Supporting Information

Generation and Reactions of Heteroaromatic Lithium Compounds by Using In-Line Mixer in a Continuous Flow Microreactor System at Mild Conditions

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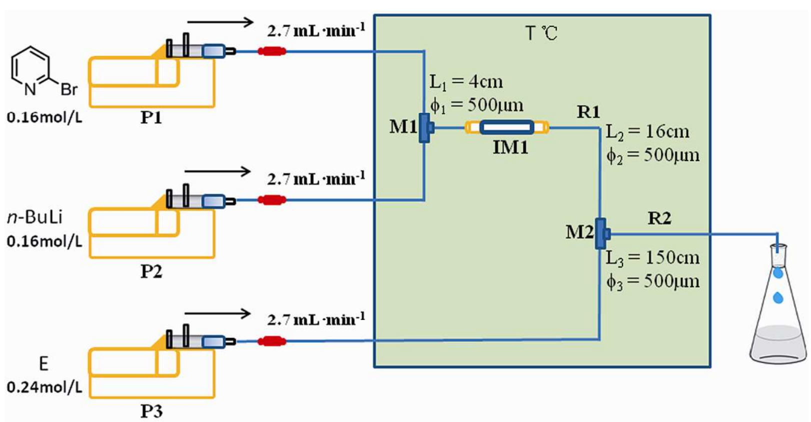
General Information

^{1}HNMR spectra ^{13}C-NMR spectra were recorded on JEOL ECA NMR spectrometer (^{1}H 400 MHz, ^{13}C 100 MHz). HPLC analysis was performed on Agilent 1200 (DAD: 254 nm, column: agilent zorbax eclipse XDB-C18 (4.6×150 mm, I.D. 5 μm)). ESI mass spectra were recorded on Bruker micrOTOF II. All reagents were obtained from commercial sources and used without further purification. THF and hexane were distilled from blue solutions containing sodium benzophenone ketyl. The microsyringe pumps (ALC-IP 900) with flow rate 0.001-27 mL min^{-1} were purchased from Shanghai Alcott Biotech Co., LTD. The stainless steel T-shaped micromixers (BUSHING JOINT 3WAY JOINT 1/16 OTW), the stainless steel In-line Mixer (50 μL Internal Volume) and the stainless steel microtube reactors (SUS TUBE 1/16 × 0.5 cm × 5 m) were purchased from Dima Technology Co., Ltd. Each part of the microreactor system was connected with PEEK fittings (Standard Version 5/pkg).

Microreactor System



The microreactor system which was studied contained six parts: three microsyringe pumps (P1, P2 and P3), two T-shaped micromixers (M1, M2), two stainless steel microtubes (R1, R2), an In-line Mixer (IM1), a cooling bath and collection devices. The microtube (R1, □ = 500 μm) was a 20 cm long stainless steel tube which was divided into two sections (L_1 = 4 cm and L_2 = 16 cm) within the In-line Mixer (IM1). The microtube (R2, □$_3$ = 500 μm) was a 150 cm long stainless steel tube. The solutions of reactants were injected through the microtube, cooled in the cooling bath, mixed in M1 and IM1 then M2, and finally collected from the end of the microtube.

Experimental data

The analytical data of diphenyl(pyridin-2-yl)methanol (**1a**)[1], (2-chlorophenyl)(pyridin-2-yl)methanol (**1b**)[2], 2-o-Methoxybenzoylpyridine (**1c**)[3], diphenyl(6-methoxypyridin-3-yl)methanol (**3a**)[4], diphenyl(thiophen-3-yl)methanol (**4a**)[5], diphenyl(furan-2-yl)methanol (**5a**)[6], diphenyl(thiazol-2-yl)methanol (**6a**)[7] were identical to those reported in the literature.

Diphenyl(6-(trifluoromethyl)pyridin-3-yl)methanol (**2a**): ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.64 (s, 1H), 7.87 (m, 2H), 7.45 – 7.11 (m, 10H), 6.94 (s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 149.81, 146.75 (q, J = 34.6 Hz), 145.53, 145.40, 136.67, 128.60, 128.22, 127.83, 121.69 (q, J = 274.0 Hz), 119.77, 80.70. HRMS (ESI) *m/z* calcd for (M-H) $C_{19}H_{13}F_3NO$: 328.0955, found: 328.0964.

(2-Chlorophenyl)(6-(trifluoromethyl)pyridin-3-yl)methanol (**2b**): ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.77 (s, 1H), 7.93 (d, J = 7.6 Hz, 1H), 7.85 (d, J = 8.1 Hz, 1H), 7.73 (d, J = 7.0 Hz, 1H), 7.50 – 7.38 (m, 2H), 7.37 – 7.28 (m, 1H), 6.50 (d, J = 4.2 Hz, 1H), 6.15 (d, J = 4.1 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 148.88, 147.20 (q, J = 34.7 Hz), 141.33, 139.77, 135.91, 132.35, 129.94, 129.70, 128.03, 127.72, 121.57 (q, J = 274.0 Hz), 120.39, 70.08. HRMS (ESI) *m/z* calcd for (M-H) $C_{13}H_8ClF_3NO$: 286.0252, found: 286.0249.

(2-Methoxyphenyl)bis(6-(trifluoromethyl)pyridin-3-yl)methanol (**2c**): ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.61 (s, 2H), 7.87 (m, 4H), 7.63 (d, J = 7.7 Hz, 1H), 7.41 (t, J = 7.6 Hz, 1H), 7.17 – 6.90 (m, 3H), 3.44 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.77, 149.58, 147.56 (q, J = 34.6 Hz), 143.92, 136.61, 131.37, 130.75, 129.40, 121.59 (q, J = 274.3 Hz), 121.33, 120.03, 112.28, 79.13, 55.84. HRMS (ESI) *m/z* calcd for (M+H) $C_{20}H_{15}F_6N_2O_2$: 429.1038, found: 429.1030.

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(2-Chlorophenyl)(6-methoxypyridin-3-yl)methanol (**3b**): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 (s, 1H), 7.67 (d, J = 7.9 Hz, 1H), 7.55 (d, J = 8.5 Hz, 1H), 7.36 – 7.16 (m, 3H), 6.69 (d, J = 8.6 Hz, 1H), 6.16 (s, 1H), 3.91 (s, 3H), 2.71 (br, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.87, 145.96, 140.58, 137.78, 132.33, 130.69, 129.79, 129.06, 127.62, 127.34, 111.00, 70.52, 53.65. HRMS (ESI) *m/z* calcd for (M+H) $C_{13}H_{13}ClNO_2$: 250.0635, found: 250.0635.

(2-Methoxyphenyl)bis(6-methoxypyridin-3-yl)methanol (**3c**): ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.88 (s, 2H), 7.48 (d, J = 8.6 Hz, 2H), 7.34 (dd, J = 18.1, 7.9 Hz, 2H), 6.98 (t, J = 7.9 Hz, 2H), 6.75 (d, J = 8.6 Hz, 2H), 6.11 (s, 1H), 3.82 (s, 6H), 3.48 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 162.25, 156.04, 145.66, 138.72, 134.80, 133.70, 129.24, 127.46, 120.35, 112.18, 109.16, 76.46, 55.17, 53.09. HRMS (ESI) *m/z* calcd for (M+H) $C_{20}H_{21}N_2O_4$: 353.1501, found: 353.1505.

(2-Chlorophenyl)(thiophen-3-yl)methanol (**4b**): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (d, J = 7.6 Hz, 1H), 7.28 (m, 5H), 7.04 (d, J = 4.9 Hz, 1H), 6.28 (s, 1H), 2.41 (br, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 143.75, 140.89, 132.50, 129.69, 129.0, 127.94, 127.34, 126.47, 126.27, 122.33, 69.44. HRMS (ESI) *m/z* calcd for (M+Na) $C_{11}H_9ClNaOS$: 246.9960, found: 246.9952.

