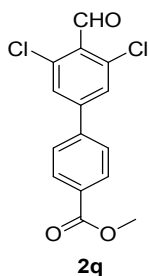
3,5-dichloro-4-formylphenyl dimethylcarbamate

The compound **2p** was prepared according to **GP C** in 0.4 mmol scale to give white solid in 93% yield (97.1 mg). Purified by column chromatography (Petroleum ether/CH₂Cl₂/EtOAc = 4:4:1).

¹H NMR (500 MHz, CDCl₃) δ 10.45 (s, 1H), 7.26 (s, 2H), 3.09 (s, 3H), 3.03 (s, 3H).

¹³C NMR (126 MHz, DMSO) δ 188.96, 154.88, 152.95, 136.41, 127.39, 124.01, 36.94, 36.72.

HRMS (ESI): *m/z* calculated for C₁₀H₁₀Cl₂NO₃⁺[M+H]⁺ 262.0038, found 262.0043.



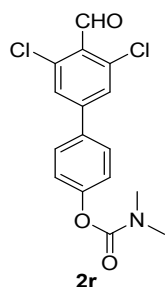
methyl 3',5'-dichloro-4'-formyl-[1,1'-biphenyl]-4-carboxylate

The compound **2q** was prepared according to **GP C** in 0.4 mmol scale to give white solid in 91% yield (112.1 mg). Purified by column chromatography (Petroleum ether/CH₂Cl₂/EtOAc = 20:20:1).

¹H NMR (500 MHz, CDCl₃) δ 10.51 (s, 1H), 8.13 (d, *J* = 6.4 Hz, 2H), 7.64 (d, *J* = 6.9 Hz, 2H), 7.61 (s, 2H), 3.95 (s, 3H).

¹³C NMR (101 MHz, CDCl₃) δ 188.32, 166.40, 145.62, 141.26, 137.57, 130.94, 130.48, 129.05, 128.37, 127.22, 52.40.

HRMS (ESI): *m/z* calculated for C₁₅H₁₁Cl₂O₃⁺[M+H]⁺ 309.0085, found 309.0079.



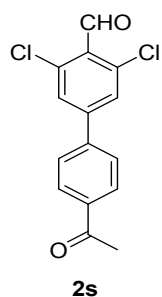
3',5'-dichloro-4'-formyl-[1,1'-biphenyl]-4-yl dimethylcarbamate

The compound **2r** was prepared according to **GP C** in 0.4 mmol scale to give white solid in 92% yield (124.0 mg). Purified by column chromatography (Petroleum ether/CH₂Cl₂/EtOAc = 10:10:1).

¹H NMR (500 MHz, DMSO) δ 10.39 (s, 1H), 7.92 (s, 2H), 7.86 (d, *J* = 7.8 Hz, 2H), 7.26 (d, *J* = 7.8 Hz, 2H), 3.07 (s, 3H), 2.94 (s, 3H).

¹³C NMR (126 MHz, CDCl₃) δ 188.38, 154.45, 152.72, 146.23, 137.52, 133.92, 128.26, 128.14, 128.04, 122.64, 36.79, 36.53.

HRMS (ESI): *m/z* calculated for C₁₆H₁₄Cl₂NO₃⁺[M+H]⁺ 338.0351, found 338.0345.



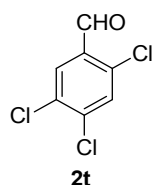
4'-acetyl-3,5-dichloro-[1,1'-biphenyl]-4-carbaldehyde

The compound **2s** was prepared according to **GP C** in 0.4 mmol scale to give white solid in 88% yield (102.8 mg). Purified by column chromatography (Petroleum ether/CH₂Cl₂/EtOAc = 20:20:1).

¹H NMR (500 MHz, CDCl₃) δ 10.52 (s, 1H), 8.06 (d, *J* = 8.3 Hz, 2H), 7.68 (d, *J* = 8.3 Hz, 2H), 7.63 (s, 2H), 2.65 (s, 3H).

¹³C NMR (101 MHz, CDCl₃) δ 197.32, 188.27, 145.45, 141.30, 137.56, 137.48, 129.21, 129.07, 128.34, 127.44, 26.77.

HRMS (ESI): *m/z* calculated for C₁₅H₁₁Cl₂O₂⁺[M+H]⁺ 293.0136, found 293.0139.



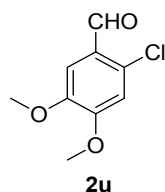
2,4,5-trichlorobenzaldehyde

The compound **2t** was prepared according to **GP B** in 0.4 mmol scale to give white solid in 65% yield (54.1 mg), according to **GP D** in 0.4 mmol scale to give white solid in 58% yield (48.3 mg). Purified by column chromatography (Petroleum ether/EtOAc = 20:1).

^1H NMR (500 MHz, DMSO) δ 10.21 (s, 1H), 8.09 (s, 1H), 8.01 (s, 1H).

^{13}C NMR (126 MHz, DMSO) δ 188.51, 138.10, 135.38, 132.87, 132.57, 131.72, 131.30.

HRMS (ESI): m/z calculated for $\text{C}_7\text{H}_4\text{Cl}_3\text{O}^+[\text{M}+\text{H}]^+$ 208.9328, found 208.9323.



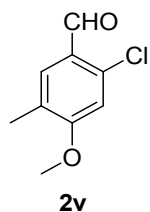
2-chloro-4,5-dimethoxybenzaldehyde

The compound **2u** was prepared according to **GP B** in 0.4 mmol scale to give white solid in 73% yield (58.4 mg), according to **GP D** in 0.4 mmol scale to give white solid in 68% yield (54.4 mg). Purified by column chromatography (Petroleum ether/EtOAc = 10:1).

^1H NMR (500 MHz, DMSO) δ 10.19 (s, 1H), 7.30 (s, 1H), 7.16 (s, 1H), 3.90 (s, 3H), 3.82 (s, 3H).

^{13}C NMR (126 MHz, DMSO) δ 188.64, 154.95, 148.62, 131.00, 125.12, 113.46, 110.34, 56.95, 56.20.

HRMS (ESI): m/z calculated for $\text{C}_9\text{H}_{10}\text{ClO}_3^+[\text{M}+\text{H}]^+$ 201.0318, found 201.0324.



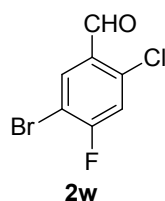
2-chloro-4-methoxy-5-methylbenzaldehyde

The compound **2v** was prepared according to **GP B** in 0.4 mmol scale to give white solid in 83% yield (61.1 mg), according to **GP D** in 0.4 mmol scale to give white solid in 75% yield (55.2 mg). Purified by column chromatography (Petroleum ether/EtOAc = 50:1).

^1H NMR (500 MHz, CDCl_3) δ 10.31 (s, 1H), 7.71 (s, 1H), 6.82 (s, 1H), 3.90 (s, 3H), 2.19 (s, 3H).

^{13}C NMR (126 MHz, CDCl_3) δ 188.75, 162.86, 137.55, 130.79, 126.59, 125.42, 111.37, 55.97, 15.63.

HRMS (ESI): m/z calculated for $\text{C}_9\text{H}_{10}\text{ClO}_2^+[\text{M}+\text{H}]^+$ 185.0369, found 185.0363.



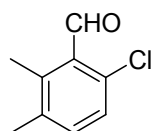
5-bromo-2-chloro-4-fluorobenzaldehyde

The compound **2w** was prepared according to **GP B** in 0.4 mmol scale to give white solid in 92% yield (86.8 mg), according to **GP D** in 0.4 mmol scale to give white solid in 60% yield (56.6 mg). Purified by column chromatography (Petroleum ether/EtOAc = 20:1).

^1H NMR (500 MHz, CDCl_3) δ 10.34 (s, 1H), 8.16 (s, 1H), 7.27 (s, 1H).

^{13}C NMR (126 MHz, CDCl_3) δ 186.91, 162.16 (d, $J = 260.8$ Hz), 137.88 (d, $J = 10.1$ Hz), 134.54 (d, $J = 2.5$ Hz), 130.05 (d, $J = 3.8$ Hz), 118.80 (d, $J = 26.5$ Hz), 109.15 (d, $J = 21.4$ Hz).

HRMS (ESI): m/z calculated for $\text{C}_7\text{H}_4\text{BrClFO}^+[\text{M}+\text{H}]^+$ 236.9118, found 236.9112.



2x

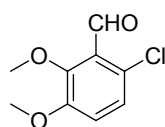
6-chloro-2,3-dimethylbenzaldehyde

The compound **2x** was prepared according to **GP B** in 0.4 mmol scale to give yellow solid in 91% yield (61.2 mg), according to **GP D** in 0.4 mmol scale to give yellow solid in 91% yield (61.2 mg). Purified by column chromatography (Petroleum ether/EtOAc = 50:1).

^1H NMR (500 MHz, CDCl_3) δ 10.63 (s, 1H), 7.26 (d, $J = 8.2$ Hz, 1H), 7.20 (d, $J = 8.1$ Hz, 1H), 2.48 (s, 3H), 2.31 (s, 3H).

^{13}C NMR (101 MHz, CDCl_3) δ 193.48, 140.30, 137.25, 135.85, 134.95, 131.35, 127.48, 20.09, 16.14.

HRMS (ESI): m/z calculated for $\text{C}_9\text{H}_{10}\text{ClO}^+[\text{M}+\text{H}]^+$ 169.0420, found 169.0427.



2y

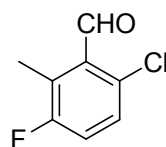
6-chloro-2,3-dimethoxybenzaldehyde

The compound **2y** was prepared according to **GP B** in 0.4 mmol scale to give white solid in 85% yield (68.0 mg), according to **GP D** in 0.4 mmol scale to give white solid in 81% yield (64.8 mg). Purified by column chromatography (Petroleum ether/EtOAc = 20:1).

^1H NMR (500 MHz, CDCl_3) δ 10.42 (s, 1H), 7.12 (d, $J = 8.8$ Hz, 1H), 7.01 (d, $J = 8.8$ Hz, 1H), 3.92 (s, 3H), 3.87 (s, 3H).

^{13}C NMR (101 MHz, DMSO) δ 190.07, 152.38, 152.00, 127.36, 126.58, 123.41, 118.59, 62.24, 56.67.

HRMS (ESI): m/z calculated for $\text{C}_9\text{H}_{10}\text{ClO}_3^+[\text{M}+\text{H}]^+$ 201.0318, found 201.0323.



2z

6-chloro-3-fluoro-2-methylbenzaldehyde

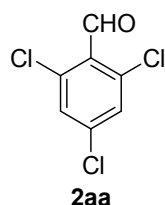
The compound **2z** was prepared according to **GP B** in 0.4 mmol scale to give white solid in 88% yield (60.5 mg), according to **GP D** in 0.4 mmol scale to give white solid in 83% yield

(57.1 mg). Purified by column chromatography (Petroleum ether/EtOAc = 50:1).

^1H NMR (400 MHz, DMSO) δ 10.42 (d, J = 1.5 Hz, 1H), 7.53-7.50 (m, 2H), 2.38 (d, J = 2.3 Hz, 3H).

^{13}C NMR (101 MHz, DMSO) δ 192.54 (d, J = 2.1 Hz), 159.84 (d, J = 244.8 Hz), 132.82 (d, J = 3.5 Hz), 132.10 (d, J = 3.1 Hz), 129.80 (d, J = 8.7 Hz), 128.30 (d, J = 18.6 Hz), 121.32 (d, J = 25.7 Hz), 11.41 (d, J = 5.8 Hz).

HRMS (ESI): m/z calculated for $\text{C}_8\text{H}_7\text{ClFO}^+[\text{M}+\text{H}]^+$ 173.0169, found 173.0166.



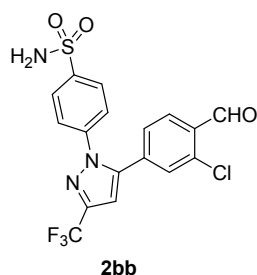
2,4,6-trichlorobenzaldehyde

The compound **2aa** was prepared according to **GP B** in 0.4 mmol scale to give white solid in 90% yield (74.9 mg), according to **GP D** in 0.4 mmol scale to give white solid in 88% yield (73.2 mg). Purified by column chromatography (Petroleum ether/EtOAc = 50:1).

^1H NMR (500 MHz, CDCl_3) δ 10.43 (s, 1H), 7.42 (s, 2H).

^{13}C NMR (126 MHz, CDCl_3) δ 187.58, 139.32, 137.69, 129.84, 128.73.

HRMS (ESI): m/z calculated for $\text{C}_7\text{H}_4\text{Cl}_3\text{O}^+[\text{M}+\text{H}]^+$ 208.9328, found 208.9333.



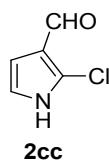
4-(5-(3-chloro-4-formylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl)benzenesulfonamide

The compound **2bb** was prepared according to **GP B** in 0.4 mmol scale to give white solid in 70% yield (120.1 mg), according to **GP D** in 0.4 mmol scale to give white solid in 47% yield (80.7 mg). Purified by column chromatography (Petroleum ether/ CH_2Cl_2 /EtOAc = 2:2:1).

^1H NMR (500 MHz, DMSO) δ 10.32 (s, 1H), 10.32 (s, 1H), 7.91 (d, J = 8.5 Hz, 2H), 7.84 (d, J = 8.1 Hz, 1H), 7.73 (s, 1H), 7.62 (d, J = 8.6 Hz, 2H), 7.54 (s, 2H), 7.49 (s, 1H), 7.36 (d, J = 7.9 Hz, 1H).

^{13}C NMR (126 MHz, DMSO) δ 189.75, 144.95, 143.17 (q, J = 37.8 Hz), 143.15, 141.07, 136.73, 135.23, 132.63, 131.47, 130.40, 128.62, 127.44, 126.64, 121.60 (q, J = 269.6 Hz), 108.28.

HRMS (ESI): m/z calculated for $\text{C}_{17}\text{H}_{12}\text{ClF}_3\text{N}_3\text{O}_3\text{S}^+[\text{M}+\text{H}]^+$ 430.0240, found 430.0247.



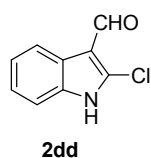
2-chloro-1H-pyrrole-3-carbaldehyde

The compound **2cc** was prepared according to **GP B** in 0.4 mmol scale to give yellow solid in 40% yield (20.6 mg), according to **GP D** in 0.4 mmol scale to give yellow solid in 32% yield (16.5 mg). Purified by column chromatography (Petroleum ether/EtOAc = 5:1).

^1H NMR (500 MHz, CDCl_3) δ 9.80 (s, 1H), 8.84 (s, 1H), 7.32-7.25 (m, 1H), 6.53-6.49 (m, 1H).

^{13}C NMR (126 MHz, CDCl_3) δ 183.14, 122.65, 121.65, 116.44, 106.12.

HRMS (ESI): m/z calculated for $\text{C}_5\text{H}_5\text{ClNO}^+[\text{M}+\text{H}]^+$ 130.0060, found 130.0065.



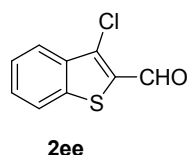
2-chloro-1H-indole-3-carbaldehyde

The compound **2dd** was prepared according to **GP B** in 0.4 mmol scale to give white solid in 49% yield (35.1 mg), according to **GP D** in 0.4 mmol scale to give white solid in 40% yield (28.6 mg). Purified by column chromatography (Petroleum ether/EtOAc = 5:1).

^1H NMR (500 MHz, DMSO) δ 12.27 (s, 1H), 10.02 (s, 1H), 7.69 (d, $J = 8.2$ Hz, 1H), 7.49 (d, $J = 8.4$ Hz, 1H), 7.43 (t, $J = 7.6$ Hz, 1H), 7.23 (t, $J = 7.5$ Hz, 1H).

^{13}C NMR (126 MHz, DMSO) δ 180.73, 137.02, 130.84, 128.14, 124.87, 121.95, 120.00, 114.86, 113.96.

HRMS (ESI): m/z calculated for $\text{C}_9\text{H}_7\text{ClNO}^+[\text{M}+\text{H}]^+$ 180.0216, found 180.0211.



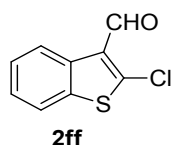
2-chlorobenzo[b]thiophene-2-carbaldehyde

The compound **2ee** was prepared according to **GP B** in 0.4 mmol scale to give white solid in 78% yield (61.2 mg), according to **GP D** in 0.4 mmol scale to give white solid in 63% yield (49.4 mg). Purified by column chromatography (Petroleum ether/EtOAc = 40:1).

^1H NMR (500 MHz, CDCl_3) δ 10.34 (s, 1H), 8.00 (d, $J = 8.1$ Hz, 1H), 7.86 (d, $J = 8.1$ Hz, 1H), 7.57 (t, $J = 7.5$ Hz, 1H), 7.52 (t, $J = 7.6$ Hz, 1H).

^{13}C NMR (101 MHz, CDCl_3) δ 183.34, 140.18, 136.50, 135.22, 130.89, 129.36, 125.85, 123.79, 123.51.

HRMS (ESI): m/z calculated for $\text{C}_9\text{H}_6\text{ClOS}^+[\text{M}+\text{H}]^+$ 196.9828, found 196.9822.



2-chlorobenzo[b]thiophene-3-carbaldehyde

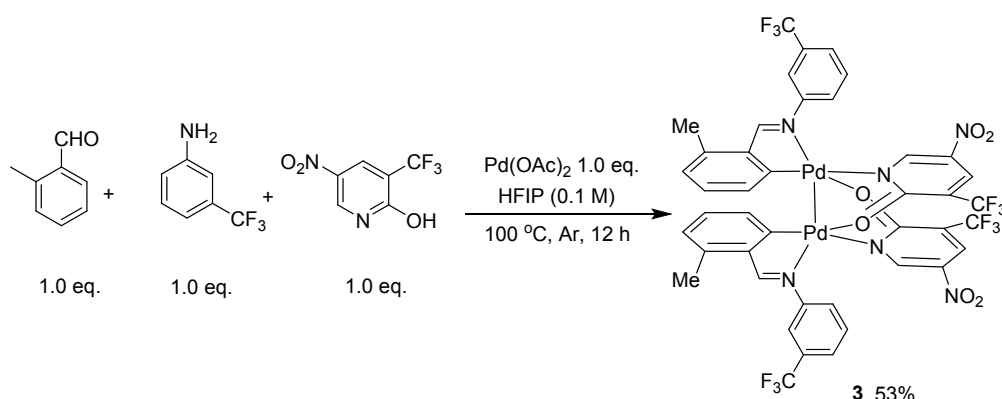
The compound **2ff** was prepared according to **GP B** in 0.4 mmol scale to give gray solid in 41% yield (32.1 mg), according to **GP D** in 0.4 mmol scale to give gray solid in 31% yield (24.3 mg). Purified by column chromatography (Petroleum ether/EtOAc = 40:1).

$^1\text{H NMR}$ (500 MHz, CDCl_3) δ 10.35 (s, 1H), 8.67 (d, $J = 8.0$ Hz, 1H), 7.75 (d, $J = 8.0$ Hz, 1H), 7.51 (t, $J = 7.7$ Hz, 1H), 7.45 (t, $J = 7.0$ Hz, 1H).

$^{13}\text{C NMR}$ (101 MHz, CDCl_3) δ 184.32, 148.34, 136.09, 135.03, 129.63, 126.62, 126.23, 124.22, 121.36.

HRMS (ESI): m/z calculated for $\text{C}_9\text{H}_6\text{ClOS}^+[\text{M}+\text{H}]^+$ 196.9828, found 196.9824.

2.6 Isolation and Subsequent Functionalization of Palladacycle

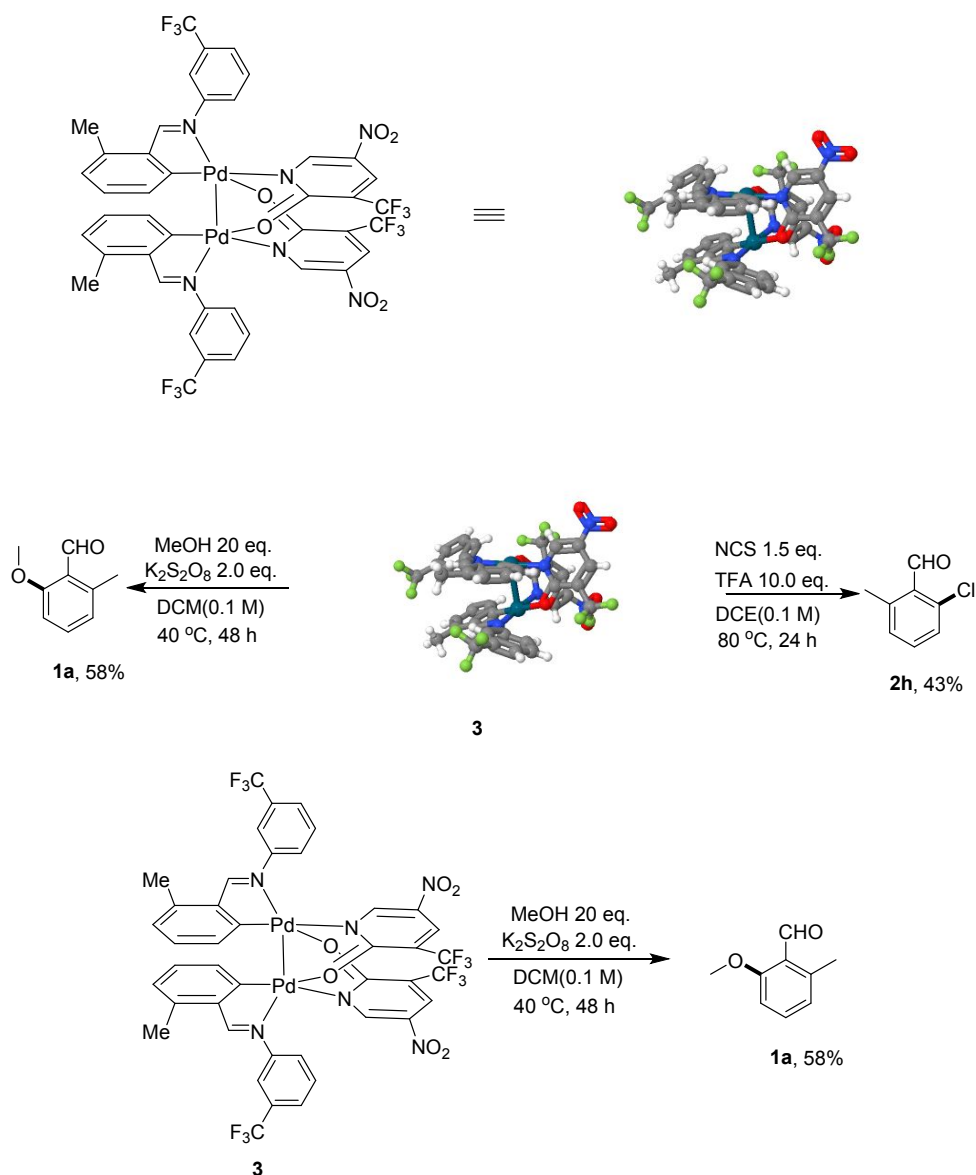


Following a previously reported procedure^[1,2], a 25 mL schlenk tube equipped with a stir bar was charged with $\text{Pd}(\text{OAc})_2$ (0.8 mmol, 179.2 mg), 5-nitro-3-(trifluoromethyl)pyridin-2-ol (0.8 mmol, 166.4 mg), The flask was evacuated and filled with argon three times. Next, 2-Methylbenzaldehyde (0.8 mmol, 96.0 mg), 3-(trifluoromethyl)aniline (0.8 mmol, 128.8 mg) and HFIP (8.0 mL) were added into the tube through syringes. The reaction was then stirred vigorously at 100 °C for 12 h. After cooling to rt, the reaction mixture was diluted with CH_2Cl_2 (20 mL), filtered through a pad of Celite, and the filtrate was then concentrated in vacuo. The residue was purified by flash silica gel column chromatography using petroleum ether/EtOAc (5: 1) as the eluting solvent to yield the desired Palladacycle **3** as a yellow solid (243.8 mg, 53%).

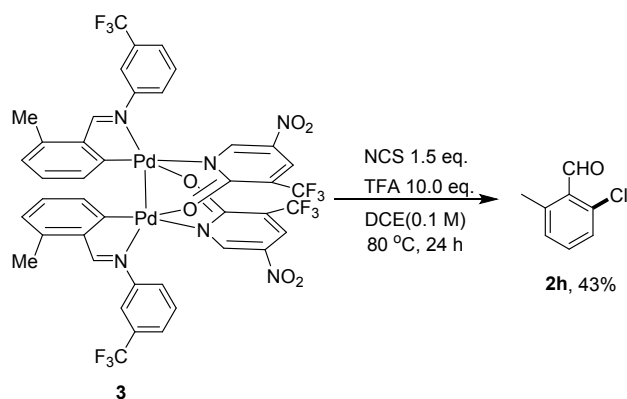
$^1\text{H NMR}$ (500 MHz, CDCl_3) δ 8.37 (d, $J = 2.9$ Hz, 2H), 8.20 (s, 2H), 7.49 (d, $J = 7.9$ Hz, 2H), 7.40 (d, $J = 7.8$ Hz, 2H), 7.28-7.25 (m, 2H), 6.90 (s, 2H), 6.78 (d, $J = 7.6$ Hz, 2H), 6.48 (t, $J = 7.7$ Hz, 2H), 5.39 (d, $J = 7.8$ Hz, 2H), 5.30 (s, 2H), 2.53 (s, 6H).

$^{13}\text{C NMR}$ (126 MHz, CDCl_3) δ 172.58, 168.34, 155.64, 151.48, 147.92, 143.38, 140.02, 132.87, 132.82, 131.89 (q, $J = 5.0$ HZ), 131.18, 130.92, 130.57, 129.20, 127.44, 127.20, 124.49, 122.76 (q, $J = 122.8$ HZ), 117.64 (q, $J = 3.9$ HZ), 116.34 (q, $J = 33.1$ HZ), 19.83.

HRMS (ESI): m/z calculated for $\text{C}_{42}\text{H}_{27}\text{F}_{12}\text{N}_6\text{O}_6\text{Pd}_2^+[\text{M}+\text{H}]^+$ 1150.9870, found 1150.9878.

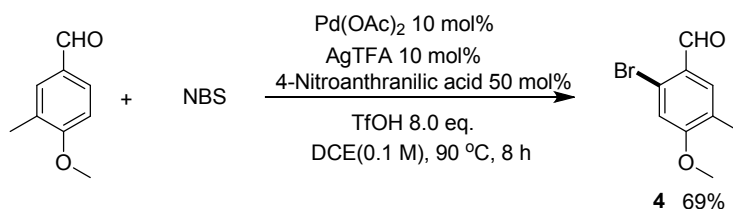


A 10 mL reaction tube with a stir bar was charged with Palladacycle **3** (0.1 mmol, 115.2 mg), $\text{K}_2\text{S}_2\text{O}_8$ (0.4 mmol, 108.0 mg), followed by the addition of Methanol (4.0 mmol, 128.0 mg) and CH_2Cl_2 (2.0 mL). The tube was then sealed and heated at 40 °C for 48 h. The reaction mixture was cooled to room temperature, filtrated via celite, washed with CH_2Cl_2 and the filtrate concentrated under reduced pressure. The resulting residue was purified by column chromatography (Petroleum ether/EtOAc = 10: 1) to provide the product **1a** as a white solid (17.4 mg, 58%).



A 10 mL reaction tube with a stir bar was charged with Palladacycle **3** (0.1 mmol, 115.2 mg), NCS (0.3 mmol, 39.9 mg), followed by the addition of TFA (2.0 mmol, 228.0 mg) and DCE (2.0 mL). The tube was then sealed and heated at 80 °C for 24 h. Upon completion, the reaction mixture was quenched by sat. NaHCO₃ (aq) (15 mL), and extracted with CH₂Cl₂ for 3 times. The combined organic layers were washed with water (25 mL), dried over anhydrous Na₂SO₄, and concentrated *in vacuo*. The crude residue was purified by column chromatography on silica gel using petroleum ether/EtOAc (50:1) as eluent to afford the desired product **2h** as a white solid (13.2 mg, 43%).

2.7 Synthesis of Key Intermediates of Natural Products and Drug.

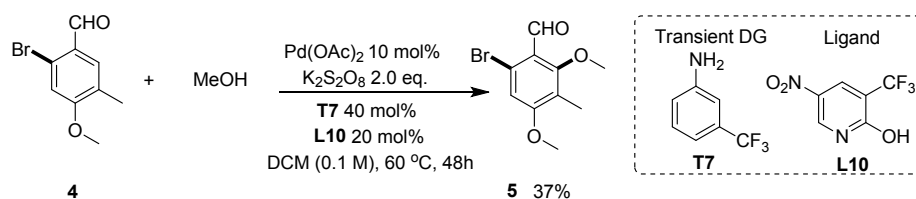


Following a previously reported procedure^[3], a sealed tube with magnetic stir bar was charged with 4-methoxy-3-methylbenzaldehyde (2.0 mmol, 300.0mg), NBS (3.0 mmol, 531 mg), Pd(OAc)₂ (0.2 mmol, 44.8 mg), AgTFA (0.2 mmol, 44.2 mg), 4-Nitroanthranilic acid (1.0 mmol, 182.0 mg) in air, followed by DCE (20.0 mL) and TfOH (16.0 mmol, 2400.0 mg). The reaction mixture was stirred at 90 °C for 8 hours. Upon completion, the reaction mixture was quenched by sat. NaHCO₃ (aq) (60 mL), and extracted with CH₂Cl₂ for 3 times. The combined organic layers were washed with water (100 mL), dried over anhydrous Na₂SO₄, and concentrated *in vacuo*. The crude residue was purified by column chromatography on silica gel using petroleum ether/CH₂Cl₂/EtOAc (40:1:1) as eluent to afford the desired product **4** as a white solid (314.6 mg, 69%).

¹H NMR (500 MHz, CDCl₃) δ 9.81 (s, 1H), 7.85 (s, 1H), 7.60 (s, 1H), 3.83 (s, 3H), 2.35 (s, 3H).

¹³C NMR (126 MHz, CDCl₃) δ 190.02, 160.55, 134.26, 133.38, 132.78, 131.65, 118.26, 60.31, 16.66.

HRMS (ESI): *m/z* calculated for C₉H₁₀BrO₂⁺[M+H]⁺ 228.9864, found 228.9867.

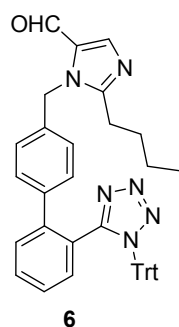
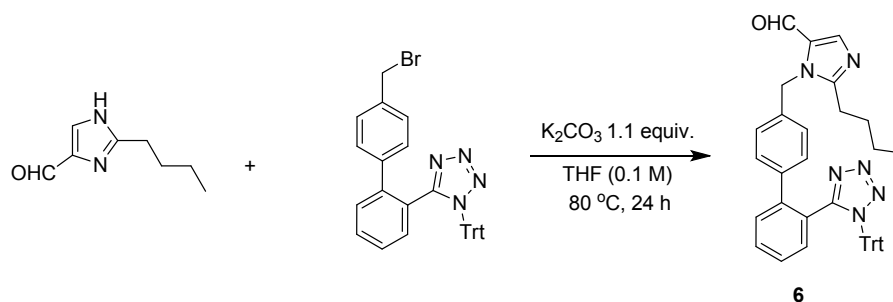


A sealed tube with magnetic stir bar was charged with 2-bromo-4-methoxy-5-methylbenzaldehyde **4** (0.4 mmol, 91.2 mg), Pd(OAc)₂ (0.04 mmol, 9.0 mg), K₂S₂O₈ (0.8 mmol, 216.0 mg), and **L10** (0.08 mmol, 16.6 mg) in air, followed by CH₂Cl₂ (4.0 mL), MeOH (8.0 mmol, 256.0 mg) and **T7** (0.16 mmol, 25.8 mg). The reaction mixture was stirred at 60 °C for 24 hours. Upon completion, the reaction mixture was cooled to room temperature and filtered through a sand funnel. The reaction filtrate was washed with water (10 mL), dried over anhydrous Na₂SO₄, and concentrated *in vacuo*. The crude residue was purified by column chromatography on silica gel using petroleum ether/EtOAc (10:1) as eluent to afford the desired product **5** as a red solid (38.2 mg, 37%).

¹H NMR (500 MHz, CDCl₃) δ 10.37 (s, 1H), 6.43 (s, 1H), 3.92 (s, 3H), 3.92 (s, 3H), 2.28 (s, 3H).

¹³C NMR (126 MHz, CDCl₃) δ 190.37, 162.45, 161.72, 129.43, 120.80, 116.77, 93.93, 56.26, 55.93, 14.94.

HRMS (ESI): *m/z* calculated for C₁₀H₁₂BrO₃⁺[M+H]⁺ 258.9970, found 258.9967.



2-butyl-1-((2'-(1-trityl-1H-tetrazol-5-yl)-[1,1'-biphenyl]-4-yl)methyl)-1H-imidazole-5-carbaldehyde

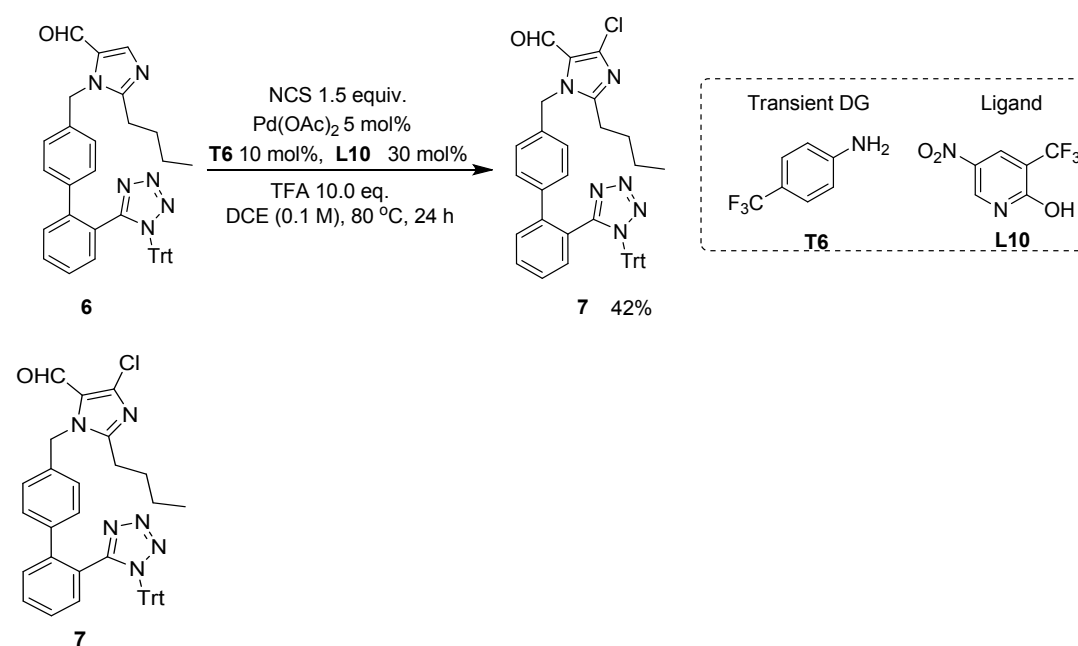
Following a previously reported procedure^[4], a sealed tube with magnetic stir bar was charged with 2-butyl-1H-imidazole-4-carbaldehyde (0.8 mmol, 121.6 mg), 5-(4-(bromomethyl)-[1,1'-biphenyl]-2-yl)-1-trityl-1H-tetrazole (0.8 mmol, 444.8 mg), K₂CO₈ (0.88 mmol, 121.4 mg) in a solvent THF (8.0 mL). The reaction mixture was stirred 24 hours at 80 °C. Upon completion, the reaction mixture was filtered through a sand core funnel, it was then diluted with water (50 mL) and the mixture was extracted with CH₂Cl₂ (50mLx3).

The organic layer were dried with anhydrous Na₂SO₄. The solution was concentrated in vacuo and purified by column chromatography on silica gel using petroleum ether/CH₂Cl₂/EtOAc (1:1:1) as the eluent to afford the desired product **6** as a Light yellow solid (409.3 mg, 81%).

¹H NMR (500 MHz, CDCl₃) δ 9.77 (s, 1H), 7.97 (dd, *J* = 7.4, 1.4 Hz, 1H), 7.52 – 7.44 (m, 2H), 7.37 (s, 1H), 7.37 – 7.35 (m, 1H), 7.33 (t, *J* = 7.3 Hz, 3H), 7.24 (t, *J* = 6.6 Hz, 6H), 7.15 (d, *J* = 8.1 Hz, 2H), 6.92 (d, *J* = 7.8 Hz, 6H), 6.83 (d, *J* = 8.0 Hz, 2H), 4.96 (s, 2H), 2.65 – 2.60 (m, 2H), 1.73 (dt, *J* = 15.5, 7.7 Hz, 2H), 1.37 (dd, *J* = 15.0, 7.5 Hz, 2H), 0.91 (t, *J* = 7.4 Hz, 3H).

¹³C NMR (126 MHz, CDCl₃) δ 185.61, 163.92, 151.00, 141.67, 141.25, 141.23, 141.10, 140.52, 133.50, 130.69, 130.28, 130.26, 130.10, 128.38, 128.31, 127.96, 127.68, 126.55, 126.35, 126.25, 126.21, 125.99, 82.94, 49.85, 29.73, 26.70, 22.50, 13.84.

HRMS (ESI): *m/z* calculated for C₄₁H₃₇N₆O⁺[M+H]⁺ 529.3029, found 529.3023.



2-butyl-4-chloro-1-((2'-(1-trityl-1H-tetrazol-5-yl)-[1,1'-biphenyl]-4-yl)methyl)-1H-imidazole-5-carbaldehyde

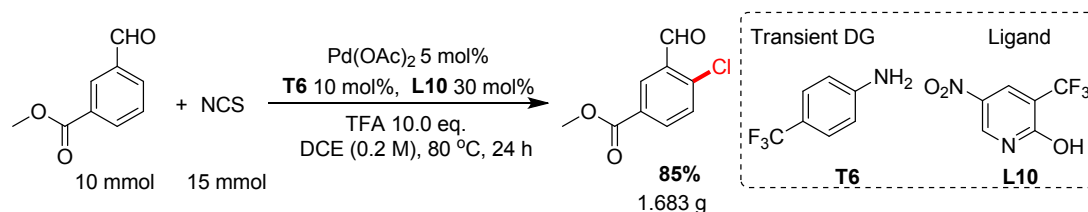
A sealed tube with magnetic stir bar was charged with substrate **6** (0.4 mmol, 251.2mg), NCS (0.6 mmol, 79.8 mg), Pd(OAc)₂ (0.02 mmol, 4.5 mg), **L10** (0.12 mmol, 25.0 mg) in air, followed by DCE (4.0 mL), **T6** (0.04 mmol, 6.4 mg) and TFA (4.0 mmol, 456.0 mg). The reaction mixture was stirred at 80 °C for 24 hours. Upon completion, the reaction mixture was quenched by sat. NaHCO₃ (aq) (30 mL), and extracted with CH₂Cl₂ for 3 times. The combined organic layers were washed with water (50 mL), dried over anhydrous Na₂SO₄, and concentrated *in vacuo*. The crude residue was purified by column chromatography on silica gel using petroleum ether/CH₂Cl₂/EtOAc (2:2:1) as eluent to afford the desired product **7** as a white solid (111.2 mg, 42%).

¹H NMR (500 MHz, CDCl₃) δ 9.92 (s, 1H), 7.96 (dd, *J* = 7.4, 1.4 Hz, 1H), 7.52 – 7.45 (m, 2H), 7.37 – 7.33 (m, 2H), 7.32 (d, *J* = 7.3 Hz, 2H), 7.27 (s, 2H), 7.25 (s, 3H), 7.24 (s, 1H), 7.14 (d, *J* = 8.1 Hz, 2H), 6.92 (d, *J* = 7.6 Hz, 6H), 6.80 (d, *J* = 8.1 Hz, 2H), 5.05 (s, 2H), 2.56 – 2.52 (m, 2H), 1.67 (dd, *J* = 15.1, 7.3 Hz, 2H), 1.34 – 1.28 (m, 2H), 0.86 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR (126 MHz, CDCl_3) δ 183.70, 163.87, 150.36, 141.51, 141.21, 141.08, 134.30, 132.76, 130.72, 130.27, 130.06, 128.34, 127.92, 127.66, 126.22, 125.54, 125.13, 82.92, 46.71, 29.14, 27.47, 22.35, 13.77.

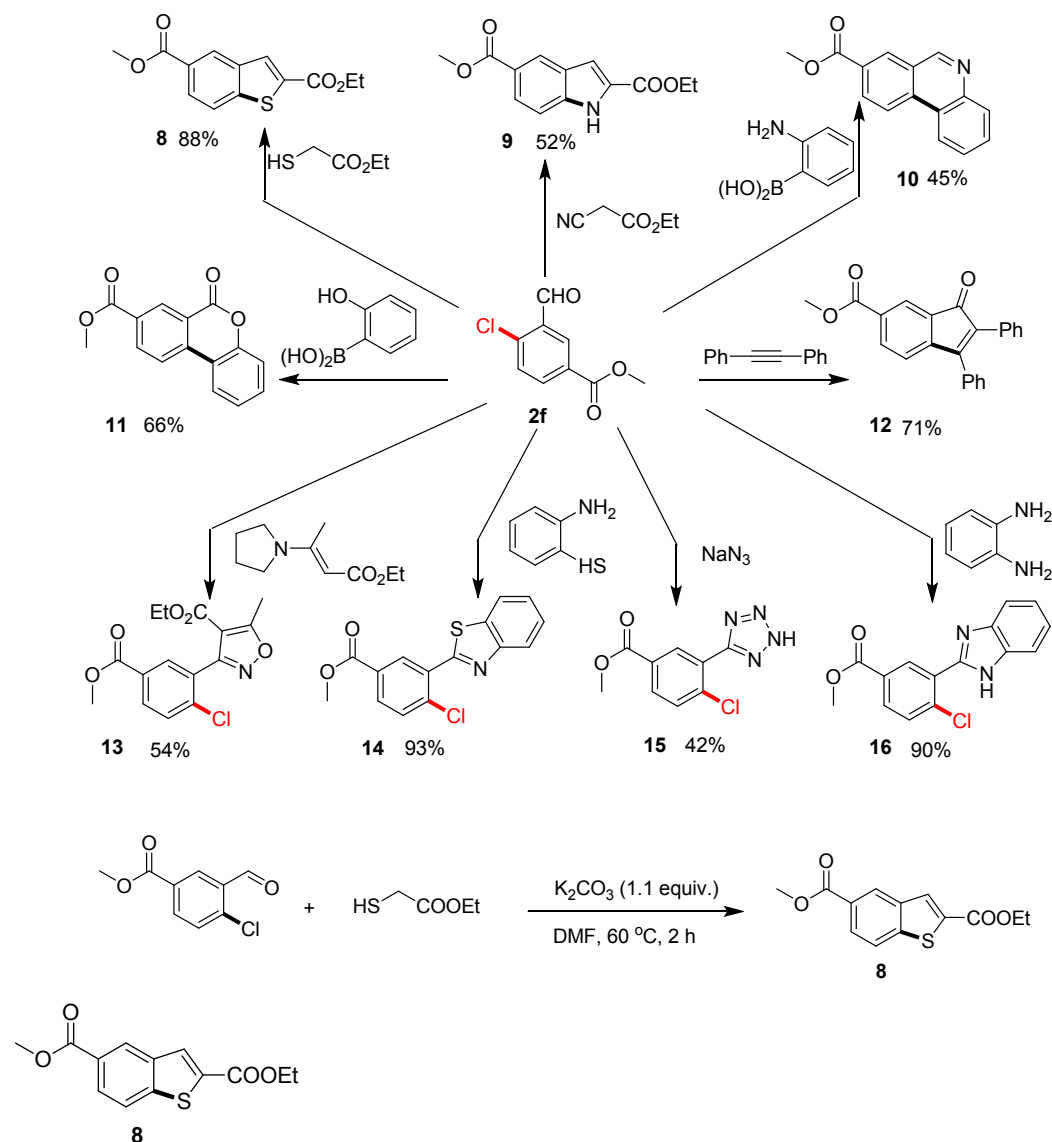
HRMS (ESI): m/z calculated for $\text{C}_{41}\text{H}_{36}\text{ClN}_6\text{O}^+[\text{M}+\text{H}]^+$ 663.2639, found 663.2632.

2.8 Gram-scale Preparation of **2f**



A sealed tube with magnetic stir bar was charged with methyl 3-formylbenzoate (10.0 mmol, 1640.0 mg), NCS (15.0 mmol, 1995.0 mg), $\text{Pd}(\text{OAc})_2$ (0.5 mmol, 112.0 mg), **L10** (3.0 mmol, 624.0 mg) in air, followed by DCE (50.0 mL), **T6** (1.0 mmol, 161.0 mg) and TFA (100.0 mmol, 11400.0 mg). The reaction mixture was stirred at 80 °C for 24 hours. Upon completion, the reaction mixture was quenched by sat. NaHCO_3 (aq) (300 mL), and extracted with CH_2Cl_2 for 3 times. The combined organic layers were washed with water (500 mL), dried over anhydrous Na_2SO_4 , and concentrated *in vacuo*. The crude residue was purified by column chromatography on silica gel using petroleum ether/EtOAc (10:1) as eluent to afford the desired product **2f** as a white solid (1.683g, 85%).

2.9 Synthesis of a Series of Biological Rings by 2f



2-ethyl 5-methyl benzo[b]thiophene-2,5-dicarboxylate

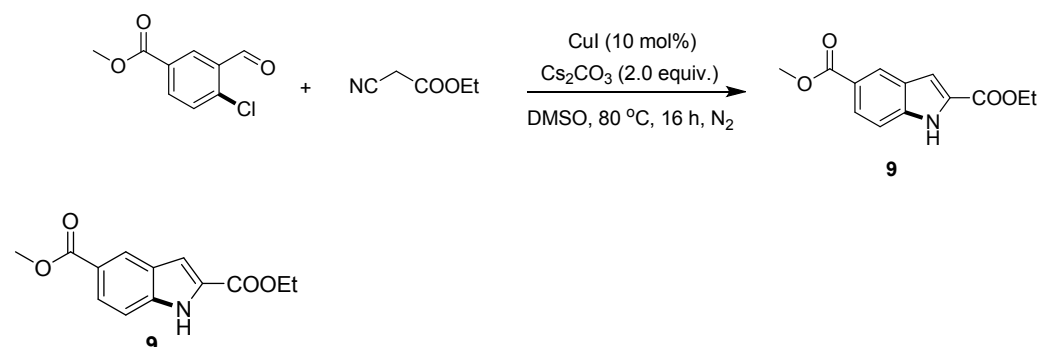
Following a previously reported procedure^[5], to a 10 mL of sealed tube were added methyl 4-chloro-3-formylbenzoate **2f** (0.4 mmol, 79.2 mg), ethyl thioglycolate (0.2 mmol, 48.0 mg), K₂CO₃ (0.44 mmol, 60.7 mg), were combined in 4.0 mL DMF, and the mixture was heated to 60 °C, for 2 h with stirring, the reaction was cooled and poured into ice-water, giving a viscous semisolid, the aqueous mixture was diluted with brine and extracted with CH₂Cl₂ (3 × 20 mL), the combined organic extract was washed sequentially with water and brine dried over anhydrous Na₂SO₄, and concentrated to dryness under the reduced pressure. The residual was purified by column chromatography on silica gel using petroleum ether/EtOAc (10:1) as eluent to give the desired product **8** as a white solid (92.9 mg, 88%).

¹H NMR (500 MHz, CDCl₃) δ 8.55 (s, 1H), 8.08 (s, 1H), 8.07 (d, *J* = 8.6 Hz, 1H), 8.07 (dd, *J* = 8.6, 1.5 Hz, 1H), 7.88 (d, *J* = 8.6 Hz, 1H), 4.41 (q, *J* = 7.1 Hz, 2H), 3.95 (s, 3H), 1.41 (t, *J* = 7.1 Hz, 3H).

¹³C NMR (126 MHz, CDCl₃) δ 166.77, 162.29, 146.15, 138.42, 135.42, 130.57, 127.38,

127.23, 127.00, 122.65, 61.78, 52.23, 14.27.

HRMS (ESI): m/z calculated for $C_{13}H_{13}O_4S^+[M+H]^+$ 265.0535, found 265.0531.



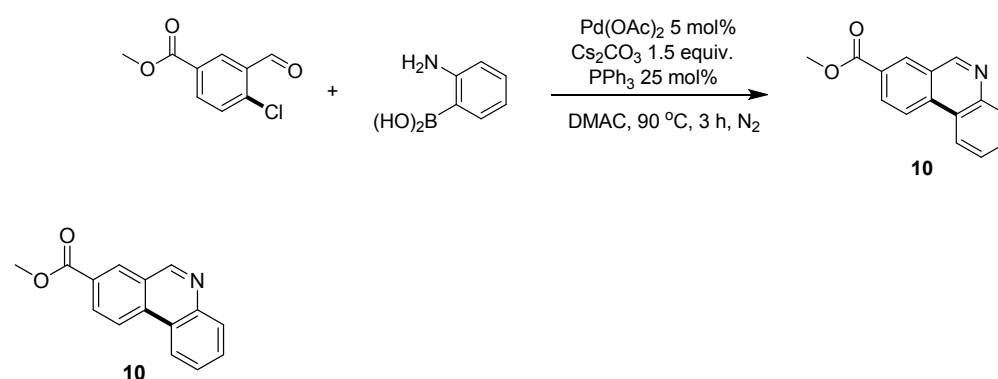
2-ethyl 5-methyl 1H-indole-2,5-dicarboxylate

Following a previously reported procedure^[6], a 25 mL schlenk tube equipped with a stir bar was charged with methyl 4-chloro-3-formylbenzoate **2f** (0.4 mmol, 79.2 mg), CuI (0.04 mmol, 7.6 mg), Cs_2CO_3 (0.8 mmol, 260.8 mg). The tube was evacuated and filled with nitrogen three times. Next, Ethyl cyanoacetate (0.44 mmol, 58.8 mg) and DMSO (4.0 mL) were added into the flask through syringes. The reaction was then stirred vigorously at $80\text{ }^\circ C$ for 16 h. Upon completion, the reaction mixture was quenched by sat. $NaHCO_3$ (aq) (30 mL), and extracted with CH_2Cl_2 for 3 times. The combined organic layers were washed with water (50 mL), dried over anhydrous Na_2SO_4 , and concentrated *in vacuo*. The crude residue was purified by column chromatography on silica gel using petroleum ether/ CH_2Cl_2 /EtOAc (20:20:1) as eluent to afford the desired product **9** as a white solid (51.4 mg, 52%).

1H NMR (500 MHz, $CDCl_3$) δ 9.39 (s, 1H), 8.47 (s, 1H), 8.01 (dd, $J = 8.7, 1.4$ Hz, 1H), 7.45 (d, $J = 8.7$ Hz, 1H), 7.31 (s, 1H), 4.44 (q, $J = 7.1$ Hz, 2H), 3.94 (s, 3H), 1.43 (t, $J = 7.1$ Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 167.63, 161.74, 139.17, 129.00, 127.04, 126.23, 125.79, 123.07, 111.66, 109.79, 61.32, 51.96, 14.34.

HRMS (ESI): m/z calculated for $C_{13}H_{14}NO_4^+[M+H]^+$ 248.0923, found 248.0931.



methyl phenanthridine-8-carboxylate

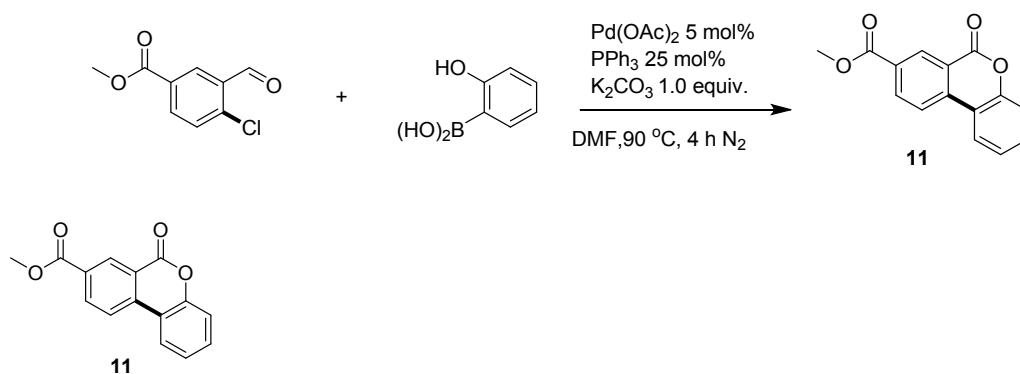
Following a previously reported procedure^[7], a 25 mL schlenk tube equipped with a stir bar was charged with methyl 4-chloro-3-formylbenzoate **2f** (0.4 mmol, 79.2 mg), $Pd(OAc)_2$ (0.02 mmol, 4.5 mg), Cs_2CO_3 (0.6 mmol, 195.6 mg), Triphenylphosphine (0.1 mmol, 26.2 mg),

2-Aminophenylboronic acid (0.48 mmol, 65.8 mg) The tube was evacuated and filled with nitrogen three times. Next, DMAC (4.0 mL) were added into the flask through syringes. The reaction was then stirred vigorously at 90 °C for 3 h. Upon completion, the reaction mixture was diluted by water (30 mL), and extracted with CH₂Cl₂ for 3 times. The combined organic layers were washed with saturation salt solution (30 mL), dried over anhydrous Na₂SO₄, and concentrated *in vacuo*. The crude residue was purified by column chromatography on silica gel using petroleum ether/EtOAc (10:1) as eluent to afford the desired product **10** as a white solid (42.7 mg, 45%).

¹H NMR (500 MHz, CDCl₃) δ 9.35 (s, 1H), 8.76 (d, *J* = 1.4 Hz, 1H), 8.64 (d, *J* = 8.6 Hz, 1H), 8.59 (d, *J* = 8.1 Hz, 1H), 8.45 (dd, *J* = 8.6, 1.7 Hz, 1H), 8.21 (d, *J* = 8.2 Hz, 1H), 7.81 (t, *J* = 7.6 Hz, 1H), 7.72 (t, *J* = 7.6 Hz, 1H), 4.02 (s, 3H).

¹³C NMR (126 MHz, CDCl₃) δ 166.32, 153.73, 145.33, 135.49, 131.04, 130.77, 130.37, 129.84, 129.06, 127.51, 125.80, 123.48, 122.78, 122.26, 52.46.

HRMS (ESI): *m/z* calculated for C₁₅H₁₂NO₂⁺[M+H]⁺ 238.0868, found 238.0861.



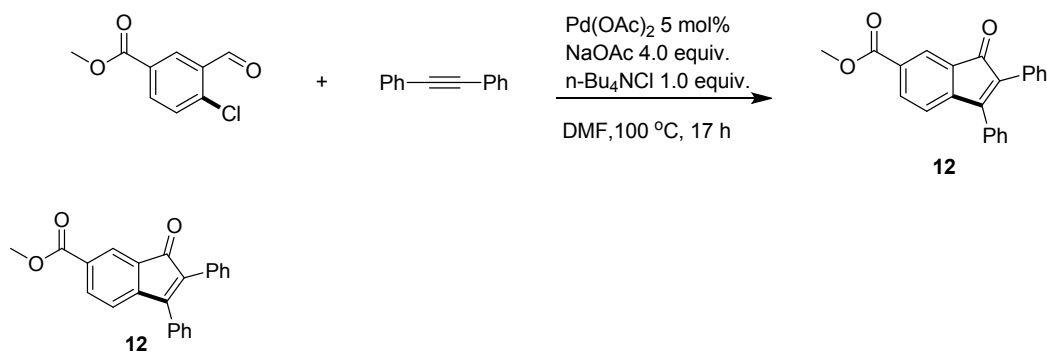
methyl 6-oxo-6H-benzo[c]chromene-8-carboxylate

Following a previously reported procedure^[8], a 25 mL schlenk tube equipped with a stir bar was charged with methyl 4-chloro-3-formylbenzoate **2f** (0.4 mmol, 79.2 mg), Pd(OAc)₂ (0.02 mmol, 4.5 mg), K₂CO₃ (0.4 mmol, 55.2 mg), Triphenylphosphine (0.1 mmol, 26.2 mg), 2-Hydroxyphenylboronic acid (0.4 mmol, 55.2 mg) The tube was evacuated and filled with nitrogen three times. Next, DMF (4.0 mL) were added into the flask through syringes. The reaction was then stirred vigorously at 90 °C for 4 h. Upon completion, the reaction mixture was diluted by water (30 mL), and extracted with CH₂Cl₂ for 3 times. The combined organic layers were washed with saturation salt solution (30 mL), dried over anhydrous Na₂SO₄, and concentrated *in vacuo*. The crude residue was purified by column chromatography on silica gel using petroleum ether/EtOAc (10:1) as eluent to afford the desired product **11** as a white solid (67.1 mg, 66%).

¹H NMR (500 MHz, CDCl₃) δ 9.04 (s, 1H), 8.44 (dd, *J* = 8.4, 1.3 Hz, 1H), 8.18 (d, *J* = 8.4 Hz, 1H), 8.09 (d, *J* = 7.8 Hz, 1H), 7.54 (t, *J* = 7.7 Hz, 1H), 7.39 (s, 1H), 7.37 (t, *J* = 7.5 Hz, 1H), 3.98 (s, 3H).

¹³C NMR (126 MHz, CDCl₃) δ 165.49, 160.32, 151.85, 138.31, 135.16, 132.32, 131.65, 130.60, 124.82, 123.41, 122.03, 121.30, 117.96, 117.30, 52.50.

HRMS (ESI): *m/z* calculated for C₁₅H₁₁O₄⁺[M+H]⁺ 255.0675, found 255.0669.



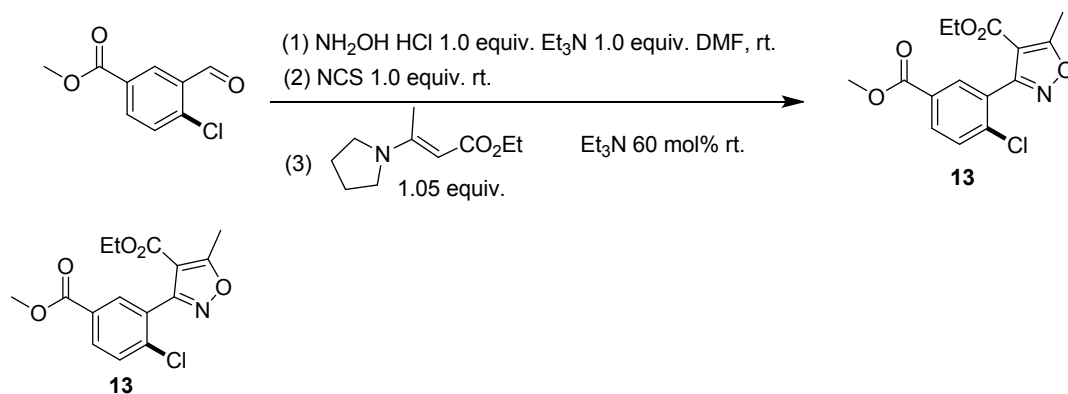
methyl 1-oxo-2,3-diphenyl-1H-indene-6-carboxylate

Following a previously reported procedure^[9], a 10 mL reaction tube with a stir bar was charged with methyl 4-chloro-3-formylbenzoate **2f** (0.4 mmol, 79.2 mg), Pd(OAc)₂ (0.02 mmol, 4.5 mg), NaOAc (1.6 mmol, 217.6 mg) n-Bu₄NCl (0.4 mmol, 111.2 mg) followed by the addition of DMF (4.0 mL) and Diphenylacetylene (0.8 mol, 142.4 mg). The flask was then sealed and heated at 100 °C for 17 h. The reaction solution was cooled to room temperature, diluted with diethyl ether (10 mL) and washed with ammonium chloride solution (10 mL×2). The organic layer were dried with anhydrous Na₂SO₄. The solution was concentrated in vacuo and purified by column chromatography on silica gel using petroleum ether/EtOAc (8:1) as the eluent to afford the desired product **12** as an red oil (96.6 mg, 71%).

