

Direct access to carbamates via acylation of arylamines with dialkyl azodicarboxylates under metal-free conditions

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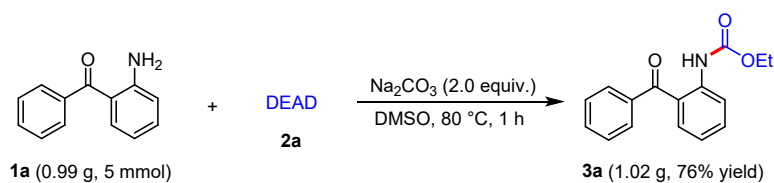
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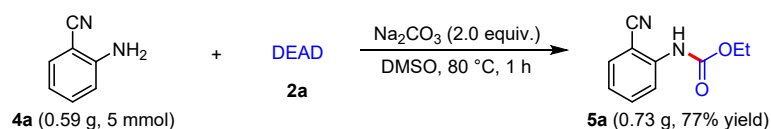
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A. Large-scale reactions:

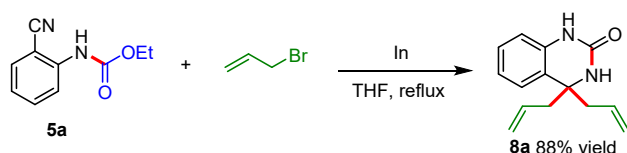


A 250 mL round bottom flask with a stir bar was fitted with a rubber septum and flame dried under high vacuum. The flask was purged with N_2 and charged with **1a** (0.99 g, 5.0 mmol, 1.0 equiv.) or **4a** (0.59 g, 5.0 mmol, 1.0 equiv.), **2a** (2.61 g, 15.0 mmol, 3.0 equiv.) Na_2CO_3 (1.06 g, 10.0 mmol, 2.0 equiv.) and DMSO (100 mL) was then added. The mixture was stirred at 80 °C until the reaction was judged to be completed by TLC analysis. Water was added and extracted with EtOAc. The organic phase was dried over anhydrous MgSO_4 and concentrated under reduced pressure. The residue was then chromatographed on silica gel to afford the desired product **3a** (1.02 g, 76% yield).

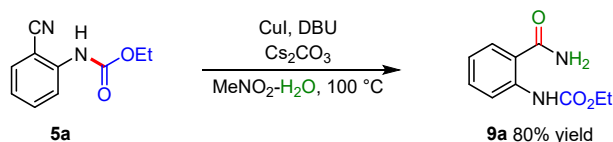


A 250 mL round bottom flask with a stir bar was fitted with a rubber septum and flame dried under high vacuum. The flask was purged with N_2 and charged with **4a** (0.59 g, 5.0 mmol, 1.0 equiv.), **2a** (2.61 g, 15.0 mmol, 3.0 equiv.) Na_2CO_3 (1.06 g, 10.0 mmol, 2.0 equiv.) and DMSO (100 mL) was then added. The mixture was stirred at 80 °C until the reaction was judged to be completed by TLC analysis. Water was added and extracted with EtOAc. The organic phase was dried over anhydrous MgSO_4 and concentrated under reduced pressure. The residue was then chromatographed on silica gel to afford the desired product **5a** (0.73 g, 77% yield).

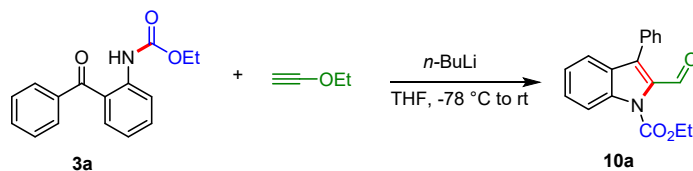
B. Synthetic transformations of **3a** and **5a**:



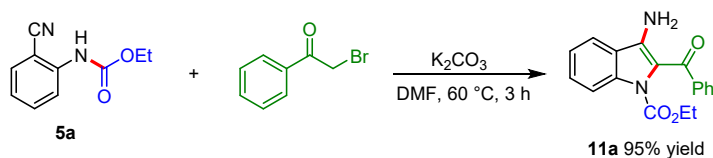
Heat a stirred mixture of **5a** (0.2 mmol, 38.2 mg), allyl bromide (0.4 mmol, 48.4 mg, 2.0 equiv.) and indium (0.2 mmol, 23 mg, 1.0 equiv.) in THF (0.4 mL) to reflux for 1 h. After the reaction was cooled down to room temperature, diluted with ethyl acetate, washed with saturated ammonium chloride (3×20 mL), dried over anhydrous MgSO_4 , filtered, and remove the solvent under reduced pressure. The product **8a** was obtained by column chromatography over silica gel using a mixture of petroleum ether and ethyl acetate as the eluent. **8a** (PE:EA = 10:1, R_f = 0.29, White solid, 88% yield). $^1\text{H NMR}$ (400 MHz, CDCl_3): δ 9.14 (s, 1H), 7.13 – 7.04 (m, 2H), 6.98 – 6.91 (m, 1H), 6.80 – 6.73 (m, 1H), 5.77 – 5.63 (m, 3H), 5.14 – 5.04 (m, 4H), 2.67 – 2.46 (m, 4H). $^{13}\text{C NMR}$ (100 MHz, CDCl_3): δ 155.3, 137.2, 132.3, 127.8, 125.0, 122.7, 122.0, 119.8, 114.7, 60.4, 46.7. Analytical data are in accordance with the literature values.¹



Add DBU (24 mg, 0.1 mmol, 0.5 equiv.), CuI (3.0 mg, 0.01 mmol, 5 mol%), Cs₂CO₃ (13 mg, 0.04 mmol, 2.0 equiv.) to a nitromethane (0.5 mL)-H₂O (0.1 mL) solution of **5a** (0.2 mmol, 38.2 mg) at room temperature. Then, heat the reaction mixture at 100 °C for 10 h and then pour into water (50 mL). Separate the organic layer and extract the aqueous layer with EtOAc. Dry the combined organic layer with anhydrous MgSO₄. Then, remove the solvent under reduced pressure. The product **9a** was obtained by column chromatography over silica gel using a mixture of petroleum ether and ethyl acetate as the eluent. **9a** (PE:EA = 10:1, R_f = 0.25, Pale yellow solid, 80% yield). ¹H NMR (400 MHz, CDCl₃): δ 10.48 (s, 1H), 8.43 – 8.35 (m, 1H), 7.48 (dd, J = 8.4, 6.9 Hz, 2H), 7.04–6.99 (m, 1H), 4.21 (q, J = 7.1 Hz, 2H), 1.31 (t, J = 7.1 Hz, 3H). ¹³C NMR (100 MHz, CDCl₃): δ 171.3, 153.9, 140.6, 133.3, 127.3, 122.1, 120.0, 117.7, 61.1, 13.9. Analytical data are in accordance with the literature values.²



n-BuLi (1.6 M in THF, 0.5 mL, 4.0 equiv.) was added slowly to ethoxyethyne (45 w/v % in hexane, 0.14 mL, 4.0 equiv.) in THF (0.8 mL) at -78 °C, and the mixture was stirred at the same temperature for 2 h and then at 0 °C for another 2 h. Then, the reaction mixture was re-cooled to -78 °C before adding **3a** (50 mg in 0.8 mL THF, 0.2 mmol, 1.0 equiv.). The mixture was then stirred at -78 °C for 1 h and at room temperature for 2 h. Then, 1.0 N HCl (2.5 mL) was added to the reaction mixture at 0 °C and stirred for 40 min at room temperature. The mixture was extracted with EtOAc, and the combined extract was washed with brine and then dried over MgSO₄. After the removal of the solvent under vacuum, the product **10a** was obtained by column chromatography over silica gel using a mixture of petroleum ether and ethyl acetate as the eluent. **10a** (PE:EA = 10:1, R_f = 0.33, Yellow solid, 81% yield). ¹H NMR (400 MHz, CDCl₃): δ 10.12 (s, 1H), 8.18 (dt, J = 8.5, 0.9 Hz, 1H), 7.63 (dt, J = 7.9, 1.1 Hz, 1H), 7.59 – 7.45 (m, 6H), 7.32 (ddd, J = 8.0, 7.1, 1.0 Hz, 1H), 4.56 (q, J = 7.1 Hz, 2H), 1.49 (t, J = 7.1 Hz, 3H). ¹³C NMR (100 MHz, CDCl₃): δ 182.6, 151.4, 137.5, 134.0, 132.3, 130.6, 129.0, 128.7, 128.5, 124.0, 122.3, 115.4, 64.3, 14.2. Analytical data are in accordance with the literature values.³



A Schlenk tube was charged with **5a** (0.2 mmol, 38.1 mg), 2-bromo-1-phenylethan-1-one (0.3 mmol, 59.7 g, 1.5 equiv.), K₂CO₃ (0.4 mmol, 55.3 mg, 2.0 equiv.) and DMF (1 mL). The mixture was stirred at 60 °C for 3 h. Then, the reaction was cooled down to room temperature, diluted with ethyl acetate, washed with saturated ammonium chloride (3×20 mL), dried over anhydrous MgSO₄, filtered, and remove the solvent under reduced pressure. The product **11a** was obtained by column chromatography over silica gel using a mixture of petroleum ether and ethyl acetate as the eluent. **11a** (PE:EA = 10:1, R_f = 0.16, Yellow solid, 95% yield). ¹H NMR (400 MHz, CDCl₃): δ 8.22 (d, J = 8.4 Hz, 1H), 7.91 – 7.70 (m, 2H), 7.65 – 7.54 (m, 2H), 7.44 (tdd, J = 8.7, 7.1, 4.7 Hz, 3H), 7.36 – 7.30 (m, 1H), 5.86 (s, 2H),

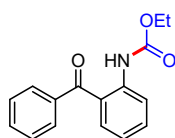
3.73 (q, $J = 7.1$ Hz, 2H), 0.84 (t, $J = 7.1$ Hz, 3H). ^{13}C NMR (100 MHz, CDCl_3): δ 187.0, 152.0, 143.2, 141.1, 138.2, 131.2, 130.0, 128.4, 127.4, 123.2, 122.1, 119.4, 116.3, 116.1, 62.9, 13.5.

Analytical data are in accordance with the literature values.⁴

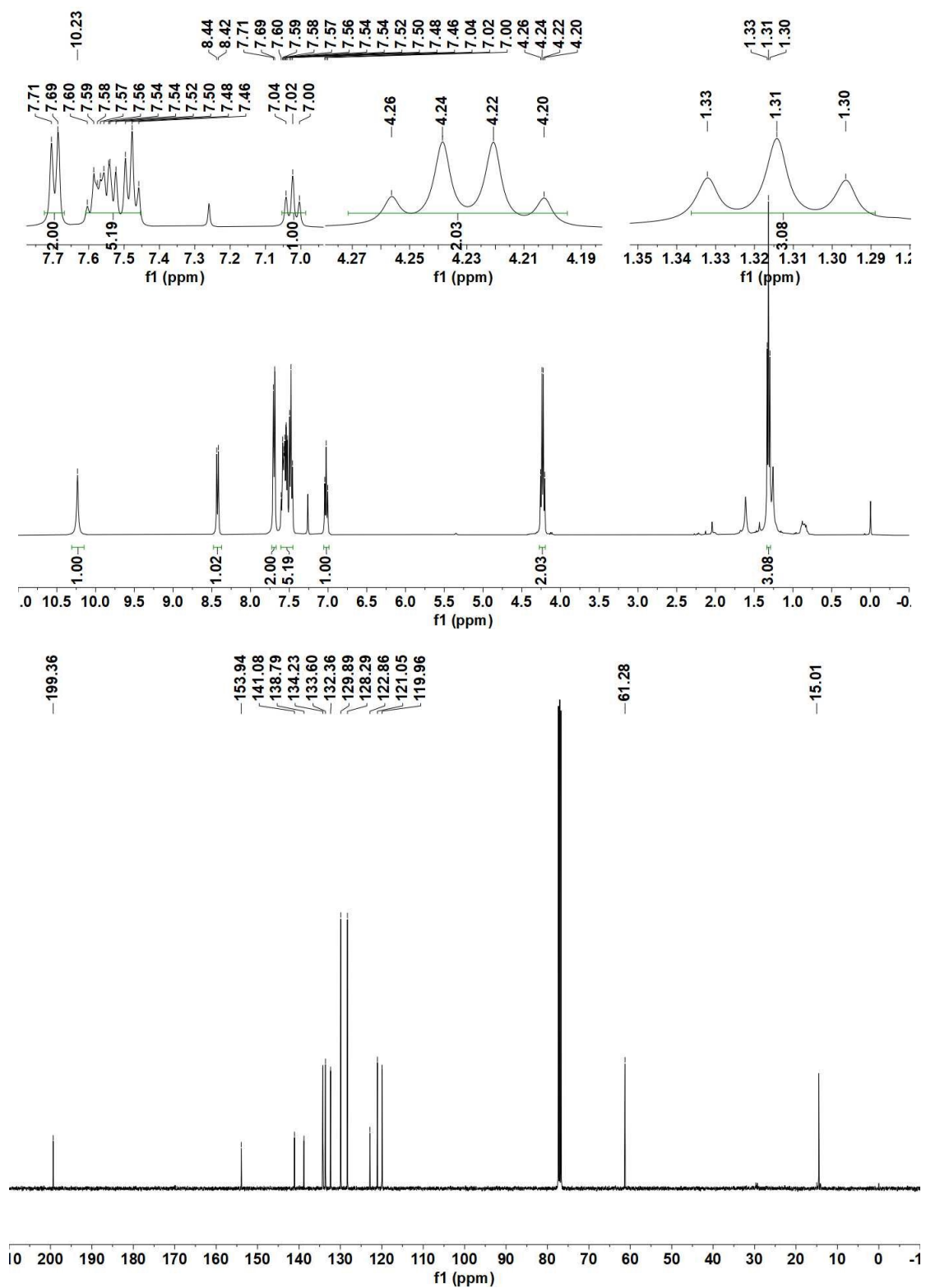
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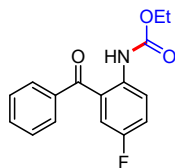
- 1 S. H. Kim, S. H. Kim, T. H. Kim and J. N. Kim, Synthesis of 4-allylquinazolines from *N*-(2-cyanoaryl)amides via the In-mediated allylation of nitrile and dehydrative cyclization cascade, *Tetrahedron Lett.*, 2010, **51**, 2774-2777.
- 2 J. Kuwabara, Y. Sawada and M. Yoshimatsu, Nitrile Hydration Reaction Using Copper Iodide/Cesium Carbonate/DBU in Nitromethane-Water, *Synlett*, 2018, **29**, 2061-2065.
- 3 N. Thirupathi, Y. K. Kumar, R. Kant and M. S. Reddy, Selective 5-*exo-dig* Cyclization of in Situ Synthesized *N*-Boc-2-aminophenyl Ethoxyethynyl Carbenols: Synthesis of Multifunctional Indoles and Their Derivatives, *Adv. Synth. Catal.*, 2014, **356**, 1823-1834.
- 4 P.-C. Diao, Q. Li, M.-J. Hu, Y.-F. Ma, W.-W. You, K. H. Hong and P.-L. Zhao, Synthesis and biological evaluation of novel indole-pyrimidine hybrids bearing morpholine and thiomorpholine moieties, *Eur. J. Med. Chem.*, 2017, **134**, 110-118.

D. NMR spectra:

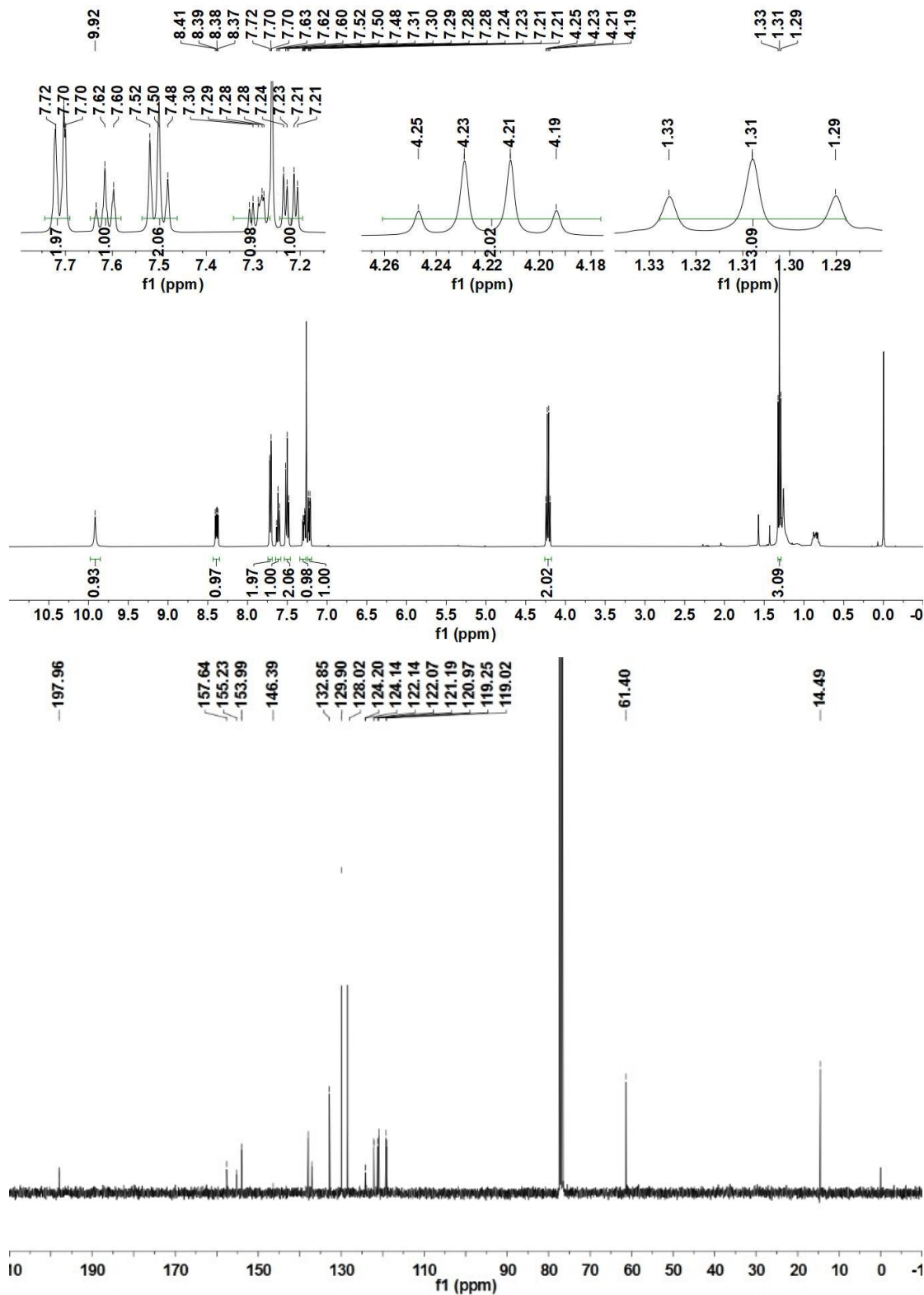


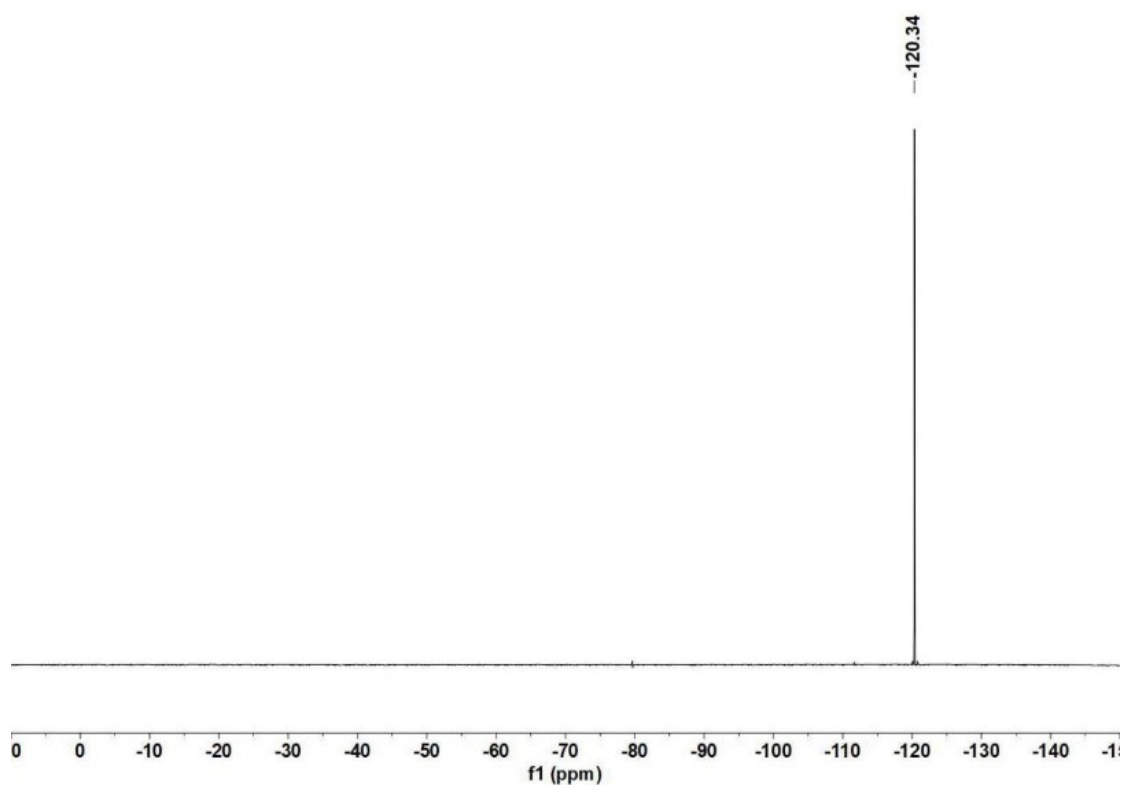
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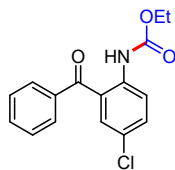




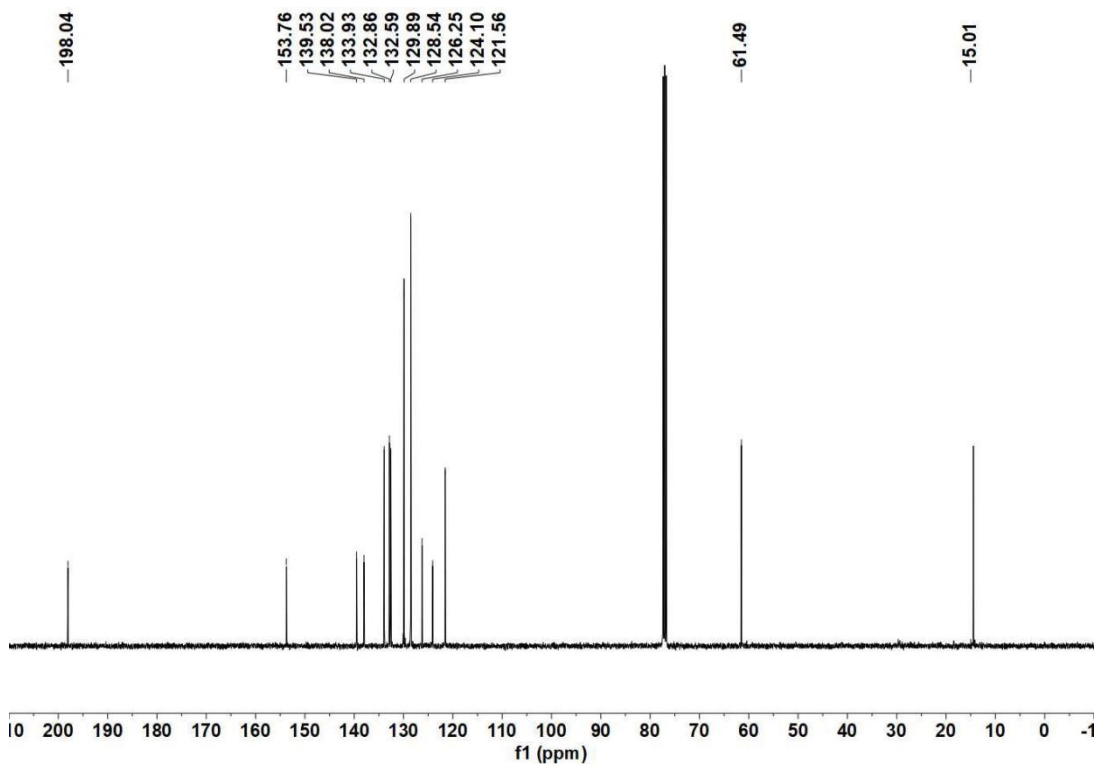
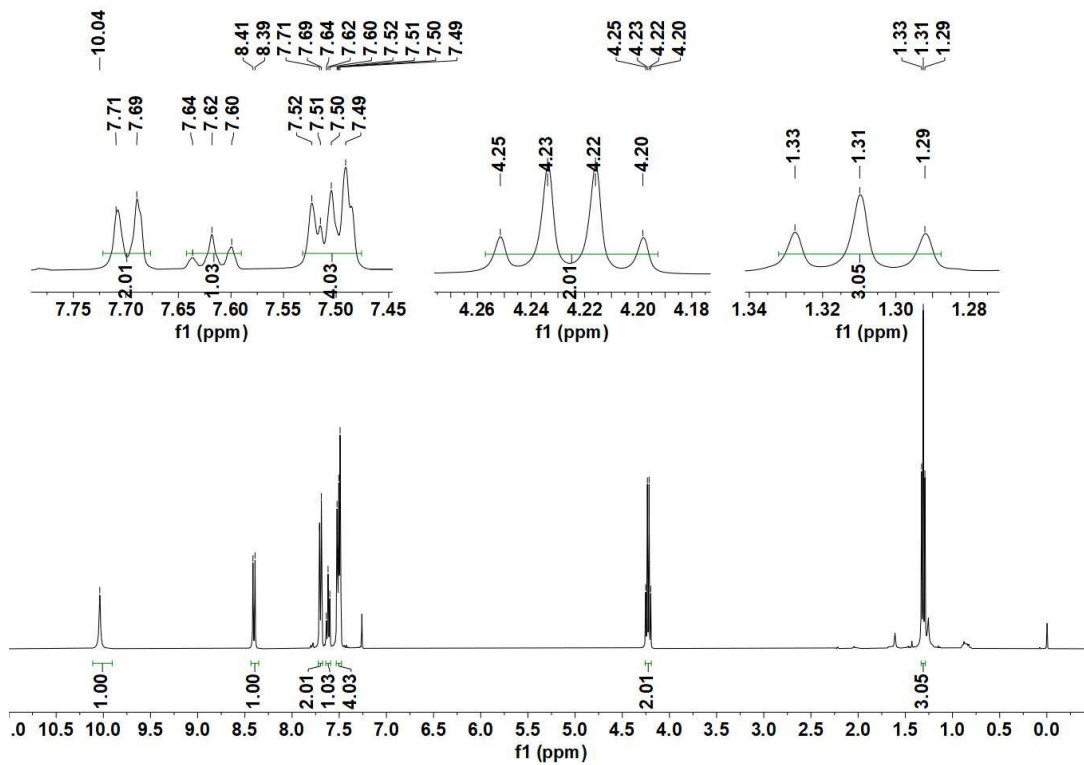
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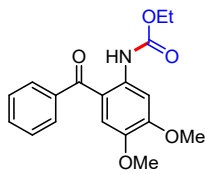




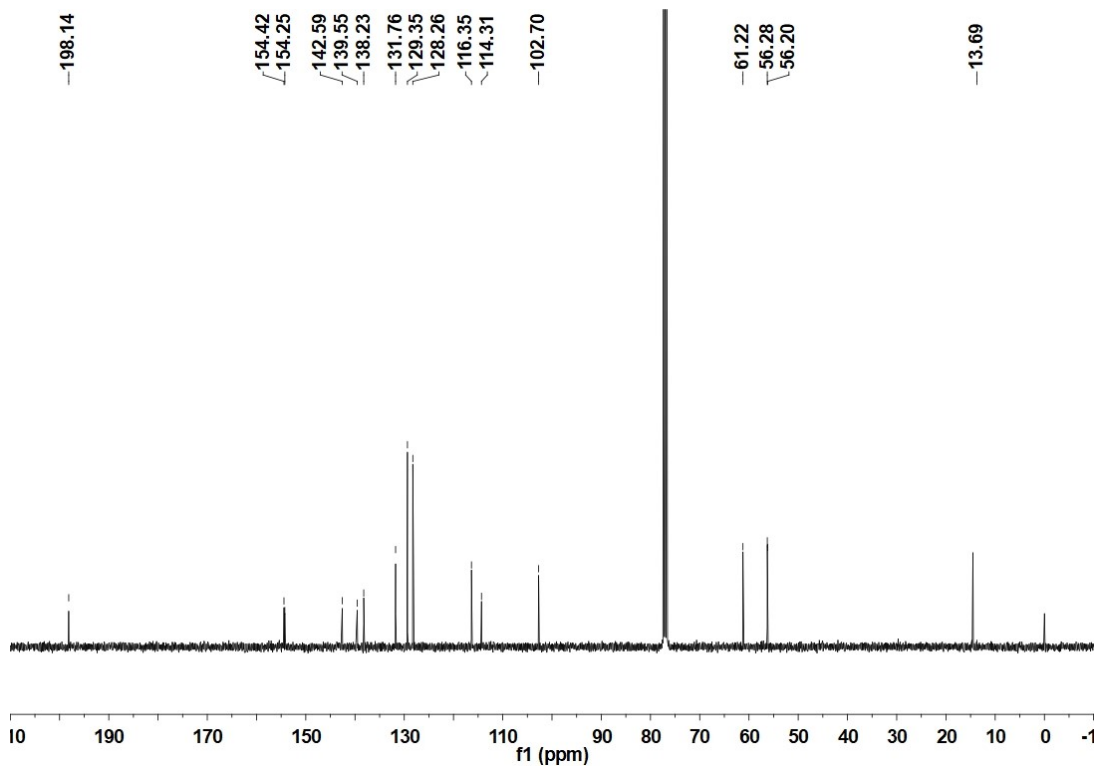
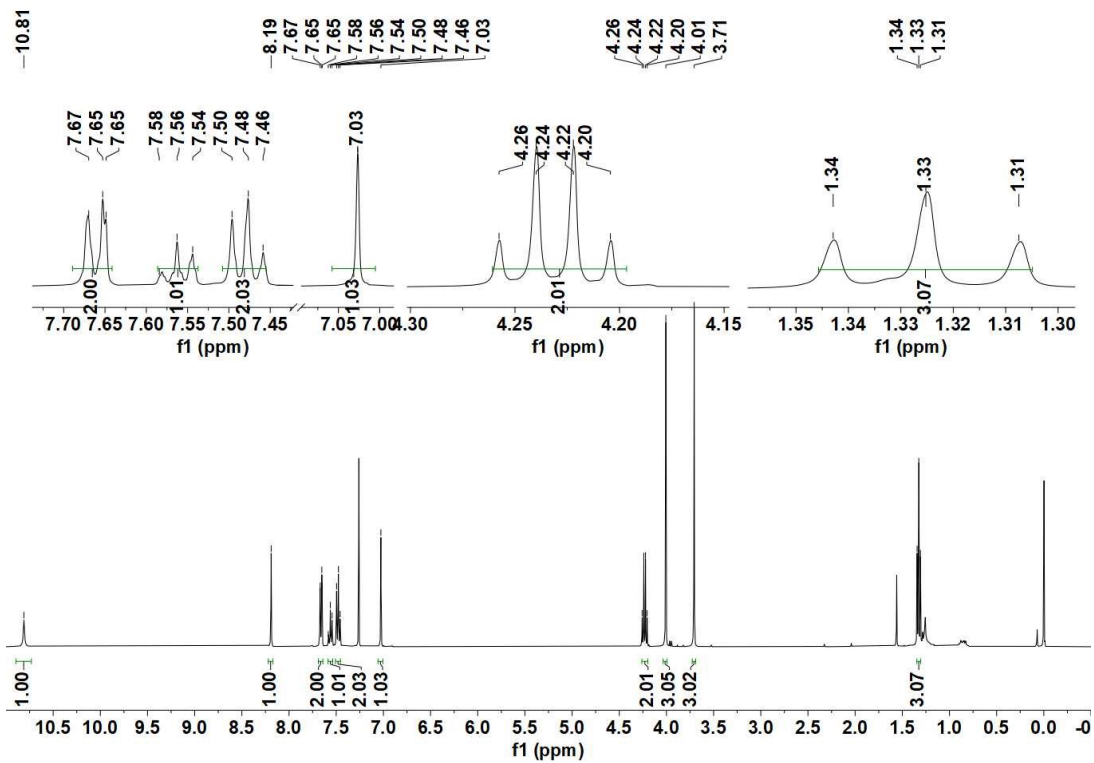


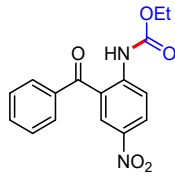
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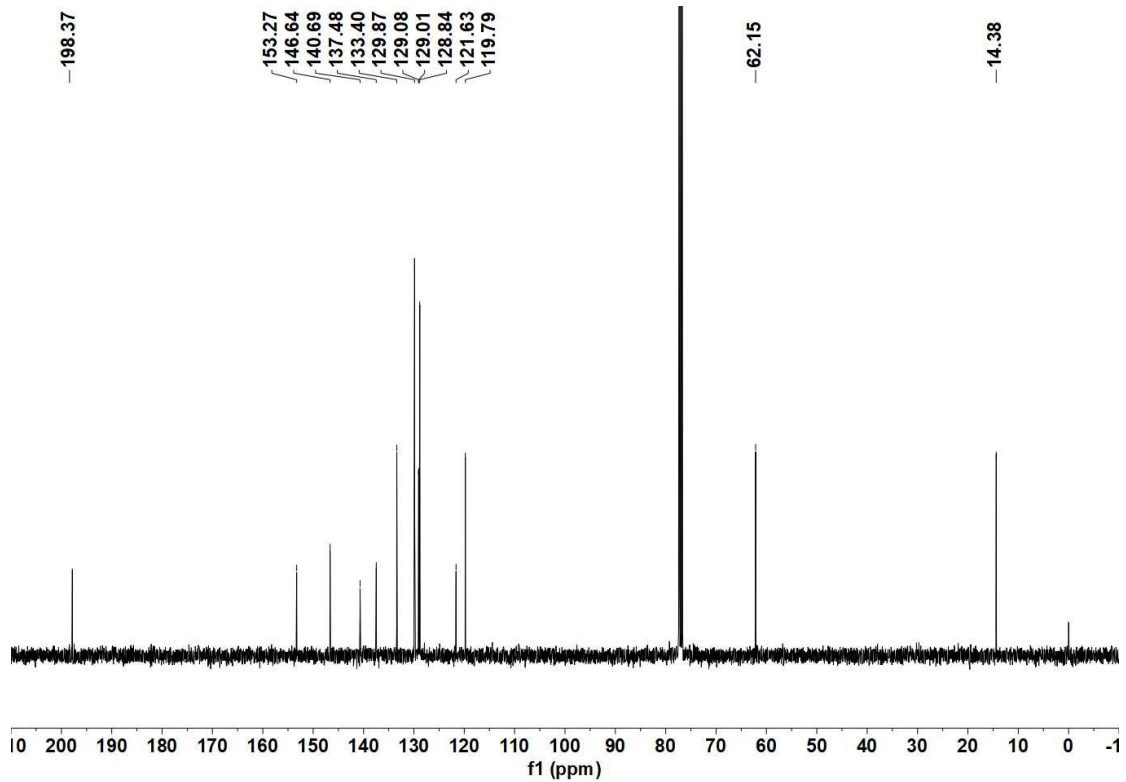
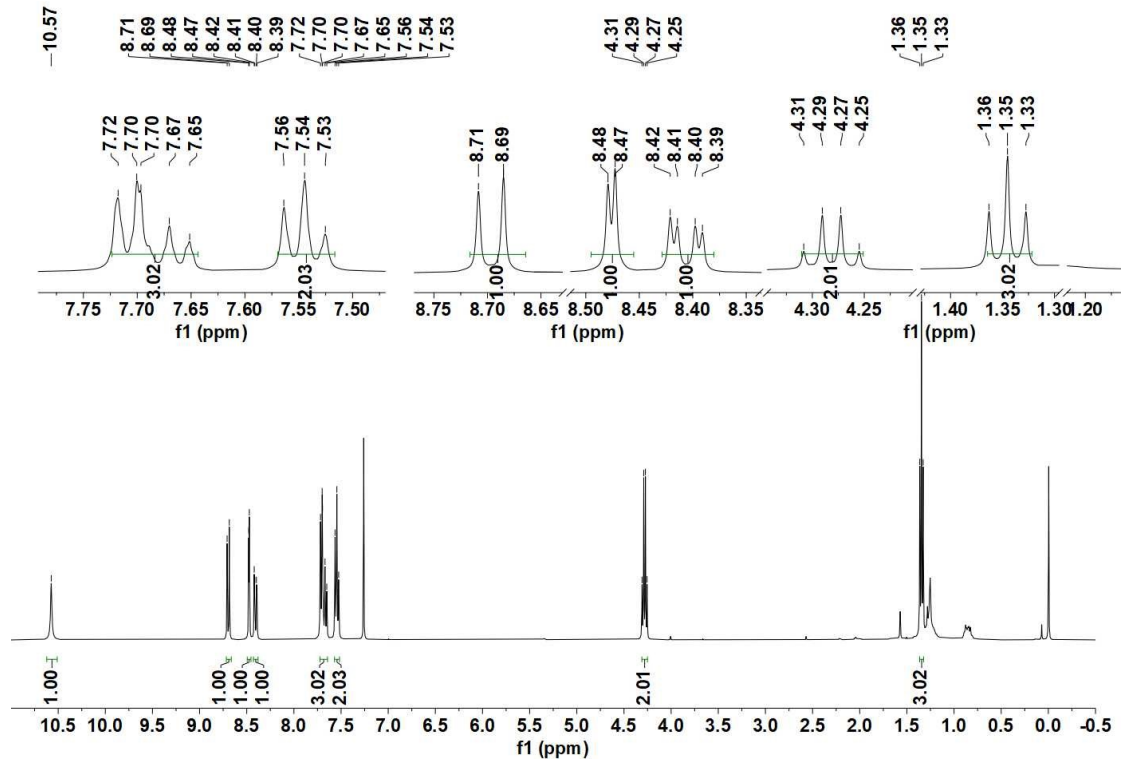


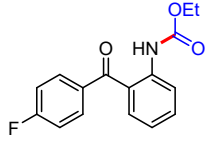
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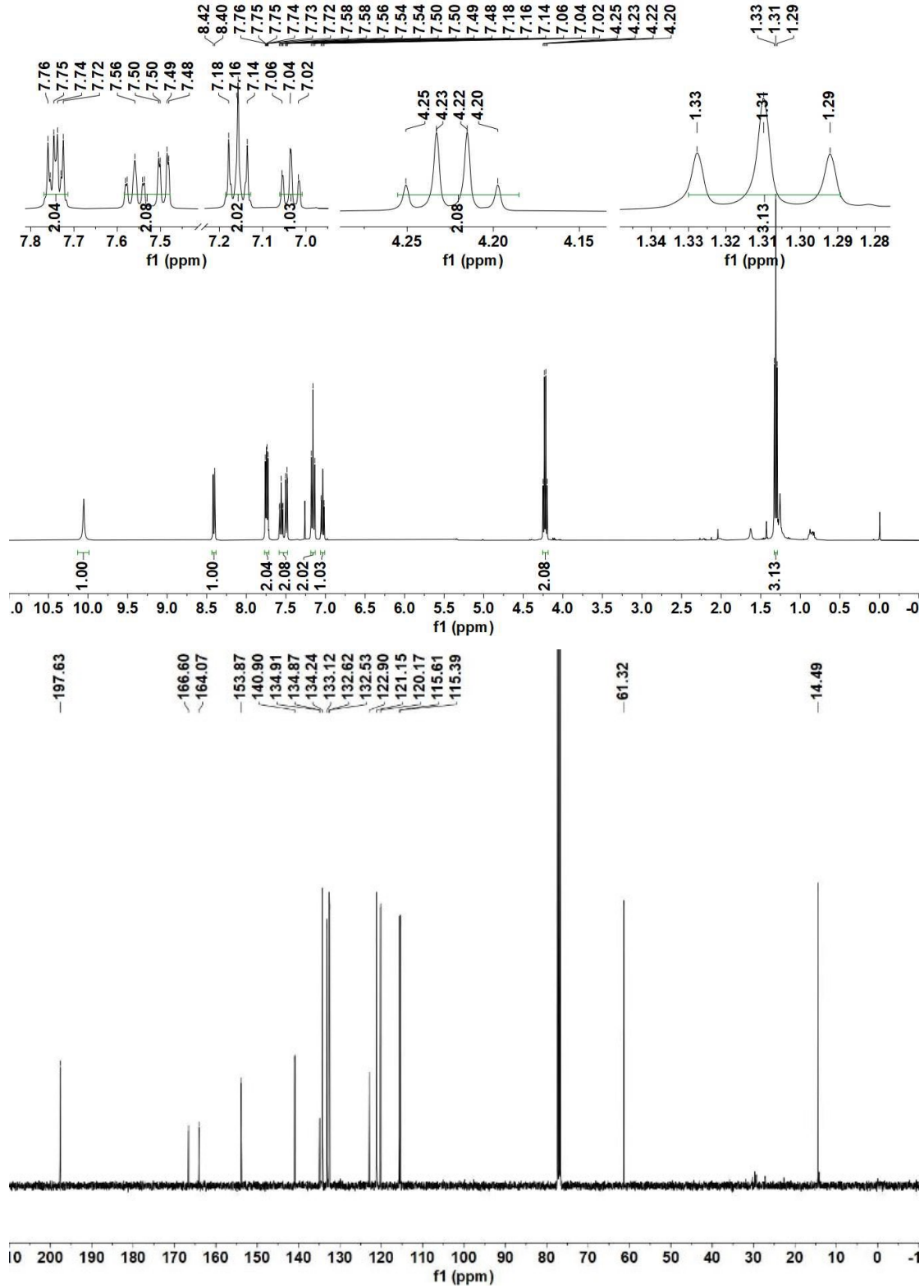


