

Pd/Ni Catalyzed selective N–H/C–H Methylation of Amides by Using Peroxides as the Methylating Reagents via a Radical Process

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1. General information

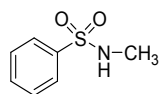
All compounds are characterized by ^1H NMR, ^{13}C NMR and MS. Analytical thin-layer chromatography is performed on glass plates precoated with silica gel impregnated with a fluorescent indicator (254 nm), and the plates are visualized by exposure to ultraviolet light. ^1H NMR and ^{13}C NMR spectra are recorded on an AVANCE 500 Bruker spectrometer operating at 500 MHz and 125 MHz in CDCl_3 , respectively, and chemical shifts are reported in ppm. GC analyses are performed on an Agilent 7890A instrument (Column: Agilent 19091J-413:30 m \times 320 μm \times 0.25 μm , H, FID detection). GC-MS data was recorded on a 5975C Mass Selective Detector, coupled with a 7890A Gas Chromatograph (Agilent Technologies).

2. General procedure

General procedure for the synthesis of N-methyl amides : To a mixture of benzene sulfonamide (0.5 mmol) **1a**, $\text{Ni}(\text{OTf})_2$ (10%mmol) and solvent ($\text{HOAc}/\text{H}_2\text{O}=1\text{ml} : 1\text{ml}$) in a reaction tube was added peroxide (3 equiv.). The reaction mixture was stirred at 120°C overnight in air. The reaction mixture was extracted with ethyl acetate (15 mL \times 3). The combined organic layers were washed with brine, dried over MgSO_4 , and concentrated in vacuo. The residue was purified by column chromatography on silica gel to afford the desired products **3**.

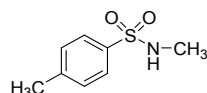
General procedure for the synthesis of C-methyl amides : To a mixture of benzene sulfonamide (0.5 mmol) **1a**, $\text{Pd}(\text{OAc})_2$ (10%mmol) and solvent (2ml) in a reaction tube was added peroxide (3 equiv.). The reaction mixture was stirred at 120°C overnight in air. The reaction mixture was extracted with ethyl acetate (15 mL \times 3). The combined organic layers were washed with brine, dried over MgSO_4 , and concentrated in vacuo. The residue was purified by column chromatography on silica gel to afford the desired products **4**.

3.Characterization data



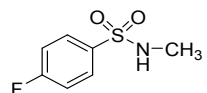
Formula: C₇H₉NO₂S
Mass: 171

N-methylbenzenesulfonamide (3a): The crude product was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 3:1) to give **3a** as white solid (61.6mg, 72%). ¹H NMR (500 MHz, Chloroform-*d*) δ 7.83 (dd, *J* = 7.6, 1.8 Hz, 2H), 7.58 – 7.41 (m, 3H), 5.26 (q, *J* = 5.5 Hz, 1H), 2.57 (d, *J* = 5.2 Hz, 3H). ¹³C NMR (126 MHz, Chloroform-*d*) δ 137.6, 131.8, 128.2, 126.2, 28.3. GC-MS (EI) *m/z*: 171.



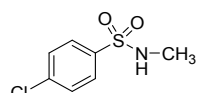
Formula: C₈H₁₁NO₂S
Mass: 185

N,4-dimethylbenzenesulfonamide (3b): The crude product was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 3:1) to give **3b** as white solid (66.6mg, 72%). ¹H NMR (500 MHz, Chloroform-*d*) δ 7.74 (dd, *J* = 8.3, 2.0 Hz, 2H), 7.31 (dd, *J* = 8.2, 2.0 Hz, 2H), 4.55 (q, *J* = 5.6 Hz, 1H), 2.64 (s, 3H), 2.42 (s, 3H). ¹³C NMR (126 MHz, Chloroform-*d*) δ 142.5, 134.8, 128.8, 126.3, 28.4, 20.6. GC-MS (EI) *m/z*: 185.



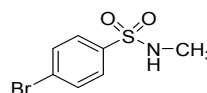
Formula: C₇H₈FNO₂S
Mass: 189

4-fluoro-N-methylbenzenesulfonamide (3c): The crude product was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 3:1) to give **3c** as white solid (69.9mg, 74%). ¹H NMR (500 MHz, Chloroform-*d*) δ 7.95 – 7.82 (m, 2H), 7.24 – 7.12 (m, 2H), 4.92 (q, *J* = 5.4 Hz, 1H), 2.63 (d, *J* = 5.3 Hz, 3H). ¹³C NMR (126 MHz, Chloroform-*d*) δ 165.2, 163.1, 133.9, 129.0, 115.5, 28.3. GC-MS (EI) *m/z*: 189.



Formula: C₇H₈ClNO₂S
Mass: 205

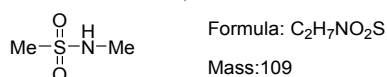
4-chloro-N-methylbenzenesulfonamide (3d): The crude product was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 3:1) to give **3d** as white solid (69.7mg, 68%). ¹H NMR (500 MHz, Chloroform-*d*) δ 7.80 (d, *J* = 8.6 Hz, 2H), 7.50 (d, *J* = 8.5 Hz, 2H), 4.57 (q, *J* = 5.5 Hz, 1H), 2.67 (d, *J* = 5.4 Hz, 3H). ¹³C NMR (126 MHz, Chloroform-*d*) δ 138.3, 136.5, 128.5, 127.7, 28.3. GC-MS (EI) *m/z*: 205.



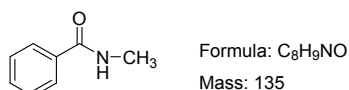
Formula: C₇H₈BrNO₂S
Mass: 249

4-bromo-N-methylbenzenesulfonamide (3e): The crude product was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 3:1) to give **3e** as white solid (89.6mg, 72%). ¹H NMR (500 MHz, Chloroform-*d*) δ 7.76 – 7.61 (m, 4H), 4.70 (q, *J* = 5.5 Hz, 1H), 2.65 (d, *J* = 5.3 Hz, 3H). ¹³C NMR (126 MHz,

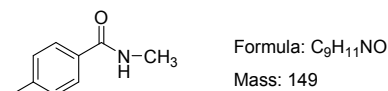
Chloroform-*d*) δ 136.9, 131.5, 127.8, 126.8, 28.3. GC-MS (EI) *m/z*: 249.



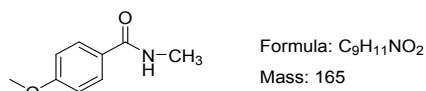
N-methylmethanesulfonamide (3f): The crude product was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 3:1) to give **3f** as white solid (37.6mg, 69%). ¹H NMR (500 MHz, Chloroform-*d*) δ 5.00 (s, 1H), 2.85 (s, 3H), 2.69 (d, *J* = 5.2 Hz, 3H). ¹³C NMR (126 MHz, Chloroform-*d*) δ 37.2, 28.3. GC-MS (EI) *m/z*: 109.



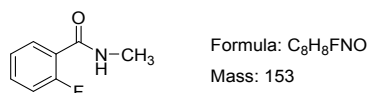
N-methylbenzamide (3g): The crude product was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 3:1) to give **3g** as white solid (40.5mg, 60%). ¹H NMR (500 MHz, Chloroform-*d*) δ 7.81 – 7.70 (m, 2H), 7.49 (t, *J* = 7.4 Hz, 1H), 7.42 (t, *J* = 7.5 Hz, 2H), 6.20 (s, 1H), 3.01 (d, *J* = 4.9 Hz, 3H). ¹³C NMR (126 MHz, Chloroform-*d*) δ 167.3, 133.7, 130.4, 127.6, 125.8, 25.9. GC-MS (EI) *m/z*: 135.



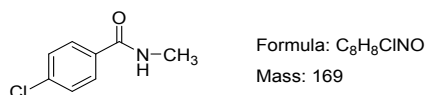
N,4-dimethylbenzamide (3h): The crude product was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 3:1) to give **3h** as white solid (49.9mg, 67%). ¹H NMR (500 MHz, Chloroform-*d*) δ 7.65 (d, *J* = 8.1 Hz, 2H), 7.20 (d, *J* = 7.9 Hz, 2H), 6.28 (s, 1H), 2.98 (d, *J* = 4.8 Hz, 3H), 2.37 (s, 3H). ¹³C NMR (126 MHz, Chloroform-*d*) δ 167.3, 140.7, 130.8, 128.2, 125.9, 25.8, 20.5. GC-MS (EI) *m/z*: 149.



