Supporting Information

"One-Pot" Multicomponent Approach to Polysubstituted 4-Aminopydines†

Jiaan Shao, Wanwan Yu, Zhanying Shao and Yongping Yu*

Institute of Materia Medica, College of Pharmaceutical Sciences, Zhejiang University, Hangzhou, 310058, P. R. China

* To whom correspondence should be addressed.

Email: yyu@zju.edu.cn

List of Contents

1. General Information:

All solvents were purified according to standard methods prior to use. Purifications of reaction products were carried out by chromatography using silica gel (200–300 mesh) or recrystallization. Melting points were recorded on a BÜCHI B–540 melting point apparatus. NMR spectra were recorded for ^{1}H NMR at 500 MHz and for ^{13}C NMR at 125 MHz. For ^{1}H NMR, tetramethylsilane (TMS) served as internal standard (δ=0) and data were reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q= quartet, m = multiplet), coupling constant(s) in Hz, and integration. For ^{13}C NMR, TMS (δ=0) or $CDCl_3$ (δ =77.26) was used as internal standard and spectra were obtained with complete proton decoupling. Low-resolution data were obtained using ESI ionization. Single crystals of compound **4c** and **4h** were measured on a Rigaku RAXIS-RAPID single-crystal diffractometer. The starting material **3a–3w** were prepared according to literature methods.[1] the starting material **1** were commercially available by their hydrochloride and were used after triethylamine pre-treated to free molecule.

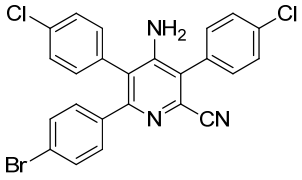
2. General Procedure for the Synthesis of 4:

A mixture of 2-aminoacetonitrile or methyl 2-aminoacetate **1**(1.1 mmol), aldehyde **2** (1.05 mmol), α-azidovinylketone **3** (1.0 mmol), and K_2CO_3 (2.1 mmol) were stirred in anhydrous DMF (6 mL) at a proper temperature (25 ^{o}C to 40 ^{o}C) for several hours. After the completeness of the reaction, the mixture was quenched with water (10 mL), and extracted three times with EtOAc. The organic layer was combined, washed with brine, dried over anhydrous Na_2SO_4 and concentrated. Purification of the crude product by recrystallization (petroleum ether : ethyl acetate = 3:1) or chromatography (silica gel; petroleum ether : ethyl acetate = 6 : 1 to 3:1) to afford **4**.

1 (a) T. L. Gilchrist and R. Mendonca, *ARKIVOC*., 2000, 769; (b) L. Liu and S. Liebeskind, *J. Am. Chem. Soc.*, 2008, **130**, 6918; (c) M. A. Khazaei, *Synthesis*, 2009, **21**, 3672; (d) C. J. Kowalski, A. E. Weber and K. W. Fields, *J. Org. Chem*., 1982, **47**, 5088.

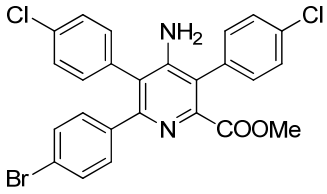
3. Characterization Data of 4:

4-amino-6-(4-bromophenyl)-3, 5-bis (4-chlorophenyl) picolinonitrile (4a):



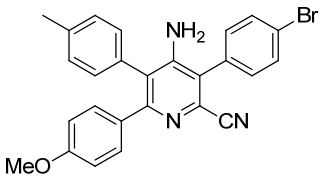
Yellow-brown solid (93%); Purified by recrystallization (petroleum ether : ethyl acetate = 3:1); mp: 229 – 231 ^{o}C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.55 (d, *J* = 8.5 Hz, 2H), 7.43 (d, *J* = 8.0 Hz, 2H), 7.39 (d, *J* = 8.0 Hz, 2H), 7.34 (d, *J* = 8.5 Hz, 2H), 7.12 (d, *J* = 8.0 Hz, 4H), 4.31 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.97, 149.89, 137.61, 136.01, 135.26, 132.56, 131.52, 131.22, 131.14, 131.07, 130.70 130.45, 130.18, 124.91, 122.87, 122.76 121.58, 116.60; HRMS (EI): m/z Calcd for $C_{24}H_{14}BrCl_2N_3$ $(M)^+$ 492.9748; Found: m/z 492.9744.

methyl 4-amino-6-(4-bromophenyl)-3, 5-bis (4-chlorophenyl)picolinate(4b):



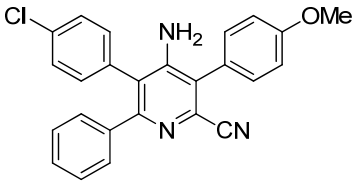
Pale yellow solid (51%); Purified by chromatography (silica gel ; petroleum ether : ethyl acetate = 6 : 1 to 3:1); mp: 187 – 188 ^{o}C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.48 (d, *J* = 8.0 Hz, 2H), 7.36 (d, *J* = 8.0 Hz, 2H), 7.32 (m, 4H), 7.16 (d, *J* = 8.0 Hz, 2H), 7.12 (d, *J* = 8.0 Hz, 2H), 4.14 (s, 2H), 3.67(s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.90, 155.49, 150.07, 148.12, 138.52, 134.62, 134.37, 133.39, 132.68, 131.77, 131.40, 131.00, 130.86, 129.83, 129.59, 122.32, 120.68, 119.64, 52.45; HRMS (EI): m/z Calcd for $C_{25}H_{17}BrCl_2N_2O_2$ $(M)^+$ 525.9850; Found: m/z 525.9846.

4-amino-3-(4-bromophenyl)-6-(4-methoxyphenyl)-5-(p-tolyl)picolinonitrile(4c):



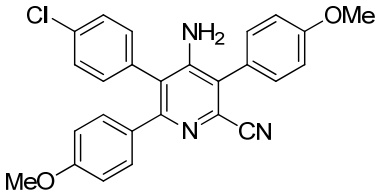
Yellow solid (71%); Purified by recrystallization (petroleum ether : ethyl acetate = 3:1); mp: 230 – 232 ^{o}C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.68 (d, *J* = 8.0 Hz, 2H), 7.37 (d, *J* = 8.0 Hz, 2H), 7.25 – 7.14 (m, 4H), 7.07 (d, *J* = 8.0 Hz, 2H), 6.70 (d, *J* = 8.5 Hz, 2H), 4.31 (s, 2H), 3.75 (s, 3H), 2.36 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.13, 157.18, 149.44, 137.75, 132.85, 131.70, 131.60, 131.57, 131.49, 131.02, 130.31, 129.94, 124.14, 123.81, 122.62, 117.03, 113.16, 55.13, 21.31; HRMS (EI): m/z Calcd for $C_{26}H_{20}BrN_3O$ $(M)^+$ 469.0790; Found: m/z 469.0794.

4-amino-5-(4-chlorophenyl)-3-(4-methoxyphenyl)-6-phenylpicolinonitrile(4d):



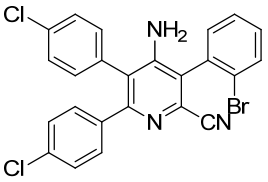
Yellow-brown solid (90%); Purified by recrystallization (petroleum ether : ethyl acetate = 3:1); mp: 172 – 175 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41 (d, *J* = 8.5 Hz, 2H), 7.33 (d, *J* = 8.5 Hz, 2H), 7.26 – 7.18 (m, 5H), 7.13 (d, *J* = 8.5 Hz, 2H), 7.08 (d, *J* = 8.5 Hz, 2H), 4.36 (s, 2H), 3.86 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.45, 157.82, 150.14, 138.99, 134.31, 133.24, 132.46, 131.70, 130.96, 129.71, 129.57, 128.09, 127.87, 125.91, 124.05, 121.44, 117.15, 115.21, 55.39; HRMS (EI): m/z Calcd for $C_{25}H_{18}ClN_3O$ $(M)^+$ 411.1138; Found: m/z 411.1140.

4-amino-5-(4-chlorophenyl)-3, 6-bis(4-methoxyphenyl)picolinonitrile(4e):



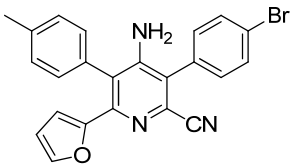
Yellow-brown solid (73%); Purified by recrystallization (petroleum ether : ethyl acetate = 3:1); mp: 139 – 141 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41 (d, *J* = 8.5 Hz, 2H), 7.36 (d, *J* = 8.5 Hz, 2H), 7.18 (d, *J* = 8.5 Hz, 2H), 7.14 (d, *J* = 8.5 Hz, 2H), 7.08 (d, *J* = 8.5 Hz, 2H), 6.72 (d, *J* = 9.0 Hz, 2H), 4.30 (s, 2H), 3.87 (s, 3H), 3.76 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.42, 159.47, 157.35, 150.01, 134.26, 133.56, 132.46, 131.69, 131.38, 131.03, 130.97, 129.81, 125.56, 124.15, 121.04, 117.20, 115.18, 113.30, 55.37, 55.21; HRMS (EI): m/z Calcd for $C_{26}H_{20}ClN_3O_2$ $(M)^+$ 411.1138; Found: m/z 411.1140.

4-amino-3-(2-bromophenyl)-5, 6-bis(4-chlorophenyl)picolinonitrile(4f):



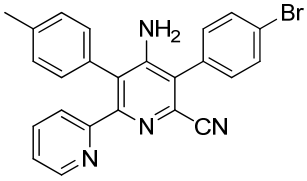
Yellow-brown solid (78%); Purified by recrystallization (petroleum ether : ethyl acetate = 3:1); mp: 194 – 196 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.80 (d, *J* = 8.0 Hz, 1H), 7.53 (t, *J* = 7.5 Hz, 1H), 7.48 – 7.34 (m, 4H), 7.25 – 7.15 (m, 5H), 7.12 (d, *J* = 8.0 Hz, 1H), 4.22 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.92, 149.75, 136.97, 134.71, 134.36, 133.93, 133.10, 132.78, 132.54, 131.84, 131.66, 131.52, 131.07, 129.95, 128.75, 128.11, 125.31, 124.25, 121.47, 116.23; HRMS (EI): m/z Calcd for $C_{24}H_{14}BrCl_2N_3$ $(M)^+$ 492.9748; Found: m/z 492.9746.

4-amino-3-(4-bromophenyl)-6-(furan-2-yl)-5-(p-tolyl)picolinonitrile(4g):



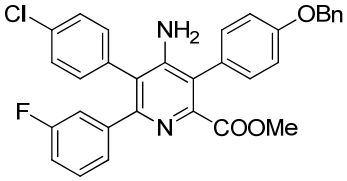
White solid (54%); Purified by chromatography (silica gel ; petroleum ether : ethyl acetate = 6 : 1 to 3:1); mp: 152 – 155 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.68 (d, *J* = 8.0 Hz, 2H), 7.40 (s, 1H), 7.39 – 7.30 (m, 4H), 7.16 (d, *J* = 8.0 Hz, 2H), 6.23 (dd, *J* = 3.5, 1.5 Hz, 1H), 5.68 (d, *J* = 3.5 Hz, 1H), 4.21 (s, 2H), 2.45 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.15, 150.97, 150.19, 147.60, 143.56, 139.10, 132.95, 132.13, 131.41, 131.29, 130.90, 129.28, 124.09, 123.94, 120.98, 116.68, 113.25, 111.36, 21.42; HRMS (EI): m/z Calcd for $C_{23}H_{16}BrN_3O$ $(M)^+$ 429.0477; Found: m/z 429.0476.

4-amino-5-(4-bromophenyl)-3-(p-tolyl)-[2, 2'-bipyridine]-6-carbonitrile(4h):



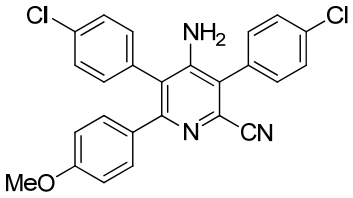
Yellow solid (75%); Purified by recrystallization (petroleum ether : ethyl acetate = 3:1); mp: 162 – 164 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.45 (t, *J* = 8.0 Hz ,1H), 7.68 (d, *J* = 8.0 Hz, 2H), 7.50 (d, *J* = 7.5 Hz, 1H), 7.36 (d, *J* = 7.0 Hz, 2H), 7.24 (m, 1H), 7.11 (m, 3H), 7.04 (t, *J* = 5.7 Hz, 2H), 4.40 (s, 2H), 2.30 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.14, 156.99 , 150.22, 149.01, 138.15, 135.79, 132.99, 131.81, 131.41, 131.35, 130.74, 129.95, 129.73, 125.25, 124.52, 123.97, 123.62, 122.59, 116.72, 21.25; HRMS (EI): m/z Calcd for $C_{24}H_{17}BrN_4$ $(M)^+$ 440.0637; Found: m/z 440.0639.

Methyl4-amino-3-(4-(benzyloxy)phenyl)-5-(4-chlorophenyl)-6-(3-fluorophenyl)picolinate(4i):



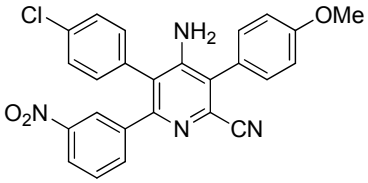
Yellow-brown solid (69%); Purified by recrystallization chromatography (silica gel ; petroleum ether : ethyl acetate = 6 : 1 to 3:1); mp: 167 – 170 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.46 (d, *J* = 7.5Hz, 2H), 7.41 (t, *J* = 7.5 Hz, 2H), 7.38 – 7.28 (m, 5H), 7.18 – 7.05 (m, 6H), 7.00 (d, *J* = 7.6 Hz, 1H), 6.89 (dd, *J* = 11.5, 5.0 Hz, 1H), 5.11 (s, 2H), 4.23 (s, 2H), 3.66 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.38, 163.30, 161.35, 158.86, 154.96, 150.41, 148.73, 142.04, 136.69, 134.16, 133.65, 131.83, 130.68, 129.66, 129.23, 128.67, 128.15, 126.22, 125.54, 120.52, 120.33, 116.92, 116.74, 115.63, 114.74, 114.57, 70.06, 52.37; HRMS (EI): m/z Calcd for $C_{32}H_{24}ClFN_2O_3$ $(M)^+$ 538.1459; Found: m/z 538.1464.

4-amino-3, 5-bis(4-chlorophenyl)-6-(4-methoxyphenyl)picolinonitrile(4j):



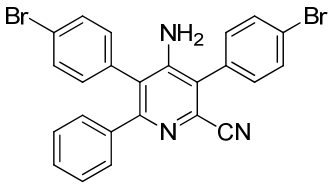
Yellow solid (50%); Purified by chromatography (silica gel ; petroleum ether : ethyl acetate = 6 : 1 to 3:1); mp: 219 – 221 ^{o}C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.52 (d, J = 8.5 Hz, 2H), 7.42 (d, J = 8.5 Hz, 2H), 7.36 (d, J = 8.5 Hz, 2H), 7.15 (m, 4H), 6.72 (d, J = 7.0 Hz, 2H), 4.31 (s, 2H), 3.76 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.56, 157.77, 149.76, 135.73, 134.41, 133.24, 132.15, 131.66, 131.19, 131.04, 130.78, 130.09, 129.88, 128.15, 124.40, 121.31, 116.84, 113.33, 55.23; HRMS (EI): m/z Calcd for $C_{25}H_{17}Cl_2N_3O$ $(M)^+$ 445.0749; Found: m/z 445.0747.

4-amino-3-(4-chlorophenyl)-5-(4-methoxyphenyl)-6-(3-nitrophenyl)picolinonitril e(4k):



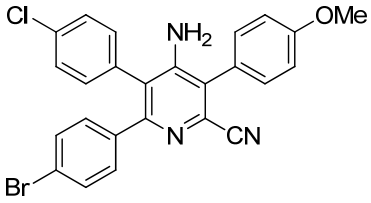
Yellow solid (87%); Purified by recrystallization (petroleum ether : ethyl acetate = 3:1); mp: 219 – 220 ^{o}C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.15 (s, 1H), 8.08 (d, J = 8.0 Hz, 1H), 7.57 (d, J = 7.5 Hz, 1H), 7.40 (m, 5H), 7.15 (d, J = 8.0 Hz, 2H), 7.09 (d, J = 8.5 Hz, 2H), 4.45 (s, 2H), 3.87 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.64, 155.04, 150.56, 147.77, 140.61, 135.46, 135.07, 133.26, 132.28, 131.55, 130.86, 130.22, 128.93, 126.55, 124.75, 123.54, 122.98, 121.60, 116.82, 115.32, 55.40; HRMS (EI): m/z Calcd for $C_{25}H_{17}ClN_4O_3$ $(M)^+$ 456.0989; Found: m/z 456.0993.

4-amino-3, 5-bis(4-bromophenyl)-6-phenylpicolinonitrile(4l):



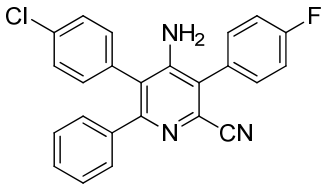
Yellow-brown solid (80%); Purified by recrystallization (petroleum ether : ethyl acetate = 3:1); mp: 221 – 222 ^{o}C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.70 (d, J = 8.5 Hz, 2H), 7.49 (d, J = 8.5 Hz, 2H), 7.37 (d, J = 8.5 Hz, 2H), 7.24 – 7.19 (m, 5H), 7.06 (d, J = 8.5 Hz, 2H), 4.34 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.24 , 149.65, 138.72, 133.40, 133.06, 132.74, 132.20, 131.91, 131.40, 131.16, 129.54, 128.25, 127.93, 124.76, 124.09, 122.67, 121.70, 116.72; HRMS (EI): m/z Calcd for $C_{24}H_{15}Br_2N_3$ $(M)^+$ 502.9633; Found: m/z 502.9630.

4-amino-6-(4-bromophenyl)-3-(4-chlorophenyl)-5-(4-methoxyphenyl)picolinonitr -ile(4m):



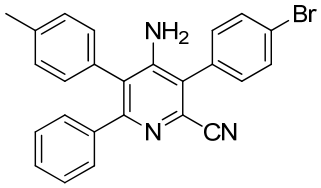
White solid (96%); Purified by recrystallization (petroleum ether : ethyl acetate = 3:1); mp:263 – 265 ^{o}C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40 (d, J = 8.5 Hz, 2H), 7.37 (d, J = 8.5 Hz, 2H), 7.33 (d, J = 8.5 Hz, 2H), 7.24 (d, J = 7.5 Hz, 2H), 7.18 (d, J = 7.5 Hz, 2H), 7.08 (d, J = 8.5 Hz, 2H), 4.36 (s, 2H), 3.87 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.52, 156.48 , 150.25, 137.87, 134.64, 132.90, 132.60, 131.59, 131.25, 131.07, 130.90, 129.96, 126.06, 123.84, 122.66, 121.30, 116.99, 115.25, 55.39; HRMS (EI): m/z Calcd for $C_{25}H_{17}BrClN_3O$ $(M)^+$ 489.0244; Found: m/z 489.0243.

4-amino-5-(4-chlorophenyl)-3-(4-fluorophenyl)-6-phenylpicolinonitrile(4n):



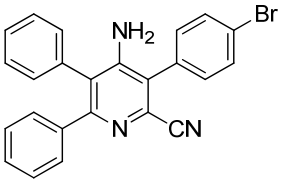
White solid (88%); Purified by recrystallization (petroleum ether : ethyl acetate = 3:1);mp: 273 – 275 ^{o}C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.51 – 7.45 (m, 2H), 7.34 (d, *J* = 8.5 Hz, 2H), 7.29 – 7.19 (m, 7H), 7.16 – 7.10 (m, 2H), 4.32 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.70, 148.22, 140.07, 139.97, 139.18, 138.59, 135.89, 135.61, 133.24, 132.54, 132.45, 131.71, 131.25, 130.72, 130.29, 129.34, 124.98, 124.66, 123.83, 123.67, 116.45; HRMS (EI): m/z Calcd for $C_{24}H_{15}ClFN_3$ $(M)^+$ 399.0939; Found: m/z 399.0933.

