

**Base-Mediated Synthesis of Highly Functionalized 2-Aminonicotinitriles from
 α -Keto Vinyl Azides and α,α -Dicyanoalkenes**

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Supporting Information

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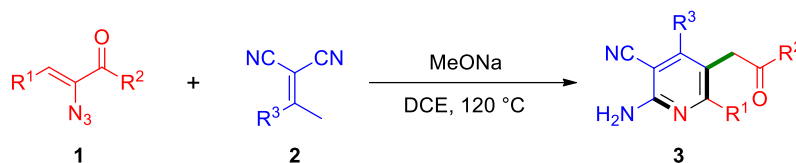
General Information:

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). Melting points were recorded on a BÜCHI B-540 melting point apparatus. NMR spectra were recorded for ^1H NMR at 500 MHz and for ^{13}C NMR at 125 MHz. For ^1H NMR, tetramethylsilane (TMS) served as internal standard ($\delta=0$) and data are reported as follows: chemical shift, integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), and coupling constant(s) in Hz. For ^{13}C NMR, TMS ($\delta=0$) or CDCl_3 ($\delta=77.16$) was used as internal standard and spectra were obtained with complete proton decoupling. HPLC analysis and the HRMS of all final products were confirmed on an Agilent 1290 HPLC-6224 Time of Flight Mass Spectrometer using Phenomenex Luna 5μ C18, 100 Å, 150 X 4.60 mm 5 micron column at a flow rate of 0.5 mL/min using linear gradients buffer B in A (B: CH_3OH containing 0.1 % formic acid, A: H_2O containing 0.1% formic acid). Mobile phase B was increased linearly from 5% to 95% over 7 min and 95% over the next 2 min, after which the column was equilibrated to 5% for 1 min. The starting materials α -keto vinyl azides **1** were prepared according to the literature methods¹ and α,α -dicyanoalkenes **2** were readily prepared from the corresponding ketones with malononitrile *via* Knoevenagel condensation.²

Reference:

- 1 (a) G. Zhang, H. Ni, W. Chen, J. Shao, H. Liu, B. Chen, Y. Yu, *Org. Lett.*, 2013, **15**, 5967; (b) R. Suresh, S. Muthusubramanian, M. Nagaraj, G. Manickam, *Tetrahedron Lett.*, 2013, **54**, 1779.
- 2 (a) D. T. Mowry, *J. Am. Chem. Soc.*, 1945, **67**, 1050; (b) A. R. Longstreet, B. S. Campbell, B. F. Gupton, D. T. McQuade, *Org. Lett.*, 2013, **15**, 5298; (c) S. Rout, S. K. Ray, R. A. Unhale, V. K. Singh, *Org. Lett.*, 2014, **16**, 5568; (d) S. L. Broman, A. U. Petersen, C. G. Tortzen, J. Vibenholt, A. D. Bond, M. B. Nielsen, *Org. Lett.*, 2012, **14**, 318.

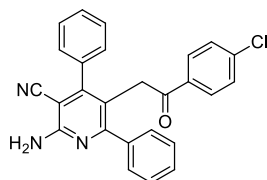
General Procedure for the Synthesis of 3:



A mixture of vinyl azide **1** (1.0 mmol), α,α -dicyanoalkenes **2** (1.0 mmol, 1.0 equiv.) and MeONa (0.5 mmol, 0.5 equiv. when R³ were aromatic groups, or 1.5 mmol, 1.5 equiv. when R³ were alkyl groups) was stirred in DCE with a well-sealed tube at 120 °C (the temperature of oil bath) for several hours. After the completeness of the reaction, the reaction mixture was quenched with water (10 mL), and then extracted three times with DCM. The combined organic extracts were washed with brine, dried over anhydrous MgSO₄ and concentrated. Purification of the crude product was carried out by chromatography (silica gel, petroleum ether: ethyl acetate=9:1 to 3:1) to afford **3a-3y**.

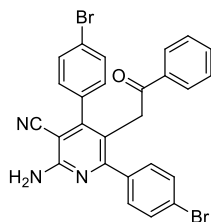
Characterization Data of compound 3

2-amino-5-(2-(4-chlorophenyl)-2-oxoethyl)-4,6-diphenylnicotinonitrile (**3a**)



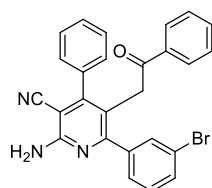
Brown-yellow solid, yield 80%, m.p. 194.3-195.8 °C, ¹H NMR (500 MHz, [D₆]DMSO) δ 7.65 – 7.62 (m, 2H), 7.44 – 7.41 (m, 2H), 7.38 (dd, J = 11.4, 4.5 Hz, 2H), 7.35 – 7.29 (m, 6H), 7.25 – 7.21 (m, 2H), 7.00 (s, 2H), 3.96 (s, 2H); ¹³C NMR (125 MHz, CDCl₃) δ 197.20, 163.28, 158.03, 156.77, 139.69, 139.62, 136.36, 134.80, 129.28, 129.20, 128.98, 128.91, 128.86, 128.60, 128.08, 128.06, 117.66, 116.25, 91.92, 40.10. HRMS (ESI): m/z calcd for C₂₆H₁₉ClN₃O [M+H]⁺: 424.1211, found: 424.1219.

2-amino-4,6-bis(4-bromophenyl)-5-(2-oxo-2-phenylethyl)nicotinonitrile (**3b**)



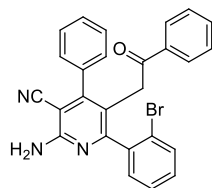
Pale yellow solid, yield 74%, m.p. 168.3-170.1 °C, ¹H NMR (500 MHz, [D₆]DMSO) δ 7.66 – 7.63 (m, 2H), 7.60 – 7.54 (m, 5H), 7.39 (t, *J* = 7.8 Hz, 2H), 7.32 – 7.28 (m, 2H), 7.20 (d, *J* = 8.4 Hz, 2H), 7.08 (s, 2H), 3.99 (s, 2H); ¹³C NMR (125 MHz, CDCl₃) δ 198.21, 162.25, 157.94, 155.75, 138.37, 136.11, 135.06, 133.67, 132.23, 131.78, 129.87, 129.77, 128.78, 127.86, 123.91, 123.52, 117.74, 115.99, 91.95, 40.11. HRMS (ESI): *m/z* calcd for C₂₆H₁₈Br₂N₃O [M+H]⁺: 547.9791, found: 547.9796.

2-amino-6-(3-bromophenyl)-5-(2-oxo-2-phenylethyl)-4-phenylnicotinonitrile (3c)



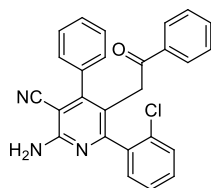
Yellow solid, yield 82%, m.p. 154.5-156.7 °C, ¹H NMR (500 MHz, [D₆]DMSO) δ 7.63 (d, *J* = 7.5 Hz, 2H), 7.56 – 7.51 (m, 3H), 7.41 – 7.34 (m, 6H), 7.30 (t, *J* = 7.7 Hz, 1H), 7.24 (d, *J* = 6.9 Hz, 2H), 7.04 (s, 2H), 3.98 (s, 2H); ¹³C NMR (125 MHz, CDCl₃) δ 198.33, 161.59, 157.91, 157.04, 141.67, 136.48, 136.21, 133.34, 131.97, 131.38, 130.07, 129.34, 128.94, 128.61, 128.05, 127.82, 126.73, 122.72, 118.08, 116.13, 92.37, 40.10. HRMS (ESI): *m/z* calcd for C₂₆H₁₉BrN₃O [M+H]⁺: 468.0706, found: 468.0710.

2-amino-6-(2-bromophenyl)-5-(2-oxo-2-phenylethyl)-4-phenylnicotinonitrile (3d)



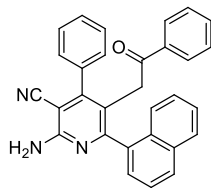
Yellow solid, yield 78%, m.p. 203.7-204.8 °C, ¹H NMR (500 MHz, [D₆]DMSO) δ 7.63 (d, *J* = 7.9 Hz, 1H), 7.55 (d, *J* = 7.6 Hz, 2H), 7.49 (dd, *J* = 14.2, 7.2 Hz, 2H), 7.38 (d, *J* = 7.9 Hz, 2H), 7.36 – 7.26 (m, 4H), 7.22 (dd, *J* = 7.7, 1.2 Hz, 1H), 7.19 – 7.13 (m, 2H), 7.08 (s, 2H), 3.86 (d, *J* = 18.3 Hz, 1H), 3.70 (d, *J* = 18.3 Hz, 1H); ¹³C NMR (125 MHz, CDCl₃) δ 197.59, 162.18, 158.13, 156.59, 140.07, 136.53, 136.10, 133.18, 132.73, 130.60, 130.24, 129.37, 128.98, 128.87, 128.50, 128.29, 128.14, 127.72, 121.29, 118.85, 116.24, 92.34, 39.33. HRMS (ESI): *m/z* calcd for C₂₆H₁₉BrN₃O [M+H]⁺: 468.0706, found: 468.0714.

2-amino-6-(2-chlorophenyl)-5-(2-oxo-2-phenylethyl)-4-phenylnicotinonitrile (3e)



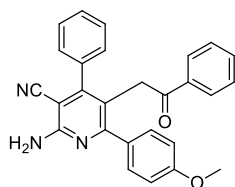
Yellow solid, yield 79%, m.p. 213.9-215.8 °C, ¹H NMR (500 MHz, [D₆]DMSO) δ 7.55 (d, *J* = 7.4 Hz, 2H), 7.52 – 7.45 (m, 3H), 7.37 (dd, *J* = 14.6, 7.6 Hz, 3H), 7.34 – 7.26 (m, 4H), 7.22 – 7.15 (m, 2H), 7.05 (s, 2H), 3.89 (d, *J* = 18.4 Hz, 1H), 3.71 (d, *J* = 18.4 Hz, 1H); ¹³C NMR (125 MHz, CDCl₃) δ 197.57, 161.01, 158.17, 156.50, 138.16, 136.51, 136.09, 133.17, 131.63, 130.61, 130.11, 129.62, 129.36, 128.96, 128.87, 128.49, 128.28, 128.16, 127.70, 127.17, 119.06, 116.24, 92.32, 39.23. HRMS (ESI): *m/z* calcd for C₂₆H₁₉ClN₃O [M+H]⁺: 424.1211, found: 424.1212.

2-amino-6-(naphthalen-1-yl)-5-(2-oxo-2-phenylethyl)-4-phenylnicotinonitrile (3f)



Yellow solid, yield 75%, m.p. 207.3-210.1 °C, ¹H NMR (500 MHz, [D₆]DMSO) δ 7.92 – 7.89 (m, 1H), 7.85 (d, *J* = 8.2 Hz, 1H), 7.56 – 7.55 (m, 1H), 7.54 – 7.49 (m, 2H), 7.46 – 7.39 (m, 4H), 7.37 (d, *J* = 7.2 Hz, 4H), 7.30 (d, *J* = 6.9 Hz, 1H), 7.24 (dd, *J* = 15.6, 8.0 Hz, 3H), 7.01 (s, 2H), 3.87 (d, *J* = 18.3 Hz, 1H), 3.62 (d, *J* = 18.3 Hz, 1H); ¹³C NMR (125 MHz, CDCl₃) δ 197.94, 162.68, 158.10, 156.71, 136.61, 136.52, 136.27, 133.72, 132.95, 130.71, 129.29, 129.07, 128.92, 128.83, 128.51, 128.31, 127.55, 126.87, 126.39, 126.30, 125.30, 125.26, 119.77, 116.33, 92.07, 39.56. HRMS (ESI): *m/z* calcd for C₃₀H₂₂N₃O [M+H]⁺: 440.1757, found: 440.1752.

2-amino-6-(4-methoxyphenyl)-5-(2-oxo-2-phenylethyl)-4-phenylnicotinonitrile (3g)

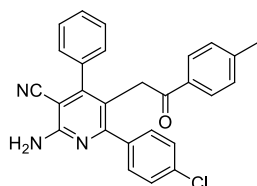


Pale yellow solid, yield 81%, m.p. 179.3-181.7 °C, ¹H NMR (500 MHz, [D₆]DMSO) δ 7.64 (d, *J* = 7.6 Hz, 2H), 7.53 (t, *J* = 7.4 Hz, 1H), 7.37 (t, *J* = 8.4 Hz, 4H), 7.32 (d, *J*

= 8.5 Hz, 3H), 7.22 (d, $J = 7.1$ Hz, 2H), 6.92 (s, 2H), 6.90 (d, $J = 8.7$ Hz, 2H), 4.01 (s, 2H), 3.71 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 198.64, 163.06, 160.16, 157.94, 156.75, 136.63, 136.58, 133.19, 132.19, 129.70, 129.15, 128.85, 128.55, 128.09, 127.83, 117.97, 116.46, 113.98, 91.55, 55.44, 40.49. HRMS (ESI): m/z calcd for $\text{C}_{27}\text{H}_{22}\text{N}_3\text{O}_2$ $[\text{M}+\text{H}]^+$: 420.1707, found: 420.1716.

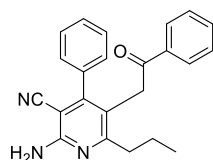
2-amino-6-(4-chlorophenyl)-5-(2-oxo-2-(p-tolyl)ethyl)-4-phenylnicotinonitrile

(3h)



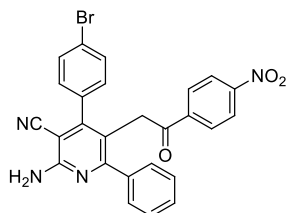
Pale yellow solid, yield 80%, m.p. 204.7-205.4 °C, ^1H NMR (500 MHz, $[\text{D}_6]\text{DMSO}$) δ 7.53 (d, $J = 8.2$ Hz, 2H), 7.42 – 7.40 (m, 2H), 7.39 – 7.35 (m, 4H), 7.34 (d, $J = 7.1$ Hz, 1H), 7.23 – 7.21 (m, 2H), 7.16 (d, $J = 8.1$ Hz, 2H), 7.00 (s, 2H), 3.94 (s, 2H), 2.29 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 197.86, 162.06, 157.86, 156.98, 144.31, 138.24, 136.30, 135.08, 133.89, 129.69, 129.32, 129.29, 128.90, 128.77, 128.05, 127.97, 118.17, 116.21, 92.25, 40.10, 21.73. HRMS (ESI): m/z calcd for $\text{C}_{27}\text{H}_{21}\text{ClN}_3\text{O}$ $[\text{M}+\text{H}]^+$: 438.1368, found: 438.1368.

2-amino-5-(2-oxo-2-phenylethyl)-4-phenyl-6-propylnicotinonitrile (3i)



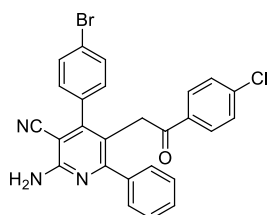
White solid, yield 80%, m.p. 157.1-158.2 °C, ^1H NMR (500 MHz, $[\text{D}_6]\text{DMSO}$) δ 7.85 (d, $J = 7.7$ Hz, 2H), 7.61 (t, $J = 7.4$ Hz, 1H), 7.47 (t, $J = 7.7$ Hz, 2H), 7.40-7.34 (m, 3H), 7.15 (d, $J = 7.6$ Hz, 2H), 6.76 (s, 2H), 4.09 (s, 2H), 2.46 (t, $J = 7.75$ Hz, 2H), 1.65-1.57 (m, 2H), 0.86 (t, $J = 7.3$ Hz, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 197.38, 165.67, 158.15, 155.51, 136.70, 136.56, 133.52, 129.13, 128.88, 128.82, 128.09, 128.05, 117.60, 116.73, 90.08, 38.97, 38.13, 22.03, 14.31. HRMS (ESI): m/z calcd for $\text{C}_{23}\text{H}_{22}\text{N}_3\text{O}$ $[\text{M}+\text{H}]^+$: 356.1757, found: 356.1758.

2-amino-4-(4-bromophenyl)-5-(2-(4-nitrophenyl)-2-oxoethyl)-6-phenylnicotinonitrile (3j)



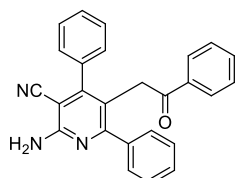
Brown-yellow solid, yield 82%, m.p. 214.7-216.3 °C, ¹H NMR (500 MHz, [D₆]DMSO) δ 8.18 (d, *J* = 8.8 Hz, 2H), 7.83 (d, *J* = 8.8 Hz, 2H), 7.57 (d, *J* = 8.4 Hz, 2H), 7.36 – 7.32 (m, 5H), 7.22 (d, *J* = 8.4 Hz, 2H), 7.06 (s, 2H), 4.08 (s, 2H); ¹³C NMR (125 MHz, CDCl₃) δ 196.95, 163.54, 158.09, 155.50, 150.50, 140.73, 139.42, 135.08, 132.35, 129.80, 129.21, 128.83, 128.78, 127.96, 124.03, 123.91, 116.99, 115.97, 91.64, 40.57. HRMS (ESI): *m/z* calcd for C₂₆H₁₈BrN₄O₃ [M+H]⁺: 513.0557, found: 513.0563.

2-amino-4-(4-bromophenyl)-5-(2-(4-chlorophenyl)-2-oxoethyl)-6-phenylnicotinonitrile (3k)



Pale yellow solid, yield 81%, m.p. 196.0-197.2 °C, ¹H NMR (500 MHz, [D₆]DMSO) δ 7.65 (d, *J* = 8.2 Hz, 2H), 7.58 (d, *J* = 7.9 Hz, 2H), 7.44 (d, *J* = 8.1 Hz, 2H), 7.33 (s, 5H), 7.21 (d, *J* = 8.0 Hz, 2H), 7.08 (s, 2H), 3.98 (s, 2H); ¹³C NMR (125 MHz, CDCl₃) δ 197.07, 163.49, 157.99, 155.50, 140.00, 139.43, 135.16, 134.51, 132.21, 129.80, 129.26, 129.09, 129.00, 128.66, 127.97, 123.88, 117.47, 116.12, 91.56, 40.05. HRMS (ESI): *m/z* calcd for C₂₆H₁₈BrClN₃O [M+H]⁺: 502.0316, found: 502.0313.

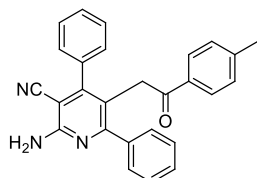
2-amino-5-(2-oxo-2-phenylethyl)-4,6-diphenylnicotinonitrile (3l)



Brown-yellow solid, yield 81%, m.p. 196.7-198.4 °C, ¹H NMR (500 MHz, [D₆]DMSO) δ 7.61 (d, *J* = 7.3 Hz, 2H), 7.52 (t, *J* = 7.4 Hz, 1H), 7.37 (dd, *J* = 7.6, 5.3

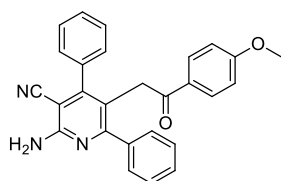
Hz, 4H), 7.35 – 7.31 (m, 6H), 7.24 (d, $J = 6.9$ Hz, 2H), 6.97 (s, 2H), 3.97 (s, 2H); ^{13}C NMR (125 MHz, CDCl_3) δ 198.44, 163.33, 157.97, 156.82, 139.74, 136.61, 136.44, 133.19, 129.22, 128.91, 128.88, 128.58, 128.54, 128.12, 128.09, 127.79, 118.00, 116.34, 91.94, 40.25. HRMS (ESI): m/z calcd for $\text{C}_{26}\text{H}_{20}\text{N}_3\text{O}$ $[\text{M}+\text{H}]^+$: 390.1601, found: 390.1603.

