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Isonitrile Alkylations: A Rapid Route to Imidazo[1,5-a]pyridine

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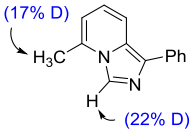
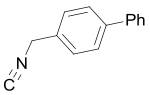


General experimental conditions:

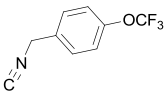
Tetrahydrofuran (THF) was freshly distilled from Na/benzophenone ketyl prior to use. Dichloromethane (CH_2Cl_2) was dried by passing through an alumina and molecular sieve drying train, marketed by Innovative Technology Inc. (Model: PS-MD-7). Other reagents were purchased at analytical or ACS grade, and used without further purification unless otherwise stated. Thin layer chromatography (TLC) was performed with UV active (w/ F-254) glass backed silica gel plates (Dynamic Adsorbents Inc.). TLC plates were visualized by exposure to short wavelength UV light (254 nm). Flash chromatography was performed using SiliaFlash® silica gel P60 (30-400 mesh) purchased from Silicycle, Florisil® (100-200 mesh) purchased from Alfa Aesar. Radial chromatography was performed on a Harrison Research Chromatotron™ using glass rotors covered with SiO_2 and leveled to 1, 2, and 4 mm thickness. ^{1}H NMR and ^{13}C NMR high resolution nuclear magnetic resonance spectra were obtained on a Bruker Avance 400 or a Bruker Avance 500 spectrometer.^{1}H NMR data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublet, m = multiplet, br = broad resonance, etc.), integration, and coupling constants (Hz). ^{13}C NMR data are reported in parts per million (ppm) on the δ scale. High resolution mass spectra (HRMS) were recorded on a Thermo-Finnegan LTQ-FTMS in APCI mode. Infrared spectra were recorded on a Perkin Elmer Frontier FT-IR spectrometer with a universal ATR sampling accessory.

General procedure for isocyanide formation from a primary amine (General procedure 1).[1] Neat amine was added to methyl formate (0.2 M) at rt and then the reaction was monitored by TLC. After the reaction was complete (~ 2 days), the solution was concentrated by rotary evaporation. The resulting crude formamide (1.0 equiv.) was dissolved in dry

CH_2Cl_2 (0.2 M), and then *i*-Pr_2NH (3 equiv.) was added. The solution was cooled to -30 ℃, and then phosphorous oxychloride (1.1 equiv.) was added dropwise. After 2 h, the reaction mixture was poured into a saturated, aqueous solution of sodium carbonate. The organic layer was separated and then the aqueous phase was extracted with CH_2Cl_2. The combined organic fractions were washed with water, brine, dried (Na_2SO_4), filtered, and concentrated. The crude isonitrile was purified by flash column chromatography on a short pad of silica gel (1.0 × 5.0 cm column for approximately 500 mg of the crude reaction mixture) to afford pure isonitrile.



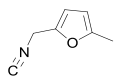
4-(Isocyanomethyl)-1,1'-biphenyl (6b): Following general procedure 1, isonitrile **6b** was prepared from 4-phenylbenzylamine (0.500 g, 2.73 mmol) as a white solid (0.417 g, 2.16 mmol) in 79% yield: IR (ATR) 3034, 2153 cm^{-1}; ^1H NMR (400 MHz, Chloroform-*d*) δ 7.65-7.55 (m, 4H), 7.47-7.33 (m, 5H), 4.66 (s, 2H); ^{13}C NMR (100 MHz, Chloroform-*d*) δ 157.82 (br), 141.49, 140.28, 131.33, 128.94, 127.72, 127.15, 45.34 (t, *J* = 7.1 Hz); HRMS calculated for $C_{14}H_{12}N^+$ 194.09643, found 194.09641 $(M+H)^+$.



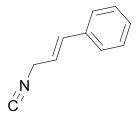
1-(Isocyanomethyl)-4-(trifluoromethoxy)benzene (6c): Following general procedure 1, isonitrile **6c** was prepared from 4-trifluoromethoxybenzylamine (0.500 g, 2.62 mmol) as a yellow liquid (0.421g, 2.09 mmol) in 80% yield:[2] IR (ATR) 2151cm^{-1}; ^1H NMR (500 MHz, Chloroform-*d*) δ 7.38 (d, *J* = 8.4 Hz, 2H), 7.24 (d, *J* = 8.4 Hz, 2H), 4.63 (s, 2H); ^{13}C NMR (126 MHz, Chloroform-*d*) δ 158.38 (t, *J* = 5.0 Hz), 149.14, 131.13, 128.21, 121.44, 121.42 (q, *J* = 120.4 Hz), 44.79 (t, *J* = 6.9 Hz); HRMS calculated for $C_9H_7F_3NO^+$ 202.04743, found 202.04739 $(M+H)^+$.

2-(Isocyanomethyl)furan (6d): Following general procedure 1, isonitrile **6d** was

prepared from furfurylamine (0.500 g, 5.15 mmol) as a yellow liquid (0.403 g, 3.76 mmol) in 73% yield, that exhibited spectral data consistent with that already published.[3]

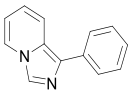


2-(Isocyanomethyl)-5-methylfuran (6e): Following general procedure 1, isonitrile **6e** was prepared from (5-methyl-2-furyl)methylamine (0.500 g, 4.50 mmol) as a yellow liquid (0.441 g, 3.65 mmol) in 81% yield: IR (ATR) 2926, 2147 cm^{-1}; ^{1}H NMR (500 MHz, Chloroform-*d*) δ 6.19 (d, *J* = 2.1 Hz, 1H), 5.92 (d, *J* = 2.1 Hz, 1H), 4.47 (s, 2H), 2.24 (s, 3H); ^{13}C NMR (126 MHz, Chloroform-*d*) δ 157.33 (t, *J* = 4.1 Hz), 153.17, 143.67, 109.90, 106.61, 38.81 (t, *J* = 6.9 Hz), 13.38; HRMS calculated for $C_7H_8ON^+$ 122.06004, found 122.06008 $(M+H)^+$.

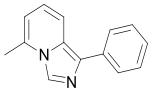


(*E*)-(3-Isocyanoprop-1-en-1-yl)benzene (6f): Following general procedure 1, isonitrile **6f** was prepared from cinnamylamine (0.500 g, 3.76 mmol) as a white solid (0.366 g, 2.56 mmol) in 68% yield:[4] IR (ATR) 3028, 2149 cm^{-1}; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.43 – 7.24 (m, 5H), 6.72 (d, *J* = 15.8 Hz, 1H), 6.18-6.07 (m, 1H), 4.27 – 4.17 (m, 2H); ^{13}C NMR (100 MHz, Chloroform-*d*) δ 157.64 (t, *J* = 5.6 Hz), 135.50, 133.11, 128.75, 128.38, 126.65, 119.42, 43.59 (t, *J* = 7.1 Hz); $C_{10}H_{10}N^+$ 144.08078, found 144.08076 $(M+H)^+$.

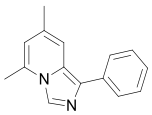
General procedure for the synthesis of imidazo[1,5-a]pyridines (General procedure 2). A hexanes solution of BuLi (1.1 equiv. 2.5 M) or a THF solution of KHMDS (1.3 equiv. 1.0 M) was added to a -78 ℃ THF solution (0.1 M) of the isonitrile (1.0 equiv.). After 5 min, a THF (0.5 M) solution of the 2-halopyridine was added. After 30 min, the reaction mixture was allowed to warm to rt and after 30 min, water was added and then the aqueous layer was extracted with EtOAc. The combined organic fractions were washed sequentially with water and brine, dried (Na_2SO_4), filtered, and then concentrated. The crude material was then purified by radial chromatography to afford pure product.



1-Phenylimidazo[1,5-a]pyridine (8a): Following general procedure 2 with benzylisonitrile (0.078 g, 0.67 mmol), 2-chloropyridine (0.075 g, 0.67 mmol) and KHMDS (0.87 mL, 0.87 mmol), afforded imidazo[1,5-a]pyridine **8a** (0.068 g, 0.35 mmol) in 53% yield:[5] IR (ATR) 3042, 1601, 1517, 1457 cm^{-1}; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.13 (s, 1H), 7.90- 7.86 (m, 3H), 7.78 (d, *J* = 9.3 Hz, 1H), 7.47-7.41 (m, 2H), 7.30 – 7.24 (m, 1H), 6.74 (dd, *J* = 9.1, 6.5 Hz, 1H), 6.53 (t, *J* = 6.7 Hz, 1H); ^{13}C NMR (126 MHz, Chloroform-*d*) δ 135.10, 131.42, 128.77, 127.49, 126.48, 126.42, 122.58, 119.98, 118.88, 112.95; HRMS calculated for $C_{13}H_{11}N_2^+$ 195.0917, found 195.0916 $(M+H)^+$.

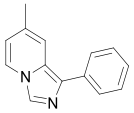


5-Methyl-1-phenylimidazo[1,5-a]pyridine (8b): Following general procedure 2 with benzylisonitrile (0.054 g, 0.46 mmol), 2-chloro-6-methylpyridine (0.059 g, 0.46 mmol) and BuLi (0.20 mL, 0.51 mmol), afforded imidazo[1,5-a]pyridine **8b** (0.069 g, 0.33 mmol) in 72% yield: IR (ATR) 3052, 1639, 1600, 1538 cm^{-1}; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.01 (s, 1H), 7.91-7.86 (m, 2H), 7.67 (d, *J* = 9.3 Hz, 1H), 7.47-7.40 (m, 2H), 7.25 (t, *J* = 7.4 Hz, 1H), 6.68 (dd, *J* = 9.3, 6.5 Hz, 1H), 6.30 (d, *J* = 6.5 Hz, 1H), 2.45 (s, 3H); ^{13}C NMR (100 MHz, Chloroform-*d*) δ 135.35, 131.91, 131.37, 128.73, 127.00, 126.47, 126.31, 124.99, 120.34, 116.18, 111.86, 18.14; HRMS calculated for $C_{14}H_{12}N_2Na^+$ 231.0893, found 231.0893 $(M+Na)^+$.

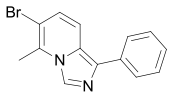


5,7-Dimethyl-1-phenylimidazo[1,5-a]pyridine (8c): Following general procedure 2 with benzylisonitrile (0.054 g, 0.46 mmol), 2-chloro-4,6-dimethylpyridine (0.065 g, 0.46 mmol) and BuLi (0.20 mL, 0.51 mmol), afforded imidazo[1,5-a]pyridine **8c** (0.079 g, 0.35 mmol) in 77% yield: IR (ATR) 3051, 2912, 1650, 1603 cm^{-1}; ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.99 (s, 1H), 7.88 (d, *J* = 7.3 Hz, 2H), 7.48-7.40 (m, 3H), 7.25 (t, *J* = 7.4 Hz, 1H), 6.23 (s, 1H), 2.49 (s, 3H), 2.27 (s, 3H); ^{13}C NMR (126 MHz, Chloroform-*d*) δ 135.53, 130.78, 130.32, 128.66, 127.44, 126.33, 126.01, 124.50,

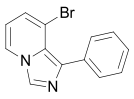
114.91, 113.97, 21.30, 17.98; HRMS calculated for $C_{15}H_{14}N_2Na^+$ 245.1049, found 245.1049 $(M+Na)^+$.



7-Methyl-1-phenylimidazo[1,5-a]pyridine (8d): Following general procedure 2 with benzylisonitrile (0.083 g, 0.71 mmol), 2-chloro-4-methylpyridine (0.090 g, 0.71 mmol) and KHMDS (0.92 mL, 0.92 mmol), afforded imidazo[1,5-a]pyridine **8d** (0.081 g, 0.39 mmol) in 55% yield: IR (ATR) 3055, 2910, 1644, 1610 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.09 (s, 1H), 7.89 – 7.87 (m, 2H), 7.83 (d, *J* = 7.2 Hz, 1H), 7.55 (s, 1H), 7.48 – 7.42 (m, 2H), 7.28 – 7.24 (m, 1H), 6.42 (dd, *J* = 7.2, 1.5 Hz, 1H), 2.32 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.26, 130.54, 129.65, 128.71, 126.98, 126.85, 126.24, 126.12, 122.03, 116.37, 115.94, 21.39; HRMS calculated for $C_{14}H_{13}N_2^+$ 209.10732, found 209.10733 $(M+H)^+$.

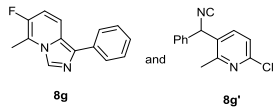


6-Bromo-5-methyl-1-phenylimidazo[1,5-a]pyridine (8e): Following general procedure 2 with benzylisonitrile (0.054 g, 0.46 mmol), 5-bromo-2-chloro-6-methylpyridine (0.095 g, 0.46 mmol) and KHMDS (0.74 mL, 0.74 mmol), afforded imidazo[1,5-a]pyridine **8e** (0.100 g, 0.35 mmol) in 77% yield: IR (ATR) 3118, 1621, 1601, 1530 cm^{-1}; ^1H NMR (500 MHz, Chloroform-*d*) δ 8.09 (s, 1H), 7.85 (d, *J* = 7.2 Hz, 2H), 7.59 (d, *J* = 9.6 Hz, 1H), 7.46 (t, *J* = 7.8 Hz, 2H), 7.30 (t, *J* = 7.4 Hz, 1H), 6.92 (d, *J* = 9.6 Hz, 1H), 2.71 (s, 3H); ^{13}C NMR (126 MHz, Chloroform-*d*) δ 134.58, 133.42, 129.62, 128.80, 126.85, 126.67, 126.15, 125.86, 124.33, 116.89, 108.81, 17.56; HRMS calculated for $C_{14}H_{11}BrN_2Na^+$ 308.99978, found 308.99984 $(M+Na)^+$.

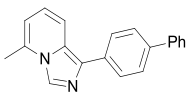


8-Bromo-1-phenylimidazo[1,5-a]pyridine (8f): Following general procedure 2 with benzylisonitrile (0.073g, 0.62 mmol), 3-bromo-2-chloropyridine (0.120 g, 0.62 mmol) and KHMDS (0.81 mL, 0.81 mmol), afforded imidazo[1,5-a]pyridine **8f** (0.099 g, 0.37 mmol) in 59% yield: IR (ATR) 3120, 1618, 1598, 1527 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.19 (s, 1H), 7.92 (d, *J* = 7.0 Hz, 1H), 7.63 (dd, *J* = 7.7, 1.3 Hz, 2H), 7.50 – 7.34 (m,

3H), 6.99 (d, *J* = 6.9 Hz, 1H), 6.44 (t, *J* = 7.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 134.74, 134.64, 131.54, 127.87, 127.43, 127.26, 124.40, 123.64, 121.68, 112.65; HRMS calculated for $C_{13}H_{10}BrN_2^+$ 273.00219, found 273.00213 $(M+H)^+$.

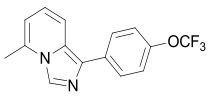


6-Fluoro-5-methyl-1-phenylimidazo[1,5-a]pyridine (8g) and 6-Chloro-3-(isocyano(phenyl)methyl)-2-methylpyridine (8g''): Following general procedure 2 with benzylisonitrile (0.054 g, 0.46 mmol), 2-chloro-5-fluoro-6-methylpyridine (0.067 g, 0.46 mmol) and KHMDS (0.74 mL, 0.74 mmol), afforded imidazo[1,5-a]pyridine **8g** (0.039 g, 0.175 mmol) in 38% yield and pyridine **8g'** (0.033 g, 0.14 mmol) in 30% yield. For **8g**: IR (ATR) 3057, 2919, 1661, 1603 cm^{-1}; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.06 (s, 1H), 7.89 – 7.80 (m, 2H), 7.71 (dd, *J* = 9.9, 5.0 Hz, 1H), 7.46 (t, *J* = 7.7 Hz, 2H), 7.34 – 7.27 (m, 1H), 6.78 (dd, *J* = 9.8, 8.2 Hz, 1H), 2.55 (d, *J* = 2.9 Hz, 3H); ^{13}C NMR (100 MHz, Chloroform-*d*) δ 150.28 (d, *J* = 234.7 Hz), 134.08 (d, *J* = 133.2 Hz), 128.81, 126.80, 126.63, 125.87 (d, *J* = 3.5 Hz), 125.11, 117.38, 117.02 (d, *J* = 9.9 Hz), 112.90 (d, *J* = 28.3 Hz), 10.56 (d, *J* = 1.4 Hz); HRMS calculated for $C_{14}H_{12}FN_2^+$ 227.0979, found 227.0980 $(M+H)^+$. For **8g'**: IR (ATR) 3068, 2135, 1582, 1563 cm^{-1}; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.66 (d, *J* = 8.2 Hz, 1H), 7.43 – 7.34 (m, 3H), 7.30 – 7.25 (m, 3H), 6.05 (s, 1H), 2.50 (s, 3H); ^{13}C NMR (100 MHz, Chloroform-*d*) δ 159.54, 156.66, 150.61, 137.86, 135.13, 130.16, 129.30, 129.08, 126.72, 122.35, 58.26, 22.18; HRMS calculated for $C_{14}H_{12}ClN_2^+$ 243.0684, found 243.0684 $(M+H)^+$.

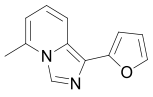


1-([1,1'-Biphenyl]-4-yl)-5-methylimidazo[1,5-a]pyridine (8h): Following general procedure 2 with 4-phenylbenzylisonitrile (0.052 g, 0.27 mmol), 2-chloro-6-methylpyridine (0.034 g, 0.27 mmol) and KHMDS (0.35 mL, 0.35 mmol), afforded imidazo[1,5-a]pyridine **8h** (0.069 g, 0.24 mmol) in 90% yield: IR (ATR) 3110, 3054, 1608, 1536 cm^{-1}; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.08 (d, *J* = 0.8 Hz, 1H), 7.98 (d, *J* = 8.4 Hz,

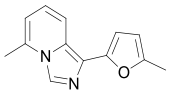
2H), 7.76 (d, *J* = 9.2 Hz, 1H), 7.73 – 7.61 (m, 4H), 7.44 (t, *J* = 7.6 Hz, 2H), 7.33 (t, *J* = 7.4 Hz, 1H), 6.77 (dd, *J* = 9.2, 6.5 Hz, 1H), 6.39 (d, *J* = 6.5 Hz, 1H), 2.54 (s, 3H); ^{13}C NMR (100 MHz, Chloroform-*d*) δ 140.93, 138.92, 134.39, 131.63, 131.49, 128.80, 127.41, 127.20, 127.14, 126.94, 126.77, 125.15, 120.49, 116.37, 112.00, 18.24; HRMS calculated for $C_{20}H_{17}N_2^+$ 285.1385, found 285.1386 $(M+H)^+$.



5-Methyl-1-(4-(trifluoromethoxy)phenyl)imidazo[1,5-a]pyridine (8i): Following general procedure 2 with 4-trifluoromethoxybenzylisonitrile (0.066 g, 0.33 mmol), 2-chloro-6-methylpyridine (0.42 g, 0.33 mmol) and KHMDS (0.43 mL, 0.43 mmol), afforded imidazo[1,5-a]pyridine **8i** (0.081 g, 0.28 mmol) in 84% yield: IR (ATR) 3114, 1638, 1537, 1503 cm^{-1}; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.08 (s, 1H), 7.90 (d, *J* = 8.8 Hz, 2H), 7.69 (d, *J* = 9.2 Hz, 1H), 7.30 (d, *J* = 8.8 Hz, 2H), 6.81 (dd, *J* = 9.2, 6.6 Hz, 1H), 6.44 (d, *J* = 6.6 Hz, 1H), 2.57 (s, 3H); ^{13}C NMR (100 MHz, Chloroform-*d*) δ 147.58 (q, *J* = 1.7 Hz), 134.15, 131.58, 130.64, 127.56, 127.20, 125.18, 121.32, 120.86, 120.59 (q, *J* = 256.8 Hz), 115.90, 112.04, 18.19; HRMS calculated for $C_{15}H_{12}OF3N_2^+$ 293.0895, found 293.0896 $(M+H)^+$.

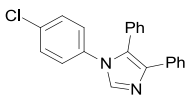


1-(Furan-2-yl)-5-methylimidazo[1,5-a]pyridine (8j): Following general procedure 2 with 2-isocyanomethylfuran (0.044 g, 0.41 mmol), 2-chloro-6-methylpyridine (0.052 g, 0.41 mmol) and KHMDS (0.53 mL, 0.53 mmol), afforded imidazo[1,5-a]pyridine **8j** (0.051 g, 0.26 mmol) in 63% yield: IR (ATR) 3123, 1643, 1612, 1539 cm^{-1}; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.00 (s, 1H), 7.87 (d, *J* = 9.2 Hz, 1H), 7.49 (br d, *J* = 1.0 Hz, 1H), 6.82- 6.75 (m, 1H), 6.75 (d, *J* = 3.3 Hz, 1H), 6.52 (dd, *J* = 3.3, 1.8 Hz, 1H), 6.41 (d, *J* = 6.5 Hz, 1H), 2.55 (s, 3H); ^{13}C NMR (100 MHz, Chloroform-*d*) δ 151.17, 140.85, 131.12, 126.75, 125.06, 124.70, 120.40, 116.97, 112.28, 111.36, 103.93, 18.14; HRMS calculated for $C_{12}H_{11}ON_2^+$ 199.0866, found 199.0866 $(M+H)^+$.



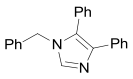
5-Methyl-1-(5-methylfuran-2-yl)imidazo[1,5-a]pyridine (8k): Following general procedure 2 with 2-isocyanomethyl-5-methylfuran (0.047 g, 0.39 mmol), 2-chloro-6-methylpyridine (0.050 g, 0.39 mmol) and KHMDS (0.51 mL, 0.51 mmol), afforded imidazo[1,5-a]pyridine **8k** (0.046 g, 0.22 mmol) in 56% yield: IR (ATR) 3108, 2920, 1618, 1643, 1584 cm^{-1}; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.00 (s, 1H), 7.83 (d, *J* = 9.2 Hz, 1H), 6.77 (dd, *J* = 9.2, 6.5 Hz, 1H), 6.62 (d, *J* = 3.1 Hz, 1H), 6.41 (d, *J* = 6.5 Hz, 1H), 6.09 (br d, *J* = 3.1 Hz, 1H), 2.56 (s, 3H), 2.41 (s, 3H); ^{13}C NMR (100 MHz, Chloroform-*d*) δ 150.71, 149.22, 131.02, 126.23, 125.00, 124.89, 119.93, 117.09, 112.19, 107.24, 104.90, 18.15, 13.78; HRMS calculated for $C_{13}H_{13}ON_2^+$ 213.1022, found 213.1022 $(M+H)^+$.