(2-Chlorophenyl)(furan-2-yl)methanol (**5b**): ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.72 (d, J = 7.9 Hz, 1H), 7.58 (s, 1H), 7.46 – 7.20 (m, 3H), 6.36 (s, 1H), 6.18 (d, J = 5.0 Hz, 1H), 6.05 (s, 1H), 5.98 (d, J = 4.9 Hz, 1H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 155.61, 142.42, 139.74, 131.22, 129.02, 128.98, 128.39, 127.20, 110.27, 107.02, 64.96. HRMS (ESI) *m/z* calcd for (M+Na) $C_{11}H_9ClNaO_2$: 231.0189, found: 231.0167.

(2-Chlorophenyl)(thiazol-2-yl)methanol (**6b**): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (d, J = 3.0 Hz, 1H), 7.61 (d, J = 7.5 Hz, 1H), 7.39 (d, J = 7.6 Hz, 1H), 7.36 – 7.25 (m, 3H), 6.50 (s, 1H), 4.14 (br, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.76, 142.30, 139.11, 132.80, 129.83, 129.80, 128.45, 127.51, 120.04, 70.38. HRMS (ESI) m/z calcd for (M+Na) $C_{10}H_8ClNOSNa$: 247.9913, found: 247.9879.

Diphenyl(quinolin-3-yl)methanol (**7a**): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.78 (s, 1H), 8.08 – 8.02 (m, 2H), 7.69 (dd, J = 14.4, 7.9 Hz, 2H), 7.51 (t, J = 7.5 Hz, 1H), 7.34 – 7.28 (m, 10H), 3.81 (br, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 151.10, 146.75, 146.05, 139.78, 134.38, 129.78, 128.90, 128.41, 128.31, 128.00, 127.85, 127.36, 127.01, 80.97. HRMS (ESI) m/z calcd for (M+H) $C_{22}H_{18}NO$: 312.1388, found: 312.1391.

(2-Chlorophenyl)(quinolin-3-yl)methanol (**7b**): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.84 (s, 1H), 8.15 (s, 1H), 8.07 (d, J = 8.5 Hz, 1H), 7.77 (d, J = 8.2 Hz, 1H), 7.71 – 7.65

(m, 2H), 7.53 (t, J = 7.5 Hz, 1H), 7.36 – 7.22 (m, 3H), 6.42 (s, 1H), 4.49 (br, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 149.66, 146.58, 140.27, 135.64, 134.66, 132.52, 130.08, 129.85, 129.38, 128.42, 128.21, 128.17, 127.90, 127.5, 127.26, 70.69. HRMS (ESI) m/z calcd for (M+H) $C_{16}H_{13}ClNO$: 270.0686, found: 270.0688.

References

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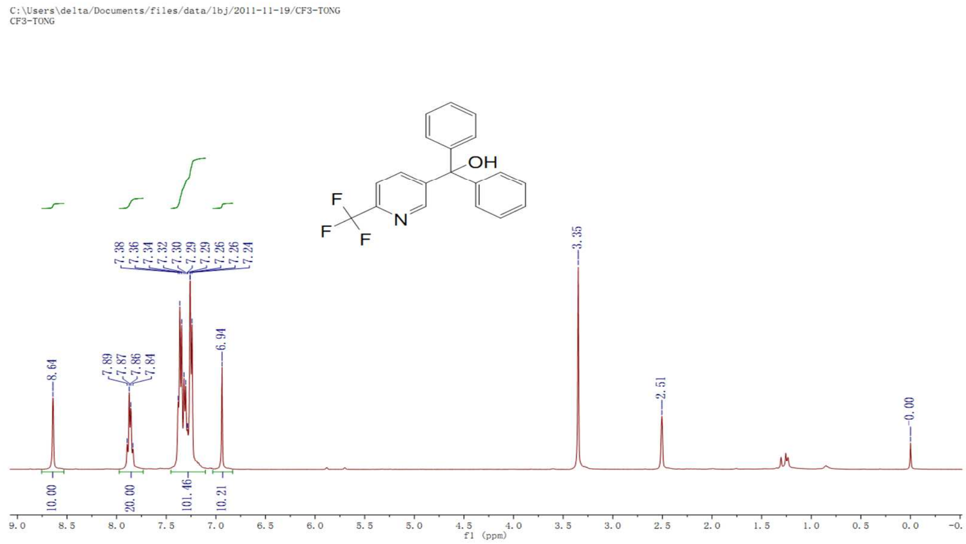
(5) Bíró, A. B.; Kotschy, A. *Eur. J. Org. Chem.* **2007**, 1364.

(6) Mongin, F.; Bucher, A.; Bazureau, J. P.; Bayh, O.; Awad, H.; Trécourt, F. *Tetrahedron Lett.* **2005**, *46*, 7989.

(7) Nutaitis, C. F.; Obaza-Nutaitis, J. *Org. Prep. and Proced. Int.* **1997**, *29*, 315.

2a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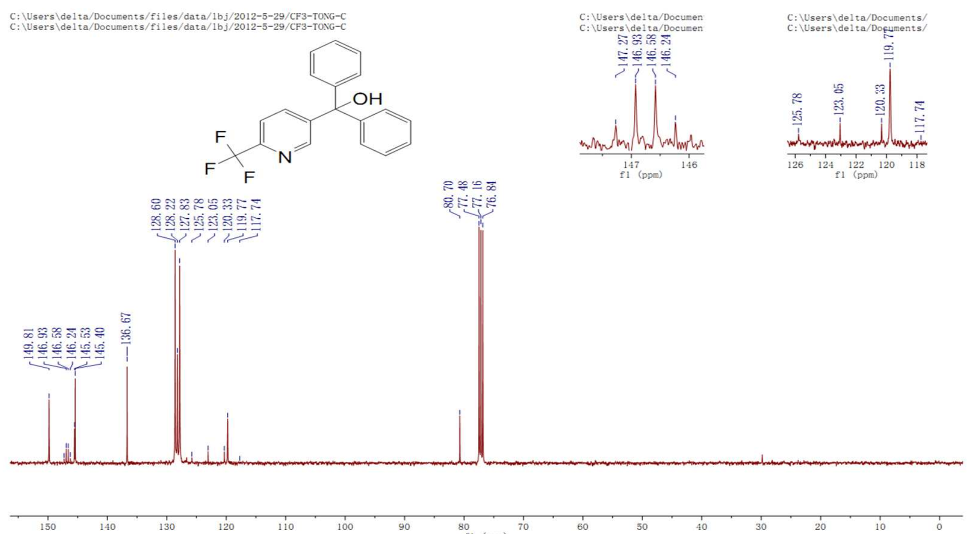
f1 (ppm)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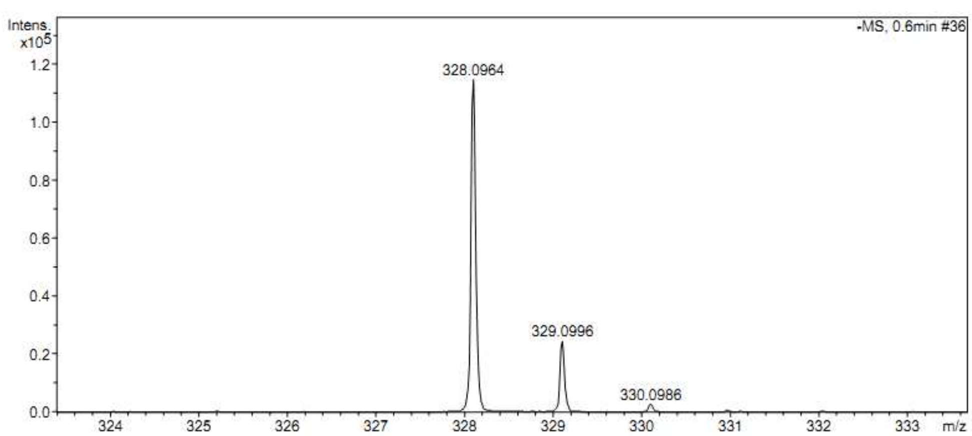
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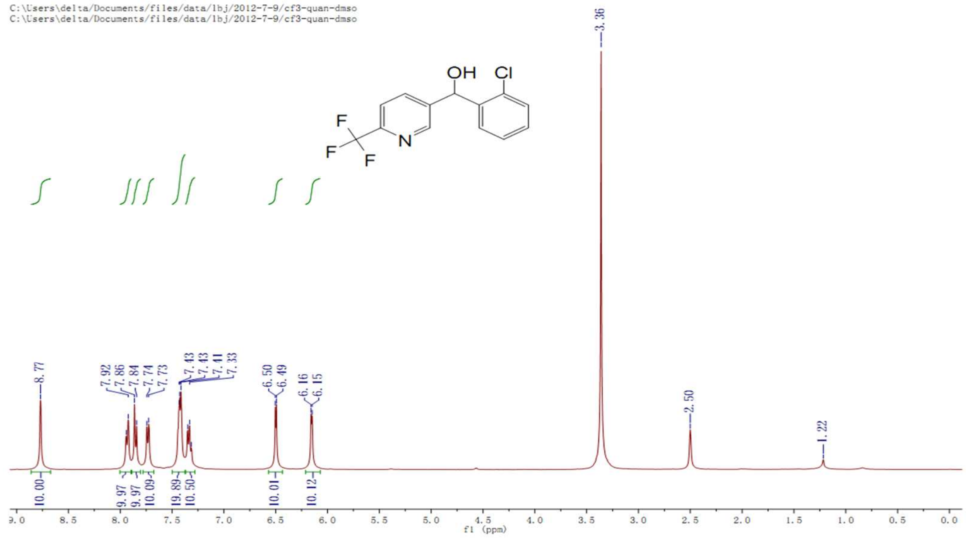
m/z

