Electronic Supplementary Material (ESI) for Organic Chemistry Frontiers.

Supporting Information

Metal-free 1,3-dipolar cyclization of azides with HFO-1233zd(*E*) under amines participation: one-step regioselective synthesis of 1-*N*-substituted 1,2,3-triazole-4-carboxamide derivatives

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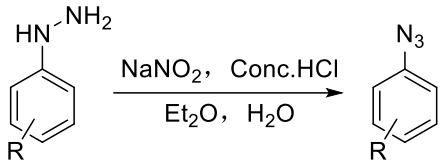
1. Experimental

General. All reactions were carried out in test tube under air atmosphere. Chemicals were purchased from commercial suppliers and used without further purification. Purification of reaction products were carried out by chromatography using silica gel (200-300 mesh). High resolution MS data were recorded on Agilent 6200 Series TOF spectrometer. NMR spectra were recorded on AVIII for ^{1}H NMR at 500/400 MHz and for ^{13}C NMR at 125/100 MHz. For ^{1}H NMR, tetramethylsilane (TMS) was served as internal standard (δ). The spectra data presented here are reported as follows: chemical shift, integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), and coupling constant(s) in Hertz. For ^{13}C NMR TMS was used as internal standard and spectra were obtained with complete proton decoupling.

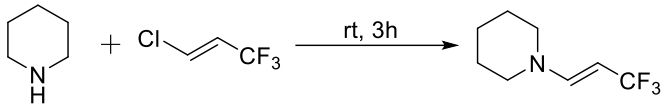
General procedure for the synthesis of aryl azide 1



S1 **1**

S1 (97%, 1.91 mL, 18.8 mmol) was dissolved in water (19 mL) and concentrated hydrochloric acid (3.44 mL) followed by the addition of ether (24 mL) and subsequently the temperature of the reaction system was controlled at zero degrees. A solution of $NaNO_2$ (1.56 g, 22.6 mmol) dissolved in water (2 mL) was slowly dropped into the above system via syringe over 30 mins with vigorous stirring, controlling the internal temperature below 5°C. Stir the solution for 1 hour. The reaction solution was filtered and the aqueous layer was washed with ether (3 x 80 mL), followed by washing the combined ether layers with brine (80 mL). The organic layer was concentrated by drying with sodium sulfate and purified by silica gel chromatography (pure petroleum ether) to give a light-yellow oil **1** (Note: Azides poses an explosion risk).

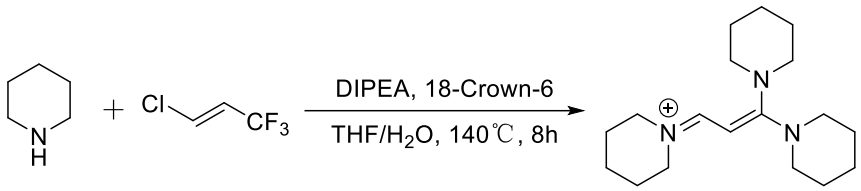
General procedure for the synthesis of (*E*)-1-(3,3,3-trifluoroprop-1-en-1-yl) piperidine A



2a **3** **A**

3 (2.63g, 20.2 mmol) was added to **2a** (6.88g, 80.8 mmol) under ice bath conditions, followed by stirring at room temperature for 3 hours. The white solid was filtered and the resulting filtrate was distilled under reduced pressure to give **A**.

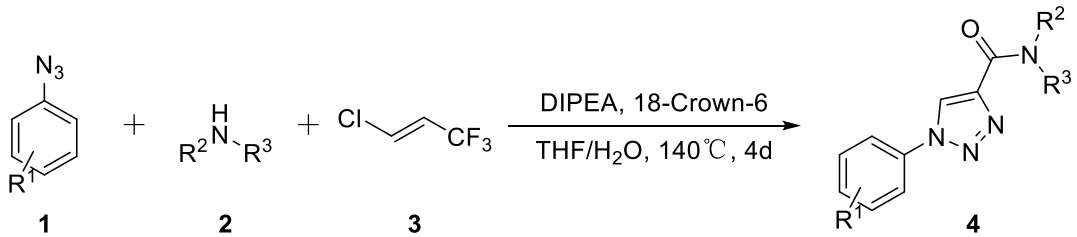
General procedure for the synthesis of 1-(3,3-di(piperidin-1-yl) allylidene) piperidin-1-ium C



2a **3** **C**

Add **2a** (5.0 mmol), DIPEA (3.0 mmol), 18-crown-6 (1.0 mmol) and THF/H_2O=3:1 (2.0 mL) to the Schlenk tube at room temperature. Subsequently trans-1-chloro-3,3,3-trifluoropropene (HFO-1233zd (*E*)) **3** (2.0 mL) was added to the mixture and the resulting mixture was stirred at 140ºC for 8 hours. The reaction was cooled to room temperature, evaporated under vacuo. The residue was purified by flash column chromatography (dichloromethane: methanol=10:1) on silica gel to give the desired products **C**.

General procedure for the synthesis of target compounds 4

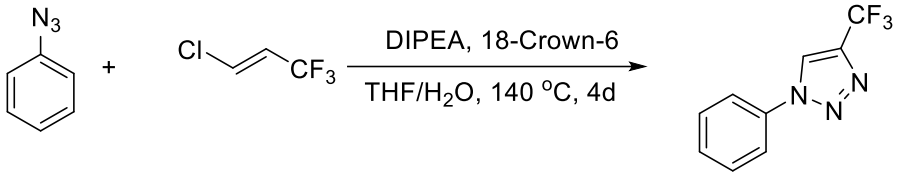


1 **2** **3** **4**

Add azobenzenes **1** (1.0 mmol), amines **2** (5.0 mmol), DIPEA (3.0 mmol), 18-crown-6

(1.0 mmol) and THF/H_2O=3:1 (2.0 mL) to the Schlenk tube at room temperature. Subsequently trans-1-chloro-3,3,3-trifluoropropene (HFO-1233zd (*E*)) **3** (2.0 mL) was added to the mixture and the resulting mixture was stirred at 140ºC for 4 days. The reaction was cooled to room temperature, evaporated under vacuo. The residue was purified by flash column chromatography (petroleum ether: ethyl acetate=10:3) on silica gel to give the desired products **4**.

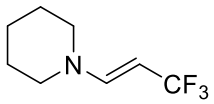
General procedure for the synthesis of target compound 5



1a **3** **5**

Add azobenzenes **1a** (1.0 mmol), DIPEA (3.0 mmol), 18-crown-6 (1.0 mmol) and THF/H_2O=3:1 (2.0 mL) to the Schlenk tube at room temperature. Subsequently trans-1-chloro-3,3,3-trifluoropropene (HFO-1233zd (*E*)) **3** (2.0 mL) was added to the mixture and the resulting mixture was stirred at 140ºC for 4 days. The reaction was cooled to room temperature, evaporated under vacuo. The residue was purified by flash column chromatography (petroleum ether: ethyl acetate=10:3) on silica gel to give the desired products **5**.

Characterization data for A

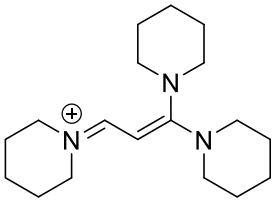


(*E*)-1-(3,3,3-trifluoroprop-1-en-1-yl) piperidine (**A**)

Yellow liquid, yield:3.5g, 98%.

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.62 (dd, J = 13.6, 1.4 Hz, 1H), 4.28 (dq, J = 13.1, 6.4 Hz, 1H), 3.01 (s, 4H), 2.79 (s, 2H), 1.84 (s, 1H), 1.53 – 1.50 (m, 3H).

Characterization data for C

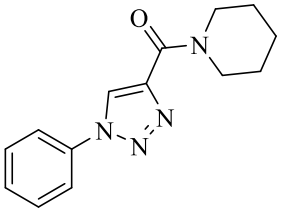


1-(3,3-di(piperidin-1-yl) allylidene) piperidin-1-ium (**C**)

Yellow liquid, yield:200mg, 82%

^{1}H NMR (400 MHz, $CDCl_3$) δ 11.13 (s, 1H), 8.03 (d, J = 12.4 Hz, 1H), 4.42 (d, J = 12.4 Hz, 1H), 3.71 – 3.62 (m, 2H), 3.53 (d, J = 3.2 Hz, 2H), 3.38 (s, 1H), 3.11 (qd, J = 7.4, 4.3 Hz, 2H), 1.93 (s, 3H), 1.76 – 1.67 (m, 6H), 1.59 – 1.54 (m, 8H), 1.46 (d, J = 6.8 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.7, 156.8, 80.8, 42.0, 26.2, 24.0, 18.7, 17.4, 12.1; HRMS calcd for $C_{18}H_{32}N_3^+$: 290.2591, found:290.2598.

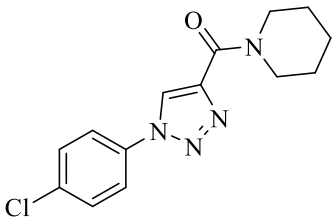
Characterization data for target compounds 4



(1-phenyl-1H-1,2,3-triazol-4-yl) (piperidin-1-yl) methanone (**4a**)

White solid, yield:174mg, 68%, m.p.: 144.7-145.5 °C.

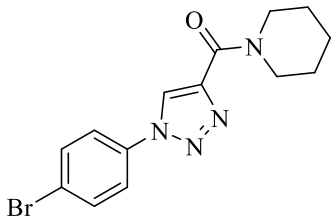
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.48 (s, 1H), 7.77 – 7.75 (m, 2H), 7.57-7.53 (m, 2H), 7.49-7.46 (m, 1H), 4.19 (d, J = 5.2 Hz, 2H), 3.75 (t, J = 4.8 Hz, 2H), 1.72 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.6, 145.30, 136.6, 129.9, 129.2, 126.0, 120.7, 48.0, 44.0, 26.8, 25.8, 24.7; HRMS calcd for $C_{14}H_{16}N_4O$+H^+: 257.1397, found: 257.1394.



(1-(4-chlorophenyl)-1H-1,2,3-triazol-4-yl) (piperidin-1-yl) methanone (**4b**)

White solid, yield:151mg, 52%, m.p.: 215.9-216.5 °C.

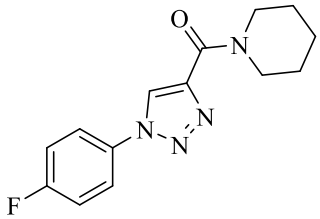
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.47 (s, 1H), 7.71 (d, J = 8.8 Hz, 2H), 7.52 (d, J = 8.8 Hz, 2H), 4.17 (s, 2H), 3.74 (s, 2H), 1.71 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.4, 145.5, 135.1, 135.1, 130.1, 126.0, 121.8, 48.0, 44.0, 26.8, 25.8, 24.7; HRMS calcd for $C_{14}H_{15}ClN_4O+H^+$: 291.1007, found: 291.1005.



(1-(4-bromophenyl)-1H-1,2,3-triazol-4-yl) (piperidin-1-yl) methanone (**4c**)

White solid, yield: 241mg, 72%, m.p.: 223.0-223.6 °C.

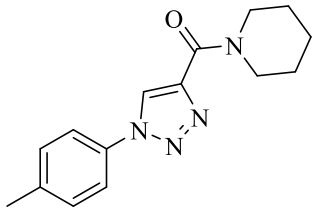
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.47 (s, 1H), 7.70 – 7.67 (m, 2H), 7.66 – 7.64 (m, 2H), 4.17 (d, J = 5.6 Hz, 2H), 3.74(t, J = 4.8 Hz, 2H), 1.71 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.4, 145.6, 135.6, 133.1, 125.9, 123.0, 122.0, 48.0, 44.0, 26.8, 25.8, 24.7; HRMS calcd for $C_{14}H_{15}BrN_4O+H^+$: 335.0502, found: 335.0505.



(1-(4-fluorophenyl)-1H-1,2,3-triazol-4-yl) (piperidin-1-yl) methanone (**4d**)

White solid, yield:140mg, 51%, m.p.: 128.6-129.4 °C.

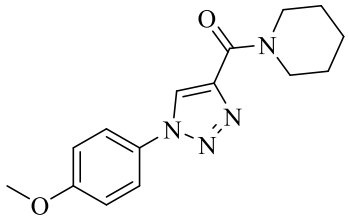
^{1}H NMR (500 MHz, $CDCl_3$): δ 8.44 (s, 1H), 7.75-7.72 (m, 2H), 7.26-7.23 (m, 2H), 4.18 (d, J = 4.5 Hz, 2H), 3.75 (d, J = 5.5 Hz, 2H), 1.71 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 163.7, 161.7, 159.5, 145.5, 126.2, 122.7 (122.72, 122.65, d, J = 8.8 Hz), 116.9 (117.0, 116.8, d, J = 22.5 Hz), 48.0, 44.0, 26.8, 25.8, 24.7; HRMS calcd for $C_{14}H_{15}FN_4O+H^+$: 275.1303, found: 275.1306.



piperidin-1-yl(1-(p-tolyl)-1H-1,2,3-triazol-4-yl) methanone (**4e**)

White solid, yield: 95mg, 35%, m.p.: 184.3-184.9 °C.

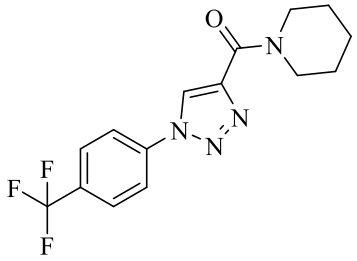
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.43 (s, 1H), 7.62 (d, J = 8.4 Hz, 2H), 7.33 (d, J = 8.0 Hz, 2H), 4.19 (d, J = 5.2 Hz, 2H), 3.75 (d, J = 5.2 Hz, 2H), 2.43 (s, 3H), 1.71 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.7, 145.2, 139.4, 134.3, 130.4, 126.0, 120.6, 48.0, 43.9, 26.8, 25.8, 24.7, 21.1; HRMS calcd for $C_{15}H_{18}N_4O+H^+$: 271.1553, found: 271.1557.



(1-(4-methoxyphenyl)-1H-1,2,3-triazol-4-yl) (piperidin-1-yl) methanone (**4f**)

White solid, yield:94mg, 33%, m.p.: 171.6-172.3 °C.

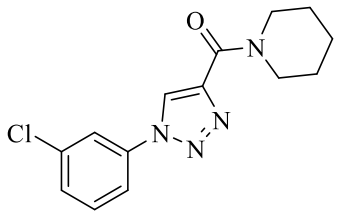
^{1}H NMR (500 MHz, $CDCl_3$): δ 8.39 (s, 1H), 7.65 (d, J = 9.0 Hz, 2H), 7.04 (d, J = 9.0 Hz, 2H), 4.19 (s, 2H), 3.88 (s, 3H), 3.75 (d, J = 5.0 Hz, 2H), 1.72 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 160.2, 147.7, 145.1, 130.0, 126.1, 122.3, 115.0, 55.7, 48.0, 44.0, 26.8, 25.8, 24.7; HRMS calcd for $C_{15}H_{18}N_4O_2+H^+$: 287.1503, found: 287.1501.



piperidin-1-yl(1-(4-(trifluoromethyl) phenyl)-1H-1,2,3-triazol-4-yl) methanone (**4g**)

White solid, yield:175mg, 54%, m.p.: 213.1-213.7 °C.

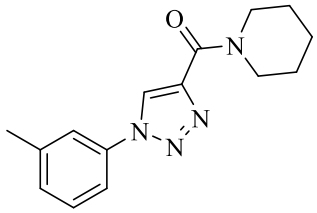
^{1}H NMR (500 MHz, $CDCl_3$): δ 8.56 (s, 1H), 7.93 (d, J = 8.5 Hz, 2H), 7.83 (d, J = 8.5 Hz, 2H), 4.18 (d, J = 5.5 Hz, 2H), 3.75 (d, J = 5.0 Hz, 2H), 1.72 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 159.3, 145.8, 139.0, 131.4, 131.2, 127.3 (127.33, 127.30, 127.27, 127.24, q, J = 3.8 Hz), 126.0, 124.5, 122.4, 120.7, 48.0, 44.0, 26.8, 25.8, 24.6; HRMS calcd for $C_{15}H_{15}F_3N_4O$+H^+: 325.1271, found: 325.1274.



(1-(3-chlorophenyl)-1H-1,2,3-triazol-4-yl) (piperidin-1-yl) methanone (**4h**)

White solid, yield:125mg, 43%, m.p.: 132.0-132.6 °C.

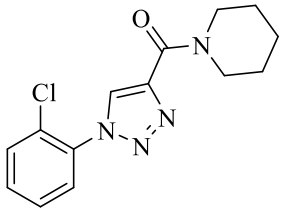
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.48 (s, 1H), 7.83 (t, J = 2.0 Hz, 1H), 7.65 (dt, J = 7.2, 1.8 Hz, 1H), 7.51-7.44 (m, 2H), 4.17 (d, J = 5.2 Hz, 2H), 3.74 (t, J = 1.2 Hz, 2H), 1.72 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.4, 145.6, 137.5, 135.8, 131.0, 129.3, 126.0, 121.0, 118.6, 48.0, 44.0, 26.8, 25.8, 24.7; HRMS calcd for $C_{14}H_{15}ClN_4O$ +H^+: 291.1007, found: 291.1005.



piperidin-1-yl(1-(m-tolyl)-1H-1,2,3-triazol-4-yl) methanone (**4i**)

White solid, yield: 46mg, 17%, m.p.: 119.7-121.1 °C.

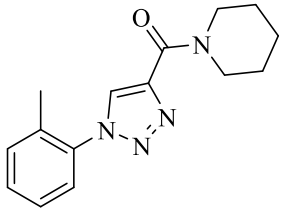
^{1}H NMR (500 MHz, $CDCl_3$): δ 8.45 (s, 1H), 7.58 (s, 1H), 7.52 (d, J = 8.0 Hz, 1H), 7.41 (t, J = 8.0 Hz, 1H), 7.28 (d, J = 7.5 Hz, 1H), 4.19 (d, J = 5.0 Hz, 2H), 3.74 (d, J = 5.0 Hz, 2H), 2.46 (s, 3H), 1.72 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 159.7, 145.2, 140.2, 136.6, 130.0, 129.7, 126.1, 121.3, 117.7, 48.0, 43.9, 26.8, 25.8, 24.7, 21.4; HRMS calcd for $C_{15}H_{18}N_4O$+H^+: 271.1553, found: 271.1557.



(1-(2-chlorophenyl)-1H-1,2,3-triazol-4-yl) (piperidin-1-yl) methanone (**4j**)

White solid, yield: 73mg, 25%, m.p.: 114.5-115.2 °C.

