Consecutive three-component synthesis of (hetero)arylated propargyl amides by chemoenzymatic amidation-Sonogashira coupling sequence

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1. General considerations

All enzyme catalyzed and coupling reactions were performed in flame dried Schlenk tubes. The enzyme catalyzed reactions were carried out under normal atmospheric conditions in an incubating shaker IKA® KS 4000i, whereas the Sonogashira coupling reactions were executed under argon atmosphere. MTBE was dried over 3 Å molecular sieves prior to use. The reaction progress was monitored qualitatively by thin layer chromatography using silica gel layered aluminium foil (60 F254 Merck, Darmstadt). The detection was made by irradiating under UV light of wavelength 254 and 366 nm or stained with $KMnO_4$, ninhydrin and molybdate solution (saturated ethanolic solution of molybdatophosphoric acid). Crude mixtures were absorbed on Celite® 545 (0.02-0.20 mm, Carl Roth GmbH Co.KG) for column chromatography through flash technique. All the chemicals that have not been synthesized, were purchased from Sigma Aldrich, Alfa Aesar and ACROS and were used as received without any further purification. CAL-B immobilized on acrylic resin (Novozyme® 435) was purchased from Sigma Aldrich and was used as received. The ^{1}H-NMR and ^{13}C-NMR spectra were measured on the device Avance DRX 500, AV or AV III 600 III 300 Bruker. Chemical shifts are given in ppm (δ) and were referenced to the internal solvent signal: d_6-acetone (^{1}H δ 2.05 ^{13}C δ 29.9), $CDCl_3$ (^{1}H δ 7.26, ^{13}C δ 77.2), d_6-DMSO (^{1}H δ 2.50 ^{13}C δ 39.5). Multiplicities are stated as: s (singlet), br s (broad singlet), d (doublet), t (triplet), q (quartet), dd (doublet of doublet), dq (doublet of quartet), m (multiplet), br m (broad multiplet). Coupling constants (*J)* are given in Hz. The assignment of the primary (CH_3), secondary (CH_2), tertiary (CH) and quaternary carbon nuclei (C_{quat}), was made using DEPT-135 spectra. The mass spectrometric investigations were carried out in the Department of Mass Spectrometry of Inorganic and Organic Chemistry of the University of Düsseldorf. The IR spectra were recorded with a Bruker Vector 22 FT-IR or Shimadzu IRAffinity-1. The intensities of the IR bands were abbreviated as w (weak), m (medium), s (strong). Melting points (uncorrected) were measured using Reichert Thermovar (PeakTeck®). Combustion analyses were measured on a Perkin Elmer Series II Analyser 2400 in the Institute for Pharmaceutical and Medicinal Chemistry Heinrich-Heine University, Düsseldorf.

2. Syntheses of Compounds 5 and 7

2.1. Chemoenzymatic three-component synthesis of 3-(hetero)arylpropargyl amides 5 (General Procedure)

To a solution of propargylamine (**2**) (55 mg, 1.00 mmol) in dry MTBE (2.0 mL) in a screw-cap Schlenk vessel, methyl ester **1** (1.20 mmol) and Novozyme® 435 (50 % w/w of respective ester substrate **1**) were successively added and reaction was allowed to shake in an incubating shaker at 45 °C for 4-24 h (for experimental details see Table 1). After the

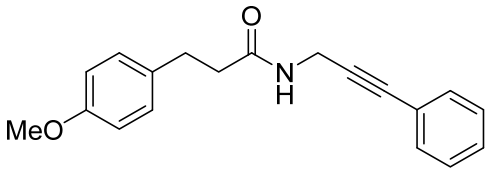
complete conversion (monitored by TLC) DMF (2.0 mL) was added to the reaction mixture which was then flushed with argon for 15 min. Then (hetero)aryl iodide **4** (1.00 mmol), TMG (115 mg, 1.00 mmol), $Pd(PPh_3)_4$ (23 mg, 0.02 mmol), and CuI (8 mg,0.04 mmol) were successively added to the reaction mixture under argon and the reaction was allowed to shake at 45 °C for 1 h. The reaction mixture was filtered to remove the enzyme beads. Then, brine (5.0 mL) was added to the filterate, followed by extraction with ethylacetate (3 x 10.0 mL). The combined organic layers were dried with anhydrous Na_2SO_4 and pure product **5** was obtained after column chromatography on silica gel (*n*-hexane/ethyl acetate).

Table 1. Experimental details of the three-component synthesis of 3-(hetero)arylpropargyl amides **5**.

Entry	Methyl ester **1**	(Hetero)aryl iodide **4**	3-(Hetero)aryl propargyl amide **5**
1[a]	233 mg (1.20 mmol) of **1a**	204 mg (1.00 mmol) of **4a**	170 mg (58 %) of **5a**
2[a]	180 mg (1.20 mmol) of **1b**	204 mg (1.00 mmol) of **4a**	132 mg (53 %) of **5b**
3[a]	180 mg (1.20 mmol) of **1b**	262 mg (1.00 mmol) of **4b**	227 mg (74 %) of **5c**
4[a]	197 mg (1.20 mmol) of **1c**	204 mg (1.00 mmol) of **4a**	142 mg (54 %) of **5d**
5[a]	195 mg (1.20 mmol) of **1d**	234 mg (1.00 mmol) of **4c**	75 mg (26 %) of **5e**
6[a]	192 mg (1.20 mmol) of **1e**	204 mg (1.00 mmol) of **4a**	132 mg (51 %) of **5f**
7[b]	199 mg (1.20 mmol) of **1f**	204 mg (1.00 mmol) of **4a**	63 mg (24 %) of **5g**
8[b]	198 mg (1.20 mmol) of **1g**	204 mg (1.00 mmol) of **4a**	204 mg (77 %) of **5h**
9[b]	219 mg (1.20 mmol) of **1h**	204 mg (1.00 mmol) of **4a**	216 mg (77 %) of **5i**
10[a]	216 mg (1.20 mmol) of **1i**	262 mg (1.00 mmol) of **4b**	288 mg (85 %) of **5j**
11[a]	233 mg (1.20 mmol) of **1h**	234 mg (1.00 mmol) of **4c**	200 mg (62 %) of **5k**
12[b]	205 mg (1.20 mmol) of **1j**	246 mg (1.00 mmol) of **4d**	191 mg (64 %) of **5l**
13[a]	190 mg (1.20 mmol) of **1k**	234 mg (1.00 mmol) of **4c**	157 mg (59 %) of **5m**
14[a]	222 mg (1.20 mmol) of **1l**	204 mg (1.00 mmol) of **4a**	202 mg (71 %) of **5n**
15[b]	130 mg (1.20 mmol) of **1m**	262 mg (1.00 mmol) of **4b**	253 mg (95 %) of **5o**
16[a]	151 mg (1.20 mmol) of **1n**	210 mg (1.00 mmol) of **4e**	164 mg (71 %) of **5p**
17[a]	171 mg (1.20 mmol) of **1o**	210 mg (1.00 mmol) of **4e**	109 mg (44 %) of **5q**
18[a]	151 mg (1.20 mmol) of **1n**	222 mg (1.00 mmol) of **4f**	151 (62 %) of **5r**
19[b]	303 mg (1.20 mmol) of **1p**	222 mg (1.00 mmol) of **4f**	217 mg (61 %) of **5s**

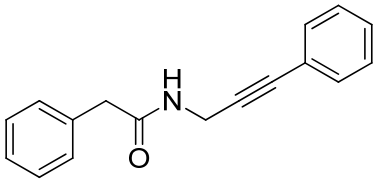
[a]24 h time for CAL-B catalyzed aminolysis. [b]4 h time for CAL-B catalyzed aminolysis.

2.1.1. 3-(4-Methoxyphenyl)-*N*-(3-phenylprop-2-yn-1-yl)propanamide (5a)



Colorless solid. Mp 101 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.48 (t, ^{3}J = 7.6 Hz, 2 H), 2.93 (t, ^{3}J = 7.6 Hz, 2 H), 3.75 (s, 3 H), 4.24 (d, ^{3}J = 5.2 Hz, 2 H), 5.63 (br s, 1 H), 6.81 (d, ^{3}J = 8.7 Hz, 2 H), 7.12 (d, ^{3}J = 8.7 Hz, 2 H), 7.28-7.43 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 30.1 (CH_2), 30.9 (CH_2), 38.7 (CH_2), 55.3 (CH_3), 83.5 (C_{quat}), 84.9 (C_{quat}), 114.1 (CH), 122.7 (C_{quat}), 128.5 (CH), 128.6 (CH), 129.5 (CH), 131.8 (CH), 132.8 (C_{quat}), 158.2 (C_{quat}), 171.9 (C_{quat}). EI-MS: *m/z* (%) = 294 ([M+H]$^+$, 2.7), 293 (M$^+$, 13.7), 292 ([M - H]$^+$, 12.4), 216 ([M - C_6H_5]$^+$, 1.7), 172 ([M - C_8H_9O]$^+$, 100), 135 ($C_9H_{11}O^+$, 20.8), 121 ($C_8H_9O^+$, 61.4), 115 ($C_9H_7^+$, 18.2), 105 ($C_7H_5O^+$, 12.9), 77 ($C_6H_5^+$, 11.7), 43 ($C_3H_7^+$, 4.9). IR (ATR) $\tilde{\nu}$ [cm^{-1}] = 3059 (w), 2995 (w), 2954 (w), 2937 (w), 2922 (w), 2906 (w), 2866 (w), 2835 (w), 1635 (s), 1610 (w), 1535 (m), 1508 (w), 1489 (w), 1446 (w), 1421 (w), 1377 (w), 1340 (w), 1319 (w), 1300 (w), 1251 (m), 1240 (s), 1211 (w), 1180 (w), 1157 (w), 1111 (w), 1078 (w), 1035 (m), 1020 (w), 941 (w), 914 (w), 883 (w), 831 (m), 813 (w), 759 (s), 713 (w), 690 (s), 661 (m). Anal. calcd. for $C_{19}H_{19}NO_2$ (293.4): C 77.79, H 6.53, N 4.77; Found: C 77.56, H 6.38, N 4.68.

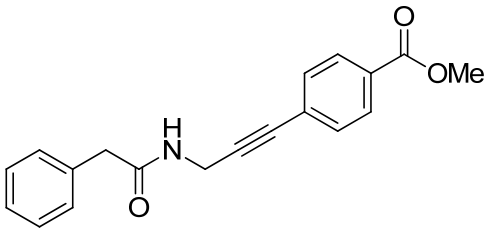
2.1.2. 2-Phenyl-*N*-(3-phenylprop-2-yn-1-yl)acetamide (5b)



Colorless solid. Mp 96 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.62 (s, 2 H), 4.24 (d, ^{3}J = 5.3 Hz, 2 H), 5.70 (br s, 1 H), 7.27-7.41 (br m, 10 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 30.3 (CH_2), 43.7 (CH_2), 83.5 (C_{quat}), 84.7 (C_{quat}), 122.6 (C_{quat}), 127.6 (CH), 128.4 (CH), 128.6 (CH), 129.2 (CH), 129.6 (CH), 131.8 (CH), 134.6 (C_{quat}), 170.7 (C_{quat}). EI-MS: *m/z* (%) = 250 ([M + H]$^+$, 7.1), 249 (M$^+$, 36.6), 248 ([M - H]$^+$, 2.0), 174 (11.9), 158 ([M - C_7H_7]$^+$, 100), 130 ($C_9H_8N^+$, 49.4), 119 ($C_8H_7O^+$, 28.7), 115 ($C_9H_7^+$, 53.2), 91 ($C_7H_7^+$, 98.3), 77 ($C_6H_5^+$, 14.0), 65 ($C_5H_5^+$, 16.9), 43 ($C_3H_7^+$, 8.9). IR (ATR) $\tilde{\nu}$ [cm^{-1}] = 3026 (w), 2939 (w), 2914 (w), 2856 (w), 2773 (w), 2735 (w), 2601 (w), 1946 (w), 1874 (w), 1805 (w), 1637 (s), 1598 (w), 1537 (s), 1490 (w), 1452 (w), 1442 (w), 1413 (w), 1386 (w), 1365 (w), 1330 (w), 1292 (w), 1278 (w), 1242 (w), 1232 (w), 1199 (w), 1182 (w), 1153 (w), 1120 (w), 1097 (w), 1070 (w), 1049 (w), 1014 (w), 999 (w), 968 (w), 939 (w), 904 (w), 871 (w), 829 (w), 802 (w), 771 (w), 754 (s), 721 (m), 686

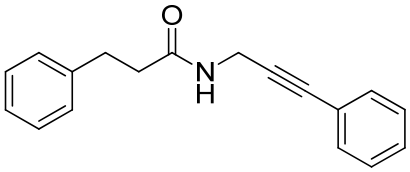
(s), 623 (w). Anal. calcd. for $C_{17}H_{15}NO$ (249.3): C 81.90, H 6.06, N 5.62; Found: C 82.08, H 6.11, N 5.58.

2.1.3. Methyl 4-(3-(2-phenylacetamido)prop-1-yn-1-yl)benzoate (5c)



Colorless solid. Mp 147 °C. ^{1}H NMR (300 MHz, d_6-DMSO): δ = 3.47 (s, 2 H), 3.85 (s, 3 H), 4.16 (d, ^{3}J = 5.3 Hz, 2 H), 7.22-7.33 (m, 5 H), 7.54 (d, ^{3}J = 8.3 Hz, 2 H), 7.94 Hz (d, ^{3}J = 8.3 Hz, 2 H), 8.64 (t, ^{3}J = 5.0 Hz, 1 H). ^{13}C NMR (75 MHz, d_6-DMSO): δ = 28.8 (CH_2), 42.0 (CH_2), 52.3 (CH_3), 80.9 (C_{quat}), 90.4 (C_{quat}), 126.4 (CH_2), 127.0 (C_{quat}), 128.2 (CH), 129.0 (CH), 129.2 (C_{quat}), 129.4 (CH), 131.7 (CH), 136.0 (C_{quat}), 165.6 (C_{quat}), 170.0 (C_{quat}). EI-MS: *m/z* (%) = 307 (M^+, 3.4), 293 ($[M - CH_3 + 1H]^+$, 13.9), 275 ($[M - MeOH]^+$, 1.6), 263 ($[M - CO_2]^+$, 7.7), 216 ($[M - C_7H_7]^+$, 1.7), 199 (2.3), 184 (2.7), 183 (8.7), 174 (3.6), 167 (17.3), 150 ($C_9H_{12}NO^+$, 10.3), 149 ($C_9H_{11}NO^{\bullet+}$, 100), 127 (13.9), 111 (3.3), 97 (7.5), 91 ($C_7H_7^+$, 7.6), 85 ($C_4H_5O_2^+$, 16.9), 83 ($C_4H_3O_2^+$, 7.5), 77 ($C_6H_5^+$, 2.5), 71 ($C_3H_3O_2^+$, 28.3), 69 ($C_3HO_2^+$, 11.3), 65 ($C_5H_5^+$, 2.3), 43 ($C_3H_7^+$, 19.1), 39 ($C_3H_3^+$, 1.6). IR (ATR) $\tilde{\nu}$ [cm^{-1}] = 3068 (w), 2954 (w), 2924 (w), 2850 (w), 2821 (w), 1716 (m), 1639 (m), 1598 (w), 1543 (w), 1490 (w), 1454 (w), 1436 (w), 1408 (w), 1328 (w), 1303 (w), 1273 (m), 1257 (m), 1228 (w), 1192 (w), 1174 (w), 1147 (w), 1109 (w), 1099 (w), 1080 (w), 1024 (w), 1014 (w), 980 (w), 916 (w), 908 (w), 860 (w), 848 (w), 829 (w), 765 (w), 746 (w), 732 (w), 694 (s), 642 (w). Anal. calcd. for $C_{19}H_{17}NO_3$ (307.3): C 74.25, H 5.58, N 4.56; Found: C 74.03, H 5.39, N 4.48.

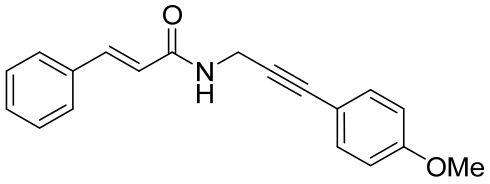
2.1.4. 3-Phenyl-*N*-(3-phenylprop-2-yn-1-yl)propanamide (5d)



Colorless solid. Mp 102 °C. ^{1}H NMR (300 MHz, d_6-acetone): δ = 2.51 (t, ^{3}J = 8.1 Hz, 2 H), 2.93 (t, ^{3}J = 8.2 Hz, 2 H), 4.21 (d, ^{3}J = 5.4 Hz, 2 H), 7.13-7.29 (m, 5 H), 7.34-7.43 (br m, 5 H), 7.50 (br s, 1 H). ^{13}C NMR (75 MHz, d_6-acetone): δ = 29.8 (CH_2), 32.3 (CH_2), 38.3 (CH_2), 82.7 (C_{quat}), 87.3 (C_{quat}), 124.0 (C_{quat}), 126.9 (CH), 129.3 (CH), 129.3 (CH), 129.4 (CH), 132.4 (CH), 142.5 (C_{quat}), 172.0 (C_{quat}). EI-MS: *m/z* (%) = 264 ($[M + H]^+$, 3.5), 263 (M^+, 17.2), 262 ($[M - H]^+$, 3.6), 203 (2.5), 172 ($[M - C_7H_7]^+$, 100), 158 ($[M - C_8H_9]^+$, 5.3), 130 ($C_9H_8N^+$,

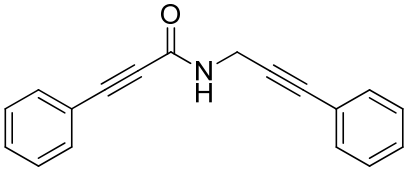
30.2), 132 ($C_9H_{10}N^+$, 5.5), 115 ($C_9H_7^+$, 17.1), 105 ($C_8H_9^+$, 18.2), 91 ($C_7H_7^+$, 19.4), 77 ($C_6H_5^+$, 7.6), 65 ($C_5H_5^+$, 3.6). IR (ATR) $\tilde{\nu}$ [cm^{-1}] = 3028 (w), 2927 (w), 2862 (w), 1633 (s), 1533 (s), 1489 (w), 1429 (w), 1379 (w), 1346 (w), 1303 (w), 1294 (w), 1263 (w), 1226 (m), 1072 (w), 1028 (w), 1012 (w), 754 (s), 688 (s), 609 (s). Anal. calcd. for $C_{18}H_{17}NO$ (263.3): C 82.10, H 6.51, N 5.32; Found: C 81.99, H 6.55, N 5.31.

2.1.5. (*E*)-*N*-(3-(4-Methoxyphenyl)prop-2-yn-1-yl)cinnamic amide (5e)



Light yellow solid. Mp 122 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.80 (s, 3 H), 4.41 (d, ^3J= 5.2 Hz, 2 H), 6.01 (br s, 1 H), 6.43 (d, ^3J = 15.6 Hz, 1 H), 6.81-6.84 (m, 2 H), 7.33-7.51 (m, 5 H), 7.52 (m, 2 H), 7.67 (d, ^3J= 15.6 Hz, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 30.4 (CH_2), 55.8 (CH_3), 83.4 (C_{quat}), 83.5 (C_{quat}), 113.9 (CH), 114.6 (C_{quat}), 120.2 (CH), 127.9 (CH), 128.8 (CH), 129.7 (CH), 133.2 (CH), 134.7 (C_{quart}), 141.5 (CH), 159.7 (C_{quat}), 165.7 (C_{quat}). EI MS (*m/z* (%)): 291 (M^+, 93), 276 ($C_{18}H_{14}NO_2^+$, 9), 260 ($C_{18}H_{14}NO^+$, 13), 214 ($C_{13}H_{12}NO_2^+$, 8), 160 ($C_{10}H_{10}NO^+$, 31), 146 ($C_9H_8NO^+$, 11), 145 ($C_{10}H_9O^+$, 25), 131 ($C_9H_7O^+$, 100), 103 ($C_8H_7^+$, 83), 77 ($C_6H_5^+$, 34). IR (ATR) $\tilde{\nu}$ [cm^{-1}] = 3287 (m), 3001 (m), 2966 (m), 2900 (m), 2358 (m), 2324 (m), 1649 (s), 1618 (s), 1607 (w), 1508 (s), 1441 (m), 1364 (w), 1296 (m), 1248 (s), 1215 (m), 1179 (m), 1109 (w), 1038 (m), 1028 (m), 972 (m), 864 (w), 825 (s), 802 (w), 764 (m), 743 (w), 721 (m), 692 (m), 640 (m). HRMS (ESI) calcd. for $C_{19}H_{17}NO_2$+H^+: 292.1332; Found: 292.1332.

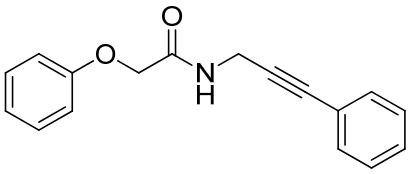
2.1.6. 3-Phenyl-*N*-(3-phenylprop-2-yn-1-yl)propiolamide (5f)



Colorless solid. Mp 119 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.38 (d, ^3J = 5.3 Hz, 2 H), 6.23 (br, 1H), 7.27-7.62 (br m, 10 H).^{13}C NMR (75 MHz , $CDCl_3$): δ = 30.6 (CH_2), 82.6 (C_{quat}), 83.8 (C_{quat}), 84.1 (C_{quat}), 85.7 (C_{quat}), 120.1 (C_{quat}), 122.4 (C_{quat}), 128.5 (CH), 128.7 (CH), 128.8 (CH), 130.4 (CH), 131.9 (CH), 132.7 (CH), 153.1 (C_{quat}). EI-MS: *m/z* (%) = 260 ([M + H]$^+$, 5.2), 259 (M^+, 29.4), 258 ([M - H]$^+$, 30.5), 241 (25.7), 230 (74.2), 215 (54.8), 182 ([M - C_6H_5]$^+$, 15.6), 154 (11.0), 129 ($C_9H_5O^+$, 100), 130 ($C_9H_8N^+$, 11.9), 115 ($C_9H_7^+$, 12.8), 101 ($C_8H_5^+$, 16.1), 89 (6.1), 77 ($C_6H_5^+$, 11.7), 63 (4.5). IR (ATR) $\tilde{\nu}$ [cm^{-1}] = 3012 (w), 2989 (w), 2929 (w),

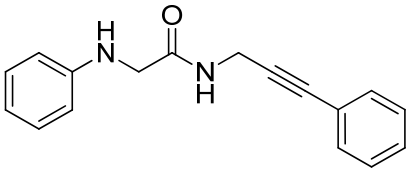
2900 (w), 2615 (w), 2594 (w), 2517 (w), 2436 (w), 2222 (w), 2185 (w), 2146 (w), 2100 (w), 2042 (w), 2015 (w), 1984 (w), 1969 (w), 1950 (w), 1897 (w), 1818 (w), 1737 (w), 1718 (w), 1647 (w), 1618 (m), 1597 (w), 1533 (m), 1487 (m), 1442 (w), 1417 (w), 1394 (w), 1384 (w), 1355 (w), 1303 (m), 1273 (w), 1257 (w), 1219 (m), 1178 (w), 1157 (w), 1097 (w), 1070 (w), 1058 (w), 1016 (w), 997 (w), 987 (w), 960 (w), 916 (w), 902 (w), 877 (w), 842 (w), 788 (w), 754 (s), 731 (w), 686 (w), 623 (w), 605 (w). Anal. calcd. for $C_{18}H_{13}NO$ (259.3): C 83.37, H 5.05, N 5.40; Found: C 83.60, H 5.11, N 5.44.

2.1.7. 2-Phenoxy-*N*-(3-phenylprop-2-yn-1-yl)acetamide (5g)



Colorless solid. Mp 93 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.39 (d, ^{3}J= 5.5 Hz, 2 H), 4.54 (s, 2 H,), 6.87 (br s, 1 H), 6.95 (m, 2 H), 7.01-7.06 (m, 1 H), 7.29-7.36 (m, 5 H), 7.41-7.45 (m, 2 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 29.6 (CH_2), 67.3 (CH_2), 83.6 (C_{quat}), 84.2 (C_{quat}), 114.7 (CH), 122.2 (CH), 122.4 (C_{quat}), 128.3 (CH), 128.6 (CH), 129.8 (CH), 131.8 (CH), 157.1 (C_{quat}), 167.9 (C_{quat}). EI MS (*m/z* (%)): 265 (M^+, 1), 172 ($C_{11}H_{10}NO^+$, 100), 149 ($C_8H_8NO_2^+$, 61), 115 ($C_9H_7^+$, 40), 77 ($C_6H_5^+$, 25). IR (ATR) $\tilde{\nu}$ [cm^{-1}] = 3306 (s), 3055 (w), 2957 (w), 2932 (w), 2922 (w), 2859 (w), 1728 (m), 1659 (s), 1597 (m), 1587 (w), 1530 (s), 1489 (m), 1449 (m), 1414 (w), 1348 (m), 1290 (m), 1263 (w), 1238 (s), 1172 (w), 1125 (w), 1092 (w), 1080 (w), 1063 (m), 1026 (w), 964 (w), 918 (w), 889 (w), 841 (m), 827 (w), 752 (s), 737 (w), 721 (w), 689 (s), 669 (w). HRMS (ESI) calcd. for $C_{17}H_{15}NO_2$+H^+: 266.1176; Found: 266.1176.

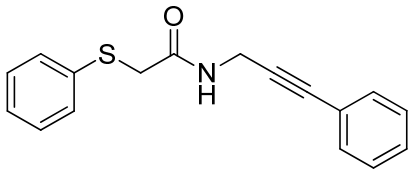
2.1.8. 2-(Phenylamino)-*N*-(3-phenylprop-2-yn-1-yl)acetamide (5h)



Yellow solid. Mp 112 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.90 (s, 2 H), 4.37 (d, ^{3}J= 5.5 Hz, 2 H), 6.71 (m, 2 H), 6.87-6.92 (m, 1 H), 7.10 (br s, 1 H), 7.27-7.46 (m, 8 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 29.7 (CH_2), 48.8 (CH_2), 83.2 (C_{quat}), 84.7 (C_{quat}), 113.3 (CH), 119.1 (CH), 122.5 (C_{quat}), 128.3 (CH), 128.5 (CH), 129.5 (CH), 131.7 (CH), 147.2 (C_{quat}), 170.5 (C_{quart}). EI-MS (*m/z* (%)): 264 (M^+, 7), 172 ($C_{11}H_{10}NO^+$, 4), 171 ($C_{11}H_9NO^+$, 19), 158 ($C_{10}H_8NO^+$, 4), 149 ($C_8H_9N_2O^+$, 4), 130 ($C_9H_8N^+$, 13), 115 ($C_9H_7^+$, 23), 106 ($C_7H_8N^+$, 100), 77 ($C_6H_5^+$, 17). IR (ATR) $\tilde{\nu}$ [cm^{-1}] = 3377 (m), 3300 (m), 3051 (w), 3032 (w), 2936 (w), 2922 (w), 2860 (w), 2359

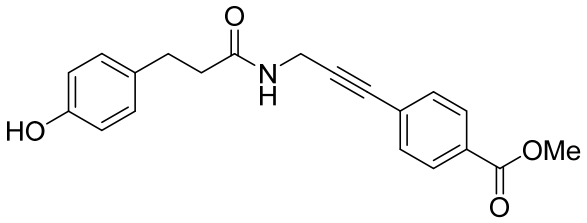
(w), 2345 (w), 2313 (w), 1647 (s), 1601 (m) 1508 (m), 1489 (m), 1441 (w), 1429 (w), 1410 (w), 1387 (m), 1354 (w), 1342 (w), 1317 (m), 1285 (w), 1263 (m), 1232 (w), 1202 (w), 1182 (m), 1152 (w), 1121 (w), 1094 (w), 1074 (m), 1026 (w), 1016 (w), 999 (w), 984 (w), 963 (w), 926 (w), 866 (w), 827 (w), 812 (w), 799 (w), 750 (s), 723 (w), 689 (s), 660 (m), 619 (w). HRMS (ESI) calcd. for $C_{17}H_{16}N_2O+H^+$: 265.1335; Found: 265.1335.

2.1.9. *N*-(3-Phenylprop-2-yn-1-yl)-2-(phenylthio)acetamide (5i)



Yellow solid. Mp 85 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.64 (s, 2 H), 4.25 (d, ^3J= 5.5 Hz, 2 H), 7.06 (br s, 1 H), 7.15-7.25 (m, 2 H), 7.27-7.37 (m, 8 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 30.3 (CH_2), 37.5 (CH_2), 83.5 (C_{quat}), 84.3 (C_{quat}), 122.4 (CH), 126.9 (CH), 128.3 (CH), 128.5 (CH), 129.4 (CH), 131.7 (C_{quat}), 134.5 (C_{quat}), 167.6 (C_{quat}). EI-MS (*m/z* (%)): 281 (M^+, 3), 172 ($C_{11}H_{10}NO^+$, 100), 123 ($C_7H_7S^+$, 16), 115 ($C_9H_7^+$, 26), 109 ($C_6H_5S^+$, 6), 77 ($C_6H_5^+$, 14). IR (ATR) $\tilde{\nu}$ [cm^{-1}] = 3283 (m), 3146 (w), 3102 (w), 3053 (w), 3017 (w), 2957 (w),2922 (m), 2874 (w), 2853 (w), 1667 (s), 1643 (m), 1584 (w), 1541 (s), 1508 (w), 1479 (w), 1437 (w), 1375 (w), 1358 (w), 1331 (w), 1308 (w), 1269 (w), 1231 (w), 1206 (s), 1175 (w), 1157 (w), 1132 (w), 1088 (w), 1070 (w), 1024 (w), 1015 (m), 999 (w), 989 (w), 964 (w), 922 (w), 916 (w), 891 (w), 877 (w), 812 (w), 799 (w), 785 (w), 758 (s), 733 (s), 706 (w), 687 (s). Anal. calcd. for $C_{20}H_{19}NO_4$ (337.4): C 72.57, H 5.37, N 4.98, S 11.40; Found: C 72.33, H 5.38, N 4.93, S 11.23.

