Electronic Supplementary Material (ESI) for Organic & Biomolecular Chemistry.

Synthesis of novel triptamine-based macrocycles using a Ugi 4-CR/click-cycloaddition consecutive reactions protocol.

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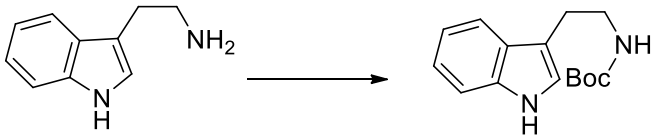
SUPPORTING INFORMATION

General considerations*:* Starting materials and solvent are commercially available and were used without further purification. Reaction progress was monitored by TLC on precoated silica gel Kieselgel 60 F254 plates; the spots were visualized under UV light (254 nm). Flash column chromatography was conducted under silica gel (230-400 mesh). Melting points were determined on a Fisher-Jhons instrument and are uncorrected. The microwave-assisted reactions were performed using a CEM Discover SynthesisTM unit (CEM corp., Matthews, NC) with a monomodal open–vessel system. ^{1}H and ^{13}C NMR spectra were recorded on Varian Unit (300 MHz) and Bruker Avance (300 MHz) spectrometers; TMS was used as internal reference. High-resolution mass spectra were recorded on a Jeol SX-102A instrument and Jeol JMS-T 100LC. IR spectra were measured on a Bruker Tensor 27 spectrophotometer. X-ray crystal structure analysis was undertaken on a BrukerSmart Apex difractometer (CCD detector).



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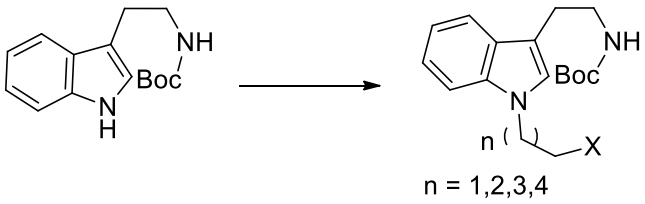
tert-butyl (2-(1H-indol-3-yl)ethyl)carbamate (5).[1] To a solution of tryptamine (1.0 g, 6.24 mmol) in dioxane/satured solution $NaHCO_3$ 1:2 (13.21 mL), di-*tert*-butyl dicarbonate (1.49 g, 6.86 mmol) was added and stirred for 2 hours. The reaction mixture was extracted with brine and EtOAc and dried over $NaSO_4$. The reaction mixture was concentrated under reduced pressure and purified by flash column chromatography (7:3 hexane/EtOAc) to give the desired as a white solid (1.58g, 98%). Mp: 97 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ ppm 8.11 (s, 1H), 7.60 (d, J = 5.7 Hz, 1H), 7.09 - 7.38 (m, 3H), 7.01 (s, 1H), 4.59 (br, 1H), 3.46 (t, J = 13.8 Hz, 2H), 2.95 (t, J_1 = 6.6 Hz, 2H), 1.44 (s, 9H); RMN ^{13}C (75 MHz, $CDCl_3$) δ/ppm: 156.06, 136.41, 127.39, 122.12, 122.01, 119.39, 118.79, 113.13, 111.16, 79.32, 41.06, 28.42, 25.85; IR (film)ν cm^{-1}: 3328, 3056, 2976, 2932, 1692; ESIHRMS m/z calcd for $C_{19}H_{14}N_2O_4Na$ [M+Na]+ 357.08, found 357.08.

[1] Bang D., Chopra N., Kent S. *J. Am. Chem. Soc.* **2004**, *126*, 12888.



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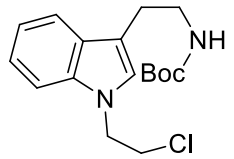
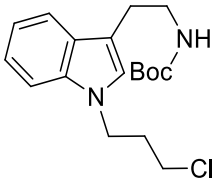
Method A. A solution of *tert*-butyl(2-(1H-indol-3-yl)ethyl)carbamate **5** (.50 g, 1.92 mmol), tetrabutylammonium iodide (1.06g, 2.88 mmol), 1,2-dichloroethane (10 mL) and NaOH 50% (5 mL) was heated up to 50 °C with vigorous stirring for 8 hours. The reaction mixture was extracted with HCl 2N and CH_2Cl_2 and dried over $NaSO_4$. The reaction mixture was concentrated under reduced pressure and purified by flash column chromatography (9:1 hexane/EtOAc).

Method B. A solution of *tert*-butyl(2-(1H-indol-3-yl)ethyl)carbamate **5** (0.50 g, 1.92 mmol), in THF anhydrous 0.5M (3.8 mL) NaH 60% in mineral oil (0.066 g, 2.3 mmol) was added and stirred for 0.5 hours at room temperature. Then 1-bromo-3-chloropropane (0.91 g, 5.76 mmol) was added and stirred vigorously for 24 hours. The reaction mixture was extracted with HCl 2N and EtOAc and dried over $NaSO_4$. The reaction mixture was concentrated under reduced pressure and purified by flash column chromatography (8:2 hexane/EtOAc).

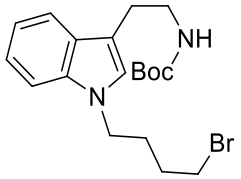
Method C. A solution of *tert*-butyl(2-(1H-indol-3-yl)ethyl)carbamate **5** (.50 g, 1.92 mmol), tetrabutylammonium iodide (0.71 g, 1.92 mmol), 1,4-dibromobutane (0.621, 2.88 mmol), NaOH 50% (5 mL) in THF 0.3M (6.4 mL) was stirred vigorously for 12 hours. The reaction mixture was extracted with HCl 2N and EtOAc and dried over $NaSO_4$. The reaction mixture was concentrated under reduced pressure and purified by flash column chromatography (9:1 hexane/EtOAc).



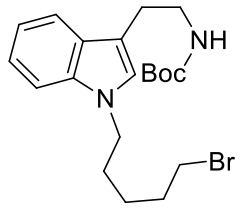
tert-butyl (2-(1-(2-chloroethyl)-1H-indol-3-yl)ethyl)carbamate. This compound was obtained using method A as pale pink solid. M.p. 67-68 °C (1.04 g, 84%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.64 (d, *J* = 7.8 Hz, 1H), 7.38 – 7.21 (m, 2H), 7.18 (d, *J* = 7.4 Hz, 1H), 6.99 (s, 1H), 4.75 (bs, 1H), 4.48 – 4.25 (m, 2H), 3.77 (t, *J* = 6.4 Hz, 2H), 3.48 (d, *J* = 5.9 Hz, 2H), 3.08 – 2.80 (m, 2H), 1.49 (s, 9H); RMN ^{13}C (75 MHz, $CDCl_3$) δ/ppm: 155.96, 136.25, 128.22, 126.04, 122.07, 119.42, 119.29, 112.58, 108.95, 79.19, 47.84, 42.49, 40.96, 28.42, 25.74; IR (film) ν, cm^{-1}: 3349, 3085, 2982, 2928, 1677;HRMS (FAB+, M+) calcd for $C_{17}H_{23}O_2N_2Cl_1$: [M+1] 322.14, found: 322.14.



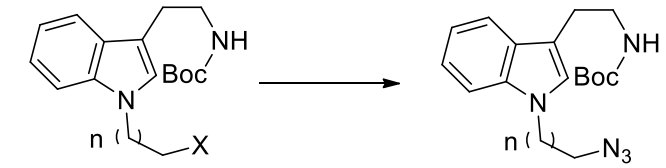
tert-butyl (2-(1-(3-bromopropyl)-1H-indol-3yl)ethyl) carbamate. This compound was obtained using method B as a yellow oil (0.52 g, 80%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.62 (d, *J* = 7.9 Hz, 1H), 7.36 (d, *J* = 8.3 Hz, 1H), 7.24 (t, *J* = 7.5 Hz, 1H), 7.13 (t, *J* = 7.4 Hz, 1H), 6.98 (s, 1H), 4.65 (bs, 1H), 4.30 (t, *J* = 6.4 Hz, 2H), 3.52 – 3.37 (m, 4H), 2.95 (t, *J* = 6.9 Hz, 2H), 2.25 (t, *J* = 6.2 Hz, 2H), 1.46 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.88, 136.24, 127.99, 125.85, 121.78, 119.03, 112.11, 109.23, 42.61, 41.82, 40.90, 32.58, 28.36.; IR (film) γ, cm^{-1} 3347, 3050, 2973, 2930, 1693, 1612, 1506, 1465, 1391, 1363, 1330, 1245, 1164, 1059, 1018, 959, 865, 739, 651, 556, 526, 463, 427; HRMS (FAB+, M+) calcd for $C_{18}H_{36}ClN_2O_2$: [M+1] 337.16, found: 337.16



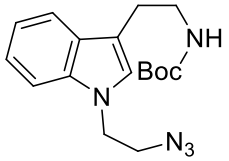
tert-butyl(2-(1-(4-bromobutyl)-1H-indol-3-yl)ethyl) carbamate. This compound was obtained using method C as yellow oil (0.57g, 75%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.59 (d, *J* = 7.8 Hz, 1H), 7.29 (d, *J* = 8.2 Hz, 1H), 7.25 – 7.17 (m, 1H), 7.10 (ddd, *J* = 8.1, 6.9, 1.1 Hz, 1H), 6.91 (s, 1H), 4.61 (s, 1H), 4.10 (t, *J* = 6.9 Hz, 2H), 3.44 (q, *J* = 6.7 Hz, 2H), 3.25 (t, *J* = 6.7 Hz, 2H), 2.93 (t, *J* = 7.0 Hz, 2H), 1.96 – 1.84 (m, 2H), 1.62 – 1.50 (m, 2H), 1.43 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.90, 136.32, 127.94, 125.49, 121.68, 119.08, 118.91, 111.97, 109.22, 51.01, 45.58, 40.97, 28.39, 27.48, 26.41, 25.75; IR (film) γ, cm^{-1} 3363, 2977, 2932, 1730, 1713, 1511, 1454, 1380, 1367, 1254, 1162, 1091, 1017, 745; HRMS (FAB+, M+) calcd for $C_{19}H_{28}BrN_2O_2$: [M+1] 395.13, found: 395.13.



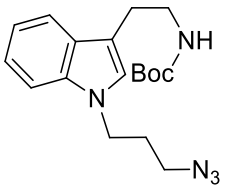
tert-butyl(2-(1-(5-bromopentyl)-1H-indol-3-yl)ethyl) carbamate. This compound was obtained using mehod C as yellow oil (0.71g, 90%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.58 (d, *J* = 7.8 Hz, 1H), 7.30 (s, 1H), 7.23 – 7.14 (m, 1H), 7.09 (td, *J* = 7.4, 6.8, 1.2 Hz, 1H), 6.91 (s, 1H), 4.60 (bs, 1H), 4.07 (t, *J* = 7.0 Hz, 2H), 3.44 (d, *J* = 6.5 Hz, 2H), 3.35 (t, *J* = 6.7 Hz, 2H), 2.93 (t, *J* = 6.9 Hz, 2H), 1.84 (m, 4H), 1.52 – 1.45 (m, 2H), 1.43 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.49, 135.90, 127.50, 125.20, 121.17, 118.42, 111.33, 108.85, 45.52, 40.57, 32.83, 31.84, 28.98, 27.99, 25.18; IR (film) γ, cm^{-1} 3342, 3052, 2925, 2854, 1693, 1613, 1511, 1459, 1394, 1365, 1247, 1169, 1041, 1013, 960, 867, 741, 671, 609, 583; HRMS (FAB+, M+) calcd for $C_{20}H_{29}BrN_2O_2$: [M+1] 408.14, found: 408.14.



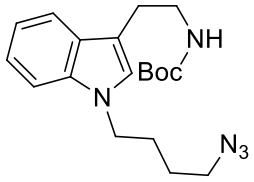
General procedure for substitution of halide by azide. *tert*-butyl(2-(1-(2-chloroethyl)-1H-indol-3-yl)ethyl)carbamate (0.50 g, 1.54 mmol) was dissolved in dimethyl sulfoxide 0.3M (5.16 mL) and sodium azide (0.02 g, 3.38 mmol) was added. The resulting solution was heated to 80 °C during 6 hours and then cooled to room temperature. The reaction mixture was quenched by addition of a saturated aqueous solution of $NaHCO_3$ and diluted with EtOAc. The aqueous layer was extracted with EtOAc and the combined organic layers were washed twice with brine, dried over Na_2SO_4, filtered and concentrated. The crude residue was used in the next reaction without further purification.



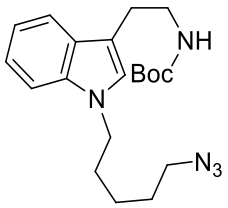
tert-butyl (2-(1-(2-azidoethyl)-1H-indol-3-yl)ethyl)carbamate. The product was obtained as pale yellow oil (0.42 g, 82%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.66 (d, J = 7.8 Hz, 1H), 7.28 (q, J = 8.0 Hz, 2H), 7.17 (t, J = 7.2 Hz, 1H), 6.95 (s, 1H), 4.91 (s, 1H), 4.16 (t, J = 5.7 Hz, 2H), 3.54 (t, J = 5.6 Hz, 3H), 3.48 (d, J = 5.5 Hz, 1H), 2.98 (t, J = 5.5 Hz, 2H), 1.51 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.14, 136.34, 128.41, 125.87, 122.10, 119.43, 112.94, 109.16, 79.00, 51.02, 45.38, 41.09, 28.54, 25.79; IR (film) ν, cm^{-1}: 3414, 3052, 2929, 2101, 1706; HRMS (FAB+, M+) calcd for $C_{17}H_{24}O_2N_5$: [M+1] 330.19, found: 330.19.



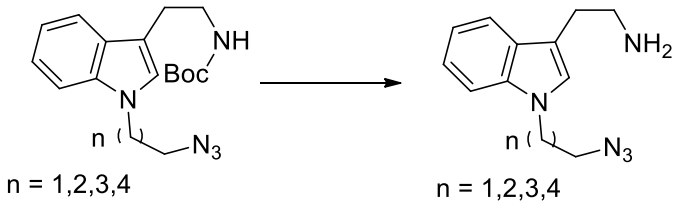
tert-butyl (2-(1-(3-azidopropyl)-1H-indol-3-yl)ethyl)carbamate. The product was obtained as pale yellow oil (0.41 g, 80%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.66 – 7.57 (d, 1H), 7.33 (d, *J* = 8.1 Hz, 1H), 7.24 (t, *J* = 7.4 Hz, 1H), 7.13 (t, *J* = 7.4 Hz, 1H), 6.93 (s, 1H), 4.65 (s, 1H), 4.36 – 3.97 (m, 2H), 3.46 (d, *J* = 6.0 Hz, 2H), 3.33 – 3.14 (m, 2H), 3.08 – 2.75 (m, 2H), 2.07 (q, *J* = 6.4 Hz, 2H), 1.45 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.06, 136.46, 128.14, 125.81, 122.01, 119.21, 112.41, 109.35, 48.55, 42.97, 41.09, 29.48, 28.54; IR (film) ν, cm^{-1}:3349, 2973, 2930, 2095,1693, 1507, 1464, 1364, 1246, 1166, 740; HRMS (FAB+, M+) calcd for $C_{18}H_{26}O_2N_5$: [M+1] 344.20, found: 344.20.



tert-butyl (2-(1-(4-azidobutyl)-1H-indol-3-yl)ethyl)carbamate. The product was obtained as pale yellow oil (0.44 g, 98%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.63 (d, *J* = 7.9 Hz, 1H), 7.33 (d, *J* = 8.1 Hz, 1H), 7.25 (t, *J* = 7.5 Hz, 1H), 7.14 (t, *J* = 7.4 Hz, 1H), 6.94 (s, 1H), 4.73 (s, 1H), 4.11 (t, *J* = 6.9 Hz, 2H), 3.47 (q, *J* = 6.6 Hz, 2H), 3.26 (t, *J* = 6.7 Hz, 2H), 2.96 (t, *J* = 7.0 Hz, 2H), 1.91 (p, *J* = 7.0 Hz, 2H), 1.59 (q, *J* = 7.1 Hz, 2H), 1.48 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.12, 136.49, 128.12, 125.70, 121.84, 119.08, 112.12, 109.42, 51.15, 45.72, 41.15, 28.57, 27.63, 26.55, 25.91; IR (film) γ, cm^{-1} 3352, 2975, 2932, 2873, 2097, 1705, 1509, 1365, 1468, 1250, 1169, 740; HRMS (FAB+, M+) calcd for $C_{19}H_{27}O_2N_5$: [M+1] 357.21, found: 357.21.



tert-butyl(2-(1-(5-azidopentyl)-1H-indol-3yl)ethyl)carbamate. The product was obtained as pale yellow oil (0.39 g, 87%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.66 – 7.48 (d, 1H), 7.30 (d, *J* = 8.1 Hz, 1H), 7.21 (t, *J* = 7.5 Hz, 1H), 7.10 (t, *J* = 7.4 Hz, 1H), 6.92 (s, 1H), 4.62 (s, 1H), 4.08 (t, *J* = 7.0 Hz, 2H), 3.44 (d, *J* = 6.0 Hz, 2H), 3.23 (t, *J* = 6.8 Hz, 2H), 2.93 (t, *J* = 6.8 Hz, 2H), 1.83 (q, *J* = 7.3 Hz, 2H), 1.58 (q, *J* = 7.2 Hz, 2H), 1.44 (s, 9H), 1.38 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.51, 135.89, 127.48, 125.21, 121.17, 118.63, 118.41, 111.32, 108.85, 78.60, 50.73, 45.53, 40.53, 29.38, 28.09, 27.97, 25.31, 23.78; IR (film) γ, cm^{-1} 3365, 2974, 2934, 2867, 2096, 1708, 1509, 1467, 1365, 1249, 1168, 741; HRMS (FAB+, M+) calcd for $C_{20}H_{29}O_2N_5$: [M+1] 371.23, found: 371.23.



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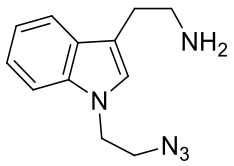
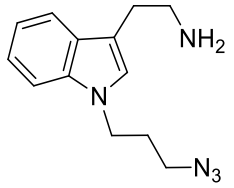
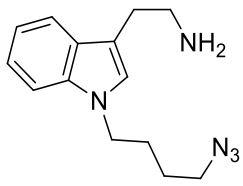
General procedure for deprotection of amide. *tert*-Butyl (2-(1-(2-azidoethyl)-1H-indol-3-yl)ethyl)carbamate (0.10 g, 0.32 mmol) was disolved in formic acid 0.3M (1 mL) and stirred at room temperature for 1 hour. The reaction mixture was ajusted to 8 pH with $NaHCO_3$ and diluted with EtOAc. The aqueous layer was extracted with EtOAc and dried over Na_2SO_4, filtered and concentrated. The crude residue was used in the next reaction without further purification.



2-(1-(2-azidoethyl)-1H-indol-3-yl)ethanamine (6a). The product was obtained as brown oil (0.06 g, 89%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.62 (d, *J* = 7.8 Hz, 1H), 7.32 – 7.18 (m, 2H), 7.17 – 7.08 (m, 1H), 6.97 (d, *J* = 3.5 Hz, 1H), 4.24 (t, *J* = 5.8 Hz, 2H), 3.65 – 3.48 (m, 3H), 3.15 – 2.84 (m, 4H).; ^{13}C NMR (75 MHz, $CDCl_3$) δ 136.17, 128.24, 125.76, 121.88, 119.27, 119.16, 113.15, 108.89, 50.93, 45.31, 42.11; IR (film) γ cm^{-1} 3357, 3052, 2926, 2855, 2101, 1612, 1466, 1352, 1267, 1181, 970, 743; HRMS (FAB+, M+) calcd for $C_{12}H_{16}N_2C$: [M+1] 230.14, found: 230.13.

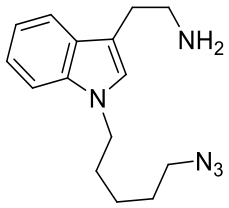


2-(1-(3-azidopropyl)-1H-indol-3-yl)ethanamine (6b). The product was obtained as brown oil (0.054 g, 70%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.58 (t, *J* = 9.9 Hz, 1H), 7.18 (ddt, *J* = 48.7, 20.2, 7.8 Hz, 3H), 6.93 (s, 1H), 4.13 (dq, *J* = 13.2, 6.6 Hz, 2H), 3.20 (dq, *J* = 13.1, 6.4 Hz, 2H), 3.09 – 2.79 (m, 4H), 1.99 (dq, *J* = 21.0, 7.7, 7.0 Hz, 2H), 1.31 – 1.07 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 136.32, 127.96, 125.82, 121.78, 119.09, 112.30, 109.18, 48.38, 42.76, 41.92, 29.28, 28.36; IR (film) γ cm-^{1} 3345, 2923, 2872, 2092, 1632, 1610, 1463, 1250, 1171, 739, 426; HRMS (FAB+, M+) calcd for $C_{13}H_{18}N_5$: [M+1] 244.15, found: 244.15.

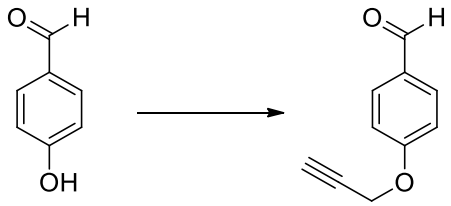


2-(1-(4-azidobutyl)-1H-indol-3-yl)ethanamine (6c). The product was obtained as yellow oil (0.04g, 62%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.56 (t, *J* = 7.0 Hz, 1H), 7.30 – 7.09 (m,

3H), 7.02 (dq, *J* = 14.1, 7.1 Hz, 2H), 4.51 (bs, 2H), 4.03 (dt, *J* = 14.9, 7.4 Hz, 2H), 3.21 – 3.06 (m, 4H), 1.84 (h, *J* = 6.9, 5.3 Hz, 2H), 1.54 (d, *J* = 22.5 Hz, 2H), 1.41 – 1.23 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 136.34, 127.86, 125.83, 121.64, 119.06, 118.88, 109.25, 50.99, 45.55, 27.46, 26.39; IR (film) γ cm^{-1} 3050, 2929, 2871, 2096, 1621, 1468, 1369, 1254, 742, 634; HRMS (FAB+, M+) calcd for $C_{14}H_{20}N_5$: [M+1] 258.17, found: 258.17.



2-(1-(5-azidopentyl)-1H-indol-3-yl)ethanamine (6d). The product was obtained as brown oil (0.06g, 82%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.59 (d, *J* = 7.8 Hz, 1H), 7.29 (d, *J* = 8.1 Hz, 1H), 7.26 – 7.14 (m, 1H), 7.10 (q, *J* = 7.1 Hz, 1H), 6.92 (s, 1H), 4.04 (t, *J* = 7.0 Hz, 2H), 3.42 (bs, 2H), 3.23 (dt, *J* = 19.7, 6.7 Hz, 4H), 3.08 – 2.89 (m, 4H), 1.81 (p, *J* = 7.2 Hz, 2H), 1.56 (d, *J* = 12.8 Hz, 4H), 1.38 (tdd, *J* = 20.3, 11.0, 4.3 Hz, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.41, 136.46, 127.92, 125.88, 121.84, 119.10, 109.47, 51.27, 45.88, 29.91, 28.63, 24.28, 9.02; IR (film) γ cm^{-1} 3293, 3051, 2934, 2861, 2096, 1673, 1612, 1466, 1371, 1251, 1164, 1014, 742; HRMS (FAB+, M+) calcd for $C_{15}H_{22}N_5$: [M+1] 272.18, found: 272.18.

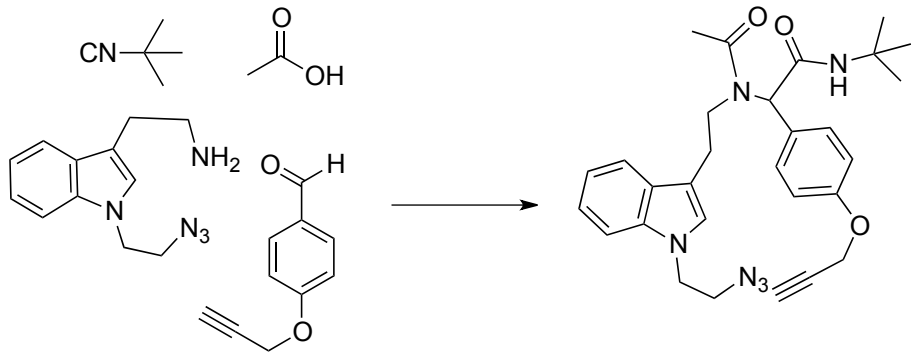


7

General procedure for *O*-alquilation. Propargyl bromide w.t. 80% in toluene (0.567 mL, 6.35 mmol) was added to a solution of 4-hydroxybenzaldehyde (.500 g, 4.09 mmol) and potassium carbonate (1.69 g, 12.28 mmol) in acetone 0.65M (7.21 mL). The reaction mixture was heated to reflux by 16 hours and then filtered over celite and concentrated under reduced pressure. The reaction mixture was purified by flash column

chromatography (8:2 hexane/EtOAc)[2] to yield the desired product as white solid. m.p. 70-72 °C (0.658 g, 99%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.81 (s, 1H), 7.76 (d, *J* = 8.6 Hz, 2H), 7.21 – 6.74 (d, *J* = 8.6 Hz, 2H), 4.69 (s, 2H), 2.56 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 190.79, 162.40, 131.91, 115.23, 76.60, 56.01; IR (film) γ cm^{-1} 3209, 2831, 2808, 2749, 2120, 1678, 1600, 1573, 1244, 1167, 1010, 825, 761, 698, 652, 507; HRMS (FAB+, M+) calcd for $C_{10}H_9O_2$: [M+1] 161.06, found: 161.06.

Optimization of Ugi adducts.



Entry	Temp.	Solvent / Concentration	Catalyst	Reaction time	Yield
1 [a]	25°C	Methanol/1M	$InCl_3$	48 h	60%
2[a]	25°C	Methanol/1M	--	48 h	75%
3 [a]	65°C	Methanol/0.3M	--	72 h	30%
4 [a,b]	50°C	Methanol/0.3M	--	2.5 h	60%
5 [a,b]	50°C	Methanol/0.3M	$InCl_3$	2.5 h	47%
6 [a,b]	120°C	Methanol/0.3M	--	2 h	75%
7 [a,b]	120°C	Methanol/0.3M	$InCl_3$	2 h	60%
8 [a,b]	120°C	Dichlorometane/ 0.3M	$InCl_3$	2 h	traces
9 [a,b]	120°C	Acetonitrile/ 0.3M	$InCl_3$	2 h	35%

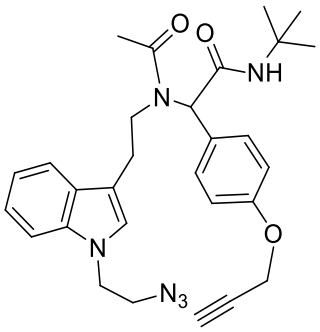
[a] 1eq. amine, 1 eq. aldehyde, 1 eq. acid, 1 eq. isocyanide, catalyst 10% mol.

[b] microwave heating.

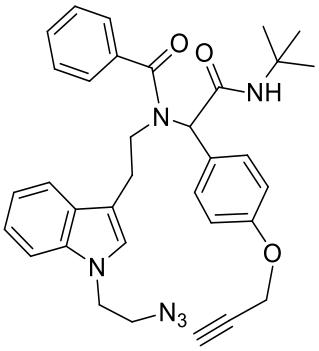
General procedure for the synthesis of Ugi adducts. A solution of 4-(prop-2-yn-1-yloxy)benzaldehyde **7** (0.10 g, 0.624 mmol), acetic acid **9** (0.037 g, 0.624 mmol), 2-(1-(2-azidoethyl)-1H-indol-3-yl)ethanamine **6a-d** (0.142 g, 0.624 mmol), t-butyl isocyanide (0.052g, 0.624 mmol) in MeOH 1M (0.62 mL) was stirred at room temperature for 48

[2] Bioorganic and Medicinal Chemistry Letters **2009**,*19*(24), 7003-7006.

hours. The reaction mixture was concentrated under reduced pressure and purified by flash column chromatography.

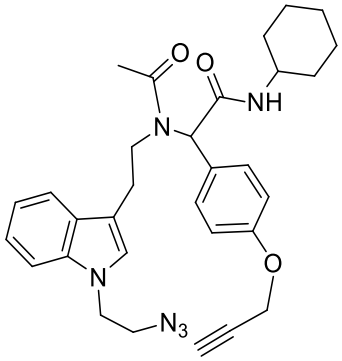


2-(N-(2-(1-(2-azidoethyl)-1H-indol-3-yl)ethyl)acetamido)-N-(tert-butyl)-2-(4-(prop-2-yn-1-yloxy)phenyl)acetamide (10). Obtained as white solid. m.p. 280-282 °C (0.24g, 75%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38 (t, *J* = 9.2 Hz, 2H), 7.20 (dt, *J* = 15.6, 7.7 Hz, 4H), 6.98 (q, *J* = 11.9, 10.7 Hz, 5H), 6.71 (s, 1H), 5.92 (s, 2H), 4.67 (s, 2H), 4.12 (q, *J* = 5.8 Hz, 2H), 3.54 (dt, *J* = 10.3, 7.2 Hz, 4H), 2.50 (s, 1H), 2.19 (s, 3H), 1.32 (s, 10H); δ 13C NMR (75 MHz, $CDCl_3$) δ 171.36, 169.12, 157.44, 135.75, 130.80, 128.60, 127.67, 125.30, 121.74, 119.06, 118.75, 115.00, 112.07, 108.77, 78.11, 75.73, 61.35, 53.31, 51.27, 50.73, 47.67, 45.07, 28.41, 25.46, 21.71; IR (film) γ cm^{-1} 3414, 3357, 2975, 2929, 2101, 1706, 1510, 1465, 1365, 1250, 1171, 1050, 963, 742; HRMS (FAB+, M+) calcd for $C_{29}H_{34}O_3N_6$: [M+1] 514.26, found: 514.27.

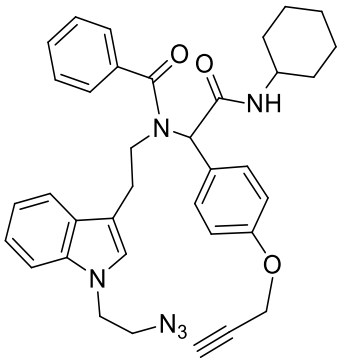


N-(2-(1-(2-azidoethyl)-1H-indol-3-yl)ethyl)-N-(2-(tert-butylamino)-2-oxo-1-(4-(prop-2-yn-1-yloxy)phenyl)ethyl)benzamide (13). Obtained as yellow pale solid. m.p. 268-270 °C (0.23 g, 64%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.58 – 7.47 (m, 2H), 7.47 – 7.44 (m, 6H),

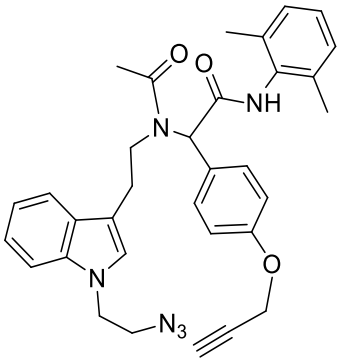
7.13 (d, *J* = 8.1 Hz, 1H), 7.08 – 6.98 (m, 1H), 6.95 - 6.89 (m, 3H), 6.62 (t, *J* = 8.2 Hz, 1H), 5.94 (s, 1H), 5.62 – 5.34 (m, 4H), 4.75 – 4.55 (m, 4H), 4.50 (d, *J* = 9.6 Hz, 2H), 3.65 (ddt, *J* = 23.5, 18.8, 6.9 Hz, 2H), 3.33 – 3.14 (m, 1H), 2.94 (ddd, *J* = 22.0, 12.7, 5.4 Hz, 1H), 2.51 (q, *J* = 5.6, 5.2 Hz, 1H), 1.51 – 1.07 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.68, 168.55, 157.82, 135.89, 135.38, 133.53, 131.19, 127.98, 127.06, 125.66, 121.89, 119.24, 118.80, 115.21, 112.00, 108.93, 78.13, 75.83, 62.30, 55.77, 50.84, 48.00, 45.18, 25.51, 21.75, 18.39; IR (film) γ, cm^{-1} 3289, 3055, 2965, 2926, 2869, 2100, 1676, 1615,1508, 1461, 1221, 1176, 1015, 738, 702, 572, 426; HRMS (FAB+, M+) calcd for $C_{34}H_{36}O_3N_6$: [M+1] 576.28, found: 576.28.



2-(N-(2-(1-(2-azidoethyl)-1H-indol-3-yl)ethyl)acetamido)-N-cyclohexyl-2-(4-(prop-2-yn-1-ylo xy)phenyl)acetamide (11). Obtained as yellow pale solid. m.p. 140-142 °C (0.23g, 67%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42 (d, *J* = 8.4 Hz, 1H), 7.33 – 7.15 (m, 3H), 7.04 (dd, *J* = 22.9, 7.9 Hz, 2H), 6.77 (s, 1H), 5.91 (d, *J* = 8.8 Hz, 1H), 4.74 – 4.64 (m, 2H), 4.17 (t, *J* = 5.9 Hz, 1H), 3.87 – 3.72 (m, 1H), 3.58 (q, *J* = 6.4, 5.3 Hz, 3H), 2.93 – 2.38 (m, 2H), 2.18 (s, 3H), 1.95 – 1.82 (m, 3H), 1.71 – 1.55 (m, 4H), 1.33 (ddd, *J* = 27.7, 11.2, 5.8 Hz, 4H), 1.19 – 1.03 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.49, 168.92, 157.58, 135.89, 130.88, 128.50, 125.51, 121.89, 119.22, 118.87, 115.10, 112.20, 108.88, 75.76, 61.49, 55.75, 50.87, 48.43, 47.98, 45.22, 32.70, 25.46, 25.39, 24.64, 21.80;IR (film) γ, cm^{-1} 3291, 2932, 2855, 2102, 1661, 1630 1510, 1467, 1331, 1231, 1179, 1015, 825; HRMS (FAB+, M+) calcd for $C_{31}H_{37}O_3N_6$: [M+1] 541.29, found: 541.29.

