ESI for

Palladium-catalyzed ligand-free and efficient Suzuki–Miyaura reaction of heteroaryl halides with MIDA boronates in water

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Contents

Materials and Methods and Experimental Procedure

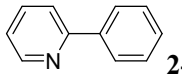
General remarks

All commercially available reagents (from Acros, Aldrich, Fluka) were used without further purification. N-methyliminodiacetic acid (MIDA) boronates used were prepared from corresponding arylboronic acids following the method reported in the literature.[1] All reactions were carried out in air. NMR spectra were recorded on a Brucker Advance II 400 spectrometer using TMS as internal standard (400 MHz for ^{1}H NMR). GC analysis was performed on Agilent GC-7890A with 4-methoxybiphenyl as internal standard. The isolated yield of products were obtained by short chromatography on a silica gel (200-300 mesh) column using petroleum ether (60-90 ºC), unless otherwise noted. Compounds described in the literature were characterized by ^{1}H NMR spectra compared with reported data.

General procedure for the Suzuki-Miyaura reaction.

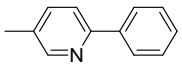
A mixture of aryl bromides (0.5 mmol), N-methyliminodiacetic acid (MIDA) boronates (0.6 mmol), (*i*-Pr)$_2$NH (1 mmol), Pd(OAc)$_2$ (2 mol%), H_2O (1 mL) was stirred at 100 ºC in air for the indicated time. The reaction mixture was added to brine (10 mL) and extracted with ethyl acetate (3 × 10 mL). The combined organic layers were concentrated in vacuo and the yield was determined by GC analysis with naphthalene as internal standard, or the product was isolated by short chromatography.

Characterization Data



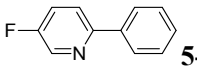
2-phenylpridine[1]

^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 8.71 (d, J = 4.4 Hz, 1H), 8.00 (d, J = 4.8 Hz, 2H), 7.77-7.72 (m, 2H), 7.48 (t, J = 7.6 Hz, 2H), 7.42 (t, J = 7.2 Hz, 1H), 7.25-7.21 (m, 1H) ppm.



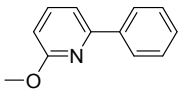
5-methyl-2-phenylpyridine[1]

^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 8.51 (s, 1H), 7.96 (d, J = 7.6 Hz, 2H), 7.61 (d, J =8.0 Hz, 1H), 7.53 (d, J = 8.4 Hz, 1H), 7.45 (t, J = 7.6 Hz, 2H), 7.38 (t, J = 7.6 Hz, 1H), 2.36 (s, 3H) ppm.



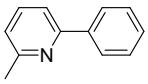
5-fluoro-2-phenylpyridine[1]

^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 8.53 (d, J = 2.8 Hz, 1H), 7.93 (d, J = 6.8 Hz, 2H), 7.71-7.68 (m, 1H), 7.46-7.38 (m, 4H) ppm.



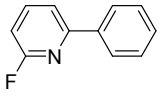
2-methoxy-6-phenylpyridine[1]

^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 8.05-8.03 (m, 2H), 7.60 (t, J = 7.6 Hz, 1H), 7.45 (t, J = 7.6 Hz, 2H), 7.40-7.36 (m, 1H), 7.33 (d, J = 7.2 Hz, 1H), 6.68 (d, J = 7.6 Hz, 1H), 4.03 (s, 3H) ppm.



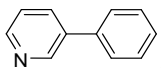
2-methyl-6-phenylpyridine[1]

^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 7.97 (d, J = 7.6 Hz, 2H), 7.62 (t, J = 7.6 Hz, 1H), 7.51 (d, J = 7.6 Hz, 1H), 7.46 (t, J = 7.2 Hz, 2H), 7.39 (t, J = 7.2 Hz, 1H), 7.09 (d, J = 7.6 Hz, 1H), 2.63 (s, 3H) ppm.



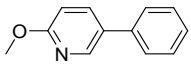
2-fluoro-6-phenylpyridine[1]

^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 8.00-7.98 (m, 2H), 7.80 (dd, J = 8.0 Hz, J = 8.0 Hz, 1H), 7.59 (dd, J = 8.0 Hz, J = 2.4 Hz, 1H), 7.47-7.41 (m, 3H), 6.83 (dd, J = 8.0 Hz, J = 2.8 Hz, 1H) ppm.



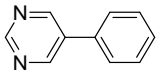
3-phenylpyridine[1]

^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 8.85 (d, J = 0.8 Hz, 1H), 8.60 (d, J = 4.8 Hz, 1H), 7.87 (d, J = 8.0 Hz, 1H), 7.58 (d, J = 8.0 Hz, 2H), 7.48 (t, J = 8.0 Hz, 2H), 7.40 (t, J = 7.6 Hz, 1H), 7.37-7.34 (m, 1H), ppm.



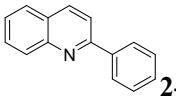
2-methoxy-5-phenylpyridine[1]

^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 8.39 (s, 1H), 7.78 (d, J = 8.4 Hz, 1H), 7.53-7.51 (m, 2H), 7.43 (t, J = 7.6 Hz, 2H), 7.34 (t, J = 7.2 Hz, 1H), 6.81 (d, J = 8.4 Hz, 1H), 3.98 (s, 3H) ppm.



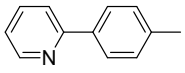
5-phenylpyrimidine[1]

^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 9.17 (s, 1H), 8.92 (s, 2H), 7.60-7.58 (m, 2H), 7.55-7.51 (m, 2H), 7.49-7.45 (m, 1H) ppm.



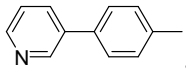
2-phenylquinoline[1]

^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 8.23 (d, J = 8.4 Hz, 1H), 8.19-8.16 (m, 3H), 7.88 (d, J = 8.4 Hz, 1H),7.83 (d, J = 8.0 Hz, 1H), 7.73 (t, J = 7.2 Hz, 1H), 7.53 (t, J = 7.6 Hz, 3H), 7.47 (t, J = 7.2 Hz, 1H) ppm.



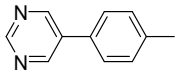
2-(p-tolyl)pyridine[1]

^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ 8.68 (d, J = 4.8 Hz, 1H), 7.90 (d, J = 8.0 Hz, 2H), 7.74-7.69 (m, *2*H), 7.29 (d, J = 8.0 Hz, 2H), 7.21-7.19 (m, 1H), 2.41 (s, 3H) ppm.



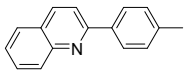
3-p-tolylpyridine[2]

^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 8.84 (d, J = 2.0 Hz, 1H, Py), 8.57-8.56 (m, 1H, Py), 7.86-7.84 (m, 1H, Py), 7.48 (d, J = 8.0 Hz, 2H, Ph), 7.35-7.32 (m, 1H, Py), 7.29 (d, J = 8.0 Hz, 2H, Ph), 2.41 (s, 3H, CH_3), ppm.



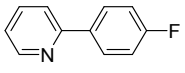
5-p-tolylpyrimidine[3]

^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 9.18 (s, 1H), 8.94 (s, 2H), 7.49 (d, J = 8.0 Hz, 2H), 7.29 (d, J = 8 Hz, 2H), 2.43 (s, 3H) ppm.



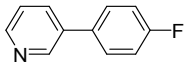
2-p-tolylquinoline[1]

^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 8.16 (dd, J = 8.4 Hz, J = 7.2 Hz, 2H), 8.07 (d, J = 8.0 Hz, 1H), 7.86 (d, J = 8.0 Hz, 1H), 7.81 (d, J = 8.4 Hz, 1H), 7.72-7.69 (m, 1H), 7.53-7.49 (m, 1H), 7.33 (d, J = 8.4 Hz, 1H), 2.43 (s, 3H) ppm.



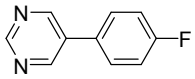
2-(4-fluorophenyl)pyridine[1]

^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 8.66 (d, J = 4.8 Hz, 1H), 7.98-7.94 (m, 2H), 7.73-7.71 (m, 1H), 7.66 (d, J = 7.2 Hz, 1H), 7.21 (t, J = 4.0 Hz, 1H), 7.14 (t, J = 7.6 Hz, 2H) ppm.



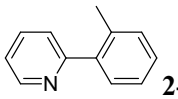
3-(4-fluorophenyl)pyridine[4]

^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 8.81 (d, J = 1.6 Hz, 1H, Py), 8.58 (dd, J = 4.8 Hz, 1.6 Hz, 1H, Py), 7.83-7.80 (m, 1H, Py), 7.55-7.51 (m, 2H, Ph), 7.37-7.34 (m, 1H, Py), 7.19-7.14 (m, 2H, Ph), ppm.



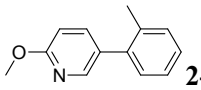
5-(4-fluorophenyl)pyrimidine[3]

^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 9.21 (s, 1H), 8.92 (s, 2H), 7.58-7.55 (m, 2H), 7.24 (t, J=8.8 Hz, 2H) ppm.