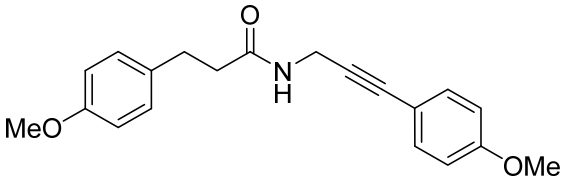
2.1.10. Methyl 4-(3-(3-(4-hydroxyphenyl)propanamido)prop-1-yn-1-yl) benzoate (5j)



Colorless solid. Mp 151 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ = 2.35 (t, ^3J= 7.9 Hz, 2 H), 2.72 (t, ^3J= 7.9 Hz, 2 H), 3.85 (s, 3 H), 4.13 (d, ^3J= 5.5 Hz, 2 H), 6.64 (d, ^3J= 8.4 Hz, 2 H), 6.99 (d, $^3J_{4,3}$= 8.4 Hz, 2 H), 7.54 (d, ^3J= 8.5 Hz, 2 H), 7.94 (d, ^3J= 8.5 Hz, 2 H), 8.38 (t, ^3J= 5.5 Hz, 1 H), 9.14 (s, 1 H). ^{13}C NMR (75 MHz, DMSO-d_6): δ = 28.5 (CH_2), 30.1 (CH_2), 37.2 (CH_2), 52.3 (CH_3), 80.7 (C_{quat}), 90.6 (C_{quat}), 115.0 (CH), 127.1 (C_{quat}), 129.0 (CH), 129.1 (C_{quat}), 129.3 (CH), 131.2 (C_{quat}), 131.6 (CH), 155.4 (C_{quat}), 165.6 (C_{quat}), 171.3 (C_{quat}). EI-MS (*m/z* (%)):

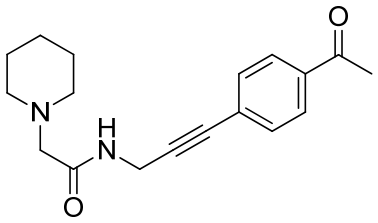
337 (M^+, 13), 336 ($[M-H]^+$, 22), 230 ($C_{13}H_{12}NO_3^+$, 100), 188 ($C_{11}H_{10}NO_2^+$, 19), 120 ($C_8H_8O^+$, 20), 107 ($C_7H_7O^+$, 52). IR (ATR) $\tilde{\nu}$ [cm^{-1}] = 3385 (m), 3291 (m), 2966 (m), 2951 (w), 2924 (w), 2845 (w),1705 (s), 1632 (s), 1601 (w), 1533 (m), 1516 (s), 1435 (m), 1362 (w), 1344 (m), 1288 (m), 1279 (s), 1259 (m), 1225 (s), 1198 (m), 1175 (m), 1103 (m), 1011 (w), 966 (w), 862 (m), 831 (w), 816 (m), 766 (s), 684 (m), 640 (w). Anal. calcd. for $C_{20}H_{19}NO_4$ (337.4): C 71.20, H 5.68, N 4.15; Found: C 70.96, H 5.38, N 4.07.

2.1.11. 3-(4-Methoxyphenyl)-*N*-(3-(4-methoxyphenyl)prop-2-yn-1-yl)propanamide (5k)



Colorless solid. Mp 114 °C. ^{1}H NMR (300 MHz, d_6-DMSO): δ = 2.37 (t, ^3J = 7.7 Hz, 2 H), 2.76 (t, ^3J = 7.5 Hz, 2 H), 3.68 (s, 3 H), 3.76 (s, 3 H), 4.06 (d, ^3J = 5.4 Hz, 2 H), 6.80 (d, ^3J = 8.7 Hz, 2 H), 6.92 (d, ^3J = 8.8 Hz, 2 H), 7.10 (d, ^3J = 8.7 Hz, 2 H), 7.34 (d, ^3J = 8.8 Hz, 2 H), 8.32 (t, ^3J = 5.3 Hz, 1 H). ^{13}C NMR (75 MHz, d_6-DMSO): δ = 28.5 (CH_2), 30.1 (CH_2), 37.1 (CH_2), 54.9 (CH_3), 55.2 (CH_3), 81.5 (C_{quat}), 85.5 (C_{quat}), 113.7 (CH), 114.3 (CH, C_{quat}), 129.2 (CH), 132.9 (CH), 133.1 (C_{quat}), 157.5 (C_{quat}), 159.3 (C_{quat}), 171.2 (C_{quat}). EI-MS: *m/z* (%) = 324 ($[M + H]^+$, 3.1), 323 (M^+, 15.2), 281 (1.3), 221 (1.6), 202 ($[M - C_8H_9O]^+$, 100), 188 ($C_{11}H_{10}NO_2^+$, 4.2), 163 ($C_{10}H_{11}O_2^+$, 2.5), 162 ($C_{10}H_{12}NO^+$, 10.1), 161 ($C_{10}H_9O_2^+$, 20.2), 145 ($C_{10}H_9O^+$, 15.6), 135 ($C_9H_{11}O^+$, 23.6), 121 ($C_8H_9O^+$, 36.4), 102 (4.8), 91 ($C_7H_7^+$, 6.4), 89 (2.3), 77 ($C_6H_5^+$, 5.9), 73 (2.0), 43 ($C_3H_7^+$, 5.0), 40 (3.6). IR (ATR) $\tilde{\nu}$ [cm^{-1}] = 3032 (w), 2962 (w), 2920 (w), 2843 (w), 1633 (m), 1604 (w), 1529 (w), 1510 (m), 1481 (w), 1462 (w), 1440 (w), 1417 (w), 1373 (w), 1344 (w), 1294 (w), 1244 (s), 1220 (w), 1176 (w), 1149 (w), 1101 (m), 1076 (m), 1029 (s), 1016 (s), 1006 (m), 939 (w), 923 (w), 860 (w), 846 (w), 802 (s), 790 (s), 767 (m), 759 (m), 729 (w), 692 (m), 651 (w), 640 (w), 623 (w). Anal. calcd. for $C_{20}H_{21}NO_3$ (323.4): C 74.28, H 6.55, N 4.33; Found: C 74.41, H 6.47, N 4.36.

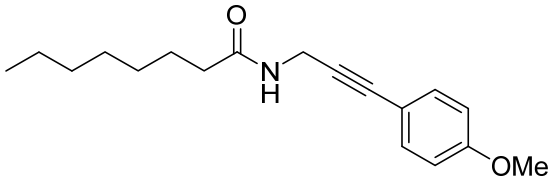
2.1.12. *N*-(3-(4-Acetylphenyl)prop-2-yn-1-yl)-2-(piperidin-1-yl)acetamide (5l)



Viscous yellow liquid. ^{1}H NMR (300 MHz, d_6-DMSO): δ = 1.38 (m, 2 H), 1.53 (m, 4 H), 2.37 (t, ^3J = 5.0 Hz, 4 H), 2.57 (s, 3 H), 2.91 (s, 2 H), 4.17 (d, ^3J = 5.9 Hz, 2 H), 7.53 (d, ^3J = 8.5

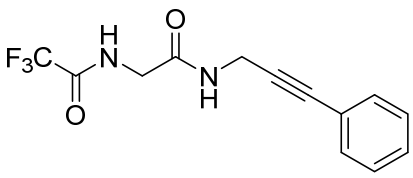
Hz, 2 H), 7.94 (d, ^3J = 8.6 Hz, 2 H), 8.19 (t, ^3J = 5.7 Hz, 1 H). ^{13}C NMR (75 MHz, d_6-DMSO): δ = 23.5 (CH_2), 25.4 (CH_2), 26.7 (CH_3), 28.5 (CH_2), 54.1 (CH_2), 61.9 (CH_2), 80.5 (C_{quat}), 90.8 (C_{quat}), 126.9 (C_{quat}), 128.4 (CH_2), 131.5 (CH_2), 136.1 (C_{quat}), 169.6 (C_{quat}), 197.2 (C_{quat}). EI-MS: *m/z* (%) = 277 (2.9), 155 ([M - $C_{10}H_7O$]$^+$, 2.5), 155 (2.5), 149 (3.4), 113 (2.6), 112 (5.0), 98 ($C_6H_{12}N^+$, 100), 84 ($C_5H_{10}N^+$, 8.5), 73 ($C_3H_7NO^+$, 20.1), 70 (6.4), 67 (2.6), 43 ($C_2H_3O^+$, 6.9). IR (ATR) $\tilde{\nu}$ [cm^{-1}] = 2933 (w), 2854 (w), 2810 (w), 2794 (w), 2756 (w), 1678 (s), 1600 (m), 1552 (w), 1504 (m), 1467 (w), 1452 (w), 1402 (w), 1386 (w), 1355 (w), 1334 (w), 1301 (w), 1259 (s), 1178 (w), 1161 (w), 1126 (w), 1111 (w), 1087 (w), 1074 (w), 1039 (w), 1014 (w), 997 (w), 983 (w) 958 (w), 902 (w), 864 (w), 839 (m), 810 (w), 794 (w), 765 (w), 746 (w), 723 (w), 696 (w), 634 (w). Anal. calcd. for $C_{18}H_{22}N_2O_2$ (298.4): C 72.46, H 7.43, N 9.39; Found: C 72.15, H 7.31, N 9.02.

2.1.13. *N*-(3-(4-Methoxyphenyl)prop-2-yn-1-yl)octanamide (5m)



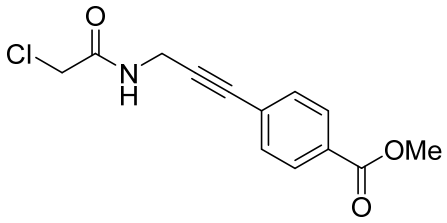
Yellow solid. Mp 78 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.86 (s, 3 H), 1.23-1.29 (m, 8 H), 1.62-1.72 (m, 2 H), 2.20 (t, ^3J = 7.3 Hz, 2 H), 3.80 (s, 3 H), 4.25 (d, ^3J = 5.1 Hz, 2 H), 5.74 (br s, 1 H), 6.80-6.83 (m, 2 H), 7.33-7.36 (m, 2 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.1 (CH_3), 22.6 (CH_2), 25.6 (CH_2), 29.0 (CH_2), 29.2 (CH_2), 30.0 (CH_2), 31.7 (CH_2), 36.6 (CH_2), 55.3 (CH_3), 83.3 (C_{quat}), 83.5 (C_{quat}), 113.9 (CH), 114.6 (C_{quat}), 138.2 (CH), 159.7 (C_{quat}), 172.7 (C_{quat}). EI-MS (*m/z* (%)): 287 (M^+, 25), 202 ($C_{12}H_{12}NO_2^+$, 36), 188 ($C_{11}H_{10}NO_2^+$, 56), 160 ($C_{10}H_{10}NO^+$, 100), 145 ($C_{10}H_9O^+$, 48). IR (ATR) $\tilde{\nu}$ [cm^{-1}] = 3296 (m), 3040 (w), 2953 (w), 2926 (m), 2851 (m), 2236 (w),1637 (s), 1605 (m), 1568 (w), 1526 (m), 1510 (s), 1456 (w), 1437 (w), 1416 (w), 1375 (w), 1321 (w), 1304 (w), 1290 (m), 1273 (w), 1246 (s), 1204 (w), 1179 (m), 1113 (w), 1086 (w), 1028 (m), 1005 (w), 939 (w), 827 (s), 802 (w), 783 (w), 721 (w), 677 (m), 654 (w), 640 (w), 608 (w). HRMS (ESI) calcd. for $C_{18}H_{25}NO_2$+H^+: 288.1958; Found: 288.1958.

2.1.14. 2,2,2-Trifluoro-*N*-(2-oxo-2-((3-phenylprop-2-yn-1-yl)amino)ethyl) acetamide (5n)



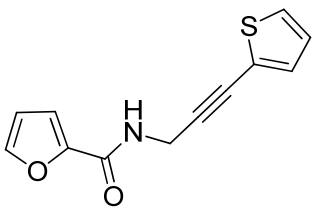
Colorless solid. Mp 137 °C. ^{1}H NMR (300 MHz , $CDCl_3$): δ = 4.07 (d, ^{3}J = 4.9 Hz, 2 H), 4.31 (d, ^{3}J = 5.2 Hz, 2 H), 6.45 (br, 1 H), 7.28-7.42 (br m, 5 H), 7.53 (br s, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 30.5 (CH_2), 42.8 (CH_2), 83.7 (C_{quat}), 84.1 (C_{quat}), 115.8 (d, ^{1}J = 287.2 Hz, C_{quat}), 122.3 (C_{quat}), 128.5 (CH), 128.9 (CH), 131.9 (CH), 157.7 (d, ^{2}J = 37.9 Hz, C_{quat}), 166.5 (C_{quat}). EI-MS: *m/z* (%) = 209 (3.0), 171 ($C_4H_6F_3N_2O_2^+$, 100), 172 ([M - C_2HF_3NO]$^+$, 14.2), 158 ($C_{10}H_8NO^+$, 9.1), 143 (15.1), 130 ($C_9H_8N^+$, 25.1), 115 ($C_9H_7^+$, 48.9), 103 ($C_8H_7^+$, 12.4), 97 ($C_2F_3O^+$, 3.1), 89 (6.8), 77 ($C_6H_5^+$, 7.8), 69 (CF_3^+, 7.4), 43 ($C_3H_7^+$, 1.9). IR (ATR) $\tilde{\nu}$ [cm^{-1}] = 3099 (w), 2916 (w), 2854 (w), 1701 (s), 1654 (s), 1556 (m), 1490 (w), 1442 (w), 1423 (w), 1386 (w), 1355 (w), 1344 (w), 1284 (w), 1213 (m), 1188 (s), 1157 (s), 1103 (w), 1091 (w), 1070 (w), 1041 (w), 1006 (w), 964 (w), 916 (w), 885 (w), 846 (w), 754 (s), 731 (w), 688 (s), 621 (w), 601 (w). Anal. calcd. for $C_{13}H_{11}F_3N_2O_2$ (284.2): C 54.93, H 3.90, N 9.86; Found: C 54.68, N 3.93, H 9.79.

2.1.15. Methyl 4-(3-(2-chloroacetamido)prop-1-yn-1-yl)benzoate (5o)



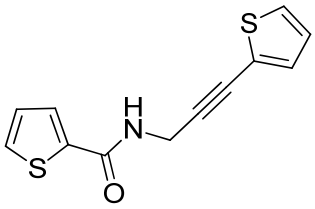
Colorless solid. Mp 132 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.91 (s, 3 H), 4.10 (s, 2 H), 4.35 (d, ^{3}J= 5.4 Hz, 2 H), 6.88 (br s, 1 H), 7.47 (d, ^{3}J= 8.5 Hz, 2 H), 7.97 (d, ^{3}J= 8.5 Hz, 2 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 30.3 (CH_2), 42.4 (CH_2), 52.3 (CH_3), 83.1 (C_{quat}), 86.8 (C_{quat}), 126.9 (C_{quat}), 129.5 (CH), 129.9 (C_{quat}), 131.7 (CH), 165.7 (C_{quat}), 166.4 (C_{quat}). EI-MS (*m/z* (%)): 230 ([M-Cl]$^+$, 100), 188 ($C_{11}H_{10}NO_2^+$, 5), 173 ($C_{11}H_9O_2^+$, 7). IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 3348 (m), 3292 (w), 3071 (w), 3005 (w), 2957 (w), 2926 (w), 1717 (s), 1649 (s), 1607 (m), 1533 (m), 1506 (w), 1437 (m), 1404 (m), 1344 (m), 1312 (m), 1277 (s), 1265 (s), 1225 (s), 1196 (w), 1180 (m), 1155 (w), 1009 (m), 1098 (w), 1082 (m), 1047 (w), 1018 (m), 966 (m), 926 (w), 862 (m), 768 (s), 739 (w), 696 (s), 642 (m). HRMS (ESI) calcd. for $C_{13}H_{12}ClNO_3$+H^+: 266.0578; Found: 266.0578.

2.1.16. *N*-(3-(Thiophen-2-yl)prop-2-yn-1-yl)furan-2-carboxamide (5p)



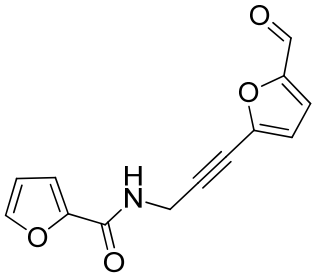
Colorless solid. Mp 67 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.47 (d, ^{3}J = 5.4 Hz, 2 H), 6.50 (dd, ^{3}J = 3.5 Hz, ^{4}J = 1.8 Hz, 1 H), 6.62 (br s, 1 H), 6.95 (dd, ^{3}J = 5.2 Hz, ^{3}J = 3.7 Hz, 1 H), 7.15 (dd, ^{3}J = 3.5 Hz, ^{4}J = 0.8 Hz, 1 H), 7.20 (m, 1 H), 7.24 (m, 1 H), 7.45 (m, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 29.9 (CH_2), 77.1 (C_{quat}), 88.6 (C_{quat}), 112.3 (CH), 114.9 (CH), 122.5 (C_{quat}), 127.1 (CH), 127.4 (CH), 132.5 (CH), 144.3 (CH), 147.6 (C_{quat}), 158.0 (C_{quat}). EI-MS: *m/z* (%) = 232 ($[M + H]^+$, 2.8), 231 (M^+, 17.7), 230 ($[M - H]^+$, 3.9), 202 ($[M - CHO]^+$, 100), 186 ($[M - CH_2S]^+$, 2.7), 184 (10.4), 174 ($C_{10}H_8NO_2^+$, 8.2), 170 (1.2), 159 (3.3), 148 ($[M - C_4H_3S]^+$, 2.1), 136 ($C_7H_6NS^+$, 8.6), 134 ($C_7H_4NS^+$, 2.9), 121 ($C_7H_5S^+$, 8.9), 109 (19.0), 95 ($C_5H_3O_2^+$, 55.6), 77 (7.9), 69 (5.1), 45 (3.6). IR (ATR) $\tilde{\nu}$ [cm^{-1}] = 3076 (w), 3041 (w), 2968 (w), 2935 (w), 2779 (w), 1672 (w), 1651 (m), 1591 (m), 1523 (m), 1477 (w), 1381 (w), 1357 (w), 1348 (w), 1294 (w), 1257 (w), 1226 (w), 1186 (s), 1143 (w), 1082 (w), 1307 (w), 1008 (m), 987 (w), 935 (w), 906 (w), 885 (w), 848 (w), 831 (w), 825 (w), 781 (w), 750 (m), 692 (s), 607 (m). Anal. calcd. for $C_{12}H_9NO_2S$ (231.3): C 62.32, H 3.92, N 6.06, S 13.86; Found: C 62.40, H 3.95, N 6.05, S 14.11.

2.1.17. *N*-(3-(Thiophen-2-yl)prop-2-yn-1-yl)thiophene-2-carboxamide (5q)



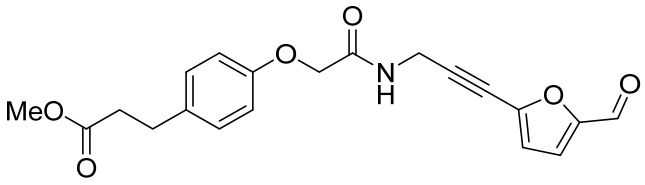
Colorless solid. Mp 120 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.48 (d, ^{3}J = 5.3 Hz, 2 H), 6.36 (br, 1 H), 6.96 (dd, ^{3}J = 5.2 Hz, 3.7 Hz, 1 H), 7.08 (dd, ^{3}J = 5.0 Hz, 3.8 Hz, 1 H), 7.20 (dd, ^{3}J = 3.6 Hz, ^{4}J = 1.9 Hz, 1 H), 7.24 (dd, ^{3}J = 5.2 Hz, ^{4}J = 1.1 Hz, 1 H), 7.49 (dd, ^{3}J = 5.0 Hz, ^{4}J = 1.1 Hz, 1 H), 7.56 (dd, ^{3}J = 3.7 Hz, ^{4}J = 1.1 Hz, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 30.8 (CH_2), 77.4 (C_{quat}), 88.7 (C_{quat}), 122.5 (C_{quat}), 127.1 (CH), 127.5 (CH), 127.8 (CH), 128.7 (CH), 130.5 (CH), 132.6 (CH), 138.3 (C_{quat}), 161.6 (C_{quat}). EI-MS: *m/z* (%) = 247 (M^+, 8.5), 246 ($[M - H]^+$, 4.6), 202 ($[M - CH_2S + H]^+$, 45.7), 186 (6.0), 183 (4.9), 136 ($C_7H_6NS^+$, 9.8), 121 ($C_7H_5S^+$, 10.6), 111 ($C_5H_3OS^+$, 100), 109 (19.8), 108 (8.9), 83 ($C_4H_3S^+$, 17.8), 69 (11.0), 45 (11.6). IR (ATR) $\tilde{\nu}$ [cm^{-1}] = 3097 (w), 3010 (w), 2981 (w), 2924 (w), 2872 (w), 2848 (w), 2358 (w), 2127 (w), 1797 (w), 1708 (w), 1624 (m), 1595 (w), 1541 (m), 1512 (w), 1479 (w), 1458 (w), 1417 (w), 1381 (w), 1359 (w), 1344 (w), 1300 (m), 1284 (m), 1253 (m), 1247 (m), 1188 (w), 1143 (m), 1095 (m), 1080 (w), 1060 (w), 1047 (w), 1031 (w), 1020 (w), 968 (w), 954 (w), 906 (w), 885 (w), 854 (m), 842 (m), 827 (w), 785 (w), 771 (w), 752 (w), 719 (m), 700 (s), 657 (w), 634 (m). Anal. calcd. for $C_{12}H_9NOS_2$ (247.3). C 58.27, H 3.67, N 5.66, S 25.93; Found: C 58.52, H 3.94, N 5.70, S 26.07.

2.1.18. *N*-(3-(5-Formylfuran-2-yl)prop-2-yn-1-yl)furan-2-carboxamide (5r)



Yellow solid. Mp 118 °C. ^{1}H NMR (300 MHz, d_6-DMSO): δ = 4.34 (d, ^{3}J = 5.7, 2 H), 6.64 (dd, ^{3}J = 3.5 Hz, ^{4}J = 1.7 Hz, 1 H), 7.03 (d, ^{3}J = 3.7 Hz, 1 H), 7.16 (dd, ^{3}J = 3.5 Hz, ^{4}J = 0.7 Hz, 1 H), 7.56 (d, ^{3}J = 3.7 Hz, 1 H), 7.87 (m, 1 H), 8.99 (t, ^{3}J = 5.6 Hz, 1 H), 9.56 (s, 1 H). ^{13}C NMR (75 MHz, d_6-DMSO): δ = 28.6 (CH_2), 71.0 (C_{quat}), 95.0 (C_{quat}), 112.0 (CH), 114.1 (CH), 117.7 (CH), 123.4 (CH), 140.1 (C_{quat}), 145.5 (CH), 147.3 (C_{quat}), 152.1 (C_{quat}), 157.6 (C_{quat}), 178.1 (C_{quat}). EI-MS: *m/z* (%) = 244 ($[M + H]^+$, 5.1) , 243 (M^+, 37.3), 214 ($[M - CHO]^+$, 64.0), 215 ($[M - CO]^+$, 10.0), 186 ($[M - C_2HO_2]^+$, 39.0), 168 (11.9), 148 ($C_8H_6NO_2^+$, 12.9), 140 (8.3), 131 (5.6), 130 (11.5), 121 ($C_7H_5O_2^+$, 5.3), 115 (10.1), 103 (11.9), 95 ($C_5H_3O_2^+$, 100), 77 (5.6), 75 (7.0), 67 ($C_4H_3O^+$, 6.1), 63 (5.1), 43 ($C_3H_7^+$, 5.4), 39 ($C_3H_3^+$, 13.1). IR (ATR) $\tilde{\nu}$ [cm^{-1}] = 3103 (w), 2985 (w), 2825 (w), 1668 (m), 1647 (m), 1597 (w), 1521 (w), 1506 (m), 1471 (m), 1408 (w), 1390 (m), 1348 (w), 1309 (w), 1284 (w), 1267 (w), 1230 (w), 1188 (w), 1147 (w), 1103 (w), 1080 (w), 1053 (w), 1033 (m), 1020 (m), 1006 (w), 985 (w), 966 (m), 916 (w), 896 (w), 812 (s), 798 (w), 775 (w), 756 (s), 659 (w), 626 (w), 601 (w). Anal. calcd. for $C_{13}H_9NO_4$ (243.2): C 64.20, H 3.73, N 5.76; Found: C 64.12, H 4.02, N 5.82.

2.1.19. Methyl 3-(4-2-((3-(5-formylfuran-2-yl)prop-2-yn-1-yl)amino)-2-oxoethoxy)phenyl) propanoate (5s)



Yellow solid. Mp 83 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.60 (t, ^{3}J = 7.9 Hz, 2 H), 2.90 (t, ^{3}J = 7.9 Hz, 2 H), 3.66 (s, 3 H), 4.42 (d, ^{3}J = 5.7 Hz, 2 H), 4.51 (s, 2 H), 6.71 (d, ^{3}J = 3.69 Hz, 1 H), 6.84-6.91 (m, 3 H), 7.14-7.21 (m, 3 H), 9.61 (s, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 29.3 (CH_2), 30.0 (CH_2), 35.8 (CH_2), 51.6 (CH_3), 67.4 (CH_2), 72.9 (C_{quat}), 92.1 (C_{quat}), 114.8 (CH), 117.4 (CH), 120.8 (CH), 129.6 (CH), 134.5 (C_{quat}), 141.0 (C_{quat}), 152.5 (C_{quat}), 155.5 (C_{quat}), 168.2 (C_{quat}), 173.2 (C_{quat}), 177.3 (C_{quat}). EI-MS (*m/z* (%)): 369 (M^+, 5), 190 ($C_{10}H_8NO_3^+$, 100), 179 ($C_{10}H_{11}O_3^+$, 15), 133 ($C_8H_5O_2^+$, 43). IR (ATR) $\tilde{\nu}$ [cm^{-1}] = 3381 (w), 3307 (m), 3055 (w), 2932 (w), 2849 (w), 1734 (m), 1724 (m), 1680 (m), 1659 (s), 1624 (w), 1597 (w), 1530 (s),

1510 (m), 1489 (w), 1449 (m), 1437 (w), 1395 (w), 1348 (m), 1323 (w), 1290 (w), 1277 (w), 1265 (w), 1236 (s), 1206 (w), 1192 (w), 1179 (w), 1152 (w), 1111 (w), 1092 (w), 1063 (m), 1024 (w), 1016 (w), 1001 (w), 978 (w), 966 (w), 889 (w), 841 (w), 827 (w), 812 (w), 752 (s), 721 (w), 689 (s), 669 (w), 617 (w). HRMS (ESI) calcd. for $C_{20}H_{19}NO_6+H^+$: 370.1285; Found: 370.1285.

2.2. Chemoenzymatic four-component synthesis of 3-(4-1,2,3-triazolyl)phenyl propargyl amides 7 (General Procedure)

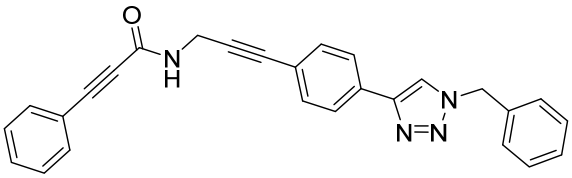
To a solution of propargylamine (**2**) (55 mg, 1.00 mmol) in dry MTBE (2.0 mL) in a screw-cap Schlenk vessel, methyl ester **1** (1.20 mmol) and Novozyme® 435 (50 % w/w of respective ester substrate **1**) were successively added and reaction was allowed to shake in an incubating shaker at 45 °C for 4 or 24 h (for experimental details see Table 2). After the complete conversion (monitored by TLC), DMF (2.0 mL) was added to the reaction mixture, which was then flushed with argon for 15 min. Then (4-iodophenyl)ethynyl trimethylsilane (**4i**) ((300 mg, 1.00 mmol), TMG (115 mg, 1.00 mmol), $Pd(PPh_3)_4$ (23 mg, 0.02 mmol), and CuI (8 mg,0.04 mmol) were successively added to the reaction mixture under argon and the reaction was allowed to shake at 45 °C for 1 h. Then potassium fluoride (58 mg, 1.00 mmol) was added to the reaction mixture and after 10 min benzyl azide (**6**) (133 mg, 1.00 mmol) was added. After 1 h of shaking in the incubating shaker the reaction mixture was filtered to remove the enzyme beads. Then, brine (5.0 mL) was added to the filtrate followed by extraction with ethyl acetate (3 x 10.0 mL). The combined organic layers were dried with anhydrous Na_2SO_4 and pure product **7** was obtained after column chromatography on silica gel (*n*-hexane/ethylacetate).

Table 2. Experimental details of the chemoenzymatic four-component synthesis of 3-(4-1,2,3-triazolyl)phenyl propargyl amides **7**.

Entry	Methyl ester **1**	3-(4-1,2,3-Triazolyl)phenyl propargyl amide **7**
1[a]	192 mg (1.20 mmol) of **1e**	259 mg (62 %) of **7a**
2[b]	199 mg (1.20 mmol) of **1f**	245 mg (58 %) of **7b**

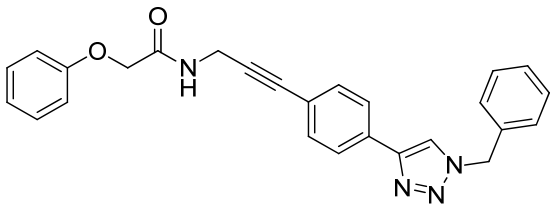
[a]24 h time for CAL-B catalyzed aminolysis. [b]4 h time for CAL-B catalyzed aminolysis.