2-amino-5-(2-oxo-2-(p-tolyl)ethyl)-4,6-diphenylnicotinonitrile (3m)



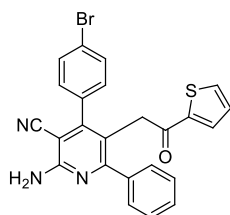
Brown solid, yield 81%, m.p. 183.1-184.9 °C, ^1H NMR (500 MHz, $[\text{D}_6]\text{DMSO}$) δ 7.53 (d, $J = 8.2$ Hz, 2H), 7.37 (d, $J = 7.4$ Hz, 2H), 7.35 – 7.32 (m, 6H), 7.25 – 7.22 (m, 2H), 7.15 (d, $J = 8.0$ Hz, 2H), 6.96 (s, 2H), 3.93 (s, 2H), 2.28 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 197.93, 163.30, 157.94, 156.80, 144.02, 139.78, 136.47, 134.07, 129.21, 129.17, 128.86, 128.83, 128.54, 128.13, 128.10, 127.94, 118.10, 116.37, 91.90, 40.13, 21.69. HRMS (ESI): m/z calcd for $\text{C}_{27}\text{H}_{22}\text{N}_3\text{O}$ $[\text{M}+\text{H}]^+$: 404.1757, found: 404.1763.

2-amino-5-(2-(4-methoxyphenyl)-2-oxoethyl)-4,6-diphenylnicotinonitrile (3n)



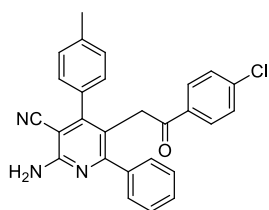
Orange solid, yield 80%, m.p. 188.8-189.5 °C, ^1H NMR (500 MHz, $[\text{D}_6]\text{DMSO}$) δ 7.63 (d, $J = 8.8$ Hz, 2H), 7.40 – 7.34 (m, 3H), 7.33 (s, 5H), 7.23 (d, $J = 6.8$ Hz, 2H), 6.95 (s, 2H), 6.86 (d, $J = 8.8$ Hz, 2H), 3.90 (s, 2H), 3.76 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 196.74, 163.58, 163.28, 157.90, 156.78, 139.78, 136.48, 130.13, 129.54, 129.16, 128.85, 128.81, 128.52, 128.16, 128.13, 118.27, 116.39, 113.67, 91.90, 55.54, 39.80. HRMS (ESI): m/z calcd for $\text{C}_{27}\text{H}_{22}\text{N}_3\text{O}_2$ $[\text{M}+\text{H}]^+$: 420.1707, found: 420.1705.

2-amino-4-(4-bromophenyl)-5-(2-oxo-2-(thiophen-2-yl)ethyl)-6-phenylnicotinonitrile (3o)



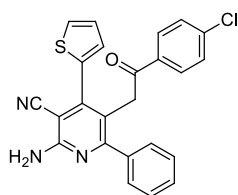
Brown solid, yield 85%, m.p. 215.4-216.2 °C, ¹H NMR (500 MHz, [D₆]DMSO) δ 7.90 (d, *J* = 4.4 Hz, 1H), 7.59 (d, *J* = 8.1 Hz, 2H), 7.54 (d, *J* = 2.9 Hz, 1H), 7.36 (s, 5H), 7.23 (d, *J* = 8.0 Hz, 2H), 7.04 (m, 3H), 3.93 (s, 2H); ¹³C NMR (125 MHz, CDCl₃) δ 190.69, 163.64, 157.95, 155.60, 143.01, 139.46, 135.19, 134.09, 132.18, 131.95, 129.96, 129.05, 128.63, 128.18, 128.12, 123.83, 117.54, 116.11, 91.57, 40.54. HRMS (ESI): *m/z* calcd for C₂₄H₁₇BrN₃OS [M+H]⁺: 474.0270, found: 474.0276.

2-amino-5-(2-(4-chlorophenyl)-2-oxoethyl)-6-phenyl-4-(p-tolyl)nicotinonitrile (3q)



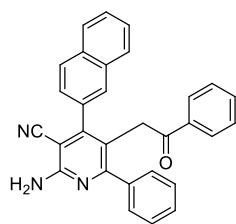
Pale yellow solid, yield 80%, m.p. 201.2-203.5 °C, ¹H NMR (500 MHz, [D₆]DMSO) δ 7.63 (d, *J* = 8.7 Hz, 2H), 7.43 (d, *J* = 8.7 Hz, 2H), 7.35 – 7.31 (m, 5H), 7.17 (d, *J* = 7.8 Hz, 2H), 7.11 (d, *J* = 8.1 Hz, 2H), 6.94 (s, 2H), 3.96 (s, 2H), 2.24 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 197.30, 163.23, 158.00, 156.93, 139.77, 139.64, 139.24, 134.87, 133.40, 129.60, 129.27, 128.92, 128.82, 128.60, 128.07, 127.98, 117.87, 116.44, 92.04, 40.12, 21.39. HRMS (ESI): *m/z* calcd for C₂₇H₂₁ClN₃O [M+H]⁺: 438.1368, found: 438.1369.

2-amino-5-(2-(4-chlorophenyl)-2-oxoethyl)-6-phenyl-4-(thiophen-2-yl)nicotinonitrile (3r)



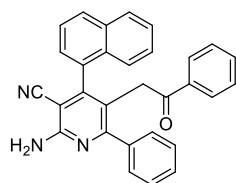
Brown solid, yield 82%, m.p. 202.7-204.1 °C, ¹H NMR (500 MHz, [D₆]DMSO) δ 7.75 (d, *J* = 8.6 Hz, 2H), 7.66 (dd, *J* = 5.0, 1.1 Hz, 1H), 7.48 (d, *J* = 8.6 Hz, 2H), 7.35 – 7.32 (m, 5H), 7.11 (dd, *J* = 3.5, 1.1 Hz, 1H), 7.08 – 7.04 (m, 3H), 4.06 (s, 2H); ¹³C NMR (125 MHz, CDCl₃) δ 197.12, 163.42, 158.12, 149.61, 139.87, 139.54, 135.39, 134.72, 129.46, 129.40, 129.10, 128.99, 128.65, 128.16, 128.04, 127.65, 118.92, 116.18, 92.81, 40.59. HRMS (ESI): *m/z* calcd for C₂₄H₁₇ClN₃OS [M+H]⁺: 430.0775, found: 430.0779.

2-amino-4-(naphthalen-2-yl)-5-(2-oxo-2-phenylethyl)-6-phenylnicotinonitrile (3s)



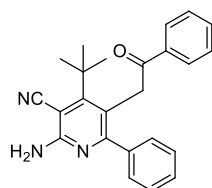
Brown-yellow solid, yield 79%, m.p. 200.1-202.2 °C, ¹H NMR (500 MHz, [D₆]DMSO) δ 7.92 (d, *J* = 8.5 Hz, 1H), 7.90 – 7.87 (m, 2H), 7.83 (s, 1H), 7.58 – 7.55 (m, 2H), 7.54 – 7.50 (m, 2H), 7.43 (t, *J* = 7.4 Hz, 1H), 7.39 – 7.36 (m, 3H), 7.34 (dd, *J* = 7.5, 5.0 Hz, 3H), 7.25 (t, *J* = 7.8 Hz, 2H), 7.01 (s, 2H), 4.02 (s, 2H); ¹³C NMR (125 MHz, CDCl₃) δ 198.50, 163.39, 158.02, 156.71, 139.77, 136.51, 133.85, 133.30, 133.11, 133.02, 128.92, 128.84, 128.59, 128.44, 128.14, 127.89, 127.87, 127.72, 127.01, 126.79, 125.44, 118.27, 116.40, 92.06, 40.28. HRMS (ESI): *m/z* calcd for C₃₀H₂₂N₃O [M+H]⁺: 440.1757, found: 440.1764.

2-amino-4-(naphthalen-1-yl)-5-(2-oxo-2-phenylethyl)-6-phenylnicotinonitrile (3t)



Yellow solid, yield 78%, m.p. 210.1-212.0 °C, ¹H NMR (500 MHz, [D₆]DMSO) δ 7.94 (dd, *J* = 5.5, 3.9 Hz, 1H), 7.88 (d, *J* = 8.3 Hz, 1H), 7.54 (dt, *J* = 6.3, 2.8 Hz, 2H), 7.48 – 7.41 (m, 5H), 7.38 – 7.33 (m, 5H), 7.31 (dd, *J* = 7.1, 0.9 Hz, 1H), 7.22 (t, *J* = 7.8 Hz, 2H), 7.03 (s, 2H), 3.97 (d, *J* = 18.3 Hz, 1H), 3.64 (d, *J* = 18.3 Hz, 1H); ¹³C NMR (125 MHz, CDCl₃) δ 198.07, 163.44, 158.05, 155.42, 139.67, 136.50, 133.60, 133.42, 132.97, 130.27, 129.62, 128.98, 128.77, 128.59, 128.32, 127.56, 127.25, 127.23, 126.50, 125.42, 124.62, 119.45, 116.01, 92.85, 39.78. HRMS (ESI): *m/z* calcd for C₃₀H₂₂N₃O [M+H]⁺: 440.1757, found: 440.1759.

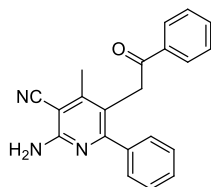
2-amino-4-(tert-butyl)-5-(2-oxo-2-phenylethyl)-6-phenylnicotinonitrile (3u)



Pale yellow solid, yield 83%, m.p. 218.2-219.1 °C, ¹H NMR (500 MHz, [D₆]DMSO) δ 7.83 – 7.80 (m, 2H), 7.61 – 7.57 (m, 1H), 7.45 (t, *J* = 7.8 Hz, 2H), 7.30 – 7.24 (m,

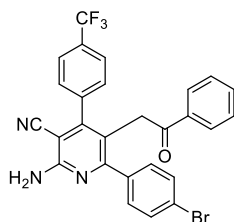
3H), 7.15 (dd, $J = 7.8, 1.6$ Hz, 2H), 6.63 (s, 2H), 4.53 (s, 2H), 1.50 (s, 9H); ^{13}C NMR (125 MHz, CDCl_3) δ 198.45, 165.46, 163.35, 159.83, 141.10, 136.57, 133.33, 128.74, 128.58, 128.41, 127.87, 127.71, 119.49, 117.21, 90.42, 42.32, 39.25, 32.33. HRMS (ESI): m/z calcd for $\text{C}_{24}\text{H}_{24}\text{N}_3\text{O}$ $[\text{M}+\text{H}]^+$: 370.1914, found: 370.1913.

2-amino-4-methyl-5-(2-oxo-2-phenylethyl)-6-phenylnicotinonitrile (3v)



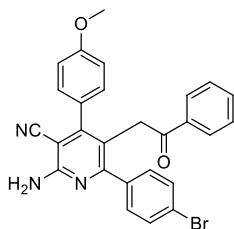
Pale yellow solid, yield 79%, m.p. 198.2-200.4 °C, ^1H NMR (500 MHz, $[\text{D}_6]\text{DMSO}$) δ 7.94 (d, $J = 7.2$ Hz, 2H), 7.65 (t, $J = 7.4$ Hz, 1H), 7.51 (t, $J = 7.8$ Hz, 2H), 7.36 – 7.31 (m, 3H), 7.26 – 7.21 (m, 2H), 6.78 (s, 2H), 4.28 (s, 2H), 2.24 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 197.14, 162.41, 157.93, 153.41, 139.81, 136.37, 133.73, 128.92, 128.90, 128.65, 128.23, 128.15, 118.15, 116.60, 92.49, 39.97, 29.85. HRMS (ESI): m/z calcd for $\text{C}_{21}\text{H}_{18}\text{N}_3\text{O}$ $[\text{M}+\text{H}]^+$: 328.1444, found: 328.1439.

2-amino-6-(4-bromophenyl)-5-(2-oxo-2-phenylethyl)-4-(4-(trifluoromethyl)phenyl)nicotinonitrile (3w)



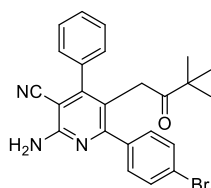
Yellow solid, yield 83%, m.p. 202.7-203.3 °C, ^1H NMR (500 MHz, $[\text{D}_6]\text{DMSO}$) δ 7.75 (d, $J = 8.2$ Hz, 2H), 7.59 (dd, $J = 15.3, 7.9$ Hz, 4H), 7.54 (t, $J = 7.4$ Hz, 1H), 7.50 (d, $J = 8.1$ Hz, 2H), 7.36 (dd, $J = 14.3, 8.1$ Hz, 4H), 7.16 (s, 2H), 4.00 (s, 2H); ^{13}C NMR (125 MHz, CDCl_3) δ 198.17, 162.40, 157.89, 155.36, 139.82, 138.27, 136.06, 133.73, 131.83, 129.89, 128.76, 128.73, 127.80, 127.78, 126.02, 125.99, 125.96, 123.62, 115.80, 91.71, 39.94. HRMS (ESI): m/z calcd for $\text{C}_{27}\text{H}_{18}\text{BrF}_3\text{N}_3\text{O}$ $[\text{M}+\text{H}]^+$: 536.0580, found: 536.0585.

2-amino-6-(4-bromophenyl)-4-(4-methoxyphenyl)-5-(2-oxo-2-phenylethyl)nicotinonitrile (3x)



Brown solid, yield 80%, m.p. 85.2-86.7 °C, ¹H NMR (500 MHz, [D₆]DMSO) δ 7.65 (d, *J* = 7.4 Hz, 2H), 7.55 (d, *J* = 8.3 Hz, 3H), 7.39 (t, *J* = 7.8 Hz, 2H), 7.31 (d, *J* = 8.4 Hz, 2H), 7.17 (d, *J* = 8.6 Hz, 2H), 6.98 (s, 2H), 6.92 (d, *J* = 8.7 Hz, 2H), 4.00 (s, 2H), 3.70 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 198.47, 161.98, 160.30, 157.98, 156.93, 138.78, 136.50, 133.38, 131.72, 129.96, 129.52, 128.65, 128.43, 127.87, 123.33, 118.35, 116.38, 114.41, 92.60, 55.35, 40.27. HRMS (ESI): *m/z* calcd for C₂₇H₂₁BrN₃O₂ [M+H]⁺: 498.0812, found: 498.0839.

2-amino-6-(4-bromophenyl)-5-(3,3-dimethyl-2-oxobutyl)-4-phenylnicotinonitrile (3y)



Light brown solid, yield 76%, m.p. 179.8-181.2 °C, ¹H NMR (500 MHz, [D₆]DMSO) δ 7.64 (d, *J* = 8.5 Hz, 2H), 7.50 – 7.45 (m, 3H), 7.22 (d, *J* = 8.4 Hz, 2H), 7.16 (d, *J* = 6.3 Hz, 2H), 6.97 (s, 2H), 3.49 (s, 2H), 0.68 (s, 9H); ¹³C NMR (125 MHz, CDCl₃) δ 213.40, 161.93, 157.77, 156.81, 138.71, 136.33, 131.62, 129.90, 129.30, 128.88, 128.04, 123.34, 117.88, 116.11, 92.25, 44.10, 38.67, 26.51. HRMS (ESI): *m/z* calcd for C₂₄H₂₃BrN₃O [M+H]⁺: 448.1019, found: 448.1034.

X-ray Crystallography Data of 3a (CCDC No. 1431902)

Single crystals of compound **3a** were measured on a Rigaku RAXIS-RAPID single-crystal diffractometer.

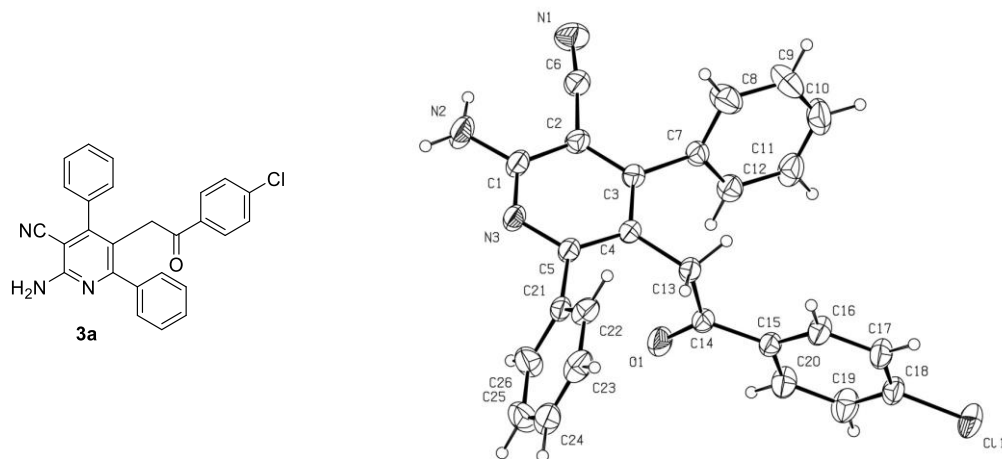


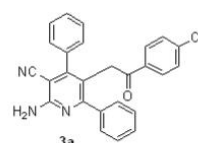
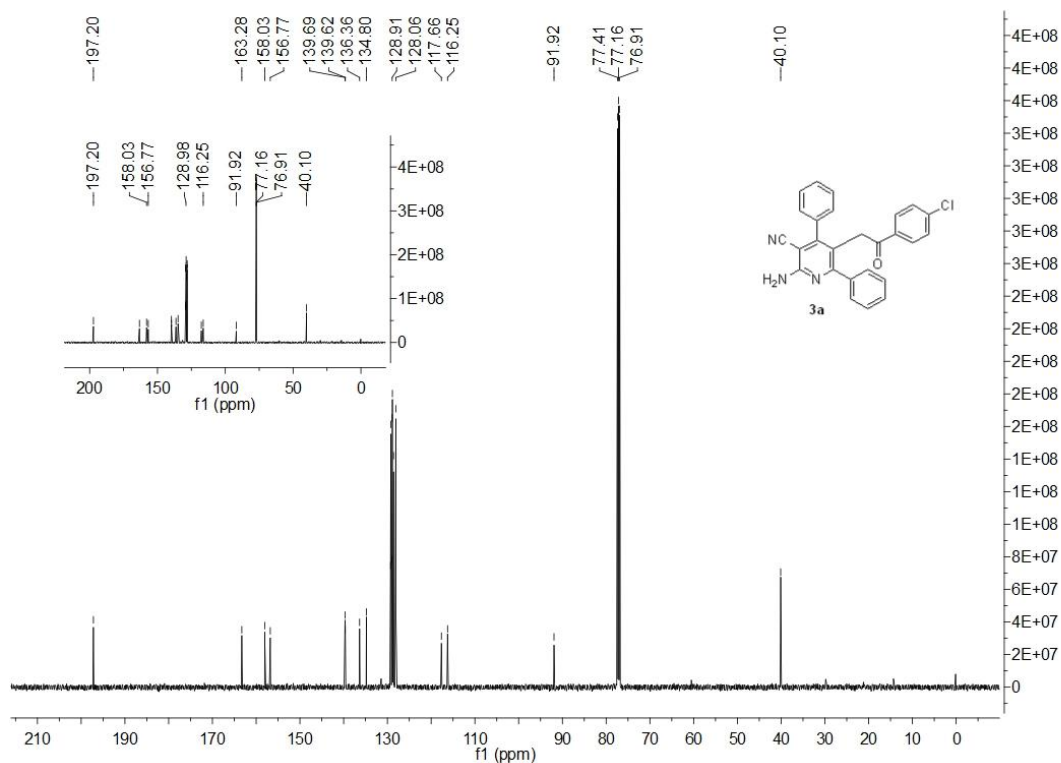
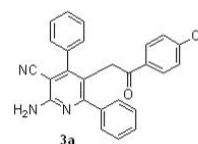
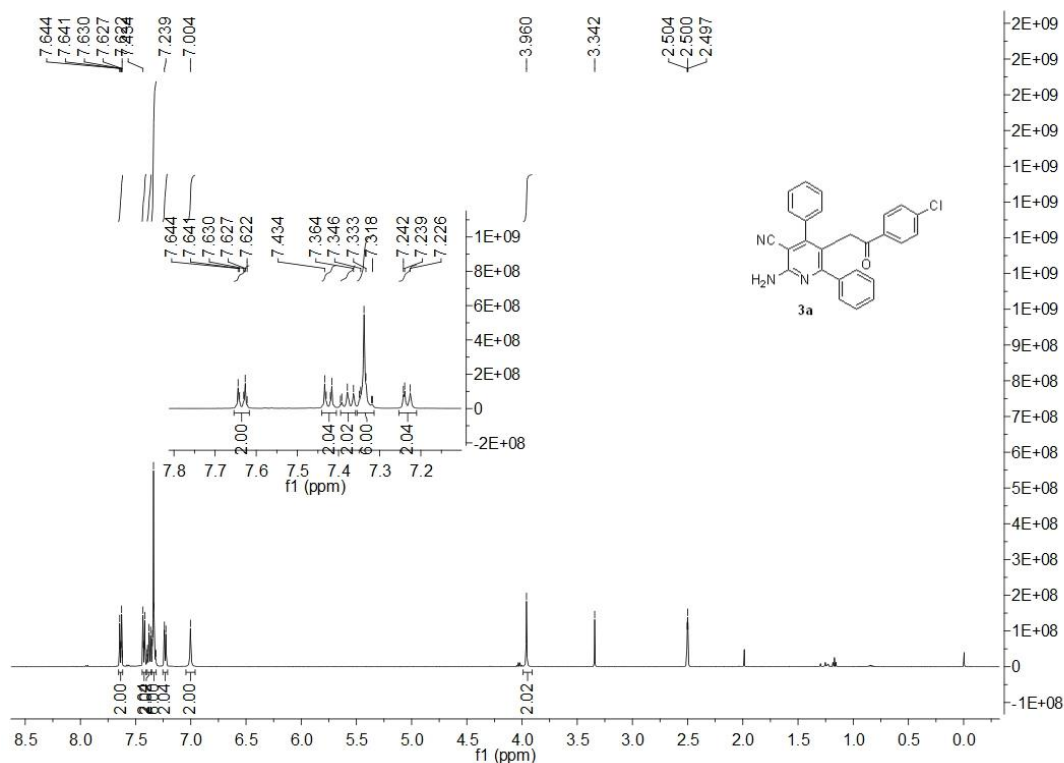
Figure S1. X-ray crystal structure of **3a**