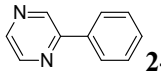
2-(*o*-tolyl)pyridine[1]

^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 8.68 (m, 1H), 7.72-7.68 (m, 1H), 7.38 (t, J = 7.2 Hz, 2H), 7.29-7.19 (m, 4H), 2.36 (s, 3H) ppm.



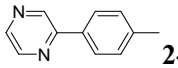
2-methoxy-5-(*o*-tolyl)pyridine[1]

^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 8.13 (d, J = 2.8 Hz, 1H), 7.54 (dd, J = 8.8, 2.4 Hz, 1H), 7.28-7.18 (m, 4H), 6.80 (d, J = 8.0, 1H), 3.98 (s, 3H), 2.27 (s, 3H) ppm.



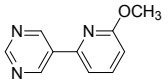
2-phenylpyrazine[1]

^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 9.04 (s, 1H), 8.64 (s, 1H), 8.51 (d, J = 2.4 Hz, 1H), 8.02 (d, J = 7.6 Hz, 2H), 7.54-7.46 (m, 3H) ppm.



2-(*p*-tolyl)pyrazine[1]

^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ = 8.98 (s, 1H), 8.58 (s, 1H), 8.45 (d, J = 2.4 Hz, 1H), 7.90 (d, J = 8.0 Hz, 2H), 7.29 (d, J = 8.0 Hz, 2H), 2.40 (s, 3H) ppm.



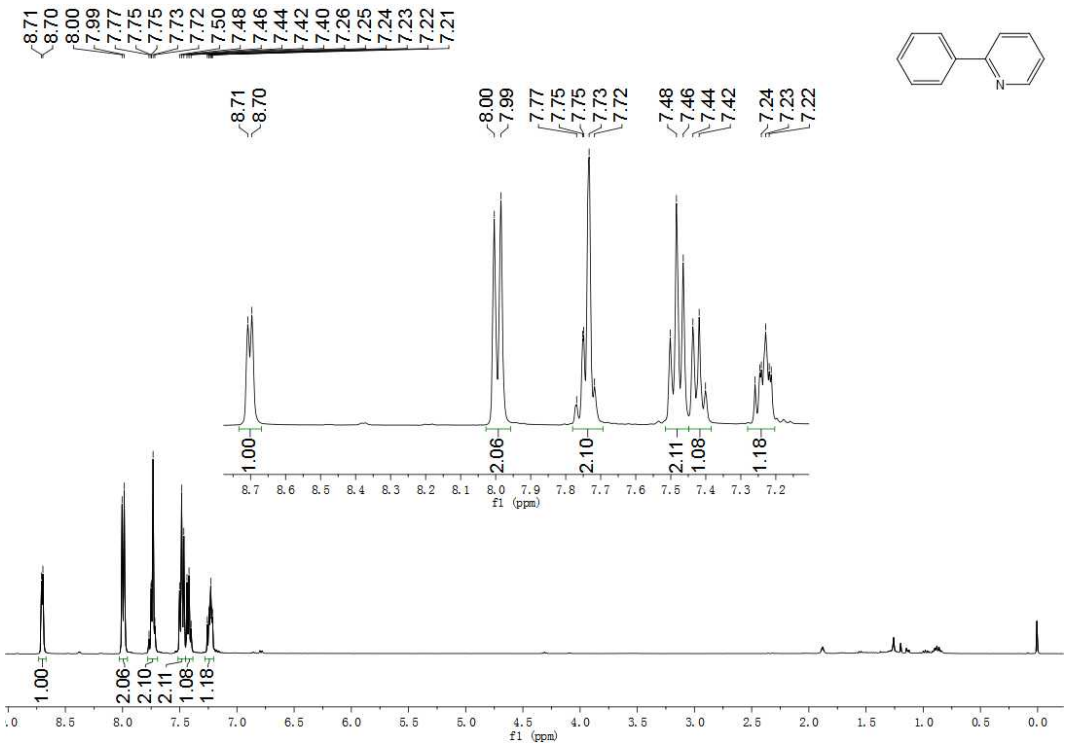
5-(6-methoxypyridin-2-yl)pyrimidine[5]

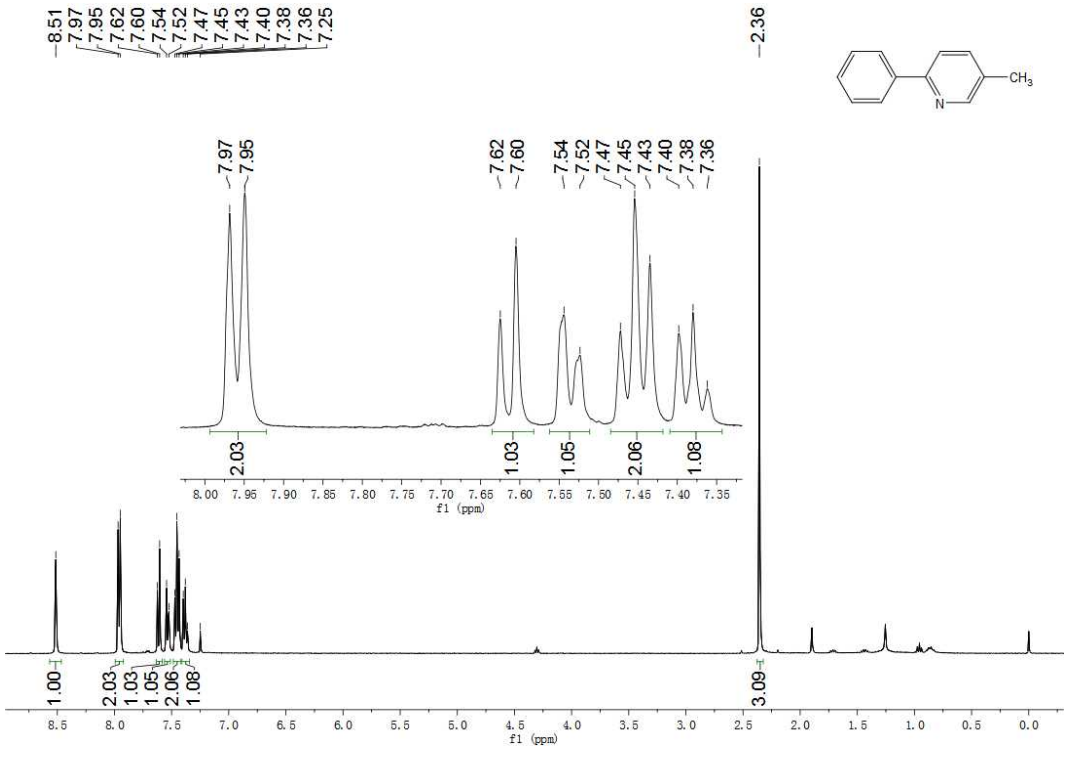
^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 9.35 (s, 2H), 9.24 (s, 1H), 7.70 (dd, J = 8.3, 7.4 Hz, 1H), 7.37 (dd, J = 7.3, 0.5 Hz, 1H), 7.26 (s, 1H), 6.81 (d, J = 8.3 Hz, 1H), 4.04 (s, 3H).

References

1. X. F. Rao, C. Liu, et al. *Asian J. Org. Chem,* 2013, **2**, 514.
2. S. Shi and Y. Zhang, *Green Chem.*, 2008, **10**, 868.
3. C. Liu, N. Han, X. Song and J. Qiu, *Eur. J. Org. Chem.*, 2010, 5548.
4. M. Feuerstein, H. Doucet and M. Santelli, *J. Organomet. Chem.*, 2003, **687**, 327.
5. G. Philippe, Gros, Y. Fort, Synthesis, 1999, 754 – 756.

