Electronic Supplementary Material (ESI) for Medicinal Chemistry Communications.

Supporting Information

Triazole Containing Novobiocin and Biphenyl Amides as Hsp90 C-Terminal Inhibitors

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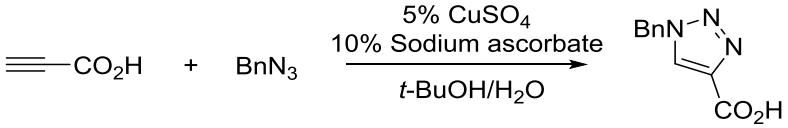
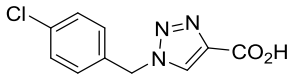
Chemistry General. The ^{1}H (500 and 400 MHz) and ^{13}C NMR (125 and 100 MHz) spectra were recorded on 500 and 400 MHz spectrometer. Data are reported as p = pentet, q = quartet, t = triplet, d = doublet, s = singlet, bs = broad singlet, m = multiplet; coupling constant(s) in Hz. High resolution mass spectral data were obtained on a time-of-flight mass spectrometer and analysis was performed using electrospray ionization. TLC was performed on glass backed silica gel plates with spots visualized by UV light. All solvents were reagent grade and, when necessary, were purified and dried by standard methods.

Synthesis and Compound Characterization

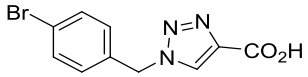
General procedure fot the synthesis of triazolyl acids 7.



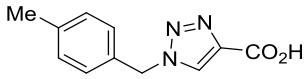
The triazolyl acids **7** were synthesized according to a literature procedure.[1] To a 100 mL sealed tube was added $CuSO_4$ (16 mg, 0.1 mmol), sodium ascorbate (40 mg, 0.2 mmol) and H_2O (2 mL). The mixture was then treated with azide (266 mg, 2.0 mmol) and *t*-BuOH (2 mL) and then propiolic acid (168 mg, 2.4 mmol), the tube was sealed and the mixture was stirred overnight. The mixture was then added saturated $NaHCO_3$ solution, extracted with ether (10 mL×2). The organic layer was then discarded, and the aqueous layer was acidified with 1N H_2SO_4, and extracted with EtOAc (15 mL×3) and dried over Na_2SO_4. The solvent was evaporated to afford the title trizole acid (334 mg, 82% yield) as a white solid which is usually pure enough to be used in the next step. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (s, 1 H), 7.44-7.40 (m, 3 H), 7.34-7.28 (m, 2 H), 5.60 (s, 2 H). HNMR is consistent with the literature.[1]



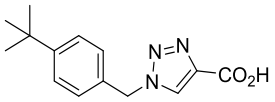
1-(4-Chlorobenzyl)-1H-1,2,3-triazole-4-carboxylic acid (**7g**): The reaction of 4-chlorobenzyl azide (6.9 mmol, 1.64 g), $CuSO_4$ (56 mg, 0.35 mmol), sodium ascorbate (140 mg, 0.7 mmol), and propiolic acid (590 mg, 8.4 mmol) in *t*-BuOH (8 mL) and H_2O (8 mL) to afford the title triazole acid (987 mg, 60% yield) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.14 (s, 1 H), 8.79 (s, 1 H), 7.49-743 (m, 2 H), 7.40-7.35 (m, 2 H), 5.66 (s, 2 H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 161.6, 139.9, 134.6, 133.0, 130.0, 129.1, 128.8, 52.2; HRMS (TOF-ESI) calcd for $C_{10}H_8ClN_3O_2Na[M+Na]^+$: 260.0203, found: 260.0200.



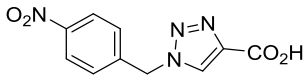
1-(4-Bromobenzyl)-1H-1,2,3-triazole-4-carboxylic acid (**7h**): The reaction of 4-bromobenzyl azide (5 mmol, 1.06 g), $CuSO_4$ (40 mg, 0.25 mmol), sodium ascorbate (100 mg, 0.5 mmol), and propiolic acid (420 mg, 6 mmol) in *t*-BuOH (6 mL) and H_2O (6 mL) to afford the title triazole acid (575 mg, 40% yield) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.74 (s, 1 H), 7.61-7.57 (m, 2 H), 7.33-7.28 (m, 2 H), 5.63 (s, 2 H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 161.7, 140.3, 135.0, 131.7, 130.3, 128.9, 121.6, 52.2; HRMS (TOF-ESI) calcd for $C_{10}H_8BrN_3O_2Na[M+Na]^+$: 303.9698, found: 303.9705.



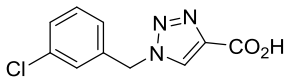
1-(4-Methylbenzyl)-1H-1,2,3-triazole-4-carboxylic acid (**7i**): The reaction of 4-methylbenzyl azide (636 mg, 4.32 mmol), $CuSO_4$ (35 mg, 0.22 mmol), sodium ascorbate (86 mg, 0.43 mmol), and propiolic acid (364 mg, 5.2 mmol) in *t*-BuOH (6 mL) and H_2O (6 mL) to afford the title triazole acid (712 mg, 76% yield) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.74 (s, 1 H), 7.25 (d, J = 8.0 Hz, 2 H), 7.19 (d, J = 8.0 Hz, 2 H), 5.59 (s, 2 H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 161.6, 139.8, 137.6, 132.6, 129.3, 128.9, 128.0, 52.8, 20.7; HRMS (TOF-ESI) calcd for $C_{11}H_{11}N_3O_2Na[M+Na]^+$: 240.0749; found: 240.0742.



1-(4-t-Butylbenzyl)-1H-1,2,3-triazole-4-carboxylic acid (**7k**): The reaction of 4-*t*-butylbenzyl azide (4.68 mmol, 886 mg), $CuSO_4$ (37 mg, 0.23 mmol), sodium ascorbate (93 mg, 0.47 mmol), and propiolic acid (328 mg, 4.68 mmol) in *t*-BuOH (8 mL) and H_2O (8 mL) to afford the title triazole acid (750 mg, 62% yield) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.77 (s, 1 H), 7.43-7.36 (m, 2 H), 7.31-7.25 (m, 2 H), 5.60 (s, 2 H), 1.26 (s, 9 H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 161.6, 150.8, 139.8, 132.7, 128.9, 127.8, 125.6, 52.7, 34.3, 31.0; HRMS (TOF-ESI) calcd for $C_{14}H_{17}N_3O_2Na[M+Na]^+$; 282.1218; found: 282.1215.

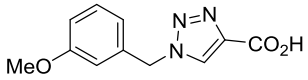


1-(4-Nitrobenzyl)-1H-1,2,3-triazole-4-carboxylic acid (**7l**): The reaction of 4-nitrobenzyl azide (777 mg, 4.36 mmol), $CuSO_4$ (35 mg, 0.22 mmol), sodium ascorbate (86 mg, 0.436 mmol), and propiolic acid (305 mg, 4.36 mmol) in *t*-BuOH (10 mL) and H_2O (10 mL) to afford the title triazole acid (940 mg, 87% yield) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.18 (s, 1 H), 8.86 (s, 1 H), 8.25 (d, J = 8.8 Hz, 2 H), 7.57 (d, J = 8.8 Hz, 2 H), 5.84 (s, 2 H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 161.5, 147.3, 142.9, 140.0, 129.5, 129.1, 124.0, 52.1; HRMS (TOF-ESI) calcd for $C_{10}H_8N_4O_4Na[M+Na]^+$: 271.0443, found: 277.0436.

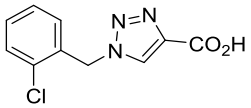


1-(3-Chlorobenzyl)-1H-1,2,3-triazole-4-carboxylic acid (**7n**): The reaction of 3-chlorobenzyl azide (309 mg, 1.84 mmol), propiolic acid (126 mg, 1.8 mmol), $CuSO_4$ (15 mg, 0.092 mmol), sodium ascorbate (37 mg, 0.184 mmol) in *t*-BuOH (10 mL) and H_2O (10 mL) afforded the title compound (280 mg, 66% yield) as an off-white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.14 (bs, 1 H), 8.83 (s, 1 H), 7.49-7.45 (m, 1 H), 7.44-7.40 (m, 2 H), 7.34-

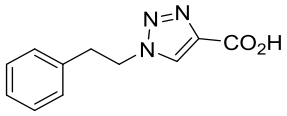
7.27 (m, 1 H), 5.67 (s, 2 H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 161.6, 139.9, 137.9, 133.3, 130.7, 129.2, 128.3, 128.0, 126.8, 52.2; HRMS (TOF-ESI) calcd for $C_{10}H_8ClN_3O_2Na[M+Na]^+$: 260.0203, found: 260.0210.



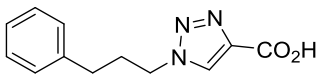
1-(3-Methoxybenzyl)-1H-1,2,3-triazole-4-carboxylic acid (**7o**): The reaction of 3-methoxylbenzyl azide (734 mg, 4.5 mmol), $CuSO_4$ (36 mg, 0.225 mmol), sodium ascorbate (89 mg, 0.45 mmol), and propiolic acid (280 mg, 4.0 mmol) in *t*-BuOH (10 mL) and H_2O (10 mL) to afford the title triazole acid (690 mg, 74% yield) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.12 (s, 1 H), 8.78 (s, 1 H), 7.30 (t, *J* = 8.0 Hz, 1 H), 6.96-6.87 (s, 3 H), 5.61 (s, 2 H), 3.75 (s, 3 H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 161.6, 159.4, 139.8, 137.0, 130.0, 129.0, 120.1, 113.8, 113.7, 55.1, 52.9; HRMS (TOF-ESI) calcd for $C_{11}H_{11}N_3O_3Na[M+Na]^+$: 256.0698, found: 256.0694.