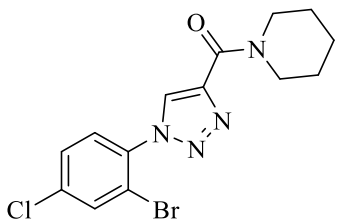
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.46 (s, 1H), 7.63-7.59 (m, 2H), 7.51– 7.44 (m, 2H), 4.20 (s, 2H), 3.75 (t, J = 4.8 Hz, 2H), 1.72 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 159.5, 144.5, 134.5, 131.1, 130.9, 130.0, 128.9, 128.0, 127.7, 48.0, 44.0, 26.8, 25.8, 24.7; HRMS calcd for $C_{14}H_{15}ClN_4O+H^+$: 291.1007, found: 291.1005.



piperidin-1-yl(1-(o-tolyl)-1H-1,2,3-triazol-4-yl) methanone (**4k**)

White solid, yield: 51mg, 19%, m.p.: 111.3-112.0 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.24 (s, 1H), 7.45 – 7.42 (m, 1H), 7.39 (d, J = 7.5 Hz, 1H), 7.35 – 7.33 (m, 2H), 4.24 (s, 2H), 3.75 (t, J = 5.0 Hz, 2H), 2.24 (s, 3H), 1.73 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 159.7, 144.6, 136.0, 133.7, 131.6, 130.2, 129.6, 127.0, 125.9, 48.0, 44.0, 26.8, 25.8, 24.7, 17.9; HRMS calcd for $C_{15}H_{18}N_4O+H^+$: 271.1553, found: 271.1557.

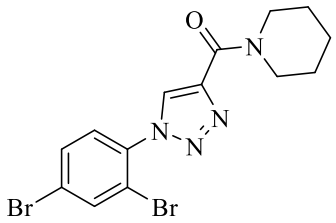


(1-(2-bromo-4-chlorophenyl)-1H-1,2,3-triazol-4-yl) (piperidin-1-yl) methanone (**4l**)

White solid, yield:291mg, 79%, m.p.: 114.8-115.3 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.42 (s, 1H), 7.79 (t, J = 1.2 Hz, 1H), 7.50 (d, J = 1.2

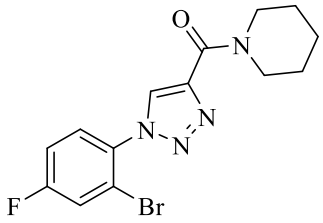
Hz, 2H), 4.20 (d, J = 4.8 Hz, 2H), 3.75 (t, J = 5.0 Hz, 2H), 1.73 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.4, 144.7, 137.0, 134.8, 133.7, 130.0, 128.9, 128.7, 119.3, 48.0, 44.0, 26.8, 25.8, 24.7; HRMS calcd for $C_{14}H_{14}BrClN_4O+H^+$: 369.0112, found: 369.0114.



(1-(2,4-dibromophenyl)-1H-1,2,3-triazol-4-yl) (piperidin-1-yl) methanone (**4m**)

White solid, yield:152mg, 77%, m.p.: 130.2-131.0 °C.

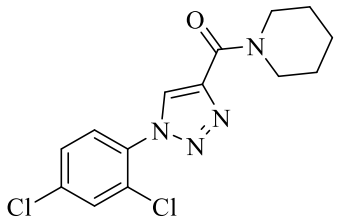
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.42 (s, 1H), 7.94 (d, J = 2.4 Hz, 1H), 7.64 (dd, J = 8.4, 2.0 Hz, 1H), 7.43 (d, J = 8.4 Hz, 1H), 4.19 (s, 2H), 3.74 (t, J = 4.8 Hz, 2H), 1.72 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.3, 144.7, 136.5, 135.2, 131.9, 130.0, 129.0, 124.8, 119.4, 48.0, 44.0, 26.8, 25.8, 24.7; HRMS calcd for $C_{14}H_{14}Br_2N_4O+H^+$: 412.9607, found: 412.9609.



(1-(2-bromo-4-fluorophenyl)-1H-1,2,3-triazol-4-yl) (piperidin-1-yl) methanone (**4n**)

White solid, yield:162mg, 86%, m.p.: 97.5-98.0 °C.

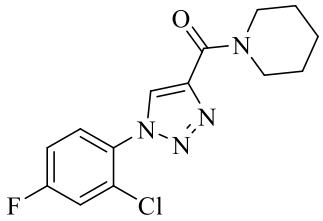
^{1}H NMR (500 MHz, $CDCl_3$): δ 8.38 (s, 1H), 7.56 – 7.51 (m, 2H), 7.25 – 7.21 (m, 1H), 4.20 (s, 2H), 3.77 – 3.75 (t, J = 5.0 Hz, 2H), 1.73 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 163.9, 161.8, 159.4, 144.6, 130.2, 129.4 (129.39, 129.31, d, J = 10.0 Hz), 121.3 (121.41, 121.21, d, J = 25.0 Hz), 119.8 (119.84, 119.76, d, J = 10.0 Hz), 115.9 (115.95, 115.77, d, J = 22.5 Hz), 48.0, 44.0, 26.8, 25.8, 24.7; HRMS calcd for $C_{14}H_{14}BrFN_4O+H^+$: 353.0408, found: 353.0406.



(1-(2,4-dichlorophenyl)-1H-1,2,3-triazol-4-yl) (piperidin-1-yl) methanone (**4o**)

White solid, yield:71mg, 62%, m.p.: 135.8-136.3 °C.

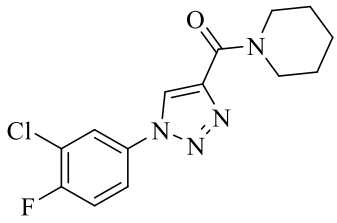
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.45 (s, 1H), 7.62 (d, J = 2.0 Hz, 1H), 7.57 (d, J = 8.4 Hz, 1H), 7.45 (dd, J = 8.4, 2.4 Hz, 1H), 4.18 (s, 2H), 3.75 (t, J = 4.6 Hz, 2H), 1.73 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.3, 144.7, 136.7, 133.1, 130.8, 129.9, 129.6, 128.4, 100.0, 48.0, 44.0, 26.8, 25.8, 24.7; HRMS calcd for $C_{14}H_{14}Cl_2N_4O+H^+$: 325.0617, found: 325.0618.



(1-(2-chloro-4-fluorophenyl)-1H-1,2,3-triazol-4-yl) (piperidin-1-yl) methanone (**4p**)

White solid, yield:117mg, 78%, m.p.: 141.3-141.8 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.42 (s, 1H), 7.60 (dd, J = 8.8, 5.2 Hz, 1H), 7.35 (dd, J = 8.0, 2.8 Hz, 1H), 7.21 -7.16 (m, 1H), 4.19 (s, 2H), 3.74 (t, J = 4.6 Hz, 2H), 1.72 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.1, 161.6, 159.4, 144.7, 130.4 (130.46, 130.35, d, J = 11.0 Hz), 130.1, 129.1 (129.13, 129.04, d, J = 9.0 Hz), 118.4 (118.40, 118.14, d, J = 26.0 Hz), 115.4 (115.52, 115.29, d, J = 23.0 Hz), 48.0, 44.0, 26.8, 25.8, 24.7; HRMS calcd for $C_{14}H_{14}ClFN_4O+H^+$: 309.0913, found: 309.0911.

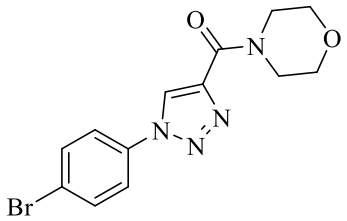


(1-(3-chloro-4-fluorophenyl)-1H-1,2,3-triazol-4-yl) (piperidin-1-yl) methanone (**4q**)

White solid, yield:293mg, 95%, m.p.: 163.4-164.1 °C.

For the gram-scale reaction of 4-azido-2-chloro-1-fluorobenzene (**1q**, 1 g, 5.85 mmol), HFO-1233zd (*E*) and piperidine under the standard reaction condition afforded product **4q** in 70% yield.

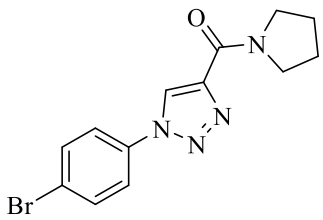
^{1}H NMR (500 MHz, $CDCl_3$): δ 8.45 (s, 1H), 7.89 (dd, J = 6.5, 3.0 Hz, 1H), 7.65 – 7.62 (m, 1H), 7.33 (t, J = 8.5 Hz, 1H), 4.17 (d, J = 5.0 Hz, 2H), 3.74 (t, J = 5.0 Hz, 2H), 1.72 (t, J = 8.5 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 159.3, 157.3, 145.7, 133.1, 126.1, 123.3, 122.8 (122.91, 122.76, d, J = 18.8 Hz), 120.4 (120.43, 120.37, d, J = 7.5 Hz), 117.8 (117.91, 117.72, d, J = 23.8 Hz), 48.0, 44.0, 26.8, 25.8, 24.6; HRMS calcd for $C_{14}H_{14}ClFN_4O+H^+$: 309.0913, found: 309.0911.



(1-(4-bromophenyl)-1H-1,2,3-triazol-4-yl) (morpholino)methanone (**4r**)

White solid, yield:239mg, 71%, m.p.: 213.4-214.1 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.52 (s, 1H), 7.71 – 7.68 (m, 2H), 7.66 – 7.64 (m, 2H), 4.40 – 4.38 (m, 2H), 3.81 (d, J = 8.8 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.4, 145.1, 135.4, 133.2, 126.4, 123.2, 122.1 67.3, 66.9, 47.4, 43.2; HRMS calcd for $C_{13}H_{13}BrN_4O_2+H^+$: 337.0295, found: 337.0294.

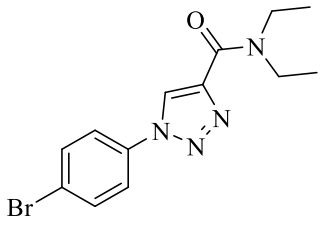


(1-(4-bromophenyl)-1H-1,2,3-triazol-4-yl) (pyrrolidin-1-yl) methanone (**4s**)

White solid, yield:163mg, 51%, m.p.: 218.6-219.3 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.55 (s, 1H), 7.70 -7.65 (m, 4H), 4.16 (t, J = 7.0 Hz, 2H), 3.70 (t, J = 7.0 Hz, 2H), 2.04 (p, J = 6.5 Hz, 2H), 1.94 (p, J = 6.5 Hz, 2H); ^{13}C

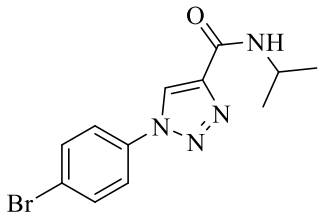
NMR (125 MHz, $CDCl_3$): δ 159.1, 146.0, 135.6, 133.1, 125.5, 123.0, 122.0, 48.8, 47.1, 26.6, 23.8; HRMS calcd for $C_{13}H_{13}BrN_4O+H^+$: 321.0346, found: 321.0348.



1-(4-bromophenyl)-*N, N*-diethyl-1H-1,2,3-triazole-4-carboxamide (**4t**)

White solid, yield:164mg, 51%, m.p.: 182.2-183.0 °C.

^1H NMR (500 MHz, $CDCl_3$): δ 8.51 (s, 1H), 7.69 - 7.64 (m, 4H), 4.01 (q, J = 7.0 Hz, 2H), 3.57 (q, J = 7.0 Hz, 2H), 1.35 (t, J = 7.0 Hz, 3H), 1.26 (t, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 160.1, 145.9, 135.6, 133.1, 126.0, 123.0, 122.0, 43.1, 41.4, 14.8, 12.8; HRMS calcd for $C_{13}H_{15}BrN_4O+H^+$: 323.0502, found: 323.0505.

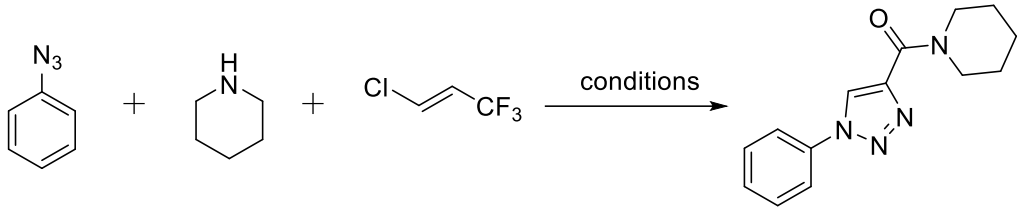


1-(4-bromophenyl)-*N*-isopropyl-1H-1,2,3-triazole-4-carboxamide (**4u**)

White solid, yield:77mg, 25%, m.p.: 217.6-218.1 °C.

^1H NMR (500 MHz, $CDCl_3$): δ 8.48 (s, 1H), 7.70 – 7.68 (m, 2H), 7.65 – 7.63 (m, 2H), 7.03 (d, J = 7.0 Hz, 1H), 4.34 – 4.27 (m, 1H), 1.30 (d, J = 6.5 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 158.8, 144.4, 135.6, 133.1, 126.4, 123.2, 122.1, 41.4, 22.8; HRMS calcd for $C_{12}H_{13}BrN_4O+H^+$: 309.0346, found: 309.0343.

2. Optimization of reaction conditions[a]



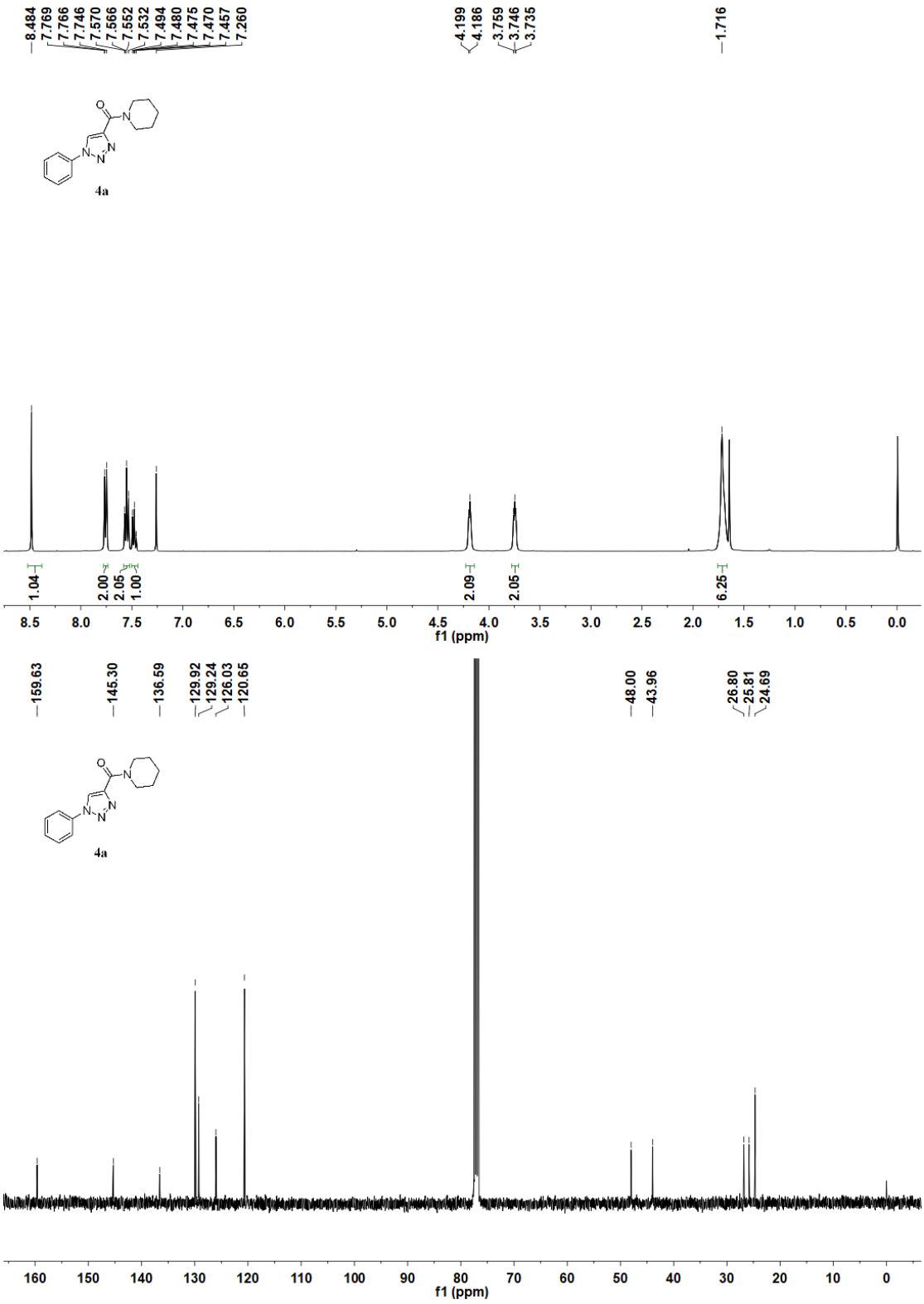
1a **2a** **3** **4a**

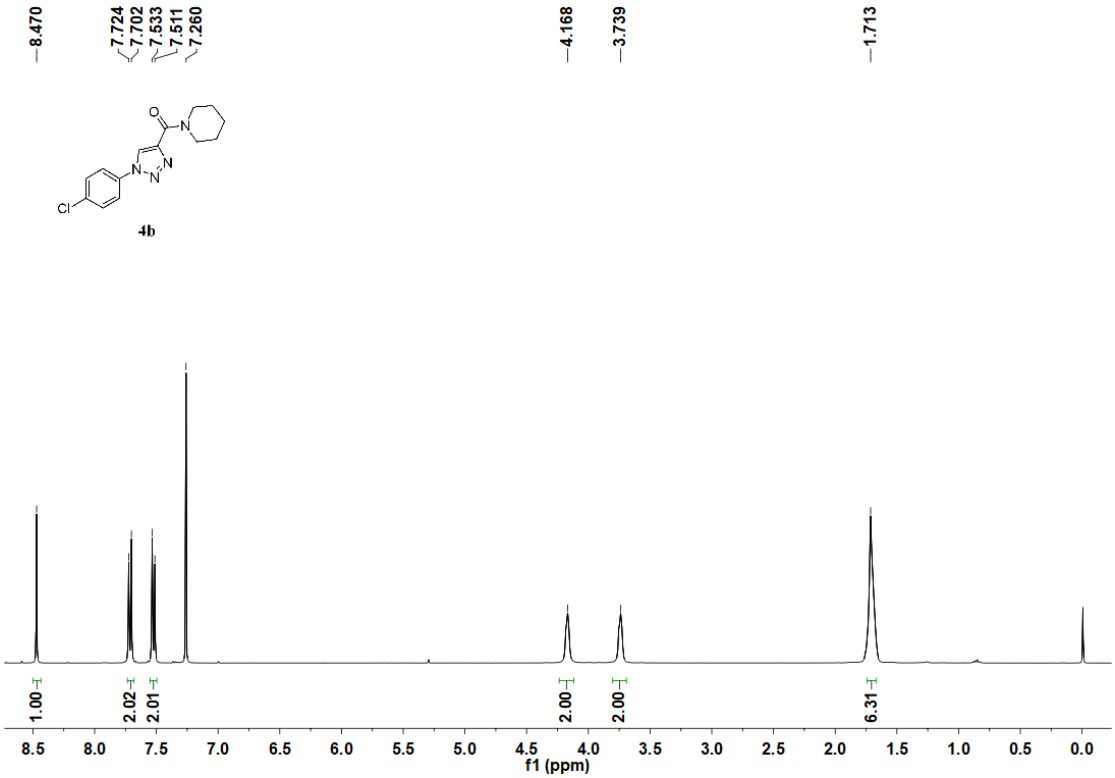
Entry	Additive	Base	Temp (℃)	Yield (%)
1	/	LiOH	50	Trace
2	/	/	50	Trace
3	/	DABCO	50	9
4	/	DBU	50	3
5	/	Et_3N	50	4
6	/	DMAP	50	6
7	/	DMA	50	8
8	/	DIPEA	50	10
9	/	DABCO	80	13
10	/	DIPEA	80	14
11	TPGS-750-M	DABCO	80	16
12	TPGS-750-M	DIPEA	80	22
13	TPGS-750-M	DABCO	100	33
14	TPGS-750-M	DIPEA	100	38
15	18-crown-6	DABCO	100	36
16	18-crown-6	DIPEA	100	42
17	TBAHS	DABCO	100	28
18	TBAHS	DIPEA	100	31
19	TPGS-750-M	DABCO	120	35
20	TPGS-750-M	DIPEA	120	43
21	18-crown-6	DABCO	120	44
22	18-crown-6	DIPEA	120	52

23	TBAHS	DABCO	120	38
24	TBAHS	DIPEA	120	42
25	18-crown-6	DABCO	140	46
26	18-crown-6	DIPEA	140	68
27	18-crown-6	DMAP	140	38
28	18-crown-6	DMA	140	50
29	18-crown-6	DIPEA	150	65
30	18-crown-6	DIPEA	150	67

[a]Reaction conditions unless otherwise specified:**1a** (1.0 mmol), **2a** (5.0 mmol), **3** (2.0 mL), base (3.0 mmol), additive (1.0 mmol), 2.0 mL of solvent (THF/H_2O=3:1), 4 days in the Schlenk tube, Isolated yields. TPGS–750–M: Poly(oxy–1,2–ethanediyl), α–[4–[[3,4–dihydro–2,5,7,8–tetramethyl–2–(4,8,12–trimethyltridecyl) –2H–1–benzopyran–6–yl] oxy] –1,4–dioxobutyl] –ω–methoxy–Polymer. TBAHS: Tetrabutylammonium hydrogen sulfate. [b]5.0 mmol of DIPEA was used.