¹H NMR (500 MHz, CDCl₃) δ 8.21 (d, *J* = 1.1 Hz, 1H), 8.12 (dd, *J* = 7.7, 1.4 Hz, 1H), 7.46 – 7.42 (m, 3H), 7.38 (dd, *J* = 6.6, 3.0 Hz, 2H), 7.30 – 7.26 (m, 5H), 7.23 (d, *J* = 7.7 Hz, 1H), 3.94 (s, 3H).

¹³C NMR (126 MHz, CDCl₃) δ 195.10, 166.06, 154.39, 149.62, 135.55, 134.63, 132.29, 130.96, 130.85, 130.28, 130.01, 129.55, 128.94, 128.47, 128.19, 128.15, 123.59, 120.95, 52.30.

HRMS (ESI): *m/z* calculated for C₂₃H₁₇O₃⁺[M+H]⁺ 341.1178, found 341.1185.



methyl 3-(1H-benzo[d]imidazol-2-yl)-4-chlorobenzoate

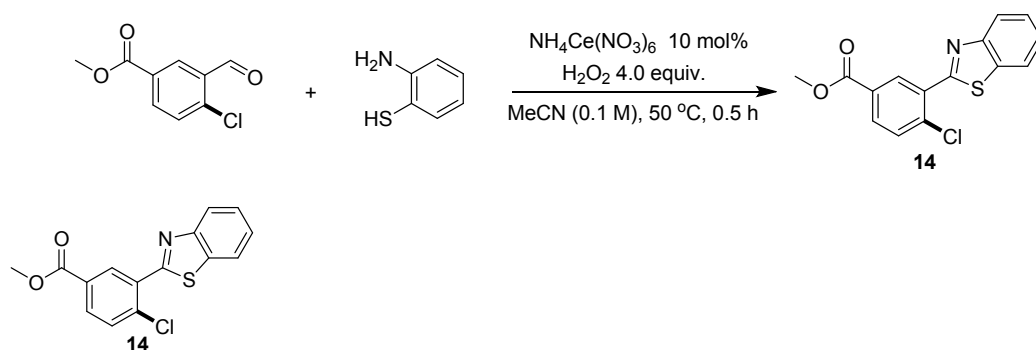
Following a previously reported procedure^[10], a sealed tube with magnetic stir bar was charged with methyl 4-chloro-3-formylbenzoate **2f** (0.4 mmol, 79.2 mg), followed by the addition of NH₂OH · HCl (0.4 mmol, 27.6 mg) and DMF (4.0 mL), the reaction solution was stirred at 0 °C. Next followed by the addition Et₃N (0.4 mmol, 40.4 mg), in the reaction solution at 0 °C. After the completion of the dropwise addition, the reaction solution was reacted at room temperature for 2 h. Then, the reaction liquid was cooled to 0 °C, and

N-chlorosuccinimide (NCS) (0.4 mmol, 53.2 mg) was slowly added to the reaction liquid. The temperature was slowly raised from 0 °C to room temperature overnight. Next Ethyl crotonate (0.42 mmol, 47.9 mg), Et₃N (0.24 mmol, 24.2 mg) was dissolved in 5 mL of absolute ethanol, and then slowly added to the reaction solution at room temperature. The reaction was allowed to react at room temperature for 16 h. After the reaction was completed, the reaction solution was diluted with 30 mL of water and then extracted three times with dichloromethane (3×20 mL). the combined organic extract was washed with brine dried over anhydrous Na₂SO₄, and concentrated to dryness under the reduced pressure. The residual was purified by column chromatography on silica gel using petroleum ether/EtOAc (8:1) as eluent to give desired product **13** as a white solid (70.4 mg, 54%).

¹H NMR (500 MHz, CDCl₃) δ 8.05 (s, 1H), 8.03 (d, *J* = 2.1 Hz, 1H), 7.51 (d, *J* = 8.2 Hz, 1H), 4.09 (q, *J* = 7.1 Hz, 2H), 3.87 (s, 3H), 2.73 (s, 3H), 1.02 (t, *J* = 7.1 Hz, 3H).

¹³C NMR (126 MHz, CDCl₃) δ 175.43, 165.55, 161.24, 160.01, 139.04, 132.13, 131.66, 129.48, 129.21, 128.75, 109.71, 60.59, 52.28, 13.62, 13.07.

HRMS (ESI): *m/z* calculated for C₁₅H₁₅ClNO₅⁺[M+H]⁺ 324.0639, found 324.0633.



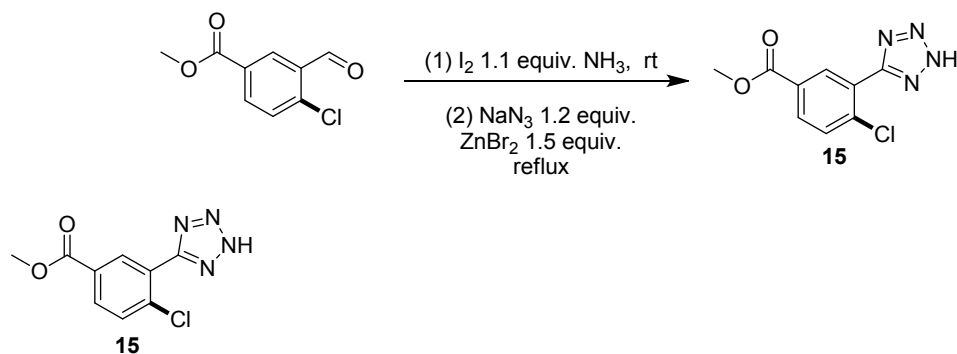
methyl 3-(benzo[d]thiazol-2-yl)-4-chlorobenzoate

Following a previously reported procedure^[11], a sealed tube with magnetic stir bar was charged with methyl 4-chloro-3-formylbenzoate **2f** (0.4 mmol, 79.2 mg), 2-Aminobenzenethiol (0.4 mmol, 50.0 mg), NH₄Ce(NO₃)₆ (0.04 mmol, 21.9 mg), H₂O₂ (30%) 0.4 mL (1.6 mol, 4.0 equiv.) in a solvent MeCN (4.0 mL). The reaction mixture was stirred 0.5 hours at 50 °C. Upon completion, the reaction mixture was diluted with water (50 mL) and the mixture was extracted with CH₂Cl₂ (50mLx3). The organic layer was dried with anhydrous Na₂SO₄. The solution was concentrated in vacuo and purified by column chromatography on silica gel using petroleum ether/ CH₂Cl₂/EtOAc (20:20:1) as the eluent to afford the desired product **14** as a white solid (112.7 mg, 93%).

¹H NMR (500 MHz, CDCl₃) δ 8.88 (d, *J* = 2.1 Hz, 1H), 8.16 (d, *J* = 8.2 Hz, 1H), 8.05 (dd, *J* = 8.4, 2.1 Hz, 1H), 7.96 (d, *J* = 8.0 Hz, 1H), 7.61 (d, *J* = 8.4 Hz, 1H), 7.54 (t, *J* = 7.7 Hz, 1H), 7.45 (t, *J* = 7.6 Hz, 1H), 3.96 (s, 3H).

¹³C NMR (126 MHz, CDCl₃) δ 165.66, 162.94, 152.52, 137.34, 136.13, 132.97, 132.59, 131.64, 131.06, 129.37, 126.44, 125.70, 123.70, 121.41, 52.44.

HRMS (ESI): *m/z* calculated for C₁₅H₁₁ClNO₂S⁺[M+H]⁺ 304.0199, found 304.0193.



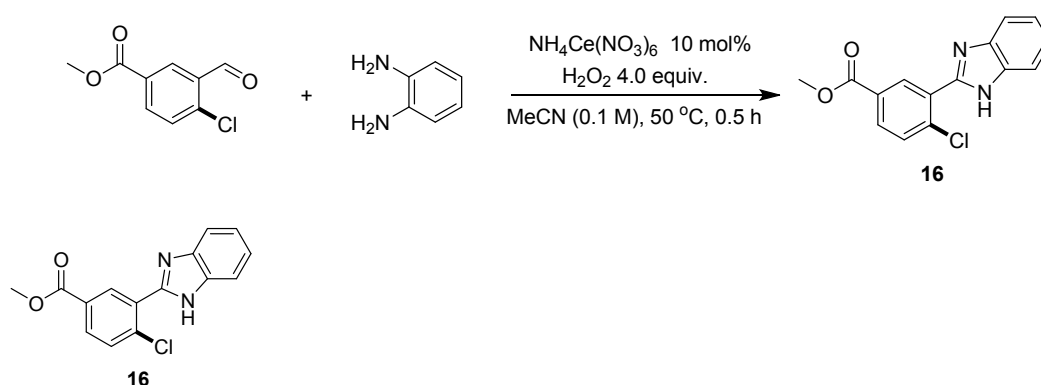
methyl 4-chloro-3-(2H-tetrazol-5-yl)benzoate

Following a previously reported procedure^[12], a sealed tube with magnetic stir bar was charged with methyl 4-chloro-3-formylbenzoate **2f** (0.4 mmol, 79.2 mg), iodine (0.44 mol, 111.8 mg), followed by the addition of NH₃ • H₂O (2.5 mL, 28%) and THF (1.5 mL). After reacting for 1 hour at room temperature, the reaction liquid gradually changed from black to colorless, and the reaction was completed. Next followed by the addition NaN₃ (0.48 mmol, 31.2 mg), ZnBr₂ (0.6 mmol, 135.0 mg), The reaction solution was refluxed at 80 °C for 48 h, then 10 mL of HCl (1 M) and 15 mL of ethyl acetate were added, and the mixture was stirred until the solid disappeared, the aqueous phase was adjusted to pH = 1, and then the organic phase was extracted. The organic layer was dried with anhydrous Na₂SO₄. The solution was concentrated in vacuo and purified by column chromatography on silica gel using petroleum ether/EtOAc (8:1) as the eluent to afford the desired product **15** as a light yellow solid (39.9 mg, 42%).

¹H NMR (500 MHz, DMSO) δ 11.87 (s, 1H), 8.37 (s, 1H), 8.35 (d, *J* = 2.1 Hz, 1H), 7.91 (dd, *J* = 8.4, 2.1 Hz, 1H), 7.64 (d, *J* = 8.4 Hz, 1H), 3.87 (s, 3H).

¹³C NMR (126 MHz, DMSO) δ 165.55, 144.30, 137.21, 131.28, 131.22, 130.92, 129.31, 127.74, 52.91.

HRMS (ESI): *m/z* calculated for C₉H₈ClN₄O₂⁺[M+H]⁺ 239.0366, found 239.0371.



methyl 3-(1H-benzo[d]imidazol-2-yl)-4-chlorobenzoate

Following a previously reported procedure^[11], a sealed tube with magnetic stir bar was charged with methyl 4-chloro-3-formylbenzoate **2f** (0.4 mmol, 79.2 mg), O-phenylenediamine (0.4 mmol, 43.2 mg), NH₄Ce(NO₃)₆ (0.04 mmol, 21.9 mg), H₂O₂ (30%) 0.4 mL (1.6 mol, 4.0 equiv.) in a solvent MeCN (4.0 mL). The reaction mixture was stirred 0.5 hours at 50 °C. Upon completion, the reaction mixture was diluted with water (50 mL)

and the mixture was extracted with CH₂Cl₂ (50mLx3). The organic layer was dried with anhydrous Na₂SO₄. The solution was concentrated in vacuo and purified by column chromatography on silica gel using petroleum ether/ CH₂Cl₂/EtOAc (20:20:1) as the eluent to afford the desired product **16** as a light yellow solid (102.9 mg, 90%).

¹H NMR (500 MHz, CDCl₃) δ 10.72 (s, 1H), 8.91 (d, *J* = 2.1 Hz, 1H), 7.97 (dd, *J* = 8.4, 2.1 Hz, 1H), 7.68 (s, 2H), 7.50 (d, *J* = 8.4 Hz, 1H), 7.32 (d, *J* = 3.1 Hz, 1H), 7.30 (d, *J* = 3.2 Hz, 1H), 3.87 (s, 3H).

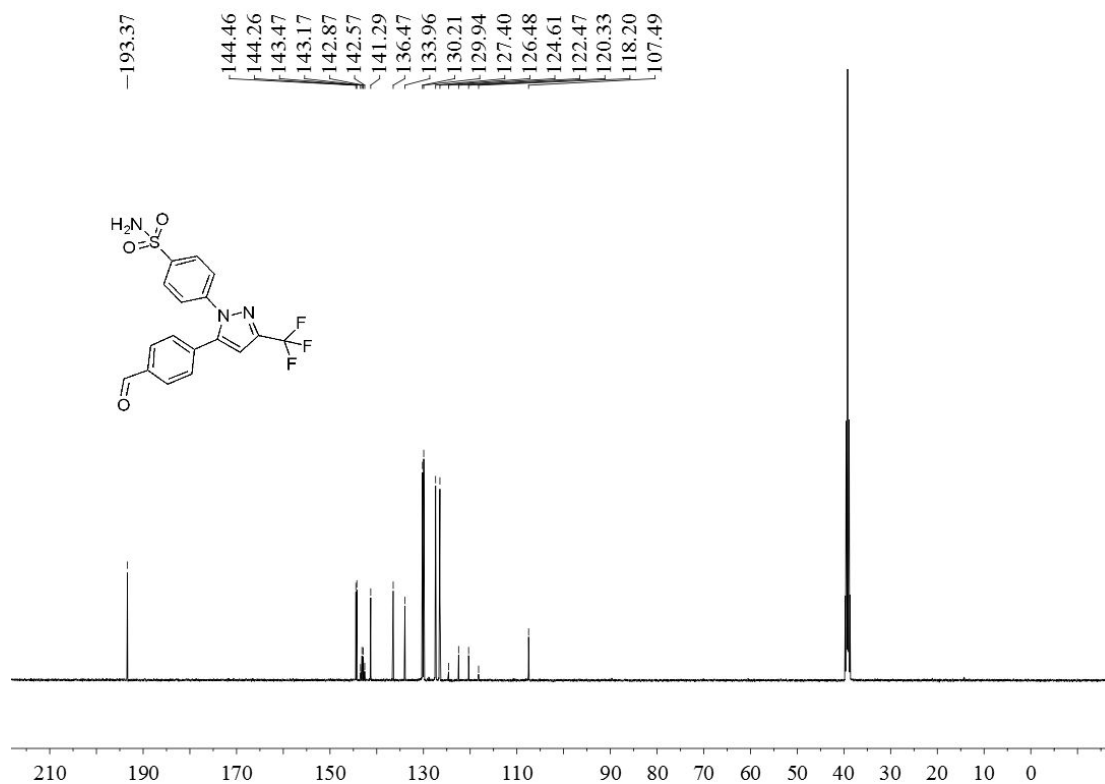
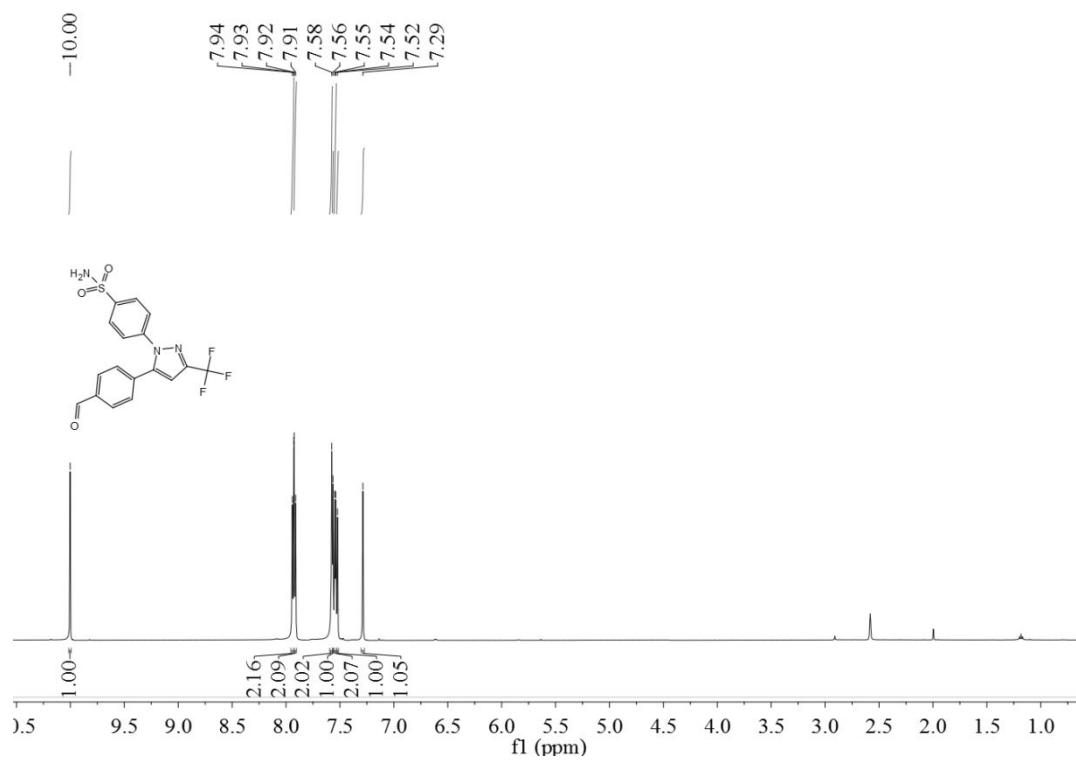
¹³C NMR (126 MHz, DMSO) δ 165.52, 148.48, 143.62, 136.85, 135.22, 132.96, 131.69, 130.63, 129.32, 123.52, 122.42, 119.68, 112.38, 53.01.

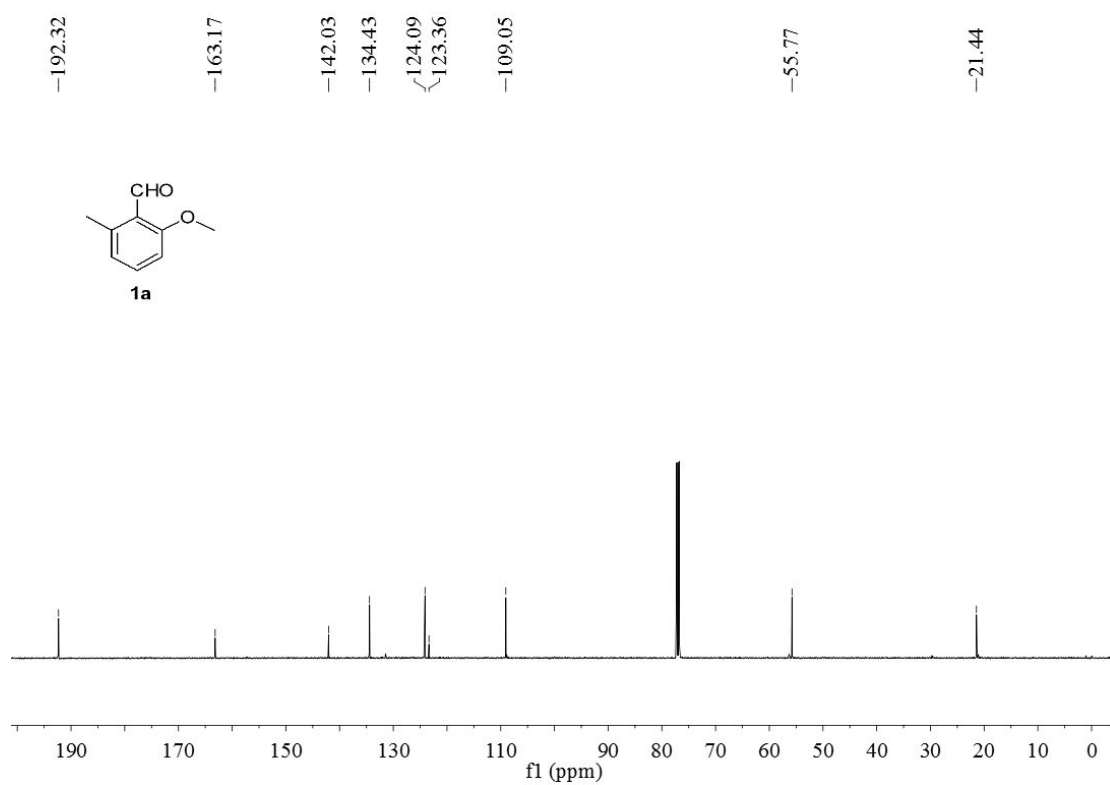
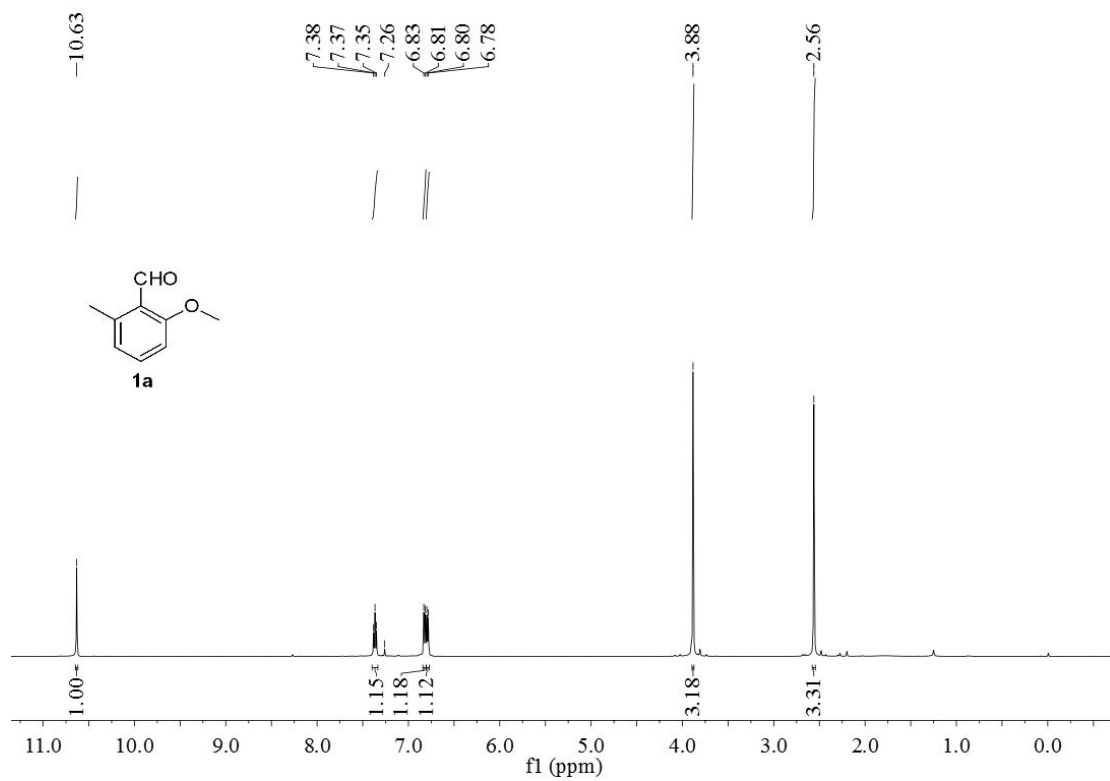
HRMS (ESI): *m/z* calculated for C₁₅H₁₂ClN₂O₂⁺[M+H]⁺ 287.0587, found 287.0583.

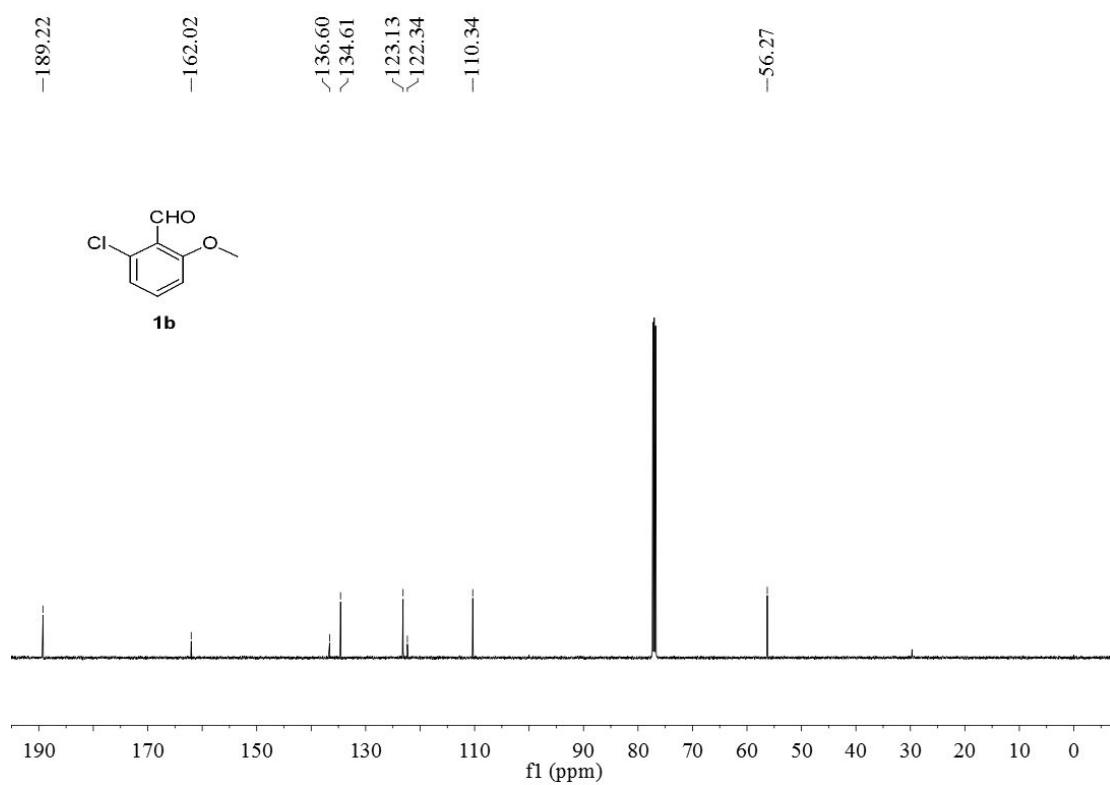
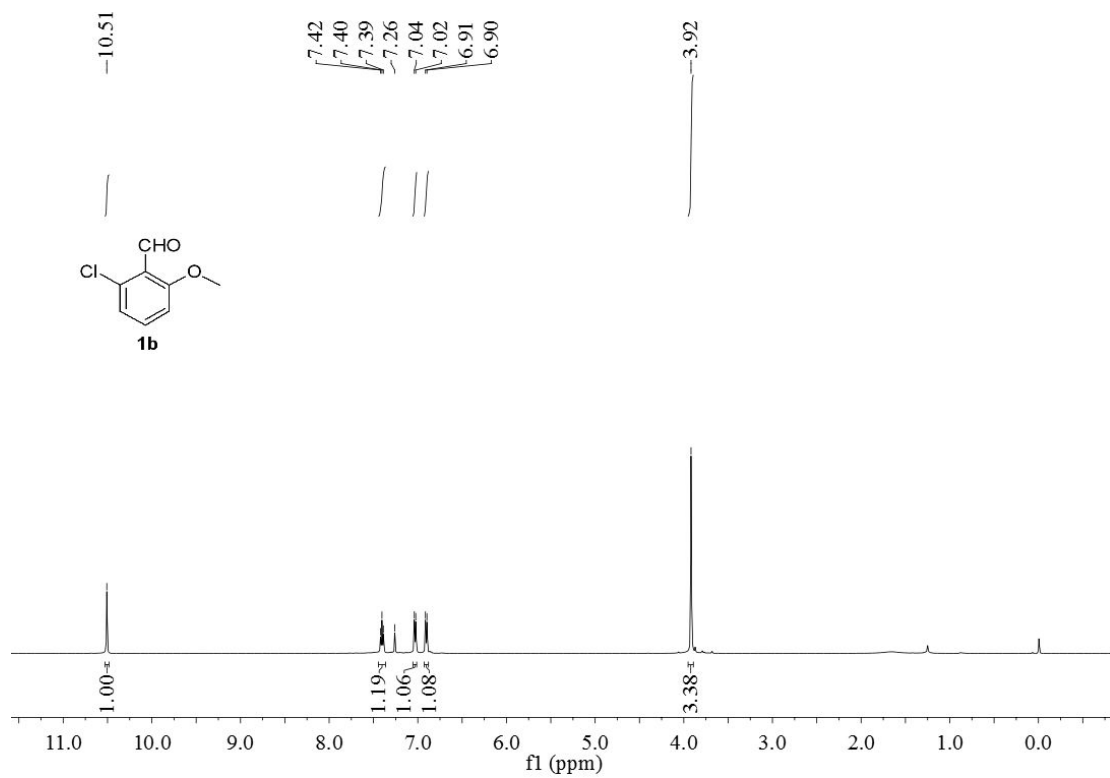
3. References

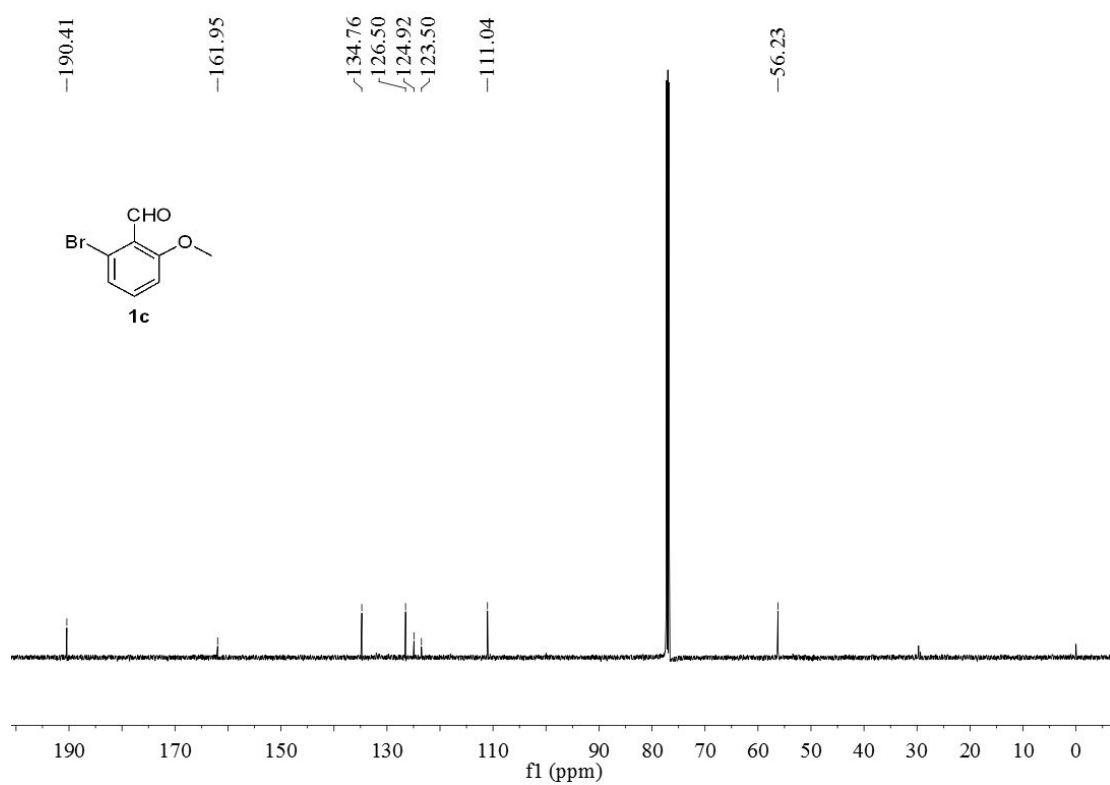
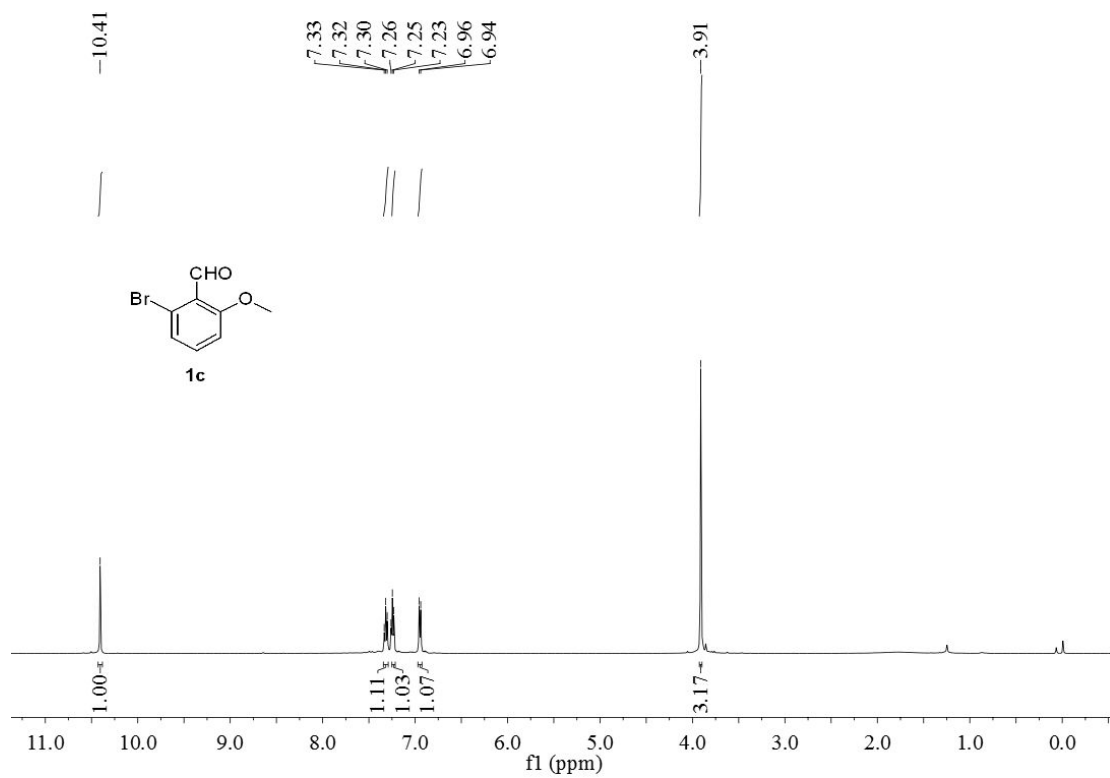
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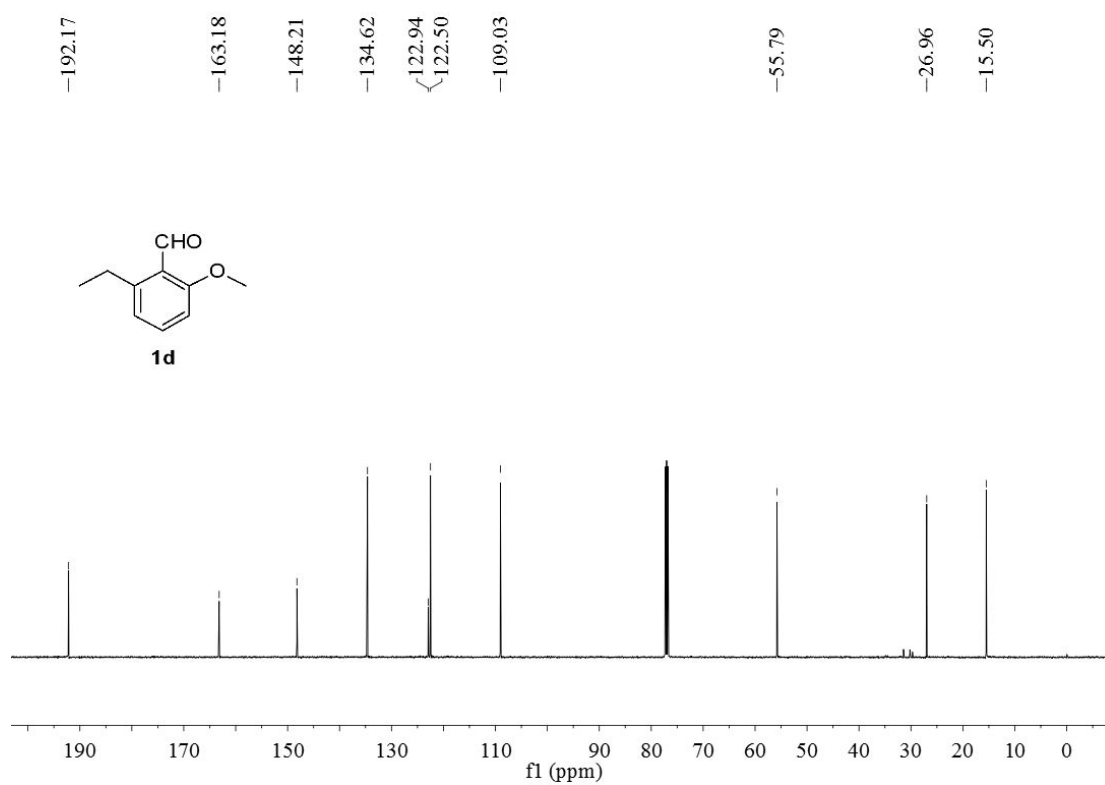
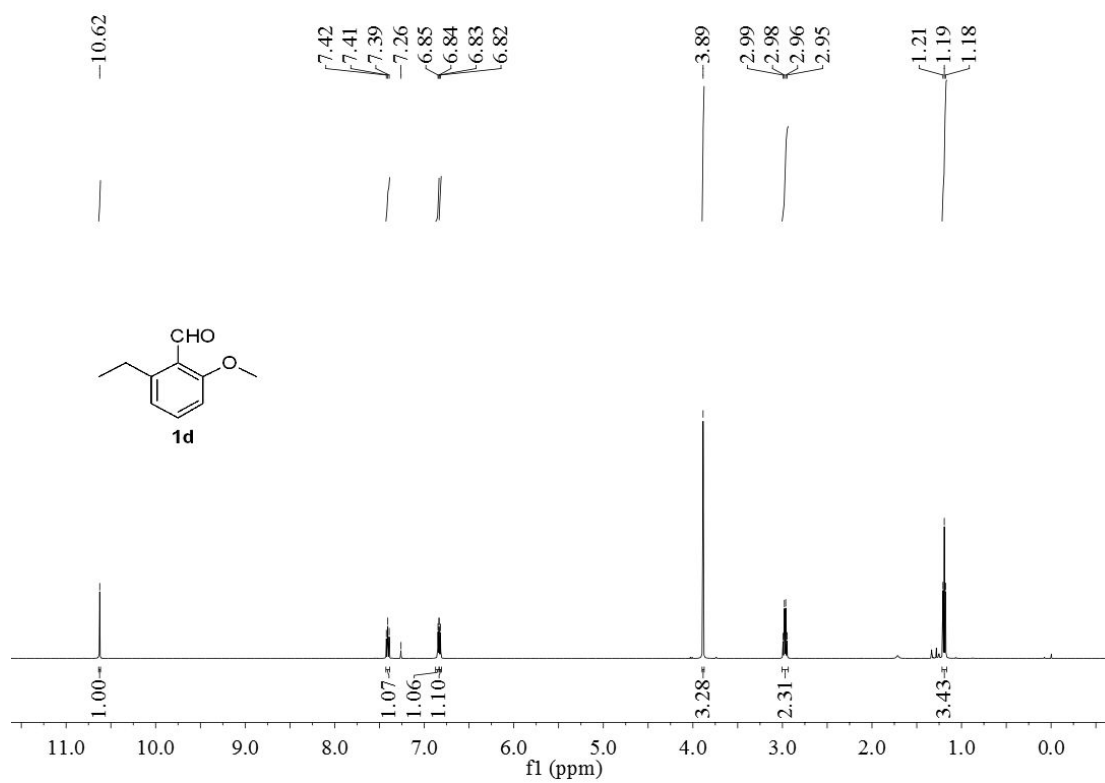
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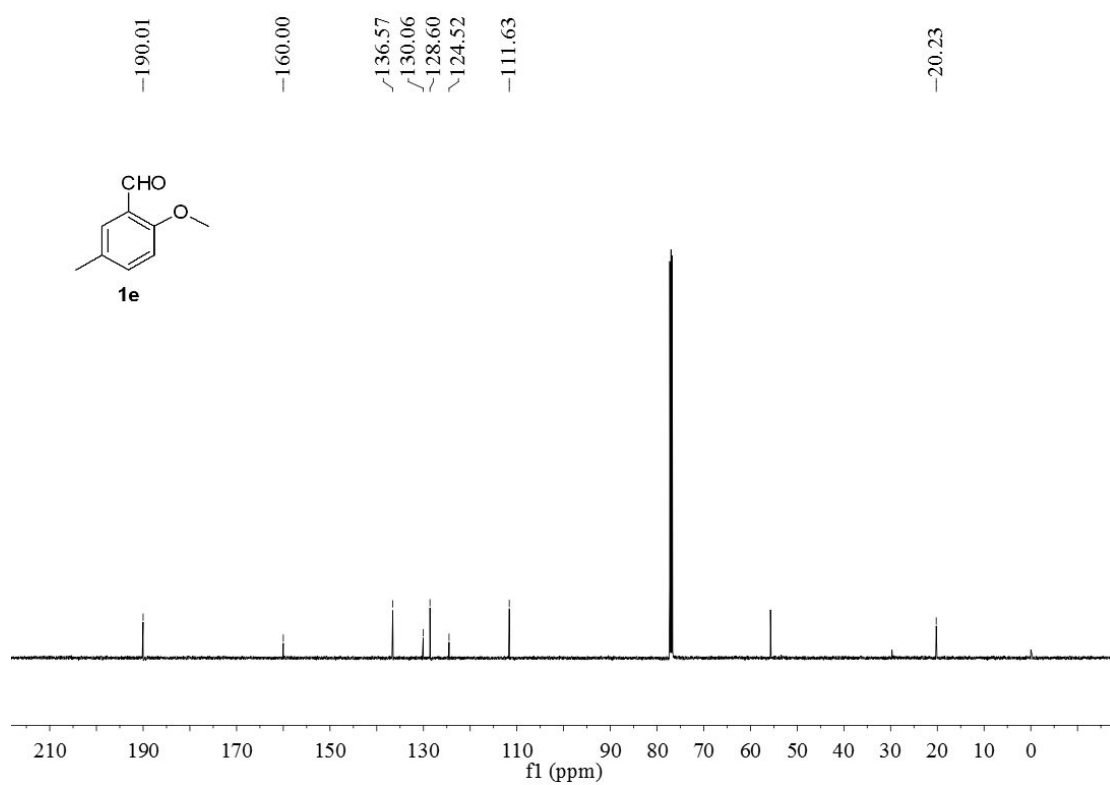
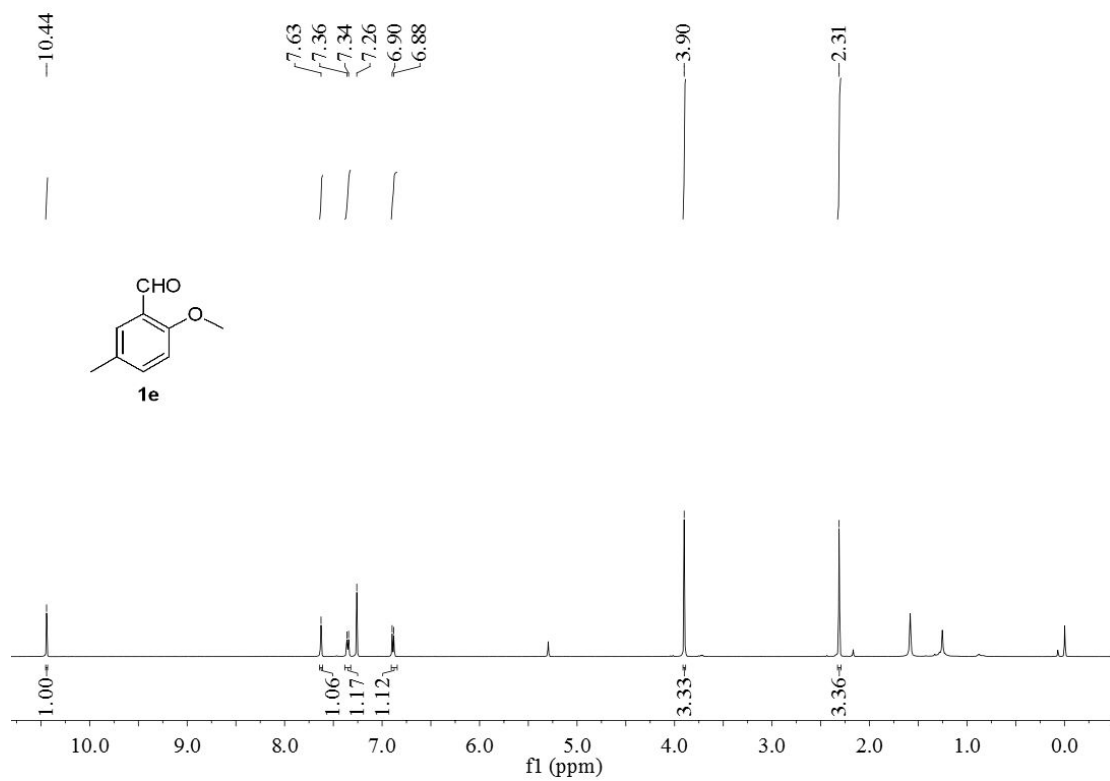


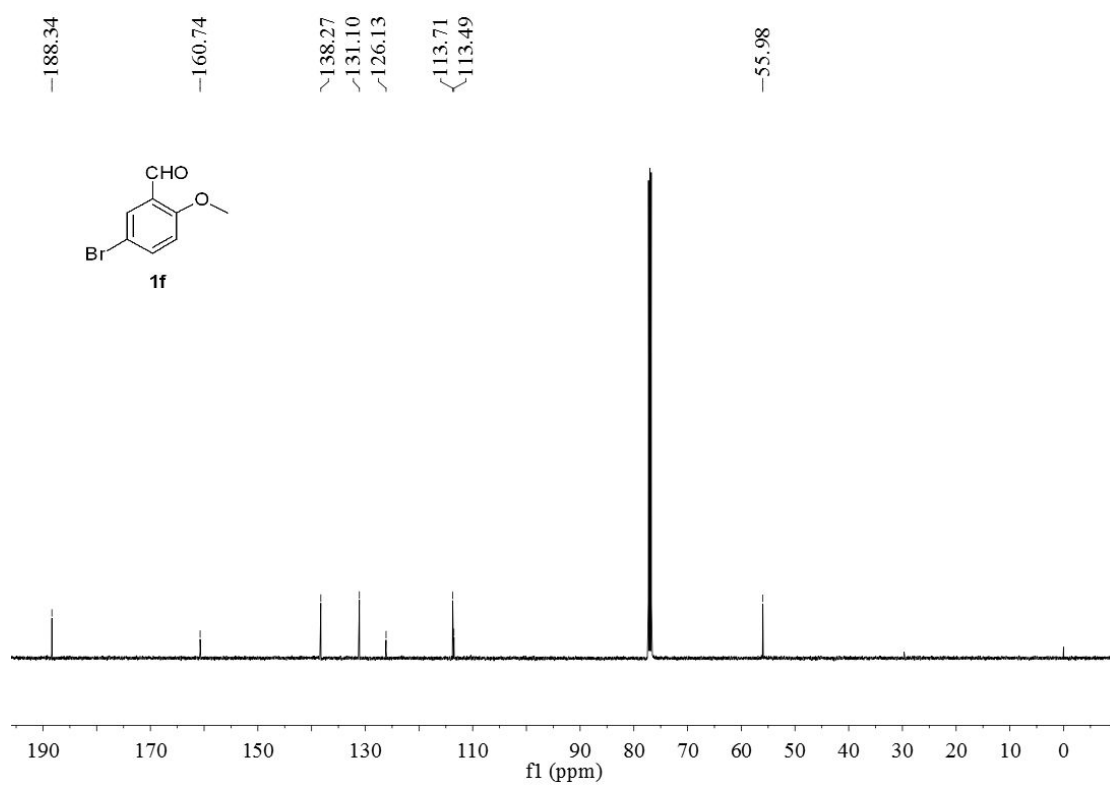
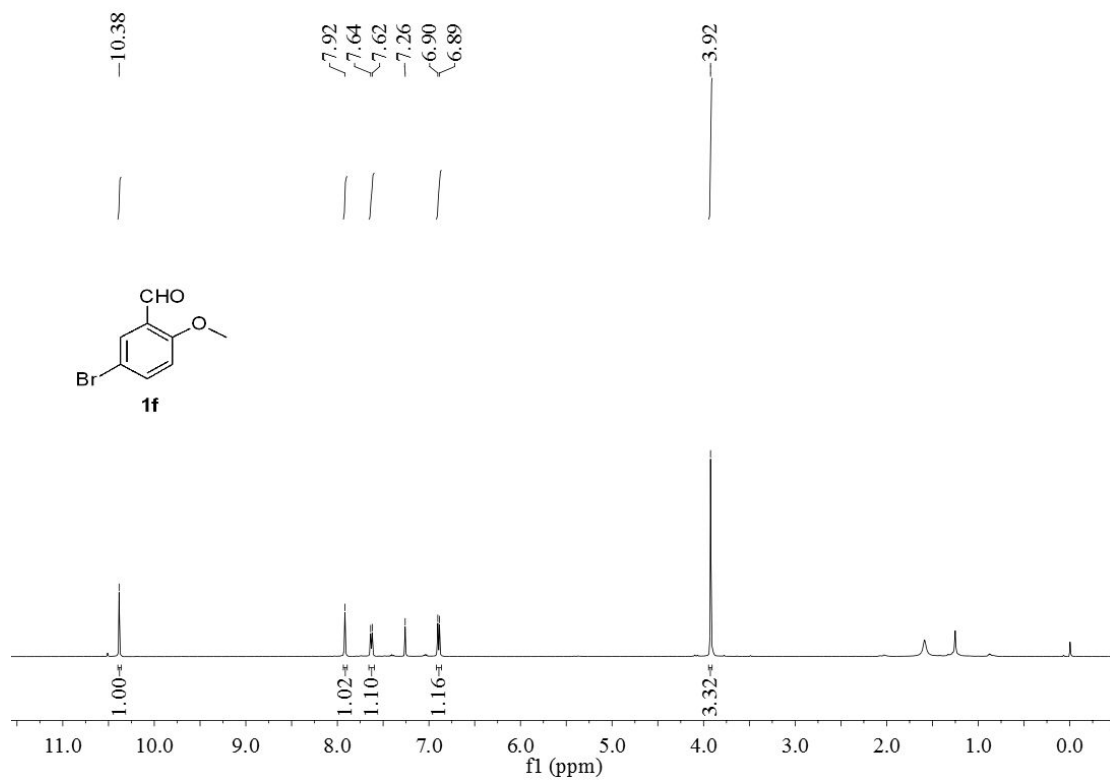


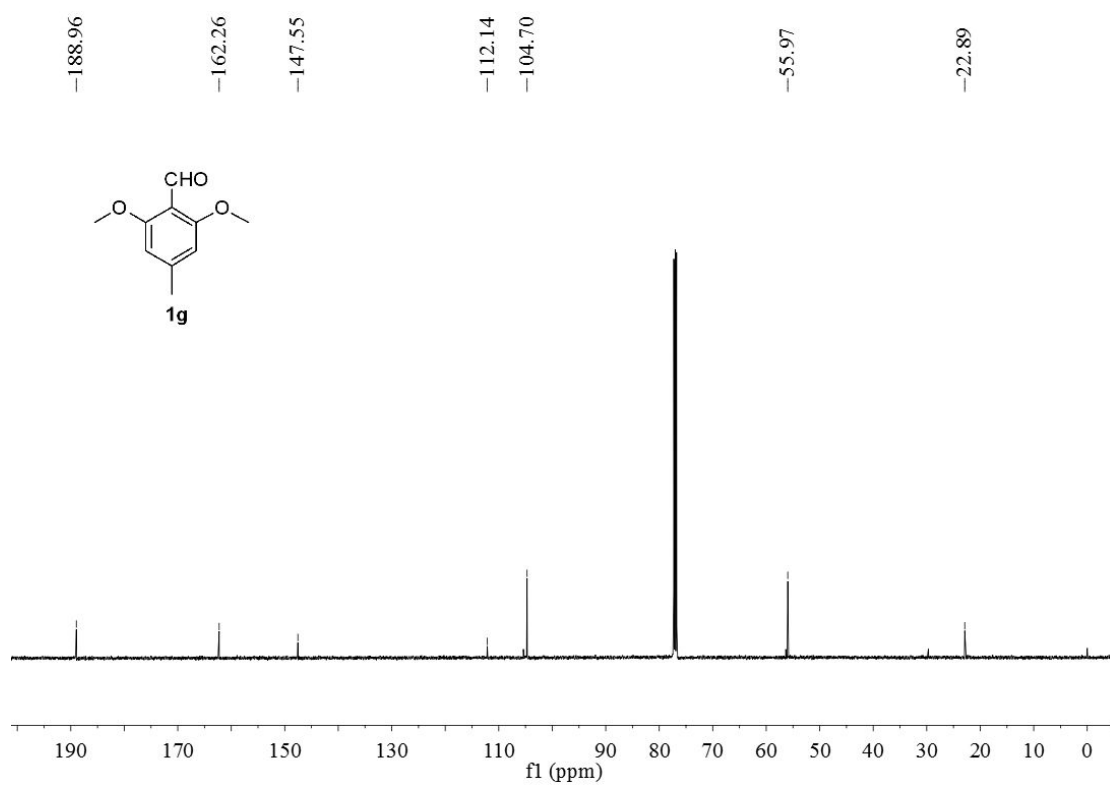
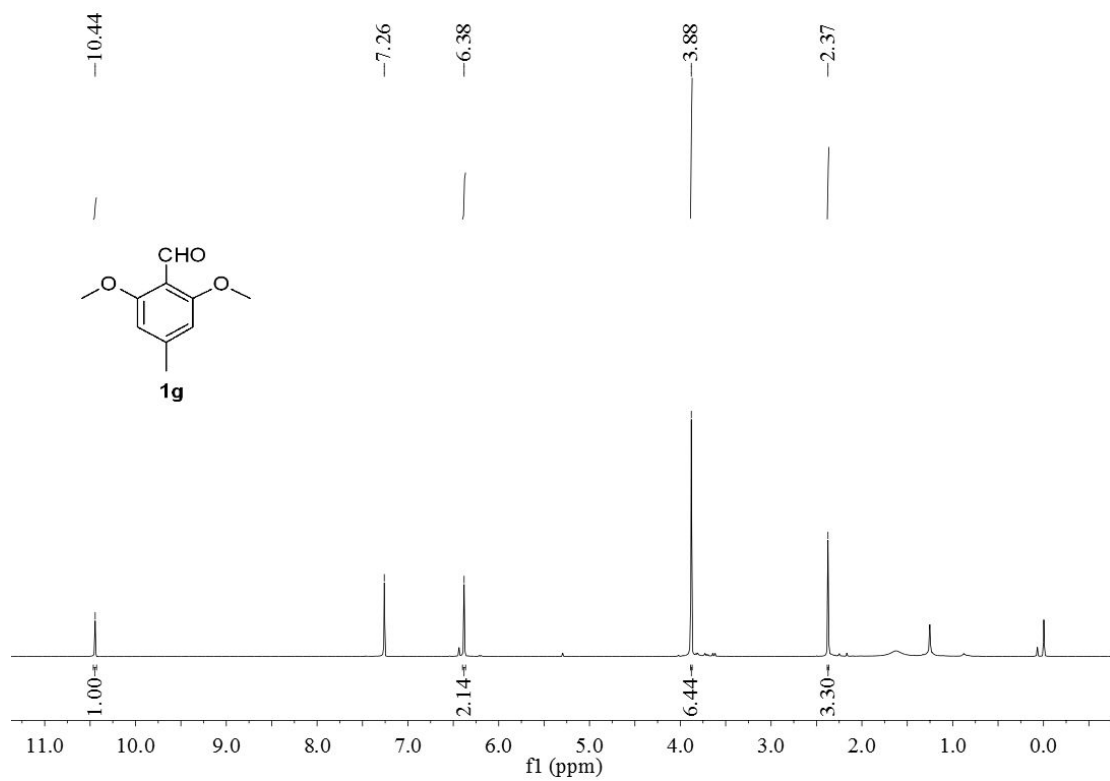


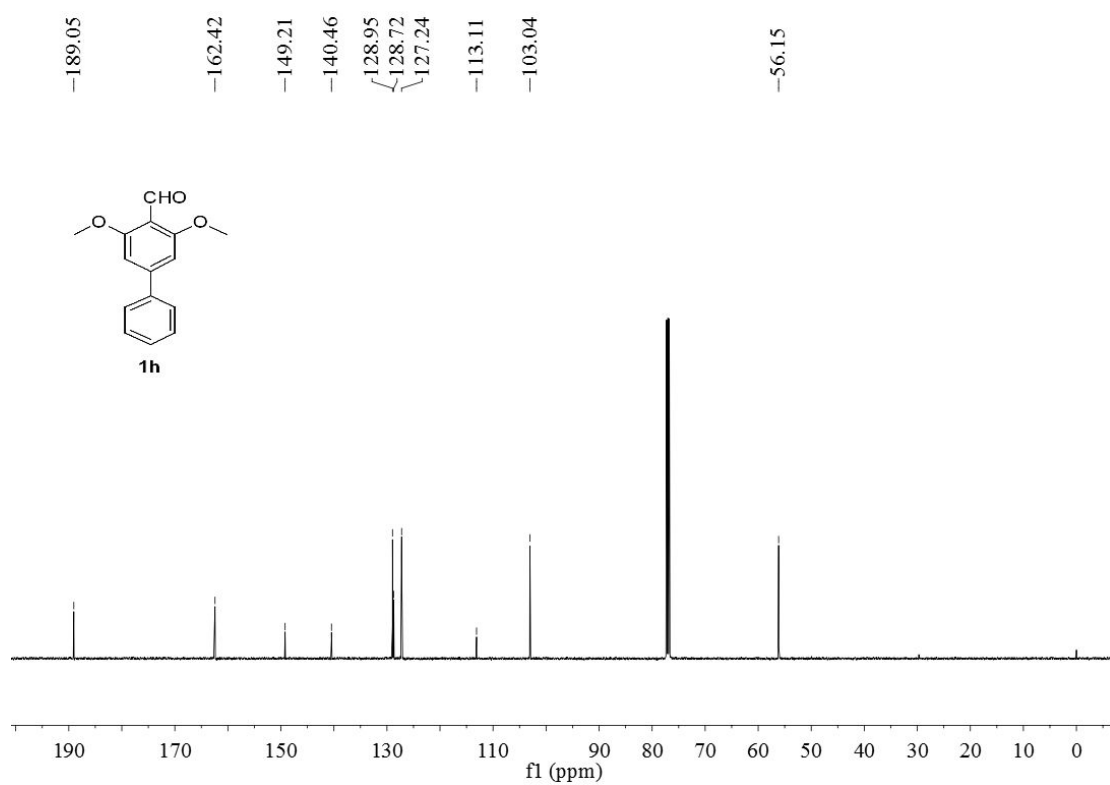
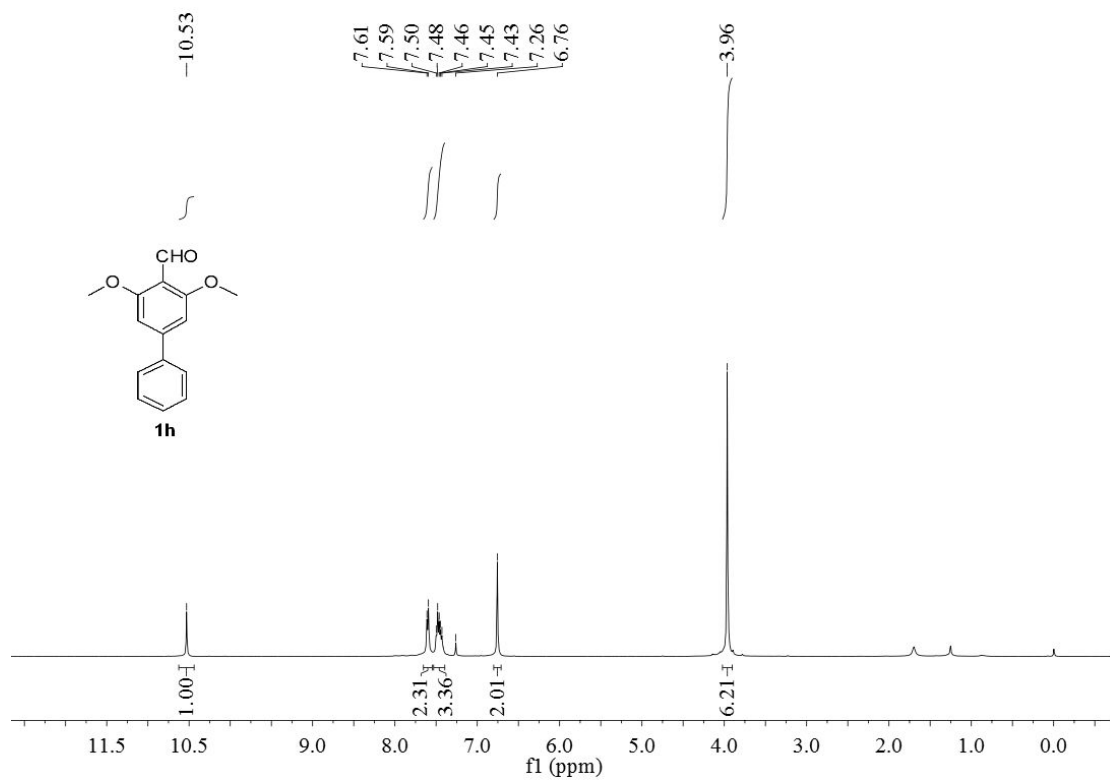


