Electronic Supplementary Material (ESI) for RSC Advances.

A two-step continuous flow synthesis of 1,4-disubstituted 1,2,3-triazoles under metal- and azide-free conditions

Jiajia Gu, Zheng Fang, Zhao Yang, Xin Li, Ning Zhu, Li Wan, Ping Wei and Kai Guo

College of Biotechnology and Pharmaceutical Engineering, Nanjing Tech University, 30 Puzhu Rd S., Nanjing 211816, China.

guok@njtech.edu.cn

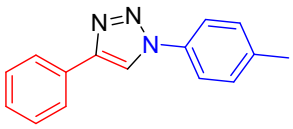
1. General details

Reaction solvents were obtained commercially, and used without further purification. Commercial reagents were used as received. Reaction were monitored by thin-layer chromatography (TLC) on 0.25mm precoated Merck Silica Gel 60 F254, visualizing with ultraviolet light. $^{1}H/^{13}C$ NMR spectra were recorded on 400'54 ascend purchased from Bruker Biospin AG, operating at 400/100 MHz, respectively. Chemical shifts (δ) are reported in parts per million (ppm) downfield from tetramethylsilane (TMS), which was used as internal standard. High-resolution mass spectra (HRMS) were obtained from an Agilent 6520 LC-MS instrument. Flash column chromatography was performed on Merck Silica Gel 60 (200-300mesh) using petroleum ether and ethyl acetate.

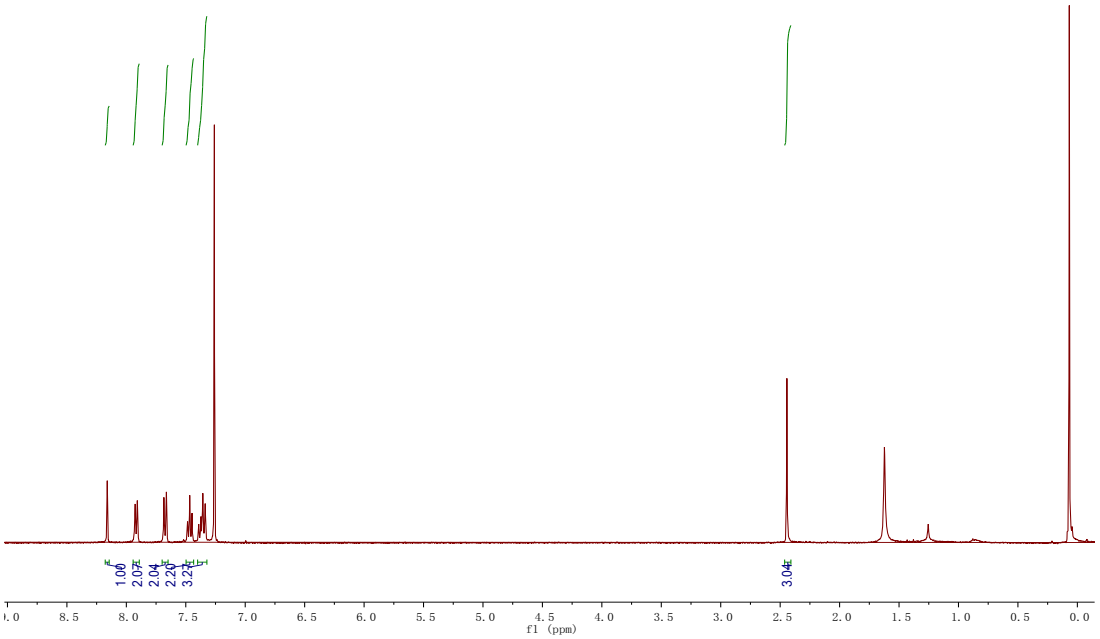
2. Experimental procedure

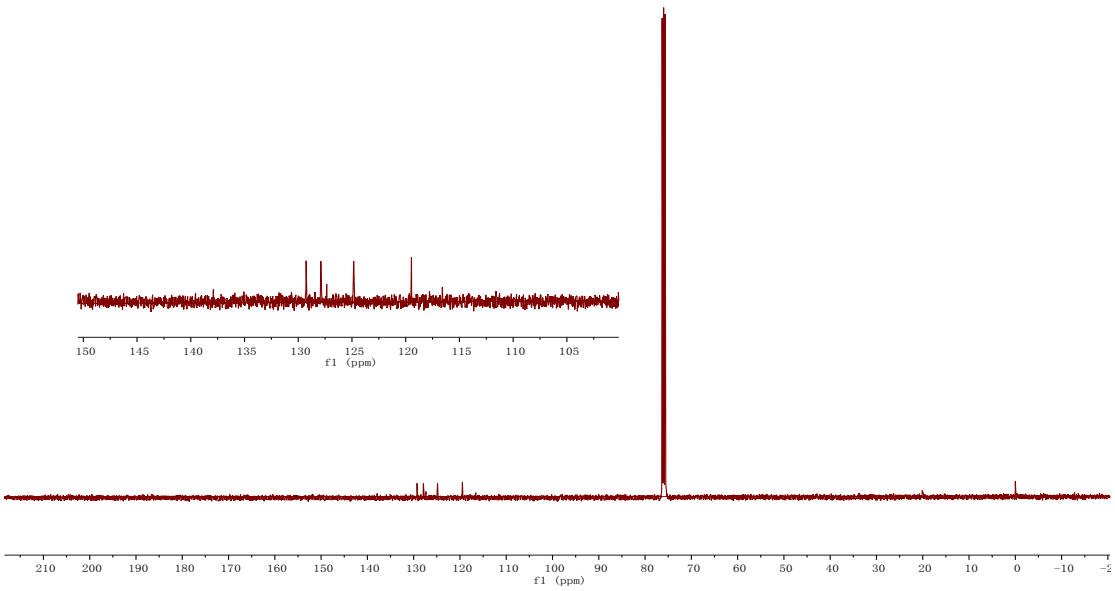
General procedure for synthesis of compound 3: 5mmol of acetophenones (**1**) was dissolved in 50mL dioxane, which was placed into syringe A. And 5mmol of tosylhydrazine was dissolved in 50mL dioxane, which was placed into syringe B. Anilines (**2**, 3mmol, 1.2eq), I_2 (0.25mmol, 0.2eq) and TBHP (70wt% in water, 5mmol, 2eq) were dissolves in 50mL dioxane, which was placed into syringe C. The flow rate of syringes A, B and C were 0.1mL/min, 0.1mL/min, and 0.2mL/min, respectively. And the temperature of the two oil baths was set in 50˚C and 80˚C, respectively. The reaction liquid was collected, and then quenched by $NaHSO_3$ solution and extracted with ethyl acetate, washed with H_2O. The organic layer was dried over anhydrous sodium sulfate and solvent was removed under vacuum. And the crude product was purified by flash chromatography on silica gel by gradient elution with ethyl acetate in petroleum ether to obtain the product **3**.

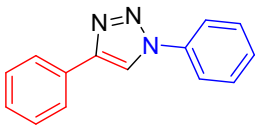
3. NMR Spectra



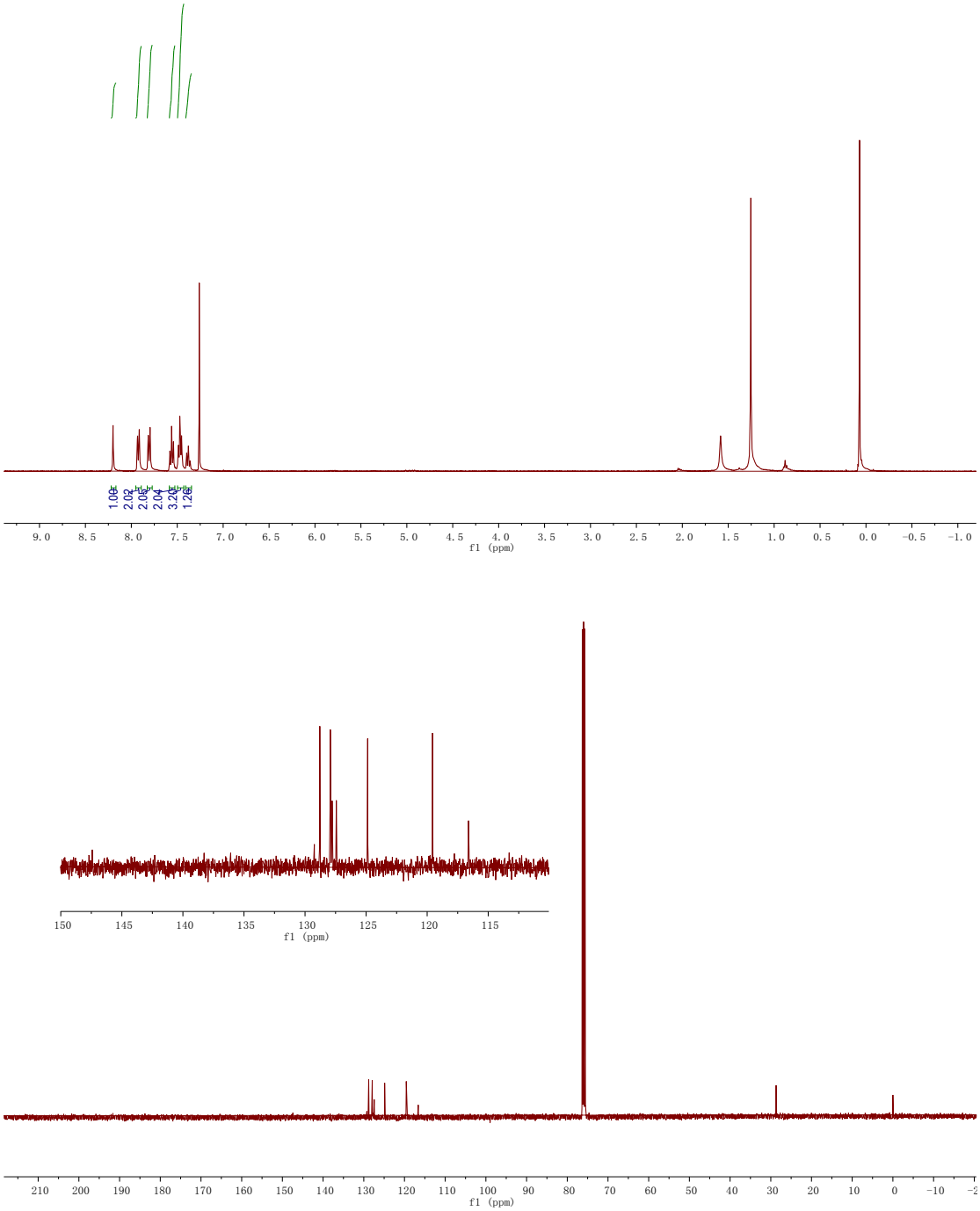
4-phenyl-1-p-tolyl-1H-1,2,3-triazole (**3a**): White solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 (s, 1H), 7.92 (d, *J* = 7.2 Hz, 2H), 7.67 (d, *J* = 8.4 Hz, 2H), 7.47 (t, *J* = 7.5 Hz, 2H), 7.36 (dd, *J* = 14.0, 7.8 Hz, 3H), 2.44 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 146.25, 137.90, 129.26, 128.43, 127.90, 127.35, 124.84, 119.46, 117.79, 116.59, 20.11; HRMS (ESI) m/z calcd for $C_{15}H_{13}N_3$ $[M+H]^+$ 236.1182, found 236.1195.

