

Supporting Information

Direct oxidative amination of aromatic aldehydes with amines in continuous flow system using metal-free catalyst

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1. General details

Reaction solvents were obtained commercially, and used without further purification. Commercial reagents were used as received. Reactions were monitored by thin-layer chromatography (TLC) on 0.25mm precoated Merck Silica Gel 60 F254, visualizing with ultraviolet light. $^1\text{H}/^{13}\text{C}$ NMR spectra were recorded on 400'54 ascend purchased from Bruker Biospin AG, operating at 400/100 MHz, respectively. Chemical shifts (δ) are reported in parts per million (ppm) downfield from tetramethylsilane (TMS), which was used as internal standard. Flash column chromatography was performed on Merck Silica Gel 60 (200-300mesh) using petroleum ether and ethyl acetate.

2. Experimental procedure

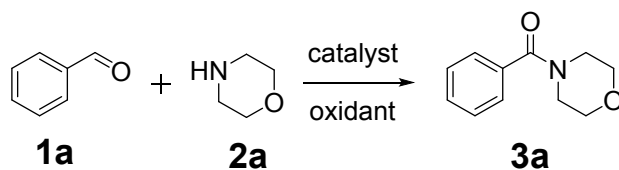
2.1. General procedure for synthesis of compound 3a by benzaldehyde with morpholine

0.01mol of benzaldehyde, H_2O_2 (30wt% in water, 0.04mol, 2eq), NaBr (5 mol%) and H_2SO_4 (1 mol%) were dissolved in 30mL dioxane, which was in syringe A. Morpholine (0.02mol, 2eq) was dissolved in 30mL dioxane, which was in syringe B. The flow rates of syringe A and B were both 0.1mL/min. And the temperature of the oil bath was set at 80°C. The reaction liquid was collected, and dissolved in ethyl acetate, washed with H_2O . The organic layer was dried over anhydrous sodium sulfate and solvent was removed under vacuum. And the crude product was purified by flash chromatography on silica gel by gradient elution with ethyl acetate in petroleum ether to obtain the amide product **3a**.

2.2. General procedure for synthesis of compound 3a by benzyl alcohol with morpholine

0.01mol of benzyl alcohol, morpholine (0.02mol, 2eq) were dissolved in 30mL dioxane, which was in syringe A. And H_2O_2 (30wt% in water, 0.05mol, 5eq), NaBr (10 mol%) and H_2SO_4 (1 mol%) were dissolved in 30mL dioxane, which was in syringe B. The flow rates of syringe A and B were both 0.1mL/min. And the temperature of the oil bath was set at 80°C. The reaction liquid was collected, and dissolved in ethyl acetate, washed with H_2O . The organic layer was dried over anhydrous sodium sulfate and solvent was removed under vacuum. And the crude product was purified by flash chromatography on silica gel by gradient elution with ethyl acetate in petroleum ether to obtain the amide product **3a**.

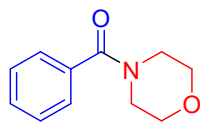
2.3. The optimization of reaction conditions in continuous flow system



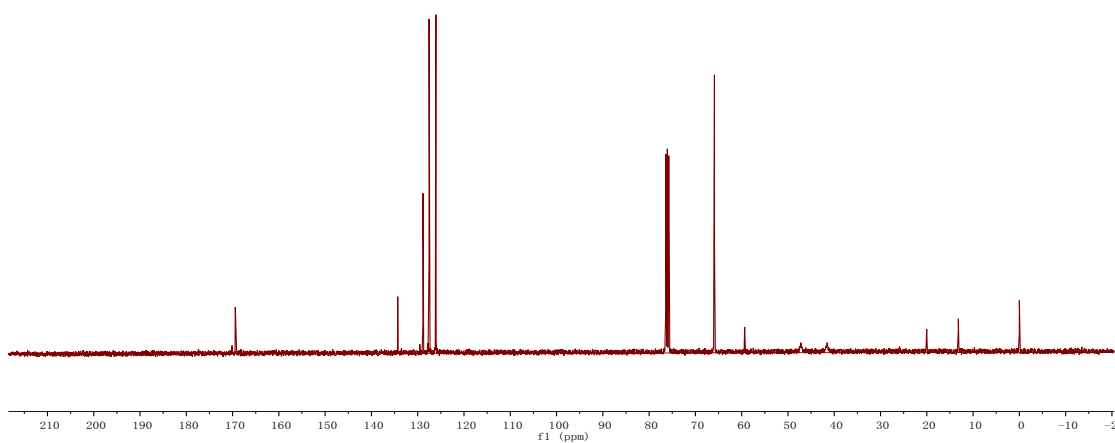
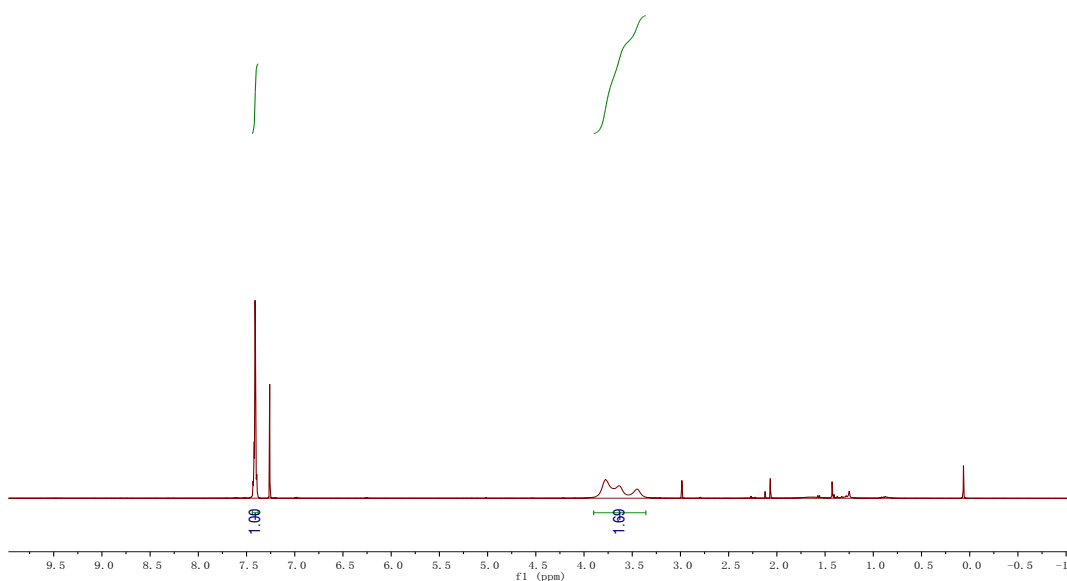
Entry	Flow rate (mL/min)		T (°C)	t (min)	Yield (%) ^b
	A	B			
1	0.05	0.05	80	50	94
2	0.1	0.1	80	25	96
3	0.2	0.2	80	12.5	74
4	0.5	0.5	80	5	48
5	0.1	0.1	50	25	79
6	0.1	0.1	100	25	87
7 ^c	0.1	0.1	80	25	94

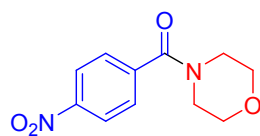
^a Reaction conditions: solution A: 0.33M of aldehyde, 0.67M of hydrogen peroxide (30wt% in water), 5mol% of sodium bromide and 1mol% of sulphuric acid in dioxane; solution B: 0.67M of amine in the dioxane. ^b Isolated yield. ^c solution A: 0.33M of aldehyde, 1.0M of hydrogen peroxide (30wt% in water), 5mol% of sodium bromide and 1mol% of sulphuric acid in dioxane; solution B: 0.67M of amine in the dioxane.