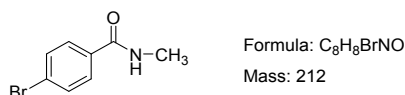
4-methoxy-N-methylbenzamide (3i): The crude product was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 3:1) to give **3i** as white solid (51.2mg, 62%). ¹H NMR (500 MHz, Chloroform-*d*) δ 7.72 (d, *J* = 8.8 Hz, 2H), 6.89 (d, *J* = 8.8 Hz, 2H), 6.24 (s, 1H), 3.83 (s, 3H), 2.97 (d, *J* = 4.8 Hz, 3H). ¹³C NMR (126 MHz, Chloroform-*d*) δ 166.8, 161.1, 127.6, 126.0, 112.7, 54.4, 25.8. GC-MS (EI) *m/z*: 165.



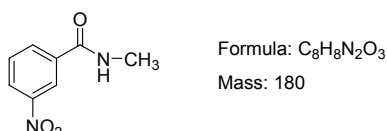
2-fluoro-N-methylbenzamide (3j): The crude product was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 3:1) to give **3j** as white solid (40.5mg, 53%). ¹H NMR (500 MHz, Chloroform-*d*) δ 8.14 – 8.07 (m, 1H), 7.48 – 7.42 (m, 1H), 7.28 – 7.24 (m, 1H), 7.10 (dd, *J* = 12.1, 8.3 Hz, 1H), 6.76 (s, 1H), 3.04 (s, 3H). ¹³C NMR (126 MHz, Chloroform-*d*) δ 163.1, 132.2, 131.1, 123.8, 120.0, 115.1, 114.9, 25.9. GC-MS (EI) *m/z*: 153.



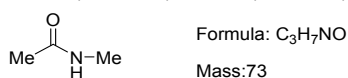
4-chloro-N-methylbenzamide (3k): The crude product was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 3:1) to give **3k** as white solid (58.3mg, 69%). ¹H NMR (500 MHz, Chloroform-*d*) δ 7.69 (d, *J* = 8.6 Hz, 2H), 7.38 (d, *J* = 8.4 Hz, 2H), 6.33 (s, 1H), 2.99 (d, *J* = 4.8 Hz, 3H). ¹³C NMR (126 MHz, Chloroform-*d*) δ 166.3, 136.6, 132.0, 127.8, 127.3, 25.9. GC-MS (EI) *m/z*: 169.



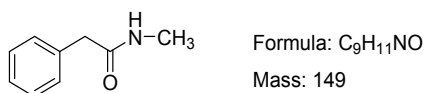
4-bromo-N-methylbenzamide (3l): The crude product was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 3:1) to give **3l** as white solid (63.6mg, 60%). ¹H NMR (500 MHz, Chloroform-*d*) δ 7.62 (d, *J* = 8.5 Hz, 2H), 7.53 (d, *J* = 8.5 Hz, 2H), 6.38 (s, 1H), 2.98 (d, *J* = 4.8 Hz, 3H). ¹³C NMR (126 MHz, Chloroform-*d*) δ 166.4, 130.8, 127.5, 125.0, 25.9. GC-MS (EI) *m/z*: 212.



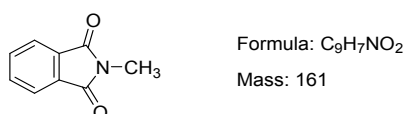
N-methyl-3-nitrobenzamide (3m): The crude product was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 3:1) to give **3m** as white solid (49.5mg, 55%). ¹H NMR (500 MHz, Chloroform-*d*) δ 8.58 (t, *J* = 2.0 Hz, 1H), 8.39 – 8.31 (m, 1H), 8.16 (d, *J* = 7.7 Hz, 1H), 7.65 (t, *J* = 8.0 Hz, 1H), 6.41 (s, 1H), 3.07 (d, *J* = 4.8 Hz, 3H). ¹³C NMR (126 MHz, Chloroform-*d*) δ 164.9, 147.2, 135.2, 132.2, 128.9, 125.0, 120.7, 26.1. GC-MS (EI) *m/z*: 180.



N-methylacetamide (3n): The crude product was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 3:1) to give **3n** as white solid (23.7mg, 65%). ¹H NMR (500 MHz, Chloroform-*d*) δ 7.20 (s, 1H), 2.53 (d, *J* = 4.8 Hz, 3H), 1.76 (s, 3H). ¹³C NMR (126 MHz, Chloroform-*d*) δ 170.5, 25.0, 21.6. GC-MS (EI) *m/z*: 73.

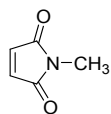


N-methyl-2-phenylacetamide (3o): The crude product was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 3:1) to give **3o** as white solid (52.2mg, 70%). ¹H NMR (500 MHz, Chloroform-*d*) δ 7.39 – 7.23 (m, 5H), 5.38 (s, 1H), 3.58 (s, 2H), 2.75 (d, *J* = 4.9 Hz, 3H). ¹³C NMR (126 MHz, Chloroform-*d*) δ 170.6, 133.9, 128.6, 128.1, 126.4, 42.8, 25.5. GC-MS (EI) *m/z*: 149.



2-methylisoindoline-1,3-dione (3p): The crude product was purified by column

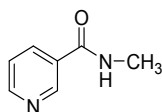
chromatography on silica gel (petroleum ether/ethyl acetate = 3:1) to give **3p** as white solid (55.5mg, 69%). ¹H NMR (500 MHz, Chloroform-*d*) δ 7.85 – 7.73 (m, 2H), 7.72 – 7.60 (m, 2H), 3.13 (s, 3H). ¹³C NMR (126 MHz, Chloroform-*d*) δ 167.4, 132.9, 131.2, 122.1, 22.9. GC-MS (EI) *m/z*: 161.



Formula: C₅H₅NO₂

Mass: 111

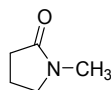
1-methyl-1H-pyrrole-2,5-dione (3q): The crude product was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 3:1) to give **3q** as white solid (34.4mg, 62%). ¹H NMR (500 MHz, Chloroform-*d*) δ 6.69 (s, 2H), 2.99 (s, 3H). ¹³C NMR (126 MHz, Chloroform-*d*) δ 169.8, 133.2, 22.7. GC-MS (EI) *m/z*: 111.



Formula: C₇H₈N₂O

Mass: 136

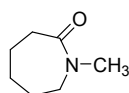
N-methylnicotinamide (3r): The crude product was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 3:1) to give **3r** as white solid (46.9mg, 69%). ¹H NMR (500 MHz, Chloroform-*d*) δ 8.95 (d, *J* = 1.9 Hz, 1H), 8.66 – 8.56 (m, 1H), 8.08 (d, *J* = 7.9 Hz, 1H), 7.33 – 7.28 (m, 1H), 7.19 (s, 1H), 2.96 (d, *J* = 4.7 Hz, 3H). ¹³C NMR (126 MHz, Chloroform-*d*) δ 165.5, 150.9, 147.0, 134.2, 129.4, 122.5, 25.9. GC-MS (EI) *m/z*: 136.



Formula: C₅H₉NO

Mass: 99

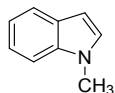
1-methylpyrrolidin-2-one (3s): The crude product was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 3:1) to give **3s** as white solid (37.6mg, 76%). ¹H NMR (500 MHz, Chloroform-*d*) δ 3.11 (t, *J* = 5.0 Hz, 2H), 2.54 (s, 3H), 2.06 (t, *J* = 7.5 Hz, 2H), 1.79 – 1.68 (m, 2H). ¹³C NMR (126 MHz, Chloroform-*d*) δ 173.9, 48.2, 29.5, 28.3, 16.4. GC-MS (EI) *m/z*: 99.



Formula: C₇H₁₃NO

Mass: 127

1-methylazepan-2-one (3t): The crude product was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 3:1) to give **3t** as white solid (47.6mg, 75%). ¹H NMR (500 MHz, Chloroform-*d*) δ 3.14 – 3.00 (m, 2H), 2.75 – 2.58 (m, 3H), 2.21 (dp, *J* = 15.7, 6.0, 5.5 Hz, 2H), 1.53 – 1.21 (m, 6H). ¹³C NMR (126 MHz, Chloroform-*d*) δ 174.6, 50.1, 35.7, 34.5, 28.6, 26.4, 22.2. GC-MS (EI) *m/z*: 127.

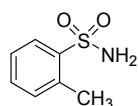


Formula: C₉H₉N

Mass: 131

1-methyl-1H-indole (3v): The crude product was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 3:1) to give **3v** as white solid (43.2mg, 66%). ¹H NMR (500 MHz, Chloroform-*d*) δ 8.15 – 7.97 (m, 1H), 7.70 – 7.48 (m, 3H), 7.28 (dt, *J* = 9.3, 3.1 Hz, 1H), 6.95 – 6.79 (m, 1H), 3.92 (s, 3H). ¹³C NMR (126 MHz, Chloroform-*d*) δ 136.2, 128.3, 128.0, 120.9, 120.3, 118.7, 108.7, 100.3, 31.9. GC-MS

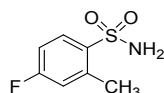
(EI) m/z : 131.