General procedure for the synthesis of imidazoles (General procedure 3). A hexanes solution of BuLi (1.1 equiv. 2.5 M) or a THF solution of KHMDS (1.3 equiv. 1.0 M) was added to a -78 ℃ THF solution (0.1 M) of the isonitrile (1.0 equiv.). After 5 min, a THF (0.5 M) solution of the imidoyl chloride was added. After 30 min, the reaction mixture was allowed to warm to rt. After 30 min, water was added and then the aqueous layer was extracted with EtOAc. The combined organic fractions were washed sequentially with water and brine, dried (Na_2SO_4), filtered, and then concentrated. The crude product was then purified by radial chromatography to afford pure imidazole.

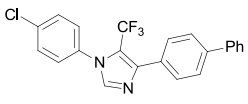


1-(4-Chlorophenyl)-4,5-diphenyl-1H-imidazole (9a): Following general procedure 3 with benzylisonitrile (0.054 g, 0.46 mmol), *N*-(4-chlorophenyl)benzimidoyl chloride (0.115 g, 0.46 mmol) and BuLi (0.20 mL, 0.51 mmol), afforded imidazole **9a** (0.077 g, 0.23 mmol) in 50% yield: IR (ATR) 3049, 1601, 1498 cm^{-1}; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.76 (s, 1H), 7.53 (d, *J* = 7.1 Hz, 2H), 7.35 – 7.18 (m, 8H), 7.18-7.12 (m, 2H), 7.05 (d, *J* = 8.6 Hz, 2H); ^{13}C NMR (100 MHz, Chloroform-*d*) δ

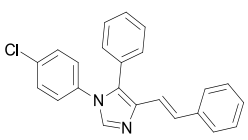
139.18, 137.20, 134.95, 134.19, 133.86, 130.77, 129.80, 129.47, 128.77, 128.54, 128.35, 128.22, 127.22, 126.92, 126.81; HRMS calculated for $C_{21}H_{16}ClN_2^+$ 331.0997, found 331.0996 $(M+H)^+$.



1-Benzyl-4,5-diphenyl-1H-imidazole (9b): Following general procedure 3 with benzylisonitrile (0.054 g, 0.46 mmol), *N*-benzylbenzimidoyl chloride (0.106 g, 0.46 mmol) and BuLi (0.20 mL, 0.51 mmol), afforded imidazole **9b** (0.087 g, 0.28 mmol) in 61% yield:[6] IR (ATR) 3062, 1603, 1506 cm^{-1}; ^1H NMR (400 MHz, Chloroform-*d*) δ 7.64 (s, 1H), 7.52 – 7.47 (m, 2H), 7.42 – 7.33 (m, 3H), 7.30 – 7.24 (m, 3H), 7.23 – 7.16 (m, 4H), 7.16 – 7.09 (m, 1H), 6.97 – 6.94 (m, 2H), 4.96 (s, 2H); ^{13}C NMR (100 MHz, Chloroform-*d*) δ 138.30, 137.14, 136.61, 134.54, 130.96, 130.55, 128.94, 128.83, 128.80, 128.73, 128.15, 127.92, 126.93, 126.52, 126.35, 48.77; HRMS calculated for $C_{22}H_{19}N_2^+$ 311.1542, found 311.1543 $(M+H)^+$.

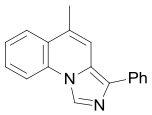


4-([1,1'-Biphenyl]-4-yl)-1-(4-chlorophenyl)-5-(trifluoromethyl)-1H-imidazole (9c): Following general procedure 3 with 4-phenylbenzylisonitrile (0.052 g, 0.27 mmol), *N*-(4-chlorophenyl)-2,2,2-trifluoroacetimidoyl chloride (0.065 g, 0.27 mmol) and KHMDS (0.35 mL, 0.35 mmol), afforded imidazole **9c** (0.064 g, 0.16 mmol) in 60% yield: IR (ATR) 3091, 1512, 1500 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.80-7.76 (m, 2H), 7.75 – 7.65 (m, 5H), 7.56 – 7.44 (m, 4H), 7.44-7.38 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.08, 141.42, 140.59, 140.07, 135.83, 134.18, 131.51, 129.82, 129.41, 128.85, 127.54, 127.16, 126.99, 121.02 (t, *J* = 269.7 Hz), 117.66 (t, *J* = 38.4 Hz); HRMS calculated for $C_{22}H_{15}N_2ClF_3^+$ 399.0869, found 399.0870 $(M+H)^+$.

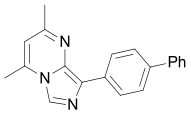


(*E*)-1-(4-Chlorophenyl)-5-phenyl-4-styryl-1H-imidazole (9d): Following general procedure 3 with (*E*)-(3-isocyanoprop-1-en-1-yl)benzene (0.051 g, 0.36 mmol), *N*-(4-chlorophenyl)-benzlimidoyl chloride (0.089 g, 0.36

mmol) and KHMDS (0.46 mL, 0.46 mmol), afforded imidazole **9d** (0.072 g, 0.21 mmol) in 57% yield: IR (ATR) 3039, 1598, 1494 cm^{-1}; ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.72 (s, 1H), 7.50 (d, *J* = 16.0 Hz, 1H), 7.46 (d, *J* = 7.3 Hz, 2H), 7.38 – 7.33 (m, 3H), 7.32-7.27 (m, 4H), 7.21 (br t, *J* = 7.3 Hz, 1H), 7.18-7.14 (m, 2H), 7.07 – 6.97 (m, 3H); ^{13}C NMR (126 MHz, Chloroform-*d*) δ 138.38, 137.93, 137.66, 134.86, 133.82, 130.22, 130.07, 129.64, 128.71, 128.65, 128.58, 128.18, 127.25, 126.47, 126.44, 118.88; HRMS calculated for $C_{23}H_{18}N_2Cl^+$ 357.11530, found 357.11546 $(M+H)^+$.

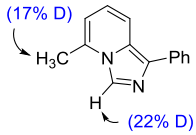


5-Methyl-3-phenylimidazo[1,5-a]quinolone (10a): Following general procedure 2 with benzylisonitrile (0.054 g, 0.46 mmol), 2-chloro-4-methylquinoline (0.082 g, 0.46 mmol) and BuLi (0.20 mL, 0.51 mmol), afforded imidazo[1,5-a]quinoline **10a** (0.098 g, 0.38 mmol) in 82% yield: IR (ATR) 3057, 1601, 1478 cm^{-1}; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.54 (s, 1H), 7.90 – 7.84 (m, 3H), 7.70 (d, *J* = 8.0 Hz, 1H), 7.51 – 7.45 (m, 3H), 7.44 – 7.36 (m, 2H), 7.30 (br t, *J* = 7.4 Hz, 1H), 2.44 (s, 3H); ^{13}C NMR (100 MHz, Chloroform-*d*) δ 135.02, 133.00, 131.00, 128.73, 128.49, 128.17, 127.12, 126.70, 126.58, 125.41, 125.38, 124.75, 124.55, 116.05, 114.52, 19.42; HRMS calculated for $C_{18}H_{14}N_2Na^+$ 281.1049, found 281.1049 $(M+Na)^+$.

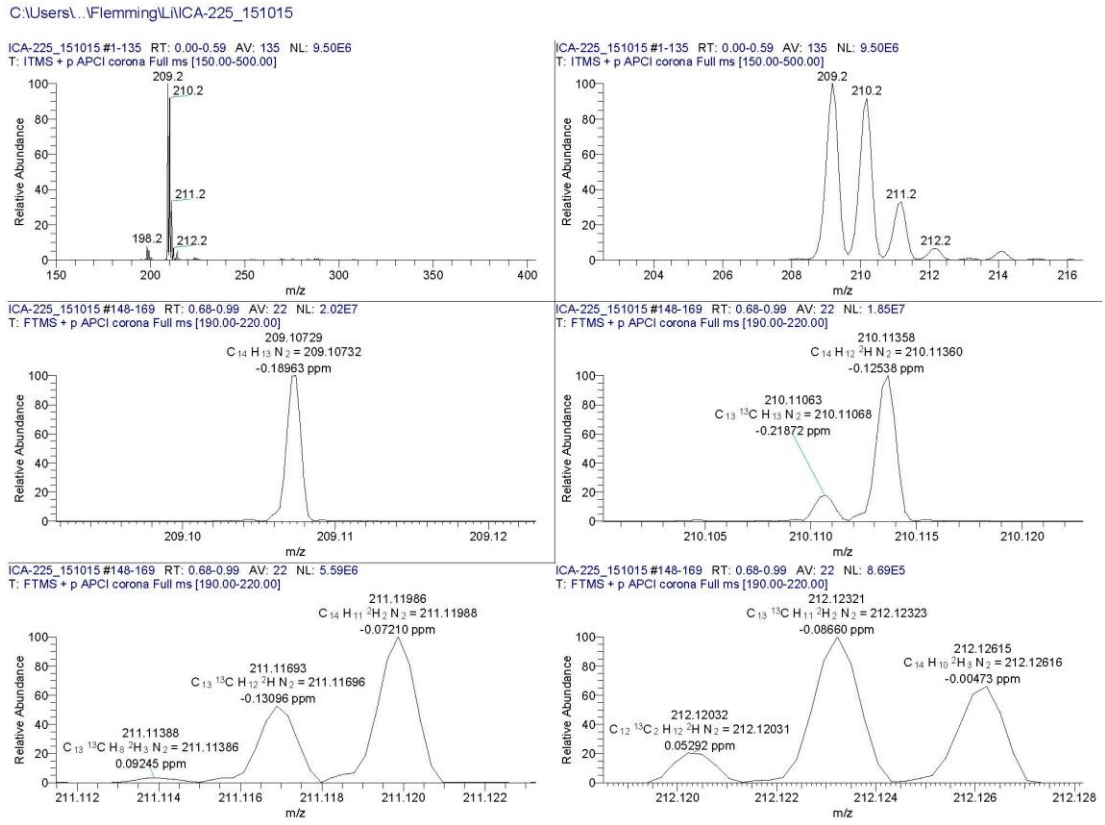


8-([1,1'-Biphenyl]-4-yl)-2,4-dimethylimidazo[1,5-a]pyrimidine (11a): Following general procedure 2 with 4-phenylbenzylisonitrile (0.030 g, 0.16 mmol), 2-chloro-4,6-dimethyl pyrimidine (0.022 g, 0.16 mmol) and KHMDS (0.20 mL, 0.2 mmol), afforded imidazo[1,5-a]pyrimidine **11a** (0.035 g, 0.12 mmol) in 76% yield: IR (ATR) 3049, 1557, 1499 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.49 (d, *J* = 8.2 Hz, 2H), 7.95 (s, 1H), 7.71-7.68 (m, 4H), 7.47-7.42 (m, 2H), 7.33 (t, *J* = 7.3 Hz, 1H), 6.33 (s, 1H), 2.56 (s, 3H), 2.55 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.85, 141.24, 138.98, 138.66, 135.24, 133.51,

128.75, 127.60, 127.12, 126.97, 126.92, 126.23, 121.61, 109.25, 25.02, 17.56; HRMS calculated for $C_{20}H_{18}N_3^+$ 300.1495, found 300.1495 $(M+H)^+$.



Deuteo-5-methyl-1-phenylimidazo[1,5-a]pyridine (d-8b): Following general procedure 3 with d_2-benzylisonitrile[7] (10 mg, 0.085 mmol), 2-chloro-6-methylpyridine (11 mg, 0.085 mmol) and BuLi (0.04 mL, 0.094 mmol), afforded deuterated imidazo[1,5-a]pyridine (**d-8b**) (0.011g, 0.054 mmol) in 63% yield (^{1}H NMR integration indicated 22% deuteration at the imidazole carbon and 17% deuteration at the methyl group): IR (ATR) 3040, 1603, 1517, 1457 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (s, 0.78H), 7.90 (d, *J* = 7.3 Hz, 2H), 7.75 (d, *J* = 9.2 Hz, 1H), 7.49 - 7.41 (m, 2H), 7.28 (t, *J* = 7.4 Hz, 1H), 6.79 (dd, *J* = 9.2, 6.5 Hz, 1H), 6.43 (d, *J* = 6.5 Hz, 1H), 2.60 – 2.55 (m, 2.5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.25 (br), 132.06, 131.41, 128.73, 127.07, 126.57, 126.38, 125.03, 120.33, 116.37, 111.95, 18.25, 18.00 (t, *J* = 19.7 Hz); HRMS calculated for $C_{14}H_{13}N_2^+$ 209.1073, found 209.1073 $(M+H)^+$; for $C_{14}H_{12}DN_2^+$ 210.1136, found 210.1136 $(M+H)^+$; for $C_{14}H_{11}D_2N_2^+$ 211.1199, found 211.1199 $(M+H)^+$; for $C_{14}H_{10}D_3N_2^+$ 212.1262, found 212.1261 $(M+H)^+$.



HRMS spectra for deuteo-5-methyl-1-phenylimidazo[1,5-a]pyridine (**d-8b**)

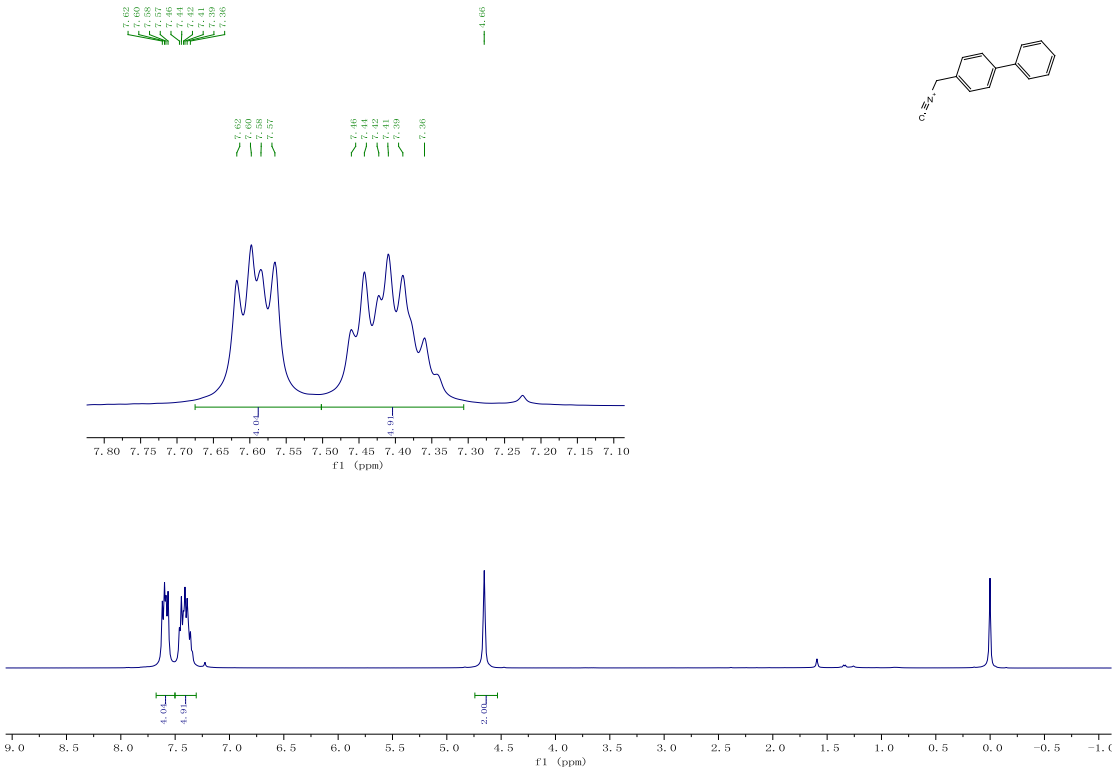


Figure S1. ^{1}H NMR spectrum ($CDCl_3$, 400 MHz) for 4-(Isocyanomethyl)-1,1'-biphenyl **(6b)**

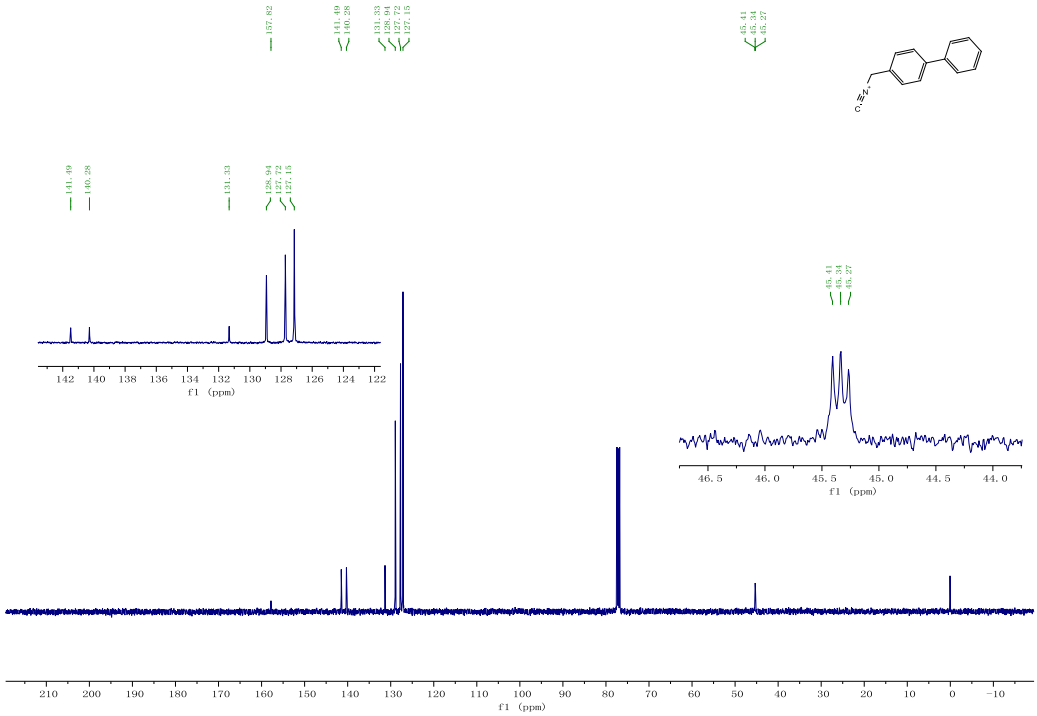


Figure S2. ^{13}C NMR spectrum ($CDCl_3$, 100 MHz) for 4-(Isocyanomethyl)-1,1'-biphenyl **(6b)**

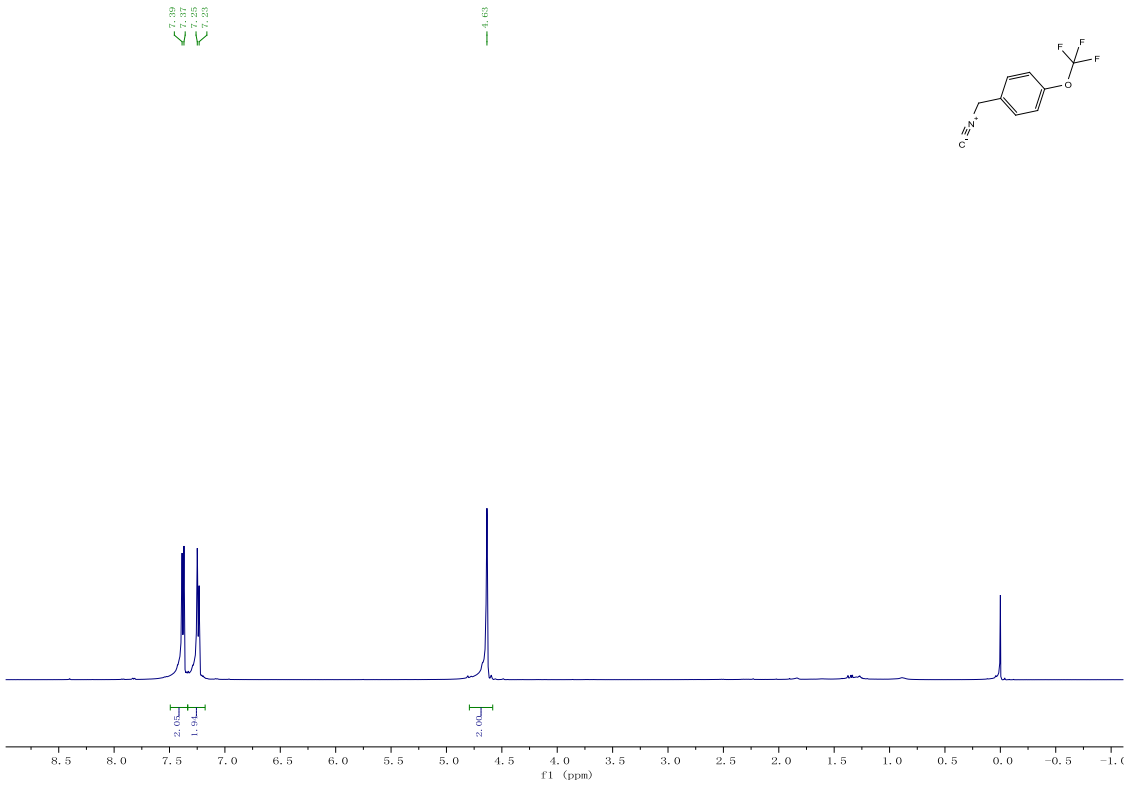


Figure S3. ^{1}H NMR spectrum ($CDCl_3$, 500 MHz) for 1-(Isocyanomethyl)-4-(trifluoromethoxy)benzene **(6c)**