NMR Spectra for Products





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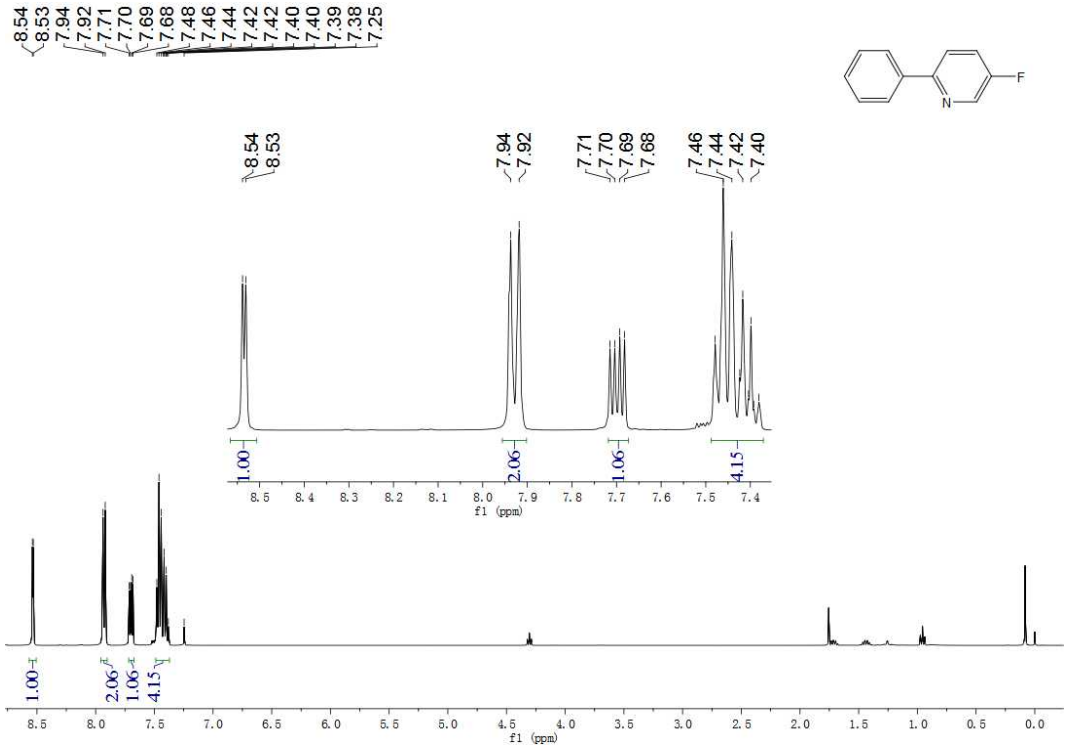
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7.68
7.48
7.46
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7.42
7.40
7.40
7.39
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7.25
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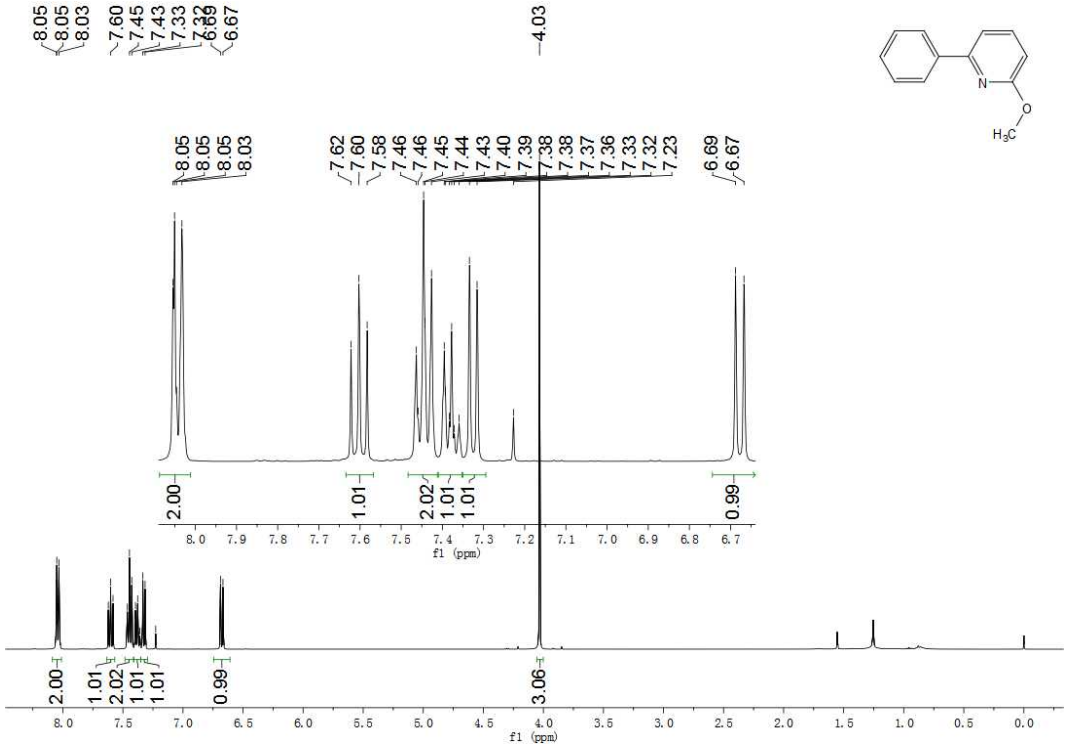
2.06
1.06
4.15
f1 (ppm)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4.03
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7.37
7.36
7.33
7.32
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6.67
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1.01
2.02
1.01
1.01
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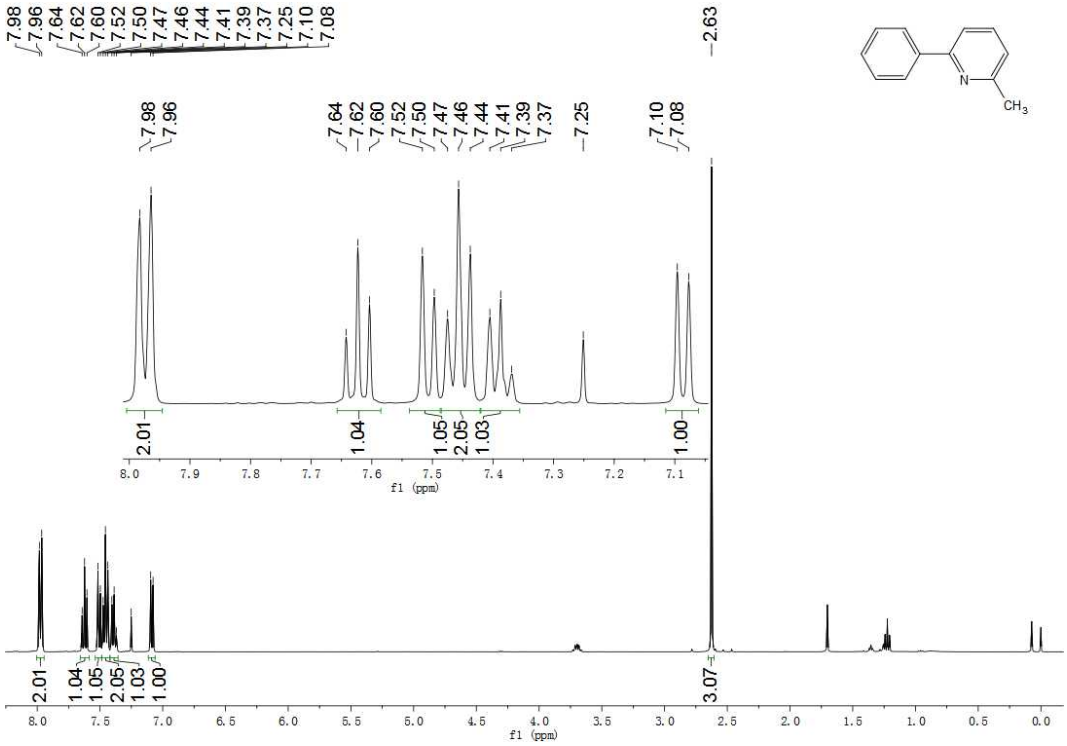
3.06
f1 (ppm)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7.41
