

Supporting Information

Highly Efficient Chemoselective Synthesis of Polysubstituted Pyrroles via Isocyanide-Based Multicomponent Domino Reactions

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General Information

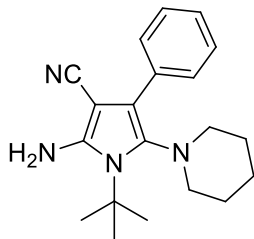
Melting points were recorded on an Electrothermal digital melting point apparatus and were uncorrected. IR spectra were recorded on a Varian FT-1000 spectrophotometer using KBr optics. ^1H NMR and ^{13}C NMR spectra were recorded on a Varian INOVA 300 or 400 MHz (^1H NMR) and 75 or 100 MHz (^{13}C NMR) spectrometer using DMSO- d_6 as solvent and TMS as internal standard. High resolution mass spectra were obtained using GCT-TOF instrument with EI or ESI source.

General procedure for highly efficient chemoselective synthesis of polysubstituted pyrroles (4a-4n) and (5a-5e)

Typically, in a 25 mL round bottom flask, gem-diactivated olefin (1.0 mmol) was dissolved in CH₃CN (2.0 ml), then amine (1.0 mmol) with isocyanide (1.0 mmol) was added to the reaction system under reflux conditions. Upon completion, monitored by TLC, the residue was directly purified by flash column chromatography by using ethyl acetate and petroleum ether as eluents to afford the pure product.

Analytical and spectral data for compounds 4 and 5

(4a) 2-amino-1-(tert-butyl)-4-phenyl-5-(piperidin-1-yl)-1H-pyrrole-3-carbonitrile



White solid; m.p: 187-188 °C;

IR (KBr, ν , cm^{-1}): 3460, 3352, 2190, 1629, 1530, 1469, 1396, 1220;

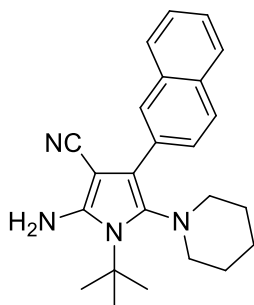
^1H NMR (DMSO- d_6 , 400 MHz) (δ , ppm): 7.81-7.70 (m, 5H, Ar-H), 5.39 (s, 2H, NH_2), 3.33-3.30 (m, 2H, CH_2), 2.96-2.93 (m, 2H, CH_2), 2.12 (s, 9H, CH_3), 2.01-1.98 (m, 1H, CH_2), 1.81-1.76 (m, 4H, CH_2), 1.25-1.23 (m, 1H, CH_2);

^{13}C NMR (DMSO- d_6 , 75 MHz) (δ , ppm): 144.6, 135.1, 135.0, 130.9, 128.2, 127.5, 119.4, 118.0, 76.2, 59.4, 54.8, 31.3, 26.0, 23.8;

HRMS (ESI): m/z calcd for: 323.2236 $[\text{M}+\text{H}]^+$, found: 323.2236.

(4b)

2-amino-1-(tert-butyl)-4-(naphthalen-2-yl)-5-(piperidin-1-yl)-1H-pyrrole-3-carbonitrile



Yellow solid; m.p: 200-201 °C;

IR (KBr, ν , cm^{-1}): 3433, 3344, 2200, 1631, 1603, 1539, 1498, 1457, 1223;

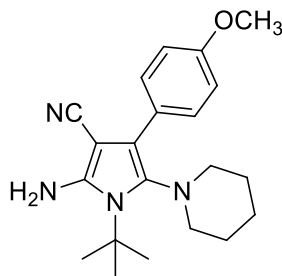
^1H NMR (DMSO- d_6 , 400 MHz) (δ , ppm): 7.93-7.90 (m, 3H, Ar-H), 7.82 (s, 1H, Ar-H), 7.53-7.51 (m, 2H, Ar-H), 7.43 (d, $J = 8.0$ Hz, 1H, Ar-H), 5.02 (s, 2H, NH_2), 2.96-2.93 (m, 2H, CH_2), 2.53-2.50 (m, 2H, CH_2), 1.71 (s, 9H, CH_3), 1.53-1.50 (m, 1H, CH_2), 1.31 (s, 4H, CH_2), 0.78-0.76 (m, 1H, CH_2);

^{13}C NMR (DMSO- d_6 , 75 MHz) (δ , ppm): 149.5, 140.1, 137.8, 137.3, 137.2, 134.1, 133.0, 132.7, 132.4, 131.4, 131.2, 124.0, 122.8, 81.1, 64.3, 59.6, 36.0, 30.7, 28.5;

HRMS (ESI): m/z calcd for: 373.2392 $[\text{M}+\text{H}]^+$, found: 373.2391.

(4c)

2-amino-1-(tert-butyl)-4-(4-methoxyphenyl)-5-(piperidin-1-yl)-1H-pyrrole-3-carbonitrile



White solid; m.p: 194-195 °C;

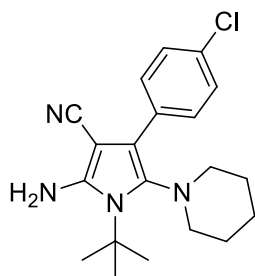
IR (KBr, ν , cm^{-1}): 3411, 3333, 2187, 1645, 1618, 1512, 1449, 1262;

^1H NMR (DMSO- d_6 , 400 MHz) (δ , ppm): 7.21 (d, J = 8.4 Hz, 2H, Ar-H), 6.97 (d, J = 8.4 Hz, 2H, Ar-H), 6.24 (s, 2H, NH₂), 3.76 (s, 3H, OCH₃), 3.61-3.59 (m, 1H, CH₂), 3.18-3.11 (m, 3H, CH₂), 1.44 (s, 4H, CH₂), 1.23 (s, 10H, CH₂ and CH₃), 0.88 (s, 1H, CH₂);

^{13}C NMR (DMSO- d_6 , 75 MHz) (δ , ppm): 168.8, 159.4, 159.2, 133.8, 125.9, 118.0, 114.4, 90.6, 69.1, 63.0, 55.5, 46.5, 43.2, 27.0, 25.7, 25.4, 24.2.

HRMS (ESI): m/z calcd for: 353.2341 $[\text{M}+\text{H}]^+$, found: 353.2339.

(4d) 2-amino-1-(tert-butyl)-4-(4-chlorophenyl)-5-(piperidin-1-yl)-1H-pyrrole-3-carbonitrile



White solid; m.p: 187-188 °C;

IR (KBr, ν , cm^{-1}): 3471, 3319, 2205, 1638, 1536, 1491, 1471, 1454, 1219;

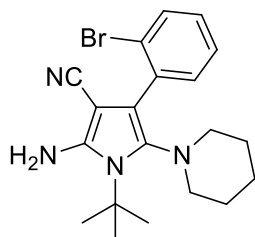
^1H NMR (DMSO- d_6 , 400 MHz) (δ , ppm): 7.44 (d, J = 8.4 Hz, 2H, Ar-H), 7.30 (d, J = 8.4 Hz, 2H, Ar-H), 5.04 (s, 2H, NH₂), 2.91-2.88 (m, 2H, CH₂), 2.54-2.51 (m, 2H, CH₂), 1.68 (s, 9H, CH₃), 1.60-1.57 (m, 1H, CH₂), 1.40-1.38 (m, 4H, CH₂), 0.91-0.88 (m, 4H, CH₂);

^{13}C NMR (DMSO- d_6 , 75 MHz) (δ , ppm): 144.8, 135.2, 133.8, 132.7, 132.3, 128.3, 118.1, 117.8, 75.8, 59.5, 54.8, 31.2, 26.0, 23.8.

HRMS (ESI): m/z calcd for: 357.1846 $[\text{M}+\text{H}]^+$, found: 357.1847.

(4e)

2-amino-4-(2-bromophenyl)-1-(tert-butyl)-5-(piperidin-1-yl)-1H-pyrrole-3-carbonitrile



White solid; m.p: 215-216 °C;

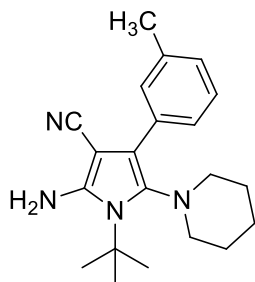
IR (KBr, ν , cm^{-1}): 3449, 3367, 2194, 1616, 1532, 1492, 1462, 1223;

^1H NMR (DMSO- d_6 , 400 MHz) (δ , ppm): 7.68 (d, J = 8.0 Hz, 1H, Ar-H), 7.40-7.30 (m, 3H, Ar-H), 4.96 (s, 2H, NH_2), 3.01-2.88 (m, 2H, CH_2), 2.59-2.54 (m, 1H, CH_2), 2.24-2.20 (m, 1H, CH_2), 1.69 (s, 9H, CH_3), 1.56-1.53 (m, 1H, CH_2), 1.38-1.36 (M, 4H, CH_2), 0.79-0.76 (m, 1H, CH_2);

^{13}C NMR (DMSO- d_6 , 75 MHz) (δ , ppm): 144.4, 135.6, 134.9, 134.0, 132.7, 130.2, 127.4, 126.0, 118.4, 117.5, 76.2, 59.6, 55.5, 53.1, 31.3, 26.0, 23.8.

HRMS (ESI): m/z calcd for: 401.1341 $[\text{M}+\text{H}]^+$, found: 401.1333.

(4f) 2-amino-1-(tert-butyl)-5-(piperidin-1-yl)-4-(m-tolyl)-1H-pyrrole-3-carbonitrile



White solid; m.p: 221-222 °C;

IR (KBr, ν , cm^{-1}): 3468, 3381, 2193, 1621, 1587, 1535, 1470, 1375, 1217;

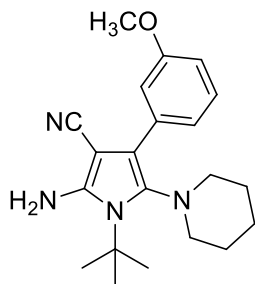
^1H NMR (DMSO- d_6 , 400 MHz) (δ , ppm): 7.26 (t, J = 7.6 Hz, 1H, Ar-H), 7.13 (d, J = 7.6 Hz, 1H, Ar-H), 7.09-7.05 (m, 2H, Ar-H), 4.93 (s, 2H, NH_2), 2.89-2.86 (m, 2H, CH_2), 2.54-2.51 (m, 2H, CH_2), 1.88 (s, 9H, CH_3), 1.59-1.56 (m, 1H, CH_2), 1.39-1.35 (m, 4H, CH_2), 0.87-0.85 (m, 1H, CH_2);

^{13}C NMR (DMSO- d_6 , 75 MHz) (δ , ppm): 144.5, 137.2, 135.0, 134.8, 131.4, 128.2, 128.1, 128.0, 119.5, 118.1, 76.1, 59.4, 54.8, 31.3, 26.0, 23.8, 21.5.

HRMS (ESI): m/z calcd for: 337.2392 $[\text{M}+\text{H}]^+$, found: 337.2392.

(4g)

2-amino-1-(tert-butyl)-4-(3-methoxyphenyl)-5-(piperidin-1-yl)-1H-pyrrole-3-carbonitrile



White solid; m.p: 198-199 °C;

IR (KBr, ν , cm^{-1}): 3407, 3343, 2200, 1636, 1539, 1489, 1469, 1227;

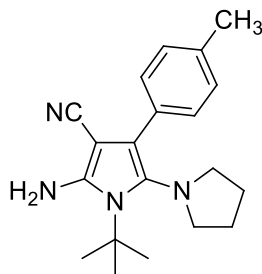
^1H NMR (DMSO- d_6 , 400 MHz) (δ , ppm): 7.33 (t, J = 7.6 Hz, 1H, Ar-H), 7.16 (d, J = 7.6 Hz, 1H, Ar-H), 7.03 (d, J = 7.6 Hz, 1H, Ar-H), 6.93 (d, J = 7.2 Hz, 1H, Ar-H), 4.80 (s, 2H, NH_2), 3.72 (s, 3H, OCH_3), 2.94-2.28 (m, 4H, CH_2), 1.68 (s, 9H, CH_3), 1.55-1.52 (m, 1H, CH_2), 1.36 (s, 4H, CH_2), 0.78 (s, 1H, CH_2);

^{13}C NMR (DMSO- d_6 , 75 MHz) (δ , ppm): 158.1, 144.0, 135.1, 133.2, 129.6, 123.3, 120.0, 118.0, 115.4, 111.5, 77.1, 59.3, 55.6, 53.1, 31.3, 26.1, 23.9.

HRMS (ESI): m/z calcd for: 353.2341 $[\text{M}+\text{H}]^+$, found: 353.2340.

(4h)

2-amino-1-(tert-butyl)-5-(pyrrolidin-1-yl)-4-(p-tolyl)-1H-pyrrole-3-carbonitrile



White solid; m.p: 210-211 °C;

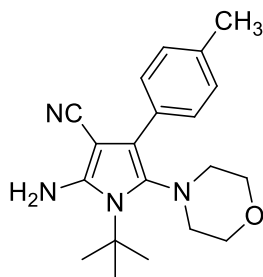
IR (KBr, ν , cm^{-1}): 3432, 3323, 2190, 1644, 1619, 1432, 1365, 1197;

^1H NMR (DMSO- d_6 , 400 MHz) (δ , ppm): 7.21 (s, 4H, Ar-H), 6.27 (s, 2H, NH_2), 3.38-3.35 (m, 3H, CH_2), 2.82-2.81 (m, 1H, CH_2), 2.30 (s, 3H, CH_3), 1.71-1.69 (m, 3H, CH_2), 1.55-1.53 (m, 1H, CH_2), 1.23 (s, 9H, CH_3);

^{13}C NMR (DMSO- d_6 , 75 MHz) (δ , ppm): 169.3, 160.1, 138.0, 137.7, 129.6, 125.1, 117.9, 90.1, 67.9, 62.9, 46.8, 46.6, 27.1, 26.3, 23.3, 21.1.

HRMS (ESI): m/z calcd for: 321.2079 $[\text{M}-\text{H}]$, found: 321.2090.