Formula: $C_7H_9NO_2S$

Mass: 171

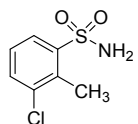
2-methylbenzenesulfonamide (4a): The crude product was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 3:1) to give **4a** as white solid (55.8mg, 65%). 1H NMR (500 MHz, DMSO- d_6) δ 7.82 (d, $J = 7.7$ Hz, 1H), 7.43 (t, $J = 7.4$ Hz, 1H), 7.36 – 7.29 (m, 4H), 2.56 (s, 3H). ^{13}C NMR (126 MHz, DMSO- d_6) δ 141.6, 135.3, 131.6, 131.3, 126.4, 125.5, 19.3. GC-MS (EI) m/z : 171.



Formula: $C_7H_8FNO_2S$

Mass: 189

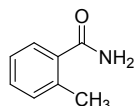
4-fluoro-2-methylbenzenesulfonamide (4b): The crude product was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 3:1) to give **4b** as white solid (54.8mg, 58%). 1H NMR (500 MHz, DMSO- d_6) δ 7.84 (dd, $J = 8.8, 5.9$ Hz, 1H), 7.39 (s, 2H), 7.22 (dd, $J = 10.0, 2.7$ Hz, 1H), 7.18 – 7.12 (m, 1H), 2.55 (s, 3H). ^{13}C NMR (126 MHz, DMSO- d_6) δ 163.8, 161.8, 139.1, 138.1, 129.4, 118.1, 112.1, 19.3. GC-MS (EI) m/z : 189.



Formula: $C_7H_8ClNO_2S$

Mass: 205

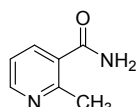
3-chloro-2-methylbenzenesulfonamide (4c): The crude product was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 3:1) to give **4c** as white solid (44.1mg, 43%). 1H NMR (500 MHz, DMSO- d_6) δ 7.81 (d, $J = 7.8$ Hz, 1H), 7.64 (d, $J = 7.9$ Hz, 1H), 7.55 (s, 2H), 7.35 (t, $J = 8.0$ Hz, 1H), 2.58 (s, 3H). ^{13}C NMR (126 MHz, DMSO- d_6) δ 143.8, 135.0, 133.0, 132.0, 126.7, 125.5, 16.1. GC-MS (EI) m/z : 205.



Formula: C_8H_9NO

Mass: 135

2-methylbenzamide (4d): The crude product was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 3:1) to give **4d** as white solid (34.4mg, 51%). 1H NMR (500 MHz, Chloroform- d) δ 7.43 (dd, $J = 7.5, 1.3$ Hz, 1H), 7.32 (td, $J = 7.5, 1.4$ Hz, 1H), 7.24 – 7.16 (m, 2H), 6.33 (s, 1H), 5.89 (s, 1H), 2.48 (s, 3H). ^{13}C NMR (126 MHz, Chloroform- d) δ 171.4, 135.3, 134.3, 130.2, 129.3, 126.0, 124.8, 19.0. GC-MS (EI) m/z : 135.

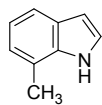


Formula: $C_7H_8N_2O$

Mass: 136

2-methylnicotinamide (4e): The crude product was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 3:1) to give **4e** as white solid (35.4mg, 52%). 1H NMR (500 MHz, Chloroform- d) δ 8.57 (dd, $J = 4.9, 1.6$ Hz, 1H), 7.75 (dd, $J = 7.7, 1.8$ Hz, 1H), 7.18 (dd, $J = 7.7, 4.9$ Hz, 1H), 5.93 (d, $J = 61.4$ Hz, 2H), 2.72 (s, 3H). ^{13}C NMR (126 MHz, Chloroform- d) δ 169.4, 155.4, 149.6, 133.9,

129.6, 119.8, 22.2. GC-MS (EI) m/z : 136.

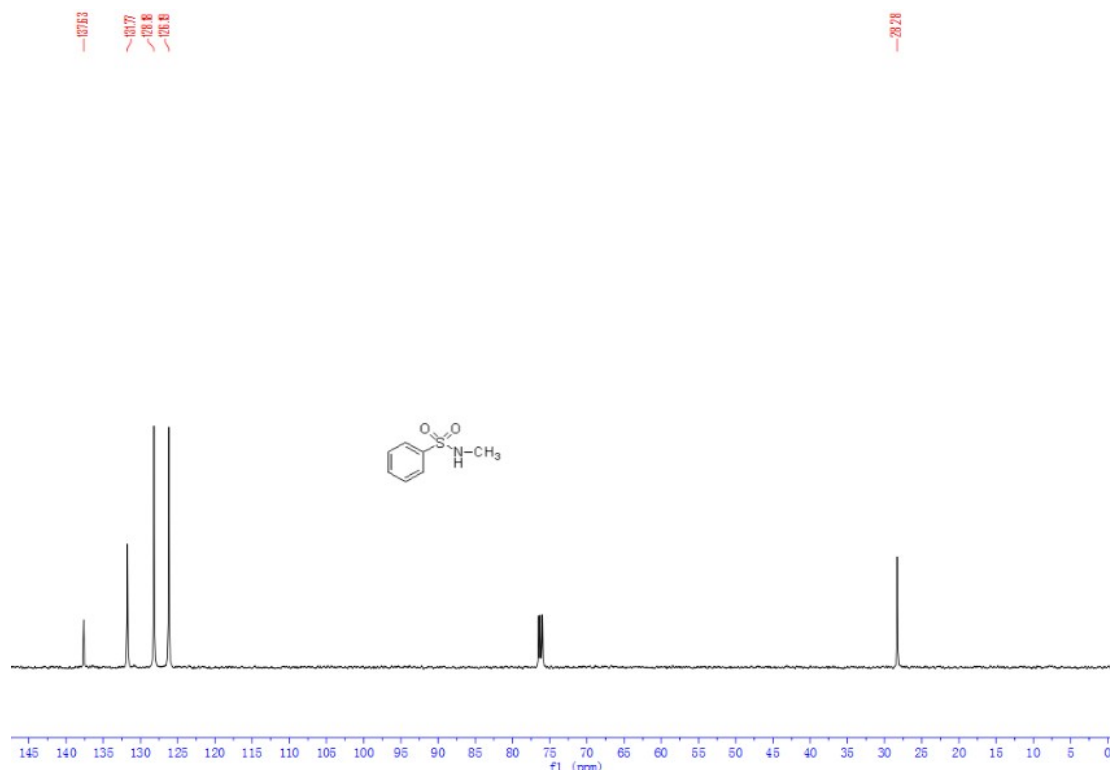
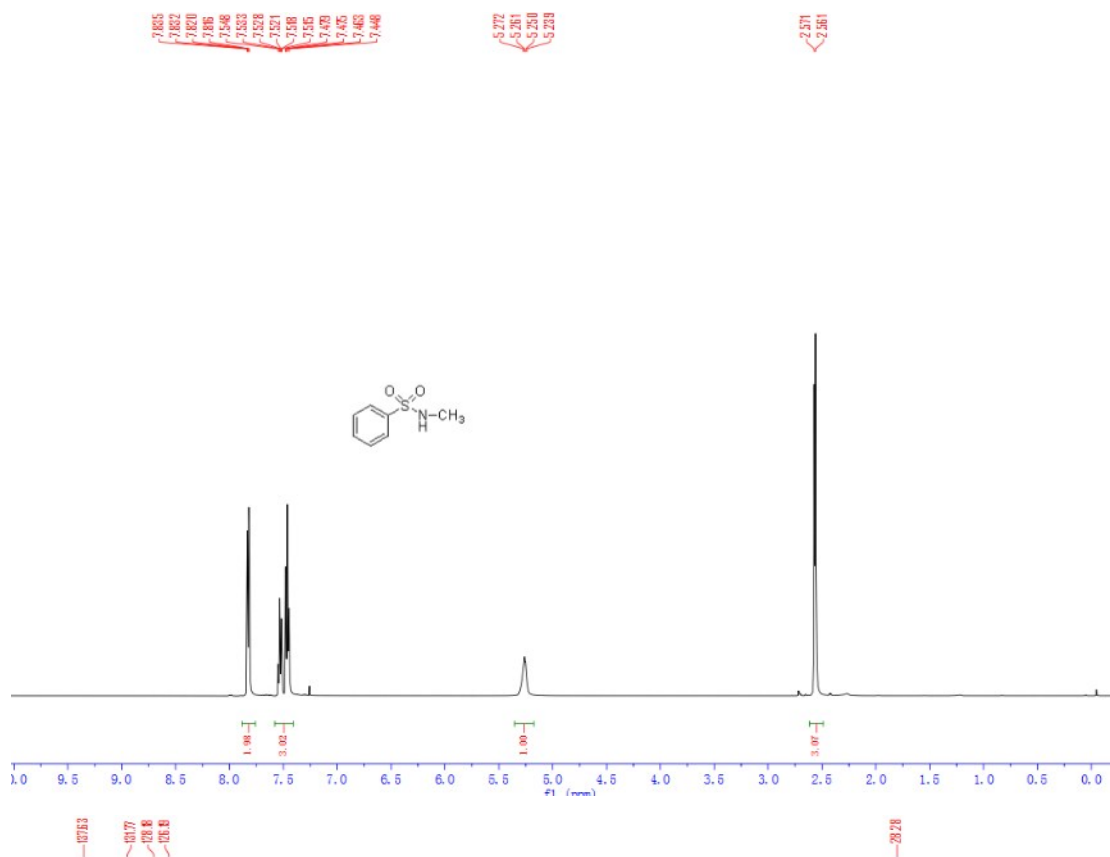