4-amino-3-(4-bromophenyl)-6-phenyl-5-(p-tolyl)picolinonitrile(4o):



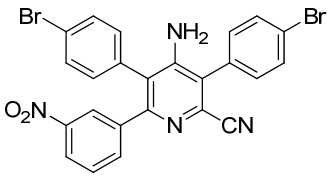
White solid (66%); Purified by chromatography (silica gel ; petroleum ether : ethyl acetate = 6 : 1 to 3:1); mp: 197 – 198 ^{o}C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.70 (d, *J* = 8.5 Hz, 2H), 7.39 (d, *J* = 8.0 Hz, 2H), 7.27 (d, *J* = 7.5 Hz, 2H), 7.20 – 7.14 (m, 5H), 7.05 (d, *J* = 8.0 Hz, 2H), 4.33 (s, 2H), 2.34 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.22, 149.88, 139.14, 138.27, 133.01, 131.20, 130.19, 129.94, 129.75, 129.61, 128.32, 127.99, 127.73, 125.80, 124.55, 123.95, 123.07, 116.92, 21.28; HRMS (EI): m/z Calcd for $C_{25}H_{18}BrN_3$ $(M)^+$ 439.0684; Found: m/z 439.0687.

4-amino-3-(4-bromophenyl)-5, 6-diphenylpicolinonitrile(4p):



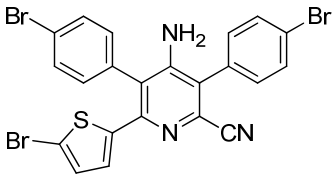
White solid (77%); Purified by chromatography (silica gel ; petroleum ether : ethyl acetate = 6 : 1 to 3:1); mp: 263 – 265 °C; ^{1}H NMR (500 MHz, DMSO) δ 7.79 (d, *J* = 8.5 Hz, 2H), 7.50 (d, *J* = 8.5 Hz, 2H), 7.43 – 7.29 (m, 3H), 7.19 (m, 7H), 5.30 (s, 2H); ^{13}C NMR (125 MHz, DMSO) δ 157.76, 151.26, 139.84, 134.86, 132.84, 132.46, 132.46, 131.51, 131.71, 129.74, 129.65, 128.53, 128.14, 127.94, 124.79, 123.33, 123.11, 117.65; HRMS (EI): m/z Calcd for $C_{24}H_{16}BrN_3$ $(M)^+$ 425.0528; Found: m/z 425.0529.

4-amino-3, 5-bis(4-bromophenyl)-6-(3-nitrophenyl)picolinonitrile(4q):



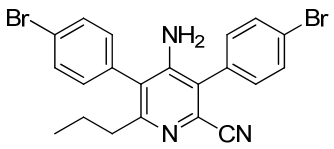
Light yellow solid (91%); Purified by recrystallization (petroleum ether : ethyl acetate = 3:1); mp: 289 – 291 °C; ^{1}H NMR (500 MHz, DMSO) δ 8.20 – 8.13 (m, 1H), 8.10 (s, 1H), 7.87 – 7.83 (d, *J* = 8.5 Hz 2H), 7.63 (m, 3H), 7.57 (t, *J* = 8.0 Hz, 1H), 7.54 – 7.50 (d, *J* = 8.5 Hz ,2H), 7.29 – 7.21 (d, *J* = 8.5 Hz, 2H), 5.75 (s, 2H); ^{13}C NMR (125 MHz, DMSO) δ 154.85, 151.37, 147.16, 140.73, 135.78, 133.15, 132.67, 132.46, 132.33, 132.12, 131.74, 131.39, 129.29, 125.03, 124.04, 122.90, 122.76 121.85, 121.74, 117.00; HRMS (EI): m/z Calcd for $C_{24}H_{14}Br_2N_4O_2$ $(M)^+$ 547.9484; Found: m/z 547.9487.

4-amino-3, 5-bis(4-bromophenyl)-6-(5-bromothiophen-2-yl)picolinonitrile(4r):



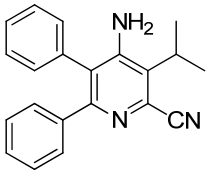
White solid (61%); Purified by chromatography (silica gel ; petroleum ether : ethyl acetate = 6 : 1 to 3:1); mp: 249 – 250 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.73 (d, *J* = 8.5 Hz, 2H), 7.70 (d, *J* = 8.5 Hz, 2H), 7.34 (d, *J* = 8.5 Hz, 2H), 7.20 (d, *J* = 8.5 Hz, 2H), 6.78 (d, *J* = 4.0 Hz, 1H), 6.19 (d, *J* = 4.0 Hz, 1H), 4.14 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.36 150.04, 144.34, 133.92, 133.11, 132.70, 132.21, 131.58, 131.29, 130.83, 130.49, 128.91, 128.10, 126.82, 124.93, 124.03, 119.07, 116.95; HRMS (EI): m/z Calcd for $C_{22}H_{12}Br_3N_3S$ $(M)^+$ 586.8032; Found: m/z 586.8035.

4-amino-3, 5-bis(4-bromophenyl)-6-propylpicolinonitrile(4s):



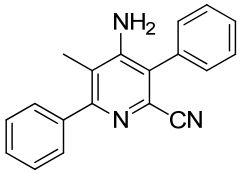
Light yellow solid (43%); Purified by chromatography (silica gel ; petroleum ether : ethyl acetate = 6 : 1 to 3:1); mp: 198 – 201 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.68 (m, 4H), 7.32 (d, *J* = 8.5 Hz, 2H), 7.15 (d, *J* = 8.5 Hz, 2H), 4.01 (s, 2H), 2.45 – 2.39 (m, 2H), 1.65 – 1.58 (m, 2H), 0.83 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.09, 149.12, 133.57, 133.28, 133.21, 132.24, 131.7, 131.57, 131.54, 124.16, 124.07, 123.28, 122.67, 117.18, 29.93, 22.78, 14,24; HRMS (EI): m/z Calcd for $C_{21}H_{17}Br_2N_3$ $(M)^+$ 468.9789; Found: m/z 468.9791.

4-amino-3-isopropyl-5, 6-diphenylpicolinonitrile (4t):



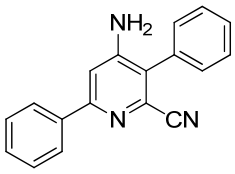
White solid (95%); Purified by recrystallization (petroleum ether : ethyl acetate = 3:1); mp: 208 – 210 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37-7.31 (m, 3H), 7.23 – 7.17 (m, 2H), 7.16 – 7.10 (m, 5H), 4.45 (s, 2H), 3.57 (m, 1H), 1.51 (d, J = 7.0 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.77, 149.89, 139.20, 134.70, 131.67, 130.37, 129.51, 129.36, 129.00, 128.26, 127.74, 127.63, 123.85, 117.69, 29.24, 20.00; HRMS (EI): m/z Calcd for $C_{21}H_{19}N_3$ $(M)^+$ 313.1579; Found: m/z 313.1572.

4-amino-5-methyl-3, 6-diphenylpicolinonitrile(4u):



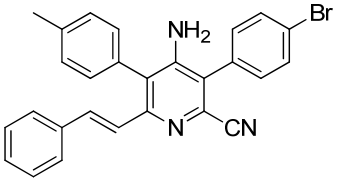
Brown solid (80%); Purified by chromatography (silica gel ; petroleum ether : ethyl acetate = 6 : 1 to 3:1); mp: 158 – 160 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.58 – 7.55 (m, 2H), 7.52 – 45 (m, 8H), 4.38 (s, 2H), 2.18 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.30, 150.28, 139.61, 132.59, 130.44, 129.69, 129.43, 129.13, 128.87, 128.41, 128.30, 125.52, 117.28, 117.17, 14.42; HRMS (EI): m/z Calcd for $C_{19}H_{15}N_3$ $(M)^+$ 285.1266; Found: m/z 285.1264.

4-amino-3, 6-diphenylpicolinonitrile(4v):



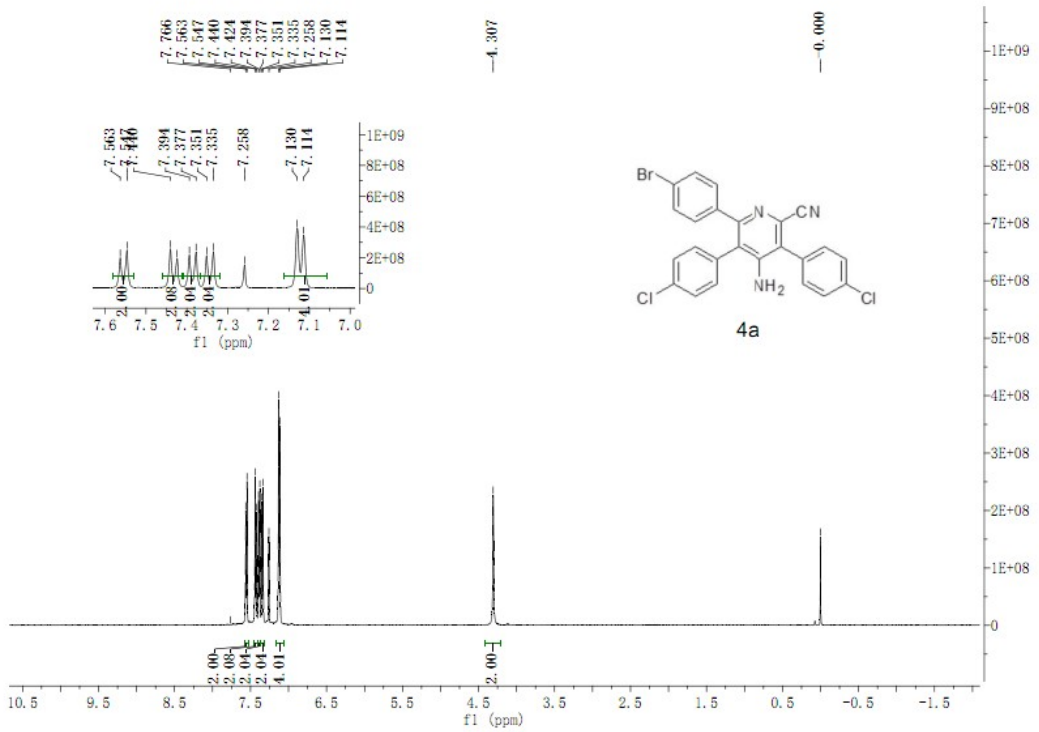
Yellow solid (50%); Purified by chromatography (silica gel ; petroleum ether : ethyl acetate = 6 : 1 to 3:1); mp: 85 – 88 ^{o}C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.98 (d, *J* = 7.0 Hz, 2H), 7.56 (t, *J* = 7.5 Hz, 2H), 7.50 – 7.45 (m, 6H), 7.18 (s, 1H), 4.42 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.13, 151.80, 137.91, 133.56, 132.02, 129.63, 129.48, 128.79, 126.90, 126.12, 117.16, 107.99; HRMS (EI): m/z Calcd for $C_{18}H_{13}N_3$ $(M)^+$ 271.1109; Found: m/z 271.1111.

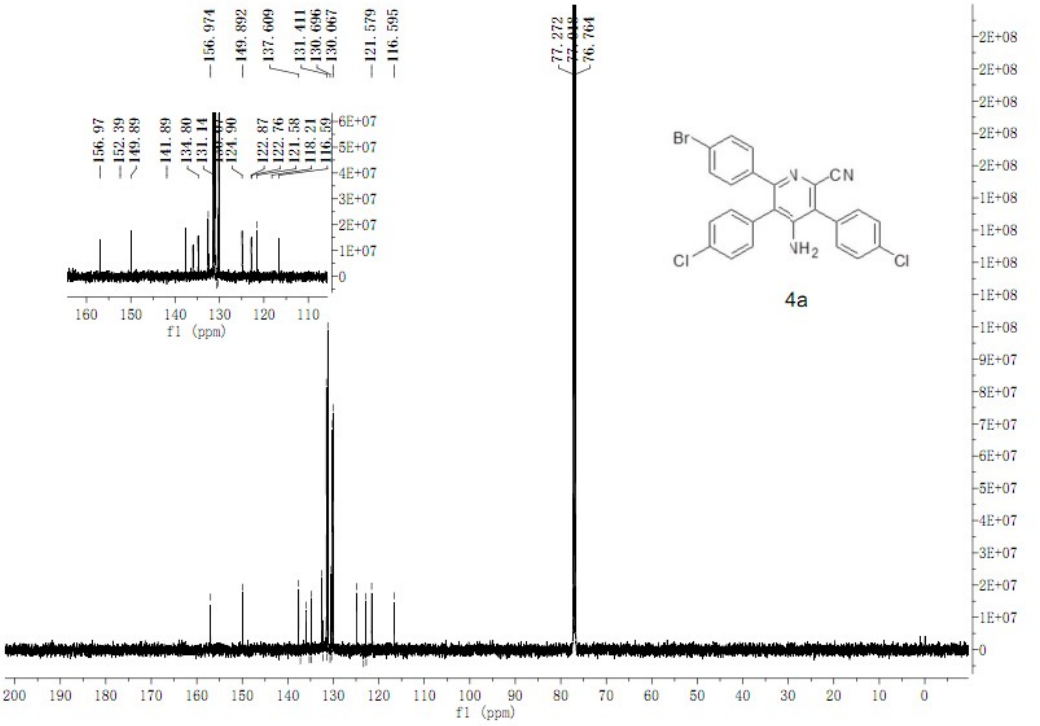
(E)-4-amino-3-(4-bromophenyl)-6-styryl-5-(p-tolyl)picolinonitrile(4w):

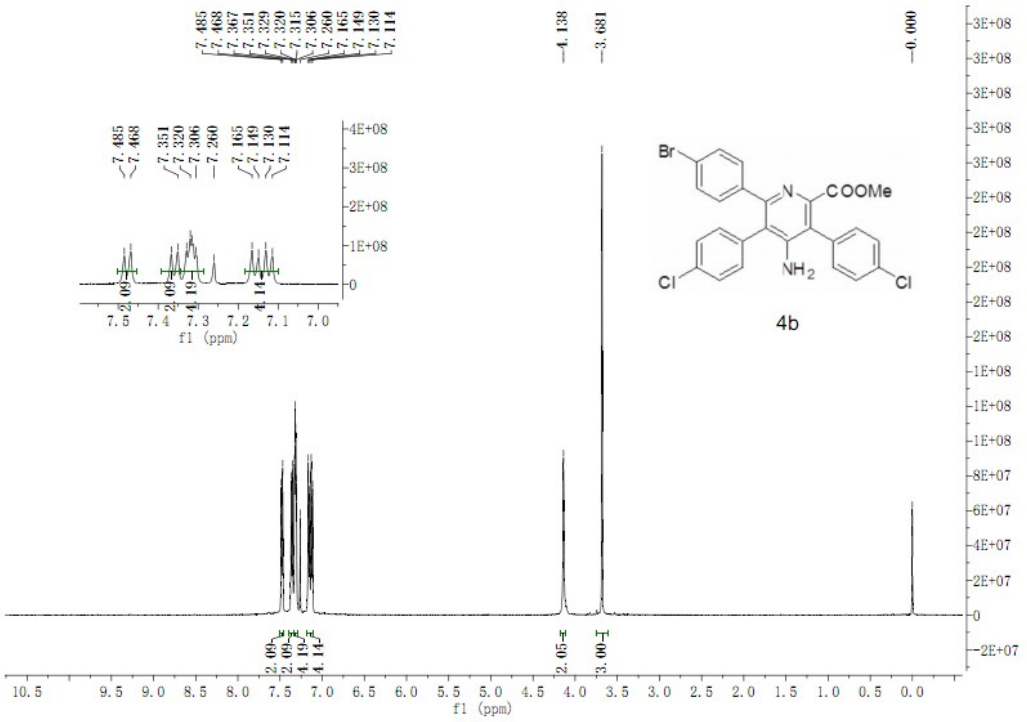


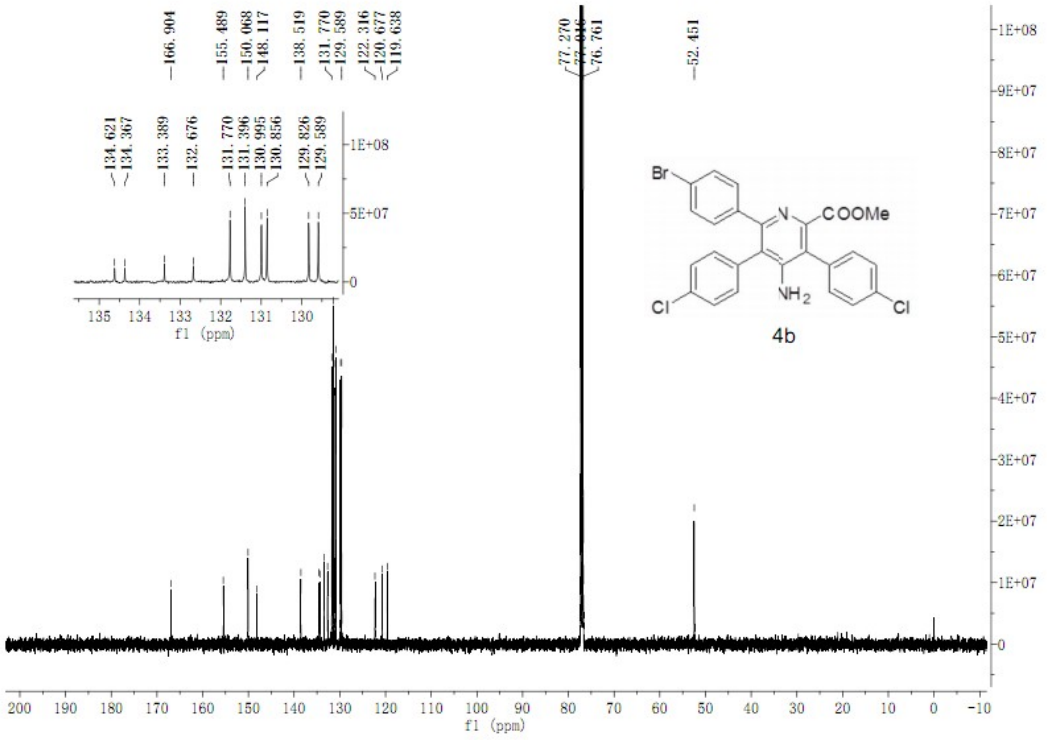
Light yellow solid (57%); Purified by chromatography (silica gel ; petroleum ether : ethyl acetate = 6 : 1 to 3:1); mp: 200 – 202 ^{o}C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.83 (d, *J* = 15.5 Hz, 1H), 7.69 – 7.68 (m, 2H), 7.38 – 7.35 (m, 6H), 7.29 (t, *J* = 7.5 Hz, 2H), 7.24 – 7.20 (m, 3H), 6.73 (d, *J* = 15.5 Hz, 1H), 4.16 (s, 2H), 2.47 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.44, 148.57, 137.81, 135.56, 134.16, 131.91, 130.98, 130.59, 130.45, 129.47, 129.43, 128.78, 127.56, 127.45, 126.37, 123.06, 122.79, 122.70, 122.14, 116.13, 20.38; HRMS (EI): m/z Calcd for $C_{27}H_{20}BrN_3$ $(M)^+$ 465.0841; Found: m/z 465.0839.