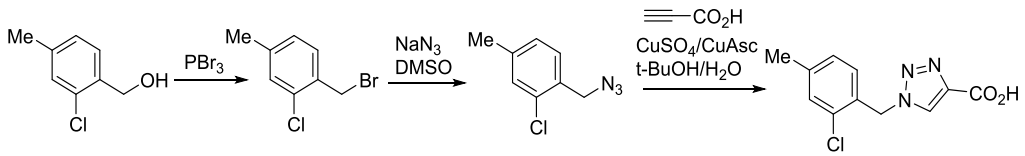
1-(2-Chlorobenzyl)-1H-1,2,3-triazole-4-carboxylic acid (**7p**): The reaction of 2-chlorobenzyl azide (4.87 mmol, 816 mg), $CuSO_4$ (40 mg, 0.25 mmol), sodium ascorbate (99 mg, 0.5 mmol), and propiolic acid (420 mg, 6.0 mmol) in *t*-BuOH (8 mL) and H_2O (8 mL) to afford the title triazole acid (817 mg, 71% yield) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.15 (bs, 1 H), 8.74 (s, 1 H), 7.56-7.51 (m, 1 H), 7.45-7.35 (m, 2 H), 7.28-7.23 (m, 1 H), 5.77 (s, 2 H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 161.6, 139.7, 132.8, 132.6, 130.5, 130.4, 129.6, 129.5, 127.8, 50.8; HRMS (TOF-ESI) calcd for $C_{10}H_8ClN_3O_2Na[M+Na]^+$: 260.0203, found: 260.0201.



1-Phenethyl-1H-1,2,3-triazole-4-carboxylic acid (**7r**): The reaction of 2-phenylethylazide (721 mg, 4.9 mmol), propiolic acid (274 mg, 3.92 mmol), $CuSO_4$ (40 mg, 0.25 mmol) and sodium ascorbate (100 mg, 0.50 mmol) in *t*-BuOH/H_2O (10 mL/10 mL) afforded the title acid (635 mg, 75% yield) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.05 (s, 1 H), 8.59 (s, 1 H), 7.32-7.24 (m, 2 H), 7.24-7.15 (m, 3 H), 4.67 (t, *J* = 7.2 Hz, 2 H), 3.20 (t, *J* = 7.2 Hz, 2 H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 161.7, 139.4, 137.3, 128.9, 128.7, 128.4, 126.6, 50.6, 35.4; HRMS (TOF-ESI) calcd for $C_{11}H_{11}N_3O_2Na[M+Na]^+$: 240.0749, found: 240.0746.

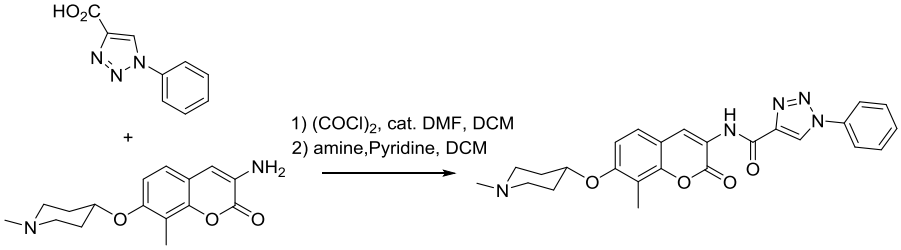


1-(3-Phenylpropyl)-1H-1,2,3-triazole-4-carboxylic acid (**7s**): The reaction of 3-phenylpropylazide (604 mg, 3.75 mmol), propiolic acid (224 mg, 3.2 mmol), $CuSO_4$ (25.6 mg, 0.16 mmol, 5 mol%) and sodium ascorbate (63 mg, 0.32 mmol, 10 mol%) in *t*-BuOH/H_2O (10 mL/10 mL) afforded the title acid (631 mg, 85% yield) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.06 (bs, 1 H), 8.74 (s, 1 H), 7.33-7.26 (m, 2 H), 7.24-7.16 (m, 3 H), 4.42 (t, *J* = 7.2 Hz, 2 H), 2.57 (t, *J* = 7.2 Hz, 2 H), 2.17 (pent, *J* = 7.2 Hz, 2 H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 161.7, 140.6, 128.8, 128.4, 128.3, 126.0, 49.2, 31.8, 31.0 ; HRMS (TOF-ESI) calcd for $C_{12}H_{14}N_3O_2[M+H]^+$: 232.1086, found: 232.1075.



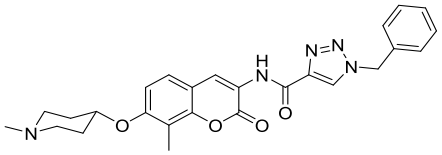
1-(2-Chloro-4-methylbenzyl)-1H-1,2,3-triazole-4-carboxylic acid (**7t**): To a solution of 2-chloro-4-methylbenzyl alcohol (4 mmol, 626 mg) in dry DCM (10 mL) was added PBr_3 (mL, 4.4 mmol) dropwise at 0^oC. The solution was stirred for 30 min at 0^oC and quenched with $NaHCO_3$ solution. The organic phase was separated and the aqueous phase extracted with DCM (10 mL×3). The combined organic phase was washed with brine, dried over Na_2SO_4 and evaporated to dryness. The residue was dissolved in dry DMSO (10 mL), treated with NaN_3 (390 mg, 6 mmol) and the mixture was stirred at 50^oC overnight. Then the reaction mixture was poured into water, extracted with ether (15 mL×3), dried over Na_2SO_4 and evaporated to get the azide (283 mg). The azide was then dissolved in *t*-BuOH (8 mL) and to the solution was added $CuSO_4$ (13 mg, 0.078 mmol), sodium ascorbate (31 mg, 0.156 mmol), H_2O (8 mL) and propiolic acid (109 mg, 1.56 mmol) and the mixture was sealed and stirred at room temperature overnight. The resulting suspension was poured into $NaHCO_3$ solution, and extracted with ether (15 mL×2) and the ethereal solution was discarded. The aqueous phase was acidified with 1N H_2SO_4 and extracted with EtOAc (15 mL×3), and the combined organic phase dried over Na_2SO_4 and evaporated to dryness to obtain the final acid (217 mg, 55% yield) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.13 (bs, 1 H), 8.69 (s, 1 H), 7.36 (s, 1 H), 7.20 (s, 2 H), 5.71 (s, 2 H), 2.30 (s,3 H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 161.6, 140.5, 139.6, 132.4, 130.6, 129.9, 129.7, 129.3, 128.4, 50.6, 20.3; HRMS (TOF-ESI) calcd for $C_{11}H_{10}ClN_3O_2Na[M+Na]^+$: 274.0359, found: 274.0354.

General procedure for the amide coupling reaction:

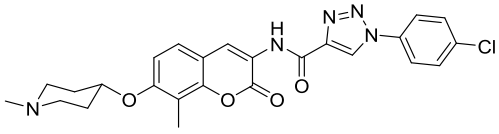


N-(8-methyl-7-((1-methylpiperidin-4-yl)oxy)-2-oxo-2H-chromen-3-yl)-1-phenyl-1H-1,2,3-triazole-4-carboxamide (**4a**): to a solution of the triazole acid (0.13 mmol) in dry DCM (3 mL) was added sequentially $(COCl)_2$ (0.40 mmol) and DMF (5 µL) under Ar and the resulting solution was stirred at room temperature overnight. Then the solvent was removed *in vacuo* and the residue was put on the high vacuum for 30 min. To another oven-dried RBF was added the amine (0.067 mmol), dry DCM (3 mL) and pyridine (0.6 mmol). To the above solution was added a solution of the acid chloride in dry DCM (4 mL) via a syringe dropwise. After addition the solution was stirred at room temperature overnight. Then the mixture was directly loaded on a silica gel column and eluded with 5% MeOH in DCM to afford the title product (13 mg, 43% yield). ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.64 (s, 1 H), 9.59 (s, 1 H), 8.65 (s, 1 H), 8.06-8.01 (m, 2 H), 7.68-7.62 (m, 3 H), 7.60-7.54 (m, 1 H), 7.20-7.15 (m, 1 H), 4.80-4.60 (m, 1 H), 3.05-2.80

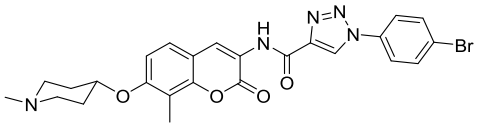
(m, 2 H), 2.60-2.40 (m, 2 H), 2.70 (s, 3 H), 2.12-1.98 (m, 2 H), 1.94-1.74 (m, 2 H); One methyl group overlays with solvent residue peaks. ^{13}C NMR (125 MHz, DMSO-d_6) δ 158.2, 157.9, 156.4, 149.2, 142.5, 136.1, 130.0, 129.4, 126.2, 125.6, 125.1, 120.8, 120.6, 113.6, 112.8, 110.8, 51.1, 44.4, 29.0, 8.2; HRMS (TOF-ESI) calcd for $C_{25}H_{26}N_5O_4[M+H]^+$: 460.1985, found: 460.1971.