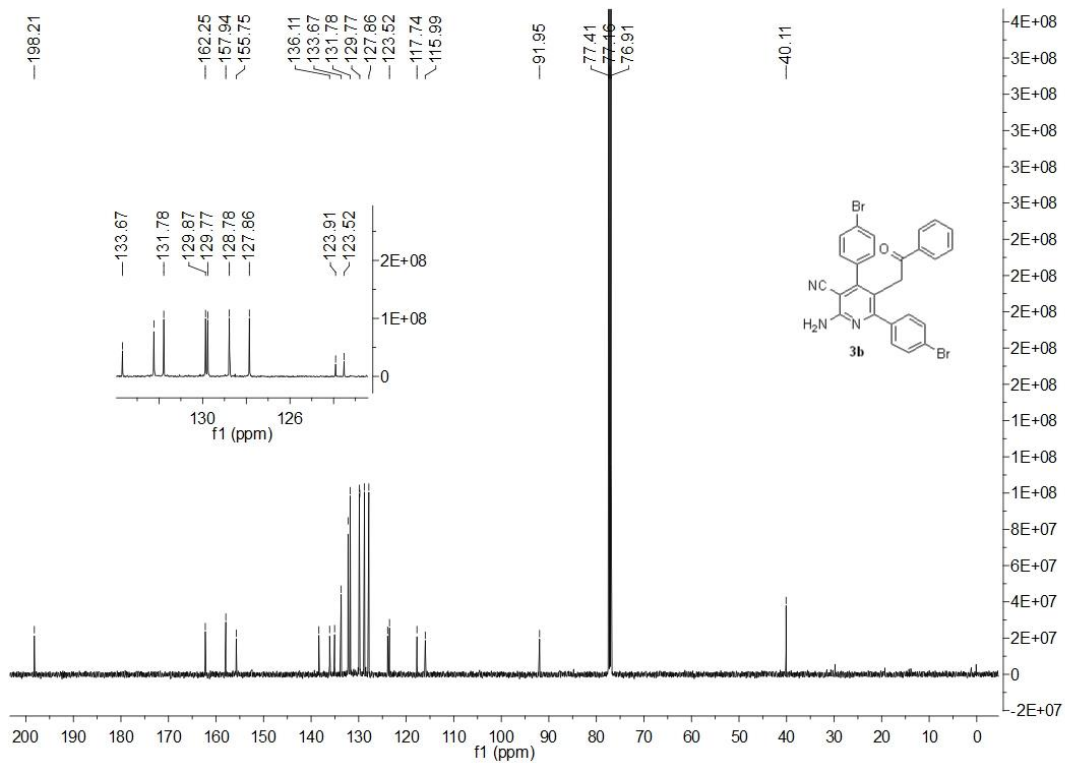
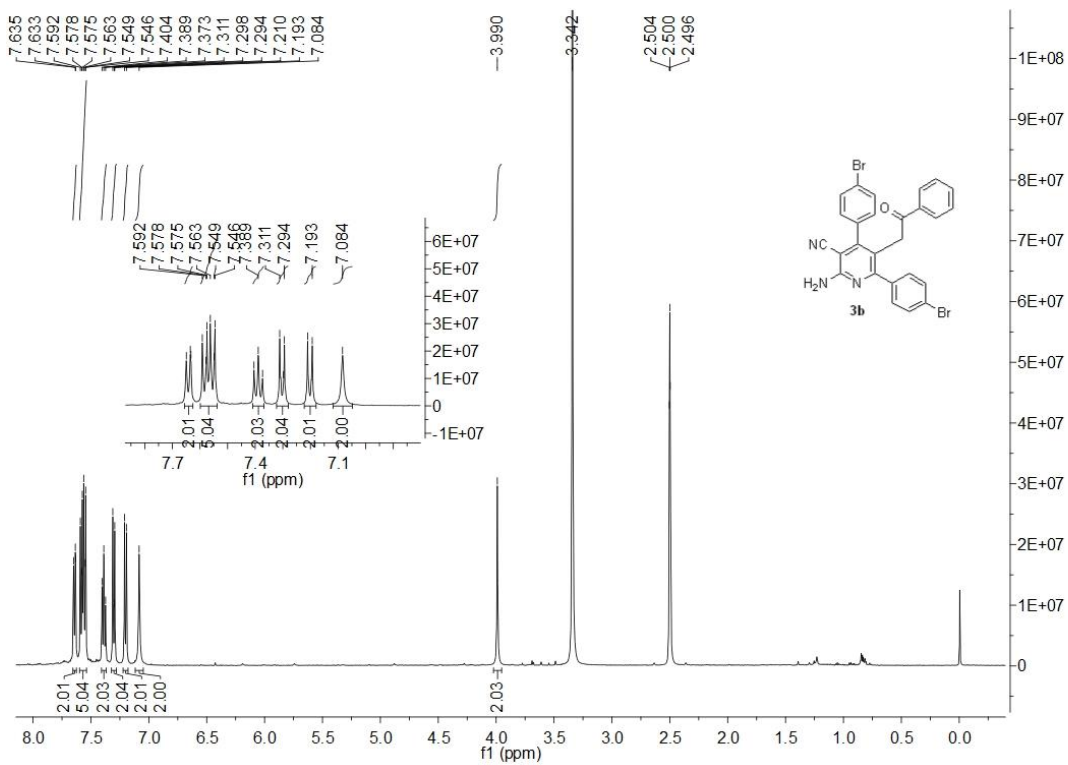
Table S1. X-ray crystallography data of **3a**

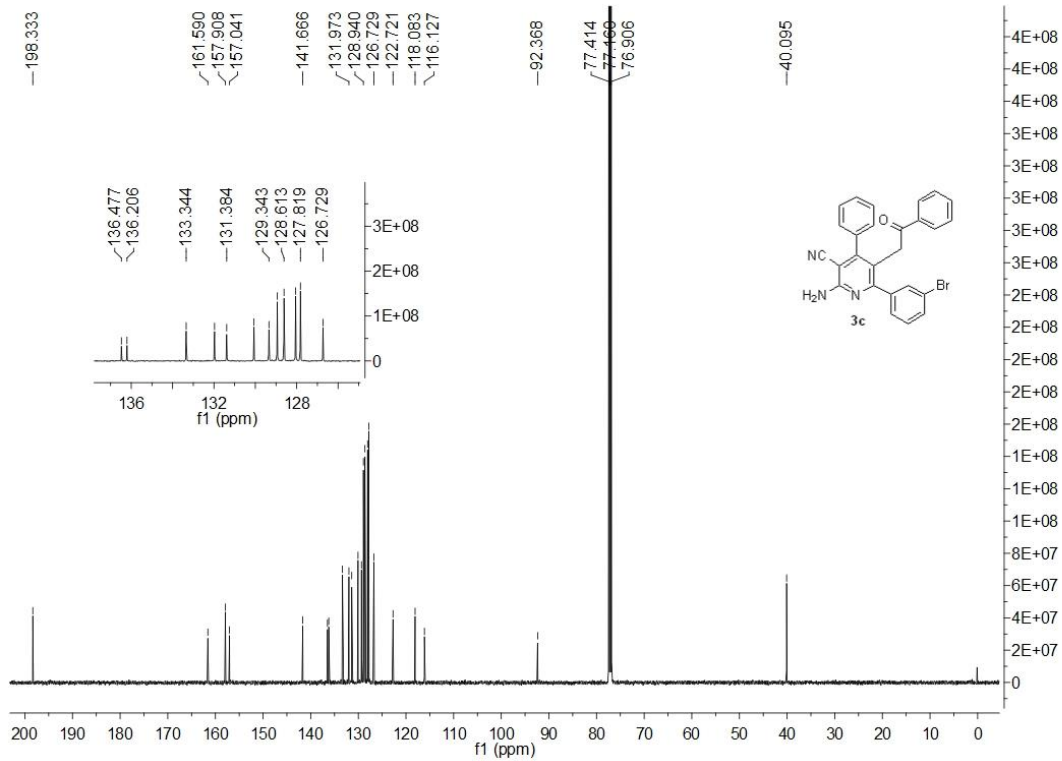
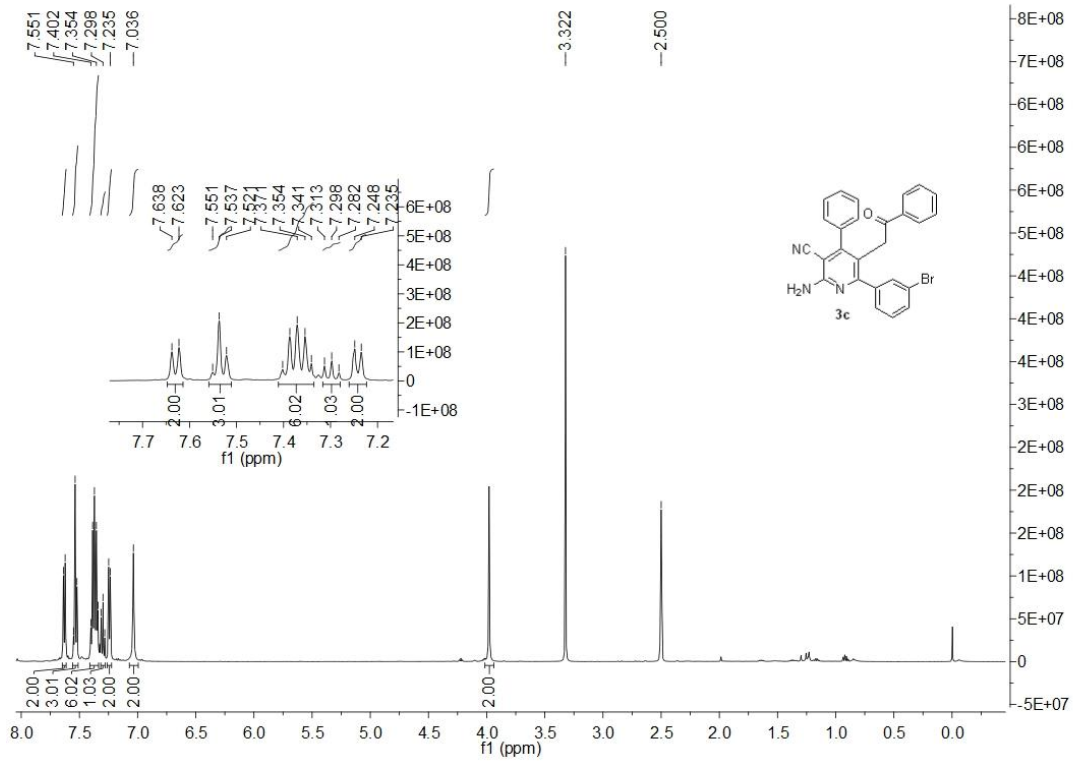
Formula moiety	C ₂₆ H ₁₈ ClN ₃ O
Formula sum	C ₂₆ H ₁₈ ClN ₃ O
Formula weight	423.88
Temperature	293(2) K
Crystal system	monoclinic
Space group	P 1 21 /c 1
Unit cell dimensions	a= 12.1894(9) Å b= 9.6526(7) Å c= 20.0169(17) Å alpha=90.00 deg. beta = 109.306(6) deg. gamma = 90.00 deg.
Volume	2222.7 (3) Å ³
Z	4
Calculated density	1.267 g/cm ³
Absorption coefficient	0.194 mm ⁻¹
F(000)	880.0
Crystal size	0.45 x 0.28 x 0.2 mm
Theta range for data collection	3.0113 to 29.4476 deg
Reflections collected / unique	9063 / 4066 [R(int) = 0.0356]

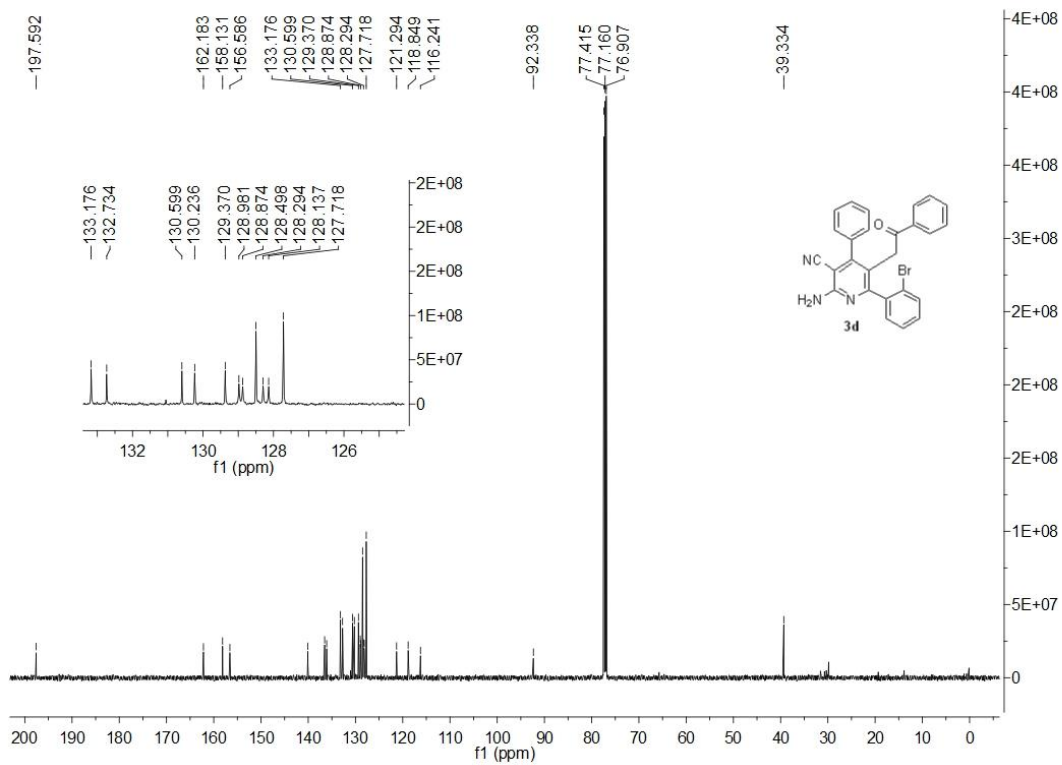
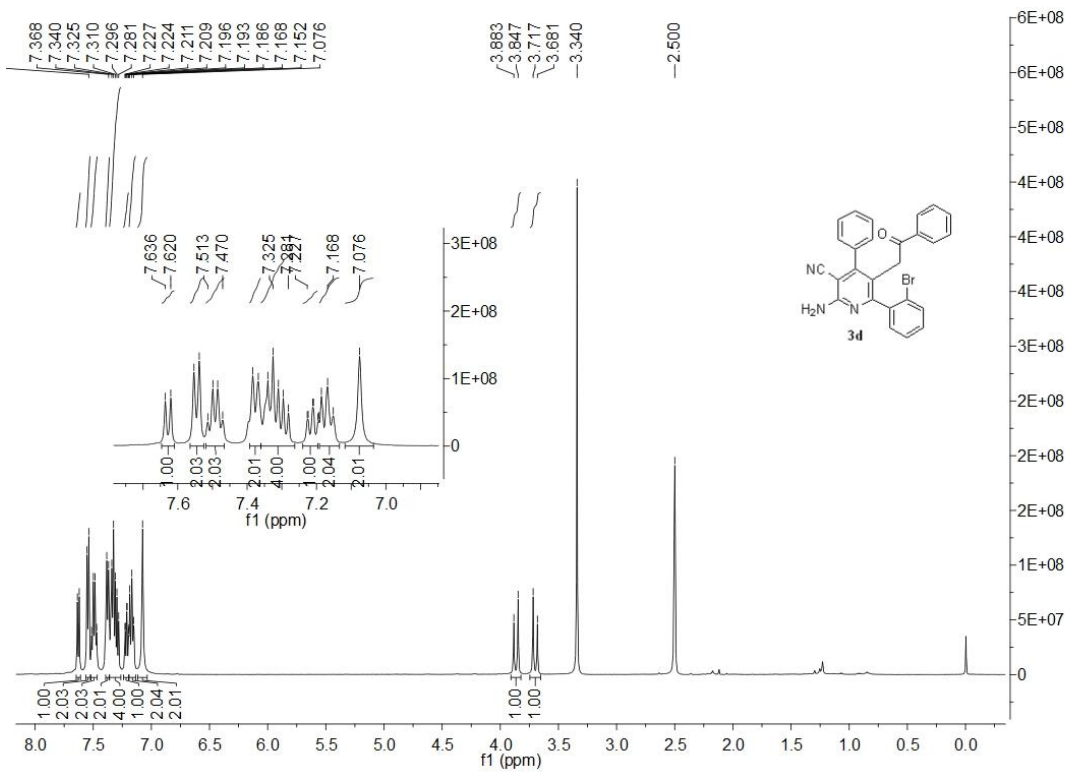
Data / restraints / parameters	4066 / 1 / 285
Goodness-of-fit on F2	1.023
Final R indices [$I > 2\sigma(I)$]	R1 = 0.0512, wR2 = 0.1103
R indices (all data)	R1 = 0.0906, wR2 = 0.1309