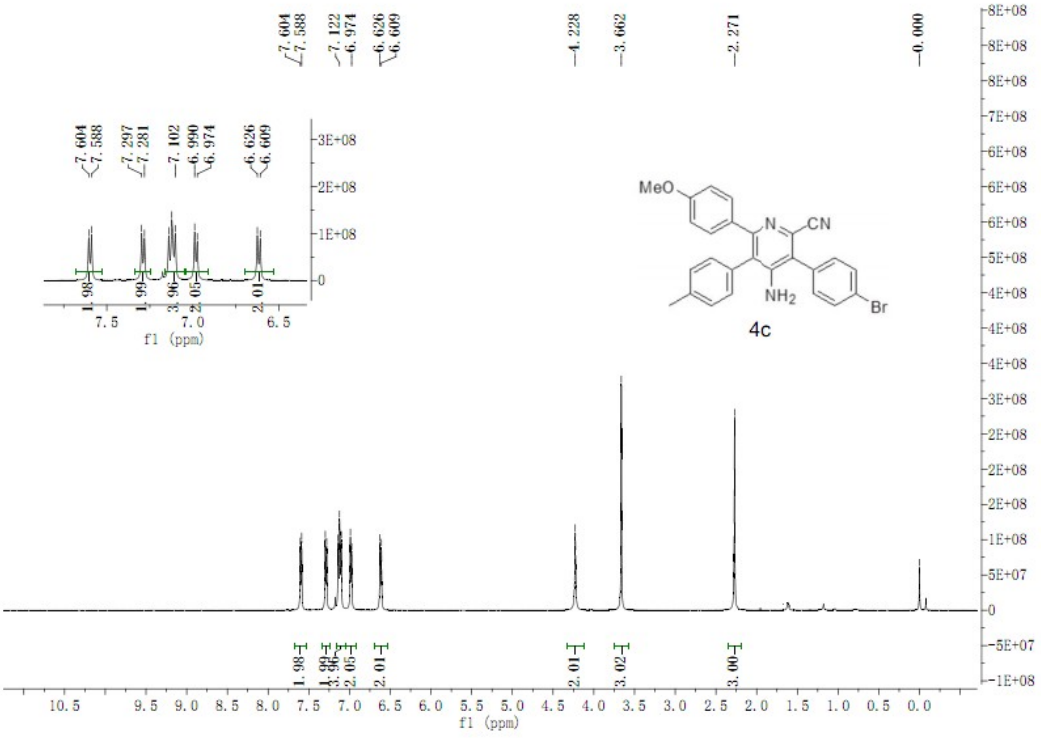
4. ^{1}H NMR and ^{13}C NMR Spectra:

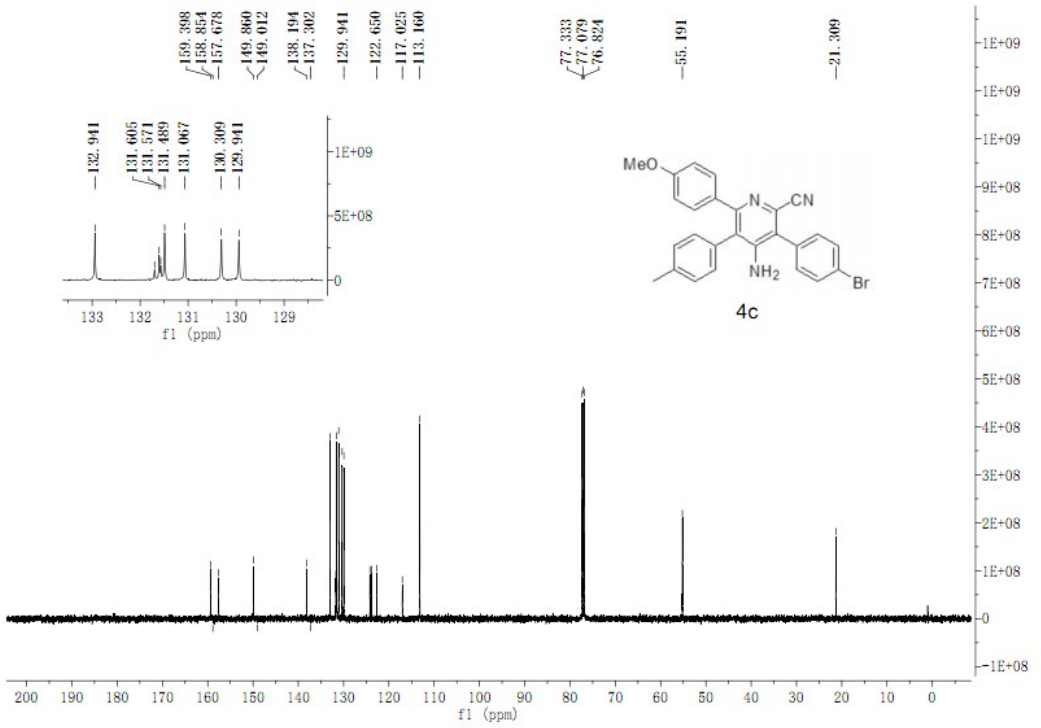


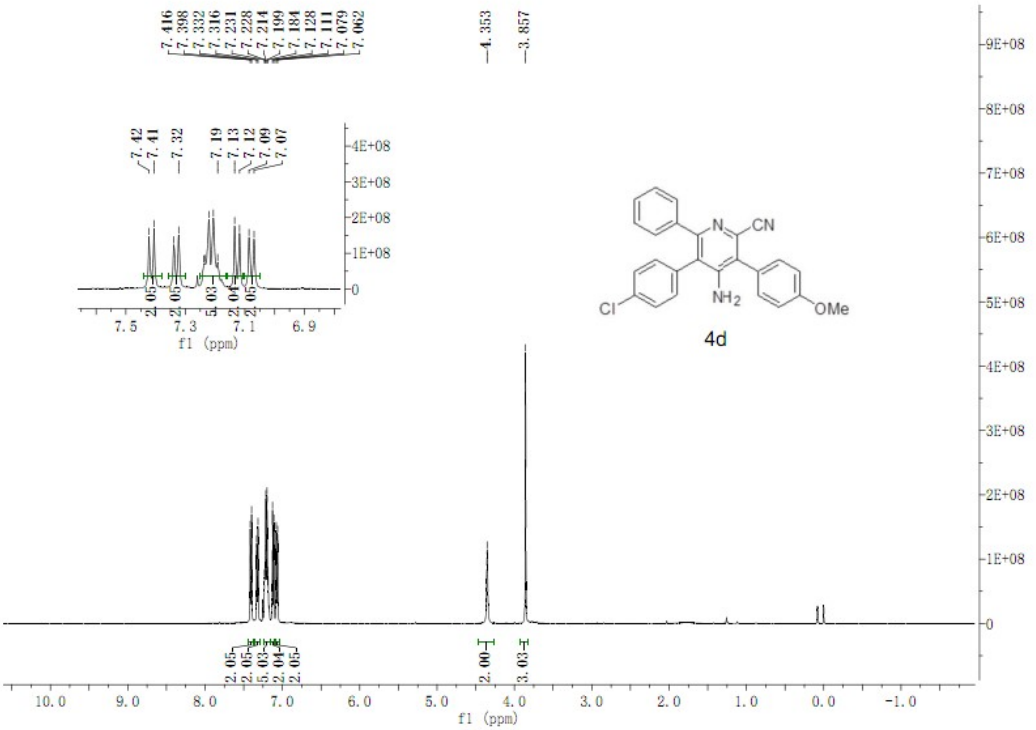


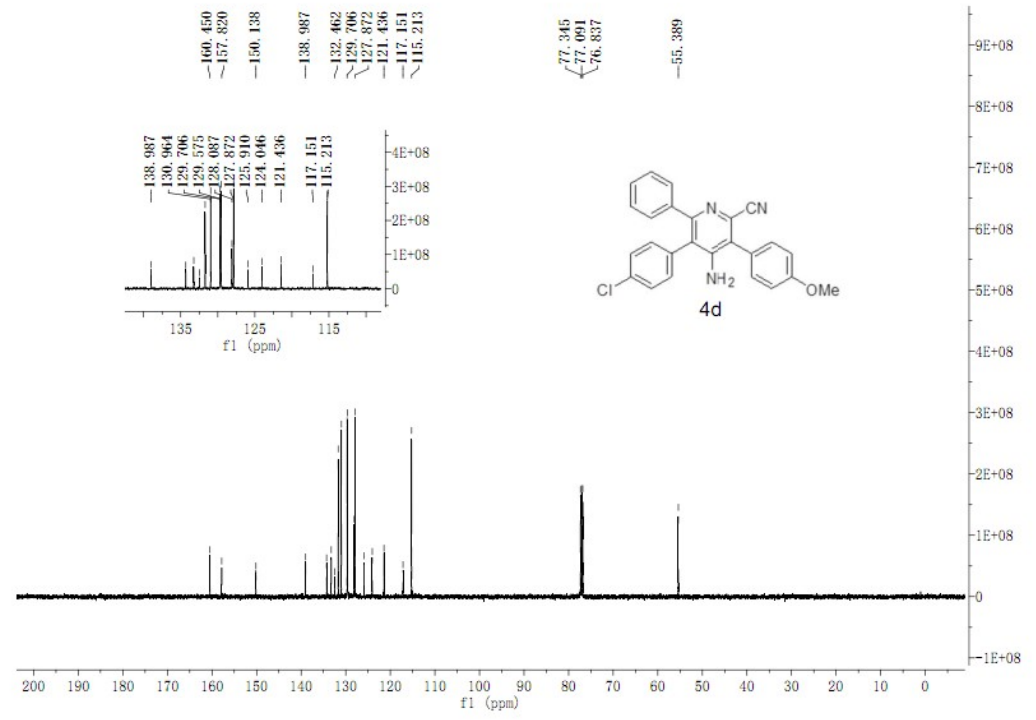

7.485
7.468
7.367
7.351
7.329
7.320
7.315
7.306
7.260
7.165
7.149
7.130
7.114
4.138
3.681
0.000
Br
N
COOMe
NH2
Cl
Cl
4b
f1 (ppm)

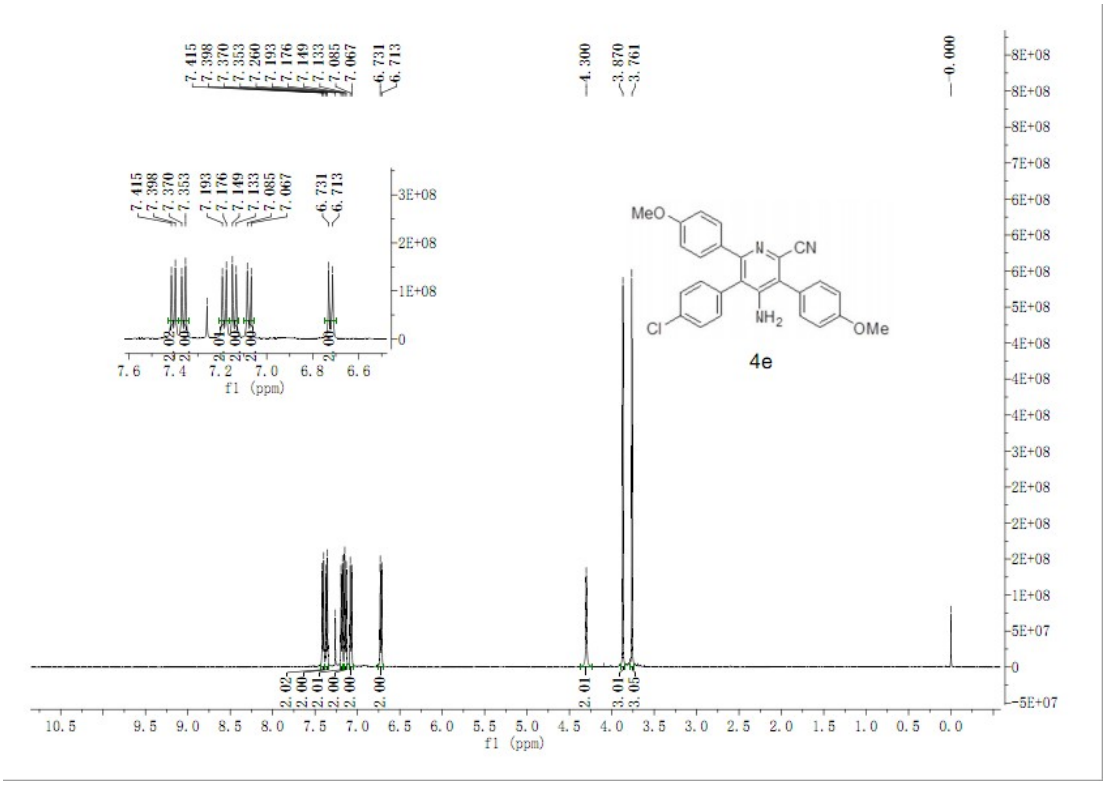

166.904
155.489
150.068
148.117
138.519
131.770
129.589
122.316
120.677
119.638
77.270
76.761
52.451
134.621
134.367
133.389
132.676
131.770
131.396
130.995
130.856
129.826
129.589
Br
N
COOMe
NH2
Cl
Cl
4b
f1 (ppm)

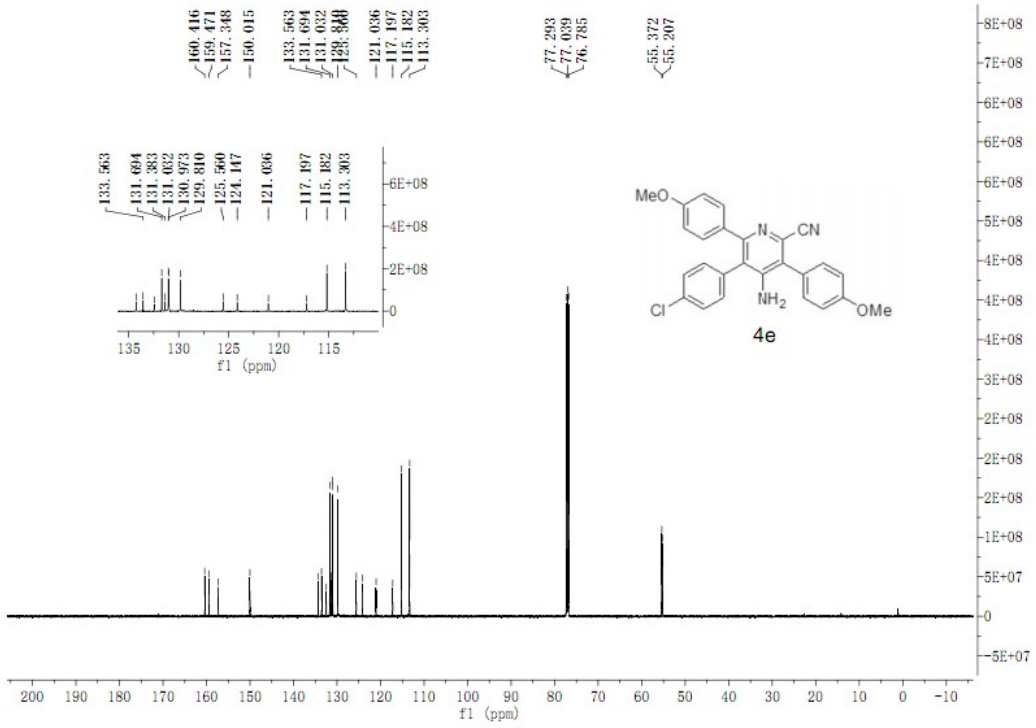

7.604
7.588
7.122
6.974
6.626
6.609
4.228
3.662
2.271
0.000
MeO
CN
NH2
Br
4c
f1 (ppm)

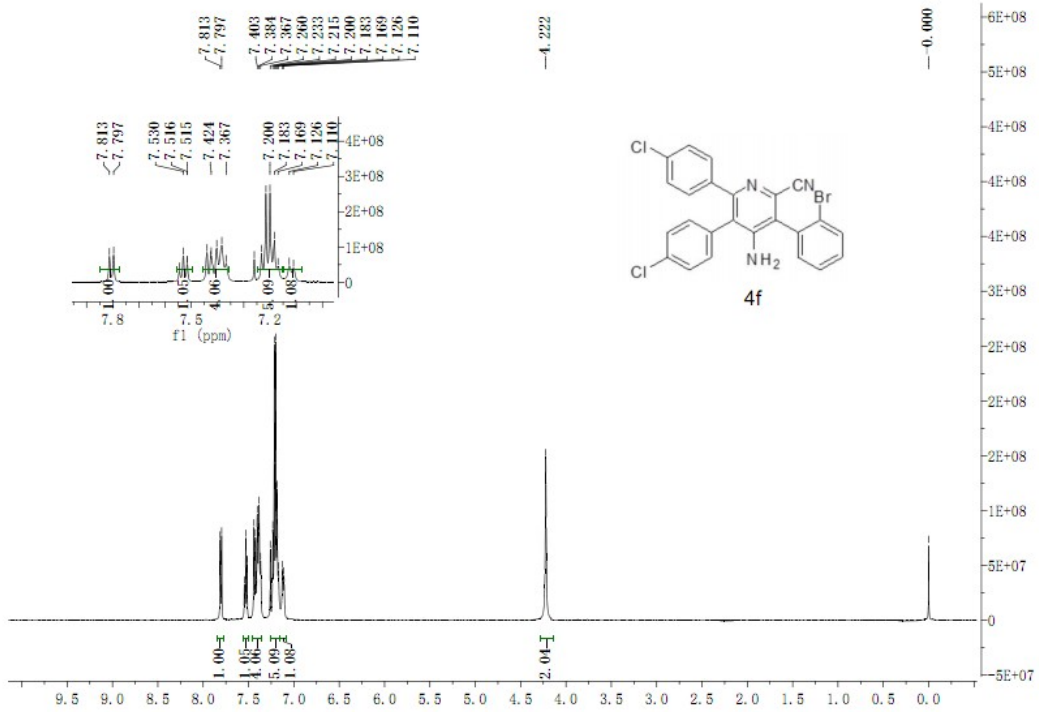

159.398
158.854
157.678
149.860
149.012
138.194
137.302
129.941
122.650
117.025
113.160
77.333
77.079
76.824
55.191
21.309
MeO
CN
NH2
Br
4c
f1 (ppm)

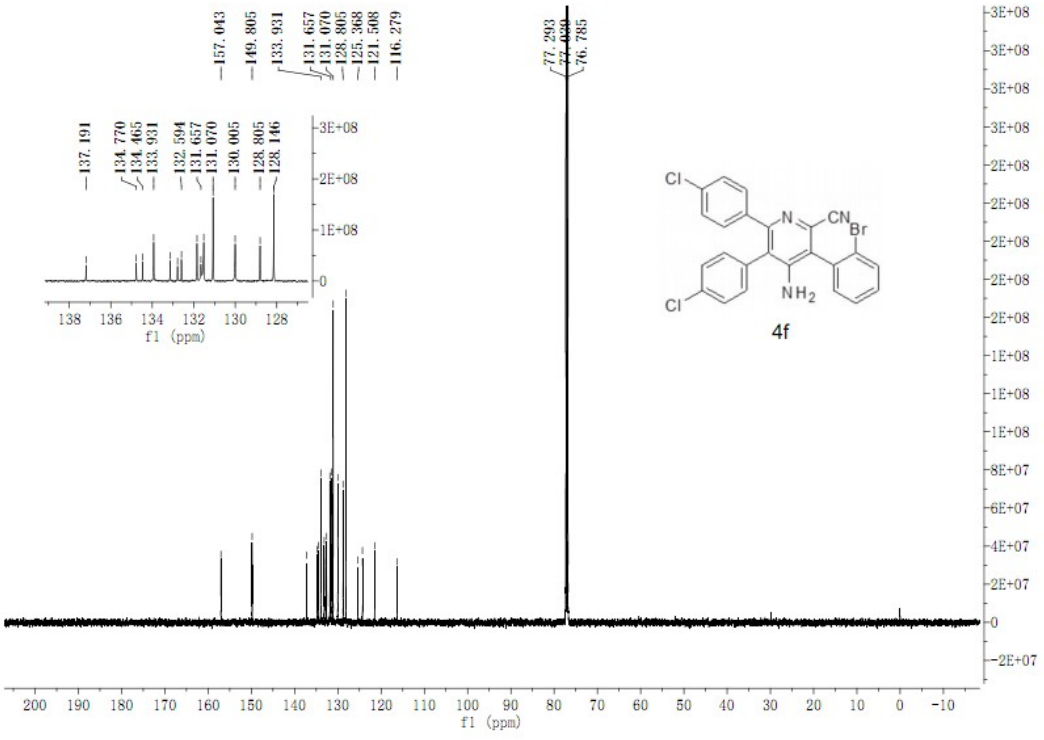

7.416
7.398
7.332
7.316
7.231
7.228
7.214
7.199
7.184
7.128
7.111
7.079
7.062
4.353
3.857
7.42
7.41
7.32
7.19
7.13
7.12
7.09
7.07
CN
NH2
Cl
OMe
4d
f1 (ppm)