2b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7.86
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7.73
7.43
7.43
7.41
7.33
6.50
6.49
6.16
6.15
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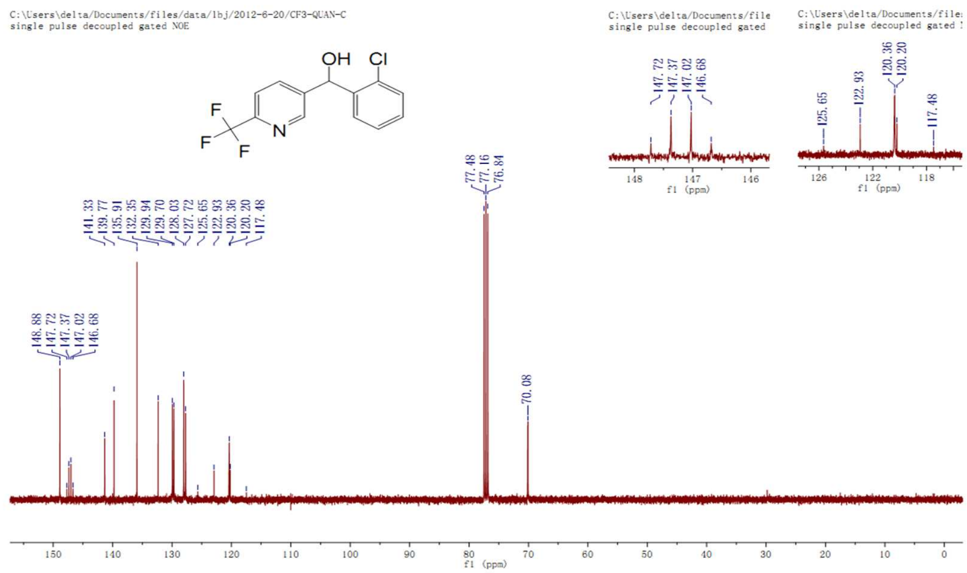
10.12
f1 (ppm)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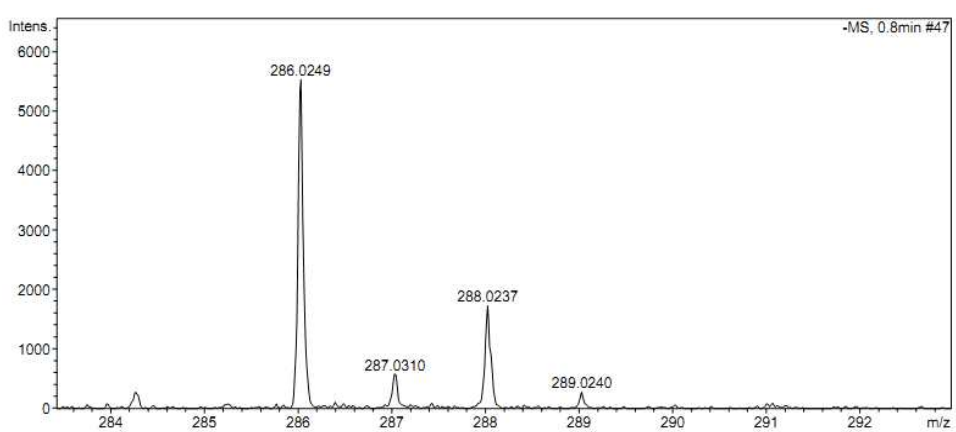
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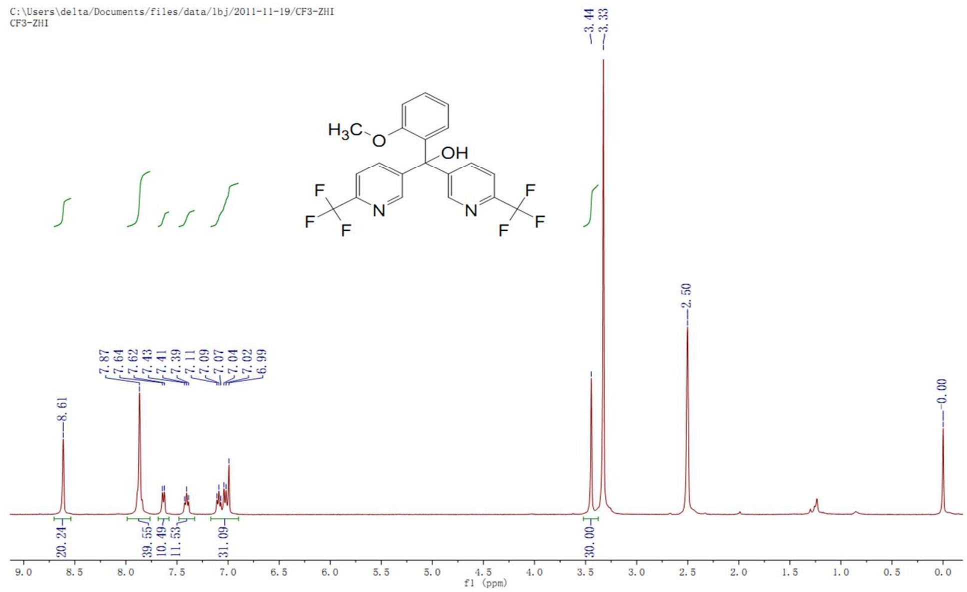
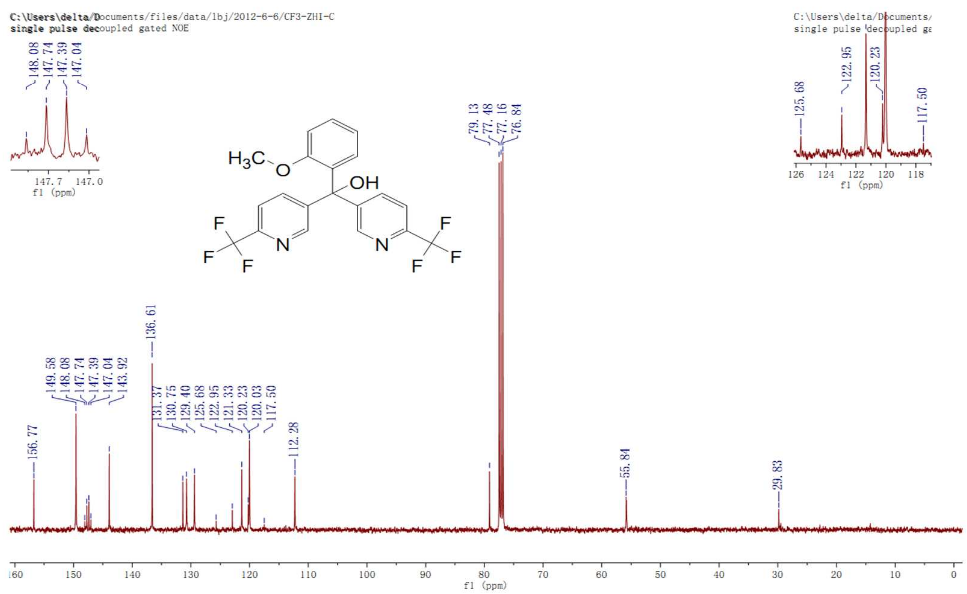
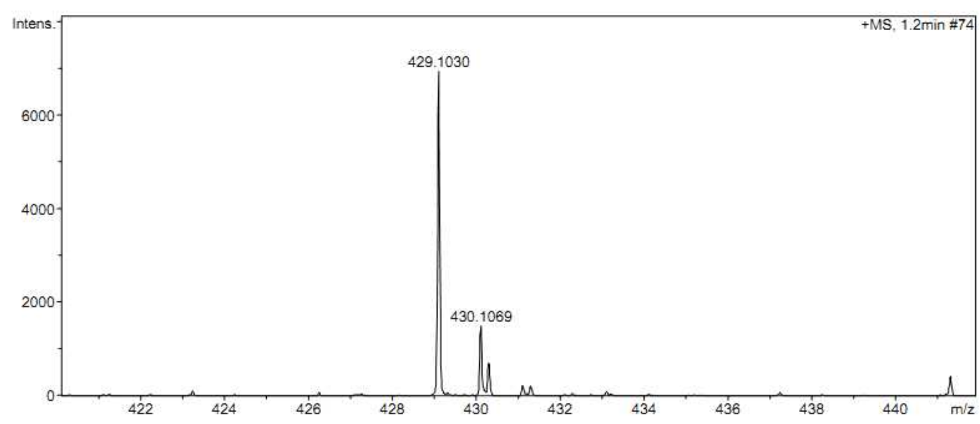
2c