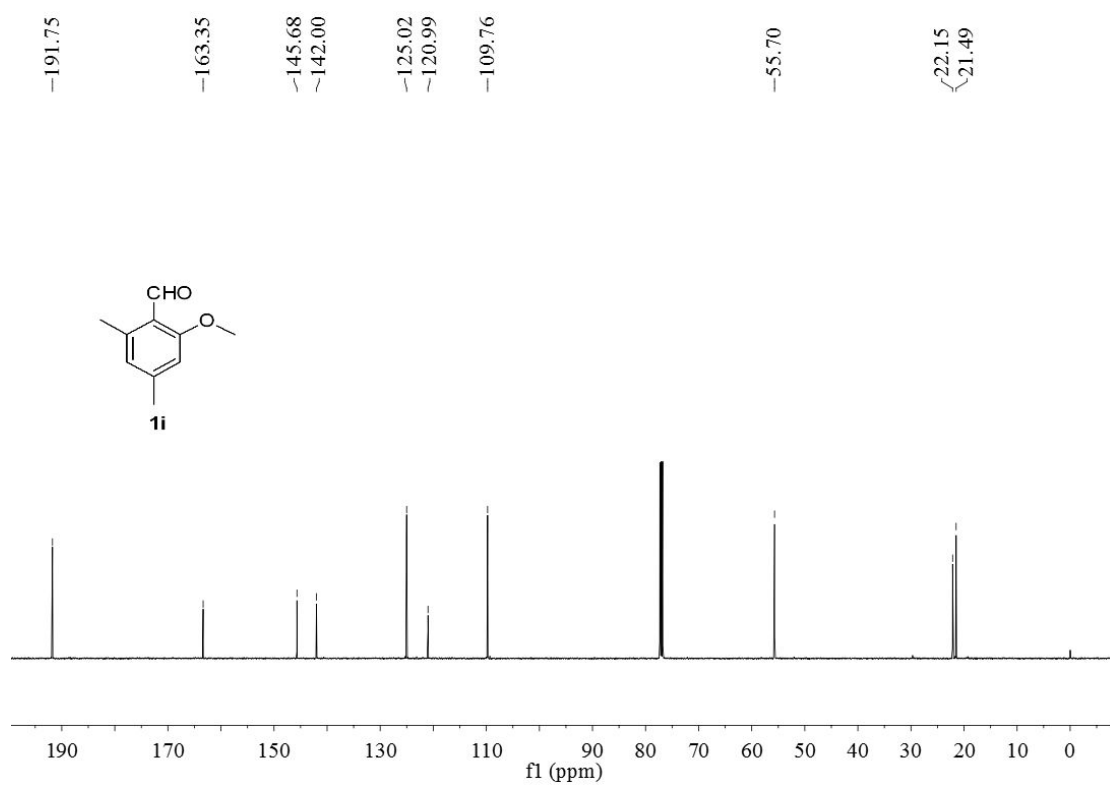
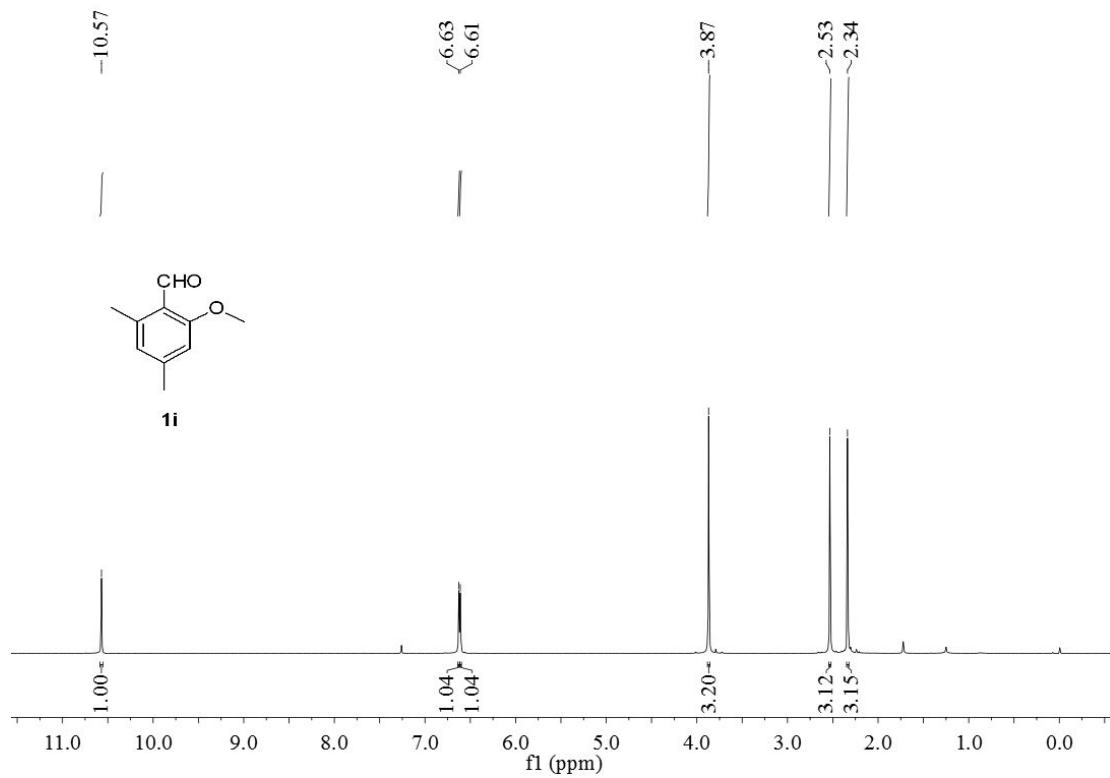


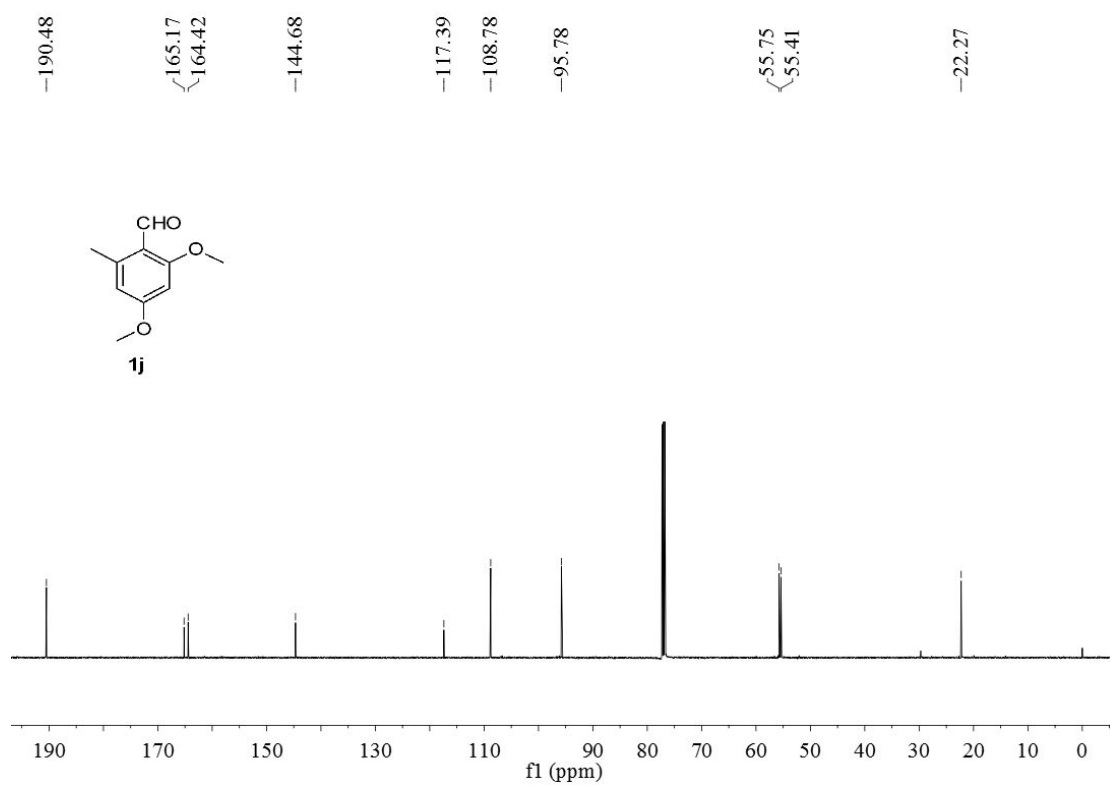
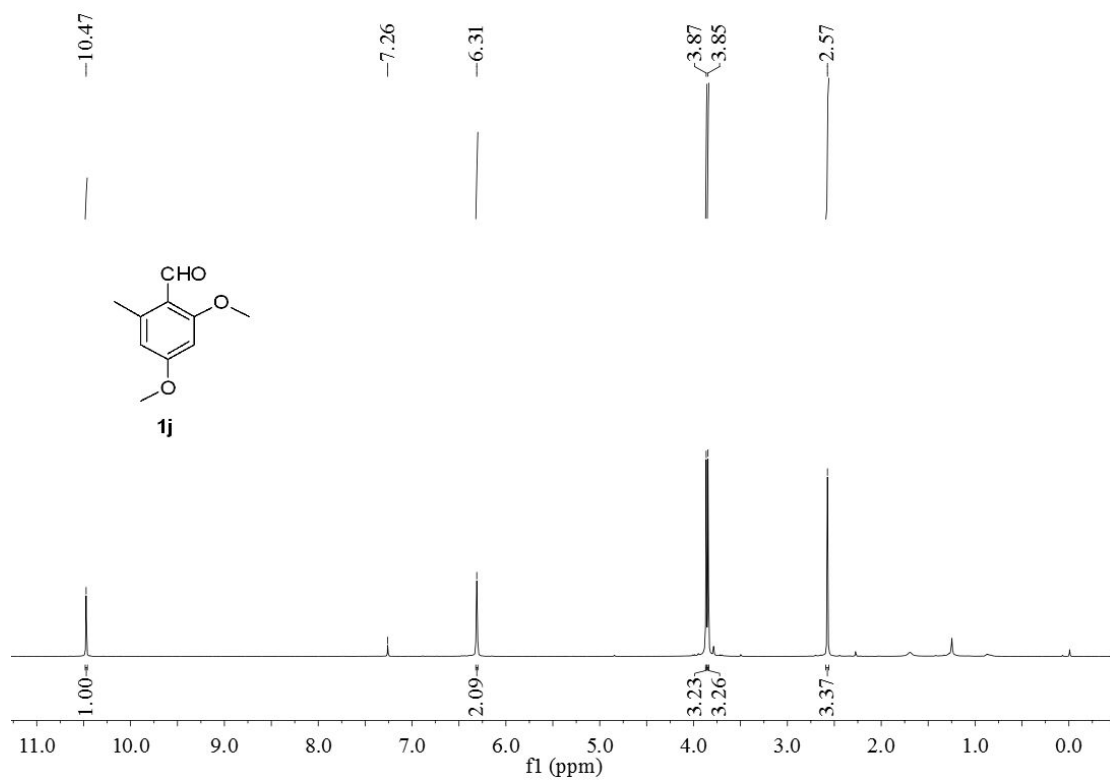


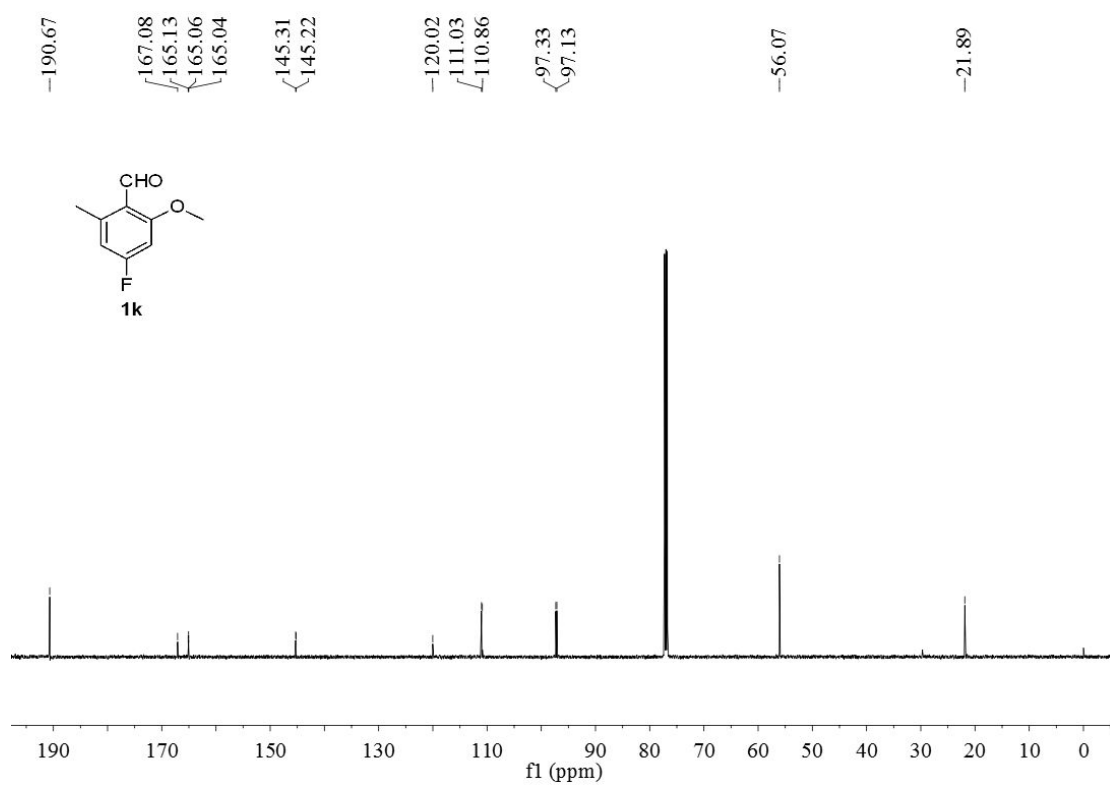
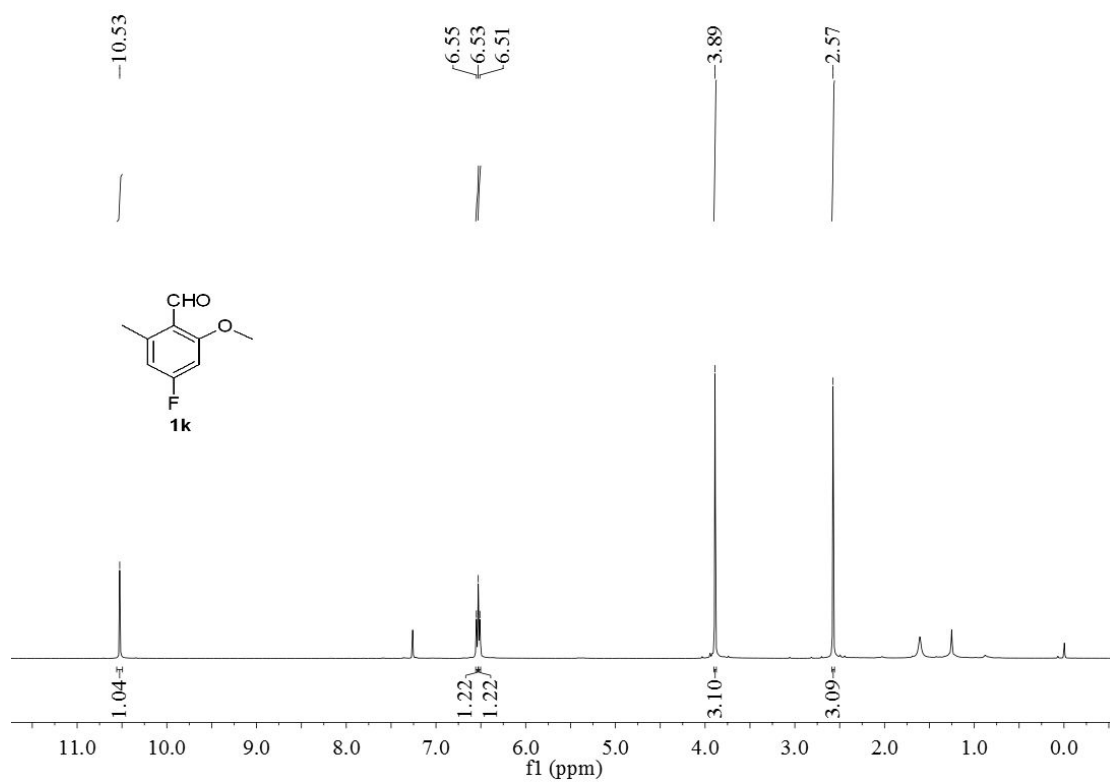


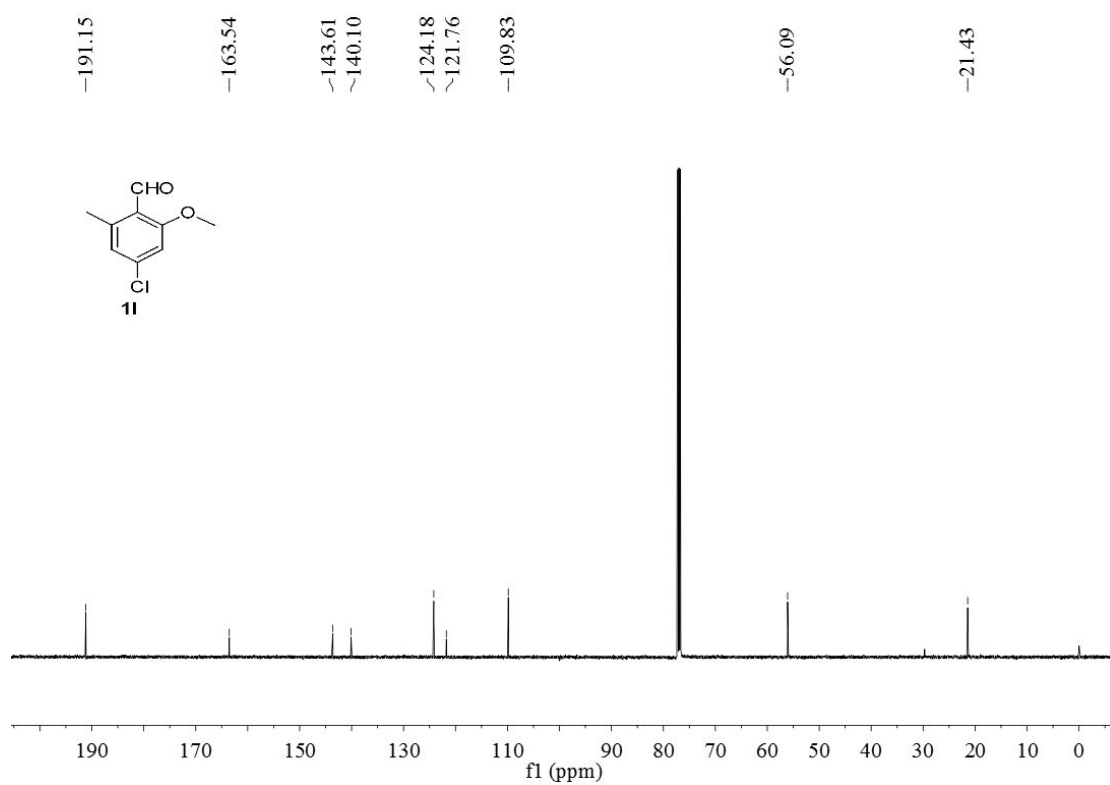
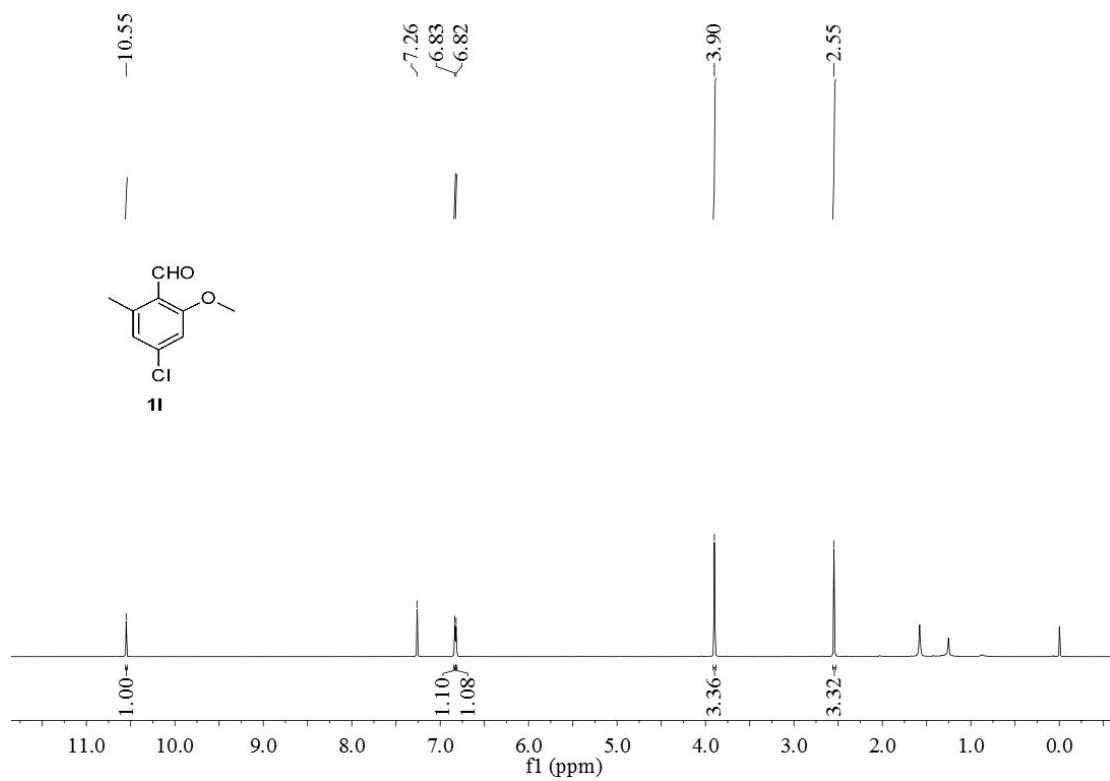


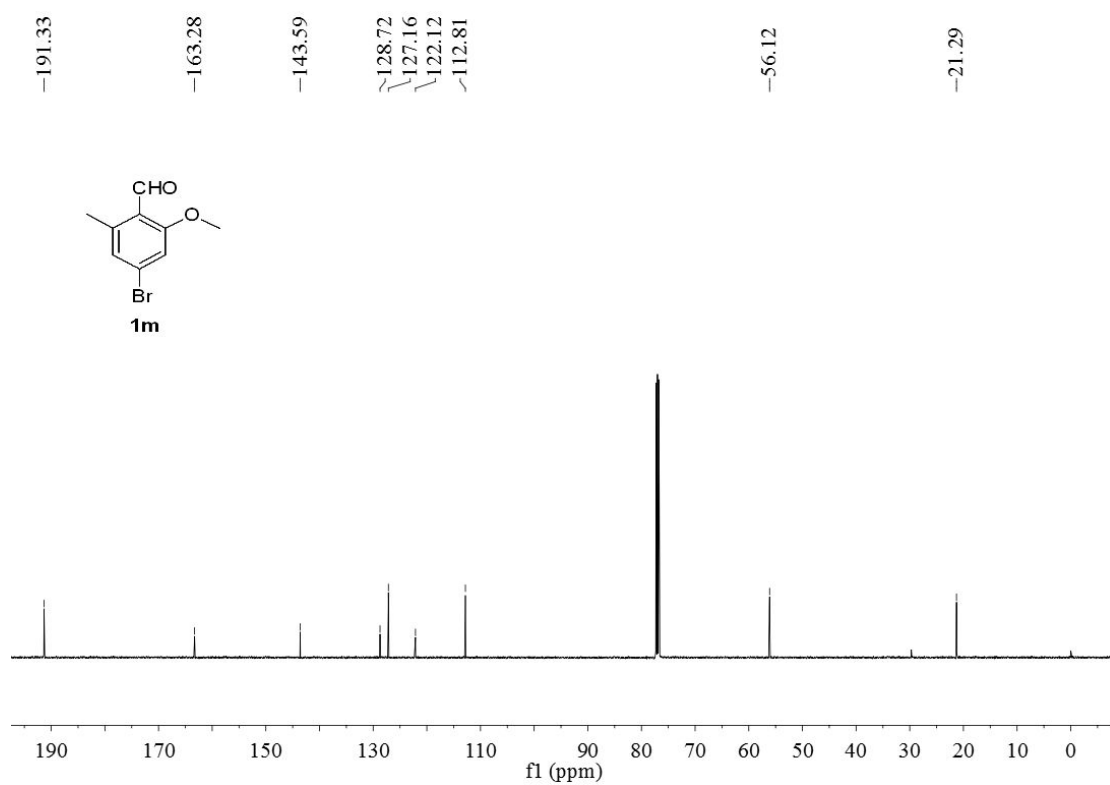
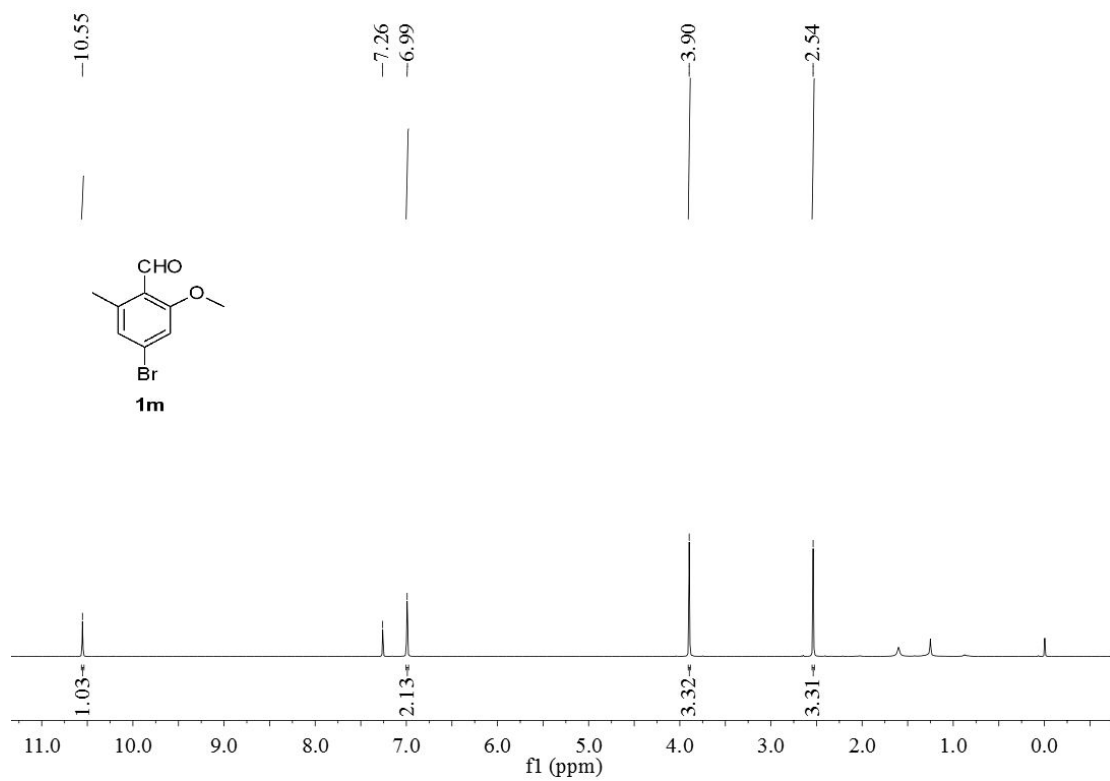


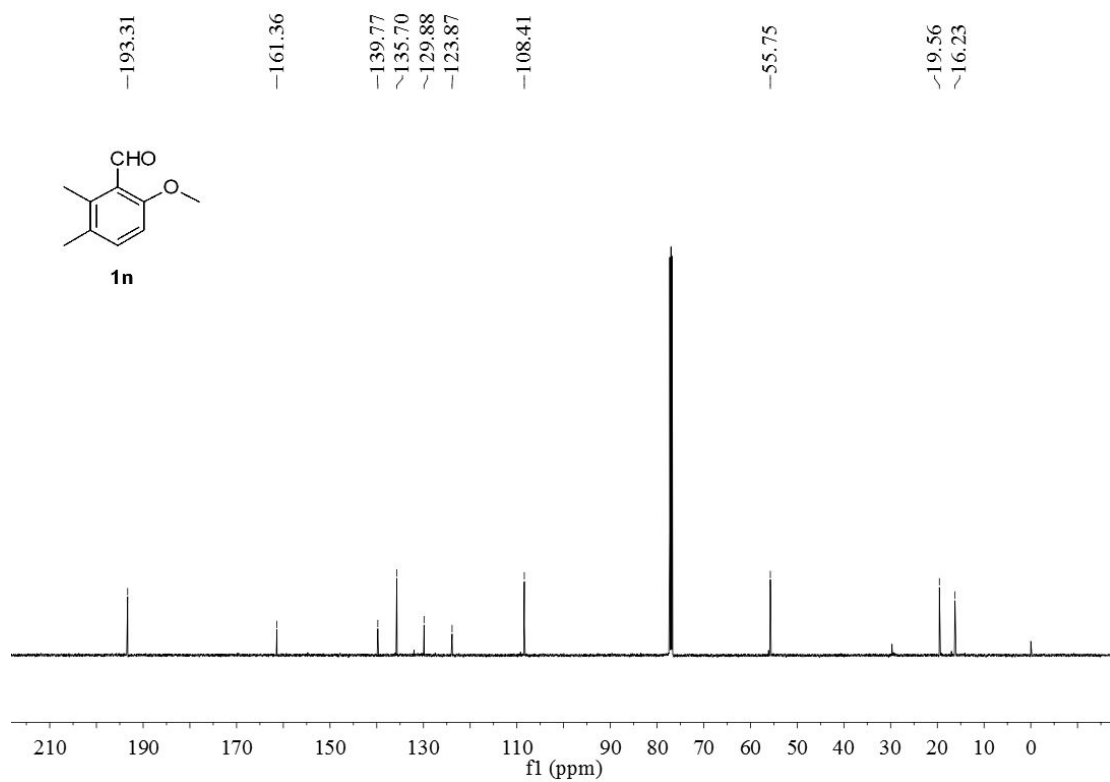
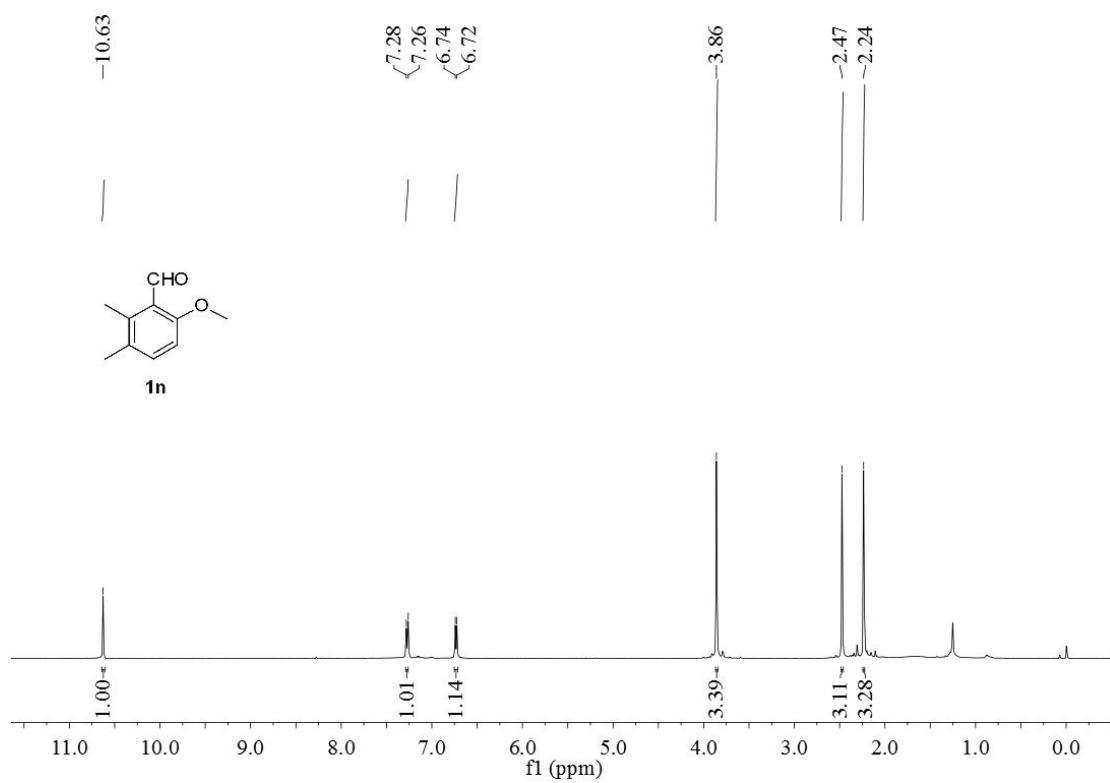


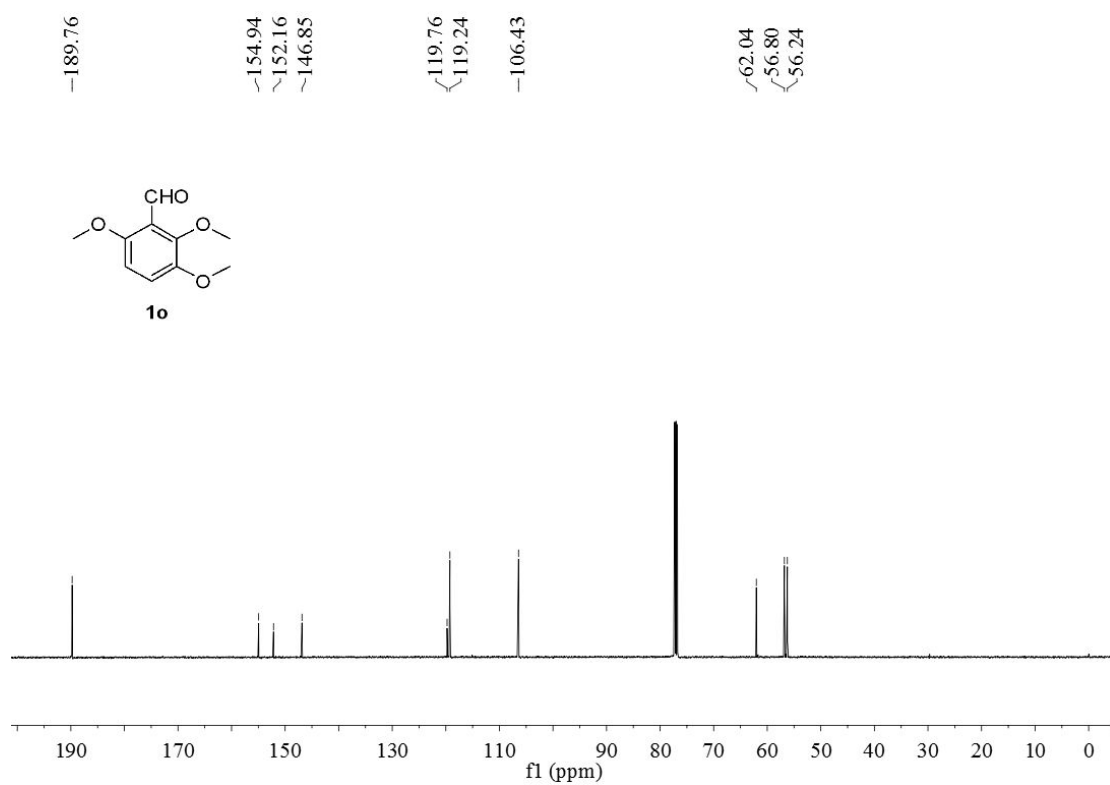
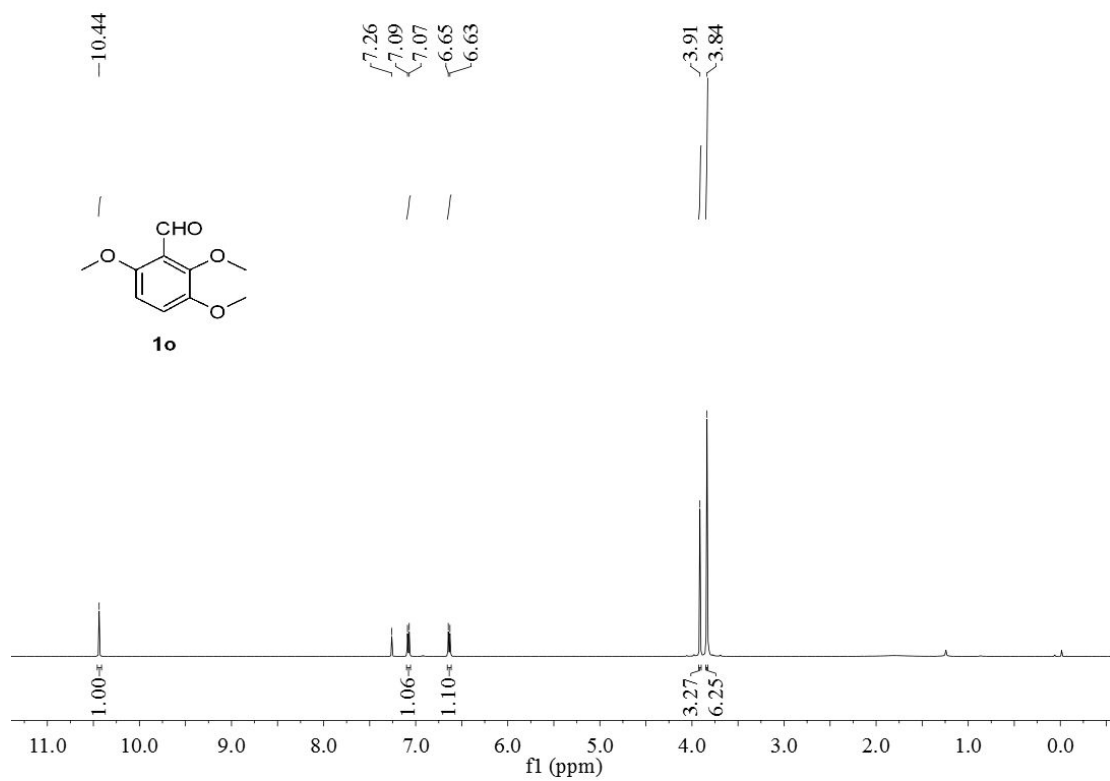


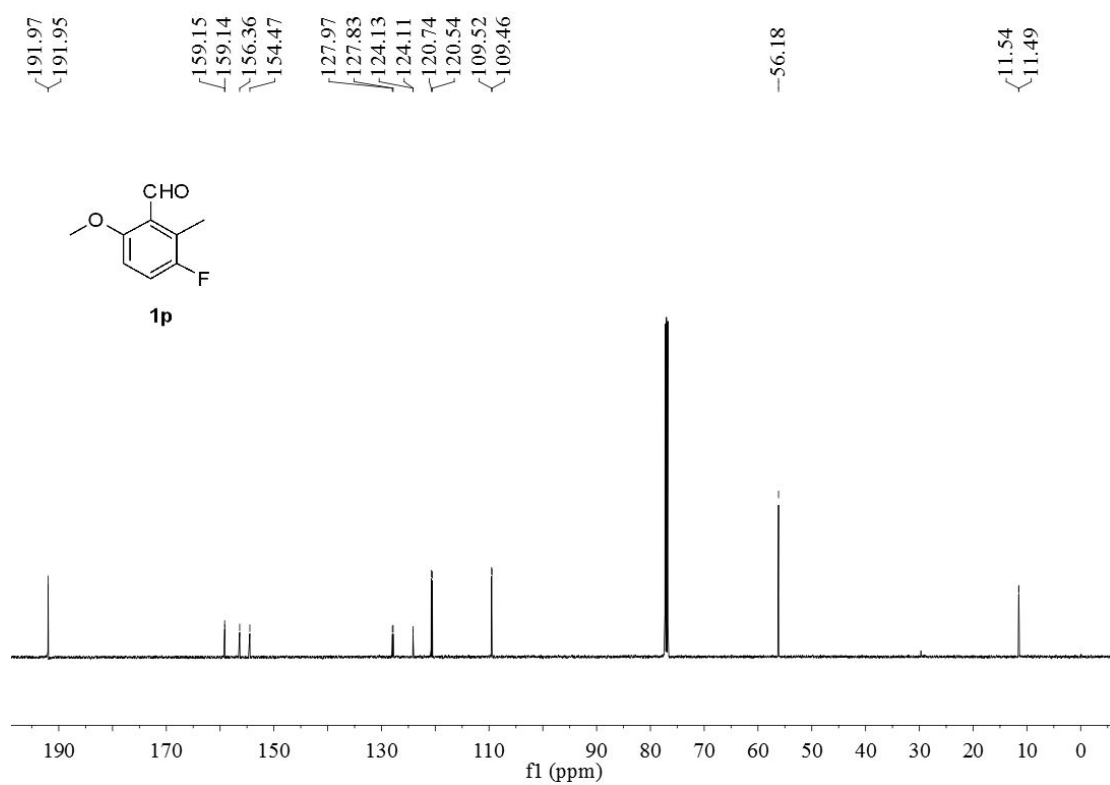
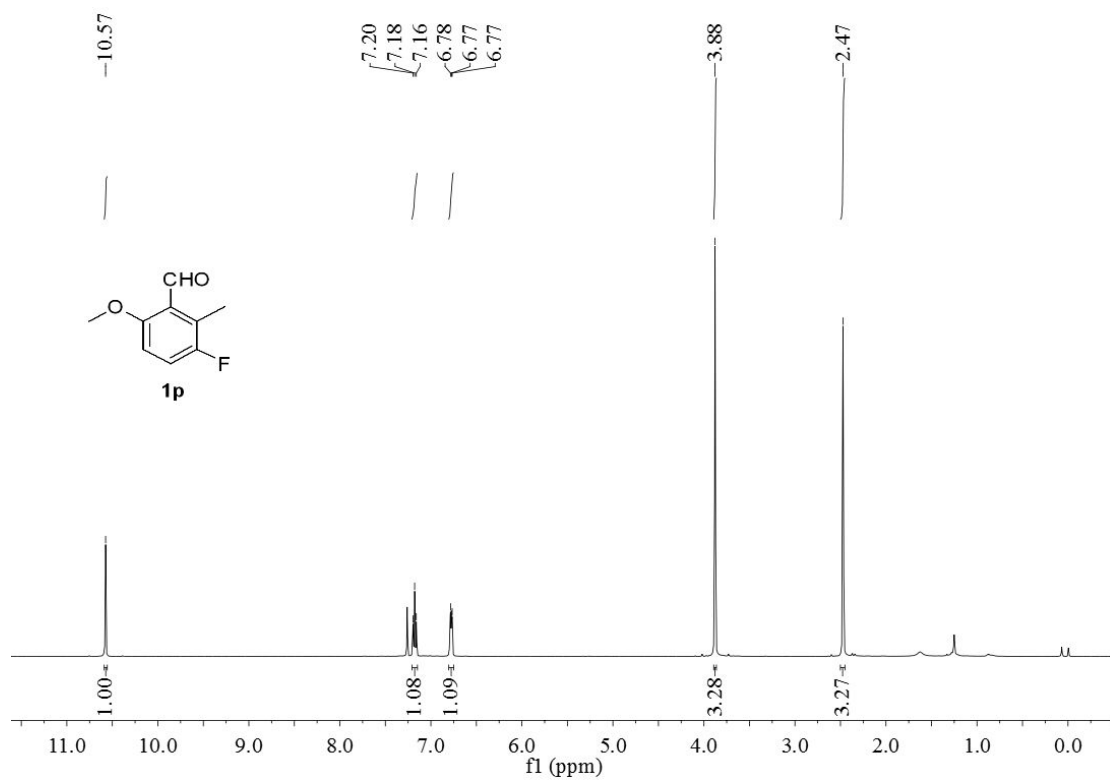


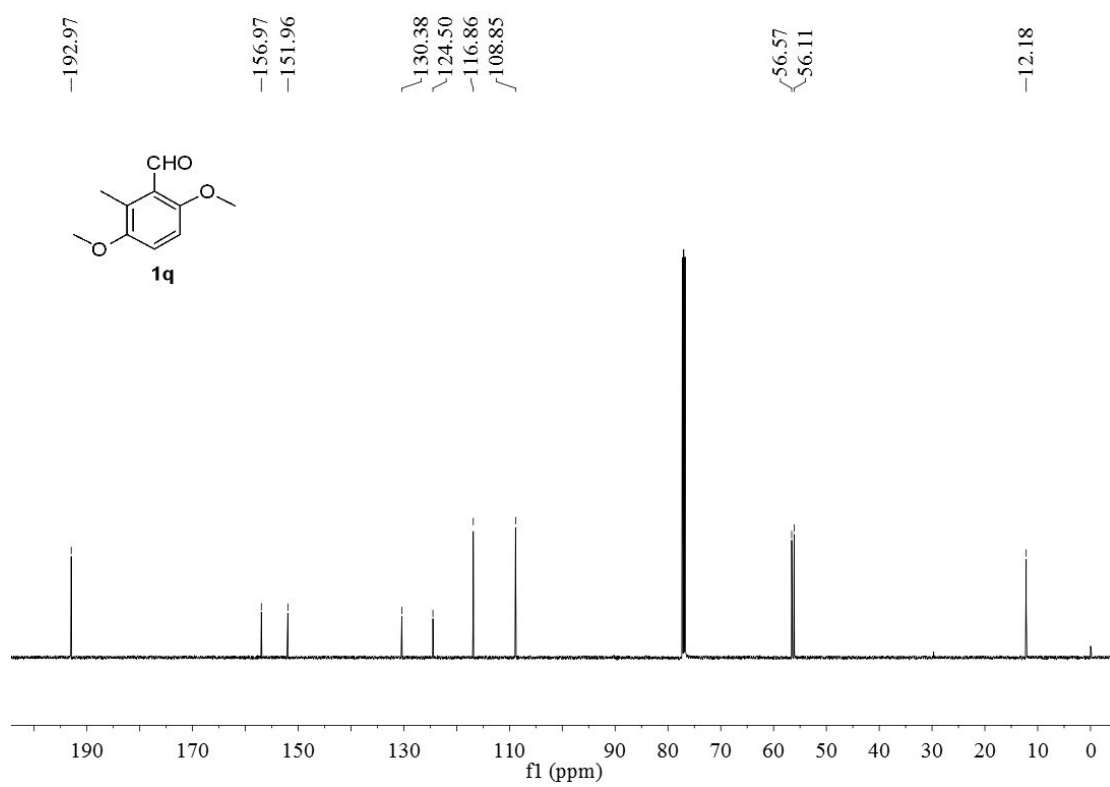
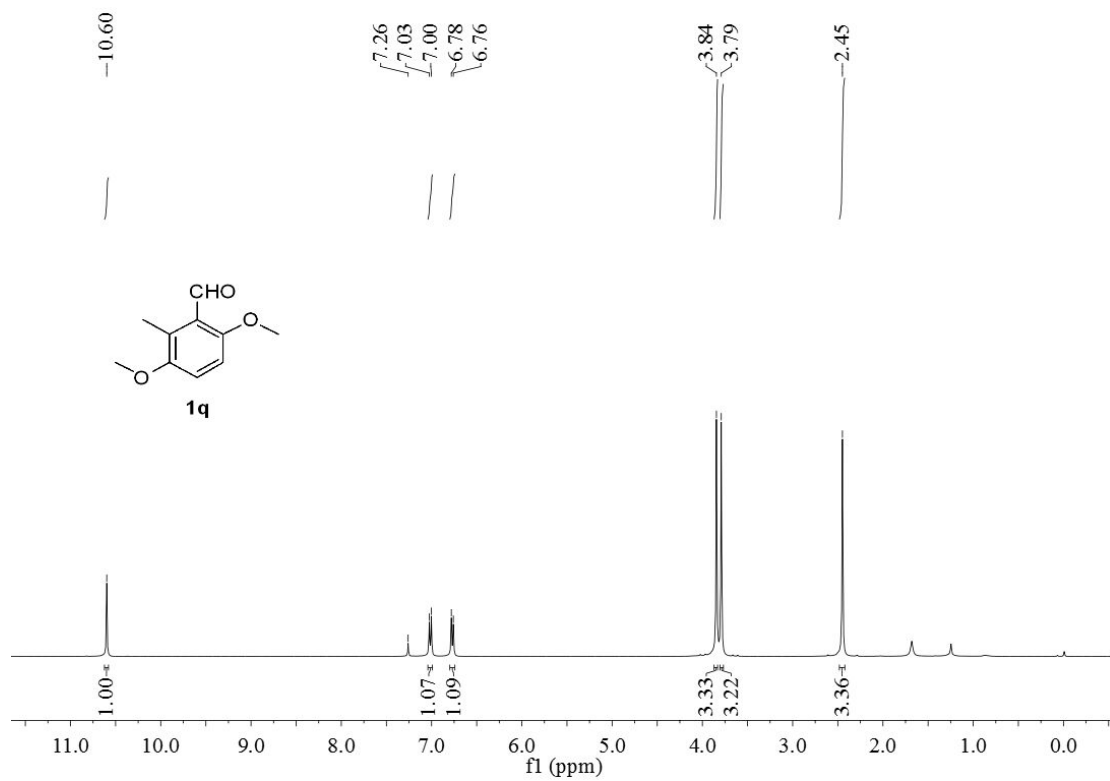


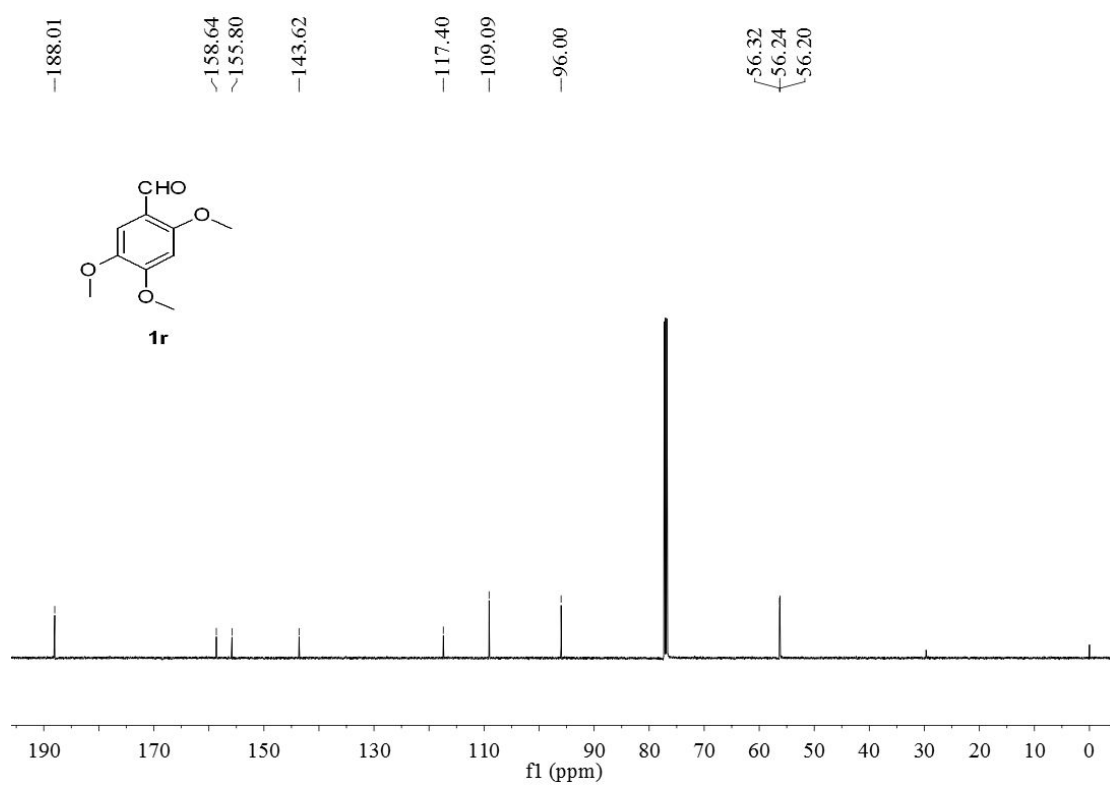
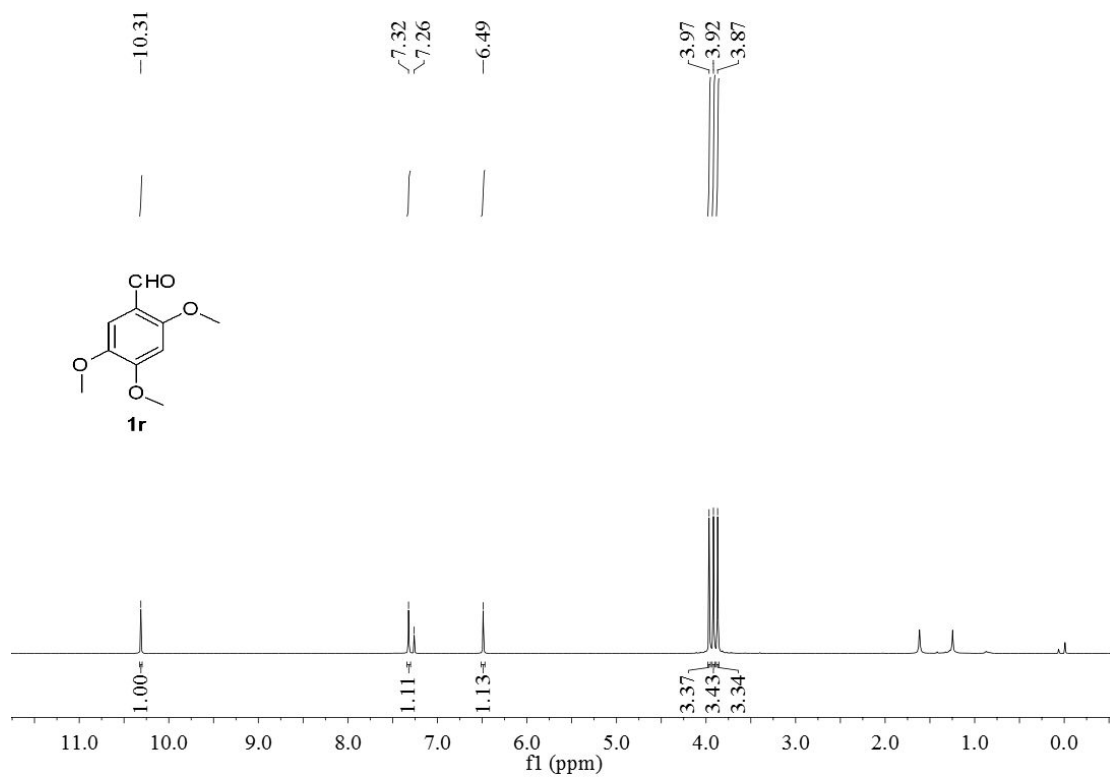


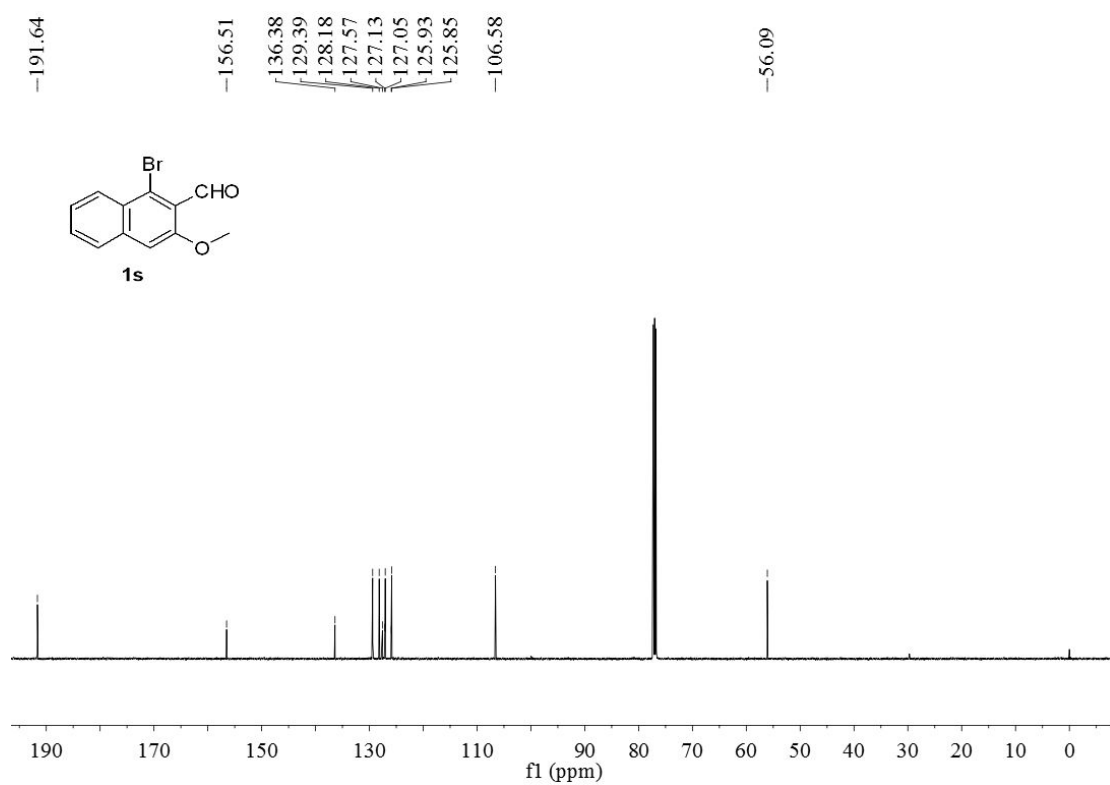
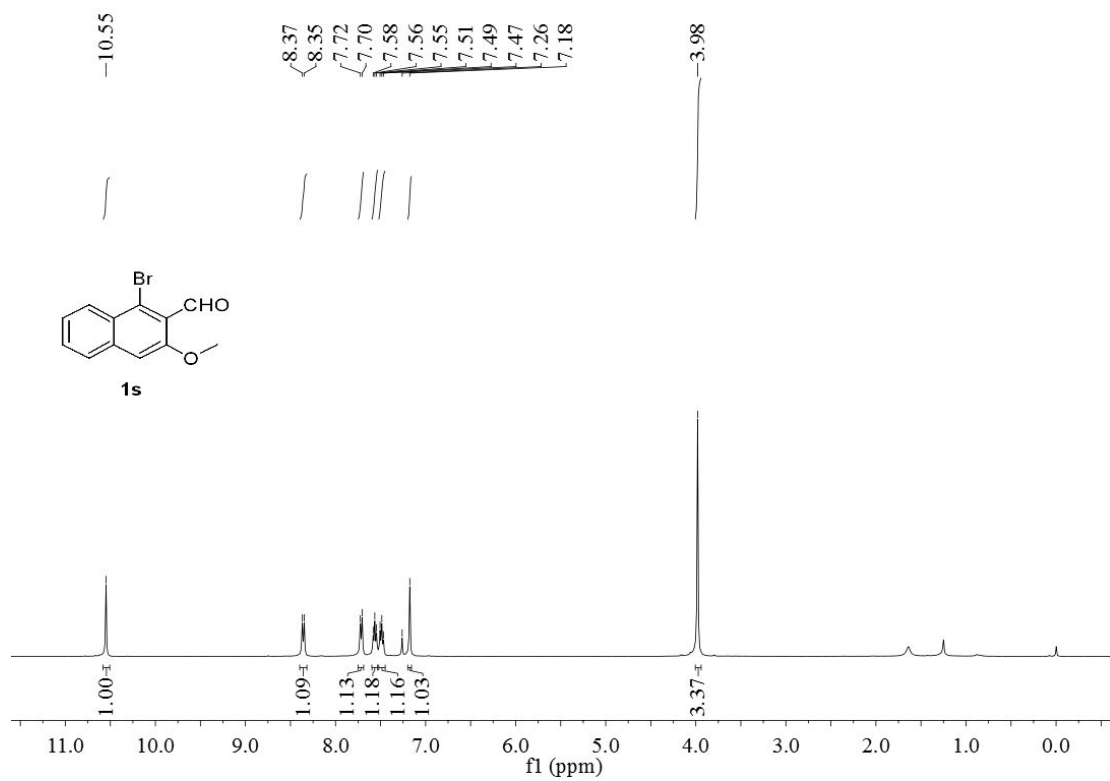