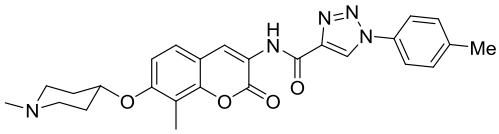
1-Benzyl-N-(8-methyl-7-((1-methylpiperidin-4-yl)oxy)-2-oxo-2H-chromen-3-yl)-1H-1,2,3-triazole-4-carboxamide (**4b**): Following the general procedure, the title compound was obtained as a white solid (15 mg, 47% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.65 (s, 1 H), 8.69 (s, 1 H), 8.05 (s, 1 H), 7.50-7.22 (m, 6 H), 6.90-6.83 (m, 1 H), 5.62 (s, 2 H), 4.48 (bs, 1 H), 2.74-2.56 (m, 2 H), 2.50-2.24 (m, 8 H), 2.12-1.98 (m, 2 H), 1.98-1.83 (m, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.71, 158.68, 157.0, 149.7, 143.1, 133.6, 129.3, 129.2, 128.3, 125.6, 125.4, 124.7, 121.0, 115.3, 113.1, 110.3, 72.3, 54.6, 52.2, 46.2, 30.7, 8.3; HRMS (TOF-ESI) calcd for $C_{26}H_{28}N_5O_4[M+H]^+$: 474.2152; found: 474.2141.



1-(4-chlorophenyl)-N-(8-methyl-7-((1-methylpiperidin-4-yl)oxy)-2-oxo-2H-chromen-3-yl)-1H-1,2,3-triazole-4-carboxamide (**4c**): Following the general procedure, the title compound was obtained as light yellow solid (19 mg, 58% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.71 (s, 1 H), 8.76 (s, 1 H), 8.58, s, 1 H), 7.82-7.73 (m, 2 H), 7.63-7.54 (m, 2 H), 7.35 (d, J = 8.4 Hz, 1 H), 6.89 (d, J = 8.4 Hz, 1 H), 4.56-4.46 (m, 1 H), 2.78-2.63 (m, 2 H), 2.55-2.40 (m, 2 H), 2.38 (s, 3 H), 2.37 (s, 3 H), 2.16-2.03 (m, 2 H), 2.02-1.89 (m, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$ with minor CD_3OD) δ 158.7, 158.4, 156.8, 149.5, 143.0, 135.3, 134.6, 130.0, 125.6, 125.3, 124.0, 121.8, 120.6, 115.0, 112.9, 110.1, 70.8, 51.4, 45.4, 29.4, 29.1, 8.0; HRMS (TOF-ESI) calcd for $C_{25}H_{25}ClN_5O_4[M+H]^+$: 494.1595; found: 494.1614.

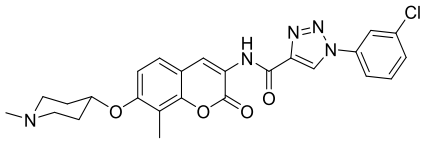


1-(4-Bromophenyl)-N-(8-methyl-7-((1-methylpiperidin-4-yl)oxy)-2-oxo-2H-chromen-3-yl)-1H-1,2,3-triazole-4-carboxamide (**4d**): Following the general procedure, title compound was obtained as light yellow solid (23 mg, 72% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.71 (s, 1 H), 8.77 (s, 1 H), 8.58 (s, 1 H), 7.78-7.67 (m, 3 H), 7.36 (d, J = 8.4 Hz, 1 H), 6.90 (d, J = 8.4 Hz, 1 H), 4.63-4.42 (m, 1 H), 2.84-2.70 (m, 2 H), 2.55-2.40 (m, 2 H), 2.43 (s, 3 H), 2.38 (s, 3 H), 2.15 (m, 2 H), 2.00 (m, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.7, 157.4, 148.8, 142.6, 134.3, 131.2, 124.7, 123.9, 122.6, 122.5, 121.2, 120.1, 114.3, 112.2, 109.2, 50.8, 44.7, 29.0, 7.4; HRMS (TOF-ESI) calcd for $C_{25}H_{25}{}^{79}BrN_5O_4[M+H]^+$: 538.1090; found: 538.1089.

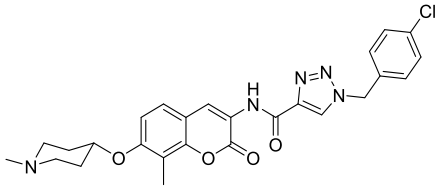


1-(4-methylphenyl)-N-(8-methyl-7-((1-methylpiperidin-4-yl)oxy)-2-oxo-2H-chromen-3-yl)-1H-1,2,3-triazole-4-carboxamide (**4e**): Following the general procedure, the title compound was obtained as a white solid (17 mg, 53% yield). ^{1}H NMR (400 MHz, $CDCl_3$)

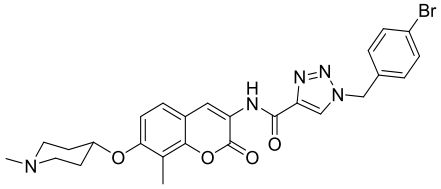
δ 9.71 (s, 1 H), 8.75 (s, 1 H), 8.55 (s, 1 H), 7.64-7.70 (m, 2 H), 7.41-7.36 (m, 2 H), 7.34 (d, *J* = 8.8 Hz, 1 H), 6.89 (d, *J* = 8.8 Hz, 1 H), 4.54-4.41 (m, 1 H), 2.75-2.58 (m, 2 H), 2.46 (s, 3 H), 2.44-2.31 (m, 8 H), 2.10-1.99 (m, 2 H), 1.99-1.87 (m, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.7, 158.6, 157.1, 149.7, 143.2, 139.8, 134.1, 130.4, 125.5, 124.8, 123.7, 121.0, 120.6, 115.3, 113.0, 110.3, 52.3, 46.2, 30.7, 21.1, 8.3; HRMS (TOF-ESI) calcd for $C_{26}H_{28}N_5O_4[M+H]^+$: 474.2141; found: 474.2143.



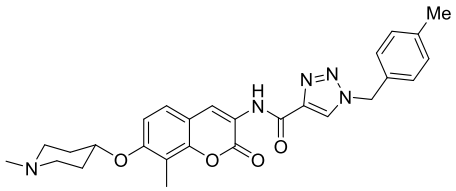
1-(3-Chlorophenyl)-N-(8-methyl-7-((1-methylpiperidin-4-yl)oxy)-2-oxo-2H-chromen-3-yl)-1H-1,2,3-triazole-4-carboxamide (**4f**): following the general procedure, the title compound was obtained as an off-white solid (20 mg, 67% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.69 (s, 1 H), 8.75 (s, 1 H), 8.60 (s, 1 H), 7.86 (s, 1 H), 7.75-7.66 (m, 1 H), 7.60-7.51 (m, 2 H), 7.34 (d, *J* = 8.4 Hz, 1 H), 6.89 (d, *J* = 8.4 Hz, 1 H), 4.55-4.42 (m, 1 H), 2.78-2.60 (m, 2 H), 2.5-2.36 (m, 2 H), 2.36 (s, 6 H), 2.15-2.00 (m, 2 H), 2.00-1.80 (m, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.1, 157.7, 156.7, 149.2, 142.6, 137.1, 134.2, 131.6, 129.2, 126.2, 125.8, 125.3, 120.6, 120.4, 119.2, 113.5, 112.6, 110.9, 71.8, 51.7, 45.6, 30.1, 8.1; HRMS (TOF-ESI) calcd for $C_{25}H_{25}{}^{35}ClN_5O_4[M+H]^+$: 494.1595; found: 494.1584.



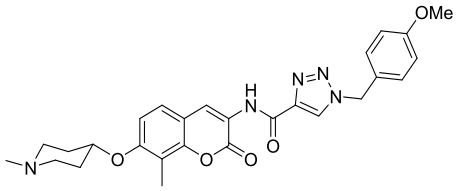
1-(4-Chlorobenzyl)-N-(8-methyl-7-((1-methylpiperidin-4-yl)oxy)-2-oxo-2H-chromen-3-yl)-1H-1,2,3-triazole-4-carboxamide (**4g**): Following the general procedure, the 4-chlorobenzyl analogue was obtained as a white solid (24 mg, 79% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.65 (s, 1 H), 8.71 (s, 1 H), 8.06 (s, 1 H), 7.43-7.39 (m, 2 H), 7.33 (d, *J* = 8.4 Hz, 1 H), 7.30-7.25 (m, 2 H), 6.88 (d, *J* = 8.4 Hz, 1 H), 5.60 (s, 2 H), 4.60-4.48 (m, 1 H), 2.85-2.66 (m, 2 H), 2.65-2.55 (m, 2 H), 2.42 (s, 3 H), 2.36 (s, 3 H), 2.23-2.08 (m, 2 H), 2.05-1.92 (m, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.8, 158.6, 156.9, 149.8, 143.3, 135.4, 132.2, 129.6, 125.6, 124.8, 121.1, 115.3, 113.2, 110.3, 53.9, 51.9, 46.0, 31.0, 30.2, 8.4; HRMS (TOF-ESI) calcd for $C_{26}H_{27}ClN_5O_4[M+H]^+$: 508.1752; found: 508.1740.