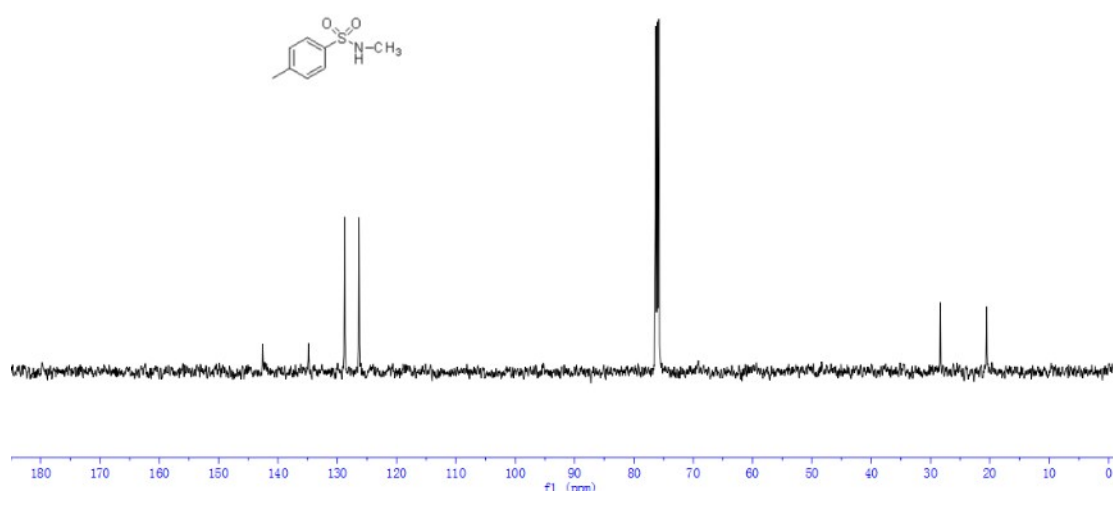
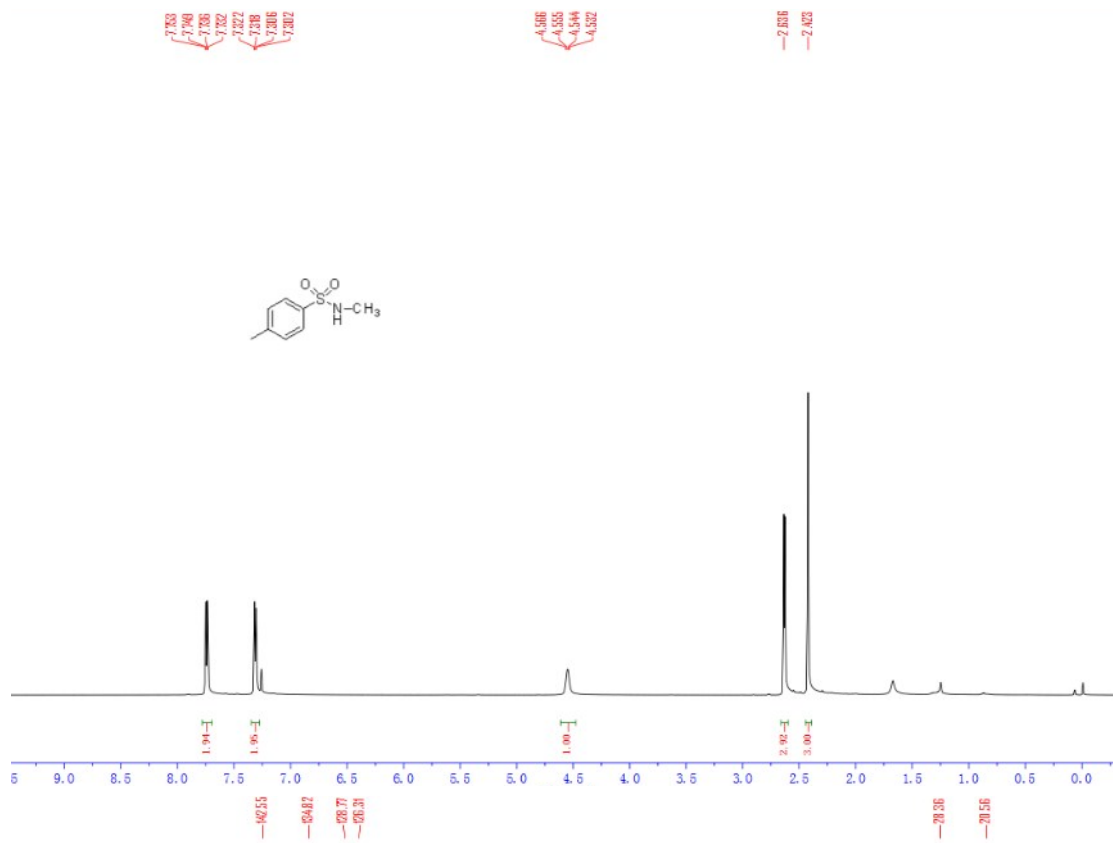
Formula: C₉H₉N

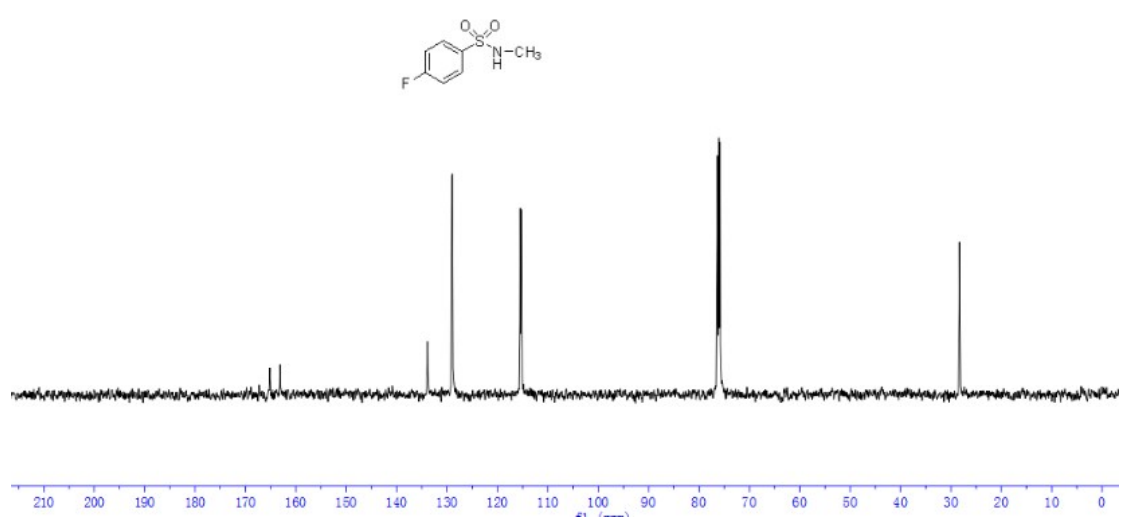
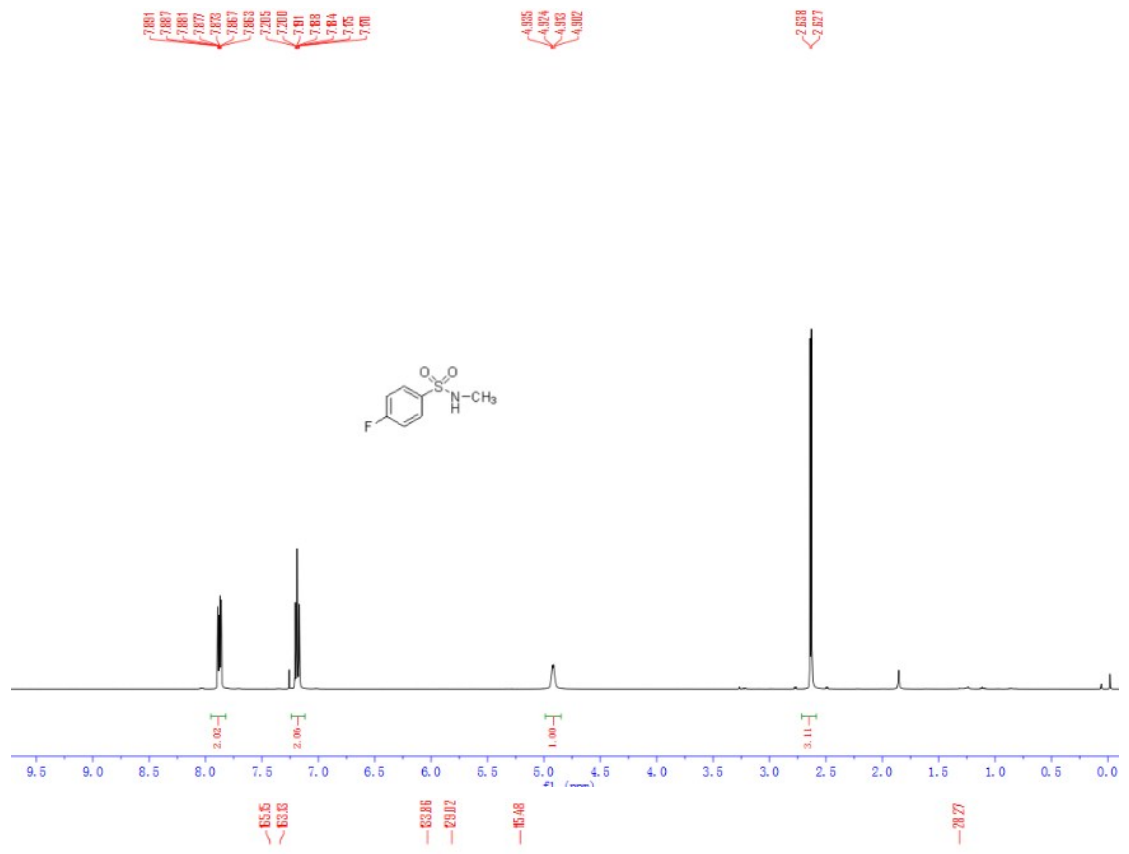
Mass: 131