3. NMR spectra



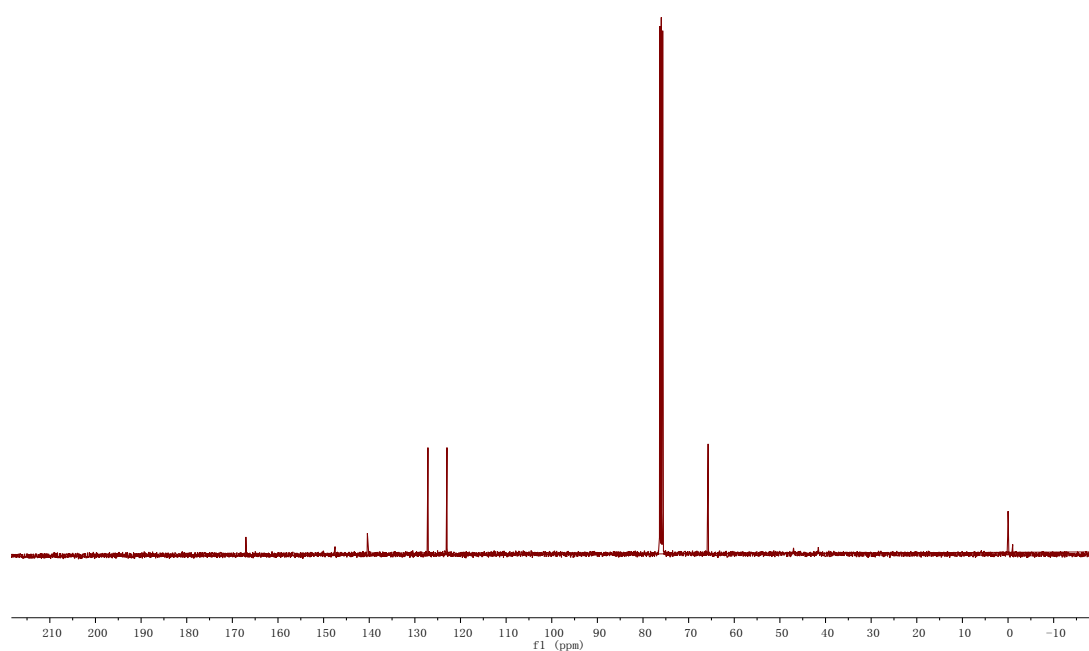
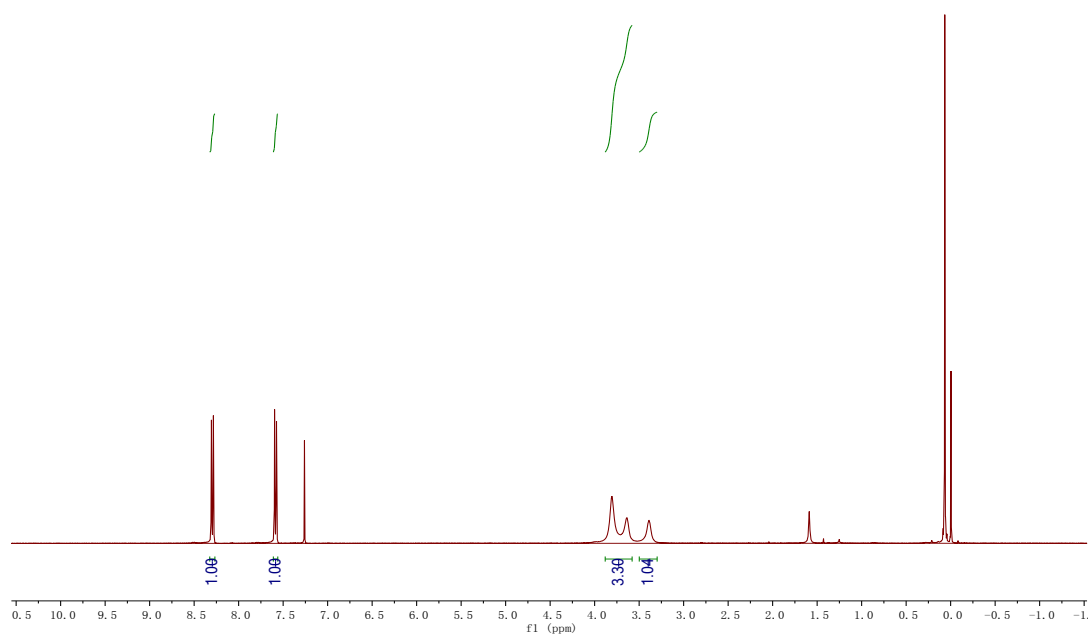
Benzoyl morpholine (3a). White solid; 1.24g, 96% yield; m.p.=72-74°C; ^1H NMR (400 MHz, CDCl_3) δ 7.38–7.31 (m, 5H), 3.80–3.28 (m, 8H); ^{13}C NMR (101 MHz, CDCl_3) δ 170.1, 169.4, 134.3, 128.9, 127.5, 126.1, 65.9, 59.4, 20.0, 13.2; HRMS (ESI) m/z calcd for $\text{C}_{11}\text{H}_{13}\text{NO}_2$ $[\text{M}+\text{H}]^+$ 192.1019, found 192.1040..

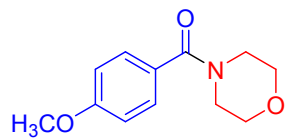




N-(4-Nitrobenzoyl)morpholine (**3b**). Light yellow solid; 1.43g, 94%

yield; m.p.=101-102°C; ¹H NMR (400 MHz, CDCl₃) δ 8.32–8.27 (m, 2H), 7.61–7.56 (m, 2H), 3.72 (d, *J* = 67.2 Hz, 6H), 3.39 (s, 2H); ¹³C NMR (101 MHz, CDCl₃) δ 167.0, 147.5, 140.4, 127.1, 123.0, 65.7; HRMS (ESI) *m/z* calcd for C₁₁H₁₁N₂O₄ [M+H]⁺ 237.0831, found 237.0857.



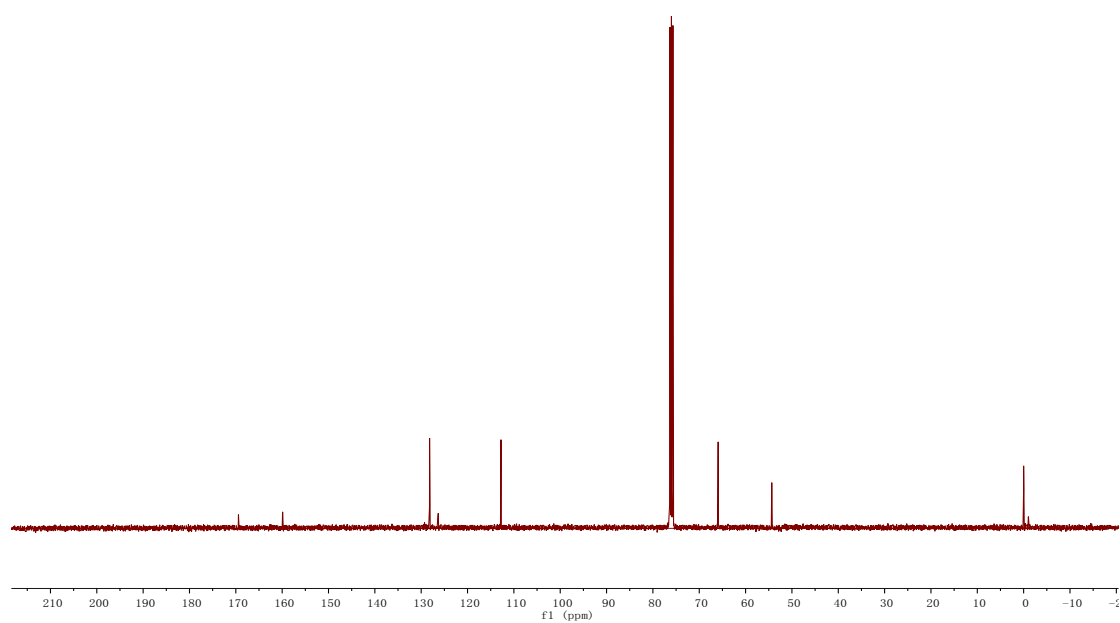
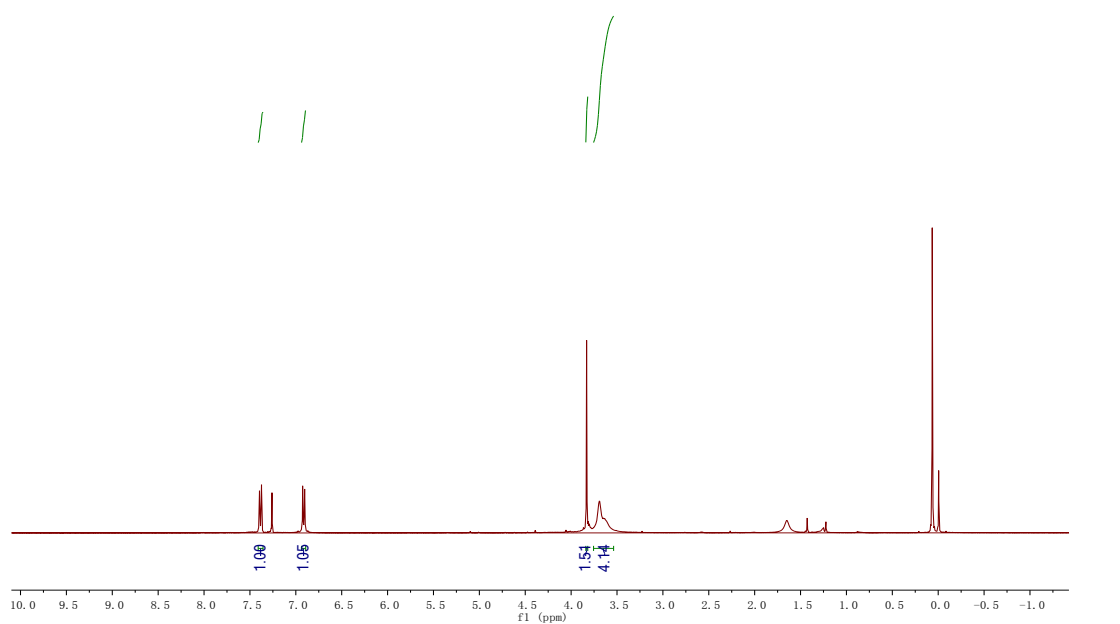


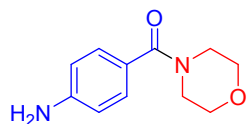
N-(4-Methoxybenzoyl)morpholine (**3c**). Yellow oil; 1.37g, 93% yield;

^1H NMR (400 MHz, CDCl_3) δ 7.41–7.36 (m, 2H), 6.94–6.89 (m, 2H), 3.84 (d, $J = 3.2$ Hz, 3H),