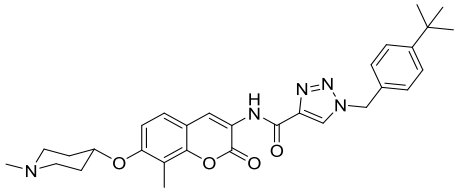
1-(4-Bromobenzyl)-N-(8-methyl-7-((1-methylpiperidin-4-yl)oxy)-2-oxo-2H-chromen-3-yl)-1H-1,2,3-triazole-4-carboxamide (**4h**): Following the general procedure, the 4-bromobenzyl analogue was obtained as a white solid (24 mg, 73% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.65 (s, 1 H), 8.70 (s, 1 H), 8.07 (s, 1 H), 7.60-7.54 (m, 2 H), 7.33 (d, *J* = 8.4 Hz, 1 H), 7.24-7.19 (m, 2 H), 6.88 (d, *J* = 8.4 Hz, 1 H), 5.58 (s, 2 H), 4.51 (bs, 1 H), 2.80-2.61 (m, 2 H), 2.55-2.40 (m, 2 H), 2.37 (s, 3 H), 2.36 (s, 3 H), 2.14-2.02 (m, 2 H), 2.01-1.88 (m, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.7, 158.6, 157.0, 149.7, 143.3, 132.7, 132.5, 129.8, 125.6, 125.5, 124.9, 123.4, 121.0, 115.3, 113.1, 110.3, 53.9, 52.1, 46.1, 30.9, 30.5, 8.4; HRMS (TOF-ESI) calcd for $C_{26}H_{27}{}^{79}BrN_5O_4[M+H]^+$: 552.1246; found: 552.1235.



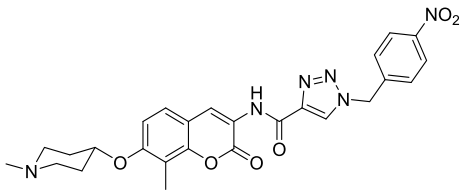
1-(4-Methylbenzyl)-N-(8-methyl-7-((1-methylpiperidin-4-yl)oxy)-2-oxo-2H-chromen-3-yl)-1H-1,2,3-triazole-4-carboxamide (**4i**): Following the general procedure, the 4-methylbenzyl analogue was obtained as a white solid (17 mg, 59% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.65 (s, 1 H), 8.70 (s, 1 H), 8.02 (s, 1 H), 7.33 (d, *J* = 8.8 Hz, 1 H), 7.23 (s, 4 H), 6.87 (d, *J* = 8.8 Hz, 1 H), 5.57 (s, 2 H), 4.56 (bs, 1 H), 2.82-2.70 (m, 2 H), 2.70-2.52 (m, 2 H), 2.45 (bs, 3 H), 2.39 (s, 3 H), 2.36 (s, 3 H), 2.26-2.11 (m, 2 H), 2.08-1.93 (m, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.8, 158.7, 156.7, 149.7, 143.0, 139.2, 130.6, 130.0, 128.4, 125.5, 124.6, 121.2, 115.2, 113.3, 110.2, 54.5, 51.8, 45.8, 30.9, 30.0, 21.2, 8.4; HRMS (TOF-ESI) calcd for $C_{27}H_{30}N_5O_4[M+H]^+$: 488.2298; found: 488.2293.



1-(4-Methoxybenzyl)-N-(8-methyl-7-((1-methylpiperidin-4-yl)oxy)-2-oxo-2H-chromen-3-yl)-1H-1,2,3-triazole-4-carboxamide (**4j**): Following the general procedure, the 4-methoxybenzyl analogue was obtained as a white solid (20 mg, 67% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.64 (s, 1 H), 8.70 (s, 1 H), 8.01 (s, 1 H), 7.35-7.28 (m, 2 H), 6.97-6.92 (m, 2 H), 6.87 (d, *J* = 8.4 Hz, 1 H), 5.55 (s, 2 H), 4.53 (bs, 1 H), 3.84 (s, 3 H), 2.82-2.67 (m, 2 H), 2.65-2.45 (m, 2 H), 2.41 (bs, 3 H), 2.35 (s, 3 H), 2.19-2.07 (m, 2 H), 2.04-1.90 (m, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.2, 158.8, 158.7, 156.8, 149.7, 143.0, 129.9, 125.5, 125.4, 124.7, 121.2, 115.3, 114.7, 113.2, 110.3, 55.4, 54.2, 51.9, 45.9, 30.9, 30.2, 8.4; HRMS (TOF-ESI) calcd for $C_{27}H_{30}N_5O_5[M+H]^+$: 504.2247; found: 504.2249.

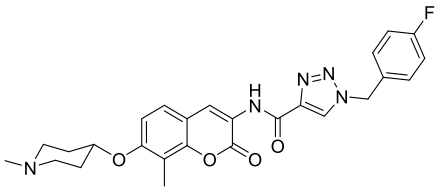


1-(4-tert-Butylbenzyl)-N-(8-methyl-7-((1-methylpiperidin-4-yl)oxy)-2-oxo-2H-chromen-3-yl)-1H-1,2,3-triazole-4-carboxamide (**4k**): Following the general procedure, the title compound was obtained as a white solid (25 mg, 71% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.63 (s, 1 H), 8.68 (s, 1 H), 8.01 (s, 1 H), 7.45-7.39 (m, 2 H), 7.33-7.28 (m, 1 H), 7.28-7.23 (m, 1 H), 6.85 (d, *J* = 8.4 Hz, 1 H), 5.56 (s, 2 H), 2.80-2.60 (m, 2 H), 2.55-2.35 (m, 2 H), 2.36 (s, 3 H), 2.34 (s, 3 H), 2.16-2.00 (m, 2 H), 2.00-1.87 (m, 2 H), 1.32 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.8, 158.7, 156.9, 152.5, 149.7, 143.0, 130.5, 128.2, 126.3, 125.6, 125.5, 124.7, 121.1, 115.3, 113.2, 110.3, 54.4, 52.0, 46.1, 34.7, 31.2, 30.5, 8.4; HRMS (TOF-ESI) calcd for $C_{30}H_{36}N_5O_4[M+H]^+$: 530.2767; found: 530.2773.

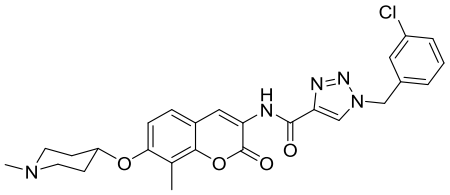


1-(4-Nitrobenzyl)-N-(8-methyl-7-((1-methylpiperidin-4-yl)oxy)-2-oxo-2H-chromen-3-yl)-1H-1,2,3-triazole-4-carboxamide (**4l**): Following the general procedure, the title compound was obtained as a yellow solid (17 mg, 55% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.65 (s, 1 H), 8.69 (s, 1 H), 8.27 (d, *J* = 8.4 Hz, 2 H), 8.20 (s, 1 H), 7.48 (d, *J* = 8.4 Hz, 2 H), 7.34

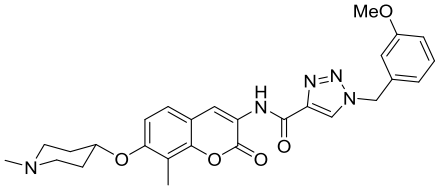
(d, J = 8.4 Hz, 1 H), 6.86 (d, J = 8.4 Hz, 1 H), 5.75 (s, 2 H), 4.73 (bs, 1 H), 3.20-2.93 (m, 2 H), 2.80-2.60 (m, 2 H), 2.60-2.40 (m, 2 H), 2.35 (s, 3 H), 2.23-2.10 (m, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.5, 158.4, 156.0, 149.7, 148.3, 143.5, 140.6, 128.5, 126.0, 125.9, 124.54, 124.50, 121.4, 115.0, 113.6, 109.9, 53.6, 50.0, 44.5, 29.7, 28.0, 8.4; HRMS (TOF-ESI) calcd for $C_{26}H_{27}N_6O_6[M+H]^+$: 519.1992; found: 519.2000.



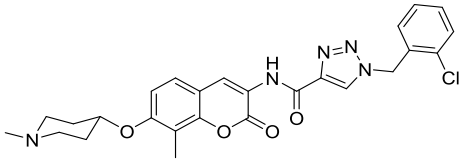
1-(4-Fluorobenzyl)-N-(8-methyl-7-((1-methylpiperidin-4-yl)oxy)-2-oxo-2H-chromen-3-yl)-1H-1,2,3-triazole-4-carboxamide (**4m**): Following the general procedure, the title compound was obtained as a white solid (19 mg, 58% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.61 (s, 1 H), 8.66 (s, 1 H), 8.04 (s, 1 H), 7.36-7.28 (m, 3 H), 7.13-7.05 (m, 2 H), 6.84 (d, J = 8.4 Hz, 1 H), 5.57 (s, 2 H), 4.51-4.40 (m, 1 H), 2.75-2.57 (m, 2 H), 2.50-2.35 (m, 2 H), 2.33 (s, 3 H), 2.32 (s, 3 H), 2.10-1.97 (m, 2 H), 1.96-1.85 (m, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.0, 162.0, 158.6, 157.9 (d, J_{C-F} = 211.3 Hz), 149.7, 143.2, 130.23, 130.17, 129.5 (d, J_{C-F} = 3.6 Hz), 125.5 (d, J_{C-F} = 5.5 Hz), 124.8, 121.0, 116.4, 116.3, 115.3, 113.0, 110.3, 53.8, 52.2, 46.1, 30.6, 29.6, 8.3; ^{19}F NMR (MHz, $CDCl_3$) δ (-111.6)-(-111.9); HRMS (TOF-ESI) calcd for $C_{26}H_{27}FN_5O_4[M+H]^+$: 492.2047; found: 492.2035.