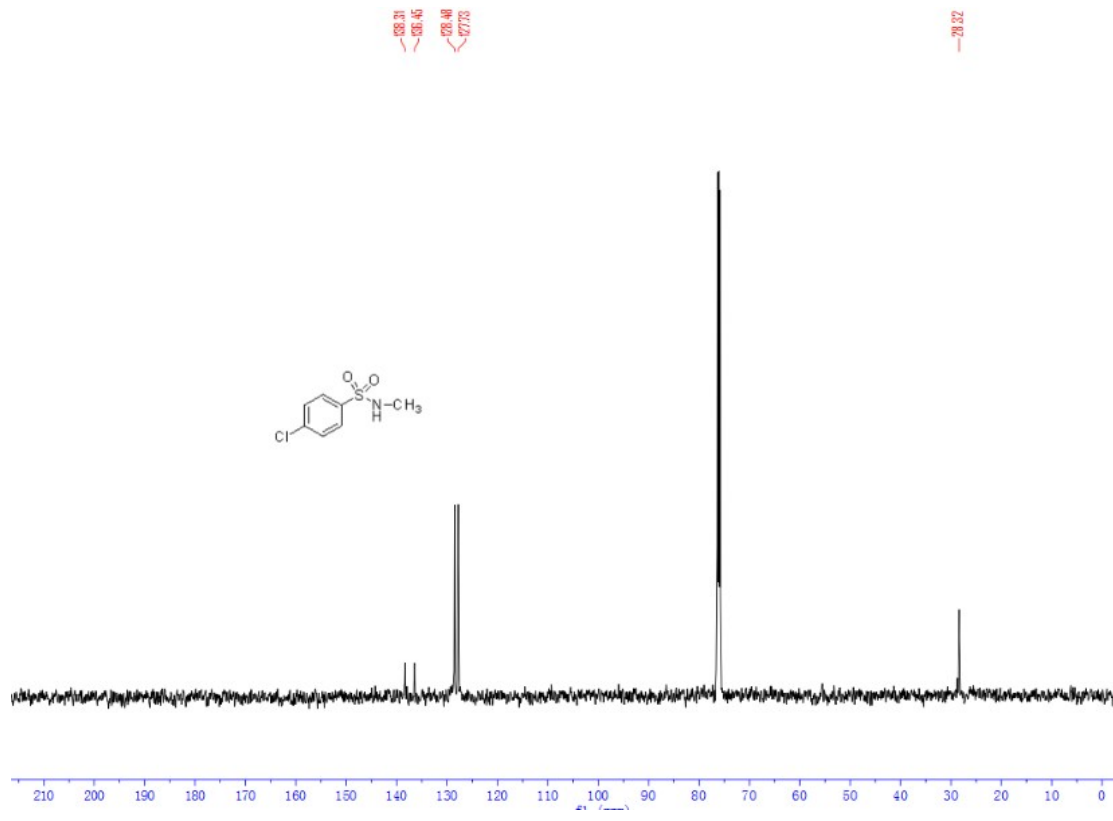
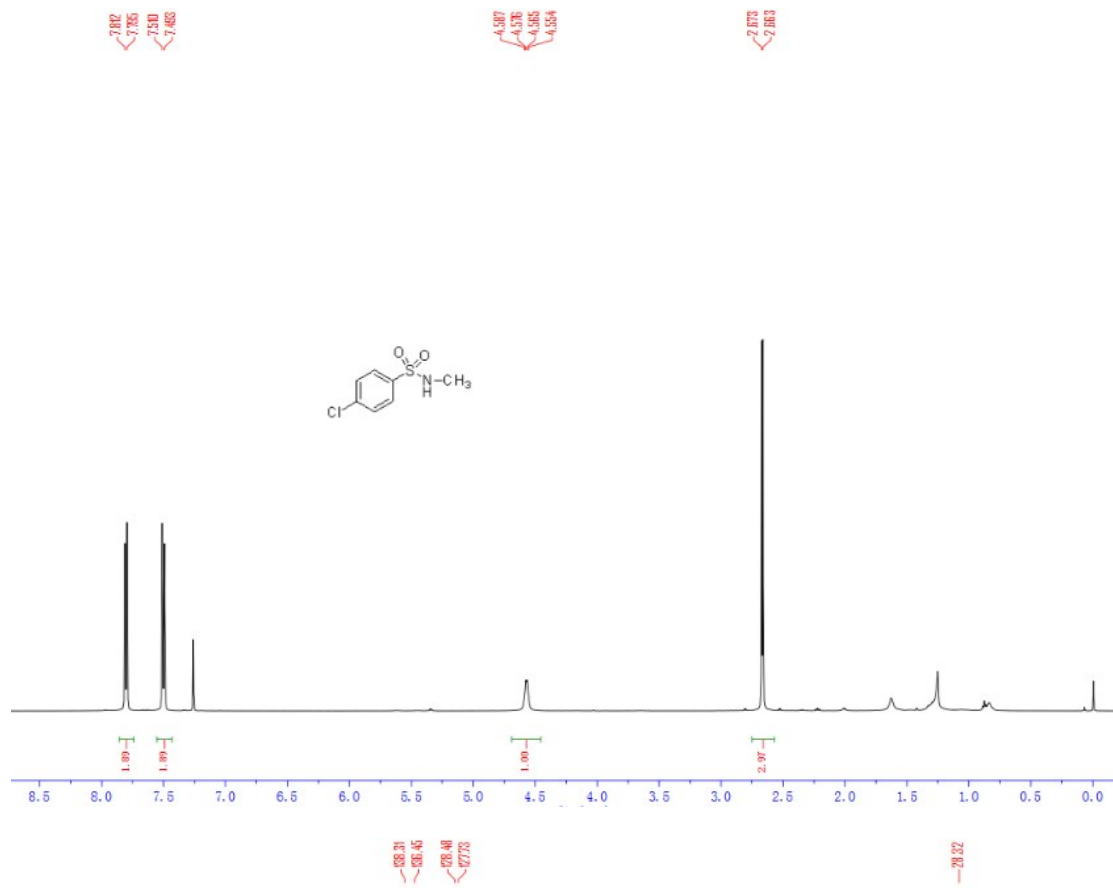
7-methyl-1H-indole (4f): The crude product was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 3:1) to give **4f** as white solid (36.0mg, 55%). ¹H NMR (500 MHz, Chloroform-*d*) δ 8.05 (s, 1H), 7.54 (d, J = 7.8 Hz, 1H), 7.21 (t, J = 2.7 Hz, 1H), 7.11 – 7.00 (m, 2H), 6.63 – 6.56 (m, 1H), 2.52 (s, 3H). ¹³C NMR (126 MHz, Chloroform-*d*) δ 134.5, 126.4, 122.9, 121.5, 119.2, 119.1, 117.5, 102.2, 15.7. GC-MS (EI) m/z : 131.