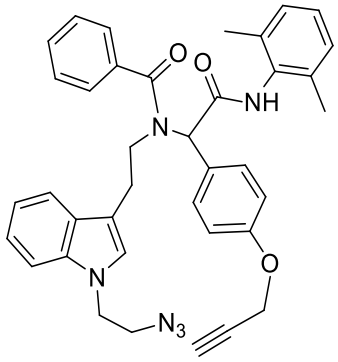


N-(2-(1-(2-azidoethyl)-1H-indol-3-yl)ethyl)-N-(2-(cyclohexylamino)-2-oxo-1-(4-(prop-2-yn-1-yloxy)phenyl)ethyl)benzamide (14). Obtained as yellow pale solid. m.p. 167-169 °C (0.24 g, 65%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.62 – 7.35 (m, 7H), 7.04 (tt, *J* = 38.9, 10.7 Hz, 4H), 6.70 – 5.96 (m, 1H), 4.69 (s, 1H), 4.16 – 4.01 (m, 1H), 3.93 – 3.74 (m, 1H), 3.54 – 3.44 (m, 2H), 2.52 (s, 1H), 2.44 – 2.09 (m, 1H), 1.91 (d, *J* = 12.1 Hz, 2H), 1.70 – 1.58 (m, 2H), 1.45 – 1.26 (m, 2H), 1.12 (q, *J* = 14.9, 13.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.07, 169.08, 157.98, 137.08, 136.17, 131.10, 129.77, 128.95, 126.87, 125.80, 122.04, 119.37, 115.55, 109.03, 78.57, 76.21, 56.16, 51.19, 48.86, 45.47, 33.11, 25.18, 25.07; IR (film), γ cm^{-1} 3293, 3060, 2969, 2102, 1678, 1622, 1601, 1510, 1465, 1365, 1221, 1175, 1016, 744; HRMS (FAB+, M+) calcd for $C_{36}H_{38}O_3N_6$: [M+1] 602.30, found: 602.30.

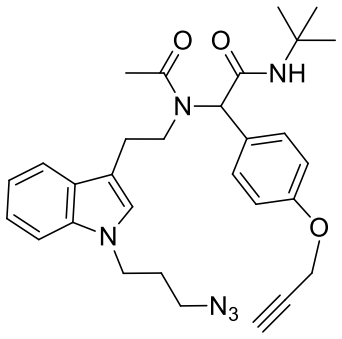


2-(N-(2-(1-(2-azidoethyl)-1H-indol-3-yl)ethyl)acetamido)-N-(2,6-dimethylphenyl)-2-(4-(prop-2-yn-1-yloxy)phenyl)acetamide (12). Obtained as white solid. m.p. 174-176°C (0.16g, 46%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.59 – 7.52 (m, 4H), 7.31 – 7.22 (m, 4H), 7.07 – 7.04 (m, 5H), 6.76 (s, 1H), 6.05 (s, 1H), 4.72 (d, J = 2.4 Hz, 2H), 4.14 (q, J = 7.0, 6.4 Hz, 4H), 3.56 (dt, J = 11.8, 5.9 Hz, 6H), 2.89 (ddd, J = 15.7, 9.8, 5.8 Hz, 1H), 2.54 (q, J = 3.0

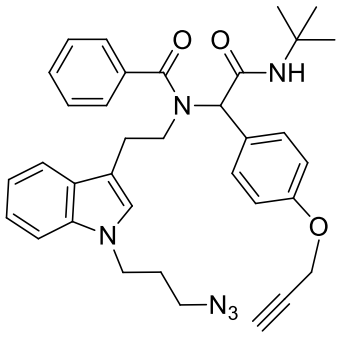
Hz, 3H), 2.16 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.67, 168.55, 157.82, 135.89, 135.37, 133.53, 131.19, 127.97, 125.66, 121.89, 119.24, 118.79, 115.21, 111.99, 108.92, 78.13, 75.83, 62.30, 55.77, 50.84, 48.00, 45.18, 25.51, 21.75, 18.40; IR (film) γ, cm^{-1} 3270, 3130, 3048, 2928, 2863, 2101, 1896, 1665, 1617, 1508, 1467, 1372, 1228, 1176, 1011, 831, 742, 427; HRMS (FAB+, M+) calcd for $C_{33}H_{34}O_3N_6$: [M+1] 562.26, found: 562.26.



N-(2-(1-(2-azidoethyl)-1H-indol-3-yl)ethyl)-N-(2-((2,6-dimethylphenyl)amino)-2-oxo-1-(4-(prop-2-yn-1-yloxy)phenyl)ethyl)benzamide (15). Obtained as yellow pale solid. m.p. 149-151 °C (0.16 g, 40%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.46 – 7.37 (m, 7H), 7.08 - 6.99 (m, 8H), 6.66 – 6.35 (m, 1H), 6.21 (s, 1H), 4.70 (s, 2H), 4.03 – 3.95 (m, 2H), 3.62 – 3.34 (m, 5H), 2.55 (s,1H), 2.12 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.82, 170.92, 168.31, 157.68, 136.41, 135.63, 135.26, 135.08, 133.55, 132.69, 130.93, 129.69, 128.39, 128.03, 127.87, 126.31, 125.33, 121.50, 118.82, 115.08, 108.57, 78.05, 75.77, 60.14, 55.63, 44.86, 30.60, 20.76, 18.38, 13.94; IR (film) γ, cm^{-1} 3274, 3056, 3010, 2936, 2102, 1668, 1611, 1510, 1466, 1377, 1231, 745, 610; HRMS (FAB+, M+) calcd for $C_{38}H_{35}O_3N_6$: [M+1] 623.27, found: 623.27.

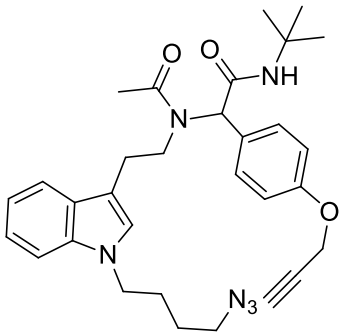


2-(N-(2-(1-(3-azidopropyl)-1H-indol-3-yl)ethyl)acetamido)-N-(tert-butyl)-2-(4-(prop-2-yn-1-yloxy)phenyl)acetamide (16). Obtained as white solid. m.p. 121-123 °C (0.237 g, 72%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40 (d, *J* = 8.3 Hz, 2H), 7.27 (d, *J* = 6.4 Hz, 1H), 7.15 – 6.98 (m, 5H), 6.89 – 6.66 (m, 1H), 5.82 (dt, *J* = 43.0, 10.3 Hz, 1H), 5.21 – 5.13 (m, 1H), 4.65 (d, *J* = 24.7 Hz, 1H), 4.25 – 3.95 (m, 2H), 3.64 – 3.46 (m, 2H), 2.77 (dd, *J* = 15.3, 7.5 Hz, 1H), 2.39 – 2.28 (m, 2H), 2.17 – 2.09 (m, 3H), 1.32 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.33, 169.41, 167.45, 157.83, 131.76, 129.96, 128.94, 128.23, 127.74, 115.05, 114.92, 111.79, 78.19, 75.65, 75.08, 64.30, 58.32, 51.40, 30.57, 29.58, 28.72, 28.51, 28.43, 28.36; IR γ (film) cm-^{1} 3305, 305, 2967, 2929, 2099, 1679, 1624, 1510, 1454, 1223, 1017, 749; HRMS (FAB+, M+) calcd for $C_{30}H_{37}O_3N_6$: [M+1] 529.28, found: 529.28.

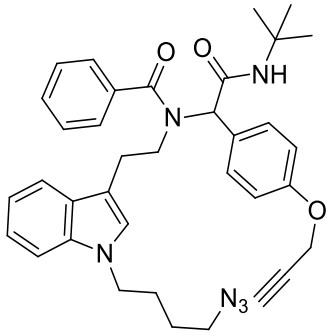


N-(2-(1-(3-azidopropyl)-1H-indol-3-yl)ethyl)-N-(2-(tert-butylamino)-2-oxo-1-(4-(prop-2-yn-1-yloxy)phenyl)ethyl)benzamide (17). Obtained as yellow pale oil. (0.228 g, 62%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.56 – 7.45 (m, 7H), 7.25 – 6.99 (m, 6H), 6.99 – 6.85 (m, 1H), 6.37 (dd, *J* = 95.6, 61.0 Hz, 2H), 4.70 (s, 3H), 4.02 (s, 2H), 3.69 – 3.48 (m, 2H), 3.19 – 3.06 (m, 2H), 2.56 (s, 1H), 2.49 – 2.26 (m, 1H), 2.04 – 1.84 (m, 2H), 1.39 (d, *J* = 5.1 Hz,

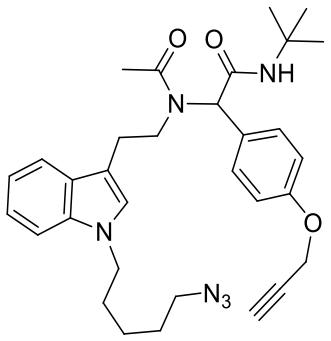
11H);^{13}C NMR (75 MHz, $CDCl_3$) δ 173.02, 169.29, 157.86, 137.09, 136.14, 131.05, 129.63, 128.83, 126.76, 125.61, 121.74, 118.94, 115.43, 109.19, 78.53, 76.22, 56.02, 51.73, 48.48, 42.80, 29.38, 28.81; IR (film) γ, cm^{-1} 3419, 3305, 2967, 2929, 2099, 1679, 1624, 1510, 1223, 1179, 1017, 749; HRMS (FAB+, M+) calcd for $C_{35}H_{38}O_3N_6$: [M+1] 591.30, found: 591.30.



2-(N-(2-(1-(4-azidobutyl)-1H-indol-3-yl)ethyl)acetamido)-N-(tert-butyl)-2-(4-(prop-2-yn-1-yloxy)phenyl)acetamide (18). Obtained as brown solid. m.p. 86-87 °C (0.28g, 82%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.59 (d, J = 7.8 Hz, 1H), 7.45 (d, J = 7.8 Hz, 1H), 7.41 – 7.02 (m, 10H), 7.00 – 6.90 (m, 1H), 6.20 (d, J = 5.0 Hz, 1H), 5.94 (d, J = 4.9 Hz, 1H), 5.53 (s, 1H), 5.39 (s, 1H), 4.12 (t, J = 6.8 Hz, 4H), 3.61 (dq, J = 19.3, 6.4 Hz, 4H), 3.26 (t, J = 6.7 Hz, 2H), 2.97 (q, J = 6.8, 5.1 Hz, 2H), 1.92 (s, 3H), 1.30 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.64, 169.53, 157.75, 136.17, 131.12, 129.05, 127.73, 125.51, 121.73, 118.98, 115.30, 111.48, 109.39, 76.14, 61.62, 60.45, 55.97, 51.54, 51.07, 48.08, 45.60, 28.74, 27.56, 26.44, 22.04, 14.32; IR (film) γ cm^{-1} 3290, 3059, 2962, 2930, 2870, 2094, 1675, 1624, 1508, 1221, 1176, 1011, 741, 522, 427; HRMS (FAB+, M+) calcd for $C_{31}H_{39}O_3N_6$: [M+1] 543.30, found: 543.30.

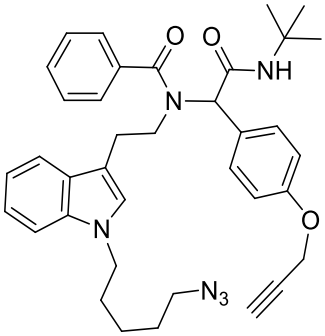


N-(2-(1-(4-azidobutyl)-1H-indol-3-yl)ethyl)-N-(2-(tert-butylamino)-2-oxo-1-(4-(prop-2-yn-1-yloxy)phenyl)ethyl)benzamide (19). Obtained as yellow pale solid. m.p. 108-109 °C (0.1g, 26%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.64 – 7.37 (m, 7H), 7.35 – 6.95 (m, 6H), 6.84 (s, 1H), 6.66 – 6.28 (m, 1H), 6.15 – 5.87 (m, 1H), 5.40 (s, 1H), 5.15 (d, *J* = 5.6 Hz, 1H), 4.96 (d, *J* = 6.9 Hz, 1H), 4.73 – 4.66 (m, 1H), 4.01 (q, *J* = 50.0, 44.6 Hz, 5H), 3.50 (s, 2H), 3.19 (t, *J* = 6.8 Hz, 1H), 2.31 (s, 1H), 1.73 (d, *J* = 19.7 Hz, 2H), 1.36 (q, *J* = 5.1, 3.0 Hz, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.49, 168.91, 157.58, 135.89, 130.88, 128.50, 127.81, 125.51, 121.88, 119.22, 118.87, 115.10, 114.74, 112.20, 108.88, 78.18, 75.76, 61.49, 55.75, 50.87, 48.43, 47.98, 45.22, 32.91, 32.69, 25.46, 25.39, 25.33, 24.68, 24.64, 21.80; IR (film) γ cm^{-1} 3288, 3055, 2960, 2927, 2869, 2094, 1678, 1616, 1508, 1221, 1176, 1017, 740, 702, 427; HRMS (FAB+, M+) calcd for $C_{36}H_{41}O_3N_6$: [M+1] 605.32, found: 605.32.

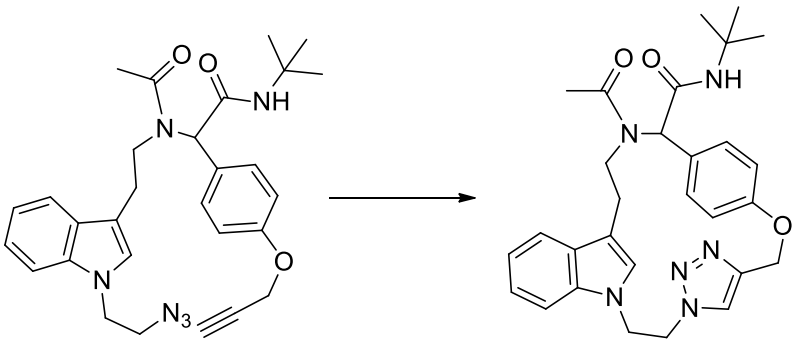


2-(N-(2-(1-(5-azidopentyl)-1H-indol-3-yl)ethyl)acetamido)-N-(tert-butyl)-2-(4-(prop-2-yn-1-yloxy)phenyl)acetamide (20). Obtained as yellow pale solid. m.p. 105-106 °C (0.30g, 85%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.54 – 7.34 (m, 2H), 7.33 – 7.08 (m, 3H), 7.08 – 6.94 (m, 2H), 6.90 (d, *J* = 8.3 Hz, 1H), 6.70 (q, *J* = 10.0, 8.5 Hz, 1H), 5.96 – 5.85 (m, 1H), 5.16 (d, *J* = 4.9 Hz, 1H), 4.99 (d, *J* = 9.6 Hz, 1H), 4.69 (s, 1H), 4.34 – 4.12 (m, 1H), 3.97 (dd, *J* = 11.9, 6.6 Hz, 2H), 3.56 (q, *J* = 7.7, 7.0 Hz, 2H), 2.77 (dd, *J* = 13.5, 6.9 Hz,

1H), 2.18 – 2.10 (m, 3H), 1.94 – 1.67 (m, 4H), 1.33 (s, 9H), 1.35 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.48, 169.26, 158.29, 135.96, 130.94, 127.50, 125.42, 121.51, 118.64, 115.00, 111.16, 109.21, 76.18, 61.94, 51.46, 49.92, 47.96, 45.67, 29.74, 29.47, 28.59, 25.58, 23.77, 21.88; IR (film) γ, cm^{-1} 3292, 3055, 2929, 2865, 2093, 1677, 1623, 1507, 1220, 1177, 1011, 740, 521, 426; HRMS (FAB+, M+) calcd for $C_{32}H_{41}O_3N_6$: [M+1] 557.32, found: 557.32.

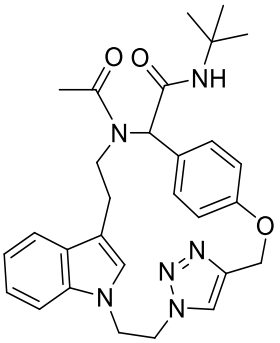


N-(2-(1-(5-azidopentyl)-1H-indol-3-yl)ethyl)-N-(2-(tert-butylamino)-2-oxo-1-(4-(prop-2-yn-1-yloxy)phenyl)ethyl)benzamide (21). Obtained as brown oil (0.23g, 59%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44 (d, *J* = 9.4 Hz, 7H), 7.18 – 6.96 (m, 4H), 6.95 – 6.77 (m, 1H), 6.67 – 6.32 (m, 1H), 6.14 – 5.84 (m, 1H), 5.17 (d, *J* = 6.2 Hz, 1H), 4.97 (d, *J* = 11.1 Hz, 1H), 4.69 (s, 1H), 4.32 – 4.06 (m, 2H), 4.00 – 3.73 (m, 1H), 3.48 (dq, *J* = 18.6, 10.0, 7.6 Hz, 1H), 2.77 – 2.01 (m, 1H), 1.92 – 1.63 (m, 3H), 1.57 (s, 9H), 1.36 (d, *J* = 3.5 Hz, 9H), 1.00 – 0.80 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.82, 170.92, 157.68, 136.41, 135.63, 135.25, 130.92, 129.68, 129.22, 128.39, 128.03, 127.87, 126.92, 126.31, 125.33, 121.49, 118.82, 115.08, 108.57, 78.05, 75.77, 60.14, 55.62, 50.61, 44.85, 30.60, 20.76, 18.37, 13.94; IR (film) γ cm^{-1} 3303, 3059, 2965, 2937, 2869, 2097, 1680, 1621, 1510, 1453, 1224, 1179, 1020, 748; HRMS (FAB+, M+) calcd for $C_{37}H_{43}O_3N_6$: [M+1] 619.33, found: 619.33.

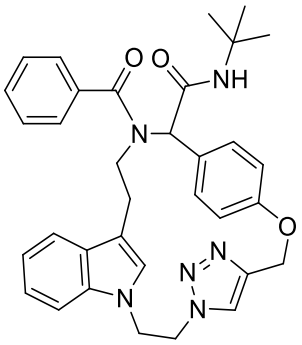


10 22

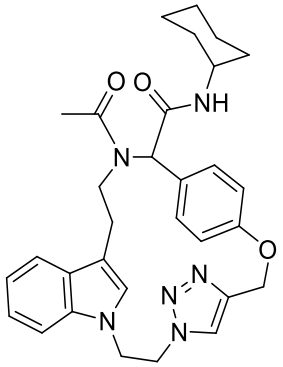
General procedure for the synthesis of macrocycles. A solution of 2-(*N*-(2-(1-(2-azidoethyl)-*1H*-indol-3-yl)ethyl)acetamido)-*N*-(tert-butyl)-2-(4-(prop-2-yn-1-yloxy)phenyl)acetamide (0.10 g, 0.194 mmol), copper bromide (0.01 g, 0.077 mmol), 1,8-diazabicyclo[5.4.0]undec-7-ene (0.029 g, 0.194 mmol), in toluene 0.005M (38.8 mL) was heated to 110 ºC, under microwave irradiation (300 W) for 2 hours. The reaction mixture was concentrated under reduced pressure and purified by TLC (9:1 DCM / Methanol).



Macrocycle 22. Obtained as white solid. m.p. 278-280 °C (0.075g, 75%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44 (d, *J* = 7.9 Hz, 1H), 7.24 (t, *J* = 5.7 Hz, 3H), 7.11 (ddd, *J* = 8.2, 6.4, 1.7 Hz, 1H), 7.04 (s, 1H), 6.90 (d, *J* = 8.3 Hz, 2H), 5.80 (s, 1H), 5.63 (s, 1H), 5.55 (d, *J* = 6.9 Hz, 1H), 5.50 – 5.30 (m, 2H), 4.81 – 4.37 (m, 4H), 3.48 – 3.10 (m, 1H), 2.73 (td, *J* = 13.7, 5.6 Hz, 1H), 2.28 (s, 3H), 1.94 (ddd, *J* = 15.4, 12.2, 4.4 Hz, 1H), 1.34 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.20, 169.53, 157.25, 135.38, 128.03, 127.57, 125.06, 123.61, 122.32, 119.73, 119.12, 112.19, 108.68, 62.00, 61.81, 51.74, 51.08, 46.36, 46.29, 28.74, 25.16, 22.07; IR (film) γ, cm^{-1} 3383, 3013, 2978, 2933, 1799, 1693, 1600, 1509, 1310, 1253, 1217, 1164, 1026, 833, 757, 667; HRMS (FAB+, M+) calcd for $C_{29}H_{35}O_3N_6$: [M+1] 515.27, found: 515.27.

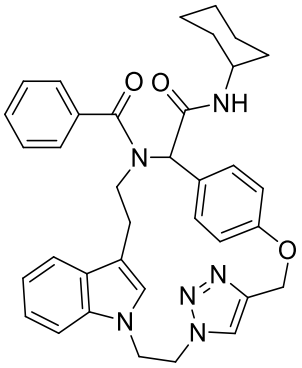


Macrocycle 25. Obtained as white solid. m.p. 276-278 °C (0.067g, 67%) ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44 (d, *J* = 3.0 Hz, 5H), 7.21 – 7.07 (m, 5H), 6.92 (dd, *J* = 12.2, 7.9 Hz, 4H), 6.59 (d, *J* = 8.0 Hz, 1H), 5.94 (s, 1H), 5.77 (s, 1H), 5.59 – 5.31 (m, 4H), 4.72 – 4.60 (m, 1H), 4.51 – 4.38 (m, 3H), 3.28 – 2.86 (m, 3H), 2.48 (td, *J* = 13.5, 5.2 Hz, 1H), 1.99 (qd, *J* = 14.6, 13.1, 5.7 Hz, 3H), 1.38 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.54, 168.95, 157.10, 143.91, 137.03, 135.13, 129.15, 128.43, 127.45, 127.10, 126.26, 124.55, 123.45, 121.85, 119.20, 112.13, 108.26, 62.19, 61.54, 51.58, 51.04, 50.49, 46.85, 45.62, 29.49, 28.55, 25.47; IR (film) γ, cm_{-1} 3402, 3050, 2971, 2929, 1672, 1629, 1510, 1458, 1390, 1364, 1176, 996, 991, 867, 733, 698, 521, 450; HRMS (FAB+, M+) calcd for $C_{34}H_{37}O_3N_6$: [M+1] 577.26, found: 577.29.

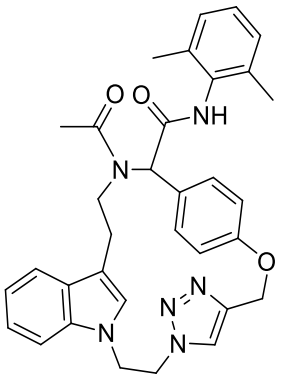


Macrocycle 23. Obtained as yellow pale solid. m.p. 110-112 °C (0.086g, 86%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43 (d, *J* = 7.8 Hz, 2H), 7.29 – 7.17 (m, 3H), 7.14 – 7.03 (m, 2H), 6.88 (d, *J* = 8.3 Hz, 2H), 5.85 (s, 1H), 5.79 (d, *J* = 7.9 Hz, 1H), 5.60 (s, 1H), 5.38 (q, *J* = 14.4 Hz, 6H), 3.78 (s, 0H), 3.31 (t, *J* = 14.2 Hz, 2H), 3.15 (d, *J* = 17.0 Hz, 0H), 2.84 – 2.64 (m, 1H), 2.26 (s, 2H), 2.17 (d, *J* = 10.6 Hz, 1H), 1.91 (d, *J* = 10.1 Hz, 6H), 1.63 (d, *J* = 13.4 Hz, 2H), 1.41 – 0.84 (m, 8H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.08, 169.12, 157.06,

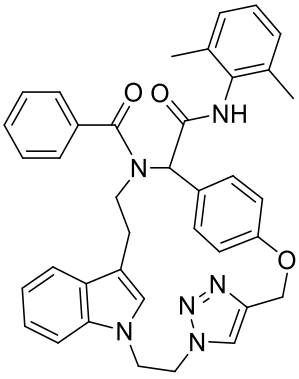
143.96, 135.24, 127.79, 127.21, 124.84, 123.42, 122.13, 119.54, 118.89, 111.97, 108.54, 61.58, 50.90, 48.56, 46.15, 32.70, 25.41, 24.93, 24.64, 21.85; IR (film) γ, cm^{-1} 3274, 2928, 2853, 1628, 1508, 1447, 1369, 1216, 1174, 1000, 731, 644, 560, 503, 424; HRMS (FAB+, M+) calcd for $C_{33}H_{39}O_4N_3$: [M+1] 541.29, found: 541.29.



Macrocycle 26. Obtained as yellow pale solid. m.p. 251-252 °C (0.070g, 70%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.53 – 7.49 (m, 2H), 7.45 (d, *J* = 3.7 Hz, 4H), 7.40 (s, 1H), 7.26 (s, 1H), 7.14 (t, *J* = 8.3 Hz, 1H), 7.07 (s, 1H), 6.90 (dd, *J* = 15.0, 7.5 Hz, 3H), 6.58 (d, *J* = 7.8 Hz, 1H), 6.01 (s, 1H), 5.72 (d, *J* = 8.1 Hz, 1H), 5.53 – 5.29 (m, 1H), 4.73 – 4.33 (m, 4H), 3.86 (dtt, *J* = 11.4, 8.4, 4.0 Hz, 1H), 3.21 (dp, *J* = 20.2, 7.2, 6.0 Hz, 1H), 2.90 (ddd, *J* = 15.1, 12.1, 5.0 Hz, 1H), 2.51 (td, *J* = 13.6, 5.2 Hz, 1H), 2.00 – 1.92 (m, 3H), 1.81 – 1.55 (m, 5H), 1.45 – 1.28 (m, 2H), 1.25 (s, 1H), 1.12 (ddd, *J* = 25.3, 15.6, 8.1 Hz, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.57, 168.81, 157.13, 137.00, 135.26, 129.15, 128.45, 127.44, 126.90, 126.23, 124.52, 123.45, 121.86, 119.22, 118.80, 112.14, 112.14, 108.27, 61.88, 61.57, 51.06, 48.71, 46.91, 45.61, 32.73, 25.41, 24.65; IR (film) γ, cm^{-1} 3404, 3120, 3067, 2924, 2851, 1667, 1628, 1509, 1360, 1131, 995, 733, 699, 517, 424; HRMS (FAB+, M+) calcd for $C_{36}H_{39}O_3N_6$: [M+1] 603.30, found: 603.30

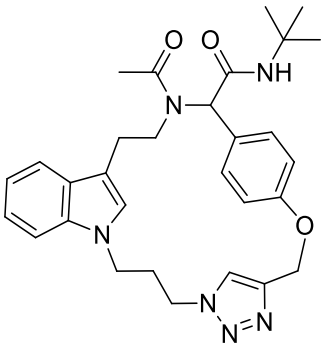


Macrocycle 24. Obtained as brown solid. m.p. 174-175 °C (0.060g, 60%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.49 (d, J = 7.5 Hz, 1H), 7.38 (d, J = 7.9 Hz, 1H), 7.22 (q, J = 8.4, 7.8 Hz, 2H), 7.15 – 6.97 (m, 4H), 6.91 (d, J = 8.0 Hz, 2H), 6.00 (d, J = 6.9 Hz, 1H), 5.67 (d, J = 7.1 Hz, 1H), 5.34 (d, J = 4.4 Hz, 1H), 4.63 (td, J = 12.4, 11.9, 5.8 Hz, 1H), 4.47 (dt, J = 12.1, 5.5 Hz, 2H), 3.63 – 3.24 (m, 1H), 3.13 – 2.88 (m, 1H), 2.70 (tt, J = 19.9, 9.7 Hz, 1H), 2.18 (s, 10H), 2.06 – 1.92 (m, 1H), 1.25 (d, *J* = 6.2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.12, 169.12, 157.22, 143.70, 135.70, 135.28, 133.58, 127.99, 127.73, 127.15, 126.40, 124.95, 123.53, 122.09, 119.51, 118.85, 111.72, 108.57, 62.14, 61.24, 50.74, 46.03, 45.78, 21.78, 18.40; IR (film) γ cm^{-1} 3238, 3129, 2922, 2855, 1673, 1610, 1465, 1370, 1219, 1174, 998, 771, 737,505, 424; HRMS (FAB+, M+) calcd for $C_{33}H_{35}O_3N_6$: [M+1] 563.27, found: 563.27.

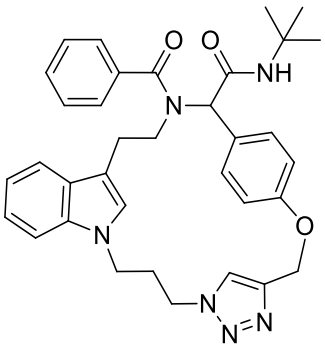


Macrocycle 27. Obtained as white solid. m.p. 172-174 °C (0.080g, 80%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.46 (s, 1H), 7.38 (d, *J* = 7.8 Hz, 1H), 7.22 (d, *J* = 7.0 Hz, 3H), 7.15 – 6.97 (m, 8H), 6.91 (d, *J* = 8.4 Hz, 3H), 6.01 (s, 1H), 5.68 (s, 1H), 5.34 (d, *J* = 4.7 Hz, 2H), 4.72 – 4.39 (m, 5H), 3.35 (ddd, *J* = 17.1, 13.0, 4.5 Hz, 1H), 3.06 (ddd, *J* = 15.7, 12.3, 5.4 Hz, 1H), 2.81 – 2.58 (m, 1H), 2.18 (s, 7H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.12, 169.10,

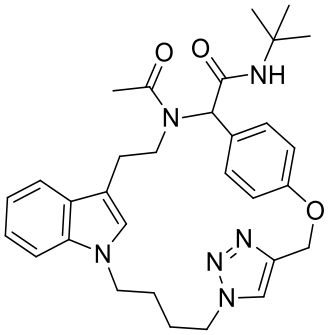
157.23, 143.72, 135.70, 135.28, 133.56, 128.00, 127.74, 127.17, 126.40, 124.94, 123.53, 122.11, 119.53, 118.87, 111.75, 108.57, 62.15, 61.28, 50.77, 46.03, 45.82, 30.83, 24.99, 21.80, 18.41; IR(film) γ, cm^{-1} 3252, 3129, 2924, 2858, 1674, 1611, 1506, 1466, 1370 1219, 1174, 998, 771, 739, 505, 425; HRMS (FAB+, M+) calcd for $C_{36}H_{39}O_3N_6$: [M+1] 603.30, found: 603.30.



Macrocycle 28. Obtained as yellow pale solid. m.p. 255-256 °C (0.048g, 48%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45 (t, *J* = 8.7 Hz, 3H), 7.27 (d, *J* = 5.9 Hz, 3H), 7.18 (d, *J* = 18.2 Hz, 2H), 7.05 (dd, *J* = 26.4, 8.0 Hz, 3H), 6.02 (s, 1H), 5.66 – 5.35 (m, 4H), 4.74 – 4.57 (m, 1H), 4.31 – 4.02 (m, 2H), 3.79 (ddd, *J* = 15.2, 10.8, 4.4 Hz, 1H), 3.52 (dddd, *J* = 22.9, 17.3, 11.7, 4.8 Hz, 2H), 3.29 (ddd, *J* = 15.9, 12.1, 4.6 Hz, 1H), 2.79 (dt, *J* = 11.1, 4.1 Hz, 1H), 2.65 (td, *J* = 12.7, 5.8 Hz, 1H), 2.52 – 2.37 (m, 1H), 2.26 (s, 3H), 1.31 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.00, 169.03, 157.26, 144.07, 135.19, 128.72, 128.07, 127.35, 123.66, 121.80, 119.33, 118.28, 110.77, 109.45, 61.72, 60.53, 51.54, 48.73, 45.96, 42.00, 28.57, 26.70, 24.81, 21.75; IR (KBr) γ, cm^{-1} 3393, 2964, 2926, 1666, 1629, 1508, 1455, 1367, 1216, 1178, 994, 809, 741, 504; HRMS (FAB+, M+) calcd for $C_{30}H_{37}O_3N_6$: [M+1] 529.29, found: 529.29.

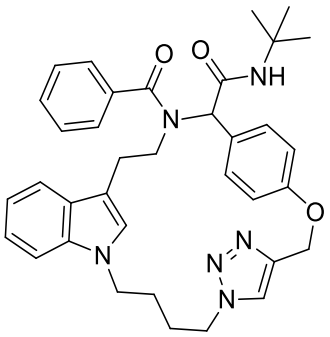


Macrocycle 29. Obtained as white solid. m.p. 276-277 °C (0.059g, 59%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.56 (d, *J* = 8.3 Hz, 2H), 7.44 (d, *J* = 5.0 Hz, 7H), 7.24 (d, *J* = 9.5 Hz, 1H), 7.19 – 6.95 (m, 5H), 6.90 – 6.77 (m, 1H), 6.48-6.15 (m, 1H), 5.62 (d, *J* = 10.4 Hz, 1H), 5.58 – 5.36 (m, 2H), 4.10 (dd, *J* = 26.3, 14.4 Hz, 2H), 3.82 – 3.68 (m, 1H), 3.56 – 3.28 (m, 2H), 3.19 (d, *J* = 11.2 Hz, 1H), 2.81 – 2.65 (m, 1H), 2.39 – 1.54 (m, 1H), 1.35 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.52, 168.66, 157.36, 144.01, 136.90, 135.07, 129.17, 128.54, 128.40, 126.97, 126.39, 123.65, 121.57, 119.00, 118.32, 110.76, 109.10, 61.71, 61.04, 51.62, 49.10, 45.94, 41.83, 28.61, 26.63, 25.07; IR γ (KBr) cm^{-1} 3406, 2967, 2928, 1673, 1627, 1510, 1218, 1178, 998, 830, 738, 697; HRMS (FAB+, M+) calcd for $C_{35}H_{39}O_3N_6$: [M+1] 591.30, found: 591.30.