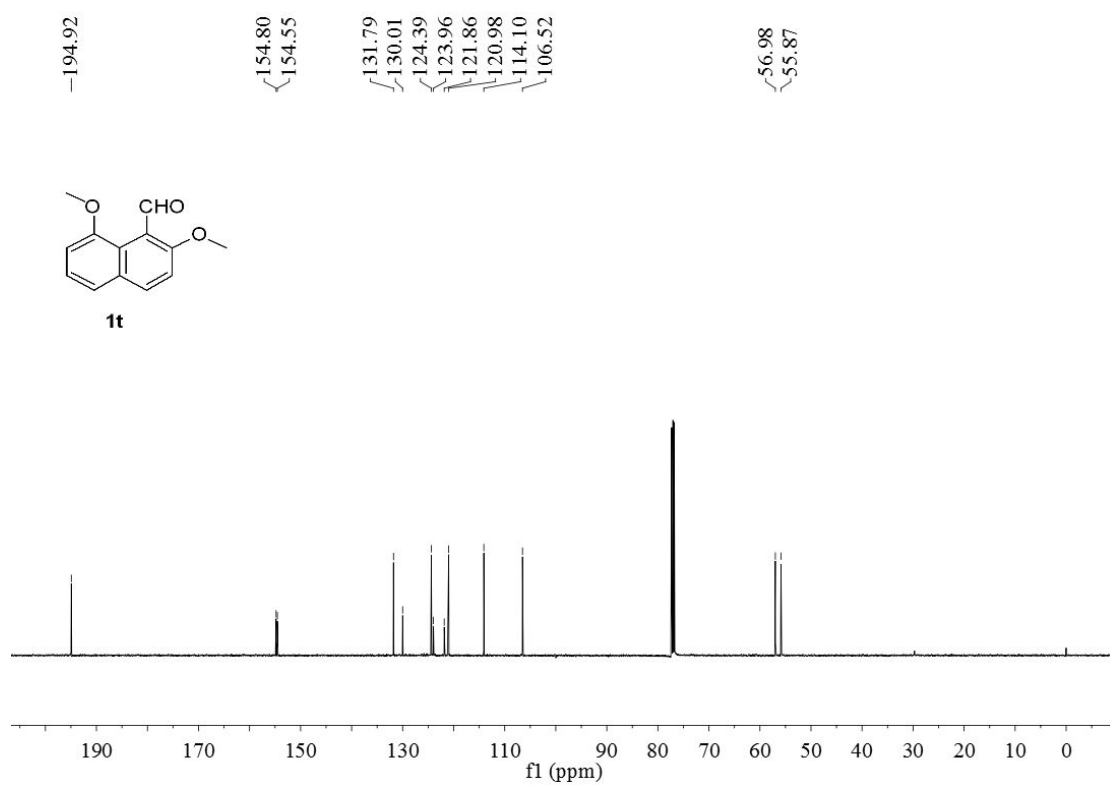
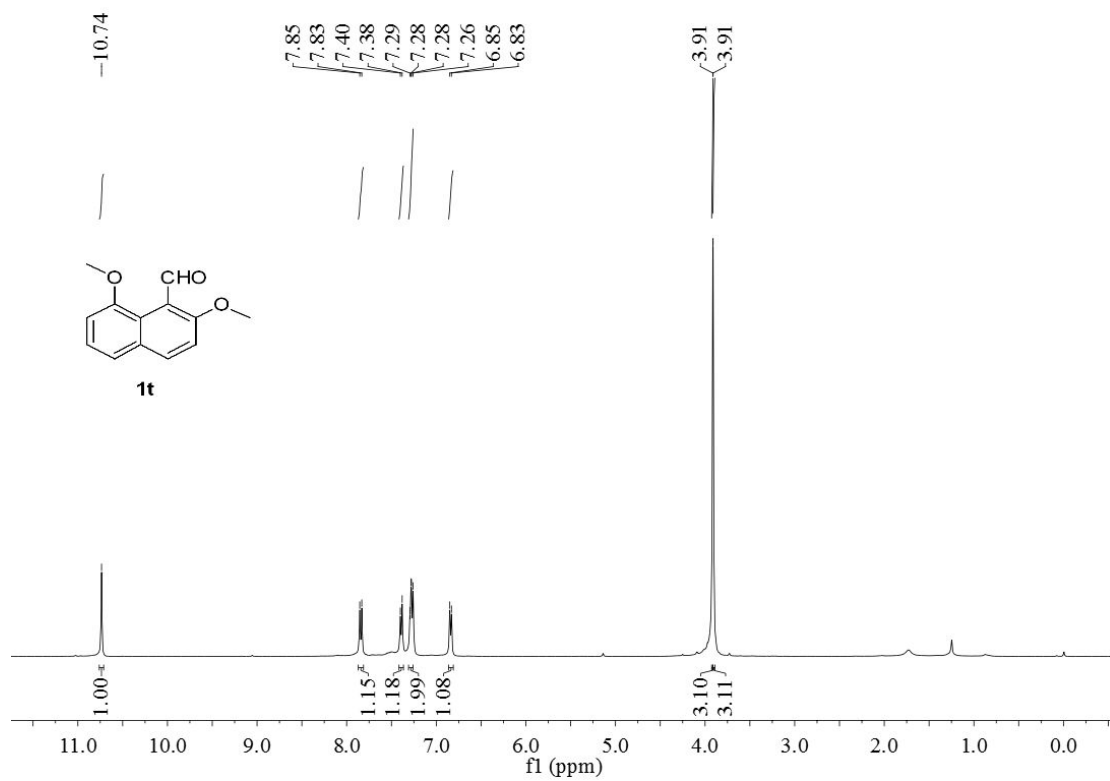


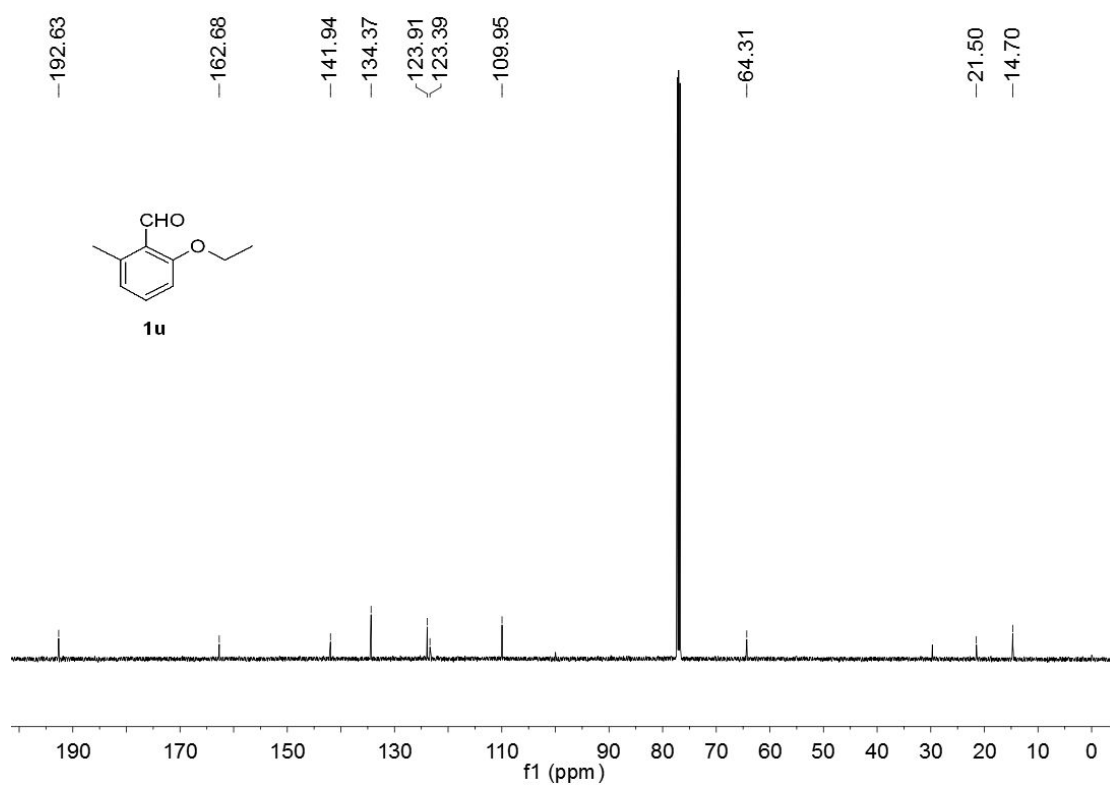
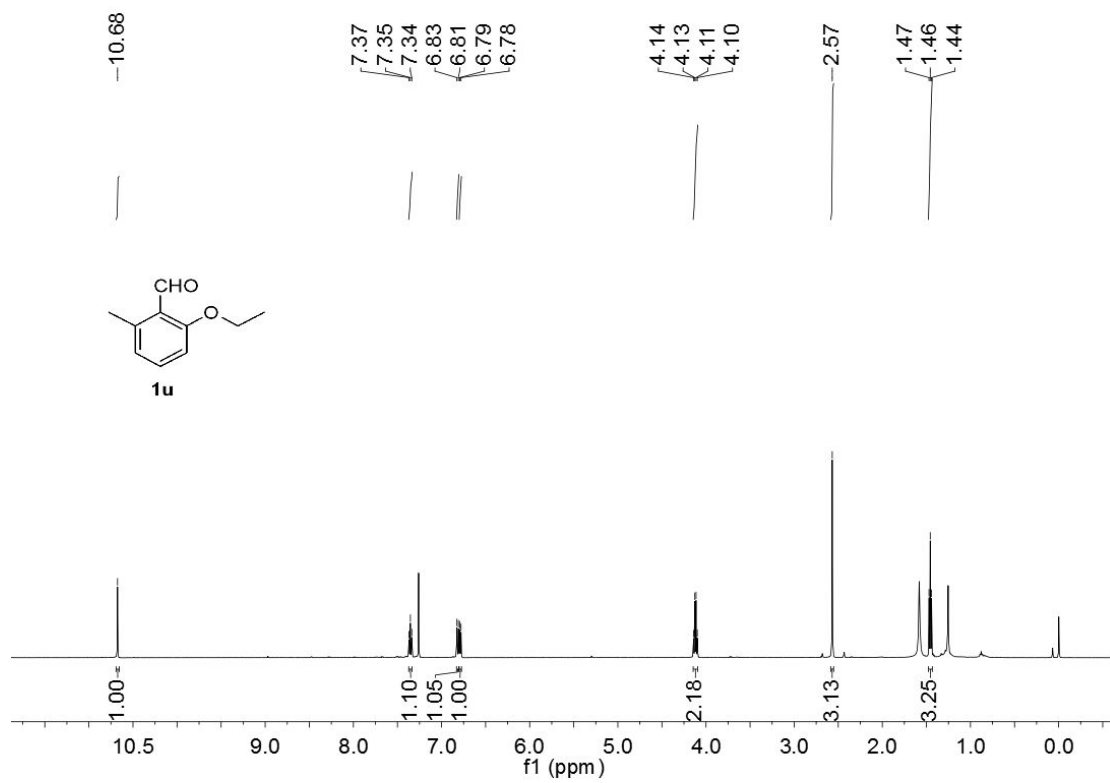


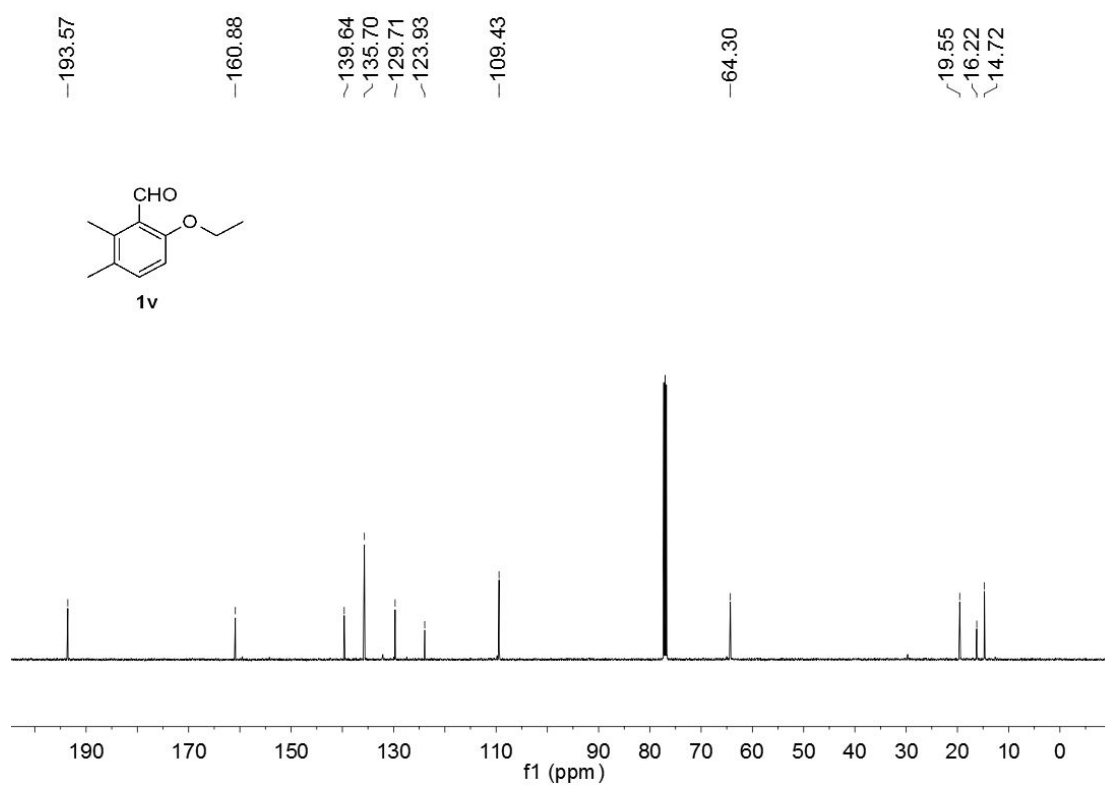
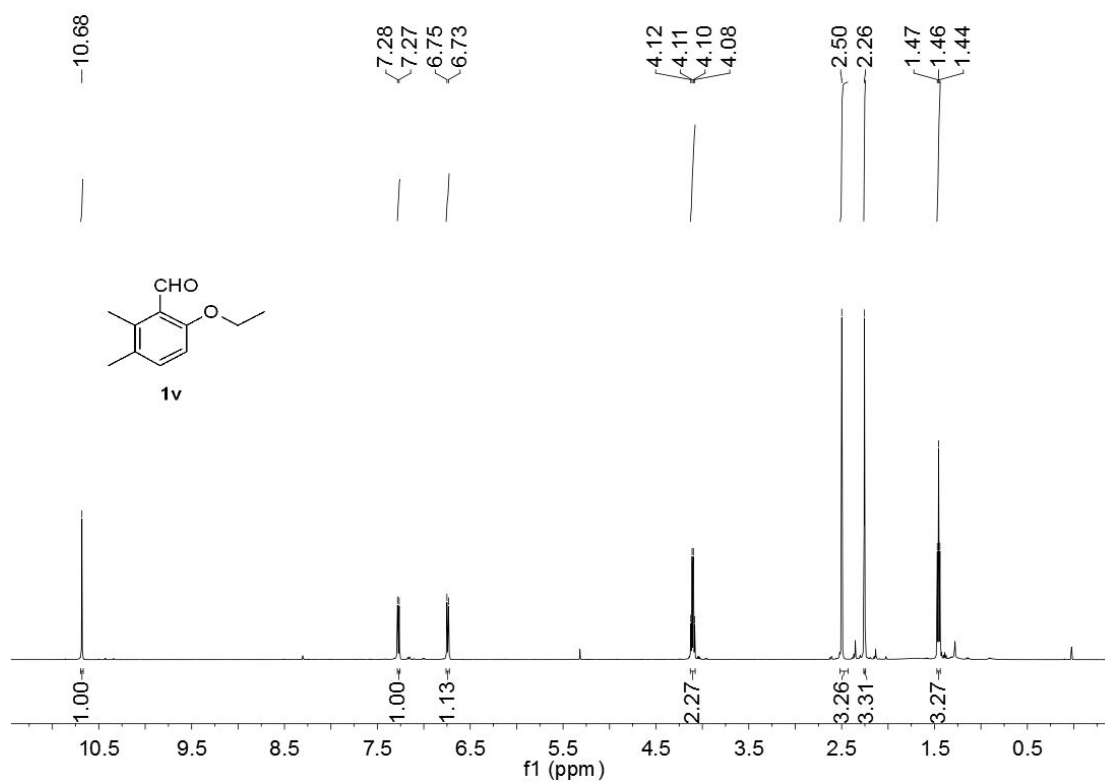


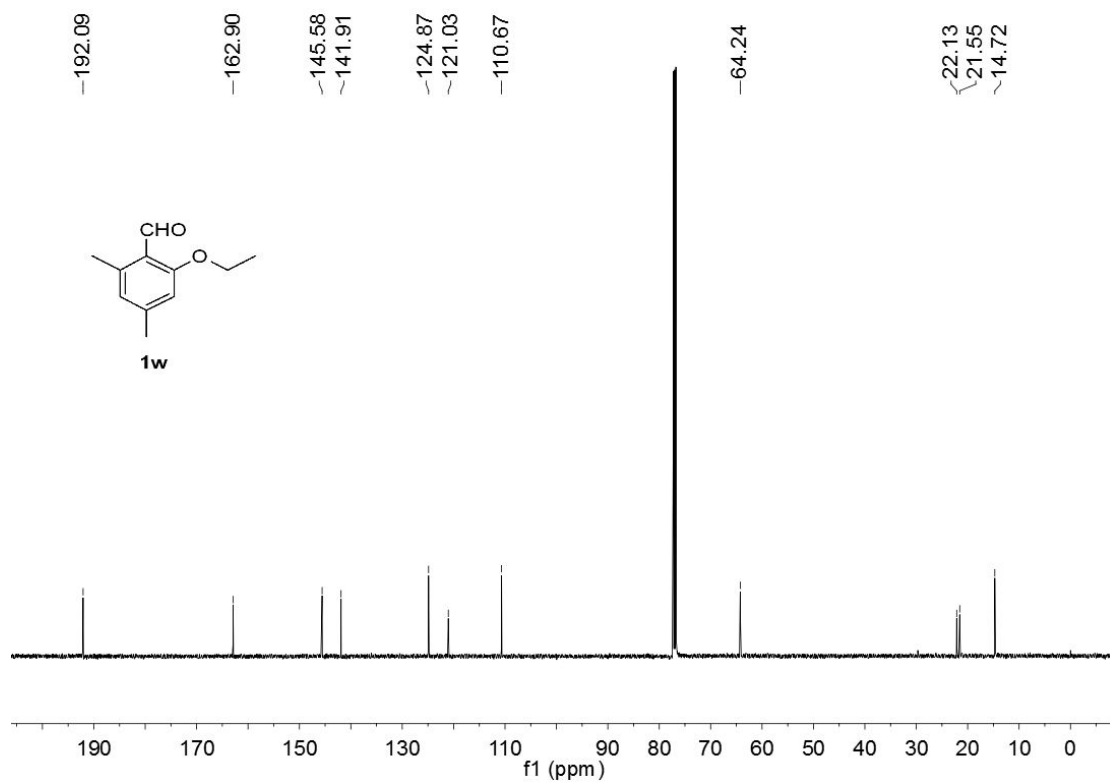
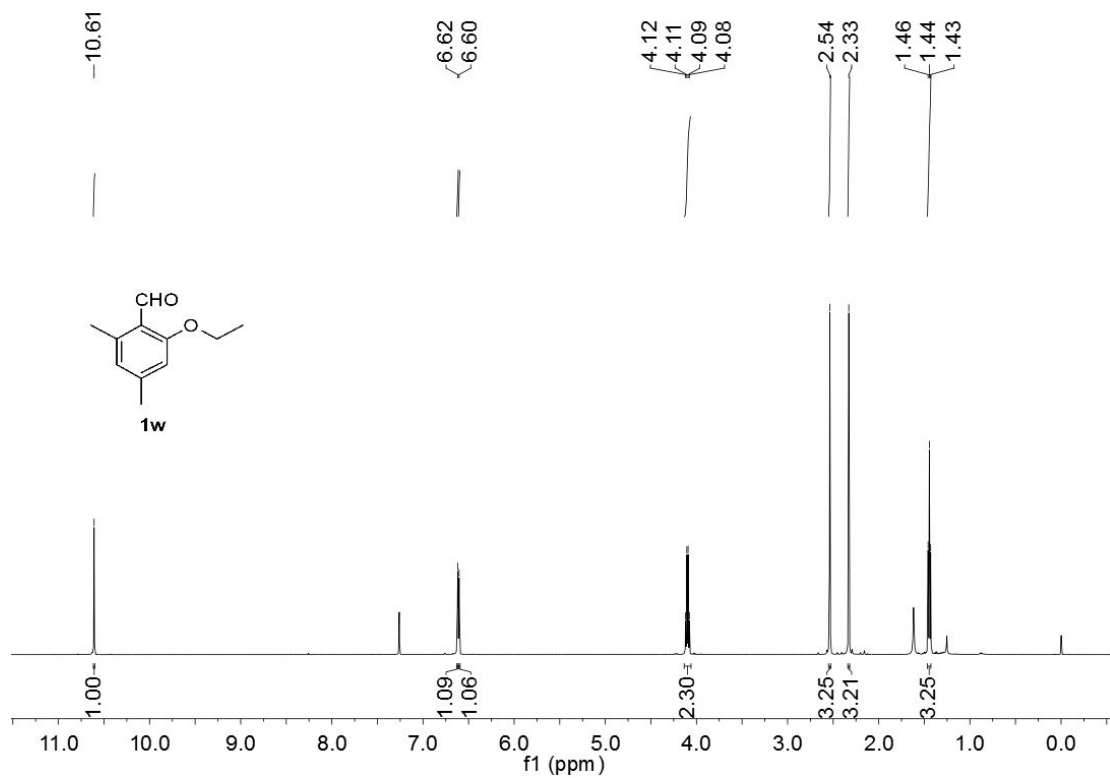


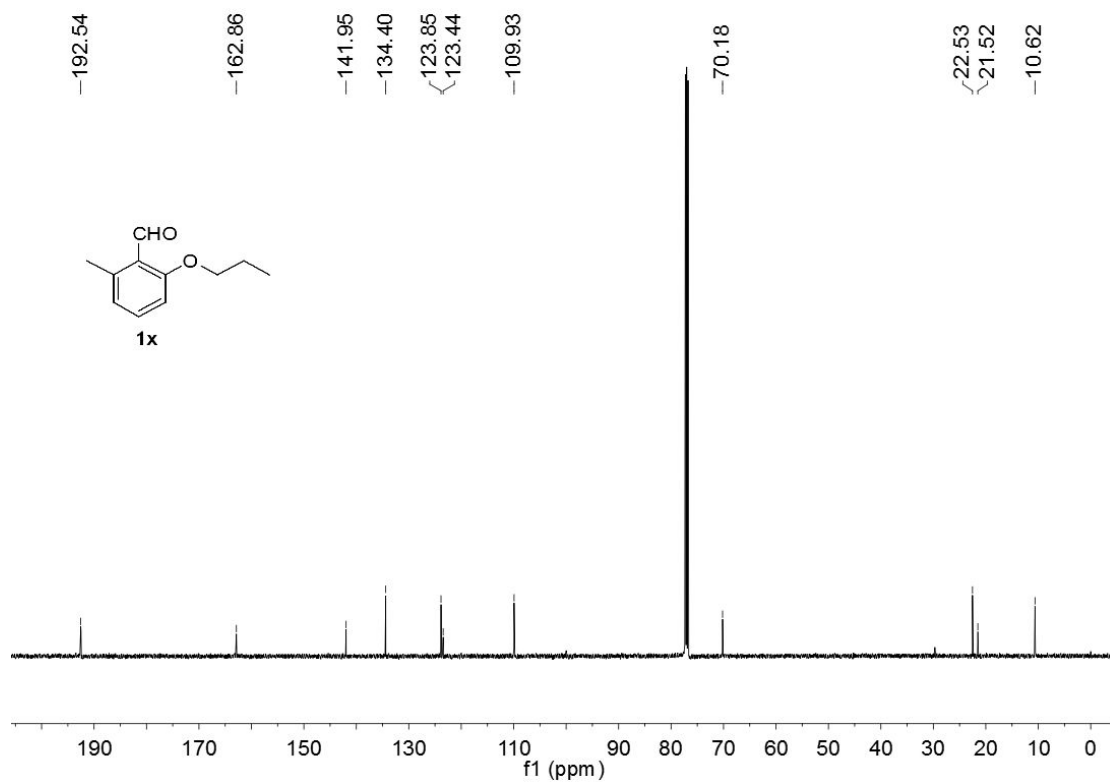
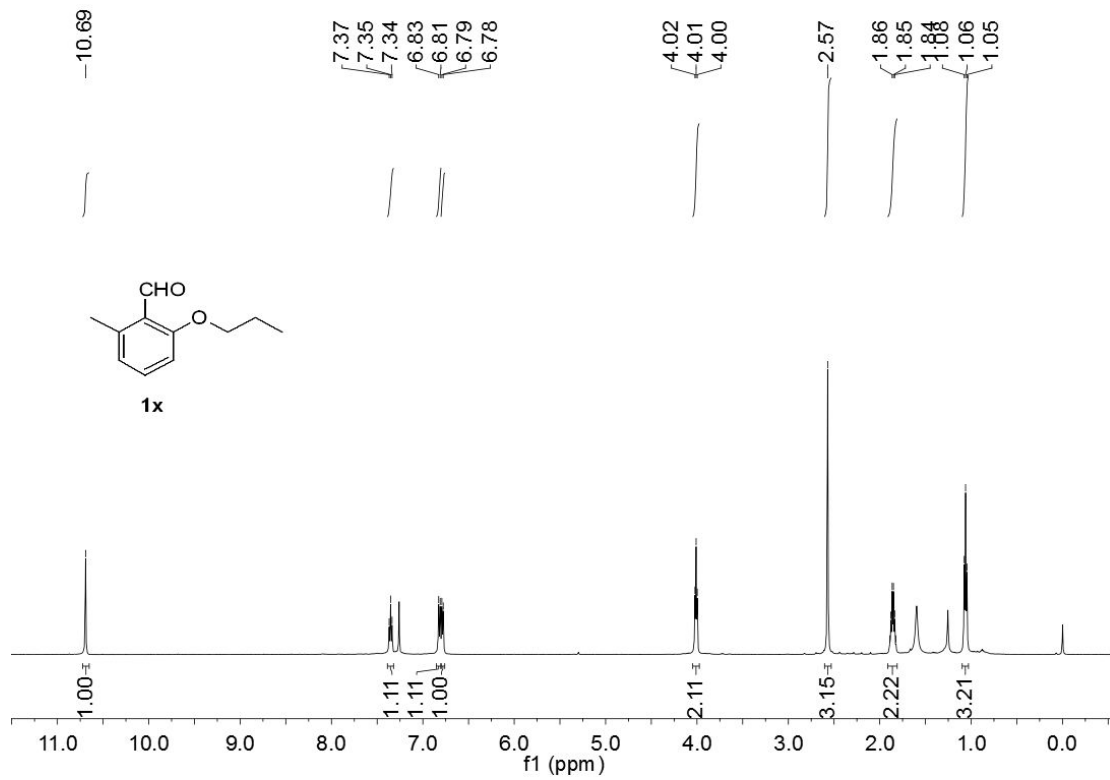


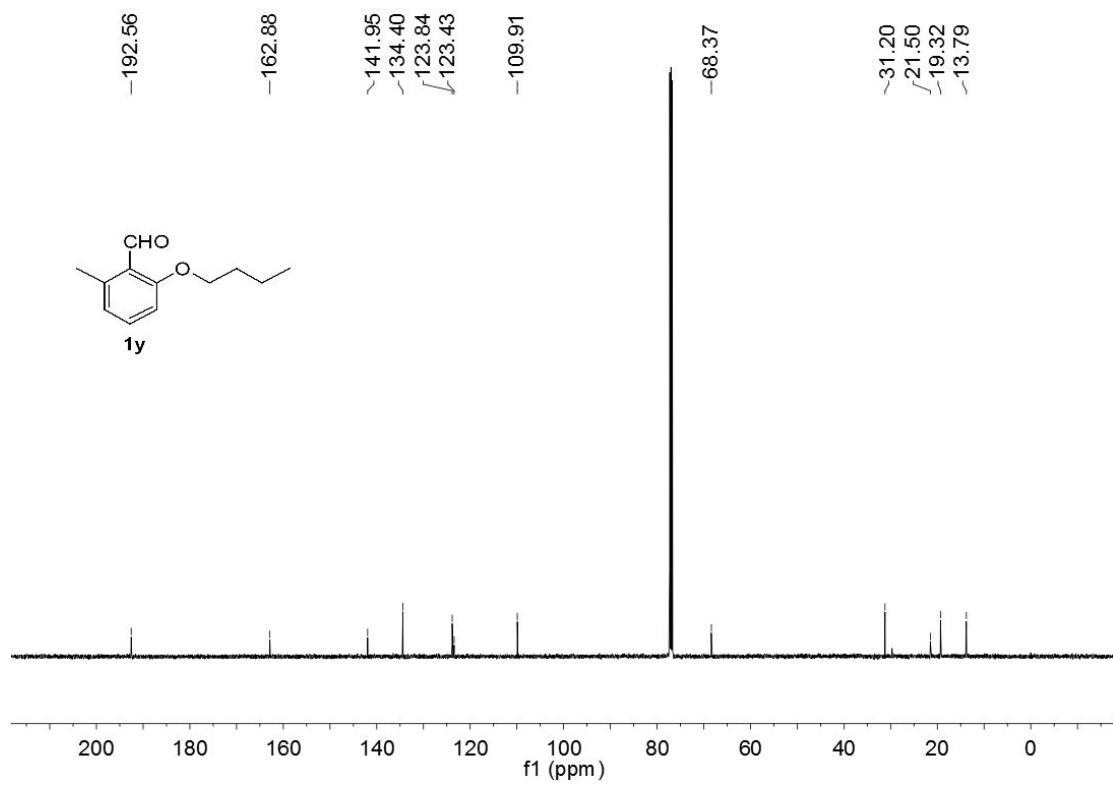
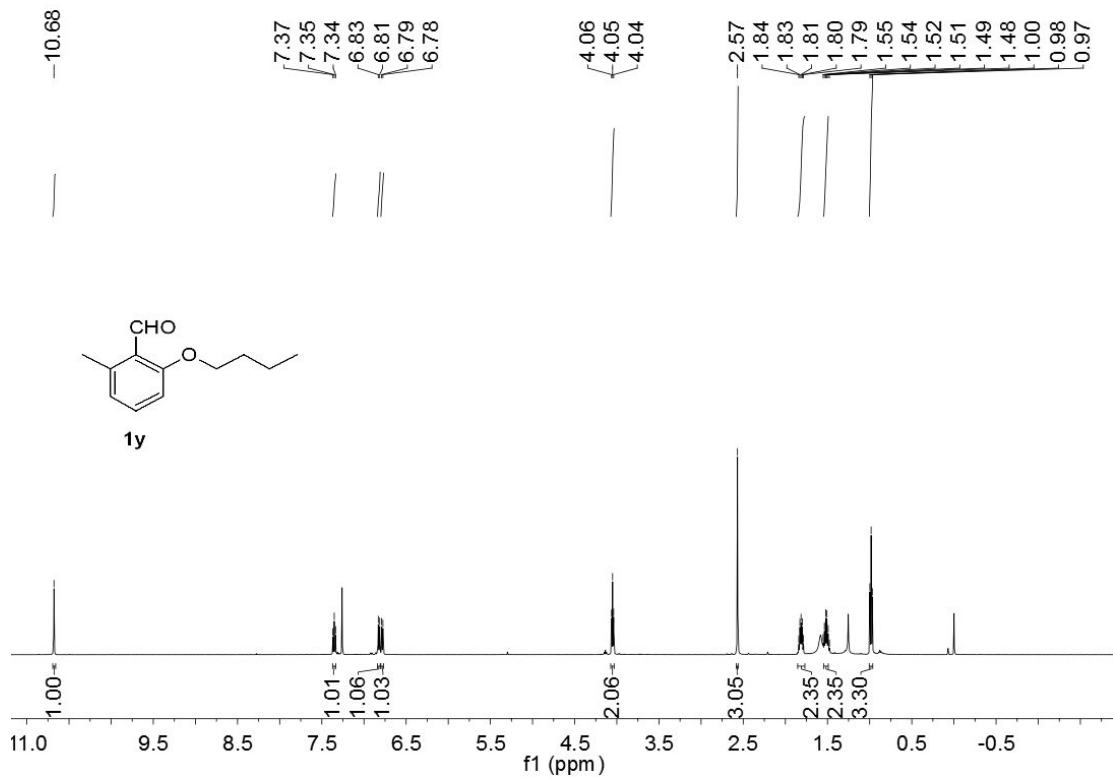


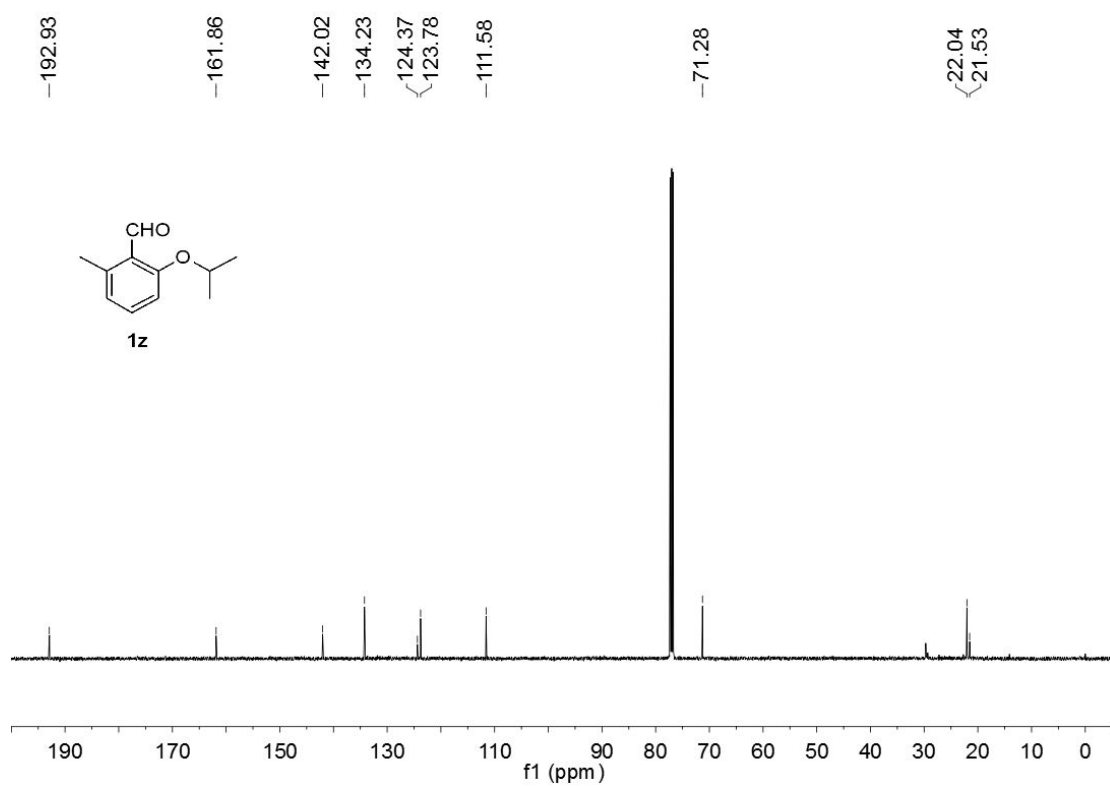
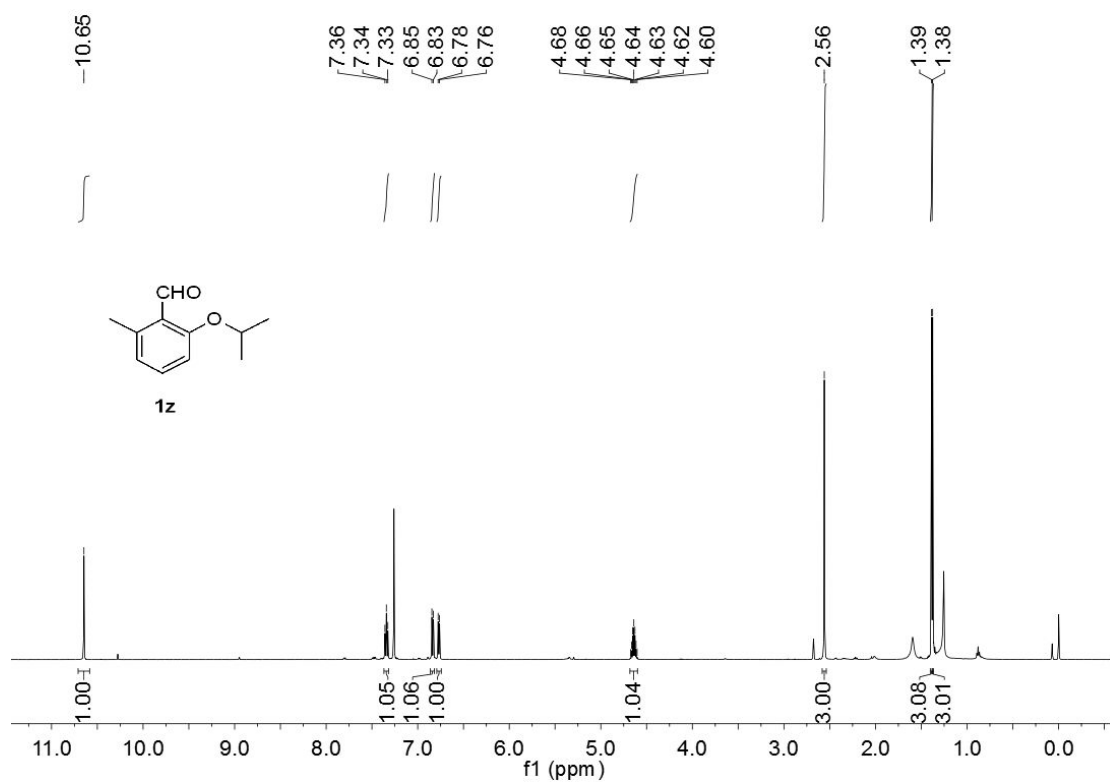


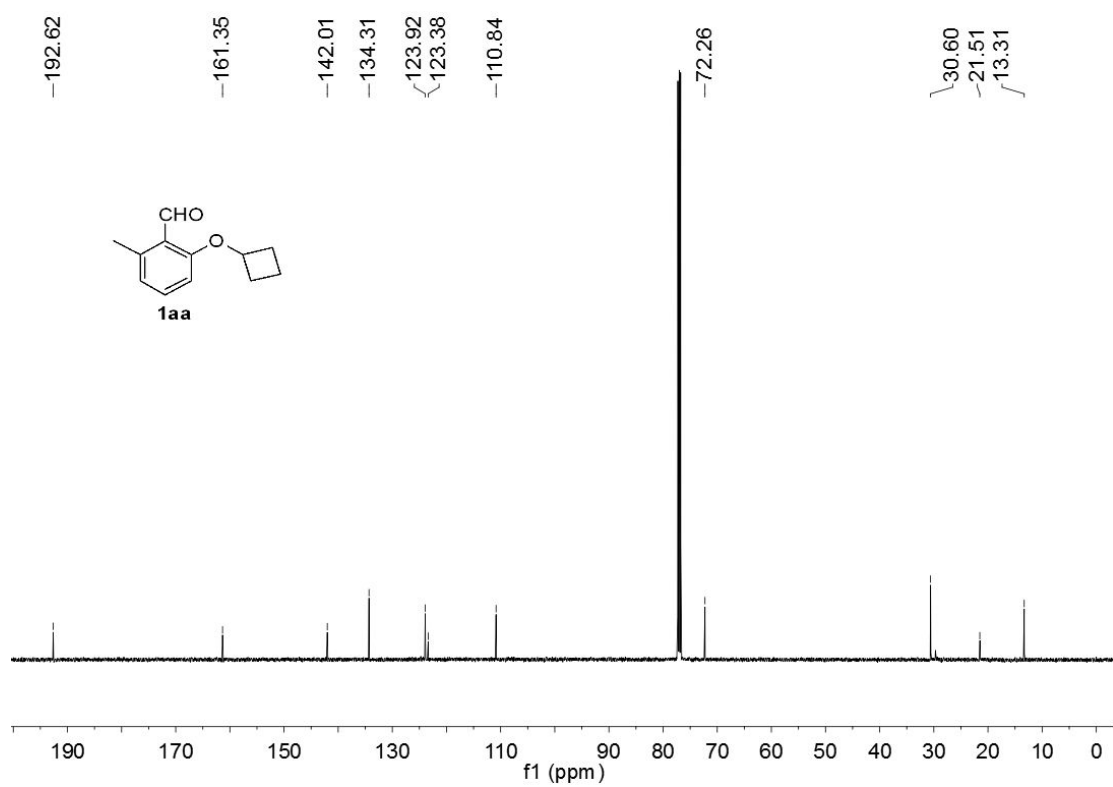
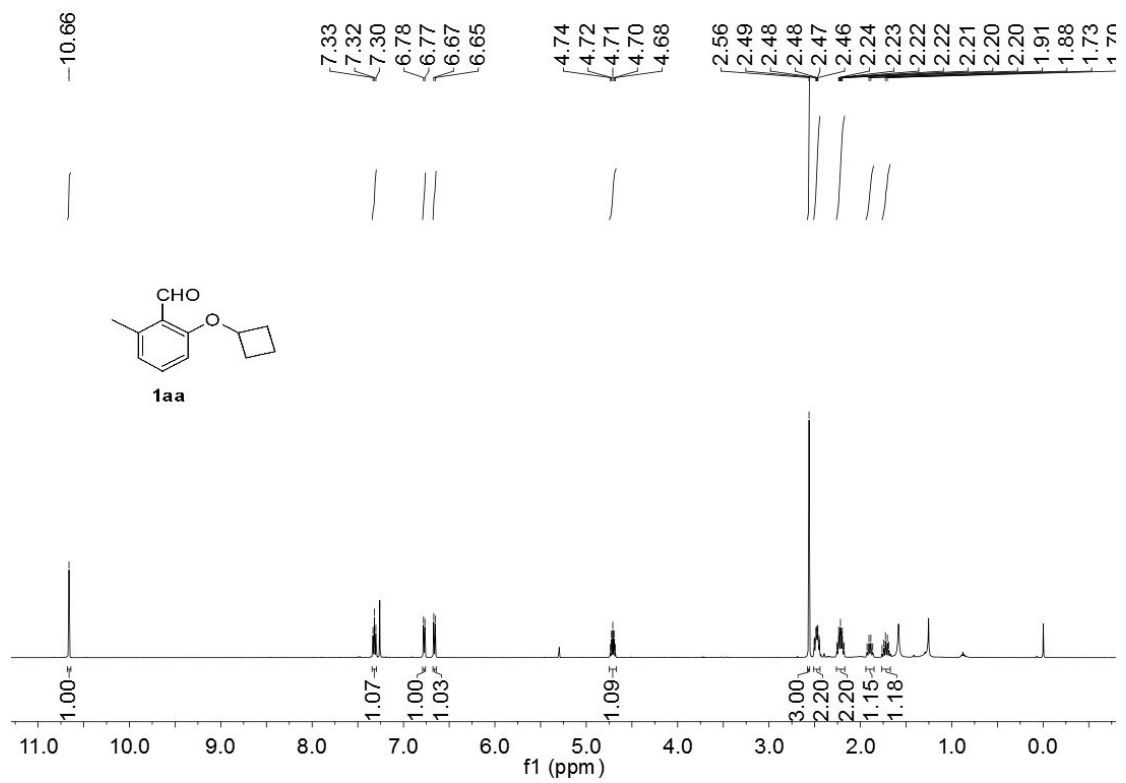


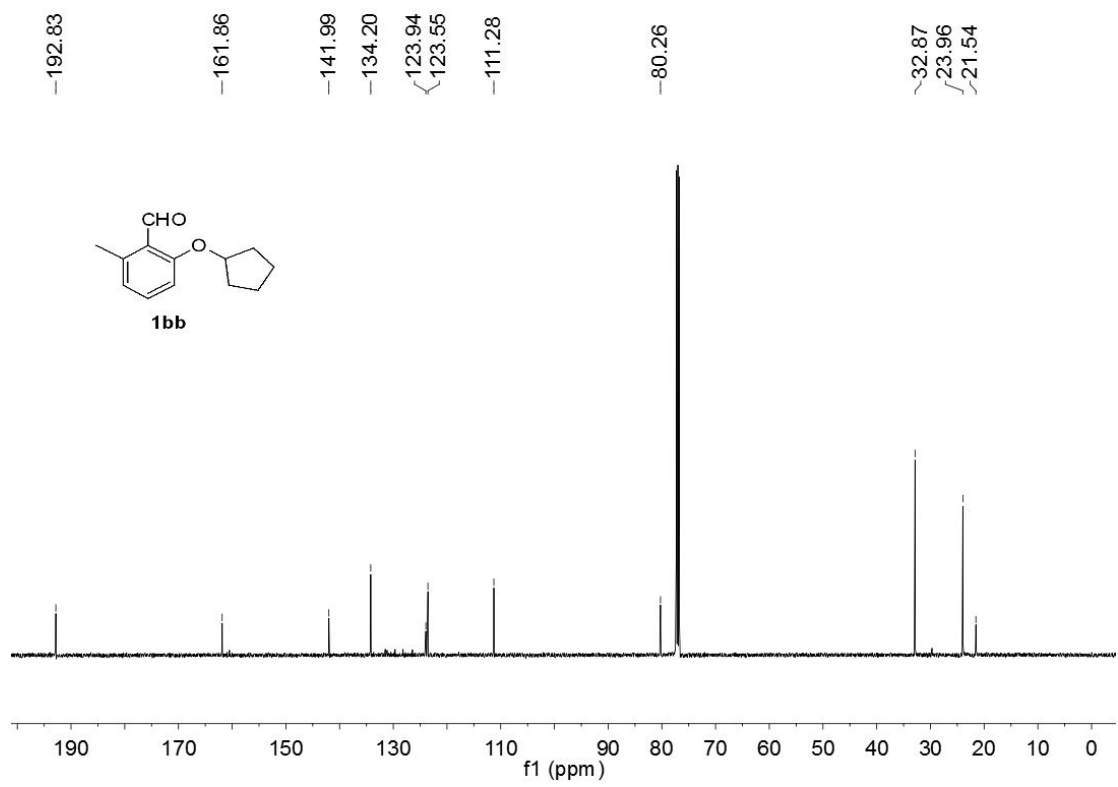
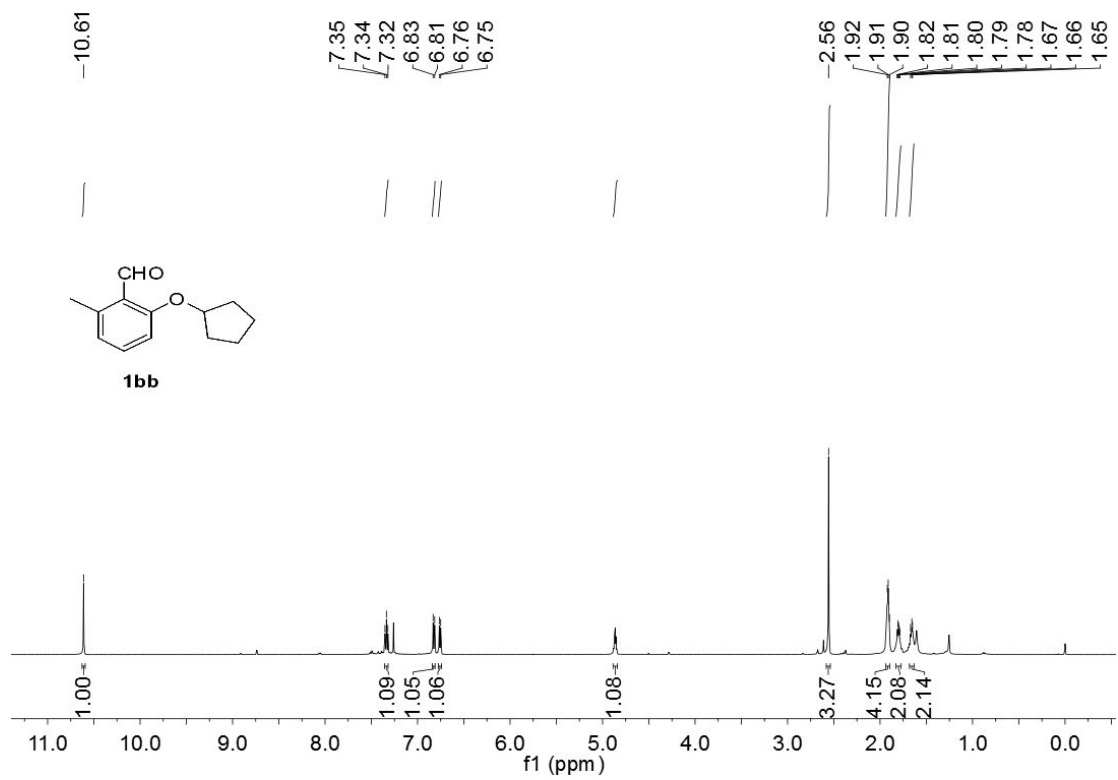


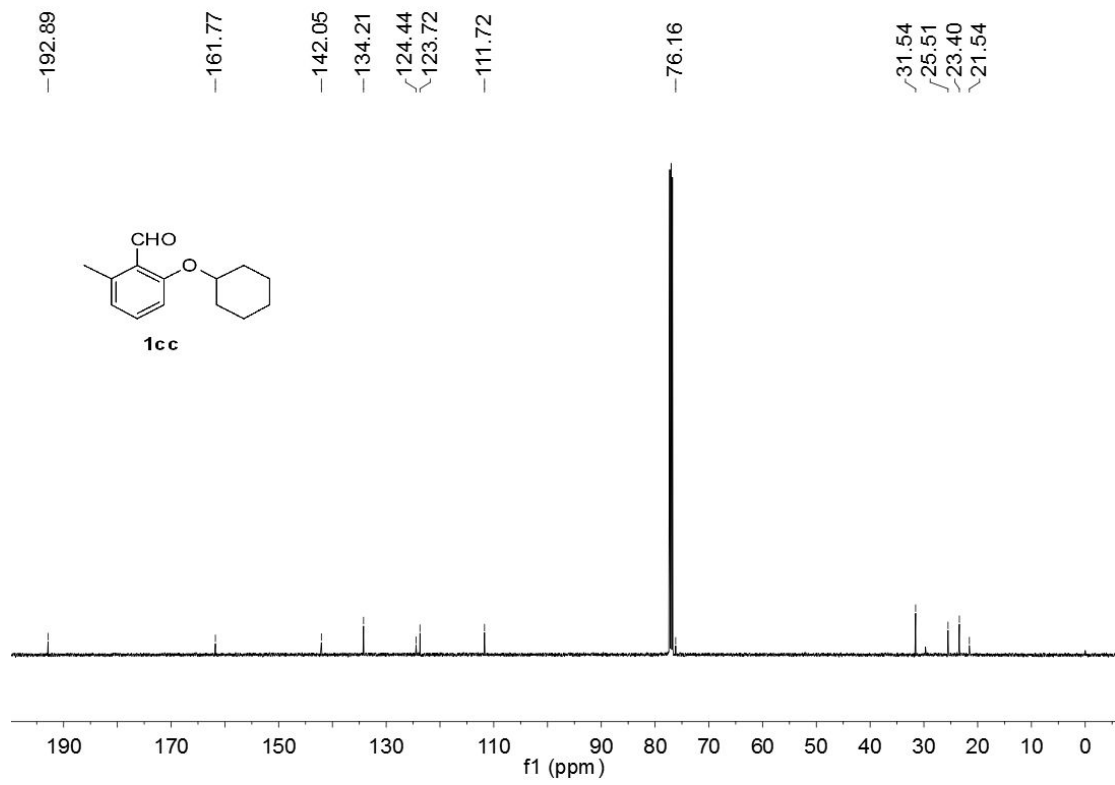
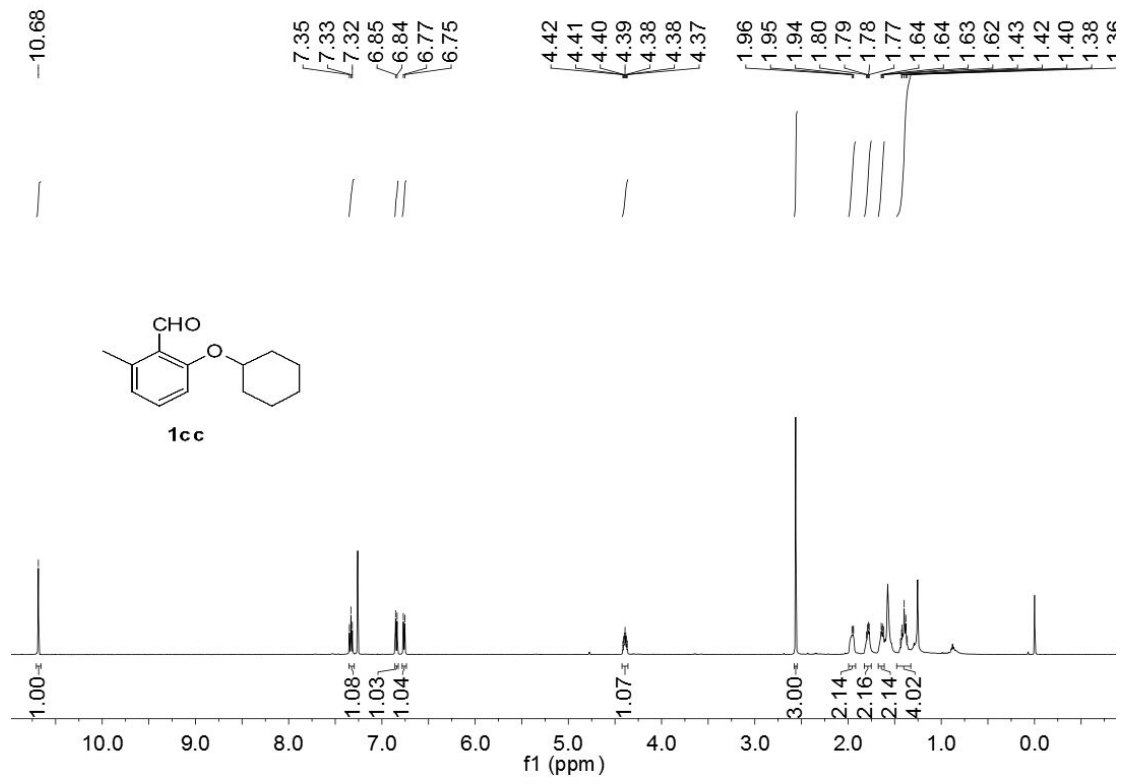


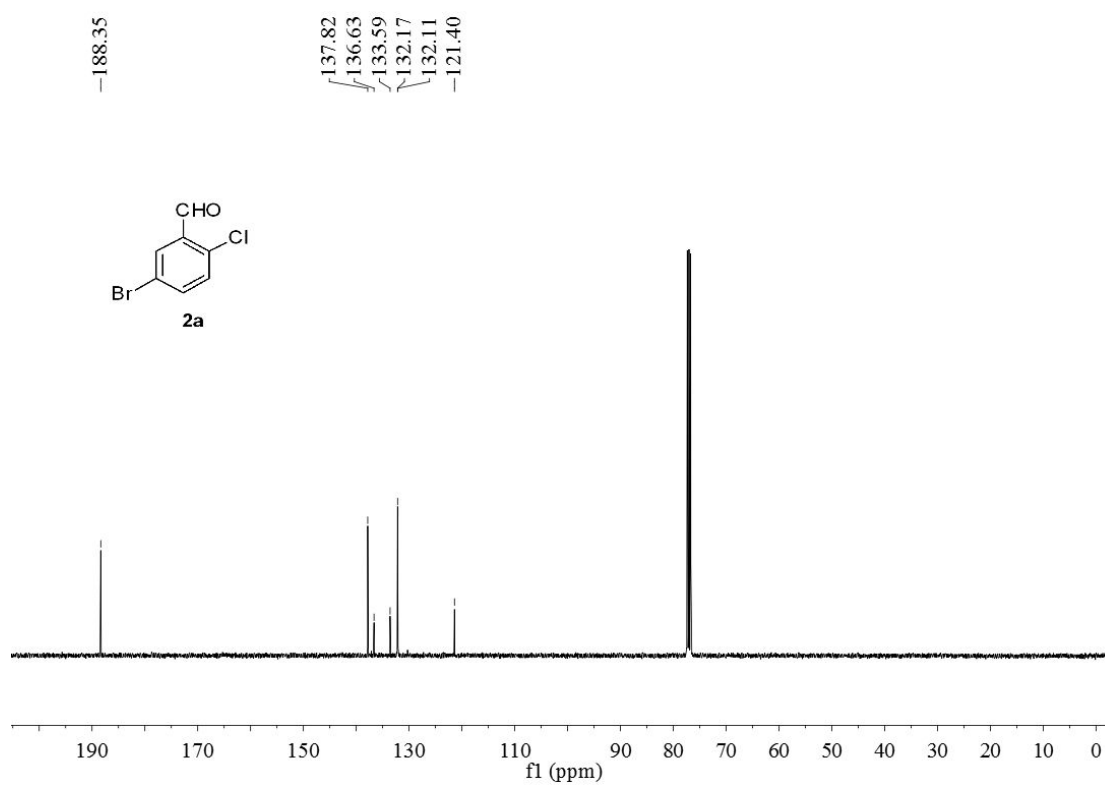
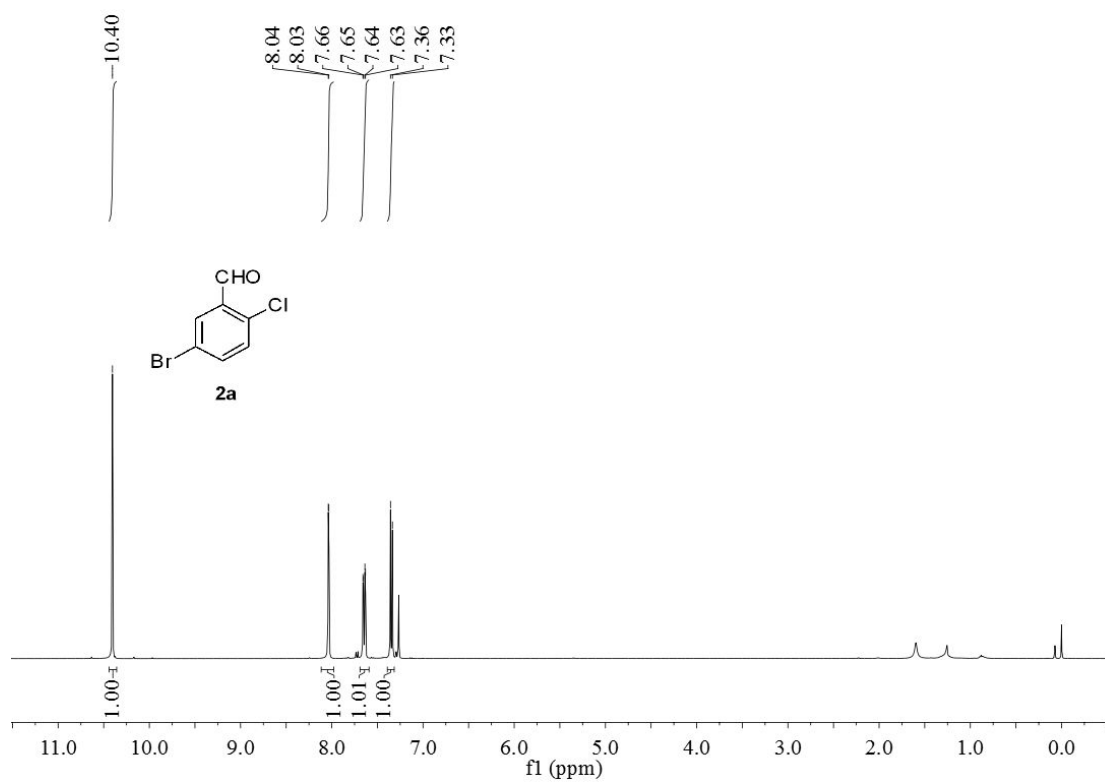


