Highly selective Difluoromethylations of β-keto Amides with $TMSCF_2Br$ under mild conditions

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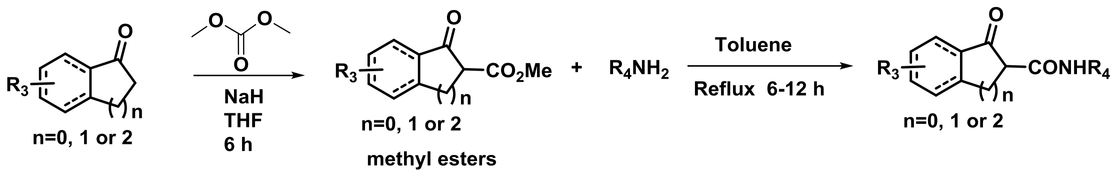
A. General Information:

Unless otherwise stated, all commercial reagents and solvents were used without further additional purification. Analytical TLC was visualized with UV light at 254 nm. Thin layer chromatography was carried out on TLC aluminum sheets with silica gel 60 F_{254}. Purification of reaction products was carried out with chromatography on silica gel 60 (200-300 mesh). ^{1}H NMR (400 MHz) spectra was obtained at 25 ℃; ^{13}C NMR (126 MHz) were recorded on a VARIAN INOVA-400M and AVANCE II 400 spectrometer at 25 ℃. Chemical shifts are reported as δ (ppm) values relative to TMS as internal standard and coupling constants (J) in Hz.. Mass spectra are reported by using electron ionization and electrospray ionization techniques. Melting points were determined with a hot plate apparatus.

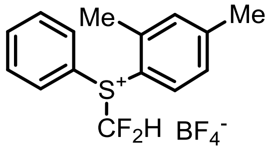
Materials:

1. β-keto amides



β-keto methyl esters were prepared according to the literature procedures (*Eur. J. Org. Chem.* **2010**, *34*, 6525–6530;). NaH (50 mmol, 2.5 g, 2.5 eq., 60% dispersion in mineral oil) and anhydrous dimethyl carbonate (***DMC***, 5 mL) and anhydrous THF (100 mL) were added sequentially to a dry three-necked flask equipped with a septum, condenser, argon inlet, and a large stirring egg. The **1-indanone** (20 mmol, 1 eq), solubilized in anhydrous THF (20 mL), was added *via* a dropping funnel for the course of 30 minutes. The heterogeneous mixture was brought to reflux, and heated for 6h at this temperature. The reaction was allowed to cool and cautiously quenched at 0 ℃ with H_2O (10 mL). The mixture was transferred to a separative funnel with EtOAc while adding additional 50 mL of 1M HCl. The reaction was extracted with EtOAc (50 mL x 3) and the combined organic layers washed with a saturated brine solution before being dried over solid anhydrous magnesium sulfate and the crude methyl esters was purified by column chromatography. β-keto amides **1a-1v** were prepared according to the literature procedure (*Adv. Synth. Catal.* **2016**, *358*, 737-745). To a flask equipped with a reflux condenser was added β-keto methyl ester (1 mmol), corresponding amides $\mathbf{R_4NH_2}$ (1.5 mmol). The mixture was refluxed until complete conversion was observed by TLC, then concentrated under reduced pressure and the crude residue was purified by column chromatography and recrystallization. The 1-indanone derivates were purchased from Energy-Chemical, Aladdin and Adamas.

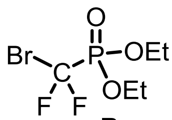
2. Difluoromethylation reagents



B1 was prepared according to the method of Xiao's group (*RSC Adv.* **2016**, *6*, 35705-35708).

$\mathbf{HCF_2OTf}$ (**B2**) was prepared according to the method of Hartwig (*Angew. Chem. Int. Ed.* **2013**, *52*, 1 – 5).

$\mathbf{Ph_3P^+CF_2CO_2^-}$ **(B3)** was prepared according to the method of Xiao's group (*Chem. Commun.* **2013**, 49, 7513-7515.)



$\mathbf{B_4}$ and $\mathbf{TMSCF_2Br}$ were purchased from TCI.

3. Phase transfer catalysts

Cinchona alkaloid derived phase-transfer catalysts were prepared according to our previous papers (*Green Chem.* **2016,** *18*, 5493-5499. *J. Org. Chem.* **2016**, *81*, 7042-7050.)

4. Commercial grade reagents and solvents:

D-[toluene] was purchased from Sigma-Aldrich; Commercial grade reagents, bases and solvents were purchased from Enokai, Meryer and Energy-Chemical without further purifications.

B. General procedure for the difluoromethylation of β-keto amides

1. Optimization of the reaction conditions for the α-difluoromethylation of β-keto amide 1a[a]

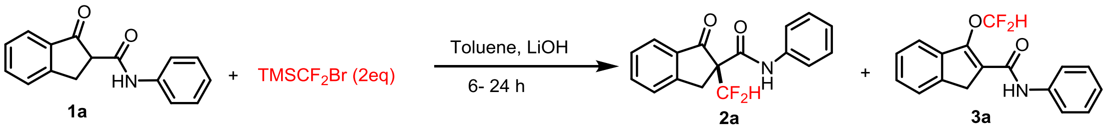
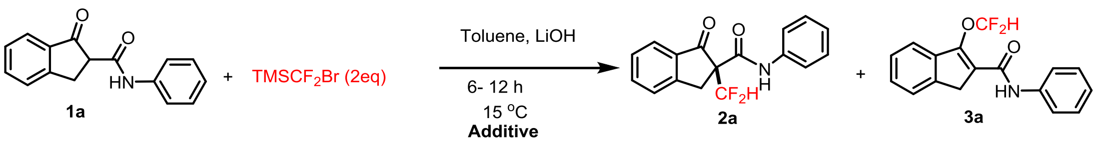


Table 1 Temperature screening

Entry	T [°C]	Time [h]	Yield [%][b]	C/O[c]
1	25	12	81	96/4
2	60	6	61	92/8
3	20	12	83	96/4
4	**15**	**12**	**85**	**96/4**
5	10	12	83	96/4
6	0	24	67	92/8
6	-10	24	32	92/8

[a] The reaction of **1a** (0.1 mmol) with $TMSCF_2Br$ (2.0 equiv.) was carried out in the presence of LiOH (3.0 equiv.) in Toluene (1 mL, 0.1 M). [b] Yield of isolated product. [c] ^{19}F NMR with trifluorotoluene as the internal standard.

Table 2 Additive screening



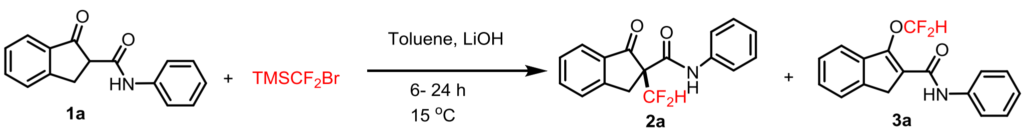
Entry	Additive (10 mol%)	Time [h]	Yield [%][b]	C/O[C]
1	(*n*-Bu)4NBr	6	82	93/7
2	(*n*-Bu)4NCl	6	77	91/9
3	(*n*-Bu)4NI	6	76	91/9

4	(n-Bu)$_4$NF	6	78	91/9
5	(n-Bu)$_4$N(PF$_6$)	6	78	92/8
6	$CH_3(CH_2)_{15}(CH_3)_3NBr$	6	81	91/9
7	LiI	3	78	93/7
8	LiCl	3	76	93/7
9	**-**	**12**	**85**	**96/4**

[a] The reaction of **1a** (0.1 mmol) with $TMSCF_2Br$ (2.0 equiv.) was carried out in the presence of LiOH (3.0 equiv.) in Toluene (1 mL, 0.1 M). [b] Yield of isolated product. [c] ^{19}F NMR with trifluorotoluene as the internal standard.

Evaluating the function of ammonium salts were shown in Table 2. Adding ammonium salts, LiI and LiCl could accelerate the reaction, but the C/O selectivities were slightly lower compared with additive free.

Table 3 Screening of the concentration and the dosage of $TMSCF_2Br$

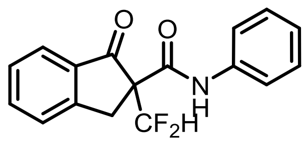


Entry	**Concentration**	$TMSCF_2Br$ (equiv.)	Time [h]	Yield [%][b]	C/O[C]
1	0.1 M	2.0	12	85	96/4
2	0.2 M	2.0	6	82	94/6
3	0.3 M	2.0	6	78	90/10
4	0.08 M	2.0	16	88	96/4
5	**0.04 M**	**2.0**	**16**	**89**	**98/2**
6	0.02 M	2.0	24	72	96/4
7	0.04 M	3.0	16	89	98/2
8	**0.04 M**	**1.5**	**24**	**91**	**98/2**
9	0.04 M	1.3	24	85	98/2

[a] The reaction of **1a** (0.1 mmol) with $TMSCF_2Br$ was carried out in the presence of LiOH (3.0 equiv.) in Toluene at 15 °C. [b] Yield of isolated product. [c] ^{19}F NMR with trifluorotoluene as the internal standard.

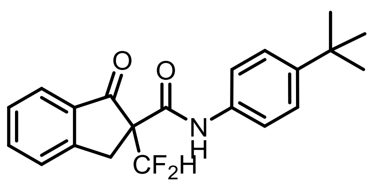
2. General proceduce for the C-difluoromethylation of β-keto amides

The reactions were performed with β-keto amide **1a-1v** (0.1 mmol), LiOH (7.2 mg, 0.3 mmol) in 2.5 mL dry toluene. The reaction mixture was was stirred at 15℃ for 5 min. Then $TMSCF_2Br$ (0.15 mmol) was added slowly, and the reaction was stirred at this temperature for 24 h. After the reaction was completed, the mixture was diluted with EtOAc (20 mL), washed with water (3 × 10 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The residue was subject to crude ^{19}F-NMR to give the C/O isomer ratio (trifluoromethyl benzene 8 μL as internal standard). Subsequently, the residue was purified by flash chromatography (silica gel; petroleum ether/ethyl acetate=25:1–2:1) to afford the α-difluoromethylation products.



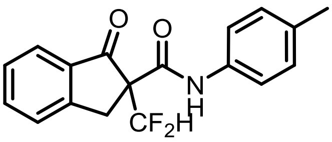
2a

(White wax,27.1 mg, 90% yield, C/O = 98:2); ^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.18 (s, 1H), 7.88 – 7.67 (m, 2H), 7.63 – 7.52 (m, 3H), 7.49 – 7.29 (m, 3H), 7.21 – 7.05 (m, 1H), 6.22 (t, *J* = 55.5 Hz, 1H), 4.10 (d, *J* = 18.3 Hz, 1H), 3.55 (d, *J* = 18.3 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 200.84 (d, *J* = 4.8 Hz), 160.94 (d, *J* = 9.1 Hz), 153.93, 137.09, 136.96, 129.07, 128.15, 126.62, 125.02, 120.15， 115.42 (m), 64.98 (d, *J* = 39.9 Hz). ^{19}F NMR (376 MHz, Chloroform-*d*) δ -121.15 (dd, *J* = 280.0, 55.3 Hz, 1F), -123.85 (dd, *J* = 280.0, 55.8 Hz, 1F). HRMS Calcd. for $[C_{17}H_{13}F_2NO_2+Na]^+$ requires m/z 324.0812, found m/z 324.0815.



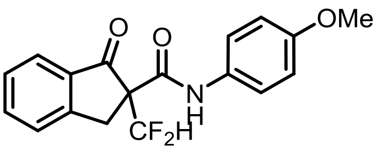
2b

(White solid, 33.2 mg, 93% yield, C/O = 99:1); m. p. 83-85 ℃; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.12 (s, 1H), 7.80 (d, *J* = 7.8 Hz, 1H), 7.69 (td, *J* = 7.5, 1.2 Hz, 1H), 7.61 – 7.47 (m, 3H), 7.46 – 7.30 (m, 3H), 6.22 (t, *J* = 55.5 Hz, 1H), 4.09 (d, *J* = 18.3 Hz, 1H), 3.54 (d, *J* = 18.3 Hz, 1H), 1.30 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 200.90, 160.86 (d, *J* = 3.7 Hz), 153.98, 148.07, 136.92, 134.54, 128.14, 126.65, 125.91, 125.01, 119.02 – 111.13 (m), 65.19, 64.99 (t, *J* = 20.0 Hz), 34.46, 31.35. ^{19}F NMR (376 MHz, Chloroform-*d*) δ -121.14 (dd, *J* = 280.0, 55.4 Hz, 1F), -123.92 (dd, *J* = 280.0, 55.4 Hz, 1F). HRMS Calcd. for $[C_{21}H_{21}F_2NO_2+Na]^+$ requires m/z 380.1438, found m/z 380.1440.



2c

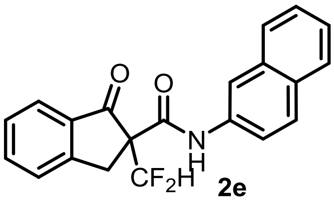
(Light yellow solid, 29.0 mg, 92% yield, C/O = 98:2); m. p. 70-73 ℃; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.10 (s, 1H), 7.87 – 7.61 (m, 2H), 7.61 – 7.39 (m, 4H), 7.14 (d, *J* = 8.1 Hz, 2H), 6.22 (t, *J* = 55.5 Hz, 1H), 4.09 (d, *J* = 18.2 Hz, 1H), 3.54 (d, *J* = 18.3 Hz, 1H), 2.31 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 200.91 (d, *J* = 5.6 Hz), 162.37 – 160.04 (m), 153.98, 136.93, 134.66 (d, *J* = 13.6 Hz), 129.57, 128.14, 126.64, 125.01, 120.19, 115.51 (dd, *J* = 251.7, 250.4 Hz), 64.96 (t, *J* = 19.9 Hz), 30.78 – 27.62 (m), 20.93. ^{19}F NMR (376 MHz, Chloroform-*d*) δ -121.17 (dd, *J* = 280.0, 55.2 Hz, 1F), -123.93 (dd, *J* = 280.0, 55.2 Hz, 1F). HRMS Calcd. for $[C_{18}H_{15}F_2NO_2+Na]^+$ requires m/z 338.0969, found m/z 338.0965.



2d

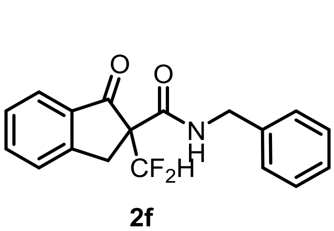
(Light yellow solid, 30.1 mg, 91% yield, C/O = 98:2); m. p. 92-95 ℃; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.06 (s, 1H), 7.88 – 7.64 (m, 2H), 7.60 – 7.52 (m, 1H), 7.51 –

7.36 (m, 3H), 6.95 – 6.79 (m, 2H), 6.22 (t, *J* = 55.5 Hz, 1H), 4.09 (d, *J* = 18.2 Hz, 1H), 3.79 (s, 3H), 3.54 (d, *J* = 18.3 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ200.95 (d, *J* = 5.3 Hz), 160.83, 156.84, 153.98, 136.92, 134.57 (d, *J* = 2.1 Hz), 130.26, 128.13, 126.64, 125.00, 119.16 – 111.41 (m), 114.17, 64.86 (d, *J* = 39.8 Hz), 55.48, 30.01. ^{19}F NMR (376 MHz, Chloroform-*d*) δ -121.14 (dd, *J* = 279.8, 55.7 Hz, 1F), -124.00 (dd, *J* = 279.8, 55.7 Hz, 1F). HRMS Calcd. for $[C_{18}H_{15}F_2NO_3+Na]^+$ requires m/z 354.0918, found m/z 354.0910.



2e

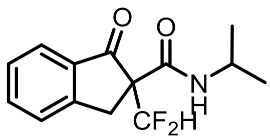
(White wax, 29.8 mg, 85% yield, C/O = 97:3); ^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.73 (s, 1H), 7.98 (t, *J* = 8.0 Hz, 2H), 7.86 – 7.75 (m, 2H), 7.69 – 7.59 (m, 2H), 7.58 – 7.36 (m, 5H), 6.25 (t, *J* = 55.5 Hz, 1H), 4.08 (d, *J* = 18.3 Hz, 1H), 3.52 (d, *J* = 18.3 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ200.18 (d, *J* = 4.8 Hz), 160.53(d, *J* = 5.3 Hz) , 152.99, 135.99, 132.99, 130.80, 127.17, 125.71, 125.63, 125.47, 125.11, 124.87, 124.59, 124.07, 119.41, 118.54 – 108.91 (m), 118.5, 64.14 (t, *J* = 19.8 Hz). ^{19}F NMR (376 MHz, Chloroform-*d*) δ -120.68 (dd, *J* = 279.5, 55.7 Hz, 1F), -123.62 (dd, *J* = 279.5, 55.7 Hz, 1F). HRMS Calcd. for $[C_{21}H_{15}F_2NO_2+Na]^+$ requires m/z 374.0969, found m/z 374.0975.



2f

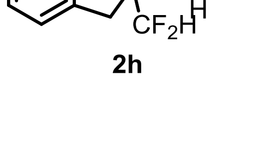
(White wax, 28.6 mg, 91% yield, C/O = 98:2); ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.76 (d, *J* = 7.7 Hz, 1H), 7.68 (td, *J* = 7.5, 1.2 Hz, 1H), 7.55 (t, *J* = 7.4 Hz, 2H), 7.42 (d, *J* = 7.5 Hz, 1H), 7.34 (dd, *J* = 7.9, 6.3 Hz, 2H), 7.28 – 7.23 (m, 2H), 6.17 (t, *J* = 55.5

Hz, 1H), 4.60 (dd, J = 14.9, 6.0 Hz, 1H), 4.41 (dd, J = 14.9, 5.4 Hz, 1H), 4.06 (d, J = 18.2 Hz, 1H), 3.50 (d, J = 18.2 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 200.44 (d, J = 5.8 Hz), 164.55 – 159.36 (m), 154.03, 137.41, 136.72, 134.53 (d, J = 2.4 Hz), 128.82, 128.05, 127.67, 127.56, 126.64, 124.93, 20.29 – 110.88 (m), 118.15, 115.66, 113.17, 64.53 (d, J = 40.0 Hz), 44.25, 29.89. ^{19}F NMR (376 MHz, Chloroform-*d*) δ -121.50 (dd, J = 280.2, 55.3 Hz, 1F), -124.41 (dd, J = 280.2, 55.3 Hz, 1F). HRMS Calcd. for $[C_{18}H_{15}F_2NO_2+Na]^+$ requires m/z 338.0969, found m/z 338.0971.



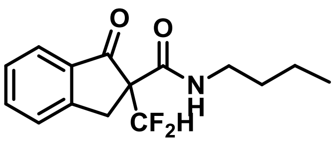
2g

(Light yellow solid, 25.1 mg, 94% yield, C/O = 99:1); m. p. 81-83 ℃; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.83 – 7.63 (m, 2H), 7.54 (d, J = 7.7 Hz, 1H), 7.41 (t, J = 7.5 Hz, 1H), 7.08 (d, J = 7.7 Hz, 1H), 6.14 (t, J = 55.6 Hz, 1H), 4.19 – 3.96 (m, 2H), 3.46 (d, J = 18.2 Hz, 1H), 1.23 (d, J = 6.6 Hz, 3H), 1.15 (d, J = 6.6 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ200.74 (d, J = 5.4 Hz), 164.48 – 160.83 (m), 154.04, 136.59, 134.61 (d, J = 2.3 Hz), 127.94, 126.61, 124.81, 115.76 (dd, J = 250.9, 249.4 Hz), 64.40 (t, J = 19.9 Hz), 42.42, 29.81 (dd, J = 3.7, 2.1 Hz),22.47, 22.31. ^{19}F NMR (376 MHz, Chloroform-*d*) δ -121.51 (dd, J = 279.7, 55.5 Hz, 1F), -124.90 (dd, J = 279.7, 55.5 Hz, 1F). HRMS Calcd. for $[C_{14}H_{15}F_2NO_2+Na]^+$ requires m/z 290.0969, found m/z 290.0964.



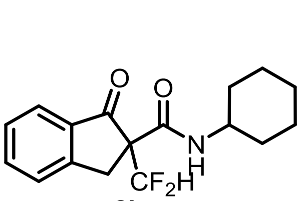
2h

(White solid, 28.3 mg, 93% yield, C/O = 99:1); m. p. 103-106 ℃; [1]H NMR (400 MHz, Chloroform-*d*) δ 7.76 (d, *J* = 7.7 Hz, 1H), 7.68 (td, *J* = 7.5, 1.2 Hz, 1H), 7.54 (dt, *J* = 7.7, 1.0 Hz, 1H), 7.46 – 7.39 (m, 1H), 7.13 (s, 1H), 6.12 (t, *J* = 55.7 Hz, 1H), 4.01 (d, *J* = 18.2 Hz, 1H), 3.43 (d, *J* = 18.2 Hz, 1H), 1.37 (s, 9H). [13]C NMR (101 MHz, $CDCl_3$) δ201.06 (d, *J* = 6.0 Hz), 161.78 (d, *J* = 6.4 Hz), 154.09, 136.57, 134.67, 127.91, 126.63, 124.79, 118.85 – 109.99 (m), 65.02 (t, *J* = 19.7 Hz), 51.99, 30.91 – 28.40 (m), 28.48. [19]F NMR (376 MHz, Chloroform-*d*) δ -121.16 (dd, *J* = 279.2, 55.9 Hz, 1F), -125.12 (dd, *J* = 279.2, 55.9 Hz, 1F). HRMS Calcd. for $[C_{15}H_{17}F_2NO_2+Na]^+$ requires m/z 304.1125, found m/z 304.1128.



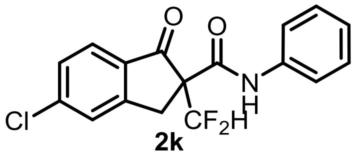
2i

(White wax, 25.8 mg, 92% yield, C/O = 99:1); [1]H NMR (400 MHz, Chloroform-*d*) δ 8.04 (dd, *J* = 7.9, 1.3 Hz, 1H), 7.54 (td, *J* = 7.5, 1.4 Hz, 1H), 7.42 – 7.22 (m, 2H), 6.61 (t, *J* = 5.8 Hz, 1H), 6.40 (t, *J* = 55.5 Hz, 1H), 3.45 – 3.02 (m, 3H), 2.90 (ddt, *J* = 41.1, 13.5, 4.0 Hz, 2H), 2.50 – 2.04 (m, 1H), 1.55 – 1.39 (m, 2H), 1.28 (dt, *J* = 14.9, 7.3 Hz, 2H), 0.88 (t, *J* = 7.3 Hz, 3H). [13]C NMR (101 MHz, $CDCl_3$) δ 195.36 (d, *J* = 6.3 Hz), 162.39 (d, *J* = 6.7 Hz), 144.79, 135.08, 131.07 (d, *J* = 2.2 Hz), 128.93, 128.10, 126.94, 116.35 (dd, *J* = 250.8, 247.8 Hz), 61.66 (dd, *J* = 21.3, 19.4 Hz)， 40.01, 31.25, 25.33, 22.62, 19.90, 13.65. [19]F NMR (376 MHz, Chloroform-*d*) δ -122.04 (dd, *J* = 279.7, 55.2 Hz, 1F), -130.86 (dd, *J* = 279.7, 55.2 Hz, 1F). HRMS Calcd. for $[C_{15}H_{17}F_2NO_2+Na]^+$ requires m/z 304.1125, found m/z 304.1121.



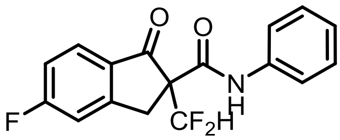
2j

(Light yellow solid, 28.9 mg, 94% yield, C/O = 99:1); m. p. 76-79 ℃; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.82 – 7.64 (m, 2H), 7.61 – 7.34 (m, 2H), 7.16 (d, *J* = 7.9 Hz, 1H), 6.12 (t, *J* = 55.7 Hz, 1H), 4.03 (d, *J* = 18.3 Hz, 1H), 3.79 (dtd, *J* = 10.1, 6.7, 6.3, 3.9 Hz, 1H), 3.46 (d, *J* = 18.2 Hz, 1H), 1.95 (d, *J* = 12.2 Hz, 1H), 1.91 – 1.53 (m, 4H), 1.48 – 1.08 (m, 5H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 200.89, 162.05, 161.98, 161.96, 154.04, 136.59, 134.59 (d, *J* = 2.3 Hz), 127.92, 126.59, 124.80, 119.80 – 106.40 (m), 64.36 (t, *J* = 19.8 Hz), 48.95, 32.59, 29.84, 29.79, 25.42, 24.51. ^{19}F NMR (376 MHz, Chloroform-*d*) δ -121.36 (dd, *J* = 279.3, 55.8 Hz, 1F), -124.84 (dd, *J* = 279.3, 55.8 Hz, 1F). HRMS Calcd. for $[C_{17}H_{19}F_2NO_2+Na]^+$ requires m/z 330.1282, found m/z 330.1285.



2k

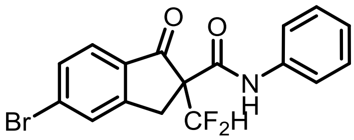
(White solid, 29.5 mg, 88% yield, C/O = 98:2); m. p. 118-121 ℃; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.11 (s, 1H), 7.74 (d, *J* = 8.2 Hz, 1H), 7.65 – 7.50 (m, 3H), 7.47 – 7.30 (m, 3H), 7.16 (d, *J* = 7.4 Hz, 1H), 6.22 (t, *J* = 55.4 Hz, 1H), 4.08 (d, *J* = 18.5 Hz, 1H), 3.52 (d, *J* = 18.5 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 199.37, 160.56, 155.24, 143.87, 136.99, 132.95 (d, *J* = 2.3 Hz), 129.14, 129.13, 126.91, 126.09, 125.16, 120.18, 117.96 – 110.65 (m), 65.21 (t, *J* = 20.0 Hz), 29.68. ^{19}F NMR (376 MHz, Chloroform-*d*) δ -121.10 (dd, *J* = 280.6, 55.2 Hz, 1F), -122.87 – -124.86 (dd, *J* = 280.6, 55.2 Hz, 1F). HRMS Calcd. for $[C_{17}H_{12}F_2NClO_2+Na]^+$ requires m/z 358.0422, found m/z 358.0426.