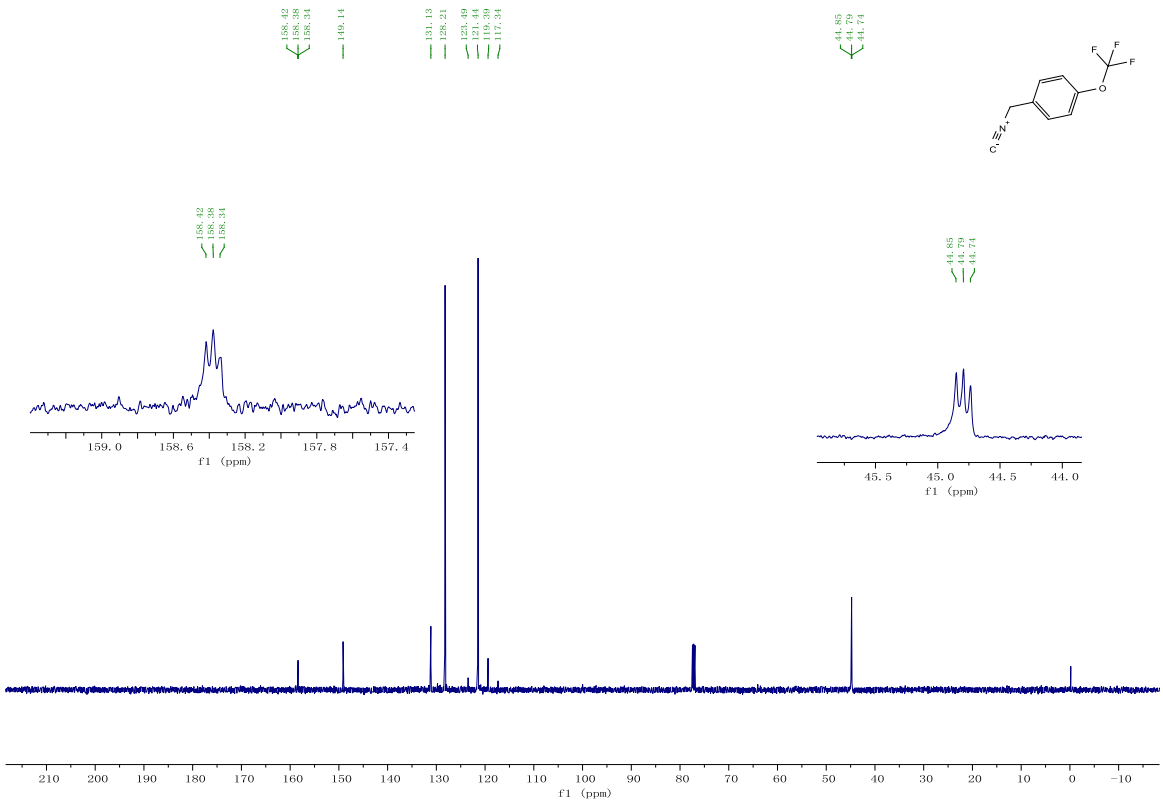


Figure S4. ^{13}C NMR spectrum ($CDCl_3$, 126 MHz) for 1-(Isocyanomethyl)-4-(trifluoromethoxy)benzene **(6c)**

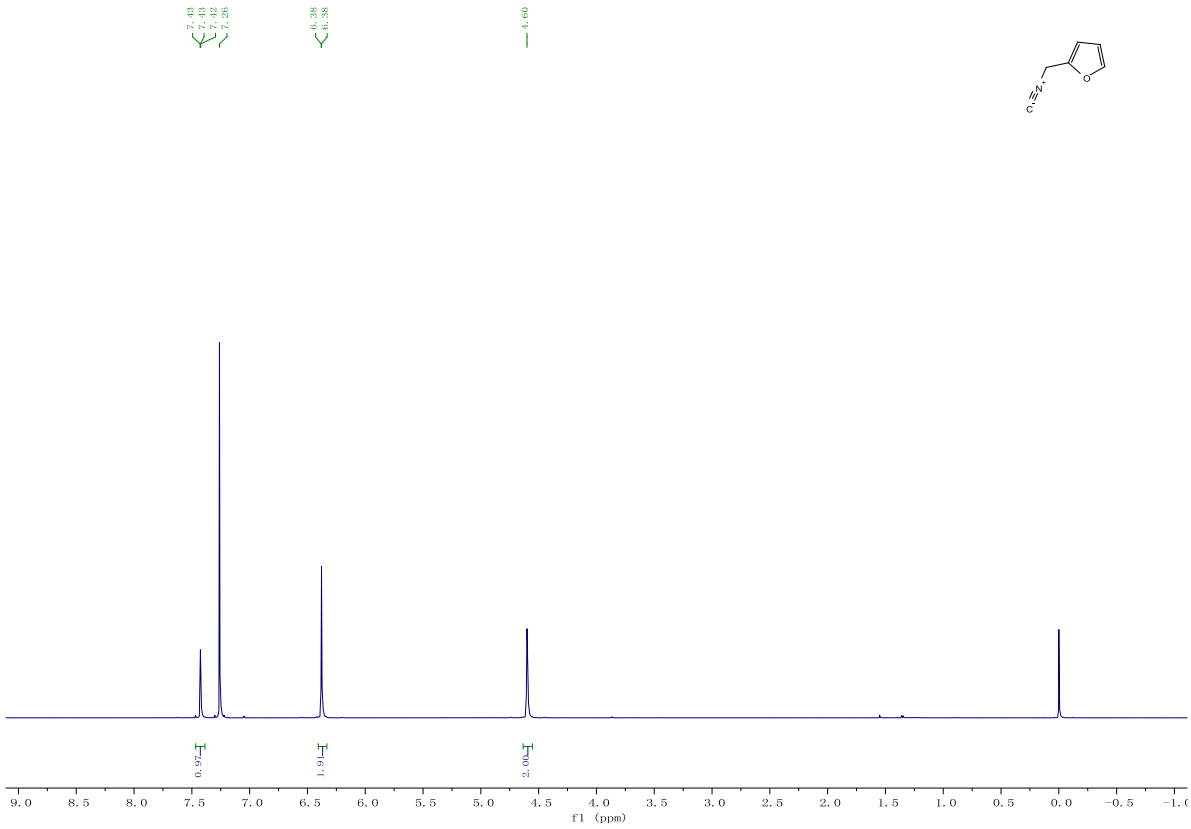


Figure S5. ^{1}H NMR spectrum ($CDCl_3$, 500 MHz) for 2-(Isocyanomethyl)furan **(6d)**

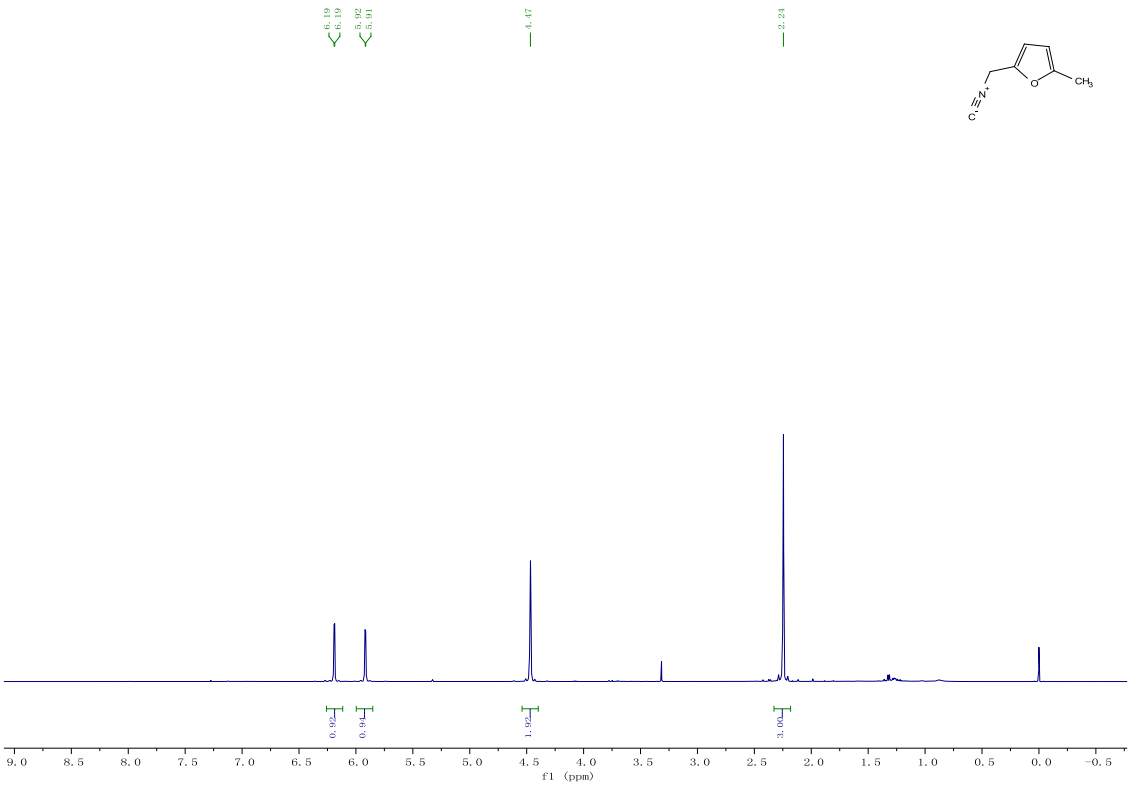


Figure S6. ^{1}H NMR spectrum ($CDCl_3$, 500 MHz) for 2-(Isocyanomethyl)-5-methylfuran **(6e)**

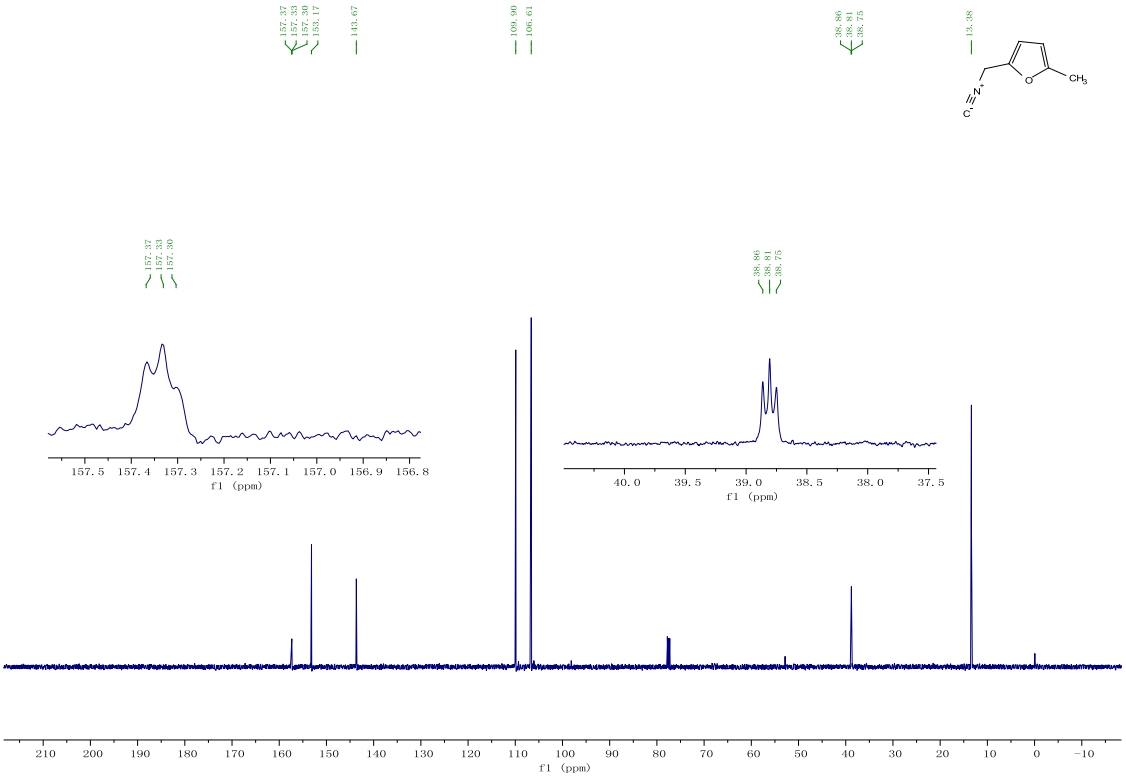


Figure S7. ^{13}C NMR spectrum ($CDCl_3$, 126 MHz) for 2-(Isocyanomethyl)-5-methylfuran **(6e)**

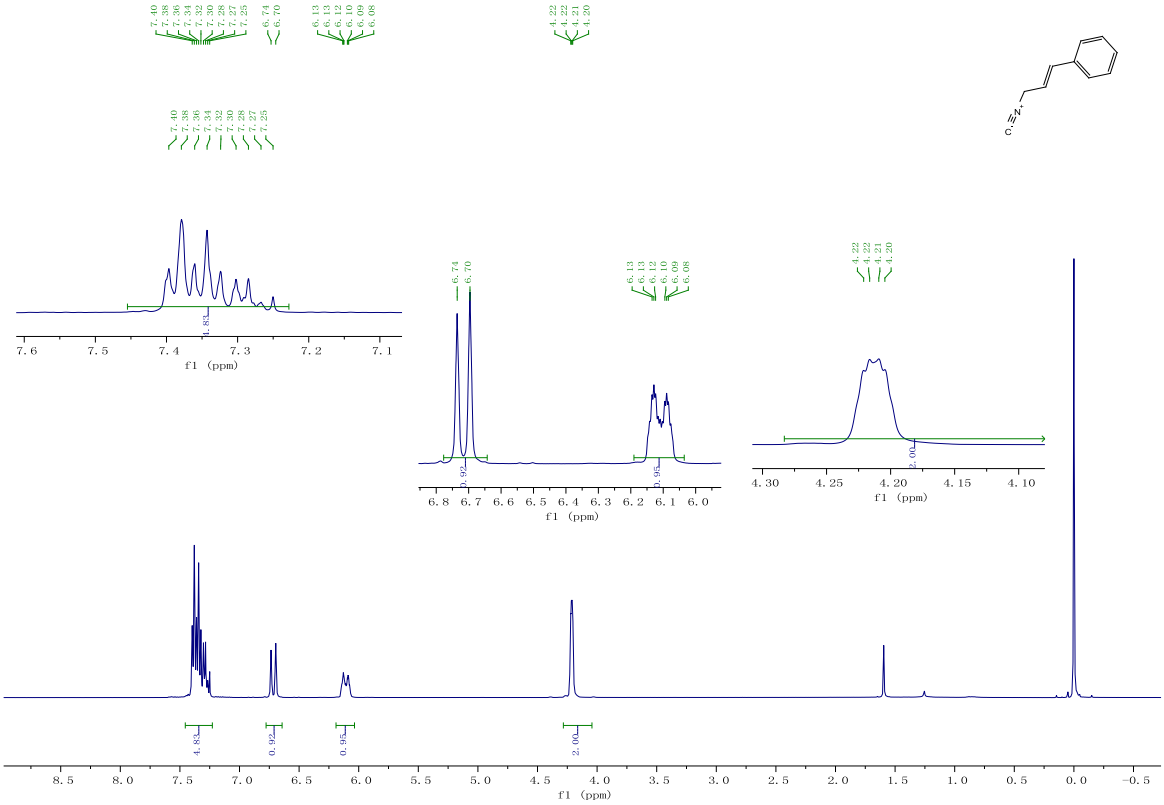


Figure S8. ^{1}H NMR spectrum ($CDCl_3$, 400 MHz) for (*E*)-(3-Isocyanoprop-1-en-1-yl)benzene **(6f)**

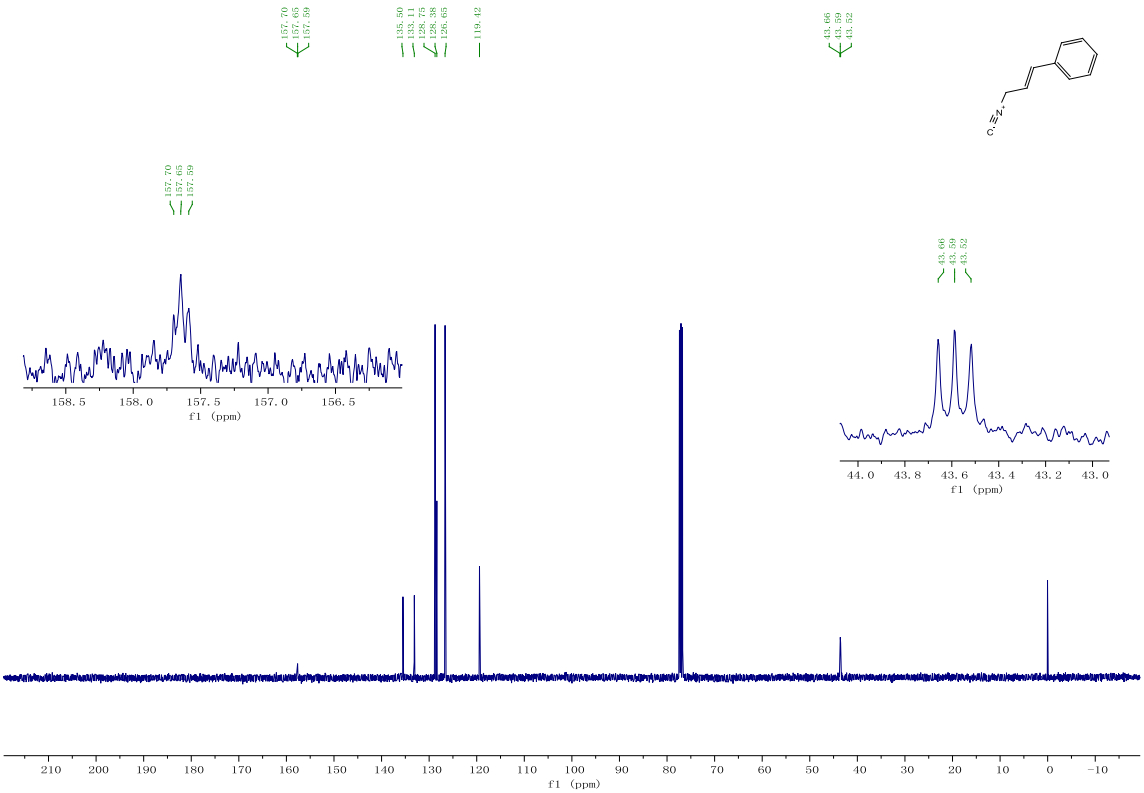


Figure S9. ^{13}C NMR spectrum ($CDCl_3$, 100 MHz) for (*E*)-(3-Isocyanoprop-1-en-1-yl)benzene **(6f)**

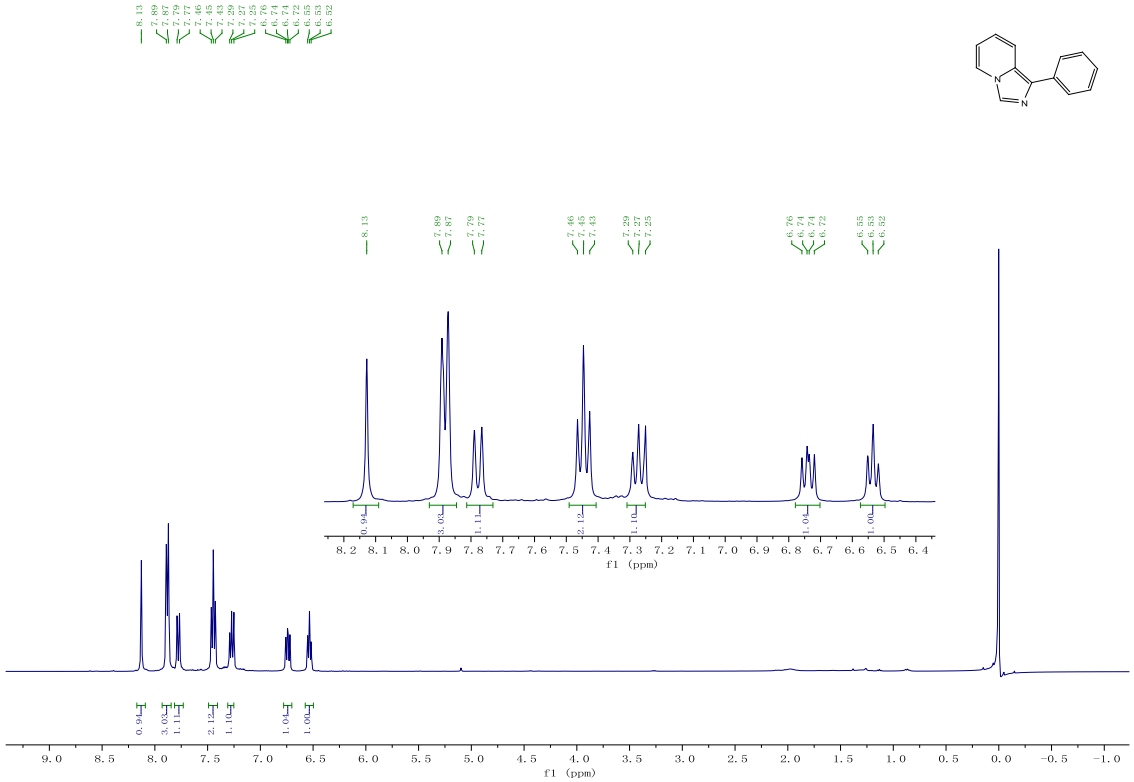


Figure S10. ^{1}H NMR spectrum ($CDCl_3$, 400 MHz) for 1-Phenylimidazo[1,5-a]pyridine **(8a)**

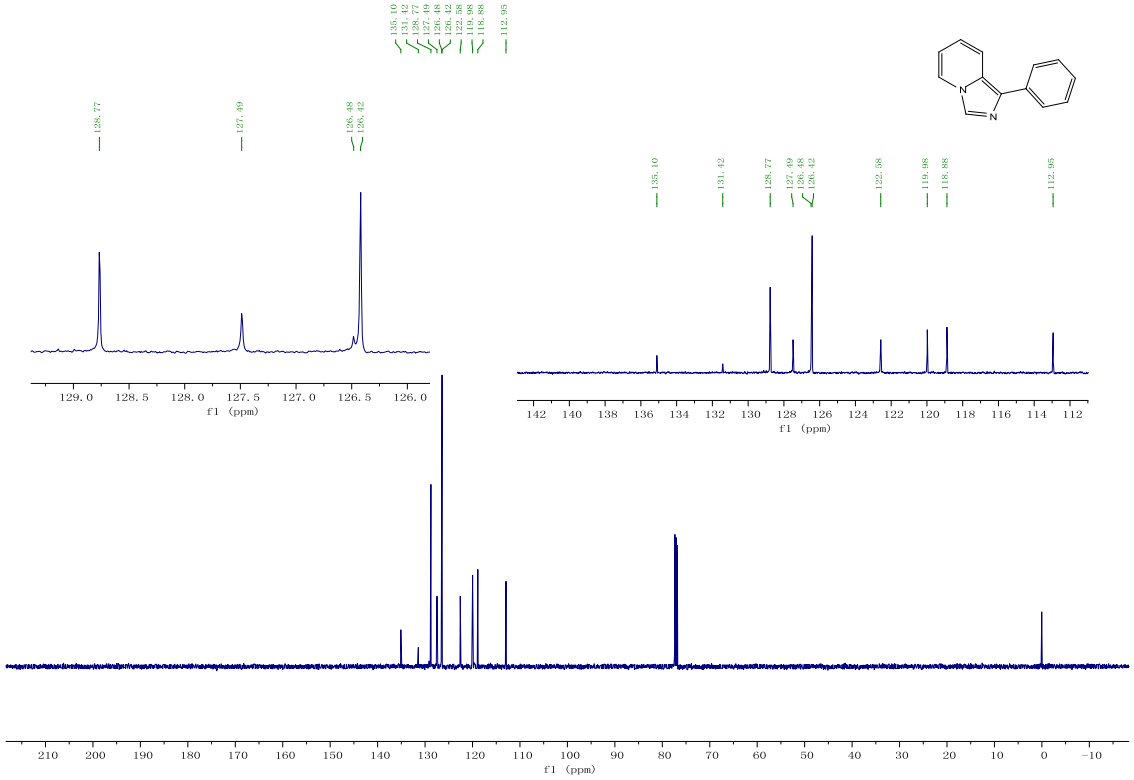


Figure S11. ^{13}C NMR spectrum ($CDCl_3$, 126 MHz) for 1-Phenylimidazo[1,5-a]pyridine **(8a)**