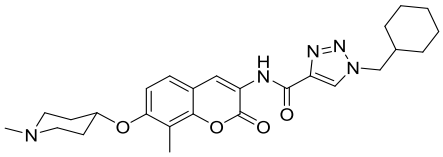
1-(3-Chlorobenzyl)-N-(8-methyl-7-((1-methylpiperidin-4-yl)oxy)-2-oxo-2H-chromen-3-yl)-1H-1,2,3-triazole-4-carboxamide (**4n**): Following the general procedure, the 3-chlorobenzyl analogue was obtained as a white solid (15 mg, 44% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.65 (s, 1 H), 8.70 (s, 1 H), 8.09 (s, 1 H), 7.42-7.30 (m, 4 H), 7.23-7.19 (m, 1 H), 6.90-6.85 (d, J = 8.4 Hz, 1 H), 5.60 (s, 2 H), 4.56-4.44 (m, 1 H), 2.75-2.62 (m, 2 H), 2.50-2.35 (m, 2 H), 2.36 (s, 6 H), 2.18-2.00 (m, 2 H), 2.00-1.87 (m, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.7, 158.5, 157.1, 149.7, 143.3, 135.5, 135.3, 130.6, 129.4, 128.3, 126.2, 125.7, 125.5, 124.9, 121.0, 115.3, 113.1, 110.3, 72.1, 53.9, 52.2, 46.2, 30.6, 29.7, 8.4; HRMS (TOF-ESI) calcd for $C_{26}H_{27}ClN_5O_4[M+H]^+$: 508.1752, found: 508.1749.



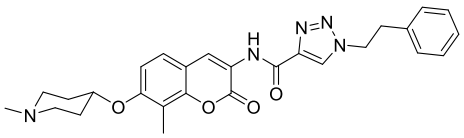
1-(3-Methoxybenzyl)-N-(8-methyl-7-((1-methylpiperidin-4-yl)oxy)-2-oxo-2H-chromen-3-yl)-1H-1,2,3-triazole-4-carboxamide (**4o**): Following the general procedure, the title compound was obtained as a light yellow solid (21 mg, 62% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.63 (s, 1 H), 8.68 (s, 1 H), 8.04 (s, 1 H), 7.35-7.29 (m, 2 H), 6.95-6.80 (m, 4 H), 5.56 (s, 2 H), 4.54 (bs, 1 H), 3.80 (s, 3 H), 2.85-2.70 (m, 2 H), 2.70-2.50 (m, 2 H), 2.43 (s, 3 H), 2.34 (s, 3 H), 2.25-2.05 (m, 2 H), 2.05-1.90 (m, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.2, 158.73, 158.68, 158.67, 149.7, 143.1, 135.0, 134.0, 125.7, 125.6, 124.6, 121.2, 120.4, 115.2, 114.6, 113.9, 113.3, 110.2, 53.3, 54.6, 51.7, 45.7, 29.8, 8.4; HRMS (TOF-ESI) calcd for $C_{27}H_{30}N_5O_5[M+H]^+$: 504.2247; found: 504.2242.



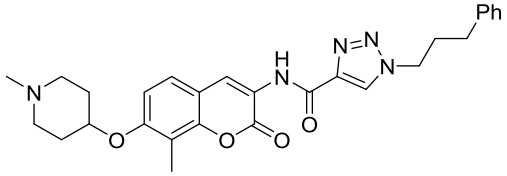
1-(2-Chlorobenzyl)-N-(8-methyl-7-((1-methylpiperidin-4-yl)oxy)-2-oxo-2H-chromen-3-yl)-1H-1,2,3-triazole-4-carboxamide (**4p**): Following the general procedure, the 2-chlorobenzyl analogue was obtained as a white solid (30 mg, 98% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.66 (s, 1 H), 8.71 (s, 1 H), 8.15 (s, 1 H), 7.51-7.47 (m, 1 H), 7.42-7.35 (m, 1 H), 7.35-7.31 (m, 3 H), 6.88 (d, *J* = 8.4 Hz, 1 H), 5.76 (s, 2 H), 4.53 (bs, 1 H), 2.80-2.68 (m, 2 H), 2.62-2.46 (m, 2 H), 2.42 (bs, 3 H), 2.36 (s, 3 H), 2.22-2.06 (m, 2 H), 2.04-1.90 (m, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.7, 156.8, 149.7, 143.0, 133.8, 131.5, 130.79, 130.77, 130.2, 127.8, 125.9, 125.5, 124.7, 121.1, 115.3, 113.2, 110.3, 52.0 (two peaks overlapped), 45.9, 30.9, 30.2, 8.4; HRMS (TOF-ESI) calcd for $C_{26}H_{27}ClN_5O_4[M+H]^+$: 508.1752; found: 508.1739.



1-(Cyclohexylmethyl)-N-(8-methyl-7-((1-methylpiperidin-4-yl)oxy)-2-oxo-2H-chromen-3-yl)-1H-1,2,3-triazole-4-carboxamide (**4q**): Following the general procedure, the title compound was obtained as an off-white solid (25 mg, 78% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.66 (s, 1 H), 8.73 (s, 1 H), 8.11 (s, 1 H), 7.34 (d, *J* = 8.4 Hz, 1 H), 6.88 (d, *J* = 8.4 Hz, 1 H), 4.58-4.46 (m, 1 H), 4.29 (d, *J* = 7.2 Hz, 1 H), 2.78-2.66 (m, 2 H), 2.58-2.42 (m, 2 H), 2.40 (s, 3 H), 2.36 (s, 3 H), 2.20-2.05 (m, 2 H), 2.05-1.86 (m, 3 H), 1.85-1.60 (m, 5 H), 1.35-1.15 (m, 3 H), 1.12-0.97 (m, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.0, 158.7, 156.9, 149.7, 142.6, 126.0, 125.5, 124.7, 121.2, 115.3, 113.2, 110.3, 56.9, 52.0, 46.0, 38.7, 30.4, 25.9, 25.4, 8.4; HRMS (TOF-ESI) calcd for $C_{26}H_{33}N_5O_4Na[M+Na]^+$: 502.2430; found: 502.2425.

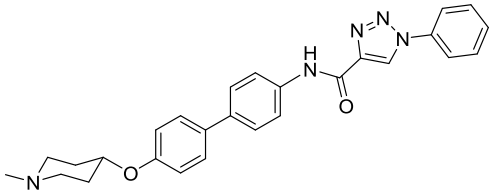


N-(8-methyl-7-((1-methylpiperidin-4-yl)oxy)-2-oxo-2H-chromen-3-yl)-1-phenethyl-1H-1,2,3-triazole-4-carboxamide (**4r**): Following the general procedure, the title compound **4r** was obtained as a light yellow solid (10 mg, 30% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.64 (s, 1 H), 8.70 (s, 1 H), 7.85 (s, 1 H), 7.36-7.25 (m, 4 H), 7.15-7.09 (m, 2 H), 6.90-6.85 (m, 1 H), 4.70 (t, *J* = 7.2 Hz, 2 H), 4.55-4.40 (m, 1 H), 3.28 (t, *J* = 7.2 Hz, 2 H), 2.76-2.60 (m, 2 H), 2.50-2.35 (m, 2 H), 2.36 (s, 6 H), 2.12-2.00 (m, 2 H), 1.98-1.86 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.75, 158.74, 157.0, 149.7, 142.5, 136.3, 129.0, 128.6, 127.4, 125.9, 125.4, 124.7, 121.1, 115.3, 113.1, 110.3, 72.2 (b), 52.3 (b), 52.1, 46.2, 36.5, 30.7, 8.4; HRMS (TOF-ESI) calcd for $C_{27}H_{30}N_5O_4[M+H]^+$: 488.2298; found: 488.2298.

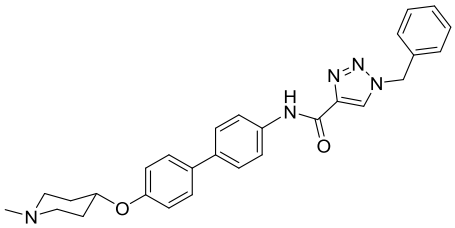


N-(8-methyl-7-((1-methylpiperidin-4-yl)oxy)-2-oxo-2H-chromen-3-yl)-1-(3-phenylpropyl)-1H-1,2,3-triazole-4-carboxamide (**4s**): following the general procedure, the title compound was obtained as a white solid (14 mg, 41% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.66 (s, 1 H), 8.73 (s, 1 H), 8.12 (s, 1 H), 7.37-7.31 (m, 1 H), 7.28-7.22 (m, 1 H), 7.22-7.18 (m, 2 H), 6.90-6.85 (m, 1 H), 4.62-4.52 (m, 1 H), 4.46 (t, *J* = 7.2 Hz, 2 H), 2.90-2.75 (m, 2 H), 2.71 (t, *J* = 7.2 Hz, 2 H), 2.68-2.52 (m, 2 H), 2.46

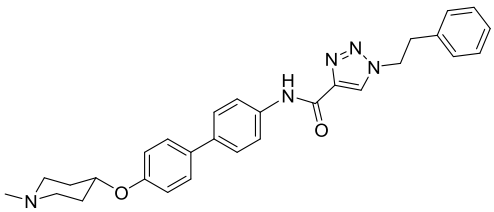
(s, 3 H), 2.63 (s, 3 H), 2.34 (pent, *J* = 7.2 Hz, 2 H), 2.28-2.12 (m, 2 H), 2.08-1.95 (m, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.9, 158.7, 156.7, 149.8, 142.8, 139.7, 128.8, 128.5, 126.6, 125.7, 125.6, 124.7, 121.3, 115.3, 113.4, 110.2, 51.7, 50.0, 45.7, 32.4, 31.5, 29.9, 8.4; HRMS (TOF-ESI) calcd for $C_{28}H_{32}N_5O_4[M+H]^+$: 502.2454; found: 502.2436.