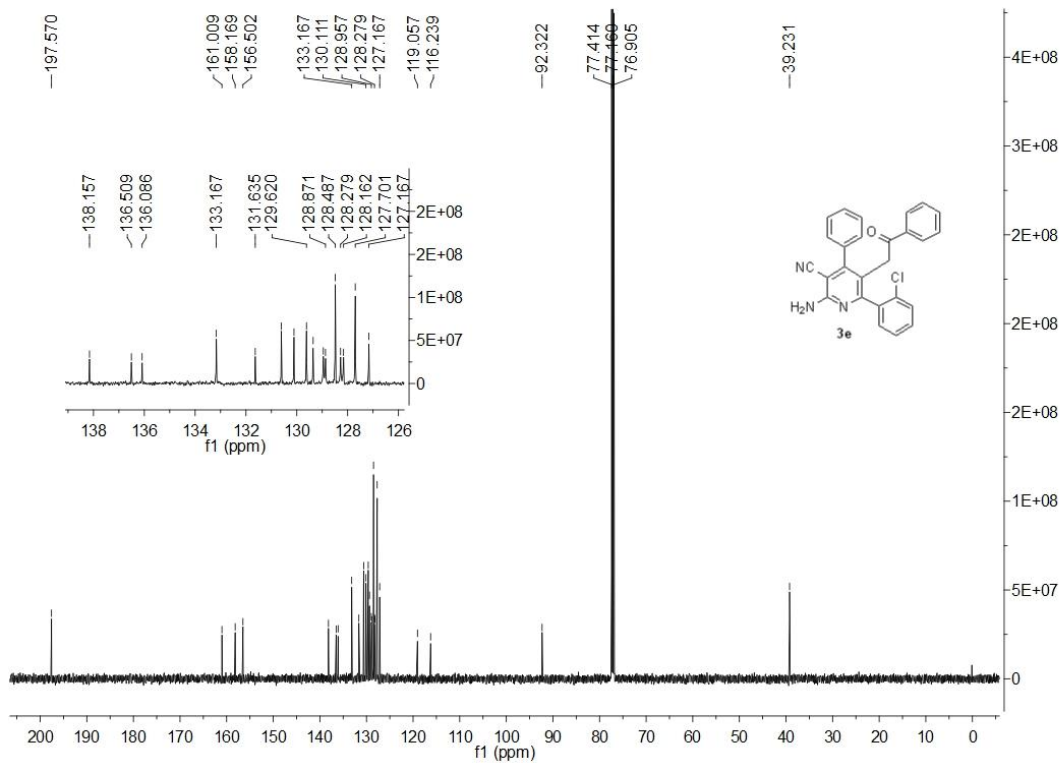
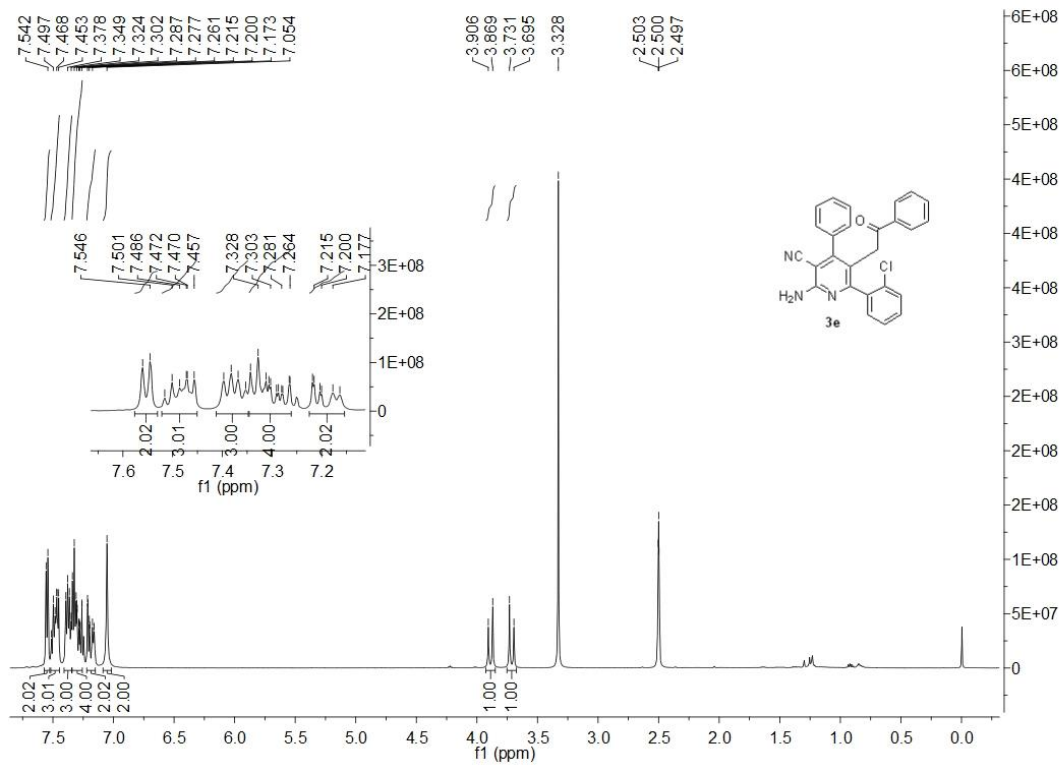
^1H NMR and ^{13}C NMR Spectra of Final Products

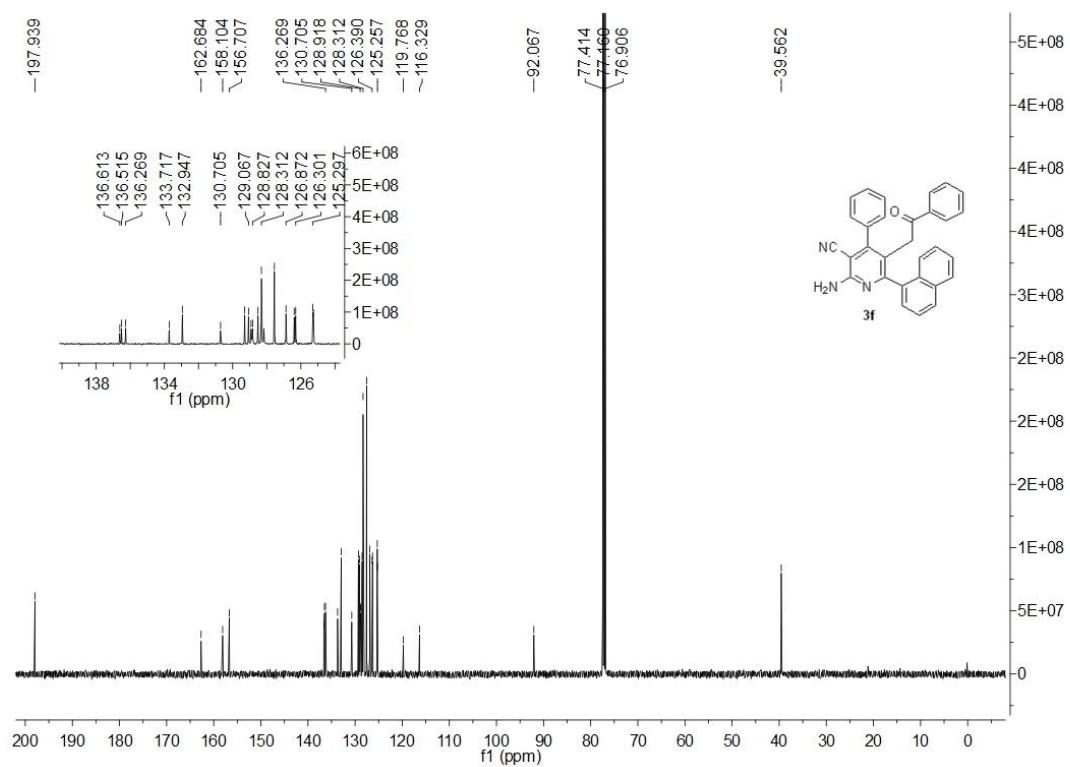
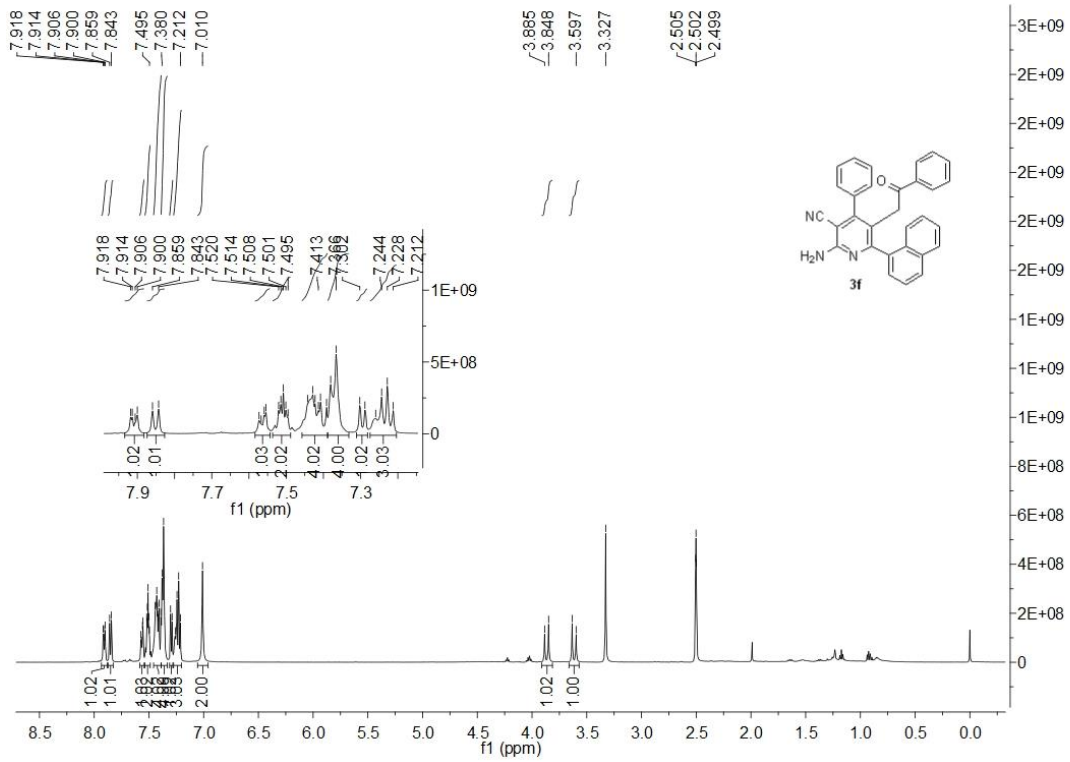


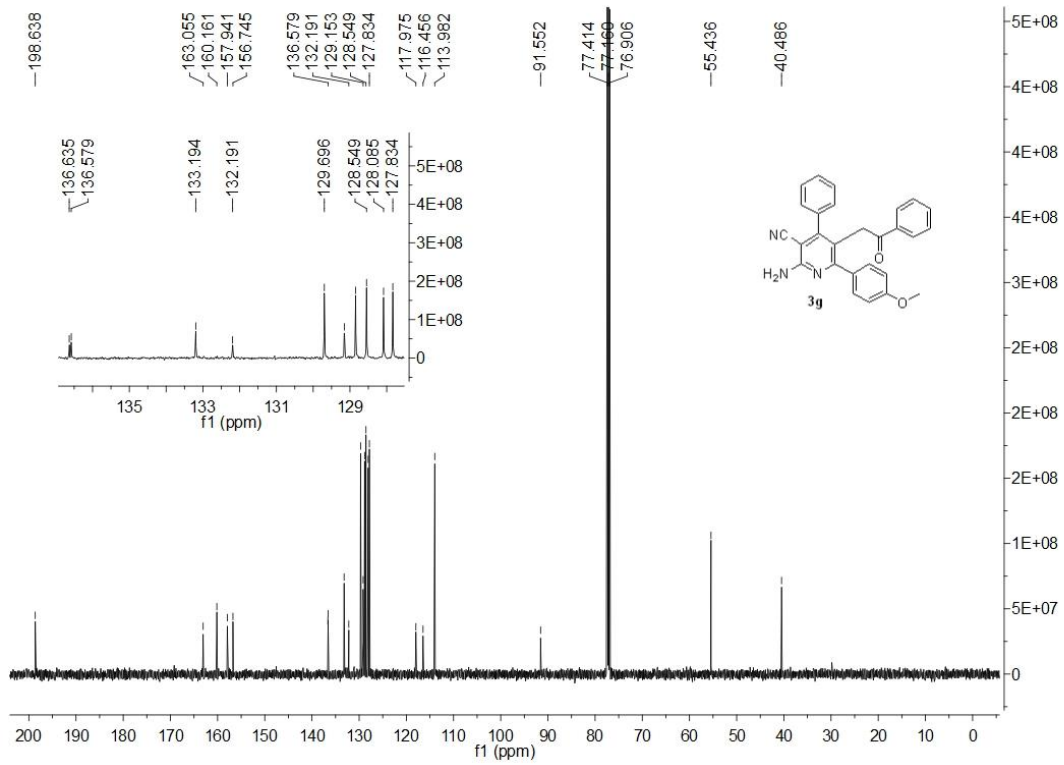
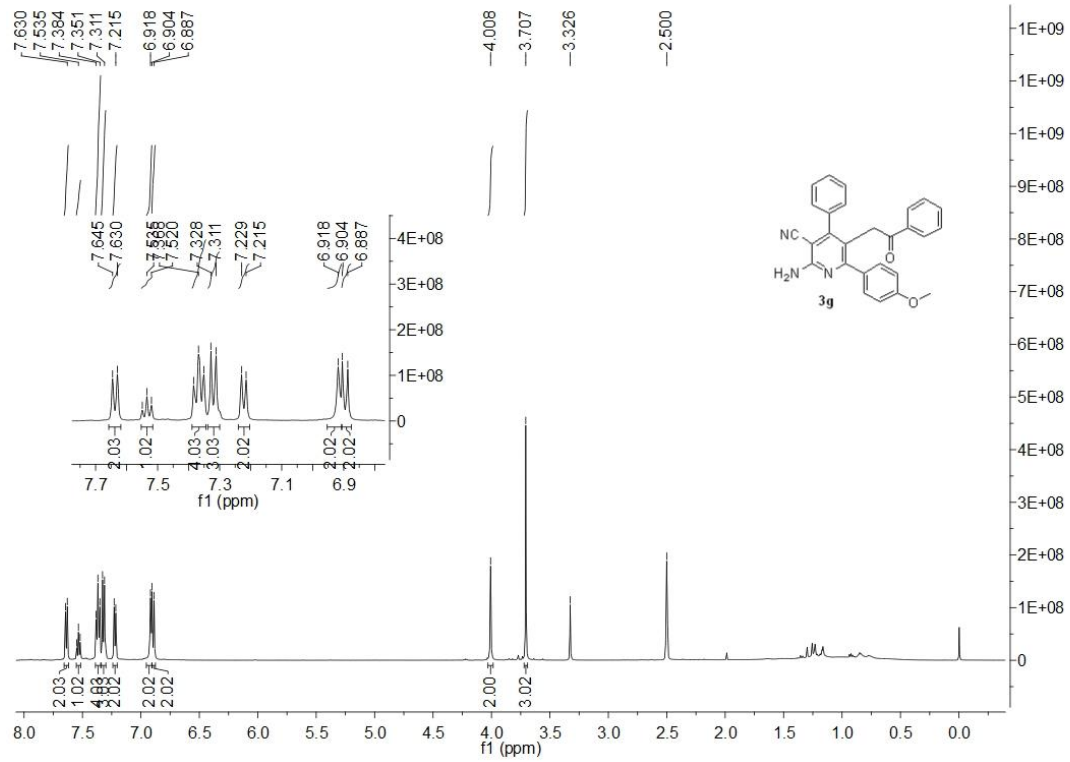


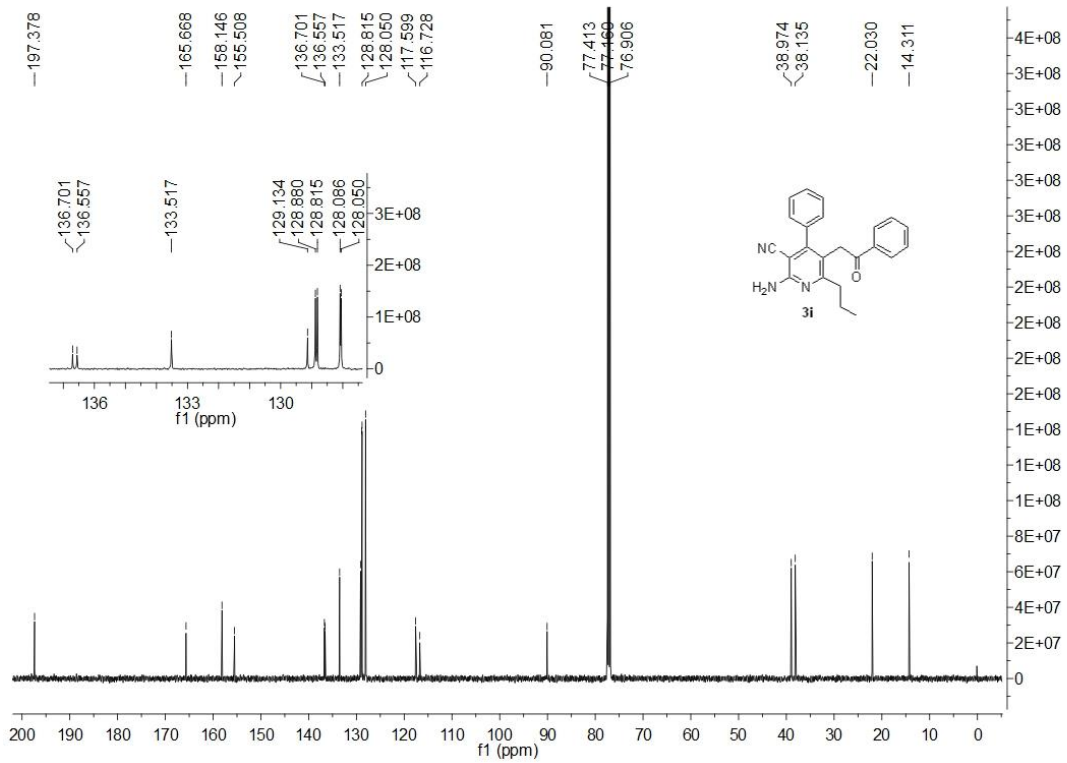
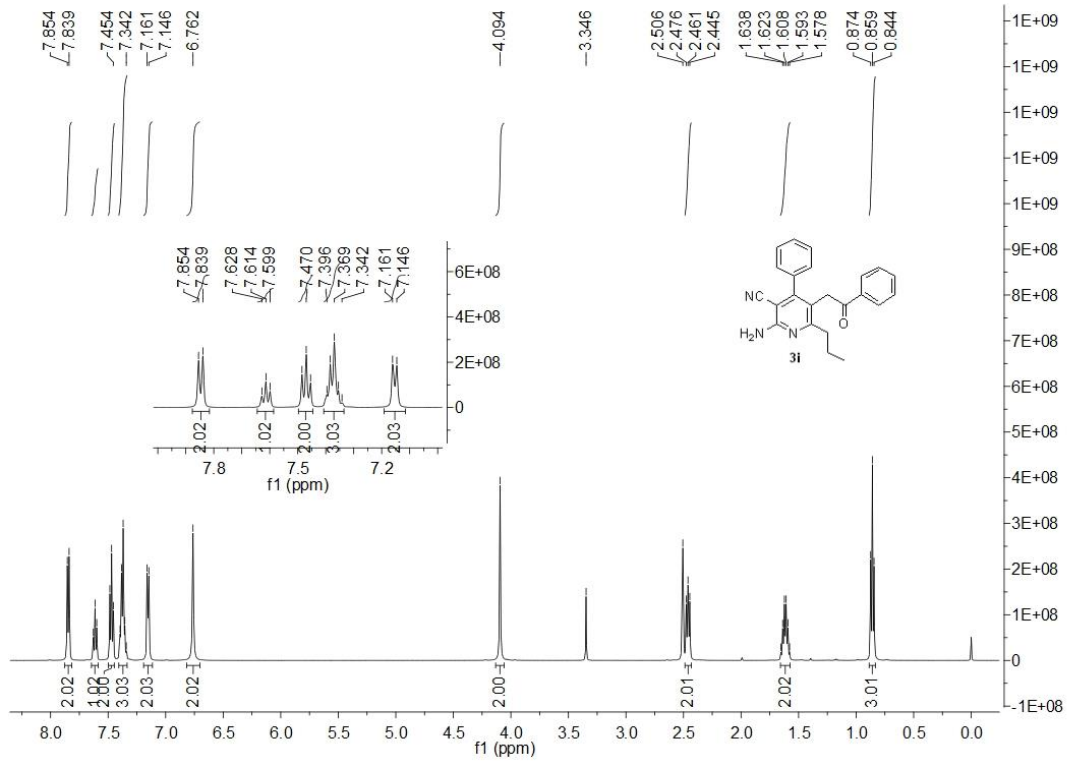