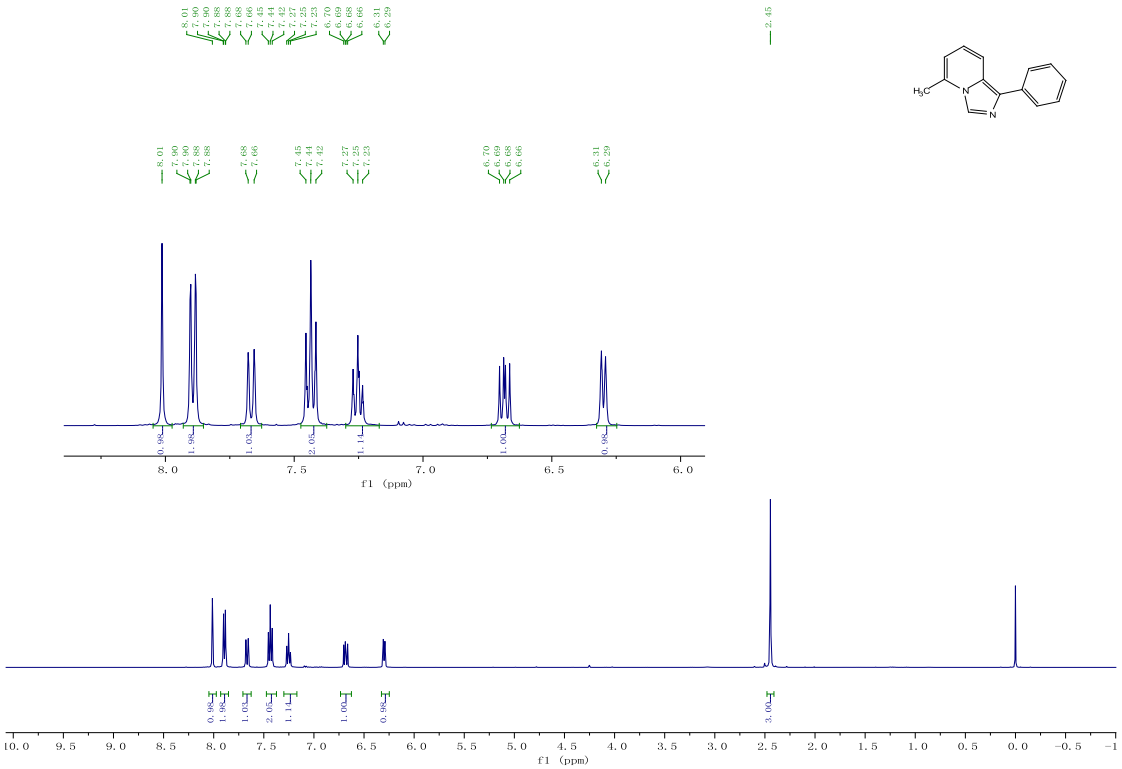


Figure S12. ^{1}H NMR spectrum ($CDCl_3$, 400 MHz) for 5-Methyl-1-phenylimidazo[1,5-a]pyridine **(8b)**

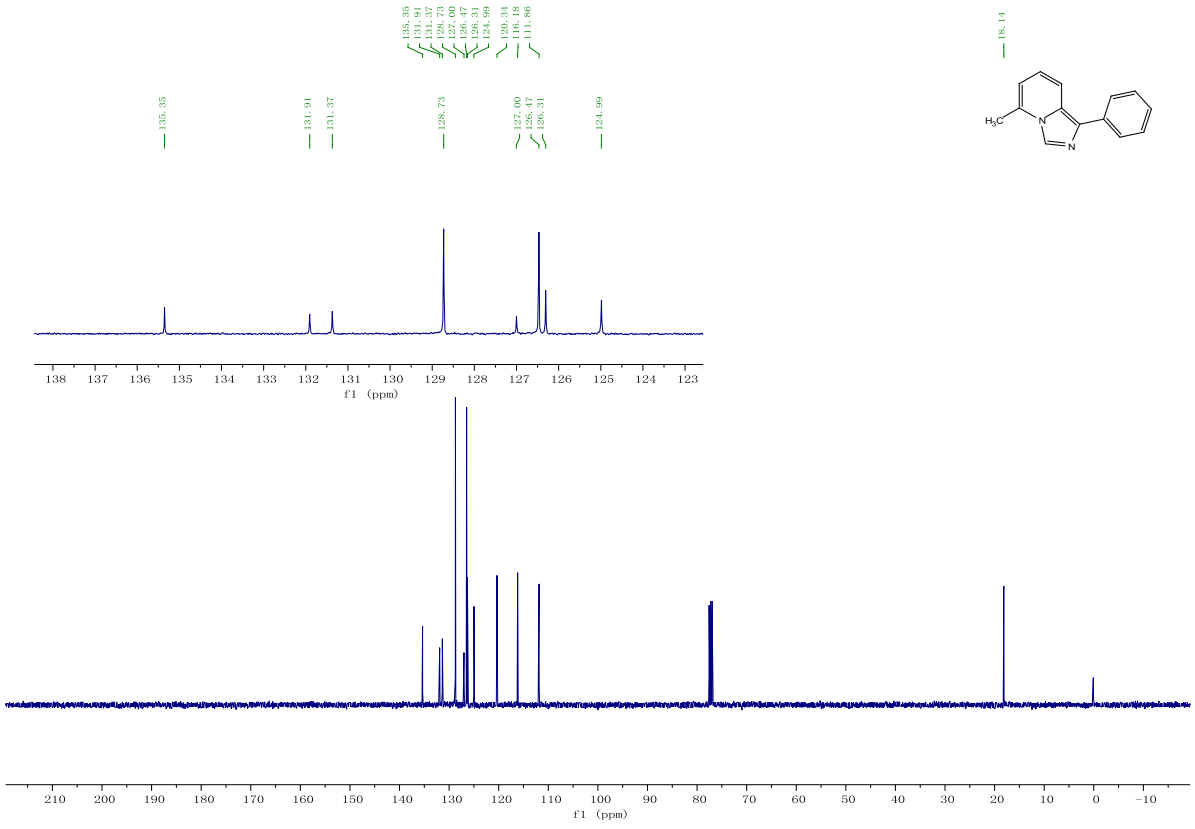


Figure S13. ^{13}C NMR spectrum ($CDCl_3$, 100 MHz) for 5-Methyl-1-phenylimidazo[1,5-a]pyridine **(8b)**

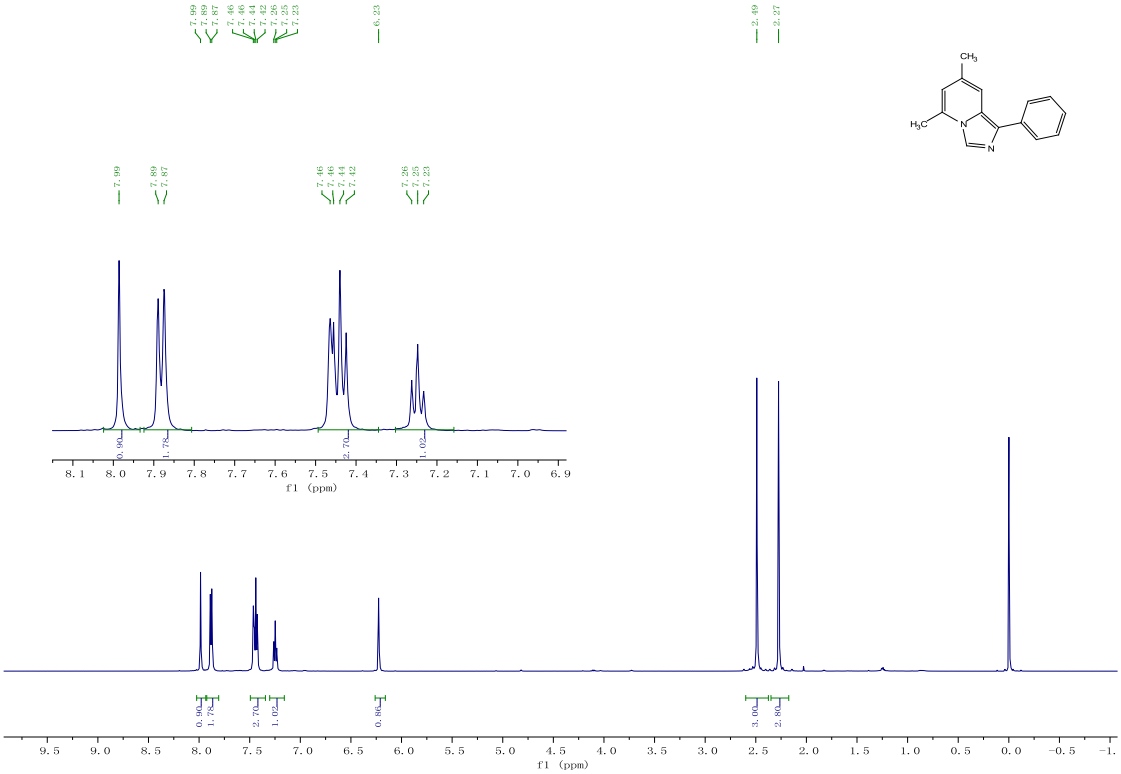


Figure S14. ^{1}H NMR spectrum ($CDCl_3$, 500 MHz) for 5,7-Dimethyl-1-phenylimidazo[1,5-a]pyridine **(8c)**

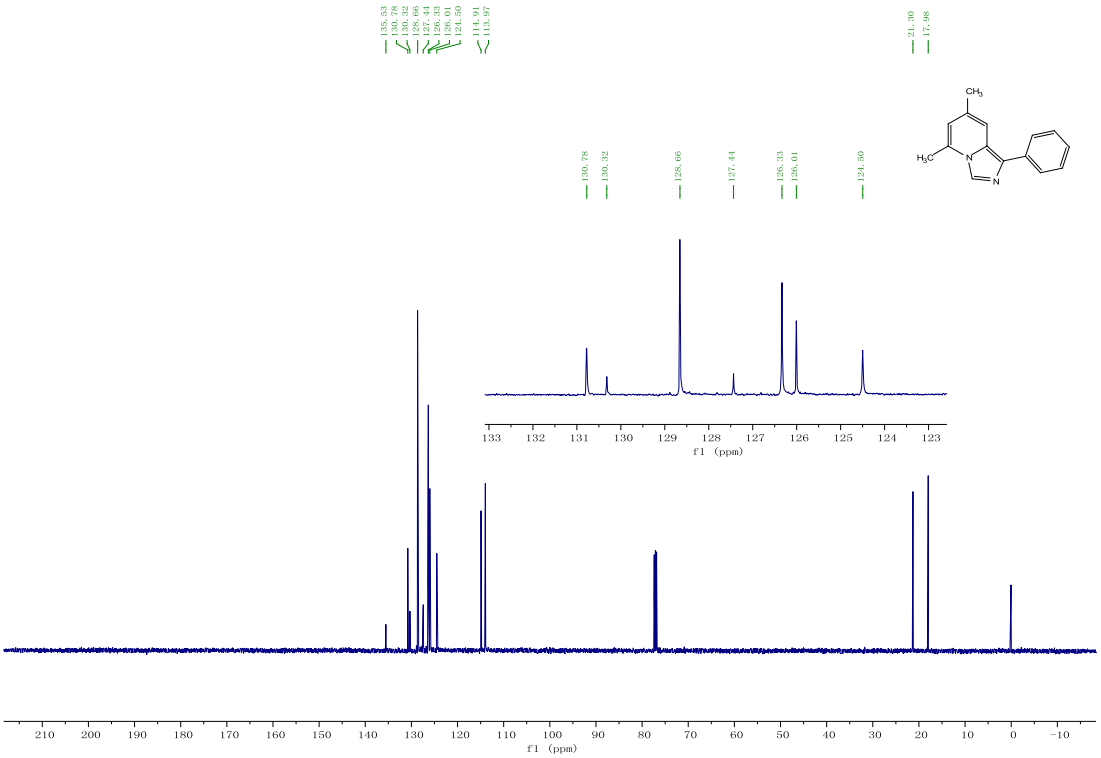


Figure S15. ^{13}C NMR spectrum ($CDCl_3$, 126 MHz) for 5,7-Dimethyl-1-phenylimidazo[1,5-a]pyridine **(8c)**

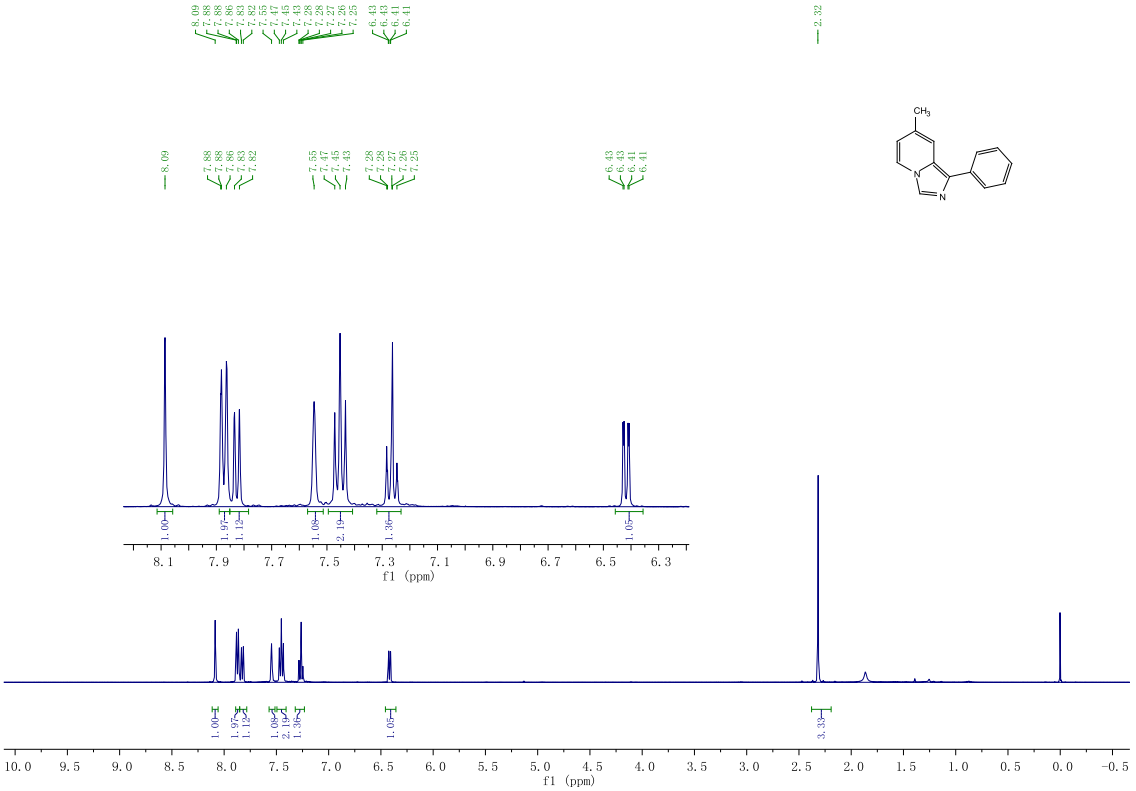


Figure S16. ^{1}H NMR spectrum ($CDCl_3$, 400 MHz) for 7-Methyl-1-phenylimidazo[1,5-a]pyridine **(8d)**

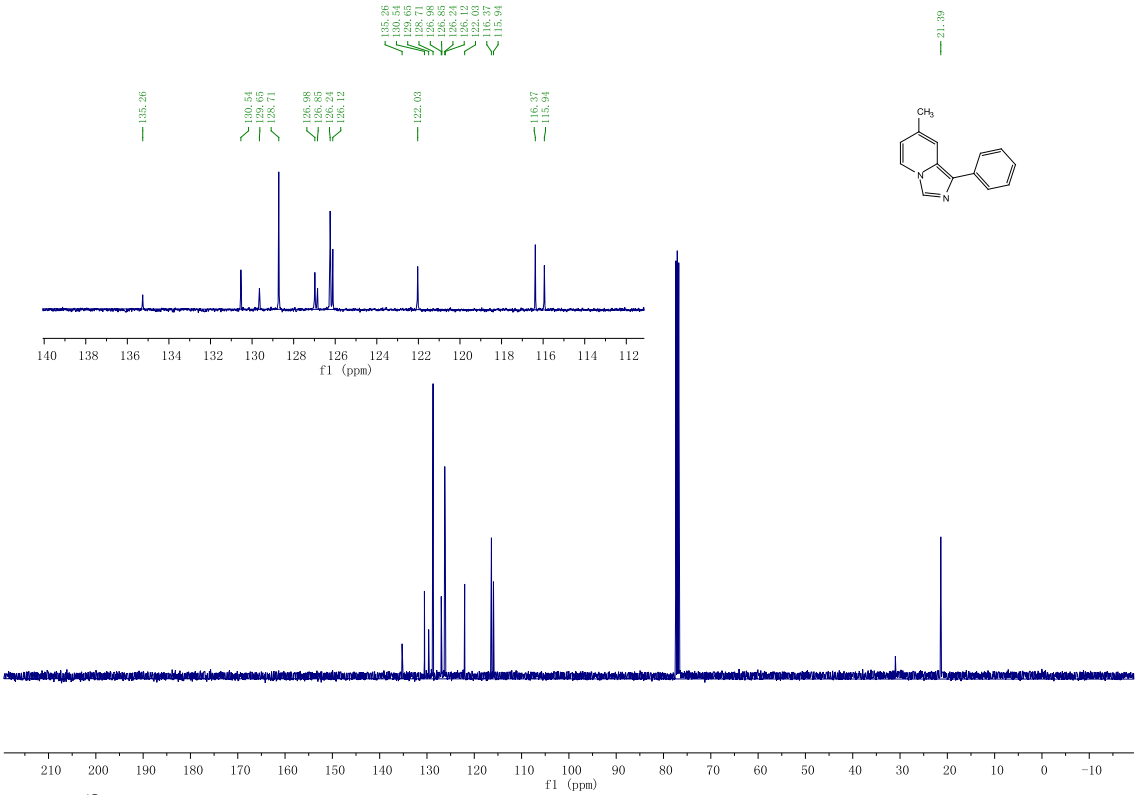


Figure S17. ^{13}C NMR spectrum ($CDCl_3$, 100 MHz) for 7-Methyl-1-phenylimidazo[1,5-a]pyridine **(8d)**

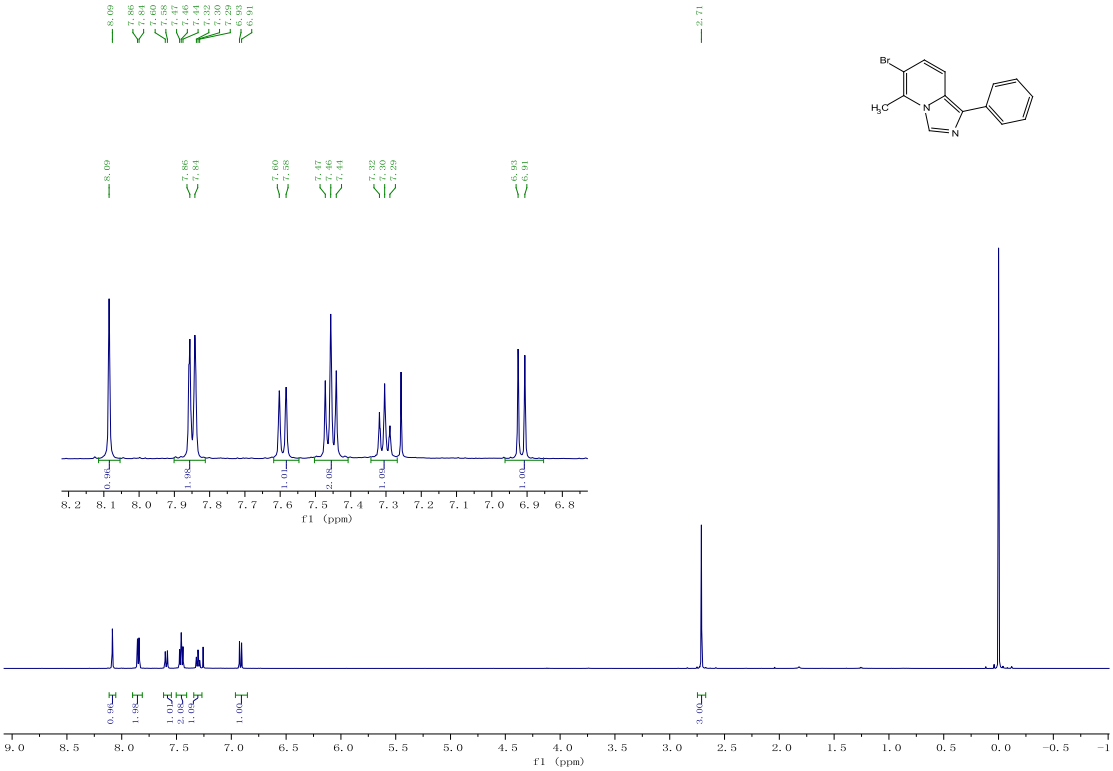


Figure S18. ^{1}H NMR spectrum ($CDCl_3$, 500 MHz) for 6-Bromo-5-methyl-1-phenylimidazo[1,5-a]pyridine **(8e)**