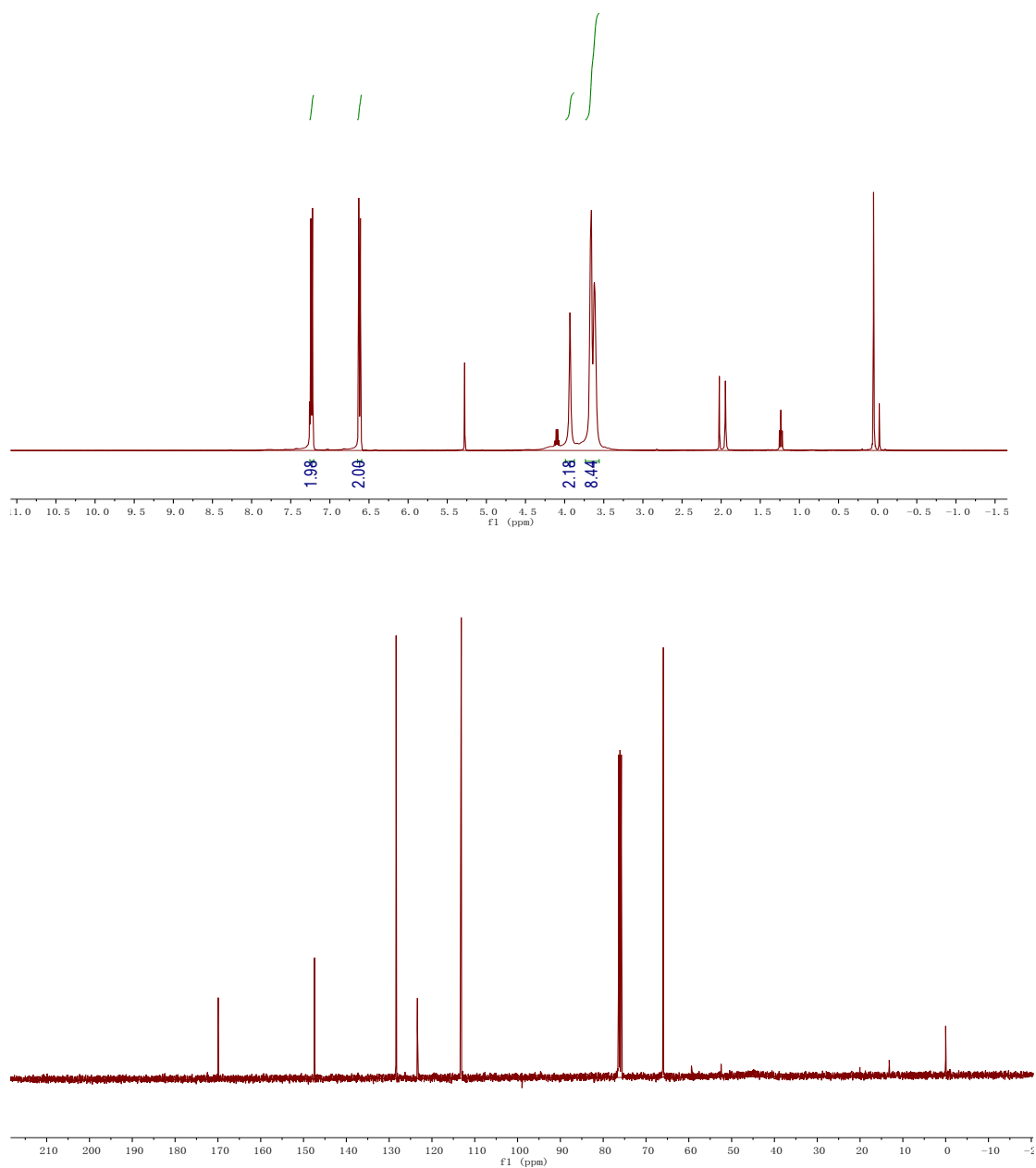
3.76–3.54 (m, 8H); ^{13}C NMR (101 MHz, CDCl_3) δ 169.4, 159.9, 128.2, 126.3, 112.8, 65.9, 54.3;

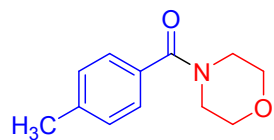
HRMS (ESI) m/z calcd for $\text{C}_{12}\text{H}_{15}\text{NO}_3$ $[\text{M}+\text{H}]^+$ 222.1085, found 222.1094.





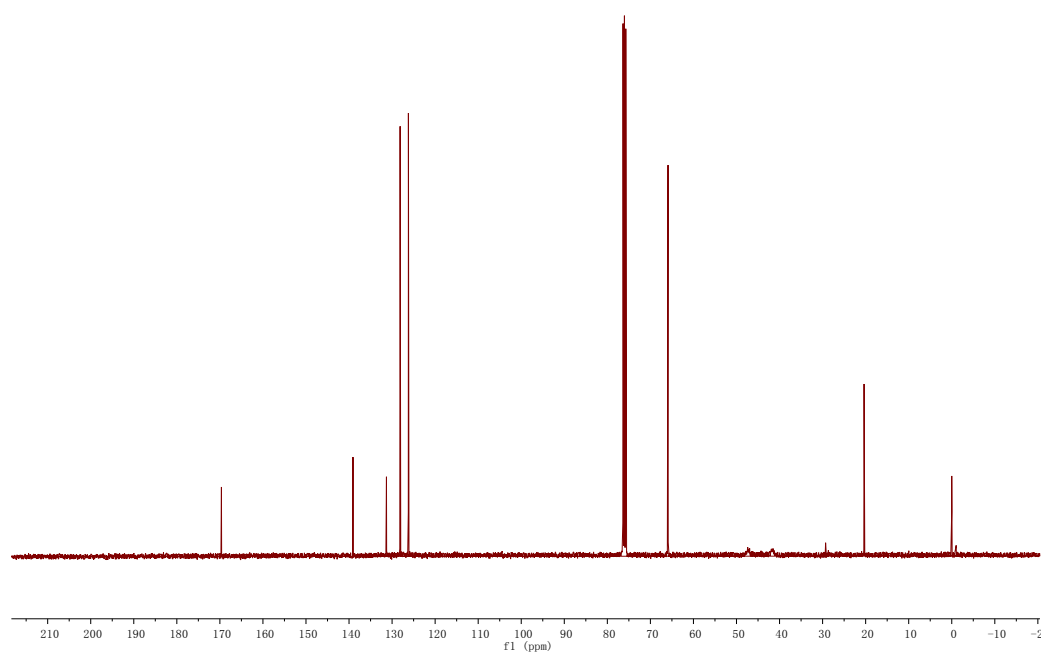
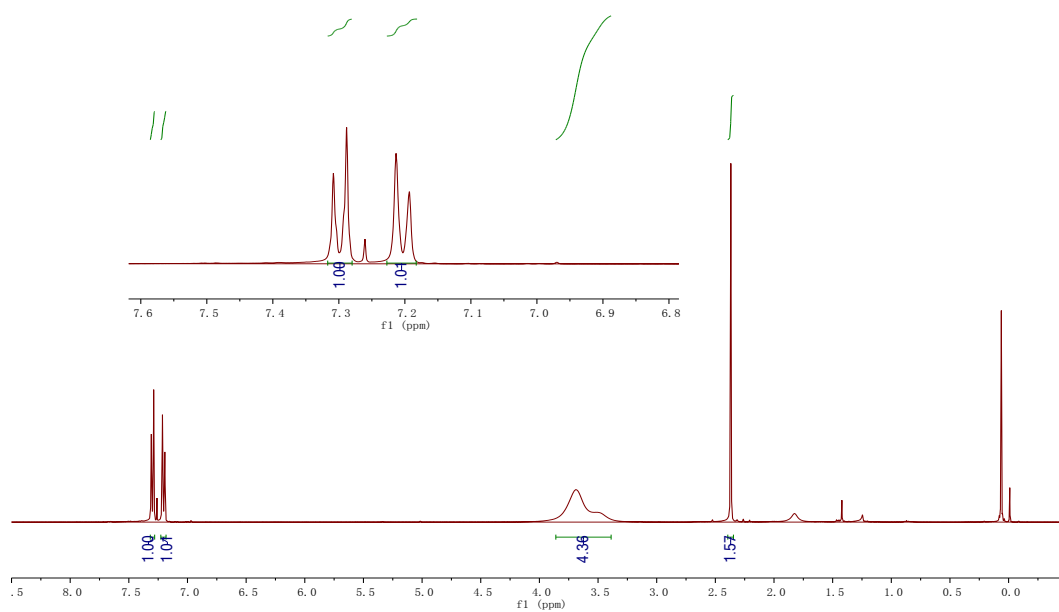
N-(4-Aminobenzoyl)morpholine (**3d**). White solid; 1.12g, 82% yield; ^1H NMR (400 MHz, CDCl_3) δ 7.26–7.21 (m, 2H), 6.65–6.59 (m, 2H), 3.93 (s, 2H), 3.73–3.56 (m, 8H); White solid; 1.12g, 82% yield; ^1H NMR (400 MHz, CDCl_3) δ 7.26–7.21 (m, 2H), 6.65–6.59 (m, 2H), 3.93 (s, 2H), 3.73–3.56 (m, 8H); ^{13}C NMR (101 MHz, CDCl_3) δ 169.9, 147.4, 128.4, 123.4, 113.2, 65.9, 59.4, 52.4, 20.0, 13.2; HRMS (ESI) m/z calcd for $\text{C}_{11}\text{H}_{14}\text{N}_2\text{O}_2$ $[\text{M}+\text{H}]^+$ 207.1089, found 207.1096.

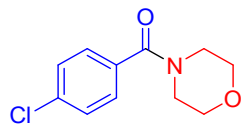




N-(4-Methylbenzoyl)morpholine (**3f**). Light yellow oil; 1.24g, 91% yield;

^1H NMR (400 MHz, CDCl_3) δ 7.30 (d, $J = 8.1$ Hz, 2H), 7.20 (d, $J = 8.0$ Hz, 2H), 3.69 (s, 8H), 2.37 (s, 3H); ^{13}C NMR (101 MHz, CDCl_3) δ 169.6, 139.1, 131.3, 128.1, 126.2, 65.9, 29.3, 20.4; HRMS (ESI) m/z calcd for $\text{C}_{12}\text{H}_{15}\text{NO}_2$ $[\text{M}+\text{H}]^+$ 206.1136, found 206.1147.