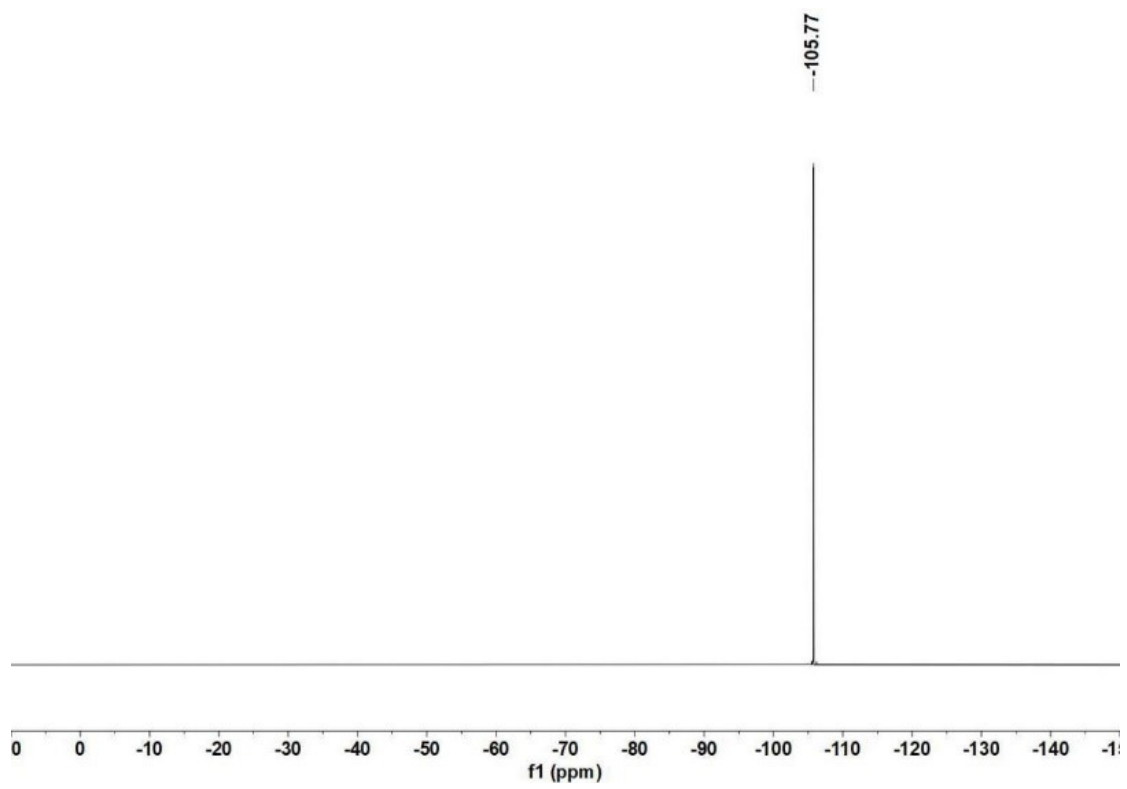
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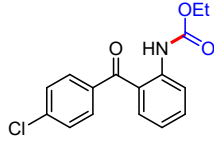




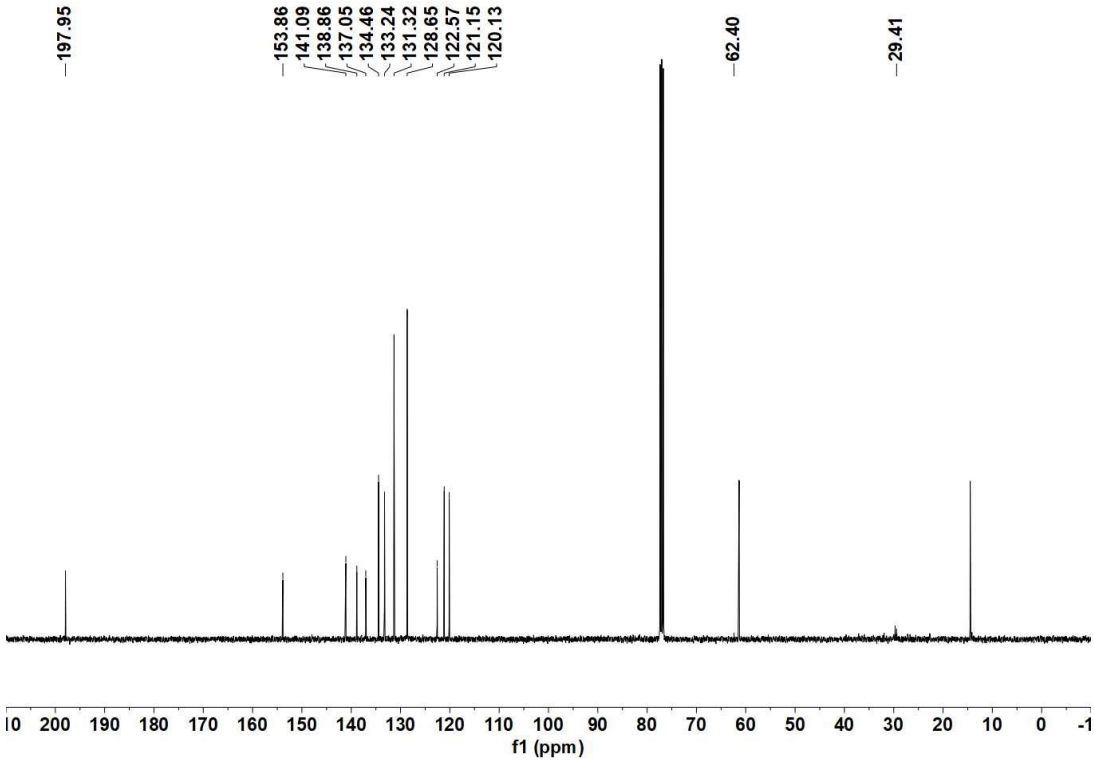
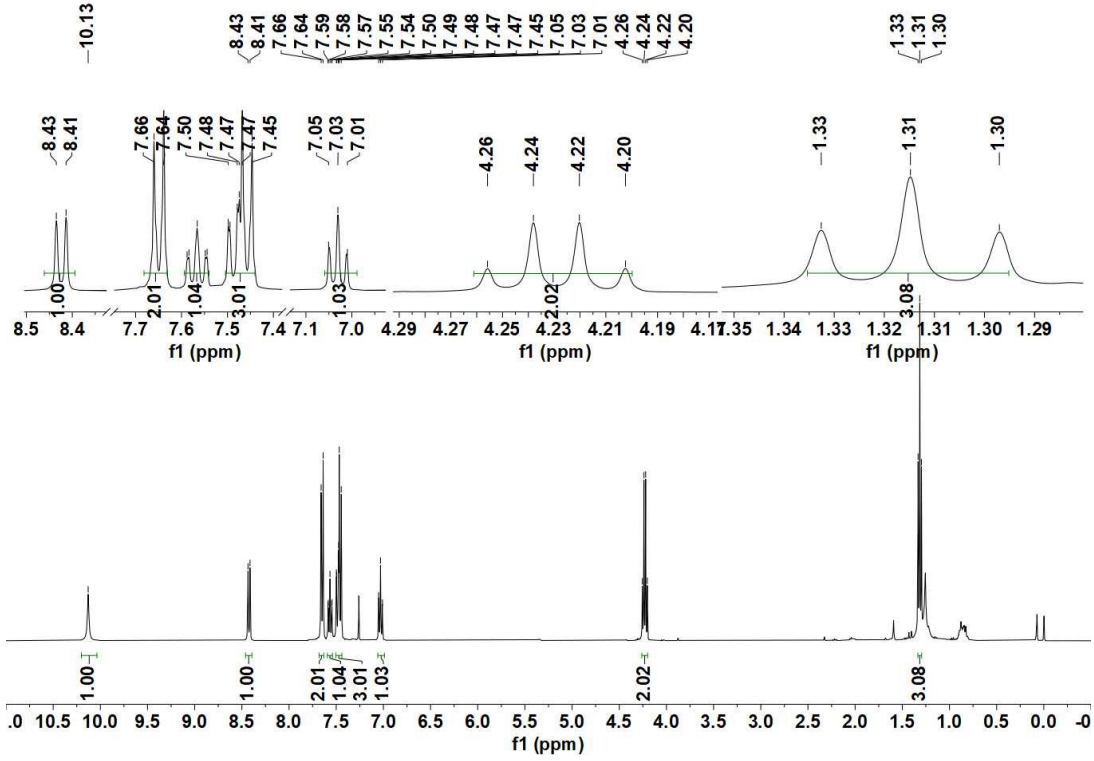
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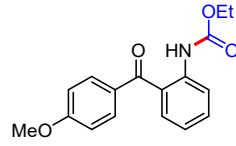




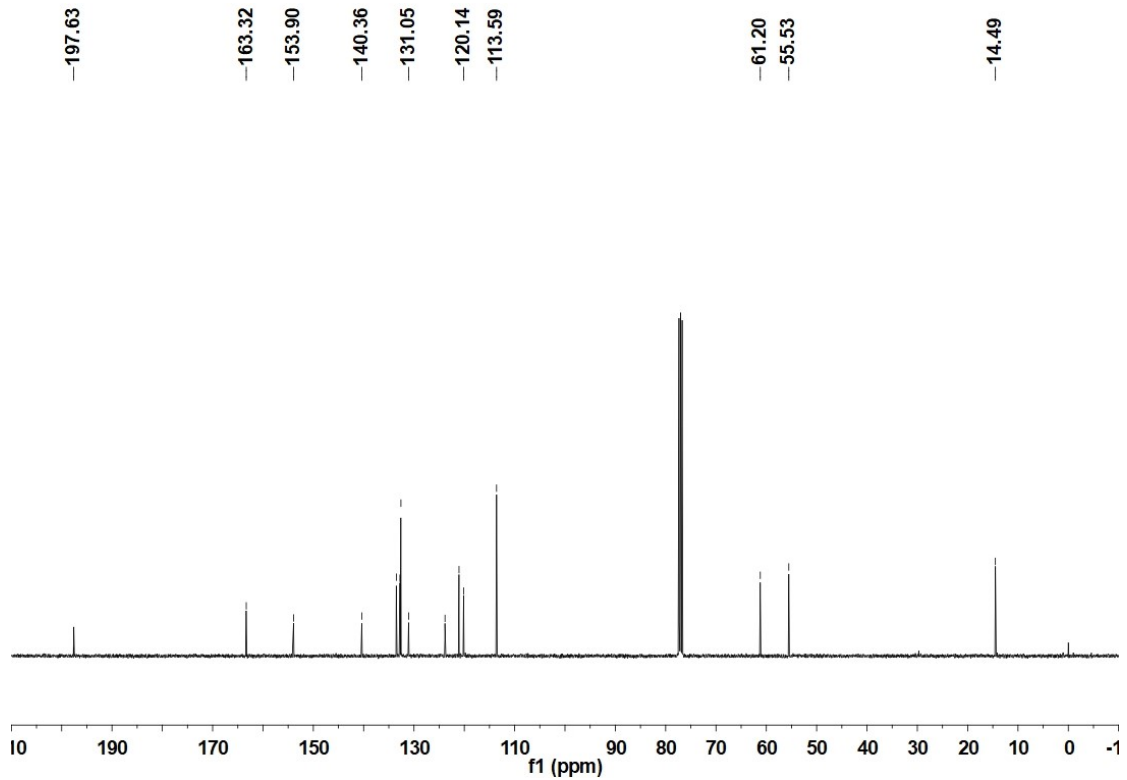
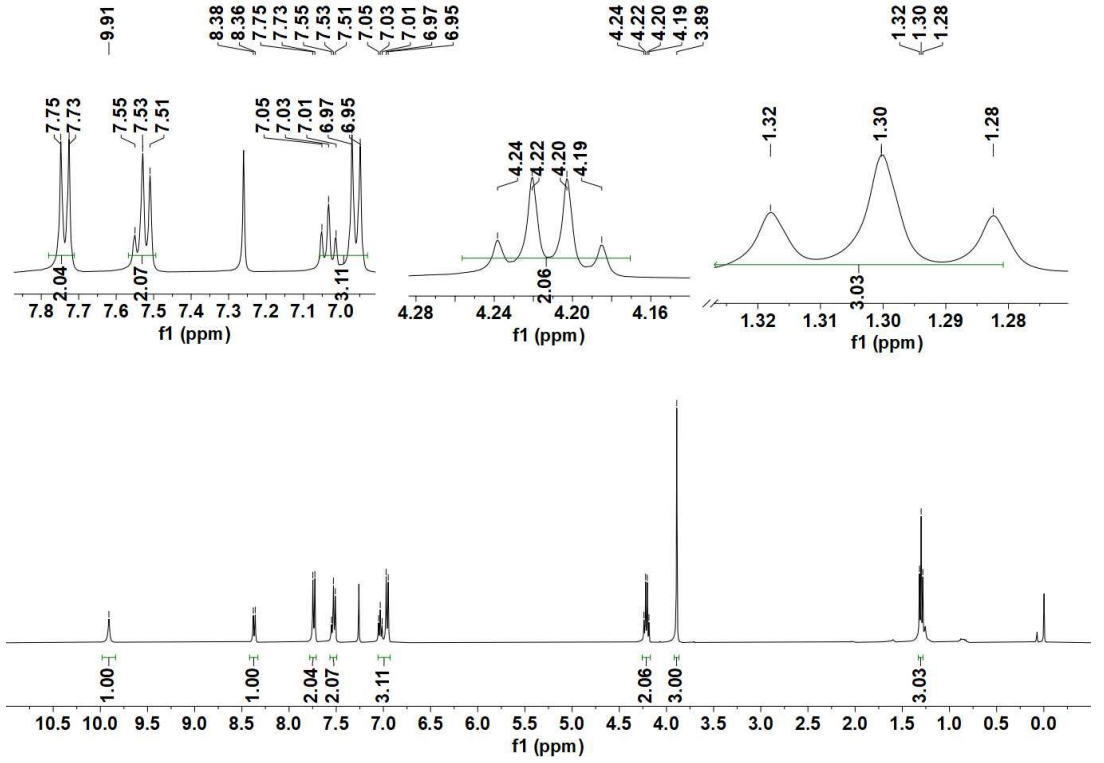


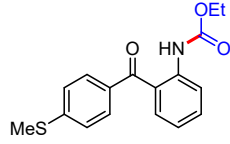
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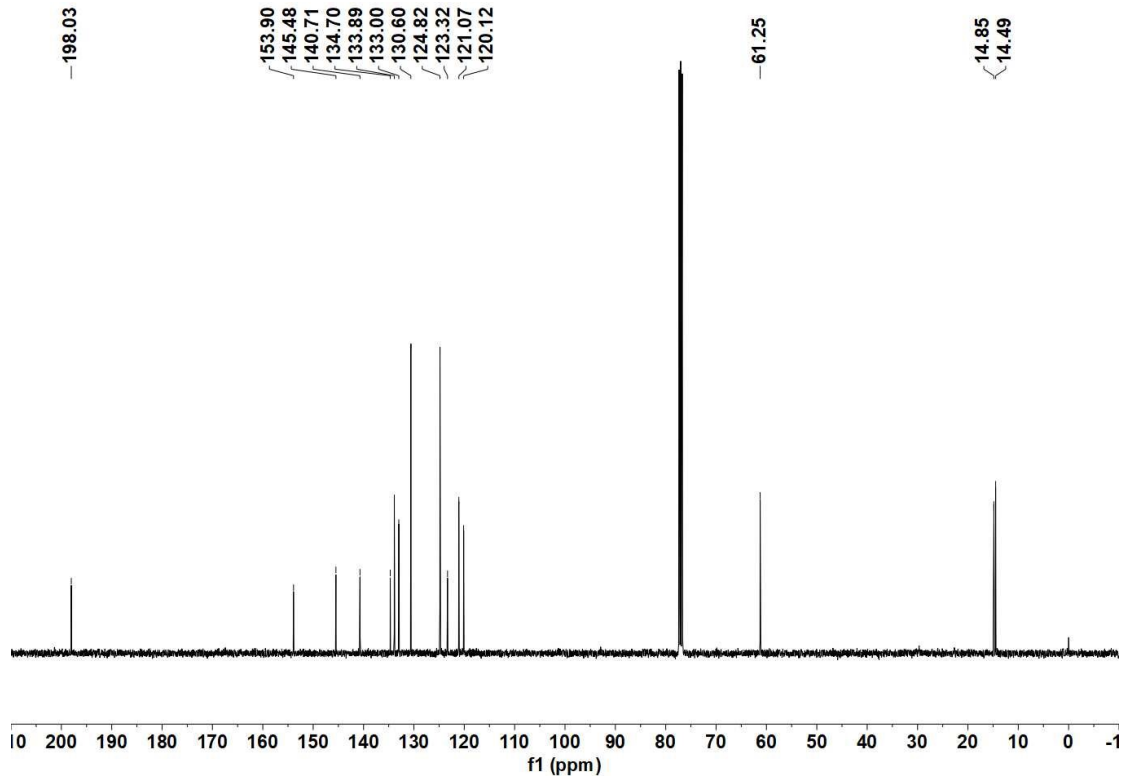
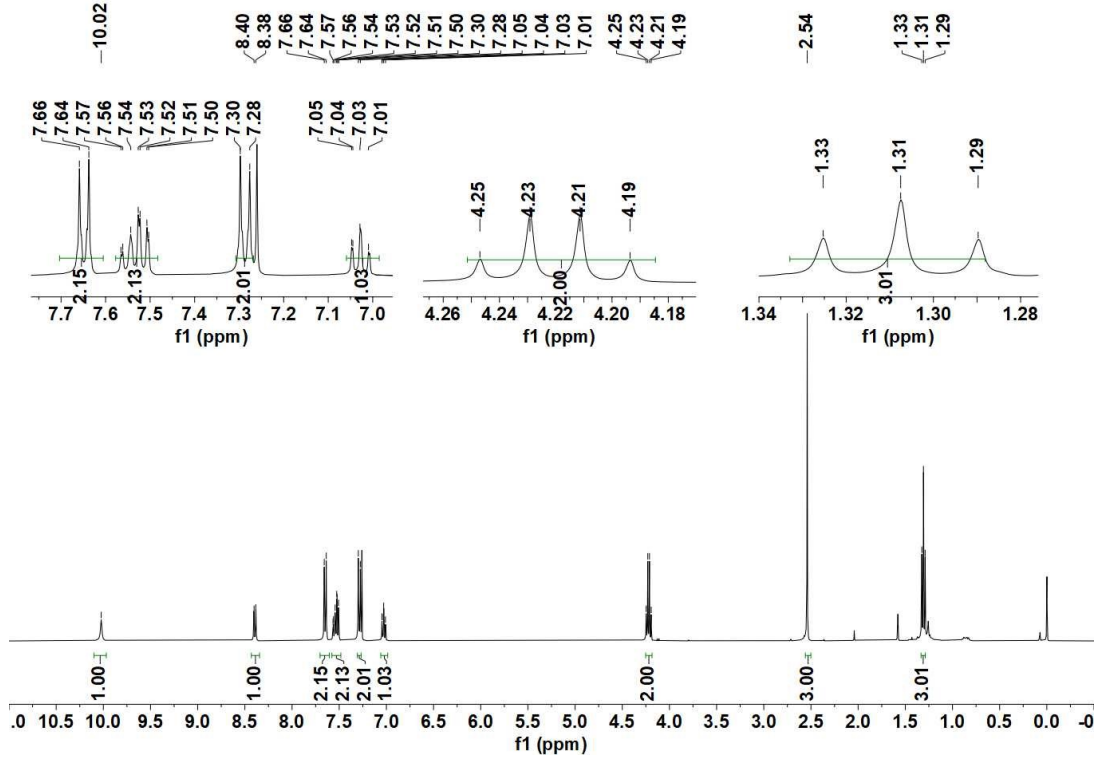


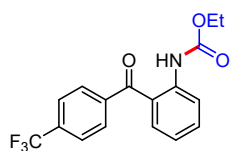
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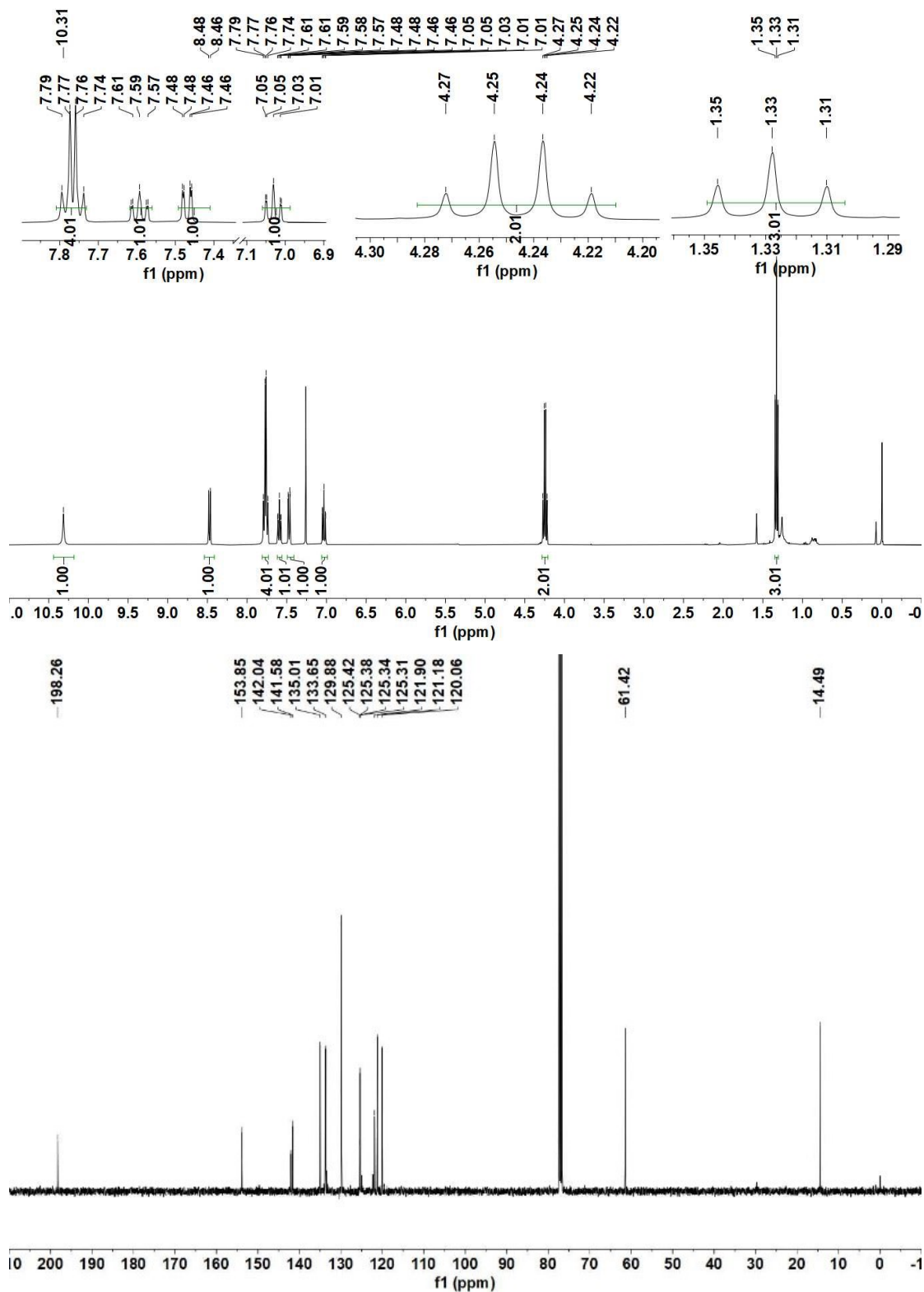


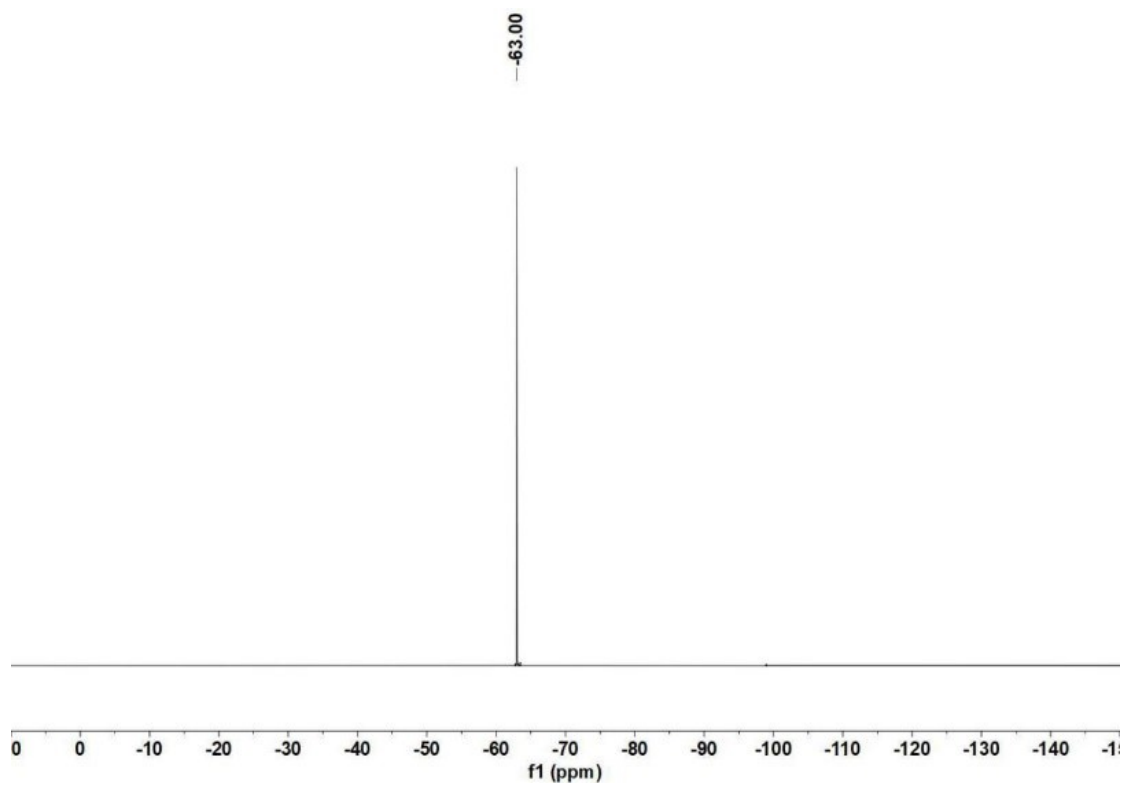
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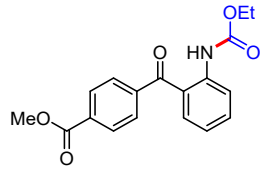




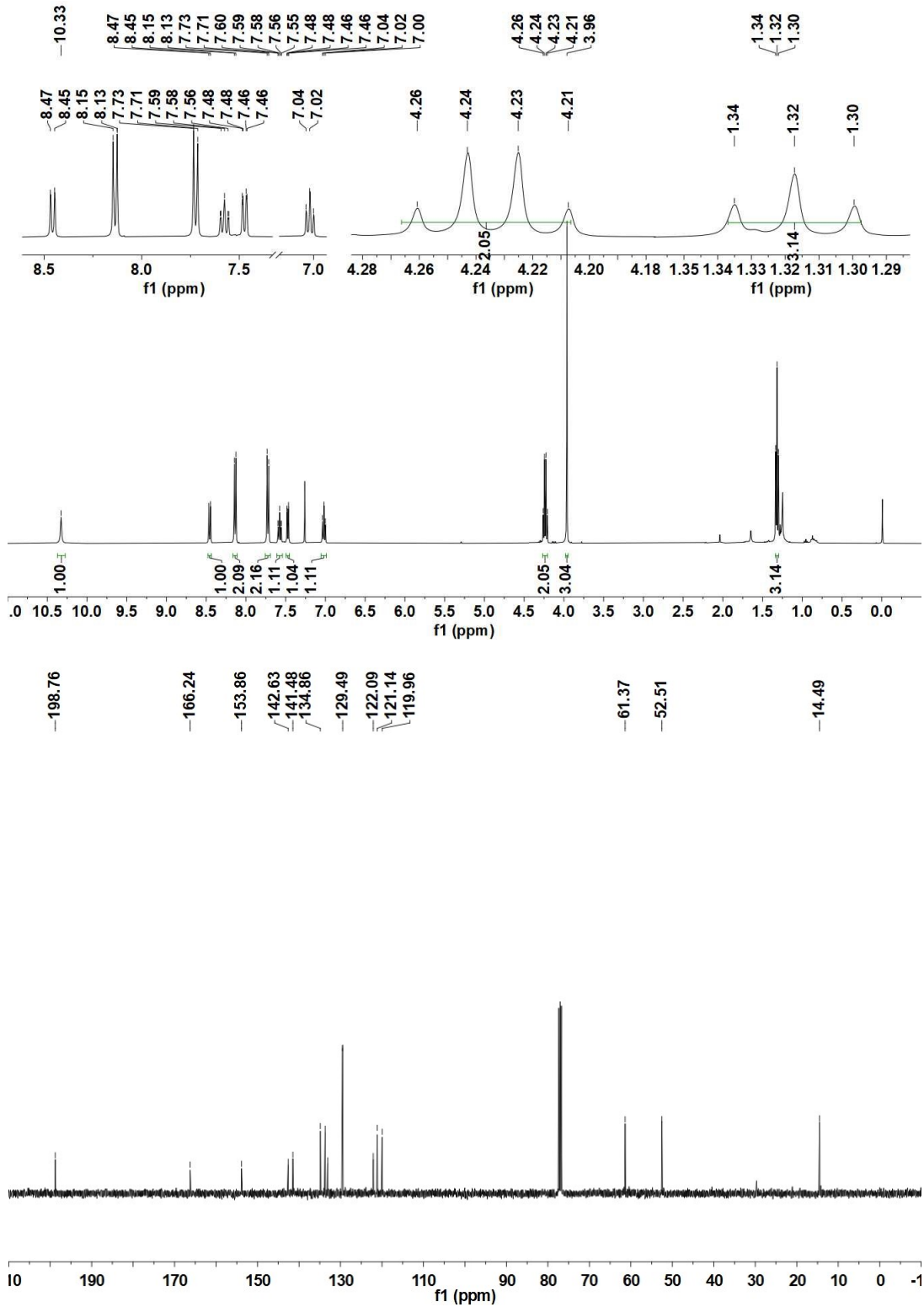
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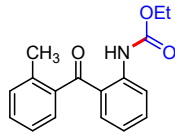




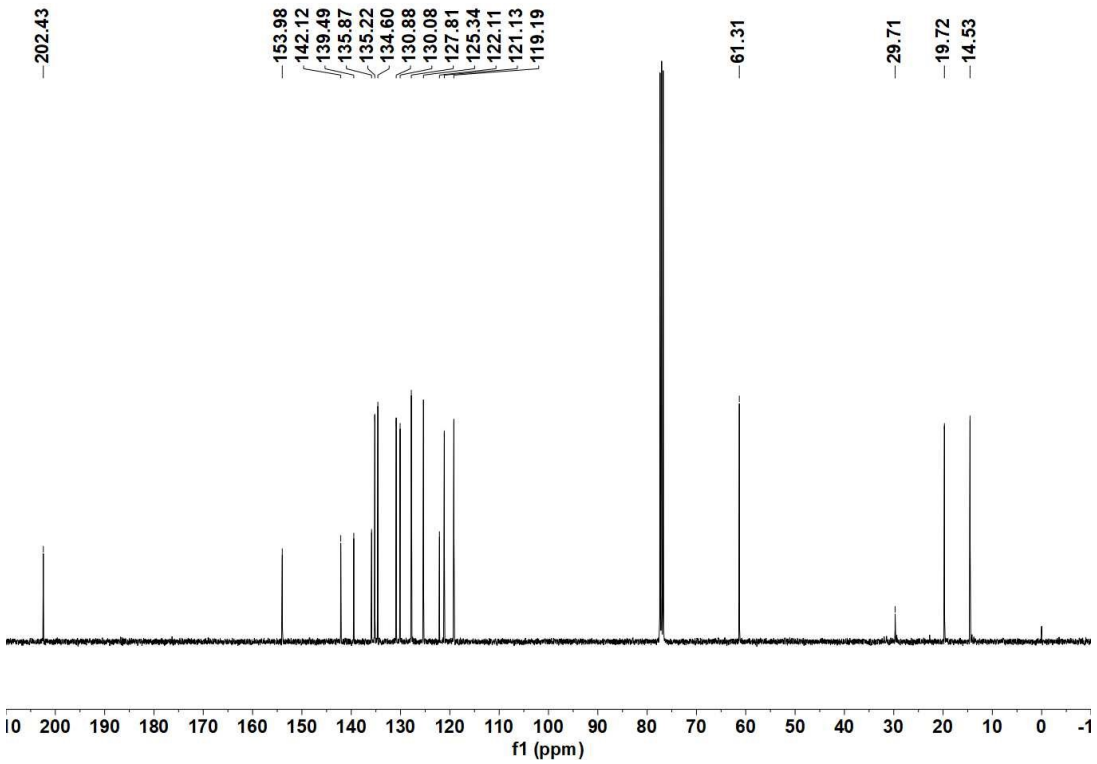
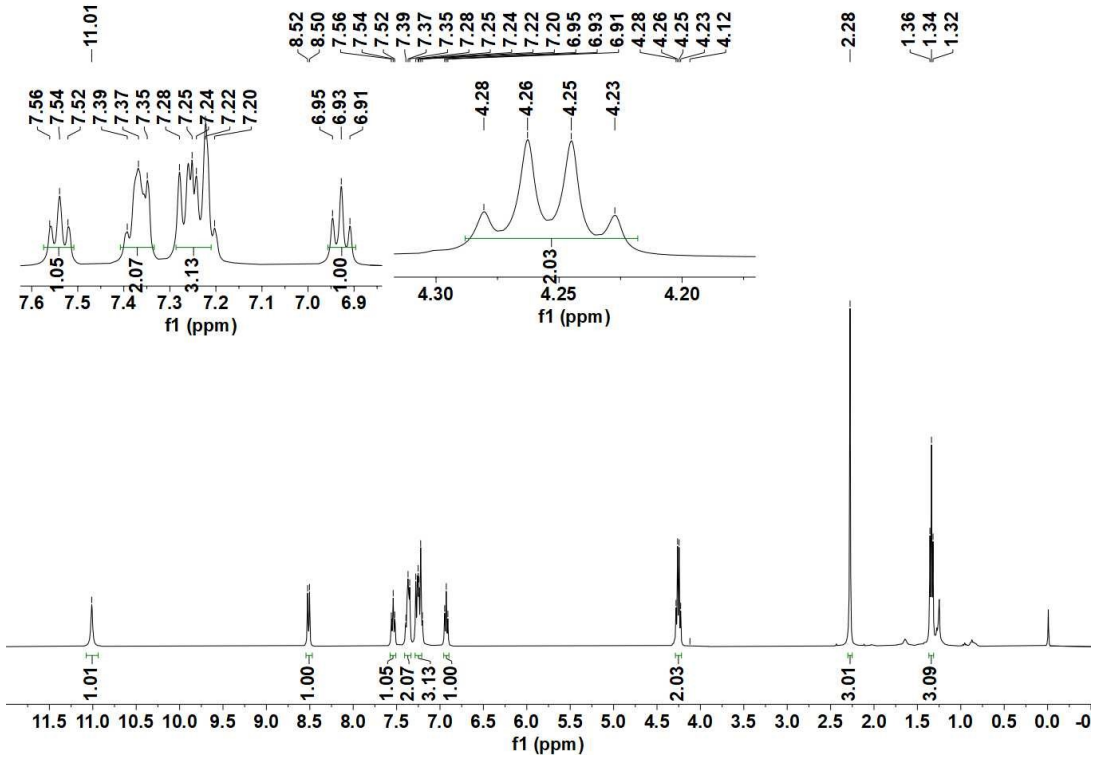


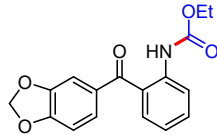
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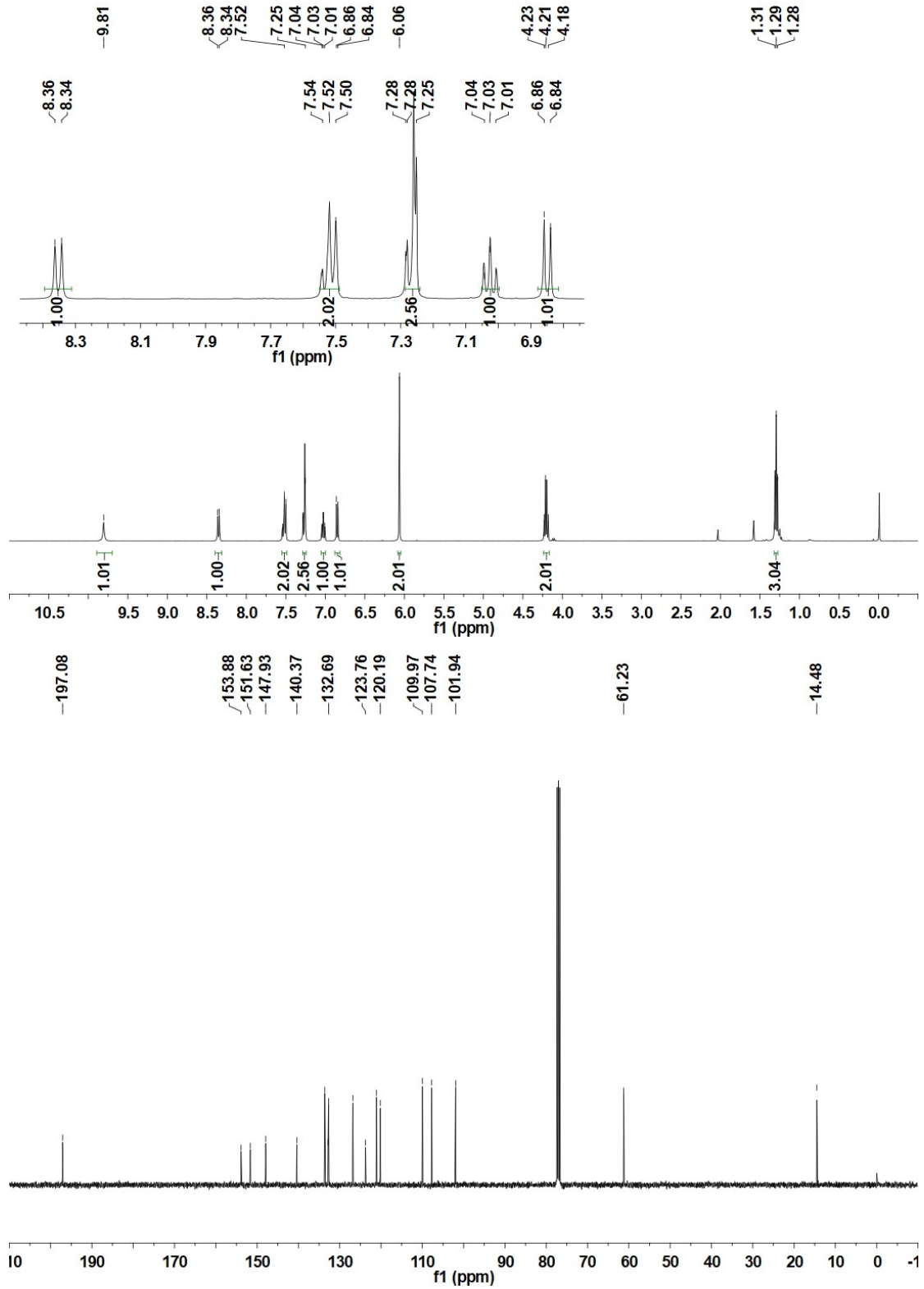


