Experimental Investigation on the Mechanism of Chelation-Assisted, Copper(II) Acetate-Accelerated Azide-Alkyne Cycloaddition

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Supporting Information

1. Materials and General Methods

Reagents and solvents were purchased from various commercial sources and used without further purification unless otherwise stated. The purity of $Cu(OAc)_2 \cdot H_2O$ is over 99%. Analytical thin-layer chromatography (TLC) was performed using TLC plates precoated with silica gel 60 F254. Flash column chromatography was performed using 40-63 μm (230-400 mesh ASTM) silica gel as the stationary phase. Silica gel was carefully flame-dried under vacuum to remove adsorbed moisture before use. ^{1}H and ^{13}C NMR spectra were recorded at 300 and 75 MHz or 500 and 125 MHz, respectively. ^{1}H NMR kinetic studies were conducted using a 500 MHz spectrometer. All chemical shifts were reported in δ units relative to tetramethylsilane. High resolution mass spectra were obtained at the Mass Spectrometry Laboratory at FSU. Spectrophotometric and fluorimetric measurements were conducted on a Varian Cary 100 Bio UV-Visible Spectrophotometer and a Varian Cary Eclipse Fluorescence Spectrophotometer, respectively. The synthesis of compound **7** followed a known procedure.[1] Azide and triazole products that are not listed in section 3 (Characterizations of new compounds prepared in the screening experiments) are previous reported.[2,3]

2. Representative procedure for conditional screening experiments

To an azide solution (0.2 mmol in 0.5 mL) in a 1-dram vial was added an alkyne (0.22 mmol) and $Cu(OAc)_2 \cdot H_2O$ (25 μL, 0.4 M in H_2O). The reaction mixture was stirred between 500-600 rps and TLCs were typically taken every 5 min for shorter reactions and every 15 to 30 min for longer reactions to monitor the disappearance of the azide component. Completion time was dependent on stirring rate, the size and shape of the stir bar, and the reaction container. Essentially the variation in completion time largely arose from the heterogeneous nature of the reaction. Therefore, in order to obtain consistent reaction completion times, same type of container and stirring rate were used for all the reactions in the screening experiments. All experiments were conducted in triplicates or more.

Figure S1. Azide **1** (A and C) and **2** (B and D) reacted with phenylacetylene in organic solvents (from left to right: CH_3CN, THF, CH_2Cl_2, and toluene) at the start of the reactions (top) and after the reactions were completed (bottom).

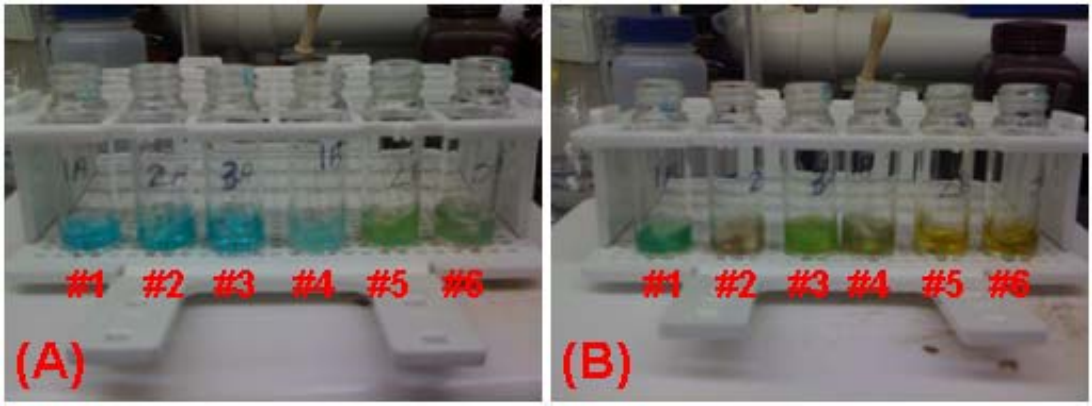


Figure S2. Azide **1** (#1-3) or **2** (#4-6) reacted with phenylacetylene in different alcoholic solvents (#1/4: t-BuOH, #2/5: MeOH, #3/6: i-PrOH). (A) Colors at the start of the reaction; (B) colors at the end of the reaction 5 min later.

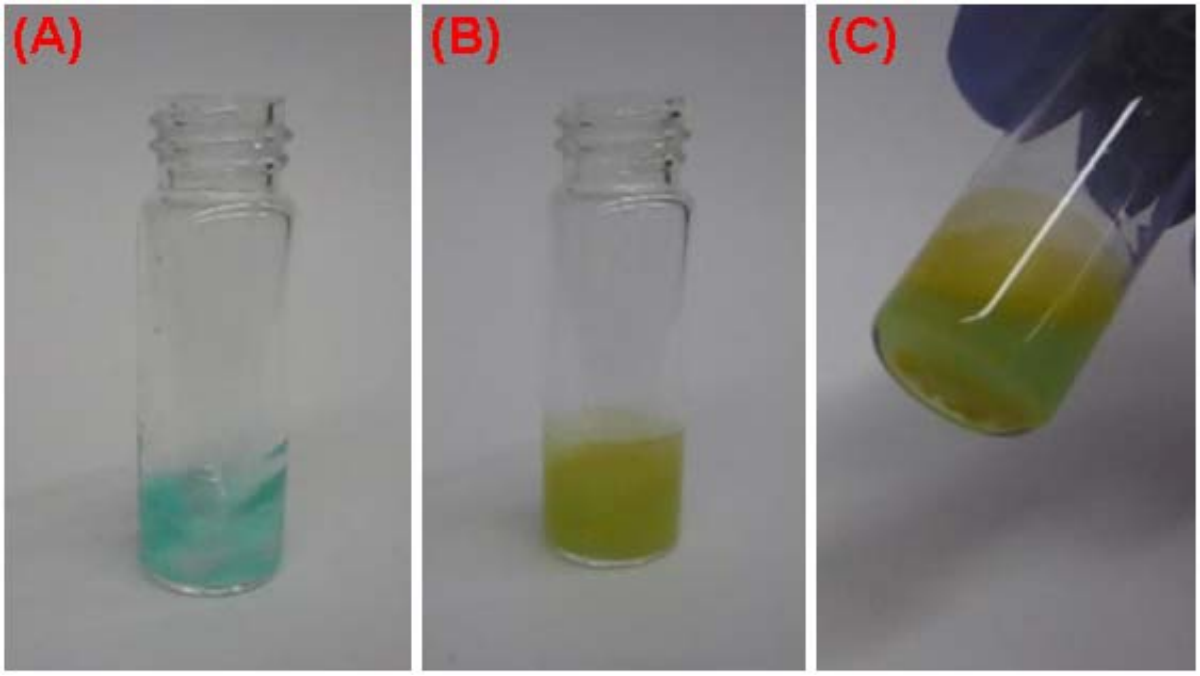
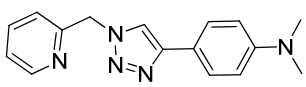


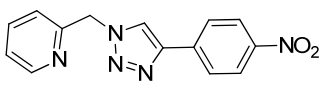
Figure S3. Left: beginning of reaction (Table 1, Entry 8, **T1**); Middle: end of reaction after 5 min; Right: View of the yellow organic solid in green-colored aqueous solution. In pure water in the absence of a pH buffer, the reaction took 40 min to complete.

3. Characterizations of new compounds

General procedure for preparative syntheses of the triazole compounds. Azide (0.2 mmol) in 1-dram vials was dissolved in CH_3CN (0.5 mL). In the case of azide **3**, one equivalent of triethylamine (TEA) was added. To the azide solution the alkyne was added (0.22 mmol), which was followed by the addition of $Cu(OAc)_2$ (25 μL, 0.4 M in H_2O). The reaction mixture was stirred for 18 h to ensure completion. The reaction mixture was filtered through a pad of either silica or alumina gel. The product was obtained upon solvent removal. No chromatography or further workup was necessary unless otherwise noted.

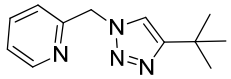


The product was isolated in 94% yield (52.6 mg) as an off-white powder. ^{1}H NMR (500 MHz, $CDCl_3$): δ/ppm 8.59 (ddd, J = 4.9, 1.7, 0.9 Hz, 1H), 7.76 (s, 1H), 7.69 (dt, J = 9.0, 2.2 Hz, 2H), 7.65 (td, J = 7.8, 1.8 Hz, 1H), 7.23 (ddd, J = 7.5, 7.5, 1.0 Hz, 1H), 7.18 (d, J = 7.8 Hz, 1H), 6.74 (dt, J = 9.0, 2.2 Hz, 2H), 5.66 (s, 2H), 2.96 (s, 6H). ^{13}C NMR (125 MHz, $CDCl_3$): δ/ppm 155.1, 150.7, 149.8, 148.9, 137.4, 126.9, 123.4, 122.4, 119.1, 118.8, 112.7, 55.8, 40.6. HRMS $[M+H]^+$: 280.1562 (calc.), 280.1563 (found).

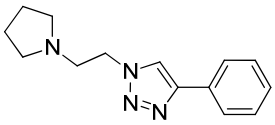


The product was isolated in 98% yield (55.6 mg) as a light yellow solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ/ppm 8.63 (ddd, J = 5.0, 1.8, 1.0 Hz, 1H), 8.27 (dt,

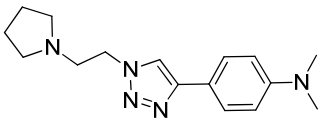
J = 8.9, 2.2 Hz, 2H), 8.13 (s, 1H), 8.00 (dt, J = 9.0, 2.2 Hz, 2H), 7.73 (td, J = 7.8, 1.8 Hz, 1H), 7.34-7.28 (m, 2H), 5.73 (s, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ/ppm 154.0, 150.2, 147.5, 146.2, 137.7, 137.0, 126.3, 124.5, 123.9, 122.9, 122.0, 56.0. HRMS $[M+H]^+$: 282.0991 (calc.), 282.0994 (found).



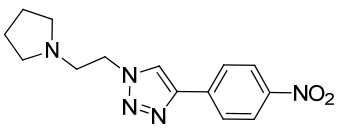
The product was isolated in 73% yield (31.7 mg) as a colorless solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ/ppm 8.61 (d, J = 4.7 Hz, 1H), 7.69 (t, J = 7.0 Hz, 1H), 7.40 (s, 1H), 7.30-7.25 (m, 1H), 7.17 (d, J = 7.8 Hz, 1H), 5.63 (s, 2H), 1.35 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$): δ/ppm 158.3, 155.1, 149.8, 137.5, 123.4, 122.5, 119.2, 55.7, 30.9, 30.5. HRMS $[M+Na]^+$: 239.1273 (calc.), 239.1271 (found).



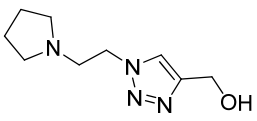
The product was isolated in 97% yield (47.1 mg) as a clear filmy solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ/ppm 7.90 (s, 1H), 7.83 (dt, , J = 7.2 Hz, 1.3, 2H), 7.41 (t, J = 7.6 Hz, 2H), 7.32 (tt, J = 7.4, 1.6 Hz, 1H), 4.51 (t, J = 6.6 Hz, 2H), 2.98 (t, J = 6.5 Hz, 2H), 2.58-2.53 (m, 4H), 1.81-1.75 (m, 4H). ^{13}C NMR (125 MHz, $CDCl_3$): δ/ppm 147.7, 130.9, 128.9, 128.1, 125.8, 120.3, 55.7, 54.2, 49.6, 23.7. HRMS $[M+H]^+$: 243.1610 (calc.), 243.1609 (found).



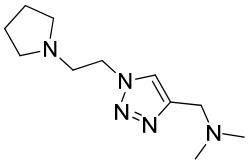
The product was isolated in 86% yield (48.9 mg) as an off-white solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ/ppm 7.74 (s, 1H), 7.70 (d, J = 9.0 Hz, 2H), 6.77 (d, J = 9.0 Hz, 2H), 4.50 (t, J = 6.9 Hz, 2H), 2.99-2.96 (m, 8H), 2.58-2.54 (m, 4H), 1.81-1.75 (m, 4H). ^{13}C NMR (125 MHz, $CDCl_3$): δ/ppm 150.5, 148.3, 126.8, 119.2, 118.9, 112.7, 55.8, 54.4, 49.6, 40.7, 23.8. HRMS $[M+H]^+$: 286.2032 (calc.), 286.2030 (found).



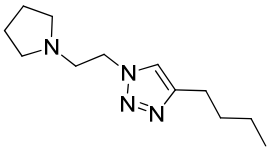
The product was isolated in 95% yield (54.5 mg) as a light yellow solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ/ppm 8.30 (d, J = 9.0 Hz, 2H), 8.07 (s, 1H), 8.02 (d, J = 9.0 Hz, 2H), 4.56 (t, J = 6.3 Hz, 2H), 3.01 (t, J = 6.3 Hz, 2H), 2.61-2.55 (m, 4H), 1.83-1.77 (m, 4H). ^{13}C NMR (125 MHz, $CDCl_3$): δ/ppm 147.4, 145.6, 137.4, 126.3, 124.5, 122.0, 55.6, 54.3, 49.8, 23.8. HRMS $[M+H]^+$: 288.1460 (calc.), 288.1457 (found).



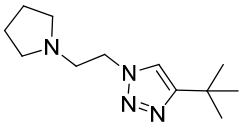
The product was isolated in 78% yield (30.7 mg) as a clear oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ/ppm 7.70 (s, 1H), 4.77 (d, J = 1.9 Hz, 2H), 4.47 (td, J = 6.6, 1.0 Hz, 2H), 2.90 (td, J = 6.7, 0.8 Hz, 2H), 2.59-2.50 (m, 4H), 1.83-1.75 (m, 4H). ^{13}C NMR (125 MHz, $CDCl_3$): δ/ppm 147.9, 122.6, 56.4, 55.7, 54.3, 49.5, 23.7. HRMS $[M+H]^+$: 197.1402 (calc.), 197.1404 (found).



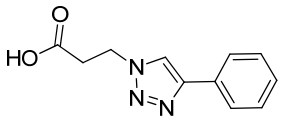
The product was isolated in 69% yield (30.8 mg) as a yellow, oily solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ/ppm 7.64 (s, 1H), 4.46 (td, J = 6.5, 1.9 Hz, 2H), 3.60 (d, J = 2.0 Hz, 2H), 2.93 (td, J = 6.7, 1.6 Hz, 2H), 2.55-2.50 (m, 4H), 2.25 (d, J = 2.4 Hz, 6H), 1.79-1.73 (m, 4H). ^{13}C NMR (125 MHz, $CDCl_3$): δ/ppm 144.7, 123.4, 55.7, 54.4, 54.2, 49.5, 45.1, 23.6. HRMS $[M+H]^+$: 224.1875 (calc.), 224.1881 (found).



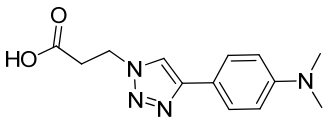
The product was isolated in 76% yield (34.0 mg) as a clear filmy solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ/ppm 7.36 (s, 1H), 4.42 (t, J = 6.8 Hz, 2H), 2.92 (t, J = 6.8 Hz, 2H), 2.69 (t, J = 7.7 Hz, 2H), 2.55-2.50 (m, 4H), 1.80-1.73 (m, 4H), 1.67-1.59 (m, 2H), 1.41-1.32 (m, 2H), 0.91 (t, J = 7.4 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ/ppm 148.4, 121.2, 55.8, 54.3, 49.4, 31.8, 25.6, 23.7, 22.5, 14.0. HRMS $[M+H]^+$: 223.1924 (calc.), 223.1923 (found).



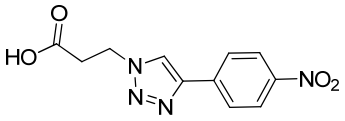
The product was isolated in 96% yield (37.7 mg) as a light yellow solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ/ppm 7.34 (s, 1H), 4.45 (t, J = 7.0 Hz, 2H), 2.96 (t, J = 7.0 Hz, 2H), 2.59-2.53 (m, 4H), 1.83-1.77 (m, 4H), 1.36 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$): δ/ppm 157.8, 119.1, 55.9, 54.4, 49.5, 30.9, 30.6, 23.8. HRMS $[M+H]^+$: 223.1923 (calc.), 223.1911 (found).



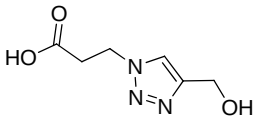
The crude product was subjected to an acidic workup (pH ~ 1). The acidic aqueous layer was neutralized with sodium bicarbonate and then the compound was extracted to the organic phase using EtOAc. The pure product in 100% yield (43.4 mg) as a white solid was afforded upon solvent removal under a reduced pressure. ^{1}H NMR (500 MHz, CD_3OD): δ/ppm 8.26 (s, 1H), 7.78 (dt, J = 7.2, 1.3 Hz, 2H), 7.41 (t, J = 7.5 Hz, 2H), 7.32 (tt, J = 7.4, 1.4 Hz, 1H), 4.70 (t, J = 6.7 Hz, 2H), 3.01 (t, J = 6.6 Hz, 2H). ^{13}C NMR (125 MHz, CD_3OD): δ/ppm 173.9, 148.9, 131.9, 130.1, 129.4, 126.8, 122.8, 47.3, 35.3. HRMS $[M+Na]^+$: 240.0749 (calc.), 240.0744 (found).



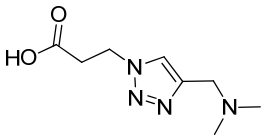
The crude product was dissolved in EtOAc and subjected to an acidic workup (pH ~ 1). The acidic aqueous layer was neutralized with sodium bicarbonate and then the compound was extracted to the organic phase using EtOAc. The organic layer was dried with sodium sulfate. Following solvent removal under a reduced pressure, the product was obtained in 76% yield (39.4 mg) as a light pink solid. ^{1}H NMR (500 MHz, CD_3OD): δ/ppm 8.12 (s, 1H), 7.62 (J = 8.8 Hz, 2H), 6.80 (d, J = 8.7 Hz, 2H), 4.67 (t, J = 6.6 Hz, 2H), 3.04-2.97 (m, 8H). ^{13}C NMR (125 MHz, CD_3OD): δ/ppm 174.3, 152.3, 149.5, 127.7, 121.2, 119.9, 114.0, 47.3, 40.9, 35.5. HRMS $[M+Na]^+$: 283.1171 (calc.), 283.1175 (found).



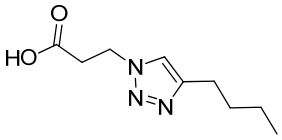
The crude product, after filtering through a pad of silica gel using EtOAc, was subjected to an acidic workup (pH ~ 1). The organic layer was dried with sodium sulfate. The product was isolated in 69% yield (36.2 mg) as a light yellow solid. ^{1}H NMR (500 MHz, CD_3OD): δ/ppm 8.55 (s, 1H), 8.32 (d, J = 8.9 Hz, 2H), 8.07 (d, J = 8.9 Hz, 2H), 4.74 (t, J = 6.5 Hz, 2H), 3.04 (t, J = 6.5 Hz, 2H). ^{13}C NMR (125 MHz, CD_3OD): δ/ppm 173.9, 148.8, 146.6, 138.3, 127.4, 125.4, 124.7, 47.5, 35.1. HRMS $[M+Na]^+$: 285.0600 (calc.), 285.0600 (found).



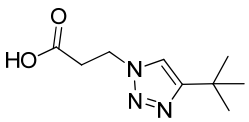
The crude product was dissolved in MeOH and the solvent was removed under a reduced pressure. It was repeated for several times until all TEA was removed to afford the product in 50% yield (17.2 mg) as a yellow solid. ^{1}H NMR (500 MHz, CD_3OD): δ/ppm 7.92 (s, 1H), 4.68-4.60 (m, 4H), 2.82 (t, J = 6.8 Hz, 2H). ^{13}C NMR (125 MHz, CD_3OD): δ/ppm 176.0, 149.0, 124.6, 56.6, 48.0, 37.2. HRMS $[M+Na]^+$: 194.0542 (calc.), 194.0538 (found).



The crude product was dissolved in MeOH and the solvent was removed under a reduced pressure. It was repeated for several times until all TEA was removed to afford the product in 98% yield as a white solid. ^{1}H NMR (500 MHz, CD_3OD): δ/ppm 8.16 (s, 1H), 4.68 (t, J = 6.5 Hz, 2H), 4.25 (s, 2H), 2.79 (t, J = 6.8 Hz, 2H), 2.72 (s, 6H). ^{13}C NMR (125 MHz, CD_3OD): δ/ppm 177.7, 139.3, 127.8, 52.9, 43.3, 38.6. HRMS $[M+H]^+$: 199.1195 (calc.), 199.1191 (found).



The crude product, after filtering through a pad of silica gel using EtOAc, was subjected to an acidic workup (pH ~ 1) to afford the pure product in 31% yield (12.3 mg) as a yellow oil. ^{1}H NMR (500 MHz, CD_3OD): δ/ppm 7.23 (s, 1H), 4.61 (t, J = 6.6 Hz, 2H), 2.94 (t, J = 6.6 Hz, 2H), 2.68 (t, J = 7.5 Hz, 2H), 1.68-1.59 (m, 2H), 1.42-1.33 (m, 2H), 0.95 (t. J = 7.4 Hz, 3H). ^{13}C NMR (125 MHz, CD_3OD): δ/ppm 174.1, 149.2, 123.7, 47.1, 35.4, 32.9, 26.1, 23.4, 14.3. HRMS $[M+H]^+$: 198.1242 (calc.), 198.1238 (found).



The crude product, after filtering through a pad of silica gel using EtOAc, was subjected to an acidic workup (pH ~ 1) to afford the pure product in 90% yield (35.5 mg) as a yellow oil. ^{1}H NMR (500 MHz, CD_3OD): δ/ppm 7.75 (s, 1H), 4.61 (t, J = 6.6 Hz, 2H), 2.95 (t, J = 6.7 Hz, 2H), 1.33 (s, 9H). ^{13}C NMR (125 MHz, CD_3OD): δ/ppm 174.0, 158.5, 121.8, 47.0, 35.3, 31.8, 30.8. HRMS $[M+Na]^+$: 220.1062 (calc.), 220.1064 (found).