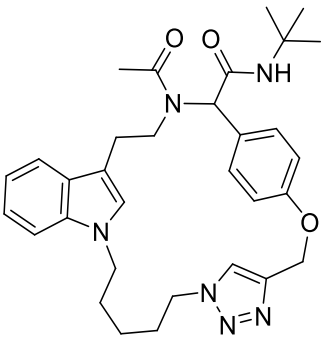


Macrocycle 30. Obtained as yellow solid. m.p. 93-94 °C (0.048g, 48%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45 (dt, *J* = 7.8, 1.0 Hz, 1H), 7.37 – 7.33 (m, 2H), 7.30 (s, 1H), 7.24 – 7.13 (m, 4H), 7.06 (ddd, *J* = 8.0, 6.7, 1.4 Hz, 1H), 6.96 – 6.92 (m, 2H), 6.06 (d, *J* = 77.9 Hz, 2H), 5.54 (s, 1H), 5.39 (s, 1H), 4.44 (dd, *J* = 13.6, 6.7 Hz, 1H), 4.10 (tt, *J* = 12.7, 6.0 Hz, 3H), 3.92 – 3.82 (m, 1H), 3.47 (ddd, *J* = 15.4, 12.7, 5.5 Hz, 2H), 3.33 – 3.20 (m, 1H), 2.87 (td, *J* = 13.4, 5.1 Hz, 1H), 2.30 (s, 3H), 2.26 – 2.21 (m, 1H), 2.20 – 2.07 (m, 2H), 1.34 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.32, 169.33, 157.64, 144.79, 136.02, 131.32, 127.95, 127.39, 124.01, 121.88, 121.68, 118.98, 118.52, 115.10, 111.78, 109.06, 62.01, 61.17,

51.54, 49.76, 46.97, 44.54, 28.60, 27.61, 26.58, 25.24, 21.89; IR γ (film) cm^{-1} 3302, 2961, 2921, 2853, 1675, 1625, 1508, 1452, 1217, 1176, 1003, 738, 520; HRMS (FAB+, M+) calcd for $C_{31}H_{39}O_3N_6$: [M+1] 543.30, found: 543.30.

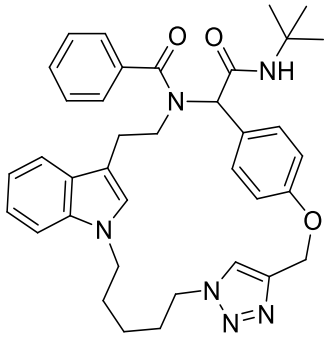


Macrocycle 31. Obtained as brown solid. m.p. 82-83 °C (0.092g, 92%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.46 (qd, *J* = 9.3, 6.1, 4.9 Hz, 9H), 7.27 (d, *J* = 9.4 Hz, 1H), 7.15 – 7.01 (m, 3H), 6.97 (d, *J* = 8.4 Hz, 2H), 6.80 (q, *J* = 7.0 Hz, 1H), 6.34 (d, *J* = 7.7 Hz, 1H), 6.07 (d, *J* = 12.1 Hz, 1H), 5.80 (d, *J* = 11.5 Hz, 1H), 5.39 (s, 2H), 5.29 – 5.09 (m, 1H), 4.39 (dt, *J* = 13.6, 6.4 Hz, 1H), 4.12 – 3.97 (m, 2H), 3.97 – 3.73 (m, 2H), 3.56 – 3.00 (m, 1H), 2.76 – 2.50 (m, 1H), 2.18 – 1.99 (m, 2H), 1.67 – 1.55 (m, 5H), 1.36 (d, *J* = 5.7 Hz, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.70, 168.87, 157.52, 136.86, 135.79, 131.29, 128.59, 127.71, 126.46, 124.02, 121.92, 121.37, 118.61, 115.19, 108.73, 61.82, 51.54, 49.69, 44.98, 44.38, 29.57, 28.56, 26.32; IR (KBr) γ, cm^{-1} 2962, 2866, 1677, 1616,1219, 1177, 1011, 735, 525; HRMS (FAB+, M+) calcd for $C_{36}H_{40}N_6O_3$: 605.32, found: 605.32.

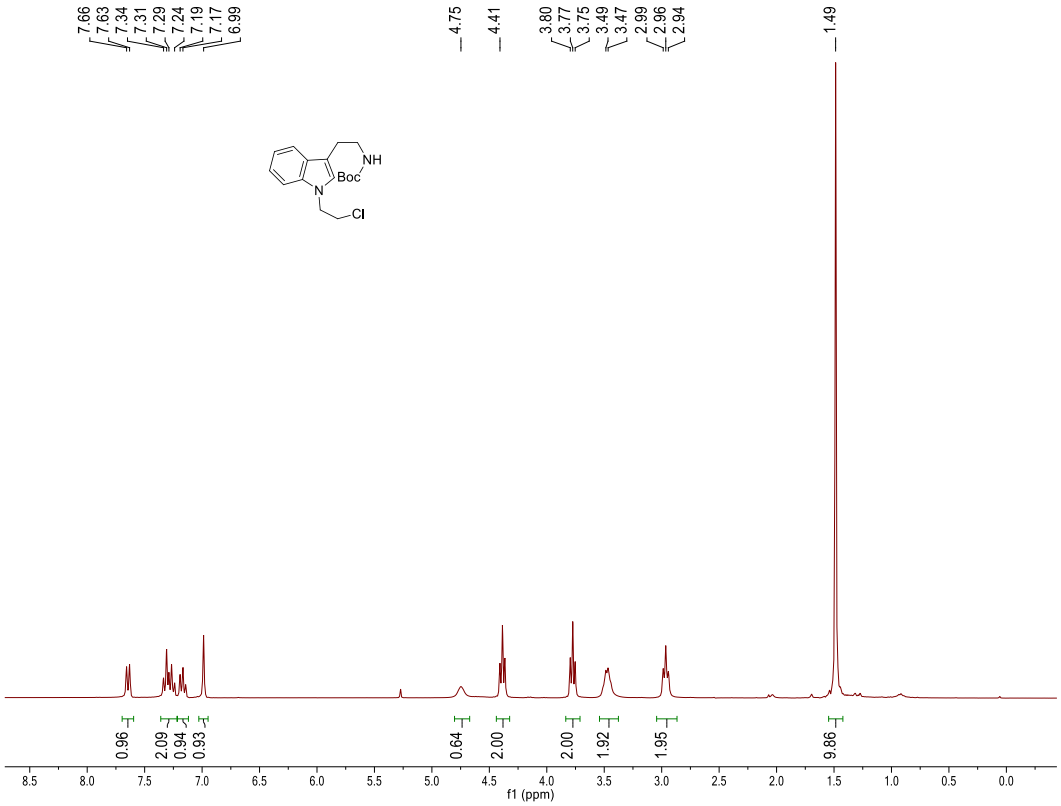


Macrocycle 32. Obtained as brown solid. M.p. 98-100 °C (0.038g, 38%)^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41 (t, *J* = 8.4 Hz, 3H), 7.31 – 7.20 (m, 1H), 7.19 – 6.98 (m, 5H), 6.24 (s,

1H), 6.02 (s, 1H), 5.65 (s, 1H), 5.35 (s, 2H), 4.12 (ddt, *J* = 14.1, 10.5, 5.4 Hz, 2H), 4.04 – 3.82 (m, 2H), 3.66 – 3.28 (m, 4H), 2.66 – 2.52 (m, 1H), 2.18 (s, 3H), 1.98 (ddd, *J* = 13.9, 11.4, 5.2 Hz, 1H), 1.78 – 1.53 (m, 3H), 1.31 (s, 9H), 1.06 – 0.91 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.39, 169.29, 157.90, 143.97, 135.59, 131.51, 128.15, 127.65, 125.69, 122.35, 121.48, 118.85, 118.49, 115.22, 110.71, 109.34, 61.72, 60.71, 53.36, 51.50, 50.27, 47.15, 46.22, 29.58, 28.64, 28.56, 28.30, 25.35, 24.12, 21.76. IR (KBr) γ, cm^{-1} 3304, 2925, 2863, 1675, 1623, 1508, 1362, 1217, 1177, 734, 427; HRMS (FAB+, M+) calcd for $C_{32}H_{40}N_6O_3$: 556.32, found: 556.32.