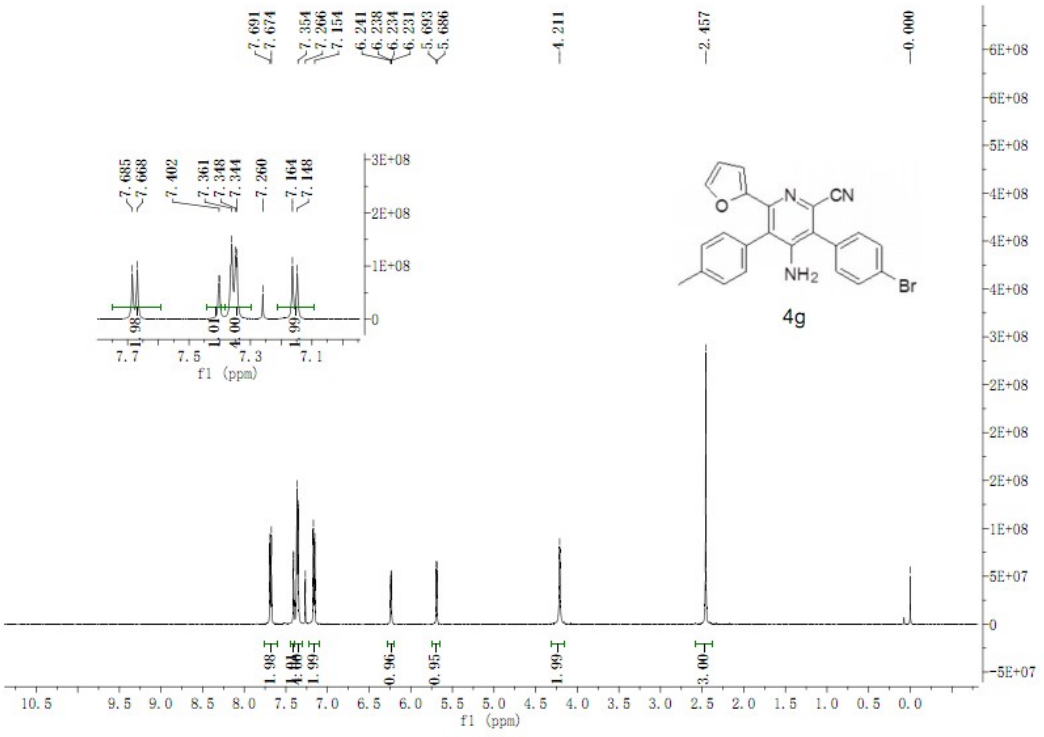

160.450
157.820
150.138
138.987
132.462
129.706
127.872
121.436
117.151
115.213
77.345
77.091
76.837
55.389
CN
NH2
Cl
OMe
4d
f1 (ppm)

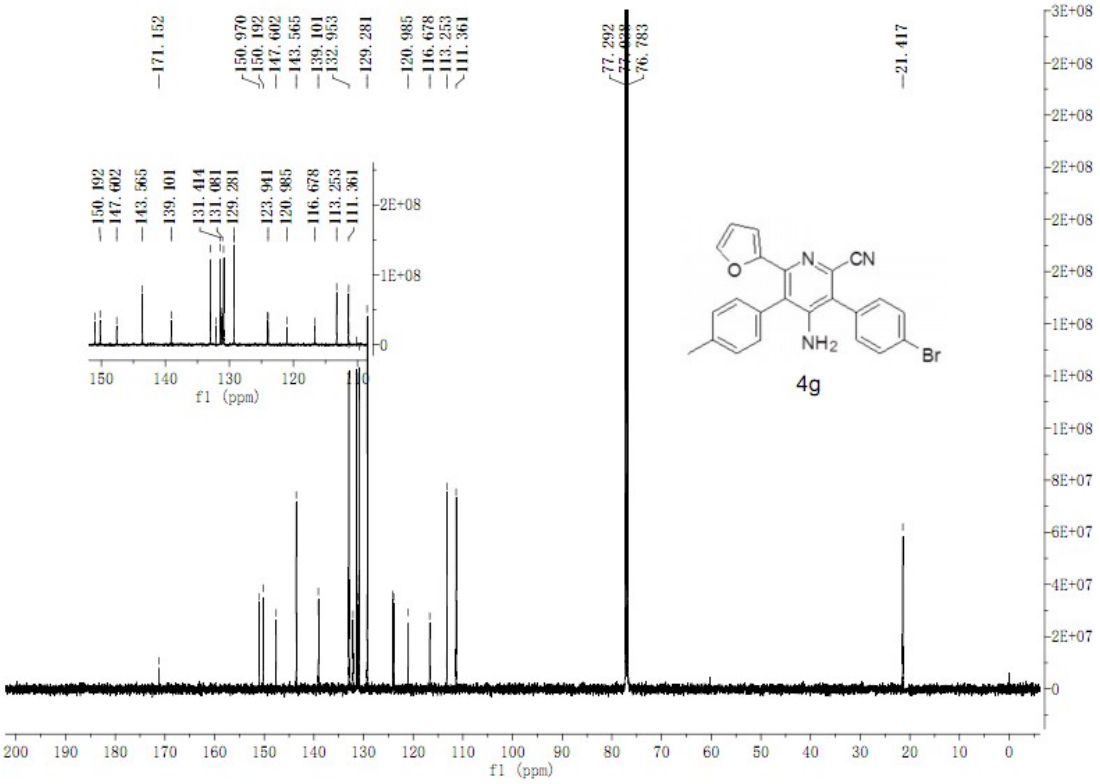

7.415
7.398
7.370
7.353
7.260
7.193
7.176
7.149
7.133
7.085
7.067
6.731
6.713
4.300
3.870
3.761
0.000
MeO
CN
N
NH2
Cl
OMe
4e
f1 (ppm)

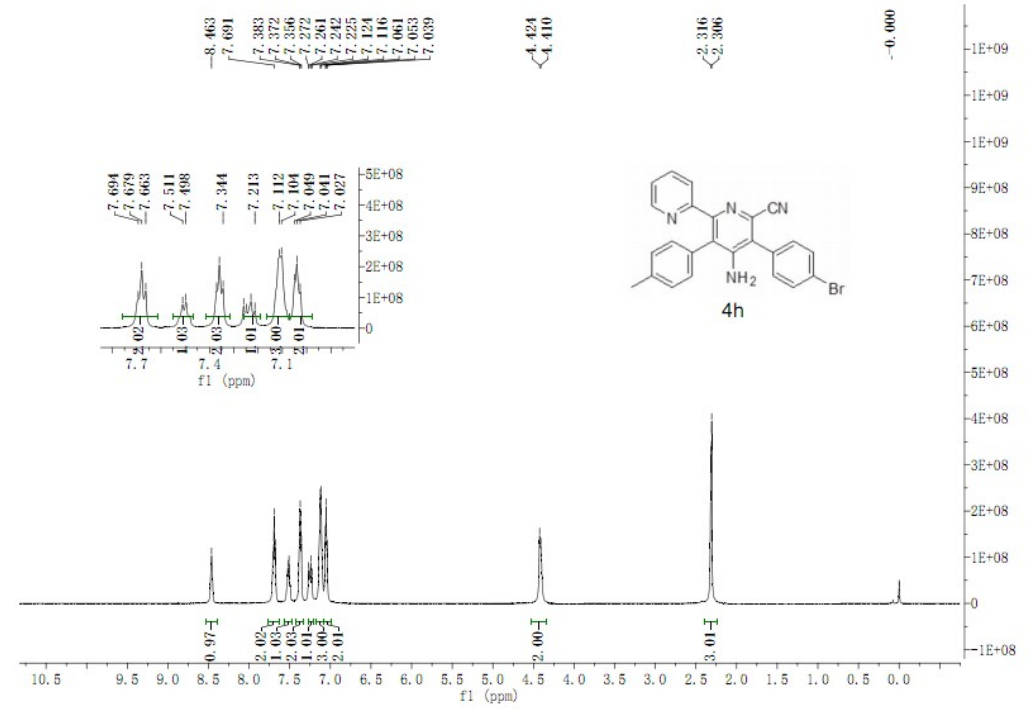

160.416
159.471
157.348
150.015
133.563
131.694
131.032
130.973
129.810
125.560
124.147
121.036
117.197
115.182
113.303
77.293
77.039
76.785
55.372
55.207
MeO
CN
N
NH2
Cl
OMe
4e
f1 (ppm)

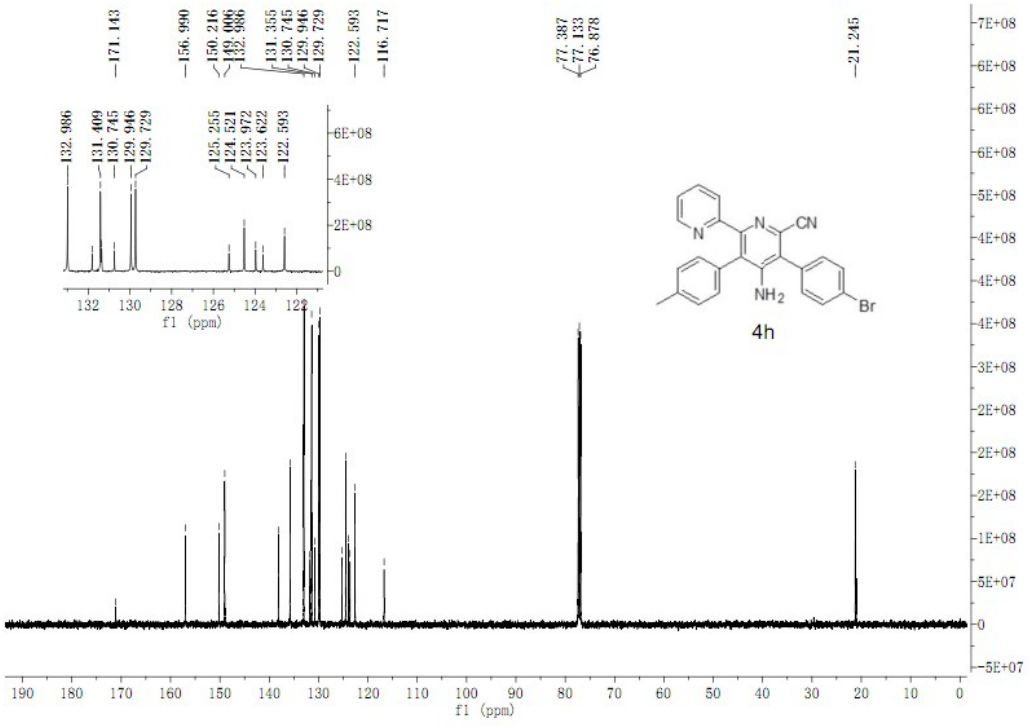

7.813
7.797
7.403
7.384
7.367
7.260
7.233
7.215
7.200
7.183
7.169
7.126
7.110
4.222
0.000
Cl
N
CN
Br
NH2
Cl
4f
f1 (ppm)

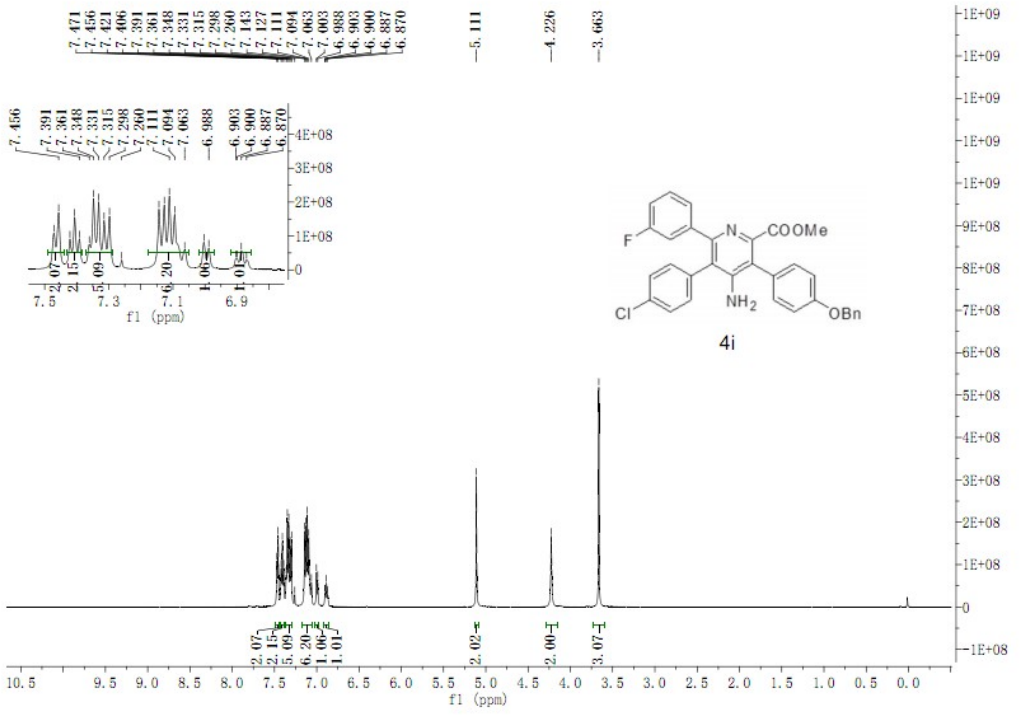

157.043
149.805
133.931
131.657
131.070
128.805
125.368
121.508
116.279
77.293
77.039
76.785
137.191
134.770
134.465
133.931
132.594
131.657
131.070
130.005
128.805
128.146
Cl
N
CN
Br
NH2
Cl
4f
f1 (ppm)

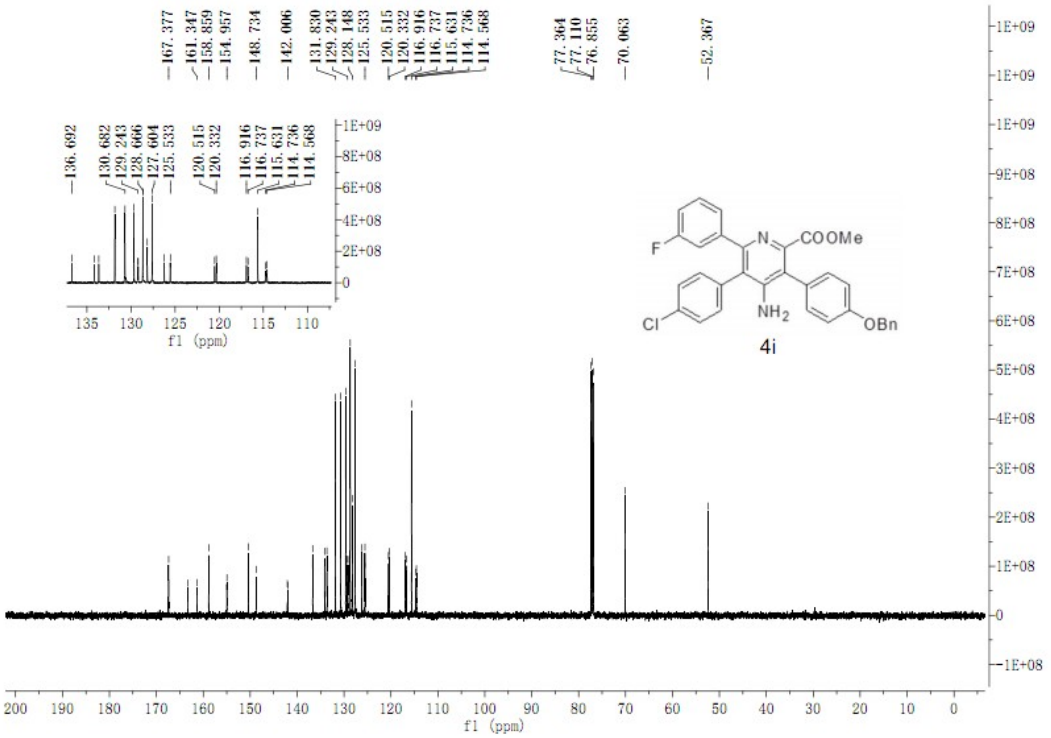

7.691
7.674
7.354
7.266
7.154
6.241
6.238
6.234
6.231
5.693
5.686
4.211
2.457
0.000
7.685
7.668
7.402
7.361
7.348
7.344
7.260
7.164
7.148
CN
NH2
Br
4g
f1 (ppm)

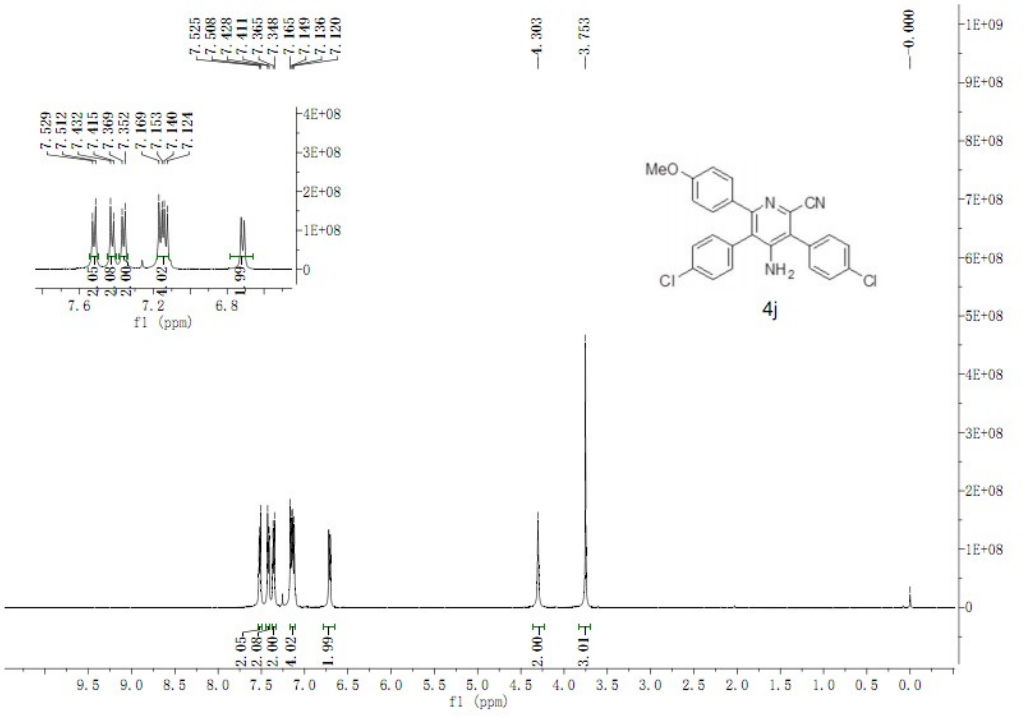

171.152
150.970
150.192
147.602
143.565
139.101
132.953
129.281
120.985
116.678
113.253
111.361
77.292
76.783
21.417
CN
NH2
Br
4g
f1 (ppm)

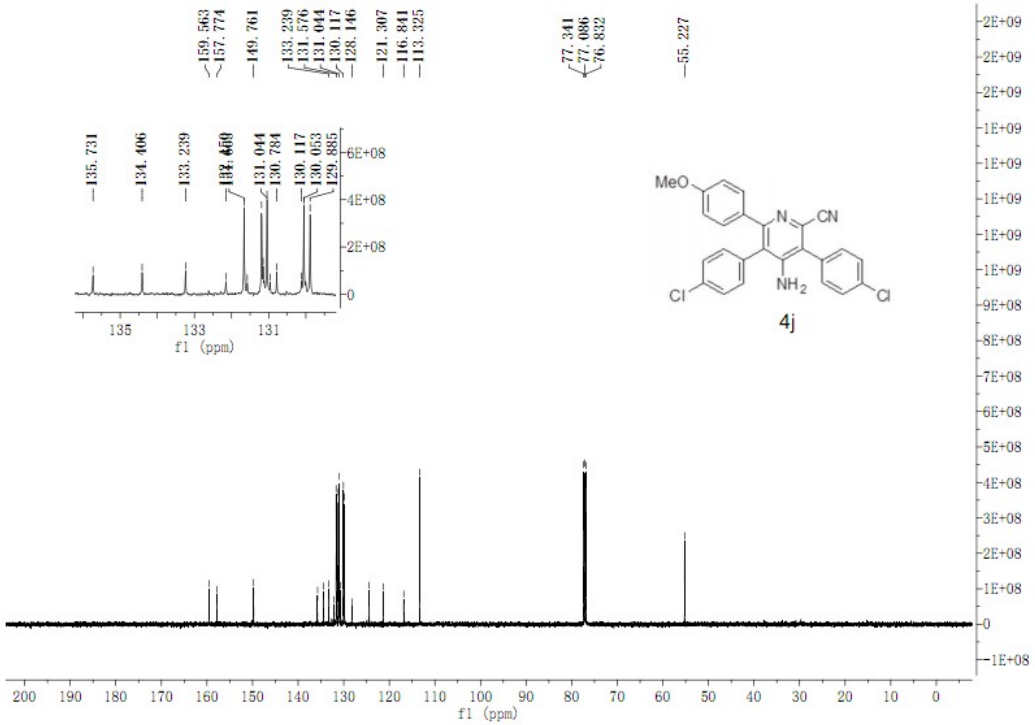

8.463
7.691
7.383
7.372
7.356
7.272
7.261
7.242
7.225
7.124
7.116
7.061
7.053
7.039
4.424
4.410
2.316
2.306
0.000
7.694
7.679
7.663
7.511
7.498
7.344
7.213
7.112
7.104
7.049
7.041
7.027
f1 (ppm)
CN
N
NH2
Br
4h
0.97
2.02
1.03
2.03
1.01
3.00
2.01
2.00
3.01