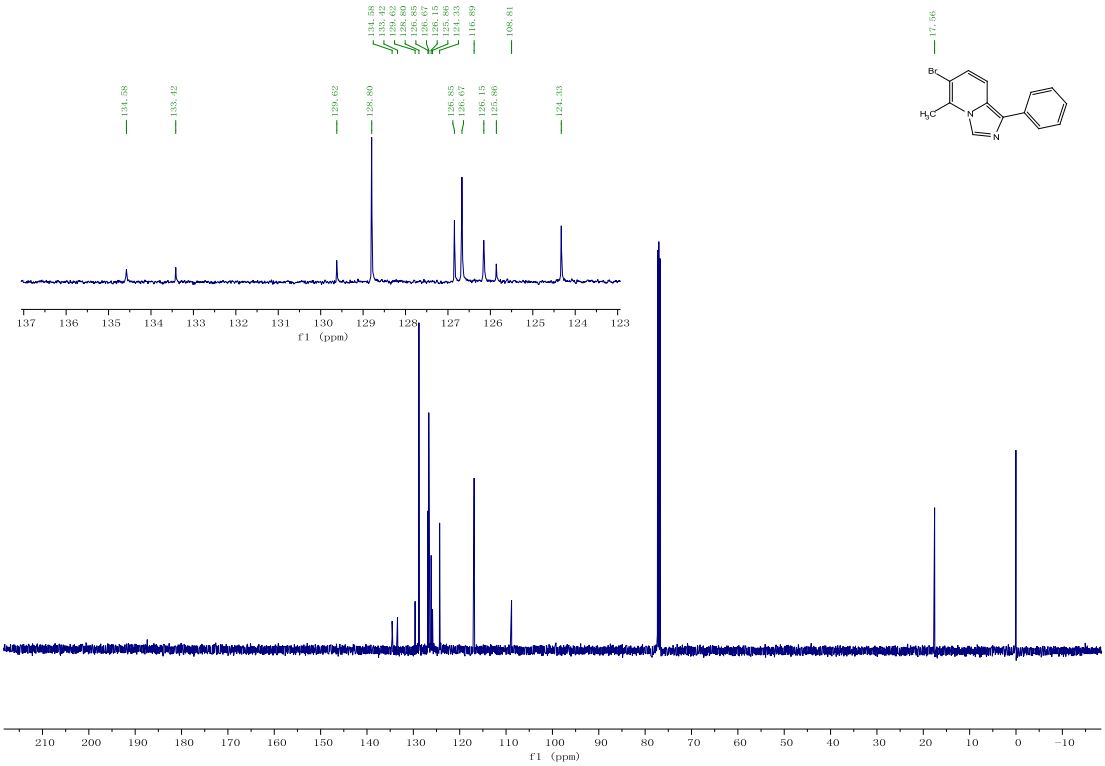


Figure S19. ^{13}C NMR spectrum ($CDCl_3$, 126 MHz) for 6-Bromo-5-methyl-1-phenylimidazo[1,5-a]pyridine **(8e)**

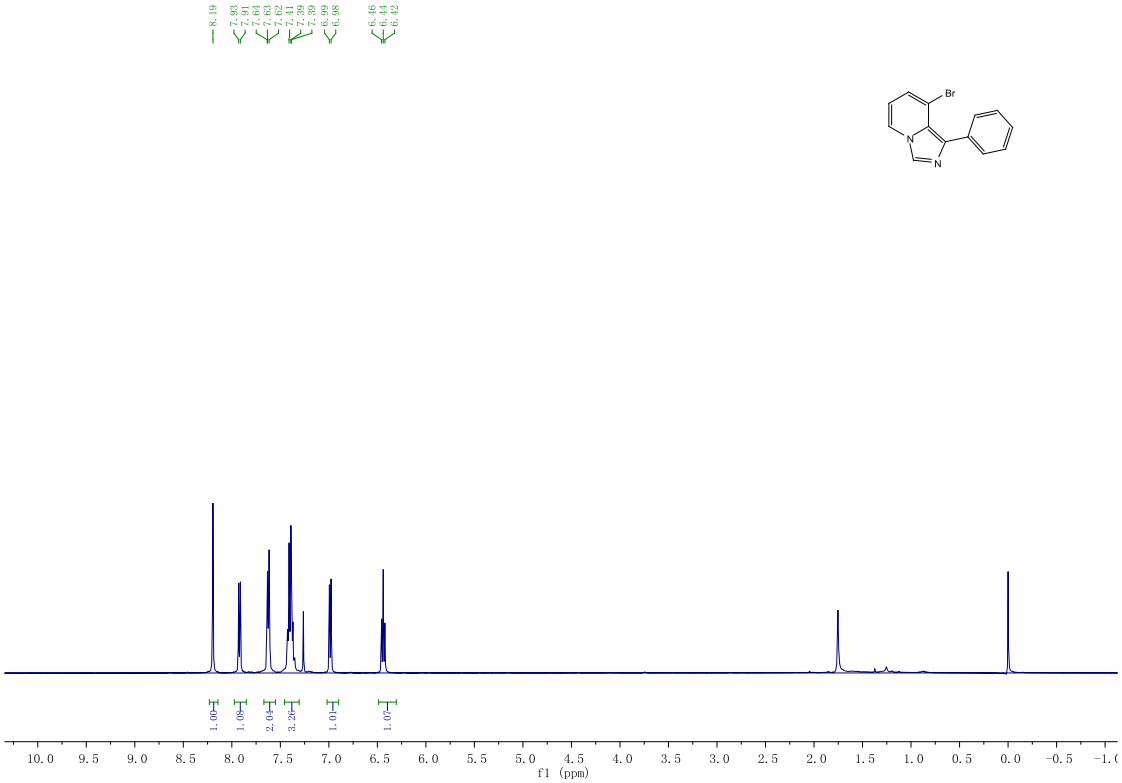


Figure S20. ^{1}H NMR spectrum ($CDCl_3$, 400 MHz) for 8-Bromo-1-phenylimidazo[1,5-a]pyridine **(8f)**

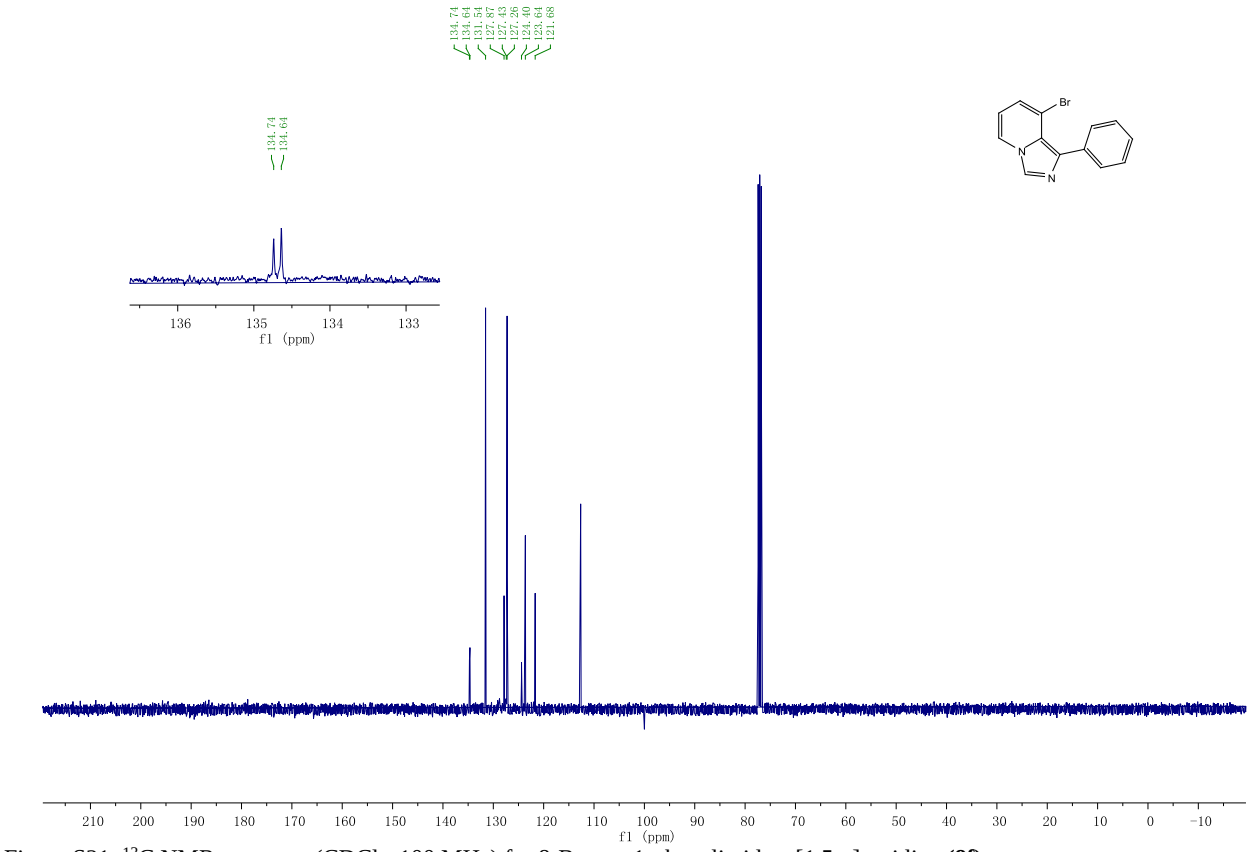


Figure S21. ^{13}C NMR spectrum ($CDCl_3$, 100 MHz) for 8-Bromo-1-phenylimidazo[1,5-a]pyridine **(8f)**

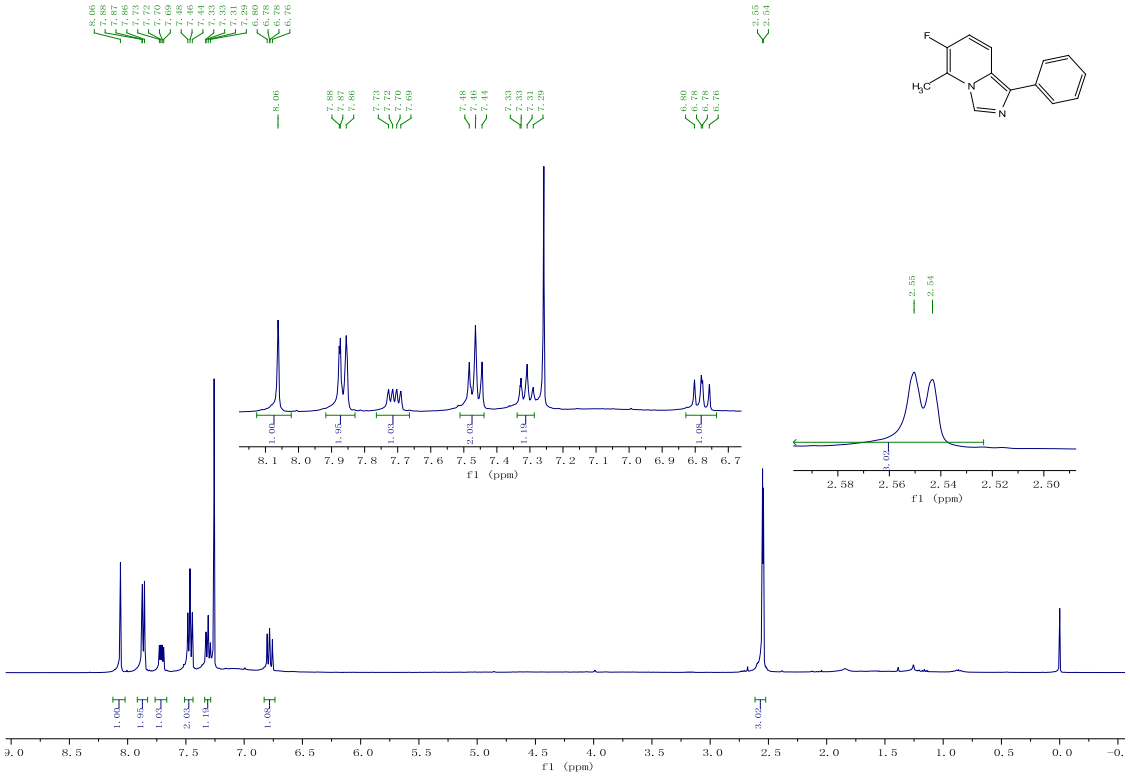


Figure S22. ^{1}H NMR spectrum ($CDCl_3$, 400 MHz) for 6-Fluoro-5-methyl-1-phenylimidazo[1,5-a]pyridine **(8g)**

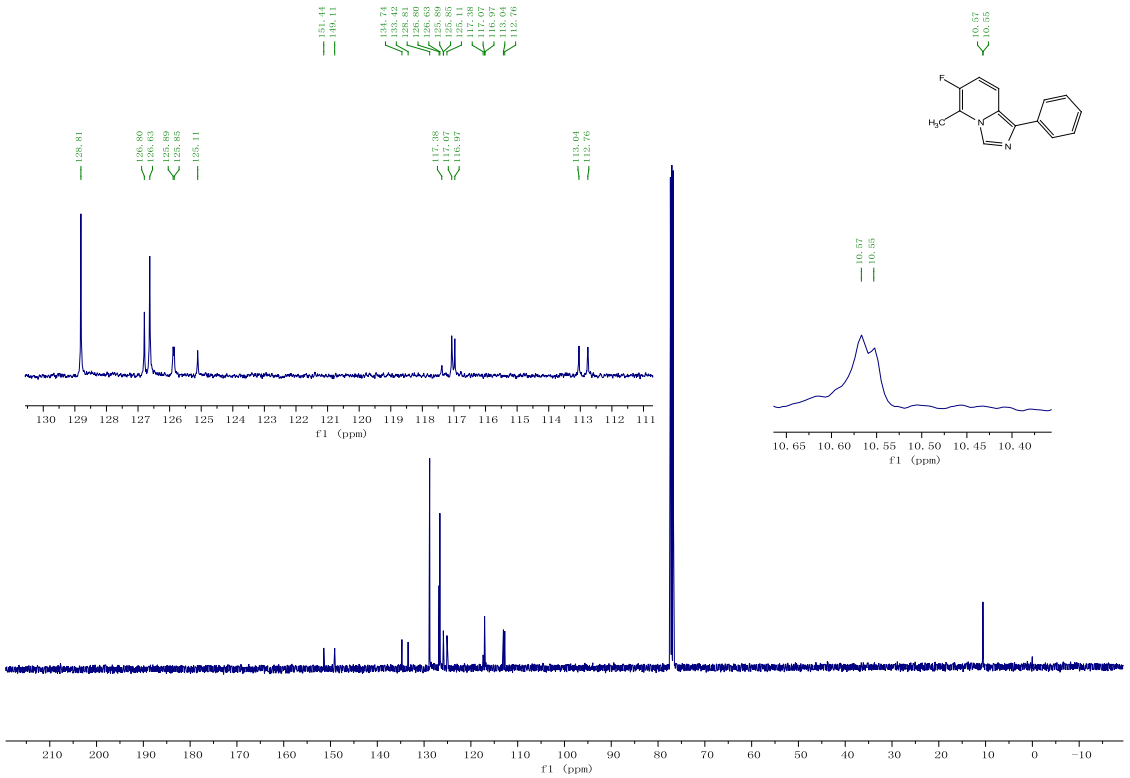


Figure S23. ^{13}C NMR spectrum ($CDCl_3$, 100 MHz) for 6-Fluoro-5-methyl-1-phenylimidazo[1,5-a]pyridine **(8g)**

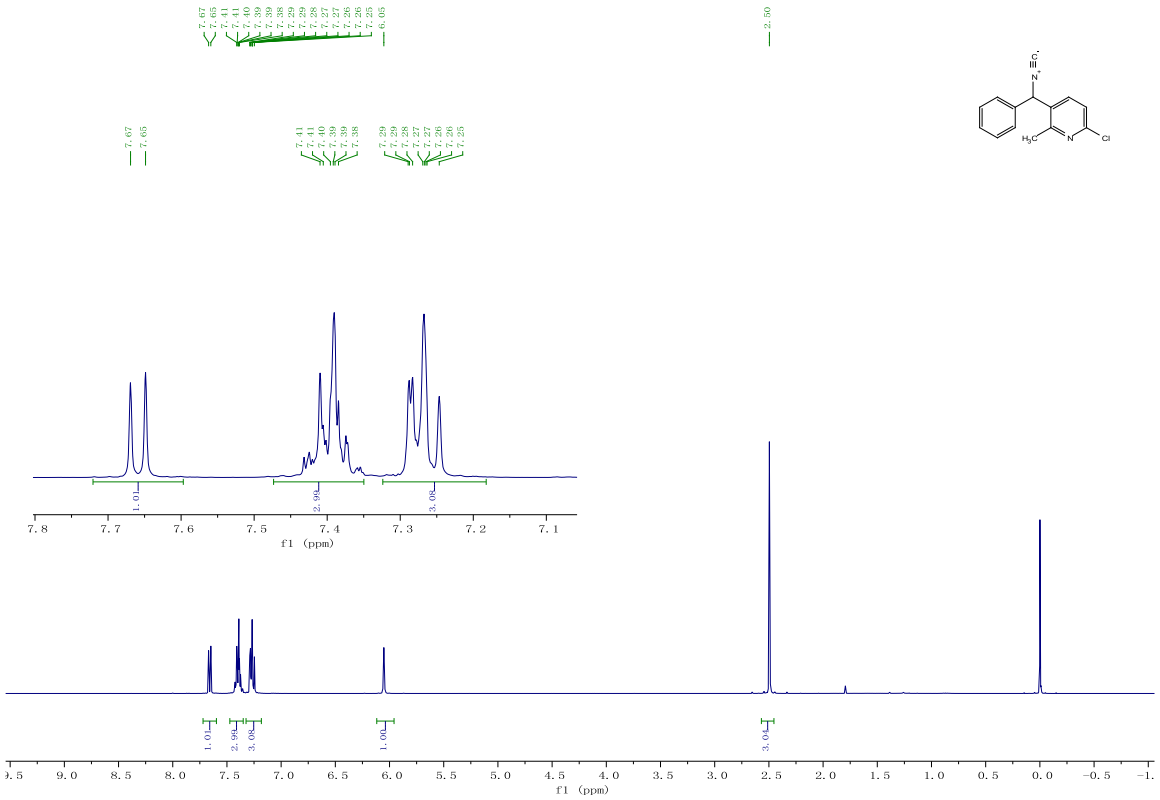


Figure S24. ^{1}H NMR spectrum ($CDCl_3$, 400 MHz) for 6-Chloro-3-(isocyano(phenyl)methyl)-2-methylpyridine (**8g'**)

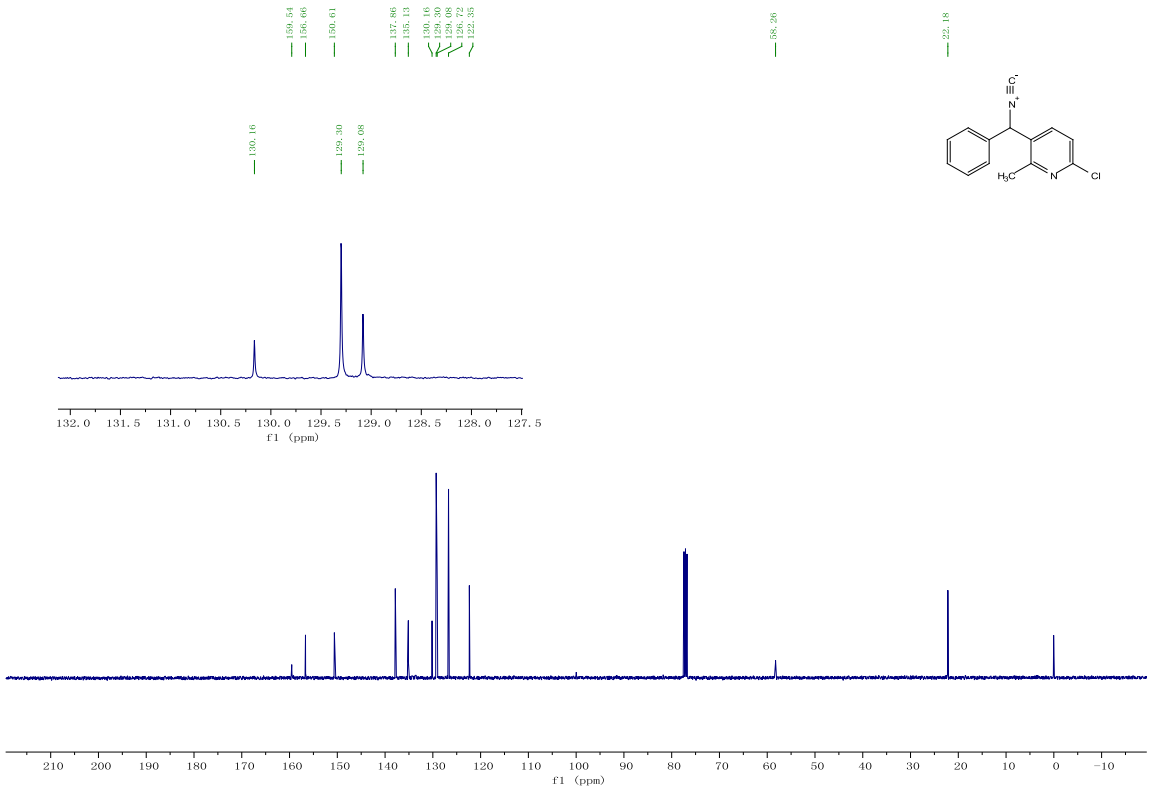


Figure S25. ^{13}C NMR spectrum ($CDCl_3$, 100 MHz) for 6-Chloro-3-(isocyano(phenyl)methyl)-2-methylpyridine (**8g'**)