Macrocycle 33. Obtained as yellow solid. M.p. 99-100 °C (0.052g, 52%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.63 – 7.37 (m, 12H), 7.29 – 6.98 (m, 4H), 6.82 (q, *J* = 7.8, 7.1 Hz, 1H), 6.64 – 6.26 (m, 1H), 6.20 – 6.00 (m, 1H), 5.46 – 5.07 (m, 2H), 4.32 – 3.20 (m, 6H), 2.74 – 2.02 (m, 1H), 1.67 (tt, *J* = 18.4, 9.4 Hz, 3H), 1.45 – 0.79 (m, 13H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.82, 168.99, 158.38, 157.97, 133.00, 131.73, 130.80, 129.93, 128.57, 128.27, 126.49, 121.29, 118.54, 115.19, 109.04, 61.92, 55.83, 51.59, 50.33, 46.01, 29.62, 28.63, 28.33, 24.08, 23.68; IR (KBr) γ, cm^{-1} 3302, 3056, 2927, 1677, 1615, 1508, 1450, 1220, 1177, 732, 427; ; HRMS (FAB+, M+) calcd for $C_{37}H_{43}N_6O_3$: 619.33, found: 619.33.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7.17
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3.49
3.47
2.99
2.96
2.94
1.49
NH
Boc
N
Cl
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0.94
0.93
0.64
2.00
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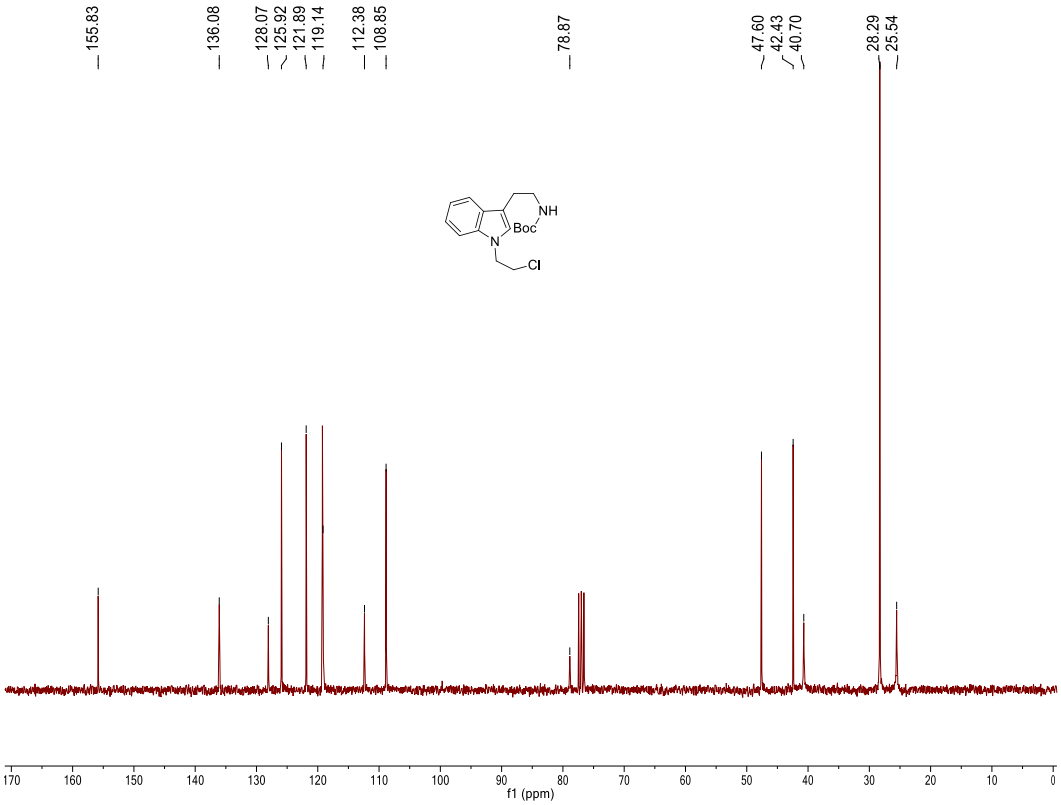
9.86
f1 (ppm)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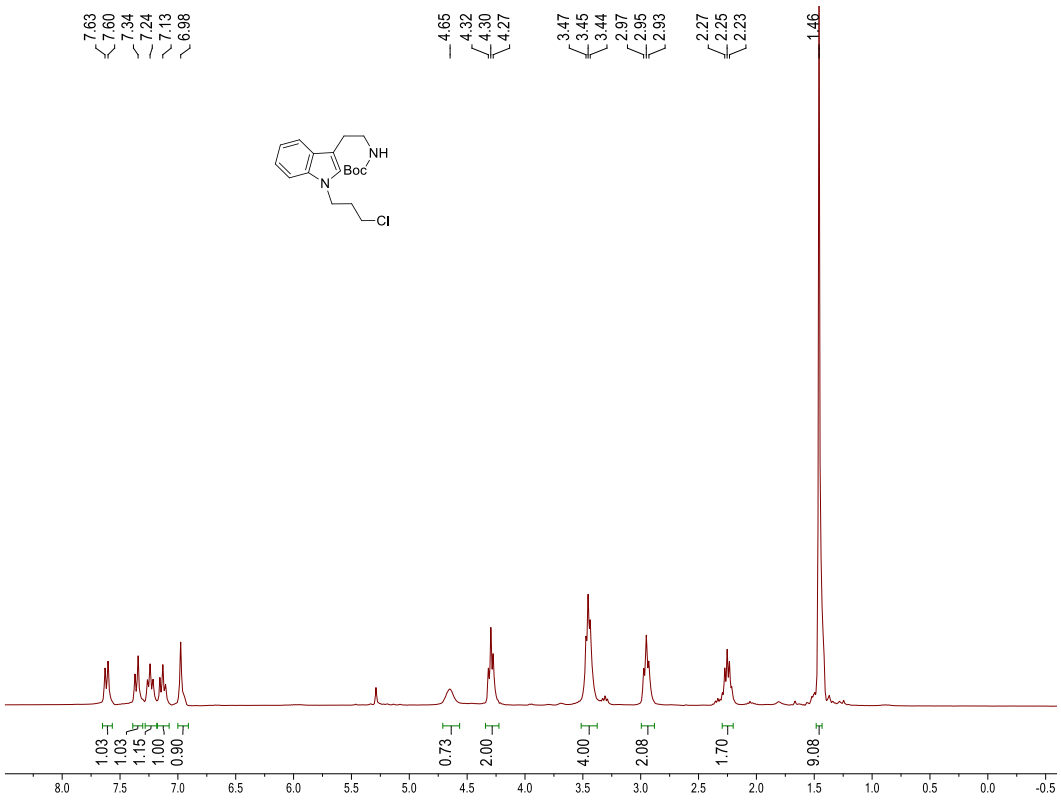
NH
Boc
N
Cl
f1 (ppm)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2.93
2.27
2.25
2.23
1.46
NH
Boc
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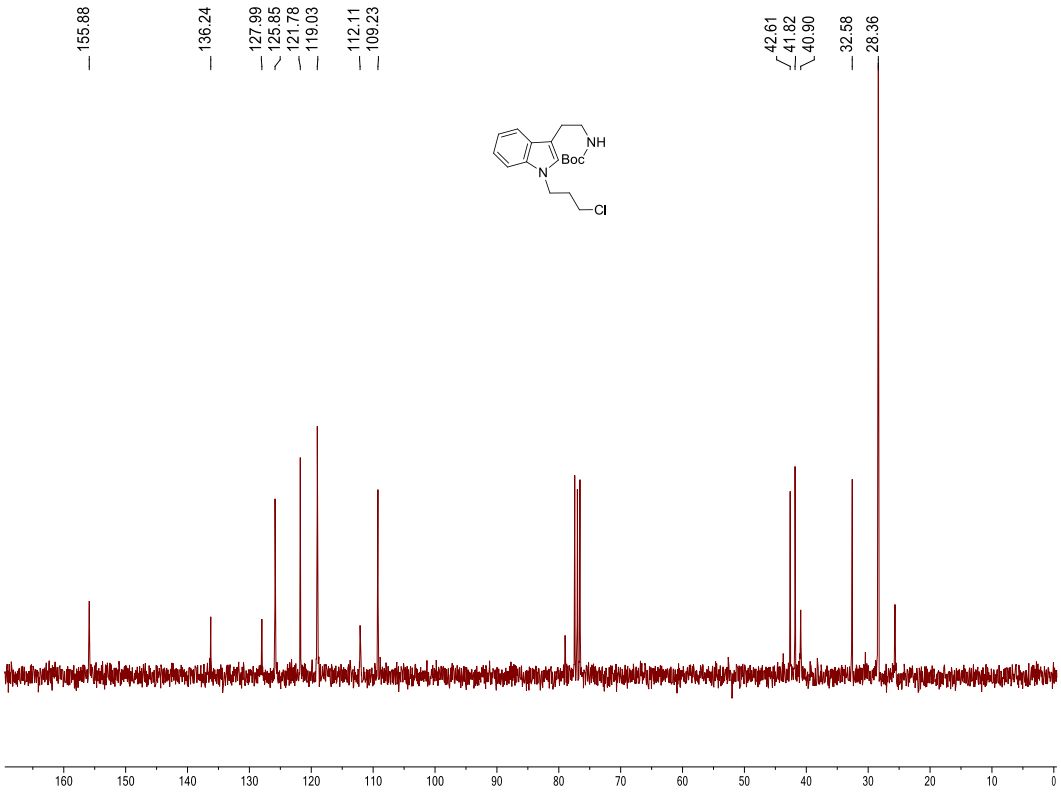
9.08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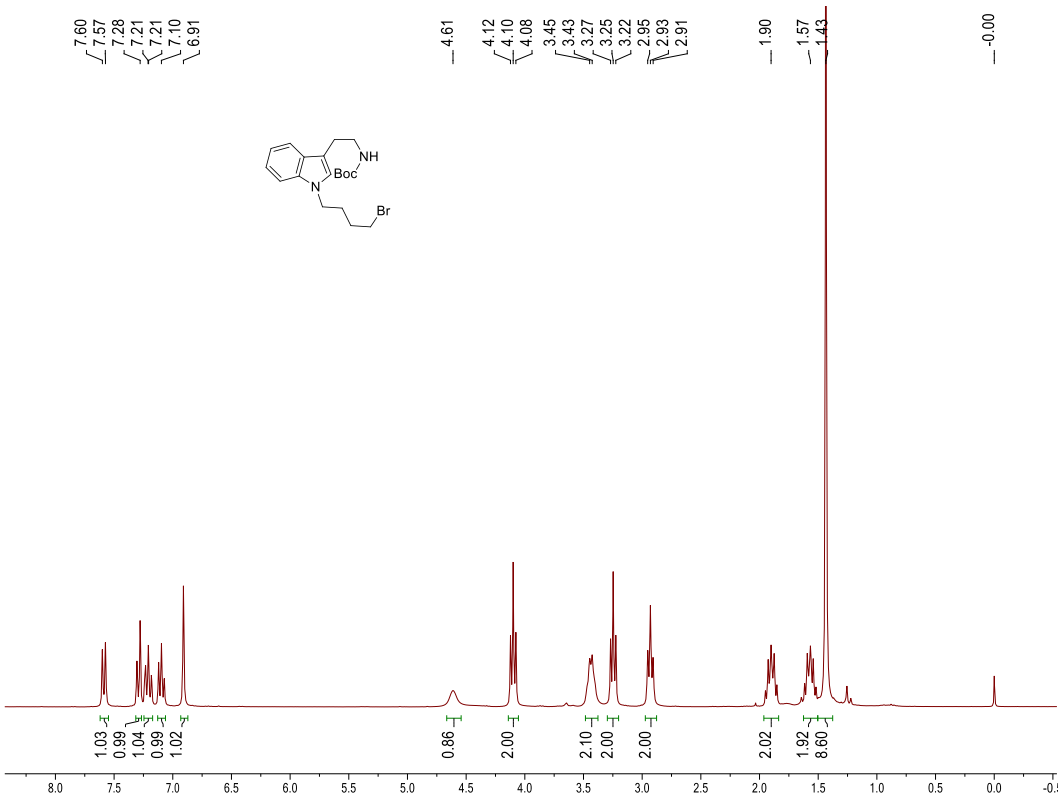
Boc
N
Cl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3.22
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2.93
2.91
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1.43
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Boc
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Br
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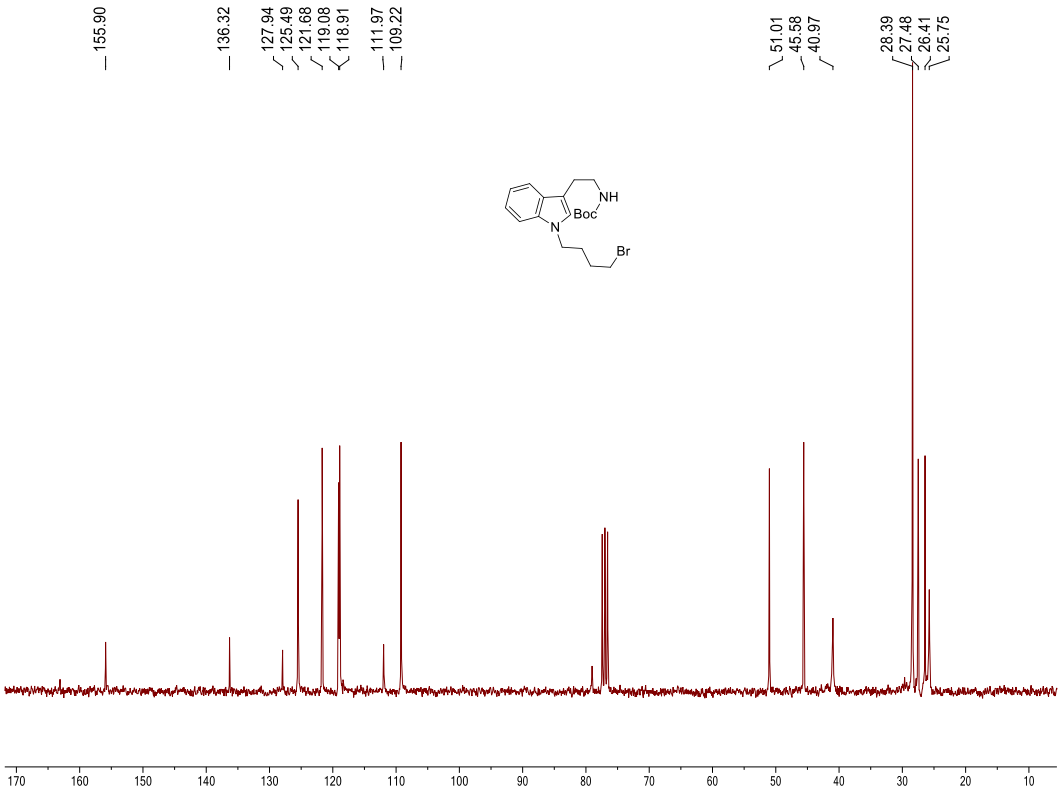
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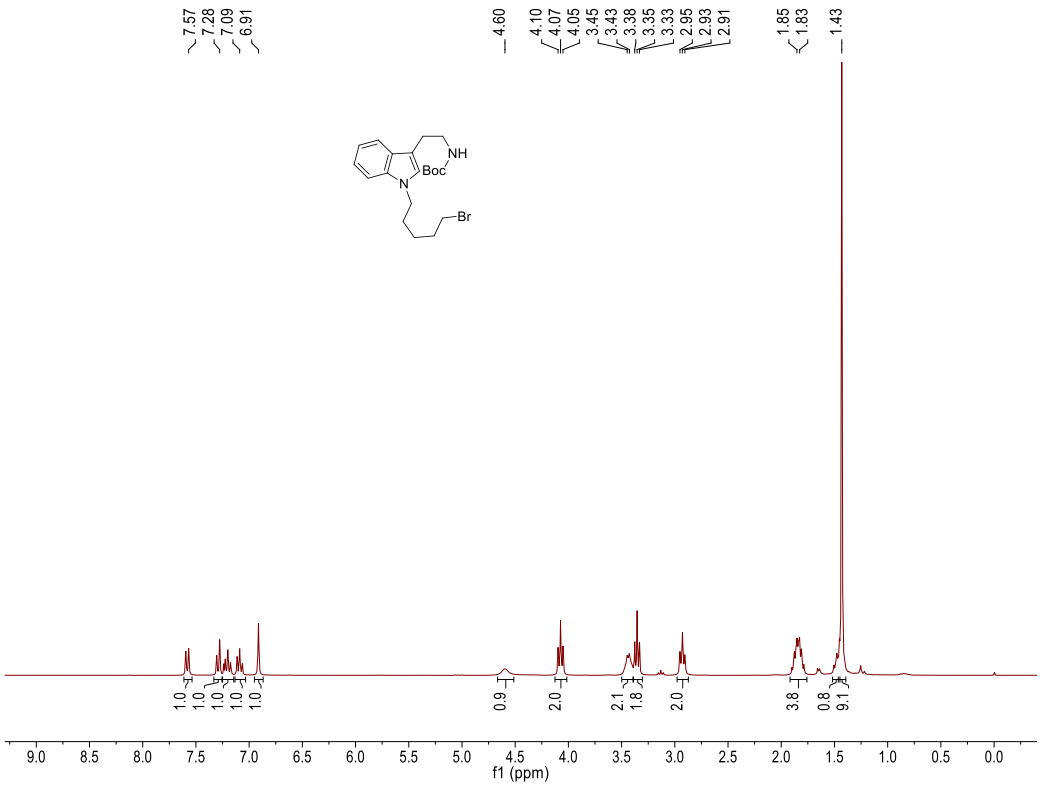
Br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4.07
4.05
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3.38
3.35
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2.91
1.85
1.83
1.43
NH
Boc
N
Br
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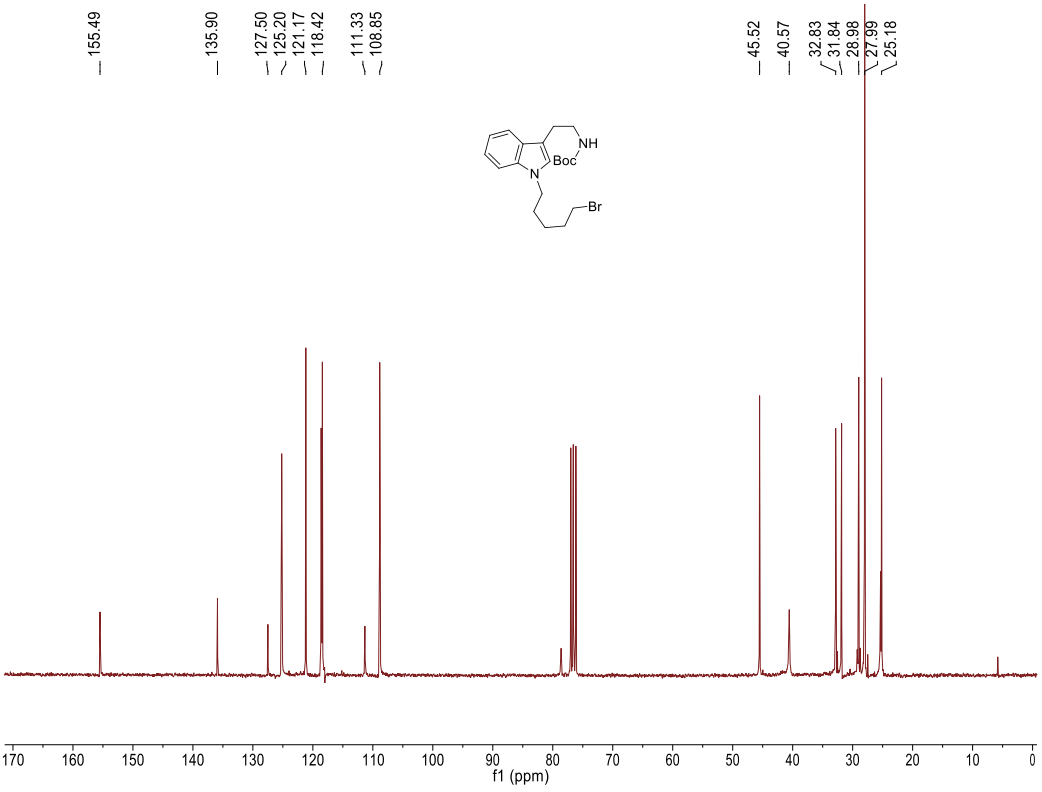
1.0