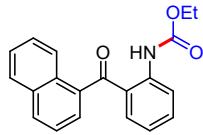
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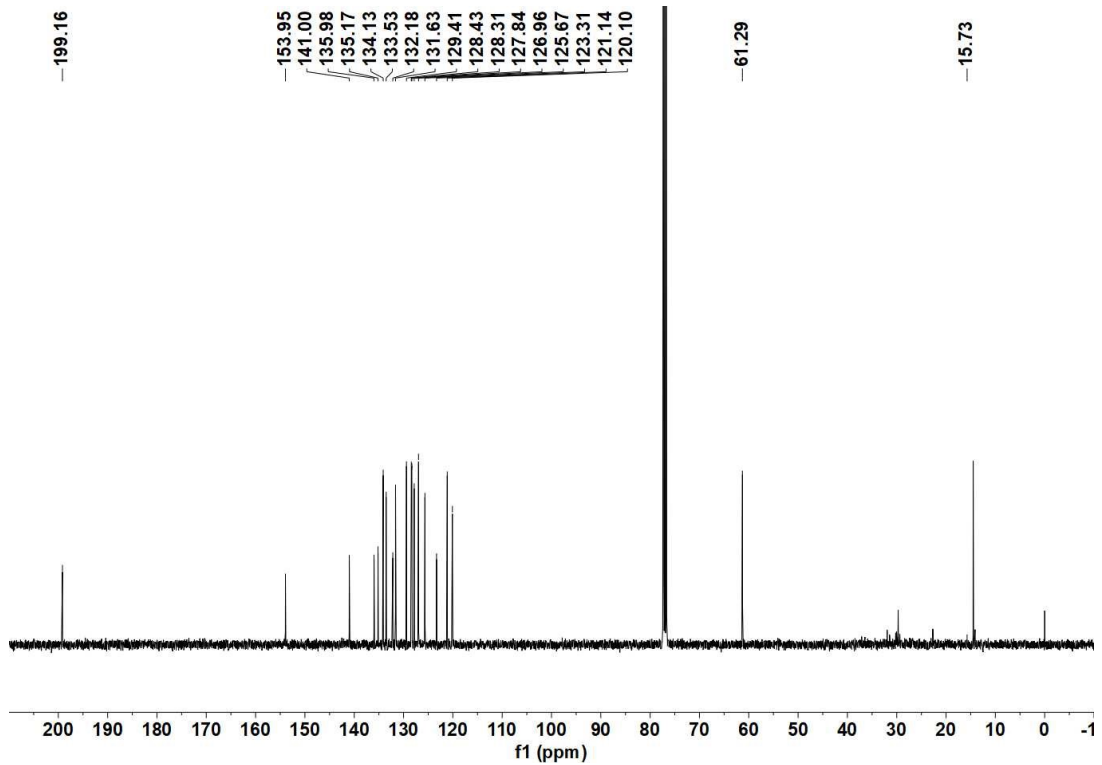
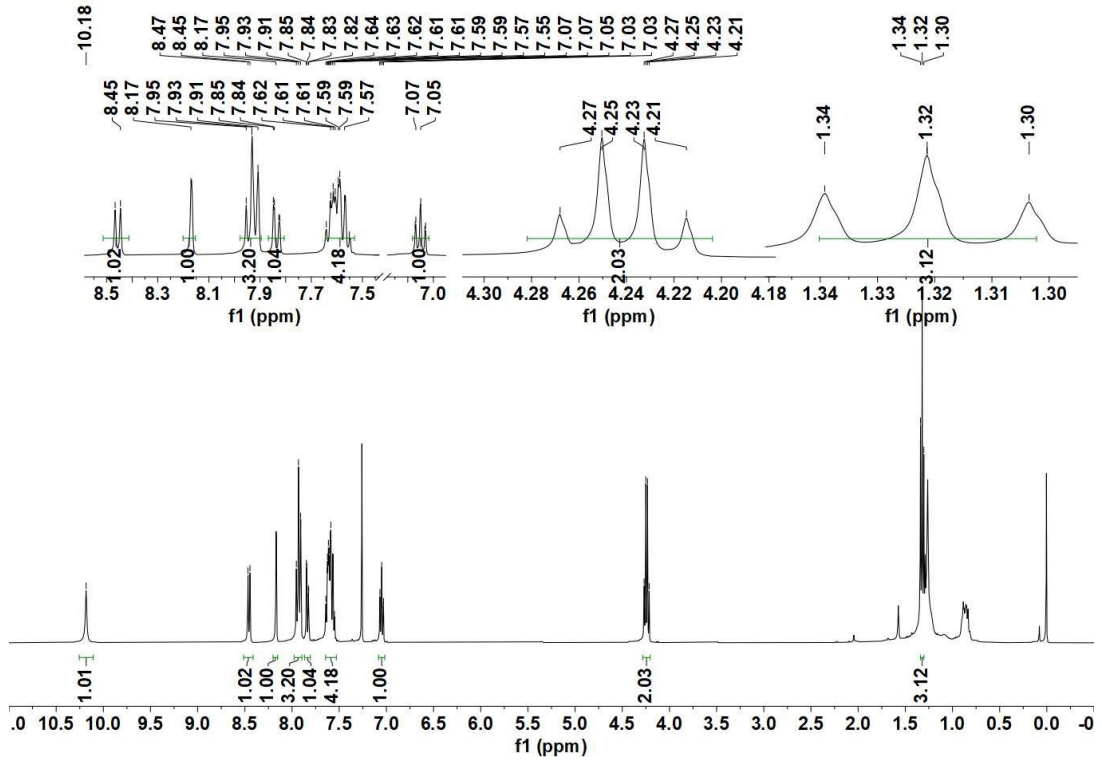


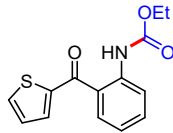
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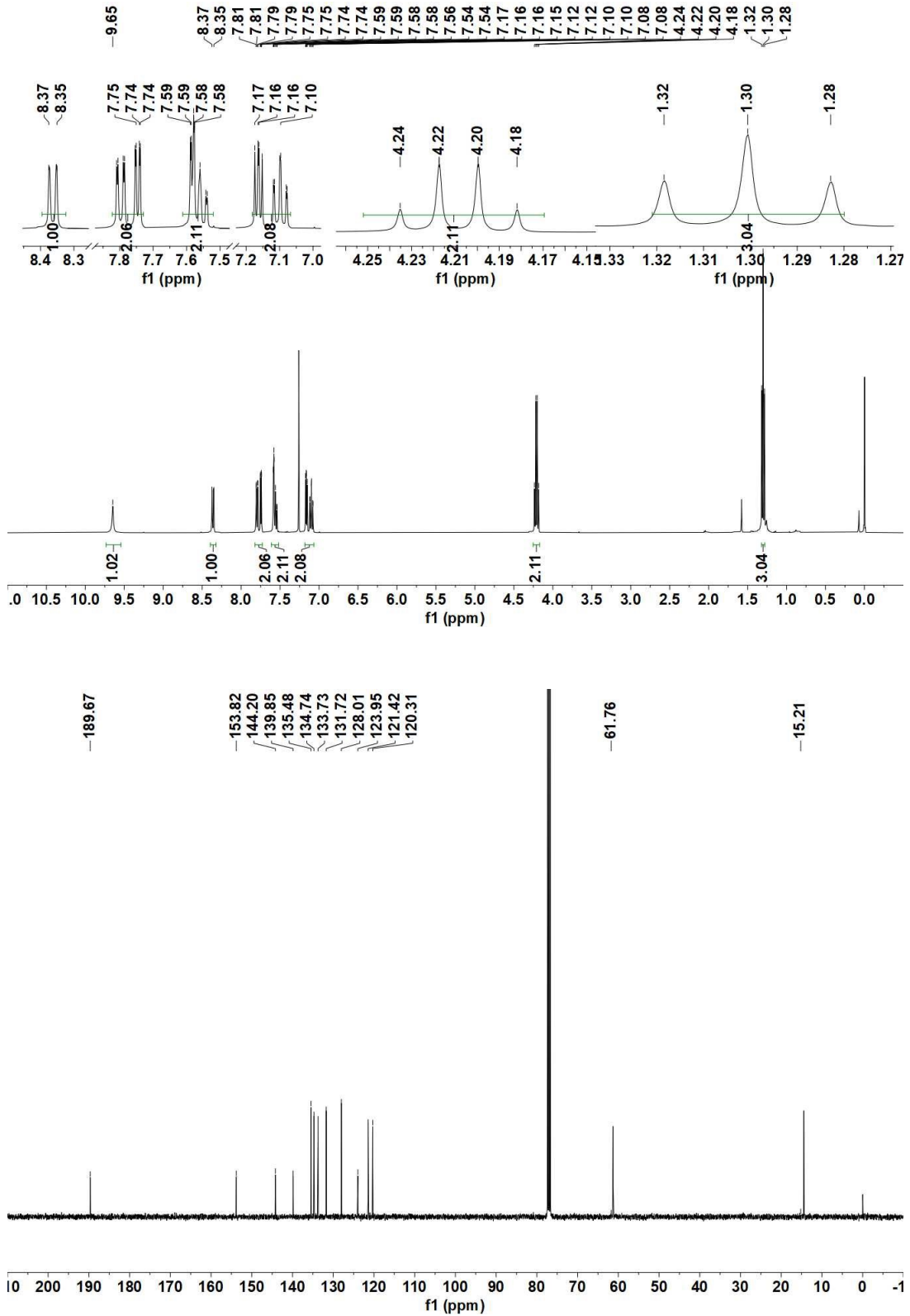


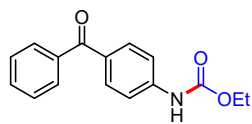
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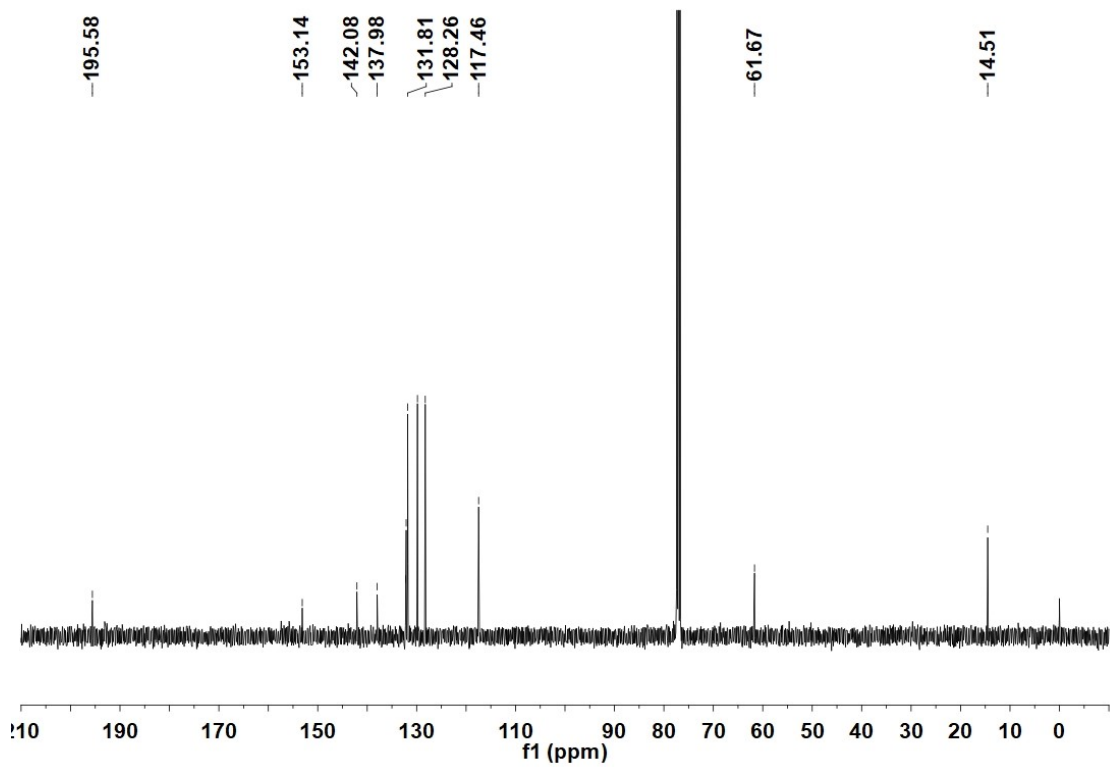
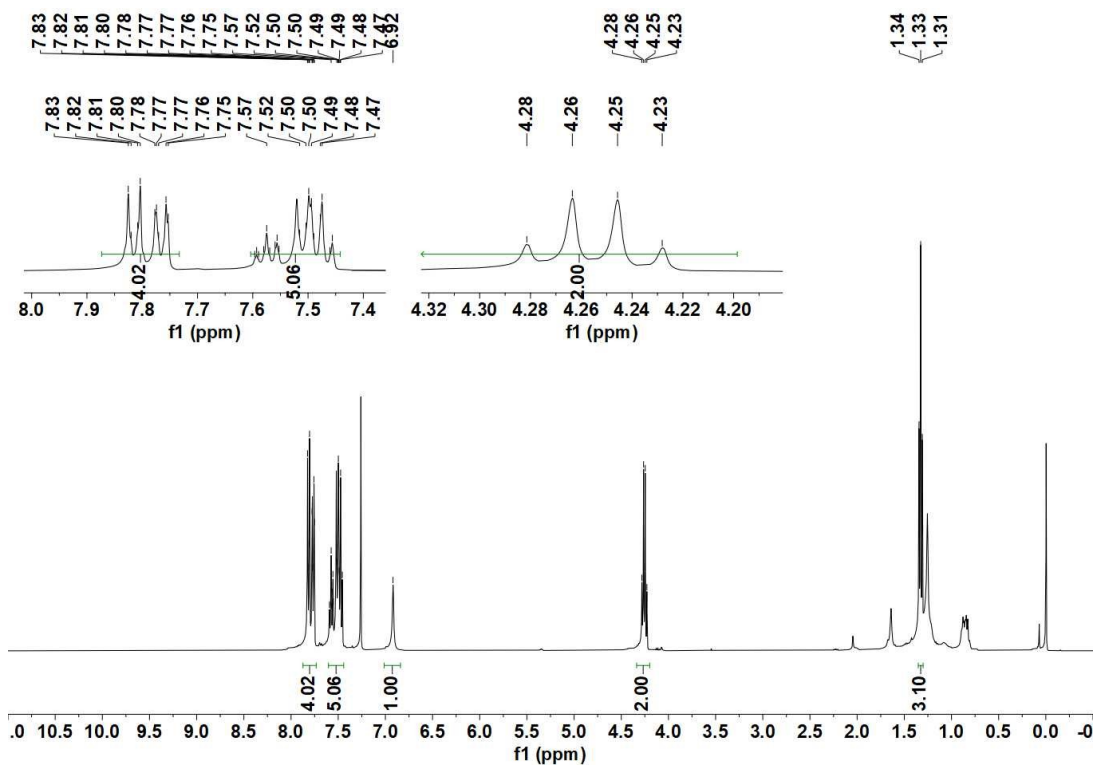


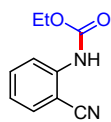
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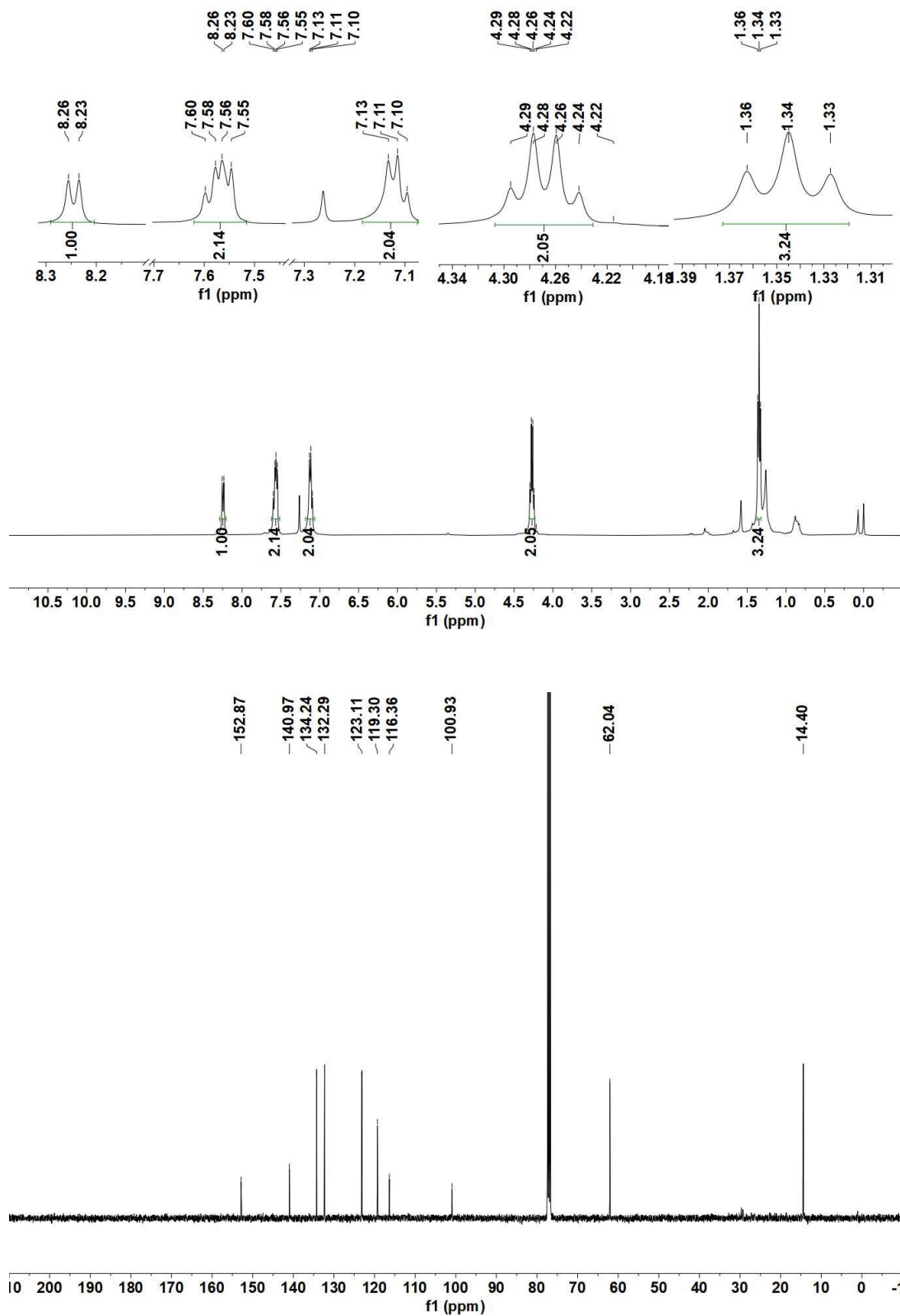


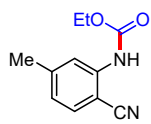
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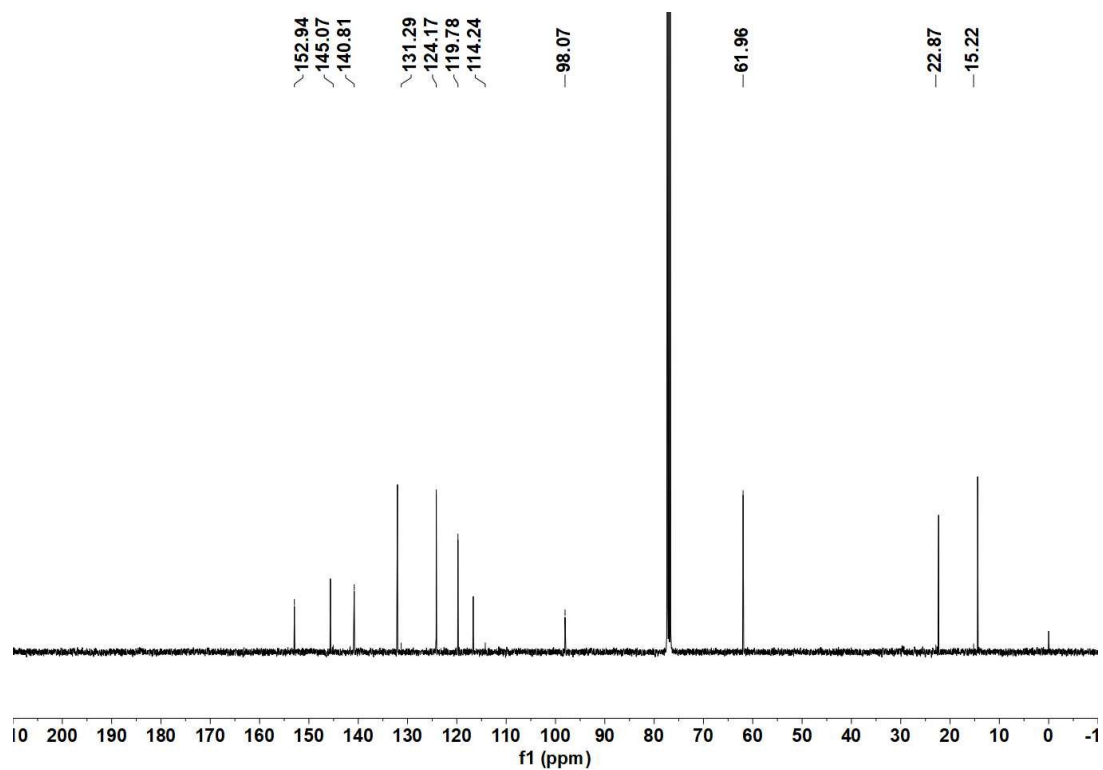
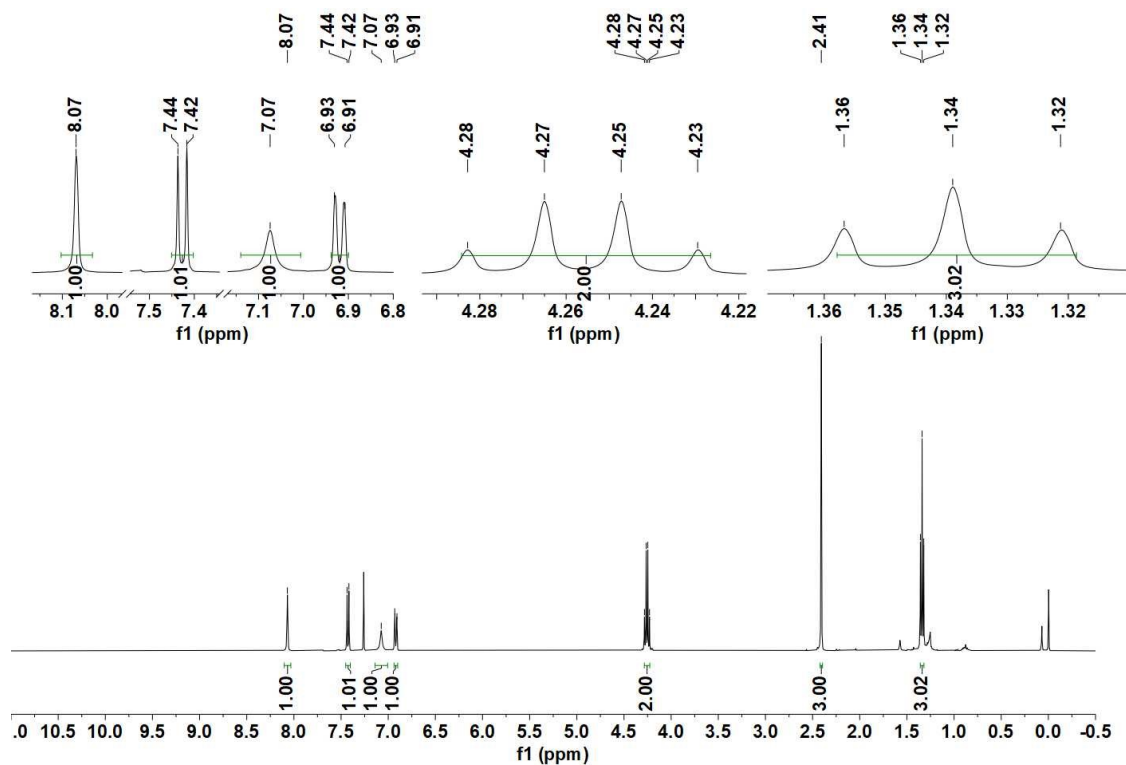


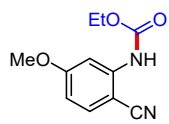
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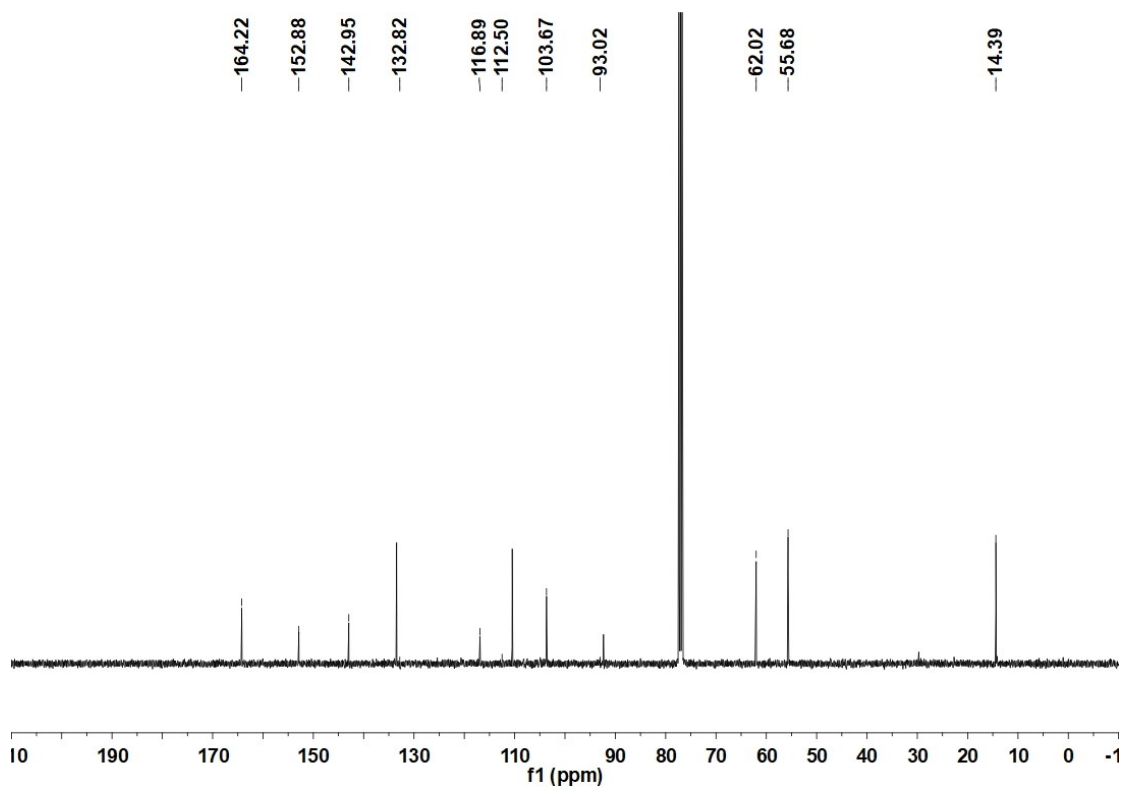
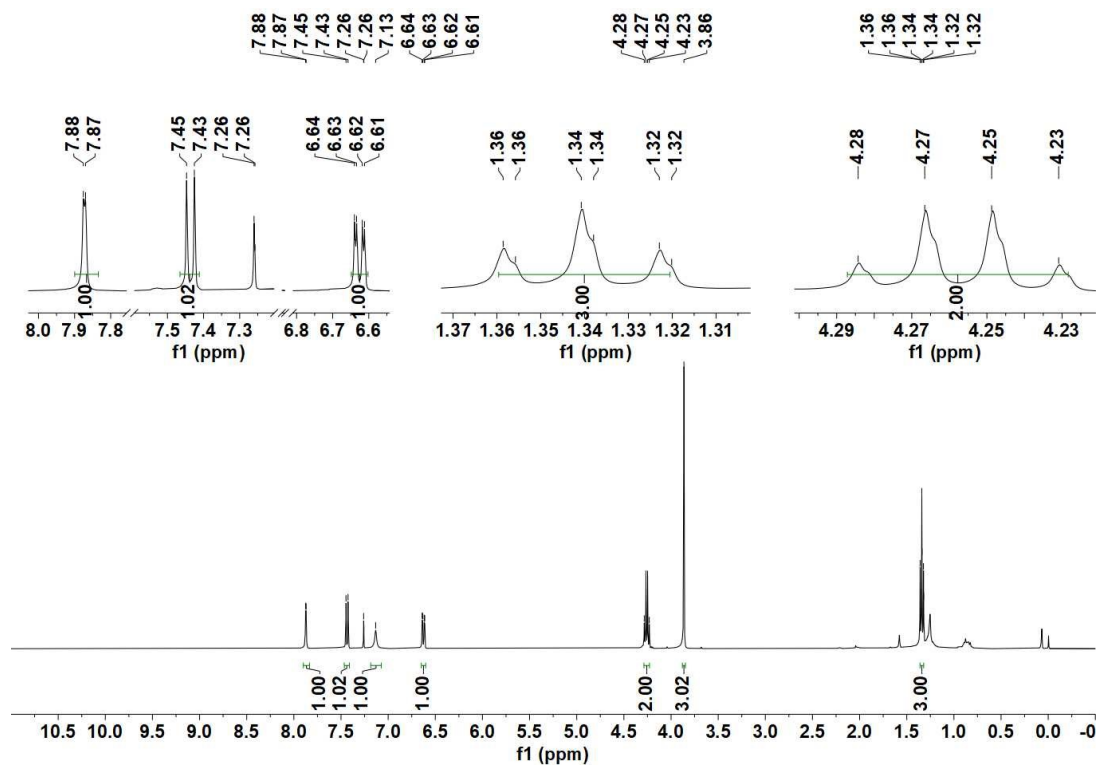


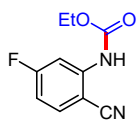
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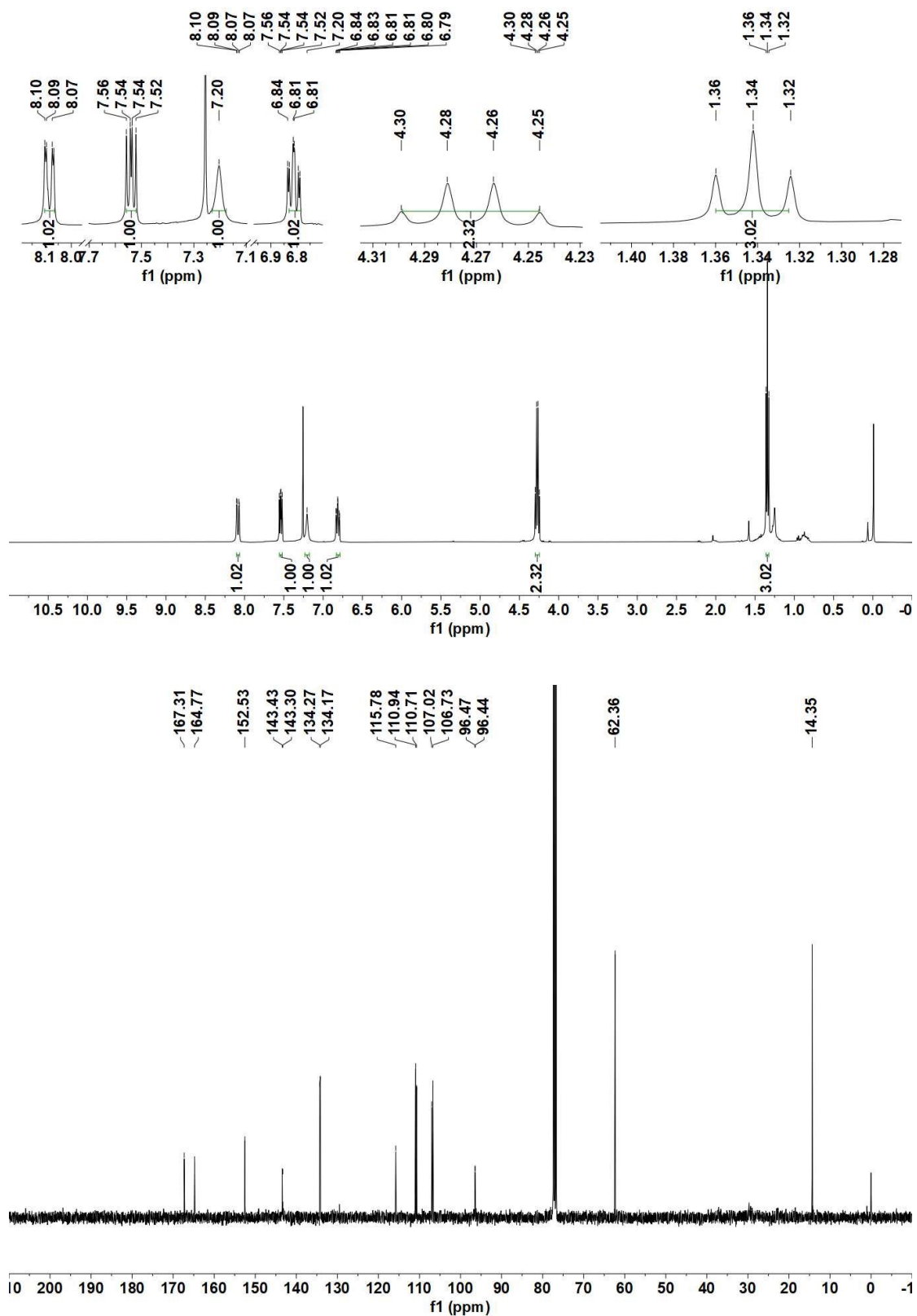


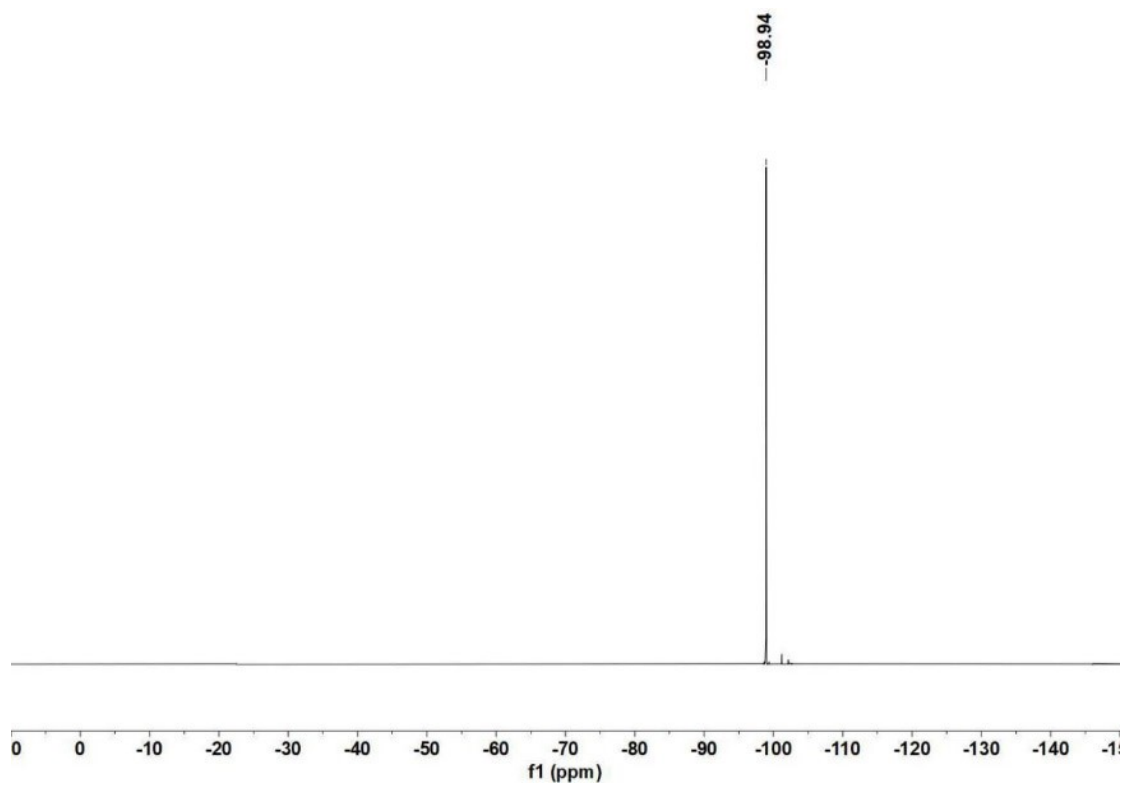
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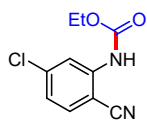




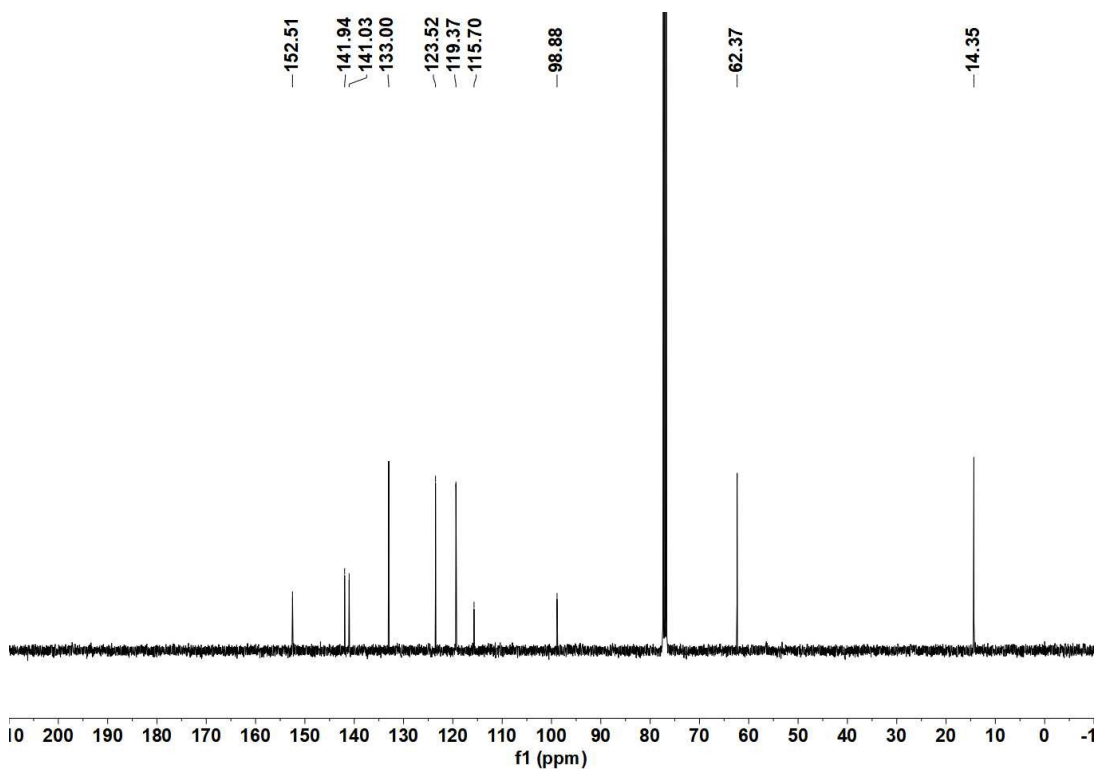
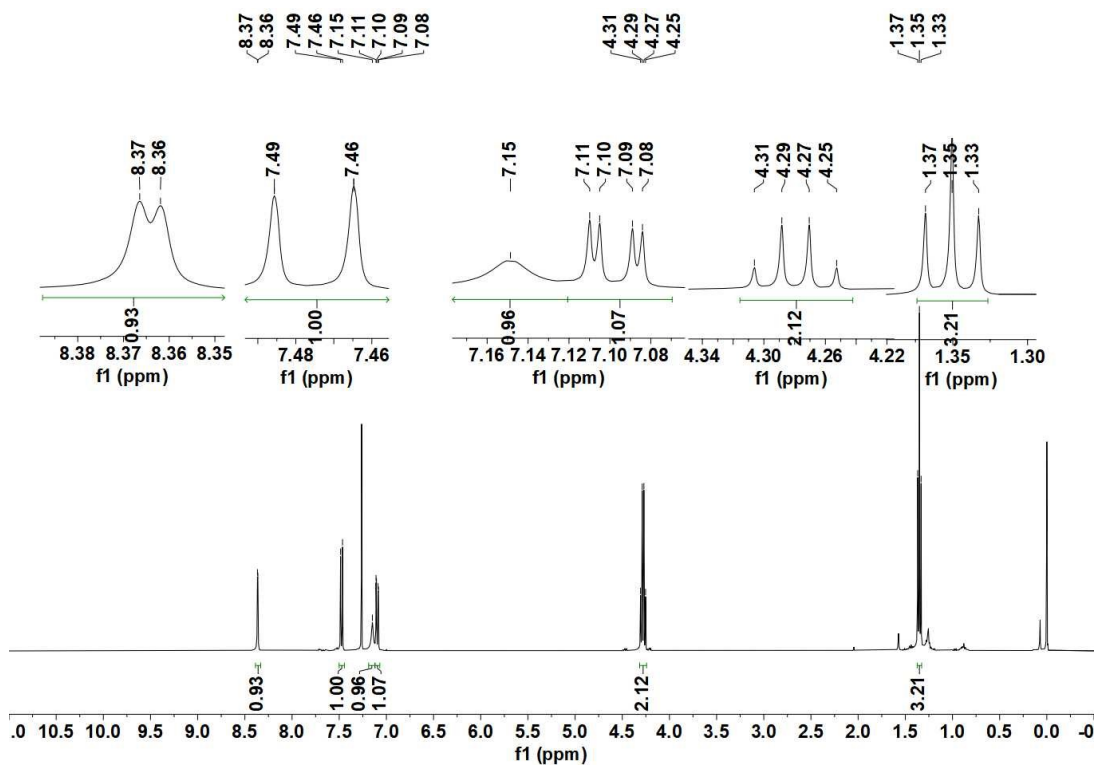
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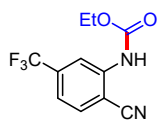