2.2.1. *N*-(3-(4-(1-Benzyl-1H-1,2,3-triazol-4-yl)phenyl)prop-2-yn-1-yl)-3-phenyl propiolamide (7a)



Yellow solid. Mp 150 °C. ^{1}H NMR (300 MHz, d_6-DMSO): δ = 4.23 (d, ^{3}J = 5.5 Hz, 2 H), 5.65 (s, 2 H), 7.33-7.61 (br m, 12 H), 7.86 (d, ^{3}J = 8.3 Hz, 2 H), 8.70 (s, 1 H), 9.36 (t, ^{3}J = 5.3 Hz, 1 H).^{13}C NMR (75 MHz, d_6-DMSO): δ = 30.7 (CH_2), 53.1 (CH_2), 81.8 (C_{quat}), 83.4 (C_{quat}), 83.9 (C_{quat}), 86.8 (C_{quat}), 119.6 (C_{quat}), 122.1 (CH), 123.3 (C_{quat}), 125.3 (CH), 127.9 (CH), 128.2 (CH), 128.8 (CH), 129.0 (CH), 130.4 (CH), 130.8 (C_{quat}), 132.0 (CH), 132.2 (CH), 135.9 (C_{quat}), 145.9 (C_{quat}), 152.1(C_{quat}). MALDI-MS: *m/z* = 417 ([M + H]$^{+}$). IR (ATR) $\tilde{\nu}$ [cm^{-1}] = 3037 (w), 2993 (w), 2954 (w), 2922 (w), 2360 (w), 2343 (w), 2331 (w), 2225 (w), 1637 (s), 1535 (m), 1419 (w), 1296 (w), 1217 (w), 1190 (w), 1074 (w), 1049 (w), 1020 (w), 977 (w), 844 (w), 800 (m), 754 (s), 713 (m), 686 (m), 617 (w). Anal. calcd. for $C_{27}H_{20}N_4O$ (422.5): C 77.87, H 4.84 N 13.45; Found: C 77.59 H 4.66 N 13.35.

2.2.2. *N*-(3-(4-(1-Benzyl-1H-1,2,3-triazol-4-yl)phenyl)prop-2-yn-1-yl)-2-phenoxy acetamide (7b)

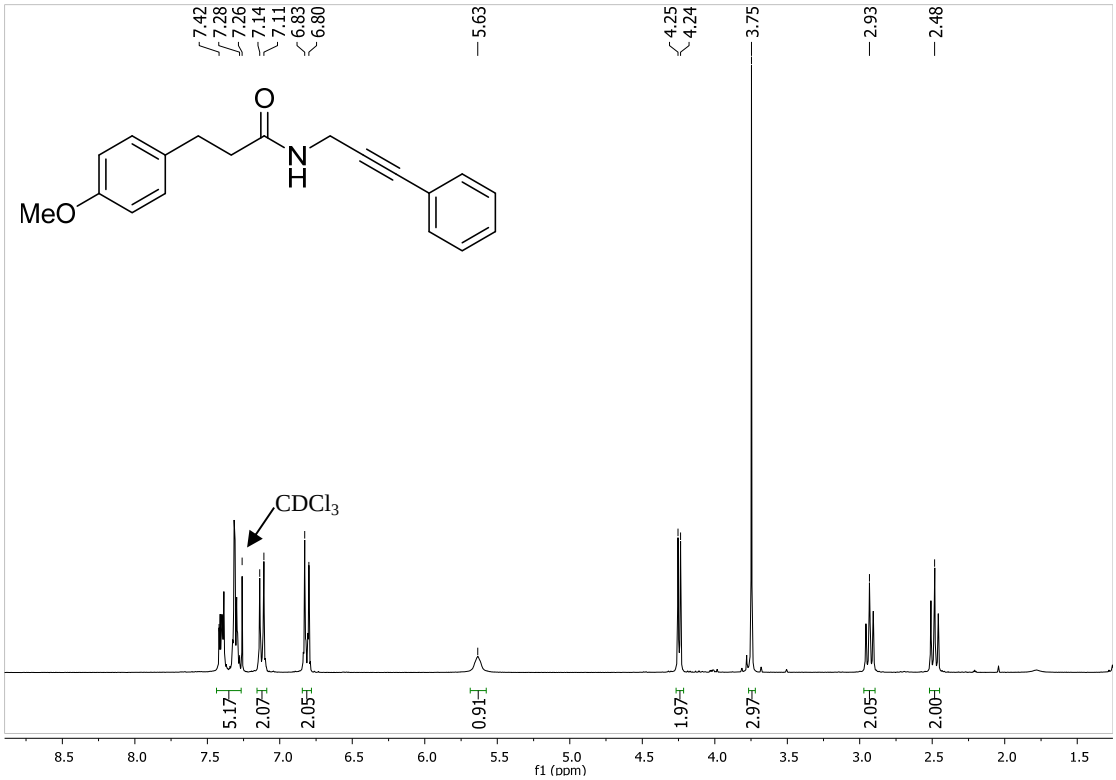


Yellow solid. Mp 147 °C. ^{1}H NMR (300 MHz, d_6-DMSO): δ = 4.21 (d, ^{3}J = 5.6 Hz, 2 H), 4.54 (s, 2 H), 5.65 (s, 2 H), 6.97-7.00 (m, 3 H), 7.28-7.39 (br m, 7 H), 7.45 (d, ^{3}J = 8.4 Hz, 2 H), 7.59-7.62 (m, 1 H), 7.86 (d, ^{3}J = 8.4 Hz, 2 H), 8.69 (s, 1 H).^{13}C NMR (75 MHz, d_6-DMSO): δ = 28.5 (CH_2), 53.1 (CH_2), 66.8 (CH_2), 81.3 (C_{quat}), 87.7 (C_{quat}), 114.7 (CH), 121.2 (CH), 121.5 (C_{quat}), 122.1 (CH), 125.3 (CH), 127.9 (CH), 128.2 (CH), 129.5 (CH), 130.7 (C_{quat}), 132.0 (CH), 135.9 (C_{quat}), 145.9 (C_{quat}), 157.6 (C_{quat}), 167.7 (C_{quat}). MALDI-MS: *m/z* = 423 ([M + H]$^{+}$). IR (ATR) $\tilde{\nu}$ [cm^{-1}] = 3034 (w), 2922 (w), 2910 (w), 2856 (w), 1662 (s), 1598 (w), 1587 (w), 1519 (m), 1489 (s), 1456 (w), 1435 (w), 1409 (w), 1350 (w), 1286 (w), 1242 (s), 1226 (s), 1170 (w), 1080 (w), 1060 (w), 1047 (w), 1028 (w), 1018 (w), 1001 (w), 835 (m), 798 (m), 756 (s), 721 (s), 657 (w), 603 (w). Anal. calcd. for $C_{26}H_{22}N_4O_2$ (422.5): C 73.92, H 5.25, N 13.26; Found: C 74.06, N 5.32, H 13.47.

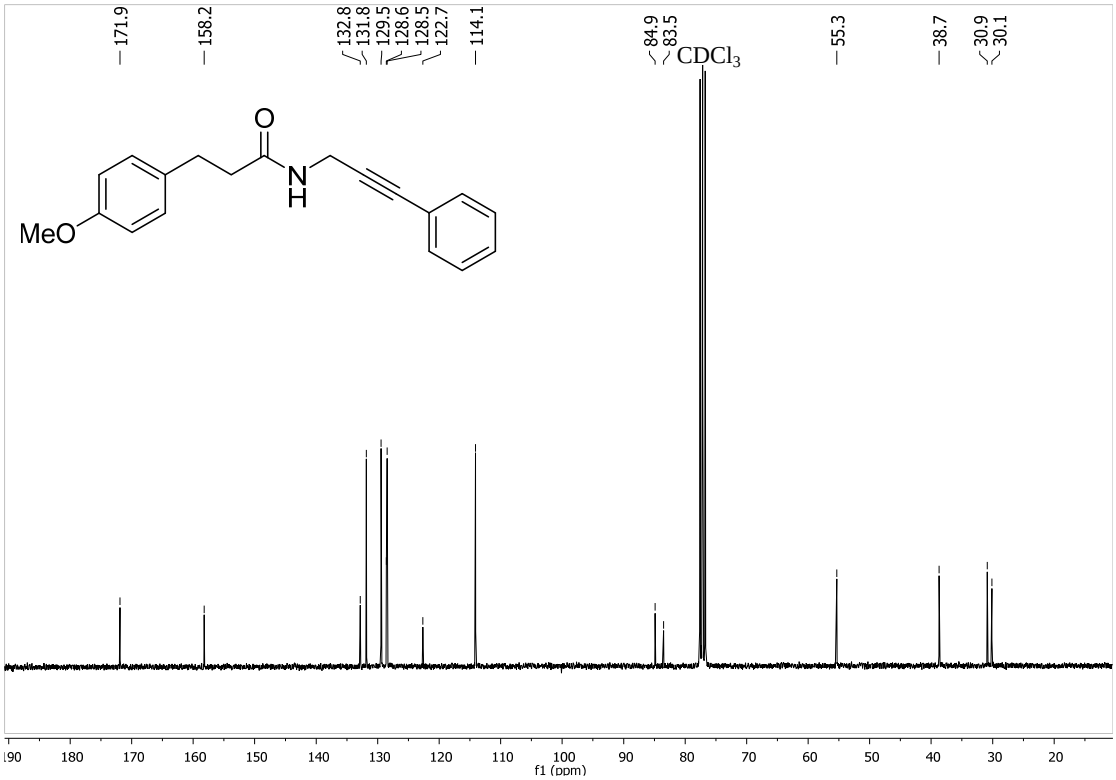
3. NMR Spectra of 3-(Hetero)Arylpropargyl Amides 5

3.1. 3-(4-Methoxyphenyl)-*N*-(3-phenylprop-2-yn-1-yl)propanamide (5a)

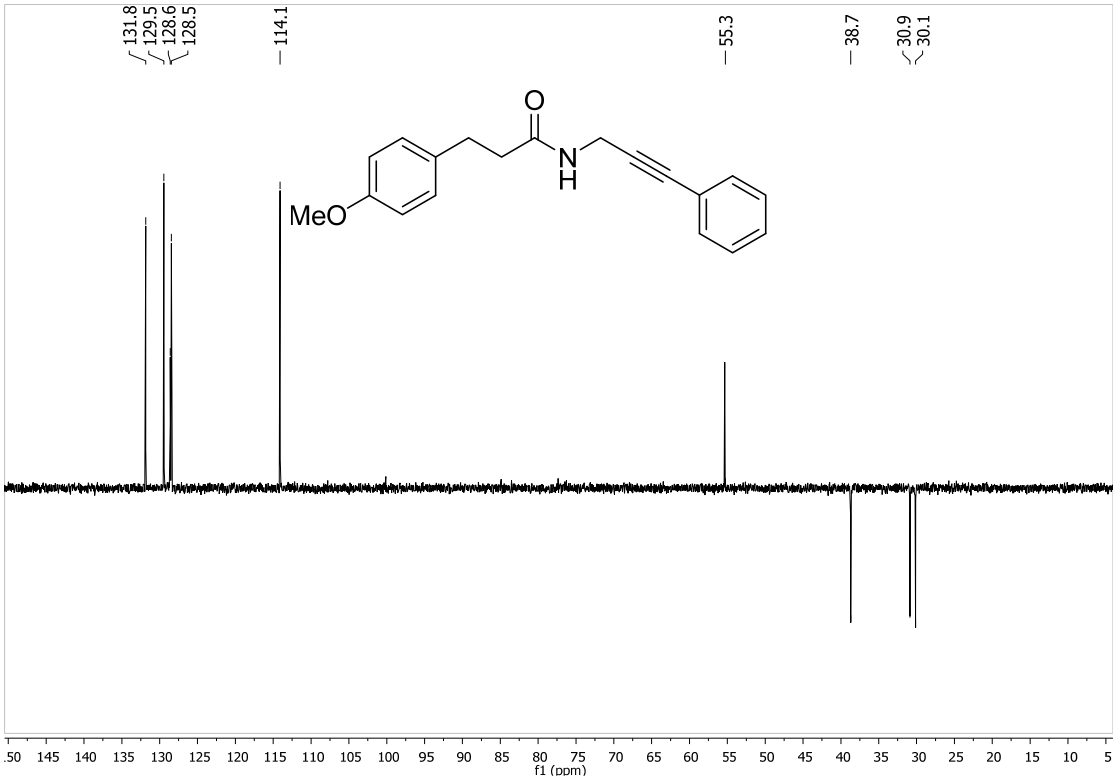
^{1}H NMR spectrum of compound 5a (300 MHz, $CDCl_3$, *T* = 296 K).



^{13}C NMR spectrum of compound 5a (75 MHz, $CDCl_3$, *T* = 296 K).

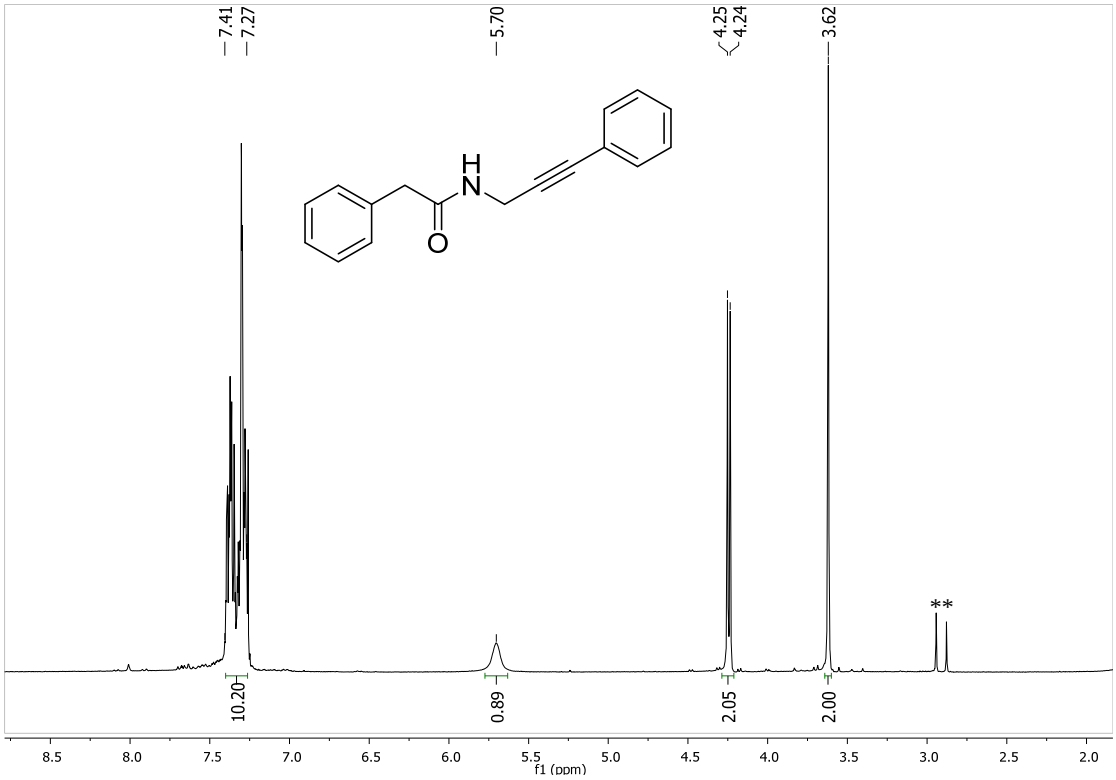


DEPT 135 ^{13}C NMR spectrum of compound 5a (75 MHz, $CDCl_3$, *T* = 296 K).



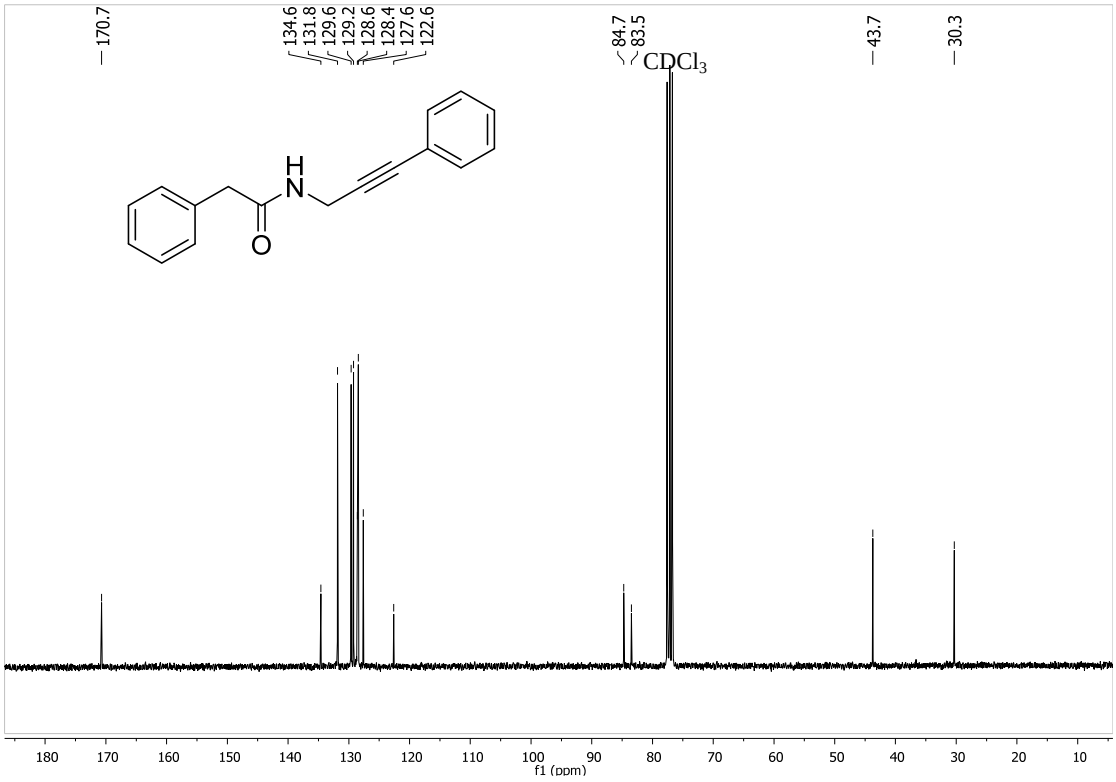
3.2. 2-Phenyl-*N*-(3-phenylprop-2-yn-1-yl)acetamide (5b)

^{1}H NMR spectrum of compound 5b (300 MHz, $CDCl_3$, *T* = 296 K).

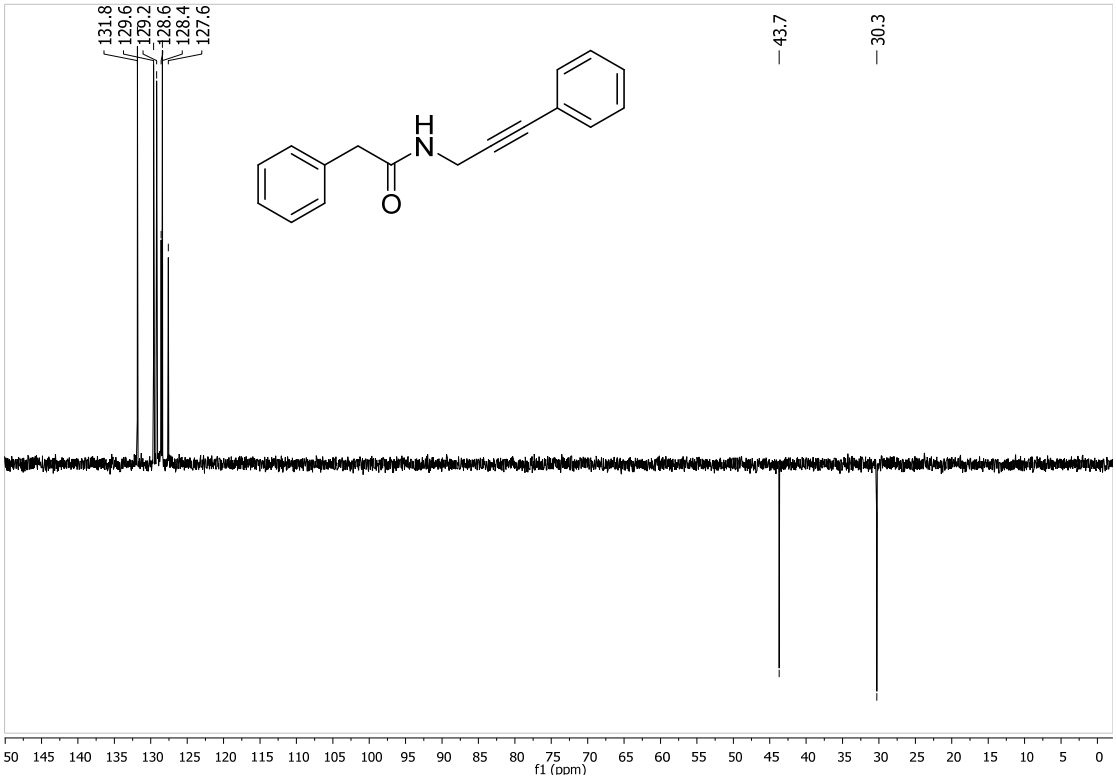


*Impurities from the residual solvent.

^{13}C NMR spectrum of compound 5b (75 MHz, $CDCl_3$, *T* = 296 K).

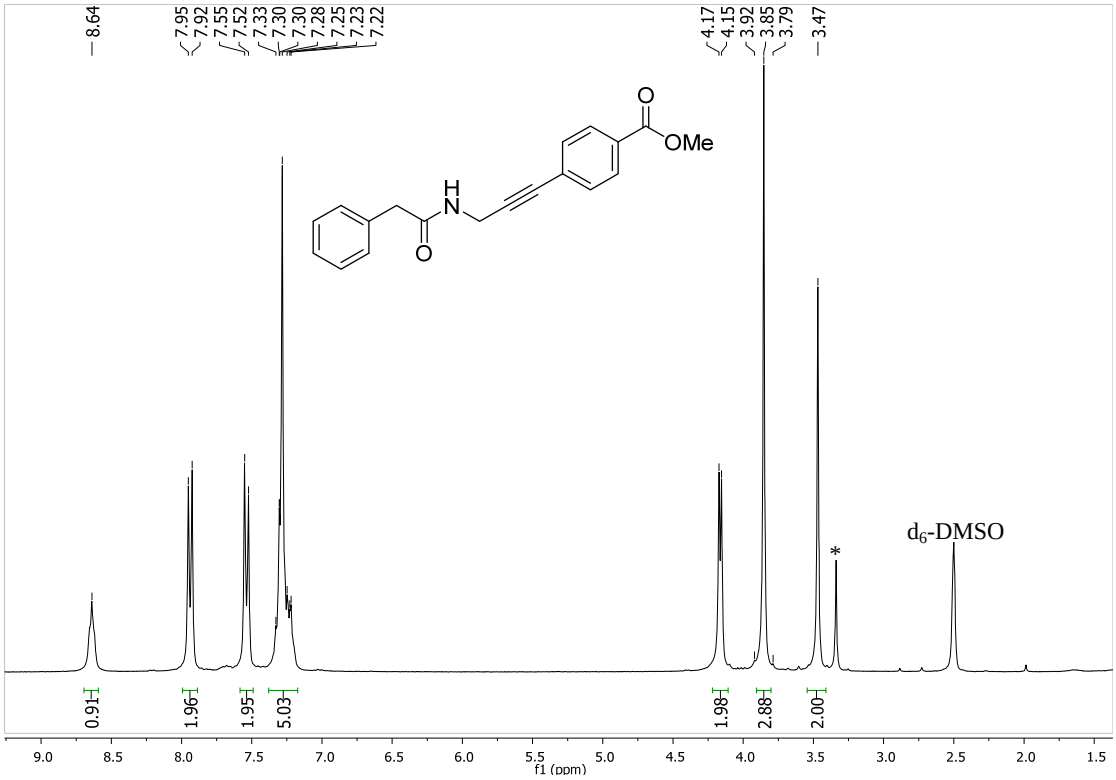


DEPT 135 ^{13}C NMR spectrum of compound 5b (75 MHz, $CDCl_3$, *T* = 296 K).



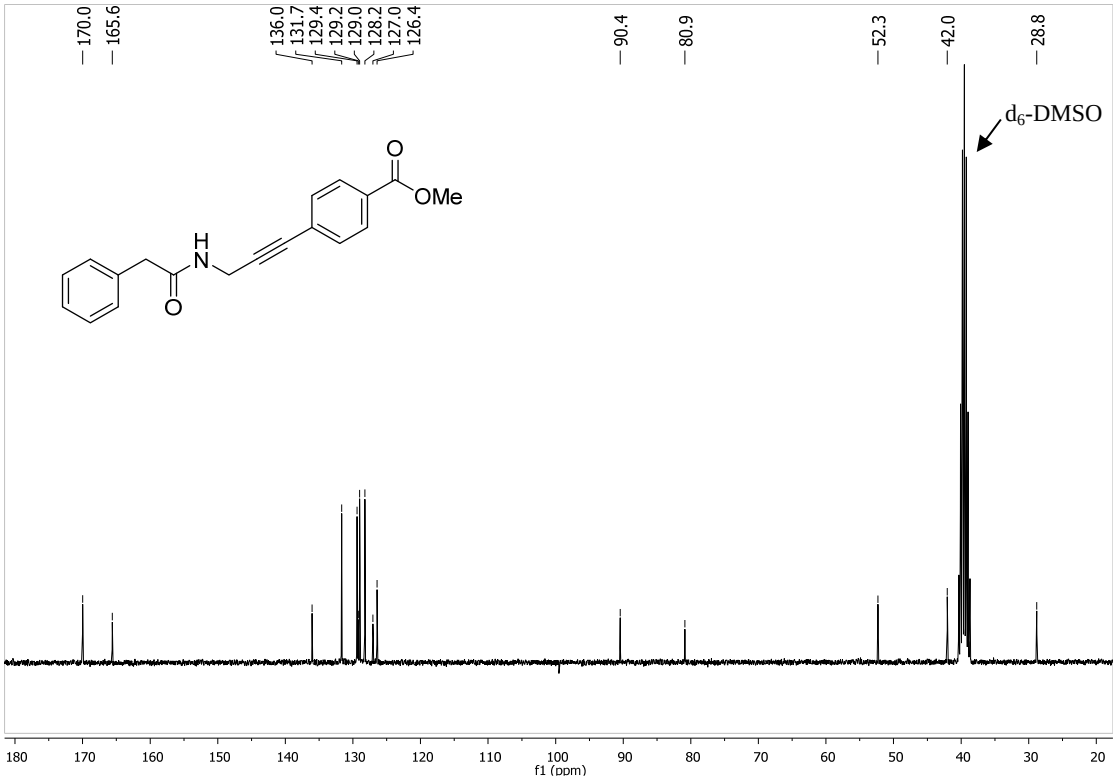
3.3. Methyl 4-(3-(2-phenylacetamido)prop-1-yn-1-yl)benzoate (5c)

^{1}H NMR spectrum of compound 5c (300 MHz, d_6-DMSO, *T* = 296 K).

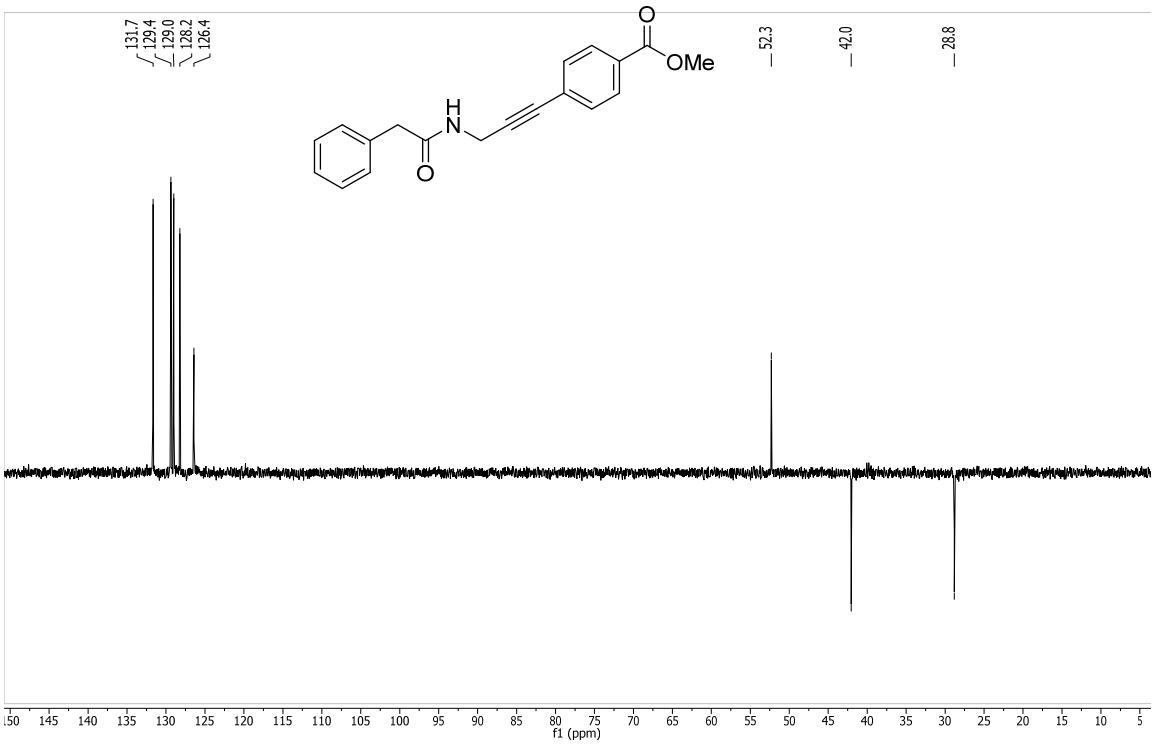


*HDO exchange peak.

^{13}C NMR spectrum of compound 5c (75 MHz, d_6-DMSO, *T* = 296 K).