3b

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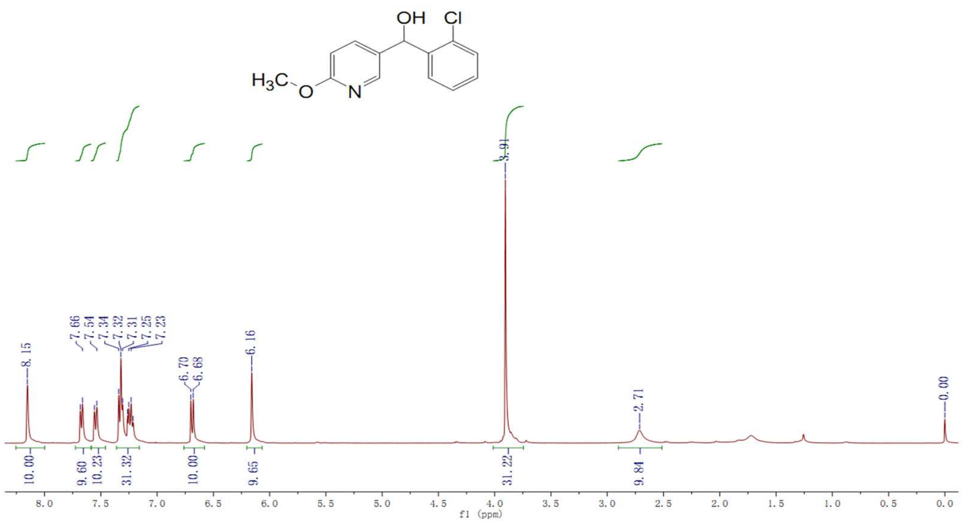
CH3O-quan



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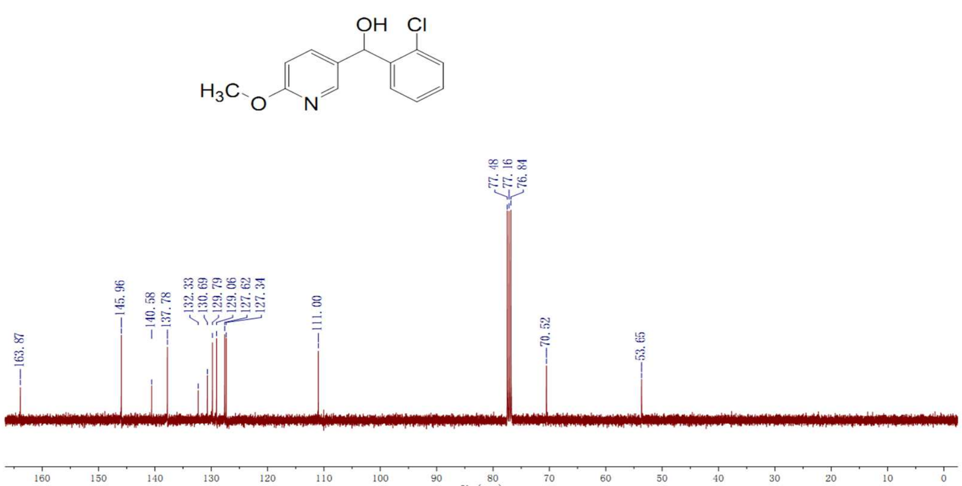