4. Synthesis and characterizations of compounds 7-9

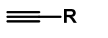
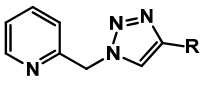
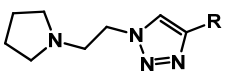
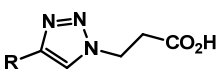
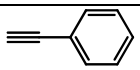
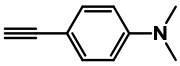
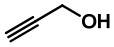
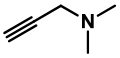
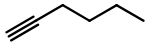
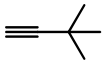
Compound 7.[1] ^{1}H NMR (300 MHz, $CDCl_3$): δ/ppm 7.68 (d, J = 9.5 Hz, 1H), 7.44-7.36 (m, 3H), 6.43 (d, J = 9.5 Hz, 1H), 3.27 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ/ppm 160.1, 153.5, 142.6, 127.9, 127.6, 125.5, 120.1, 119.0, 117.1, 82.0, 80.6.

Compound 8. 2-Picolylazide **1** (27.2 mg, 0.20 mmol) was added to a 2-dram sample vial along with a seed stir bar. tBuOH (0.5 mL), **7** (34.0 mg, 0.20 mmol), CH_3CN (0.5 mL) were added sequentially followed by the $Cu(OAc)_2 \cdot H_2O$ stock solution in water (25 µL, 0.4 M, 10 µmol). The reaction mixture was capped and allowed to stir at rt for 1 h. The solution was diluted with CH_2Cl_2 and dried down on a rotatory evaporator. The mixture was diluted with CH_2Cl_2 and loaded onto a short plug of silica gel. After elution with EtOAc, the solvent was removed under vacuum to afford the pure product as a white solid **8** (60.2 mg, 99%). ^{1}H NMR (300 MHz, DMSO-d_6): δ/ppm 8.86 (s, 1H), 8.56 (d, J = 4.5 Hz, 1H), 8.08 (d, J = 9.5 Hz, 1H), 7.90-7.77 (m, 4H), 7.39-7.37 (m, 2H), 6.48 (d, J = 9.5 Hz, 1H), 5.79 (s, 2H). ^{13}C NMR (75 MHz, DMSO-d_6): δ/ppm 169.4, 164.2, 163.6, 159.0, 154.6, 153.4, 146.9, 143.7, 138.6, 133.2, 132.8, 131.8, 130.7, 127.7, 125.3, 121.7, 64.2. HRMS (ESI) $[M+H]^+$ 305.1038 (calcd.), 305.1052 (found).

Compound 9. Compound **7** (34.0 mg, 0.20 mmol), TBTA (5.3 mg, 0.01 mmol) and $Cu(OAc)_2 \cdot H_2O$ (40.3 mg, 0.20 mmol) were added in a vial containing CH_3CN (5 mL) and stirred at rt for 12 h. The mixture was dried down on a rotatory evaporator. The residue was loaded onto a short plug of silica gel which was eluted using CH_2Cl_2/EtOAc from 100/0 to 0/100. After combining the correct fractions, the solvent was removed under vacuum to afford the product as a white solid (13.6 mg, 20%). ^{1}H NMR (500 MHz, DMSO-d_6): δ/ppm 8.09 (d, J = 9.5 Hz, 2H), 7.78 (d, J = 8.0 Hz, 2H), 7.71 (s, 2H), 7.58 (d, J = 7.9 Hz, 2H), 6.56 (d, J = 9.5 Hz, 2H). ^{13}C NMR (125 MHz, DMSO-d_6): δ/ppm 158.8, 152.9, 142.8, 128.5, 127.8, 122.9, 119.9, 119.4, 117.0, 81.6, 75.3. HRMS (EI^+) 338.0579 (calcd.), 338.0579 (found).

5. Alkyne screening experiment conducted in CH_3CN

Table S1. Effect of alkyne on the $Cu(OAc)_2$-accelerated reactions involving chelating azides **1**-**3**.[a]

Entry		Time[b] 	Time[b] 	Time[b] 
1		55 min	3.5 h	8 h (92%)[c]
2		10 min	30 min	8 h (94%)[c]
3		30 min	30 min	60 min
4		< 5 min	60 min	90 min
5		< 5 min	8 h (92%),[c] 75 min[d]	N.R.[e]
6		3.5 h	8 h (81%)[c]	8 h (72%)[c]
7		8 h (18%)[c]	8 h (22%)[c]	8 h (3%)[c]

a. Reaction conditions: organic azide (0.2 mmol), alkyne (0.22 mmol), $Cu(OAc)_2$ (5 mol%), in CH_3CN (0.5 mL), rt. For reactions involving azide **3**, TEA (0.2 mmol) was included. b. Time for azide to completely disappear on TLC, followed by the confirmation of full conversion by ^1H NMR. c. Incomplete conversion with percentage yield in parenthesis. d. 10 mol% $Cu(OAc)_2$ was used. e. N.R.: no reaction.

6. Table S2. Reaction order data from the work by Finn *et al.* and Mizuno *et al.* for comparison

entry	component	alkyne	azide	copper	solvent	order
1 (HPLC)[a]	phenylacetylene	10-25 mM	1 mM	0.1 mM	DMSO/H_2O (4/1)	0
2 (HPLC)[a]	benzylazide	1 mM	1-25 mM	0.1 mM	DMSO/H_2O (4/1)	-0.25
3 (HPLC)[a]	copper(I)	0.4 mM	0.4 mM	0.04-0.16 mM	DMSO/H_2O (4/1)	2.0
4 (GC)[b]	phenylacetylene	0.32-1.59 M	0.58 M	0.58 mM	CH_3CN	0
5 (GC)[b]	benzylazide	0.58 M	0.32-1.58 M	0.58 mM	CH_3CN	1
6 (GC)[b]	copper(II)	0.58 M	0.58 M	0.29-2.31 mM	CH_3CN	1[c]

a. Data reported by Finn, Fokin, *et al.* where $CuSO_4$/sodium ascorbate was the catalyst in an aqueous system.[4] b. Data reported by Mizuno, *et al.* where dicopper(II)-substituted silicotungstate was the precatalyst.[5] c. The first-order is consistent with the involvement of a stable dicopper(II)-substituted silicotungstate catalyst that is not in equilibrium with monomeric copper(II) species.

7. Representative procedure of the fluorescence assay

The stock solution of **7** (100 μM) in MeOH, **1** (50 mM) in MeOH and $Cu(OAc)_2{\cdot}H_2O$ (1 mM) in H_2O were prepared. The stock solutions of **7** (300 μL), **1** (300 μL), $Cu(OAc)_2{\cdot}H_2O$ (30 μL) and MeOH (2370 μL) were successively added via syringes to a cuvette with a seed stir bar. The mixture was capped and allowed to stir. The fluorescence intensity (λ_{ex} 320 nm and λ_{em} 400 nm) was determined every 0.25 min at 22 °C. The initial reaction rates were calculated according to the following derived equation.[6]

$$V = \frac{d[\mathbf{8}]}{dt} \approx \frac{\Delta[\mathbf{8}]}{\Delta t} = \frac{[\mathbf{8}]}{t}$$

$$I_0 \equiv k_{(\mathbf{7})}[\mathbf{7}]_0$$

$$I_\infty \equiv k_{(\mathbf{8})}[\mathbf{7}]_0$$

$$I_t = k_{(\mathbf{8})}[\mathbf{8}] + k_{(\mathbf{7})}([\mathbf{7}]_0 - [\mathbf{8}]) = \left(k_{(\mathbf{8})} - k_{(\mathbf{7})}\right)[\mathbf{8}] + k_{(\mathbf{7})}[\mathbf{7}]_0$$

$$[\mathbf{8}] = \frac{I_t - I_0}{k_{(\mathbf{8})} - k_{(\mathbf{7})}} = \frac{(I_t - I_0)[\mathbf{7}]_0}{I_\infty - I_0}$$

$$V \approx \frac{[7]}{t} = \frac{(I_t - I_0)[\mathbf{7}]_0}{(I_\infty - I_0)t}$$

8. Representative procedure of the ^{1}H NMR assay

Stock solutions of **7** (100 mM) in CD_3CN, **1** (100 mM) in CD_3CN, and $Cu(OAc)_2 \cdot H_2O$ (100 mM) in H_2O were prepared. The stock solutions of **7** (100 μL), **1** (100 μL), $Cu(OAc)_2 \cdot H_2O$ (10 μL), and CD_3CN (790 μL) were successively added via syringes to a vial. The combined solution was mixed for about 10 seconds before being transferred to an NMR tube (~0.6 mL). The reaction progress (production of triazole **8**) was monitored on a 500 MHz instrument. The data was collected every 5 min at 22 ^oC.

9. Deuterium kinetic isotope effect and substituent effect experiments

Stock solutions (200 mM) of both 2-picolylazide (**1**) and alkyne were prepared in CD_3CN. A fresh $Cu(OAc)_2$ stock solution (100 mM) in water was prepared daily. Both 2-picolylazide (**1**) and alkyne stock solutions (100 μL each) were added to a small vial followed by 790 μL of CD_3CN. After the target temperature of 313 K was reached and equilibrated in the NMR spectrometer, $Cu(OAc)_2$ stock solution (10 μL) was added to the vial to give a 1 mL total volume with the final concentrations of 2-picolylazide (**1**) and alkyne being 20 mM each and a $Cu(OAc)_2$ final concentration of 1 mM. The reaction mixture was then transferred into an NMR sample tube and loaded into the spectrometer. Multiple data scans were collected until the reaction was complete. Once complete, the percent conversion was calculated by determining the ratio of product to starting material through integration. The conversion data were plotted vs. time. The rate of the reaction was obtained from the slope of the linear portion immediately after the induction period.

10. Procedures for preparing the single crystals for X-ray diffraction

Synthesis of complex $[Cu_2(1)_2(OAc)_4]$. *Warning! Low molecular weight organic azides used in this study are potentially explosive. Appropriate protection measures should always be taken when handling these compounds.* Solutions of $Cu(OAc)_2 \cdot H_2O$ (0.20 g, 1.0 mmol) in CH_3CN (5 mL) and ligand **1** (0.27 g, 2.0 mmol) in CH_3CN (5 mL) were mixed. There was no initial color change of the solution. The solution was heated to 60 °C and stirred for ~ 4 h. The color of the solution turns deep green. The solvent was removed under a reduced pressure. The resulting deep green solid was washed with diethyl ether (3 × 10 mL) to afford the complex in powder form. The product was dissolved in a minimal amount of CH_3CN and filtered through a piece of glass microfiber. Slow evaporation of the CH_3CN solution gave dark green crystals that were suitable for X-ray diffraction. Yield = 0.554 g; 88%. Anal. Calcd for $C_{20}H_{24}Cu_2N_8O_8$: C, 38.04; H, 3.83; N, 17.74. Found: C, 38.00; H, 3.83; N, 17.45. λ_{max}/nm (ε_{max}/dm^3 mol^{-1} cm^{-1}) (CH_3OH), 701 (380).

Synthesis of complex $[Cu_2(6)_2](OAc)_4]$. *Warning! Low molecular weight organic azides used in this study are potentially explosive. Appropriate protection measures should always be taken when handling these compounds.* Complex $[Cu_2(\mathbf{6})_2](OAc)_4]$ was obtained by following a procedure analogous to that described for $[Cu_2(\mathbf{1})_2(OAc)_4]$. Azide **6** (0.30 g, 2.0 mmol) was used in place of 2-picolylazide **1**. The

product was dissolved in a minimal amount of CH_3CN and filtered through a piece of glass microfiber. Deep-green single crystals suitable for X-ray diffraction were obtained after the slow evaporation of the CH_3CN solution. Yield = 0.590 g; 89.5%. Anal. Calcd for $C_{22}H_{28}Cu_2N_8O_8$: C, 40.06; H, 4.28; N, 16.99. Found: C, 40.29; H, 4.26; N, 16.92. λ_{max}/nm (ε_{max}/dm^3 mol^{-1} cm^{-1}) (CH_3OH), 703 (390).

Synthesis of complex $[Cu_2(3)_4]_n$. *Warning! Low molecular weight organic azides used in this study are potentially explosive. Appropriate protection measures should always be taken when handling these compounds.* A solution of $Cu(OAc)_2{\cdot}H_2O$ (0.0995 g, 0.50 mmol) in CH_3CN (5 mL) was added into a solution of azidopropionic acid (0.115 g, 1.0 mmol) in CH_3CN (5 mL). The resulting mixture was heated to 45 °C and stirred for 1 h. The color of the solution becomes dark green. The solvent was subsequently removed under a reduced pressure. The resulting green solid was washed with diethyl ether (3 × 20 mL) to afford the complex in powder form in 81% yield. The product was dissolved in a minimal amount of CH_3CN and filtered through a piece of glass microfiber. Slow evaporation of the CH_3CN solution gave dark green crystals that were suitable for X-ray diffraction. Anal. Calcd for $C_6H_8CuN_6O_4$: C, 24.70; H, 2.76; N, 28.81. Found: C, 24.97; H, 2.72; N, 28.04.

Synthesis of complex $[Cu_{14}(tBuC{\equiv}C)_{10}(OAc)_4]$ and [tBuC≡CtBu]. 3,3-Dimethylbutyne (tBuC≡CH) (0.082 g, 1.0 mmol) in CH_3OH (2 mL) was added to a CH_3OH solution (5 mL) of $Cu(OAc)_2{\cdot}H_2O$ (0.20 g, 1.0 mmol) with continuous stirring. The color of the solution turns deep green. The solution was left to stand overnight in a closed vessel at rt. On the next day, white and yellow single crystals were precipitated out from the solution. The single crystals were collected by filtration and were separated. **Complex $[Cu_{14}(tBuC{\equiv}C)_{10}(OAc)_4]$:** Yield = 28%. Anal. Calcd for $C_{68}Cu_{14}O_8H_{12}$: C, 42.34; H, 4.91. Found: C, 42.37; H, 5.25. **Compound [tBuC≡CtBu]:** Yield = 45%. Anal. Calcd for $C_{24}H_{36}$: C, 88.82; H, 11.18. Found: C, 88.91; H, 11.12.

Isolation of $[Cu_4(OAc)_4(OCH_3)_4]$. 2-Picolylazide **1** (50 mg, 0.37 mmol) was dissolved in CH_3CN (~1 mL). Separately, $Cu(OAc)_2{\cdot}H_2O$ (74.4 mg, 0.37 mmol) was dissolved in a mixed solvent of CH_3CN and CH_3OH. The two solutions were combined, and the solvent was removed under vacuum. The resulting powder was washed with diethyl ether (3 × 15 mL). The product was then dissolved with a minimal amount of CH_3OH, filtered through a small plug of glass microfiber and set up in vapor diffusion chambers with diethyl ether. After 3-4 days, blue crystals that were suitable for X-ray diffraction formed. Upon solving the structure, it was determined to be the known compound $[Cu_4(OAc)_4(OCH_3)_4]$.

11. Additional figures

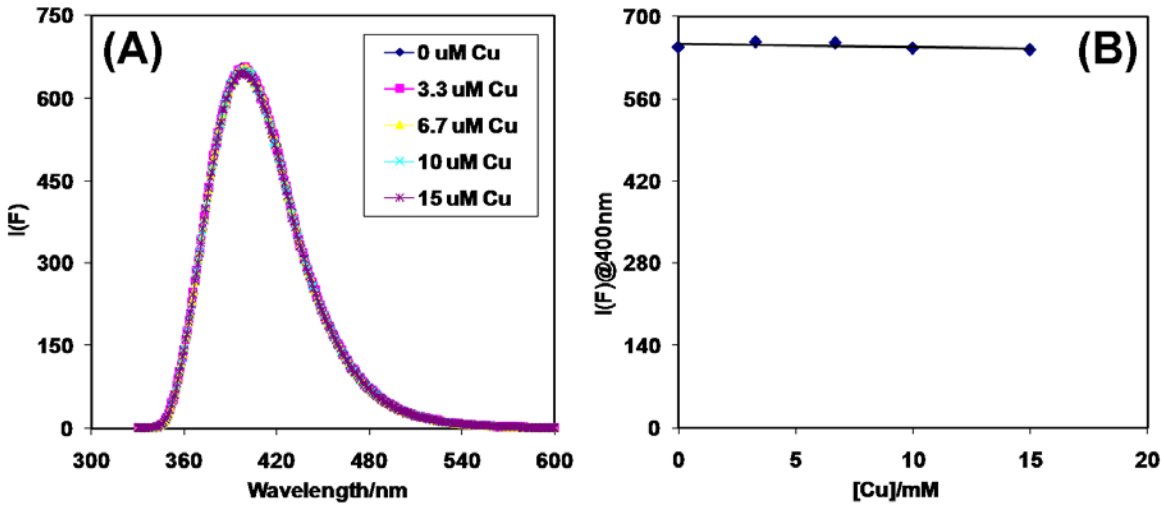


Figure S4. (A) Fluorimetric titration of **8** (10.0 μM, λ_{ex} 320 nm) with $Cu(OAc)_2 \cdot H_2O$ (0-15.0 μM) in CH_3OH. (B) Fluorescence intensity values at 400 nm *vs.* $[Cu(OAc)_2 \cdot H_2O]$.

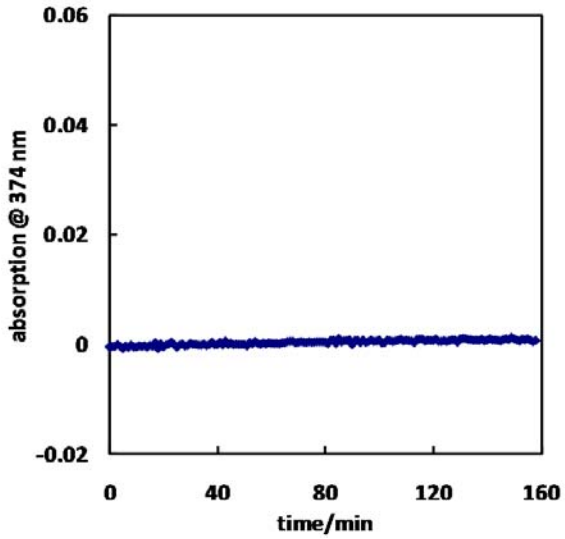


Figure S5. Time course of absorption at 374 nm with initial condition: [**7**] = 10 μM, [**1**] = 5 mM and $[Cu(OAc)_2 \cdot H_2O]$ = 10 μM in CH_3OH.

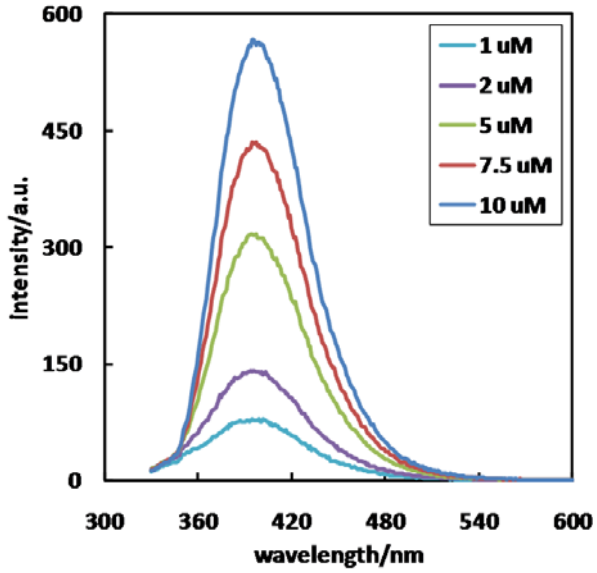


Figure S6. Spectra (λ_{ex} 320 nm) of the reactions shown in Figure 6 after 48 h, assuming full conversions are achieved. Conditions: [**1**] = 5 mM, [$Cu(OAc)_2 \cdot H_2O$] = 10 μM, and [**7**] = 1-10 μM in CH_3OH at 25 °C.

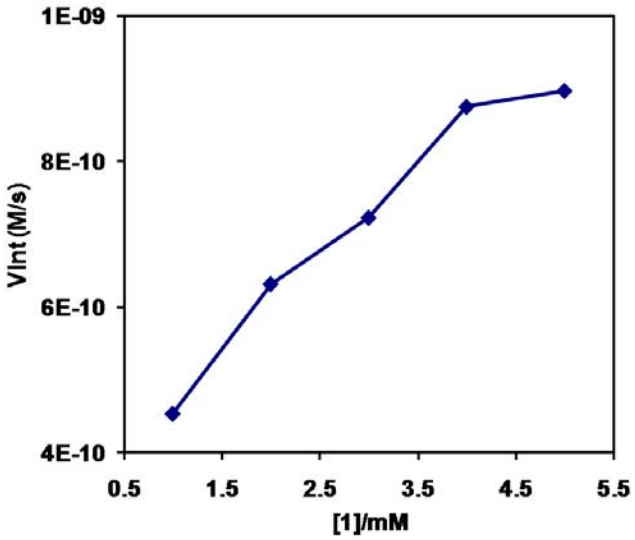


Figure S7. The dependence of V_{int} on [**1**]. Conditions: [**7**] = 10 μM, [$Cu(OAc)_2 \cdot H_2O$] = 10 μM, and [**1**] = 0.5-3.5 mM in CH_3OH.

