

Palladium-Catalyzed Radical Cascade Difluoroalkylation/Cyclization of Acrylamide with Ethyl Difluorobromoacetate

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General Remarks: Column chromatography was carried out on silica gel. Unless noted ^1H NMR spectra were recorded on 400 MHz in CDCl_3 , ^{13}C NMR spectra were recorded on 100 MHz in CDCl_3 , ^{19}F NMR spectra were recorded on 376 MHz in CDCl_3 , and ^{31}P NMR spectra were recorded on 162 MHz in CDCl_3 . IR spectra were recorded on an FT-IR spectrometer and only major peaks are reported in cm^{-1} . Melting points were determined on a microscopic apparatus and were uncorrected. All new products were further characterized by HRMS (high resolution mass spectra), high resolution mass spectrometry (HRMS) spectra was obtained on a microTOF-Q instrument equipped with an ESI source; copies of their ^1H NMR and ^{13}C NMR spectra are provided.

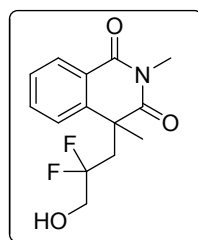
Table S1. Optimization of reaction conditions

Entry	[Pd] (mol %)	Ligand (%)	(mol %)	Base (equiv.)	Solvent	Temperature	Yield (%)
1	10% $\text{PdCl}_2(\text{PPh}_3)_2$	20% DPE-phos		2eq. K_2CO_3	dioxane	80	25%
2	10% $\text{PdCl}_2(\text{PPh}_3)_2$	20% Xantphos		2eq. K_2CO_3	dioxane	100	N.R.
3	10% $\text{PdCl}_2(\text{PPh}_3)_2$	20% Xantphos		2eq. Cs_2CO_3	dioxane	100	N.R.
4	5% $\text{Pd}(\text{PPh}_3)_4$	10% DPE-phos		2eq. K_2CO_3	dioxane	100	15%
5 ^a	5% $\text{Pd}(\text{PPh}_3)_4$	10% DPE-phos		2eq. K_2CO_3	dioxane	80	16%

a: 2 eq. IC_4F_9 was used instead of $\text{BrCF}_2\text{PO}(\text{OEt})_2$.

Reduction of **3a** to **3aa**

To a solution of **3a** (0.3 mmol) in THF/ H_2O (50:1, 5.0 mL) was added NaBH_4 (0.3 mmol) in batches at 0 °C. Then, the reaction was carried out at r.t. for 6h. After the reaction, 3 mL water was added to quench the reaction, and the resulting mixture was extracted twice with EtOAc. The combined organic extracts were washed with brine, dried over Na_2SO_4 and concentrated. Purification of the crude product by flash column chromatography afforded the product **3aa** (petroleum ether/ethyl acetate as eluent (3:1)).



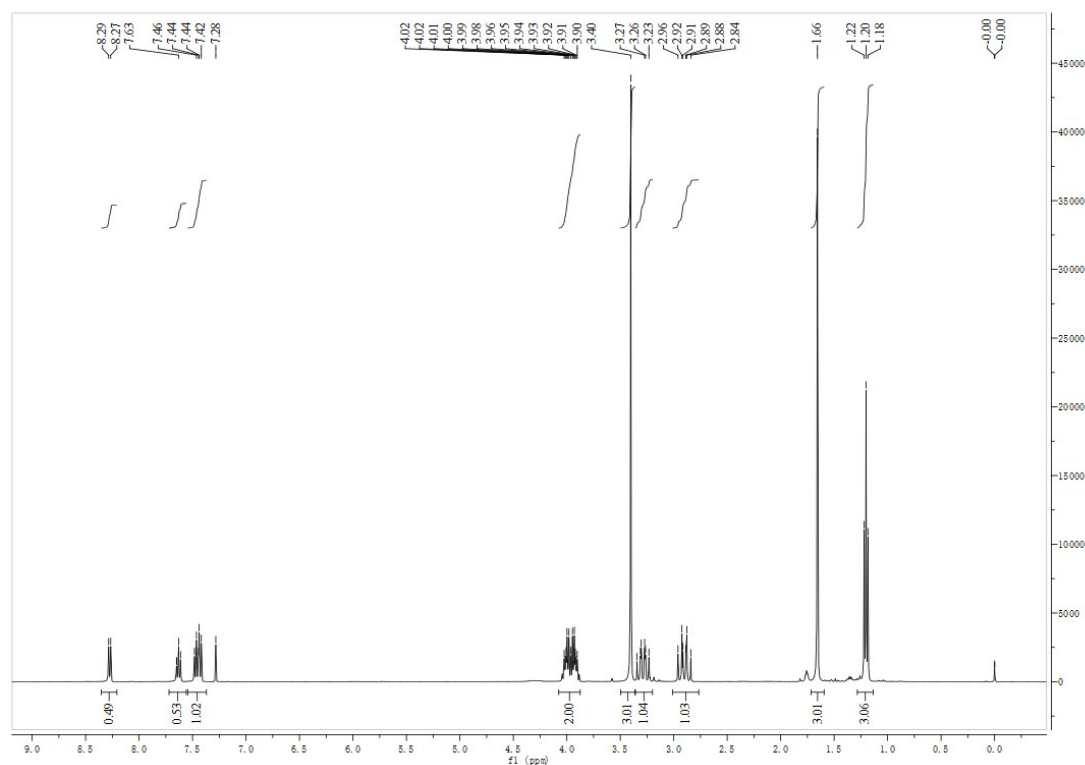
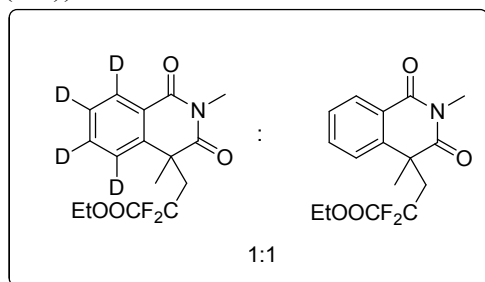
M.P.=94-95 °C, **3aa**, 72mg

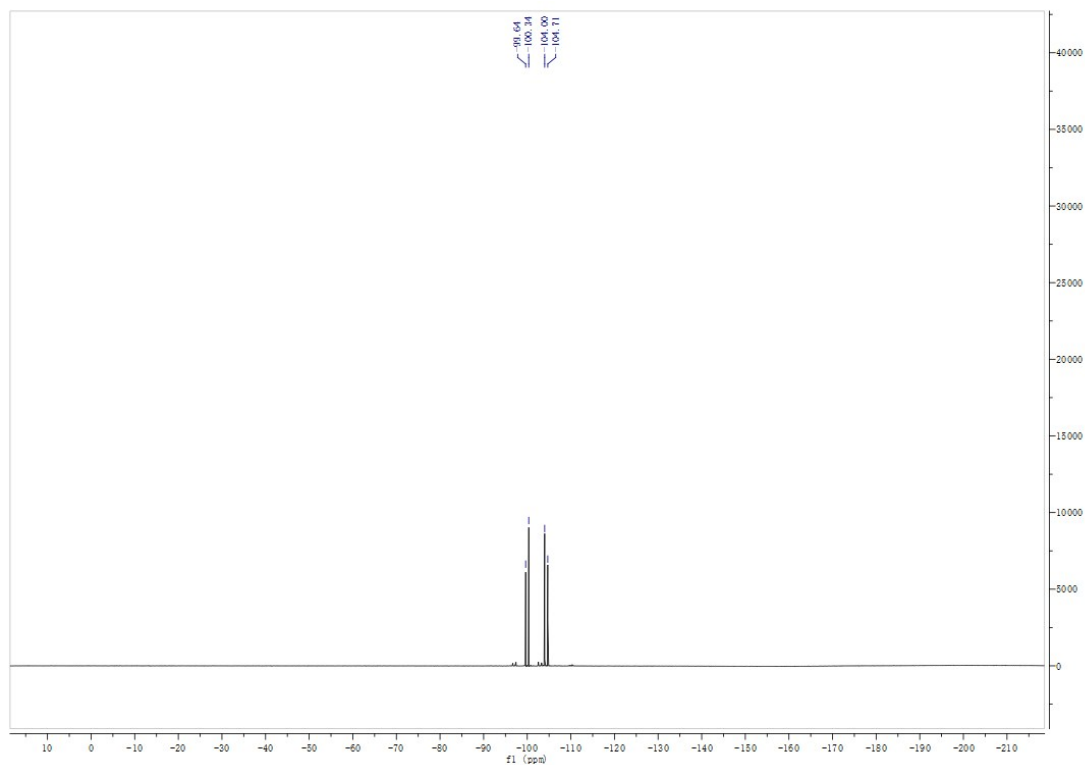
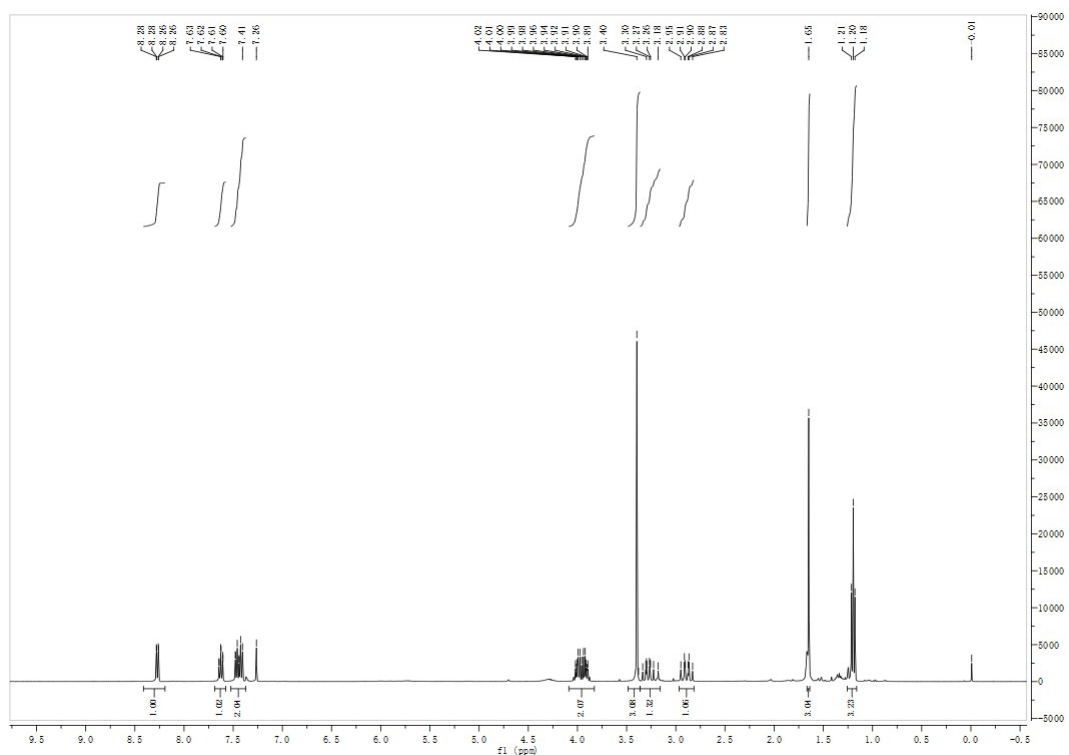
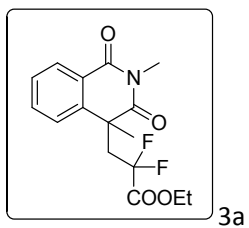
^1H NMR (400 MHz, CDCl_3): 8.24-8.26 (m, 1 H), 7.62-7.66 (m, 1 H), 7.43-7.48 (m, 2 H), 3.37-

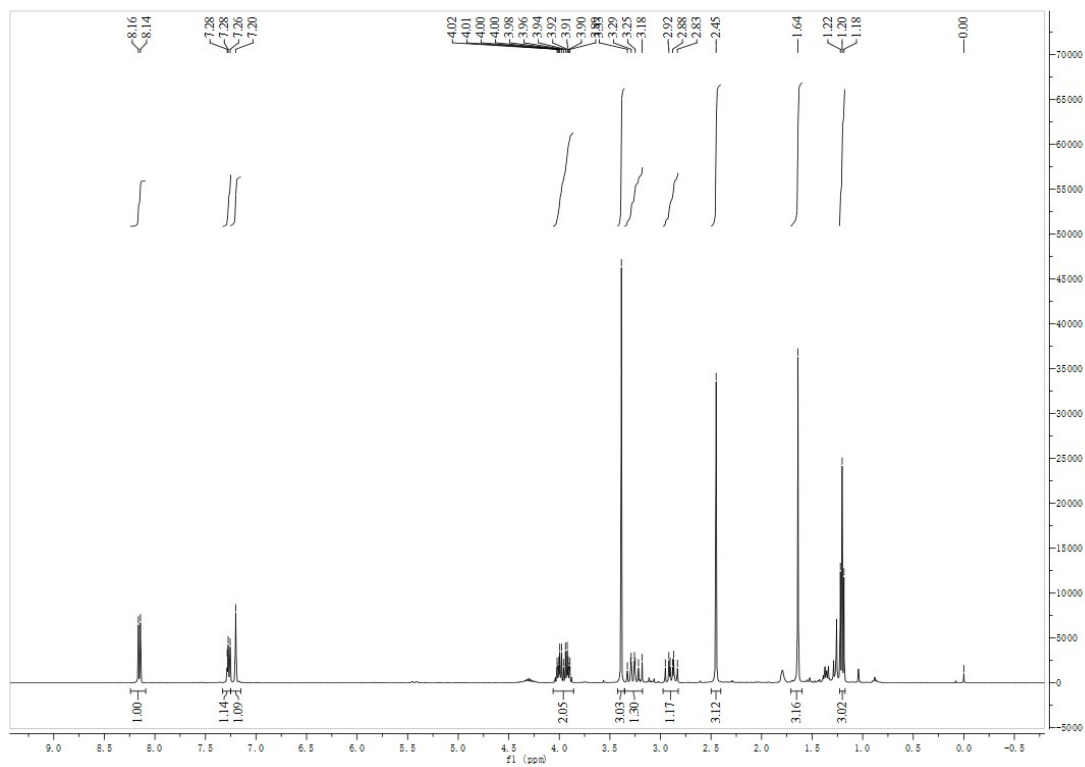
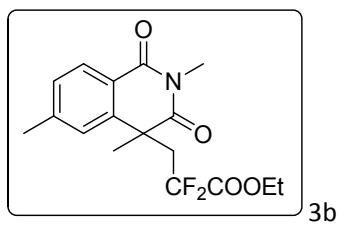
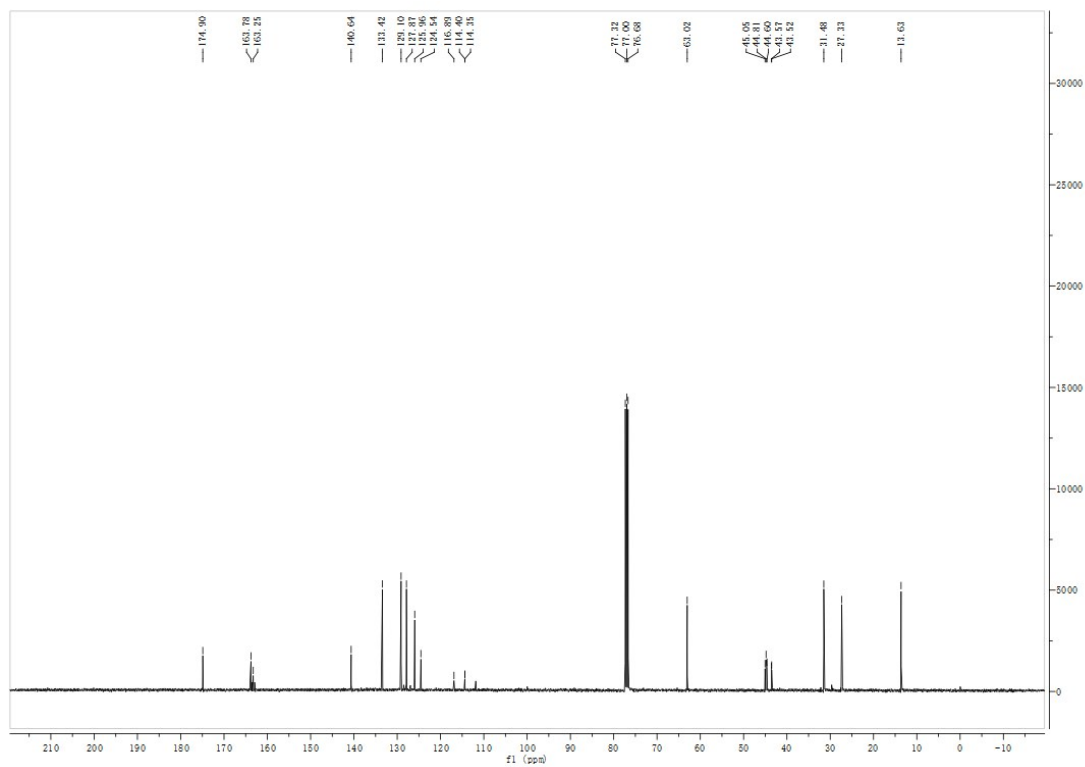
3.46 (m, 1 H), 3.34 (s, 3 H), 3.12-3.24 (m, 1 H), 2.65-2.74 (m, 2 H), 1.62 (s, 3 H); ^{19}F NMR (376 MHz, CDCl_3) δ ppm -103.07 (d, $J = 255.68$ Hz, 1 F), -105.05 (d, $J = 255.68$ Hz, 1 F); ^{13}C NMR (100 MHz, CDCl_3): 175.9, 164.1, 141.9, 133.5, 128.9, 127.5, 125.8, 124.3, 124.0, 121.8, 119.4, 64.6, 64.3, 64.0, 43.7, 43.5, 43.3, 31.6, 27.3; IR (cm^{-1}): 3471, 2944, 2885, 1709, 1662, 1470, 1423, 1314, 1168, 1068, 905, 765, 702;

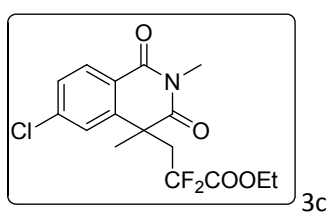
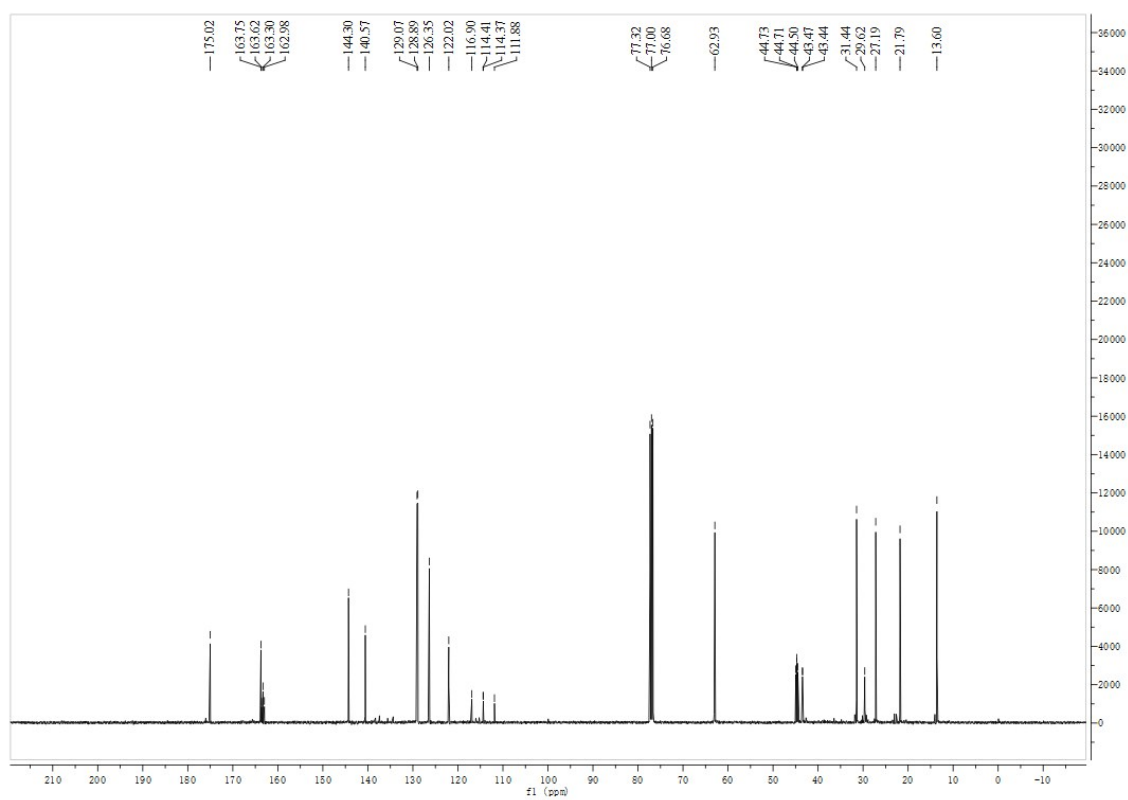
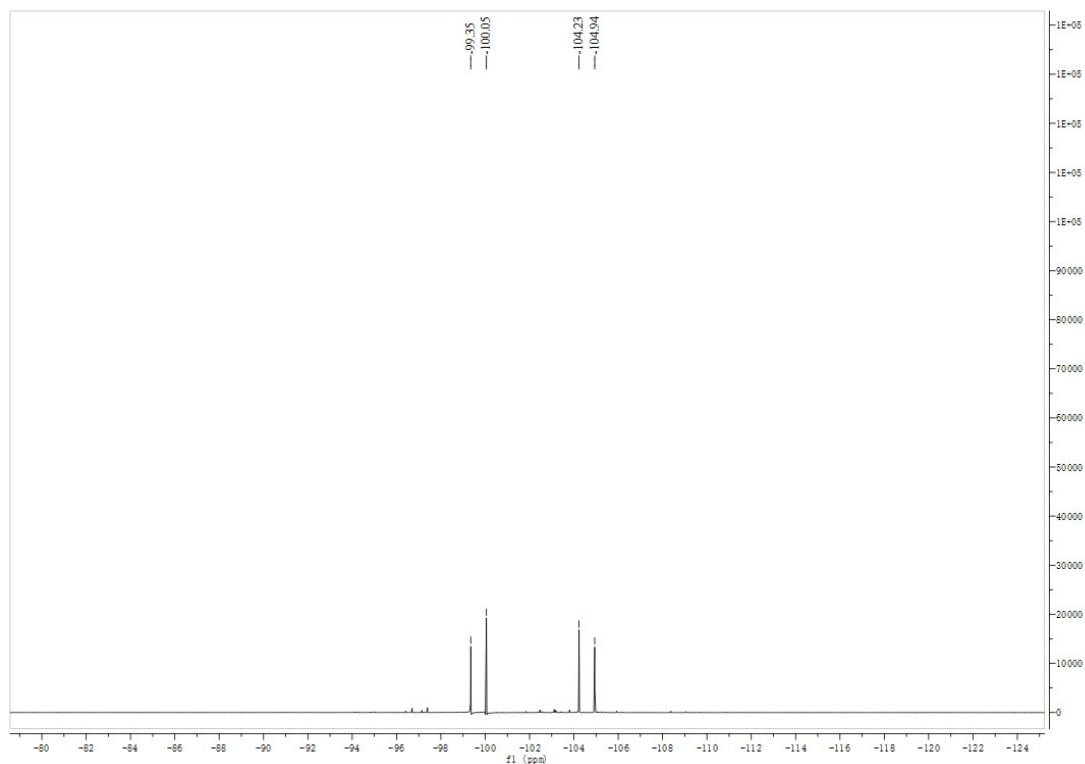
KIE experiment