3. ^{1}H and ^{13}C NMR Spectra for **4** and **5**

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4b
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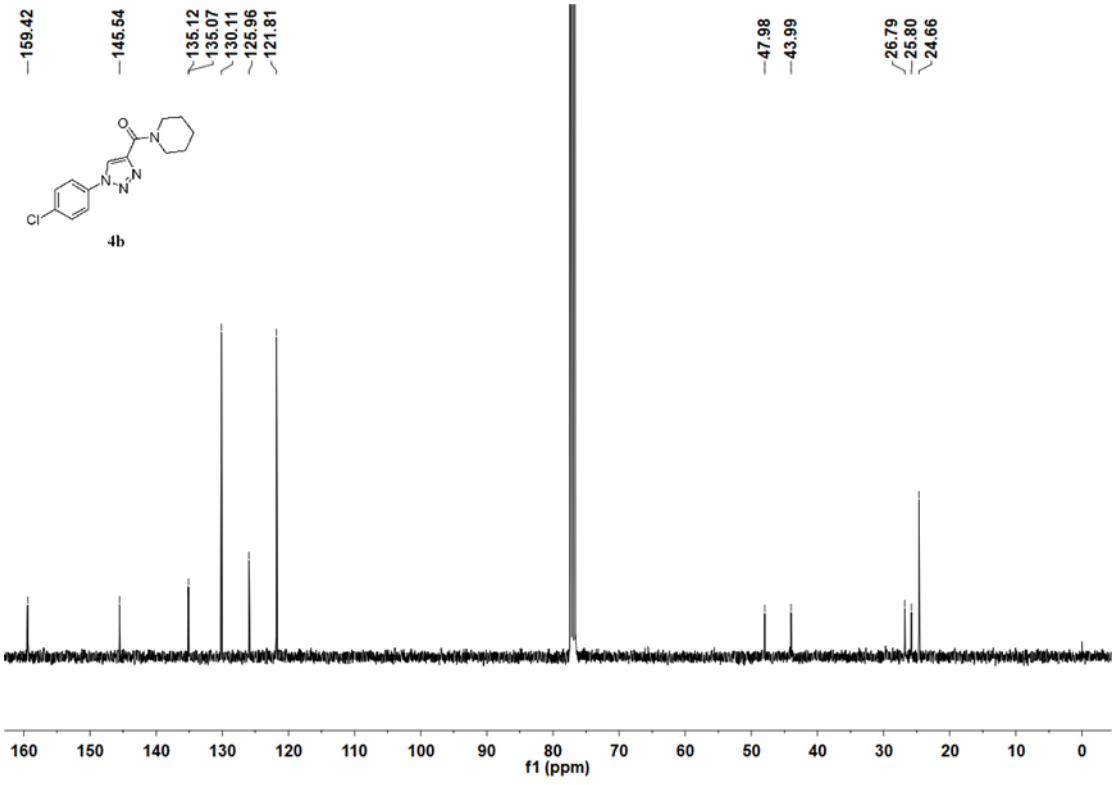
2.01
2.00
2.00
6.31
f1 (ppm)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26.79
25.80
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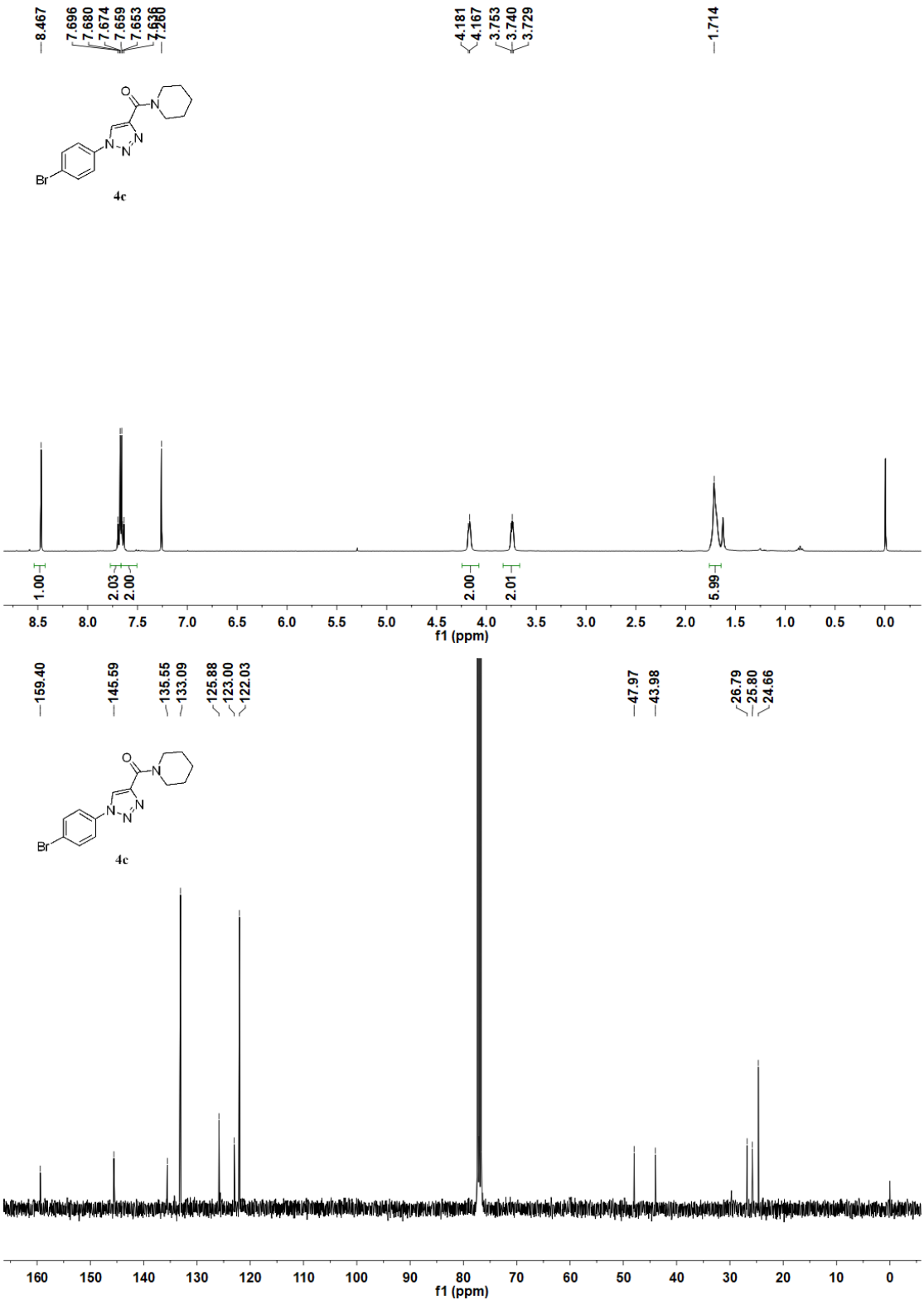
4b
f1 (ppm)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3.729
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Br
4c
1.00
2.03
2.00
2.00
2.01
5.99
f1 (ppm)
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145.59
135.55
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123.00
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25.80
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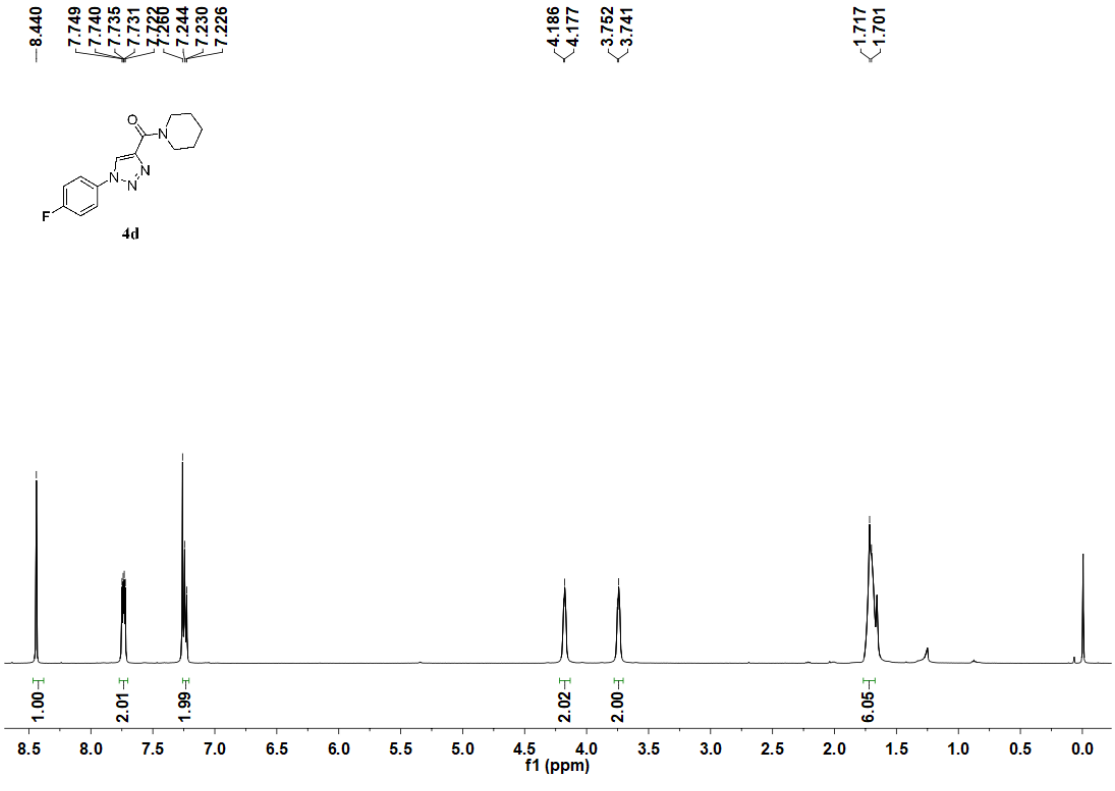
Br
4c
f1 (ppm)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3.741
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1.701
4d
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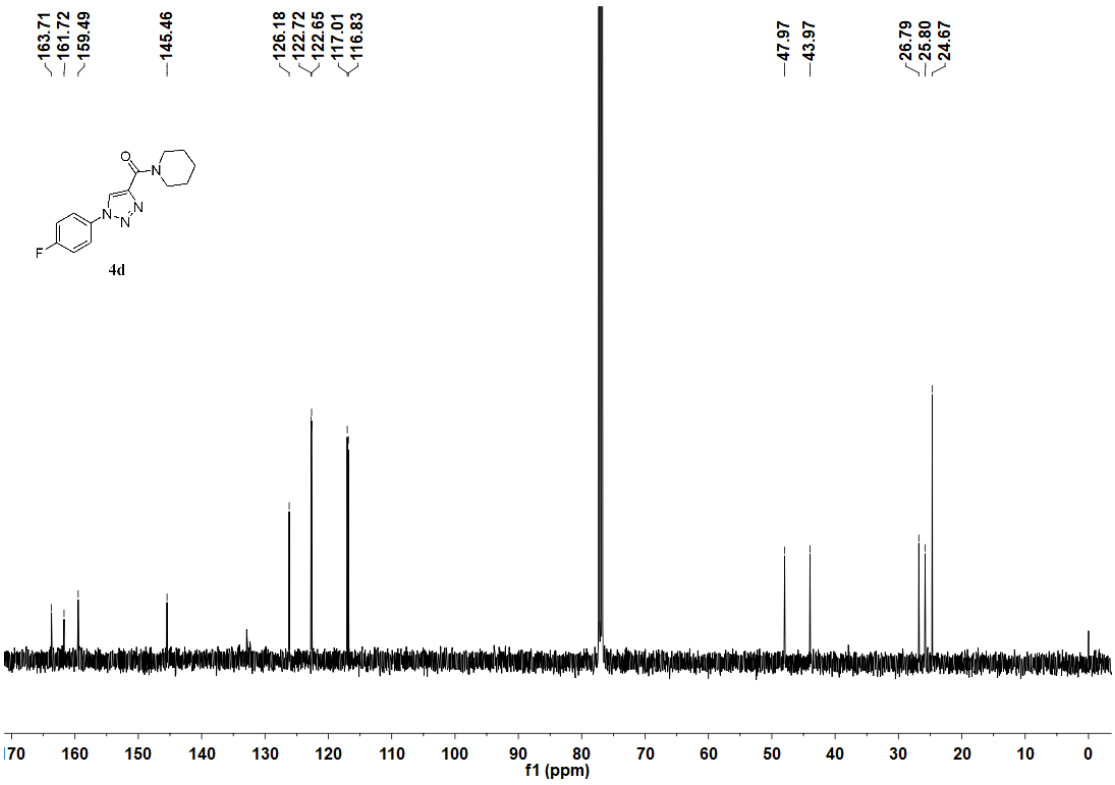
2.02