2l

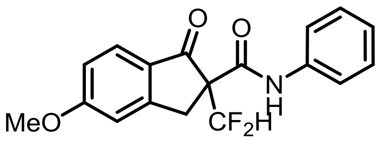
(White solid, 27.1 mg, 85% yield, C/O = 97:3); m. p. 125-127 ℃; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.14 (s, 1H), 7.84 (dd, *J* = 8.5, 5.2 Hz, 1H), 7.62 – 7.50 (m, 2H), 7.35 (t, *J* = 7.9 Hz, 2H), 7.26 – 7.07 (m, 3H), 6.22 (t, *J* = 55.4 Hz, 1H), 4.10 (d, *J* = 18.5 Hz, 1H), 3.53 (d, *J* = 18.5 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 198.92, 169.76, 167.16, 160.68, 157.03 (d, *J* = 10.9 Hz), 137.01, 129.12, 127.62 (d, *J* = 11.0 Hz), 125.14, 120.17, 113.52 (d, *J* = 22.8 Hz), 65.30 (t, *J* = 19.9 Hz). ^{19}F NMR (376 MHz, Chloroform-*d*) δ -97.81 (d, *J* = 5.4 Hz, 1F),

-121.22 (dd, *J* = 280.5, 55.2 Hz, 1F), -123.97 (dd, *J* = 280.5, 55.2 Hz, 1F). HRMS Calcd. for $[C_{17}H_{12}F_3NO_2+Na]^+$ requires m/z 342.0718, found m/z 342.0723.



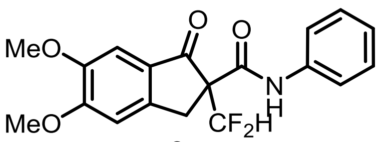
2m

(White solid, 33.3 mg, 88% yield, C/O = 98:2); m. p. 115-1117 ℃; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.03 (s, 1H), 7.70 (d, *J* = 1.4 Hz, 1H), 7.63 – 7.45 (m, 4H), 7.32 – 7.21 (m, 2H), 7.16 – 7.01 (m, 1H), 6.14 (t, *J* = 55.4 Hz, 1H), 4.02 (d, *J* = 18.4 Hz, 1H), 3.46 (d, *J* = 18.4 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 198.61, 154.22, 135.92, 131.85, 130.95, 128.97, 128.08, 125.04, 124.13, 119.13, 115.43 (d, *J* = 251.5 Hz), 64.07 (t, *J* = 20.1 Hz), 28.68, 28.57. ^{19}F NMR (376 MHz, Chloroform-*d*) δ -121.06 (dd, *J* = 280.6, 55.2 Hz, 1F), -123.85 (dd, *J* = 280.6, 55.2 Hz, 1F). HRMS Calcd. for $[C_{17}H_{12}F_2BrNO_2+Na]^+$ requires m/z 401.9917, found m/z 401.9912.



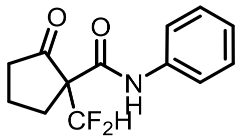
2n

(Light yellow solid, 30.8 mg, 93% yield, C/O = 99:1); m. p. 142-146 ℃; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.31 (s, 1H), 7.73 (d, *J* = 8.4 Hz, 1H), 7.64 – 7.50 (m, 2H), 7.34 (t, *J* = 7.9 Hz, 2H), 7.24 – 7.07 (m, 1H), 7.03 – 6.84 (m, 2H), 6.22 (t, *J* = 55.5 Hz, 1H), 4.03 (d, *J* = 18.3 Hz, 1H), 3.92 (s, 3H), 3.48 (d, *J* = 18.3 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ198.37 (d, *J* = 5.4 Hz), 167.17, 161.34 (d, *J* = 2.4 Hz), 157.34, 137.22, 129.07, 126.86, 124.93, 120.14, 118.67 – 112.51 (m), 116.82, 109.40, 65.10 (t, *J* = 20.0 Hz), 55.95. ^{19}F NMR (376 MHz, Chloroform-*d*) δ -121.51 (dd, *J* = 279.5, 55.6 Hz, 1F), -123.27 – -124.89 (dd, *J* = 279.5, 55.6 Hz, 1F). HRMS Calcd. for $[C_{18}H_{15}F_2NO_3+Na]^+$ requires m/z 354.0918, found m/z 354.0925.



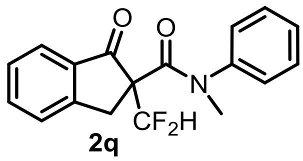
2o

(Light yellow solid, 32.1 mg, 89% yield, C/O = 99:1); m. p. 172-174 ℃; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.30 (s, 1H), 7.65 – 7.51 (m, 2H), 7.41 – 7.29 (m, 2H), 7.21 – 7.08 (m, 2H), 6.97 (s, 1H), 6.22 (t, *J* = 55.6 Hz, 1H), 4.01 (s, 3H), 3.98 (d, *J* = 18.2 Hz, 1H), 3.92 (s, 3H), 3.44 (d, *J* = 18.2 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 198.68 (d, *J* = 5.6 Hz), 161.42 (d, *J* = 6.5 Hz), 157.52, 150.36, 150.10, 137.22, 129.07, 127.07 (d, *J* = 2.3 Hz), 124.93, 120.14, 118.57 – 111.62 (m), 107.31, 104.74, 65.24 (t, *J* = 20.0 Hz, 56.58, 56.20. ^{19}F NMR (376 MHz, Chloroform-*d*) δ -121.67 (dd, *J* = 279.2, 55.6 Hz, 1F), -124.11 (dd, *J* = 279.2, 55.6 Hz, 1F). HRMS Calcd. for $[C_{19}H_{17}F_2NO_4+Na]^+$ requires m/z 384.1023, found m/z 384.1021.



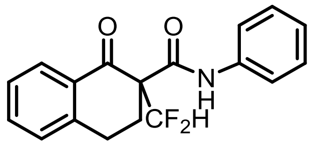
2p

(Colourless oil, 20.0 mg, 93% yield, C/O = 90:10); ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.64 (s, 1H), 7.64 – 7.48 (m, 2H), 7.45 – 7.30 (m, 2H), 7.21 – 7.07 (m, 1H), 6.06 (t, *J* = 55.5 Hz, 1H), 3.02 – 2.80 (m, 1H), 2.66 – 2.32 (m, 3H), 2.23 – 1.85 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 214.97 (d, *J* = 4.7 Hz), 160.68, 137.00, 129.10, 125.07, 120.02, 119.16 – 111.18 (m), 64.98 (t, *J* = 20.0 Hz), 39.68, 39.67, 26.25, 26.23, 26.21, 19.23. ^{19}F NMR (376 MHz, Chloroform-*d*) δ -119.06 (dd, *J* = 283.3, 55.3 Hz, 1F), -123.64 (dd, *J* = 283.3, 55.3 Hz, 1F). HRMS Calcd. for $[C_{13}H_{13}F_2NO_2+Na]^+$ requires m/z 276.0812, found m/z 276.0803.



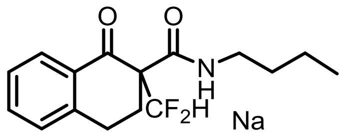
2q

(White wax, 23.6 mg, 75% yield, C/O = 98:2); ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.48 – 7.30 (m, 2H), 7.18 (t, *J* = 7.5 Hz, 1H), 7.12 – 6.80 (m, 6H), 6.59 (t, *J* = 55.1 Hz, 1H), 3.50 (d, *J* = 18.4 Hz, 1H), 3.34 (d, *J* = 18.4 Hz, 1H), 3.24 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 198.61, 167.29 (d, *J* = 9.8 Hz), 152.27, 139.86, 134.83, 128.92, 128.67, 128.66, 127.37, 125.73, 124.48, 116.55 (dd, *J* = 251.8, 238.9 Hz), 63.86 (dd, *J* = 23.1, 18.6 Hz), 40.03, 31.69. ^{19}F NMR (376 MHz, Chloroform-*d*) δ -124.35 (d, *J* = 55.0 Hz, 1F), -125.10 (d, *J* = 55.0 Hz, 1F). HRMS Calcd. for $[C_{18}H_{15}F_2NO_2+Na]^+$ requires m/z 338.0969, found m/z 338.0975.



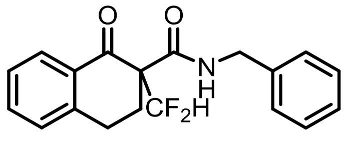
2r

(White wax, 27.4 mg, 87% yield, C/O = 96:4); [1]H NMR (400 MHz, Chloroform-*d*) δ 8.55 (s, 1H), 8.09 (dd, *J* = 8.0, 1.3 Hz, 1H), 7.64 – 7.46 (m, 3H), 7.39 – 7.26 (m, 4H), 7.18 – 7.08 (m, 1H), 6.51 (t, *J* = 55.3 Hz, 1H), 3.31 – 3.18 (m, 1H), 3.19 – 2.97 (m, 2H), 2.56 – 2.38 (m, 1H). [13]C NMR (101 MHz, $CDCl_3$) δ 195.68, 160.25 (d, *J* = 6.8 Hz),144.92, 135.46, 131.11 (d, *J* = 2.1 Hz), 129.04, 128.94, 128.32, 127.10, 125.06, 120.03, 116.16 (dd, *J* = 251.7, 248.7 Hz), 63.51 – 60.57 (m), 29.71, 25.27, 22.42. [19]F NMR (376 MHz, Chloroform-*d*) δ -121.62 (dd, *J* = 280.3, 55.1 Hz, 1F), -129.67 (dd, *J* = 280.3, 55.1 Hz, 1F). HRMS Calcd. for $[C_{18}H_{15}F_2NO_2+Na]^+$ requires m/z 338.0969, found m/z 338.0971.



2s

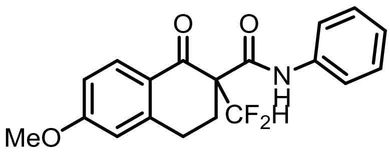
(White wax, 27.4 mg, 89% yield, C/O = 96:4); [1]H NMR (400 MHz, Chloroform-*d*) δ 8.04 (dd, *J* = 7.9, 1.3 Hz, 1H), 7.54 (td, *J* = 7.5, 1.4 Hz, 1H), 7.42 – 7.22 (m, 2H), 6.61 (t, *J* = 5.8 Hz, 1H), 6.40 (t, *J* = 55.5 Hz, 1H), 3.45 – 3.02 (m, 3H), 2.90 (ddt, *J* = 41.1, 13.5, 4.0 Hz, 2H), 2.50 – 2.04 (m, 1H), 1.55 – 1.39 (m, 2H), 1.28 (dt, *J* = 14.9, 7.3 Hz, 2H), 0.88 (t, *J* = 7.3 Hz, 3H). [13]C NMR (101 MHz, $CDCl_3$) δ 195.36 (d, *J* = 6.3 Hz), 162.39 (d, *J* = 6.7 Hz), 144.79, 135.08, 131.07 (d, *J* = 2.2 Hz), 128.93, 128.10, 126.94, 116.35 (dd, *J* = 250.8, 247.8 Hz), 61.66 (dd, *J* = 21.3, 19.4 Hz)， 40.01, 31.25, 25.33, 22.62, 19.90, 13.65. [19]F NMR (376 MHz, Chloroform-*d*) δ -122.04 (dd, *J* = 279.9, 55.2 Hz, 1F), -130.86 (dd, *J* = 279.7, 55.6 Hz, 1F). HRMS Calcd. for $[C_{16}H_{19}F_2NO_2+Na]^+$ requires m/z 318.1282, found m/z 318.1287.



2t

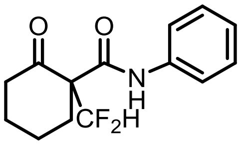
(White wax, 26.0 mg, 79% yield, C/O = 95:5); [1]H NMR (400 MHz, Chloroform-*d*) δ 7.95 (dd, *J* = 7.9, 1.4 Hz, 1H), 7.47 (td, *J* = 7.5, 1.5 Hz, 1H), 7.35 – 7.12 (m, 5H), 6.87 (t, *J* = 5.9 Hz, 1H), 6.34 (t, *J* = 55.4 Hz, 1H), 4.50 (dd, *J* = 14.9, 6.2 Hz, 1H), 4.21 (dd, *J* = 14.9, 5.1 Hz, 1H), 3.15 (ddd, *J* = 16.9, 12.5, 4.4 Hz, 1H), 2.85 (ddt, *J* = 37.9, 13.6, 4.1 Hz, 2H), 2.32 (ddd, *J*

= 13.6, 12.4, 4.6 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ195.07 (d, *J* = 6.4 Hz), 162.69 (d, *J* = 6.7 Hz), 144.75, 137.36, 135.18, 131.10 (d, *J* = 2.2 Hz), 128.97, 128.81, 128.20, 127.67, 127.44, 127.02, 116.29 (dd, *J* = 250.9, 247.8 Hz), 64.81 – 59.46 (m), 44.17, 25.34, 22.67. ^{19}F NMR (376 MHz, Chloroform-*d*) δ -122.16 (dd, *J* = 280.2, 55.1 Hz, 1F), -130.46 (dd, *J* = 280.2, 55.1 Hz, 1F). HRMS Calcd. for $[C_{19}H_{17}F_2NO_2+Na]^+$ requires m/z 352.1125, found m/z 352.1130.



2u

(Light yellow oil, 28.6 mg, 83% yield, C/O = 95:5); ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.67 (s, 1H), 8.06 (d, *J* = 8.9 Hz, 1H), 7.57 – 7.48 (m, 2H), 7.32 (dd, *J* = 8.5, 7.3 Hz, 2H), 7.12 (t, *J* = 7.4 Hz, 1H), 6.86 (dd, *J* = 8.8, 2.5 Hz, 1H), 6.70 (d, *J* = 2.5 Hz, 1H), 6.51 (t, *J* = 55.4 Hz, 1H), 3.88 (s, 3H), 3.29 – 3.09 (m, 1H), 3.03 – 2.79 (m, 2H), 2.55 – 2.28 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 193.87 (d, *J* = 6.3 Hz), 165.32, 160.52 (d, *J* = 7.0 Hz), 147.84, 137.06, 131.05, 129.01, 124.94, 119.99, 118.81 – 113.11 (m), 114.16, 112.35, 63.05 – 60.27 (m), 55.67, 25.74, 22.18. ^{19}F NMR (376 MHz, Chloroform-*d*) δ -121.78 (dd, *J* = 279.3, 55.2 Hz, 1F), -130.16 (dd, *J* = 279.3, 55.2 Hz, 1F). HRMS Calcd. for $[C_{19}H_{17}F_2NO_3+Na]^+$ requires m/z 368.1074, found m/z 368.1078.

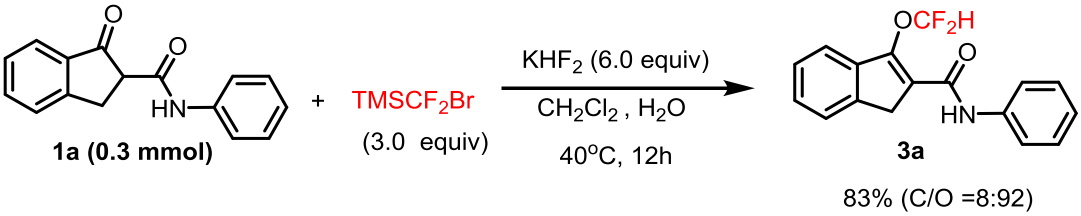


2v

(Colourless oil, 28.6 mg, 84% yield, C/O = 92:8);^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.82 (s, 1H), 7.49 – 7.37 (m, 2H), 7.34 – 7.22 (m, 2H), 7.16 – 7.01 (m, 1H), 6.19 (t, *J* = 55.1 Hz, 1H), 2.73 – 2.32 (m, 3H), 2.03 – 1.59 (m, 5H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 206.45 (dd, *J* = 3.8, 2.1 Hz), 161.24 (dd, *J* = 4.3, 1.9 Hz), 135.79, 128.08, 124.25, 119.32, 114.59 (dd, *J* =

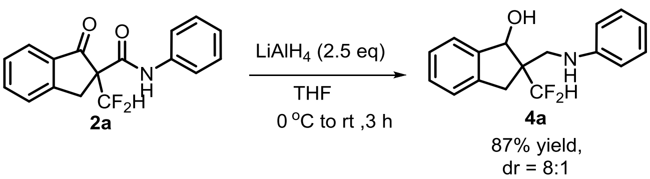
249.3, 247.0 Hz), 63.69 (t, J = 19.5 Hz), 40.20, 40.19, 26.66, 26.64, 24.22, 19.92. ^{19}F NMR (376 MHz, Chloroform-d) δ -124.13 (dd, J = 282.6, 55.2 Hz, 1F), -127.01 (dd, J = 282.6, 55.2 Hz, 1F). HRMS Calcd. for $[C_{14}H_{15}F_2NO_2+Na]^+$ requires m/z 290.0969, found m/z 290.0963.

3. General proceduce for the o-difluoromethylation of β-keto amide 1a



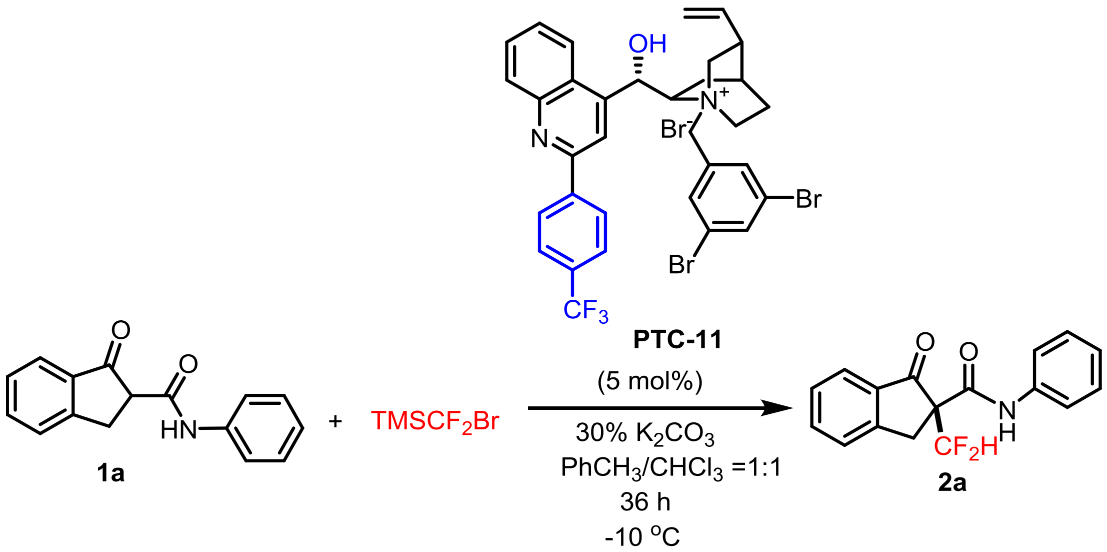
The reaction was conducted with β-keto amide **1a** (0.3 mmol) in the presence of KHF_2 (1.8 mmol) in a mixture containing CH_2Cl_2/H_2O =1:1 (0.6 mL) in pressure tubing at rt. Then $TMSCF_2Br$ (0.9 mmol) was added slowly, and the reaction was stirred at 40°C for 12 h. After the reaction was completed (confirmed by TLC analysis), the mixture was diluted with EtOAc (30 mL), washed with water (3 ×10 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The residue was subject to crude ^{19}F-NMR to give the C/O isomer ratio (trifluoromethyl benzene 8 μL as internal standard). Subsequently, the residue was purified by flash chromatography (silica gel; petroleum ether/ethyl acetate=5:1) to afford the O-difluoromethylation product **3a** (colourless oil, 74.5 mg, 83% yield, C/O = 8:92). ^{1}H NMR (400 MHz, Chloroform-d) δ 8.54 (s, 1H), 7.71 – 7.47 (m, 4H), 7.46 – 7.28 (m, 4H), 7.17 – 7.08 (m, 1H), 6.85 (t, J = 72.6 Hz, 1H), 3.78 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.69, 150.25 (m), 141.58, 137.81, 136.93, 129.11, 128.70, 127.39, 125.05, 124.45, 120.05, 119.91, 116.22 (t, J = 262.6 Hz), 35.67. ^{19}F NMR (376 MHz, Chloroform-d) δ -78.91 (d, J = 72.5 Hz). ^{19}F NMR (376 MHz, Chloroform-d) δ -78.82(s, 1F) , -79.01 (s, 1F). HRMS Calcd. for $[C_{17}H_{13}F_2NO_2+Na]^+$ requires m/z 324.0812, found m/z 324.0817.

5. Synthetic utilization of C-difluoromethylation product 2a.



The difluoromethylated compound **2a** (60.2 mg, 0.2 mmol) in anhydrous THF (1 mL) was added slowly to the mixture of lithium aluminum hydride (17.3 mg, 0.45 mmol) in anhydrous THF (1 mL) at 0 ^{o}C. After stirring for another 1 hour at the same temperature, the reaction was allowed to warm to room temperature and stirred for another 2 h. After that, the reaction was quenched by the dropwise addition of EtOAc followed by a 10% HCl. After vigorous stirring for another 20 min, the resulting mixture was extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated in vacuum. The residue was subject to crude ^{19}F-NMR to give the diastereo ratio (8:1) (trifluoromethyl benzene 8 μL as internal standard). Subsequently, the residue was purified by silica gel column chromatography (PE/EtOAc = 5:1) to give product **4a** (white was, 50.3 mg, 87% yield). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.85 (s, 1H), 7.59 – 7.45 (m, 2H), 7.42 – 7.21 (m, 7H), 7.19 – 7.07 (m, 1H), 6.17 (t, *J* = 55.3 Hz, 1H), 5.77 (s, 1H), 3.42 (s, 2H), 2.90 (t, *J* = 15.0 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ168.01 (d, *J* = 3.9 Hz), 141.17, 137.84, 137.12, 129.07, 127.66, 125.02, 124.50, 123.72, 120.44116.81 (t, *J* = 246.3 Hz), 116.81 (t, *J* = 246.3 Hz), 79.22 (d, *J* = 3.3 Hz), 62.78 (t, *J* = 17.9 Hz), 33.96 (t, *J* = 4.4 Hz). ^{19}F NMR (376 MHz, Chloroform-*d*) δ -122.57 (dd, *J* = 283.4, 55.4 Hz, 1F), -124.05 (dd, *J* = 283.4, 55.4 Hz, 1F). HRMS Calcd. for $[C_{17}H_{17}F_2NO_2+Na]^+$ requires m/z 312.1176, found m/z 312.1183.

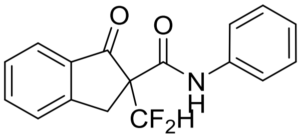
6. General proceduce for the asymmetric difluoromethylation of β-keto amide 1a



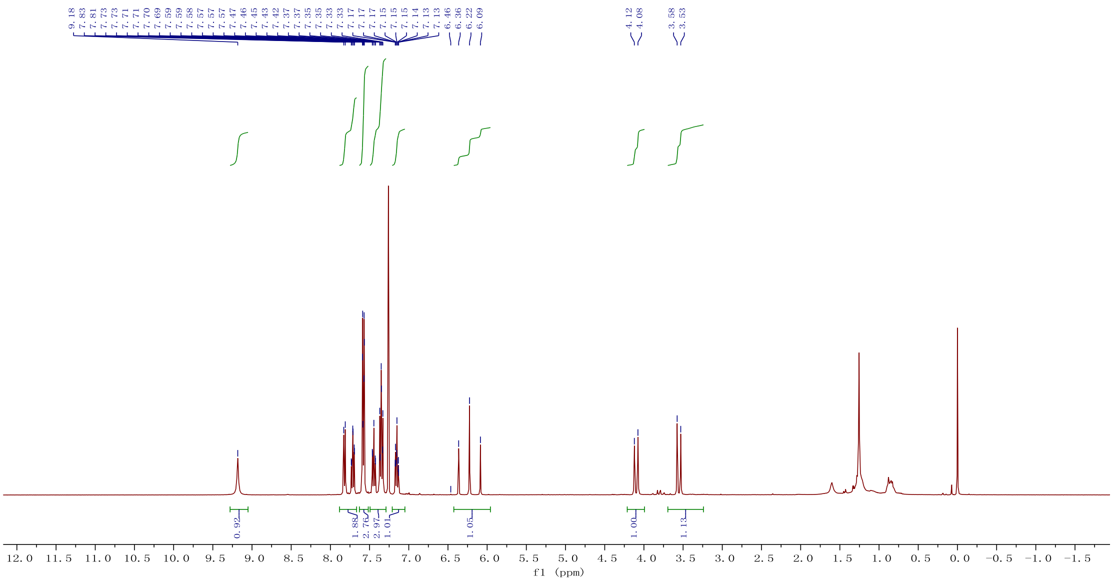
The reaction was performed with β-keto amide **1a** (0.1 mmol), 30% K_2CO_3 (0.5 mL) in $PhCH_3/CHCl_3$ =1 :1 (2 mL). The reaction mixture was was stirred at -10℃ for 5 min.

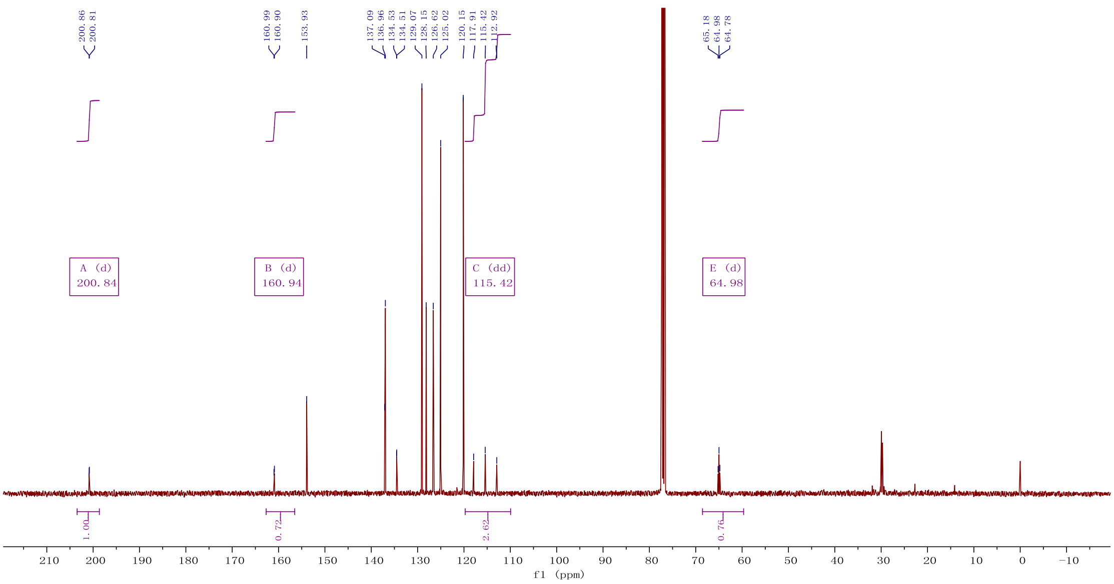
Then $TMSCF_2Br$ (0.2 mmol) was added slowly, and the reaction was stirred at this temperature for 36 h. After the reaction was completed, the mixture was diluted with EtOAc (20 mL), washed with water (3 × 10 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The residue w was purified by flash chromatography (silica gel; petroleum ether/ethyl acetate=25:1–2:1) to afford the α-difluoromethylation products. The ee value was determined by chiral HPLC(Chiralcel AD-H) using n-Hexane/ isopropanol =95:5 as mobile phase at 25 ℃.