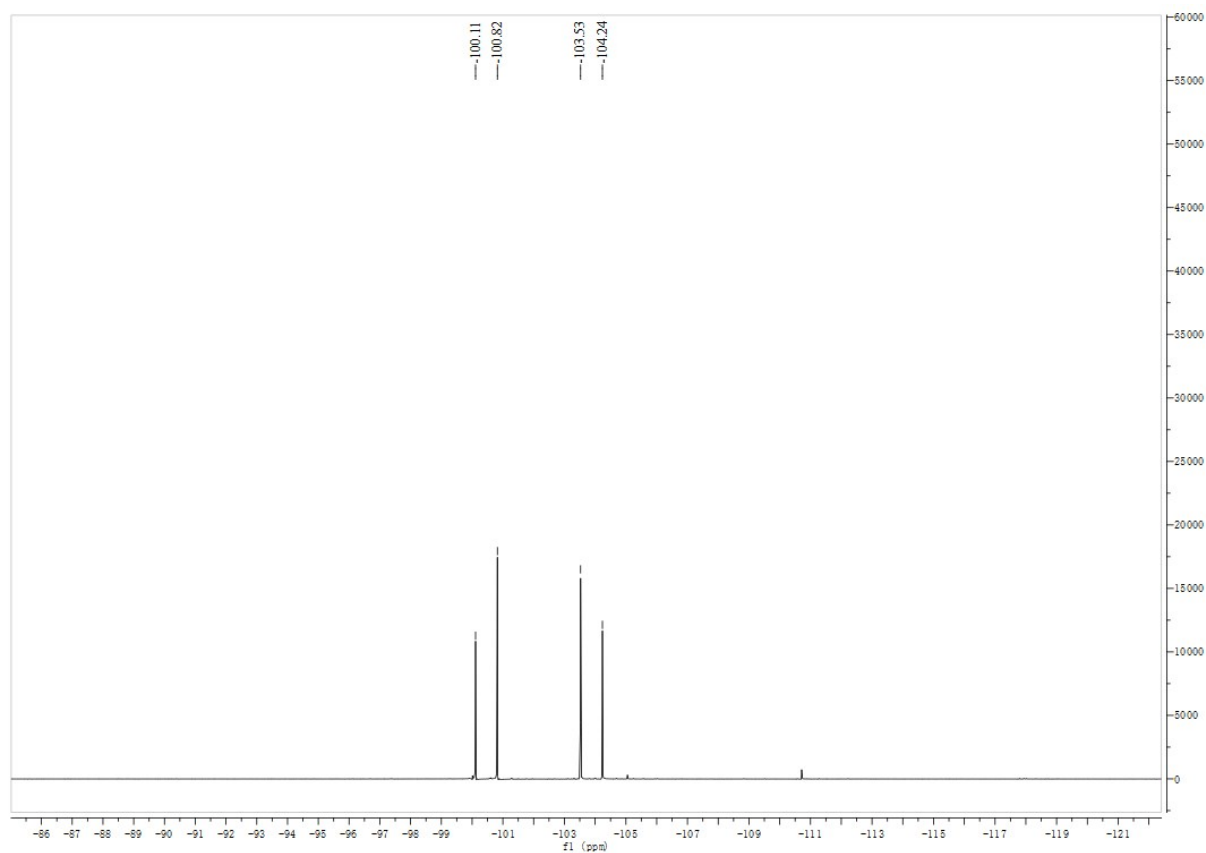
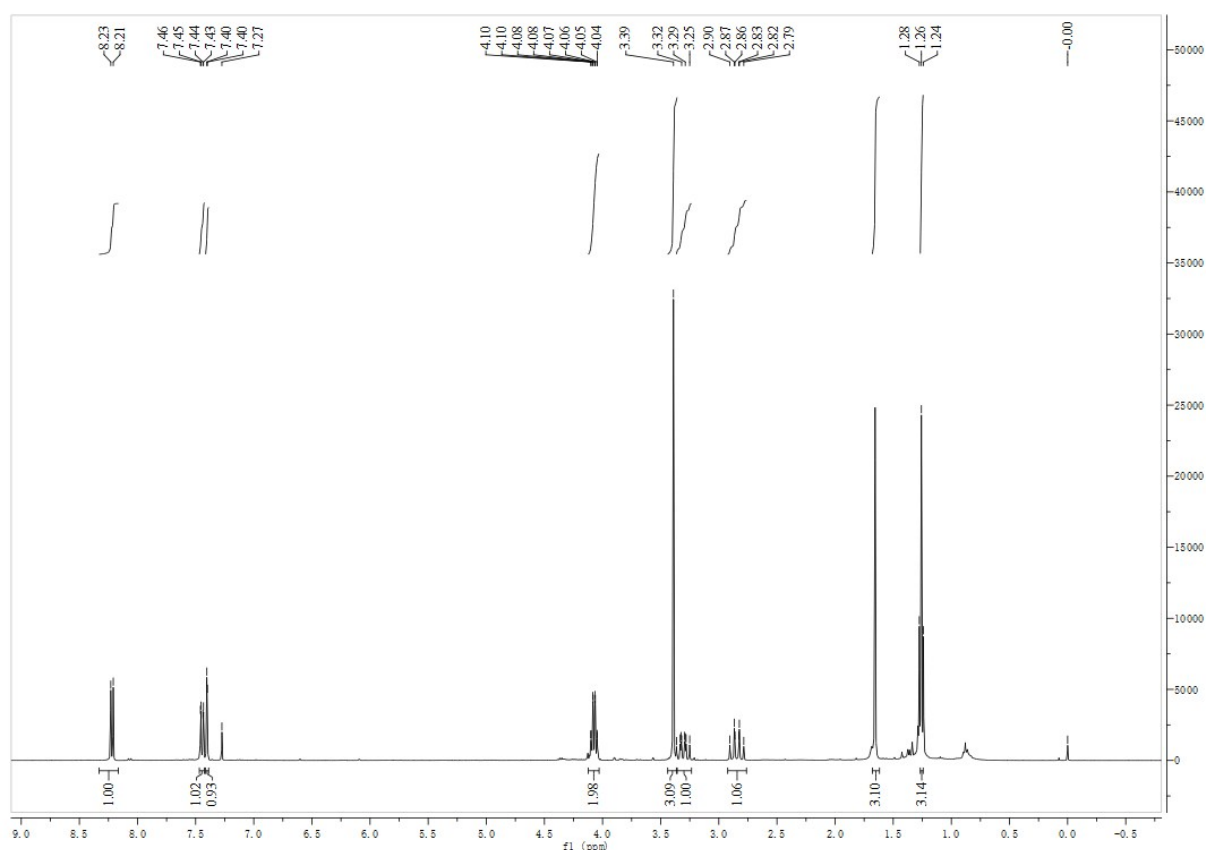
An oven-dried Schlenk tube (10 mL) was equipped with a magnetic stir bar, *N*-methacryloyl-*N*-methylbenzamide (**1a**, 0.2 mmol), pentadeuterated **1a-d₅** (0.2 mmol), ethyl 2-bromo-2,2-difluoroacetate (**2**, 1.2 mmol), 10% $\text{PdCl}_2(\text{PPh}_3)_2$ (0.04 mmol, 28 mg), 20% DPE-phos (0.08 mmol, 43mg), and K_2CO_3 (2 equiv., 110 mg). The flask was evacuated and backfilled with Ar for 3 times. Then dioxane (3.0 mL) was added with syringe under Ar. The reaction mixture was then stirred for 10 h at 80 °C. After the reaction, 3 mL water was added to quench the reaction, and the resulting mixture was extracted twice with EtOAc. The combined organic extracts were washed with brine, dried over Na_2SO_4 and concentrated. Purification of the crude product by flash column chromatography afforded the product (petroleum ether/ethyl acetate as eluent (6:1)).

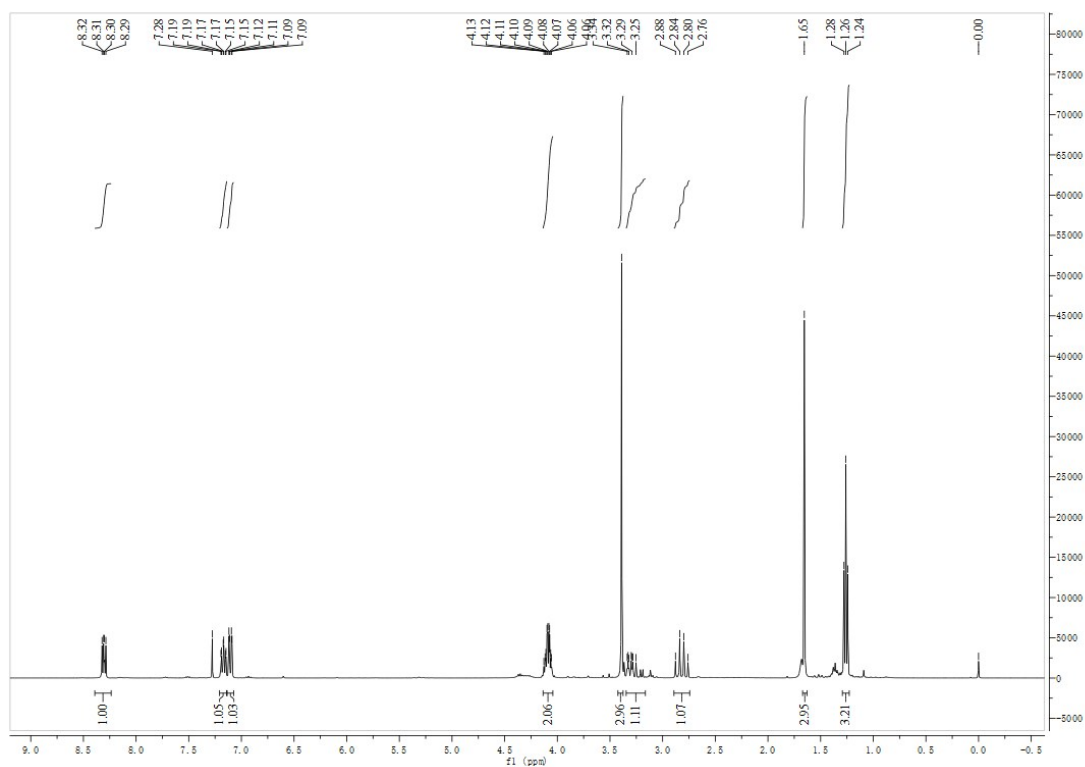
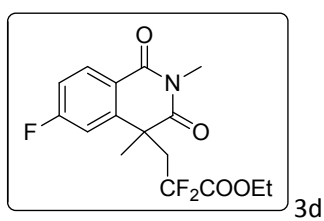
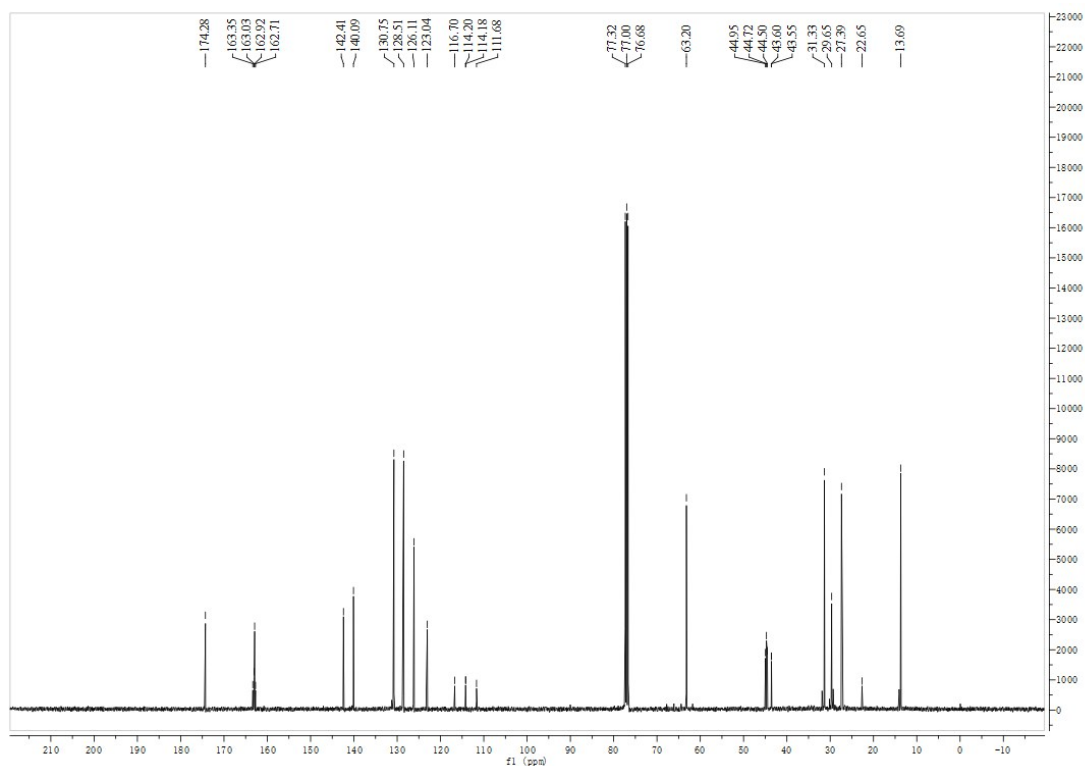


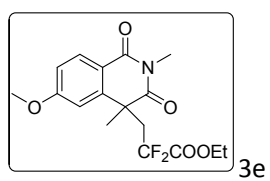
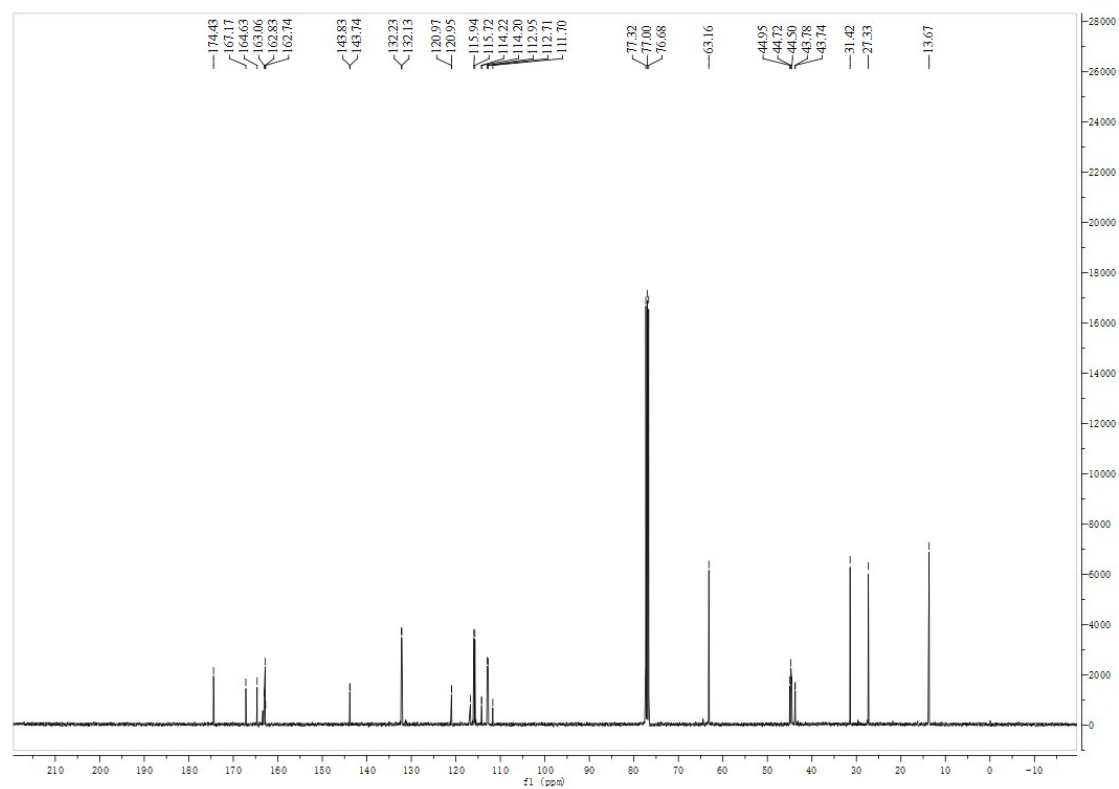
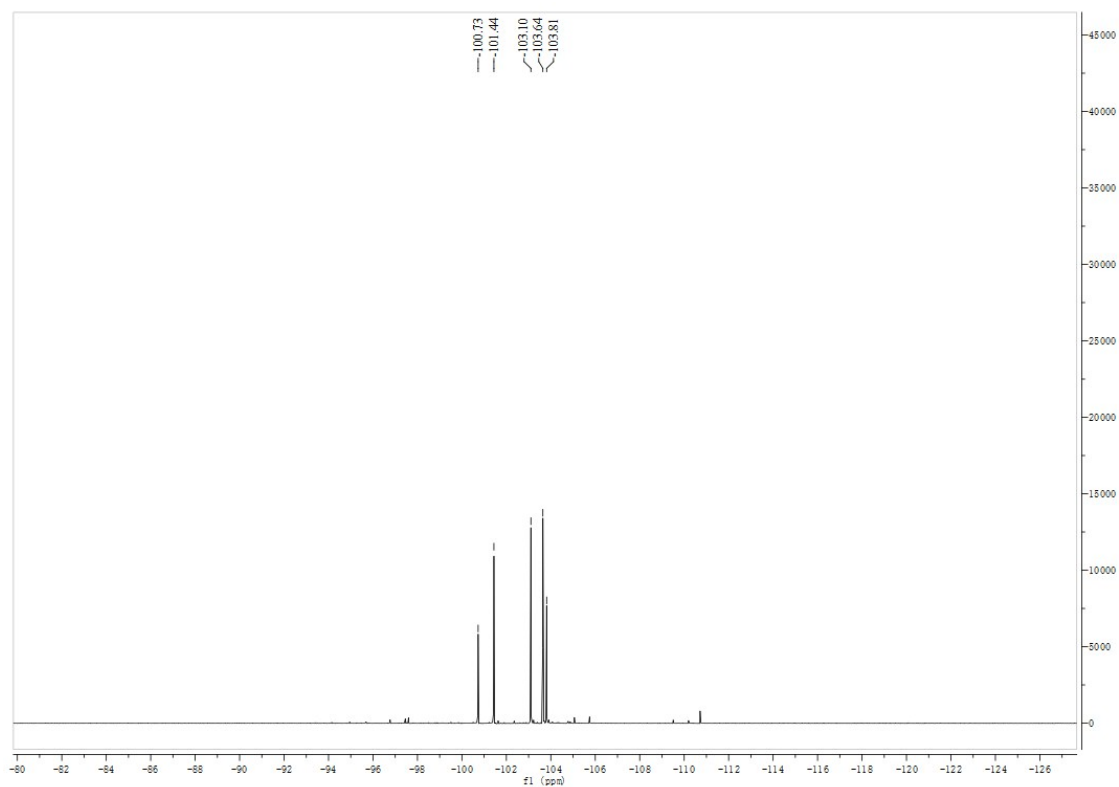


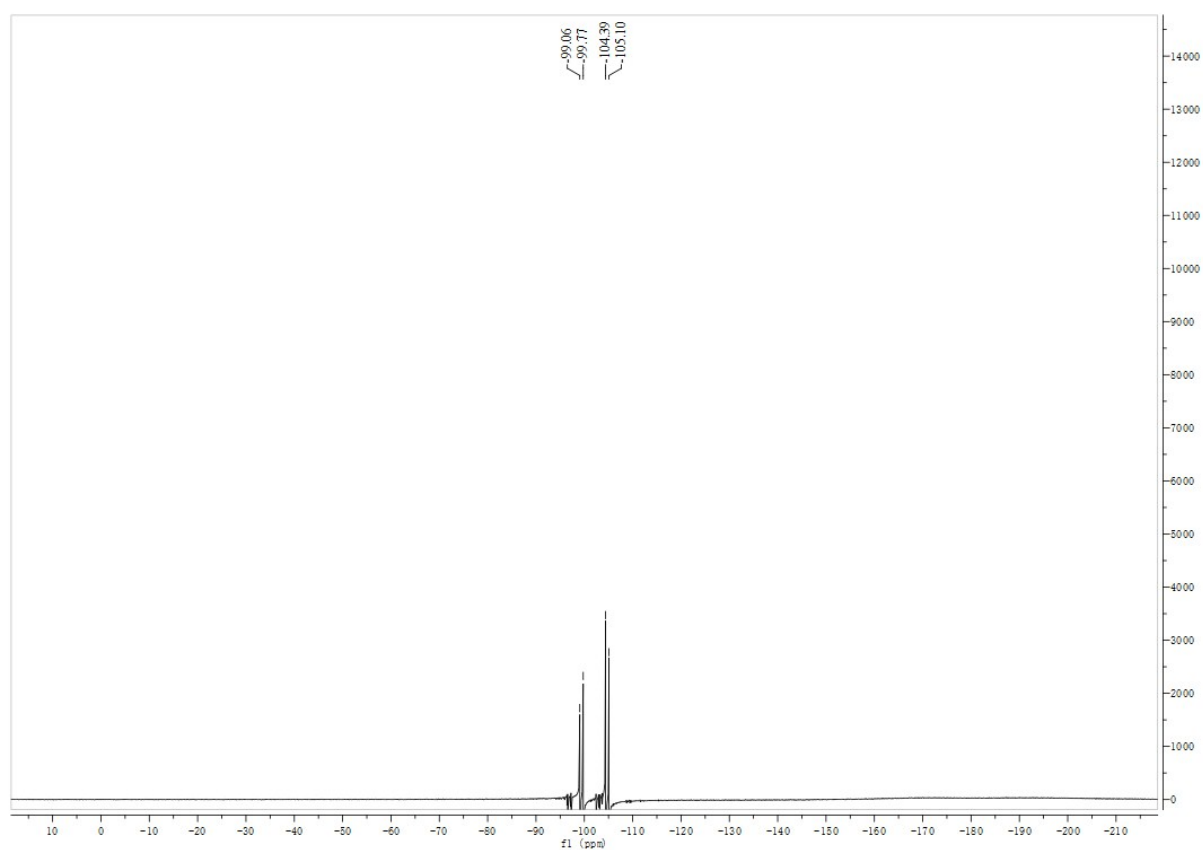
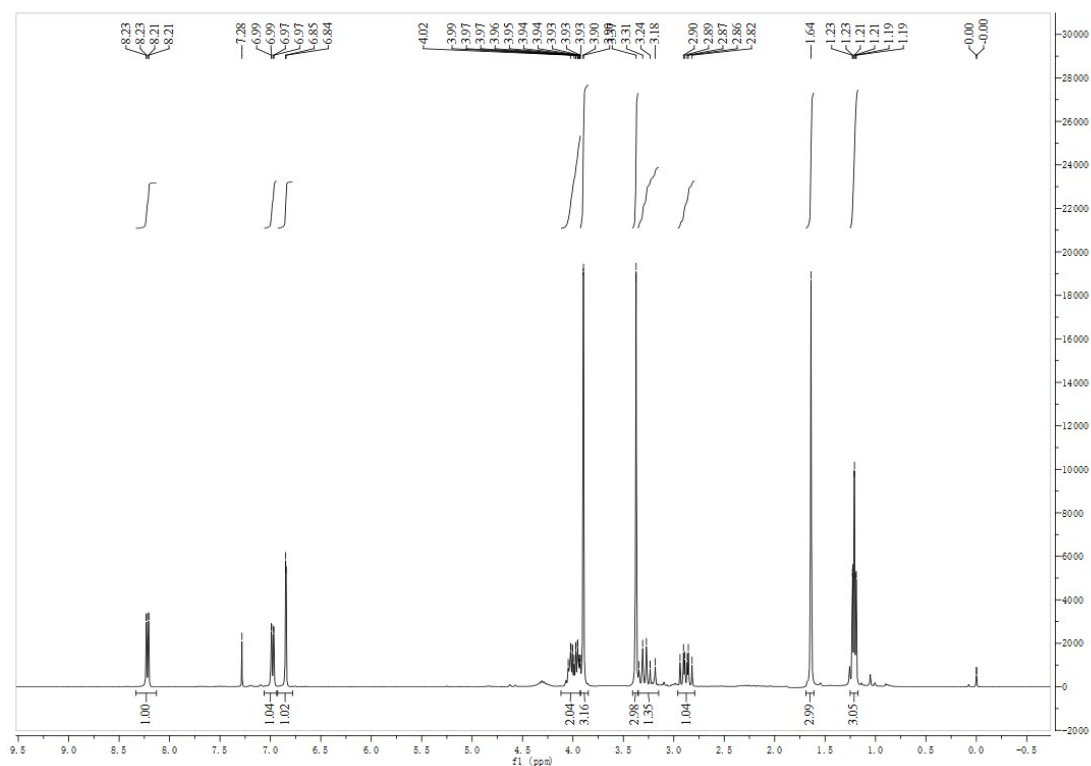


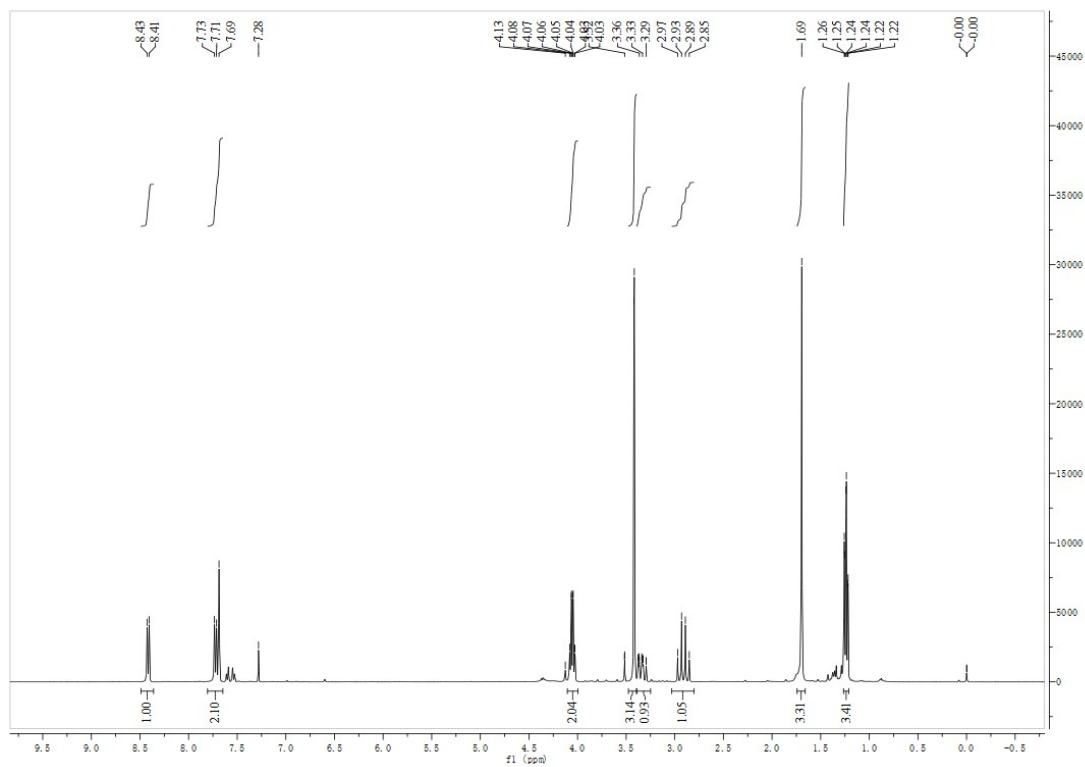
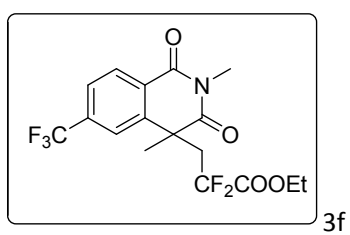
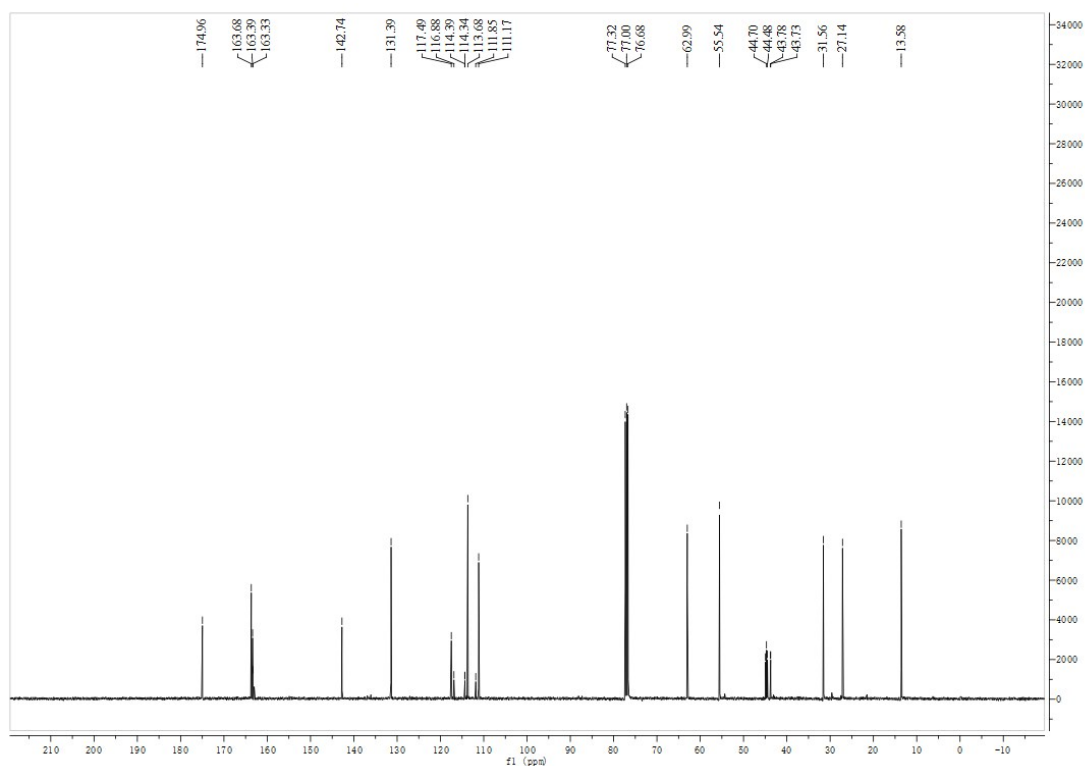