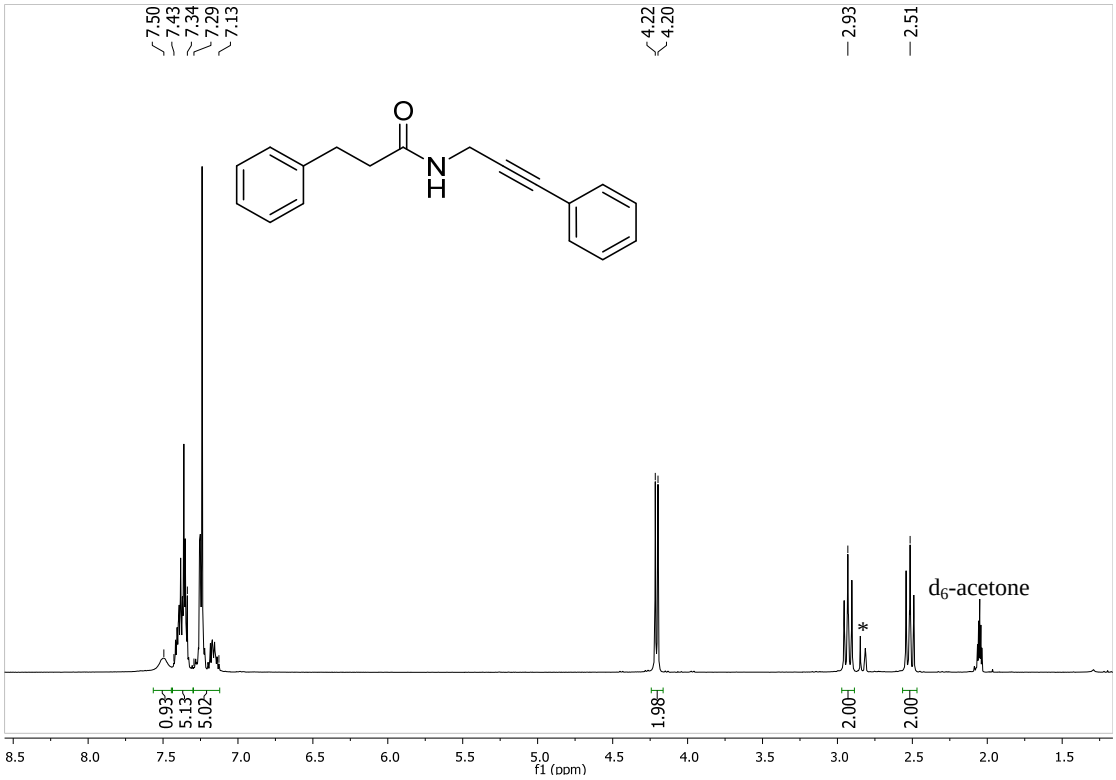


DEPT 135 ^{13}C NMR spectrum of compound 5c (75 MHz, d_6-DMSO, *T* = 296 K).



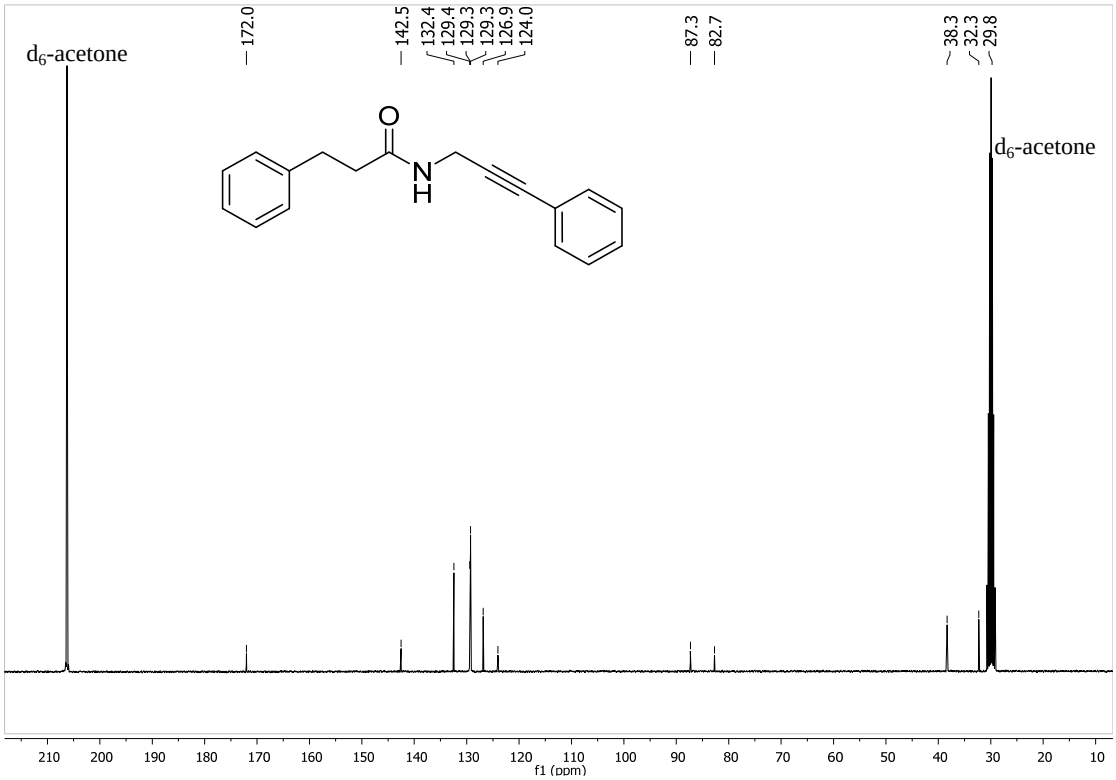
3.4. 3-Phenyl-*N*-(3-phenylprop-2-yn-1-yl)propanamide (5d)

^{1}H NMR spectrum of compound 5d (300 MHz, d_6-acetone, *T* = 296 K).

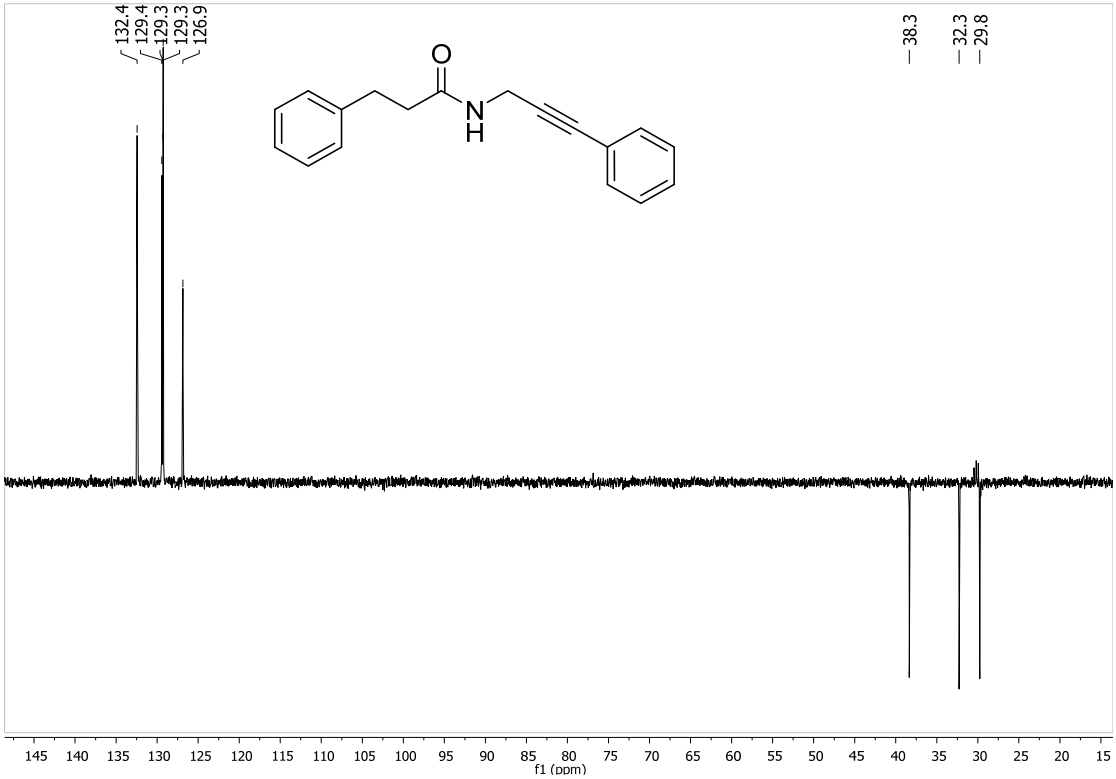


*HDO exchange peak.

^{13}C NMR spectrum of compound 5d (75 MHz, d_6-acetone, *T* = 296 K).

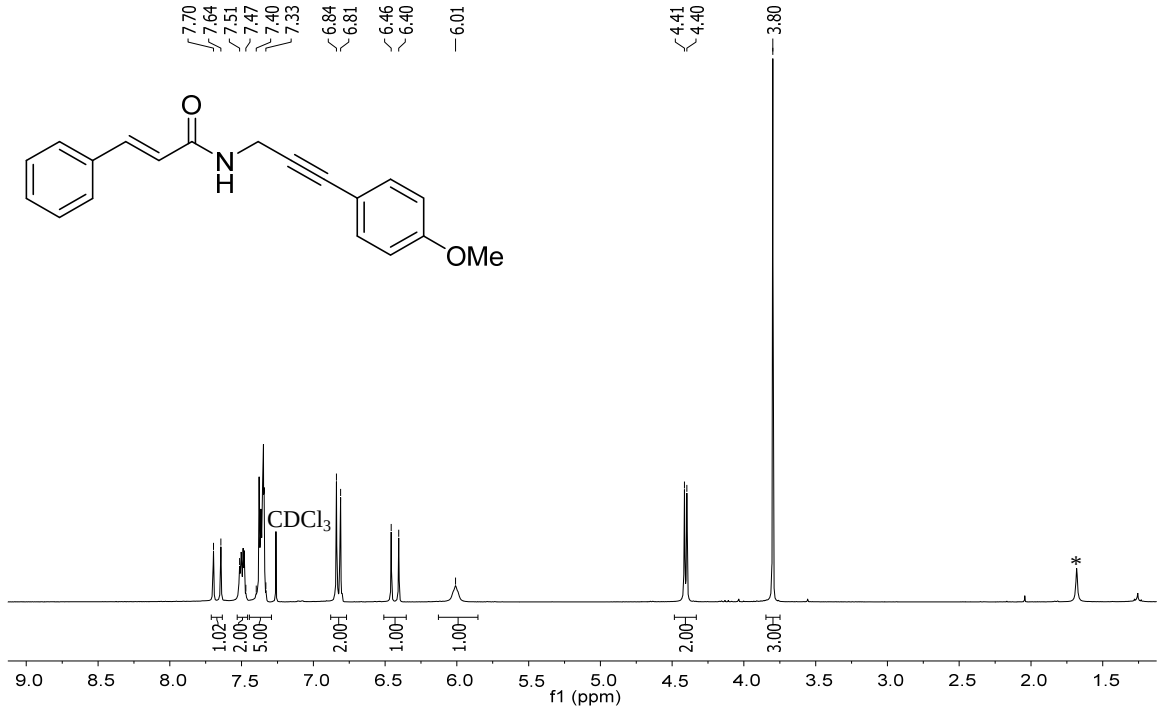


DEPT 135 ^{13}C NMR spectrum of compound 5d (75 MHz, d_6-acetone, *T* = 296 K).



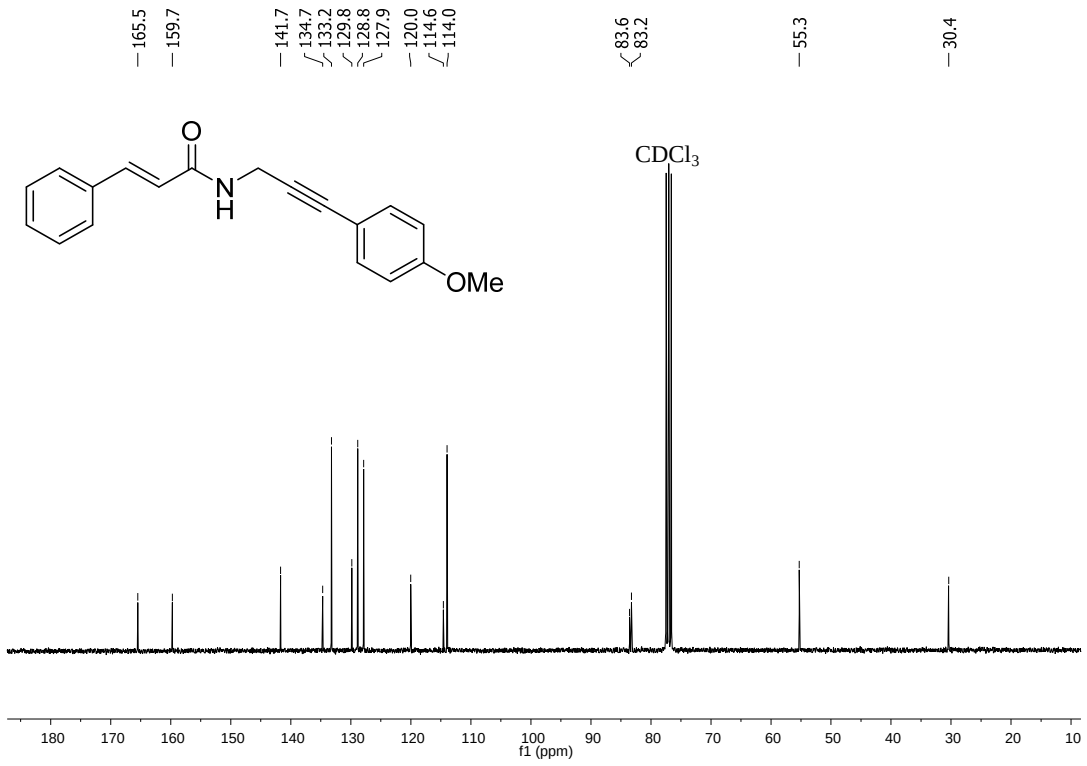
3.5. (*E*)-*N*-(3-(4-Methoxyphenyl)prop-2-yn-1-yl)cinnamic amide (5e)

^{1}H NMR spectrum of compound 5e (300 MHz, $CDCl_3$, *T* = 296 K).

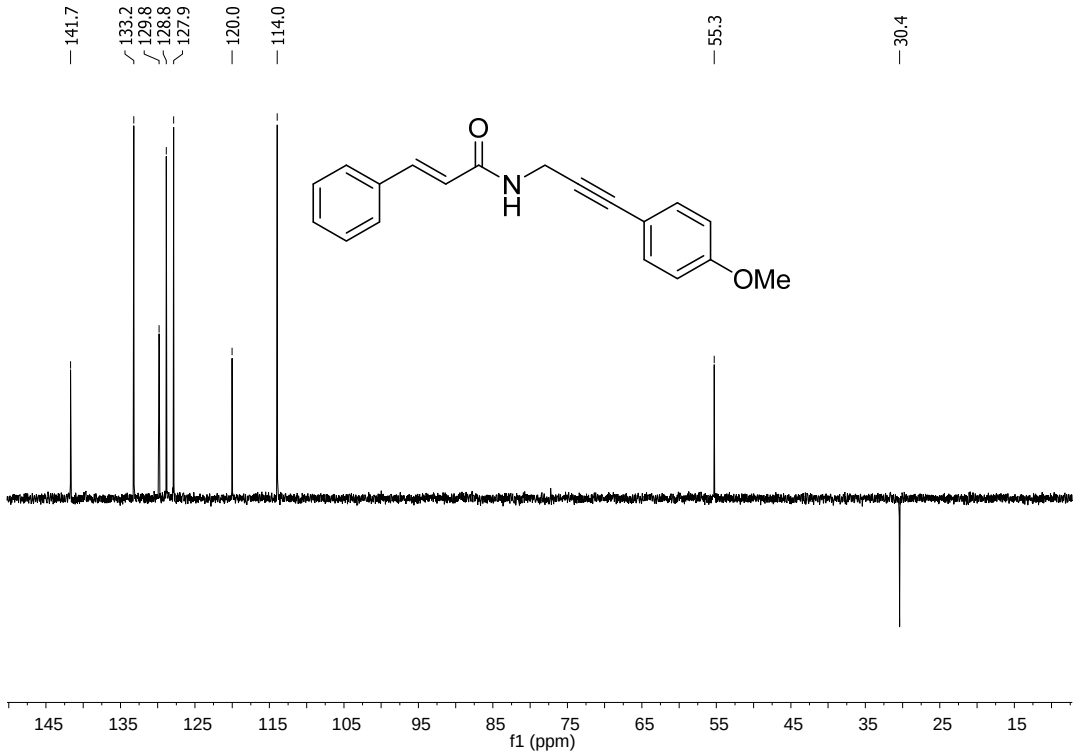


* HDO exchange peak.

^{13}C NMR spectrum of compound 5e (75 MHz, $CDCl_3$, *T* = 296 K).

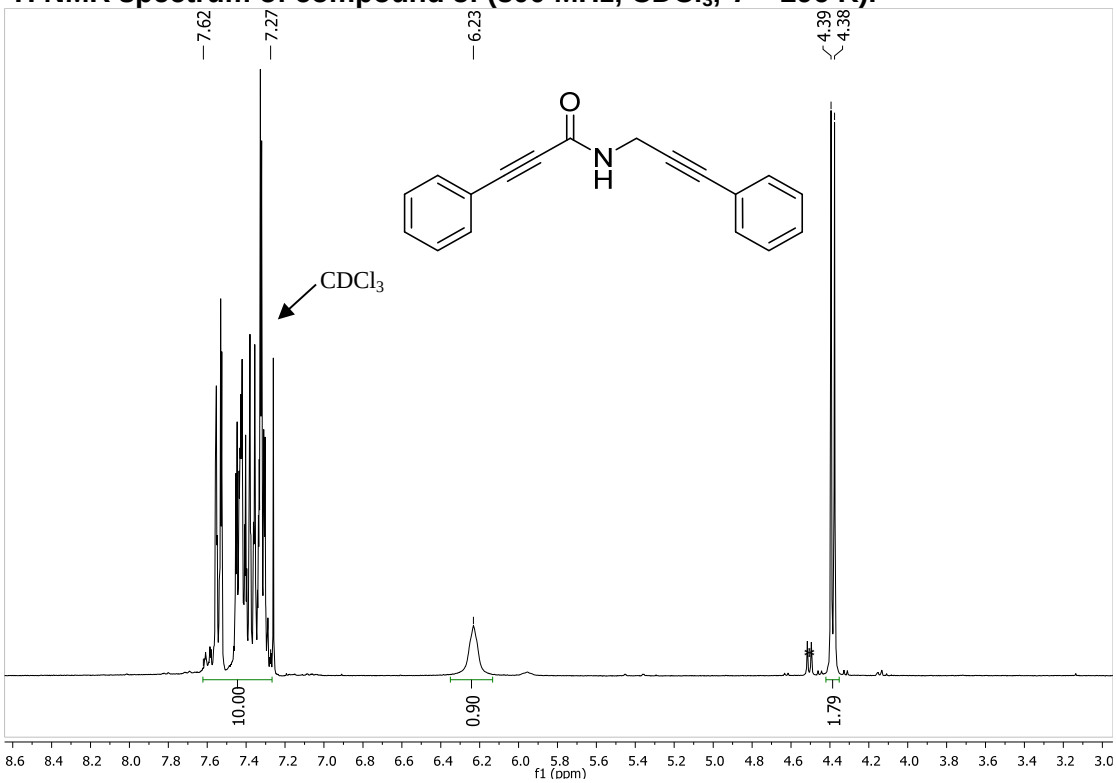


DEPT 135 ^{13}C NMR spectrum of compound 5e (75 MHz, $CDCl_3$, *T* = 296 K).



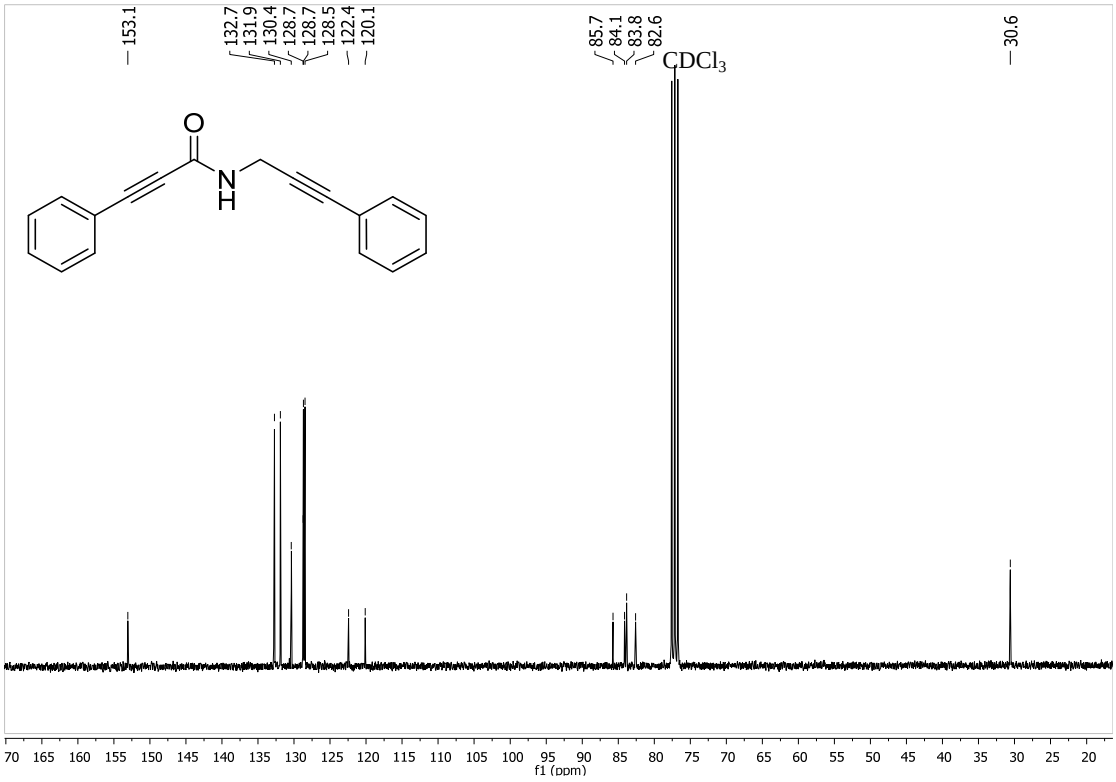
3.6. 3-Phenyl-*N*-(3-phenylprop-2-yn-1-yl)propiolamide (5f)

^{1}H NMR spectrum of compound 5f (300 MHz, $CDCl_3$, *T* = 296 K).

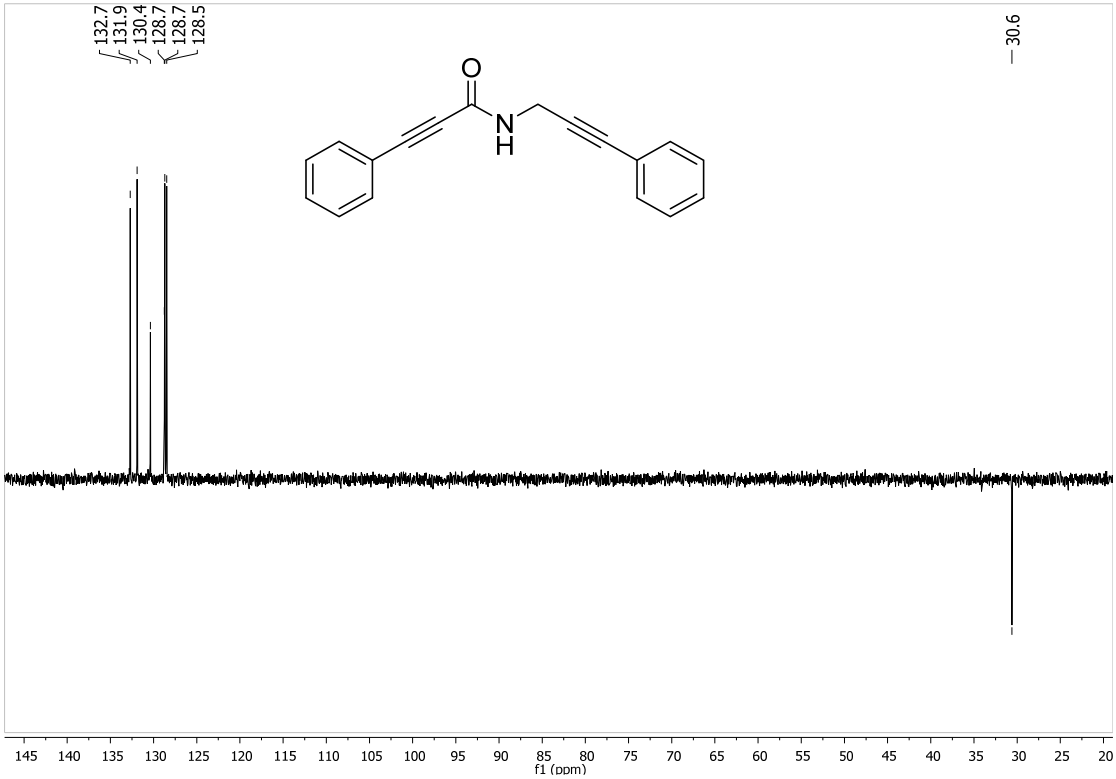


* Impurities from the residual solvent.

^{13}C NMR spectrum of compound 5f (75 MHz, $CDCl_3$, *T* = 296 K).

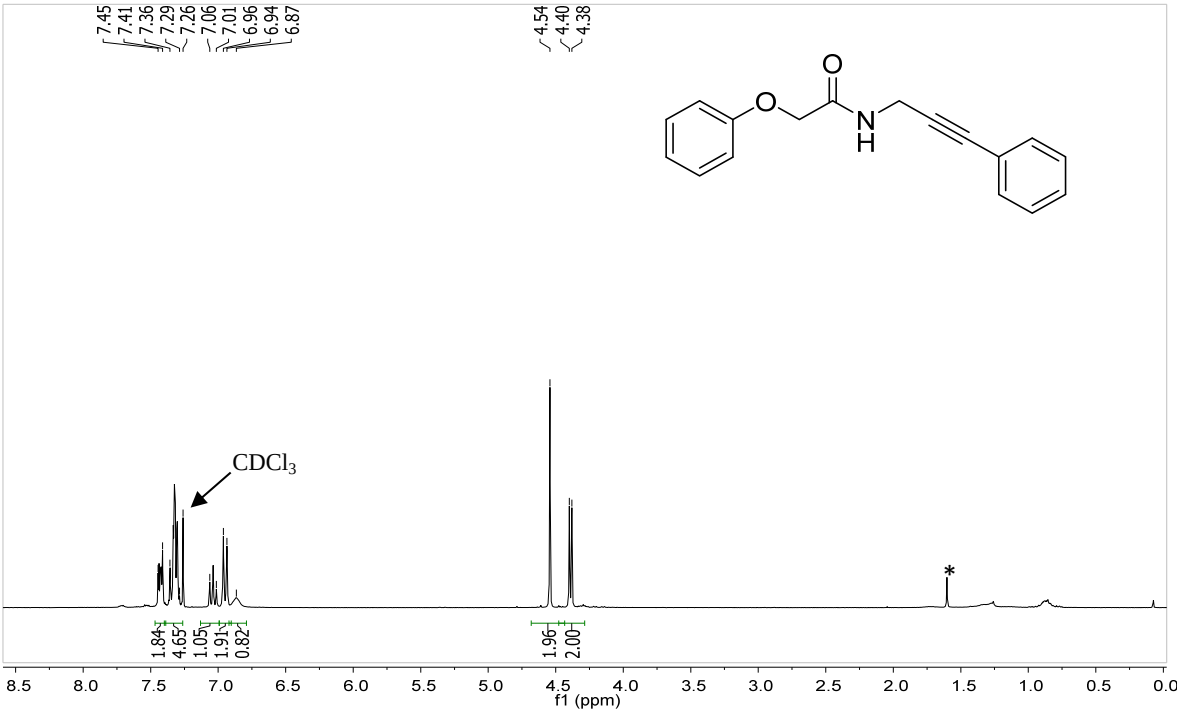


DEPT 135 ^{13}C NMR spectrum of compound 5f (75 MHz, $CDCl_3$, *T* = 296 K).



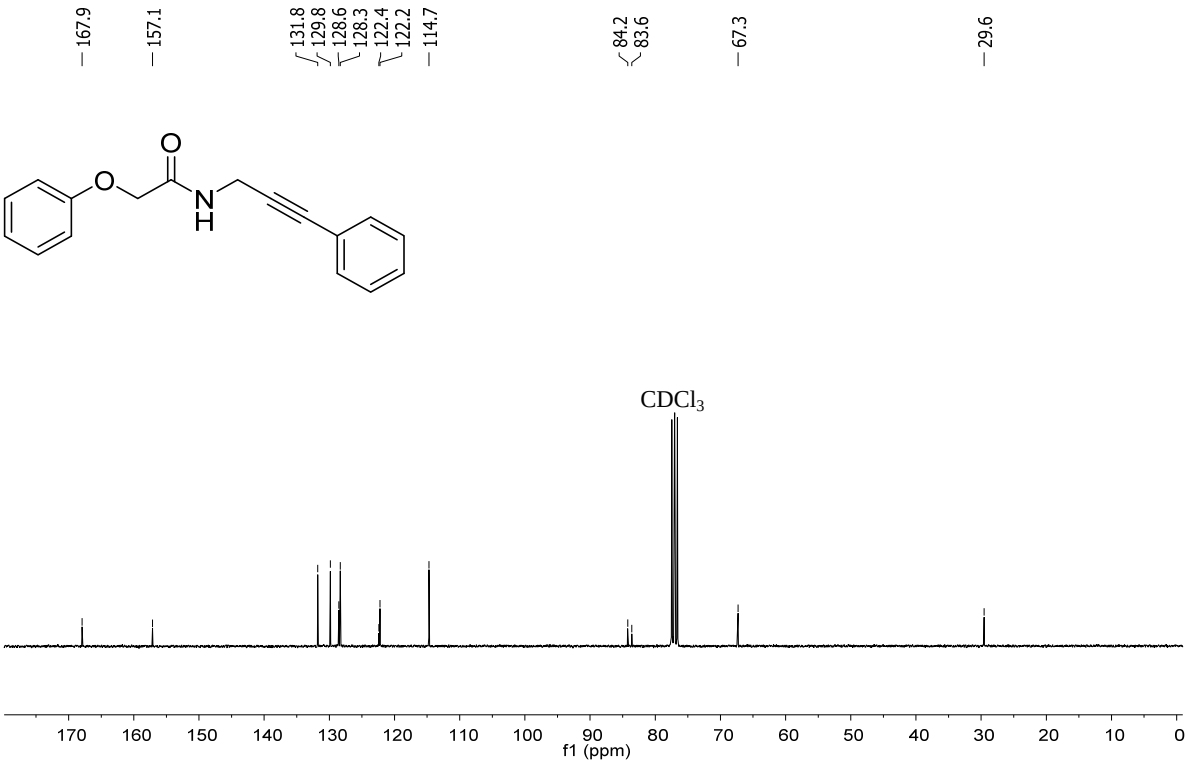
3.7. 2-Phenoxy-*N*-(3-phenylprop-2-yn-1-yl)acetamide (5g)

^{1}H NMR spectrum of compound 5g(300 MHz, $CDCl_3$, *T* = 296 K).