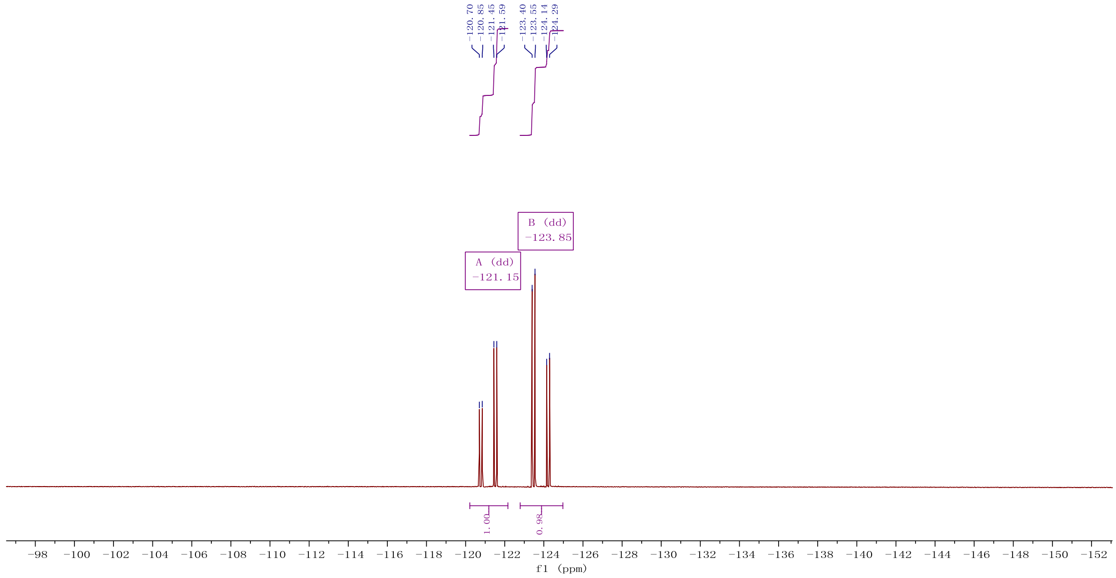
B. NMR Spectra

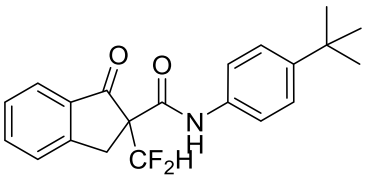


2a

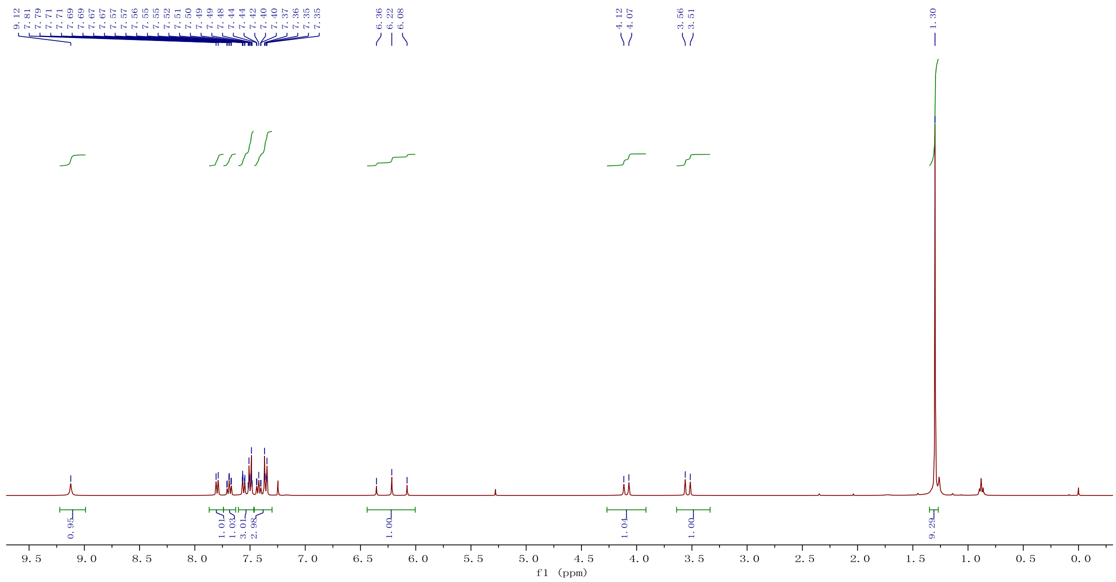


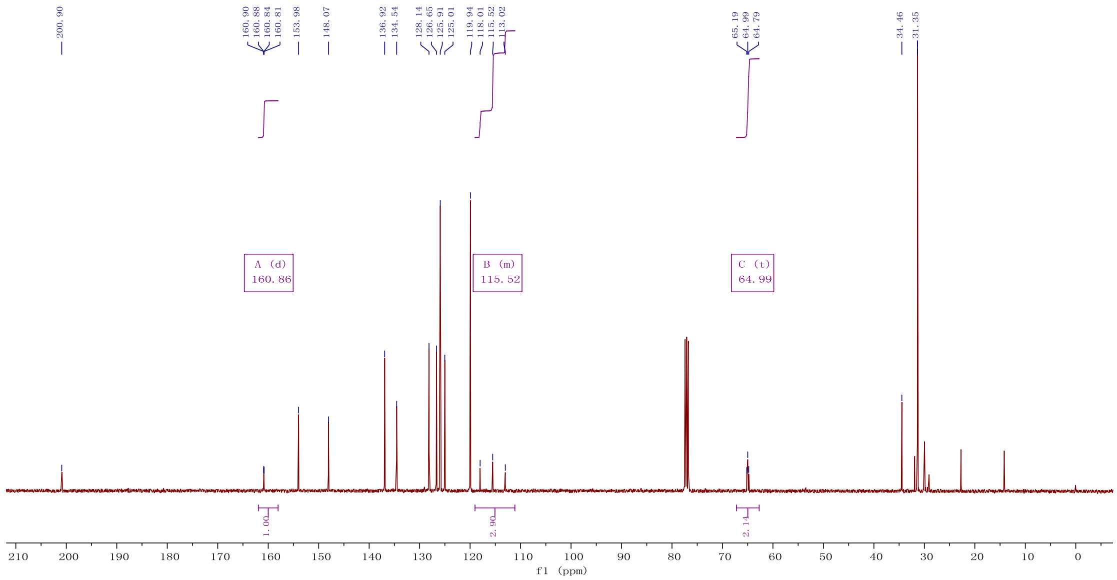






2b

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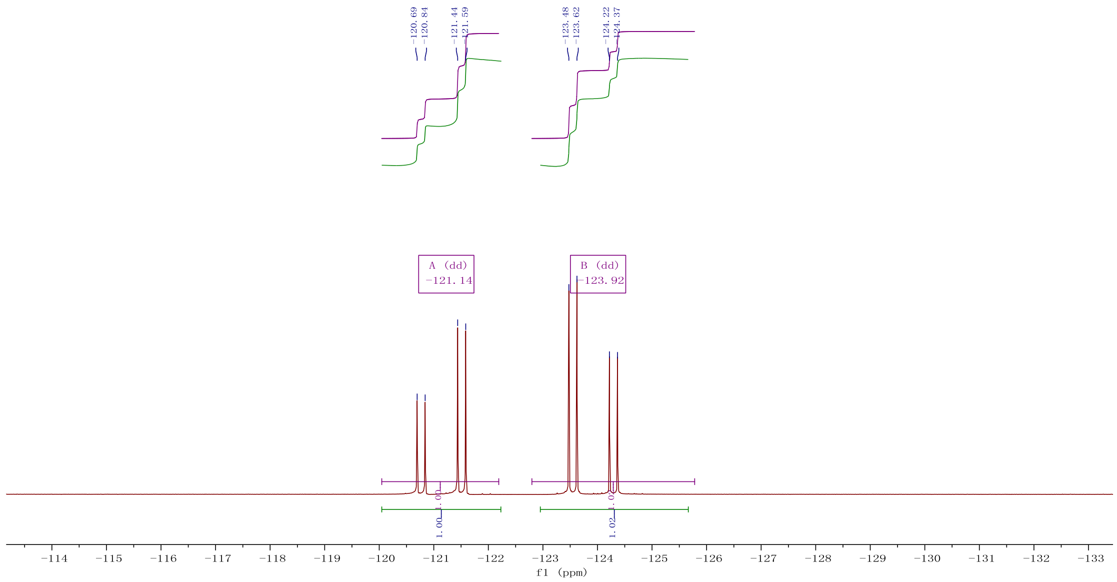
160.90
160.88
160.84
160.81
153.98
148.07
136.92
134.54
128.14
126.65
125.91
125.01
119.94
118.01
115.52
113.02
65.19
64.99
64.79
34.46
31.35
A (d)
160.86
B (m)
115.52
C (t)
64.99
1.00
2.90
2.14
f1 (ppm)


-120.69
-120.84
-121.44
-121.59
-123.48
-123.62
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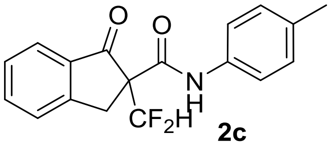
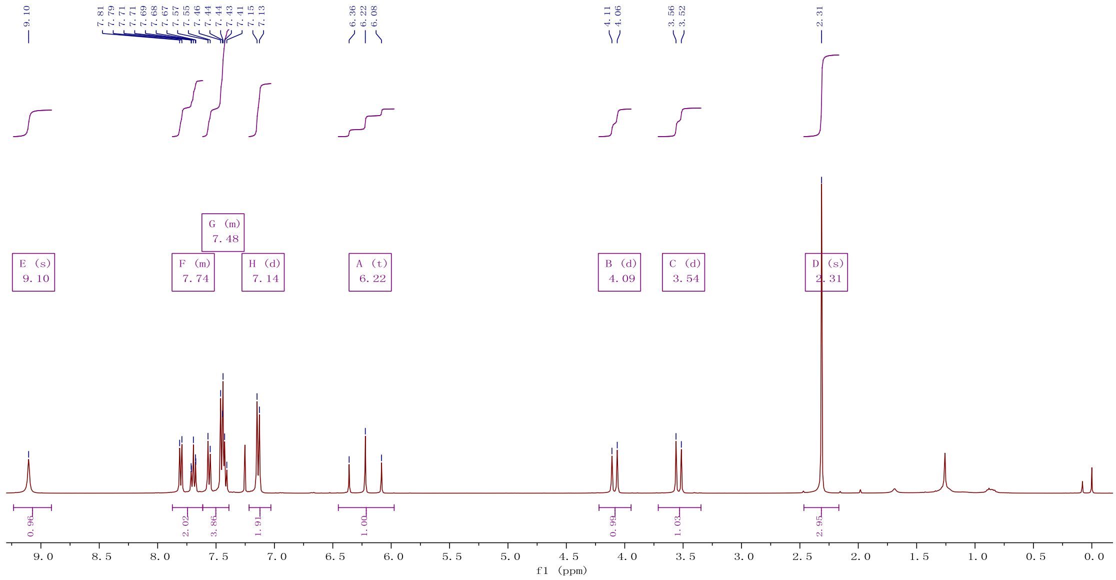
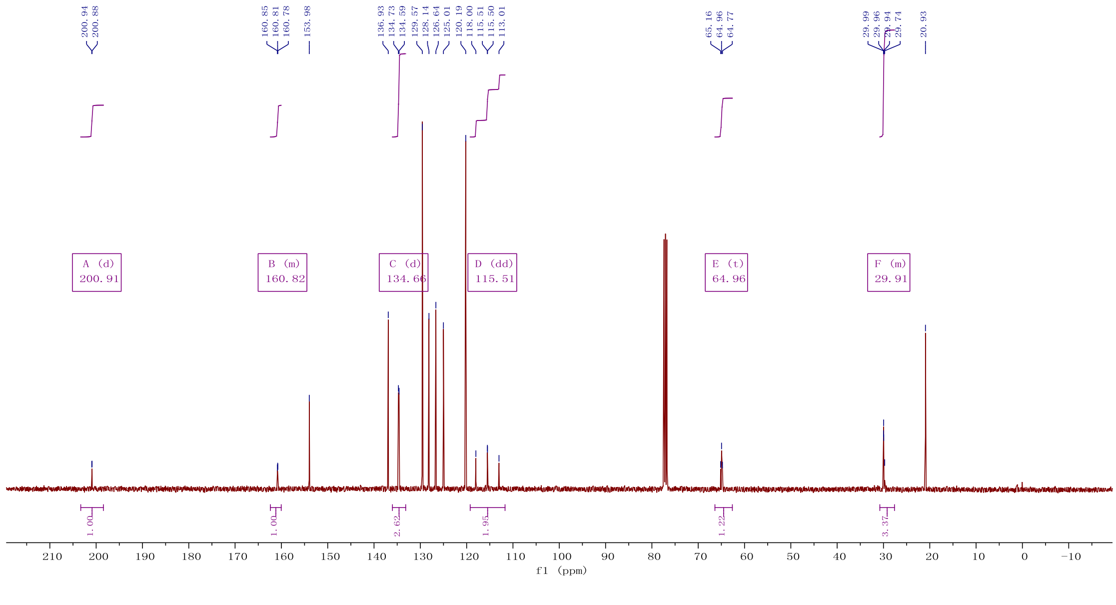
-124.37
A (dd)
-121.14
B (dd)
-123.92
1.00
1.02
f1 (ppm)



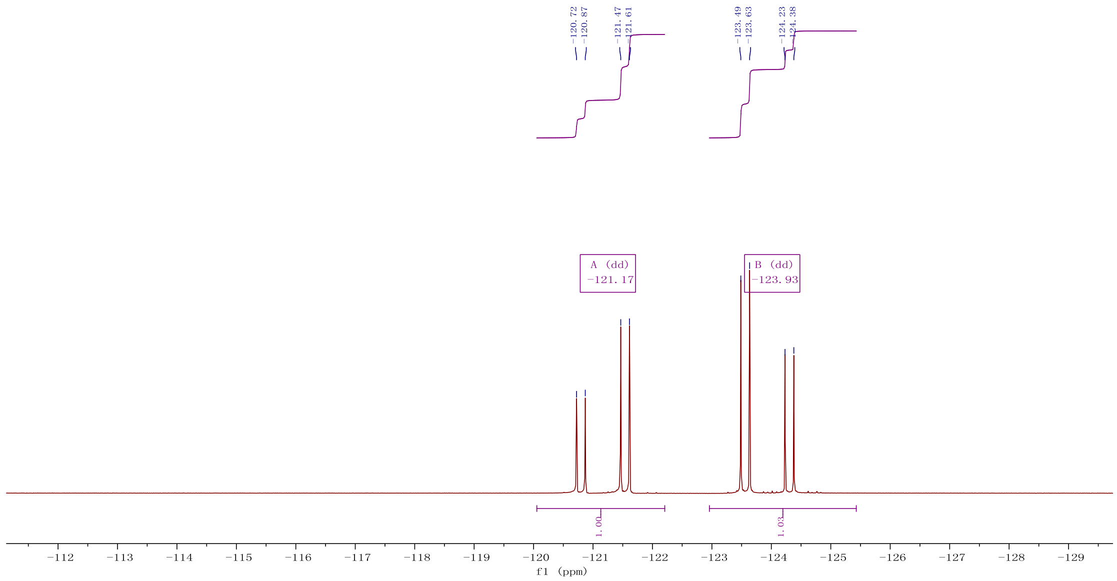
2c

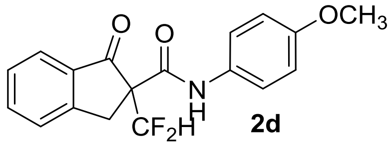


E (s) 9.10
G (m) 7.48
F (m) 7.74
H (d) 7.14
A (t) 6.22
B (d) 4.09
C (d) 3.54
D (s) 2.31
f1 (ppm)

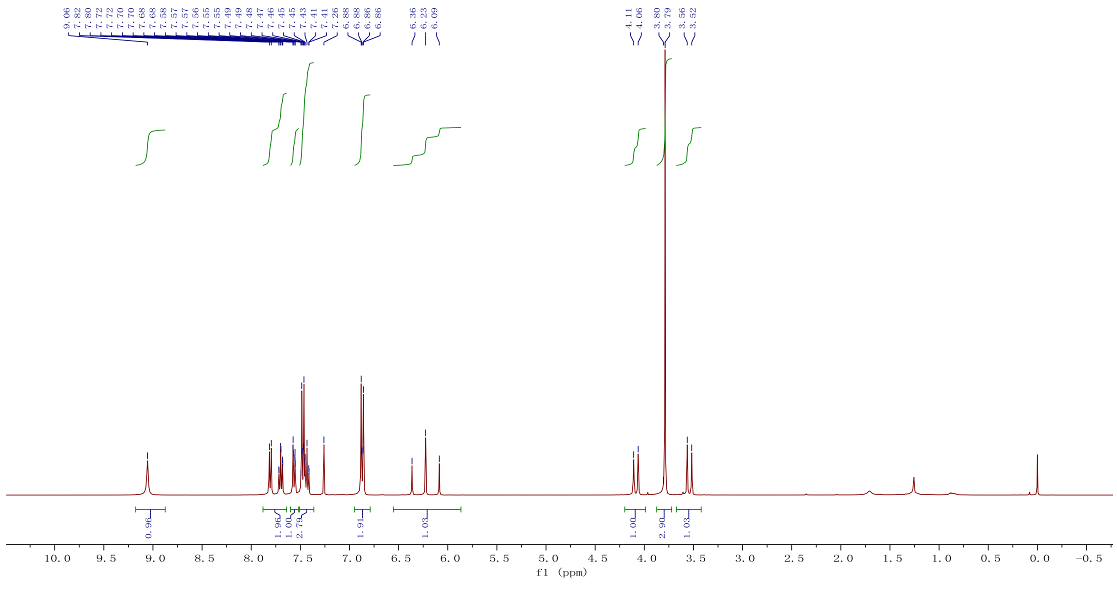


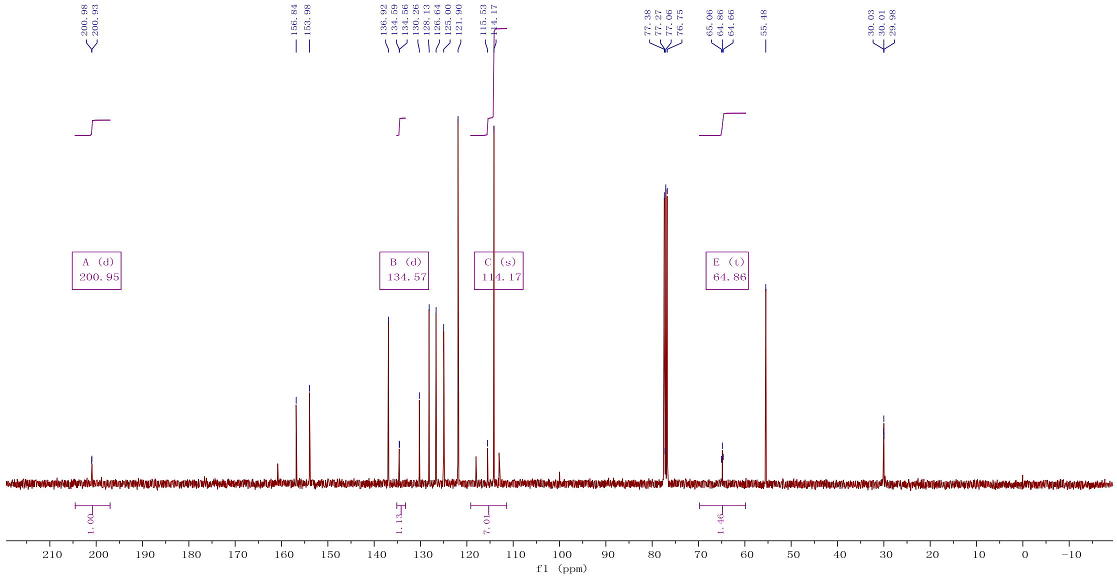
A (d) 200.91
B (m) 160.82
C (d) 134.66
D (dd) 115.51
E (t) 64.96
F (m) 29.91
f1 (ppm)





2d

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200.93
156.84
153.98
136.92
134.59
134.56
130.26
128.13
126.64
125.00
121.90
115.53
114.17
77.38
77.27
77.06
76.75
65.06
64.86
64.66
55.48
30.03
30.01
29.98
A (d)
200.95
B (d)
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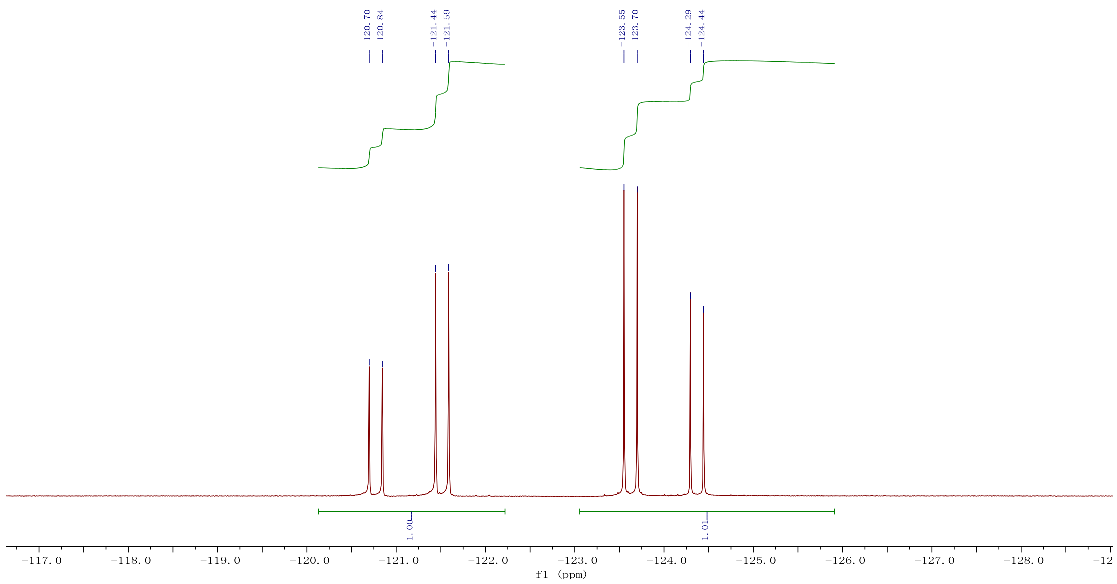
C (s)
114.17
E (t)
64.86
1.00
1.13
7.01
1.46
f1 (ppm)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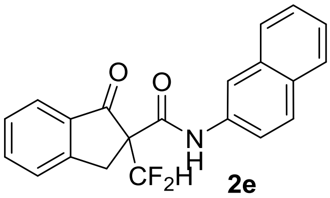
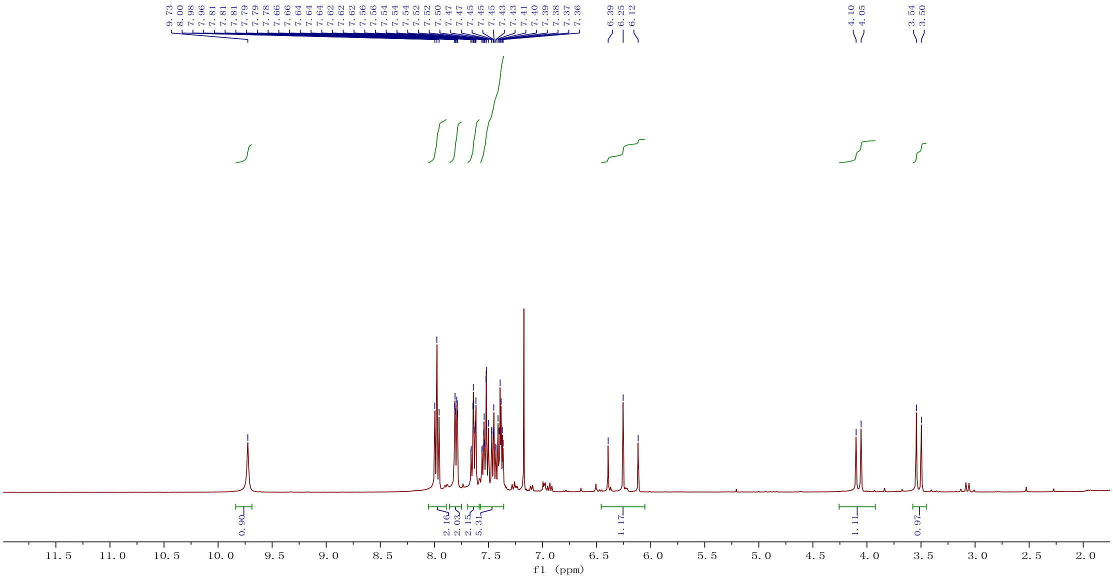
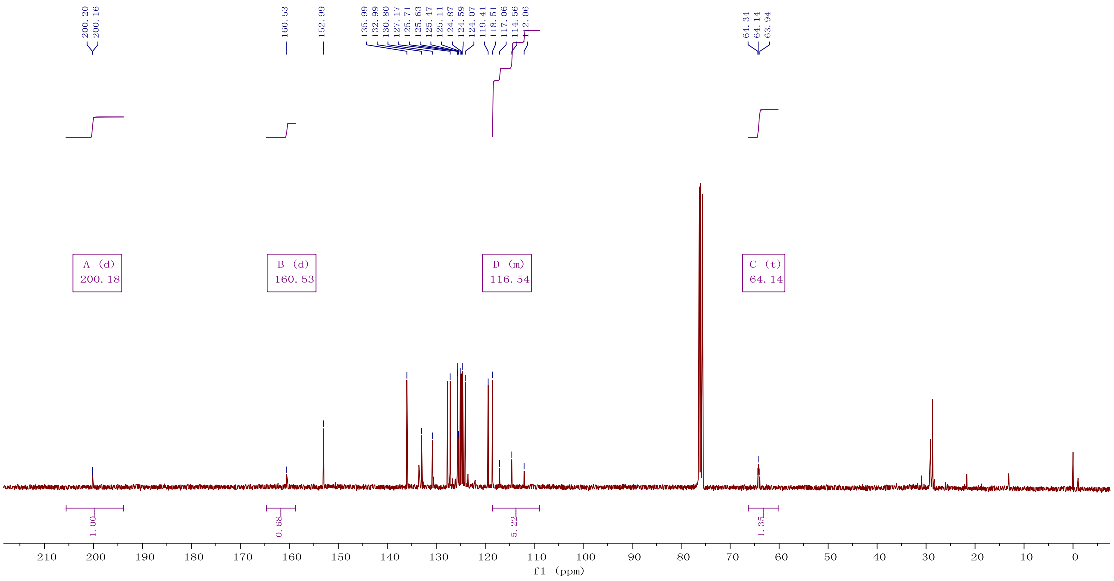
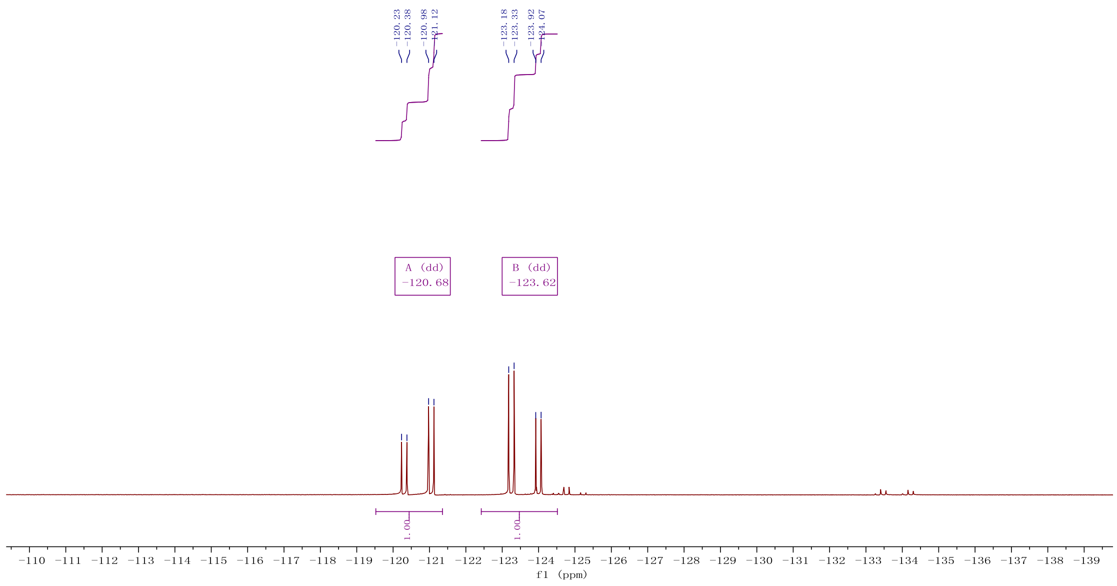
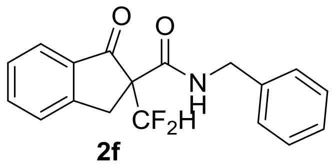
1.00
1.01
f1 (ppm)