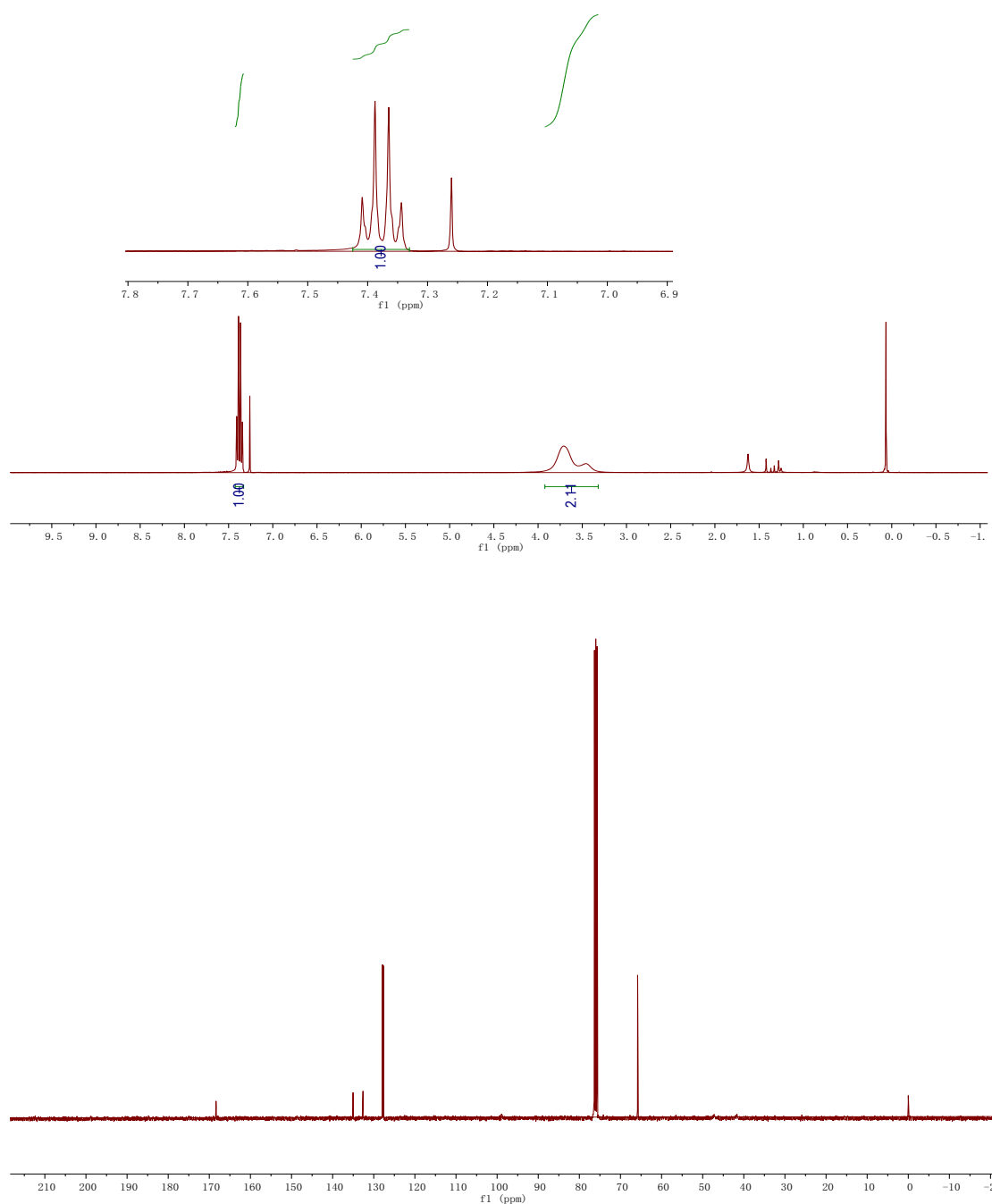


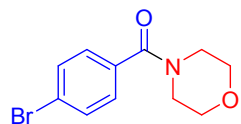
N-(4-Chlorobenzoyl)morpholine (**3g**). White solid; 1.38g, 92% yield;

m.p.=75-77°C; ^1H NMR (400 MHz, CDCl_3) δ 7.38 (q, $J = 8.5$ Hz, 4H), 3.92–3.32 (m, 8H); ^{13}C

NMR (101 MHz, CDCl_3) δ 168.4, 135.0, 132.6, 127.9, 127.6, 99.9, 65.8; HRMS (ESI) m/z calcd

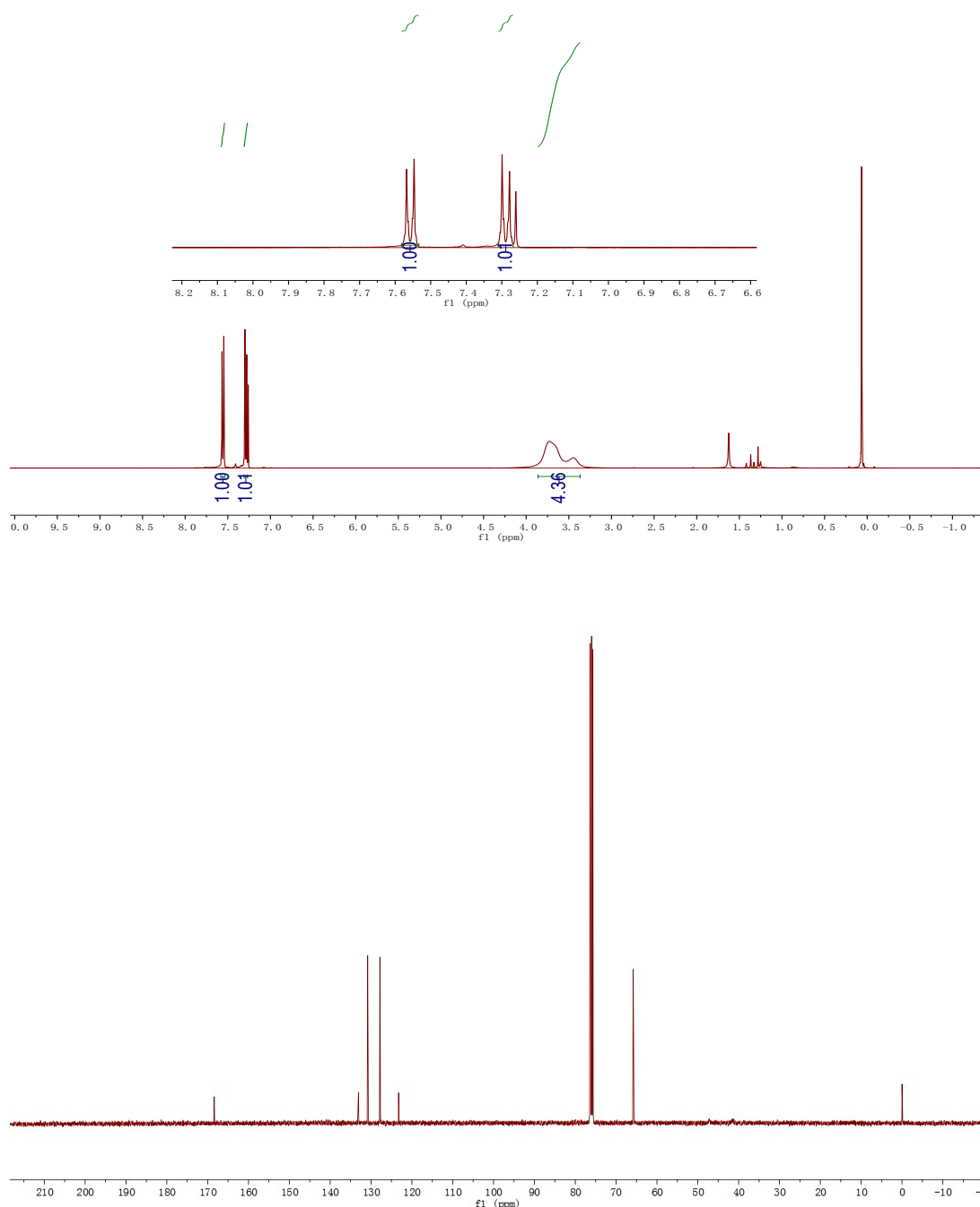
for $\text{C}_{11}\text{H}_{12}\text{ClNO}_2$ $[\text{M}+\text{H}]^+$ 226.6720, found 226.6724.

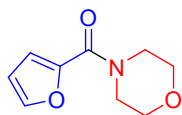




N-(4-Bromobenzoyl)morpholine (**3h**). Light yellow solid; 1.58g, 88% yield;