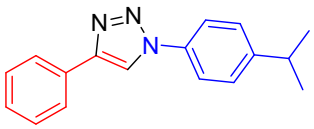




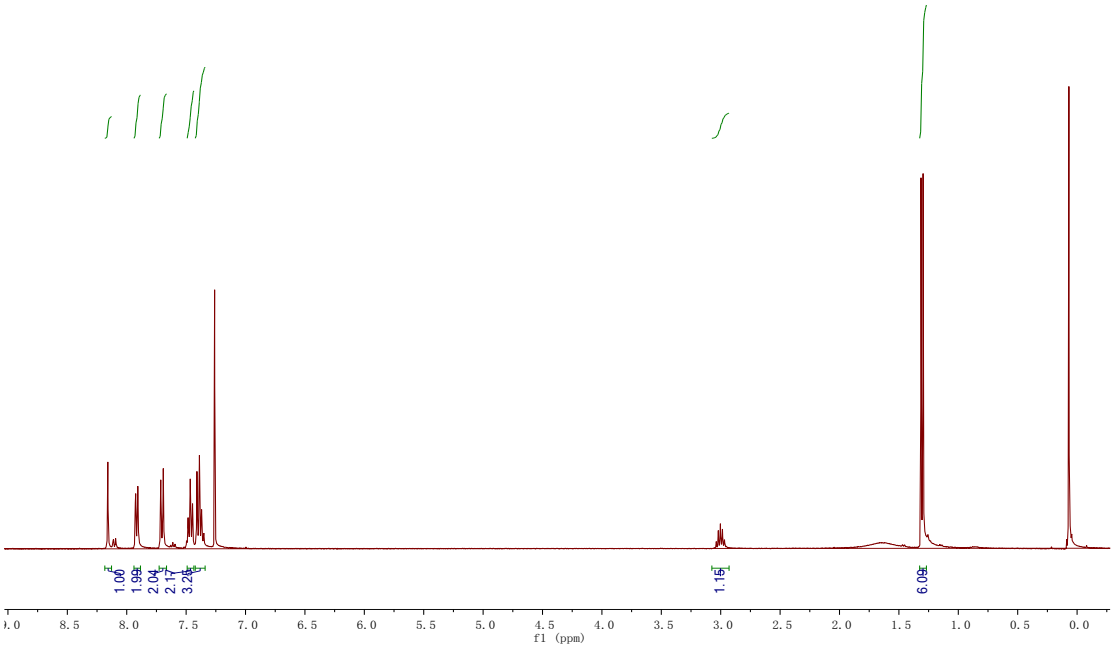


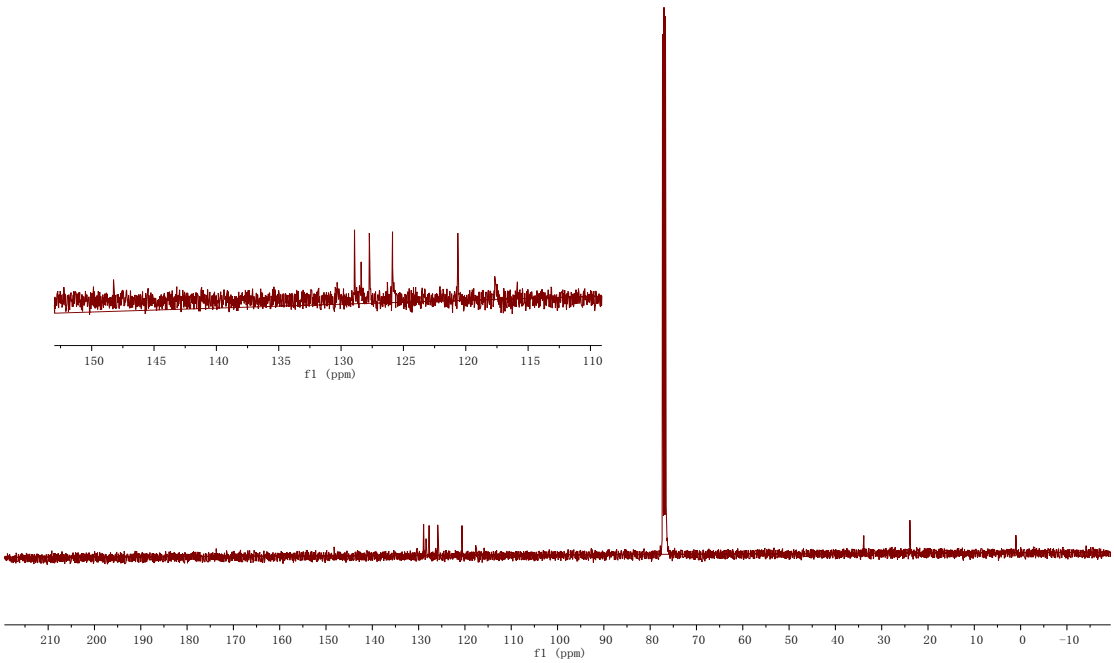
1,4-diphenyl-1H-1,2,3-triazole (**3b**): White solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20 (s, 1H), 7.92 (d, *J* = 7.3 Hz, 2H), 7.81 (d, *J* = 7.7 Hz, 2H), 7.56 (t, *J* = 7.7 Hz, 2H), 7.47 (t, *J* = 6.5 Hz, 3H), 7.38 (t, *J* = 7.4 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 147.42, 136.09, 129.24, 128.79, 127.93, 127.78, 127.44, 124.87, 119.56, 116.61; HRMS (ESI) m/z calcd for $C_{14}H_{11}N_3$ $[M+H]^+$ 222.1047, found 222.1053.

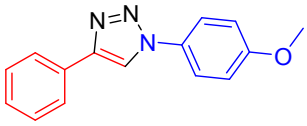




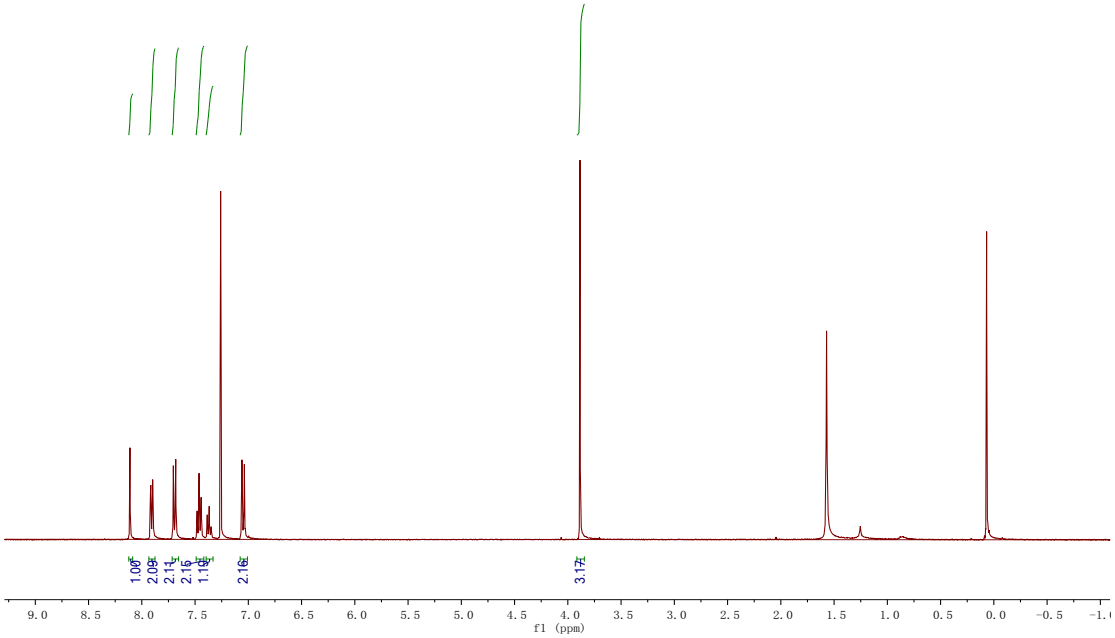
1-(4-isopropylphenyl)-4-phenyl-1H-1,2,3-triazole (**3c**): White solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 (s, 1H), 7.94–7.88 (m, 2H), 7.70 (d, *J* = 8.5 Hz, 2H), 7.46 (t, *J* = 7.5 Hz, 2H), 7.38 (dd, *J* = 15.2, 7.9 Hz, 3H), 3.00 (dt, *J* = 13.8, 6.9 Hz, 1H), 1.31 (d, *J* = 6.9 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 148.25, 130.29, 128.92, 128.39, 127.73, 125.87, 120.64, 117.66, 33.87, 23.91; HRMS (ESI) m/z calcd for $C_{17}H_{17}N_3$ $[M+H]^+$ 264.1495, found 264.1509.

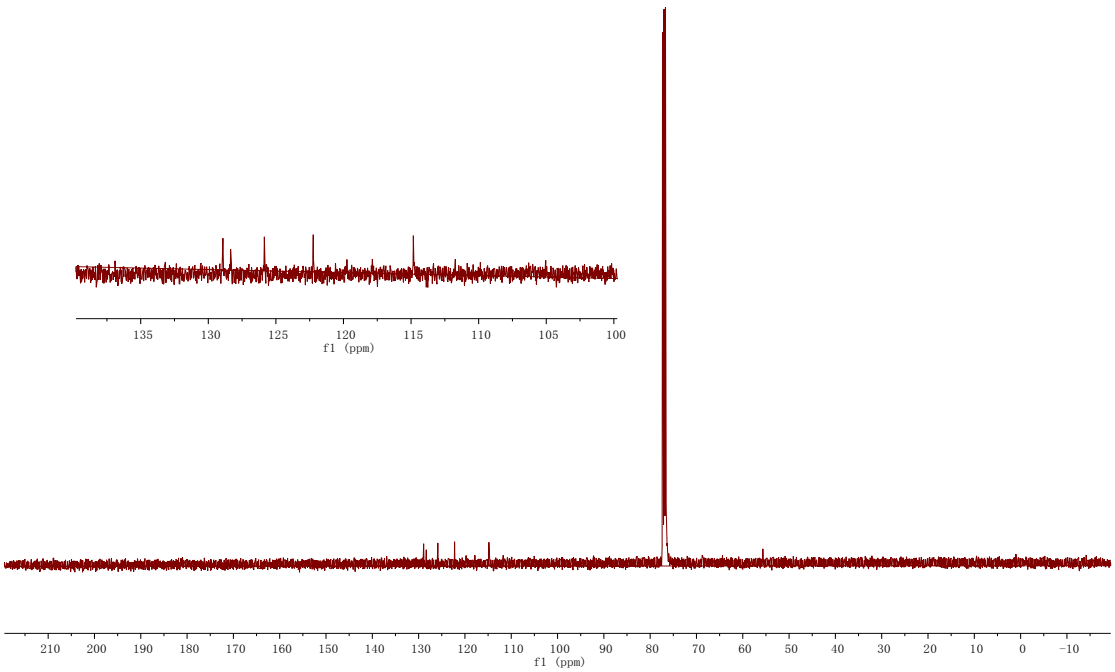


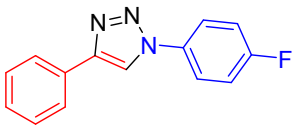




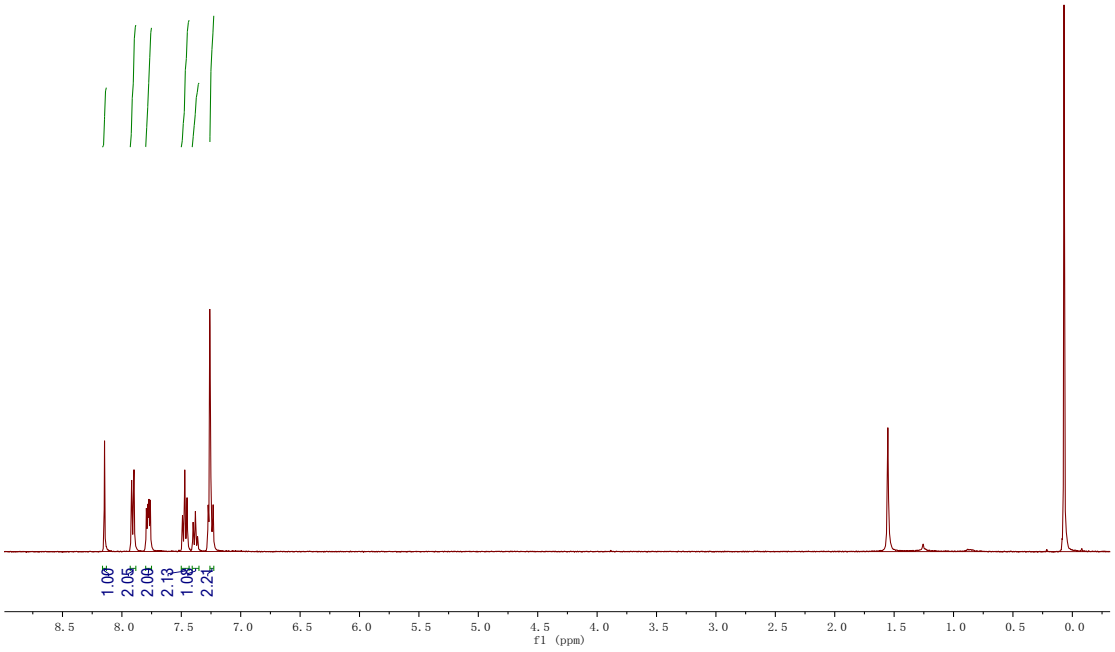
1-(4-methoxyphenyl)-4-phenyl-1H-1,2,3-triazole (**3d**): Light yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 (s, 1H), 7.93–7.88 (m, 2H), 7.71–7.65 (m, 2H), 7.46 (t, *J* = 7.5 Hz, 2H), 7.37 (t, *J* = 7.4 Hz, 1H), 7.05 (d, *J* = 9.0 Hz, 2H), 3.89 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 130.38, 128.92, 128.35, 125.85, 122.24, 117.86, 114.83, 55.66; HRMS (ESI) m/z calcd for $C_{15}H_{13}N_3O$ $[M+H]^+$ 252.1131, found 252.1146.