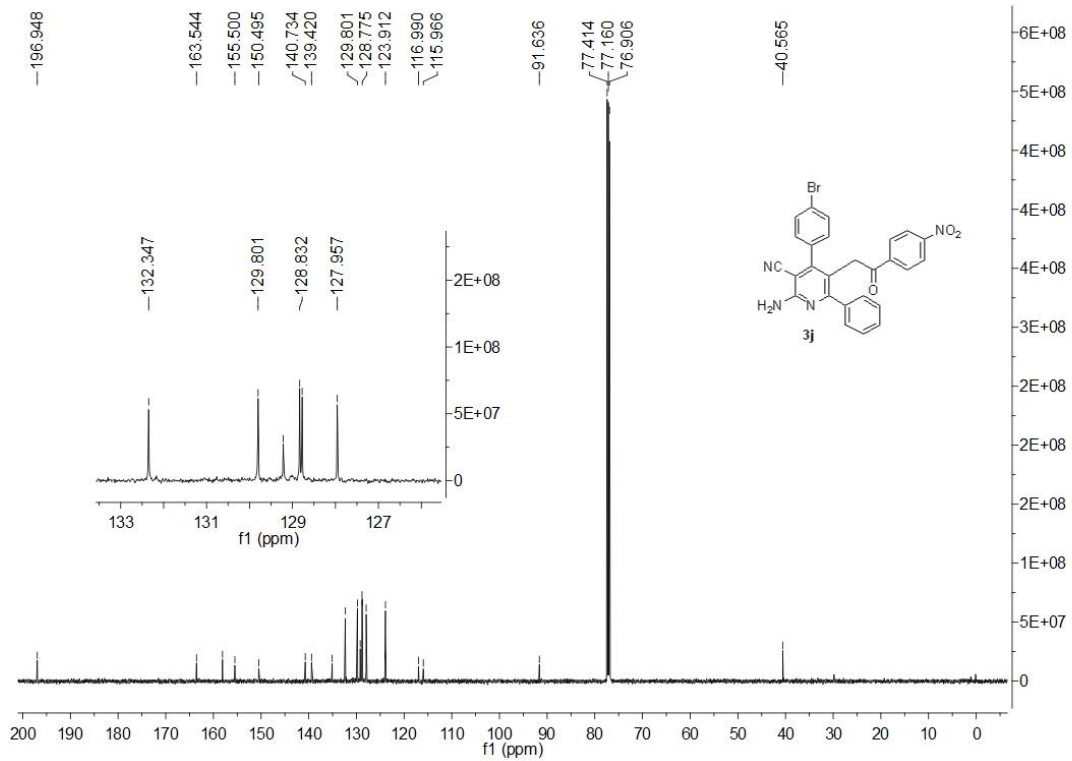
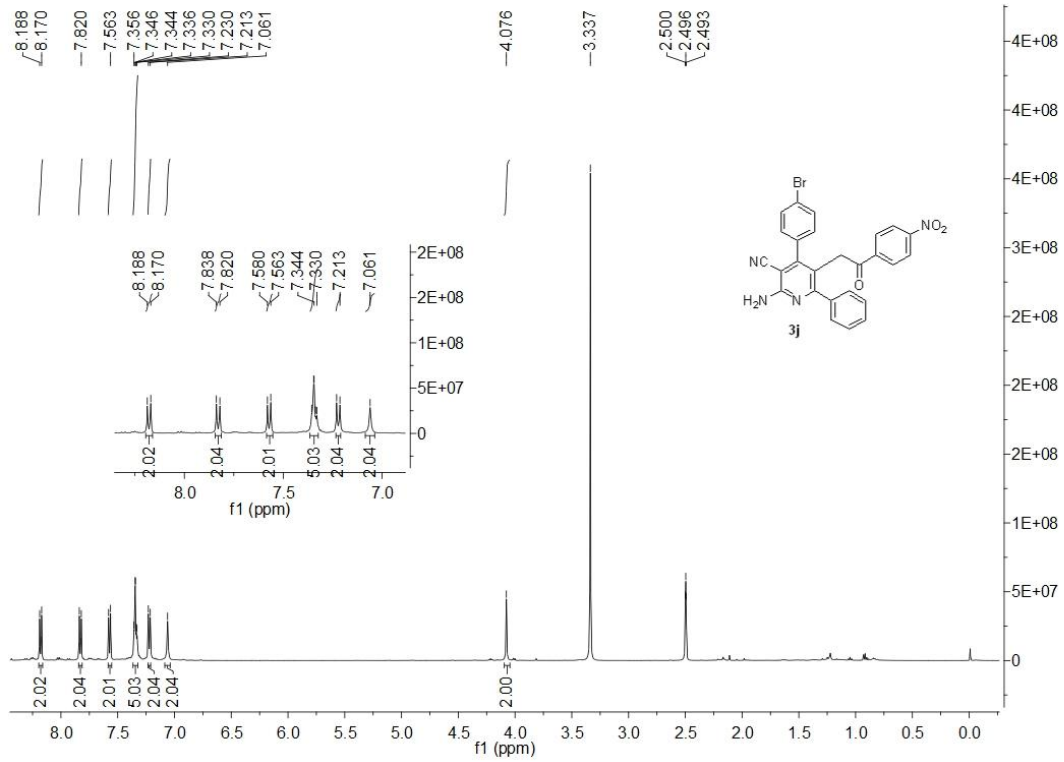


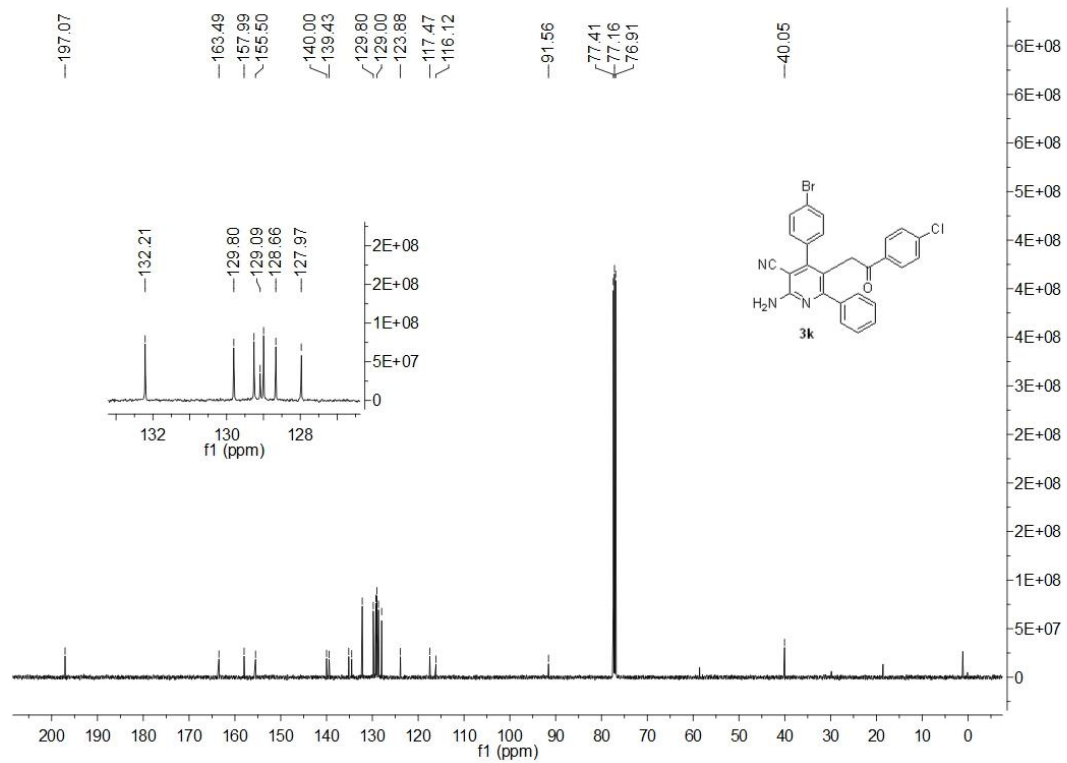
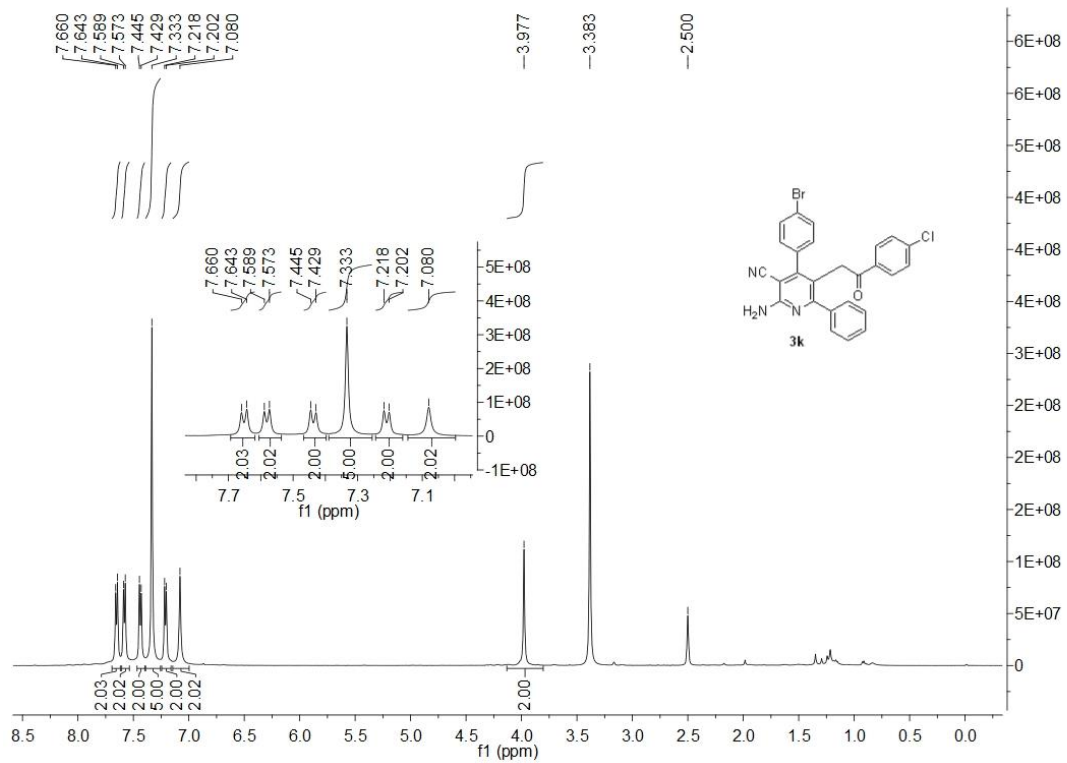


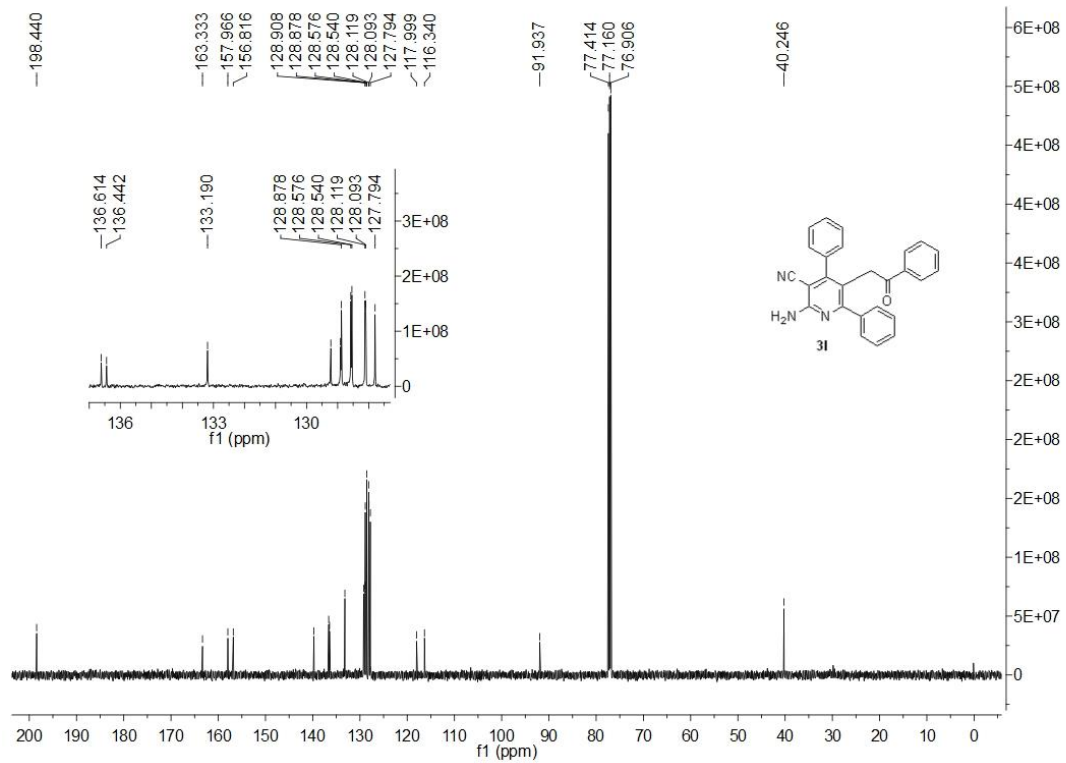
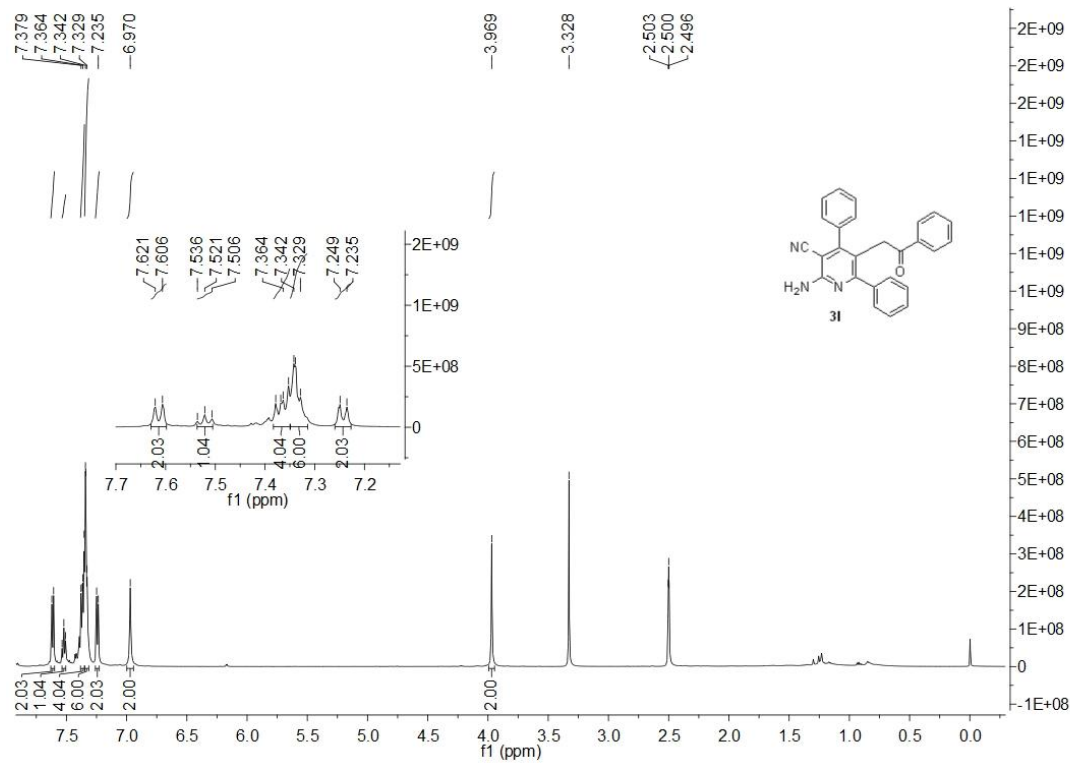


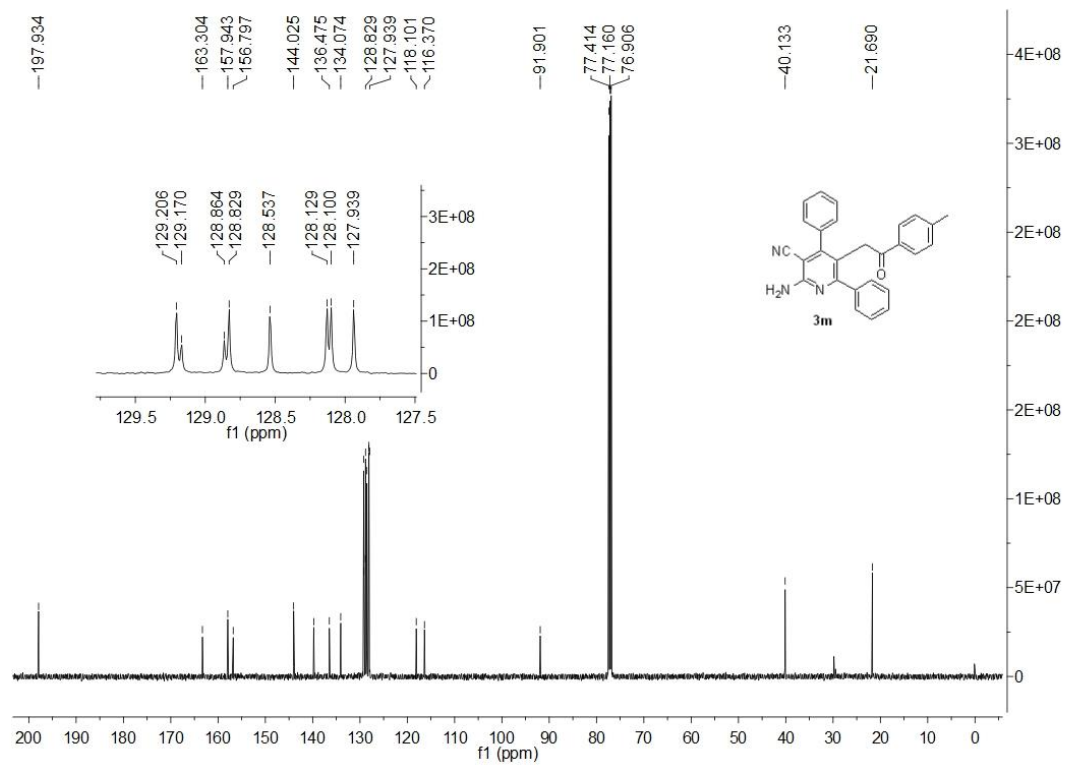
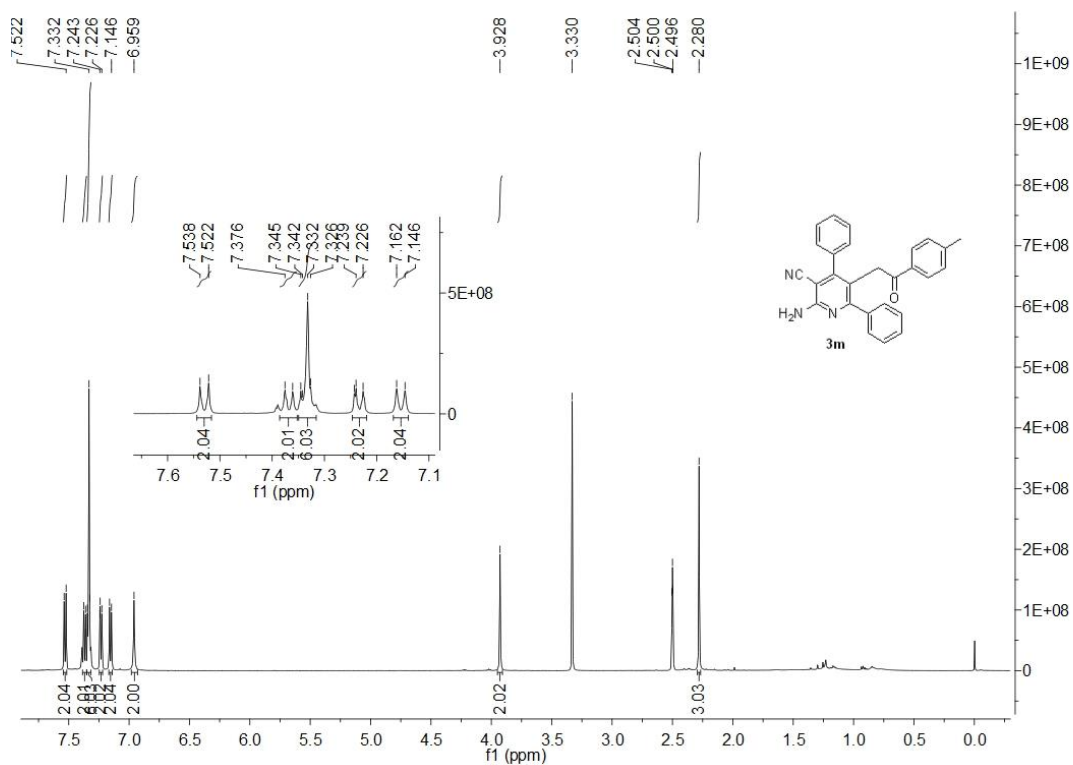