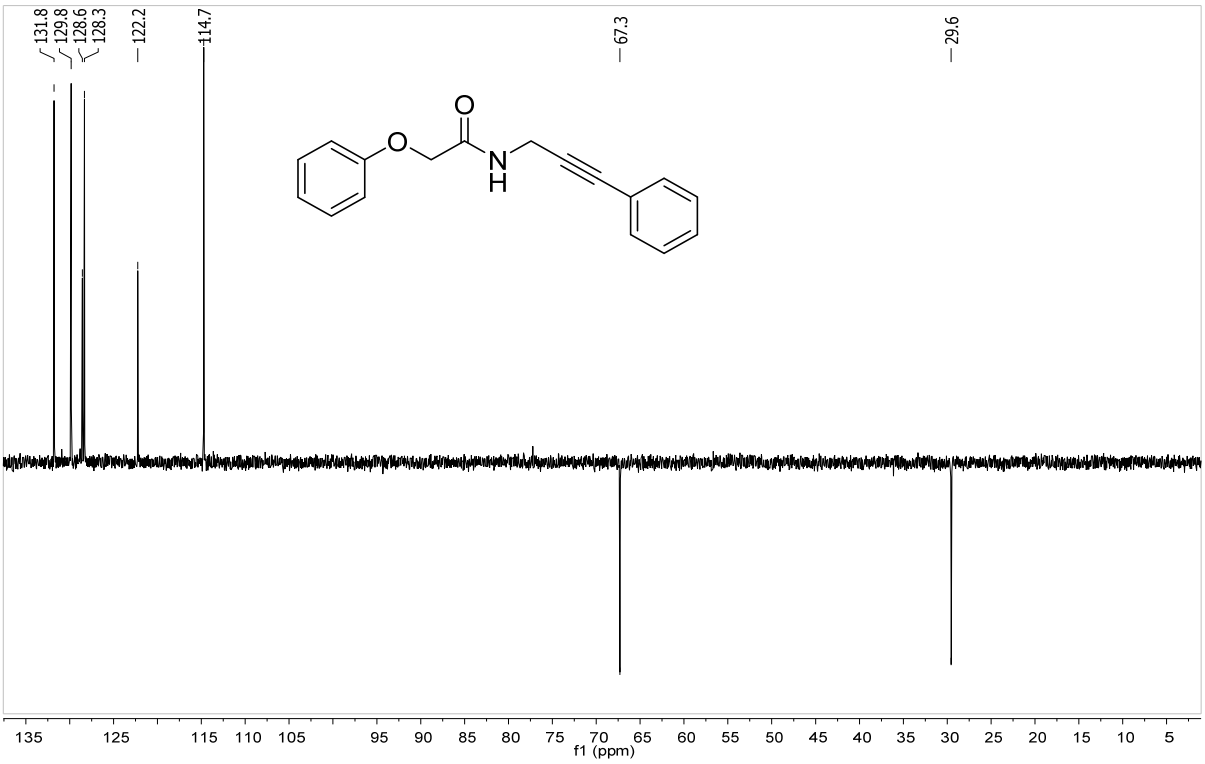


*HDO exchange peak.

^{13}C NMR spectrum of compound 5g (75 MHz, $CDCl_3$, *T* = 296 K).

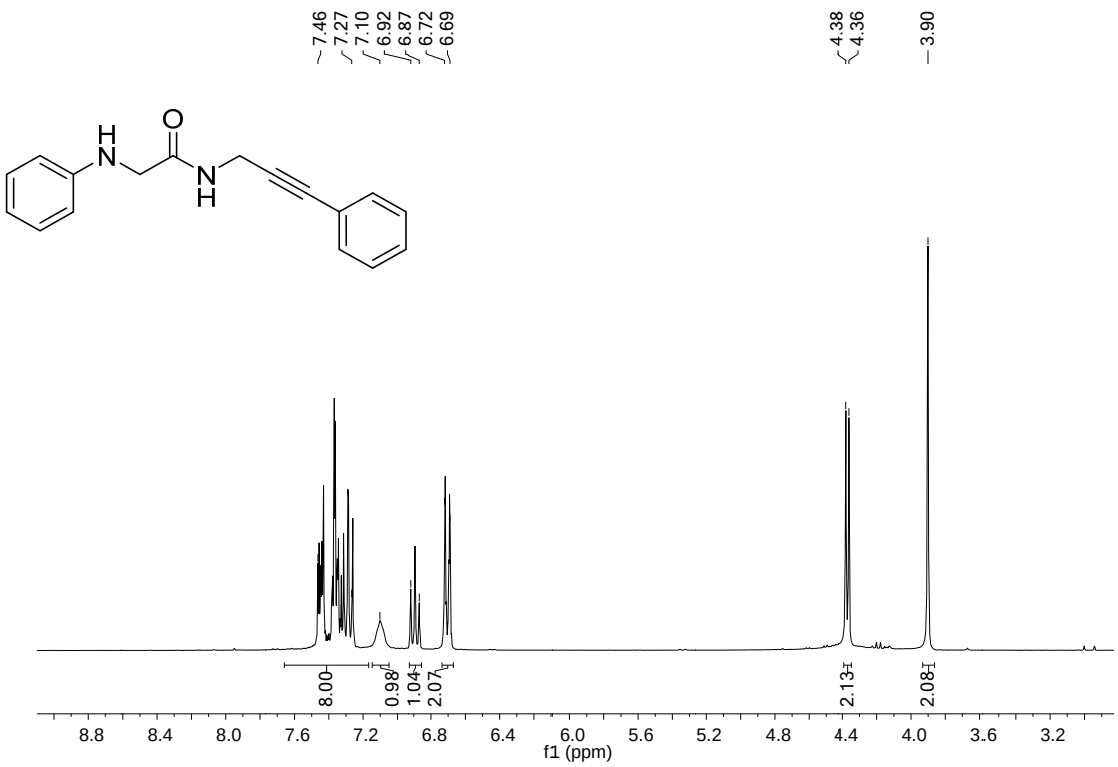


DEPT 135 ^{13}C NMR spectrum of compound 5g(75 MHz, $CDCl_3$, *T* = 296 K).

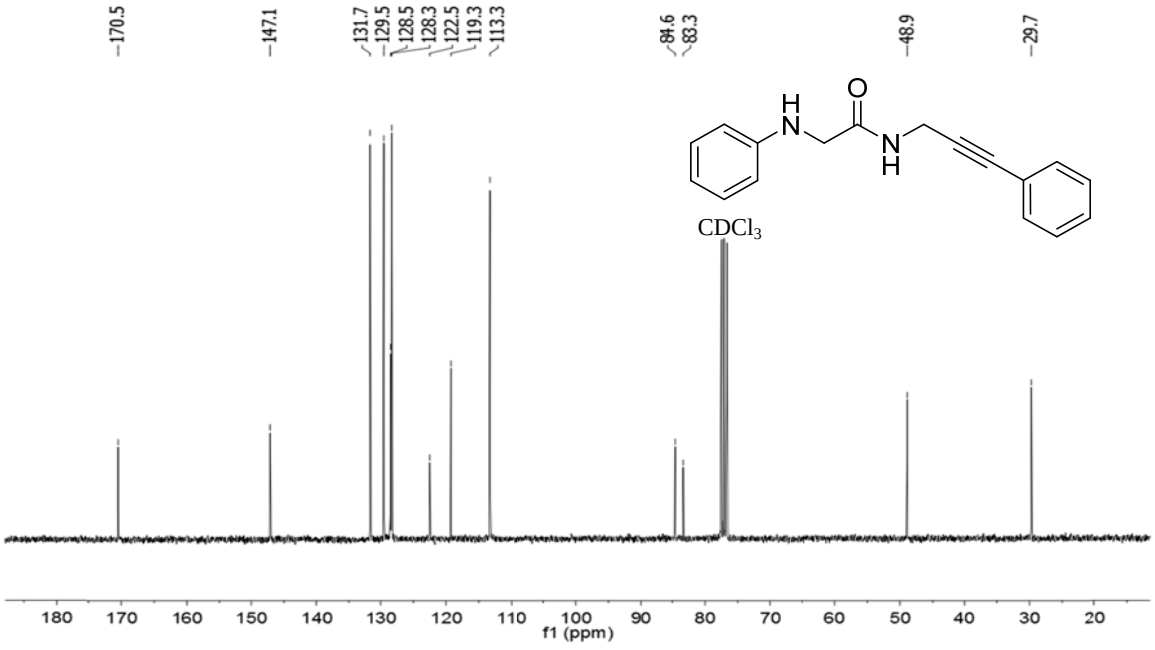


3.8. 2-(Phenylamino)-*N*-(3-phenylprop-2-yn-1-yl)acetamide (5h)

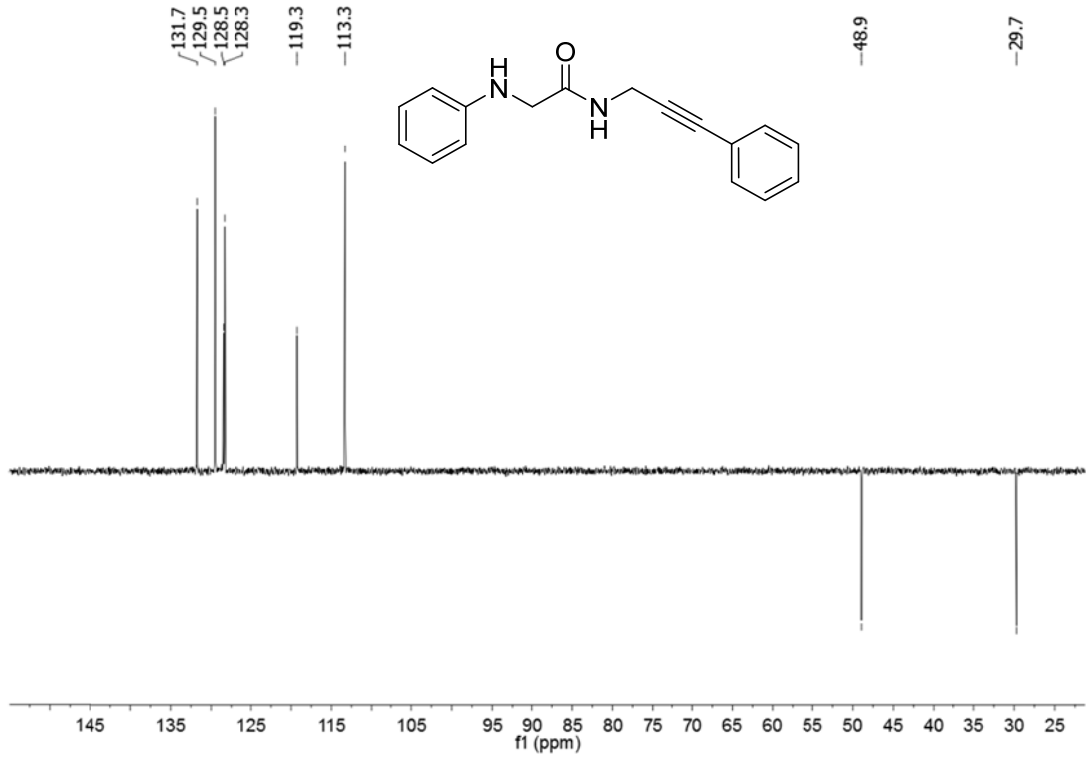
^{1}H NMR spectrum of compound 5h (300 MHz, $CDCl_3$, *T* = 296 K).



^{13}C NMR spectrum of compound 5h (75 MHz, $CDCl_3$, *T* = 296 K).

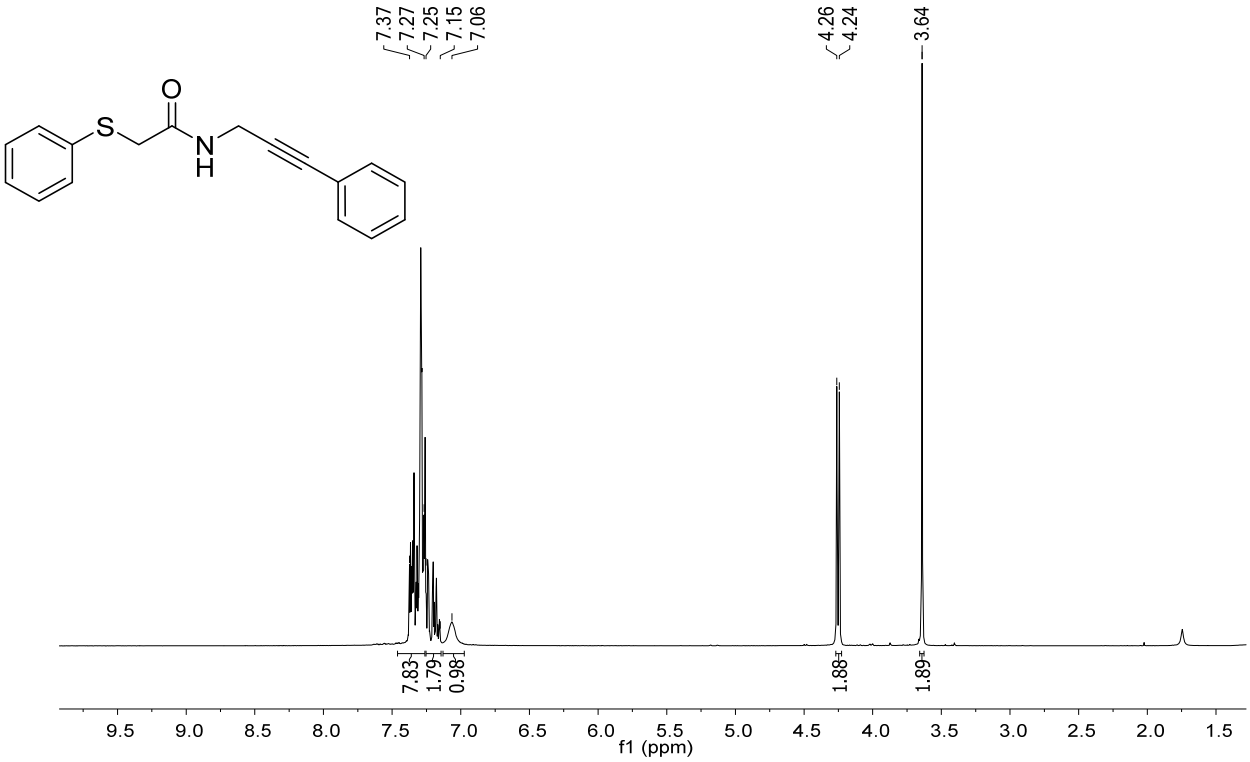


DEPT 135 ^{13}C NMR spectrum of compound 5h (75 MHz, $CDCl_3$, *T* = 296 K).

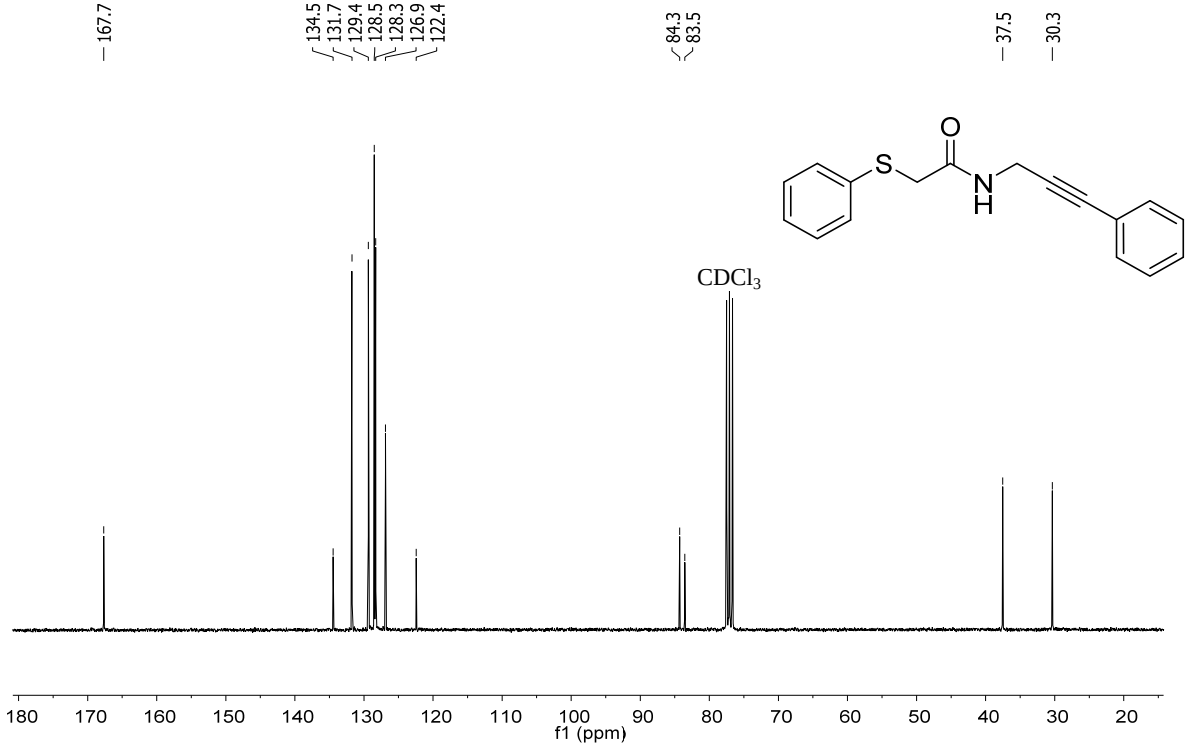


3.9. *N*-(3-Phenylprop-2-yn-1-yl)-2-(phenylthio)acetamide (5i)

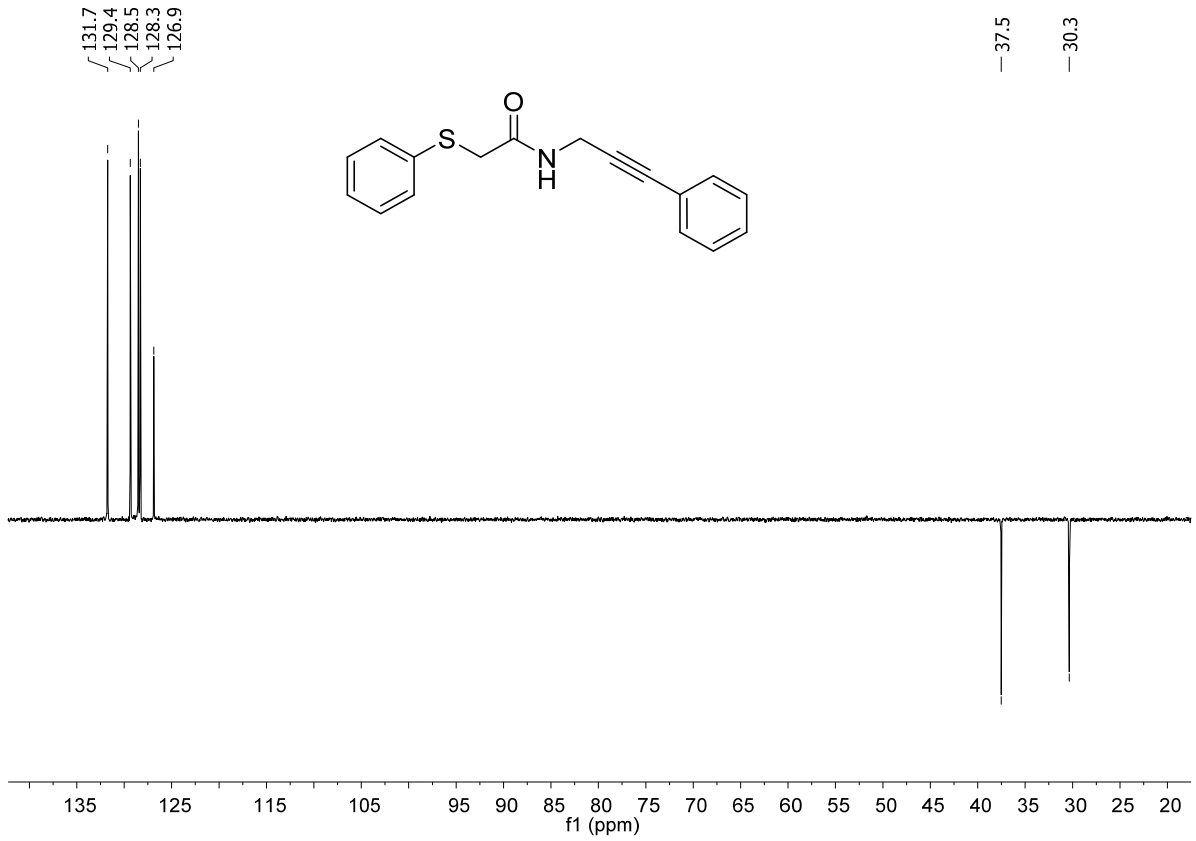
^{1}H NMR spectrum of compound 5i (300 MHz, $CDCl_3$, *T* = 296 K).



^{13}C NMR spectrum of compound 5i (75 MHz, $CDCl_3$, *T* = 296 K).

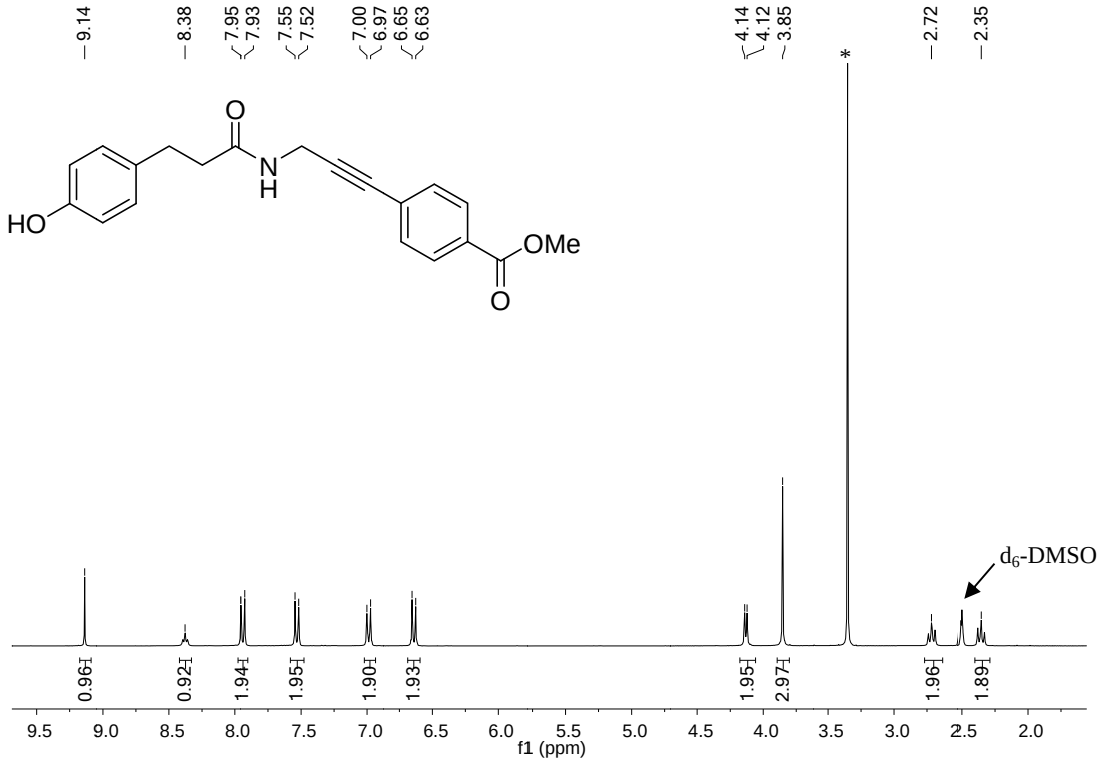


DEPT 135 ^{13}C NMR spectrum of compound 5i (75 MHz, $CDCl_3$, *T* = 296 K).



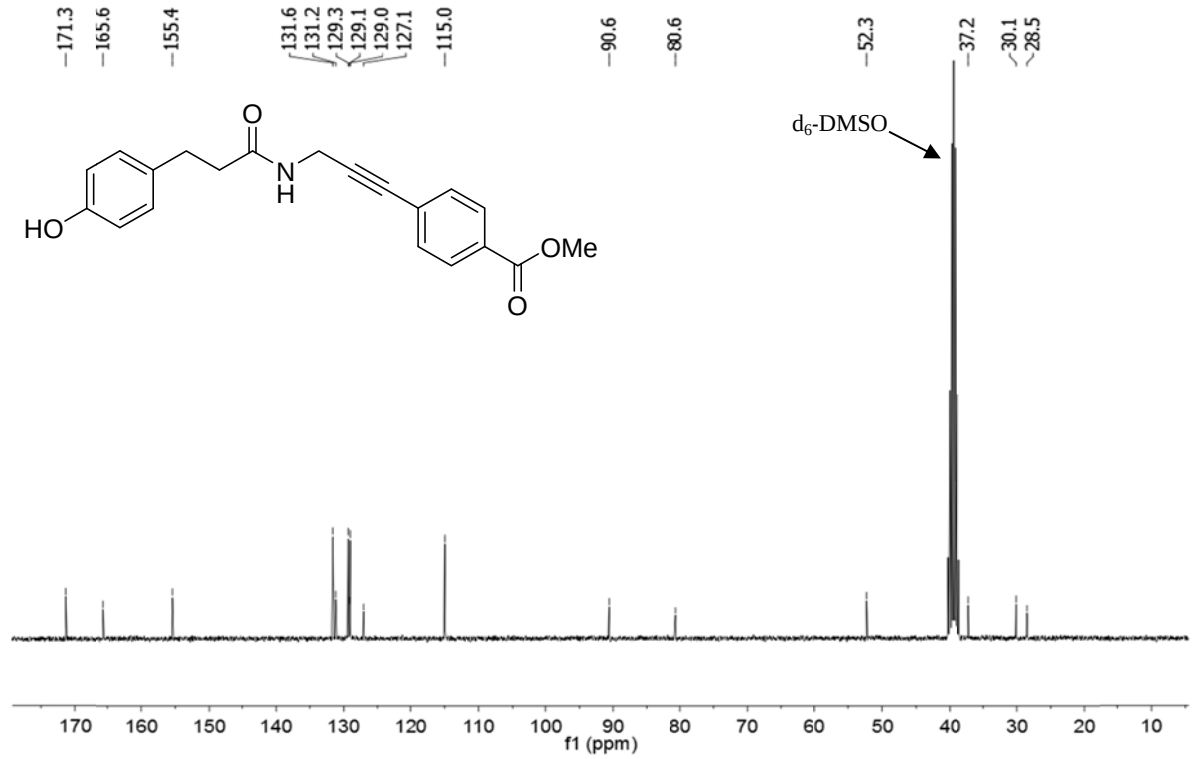
3.10. Methyl 4-(3-(3-(4-hydroxyphenyl)propanamido)prop-1-yn-1-yl) benzoate (5j)

^{1}H NMR spectrum of compound 5j (300 MHz, d_6-DMSO, *T* = 296 K).

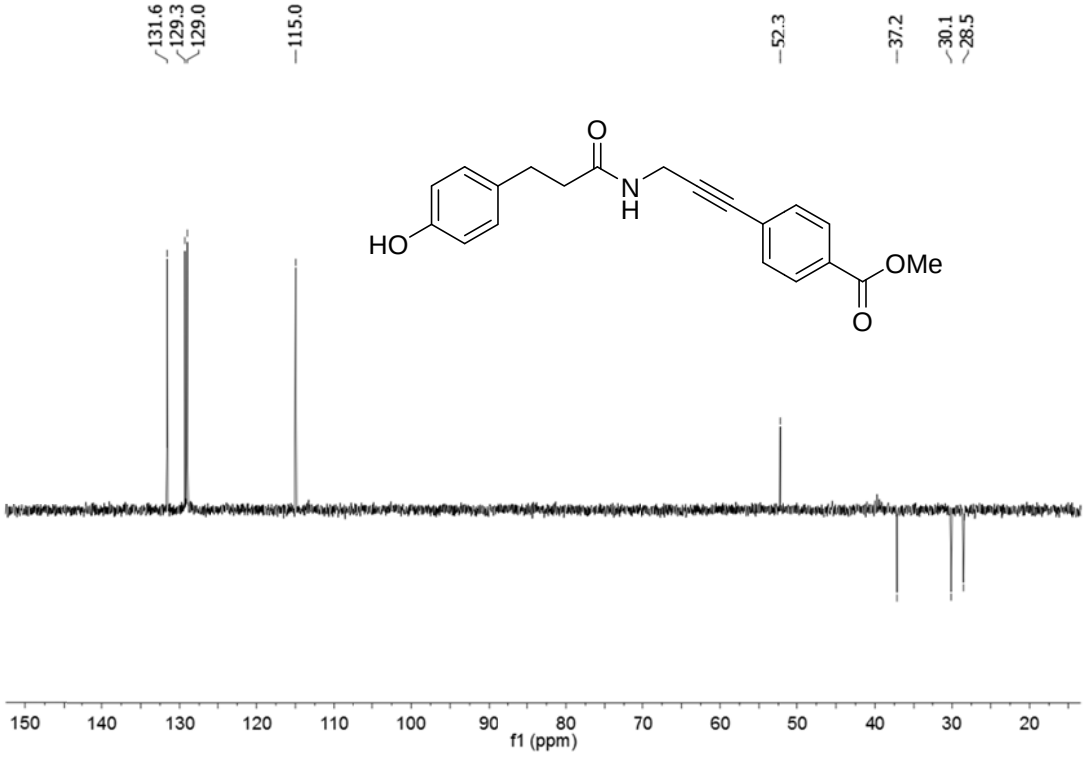


* HDO exchange peak.

^{13}C NMR spectrum of compound 5j (75 MHz, d_6-DMSO, *T* = 296 K).