1.0
1.0
1.0
0.9
2.0
2.1
1.8
2.0
3.8
0.8
9.1
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)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NH
Boc
N
Br
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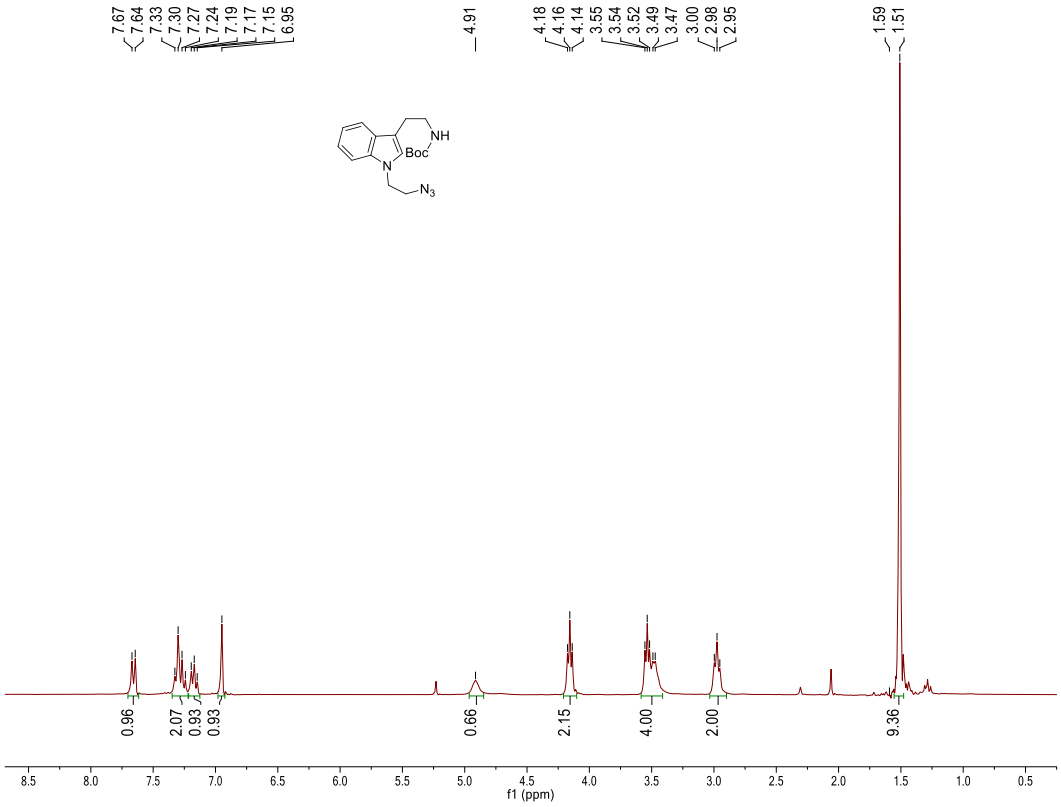
f1 (ppm)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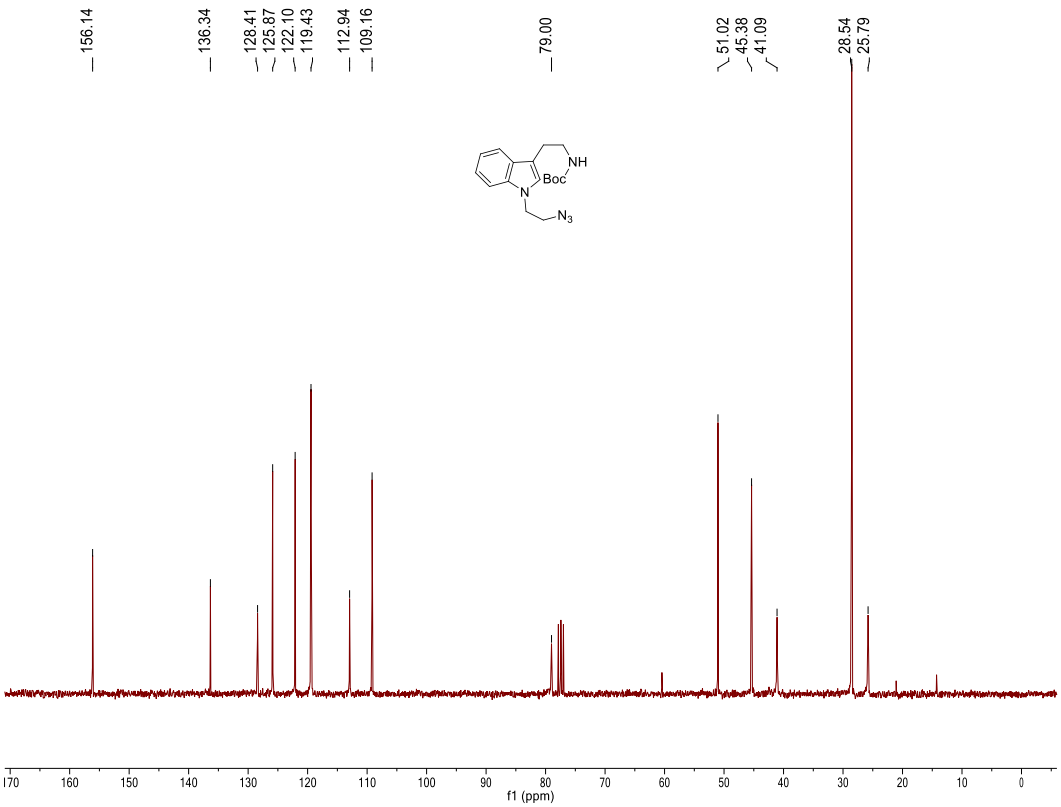
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Boc
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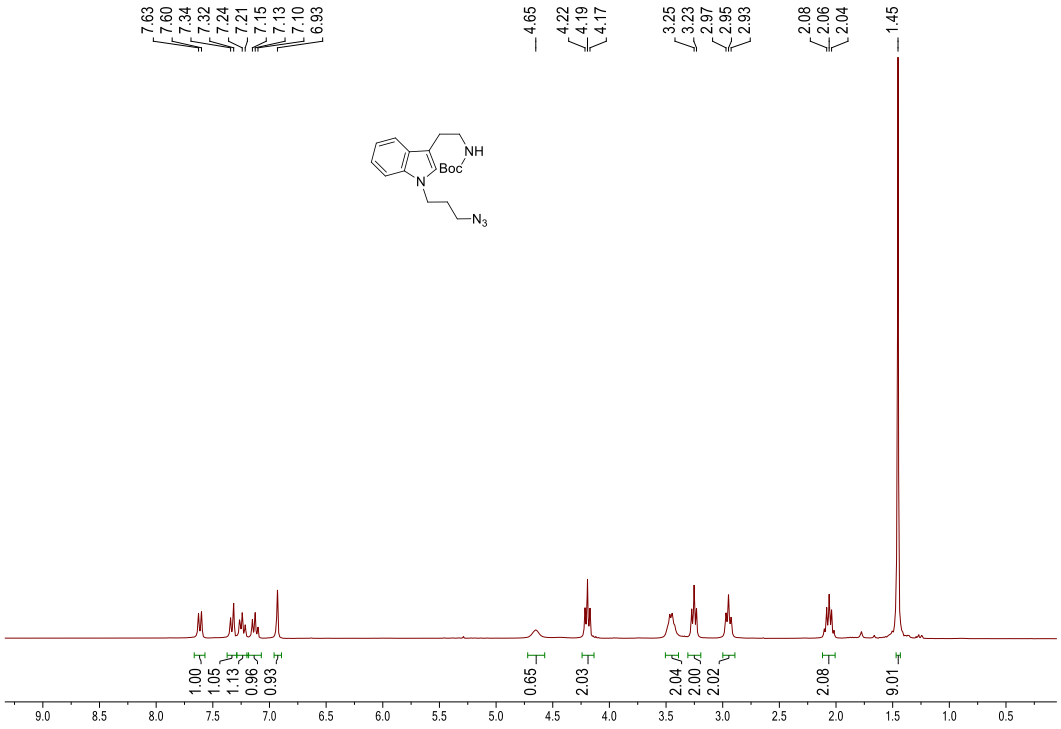
N3
f1 (ppm)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4.19
4.17
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3.23
2.97
2.95
2.93
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2.06
2.04
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Boc
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N3
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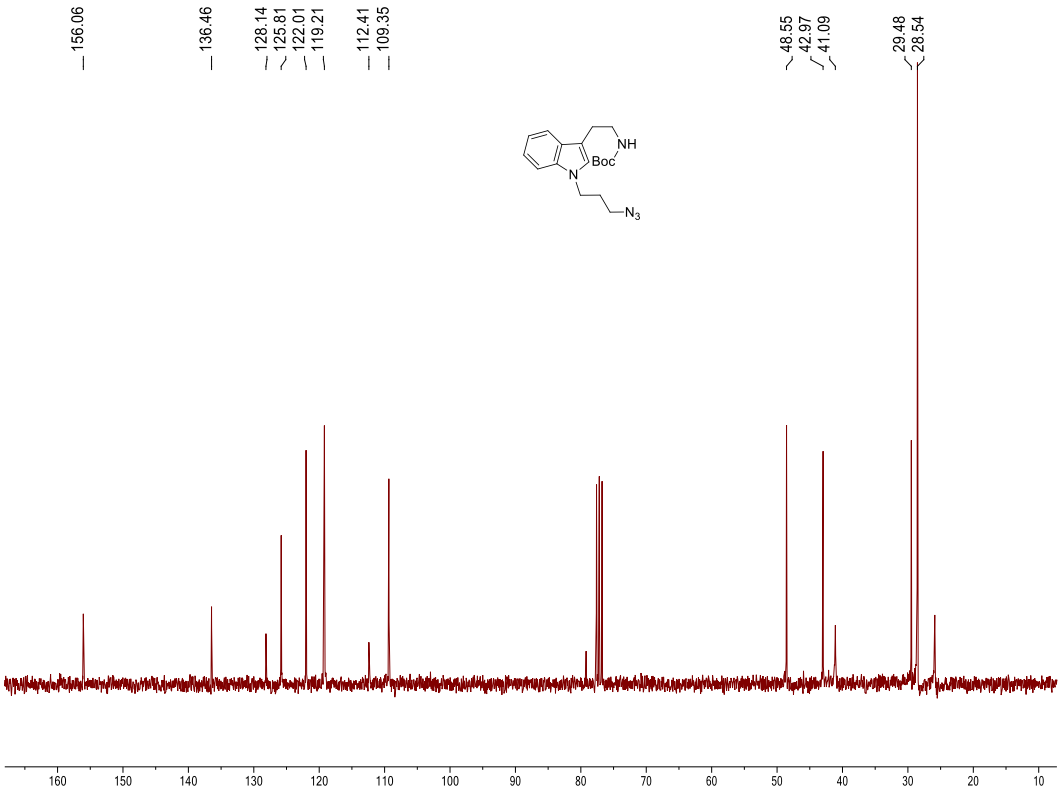
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Boc
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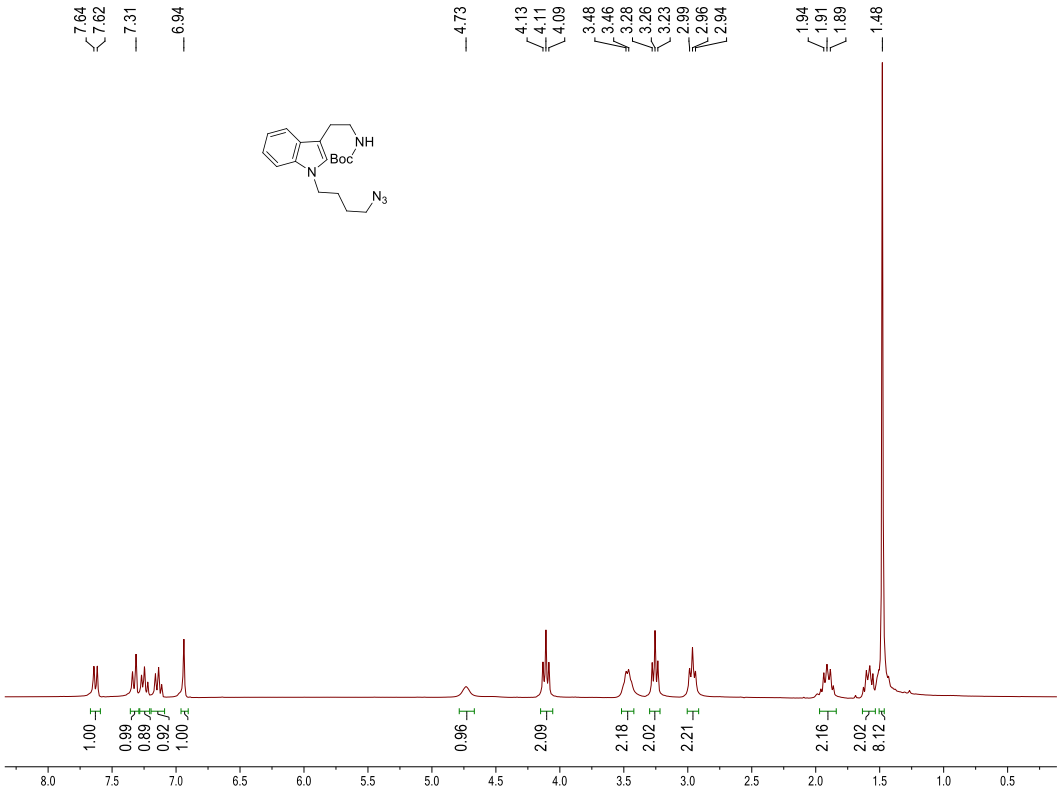
N3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Boc
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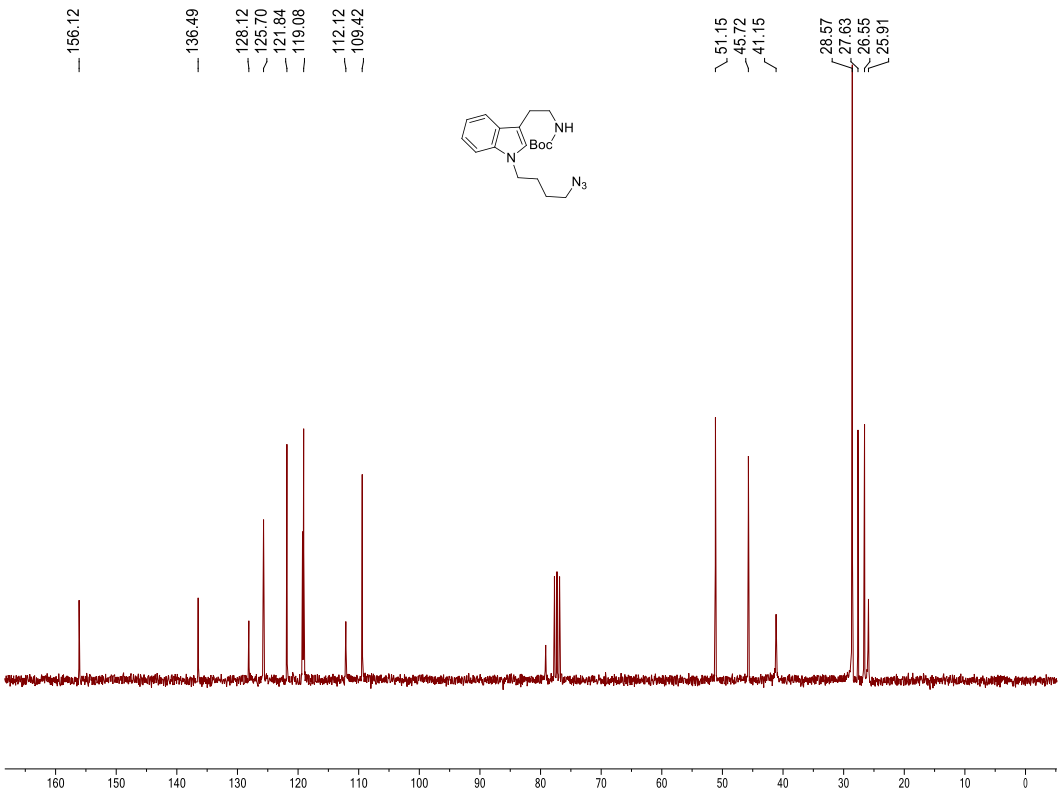
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Boc
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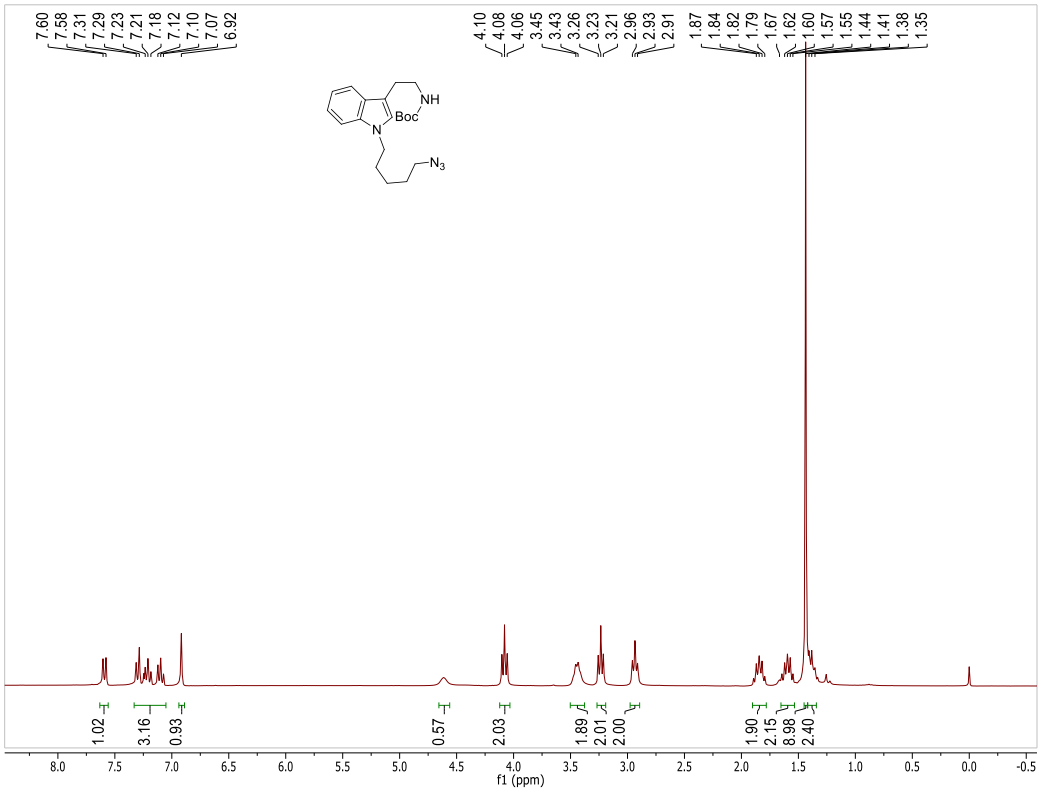
N3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1.79
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1.62
1.60
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1.35
NH
Boc
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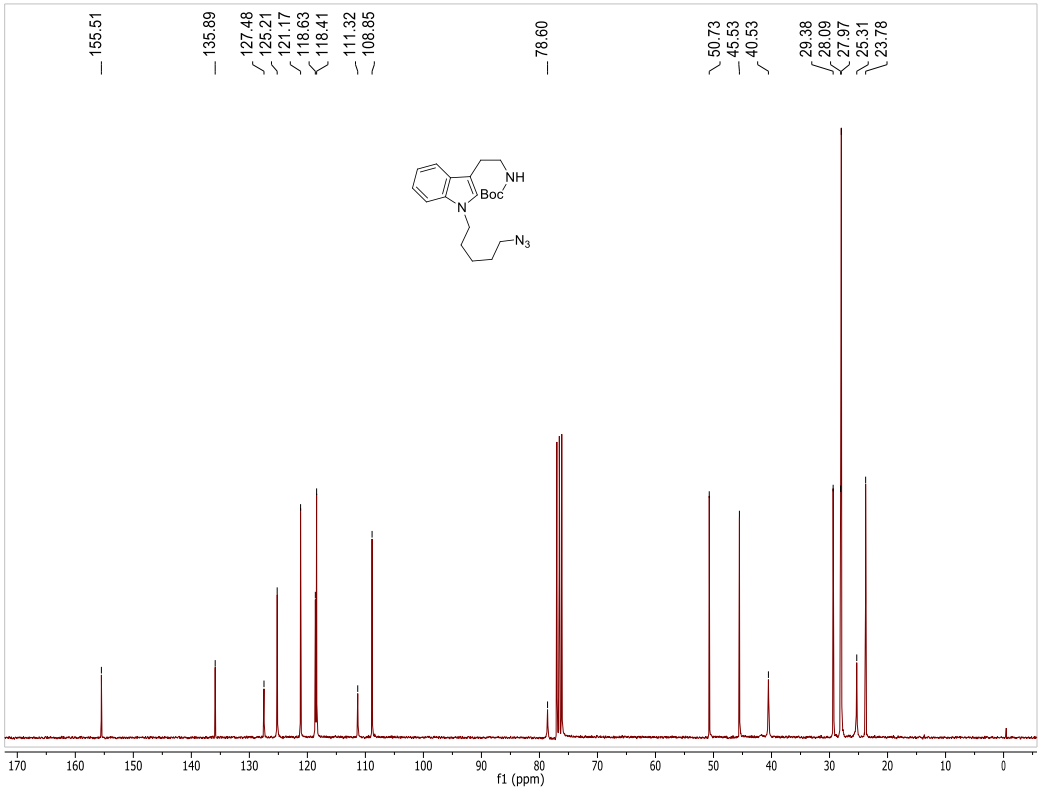
f1 (ppm)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27.97
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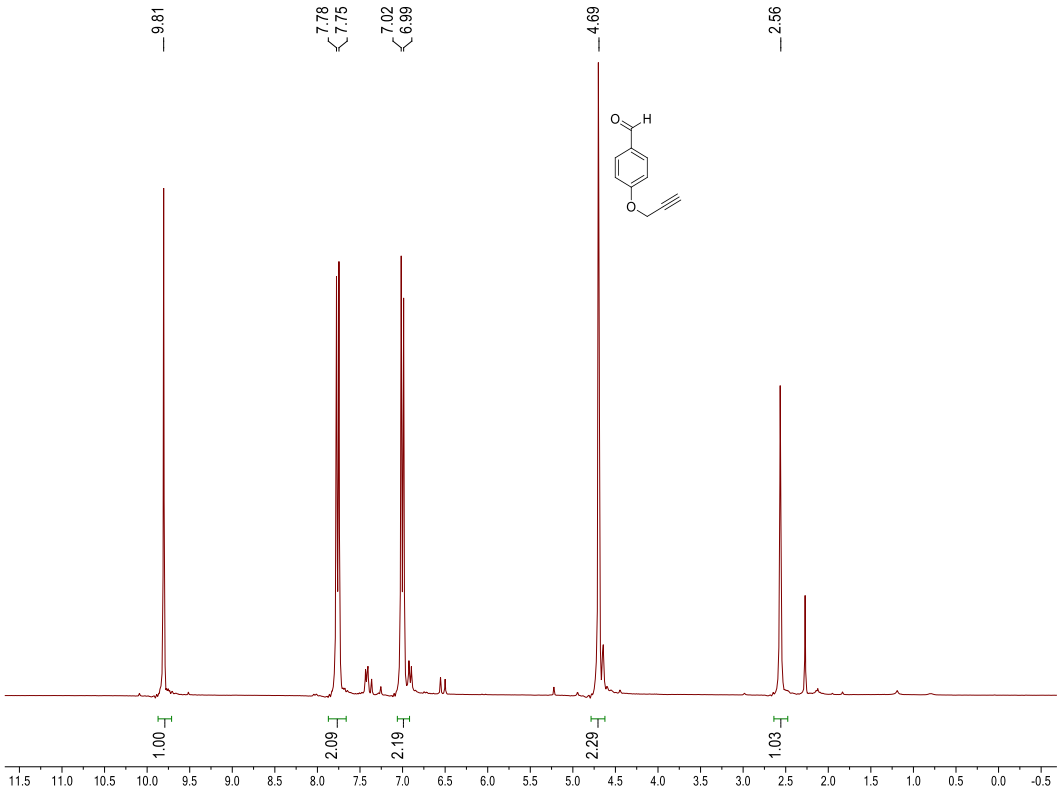
23.78
NH
Boc
N
N3
f1 (ppm)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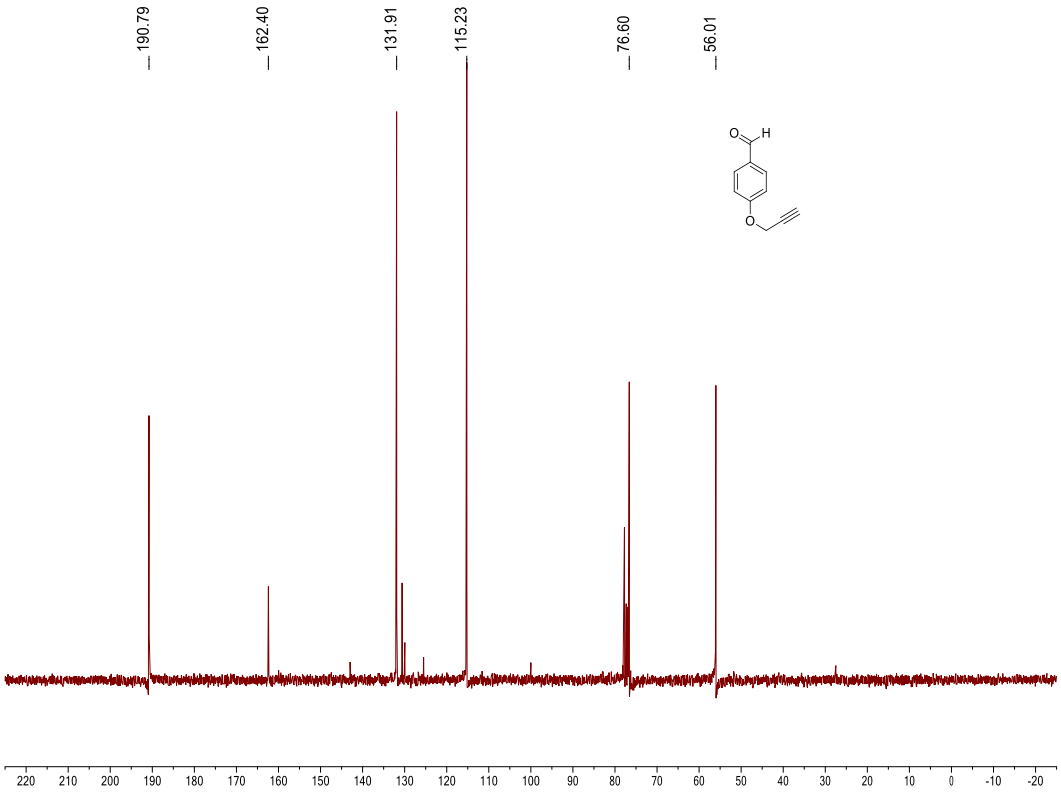
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56.01
O
H
O
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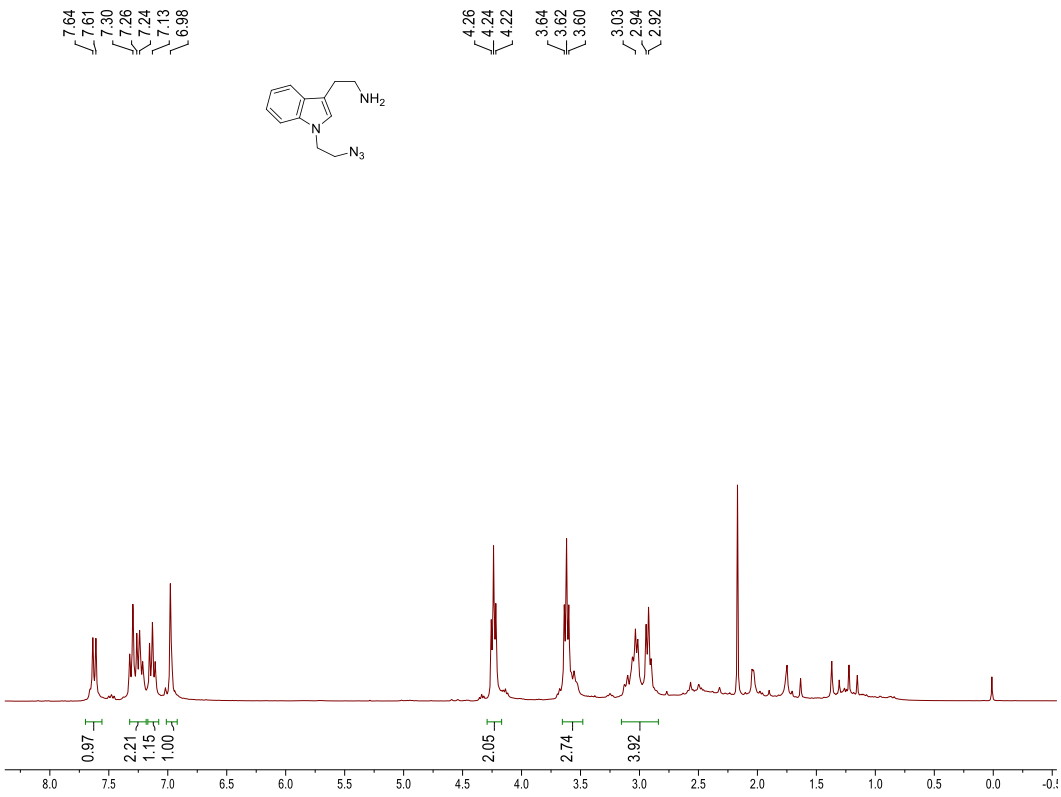
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3.03
2.94
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N
N3
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1.00