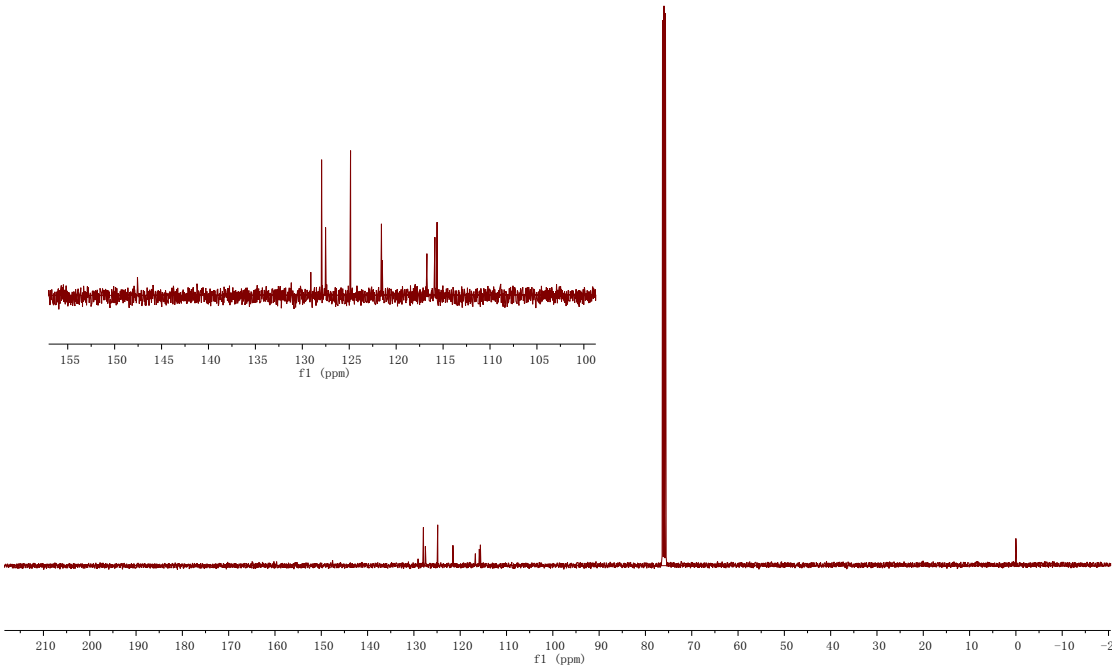


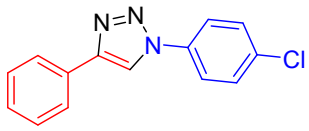




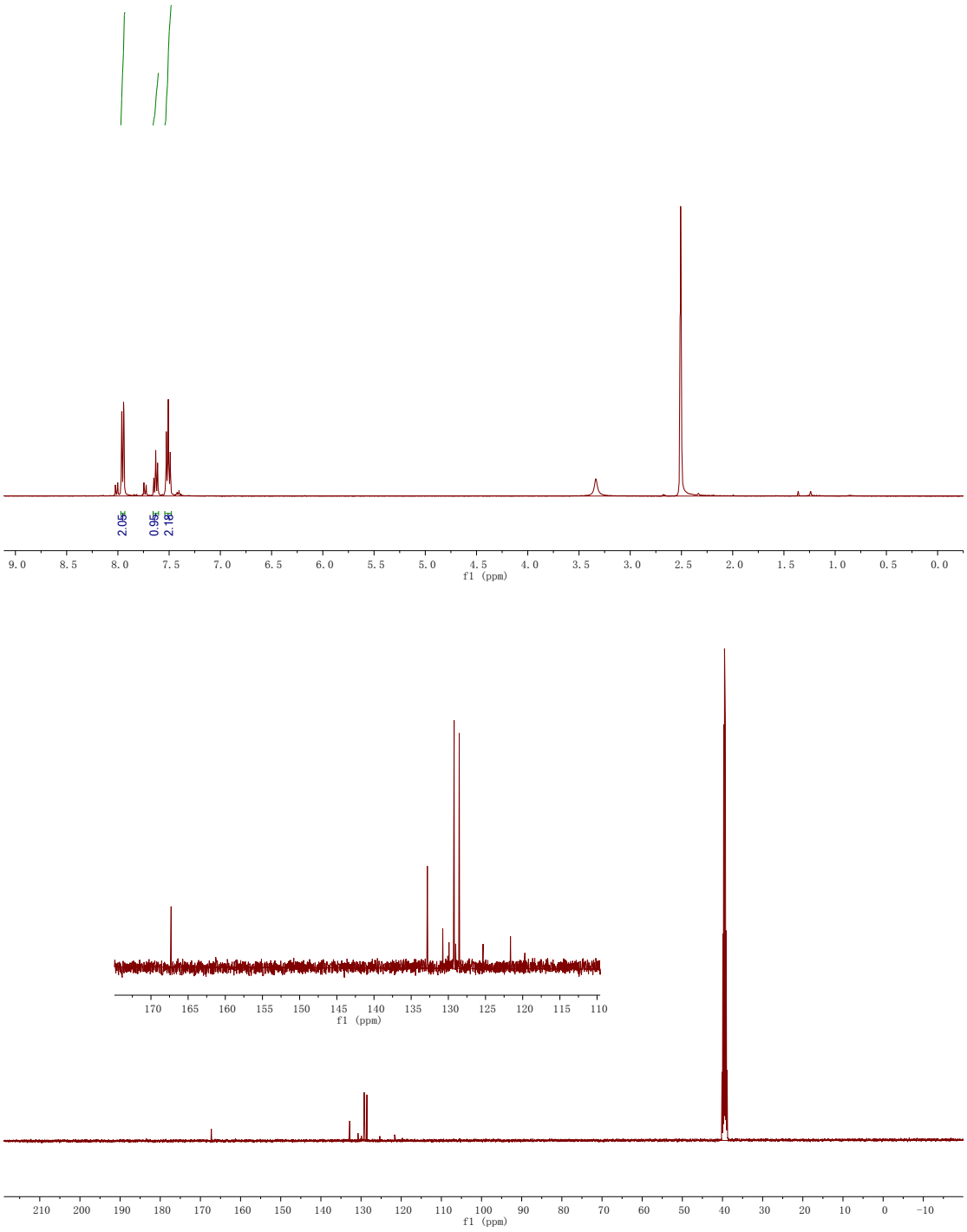
1-(4-fluorophenyl)-4-phenyl-1H-1,2,3-triazole (**3e**): White solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 (s, 1H), 7.91 (d, *J* = 7.9 Hz, 2H), 7.78 (dd, *J* = 8.8, 4.5 Hz, 2H), 7.47 (t, *J* = 7.6 Hz, 2H), 7.38 (t, *J* = 7.4 Hz, 1H), 7.24 (d, *J* = 8.3 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 147.56, 129.10, 127.95, 124.86, 121.57, 121.48, 116.72, 115.87, 115.64; HRMS (ESI) m/z calcd for $C_{14}H_{10}N_3F$ $[M+H]^+$ 240.0932, found 240.0958.

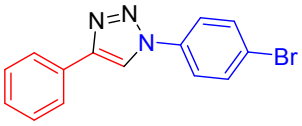




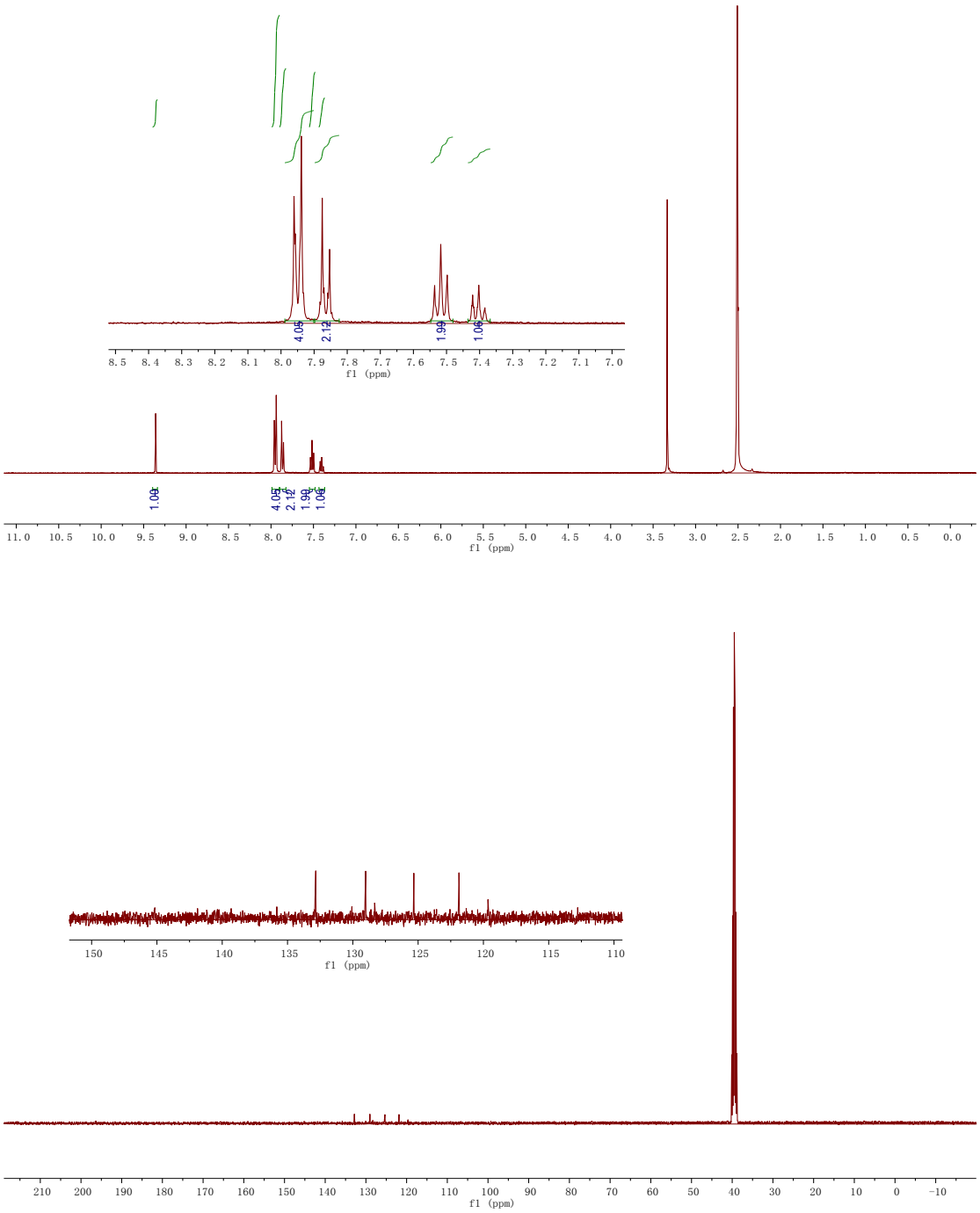


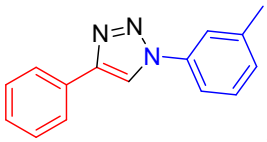
1-(4-chlorophenyl)-4-phenyl-1H-1,2,3-triazole (**3f**): Light yellow solid; ^{1}H NMR (400 MHz, DMSO) δ 7.97–7.93 (m, 4H), 7.66–7.60 (m, 2H), 7.54 –7.48 (m, 4H); ^{13}C NMR (101 MHz, DMSO) δ 167.82, 132.82, 130.75, 129.91, 129.22, 129.02, 128.53, 125.32, 121.65, 119.71; HRMS (ESI) m/z calcd for $C_{14}H_{10}N_3Cl$ $[M+H]^+$ 256.0636, found 256.0664.



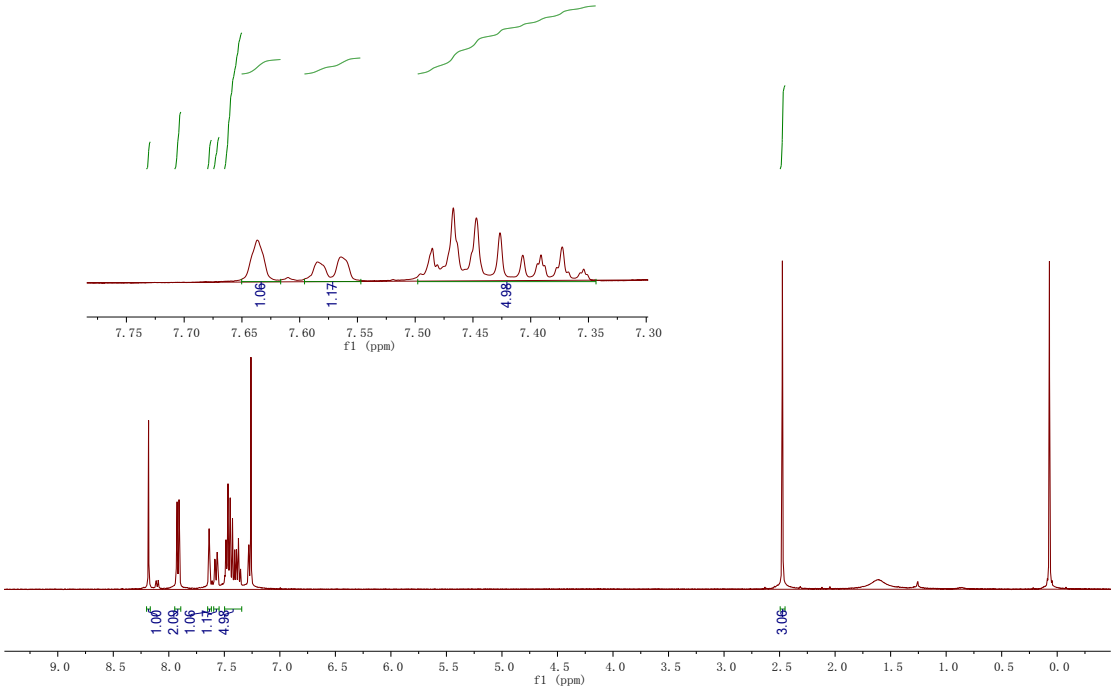


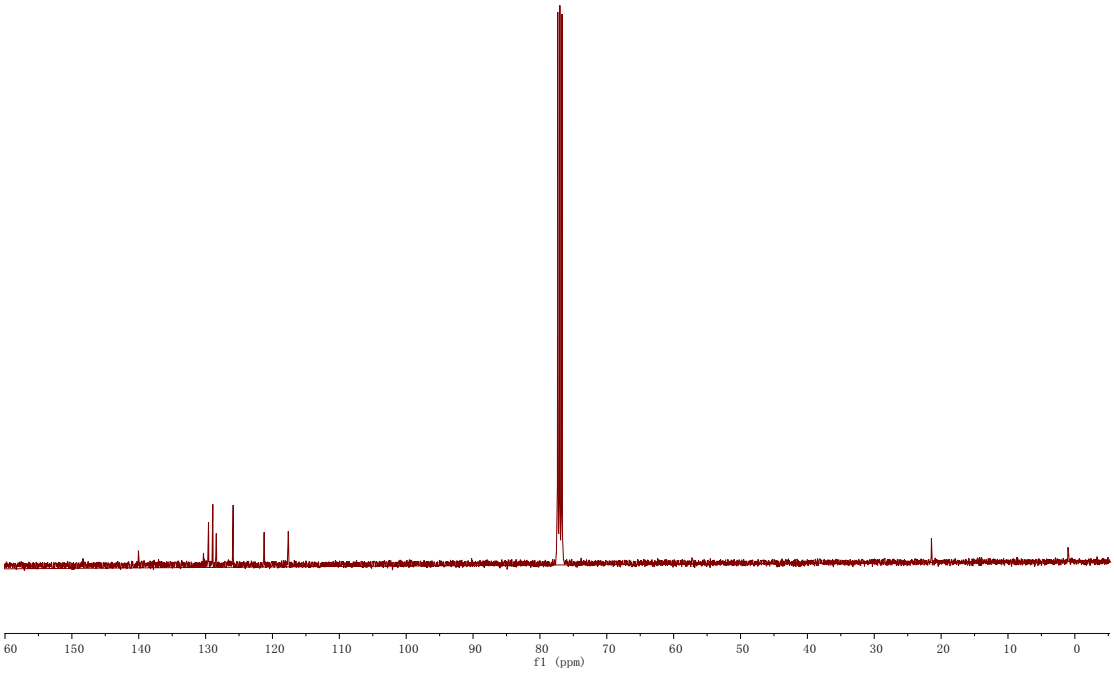
1-(4-bromophenyl)-4-phenyl-1H-1,2,3-triazole (**3g**): White solid; ^{1}H NMR (400 MHz, DMSO) δ 9.36 (s, 1H), 7.99–7.90 (m, 4H), 7.90–7.82 (m, 2H), 7.52 (t, *J* = 7.6 Hz, 2H), 7.40 (t, *J* = 7.4 Hz, 1H); ^{13}C NMR (101 MHz, DMSO) δ 145.20, 135.82, 132.84, 130.07, 129.02, 128.33, 125.33, 121.87, 119.65; HRMS (ESI) m/z calcd for $C_{14}H_{10}N_3Br$ $[M+H]^+$ 300.0131, found 300.0131.