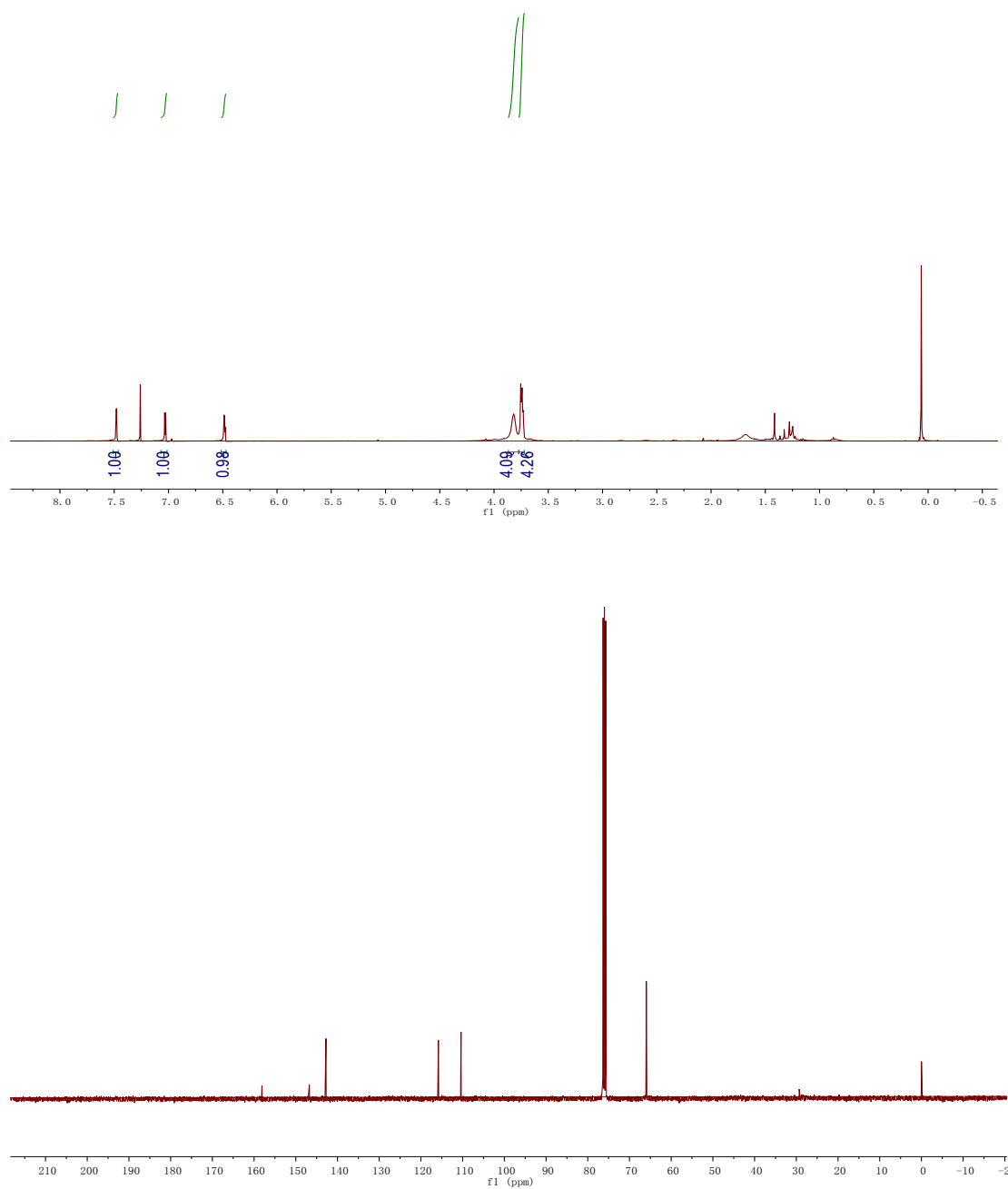
^1H NMR (400 MHz, CDCl_3) δ 7.58–7.54 (m, 2H), 7.31–7.27 (m, 2H), 3.86–3.31 (m, 8H); ^{13}C NMR (101 MHz, CDCl_3) δ 168.4, 133.1, 130.8, 127.8, 123.2, 65.8; HRMS (ESI) m/z calcd for $\text{C}_{11}\text{H}_{12}\text{BrNO}_2$ $[\text{M}+\text{H}]^+$ 271.1260, found 271.1284.

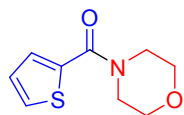




2-Furanyl-4-morpholinylmethanone (3i). Yellow oil; 1.12g, 93% yield; ^1H

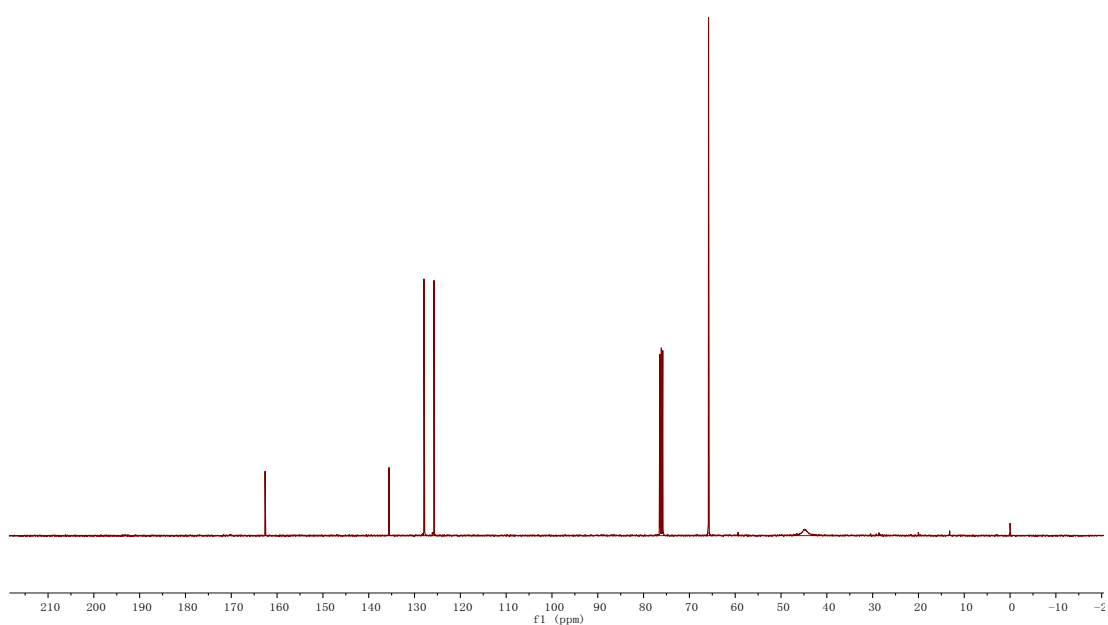
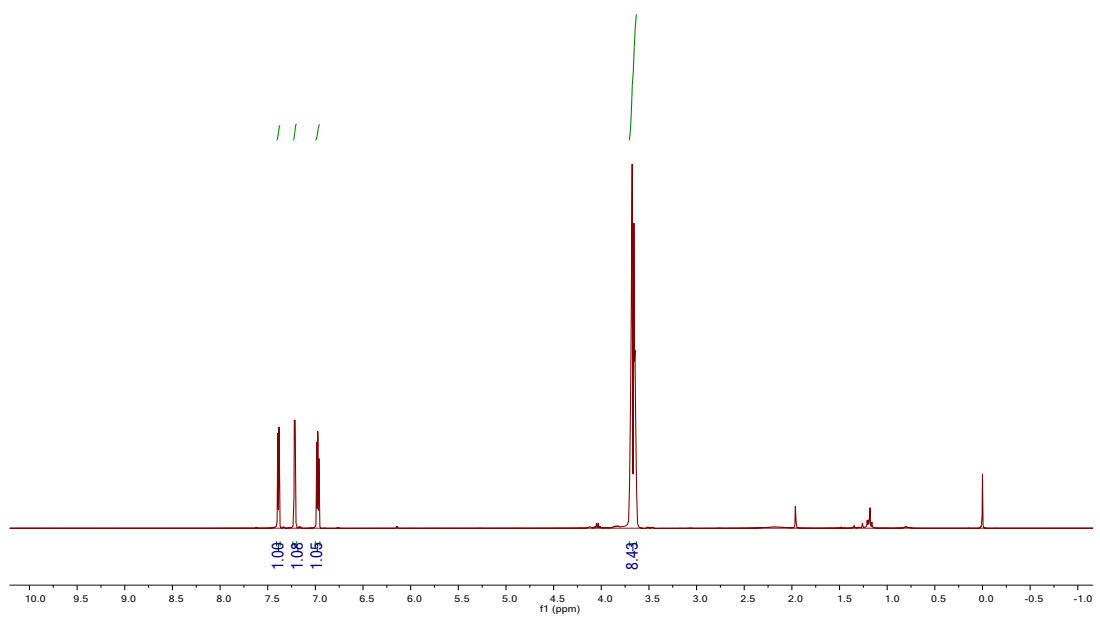
NMR (400 MHz, CDCl_3) δ 7.48 (dd, $J = 1.7, 0.8$ Hz, 1H), 7.03 (dd, $J = 3.5, 0.7$ Hz, 1H), 6.49 (dd, $J = 3.5, 1.8$ Hz, 1H), 3.82 (s, 4H), 3.77–3.72 (m, 4H); ^{13}C NMR (101 MHz, CDCl_3) δ 158.1, 146.7, 142.7, 115.8, 110.4, 65.9, 29.3; HRMS (ESI) m/z calcd for $\text{C}_9\text{H}_{11}\text{NO}_3$ $[\text{M}+\text{H}]^+$ 182.0772, found 182.0783.

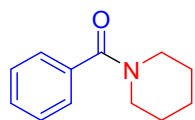




4-Morpholinyl-2-thienylmethanone (3j). Light yellow oil; 1.23g, 94% yield; ^1H

NMR (400 MHz, CDCl_3) δ 7.39 (dd, $J = 5.0, 1.0$ Hz, 1H), 7.22 (dd, $J = 3.6, 1.0$ Hz, 1H), 6.97 (dd, $J = 5.0, 3.7$ Hz, 1H), 3.71–3.63 (m, 8H); ^{13}C NMR (101 MHz, CDCl_3) δ 162.6, 135.6, 127.9, 127.8, 125.7, 65.8, 59.4, 20.0, 13.2; HRMS (ESI) m/z calcd for $\text{C}_9\text{H}_{11}\text{NO}_2\text{S}$ $[\text{M}+\text{H}]^+$ 198.0544, found 198.0568.