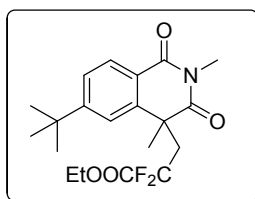
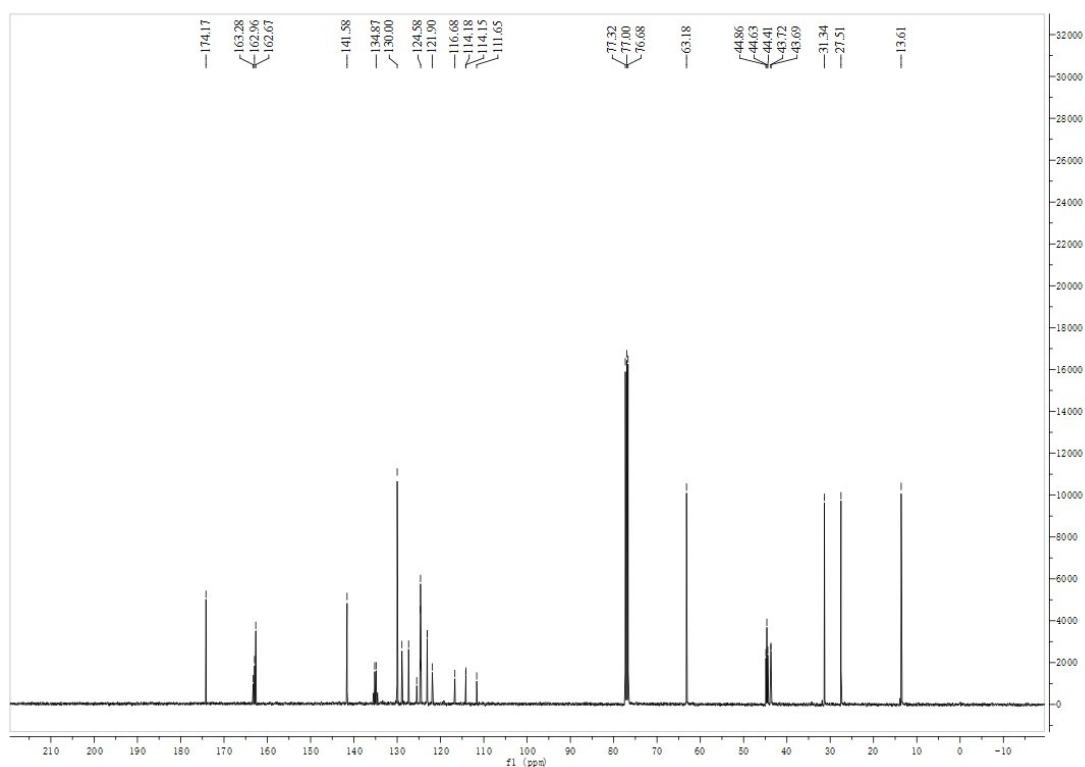
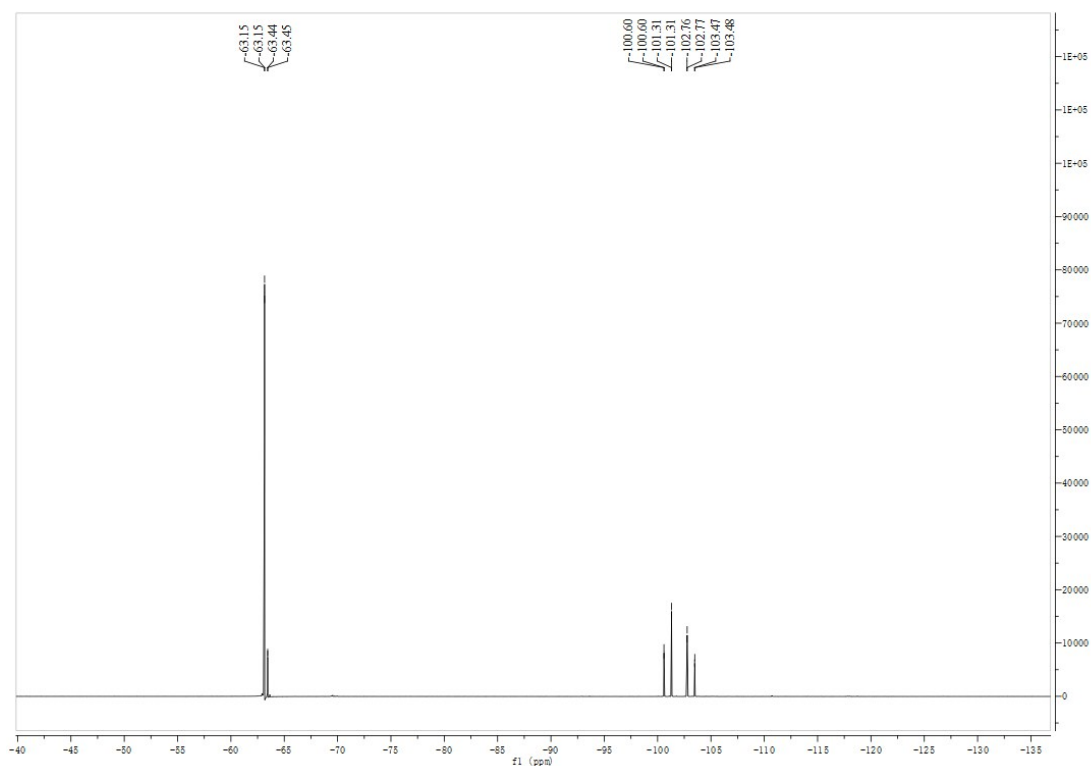




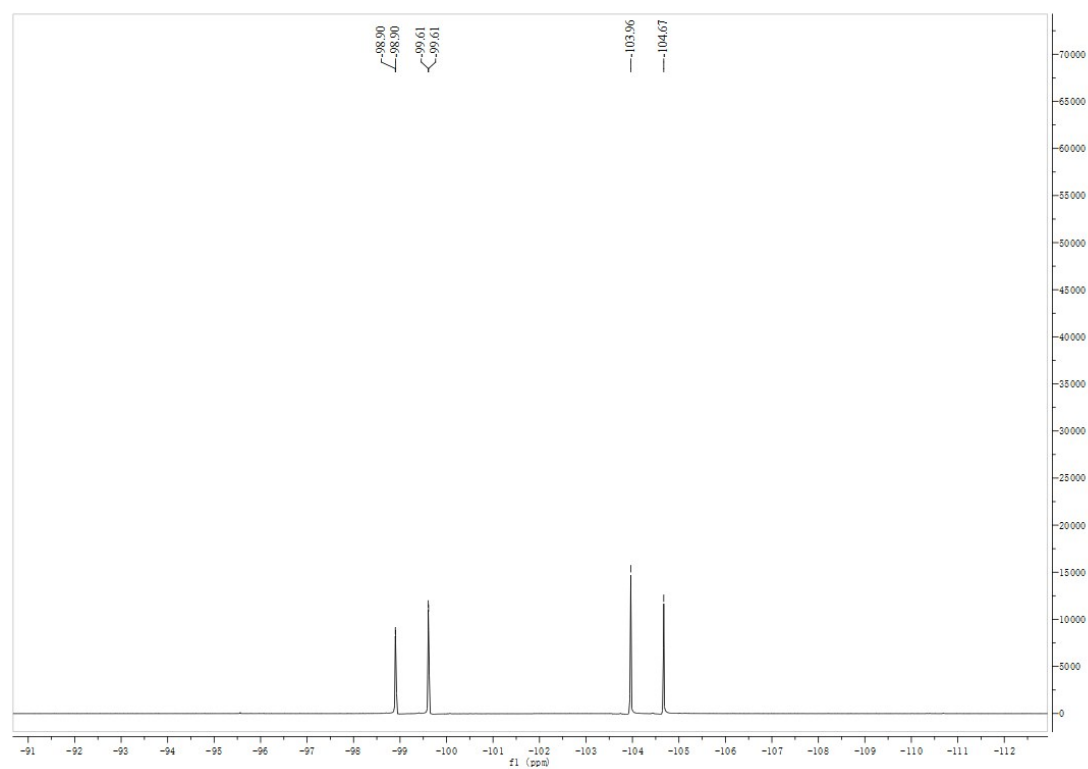
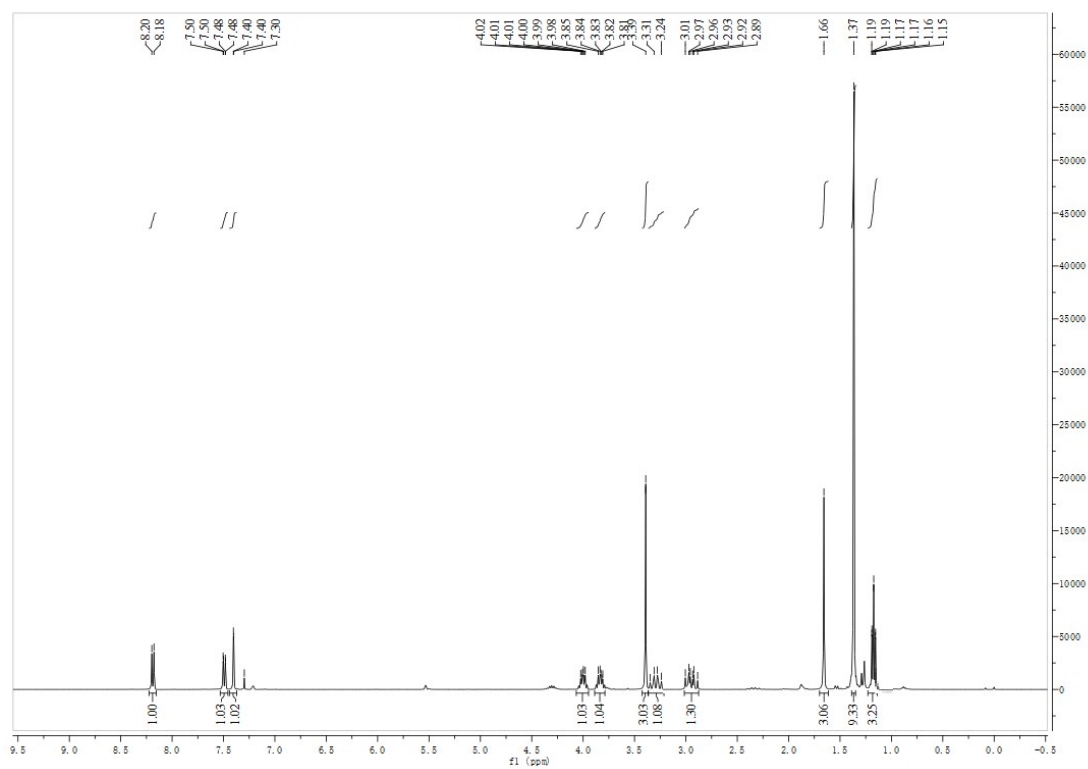


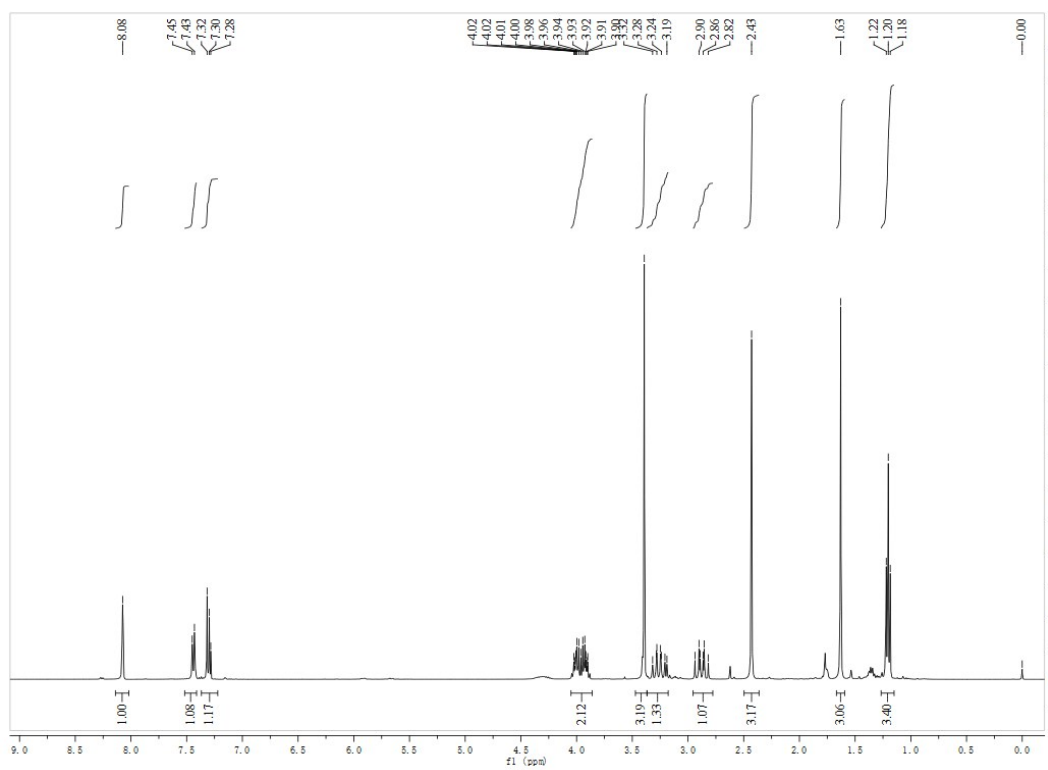
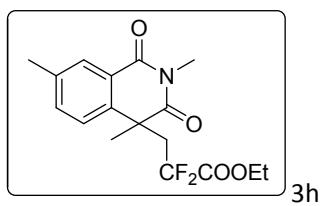
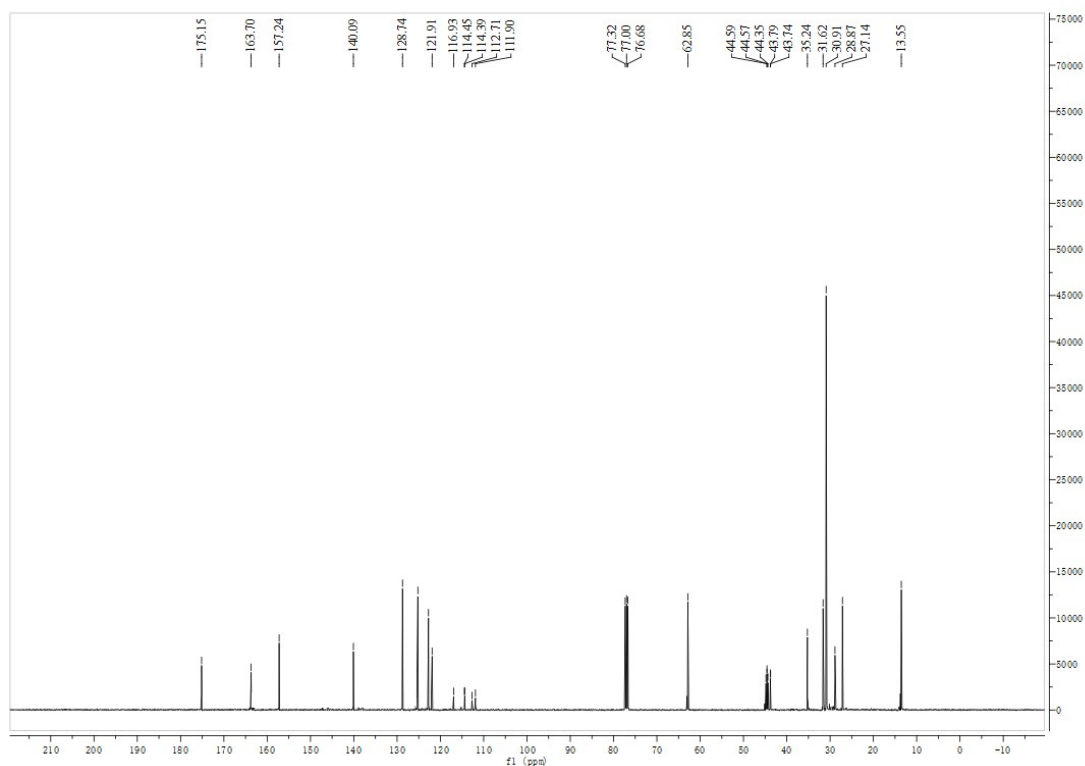


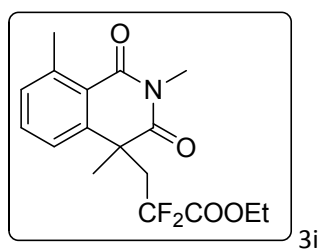
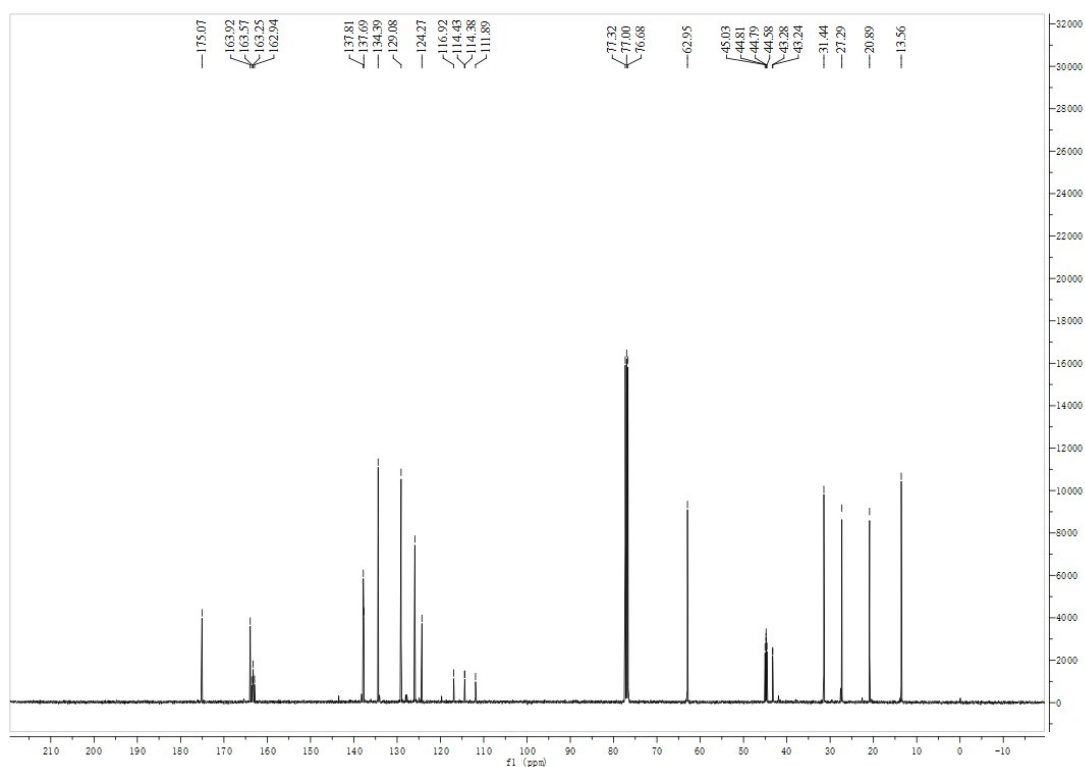
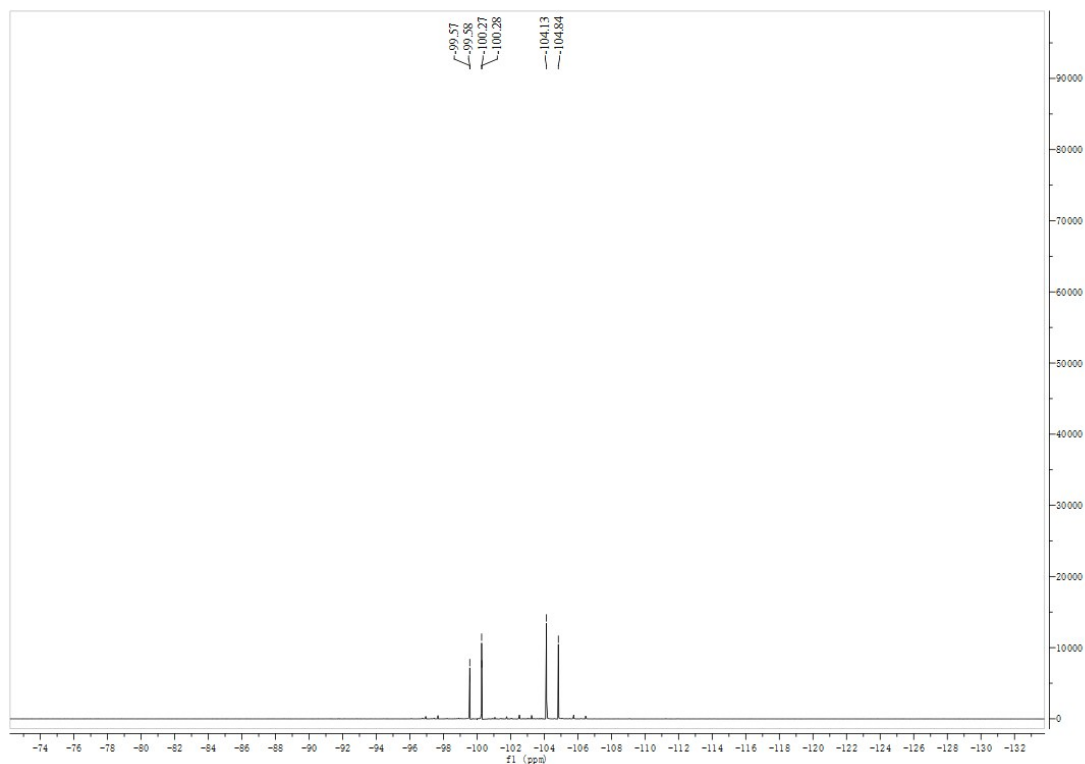