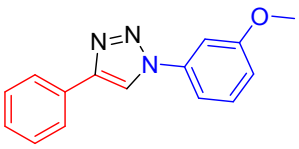




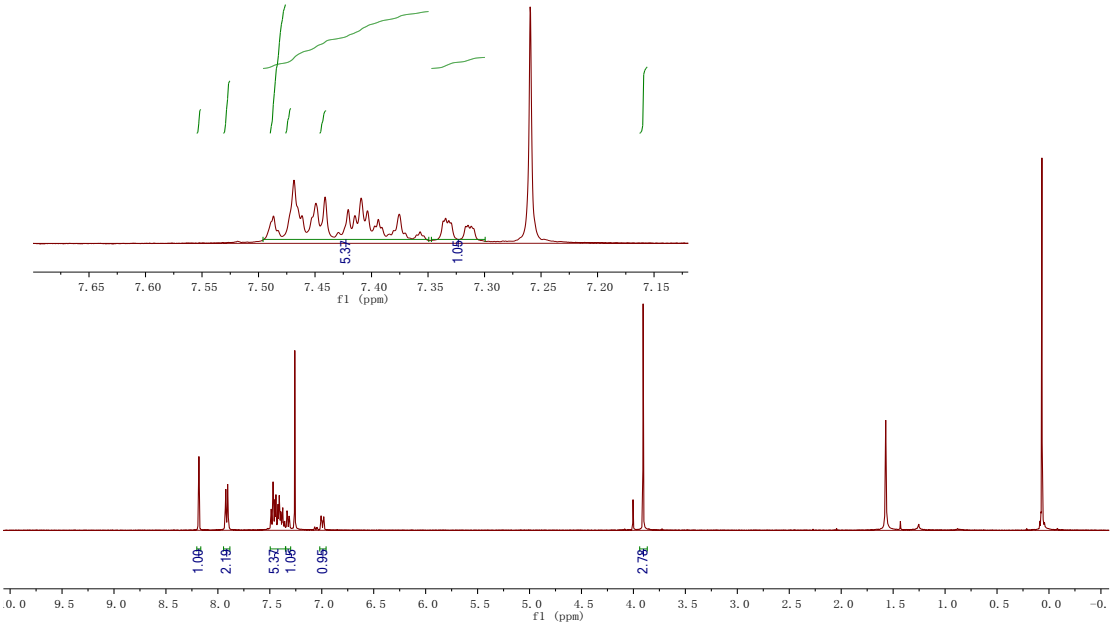
4-phenyl-1-m-tolyl-1H-1,2,3-triazole (**3h**): White solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 (s, 1H), 7.95–7.89 (m, 2H), 7.64 (s, 1H), 7.57 (d, *J* = 8.2 Hz, 1H), 7.50–7.34 (m, 5H), 2.47 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 140.05, 130.32, 129.56, 128.92, 128.40, 125.88, 121.24, 117.63, 21.45; HRMS (ESI) m/z calcd for $C_{15}H_{13}N_3$ $[M+H]^+$ 236.1182, found 236.1208.

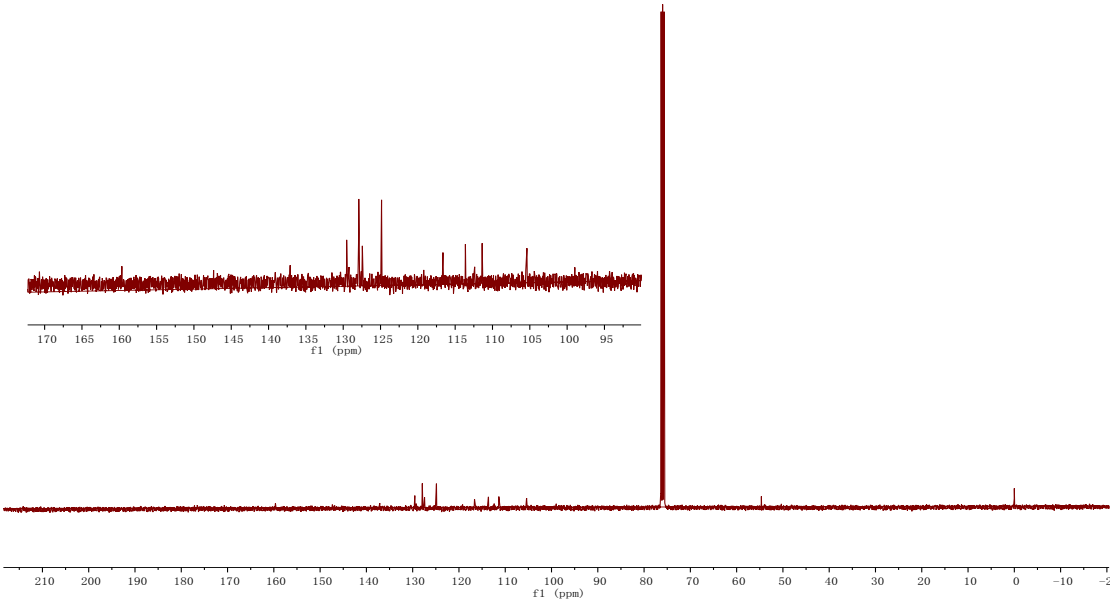


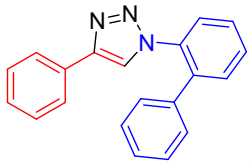




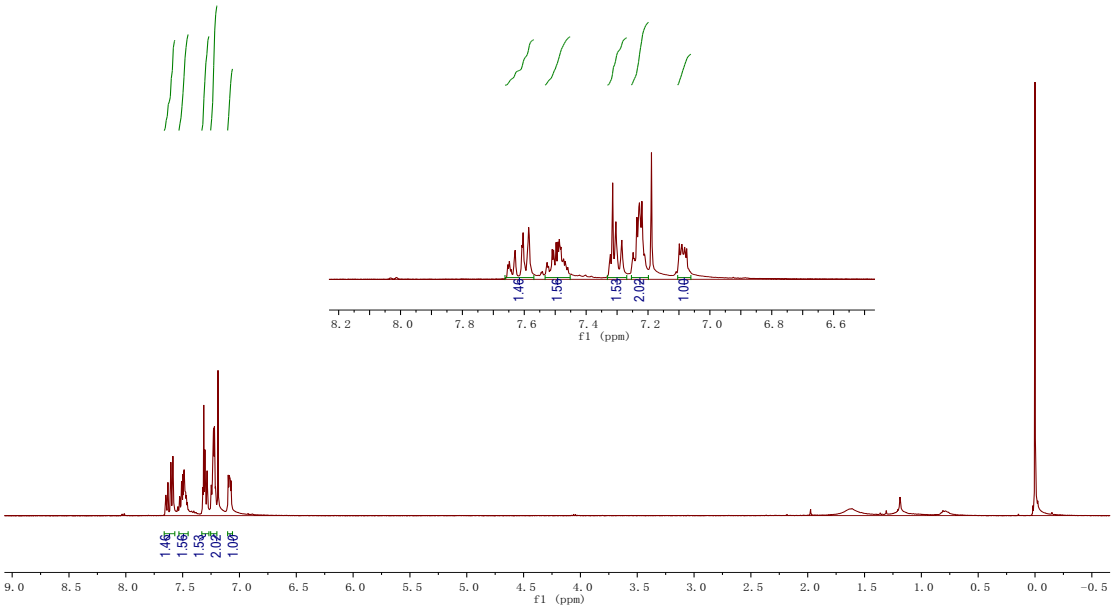
1-(3-methoxyphenyl)-4-phenyl-1H-1,2,3-triazole (**3i**): White solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 (s, 1H), 7.92 (dd, *J* = 5.2, 3.3 Hz, 2H), 7.50–7.35 (m, 5H), 7.32 (dd, *J* = 8.0, 1.1 Hz, 1H), 6.99 (dd, *J* = 8.3, 1.8 Hz, 1H), 3.91 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.65, 147.36, 137.10, 129.54, 129.23, 127.91, 127.43, 124.87, 116.64, 113.63, 111.38, 105.38, 54.65; HRMS (ESI) m/z calcd for $C_{15}H_{13}N_3O$ $[M+H]^+$ 252.1131, found 252.1125.

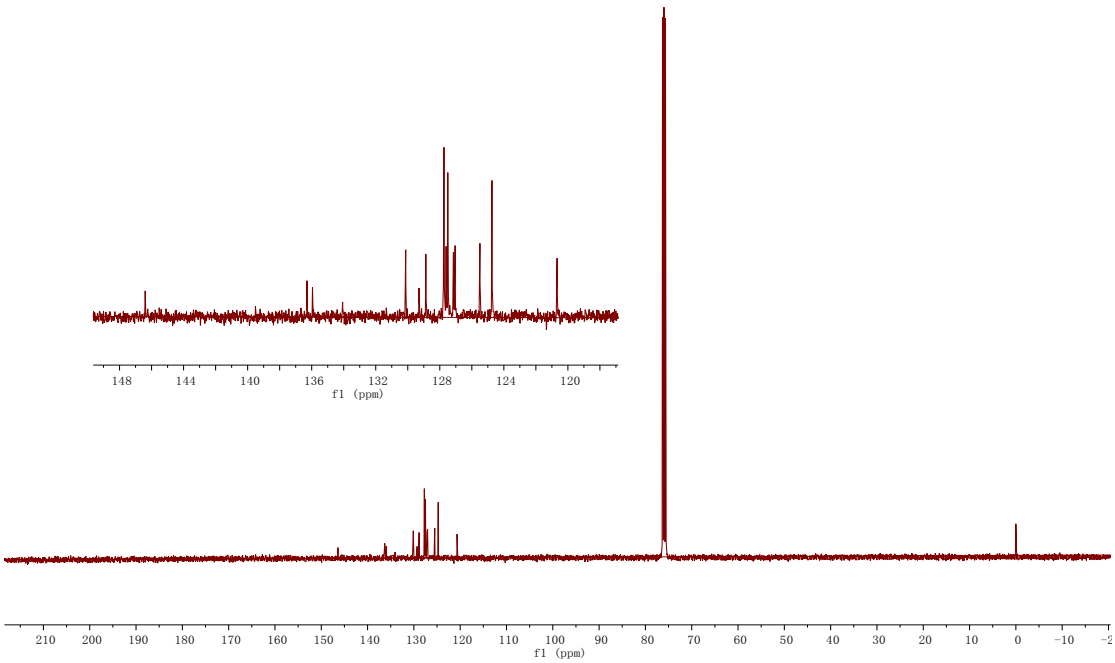


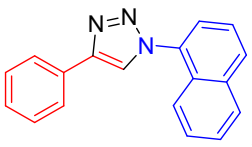




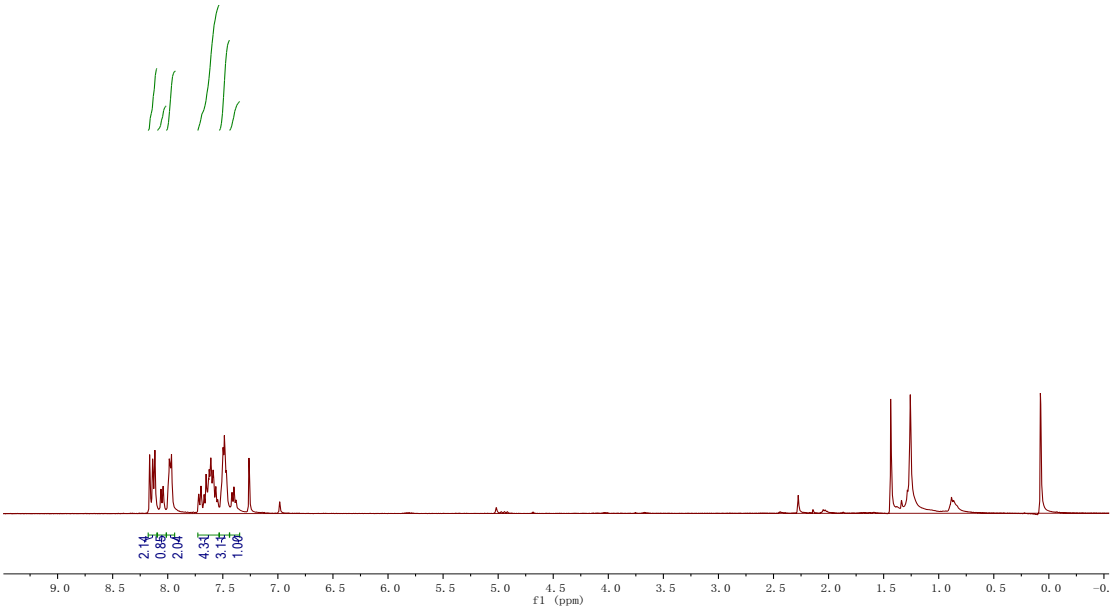
1-(biphenyl-2-yl)-4-phenyl-1H-1,2,3-triazole (**3k**): White solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66–7.57 (m, 3H), 7.53–7.45 (m, 3H), 7.31 (dd, *J* = 9.4, 5.3 Hz, 3H), 7.25–7.20 (m, 4H), 7.10–7.06 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 146.40, 136.29, 135.95, 134.26, 130.13, 129.30, 128.87, 127.76, 127.74, 127.60, 127.50, 127.15, 127.04, 125.50, 124.74, 120.68; HRMS (ESI) m/z calcd for $C_{20}H_{15}N_3O$ $[M+H]^+$ 298.1339, found 298.1377.