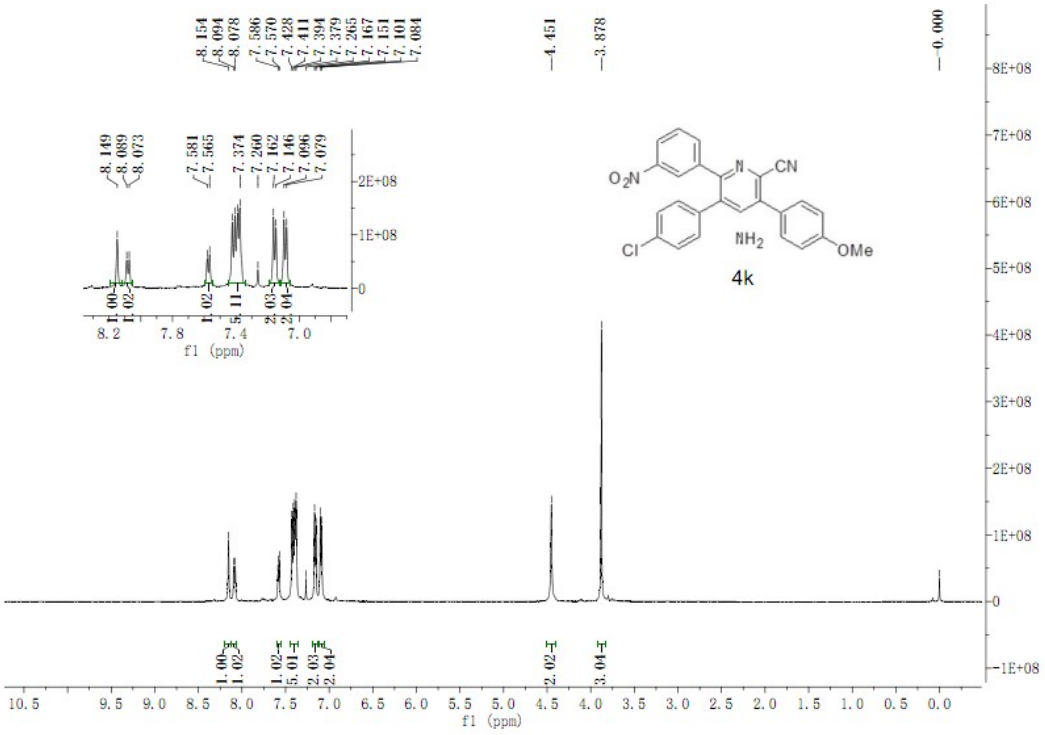

171.143
156.990
150.216
149.006
132.986
131.355
130.745
129.946
129.729
122.593
116.717
77.387
77.133
76.878
21.245
132.986
131.409
130.745
129.946
129.729
125.255
124.521
123.972
123.622
122.593
f1 (ppm)
CN
N
NH2
Br
4h

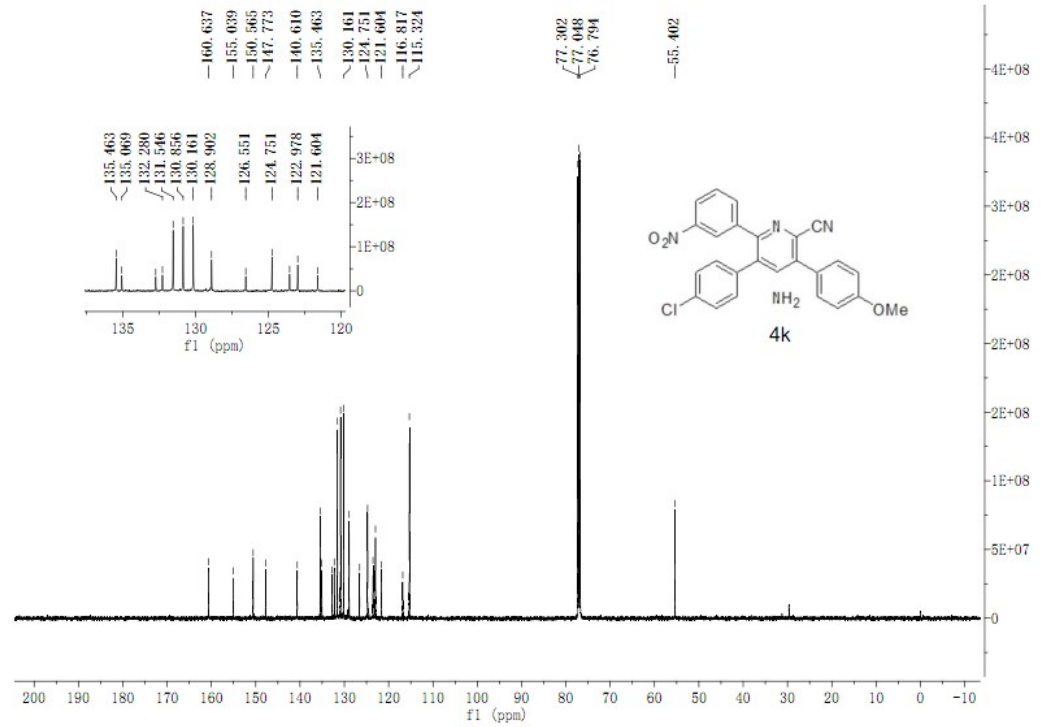

7.471
7.456
7.421
7.406
7.391
7.361
7.348
7.331
7.315
7.298
7.260
7.143
7.127
7.111
7.094
7.063
7.063
6.988
6.903
6.900
6.887
6.870
5.111
4.226
3.663
f1 (ppm)
F
Cl
COOMe
NH2
OBn
4i

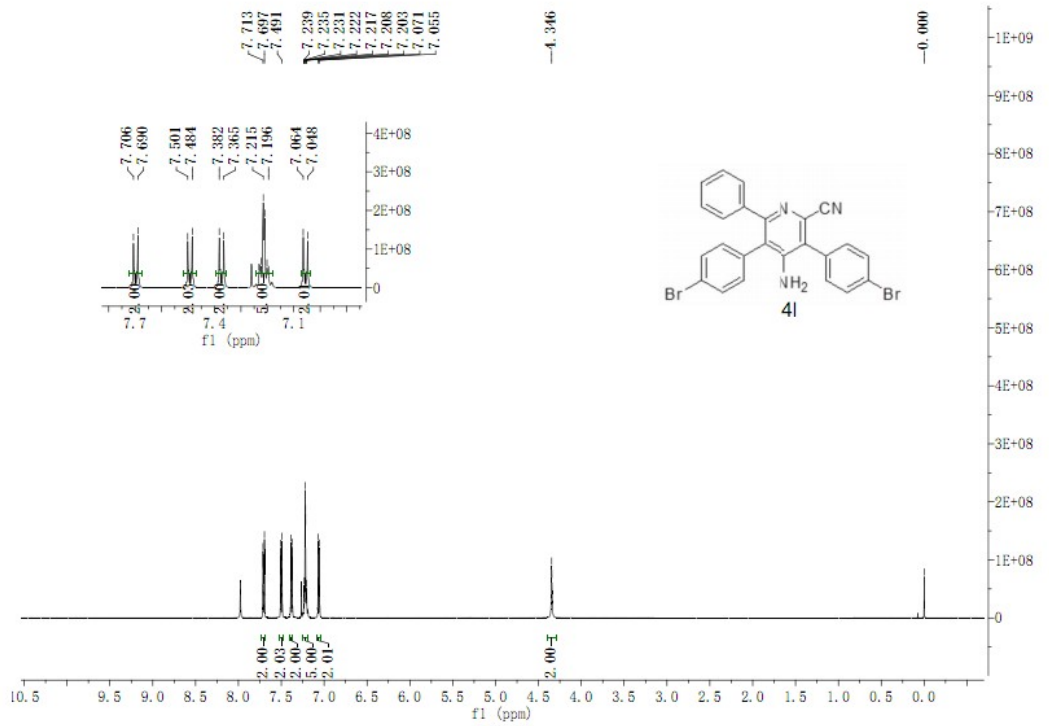

167.377
161.347
158.859
154.957
148.734
142.066
131.830
129.243
128.148
125.533
120.515
120.332
116.916
116.737
115.631
114.736
114.568
77.364
77.110
76.855
70.063
52.367
f1 (ppm)
F
Cl
COOMe
NH2
OBn
4i

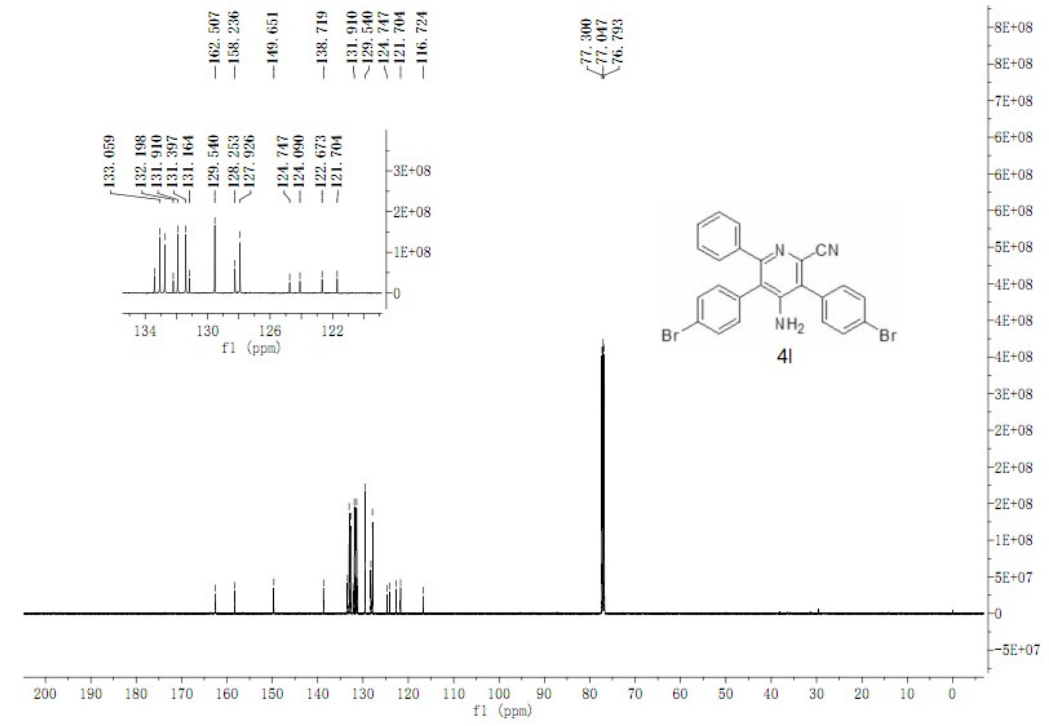

MeO
N
CN
Cl
NH2
Cl
4j
f1 (ppm)

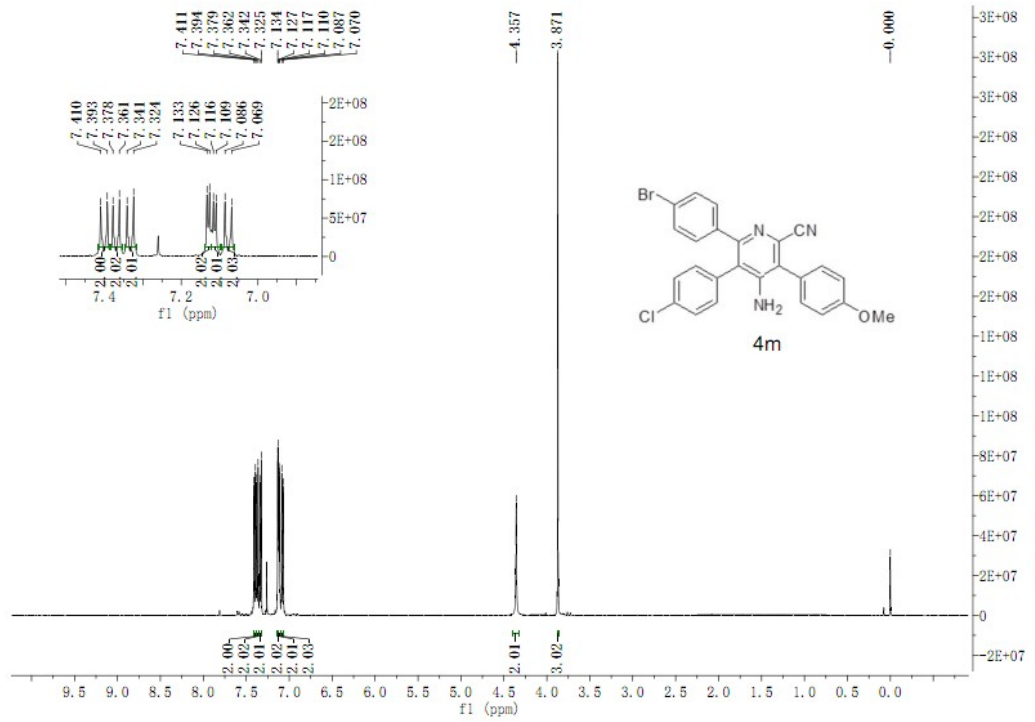

MeO
N
CN
Cl
NH2
Cl
4j
f1 (ppm)

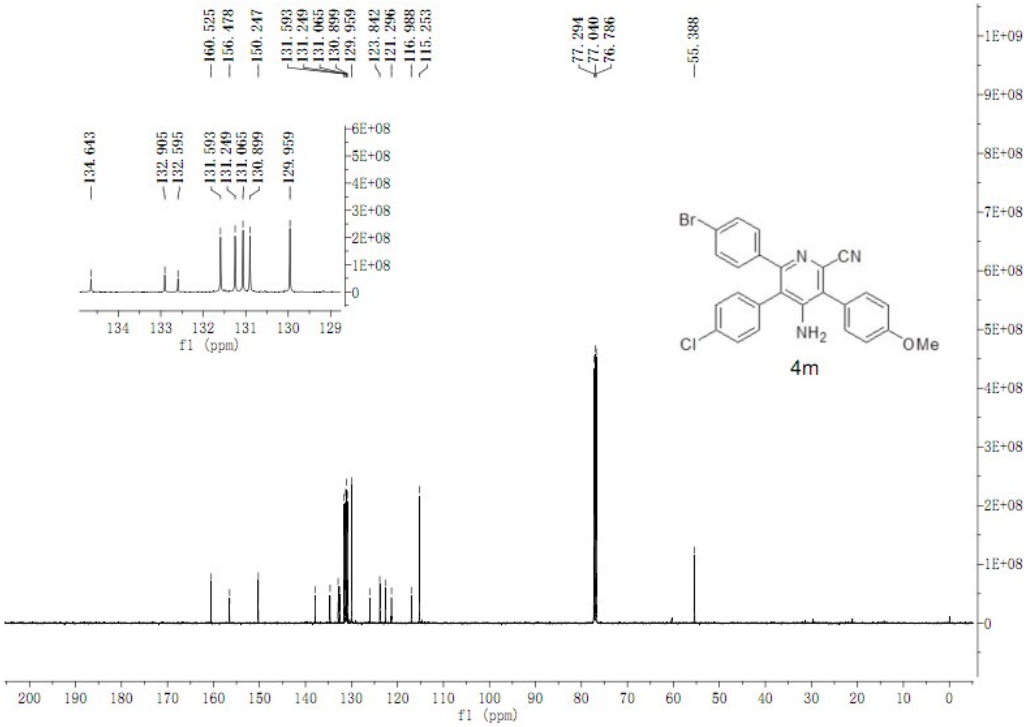

8.154
8.094
8.078
7.586
7.570
7.428
7.411
7.394
7.379
7.265
7.167
7.151
7.101
7.084
4.451
3.878
0.000
8.149
8.089
8.073
7.581
7.565
7.374
7.260
7.162
7.146
7.096
7.079
O2N
CN
N
Cl
NH2
OMe
4k
f1 (ppm)

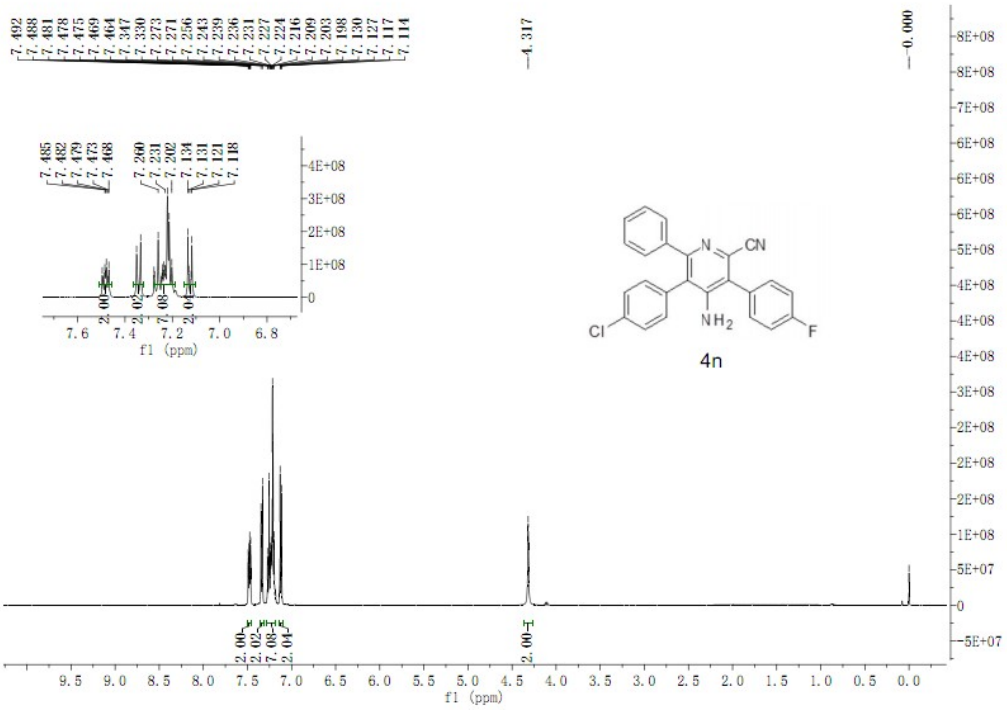

160.637
155.039
150.565
147.773
140.610
135.463
130.161
124.751
121.604
116.817
115.324
77.302
77.048
76.794
55.402
135.463
135.069
132.280
131.546
130.856
130.161
128.902
126.551
124.751
122.978
121.604
O2N
CN
N
Cl
NH2
OMe
4k
f1 (ppm)

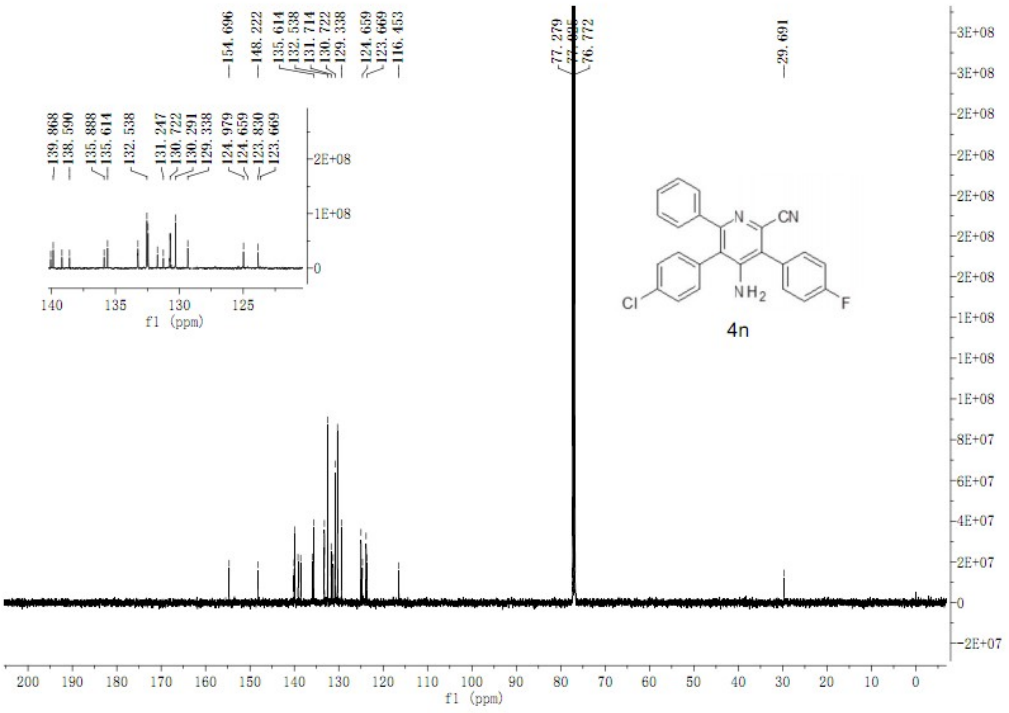

7.713
7.697
7.491
7.239
7.235
7.231
7.222
7.217
7.208
7.203
7.071
7.055
4.346
0.000
7.706
7.690
7.501
7.484
7.382
7.365
7.215
7.196
7.064
7.048
f1 (ppm)
CN
N
NH2
Br
Br
4l
2.00
2.03
2.00
5.00
2.01
2.00