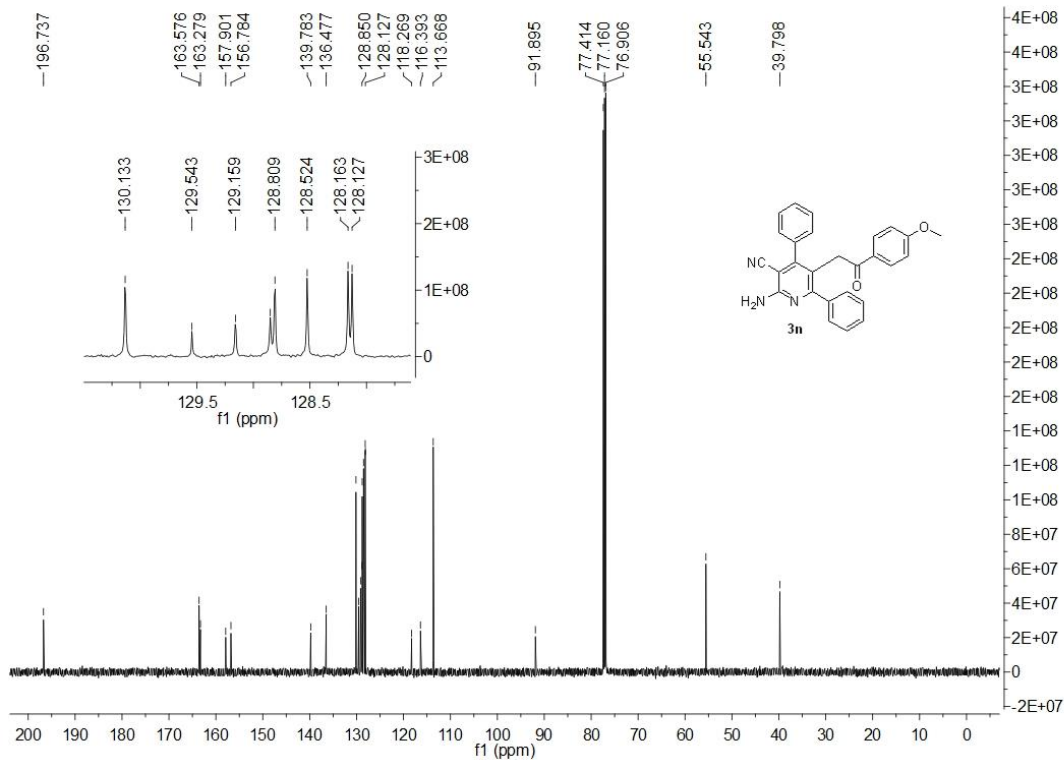
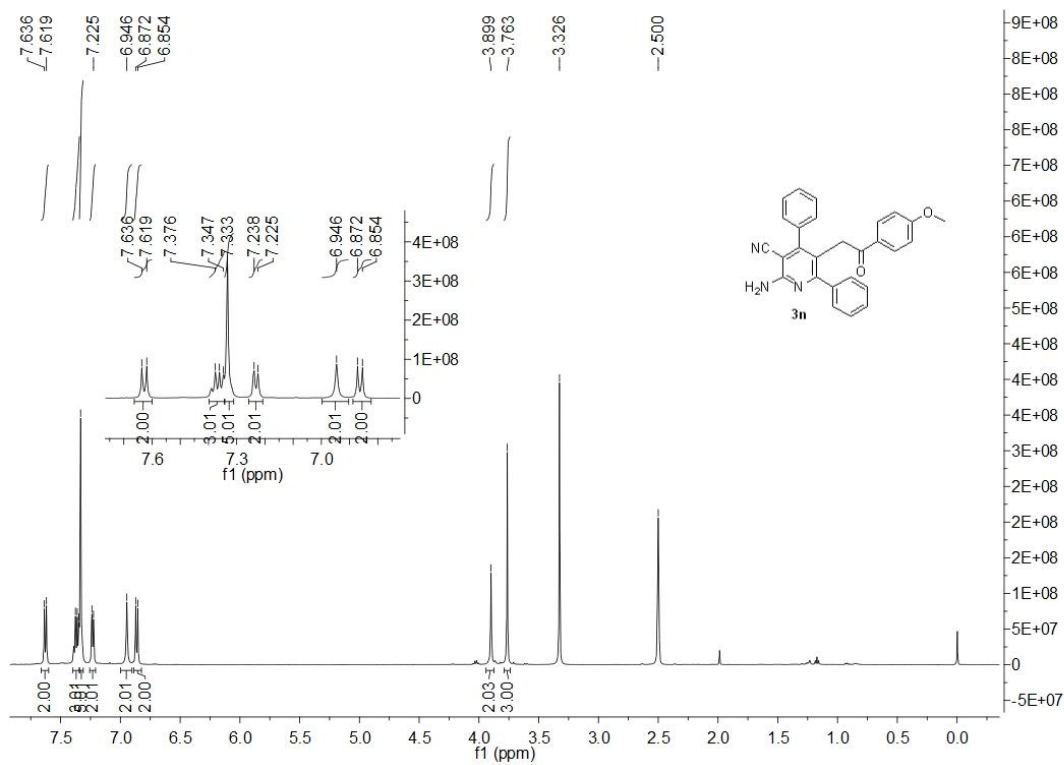


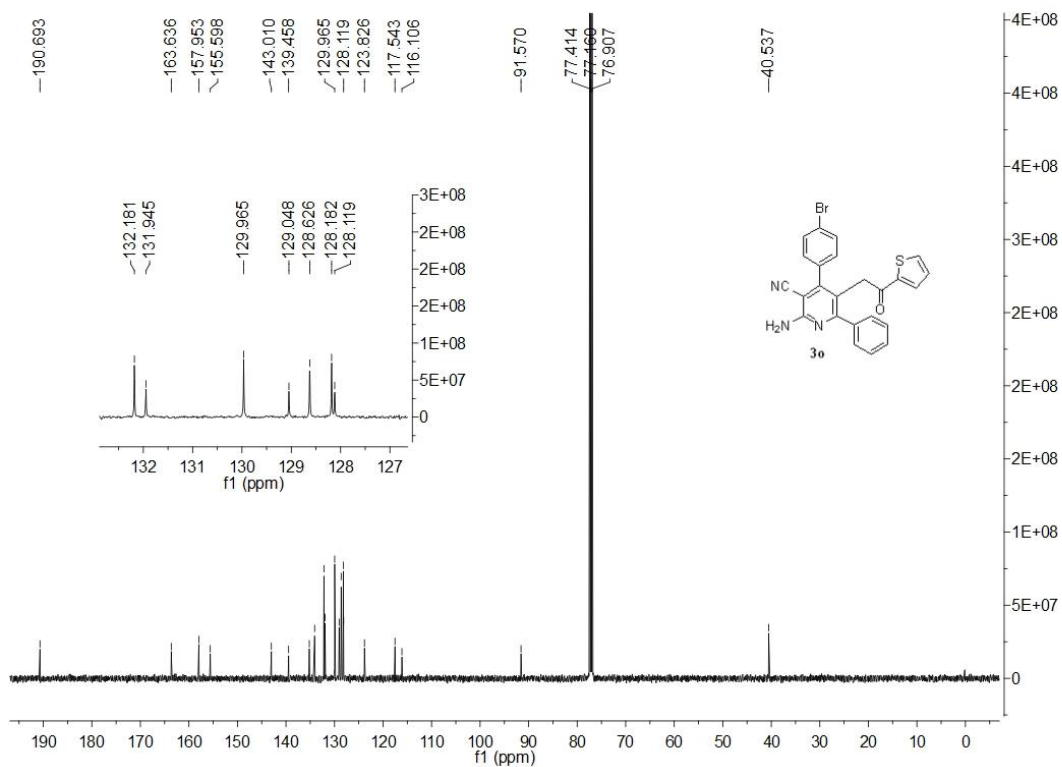
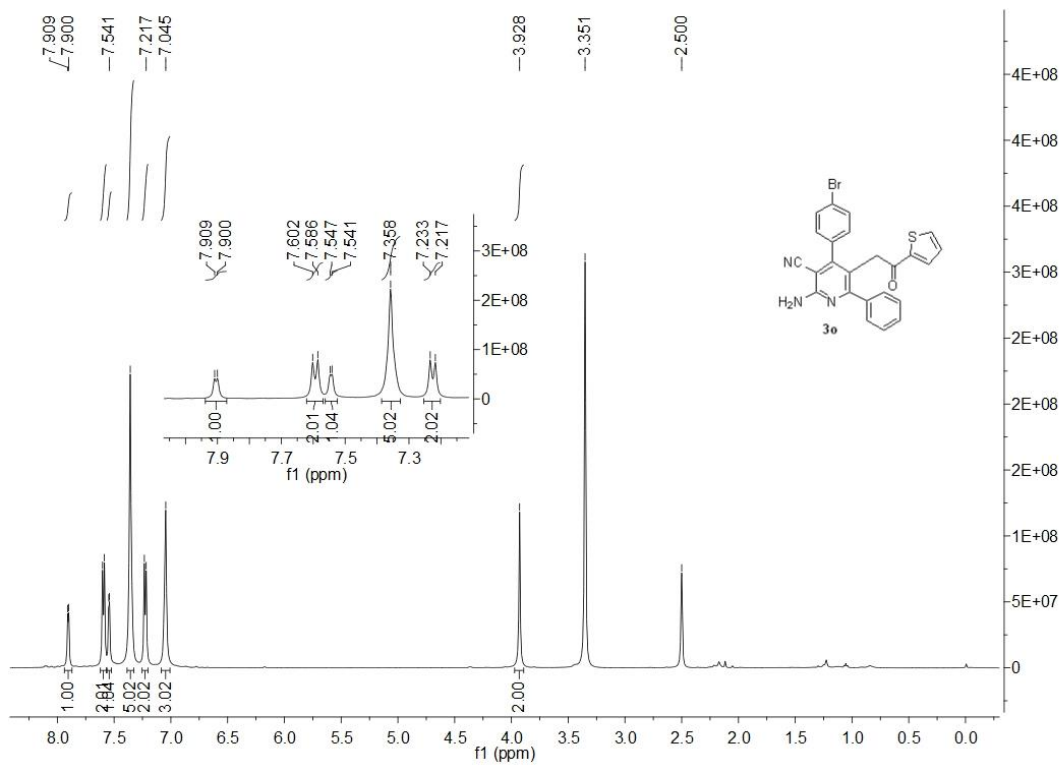


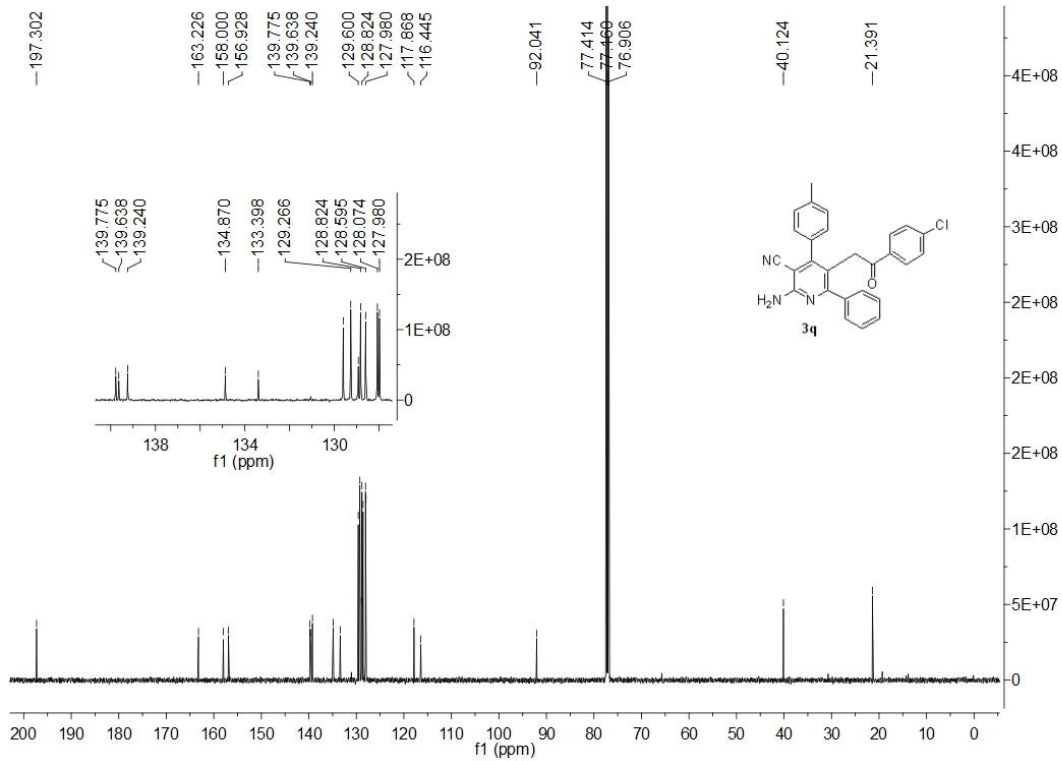
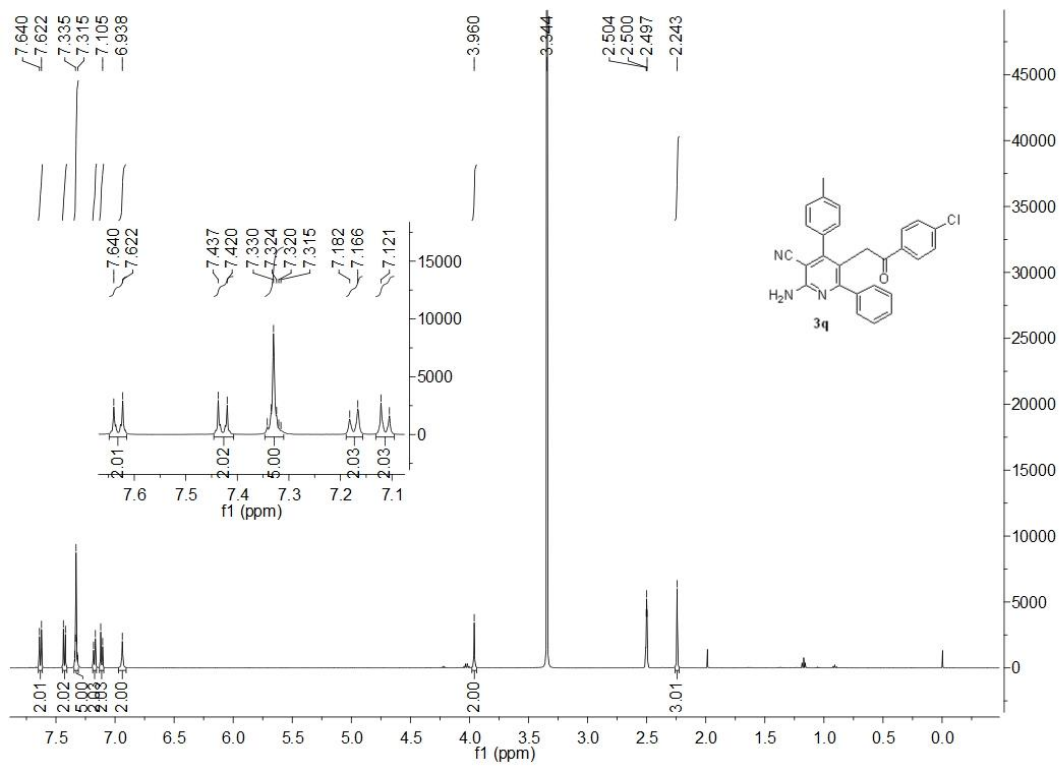


