

Boron Lewis acid-catalyzed formal insertion of isocyanides into a C-O bond of benzyl esters

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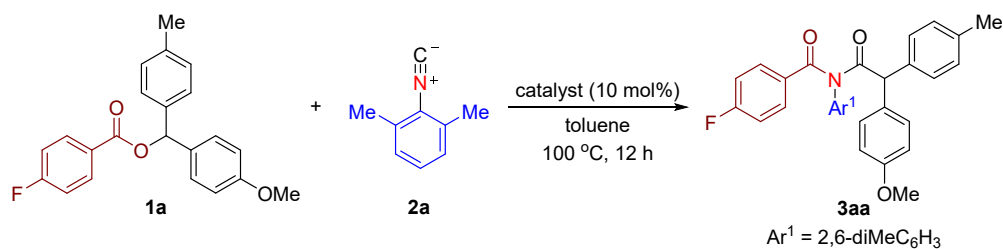
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1 General Information

All reactions were performed in flame-dried glassware using conventional Schlenk techniques under a static pressure of nitrogen unless otherwise stated. Liquids and solutions were transferred with syringes. The known esters **1**,^[1] isocyanides **2**^[2] and ArNC-B(C₅F₅)₃ adduct **6**^[3] (Ar = 2,6-diMeC₆H₃) were prepared according to reported procedures. The chiral ester (*R*)-**1ae** was prepared in 78% yield according to the known procedure.^[4] (97% ee of (*R*)-**1ae** was determined by HPLC: AD-H Column, 4/96 *i*PrOH/hexane, 0.8 mL/min, 254 nm, 35 °C; retention time = 11.51 min (minor), 15.18 min (major)). Tris(pentafluorophenyl)borane (B(C₅F₅)₃, 98%, *Energy Chemical*) was purchased from commercial suppliers and used as received. Other commercially available reagents were purchased from *Sigma-Aldrich*, *Leyan* and *Bide Chemical Company*. 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP), chlorobenzene (PhCl) and ethyl acetate (EtOAc) were purchased from *Energy Chemical* (99%, Extra Dry) and used as received. Trichloromethane (CHCl₃) was purchased from *Sinopharm Chemical Reagent*. All other solvents (hexane, toluene, tetrahydrofuran and 1,2-dichloroethane etc.) were dried and purified following standard procedures. Technical grade solvents for extraction or chromatography (Petroleum ether, CH₂Cl₂, and ethyl acetate) were distilled prior to use. Analytical thin layer chromatography (TLC) was performed on silica gel 60 F254 glass plates by *Merck*. Flash column chromatography was performed on silica gel 60 (40–63 μm, 230–400 mesh, ASTM) by *Grace* using the indicated solvents. ¹H, ¹³C NMR spectra were recorded in CDCl₃ on Bruker AV400 instruments. Chemical shifts are reported in parts per million (ppm) and are referenced to the residual solvent resonance as the internal standard (CHCl₃: δ = 7.26 ppm for ¹H NMR and CDCl₃: δ = 77.0 ppm for ¹³C NMR). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constants (Hz), and integration. The full-scan mass spectra were taken on a hybrid quadrupole-orbitrap mass spectrometer equipped with a heated electrospray ionization source (ThermoFischer Scientific, Bremen, Germany). Mass spectra were recorded on a THERMO FINNIGAN LTQ-XL. The MS inlet capillary temp always maintained at 275 °C and capillary voltage at 5 kV. No other source gases were used when digestion was performed in microdroplets. The samples were dissolved in 1:1 methanol:water.

2 Optimization of reaction conditions

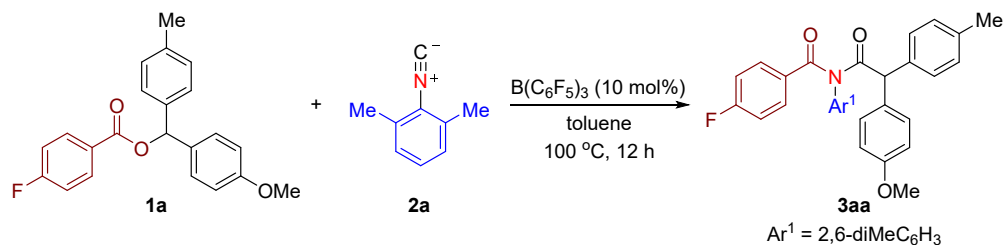
(a) Catalyst optimization^a



Entry	catalyst	yield (%) ^b
1	B(C ₆ F ₅) ₃	23
2	Zn(OTf) ₂	0
3	Sc(OTf) ₃	0
4	Cu(OTf) ₂	0
5	BF ₃ ·Et ₂ O	0
6	FeCl ₃	0
7	AlCl ₃	18
8	AgClO ₄	23
9	CF ₃ COOH	0
10	CF ₃ SO ₃ H	0

^aReaction conditions: **1a** (0.2 mmol), **2a** (0.3 mmol) and catalyst (10 mol %) in toluene (2 mL) stirred at 100 °C for 12 h. ^bThe yields were determined by ¹H NMR spectroscopy using CH₂Br₂ as the internal standard.

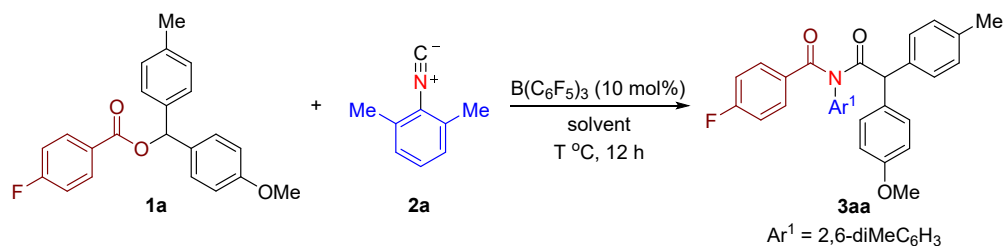
(b) Rejection time optimization^a



entry	rejection time (min)	yield (%) ^b
1	100	73
2	50	84
3	25	98
4	0	23

^aReaction conditions: A mixture of **1a** (0.2 mmol) and **2a** (0.3 mmol) in toluene (1 mL) was added dropwise to the solution of B(C₆F₅)₃ (10 mol%) at 100 °C by using a syringe pump. After addition, the reaction mixture was further stirred for 12 h. ^bThe yields were determined by ¹H NMR spectroscopy using CH₂Br₂ as the internal standard.

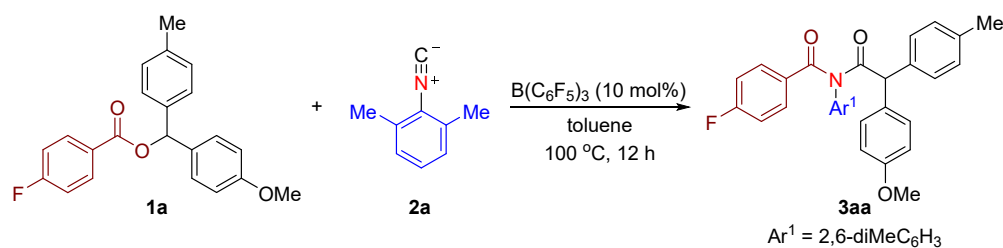
(c) Solvent optimization^a



Entry	solvent	T (°C)	yield (%) ^b
1	toluene	100	98
2	hexane	64	0
3	THF	64	0
4	DCE	80	0
5	EtOAc	72	0
6	HFIP	57	10
7	PhCl	100	97
8	CHCl ₃	57	0

^aReaction conditions: A mixture of **1a** (0.2 mmol) and **2a** (0.3 mmol) in solvent (1 mL) was added dropwise to the solution of B(C₆F₅)₃ (10 mol%) for 25 min at 100 °C by using a syringe pump. After addition, the reaction mixture was further stirred for 12 h. ^bThe yields were determined by ¹H NMR spectroscopy using CH₂Br₂ as the internal standard.

(d) Other optimizations^a

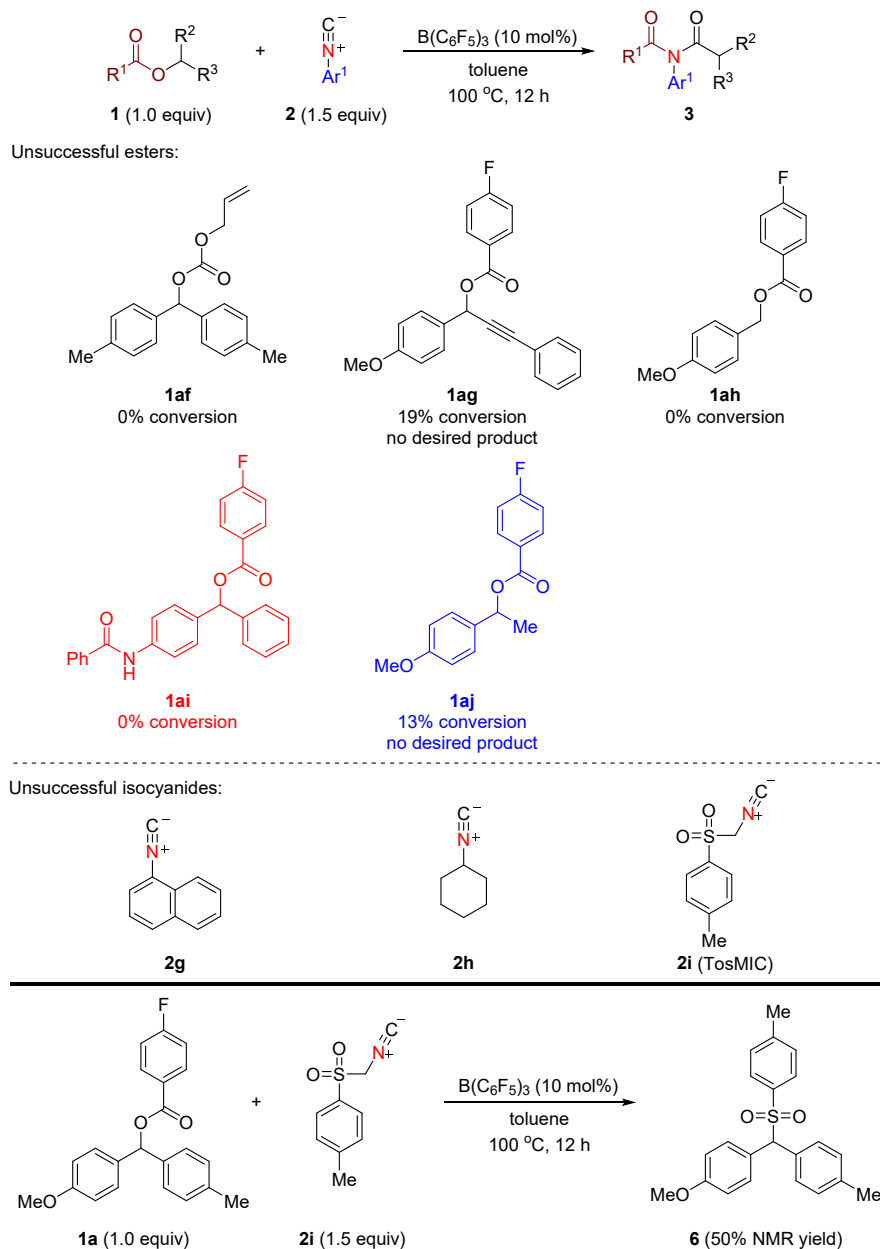


entry	Variation from standard conditions	yield (%) ^b
1	Run at 90 °C	84
2	Run at 80 °C	83
3	B(C ₆ F ₅) ₃ (5 mol%) was used	32
4	B(C ₆ F ₅) ₃ (2.5 mol%) was used	25
5	B(C ₆ F ₅) ₃ (10 mol%) and Mes ₃ P (10 mol%) was used	0

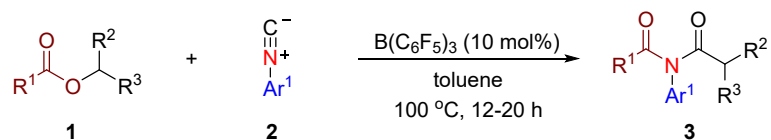
^aReaction conditions: A mixture of **1a** (0.2 mmol) and **2a** (0.3 mmol) in toluene (1 mL) was added dropwise to the solution of B(C₆F₅)₃ (10 mol%) for 25 min at 100 °C by using a syringe pump. After addition, the reaction mixture was further stirred for 12 h. ^bThe yields were determined by ¹H NMR spectroscopy using CH₂Br₂ as the internal standard.

3 Unsuccessful Substrates

Ester **1af**, **1ag**, **1ah**, **1ai** and **1aj** were unreactive in the B(C₆F₅)₃-catalyzed protocol. No target product be obtained by using isocyanide **2g** and **2h**. Interestingly, the metal-free direct sulfonylation of ester was realized under the current reaction conditions by means of TosMIC **2i** as substrate.



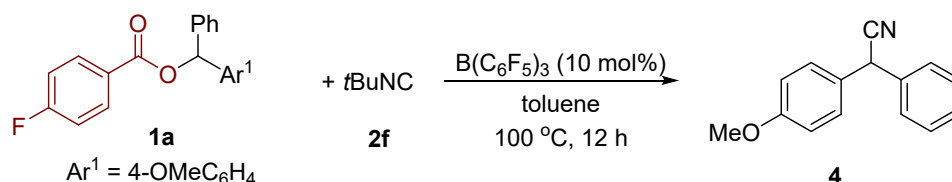
4 General Procedure for B(C₆F₅)₃ Catalyzed Isocyanide Insertions (GP)



In glove box, to a flame-dried Schlenk tube A is charged with the B(C₆F₅)₃ (10.2 mg, 0.02 mmol, 10 mol %) and toluene (0.5 mL). The solution of B(C₆F₅)₃ is removed from the glovebox and stirred at 100 °C. Then, a solution of ester **1** (0.2 mmol, 1.0 equiv) and isocyanide **2** (0.3 mmol, 1.5 equiv) in toluene (1.0 mL) is added dropwise to tube A for 25 min by using a syringe pump. After addition, the reaction was further stirred

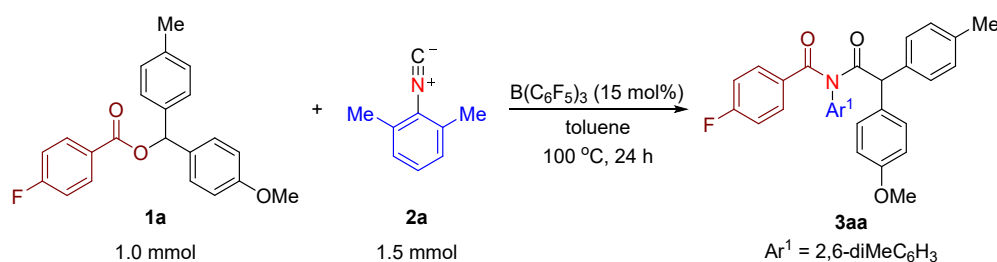
for 12-20 h at 100 °C. Evaporation of the solvents under reduced pressure afforded the crude title compound. Purification by flash column chromatography using the indicated mixtures of solvents as eluent yields the analytical pure imides **3**.

5 Direct Cyanation of Ester



In glove box, to a flame-dried Schlenk tube A is charged with the B(C₆F₅)₃ (10.2 mg, 0.02 mmol, 10 mol %) and toluene (0.5 mL). The solution of B(C₆F₅)₃ is removed from the glovebox and stirred at 100 °C. Then, a solution of ester **1a** (67.3 mg, 0.2 mmol, 1.0 equiv) and *tert*-butyl isocyanide **2f** (24.9 mg, 0.3 mmol, 1.5 equiv) in toluene (1.0 mL) is added dropwise to tube A for 25 min by using a syringe pump. After addition, the reaction was further stirred for 12 h at 100 °C. Evaporation of the solvents under reduced pressure afforded the crude title compound. Purification by flash column chromatography using petroleum ether/EtOAc (10/1) to afford 2-(4-methoxyphenyl)-2-phenylacetonitrile **4** (white solid, 42.9 mg, 96% yield).

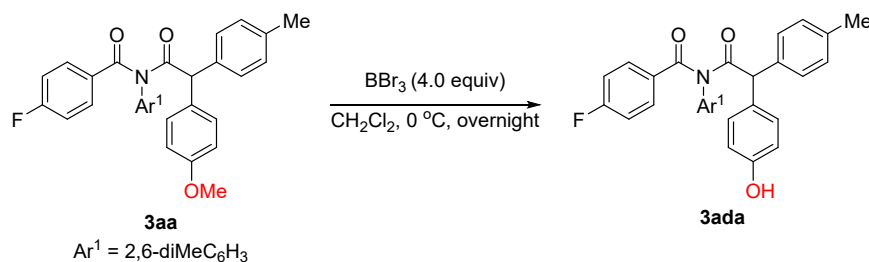
6 Scale-Up Experiment



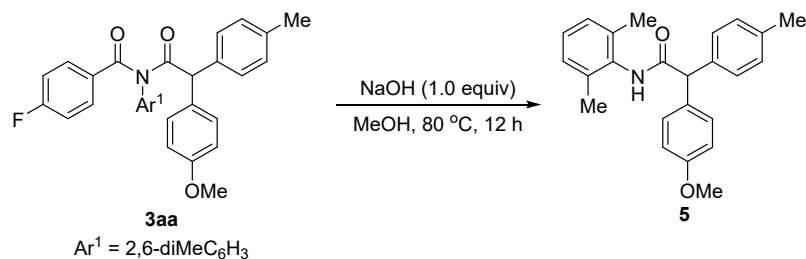
In glove box, to a flame-dried Schlenk tube A is charged with the B(C₆F₅)₃ (76.8 mg, 0.15 mmol, 15 mol %) and toluene (2.5 mL). The solution of B(C₆F₅)₃ is removed from the glovebox and stirred at 100 °C. Then, a solution of ester **1a** (350.4 mg, 1.0 mmol, 1.0 equiv) and isocyanide **2a** (196.8 mg, 1.5 mmol, 1.5 equiv) in toluene (5.0 mL) is added dropwise to tube A for 60 min by using a syringe pump. After addition, the

reaction was further stirred for 24 h at 100 °C. After the reaction completion, the mixture was evaporated under reduced pressure. Purification by flash column chromatography using petroleum ether/EtOAc (15/1) to afford pure product **3aa** (346.7 mg) in 72% yield.

7 Synthetic Transformations



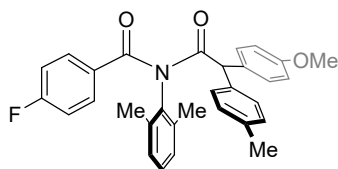
Synthesis of (3ada)^[5]: To a solution of **3aa** (0.2 mmol, 1.0 equiv, 96.3 mg) in anhydrous CH₂Cl₂ (2 mL) was added 1 M solution of boron tribromide in CH₂Cl₂ (0.8 mmol, 4.0 equiv, 0.8 mL) dropwise at 0 °C. After stirring at room temperature overnight, the reaction was quenched by the addition of water. The mixture was partitioned between ethyl acetate and water. The phases were separated, and the aqueous phase was extracted with additional ethyl acetate. The combined organic phases were washed with brine and dried over magnesium sulfate. The solution was concentrated under reduced pressure. Purification by flash column chromatography using petroleum ether/EtOAc (3/1) to afford pure product **3ada** (yellow oil, 69.6 mg) in 75% yield.



Synthesis of (5)^[6]: A solution of **3aa** (0.2 mmol, 1.0 equiv, 96.3 mg) and NaOH (0.2 mmol, 1.0 equiv, 8 mg) in MeOH (4.0 mL) was refluxed in an oil bath for 12 hours. After cooled to room temperature, the solvent was removed under reduced pressure.

The contents were subjected to flash chromatography ether/EtOAc (5/1) to give the product **5** as yellow oil (56.7 mg, 82%).

8 Characterization Data of the Products



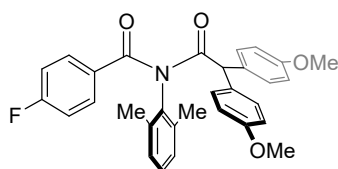
3aa

$C_{31}H_{28}FNO_3$
M = 481.57 g/mol

***N*-(2,6-dimethylphenyl)-4-fluoro-*N*-(2-(4-methoxyphenyl)-2-(*p*-tolyl)acetyl)benzamide**

(3aa): Prepared from 2-isocyano-1,3-dimethylbenzene (**2a**, 39.4 mg, 0.3 mmol) and (4-methoxyphenyl)(*p*-tolyl)methyl 4-fluorobenzoate (**1a**, 70.1 mg, 0.2 mmol) at 100 °C for 12 h according to the **GP**. Purification by flash chromatography on silica gel using petroleum ether/EtOAc (10/1 to 5/1) afforded **3aa** as a yellow oil (86.7 mg, 90% yield).

3aa: R_f = 0.30 (petroleum ether/EtOAc = 15/1). **1H NMR** (400 MHz, $CDCl_3$): δ 7.58–7.55 (m, 2H), 7.28–7.23 (m, 1H), 7.13–7.07 (m, 8H), 7.03–6.99 (m, 2H), 6.80 (d, J = 8.4 Hz, 2H), 4.82 (s, 1H), 3.75 (s, 3H), 2.29 (s, 3H), 2.00 (s, 6H) ppm. **^{13}C NMR** (100 MHz, $CDCl_3$): δ 175.4, 171.3, 164.7 (d, J = 251.3 Hz), 159.0, 137.2, 137.04, 136.99, 135.4, 132.0 (d, J = 3.3 Hz), 130.6 (d, J = 9.0 Hz), 130.4, 129.8, 129.3, 129.11, 129.09, 128.5, 115.3 (d, J = 21.9 Hz), 114.0, 55.7, 55.2, 21.0, 18.3 ppm. **^{19}F NMR** (376 MHz, $CDCl_3$) δ -107.06 (s) ppm. **HRMS** (ESI) m/z : $[M+Na]^+$ calcd. for $C_{31}H_{28}FNNaO_3$: 504.1945; Found: 504.1941.



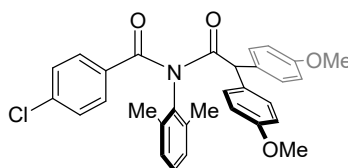
3ba

$C_{31}H_{28}FNO_4$
M = 497.57 g/mol

***N*-(2,2-bis(4-methoxyphenyl)acetyl)-*N*-(2,6-dimethylphenyl)-4-fluorobenzamide (3ba):**

Prepared from 2-isocyano-1,3-dimethylbenzene (**2a**, 39.4 mg, 0.3 mmol) and bis(4-methoxyphenyl)methyl 4-fluorobenzoate (**1b**, 87.9 mg, 0.2 mmol) at 100 °C for 12 h according to the **GP**. Purification by flash chromatography on silica gel using petroleum ether/EtOAc (20/1 to 10/1) afforded **3ba** as a yellow oil (89.7 mg, 90% yield).

3ba: R_f = 0.4 (petroleum ether/EtOAc = 10/1). **¹H NMR** (400 MHz, CDCl₃): δ 7.58–7.55 (m, 2H), 7.30–7.25 (m, 1H), 7.16–7.12 (m, 6H), 7.04–7.00 (m, 2H), 6.81 (d, J = 8.8 Hz, 4H), 4.80 (s, 1H), 3.77 (s, 6H), 2.00 (s, 6H) ppm. **¹³C NMR** (100 MHz, CDCl₃): δ 175.6, 171.3, 164.7 (d, J = 251.4 Hz), 158.9, 136.99, 136.95, 132.0 (d, J = 3.2 Hz), 130.6 (d, J = 8.9 Hz), 130.5, 129.8, 129.3, 129.1, 115.3 (d, J = 22.0 Hz), 113.9, 55.24, 55.21, 18.3 ppm. **¹⁹F NMR** (376 MHz, CDCl₃) δ -107.08 (s) ppm. **HRMS** (ESI) m/z : [M+Na]⁺ calcd. for C₃₁H₂₈FNNaO₄: 520.1895; Found: 520.1895.



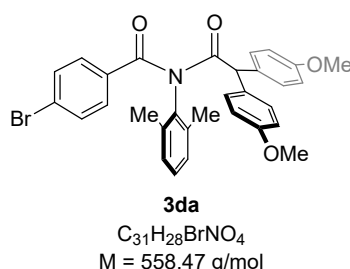
3ca
C₃₁H₂₈ClNO₄
M = 514.02 g/mol

***N*-(2,2-bis(4-methoxyphenyl)acetyl)-4-chloro-*N*-(2,6-dimethylphenyl)benzamide (3ca):**

Prepared from 2-isocyano-1,3-dimethylbenzene (**2a**, 39.4 mg, 0.3 mmol) and bis(4-methoxyphenyl)methyl 4-chlorobenzoate (**1c**, 91.9 mg, 0.2 mmol) at 100 °C for 12 h according to the **GP**. Purification by flash chromatography on silica gel using petroleum ether/EtOAc (20/1 to 10/1) afforded **3ca** as a white solid (88.3 mg, 86% yield); mp 134–136 °C.

3ca: R_f = 0.40 (petroleum ether/EtOAc = 10/1). **¹H NMR** (400 MHz, CDCl₃): δ 7.48 (d, J = 7.2 Hz, 2H), 7.33 (d, J = 7.6 Hz, 2H), 7.29–7.25 (m, 1H), 7.16 (d, J = 7.6 Hz, 2H), 7.12 (d, J = 7.6 Hz, 4H), 6.82 (d, J = 7.6 Hz, 4H), 4.78 (s, 1H), 3.77 (s, 6H), 2.00 (s, 6H) ppm. **¹³C NMR** (100 MHz, CDCl₃): δ 175.5, 171.5, 159.0, 137.8, 137.0, 136.8,

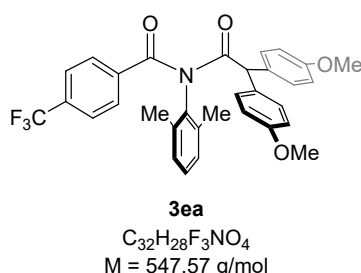
134.3, 130.4, 129.8, 129.4, 129.3, 129.1, 128.5, 114.0, 55.3, 55.2, 18.3 ppm. **HRMS** (ESI) m/z : $[M+Na]^+$ calcd. for $C_{31}H_{28}BrNO_4$: 536.1599; Found: 536.1610.



***N*-(2,2-bis(4-methoxyphenyl)acetyl)-4-bromo-*N*-(2,6-dimethylphenyl)benzamide (3da):**

Prepared from 2-isocyano-1,3-dimethylbenzene (**2a**, 39.4 mg, 0.3 mmol) and bis(4-methoxyphenyl)methyl 4-bromobenzoate (**1d**, 85.5 mg, 0.2 mmol) at 100 °C for 12 h according to the **GP**. Purification by flash chromatography on silica gel using petroleum ether/EtOAc (20/1 to 10/1) afforded **3da** as a yellow oil (88.0 mg, 79% yield).

3da: R_f = 0.40 (petroleum ether/EtOAc = 10/1). **1H NMR** (400 MHz, $CDCl_3$): δ 7.49 (d, J = 4.2 Hz, 2H), 7.40 (d, J = 4.4 Hz, 2H), 7.30–7.26 (m, 1H), 7.15 (d, J = 7.6 Hz, 2H), 7.12 (d, J = 8.4 Hz, 4H), 6.81 (d, J = 8.4 Hz, 4H), 4.78 (s, 1H), 3.76 (s, 6H), 1.99 (s, 6H) ppm. **^{13}C NMR** (100 MHz, $CDCl_3$): δ 175.5, 171.6, 158.9, 136.9, 136.7, 134.8, 131.4, 130.3, 129.8, 129.5, 129.4, 129.1, 126.3, 113.9, 55.24, 55.16, 18.3 ppm. **HRMS** (ESI) m/z : $[M+Na]^+$ calcd. for $C_{31}H_{28}BrNNaO_4$: 580.1094; Found: 580.1092.

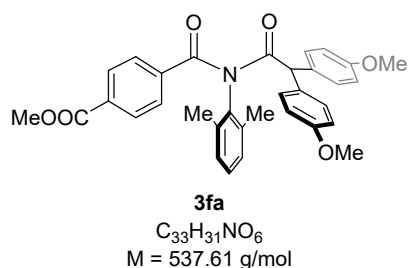


***N*-(2,2-bis(4-methoxyphenyl)acetyl)-*N*-(2,6-dimethylphenyl)-4-(trifluoromethyl)benzamide (3ea):**

Prepared from 2-isocyano-1,3-dimethylbenzene (**2a**, 39.4 mg, 0.3 mmol) and bis(4-methoxyphenyl)methyl 4-(trifluoromethyl)benzoate (**1e**, 83.3 mg, 0.2 mmol) at 100 °C for 12 h according to the **GP**. Purification by flash chromatography on silica

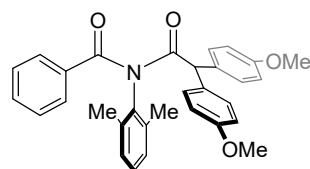
gel using petroleum ether/EtOAc (20/1 to 10/1) afforded **3ea** as a yellow oil (90.5 mg, 83% yield).

3ea: R_f = 0.35 (petroleum ether/EtOAc = 10/1). $^1\text{H NMR}$ (400 MHz, CDCl_3): δ 7.63 (s, 4H), 7.33–7.29 (m, 1H), 7.18 (d, J = 7.6 Hz, 2H), 7.09 (d, J = 8.4 Hz, 4H), 6.82 (d, J = 8.4 Hz, 4H), 4.76 (s, 1H), 3.77 (s, 6H), 2.01 (s, 6H) ppm. $^{13}\text{C NMR}$ (100 MHz, CDCl_3): δ 175.5, 171.3, 159.0, 139.5, 136.9, 136.4, 132.8 (q, J = 32.2 Hz), 130.0, 129.8, 129.5, 129.2, 127.9, 125.2 (q, J = 3.6 Hz), 123.6 (q, J = 271.1 Hz), 114.0, 55.2, 55.1, 18.2 ppm. $^{19}\text{F NMR}$ (376 MHz, CDCl_3) δ -62.91 (s) ppm. **HRMS** (ESI) m/z : $[\text{M}+\text{Na}]^+$ calcd. for $\text{C}_{32}\text{H}_{28}\text{F}_3\text{NNaO}_4$: 570.1863; Found: 570.1864.



Methyl 4-((2,2-bis(4-methoxyphenyl)acetyl)(2,6-dimethylphenyl)carbamoyl)benzoate (**3fa**: Prepared from 2-isocyano-1,3-dimethylbenzene (**2a**, 39.4 mg, 0.3 mmol) and bis(4-methoxyphenyl)methyl methyl terephthalate (**1f**, 81.3 mg, 0.2 mmol) at 100 °C for 12 h according to the **GP**. Purification by flash chromatography on silica gel using petroleum ether/EtOAc (20/1 to 10/1) afforded **3fa** as a yellow oil (83.9 mg, 78% yield).

3fa: R_f = 0.30 (petroleum ether/EtOAc = 10/1). $^1\text{H NMR}$ (400 MHz, CDCl_3): δ 8.04 (d, J = 8.0 Hz, 2H), 7.58 (d, J = 8.4 Hz, 2H), 7.32–7.28 (m, 1H), 7.17 (d, J = 7.6 Hz, 2H), 7.09 (d, J = 8.4 Hz, 4H), 6.81 (d, J = 8.4 Hz, 4H), 4.78 (s, 1H), 3.94 (s, 3H), 3.77 (s, 6H), 2.01 (s, 6H) ppm. $^{13}\text{C NMR}$ (100 MHz, CDCl_3): δ 175.4, 171.8, 166.2, 159.0, 140.2, 136.9, 136.5, 132.3, 130.1, 129.8, 129.4, 129.2, 127.5, 114.0, 55.2, 55.1, 52.3, 18.3 ppm. **HRMS** (ESI) m/z : $[\text{M}+\text{Na}]^+$ calcd. for $\text{C}_{33}\text{H}_{31}\text{NNO}_6$: 560.2044; Found: 560.2044.

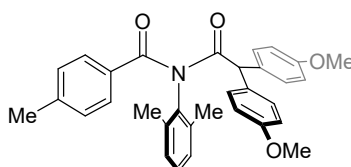
**3ga**

$C_{31}H_{29}NO_4$
M = 479.58 g/mol

***N*-(2,2-bis(4-methoxyphenyl)acetyl)-*N*-(2,6-dimethylphenyl)benzamide (3ga):**

Prepared from 2-isocyano-1,3-dimethylbenzene (**2a**, 39.4 mg, 0.3 mmol) and bis(4-methoxyphenyl)methyl benzoate (**1a**, 69.7 mg, 0.2 mmol) at 100 °C for 12 h according to the **GP**. Purification by flash chromatography on silica gel using petroleum ether/EtOAc (20/1 to 10/1) afforded **3ga** as a yellow oil (83.6 mg, 87% yield).

3ga: R_f = 0.45 (petroleum ether/EtOAc = 10/1). **¹H NMR** (400 MHz, $CDCl_3$): δ 7.56 (d, J = 7.2 Hz, 2H), 7.48–7.45 (m, 1H), 7.36–7.33 (m, 2H), 7.28–7.25 (m, 1H), 7.14 (d, J = 8.0 Hz, 6H), 6.81 (d, J = 7.2 Hz, 4H), 4.83 (s, 1H), 3.76 (s, 6H), 2.02 (s, 6H) ppm. **¹³C NMR** (100 MHz, $CDCl_3$): δ 175.4, 172.5, 158.8, 136.98, 136.96, 135.9, 131.5, 130.5, 129.8, 129.2, 129.0, 128.1, 127.9, 113.8, 55.2, 18.3 ppm. **HRMS** (ESI) m/z : $[M+Na]^+$ calcd. for $C_{31}H_{29}NNaO_4$: 502.1989; Found: 502.1989.

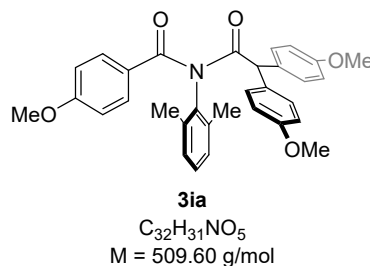
**3ha**

$C_{32}H_{31}NO_4$
M = 493.60 g/mol

***N*-(2,2-bis(4-methoxyphenyl)acetyl)-*N*-(2,6-dimethylphenyl)-4-methylbenzamide (3ha):**

Prepared from 2-isocyano-1,3-dimethylbenzene (**2a**, 39.4 mg, 0.3 mmol) and bis(4-methoxyphenyl)methyl 4-methylbenzoate (**1h**, 72.5 mg, 0.2 mmol) at 100 °C for 12 h according to the **GP**. Purification by flash chromatography on silica gel using petroleum ether/EtOAc (20/1 to 10/1) afforded **3ha** as a white solid (75.9 mg, 77% yield); mp 162–164 °C.

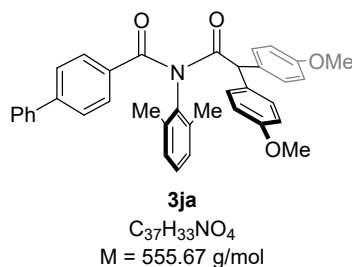
3ha: $R_f = 0.40$ (petroleum ether/EtOAc = 10/1). **$^1\text{H NMR}$** (400 MHz, CDCl_3): δ 7.47 (d, $J = 8.0$ Hz, 2H), 7.26 – 7.24 (m, 1H), 7.16 – 7.12 (m, 8H), 6.81 (d, $J = 8.8$ Hz, 4H), 4.83 (s, 1H), 3.76 (s, 6H), 2.37 (s, 3H), 2.01 (s, 6H) ppm. **$^{13}\text{C NMR}$** (100 MHz, CDCl_3): δ 175.5, 172.4, 158.8, 142.3, 137.2, 137.1, 132.9, 130.7, 129.8, 129.1, 129.0, 128.8, 128.3, 113.8, 55.3, 55.2, 21.6, 18.3 ppm. **HRMS** (ESI) m/z : $[\text{M}+\text{Na}]^+$ calcd. for $\text{C}_{32}\text{H}_{31}\text{NNaO}_4$: 516.2145; Found: 516.2144.



***N*-(2,2-bis(4-methoxyphenyl)acetyl)-*N*-(2,6-dimethylphenyl)-4-methoxybenzamide**

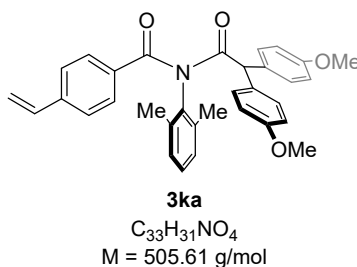
(3ia): Prepared from 2-isocyano-1,3-dimethylbenzene (**2a**, 39.4 mg, 0.3 mmol) and bis(4-methoxyphenyl)methyl 4-methoxybenzoate (**1i**, 75.7 mg, 0.2 mmol) at 100 °C for 12 h according to the **GP**. Purification by flash chromatography on silica gel using petroleum ether/EtOAc (20/1 to 10/1) afforded **3ia** as a yellow oil (68.6 mg, 67% yield).

3ia: $R_f = 0.30$ (petroleum ether/EtOAc = 10/1). **$^1\text{H NMR}$** (400 MHz, CDCl_3): δ 7.56 (d, $J = 8.8$ Hz, 2H), 7.27–7.23 (m, 1H), 7.17 (d, $J = 8.4$ Hz, 4H), 7.12 (d, $J = 7.6$ Hz, 2H), 6.81 (d, $J = 8.4$ Hz, 6H), 4.86 (s, 1H), 3.83 (s, 3H), 3.77 (s, 6H), 2.00 (s, 6H) ppm. **$^{13}\text{C NMR}$** (100 MHz, CDCl_3): δ 175.6, 171.8, 162.5, 158.8, 137.4, 137.1, 130.9, 130.7, 129.8, 129.03, 129.00, 127.7, 113.9, 113.4, 55.4, 55.3, 55.2, 18.4 ppm. **HRMS** (ESI) m/z : $[\text{M}+\text{Na}]^+$ calcd. for $\text{C}_{32}\text{H}_{31}\text{NNaO}_5$: 532.2094; Found: 532.2094.



***N*-(2,2-bis(4-methoxyphenyl)acetyl)-*N*-(2,6-dimethylphenyl)-[1,1'-biphenyl]-4-carboxamide (3ja**: Prepared from 2-isocyno-1,3-dimethylbenzene (**2a**, 39.4 mg, 0.3 mmol) and bis(4-methoxyphenyl)methyl [1,1'-biphenyl]-4-carboxylate (**1j**, 84.9 mg, 0.2 mmol) at 100 °C for 12 h according to the **GP**. Purification by flash chromatography on silica gel using petroleum ether/EtOAc (20/1 to 10/1) afforded **3ja** as a white solid (77.8 mg, 70% yield); mp 78–80 °C.

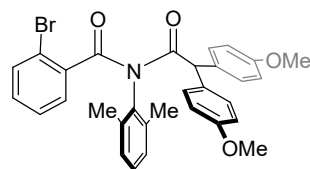
3ja: R_f = 0.40 (petroleum ether/EtOAc = 10/1). **¹H NMR** (400 MHz, CDCl₃): δ 7.65 (d, J = 8.0 Hz, 2H), 7.61–7.56 (m, 4H), 7.47–7.44 (m, 2H), 7.40–7.36 (m, 1H), 7.30–7.26 (m, 1H), 7.16 (d, J = 8.4 Hz, 6H), 6.82 (d, J = 8.8 Hz, 4H), 4.84 (s, 1H), 3.77 (s, 6H), 2.04 (s, 6H) ppm. **¹³C NMR** (100 MHz, CDCl₃): δ 175.5, 172.3, 158.9, 144.5, 140.1, 137.1, 134.5, 130.6, 129.8, 129.2, 129.1, 128.8, 128.7, 127.9, 127.3, 126.9, 113.9, 55.3, 55.2, 18.4 ppm. **HRMS** (ESI) m/z : [M+Na]⁺ calcd. for C₃₇H₃₃NNaO₄: 578.2302; Found: 578.2302.



***N*-(2,2-bis(4-methoxyphenyl)acetyl)-*N*-(2,6-dimethylphenyl)-4-vinylbenzamide (3ka**: Prepared from 2-isocyno-1,3-dimethylbenzene (**2a**, 39.4 mg, 0.3 mmol) and bis(4-methoxyphenyl)methyl 4-vinylbenzoate (**1k**, 74.9 mg, 0.2 mmol) at 100 °C for 12 h according to the **GP**. Purification by flash chromatography on silica gel using petroleum ether/EtOAc (20/1 to 10/1) afforded **3ka** as a white solid (64.7 mg, 64% yield); mp 123–125 °C.

3ka: R_f = 0.40 (petroleum ether/EtOAc = 10/1). **¹H NMR** (400 MHz, CDCl₃): δ 7.53 (d, J = 8.0 Hz, 2H), 7.37 (d, J = 8.4 Hz, 2H), 7.26 (t, J = 7.6 Hz, 1H), 7.16–7.13 (m, 6H), 6.81 (d, J = 8.8 Hz, 4H), 6.71 (dd, J = 17.6, 11.2 Hz, 1H), 5.81 (d, J = 17.6 Hz, 1H), 5.34 (d, J = 10.8 Hz, 1H), 4.83 (s, 1H), 3.76 (s, 6H), 2.01 (s, 6H) ppm. **¹³C NMR** (100

MHz, CDCl₃): δ 175.5, 172.1, 158.9, 140.8, 137.1, 137.0, 136.0, 139.4, 130.6, 129.8, 129.2, 129.0, 128.5, 125.9, 116.1, 113.9, 55.3, 55.2, 18.3 ppm. **HRMS** (ESI) m/z : [M+Na]⁺ calcd. for C₃₃H₃₁NNaO₄: 528.2145; Found: 528.2145.

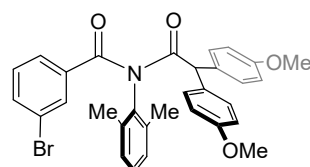
**3la**

C₃₁H₂₈BrNO₄
M = 558.47 g/mol

***N*-(2,2-bis(4-methoxyphenyl)acetyl)-2-bromo-*N*-(2,6-dimethylphenyl)benzamide (3la:**

Prepared from 2-isocyano-1,3-dimethylbenzene (**2a**, 39.4 mg, 0.3 mmol) and bis(4-methoxyphenyl)methyl 2-bromobenzoate (**11**, 85.5 mg, 0.2 mmol) at 100 °C for 12 h according to the **GP**. Purification by flash chromatography on silica gel using petroleum ether/EtOAc (20/1 to 10/1) afforded **3la** as a white solid (100.5 mg, 90% yield); mp 134–136 °C.

3la: R_f = 0.30 (petroleum ether/EtOAc = 10/1). **¹H NMR** (400 MHz, CDCl₃): δ 7.61 (d, J = 78.0 Hz, 1H), 7.33–7.29 (m, 2H), 7.28–7.23 (m, 1H), 7.18 (d, J = 7.6 Hz, 2H), 7.14–7.12 (m, 1H), 6.93 (d, J = 8.4 Hz, 4H), 6.76 (d, J = 8.8 Hz, 4H), 4.65 (s, 1H), 3.75 (s, 6H), 2.03 (s, 6H) ppm. **¹³C NMR** (100 MHz, CDCl₃): δ 173.9, 169.3, 158.9, 140.3, 137.0, 135.7, 133.0, 130.1, 129.9, 129.8, 129.4, 129.1, 126.8, 125.8, 119.2, 113.9, 55.3, 55.2, 18.1 ppm. **HRMS** (ESI) m/z : [M+Na]⁺ calcd. for C₃₁H₂₈BrNNaO₄: 580.1094; Found: 580.1094.

**3ma**

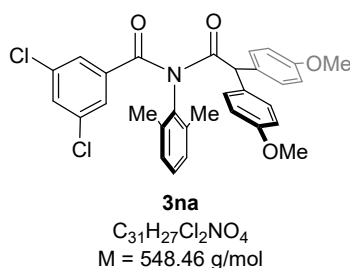
C₃₁H₂₈BrNO₄
M = 558.47 g/mol

***N*-(2,2-bis(4-methoxyphenyl)acetyl)-3-bromo-*N*-(2,6-dimethylphenyl)benzamide (3ma:**

Prepared from 2-isocyano-1,3-dimethylbenzene (**2a**, 39.4 mg, 0.3 mmol) and bis(4-

methoxyphenyl)methyl 3-bromobenzoate (**1m**, 85.5 mg, 0.2 mmol) at 100 °C for 12 h according to the **GP**. Purification by flash chromatography on silica gel using petroleum ether/EtOAc (10/1 to 5/1) afforded **3ma** as a yellow oil (89.4 mg, 80% yield).

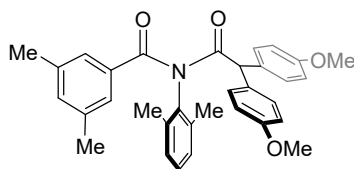
3ma: R_f = 0.40 (petroleum ether/EtOAc = 10/1). **$^1\text{H NMR}$** (400 MHz, CDCl_3): δ 7.66 (s, 1H), 7.60 (d, J = 8.0 Hz, 1H), 7.49 (d, J = 7.6 Hz, 1H), 7.31–7.23 (m, 2H), 7.17 (d, J = 7.6 Hz, 2H), 7.09 (d, J = 8.8 Hz, 4H), 6.83 (d, J = 8.4 Hz, 4H), 4.74 (s, 1H), 3.76 (s, 6H), 1.99 (s, 6H) ppm. **$^{13}\text{C NMR}$** (100 MHz, CDCl_3): δ 175.5, 171.1, 158.9, 137.9, 136.9, 136.6, 134.3, 130.4, 130.0, 129.84, 129.78, 129.4, 129.2, 126.4, 122.0, 114.1, 55.2, 55.1, 18.3 ppm. **HRMS** (ESI) m/z : $[\text{M}+\text{Na}]^+$ calcd. for $\text{C}_{31}\text{H}_{28}\text{BrNNaO}_4$: 580.1094; Found: 580.1094.



***N*-(2,2-bis(4-methoxyphenyl)acetyl)-3,5-dichloro-*N*-(2,6-dimethylphenyl)benzamide**

3na: Prepared from 2-isocyno-1,3-dimethylbenzene (**2a**, 39.4 mg, 0.3 mmol) and bis(4-methoxyphenyl)methyl 3,5-dichlorobenzoate (**1n**, 83.5 mg, 0.2 mmol) at 100 °C for 12 h according to the **GP**. Purification by flash chromatography on silica gel using petroleum ether/EtOAc (10/1 to 5/1) afforded **3na** as a white solid (104.2 mg, 95% yield); mp 132–134 °C.