2.00
6.05
f1 (ppm)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117.01
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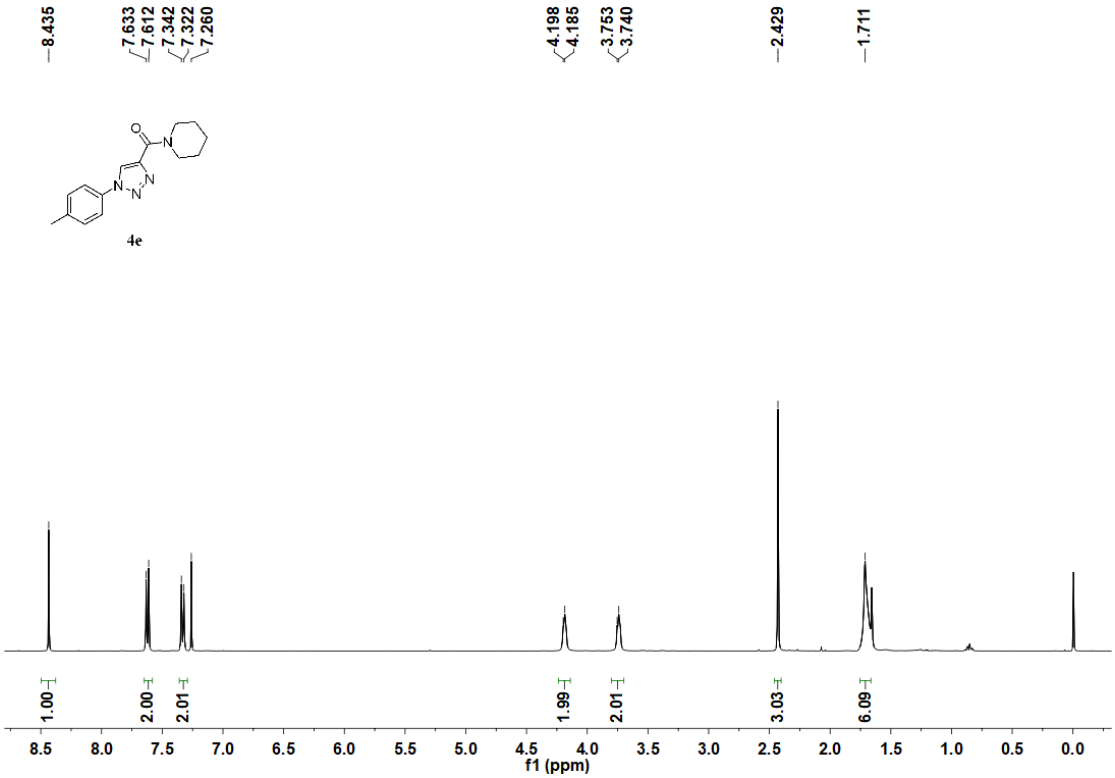
26.79
25.80
24.67
4d
f1 (ppm)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2.01
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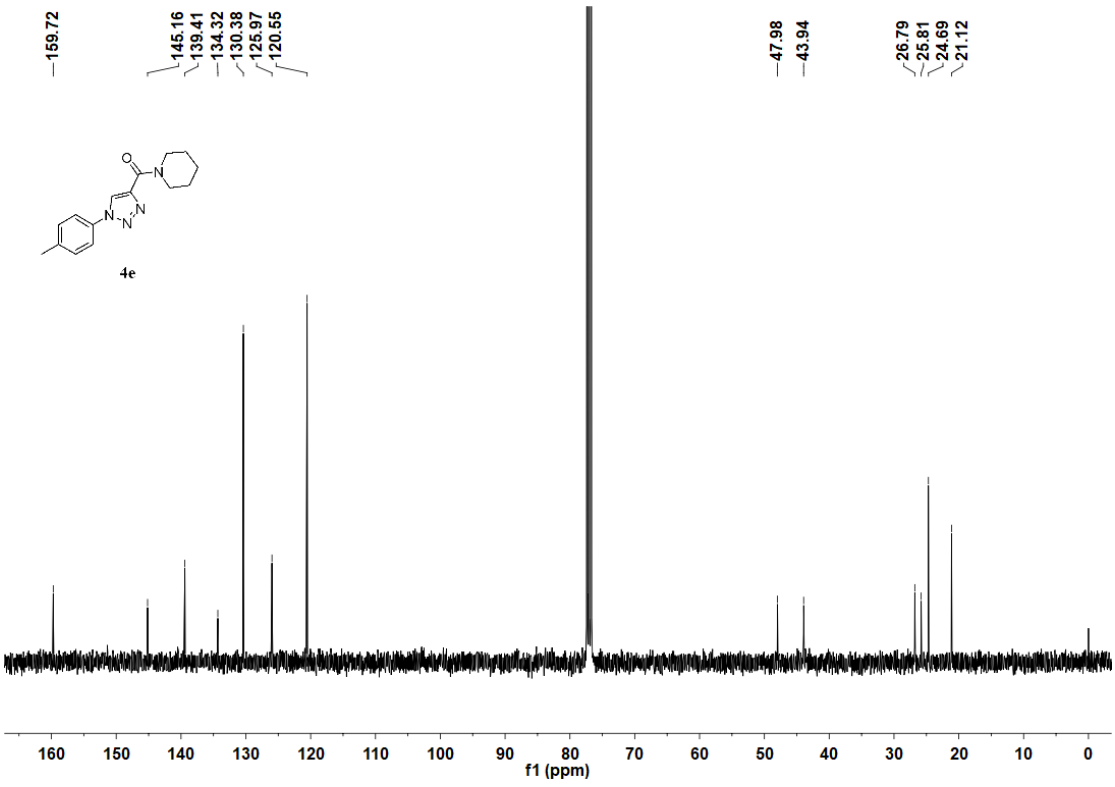
6.09
f1 (ppm)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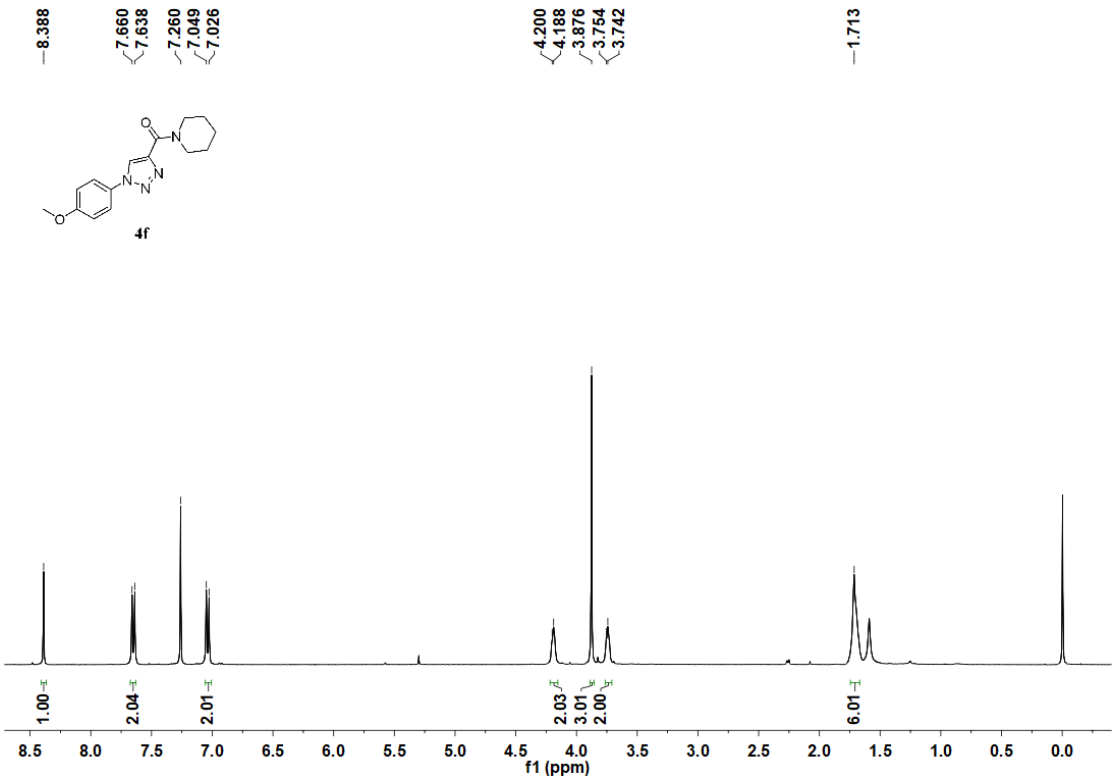
f1 (ppm)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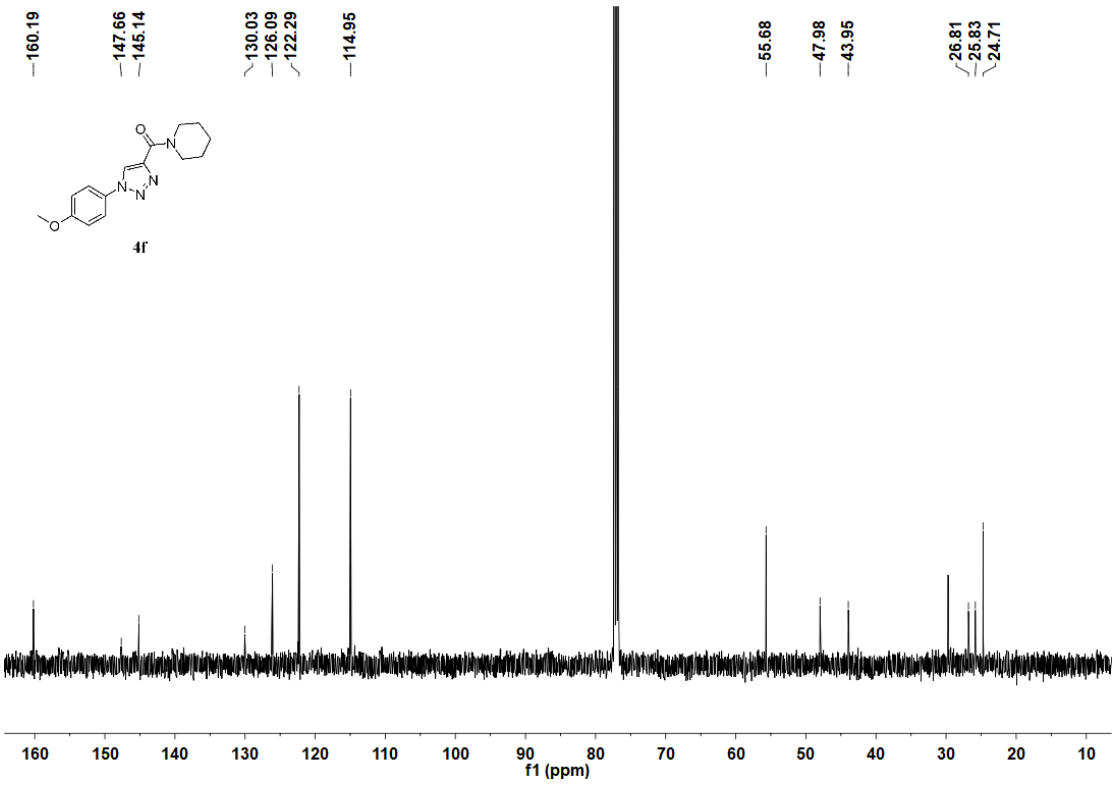
2.03
3.01
2.00
6.01
f1 (ppm)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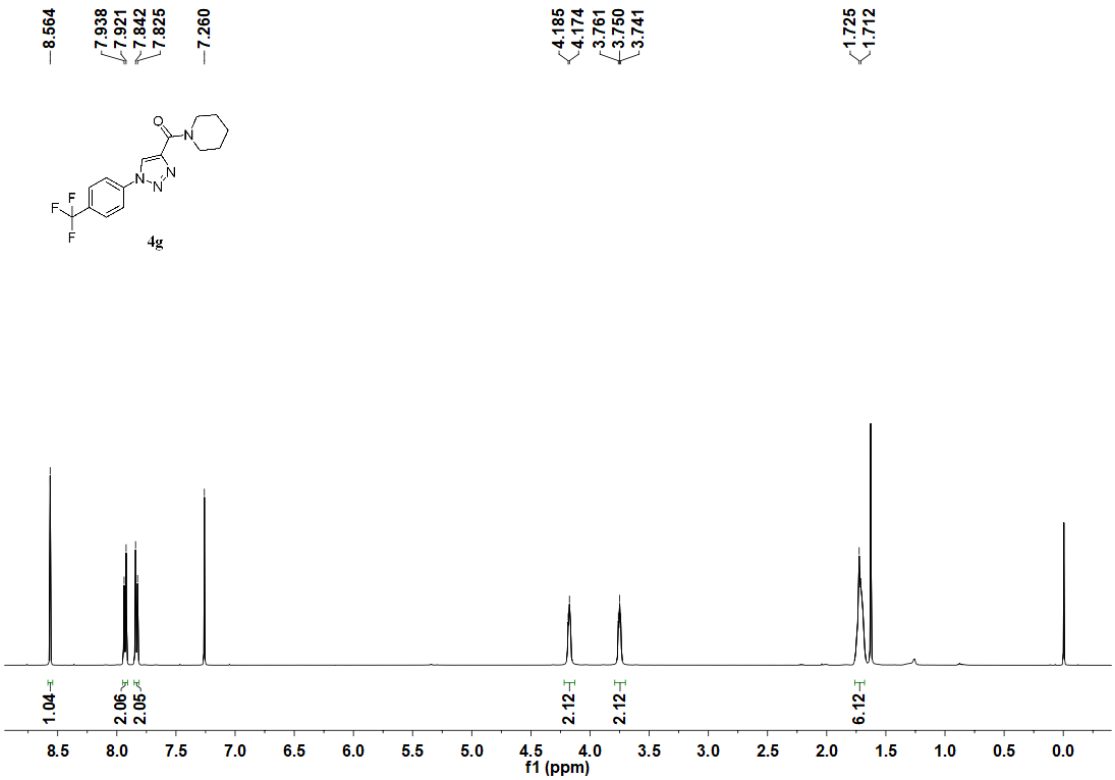
4f
f1 (ppm)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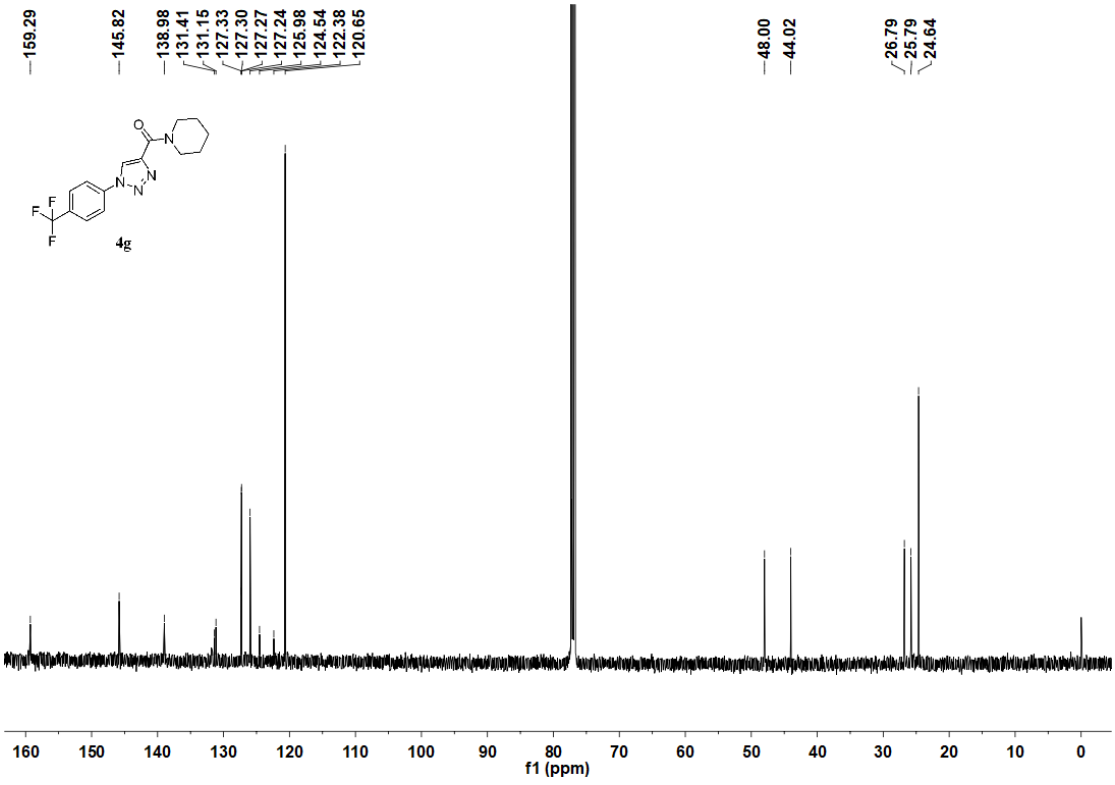
2.05
2.12
2.12
6.12
f1 (ppm)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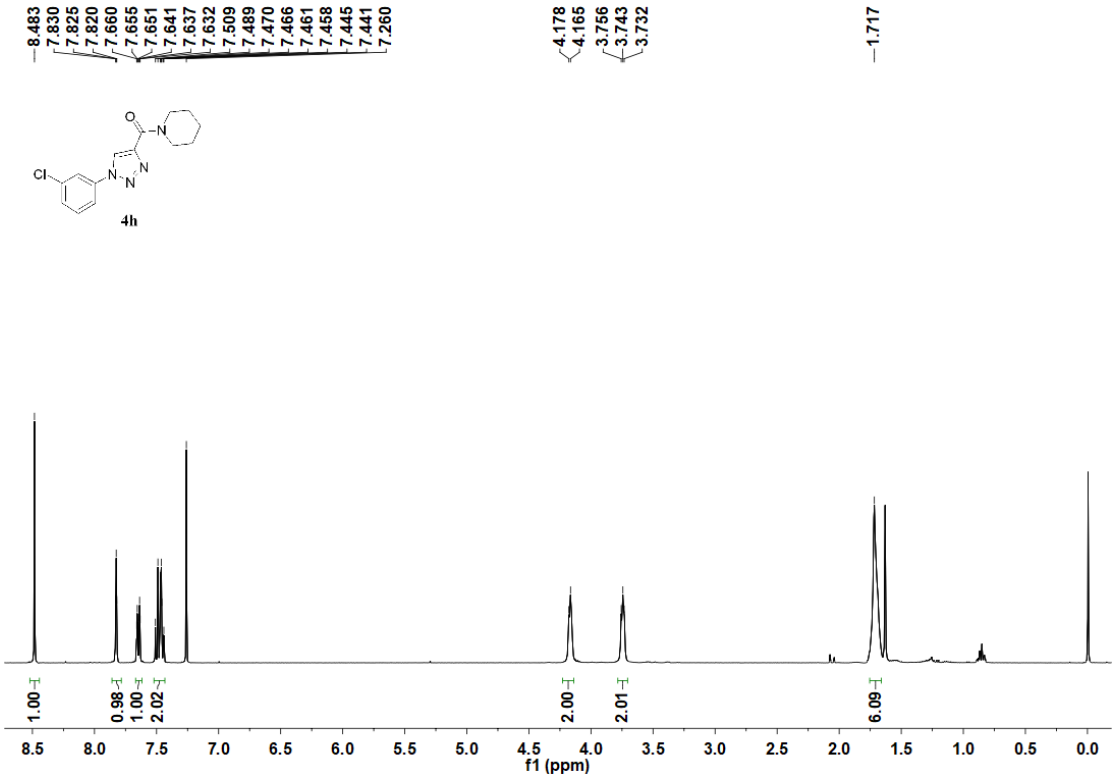
4g
f1 (ppm)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7.445
7.441
7.260
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4.165