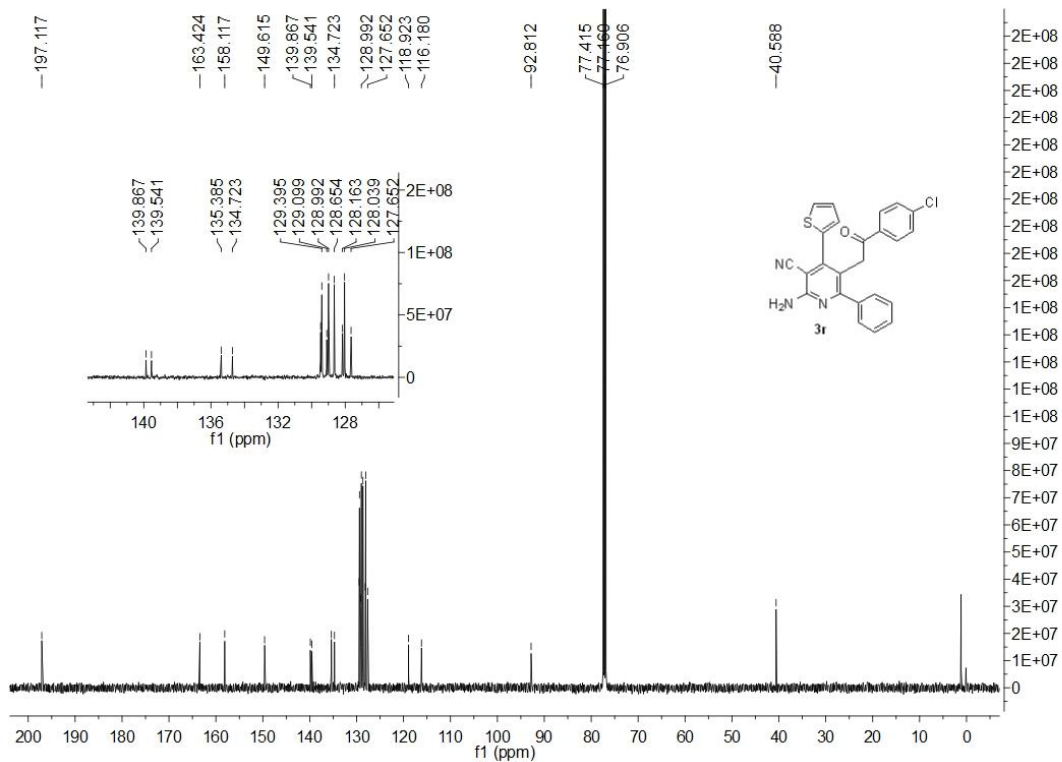
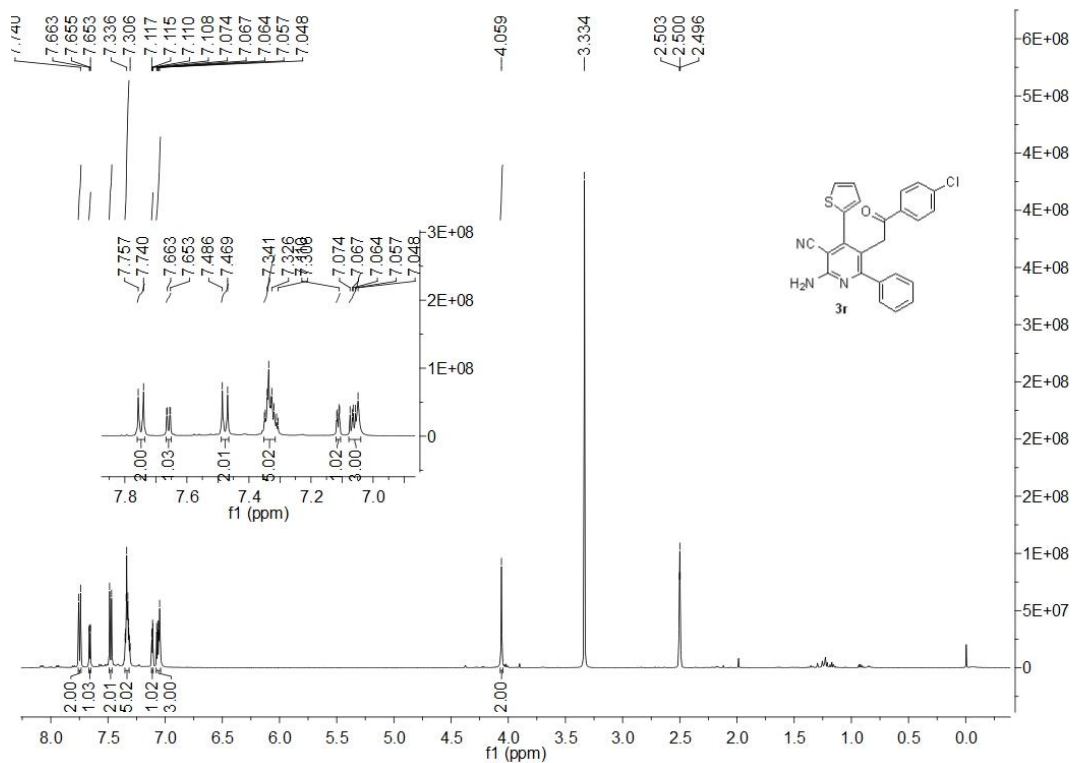


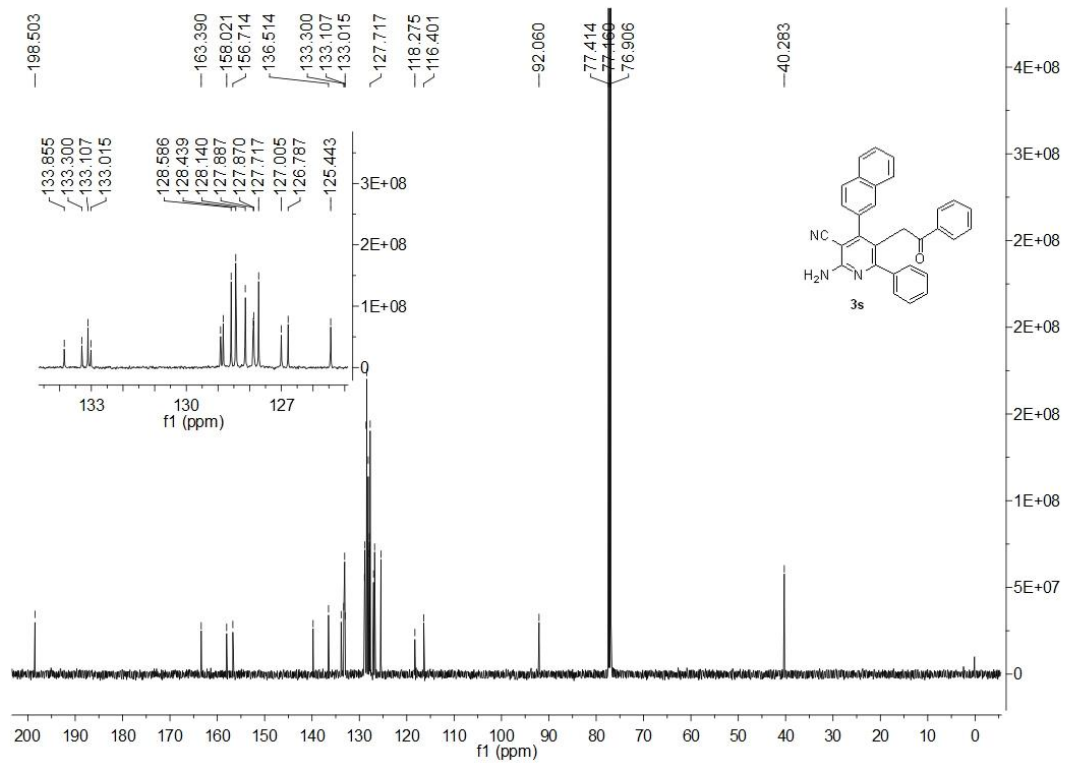
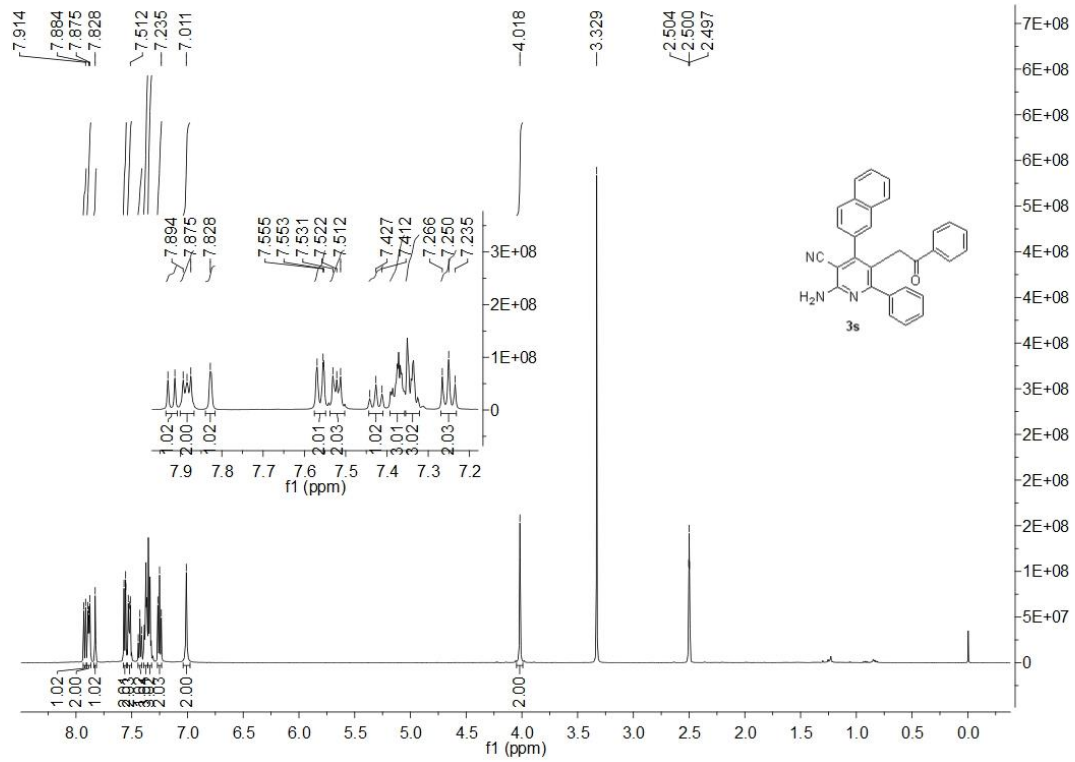


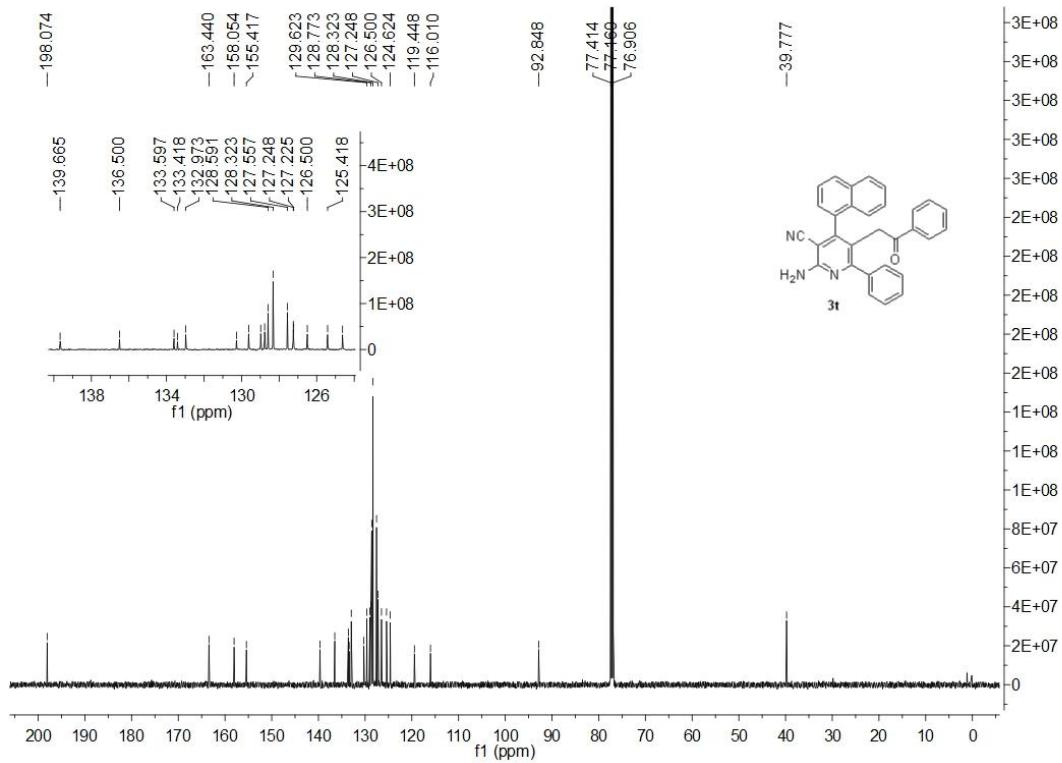
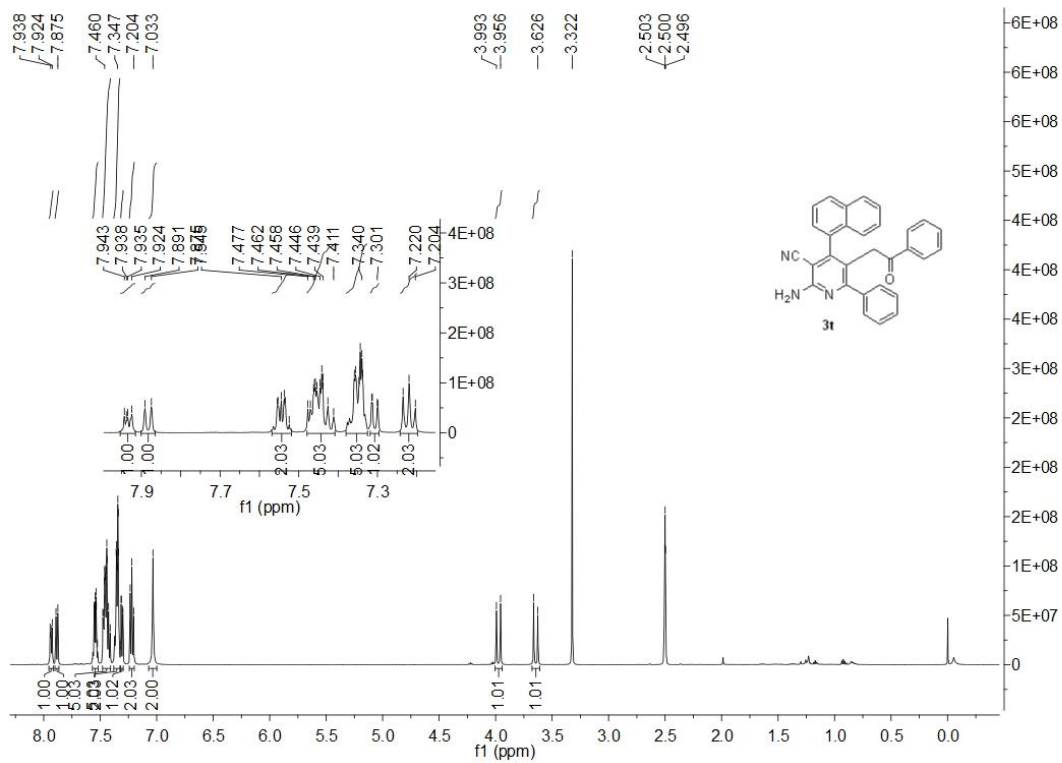


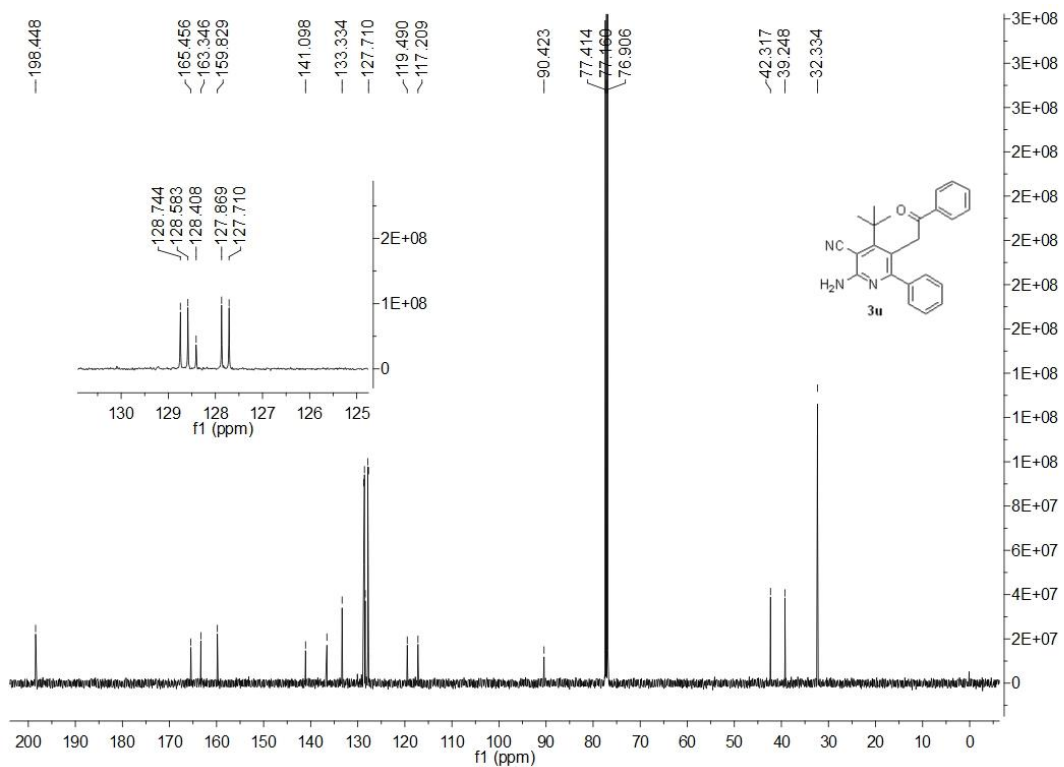
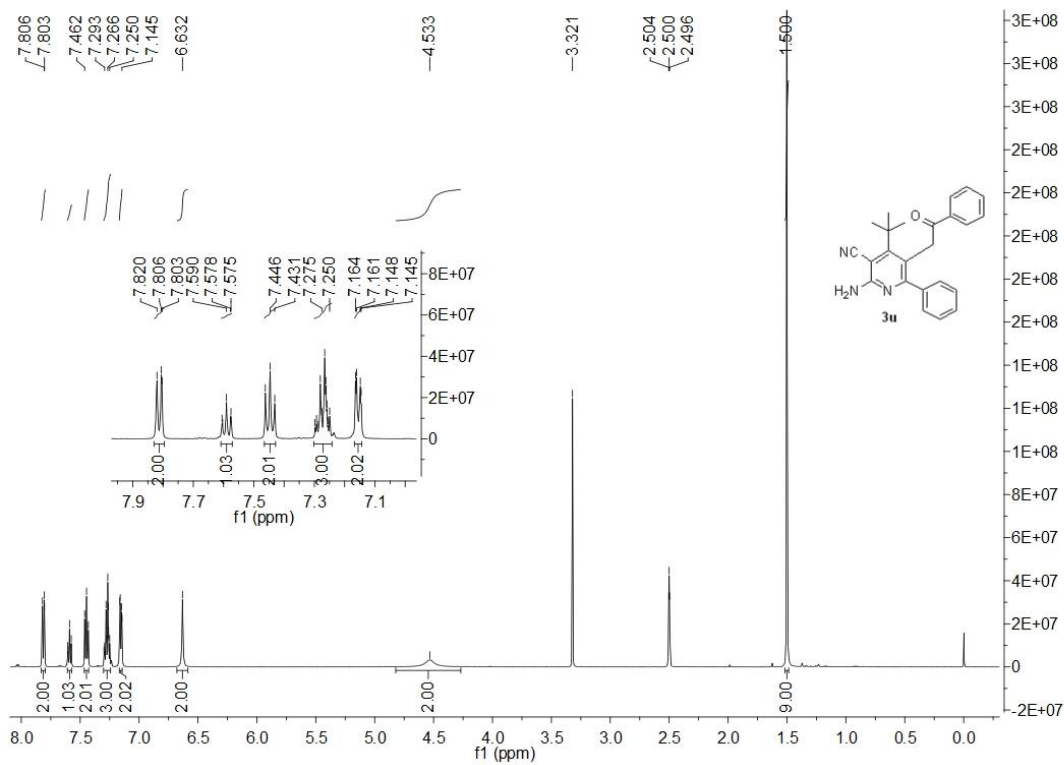