(4i) 2-amino-1-(tert-butyl)-5-morpholino-4-(p-tolyl)-1H-pyrrole-3-carbonitrile



White solid; m.p: 192-193 °C;

IR (KBr, ν , cm^{-1}): 3423, 3354, 2191, 1643, 1530, 1467, 1396, 1262, 1221;

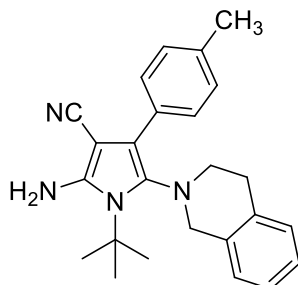
^1H NMR (DMSO- d_6 , 400 MHz) (δ , ppm): 7.18 (dd, J = 8.0 Hz, 4H, Ar-H), 4.99 (s, 2H, NH_2), 3.56-3.53 (m, 2H, CH_2), 3.39-3.37 (m, 2H, CH_2), 2.76-2.74 (m, 4H, CH_2), 2.34 (s, 3H, CH_3), 1.69 (s, 9H, CH_3);

^{13}C NMR (DMSO- d_6 , 75 MHz) (δ , ppm): 144.7, 136.8, 133.6, 131.6, 130.8, 129.0, 119.8, 117.9, 76.4, 66.7, 59.5, 53.8, 31.4, 21.2.

HRMS (ESI): m/z calcd for: 339.2185 $[\text{M}+\text{H}]^+$, found: 339.2184.

(4j)

2-amino-1-(tert-butyl)-5-(3,4-dihydroisoquinolin-2(1H)-yl)-4-(p-tolyl)-1H-pyrrole-3-carbonitrile



White solid; m.p: 218-219 °C;

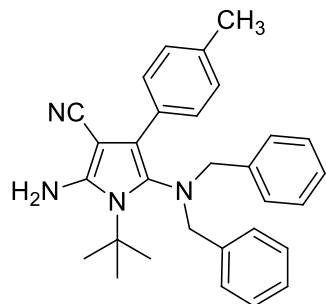
IR (KBr, ν , cm^{-1}): 3479, 3325, 2204, 1637, 1620, 1536, 1509, 1464, 1223;

^1H NMR (DMSO- d_6 , 400 MHz) (δ , ppm): 7.22 (d, J = 7.6 Hz, 2H, Ar-H), 7.15 (d, J = 7.6 Hz, 2H, Ar-H), 7.06-6.94 (m, 4H, Ar-H), 5.06 (s, 2H, NH_2), 3.89 (s, 2H, CH_2), 3.25-3.22 (m, 1H, CH_2), 2.97-2.95 (m, 2H, CH_2), 2.58-2.54 (m, 1H, CH_2), 2.28 (s, 3H, CH_3), 1.63 (s, 9H, CH_3);

^{13}C NMR (DMSO- d_6 , 75 MHz) (δ , ppm): 145.0, 136.7, 135.0, 134.0, 133.6, 131.5, 130.5, 129.2, 129.0, 126.4, 125.9, 119.8, 118.1, 76.0, 59.4, 55.1, 51.9, 31.2, 29.6, 21.2.

HRMS (ESI): m/z calcd for: 385.2392 $[\text{M}+\text{H}]^+$, found: 385.2386.

(4k) 2-amino-1-(tert-butyl)-5-(dibenzylamino)-4-(p-tolyl)-1H-pyrrole-3-carbonitrile



White solid; m.p: 185-186 °C;

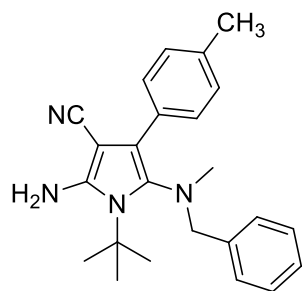
IR (KBr, ν , cm^{-1}): 3471, 3322, 3230, 2208, 1642, 1602, 1549, 1454, 1294, 1214;

^1H NMR ($\text{DMSO-}d_6$, 400 MHz) (δ , ppm): 7.32-7.25 (m, 10H, Ar-H), 7.12 (d, $J = 7.2$ Hz, 4H, Ar-H), 5.12 (s, 2H, NH_2), 4.02-3.99 (m, 2H, CH_2), 3.92-3.88 (m, 2H, CH_2), 2.36 (s, 3H, CH_3), 1.32 (s, 9H, CH_3);

^{13}C NMR ($\text{DMSO-}d_6$, 75 MHz) (δ , ppm): 145.2, 138.5, 136.8, 132.4, 131.9, 130.8, 129.4, 129.3, 128.7, 128.4, 127.5, 119.9, 118.2, 75.7, 59.8, 58.8, 30.7, 21.3.

HRMS (ESI): m/z calcd for: 449.2705 $[\text{M}+\text{H}]^+$, found: 449.2705.

(4l) 2-amino-5-(benzyl(methyl)amino)-1-(tert-butyl)-4-(p-tolyl)-1H-pyrrole-3-carbonitrile



White solid; m.p: 194-195 °C;

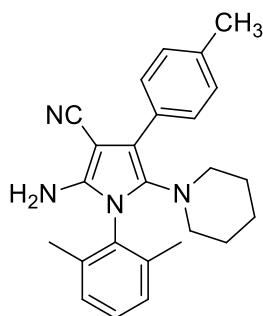
IR (KBr, ν , cm^{-1}): 3425, 3394, 3353, 3330, 2196, 1628, 1531, 1463, 1330, 1223;

^1H NMR ($\text{DMSO-}d_6$, 400 MHz) (δ , ppm): 7.26-7.19 (m, 7H, Ar-H), 7.01 (d, $J = 7.6$ Hz, 2H, Ar-H), 5.09 (s, 2H, NH_2), 3.81-3.79 (m, 1H, CH_2), 3.57-3.54 (m, 1H, CH_2), 2.58 (s, 3H, CH_3), 2.36 (s, 3H, CH_3), 1.58 (s, 9H, CH_3);

^{13}C NMR ($\text{DMSO-}d_6$, 75 MHz) (δ , ppm): 145.0, 138.3, 136.5, 133.9, 131.9, 130.2, 129.2, 129.2, 128.5, 127.4, 119.3, 118.2, 74.8, 60.8, 58.7, 45.5, 30.8, 21.2.

HRMS (ESI): m/z calcd for: 373.2392 $[\text{M}+\text{H}]^+$, found: 373.2394.

(4m) 2-amino-1-(2,6-dimethylphenyl)-5-(piperidin-1-yl)-4-(p-tolyl)-1H-pyrrole-3-carbonitrile



White solid; m.p: 230-231 °C;

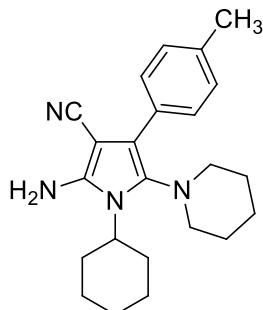
IR (KBr, ν , cm^{-1}): 3376, 3325, 3288, 2201, 1642, 1592, 1556, 1486, 1237;

^1H NMR (DMSO- d_6 , 400 MHz) (δ , ppm): 7.30-7.19 (m, 7H, Ar-H), 5.40 (s, 2H, NH_2), 2.53-2.51 (m, 4H, CH_2), 2.32 (s, 3H, CH_3), 2.03 (s, 6H, CH_3), 1.15 (s, 2H, CH_3), 0.97 (s, 4H, CH_3);

^{13}C NMR (DMSO- d_6 , 75 MHz) (δ , ppm): 144.7, 137.7, 135.8, 133.6, 131.6, 131.1, 129.2, 129.0, 128.6, 118.9, 112.9, 68.1, 52.8, 26.3, 23.8, 21.2, 18.1.

HRMS (ESI): m/z calcd for: 385.2392 $[\text{M}+\text{H}]^+$, found: 385.2395.

(4n) 2-amino-1-cyclohexyl-5-(piperidin-1-yl)-4-(p-tolyl)-1H-pyrrole-3-carbonitrile



White solid; m.p: 203-204 °C;

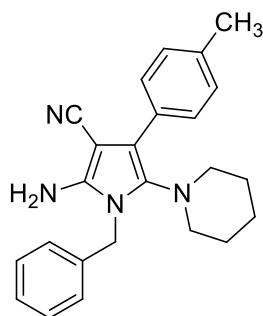
IR (KBr, ν , cm^{-1}): 3437, 3336, 3218, 2185, 1631, 1541, 1445, 1232, 1192;

^1H NMR (DMSO- d_6 , 400 MHz) (δ , ppm): 7.18 (s, 4H, Ar-H), 5.43 (s, 2H, NH_2), 4.08 (s, 1H, CH), 2.81-2.65 (m, 4H, CH_2), 2.32 (s, 3H, CH_3), 2.17-2.14 (m, 2H, CH_2), 1.84-1.82 (m, 2H, CH_2), 1.63-1.61 (m, 4H, CH_2), 1.47-1.45 (m, 4H, CH_2), 1.32-1.30 (m, 3H, CH_2), 1.10-1.05 (m, 1H, CH_2);

^{13}C NMR (DMSO- d_6 , 75 MHz) (δ , ppm): 148.9, 140.8, 136.3, 134.4, 133.7, 123.5, 76.0, 58.7, 58.3, 31.4, 28.8, 26.0.

HRMS (ESI): m/z calcd for: 363.2549 $[\text{M}+\text{H}]^+$, found: 363.2546.

(4o) 2-amino-1-benzyl-5-(piperidin-1-yl)-4-(p-tolyl)-1H-pyrrole-3-carbonitrile



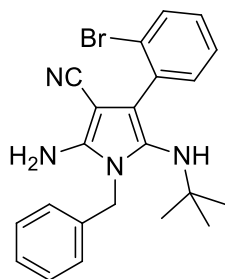
green oil;

IR (KBr, ν , cm^{-1}): 3420, 3329, 2193, 1628, 1558, 1501, 1449, 1361, 1227;

^1H NMR (CDCl_3 , 400 MHz) (δ , ppm): 7.40-7.31 (m, 5H, Ar-H), 7.20 (d, J = 8.0 Hz, 2H, Ar-H), 7.14 (d, J = 8.0 Hz, 2H, Ar-H), 5.01 (s, 2H, NH_2), 3.76 (s, 2H, CH_2), 2.83-2.81 (m, 4H, CH_2), 2.06 (s, 3H, CH_3), 1.47-1.28 (m, 6H, CH_2);

^{13}C NMR ($\text{DMSO}-d_6$, 100 MHz) (δ , ppm): 142.00, 136.85, 136.31, 133.04, 130.62, 129.42, 129.08, 128.79, 127.67, 126.11, 117.77, 114.94, 73.72, 53.56, 44.64, 26.72, 23.86, 21.22.

(5a) 2-amino-1-benzyl-4-(2-bromophenyl)-5-(tert-butylamino)-1H-pyrrole-3-carbonitrile



Yellow solid; m.p: 188-189 °C;

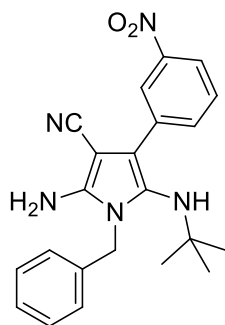
IR (KBr, ν , cm^{-1}): 3416, 3328, 2203, 1607, 1556, 1497, 1388, 1226;

^1H NMR ($\text{DMSO}-d_6$, 400 MHz) (δ , ppm): 7.68 (d, J = 8.0 Hz, 1H, Ar-H), 7.44-7.39 (m, 2H, Ar-H), 7.32-7.30 (m, 2H, Ar-H), 7.24-7.22 (m, 2H, Ar-H), 7.09 (d, J = 7.2 Hz, 2H, Ar-H), 5.75 (s, 2H, NH_2), 5.10 (s, 2H, CH_2), 3.24 (s, 1H, NH), 0.75 (s, 9H, CH_3);

^{13}C NMR ($\text{DMSO}-d_6$, 75 MHz) (δ , ppm): 145.5, 138.4, 136.2, 133.5, 133.0, 129.3, 128.7, 127.9, 127.3, 127.1, 125.8, 124.3, 118.5, 116.3, 70.1, 54.1, 44.2, 30.2.

HRMS (ESI): m/z calcd for: 423.1184 $[\text{M}+\text{H}]^+$, found: 423.1184.

(5b) 2-amino-1-benzyl-5-(tert-butylamino)-4-(3-nitrophenyl)-1H-pyrrole-3-carbonitrile



Yellow solid; m.p: 138-139 °C;

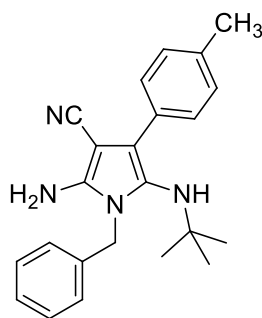
IR (KBr, ν , cm^{-1}): 3444, 3348, 2193, 1621, 1566, 1525, 1503, 1346, 1227;

^1H NMR (DMSO- d_6 , 400 MHz) (δ , ppm): 8.52 (s, 1H, Ar-H), 8.08 (t, J = 8.0 Hz, 2H, Ar-H), 7.65 (t, J = 8.0 Hz, 1H, Ar-H), 7.34 (t, J = 7.6 Hz, 2H, Ar-H), 7.25 (t, J = 7.6 Hz, 1H, Ar-H), 7.13 (d, J = 7.6 Hz, 2H, Ar-H), 5.91 (s, 2H, NH_2), 5.13 (s, 2H, CH_2), 4.26 (s, 1H, NH), 0.79 (s, 9H, CH_3);

^{13}C NMR (DMSO- d_6 , 75 MHz) (δ , ppm): 148.3, 146.7, 138.1, 137.3, 135.3, 130.0, 128.7, 127.2, 126.7, 123.1, 120.9, 118.6, 114.6, 67.6, 54.7, 44.2, 30.4.

HRMS (ESI): m/z calcd for: 390.1930 $[\text{M}+\text{H}]^+$, found: 390.1928.

(5c) 2-amino-1-benzyl-5-(tert-butylamino)-4-(p-tolyl)-1H-pyrrole-3-carbonitrile



Yellow solid; m.p: 194-195 °C;

IR (KBr, ν , cm^{-1}): 3433, 3323, 3230, 2203, 1637, 1566, 1503, 1350, 1231;

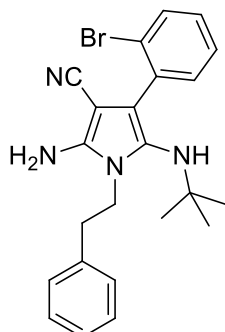
^1H NMR (DMSO- d_6 , 400 MHz) (δ , ppm): 7.745 (d, J = 8.0 Hz, 2H, Ar-H), 7.31 (t, J = 8.0 Hz, 2H, Ar-H), 7.22 (t, J = 7.6 Hz, 1H, Ar-H), 7.14 (d, J = 7.6 Hz, 2H, Ar-H), 7.10 (d, J = 8.0 Hz, 2H, Ar-H), 5.70 (s, 2H, NH_2), 5.09 (s, 2H, CH_2), 4.00 (s, 1H, NH), 2.30 (s, 3H, CH_3), 0.76 (s, 9H, CH_3);

^{13}C NMR (DMSO- d_6 , 75 MHz) (δ , ppm): 145.9, 138.4, 135.2, 132.6, 129.0, 129.0, 128.7, 127.2, 125.2, 119.1, 116.8, 68.5, 54.5, 44.1, 30.3, 21.2.