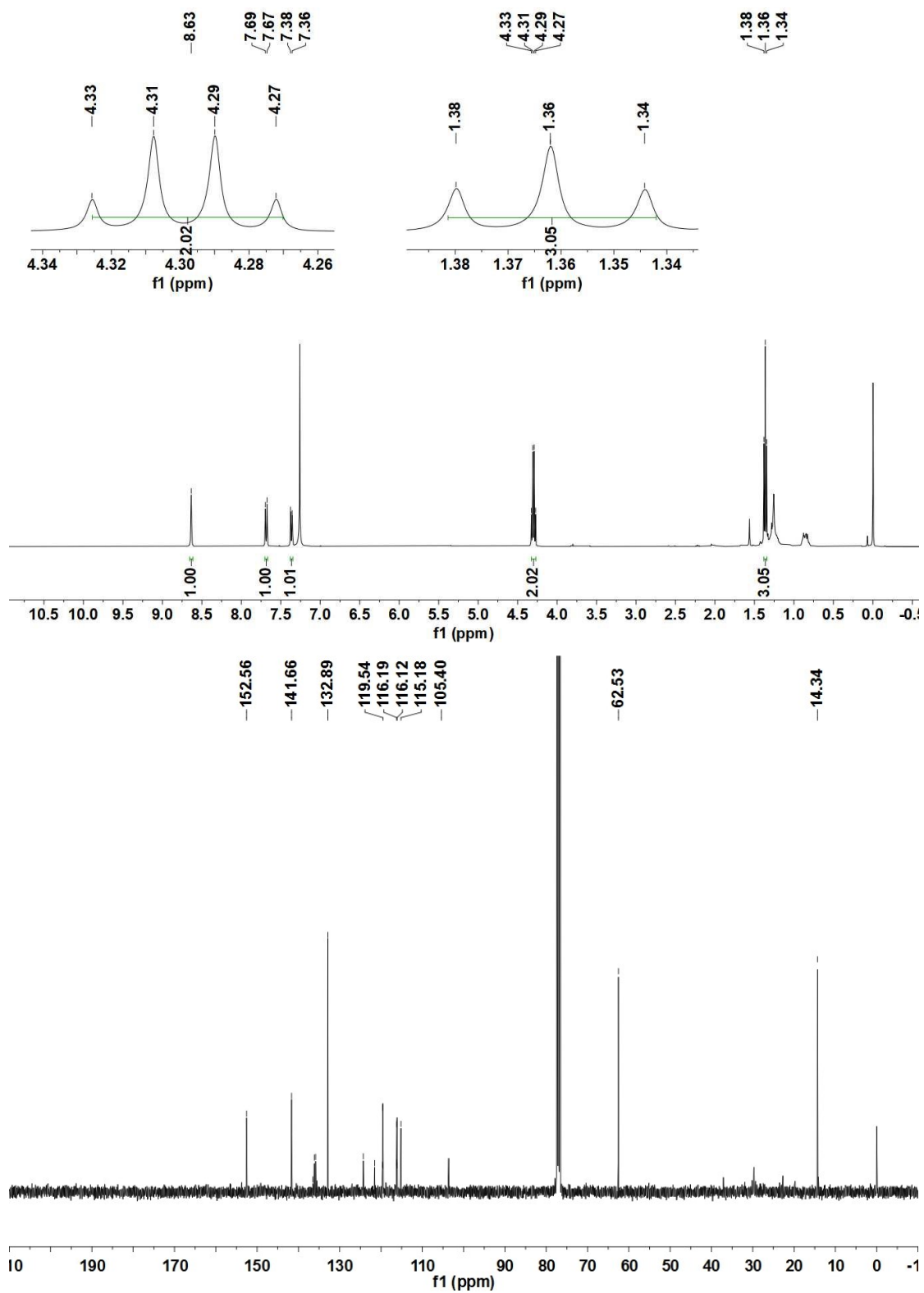


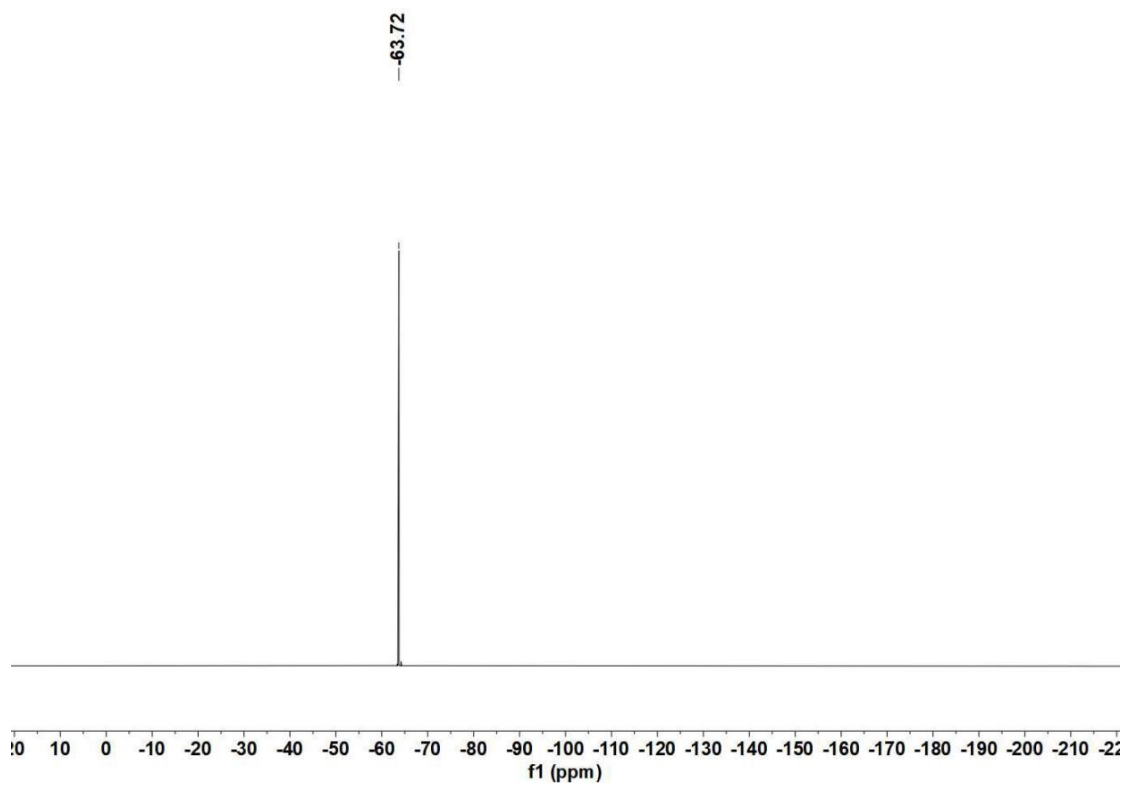
(5e)

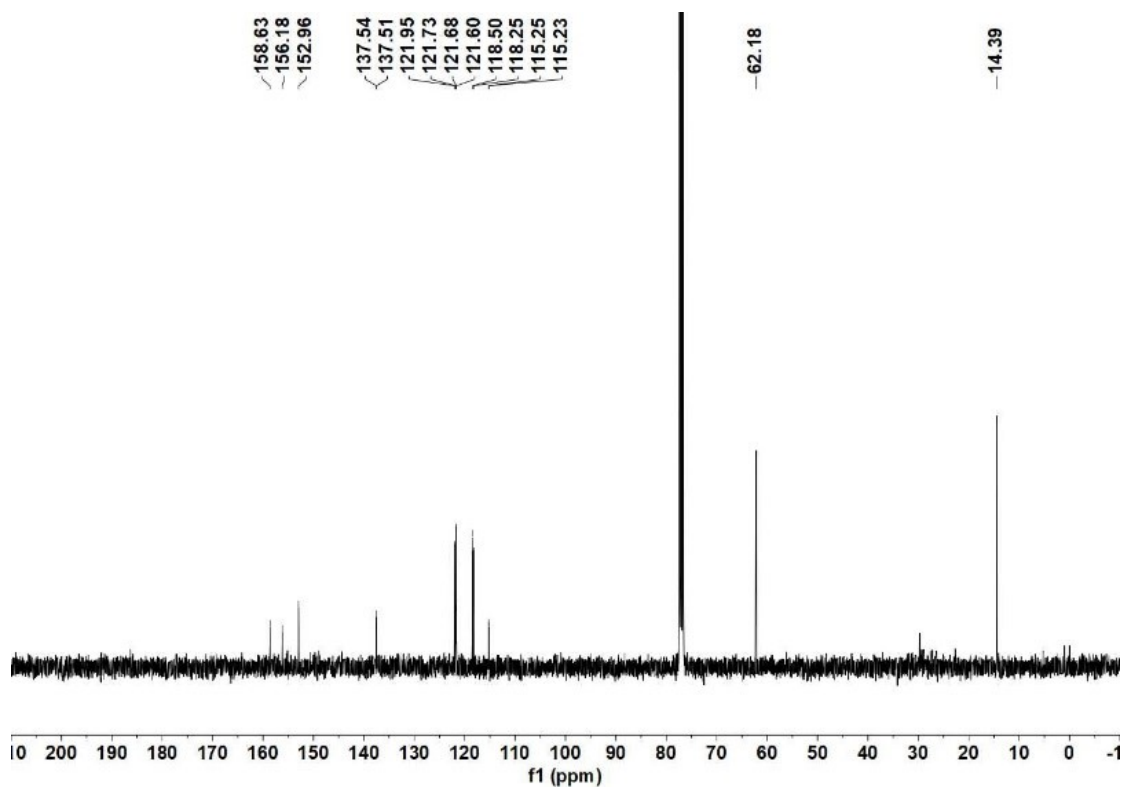
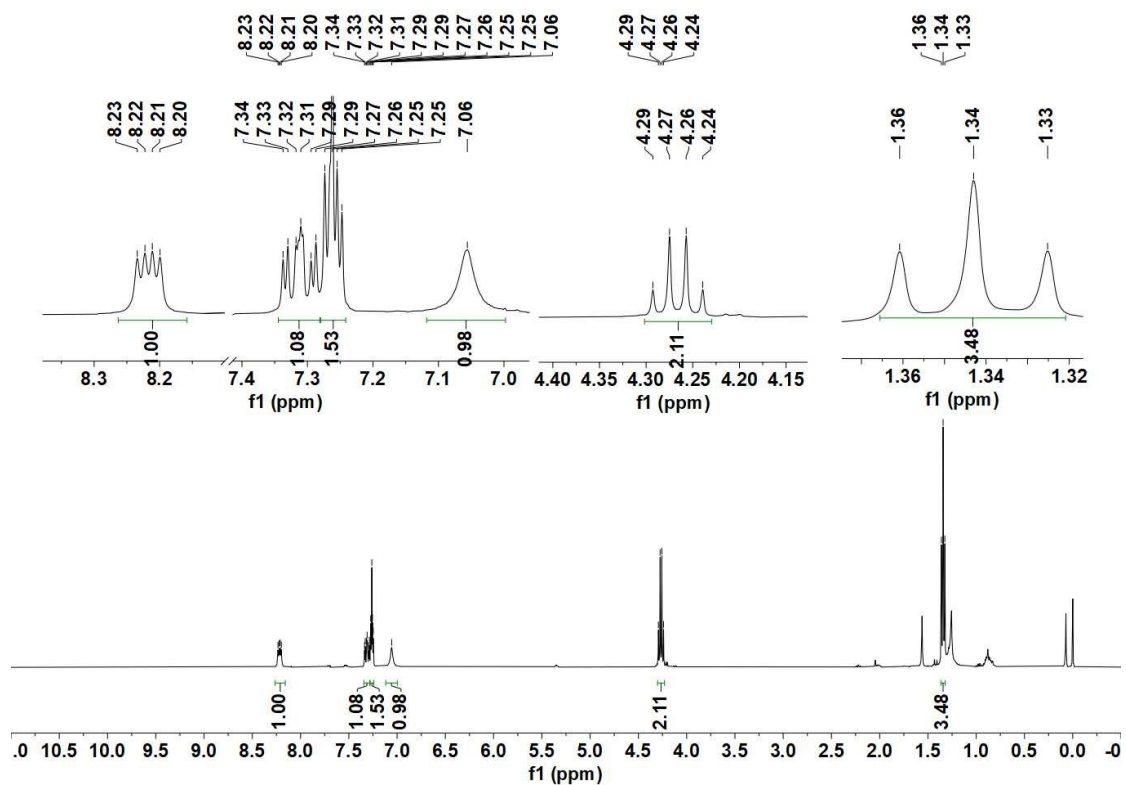
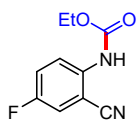


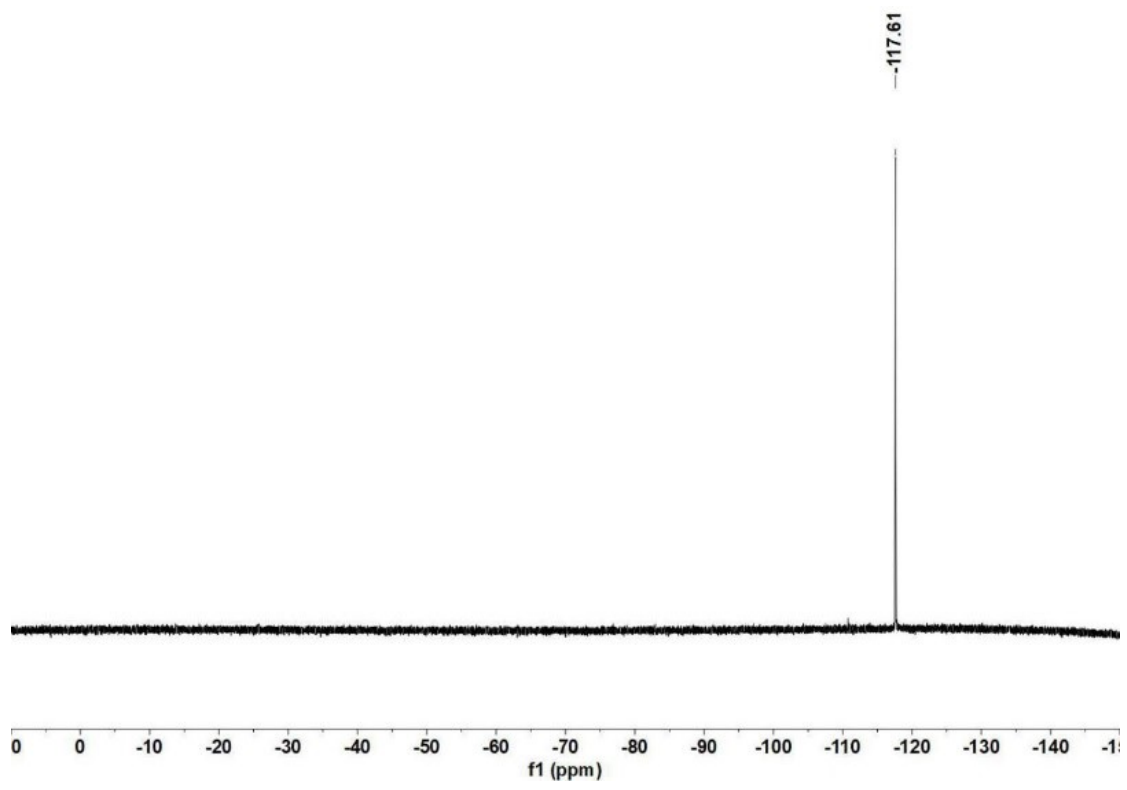


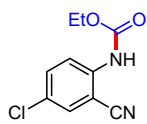
(5f)



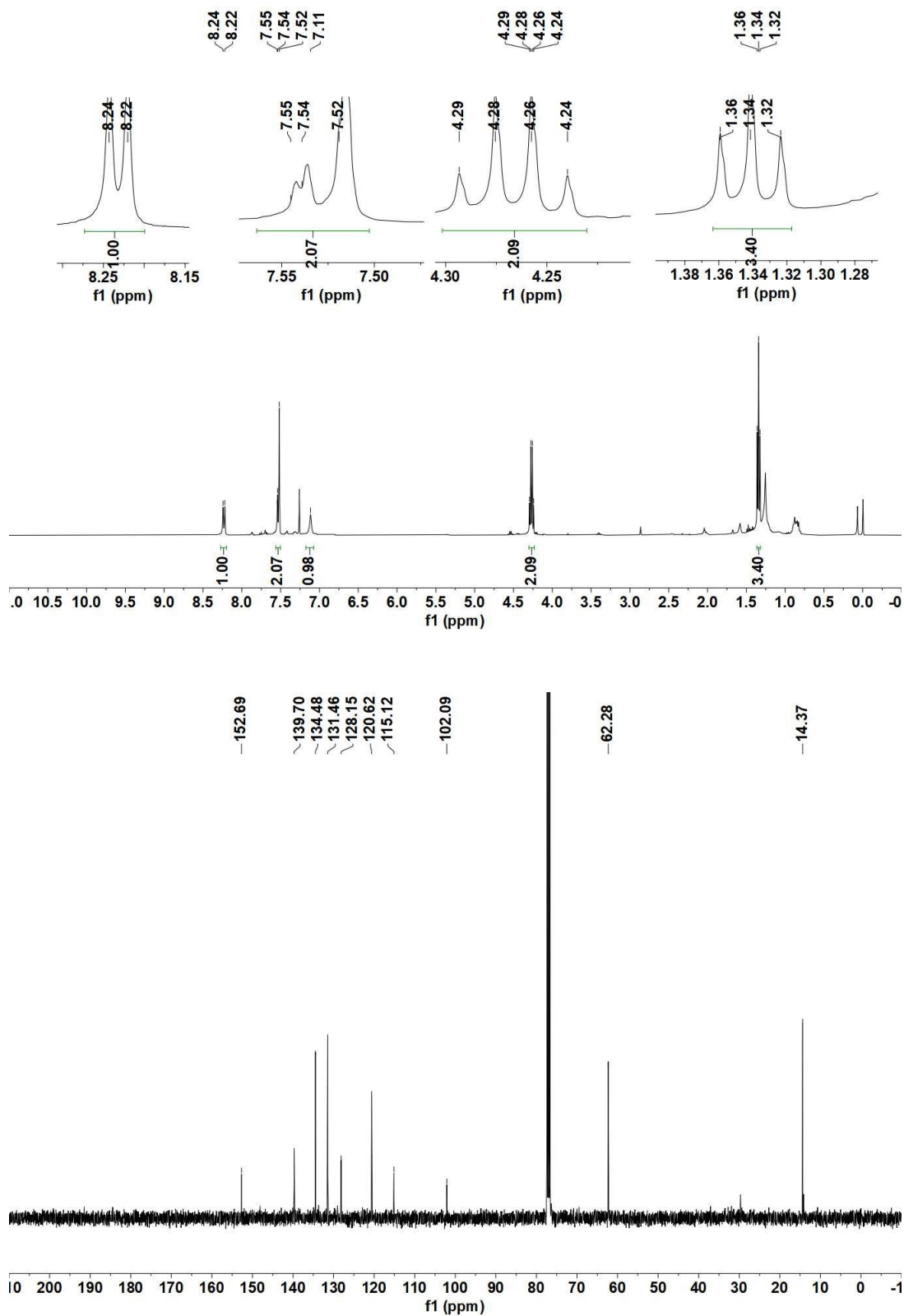


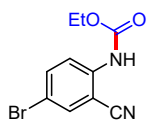




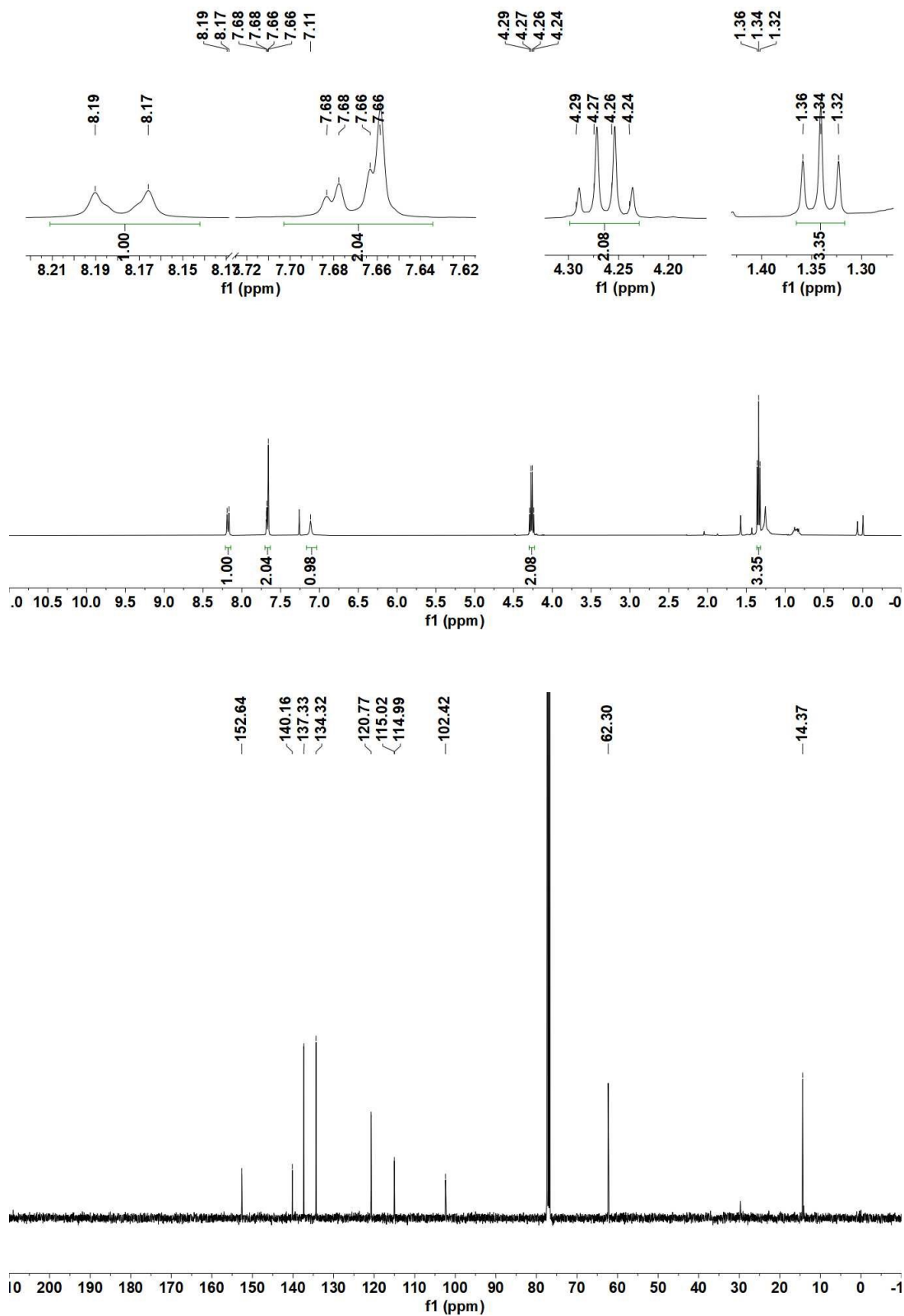


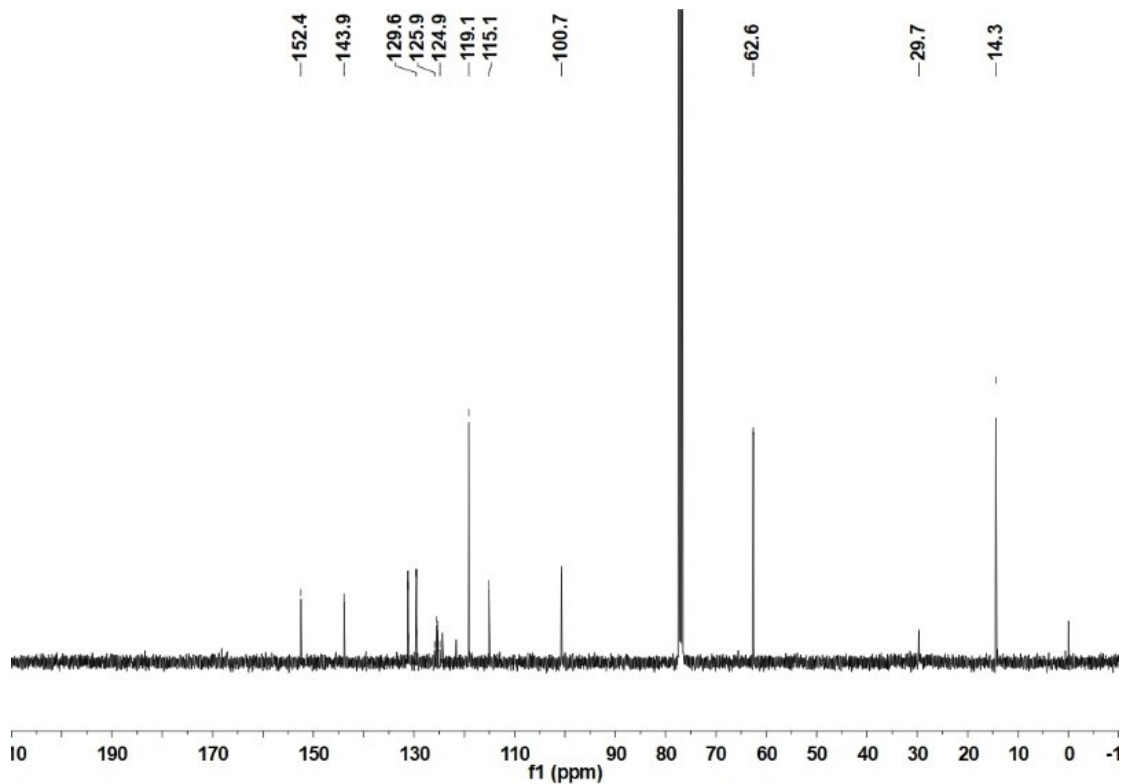
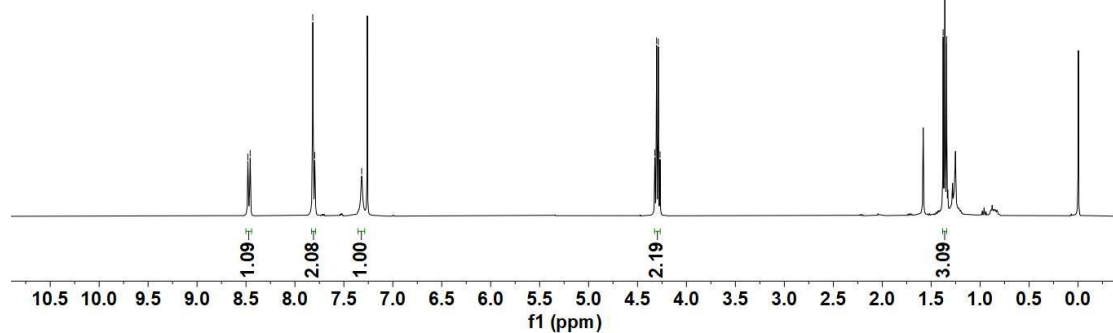
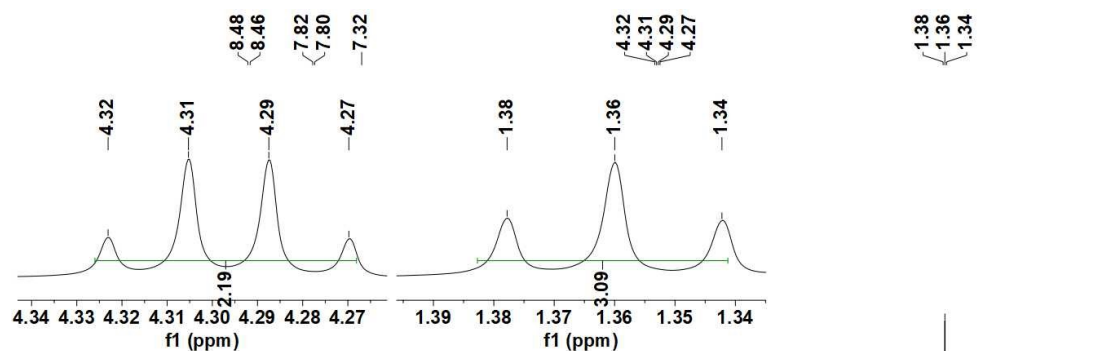
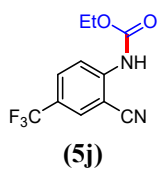
(5h)

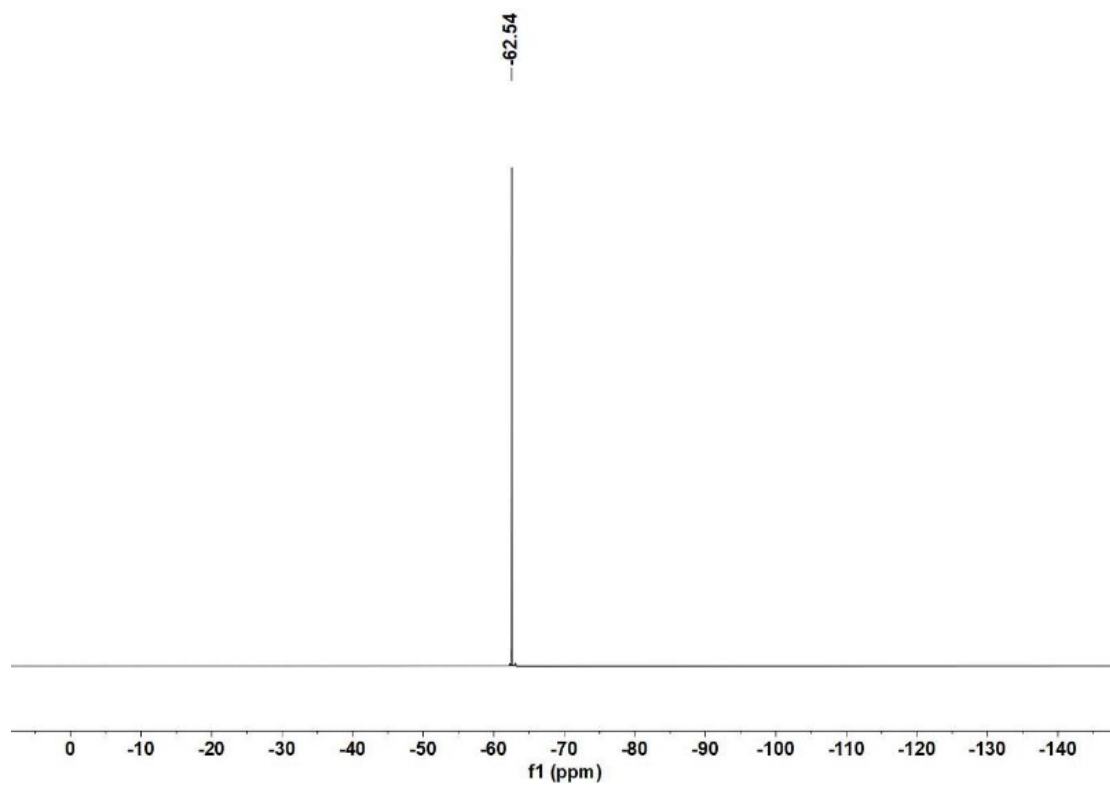


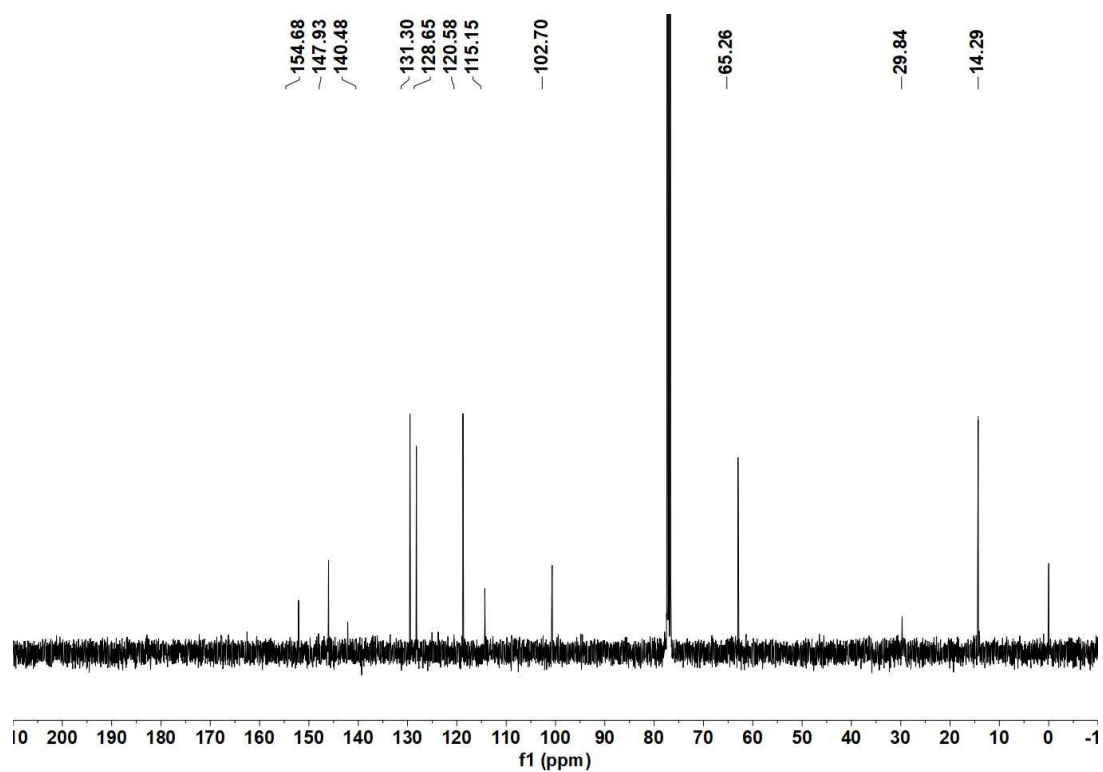
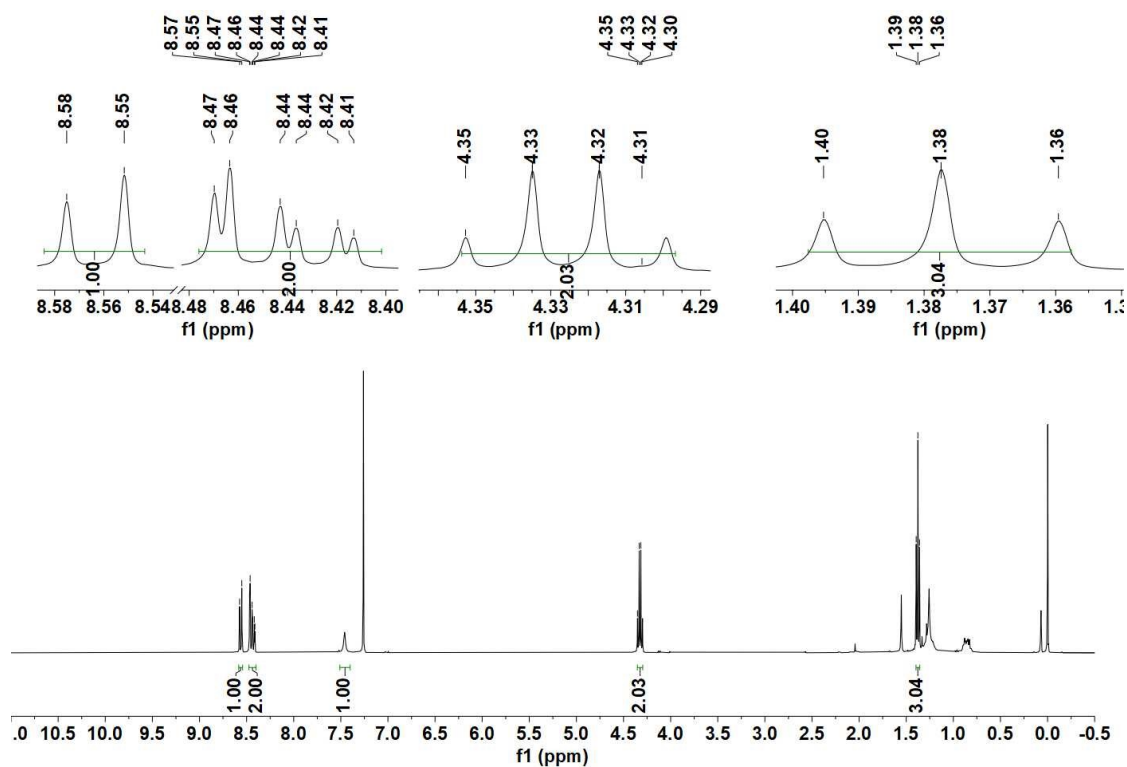
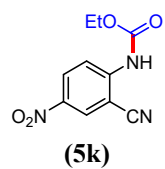


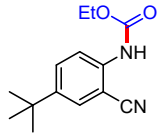
(5i)



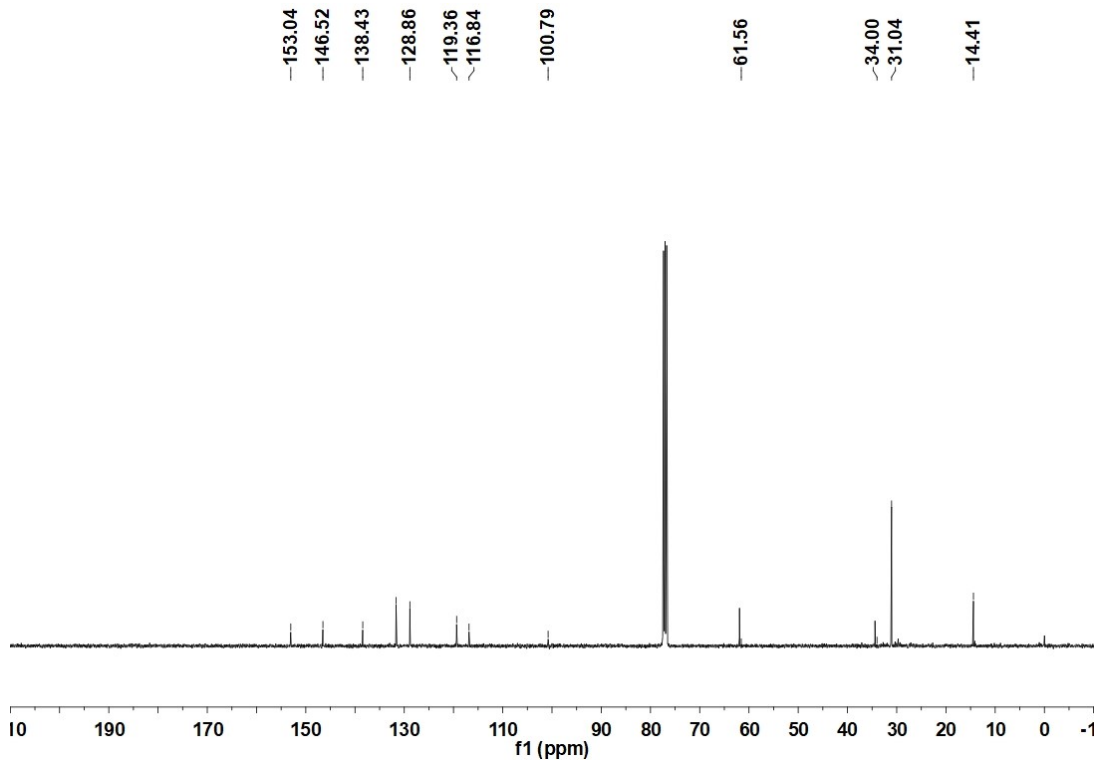
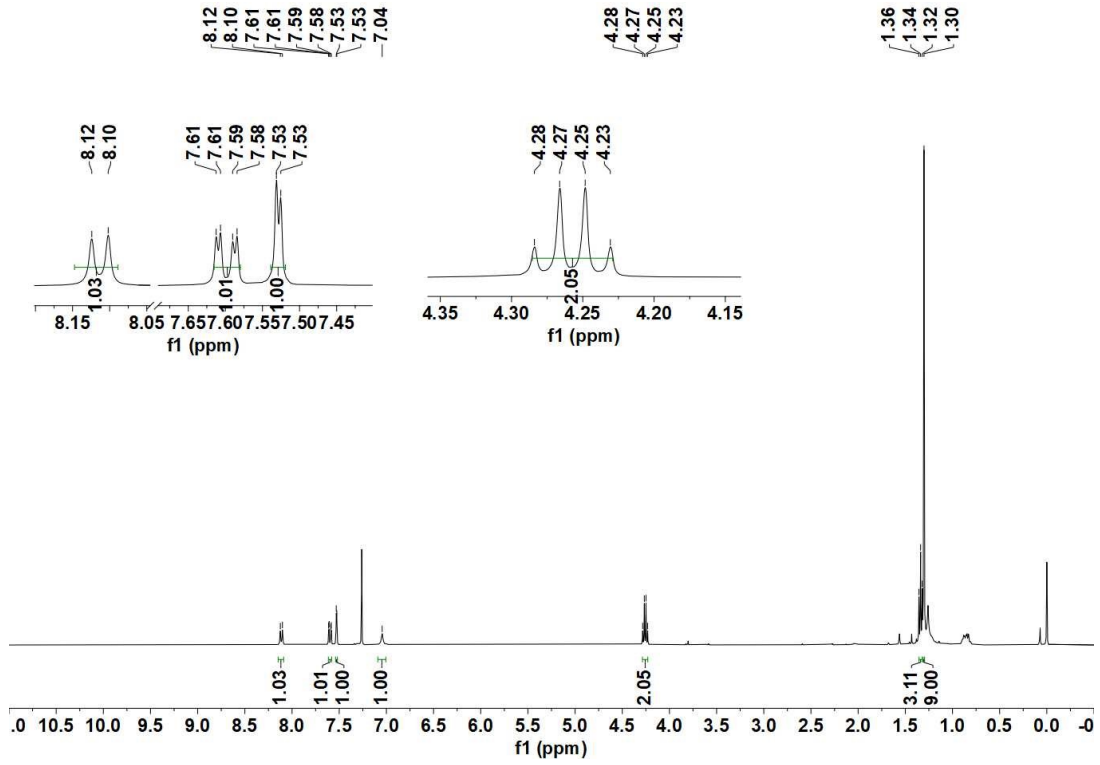