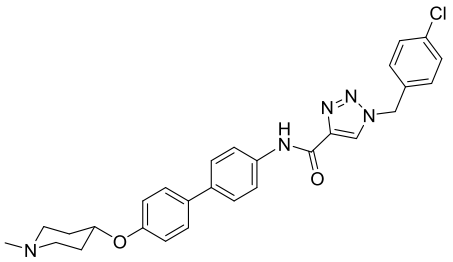
N-(4'-((1-methylpiperidin-4-yl)oxy)-[1,1'-biphenyl]-4-yl)-1-phenyl-1H-1,2,3-triazole-4-carboxamide (**5a**): Following the general procedure, the title compound was obtained as a white solid (21 mg, 70% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.07 (s, 1 H), 8.64 (s, 1 H), 7.84-7.77 (m, 4 H), 7.64-7.57 (m, 4 H), 7.57-7.50 (m, 3 H), 7.02-6.98 (m, 2 H), 4.43-4.33 (m, 1 H), 2.80-2.65 (m, 2 H), 2.38-2.25 (m, 5 H), 2.11-2.00 (m, 2 H), 1.97-1.82 (m, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.8, 156.6, 143.8, 137.1, 136.3, 135.9, 133.1, 129.9, 129.5, 127.8, 127.1, 124.2, 120.7, 120.3, 116.3, 71.3, 52.2, 45.8, 30.2; HRMS (TOF-ESI) calcd for $C_{27}H_{28}N_5O_2[M+H]^+$: 454.2243; found: 454.2238.



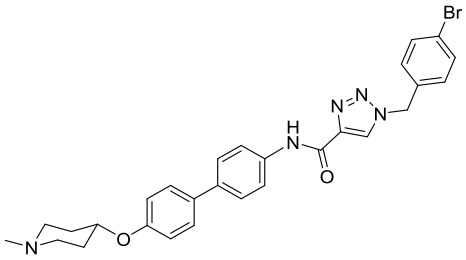
1-Benzyl-N-(4'-((1-methylpiperidin-4-yl)oxy)-[1,1'-biphenyl]-4-yl)-1H-1,2,3-triazole-4-carboxamide (**5b**): Following the general procedure, the benzyl analogue was obtained as a white solid (17 mg, 55% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.99 (s, 1 H), 8.08 (s, 1 H), 7.76-7.72 (m, 2 H), 7.60-7.50 (m, 4 H), 7.46-7.40 (m, 3 H), 7.36-7.31 (m, 2 H), 7.03-6.97 (m, 2 H), 5.62 (s, 2 H), 4.44-4.33 (1 H), 2.80-2.65 (m, 2 H), 2.40-2.22 (m, 5 H), 2.10-1.98 (m, 2 H), 1.97-1.82 (m, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.7, 156.9, 143.8, 137.0, 136.1, 133.6, 133.1, 129.4, 129.2, 128.3, 127.9, 127.2, 125.7, 120.1, 116.3, 72.1, 54.7, 52.7, 46.2, 30.9; HRMS (TOF-ESI) calcd for $C_{28}H_{30}N_5O_2[M+H]^+$: 468.2400; found: 468.2407.



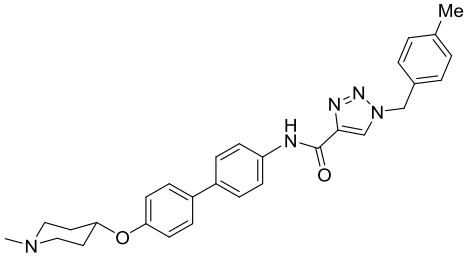
N-(4'-((1-methylpiperidin-4-yl)oxy)-[1,1'-biphenyl]-4-yl)-1-phenethyl-1H-1,2,3-triazole-4-carboxamide (**5c**): Following the general procedure, the title compound was obtained as a white solid (18 mg, 56% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.99 (s, 1 H), 7.92 (s, 1 H), 7.78-7.73 (m, 2 H), 7.60-7.50 (m, 4 H), 7.37-7.26 (m, 3 H), 7.16-7.11 (m, 2 H), 7.02-6.98 (m, 2 H), 4.70 (t, *J* = 7.2 Hz, 2 H), 4.48-4.40 (m, 1 H), 3.28 (t, *J* = 7.2 Hz, 2 H), 2.90-2.74 (m, 2 H), 2.60-2.45 (m, 2 H), 2.40 (s, 3 H), 2.17-2.06 (m, 2 H), 2.01-1.89 (m, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.7, 156.7, 143.2, 136.9, 136.3, 136.2, 133.3, 129.0, 128.6, 127.9, 127.4, 127.2, 125.9, 120.1, 116.3, 52.1, 51.9, 45.6, 36.5, 30.1, 22.6; HRMS (TOF-ESI) calcd for $C_{29}H_{32}N_5O_2[M+H]^+$: 482.2556; found: 482.2556.



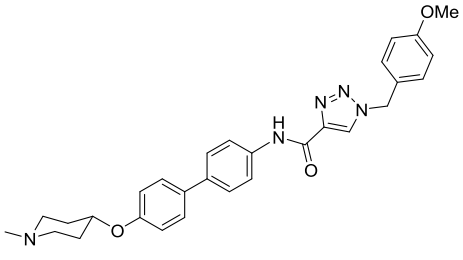
1-(4-Chlorobenzyl)-N-(4'-((1-methylpiperidin-4-yl)oxy)-[1,1'-biphenyl]-4-yl)-1H-1,2,3-triazole-4-carboxamide (**5d**): Following the general procedure, the 4-chlorobenzyl analogue was obtained (12 mg, 35% yield) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17 (s, 1 H), 7.74-7.66 (m, 2 H), 7.56-7.44 (m, 4 H), 7.39-7.32 (m, 2 H), 7.27-7.22 (m, 2 H), 6.98-6.90 (m, 2 H), 5.55 (s, 2 H), 4.44-4.32 (m, 1 H), 2.79-2.61 (m, 2 H), 2.43-2.25 (m, 5 H), 2.10-1.95 (m, 2 H), 1.95-1.80 (m, 2 H); ^{13}C NMR (125 MHz, CD_3OD with minor $CDCl_3$, ref $CDCl_3$) δ 156.2, 154.5, 141.2, 135.4, 133.2, 132.6, 131.1, 130.2, 128.0, 126.9, 125.6, 125.5, 124.2, 118.7, 114.2, 50.4, 43.7, 28.5; HRMS (TOF-ESI) calcd for $C_{28}H_{29}ClN_5O_2[M+H]^+$: 502.2010, found: 502.2006.



1-(4-Bromobenzyl)-N-(4'-((1-methylpiperidin-4-yl)oxy)-[1,1'-biphenyl]-4-yl)-1H-1,2,3-triazole-4-carboxamide (**5e**): Following the general procedure, the 4-bromobenzyl analogue was obtained as a white solid (21 mg, 57% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.53 (s, 1 H), 8.85 (s, 1 H), 7.91-7.86 (m, 2 H), 7.65-7.55 (m, 6 H), 7.37-7.32 (m, 2 H), 7.06-7.00 (m, 2 H), 5.70 (s, 2 H), 4.43 (bs, 1 H), 2.80-2.62 (m, 2 H), 2.37-2.15 (m, 5 H), 2.02-1.91 (m, 2 H), 1.74-1.62 (m, 2 H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 158.2, 156.4, 143.1, 137.3, 135.2, 135.0, 132.2, 131.8, 130.3, 127.6, 127.4, 126.2, 121.6, 120.7, 116.2, 71.6, 52.4, 52.2, 45.5, 30.3; HRMS (TOF-ESI) calcd for $C_{28}H_{29}{}^{79}BrN_5O_2[M+H]^+$: 546.1505, found: 546.1494.

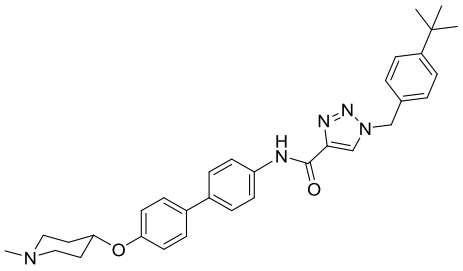


1-(4-Methylbenzyl)-N-(4'-((1-methylpiperidin-4-yl)oxy)-[1,1'-biphenyl]-4-yl)-1H-1,2,3-triazole-4-carboxamide (**5f**): Following the general procedure, the 4-methylbenzyl analogue was obtained (20 mg, 63% yield) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.01 (s, 1 H), 7.77-7.72 (m, 2 H), 7.59-7.50 (m, 4 H), 7.23 (s, 4 H), 7.01-6.97 (m, 2 H), 5.56 (s, 2 H), 4.43 (bs, 1 H), 2.86-2.73 (m, 2 H), 2.60-2.42 (m, 2 H), 2.40 (s, 3 H), 2.39 (s, 3 H), 2.17-2.05 (m, 2 H), 2.00-1.87 (m, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.2, 156.4, 143.0, 137.7, 137.4, 135.1, 132.6, 132.0, 129.4, 128.1, 127.4, 127.3, 126.2, 120.7, 116.2, 71.4, 53.0, 52.1, 45.3, 30.1, 20.7; HRMS (TOF-ESI) calcd for $C_{29}H_{32}N_5O_2[M+H]^+$: 482.2556; found: 482.2545.