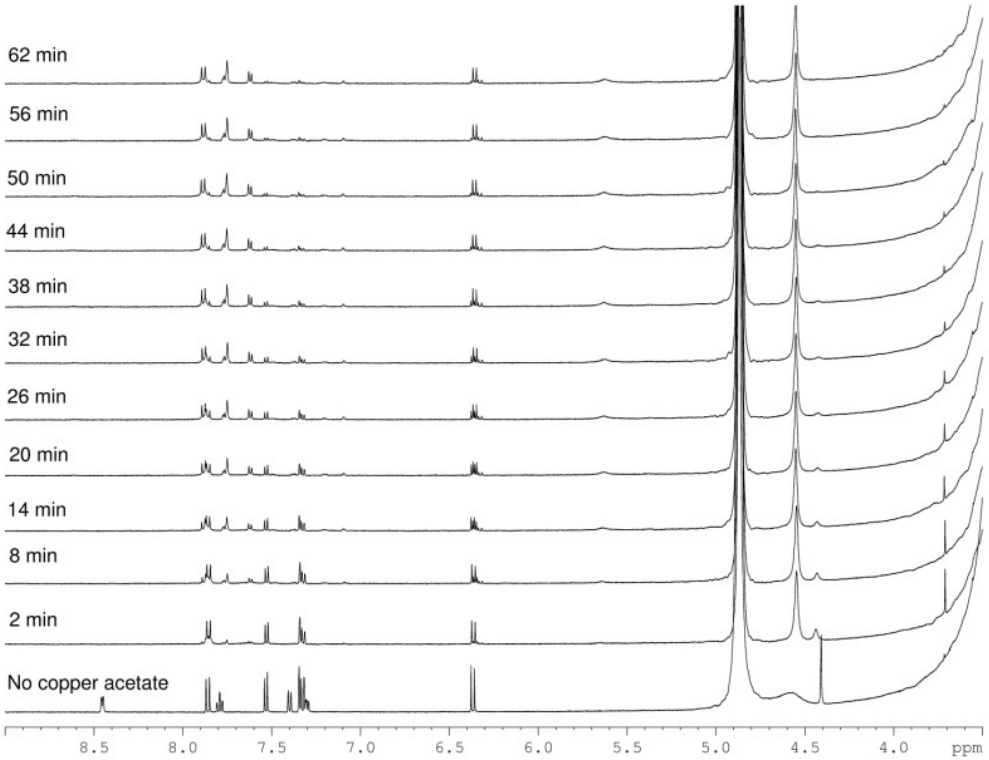


Figure S8. Time evolution of the ^{1}H NMR spectrum (bottom to top) of **7** (10 mM), **1** (10 mM) and $Cu(OAc)_2 \cdot H_2O$ (1 mM) in CD_3OD.

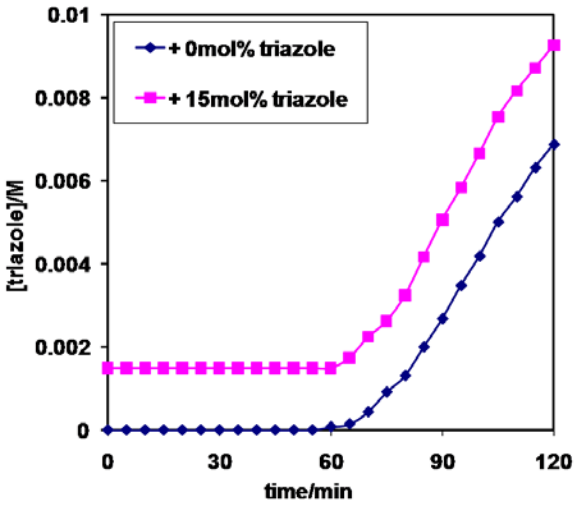


Figure S9. Time courses determined by integrating ^{1}H NMR signals of **8** in the presence or absence of initial triazole **8** addition at 15 mol%. Conditions: alkyne **7** (10 mM), 2-picolylazide **1** (10 mM), and $Cu(OAc)_2 \cdot H_2O$ (1 mM) in CD_3CN at 25 ^{o}C.

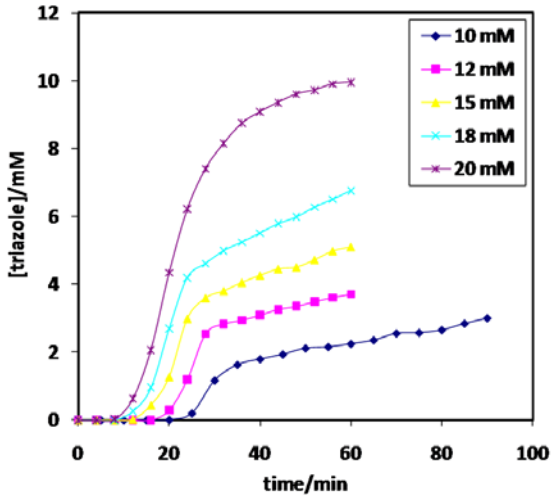


Figure S10. The dependence of reaction time course on [**2**]. Conditions: [**2**] = 10-20 mM, [$Cu(OAc)_2 \cdot H_2O$] = 1 mM, and [**7**] = 10 mM in CD_3CN at 40 °C. Full conversions of each reaction would afford **8** at 10 mM.

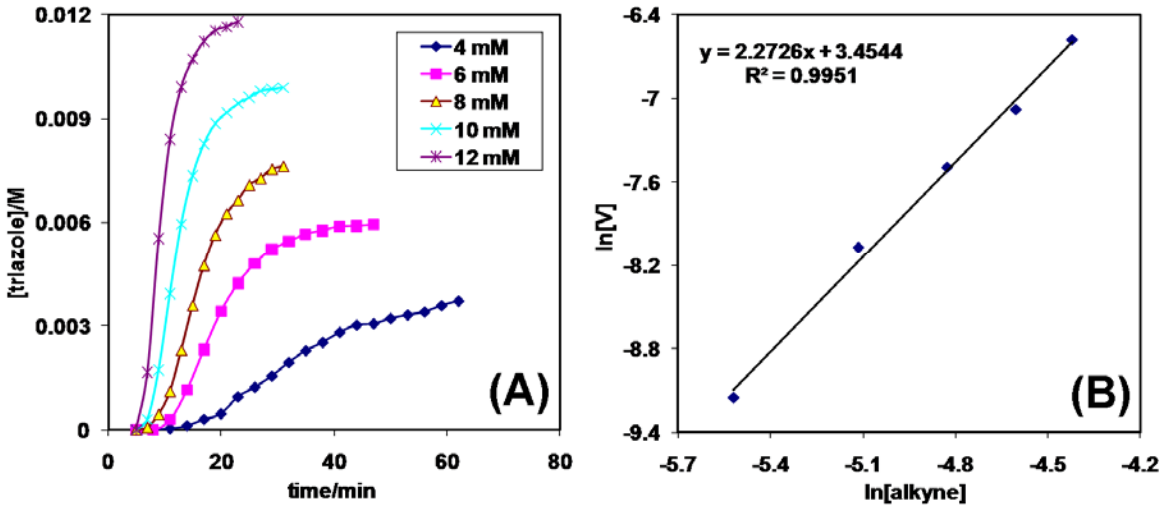


Figure S11. (A) Time courses for varying concentration of 1-ethynyl-4-nitrobenzene at 313 K. Conditions: [**2**] = 20 mM, [$Cu(OAc)_2 \cdot H_2O$] = 1 mM. Full conversions of each reaction would afford **8** at 4, 6, 8, 10, and 12 mM, respectively. (B) Plot for determining reaction order in alkyne.

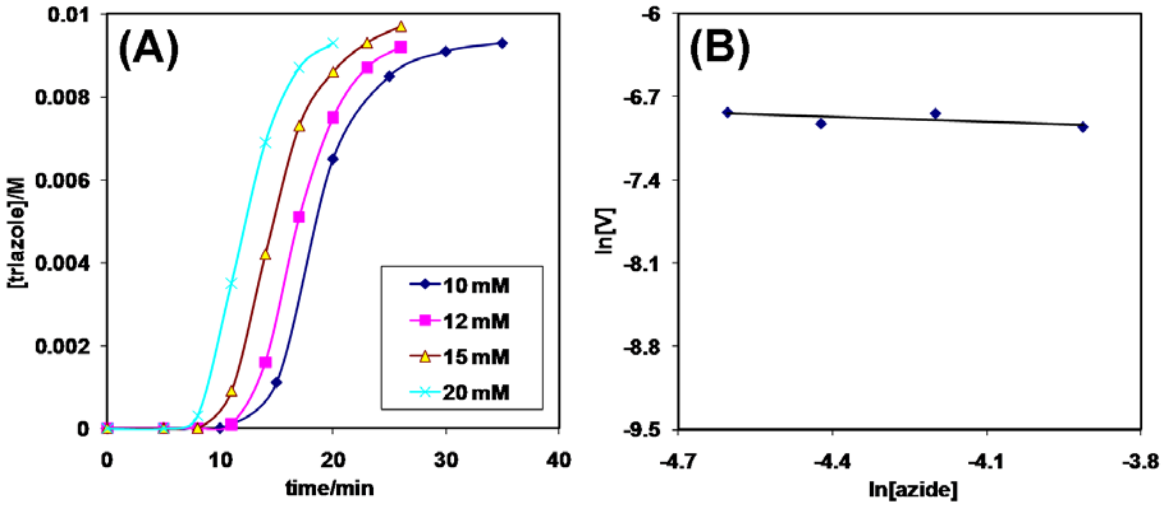


Figure S12. (A) Time courses for varying concentration of **2** at 313 K. Conditions: [1-ethynyl-4-nitrobenzene] = 10 mM, $[Cu(OAc)_2 \cdot H_2O]$ = 1 mM. Full conversions of each reaction would afford **8** at 10 mM. (B) Plot for determining reaction order of azide **2**.

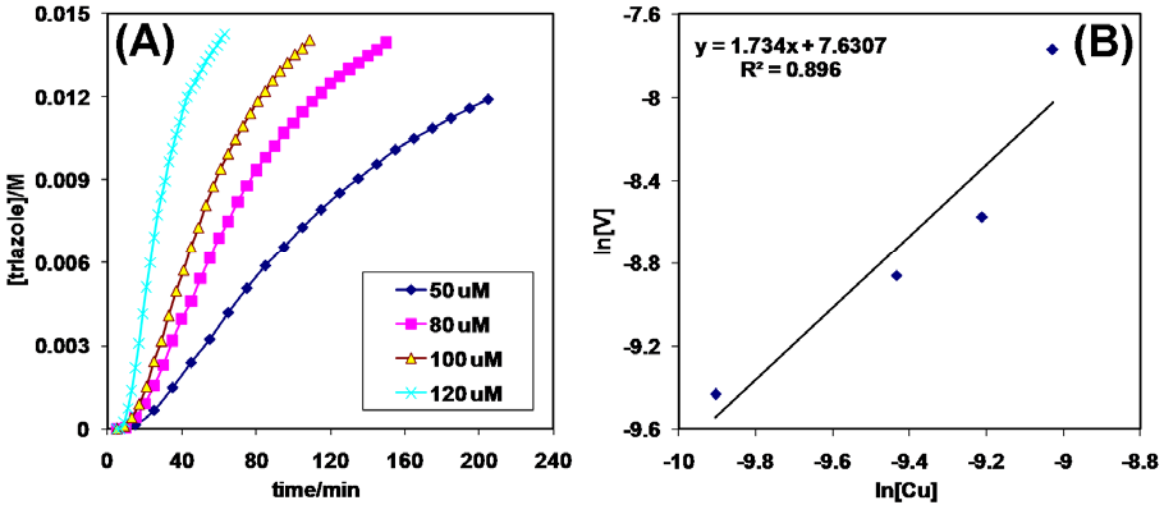


Figure S13. (A) Time courses for varying $[Cu(OAc)_2 \cdot H_2O]$ at 313 K. Conditions: [alkyne] = [**2**] =20 mM. Full conversions of each reaction would afford **8** at 20 mM. (B) Plot in determining the reaction order of $Cu(OAc)_2 \cdot H_2O$.

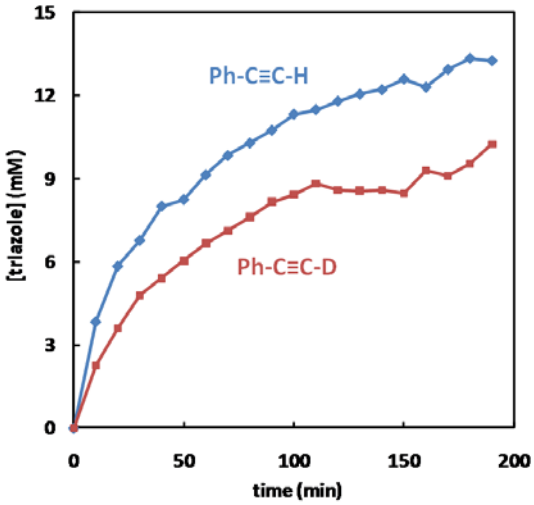


Figure S14. The time courses of triazole product formation determined by integrating ^{1}H NMR signals. Conditions: [**1**] = 20 mM, [$Cu(OAc)_2 \cdot H_2O$] = 2 mM, and [phenylacetylene] = 20 mM (cornflower) or [phenylacetylene-*d*] = 20 mM (garnet) in CD_3OD at 25 °C.

References:

(1) Chtchigrovsky, M.; Primo, A.; Gonzalez, P.; Molvinger, K.; Robitzer, M.; Quignard, F.; Taran, F. *Angew. Chem. Int. Ed.* **2009**, *48*, 5916-5920.

(2) Brotherton, W. S.; Michaels, H. A.; Simmons, J. T.; Clark, R. J.; Dalal, N. S.; Zhu, L. *Org. Lett.* **2009**, *11*, 4954-4957.

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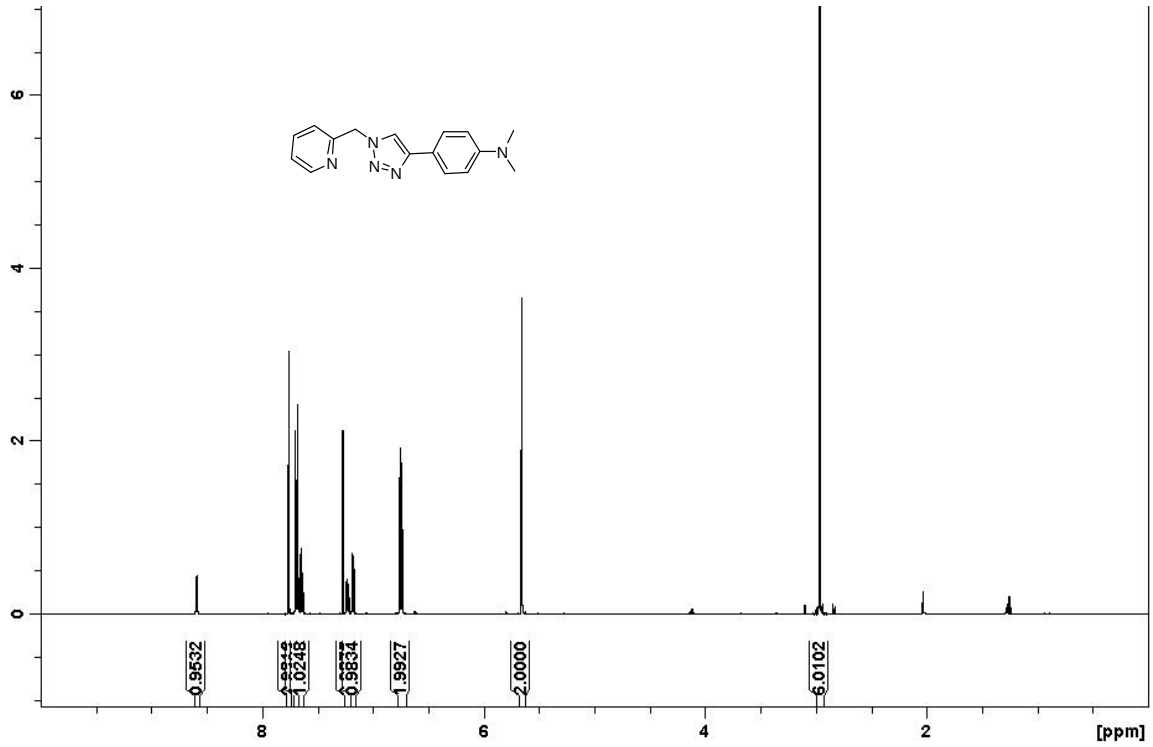
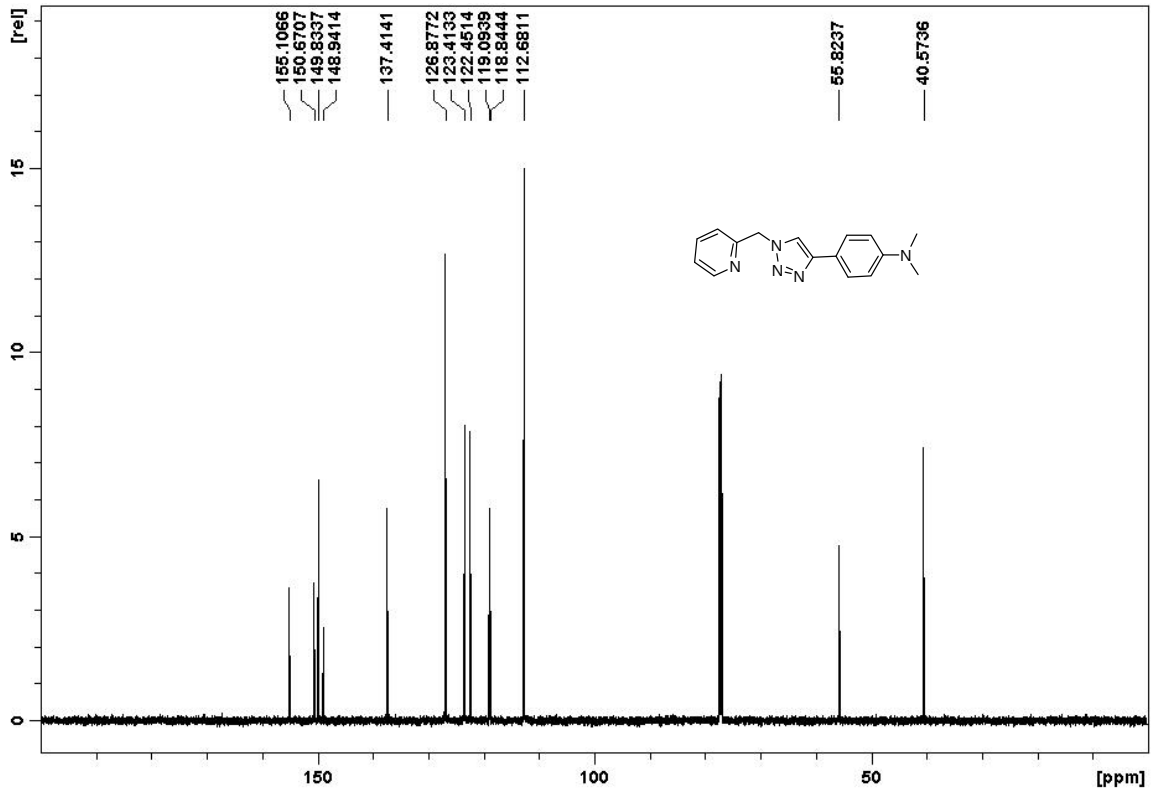
(4) Rodionov, V. O.; Fokin, V. V.; Finn, M. G. *Angew. Chem. Int. Ed.* **2005**, *44*, 2210-2215.

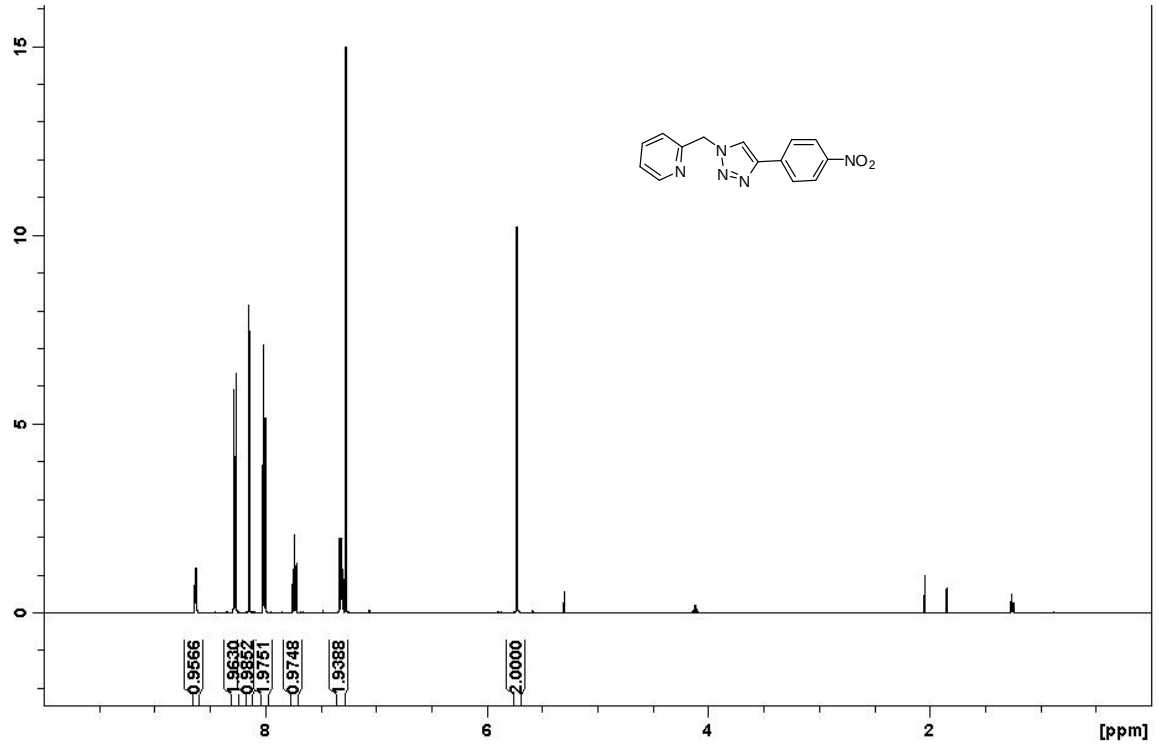
(5) Kamata, K.; Nakagawa, Y.; Yamaguchi, K.; Mizuno, N. *J. Am. Chem. Soc.* **2008**, *130*, 15304-15310.