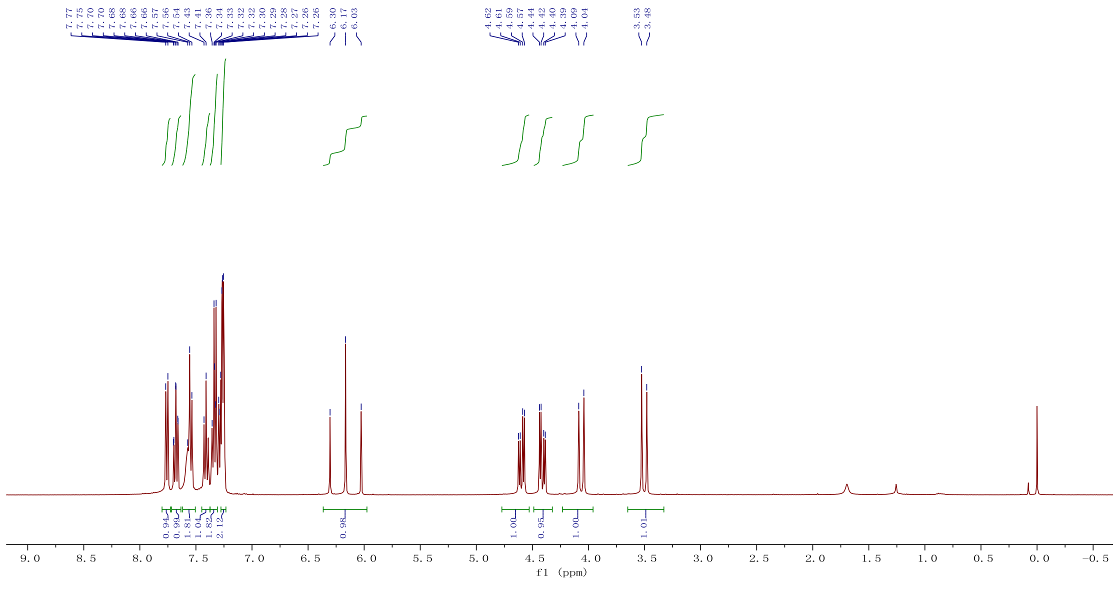


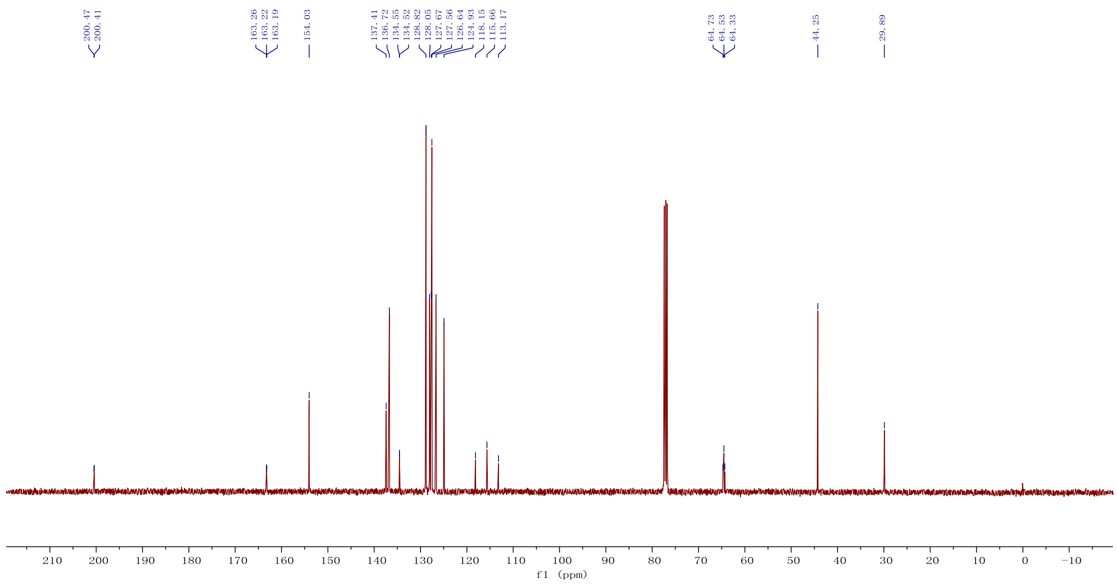






2f

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163.22
163.19
154.03
137.41
136.72
134.55
134.52
128.82
128.05
127.67
127.56
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118.15
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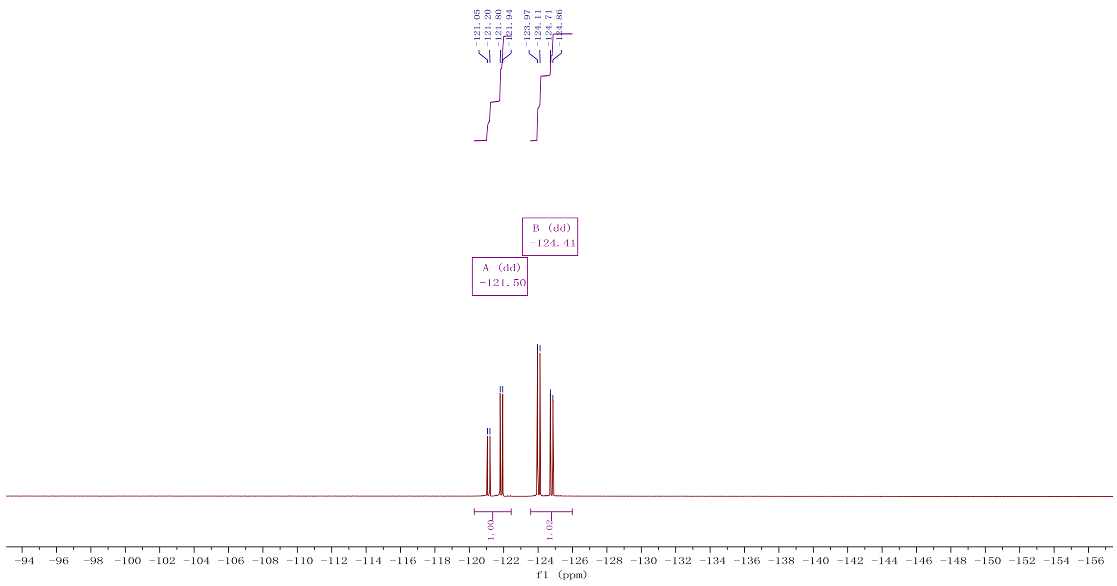
113.17
64.73
64.53
64.33
44.25
29.89
f1 (ppm)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B (dd)
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A (dd)
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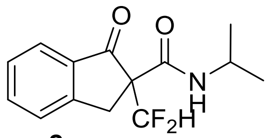
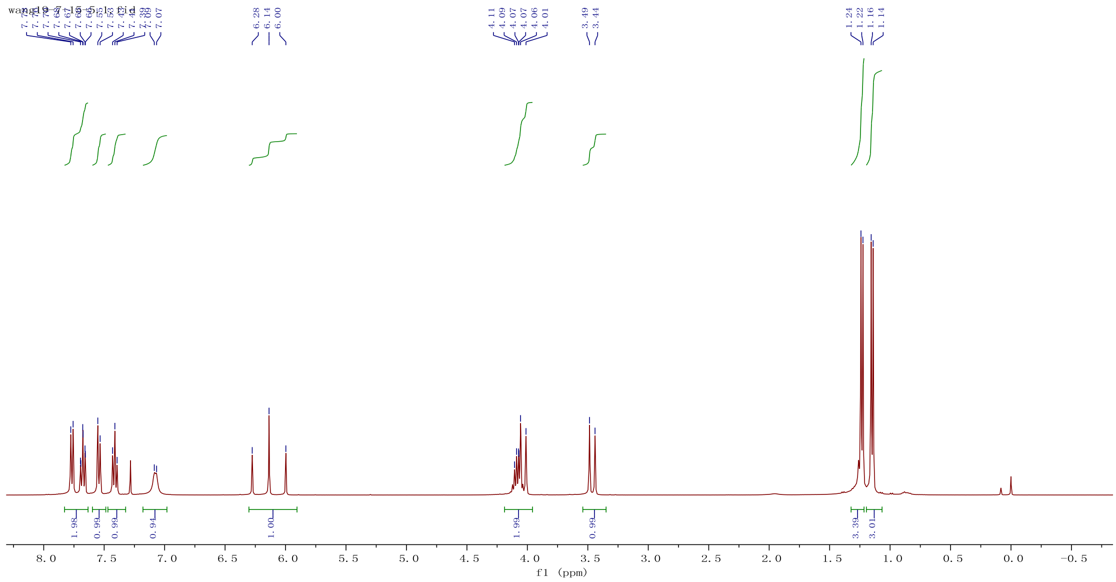
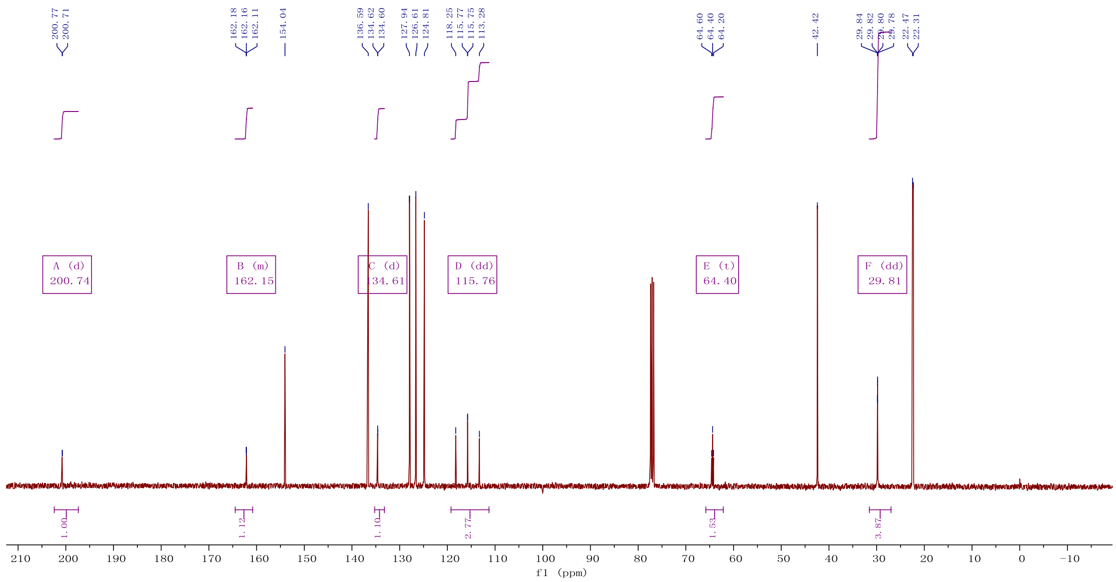
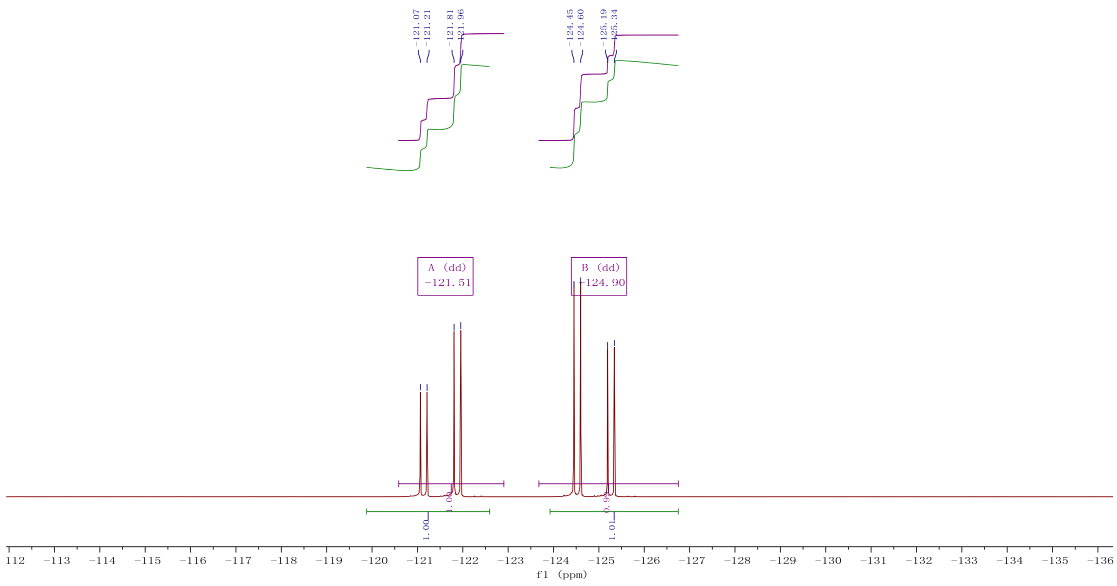
1.00
1.02
f1 (ppm)



2g







-121.07
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-124.60
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-125.34
A (dd)
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B (dd)
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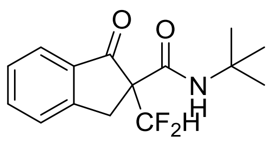
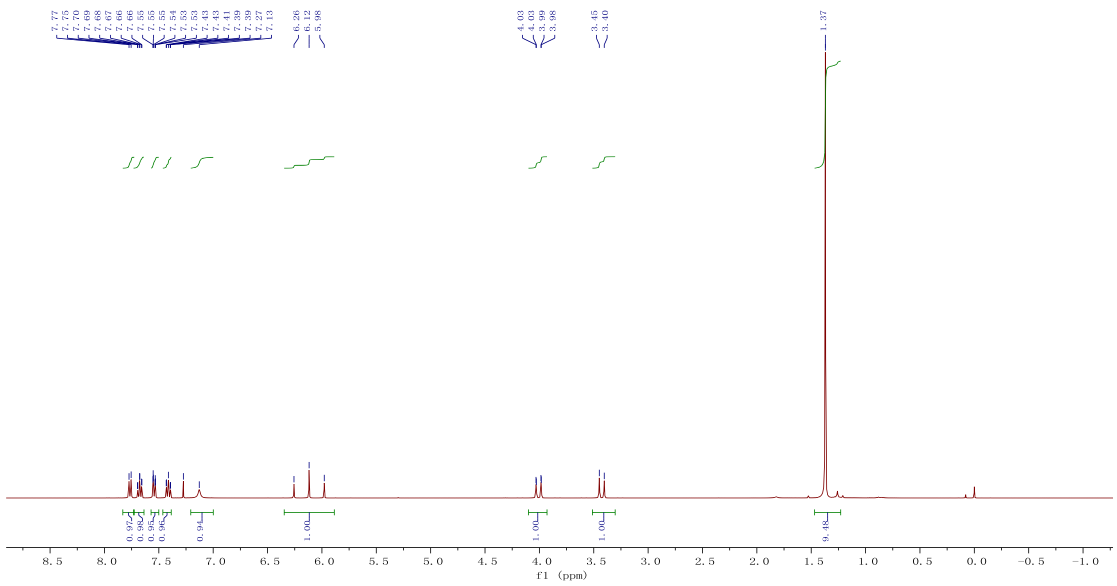
1.00
1.00
0.99
1.01
f1 (ppm)



2h



7.77
7.75
7.70
7.69
7.68
7.67
7.66
7.55
7.55
7.54
7.53
7.43
7.43
7.41
7.39
7.27
7.13
6.26
6.12
5.98
4.03
4.03
3.99
3.98
3.45
3.40
1.37
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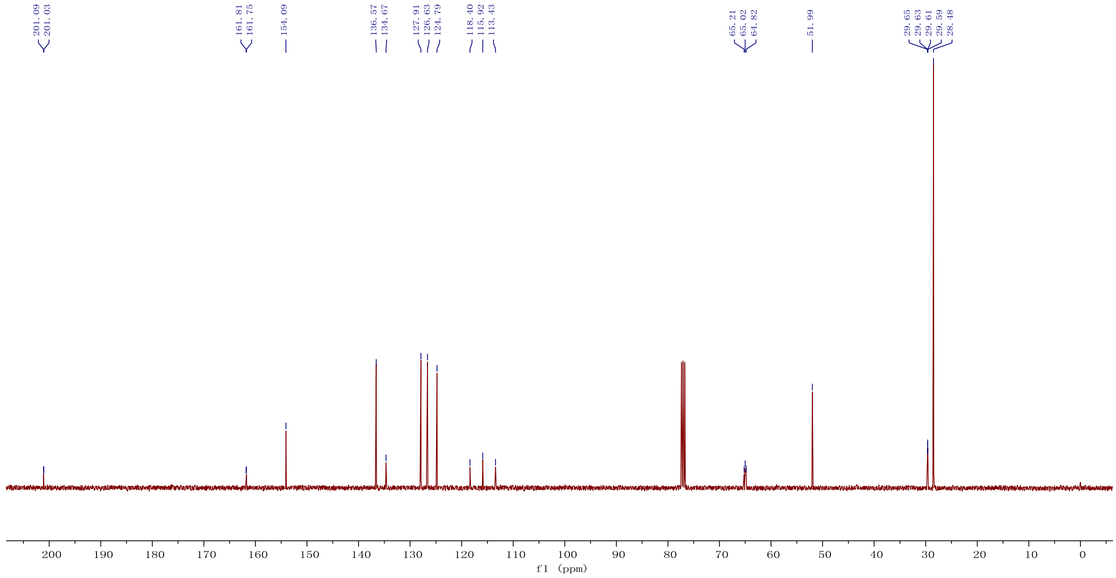
0.98
0.95
0.96
0.94
1.00
1.00
1.00
9.48
f1 (ppm)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127.91
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124.79
118.40
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65.02
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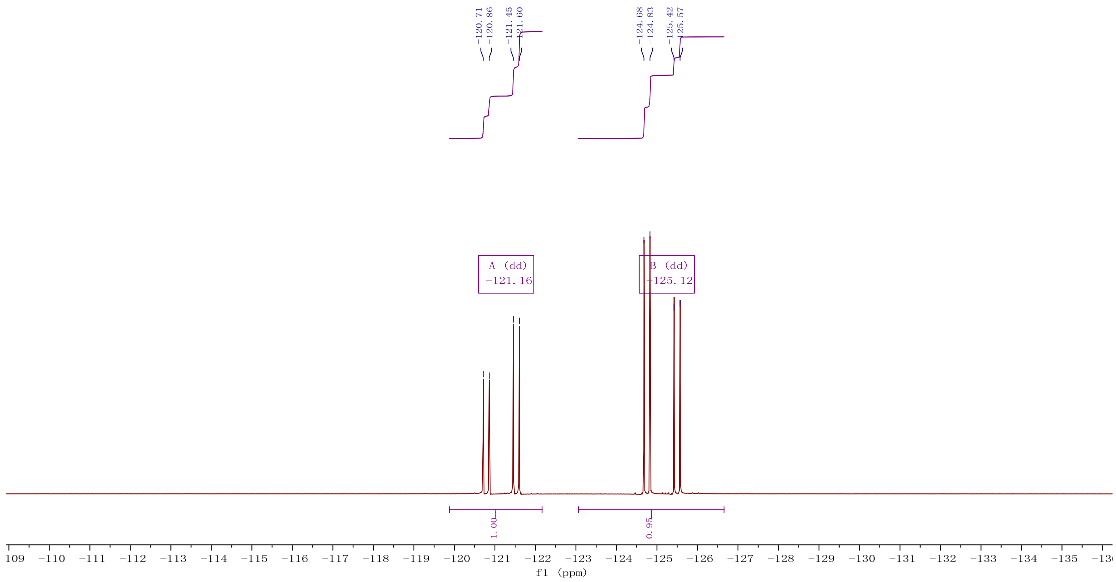
29.65
29.63
29.61
29.59
28.48
f1 (ppm)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-121.60
-124.68
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-125.57
A (dd)
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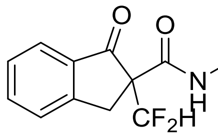
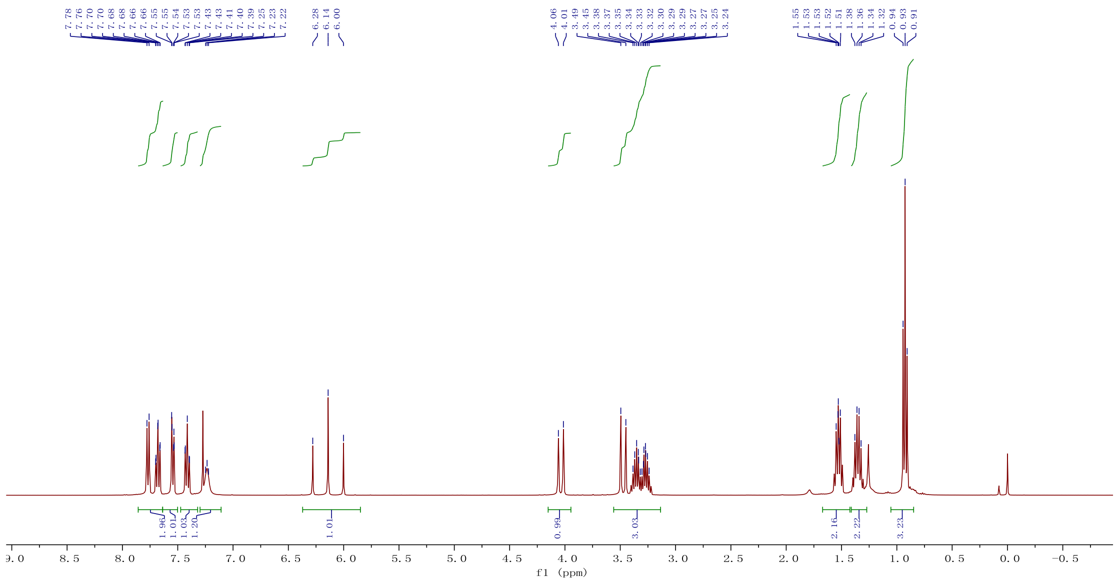
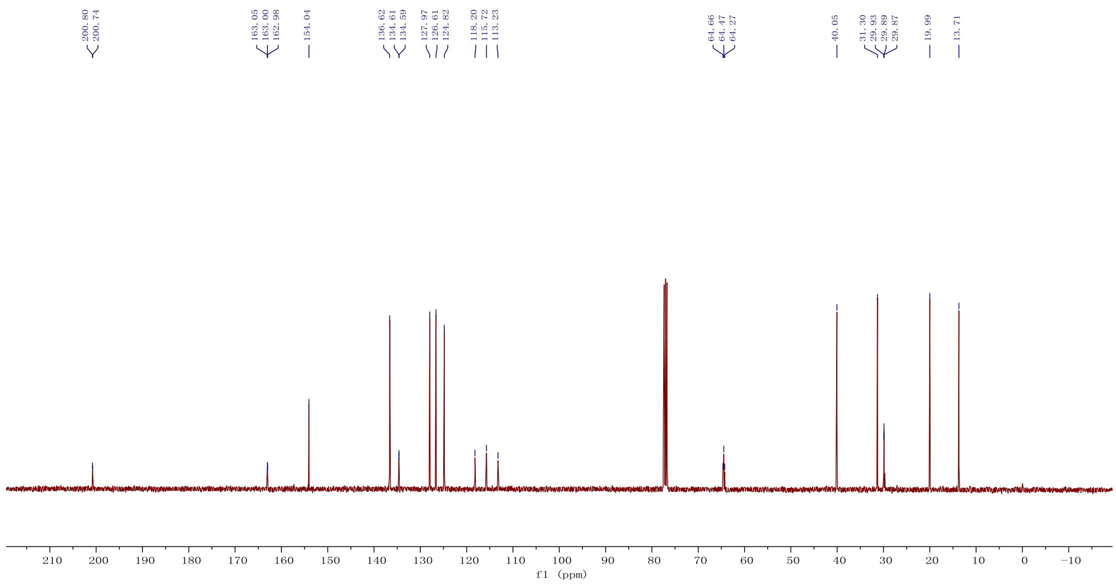
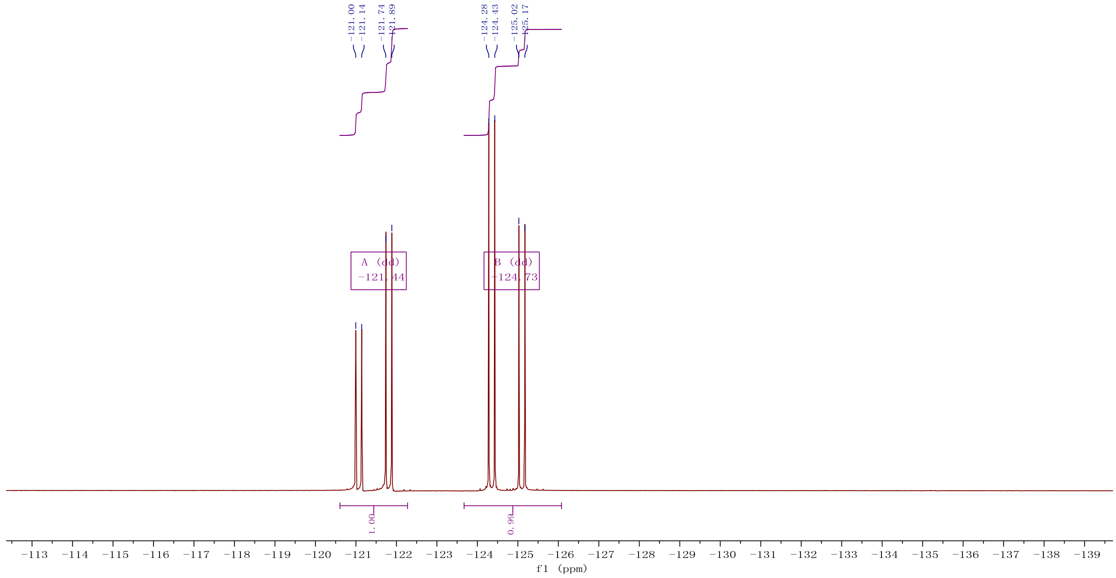
B (dd)
-125.12
1.00
0.95
f1 (ppm)