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7.37
7.25
7.10
7.08
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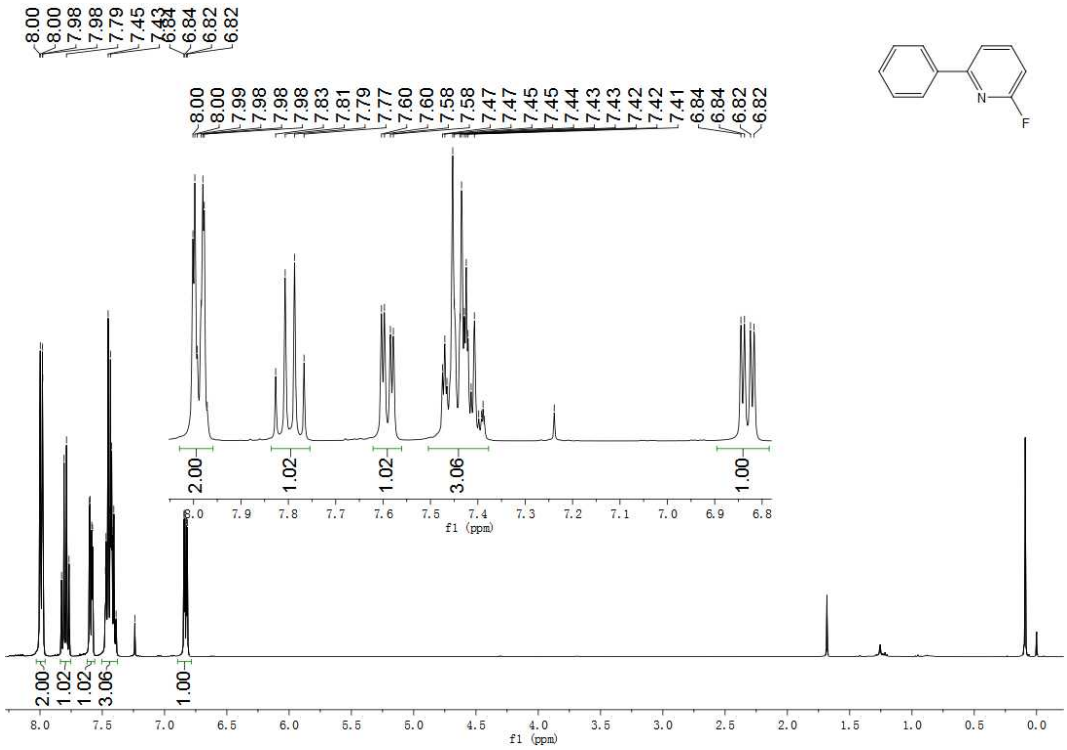
2.05
1.03
1.00
3.07
f1 (ppm)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6.82
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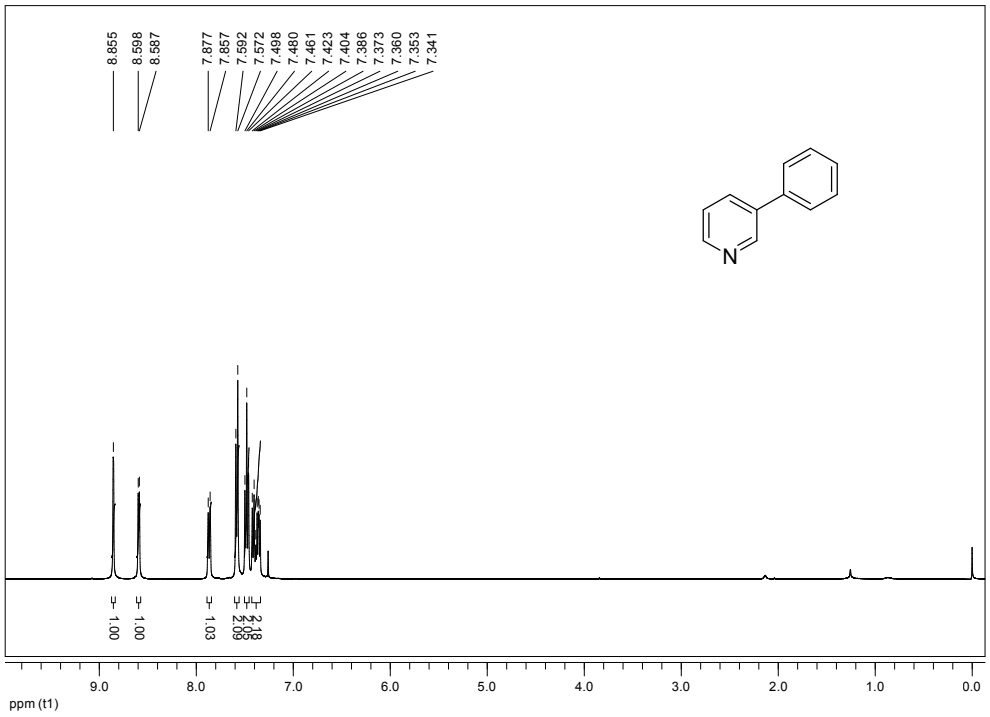
f1 (ppm)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7.0
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4.0
3.0
2.0
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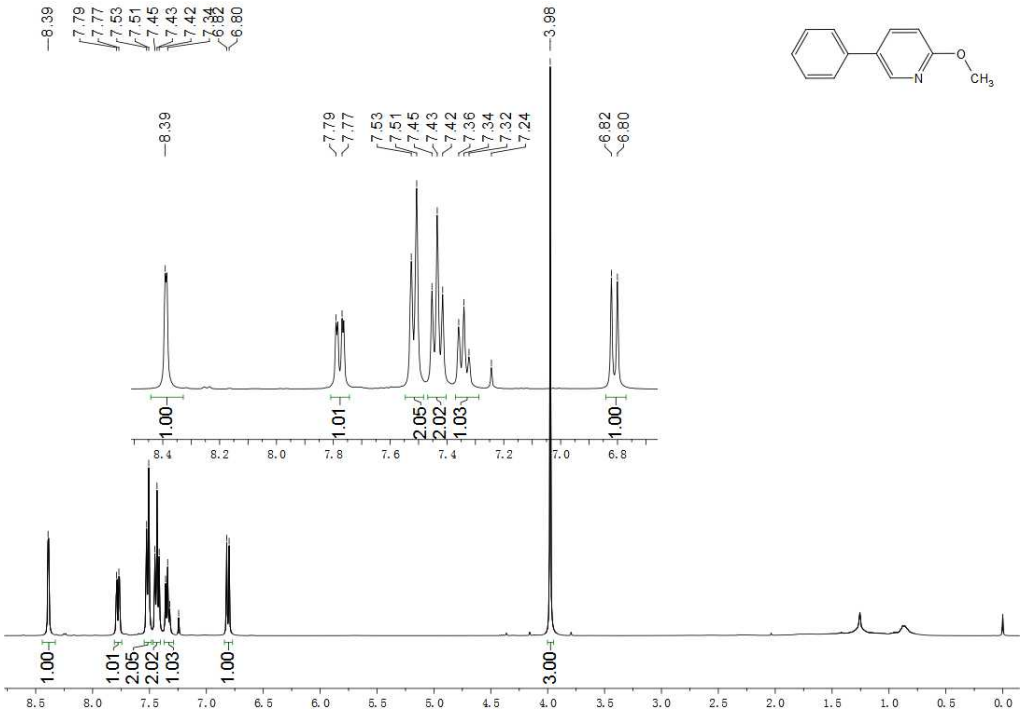
0.0
ppm (t1)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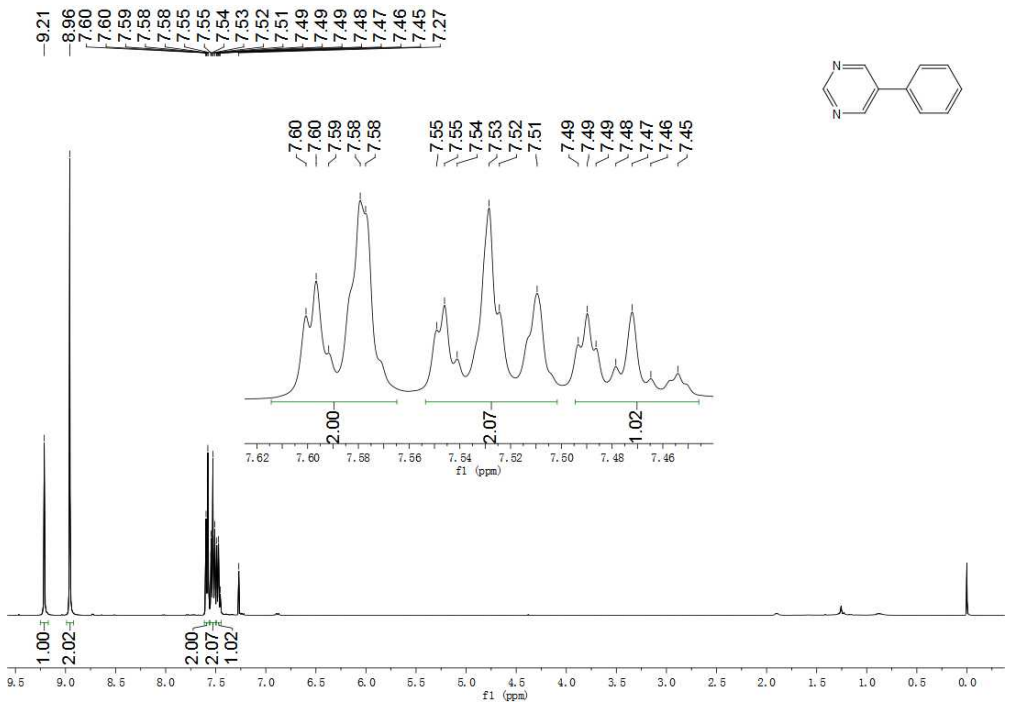
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7.53
7.52
7.51
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2.00
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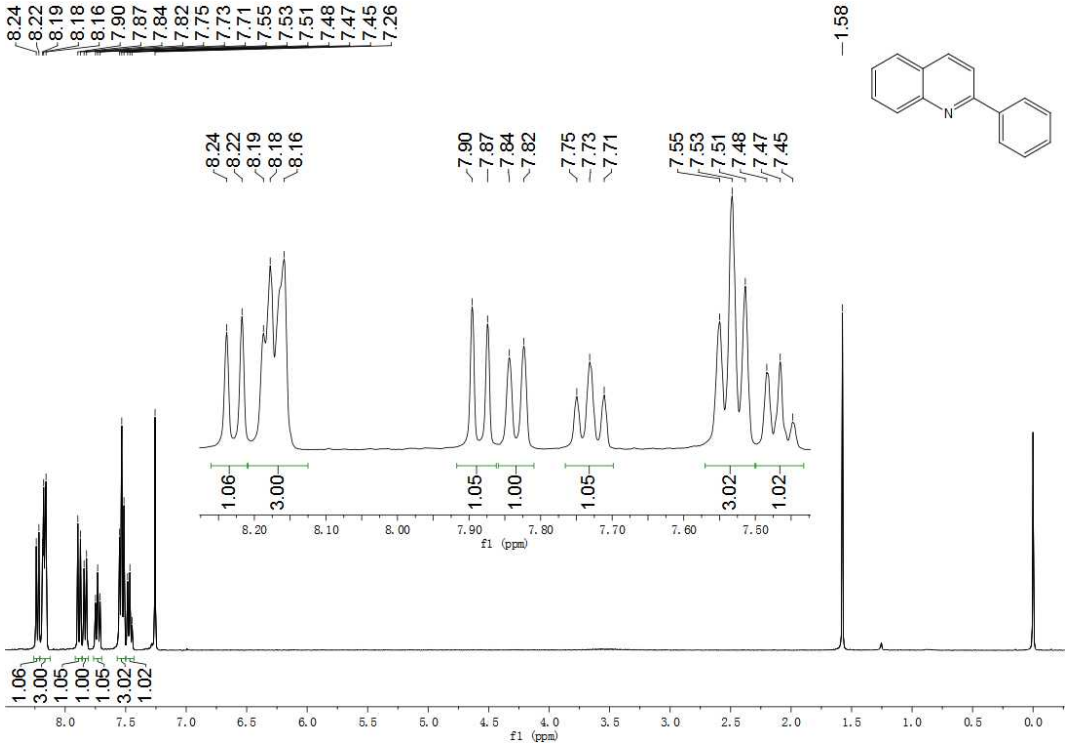