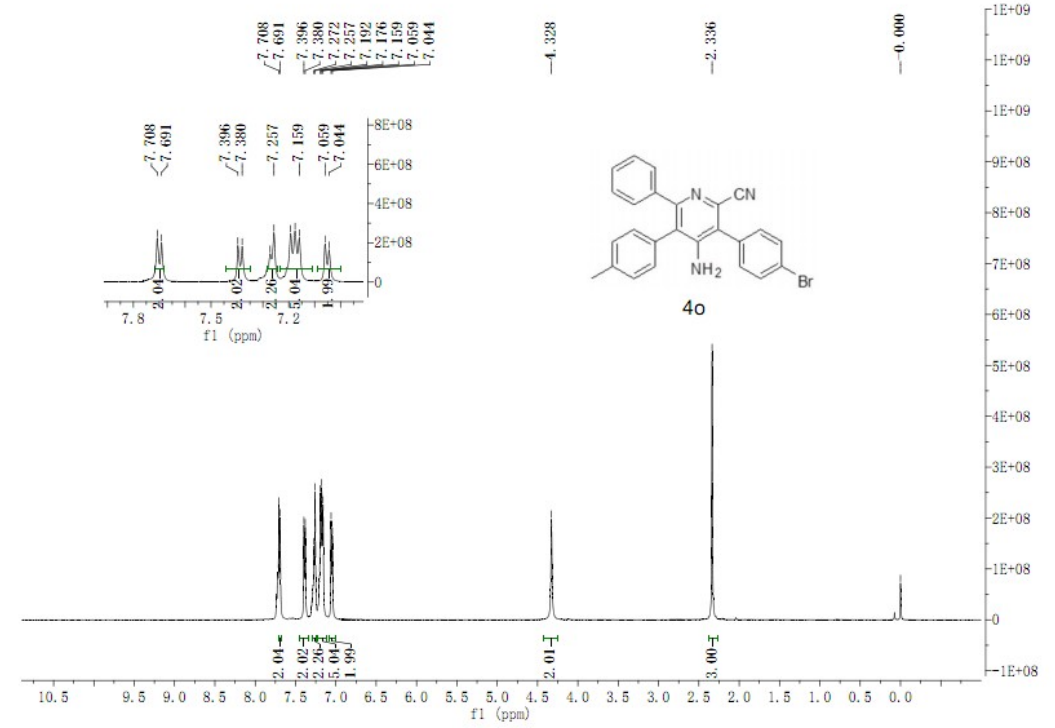

162.507
158.236
149.651
138.719
131.910
129.540
124.747
121.704
116.724
77.300
77.047
76.793
133.059
132.198
131.910
131.397
131.164
129.540
128.253
127.926
124.747
124.090
122.673
121.704
f1 (ppm)
CN
N
NH2
Br
Br
4l

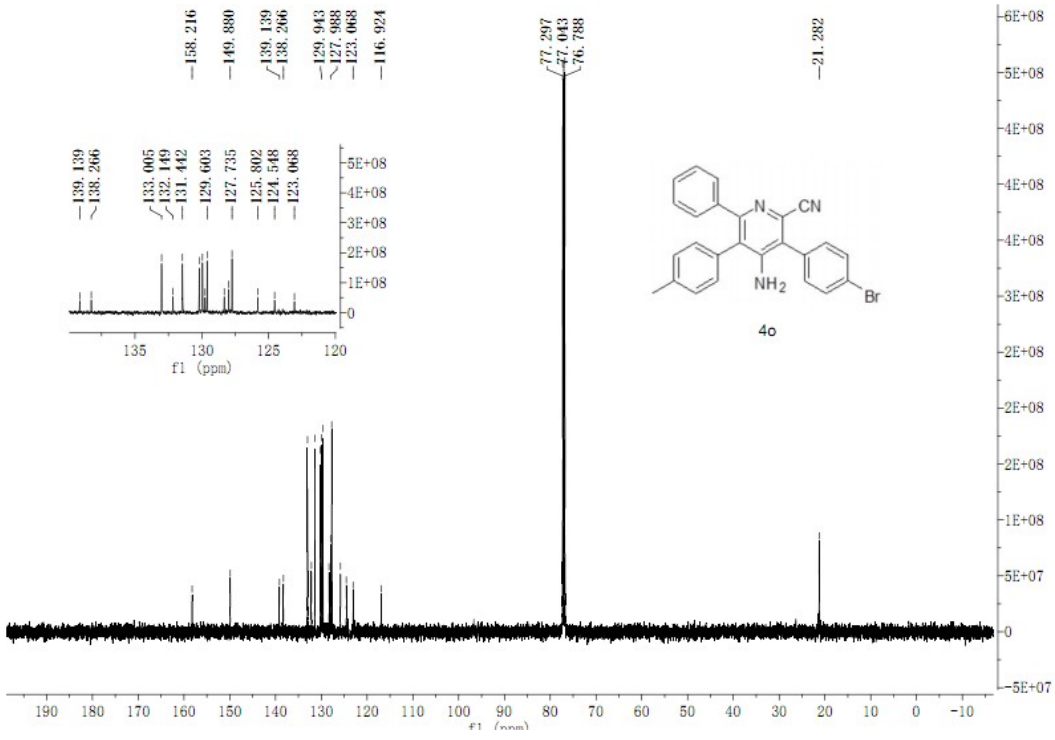

7.411
7.394
7.379
7.362
7.342
7.325
7.134
7.127
7.117
7.110
7.087
7.070
4.357
3.871
0.000
Br
N
CN
Cl
NH2
OMe
4m
f1 (ppm)

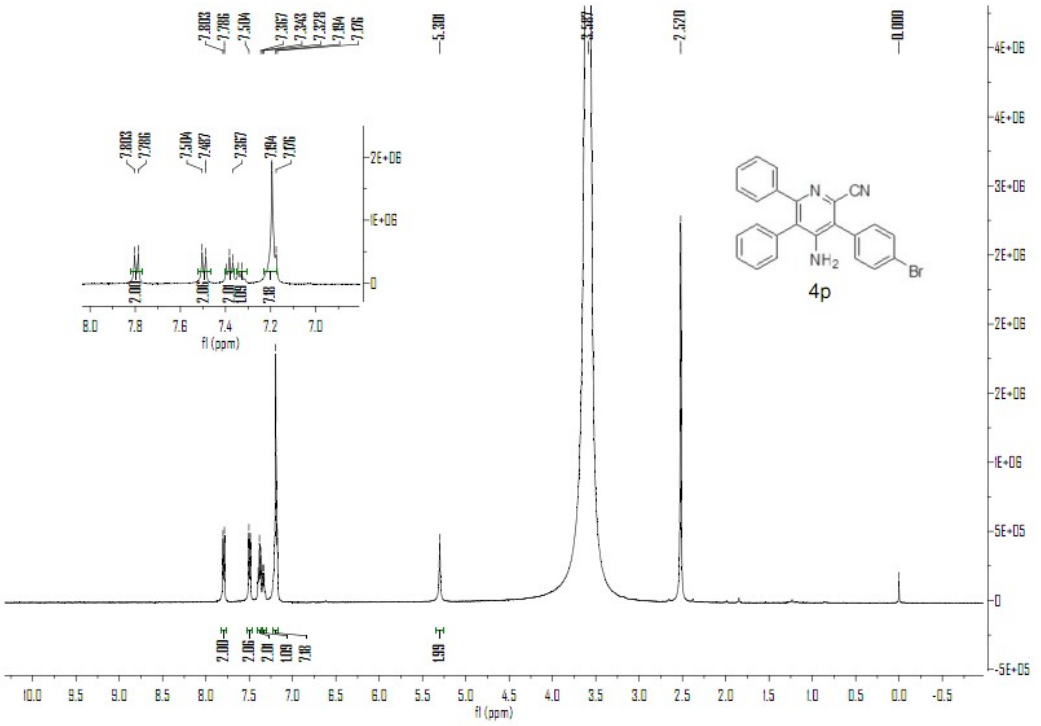

160.525
156.478
150.247
131.593
131.249
131.065
130.899
129.959
123.842
121.296
116.988
115.253
77.294
77.040
76.786
55.388
134.643
132.905
132.595
Br
N
CN
Cl
NH2
OMe
4m
f1 (ppm)

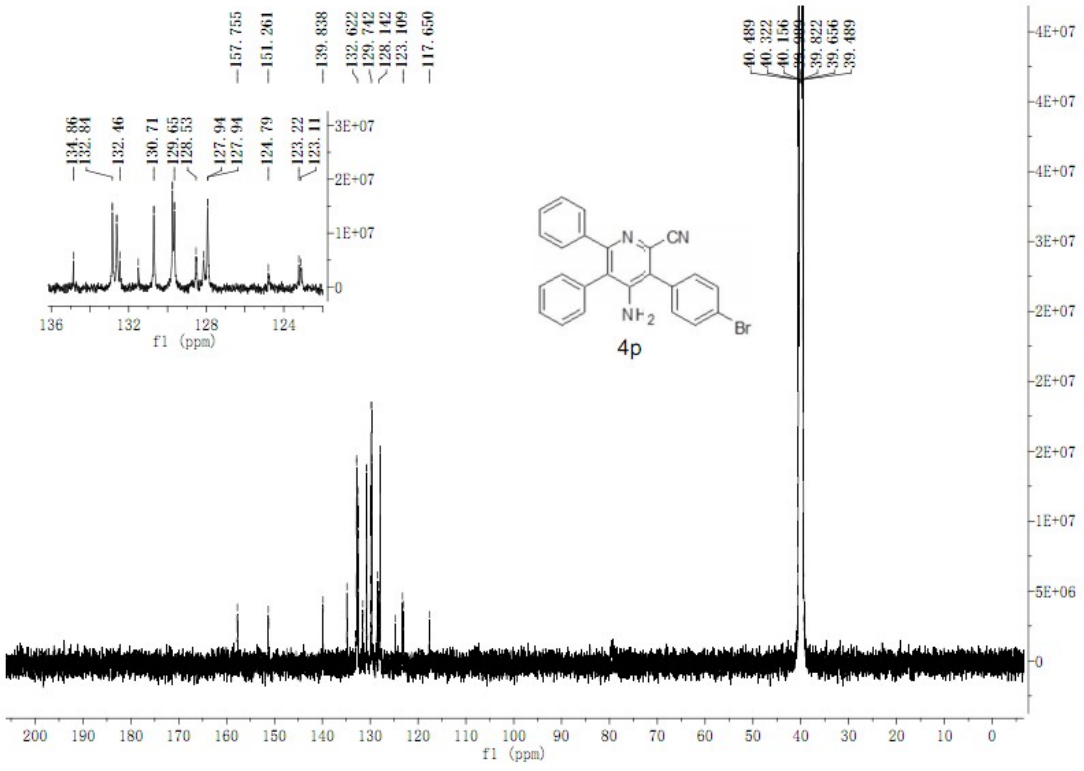

4n

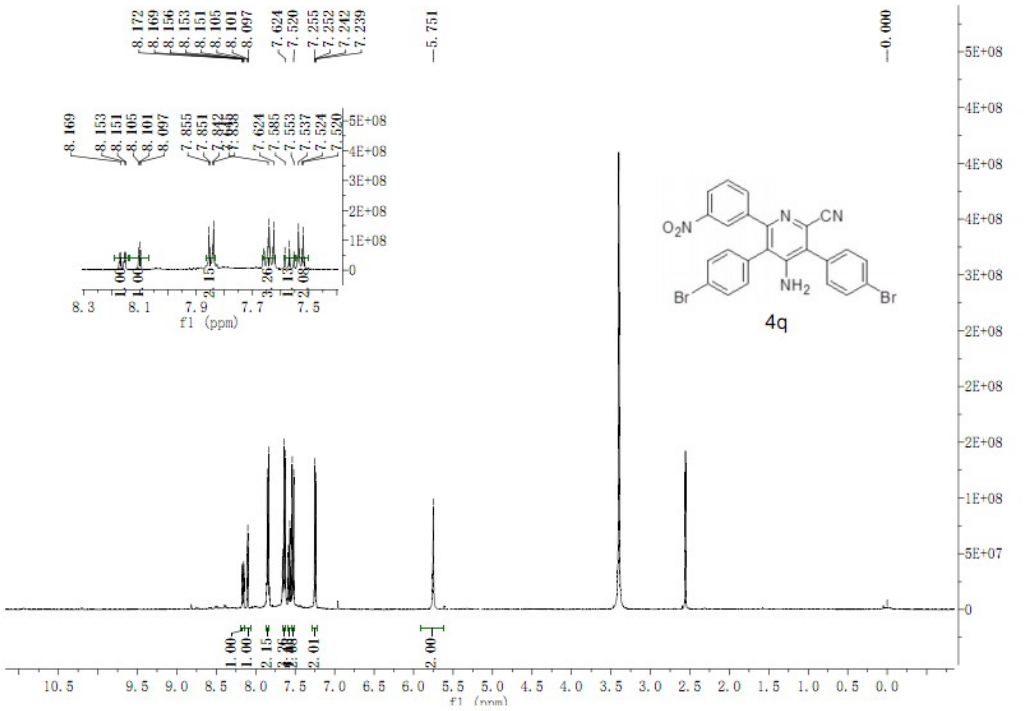

4n

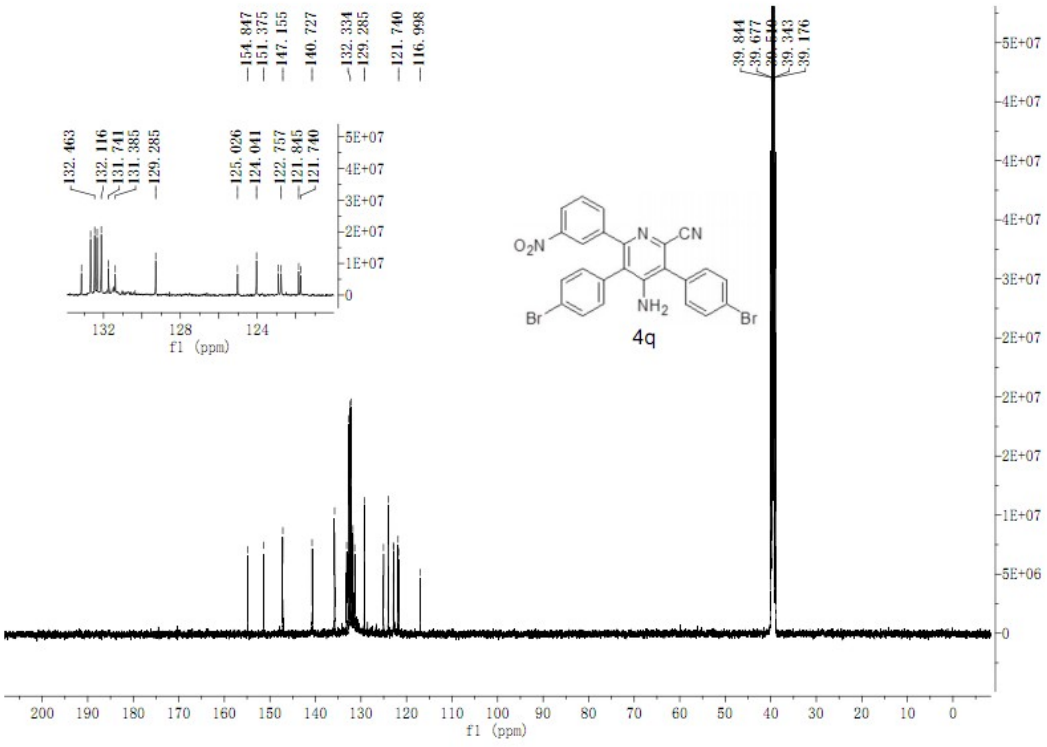

7.708
7.691
7.396
7.380
7.272
7.257
7.192
7.176
7.159
7.059
7.044
4.328
2.336
0.000
N
CN
NH2
Br
4o
f1 (ppm)

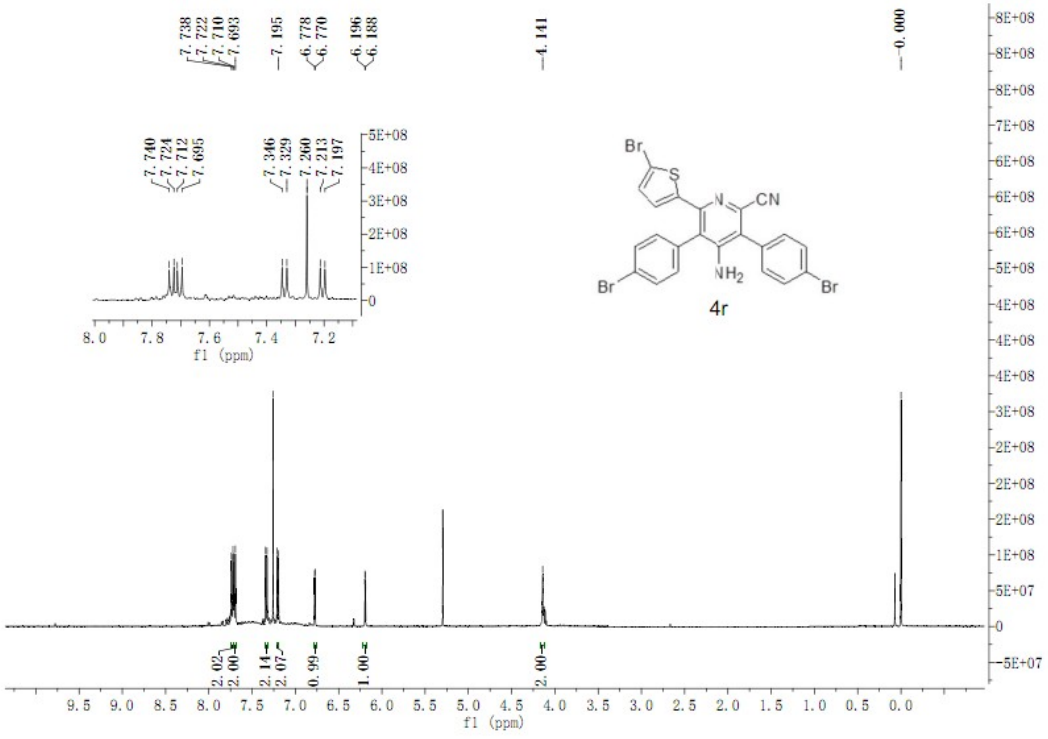

158.216
149.880
139.139
138.266
129.943
127.988
123.068
116.924
77.297
77.043
76.788
21.282
N
CN
NH2
Br
4o
f1 (ppm)