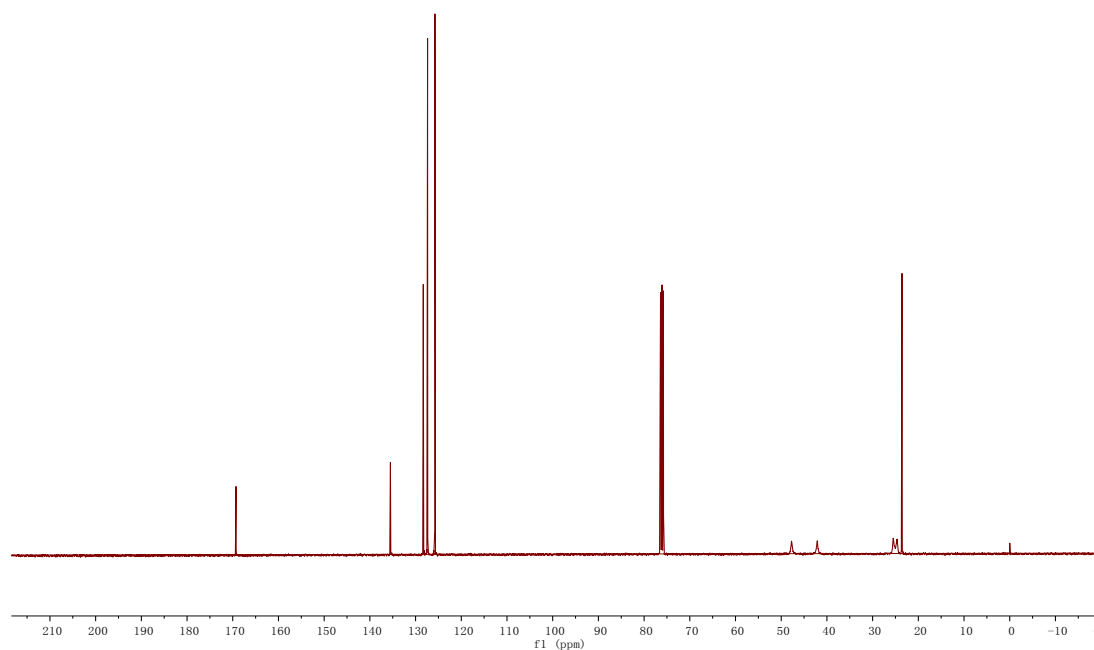
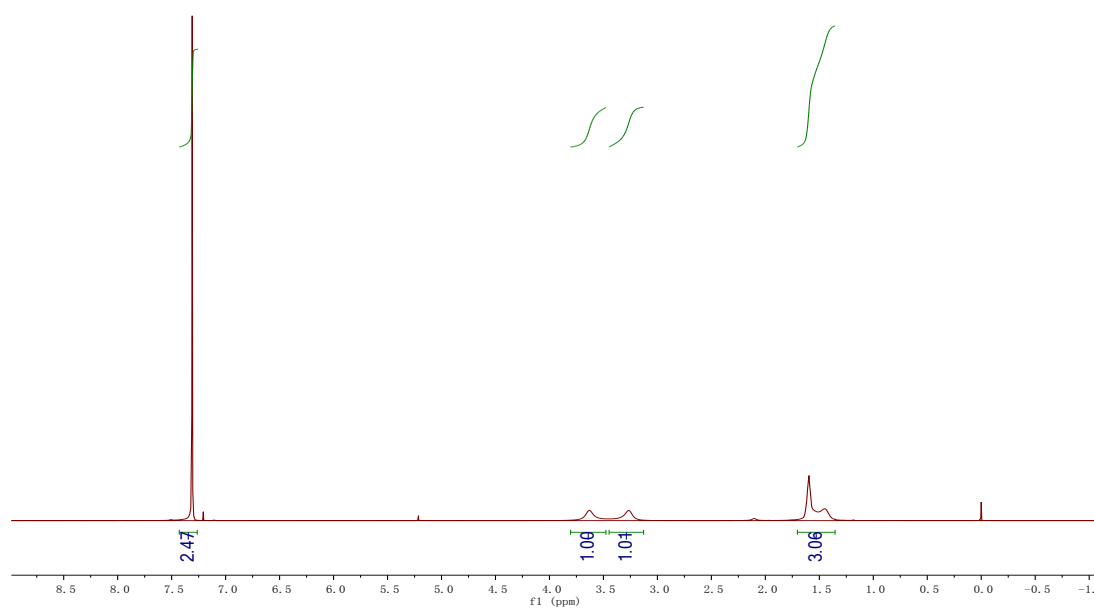


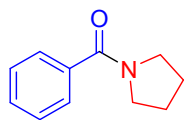
Benzoylpiperidine (3k). Colourless oil; 1.14g, 91% yield; $^1\text{H NMR}$ (400 MHz,

CDCl_3) δ 7.31(s, 5H), 3.63 (s, 2H), 3.27 (s, 2H), 1.70–1.35 (m, 6H); $^{13}\text{C NMR}$ (101 MHz, CDCl_3)

δ 169.3, 135.5, 128.3, 127.4, 125.7, 47.7, 42.1, 25.4, 24.6, 23.6; HRMS (ESI) m/z calcd for

$\text{C}_{12}\text{H}_{15}\text{NO}$ $[\text{M}+\text{H}]^+$ 190.1187, found 190.1192.



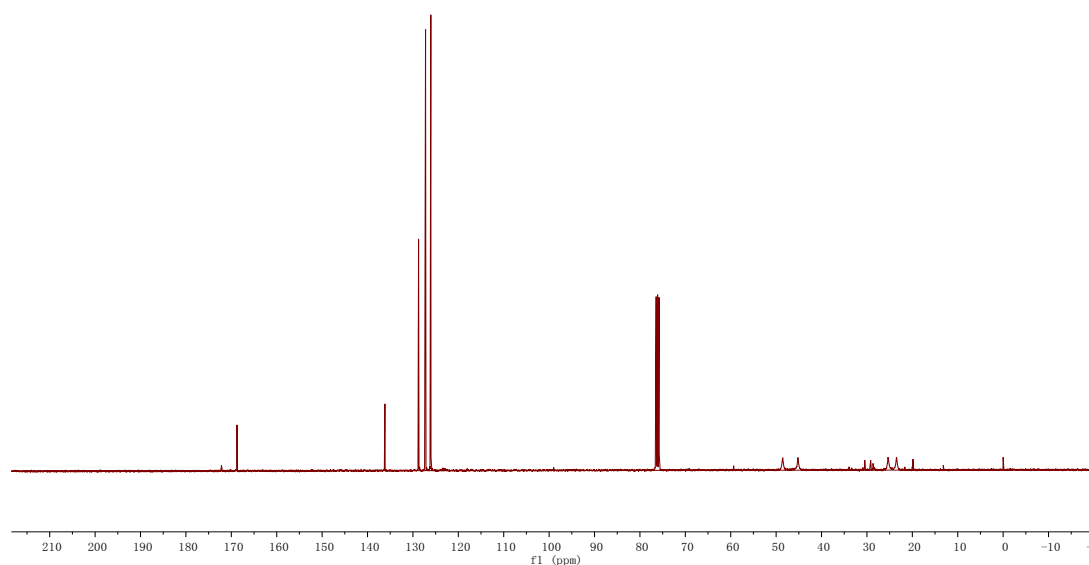
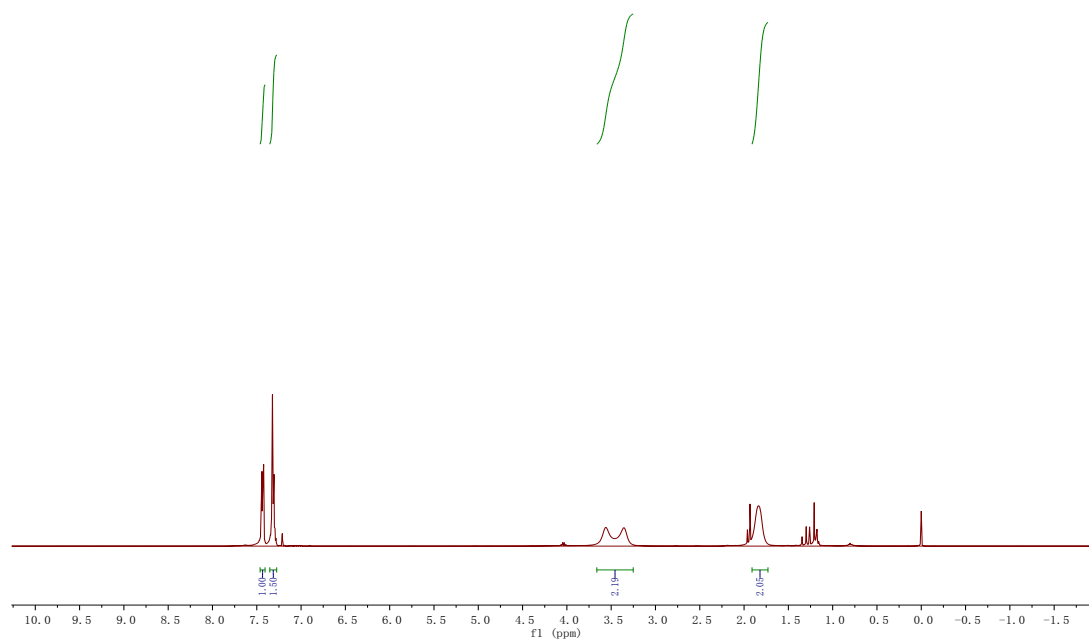


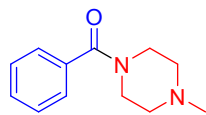
Benzoylpyrrolidine (**31**). Colourless oil; 1.05g, 90% yield; ^1H NMR (400 MHz,

CDCl_3) δ 7.43 (dt, $J = 8.5, 3.7$ Hz, 2H), 7.35–7.28 (m, 3H), 3.46 (d, $J = 81.7$ Hz, 4H), 1.84 (s, 4H);