1.02
f1 (ppm)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7.84
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7.73
7.71
7.55
7.53
7.51
7.48
7.47
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1.05
1.00
1.05
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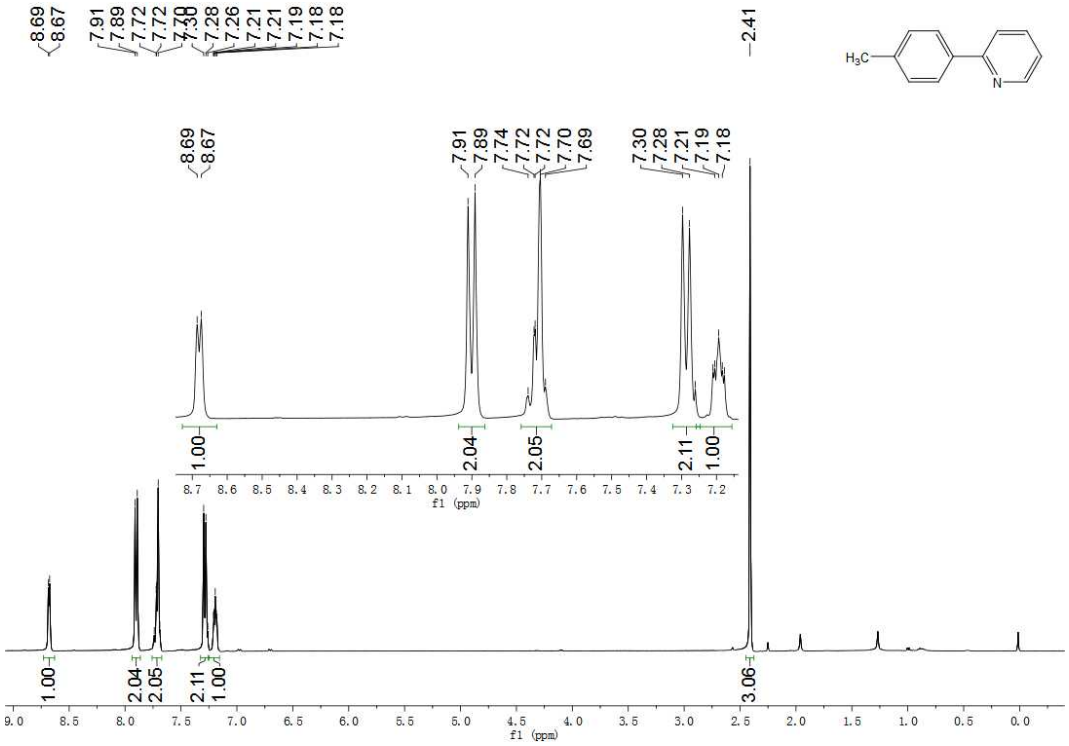
1.02
f1 (ppm)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7.72
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7.28
7.26
7.21
7.19
7.18
7.18
2.41
H3C
N
8.69
8.67
7.91
7.89
7.74
7.72
7.72
7.70
7.69
7.30
7.28
7.21
7.19
7.18
1.00
2.04
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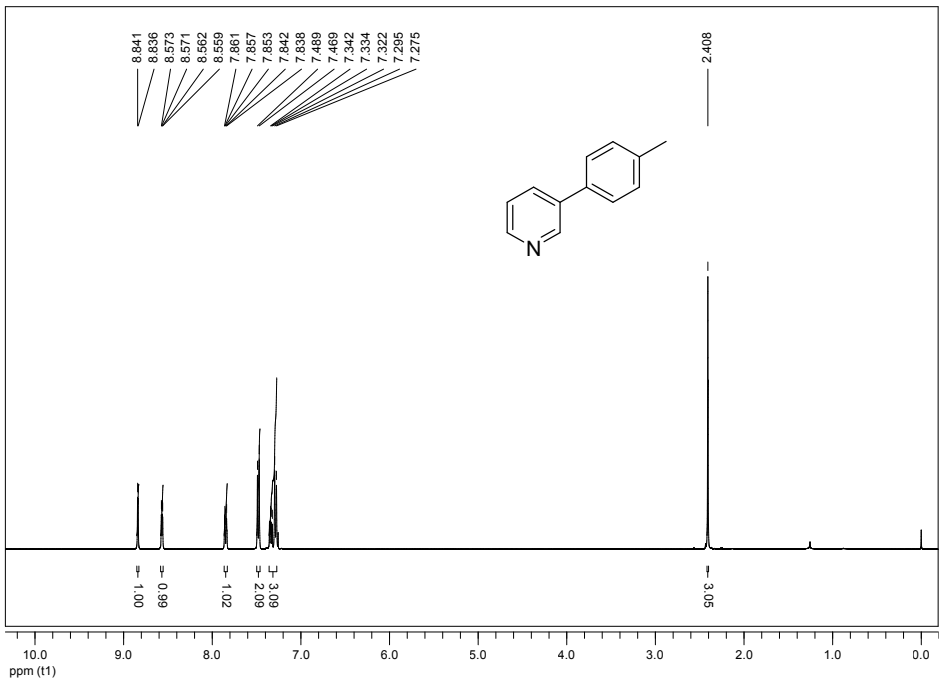
1.00
f1 (ppm)
1.00
2.04
2.05
2.11
1.00
3.06
f1 (ppm)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7.838
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7.469