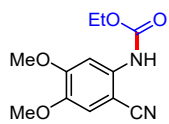




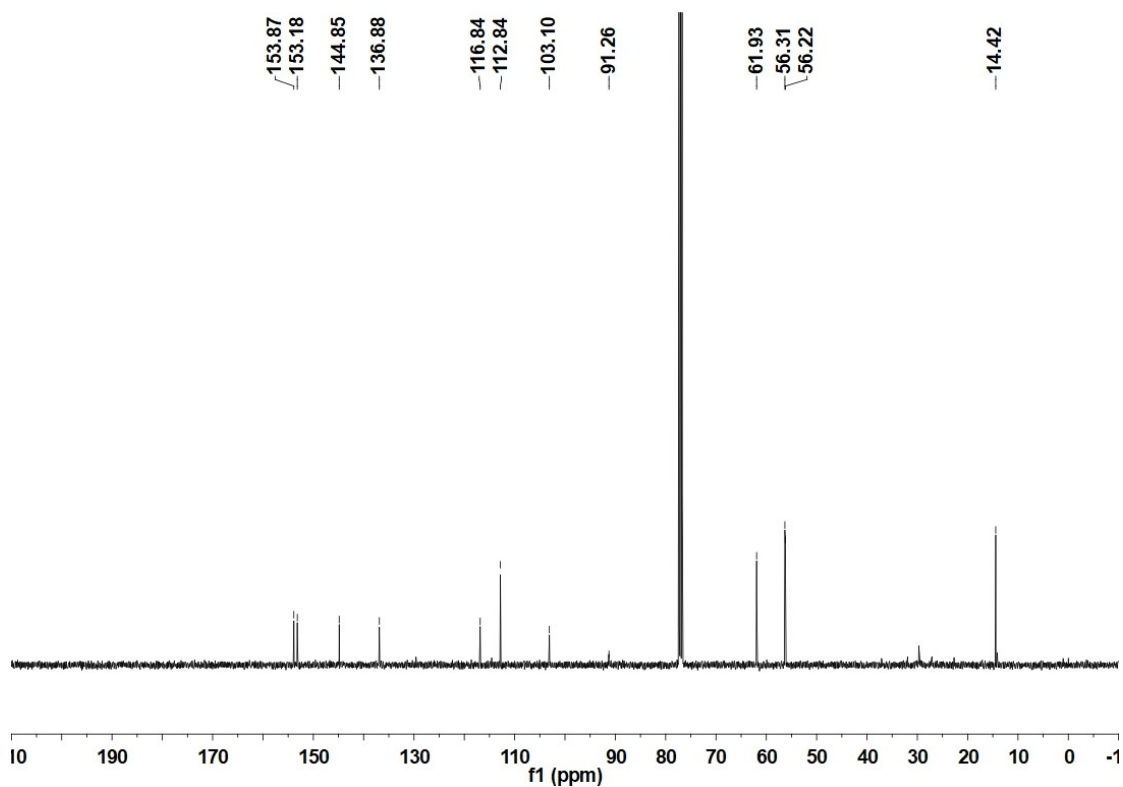
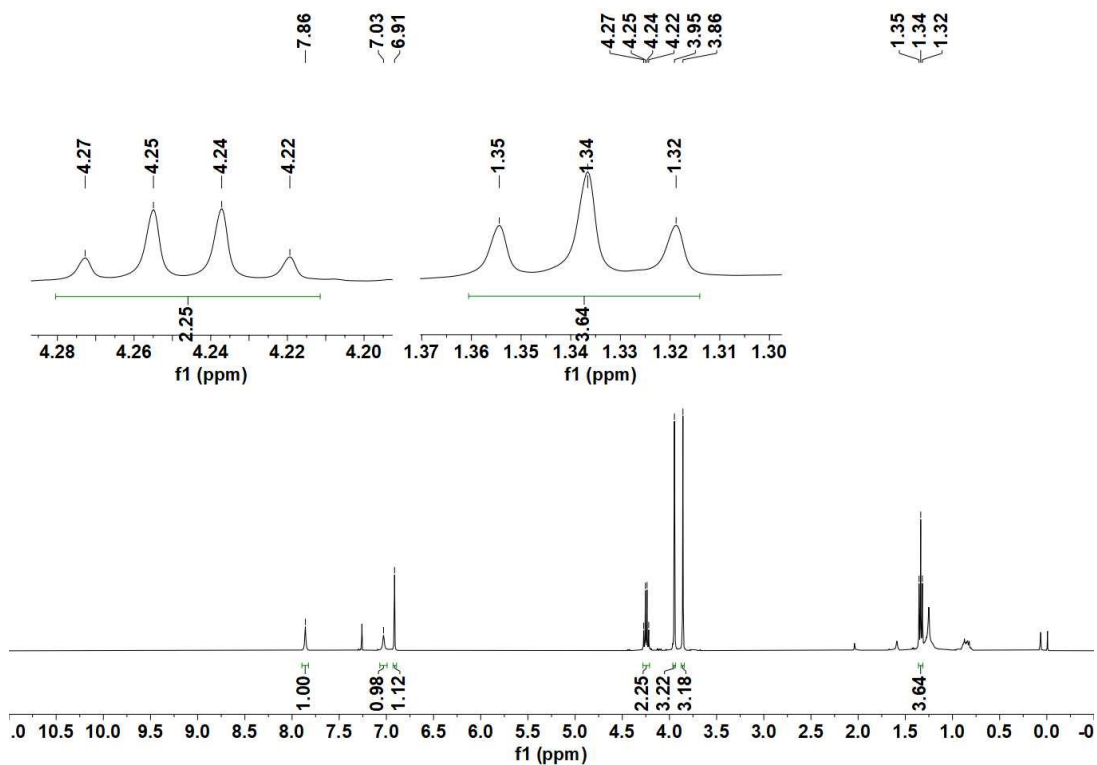


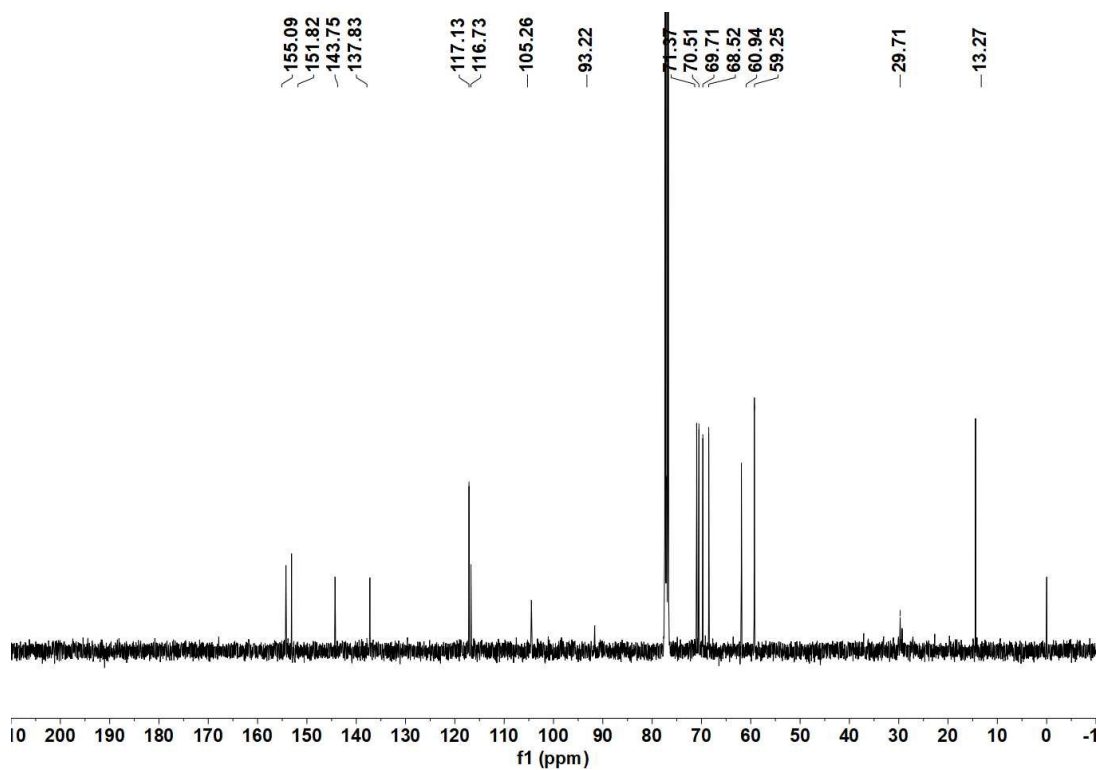
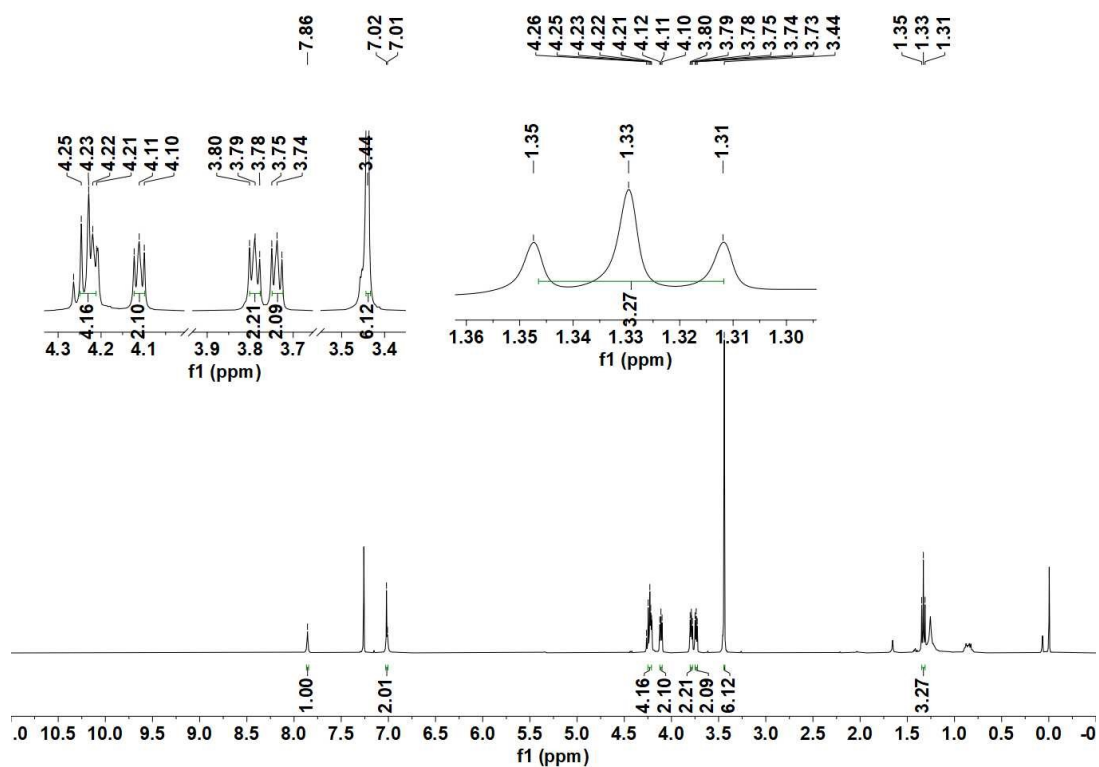
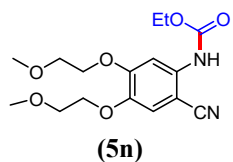
(51)

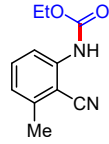




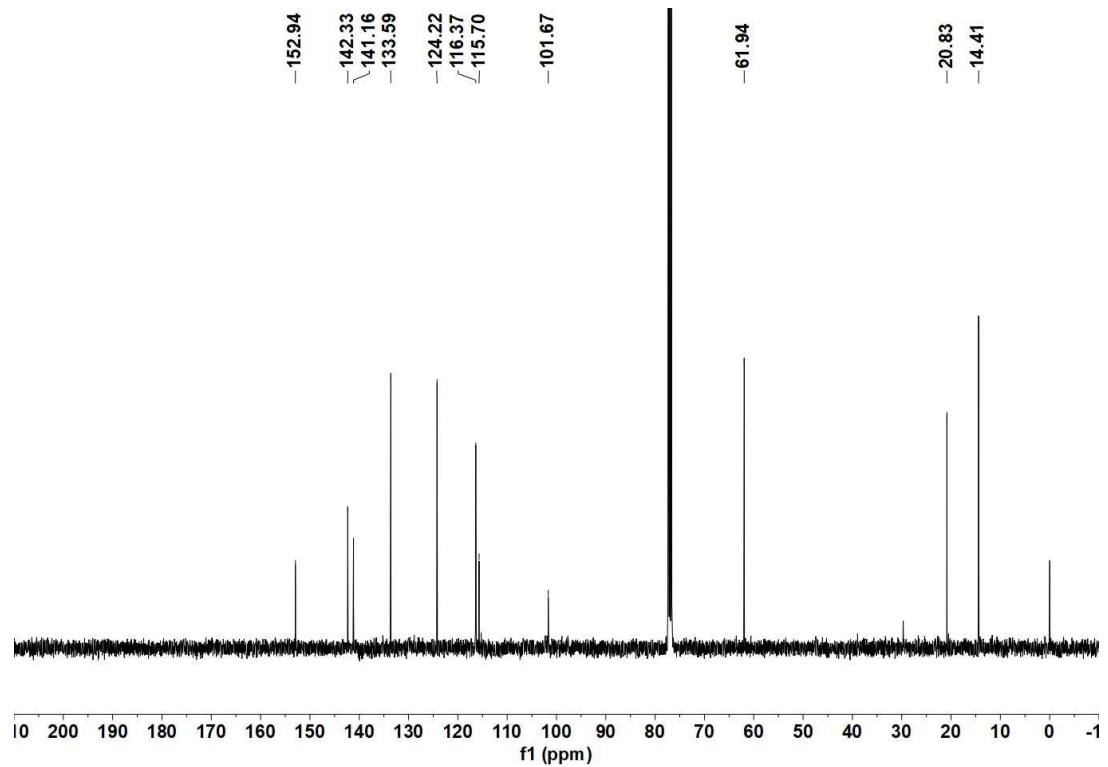
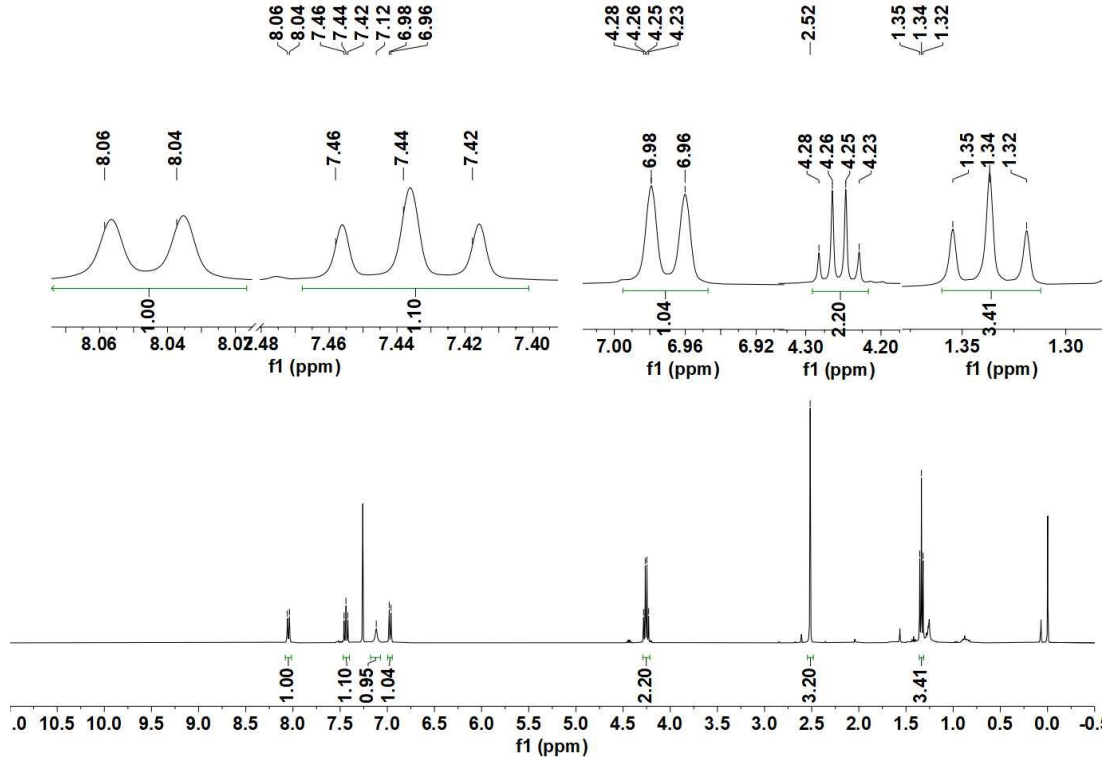
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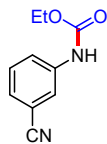




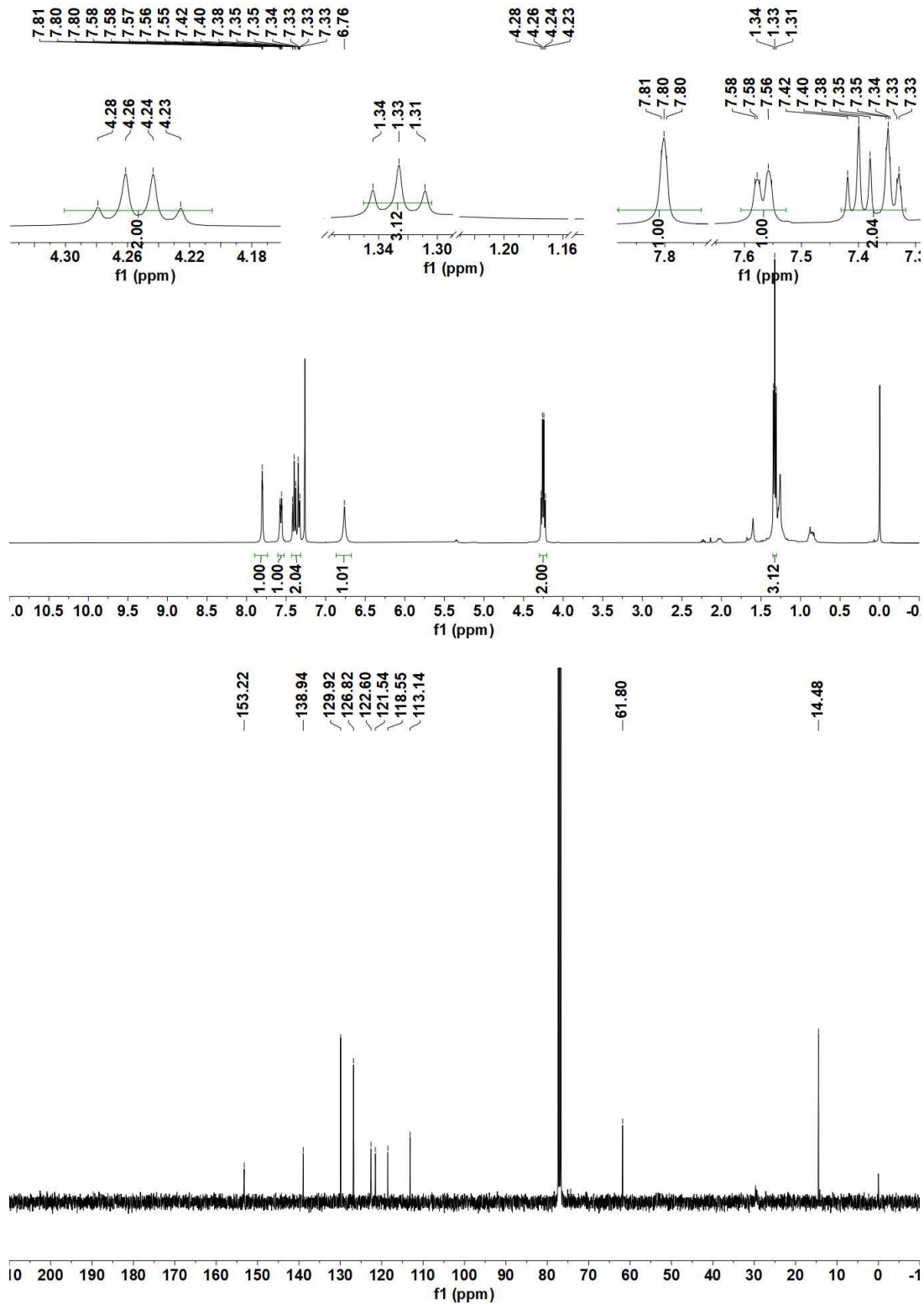


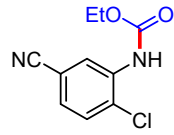
(50)



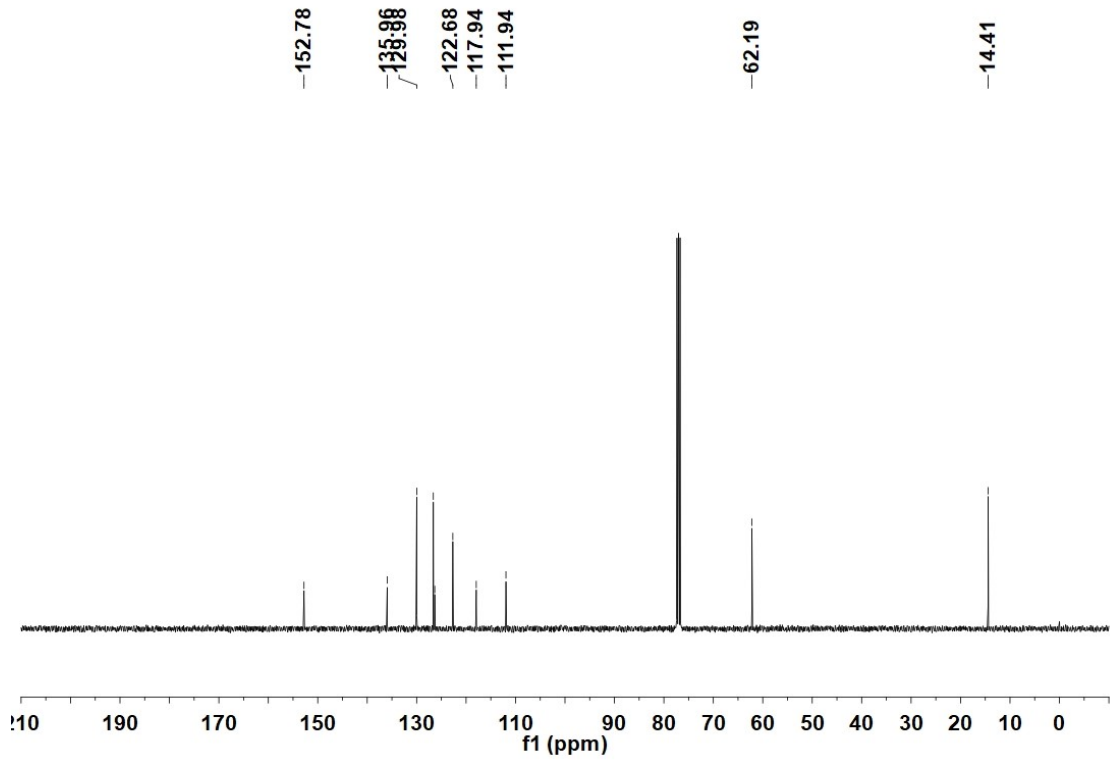
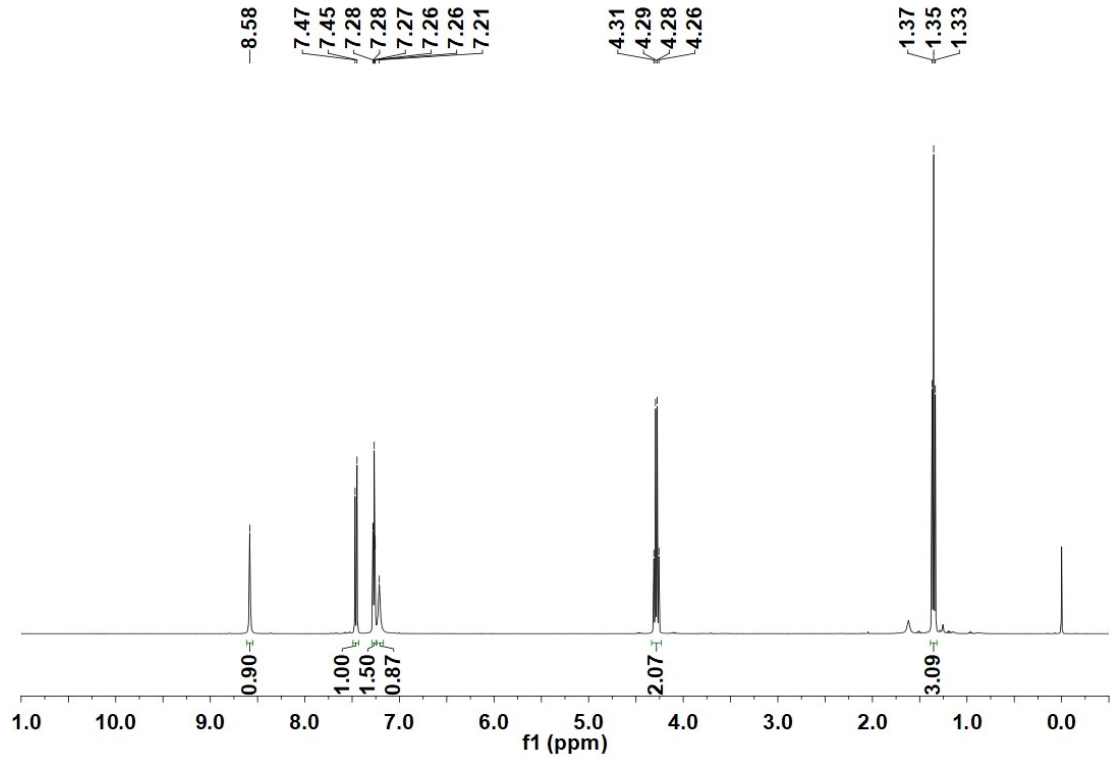


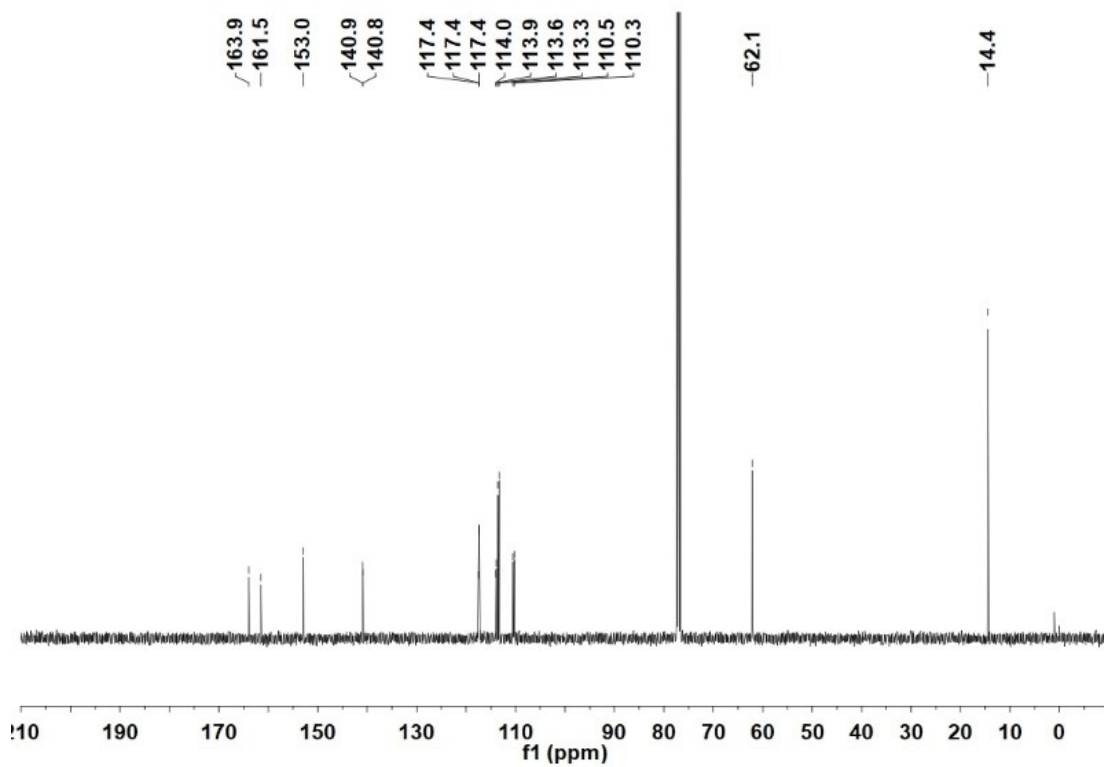
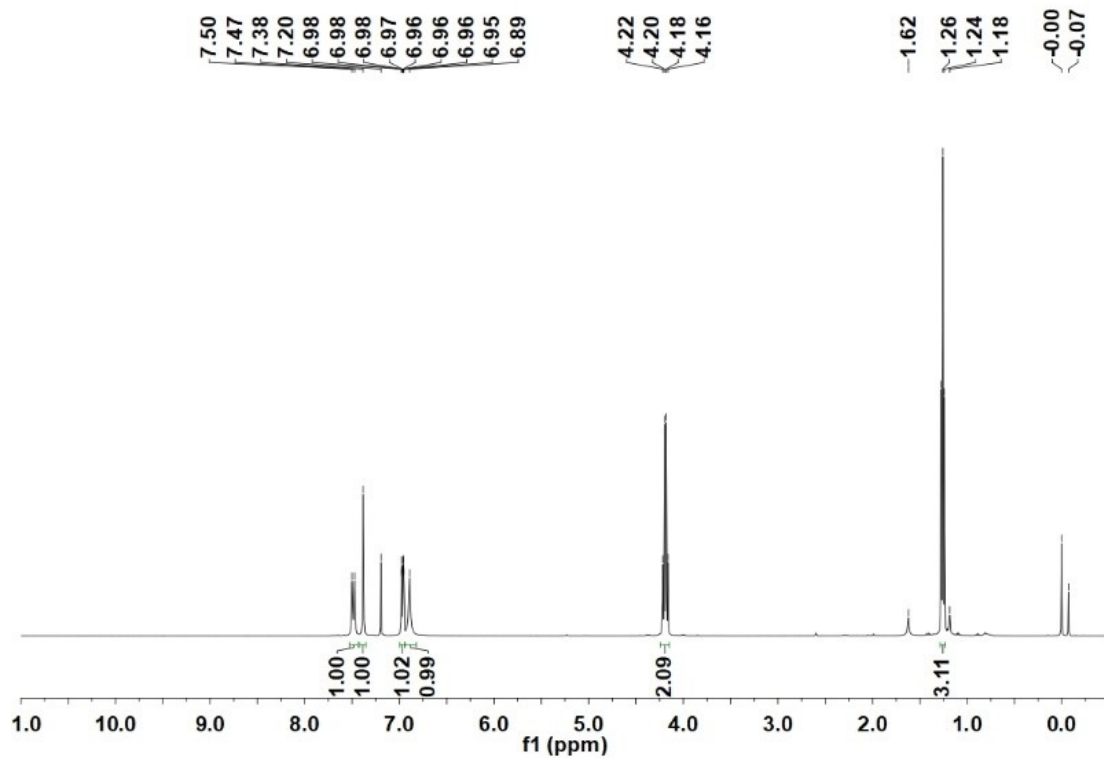
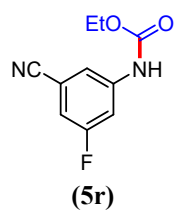
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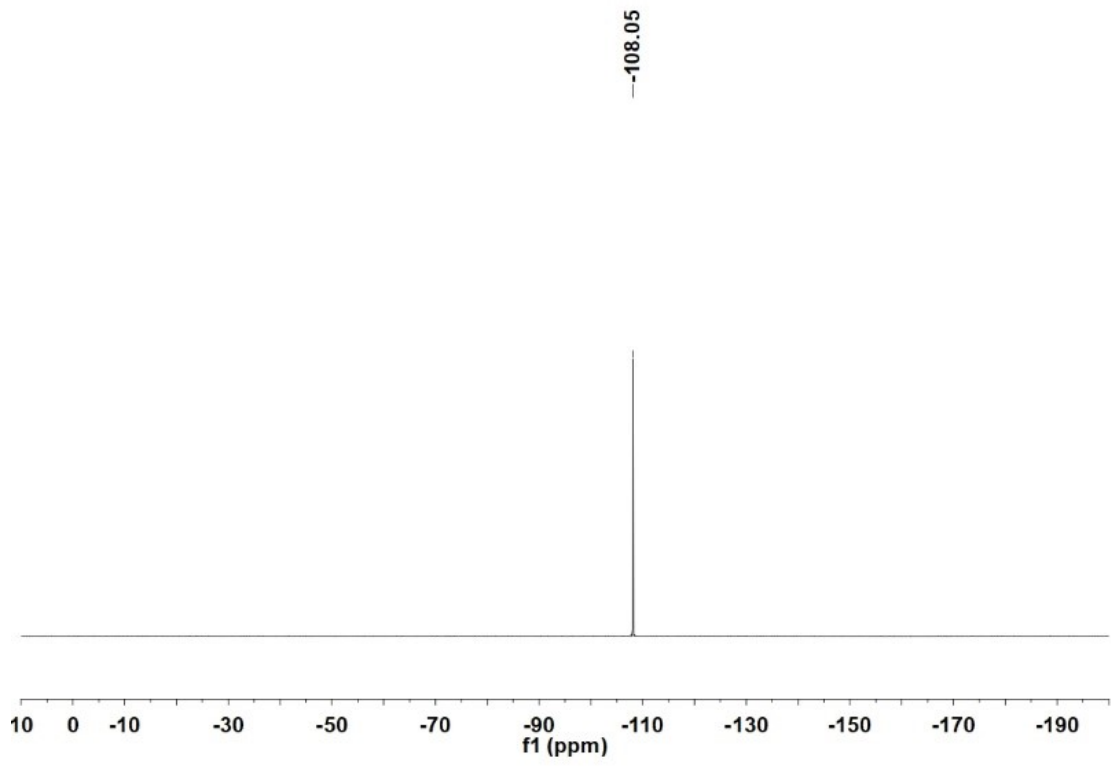


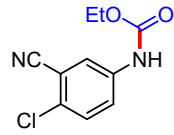


(5q)

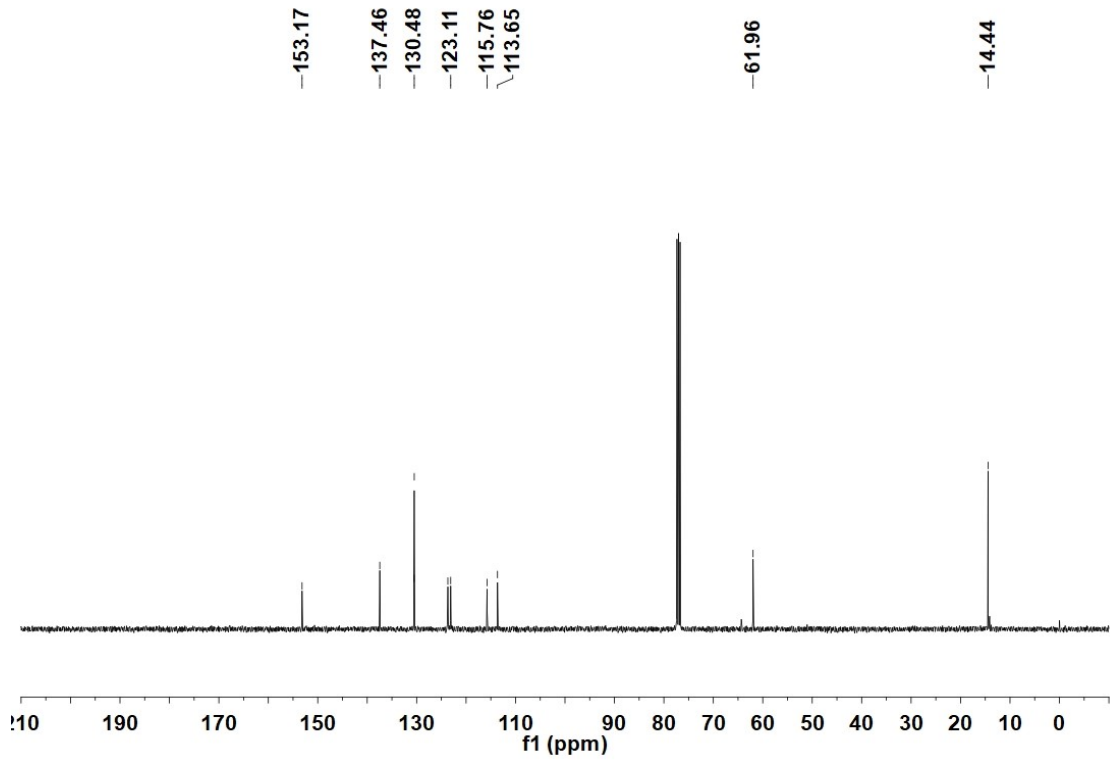
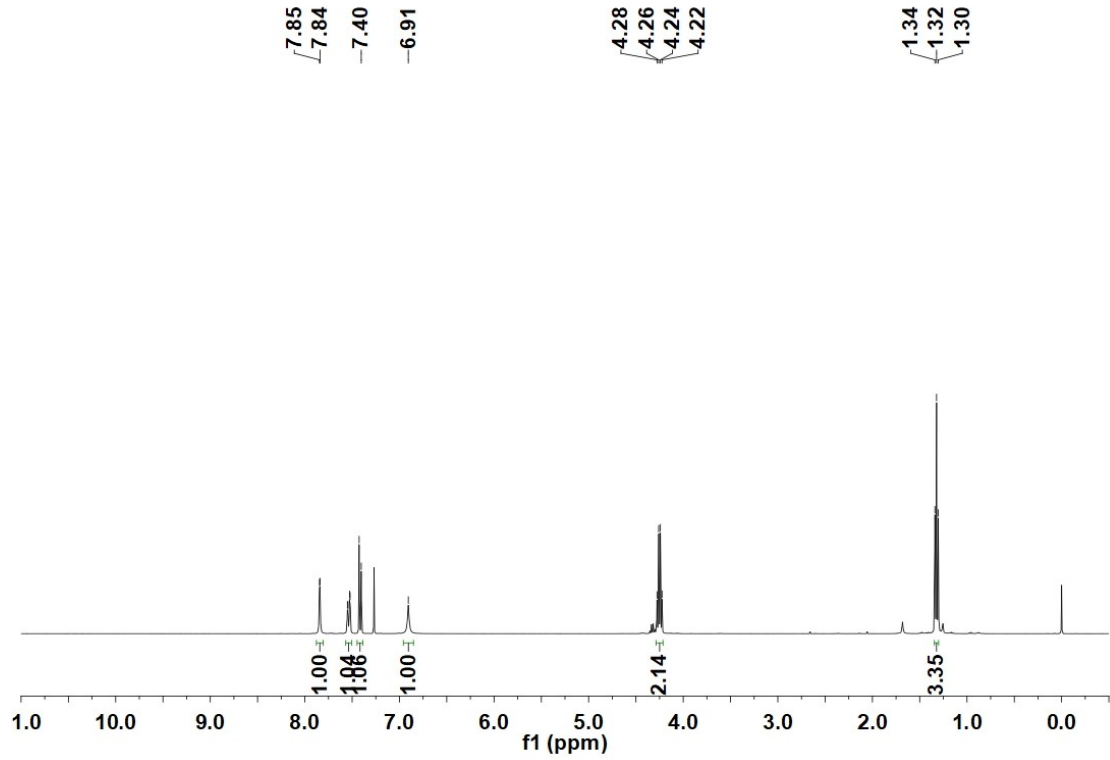