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3.743
3.732
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Cl
4h
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1.00
2.02
2.00
2.01
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f1 (ppm)
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135.82
130.98
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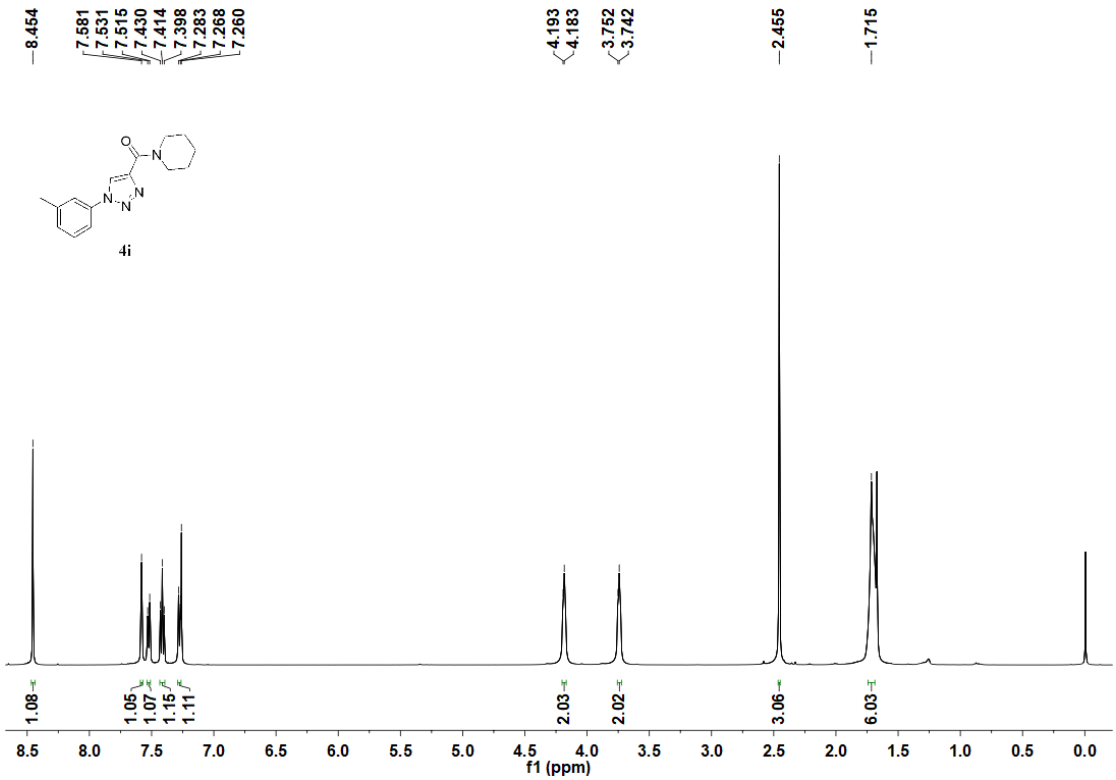
Cl
4h
f1 (ppm)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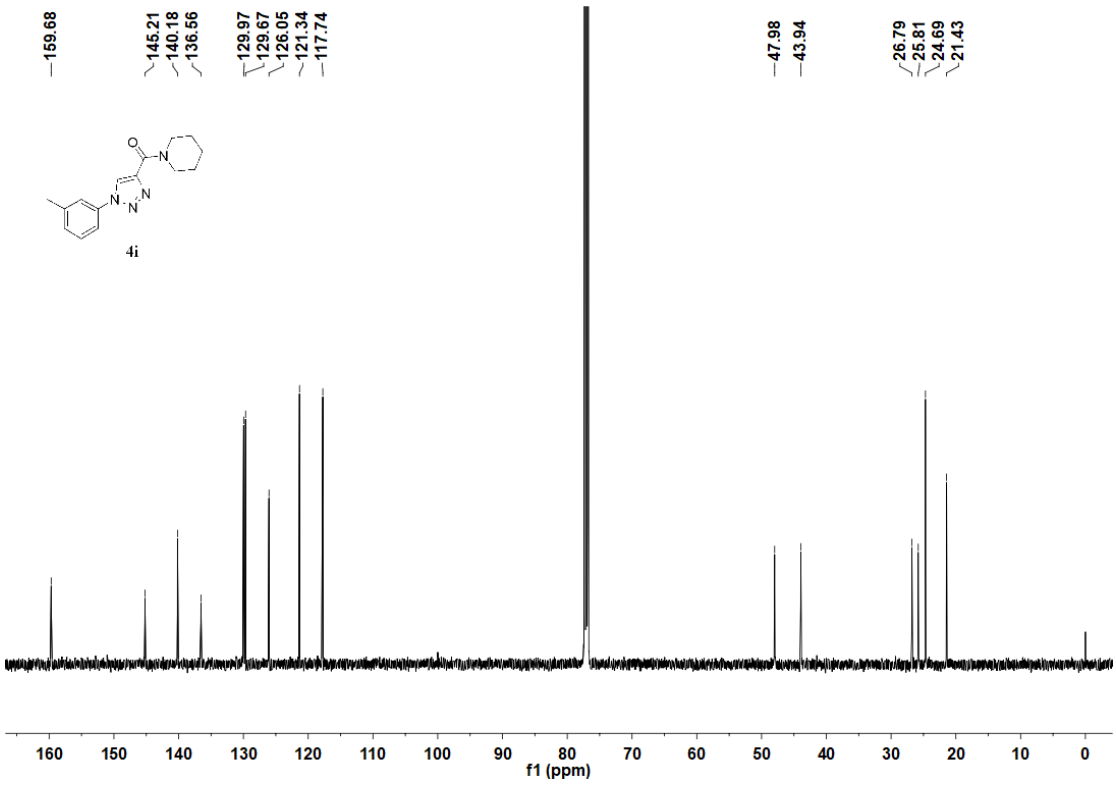
2.02
3.06
6.03
f1 (ppm)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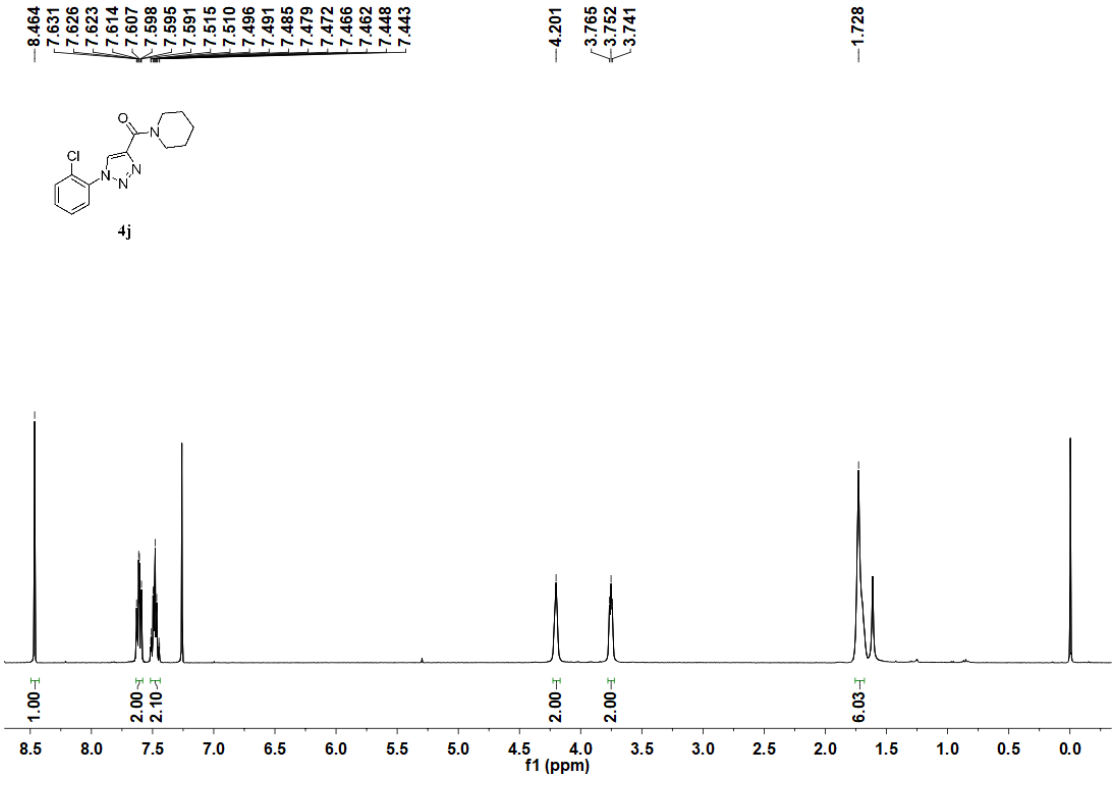
4i
f1 (ppm)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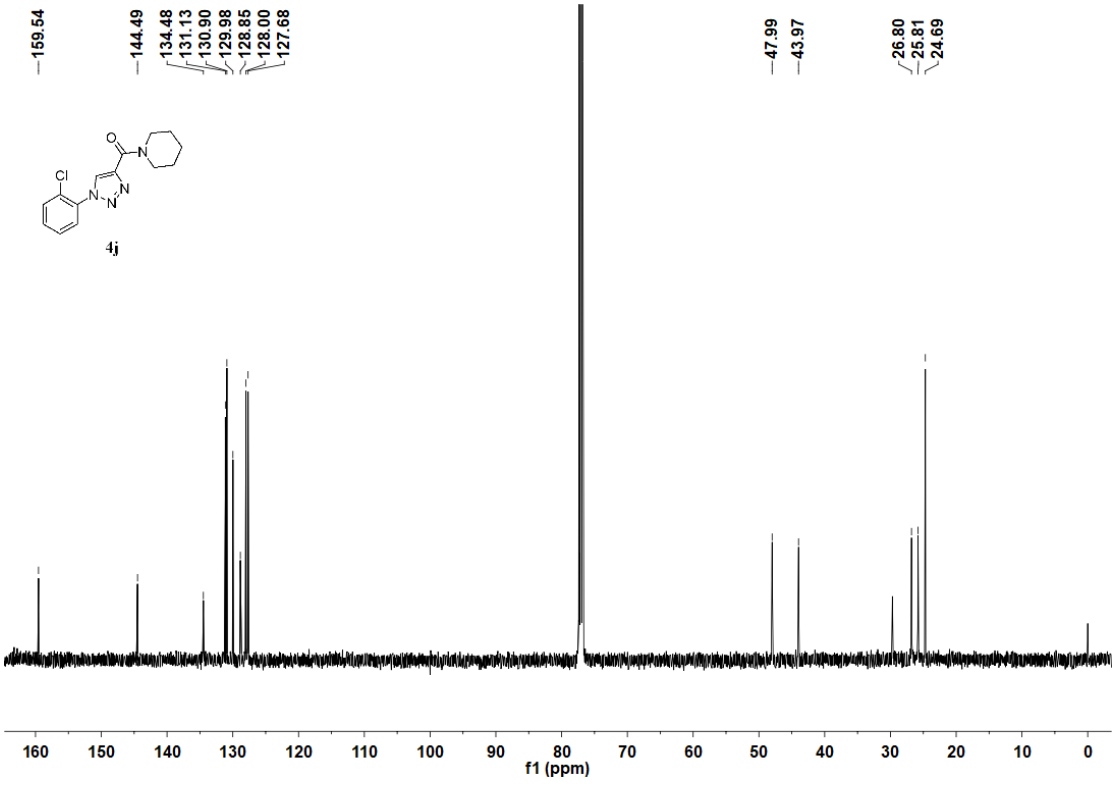
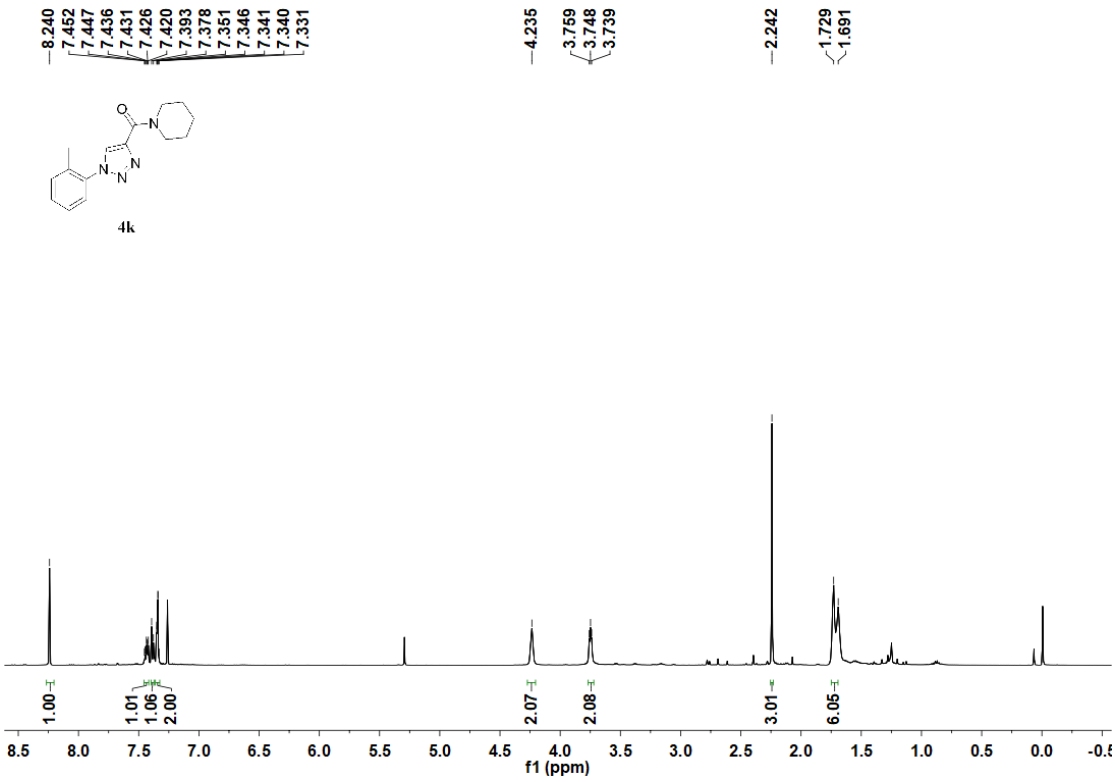
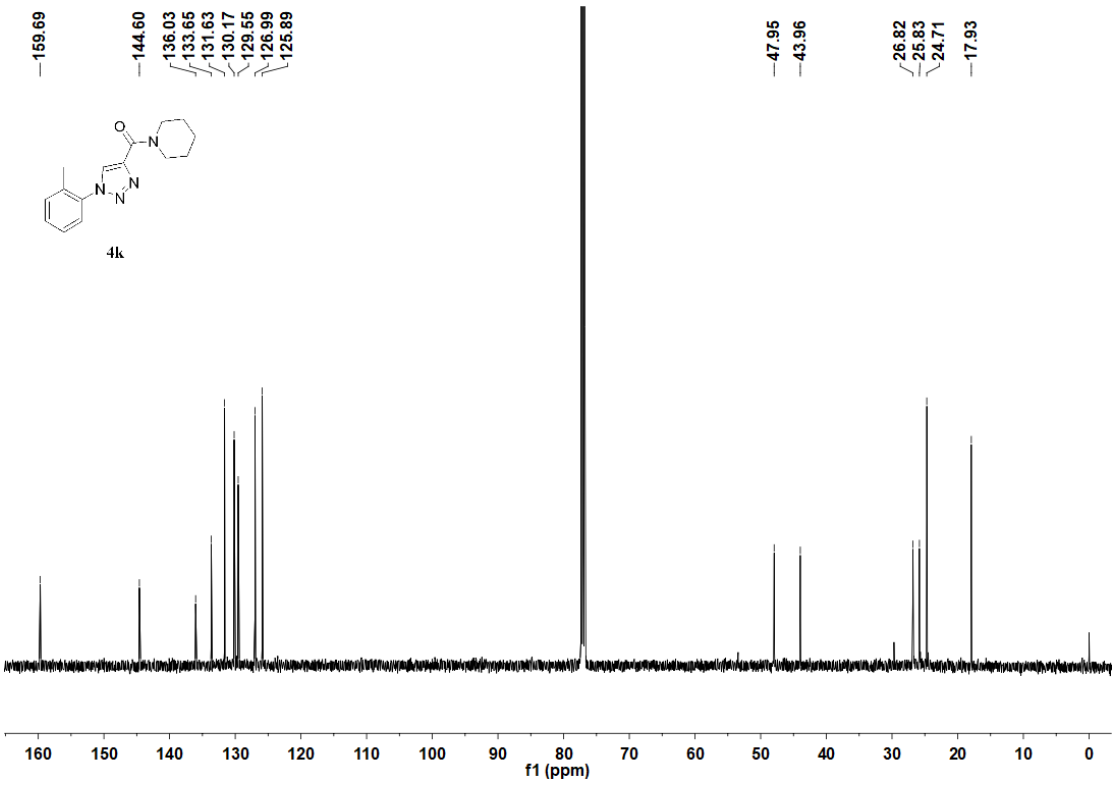
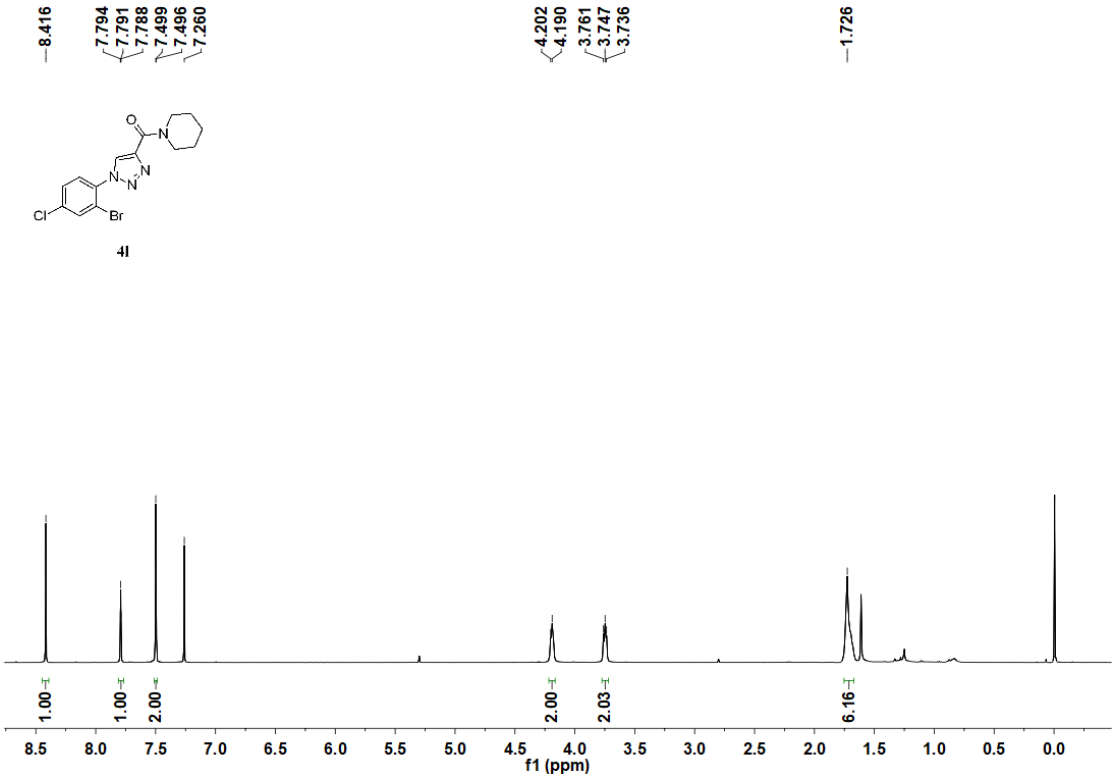
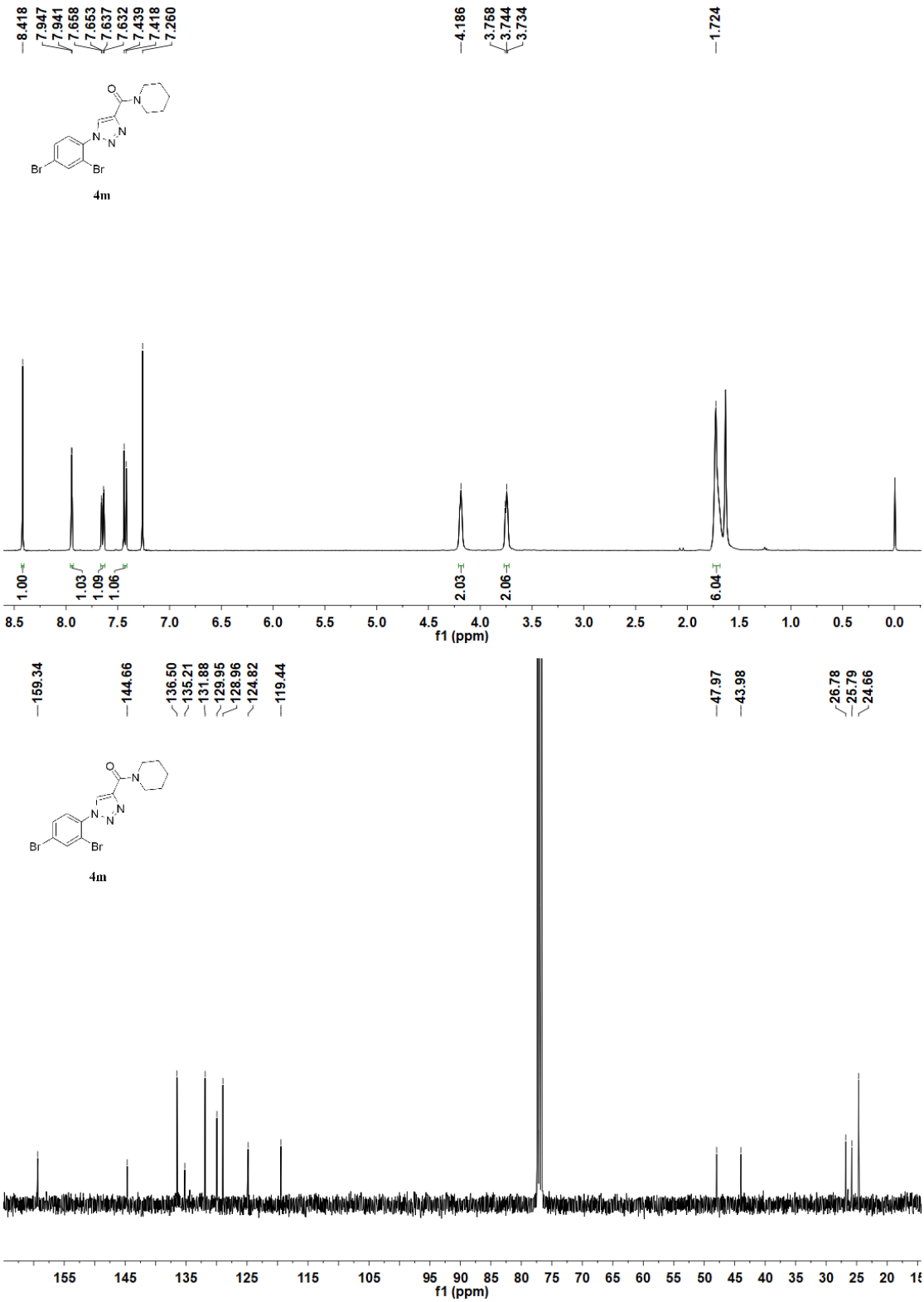
7.485
7.479
7.472
7.466
7.462
7.448
7.443
4.201
3.765
3.752
3.741
1.728
Cl
O
N
N
N
N
4j
1.00
2.00
2.10
2.00
2.00
6.03
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