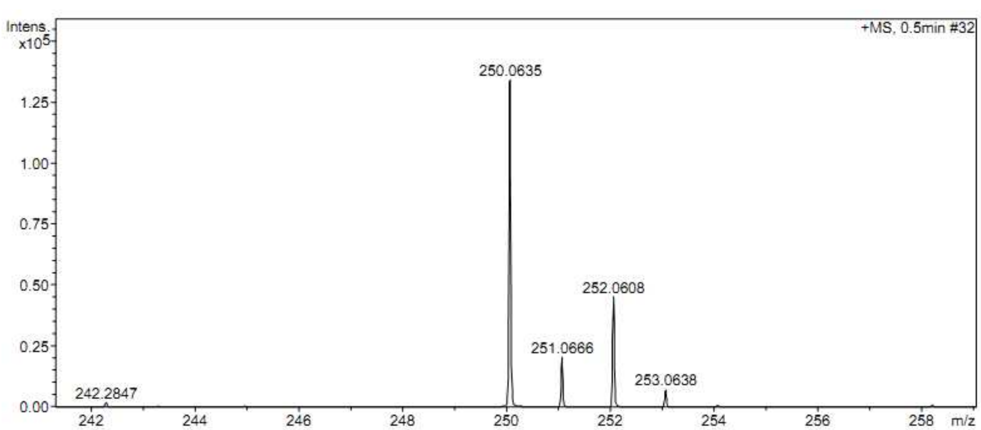

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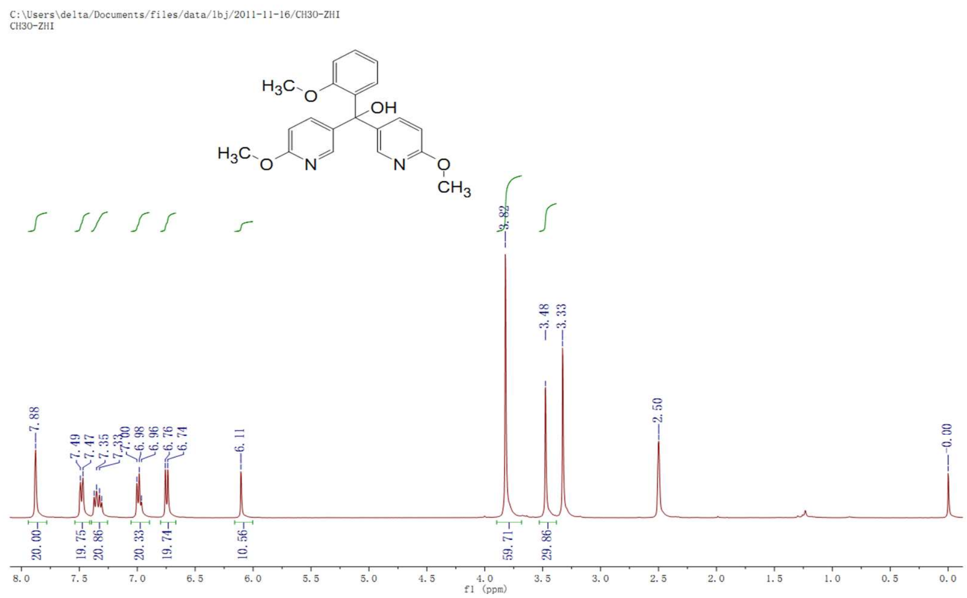

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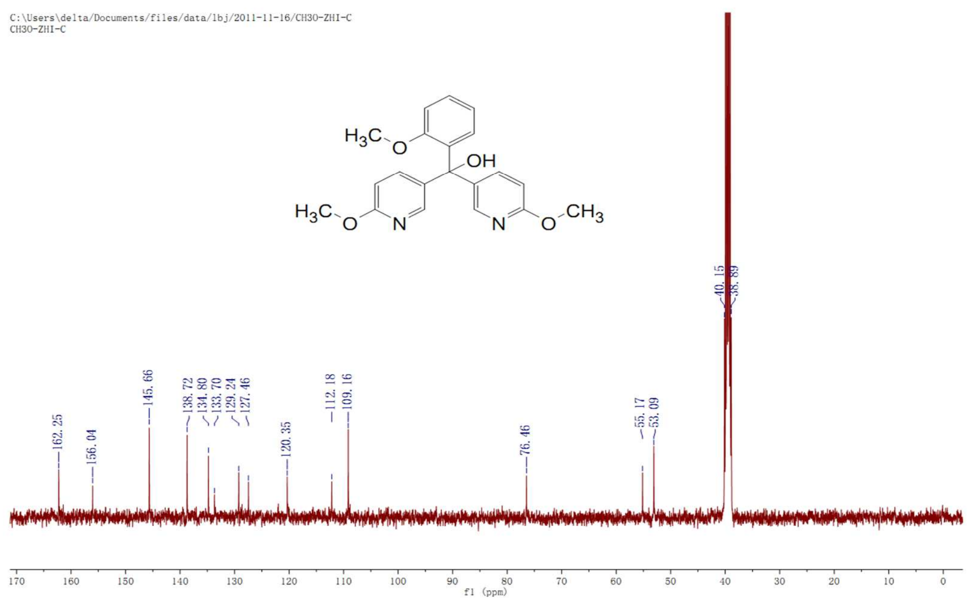

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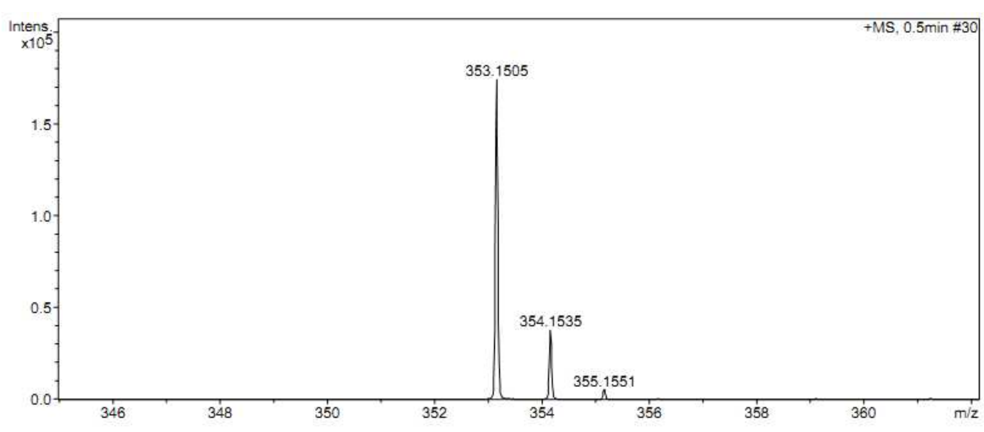

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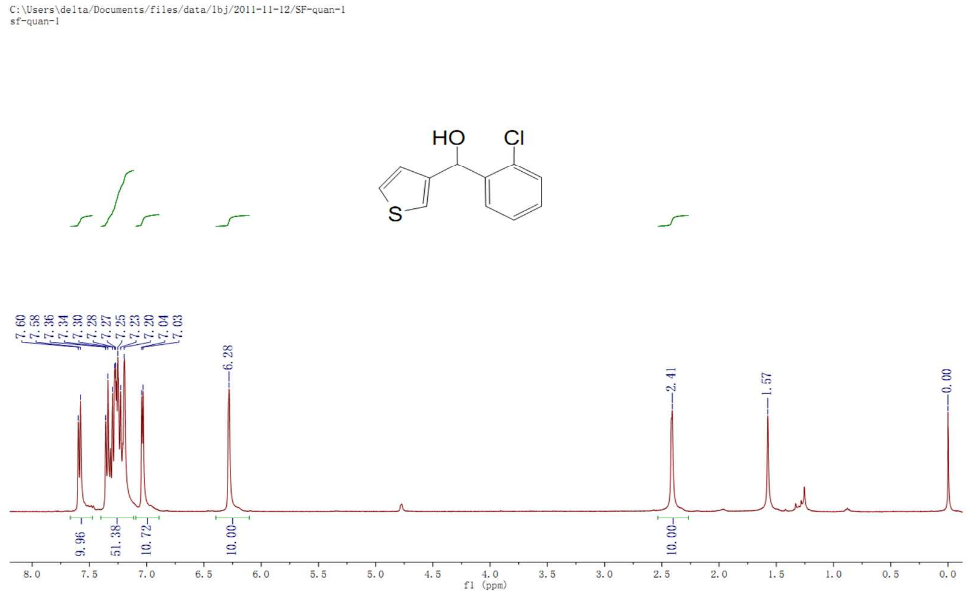
m/z