HRMS (ESI): m/z calcd for: 359.2236 $[\text{M}+\text{H}]^+$, found: 359.2230.

(5d)

2-amino-4-(2-bromophenyl)-5-(tert-butylamino)-1-phenethyl-1H-pyrrole-3-carbonitrile



Yellow solid; m.p: 163-164 °C;

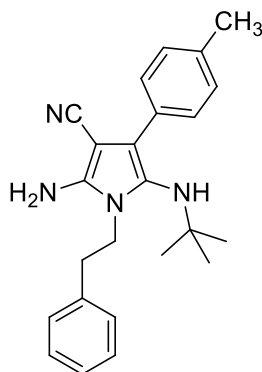
IR (KBr, ν , cm^{-1}): 3429, 3321, 2193, 1629, 1593, 1561, 1504, 1473, 1361, 1221;

^1H NMR (DMSO- d_6 , 400 MHz) (δ , ppm): 7.64 (d, J = 8.0 Hz, 1H, Ar-H), 7.37-7.21 (m, 8H, Ar-H), 5.85 (s, 2H, NH_2), 4.02-4.00 (m, 2H, CH_2), 2.92 (s, 1H, NH), 2.85-2.83 (m, 2H, CH_2), 0.75 (s, 9H, CH_3);

^{13}C NMR (DMSO- d_6 , 75 MHz) (δ , ppm): 144.8, 139.2, 136.4, 133.3, 132.9, 129.3, 129.2, 128.7, 127.8, 126.7, 125.4, 124.4, 118.6, 116.4, 70.4, 53.6, 42.6, 34.9, 30.3.

HRMS (ESI): m/z calcd for: 437.1341 $[\text{M}+\text{H}]^+$, found: 437.1324.

(5e) 2-amino-5-(tert-butylamino)-1-phenethyl-4-(p-tolyl)-1H-pyrrole-3-carbonitrile



Yellow solid; m.p: 201-202 °C;

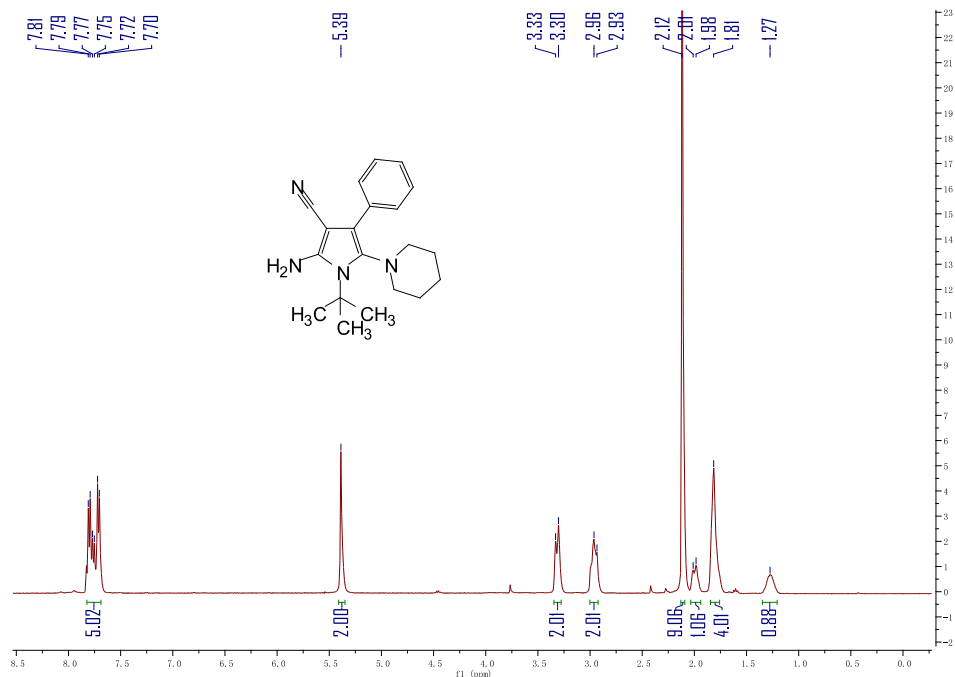
IR (KBr, ν , cm^{-1}): 3428, 3336, 2192, 1628, 1557, 1498, 1363, 1221;

^1H NMR (DMSO- d_6 , 400 MHz) (δ , ppm): 7.36 (d, J = 8.0 Hz, 2H, Ar-H), 7.32-7.27 (m, 5H, Ar-H), 7.13 (d, J = 8.0 Hz, 2H, Ar-H), 5.83 (s, 2H, NH_2), 4.00-3.96 (m, 2H, CH_2), 3.57 (s, 1H, NH), 2.84-2.80 (m, 2H, CH_2), 2.29 (s, 3H, CH_3), 0.75 (s, 9H, CH_3);

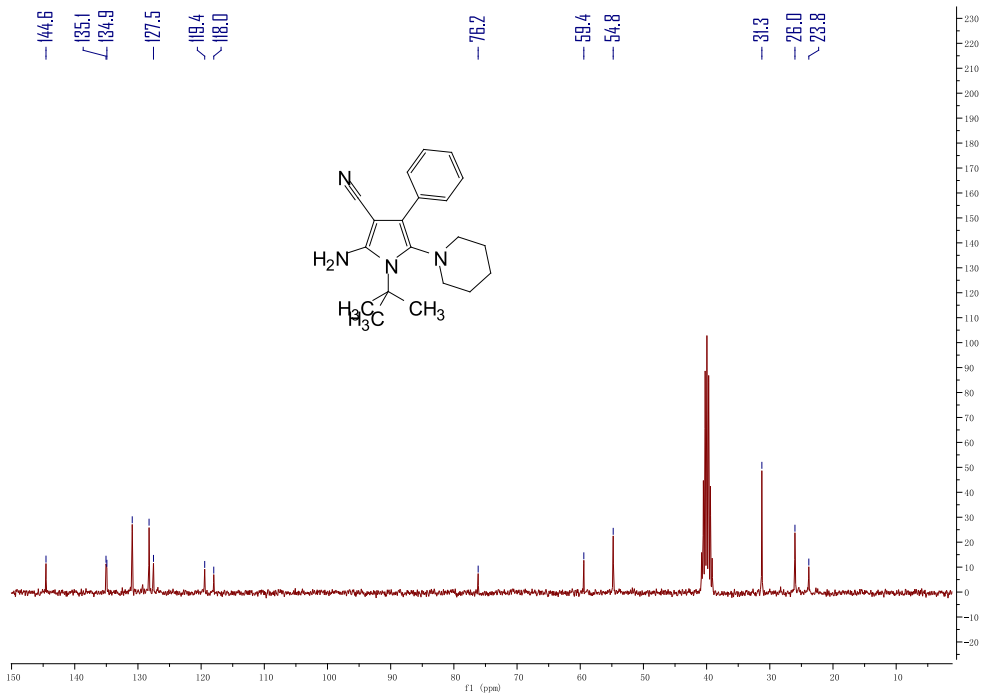
^{13}C NMR (DMSO- d_6 , 75 MHz) (δ , ppm): 145.3, 139.2, 135.1, 132.7, 129.3, 129.0, 128.9, 128.8, 126.8, 124.8, 119.2, 116.9, 68.9, 54.1, 42.6, 34.9, 30.5, 21.2.

HRMS (ESI): m/z calcd for: 373.2392 $[\text{M}+\text{H}]^+$, found: 373.2390.