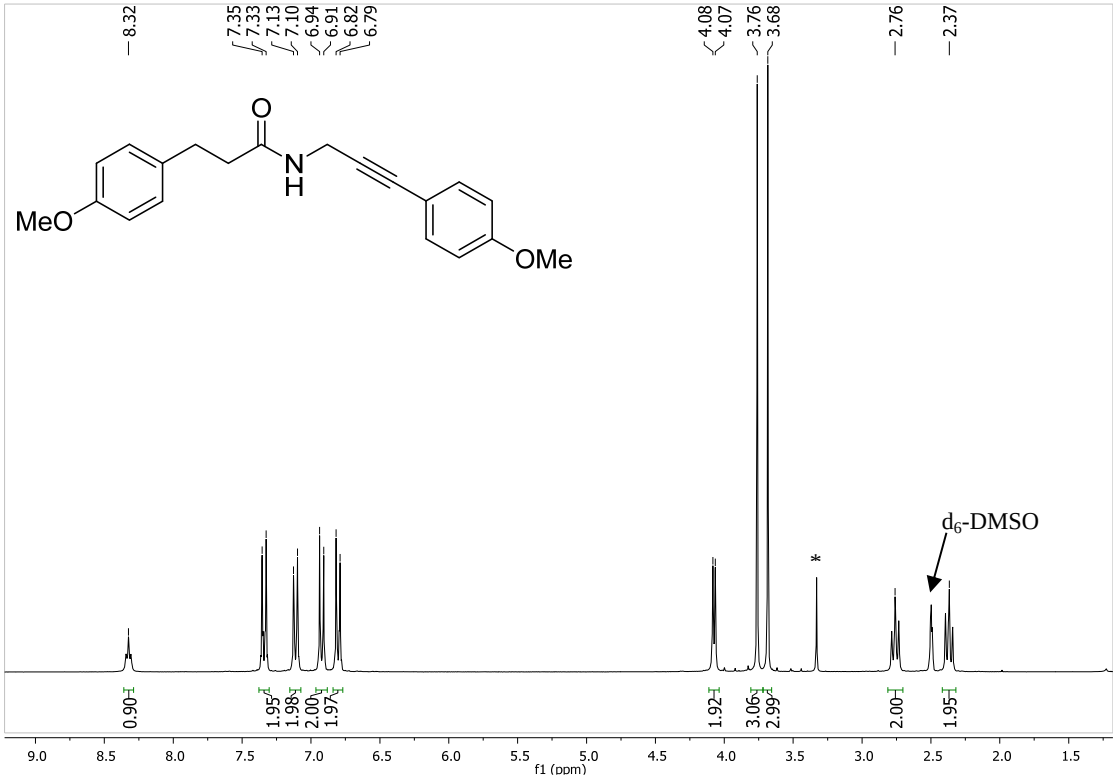


DEPT 135 ^{13}C NMR spectrum of compound 5j (75 MHz, d_6-DMSO, *T* = 296 K).



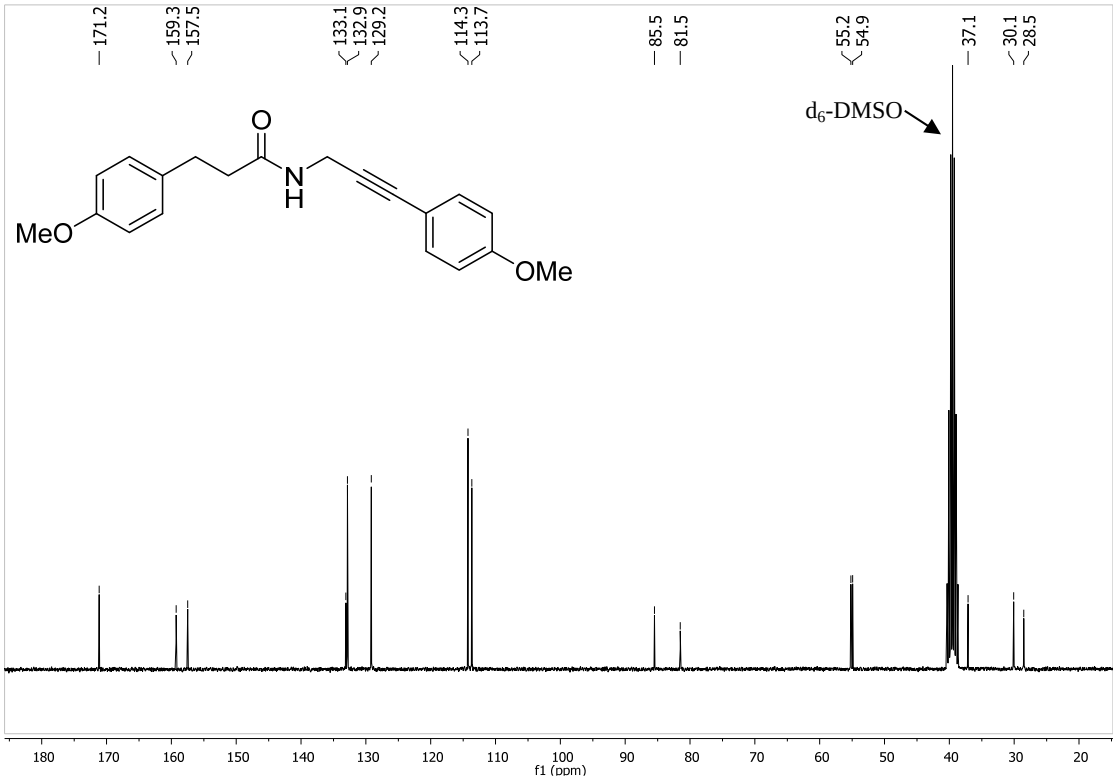
3.11. 3-(4-Methoxyphenyl)-*N*-(3-(4-methoxyphenyl)prop-2-yn-1-yl)propanamide (5k)

^{1}H NMR spectrum of compound 5k (300 MHz, d_6-DMSO, *T* = 296 K).

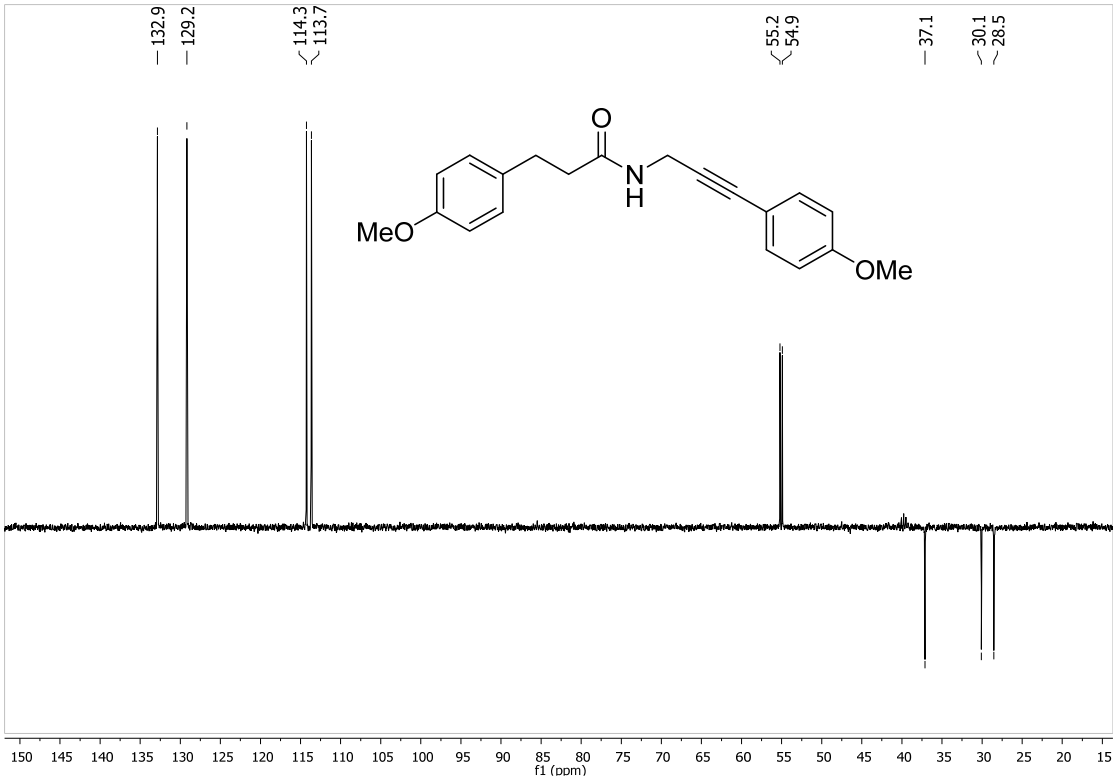


*HDO exchange peak.

^{13}C NMR spectrum of compound 5k (75 MHz, d_6-DMSO, *T* = 296 K).

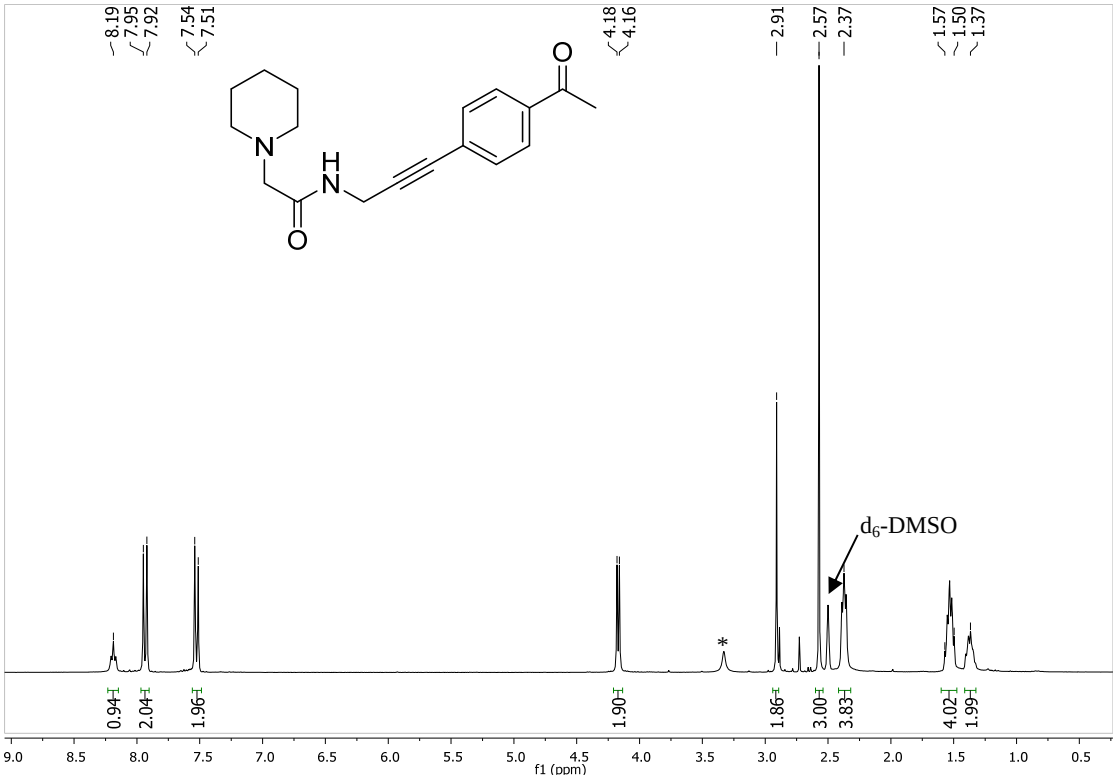


DEPT 135 ^{13}C NMR spectrum of compound 5k (75 MHz, d_6-DMSO, *T* = 296 K).



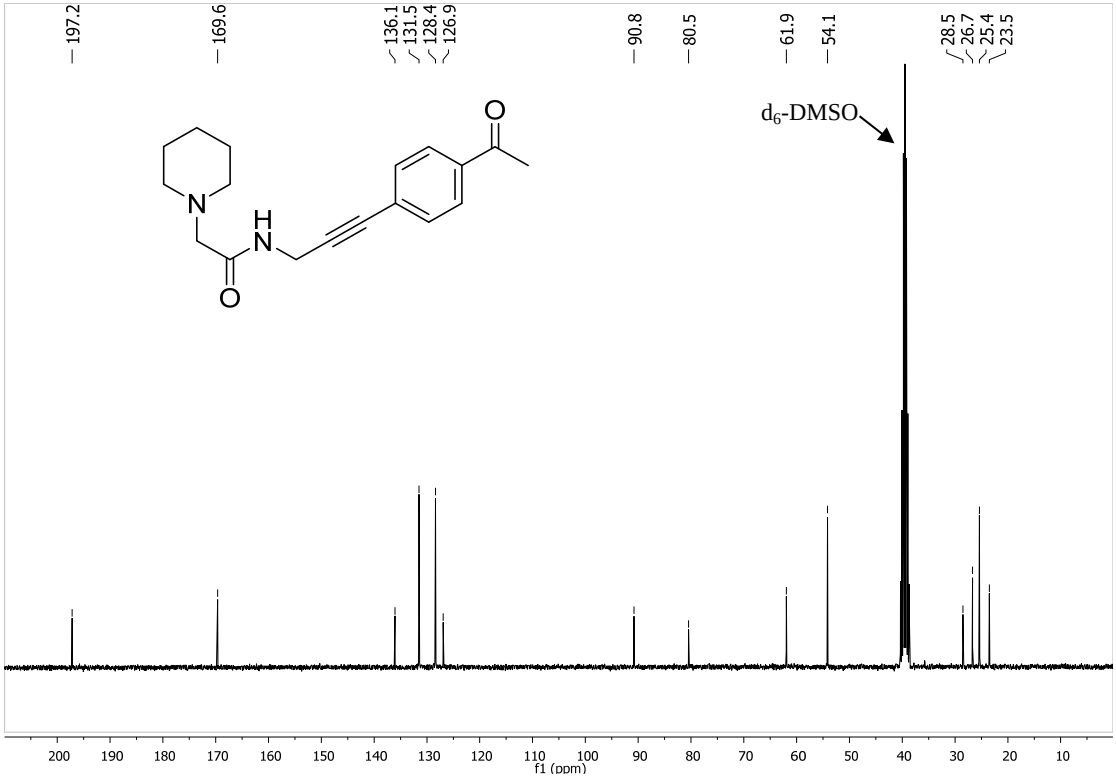
3.12. *N*-(3-(4-Acetylphenyl)prop-2-yn-1-yl)-2-(piperidin-1-yl)acetamide (5l)

^{1}H NMR spectrum of compound 5l (300 MHz, d_6-DMSO, *T* = 296 K).

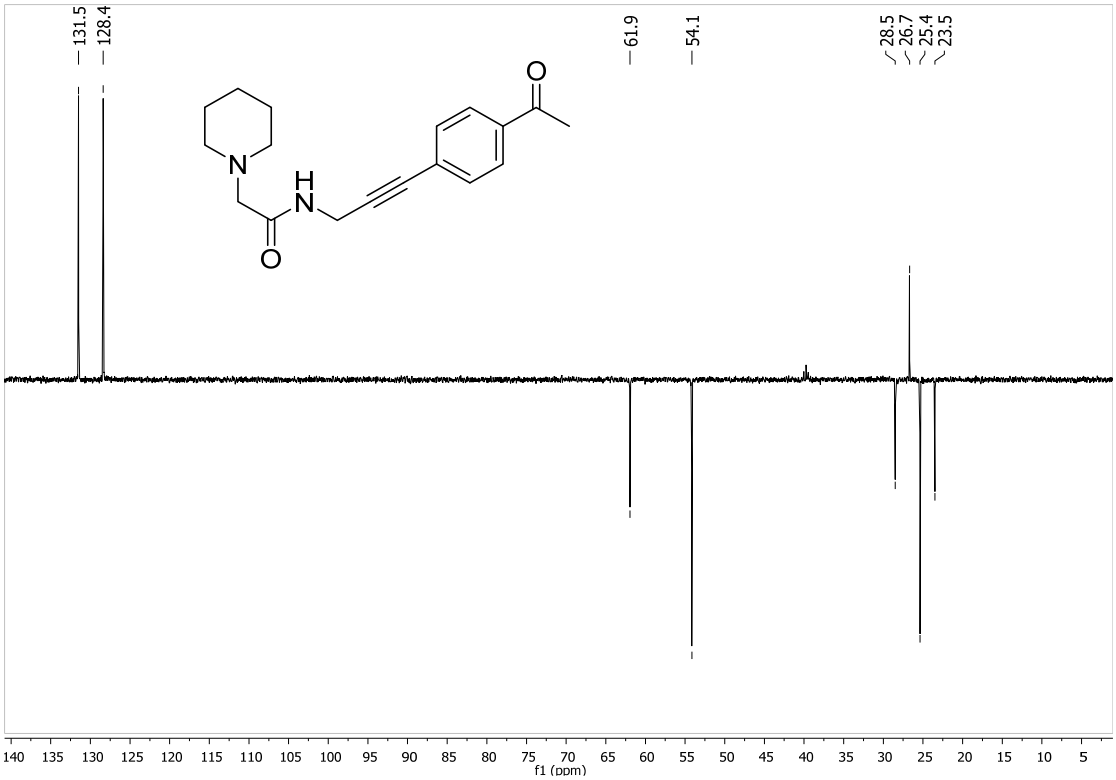


*HDO exchange peak.

^{13}C NMR spectrum of compound 5l (75 MHz, d_6-DMSO, *T* = 296 K).

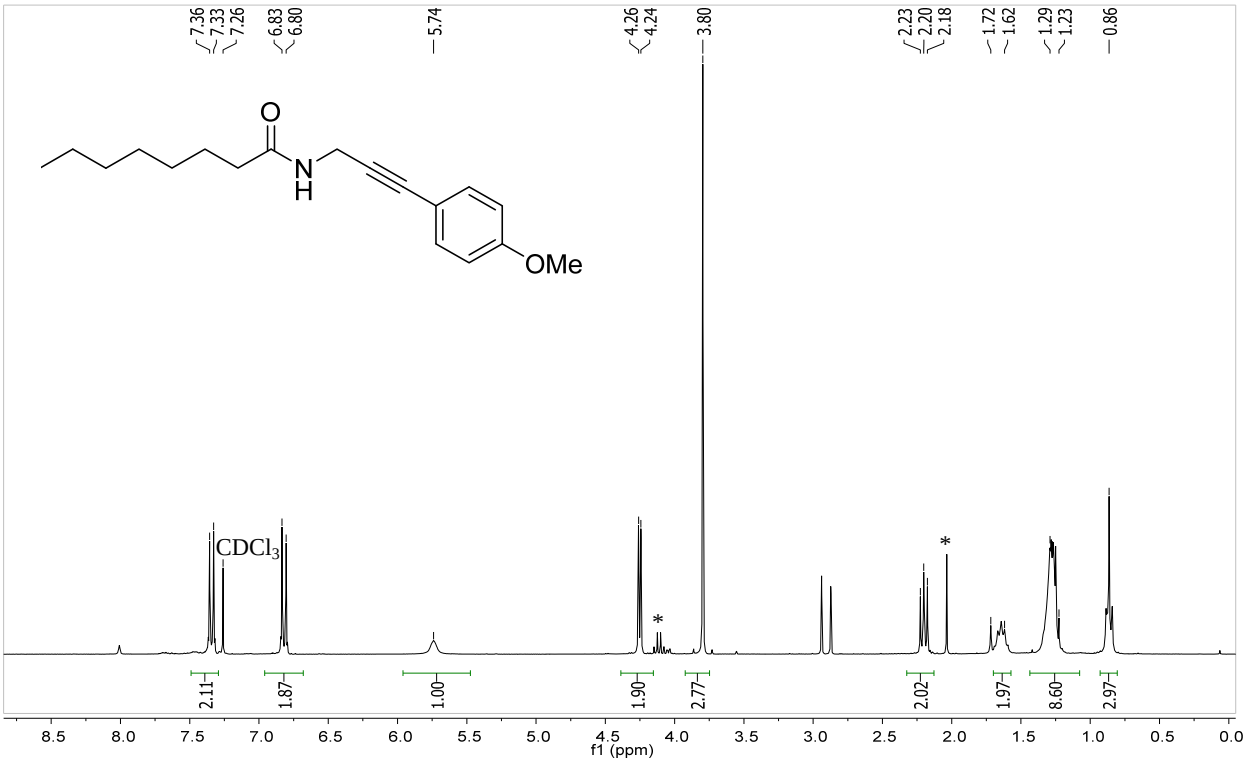


DEPT 135 ^{13}C NMR spectrum of compound 5l (75 MHz, d_6-DMSO, *T* = 296 K).



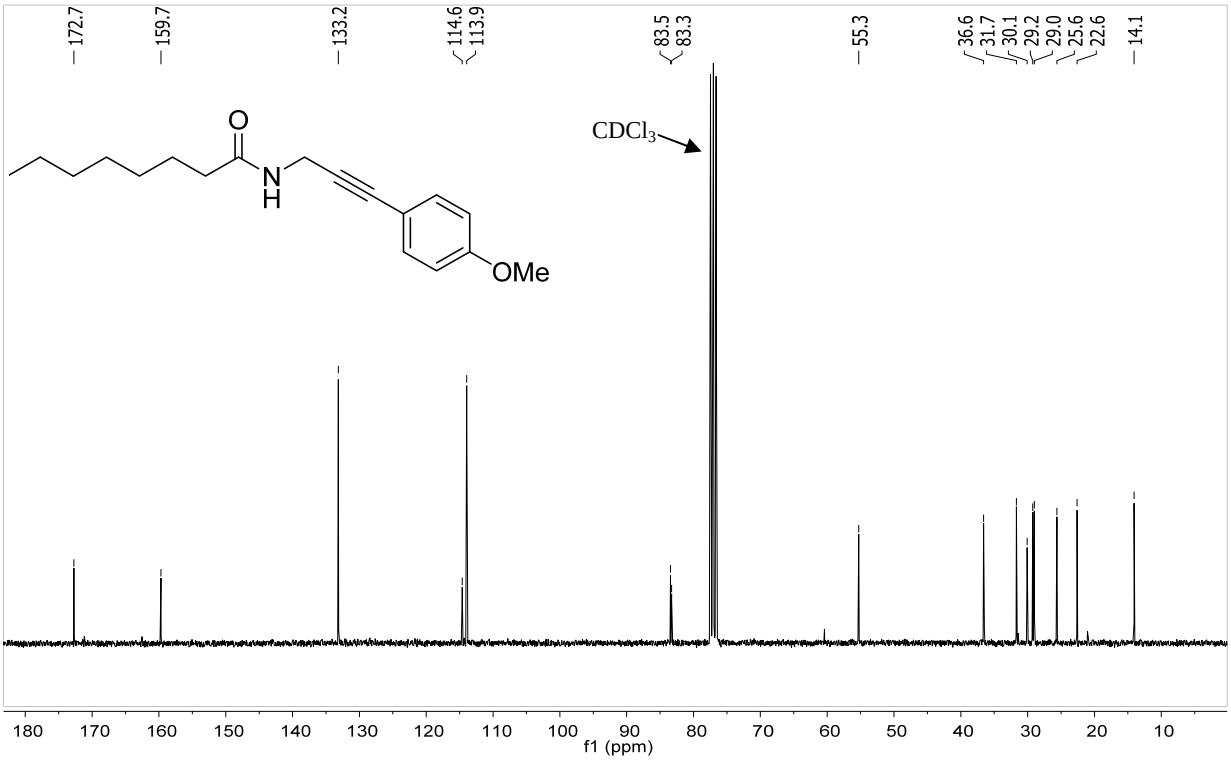
3.13. *N*-(3-(4-Methoxyphenyl)prop-2-yn-1-yl)octanamide (5m)

^{1}H NMR spectrum of compound 5m (300 MHz, $CDCl_3$, *T* = 296 K).

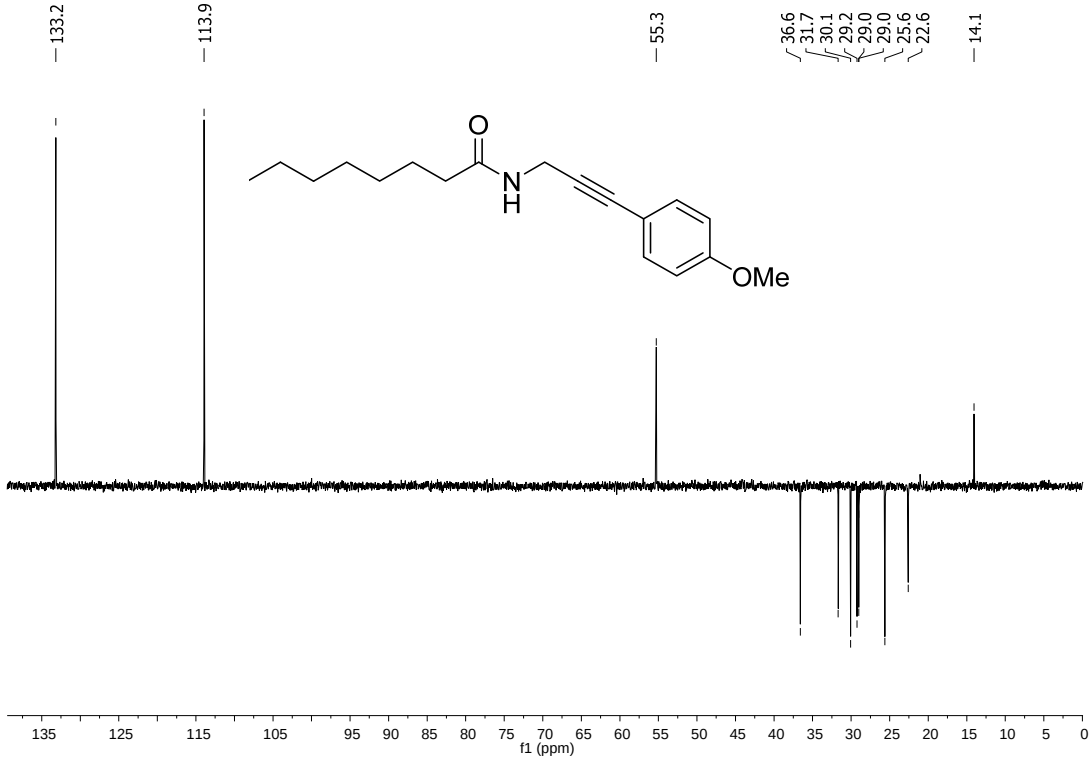


* Impurities from the residual solvent.

^{13}C NMR spectrum of compound 5m (75 MHz, $CDCl_3$, *T* = 296 K).

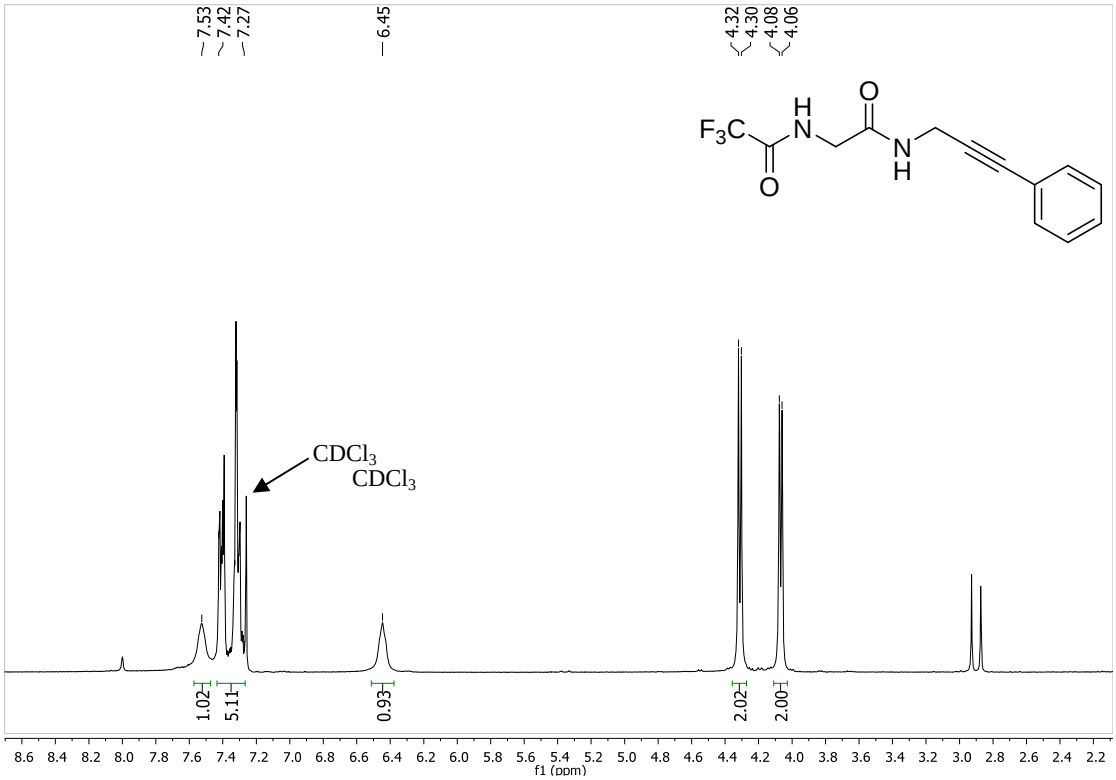


DEPT 135 ^{13}C NMR spectrum of compound 5m (75 MHz, $CDCl_3$, *T* = 296 K).