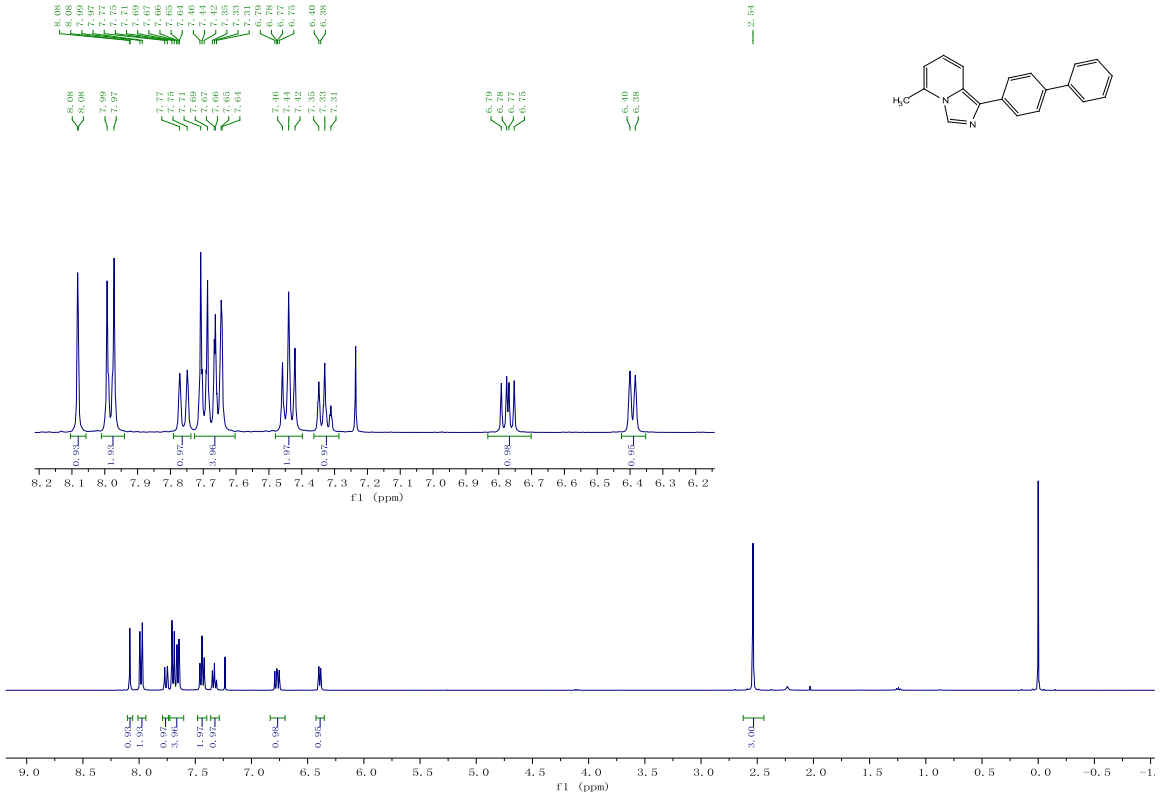


Figure S26. ^{1}H NMR spectrum ($CDCl_3$, 400 MHz) for 1-([1,1'-Biphenyl]-4-yl)-5-methylimidazo[1,5-a]pyridine **(8h)**

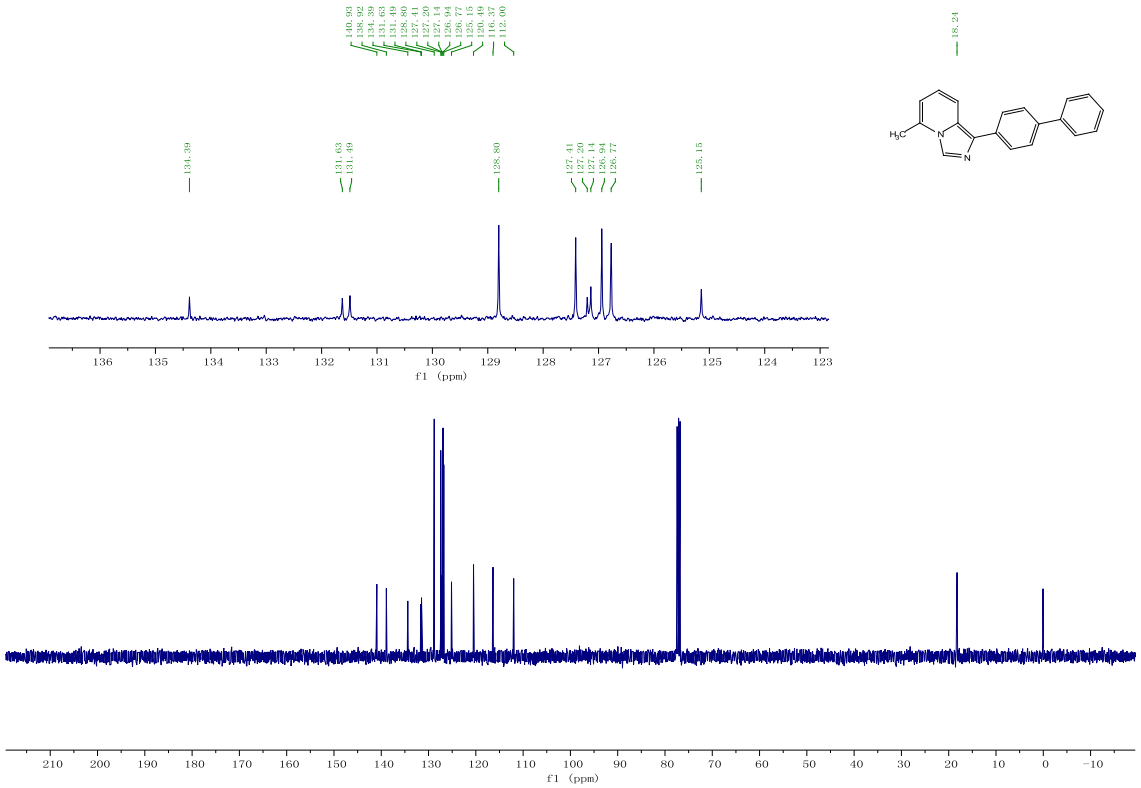


Figure S27. ^{13}C NMR spectrum ($CDCl_3$, 100 MHz) for 1-([1,1'-Biphenyl]-4-yl)-5-methylimidazo[1,5-a]pyridine **(8h)**

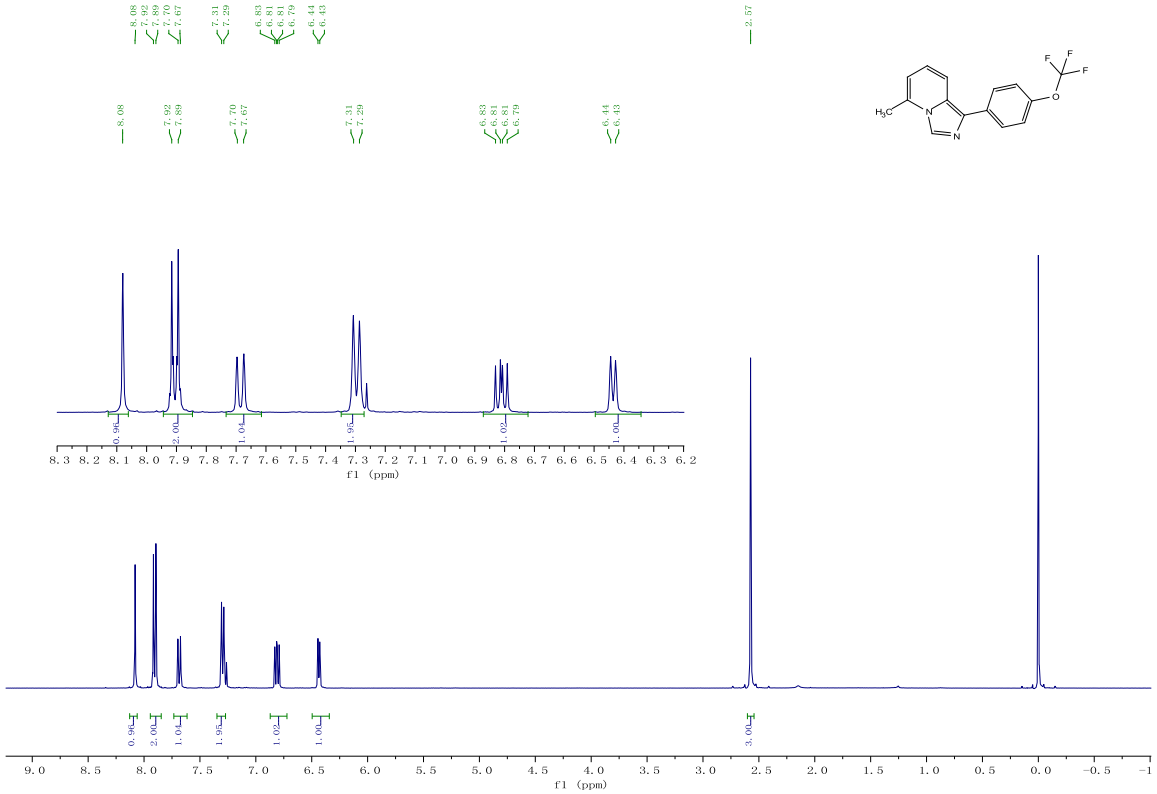


Figure S28. ^{1}H NMR spectrum ($CDCl_3$, 400 MHz) for 5-Methyl-1-(4-(trifluoromethoxy)phenyl)imidazo[1,5-a]pyridine **(8i)**

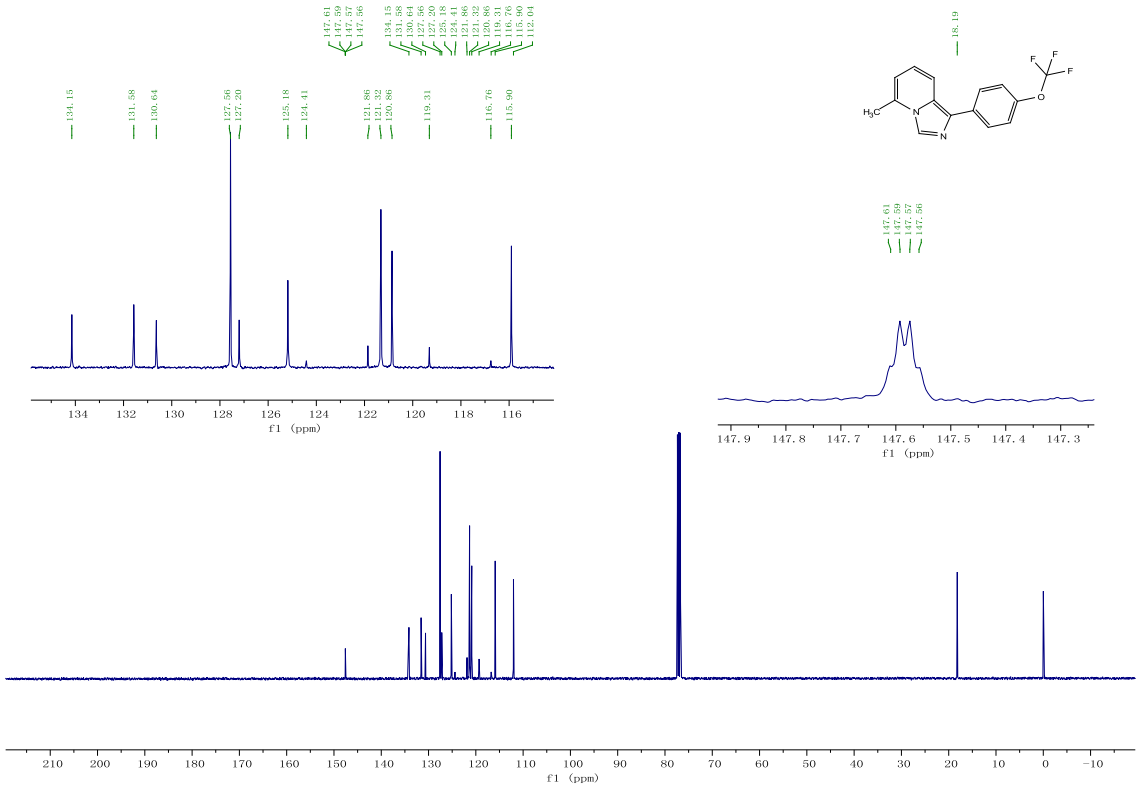


Figure S29. ^{13}C NMR spectrum ($CDCl_3$, 100 MHz) for 5-Methyl-1-(4-(trifluoromethoxy)phenyl)imidazo[1,5-a]pyridine **(8i)**

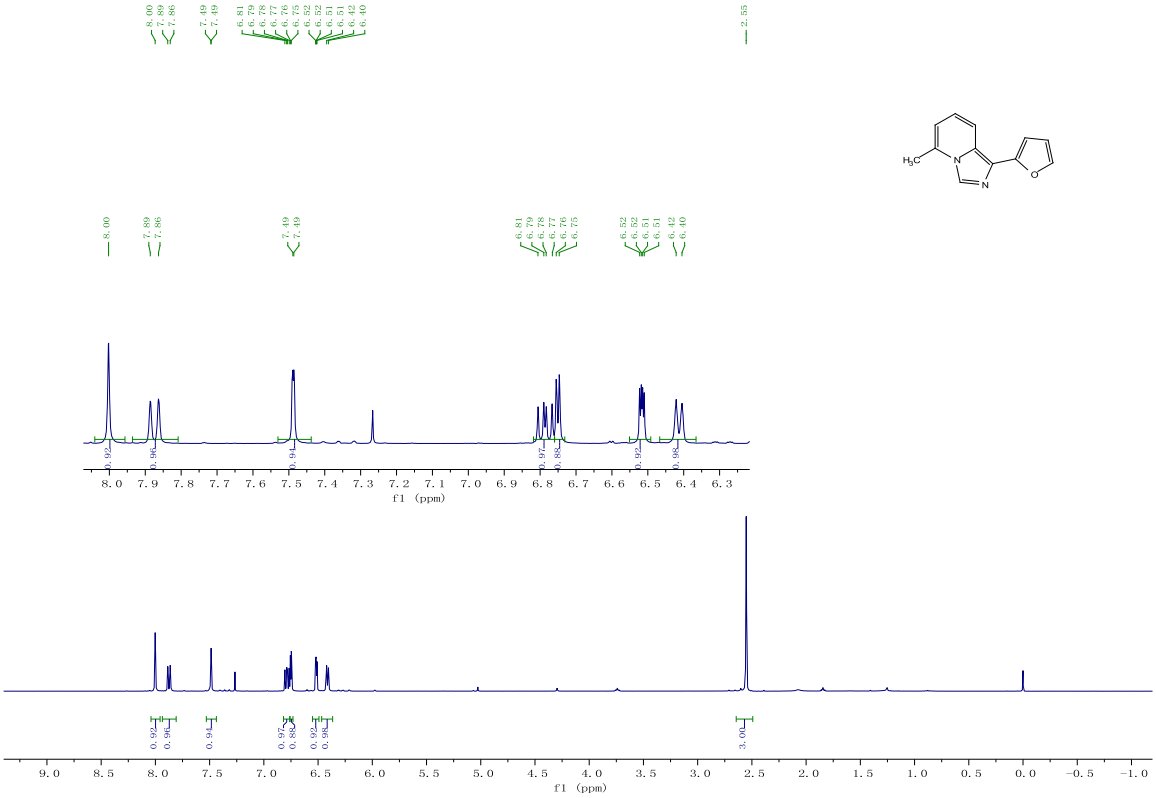


Figure S30. ^{1}H NMR spectrum ($CDCl_3$, 400 MHz) for 1-(Furan-2-yl)-5-methylimidazo[1,5-a]pyridine **(8j)**

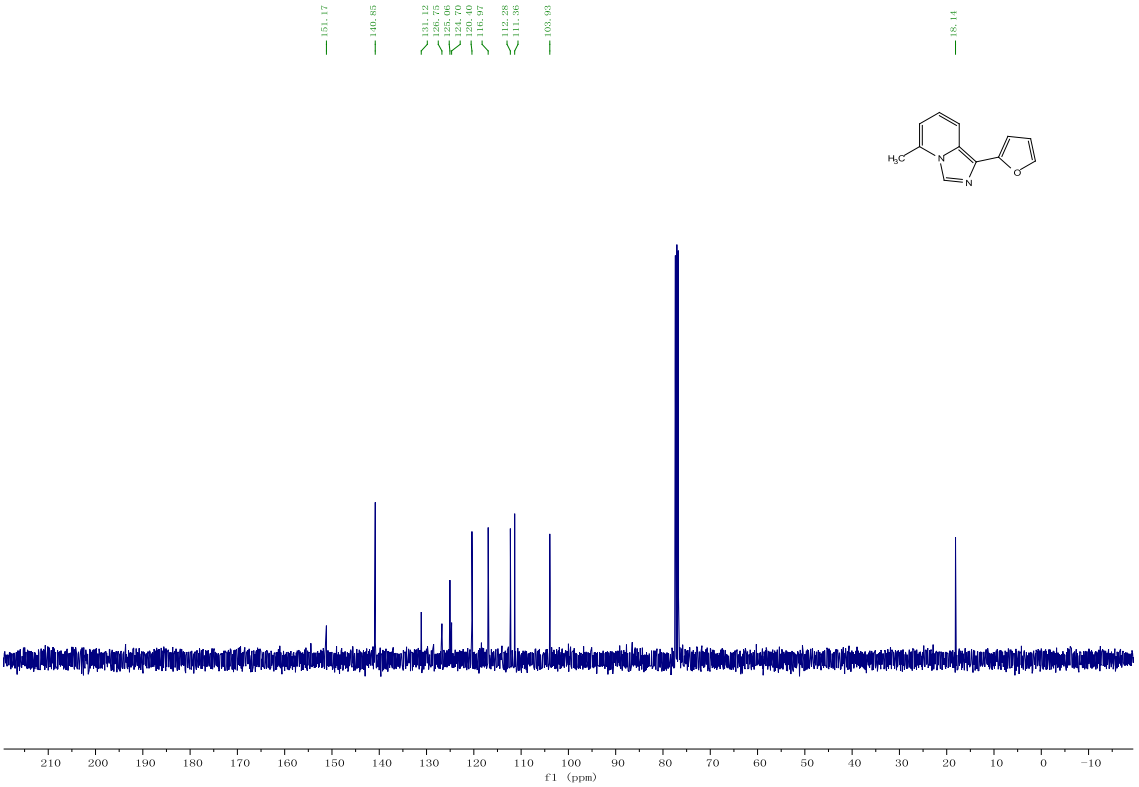


Figure S31. ^{13}C NMR spectrum ($CDCl_3$, 100 MHz) for 1-(Furan-2-yl)-5-methylimidazo[1,5-a]pyridine **(8j)**

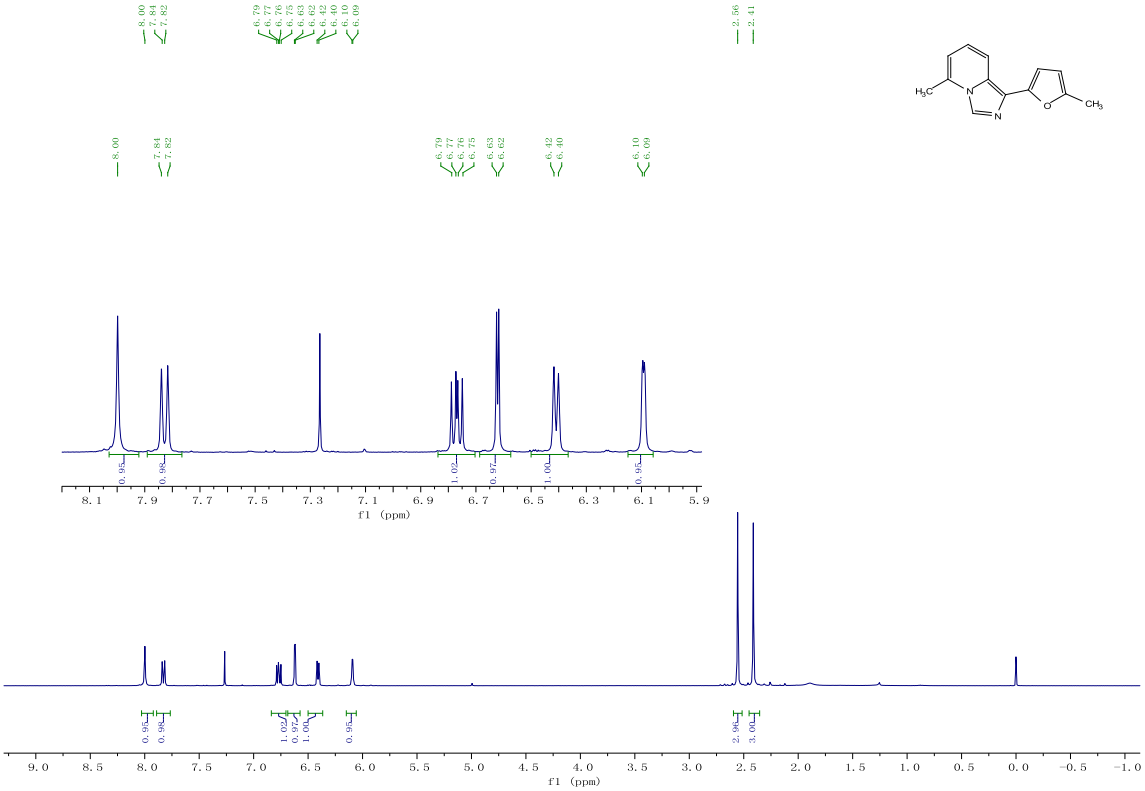


Figure S32. ^{1}H NMR spectrum ($CDCl_3$, 400 MHz) for 5-Methyl-1-(5-methylfuran-2-yl)imidazo[1,5-a]pyridine **(8k)**

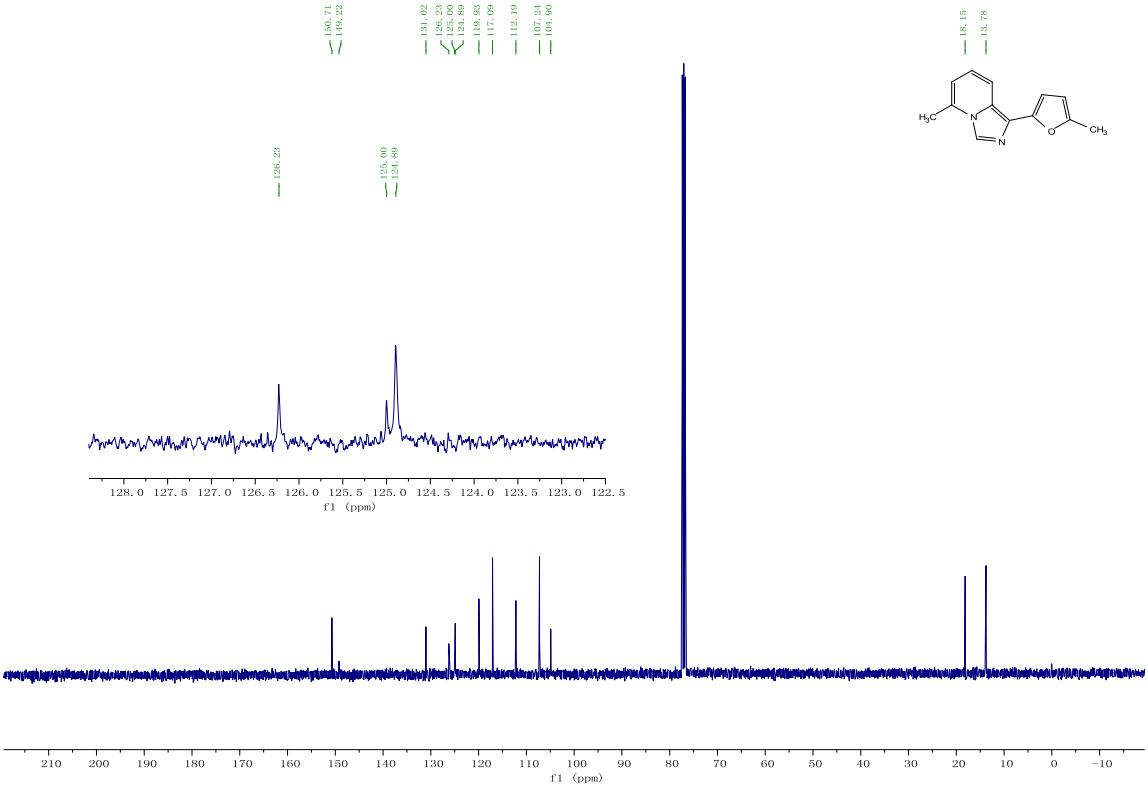


Figure S33. ^{13}C NMR spectrum ($CDCl_3$, 100 MHz) for 5-Methyl-1-(5-methylfuran-2-yl)imidazo[1,5-a]pyridine **(8k)**