2.05
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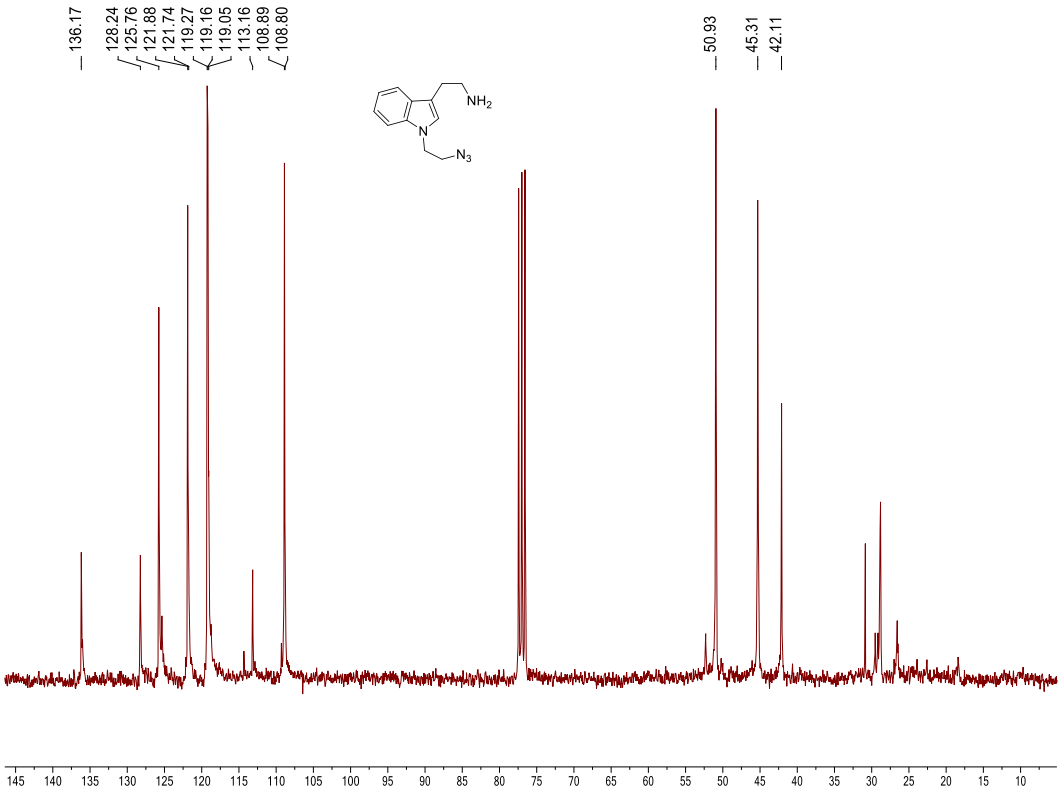
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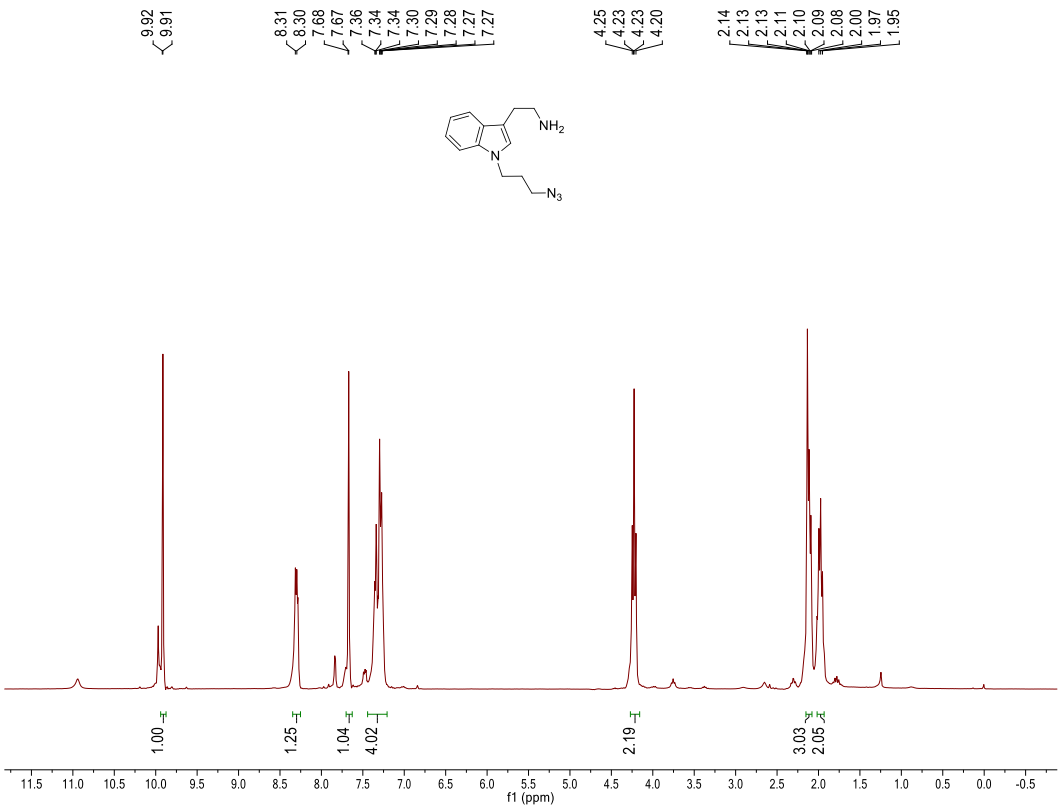
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4.02
2.19
3.03
2.05
11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
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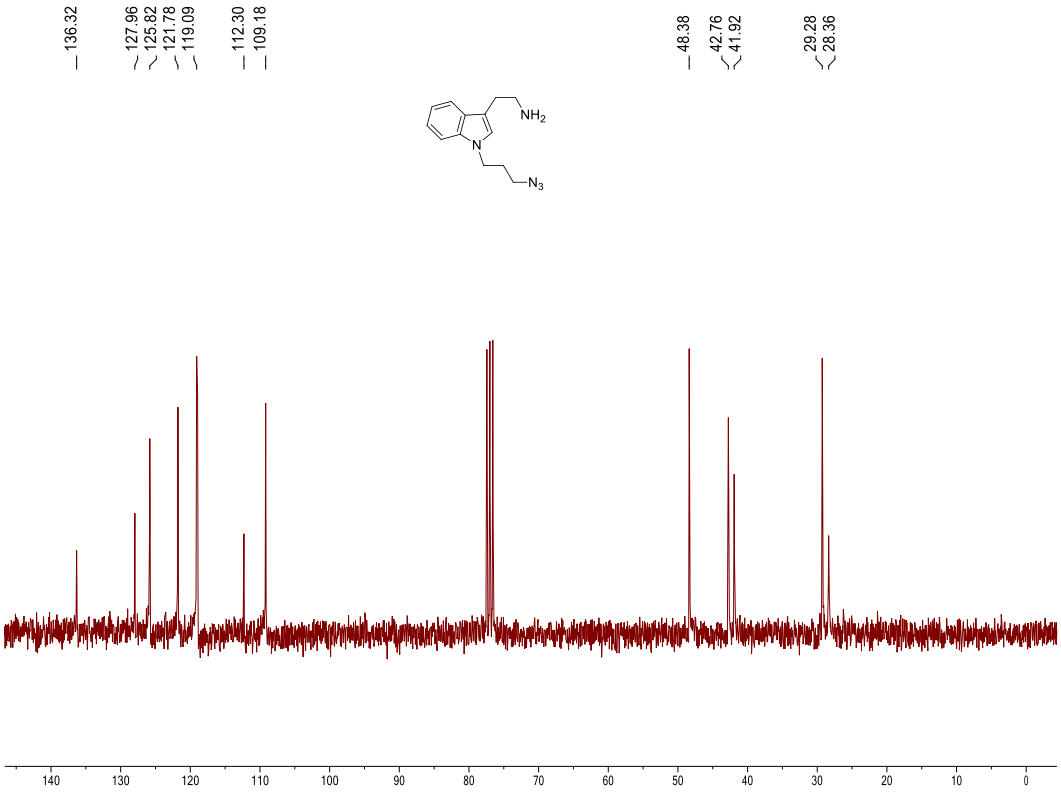
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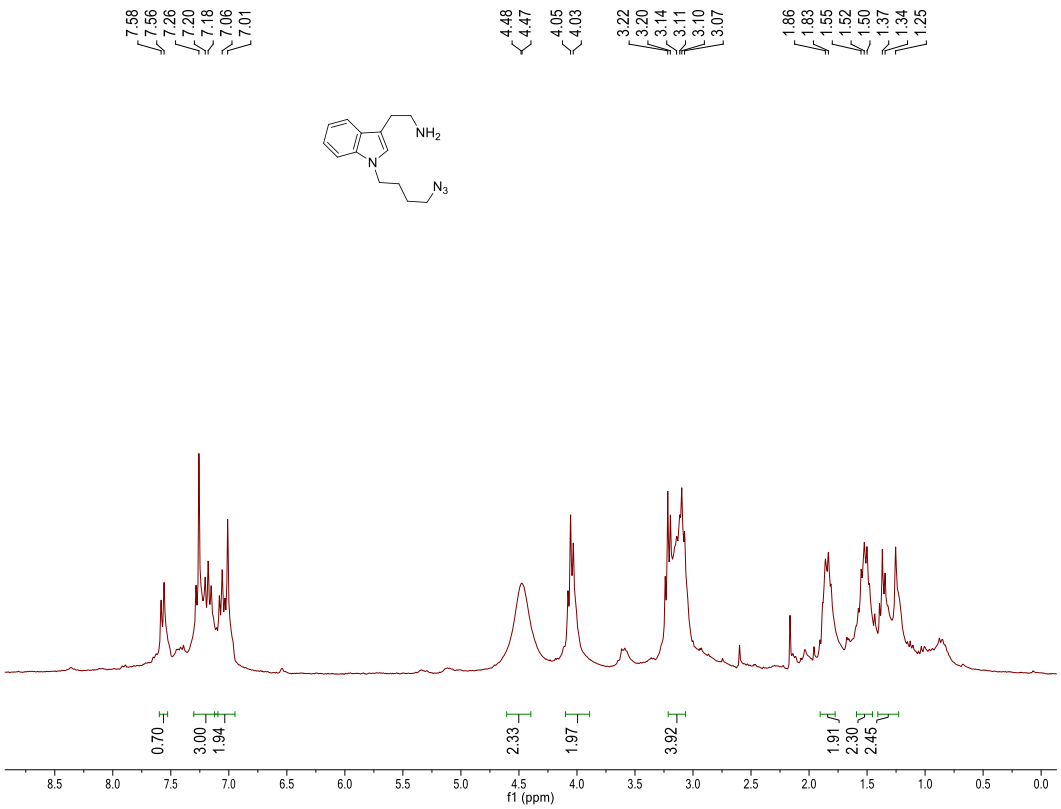
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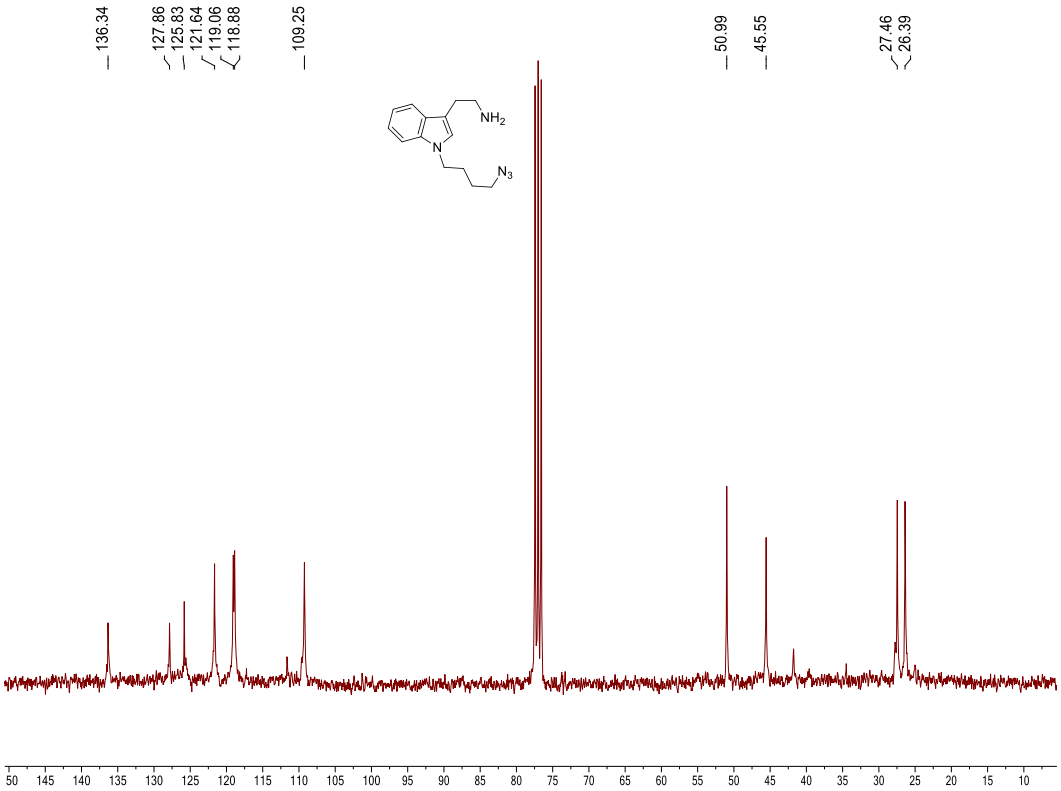
f1 (ppm)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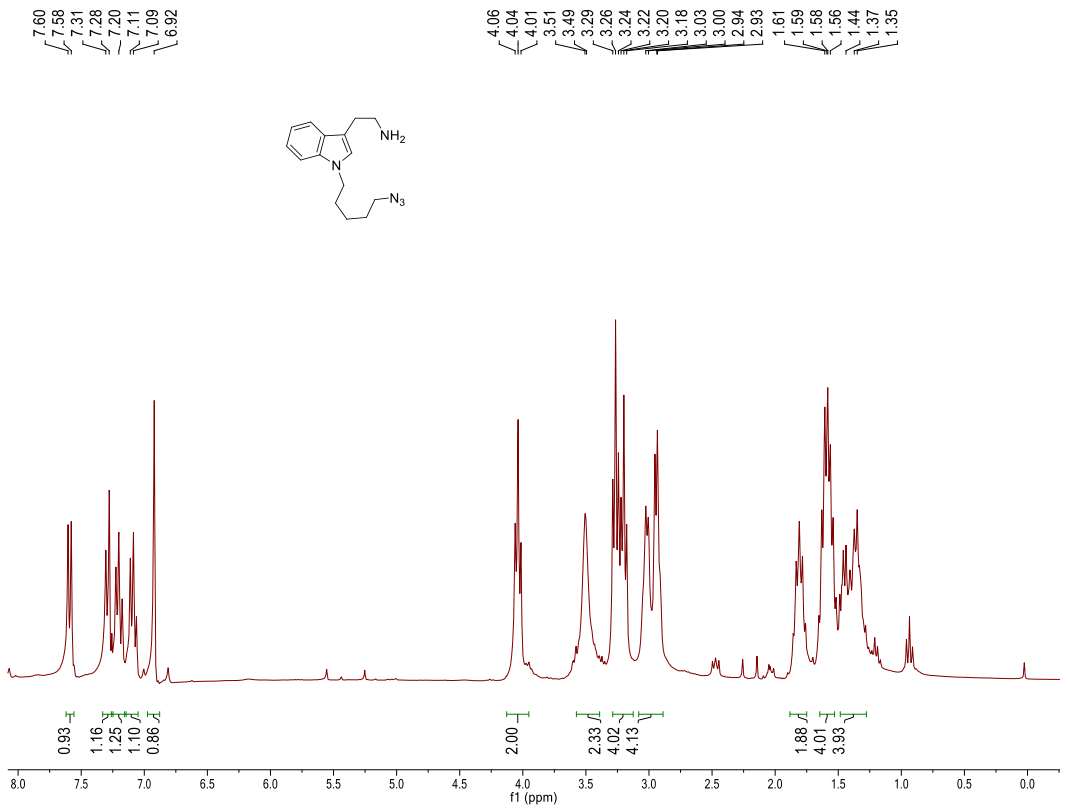
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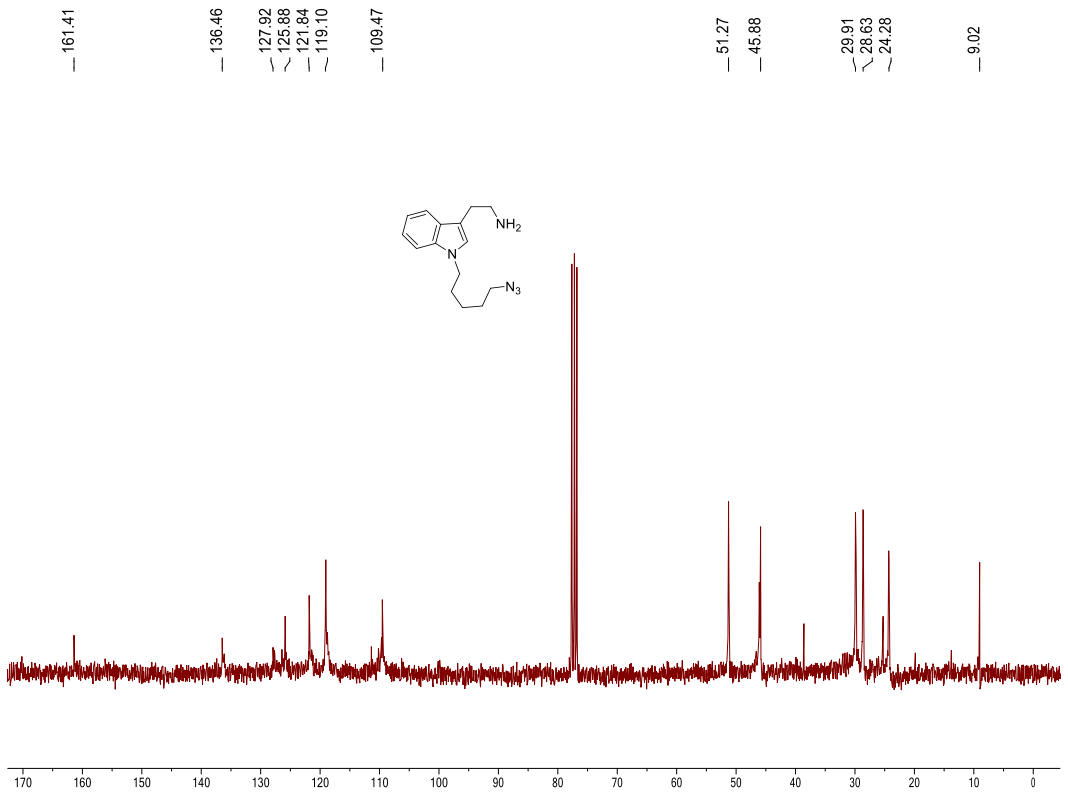
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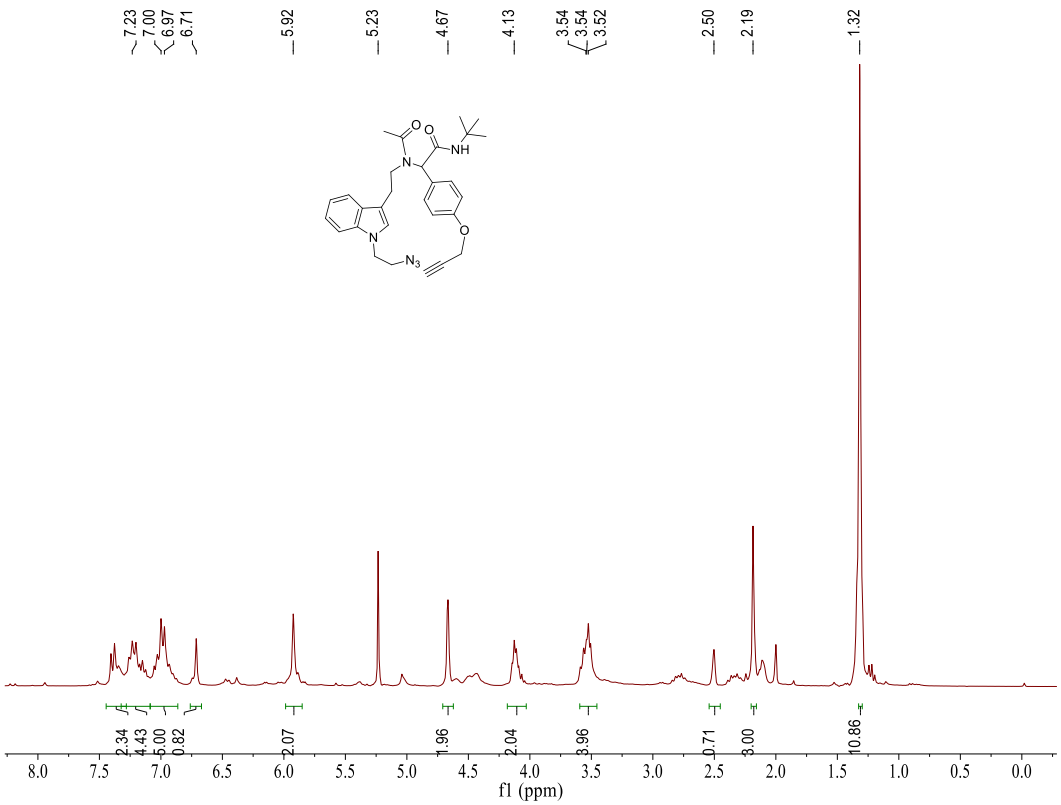
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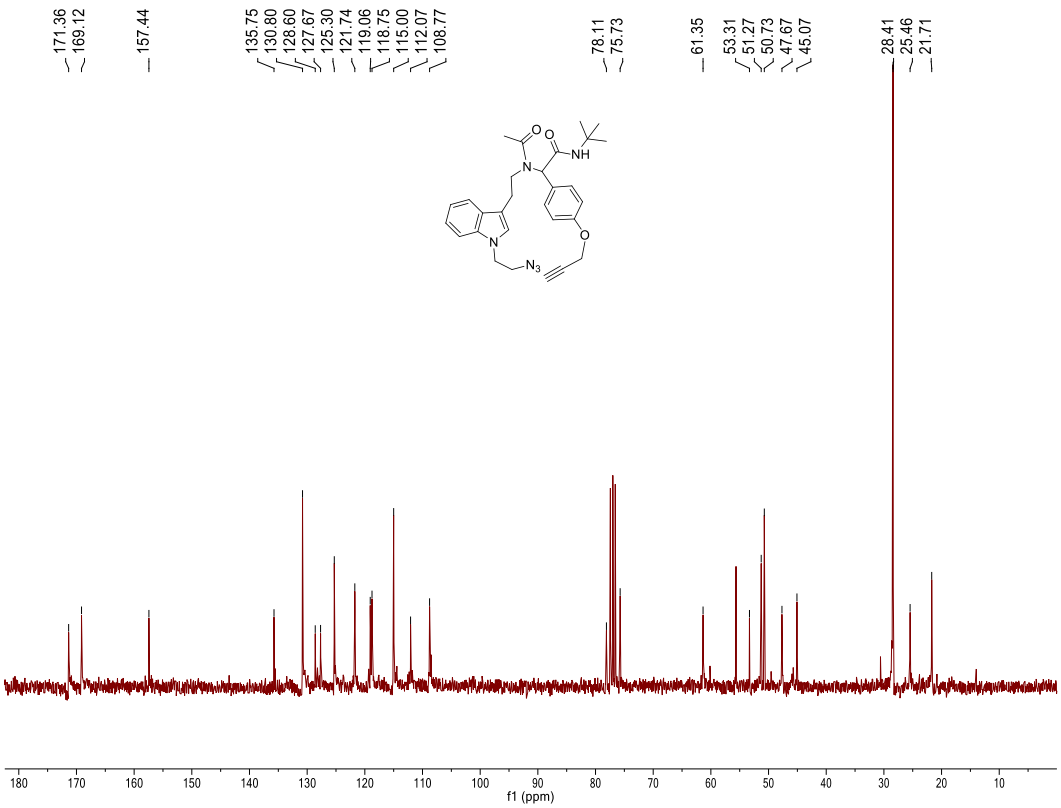
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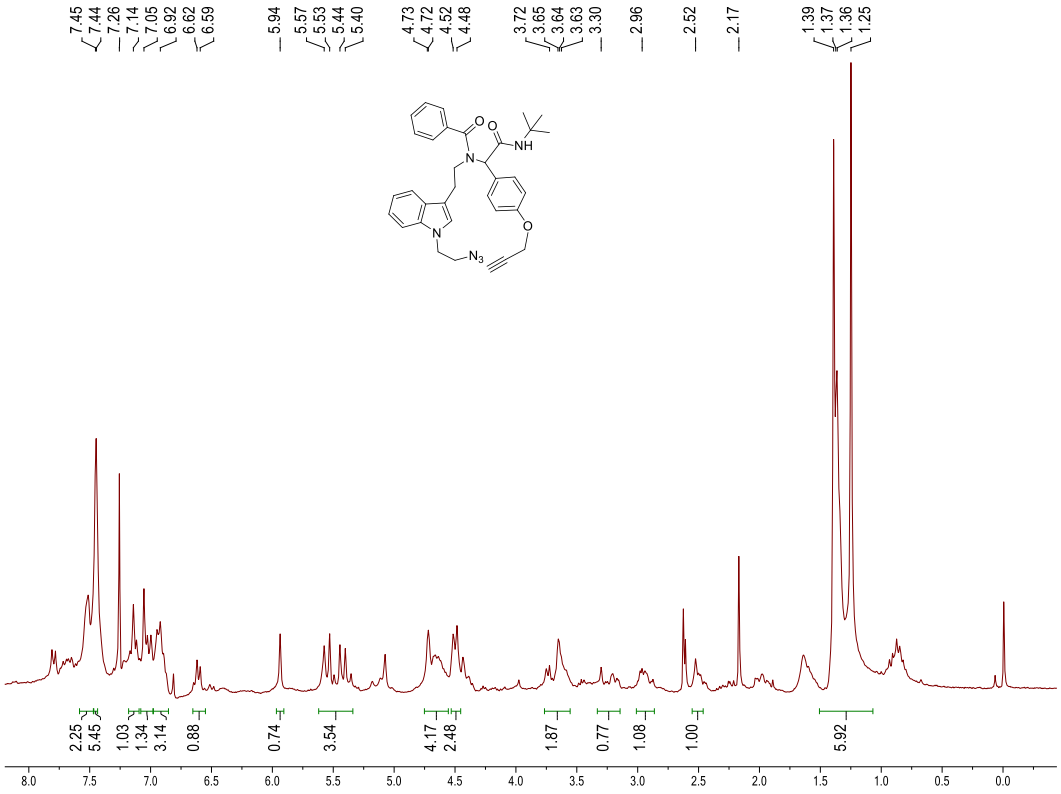
f1 (ppm)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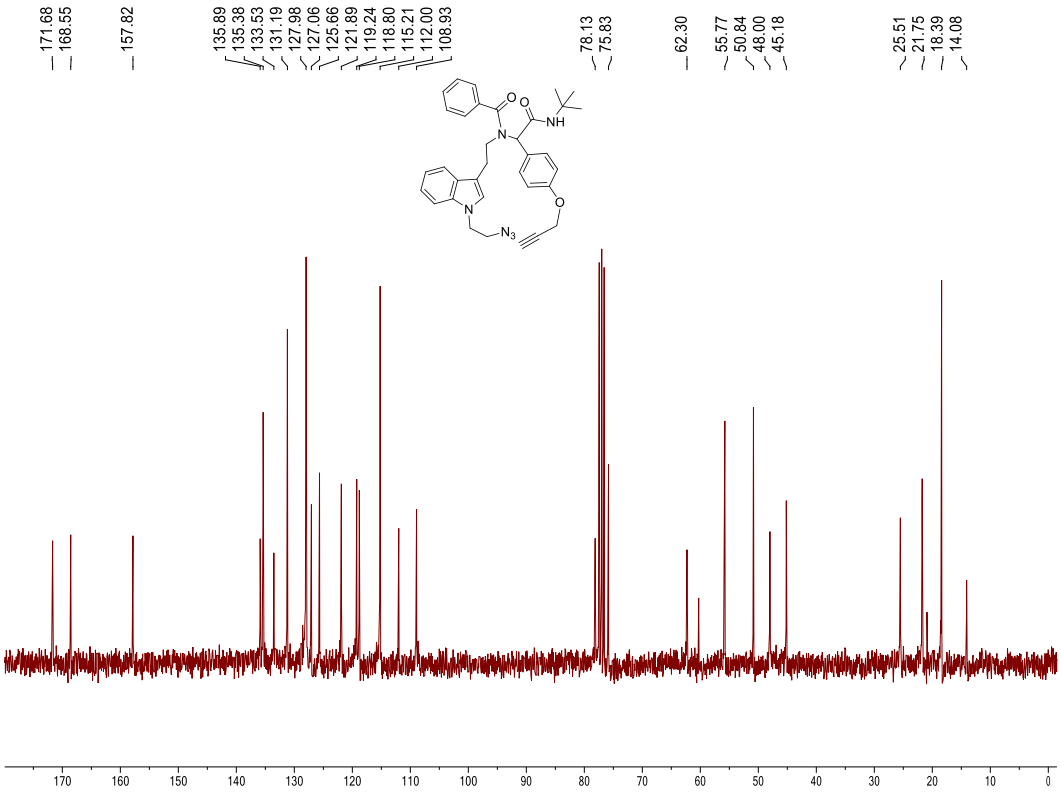
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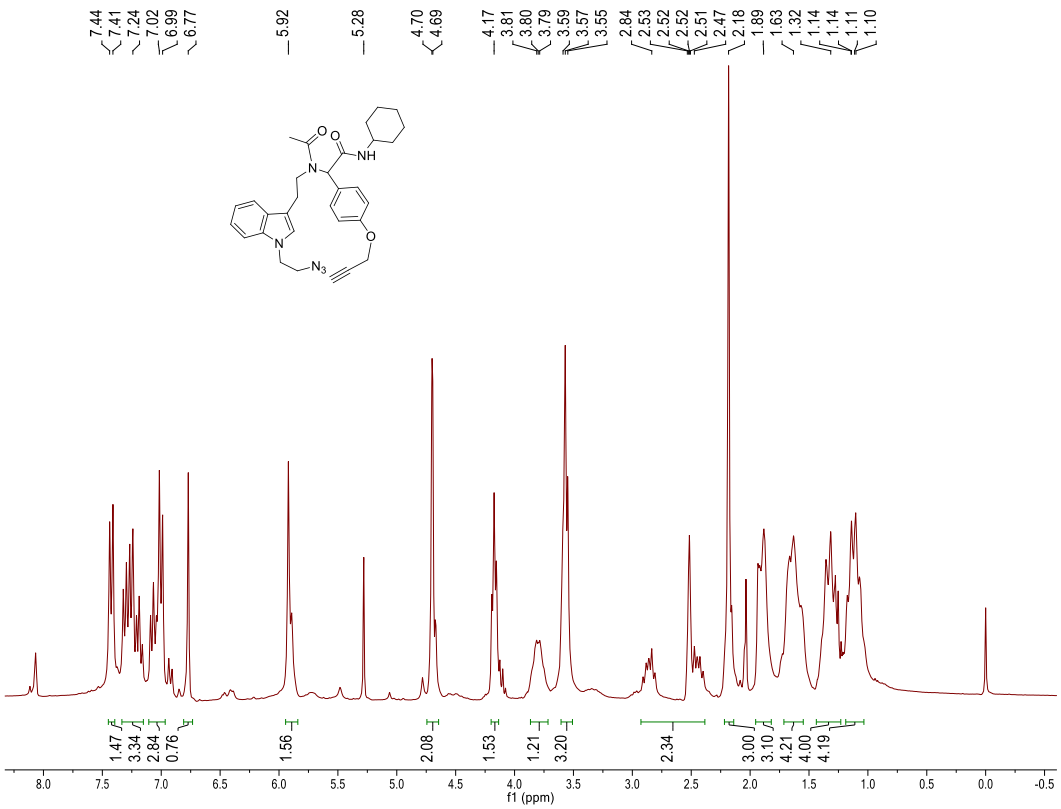
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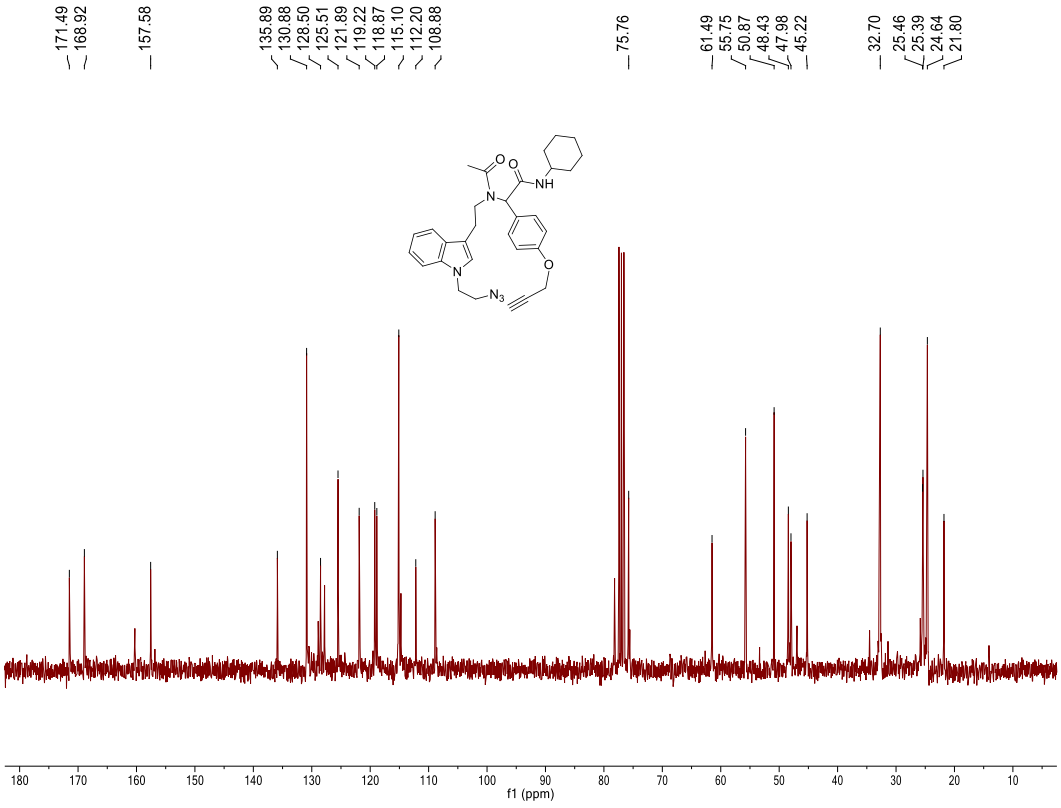
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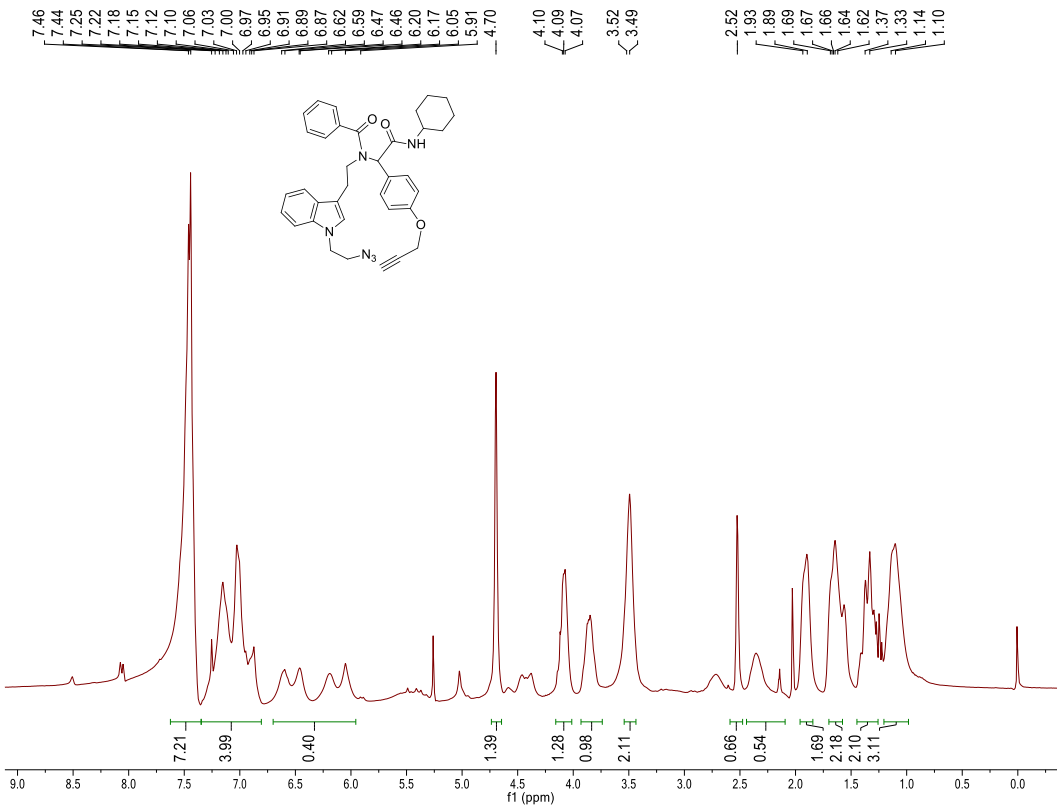
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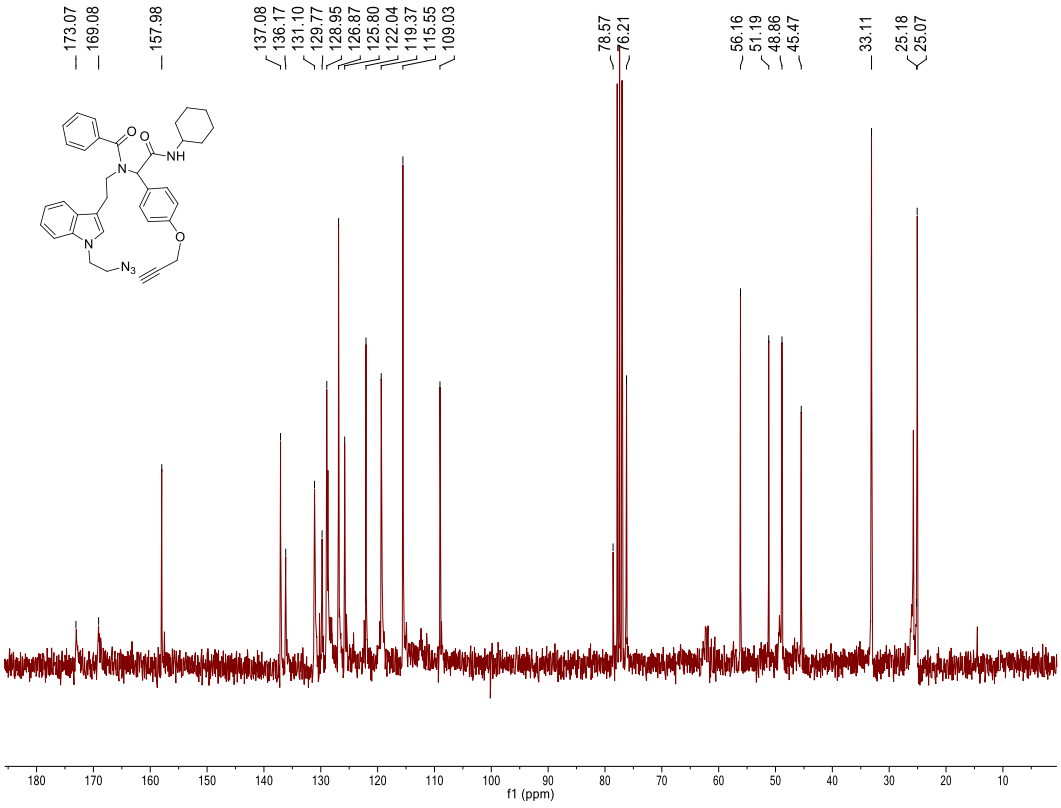
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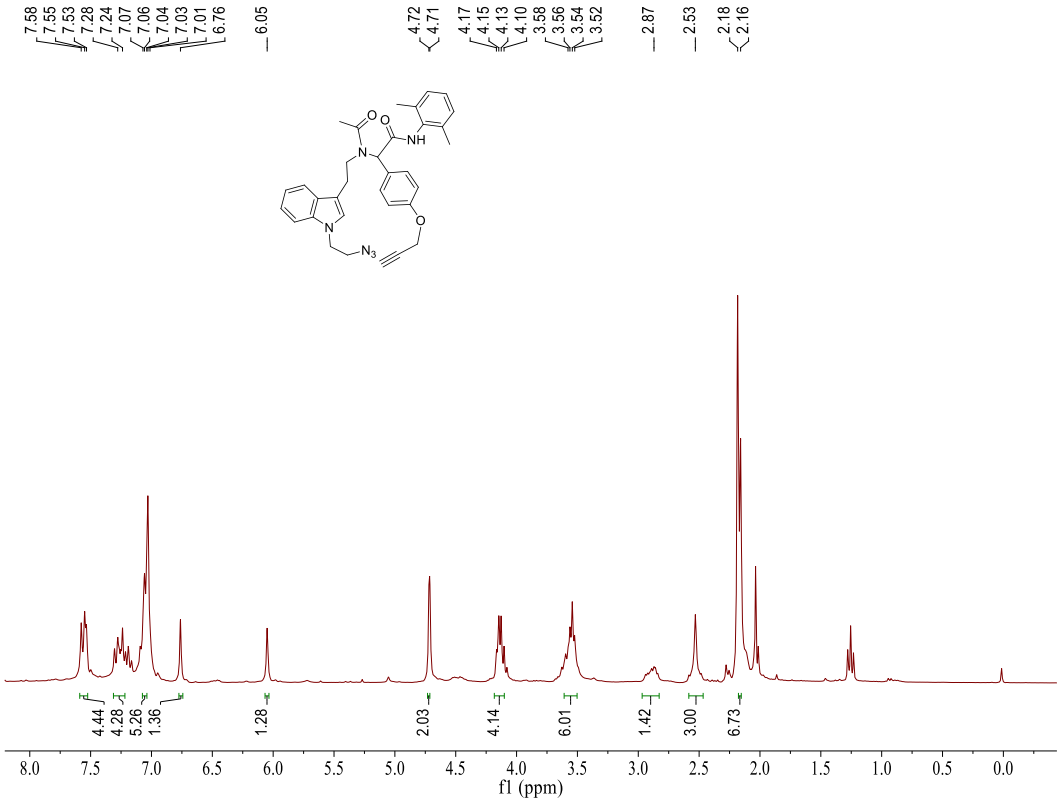
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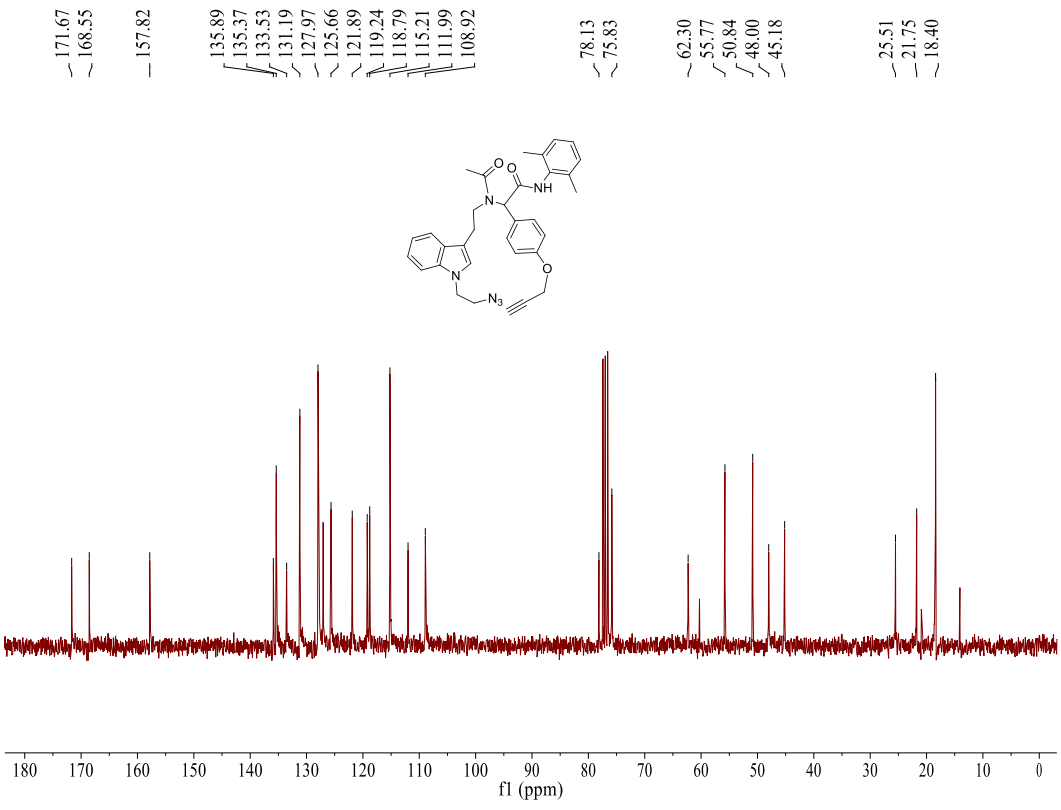
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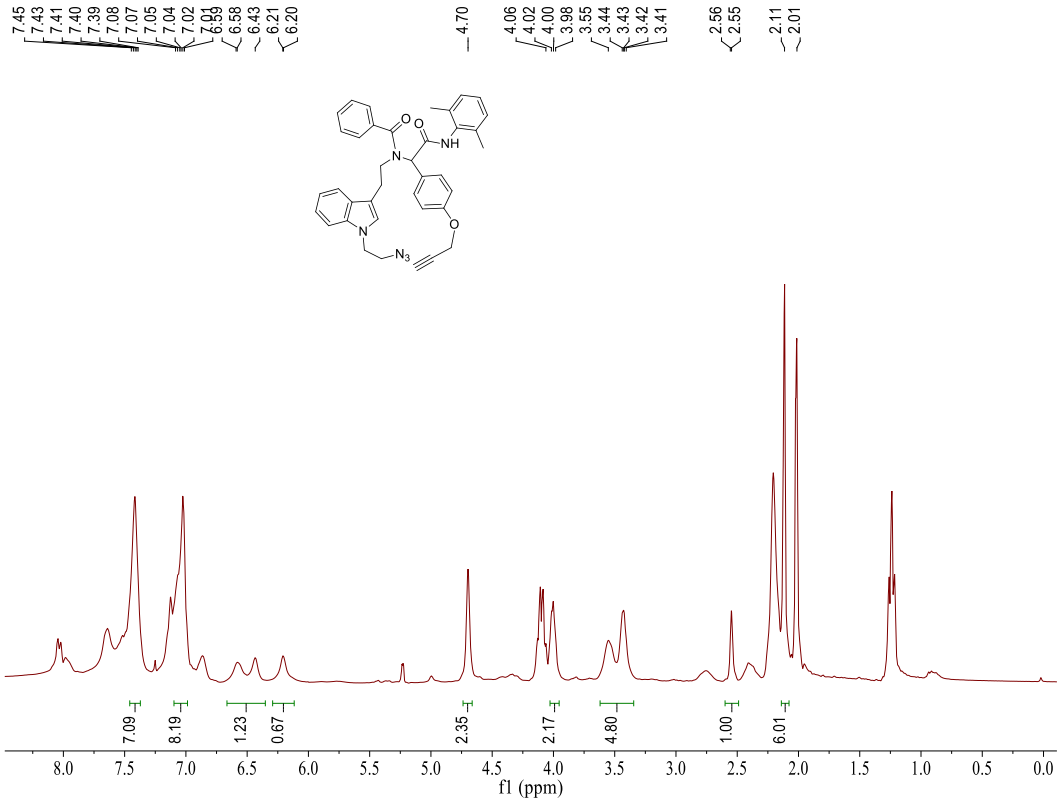
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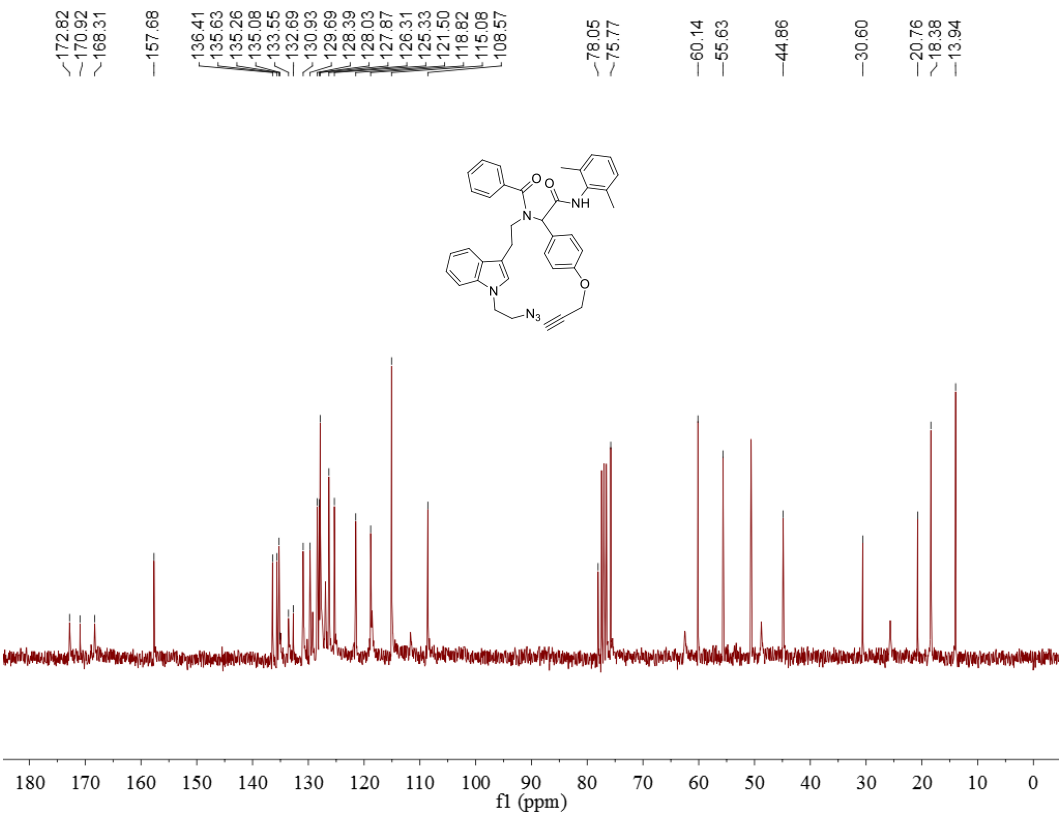
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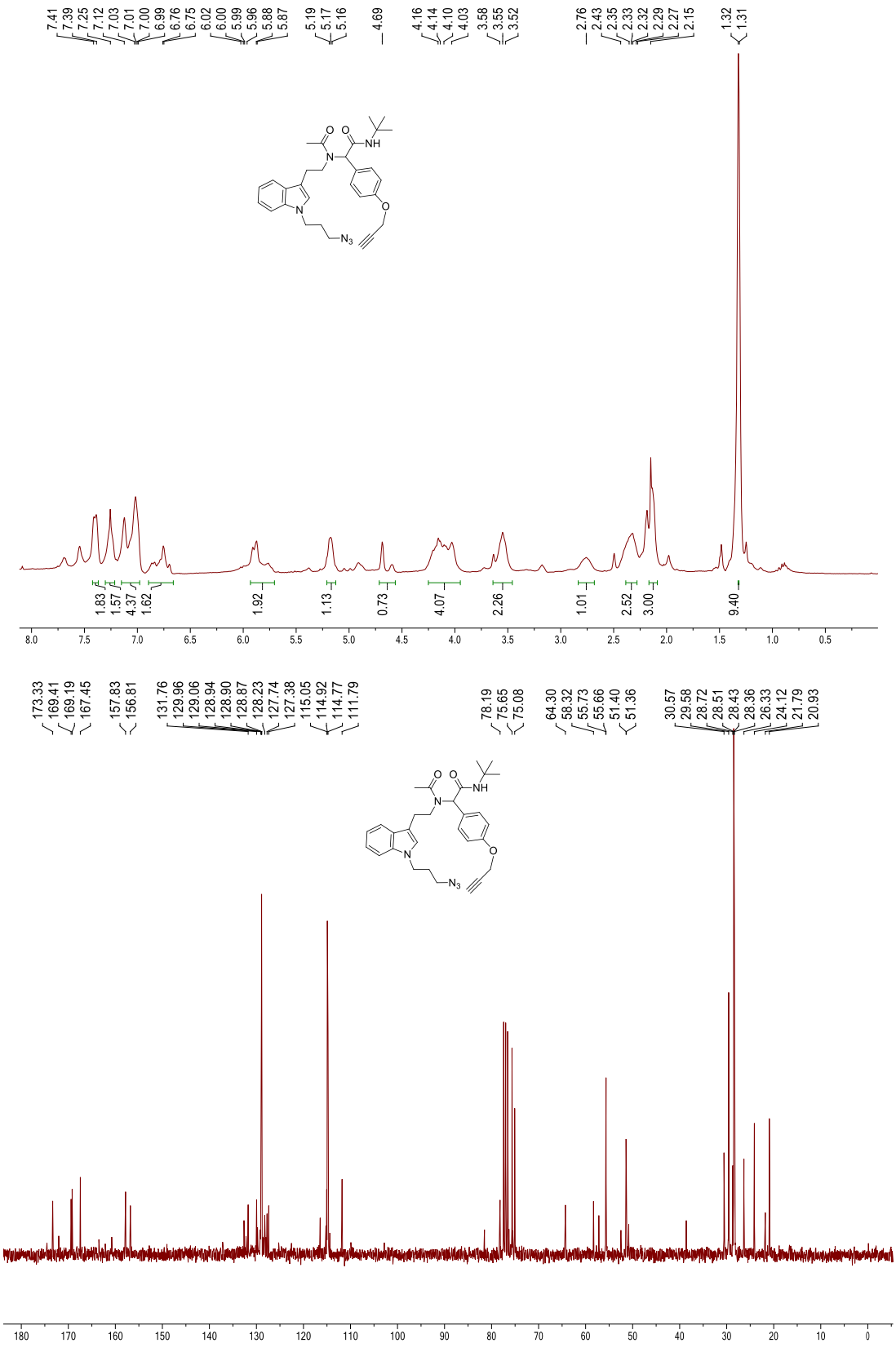
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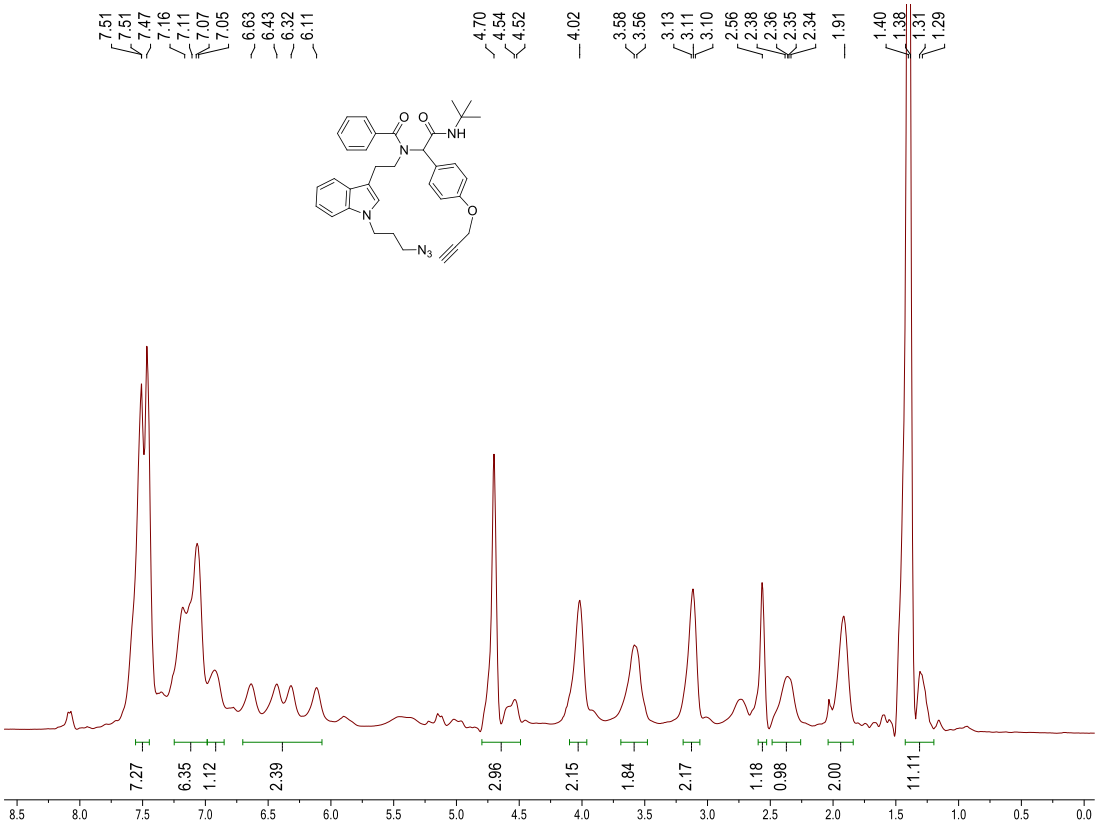
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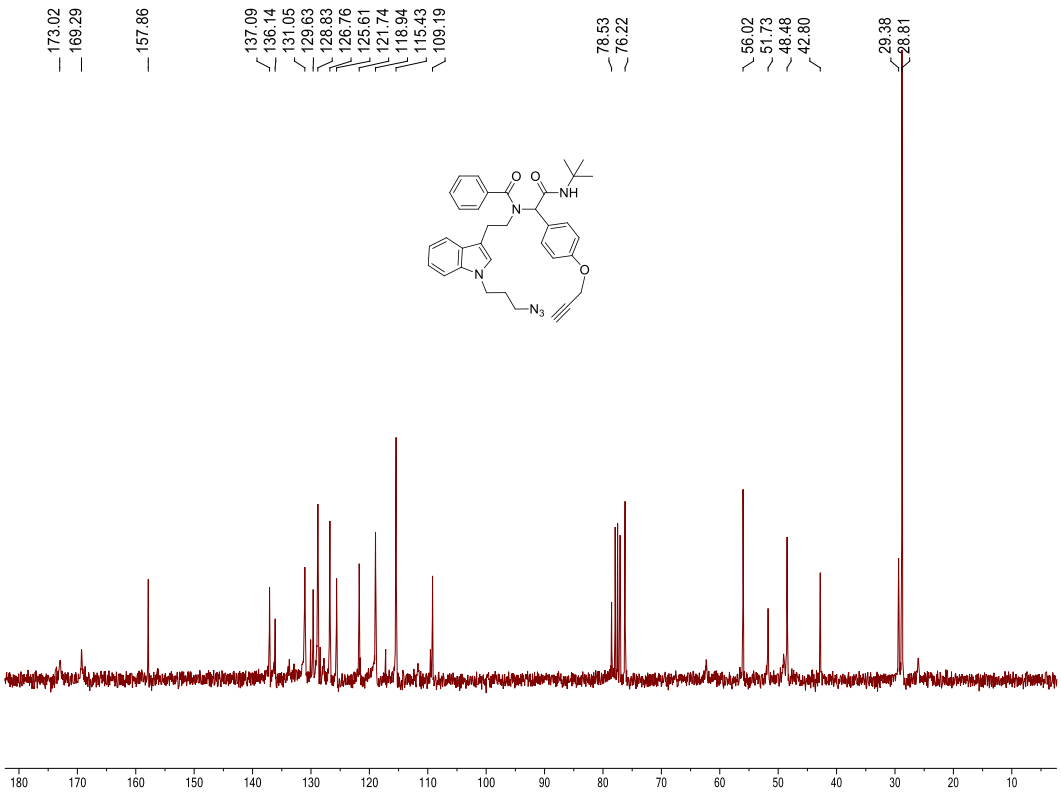
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28.81