(6) Wierzchowski, J.; Defeldecker, W. P.; Holmquist, B.; Vallee, B. V. *Anal. Biochem.* **1989**, *178*, 57-62.

Appendix: $^{1}H/^{13}C$ NMR spectra of new compounds.



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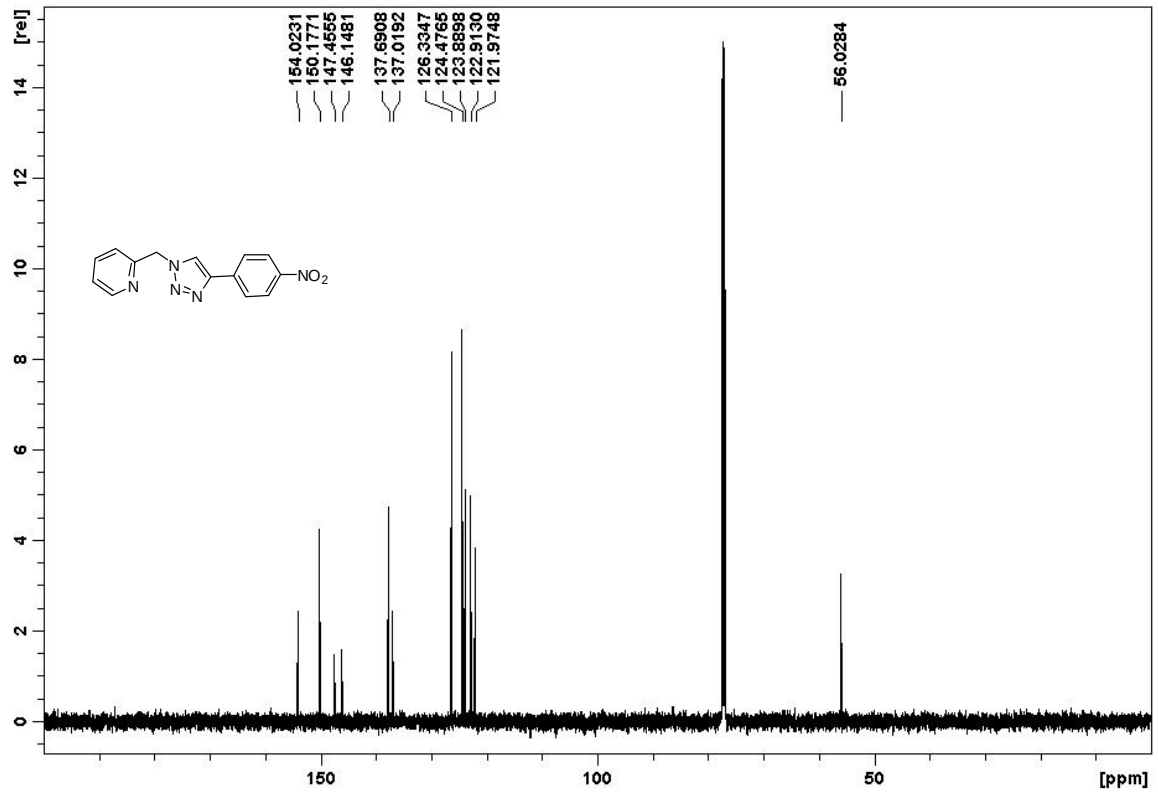
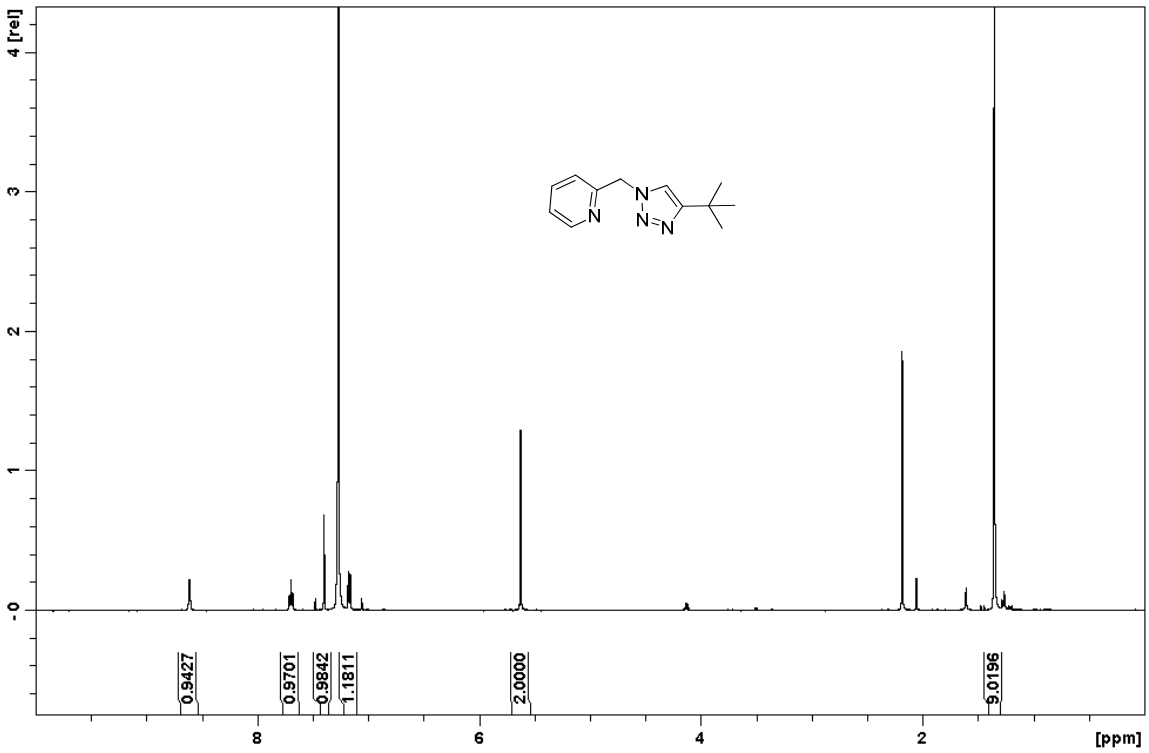
0.9852
1.9751
0.9748
1.9388
2.0000
[ppm]


154.0231
150.1771
147.4555
146.1481
137.6908
137.0192
126.3347
124.4765
123.8898
122.9130
121.9748
56.0284
[rel]
[ppm]


4 [rel]
3
2
1
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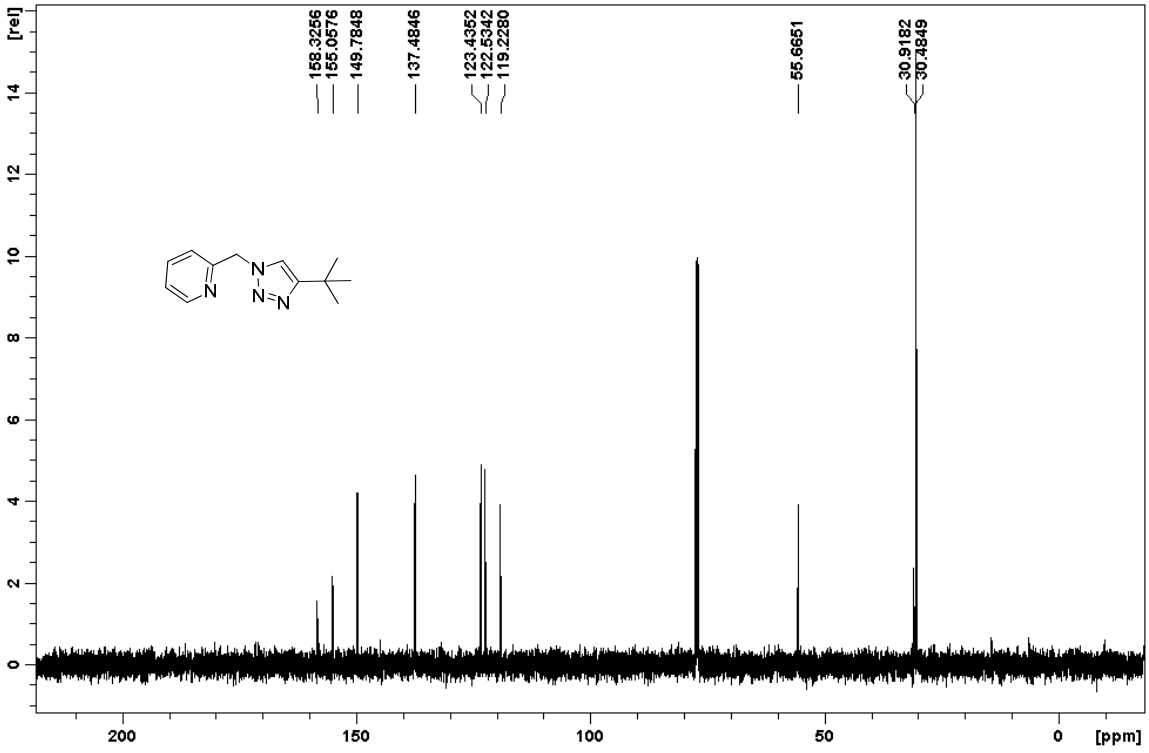
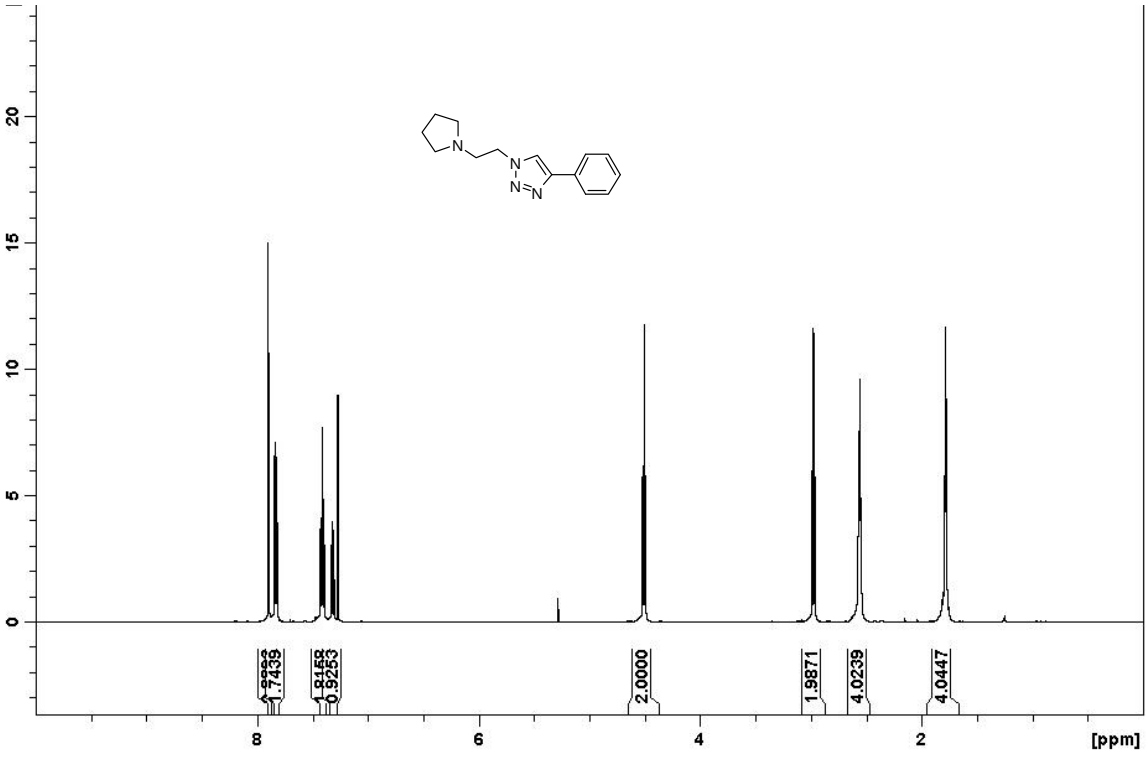
0.9427
0.9701
0.9842
1.1811
2.0000
9.0196
8
6
4
2
[ppm]


[rel]
158.3256
155.0576
149.7848
137.4846
123.4352
122.5342
119.2280
55.6651
30.9182
30.4849
14
12
10
8
6
4
2
0
200
150
100
50
0
[ppm]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0.9253
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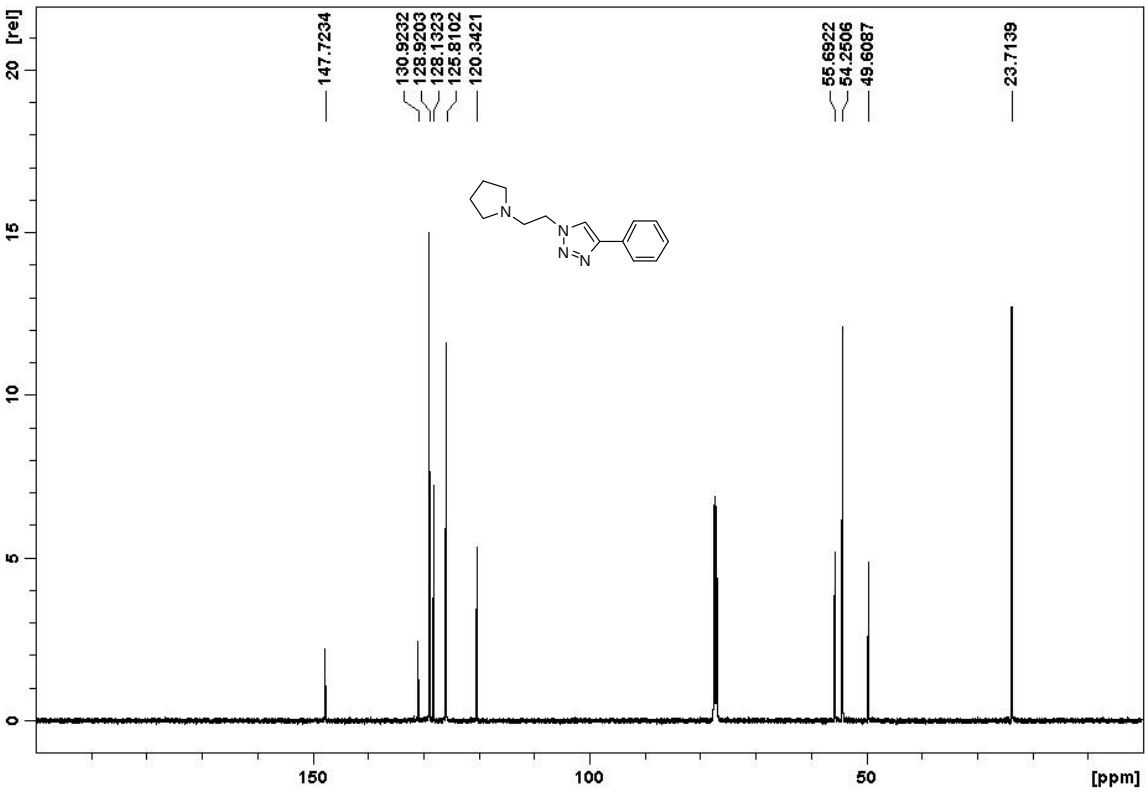
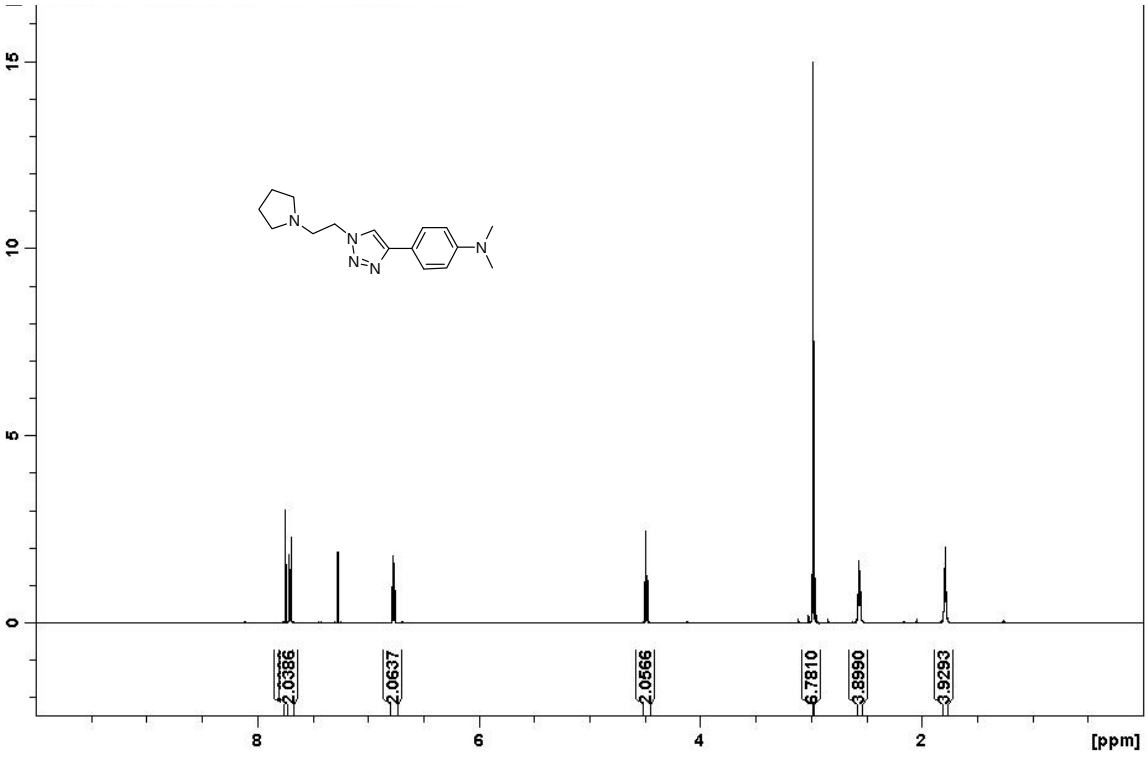
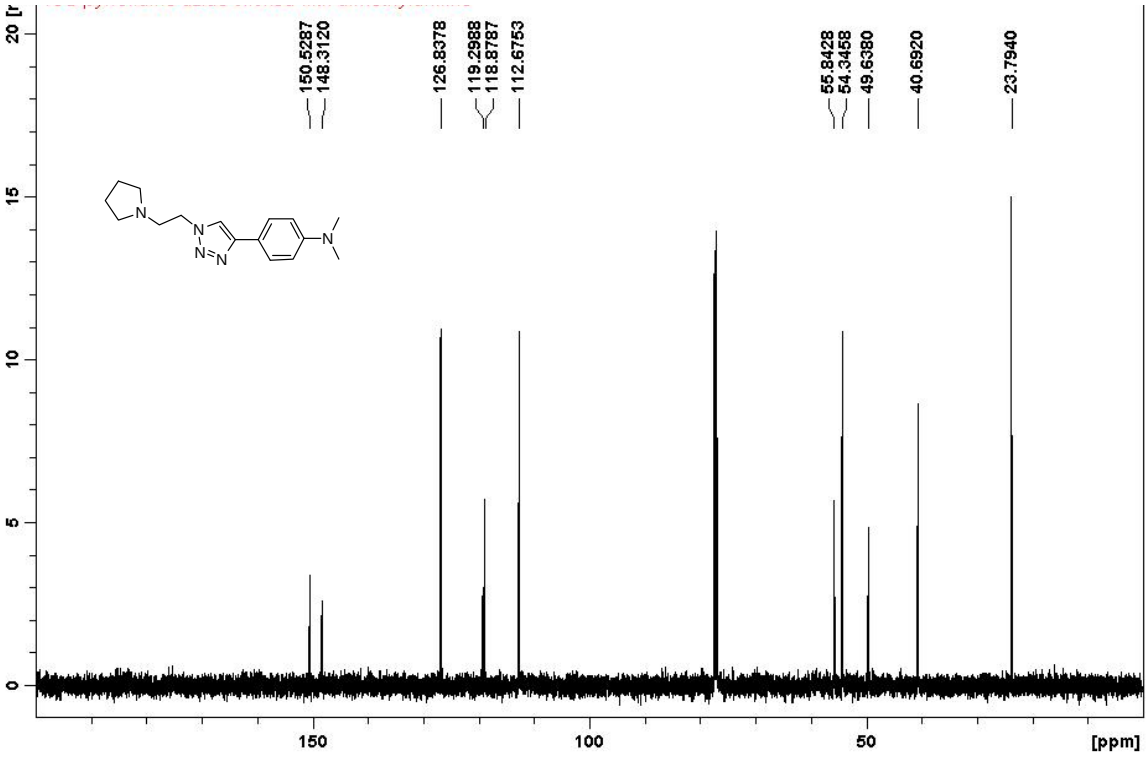
1.9871
4.0239
4.0447
8
6
4
2
[ppm]


[rel]
147.7234
130.9232
128.9203
128.1323
125.8102
120.3421
55.6922
54.2506
49.6087
23.7139
150
100
50
[ppm]


15
10
5
0
2.0386
2.0637
2.0566
6.7810
3.8990
3.9293
8
6
4
2
[ppm]