7.342
7.334
7.322
7.295
7.275
2.408
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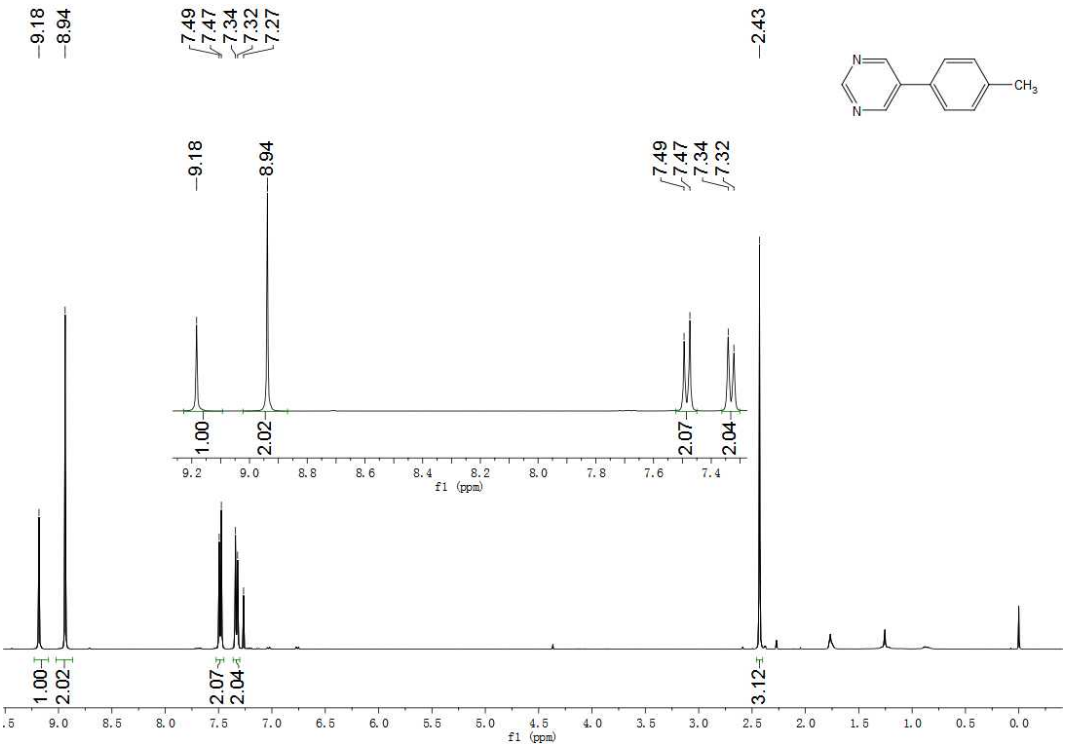
0.99
1.02
2.09
3.09
3.05
ppm (t1)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7.32
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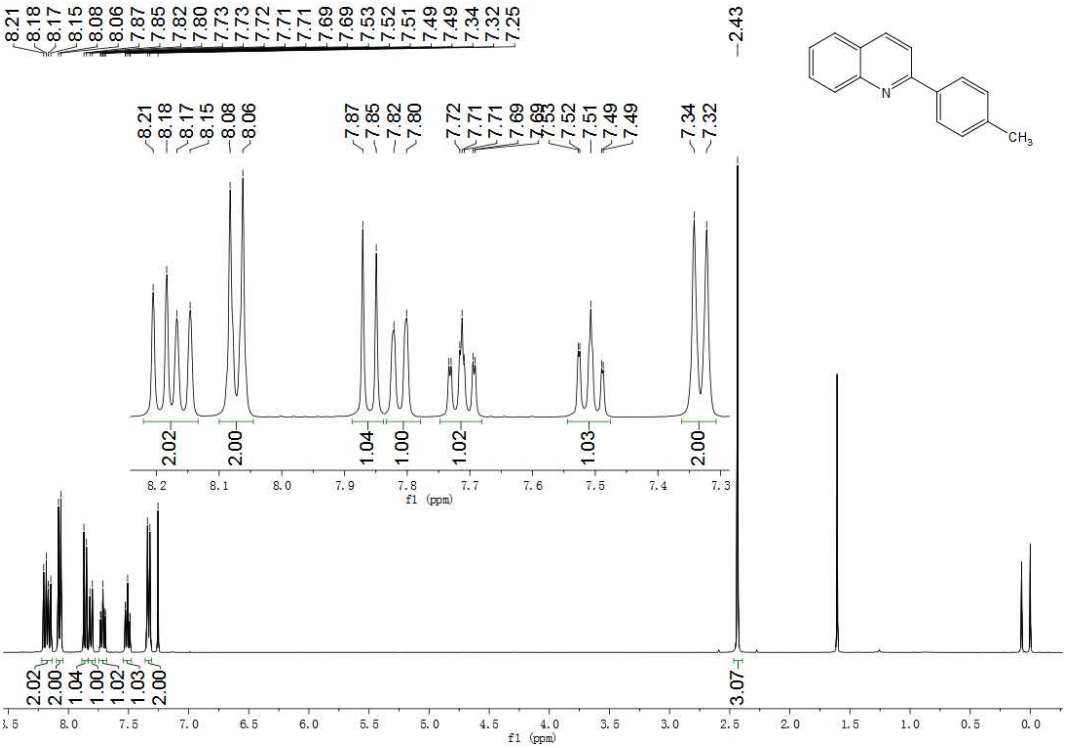
2.02
2.07
2.04
3.12
f1 (ppm)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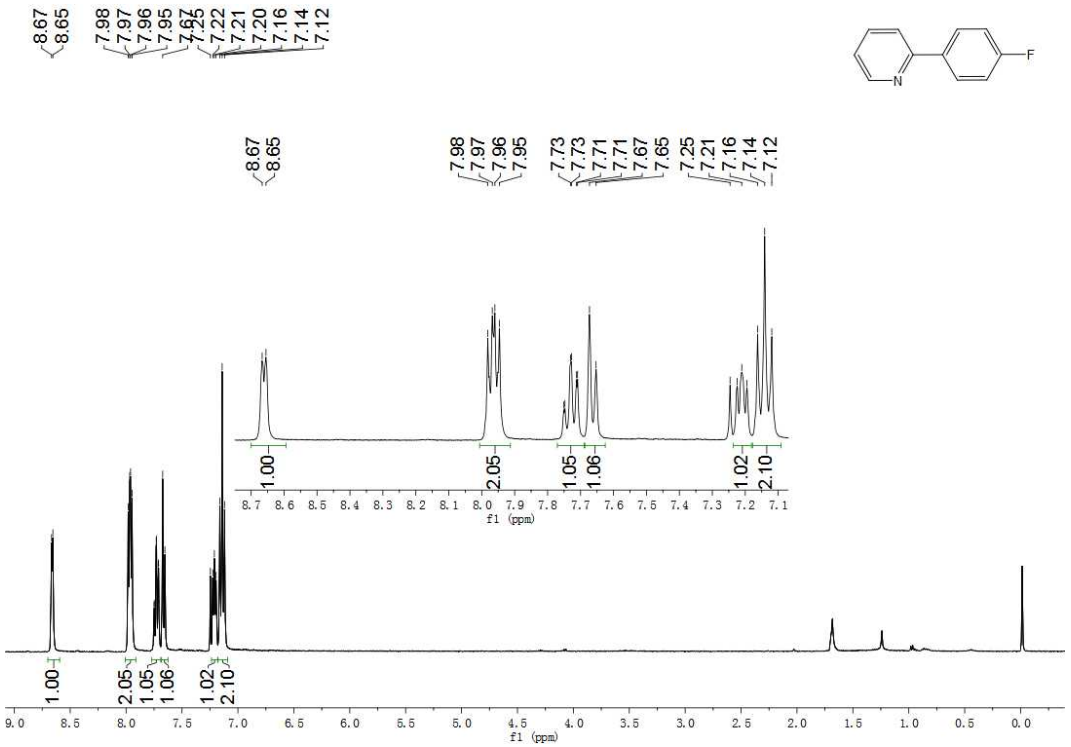
7.87
7.85
7.82
7.80
7.73
7.72
7.71
7.69
7.53
7.52
7.51
7.49
7.34
7.32
7.25
2.43
CH3
2.02
2.00
1.04
1.00
1.02
1.03
2.00
3.07
f1 (ppm)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7.96
7.95
7.73
7.71
7.67
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7.22
7.21
7.20
7.16
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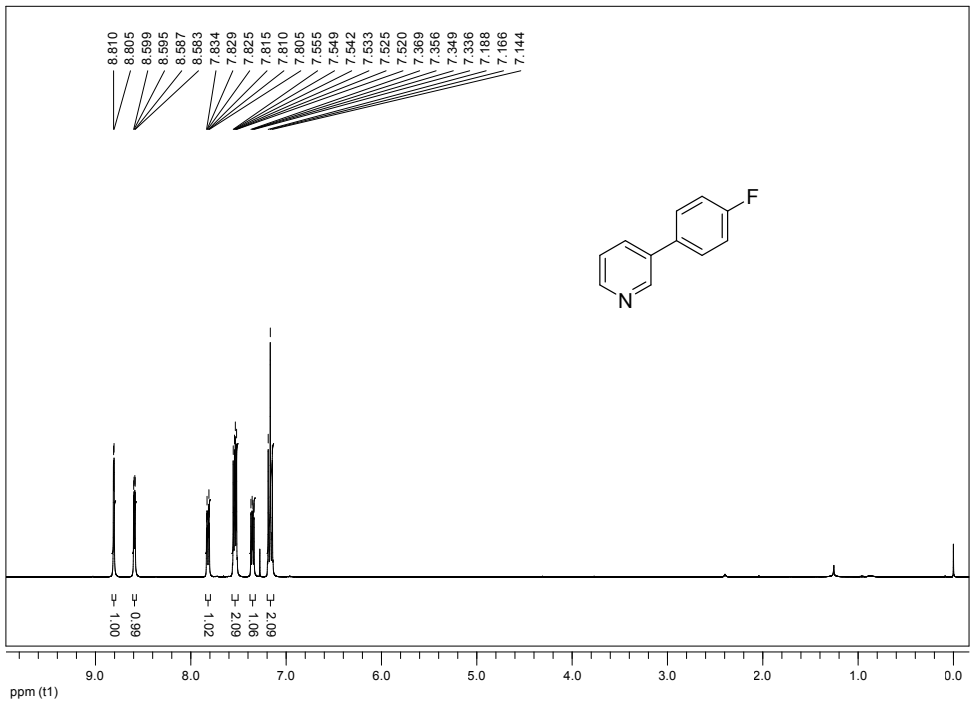
7.12
F
N
1.00
2.05
1.05
1.06
1.02
2.10