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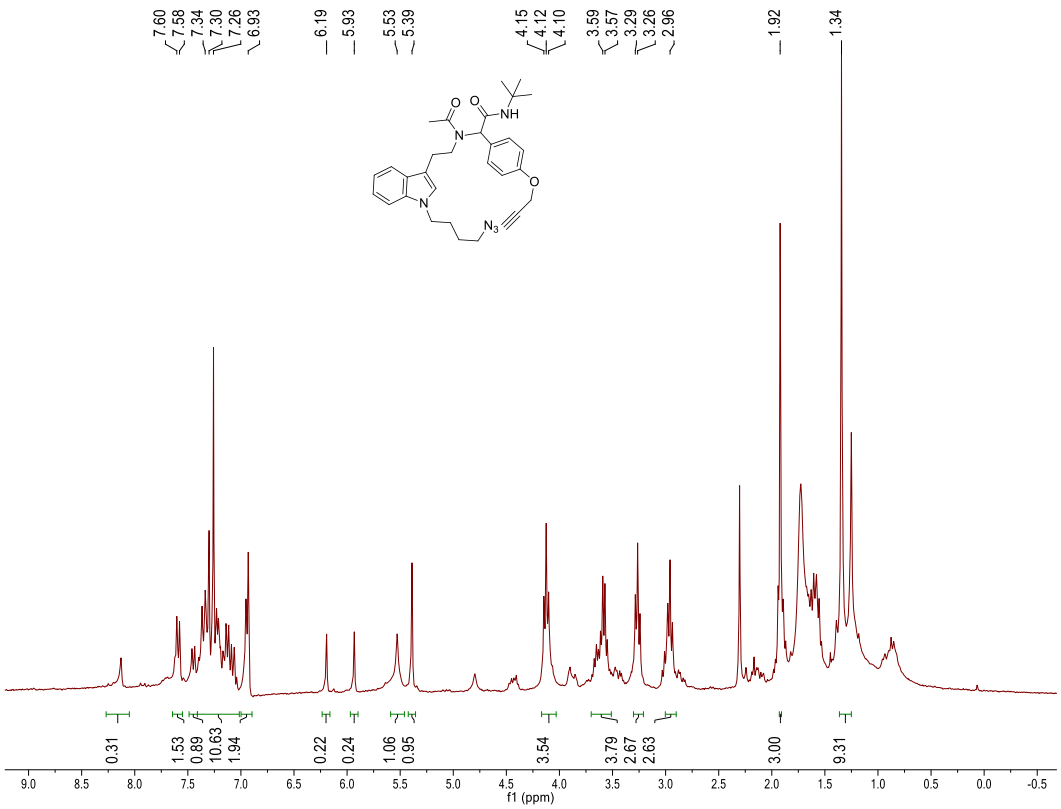
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1.34
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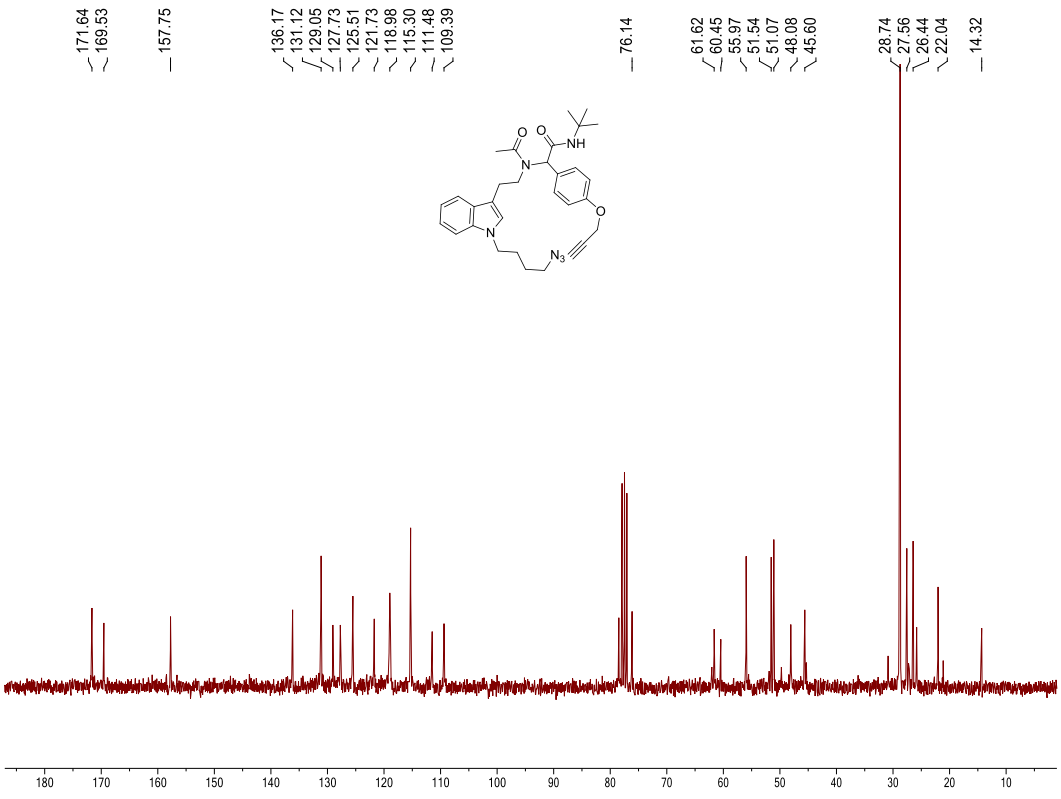
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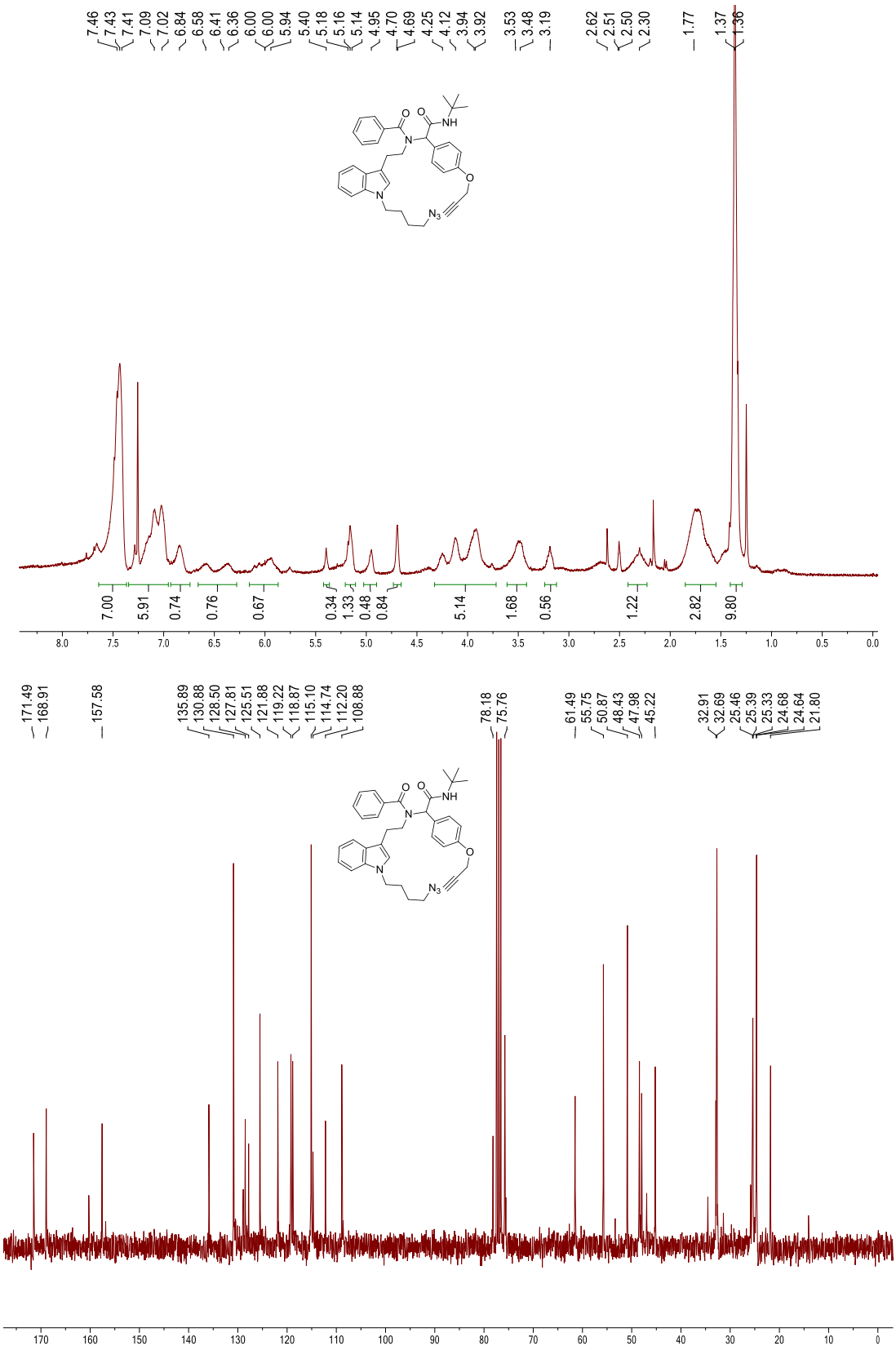
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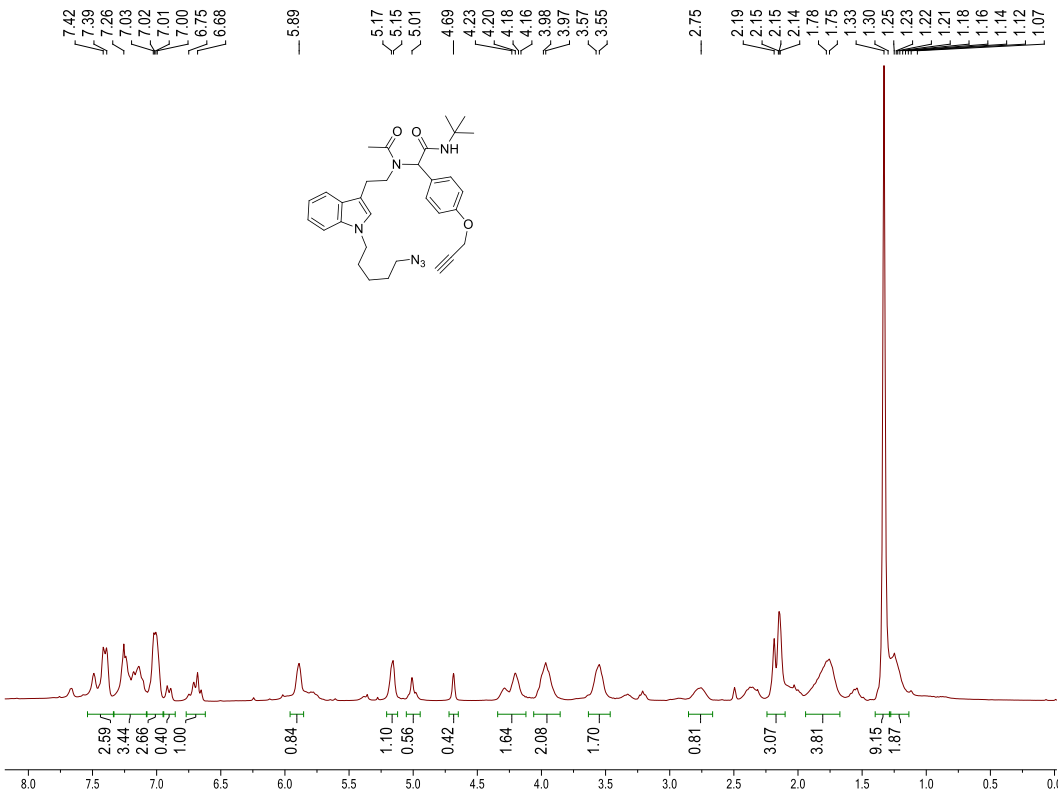
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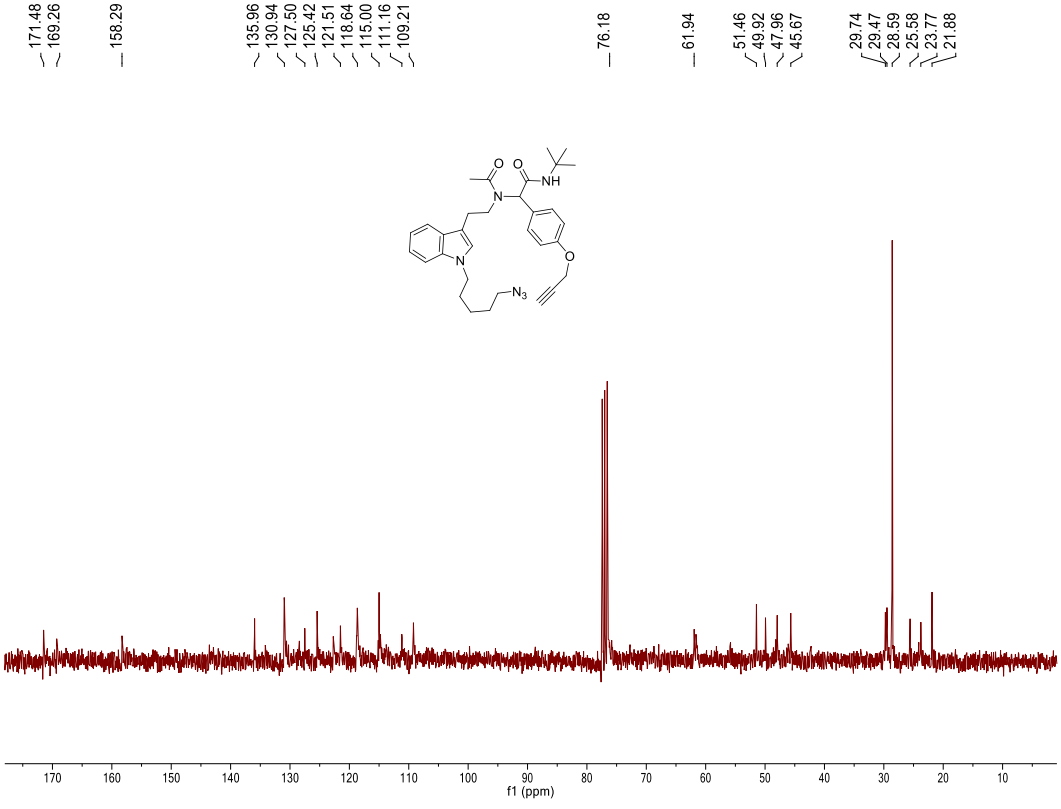
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N
O
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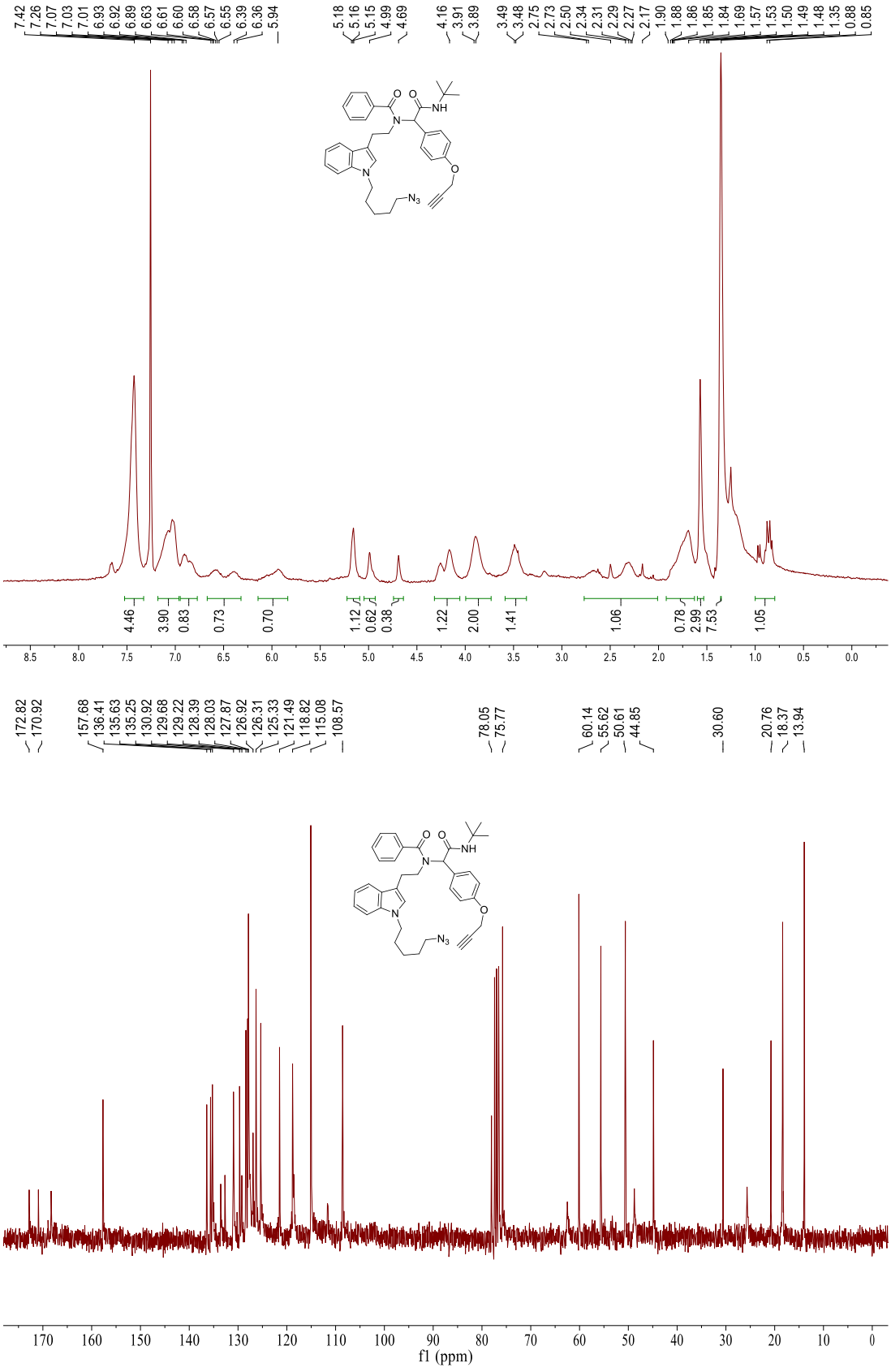
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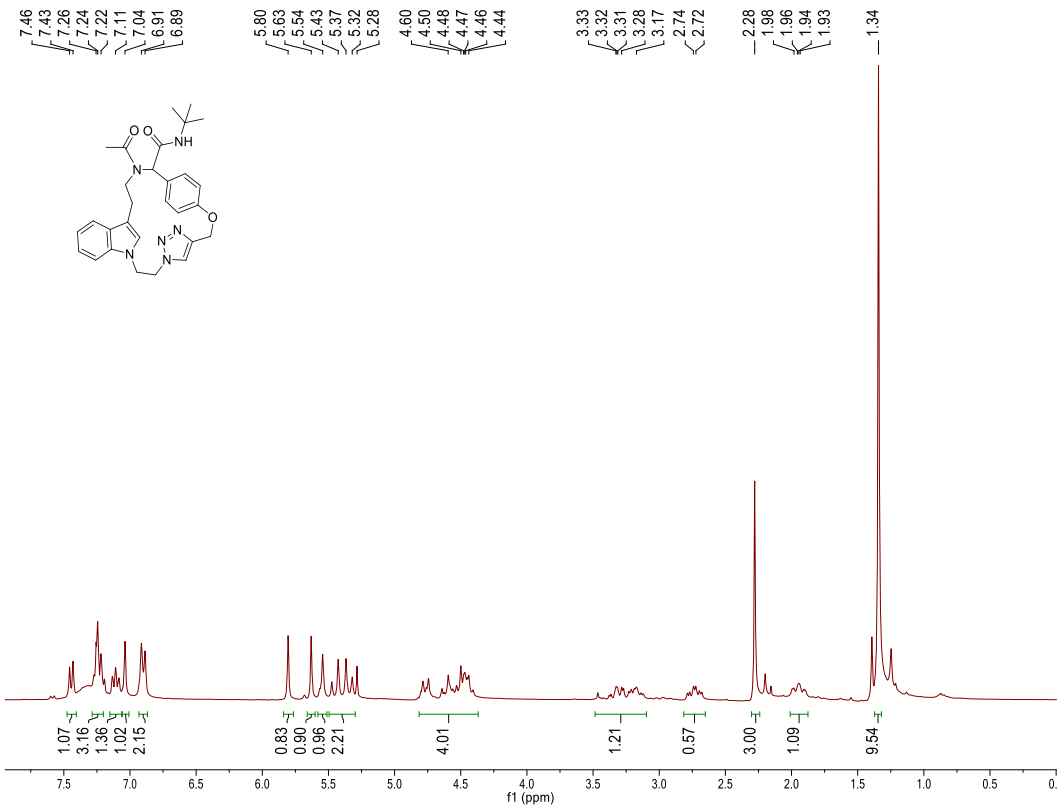
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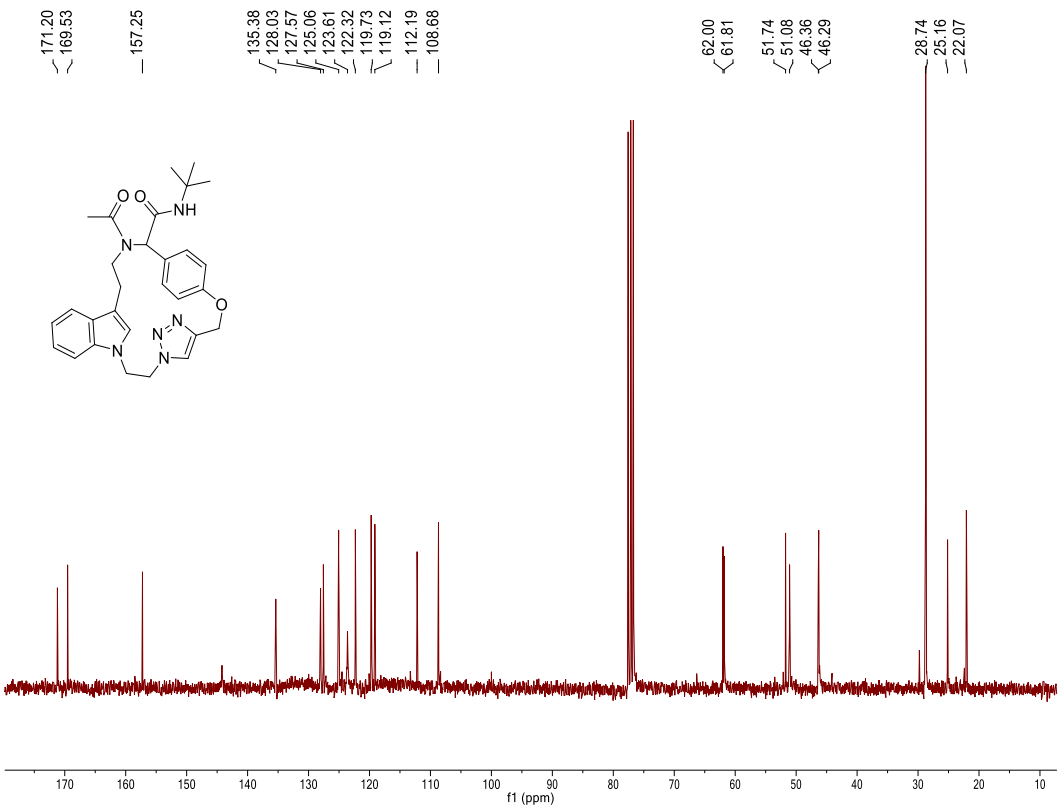
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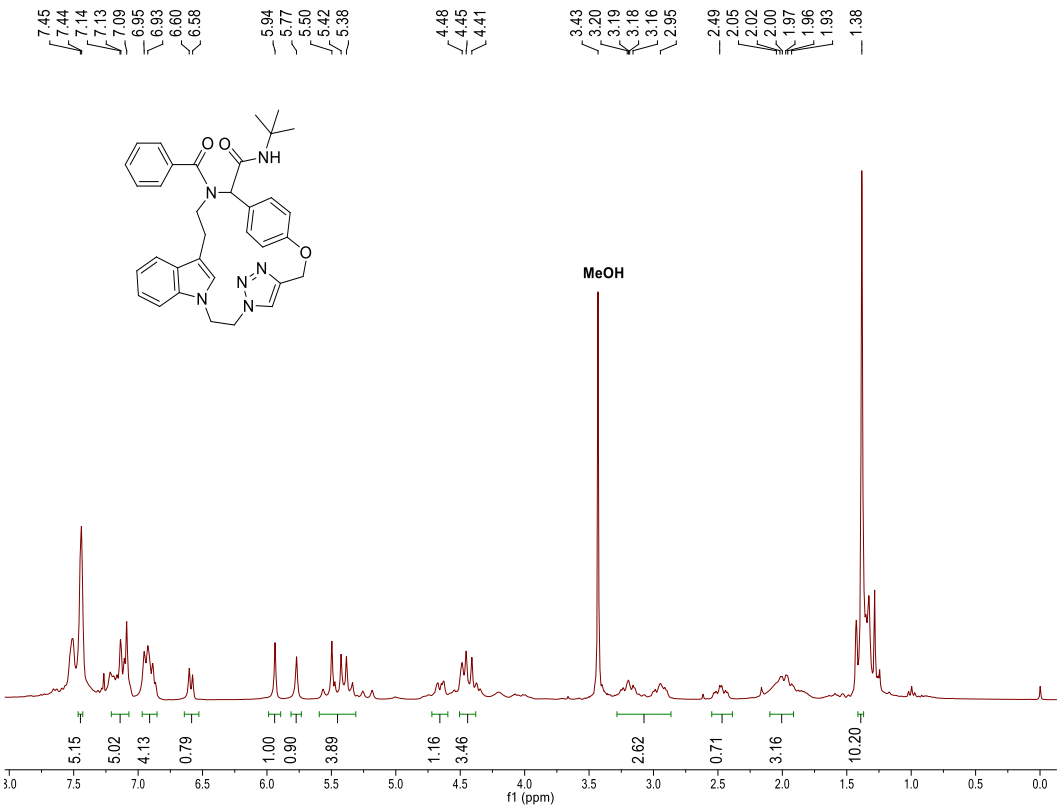
22.07
f1 (ppm)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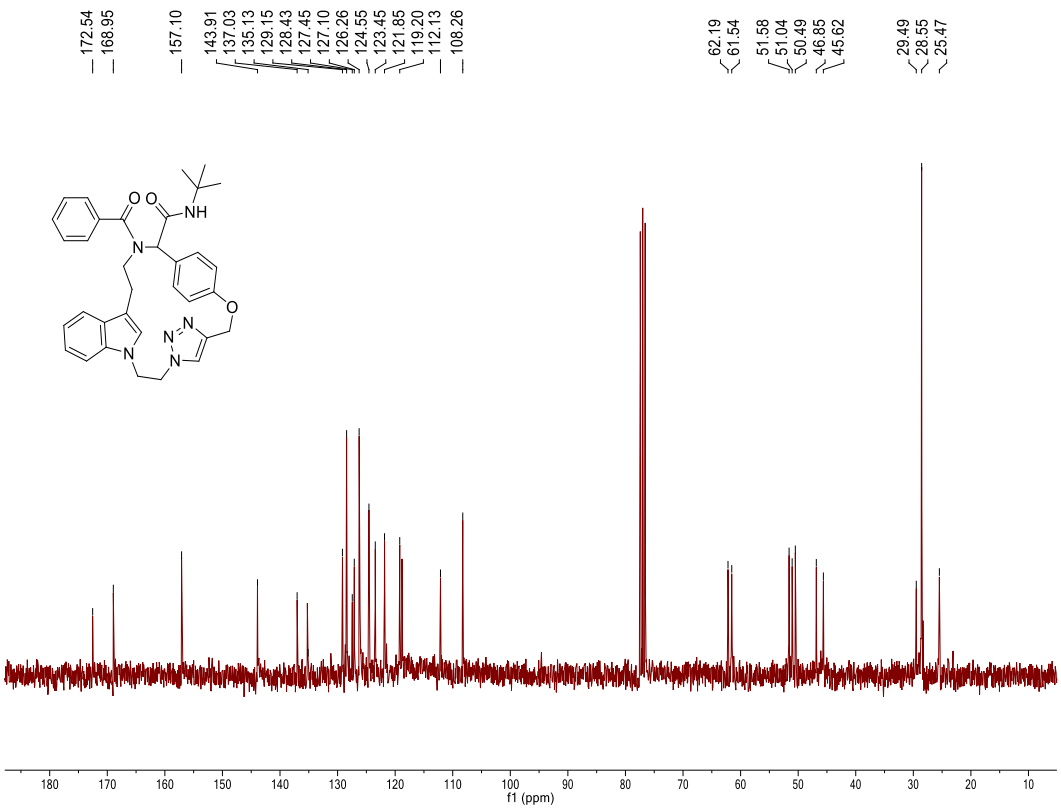
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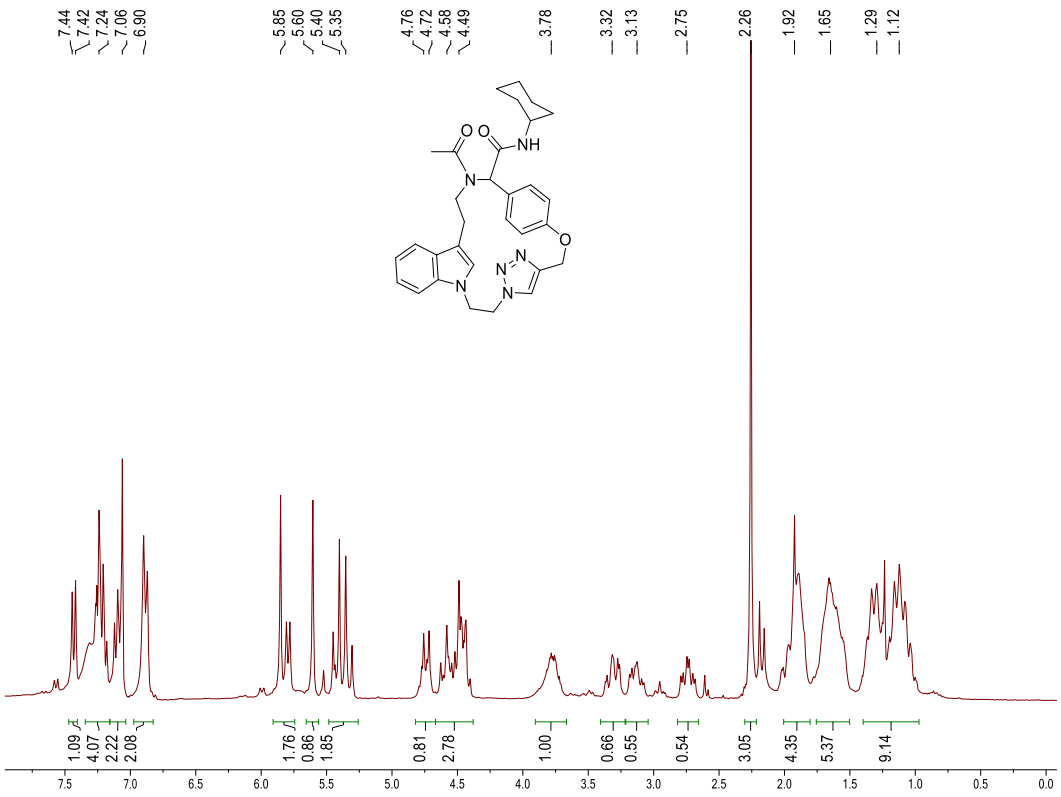
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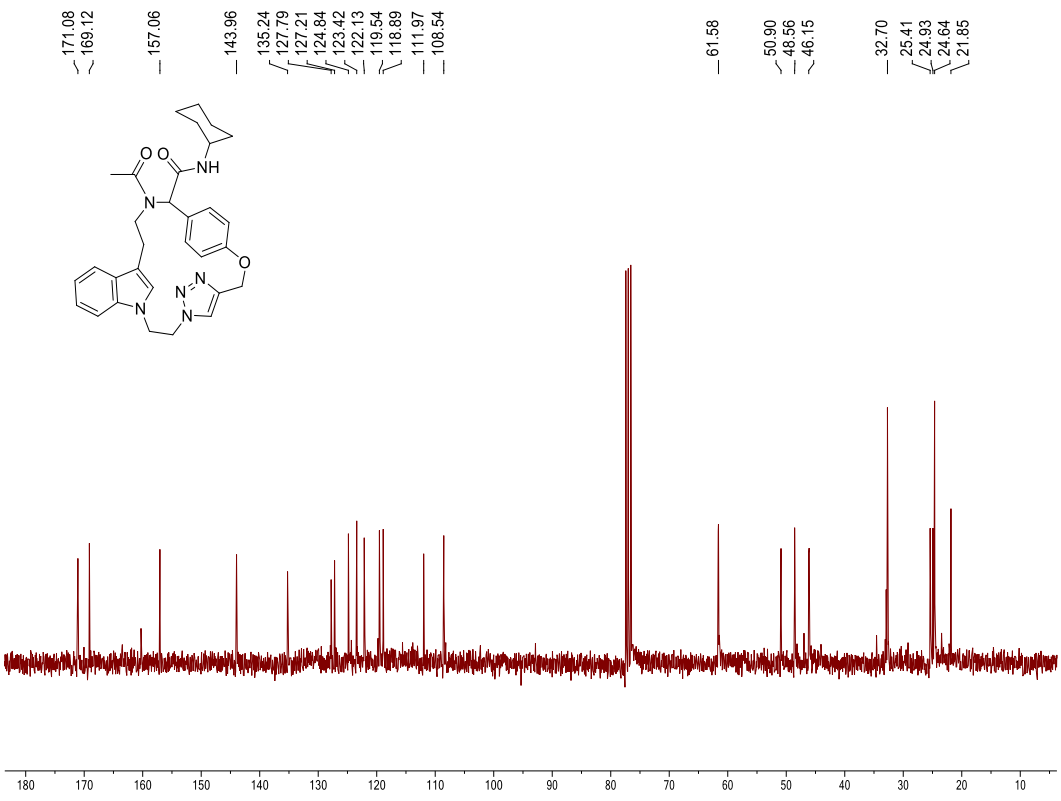
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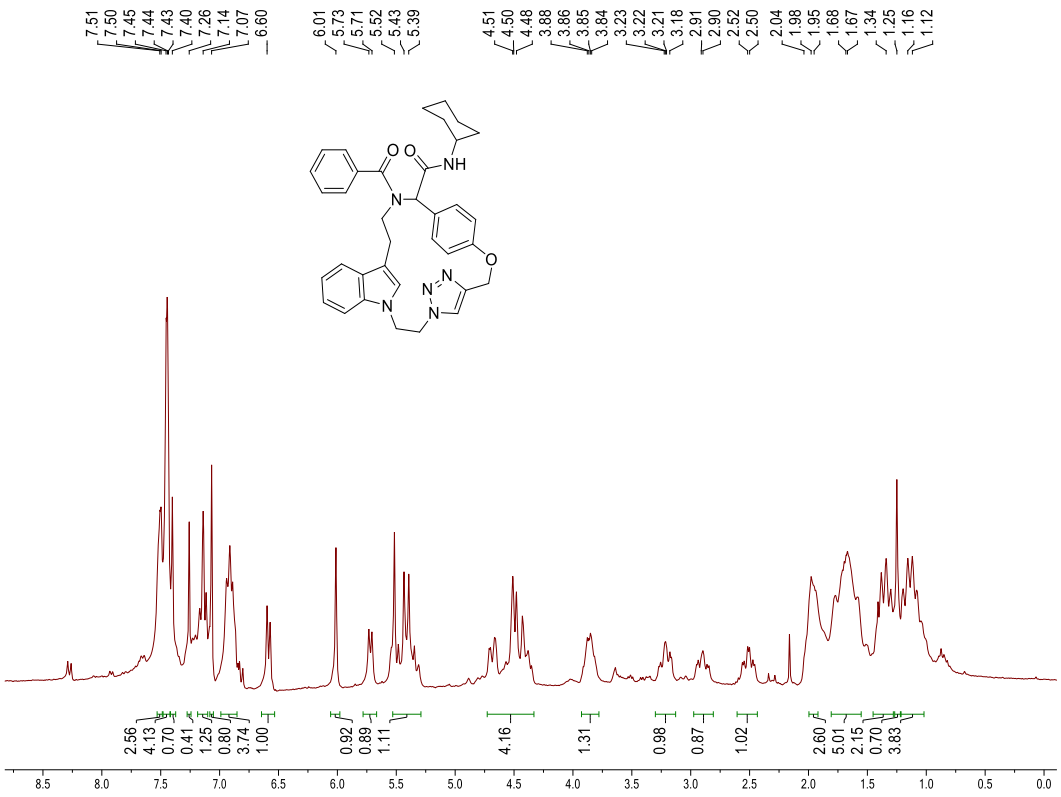
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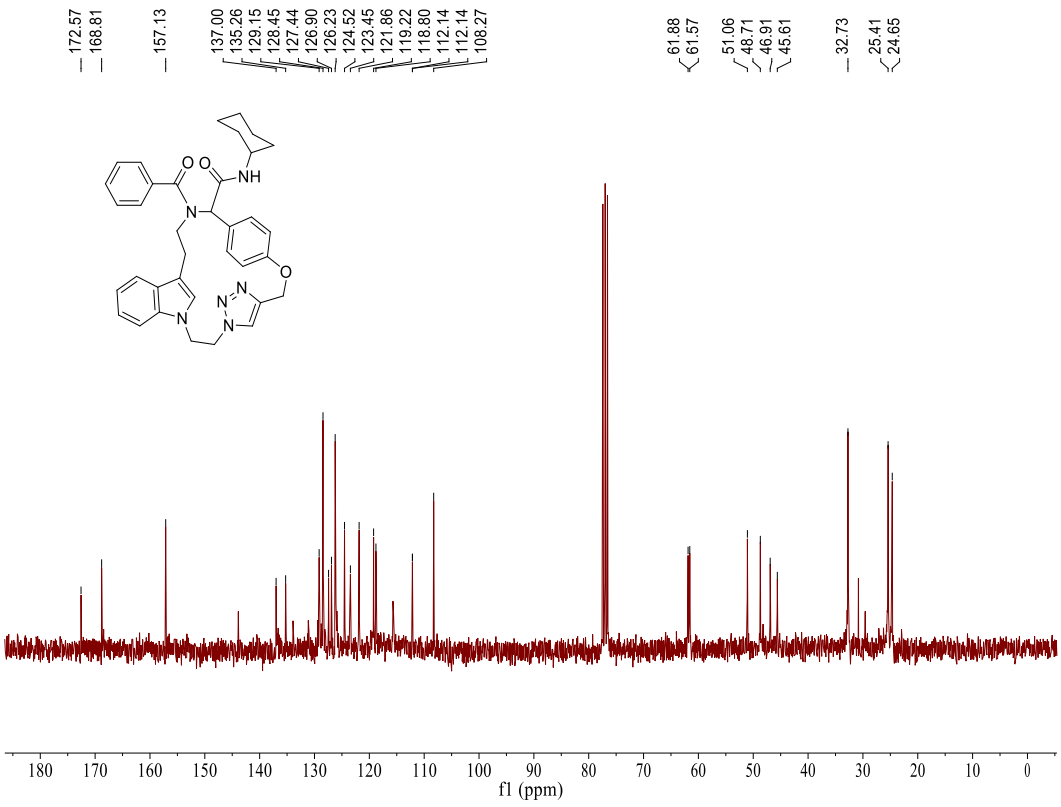
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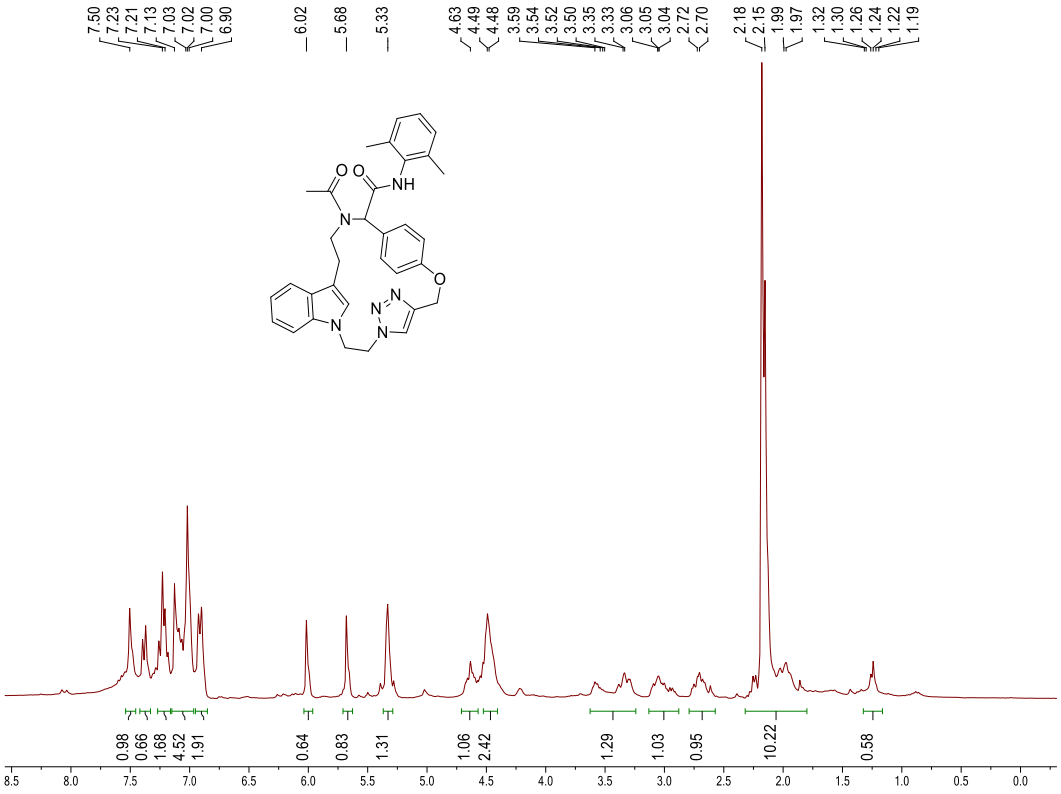
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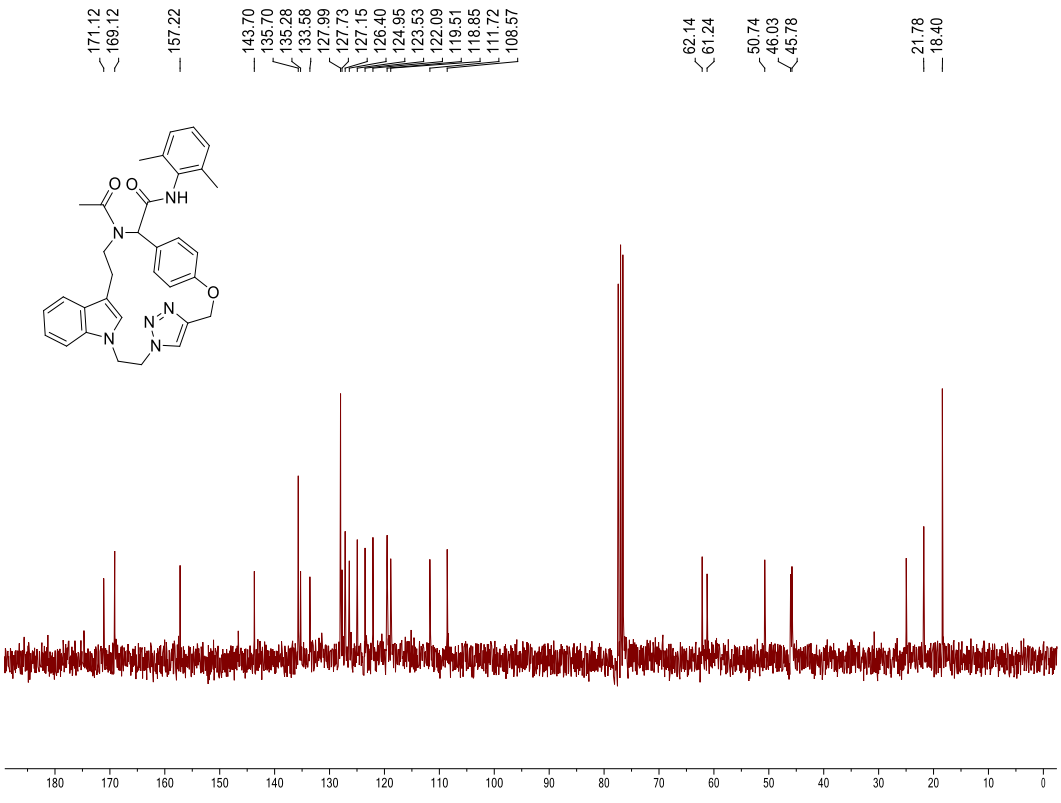
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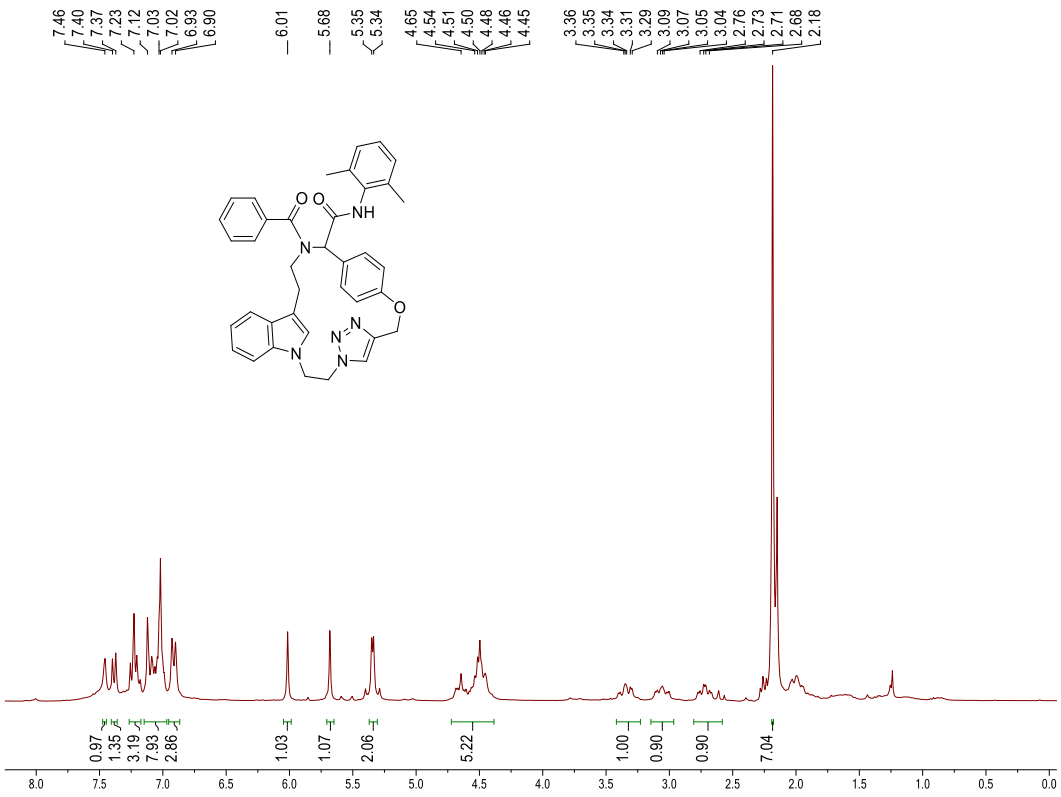
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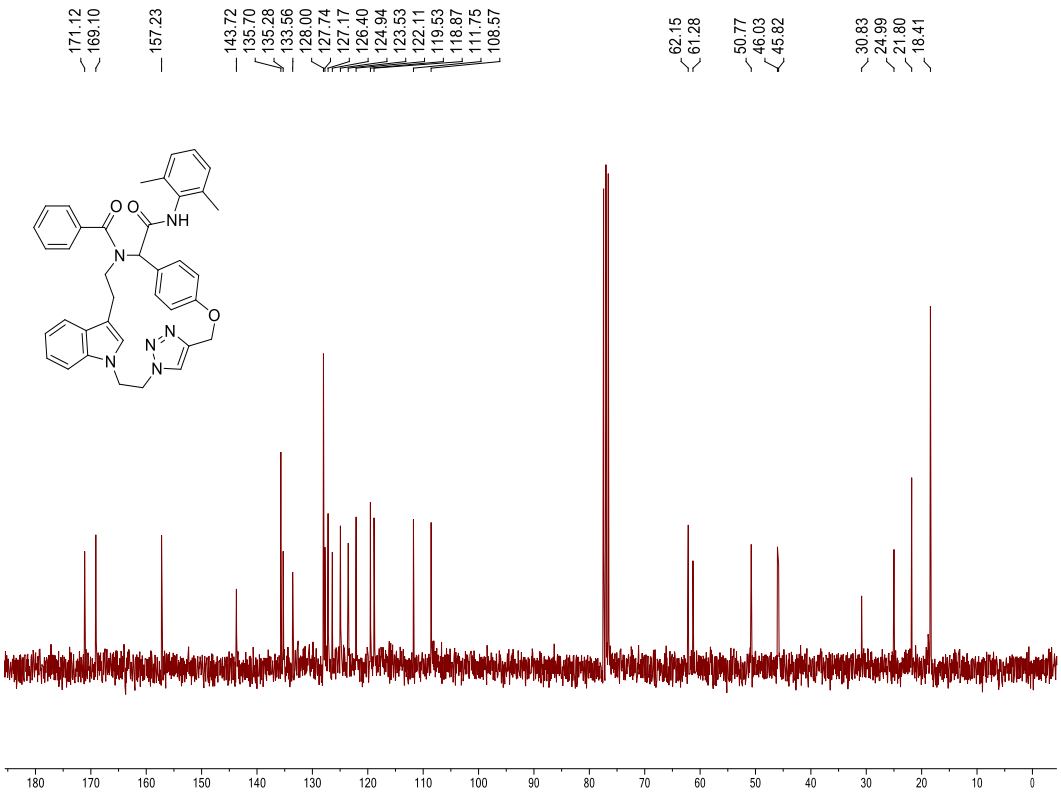
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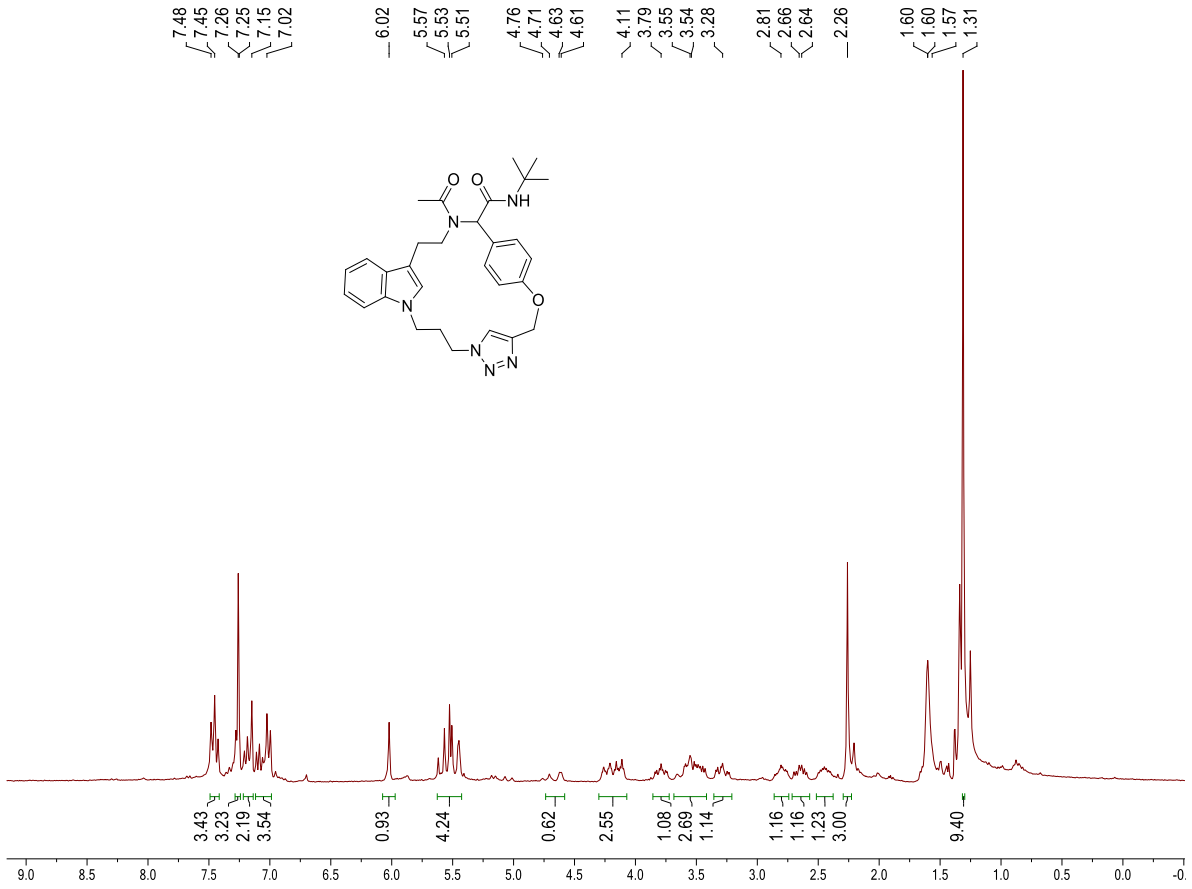
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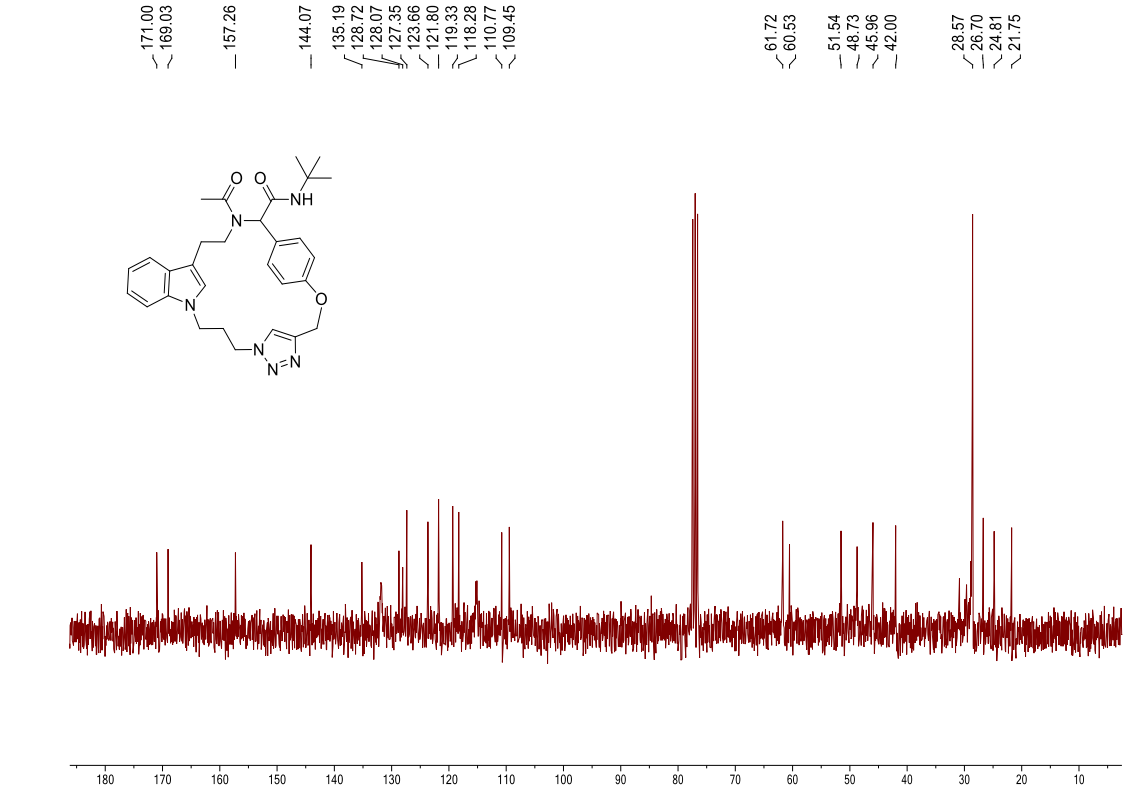
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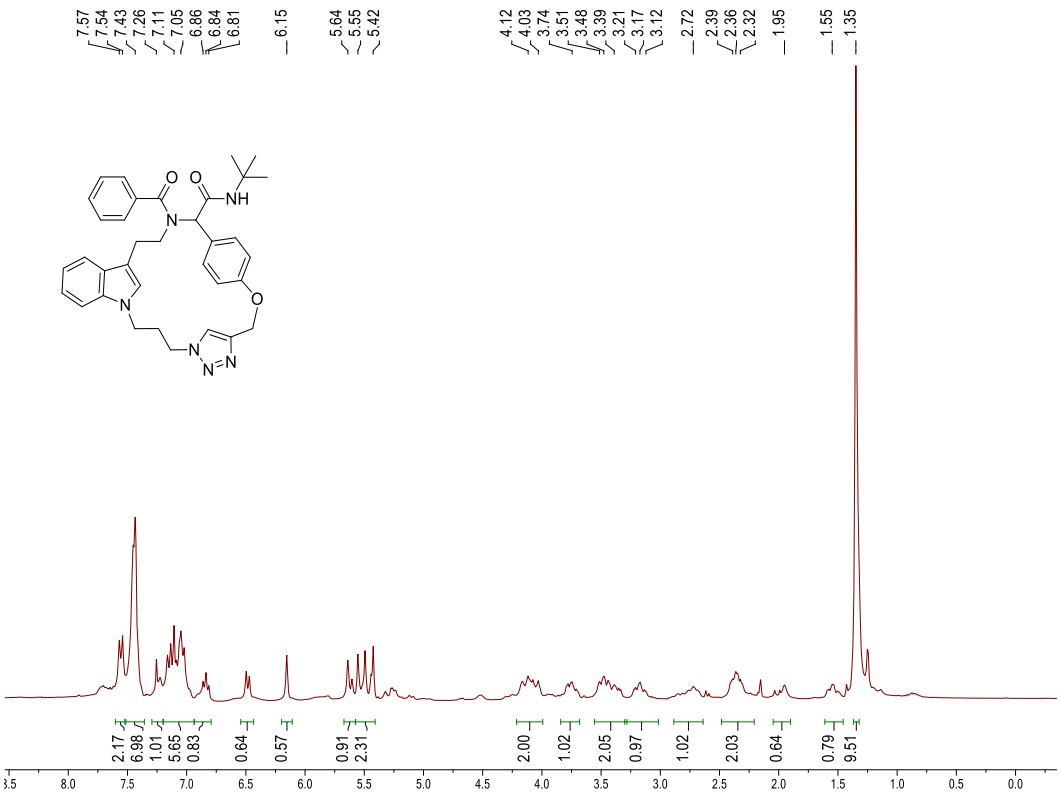
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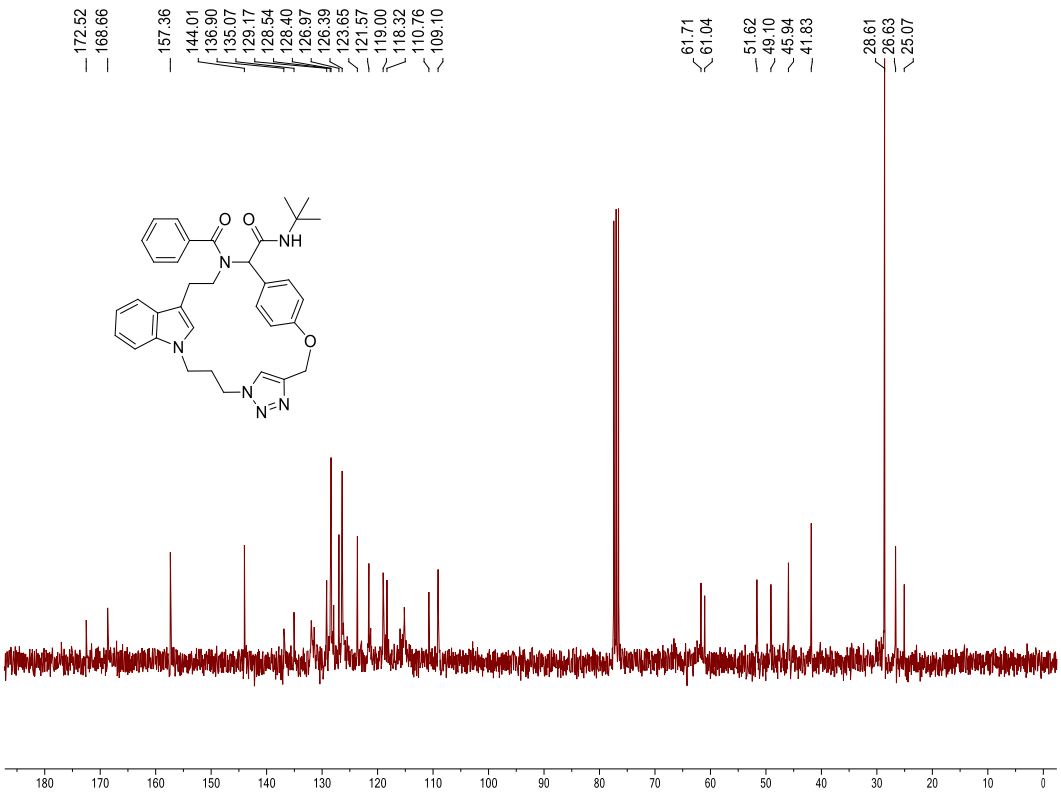
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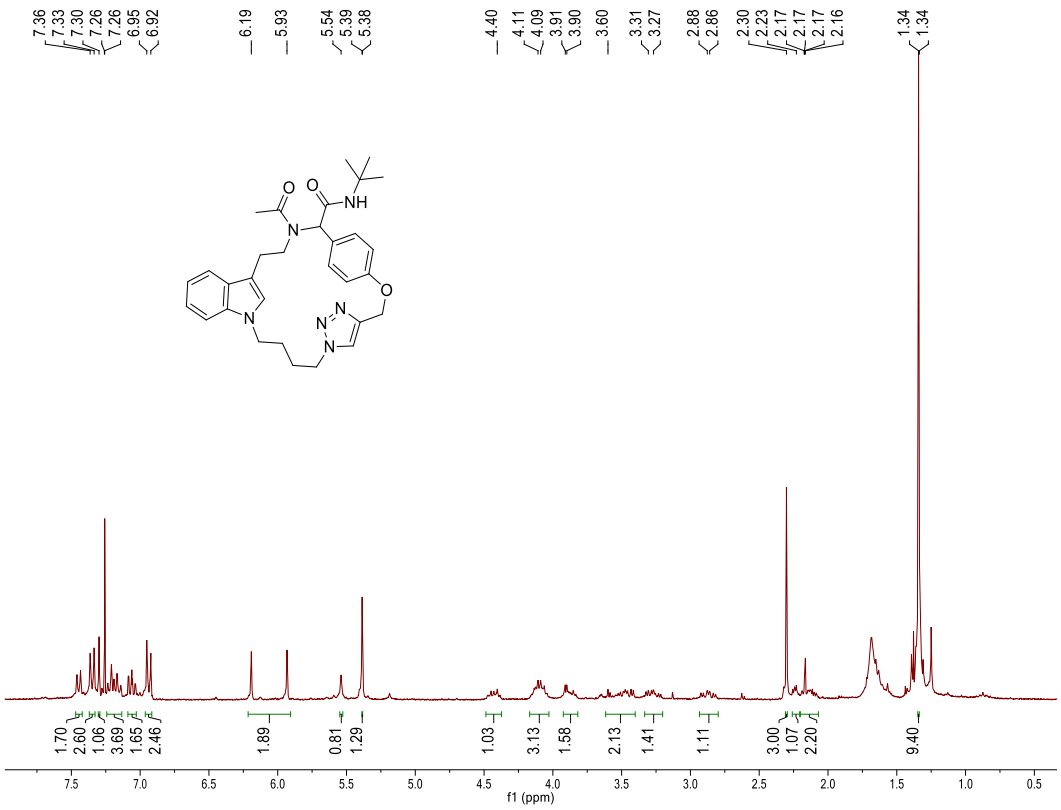