20
15
10
5
0
150.5287
148.3120
126.8378
119.2988
118.8787
112.6753
55.8428
54.3458
49.6380
40.6920
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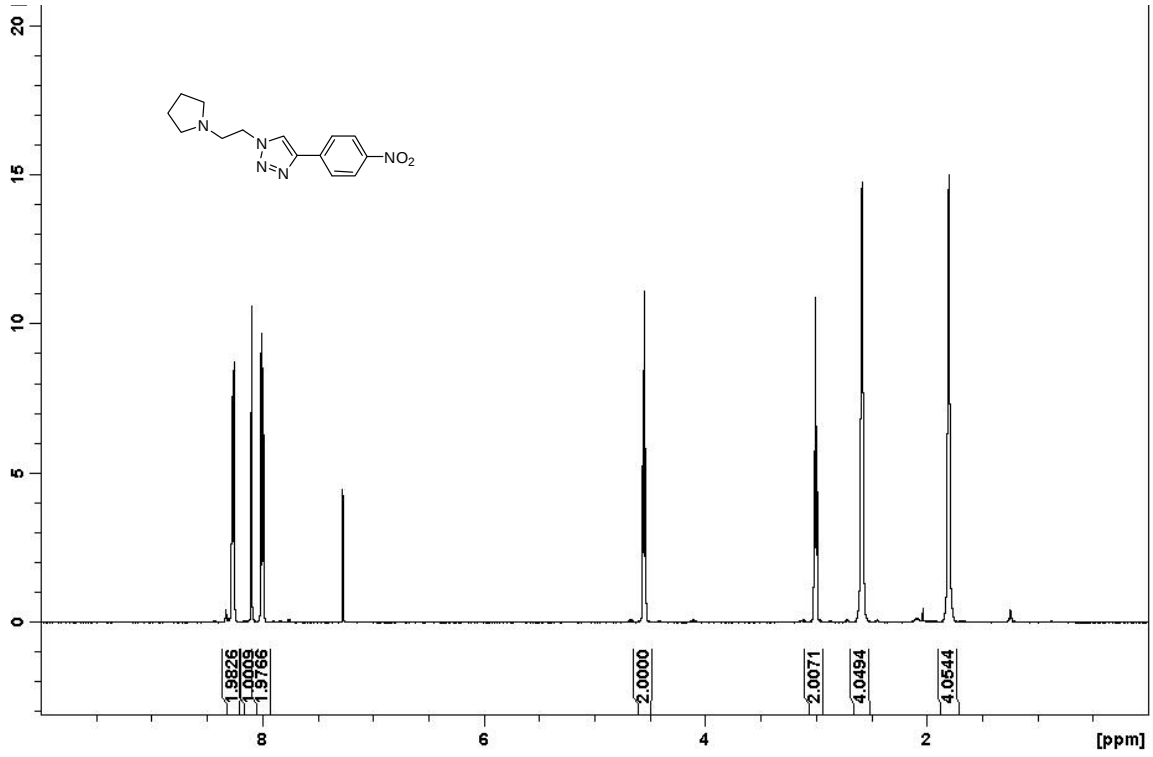
150
100
50
[ppm]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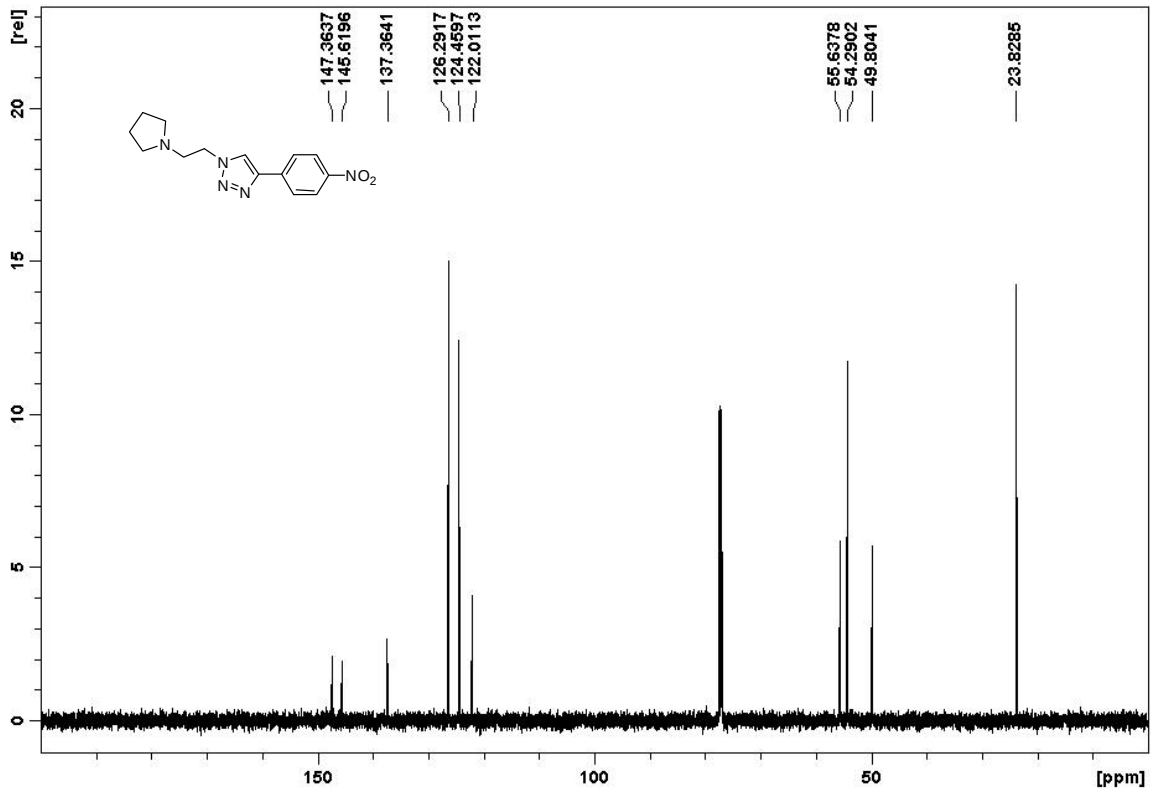
1.9766
2.0000
2.0071
4.0494
4.0544
[ppm]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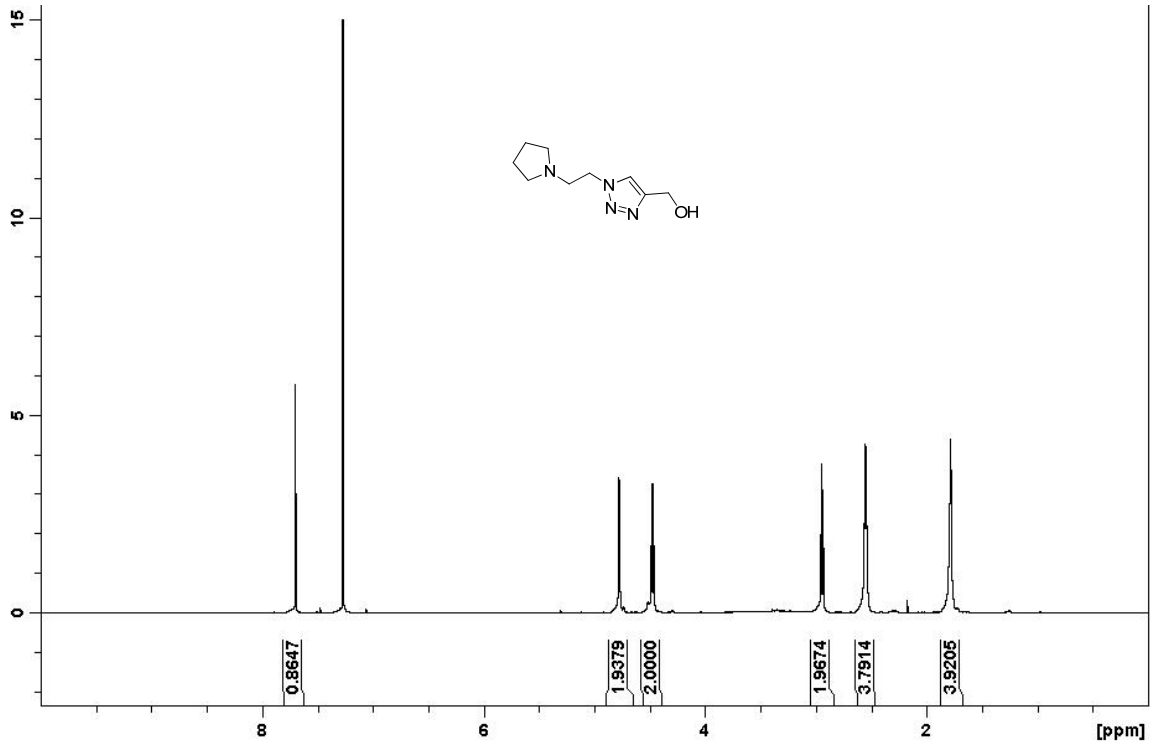
147.3637
145.6196
137.3641
126.2917
124.4597
122.0113
55.6378
54.2902
49.8041
23.8285
[ppm]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1.9674
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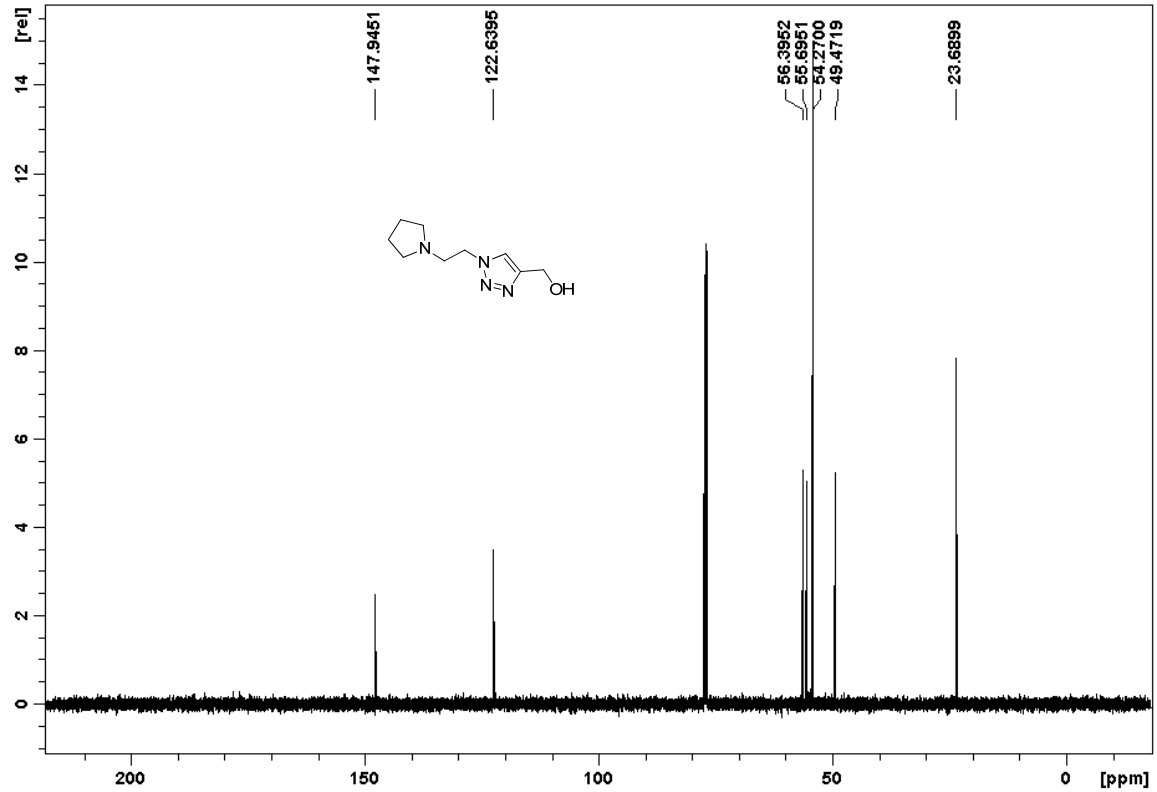
3.9205
[ppm]
OH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54.2700
49.4719
23.6899
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[ppm]
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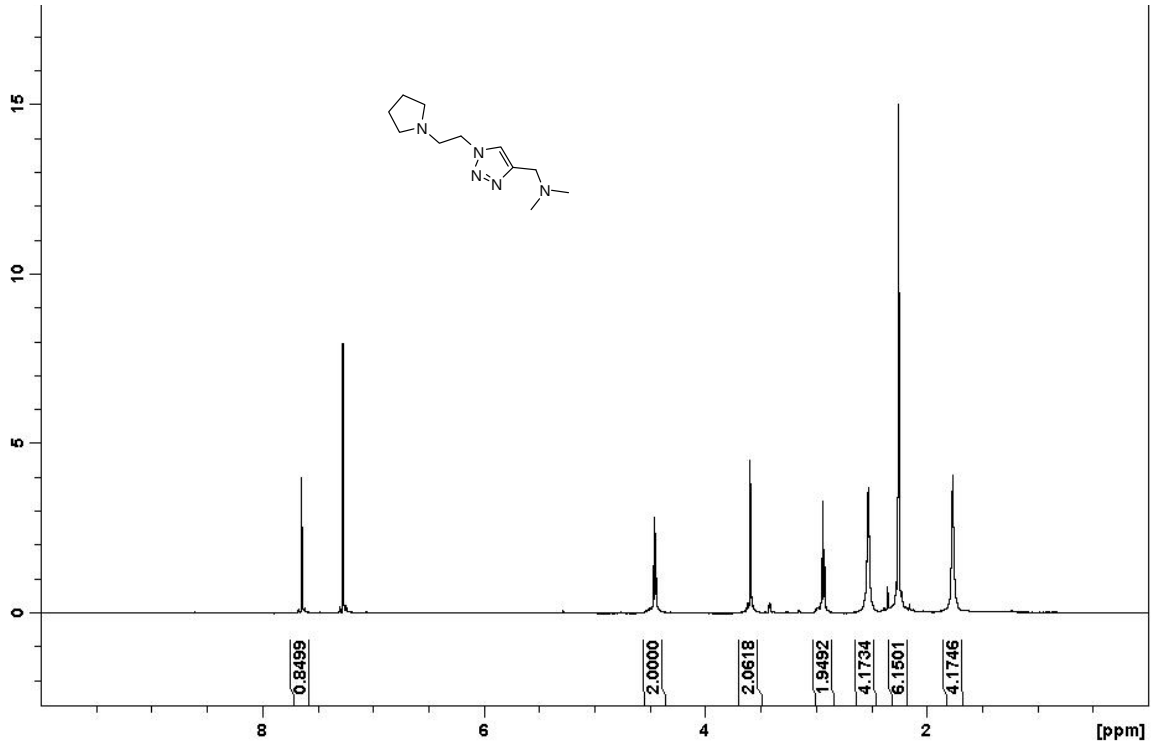
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2.0618
1.9492
4.1734
6.1501
4.1746
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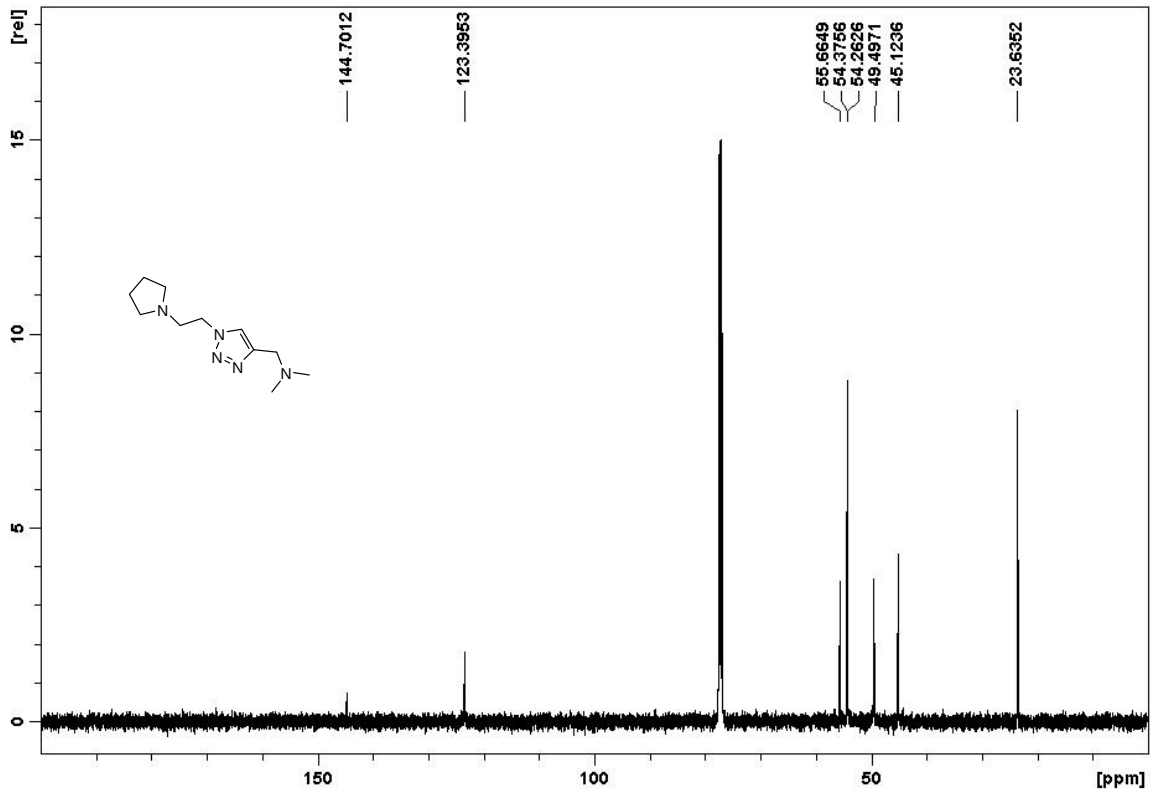
[rel]
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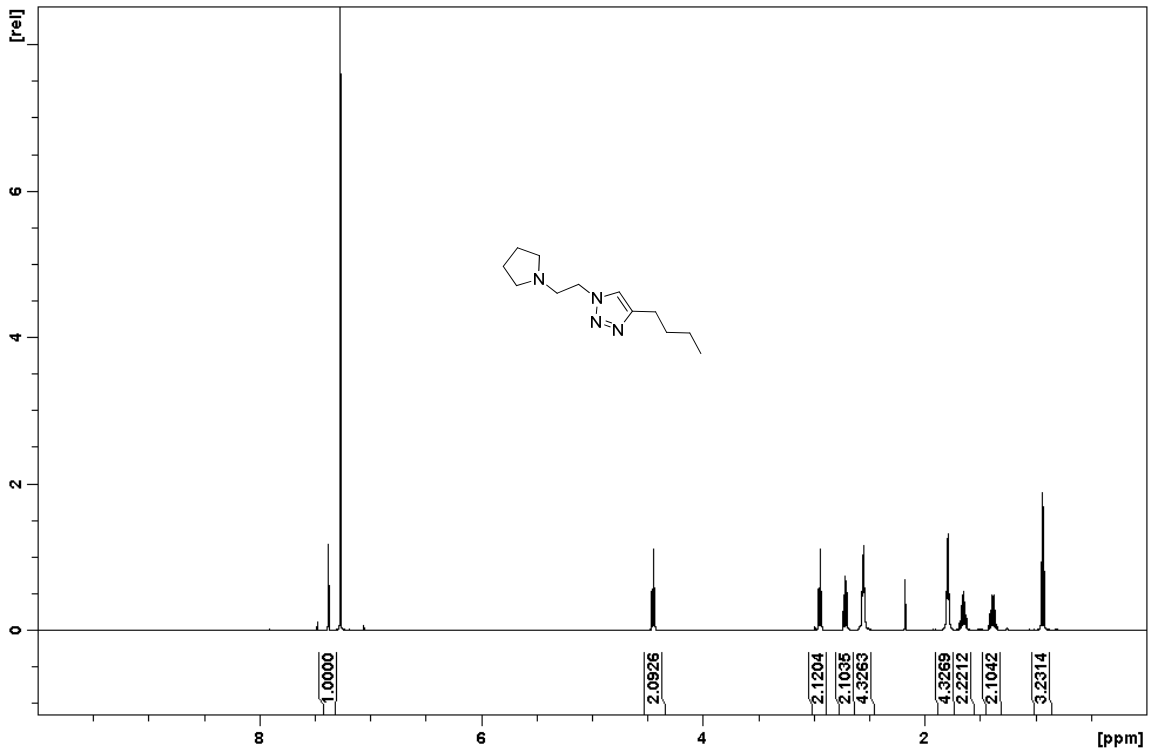
54.2626
49.4971
45.1236
23.6352
[ppm]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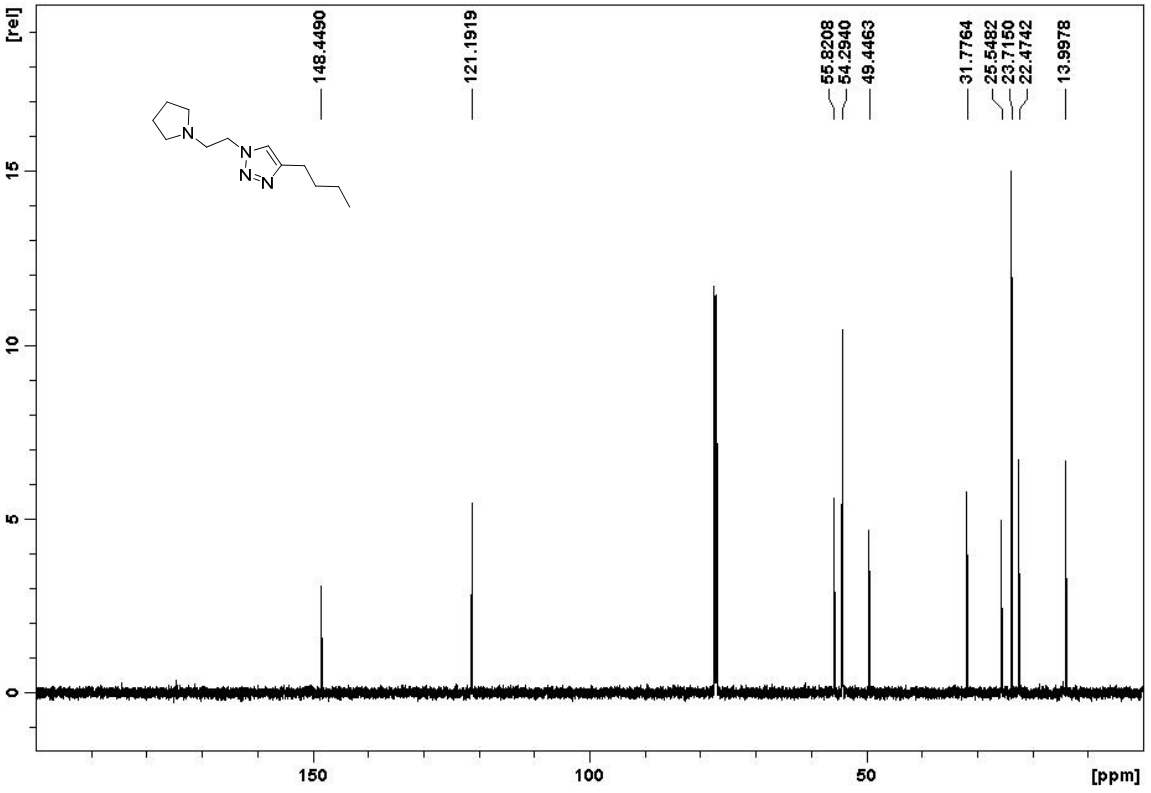
2
4
6
1.0000
2.0926
2.1204
2.1035
4.3263
4.3269
2.2212
2.1042
3.2314
8
6
4
2
[ppm]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0
5
10
15
148.4490
121.1919
55.8208
54.2940
49.4463
31.7764
25.5482
23.7150
22.4742
13.9978
150
100
50
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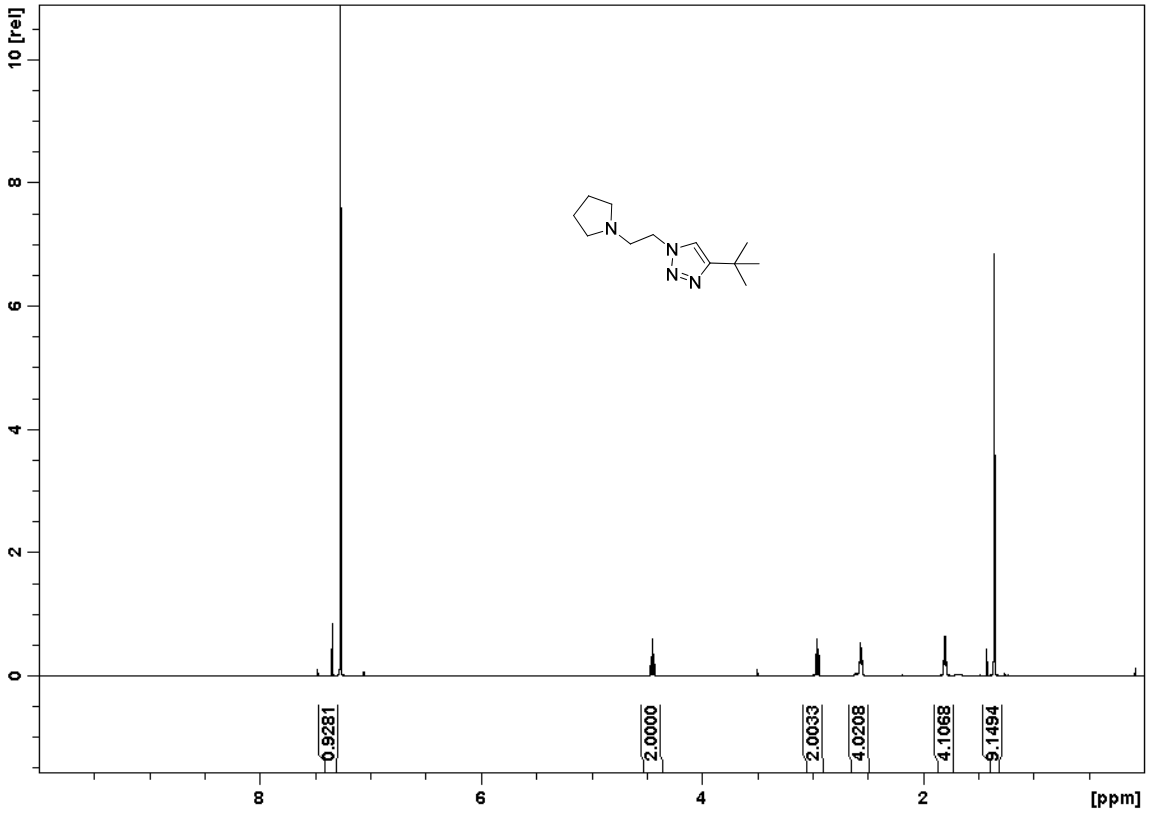
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0.9281
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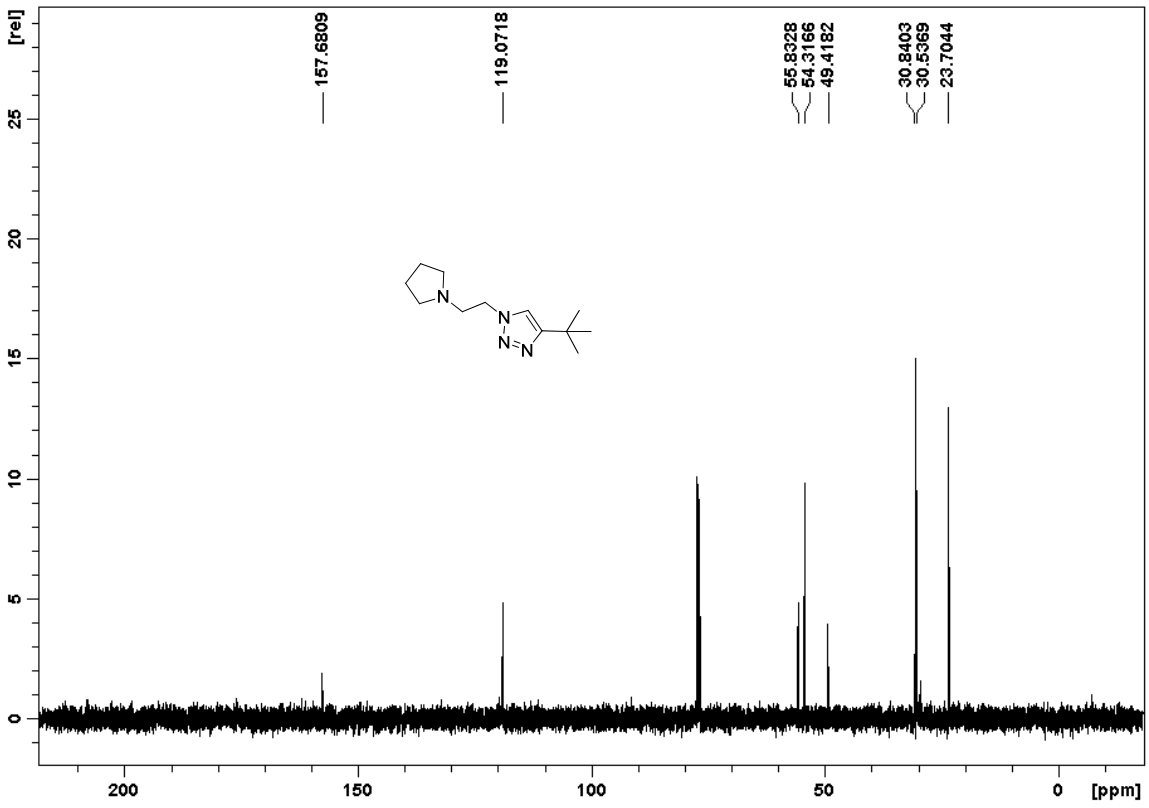
2.0033
4.0208
4.1068
9.1494
8
6
4
2
[ppm]