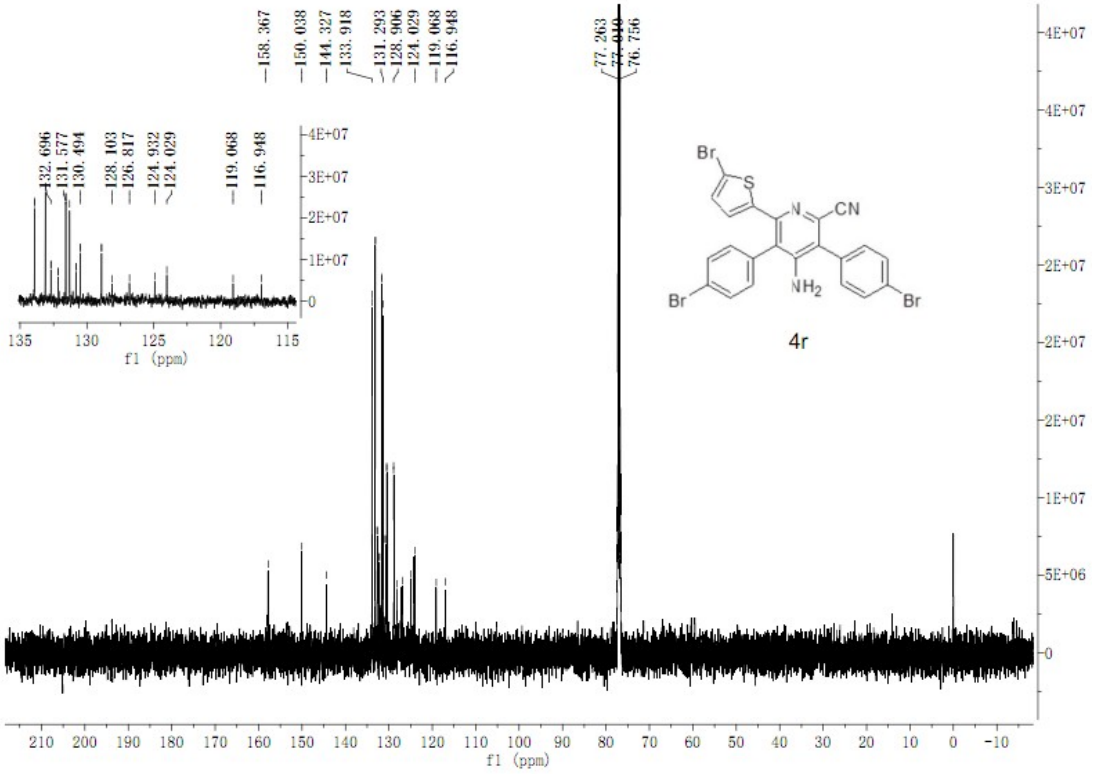

4p
f1 (ppm)

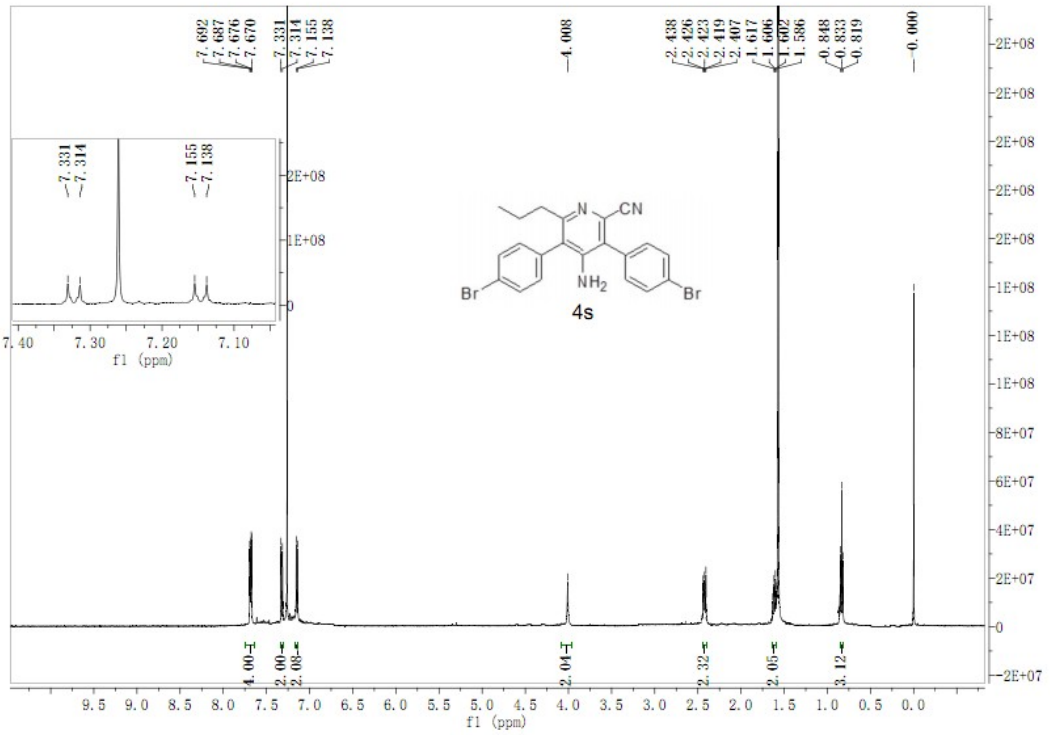

4p
f1 (ppm)

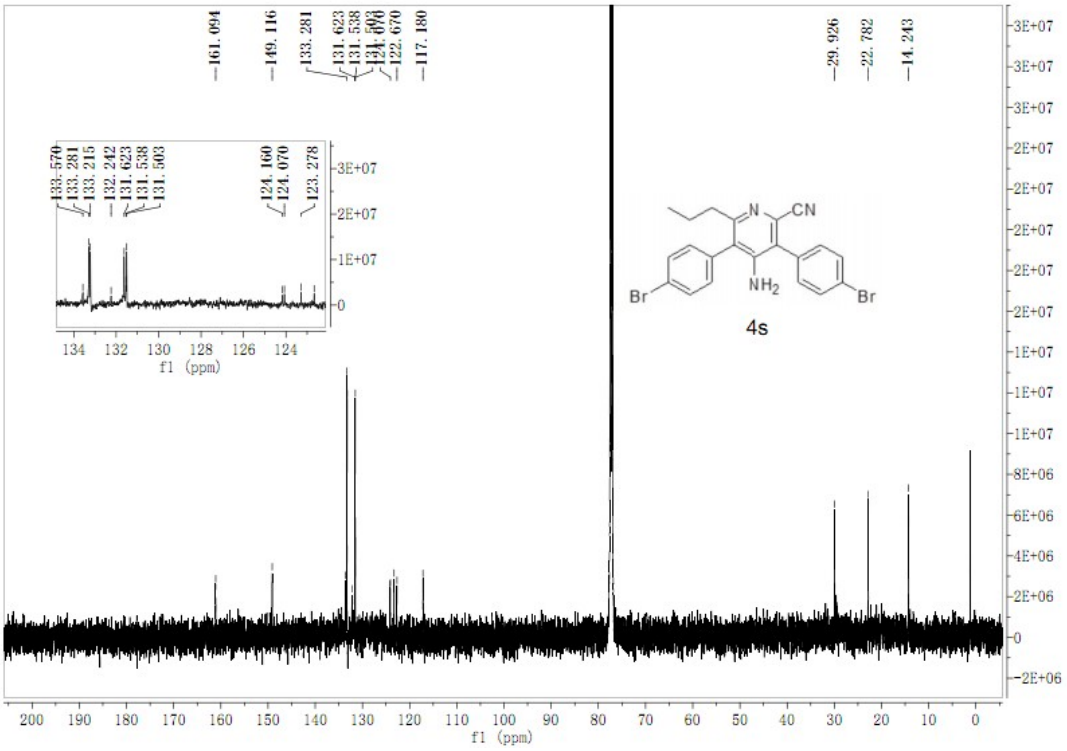

4q

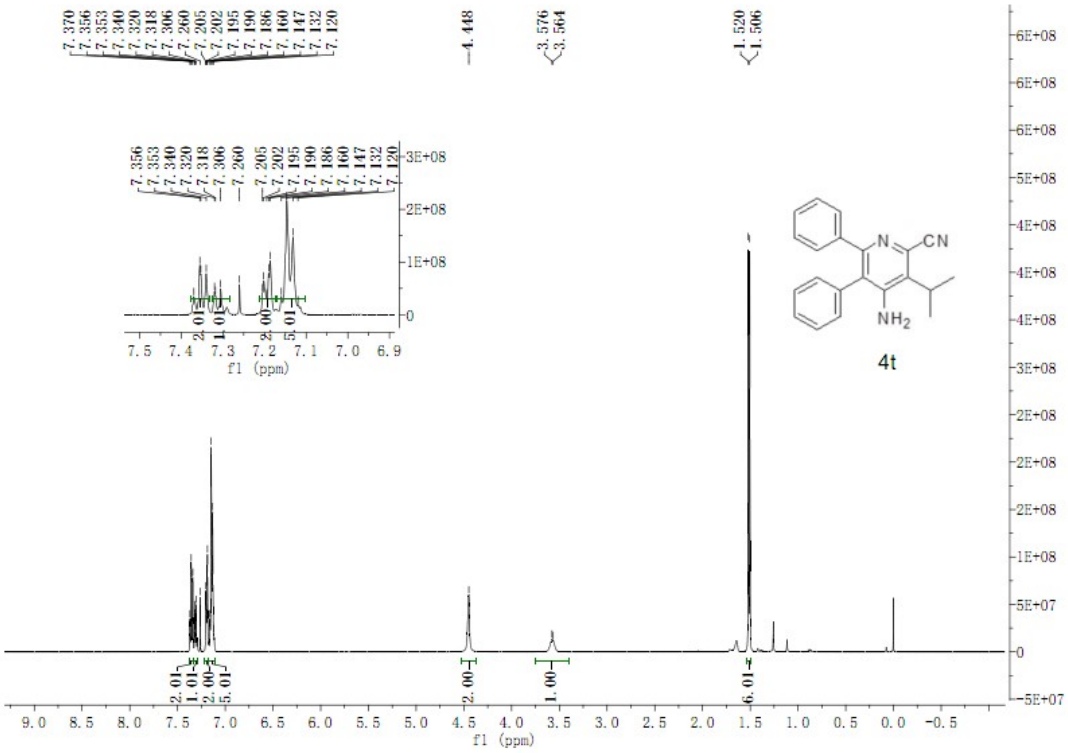

4q

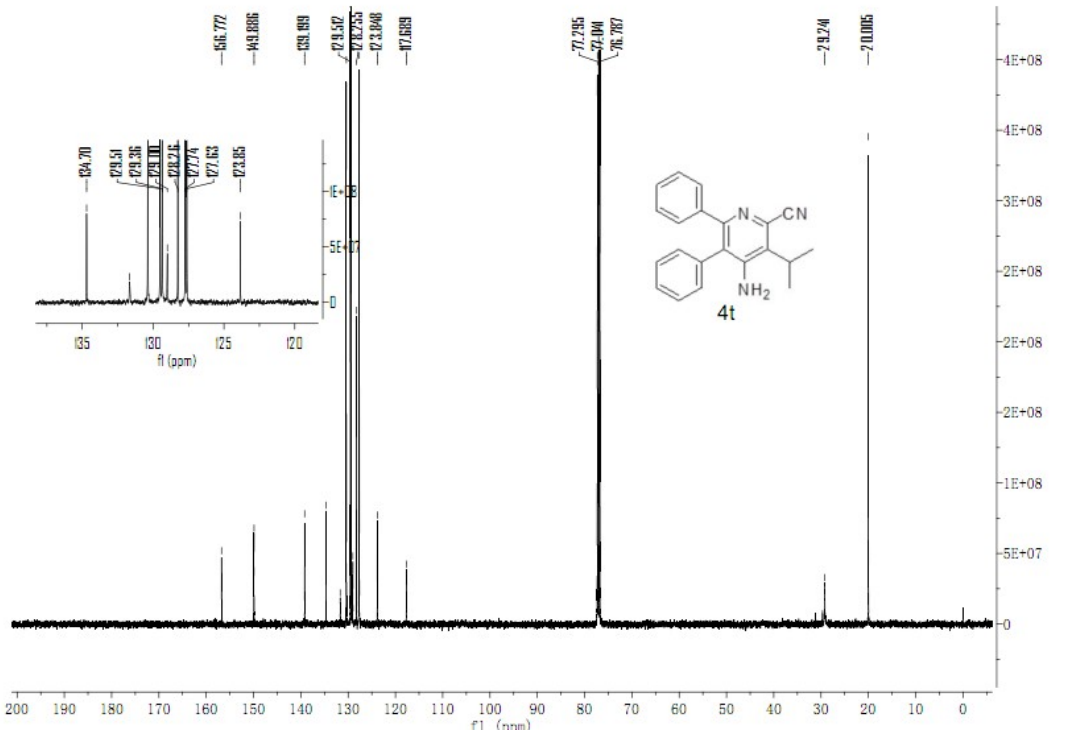

7.738
7.722
7.710
7.693
7.195
6.778
6.770
6.196
6.188
4.141
0.000
7.740
7.724
7.712
7.695
7.346
7.329
7.260
7.213
7.197
Br
S
N
CN
NH2
Br
Br
4r
f1 (ppm)
2.02
2.00
2.14
2.07
0.99
1.00
2.00

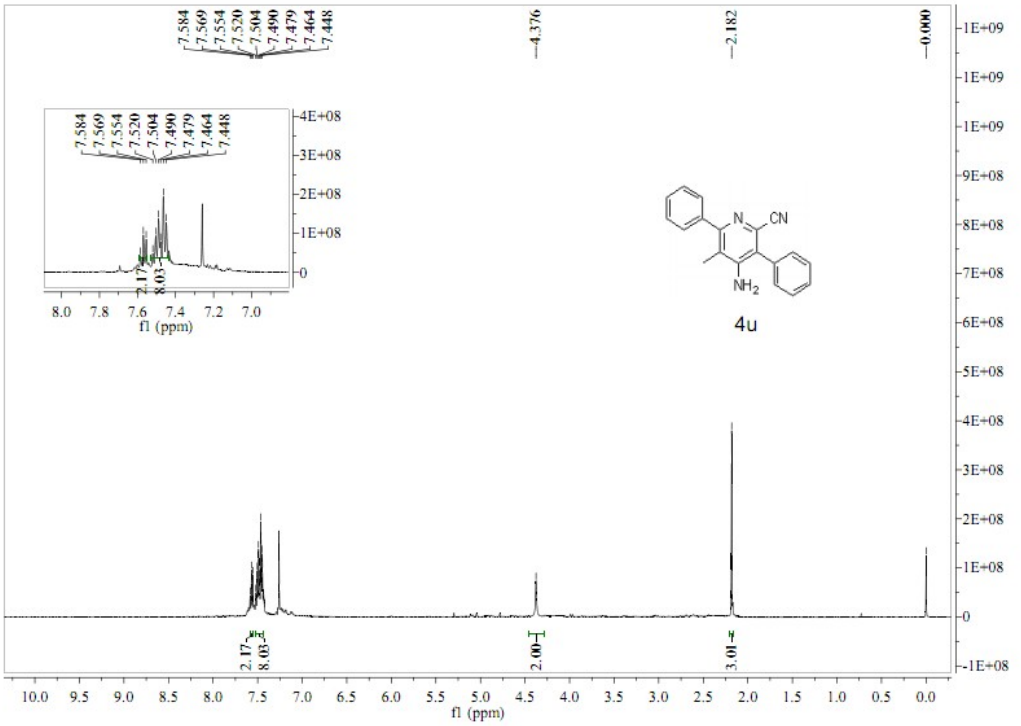

158.367
150.038
144.327
133.918
131.293
128.906
124.029
119.068
116.948
77.263
77.000
76.756
132.696
131.577
130.494
128.103
126.817
124.932
124.029
119.068
116.948
Br
S
N
CN
NH2
Br
Br
4r
f1 (ppm)

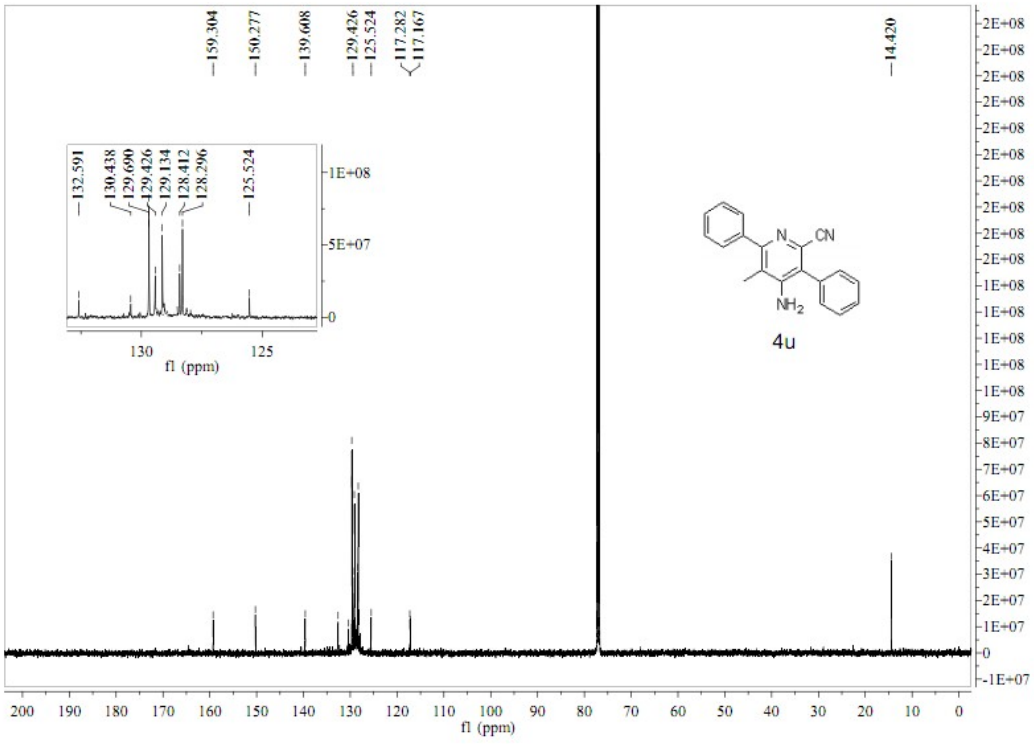

4s
f1 (ppm)

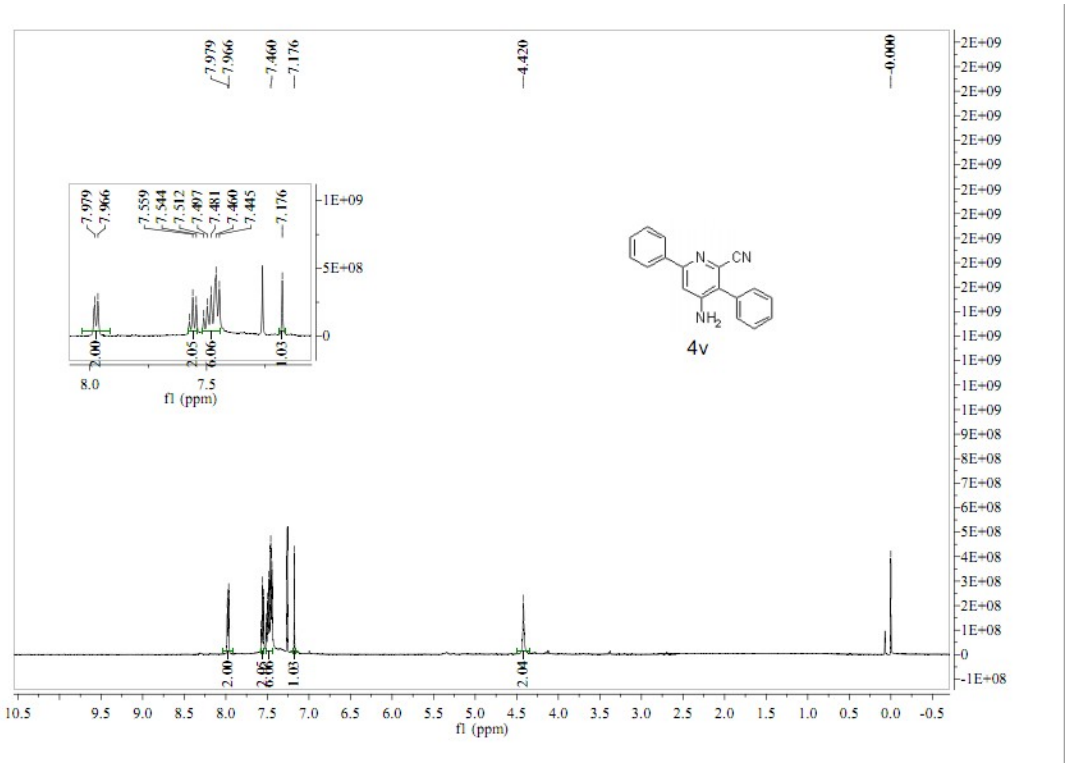

4s
f1 (ppm)