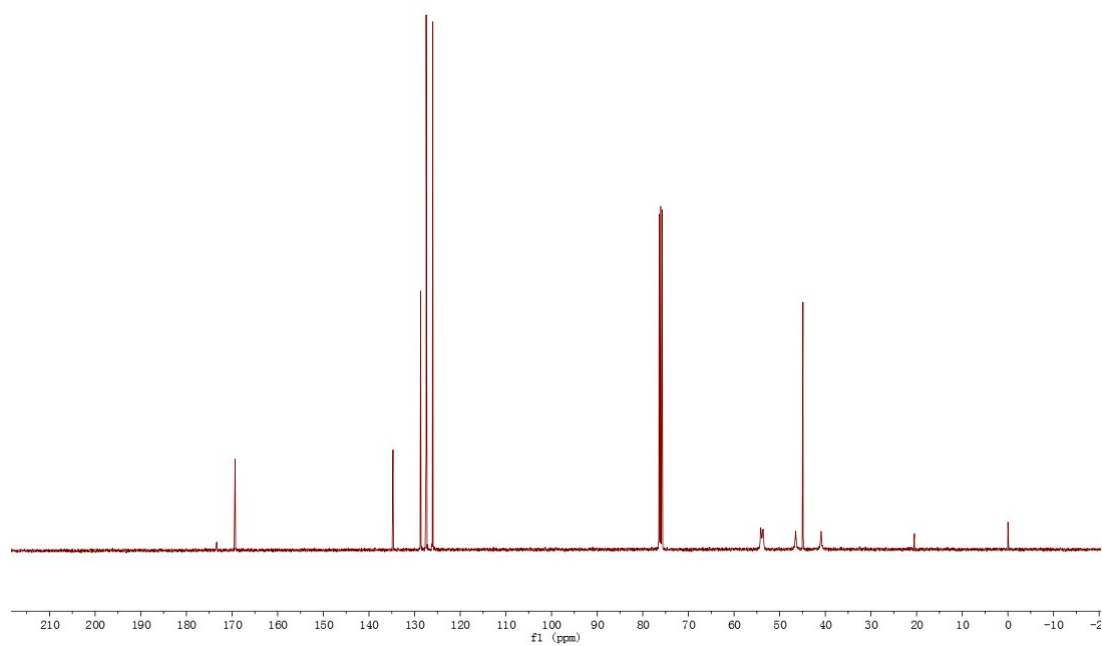
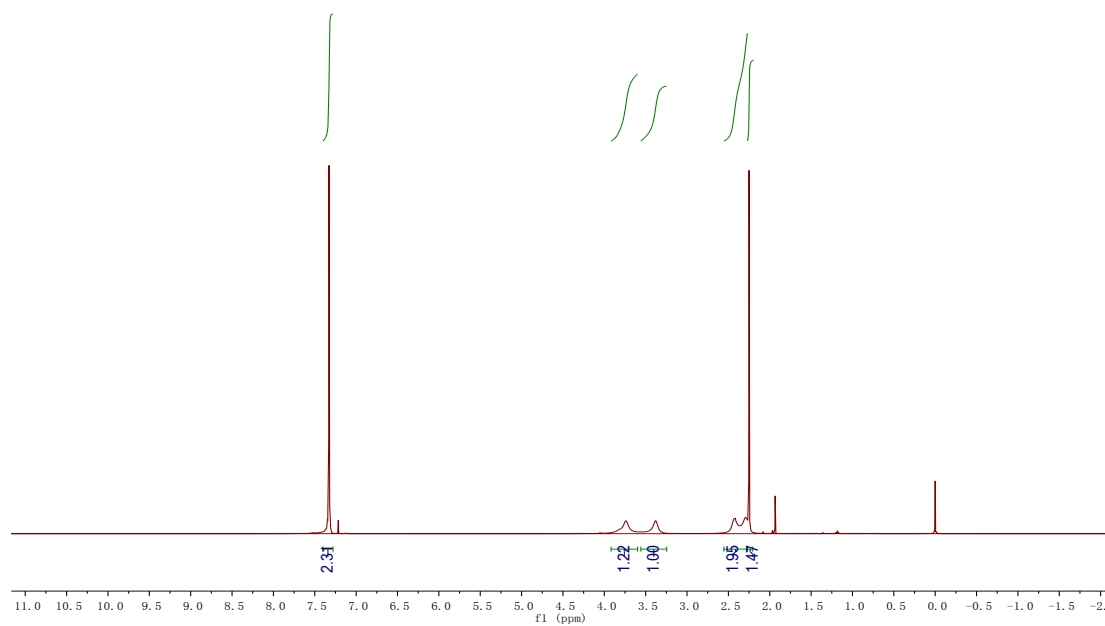
^{13}C NMR (101 MHz, CDCl_3) δ 168.7, 136.2, 128.7, 127.2, 126.0, 48.6, 45.2, 25.4, 23.5; HRMS

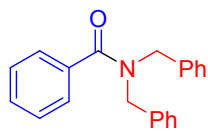
(ESI) m/z calcd for $\text{C}_{11}\text{H}_{13}\text{NO}$ $[\text{M}+\text{H}]^+$ 176.1031, found 176.1045.



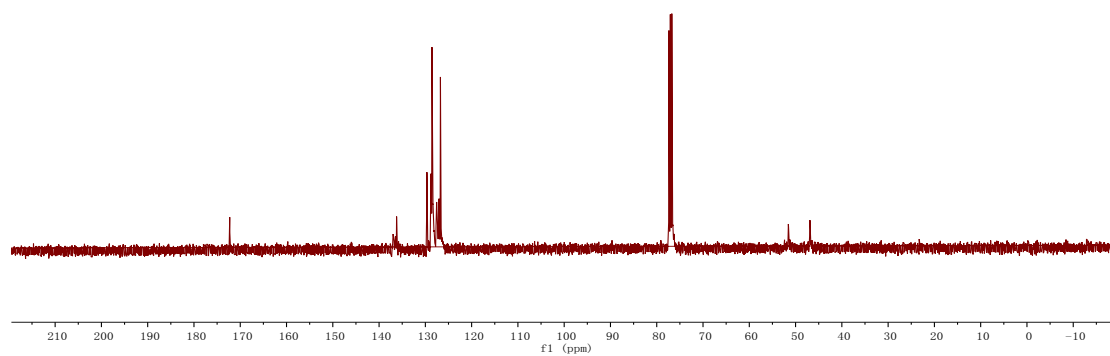
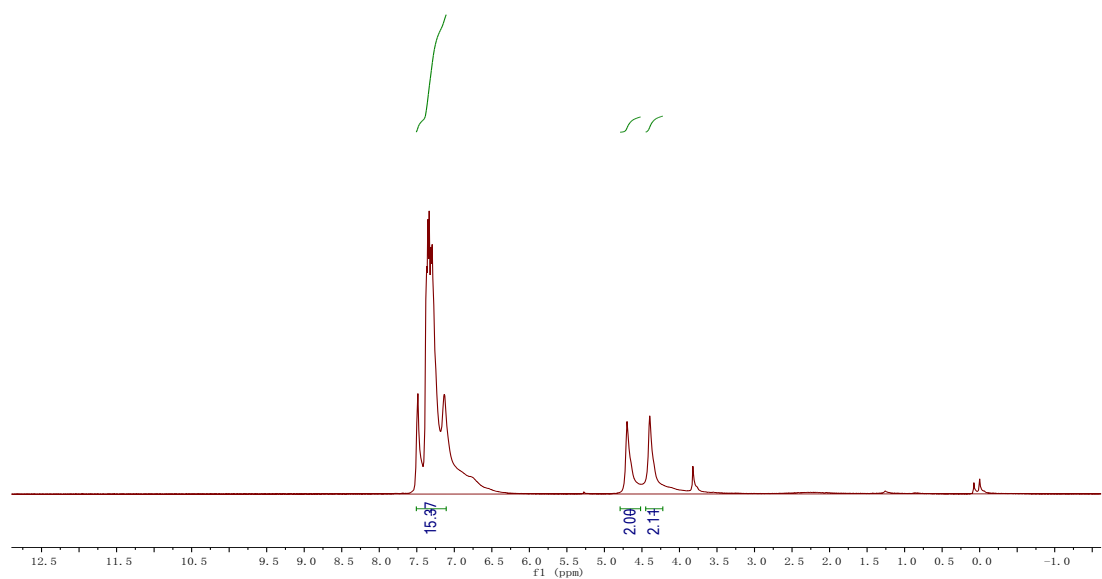


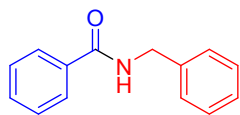
1-Benzoyl-4-methylpiperazine (3m). Yellow oil; 1.21g, 89% yield; ^1H NMR (400 MHz, CDCl_3) δ 7.40–7.28 (m, 5H), 3.74 (s, 2H), 3.34 (s, 2H), 2.55–2.27 (m, 4H), 2.25 (s, 3H); ^{13}C NMR (101 MHz, CDCl_3) δ 173.4, 169.3, 134.7, 128.7, 127.5, 126.0, 54.2, 53.6, 46.5, 44.9, 40.9, 20.5; HRMS (ESI) m/z calcd for $\text{C}_{12}\text{H}_{16}\text{N}_2\text{O}$ $[\text{M}+\text{H}]^+$ 205.1296, found 205.1305.