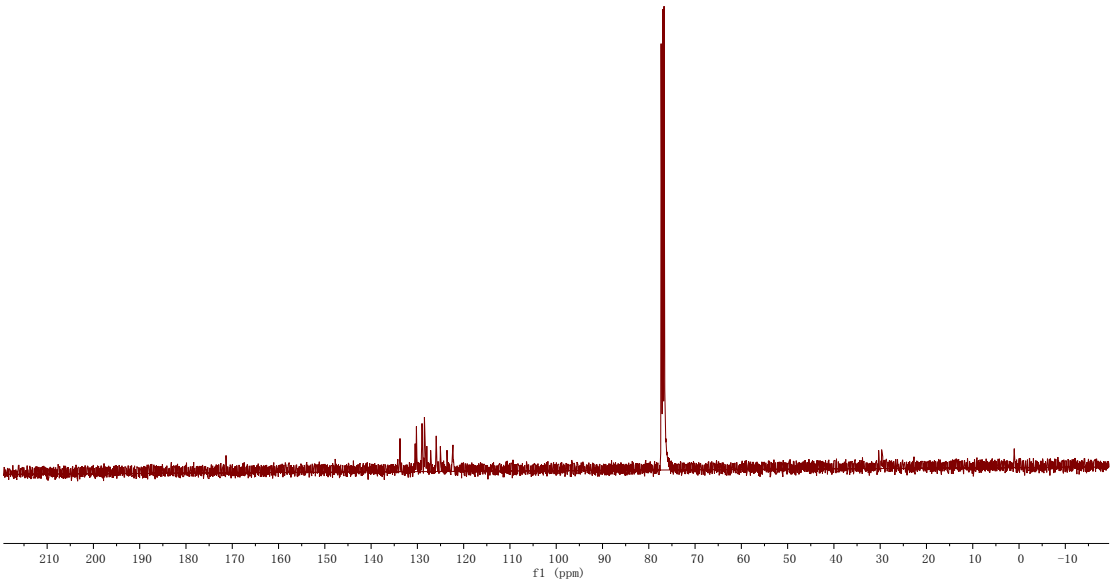


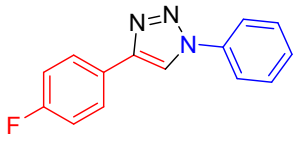




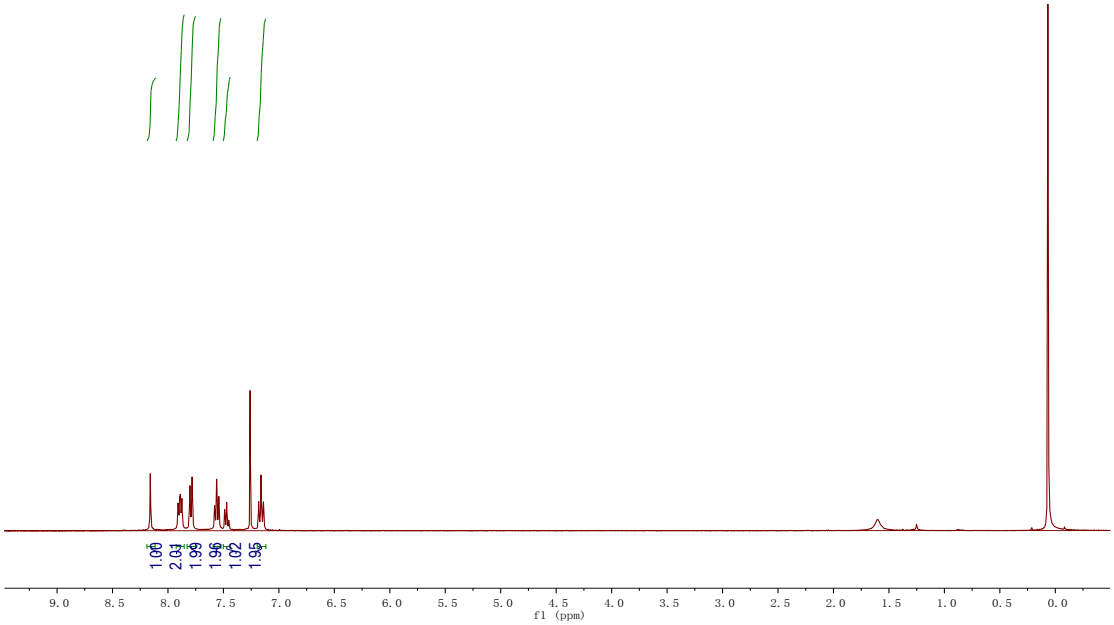
1-(naphthalen-1-yl)-4-phenyl-1H-1,2,3-triazole (**3l**): Brown oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18–8.10 (m, 2H), 8.05 (d, *J* = 8.0 Hz, 1H), 7.98 (dd, *J* = 6.7, 5.2 Hz, 2H), 7.73–7.53 (m, 4H), 7.49 (dd, *J* = 7.8, 4.2 Hz, 3H), 7.40 (t, *J* = 6.8 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 147.77, 134.23, 133.76, 130.48, 130.21, 129.00, 128.48, 128.40, 128.33, 127.96, 127.13, 125.93, 125.04, 123.60, 122.33; HRMS (ESI) m/z calcd for $C_{18}H_{13}N_3O$ $[M+H]^+$ 272.1182, found 272.1196.

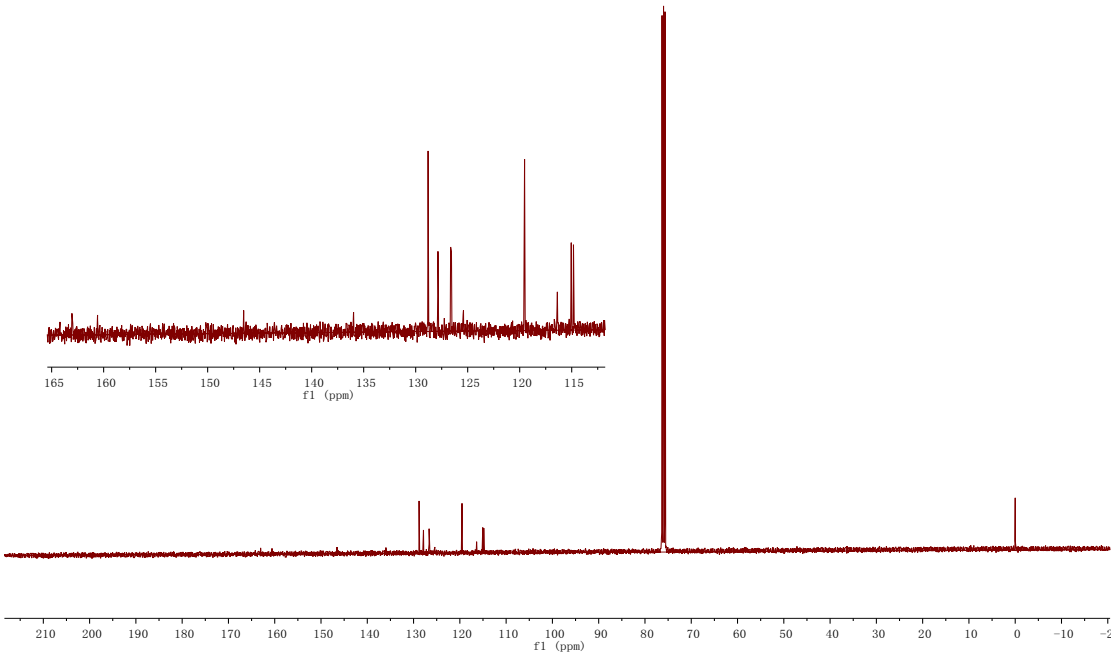


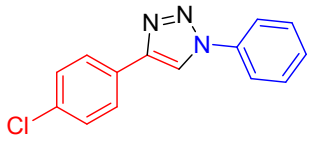




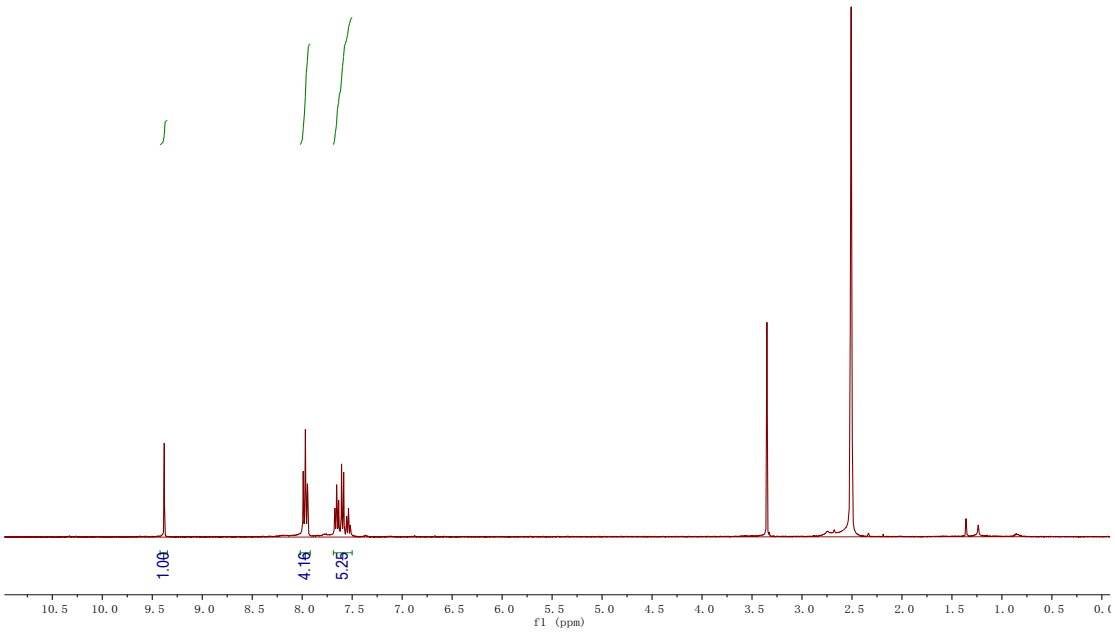
4-(4-fluorophenyl)-1-phenyl-1H-1,2,3-triazole (**3m**): White solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 (s, 1H), 7.89 (dd, *J* = 8.5, 5.4 Hz, 2H), 7.79 (d, *J* = 8.0 Hz, 2H), 7.56 (t, *J* = 7.7 Hz, 2H), 7.47 (t, *J* = 7.4 Hz, 1H), 7.16 (t, *J* = 8.6 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.05, 160.59, 146.54, 135.98, 128.81, 127.86, 126.64, 126.56, 125.44, 125.40, 119.53, 116.38, 115.05, 114.83; HRMS (ESI) m/z calcd for $C_{14}H_{10}N_3F$ $[M+H]^+$ 240.0892, found 240.0896.

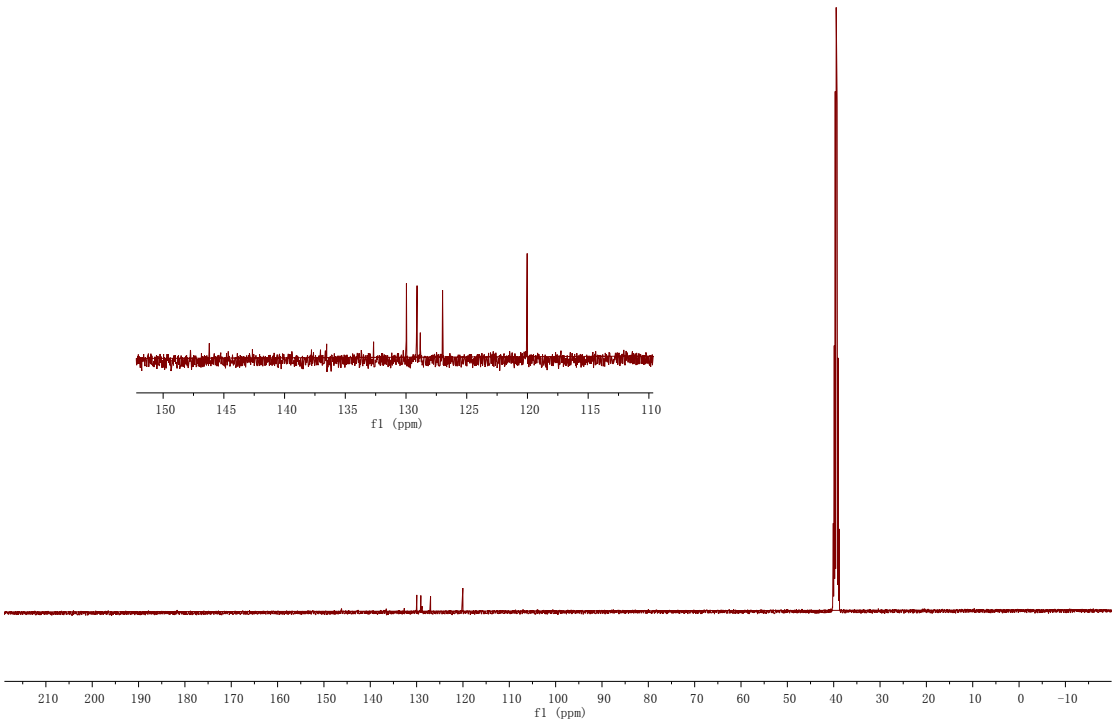


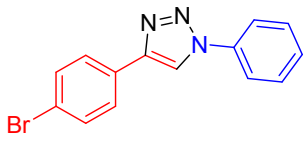




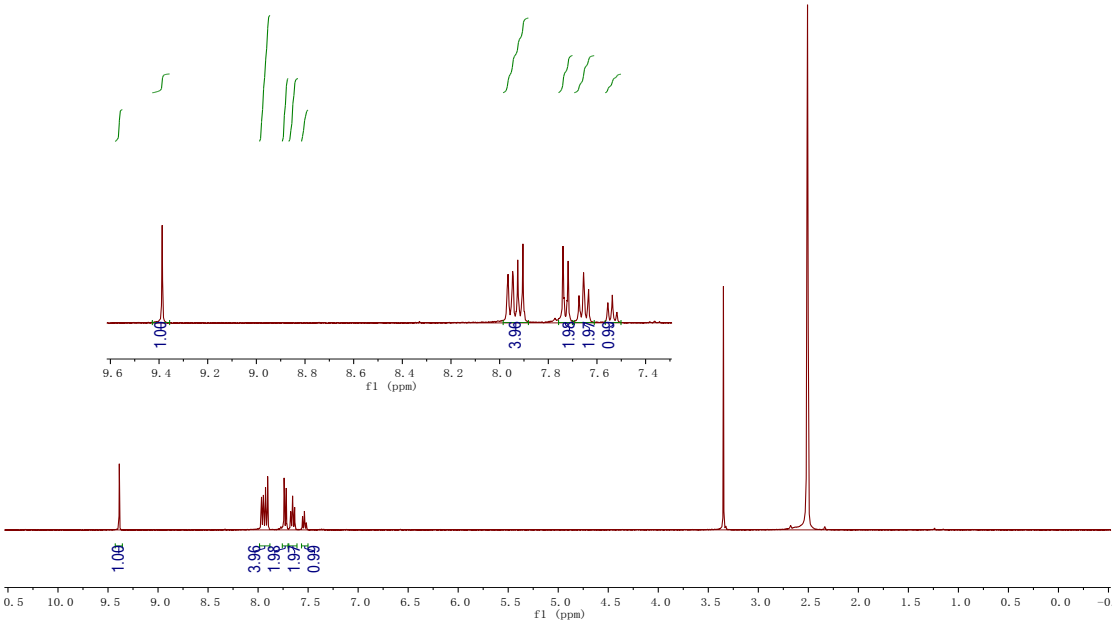
4-(4-chlorophenyl)-1-phenyl-1H-1,2,3-triazole (**3n**): White solid; ^{1}H NMR (400 MHz, DMSO) δ 9.38 (s, 1H), 7.97 (t, *J* = 8.4 Hz, 4H), 7.69–7.50 (m, 5H); ^{13}C NMR (101 MHz, DMSO) δ 146.20, 136.53, 132.67, 130.20, 129.96, 129.14, 129.09, 128.82, 126.99, 120.02; HRMS (ESI) m/z calcd for $C_{14}H_{10}N_3Cl$ $[M+H]^+$ 256.0563, found 256.0576.