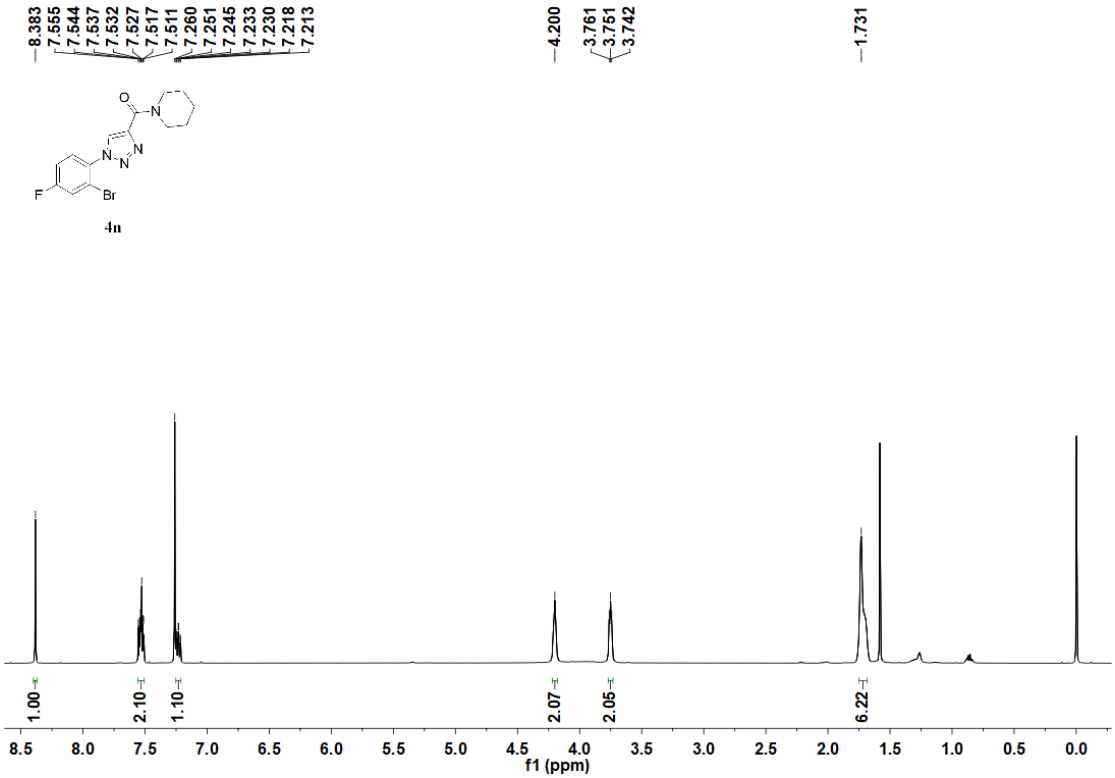

159.54
144.49
134.48
131.13
130.90
129.98
128.85
128.00
127.68
47.99
43.97
26.80
25.81
24.69
Cl
O
N
N
N
N
4j
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


8.240
7.452
7.447
7.436
7.431
7.426
7.420
7.393
7.378
7.351
7.346
7.341
7.340
7.331
4.235
3.759
3.748
3.739
2.242
1.729
1.691
4k
1.00
1.01
1.06
2.00
2.07
2.08
3.01
6.05
f1 (ppm)

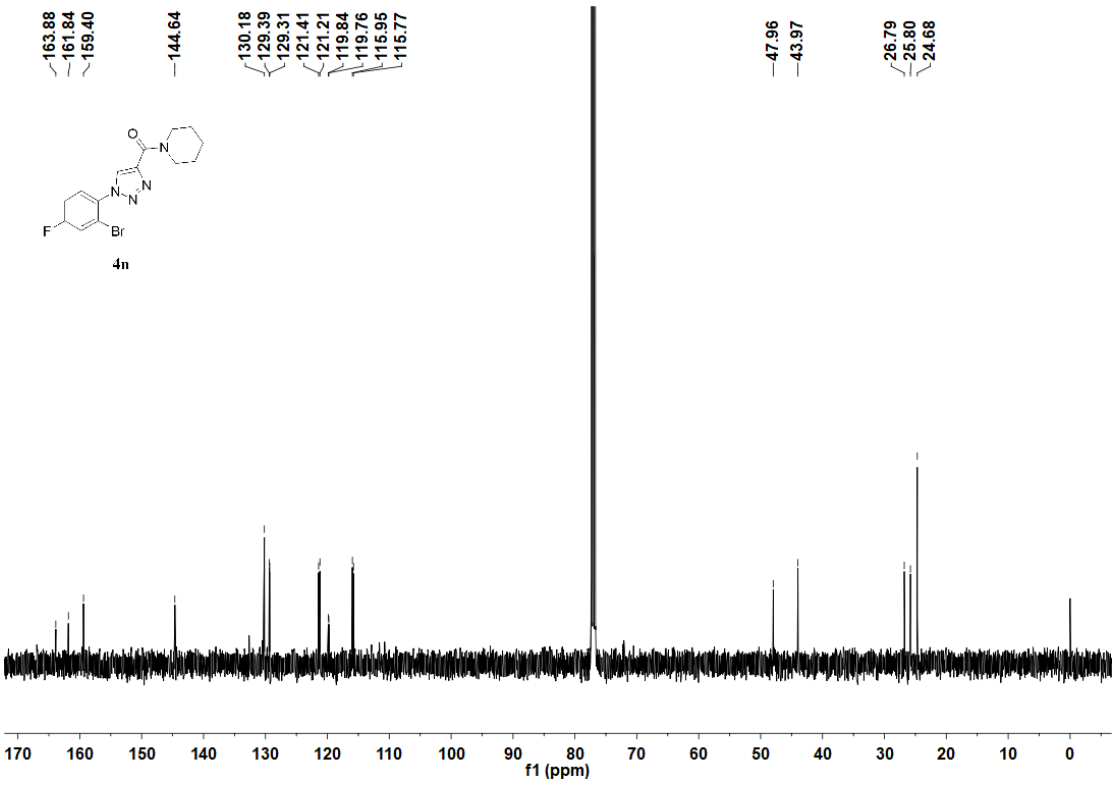

159.69
144.60
136.03
133.65
131.63
130.17
129.55
126.99
125.89
47.95
43.96
26.82
25.83
24.71
17.93
4k
f1 (ppm)


8.416
7.794
7.791
7.788
7.499
7.496
7.260
4.202
4.190
3.761
3.747
3.736
1.726
Cl
Br
4l
1.00
1.00
2.00
2.00
2.03
6.16
f1 (ppm)
159.36
144.67
137.04
134.77
133.73
130.01
128.90
128.71
119.26
47.97
43.98
26.78
25.79
24.67
Cl
Br
4l
f1 (ppm)

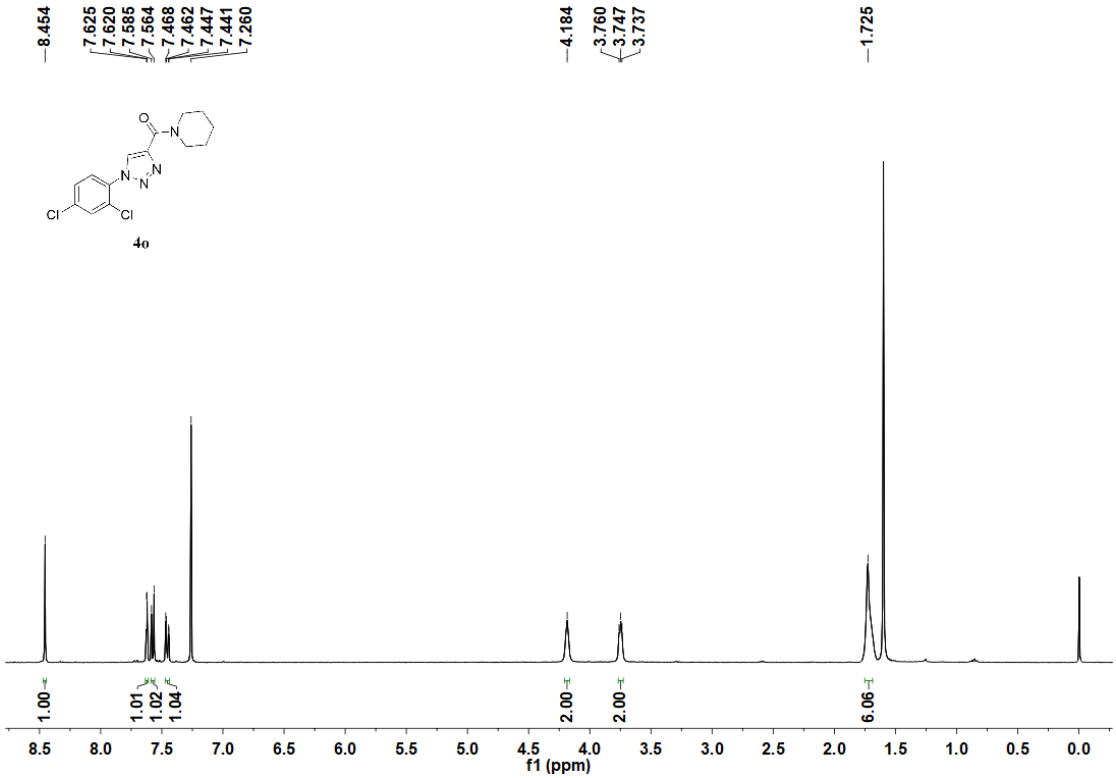

8.418
7.947
7.941
7.658
7.653
7.637
7.632
7.439
7.418
7.260
4.186
3.758
3.744
3.734
1.724
Br
Br
4m
1.00
1.03
1.09
1.06
2.03
2.06
6.04
f1 (ppm)
159.34
144.66
136.50
135.21
131.88
129.95
128.96
124.82
119.44
47.97
43.98
26.78
25.79
24.66
Br
Br
4m
f1 (ppm)


8.383
7.555
7.544
7.537
7.532
7.527
7.517
7.511
7.260
7.251
7.245
7.233
7.230
7.218
7.213
4.200
3.761
3.751
3.742
1.731
O
N
N
N
F
Br
1.00
2.10
1.10
2.07
2.05
6.22
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

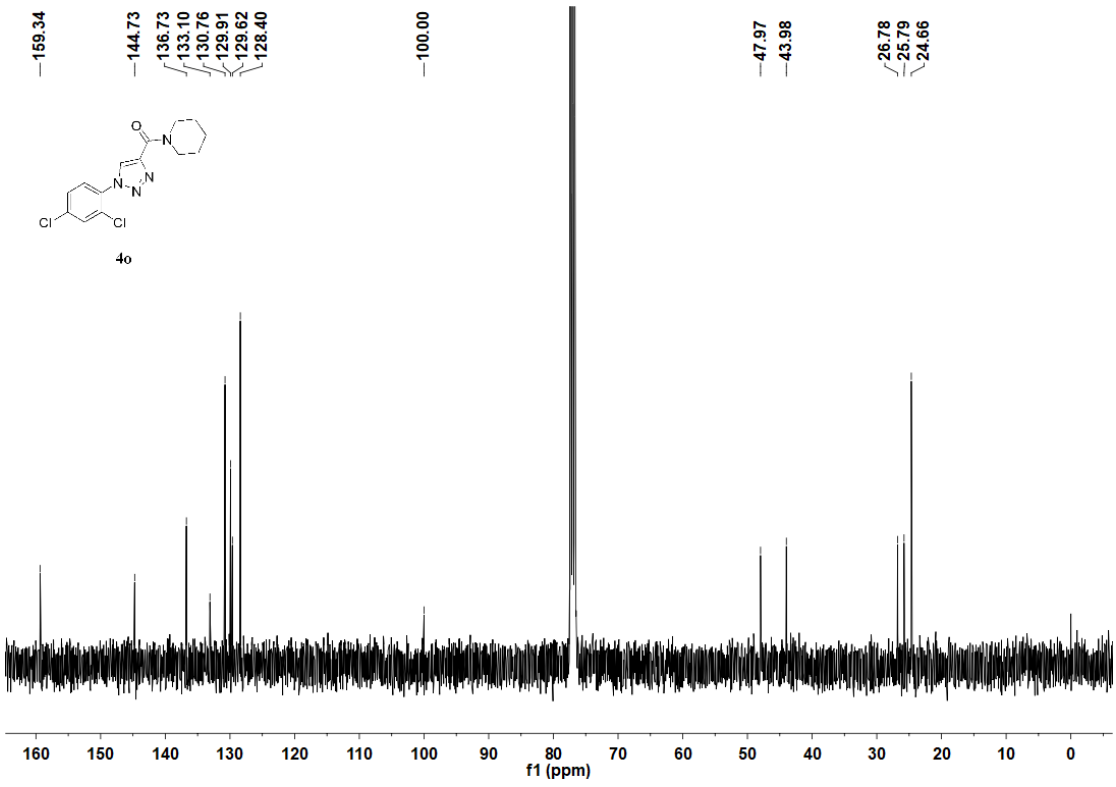
4n


163.88
161.84
159.40
144.64
130.18
129.39
129.31
121.41
121.21
119.84
119.76
115.95
115.77
47.96
43.97
26.79
25.80
24.68
O
N
N
N
F
Br
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

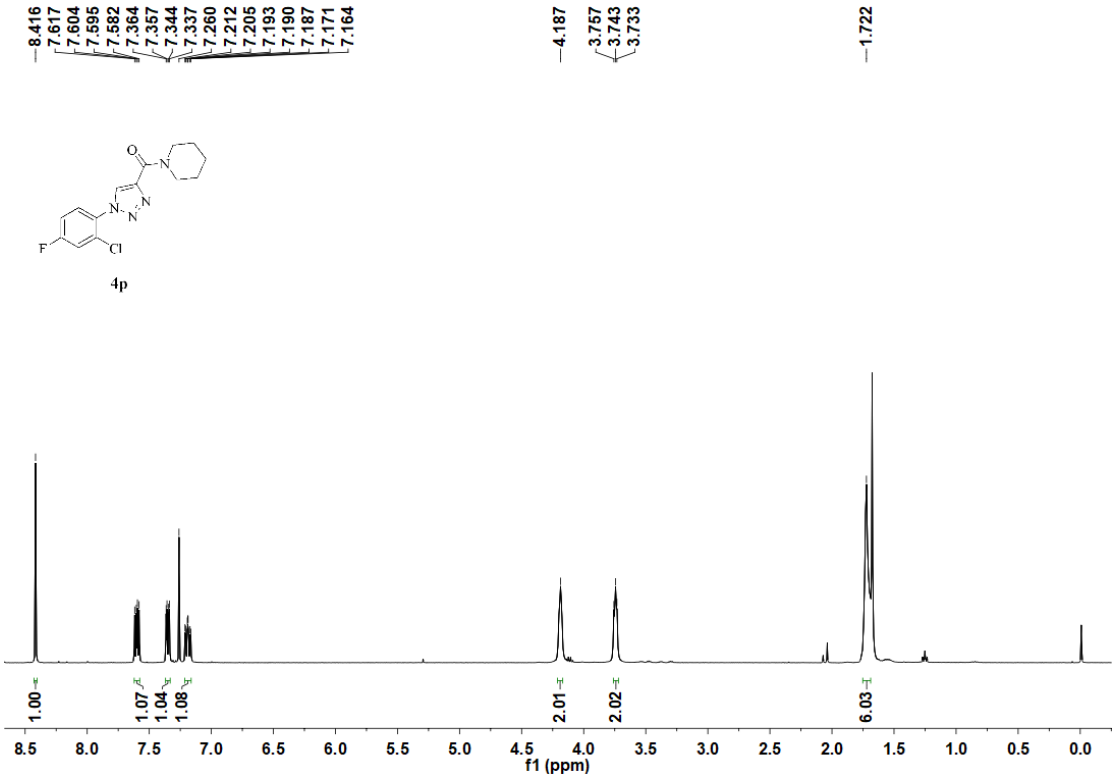
4n

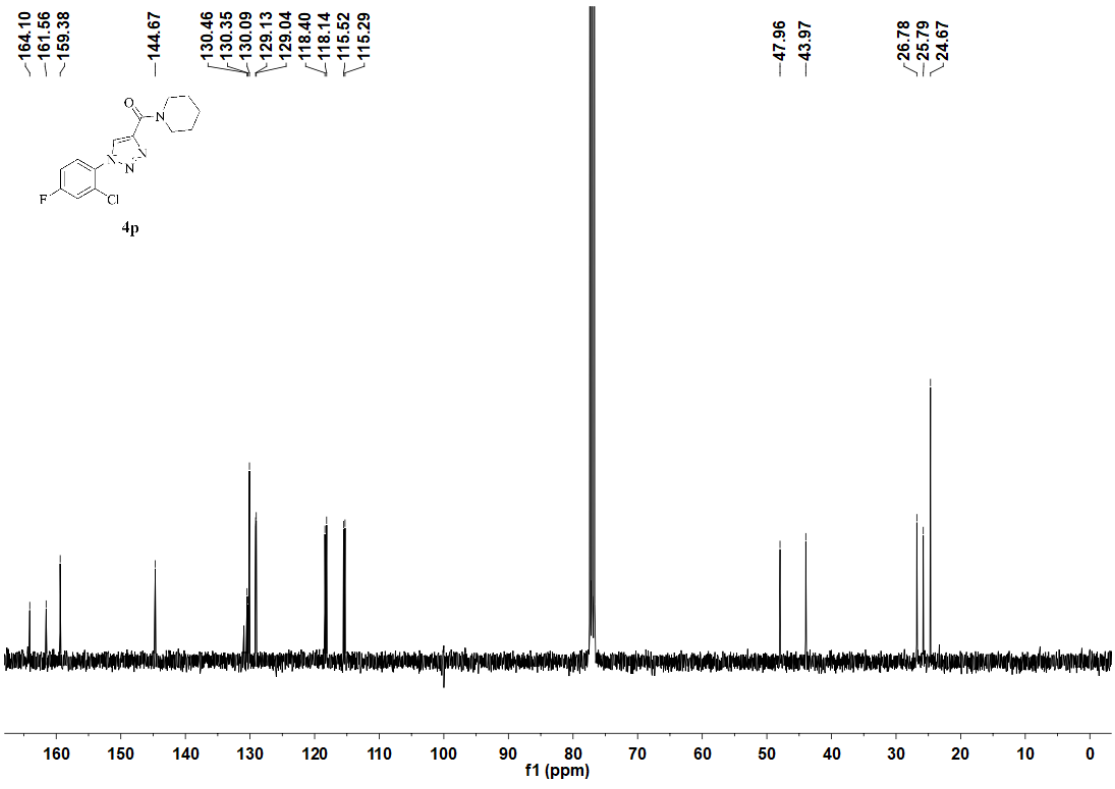

8.454
7.625
7.620
7.585
7.564
7.468
7.462
7.447
7.441
7.260
4.184
3.760
3.747
3.737
1.725
1.00
1.01
1.02
1.04
2.00
2.00
6.06
f1 (ppm)