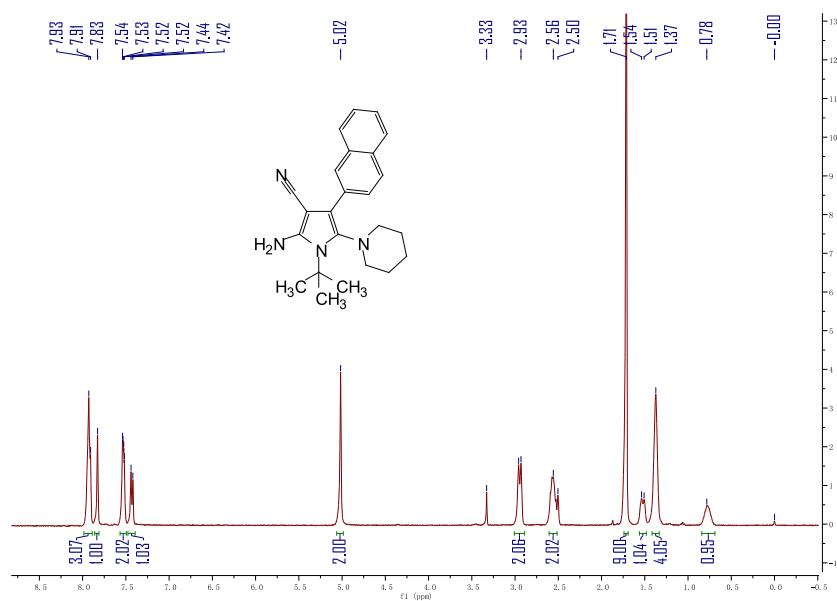
NMR spectrum of compounds 4 and 5



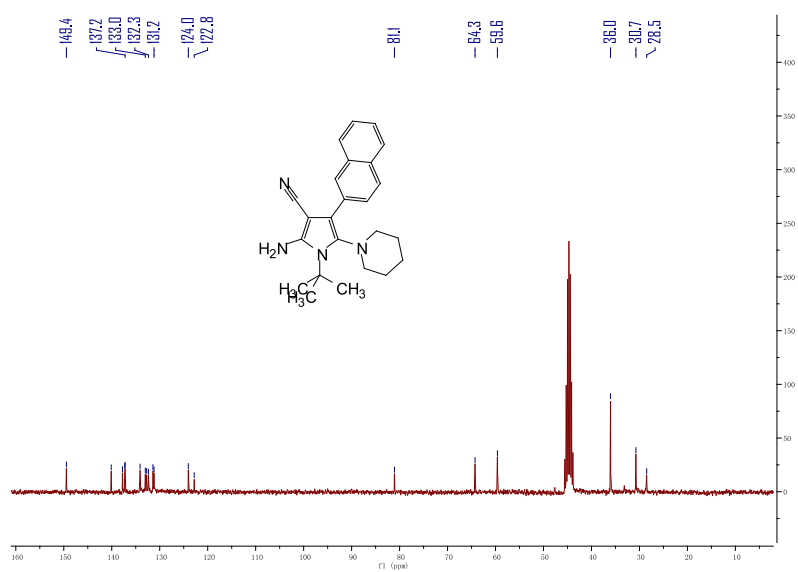
¹H NMR spectrum of compounds 4a



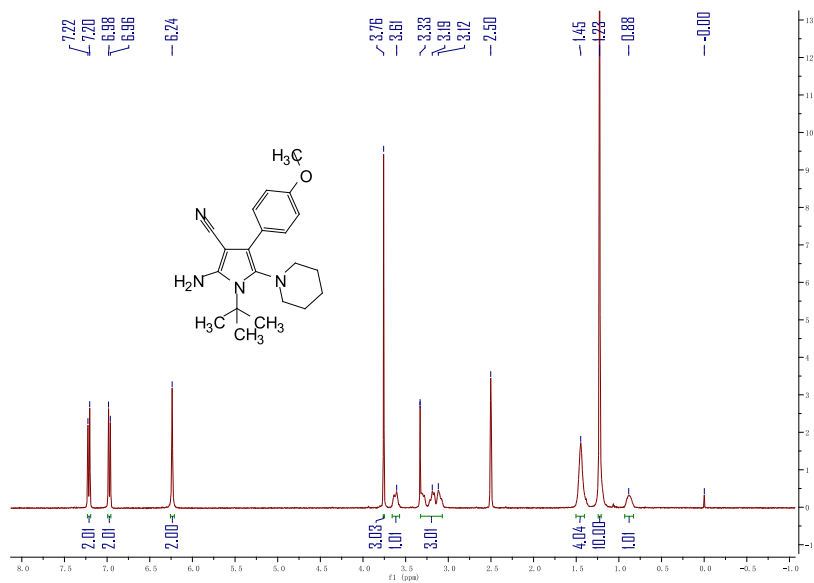
¹³C NMR spectrum of compounds 4a



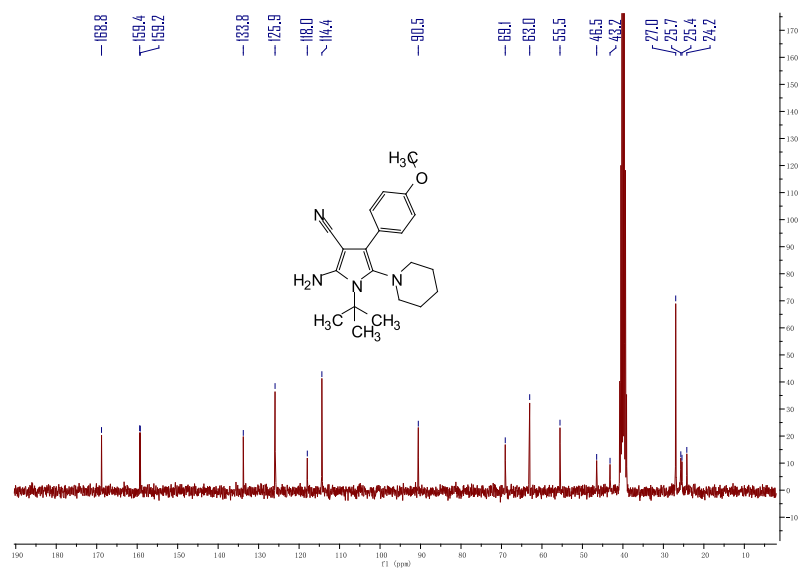
¹H NMR spectrum of compounds 4b



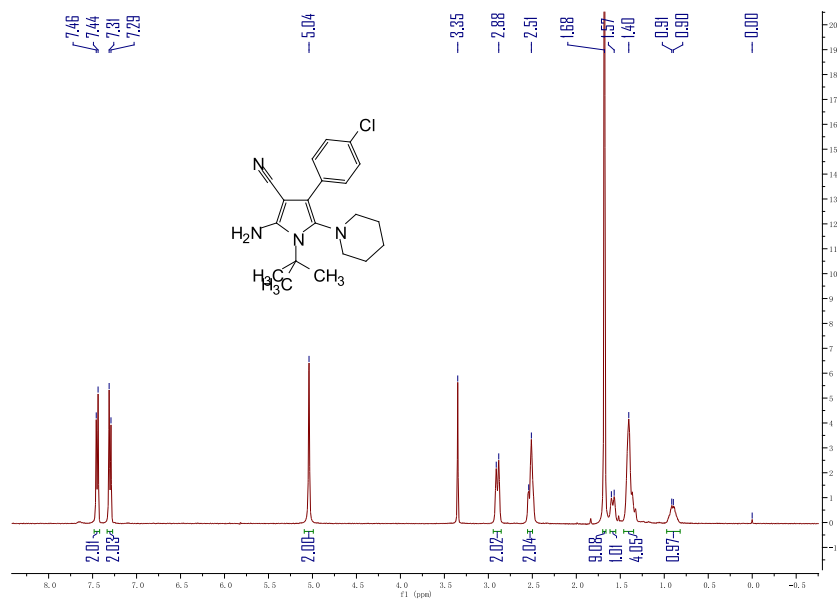
¹³C NMR spectrum of compounds 4b



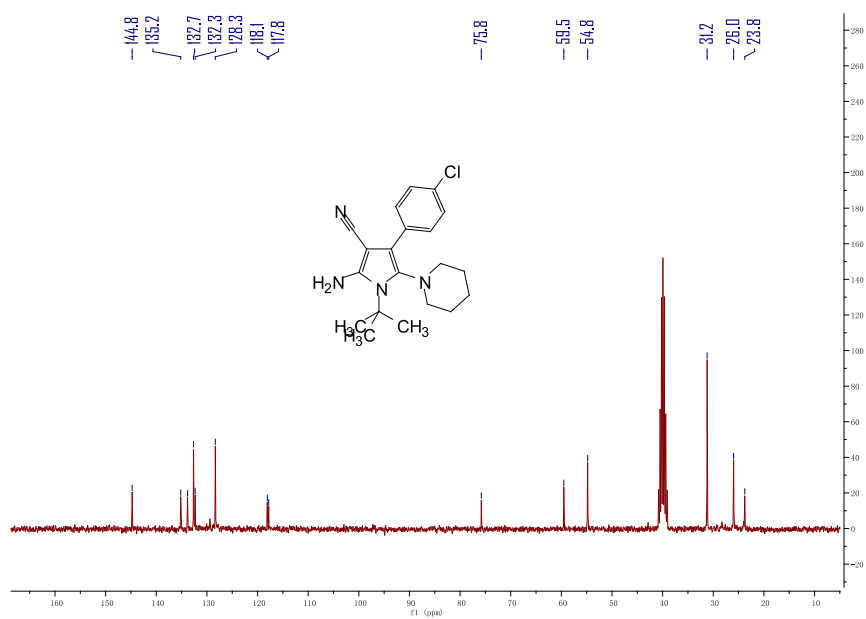
¹H NMR spectrum of compounds 4c



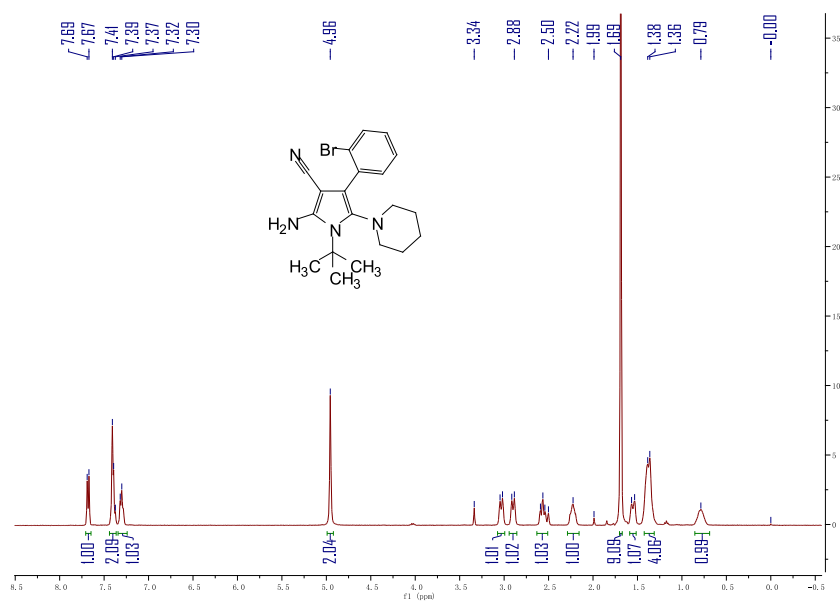
¹³C NMR spectrum of compounds 4c



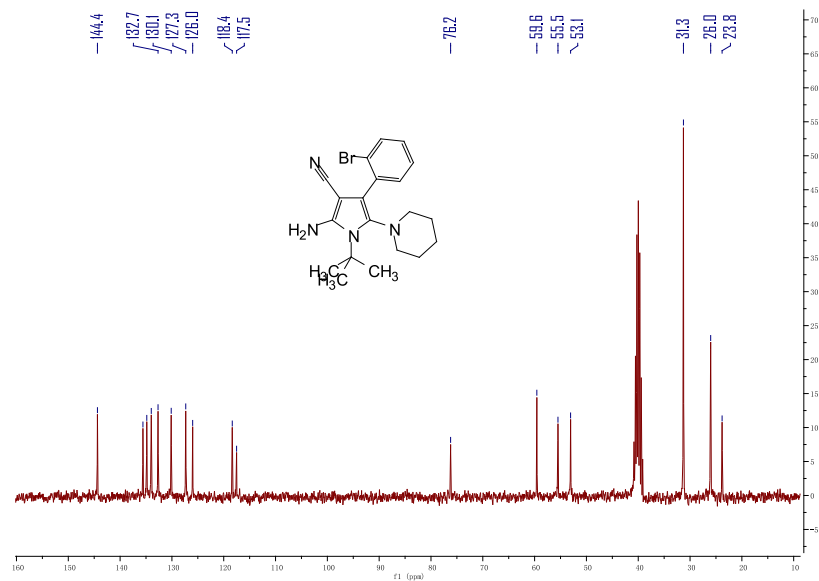
¹H NMR spectrum of compounds 4d



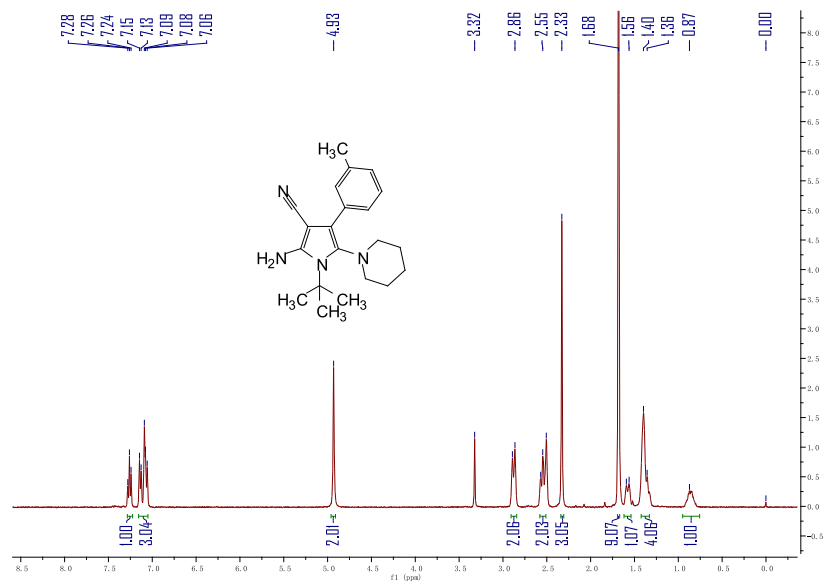
¹³C NMR spectrum of compounds 4d



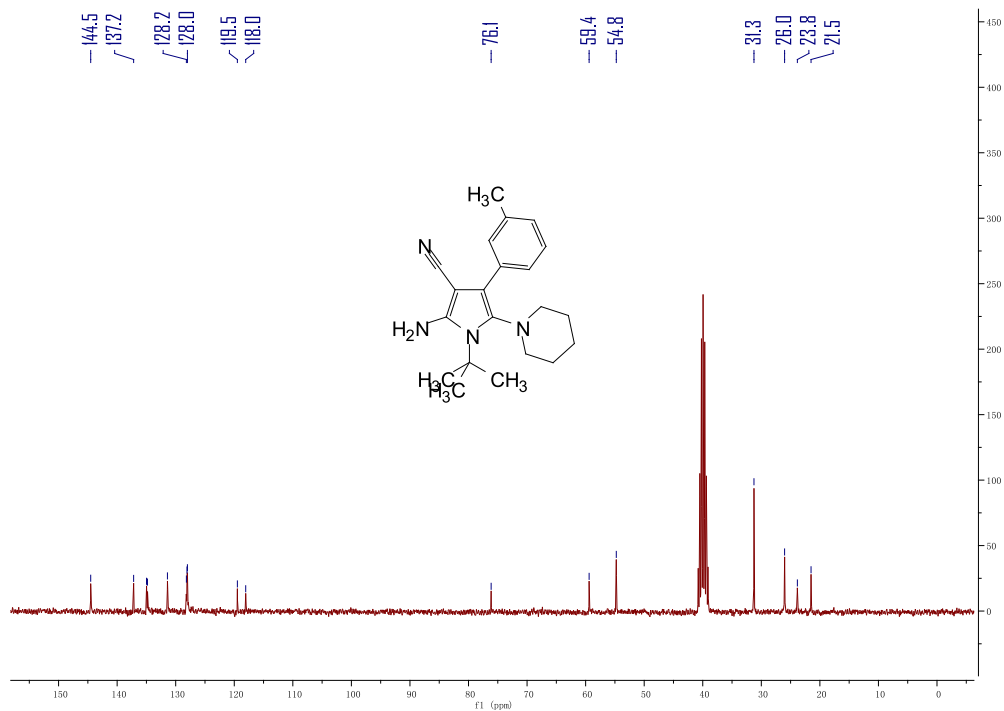
¹H NMR spectrum of compounds 4e