f1 (ppm)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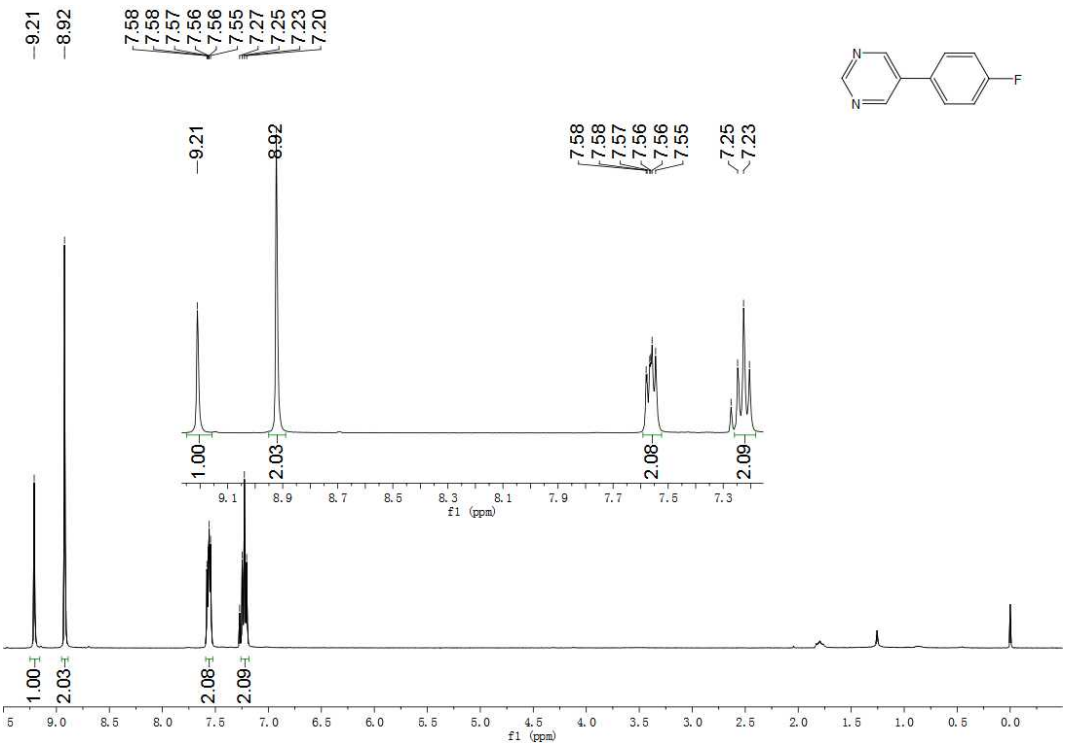
8.599
8.595
8.587
8.583
7.834
7.829
7.825
7.815
7.810
7.805
7.555
7.549
7.542
7.533
7.525
7.520
7.369
7.356
7.349
7.336
7.188
7.166
7.144
F
N
1.00
0.99
1.02
2.09
1.06
2.09
ppm (t1)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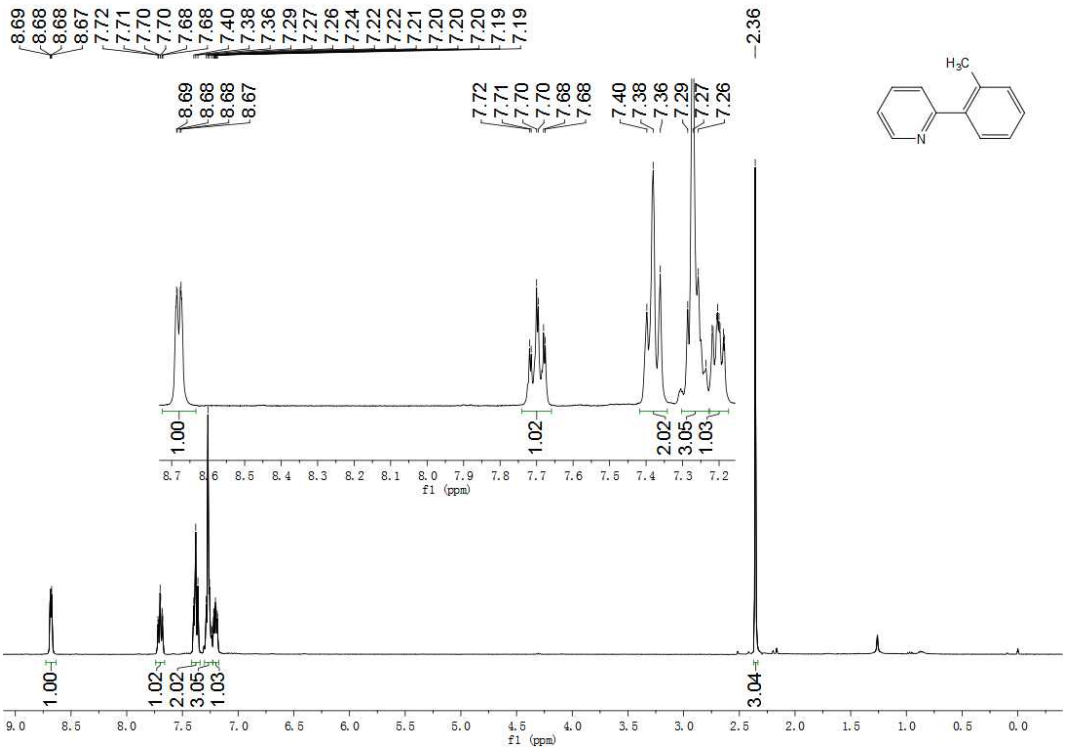
7.56
7.56
7.55
7.27
7.25
7.23
7.20
N
N
F
1.00
2.03
2.08
2.09
f1 (ppm)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8.68
8.67
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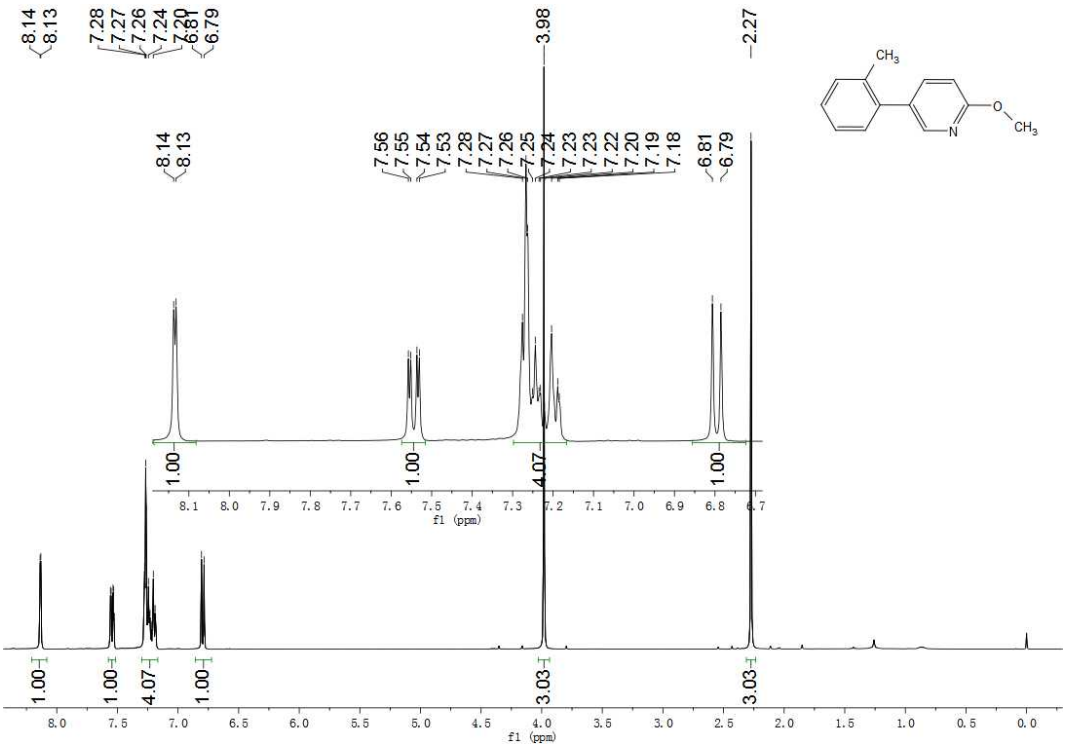
7.71
7.70
7.70
7.68
7.68
7.40
7.38
7.36
7.29
7.27
7.26
7.24
7.22
7.22
7.21
7.20
7.20
7.19
7.19
2.36
H3C
N
1.00
1.02
2.02
3.05
1.03
3.04
f1 (ppm)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8.13
7.28
7.27
7.26
7.24
7.20
6.81
6.79
3.98
2.27
CH3