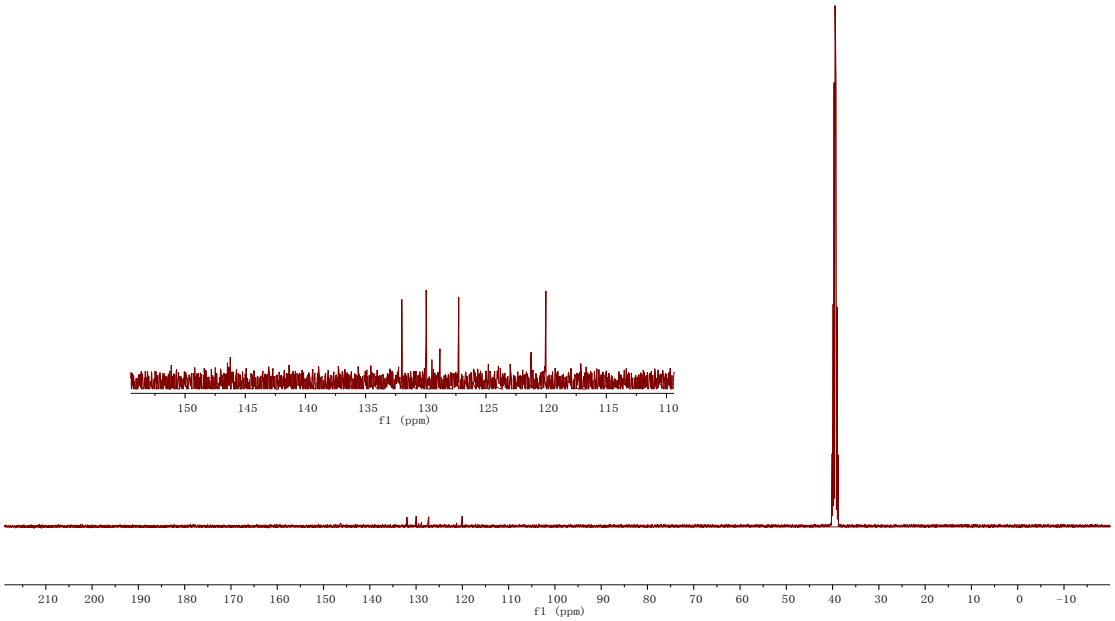


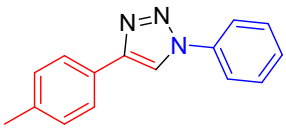




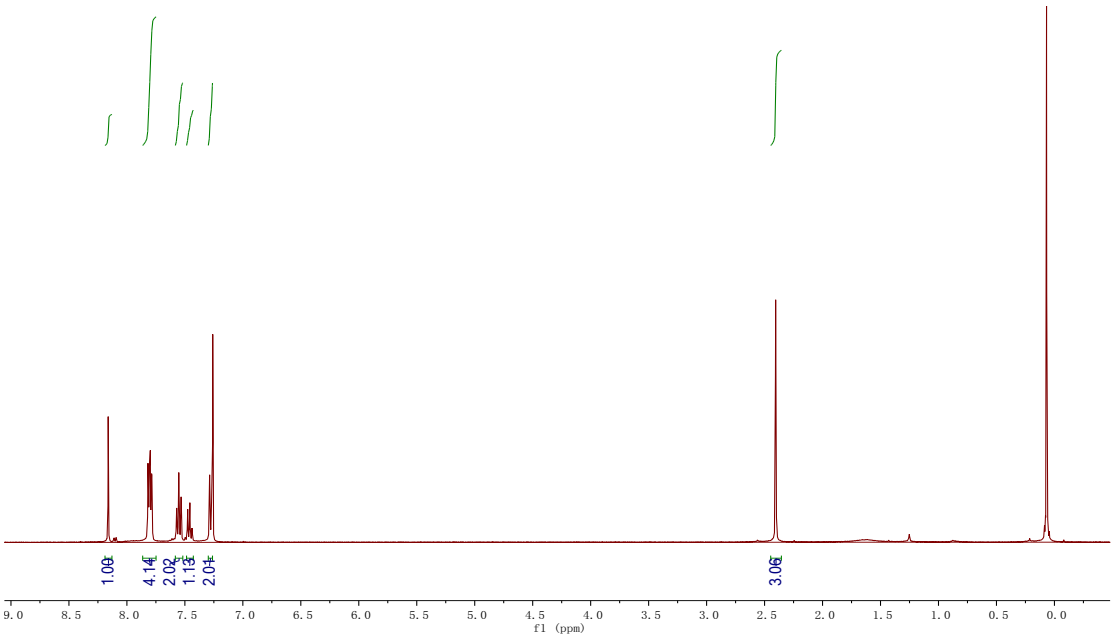
4-(4-bromophenyl)-1-phenyl-1H-1,2,3-triazole (**3o**): White solid; ^{1}H NMR (400 MHz, DMSO) δ 9.39 (s, 1H), 7.94 (dd, *J* = 16.4, 8.0 Hz, 4H), 7.73 (d, *J* = 8.5 Hz, 2H), 7.65 (t, *J* = 7.9 Hz, 2H), 7.54 (t, *J* = 7.4 Hz, 1H); ^{13}C NMR (101 MHz, DMSO) δ 146.27, 136.57, 131.99, 129.96, 129.48, 128.83, 127.27, 121.25, 120.02; HRMS (ESI) m/z calcd for $C_{14}H_{10}N_3Br$ $[M+H]^+$ 300.0038, found 300.0064.

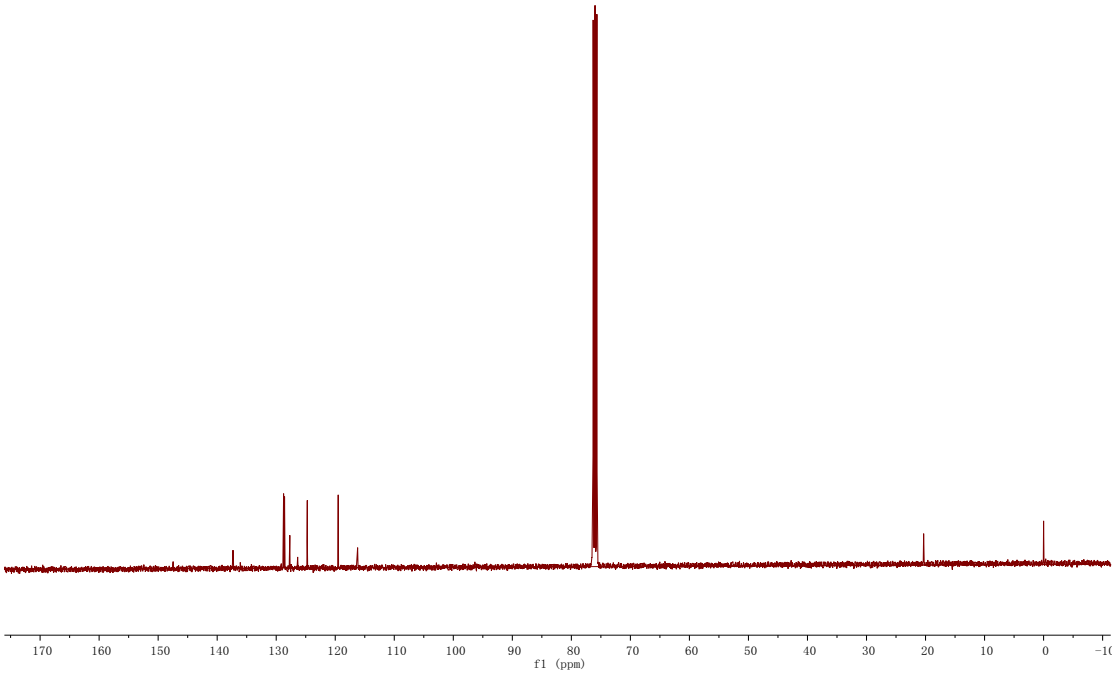


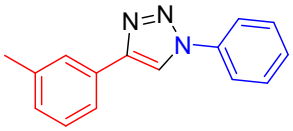




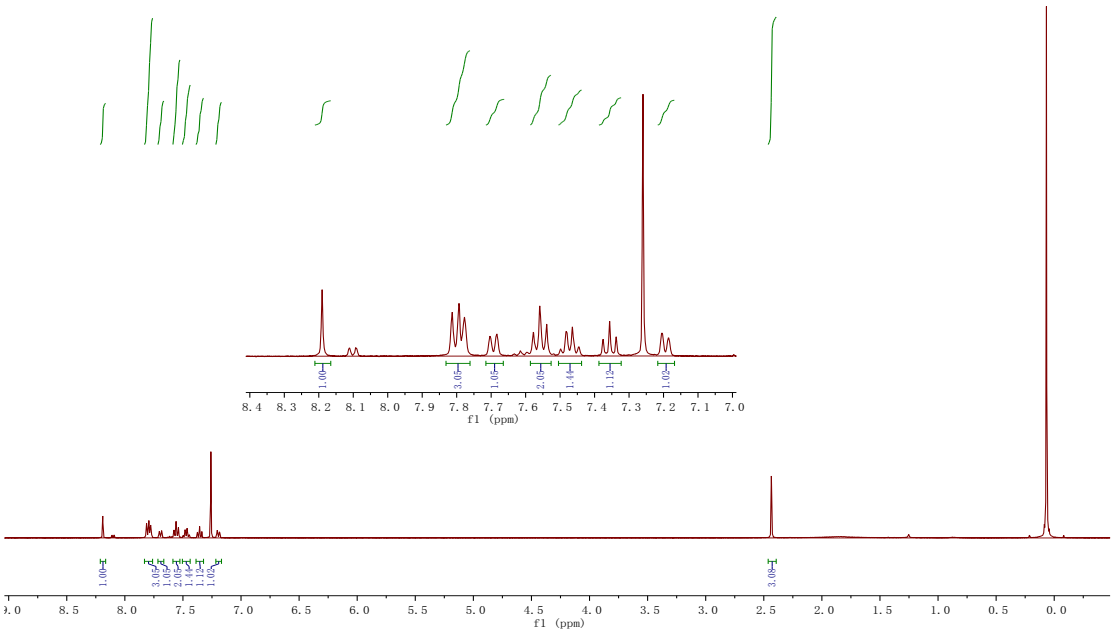
1-phenyl-4-p-tolyl-1H-1,2,3-triazole (**3p**): White solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 (s, 1H), 7.86–7.75 (m, 4H), 7.56 (dd, *J* = 10.5, 5.0 Hz, 2H), 7.46 (dd, *J* = 10.6, 4.3 Hz, 1H), 7.30–7.26 (m, 2H), 2.40 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 147.46, 137.32, 136.09, 128.75, 128.59, 127.69, 126.37, 124.73, 119.50, 116.21, 20.32; HRMS (ESI) m/z calcd for $C_{15}H_{13}N_3$ $[M+H]^+$ 236.1143, found 236.1175.