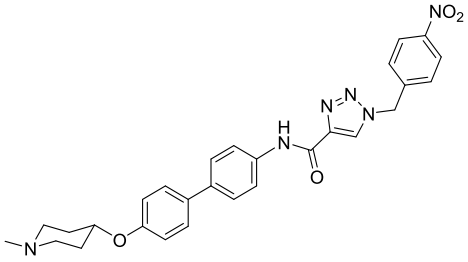


1-(4-Methoxybenzyl)-N-(4'-((1-methylpiperidin-4-yl)oxy)-[1,1'-biphenyl]-4-yl)-1H-1,2,3-triazole-4-carboxamide (**5g**): Following the general procedure, the 4-methoxybenzyl analogue **5g** was obtained as an off-white solid (14 mg, 42% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.97 (s, 1 H), 8.02 (s, 1 H), 7.75-7.69 (m, 2 H), 7.57-7.47 (m, 4 H), 7.29-7.27

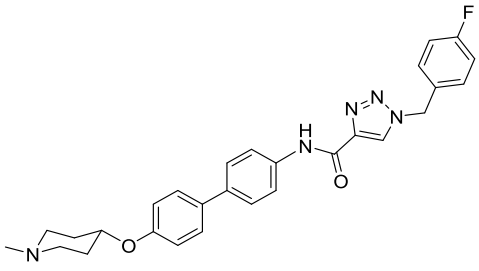
(m, 1 H), 7.00-6.90 (m, 4 H), 5.52 (s, 2 H), 4.40 (bs, 1 H), 3.82 (s, 3 H), 2.82-2.70 (m, 2 H), 2.58-2.35 (m, 2 H). 2.37 (s, 3 H), 2.15-2.03 (m, 2 H), 1.97-1.85 (m, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$ and minor CD_3OD) δ 160.1, 157.8, 156.5, 143.5, 136.9, 136.0, 133.3, 129.8, 127.9, 127.1, 125.7, 125.5, 120.1, 116.3, 114.6, 55.3, 54.2, 51.8, 45.5, 30.8; HRMS (TOF-ESI) calcd for $C_{29}H_{32}N_5O_3[M+H]^+$: 498.2505; found: 498.2499.



1-(4-tert-Butylbenzyl)-N-(4'-((1-methylpiperidin-4-yl)oxy)-[1,1'-biphenyl]-4-yl)-1H-1,2,3-triazole-4-carboxamide (**5h**): Following the general procedure, the title compound was obtained as a white solid (16 mg, 46% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.97 (s, 1 H), 8.03 (s, 1 H), 7.72 (d, *J* = 8.4 Hz, 2 H), 7.54 (d, *J* = 8.4 Hz, 2 H), 7.51 (d, *J* = 8.4 Hz, 2 H), 7.43 (d, *J* = 8.4 Hz, 2 H), 7.29-7.24 (m, 2 H), 6.97 (d, *J* = 8.4 Hz, 2 H), 5.56 (s, 2 H), 4.44 (bs, 1 H), 2.95-2.75 (m, 2 H), 2.45 (s, 3 H), 2.30-2.05 (m, 2 H), 2.05-1.90 (m, 2 H), 1.32 (s, 9 H); ^{13}C NMR (125 MHz, CD_3OD) δ 158.2, 156.2, 150.8, 143.1, 137.4, 135.1, 132.7, 127.8, 127.5, 127.3, 126.2, 125.6, 120.7, 116.3, 52.9, 34.3, 31.0, 30.7; HRMS (TOF-ESI) calcd for $C_{32}H_{38}N_5O_2[M+H]^+$: 524.3026; found: 524.3029.

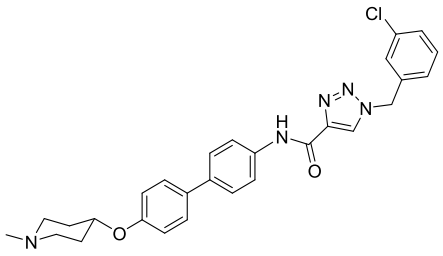


1-(4-Nitrobenzyl)-N-(4'-((1-methylpiperidin-4-yl)oxy)-[1,1'-biphenyl]-4-yl)-1H-1,2,3-triazole-4-carboxamide (**5i**): Following the general procedure the title compound was obtained as a yellow solid (20 mg, 59% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.97 (s, 1 H), 8.27 (d, *J* = 8.4 Hz, 2 H), 8.18 (s, 2 H), 7.73 (d, *J* = 8.4 Hz, 1 H), 7.56 (d, *J* = 8.4 Hz, 2 H), 7.51 (d, *J* = 8.4 Hz, 2 H), 7.47 (d, *J* = 8.4 Hz, 2 H), 6.97 (d, *J* = 8.4 Hz, 2 H), 5.73 (s, 2 H), 4.48 (bs, 1 H), 2.95-2.80 (m, 2 H), 2.75-2.55 (m, 2 H), 2.47 (s, 3 H), 2.30-2.12 (m, 2 H), 2.10-1.86 (m, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.3, 156.9, 148.4, 144.3, 140.6, 137.2, 136.0, 133.2, 128.8, 128.0, 127.3, 126.0, 124.6, 120.2, 116.4, 53.6, 53.5, 52.5, 46.0, 30.5; HRMS (TOF-ESI) calcd for $C_{28}H_{29}N_6O_4[M+H]^+$: 513.2250; found: 513.2270.

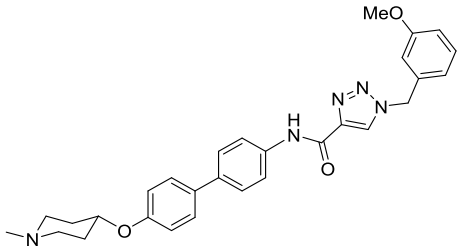


1-(4-Fluorobenzyl)-N-(4'-((1-methylpiperidin-4-yl)oxy)-[1,1'-biphenyl]-4-yl)-1H-1,2,3-triazole-4-carboxamide (**5j**): Following the general procedure, the title compound was obtained as a white solid (17 mg, 53% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.97 (s, 1 H), 8.10-8.06 (m, 1 H), 7.80-7.70 (m, 2 H), 7.60-7.49 (m, 4 H), 7.38-7.31 (m, 2 H), 7.18-7.08 (m, 2 H), 7.04-6.96 (m, 2 H), 5.59 (s, 2 H), 4.45-4.30 (m, 1 H), 2.81-2.68 (m, 2 H), 2.45-2.25 (m, 5 H), 2.13-2.00 (m, 2 H), 1.98-1.85 (m, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.1 (d, $J_{C\text{-}F}$ = 247.4 Hz), 157.6, 156.9, 143.9, 137.1, 136.1, 133.1, 130.3 (d, $J_{C\text{-}F}$ = 8.1 Hz), 129.5 (d, $J_{C\text{-}F}$ = 2.5 Hz), 127.9,

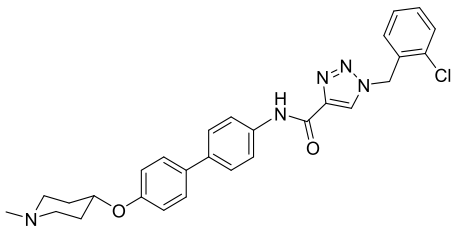
127.3, 125.6, 120.2, 116.5, 116.4, 72.1, 54.0, 54.7, 46.2, 30.9; HRMS (TOF-ESI) calcd for $C_{28}H_{29}FN_5O_2[M+H]^+$: 486.2305; found: 486.2305.



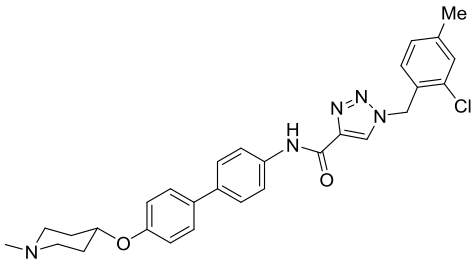
1-(3-Chlorobenzyl)-N-(4'-((1-methylpiperidin-4-yl)oxy)-[1,1'-biphenyl]-4-yl)-1H-1,2,3-triazole-4-carboxamide (**5k**): following the general procedure, the title compoun was obtained as a white solid (12 mg, 36% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.98 (s, 1 H), 8.12 (s, 1 H), 7.79-7.70 (m, 2 H), 7.61-7.48 (m, 4 H), 7.43-7.30 (m, 3 H), 7.25-7.16 (m, 2 H), 7.04-6.96 (m, 2 H), 5.59 (s, 2 H), 4.45-4.30 (m, 1 H), 2.85-2.66 (m, 2 H), 2.45-2.24 (m, 5 H), 2.11-2.00 (m, 2 H), 1.96-1.83 (m, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.5, 156.9, 144.0, 137.1, 136.0, 135.5, 135.3, 133.1, 130.6, 129.4, 128.3, 127.9, 127.2, 126.2, 125.7, 120.2, 116.3, 72.1, 53.9, 52.6, 46.2, 30.8; HRMS (TOF-ESI) calcd for $C_{28}H_{29}ClN_5O_2[M+H]^+$: 502.2010; found: 502.2005.



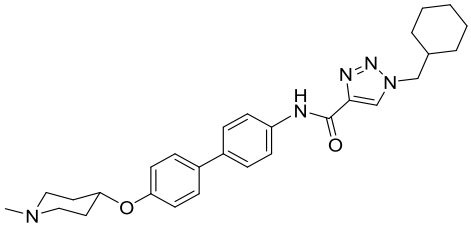
1-(3-Methoxybenzyl)-N-(4'-((1-methylpiperidin-4-yl)oxy)-[1,1'-biphenyl]-4-yl)-1H-1,2,3-triazole-4-carboxamide (**5l**): Following the general procedure, the title compound was obtained as a white solid (14 mg, 42% yield). ^{1}H NMR (400 MHz, $CDCl_3$ with MeOD) δ 8.12 (s, 1 H), 7.70-7.65 (m, 2 H), 7.51-7.43 (m, 4 H), 7.28-7.23 (m, 2 H), 6.94-6.88 (m, 2 H), 6.88-6.81 (m, 2 H), 6.79-6.76 (m,1 H); 5.50 (s, 2 H), 4.62-4.50 (m, 1 H), 3.74 (s, 3 H), 3.10-2.94 (m, 2 H), 2.62 (s, 3 H), 2.36-2.18 (m, 2 H), 2.14-2.00 (m, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.2, 157.7, 156.8, 143.7, 137.0, 136.1, 134.9, 133.2, 130.5, 127.9, 127.2, 125.7, 120.4, 120.1, 116.3, 114.5, 114.0, 71.9, 55.3, 54.6, 52.5, 46.1, 30.7; HRMS (TOF-ESI) calcd for $C_{29}H_{32}N_5O_3[M+Na]^+$: 498.2505, found: 498.2510.