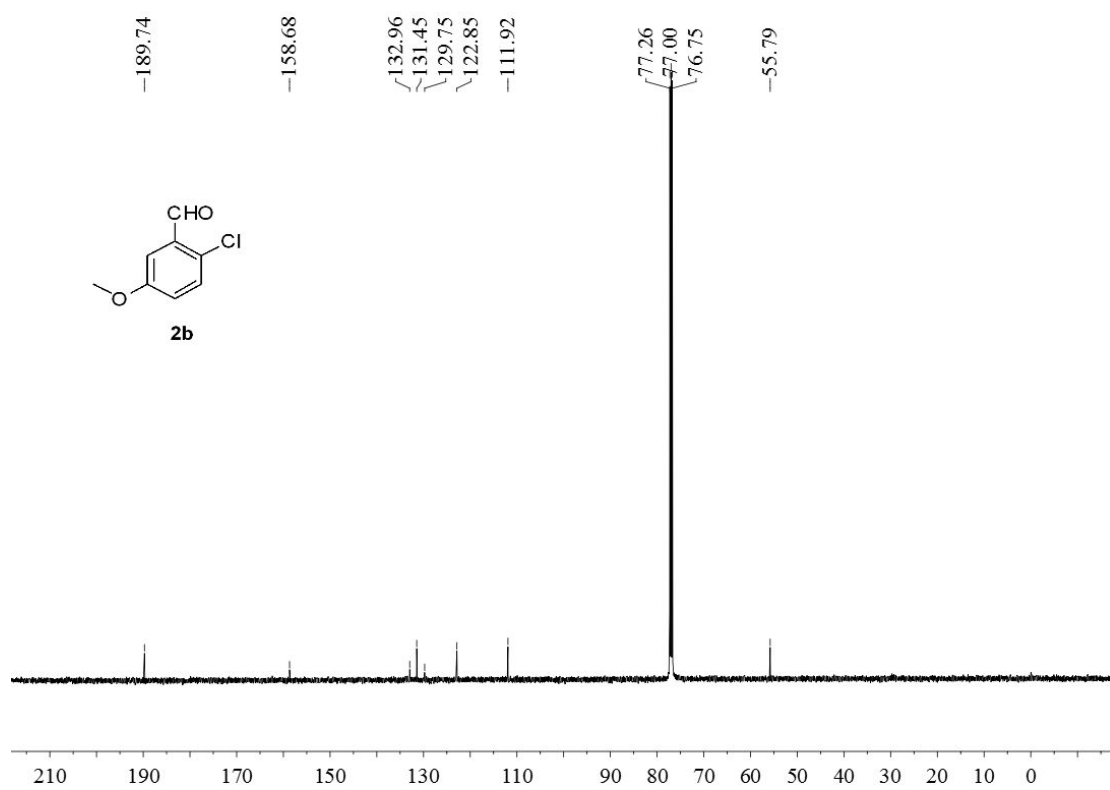
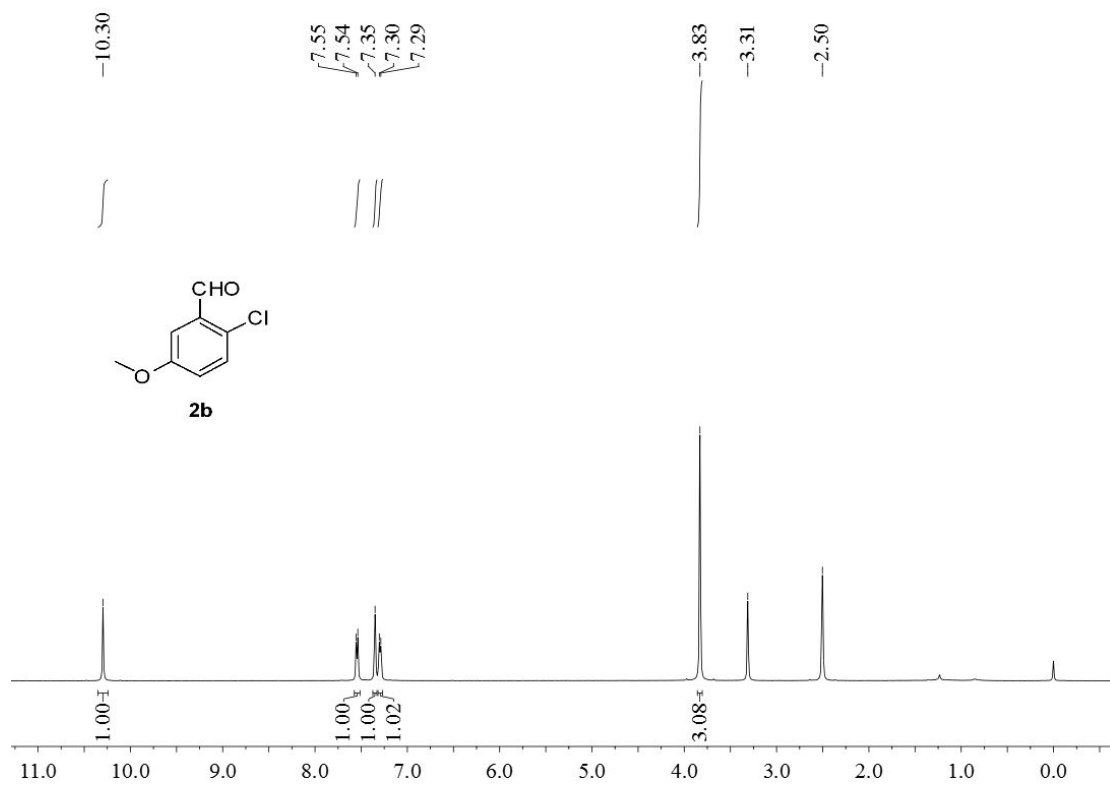


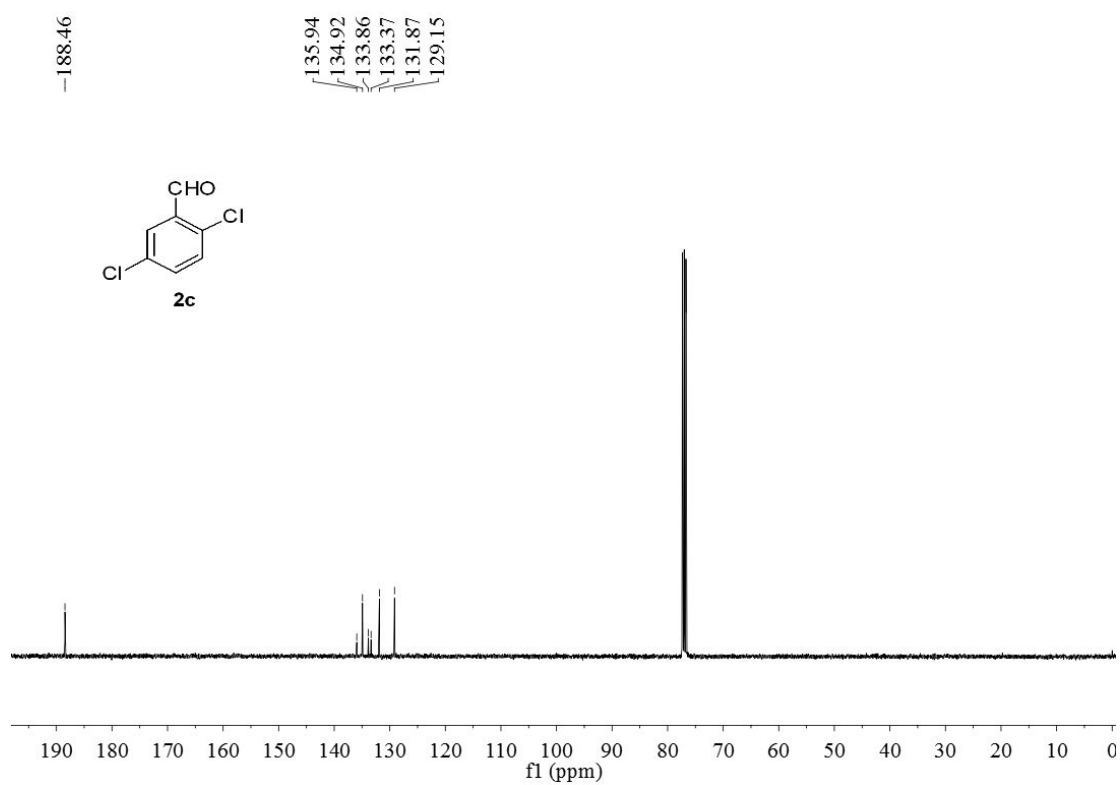
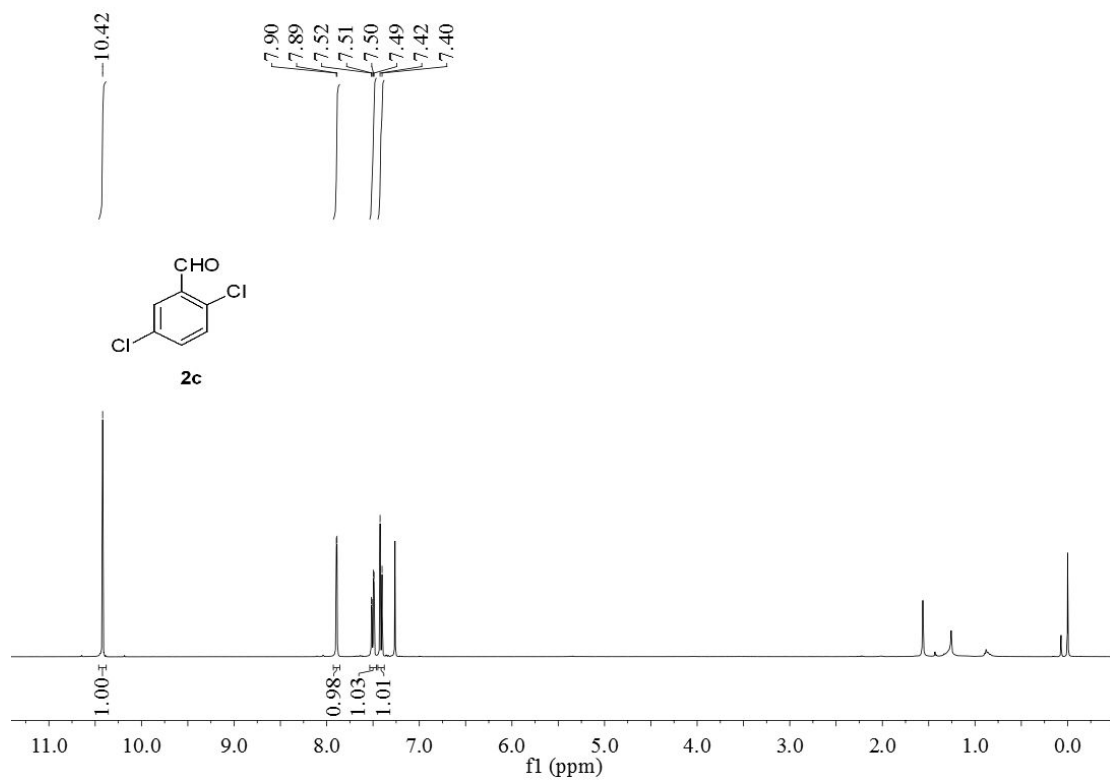


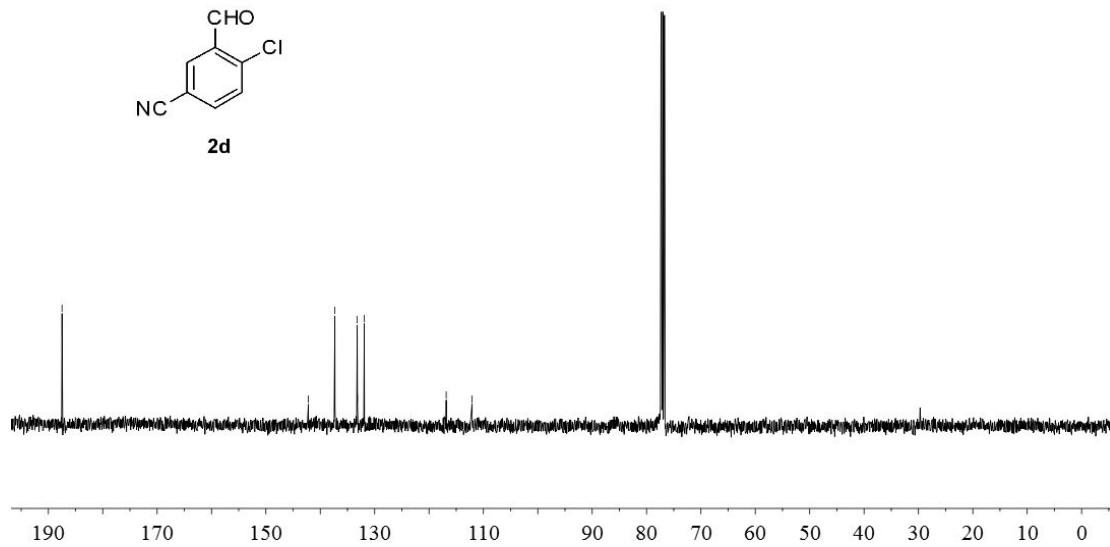
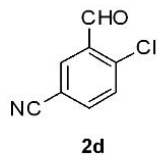
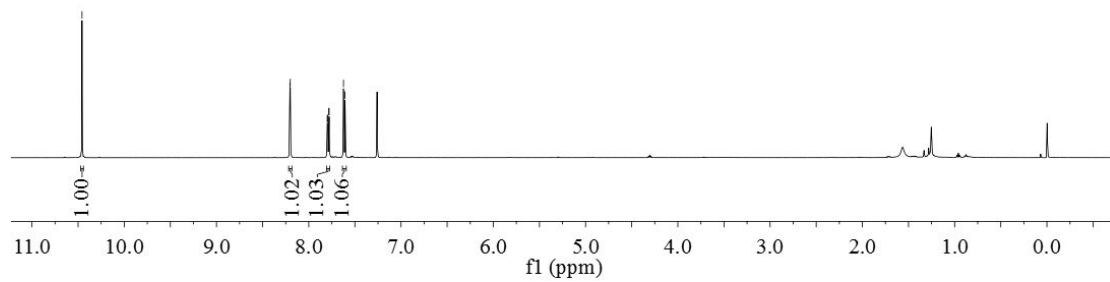
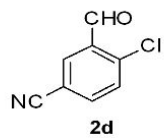
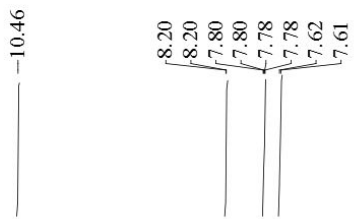


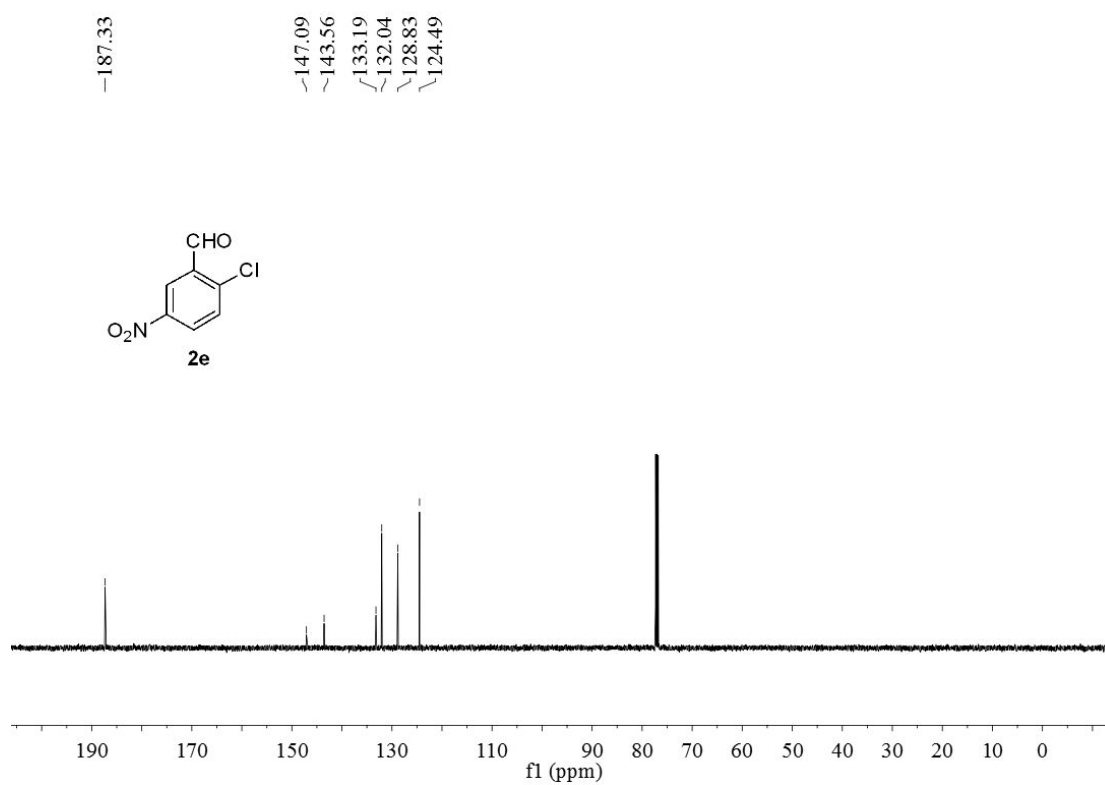
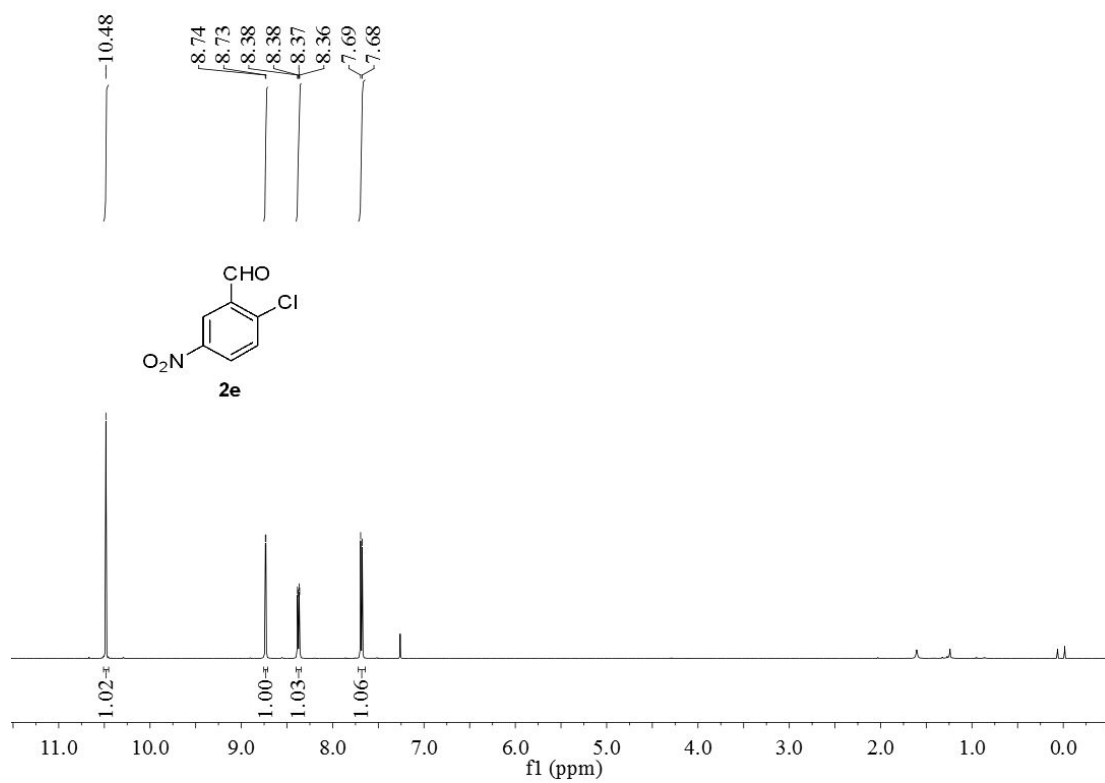


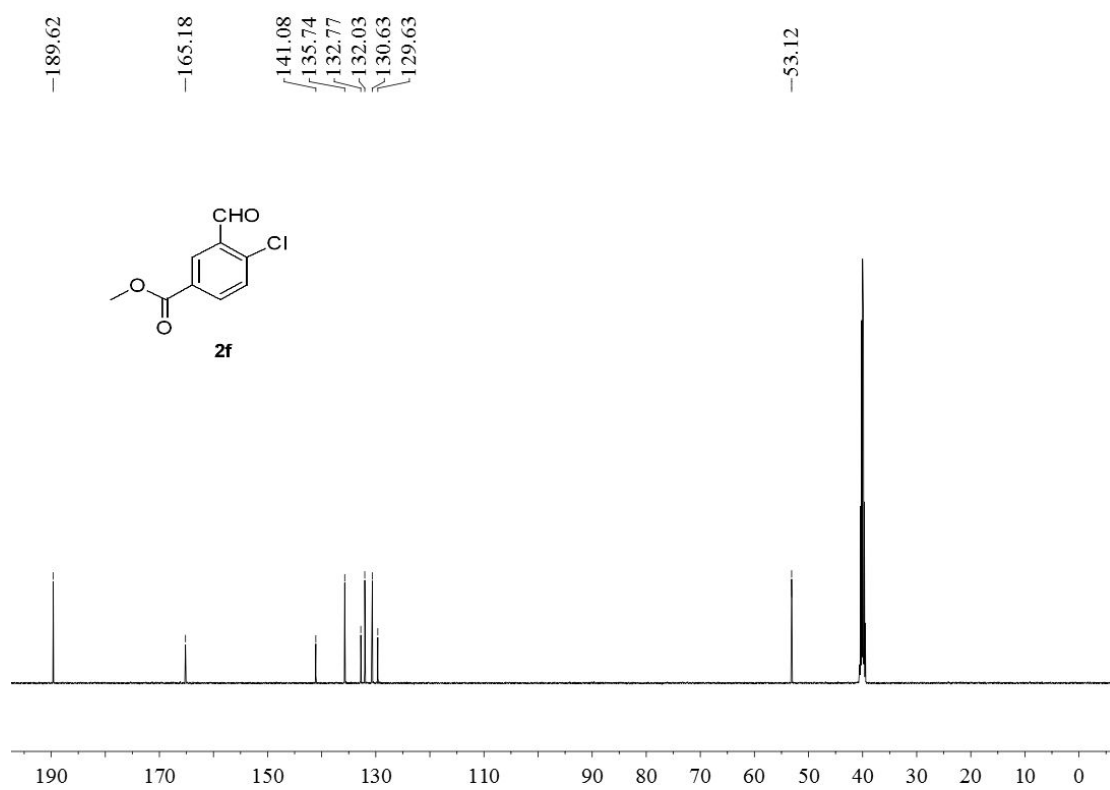
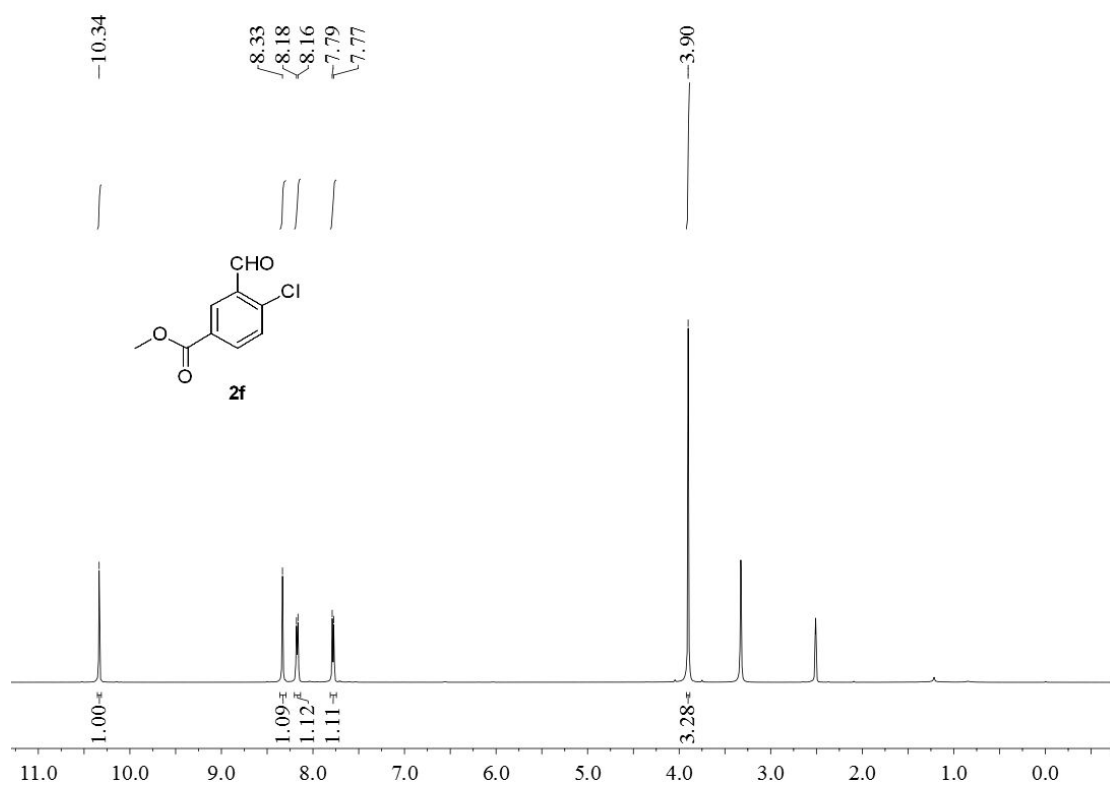


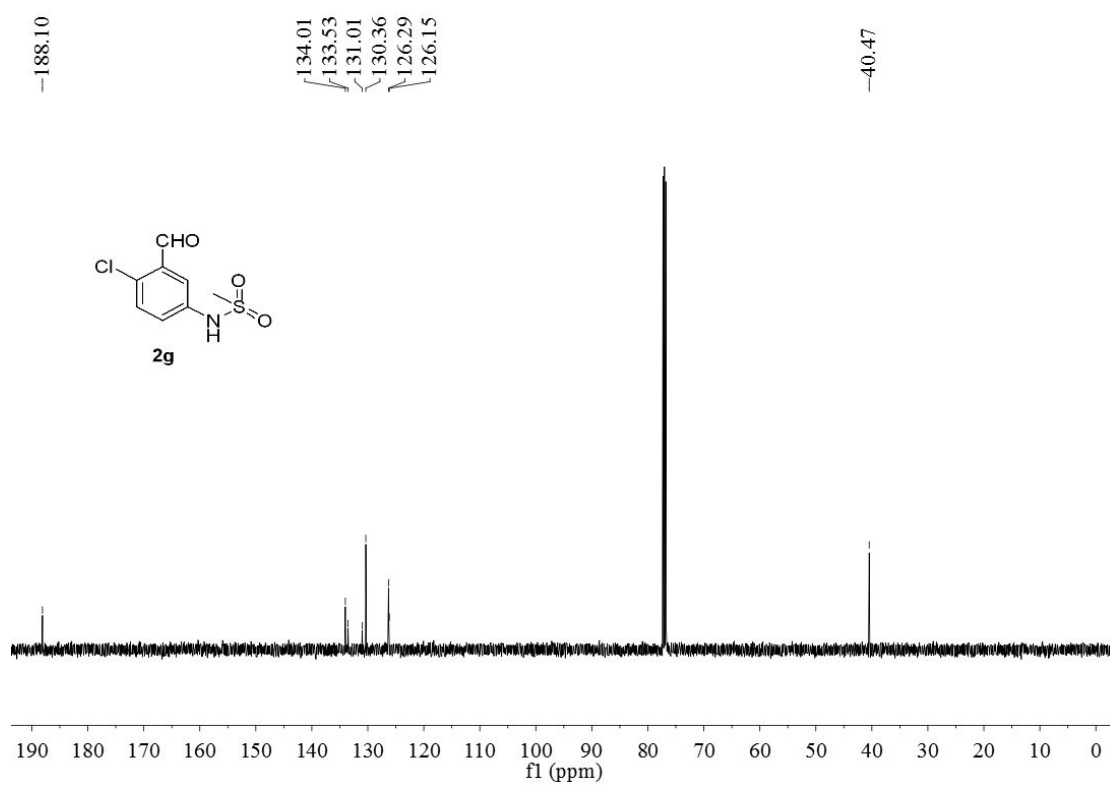
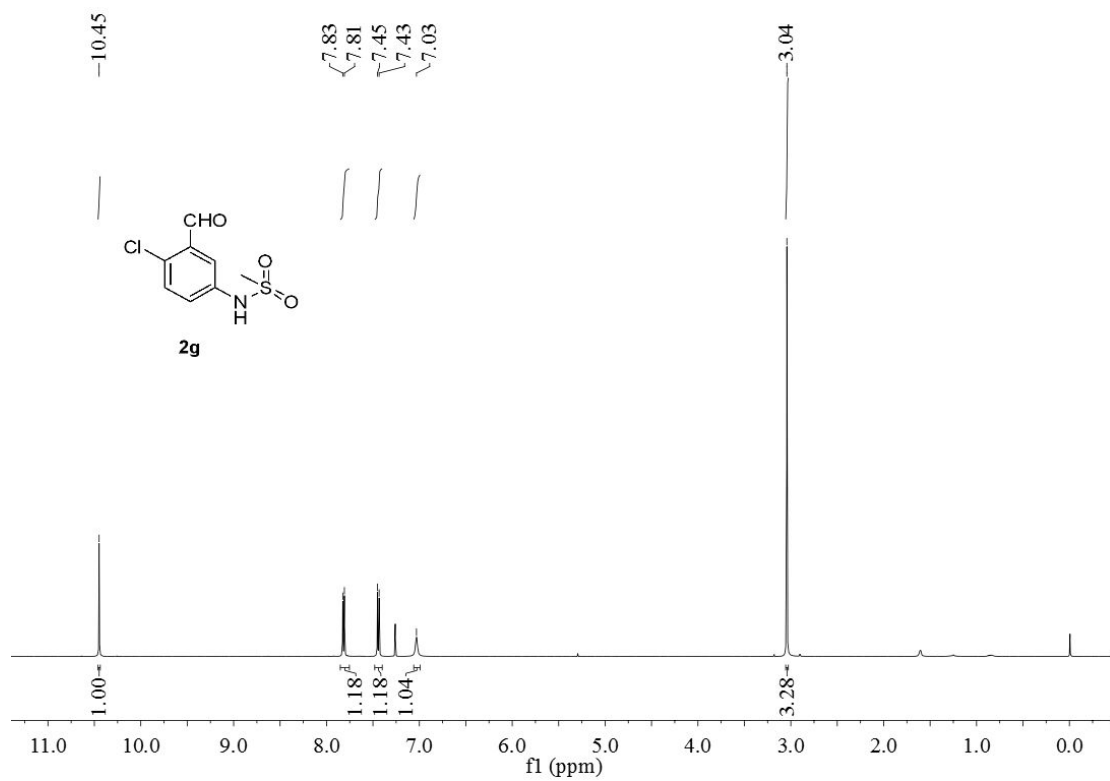


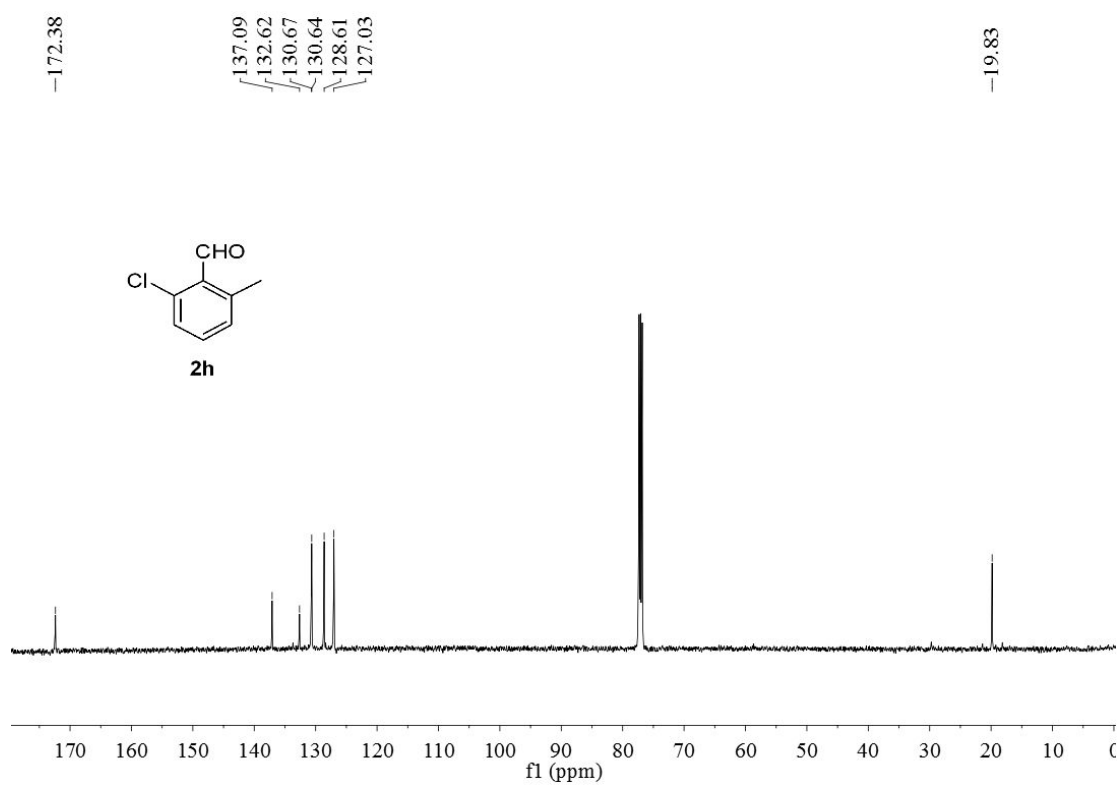
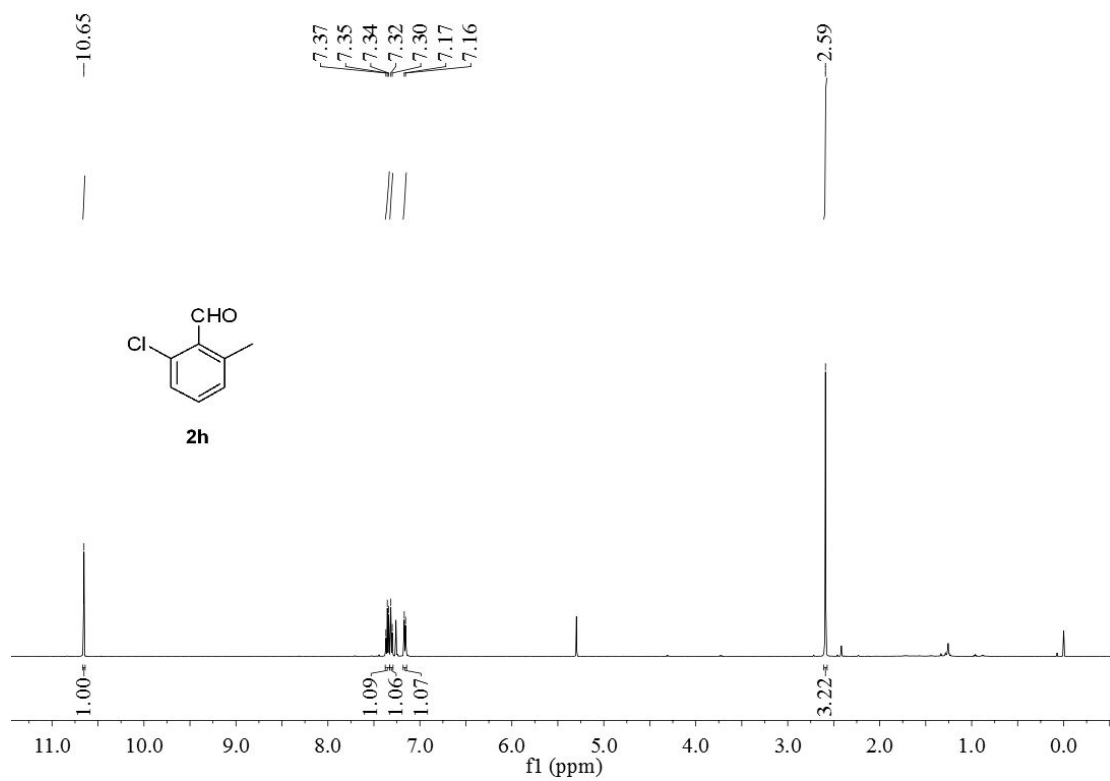


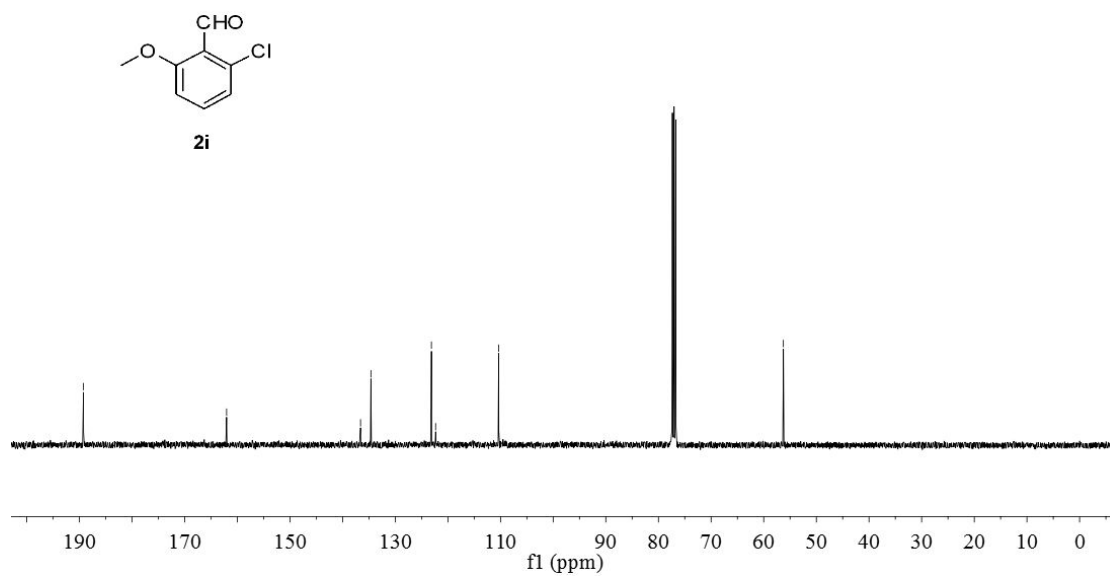
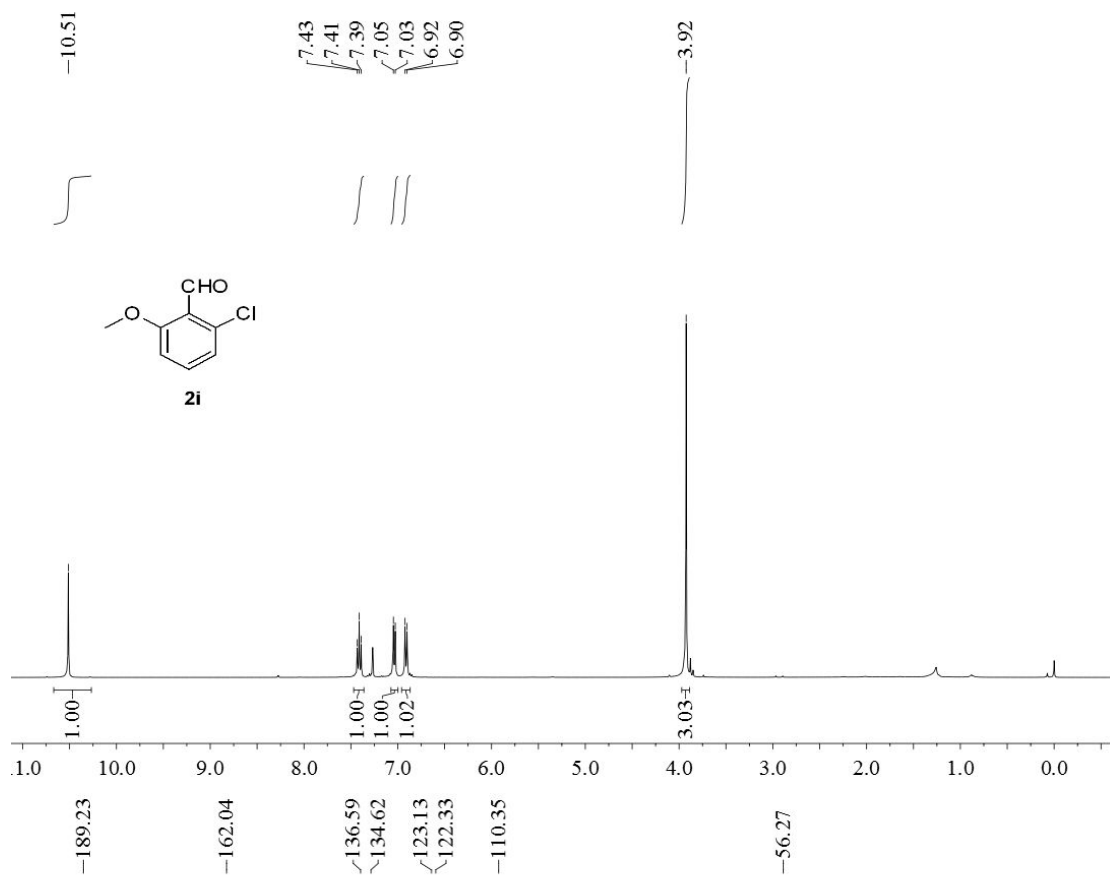


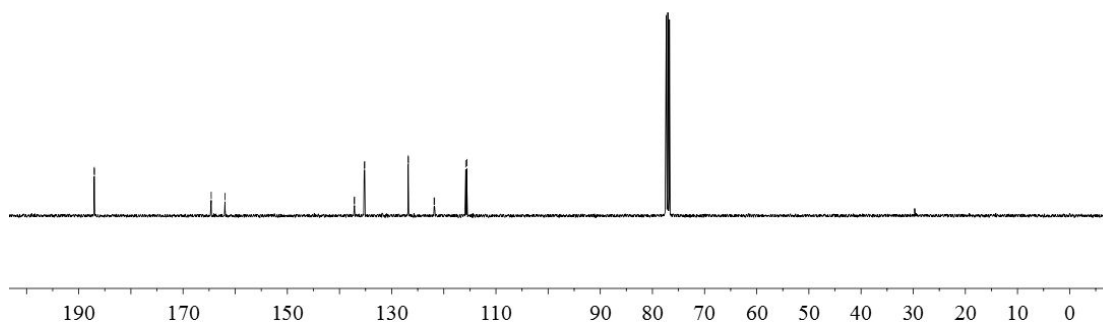
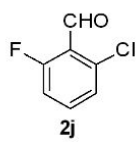
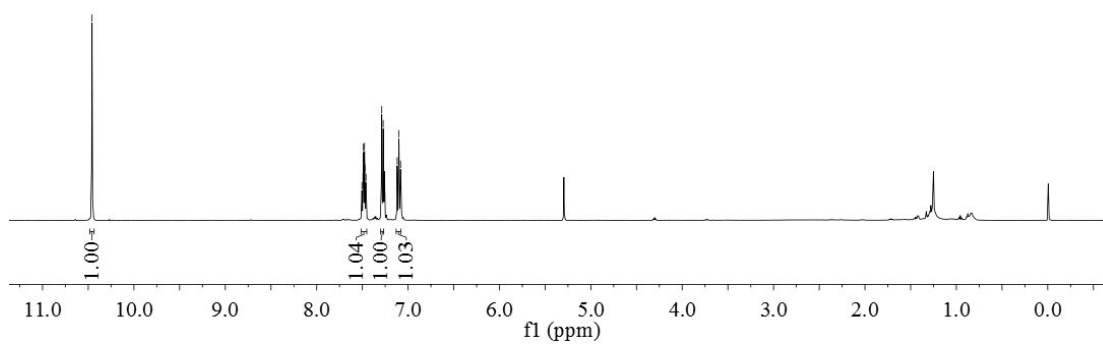
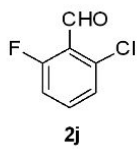
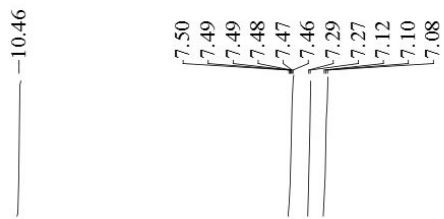


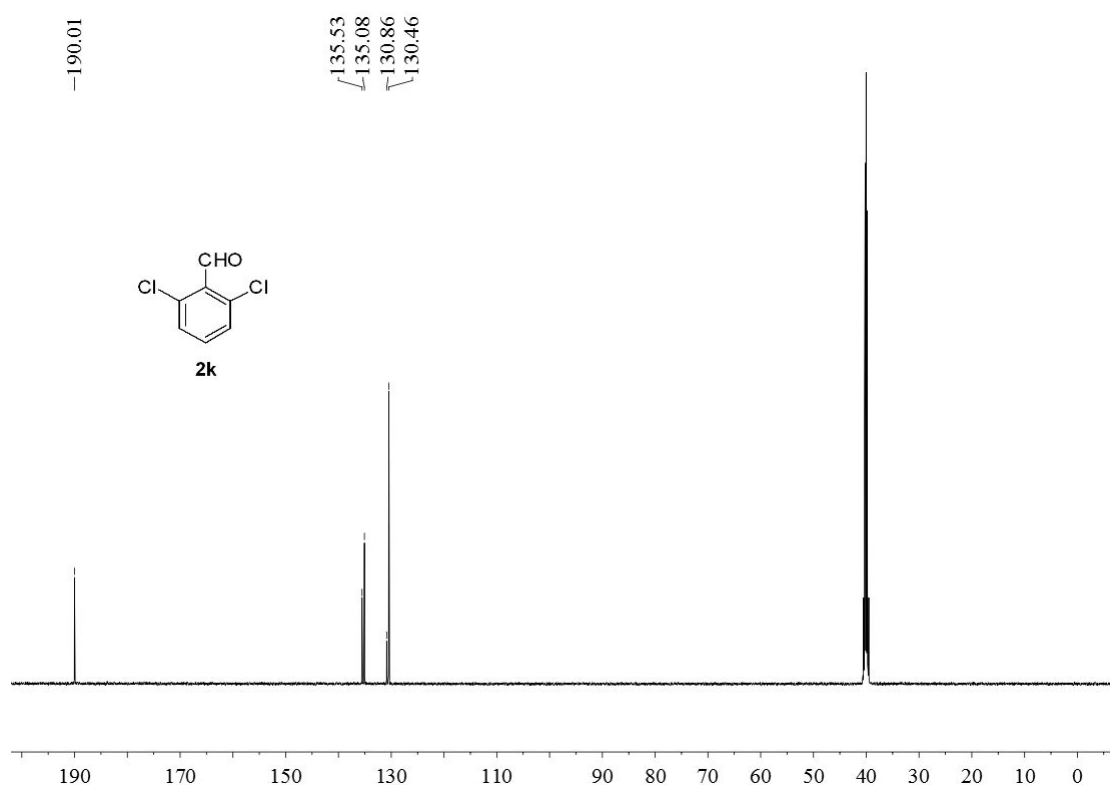
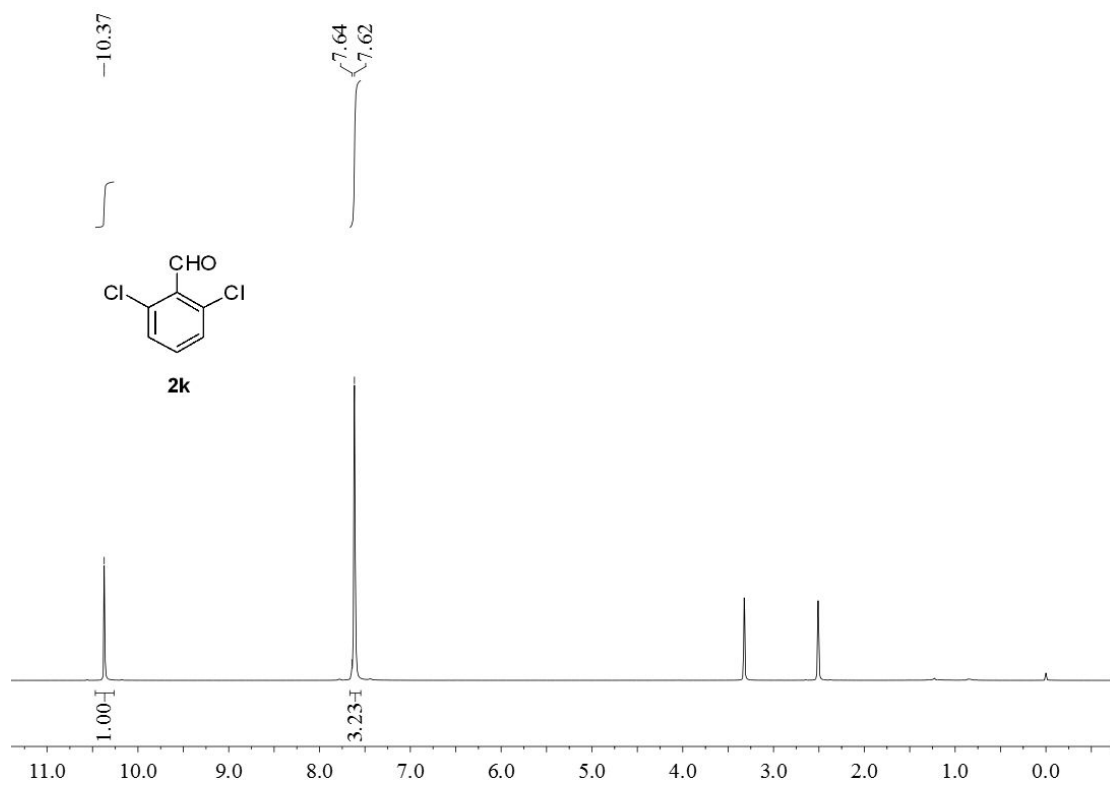


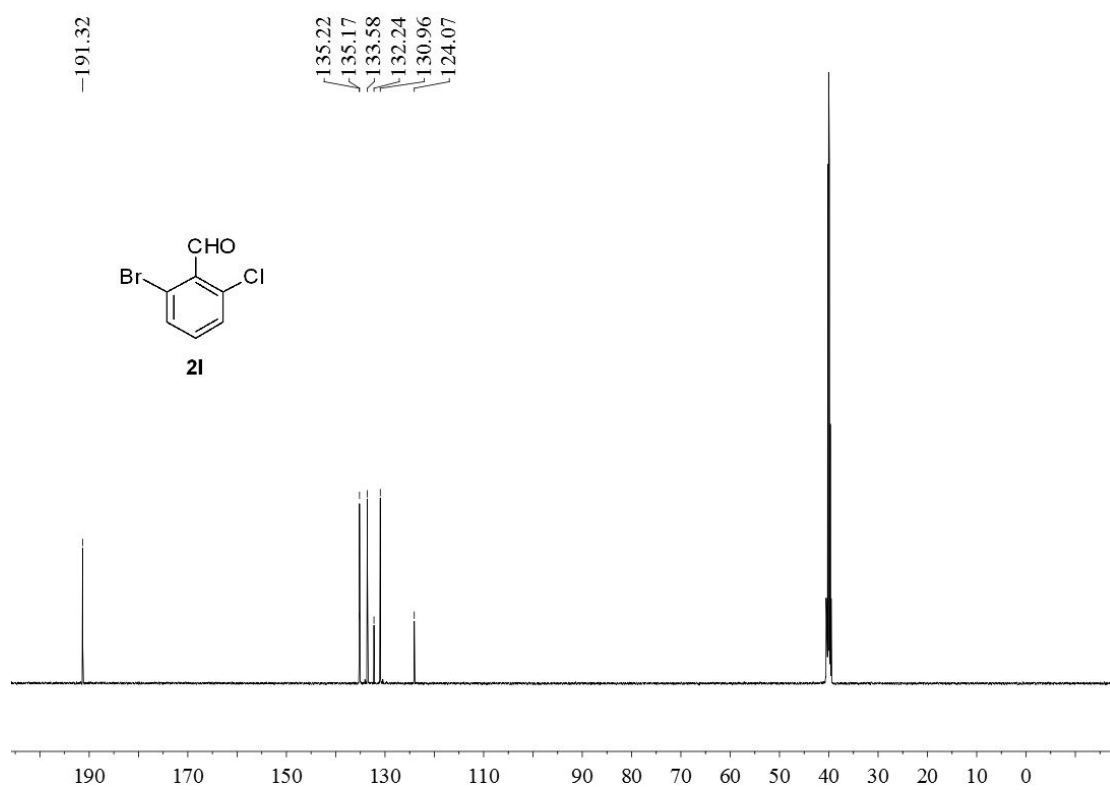
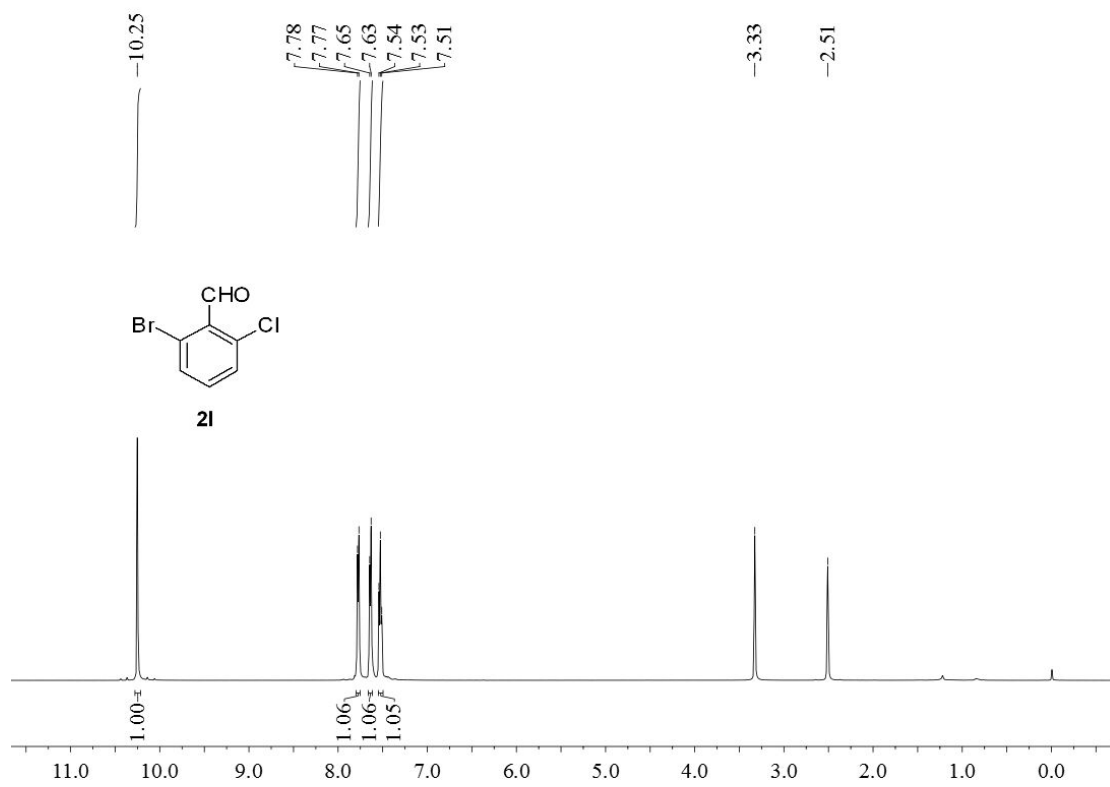