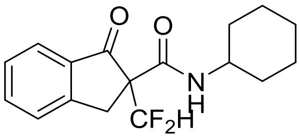


2i

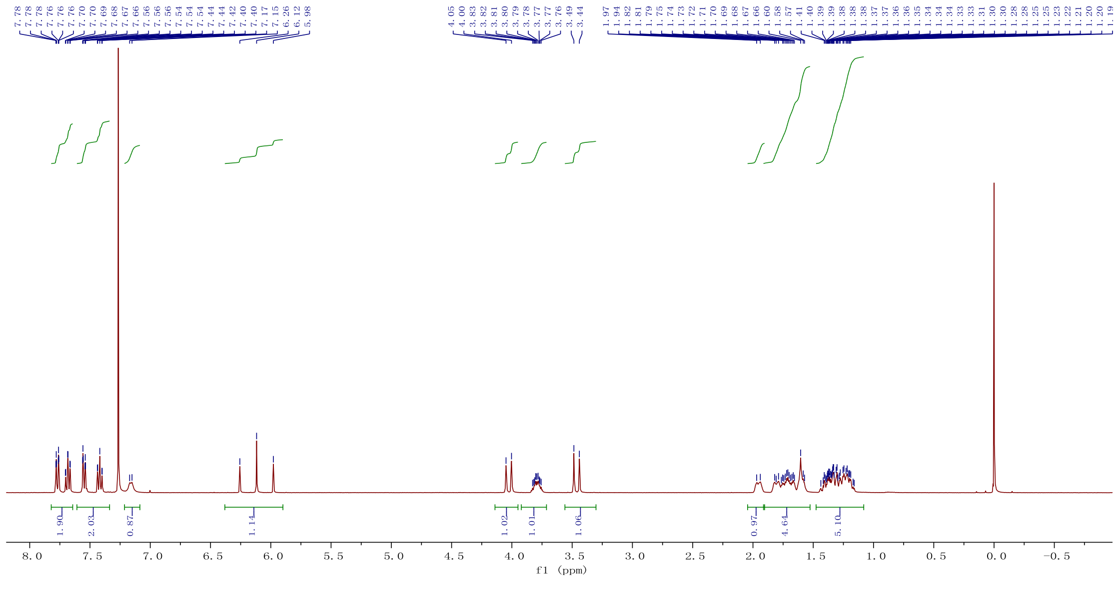


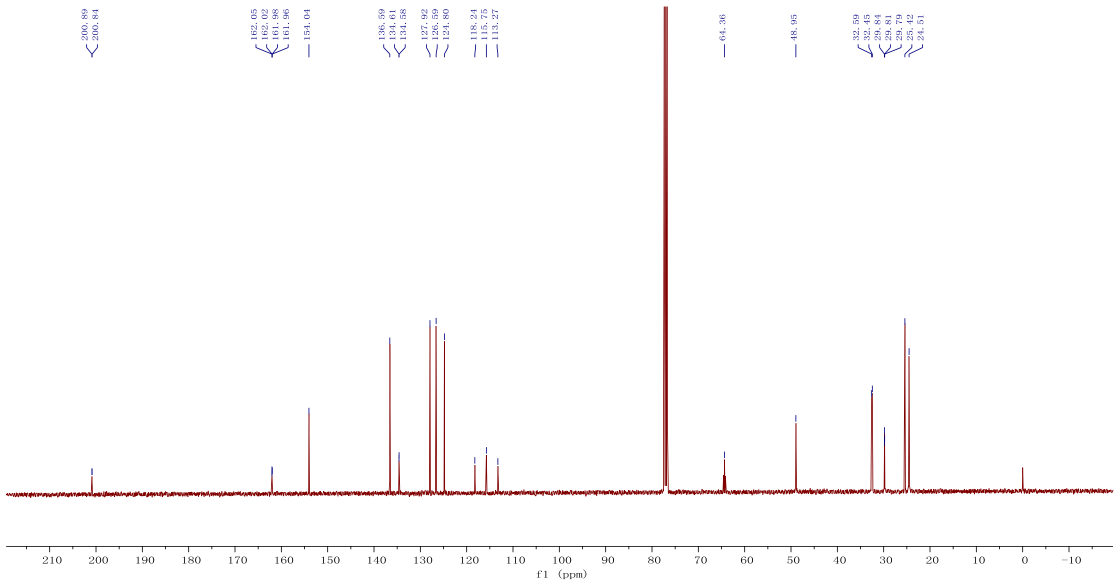






2j

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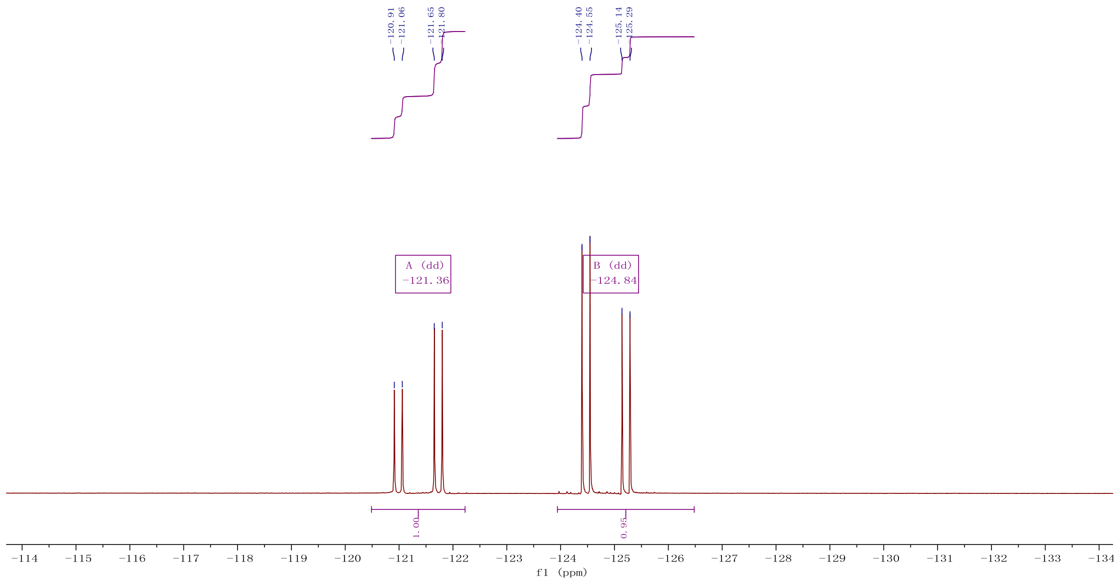
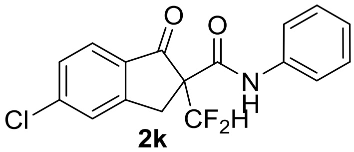
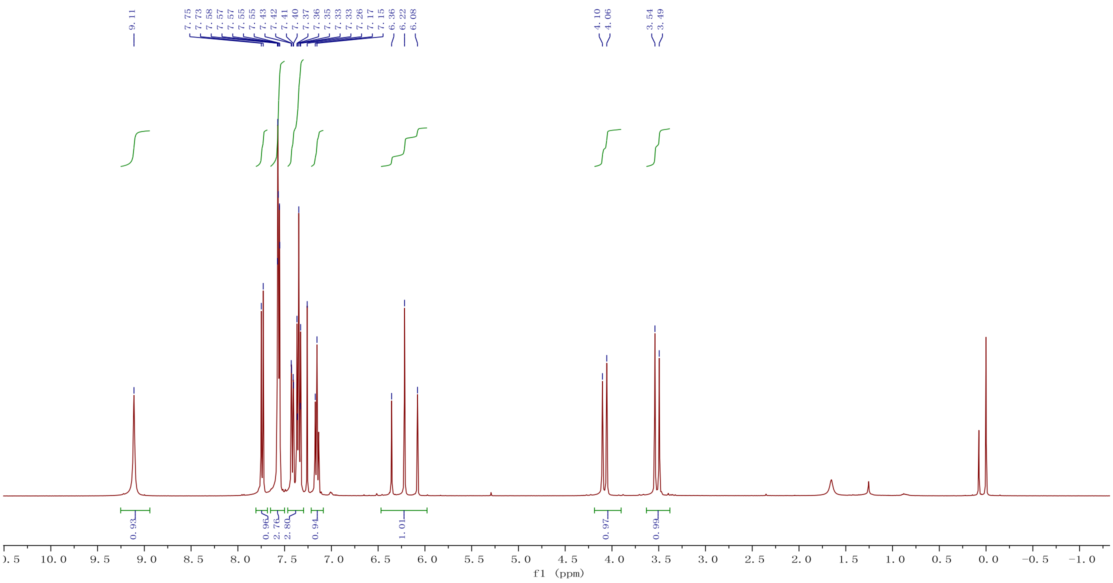
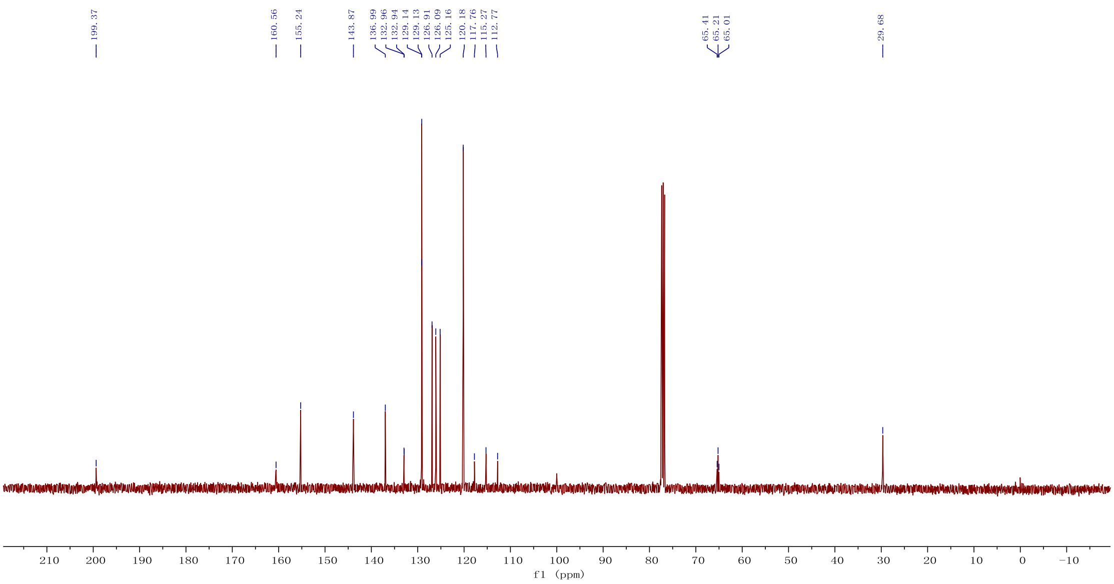
162.02
161.98
161.96
154.04
136.59
134.61
134.58
127.92
126.59
124.80
118.24
115.75
113.27
64.36
48.95
32.59
32.45
29.84
29.81
29.79
25.42
24.51
f1 (ppm)

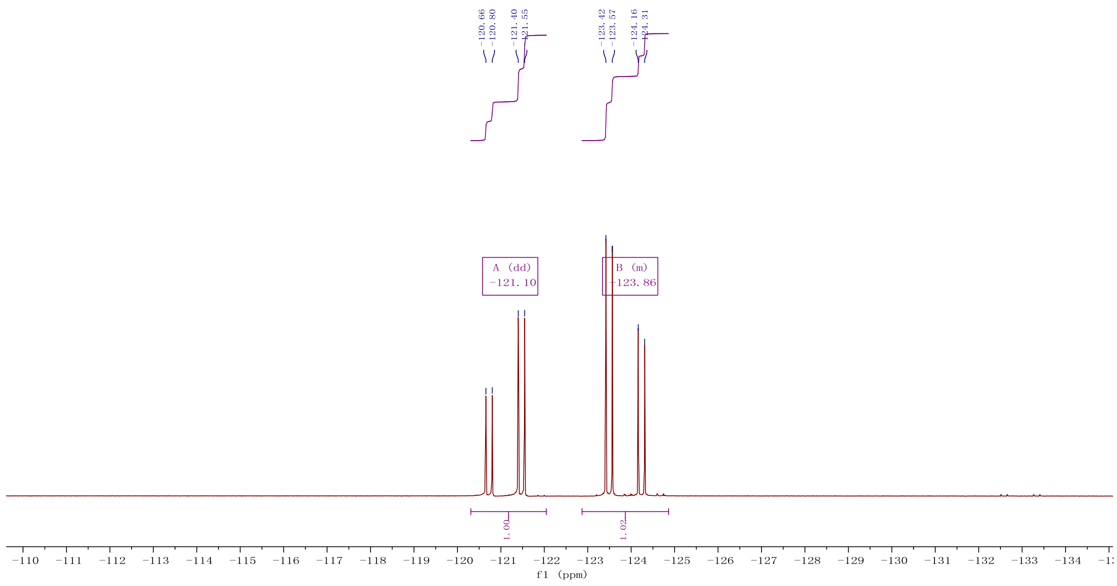

-120.91
-121.06
-121.65
-121.80
-124.40
-124.55
-125.14
-125.29
A (dd)
-121.36
B (dd)
-124.84
1.00
0.95
f1 (ppm)

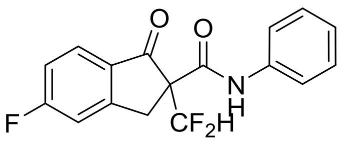


2k

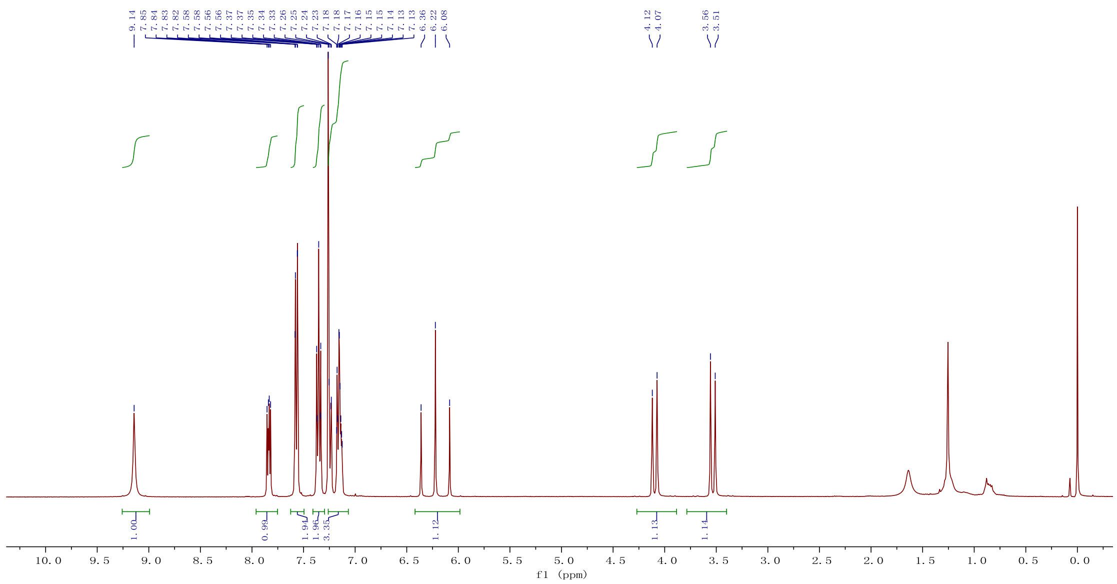


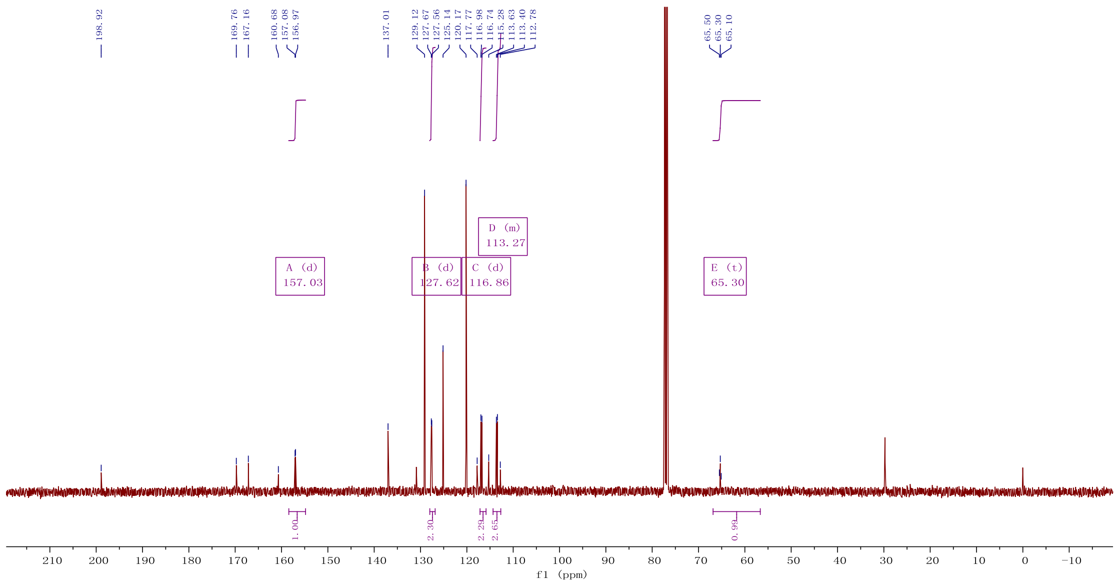






2l

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167.16
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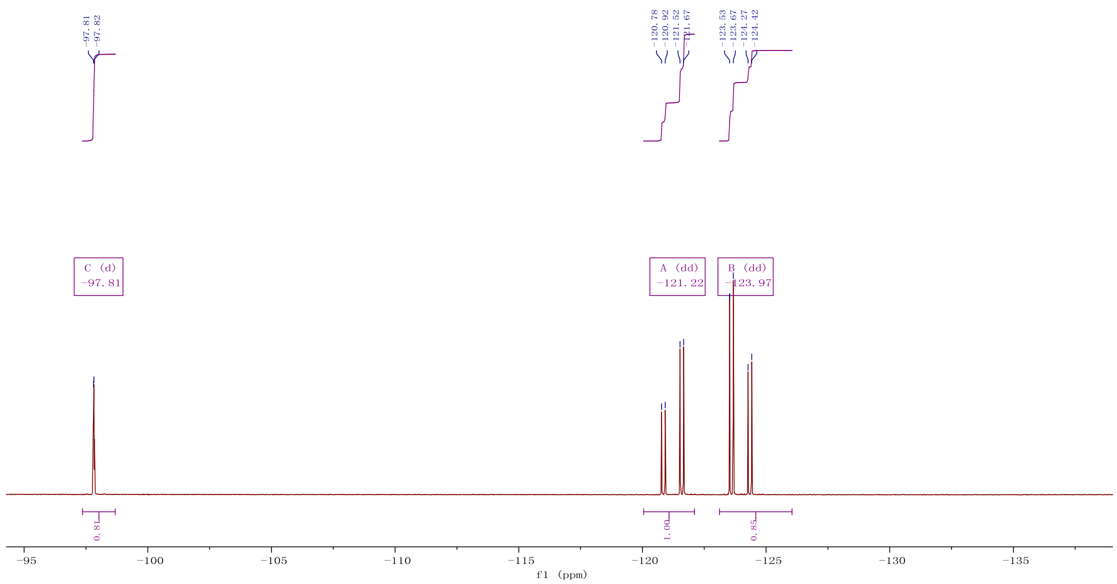
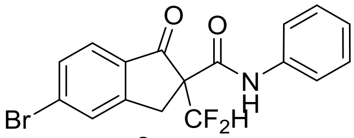
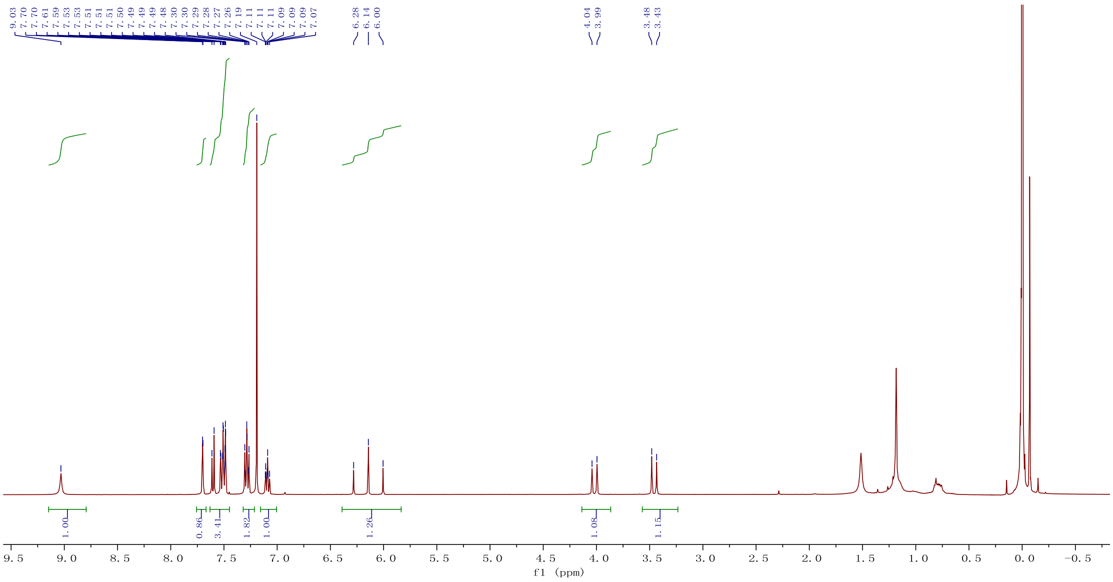
157.68
156.97
137.01
129.12
127.67
127.56
125.14
120.17
117.77
116.98
116.74
115.28
113.63
113.40
112.78
65.50
65.30
65.10
A (d)
157.03
B (d)
127.62
C (d)
116.86
D (m)
113.27
E (t)
65.30
1.00
2.30
2.29
2.65
0.99
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
−10
f1 (ppm)


-97.81
-97.82
-120.78
-120.92
-121.52
-121.67
-123.53
-123.67
-124.27
-124.42
C (d)
-97.81
A (dd)
−121.22
B (dd)
−123.97
0.81
1.00
0.85
−95
−100
−105
−110
−115
−120
−125
−130
−135
f1 (ppm)

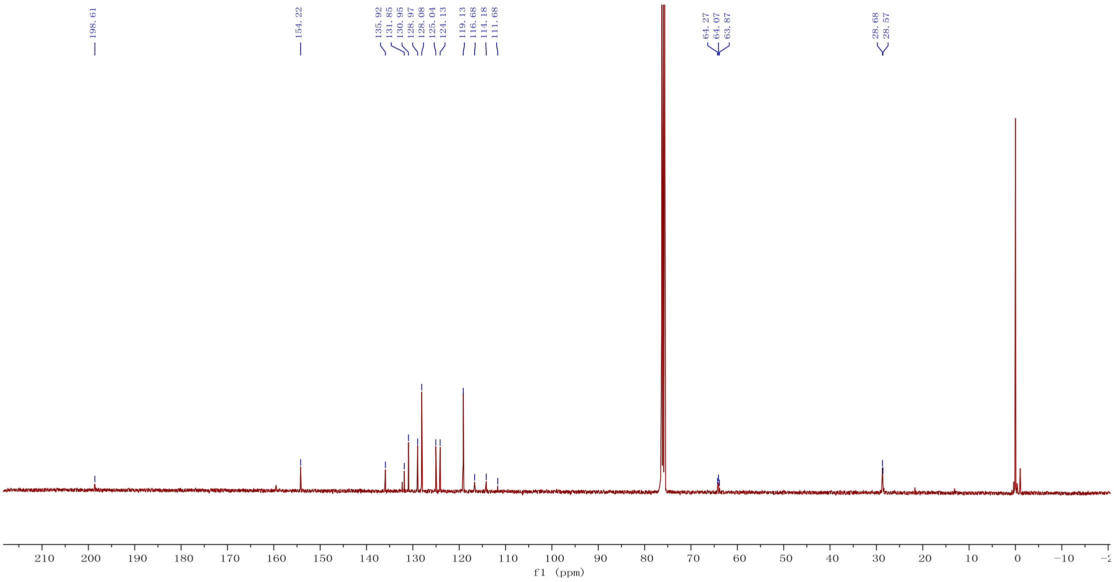


O
O
N
H
Br
CF2H

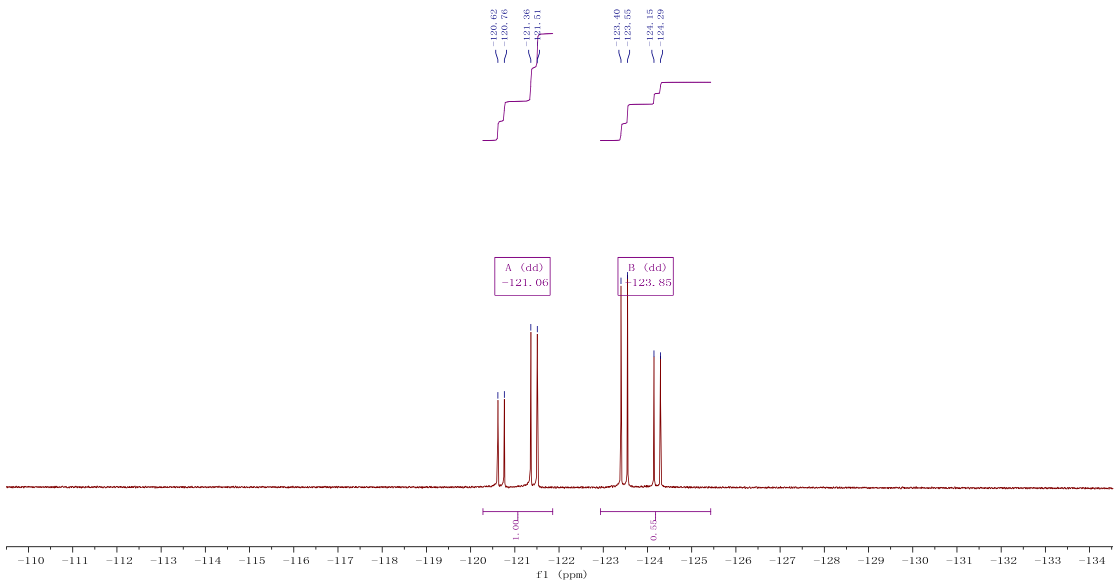
2m

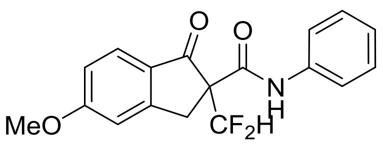


9.03 7.70 7.70 7.61 7.59 7.53 7.53 7.51 7.51 7.51 7.50 7.49 7.49 7.49 7.48 7.30 7.29 7.28 7.27 7.26 7.19 7.11 7.11 7.11 7.11 7.09 7.09 7.07
6.28 6.14 6.00
4.04 3.99
3.48 3.43
1.00 0.86 3.41 1.82 1.00 1.26 1.08 1.15
f1 (ppm)