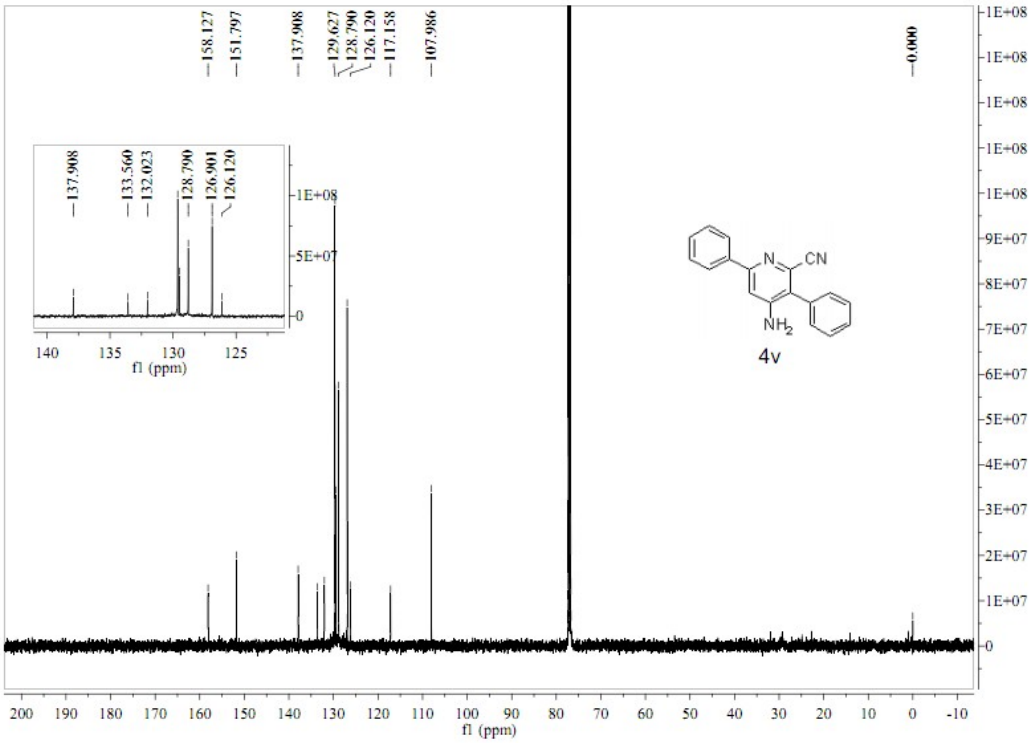

7.370
7.356
7.353
7.340
7.320
7.318
7.306
7.260
7.205
7.202
7.195
7.190
7.186
7.160
7.147
7.132
7.120
4.448
3.576
3.564
1.520
1.506
N
CN
NH2
4t
f1 (ppm)

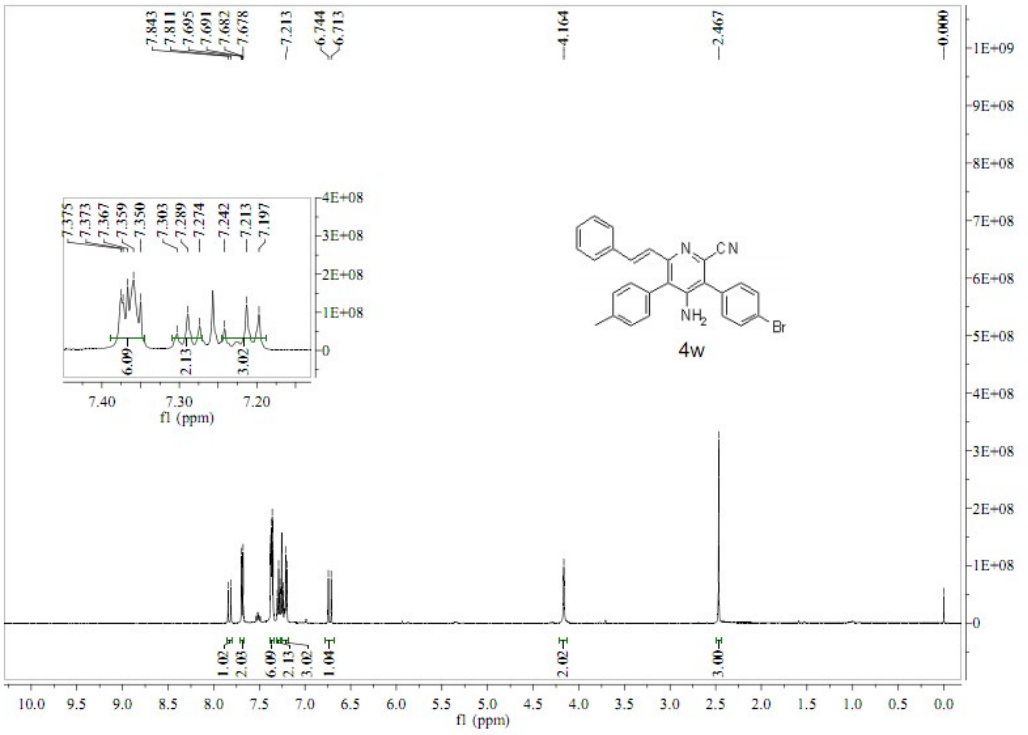

158.772
149.866
138.869
129.562
127.255
123.948
117.689
77.295
77.104
76.787
29.724
20.005
134.70
129.51
129.36
129.10
128.24
127.74
127.63
123.85
135
130
125
120
f1 (ppm)
N
CN
NH2
4t

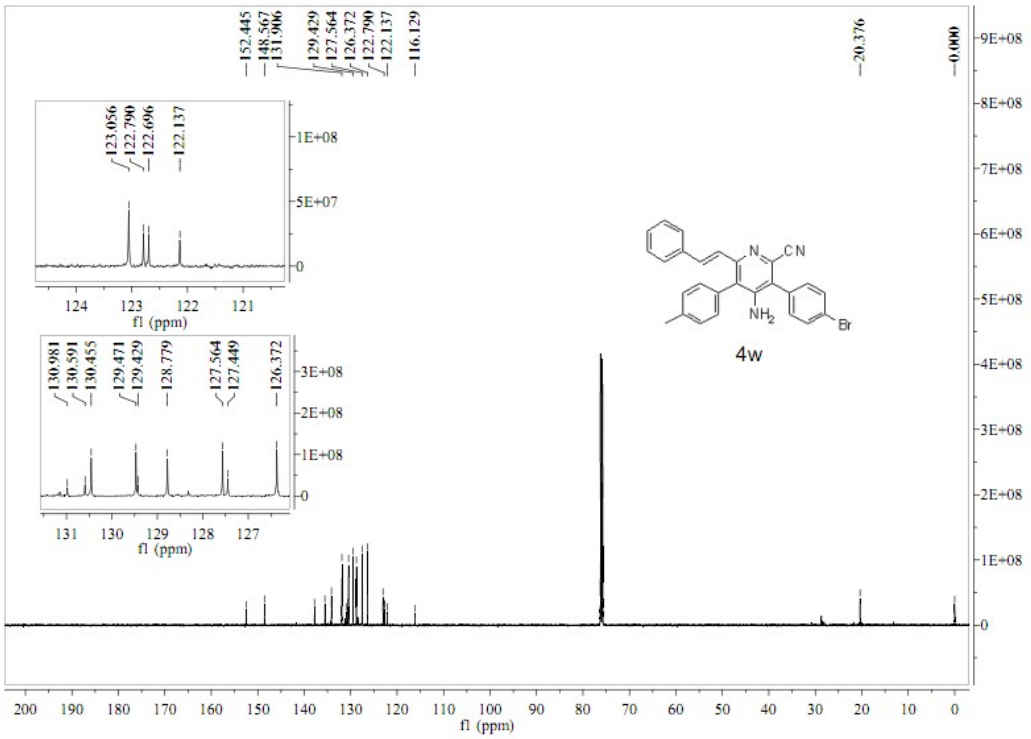

7.584
7.569
7.554
7.520
7.504
7.490
7.479
7.464
7.448
4.376
2.182
0.000
2.17
8.03
2.00
3.01
fl (ppm)
CN
NH2
4u


159.304
150.277
139.608
129.426
125.524
117.282
117.167
14.420
132.591
130.438
129.690
129.426
129.134
128.412
128.296
125.524
fl (ppm)
CN
NH2
4u

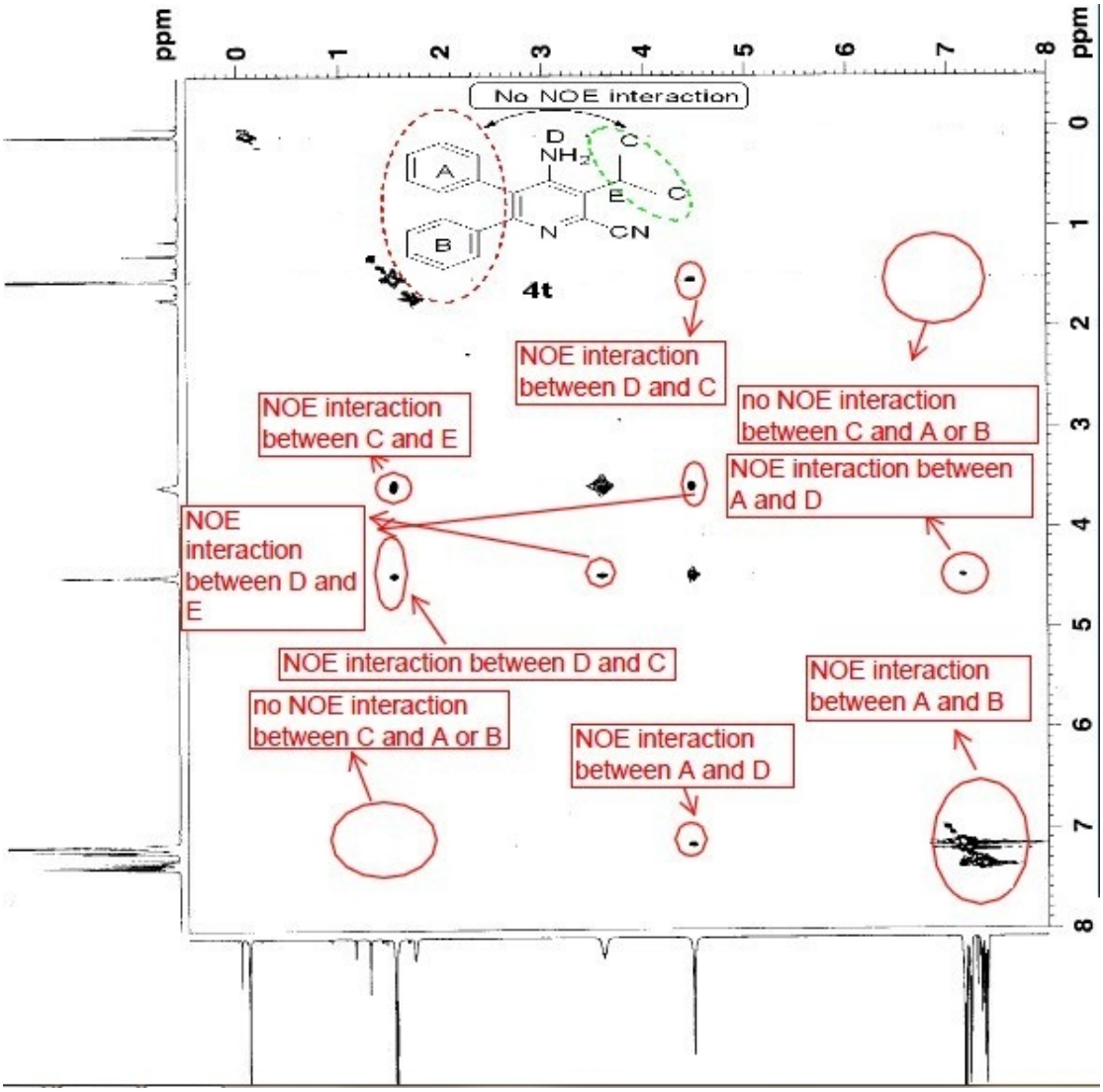

7.979
7.966
7.460
7.176
4.420
0.000
7.559
7.544
7.512
7.497
7.481
7.460
7.445
2.00
2.05
6.06
1.03
2.04
8.0
7.5
f1 (ppm)
CN
NH2
4v


158.127
151.797
137.908
129.627
128.790
126.120
117.158
107.986
0.000
133.560
132.023
126.901
140
135
130
125
f1 (ppm)
CN
NH2
4v

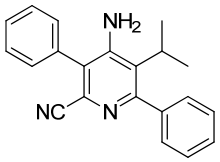

7.843
7.811
7.695
7.691
7.682
7.678
7.213
6.744
6.713
4.164
2.467
0.000
7.375
7.373
7.367
7.359
7.350
7.303
7.289
7.274
7.242
7.213
7.197
6.09
2.13
3.02
7.40
7.30
7.20
f1 (ppm)
1.02
2.03
6.09
2.13
3.02
1.04
2.02
3.00
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)
CN
N
NH2
Br
4w


152.445
148.567
131.906
129.429
127.564
126.372
122.790
122.137
116.129
20.376
0.000
123.056
122.790
122.696
122.137
124
123
122
121
f1 (ppm)
130.981
130.591
130.455
129.471
129.429
128.779
127.564
127.449
126.372
131
130
129
128
127
f1 (ppm)
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)
CN
N
NH2
Br
4w

5. 2D ^{1}H-^{1}H NOESY Spectra:



NOE interaction was not observed between isopropyl group(C and E) and phenyls groups (A and B) implied they were not at the same side of the pyridine ring, the followed possible structure of **4t** can be excluded:



6. X-ray crystallography Data of 4c and 4h:

Single crystals of compound **4c** and **4h** were measured on a Rigaku RAXIS-RAPID single-crystal diffractometer. The recrystallization solvent of **4c** and **4h** was methanol. The single crystal of **4h** contained a molecule of methanol.

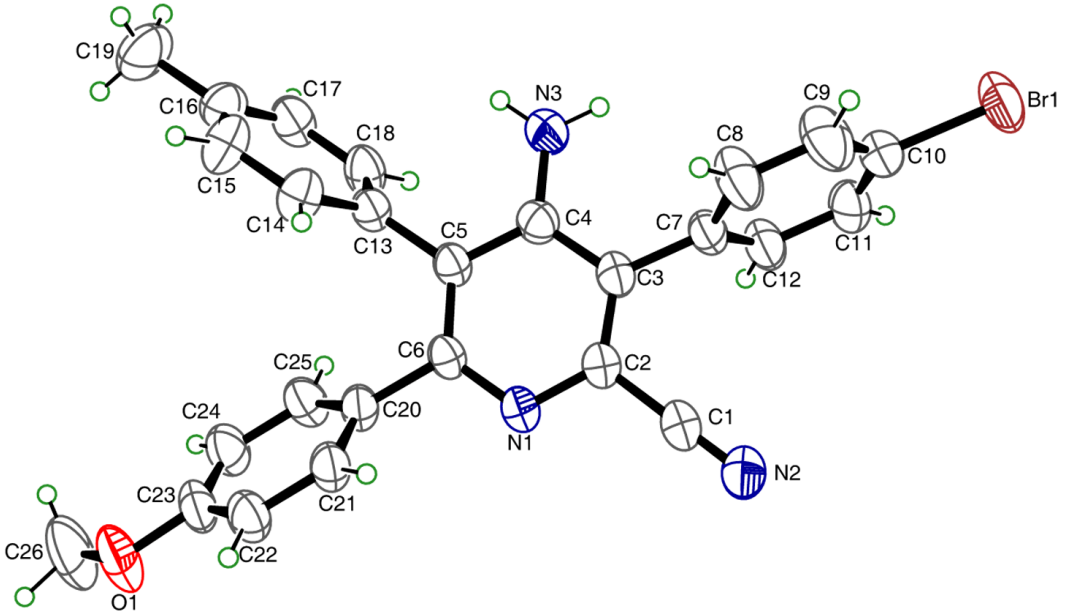


Fig. S1 X-ray crystal structure of **4c**

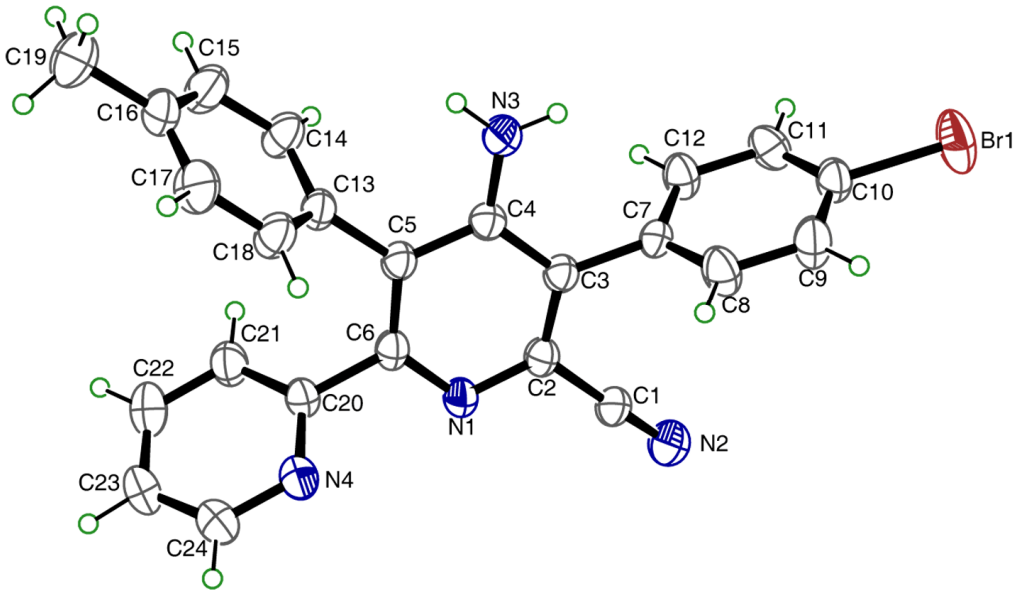


Fig. S2 X-ray crystal structure of **4h**

Table S1 X-ray crystallography data of 4c

Formula moiety	$C_{26}H_{20}BrN_3O$
Formula sum	$C_{26}H_{20}BrN_3O$
Formula weight	470.36
Temperature	296 (1) K
Crystal system	Triclinic
Space group	P-1
Unit cell dimensions	a=9.9984 (6) Å
	b=10.6788 (7) Å
	c=12.6094 (9) Å
	alpha = 68.7577 (18) deg.
	beta = 86.7228 (18) deg.
	gamma = 66.0269 (14) deg.
Volume	1140.17 (13) $Å^3$
Z	2
Calculated density	1.370 Mg/m^3
Absorption coefficient	1.825 mm^{-1}
F(000)	480
Crystal size	0.37 x 0.34 x 0.18 mm
Theta range for data collection	3.3 to 27.4 deg.
Reflections collected / unique	9008 / 3964 [R(int) = 0.0334]
Data / restraints / parameters	3964 / 0 / 283
Goodness-of-fit on F2	1.003
Final R indices [I>2sigma(I)]	R1 = 0.0416, wR2 = 0.0834
R indices (all data)	R1 = 0.0940, wR2 = 0.1233

Table S2 X-ray crystallography data of 4h

Formula moiety	$C_{24}H_{17}BrN_4$, CH_4O
Formula sum	$C_{25}H_{21}BrN_4O$
Formula weight	473.37
Temperature	296 (1) K
Crystal system	Monoclinic
Space group	P2(1)/c
Unit cell dimensions	a=14.3833 (8) Å
	b=11.4881 (6) Å
	c=14.3173 (8) Å
	alpha = 90.00 deg.
	beta = 107.727 (2) deg.
	gamma = 90.00 (14) deg.
Volume	2253.4 (2) $Å^3$
Z	4
Calculated density	1.395 Mg/m^3
Absorption coefficient	1.848 mm^{-1}
F(000)	968

Crystal size	0.37 x 0.26 x 0.18 mm
Theta range for data collection	3.4 to 27.4 deg.
Reflections collected / unique	14146 / 4400 [R(int) = 0.0434]
Data / restraints / parameters	4400 / 0 / 282
Goodness-of-fit on F2	1.002
Final R indices [I>2sigma(I)]	R1 = 0.0436, wR2 = 0.1167
R indices (all data)	R1 = 0.1029, wR2 = 0.1741