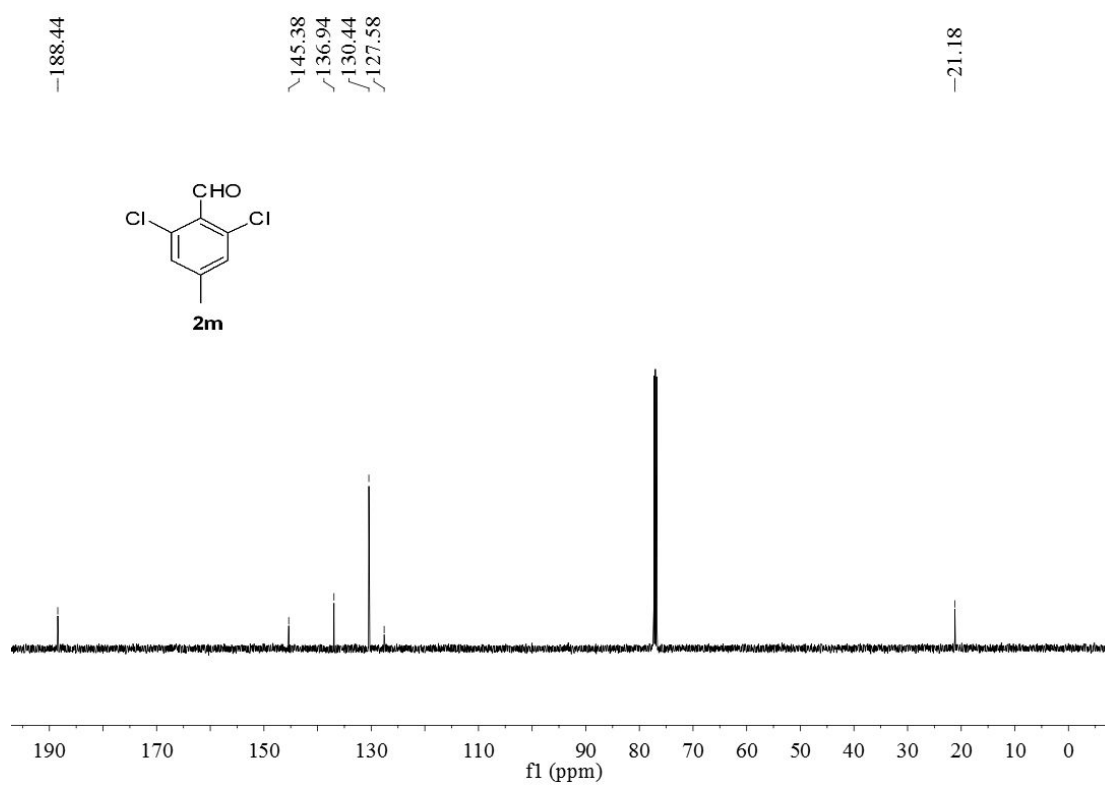
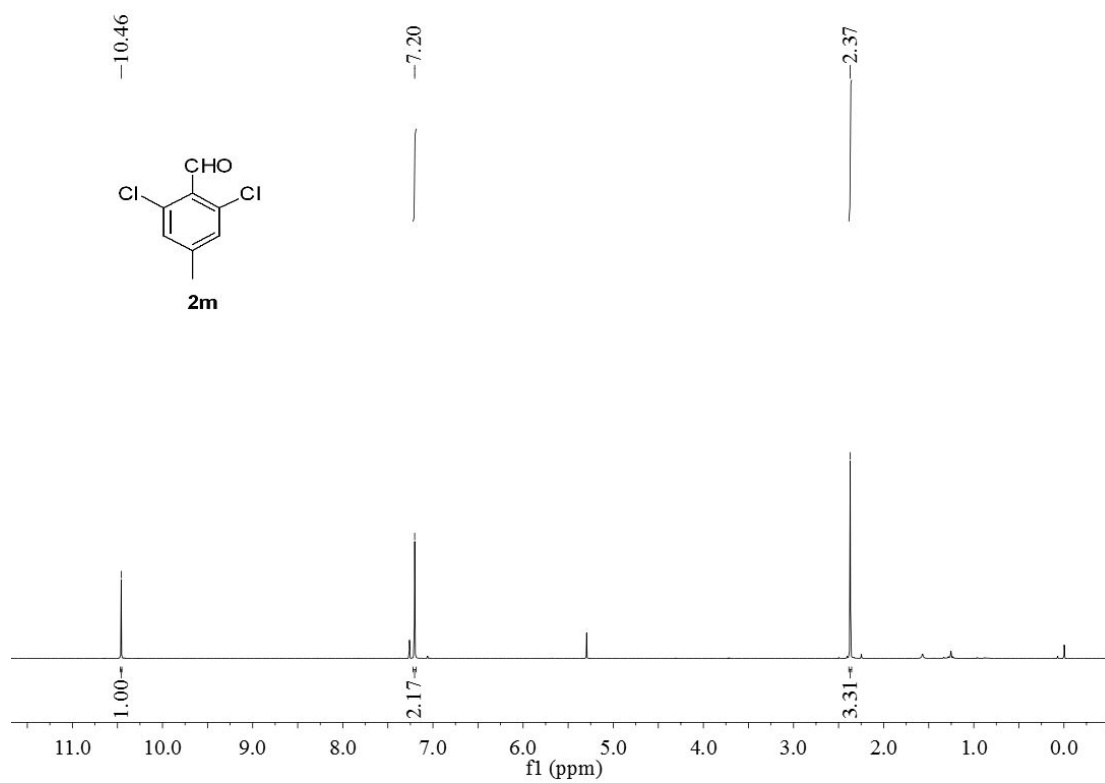


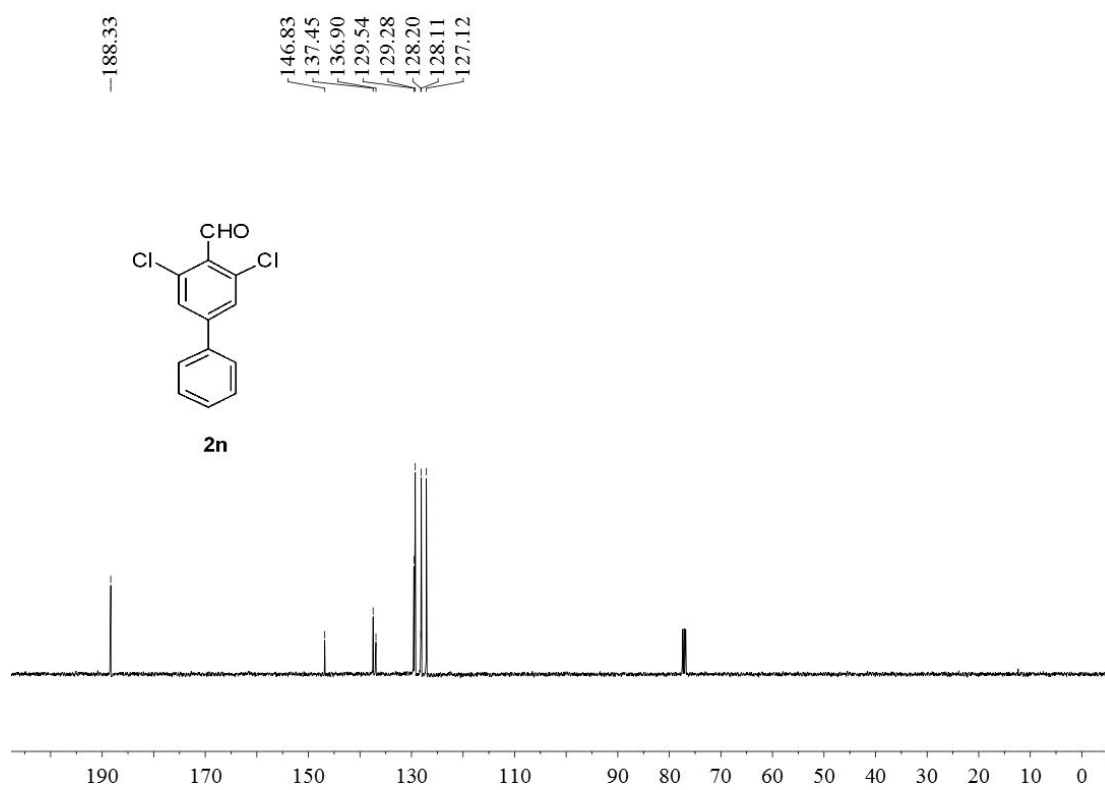
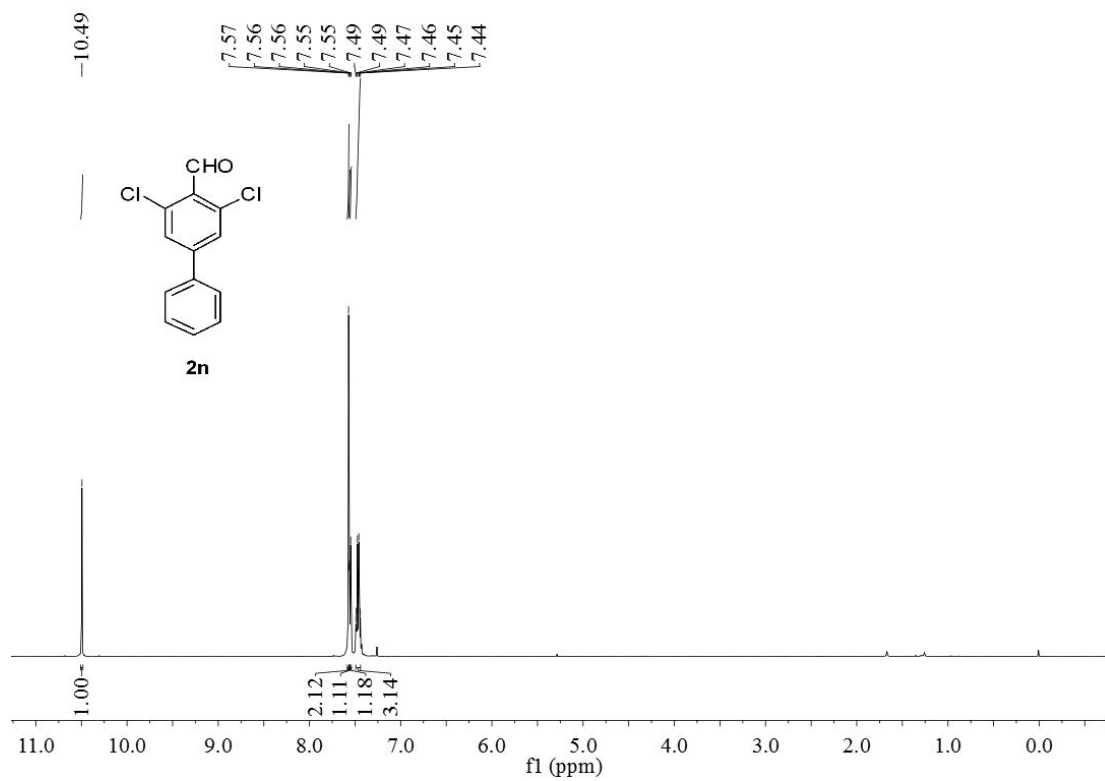


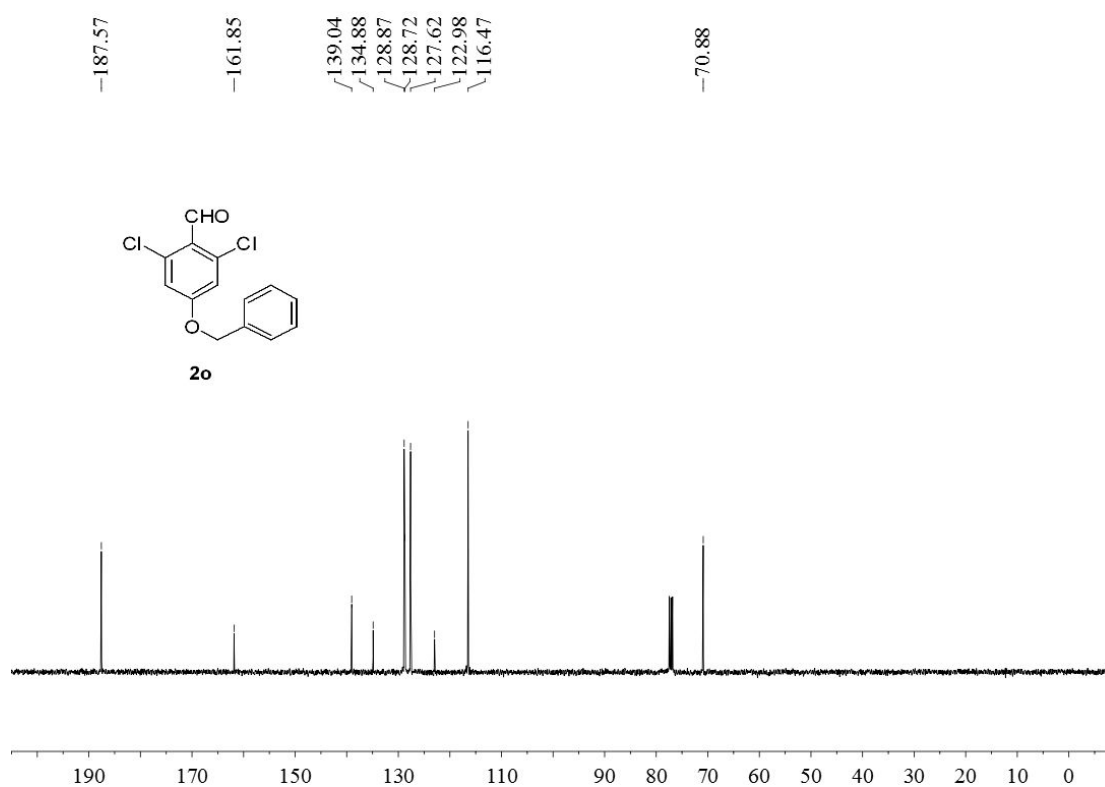
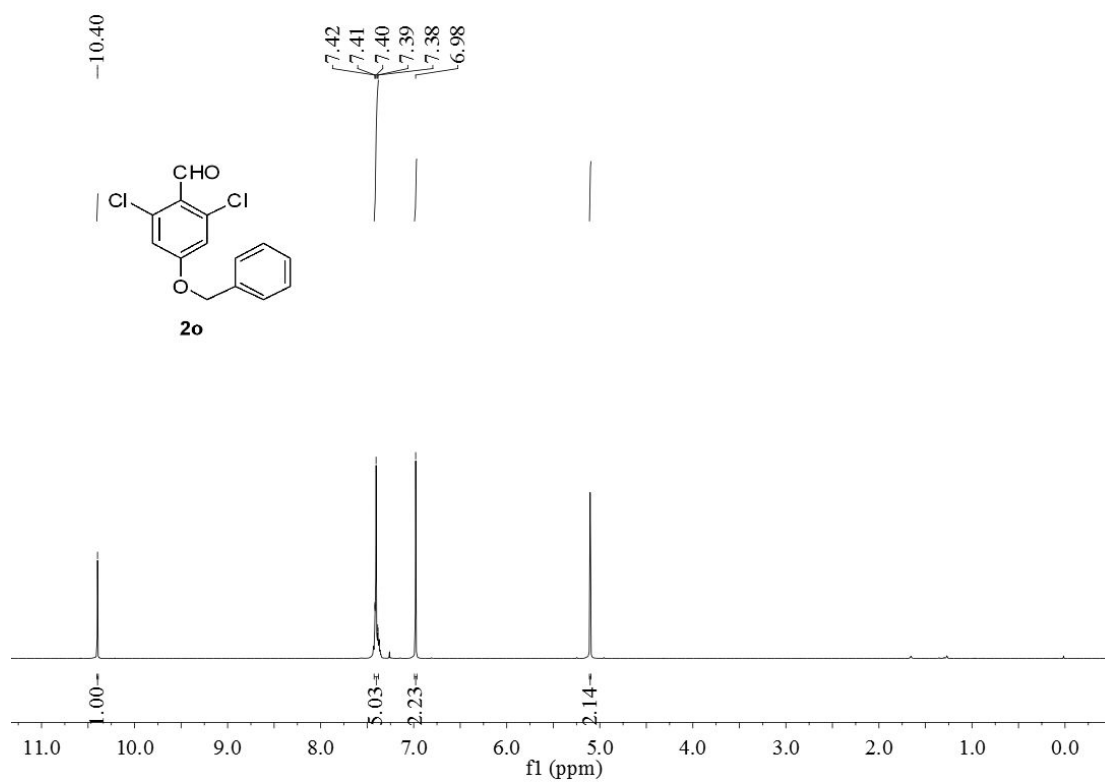


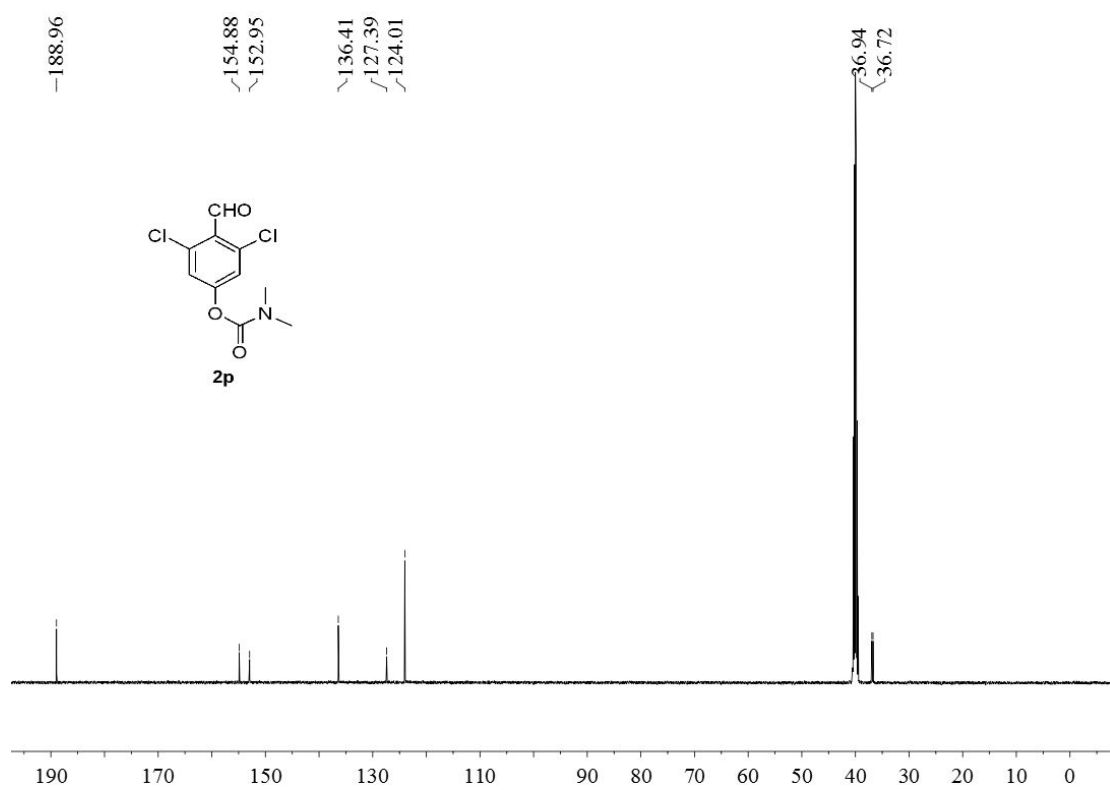
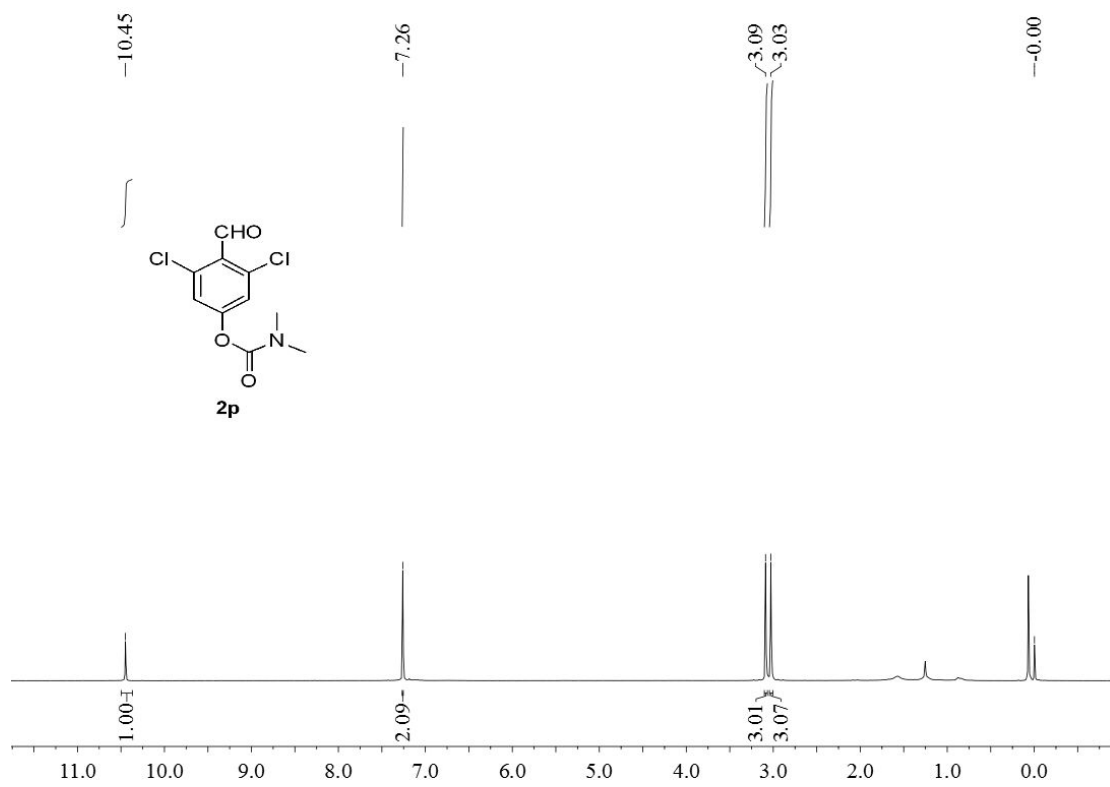


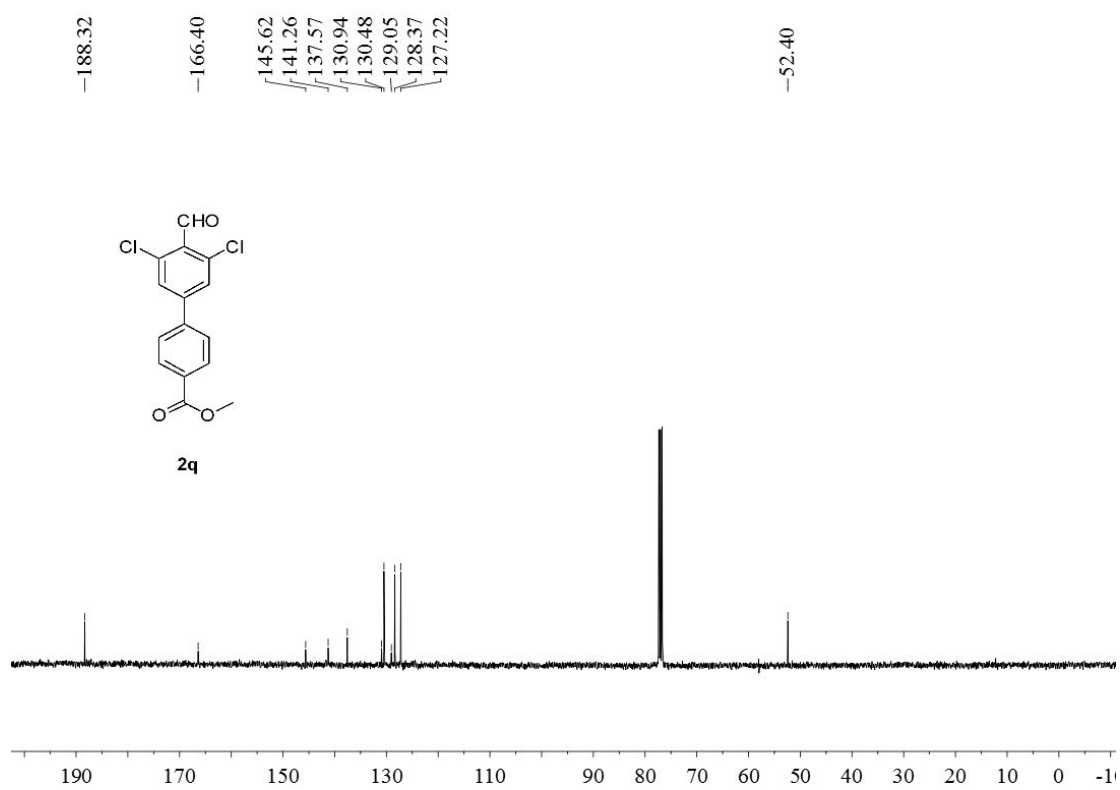
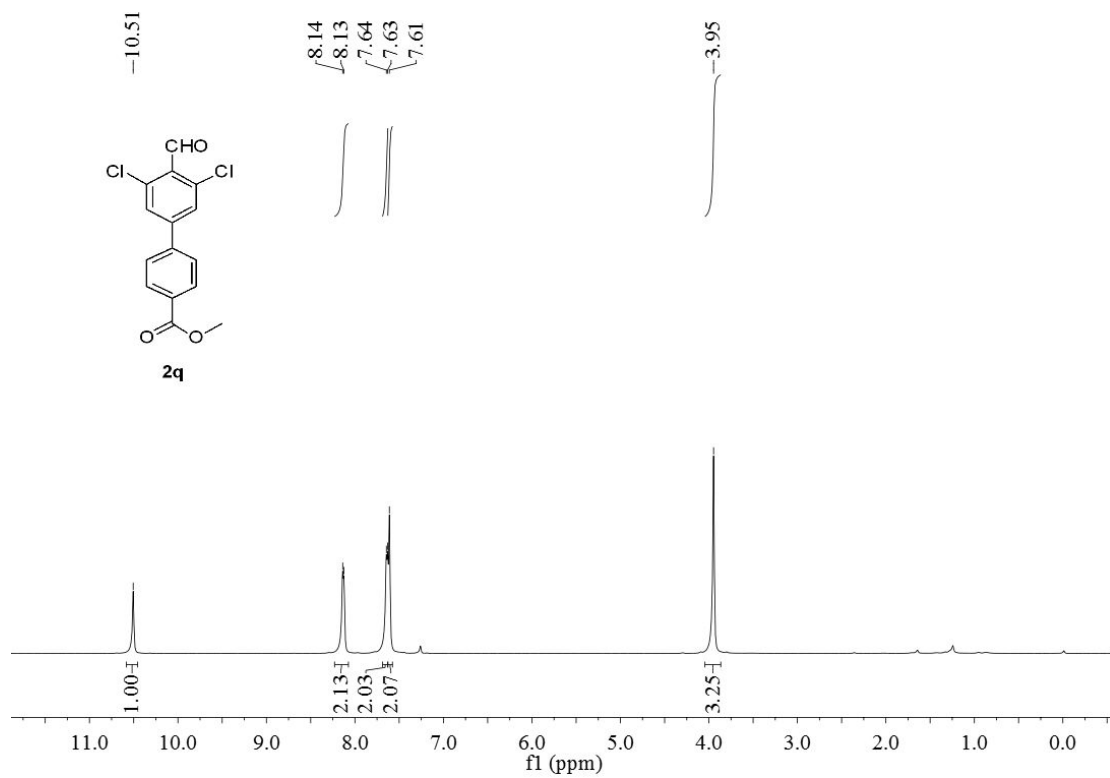


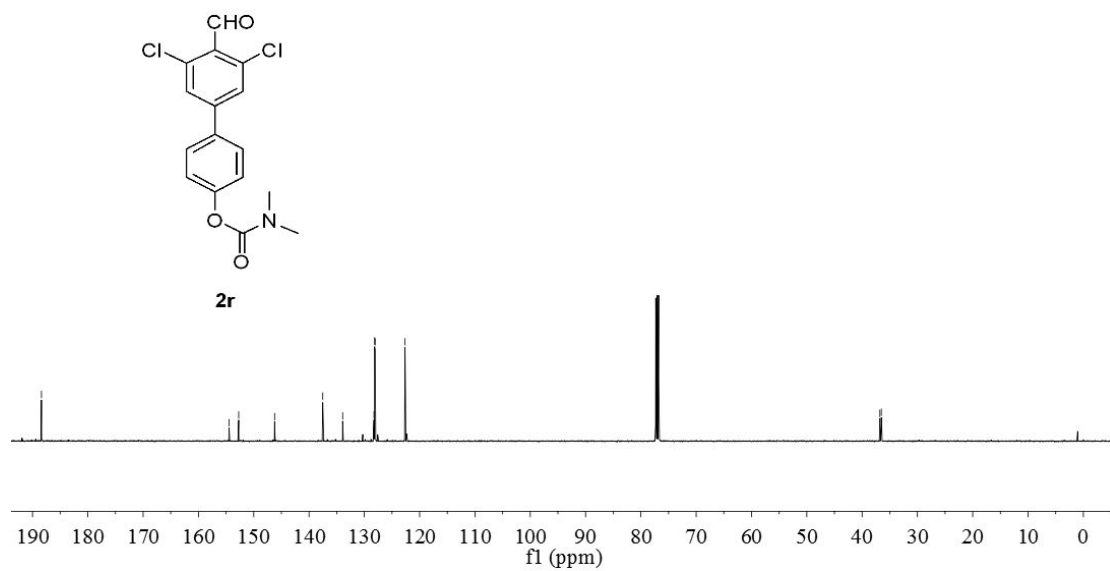
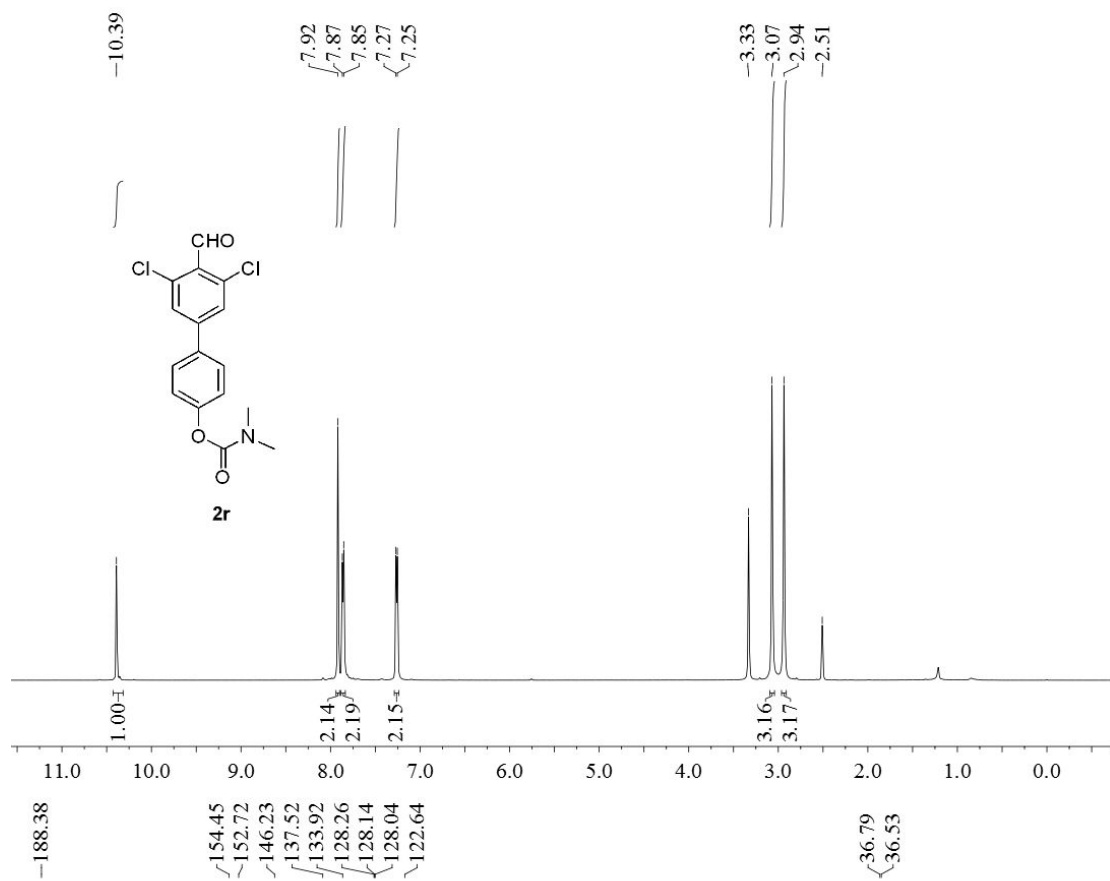


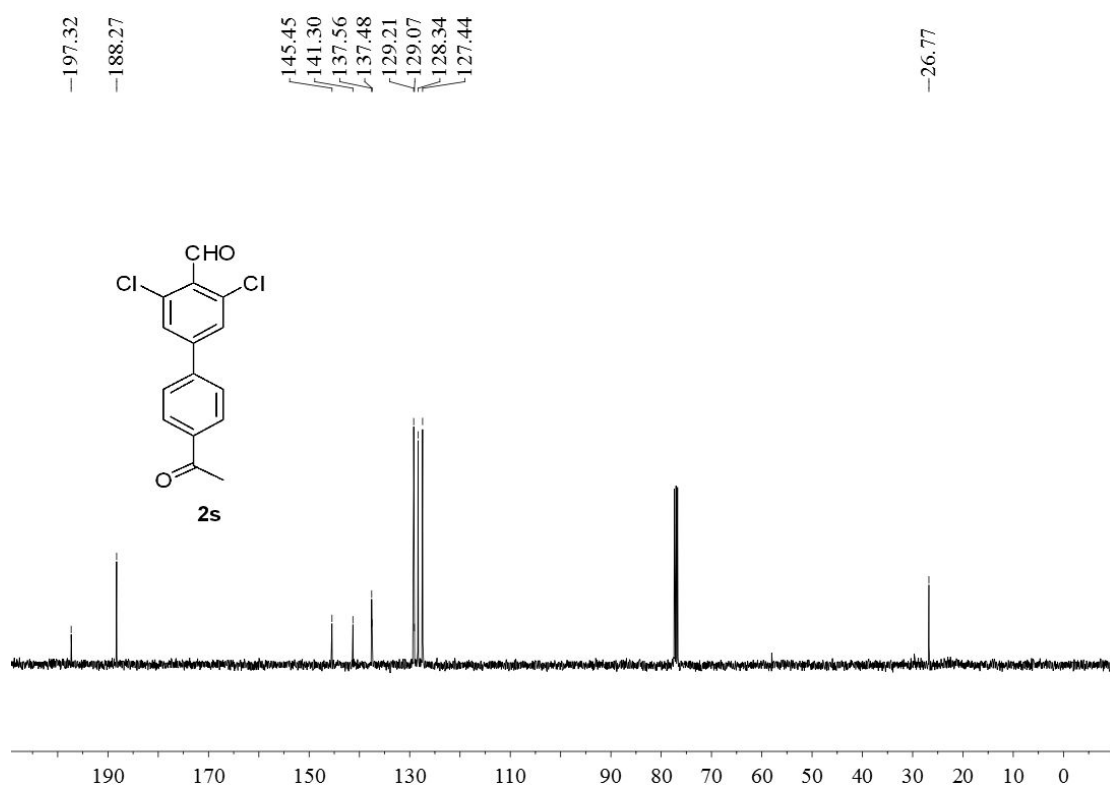
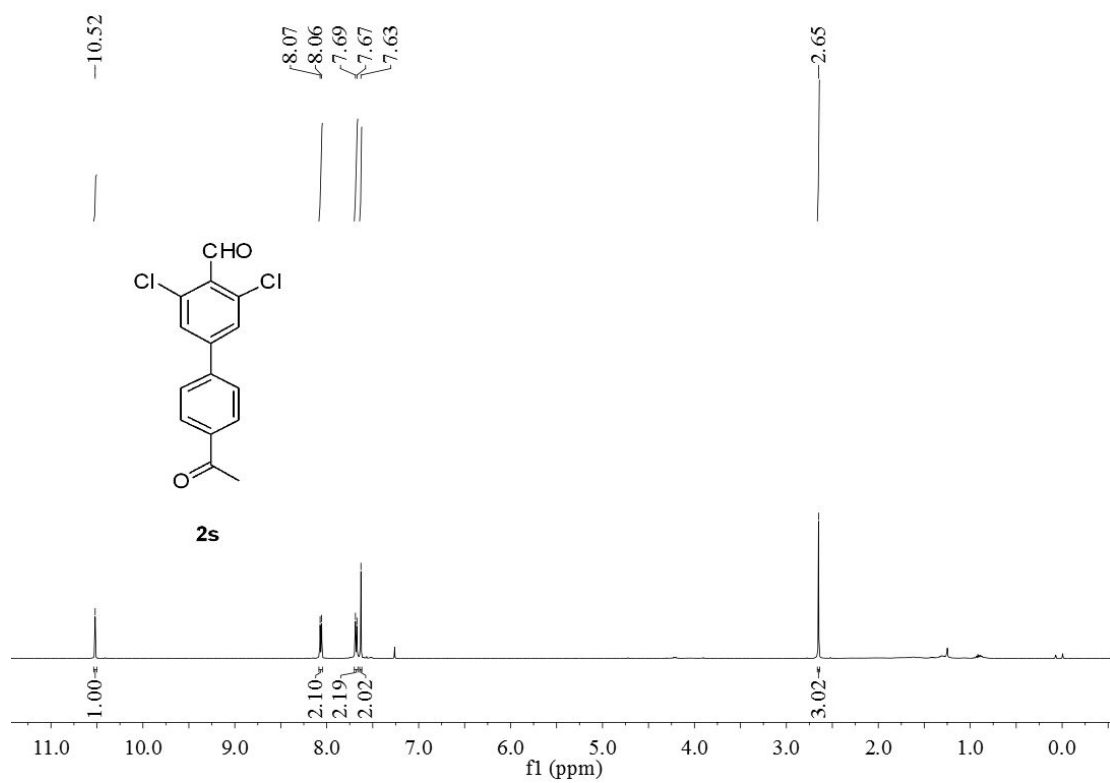


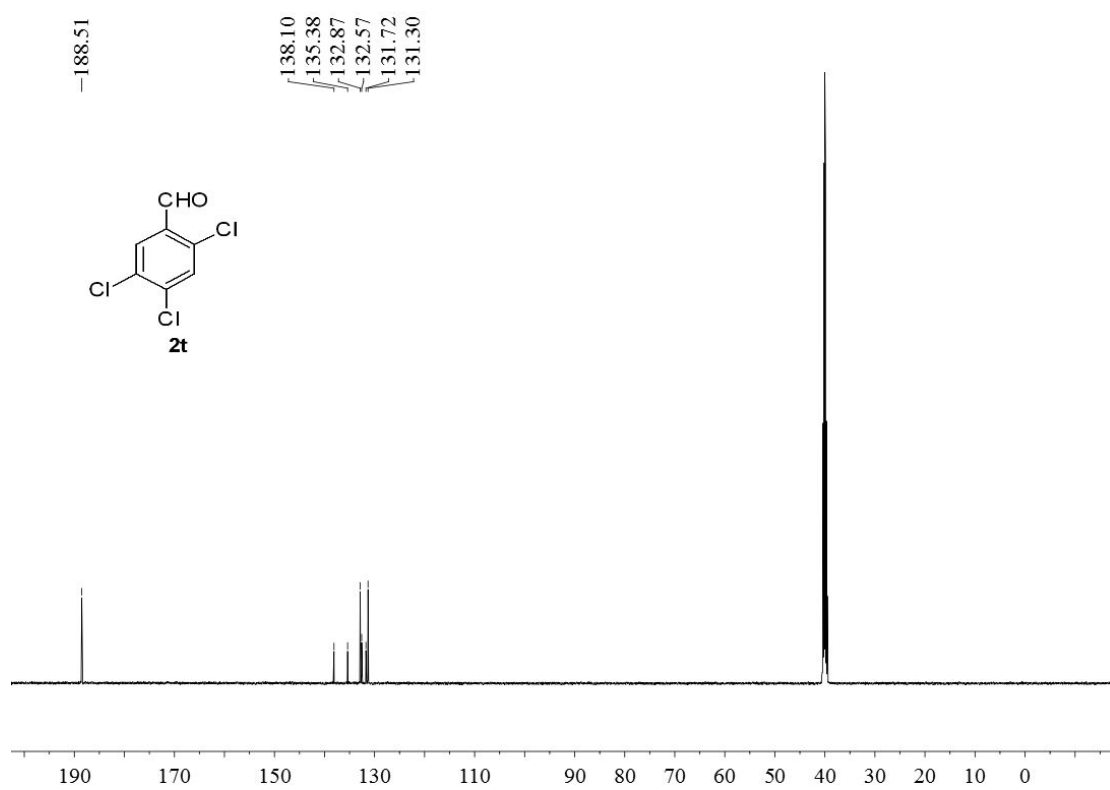
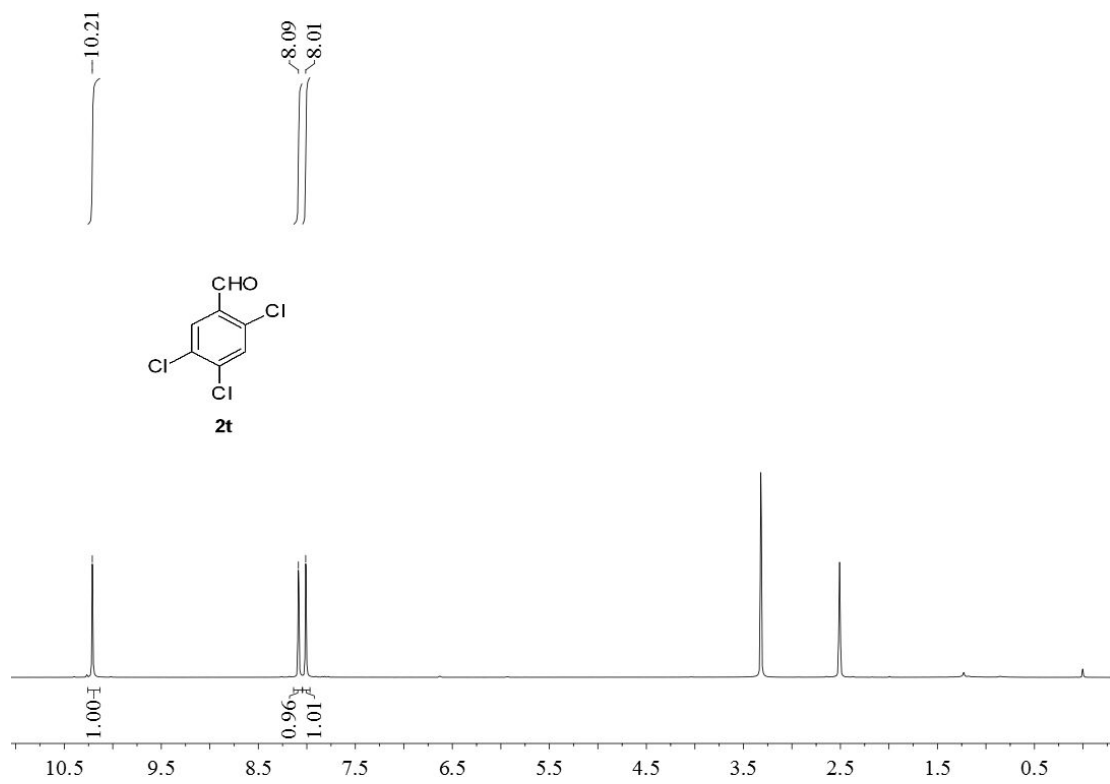


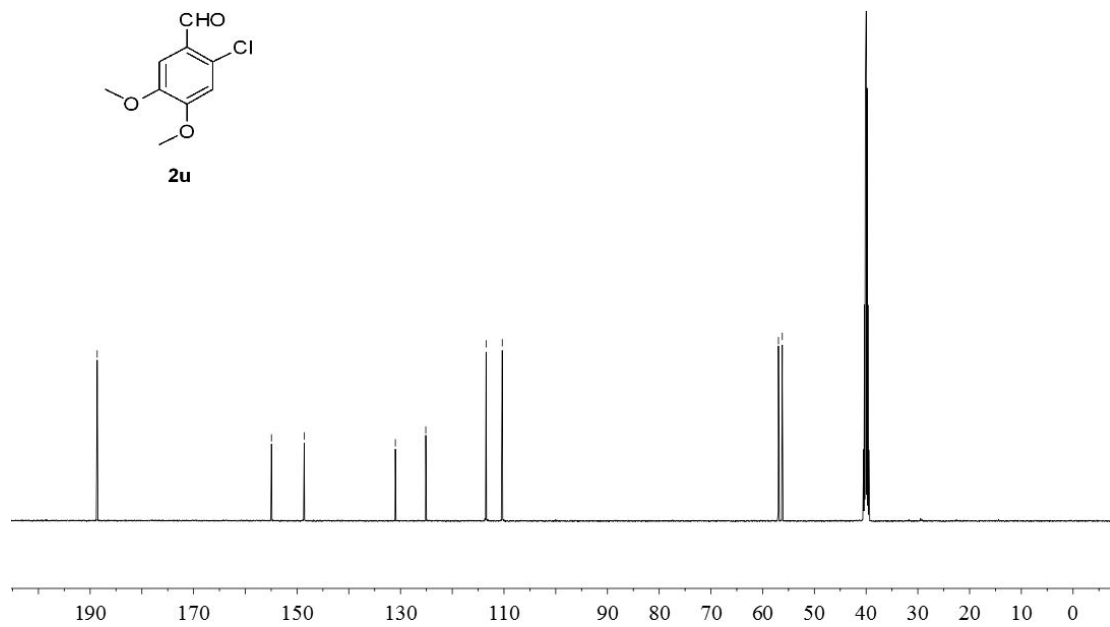
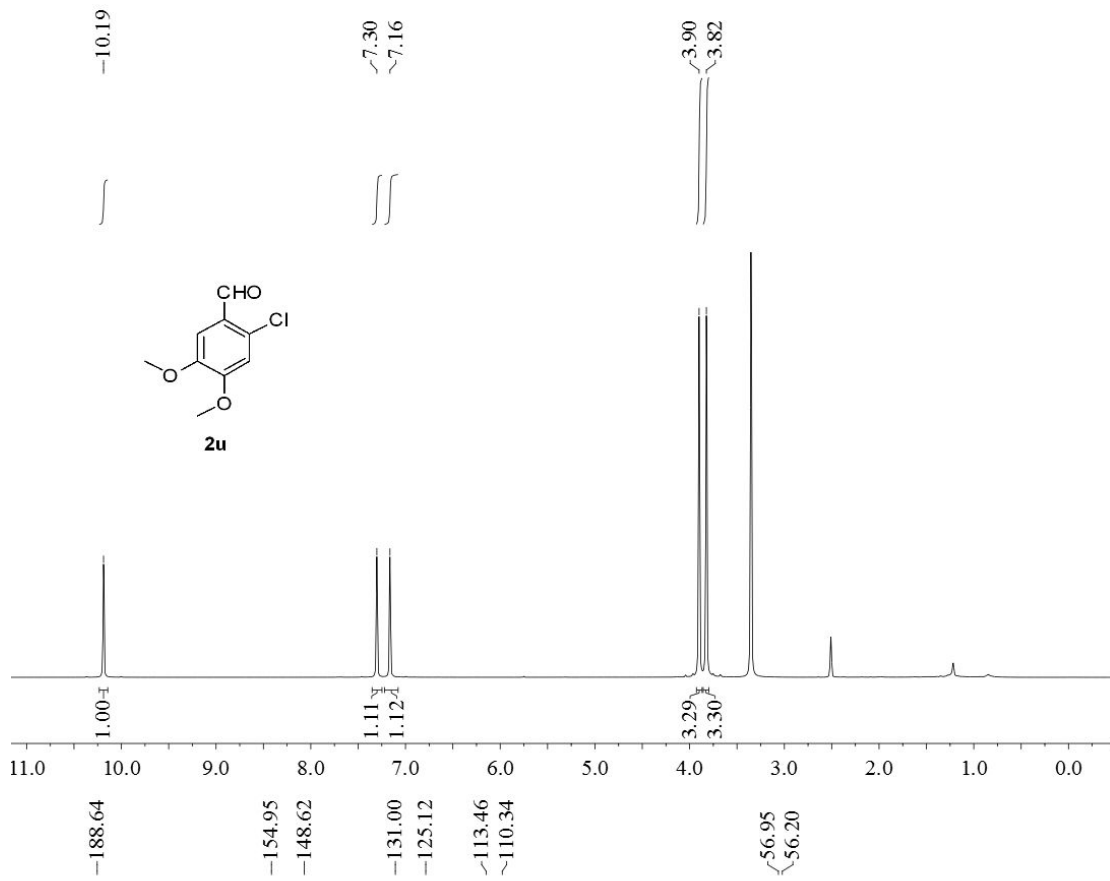


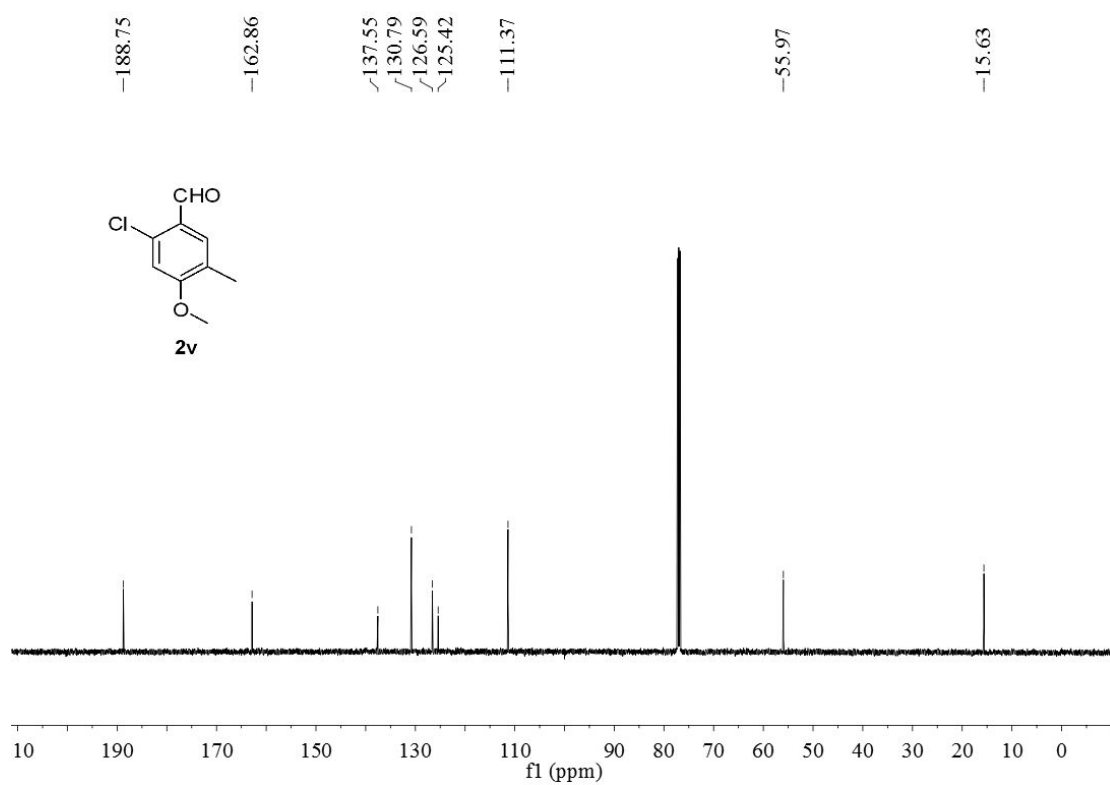
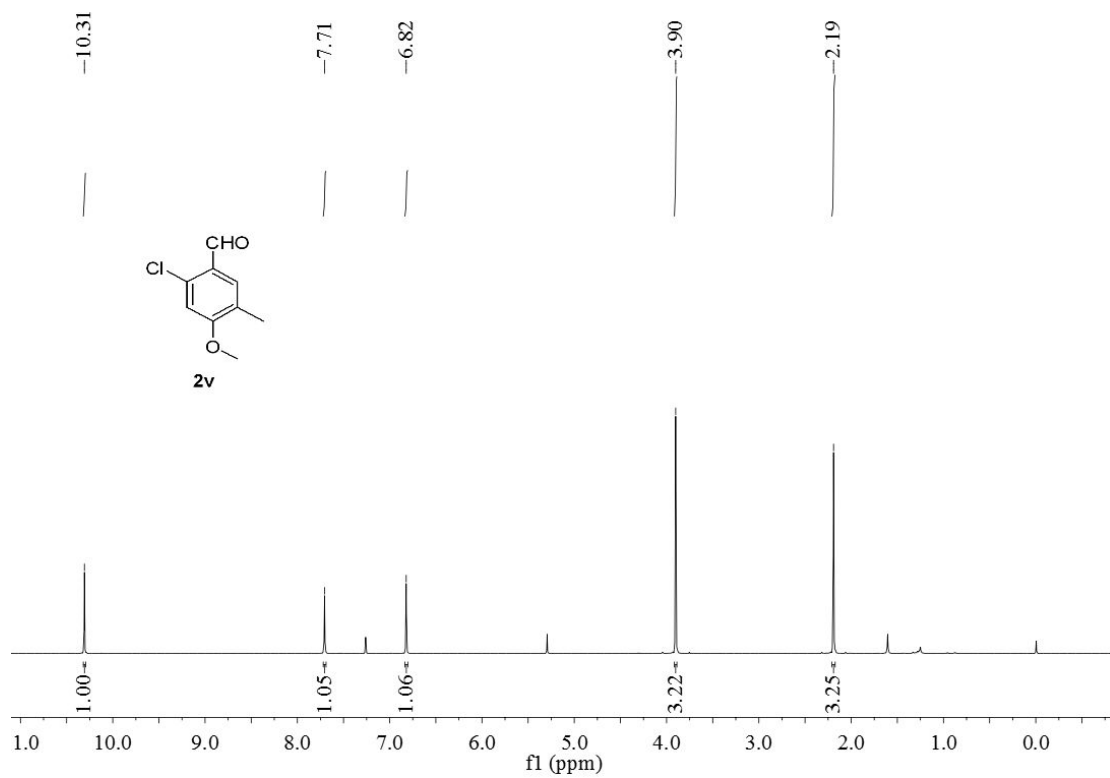


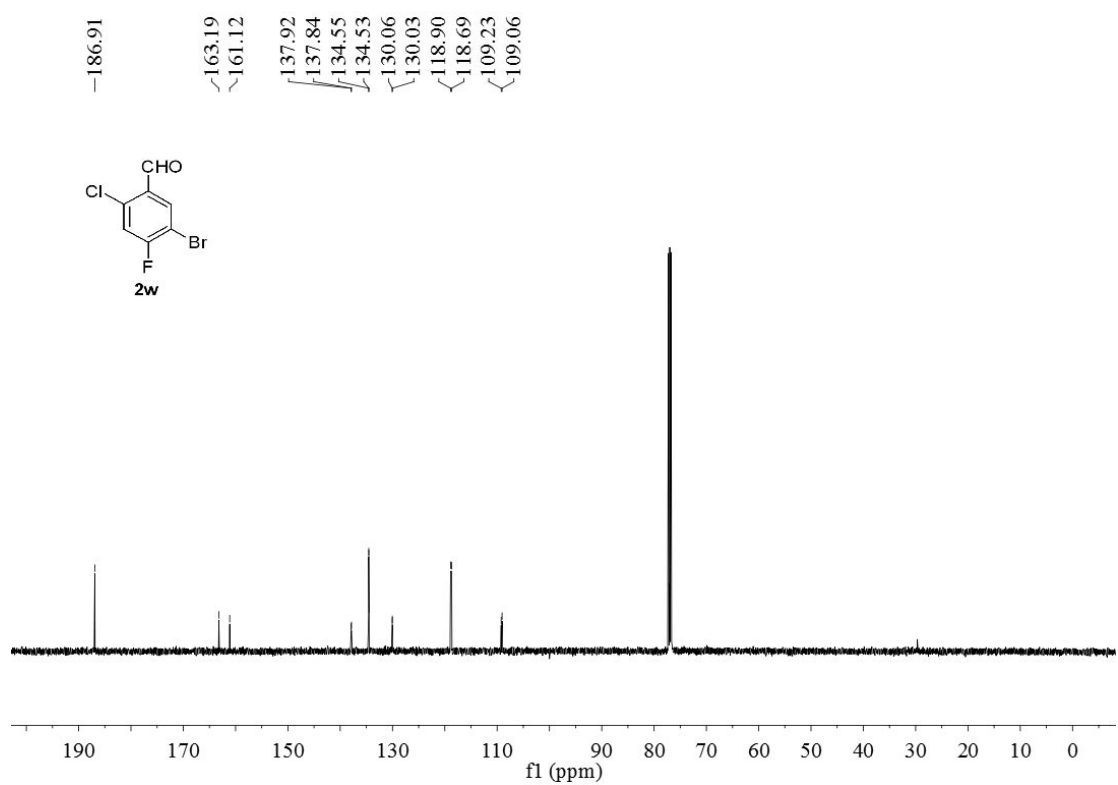
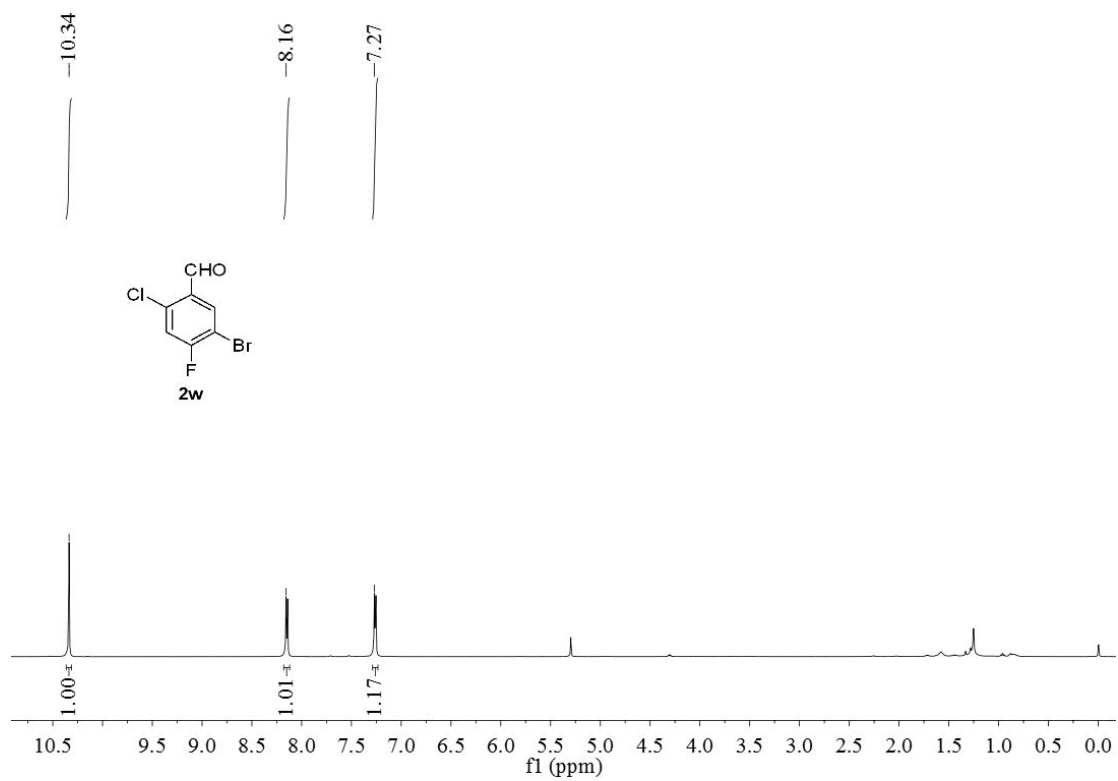