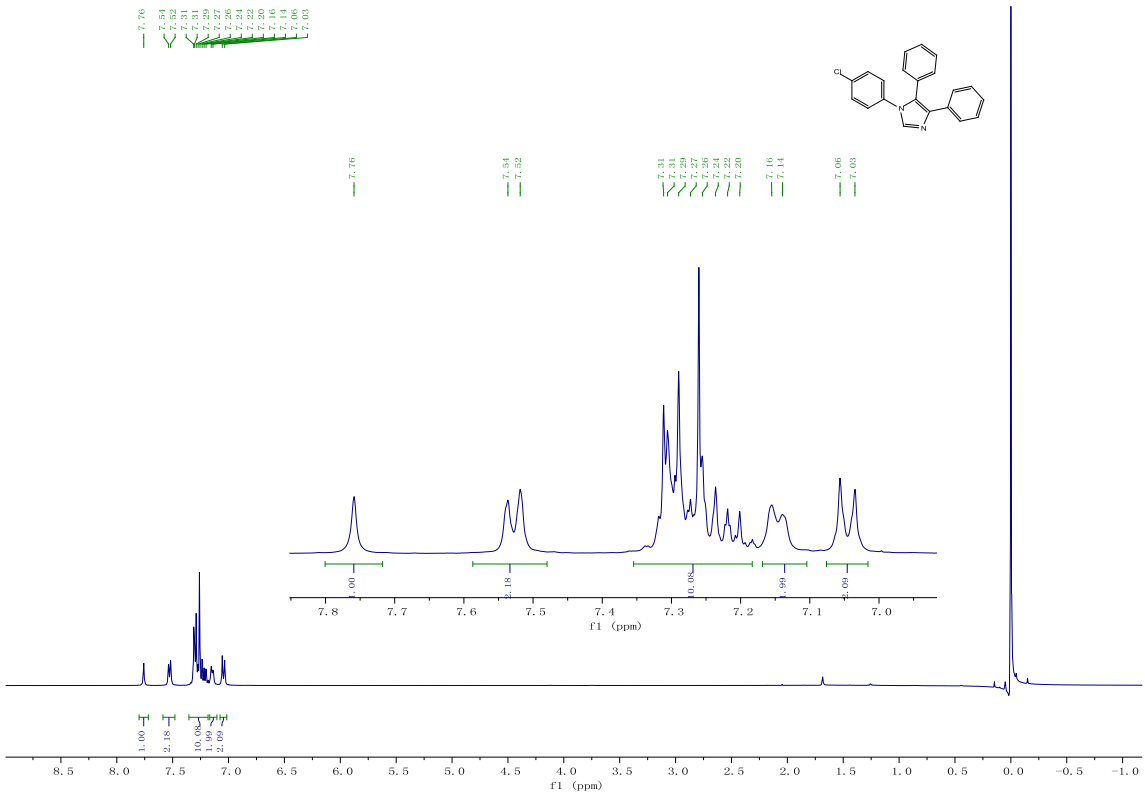


Figure S34. ^{1}H NMR spectrum ($CDCl_3$, 400 MHz) for 1-(4-Chlorophenyl)-4,5-diphenyl-1H-imidazole **(9a)**

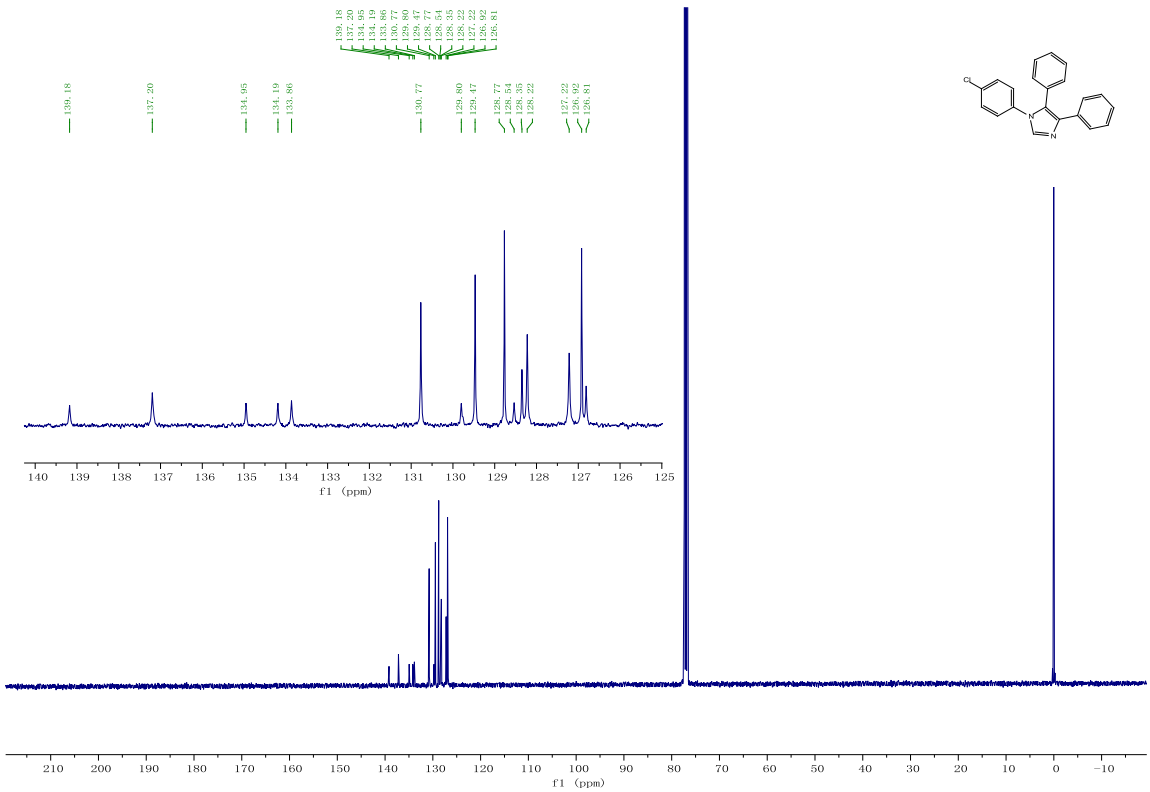


Figure S35. ^{13}C NMR spectrum ($CDCl_3$, 100 MHz) for 1-(4-Chlorophenyl)-4,5-diphenyl-1H-imidazole **(9a)**

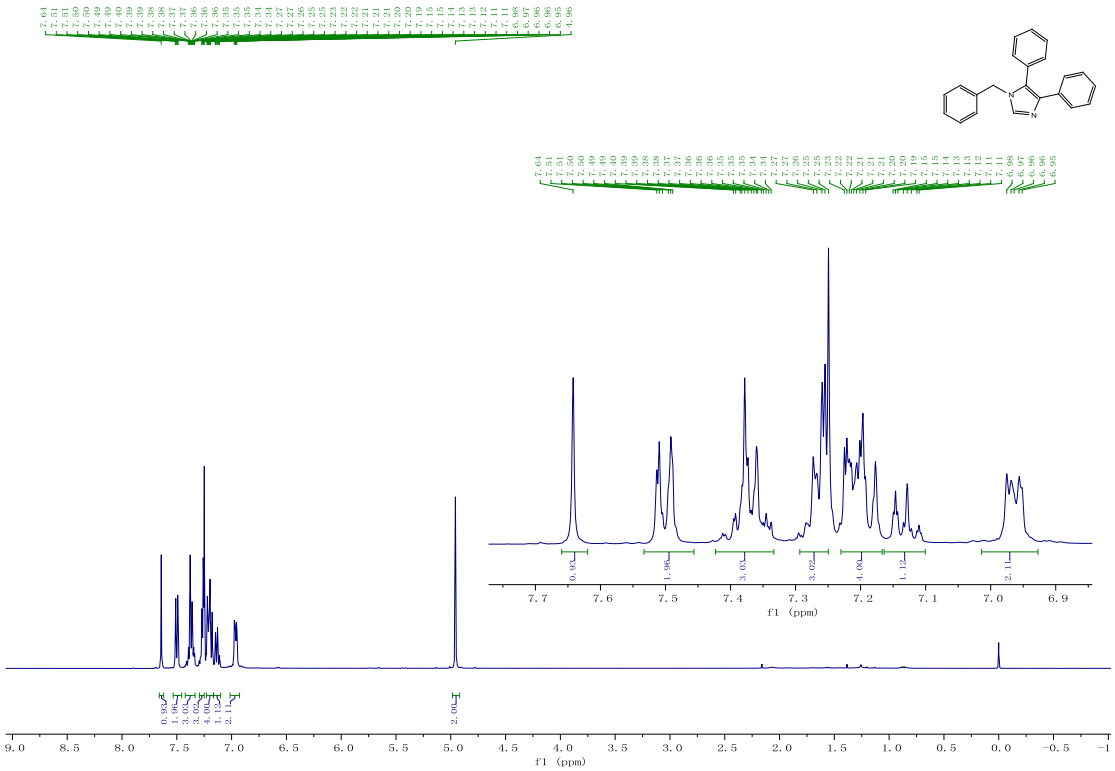


Figure S36. ^{1}H NMR spectrum ($CDCl_3$, 400 MHz) for 1-Benzyl-4,5-diphenyl-1H-imidazole **(9b)**

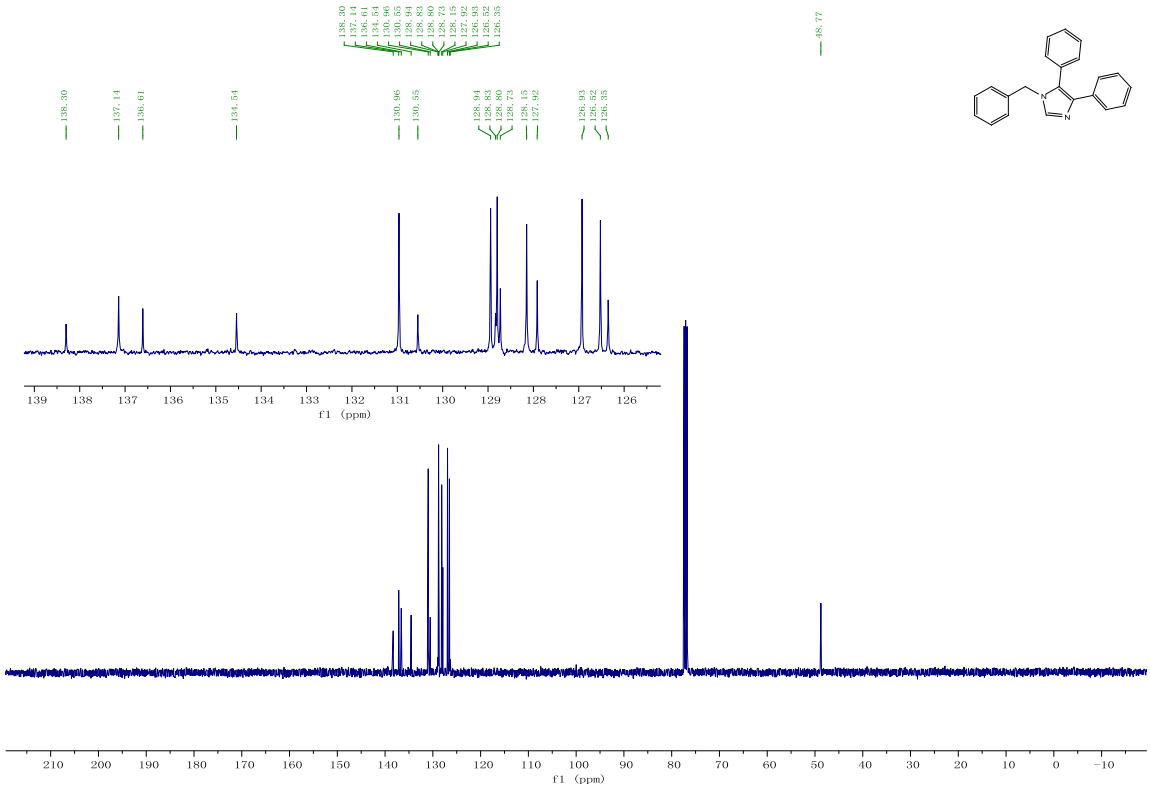


Figure S37. ^{13}C NMR spectrum ($CDCl_3$, 100 MHz) for 1-Benzyl-4,5-diphenyl-1H-imidazole **(9b)**

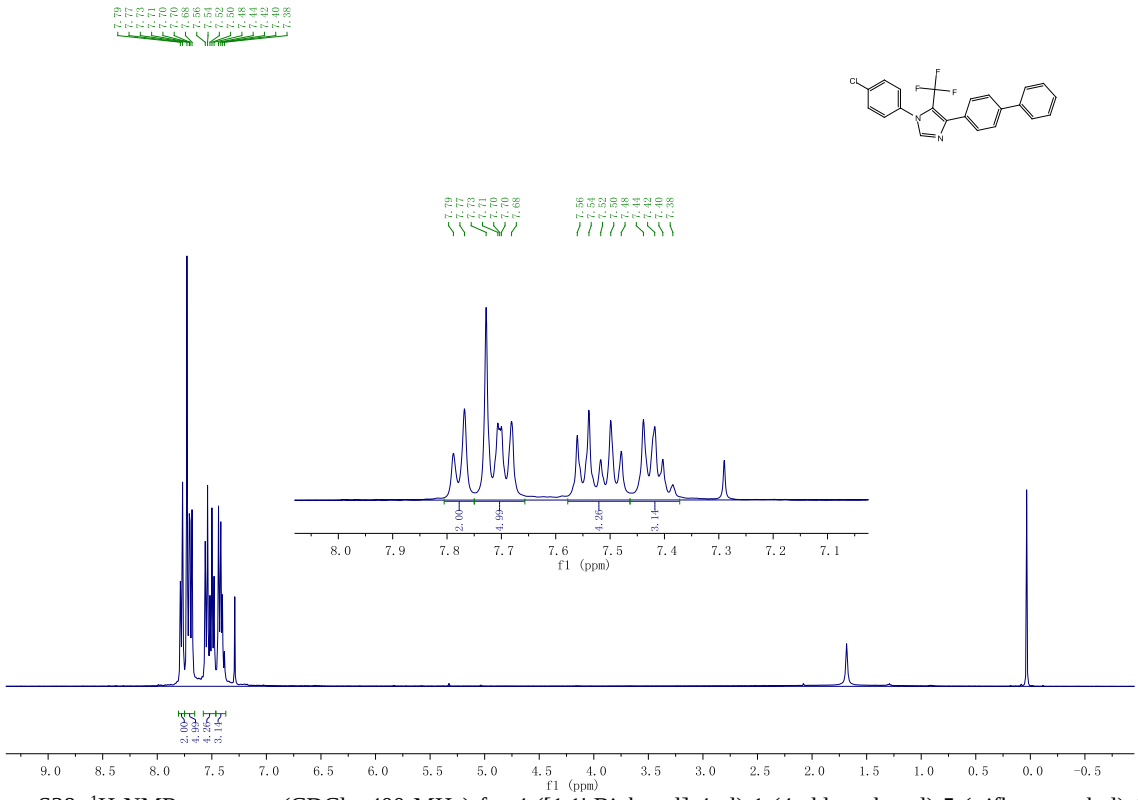


Figure S38. ^{1}H NMR spectrum ($CDCl_3$, 400 MHz) for 4-([1,1'-Biphenyl]-4-yl)-1-(4-chlorophenyl)-5-(trifluoromethyl)-1H-imidazole **(9c)**

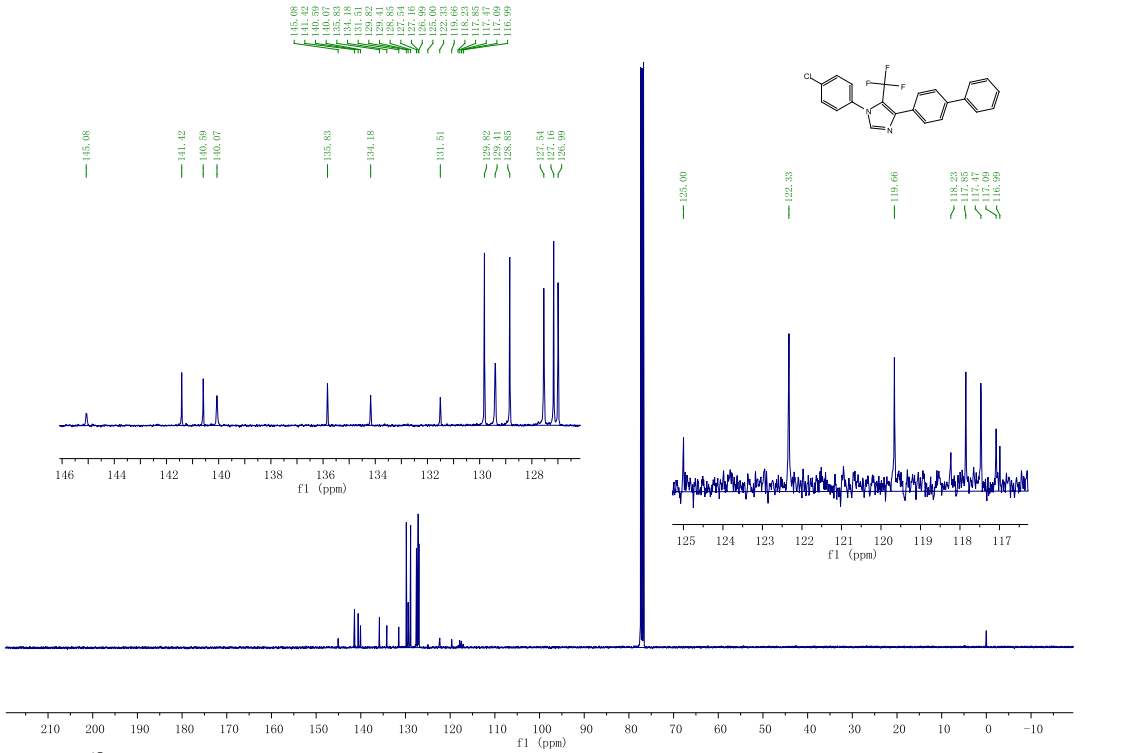


Figure S39. ^{13}C NMR spectrum ($CDCl_3$, 100 MHz) for 4-([1,1'-Biphenyl]-4-yl)-1-(4-chlorophenyl)-5-(trifluoromethyl)-1H-imidazole **(9c)**

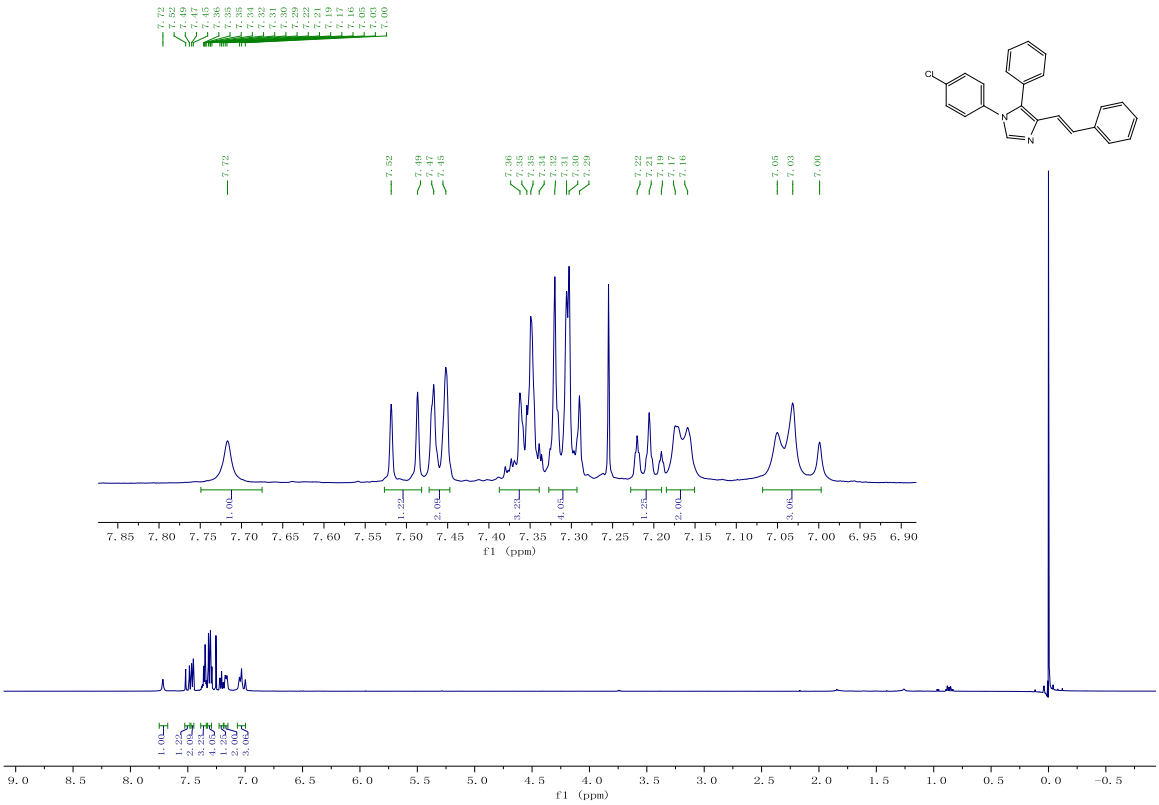


Figure S40. ^{1}H NMR spectrum ($CDCl_3$, 500 MHz) for (*E*)-1-(4-Chlorophenyl)-5-phenyl-4-styryl-1H-imidazole **(9d)**