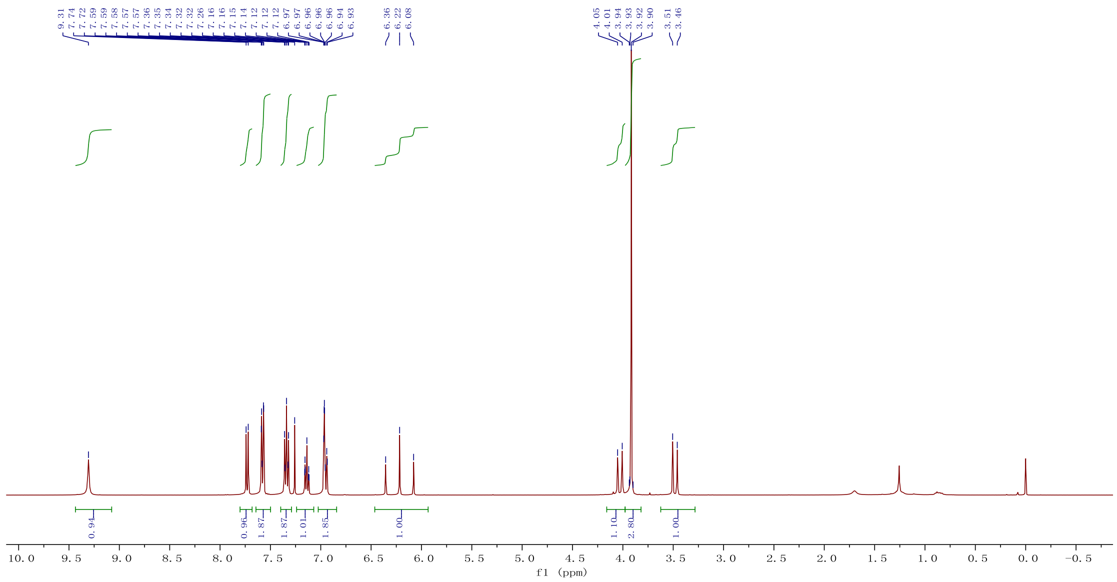


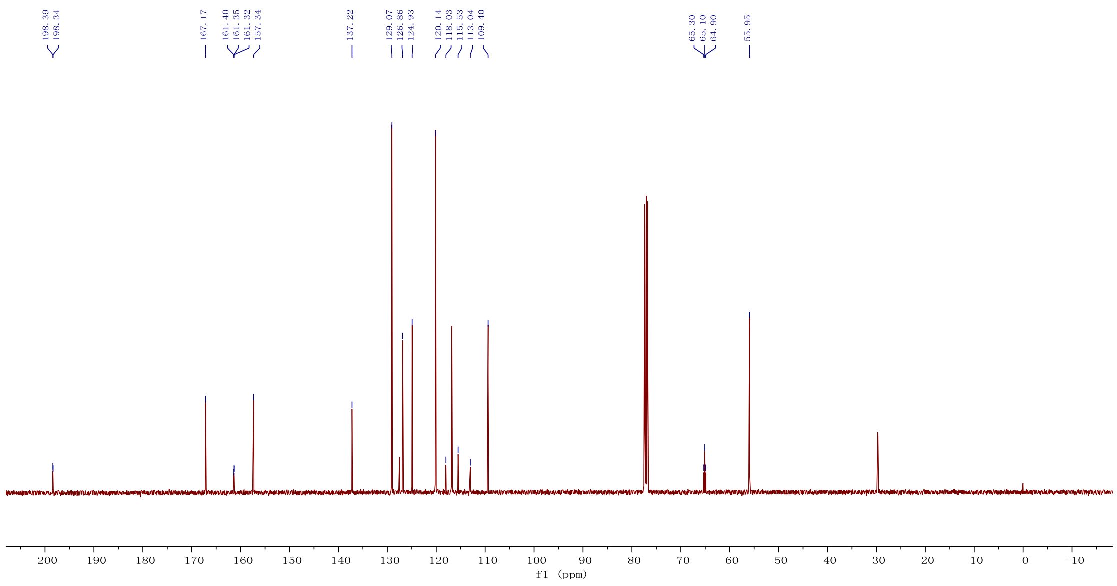
198.61
154.22
135.92 131.85 130.95 128.97 128.08 125.04 124.13 119.13 116.68 114.18 111.68
64.27 64.07 63.87
28.68 28.57
f1 (ppm)

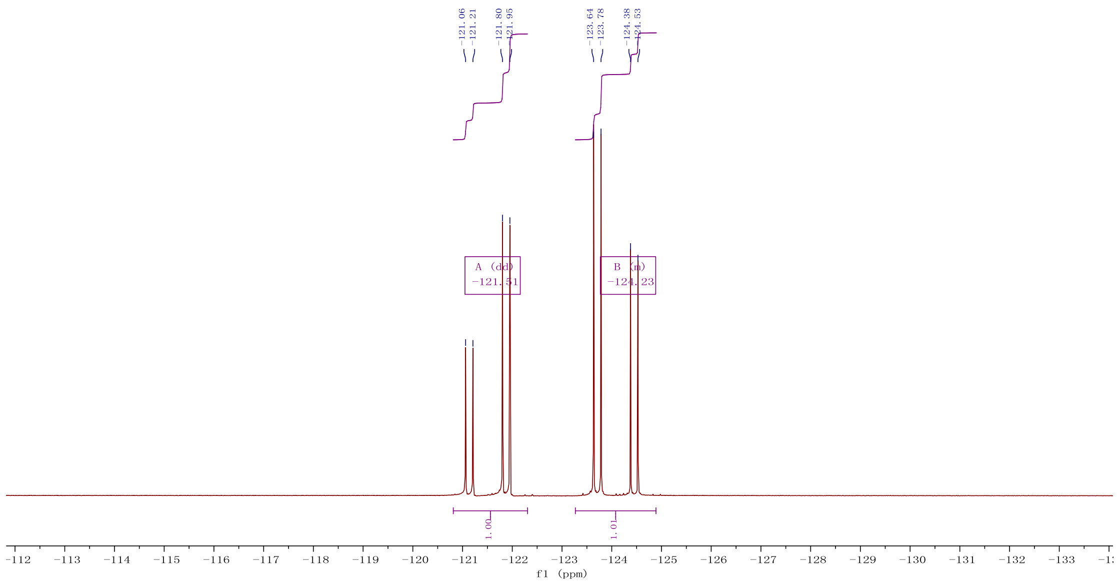


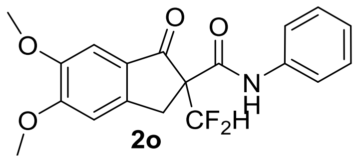


2n



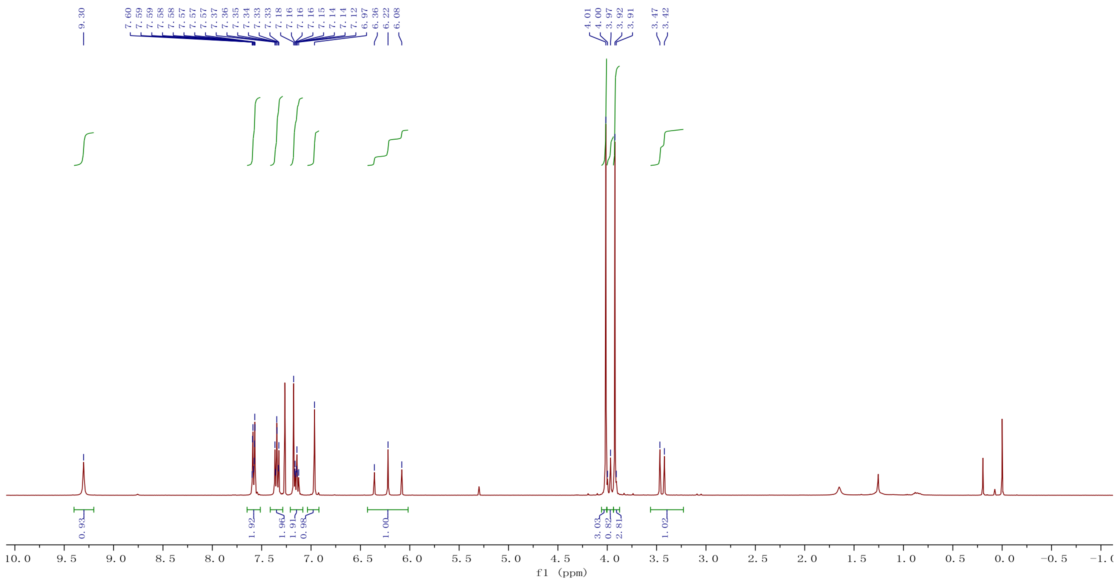

198.39
198.34
167.17
161.40
161.35
161.32
157.34
137.22
129.07
126.86
124.93
120.14
118.03
115.53
113.04
109.40
65.30
65.10
64.90
55.95
f1 (ppm)


-121.06
-121.21
-121.80
-121.95
-123.64
-123.78
-124.38
-124.53
A (dd)
-121.51
B (m)
-124.23
1.00
1.01
f1 (ppm)

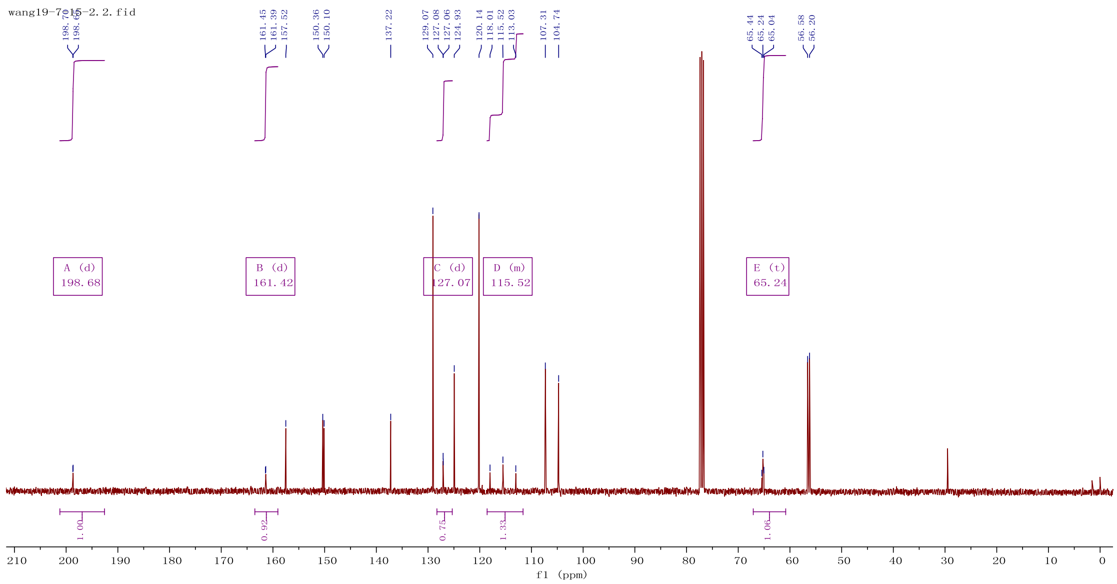


O
O
O
O
N
H
CF2H

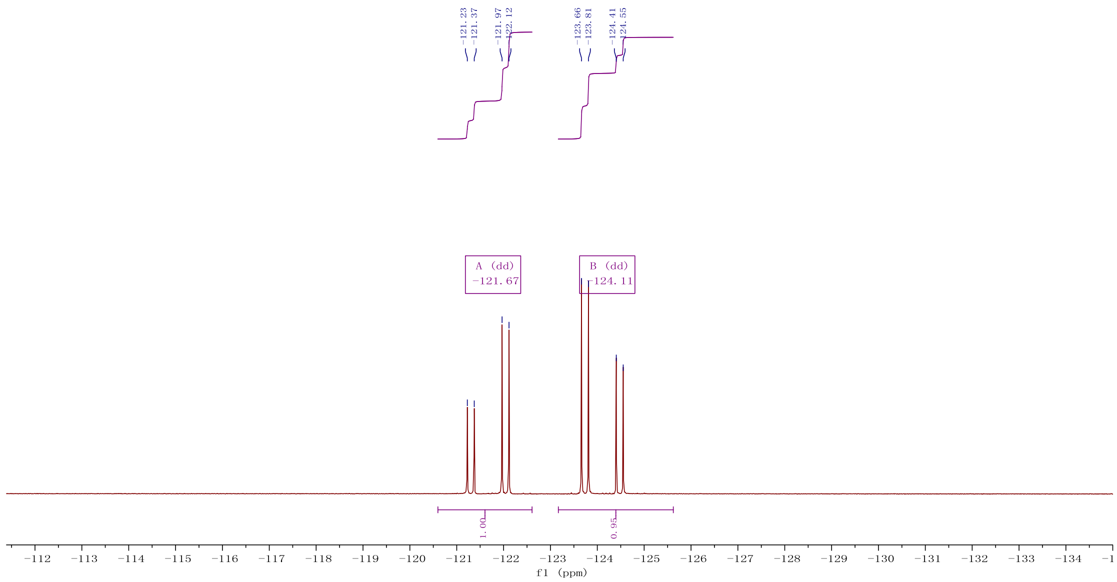
2o

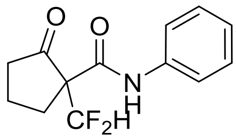


9.30
7.60 7.59 7.59 7.58 7.58 7.57 7.57 7.57 7.37 7.36 7.35 7.34 7.33 7.33 7.18 7.16 7.16 7.16 7.15 7.14 7.14 7.12 6.97 6.36 6.22 6.08
4.01 4.00 3.97 3.92 3.91
3.47 3.42
0.93
1.92
1.96
1.91
0.98
1.00
3.03
0.82
2.81
1.02
f1 (ppm)

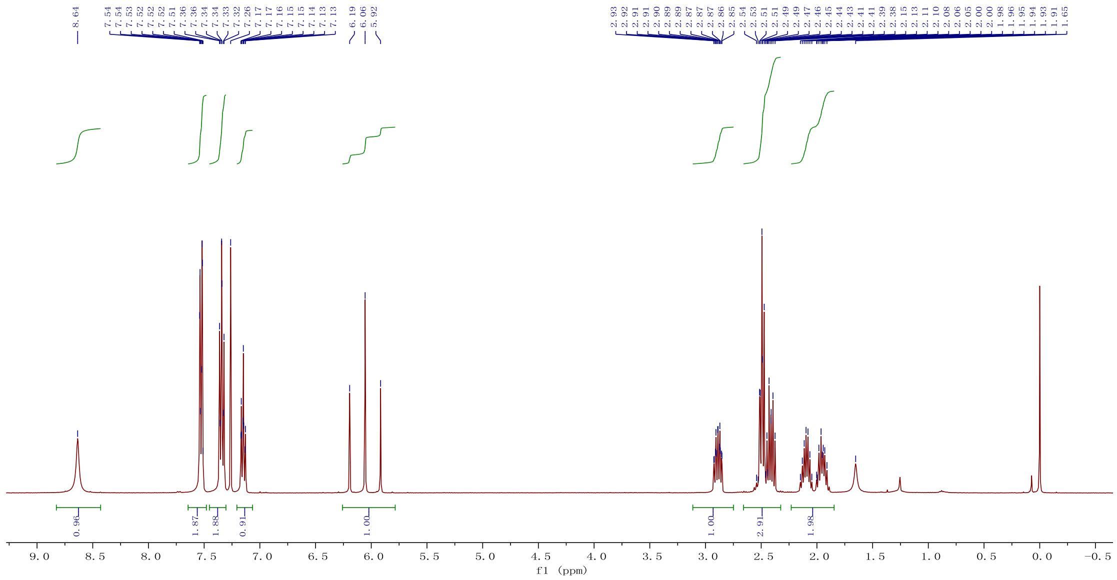


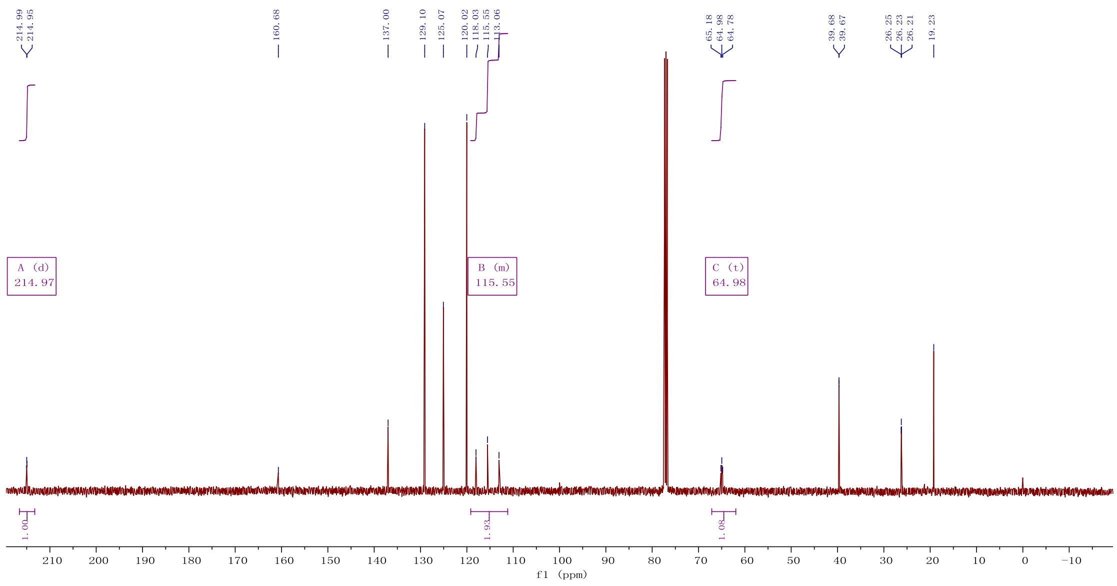
wang19-7-15-2.2.fid
161.45 161.39 157.52
150.36 150.10
137.22
129.07 127.08 127.06 124.93
120.14 118.01 115.52 113.03
107.31 104.74
65.44 65.24 65.04
56.58 56.20
A (d)
198.68
B (d)
161.42
C (d)
127.07
D (m)
115.52
E (t)
65.24
1.00
0.92
0.75
1.33
1.06
f1 (ppm)

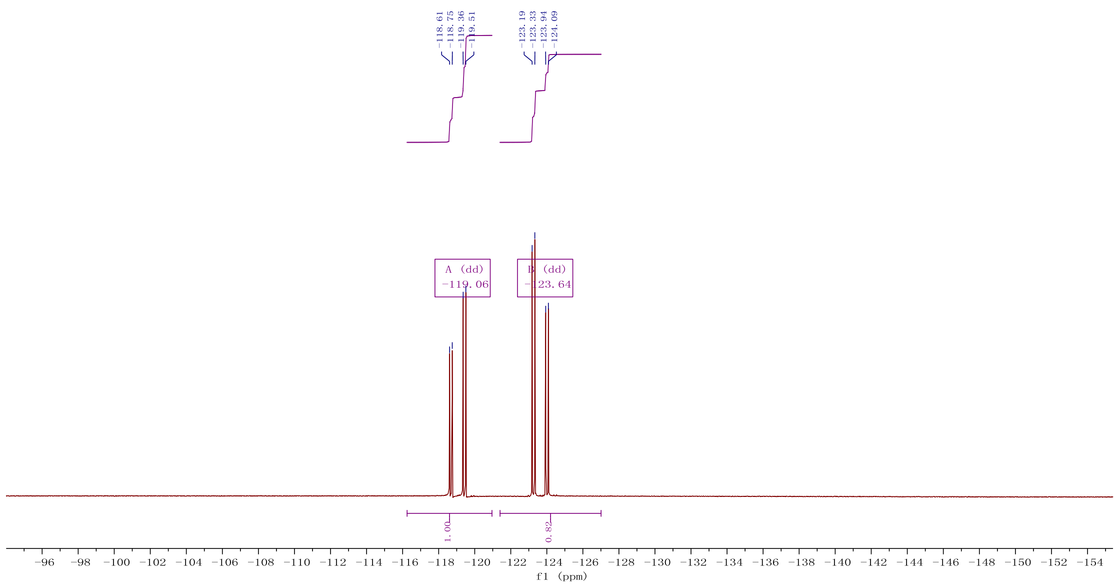


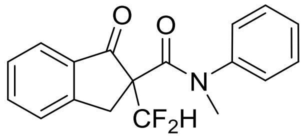


2p

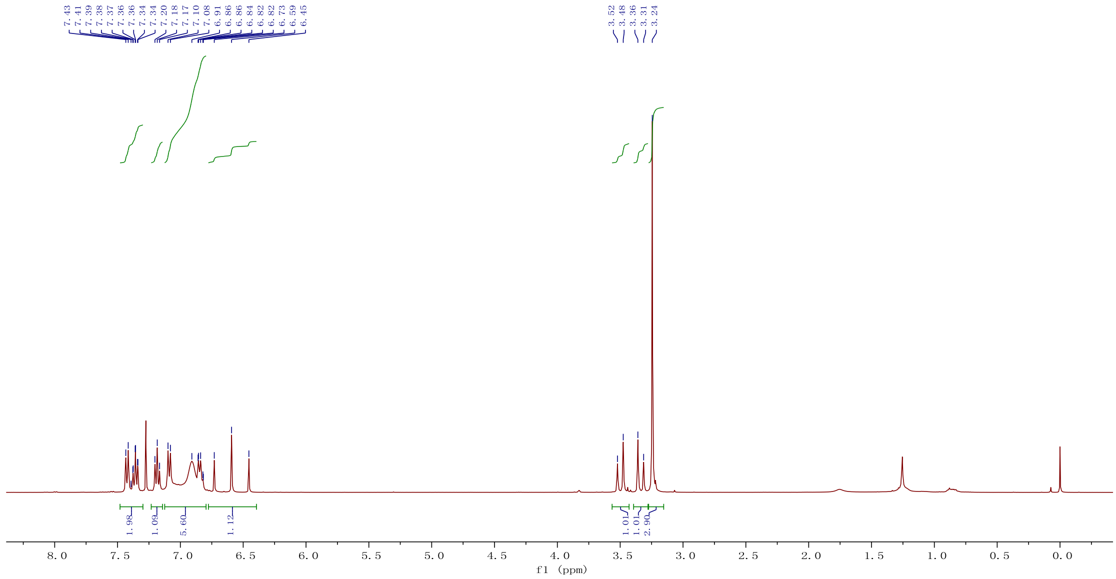


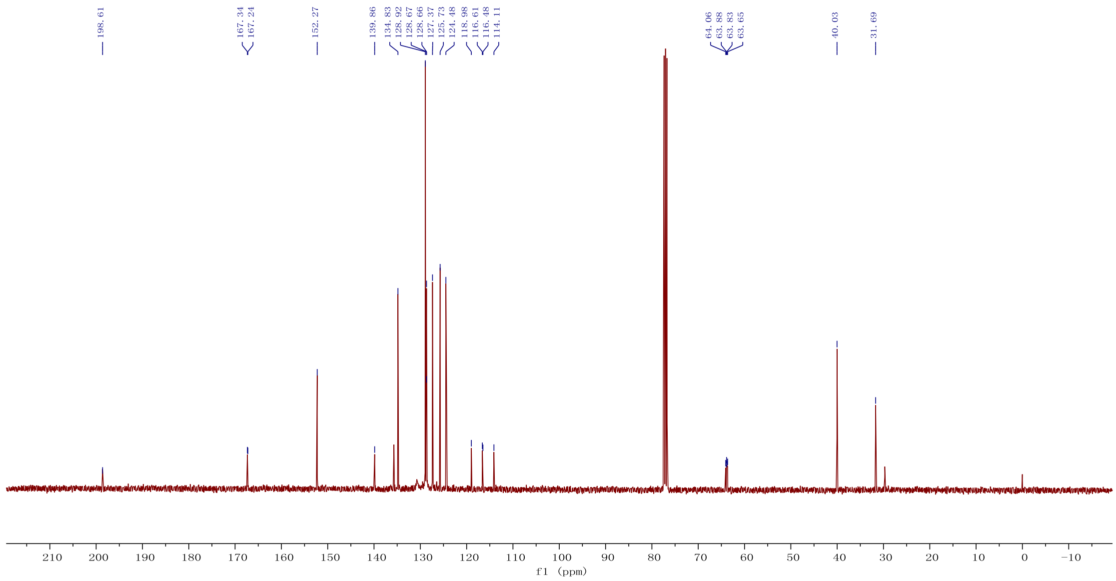

214.99
214.95
160.68
137.00
129.10
125.07
120.02
118.03
115.55
113.06
65.18
64.98
64.78
39.68
39.67
26.25
26.23
26.21
19.23
A (d)
214.97
B (m)
115.55
C (t)
64.98
1.00
1.93
1.08
f1 (ppm)