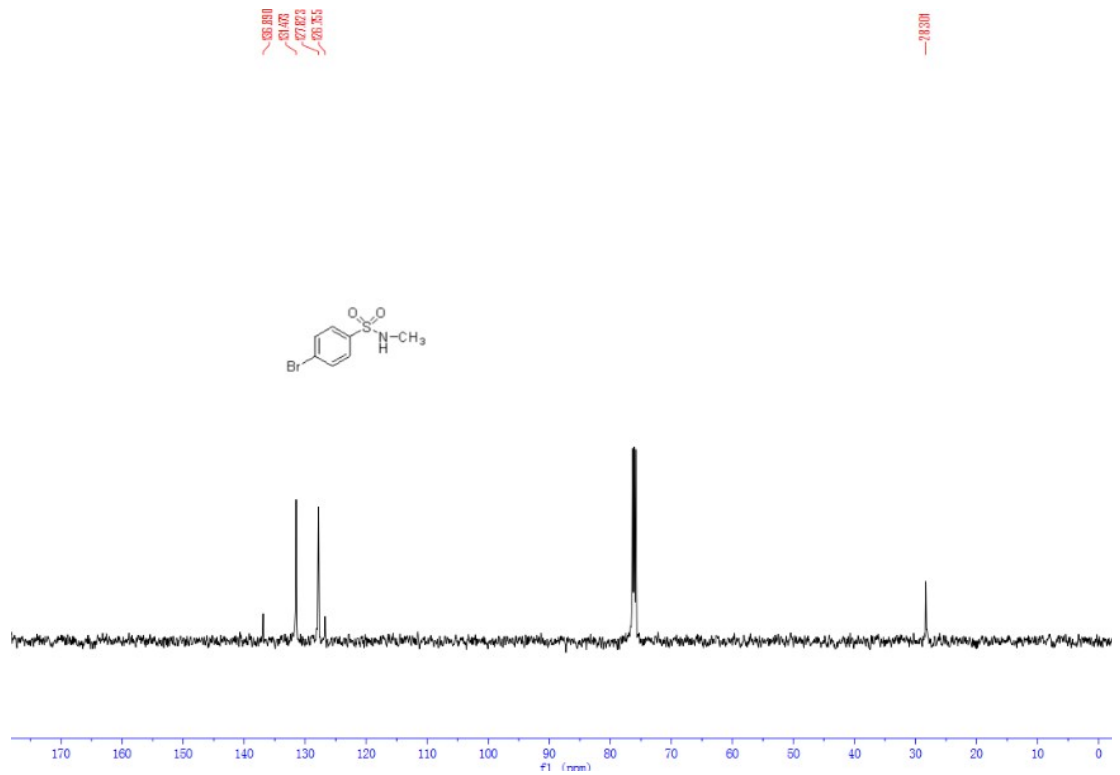
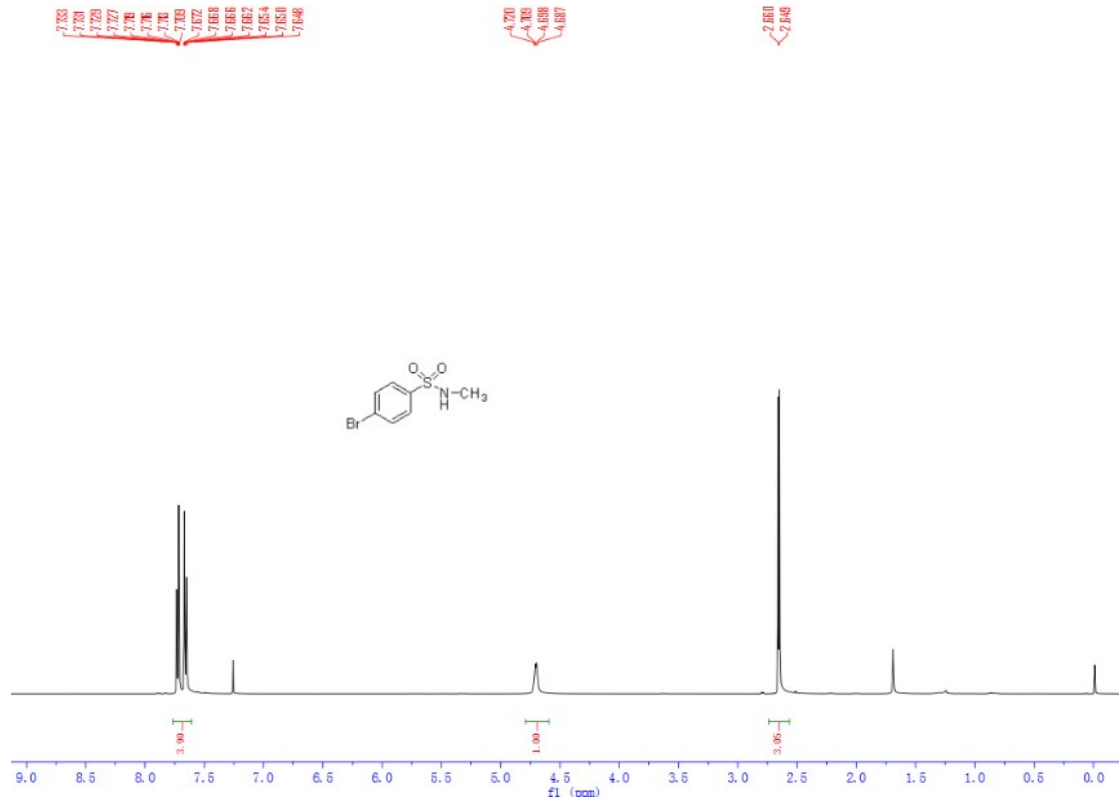
4. NMR spectra

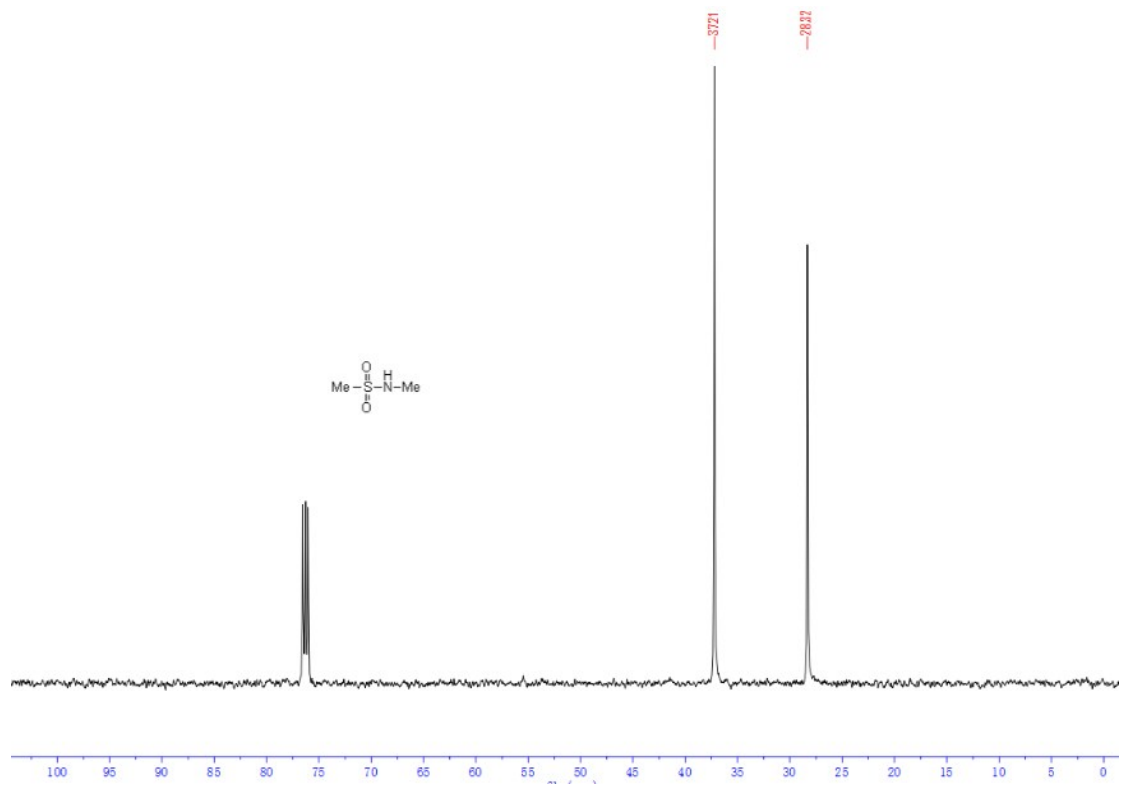
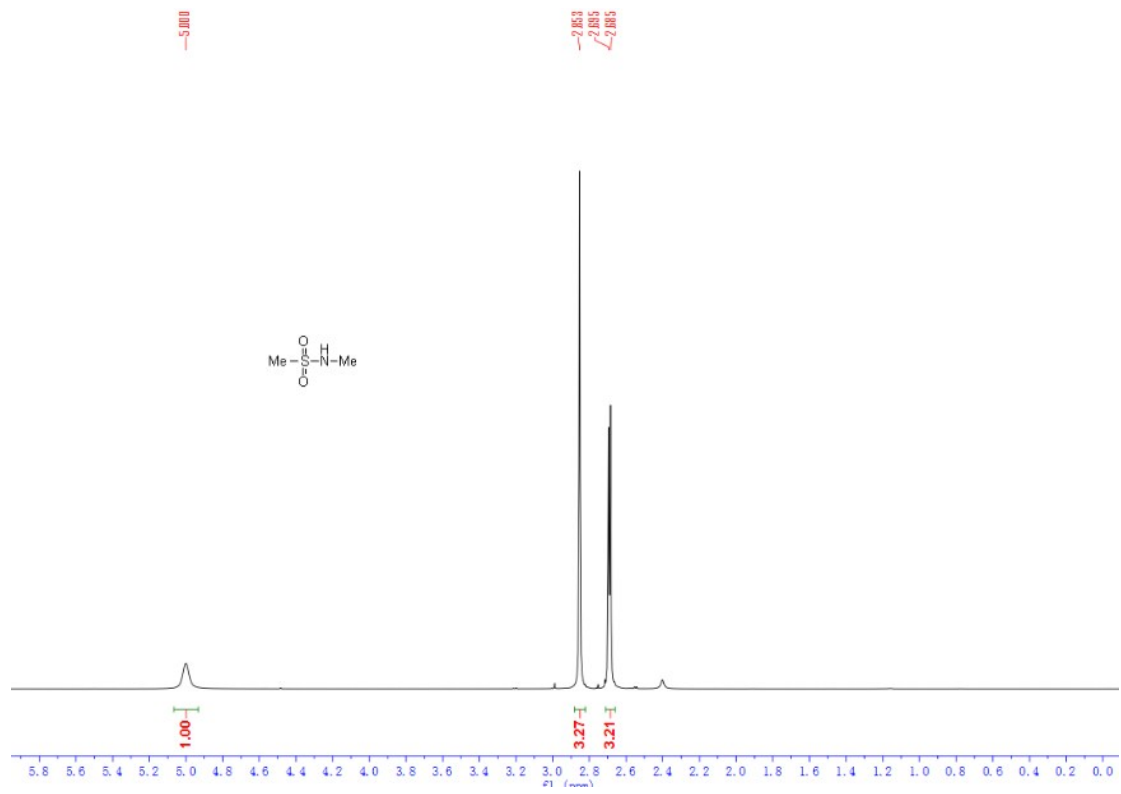