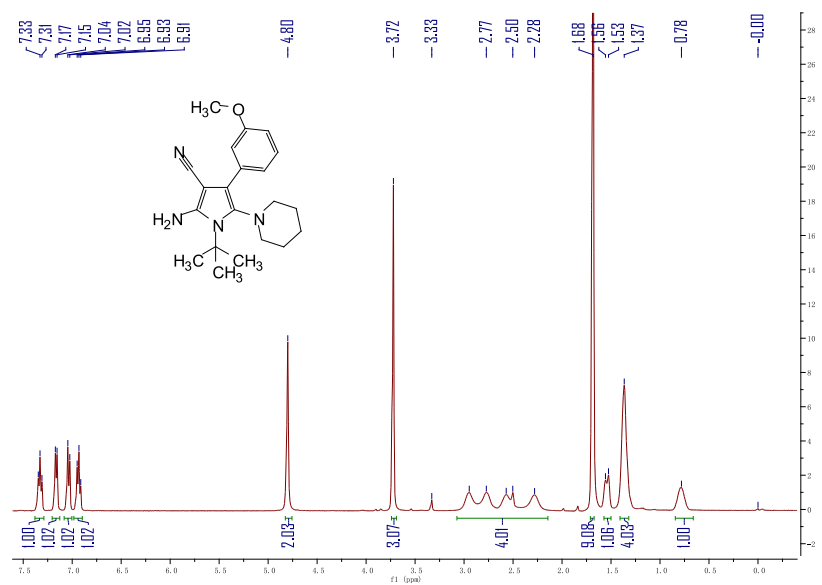
¹³C NMR spectrum of compounds 4e



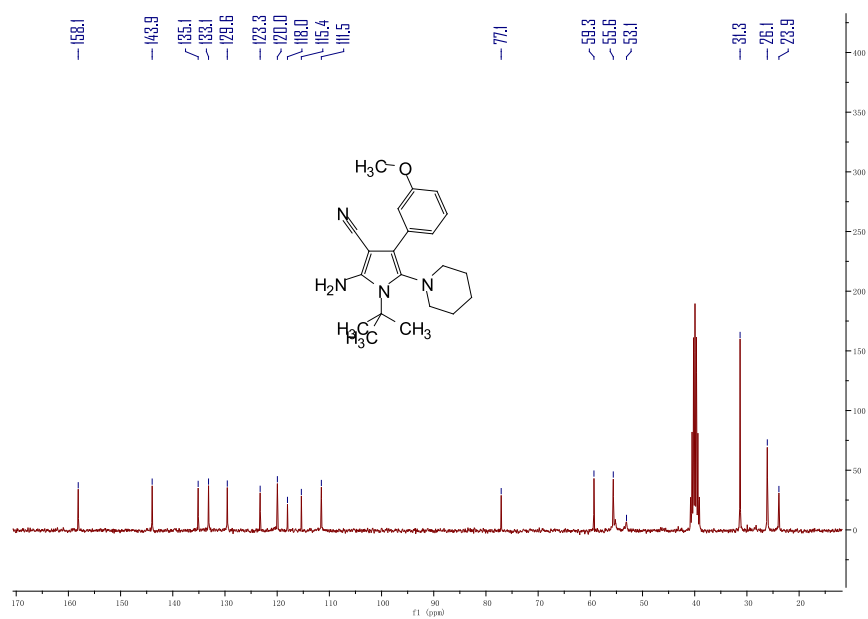
¹H NMR spectrum of compounds 4f



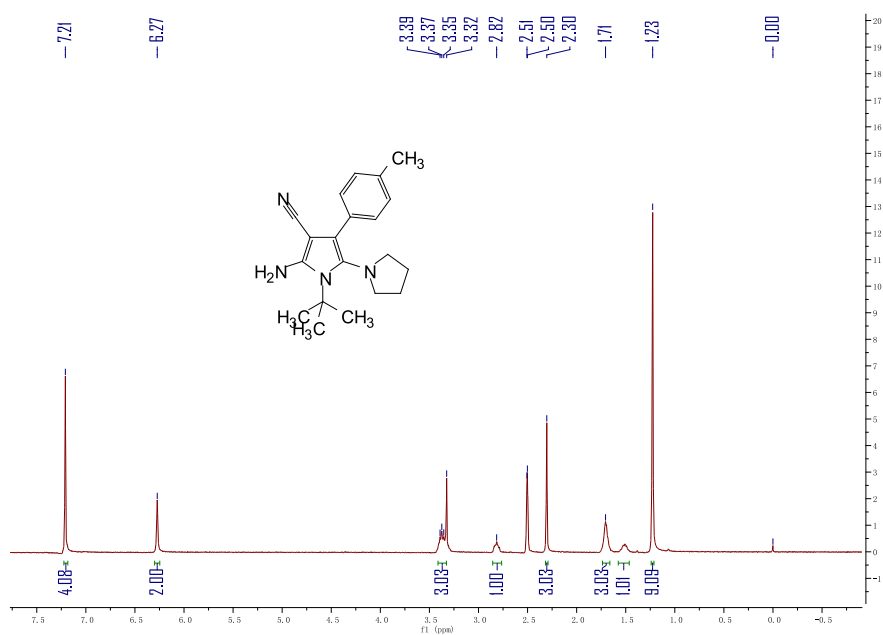
¹³C NMR spectrum of compounds 4f



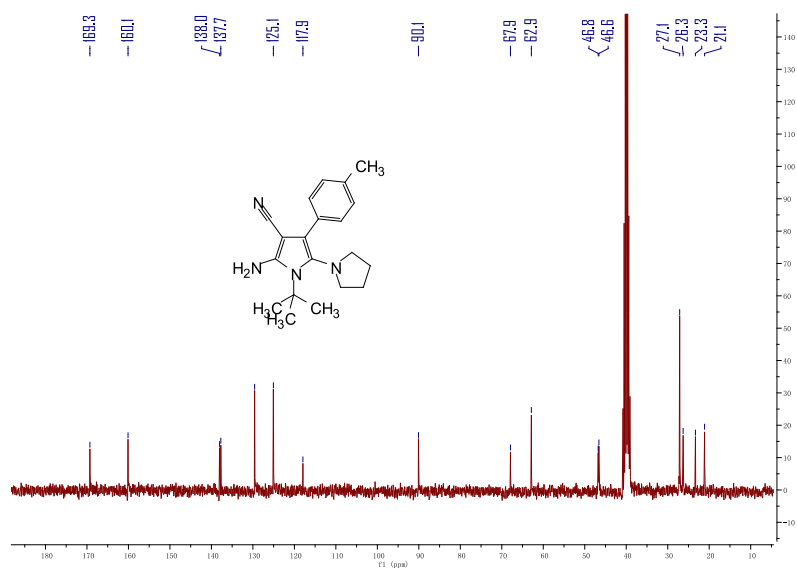
¹H NMR spectrum of compounds 4g



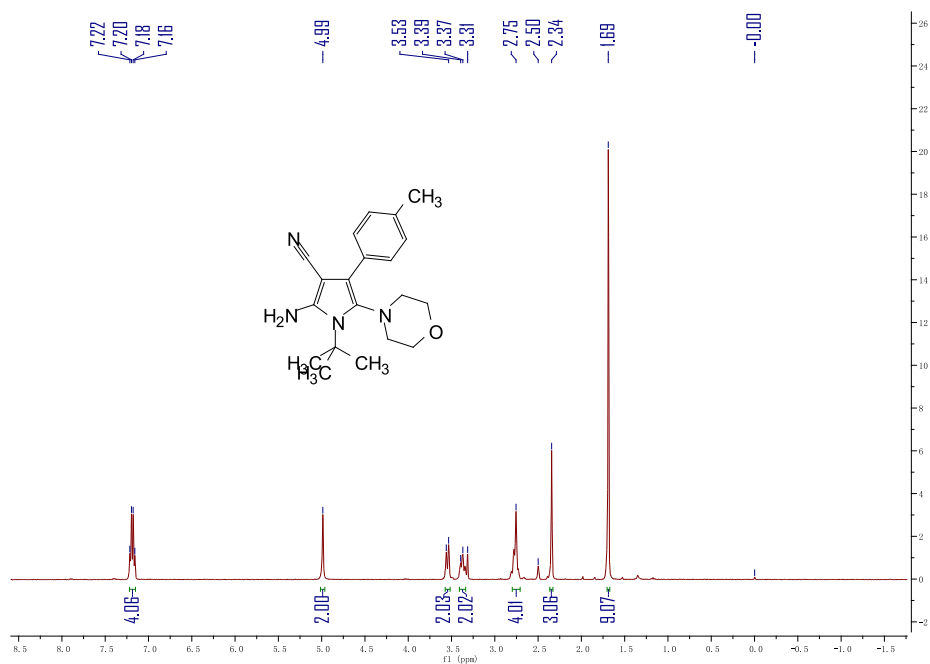
¹³C NMR spectrum of compounds 4g



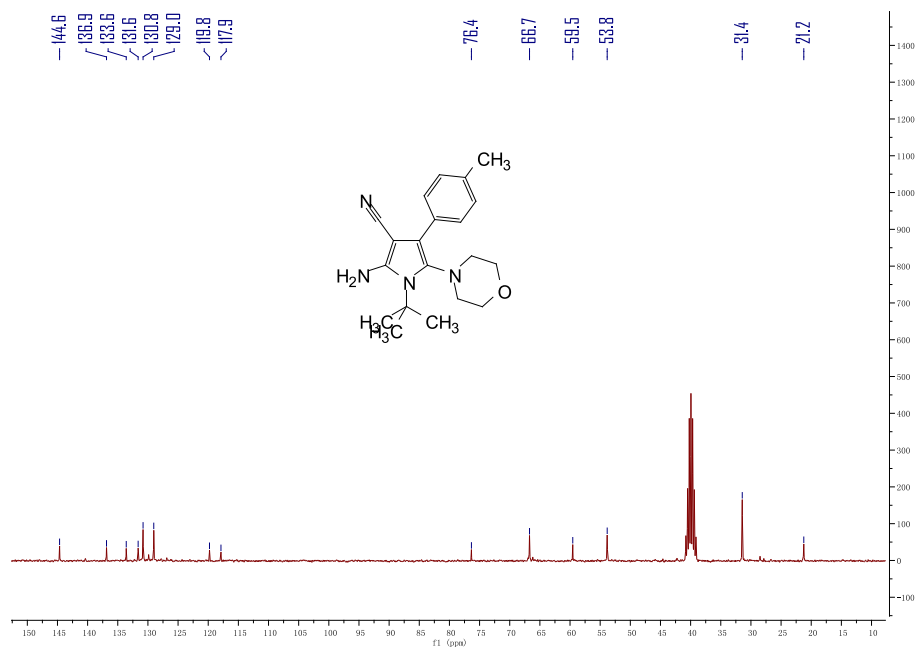
¹H NMR spectrum of compounds 4h



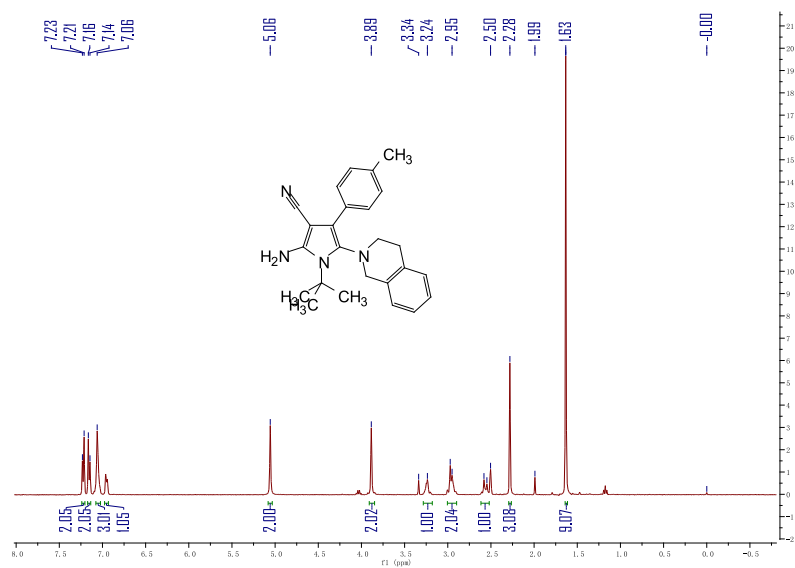
¹³C NMR spectrum of compounds 4h



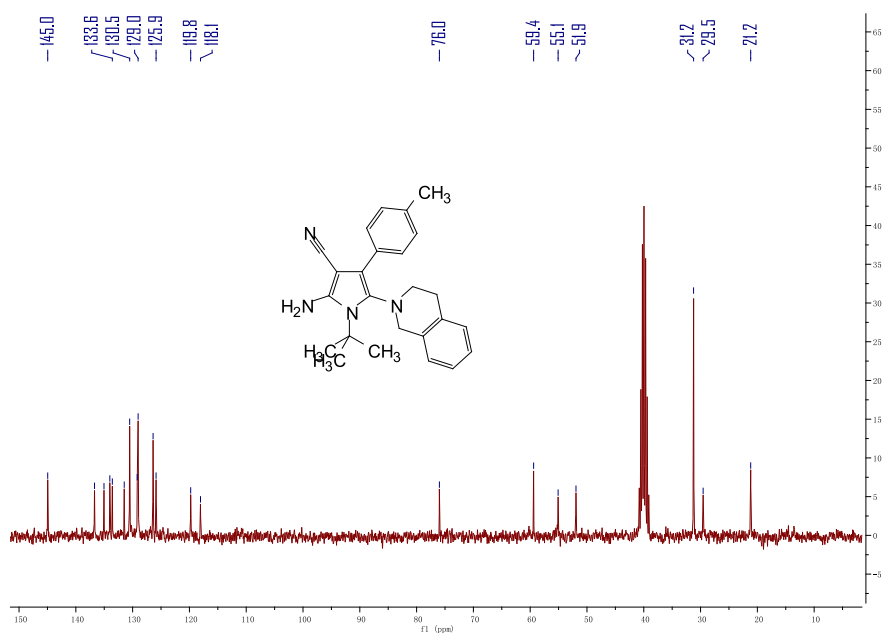
¹H NMR spectrum of compounds 4i



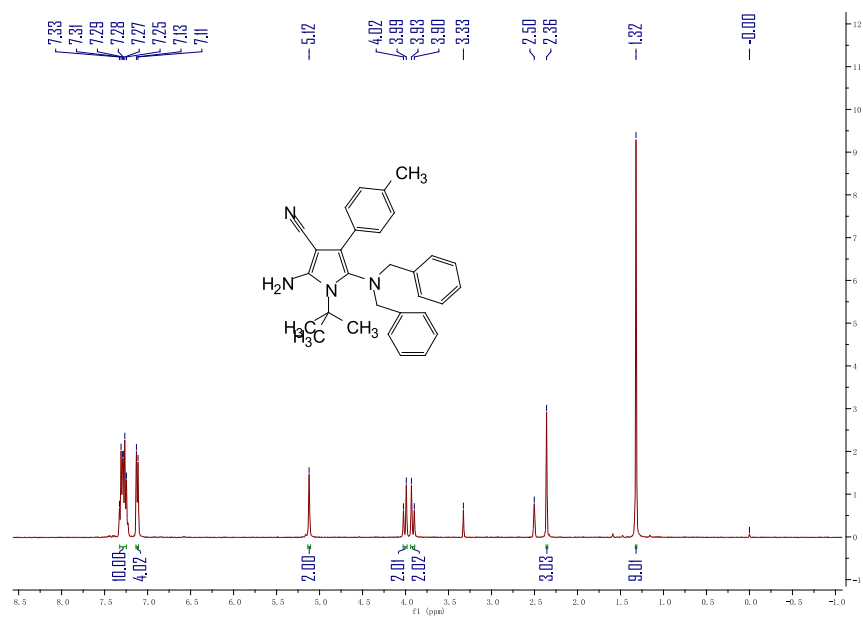
¹³C NMR spectrum of compounds 4i



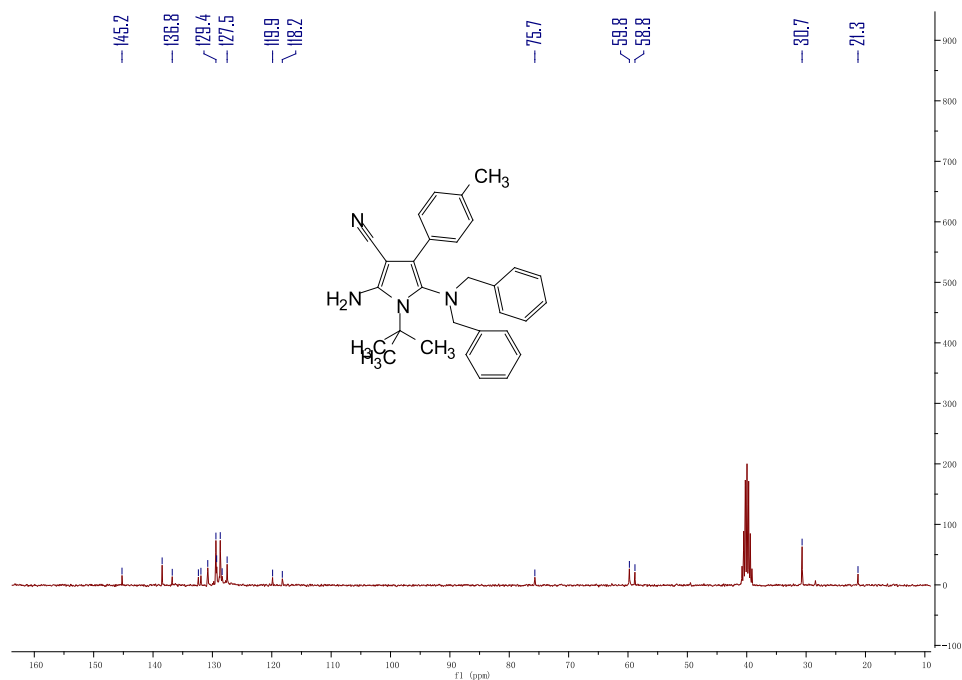
¹H NMR spectrum of compounds 4j