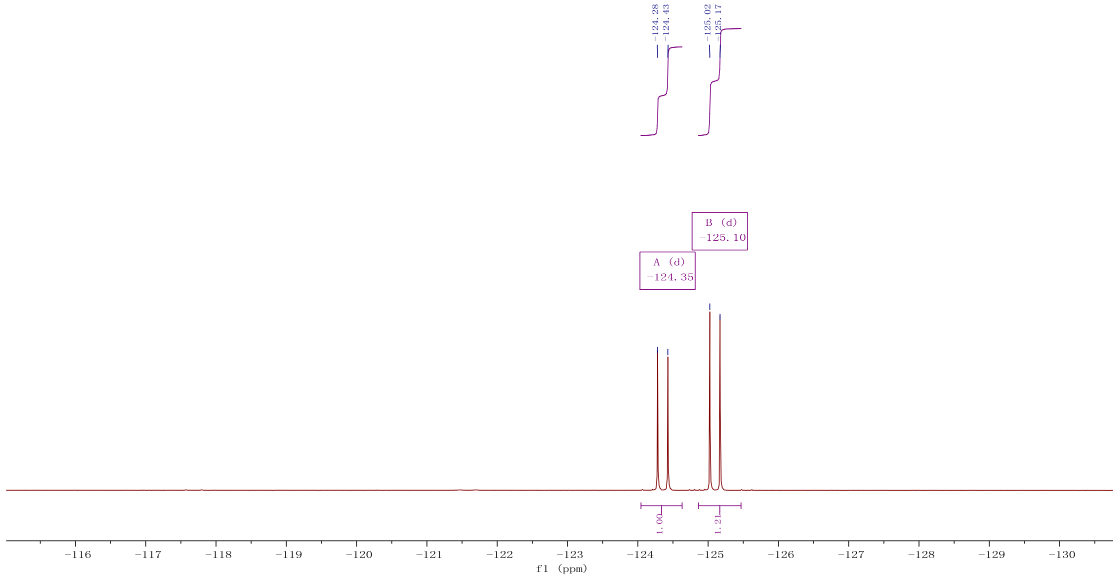

-118.61
-118.75
-119.36
-119.51
-123.19
-123.33
-123.94
-124.09
A (dd)
-119.06
B (dd)
-123.64
1.00
0.82
f1 (ppm)

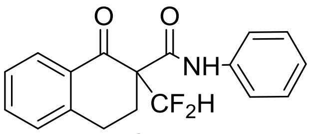

O
O
N
CF2H

2q

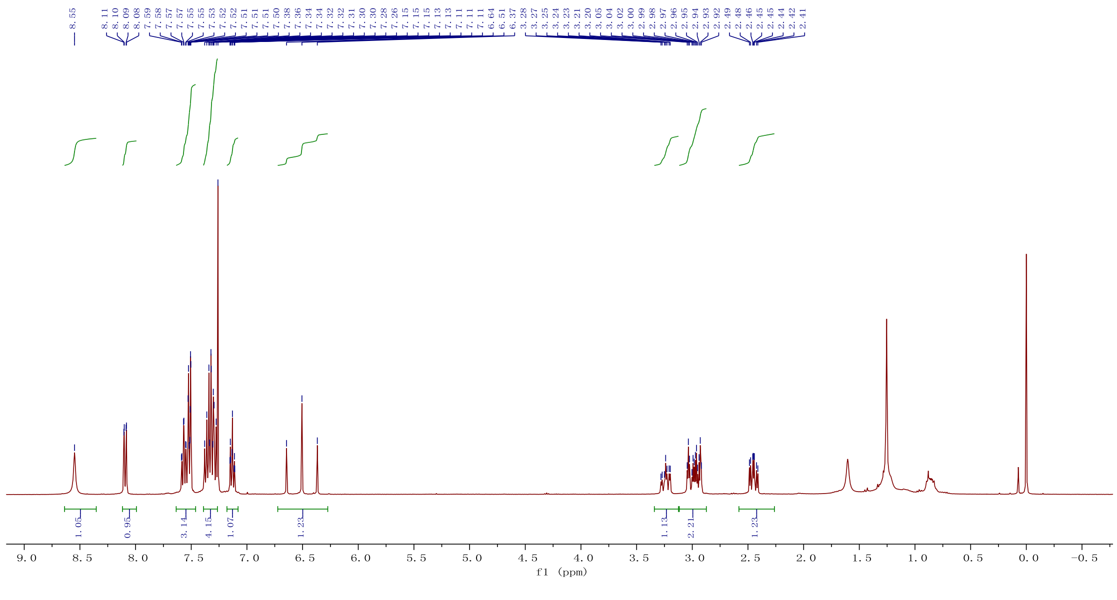

7.43 7.41 7.39 7.38 7.37 7.36 7.36 7.34 7.34 7.34 7.20 7.18 7.17 7.10 7.08 6.91 6.86 6.86 6.84 6.82 6.82 6.73 6.59 6.45
3.52 3.48 3.36 3.31 3.24
1.98 1.09 5.60 1.12
1.01 1.01 2.96
f1 (ppm)

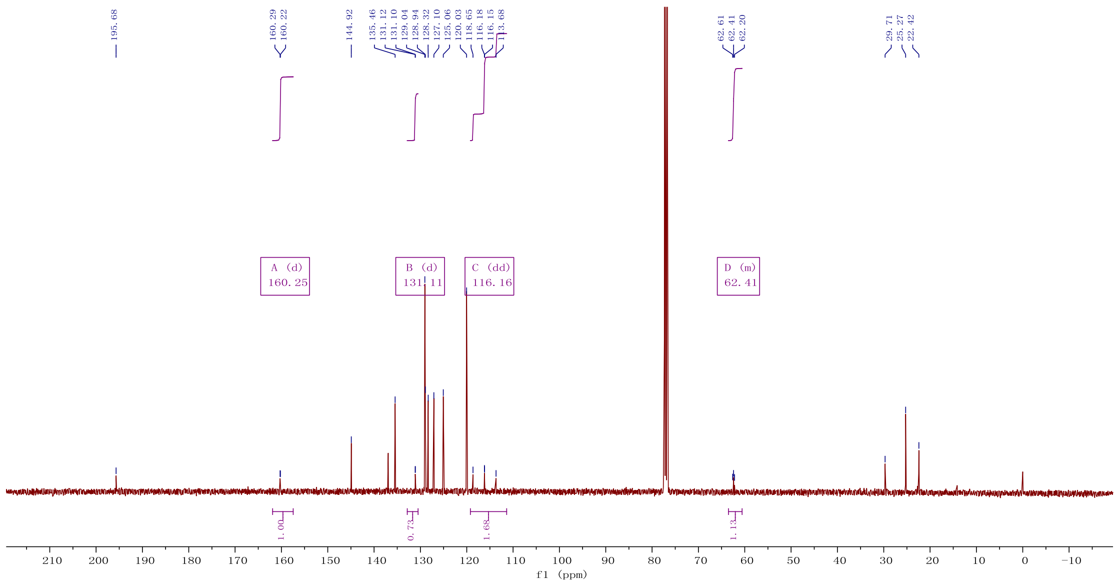

198.61
167.34 167.24
152.27
139.86 134.83 128.92 128.67 128.66 127.37 125.73 124.48 118.98 116.61 116.48 114.11
64.06 63.88 63.83 63.65
40.03
31.69
f1 (ppm)

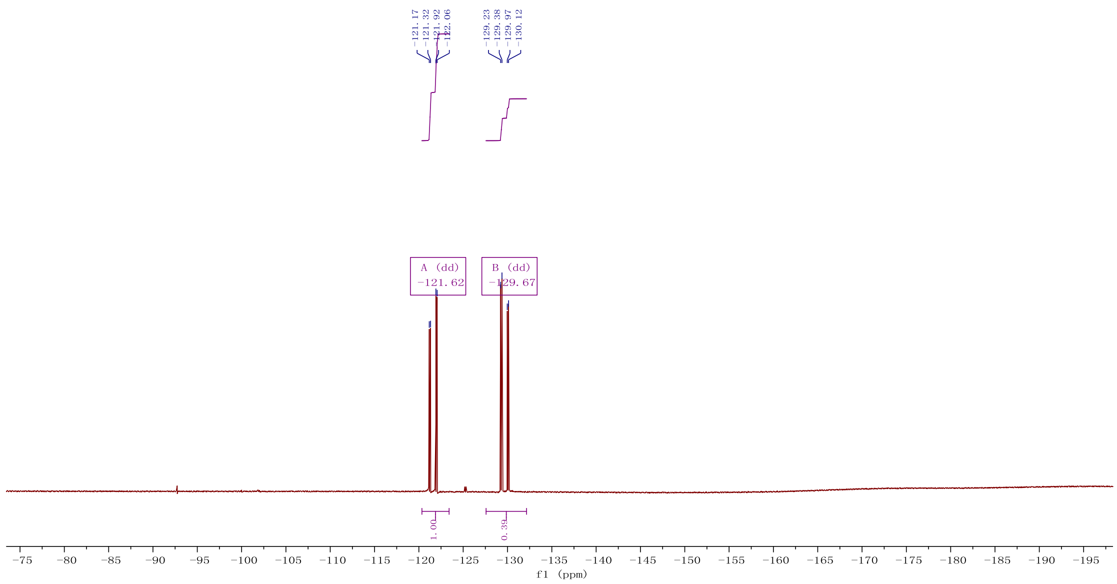


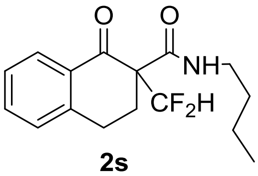


2r



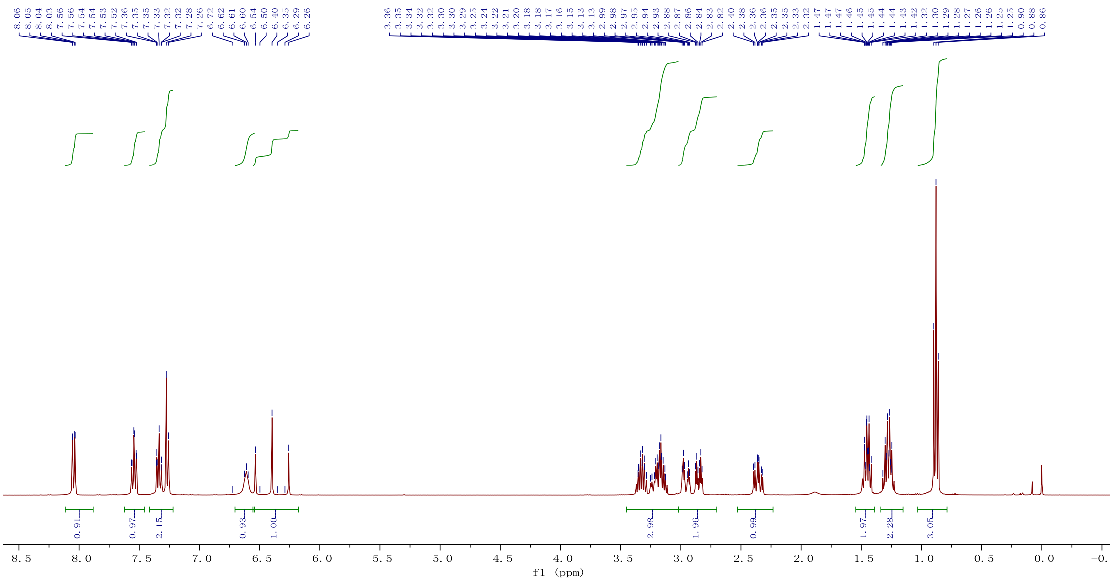

195.68
160.29
160.22
144.92
135.46
131.12
131.10
129.04
128.94
128.32
127.10
125.06
120.03
118.65
116.18
116.15
113.68
62.61
62.41
62.20
29.71
25.27
22.42
A (d)
160.25
B (d)
131.11
C (dd)
116.16
D (m)
62.41
1.00
0.73
1.68
1.13
f1 (ppm)


-121.17
-121.32
-121.92
-122.06
-129.23
-129.38
-129.97
-130.12
A (dd)
-121.62
B (dd)
-129.67
1.00
0.39
f1 (ppm)

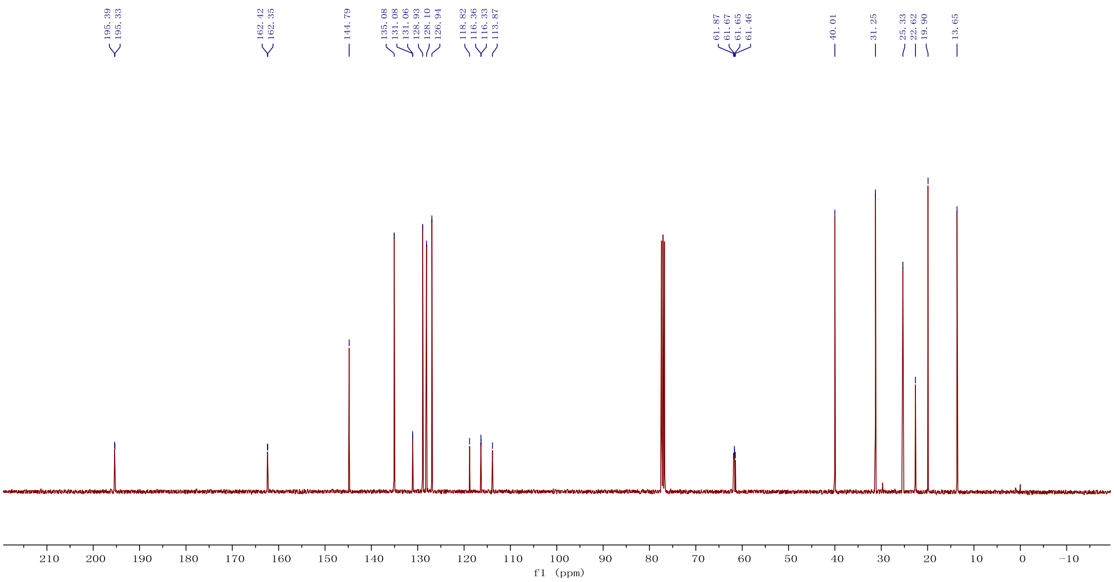


O
O
NH
CF2H

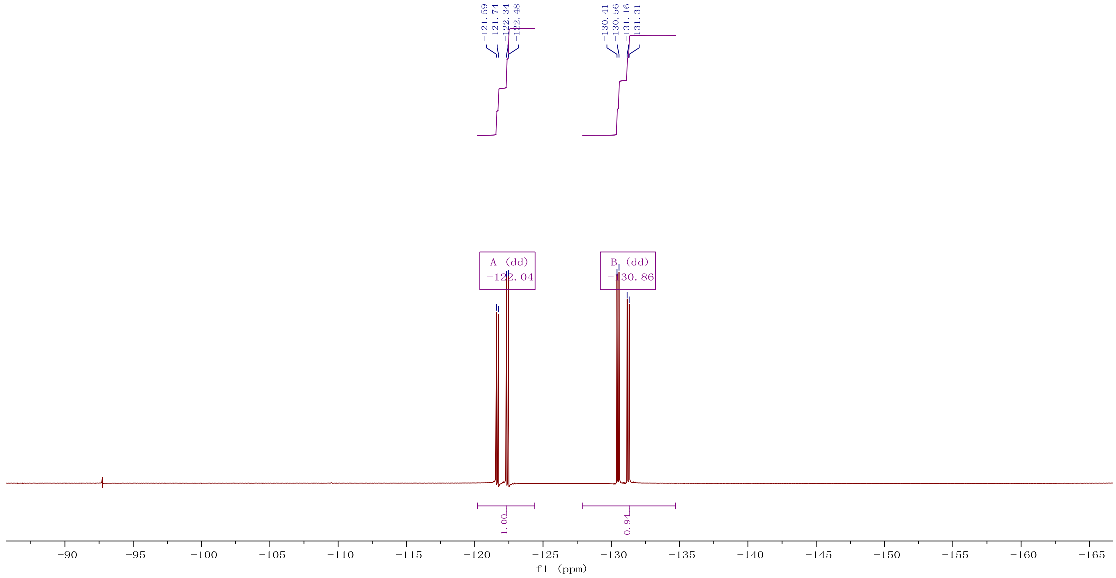
2s



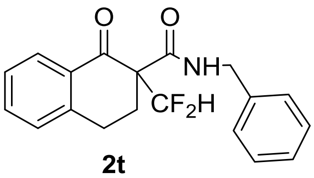
0.91
0.97
2.15
0.93
1.00
2.98
1.96
0.99
1.97
2.28
3.05
f1 (ppm)



195.39
195.33
162.42
162.35
144.79
135.08
131.08
131.06
128.93
128.10
126.94
118.82
116.36
116.33
113.87
61.87
61.67
61.65
61.46
40.01
31.25
25.33
22.62
19.90
13.65
f1 (ppm)

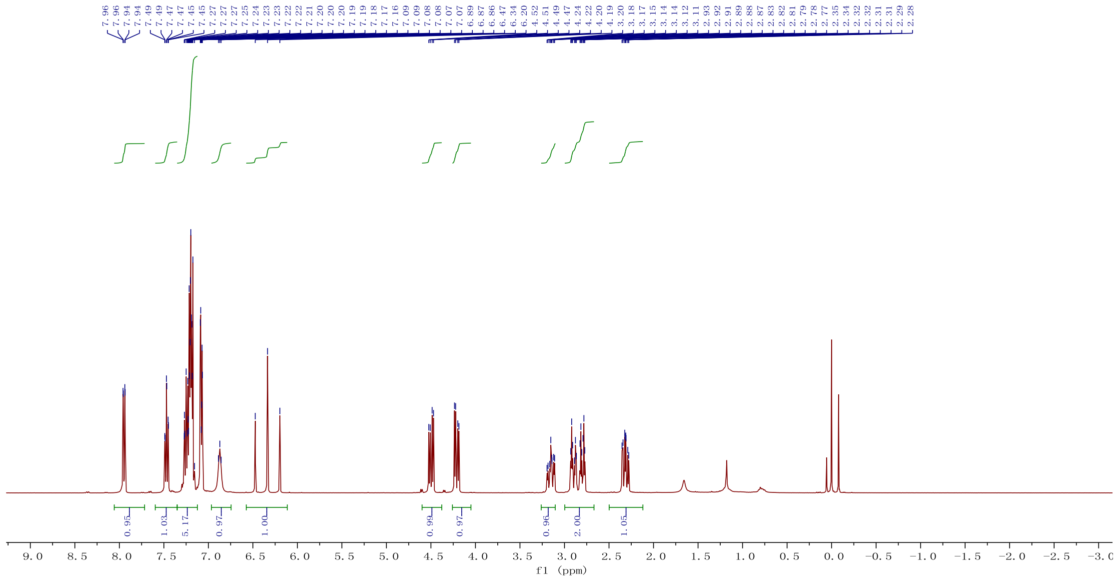


-121.59
-121.74
-122.34
-122.48
-130.41
-130.56
-131.16
-131.31
A (dd)
-122.04
B (dd)
-130.86
1.00
0.94
f1 (ppm)

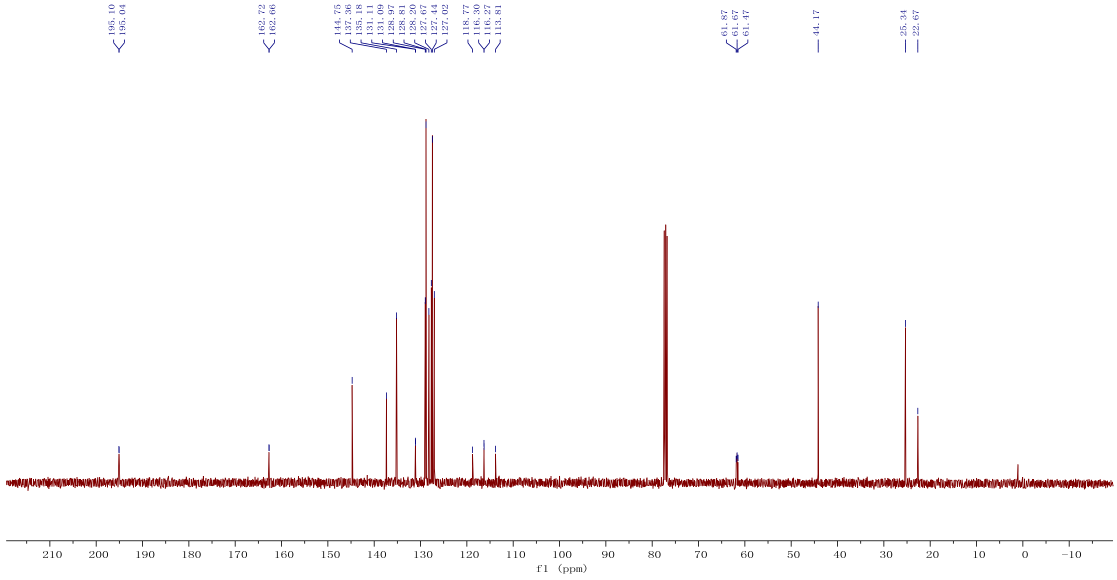


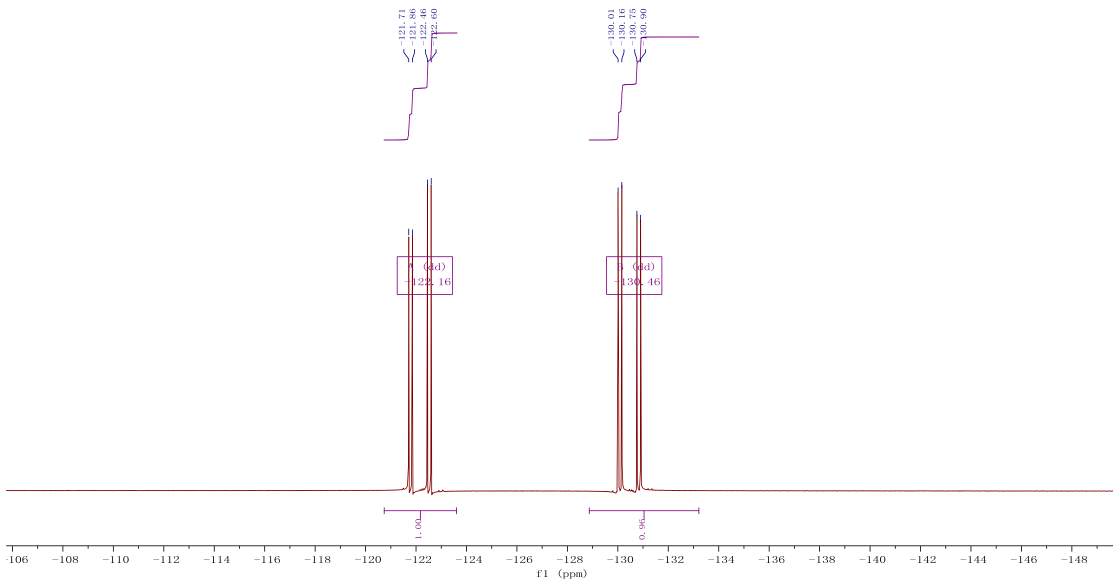
O
O
NH
CF2H

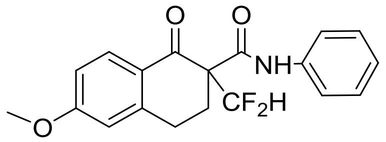
2t



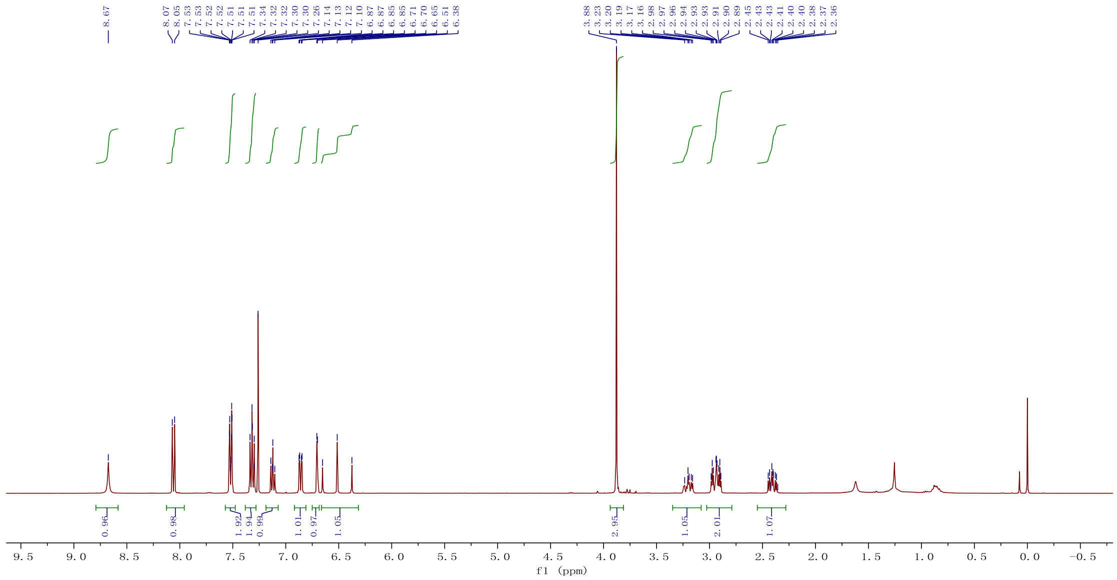
0.95
1.03
5.17
0.97
1.00
0.99
0.97
0.96
2.00
1.05
f1 (ppm)

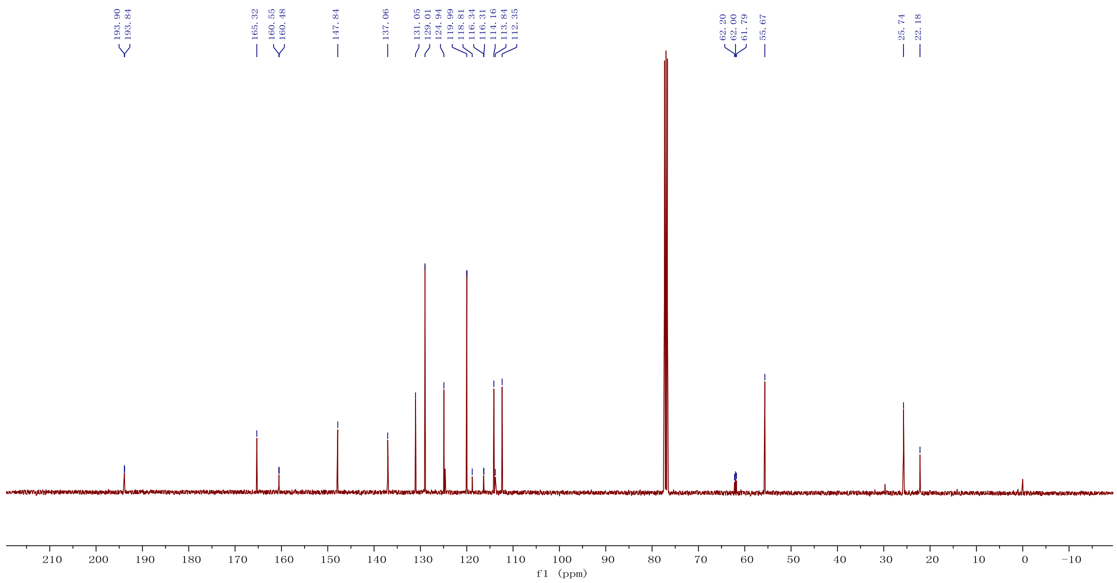

195.10
195.04
162.72
162.66
144.75
137.36
135.18
131.11
131.09
128.97
128.81
128.20
127.67
127.44
127.02
118.77
116.30
116.27
113.81
61.87
61.67
61.47
44.17
25.34
22.67
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 −10
f1 (ppm)