4b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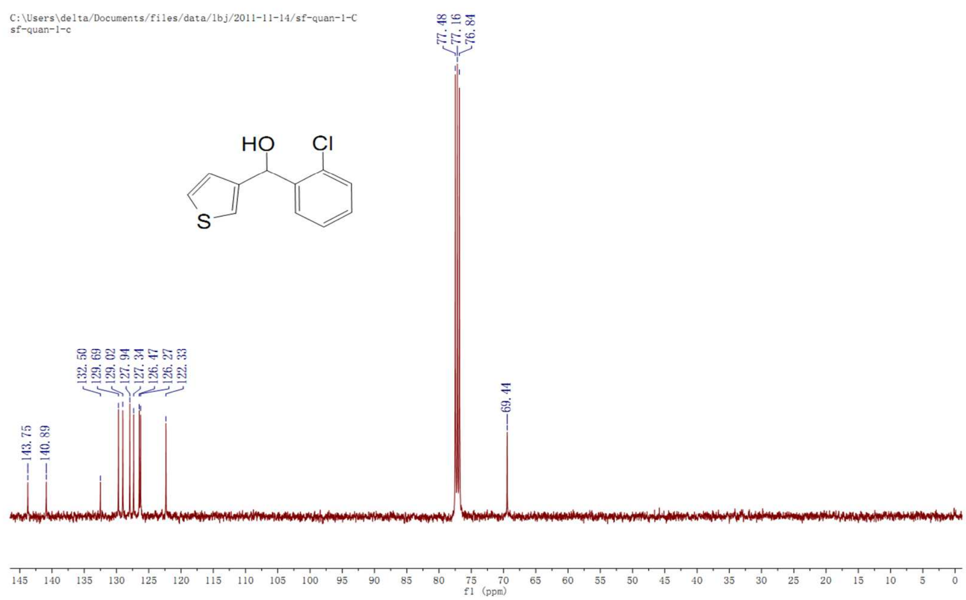
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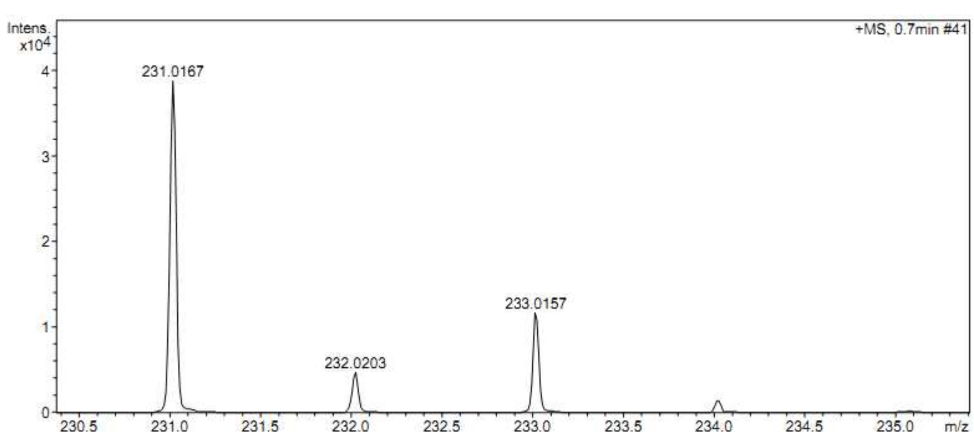
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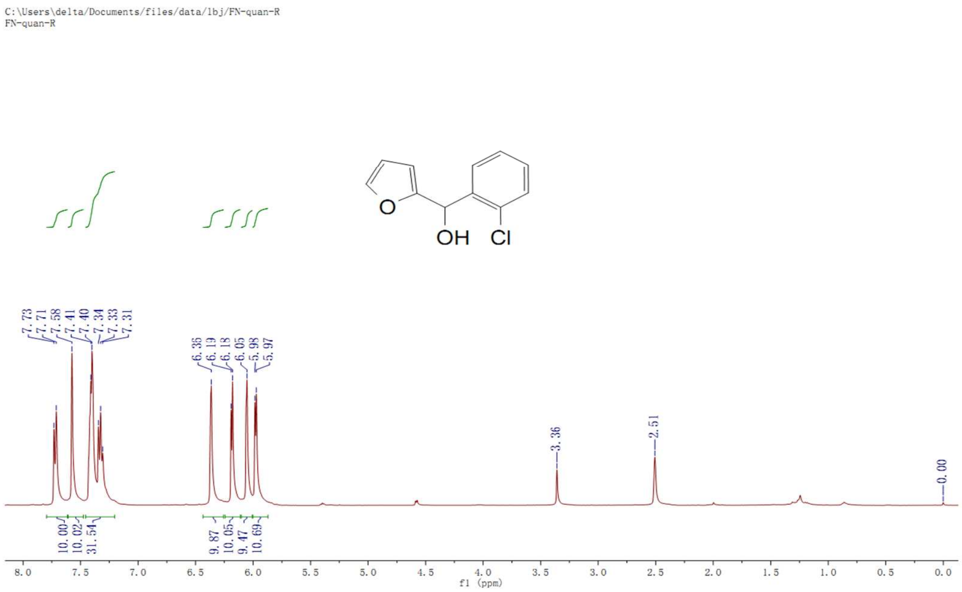
5b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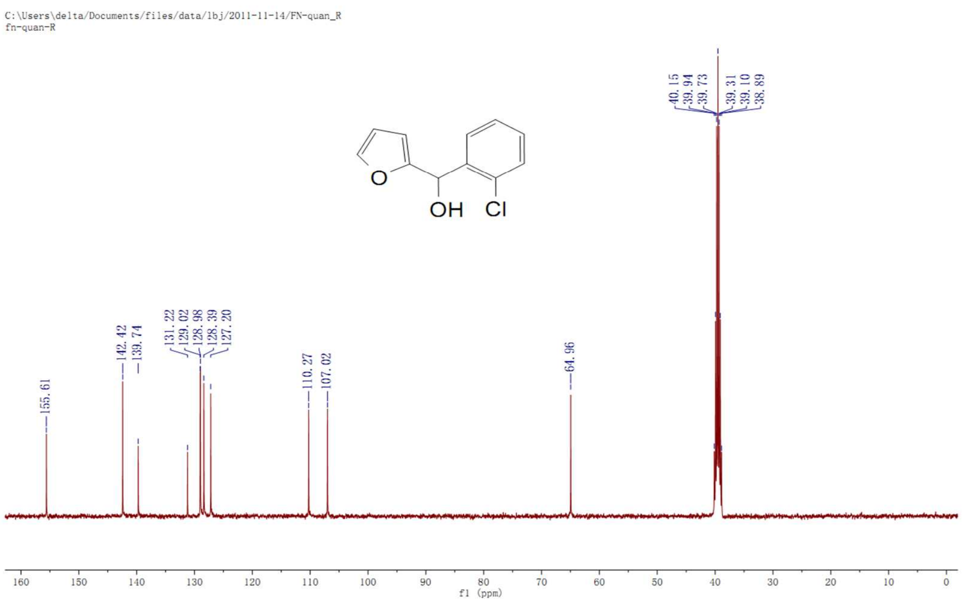
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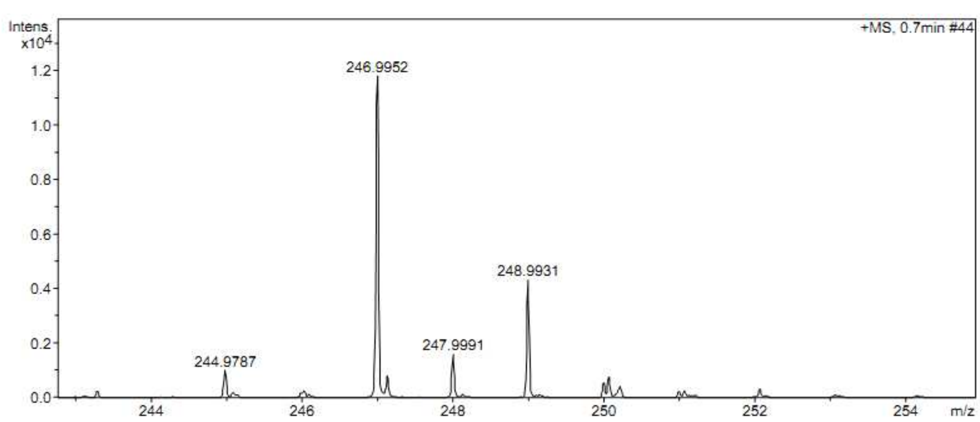
110.27 107.02
64.96
f1 (ppm)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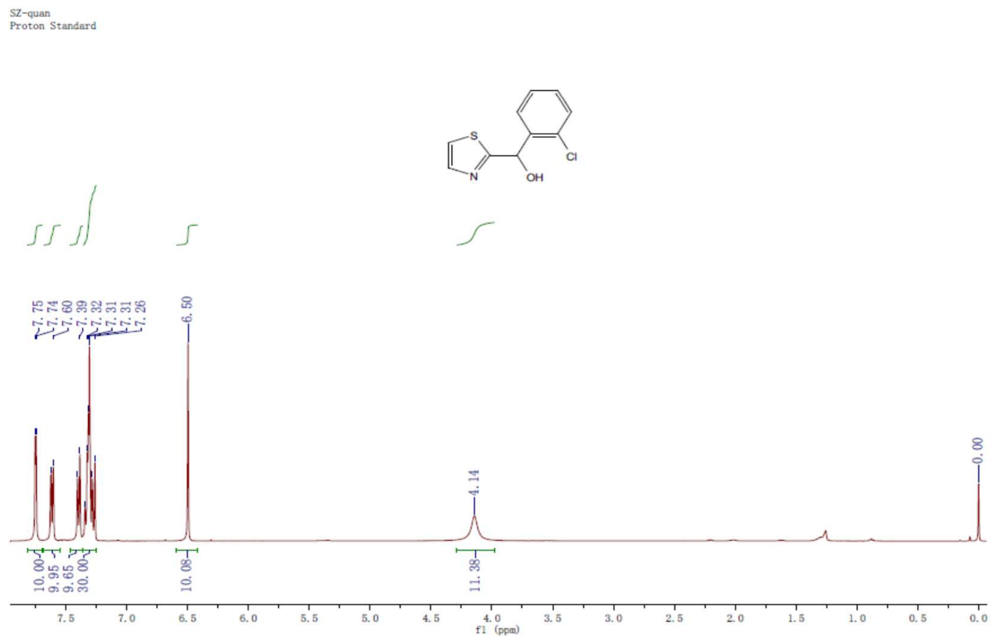
m/z