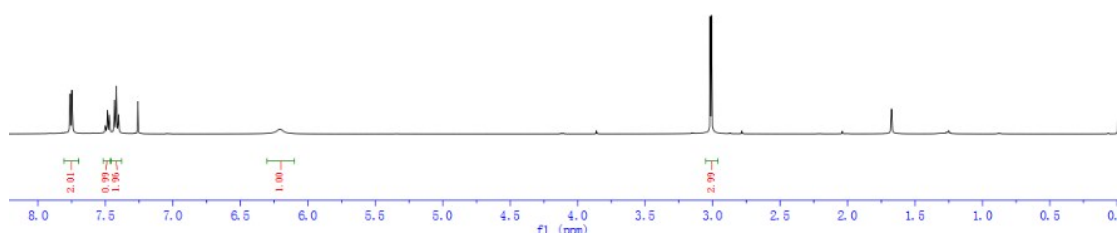




7.785
7.782
7.780
7.778
7.774
7.772
7.764
7.744

-6.205

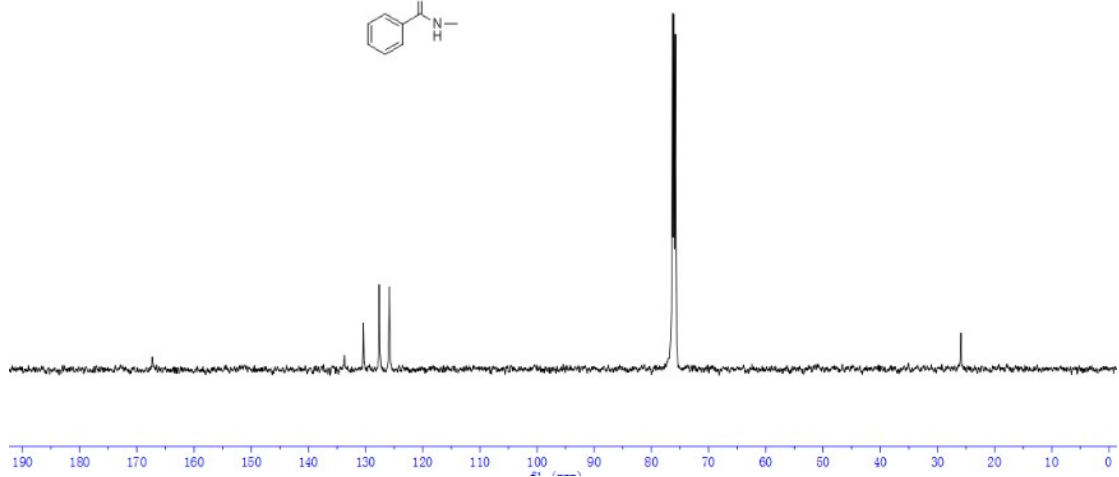
3.008
3.008

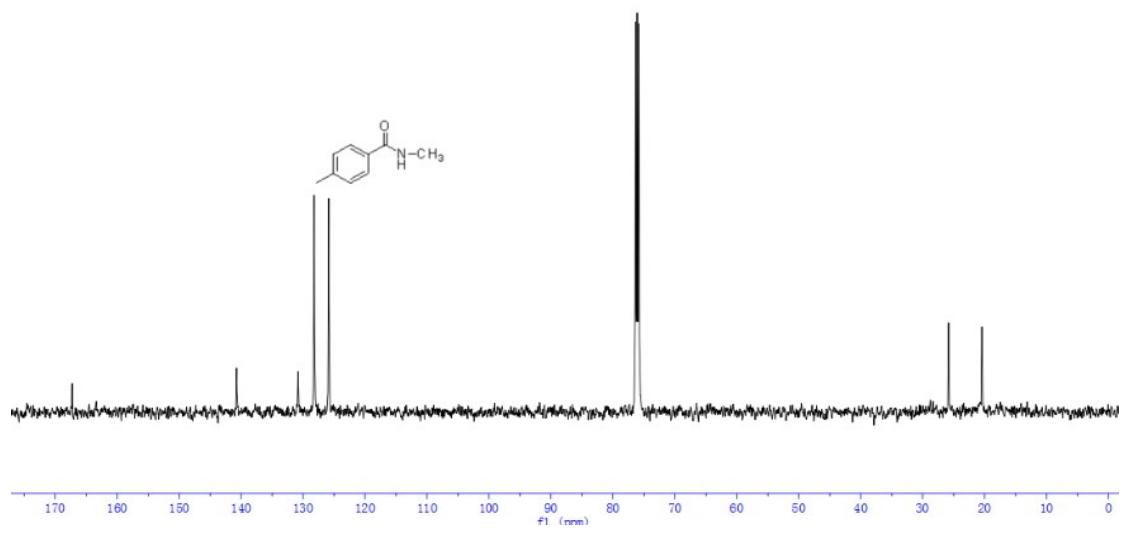
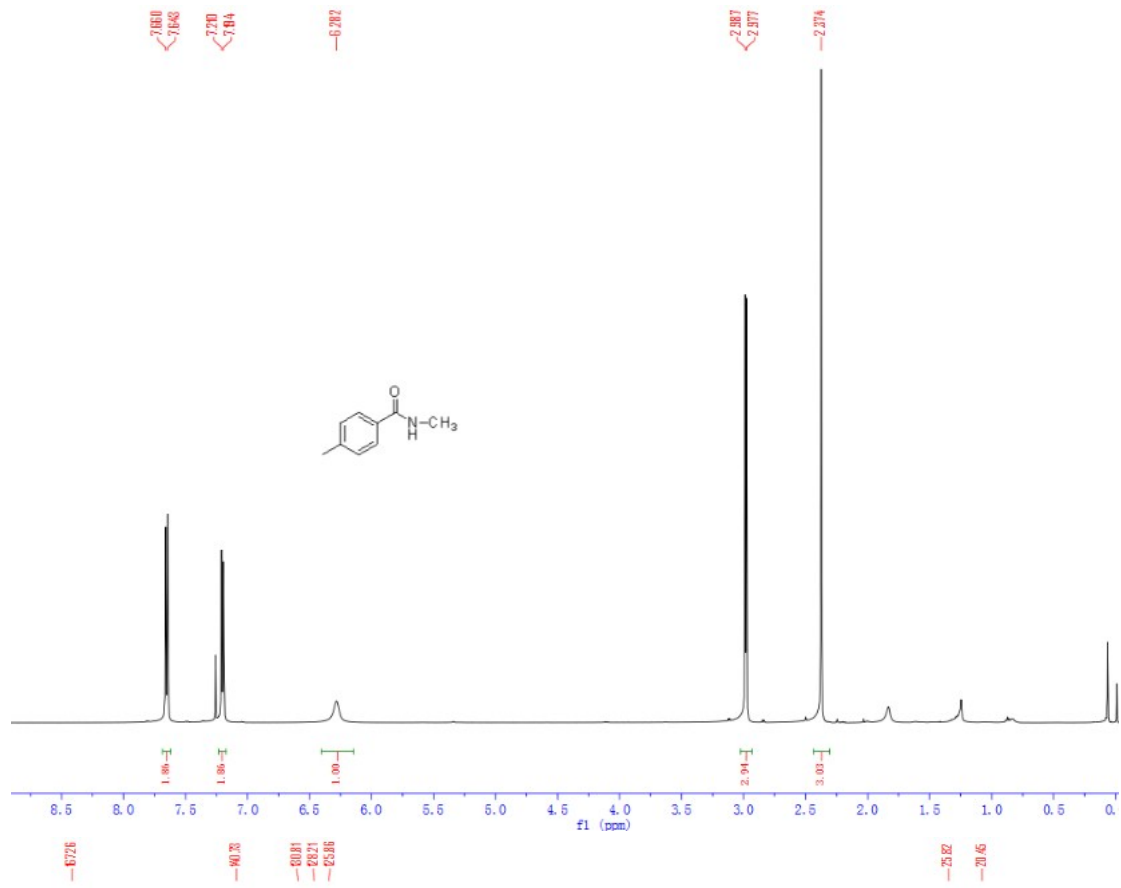