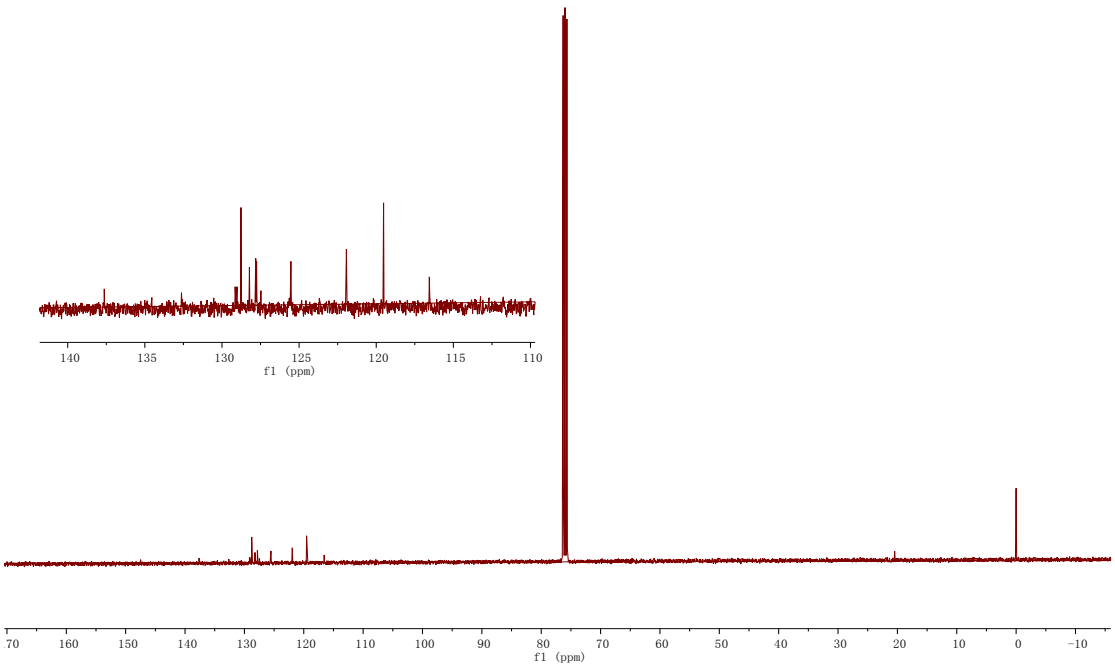


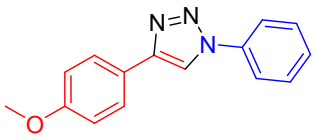




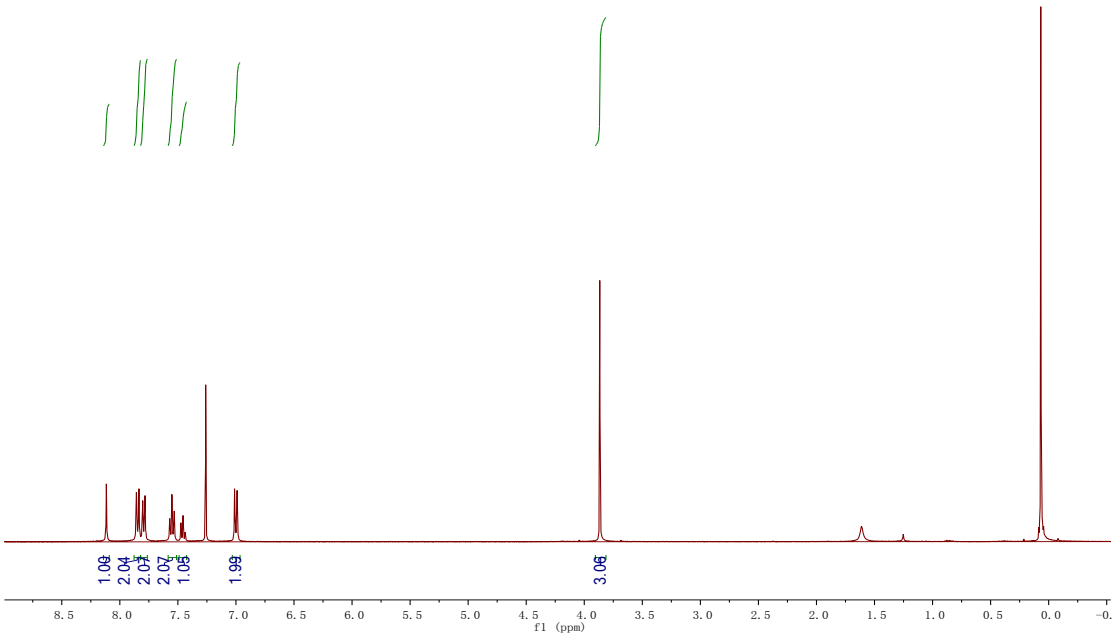
1-phenyl-4-m-tolyl-1H-1,2,3-triazole (**3q**): White solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 (s, 1H), 7.83–7.76 (m, 3H), 7.69 (d, *J* = 7.8 Hz, 1H), 7.56 (t, *J* = 7.8 Hz, 2H), 7.50–7.44 (m, 1H), 7.36 (t, *J* = 7.6 Hz, 1H), 7.20 (d, *J* = 7.5 Hz, 1H), 2.43 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 137.63, 134.56, 132.62, 128.77, 128.22, 127.81, 127.76, 125.53, 121.93, 119.52, 116.56, 20.46; HRMS (ESI) m/z calcd for $C_{15}H_{13}N_3$ $[M+H]^+$ 236.1143, found 236.1164.

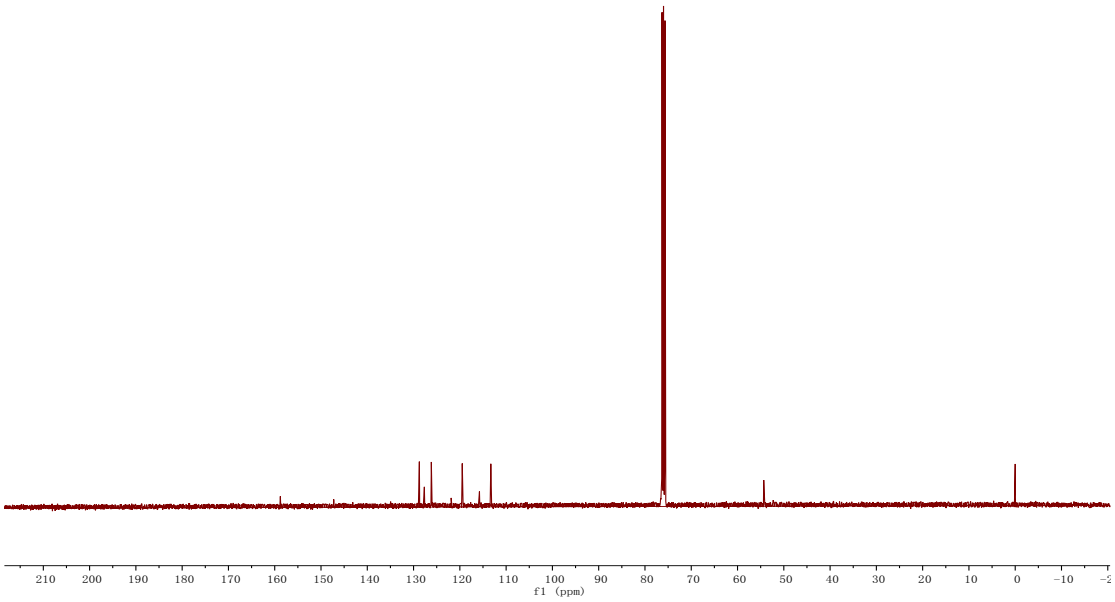


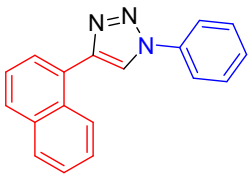




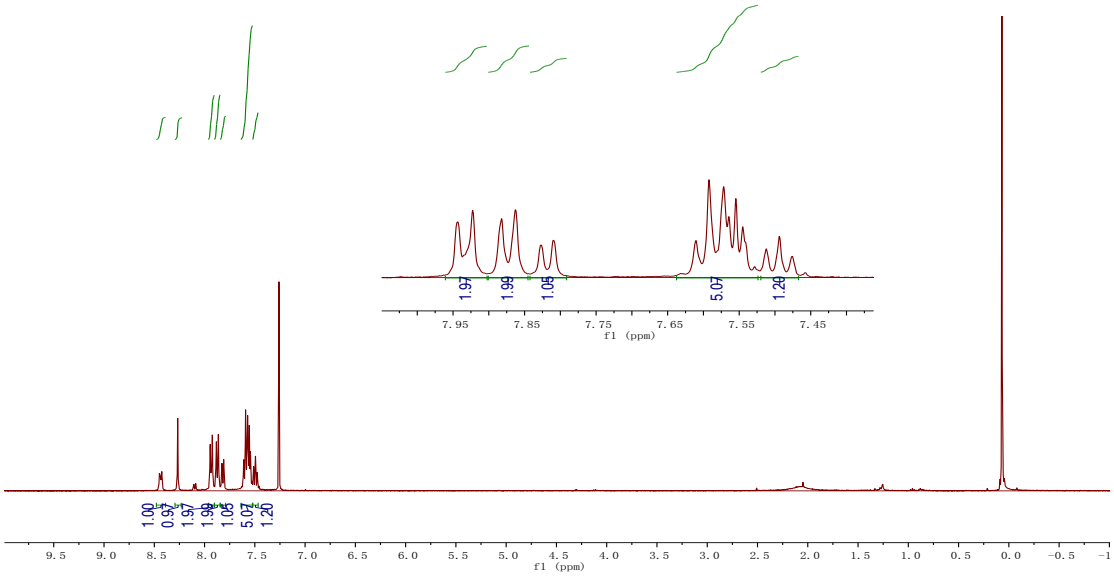
4-(4-methoxyphenyl)-1-phenyl-1H-1,2,3-triazole (**3s**): White solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 (s, 1H), 7.85 (d, *J* = 8.7 Hz, 2H), 7.79 (d, *J* = 7.9 Hz, 2H), 7.55 (t, *J* = 7.8 Hz, 2H), 7.46 (t, *J* = 7.4 Hz, 1H), 7.00 (d, *J* = 8.7 Hz, 2H), 3.87 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.78, 147.25, 134.95, 128.75, 127.67, 126.16, 121.88, 119.48 , 115.76, 113.31, 54.34; HRMS (ESI) m/z calcd for $C_{15}H_{13}N_3O$ $[M+H]^+$ 252.1092, found 252.1104.

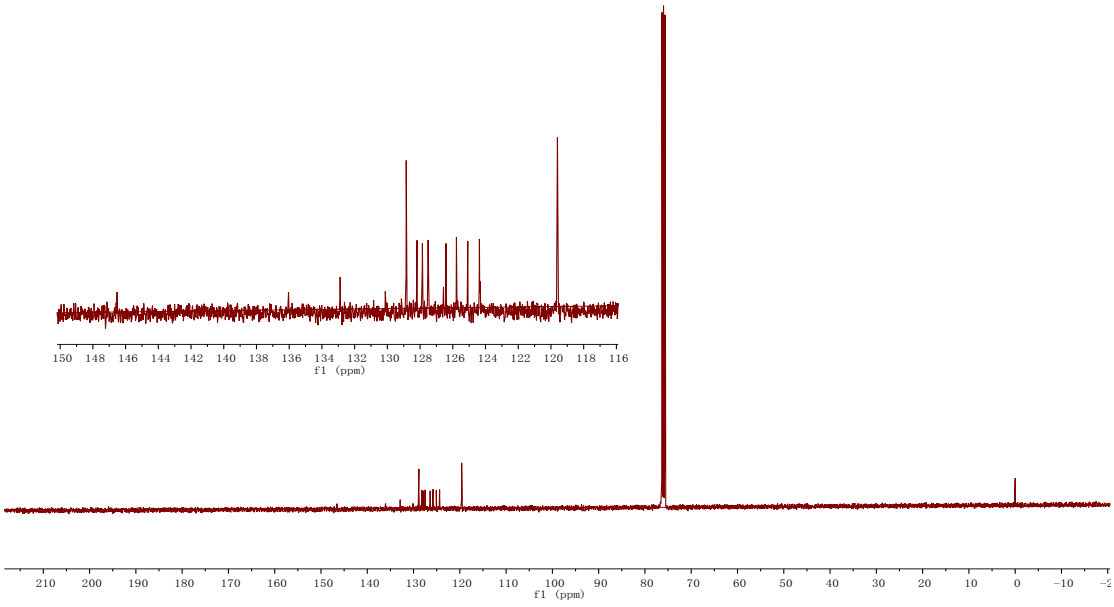


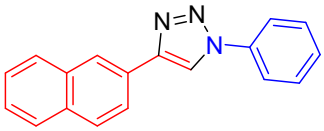




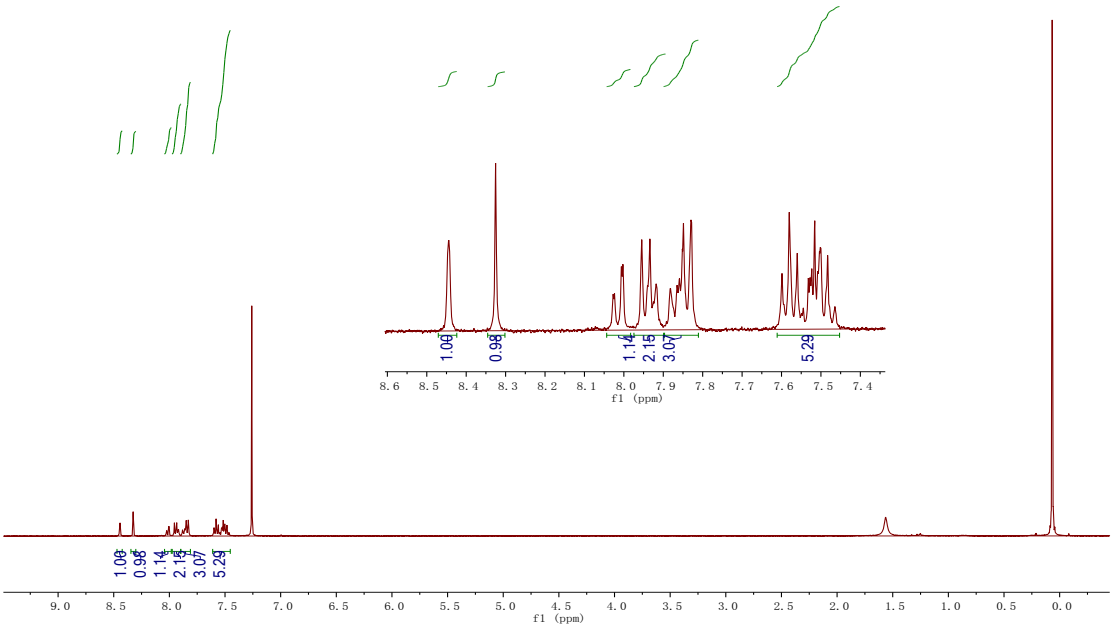
4-(naphthalen-1-yl)-1-phenyl-1H-1,2,3-triazole (**3t**): brown yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.44 (d, *J* = 9.4 Hz, 1H), 8.27 (s, 1H), 7.93 (d, *J* = 8.5 Hz, 2H), 7.87 (d, *J* = 7.8 Hz, 2H), 7.82 (d, *J* = 7.0 Hz, 1H), 7.64–7.52 (m, 5H), 7.49 (t, *J* = 7.2 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 146.58, 136.02, 132.89, 130.13, 128.85, 128.19, 127.86, 127.51, 126.57, 126.42, 125.78, 125.09, 124.37, 124.33, 119.60; HRMS (ESI) m/z calcd for $C_{18}H_{13}N_3$ $[M+H]^+$ 272.1143, found 272.1154.