6b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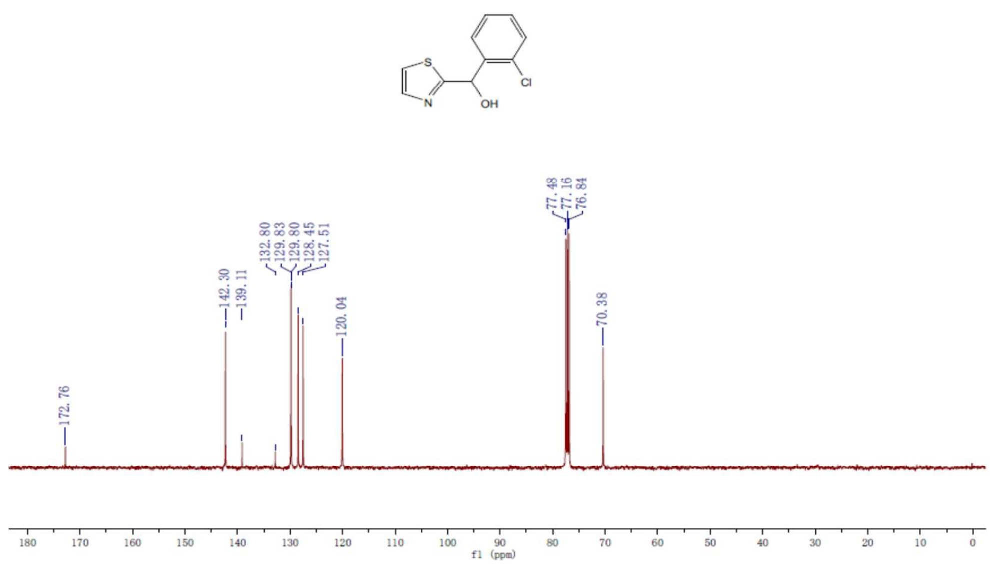
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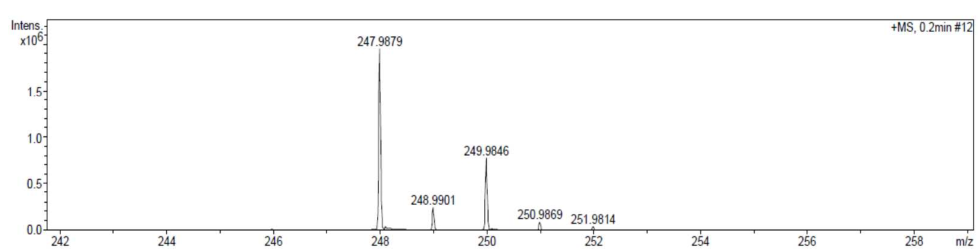
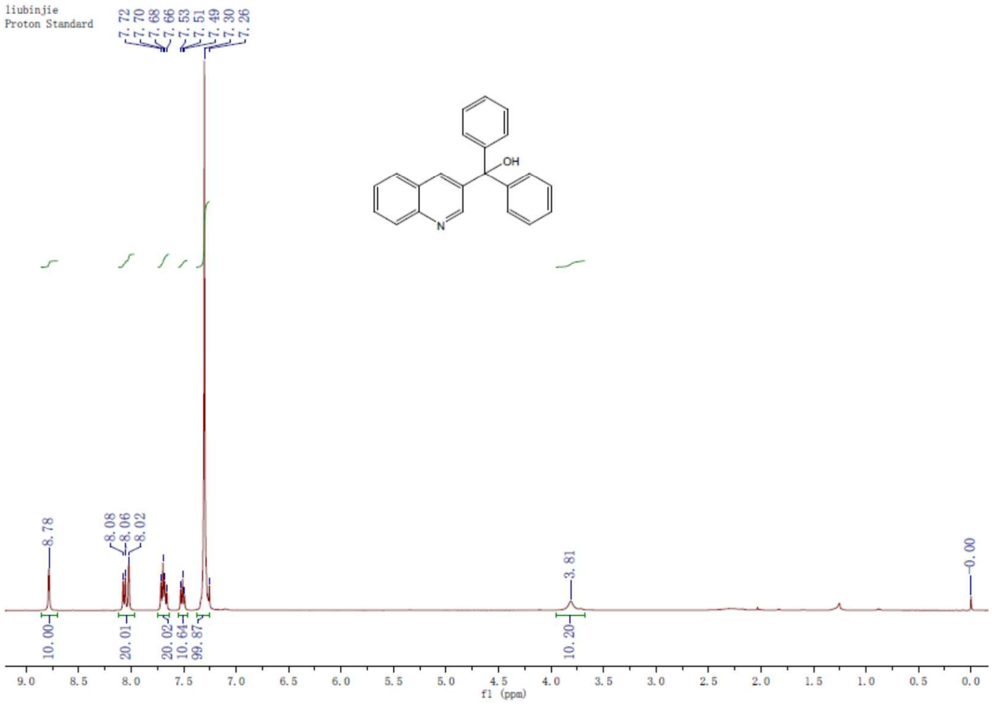
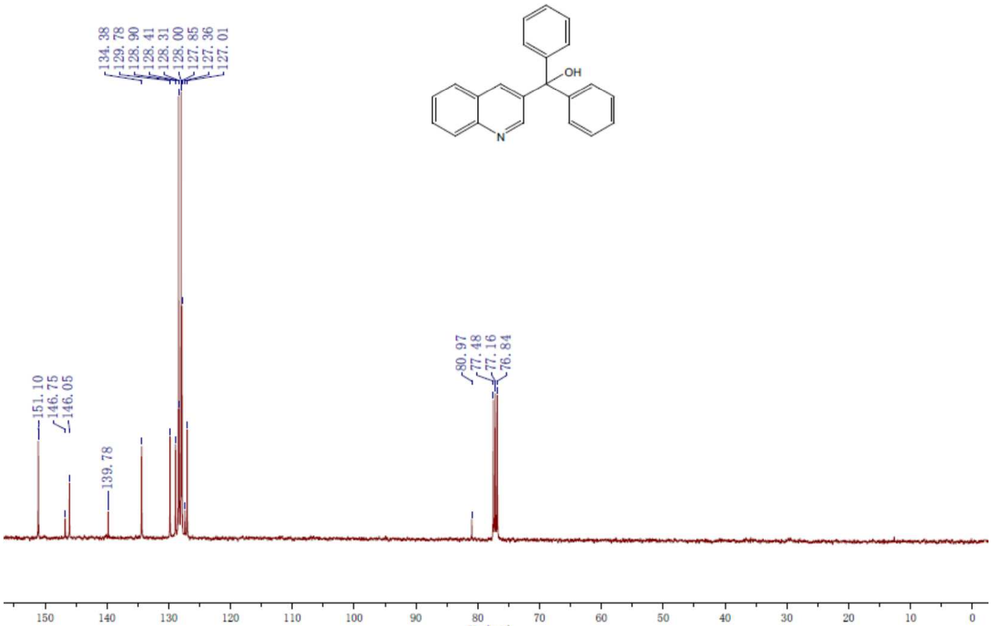
77.16
76.84
70.38
f1 (ppm)