3na: R_f = 0.30 (petroleum ether/EtOAc = 10/1). **$^1\text{H NMR}$** (400 MHz, CDCl_3): δ 7.46 (s, 1H), 7.40 (s, 2H), 7.33–7.30 (m, 1H), 7.19 (d, J = 7.6 Hz, 2H), 7.07 (d, J = 8.8 Hz, 4H), 6.84 (d, J = 8.4 Hz, 4H), 4.69 (s, 1H), 3.77 (s, 6H), 1.98 (s, 6H) ppm. **$^{13}\text{C NMR}$** (100 MHz, CDCl_3): δ 175.6, 170.1, 159.0, 138.8, 136.9, 136.3, 135.0, 131.2, 129.8, 129.7, 129.6, 129.3, 125.9, 114.2, 55.3, 55.1, 18.2 ppm. **HRMS** (ESI) m/z : $[\text{M}+\text{Na}]^+$ calcd. for $\text{C}_{31}\text{H}_{27}\text{Cl}_2\text{NNaO}_4$: 570.1209; Found: 570.1206.

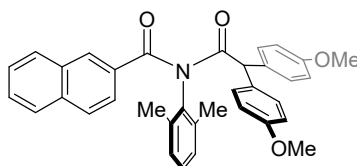
**3oa**

$C_{33}H_{33}NO_4$
M = 507.63 g/mol

***N*-(2,2-bis(4-methoxyphenyl)acetyl)-*N*-(2,6-dimethylphenyl)-3,5-dimethylbenzamide**

3oa: Prepared from 2-isocyano-1,3-dimethylbenzene (**2a**, 39.4 mg, 0.3 mmol) and bis(4-methoxyphenyl)methyl 3,5-dimethylbenzoate (**1o**, 75.3 mg, 0.2 mmol) at 100 °C for 12 h according to the **GP**. Purification by flash chromatography on silica gel using petroleum ether/EtOAc (20/1 to 10/1) afforded **3oa** as a white solid (81.2 mg, 80% yield); mp 134–136 °C.

3oa: R_f = 0.40 (petroleum ether/EtOAc = 10/1). **¹H NMR** (400 MHz, $CDCl_3$): δ 7.29–7.24 (m, 1H), 7.17–7.10 (m, 9H), 6.80 (d, J = 8.8 Hz, 4H), 4.75 (s, 1H), 3.76 (s, 6H), 2.27 (s, 6H), 2.02 (s, 6H) ppm. **¹³C NMR** (100 MHz, $CDCl_3$): δ 175.5, 172.8, 158.8, 137.7, 137.1, 137.1, 135.7, 133.4, 130.7, 129.8, 129.2, 129.1, 125.7, 113.9, 55.23, 55.20, 21.2, 18.4 ppm. **HRMS** (ESI) m/z : $[M+Na]^+$ calcd. for $C_{33}H_{33}NNaO_4$: 530.2302; Found: 530.2304.

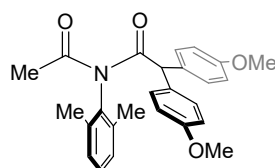
**3pa**

$C_{35}H_{31}NO_4$
M = 529.64 g/mol

***N*-(2,2-bis(4-methoxyphenyl)acetyl)-*N*-(2,6-dimethylphenyl)-1-naphthamide** (**3pa**:

Prepared from 2-isocyano-1,3-dimethylbenzene (**2a**, 39.4 mg, 0.3 mmol) and bis(4-methoxyphenyl)methyl 1-naphthoate (**1p**, 79.7 mg, 0.2 mmol) at 100 °C for 12 h according to the **GP**. Purification by flash chromatography on silica gel using petroleum ether/EtOAc (20/1 to 10/1) afforded **3pa** as a white solid (98.5 mg, 93% yield); mp 124–126 °C.

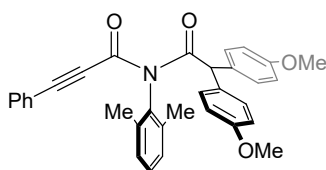
3pa: R_f = 0.40 (petroleum ether/EtOAc = 10/1). **$^1\text{H NMR}$** (400 MHz, CDCl_3): δ 8.06 (s, 1H), 7.85–7.80 (m, 2H), 7.75 (d, J = 8.0 Hz, 1H), 7.63 (d, J = 8.8 Hz, 1H), 7.56–7.48 (m, 2H), 7.31–7.27 (m, 1H), 7.18–7.15 (m, 6H), 6.82 (d, J = 8.0 Hz, 4H), 4.84 (s, 1H), 3.78 (s, 6H), 2.08 (s, 6H) ppm. **$^{13}\text{C NMR}$** (100 MHz, CDCl_3): δ 175.6, 172.6, 158.9, 137.1, 134.8, 133.1, 132.4, 130.6, 129.8, 129.3, 129.1, 129.0, 128.8, 127.9, 127.8, 127.7, 126.5, 124.5, 113.9, 55.3, 55.2, 18.4 ppm. **HRMS** (ESI) m/z : $[\text{M}+\text{Na}]^+$ calcd. for $\text{C}_{35}\text{H}_{31}\text{NNaO}_4$: 552.2145; Found: 552.2144.



3qa
 $\text{C}_{26}\text{H}_{27}\text{NO}_4$
 $M = 417.51 \text{ g/mol}$

***N*-acetyl-*N*-(2,6-dimethylphenyl)-2,2-bis(4-methoxyphenyl)acetamide (3qa:** Prepared from 2-isocyno-1,3-dimethylbenzene (**2a**, 39.4 mg, 0.3 mmol) and bis(4-methoxyphenyl)methyl acetate (**1q**, 57.3 mg, 0.2 mmol) at 100 °C for 12 h according to the **GP**. Purification by flash chromatography on silica gel using petroleum ether/EtOAc (20/1 to 10/1) afforded **3qa** as a colorless oil (66.0 mg, 79% yield).

3qa: R_f = 0.45 (petroleum ether/EtOAc = 10/1). **$^1\text{H NMR}$** (400 MHz, CDCl_3): δ 7.25–7.21 (m, 1H), 7.10 (d, J = 7.6 Hz, 2H), 7.07 (d, J = 8.8 Hz, 4H), 6.81 (d, J = 8.8 Hz, 4H), 4.97 (s, 1H), 3.76 (s, 6H), 2.49 (s, 3H), 1.86 (s, 6H) ppm. **$^{13}\text{C NMR}$** (100 MHz, CDCl_3): δ 175.1, 173.0, 158.8, 136.9, 136.4, 130.5, 129.8, 129.0, 128.8, 113.9, 55.7, 55.2, 26.8, 17.7 ppm. **HRMS** (ESI) m/z : $[\text{M}+\text{Na}]^+$ calcd. for $\text{C}_{26}\text{H}_{27}\text{NNaO}_4$: 440.1832; Found: 440.1830.

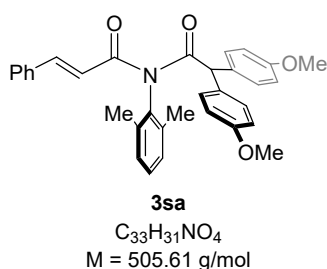


3ra
 $\text{C}_{33}\text{H}_{29}\text{NO}_4$
 $M = 503.60 \text{ g/mol}$

***N*-(2,2-bis(4-methoxyphenyl)acetyl)-*N*-(2,6-dimethylphenyl)-3-phenylpropiolamide**

3ra: Prepared from 2-isocyano-1,3-dimethylbenzene (**2a**, 39.4 mg, 0.3 mmol) and bis(4-methoxyphenyl)methyl 3-phenylpropiolate (**1r**, 74.5 mg, 0.2 mmol) at 100 °C for 12 h according to the **GP**. Purification by flash chromatography on silica gel using petroleum ether/EtOAc (20/1 to 10/1) afforded **3ra** as a yellow oil (28.2 mg, 28% yield).

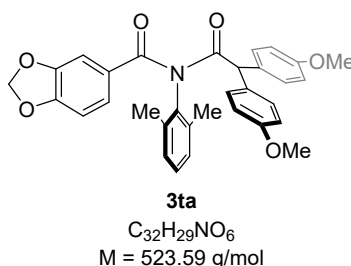
3ra: R_f = 0.40 (petroleum ether/EtOAc = 10/1). **¹H NMR** (400 MHz, CDCl₃): δ 7.39–7.35 (m, 1H), 7.28–7.24 (m, 7H), 7.15–7.12 (m, 4H), 6.85 (d, J = 8.8 Hz, 4H), 6.03 (s, 1H), 3.77 (s, 6H), 2.03 (s, 6H) ppm. **¹³C NMR** (100 MHz, CDCl₃): δ 174.1, 158.7, 154.3, 137.0, 136.6, 133.3, 130.83, 130.79, 130.2, 129.2, 128.6, 128.4, 119.5, 113.9, 93.3, 82.5, 56.1, 55.2, 17.8 ppm. **HRMS** (ESI) m/z : [M+Na]⁺ calcd. for C₃₃H₂₉NNaO₄: 526.1989; Found: 529.1986.

***N*-(2,2-bis(4-methoxyphenyl)acetyl)-*N*-(2,6-dimethylphenyl)cinnamamide (**3sa**:**

Prepared from 2-isocyano-1,3-dimethylbenzene (**2a**, 39.4 mg, 0.3 mmol) and bis(4-methoxyphenyl)methyl cinnamate (**1s**, 74.9 mg, 0.2 mmol) at 100 °C for 12 h according to the **GP**. Purification by flash chromatography on silica gel using petroleum ether/EtOAc (10/1 to 5/1) afforded **3sa** as a white solid (51.6 mg, 51% yield); mp 148–150 °C.

3sa: R_f = 0.35 (petroleum ether/EtOAc = 10/1). **¹H NMR** (400 MHz, CDCl₃): δ 7.79 (d, J = 15.6 Hz, 1H), 7.45–7.43 (m, 2H), 7.34–7.33 (m, 3H), 7.23 (d, J = 8.0 Hz, 1H), 7.18 (d, J = 8.0 Hz, 4H), 7.12 (d, J = 7.2 Hz, 2H), 6.94 (d, J = 14.8 Hz, 1H), 6.87 (d, J = 8.8 Hz, 4H), 5.42 (s, 1H), 3.77 (s, 6H), 1.93 (s, 6H) ppm. **¹³C NMR** (100 MHz, CDCl₃): δ 175.5, 168.1, 158.7, 145.2, 136.6, 134.6, 131.0, 130.4, 129.9, 129.0,

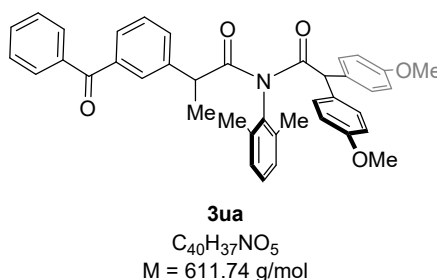
128.81, 128.77, 128.3, 119.8, 113.9, 55.9, 55.2, 17.9 ppm. **HRMS** (ESI) m/z : $[M+Na]^+$ calcd. for $C_{33}H_{31}NNaO_4$: 528.2145; Found: 528.2141.



***N*-(2,2-bis(4-methoxyphenyl)acetyl)-*N*-(2,6-dimethylphenyl)benzo[d][1,3]dioxole-5-**

carboxamide (3ta): Prepared from 2-isocyano-1,3-dimethylbenzene (**2a**, 39.4 mg, 0.3 mmol) and bis(4-methoxyphenyl)methyl benzo[d][1,3]dioxole-5-carboxylate (**1t**, 78.5 mg, 0.2 mmol) at 100 °C for 12 h according to the **GP**. Purification by flash chromatography on silica gel using petroleum ether/EtOAc (5/1) afforded **3ta** as a yellow oil (92.2 mg, 88% yield).

3ta: $R_f = 0.35$ (petroleum ether/EtOAc = 5/1). **1H NMR** (400 MHz, $CDCl_3$): δ 7.28–7.24 (m, 1H), 7.18–7.12 (m, 7H), 7.04 (s, 1H), 6.81 (d, $J = 8.4$ Hz, 4H), 6.74 (d, $J = 8.0$ Hz, 1H), 5.99 (s, 2H), 4.80 (s, 1H), 3.76 (s, 6H), 2.00 (s, 6H) ppm. **^{13}C NMR** (100 MHz, $CDCl_3$): δ 175.6, 171.5, 158.8, 150.8, 147.5, 137.3, 137.0, 130.6, 129.8, 129.5, 129.1, 129.0, 124.0, 113.9, 108.7, 107.8, 101.7, 55.3, 55.2, 18.4 ppm. **HRMS** (ESI) m/z : $[M+Na]^+$ calcd. for $C_{32}H_{29}NNaO_6$: 546.1893; Found: 546.1880.



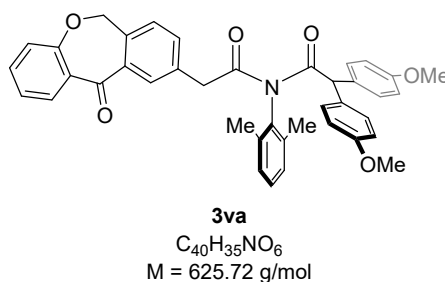
2-(3-benzoylphenyl)-*N*-(2,2-bis(4-methoxyphenyl)acetyl)-*N*-(2,6-dimethylphenyl)

propanamide (3ua): Prepared from 2-isocyano-1,3-dimethylbenzene (**2a**, 39.4 mg, 0.3 mmol) and bis(4-methoxyphenyl)methyl 2-(3-benzoylphenyl)propanoate (**1u**, 96.1 mg, 0.2 mmol) at 100 °C for 12 h according to the **GP**. Purification by flash

chromatography on silica gel using petroleum ether/EtOAc (5/1) afforded **3ua** as a yellow oil (121.0 mg, 99% yield).

3ua: R_f = 0.40 (petroleum ether/EtOAc = 5/1). $^1\text{H NMR}$ (400 MHz, CDCl_3): δ 7.75 (d, J = 8.0 Hz, 2H), 7.68 (d, J = 7.2 Hz, 1H), 7.60–7.55 (m, 2H), 7.47–7.43 (m, 3H), 7.39–7.36 (m, 1H), 7.19–7.16 (m, 1H), 7.09–6.99 (m, 4H), 6.91 (d, J = 8.0 Hz, 2H), 6.81 (d, J = 8.8 Hz, 2H), 6.69 (d, J = 8.4 Hz, 2H), 5.13 (s, 1H), 4.60 (s, 1H), 3.75 (s, 3H), 3.69 (s, 3H), 1.65 (s, 3H), 1.63 (s, 3H), 1.52 (d, J = 6.8 Hz, 3H) ppm. $^{13}\text{C NMR}$ (100 MHz, CDCl_3): δ 196.1, 176.6, 175.3, 158.7, 158.6, 140.6, 137.7, 137.4, 136.9, 136.41, 136.39, 132.4, 132.1, 130.7, 130.6, 130.0, 129.90, 129.87, 129.7, 128.9, 128.8, 128.3, 128.2, 113.80, 113.77, 55.9, 55.13, 55.08, 46.7, 20.3, 17.6 ppm.

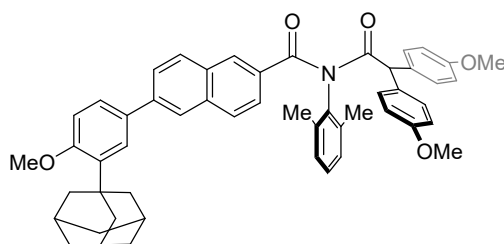
HRMS (ESI) m/z : $[\text{M}+\text{Na}]^+$ calcd. for $\text{C}_{40}\text{H}_{37}\text{NNaO}_5$: 634.2570; Found: 634.2553.



***N*-(2,6-dimethylphenyl)-2,2-bis(4-methoxyphenyl)-*N*-(2-(11-oxo-6,11-dihydrodibenzo [b,e]oxepin-9-yl)acetyl)acetamide (3va)**: Prepared from 2-isocyano-1,3-dimethylbenzene (**2a**, 39.4 mg, 0.3 mmol) and bis(4-methoxyphenyl)methyl 2-(11-oxo-6,11-dihydrodibenzo[b,e]oxepin-9-yl)acetate (**1v**, 98.9 mg, 0.2 mmol) at 100 °C for 12 h according to the **GP**. Purification by flash chromatography on silica gel using petroleum ether/EtOAc (5/1) afforded **3va** as a yellow oil (118.8 mg, 95% yield).

3va: R_f = 0.40 (petroleum ether/EtOAc = 5/1). $^1\text{H NMR}$ (400 MHz, CDCl_3): δ 8.02 (s, 1H), 7.87 (d, J = 7.6 Hz, 1H), 7.56–7.52 (m, 1H), 7.47–7.44 (m, 1H), 7.37–7.33 (m, 2H), 7.24–7.20 (m, 1H), 7.09–7.04 (m, 6H), 6.98 (d, J = 8.4 Hz, 1H), 6.78 (d, J = 8.8 Hz, 4H), 5.16 (s, 2H), 5.08 (s, 1H), 4.13 (s, 2H), 3.73 (s, 6H), 1.83 (s, 6H) ppm. $^{13}\text{C NMR}$ (100 MHz, CDCl_3): δ 190.6, 175.1, 173.6, 160.4, 158.7, 140.4, 137.0, 136.54, 136.46, 135.5, 132.8, 132.7, 130.5, 129.8, 129.4, 129.2, 129.0, 128.9, 127.8, 127.7,

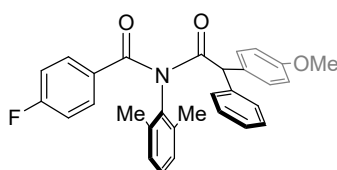
124.9, 120.7, 113.8, 73.6, 55.7, 55.2, 43.9, 17.8 ppm. **HRMS** (ESI) m/z : $[M+Na]^+$ calcd. for $C_{40}H_{35}NNaO_6$: 648.2362; Found: 648.2351.



3wa
 $C_{52}H_{51}NO_5$
 M = 769.98 g/mol

6-(3-(Adamantan-1-yl)-4-methoxyphenyl)-N-(2,2-bis(4-methoxyphenyl)acetyl)-N-(2,6-dimethylphenyl)-2-naphthamide (3wa): Prepared from 2-isocyano-1,3-dimethylbenzene (**2a**, 39.4 mg, 0.3 mmol) and bis(4-methoxyphenyl)methyl 6-(3-(adamantan-1-yl)-4-methoxyphenyl)-2-naphthoate (**1w**, 127.8 mg, 0.2 mmol) at 100 °C for 12 h according to the **GP**. Purification by flash chromatography on silica gel using petroleum ether/EtOAc (5/1) afforded **3wa** as a yellow oil (95.5 mg, 62% yield).

3wa: R_f = 0.30 (petroleum ether/EtOAc = 5/1). **¹H NMR** (400 MHz, $CDCl_3$): δ 8.06 (s, 1H), 7.98 (s, 1H), 7.84 (d, J = 8.8 Hz, 1H), 7.79–7.74 (m, 2H), 7.64 (d, J = 8.4 Hz, 1H), 7.60 (s, 1H), 7.54 (d, J = 8.4 Hz, 1H), 7.29 (t, J = 7.6 Hz, 1H), 7.19–7.16 (m, 6H), 6.99 (d, J = 8.4 Hz, 1H), 6.83 (d, J = 8.4 Hz, 4H), 4.87 (s, 1H), 3.89 (s, 3H), 3.78 (s, 6H), 2.19 (s, 6H), 2.09 (s, 9H), 1.81 (s, 6H) ppm. **¹³C NMR** (100 MHz, $CDCl_3$): δ 175.6, 172.6, 158.9, 158.8, 140.9, 138.9, 137.2, 137.1, 135.2, 132.6, 132.5, 131.1, 130.7, 129.8, 129.4, 129.2, 129.1, 128.8, 128.0, 126.3, 125.9, 125.7, 125.0, 124.7, 113.9, 112.1, 55.31, 55.26, 55.1, 40.6, 37.2, 37.1, 29.1, 18.5 ppm. **HRMS** (ESI) m/z : $[M+Na]^+$ calcd. for $C_{52}H_{51}NNaO_5$: 792.3665; Found: 792.3654.

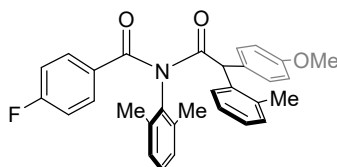


3xa
 $C_{30}H_{26}FNO_3$
 M = 467.54 g/mol

***N*-(2,6-dimethylphenyl)-4-fluoro-*N*-(2-(4-methoxyphenyl)-2-phenylacetyl)benzamide**

3xa): Prepared from 2-isocyno-1,3-dimethylbenzene (**2a**, 39.4 mg, 0.3 mmol) and (4-methoxyphenyl)(phenyl)methyl 4-fluorobenzoate (**1x**, 67.3 mg, 0.2 mmol) at 100 °C for 20 h according to the **GP**. Purification by flash chromatography on silica gel using petroleum ether/EtOAc (20/1 to 10/1) afforded **3xa** as a yellow oil (45.8 mg, 49% yield).

3xa: R_f = 0.40 (petroleum ether/EtOAc = 15/1). **¹H NMR** (400 MHz, CDCl₃): δ 7.58–7.55 (m, 2H), 7.30–7.21 (m, 6H), 7.15 (d, J = 8.0 Hz, 4H), 7.04–7.00 (m, 2H), 6.82 (d, J = 8.4 Hz, 2H), 4.86 (s, 1H), 3.77 (s, 3H), 2.00 (s, 6H) ppm. **¹³C NMR** (100 MHz, CDCl₃): δ 175.3, 171.3, 164.7 (d, J = 251.4 Hz), 138.3, 137.0, 136.9, 131.9 (d, J = 3.1 Hz), 130.6 (d, J = 8.9 Hz), 130.0, 129.9, 129.3, 129.1, 128.7, 128.6, 127.5, 115.3 (d, J = 21.9 Hz), 114.0, 56.1, 55.2, 18.3 ppm. **¹⁹F NMR** (376 MHz, CDCl₃) δ -106.99 (s) ppm. **HRMS** (ESI) m/z : [M+Na]⁺ calcd. for C₃₀H₂₆FNNaO₃: 490.1789; Found: 490.1785.



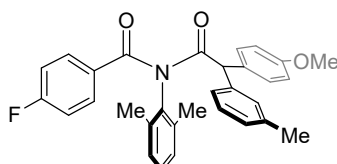
3ya
C₃₁H₂₈FNO₃
M = 481.57 g/mol

***N*-(2,6-dimethylphenyl)-4-fluoro-*N*-(2-(4-methoxyphenyl)-2-(*o*-tolyl)acetyl)benzamide**

3ya): Prepared from 2-isocyno-1,3-dimethylbenzene (**2a**, 39.4 mg, 0.3 mmol) and (4-methoxyphenyl)(*o*-tolyl)methyl 4-fluorobenzoate (**1y**, 70.1 mg, 0.2 mmol) at 100 °C for 18 h according to the **GP**. Purification by flash chromatography on silica gel using petroleum ether/EtOAc (20/1 to 10/1) afforded **3ya** as a yellow oil (54.9 mg, 57% yield).

3ya: R_f = 0.35 (petroleum ether/EtOAc = 15/1). **¹H NMR** (400 MHz, CDCl₃): δ 7.71 (d, J = 7.6 Hz, 1H), 7.65–7.61 (m, 2H), 7.33–7.19 (m, 4H), 7.11–7.04 (m, 6H), 6.78 (d, J = 8.4 Hz, 2H), 5.12 (s, 1H), 3.72 (s, 3H), 2.32 (s, 3H), 1.63 (s, 6H) ppm. **¹³C NMR**

(100 MHz, CDCl₃): δ 175.4, 171.5, 164.6 (d, J = 251.1 Hz), 158.7, 137.12, 137.08, 136.9, 135.5, 132.4 (d, J = 3.2 Hz), 131.0, 130.4 (d, J = 8.9 Hz), 130.2, 129.4, 129.32, 129.30, 129.1, 127.7, 127.6, 126.2, 115.3 (d, J = 22.0 Hz), 113.7, 55.2, 51.6, 18.74, 18.67, 17.6 ppm. **¹⁹F NMR** (376 MHz, CDCl₃) δ -107.28 (s) ppm. **HRMS** (ESI) m/z : [M+Na]⁺ calcd. for C₃₁H₂₈FNNaO₃: 504.1945; Found: 504.1940.

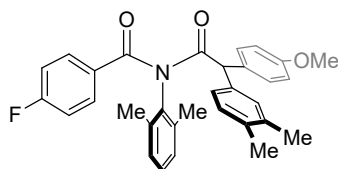


3za
C₃₁H₂₈FNO₃
M = 481.57 g/mol

***N*-(2,6-dimethylphenyl)-4-fluoro-*N*-(2-(4-methoxyphenyl)-2-(*m*-tolyl)acetyl)benzamide**

(3za): Prepared from 2-isocyano-1,3-dimethylbenzene (**2a**, 39.4 mg, 0.3 mmol) and (4-methoxyphenyl)(*m*-tolyl)methyl 4-fluorobenzoate (**1z**, 70.1 mg, 0.2 mmol) at 100 °C for 18 h according to the **GP**. Purification by flash chromatography on silica gel using petroleum ether/EtOAc (20/1 to 10/1) afforded **3za** as a yellow oil (53.0 mg, 55% yield).

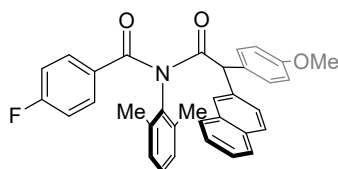
3za: R_f = 0.40 (petroleum ether/EtOAc = 15/1). **¹H NMR** (400 MHz, CDCl₃): δ 7.59–7.55 (m, 2H), 7.30–7.27 (m, 1H), 7.17–7.14 (m, 5H), 7.07–6.98 (m, 5H), 6.82 (d, J = 8.4 Hz, 2H), 4.81 (s, 1H), 3.77 (s, 3H), 2.30 (s, 3H), 2.02 (s, 3H), 1.96 (s, 3H) ppm. **¹³C NMR** (100 MHz, CDCl₃): δ 175.34, 171.37, 164.7 (d, J = 251.5 Hz), 159.0, 138.3, 138.1, 137.04, 137.02, 136.9, 132.0 (d, J = 3.3 Hz), 130.6 (d, J = 8.9 Hz), 130.1, 129.9, 129.4, 129.3, 129.11, 129.09, 128.5, 128.2, 125.79, 115.3 (d, J = 22.0 Hz), 113.9, 56.0, 55.2, 21.4, 18.3, 18.2 ppm. **¹⁹F NMR** (376 MHz, CDCl₃) δ -107.06 (s) ppm. **HRMS** (ESI) m/z : [M+Na]⁺ calcd. for C₃₁H₂₈FNNaO₃: 504.1945; Found: 504.1944.

**3aa-a**

$C_{32}H_{30}FNO_3$
M = 495.59 g/mol

N-(2,6-dimethylphenyl)-N-(2-(3,4-dimethylphenyl)-2-(4-methoxyphenyl)acetyl)-4-fluorobenzamide (3aa-a): Prepared from 2-isocyano-1,3-dimethylbenzene (**2a**, 39.4 mg, 0.3 mmol) and (3,4-dimethylphenyl)(4-methoxyphenyl)methyl 4-fluorobenzoate (**1aa**, 72.9 mg, 0.2 mmol) at 100 °C for 18 h according to the **GP**. Purification by flash chromatography on silica gel using petroleum ether/EtOAc (20/1 to 10/1) afforded **3aa-a** as a yellow oil (87.2 mg, 88% yield).

3aa-a: R_f = 0.40 (petroleum ether/EtOAc = 15/1). **1H NMR** (400 MHz, $CDCl_3$): δ 7.59–7.56 (m, 2H), 7.30–7.26 (m, 1H), 7.16–7.13 (m, 4H), 7.05–6.98 (m, 4H), 6.92 (d, J = 7.7 Hz, 1H), 6.80 (d, J = 7.6 Hz, 2H), 4.77 (s, 1H), 3.76 (s, 3H), 2.21 (s, 6H), 2.02 (s, 3H), 1.97 (s, 3H) ppm. **^{13}C NMR** (100 MHz, $CDCl_3$): δ 175.5, 171.4, 164.6 (d, J = 251.2 Hz), 158.9, 137.05, 137.00, 136.8, 135.8, 135.5, 132.0 (d, J = 3.3 Hz), 130.6 (d, J = 9.0 Hz), 130.4, 129.83, 129.79, 129.3, 129.08, 129.07, 126.1, 115.3 (d, J = 21.9 Hz), 113.9, 55.7, 55.2, 19.8, 19.3, 18.34, 18.29 ppm. **^{19}F NMR** (376 MHz, $CDCl_3$) δ -107.14 (s) ppm. **HRMS** (ESI) m/z : $[M+Na]^+$ calcd. for $C_{32}H_{30}FNNaO_3$: 518.2102; Found: 518.2100.

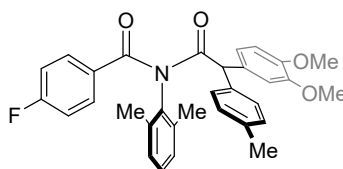
**3ab-a**

$C_{34}H_{28}FNO_3$
M = 517.60 g/mol

N-(2,6-dimethylphenyl)-4-fluoro-N-(2-(4-methoxyphenyl)-2-(naphthalen-2-yl)acetyl)benzamide (3ab-a): Prepared from 2-isocyano-1,3-dimethylbenzene (**2a**, 39.4 mg, 0.3 mmol) and (4-methoxyphenyl)(naphthalen-2-yl)methyl 4-fluorobenzoate (**1ab**, 77.3 mg, 0.2 mmol) at 100 °C for 20 h according to the **GP**. Purification by flash

chromatography on silica gel using petroleum ether/EtOAc (20/1 to 10/1) afforded **3ab-a** as a yellow oil (62.1 mg, 60% yield).

3ab-a: $R_f = 0.40$ (petroleum ether/EtOAc = 15/1). **$^1\text{H NMR}$** (400 MHz, CDCl_3): δ 7.80–7.75 (m, 3H), 7.68 (s, 1H), 7.60–7.56 (m, 2H), 7.47–7.45 (m, 2H), 7.36–7.28 (m, 2H), 7.24–7.13 (m, 4H), 7.04–7.00 (m, 2H), 6.83 (d, $J = 8.8$ Hz, 2H), 5.05 (s, 1H), 3.76 (s, 3H), 2.05 (s, 3H), 1.94 (s, 3H) ppm. **$^{13}\text{C NMR}$** (100 MHz, CDCl_3): δ 175.3, 171.3, 164.7 (d, $J = 251.5$ Hz), 159.0, 137.1, 137.0, 136.9, 135.7, 133.3, 132.6, 131.9 (d, $J = 3.2$ Hz), 130.6 (d, $J = 9.0$ Hz), 130.04, 129.97, 129.4, 129.19, 129.16, 128.4, 127.9, 127.6, 127.4, 126.7, 126.3, 126.1, 115.3 (d, $J = 22.0$ Hz), 114.0, 56.1, 55.2, 18.4, 18.3 ppm. **$^{19}\text{F NMR}$** (376 MHz, CDCl_3) δ -106.88 (s) ppm. **HRMS** (ESI) m/z : $[\text{M}+\text{Na}]^+$ calcd. for $\text{C}_{34}\text{H}_{28}\text{FNNaO}_3$: 540.1945; Found: 540.1942.



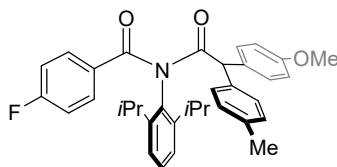
3ac-a
 $\text{C}_{32}\text{H}_{30}\text{FNO}_4$
 $M = 511.59$ g/mol

***N*-(2-(3,4-dimethoxyphenyl)-2-(*p*-tolyl)acetyl)-*N*-(2,6-dimethylphenyl)-4-fluorobenzamide (**3ac-a**):**

Prepared from 2-isocyano-1,3-dimethylbenzene (**2a**, 39.4 mg, 0.3 mmol) and (3,4-dimethoxyphenyl)(*p*-tolyl)methyl 4-fluorobenzoate (**1ac**, 76.1 mg, 0.2 mmol) at 100 °C for 20 h according to the **GP**. Purification by flash chromatography on silica gel using petroleum ether/EtOAc (20/1 to 10/1) afforded **3ac-a** as a white solid (60.4 mg, 59% yield); mp 100–102 °C.

3ac-a: $R_f = 0.45$ (petroleum ether/EtOAc = 10/1). **$^1\text{H NMR}$** (400 MHz, CDCl_3): δ 7.60–7.56 (m, 2H), 7.30–7.27 (m, 1H), 7.18 (d, $J = 7.6$ Hz, 1H), 7.14–7.08 (m, 5H), 7.05–7.00 (m, 2H), 6.79–6.72 (m, 3H), 4.81 (s, 1H), 3.85 (s, 3H), 3.79 (s, 3H), 2.31 (s, 3H), 2.08 (s, 3H), 1.95 (s, 3H) ppm. **$^{13}\text{C NMR}$** (100 MHz, CDCl_3): δ 175.3, 171.3, 164.7 (d, $J = 251.5$ Hz), 148.9, 148.4, 137.2, 137.2, 137.0, 135.3, 131.9 (d, $J = 3.2$ Hz), 130.6 (d, $J = 9.0$ Hz), 130.4, 129.3, 129.2, 129.14, 129.07, 128.5, 121.1, 115.3 (d, $J = 22.0$

Hz), 111.8, 110.9, 56.0, 55.85, 55.79, 21.0, 18.4, 18.3 ppm. **¹⁹F NMR** (376 MHz, CDCl₃) δ -106.97 (s) ppm. **HRMS** (ESI) *m/z*: [M+Na]⁺ calcd. for C₃₂H₃₀FNNaO₄: 534.2051; Found: 534.2044.

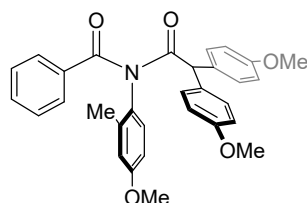


3ab
C₃₅H₃₆FNO₃
M = 537.68 g/mol

***N*-(2,6-diisopropylphenyl)-4-fluoro-*N*-(2-(4-methoxyphenyl)-2-(*p*-tolyl)acetyl)benzamide (3ab):**

Prepared from 2-isocyano-1,3-diisopropylbenzene (**2b**, 56.2 mg, 0.3 mmol) and (4-methoxyphenyl)(*p*-tolyl)methyl 4-fluorobenzoate (**1a**, 70.1 mg, 0.2 mmol) at 100 °C for 16 h according to the **GP**. Purification by flash chromatography on silica gel using petroleum ether/EtOAc (20/1 to 10/1) afforded **3ab** as a yellow oil (91.4 mg, 85% yield).

3ab: *R_f* = 0.40 (petroleum ether/EtOAc = 15/1). **¹H NMR** (400 MHz, CDCl₃): δ 7.53–7.50 (m, 2H), 7.43–7.39 (m, 1H), 7.24–7.15 (m, 6H), 7.06 (d, *J* = 8.0 Hz, 2H), 6.99–6.95 (m, 2H), 6.78 (d, *J* = 8.4 Hz, 2H), 5.08 (s, 1H), 3.74 (s, 3H), 2.94–2.83 (m, 2H), 2.28 (s, 3H), 1.02 (d, *J* = 6.8 Hz, 6H), 0.92 (d, *J* = 7.6 Hz, 3H), 0.91 (d, *J* = 7.2 Hz, 3H) ppm. **¹³C NMR** (100 MHz, CDCl₃): δ 176.4, 171.9, 164.5 (d, *J* = 251.2 Hz), 158.8, 147.1, 147.0, 136.9, 136.2, 133.5, 131.8 (d, *J* = 2.8 Hz), 131.3, 130.6 (d, *J* = 8.9 Hz), 130.0, 129.6, 129.2, 128.2, 124.5, 115.2 (d, *J* = 21.9 Hz), 113.9, 56.0, 55.2, 28.8, 24.6, 23.1, 23.0, 21.0 ppm. **¹⁹F NMR** (376 MHz, CDCl₃) δ -107.23 (s) ppm. **HRMS** (ESI) *m/z*: [M+Na]⁺ calcd. for C₃₅H₃₆FNNaO₃: 560.2571; Found: 560.2570.

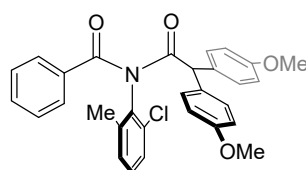


3gc
C₃₁H₂₉NO₅
M = 495.58 g/mol

***N*-(2,2-bis(4-methoxyphenyl)acetyl)-*N*-(4-methoxy-2-methylphenyl)benzamide (3gc:**

Prepared from 1-isocyano-4-methoxy-2-methylbenzene (**2c**, 44.2 mg, 0.3 mmol) and bis(4-methoxyphenyl)methyl benzoate (**1g**, 69.7 mg, 0.2 mmol) at 100 °C for 16 h according to the **GP**. Purification by flash chromatography on silica gel using petroleum ether/EtOAc (20/1 to 10/1) afforded **3gc** as a yellow oil (36.7 mg, 37% yield).

3gc: R_f = 0.30 (petroleum ether/EtOAc = 10/1). **¹H NMR** (400 MHz, CDCl₃): δ 7.48 (d, J = 7.2 Hz, 2H), 7.44–7.41 (m, 1H), 7.31–7.28 (m, 2H), 7.19–7.14 (m, 4H), 6.92 (d, J = 8.4 Hz, 1H), 6.85–6.81 (m, 5H), 6.74 (d, J = 8.4 Hz, 1H), 5.13 (s, 1H), 3.81 (s, 3H), 3.78 (s, 3H), 3.77 (s, 3H), 2.05 (s, 3H) ppm. **¹³C NMR** (100 MHz, CDCl₃): δ 176.0, 173.3, 159.7, 158.9, 158.7, 137.9, 135.6, 131.7, 130.8, 130.6, 130.6, 130.4, 130.0, 129.8, 128.13, 128.09, 116.5, 113.9, 113.8, 112.3, 55.43, 55.38, 55.25, 55.23, 18.3 ppm. **HRMS** (ESI) m/z : [M+Na]⁺ calcd. for C₃₁H₂₉NNaO₅: 518.1938; Found: 518.1935.



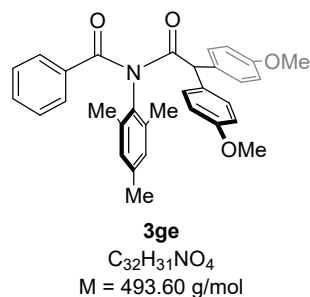
3gd
C₃₀H₂₆ClNO₄
M = 499.99 g/mol

***N*-(2,2-bis(4-methoxyphenyl)acetyl)-*N*-(2-chloro-6-methylphenyl)benzamide (3gd:**

Prepared from 1-chloro-2-isocyano-3-methylbenzene (**2d**, 45.5 mg, 0.3 mmol) and bis(4-methoxyphenyl)methyl benzoate (**1g**, 69.7 mg, 0.2 mmol) at 100 °C for 16 h according to the **GP**. Purification by flash chromatography on silica gel using petroleum ether/EtOAc (20/1 to 10/1) afforded **3gd** as a yellow oil (72.0 mg, 72% yield).

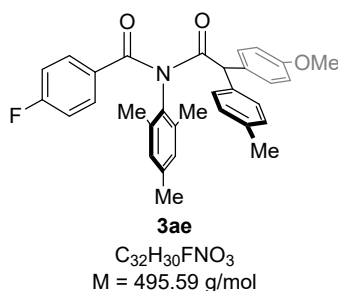
3gd: R_f = 0.50 (petroleum ether/EtOAc = 10/1). **¹H NMR** (400 MHz, CDCl₃): δ 7.60 (d, J = 7.6 Hz, 2H), 7.46–7.42 (m, 1H), 7.38 (d, J = 8.0 Hz, 1H), 7.35–7.31 (m, 2H), 7.29–7.25 (m, 1H), 7.21 (d, J = 8.4 Hz, 2H), 7.12–7.07 (m, 3H), 6.82 (d, J = 8.8 Hz,

2H), 6.81 (d, $J = 8.8$ Hz, 2H), 4.96 (s, 1H), 3.78 (s, 3H), 3.76 (s, 3H), 1.85 (s, 3H) ppm. ^{13}C NMR (100 MHz, CDCl_3): δ 174.9, 172.1, 159.0, 158.7, 140.1, 135.6, 135.5, 133.9, 131.7, 130.7, 130.0, 129.9, 129.7, 129.6, 128.1, 127.98, 127.96, 114.0, 113.7, 55.7, 55.3, 55.2, 18.3 ppm. **HRMS** (ESI) m/z : $[\text{M}+\text{Na}]^+$ calcd. for $\text{C}_{30}\text{H}_{26}\text{ClNNaO}_4$: 522.1443; Found: 522.1443.



***N*-(2,2-bis(4-methoxyphenyl)acetyl)-*N*-mesitylbenzamide (3ge**: Prepared from 2-isocyno-1,3,5-trimethylbenzene (**2e**, 43.6 mg, 0.3 mmol) and bis(4-methoxyphenyl)methyl benzoate (**1g**, 69.7 mg, 0.2 mmol) at 100 °C for 12 h according to the **GP**. Purification by flash chromatography on silica gel using petroleum ether/EtOAc (20/1 to 10/1) afforded **3ge** as a white solid (85.9 mg, 87% yield); mp 125–127 °C.

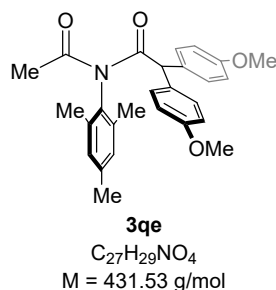
3ge: $R_f = 0.45$ (petroleum ether/EtOAc = 10/1). ^1H NMR (400 MHz, CDCl_3): δ 7.54 (d, $J = 7.2$ Hz, 2H), 7.47–7.44 (m, 1H), 7.36–7.32 (m, 2H), 7.14 (d, $J = 8.8$ Hz, 4H), 6.96 (s, 2H), 6.81 (d, $J = 8.8$ Hz, 4H), 4.86 (s, 1H), 3.76 (s, 6H), 2.35 (s, 3H), 1.97 (s, 6H) ppm. ^{13}C NMR (100 MHz, CDCl_3): δ 175.6, 172.7, 158.8, 139.0, 136.6, 136.1, 134.4, 131.5, 130.7, 129.8, 128.1, 127.9, 113.9, 55.2, 55.1, 21.1, 18.2 ppm. **HRMS** (ESI) m/z : $[\text{M}+\text{Na}]^+$ calcd. for $\text{C}_{32}\text{H}_{31}\text{NNaO}_4$: 516.2145; Found: 516.2141.



4-Fluoro-*N*-mesityl-*N*-(2-(4-methoxyphenyl)-2-(*p*-tolyl)acetyl)benzamide (3ae):

Prepared from 2-isocyano-1,3,5-trimethylbenzene (**2e**, 43.6 mg, 0.3 mmol) and (4-methoxyphenyl)(*p*-tolyl)methyl 4-fluorobenzoate (**1a**, 70.1 mg, 0.2 mmol) at 100 °C for 16 h according to the **GP**. Purification by flash chromatography on silica gel using petroleum ether/EtOAc (20/1 to 10/1) afforded **3ae** as a white solid (78.3 mg, 79% yield); mp 139–141 °C.

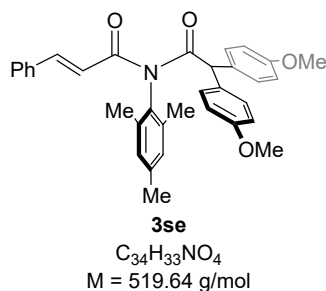
3ae: $R_f = 0.40$ (petroleum ether/EtOAc = 15/1). **¹H NMR** (400 MHz, CDCl₃): δ 7.57–7.54 (m, 2H), 7.16–7.07 (m, 6H), 7.03–6.99 (m, 2H), 6.96 (s, 2H), 6.81 (d, $J = 8.4$ Hz, 2H), 4.85 (s, 1H), 3.76 (s, 3H), 2.35 (s, 3H), 2.30 (s, 3H), 1.95 (s, 6H) ppm. **¹³C NMR** (100 MHz, CDCl₃): δ 175.6, 171.5, 164.6 (d, $J = 251.1$ Hz), 158.9, 139.1, 137.1, 136.5, 136.5, 135.4, 134.3, 132.1 (d, $J = 3.2$ Hz), 130.5 (d, $J = 8.8$ Hz), 130.4, 129.88, 129.86, 129.8, 129.2, 128.6, 115.2 (d, $J = 21.9$ Hz), 113.9, 55.5, 55.2, 21.1, 21.0, 18.2 ppm. **¹⁹F NMR** (376 MHz, CDCl₃) δ -107.25 (s) ppm. **HRMS** (ESI) m/z : [M+Na]⁺ calcd. for C₃₂H₃₀FNNaO₃: 518.2102; Found: 518.2100.



***N*-acetyl-*N*-mesityl-2,2-bis(4-methoxyphenyl)acetamide (3qe):** Prepared from 2-isocyano-1,3,5-trimethylbenzene (**2e**, 43.6 mg, 0.3 mmol) and bis(4-methoxyphenyl)methyl acetate (**1q**, 57.3 mg, 0.2 mmol) at 100 °C for 12 h according to the **GP**. Purification by flash chromatography on silica gel using petroleum ether/EtOAc (20/1 to 10/1) afforded **3qe** as a yellow oil (75.1 mg, 87% yield).

3qe: $R_f = 0.4$ (petroleum ether/EtOAc = 10/1). **¹H NMR** (400 MHz, CDCl₃): δ 7.08 (d, $J = 8.8$ Hz, 4H), 6.91 (s, 2H), 6.83–6.79 (m, 4H), 5.00 (s, 1H), 3.76 (s, 6H), 2.48 (s, 3H), 2.32 (s, 3H), 1.81 (s, 6H) ppm. **¹³C NMR** (100 MHz, CDCl₃): δ 175.3, 173.1, 158.7, 138.7, 135.9, 134.2, 130.7, 129.8, 129.6, 113.9, 55.5, 55.2, 26.8, 21.1, 17.6

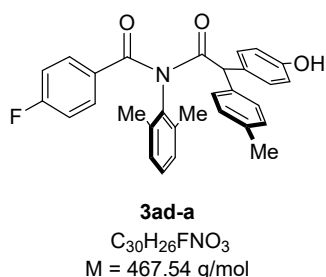
ppm. **HRMS** (ESI) m/z : $[M+Na]^+$ calcd. for $C_{27}H_{29}NNaO_4$: 454.1989; Found: 454.1989.