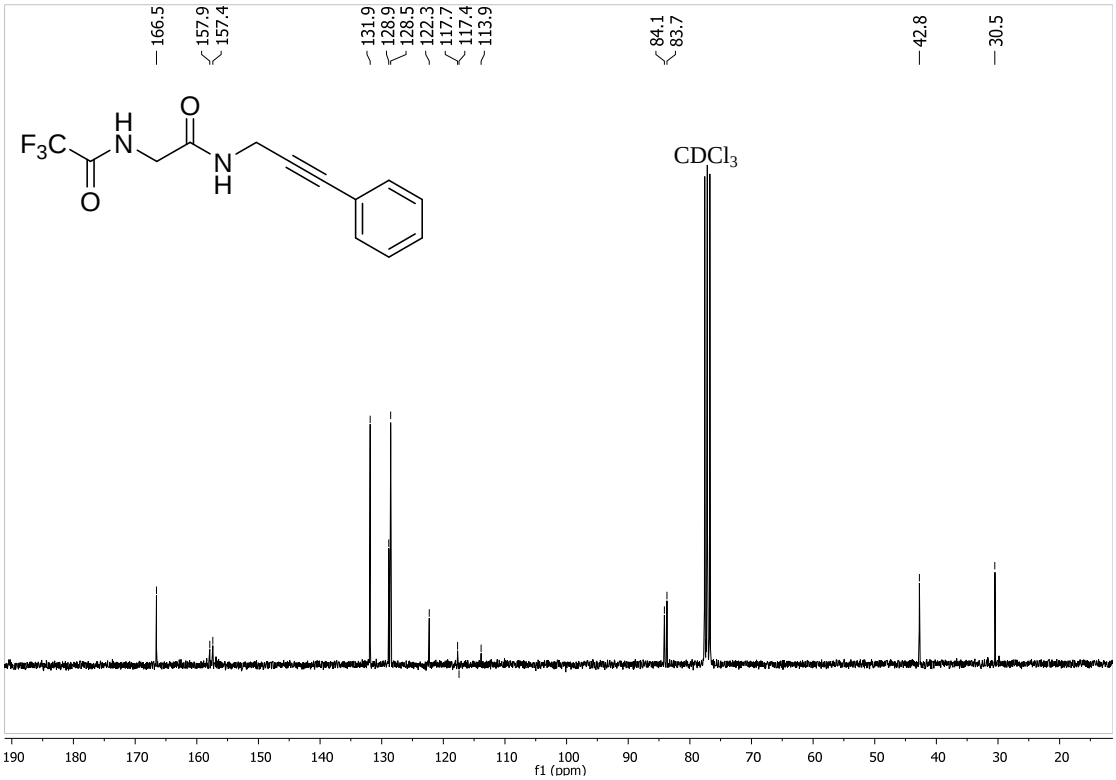


3.14. 2,2,2-Trifluoro-*N*-(2-oxo-2-((3-phenylprop-2-yn-1-yl)amino)ethyl) acetamide (5n)

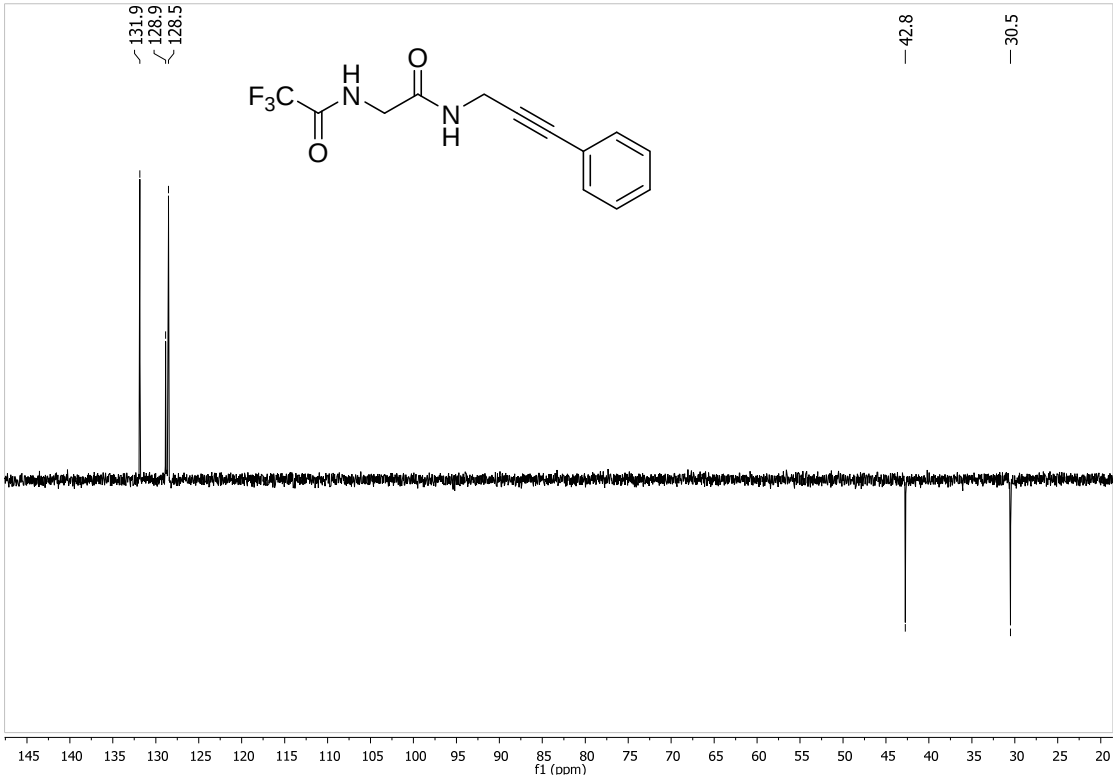
^{1}H NMR spectrum of compound 5n (300 MHz, $CDCl_3$, *T* = 296 K).



^{13}C NMR spectrum of compound 5n (75 MHz, $CDCl_3$, *T* = 296 K).

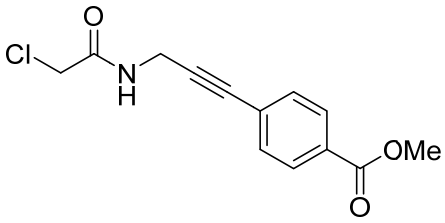


DEPT 135 ^{13}C NMR spectrum of compound 5n (75 MHz, $CDCl_3$, *T* = 296 K).



3.15. Methyl 4-(3-(2-chloroacetamido)prop-1-yn-1-yl)benzoate (5o)

^{1}H NMR spectrum of compound 5o (300 MHz, $CDCl_3$, *T* = 296 K).

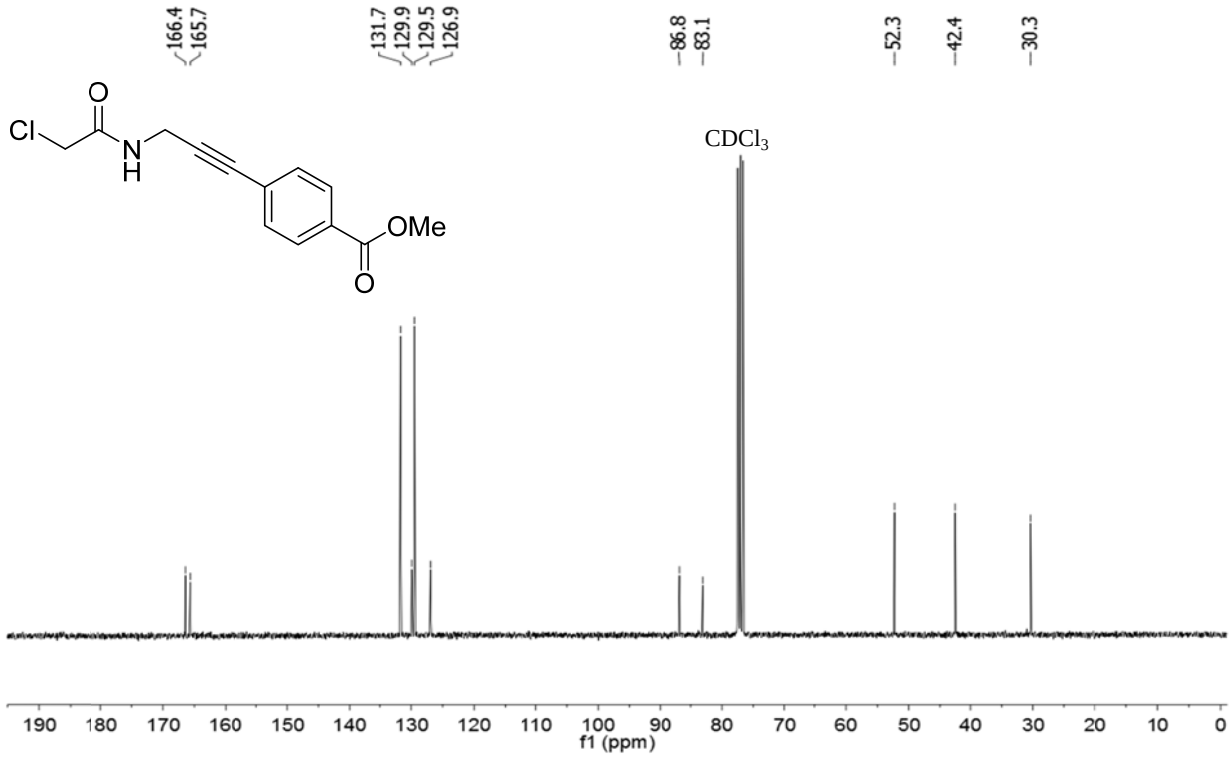


$CDCl_3$

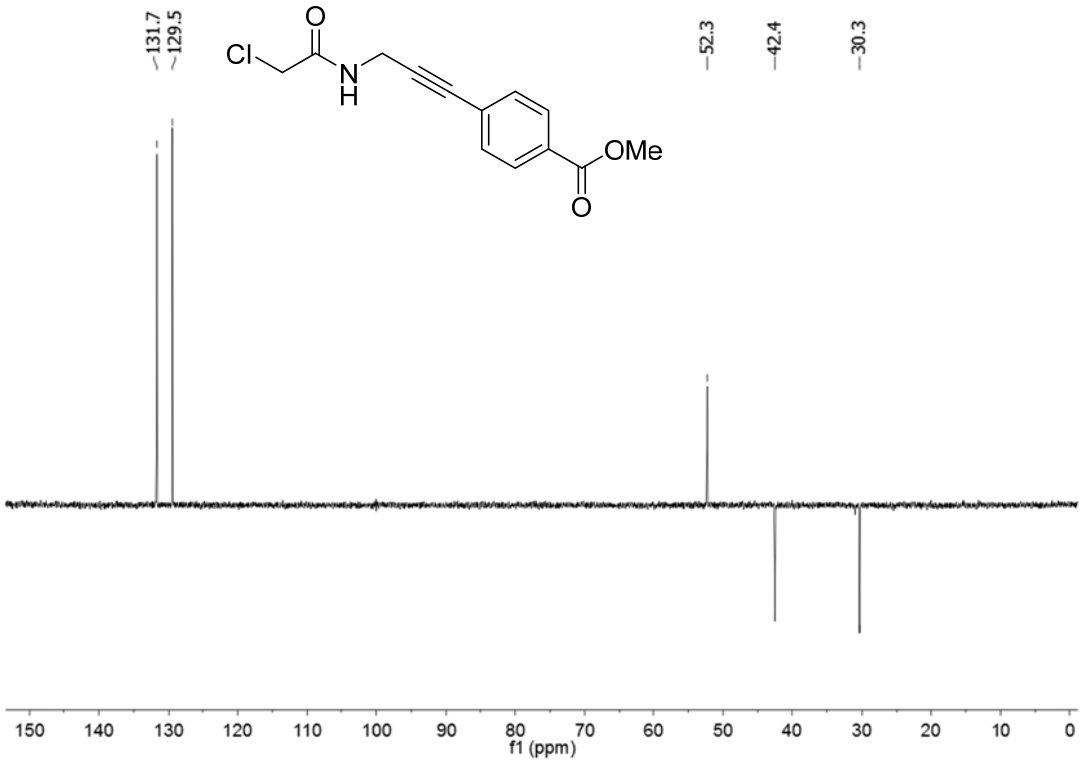
*

* HDO exchange shift.

^{13}C NMR spectrum of compound 5o (75 MHz, $CDCl_3$, *T* = 296 K).

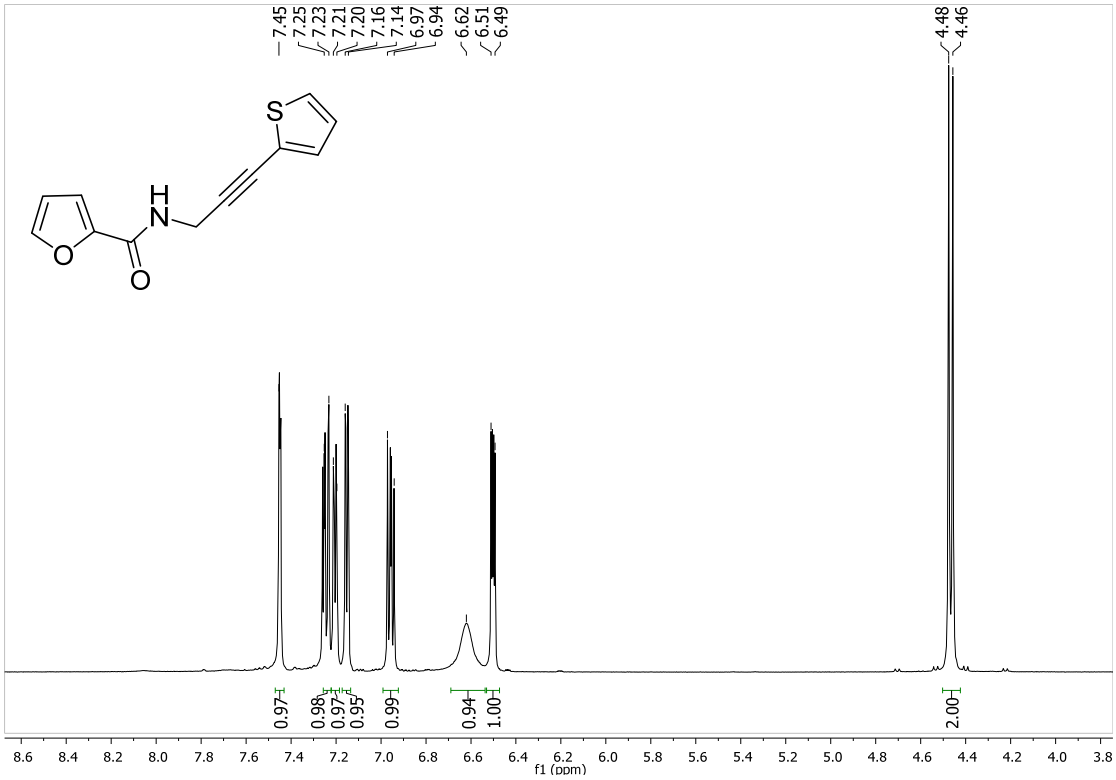


DEPT 135 ^{13}C NMR spectrum of compound 5o (75 MHz, $CDCl_3$, *T* = 296 K).

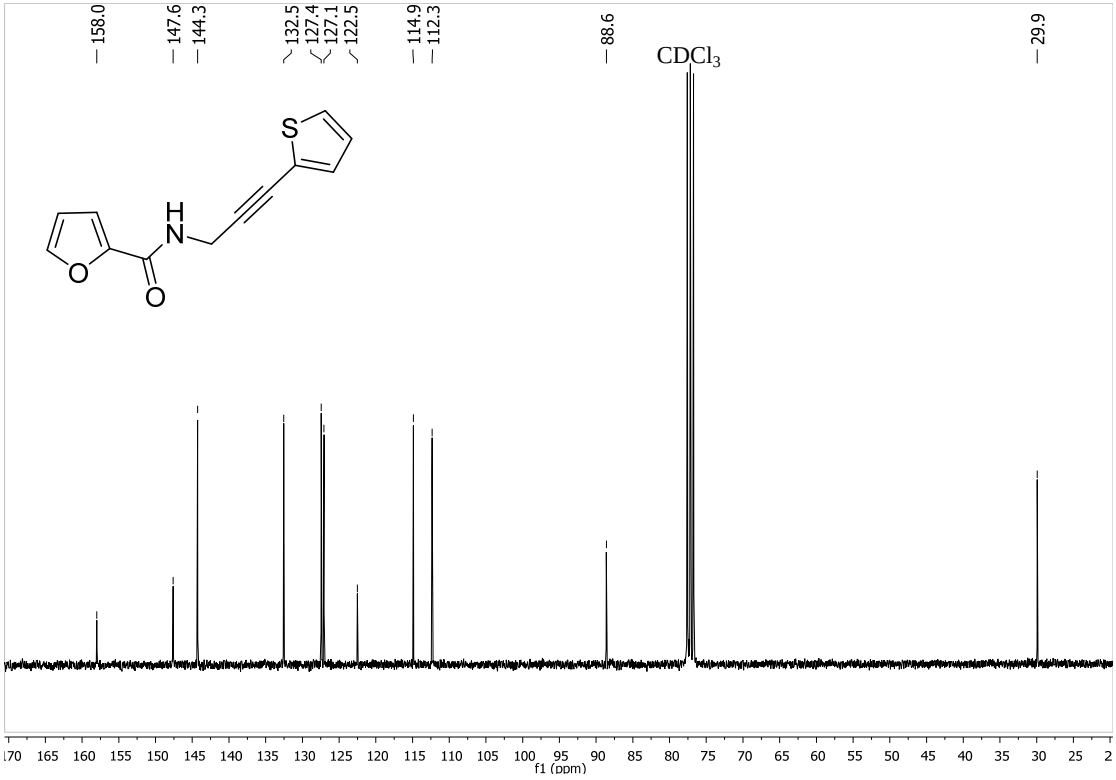


3.16. *N*-(3-(Thiophen-2-yl)prop-2-yn-1-yl)furan-2-carboxamide (5p)

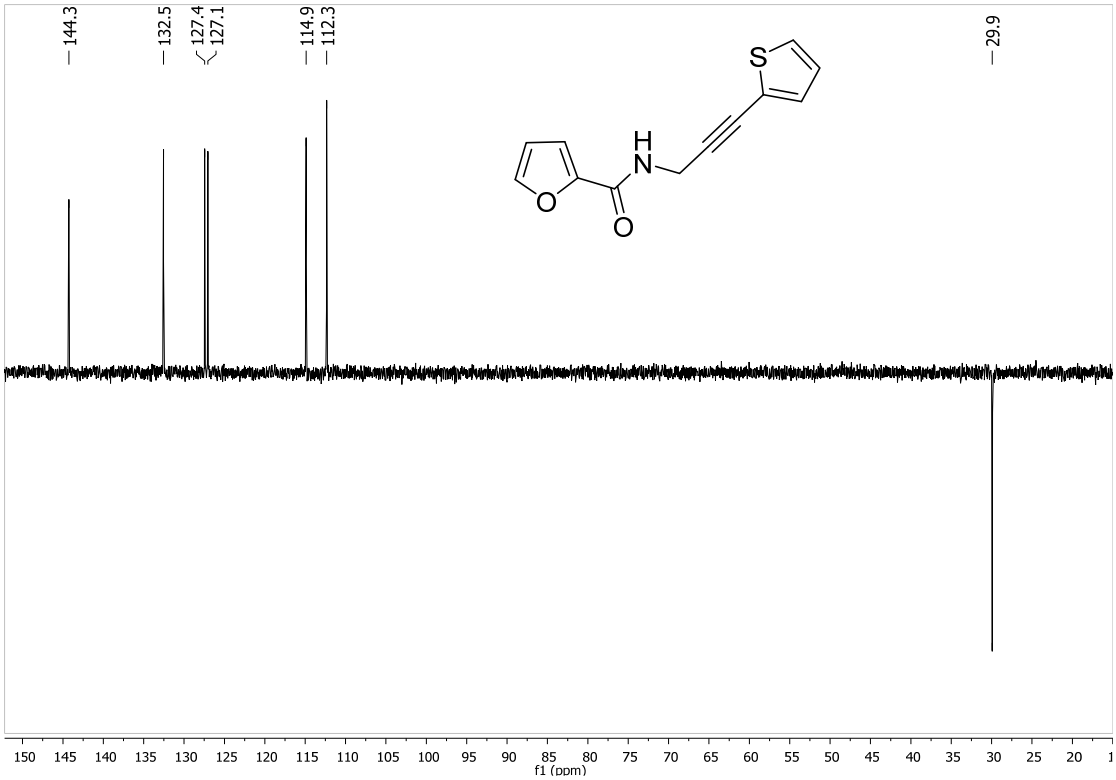
^{1}H NMR spectrum of compound 5p (300 MHz, $CDCl_3$, *T* = 296 K).



^{13}C NMR spectrum of compound 5p (75 MHz, $CDCl_3$, *T* = 296 K).

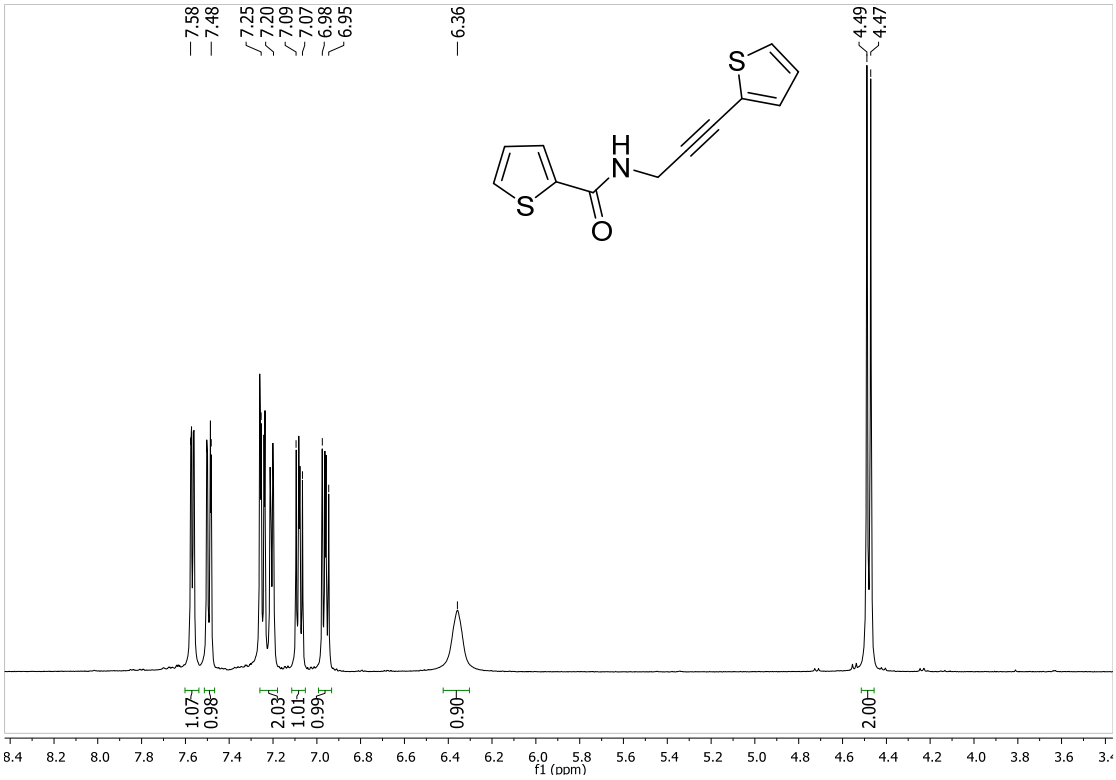


DEPT 135 ^{13}C NMR spectrum of compound 5p (75 MHz, $CDCl_3$, *T* = 296 K).

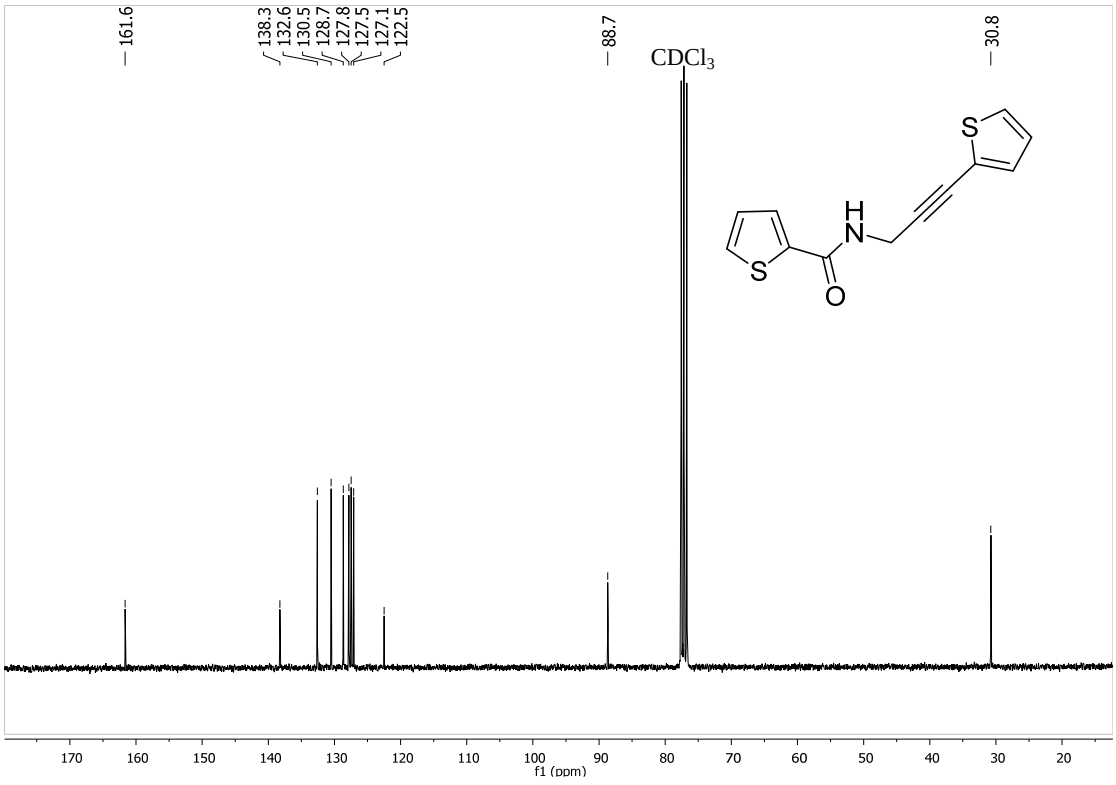


3.17. *N*-(3-(Thiophen-2-yl)prop-2-yn-1-yl)thiophene-2-carboxamide (5q)

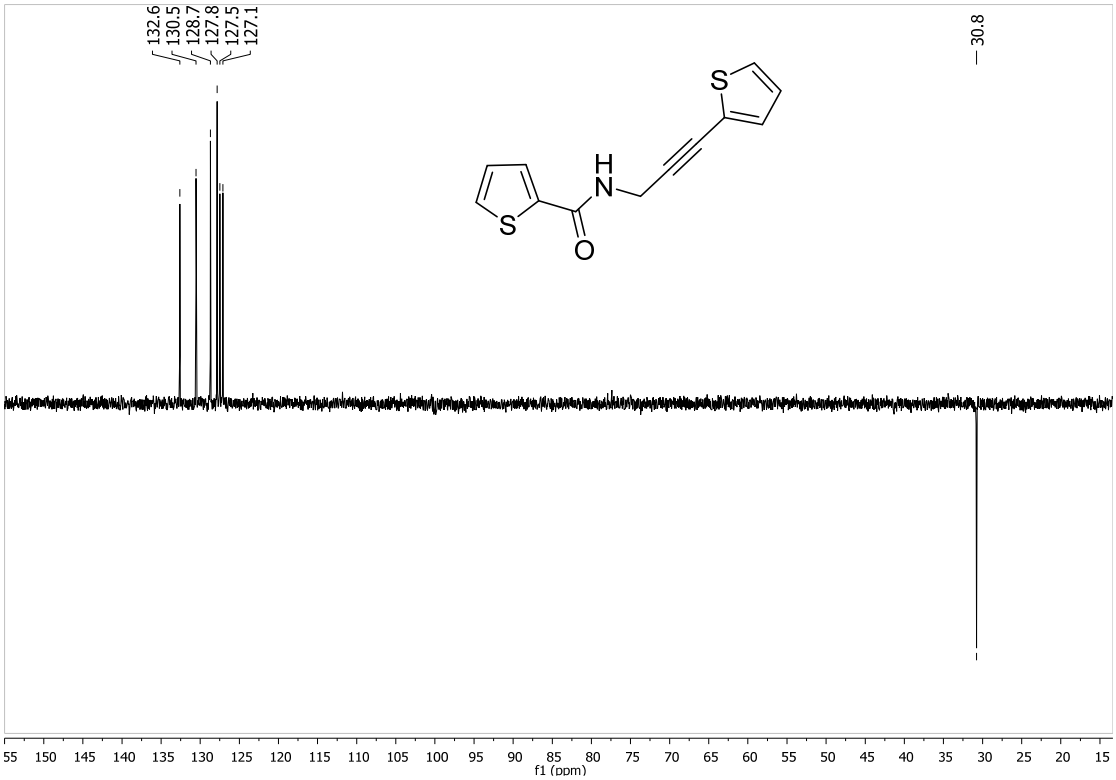
^{1}H NMR spectrum of compound 5q (300 MHz $CDCl_3$, *T* = 296 K).



^{13}C NMR spectrum of compound 5q (75 MHz, $CDCl_3$, *T* = 296 K).

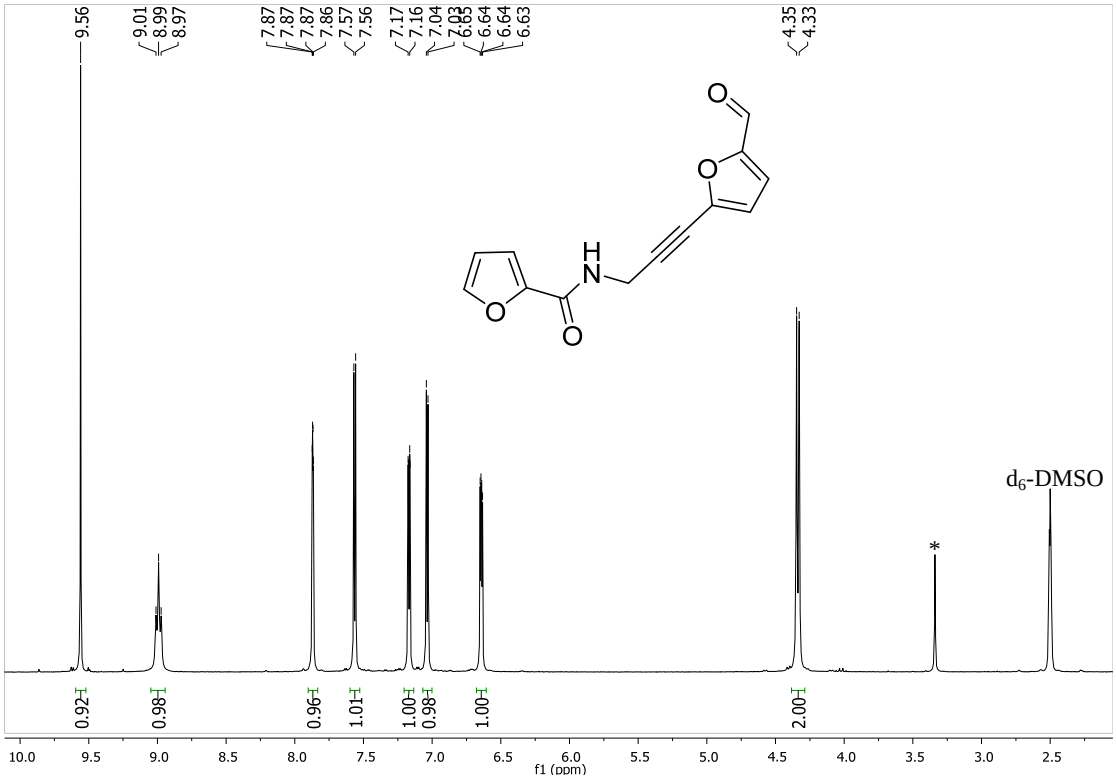


DEPT 135 ^{13}C NMR spectrum of compound 5q (75 MHz, $CDCl_3$, *T* = 296 K).