[rel]
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15
10
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30.8403
30.5369
23.7044
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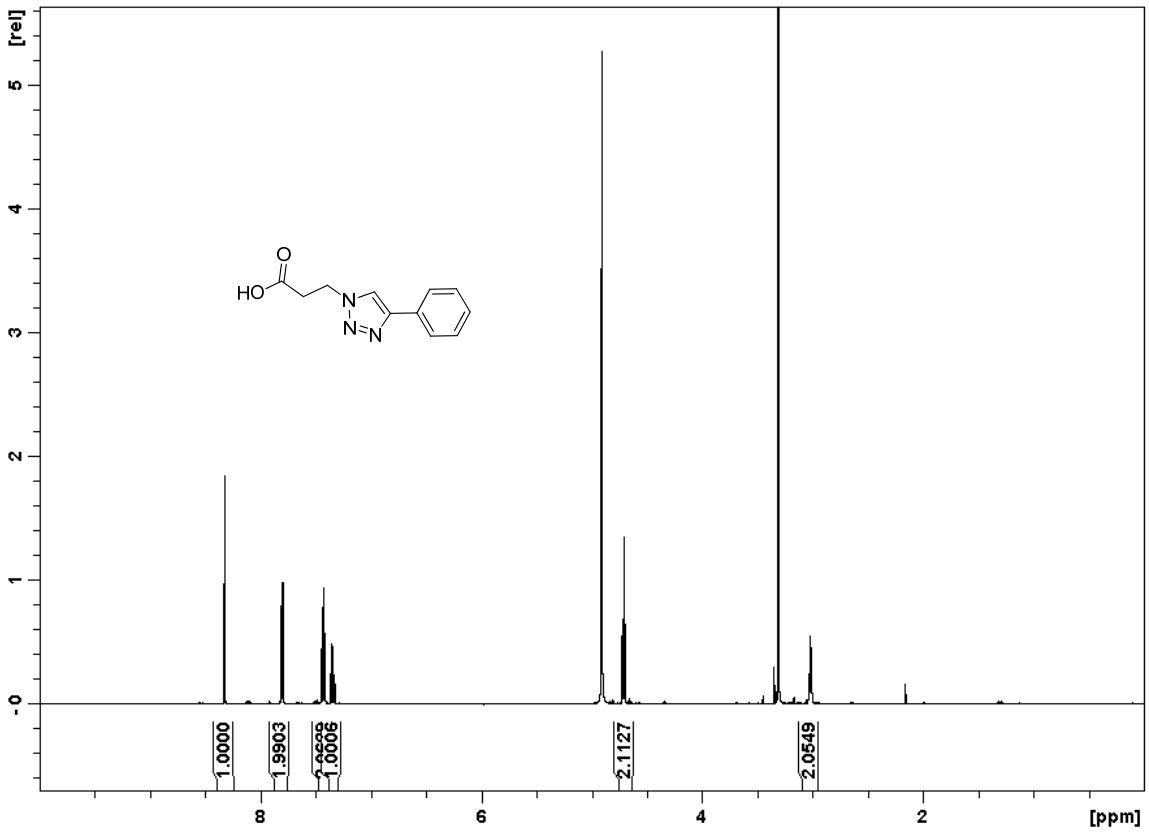
150
100
50
0
[ppm]


[rel]
5
4
3
2
1
-0
HO
O
N
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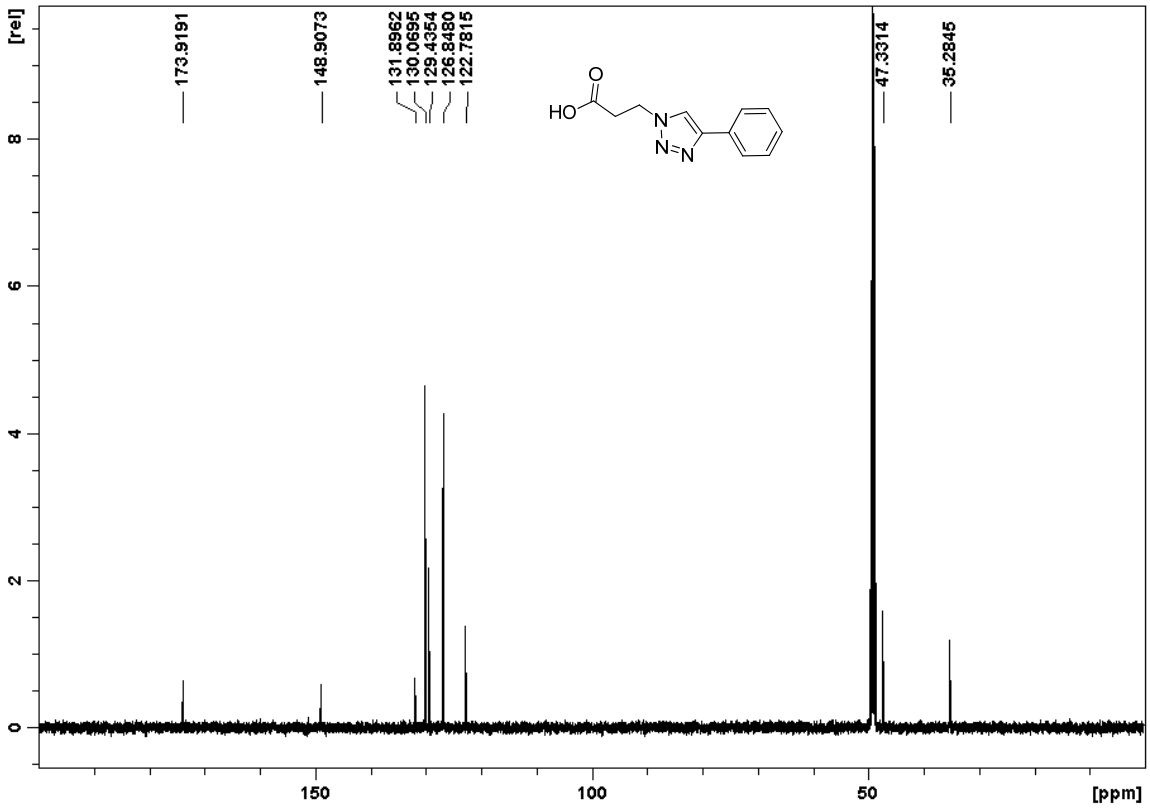
1.0006
2.1127
2.0549
8
6
4
2
[ppm]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131.8962
130.0695
129.4354
126.8480
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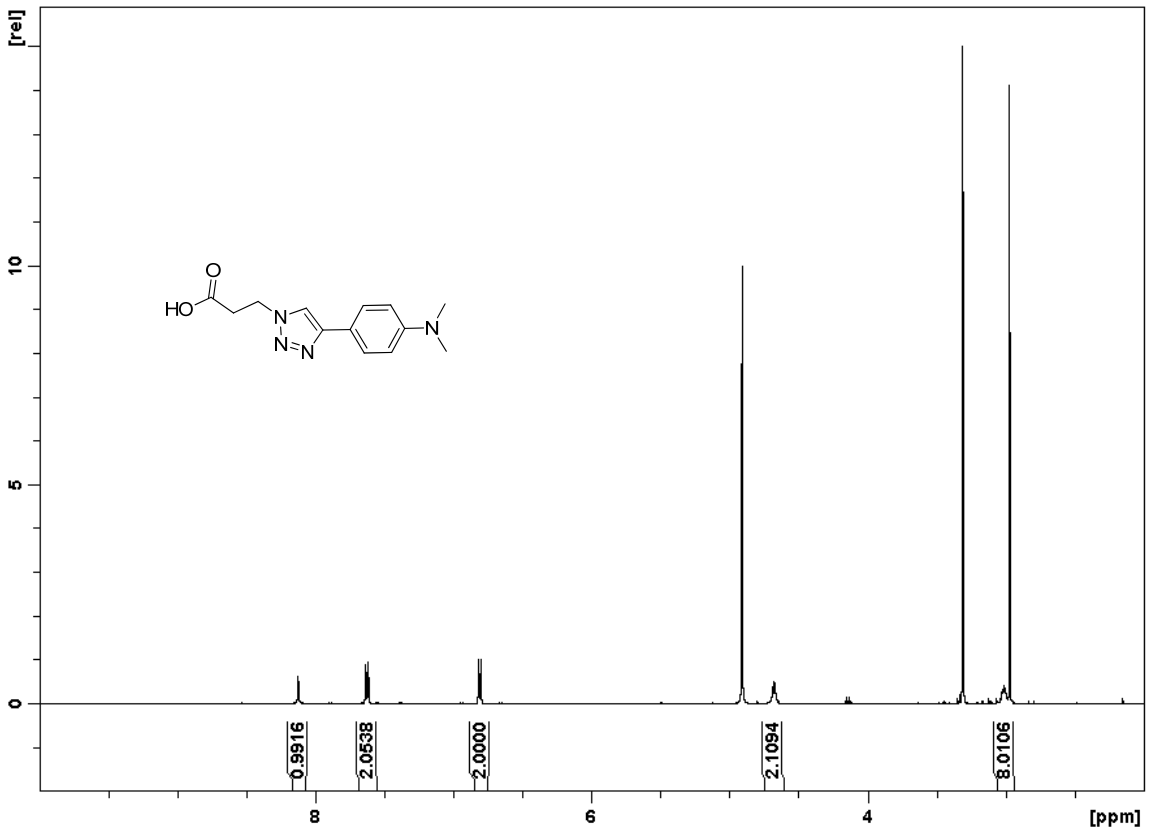
47.3314
35.2845
HO
O
N
N=N
8
6
4
2
0
150
100
50
[ppm]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10
5
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HO
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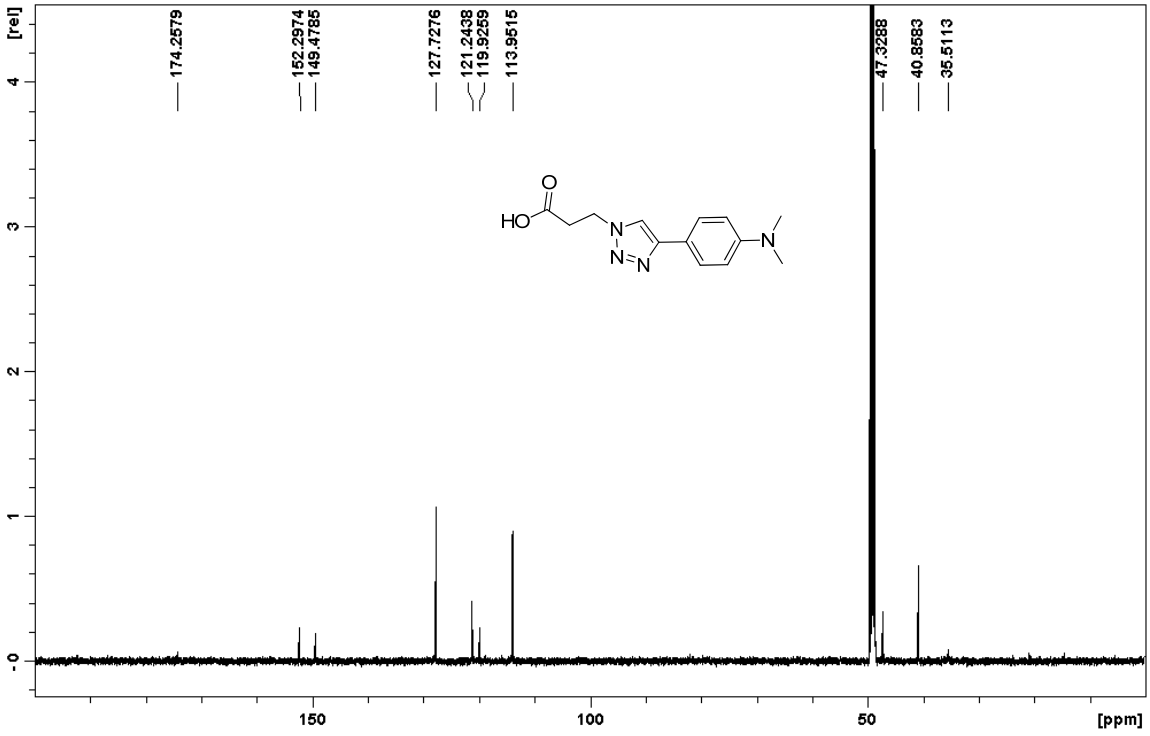
2.1094
8.0106
8
6
4
[ppm]