***N*-(2,2-bis(4-methoxyphenyl)acetyl)-*N*-mesitylcinnamamide (3se)**: Prepared from 2-isocyno-1,3,5-trimethylbenzene (**2e**, 43.6 mg, 0.3 mmol) and bis(4-methoxyphenyl)methyl cinnamate (**1s**, 74.9 mg, 0.2 mmol) at 100 °C for 12 h according to the **GP**. Purification by flash chromatography on silica gel using petroleum ether/EtOAc (20/1 to 10/1) afforded **3se** as a yellow oil (74.8 mg, 72% yield).

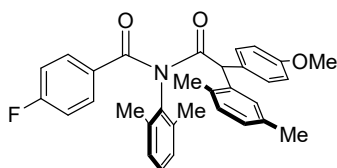
3se: R_f = 0.40 (petroleum ether/EtOAc = 10/1). **1H NMR** (400 MHz, $CDCl_3$): δ 7.78 (d, J = 15.6 Hz, 1H), 7.45–7.43 (m, 2H), 7.33–7.32 (m, 3H), 7.20 (d, J = 8.8 Hz, 4H), 6.92 (s, 3H), 6.85–6.81 (m, 4H), 5.44 (s, 1H), 3.75 (s, 6H), 2.32 (s, 3H), 1.88 (s, 6H) ppm. **^{13}C NMR** (100 MHz, $CDCl_3$): δ 175.7, 168.2, 158.6, 145.0, 138.7, 136.1, 134.6, 133.9, 131.1, 130.3, 129.9, 129.5, 128.7, 128.3, 119.8, 113.8, 55.7, 55.1, 21.1, 17.8 ppm.

HRMS (ESI) m/z : $[M+Na]^+$ calcd. for $C_{34}H_{33}NNaO_4$: 542.2302; Found: 542.2300.



***N*-(2,6-dimethylphenyl)-4-fluoro-*N*-(2-(4-hydroxyphenyl)-2-(*p*-tolyl)acetyl)benzamide (3ad-a)**: yellow oil. R_f = 0.40 (petroleum ether/EtOAc = 2/1). **1H NMR** (400 MHz, $CDCl_3$): δ 7.58–7.54 (m, 2H), 7.28–7.25 (m, 1H), 7.13 (d, J = 7.6 Hz, 2H), 7.09 (s,

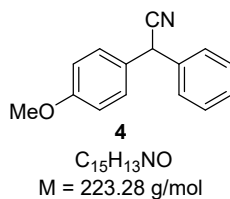
4H), 7.04–6.99 (m, 4H), 6.65–6.63 (m, 2H), 5.48 (broad s, 1H), 4.79 (s, 1H), 2.30 (s, 3H), 1.99 (s, 6H) ppm. ^{13}C NMR (100 MHz, CDCl_3): δ 175.7, 171.6, 164.7 (d, $J = 251.0$ Hz), 155.1, 137.2, 137.0, 136.9, 136.8, 135.2, 131.8 (d, $J = 3.2$ Hz), 130.6 (d, $J = 8.8$ Hz), 129.9, 129.34, 129.28, 129.1, 128.5, 115.4, 115.3 (d, $J = 21.0$ Hz), 55.7, 21.0, 18.3 ppm. ^{19}F NMR (376 MHz, CDCl_3) δ -106.76 (s) ppm. HRMS (ESI) m/z : $[\text{M}+\text{Na}]^+$ calcd. for $\text{C}_{30}\text{H}_{26}\text{FNNO}_3$: 490.1789; Found: 490.1785.



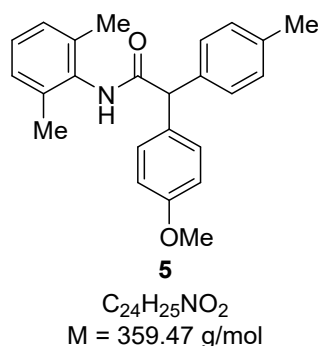
3ae-a
 $\text{C}_{32}\text{H}_{30}\text{FNO}_3$
 $M = 495.59$ g/mol

***N*-(2,6-dimethylphenyl)-*N*-(2-(2,5-dimethylphenyl)-2-(4-methoxyphenyl)acetyl)-4-fluorobenzamide (3ae-a)**: Prepared from 2-isocyano-1,3-dimethylbenzene (**2a**, 39.4 mg, 0.3 mmol) and (*R*)-(2,5-dimethylphenyl)(4-methoxyphenyl)methyl 4-fluorobenzoate ((*R*)-**1ae**, 72.9 mg, 0.2 mmol, 97% ee) at 100 °C for 20 h according to the **GP**. Purification by flash chromatography on silica gel using petroleum ether/EtOAc (20/1 to 10/1) afforded **3ae-a** as a yellow oil (28.7 mg, 29% yield, 0% ee).

3ae-a: $R_f = 0.40$ (petroleum ether/EtOAc = 15/1). ^1H NMR (400 MHz, CDCl_3): δ 7.67–7.64 (m, 2H), 7.51 (s, 1H), 7.28–7.25 (m, 2H), 7.10–7.02 (m, 6H), 6.97 (d, $J = 7.6$ Hz, 1H), 6.79–6.76 (m, 2H), 5.05 (s, 1H), 3.73 (s, 3H), 2.43 (s, 3H), 2.33 (s, 3H), 1.61 (s, 3H), 1.55 (s, 3H) ppm. ^{13}C NMR (100 MHz, CDCl_3): δ 175.6, 171.6, 164.6 (d, $J = 250.9$ Hz), 158.7, 137.2, 137.1, 137.0, 135.7, 135.2, 133.8, 132.5 (d, $J = 3.2$ Hz), 130.9, 130.3, 130.2, 129.3, 129.1, 128.3 (d, $J = 6.1$ Hz), 115.3 (d, $J = 21.9$ Hz), 113.7, 55.2, 51.5, 21.2, 18.7, 18.2, 17.6 ppm. ^{19}F NMR (376 MHz, CDCl_3) δ -107.32 (s) ppm. HRMS (ESI) m/z : $[\text{M}+\text{Na}]^+$ calcd. for $\text{C}_{32}\text{H}_{30}\text{FNNO}_3$: 518.2102; Found: 518.2098.



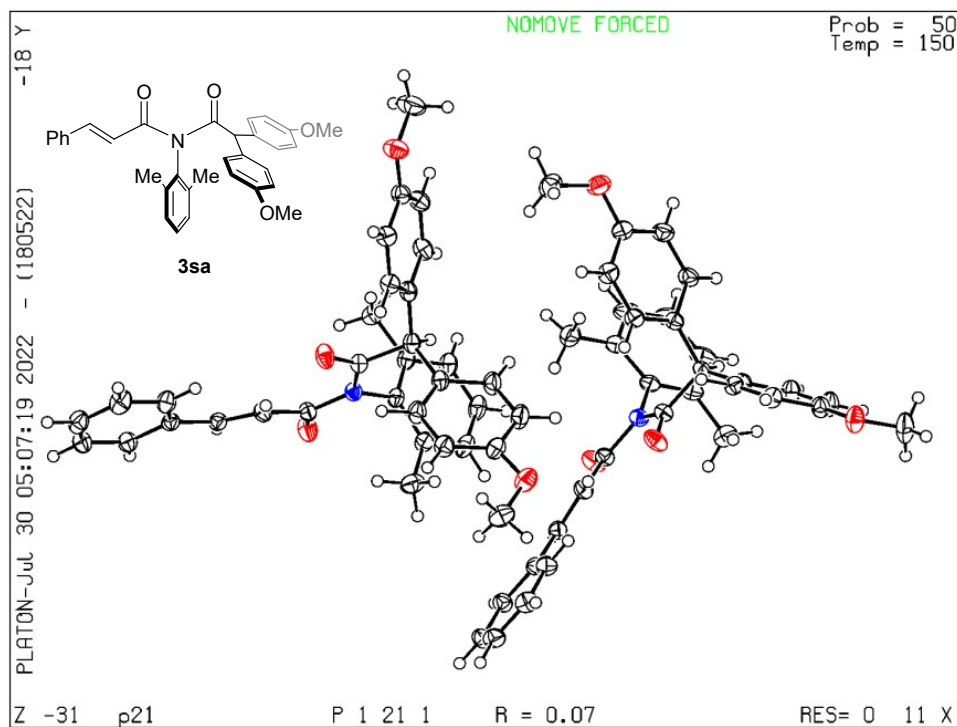
2-(4-methoxyphenyl)-2-phenylacetonitrile (4) [7]: white solid (42.9 mg, 96% yield); mp 130–132 °C; R_f = 0.5 (petroleum ether/EtOAc = 20/1). **1H NMR** (400 MHz, $CDCl_3$): 7.39–7.29 (m, 5H), 7.25 (d, J = 8.4 Hz, 2H), 6.88 (d, J = 8.4 Hz, 2H), 5.09 (s, 1H), 3.79 (s, 3H) ppm. **^{13}C NMR** (100 MHz, $CDCl_3$): δ 159.4, 136.2, 129.1, 128.9, 128.1, 127.9, 127.6, 119.9, 114.5, 55.3, 41.8 ppm.



N-(2,6-dimethylphenyl)-2-(4-methoxyphenyl)-2-(p-tolyl)acetamide (5): white solid; mp 197–199 °C. R_f = 0.3 (petroleum ether/EtOAc = 3/1). **1H NMR** (400 MHz, $CDCl_3$): δ 7.28–7.23 (m, 4H), 7.14 (d, J = 8.0 Hz, 2H), 7.01–6.98 (m, 3H), 6.86 (d, J = 8.4 Hz, 2H), 5.05 (s, 1H), 3.78 (s, 3H), 2.32 (s, 3H), 2.09 (s, 6H) ppm. **^{13}C NMR** (100 MHz, $CDCl_3$): δ 170.6, 158.7, 136.9, 136.7, 135.2, 133.8, 131.7, 130.0, 129.4, 128.7, 128.1, 127.1, 114.1, 58.2, 55.2, 21.0, 18.5 ppm. **HRMS** (ESI) m/z : $[M+Na]^+$ calcd. for $C_{24}H_{25}NNaO_2$: 382.1778; Found: 382.1776.

9 Crystal Structure of 3sa

CCDC number of **3sa** is 2262921. The crystallographic data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif



Bond precision: C-C = 0.0046 Å

Wavelength=0.71073

Cell: a=12.6134(10)

b=11.660(1)

c=19.2888(17)

alpha=90

beta=109.0800

gamma=90

Temperature: 150 K

	Calculated	Reported
Volume	2681.0(4)	2680.9(4)
Space group	P 21	P 1 21 1
Hall group	P 2yb	P 2yb
Moiety formula	C33 H31 N O4	2(C33 H31 N O4)
Sum formula	C33 H31 N O4	C66 H62 N2 O8
Mr	505.59	1011.17
Dx, g cm ⁻³	1.253	1.253
Z	4	2
Mu (mm ⁻¹)	0.082	0.082
F000	1072.0	1072.0
F000'	1072.49	
h, k, lmax	19, 18, 30	19, 18, 30
Nref	21723[11307]	20554
Tmin, Tmax	0.984, 0.988	
Tmin'	0.984	

Correction method= Not given

Data completeness= 1.82/0.95

Theta(max)= 33.914

R(reflections)= 0.0666(17178)

wR2(reflections)=
0.2280(20554)

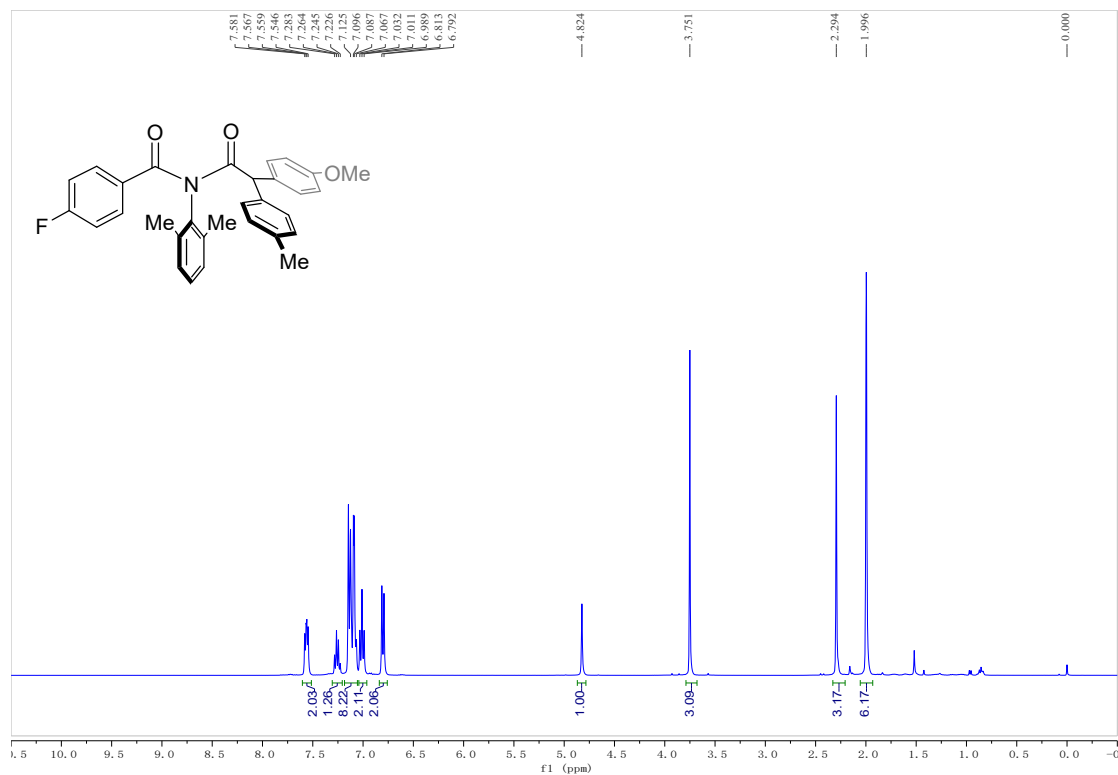
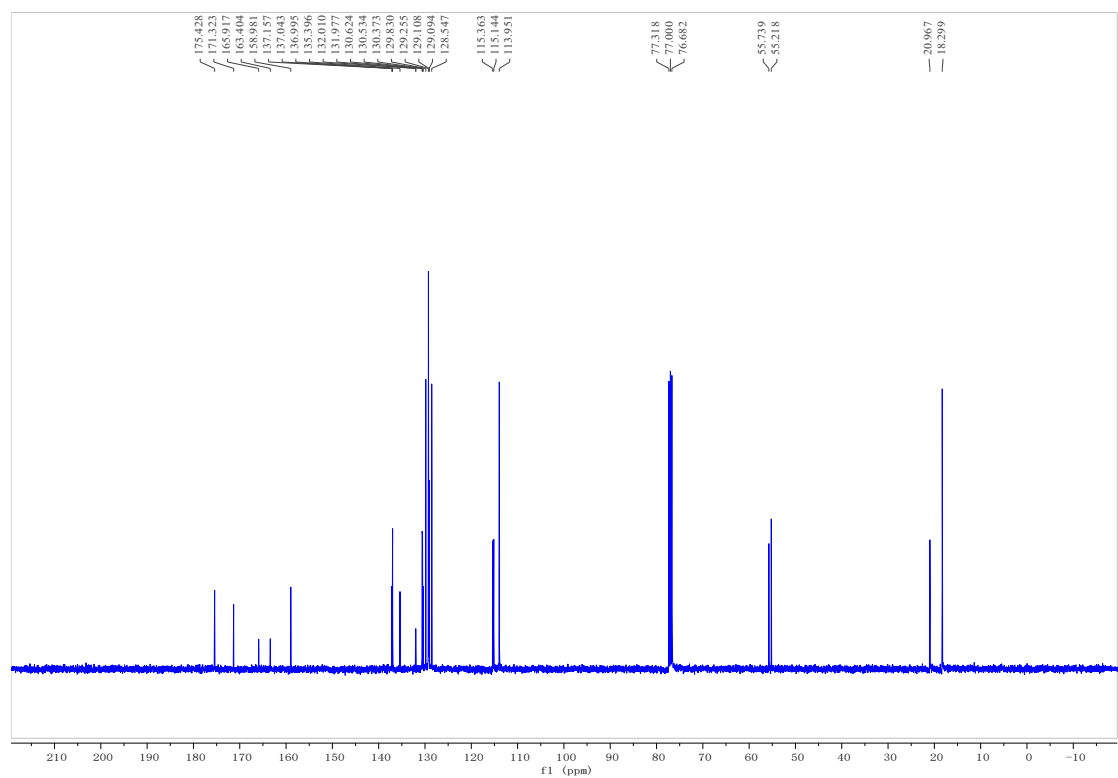
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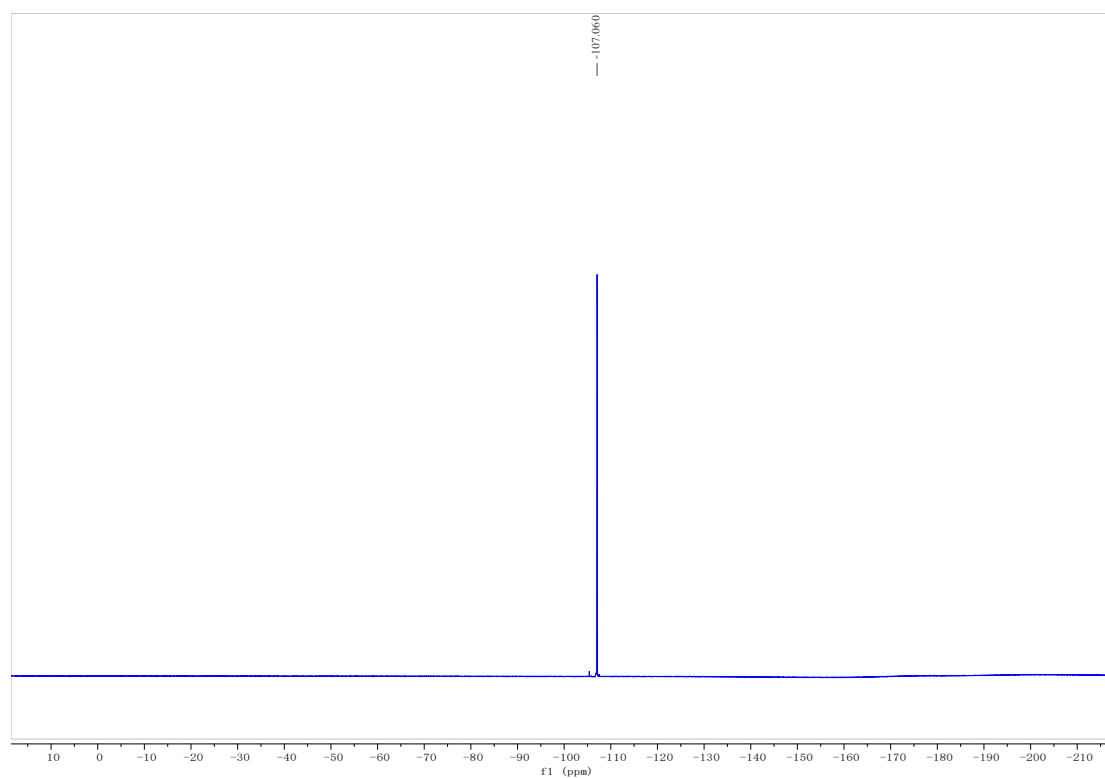
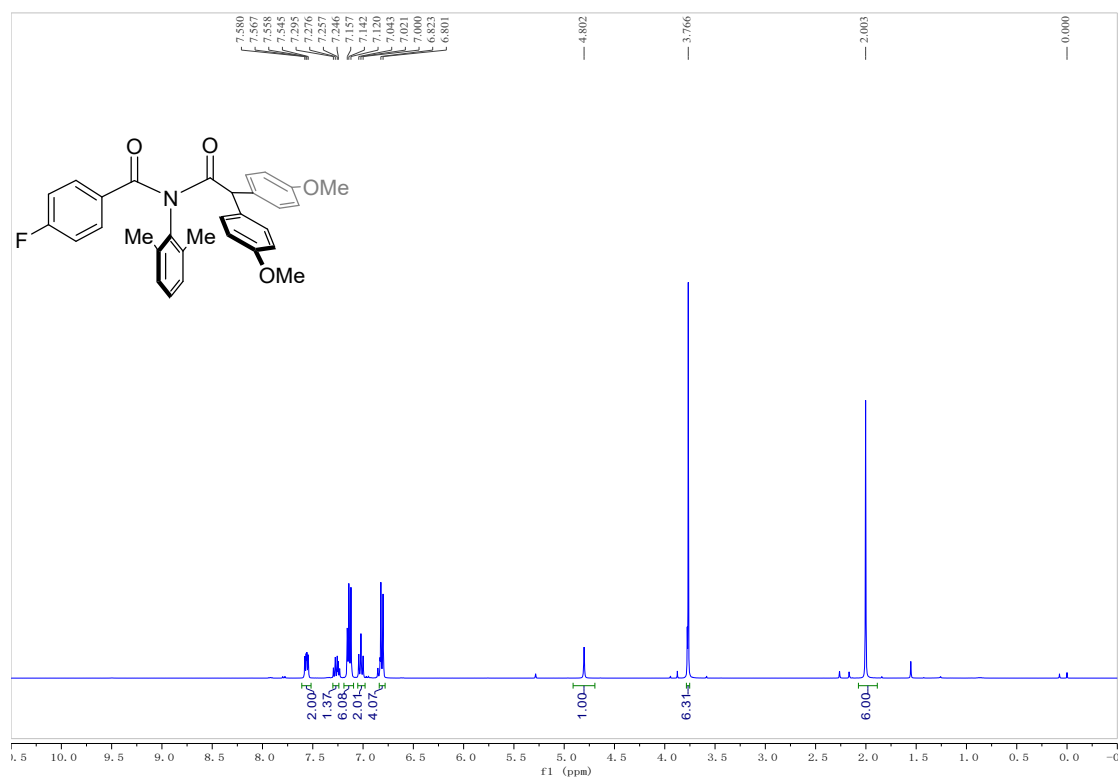
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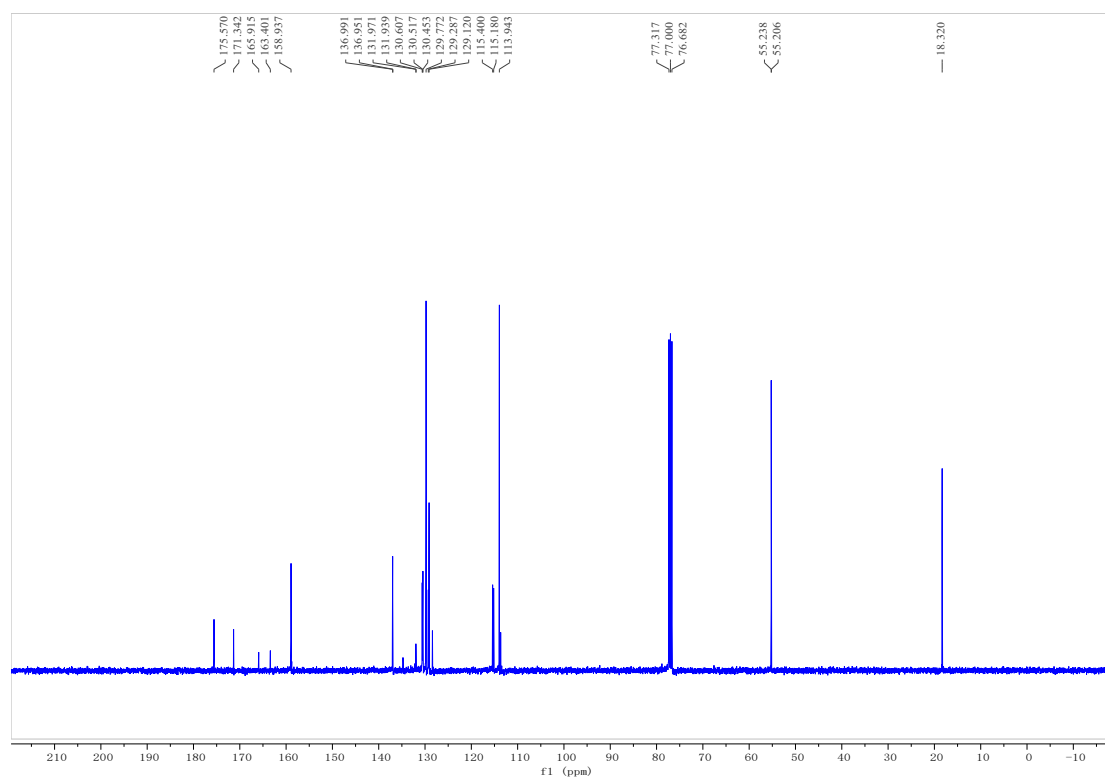
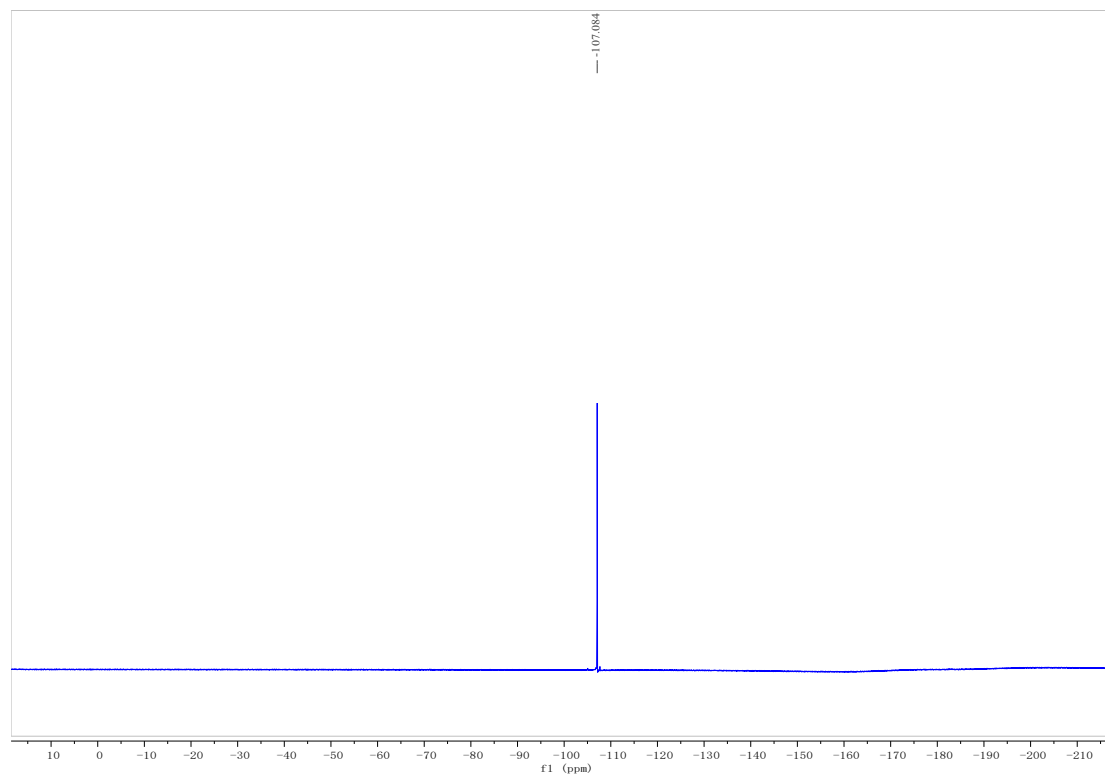
10 References

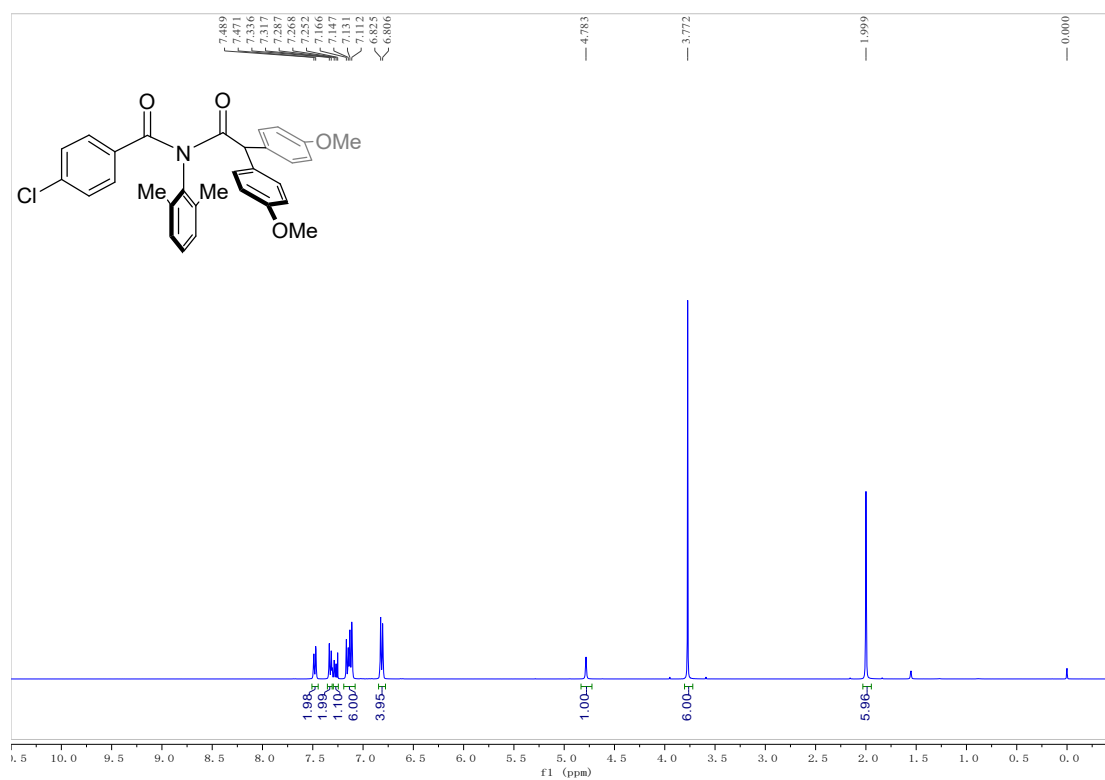
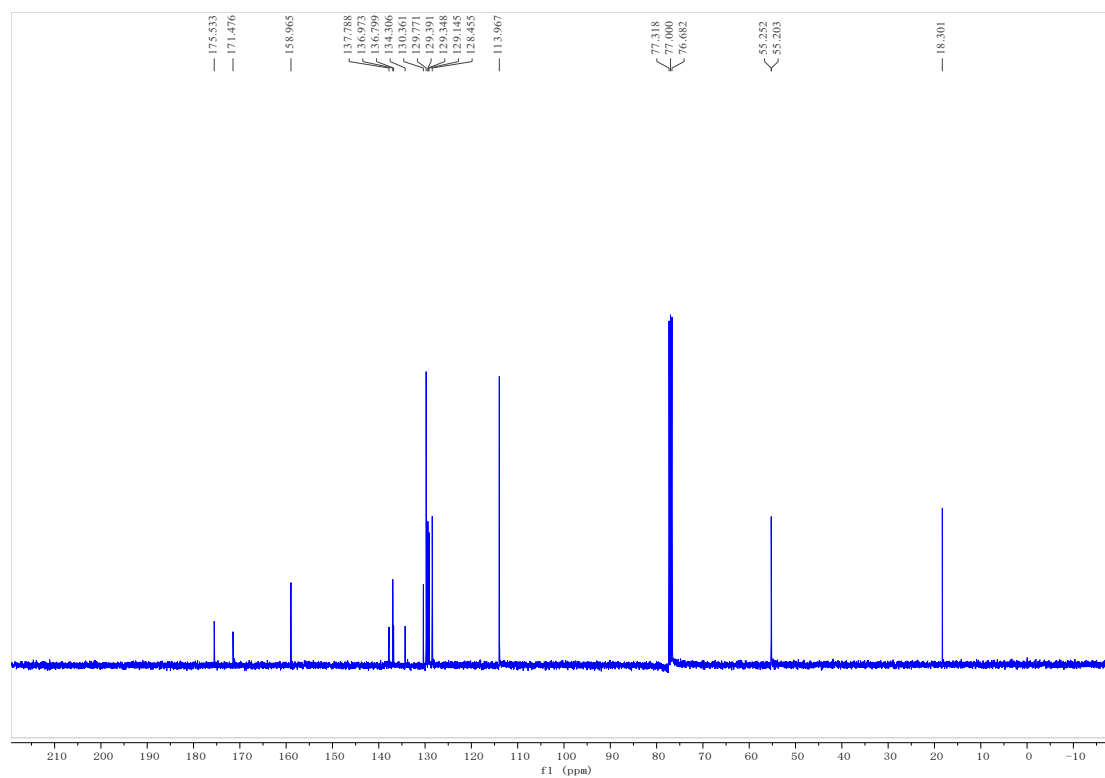
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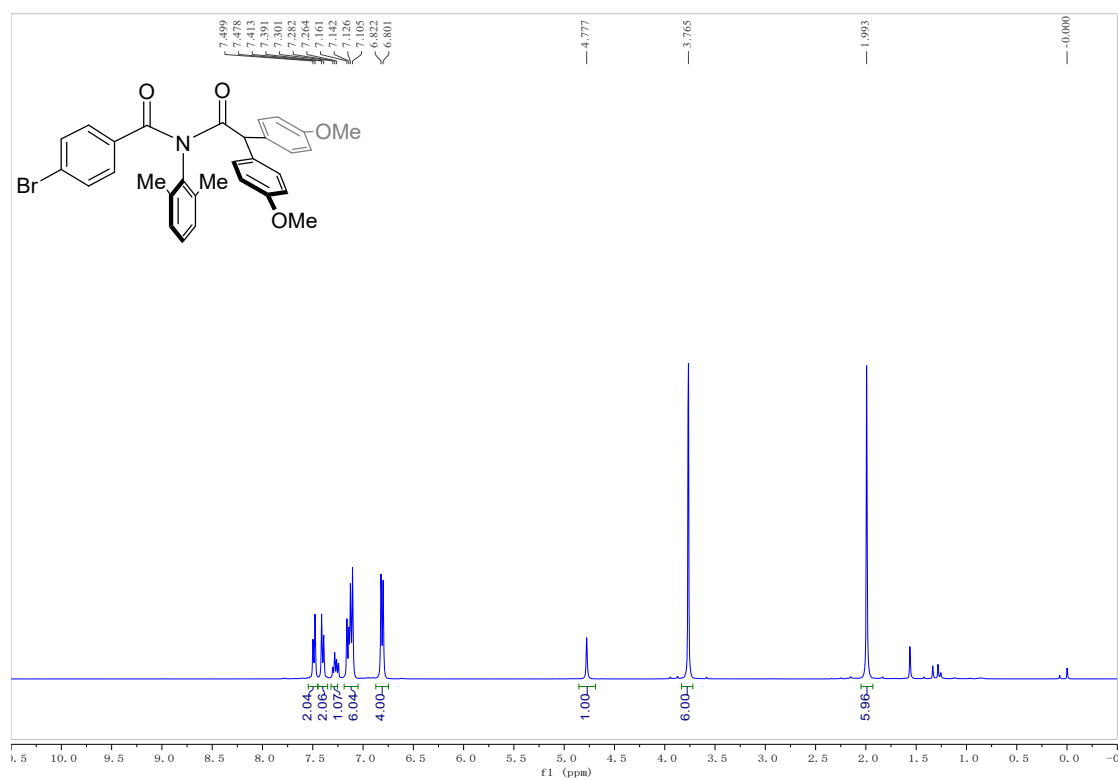
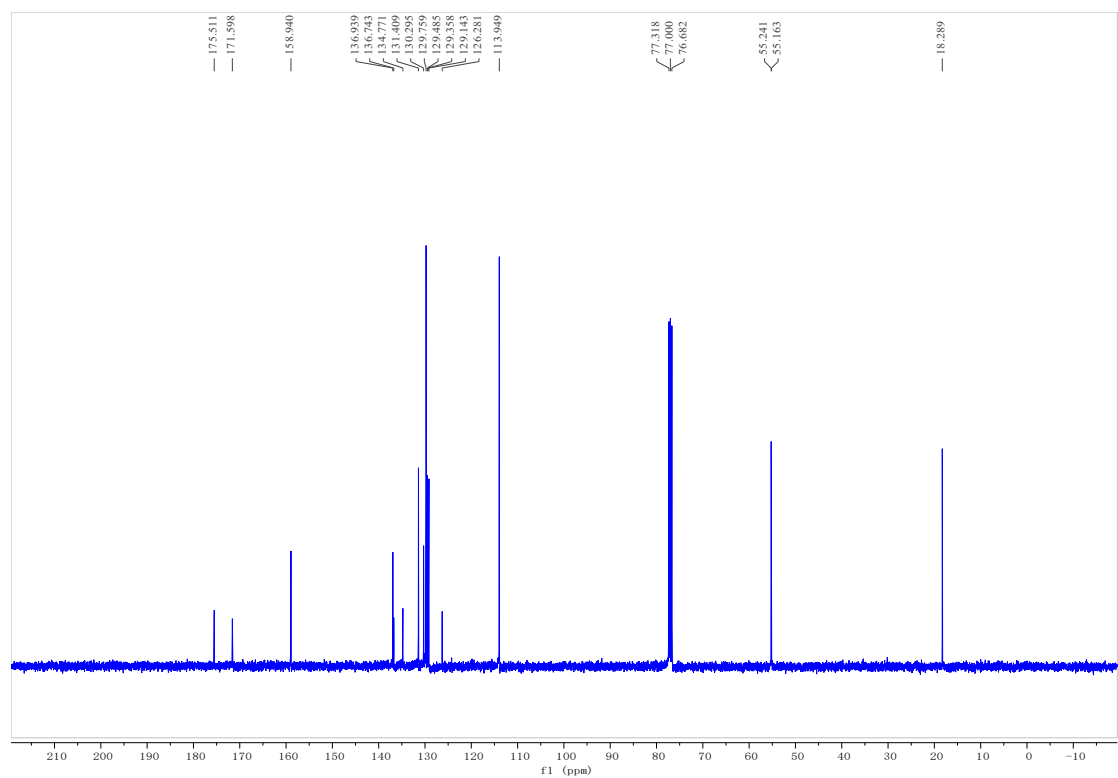
11 NMR Spectra

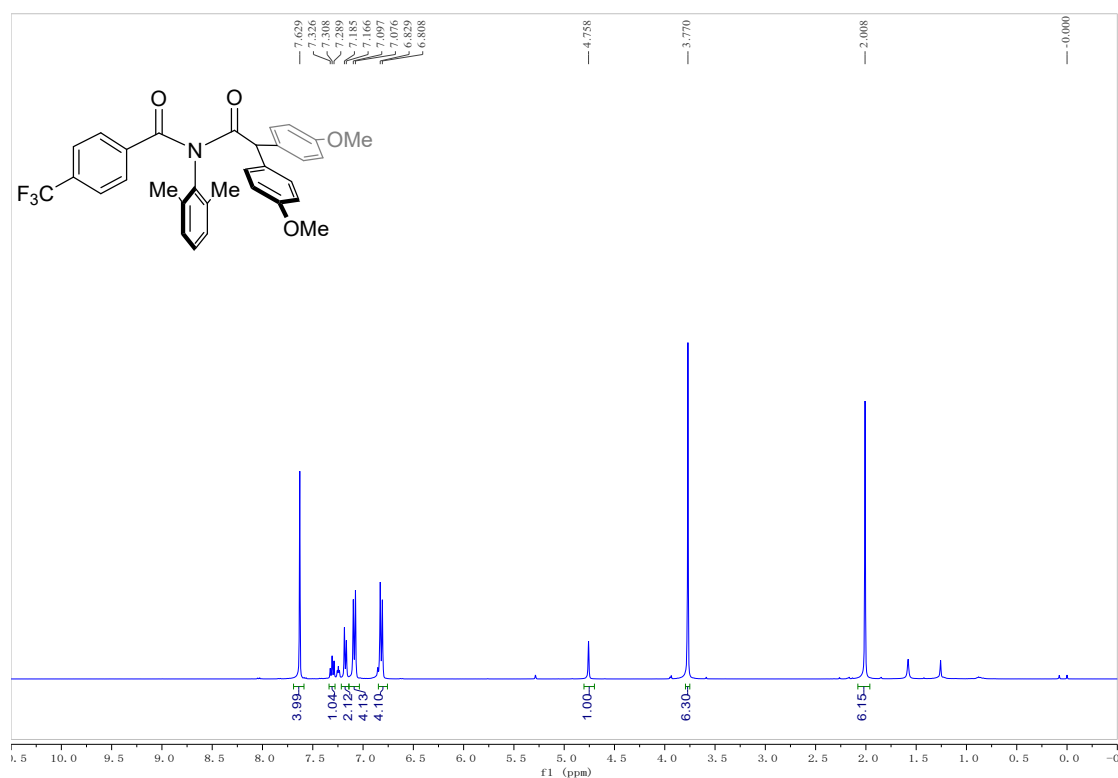
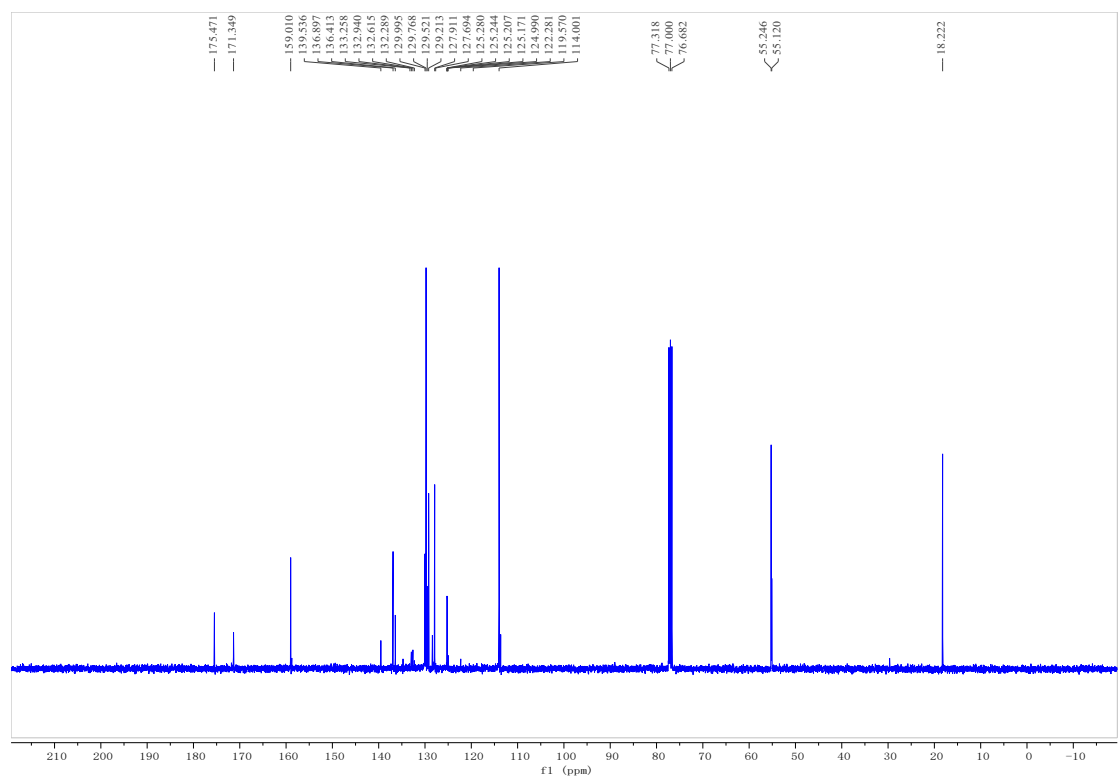
 ^1H and ^{13}C NMR Spectra for Compound 3aa: ^1H NMR (400 MHz, CDCl_3) ^{13}C NMR (100 MHz, CDCl_3)