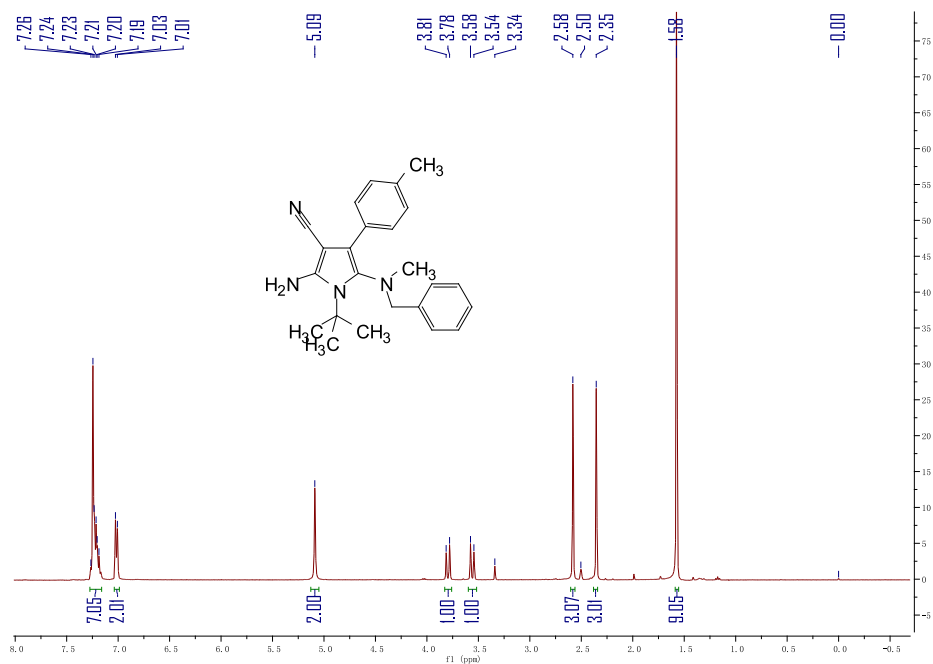
¹³C NMR spectrum of compounds 4j



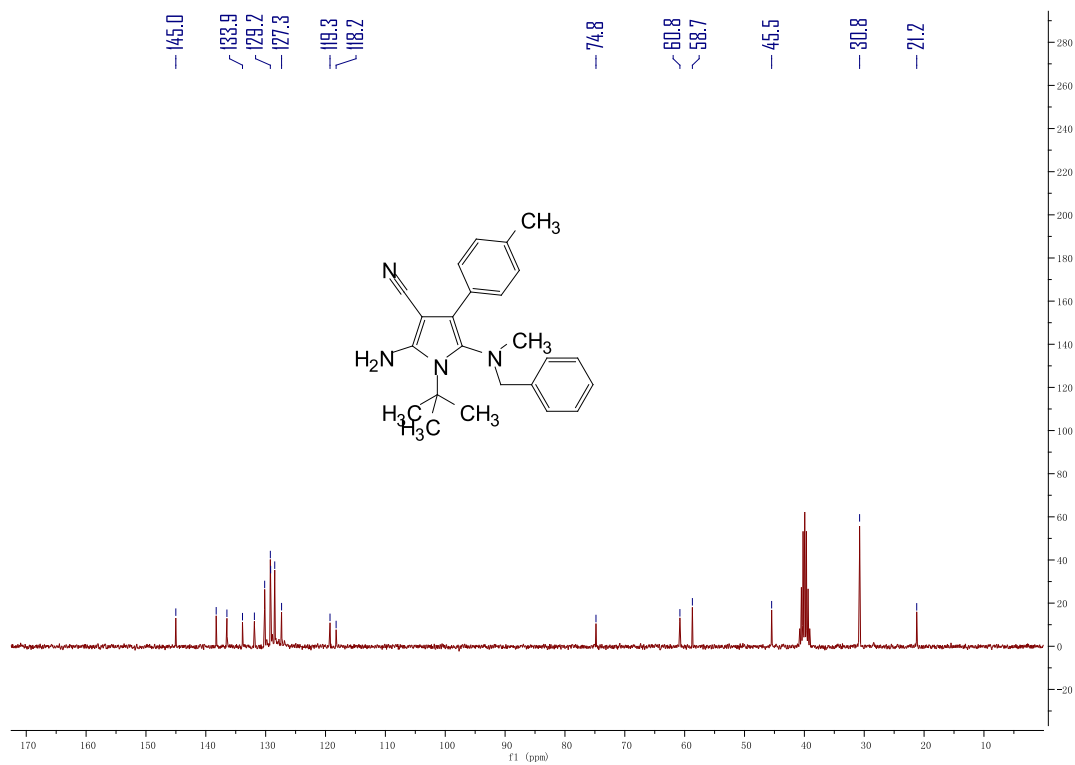
¹H NMR spectrum of compounds 4k



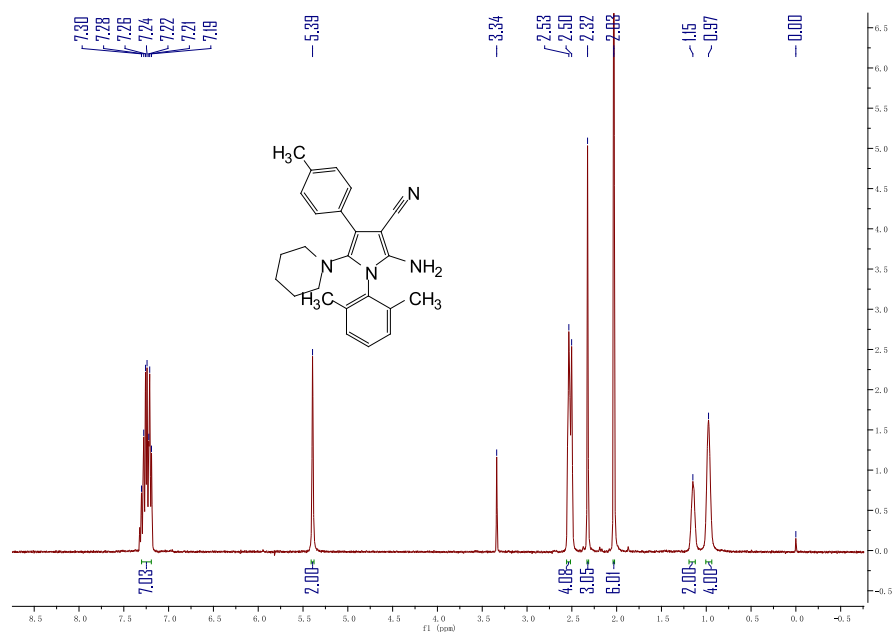
¹³C NMR spectrum of compounds 4k



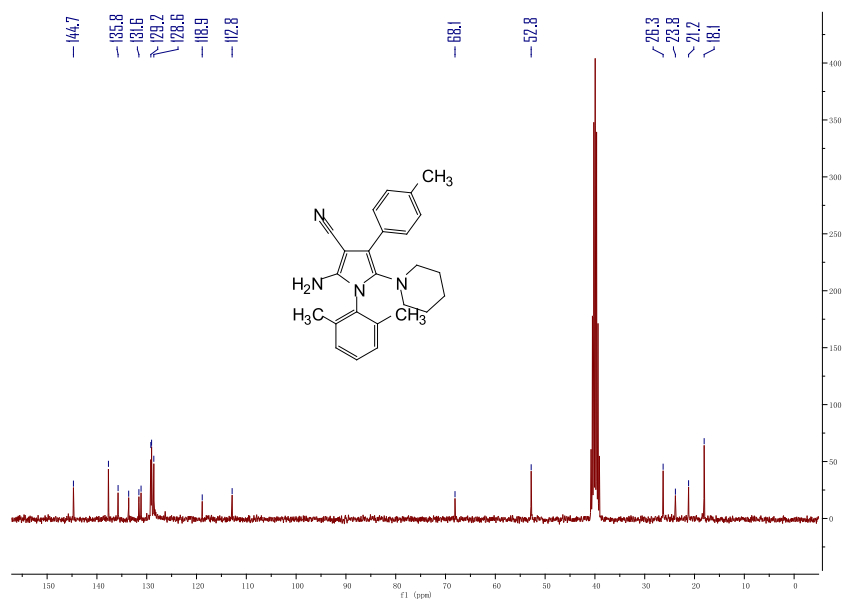
¹H NMR spectrum of compounds 4l



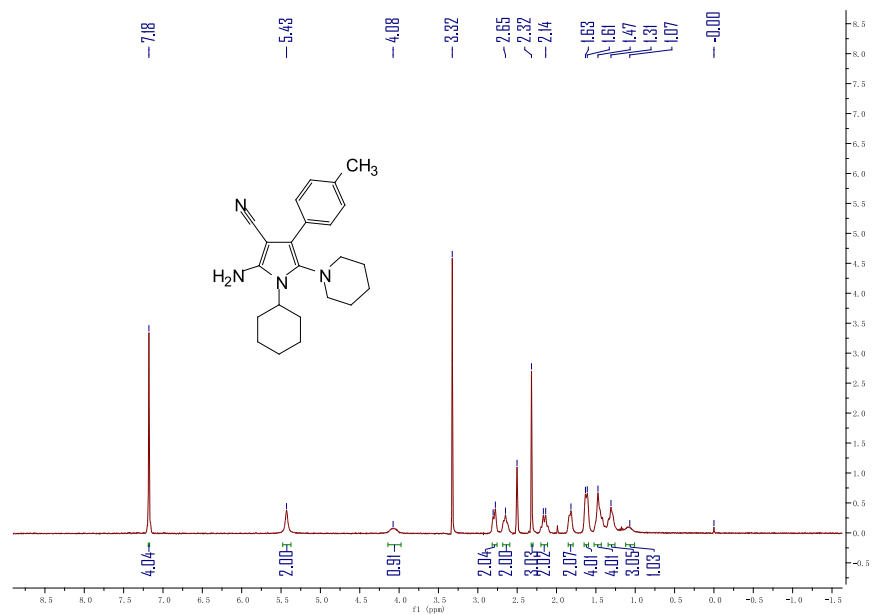
¹³C NMR spectrum of compounds 4l



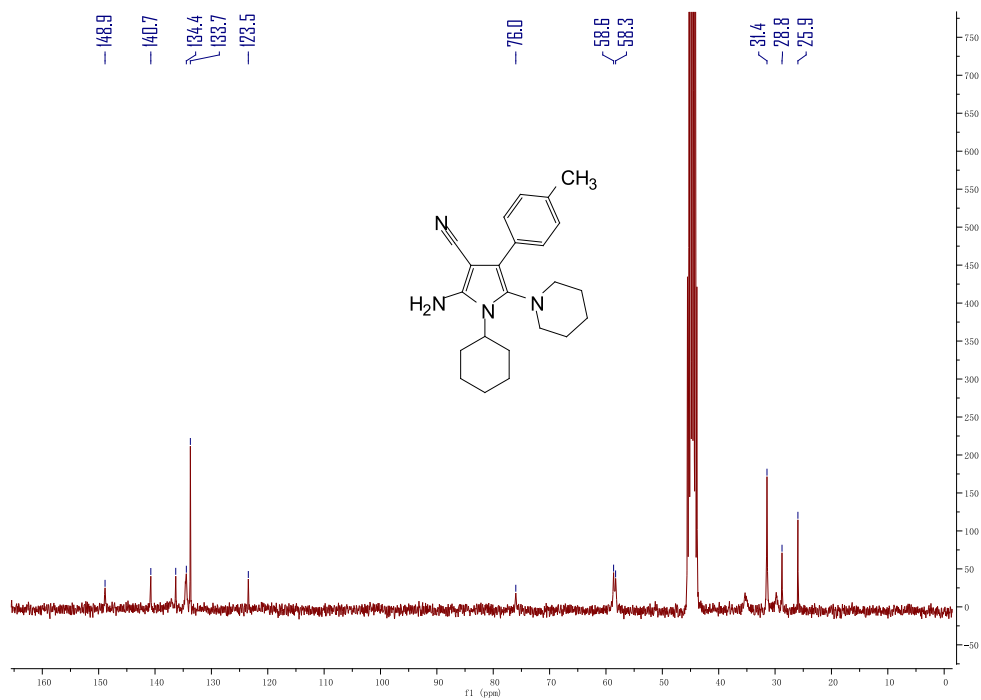
¹H NMR spectrum of compounds 4m



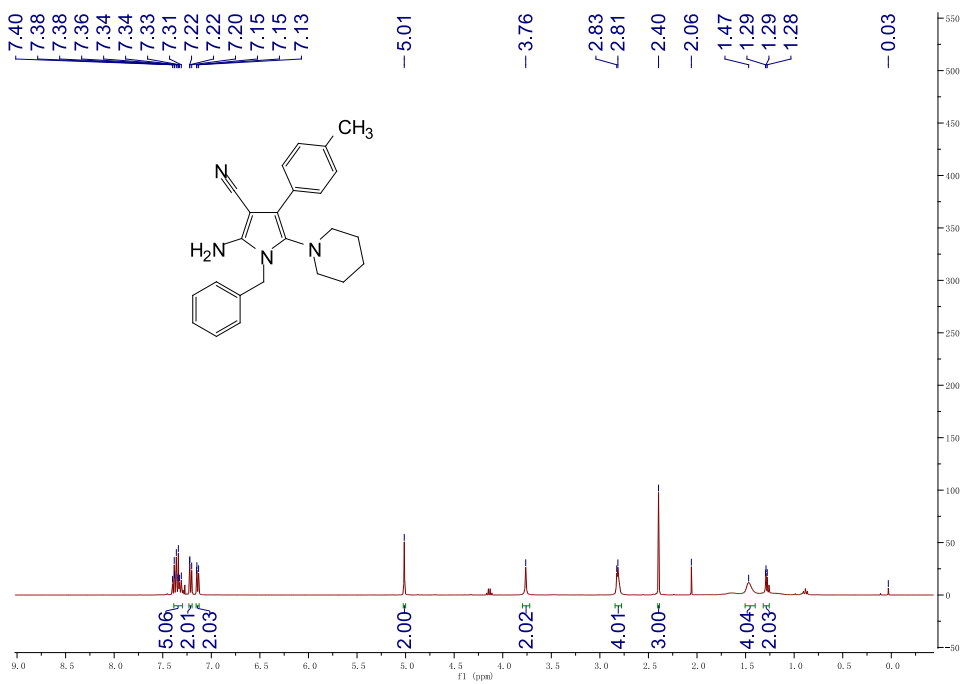
¹³C NMR spectrum of compounds 4m



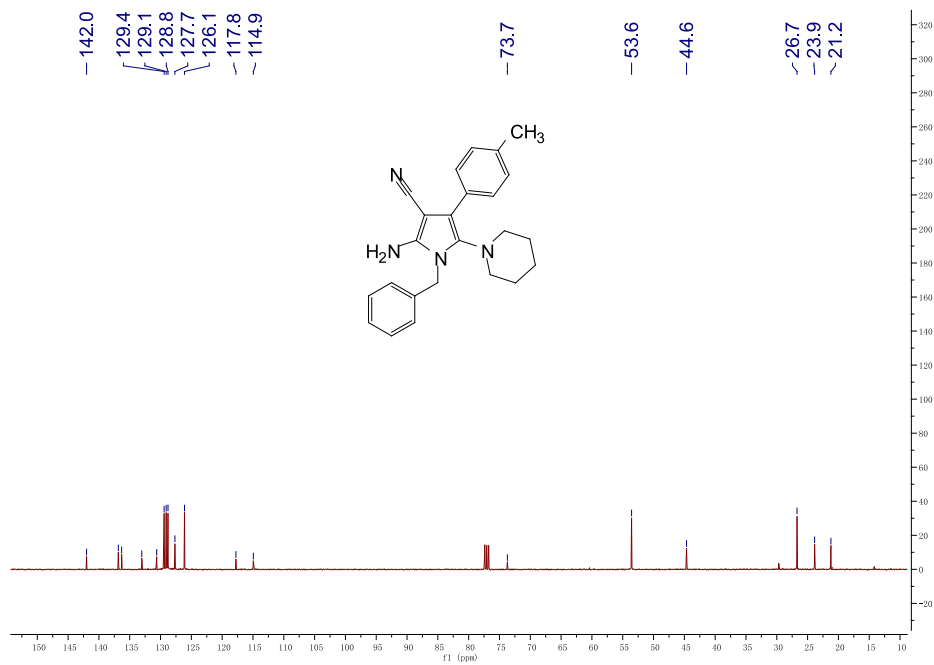
¹H NMR spectrum of compounds 4n



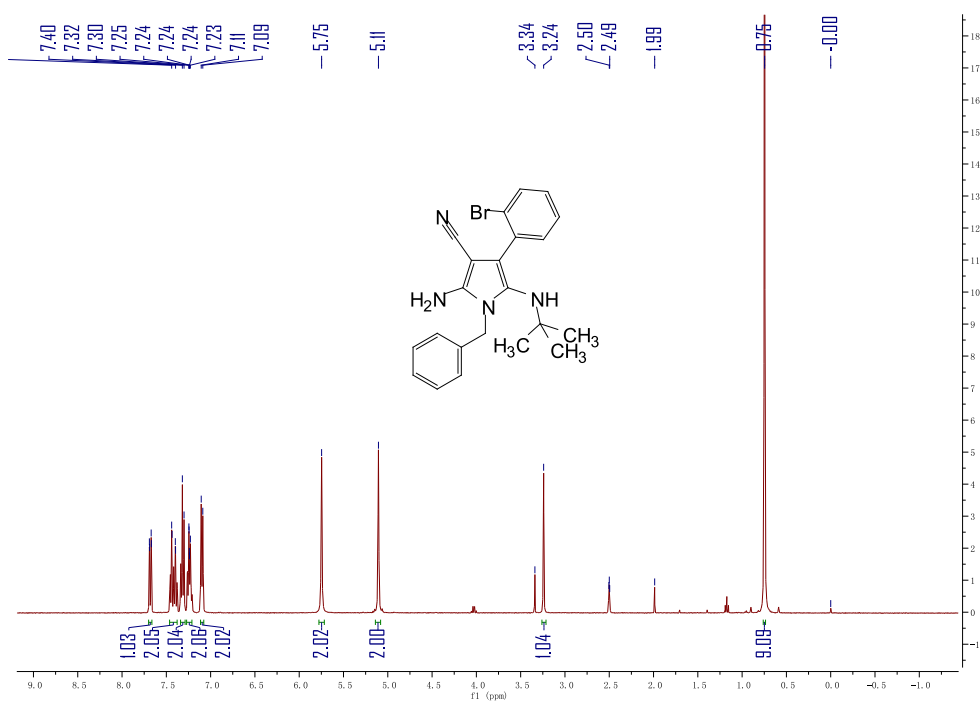
¹³C NMR spectrum of compounds 4n



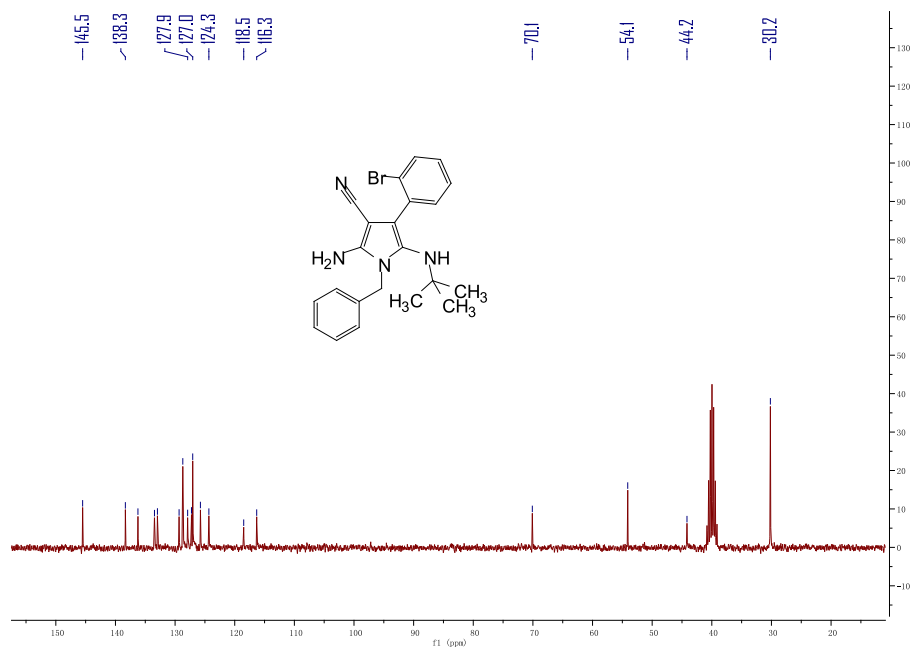
¹H NMR spectrum of compounds 4o