[rel]
4
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2
1
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127.7276
121.2438
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113.9515
47.3288
40.8583
35.5113
O
HO
N
N=N
N
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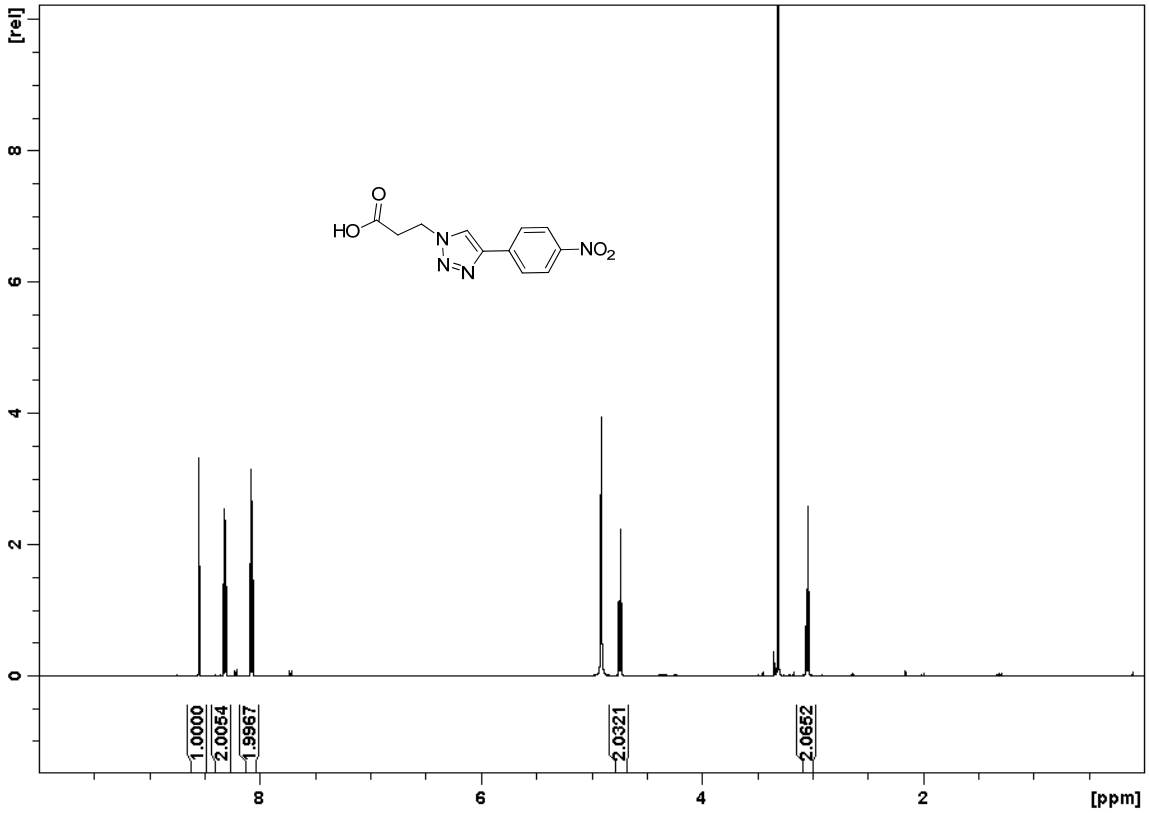
100
50
[ppm]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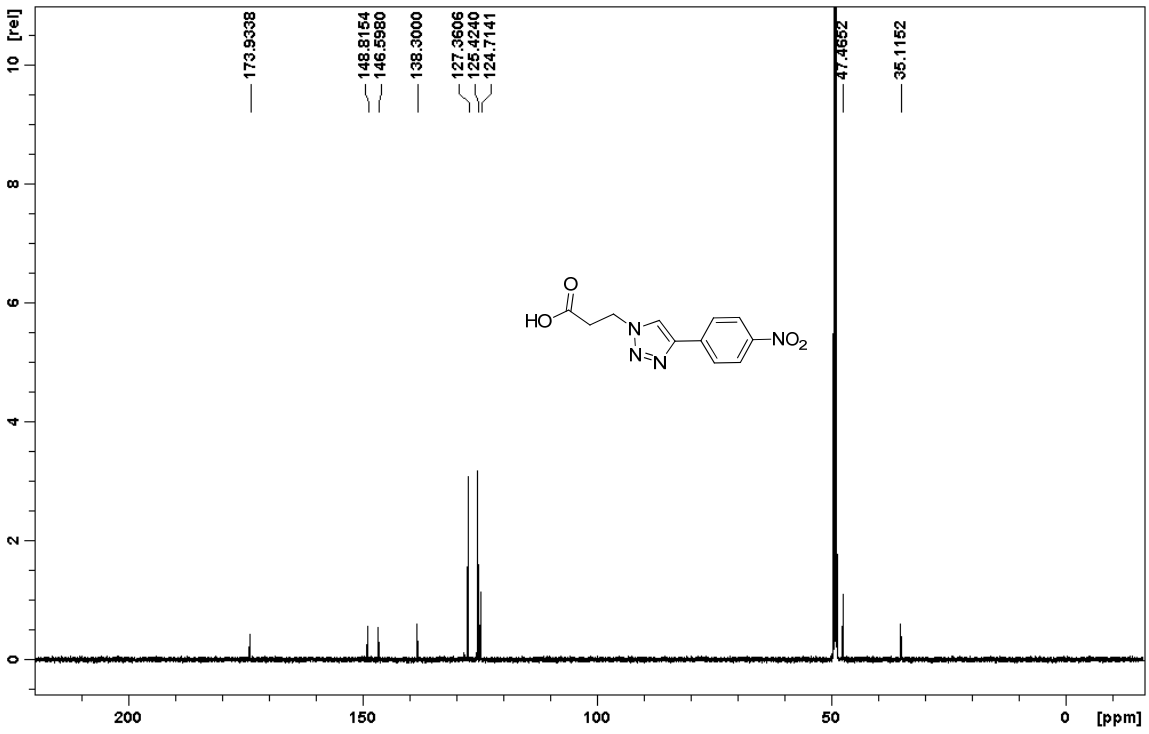
1.9967
2.0321
2.0652
[ppm]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127.3606
125.4240
124.7141
47.4652
35.1152
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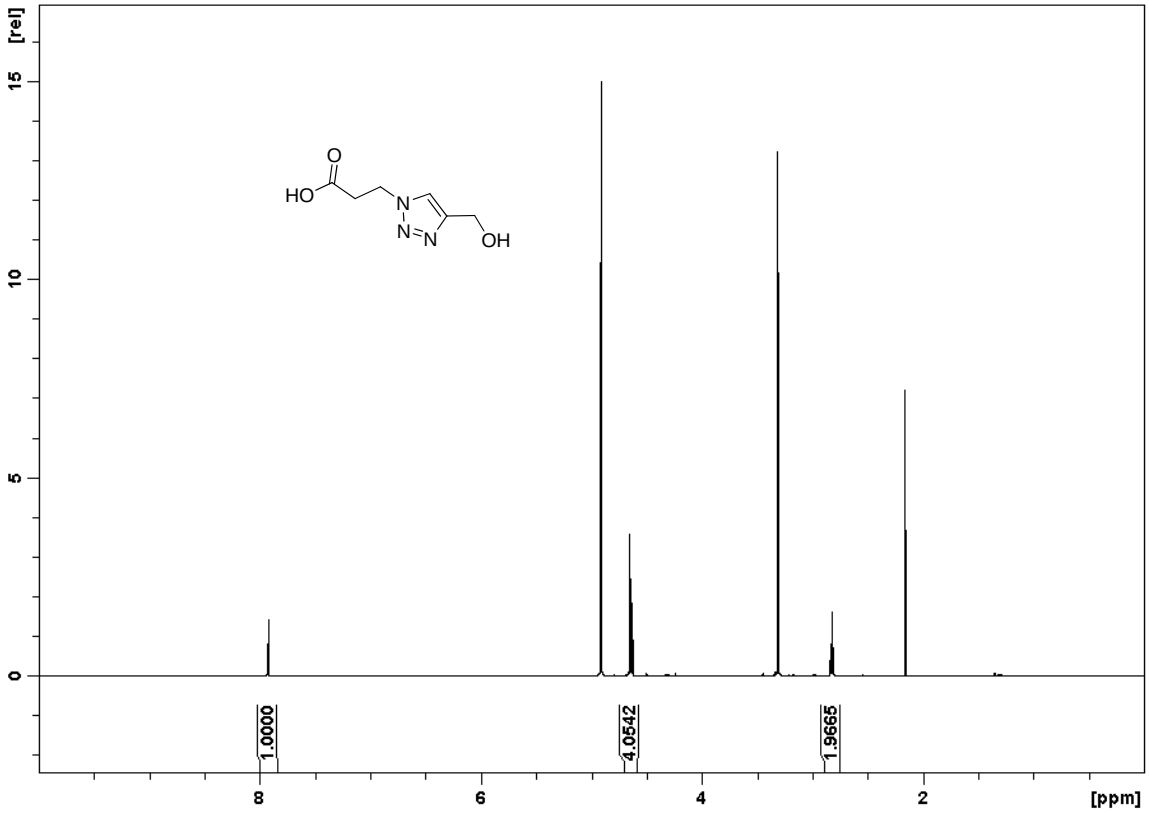
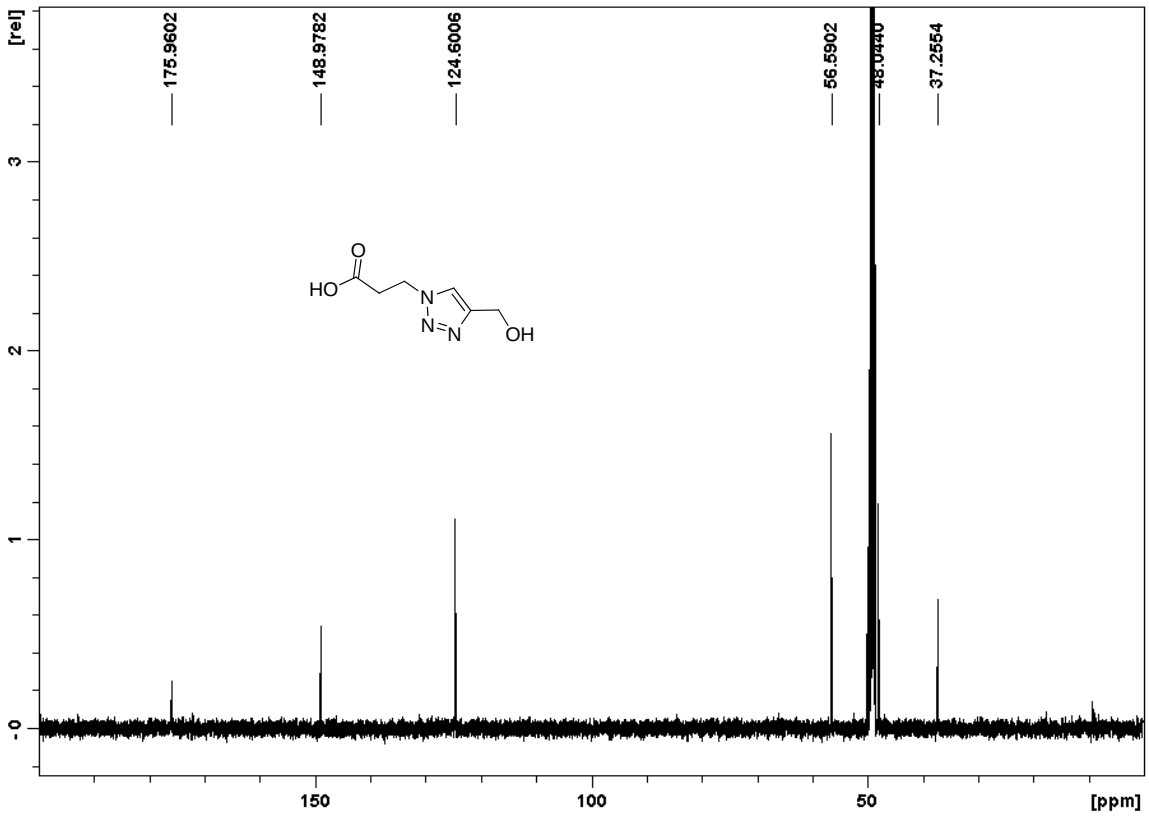

[rel]
15
10
5
0
HO
O
N
N
N
OH
1.0000
4.0542
1.9665
8
6
4
2
[ppm]


[rel]
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2
1
-0
175.9602
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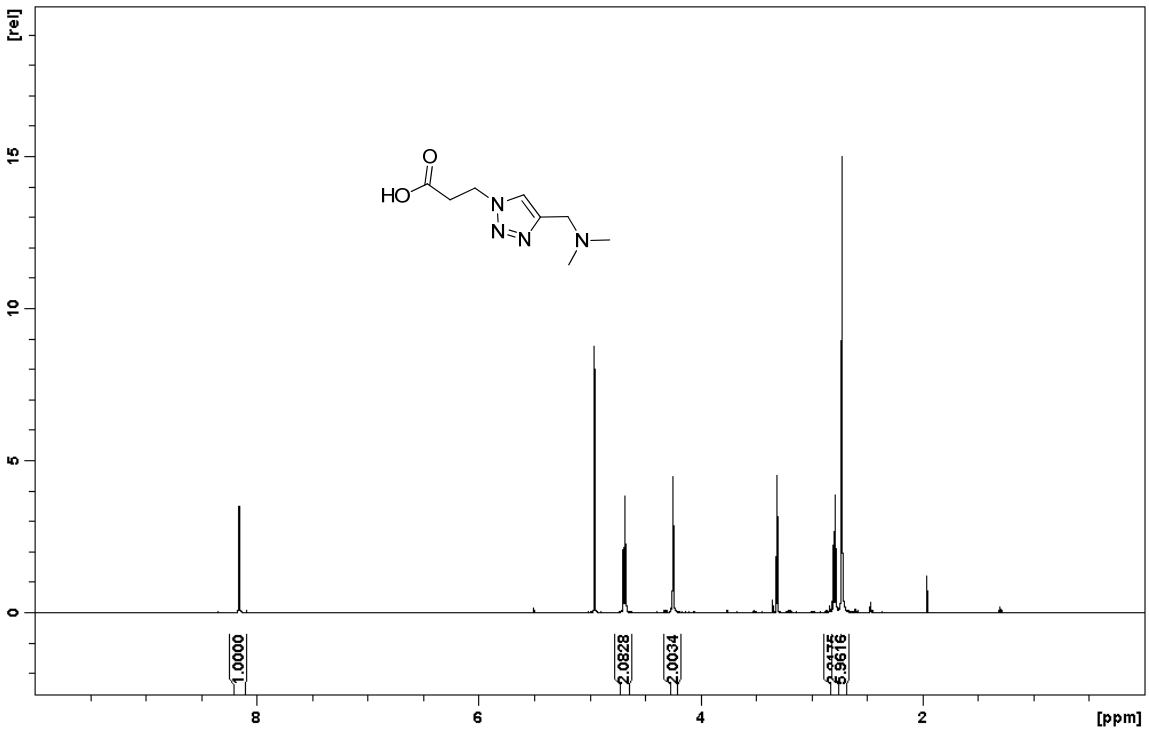
56.5902
48.0440
37.2554
HO
O
N
N
N
OH
150
100
50
[ppm]


[rel]
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10
5
0
HO
O
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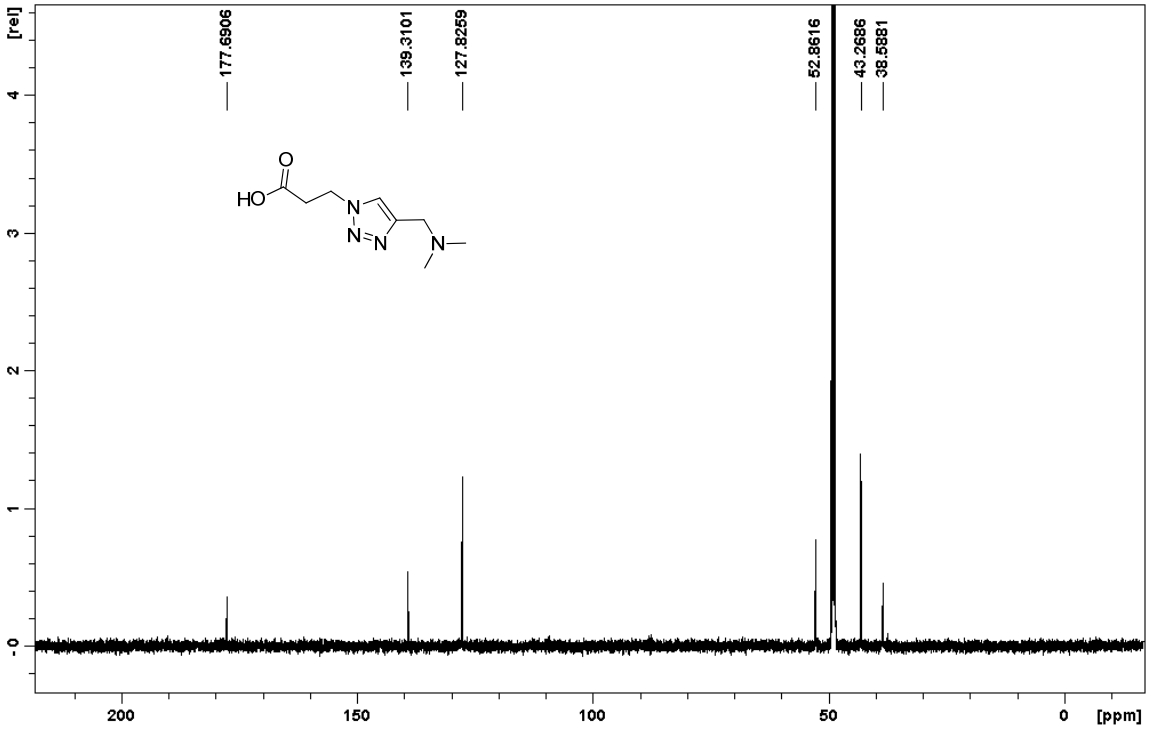
N
1.0000
2.0828
2.0034
8
6
4
2
[ppm]


[rel]
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2
1
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139.3101
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43.2686
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HO
O
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N=N
N
200
150
100
50
0
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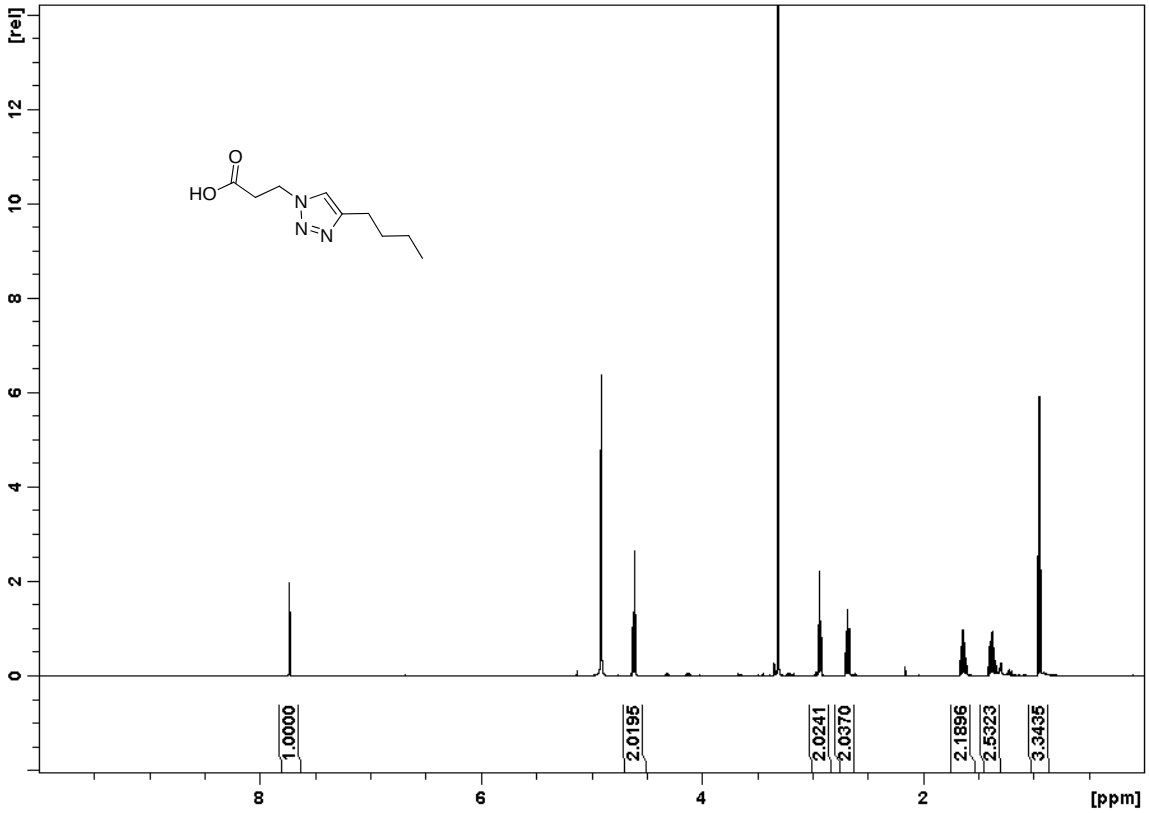
[rel]
12
10
8
6
4
2
0
HO
O
N
N
N
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2.0241
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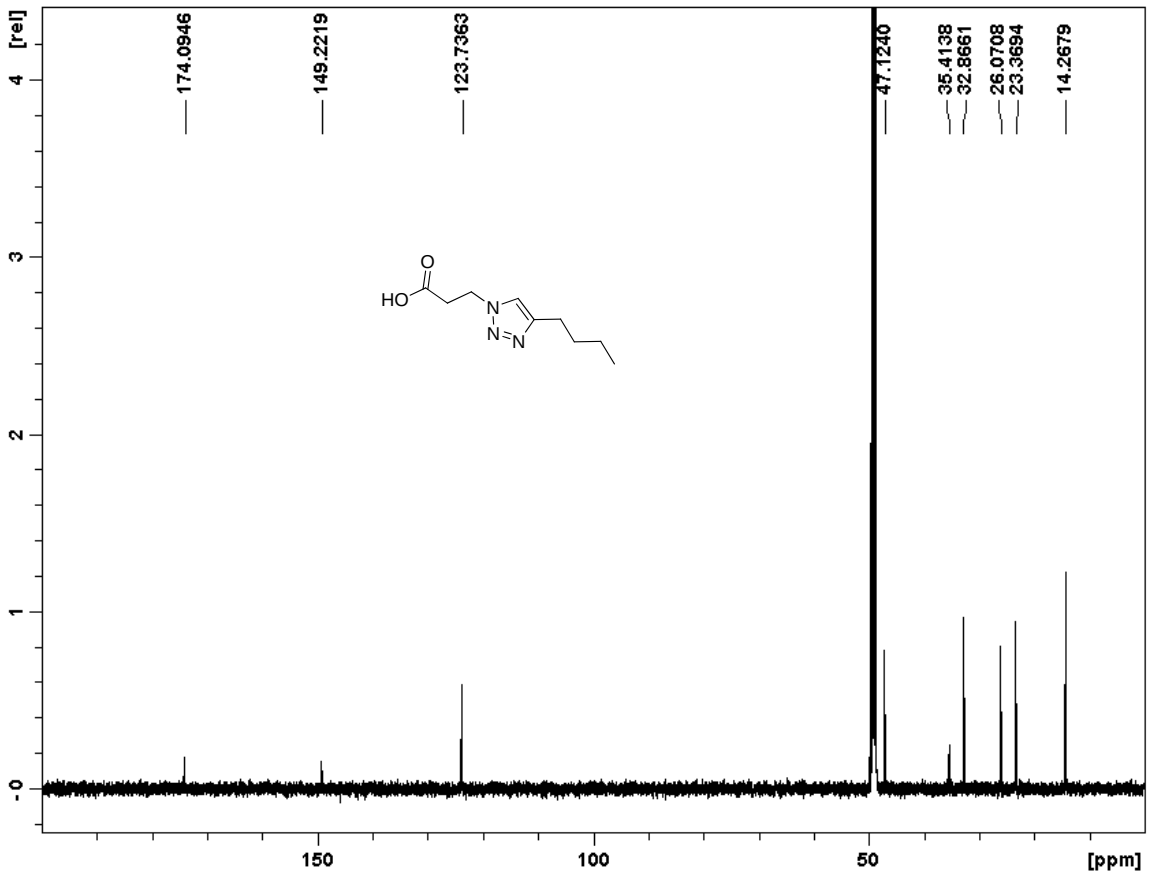
2.1896
2.5323
3.3435
8
6
4
2
[ppm]