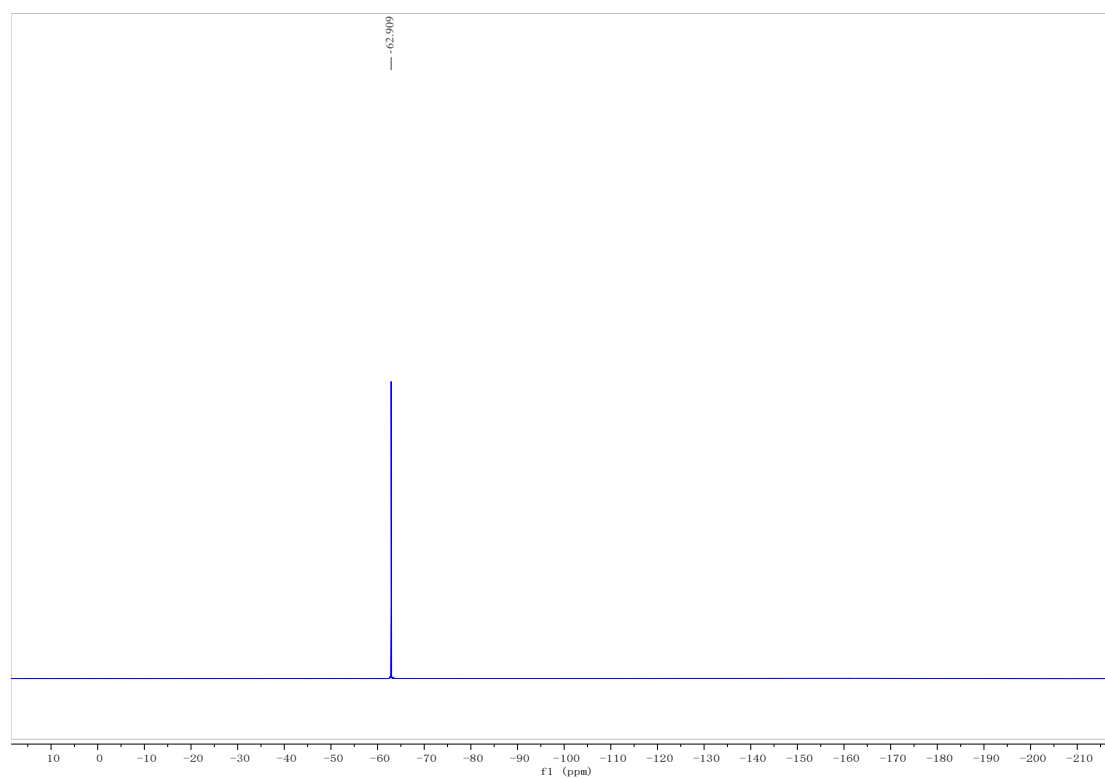
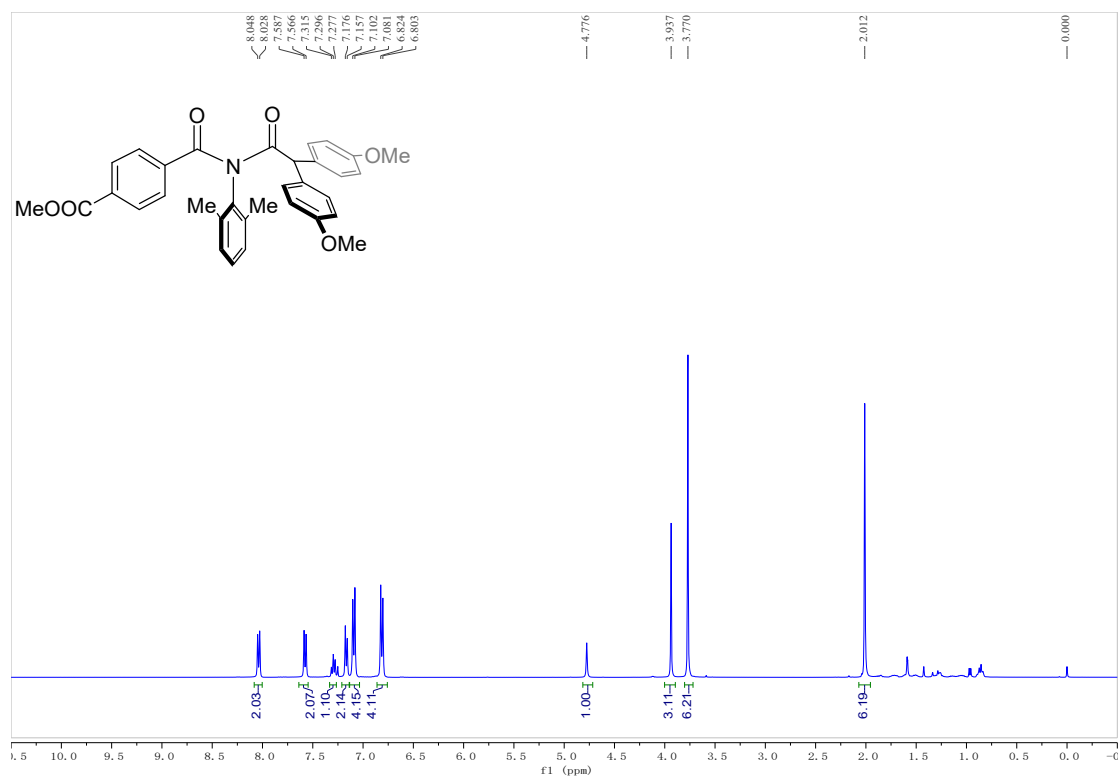
^{19}F NMR (376 MHz, CDCl_3) ^1H and ^{13}C NMR Spectra for Compound 3ba: ^1H NMR (400 MHz, CDCl_3)

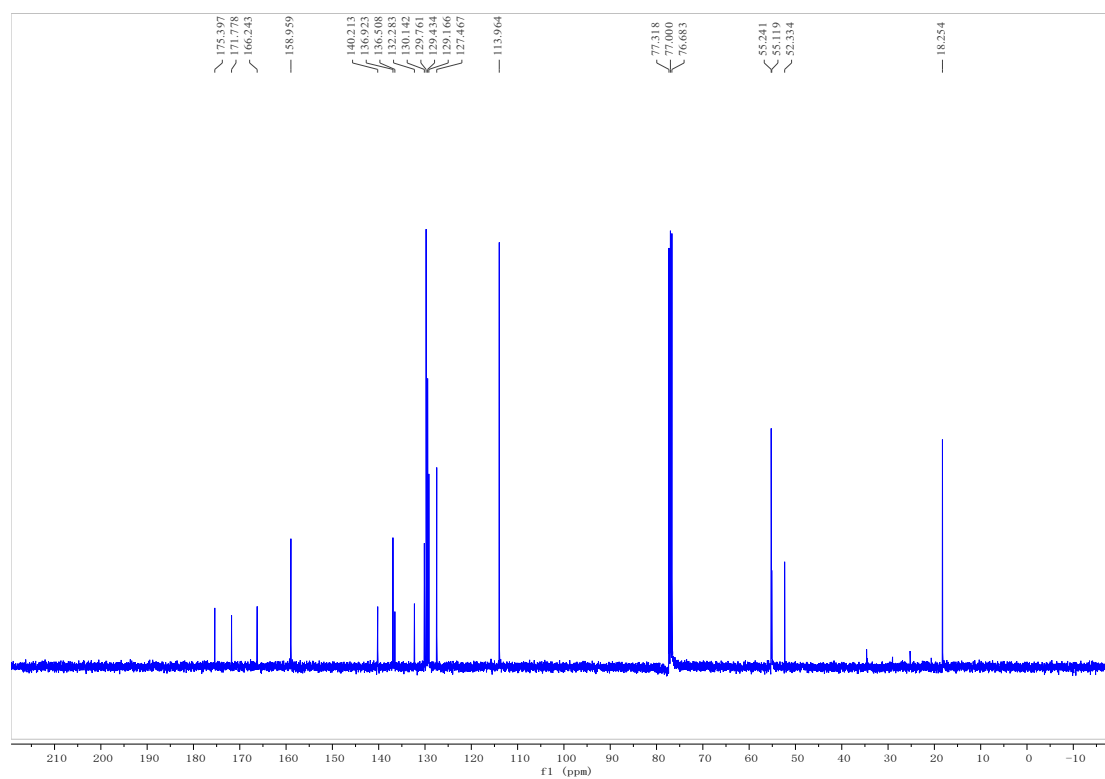
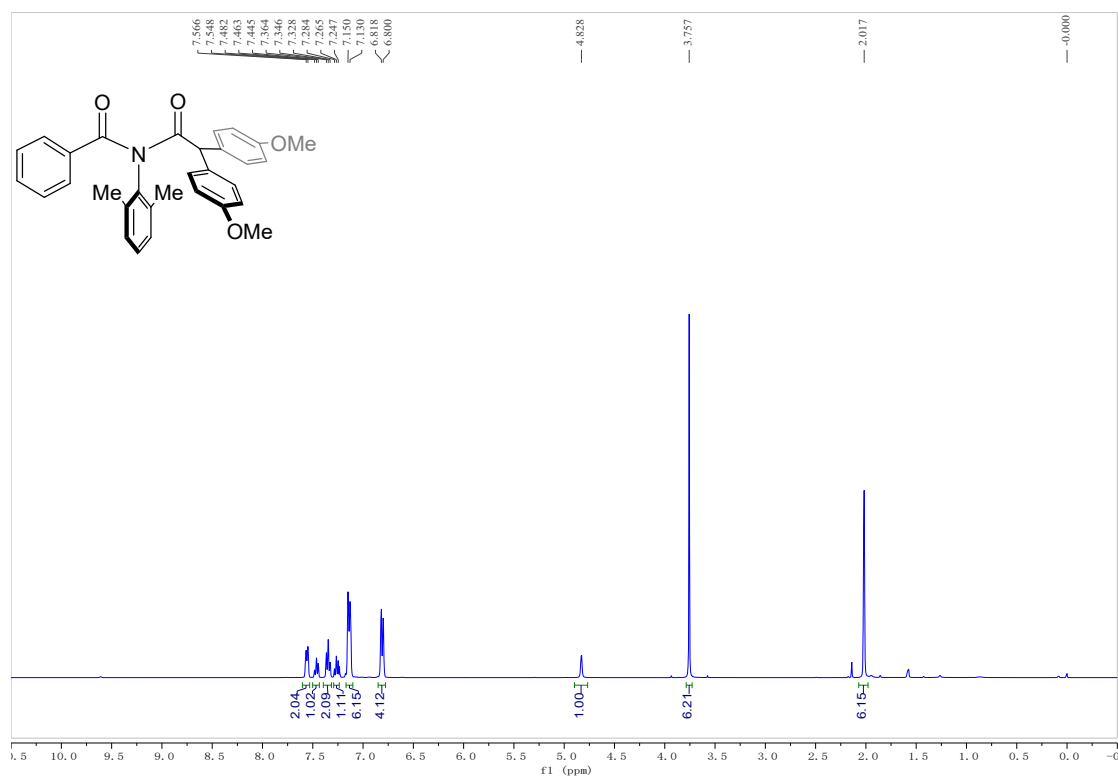
^{13}C NMR (100 MHz, CDCl_3) ^{19}F NMR (376 MHz, CDCl_3)

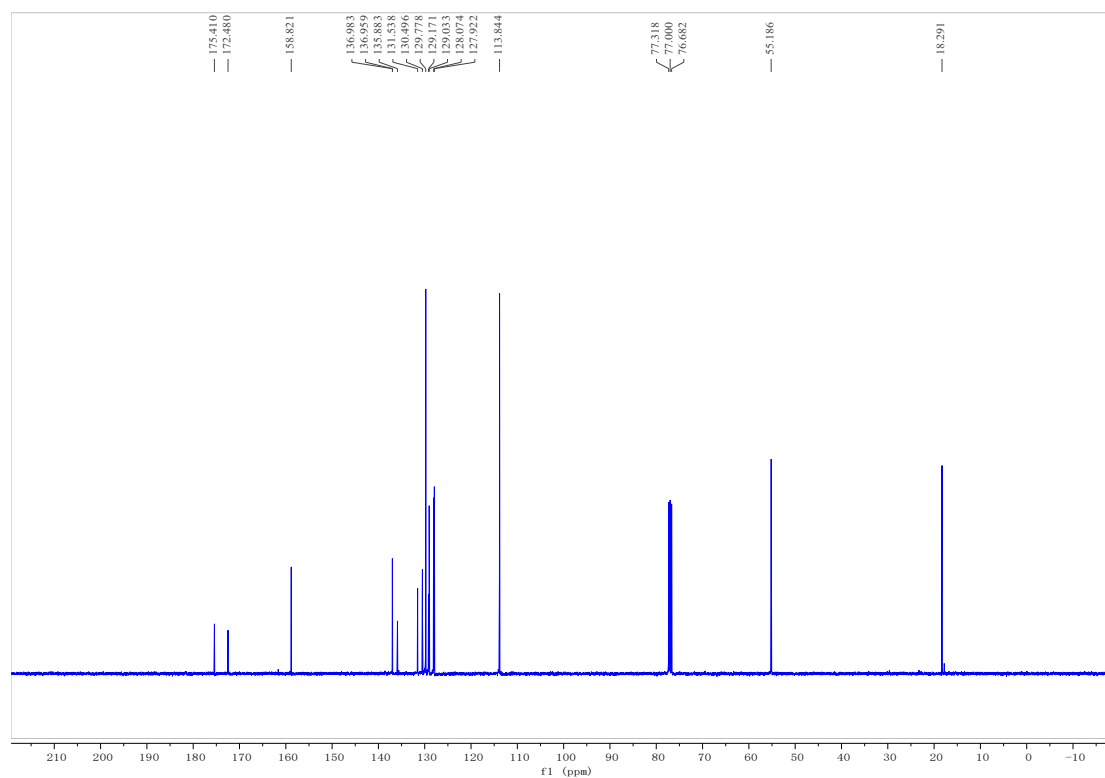
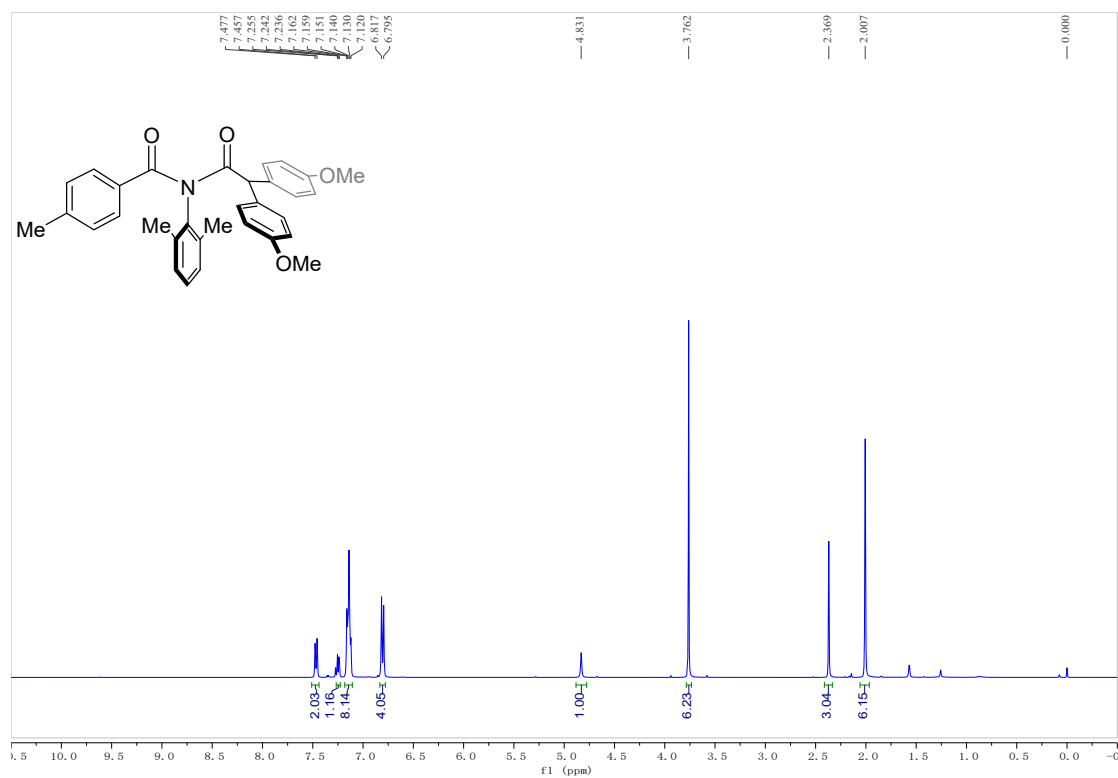
^1H and ^{13}C NMR Spectra for Compound 3ca: **^1H NMR (400 MHz, CDCl_3)** **^{13}C NMR (100 MHz, CDCl_3)**

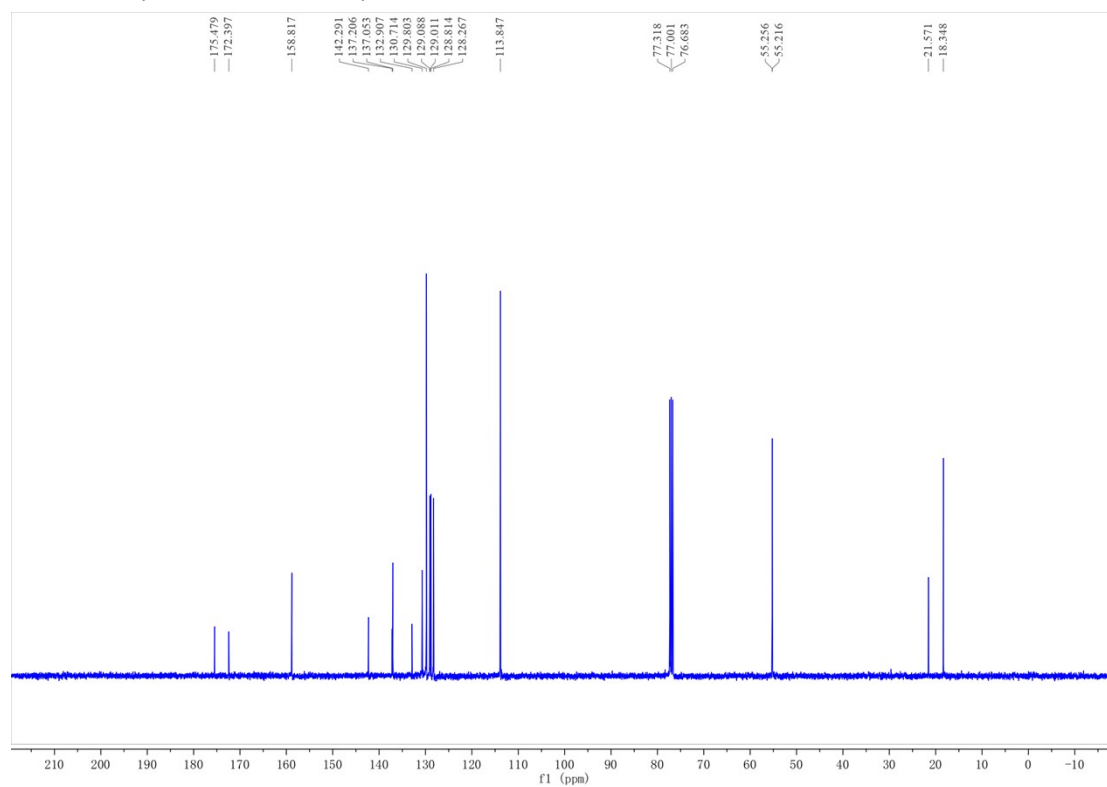
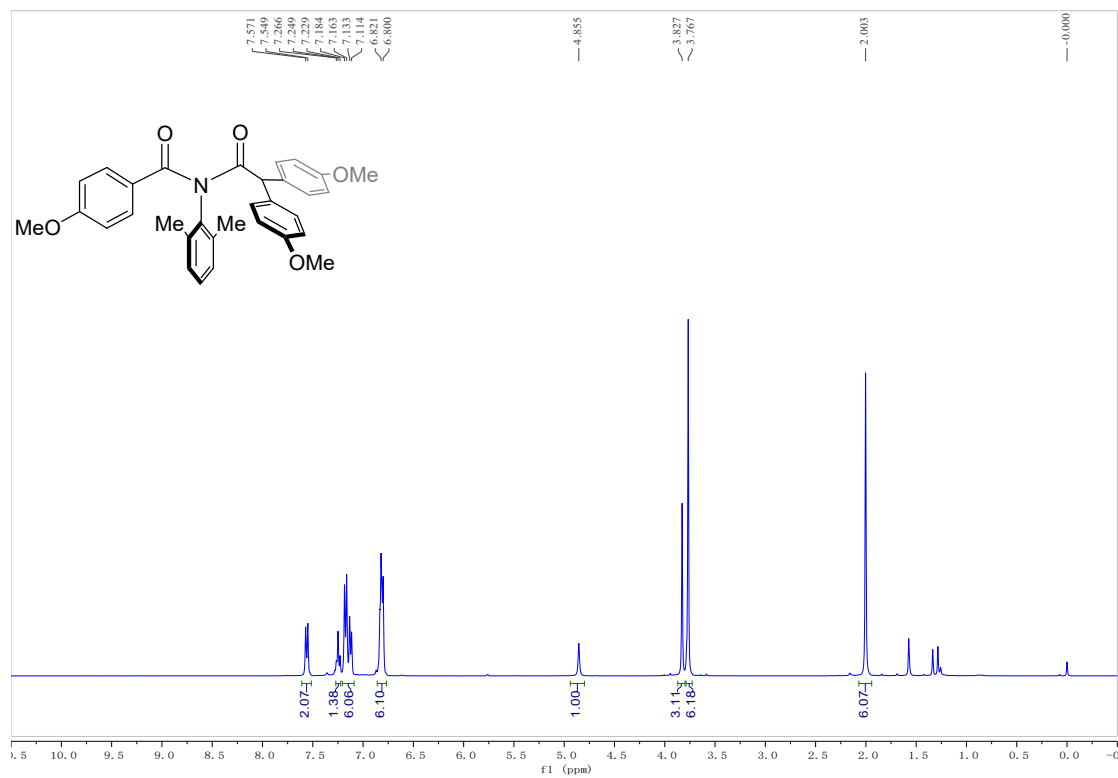
¹H and ¹³C NMR Spectra for Compound 3da:**¹H NMR (400 MHz, CDCl₃)****¹³C NMR (100 MHz, CDCl₃)**

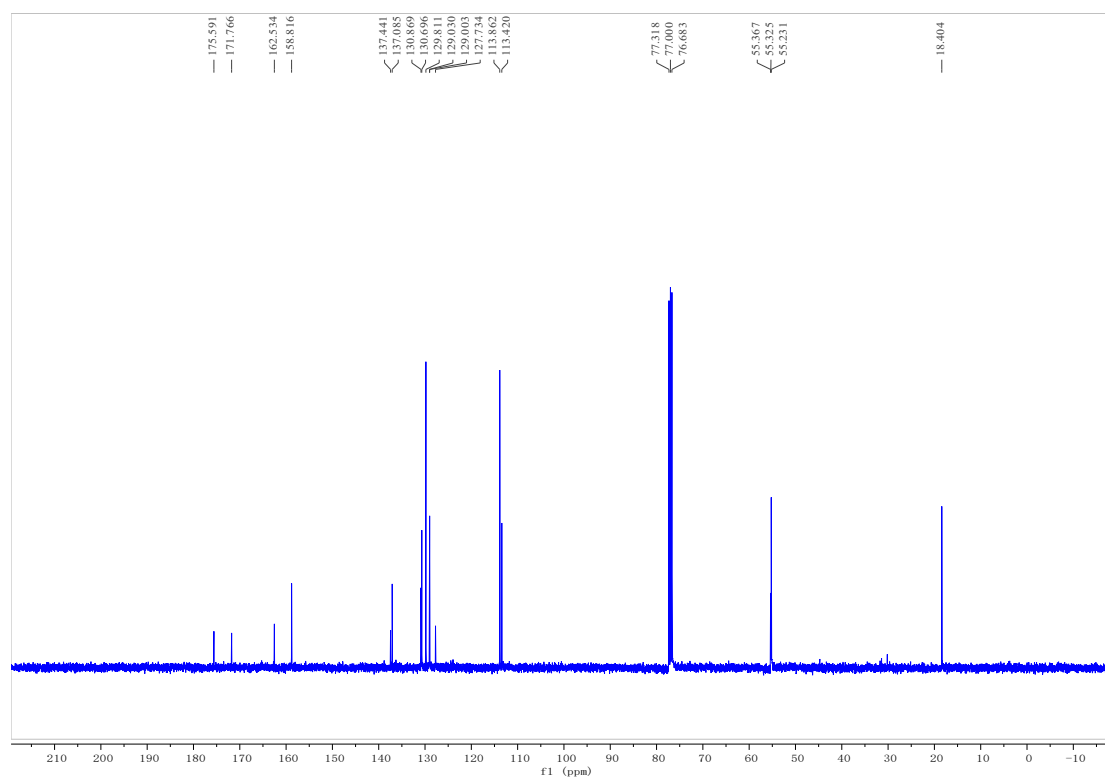
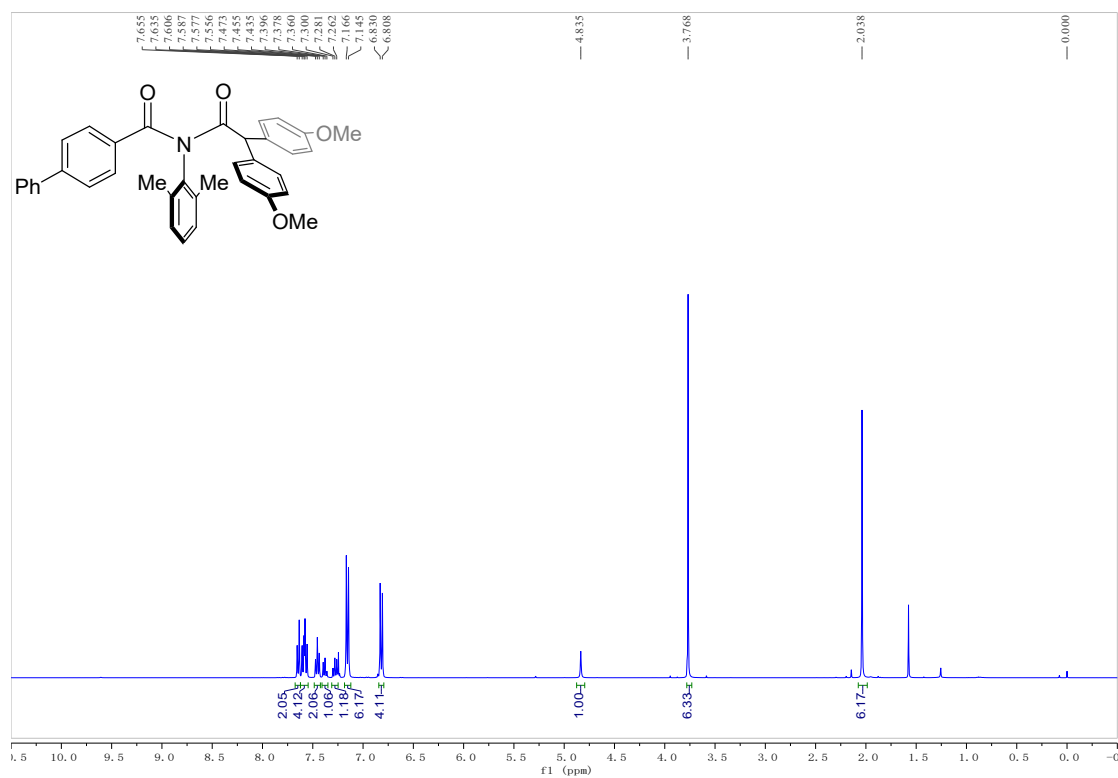
^1H and ^{13}C NMR Spectra for Compound 3ea: ^1H NMR (400 MHz, CDCl_3) ^{13}C NMR (100 MHz, CDCl_3)

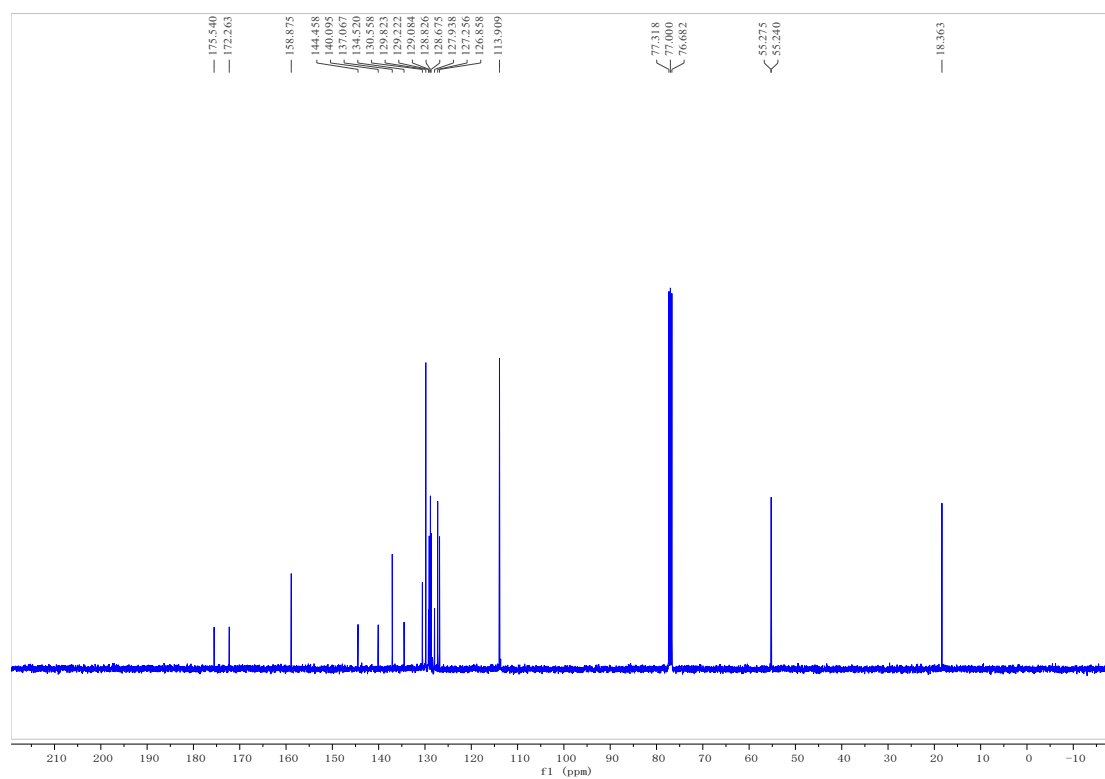
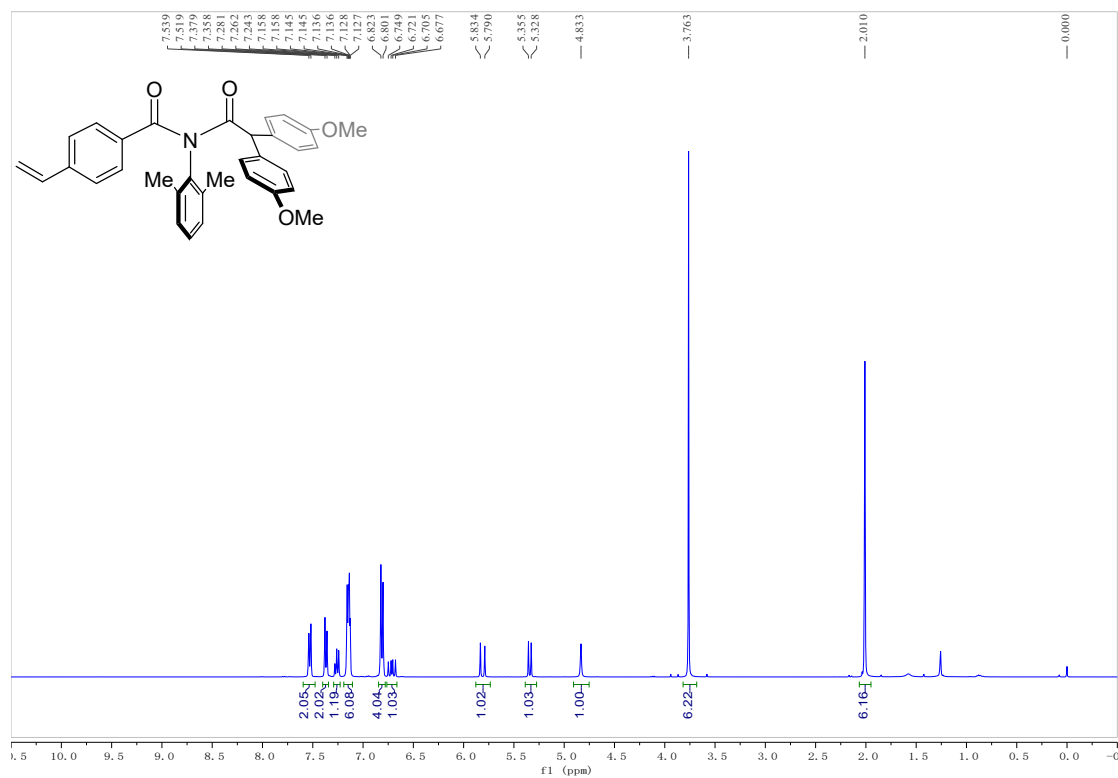
^{19}F NMR (376 MHz, CDCl_3) ^1H and ^{13}C NMR Spectra for Compound 3fa: ^1H NMR (400 MHz, CDCl_3)

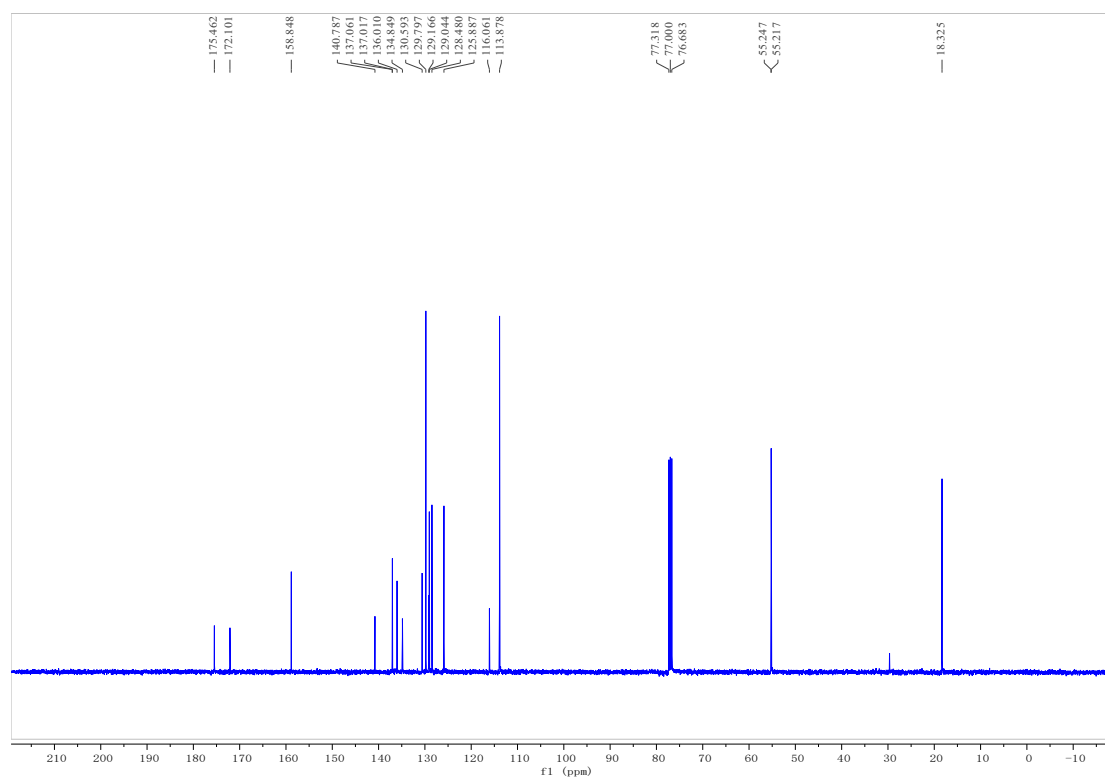
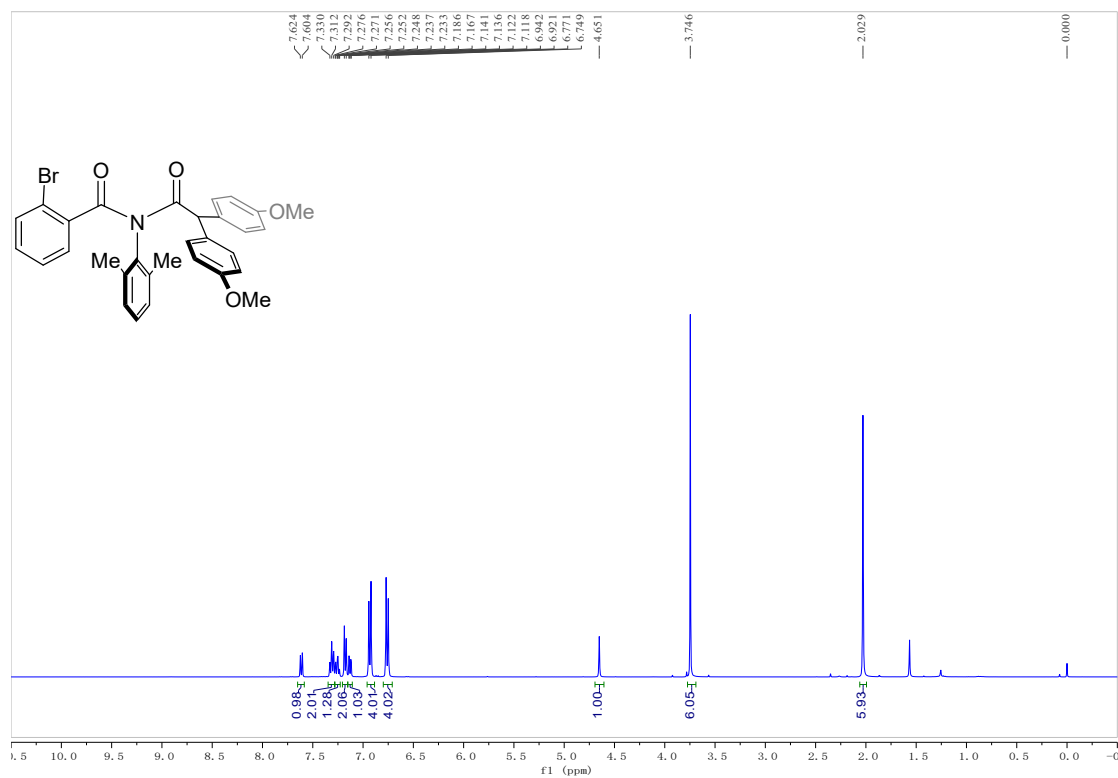
^{13}C NMR (100 MHz, CDCl_3) ^1H and ^{13}C NMR Spectra for Compound 3ga: ^1H NMR (400 MHz, CDCl_3)

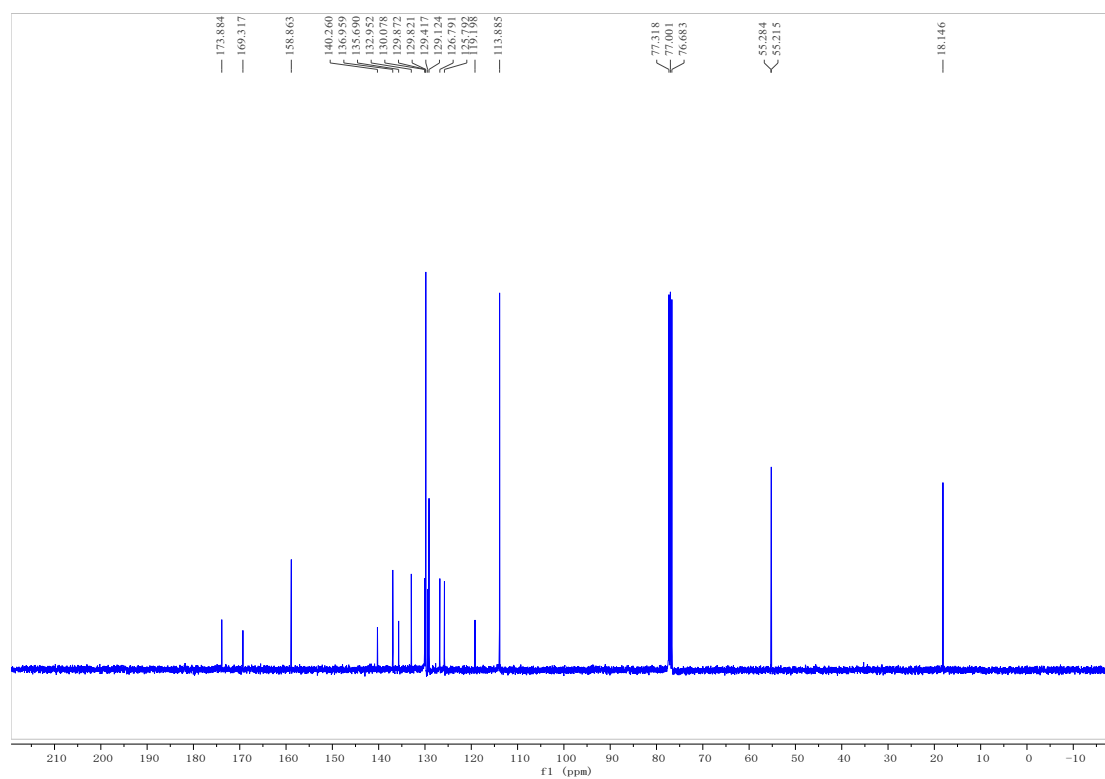
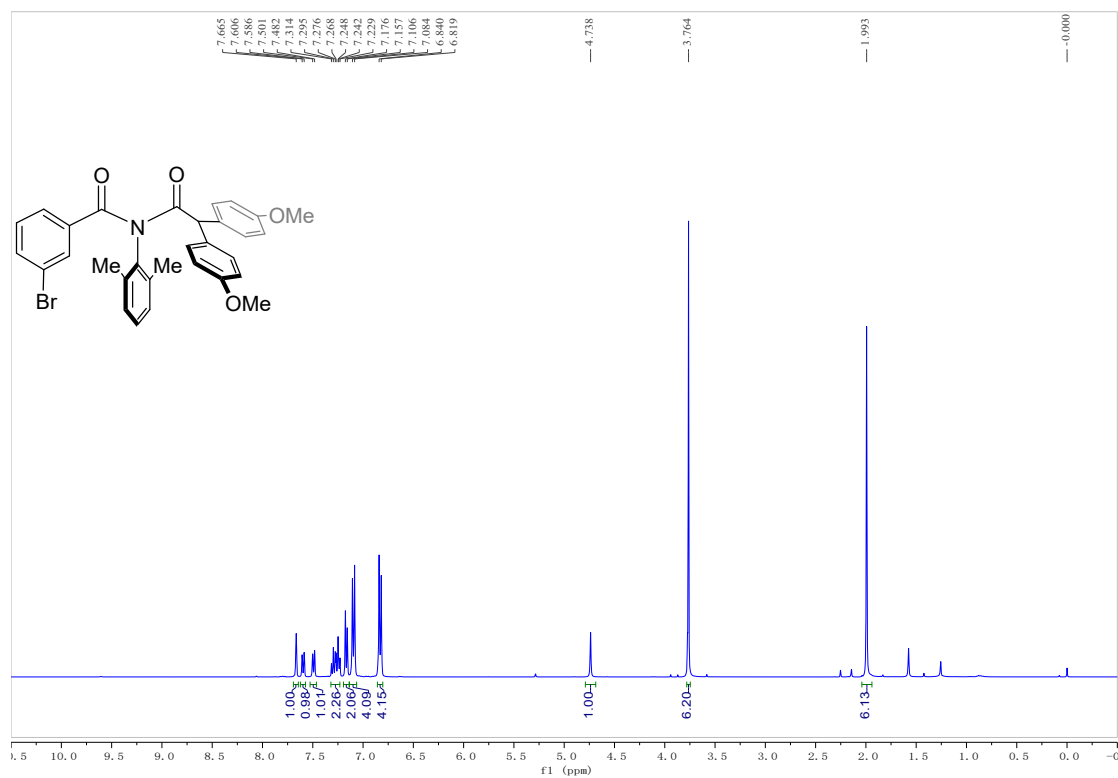
^{13}C NMR (100 MHz, CDCl_3) ^1H and ^{13}C NMR Spectra for Compound 3ha: ^1H NMR (400 MHz, CDCl_3)

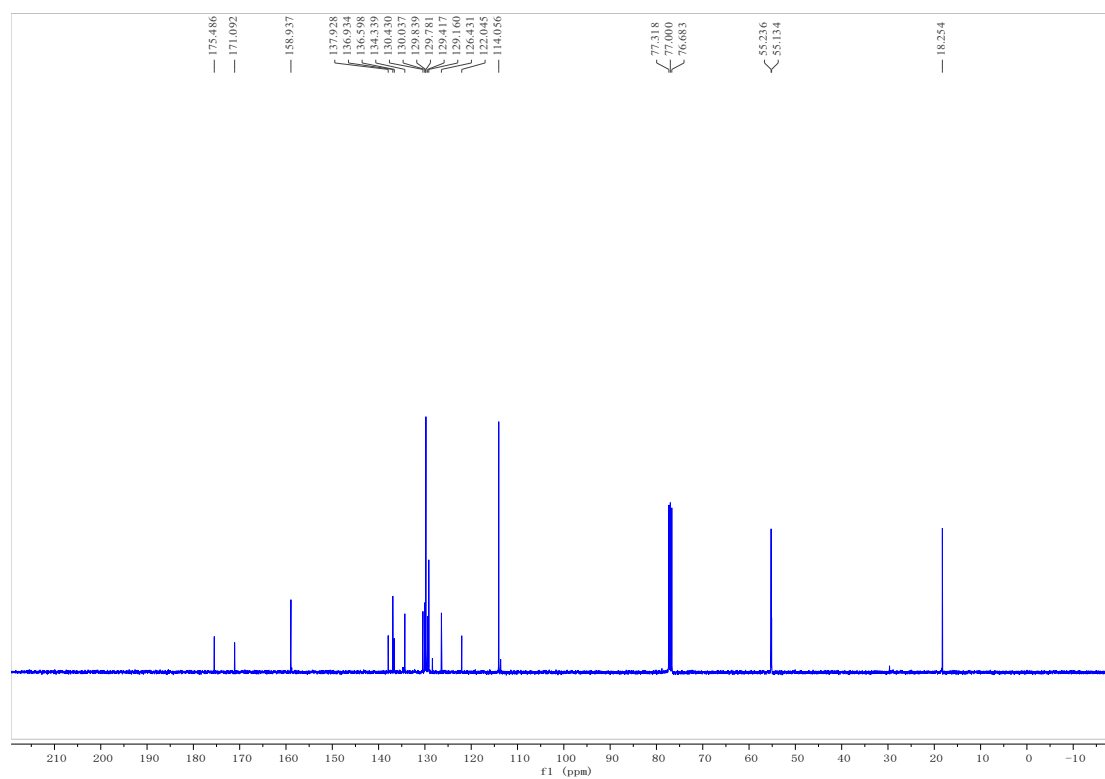
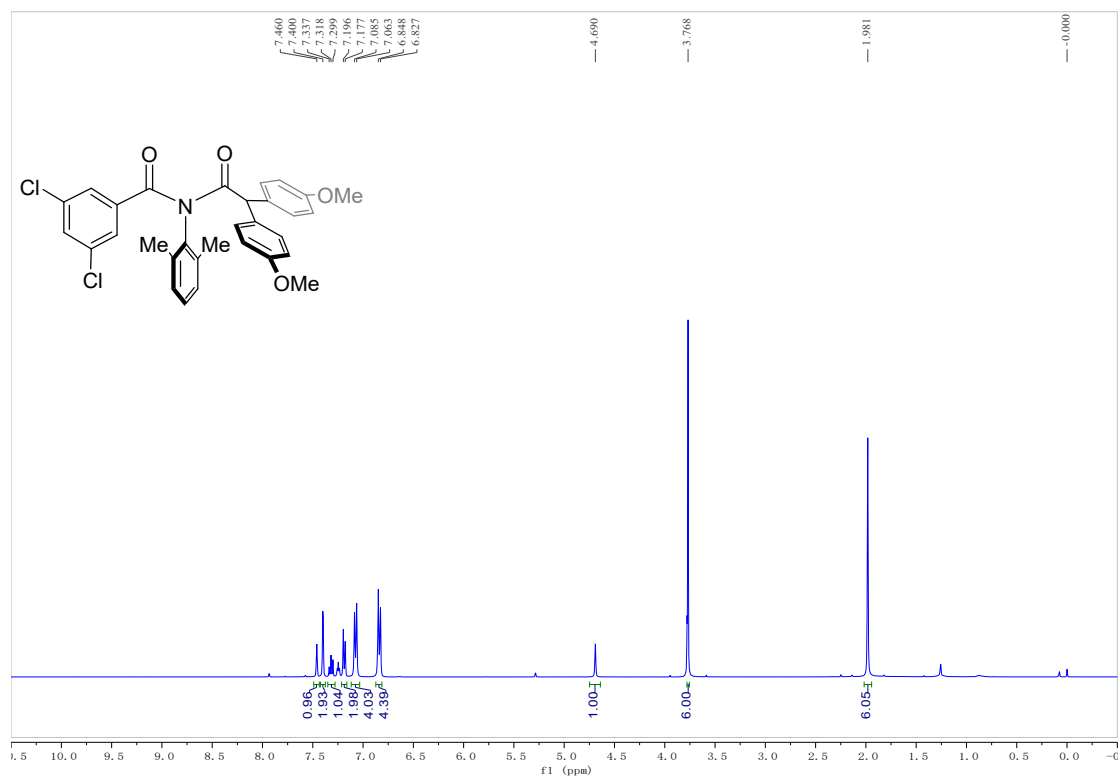
^{13}C NMR (100 MHz, CDCl_3) ^1H and ^{13}C NMR Spectra for Compound 3ia: ^1H NMR (400 MHz, CDCl_3)