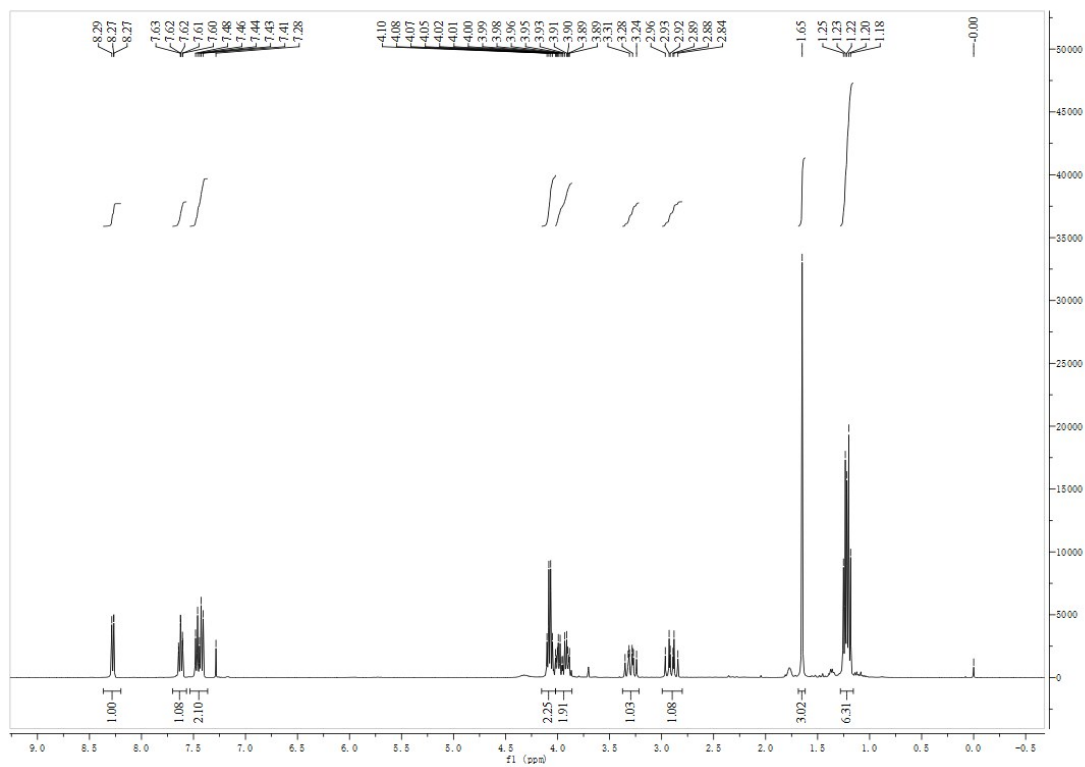
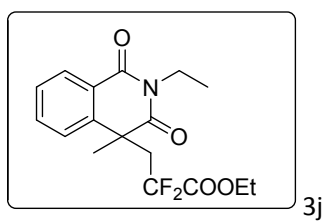
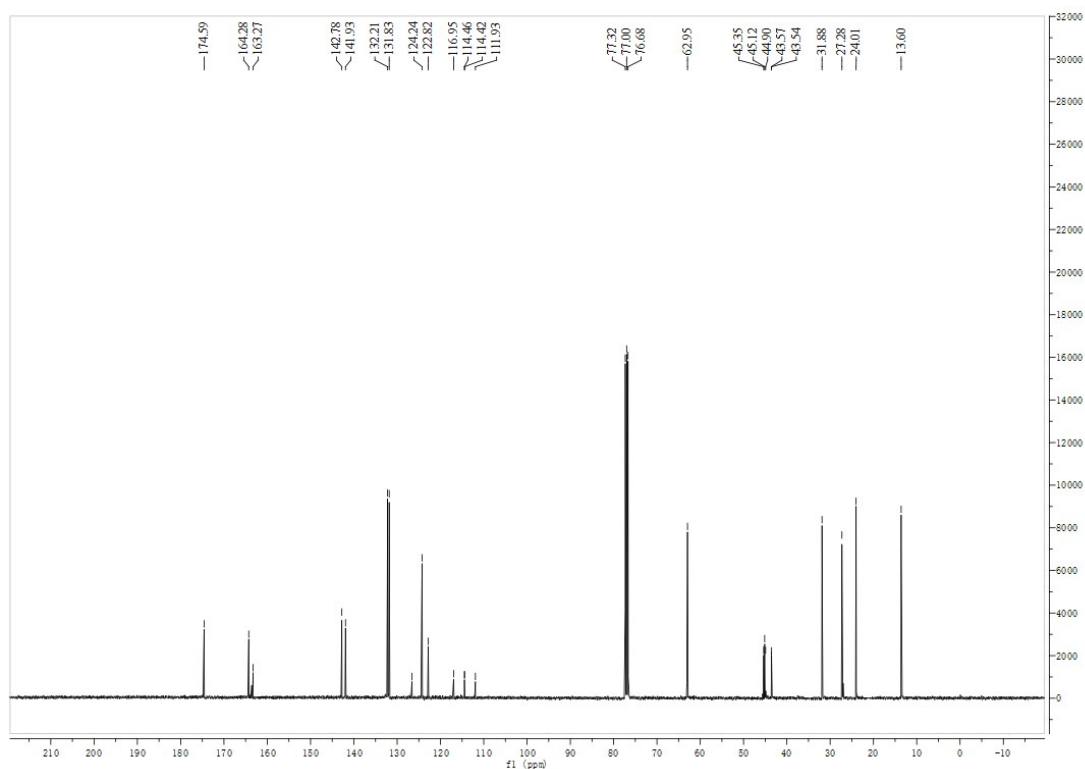


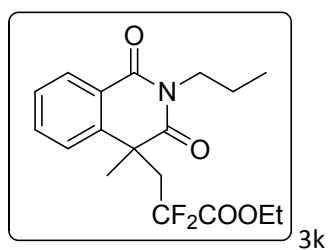
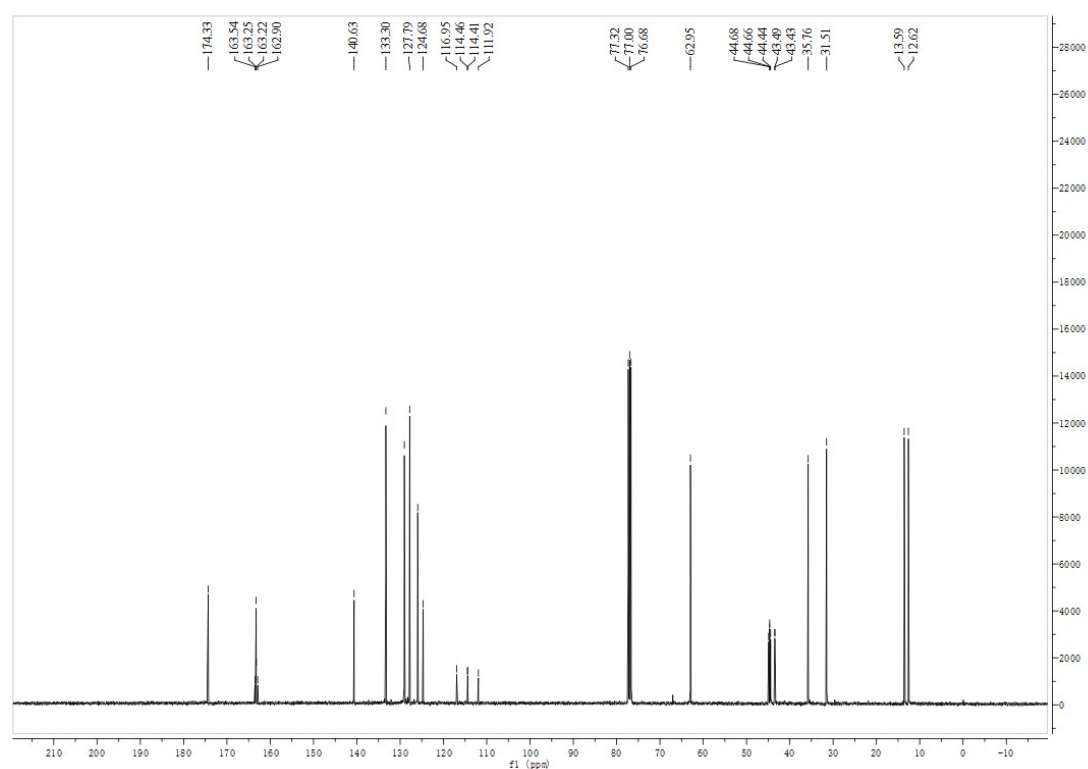
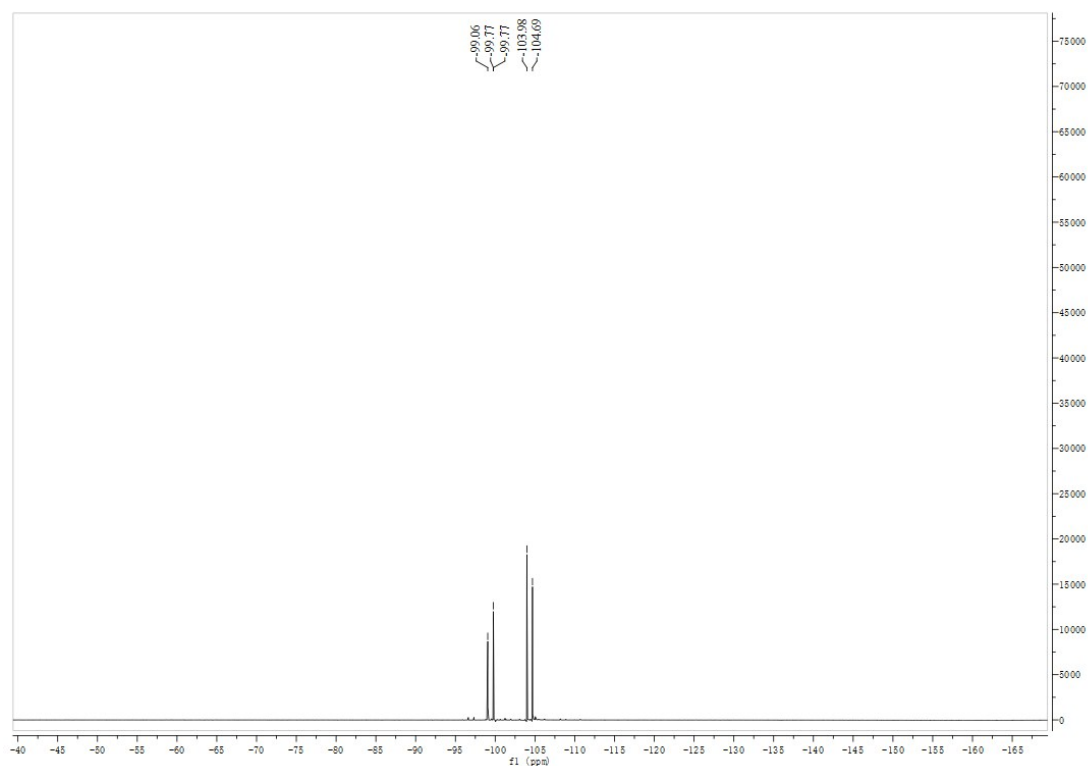
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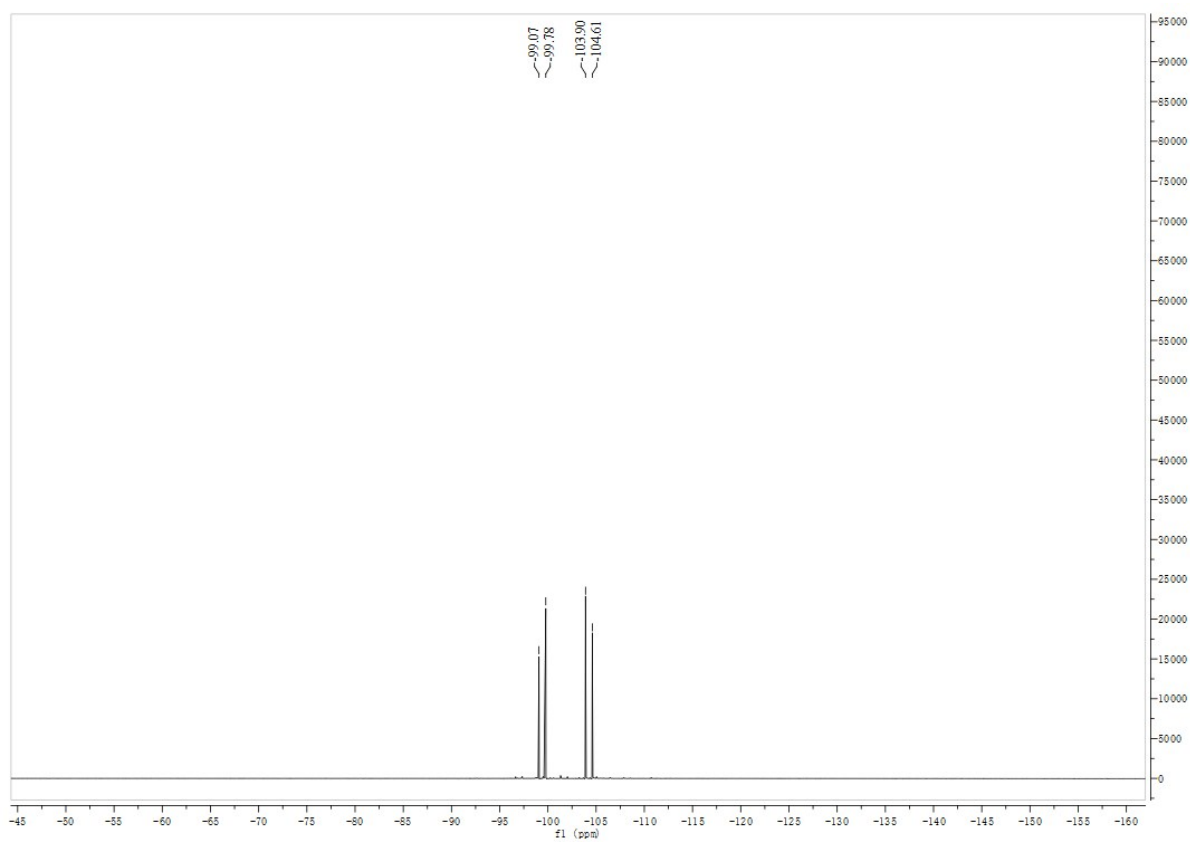
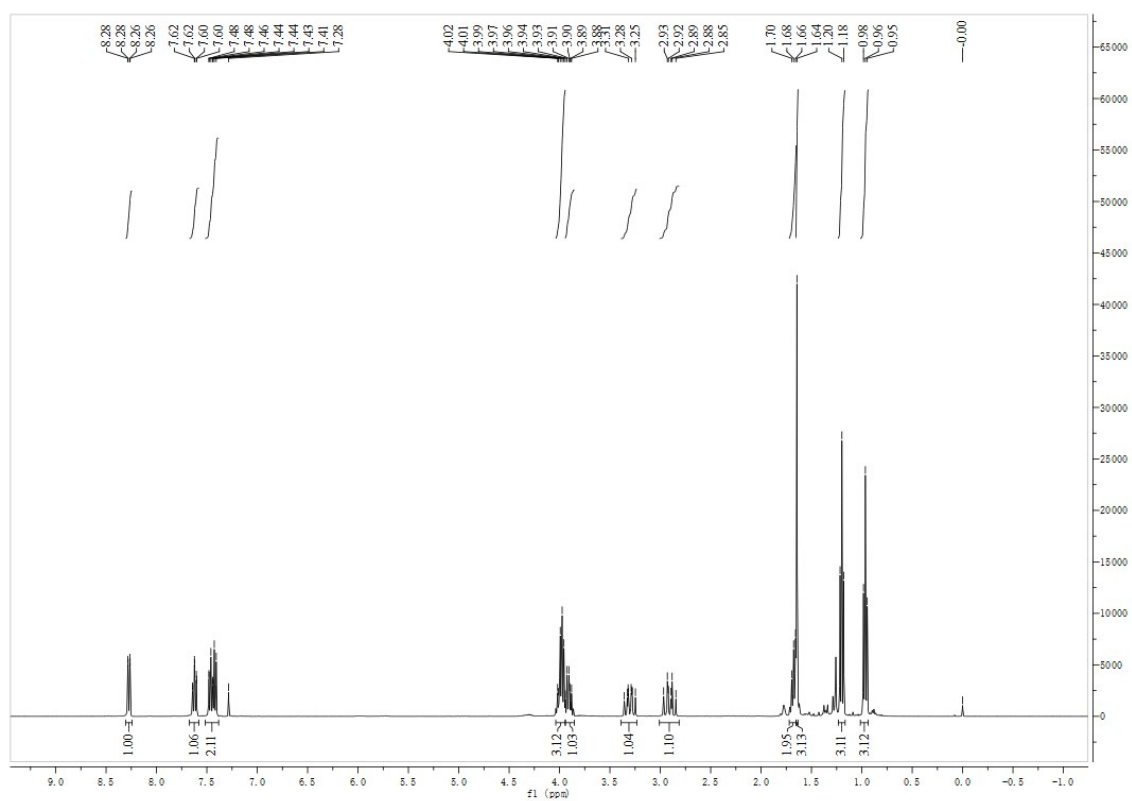


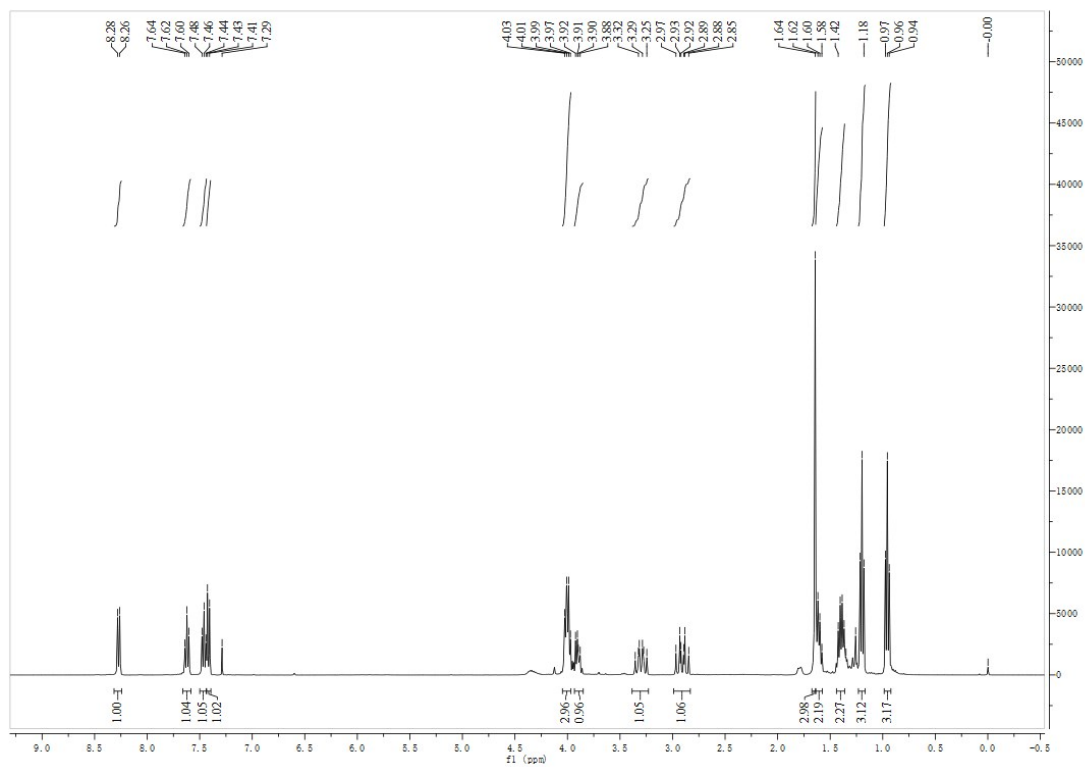
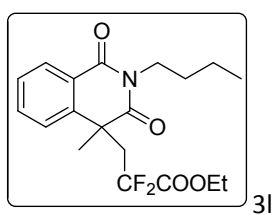
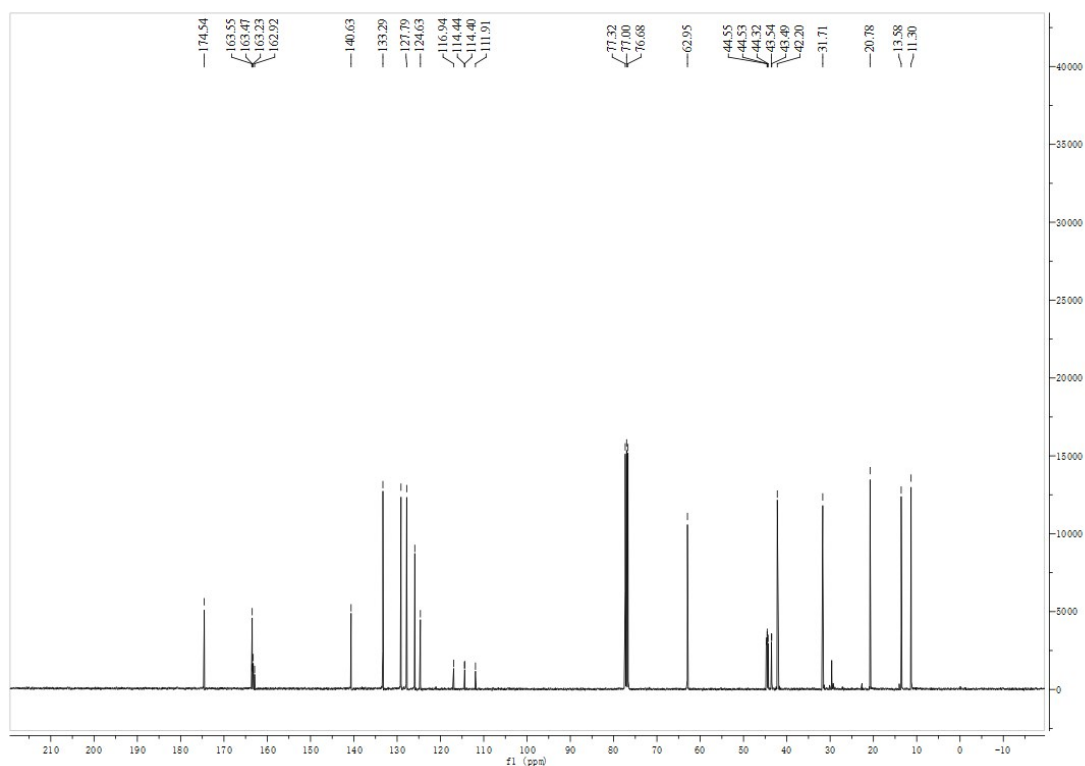


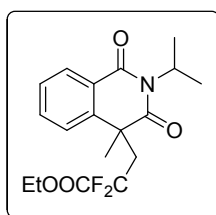
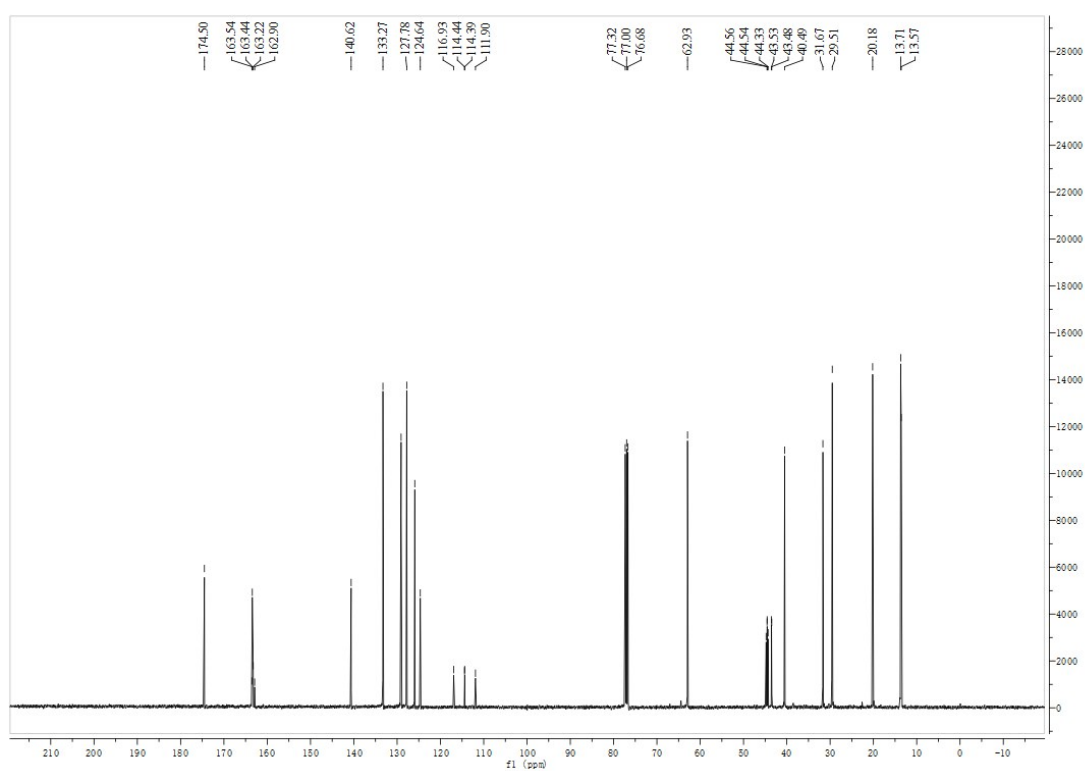
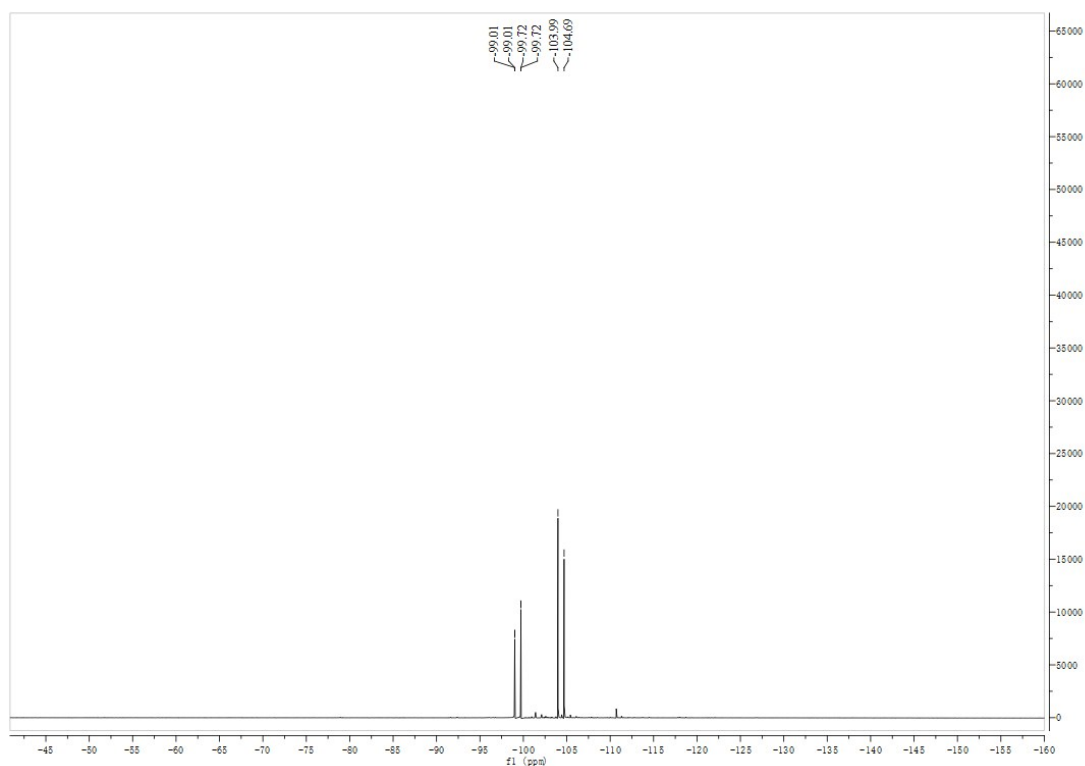