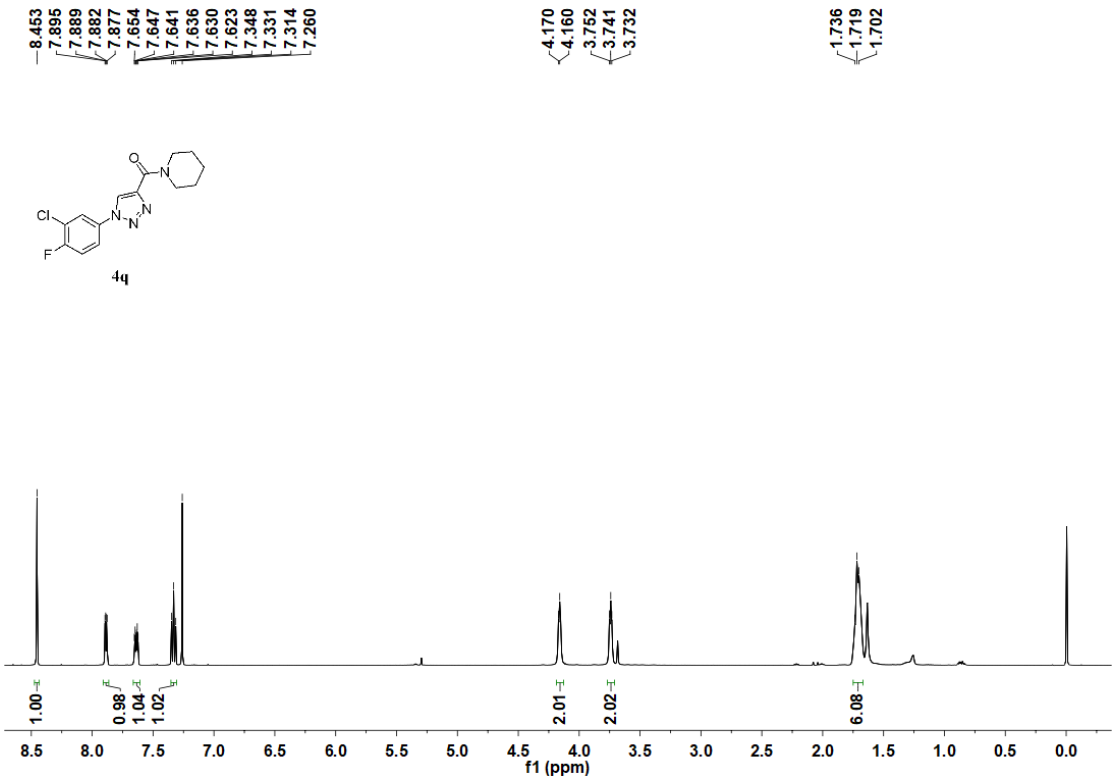
4o

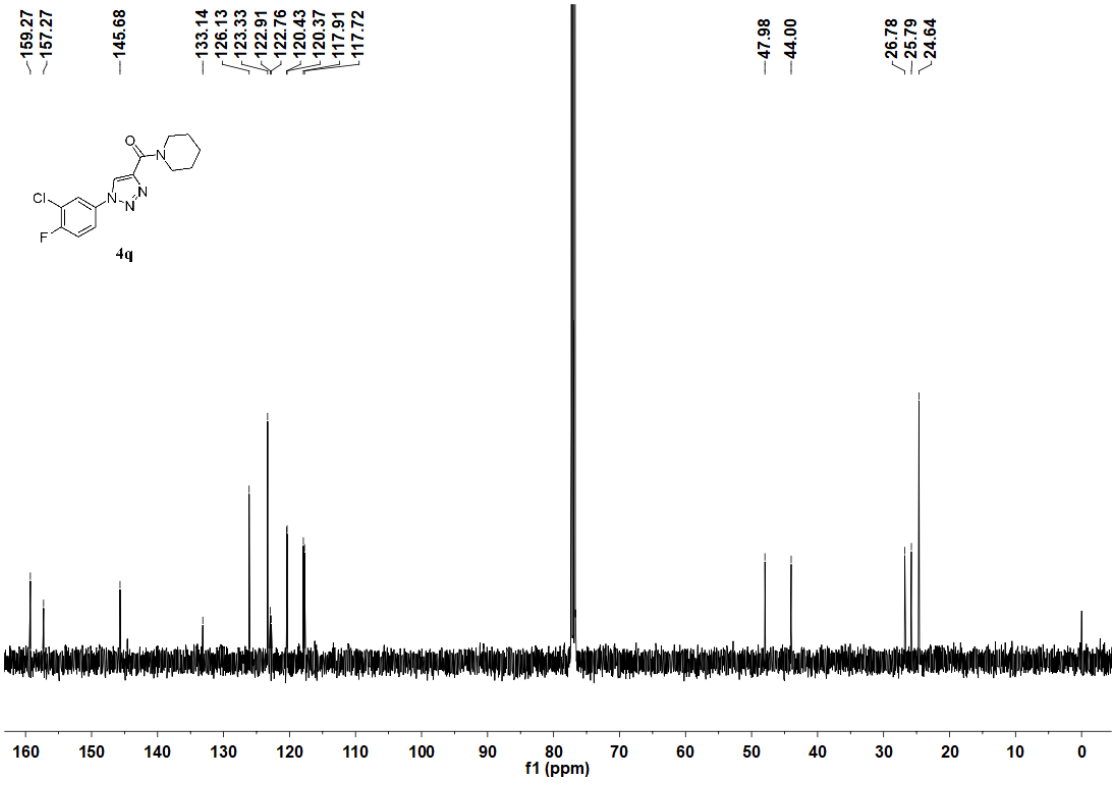

159.34
144.73
136.73
133.10
130.76
129.91
129.62
128.40
100.00
47.97
43.98
26.78
25.79
24.66
f1 (ppm)

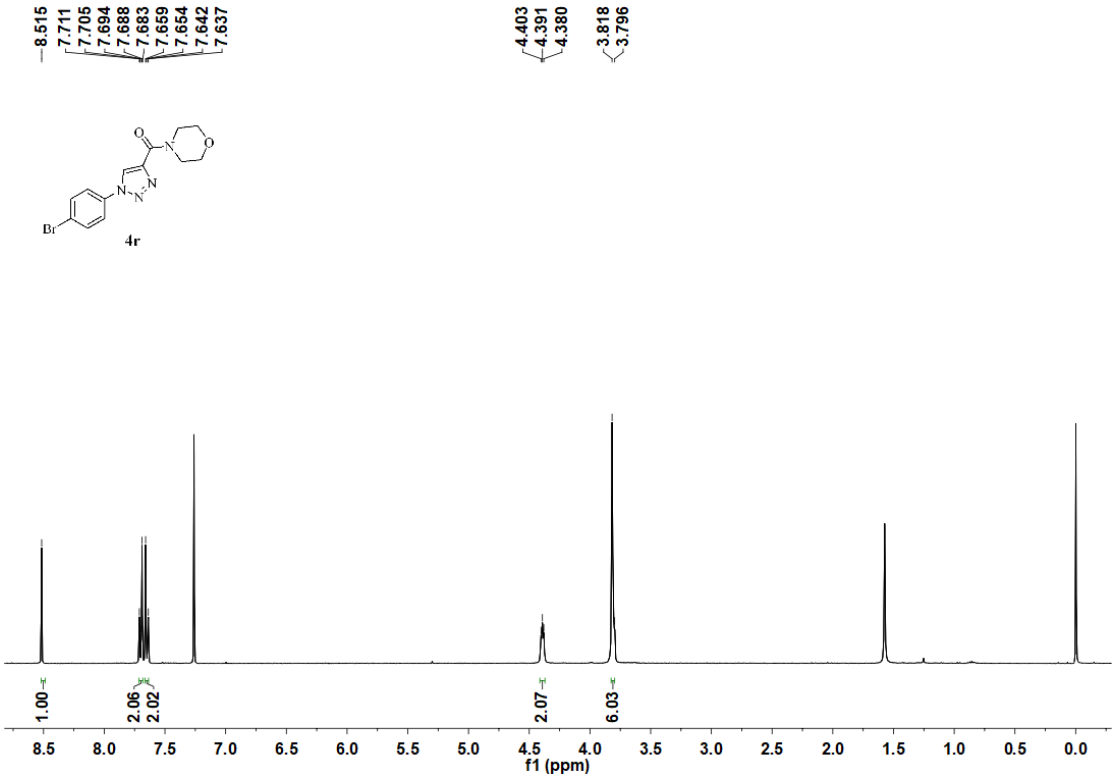
4o

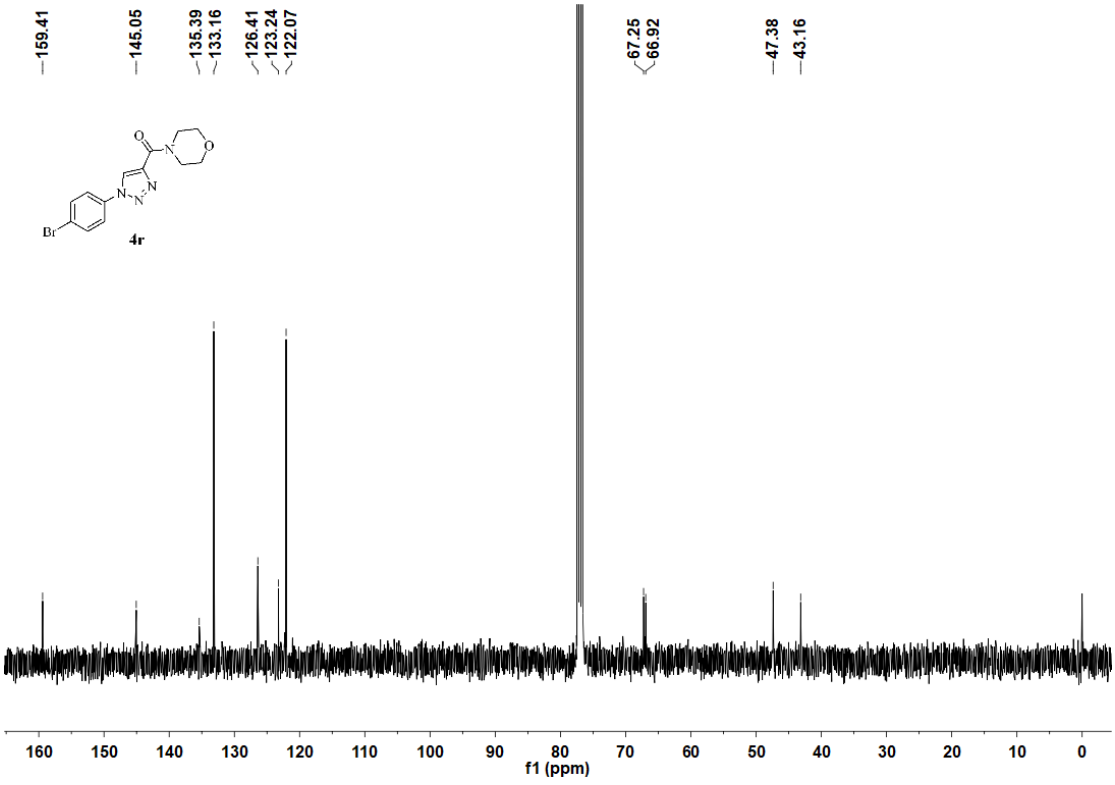

8.416
7.617
7.604
7.595
7.582
7.364
7.357
7.344
7.337
7.260
7.212
7.205
7.193
7.190
7.187
7.171
7.164
4.187
3.757
3.743
3.733
1.722
O
N
N
N
F
Cl
4p
1.00
1.07
1.04
1.08
2.01
2.02
6.03
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)


164.10
161.56
159.38
144.67
130.46
130.35
130.09
129.13
129.04
118.40
118.14
115.52
115.29
47.96
43.97
26.78
25.79
24.67
O
N
N
N
F
Cl
4p
160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


8.453
7.895
7.889
7.882
7.877
7.654
7.647
7.641
7.636
7.630
7.623
7.348
7.331
7.314
7.260
4.170
4.160
3.752
3.741
3.732
1.736
1.719
1.702
Cl
F
O
N
N
N
4q
1.00
0.98
1.04
1.02
2.01
2.02
6.08
f1 (ppm)

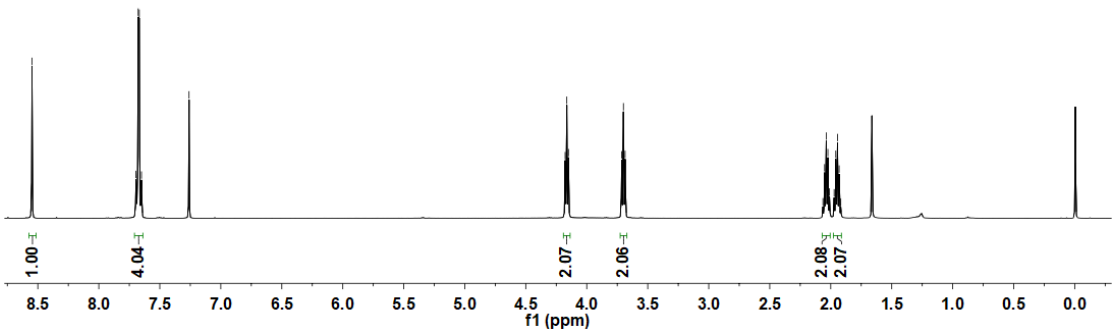

159.27
157.27
145.68
133.14
126.13
123.33
122.91
122.76
120.43
120.37
117.91
117.72
47.98
44.00
26.78
25.79
24.64
Cl
F
O
N
N
N
4q
f1 (ppm)

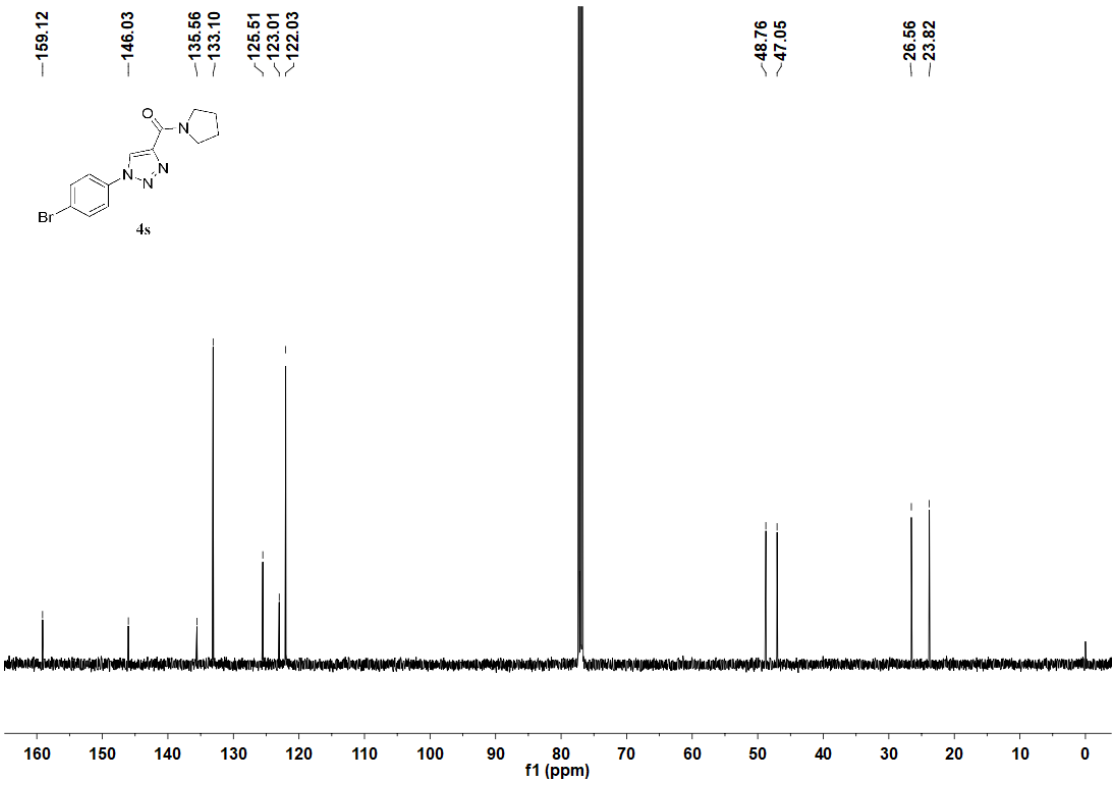

8.515
7.711
7.705
7.694
7.688
7.683
7.659
7.654
7.642
7.637
4.403
4.391
4.380
3.818
3.796
Br
4r
1.00
2.06
2.02
2.07
6.03
f1 (ppm)


159.41
145.05
135.39
133.16
126.41
123.24
122.07
67.25
66.92
47.38
43.16
Br
4r
f1 (ppm)