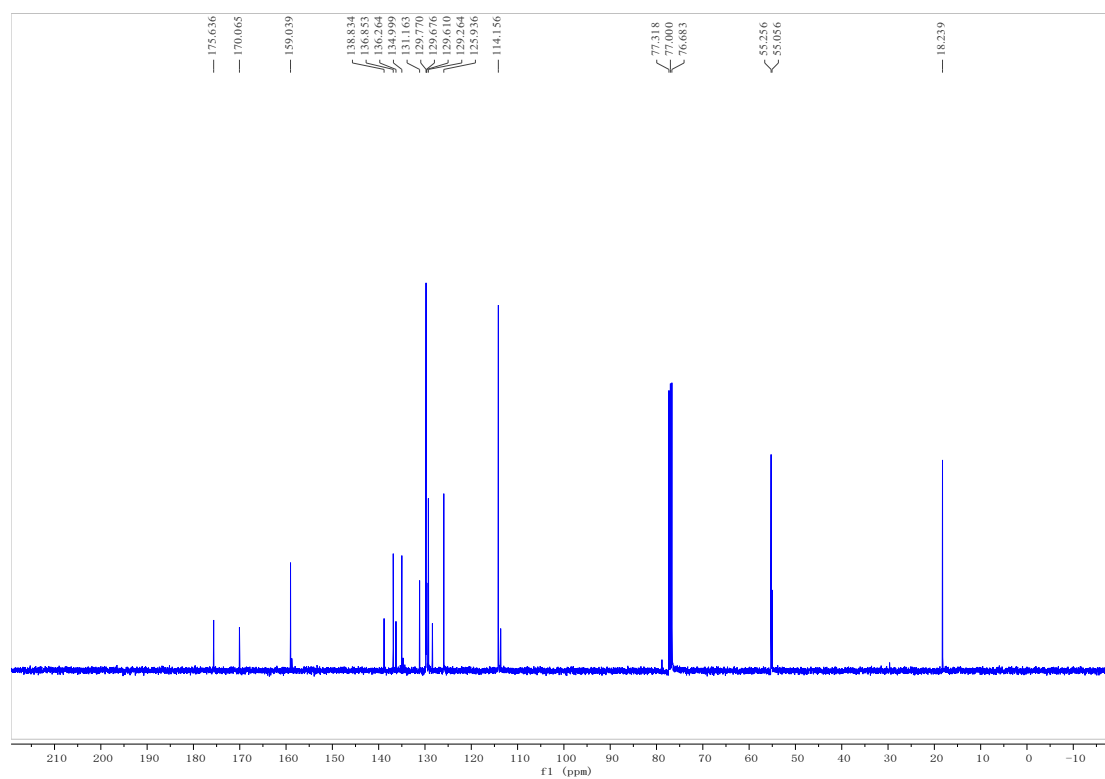
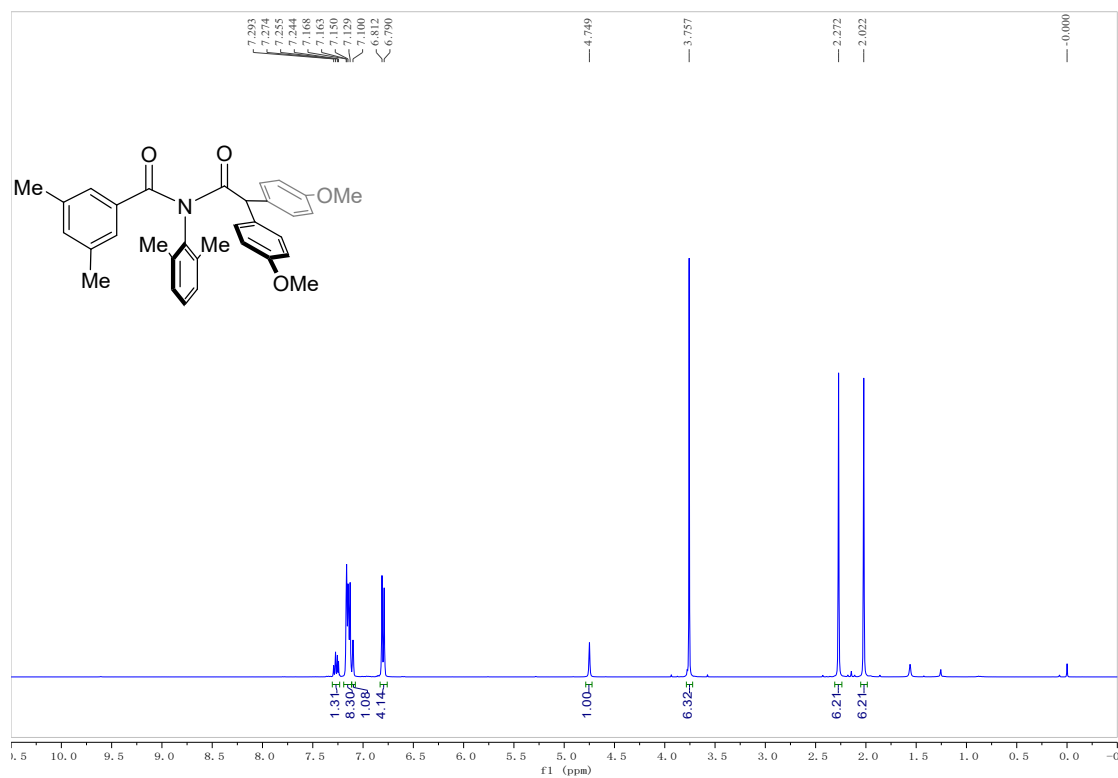
^{13}C NMR (100 MHz, CDCl_3) ^1H and ^{13}C NMR Spectra for Compound 3ja: ^1H NMR (400 MHz, CDCl_3)

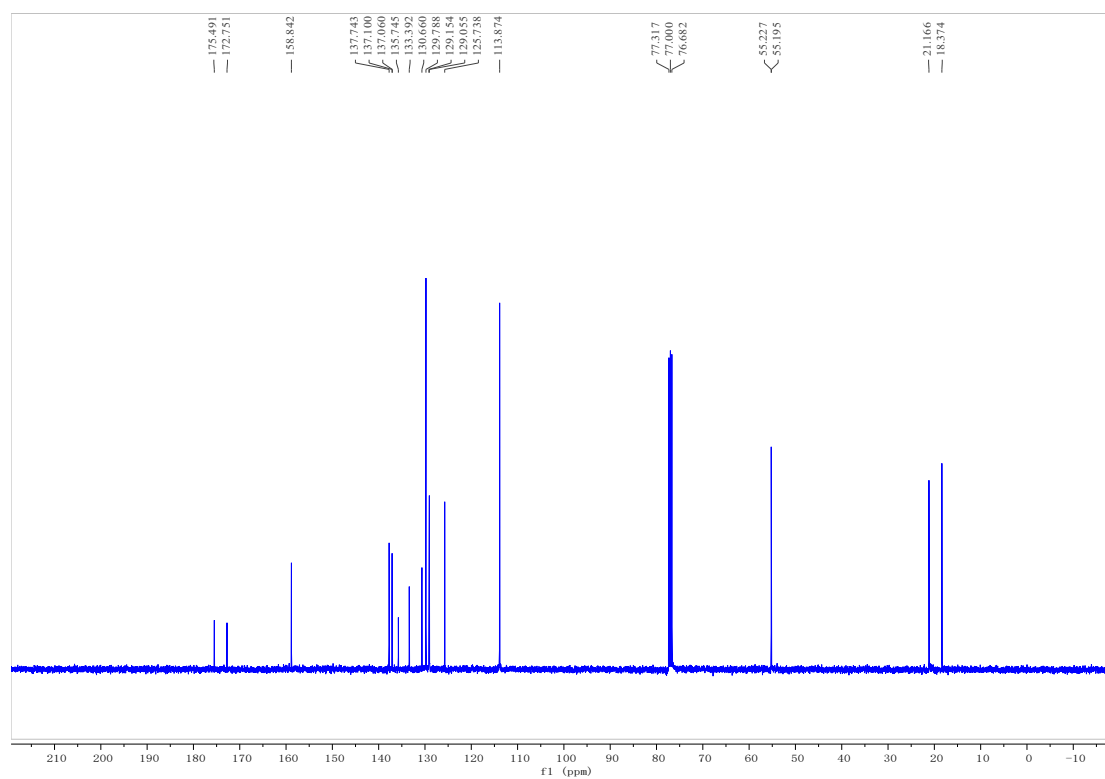
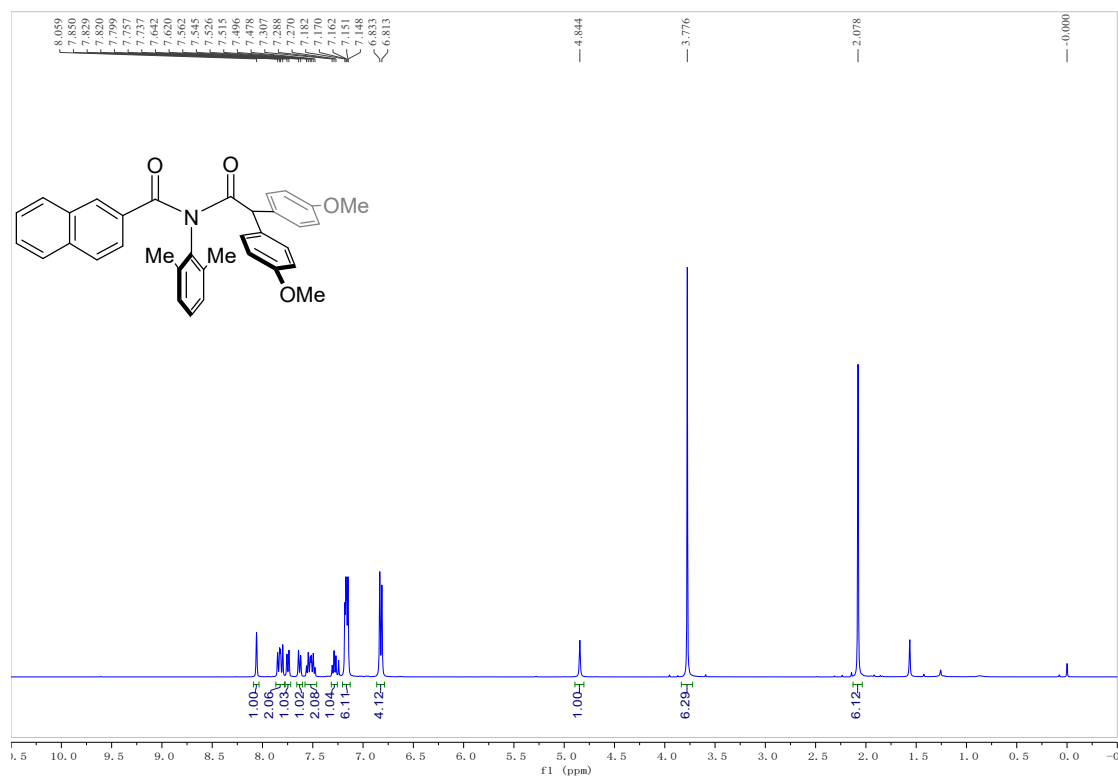
^{13}C NMR (100 MHz, CDCl_3) ^1H and ^{13}C NMR Spectra for Compound 3ka: ^1H NMR (400 MHz, CDCl_3)

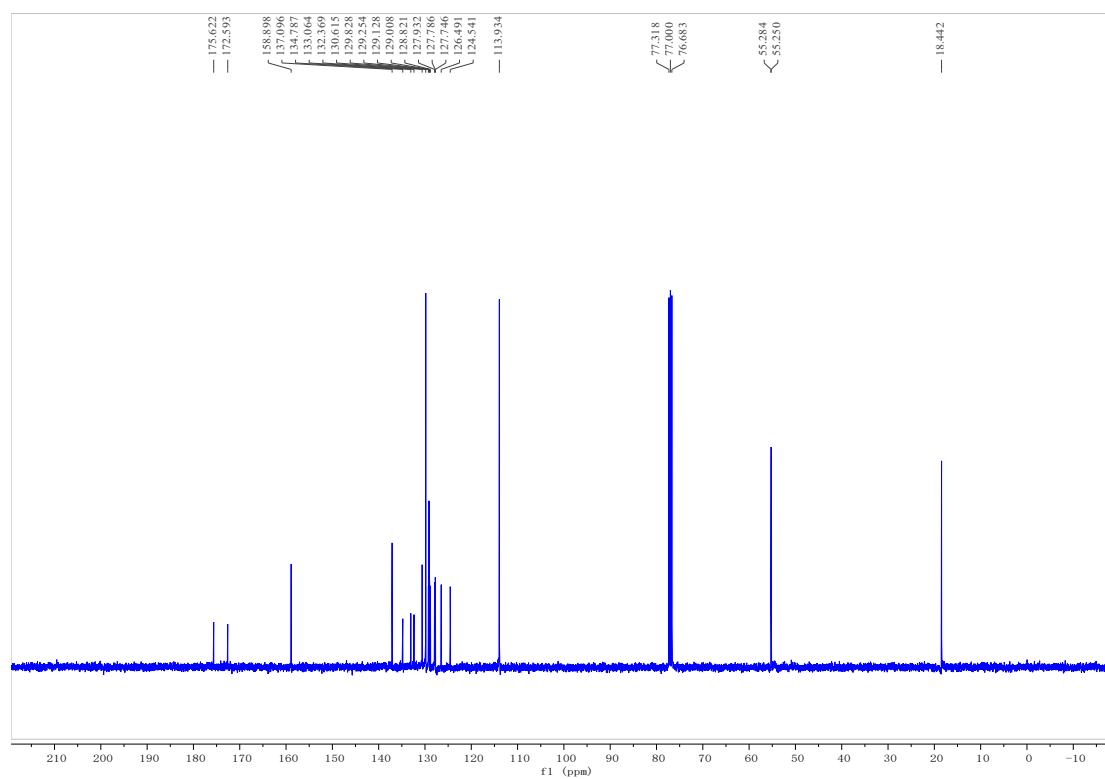
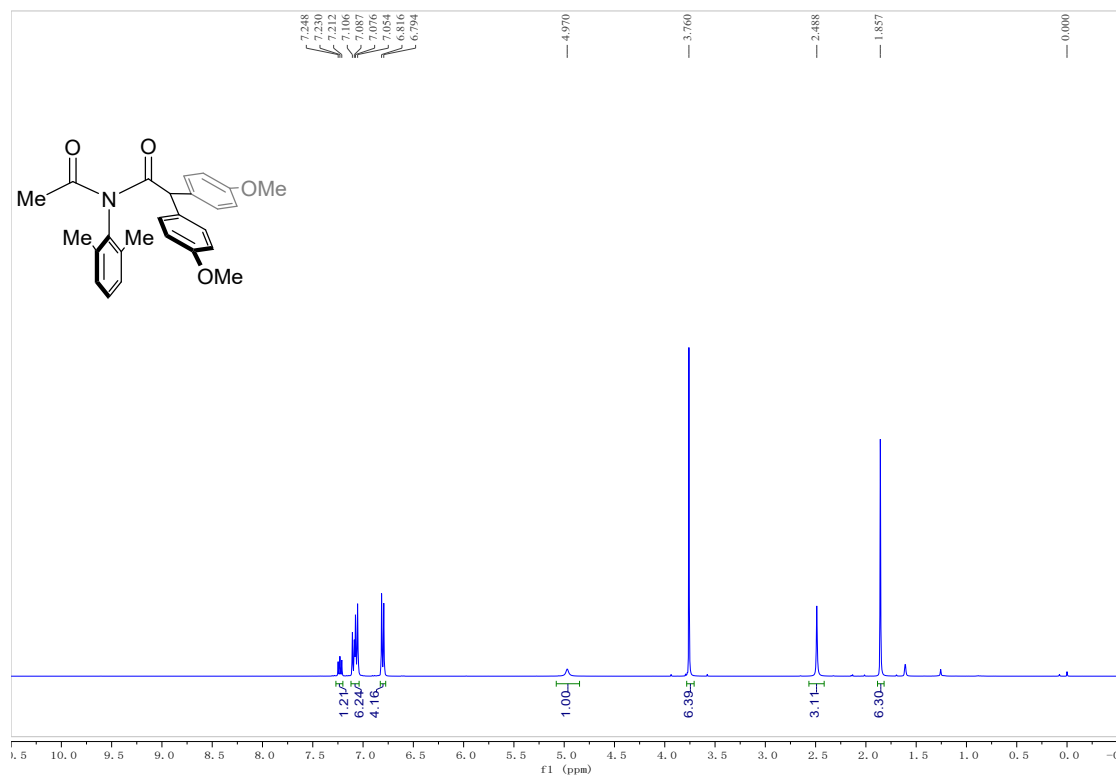
^{13}C NMR (100 MHz, CDCl_3) ^1H and ^{13}C NMR Spectra for Compound 3la: ^1H NMR (400 MHz, CDCl_3)

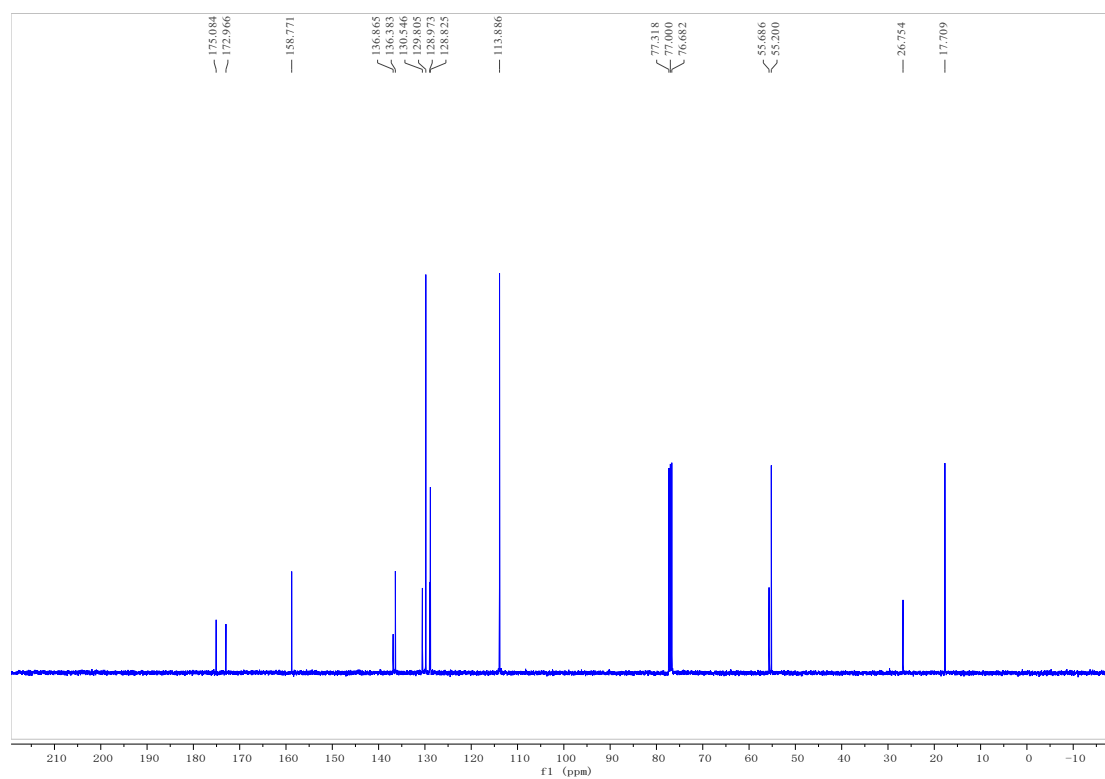
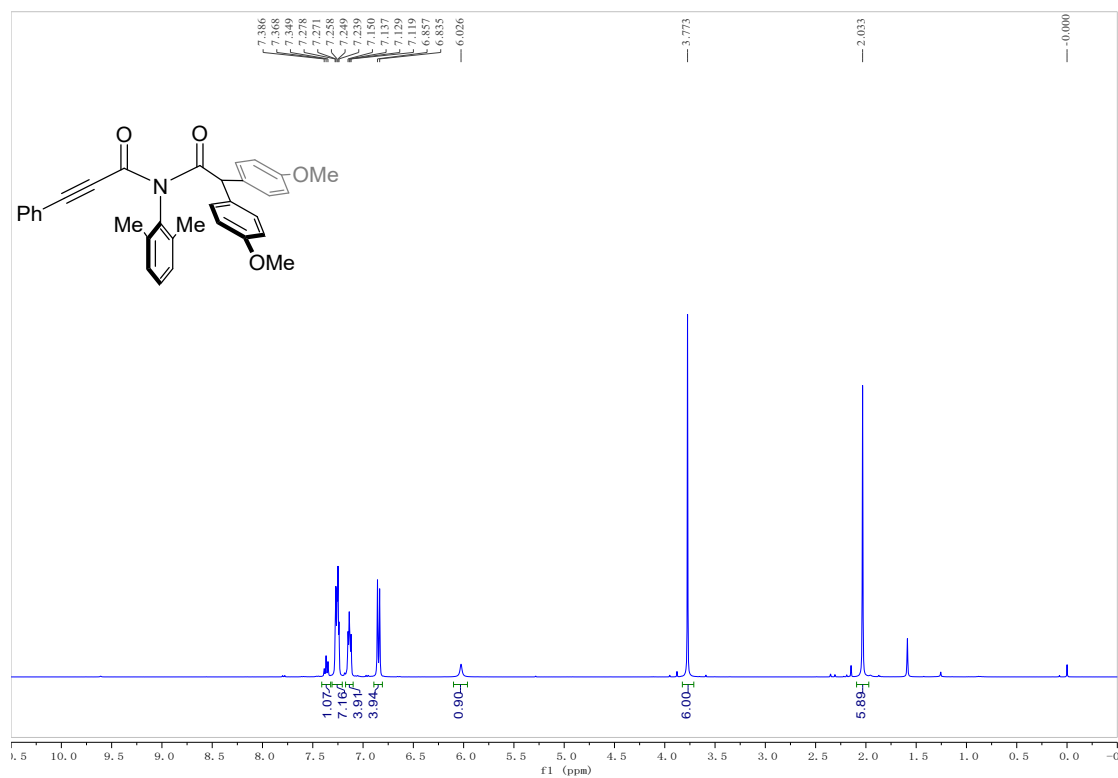
^{13}C NMR (100 MHz, CDCl_3) ^1H and ^{13}C NMR Spectra for Compound 3ma: ^1H NMR (400 MHz, CDCl_3)

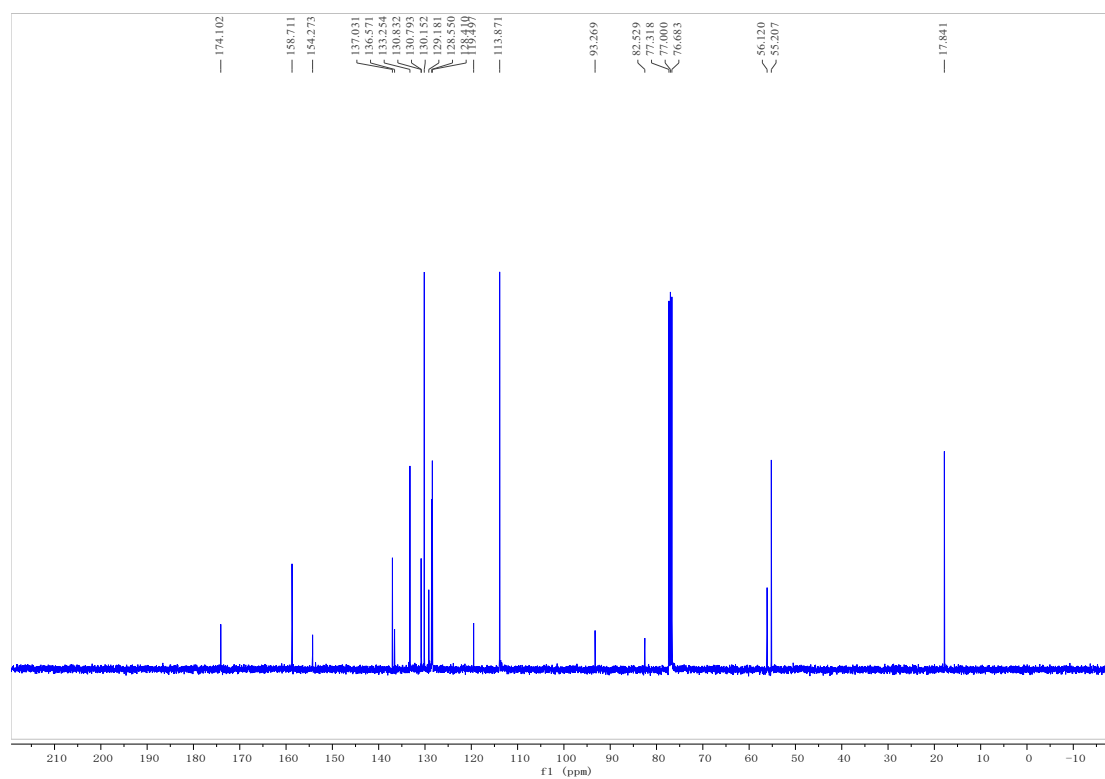
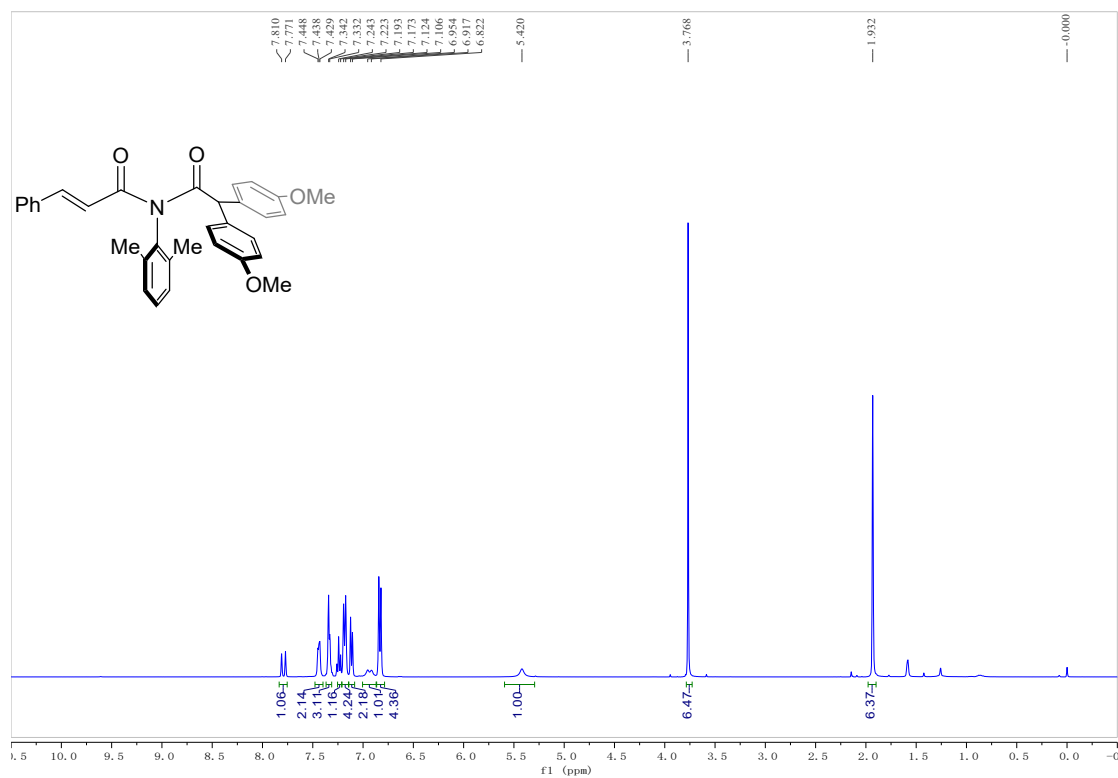
^{13}C NMR (100 MHz, CDCl_3) ^1H and ^{13}C NMR Spectra for Compound 3na: ^1H NMR (400 MHz, CDCl_3)

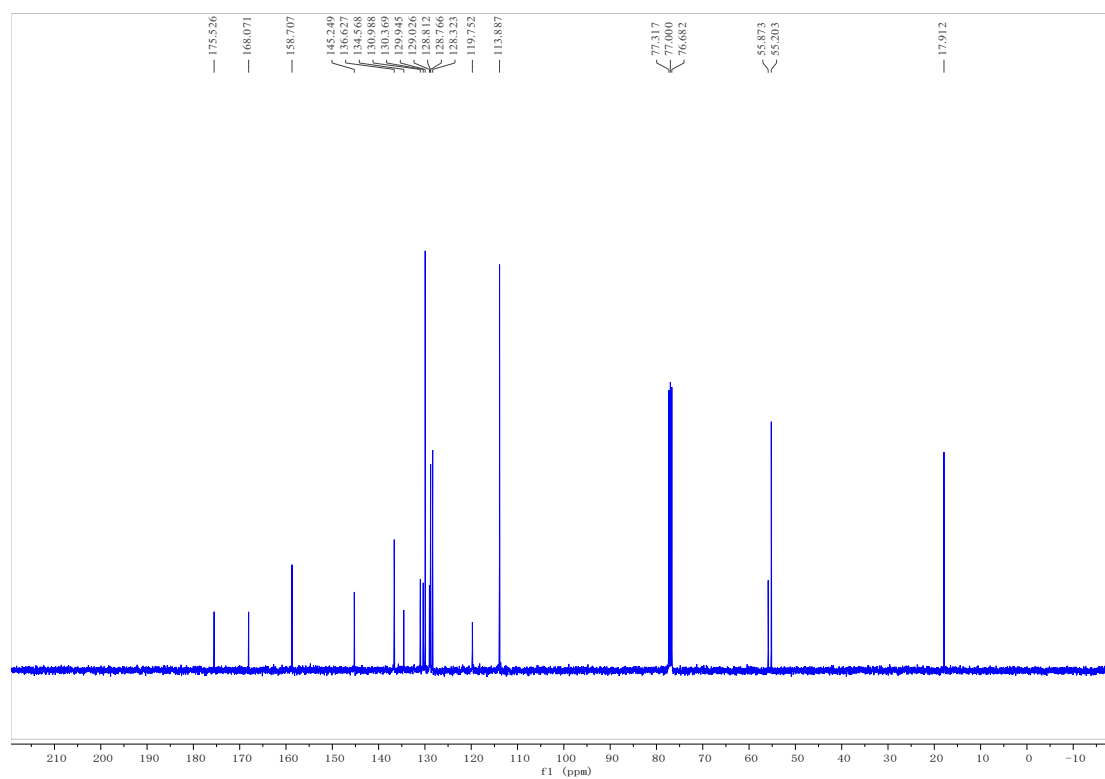
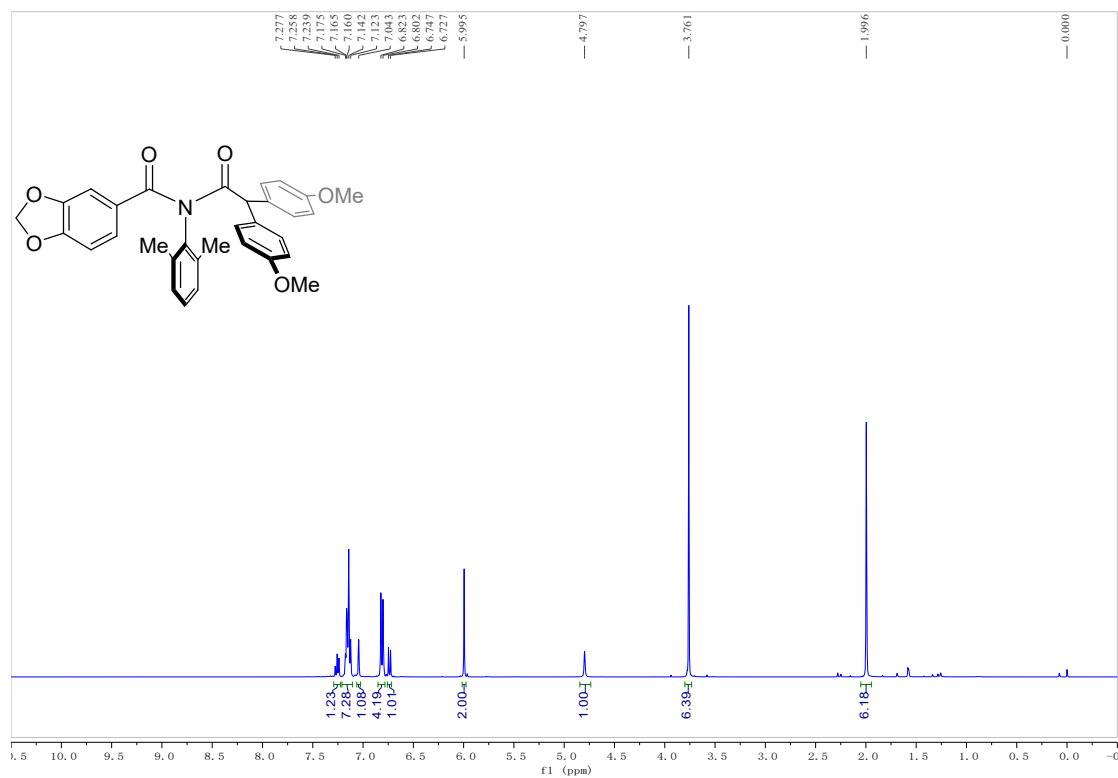
^{13}C NMR (100 MHz, CDCl_3) ^1H and ^{13}C NMR Spectra for Compound 30a: ^1H NMR (400 MHz, CDCl_3)

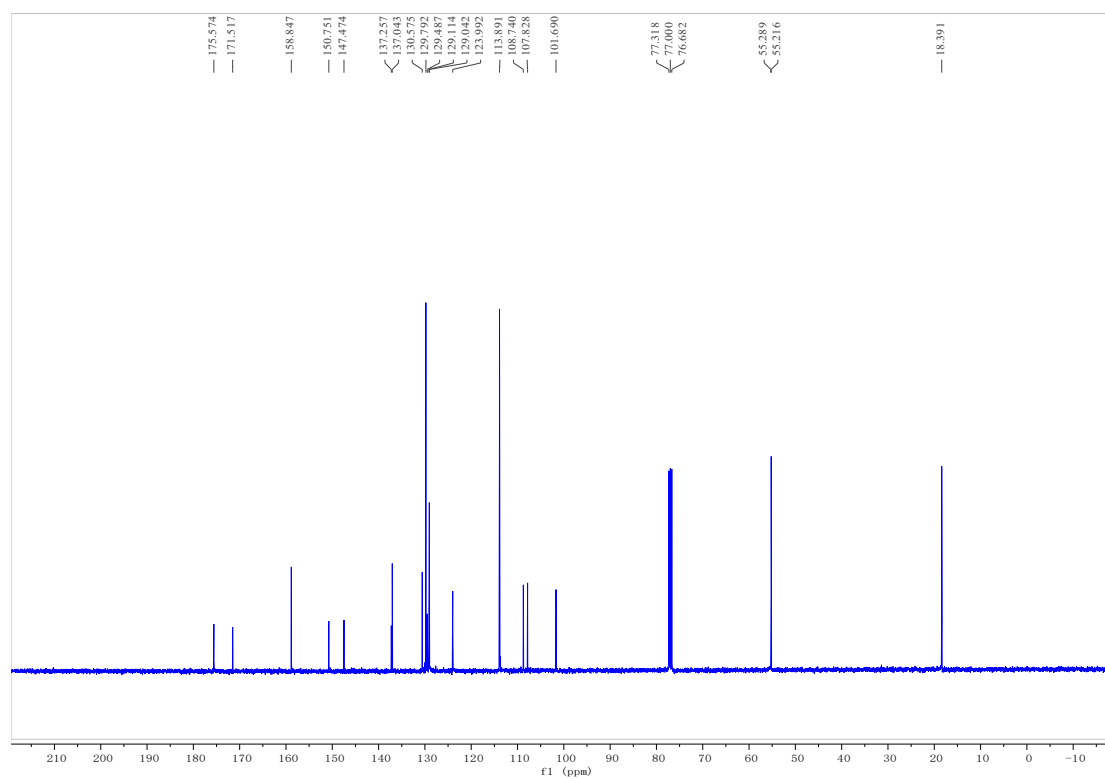
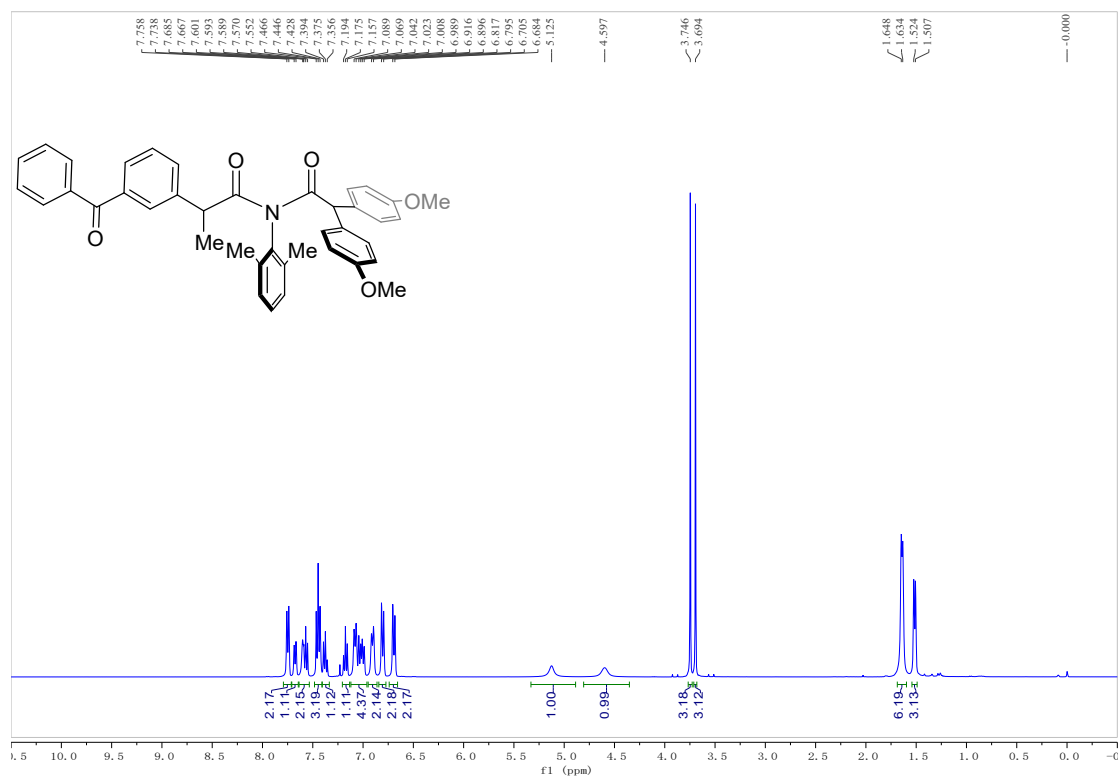
^{13}C NMR (100 MHz, CDCl_3) ^1H and ^{13}C NMR Spectra for Compound 3pa: ^1H NMR (400 MHz, CDCl_3)

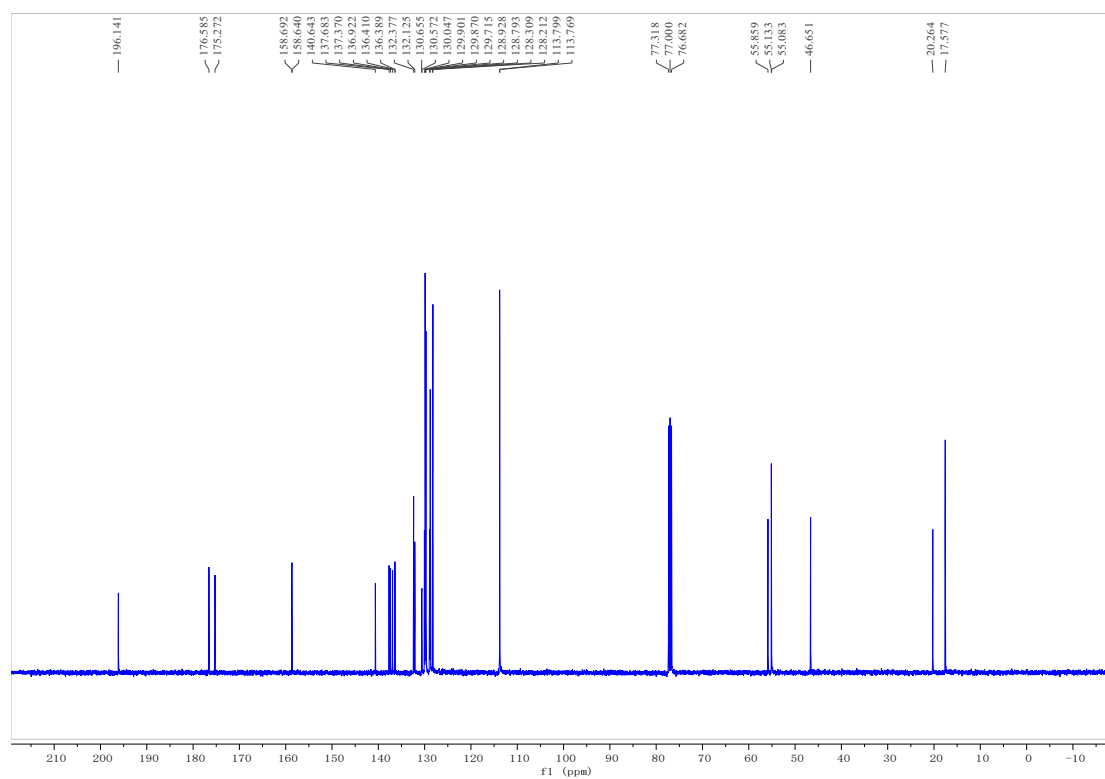
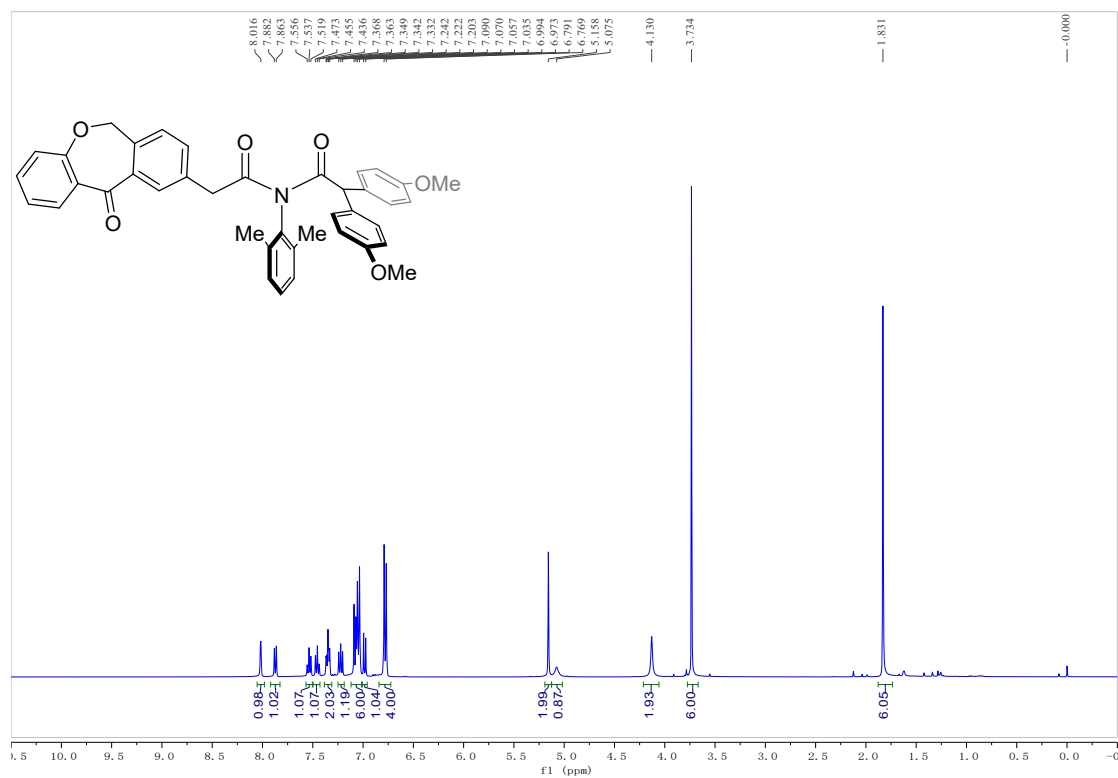
^{13}C NMR (100 MHz, CDCl_3) ^1H and ^{13}C NMR Spectra for Compound 3qa: ^1H NMR (400 MHz, CDCl_3)