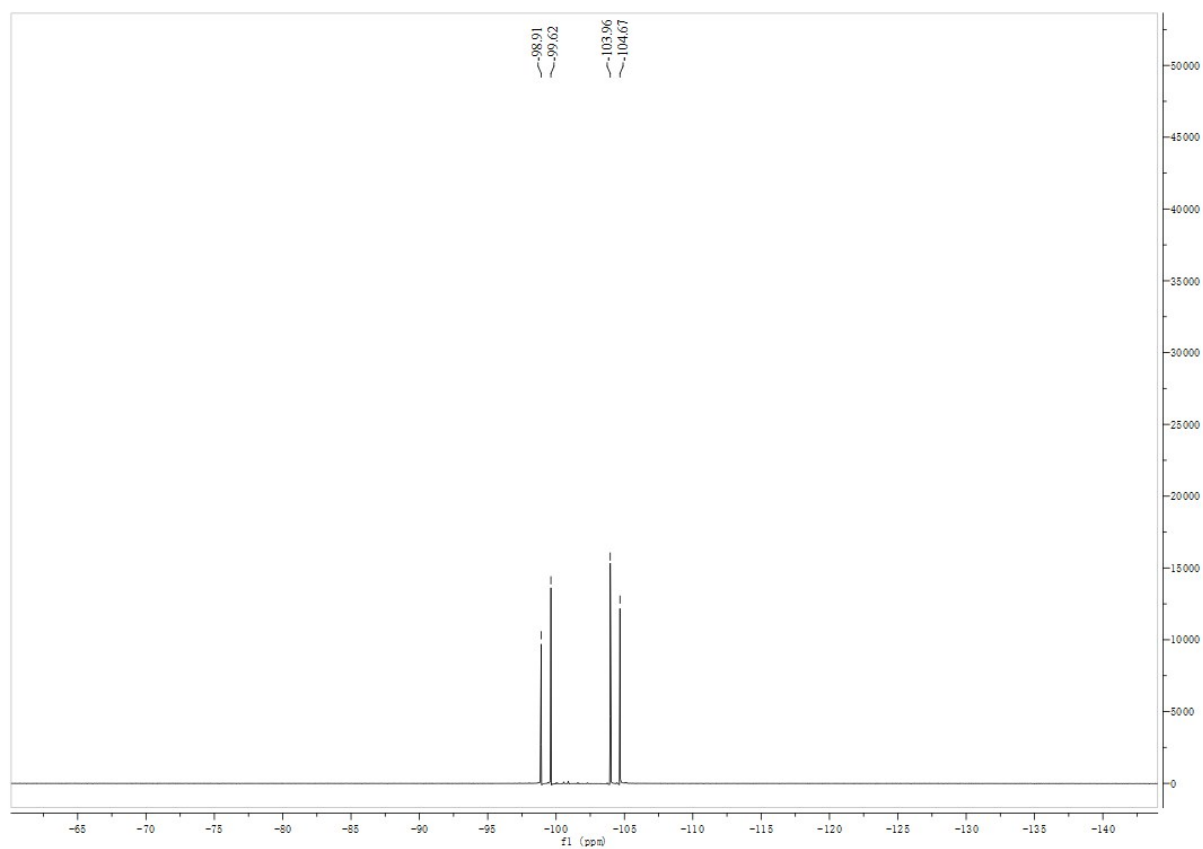
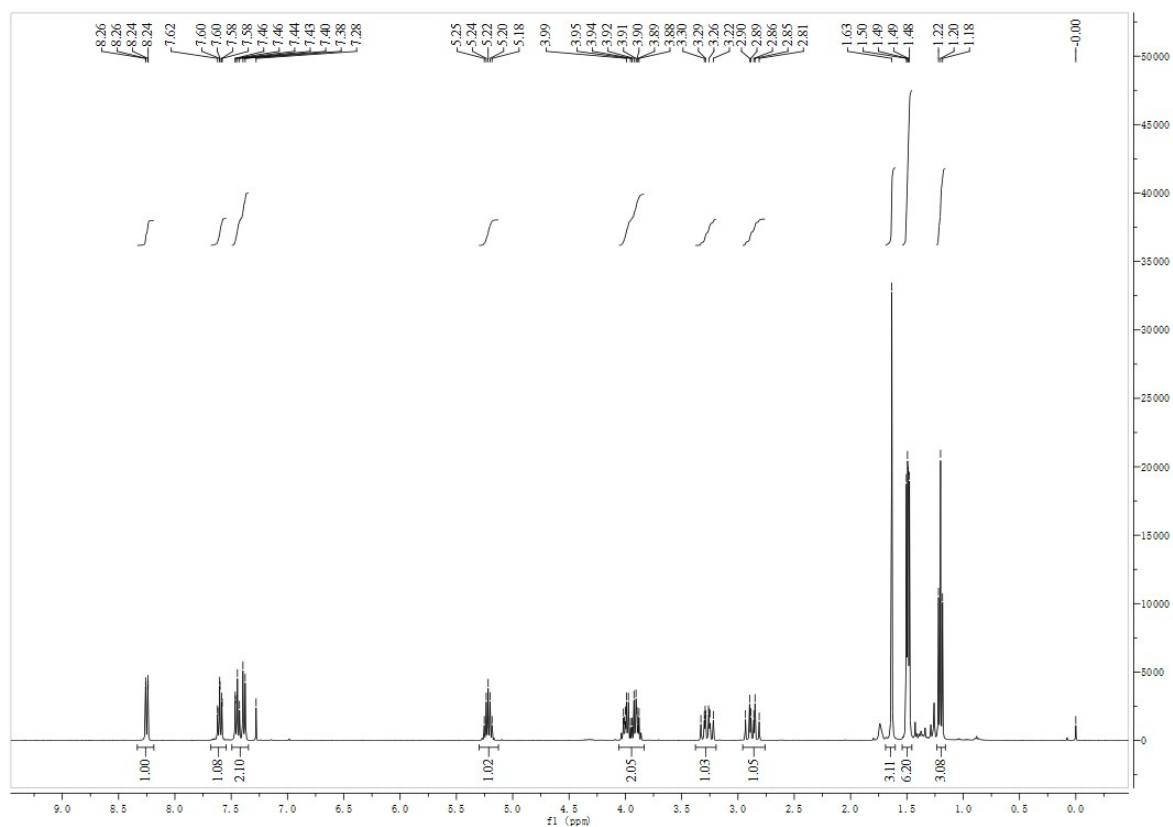


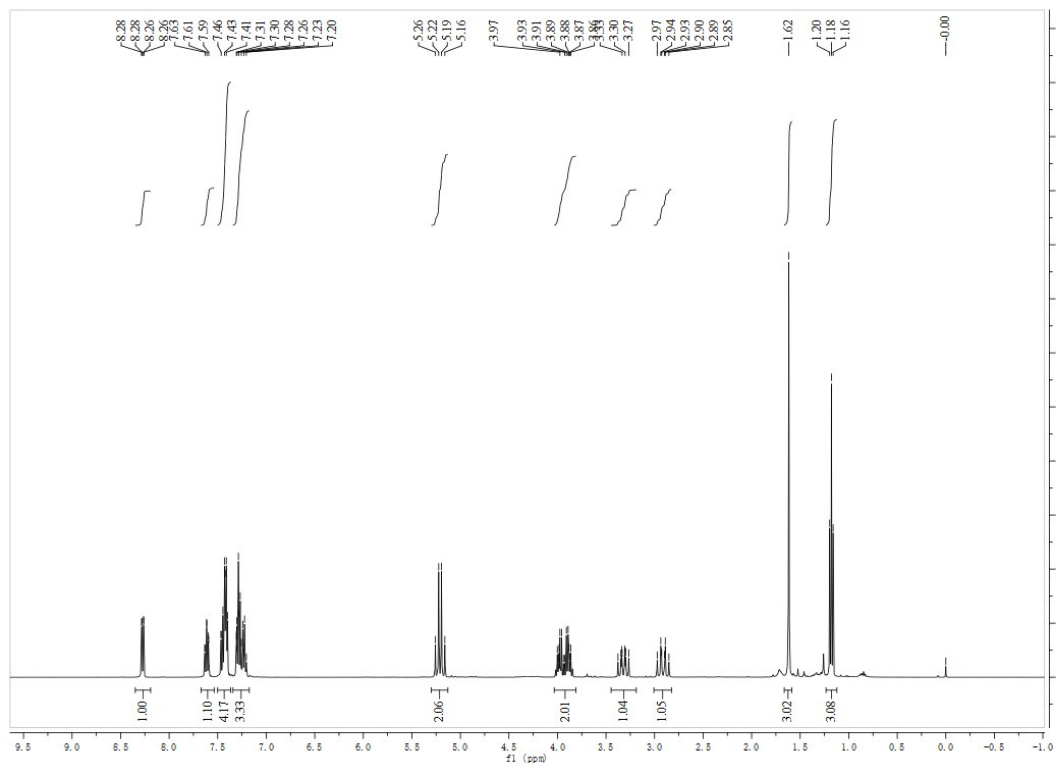
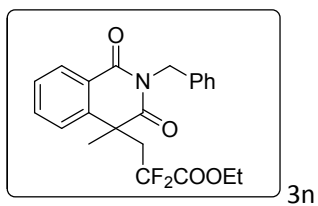
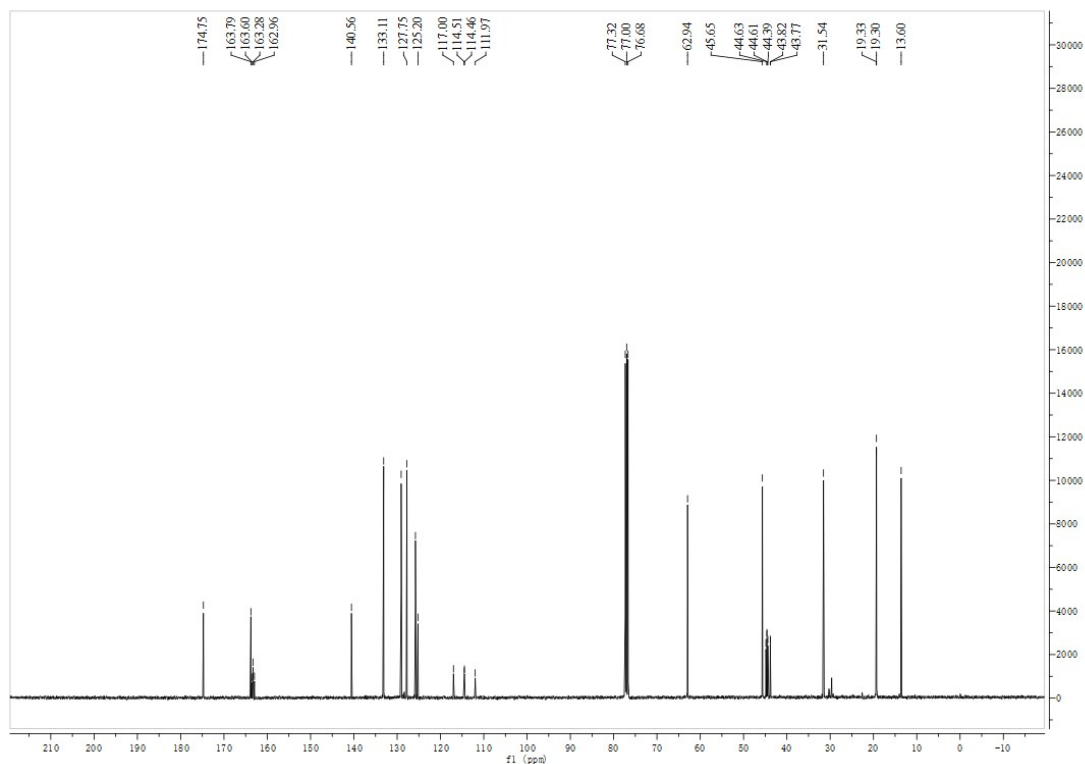


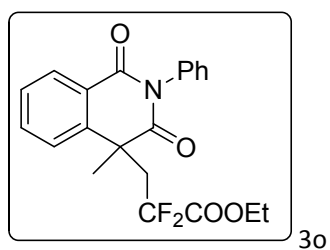
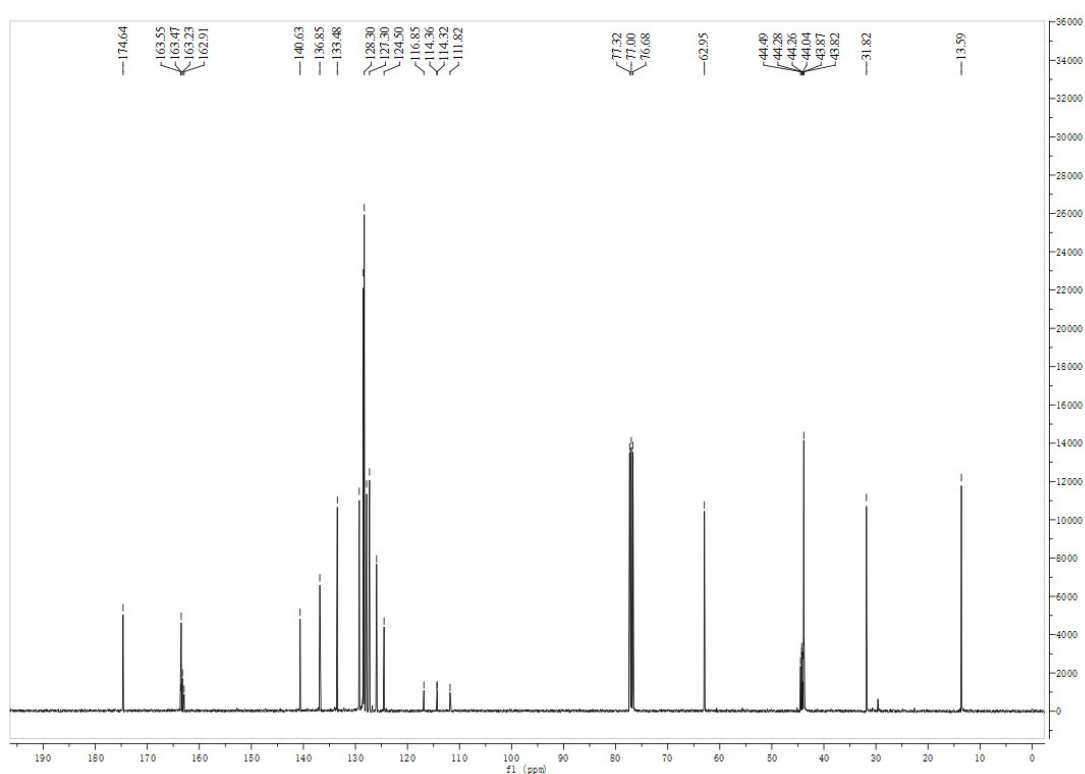
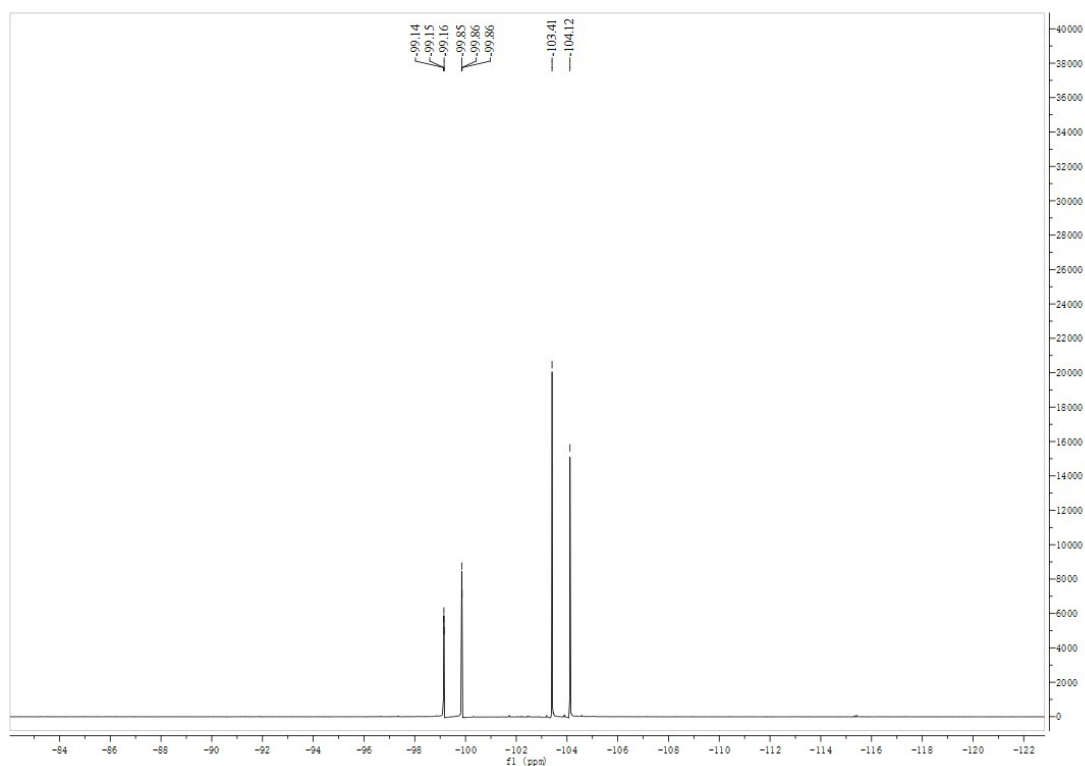


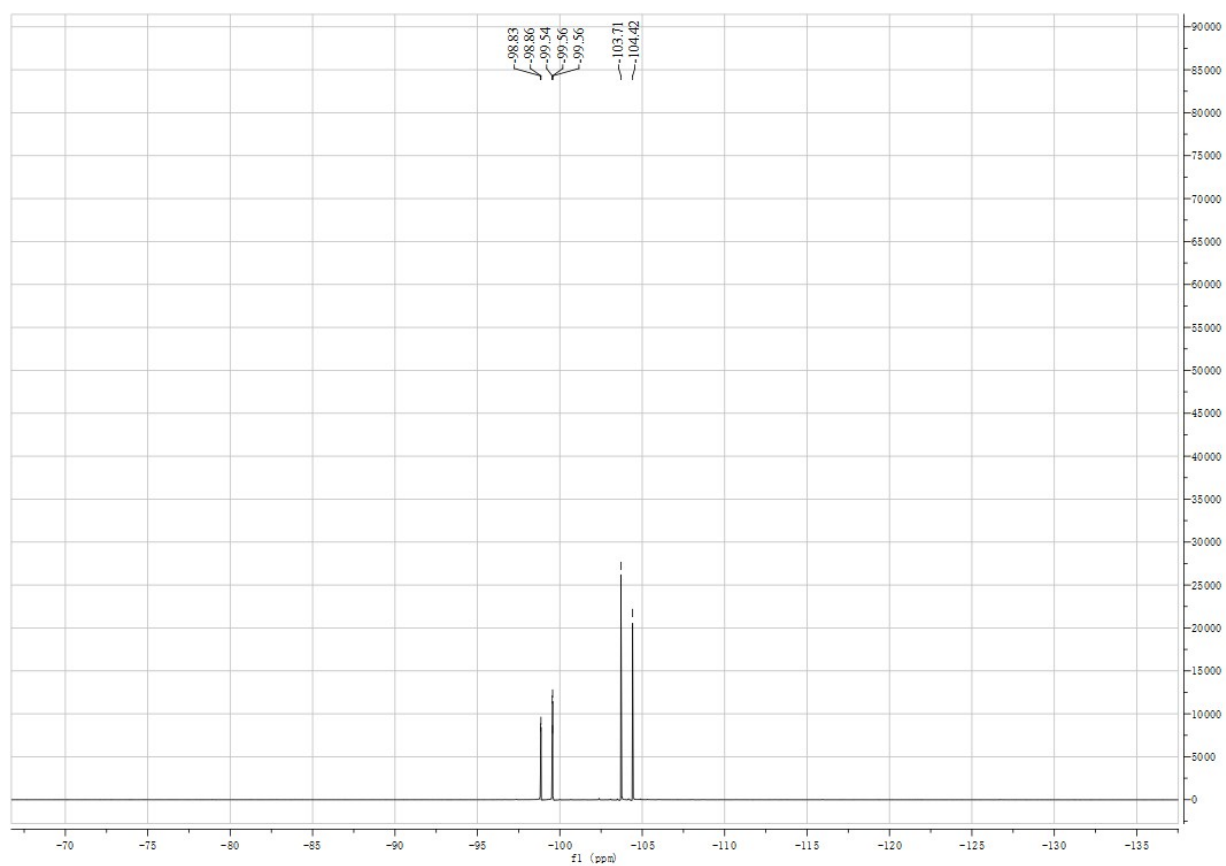
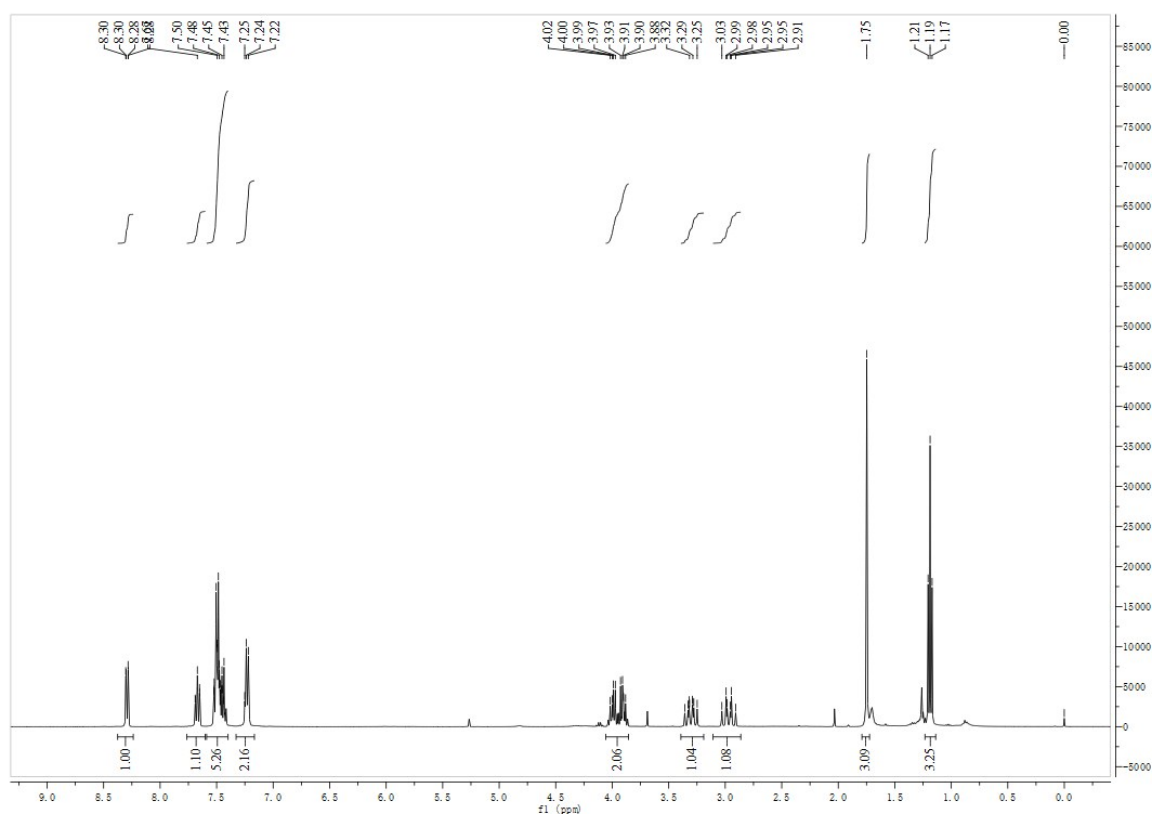