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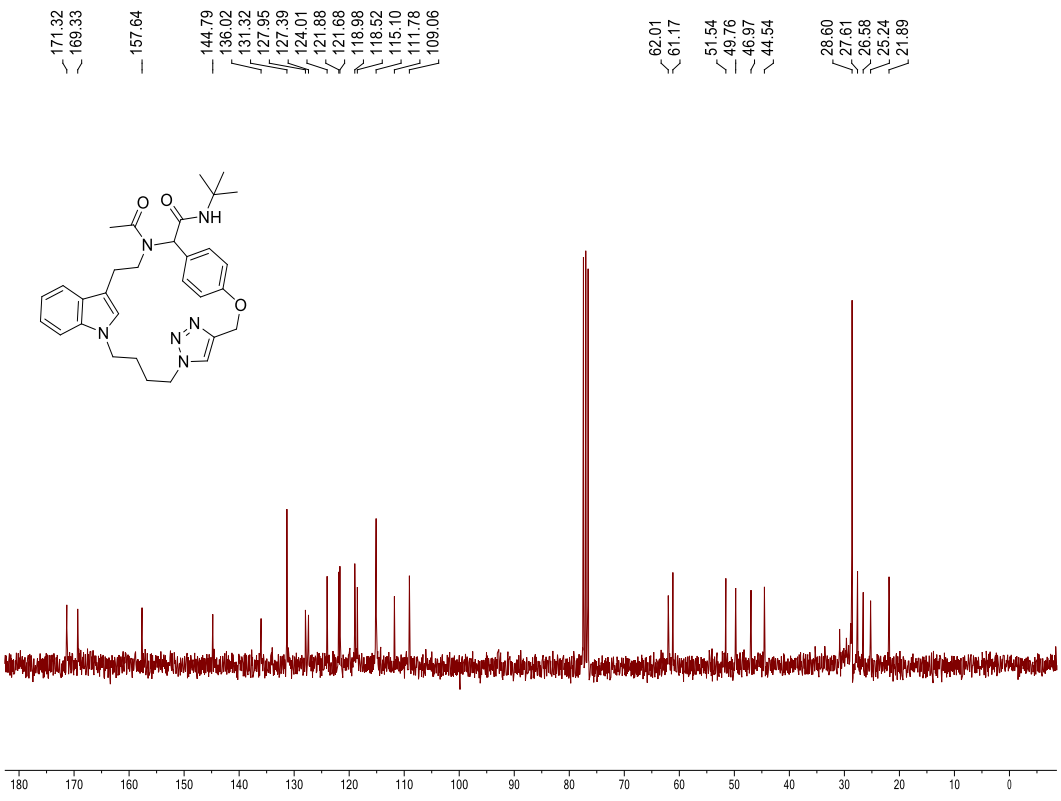
f1 (ppm)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118.52
115.10
111.78
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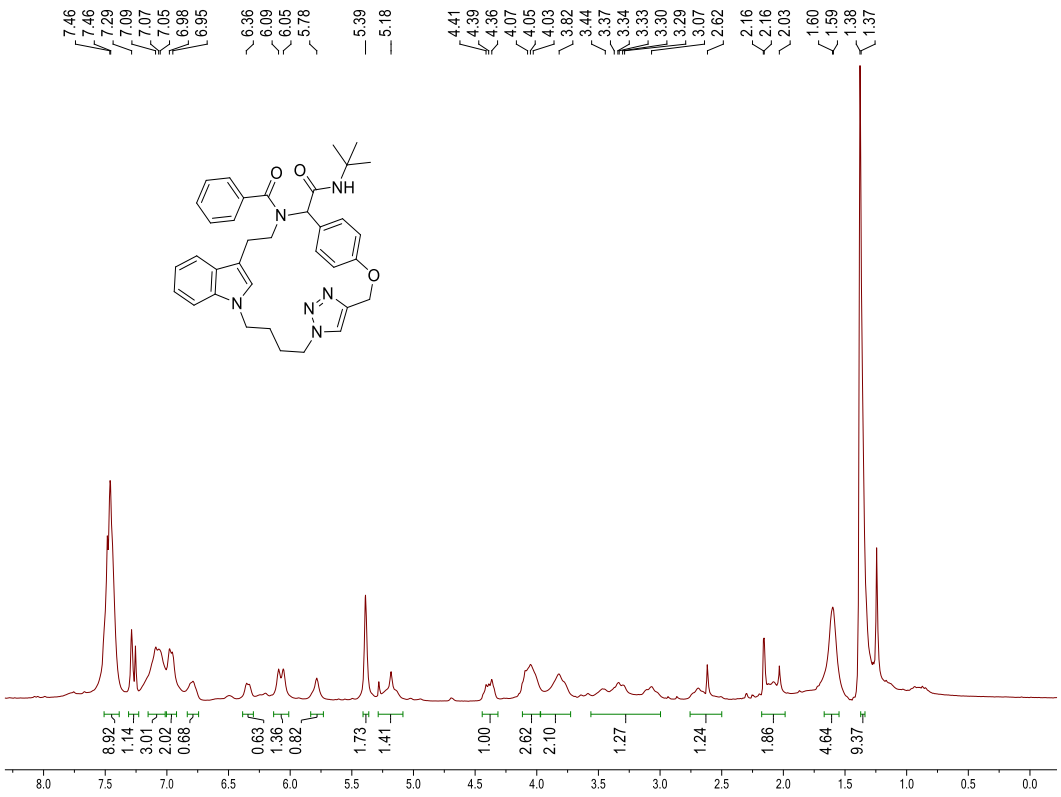
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5.18
4.41
4.39
4.36
4.07
4.05
4.03
3.82
3.44
3.37
3.34
3.33
3.30
3.29
3.07
2.62
2.16
2.16
2.03
1.60
1.59
1.38
1.37
8.92
1.14
3.01
2.02
0.68
0.63
1.36
0.82
1.73
1.41
1.00
2.62
2.10
1.27
1.24
1.86
4.64
9.37
8.0
7.5
7.0
6.5
6.0
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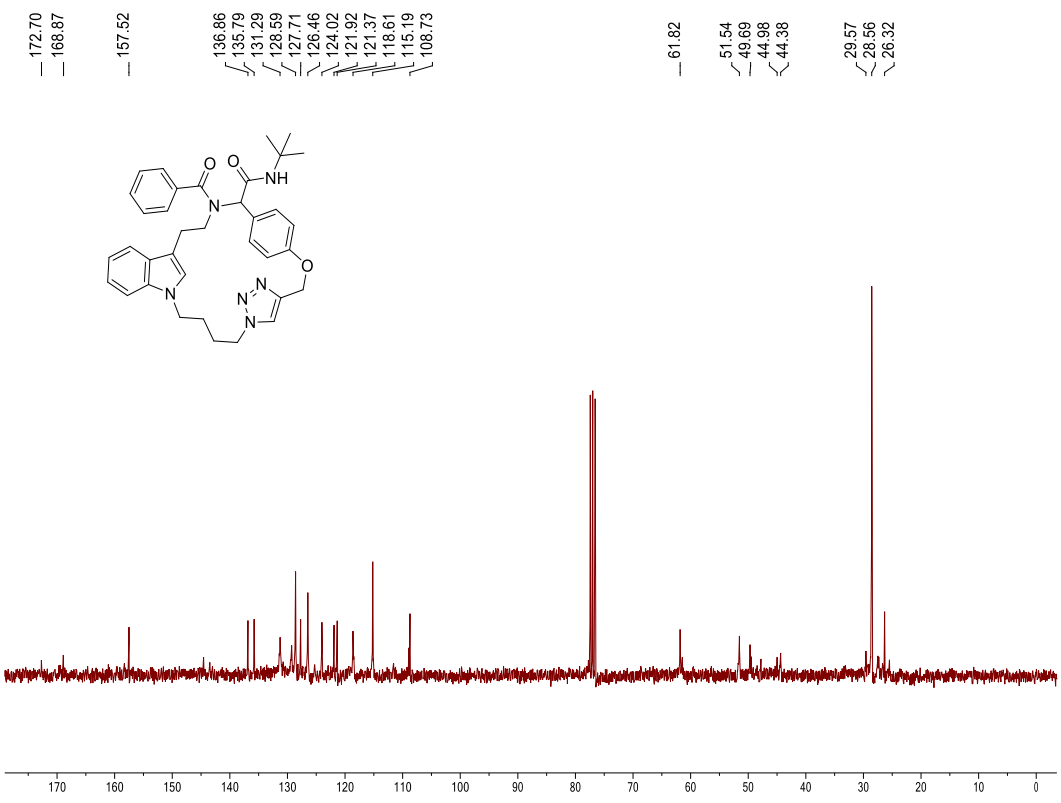
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115.19
108.73
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51.54
49.69
44.98
44.38
29.57
28.56
26.32
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150
140
130
120
110
100
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80
70
60
50
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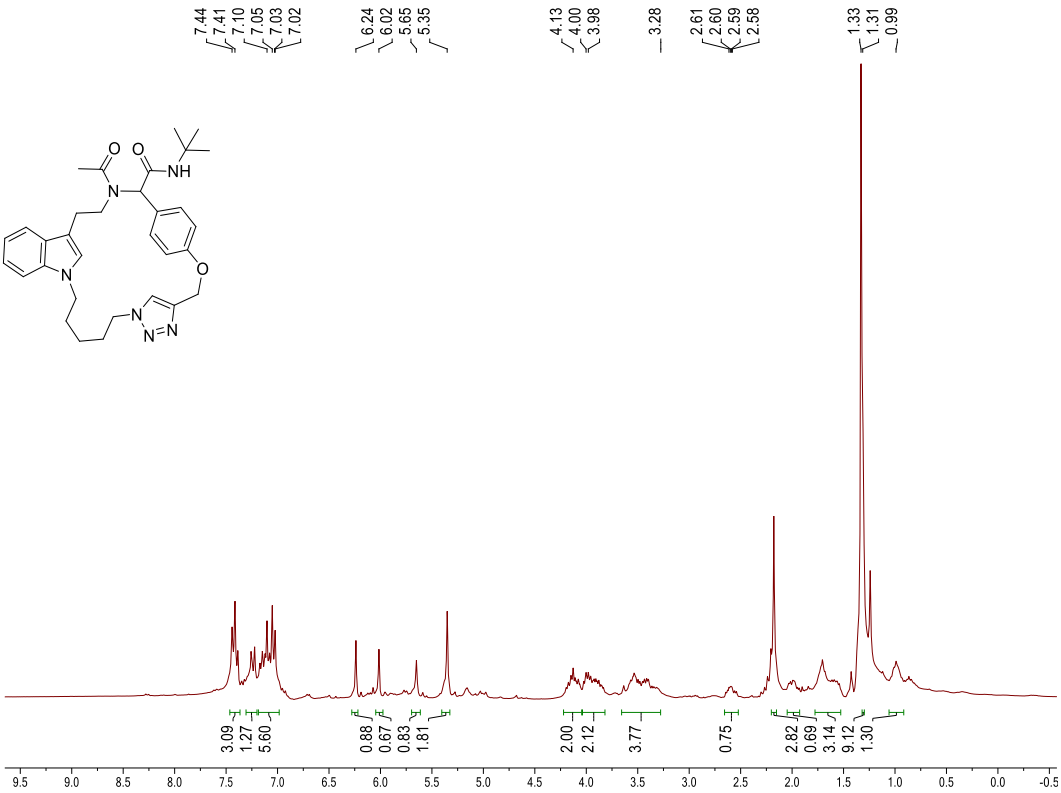
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7.02
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6.02
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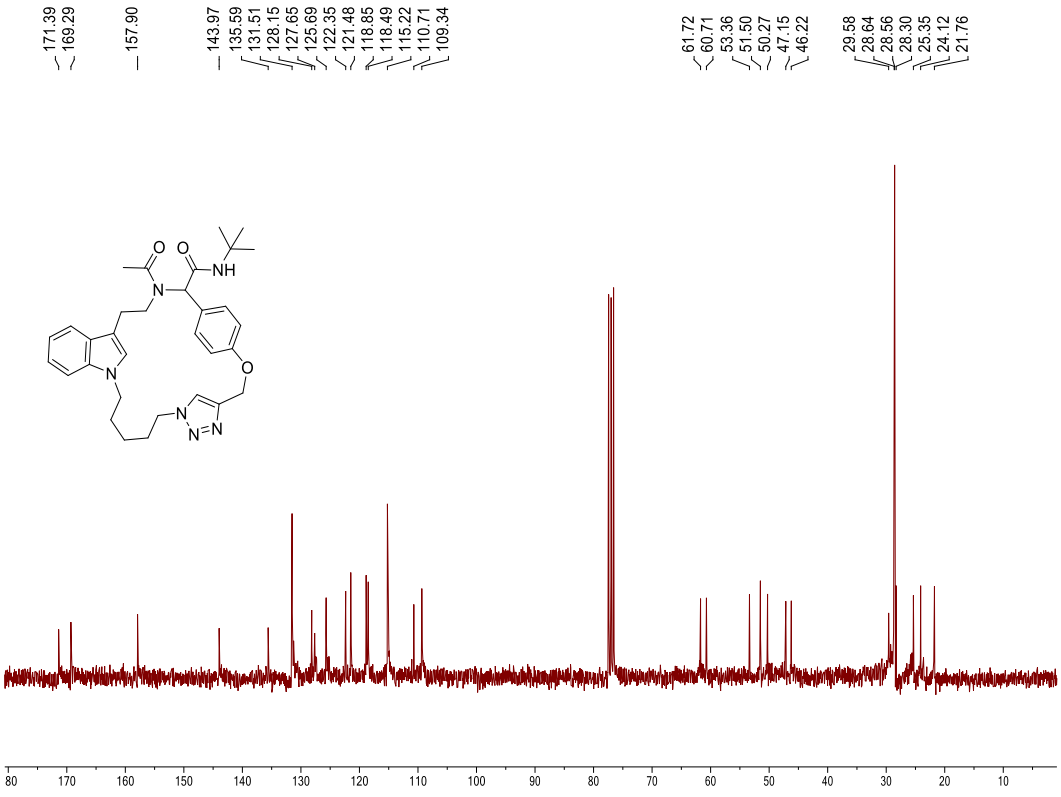
3.28
2.61
2.60
2.59
2.58
1.33
1.31
0.99
3.09
1.27
5.60
0.88
0.67
0.83
1.81
2.00
2.12
3.77
0.75
2.82
0.69
3.14
9.12
1.30
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5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109.34
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60.71
53.36
51.50
50.27
47.15
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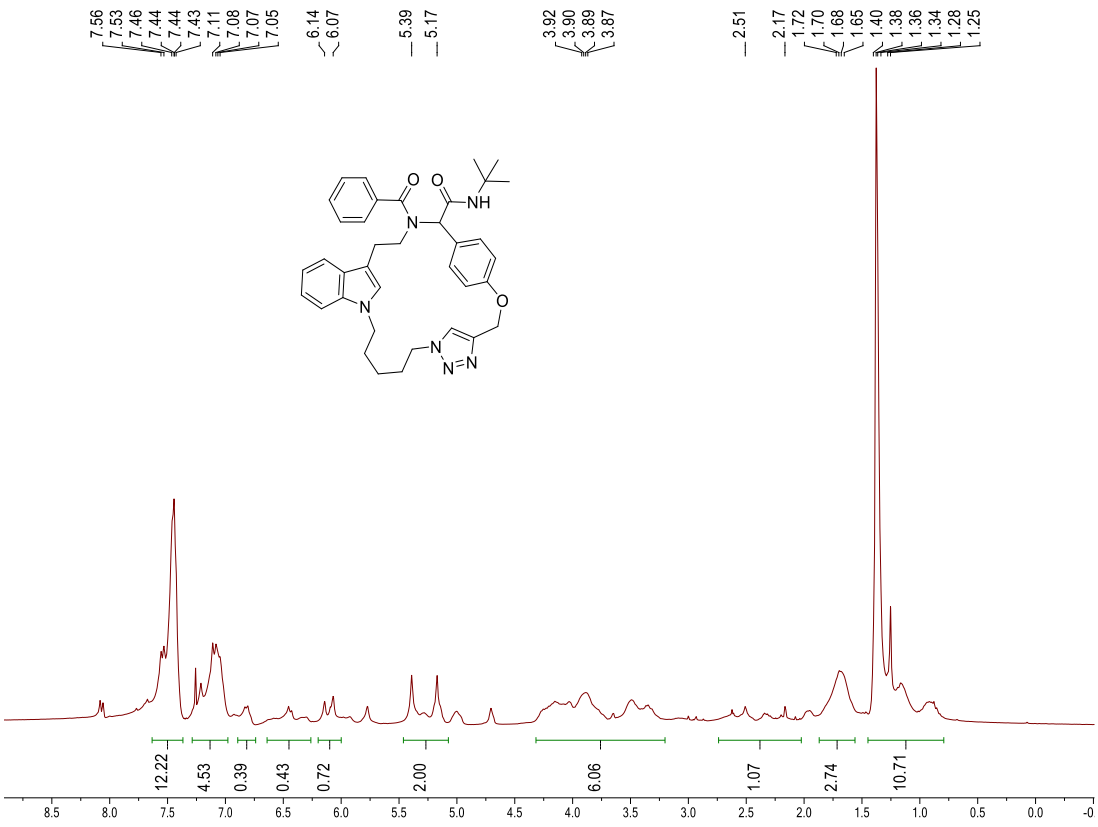
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7.46
7.44
7.44
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7.08
7.07
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6.14
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5.39
5.17
3.92
3.90
3.89
3.87
2.51
2.17
1.72
1.70
1.68
1.65
1.40
1.38
1.36
1.34
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6.06
1.07
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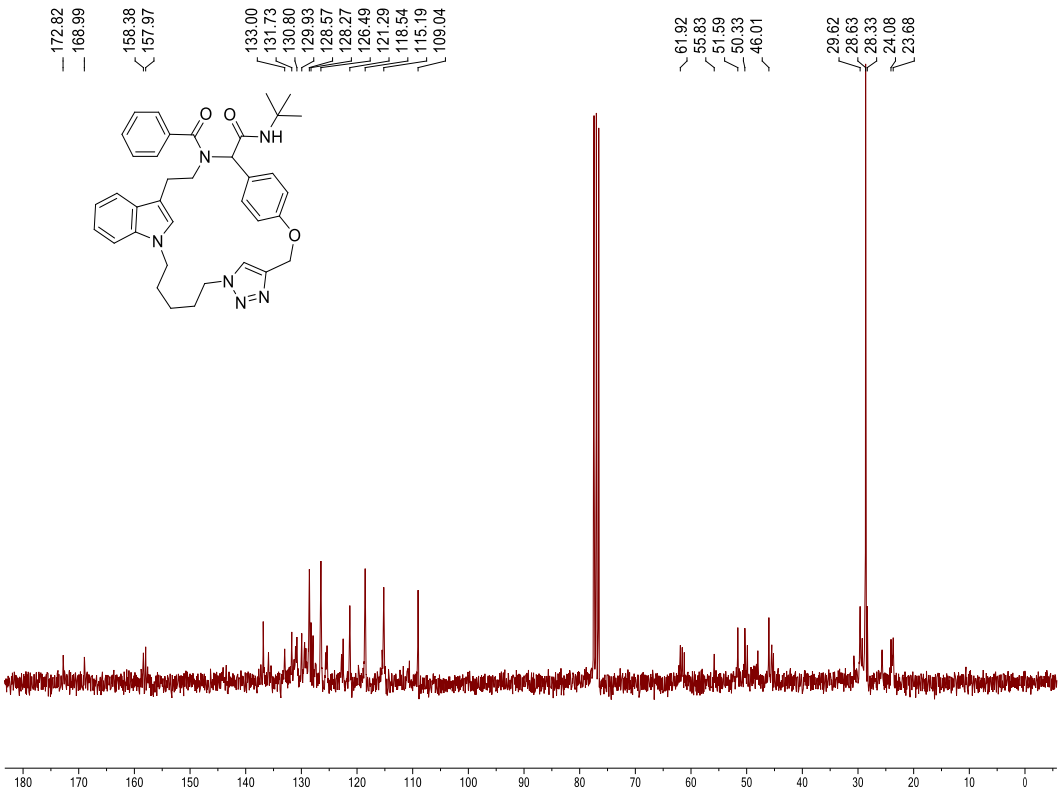
10.71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55.83
51.59
50.33
46.01
29.62
28.63
28.33
24.08
23.68