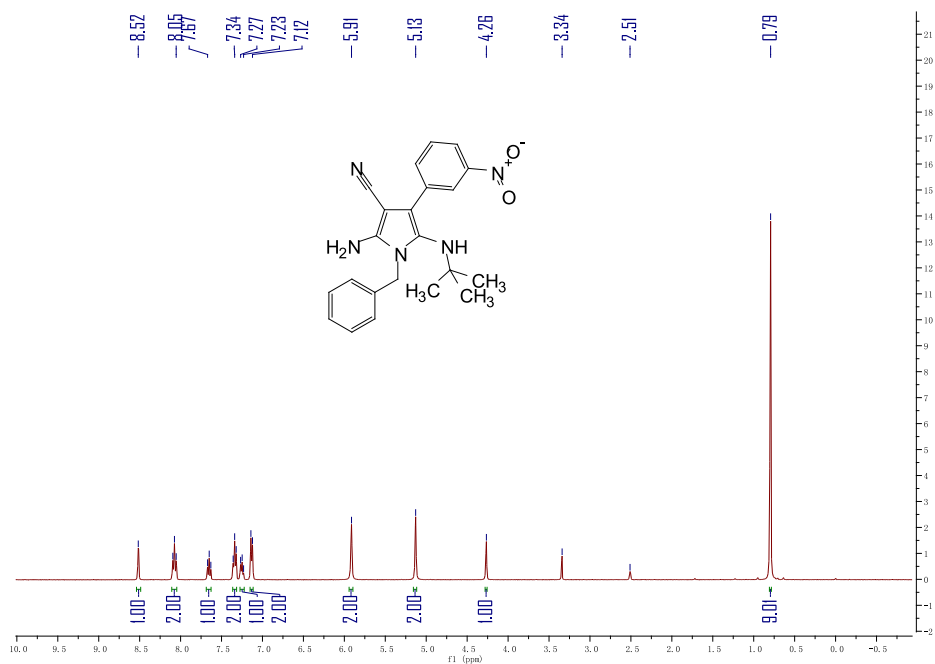
¹³C NMR spectrum of compounds 4o



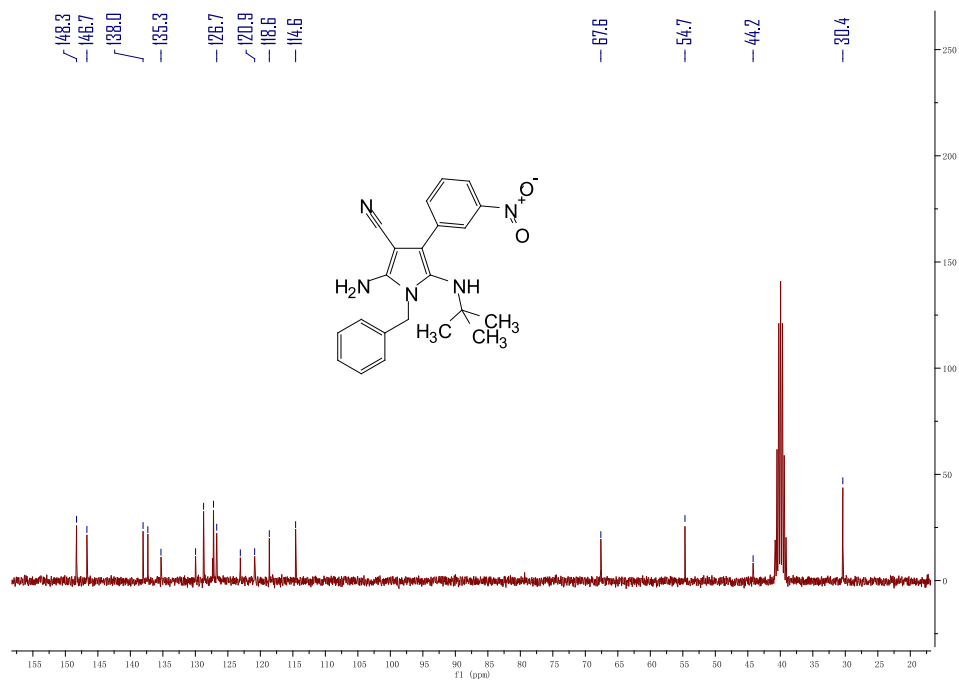
¹H NMR spectrum of compounds 5a



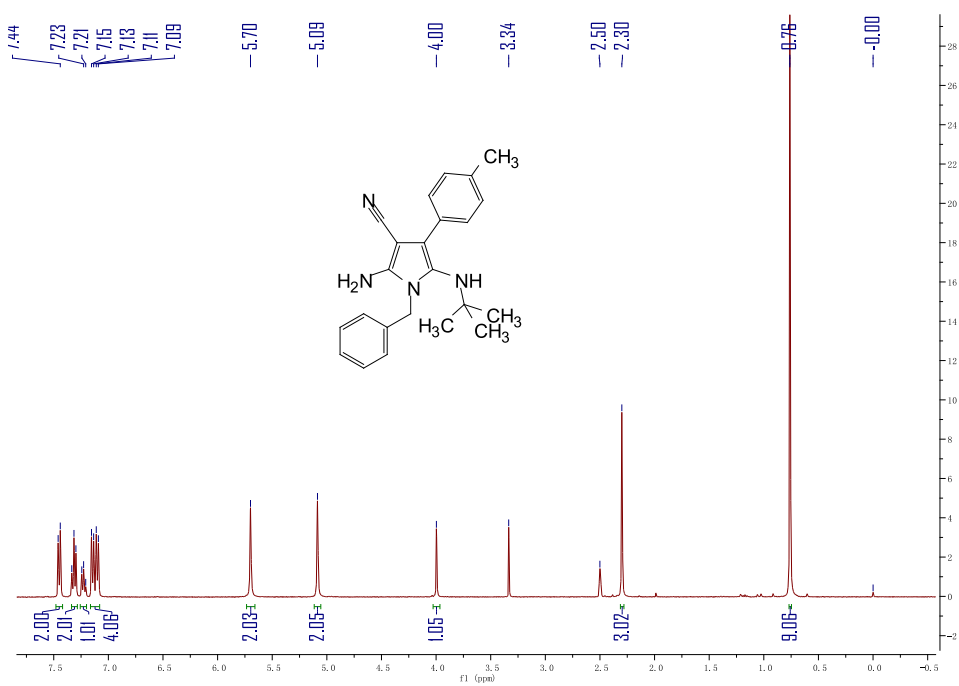
¹³C NMR spectrum of compounds 5a



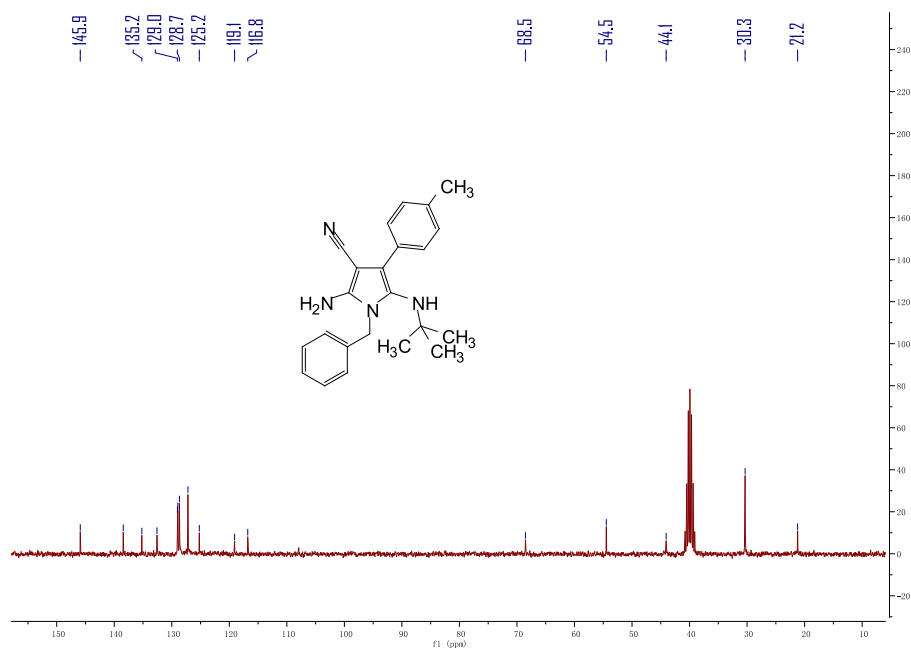
¹H NMR spectrum of compounds 5b



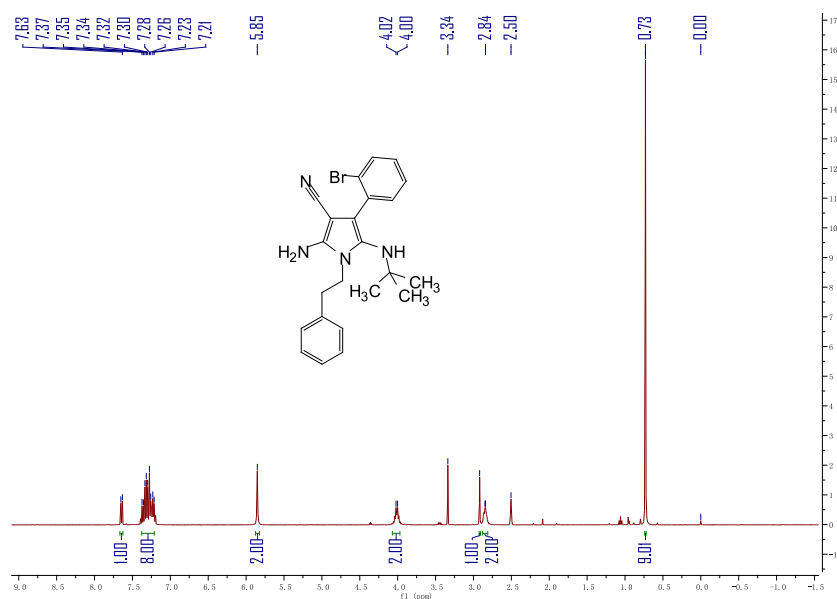
¹³C NMR spectrum of compounds 5b



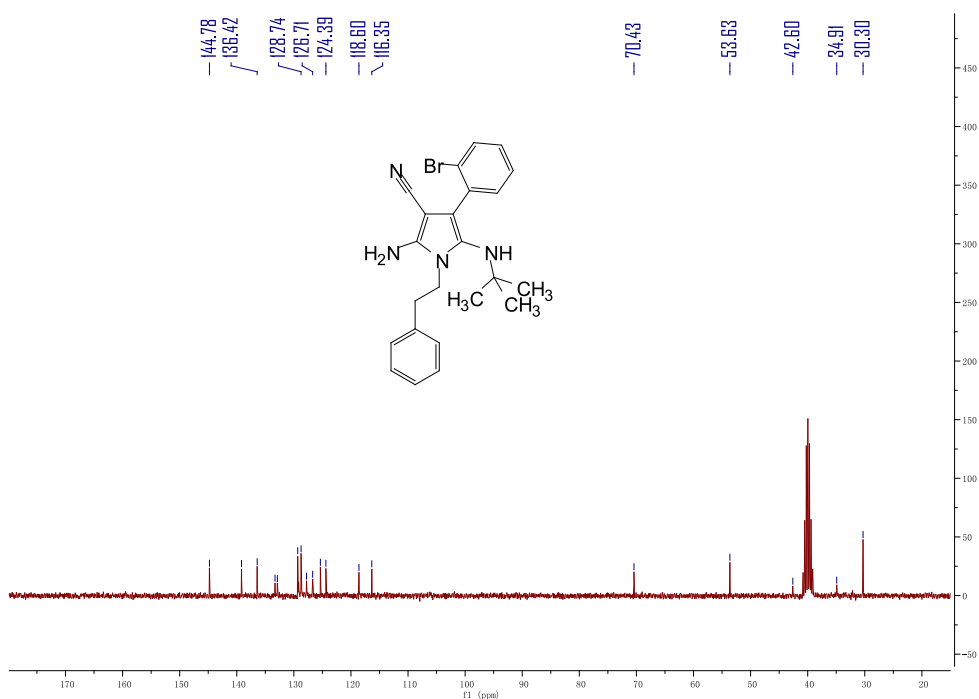
¹H NMR spectrum of compounds 5c



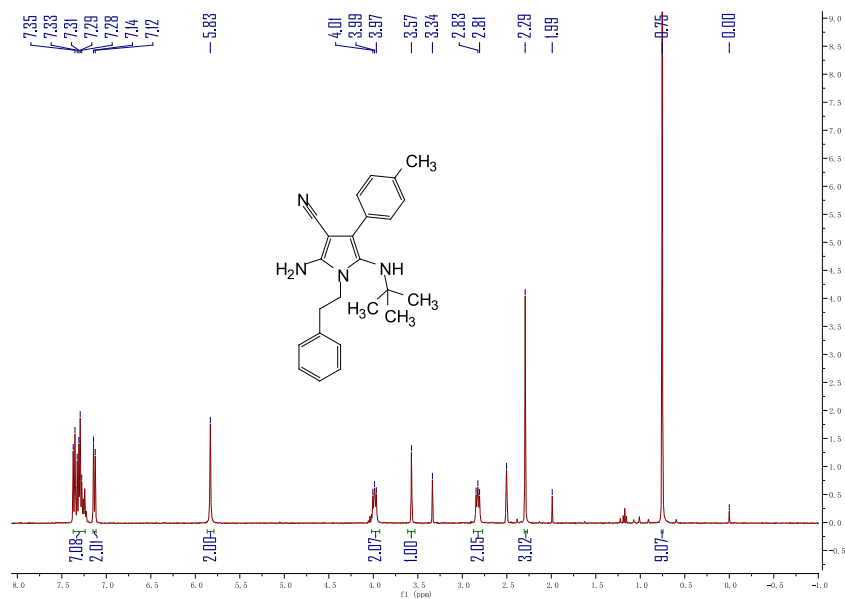
¹³C NMR spectrum of compounds 5c



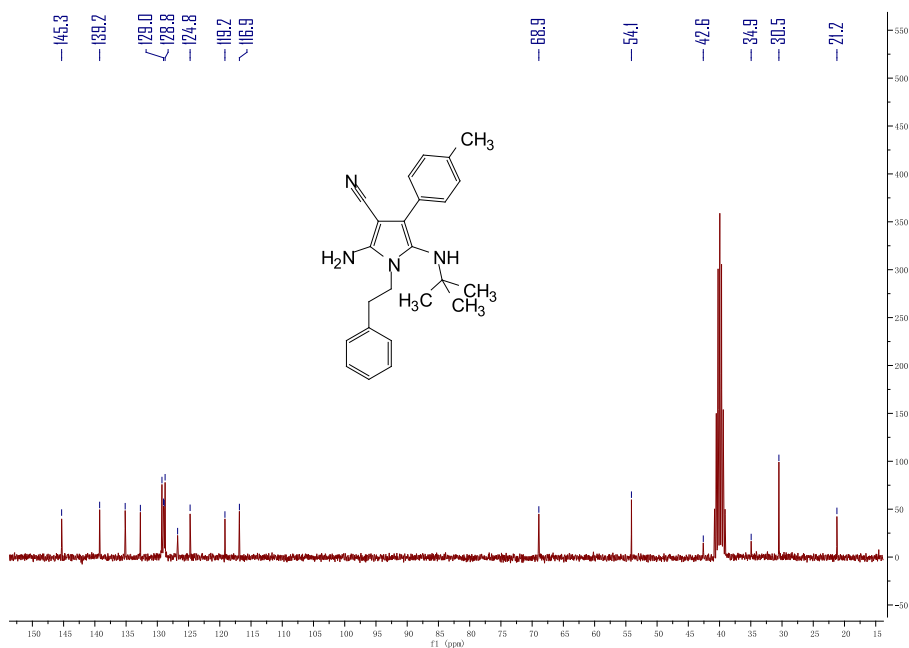
¹H NMR spectrum of compounds 5d



¹³C NMR spectrum of compounds 5d

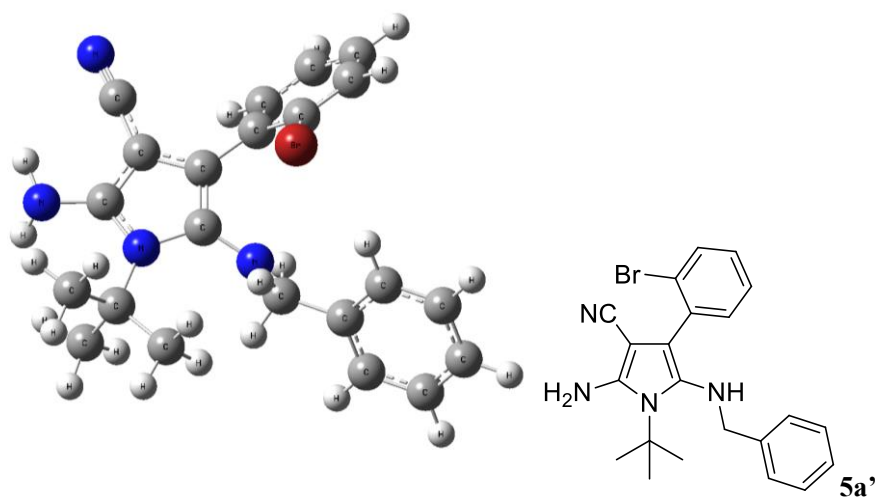


¹H NMR spectrum of compounds 5e

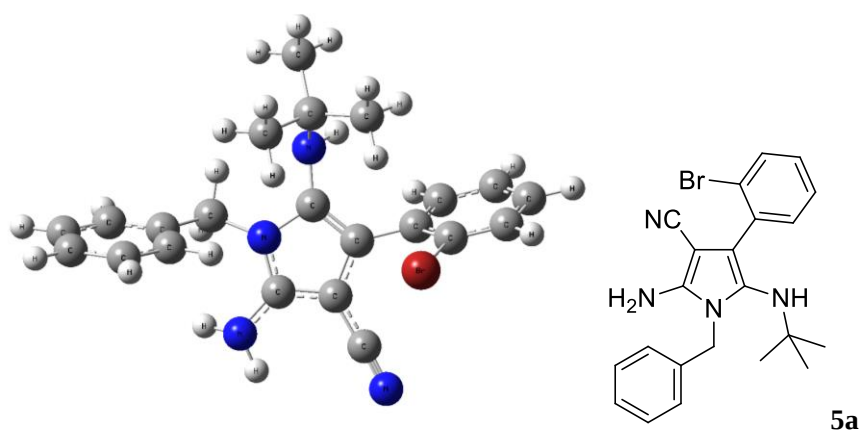