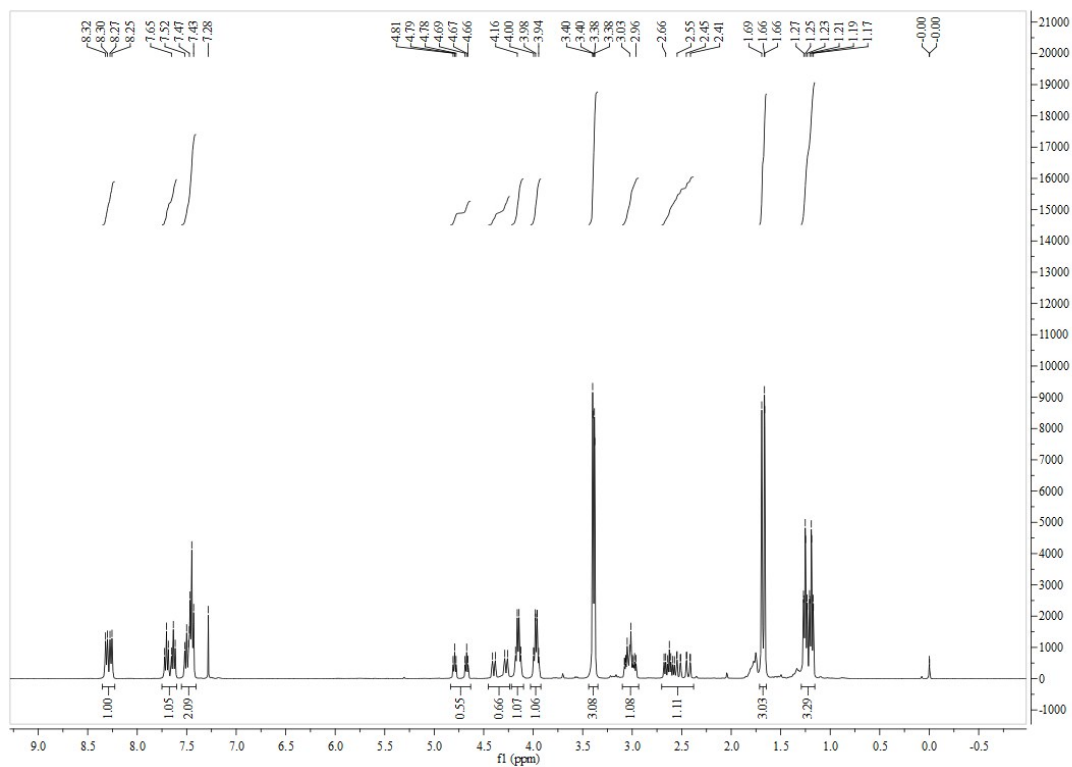
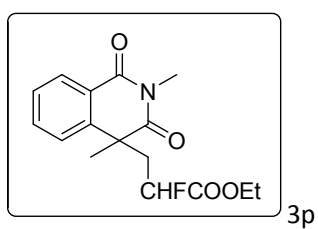
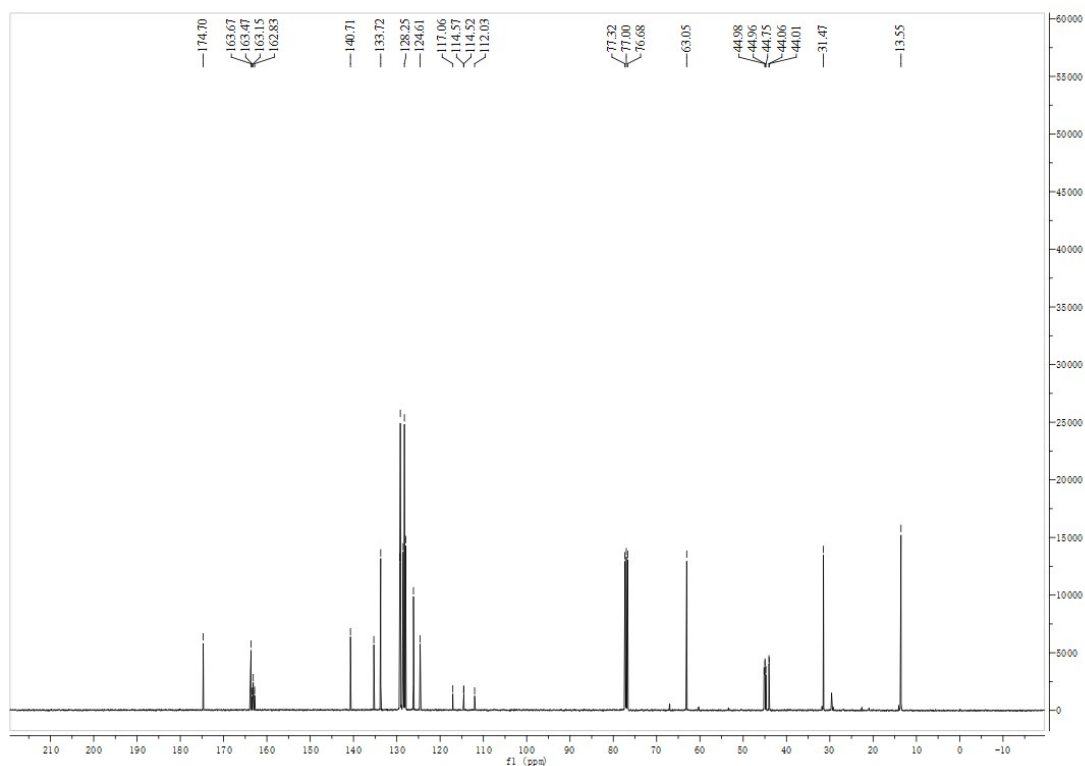
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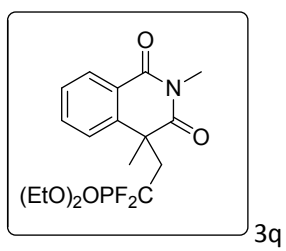
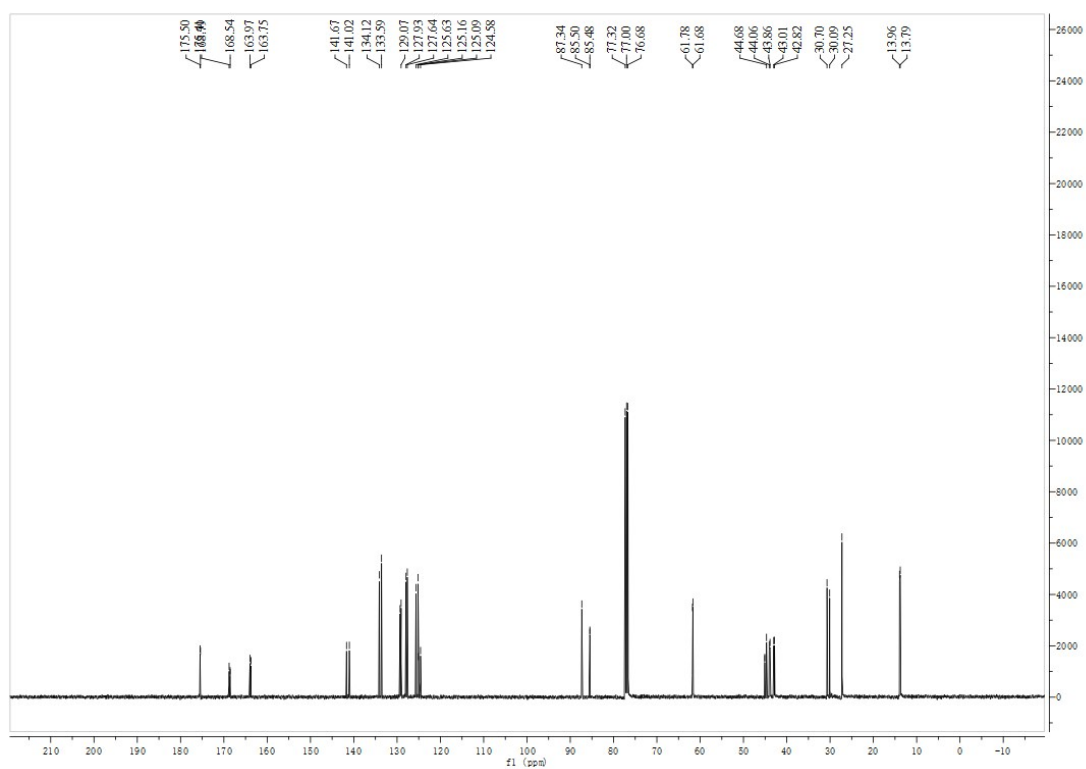
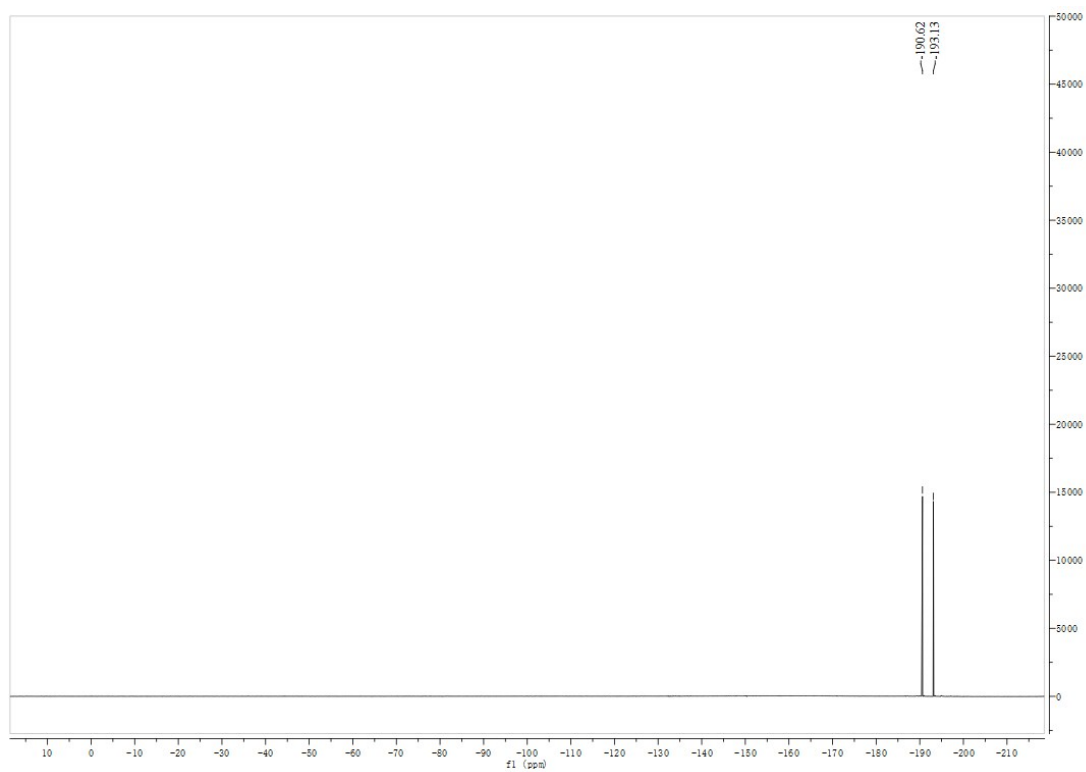


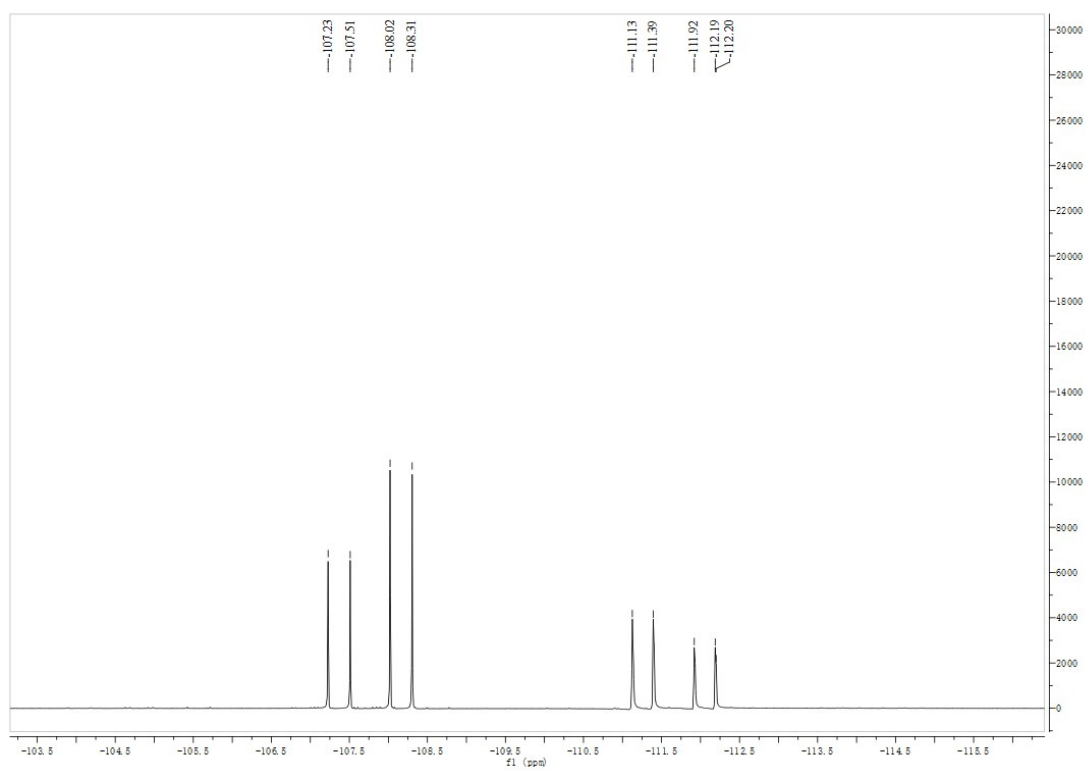
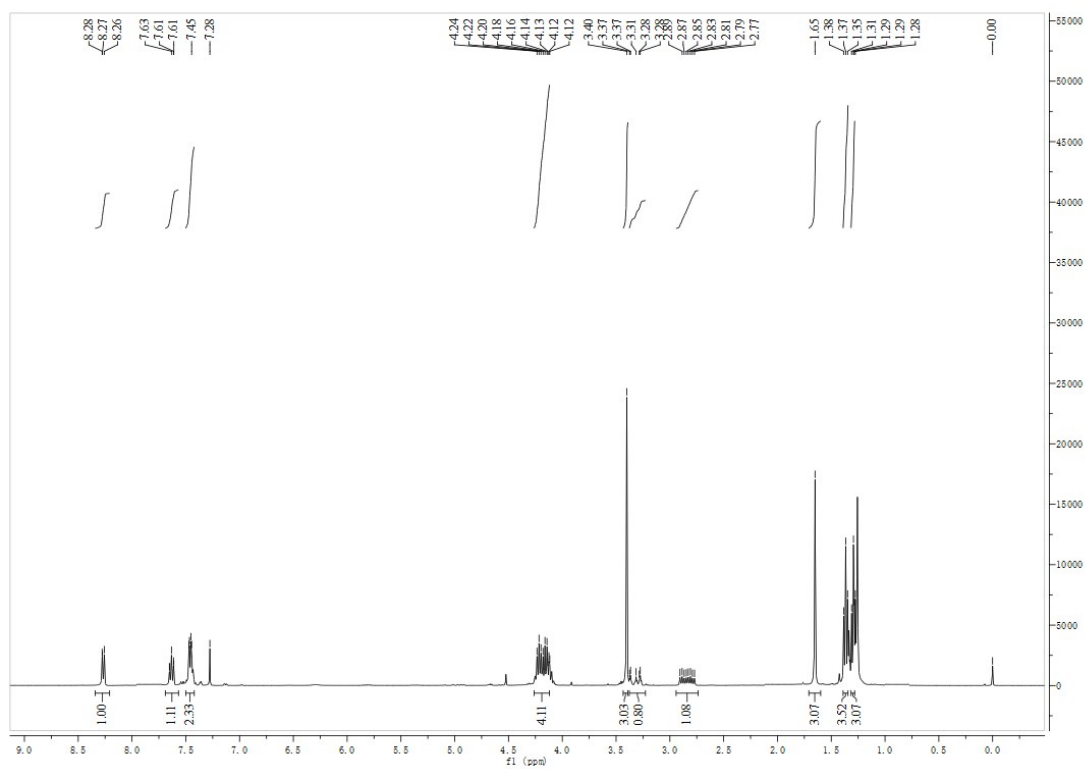


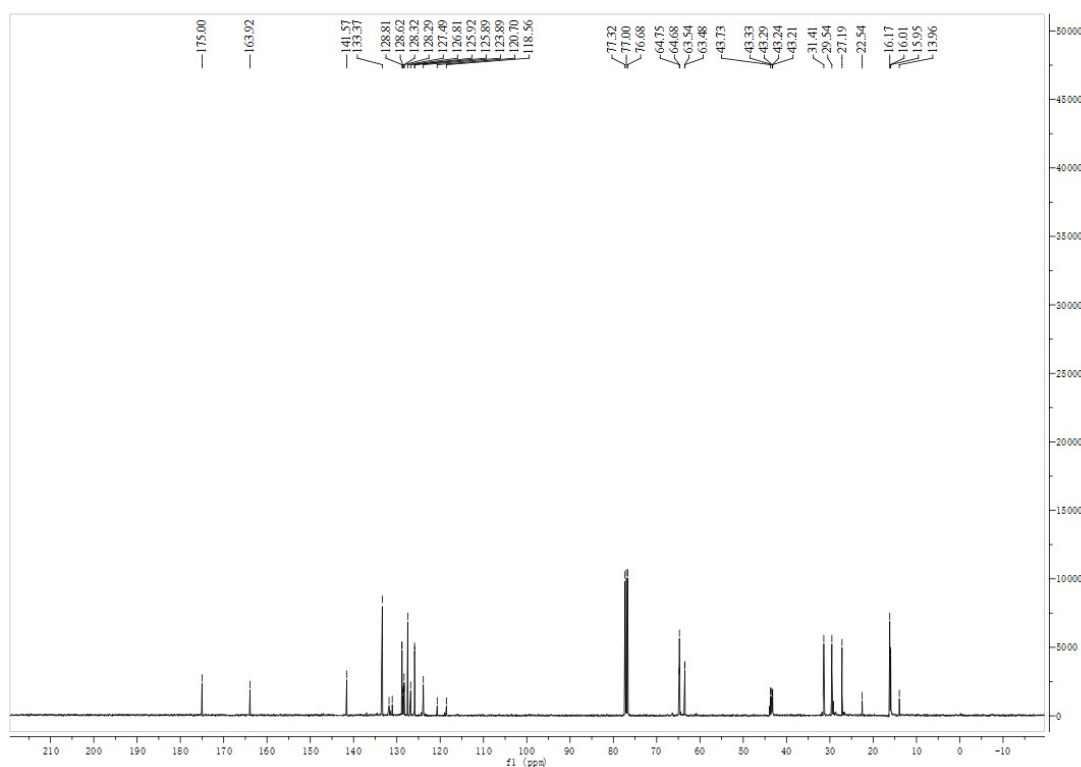


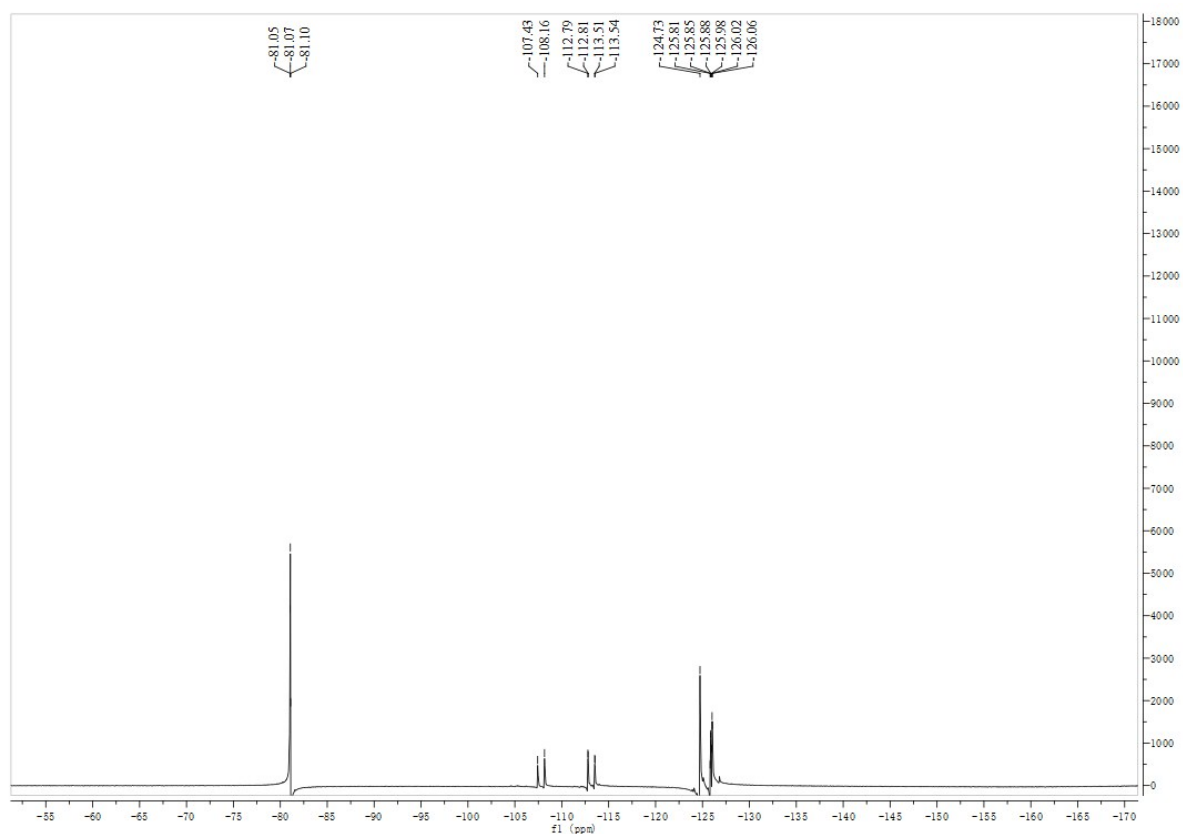
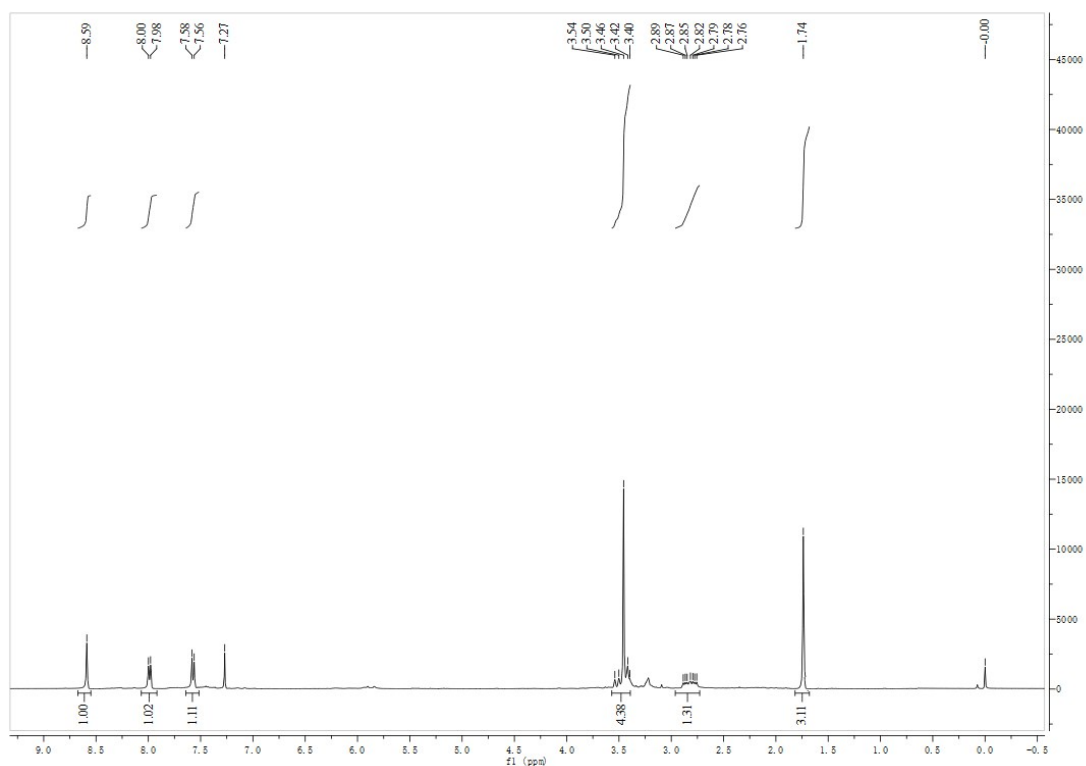


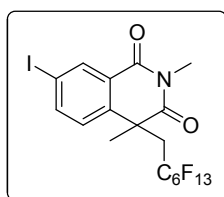
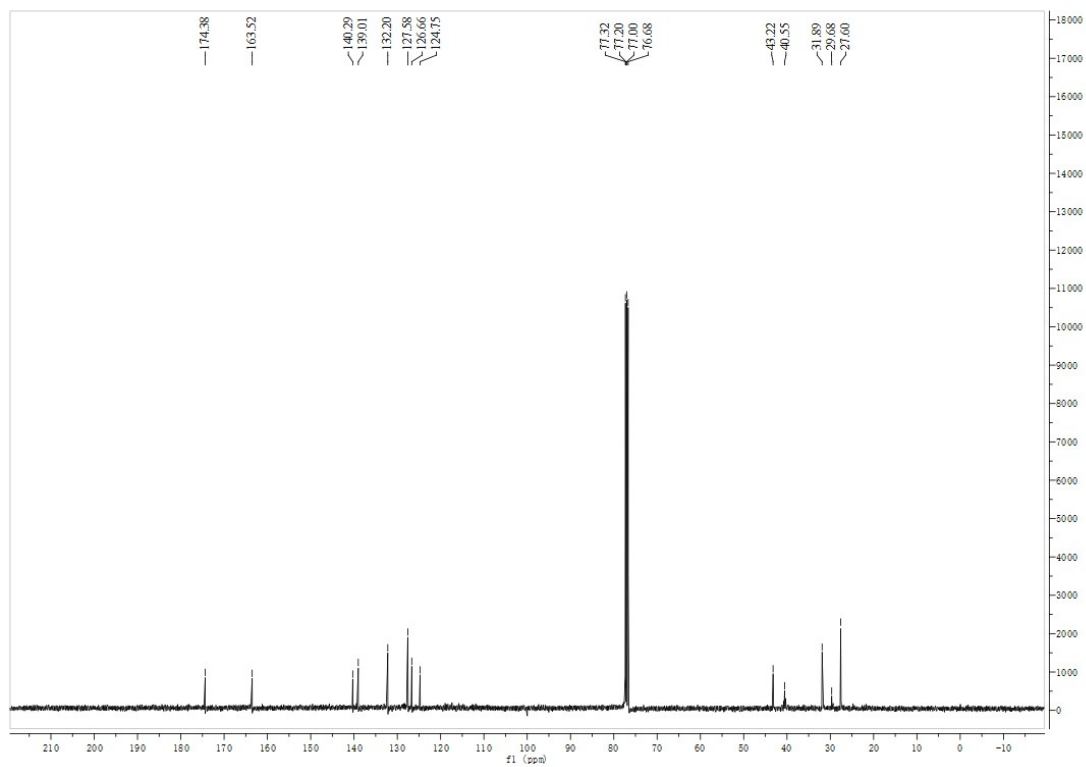