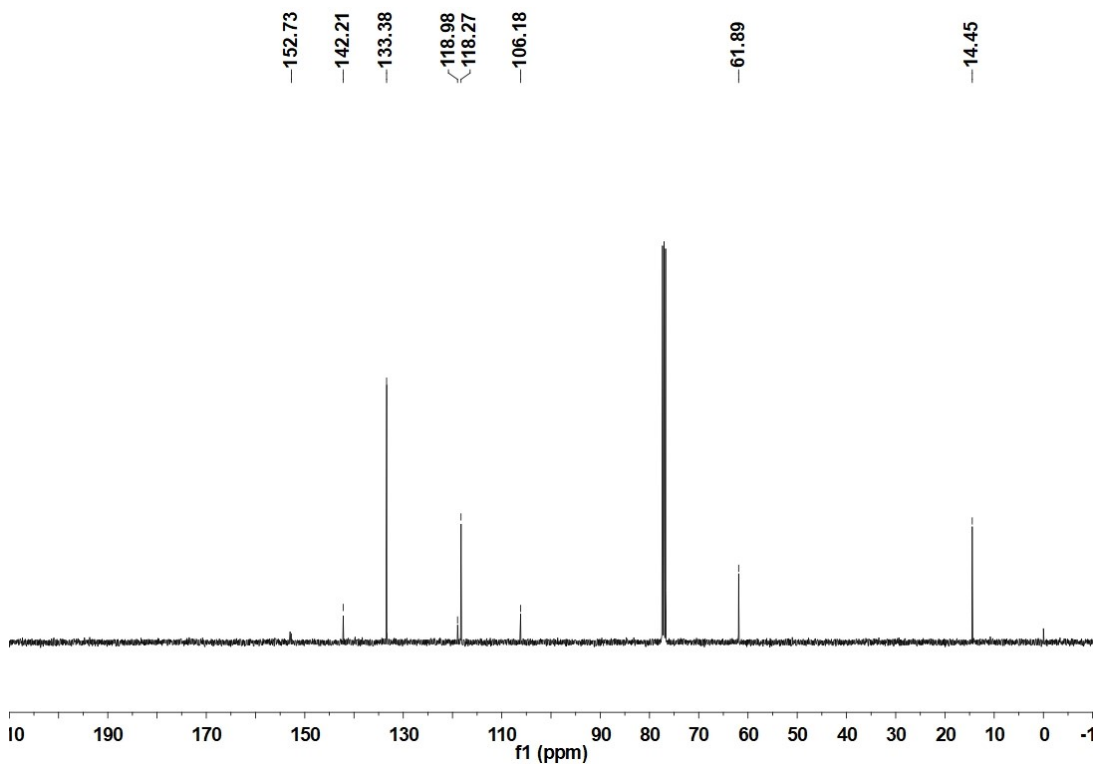
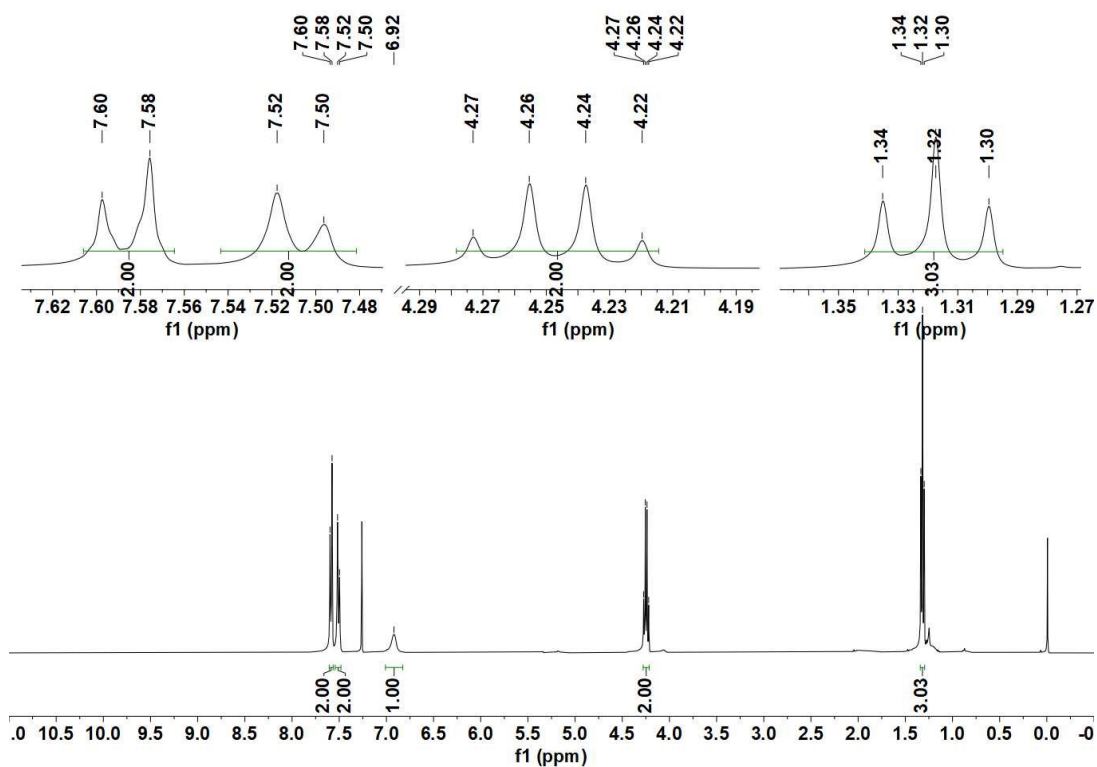
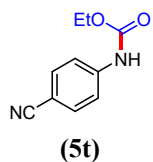


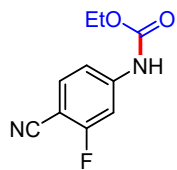




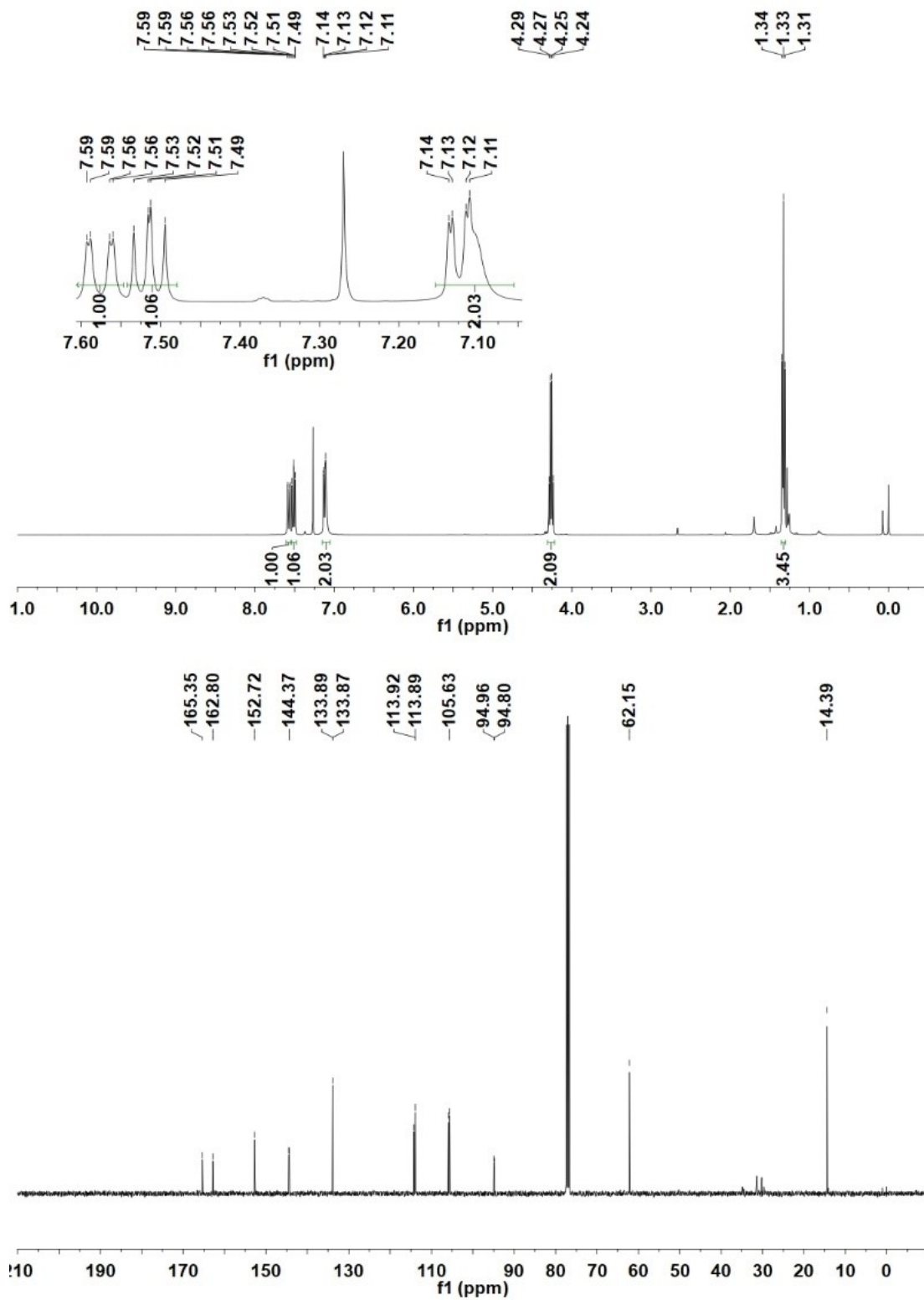
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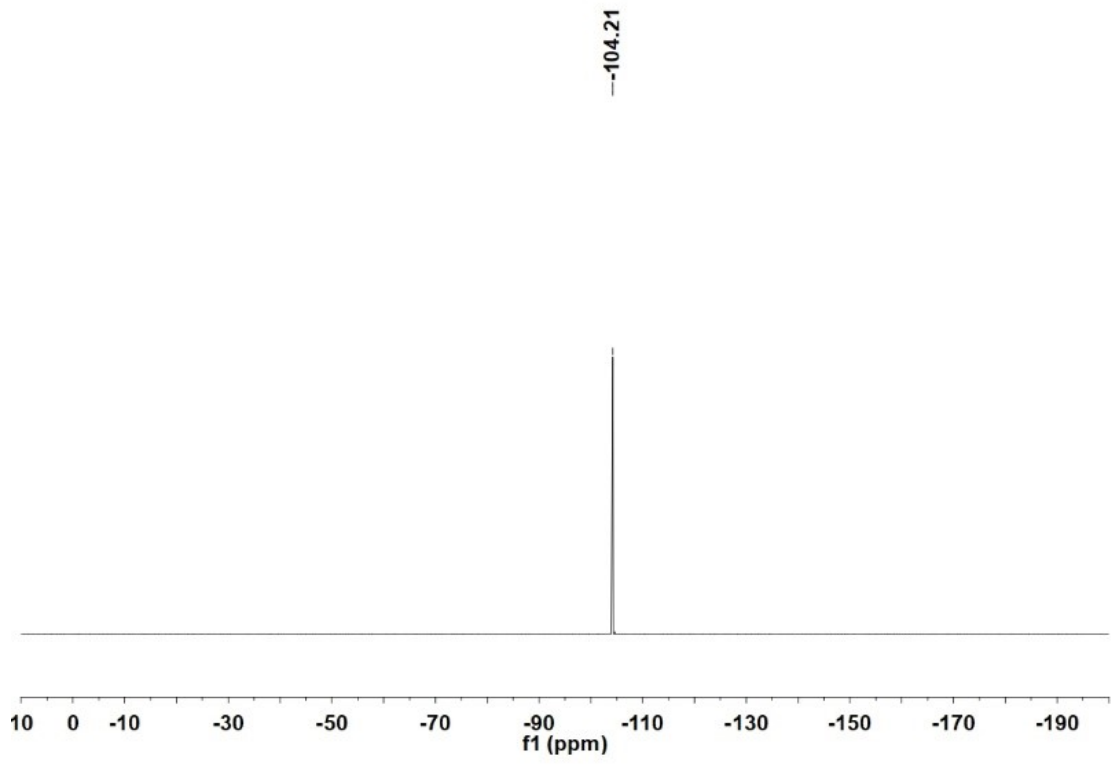


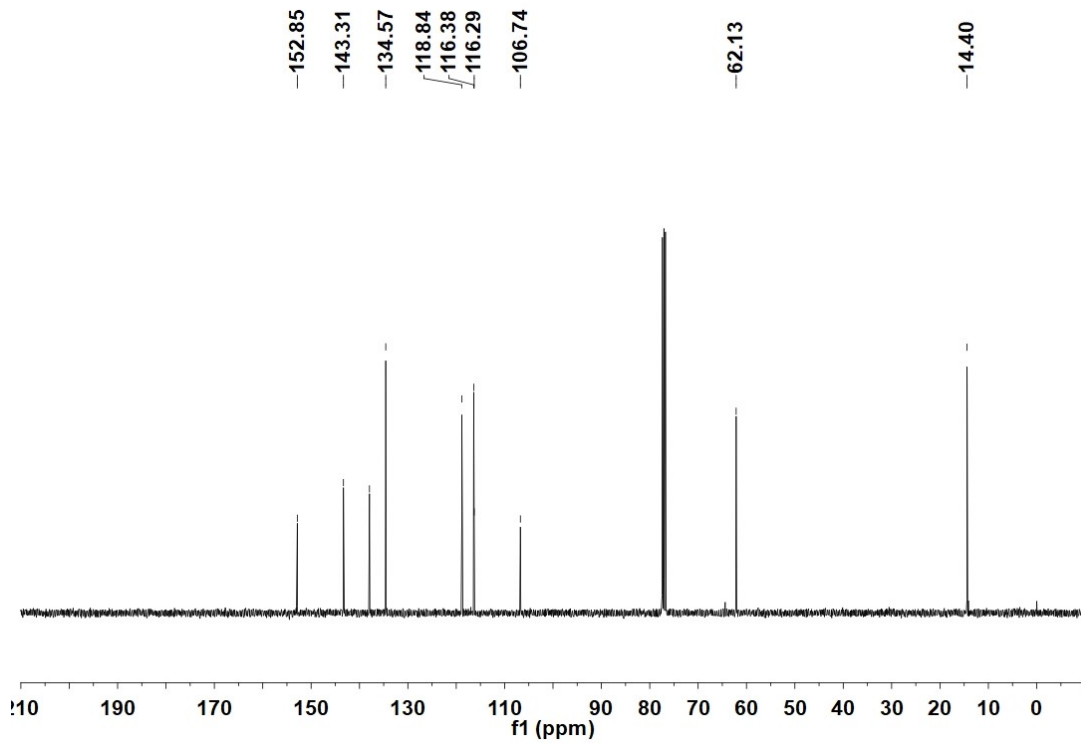
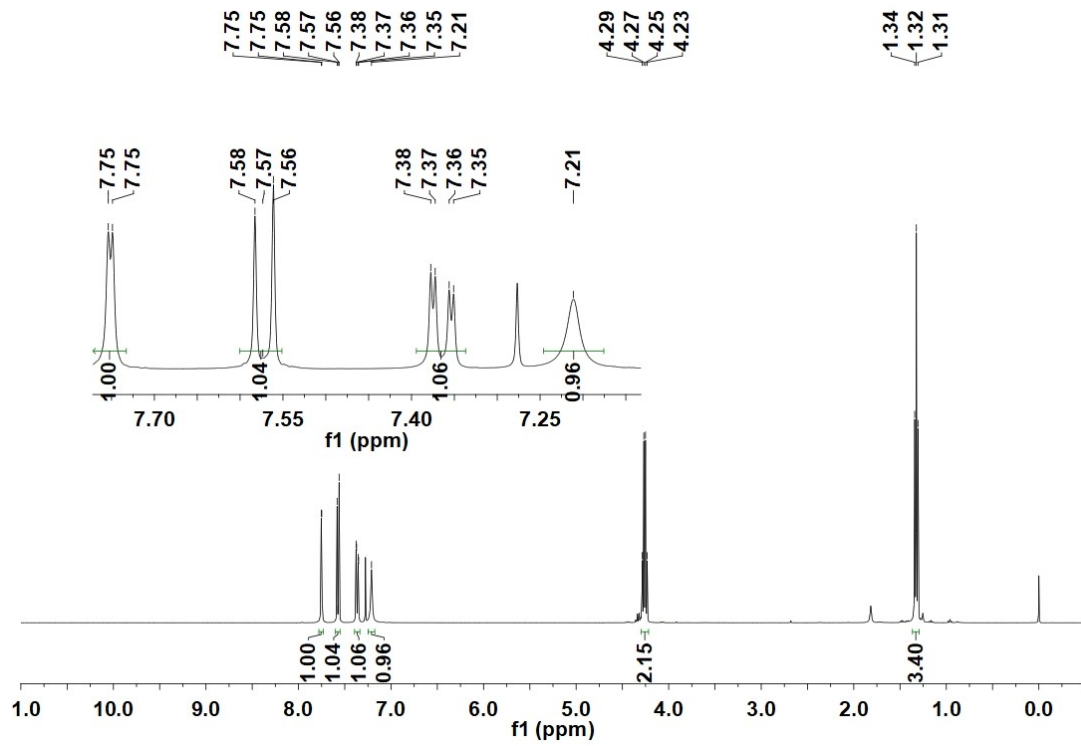
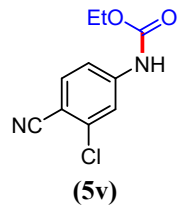


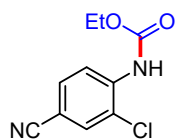


(5u)

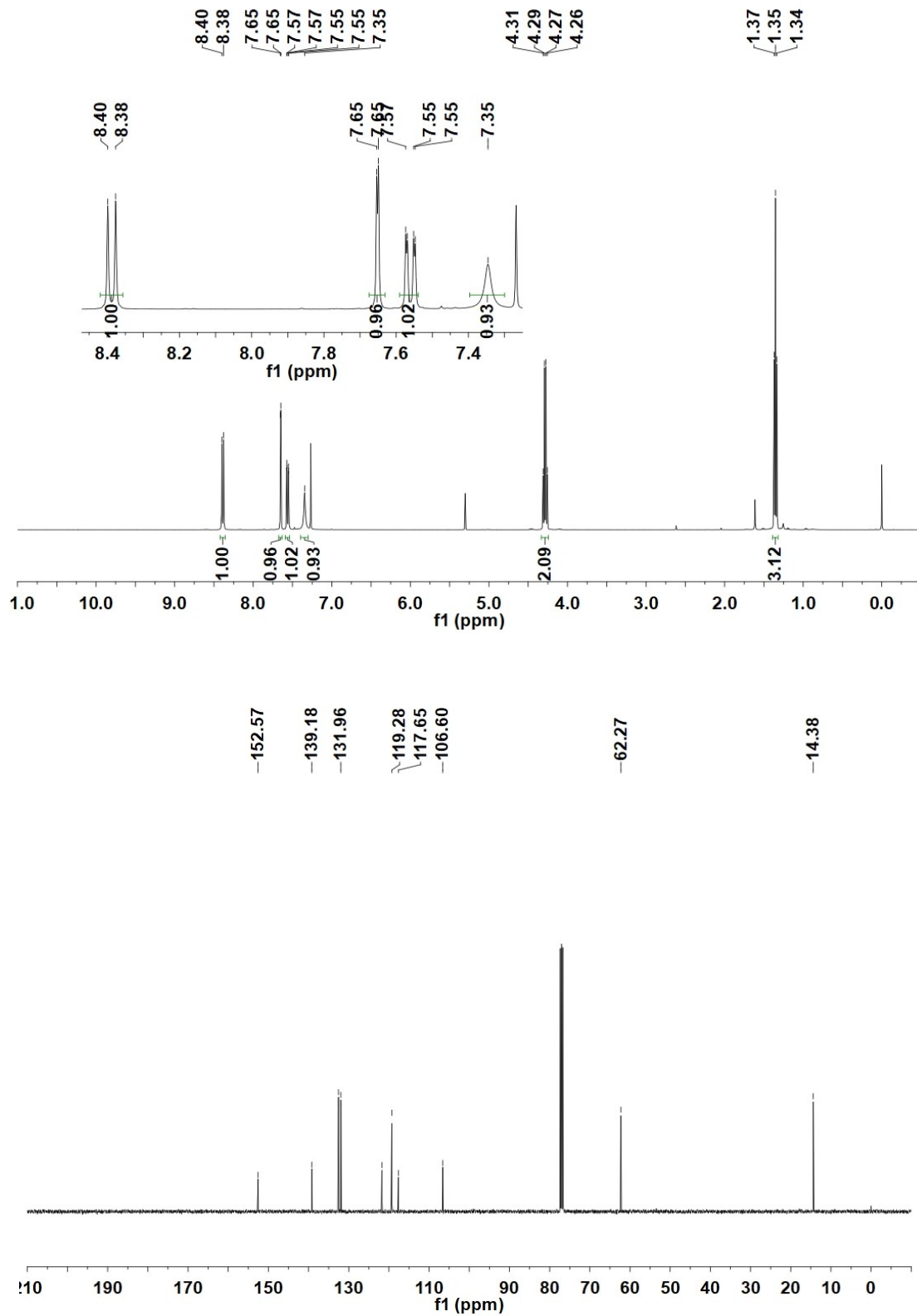


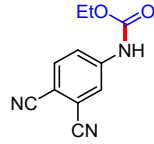




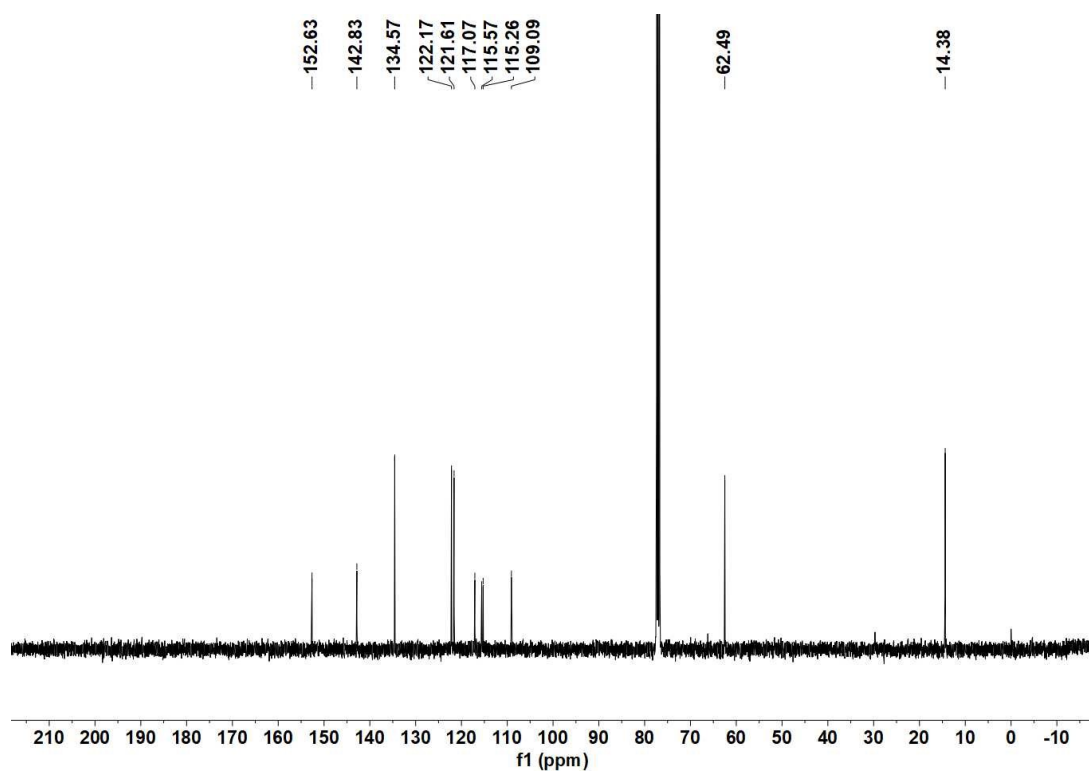
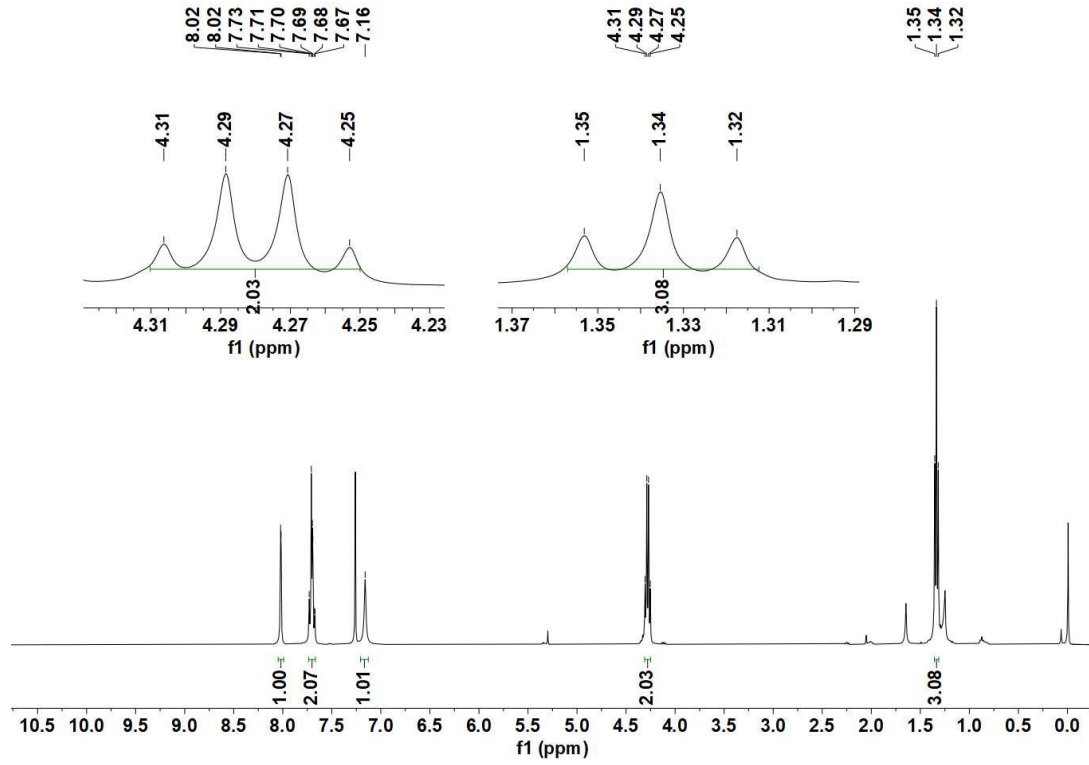


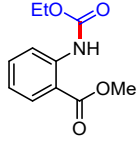
(5w)



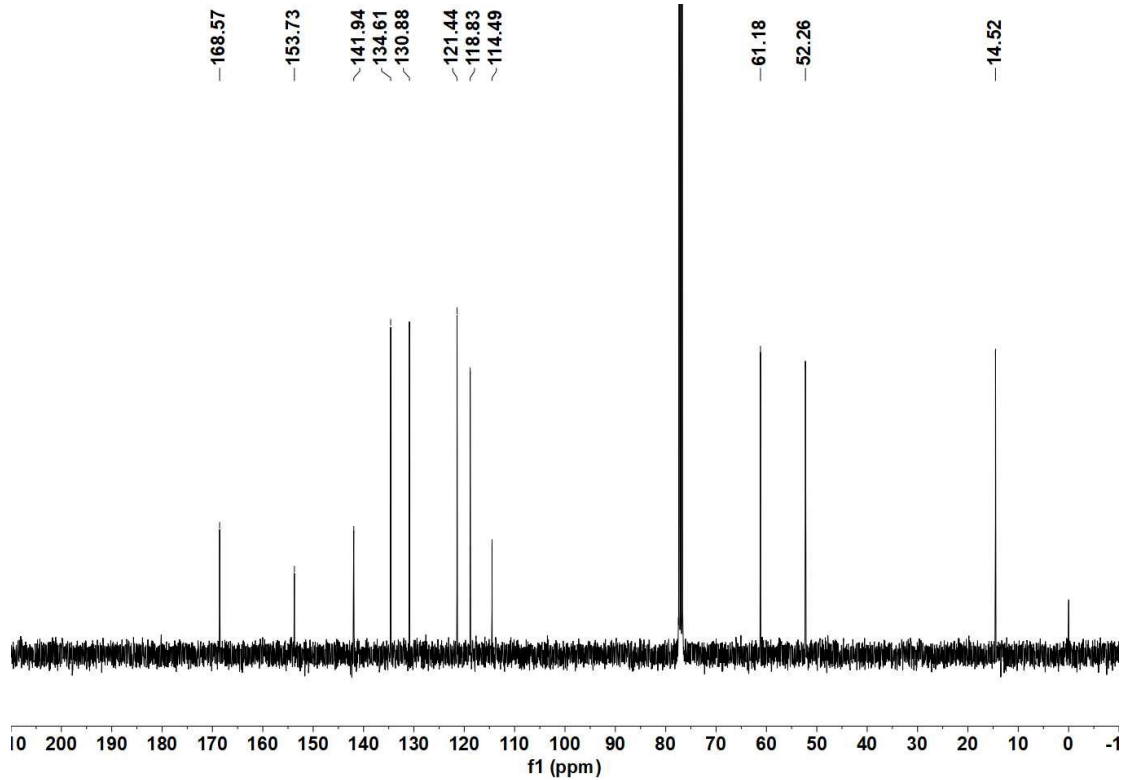
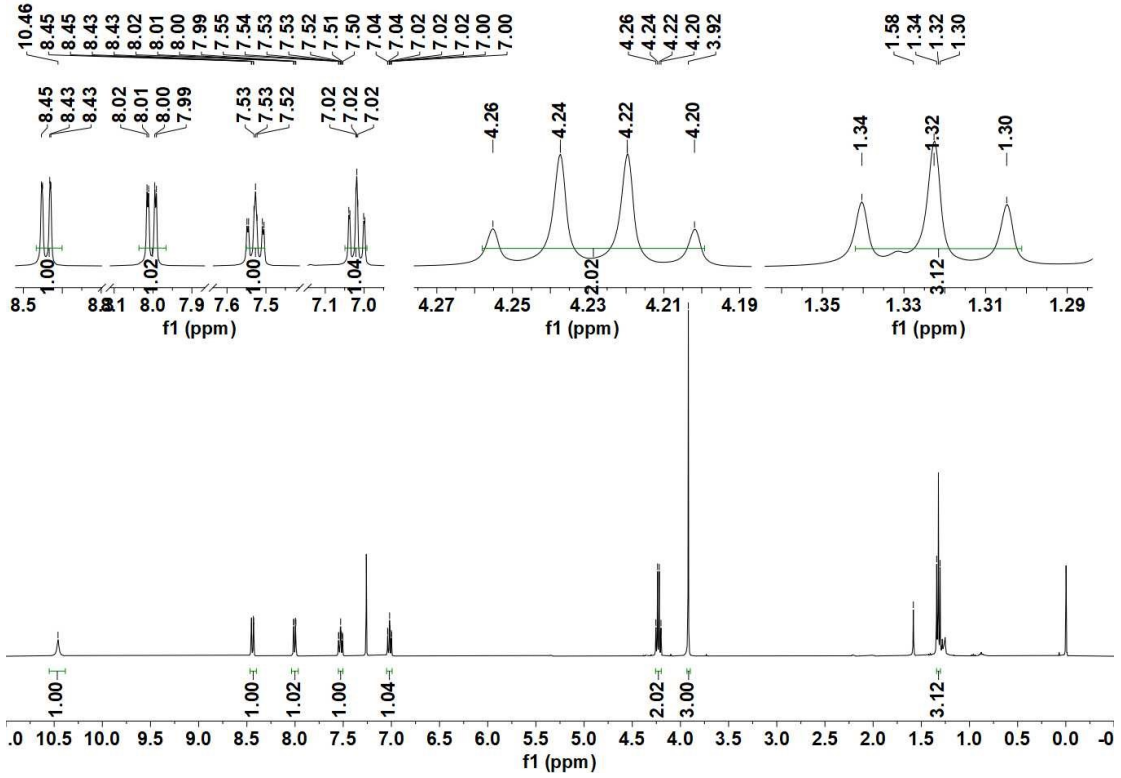


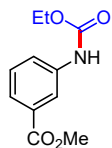
(5x)



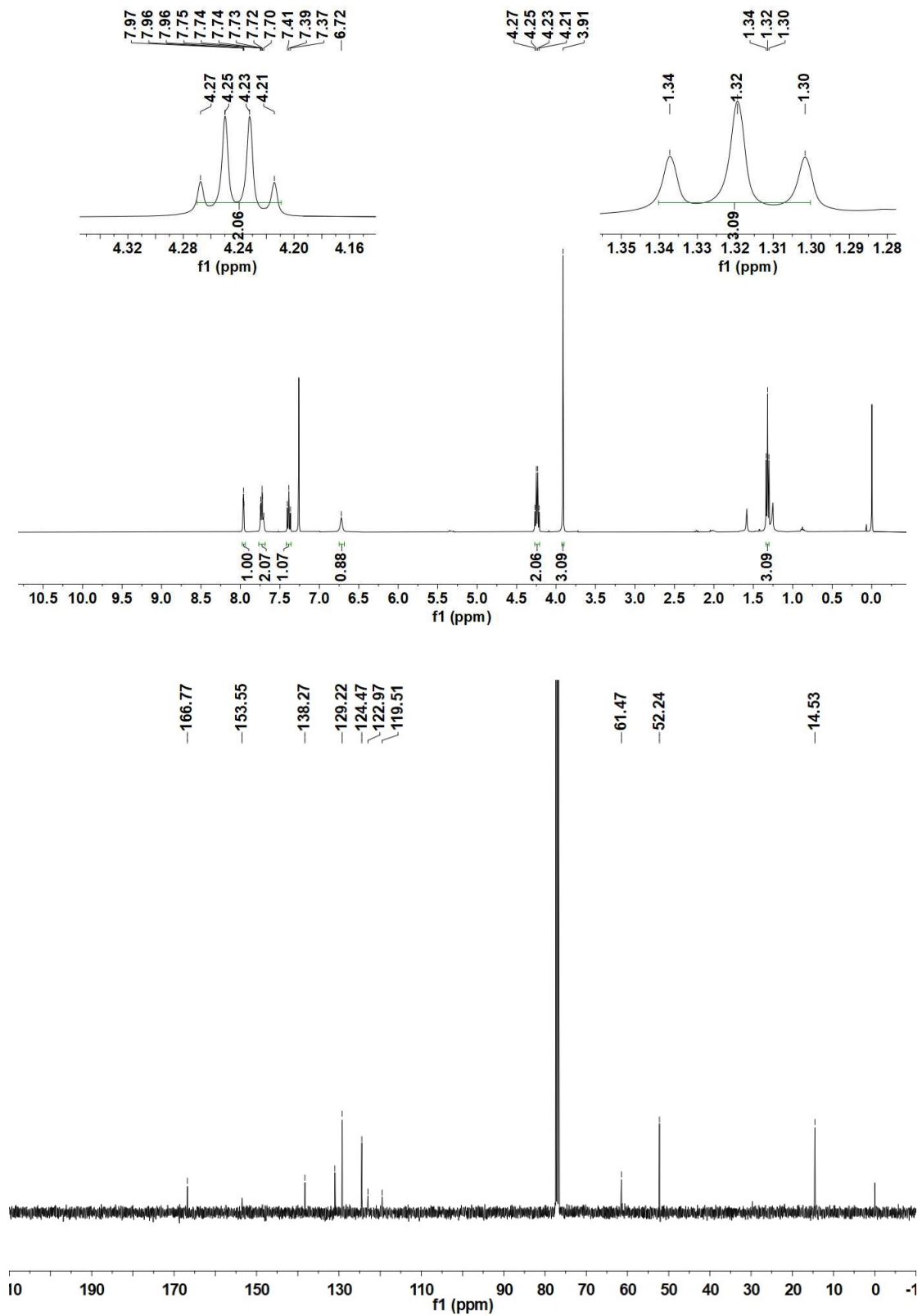


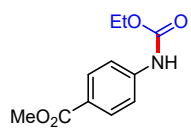
(7a)



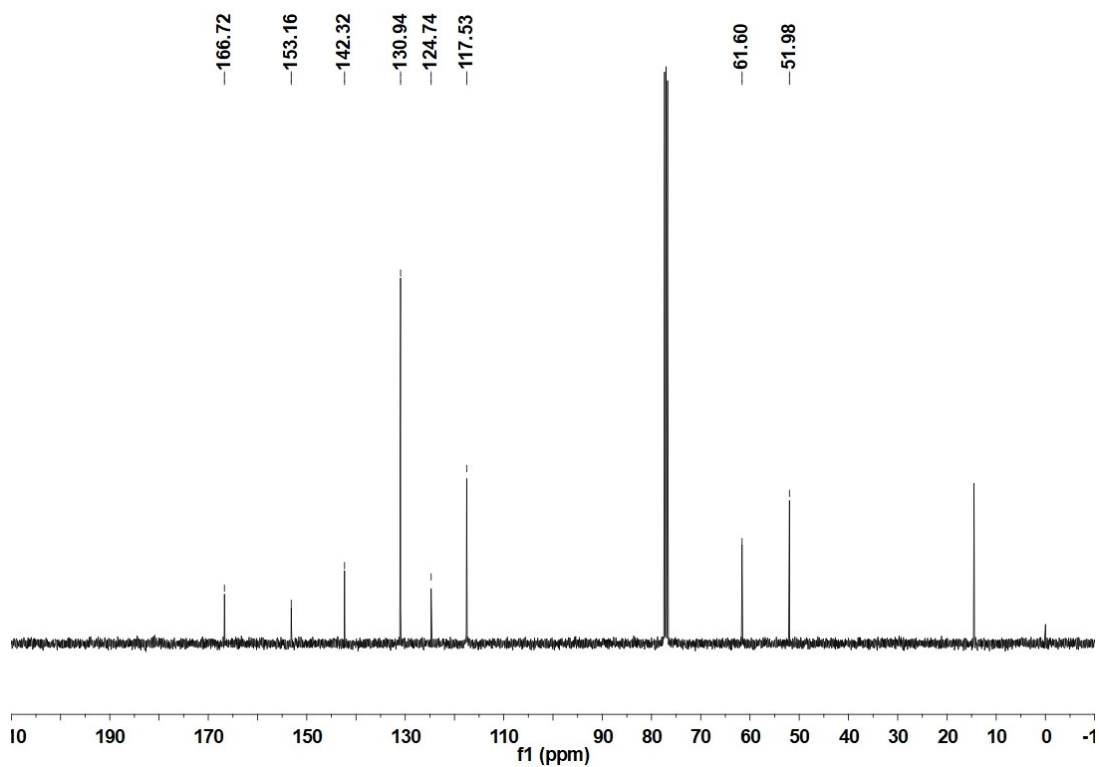
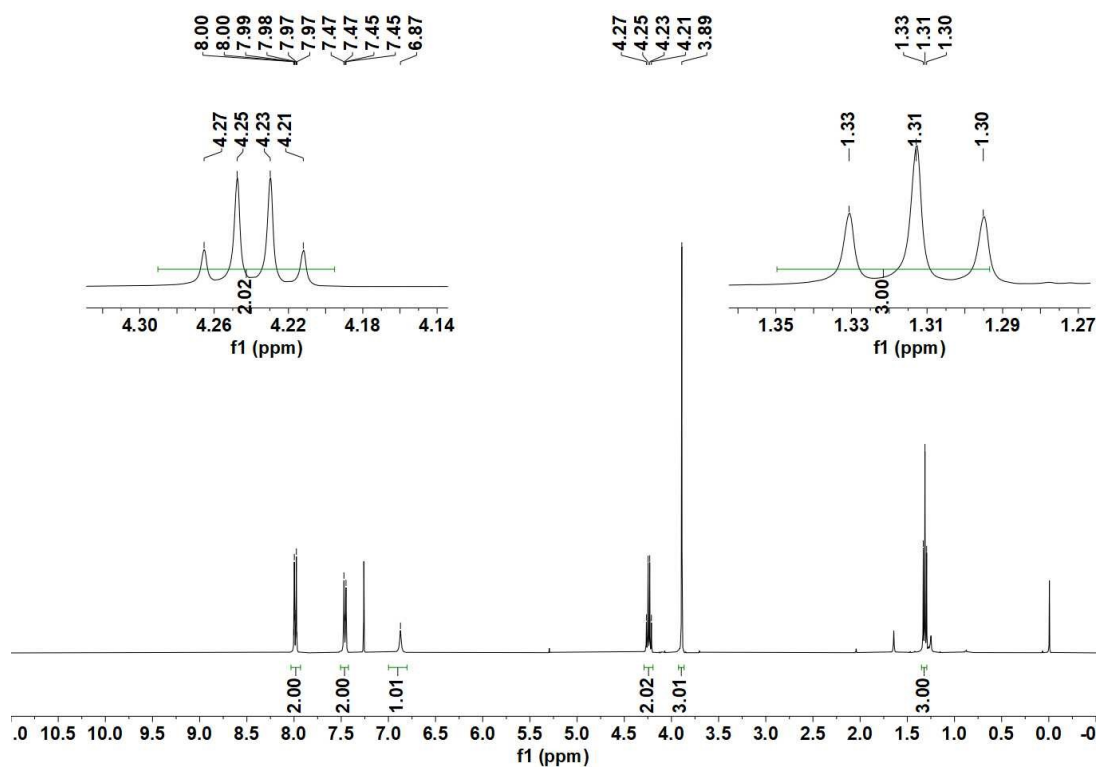


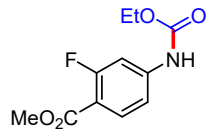
(7b)