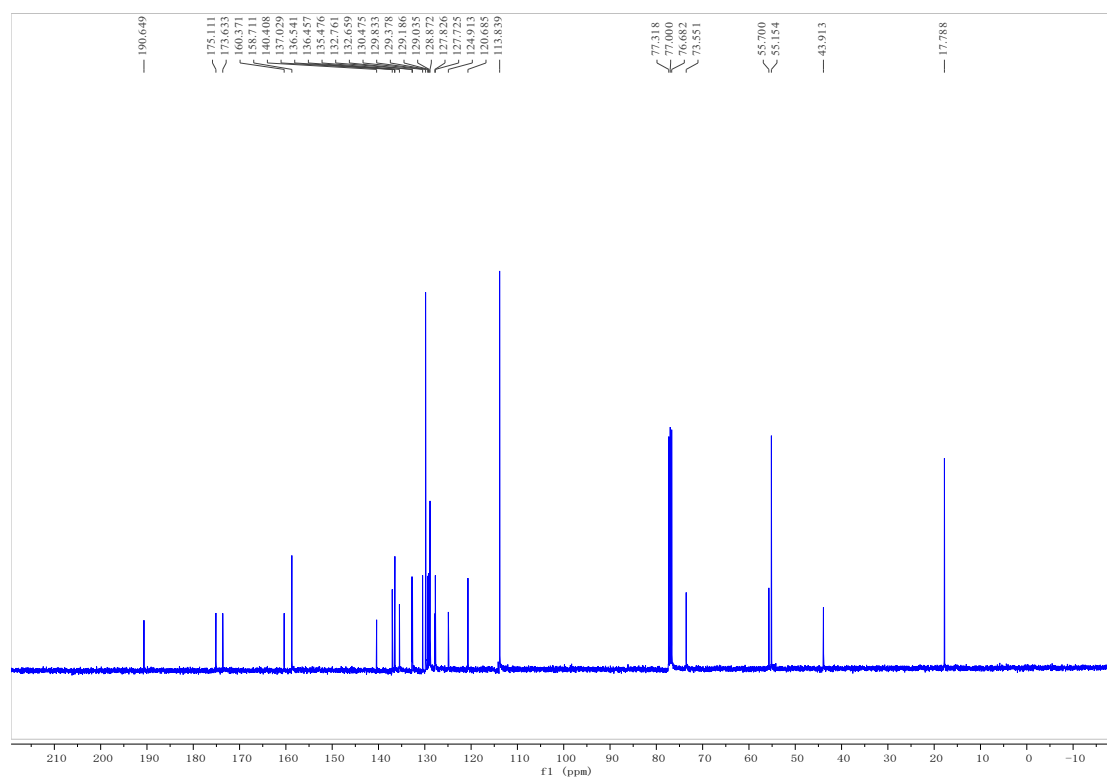
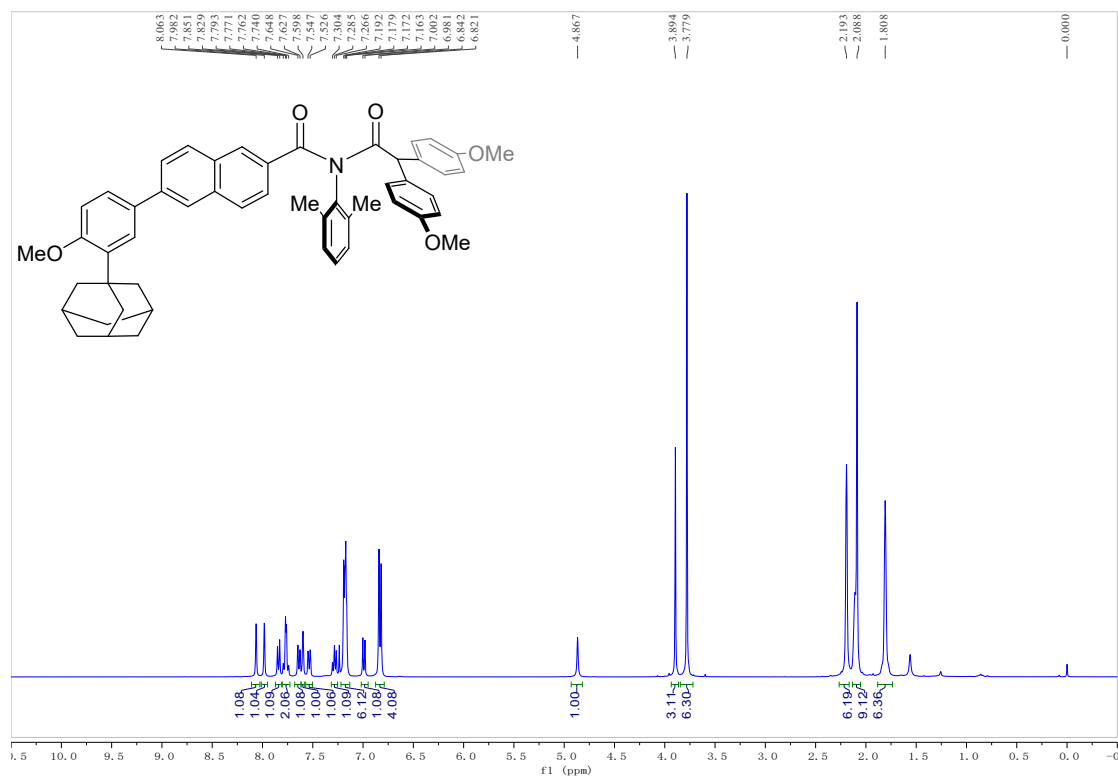
^{13}C NMR (100 MHz, CDCl_3) ^1H and ^{13}C NMR Spectra for Compound 3ra: ^1H NMR (400 MHz, CDCl_3)

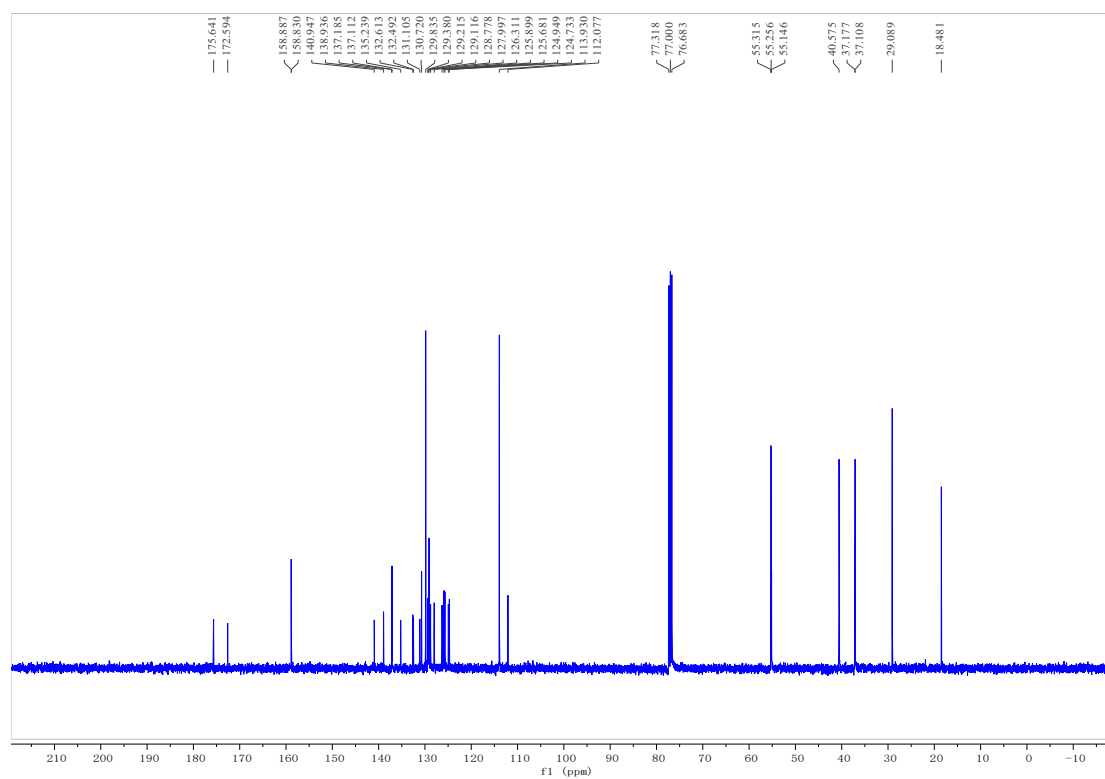
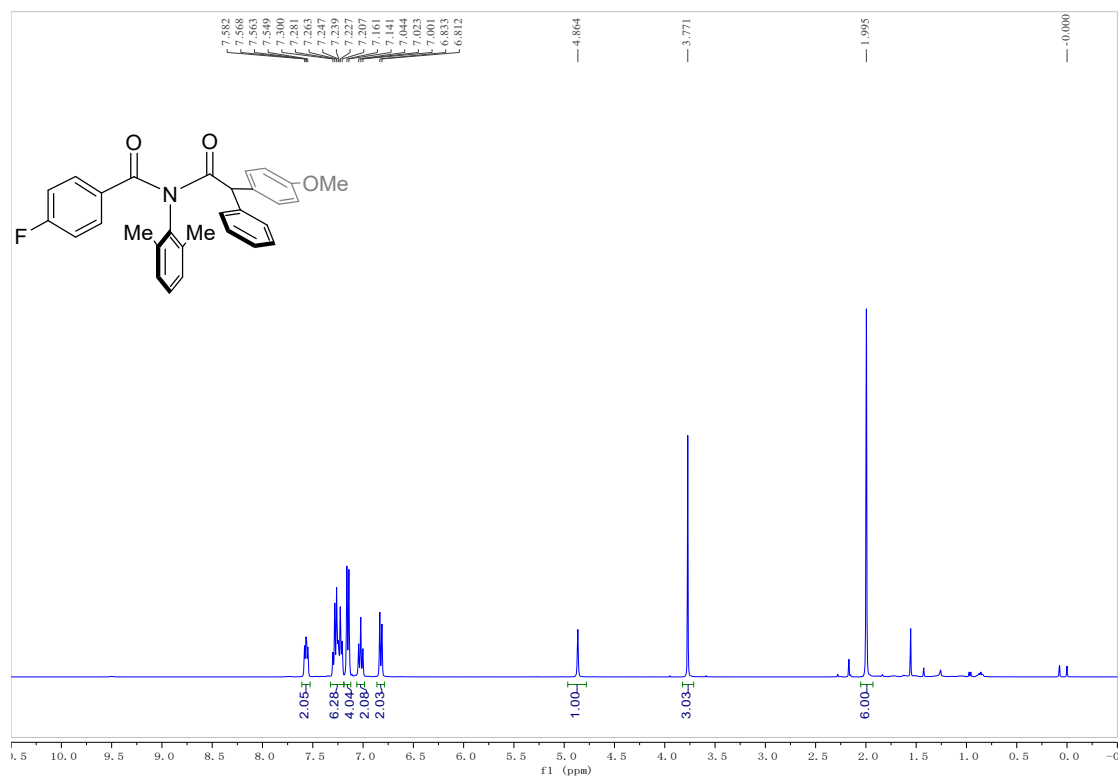
^{13}C NMR (100 MHz, CDCl_3) ^1H and ^{13}C NMR Spectra for Compound 3sa: ^1H NMR (400 MHz, CDCl_3)

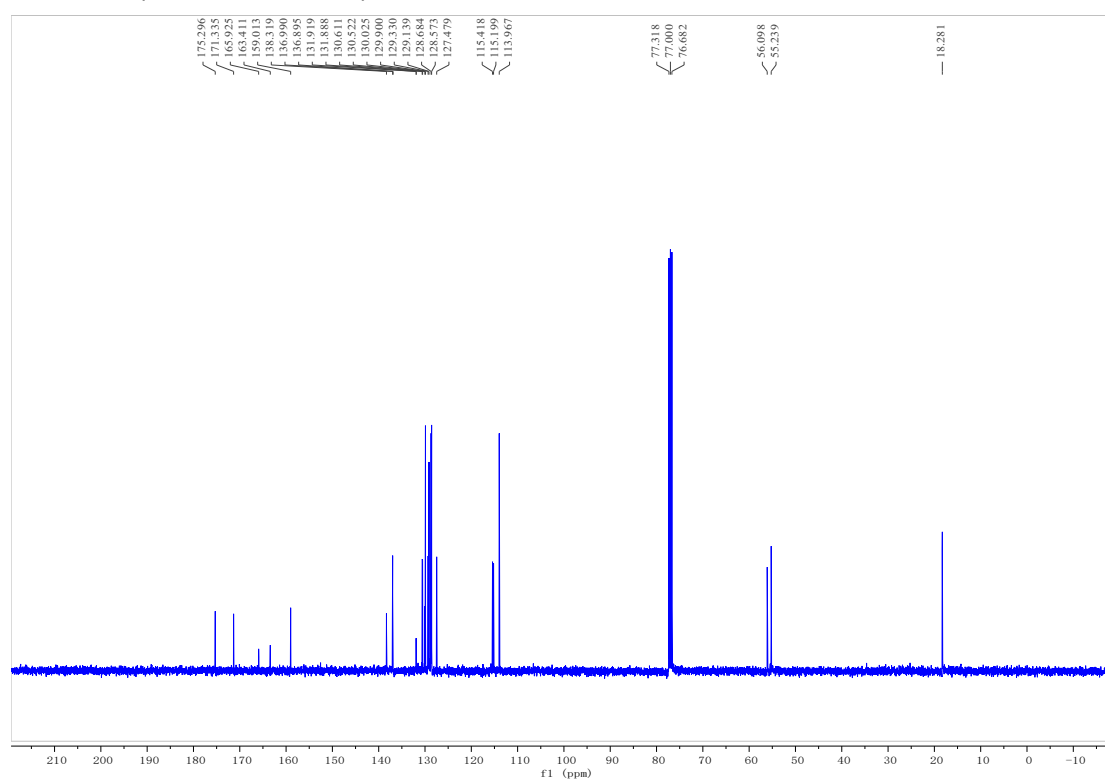
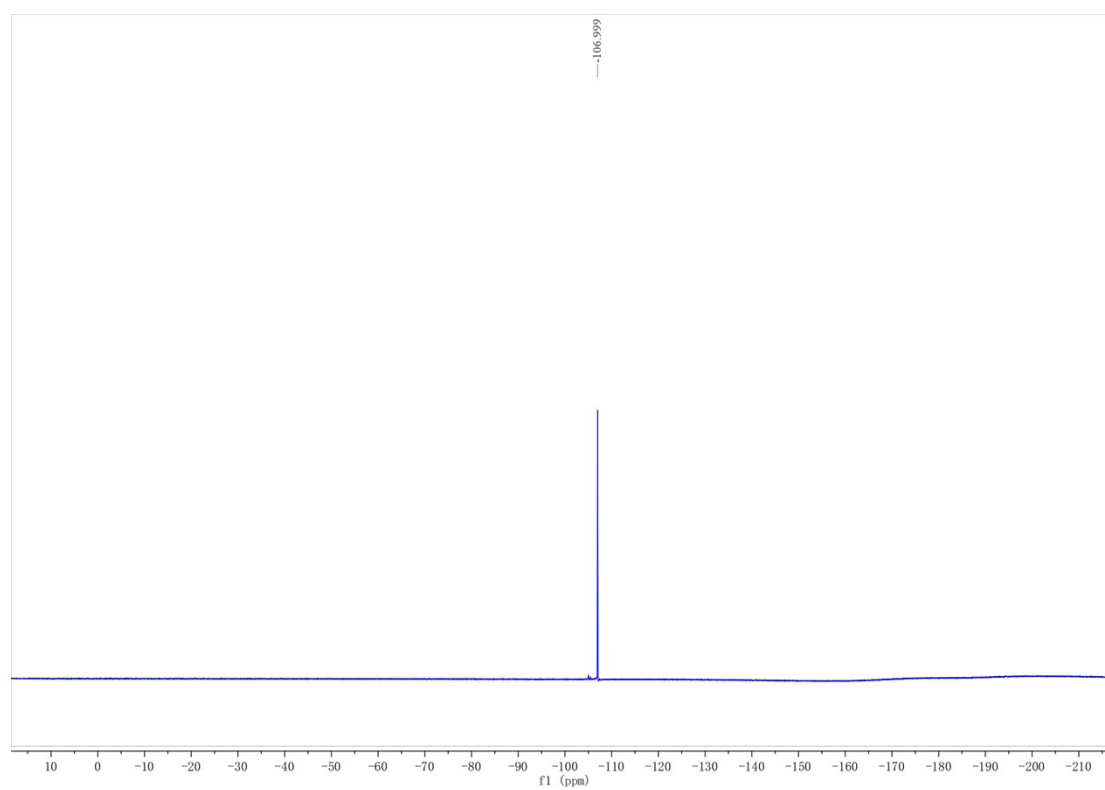
^{13}C NMR (100 MHz, CDCl_3) ^1H and ^{13}C NMR Spectra for Compound 3ta: ^1H NMR (400 MHz, CDCl_3)

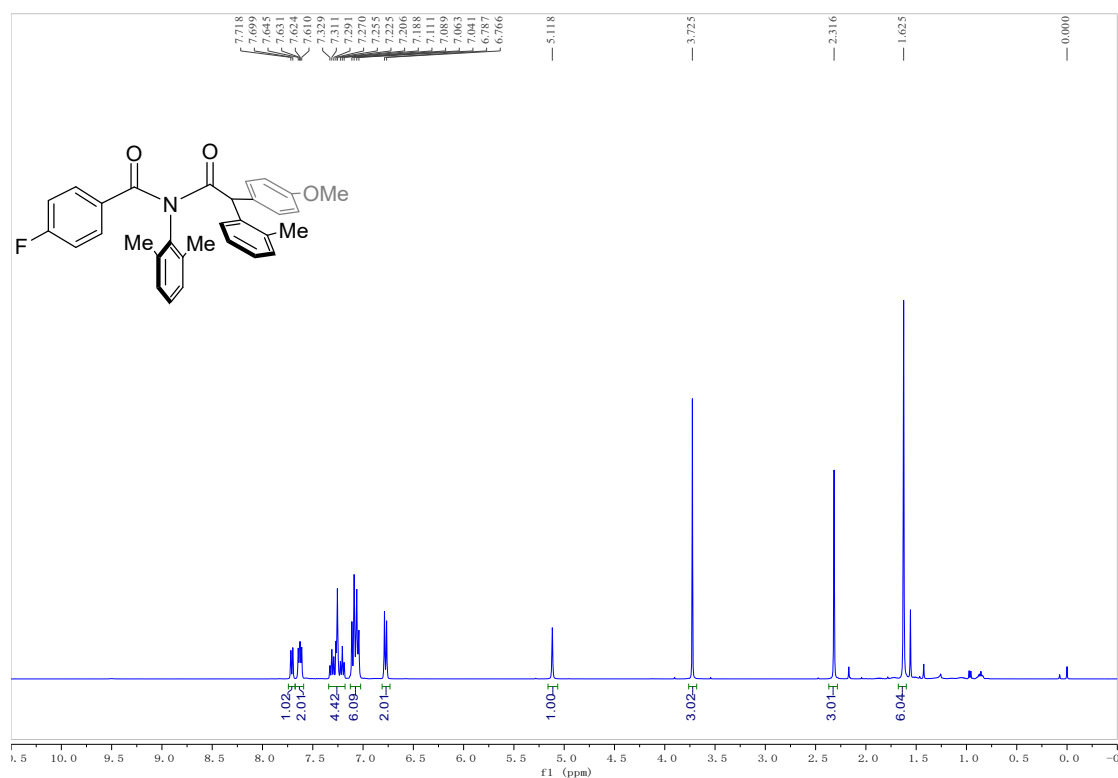
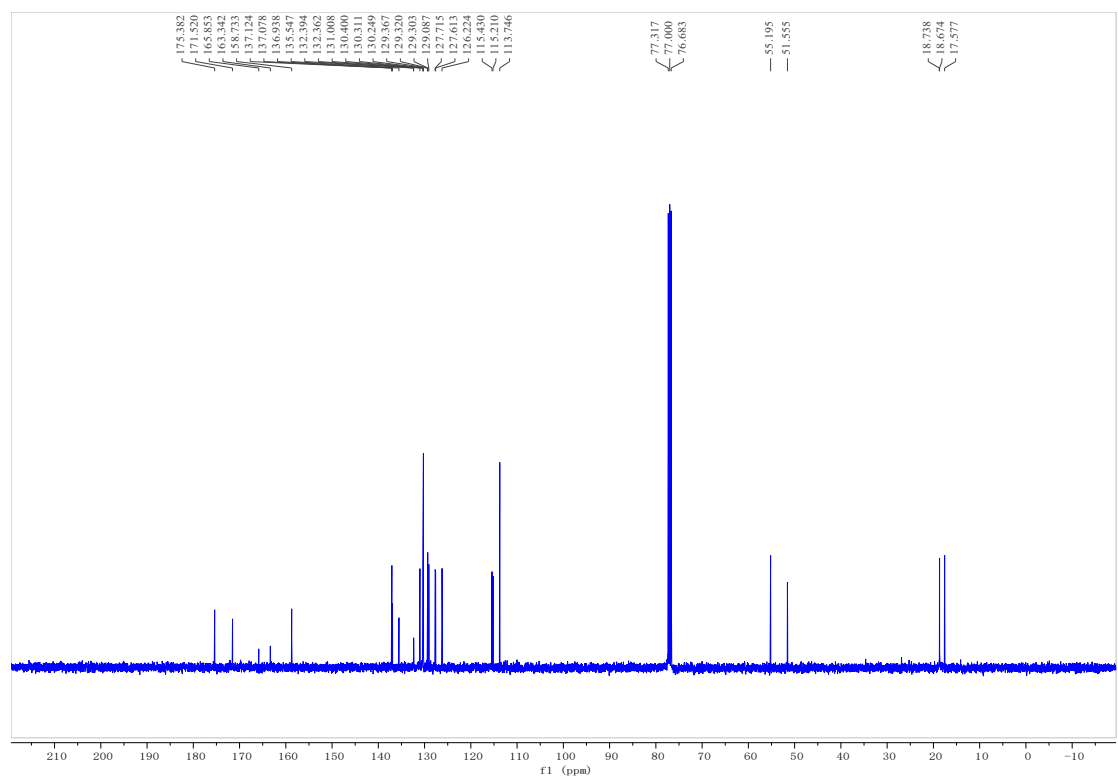
^{13}C NMR (100 MHz, CDCl_3) ^1H and ^{13}C NMR Spectra for Compound 3ua: ^1H NMR (400 MHz, CDCl_3)

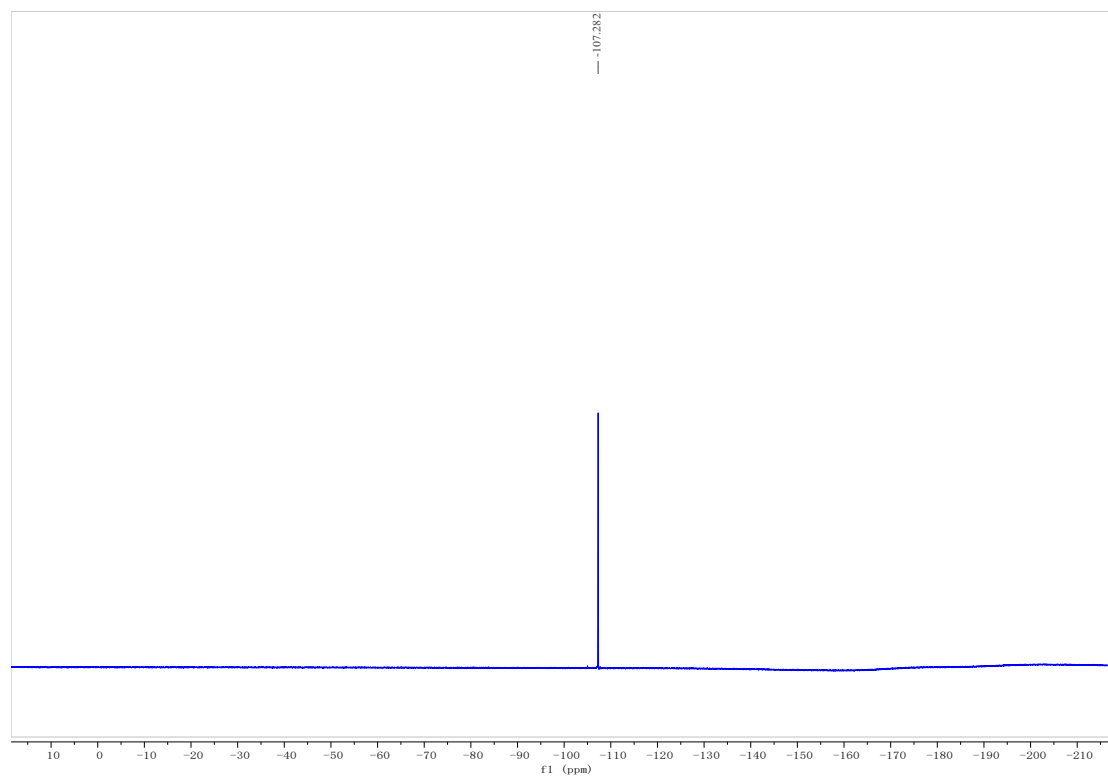
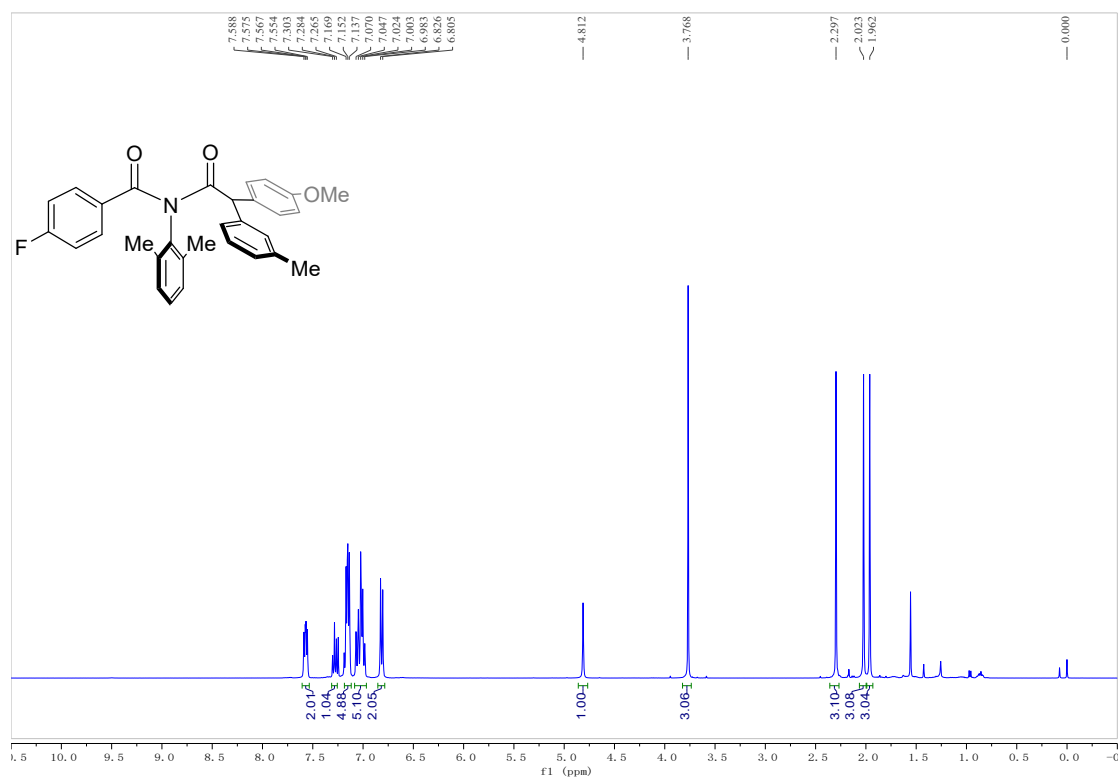
^{13}C NMR (100 MHz, CDCl_3) ^1H and ^{13}C NMR Spectra for Compound 3va: ^1H NMR (400 MHz, CDCl_3)

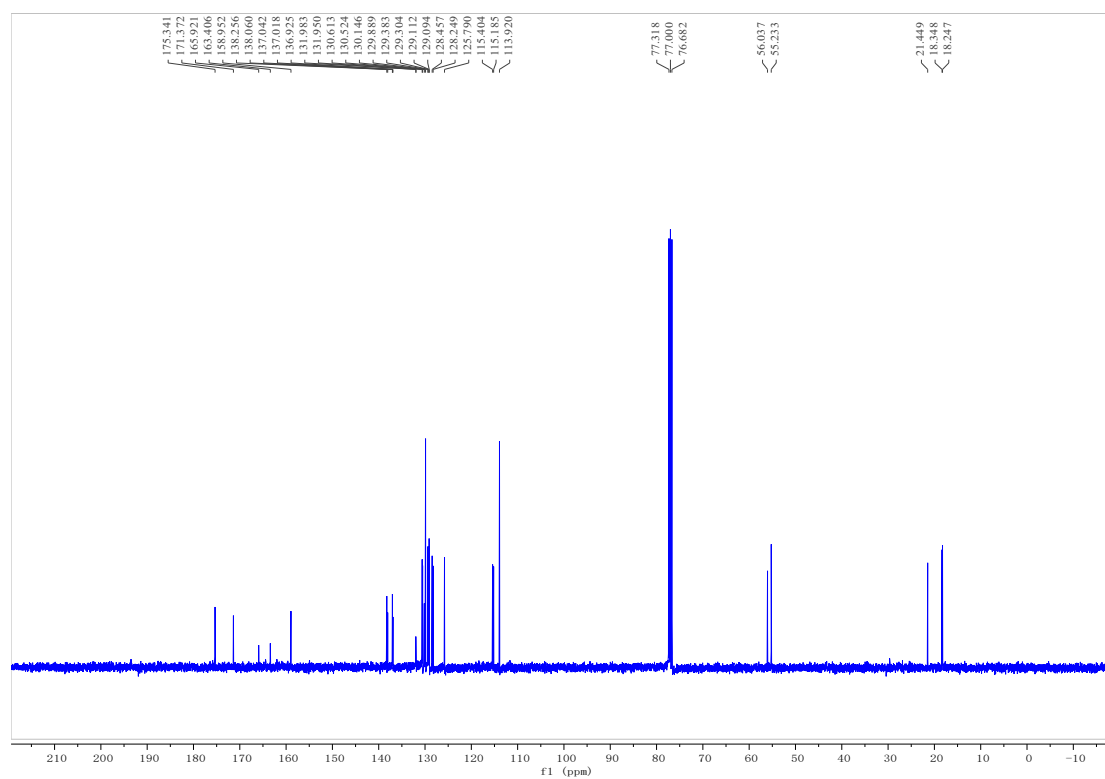
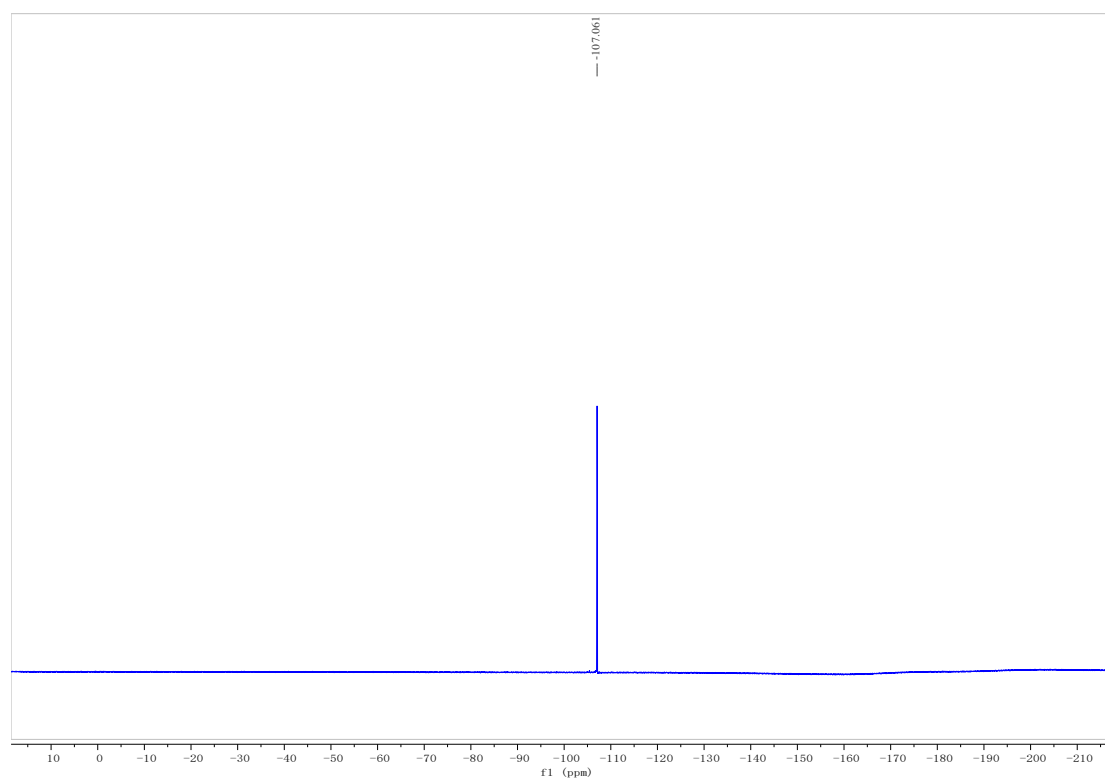
^{13}C NMR (100 MHz, CDCl_3) ^1H and ^{13}C NMR Spectra for Compound 3wa: ^1H NMR (400 MHz, CDCl_3)

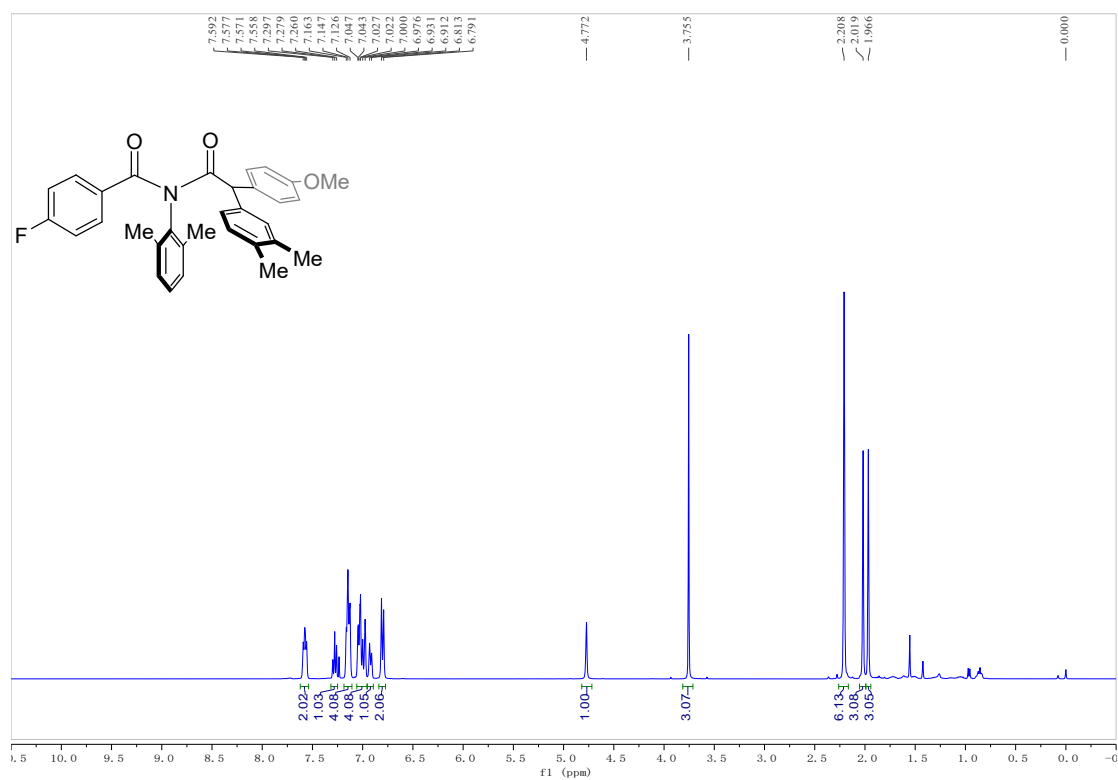
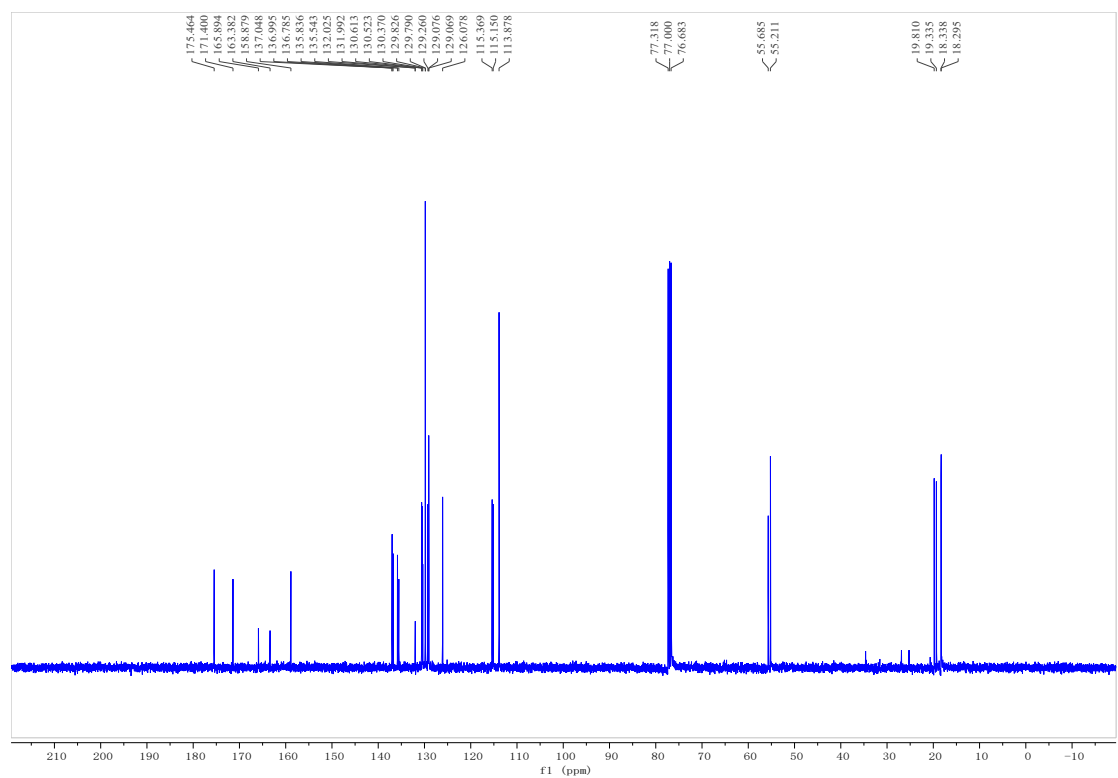
^{13}C NMR (100 MHz, CDCl_3) ^1H and ^{13}C NMR Spectra for Compound 3xa: ^1H NMR (400 MHz, CDCl_3)

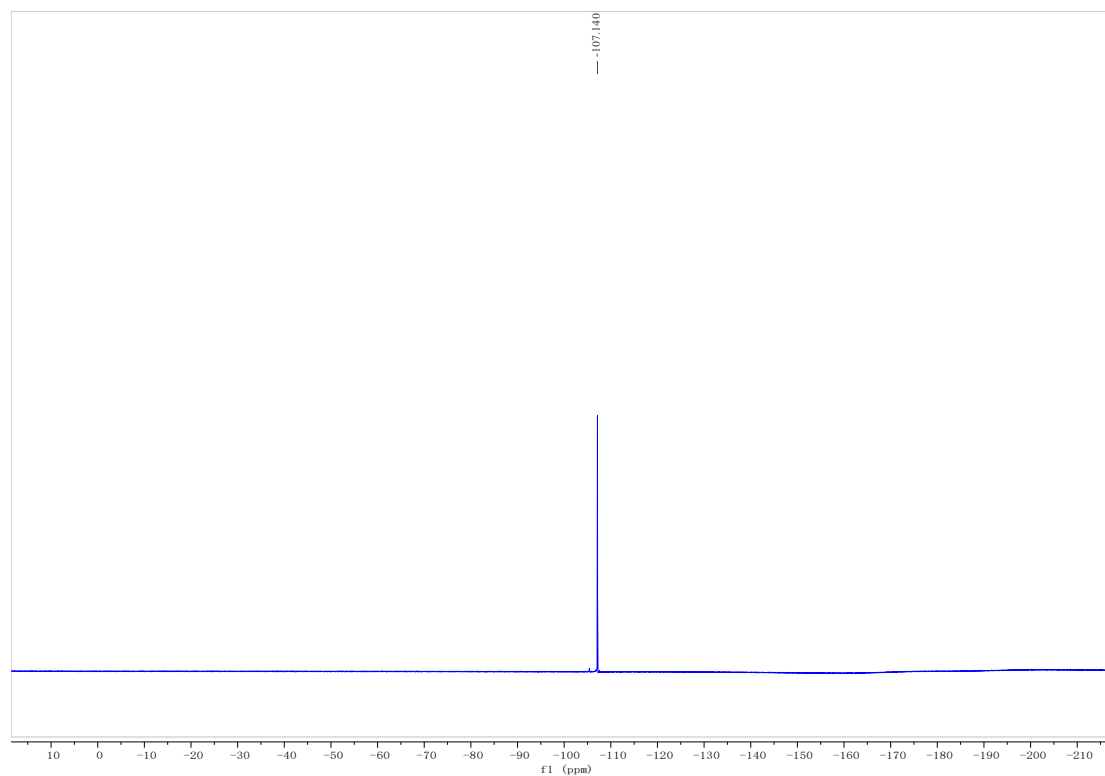
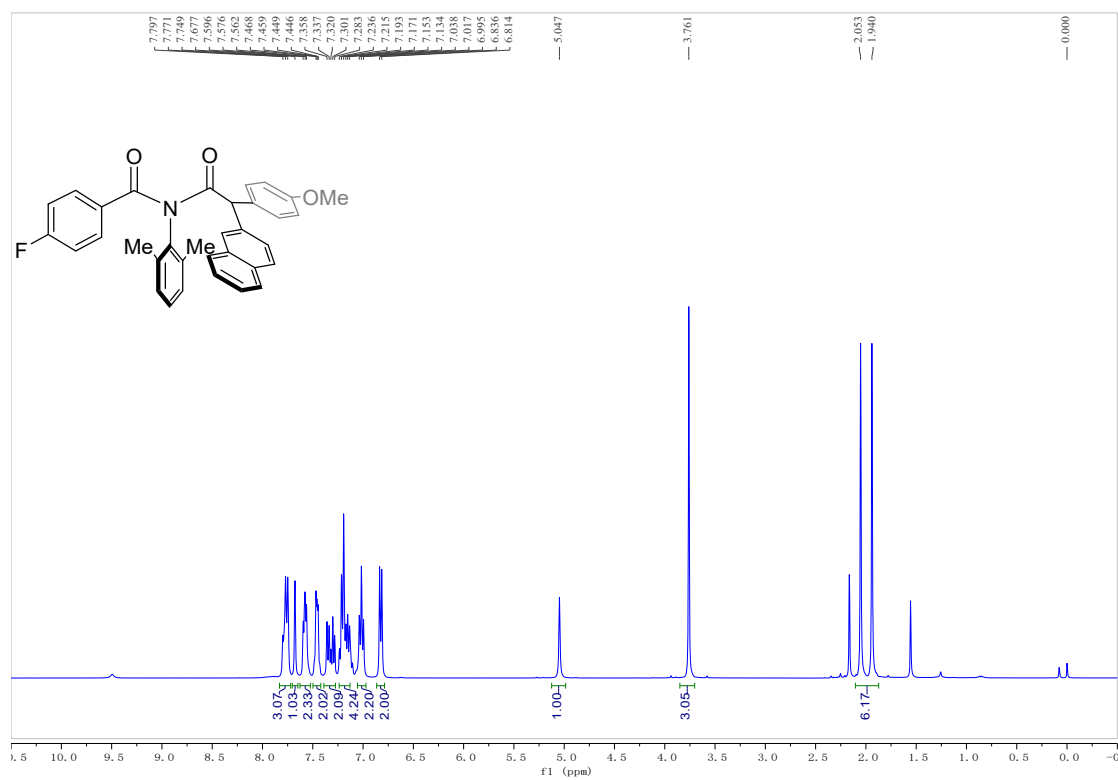
^{13}C NMR (100 MHz, CDCl_3) ^{19}F NMR (376 MHz, CDCl_3)