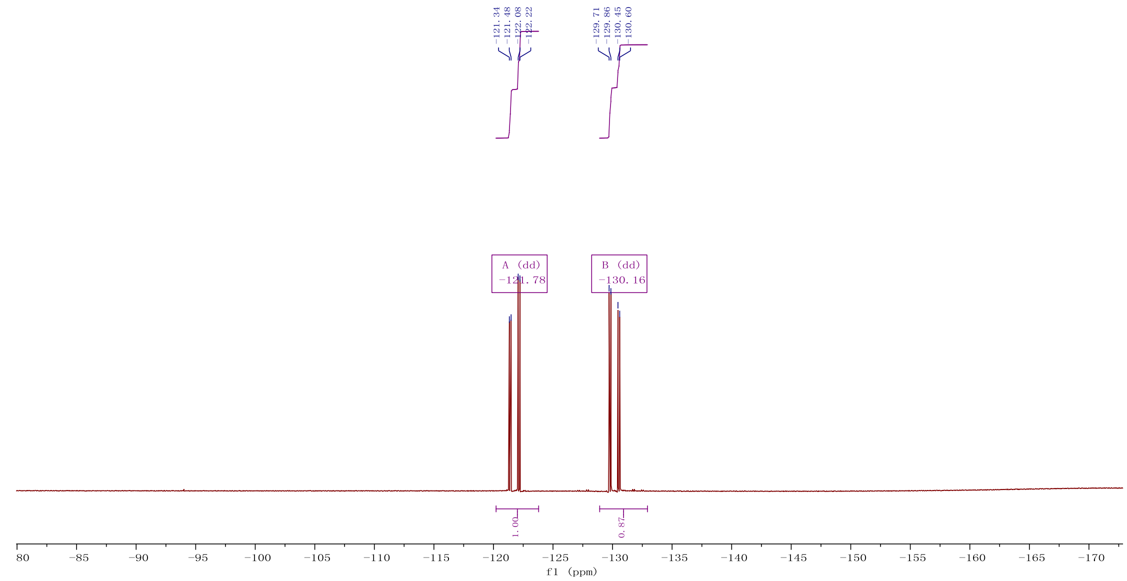

−121.71
−121.86
−122.46
−122.60
−130.01
−130.16
−130.75
−130.90
A (dd)
−122.16
B (dd)
−130.46
1.00
0.96
−106 −108 −110 −112 −114 −116 −118 −120 −122 −124 −126 −128 −130 −132 −134 −136 −138 −140 −142 −144 −146 −148
f1 (ppm)

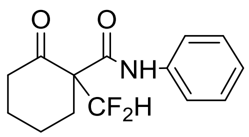


2u

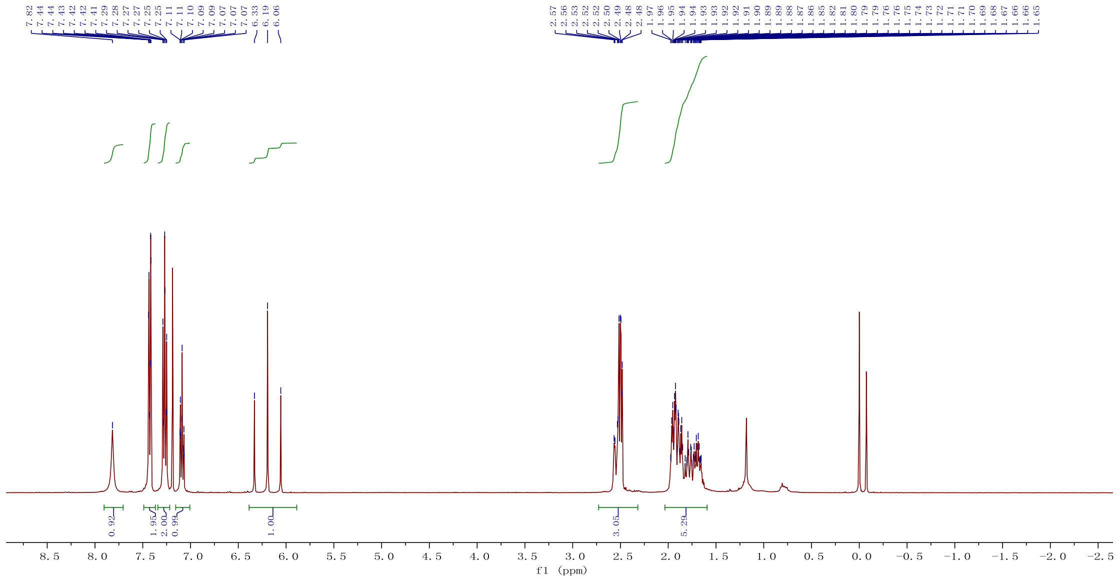


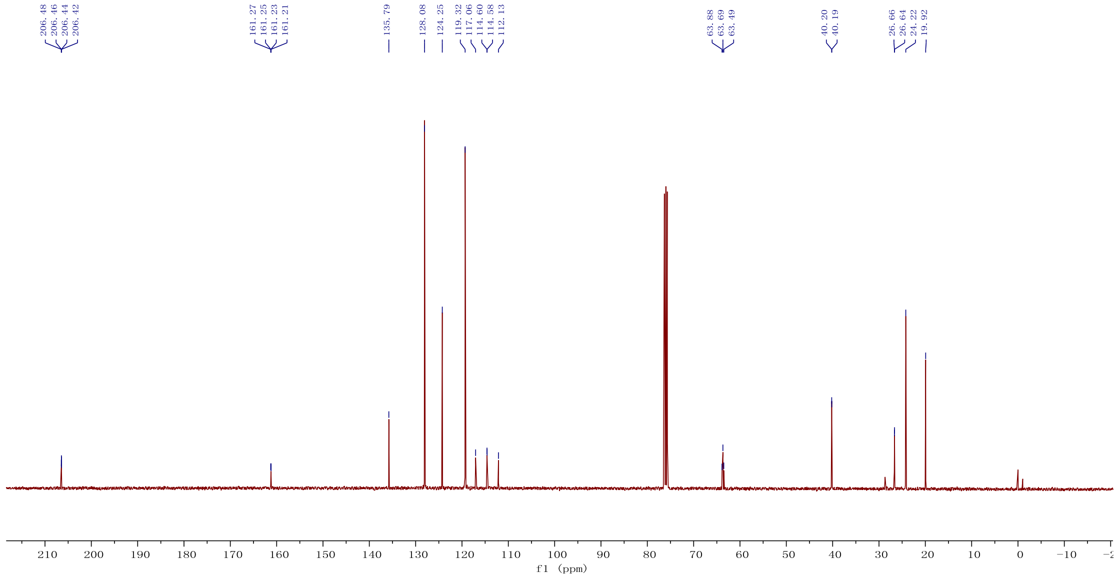


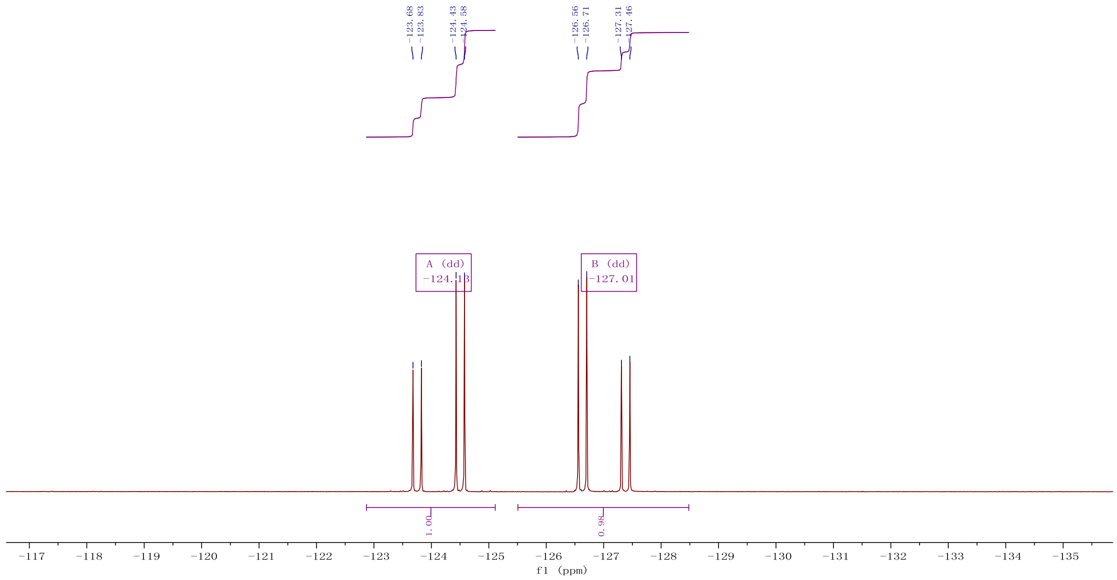




2v




206.48
206.46
206.44
206.42
161.27
161.25
161.23
161.21
135.79
128.08
124.25
119.32
117.06
114.60
114.58
112.13
63.88
63.69
63.49
40.20
40.19
26.66
26.64
24.22
19.92
f1 (ppm)


-123.68
-123.83
-124.43
-124.58
-126.56
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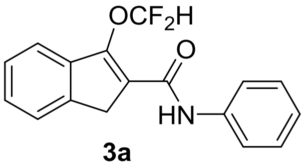
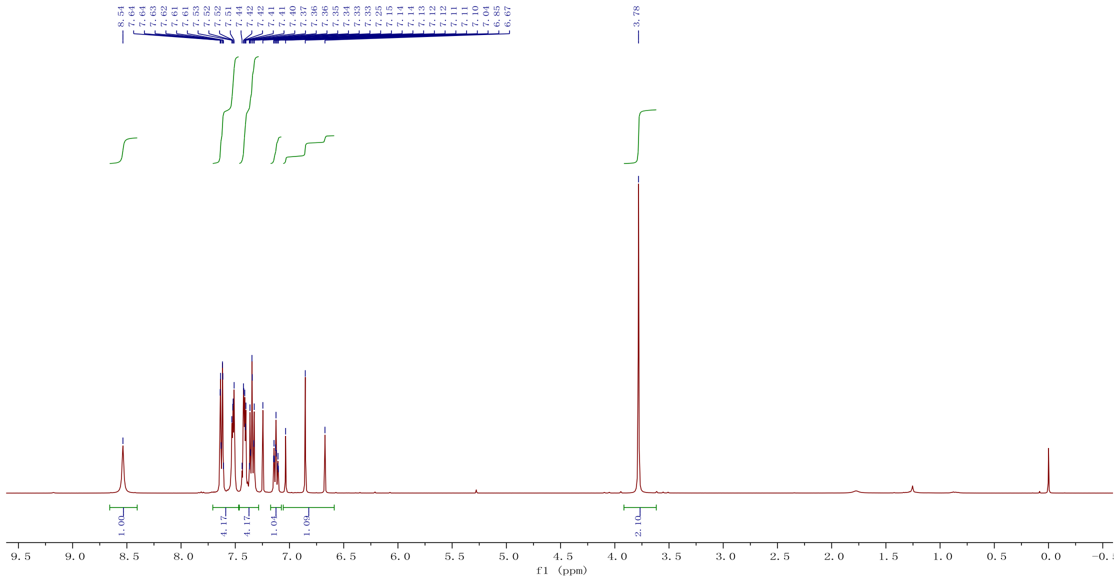
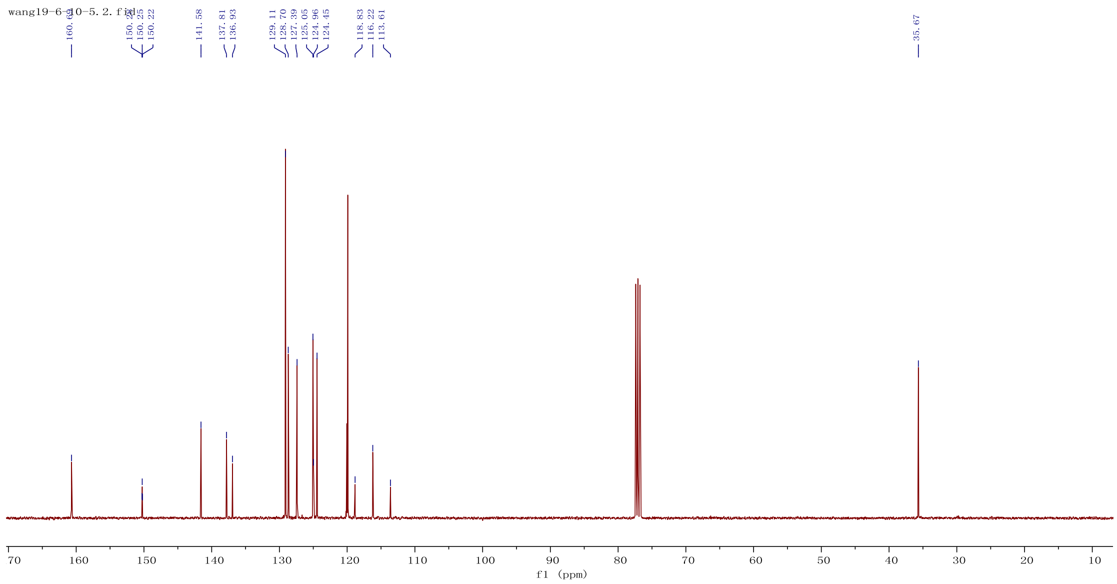
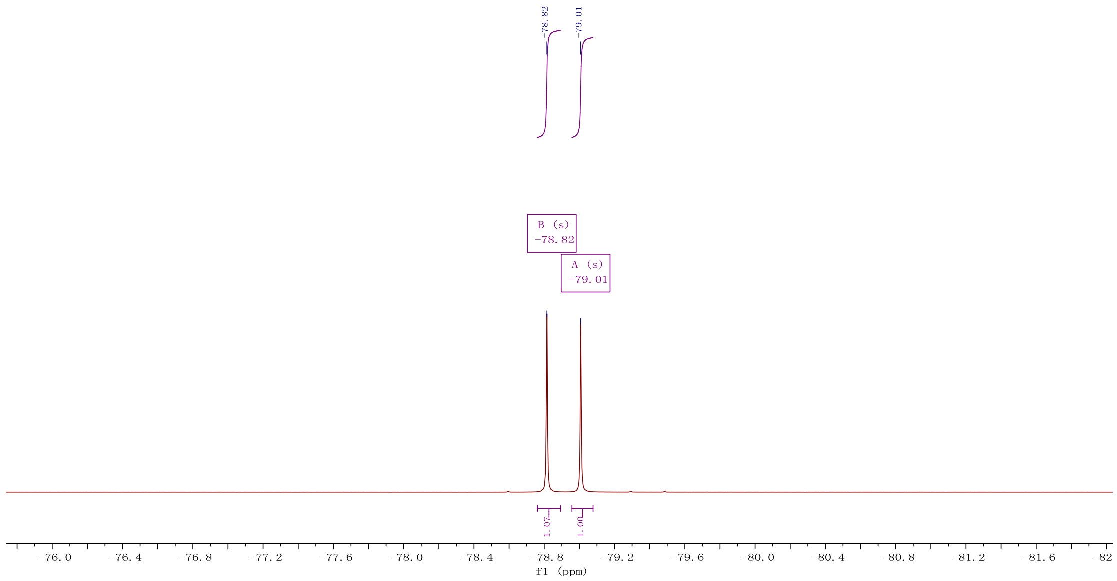
-127.46
A (dd)
-124.13
B (dd)
-127.01
1.00
0.98
f1 (ppm)

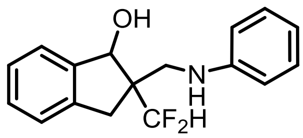


3a

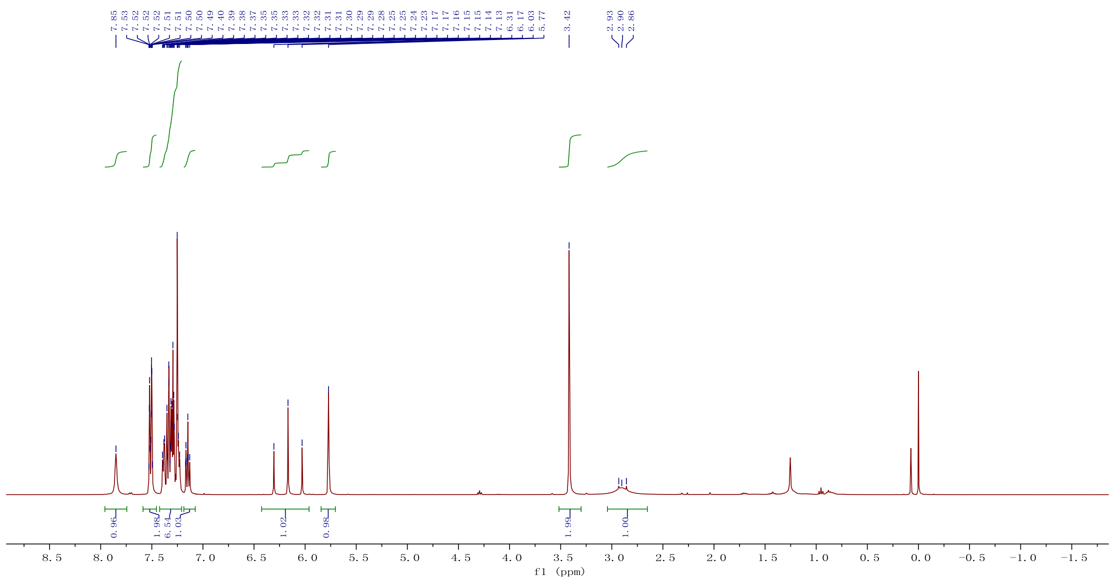


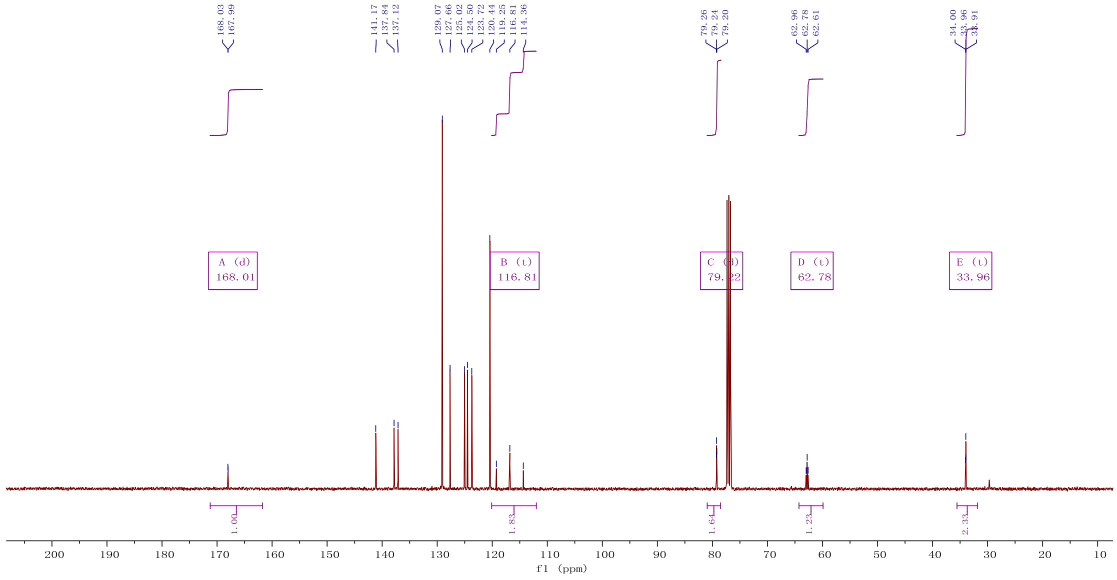


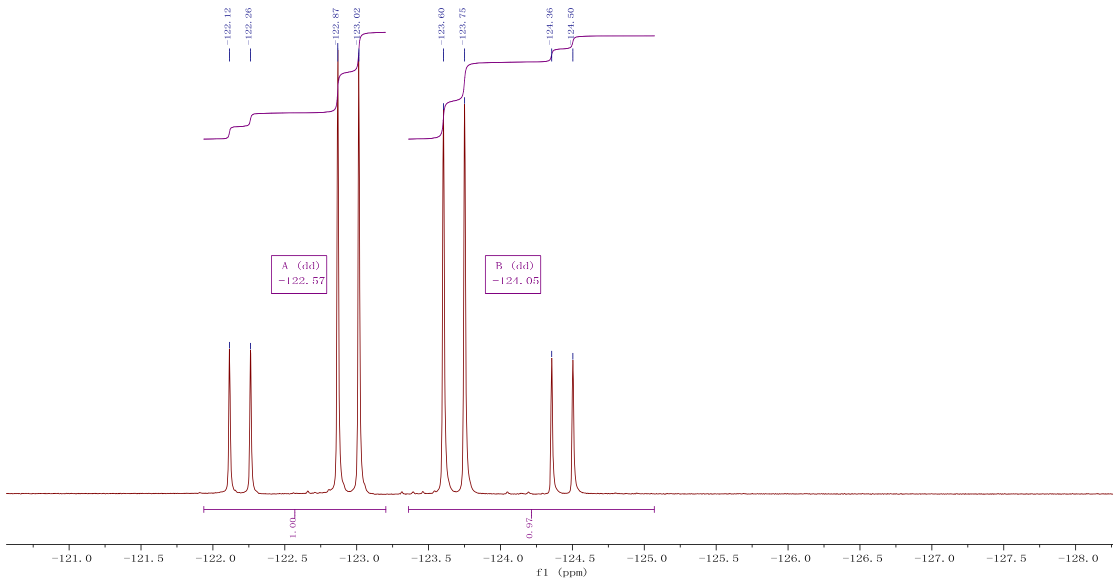




4a




168.03
167.99
141.17
137.84
137.12
129.07
127.66
125.02
124.50
123.72
120.44
119.25
116.81
114.36
79.26
79.24
79.20
62.96
62.78
62.61
34.00
33.96
33.91
A (d)
168.01
B (t)
116.81
C (d)
79.22
D (t)
62.78
E (t)
33.96
1.00
1.83
1.64
1.23
2.33
f1 (ppm)


-122.12
-122.26
-122.87
-123.02
-123.60
-123.75
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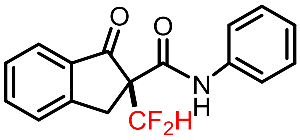
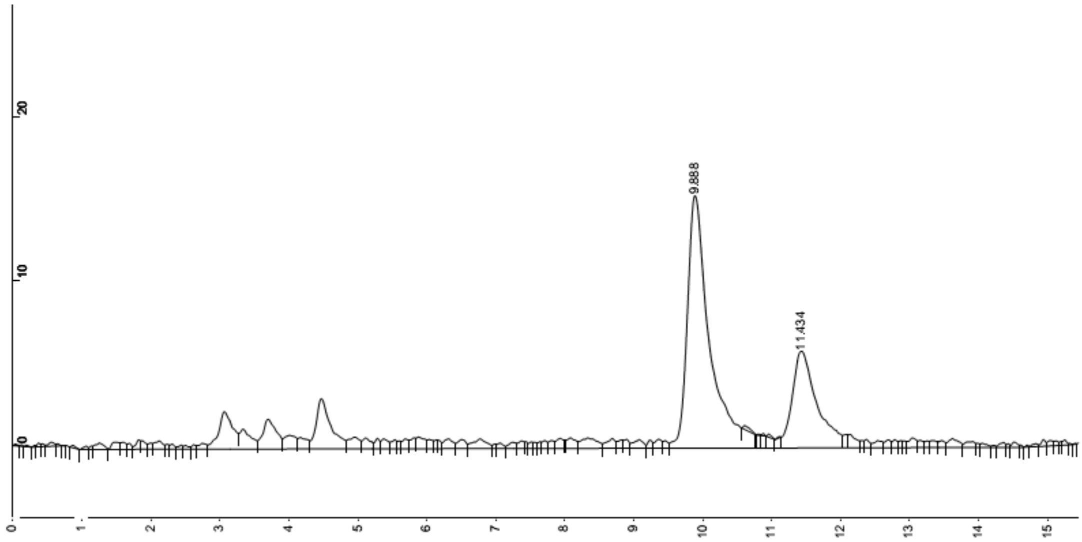
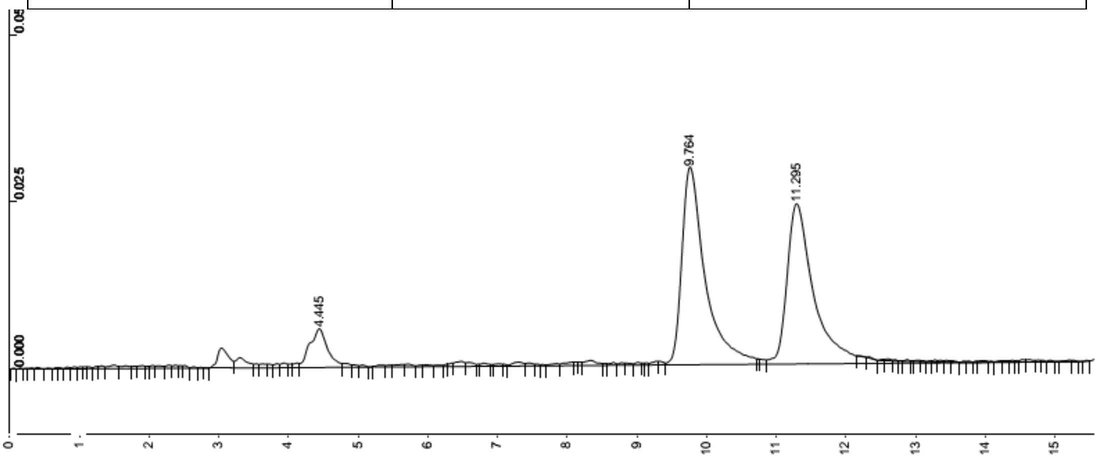
-124.50
A (dd)
-122.57
B (dd)
-124.05
1.00
0.97
f1 (ppm)



2a



R.Time	Area	Area%
9.888	**3594220**	**72.5124**
11.434	**1381728**	**27.4876**



R.Time	Area	Area%
9.764	**6917868**	**45.4364**
11.295	**6784980**	**44.5636**

Peak No	Peak Name	Result (ug/ml)	Ret. Time (min)	Time Offset (min)	Width 1/2 (sec)	Area (counts)
1		7.0086	4.445	0.000	17.7	1015669
2		47.7367	9.764	0.000	19.3	6917868
3		45.2547	11.295	0.000	22.2	6558172