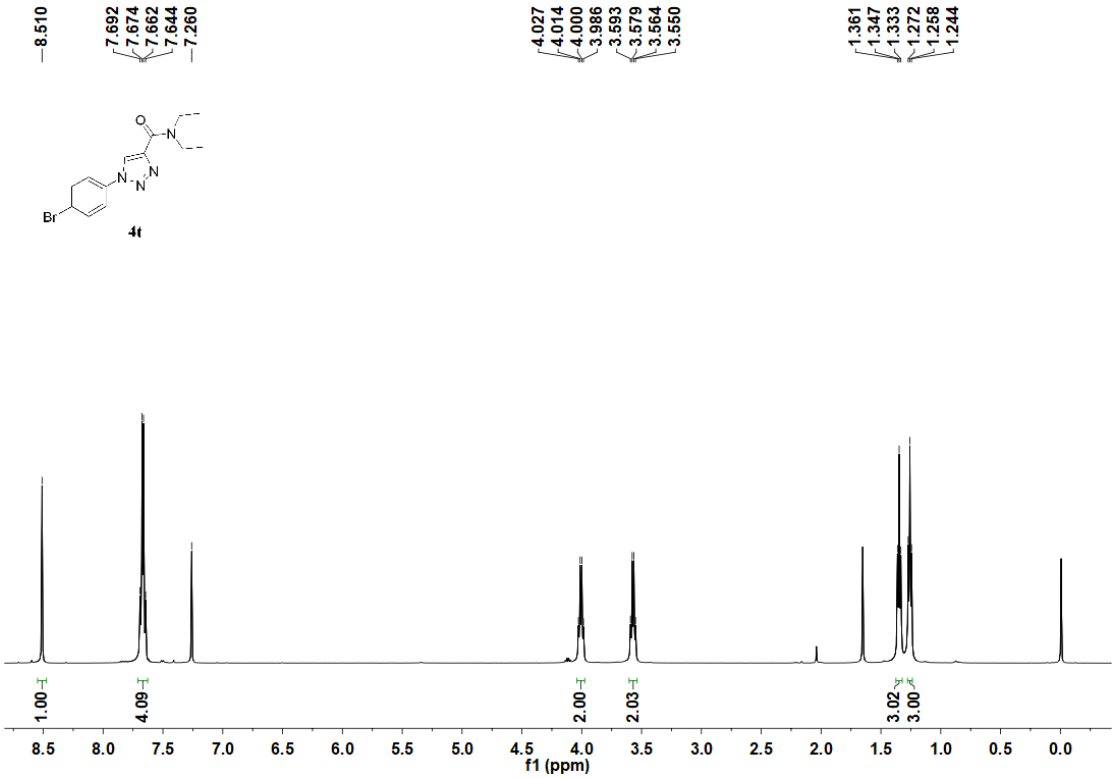

8.548
7.695
7.691
7.677
7.668
7.655
7.650
7.260
4.177
4.164
4.150
3.713
3.699
3.686
2.064
2.050
2.037
2.023
2.010
1.972
1.959
1.945
1.931
1.918
O
N
N
N
Br

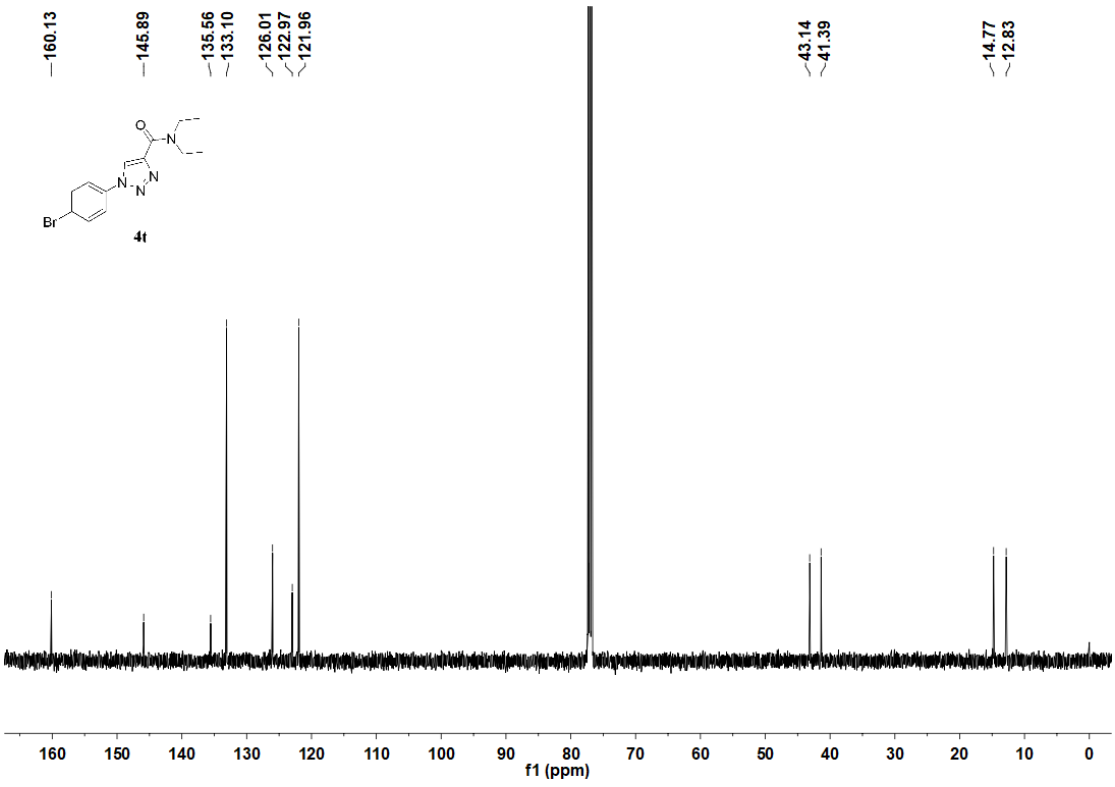
4s

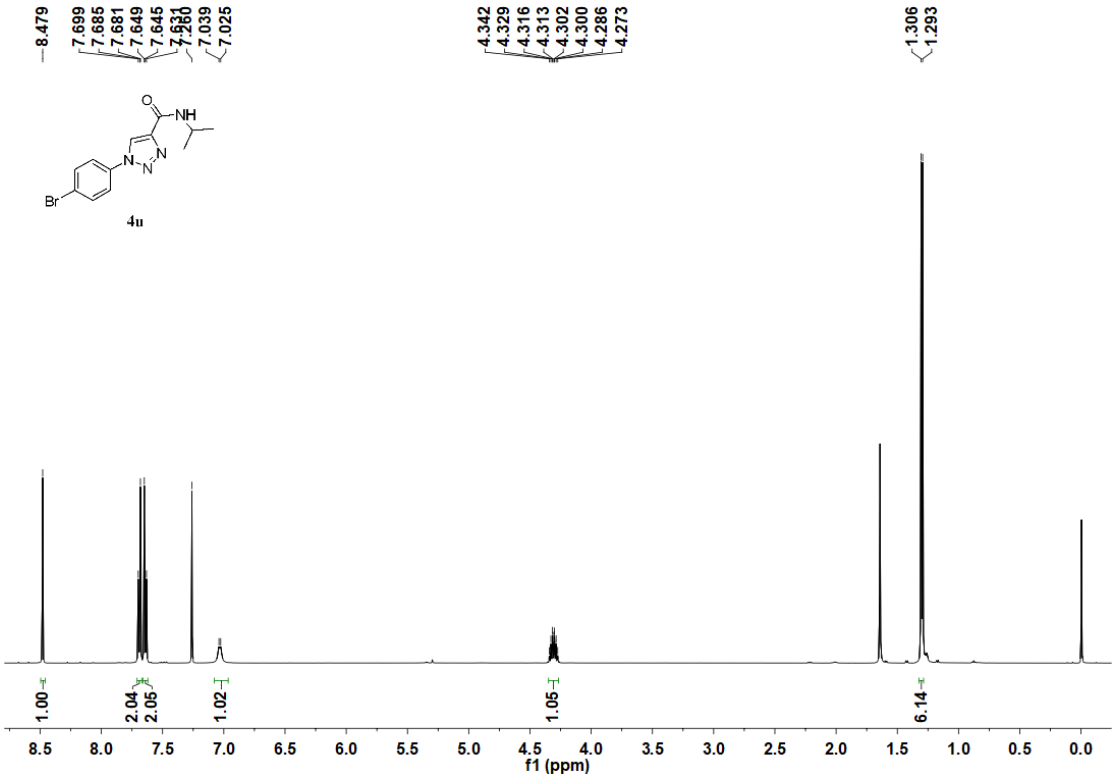

1.00
4.04
2.07
2.06
2.08
2.07
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

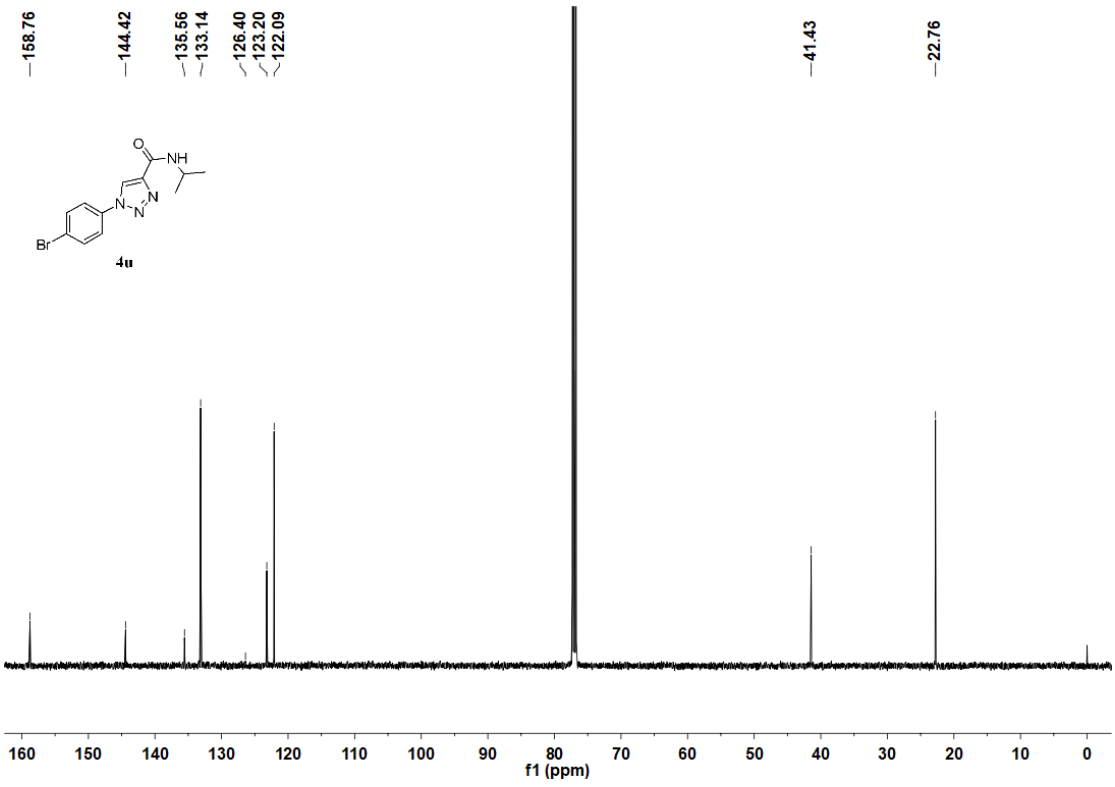

159.12
146.03
135.56
133.10
125.51
123.01
122.03
48.76
47.05
26.56
23.82
O
N
N
N
Br
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

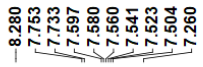
4s

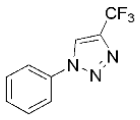

8.510
7.692
7.674
7.662
7.644
7.260
4.027
4.014
4.000
3.986
3.593
3.579
3.564
3.550
1.361
1.347
1.333
1.272
1.258
1.244
Br
4t
1.00
4.09
2.00
2.03
3.02
3.00
f1 (ppm)


160.13
145.89
135.56
133.10
126.01
122.97
121.96
43.14
41.39
14.77
12.83
Br
4t
f1 (ppm)

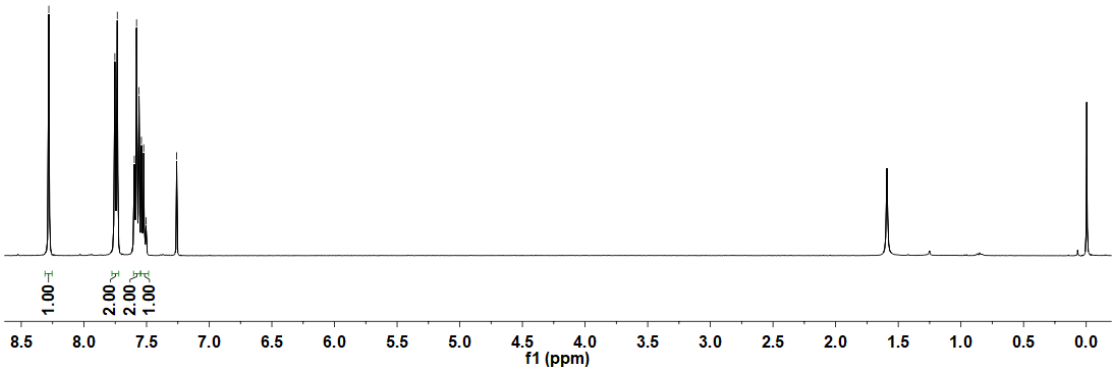

8.479
7.699
7.685
7.681
7.649
7.645
7.039
7.025
4.342
4.329
4.316
4.313
4.302
4.300
4.286
4.273
1.306
1.293
NH
N
N
N
Br
4u
1.00
2.04
2.05
1.02
1.05
6.14
f1 (ppm)


158.76
144.42
135.66
133.14
126.40
123.20
122.09
41.43
22.76
NH
N
N
N
Br
4u
f1 (ppm)

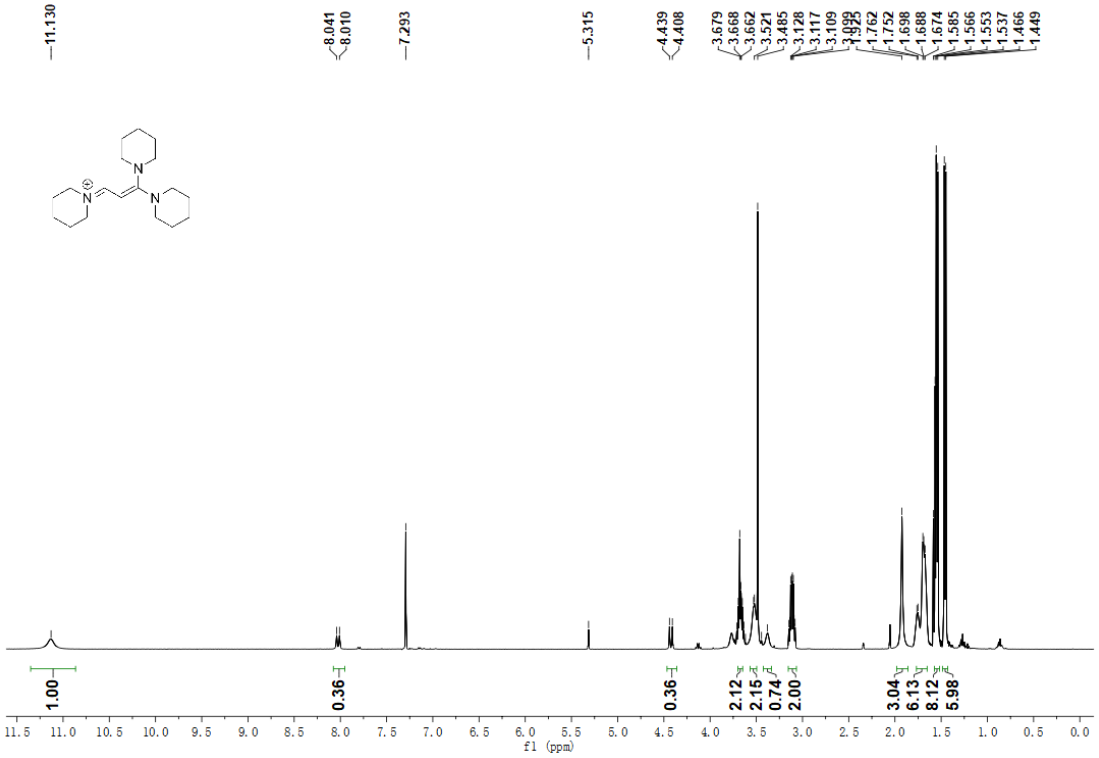

8.280
7.753
7.733
7.597
7.580
7.560
7.541
7.523
7.504
7.260

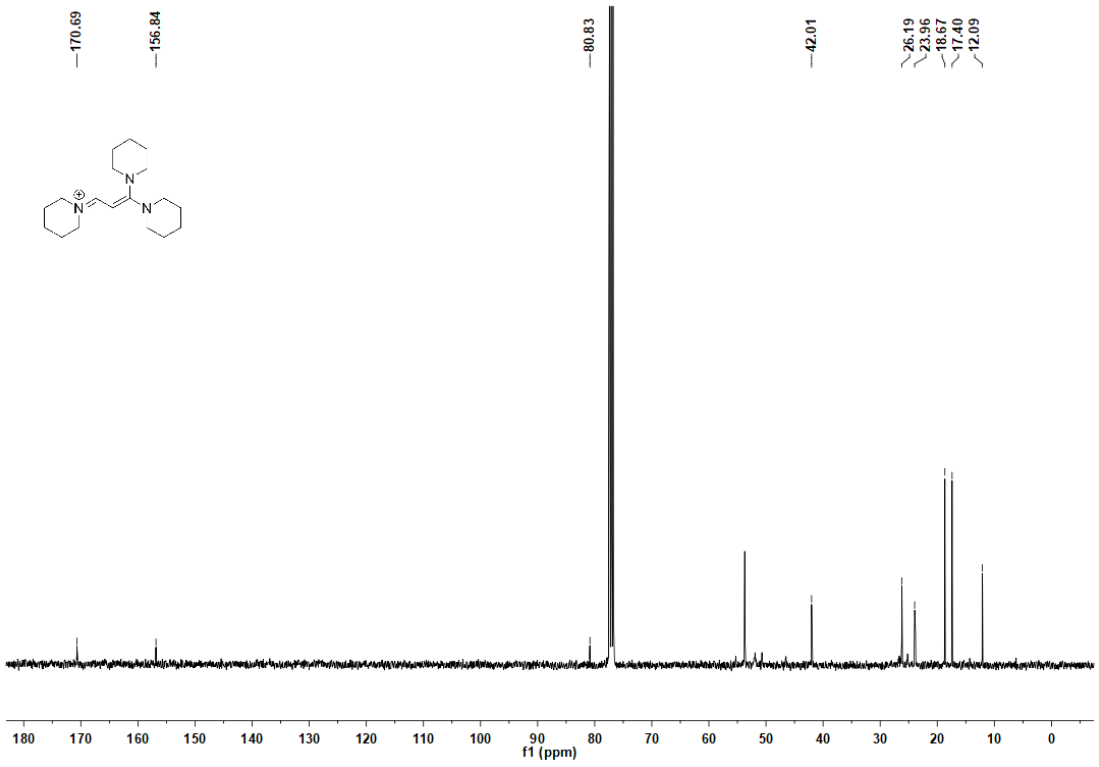

CF3
N
N
N

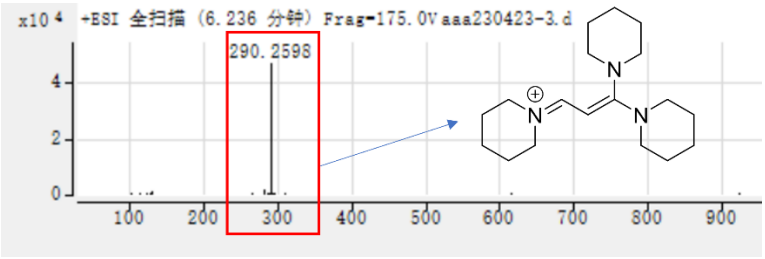
5

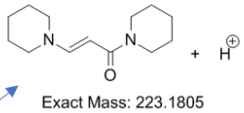

1.00
2.00
2.00
1.00
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

4. NMR/HRMS Spectra of Intermediates









Exact Mass: 223.1805

User Spectra

Fragmentor Voltage	Collision Energy	Ionization Mode
175	0	ESI