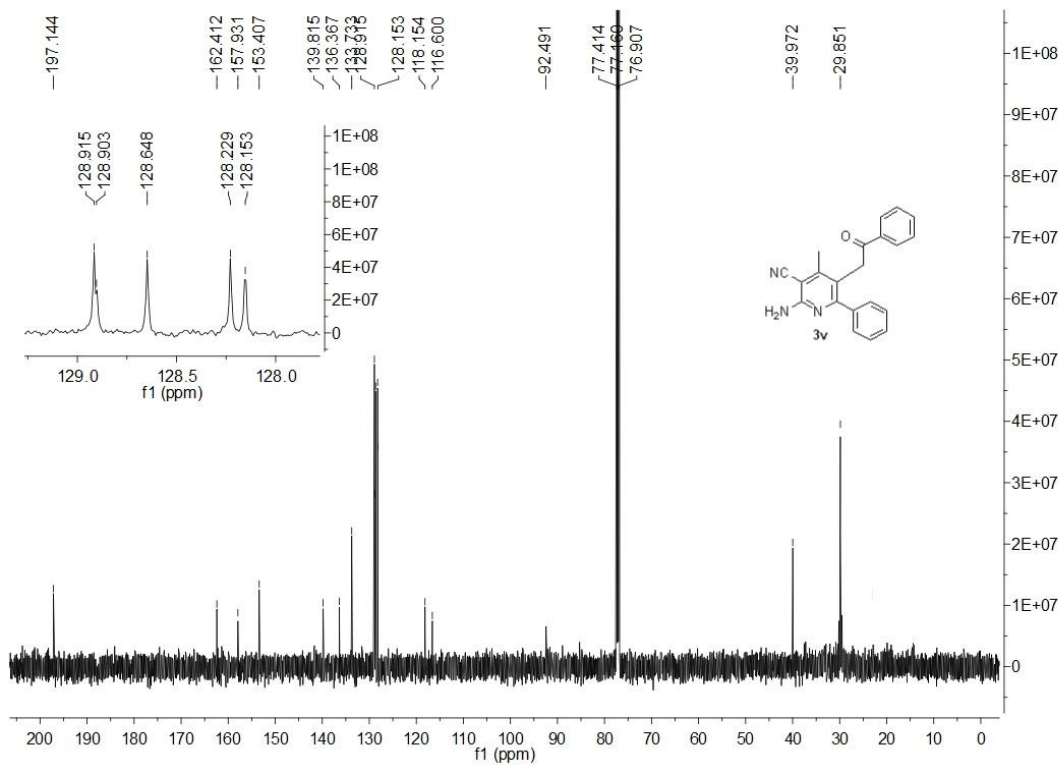
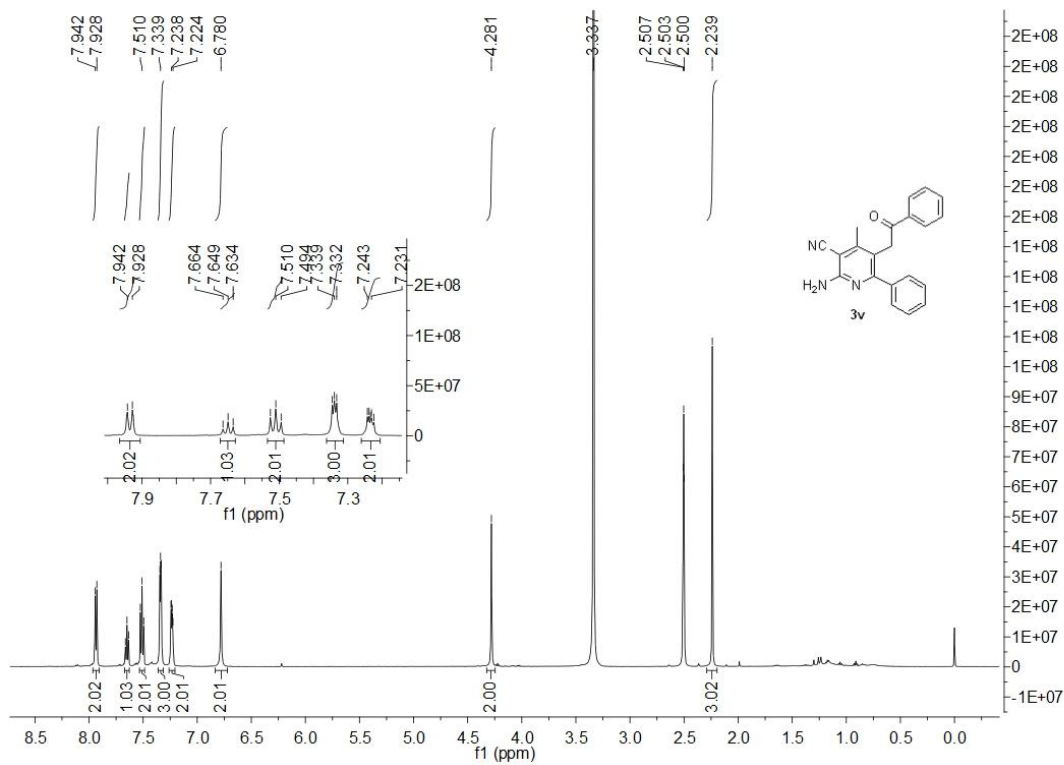


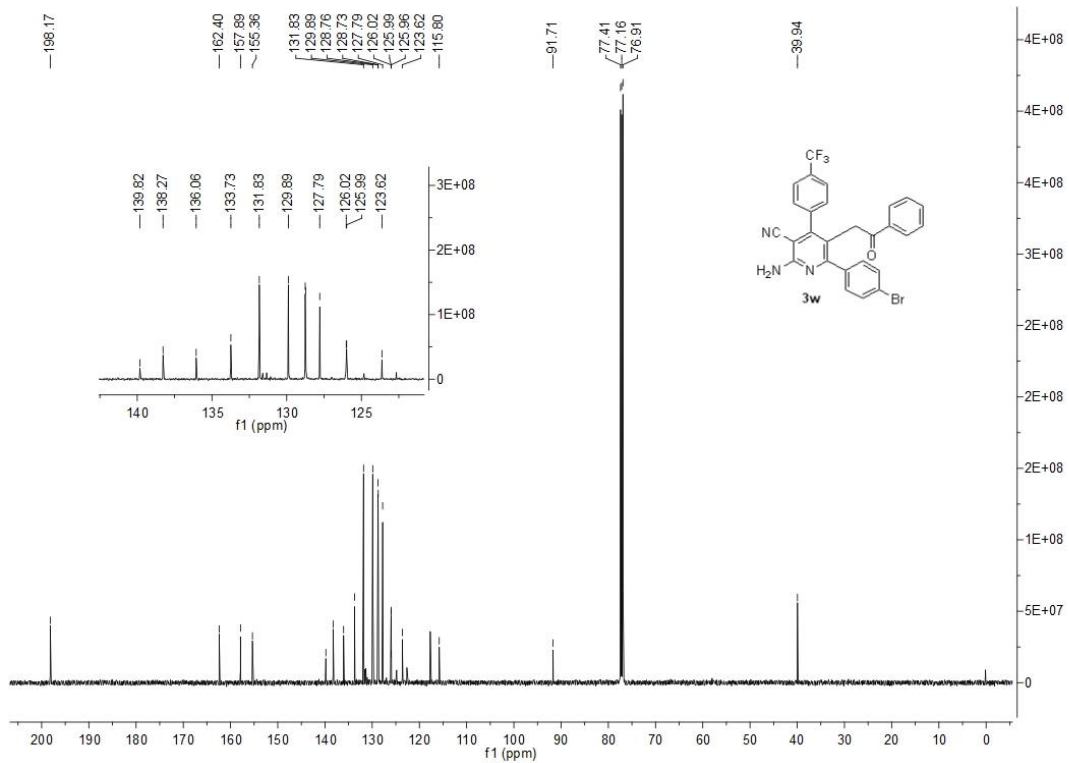
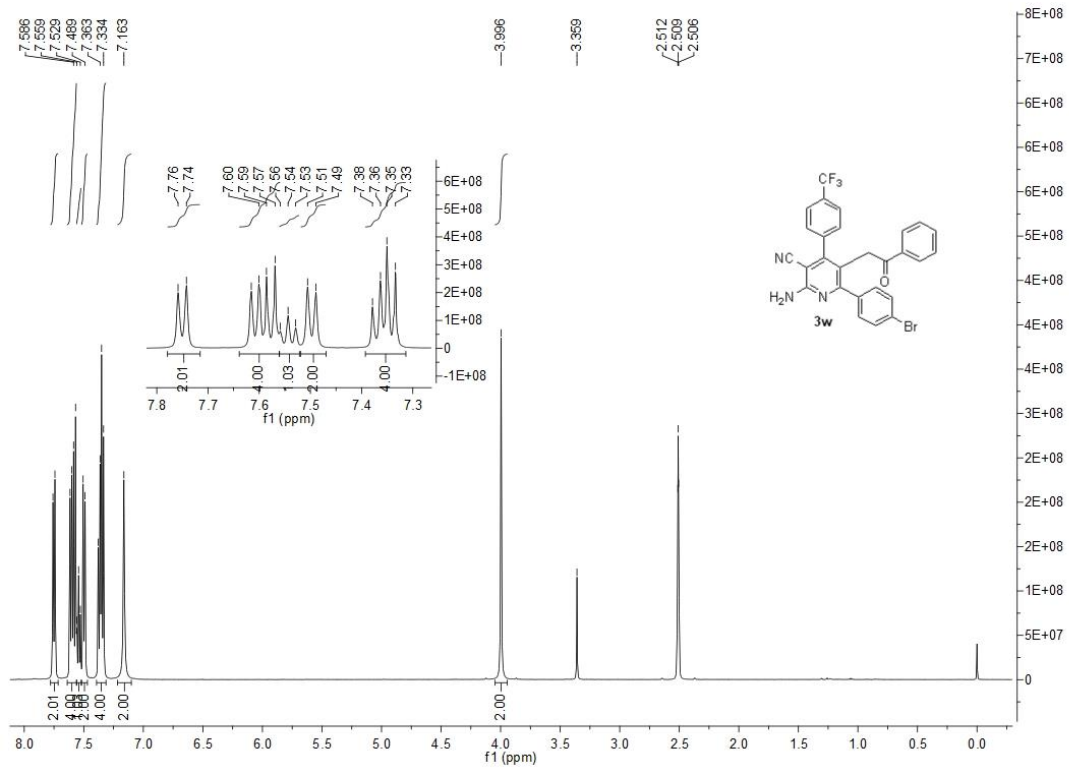


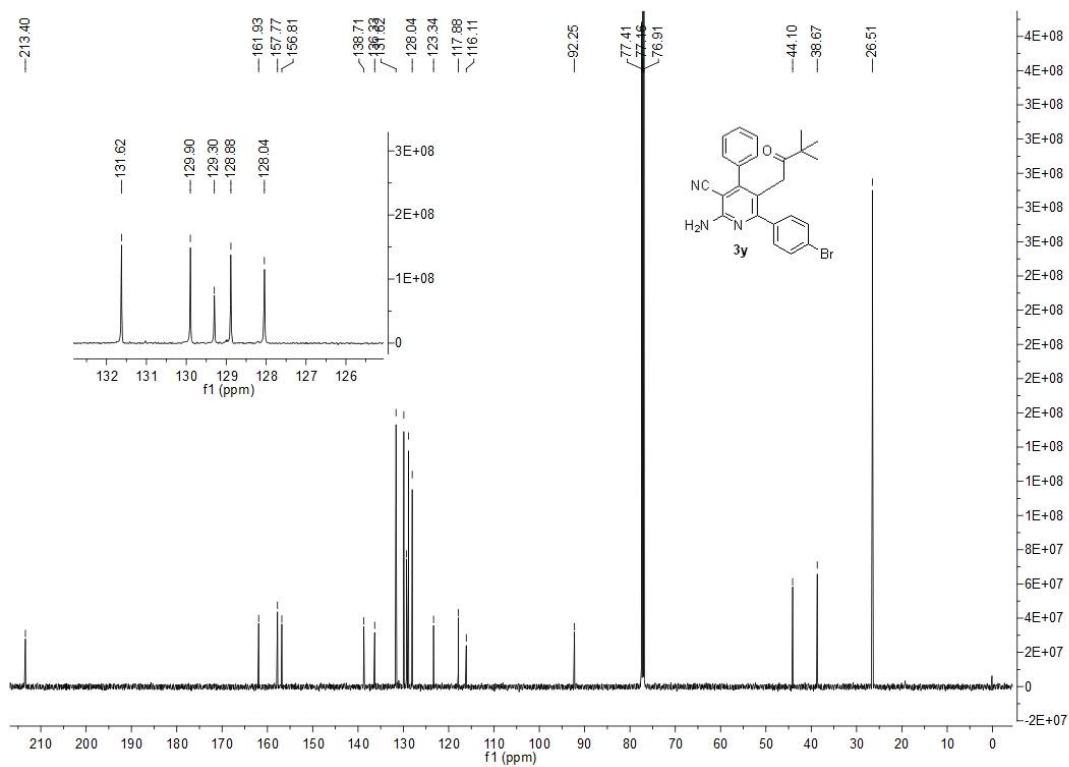
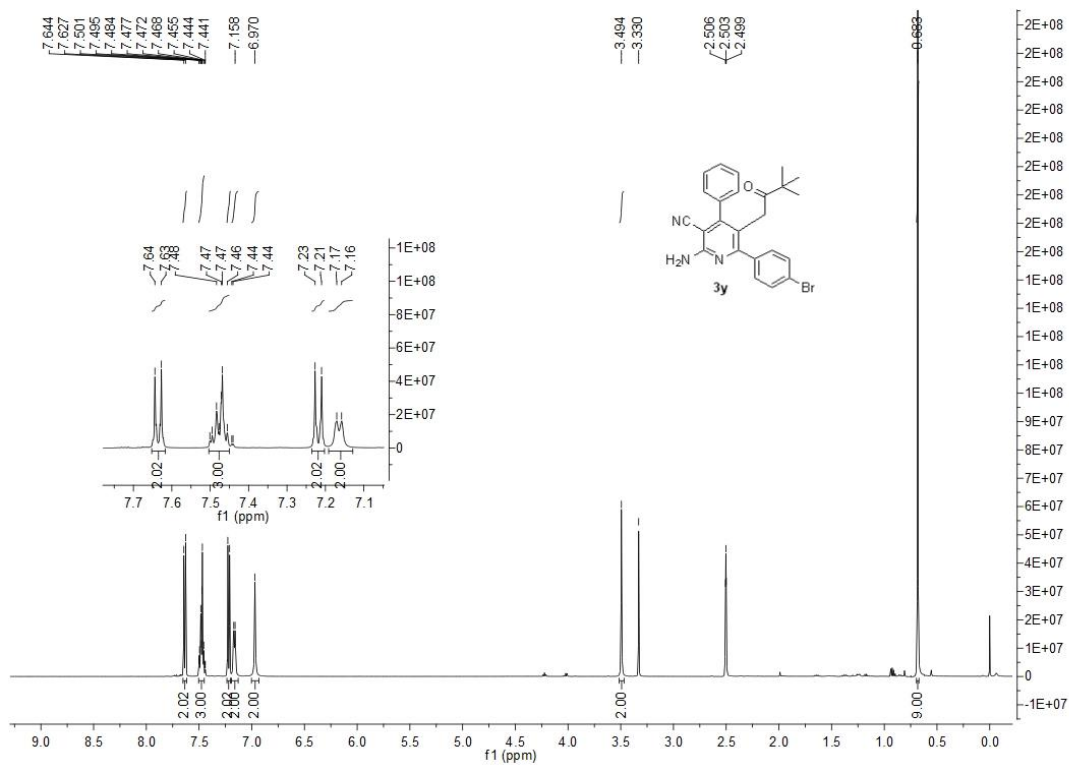












^{13}C - ^1H HMBC Spectrograms of **3v**

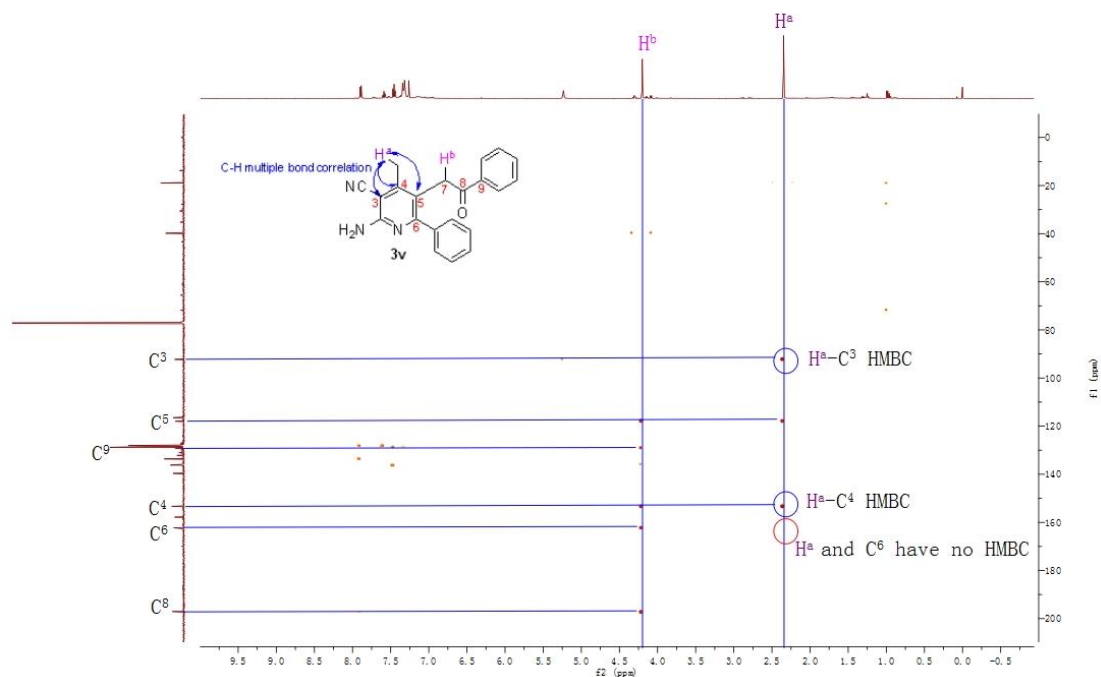


Figure S2. ^{13}C - ^1H HMBC spectrum of **3v**.

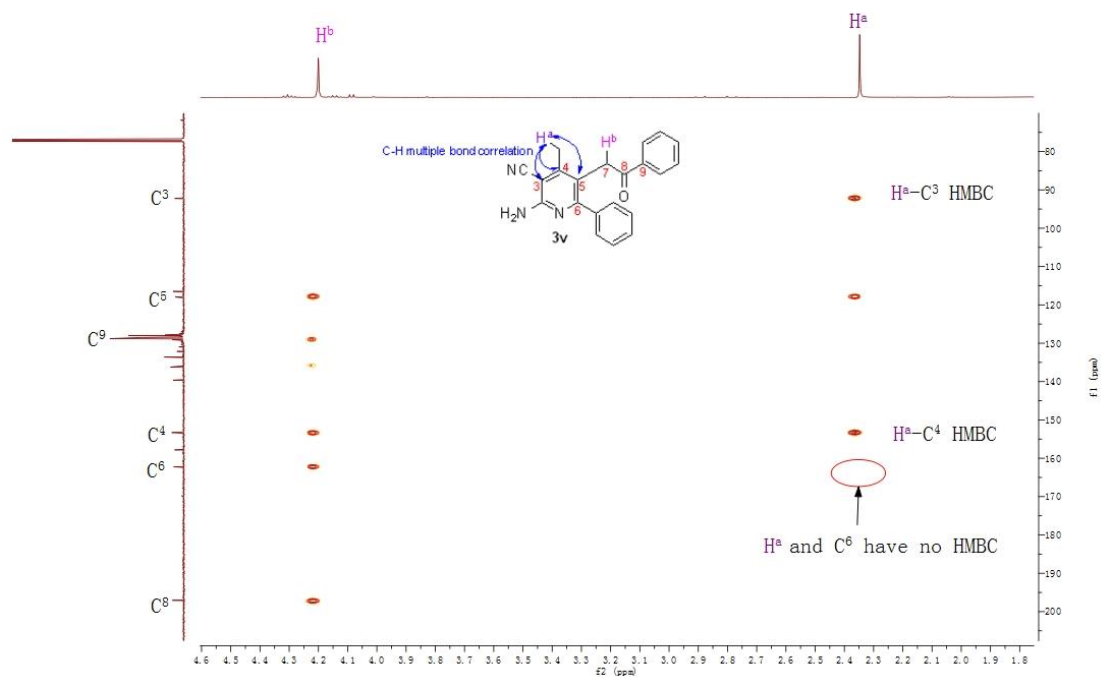


Figure S3. Partial enlarged view of ^{13}C - ^1H HMBC spectrum of **3v**.