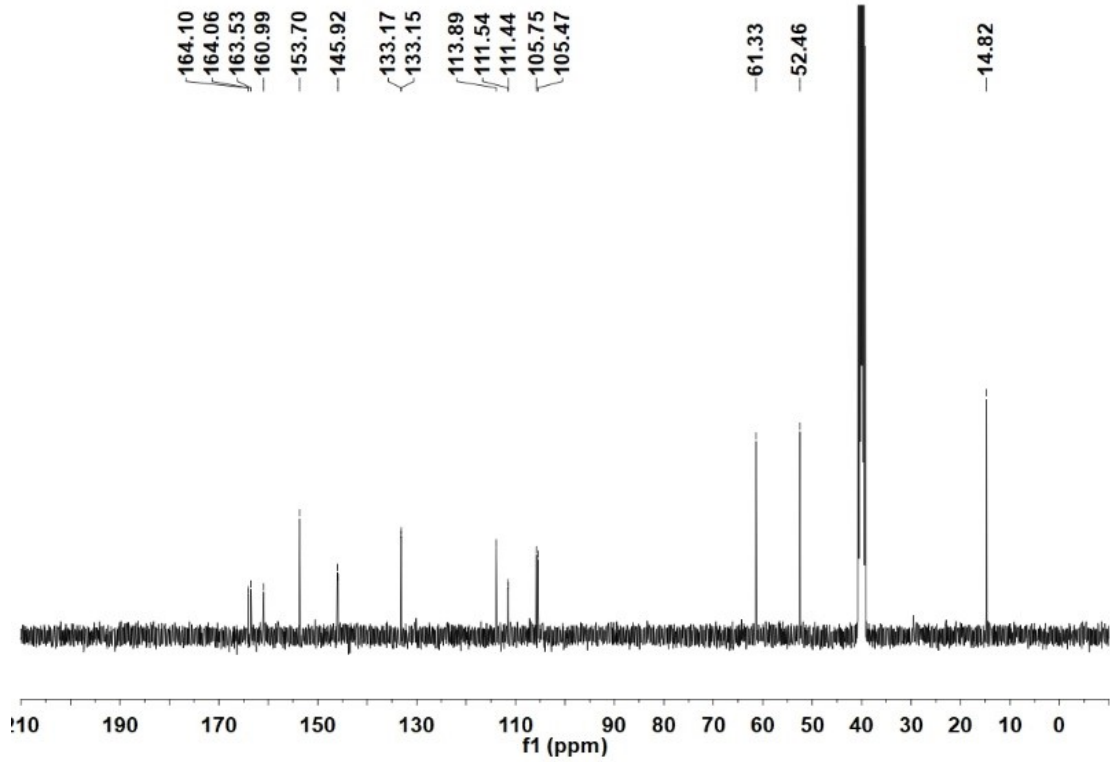
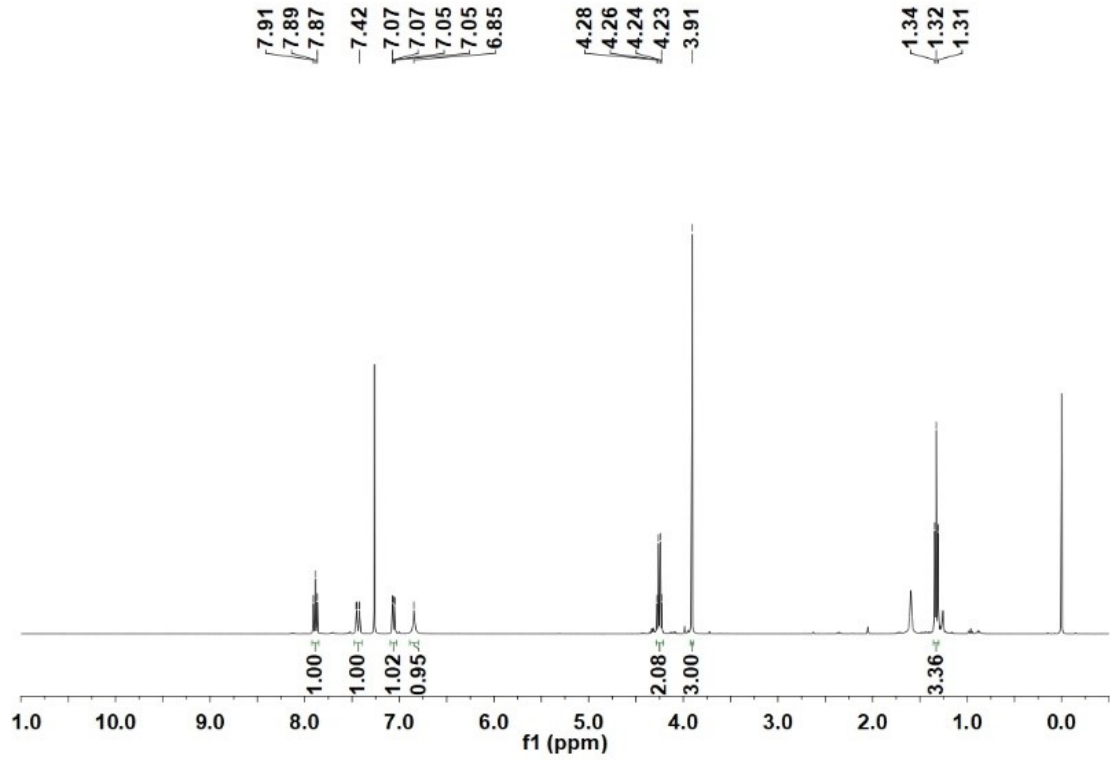


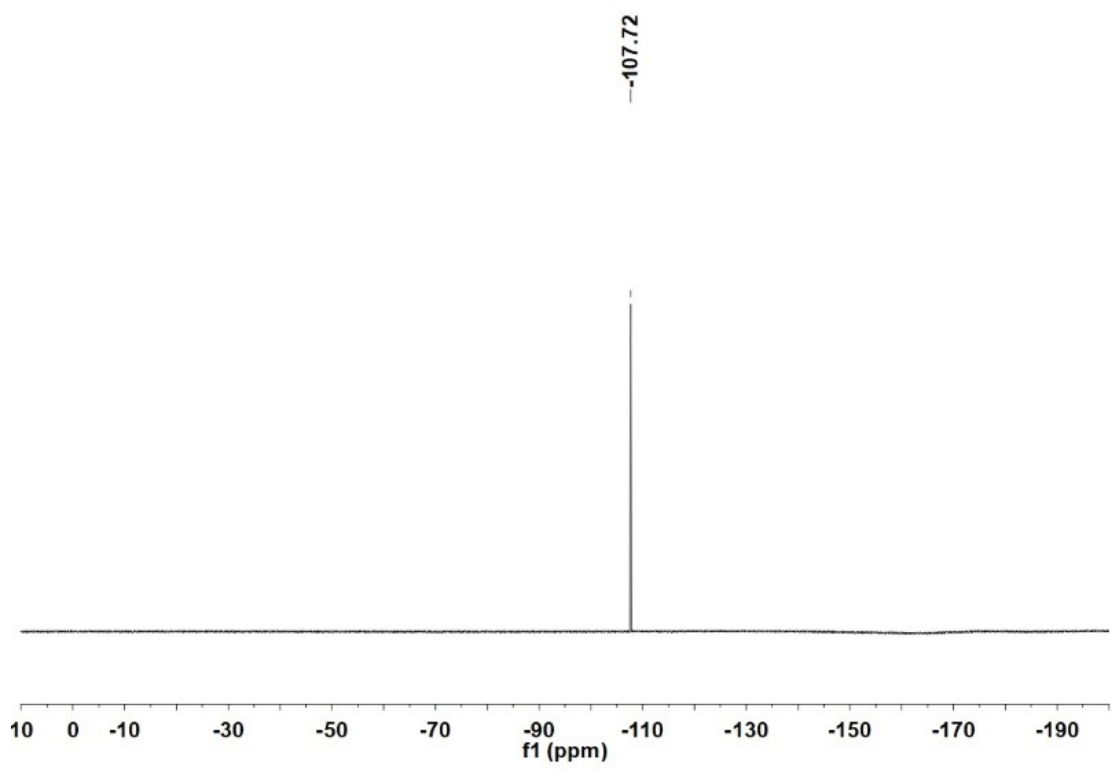
(7c)

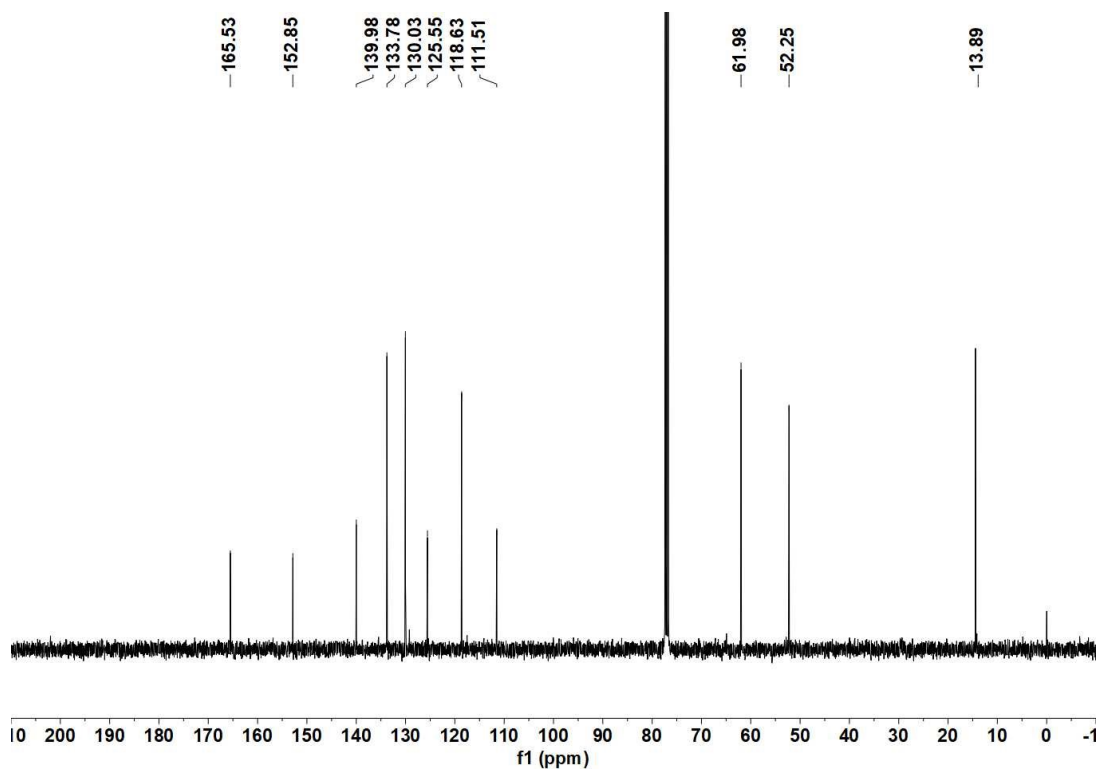
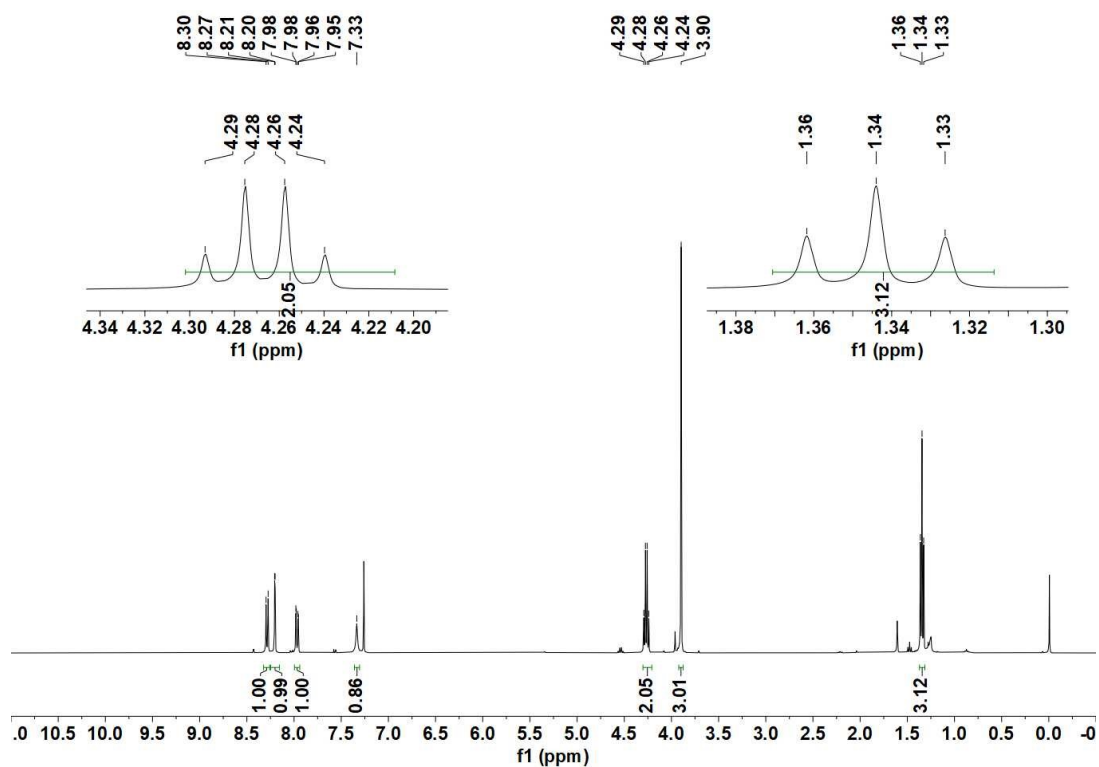
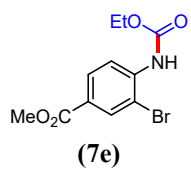


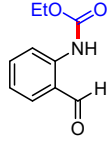


(7d)

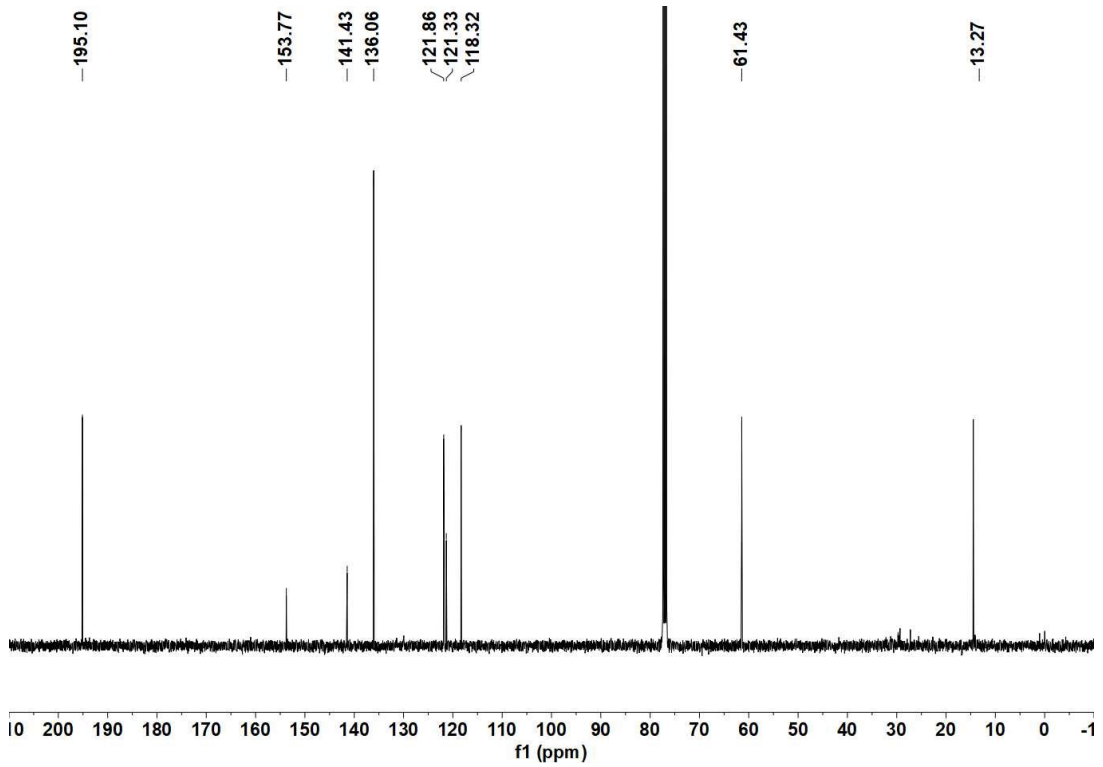
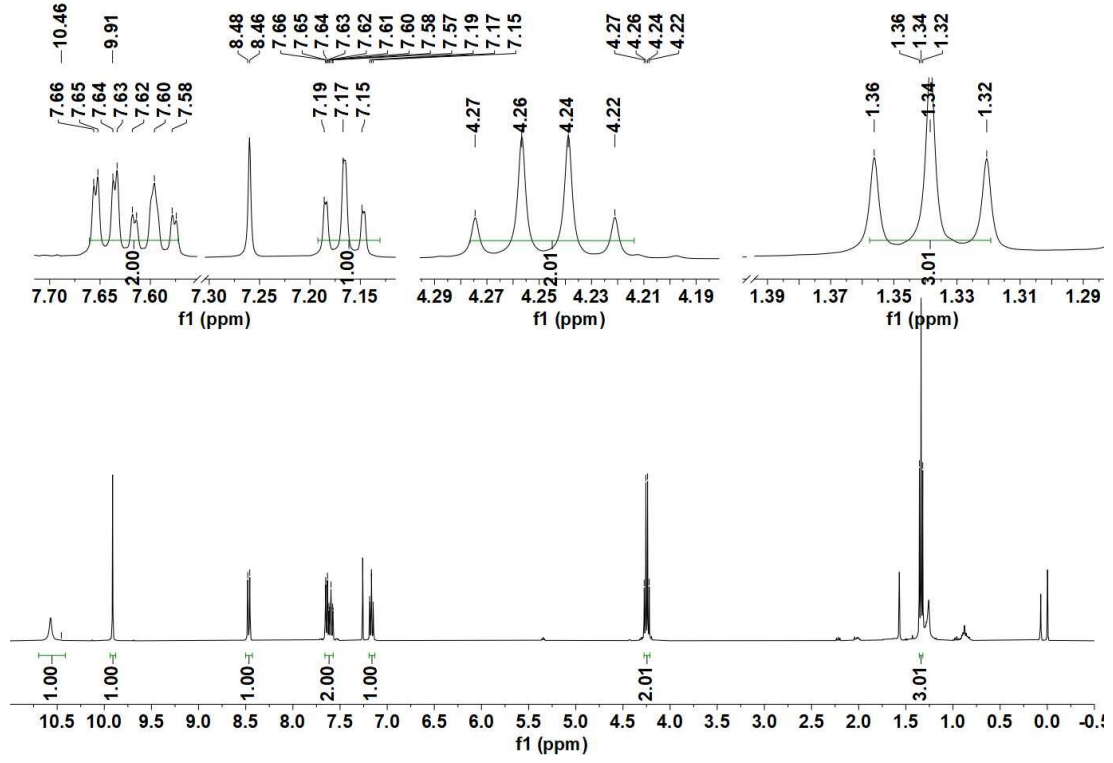


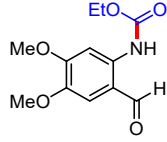




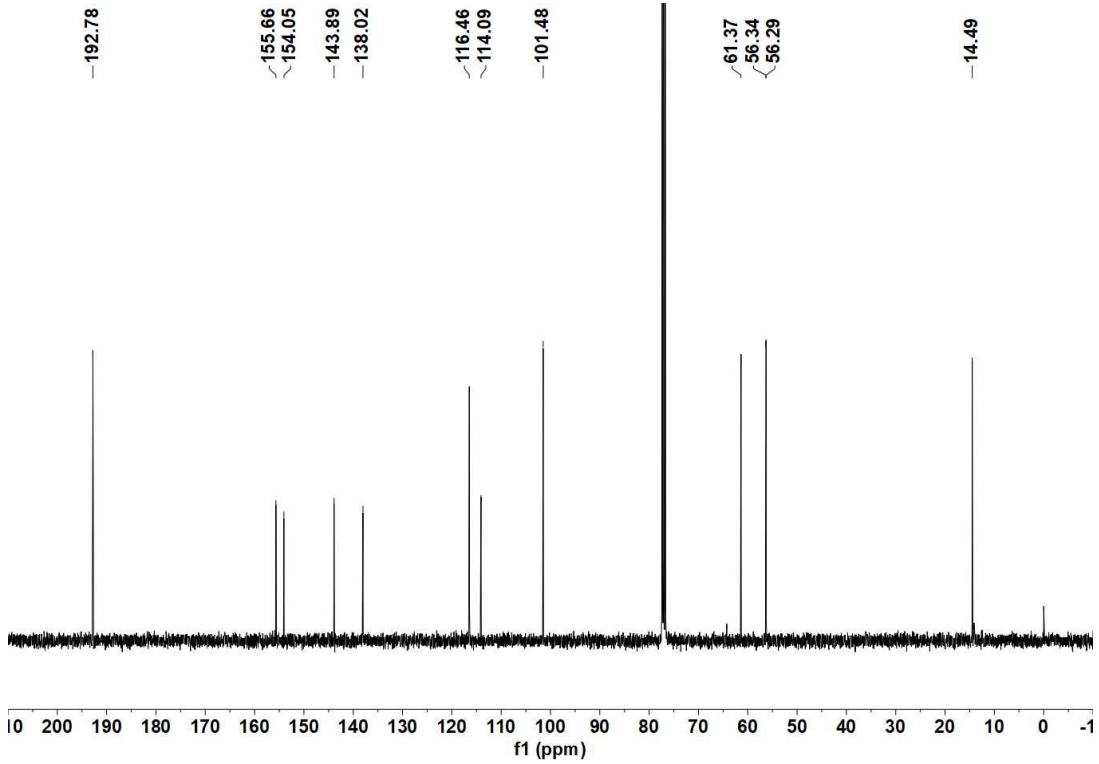
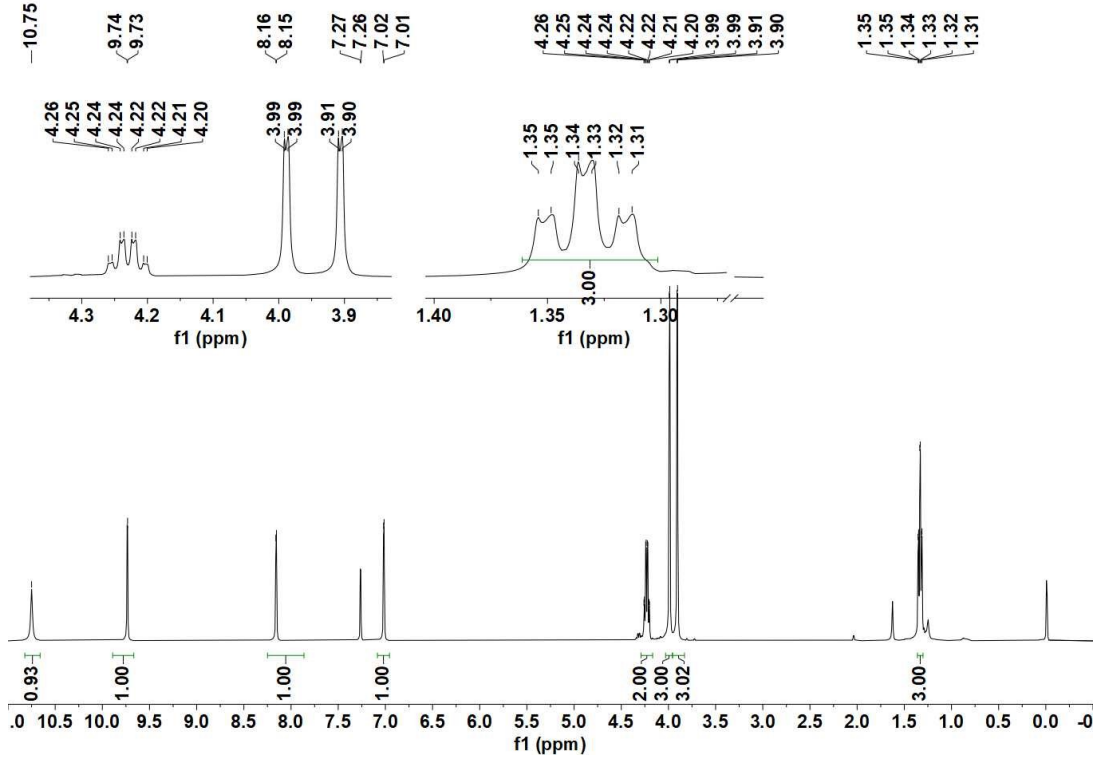


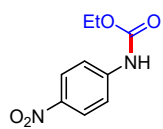
(7f)



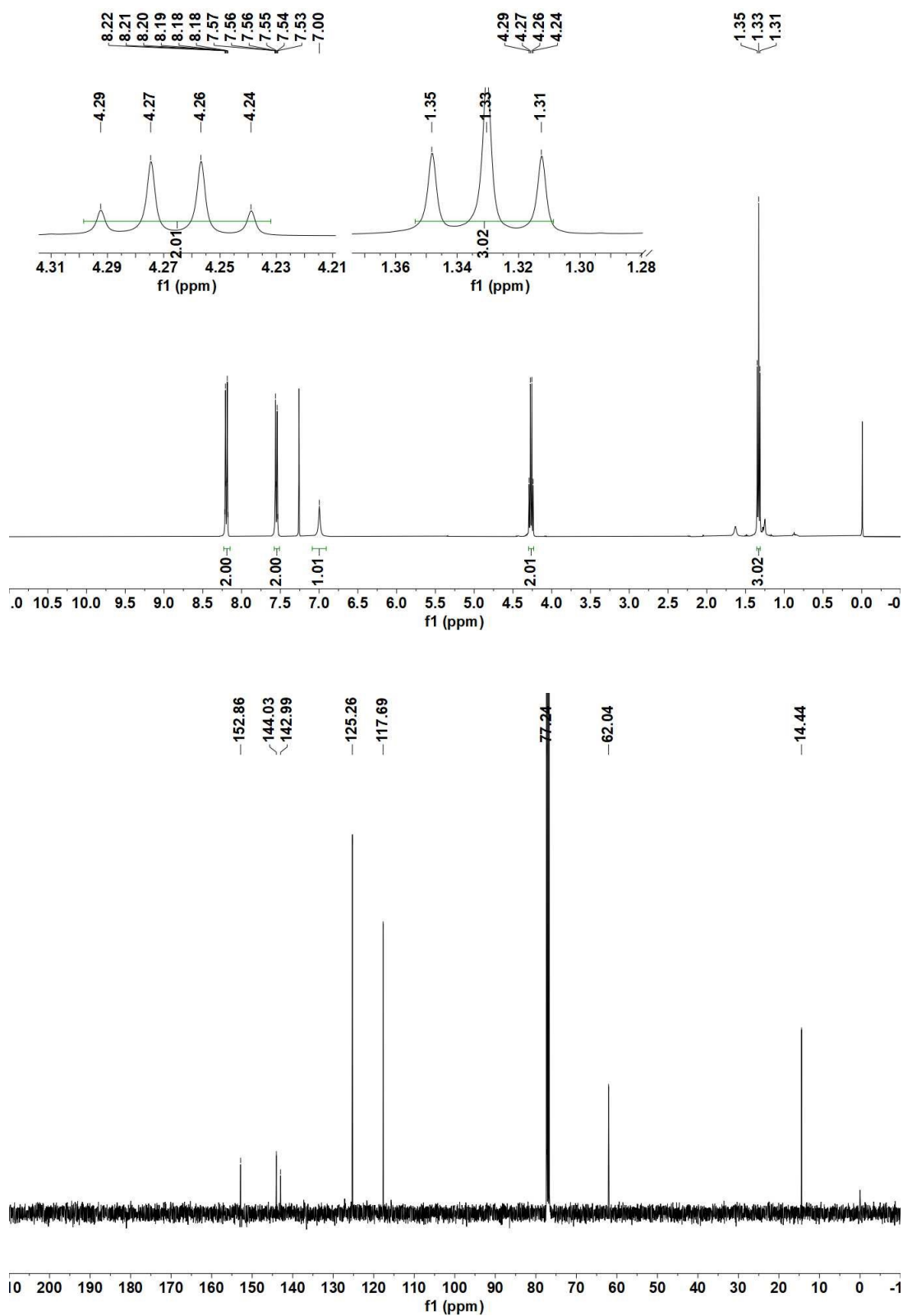


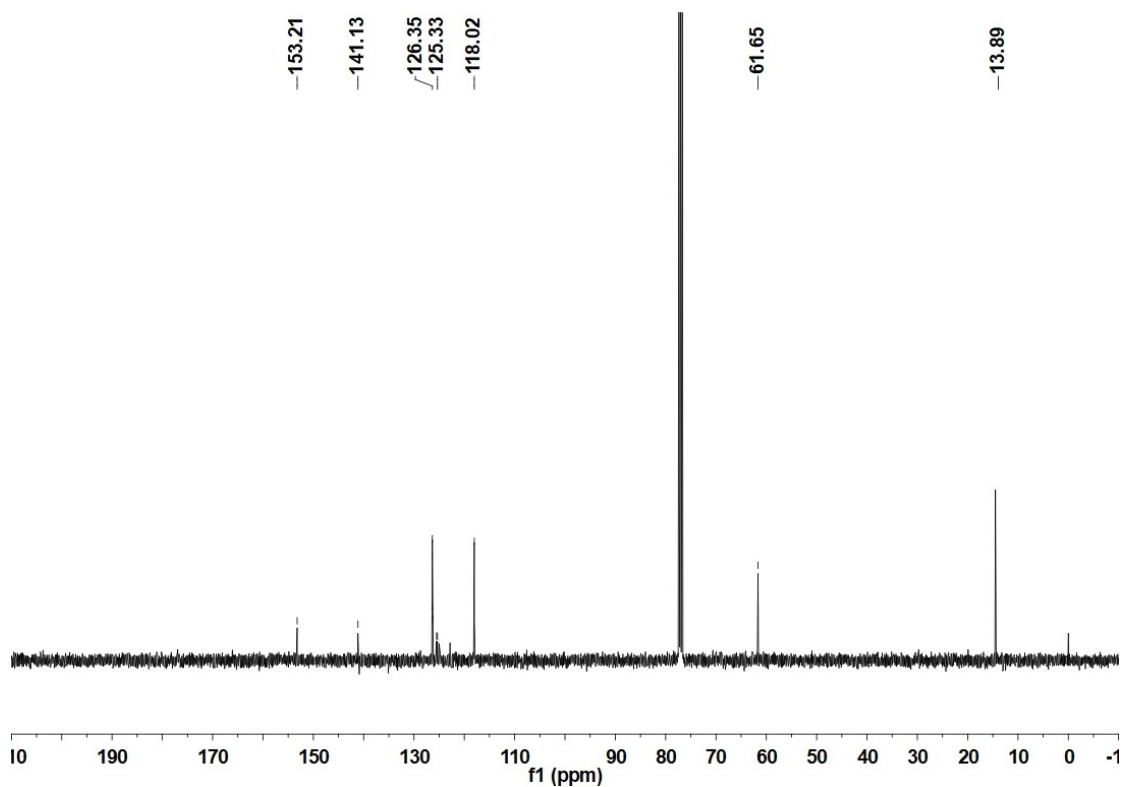
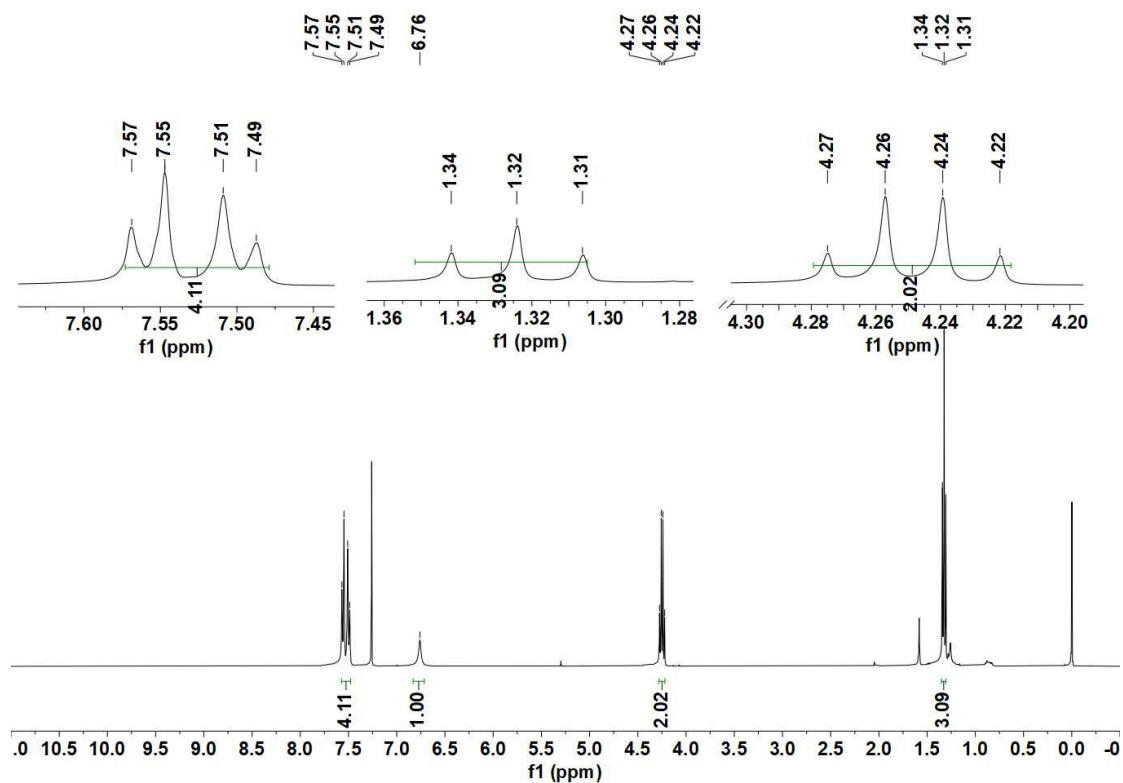
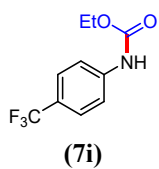
(7g)

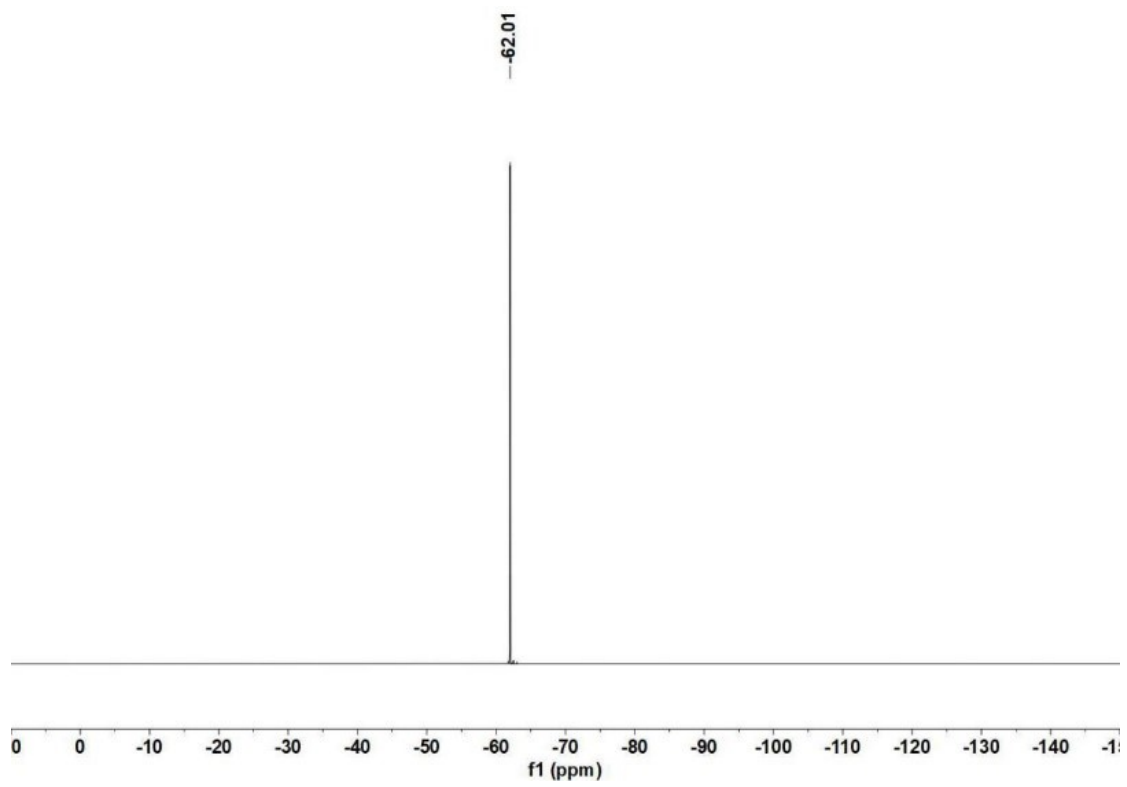


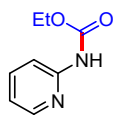


(7h)