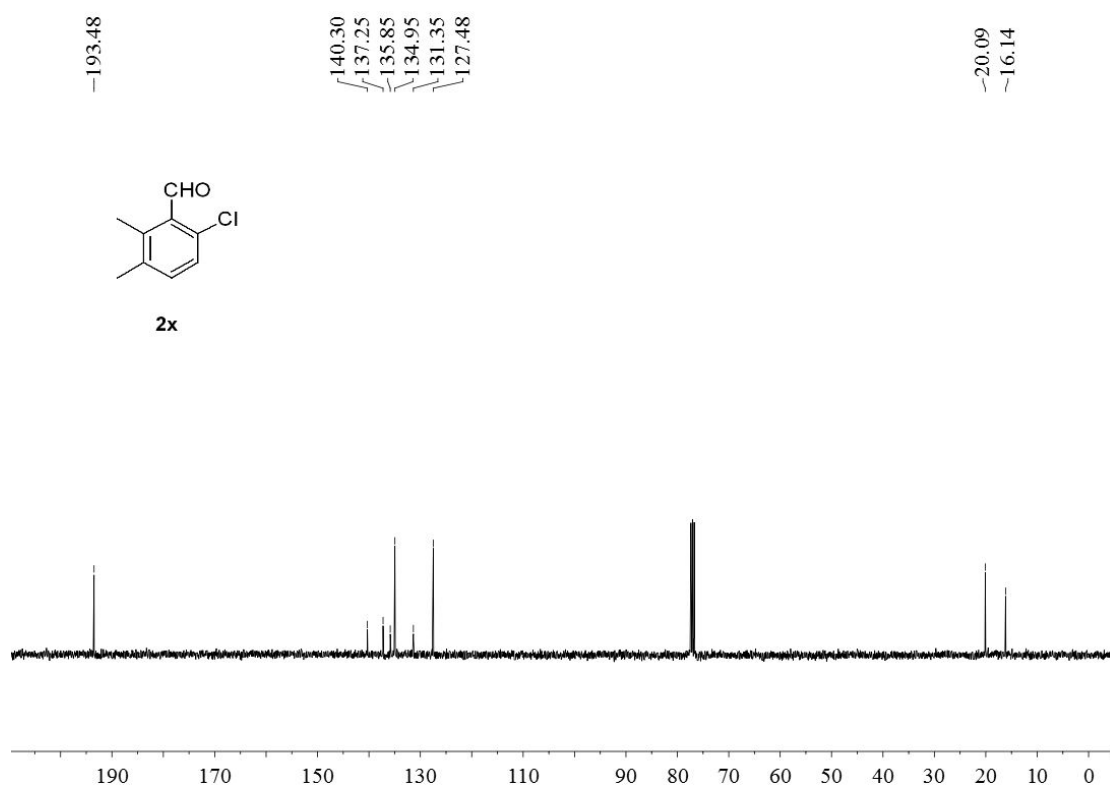
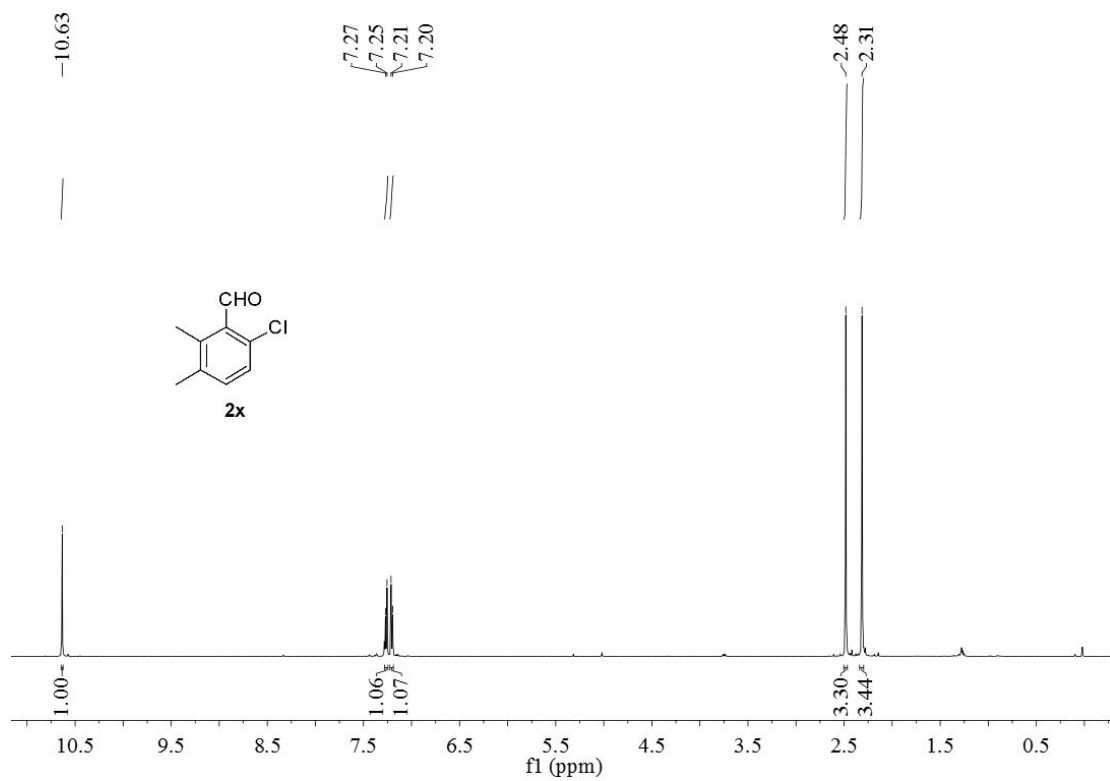


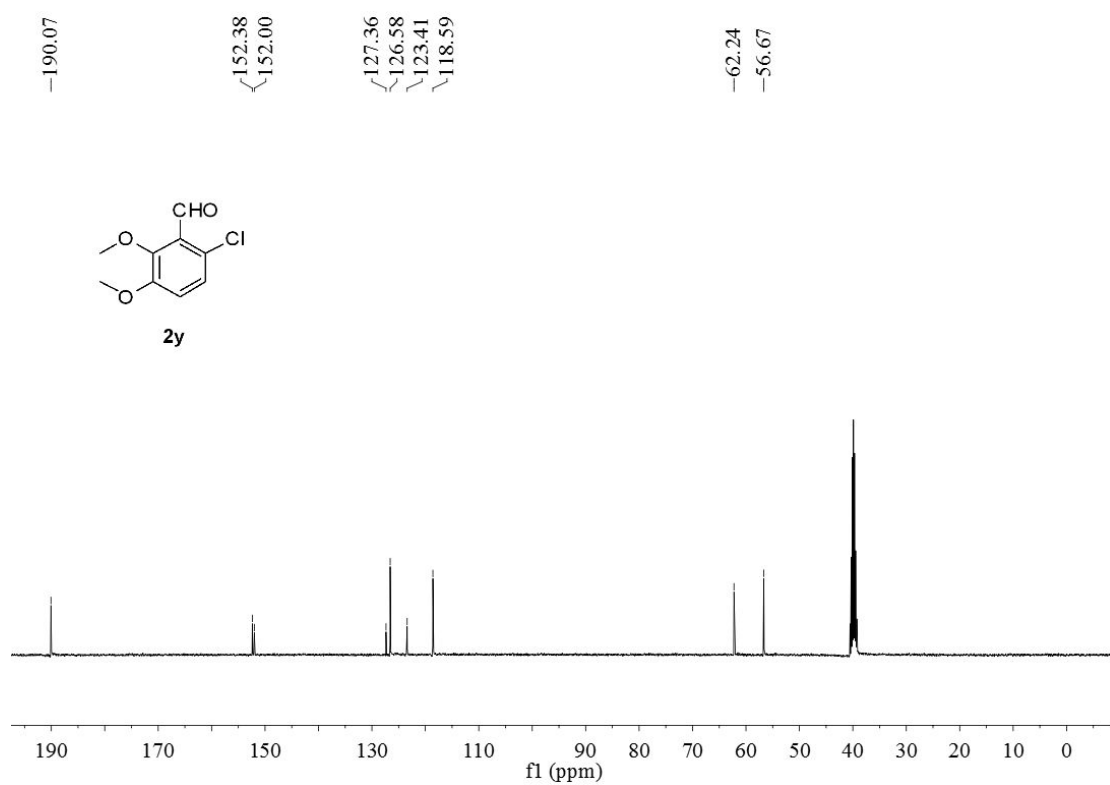
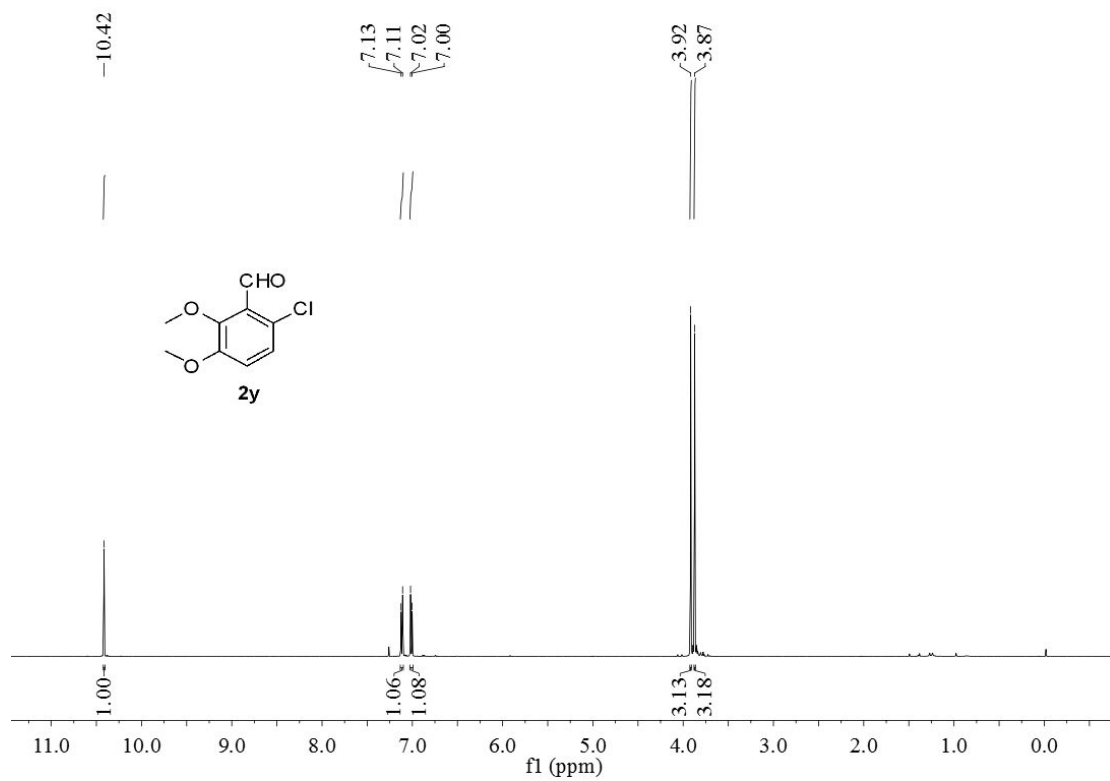


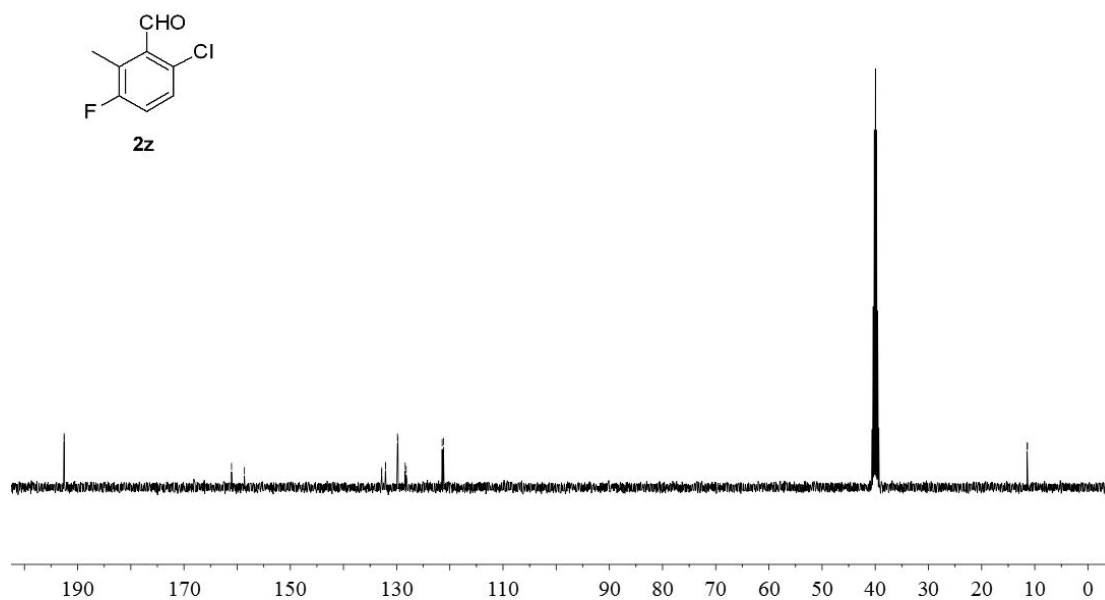
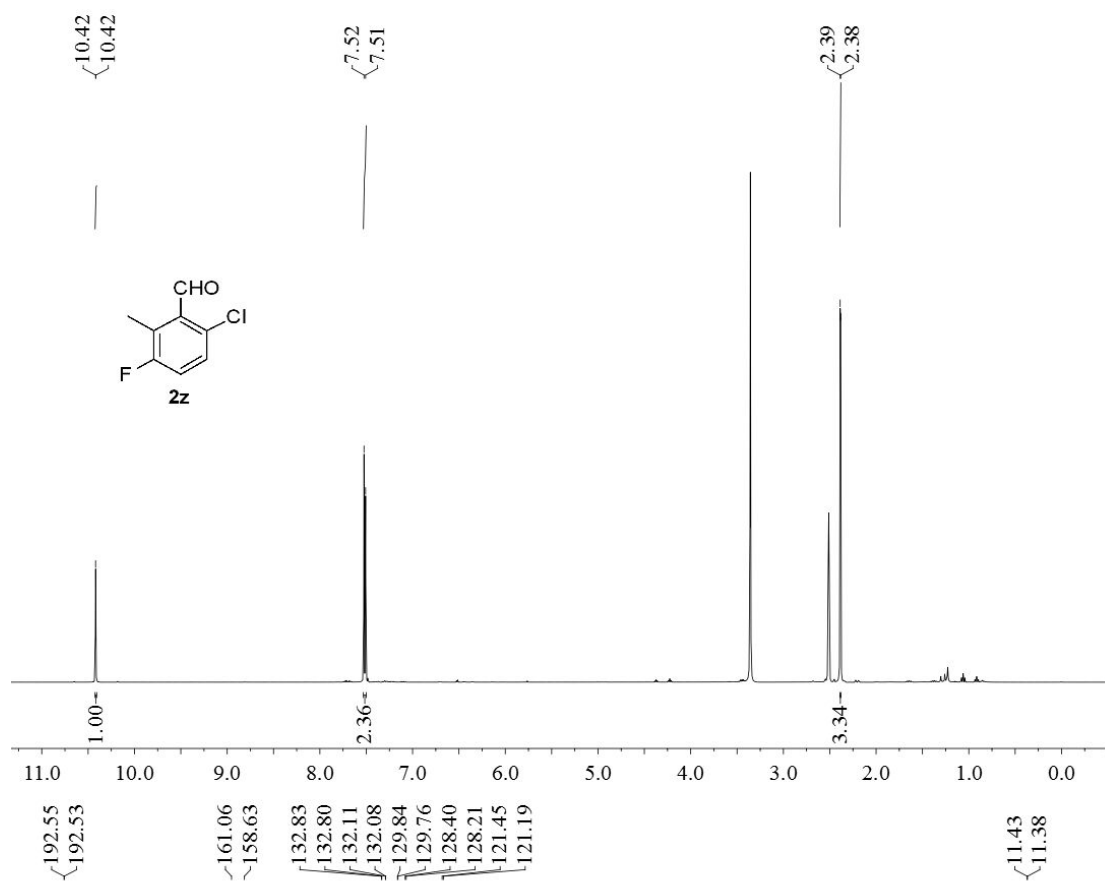


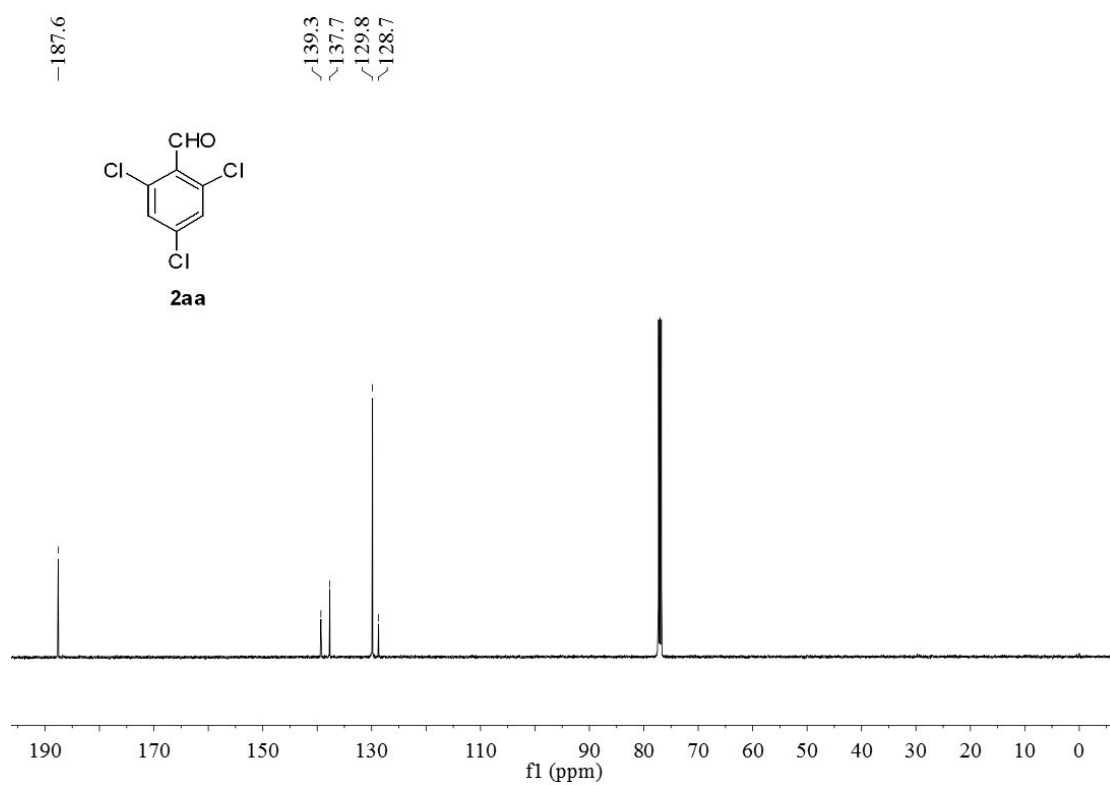
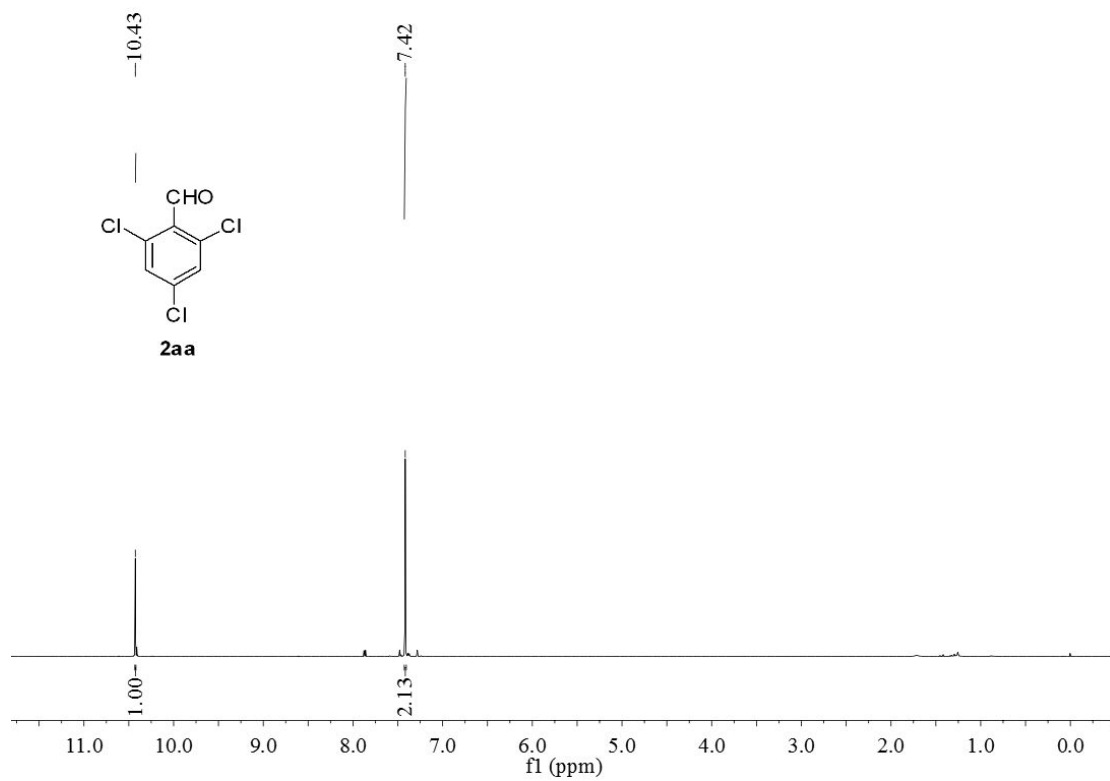


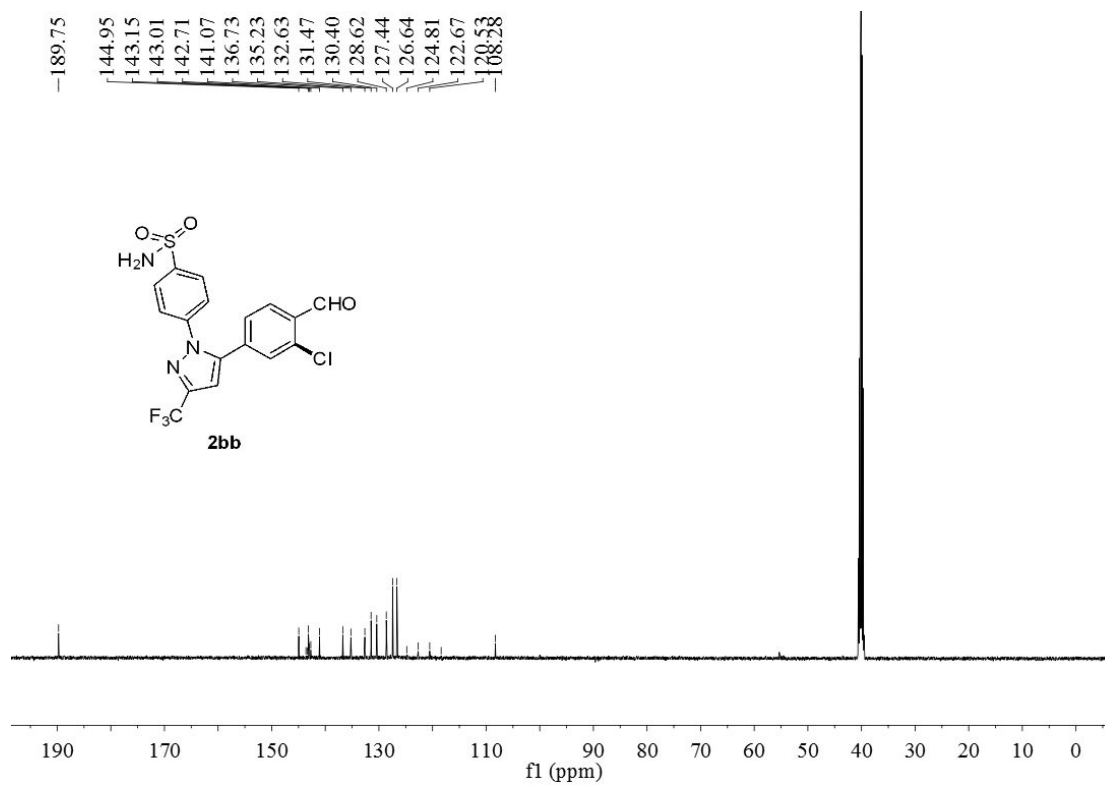
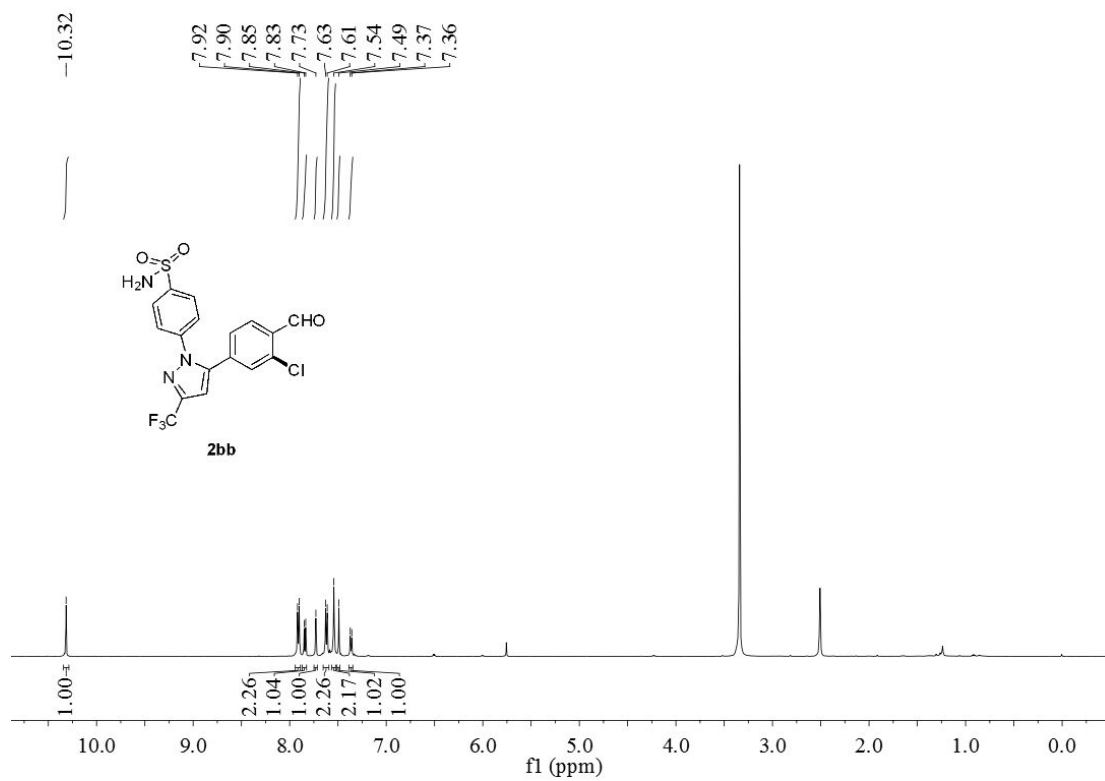


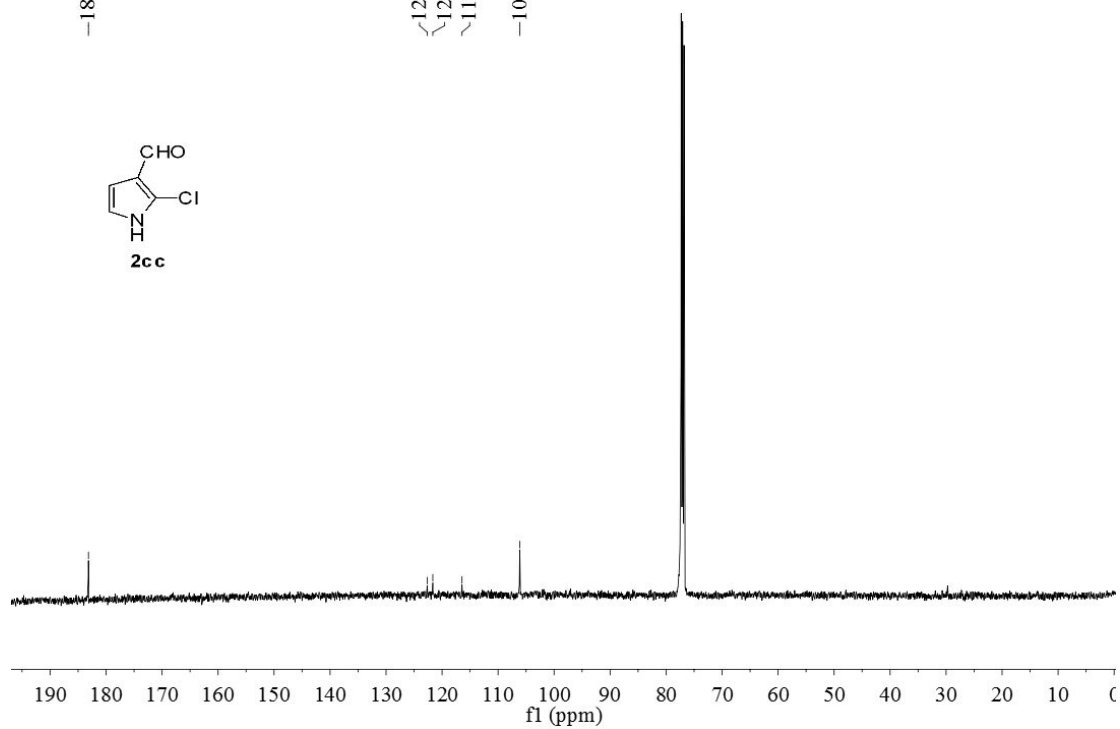
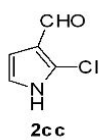
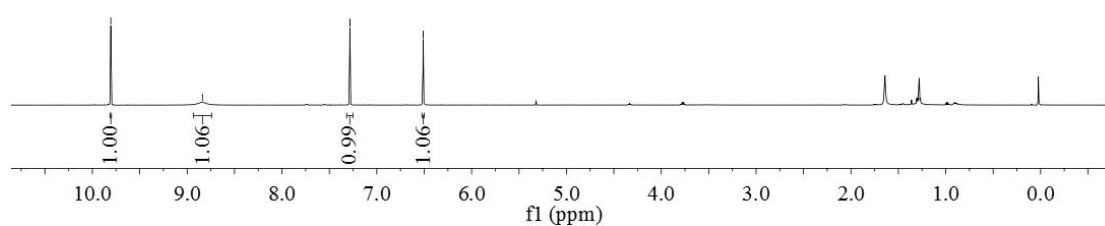
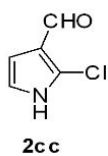
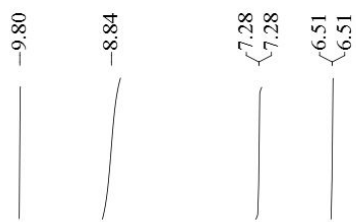


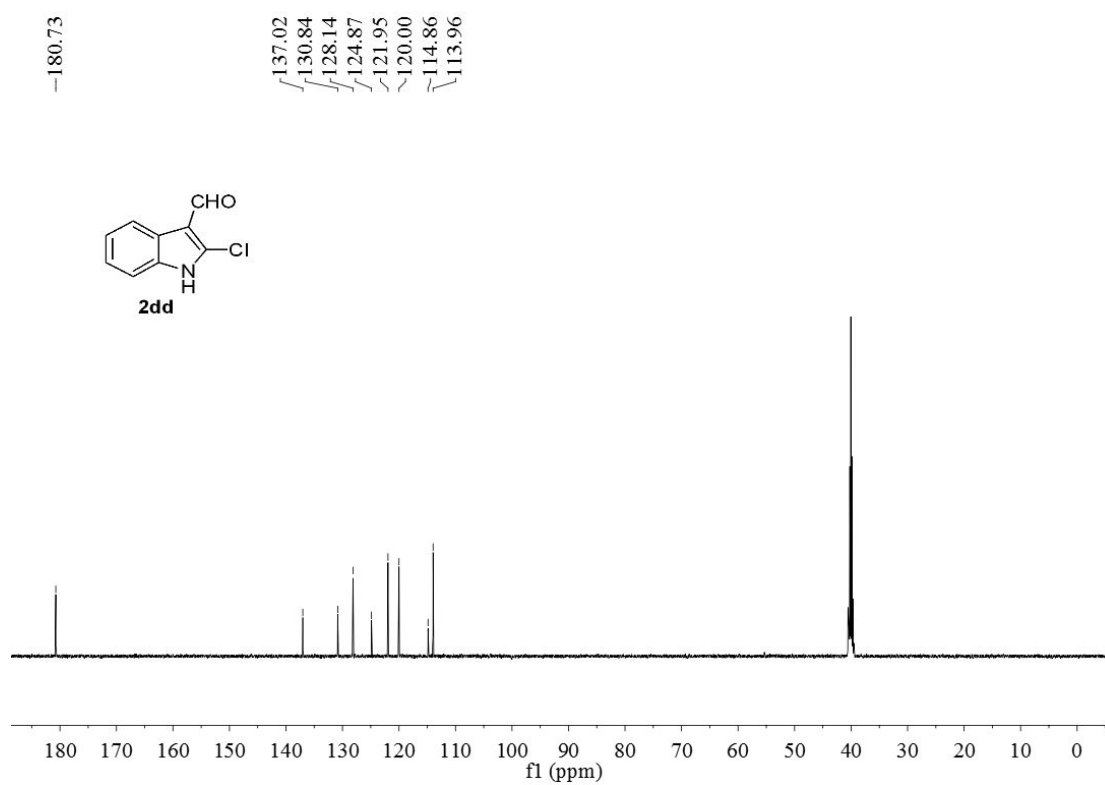
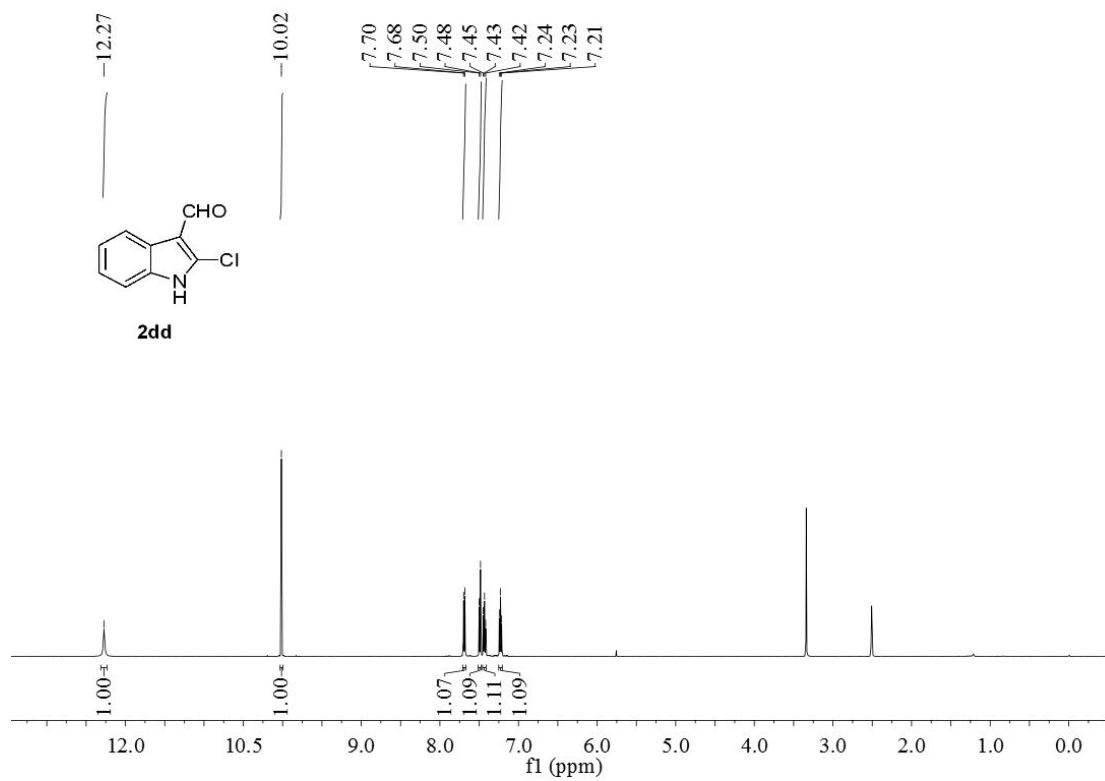


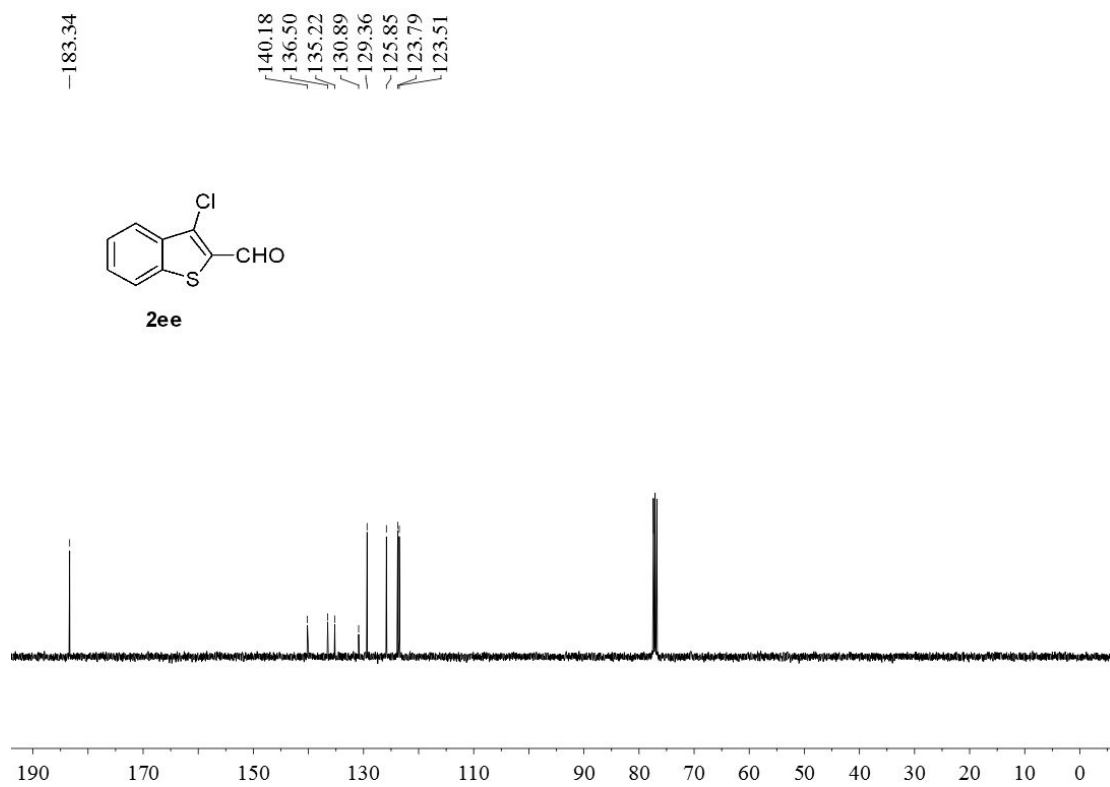
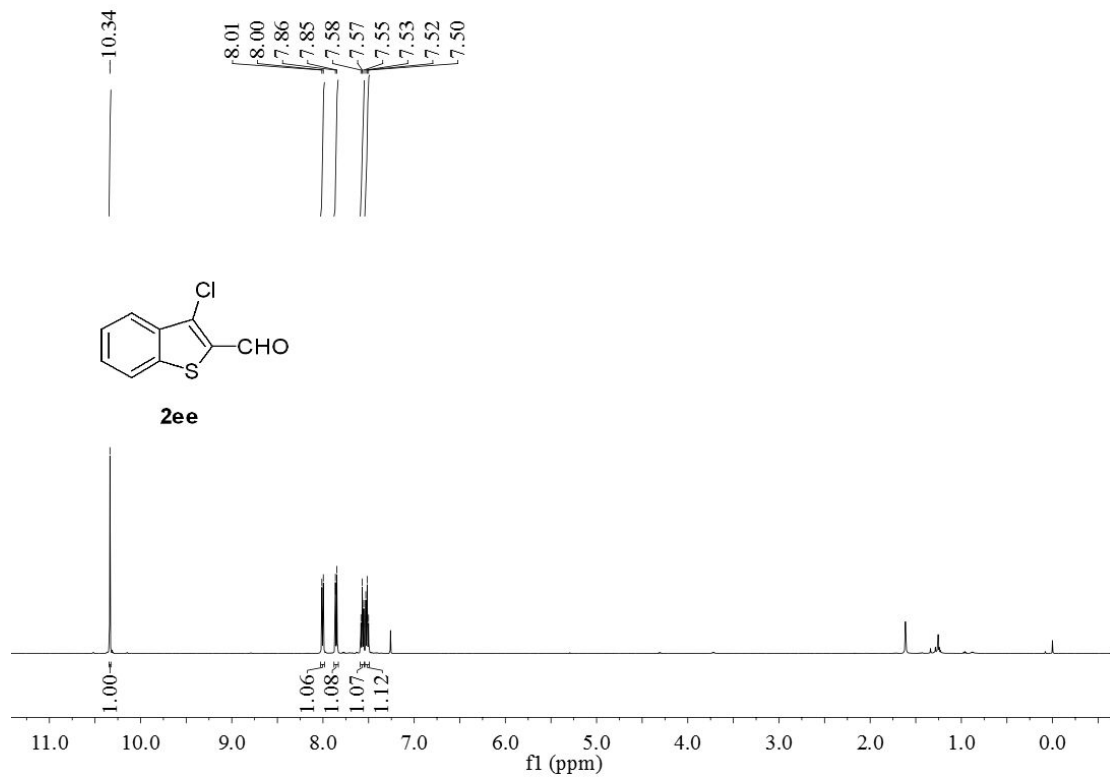


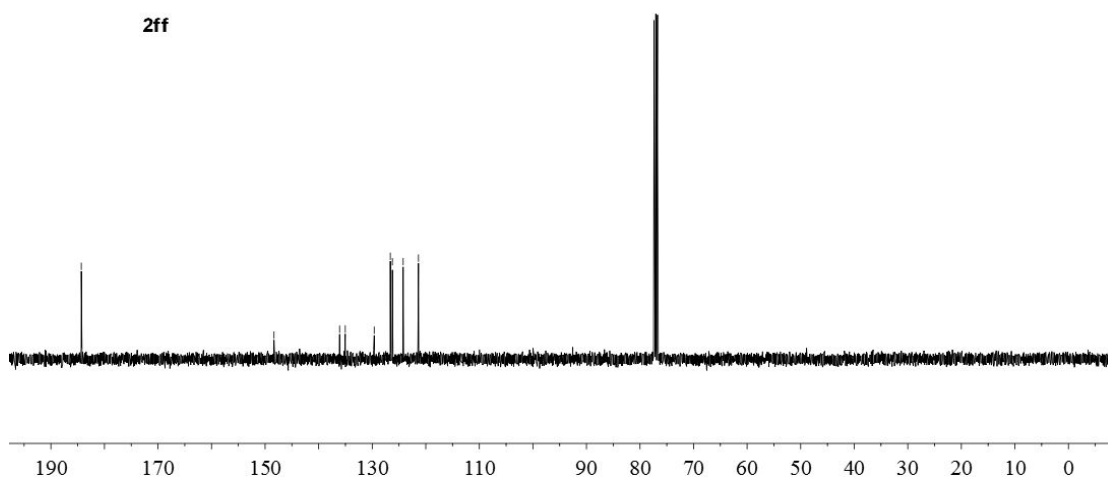
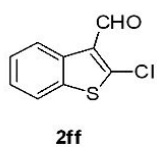
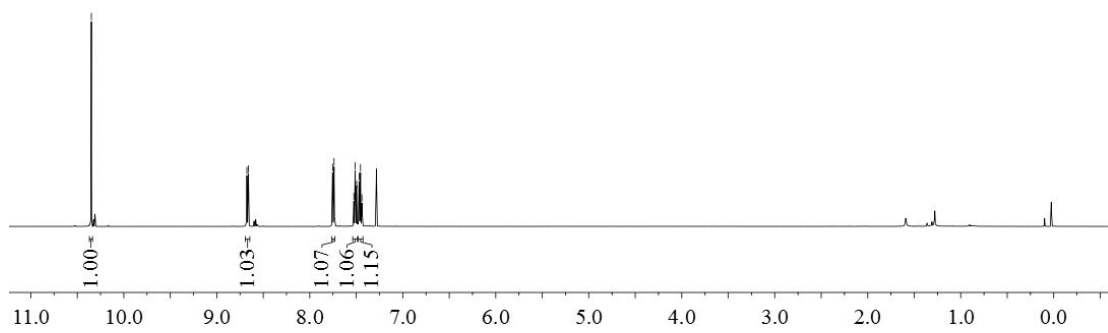
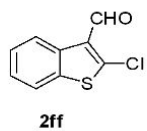
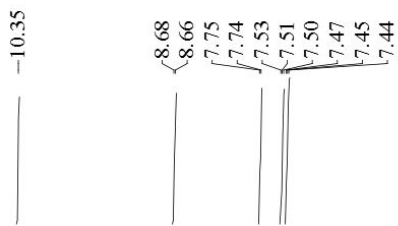


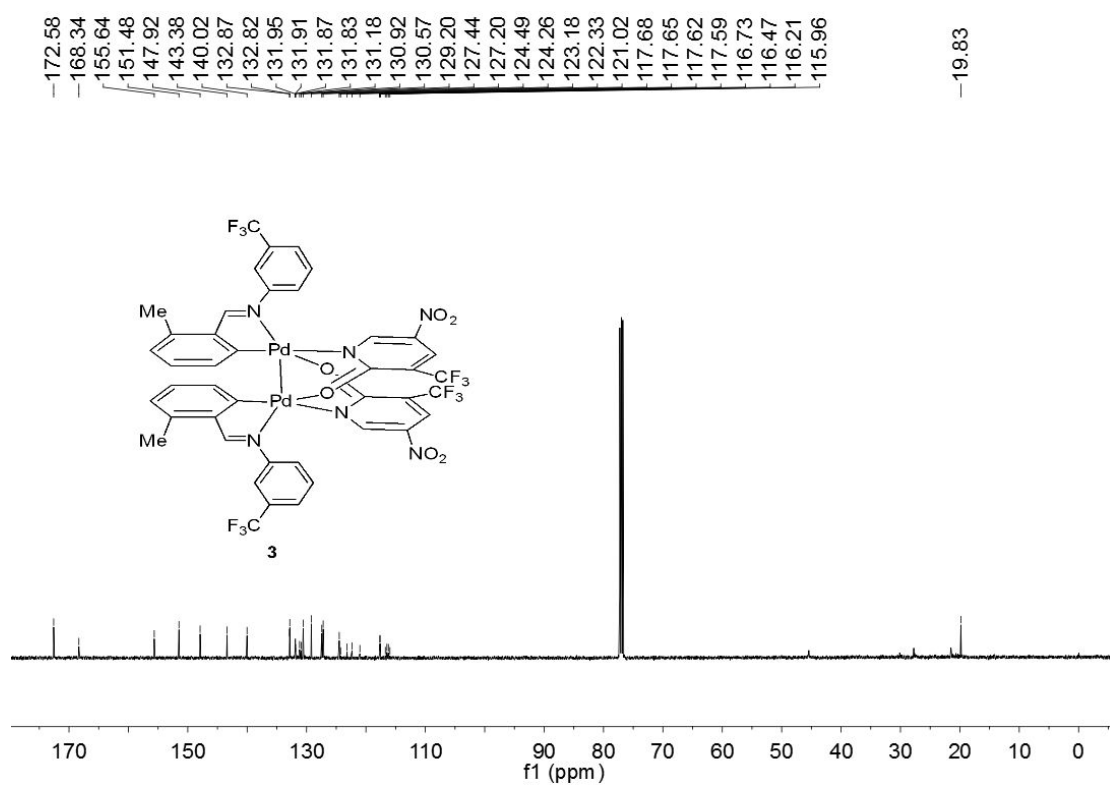
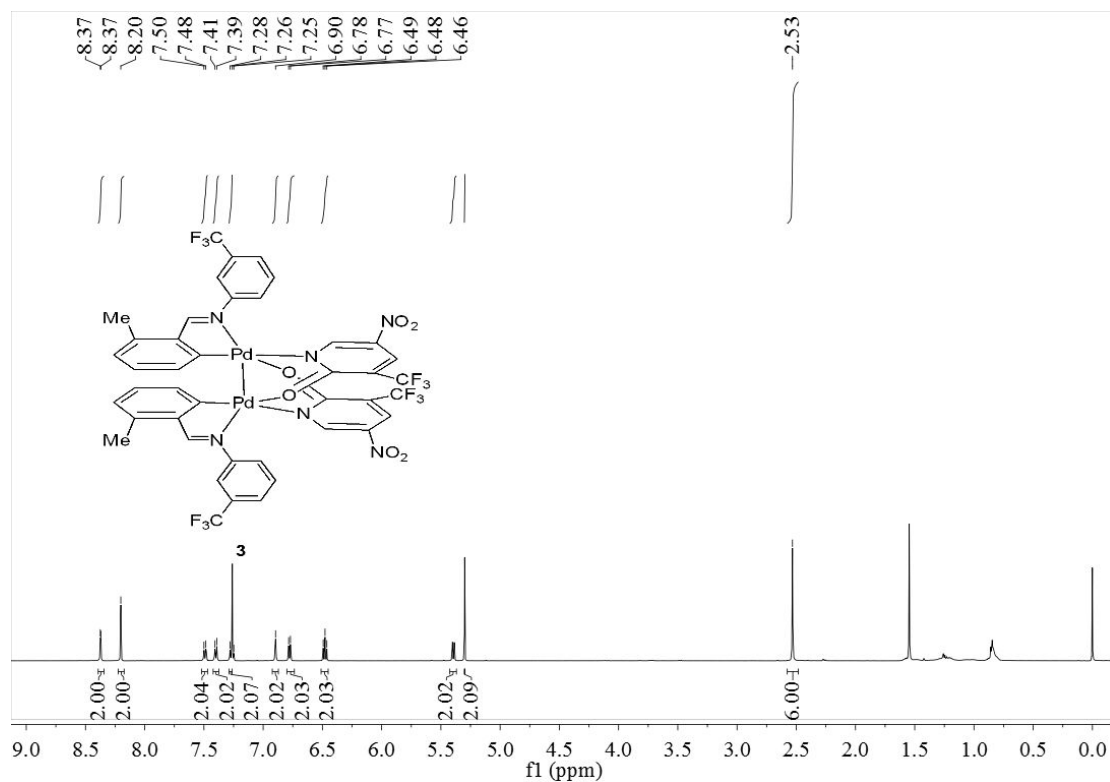


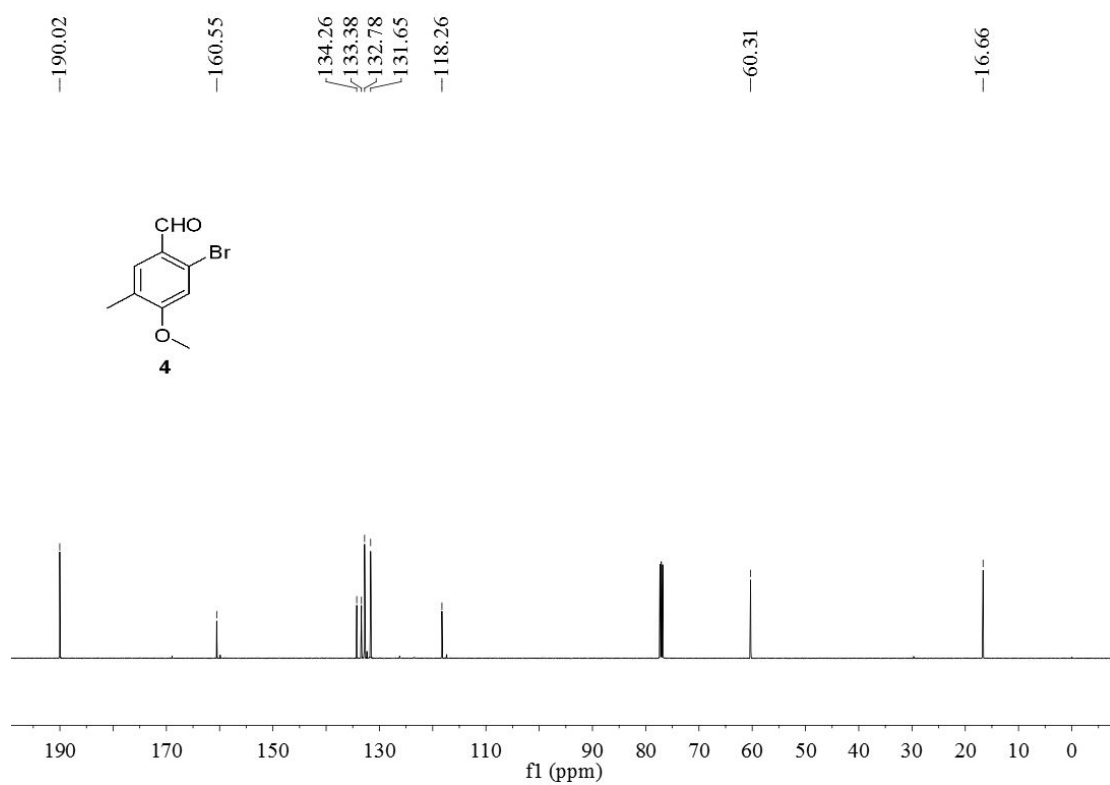
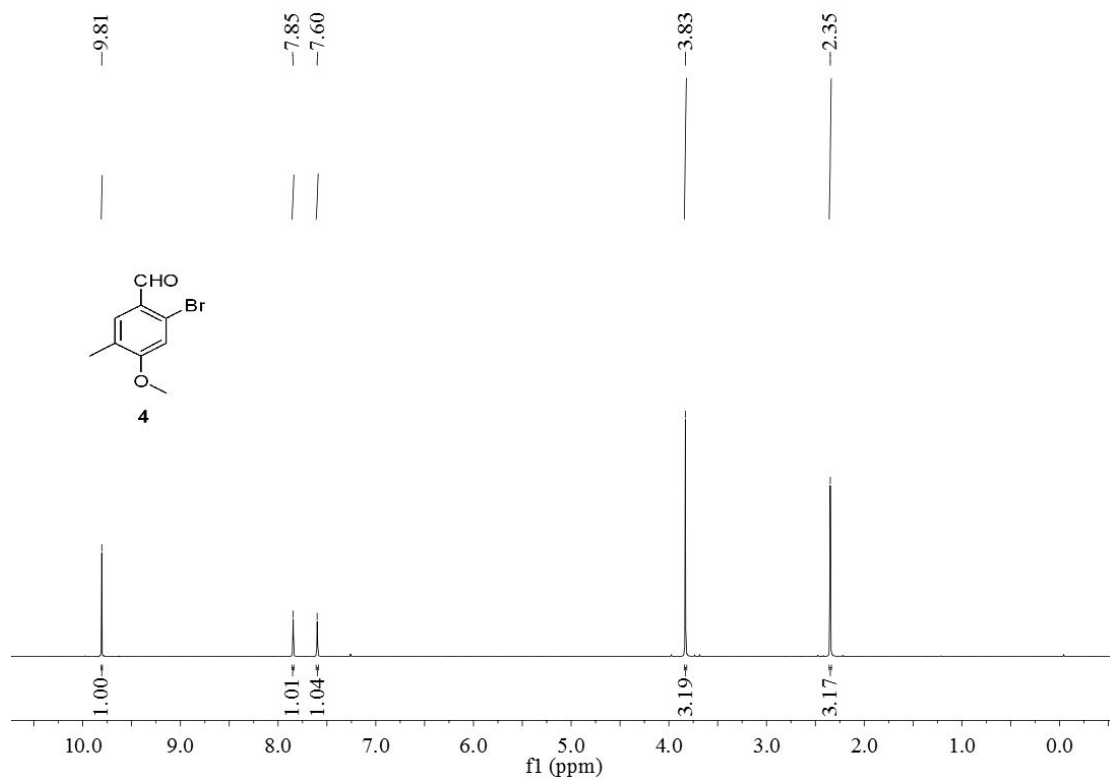


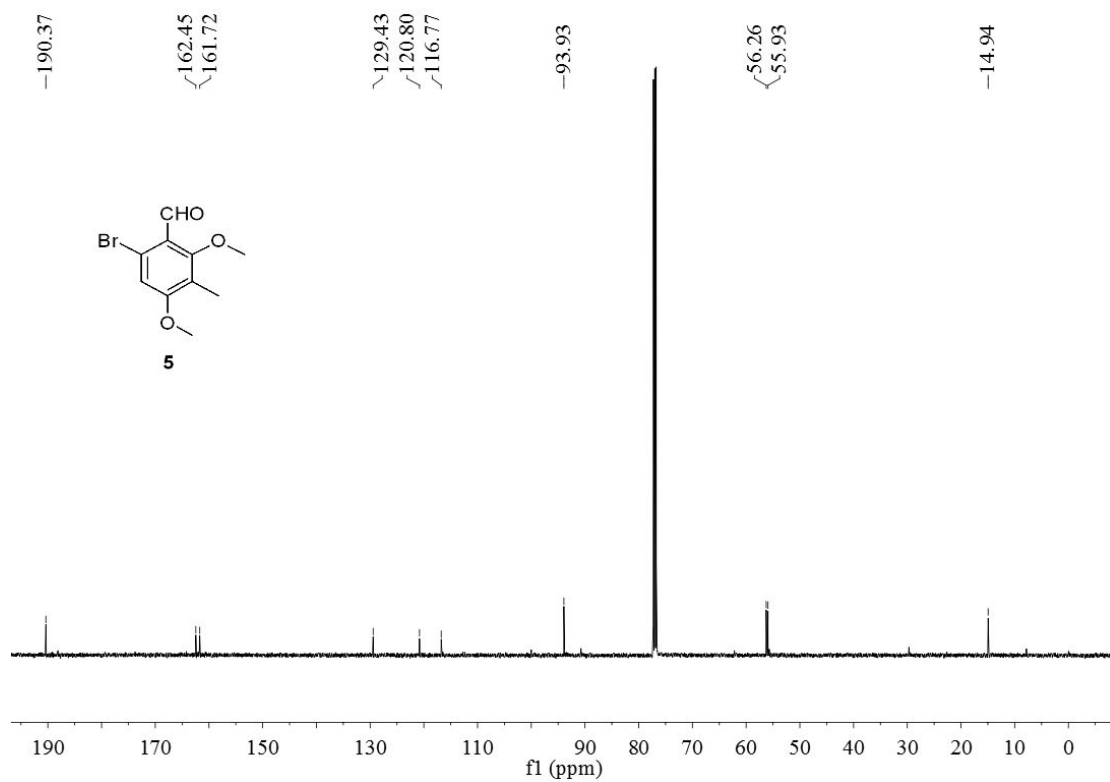
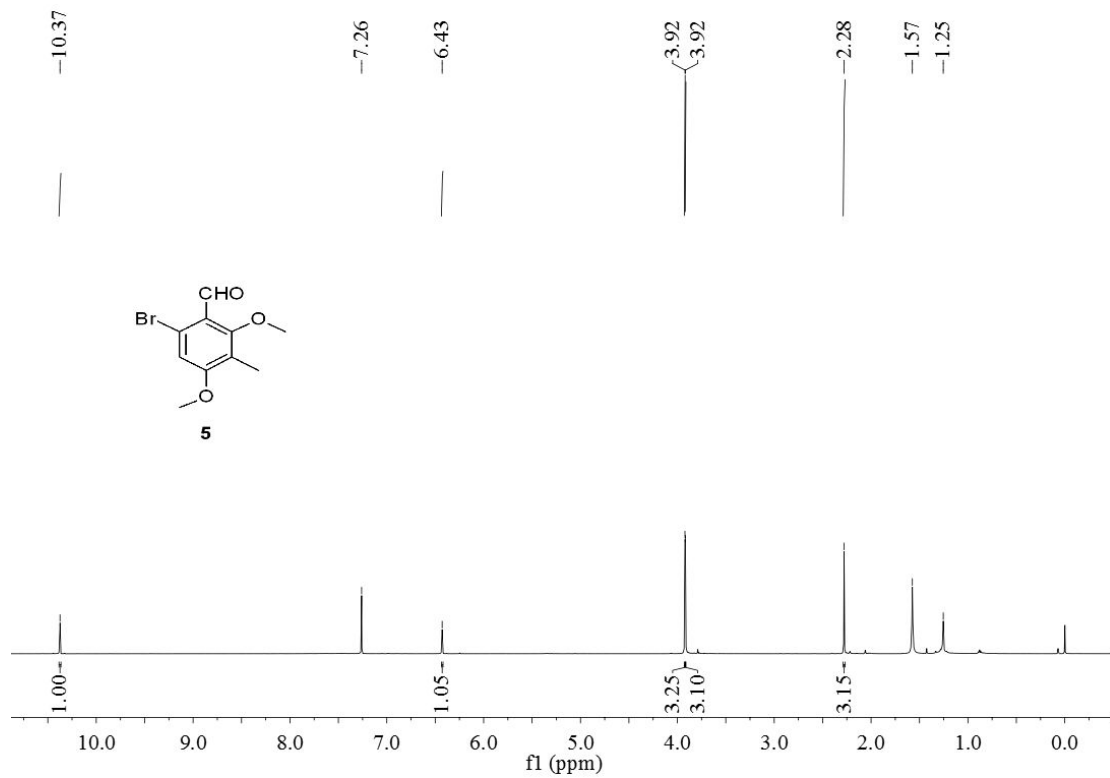