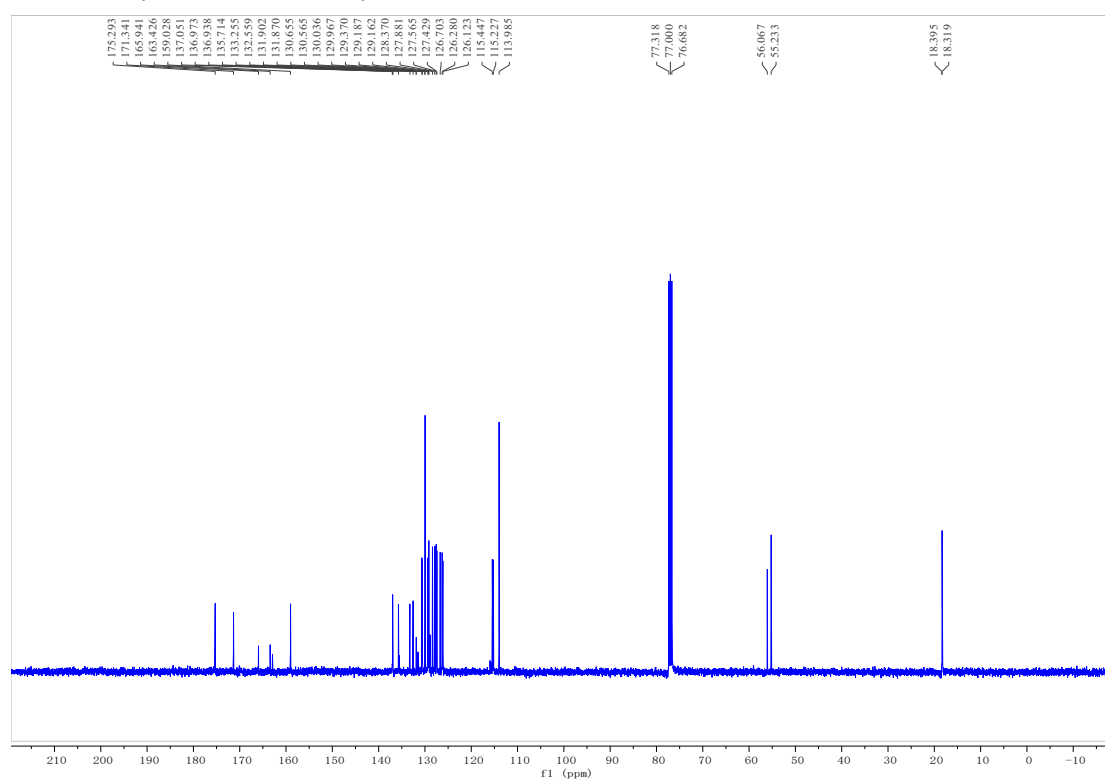
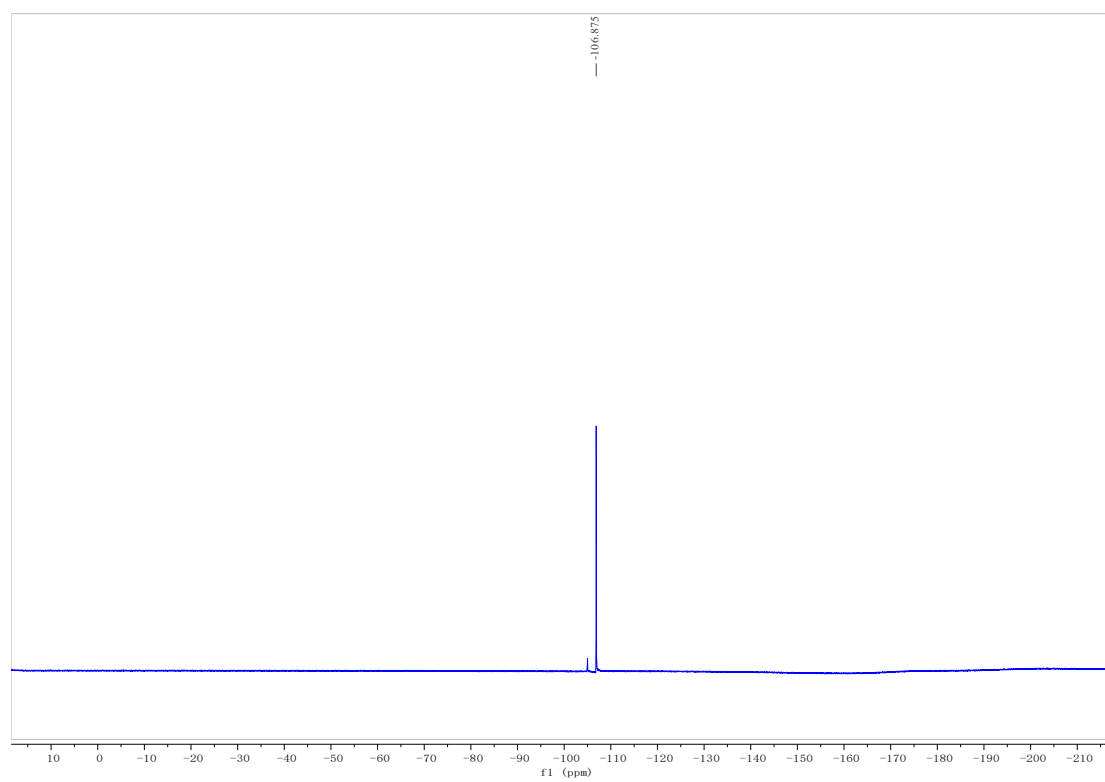
^1H and ^{13}C NMR Spectra for Compound 3ya: ^1H NMR (400 MHz, CDCl_3) ^{13}C NMR (100 MHz, CDCl_3)

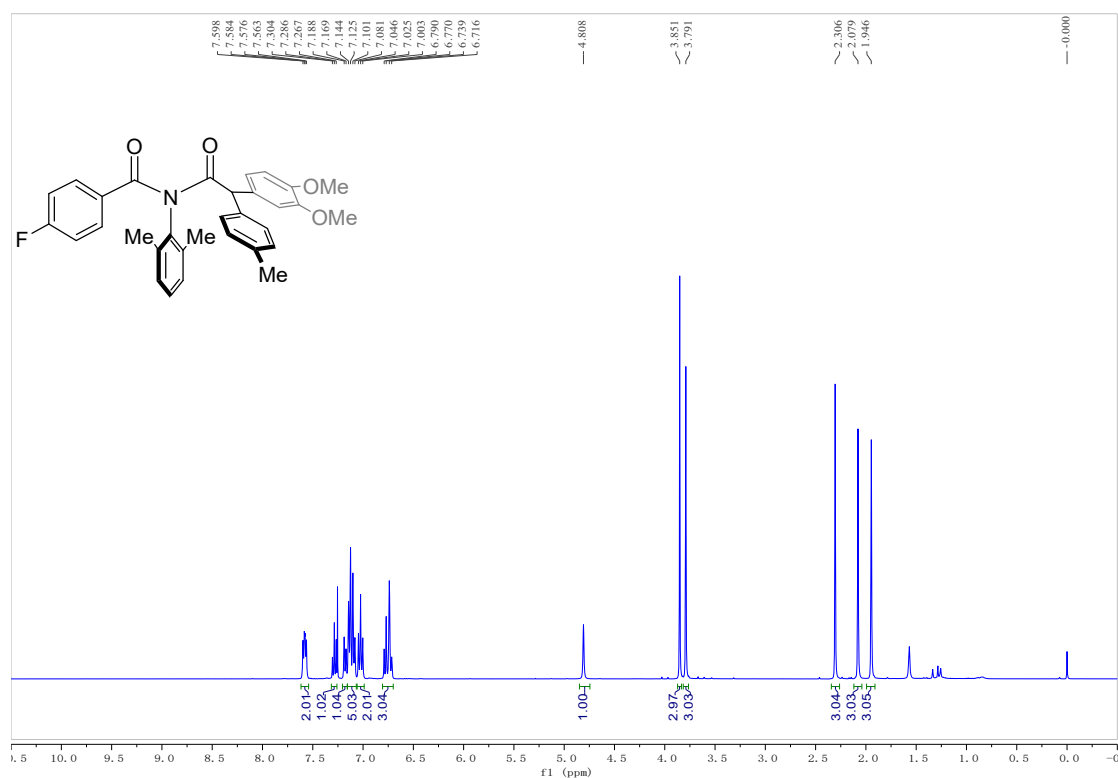
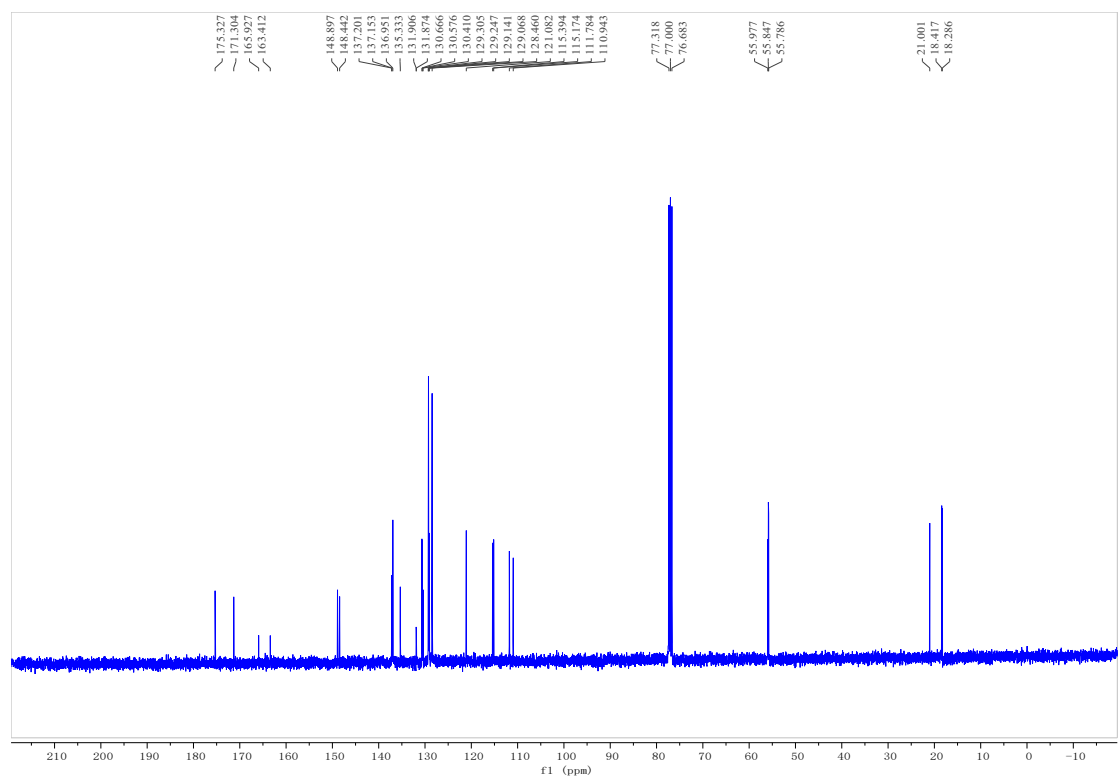
^{19}F NMR (376 MHz, CDCl_3) ^1H and ^{13}C NMR Spectra for Compound 3za: ^1H NMR (400 MHz, CDCl_3)

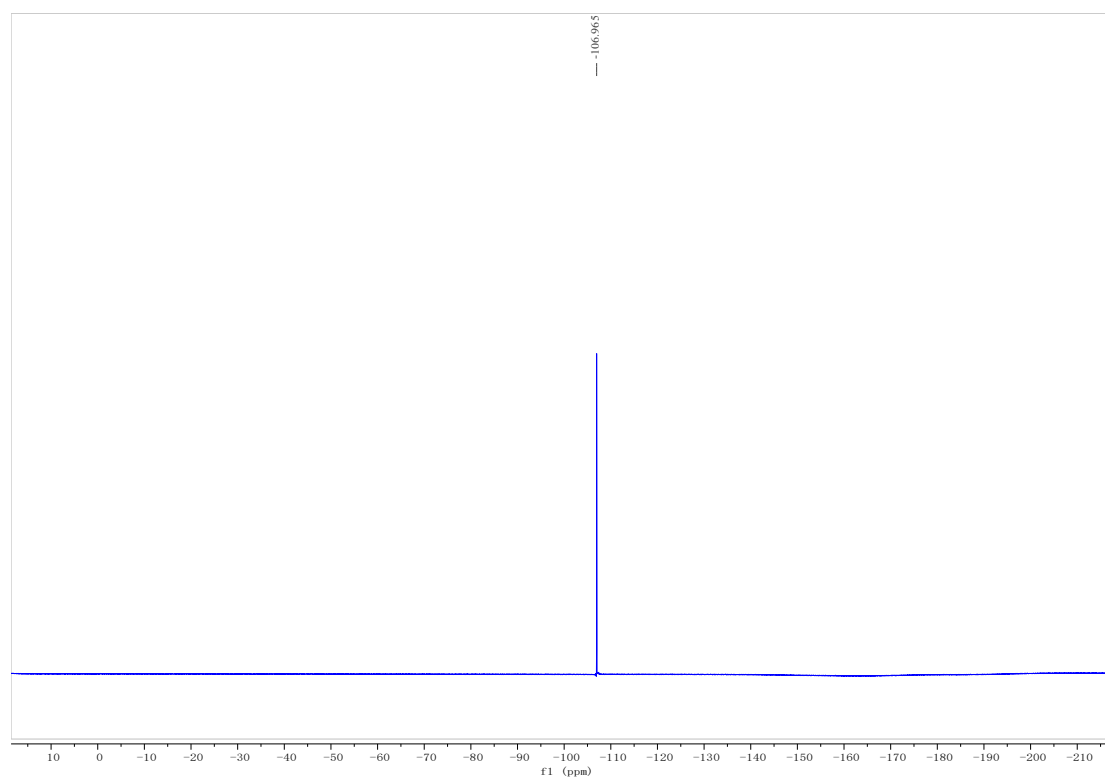
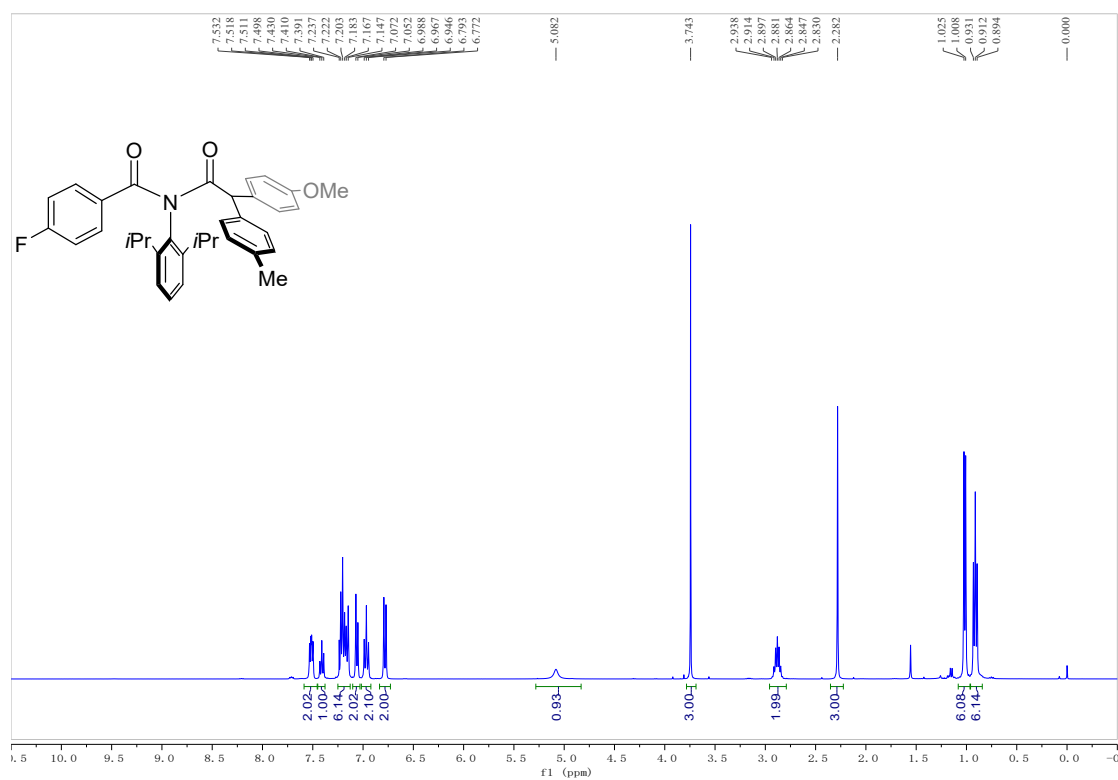
^{13}C NMR (100 MHz, CDCl_3) ^{19}F NMR (376 MHz, CDCl_3)

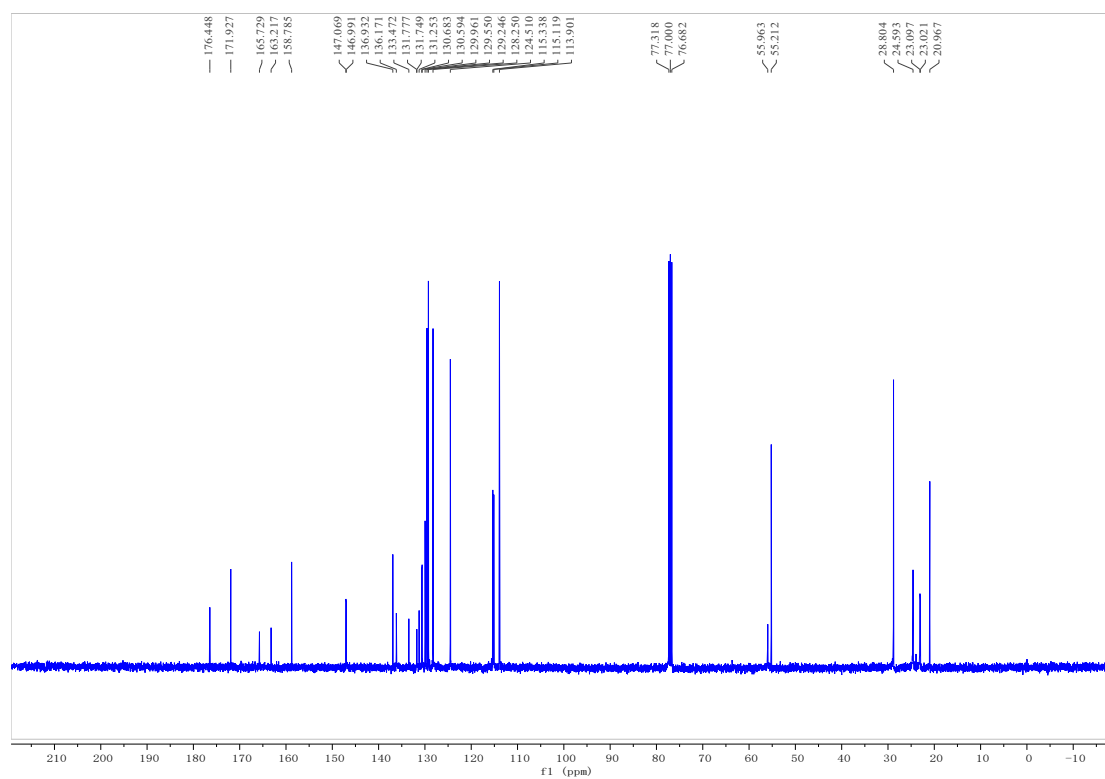
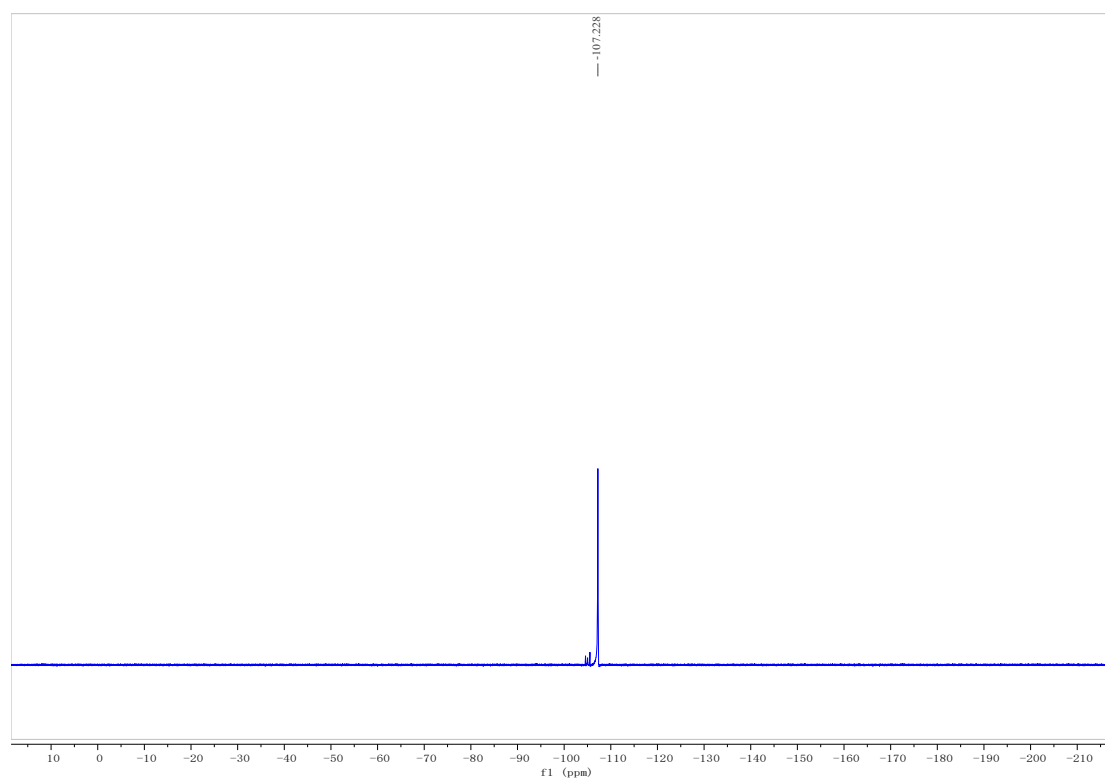
¹H and ¹³C NMR Spectra for Compound 3aa-a:**¹H NMR (400 MHz, CDCl₃)****¹³C NMR (100 MHz, CDCl₃)**

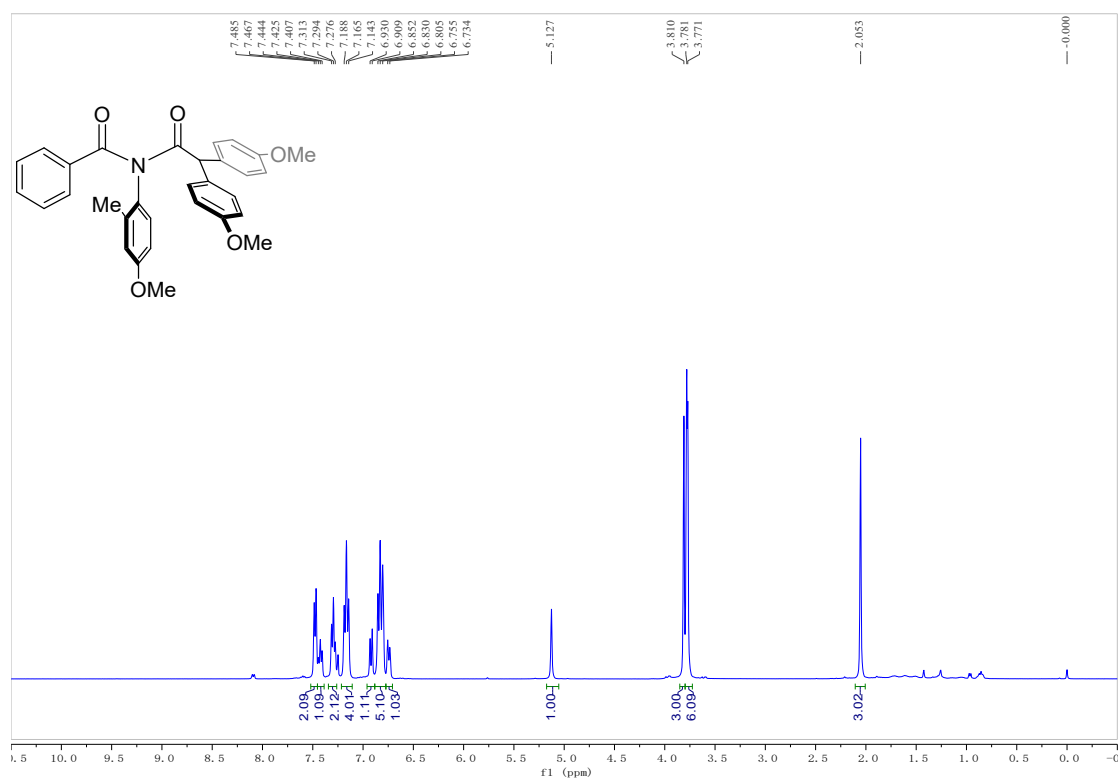
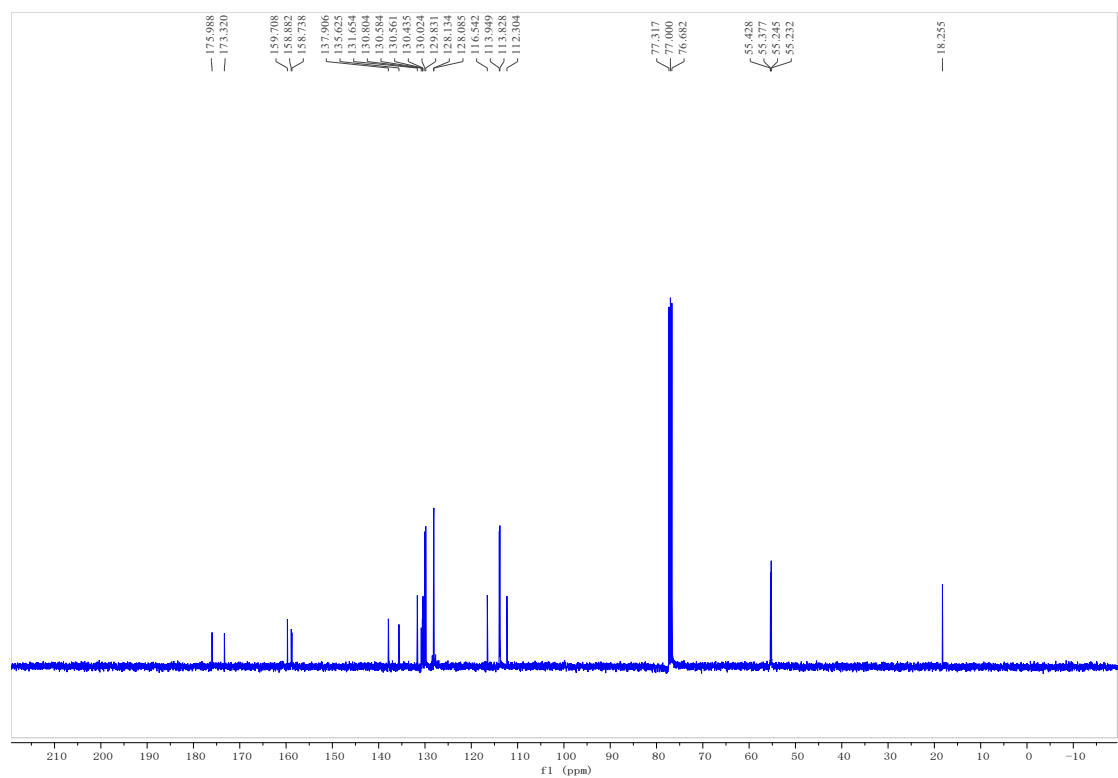
^{19}F NMR (376 MHz, CDCl_3) ^1H and ^{13}C NMR Spectra for Compound 3ab-a: ^1H NMR (400 MHz, CDCl_3)

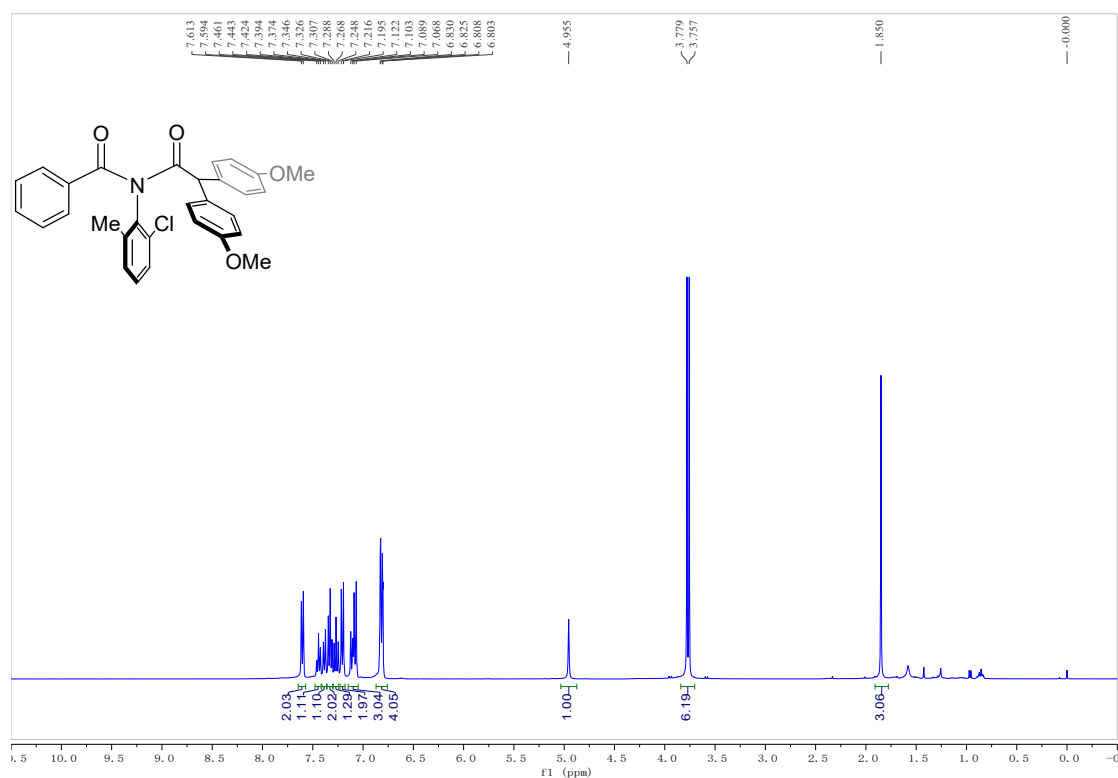
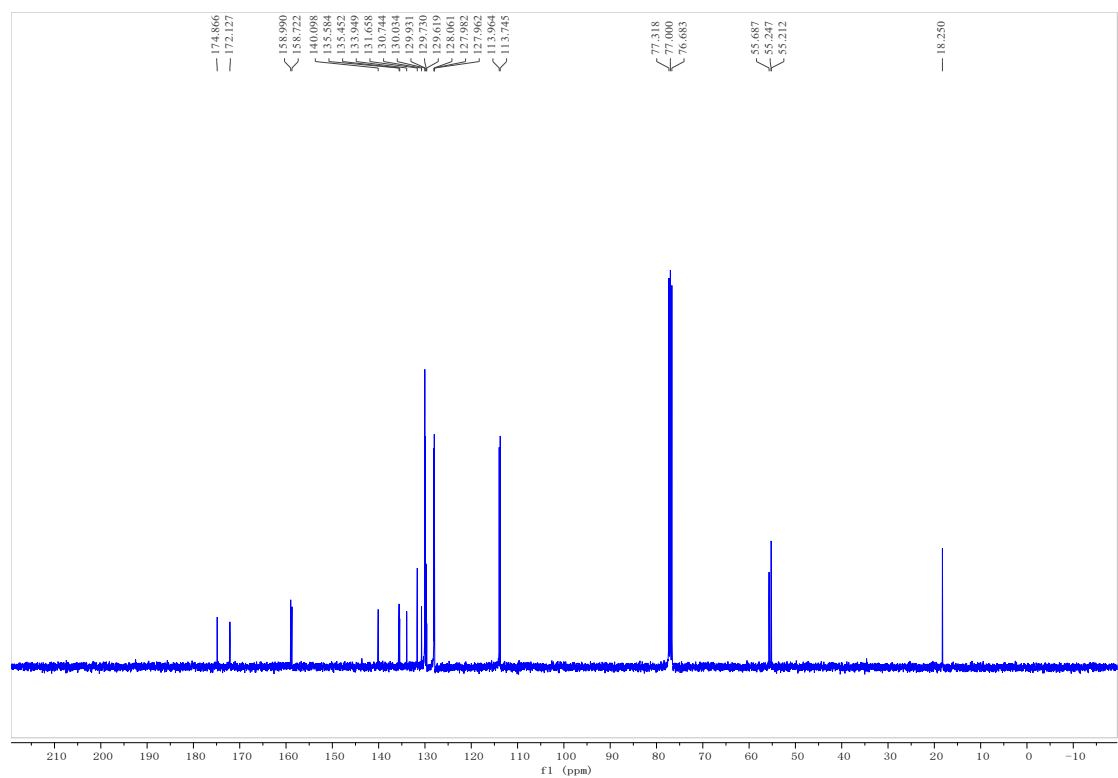
^{13}C NMR (100 MHz, CDCl_3) ^{19}F NMR (376 MHz, CDCl_3)

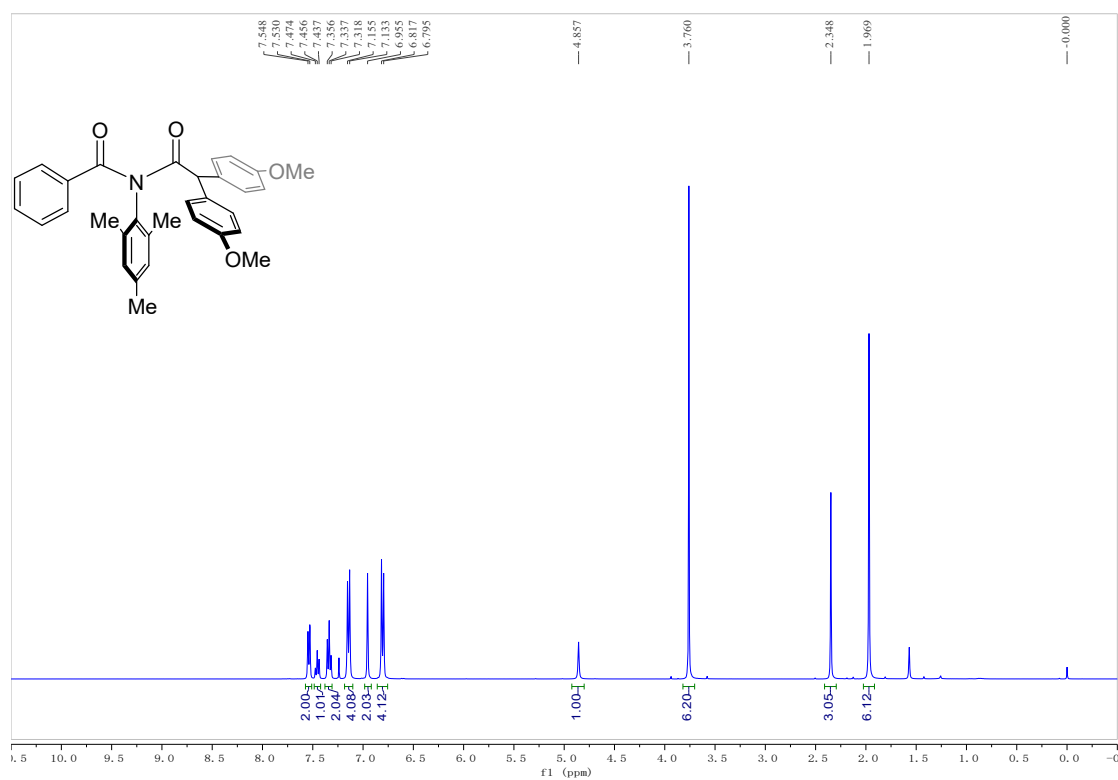
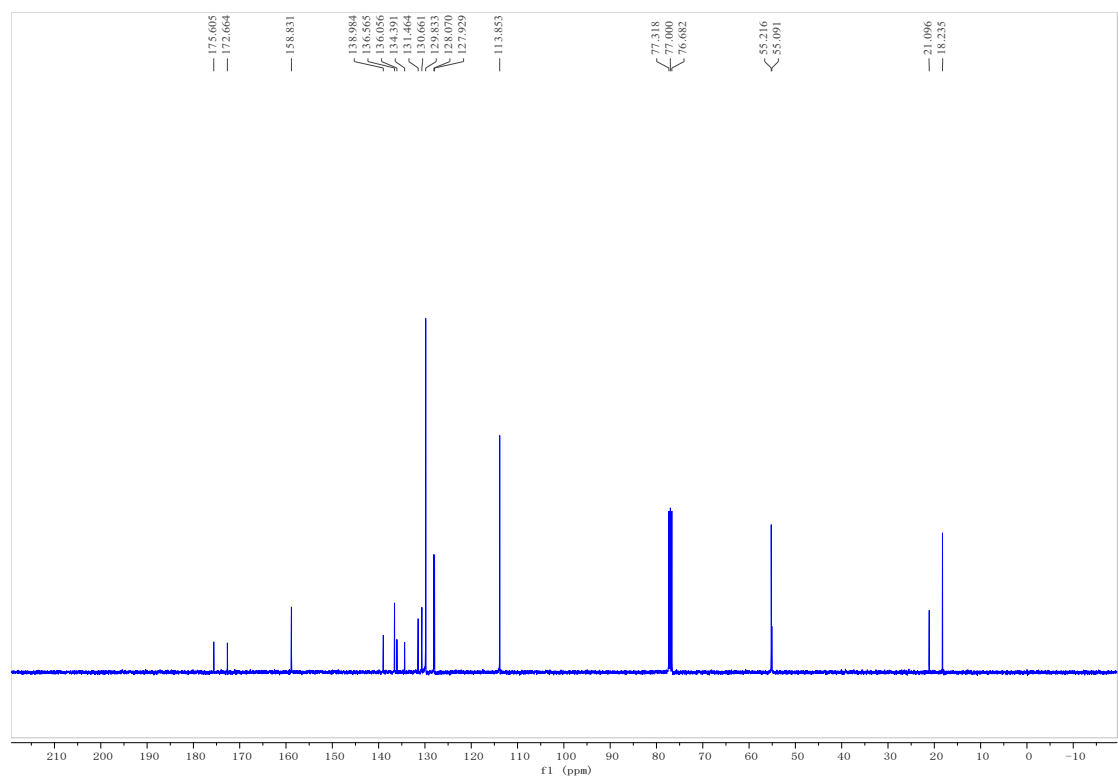
¹H and ¹³C NMR Spectra for Compound 3ac-a:**¹H NMR (400 MHz, CDCl₃)****¹³C NMR (100 MHz, CDCl₃)**

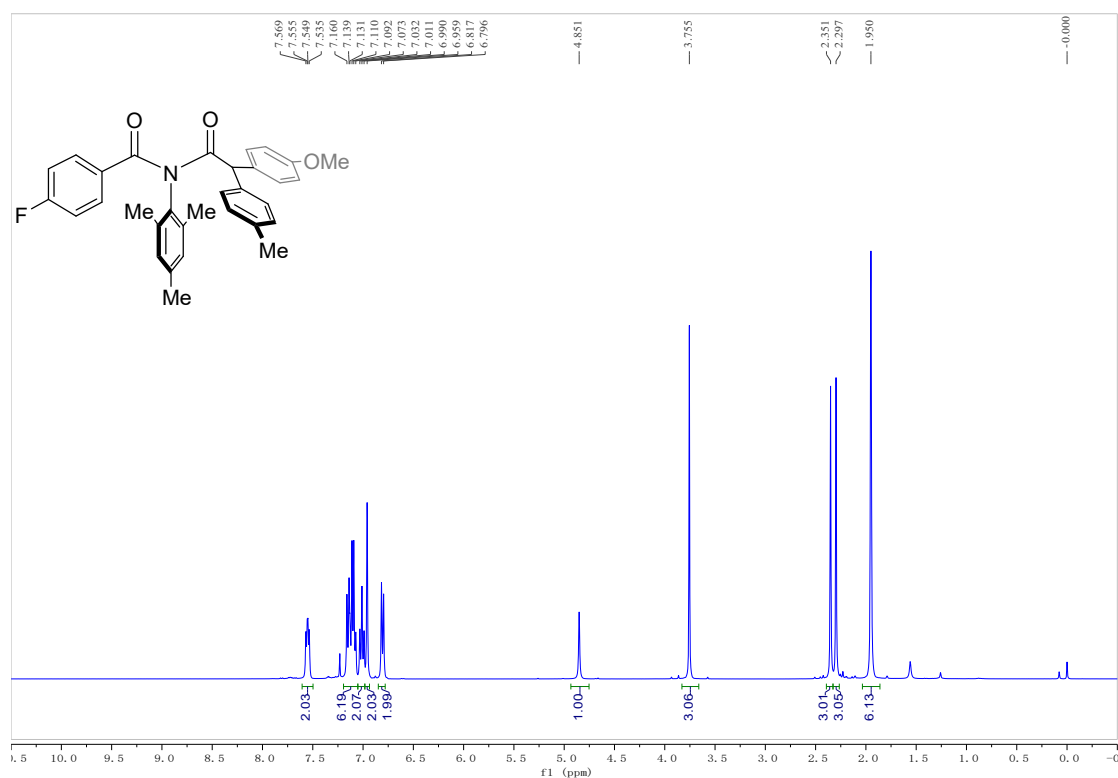
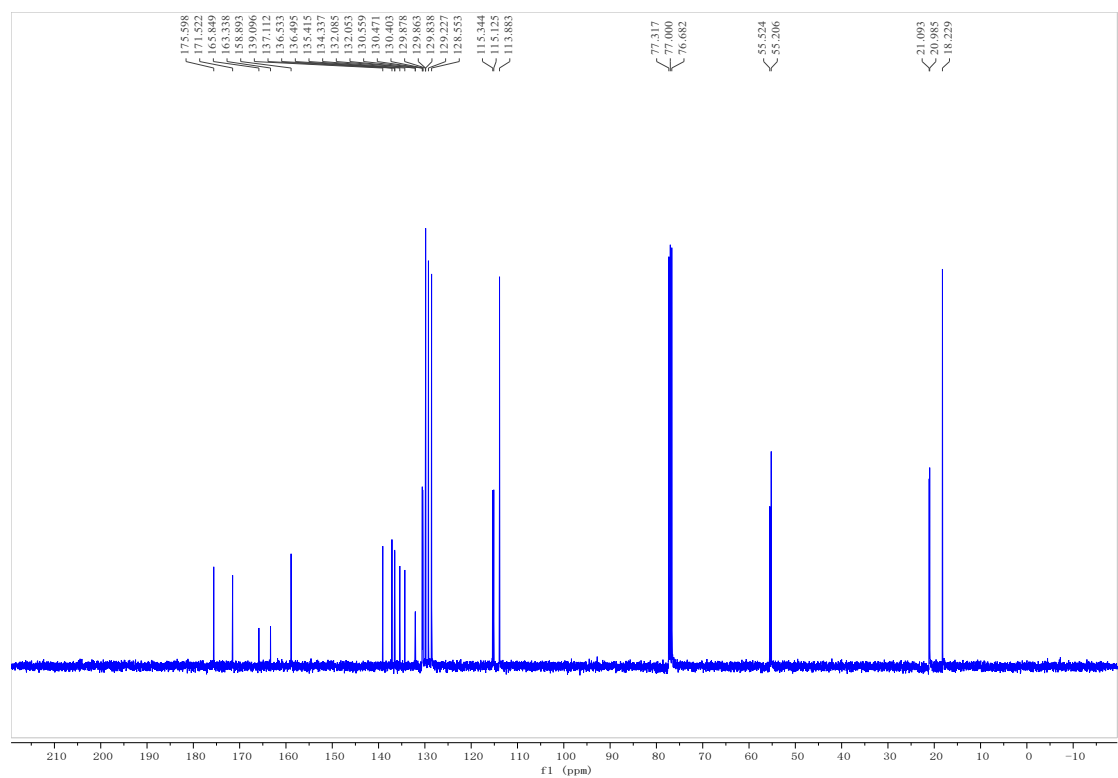
^{19}F NMR (376 MHz, CDCl_3) ^1H and ^{13}C NMR Spectra for Compound 3ab: ^1H NMR (400 MHz, CDCl_3)

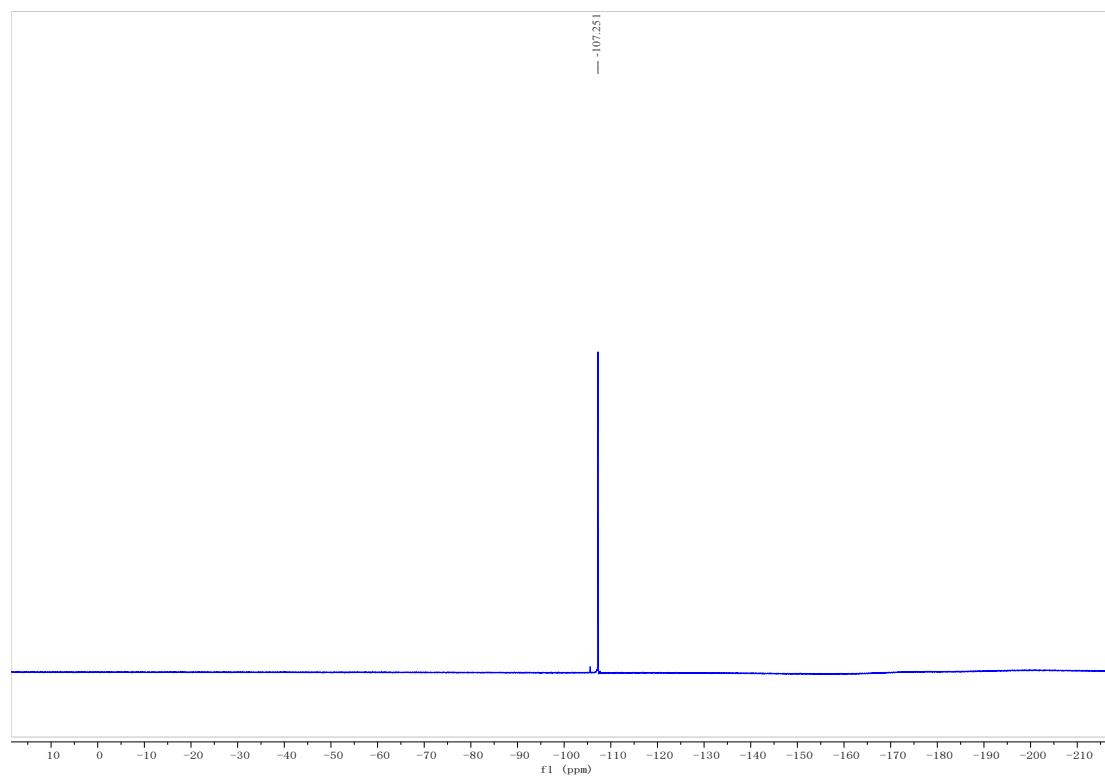
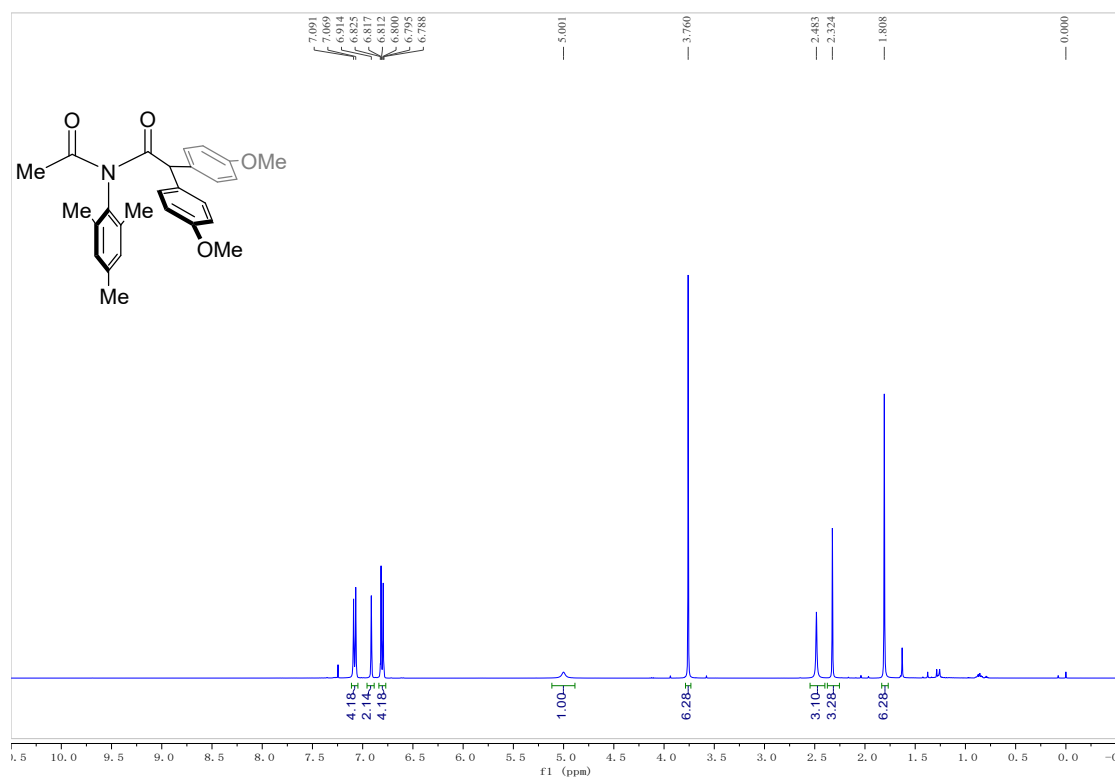
^{13}C NMR (100 MHz, CDCl_3) ^{19}F NMR (376 MHz, CDCl_3)