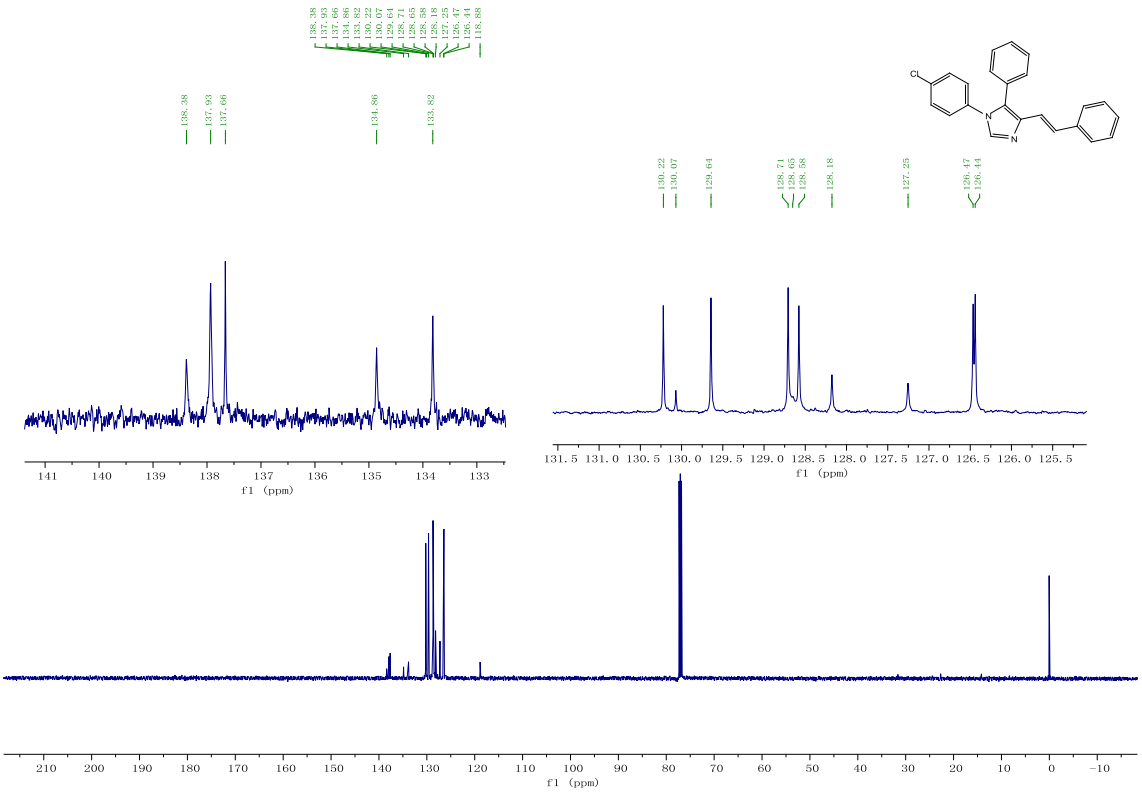


Figure S41. ^{13}C NMR spectrum ($CDCl_3$, 126 MHz) for (*E*)-1-(4-Chlorophenyl)-5-phenyl-4-styryl-1H-imidazole **(9d)**

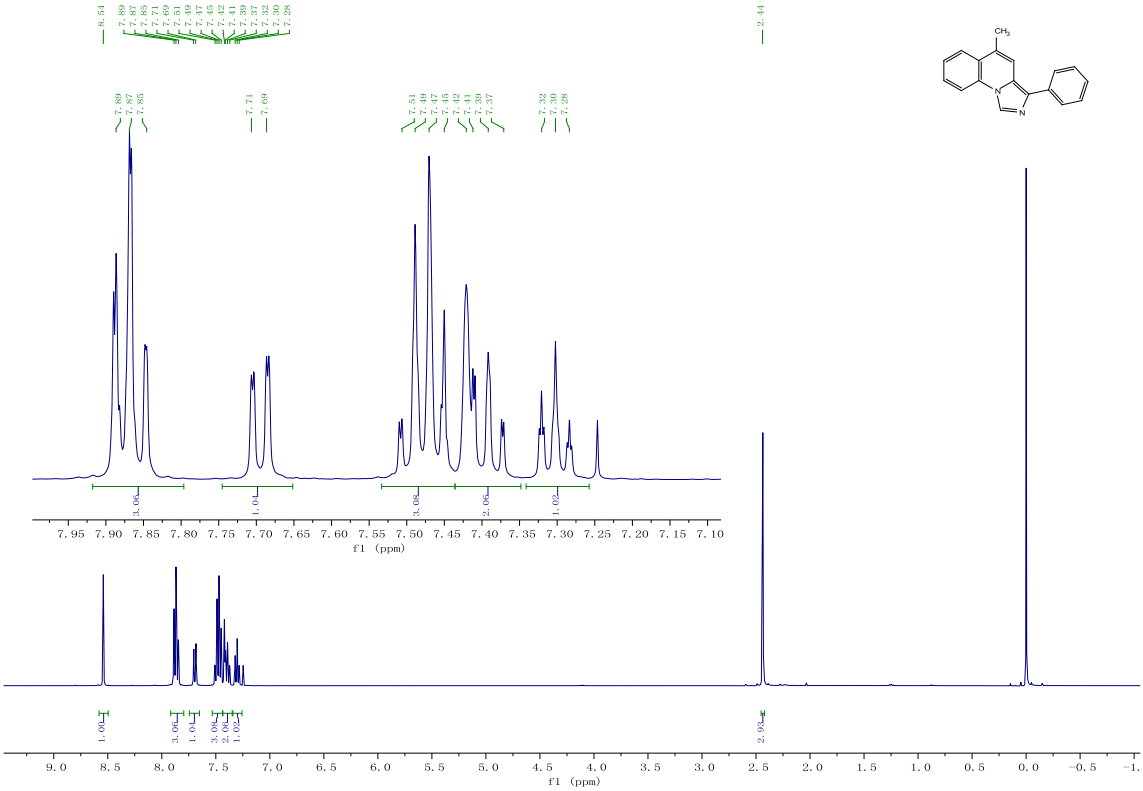


Figure S42. ^{1}H NMR spectrum ($CDCl_3$, 400 MHz) for 5-Methyl-3-phenylimidazo[1,5-a]quinolone **(10a)**

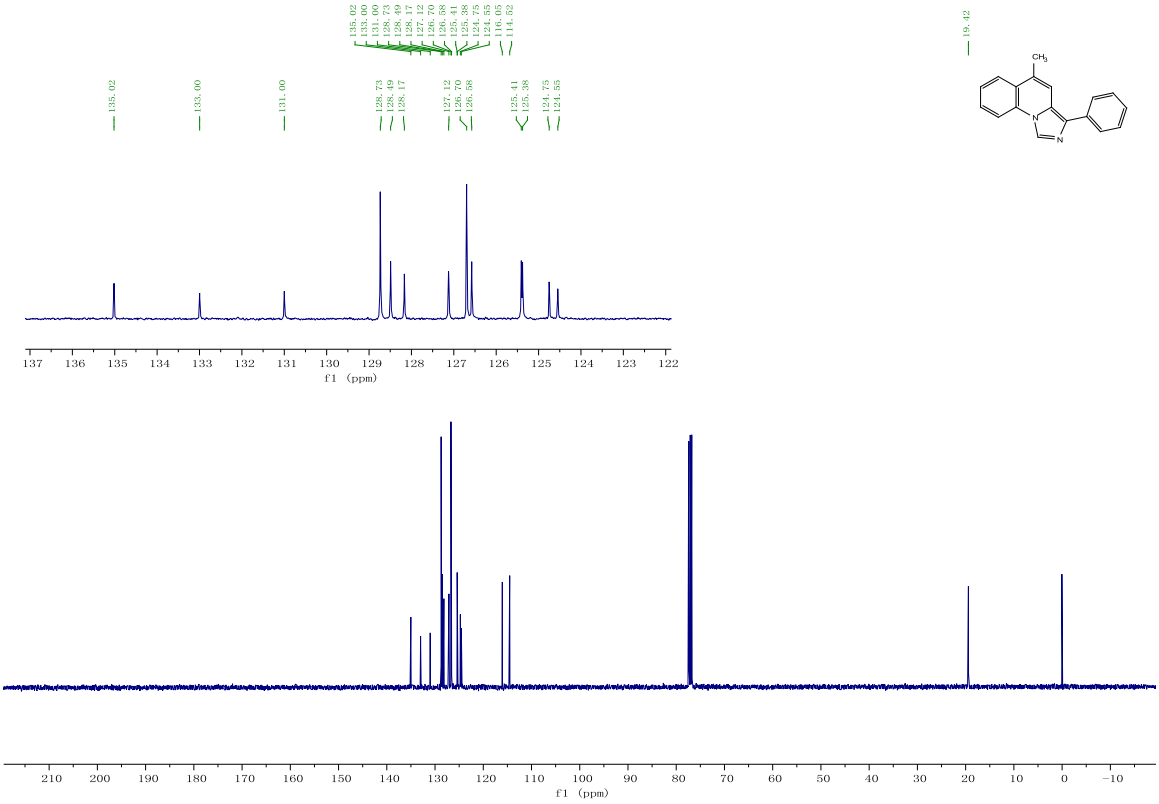


Figure S43. ^{13}C NMR spectrum ($CDCl_3$, 100 MHz) for 5-Methyl-3-phenylimidazo[1,5-a]quinolone **(10a)**

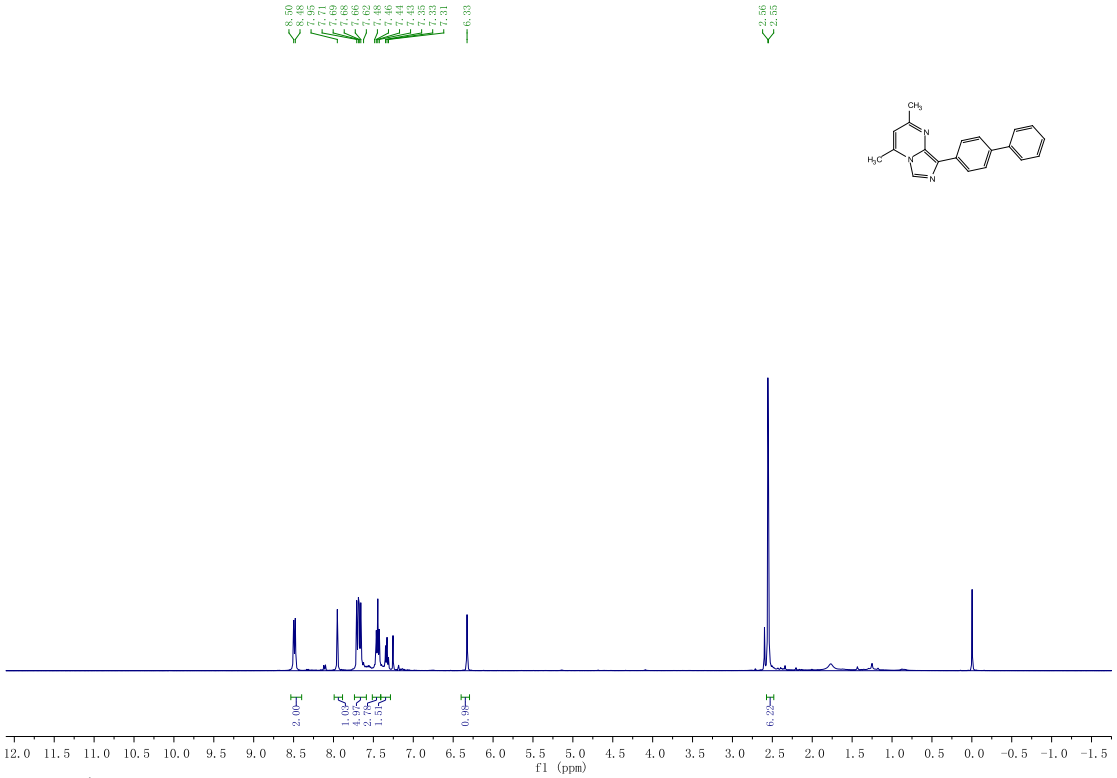


Figure S44. ^{1}H NMR spectrum ($CDCl_3$, 400 MHz) for 8-([1,1'-Biphenyl]-4-yl)-2,4-dimethylimidazo[1,5-a]pyrimidine **(11a)**

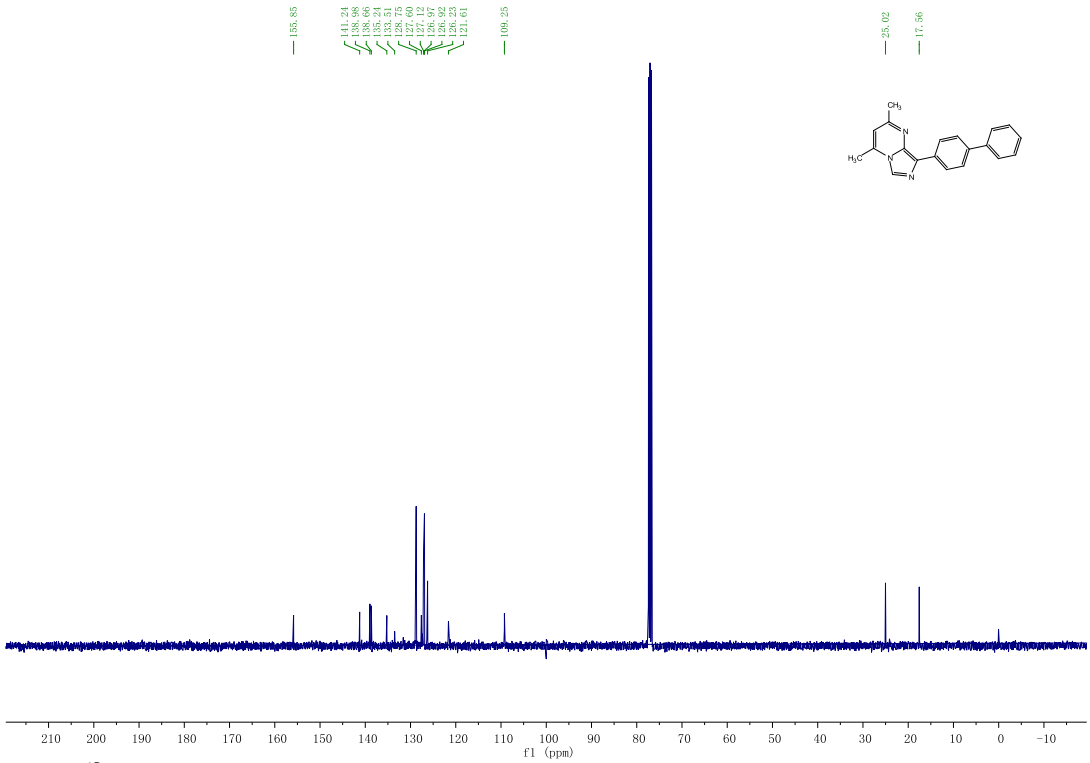


Figure S45. ^{13}C NMR spectrum ($CDCl_3$, 100 MHz) for 8-([1,1'-Biphenyl]-4-yl)-2,4-dimethylimidazo[1,5-a]pyrimidine **(11a)**

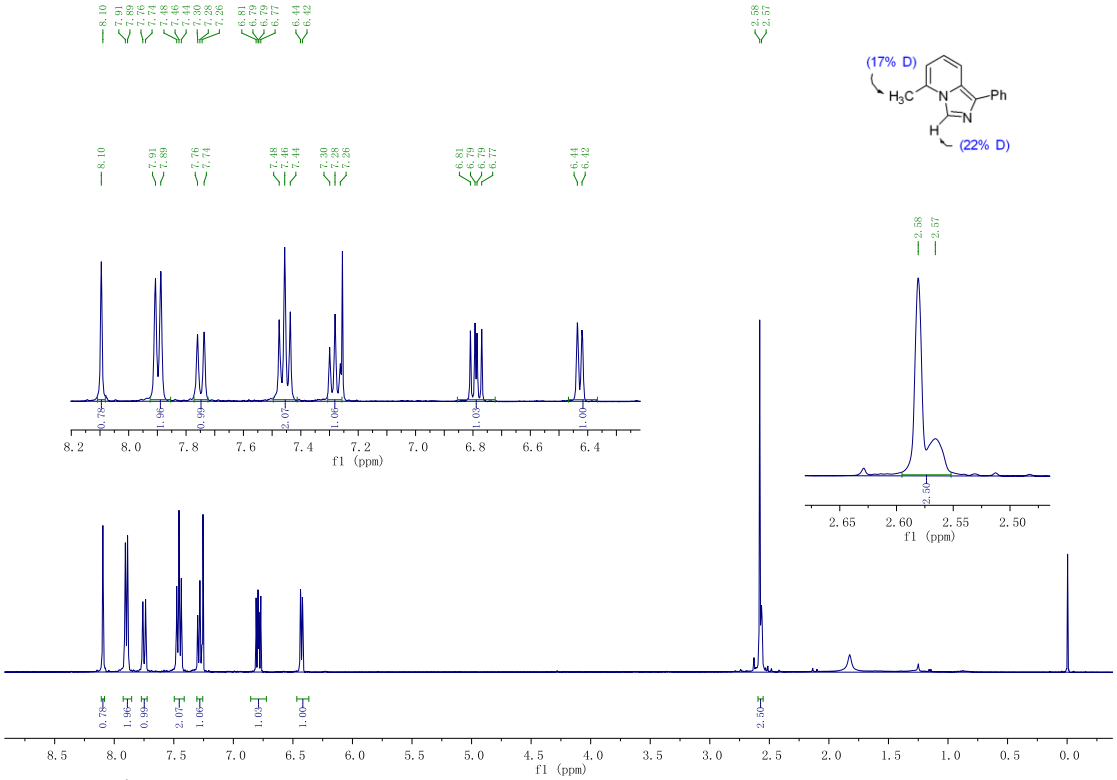


Figure S46. ^{1}H NMR spectrum ($CDCl_3$, 400 MHz) for deuterated 1-Phenylimidazo[1,5-a]pyridine **(d-8b)**

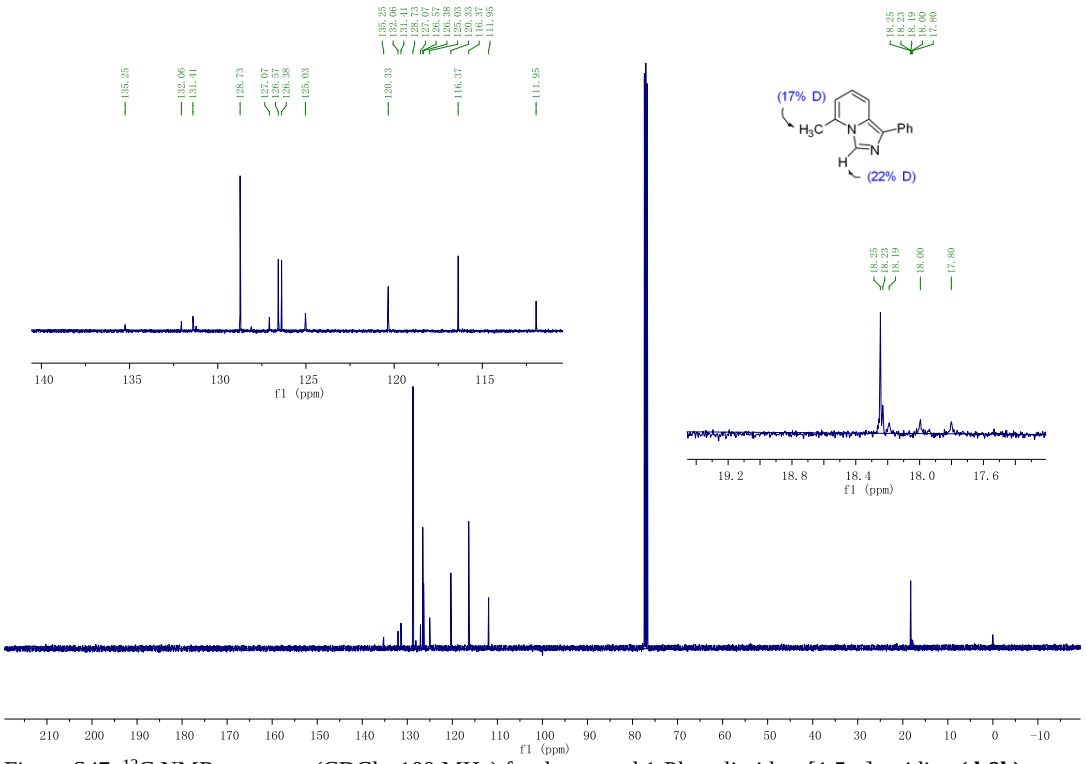


Figure S47. ^{13}C NMR spectrum ($CDCl_3$, 100 MHz) for deuterated 1-Phenylimidazo[1,5-a]pyridine **(d-8b)**

[1] T. Buyck, Q. Wang, J. Zhu, *Angew. Chem. Int. Ed.* **2013**, *52*, 12714 –12718.

[2] The data is similar to that previously reported: I. Macsari, Y. Besidski, G. Csjernyik, L. I. Nilsson, L. Sandberg, U. Yngve, K. Åhlin, T. Bueters, A. B. Eriksson, P.-E. Lund, E. Venyike, S. Oerther, K. H. Blakeman, L. Luo, P. I. Arvidsson, *J. Med. Chem.*, **2012**, *55*, 6866–6880.

[3] A. Porcheddu, G. Giacomelli, M. Salaris, *J. Org. Chem.* **2005**, *70*, 4218–4218.

[4] U. Schollkopf, K. Henneke, K. Madawinata, R. Harms, *Liebigs Ann. Chem.* **1977**, 40-47.

[5] The data is similar to that previously reported: M.-S. Yu, W.-C. Lee, Chih-Hao Chen, F.-Y. Tsai, T.-G. Ong *Org. Lett.* **2014**, *16*, 4826-4829.

[6] S. D. Sharma, P. Hazarika, D. Konwar, *Tetrahedron Lett.* **2008**, *49*, 2216–2220.

[7] D2-benzylisonitile was obtained from twice deuteration of lithiated benzylisonitrile. (a) B. Pooi, J. Lee, K. Choi, H. Hirao, S. H. Hong, *J. Org. Chem.* **2014**, *79*, 9231−9245; (b) S. S. Kim, K. W. Yang, C. S. Lee, *J. Org. Chem.* **1996**, *61*, 4827-4829.