Intens.
x10^6
+MS, 0.2min #12
247.9879
248.9901
249.9846
250.9869
251.9814
m/z

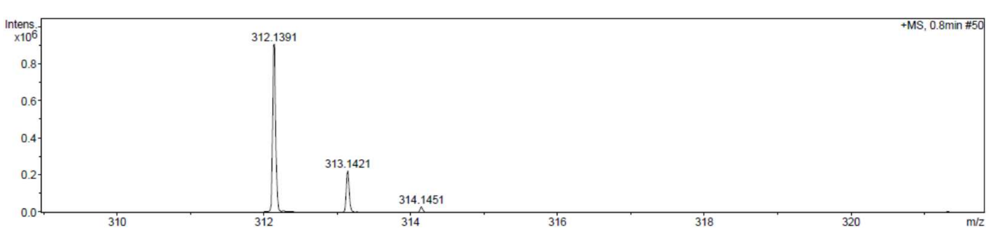
7a



liubinjie
Proton Standard
7.72 7.70 7.68 7.66 7.53 7.51 7.49 7.30 7.26
OH
N
8.78
8.08 8.06 8.02
3.81
0.00
10.00 20.01 20.02 10.64 99.87 10.20
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

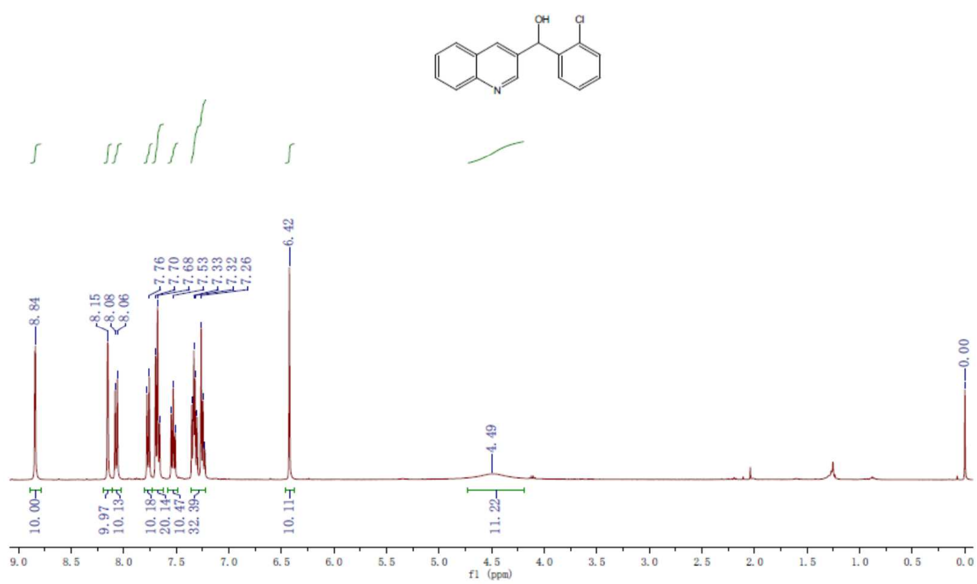


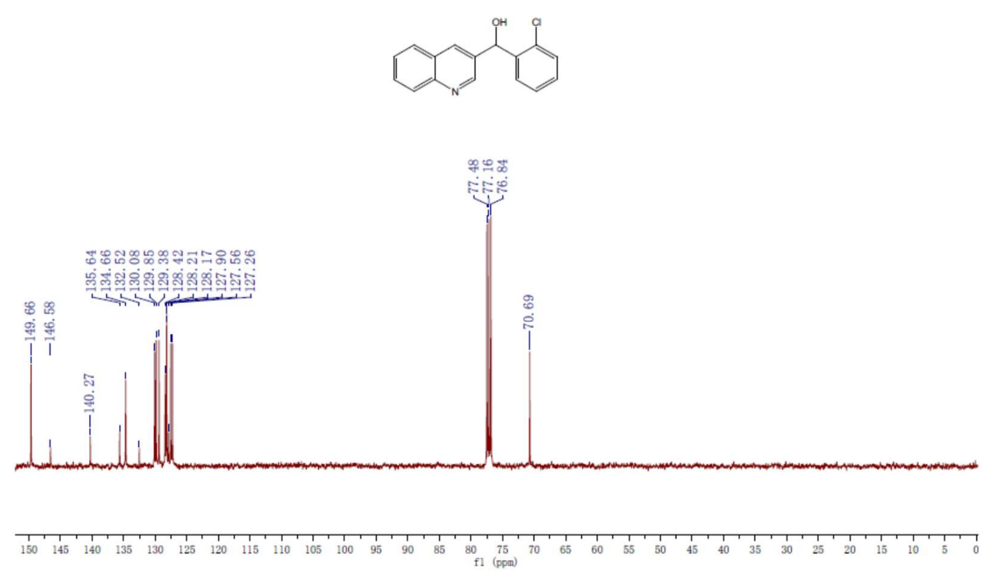
134.38 129.78 128.90 128.41 128.31 128.00 127.85 127.36 127.01
OH
N
80.97 77.48 77.16 76.84
151.10 146.75 146.05
139.78
150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

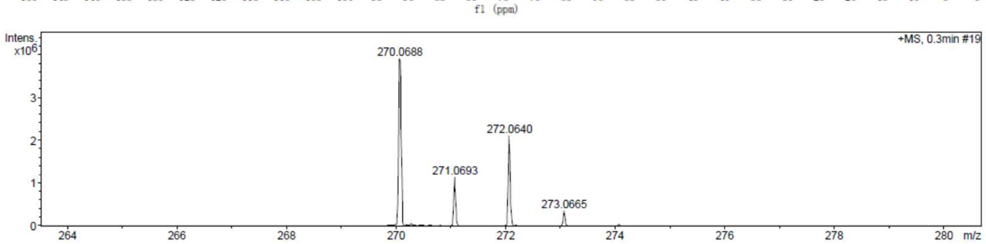


Intens.
x10^6
+MS, 0.8min #50
312.1391
313.1421
314.1451
0.8
0.6
0.4
0.2
0.0
310 312 314 316 318 320 m/z

7b


OH
Cl
N
8.84
8.15
8.08
8.06
7.76
7.70
7.68
7.53
7.33
7.32
7.26
6.42
4.49
0.00
10.00
9.97
10.13
10.18
20.14
10.47
32.39
10.11
11.22
f1 (ppm)


OH
Cl
N
149.66
146.58
140.27
135.64
134.66
132.52
130.08
129.85
129.38
128.42
128.21
128.17
127.90
127.56
127.26
77.48
77.16
76.84
70.69
f1 (ppm)


Intens.
x10^6
+MS, 0.3min #19
270.0688
271.0693
272.0640
273.0665
m/z