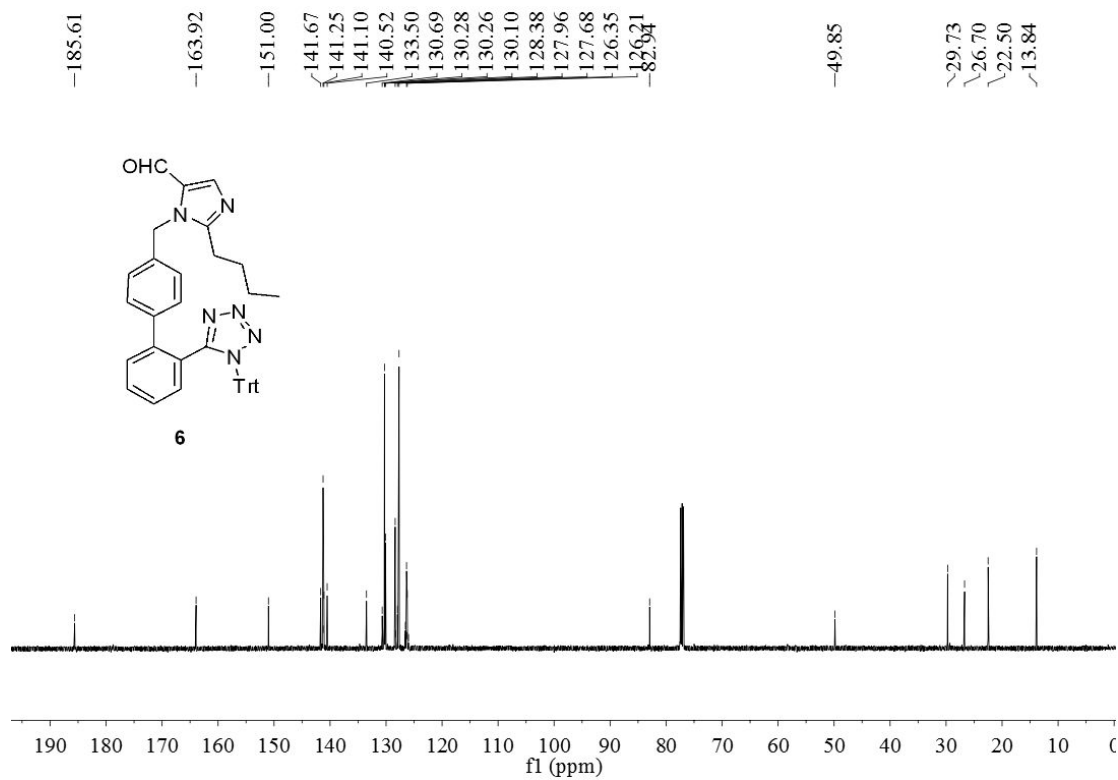
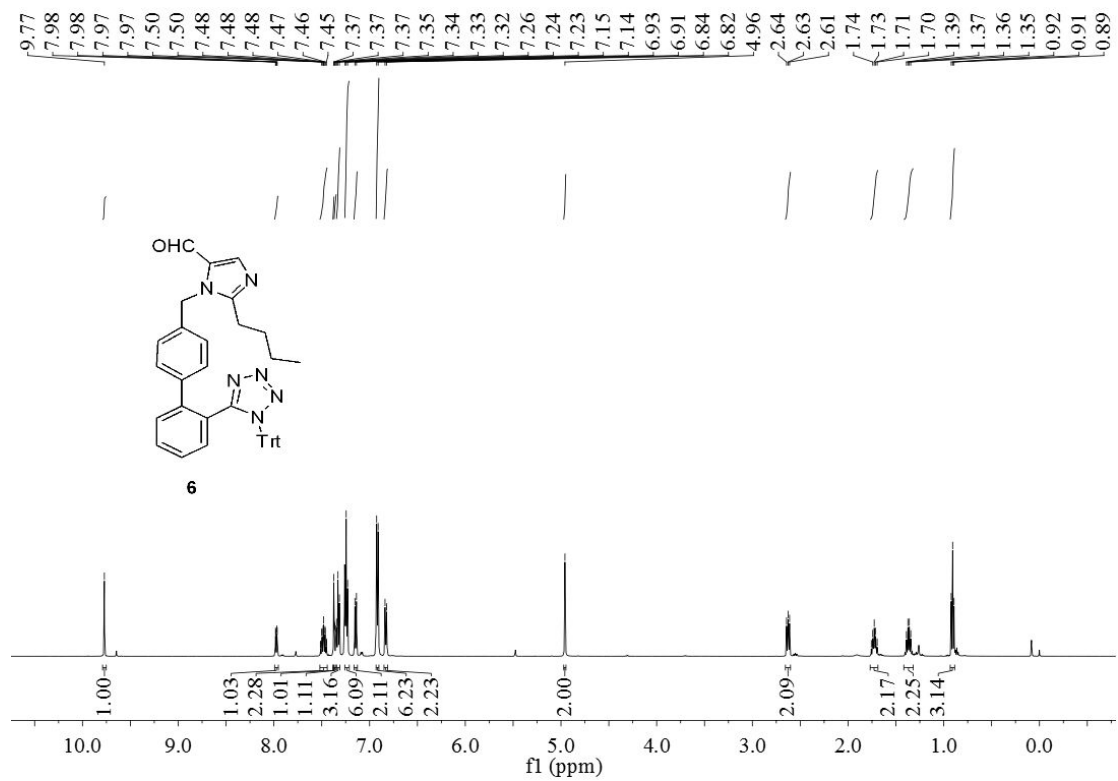


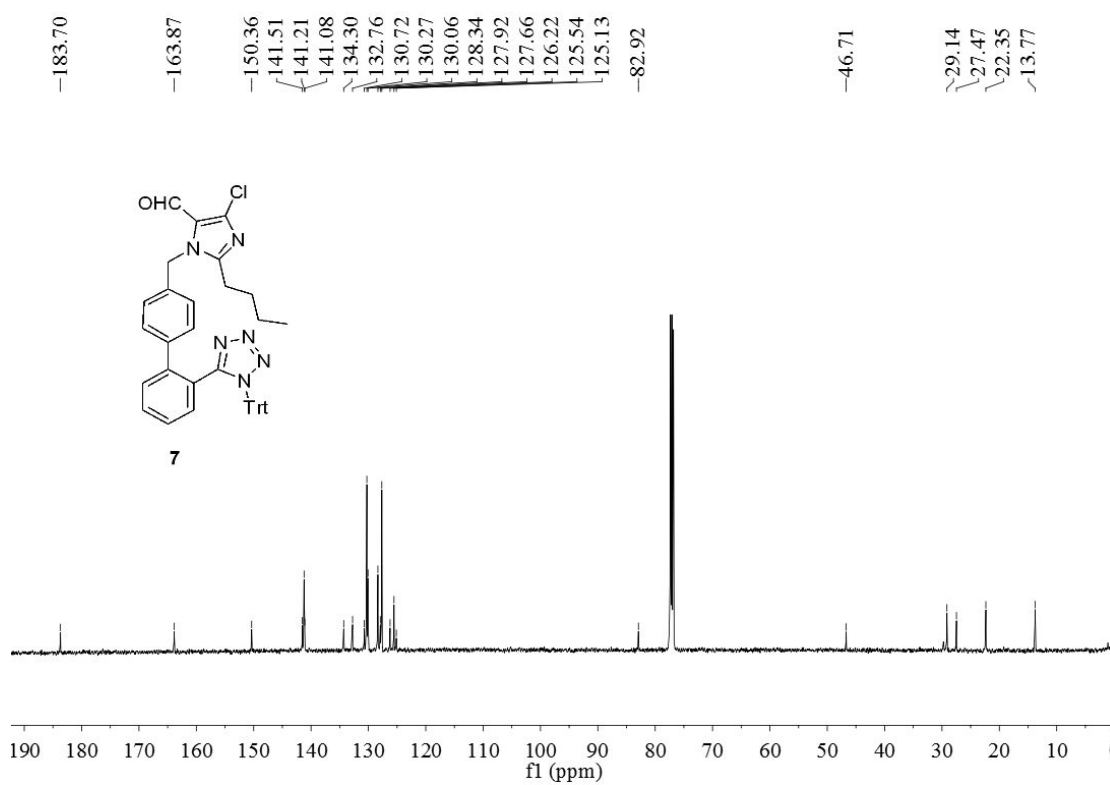
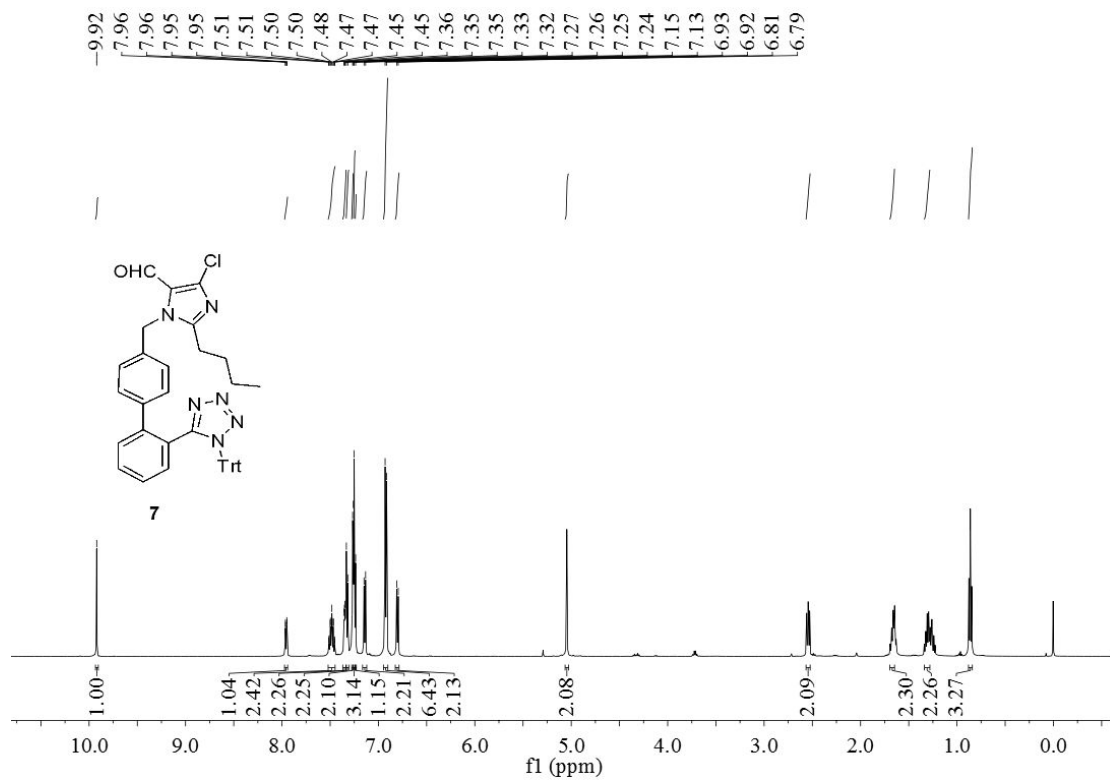


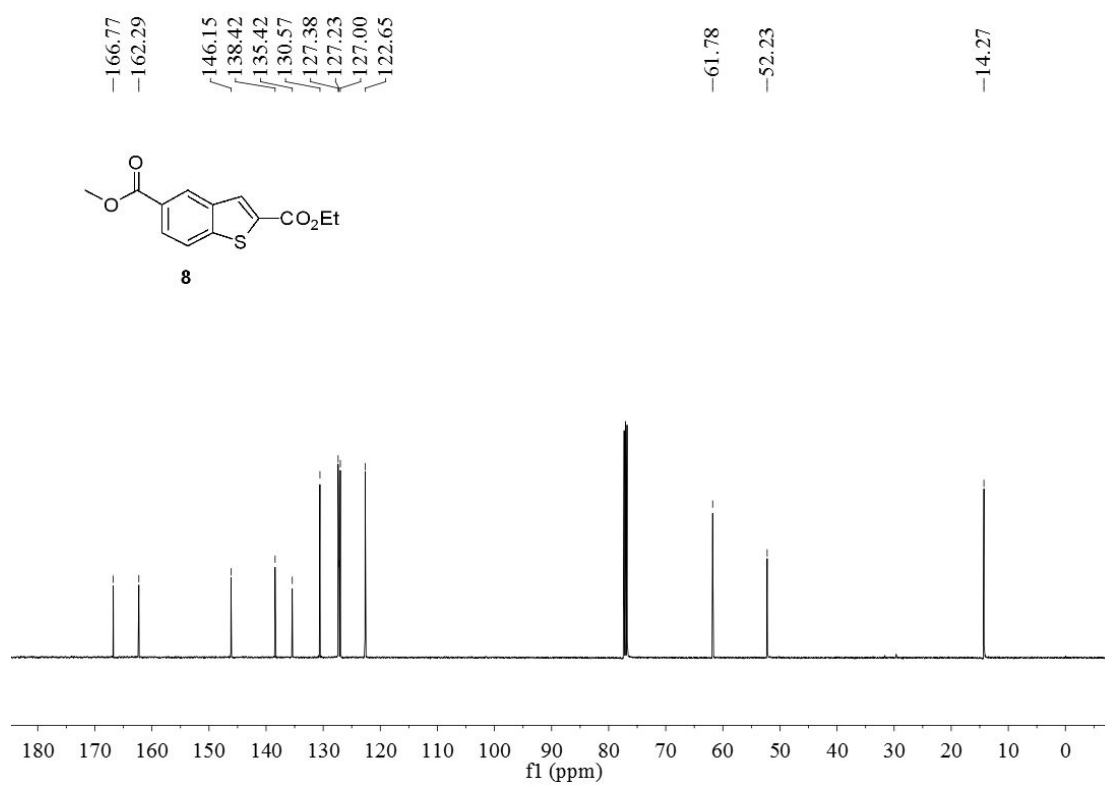
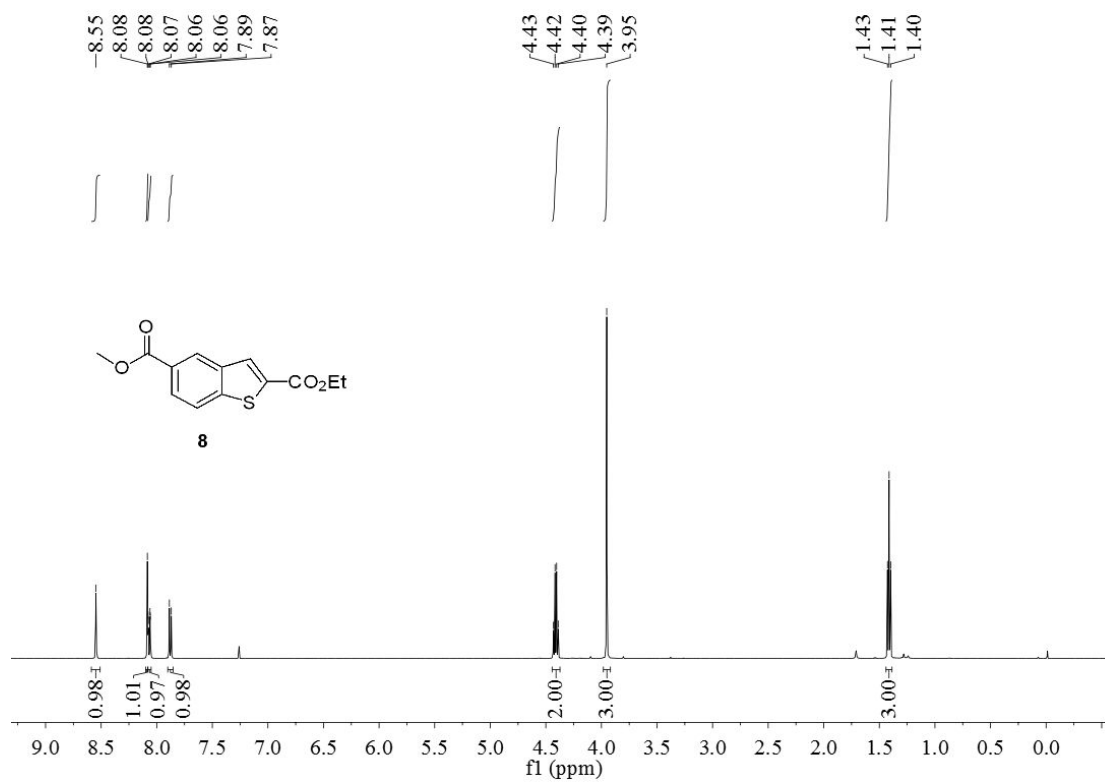


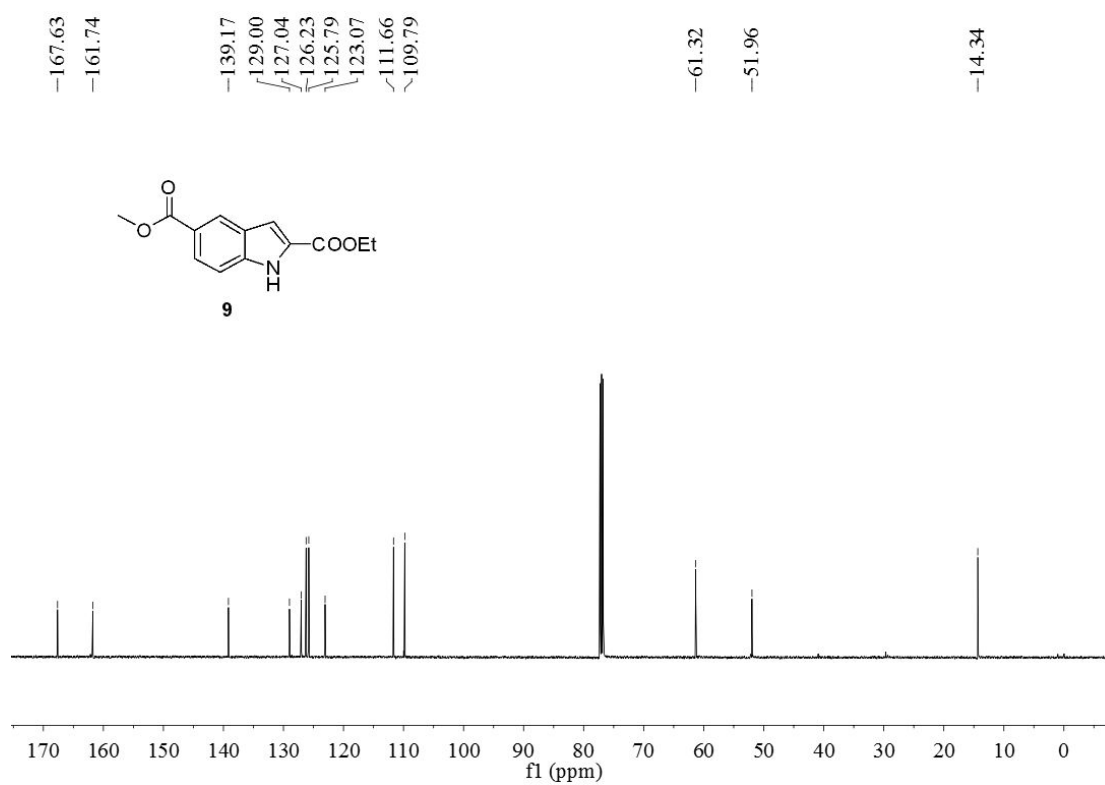
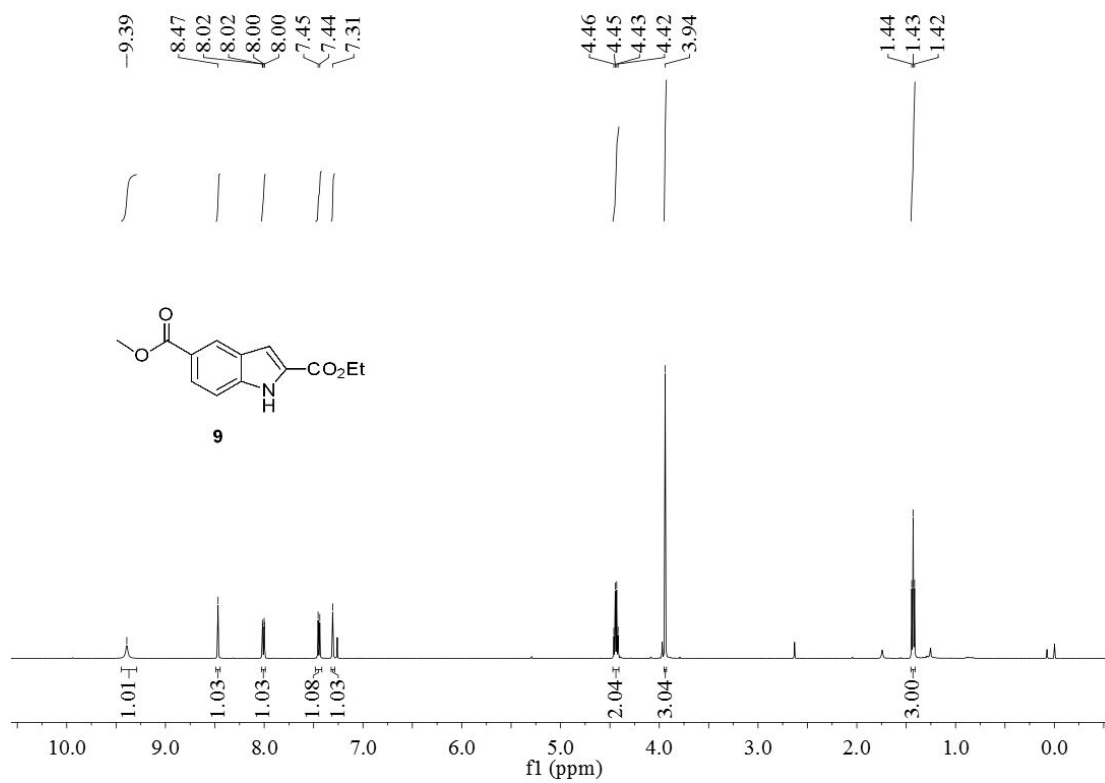


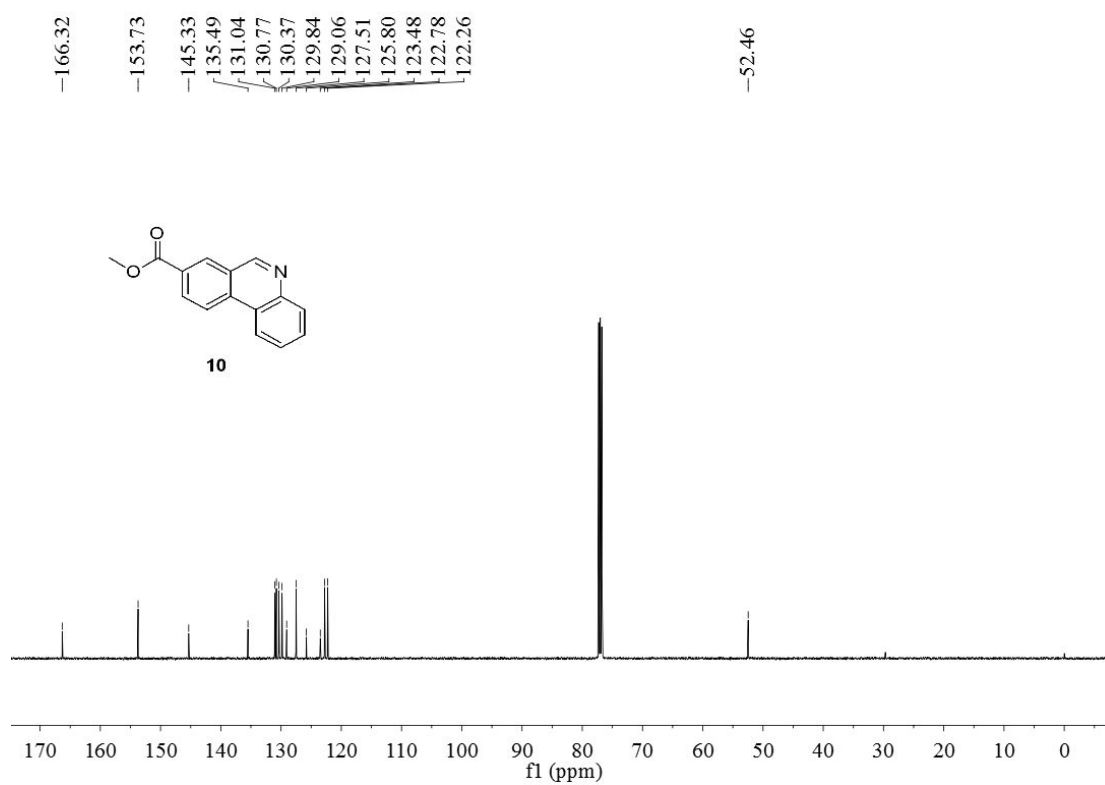
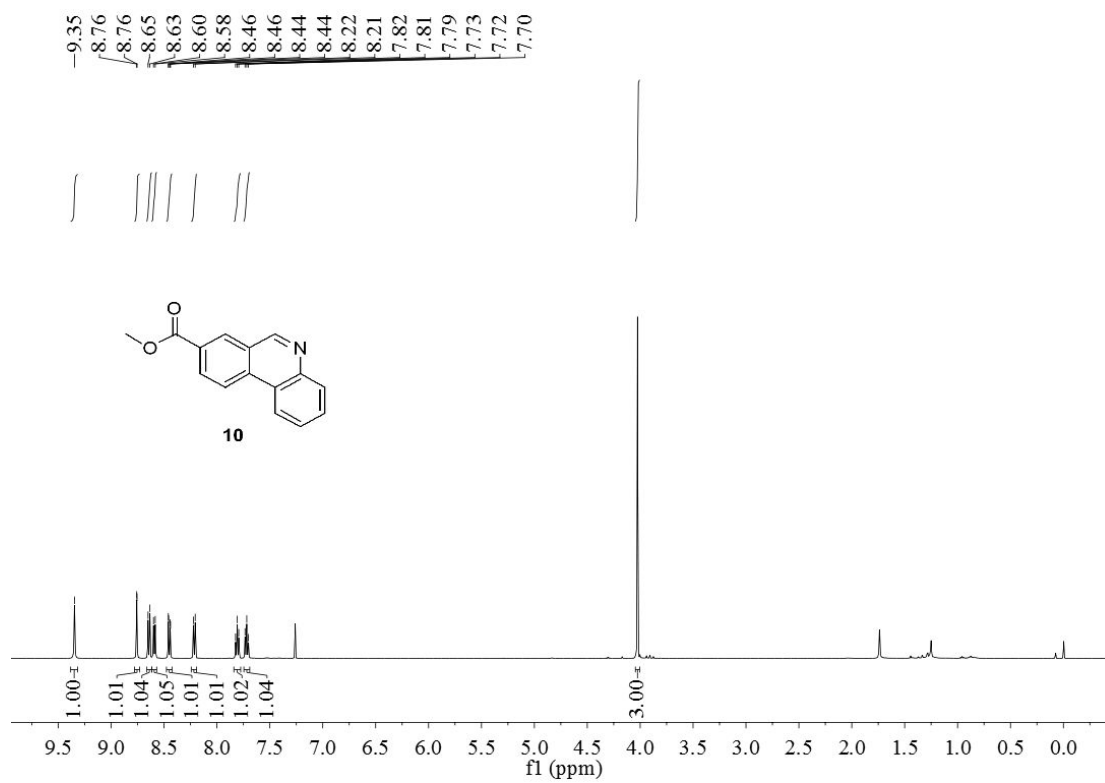


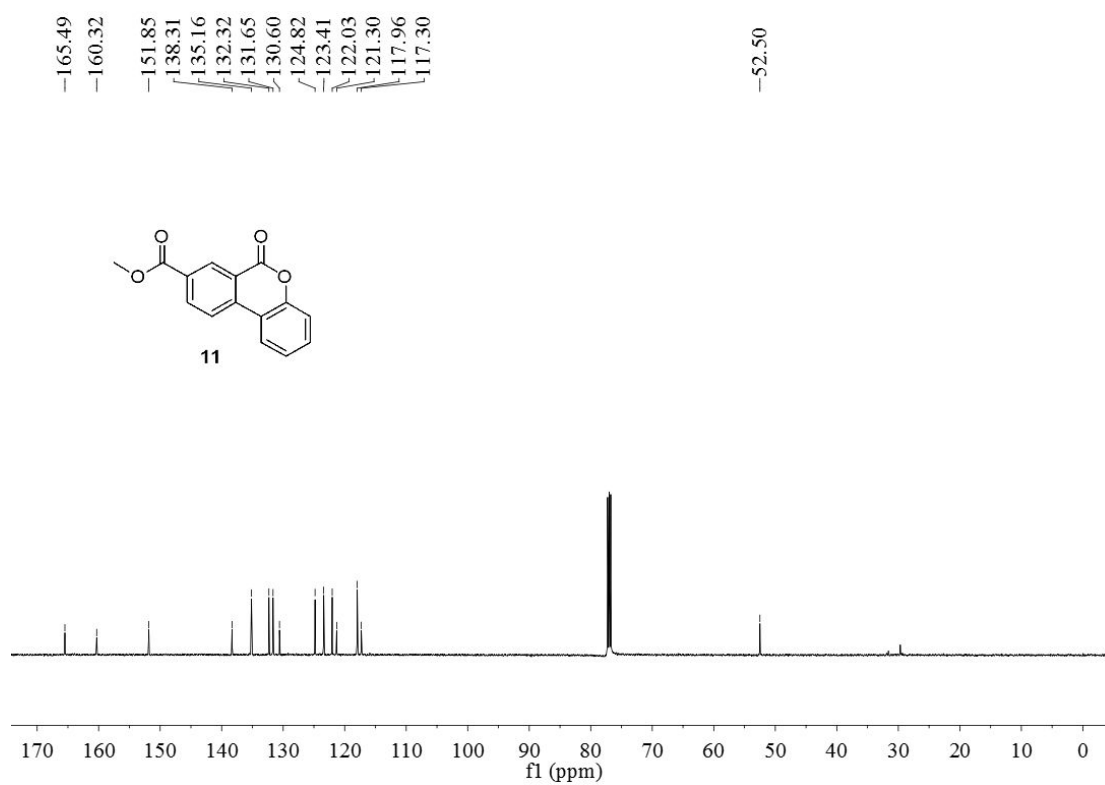
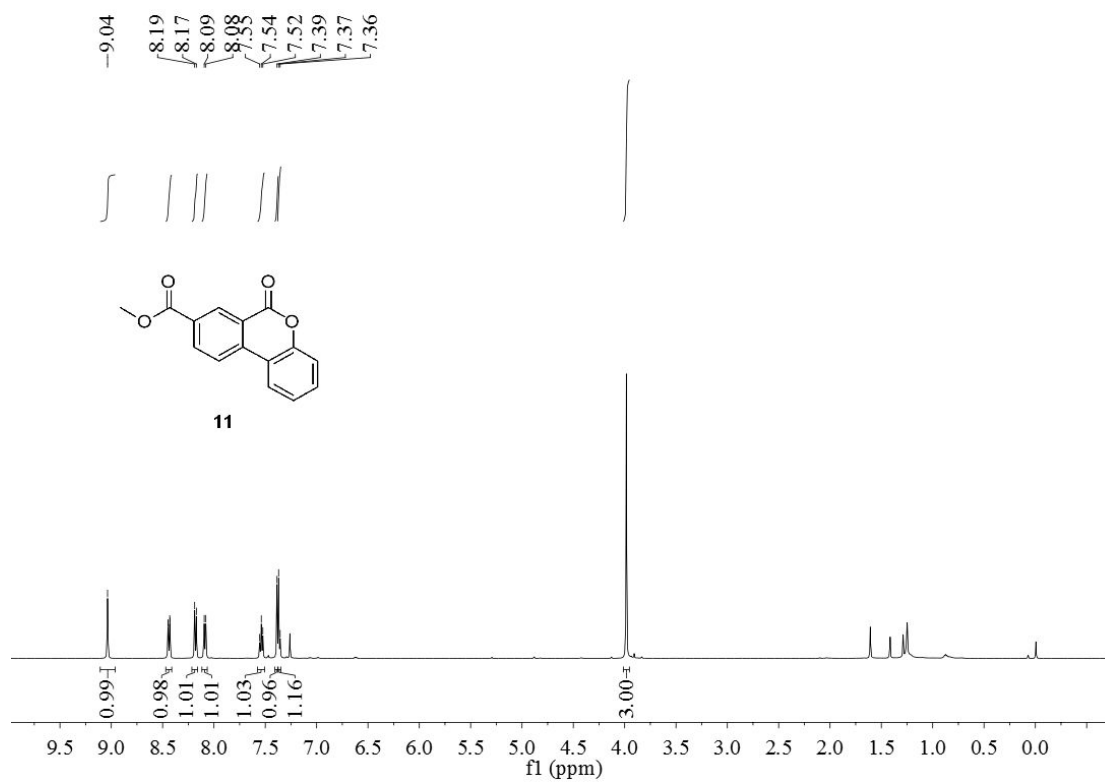


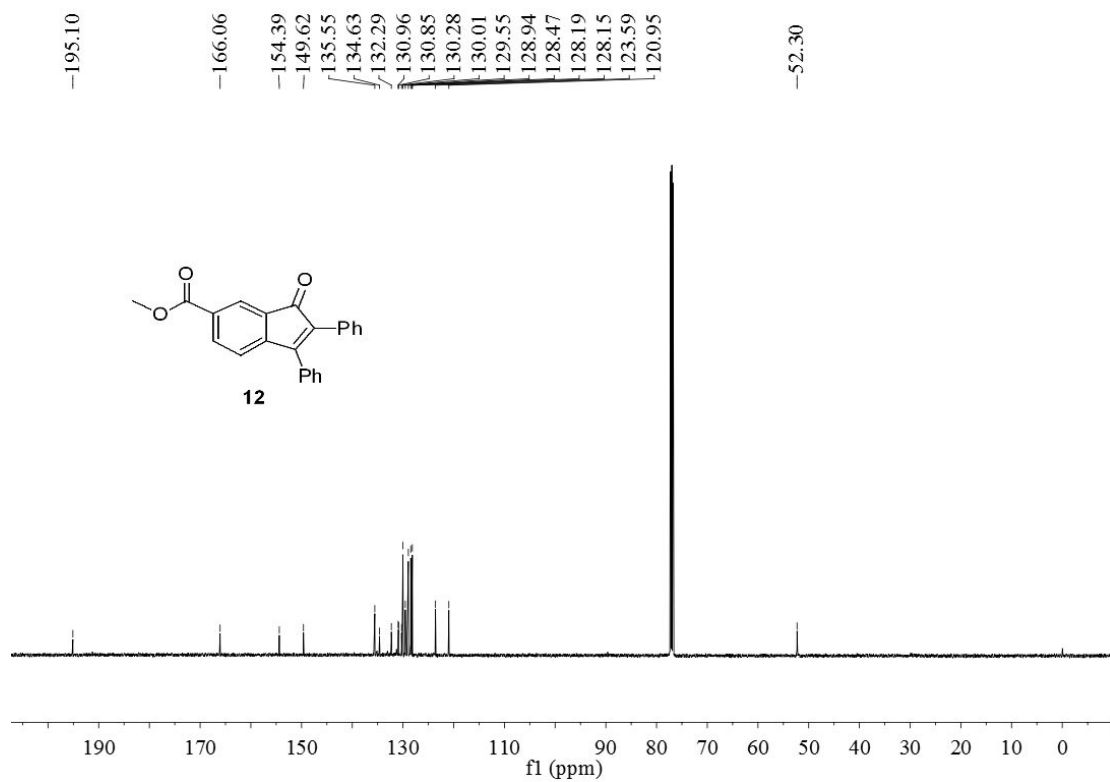
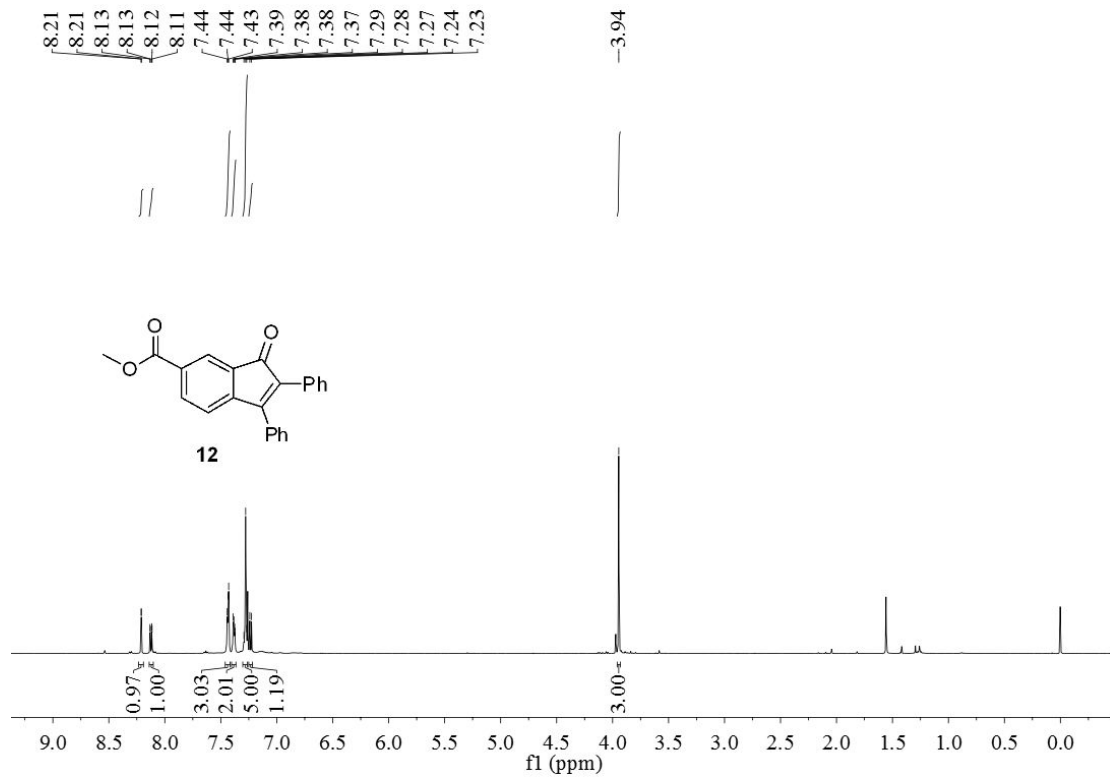


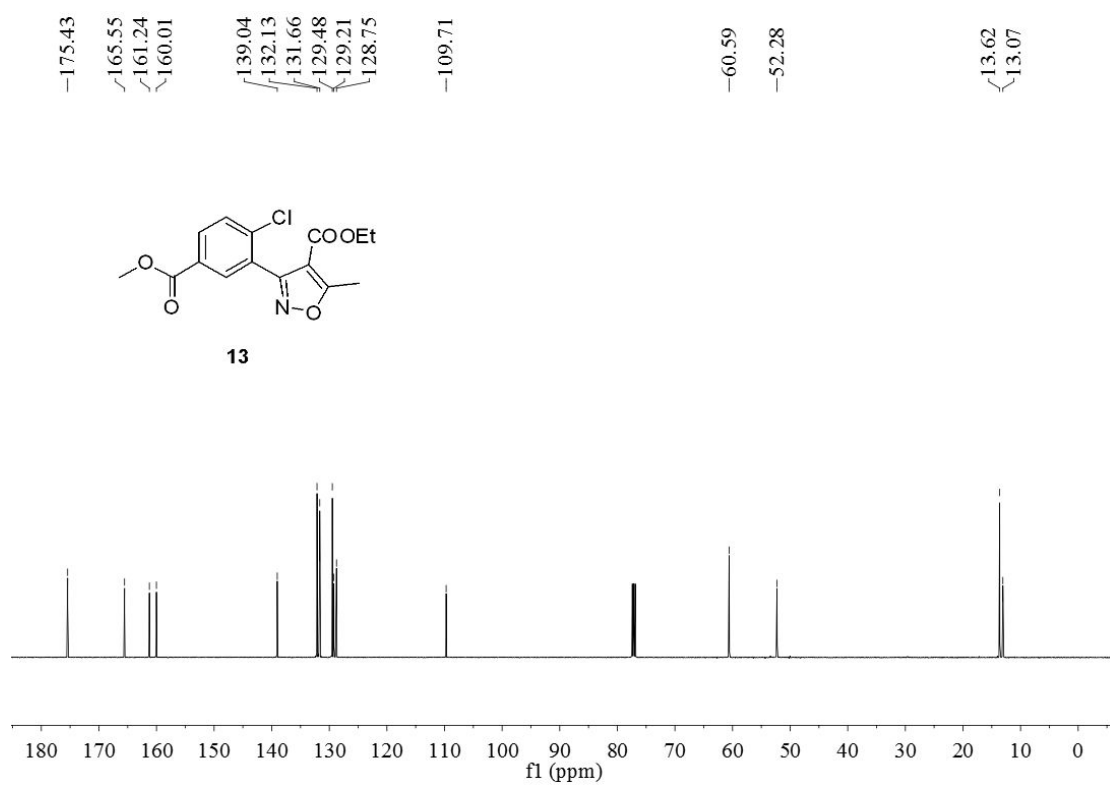
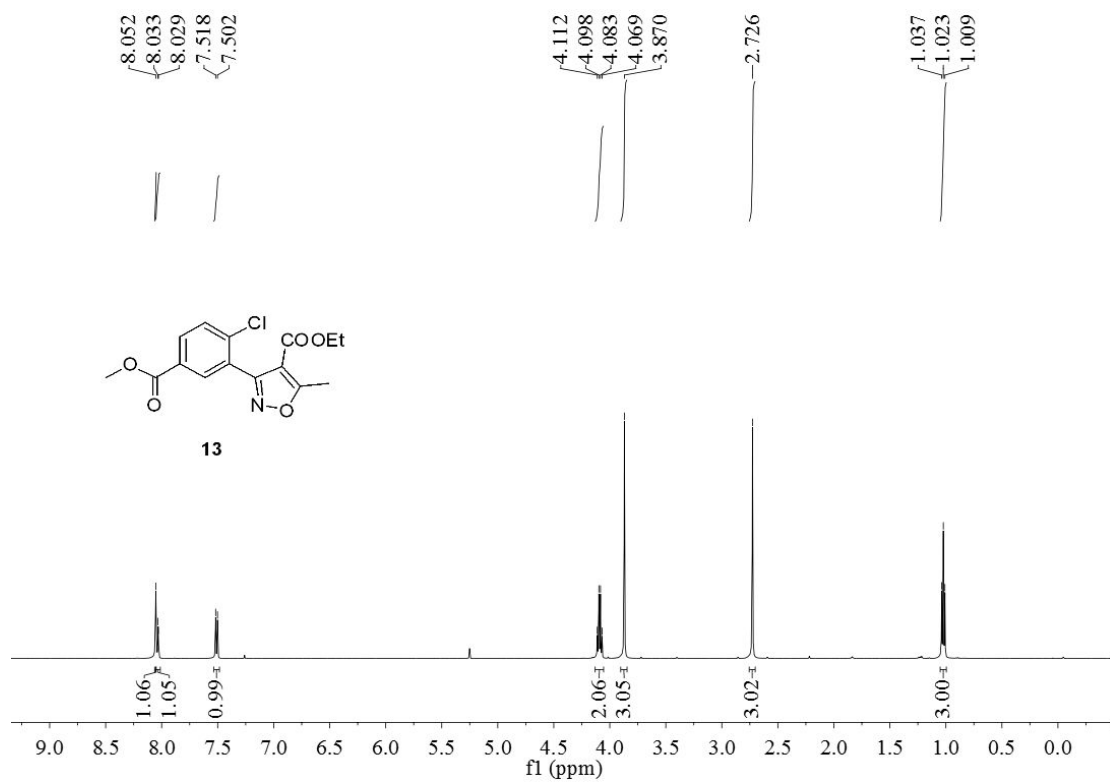


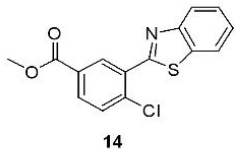
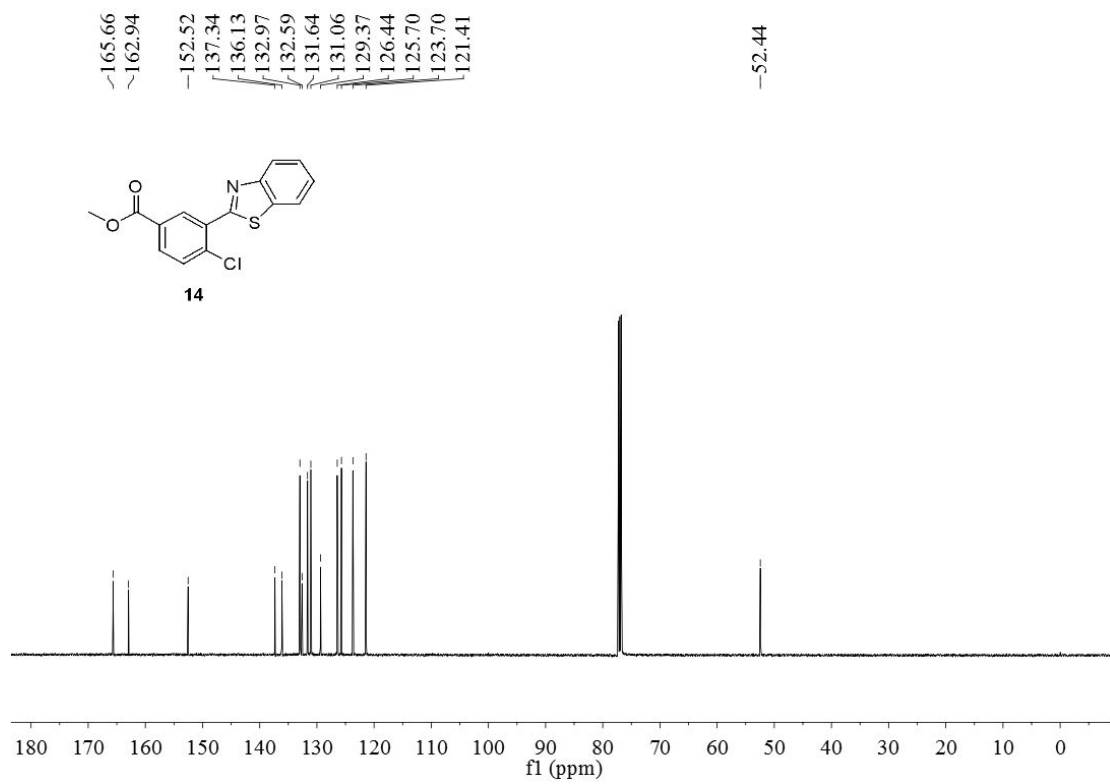
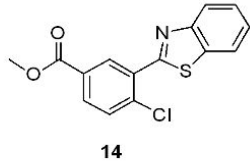
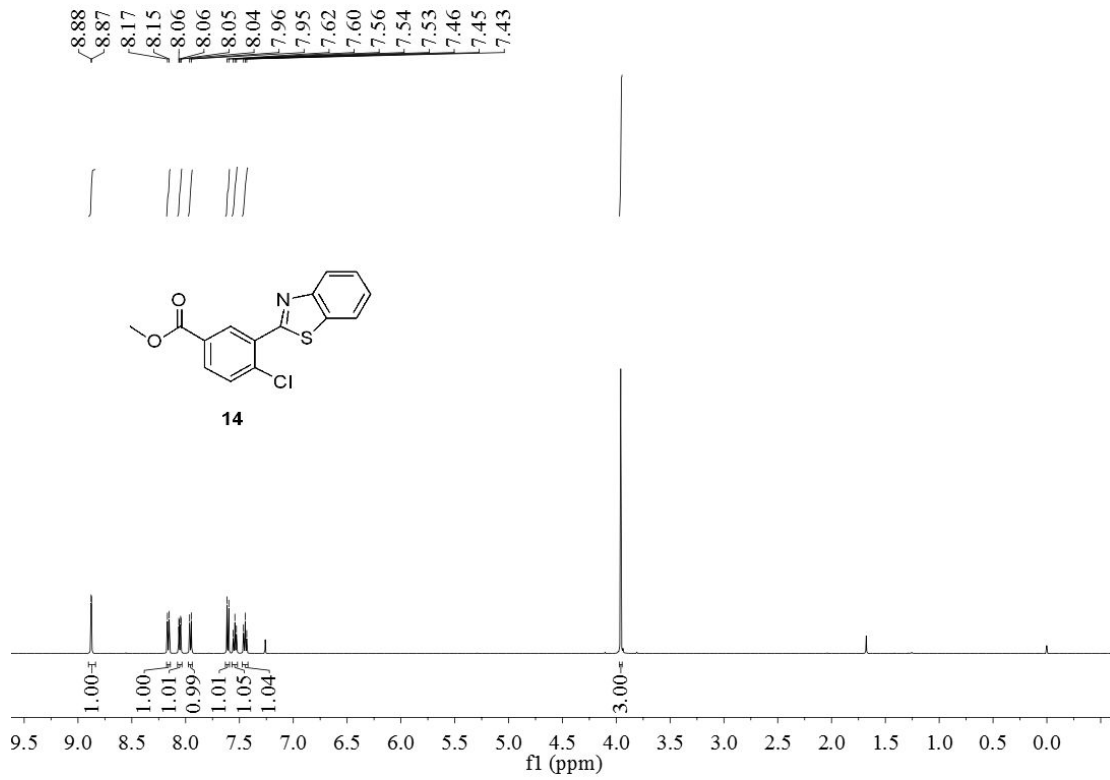


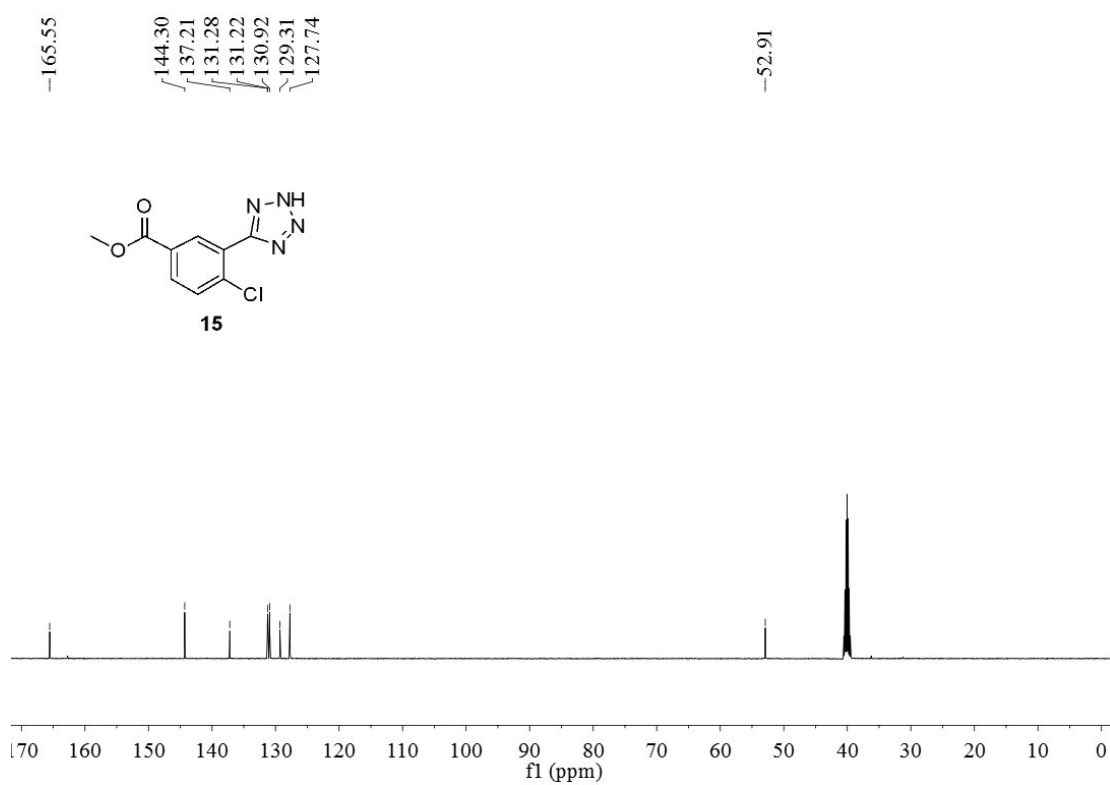
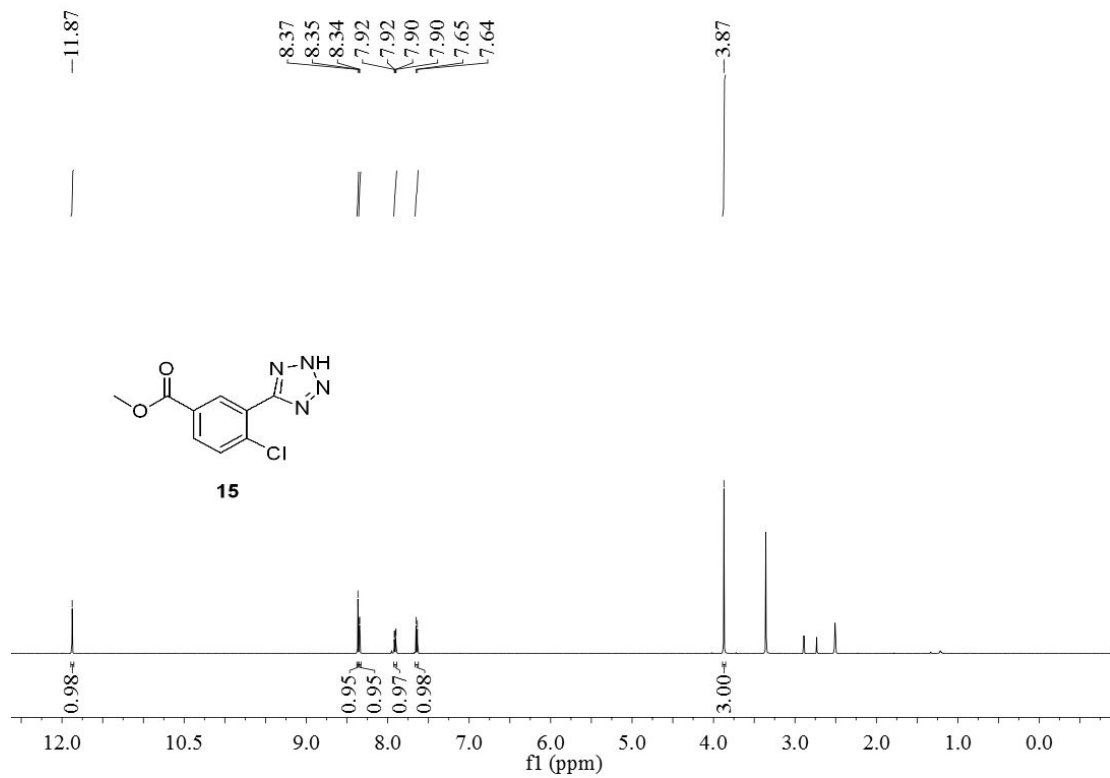


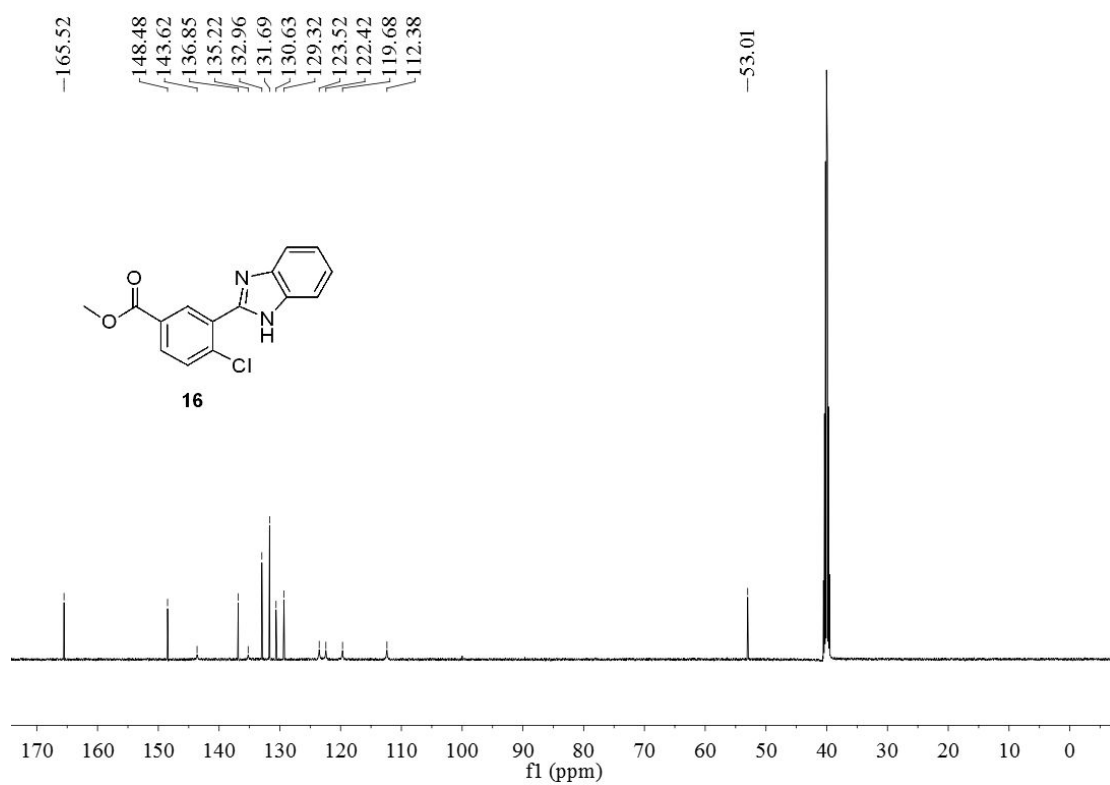
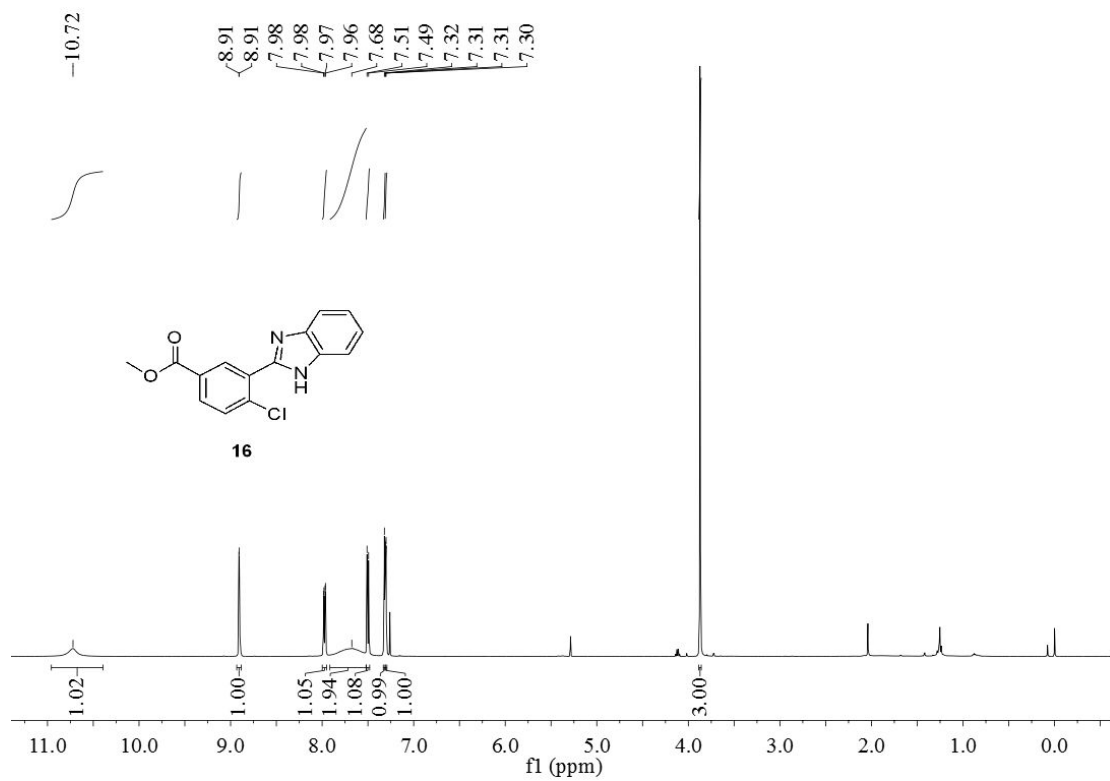












5. X-ray Structure of 3