[rel]
4
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2
1
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123.7363
47.1240
35.4138
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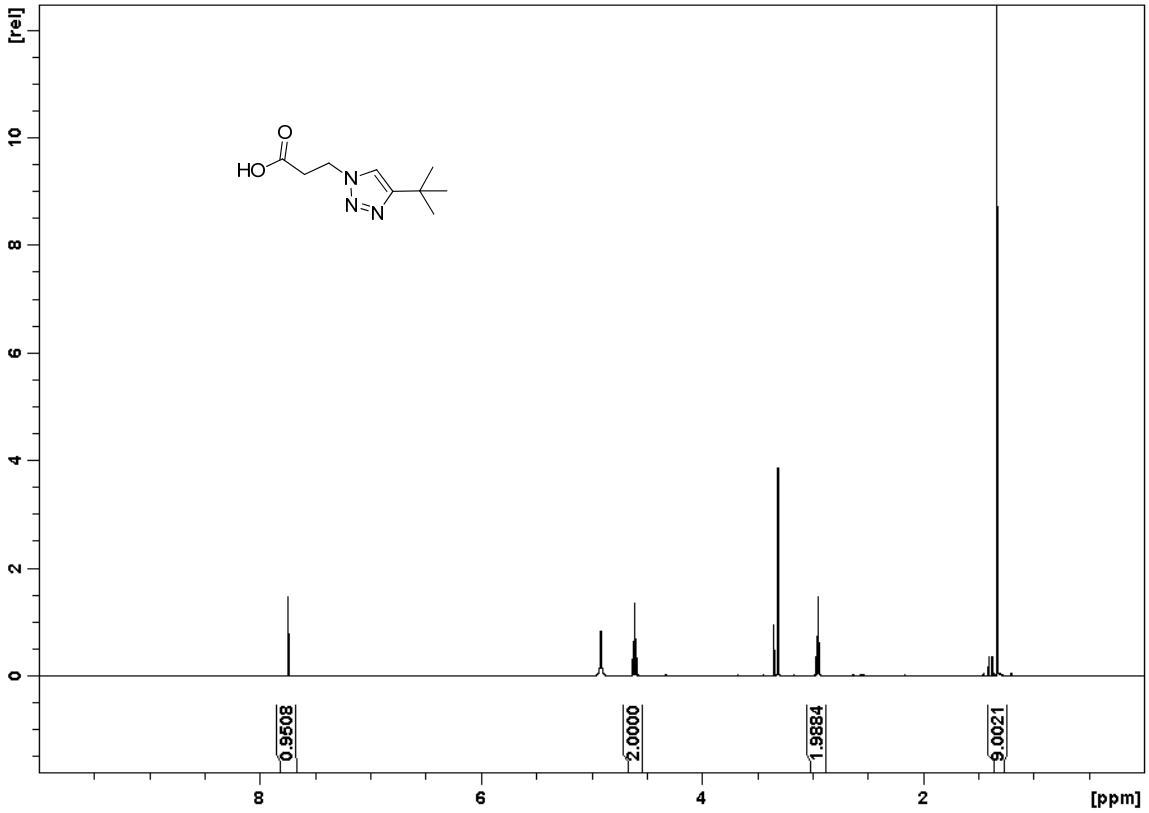
26.0708
23.3694
14.2679
HO
O
N
N
N
150
100
50
[ppm]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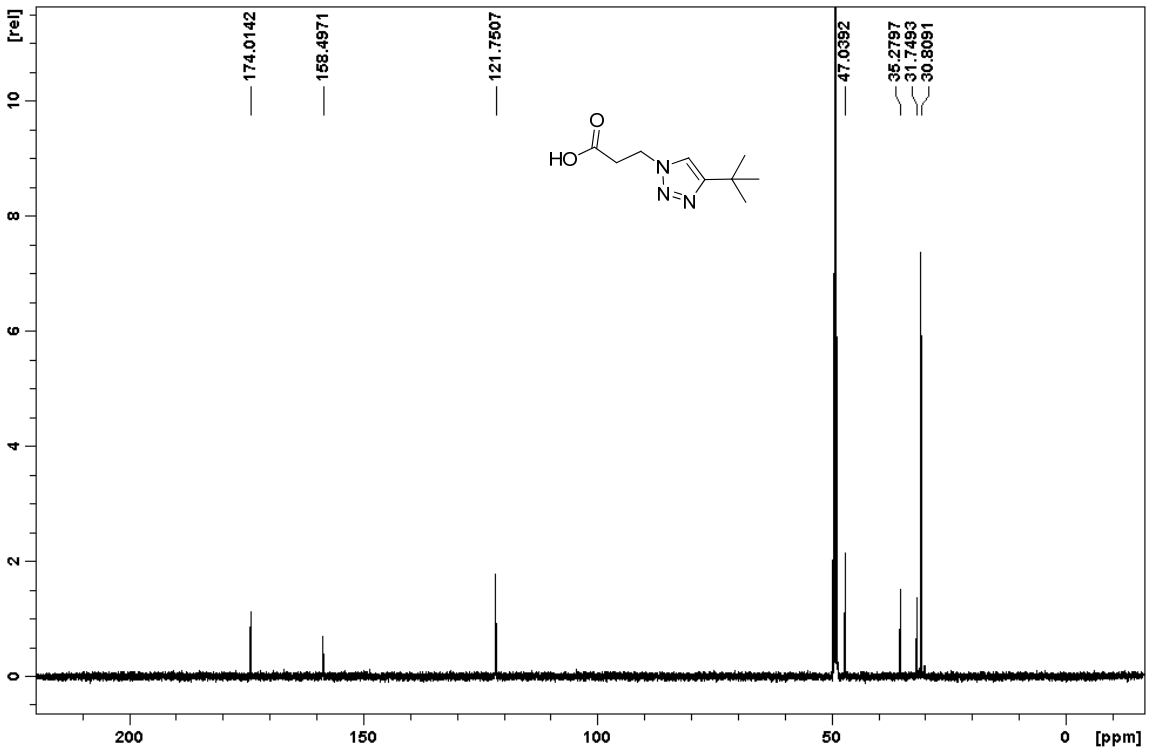
9.0021
[ppm]


[rel]
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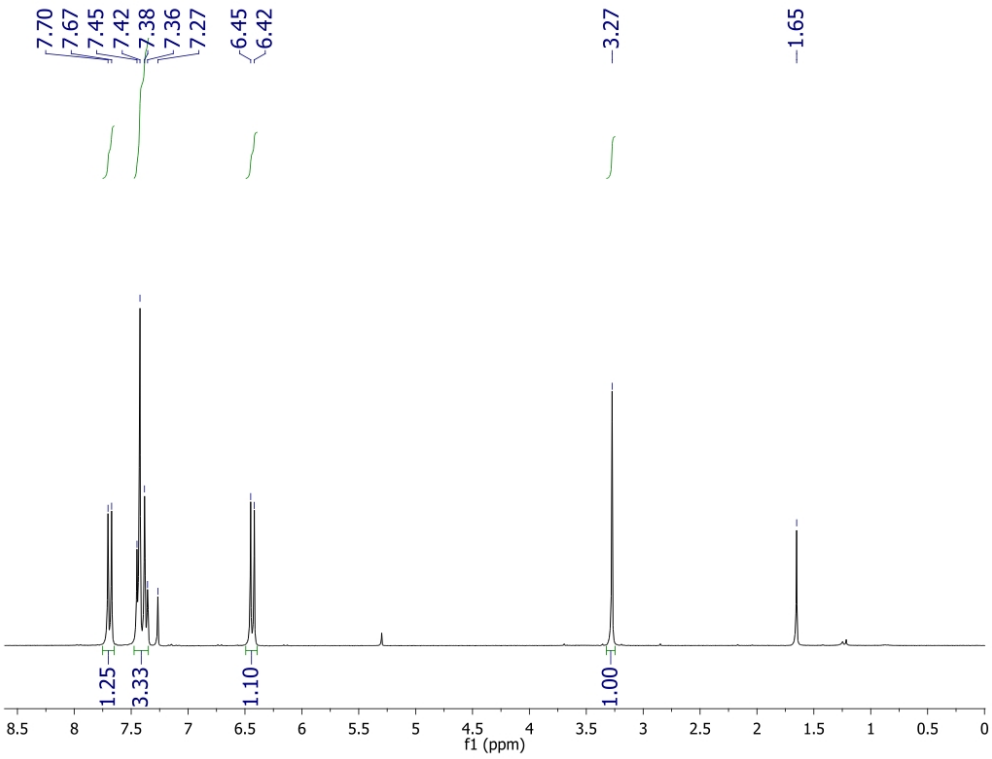
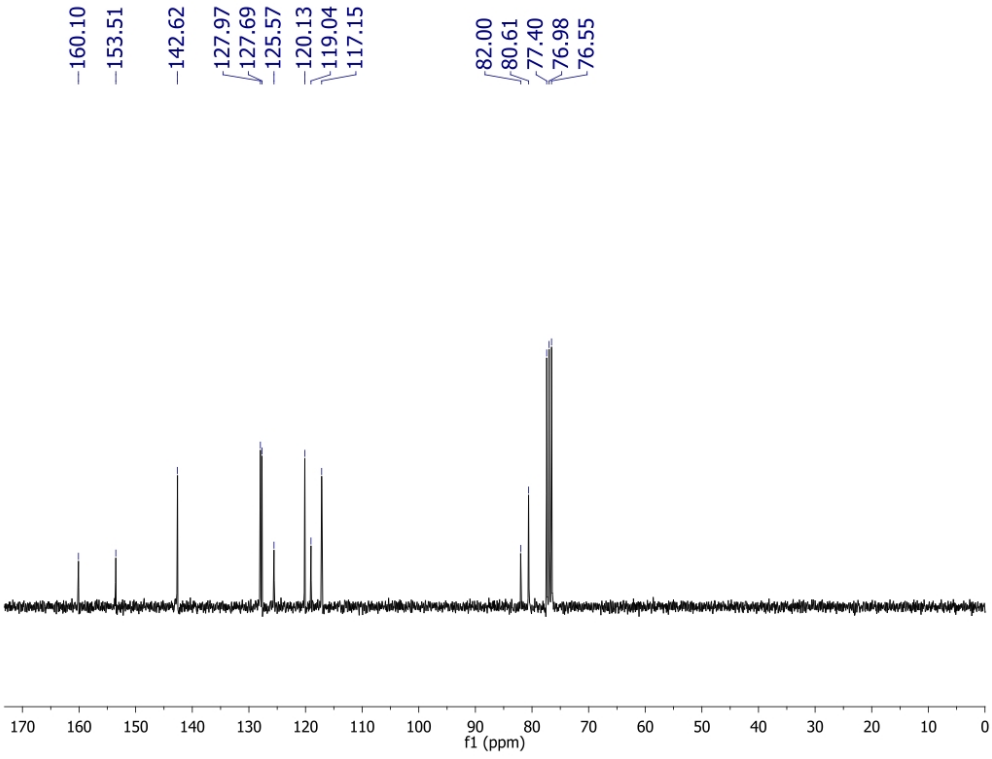
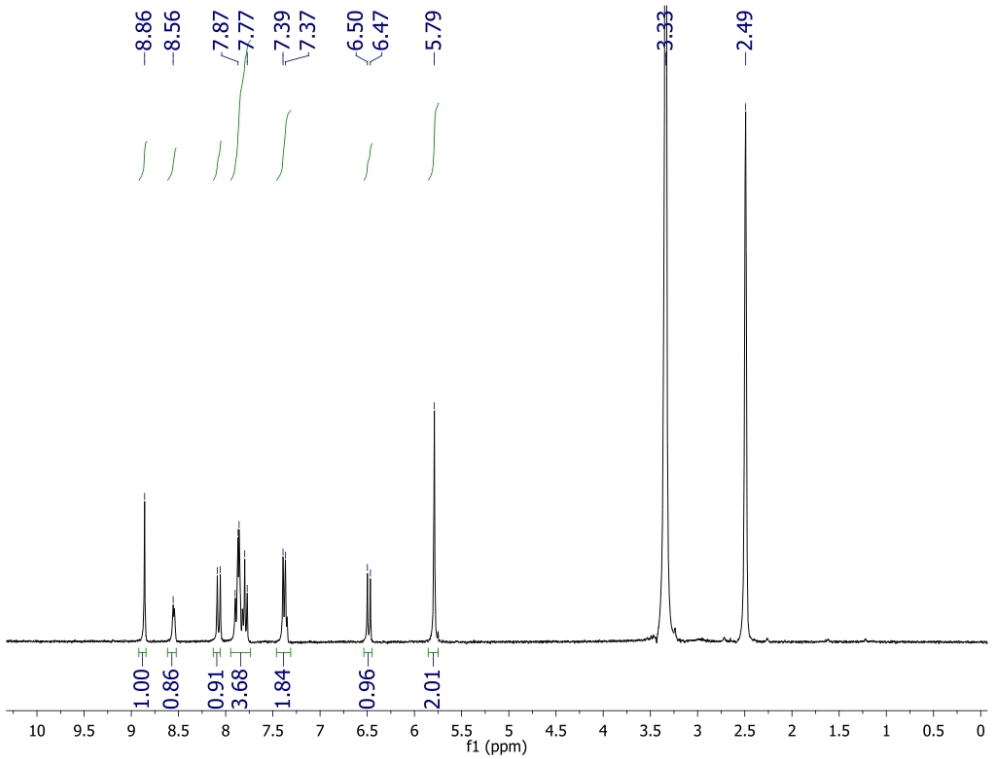
121.7507
47.0392
35.2797
31.7493
30.8091
[ppm]

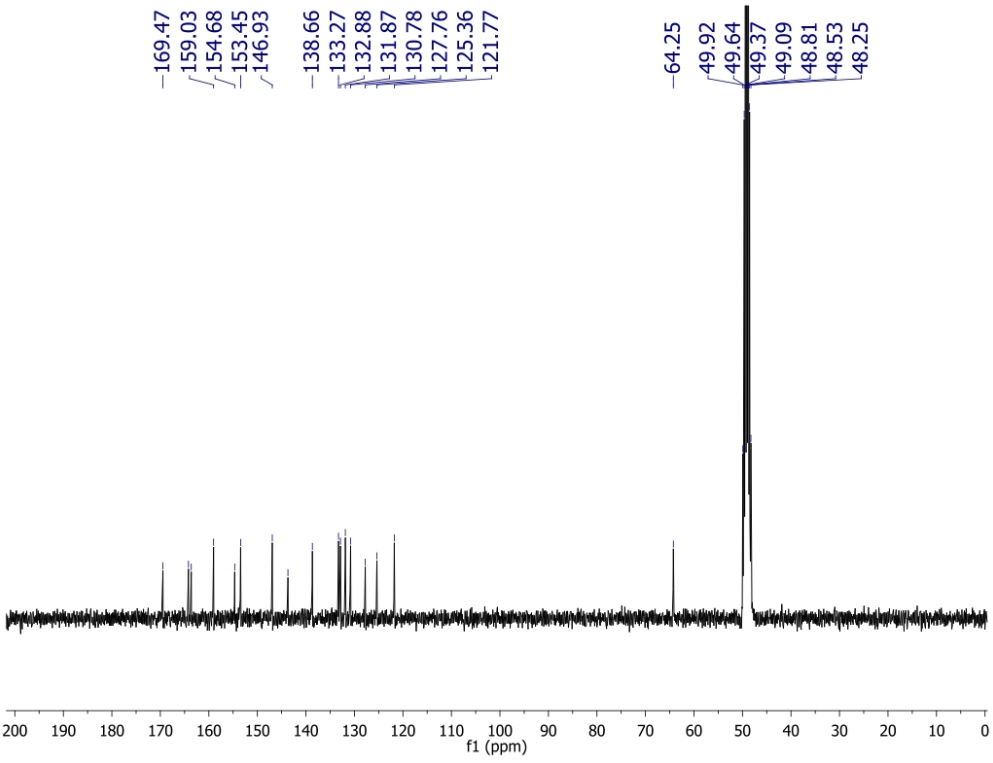
Compound **7**.


7.70
7.67
7.45
7.42
7.38
7.36
7.27
6.45
6.42
3.27
1.65
1.25
3.33
1.10
1.00
f1 (ppm)

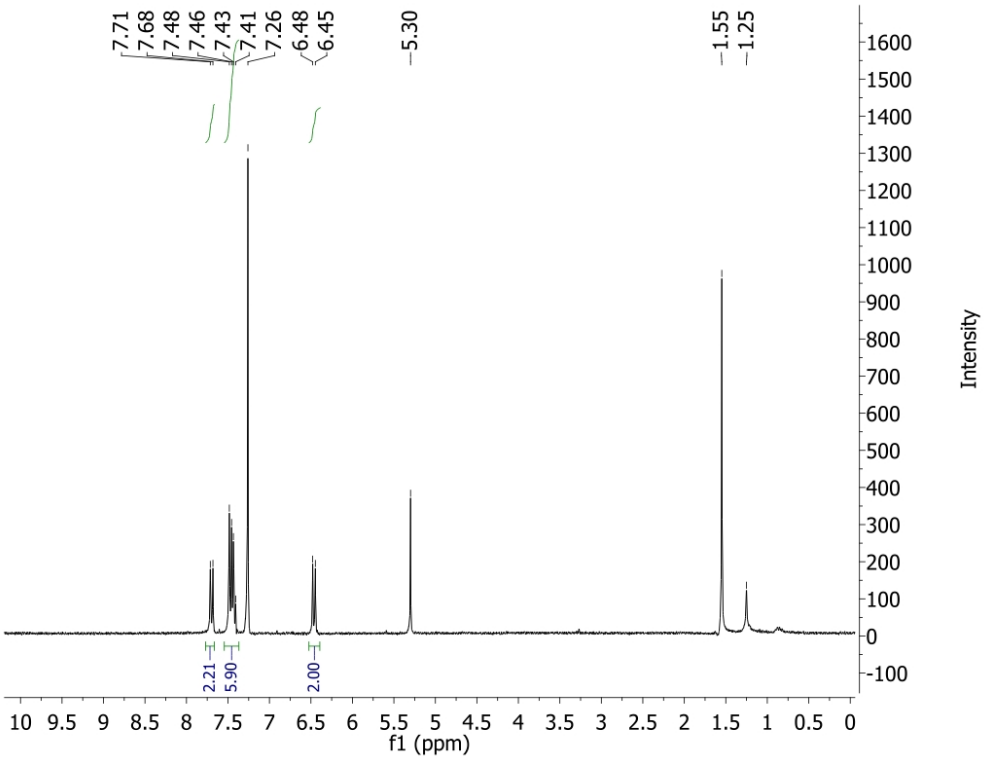

160.10
153.51
142.62
127.97
127.69
125.57
120.13
119.04
117.15
82.00
80.61
77.40
76.98
76.55
f1 (ppm)

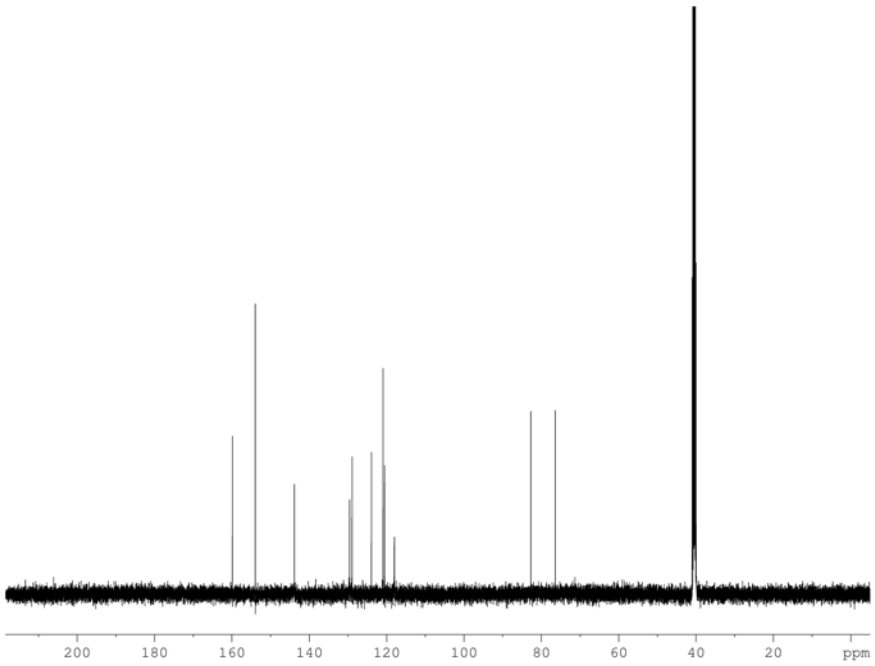
Compound **8**.


8.86
8.56
7.87
7.77
7.39
7.37
6.50
6.47
5.79
3.33
2.49
1.00
0.86
0.91
3.68
1.84
0.96
2.01
f1 (ppm)


169.47
159.03
154.68
153.45
146.93
138.66
133.27
132.88
131.87
130.78
127.76
125.36
121.77
64.25
49.92
49.64
49.37
49.09
48.81
48.53
48.25
f1 (ppm)

Compound **9**.


7.71
7.68
7.48
7.46
7.43
7.41
7.26
6.48
6.45
5.30
1.55
1.25
2.21
5.90
2.00
f1 (ppm)
Intensity


ppm