¹³C NMR spectrum of compounds 5e

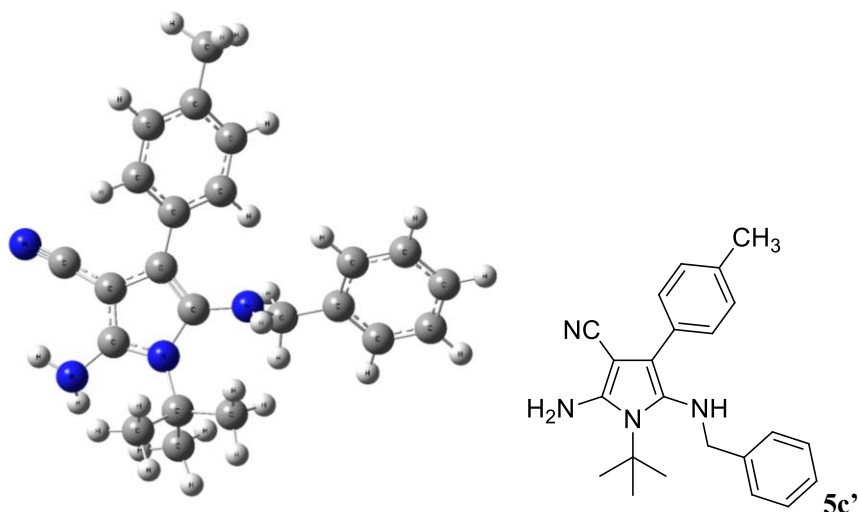
Density functional theory calculations of the possible configurations of product **5a** and **5c** at the B3LYP/6-31G level of theory.



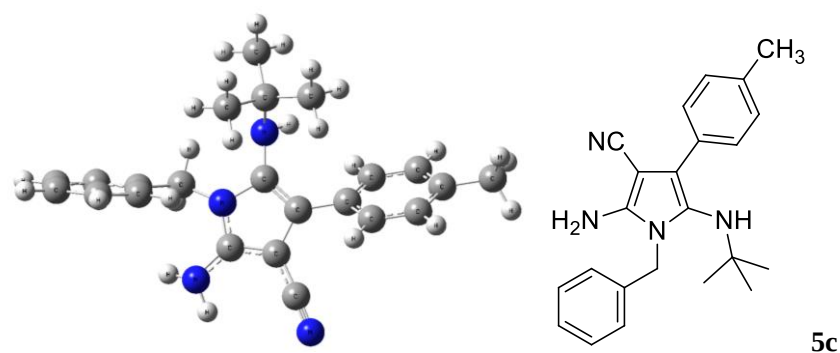
E=-3642.8791402 Hartree



E=-3642.8928071 Hartree



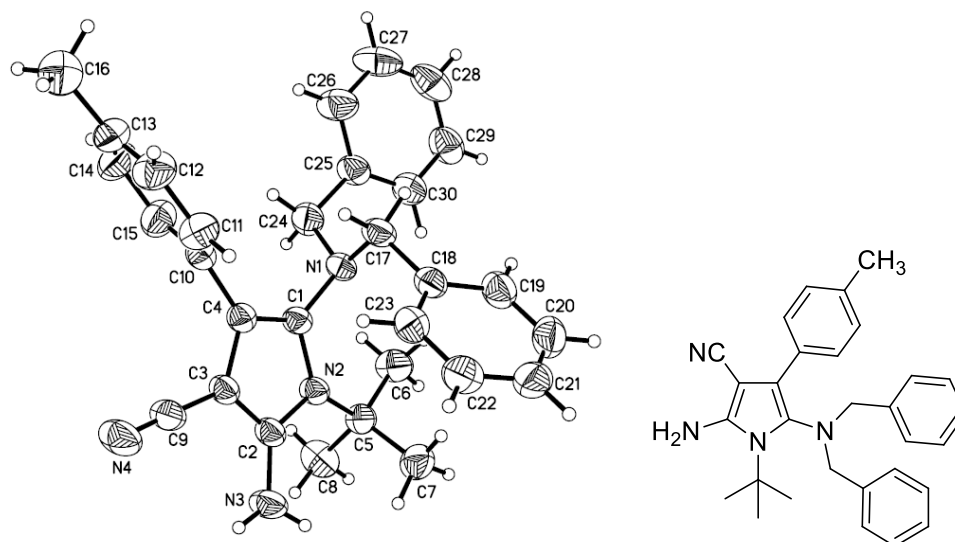
$E = -1111.0894866$ Hartree



$E = -1111.1064149$ Hartree

We found that the most stable configuration of **5a** and **5c** was 35.85 and 44.40 kJ/mol lower in energy than the most stable configuration of isomers **5a'** and **5c'**, respectively. This result suggests that intermediate **7'** could be easily transformed to more stable product **5**.

X-ray structure of compound **4k**



X-ray structure of compound **4k**