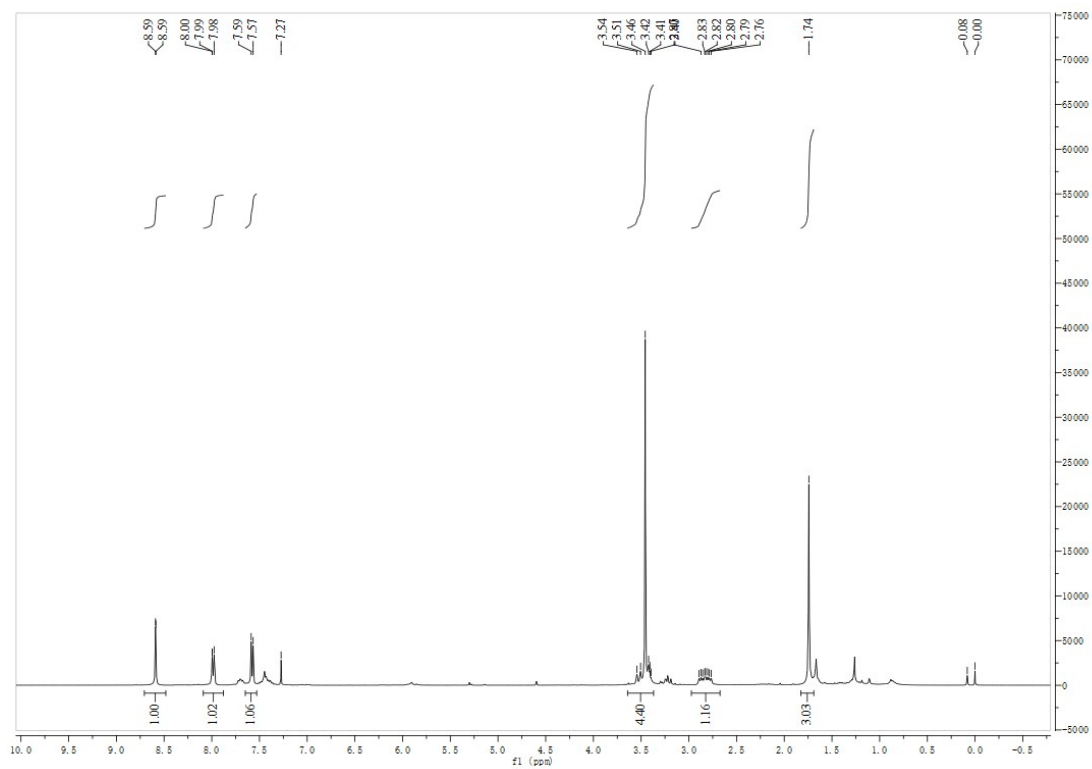


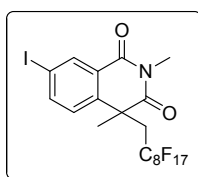
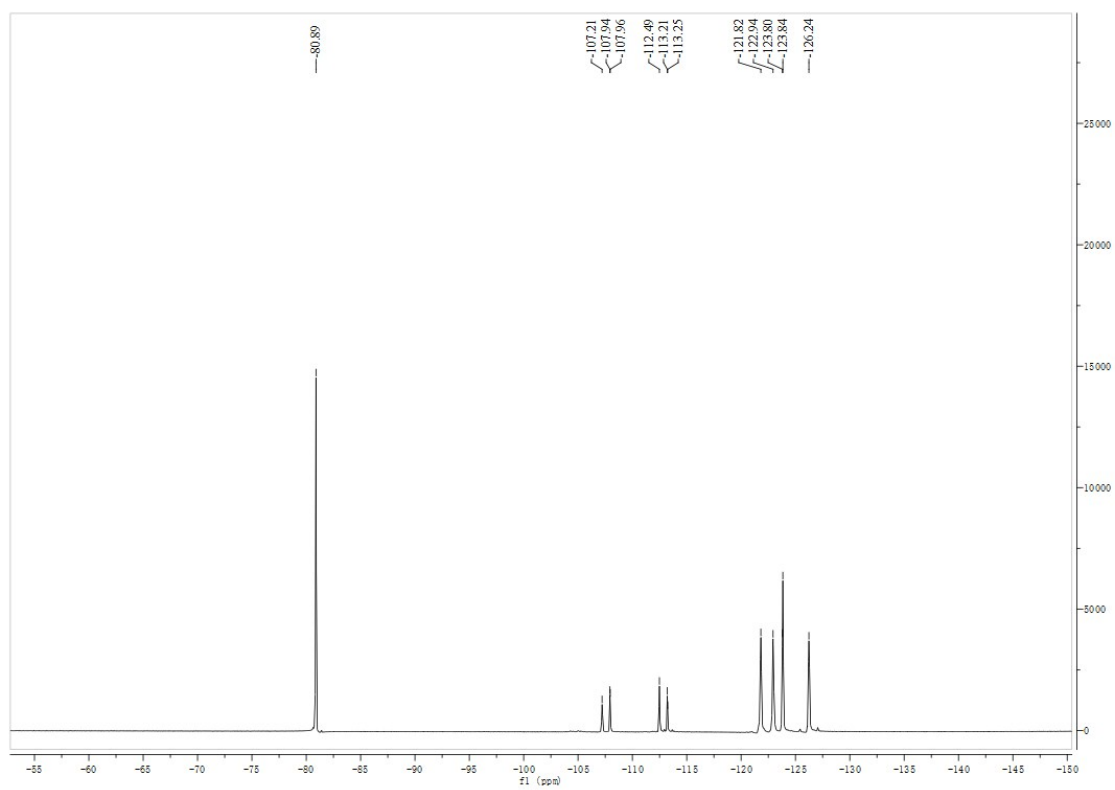
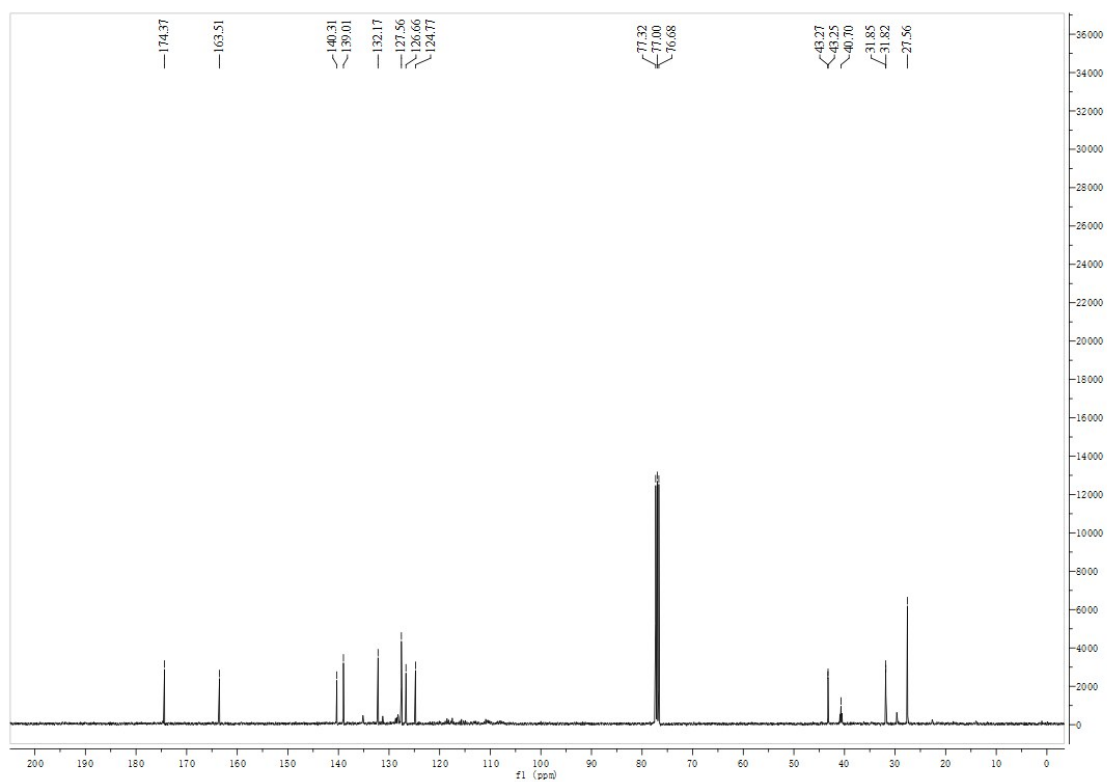




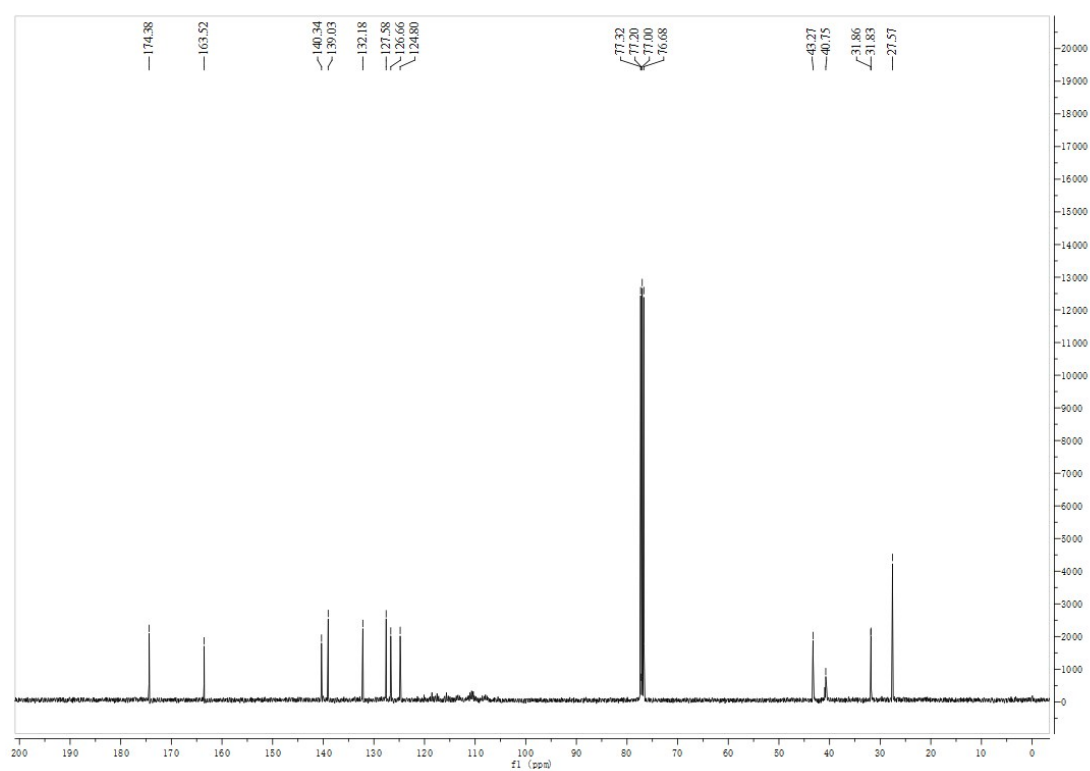
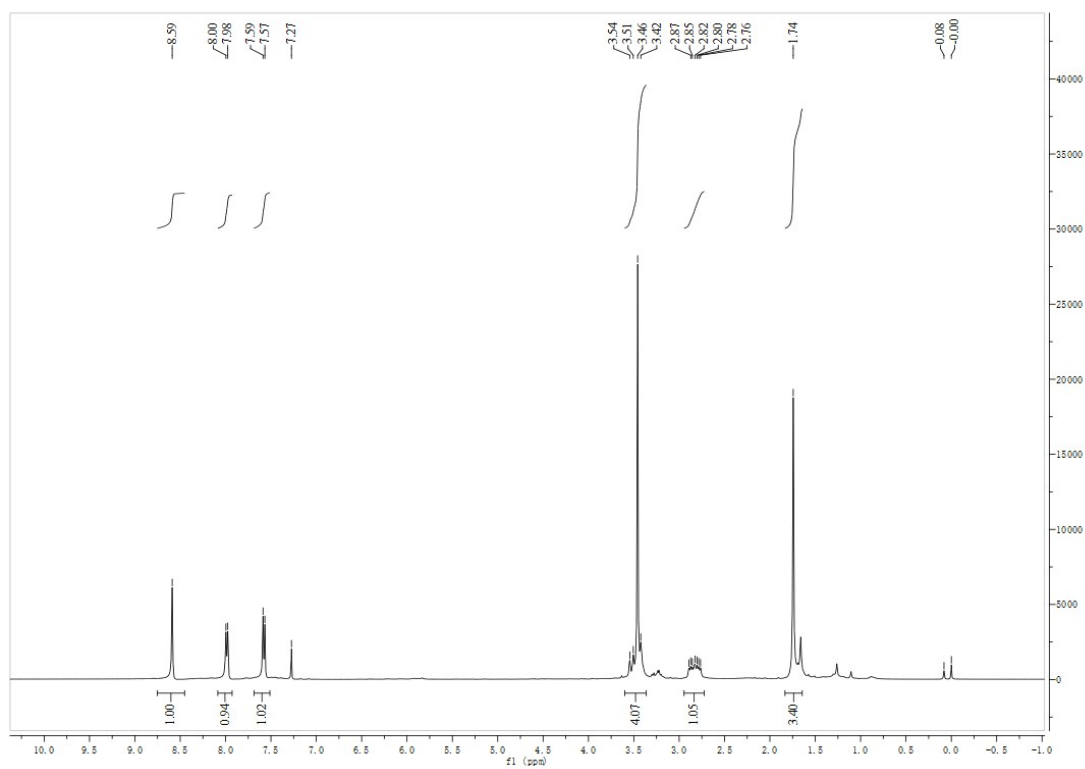


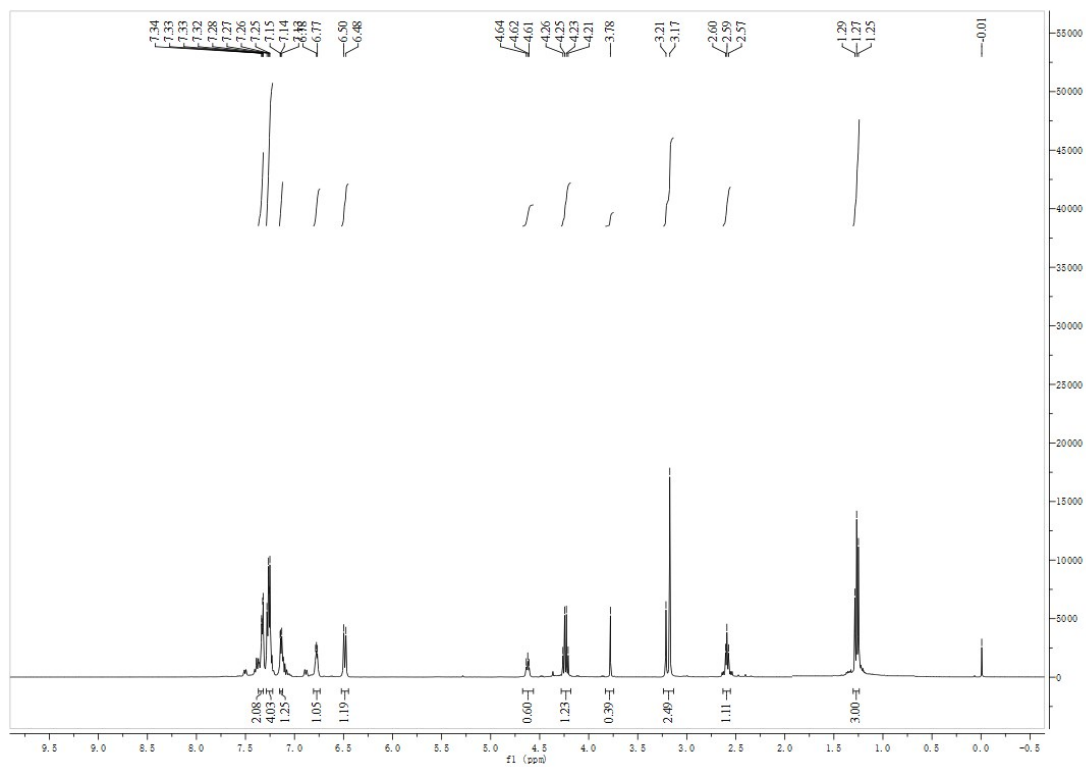
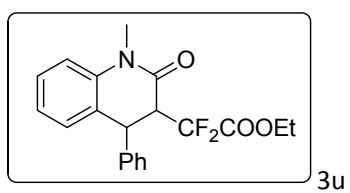
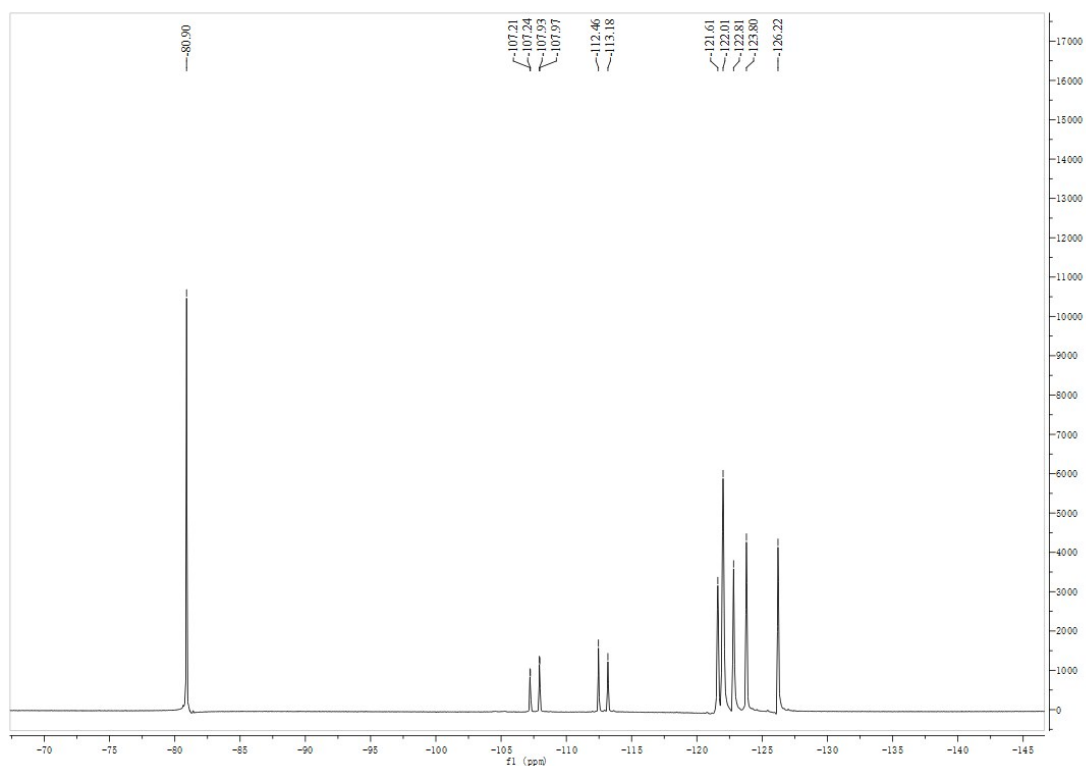
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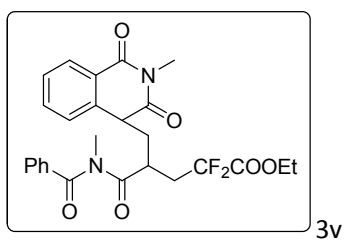
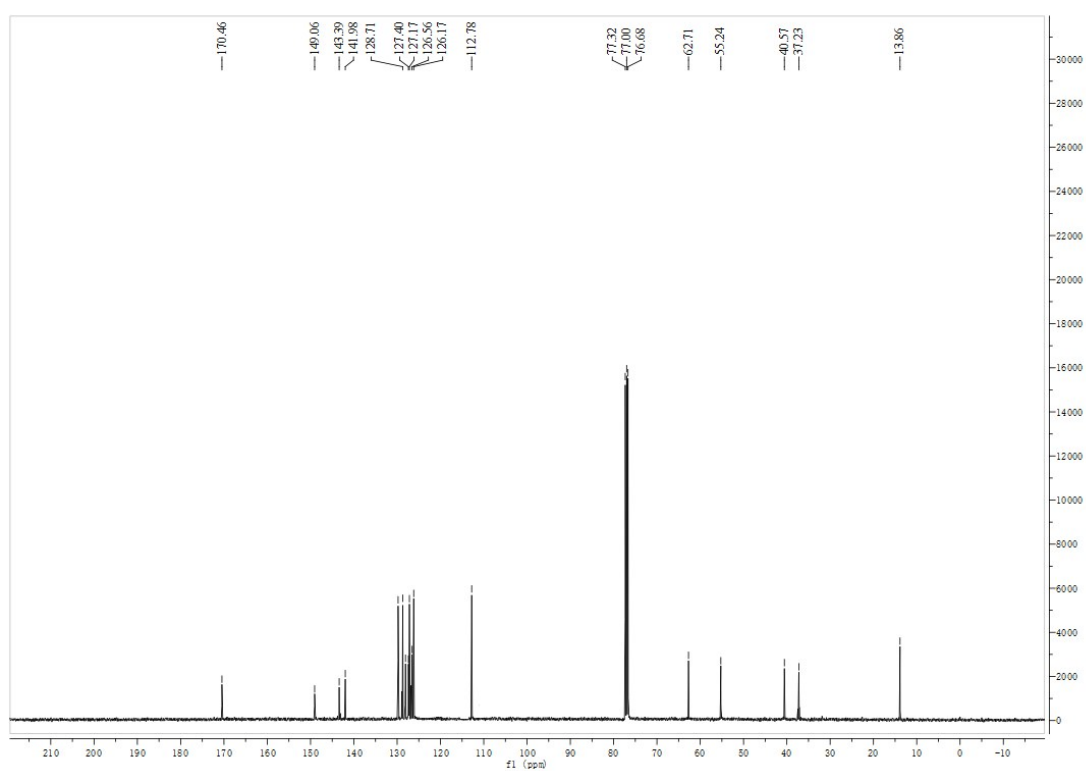
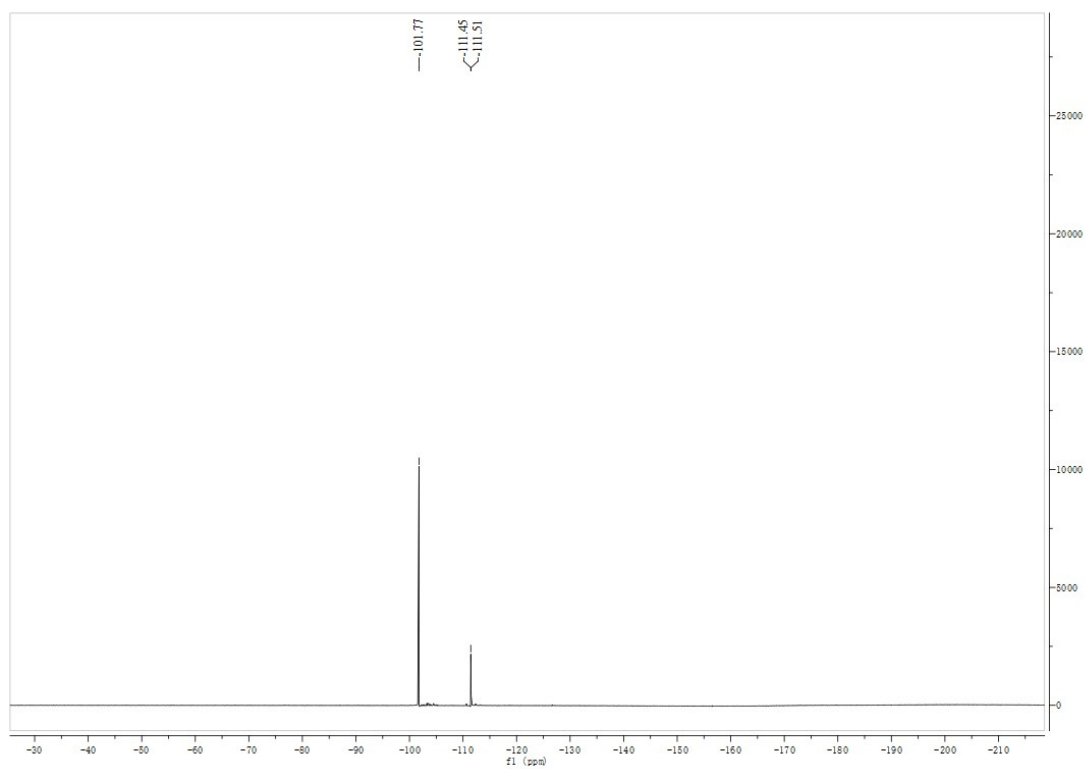