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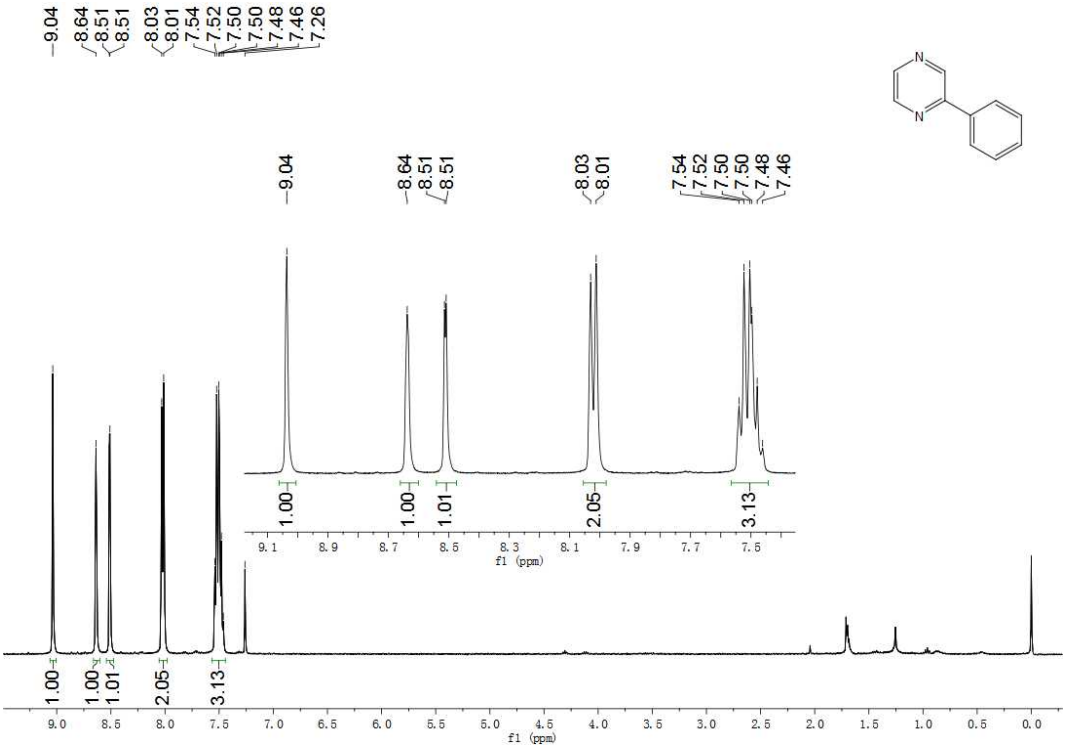
CH3
N
7.56
7.55
7.54
7.53
7.28
7.27
7.26
7.25
7.24
7.23
7.23
7.22
7.20
7.19
7.18
1.00
1.00
4.07
1.00
f1 (ppm)
1.00
1.00
4.07
1.00
3.03
3.03
f1 (ppm)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8.01
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7.52
7.50
7.50
7.48
7.46
7.26
N
N
9.04
8.64
8.51
8.51
8.03
8.01
7.54
7.52
7.50
7.50
7.48
7.46
1.00
1.00
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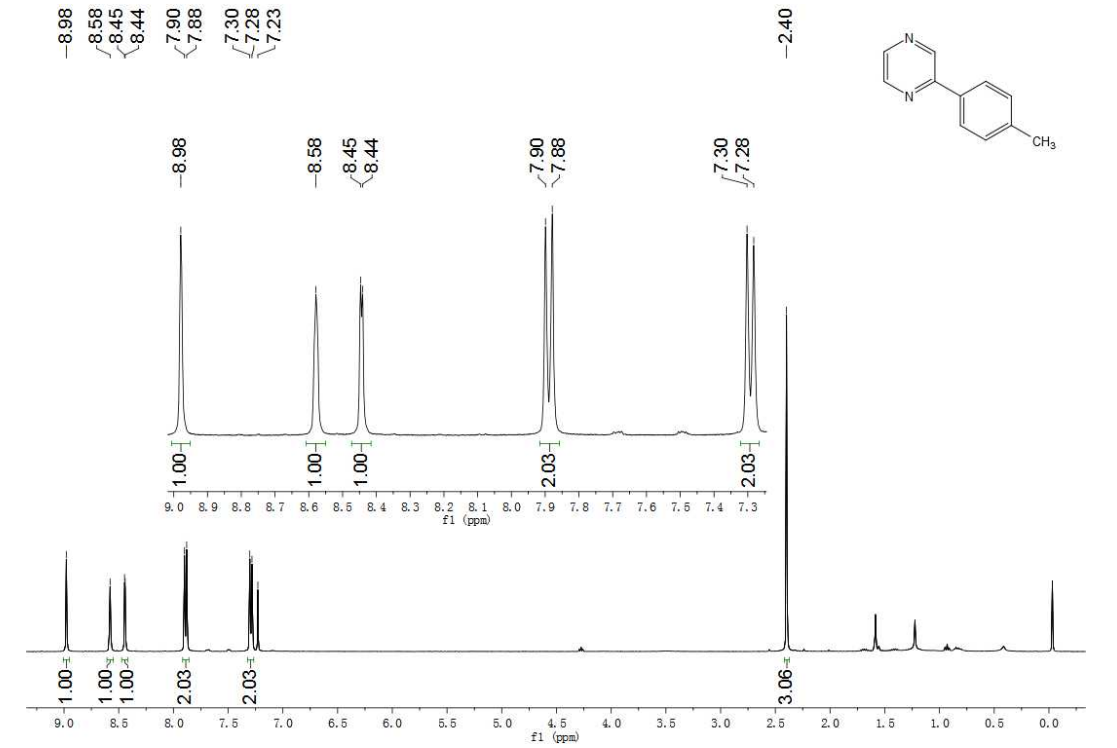
2.05
3.13
f1 (ppm)
1.00
1.00
1.01
2.05
3.13
f1 (ppm)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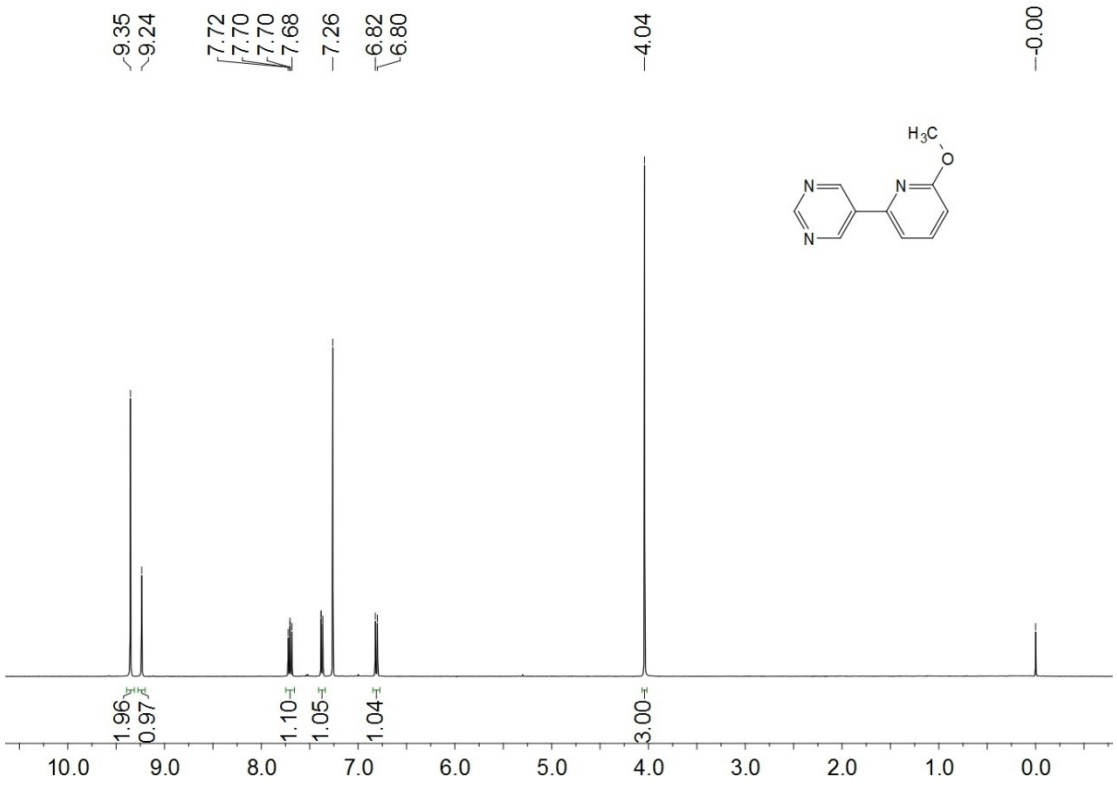
1.00
1.00
1.00
2.03
2.03
3.06
f1 (ppm)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9.24
7.72
7.70
7.70
7.68
7.26
6.82
6.80
4.04
0.00
1.96
0.97
1.10
1.05
1.04
3.00