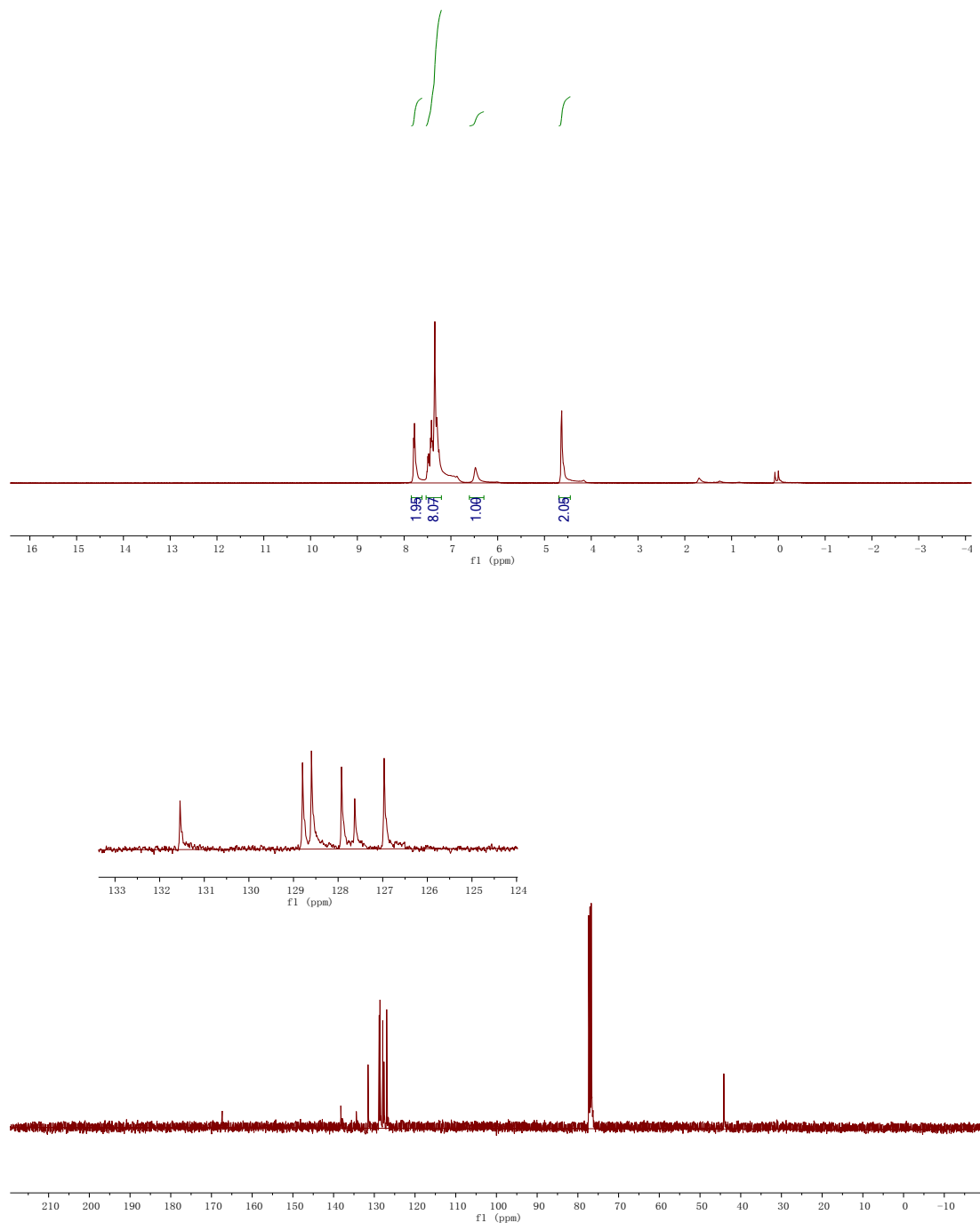


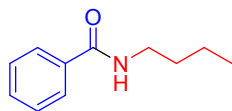
N,N-Dibenzylbenzamide (**3n**). White solid; 1.80g, 90% yield; m.p.=113-114°C; ^1H NMR (400 MHz, CDCl_3) δ 7.51–7.11 (m, 15H), 4.70 (s, 2H), 4.40 (s, 2H); ^{13}C NMR (101 MHz, CDCl_3) δ 172.3, 136.9, 136.4, 136.2, 129.7, 128.8, 128.6, 128.4, 127.6, 127.0, 126.7, 51.6, 46.9; HRMS (ESI) m/z calcd for $\text{C}_{21}\text{H}_{19}\text{NO}$ $[\text{M}+\text{H}]^+$ 302.1500, found 302.1509.



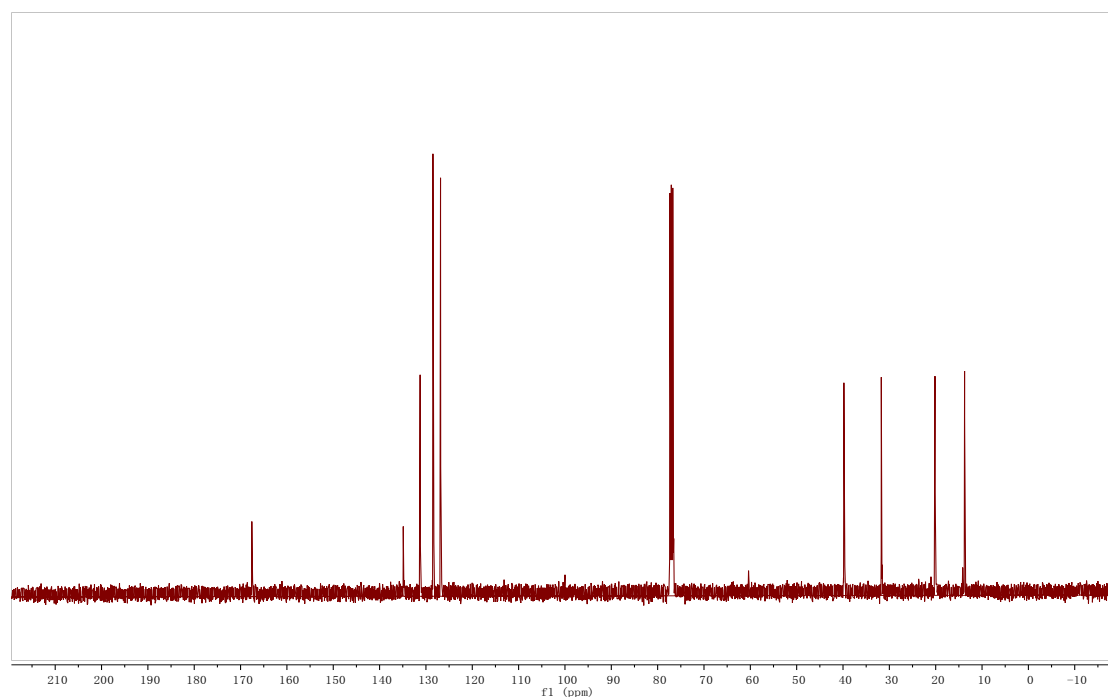
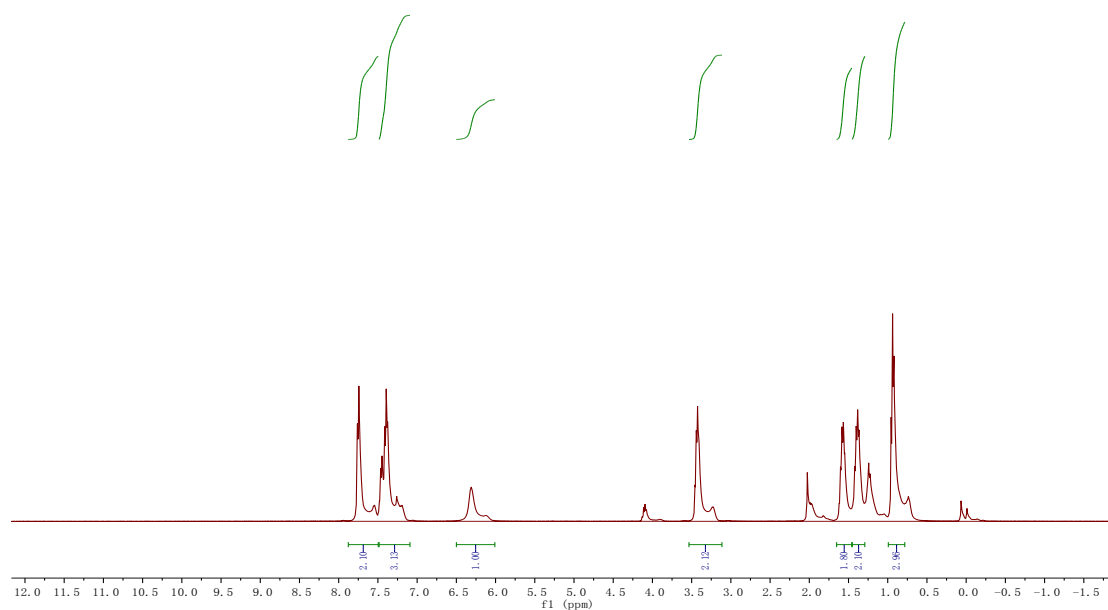


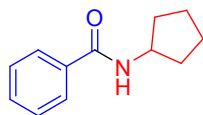
N-Benzylbenzamide (**30**). White solid; 1.16g, 83% yield; m.p.=104-106°C; ¹H NMR (400 MHz, CDCl₃) δ 7.79 (d, *J* = 7.2 Hz, 2H), 7.53–7.20 (m, 8H), 6.48 (s, 1H), 4.64 (d, *J* = 5.5 Hz, 2H); ¹³C NMR (101 MHz, CDCl₃) δ 167.4, 138.2, 134.4, 131.5, 128.8, 128.6, 127.9, 127.6, 127.0, 44.2; HRMS (ESI) *m/z* calcd for C₁₄H₁₃NO [M+H]⁺ 212.1031, found 212.1084.





N-Butylbenzamide (**3p**). White solid; 1.01g, 86% yield; m.p.=41-43°C;
¹H NMR (400 MHz, CDCl₃) δ 7.64 (dd, *J* = 93.1, 13.0 Hz, 2H), 7.48–7.09 (m, 3H), 6.22 (d, *J* = 75.4 Hz, 1H), 3.53–3.11 (m, 2H), 1.58 (dt, *J* = 14.0, 7.0 Hz, 2H), 1.39 (dd, *J* = 14.5, 7.2 Hz, 2H), 0.94 (dd, *J* = 9.2, 5.4 Hz, 3H); ¹³C NMR (101 MHz, CDCl₃) δ 167.6, 134.9, 131.2, 128.5, 126.8, 39.8, 31.7, 20.2, 13.8; HRMS (ESI) *m/z* calcd for C₁₁H₁₅NO [M+H]⁺ 178.1187, found 178.1189.





N-Cyclopentylbenzamide (**3q**). White solid; 1.05g, 84% yield; m.p.=133-

134°C; ¹H NMR (400 MHz, CDCl₃) δ 7.80–7.70 (m, 2H), 7.51–7.35 (m, 3H), 6.11 (s, 1H), 4.45–4.34 (m, 1H), 2.08 (td, *J* = 11.4, 6.1 Hz, 2H), 1.78–1.59 (m, 4H), 1.49 (td, *J* = 12.5, 6.1 Hz, 2H); ¹³C NMR (101 MHz, CDCl₃) δ 167.2, 135.0, 131.2, 128.5, 126.8, 51.7, 33.2, 23.8; HRMS (ESI) *m/z* calcd for C₁₂H₁₅NO [M+H]⁺ 190.1187, found 190.1192.