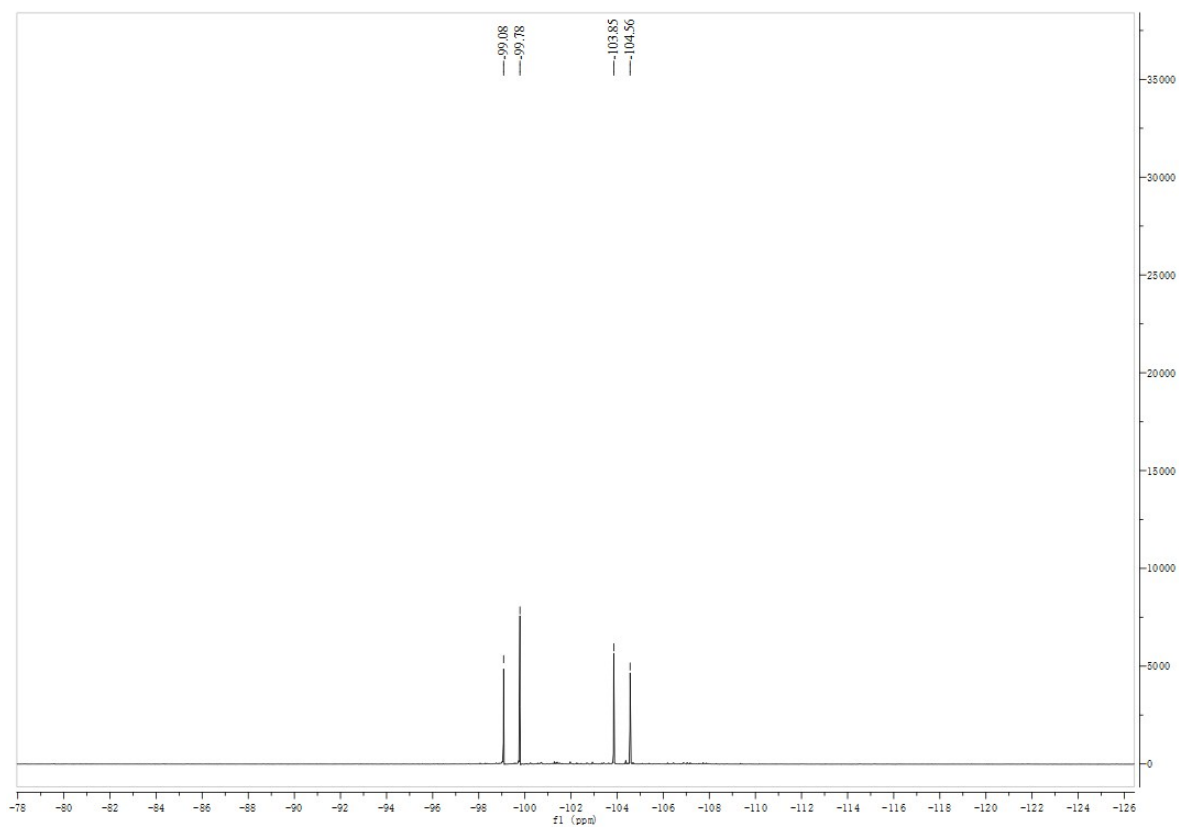
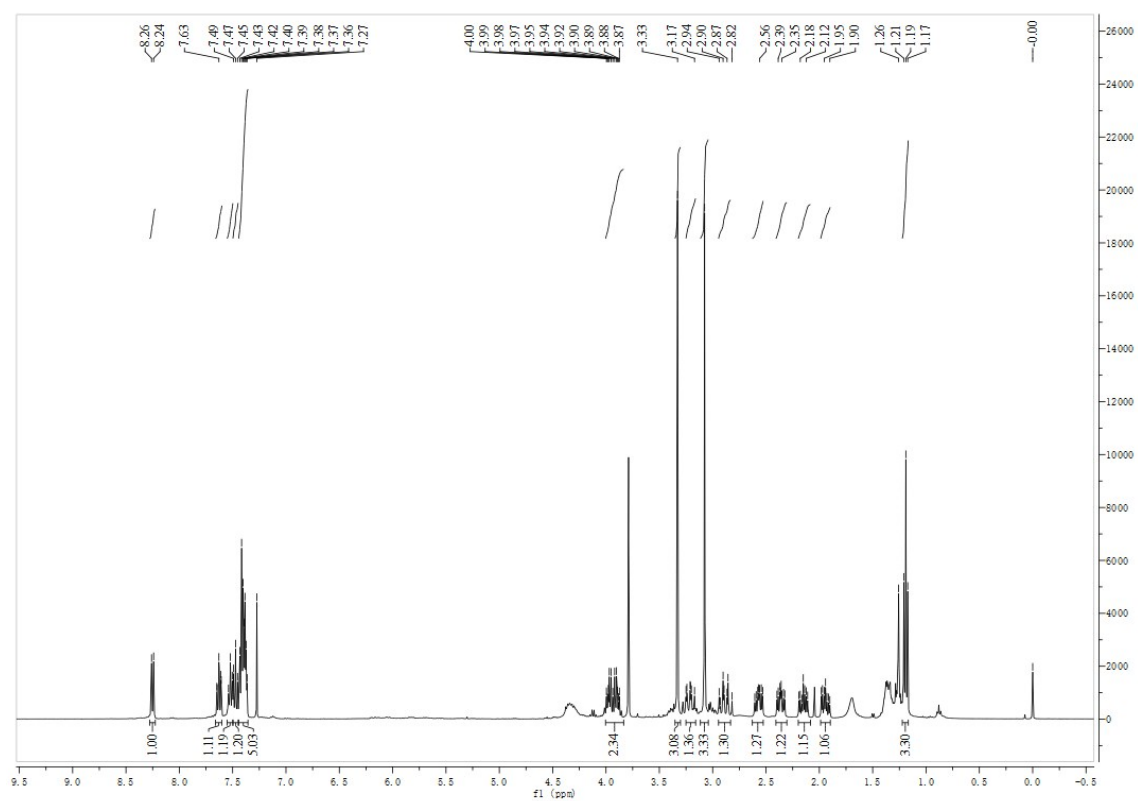


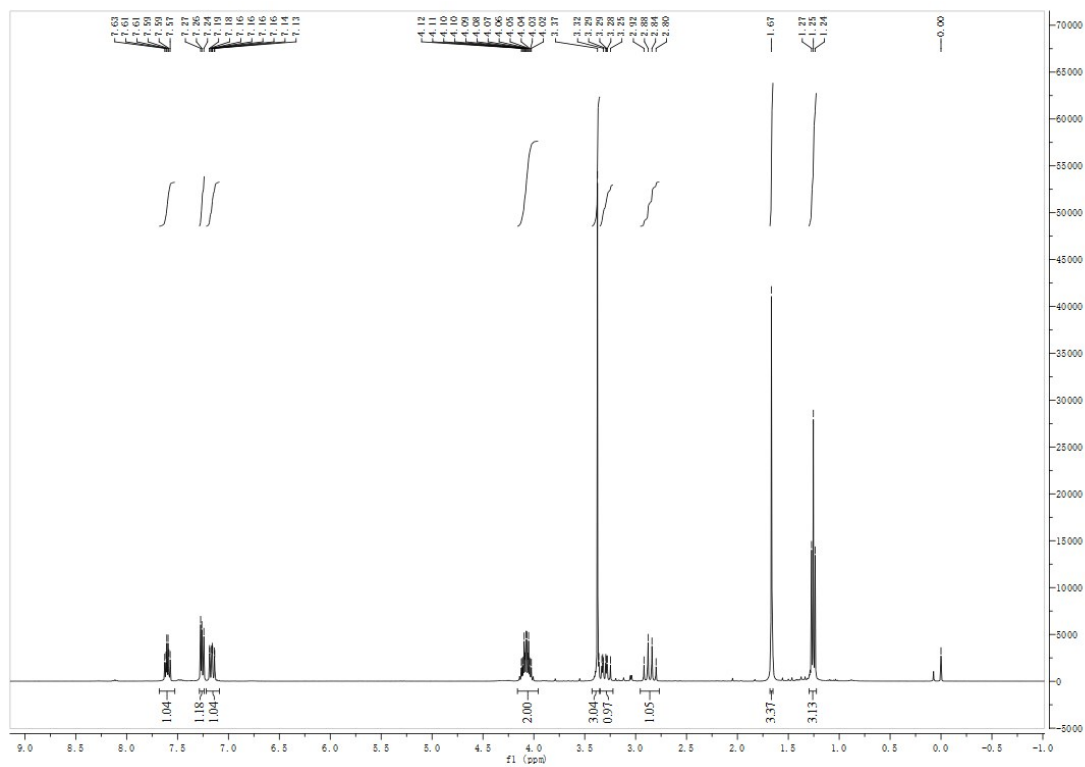
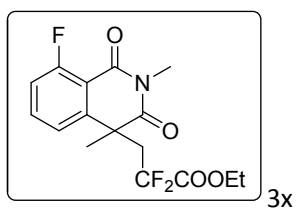
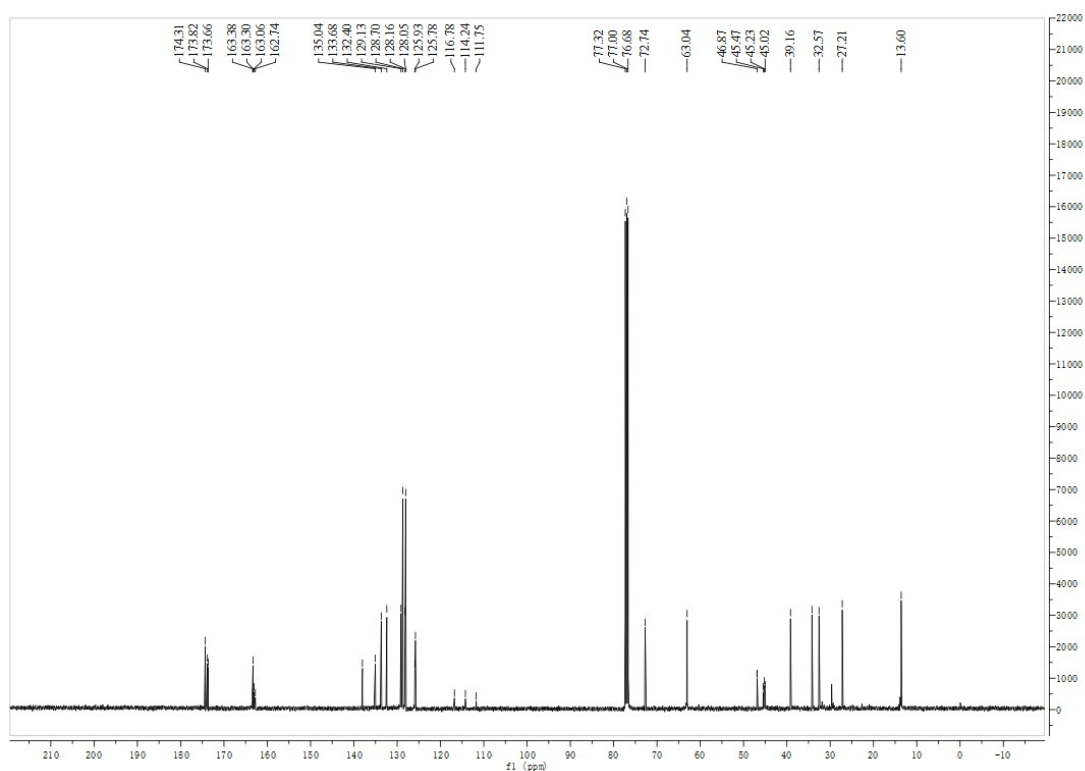
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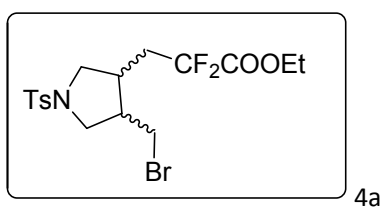
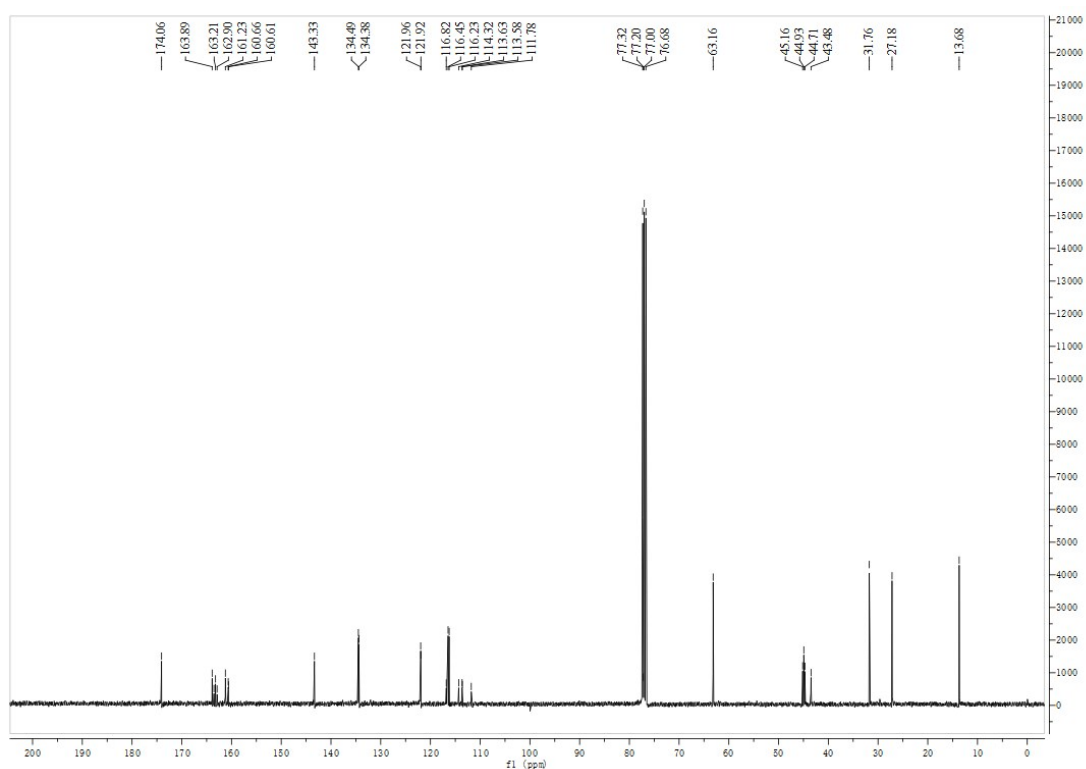
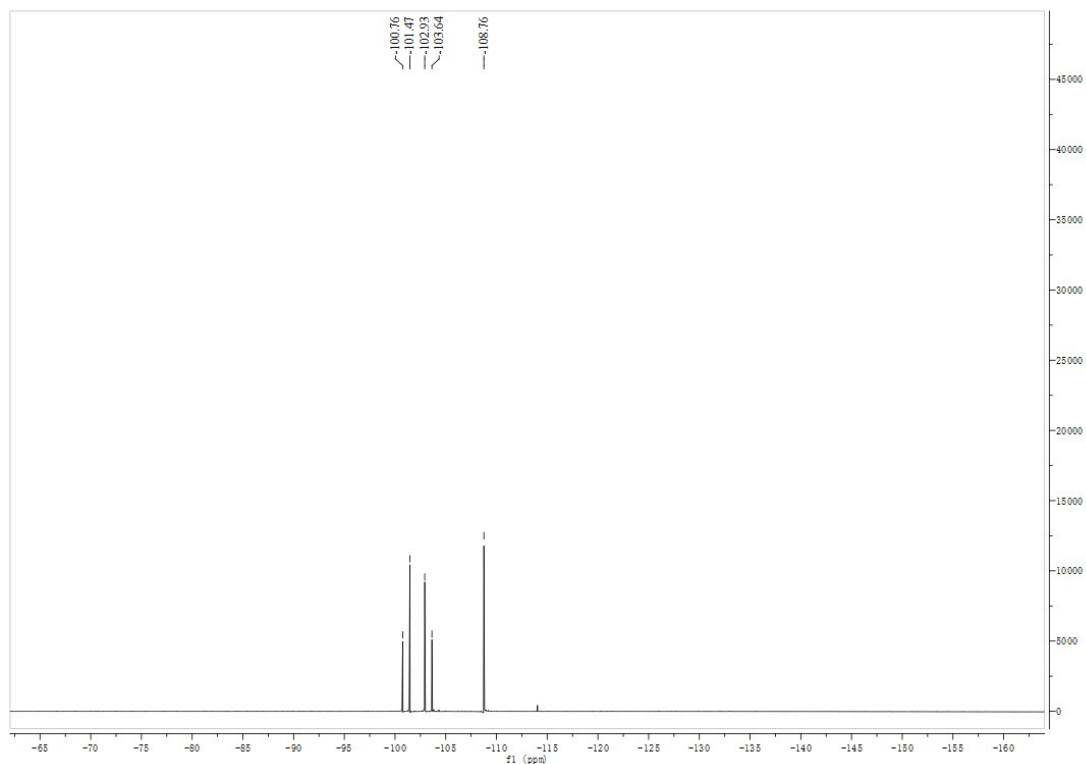


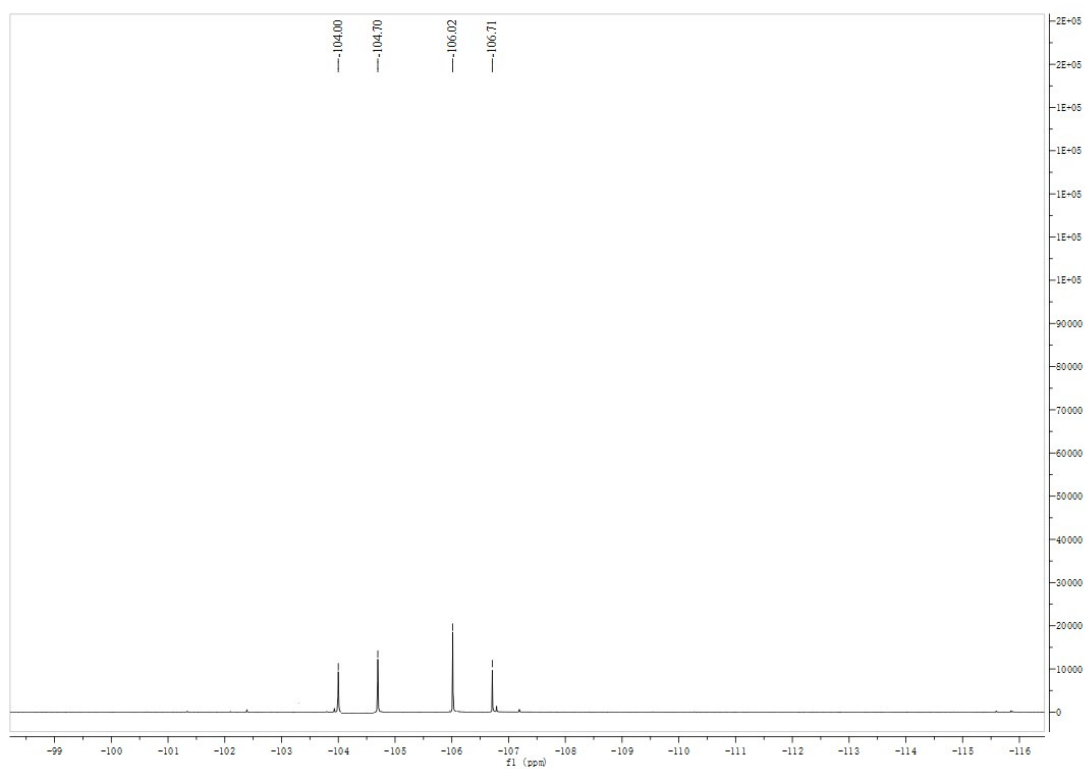
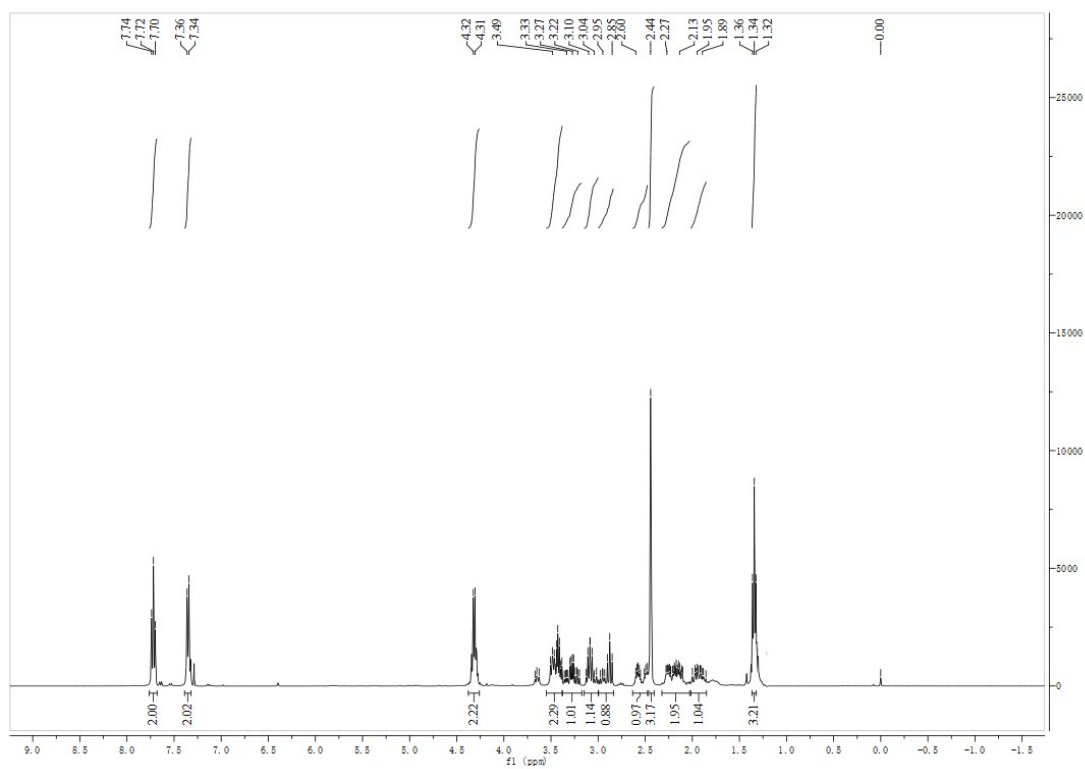


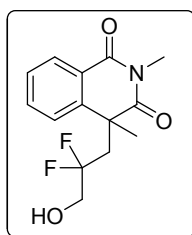
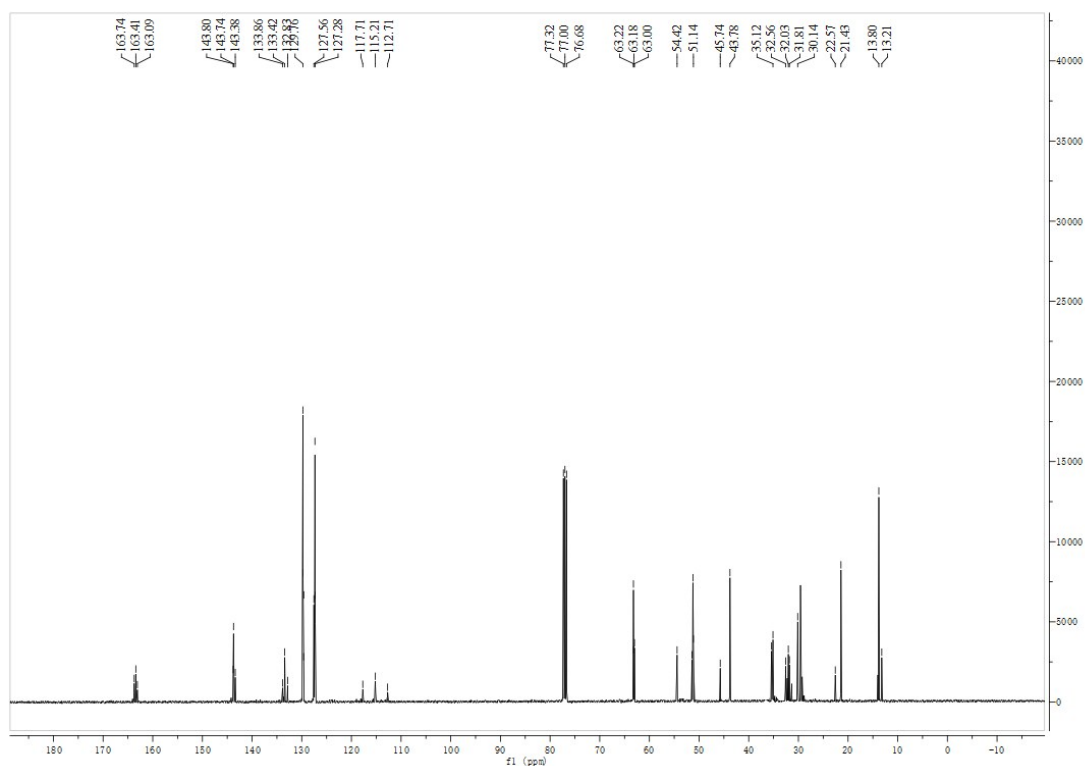












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