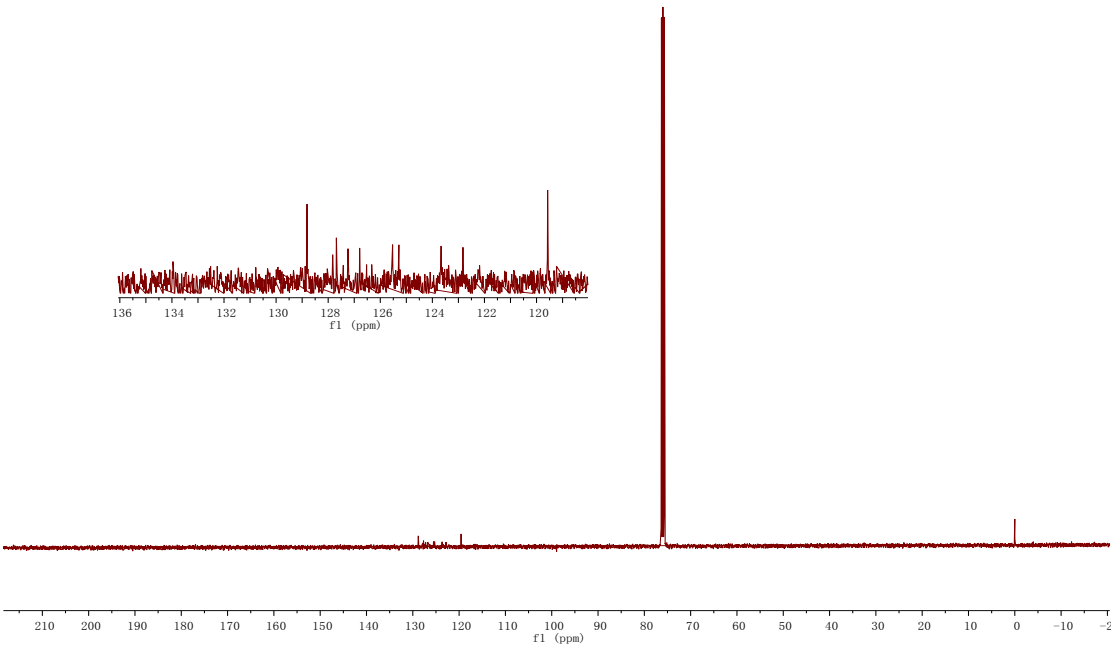


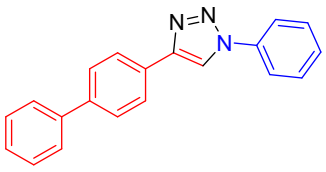




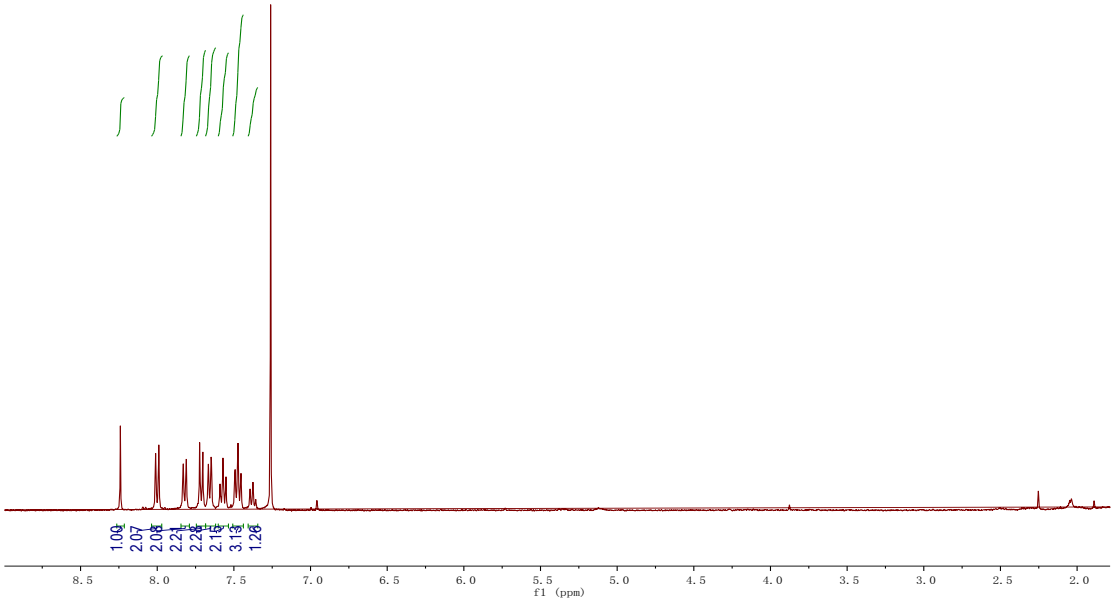
4-(naphthalen-2-yl)-1-phenyl-1H-1,2,3-triazole (**3u**): light brown yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.44 (s, 1H), 8.33 (s, 1H), 8.04–7.98 (m, 1H), 7.97–7.90 (m, 2H), 7.90–7.81 (m, 3H), 7.61–7.45 (m, 5H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 133.95, 132.53, 132.24, 128.81, 127.83, 127.68, 127.24, 126.79, 126.52, 125.53, 125.29, 123.66, 122.82, 119.57; HRMS (ESI) m/z calcd for $C_{18}H_{13}N_3$ $[M+H]^+$ 272.1143, found 272.1147.

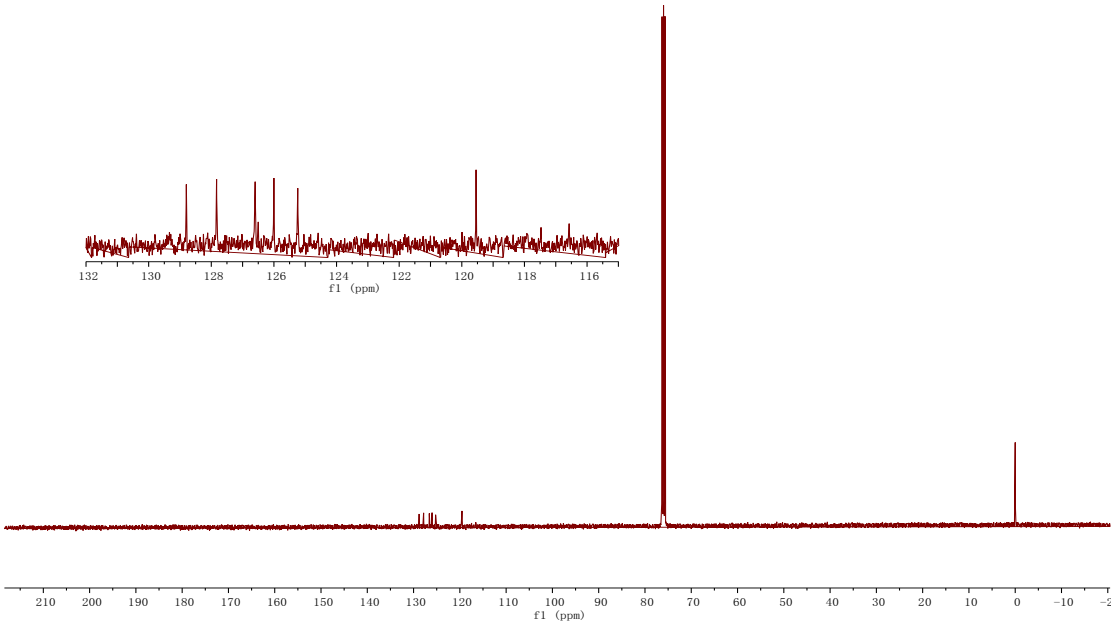


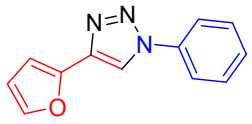




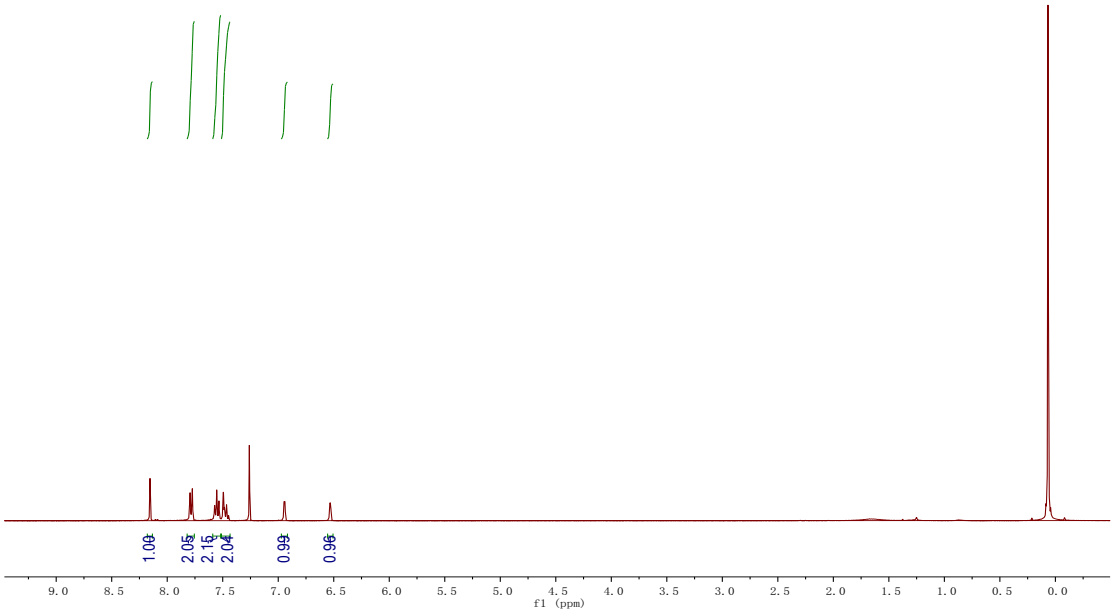
4-(biphenyl-4-yl)-1-phenyl-1H-1,2,3-triazole (**3v**): White solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24 (s, 1H), 8.00 (d, *J* = 8.3 Hz, 2H), 7.82 (d, *J* = 7.8 Hz, 2H), 7.71 (d, *J* = 8.3 Hz, 2H), 7.66 (d, *J* = 7.2 Hz, 2H), 7.57 (t, *J* = 7.8 Hz, 2H), 7.47 (t, *J* = 7.7 Hz, 3H), 7.38 (t, *J* = 7.4 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 128.80, 127.83, 127.82, 126.00, 126.50, 126.00, 125.24, 119.54, 117.48, 116.57; HRMS (ESI) m/z calcd for $C_{18}H_{13}N_3$ $[M+H]^+$ 298.1300, found 298.1327.

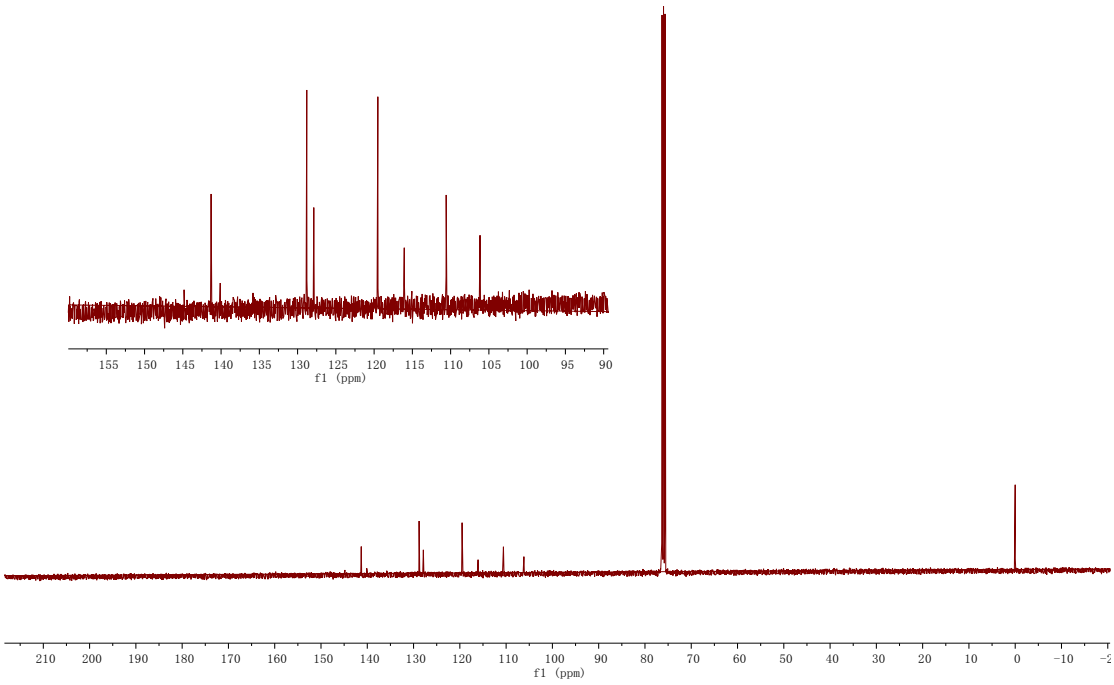


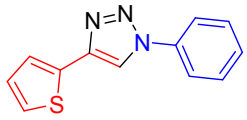




4-(furan-2-yl)-1-phenyl-1H-1,2,3-triazole (**3w**): White solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 (s, 1H), 7.78 (d, *J* = 8.1 Hz, 2H), 7.55 (t, *J* = 7.7 Hz, 2H), 7.47 (dd, *J* = 13.3, 5.7 Hz, 2H), 6.94 (d, *J* = 3.3 Hz, 1H), 6.53 (dd, *J* = 3.2, 1.7 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 144.83, 141.30, 140.11, 135.82, 128.80, 127.88, 119.51, 116.06, 110.58, 106.16; HRMS (ESI) m/z calcd for $C_{12}H_9N_3O$ $[M+H]^+$ 212.0779, found 212.0787.







1-phenyl-4-(thiophen-2-yl)-1H-1,2,3-triazole (**3x**): White solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 (s, 1H), 7.78 (d, *J* = 7.9 Hz, 2H), 7.55 (t, *J* = 7.7 Hz, 2H), 7.47 (dd, *J* = 12.5, 5.0 Hz, 2H), 7.35 (dd, *J* = 5.1, 0.9 Hz, 1H), 7.12 (dd, *J* = 5.0, 3.6 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 142.91, 135.86, 131.42, 128.79, 127.89, 126.72, 124.39, 123.55, 119.54, 116.07; HRMS (ESI) m/z calcd for $C_{12}H_9N_3S$ $[M+H]^+$ 228.0551, found 228.0583.