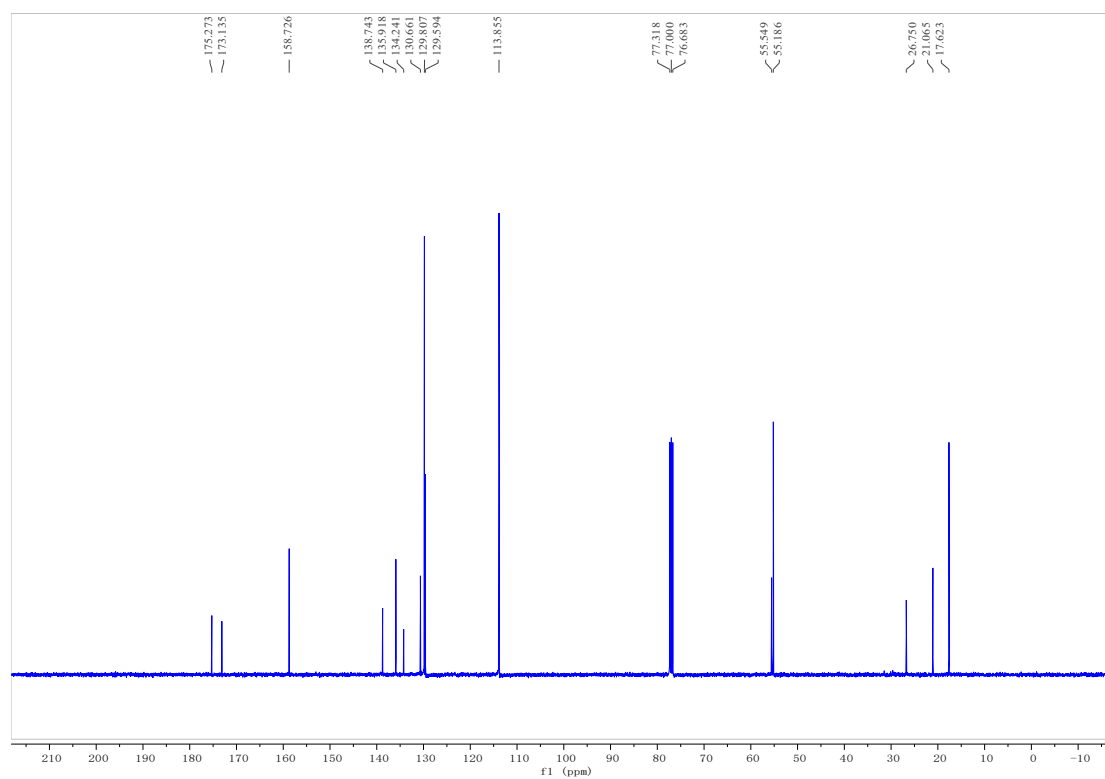
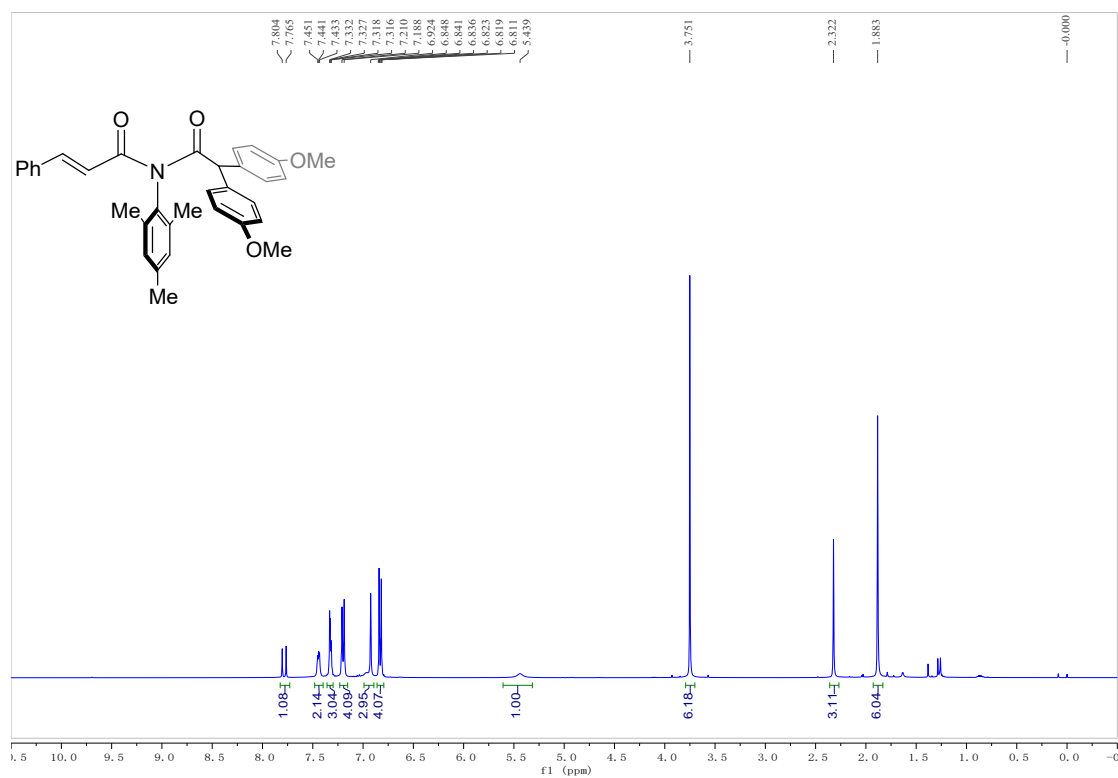
^1H and ^{13}C NMR Spectra for Compound 3gc: ^1H NMR (400 MHz, CDCl_3) ^{13}C NMR (100 MHz, CDCl_3)

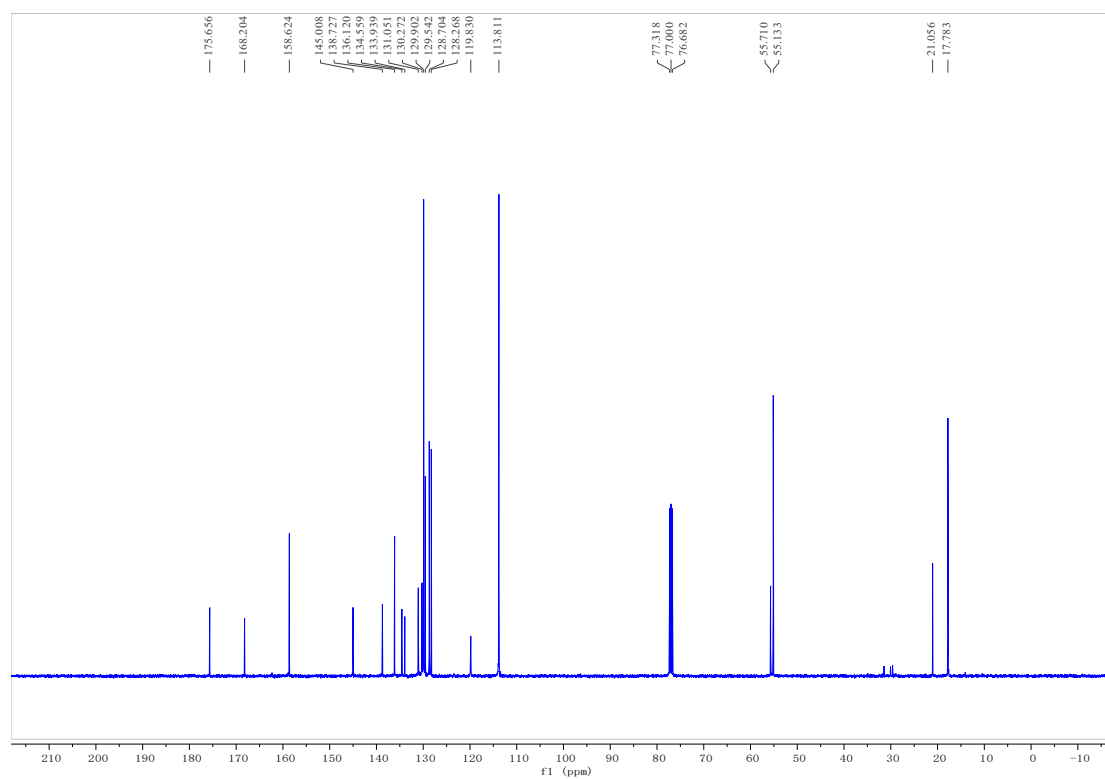
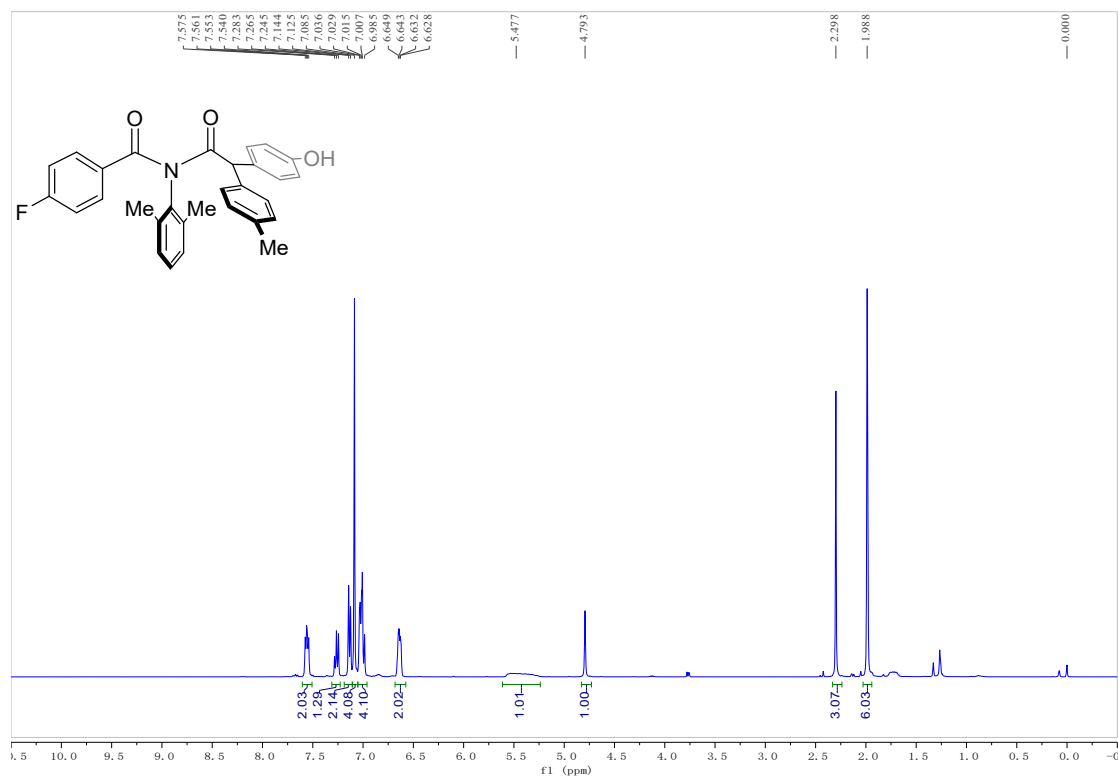
^1H and ^{13}C NMR Spectra for Compound 3gd: ^1H NMR (400 MHz, CDCl_3) ^{13}C NMR (100 MHz, CDCl_3)

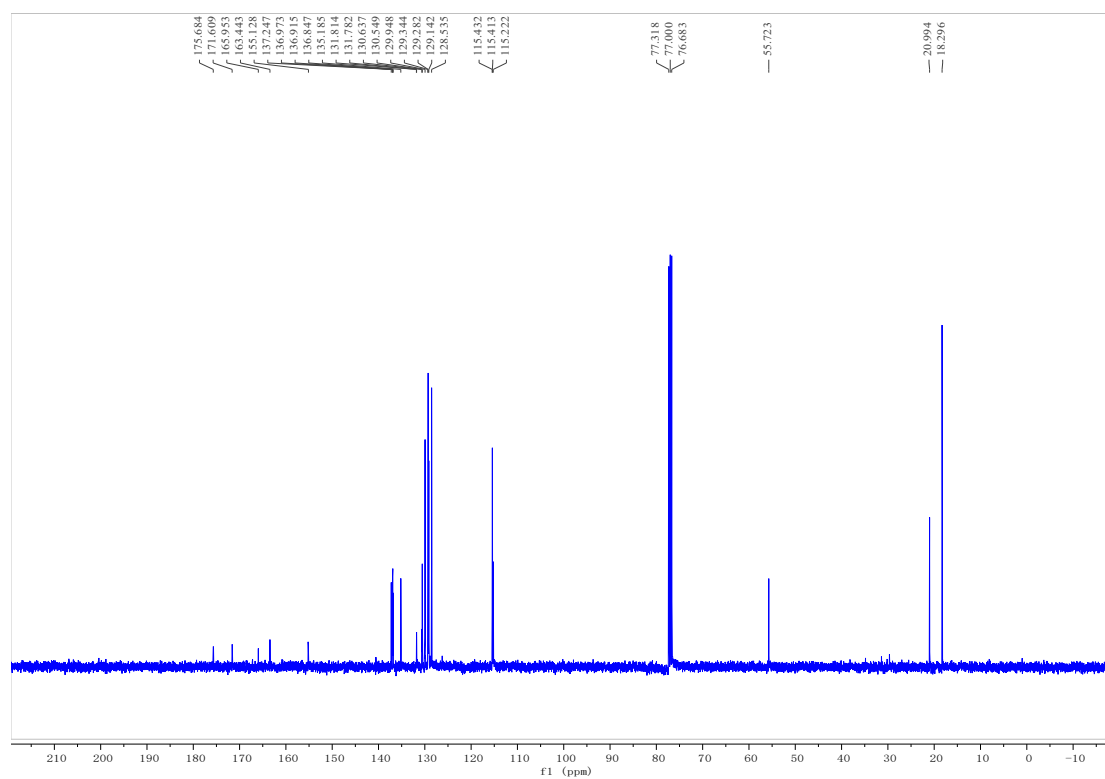
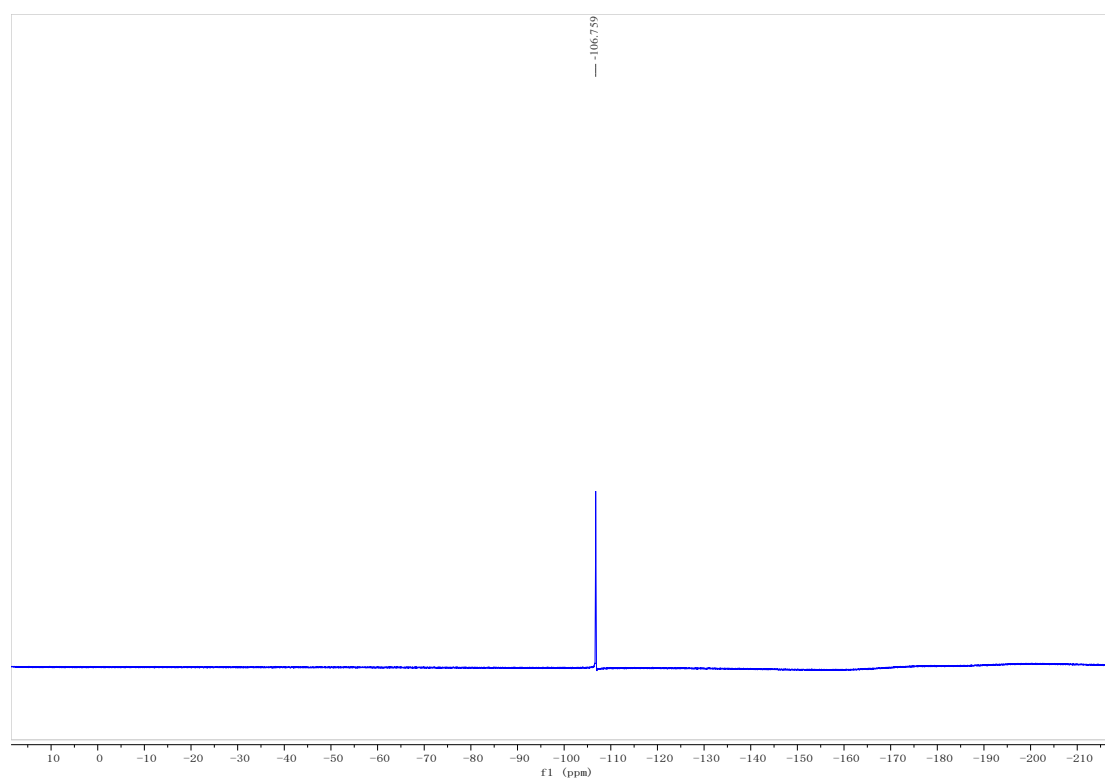
^1H and ^{13}C NMR Spectra for Compound 3ge: ^1H NMR (400 MHz, CDCl_3) ^{13}C NMR (100 MHz, CDCl_3)

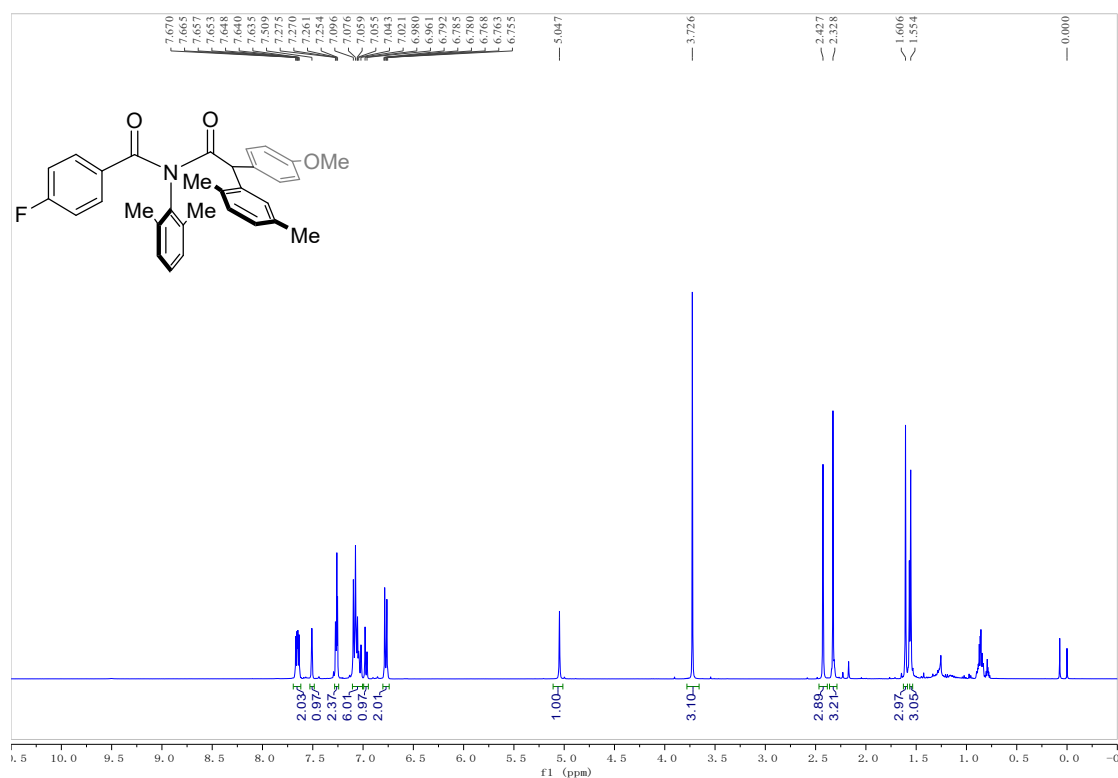
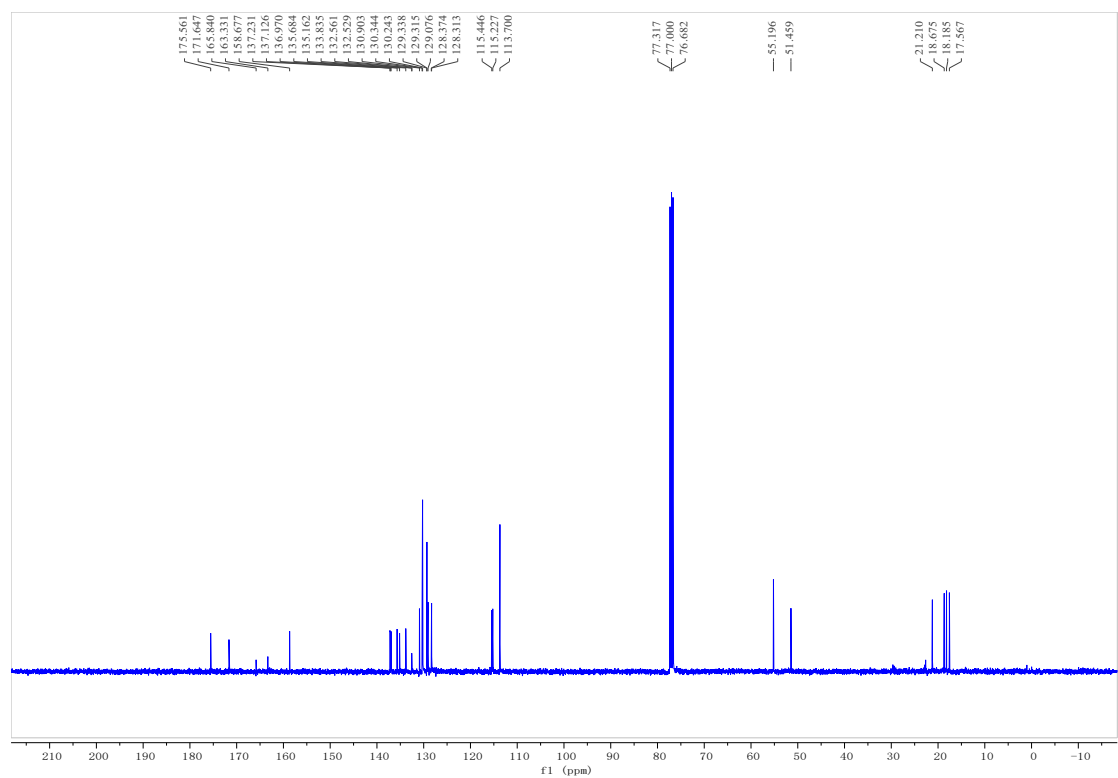
¹H and ¹³C NMR Spectra for Compound 3ae:**¹H NMR (400 MHz, CDCl₃)****¹³C NMR (100 MHz, CDCl₃)**

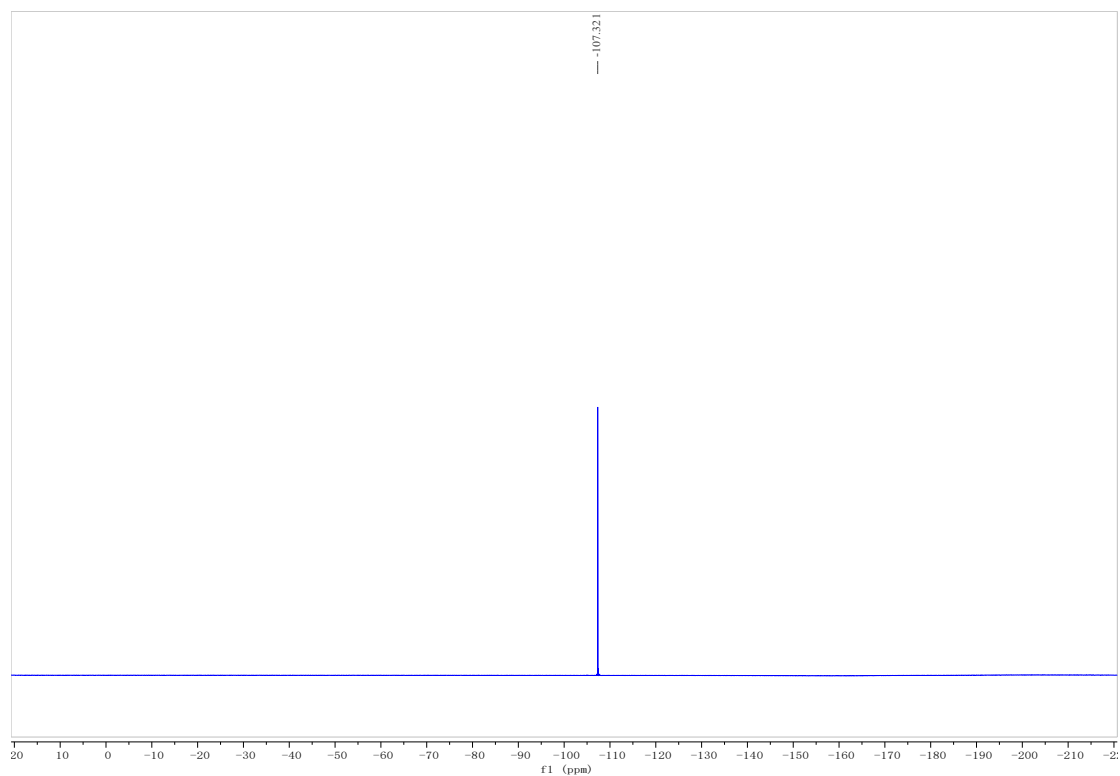
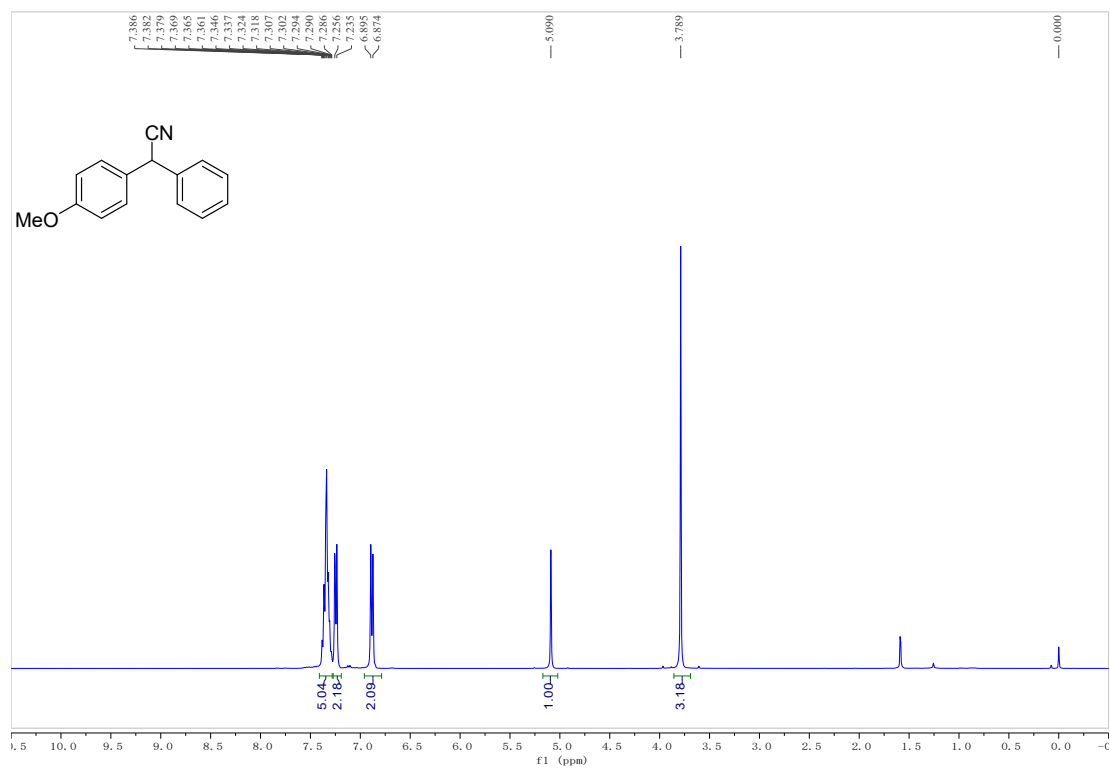
^{19}F NMR (376 MHz, CDCl_3) ^1H and ^{13}C NMR Spectra for Compound 3qe: ^1H NMR (400 MHz, CDCl_3)

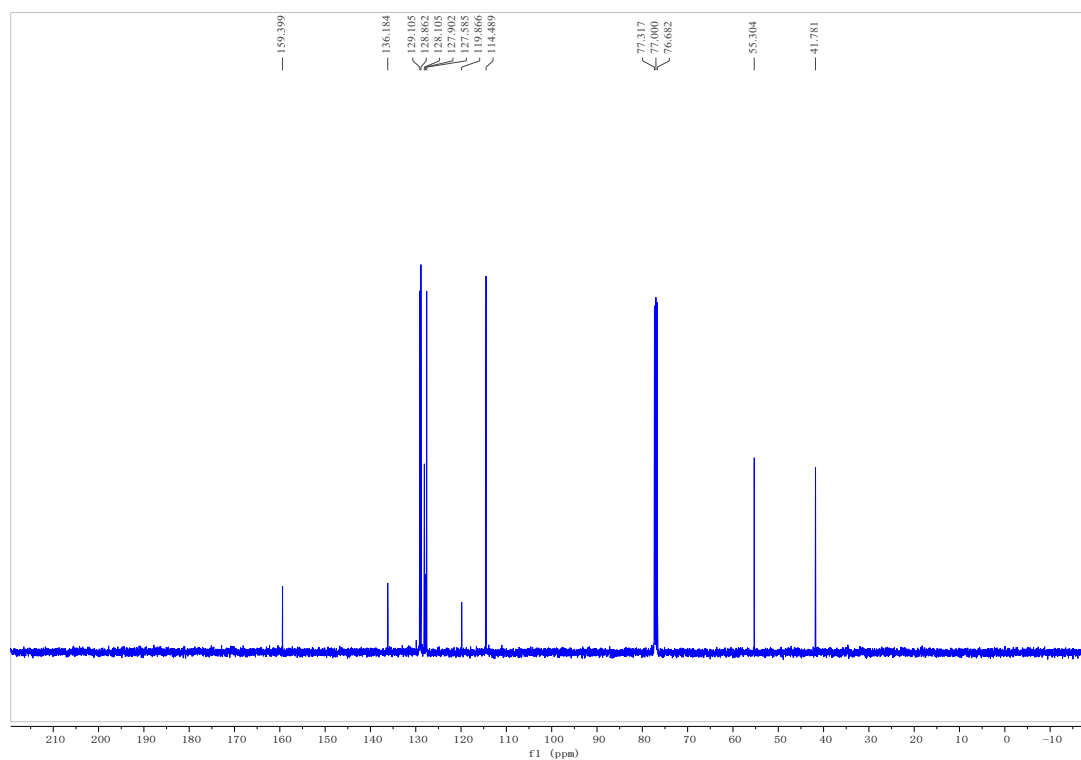
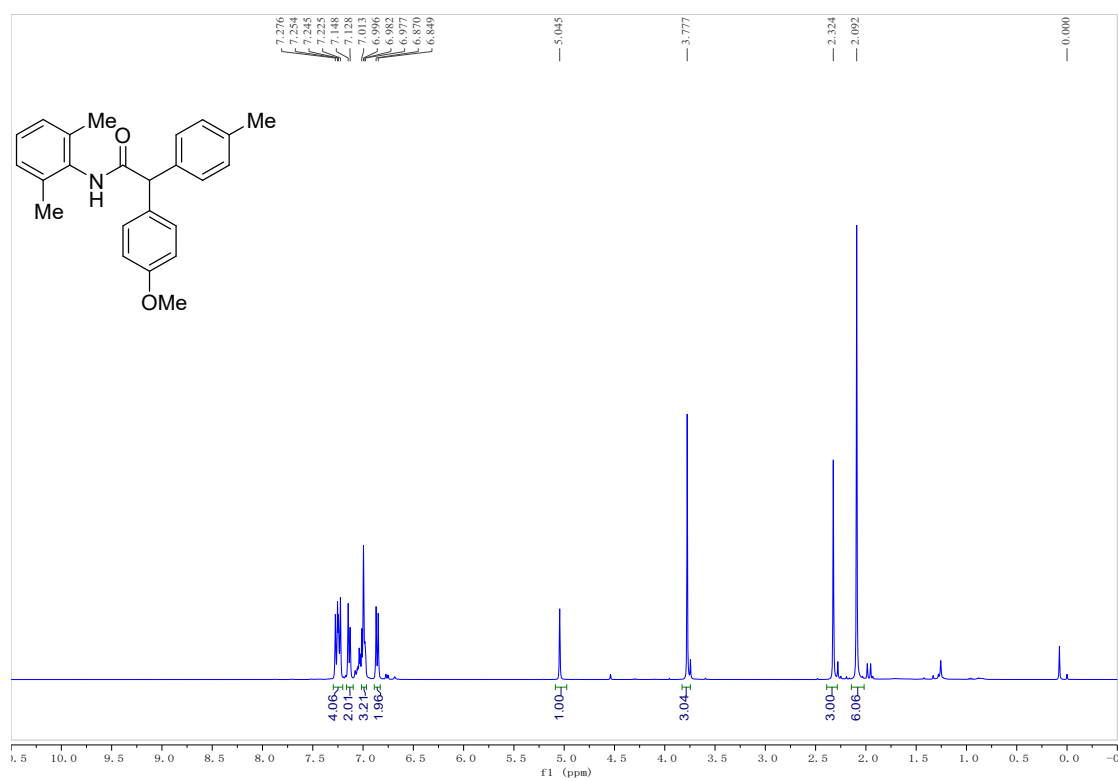
^{13}C NMR (100 MHz, CDCl_3) ^1H and ^{13}C NMR Spectra for Compound 3se: ^1H NMR (400 MHz, CDCl_3)

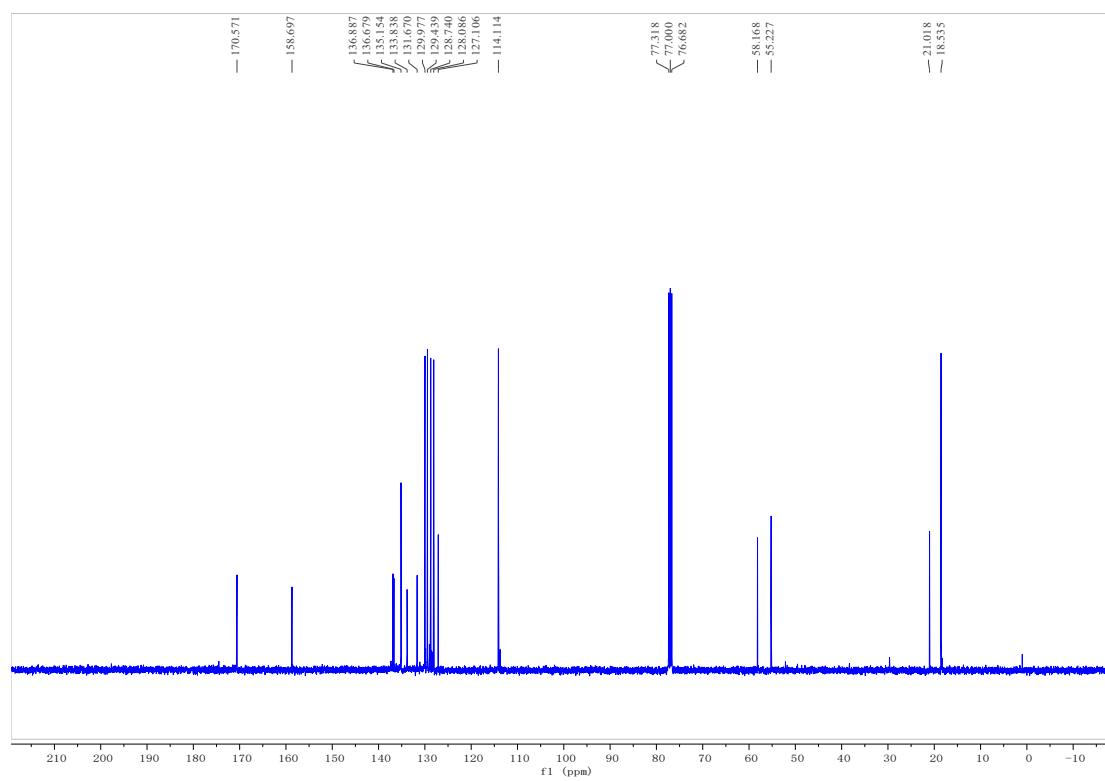
^{13}C NMR (100 MHz, CDCl_3) ^1H and ^{13}C NMR Spectra for Compound 3ad-a: ^1H NMR (400 MHz, CDCl_3)

^{13}C NMR (100 MHz, CDCl_3) ^{19}F NMR (376 MHz, CDCl_3)

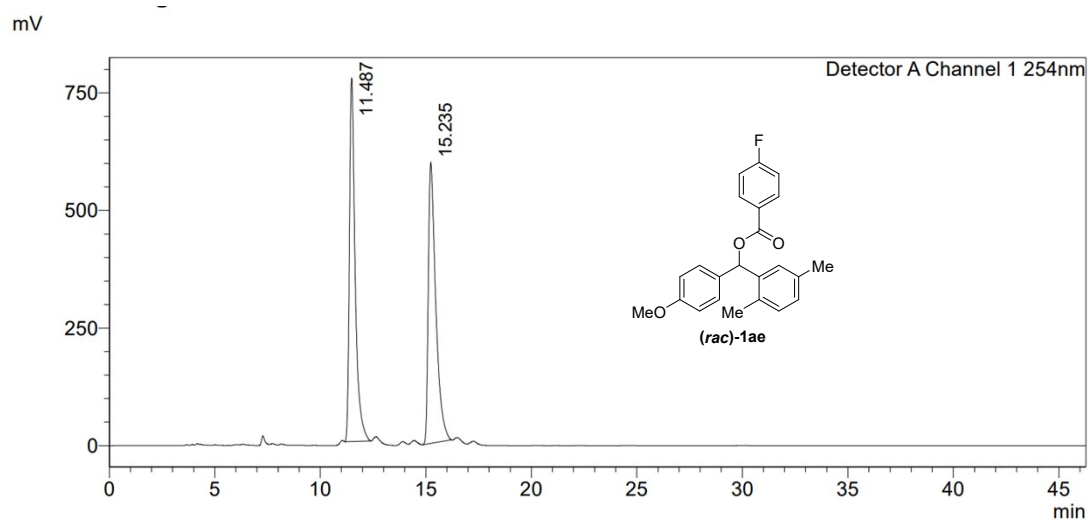
¹H and ¹³C NMR Spectra for Compound 3ae-a:**¹H NMR (400 MHz, CDCl₃)****¹³C NMR (100 MHz, CDCl₃)**

^{19}F NMR (376 MHz, CDCl_3) ^1H and ^{13}C NMR Spectra for Compound 4: ^1H NMR (400 MHz, CDCl_3)

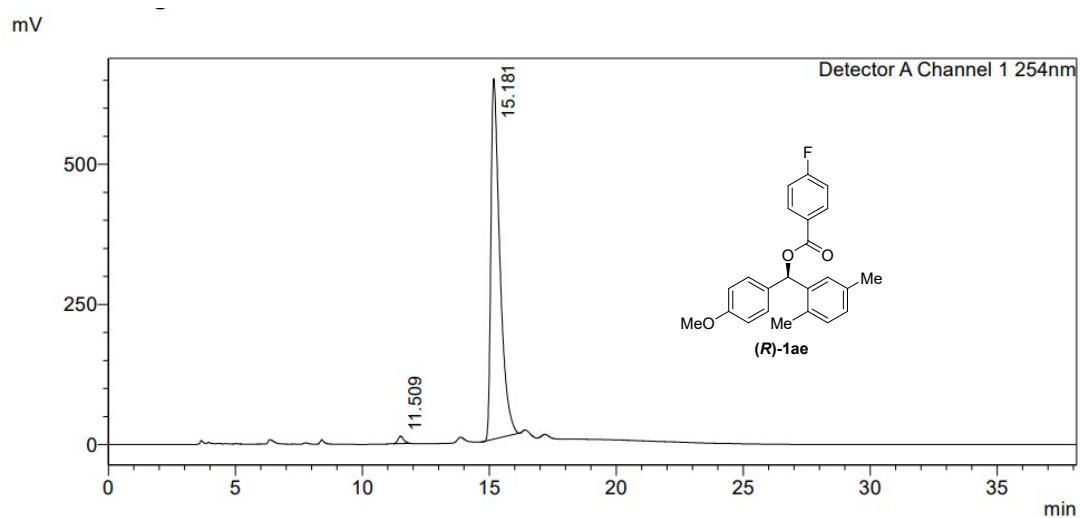
^{13}C NMR (100 MHz, CDCl_3) ^1H and ^{13}C NMR Spectra for Compound 5: ^1H NMR (400 MHz, CDCl_3)

^{13}C NMR (100 MHz, CDCl_3)

12 HPLC Spectra

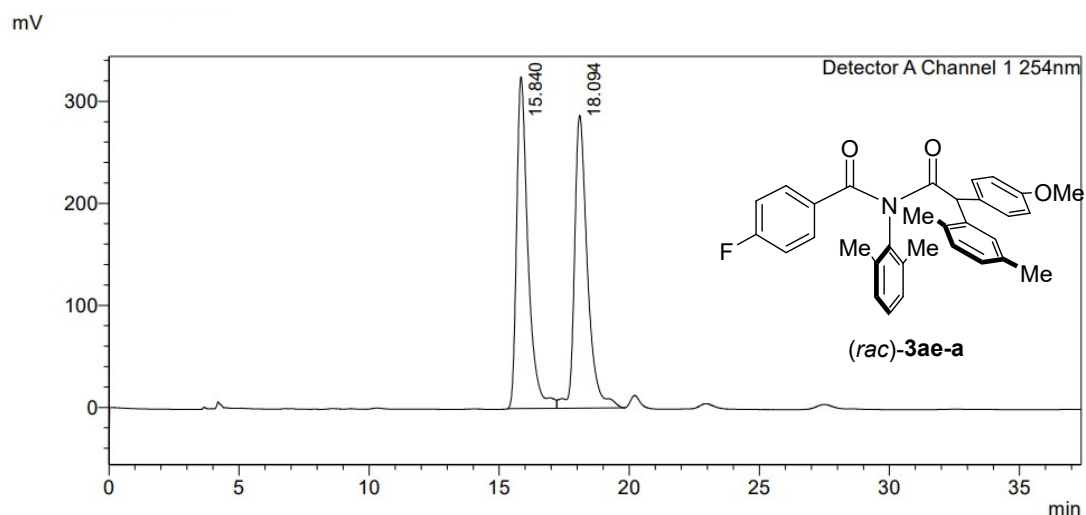


Peak#	Ret. Time	Area	Height	Peak Start	Area%	Width at 50% Height
1	11.487	14596882	772443	11.158	49.854	0.268
2	15.235	14682416	596640	14.867	50.146	0.362
Total		29279298	1369083		100.000	

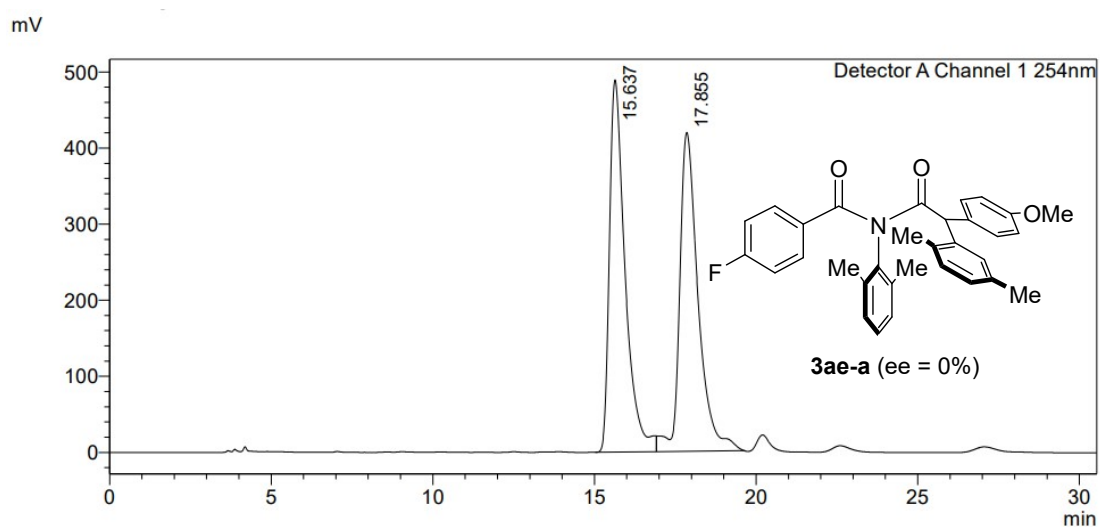


Peak#	Ret. Time	Area	Height	Peak Start	Area%	Width at 50% Height
1	11.509	210169	13103	11.242	1.314	0.246
2	15.181	15781065	642752	14.683	98.686	0.362
Total		15991234	655856		100.000	

97% ee of (*R*)-1ae was determined by HPLC: AD-H Column, 4/96 *i*PrOH/hexane, 0.8 mL/min, 254 nm, 35 °C; retention time = 11.51 min (minor), 15.18 min (major).



Peak#	Ret. Time	Area	Height	Peak Start	Area%	Width at 50% Height
1	15.840	9939101	324878	15.333	50.017	0.436
2	18.094	9932250	286957	17.217	49.983	0.492
Total		19871351	611835		100.000	



Peak#	Ret. Time	Area	Height	Peak Start	Area%	Width at 50% Height
1	15.637	16452295	488964	15.025	49.718	0.485
2	17.855	16638620	418982	16.917	50.282	0.559
Total		33090915	907947		100.000	

0% ee of **3ae-a** was determined by HPLC: AD-H Column, 2/98 *i*PrOH/hexane, 0.8 mL/min, 254 nm, 35 °C; retention time = 15.64 min, 17.86 min.