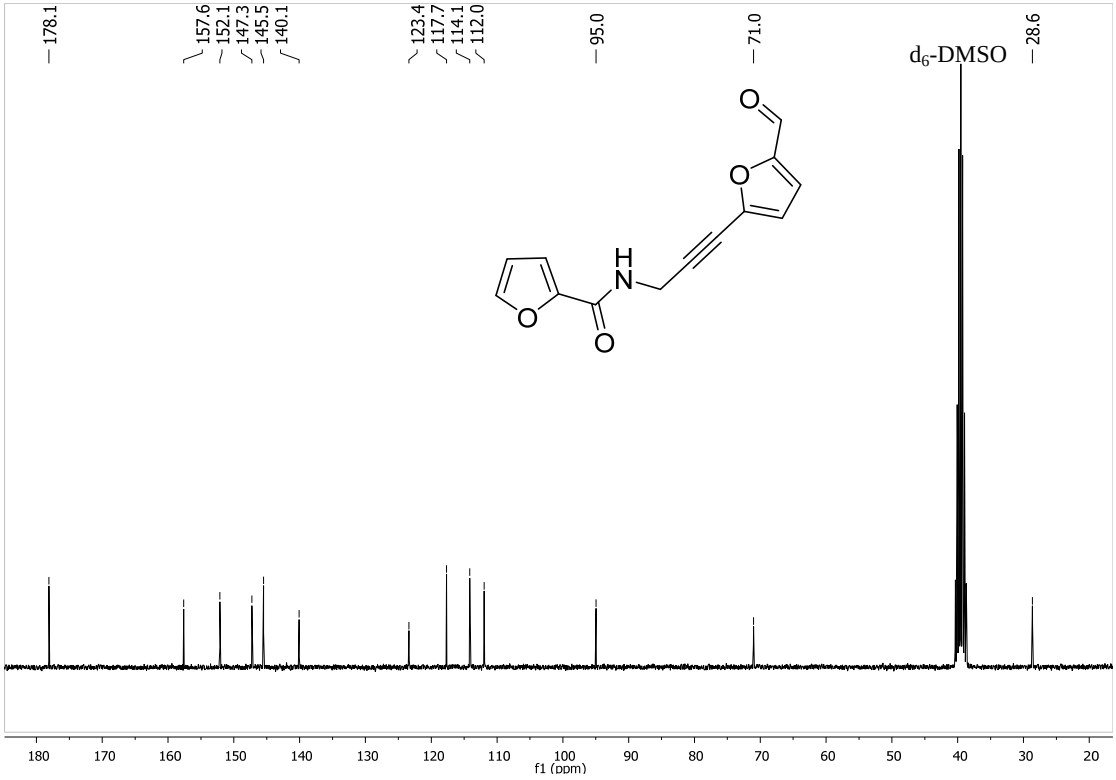
3.18. *N*-(3-(5-Formylfuran-2-yl)prop-2-yn-1-yl)furan-2-carboxamide (5r)

^{1}H NMR spectrum of compound 5r (300 MHz, d_6-DMSO, *T* = 296 K).

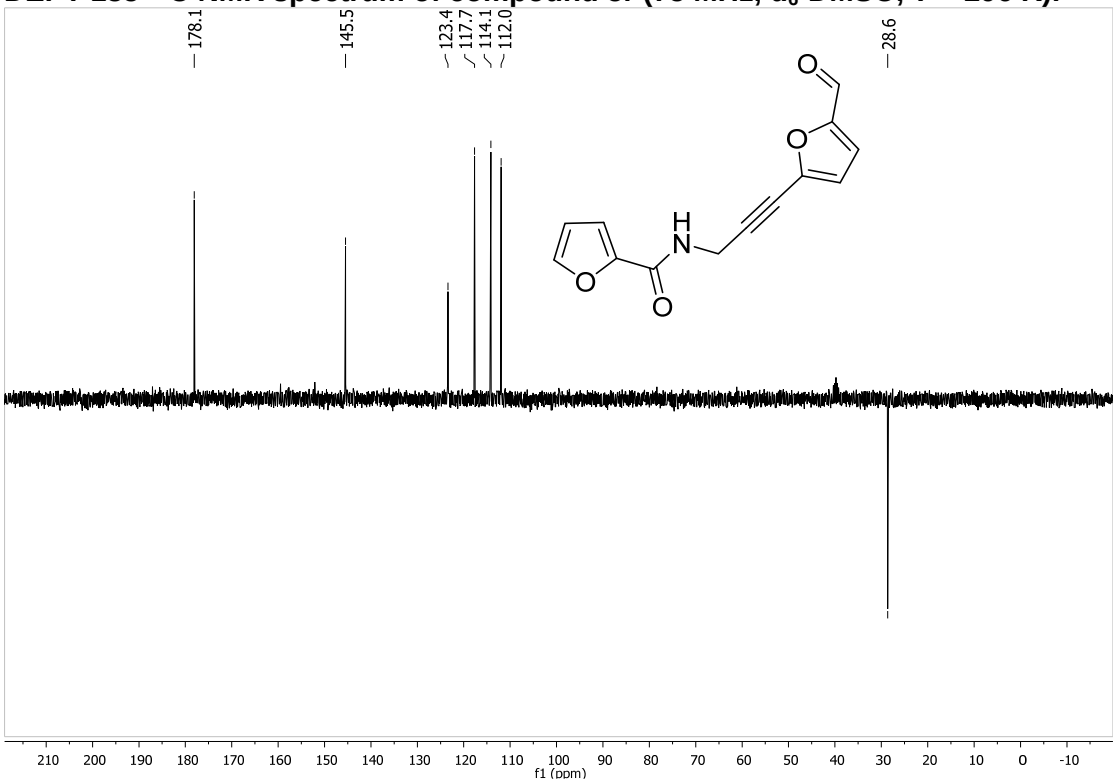


* HDO exchange peak.

^{13}C NMR spectrum of compound 5r (75 MHz, d_6-DMSO, *T* = 296 K).

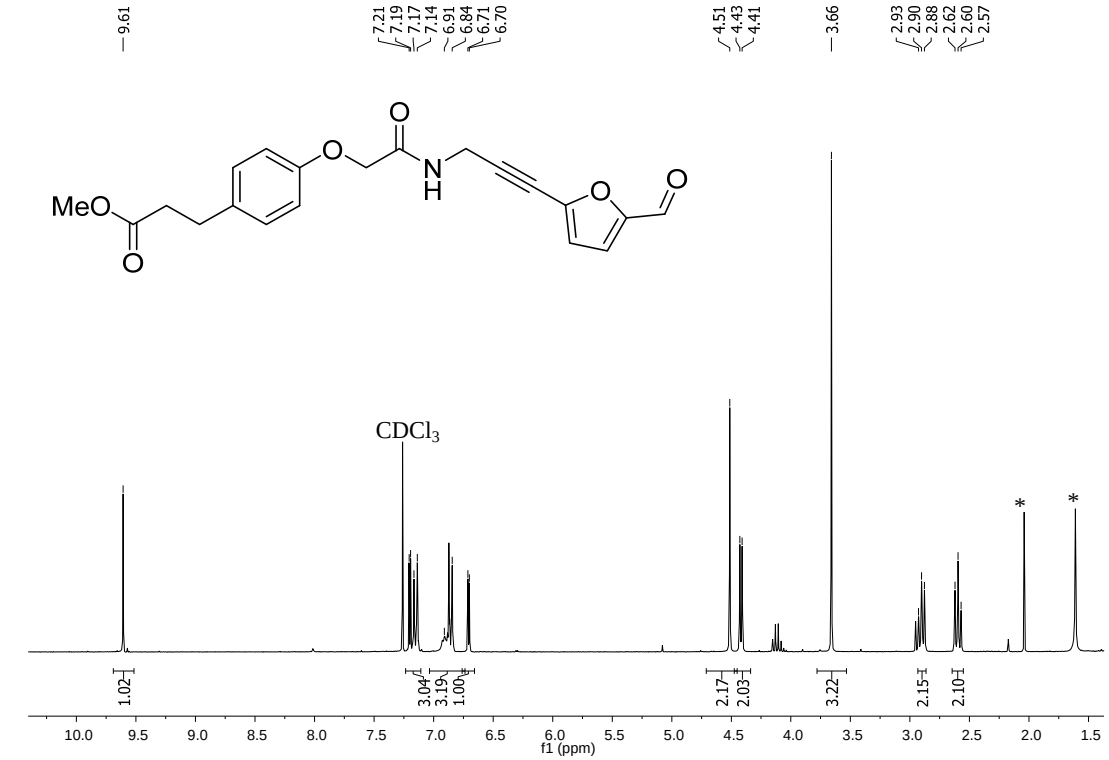


DEPT 135 ^{13}C NMR spectrum of compound 5r (75 MHz, d_6-DMSO, *T* = 296 K).



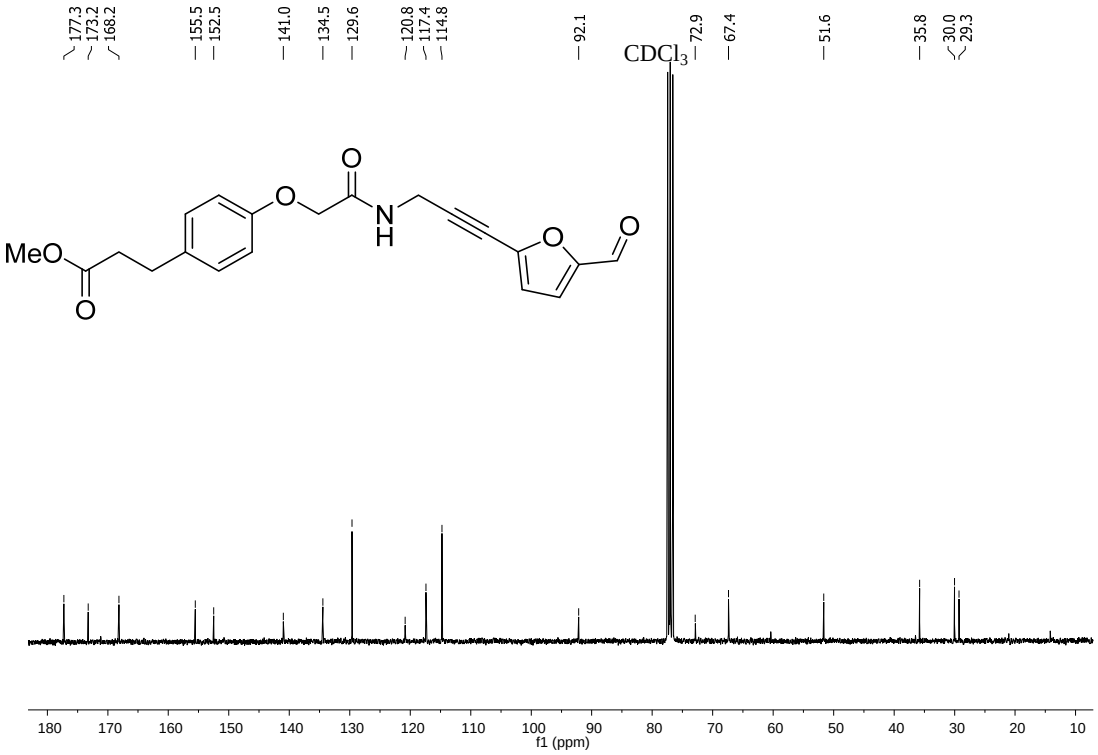
3.19. Methyl 3-(4-2-((3-(5-formylfuran-2-yl)prop-2-yn-1-yl)amino)-2-oxoethoxy)phenyl) propanoate (5s)

^{1}H NMR spectrum of compound 5s (300 MHz, $CDCl_3$, *T* = 296 K).

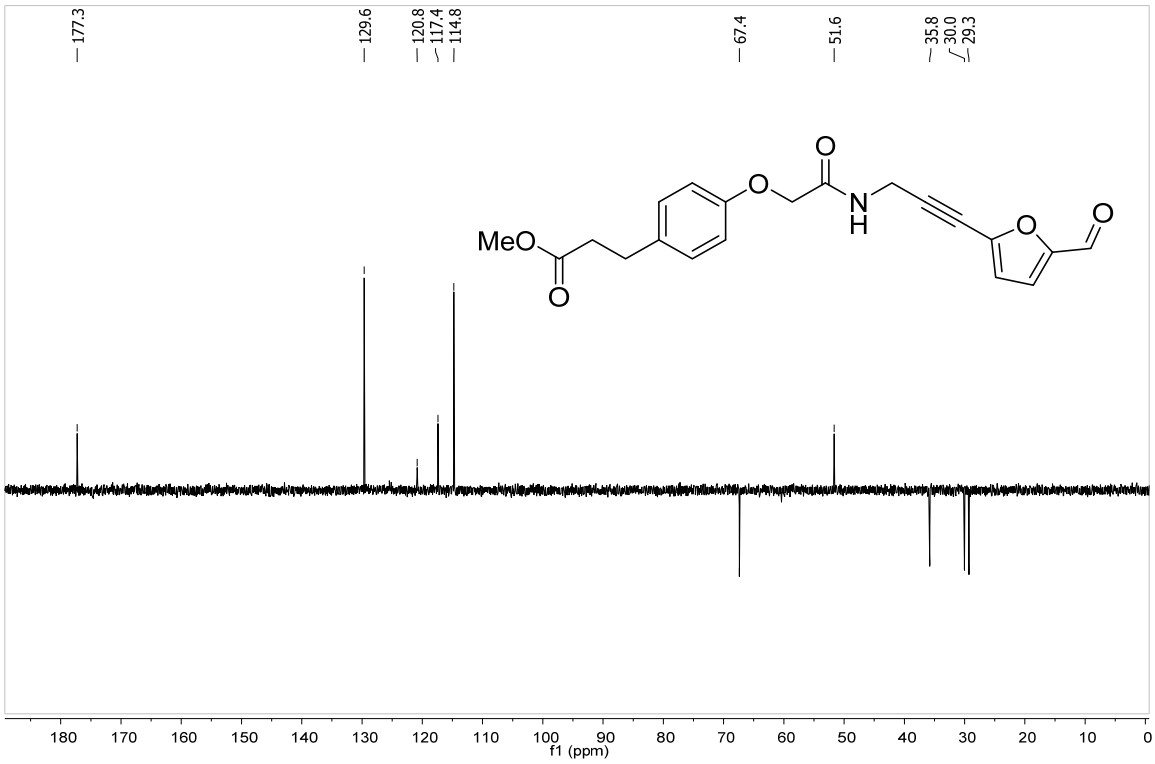


* Impurities from the residual solvent.

^{13}C NMR spectrum of compound 5s (75 MHz, $CDCl_3$, *T* = 296 K).



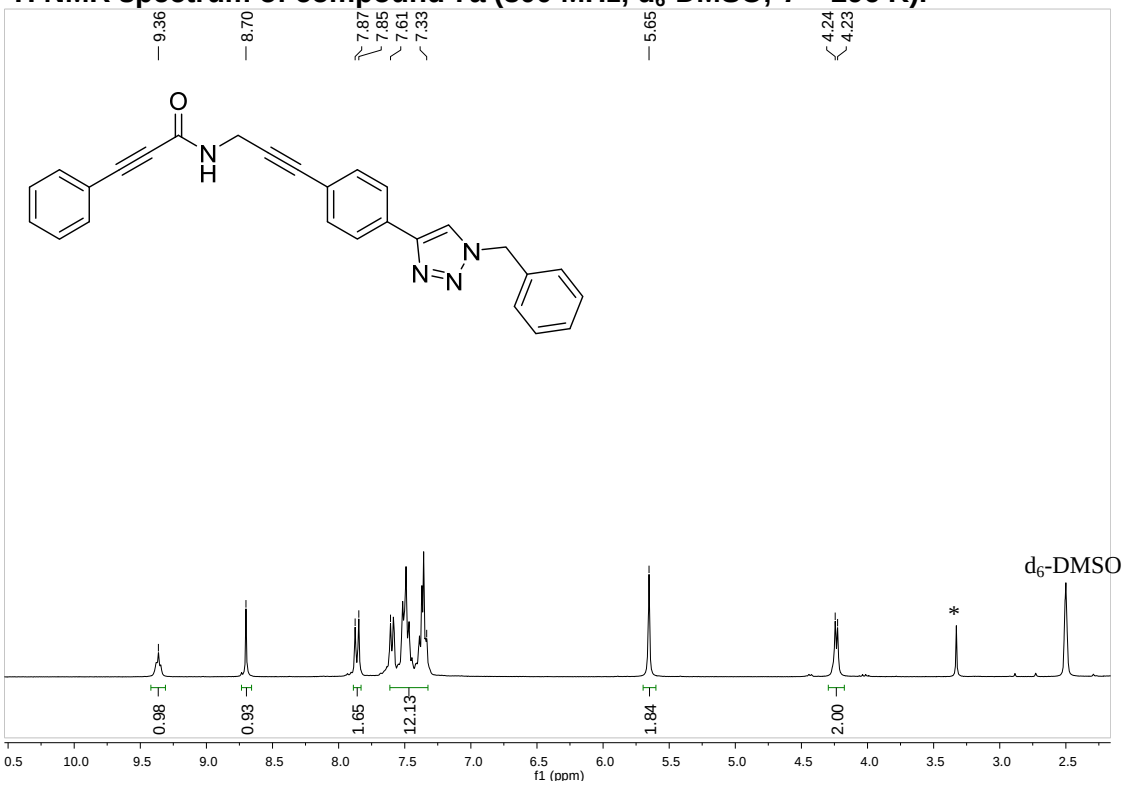
DEPT 135 ^{13}C NMR spectrum of compound 5s (75 MHz, $CDCl_3$, *T* = 296 K).



4. NMR Spectra of 3-(4-1,2,3-Triazolyl)phenyl Propargyl Amides 7

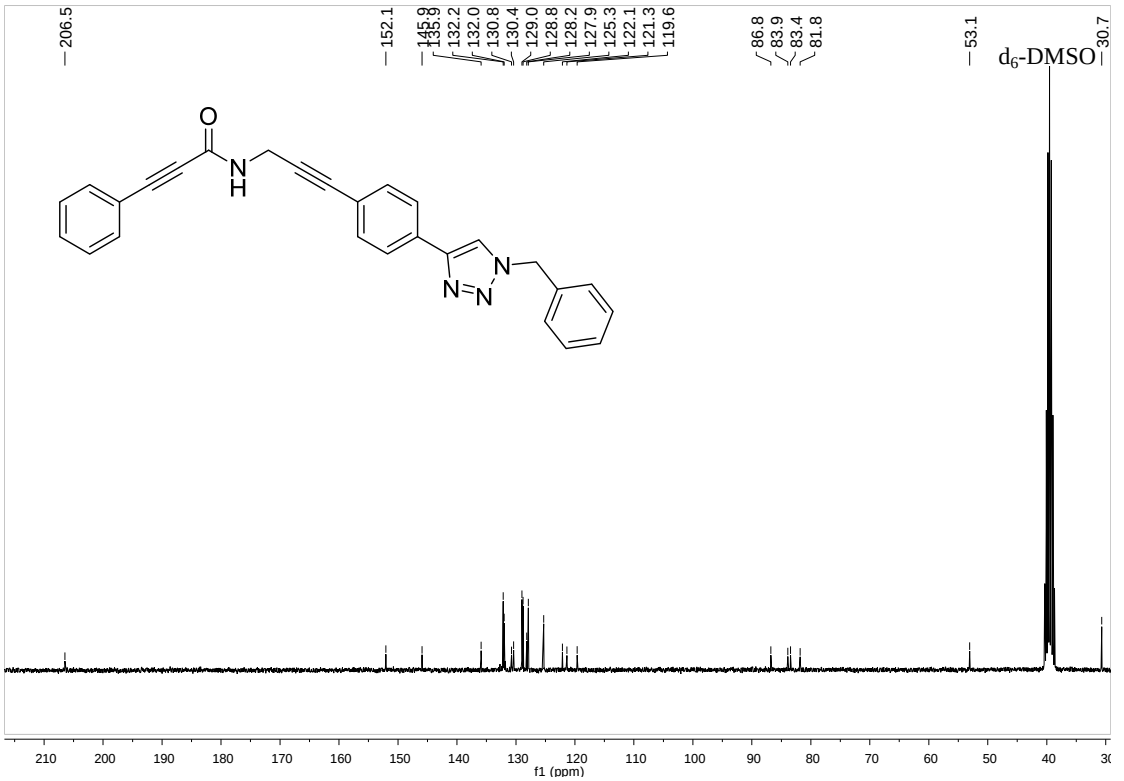
4.1. *N*-(3-(4-(1-Benzyl-1H-1,2,3-triazol-4-yl)phenyl)prop-2-yn-1-yl)-3-phenyl propiolamide (7a)

^{1}H NMR spectrum of compound 7a (300 MHz, d_6-DMSO, *T* = 296 K).

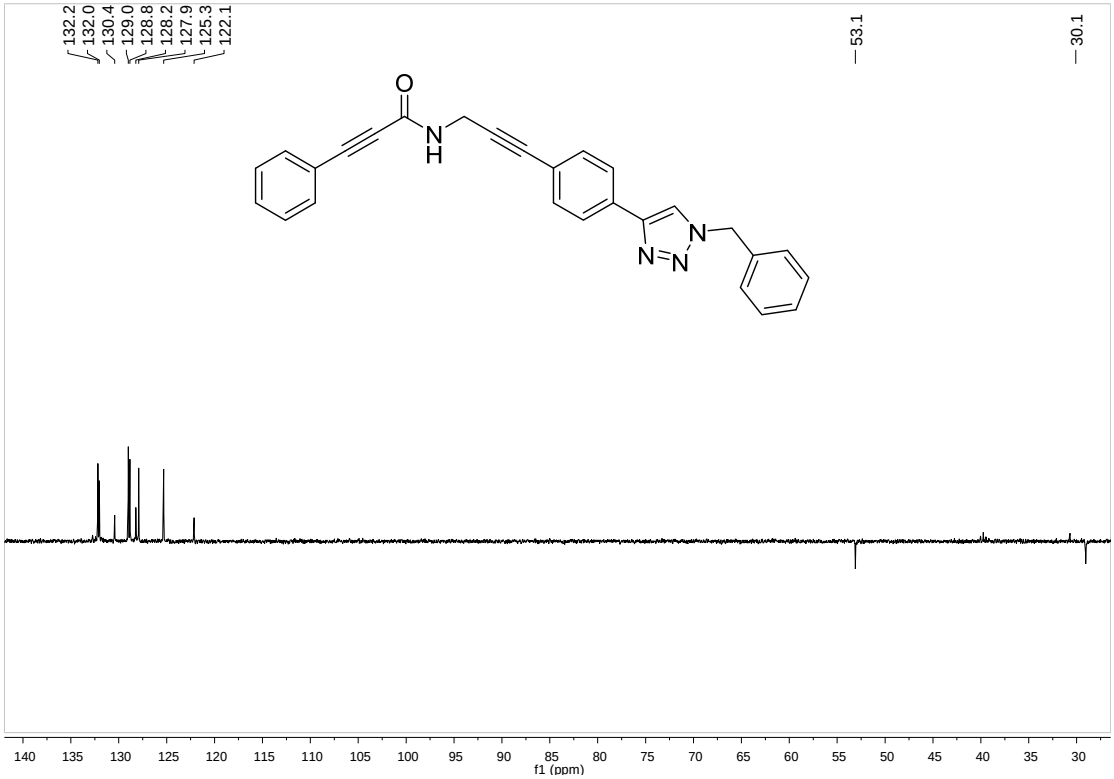


***** HDO exchange peak

^{13}C NMR spectrum of compound 7a (75 MHz, d_6-DMSO, *T* = 296 K).

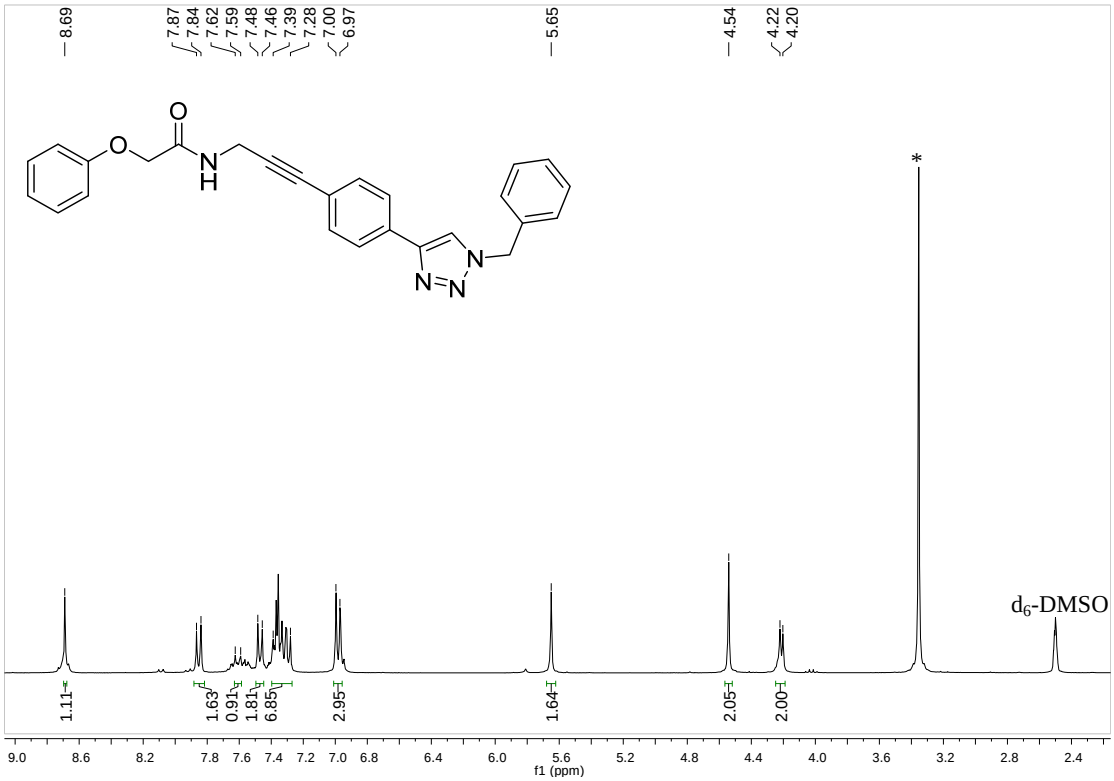


DEPT 135 ^{13}C NMR spectrum of compound 7a (75 MHz, d_6-DMSO, *T* = 296 K).



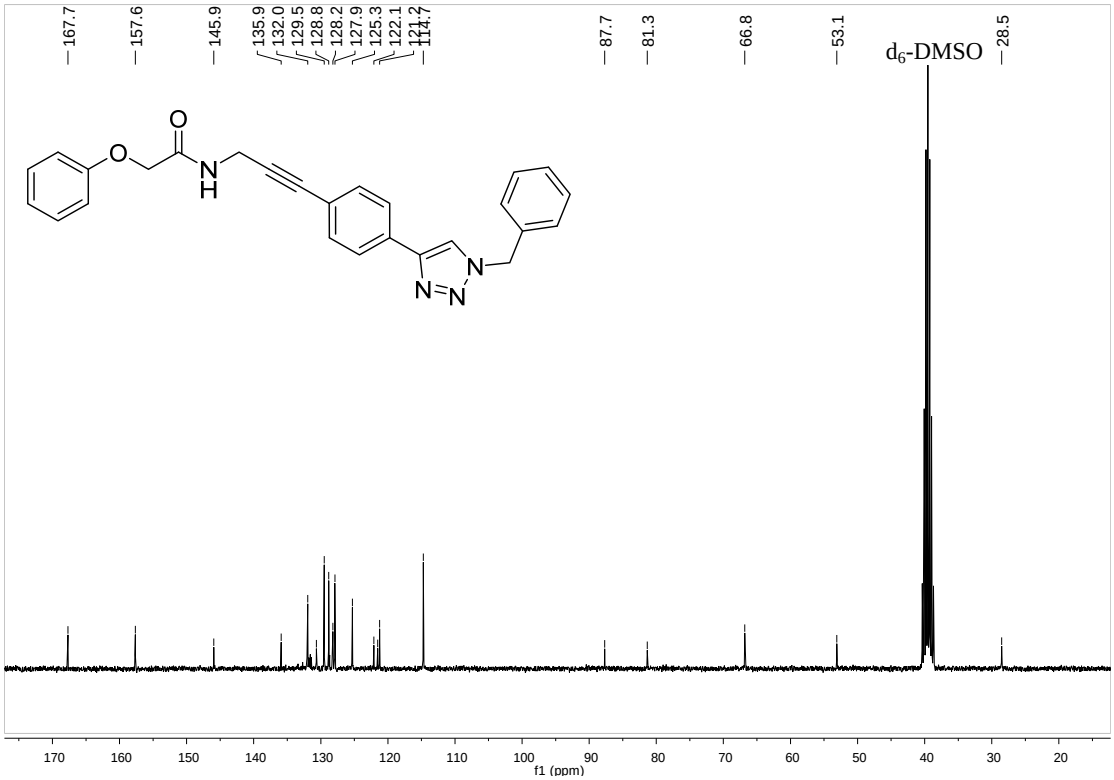
4.2. *N*-(3-(4-(1-Benzyl-1H-1,2,3-triazol-4-yl)phenyl)prop-2-yn-1-yl)-2-phenoxy acetamide (7b)

^{1}H NMR spectrum of compound 7b (300 MHz, d_6-DMSO, *T* = 296 K).



* HDO exchange peak

^{13}C NMR spectrum of compound 7b (75 MHz, d_6-DMSO, *T* = 296 K).



DEPT 135 ^{13}C NMR spectrum of compound 7b (75 MHz, d_6-DMSO, *T* = 296 K).