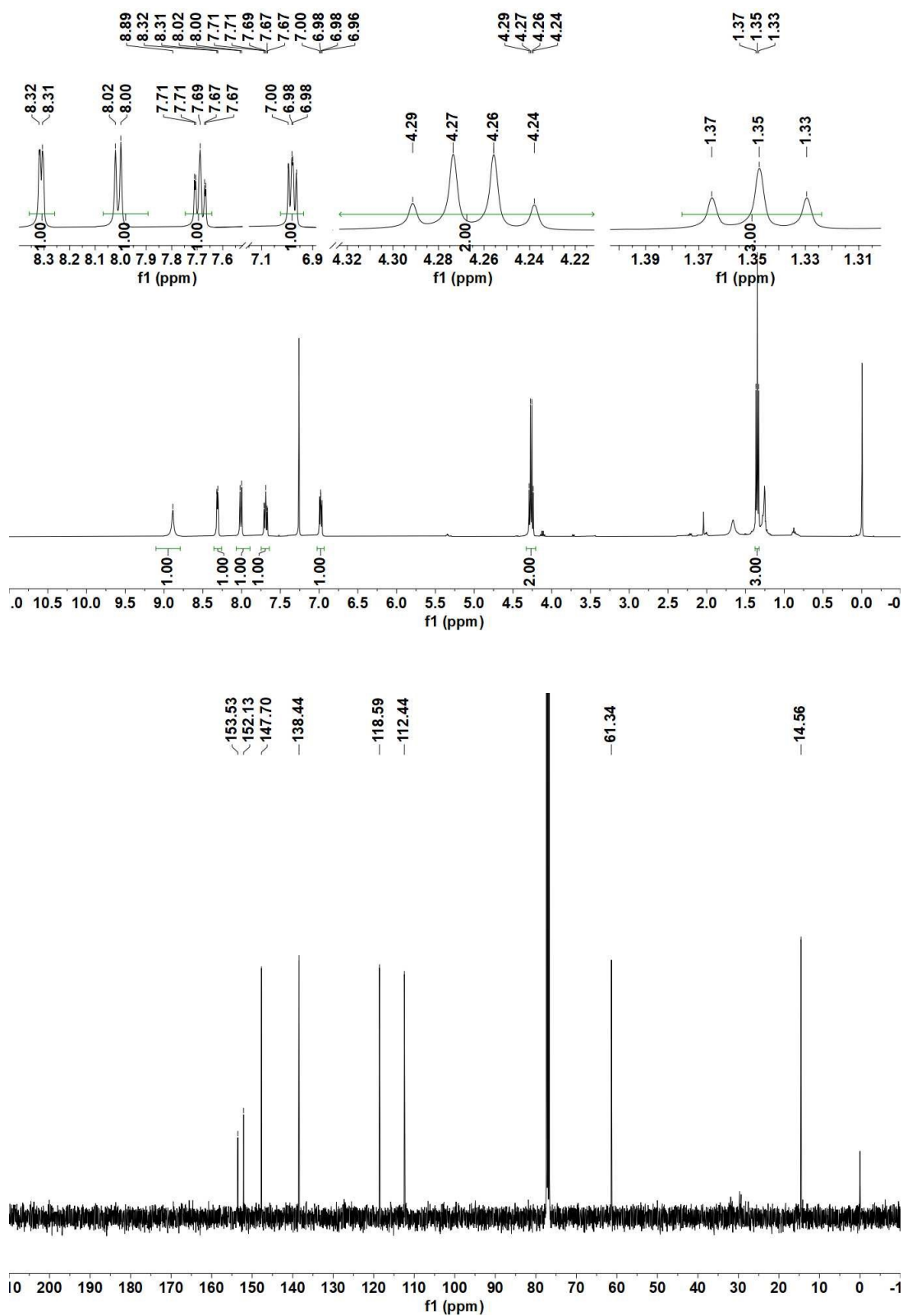


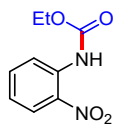




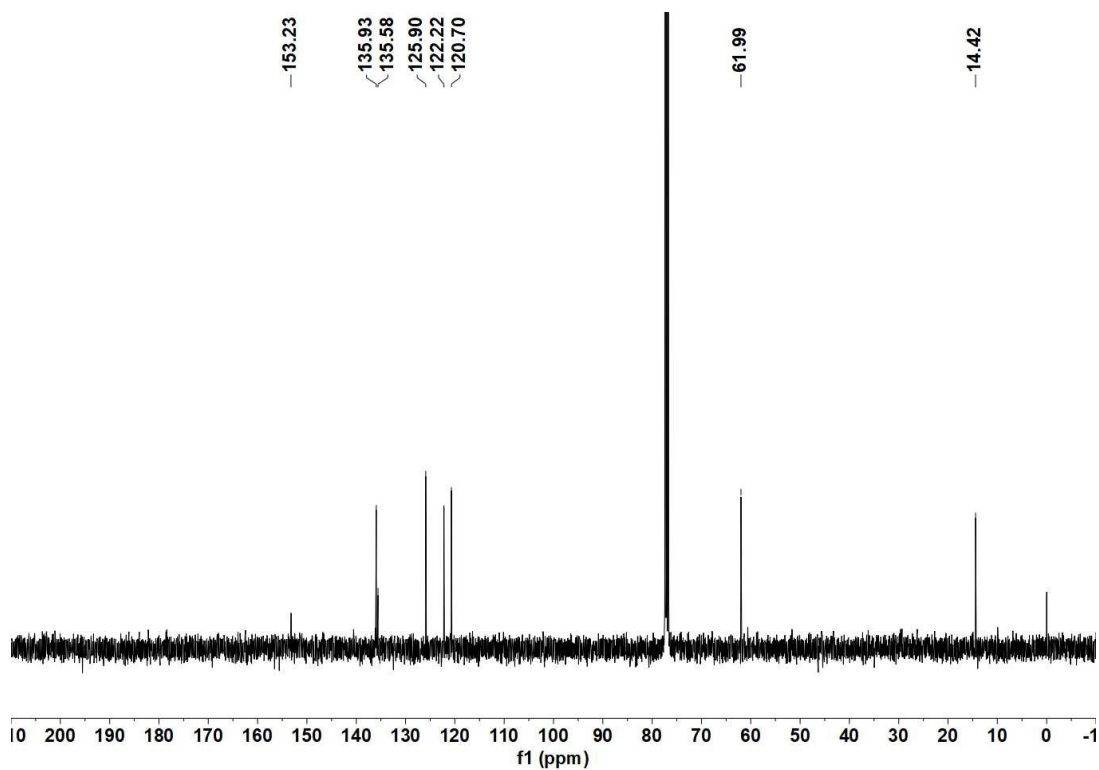
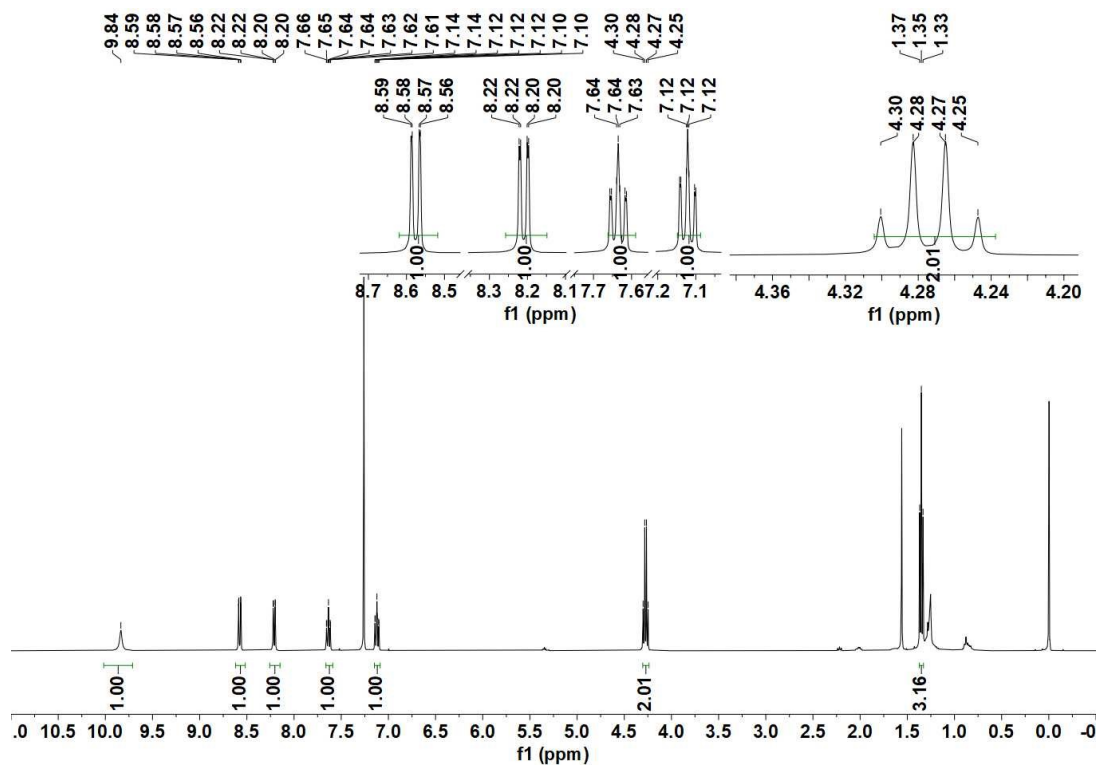


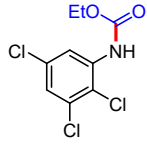
(7j)



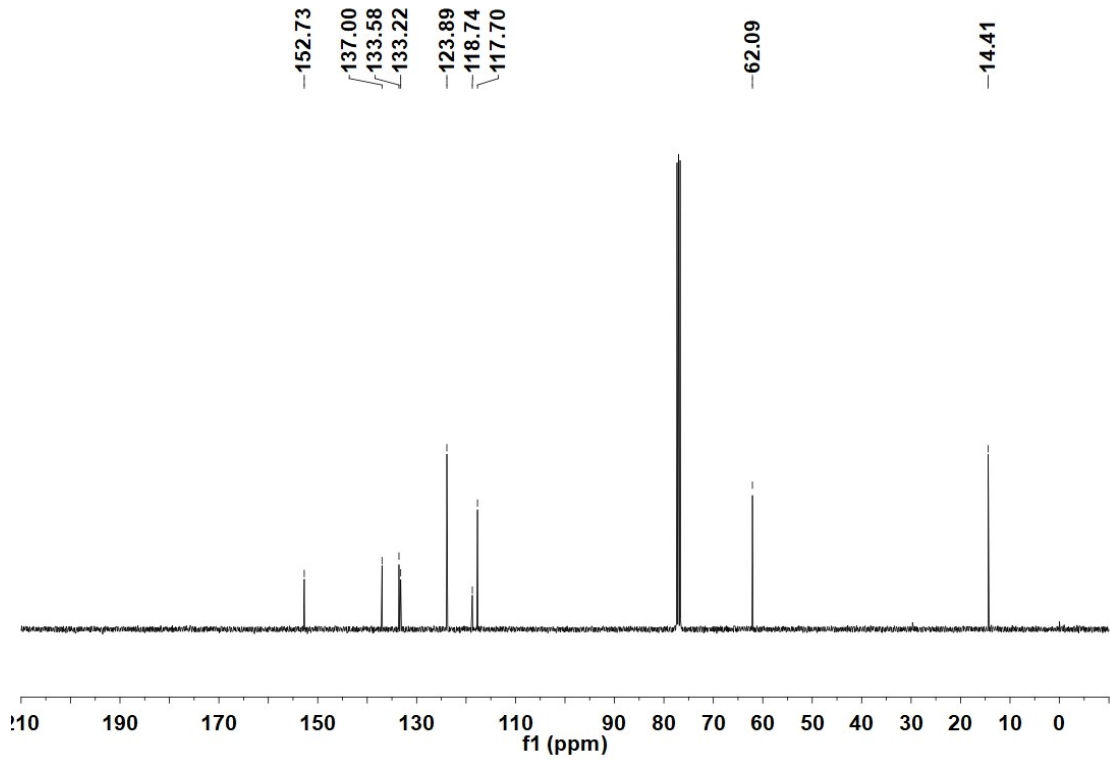
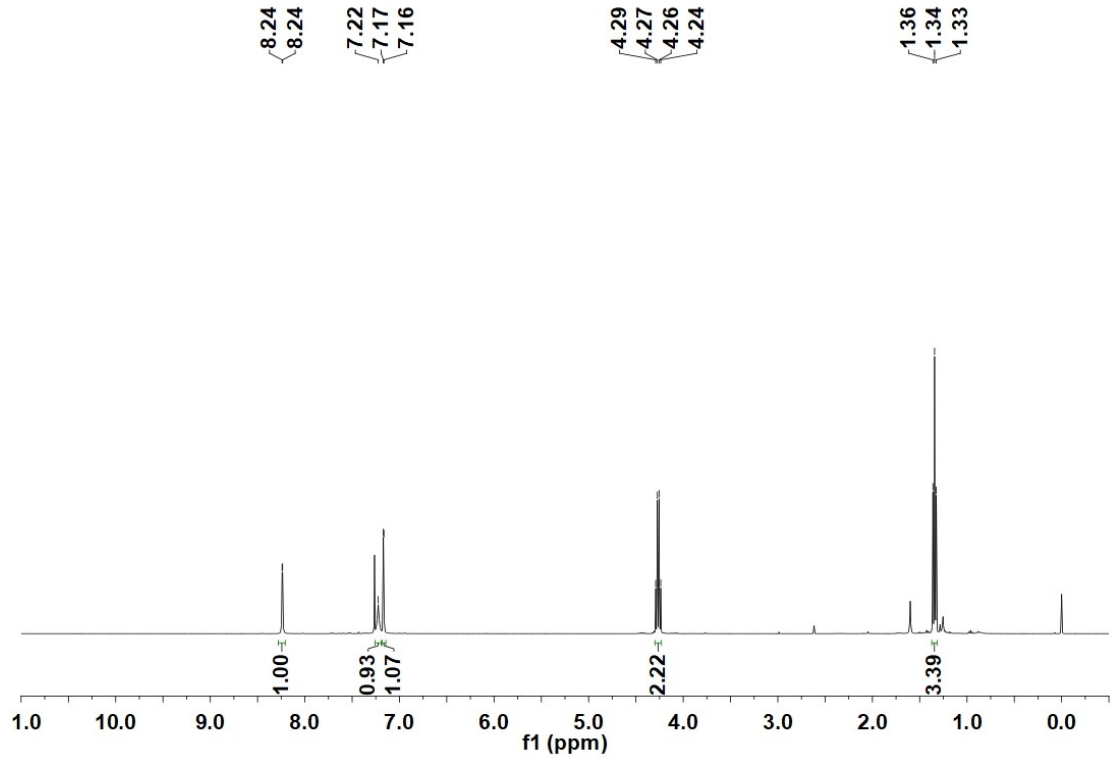


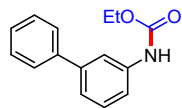
(7k)



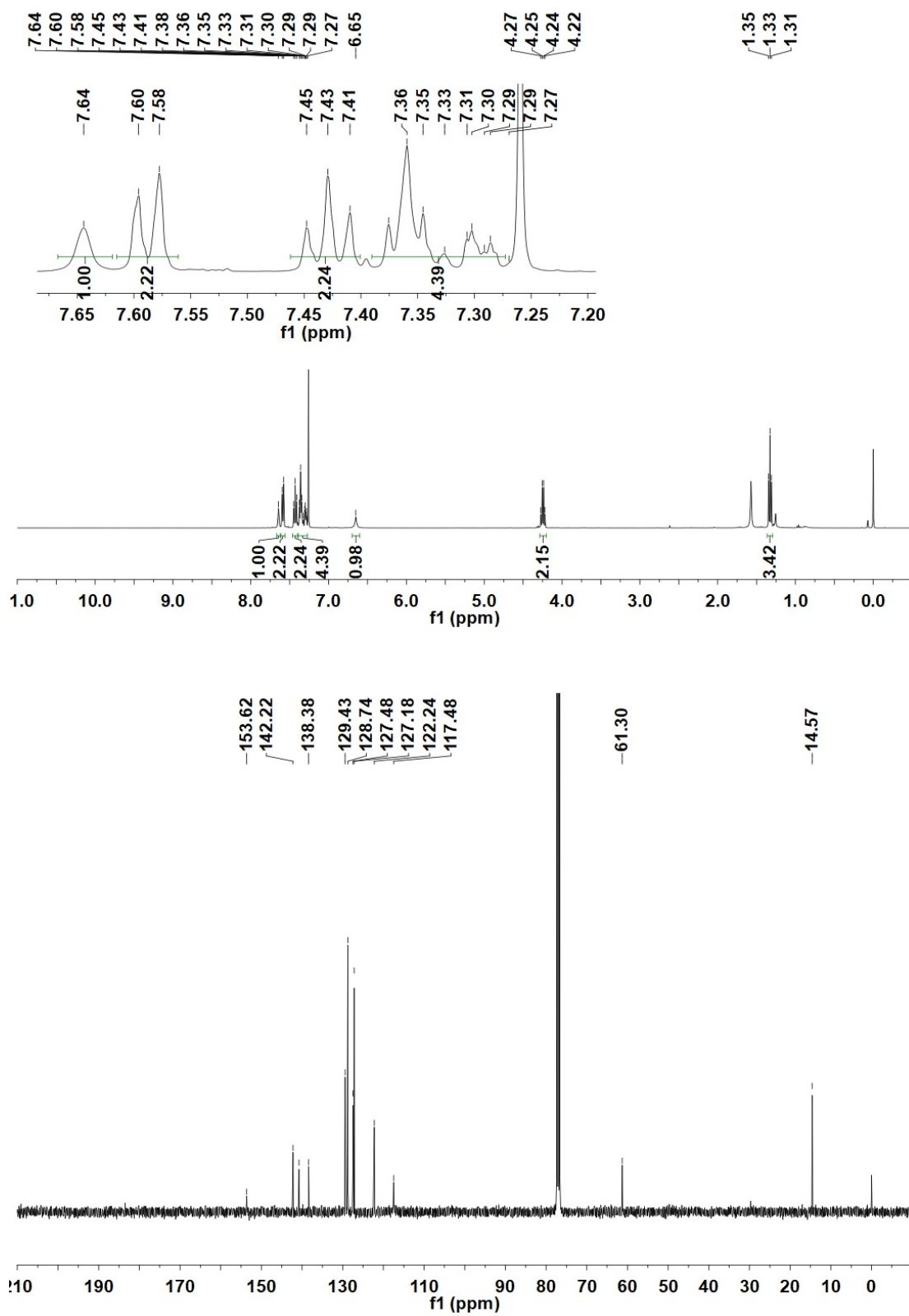


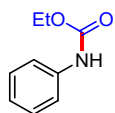
(7I)



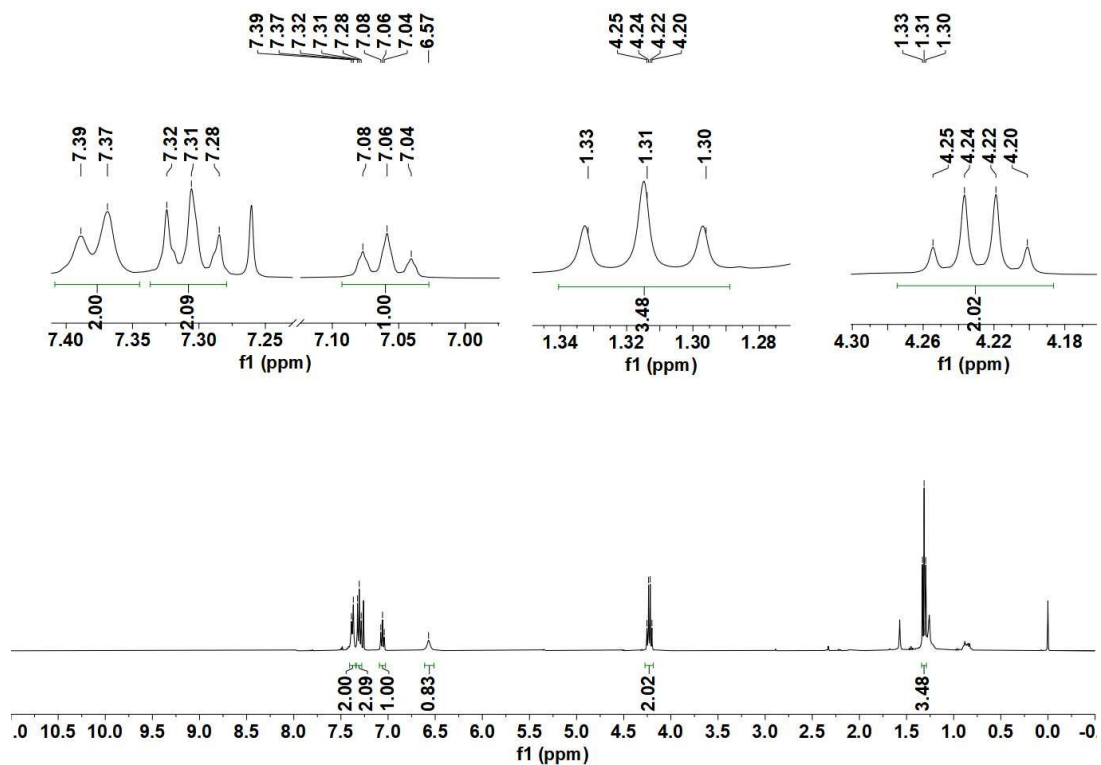


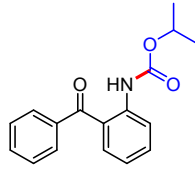
(7m)



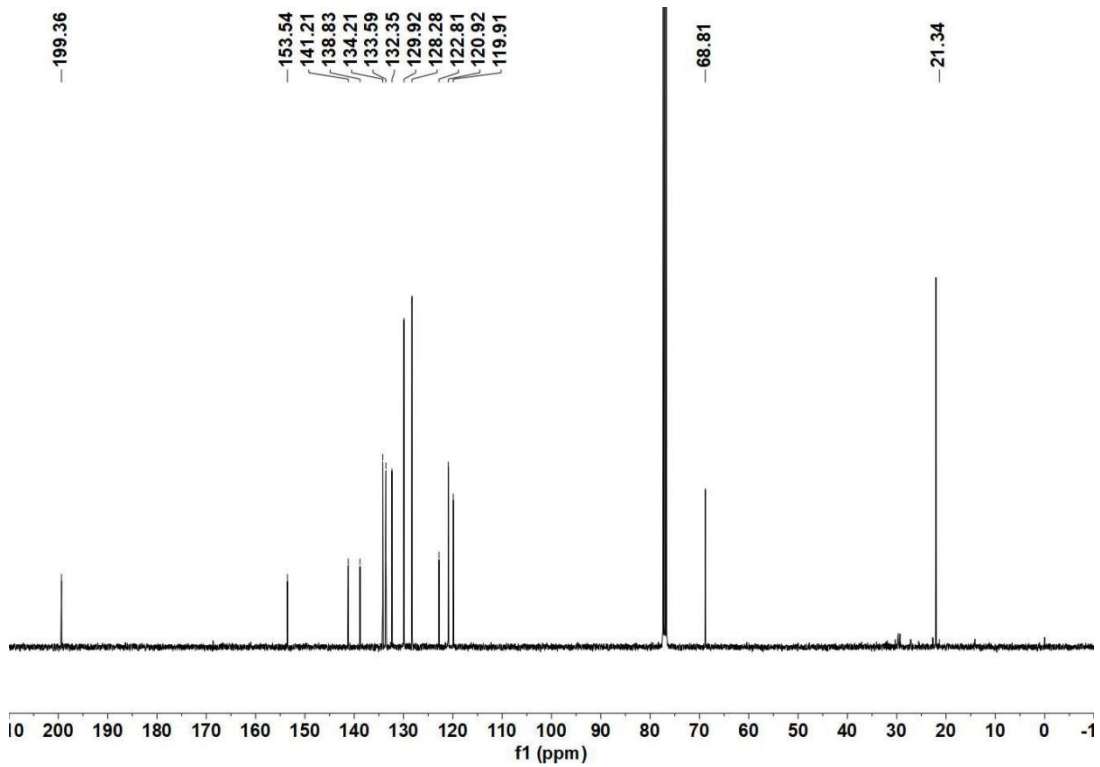
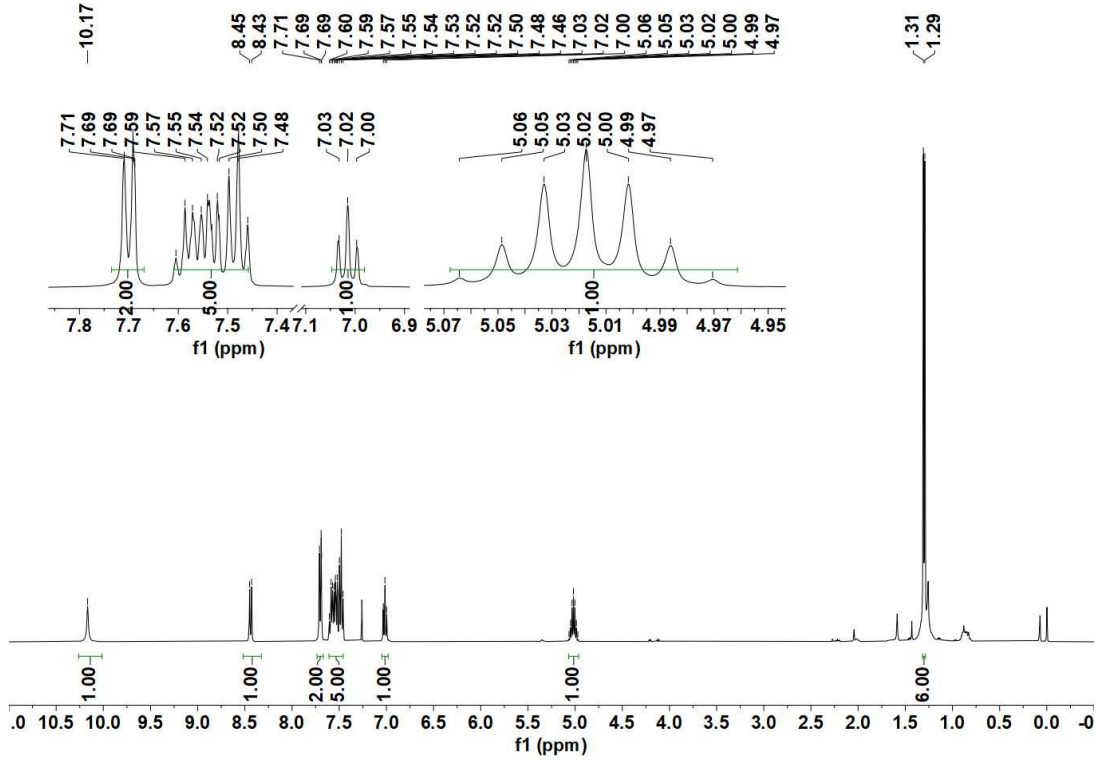


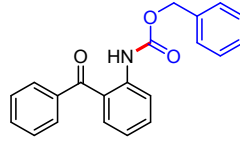
(7n)



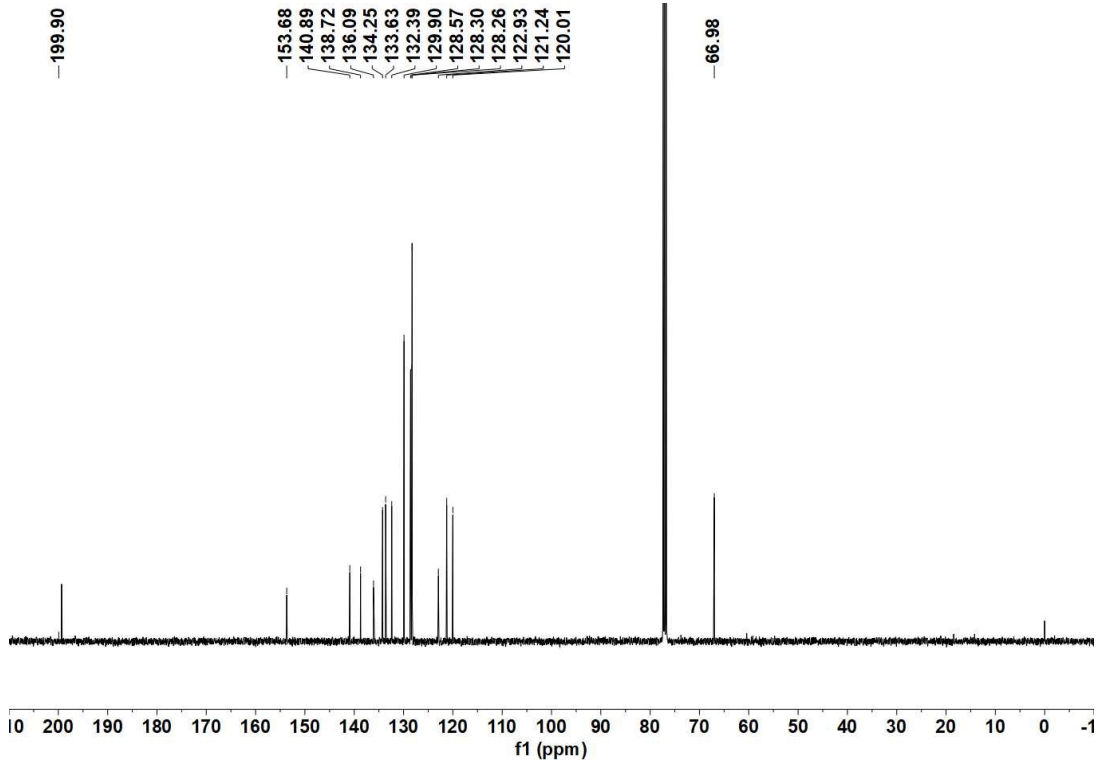
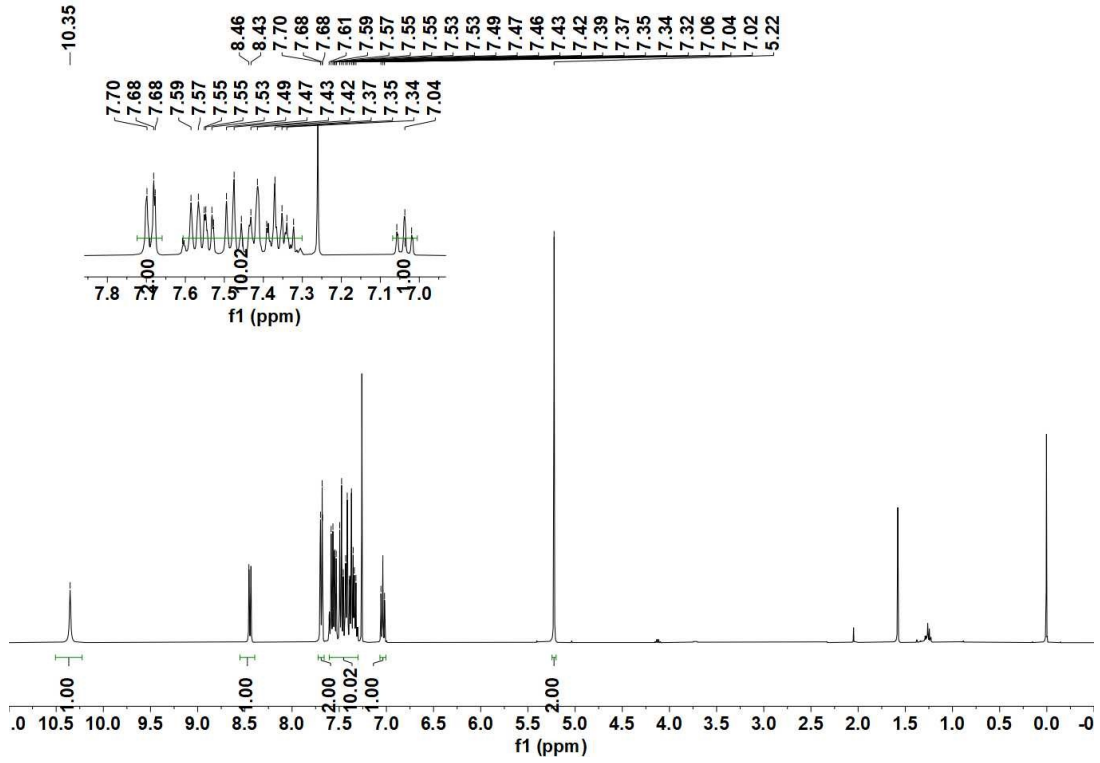


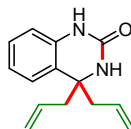
(7o)



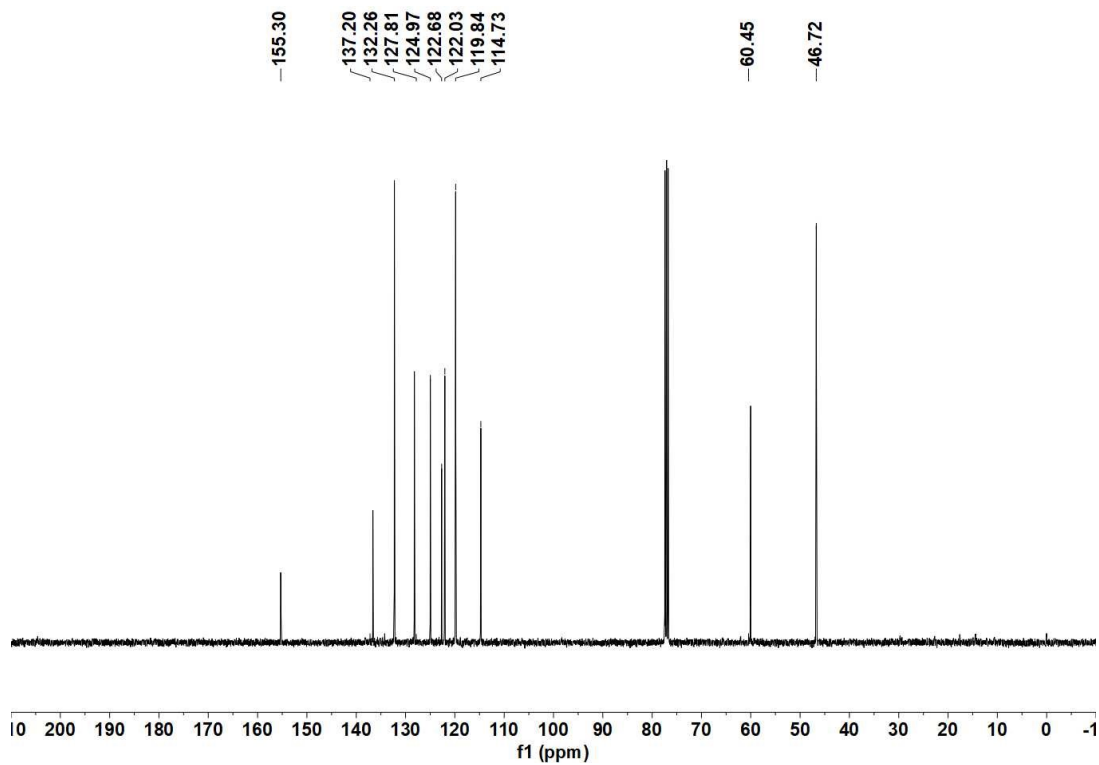
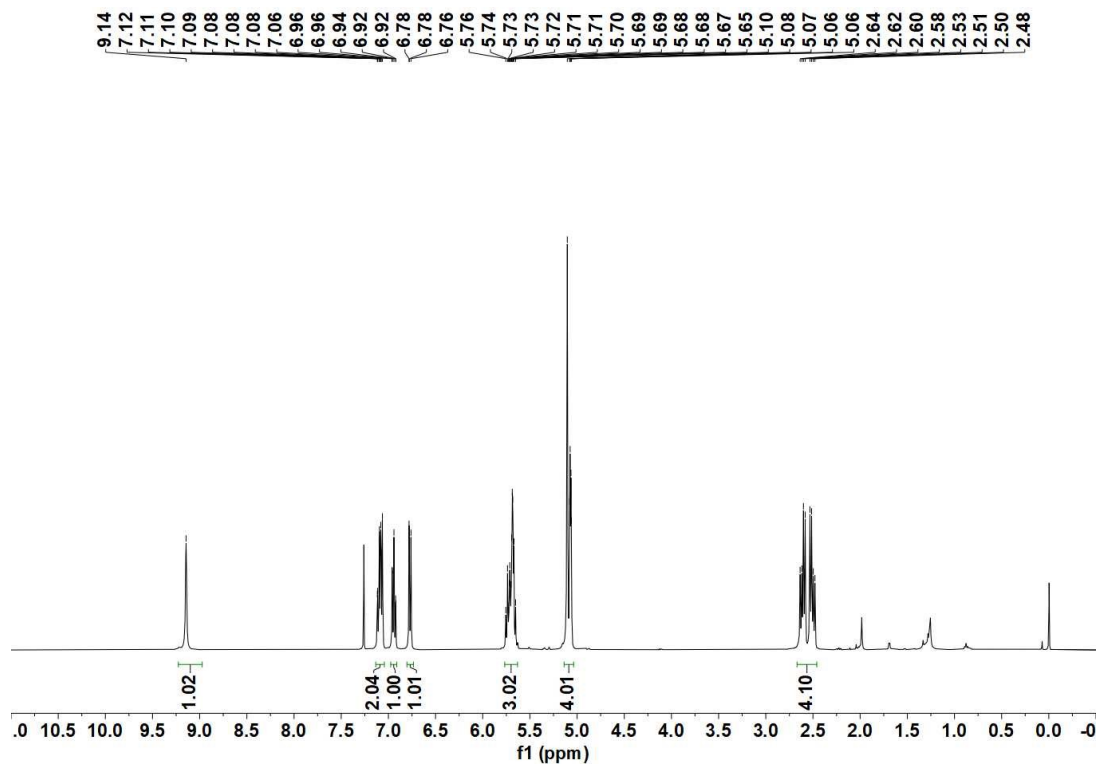


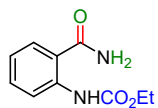
(7p)



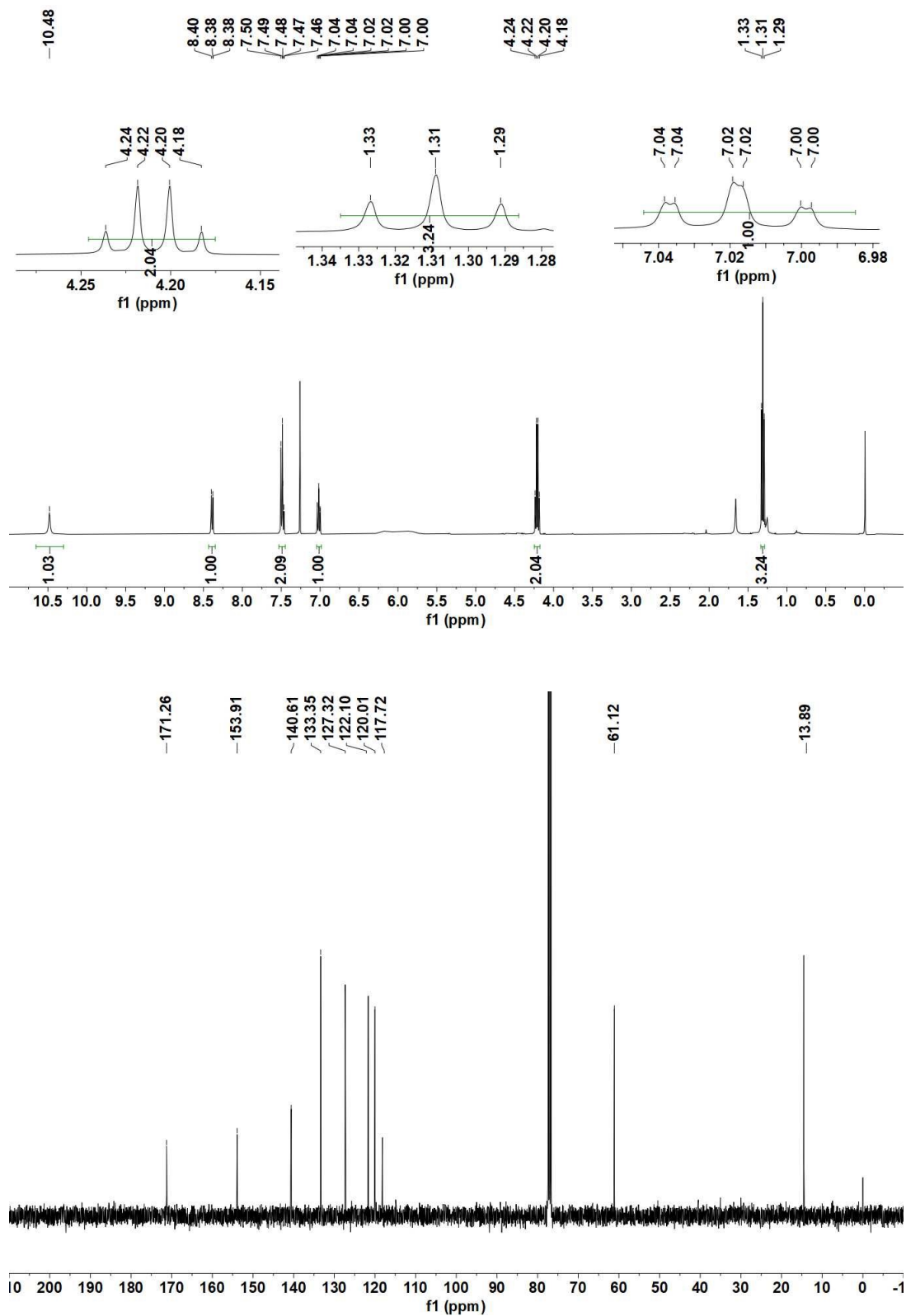


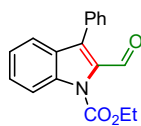
(8a)



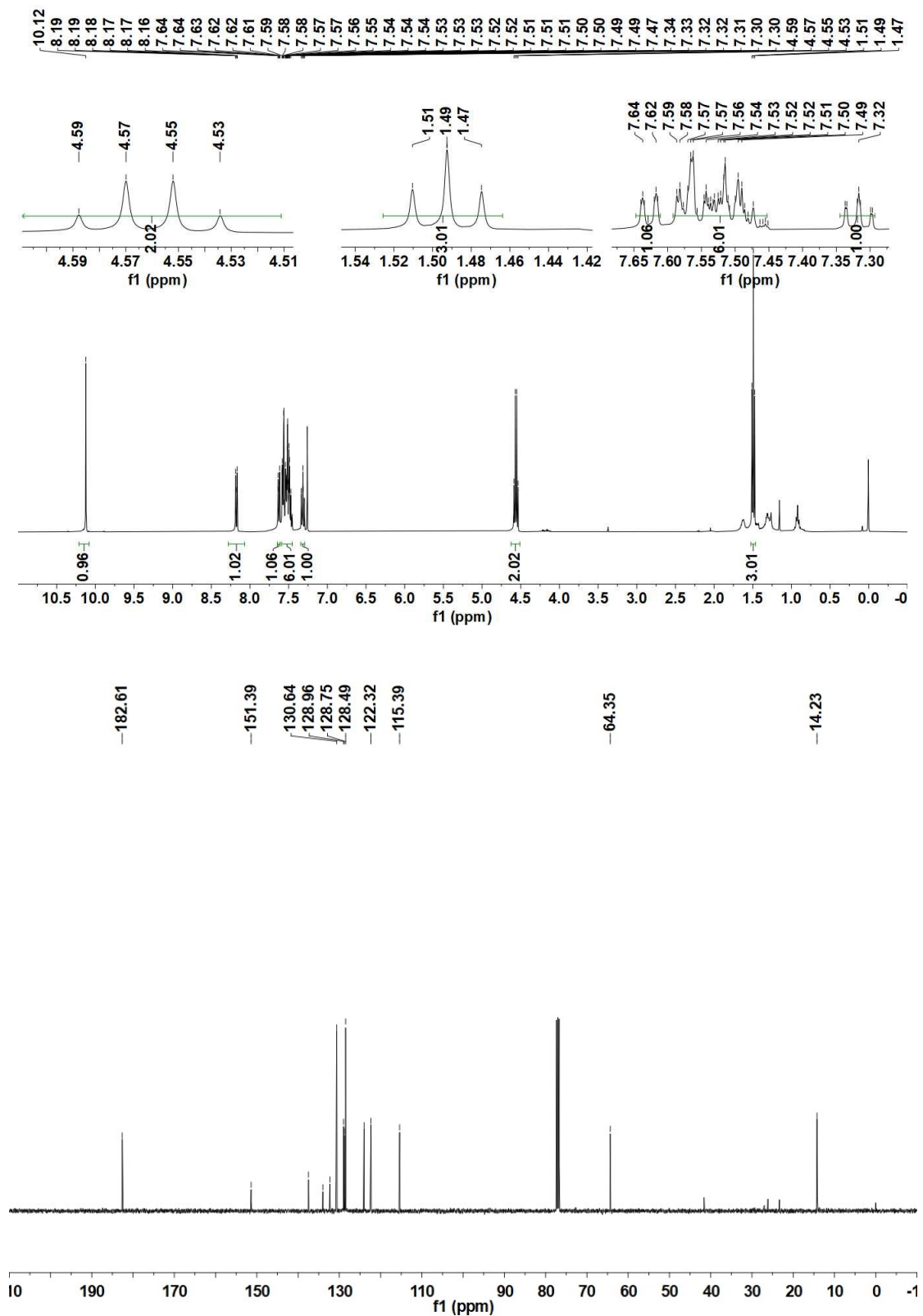


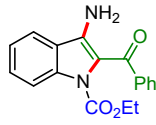
(9a)





(10a)





(11a)