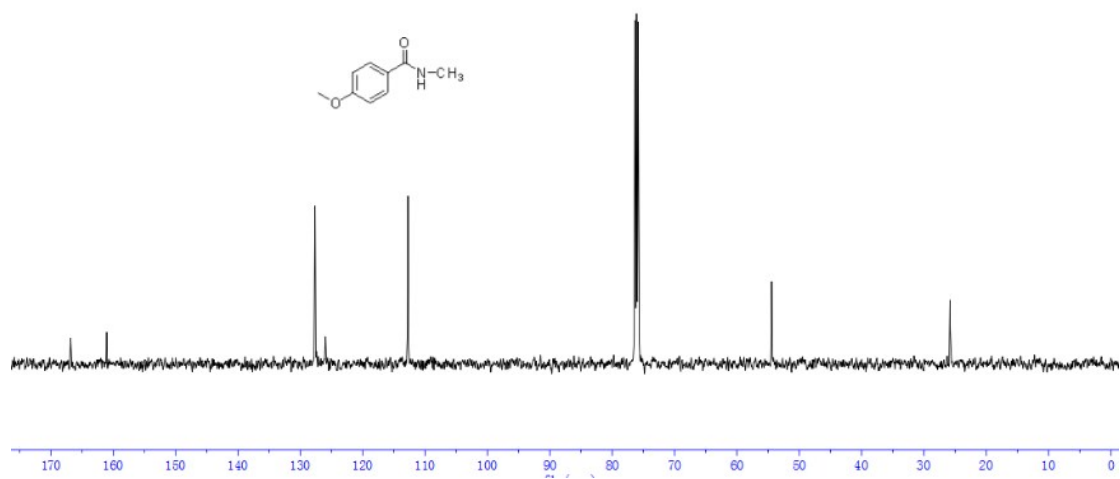
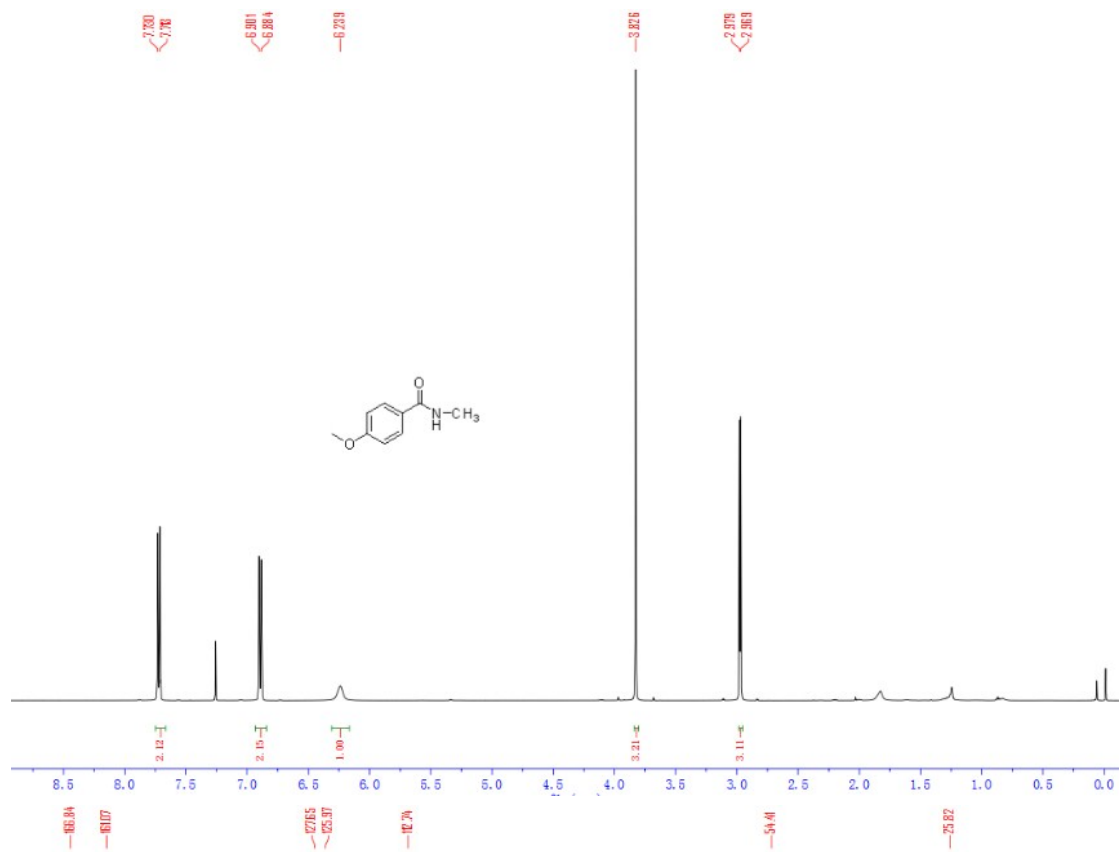
-6.206

-6.209
-6.207
-6.205
-6.204

-2.508

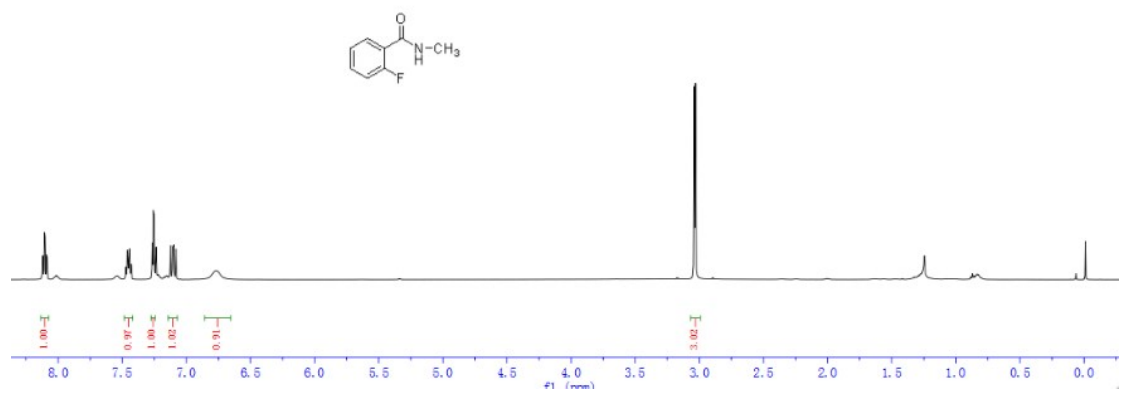






8.23
8.19
8.07
8.03
8.01
8.007
7.475
7.47
7.44
7.440
7.435
7.448
7.444
7.438
7.435
7.425
7.417
7.385
7.358
7.352
7.350
7.337
7.335
7.223
7.016
7.008
7.002
6.995

3.039
3.031



163.07
133.25
131.18
121.83
120.03
115.96
114.86
25.87