1-(2-Chlorobenzyl)-N-(4'-((1-methylpiperidin-4-yl)oxy)-[1,1'-biphenyl]-4-yl)-1H-1,2,3-triazole-4-carboxamide (**5m**): Following the general procedure, the 2-chlorobenzyl analogue 5m was obtained (12 mg, 35% yield) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.54 (s, 1 H), 8.78 (s, 1 H), 7.89 (d, J = 8.4 Hz, 2 H), 7.62-7.50 (m, 5 H), 7.47-7.35 (m,2 H), 7.34-7.25 (m, 1 H), 7.03 (d, J = 8.4 Hz, 2 H), 5.83 (s, 2 H), 4.44 (bs, 1 H), 2.80-2.62 (m, 2 H), 2.40-2.15 (m, 5 H), 2.05-1.90 (m, 2 H), 1.80-1.60 (m, 2 H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 158.1, 156.4, 142.9, 137.3, 135.2, 132.9, 132.6, 132.2, 130.6, 130.4, 129.7, 127.8, 127.4, 126.2, 120.7, 116.2, 71.5, 52.2, 51.0, 45.5, 30.2; HRMS (TOF-ESI) calcd for $C_{28}H_{29}ClN_5O_2[M+H]^+$: 502.2010; found: 502.2008.



1-(2-Chloro-4-methylbenzyl)-N-(4'-((1-methylpiperidin-4-yl)oxy)-[1,1'-biphenyl]-4-yl)-1H-1,2,3-triazole-4-carboxamide (**5n**): following the general procedure, the title compound was obtained as a white solid (17 mg, 49% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.98 (s, 1 H), 8.13 (s, 1 H), 7.78-7.72 (m, 2 H), 7.60-7.49 (m, 4 H), 7.32-7.30 (m, 1 H), 7.25-7.21 (m, 1 H), 7.16-7.10 (m, 1 H), 7.02-6.96 (m, 2 H), 5.70 (s, 2 H), 7.44-7.34 (m, 1 H), 2.85-2.67(m, 2 H), 2.38 (s, 3 H), 2.35 (s, 3 H), 2.40-2.28 (m, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.7, 156.9, 143.5, 141.5, 137.0, 136.1, 133.7, 133.1, 130.71, 130.65, 128.5, 128.3, 127.9, 127.2, 125.8, 120.1, 116.3, 72.1, 52.6, 51.8, 46.2, 30.8, 21.0; HRMS (TOF-ESI) calcd for $C_{29}H_{31}ClN_5O_2[M+H]^+$: 516.2166; found: 516.2160.



1-(Cyclohexylmethyl)-N-(4'-((1-methylpiperidin-4-yl)oxy)-[1,1'-biphenyl]-4-yl)-1H-1,2,3-triazole-4-carboxamide (**5o**): Following the general procedure, the title compound was obtained as a white solid (19 mg, 59% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.98 (s, 1 H), 8.11 (s, 1 H), 7.74 (d, *J* = 8.8 Hz, 2 H), 7.56 (d, *J* = 8.4 Hz, 2 H), 7.51 (d, *J* = 8.4 Hz, 2 H), 6.98 (d, *J* = 8.8 Hz, 2 H), 4.50-4.34 (m, 1 H), 4.27 (d, *J* = 7.2 Hz, 2 H), 2.83-2.67 (m, 2 H), 2.48-2.30 (m, 5 H), 2.05-2.00 (m, 2 H), 2.00-1.80 (m, 2 H), 1.80-1.58 (m, 6 H), 1.34-1.10 (m, 4 H), 1.10-0.95 (m, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.9, 156.8, 143.3, 137.0, 136.2, 133.3, 127.9, 127.2, 126.0, 120.1, 116.3, 57.0, 52.2, 45.8, 38.7, 30.4, 26.0, 25.4; HRMS (TOF-ESI) calcd for $C_{28}H_{36}N_5O_2[M+H]^+$: 474.2869; found: 474.2860.

MTS/PMS cell viability assay (SKBr3 and MCF-7 cells)

Cells were maintained in a 1:1 mixture of Advanced DMEM/F12 (Gibco) supplemented with non-essential amino acids, L-glutamine (2 mM), streptomycin (500 μg/mL), penicillin (100 units/mL), and 10% FBS. Cells were grown to confluence in a humidified atmosphere (37° C, 5% CO_2), seeded (2000/well, 100 μL) in 96-well plates, and allowed to attach overnight. Compound at varying concentrations in DMSO (1% DMSO final concentration) was added, and cells were returned to the incubator for 72 h. At 72 h, the number of viable cells was determined using an MTS/PMS cell proliferation kit (Promega) per the manufacturer's instructions. Cells incubated in 1% DMSO were used at 100% proliferation, and values were adjusted accordingly. IC_{50} values were calculated from separate experiments performed in triplicate using GraphPad Prism.

Promega CellTiter-Glo (CTG) luminescent assay

Antiproliferative activities against MDA-MB-468LN, MDA1986 and JMAR cell lines were performed with 384-well white plates with the Promega CellTiter-Glo (CTG) luminescent assay with 72h compound treatment. Data analysis was performed using GraphPad Prism. Selected data were further checked with MTS/PMS cell viability assay with 96-well plates, which correlated well with Promega CellTilter-Glo luminescent assay (not reported).

Sulforhodamine B Assay

The sulforhodamine B assay is used to measure drug-induced cytotoxicity and cell proliferation for large-scale drug-screening applications. Its principle is based on the ability of the protein dye sulforhodamine B to bind electrostatically on pH dependent protein basic amino acid residues of trichloroacetic acid-fixed cells. The aim is to evaluate samples showing selective growth inhibition or cell killing of particular tumor cell lines.

The SRB assay is performed by treating cells using a 10 point dose-response curve. The cells are fixed with trichloroacetic acid solution and stained with sulforhodamine B dye. The stained cells are then solubilized with 10mM Tris buffer and read for absorbance at 565nm.

Percentage growth is calculated at each of the drug concentration levels using the absorbance raw data.

Percentage growth inhibition is calculated as:

$[(Ti – Tz)/(C-Tz)] \times 100$ for concentrations for which $Ti \geq Tz$

$[(Ti – Tz)/(Tz)] \times 100$ for concentrations for which $Ti < Tz$.

Ti = Absorbance of wells at a given drug concentration level.

Tz = Absorbance time zero wells

C = Absorbance of untreated wells (media and cells only)

After growth inhibition values have been calculated, the data is plotted on Graphpad Prism software. Data is entered and plotted on a sigmoidal dose-response curve using non-linear regression.

Western blot Analyses

MCF-7 cells were cultured as described above and treated with various concentrations of drug, GDA in DMSO (1% DMSO final concentration), or vehicle (DMSO) for 24 h. Cells were harvested in cold PBS and lysed in RIPA lysis buffer containing 1 mM PMSF, 2 mM sodium orthovanadate, and protease inhibitors on ice for 1 h. Lysates were clarified at 14000g for 10 min at 4° C. Protein concentrations were determined using the Pierce BCA protein assay kit per the manufacturer's instructions. Equal amounts of protein (15 μg) were electrophoresed under reducing conditions, transferred to a PVDF membrane, and immunoblotted with the corresponding specific antibodies. Membranes

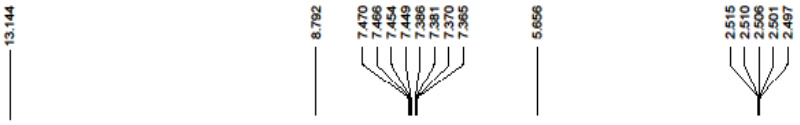
were incubated with an appropriate horseradish peroxidase-labeled secondary antibody, developed with a chemiluminescent substrate, and visualized.

Proteolytic Fingerprinting Assay

Rabbit reticulocyte (Green Hectares) incubated under conditions of protein synthesis at 30^{o}C in the presence of compound or vehicle (1% DMSO) for 10 minutes. Each reaction mixture contained 66.6% rabbit reticulocyte and 33.3% ATP regenerating system (10 mM creatine phosphate and 20 µg mL^{-1} creatine phosphokinase) and a final concentration of 75 mM KCl. Each reaction mixture contained the indicated amount of compound. After incubating, the samples were immediately placed on ice and the indicated amount of TPCK-treated trypsin (Worthington) was added to each sample. The samples digested on ice for an additional 6 minutes and the reactions were quenched by the addition of Laemmli sample buffer followed by immediate boiling. Equal amounts of each sample were electrophoresed under reducing conditions (12% acrylamide gels), transferred to PVDF, and immunoblotted with an antibody specific to the Hsp90 C-terminus. Membranes were incubated with an appropriate horseradish peroxidase-labeled secondary antibody, developed with a chemiluminescent substrate, and visualized.

References

1. Kolarovic, A.; Schnurch, M.; Mihovilovic, M. D., Tandem catalysis: from alkynoic acids and aryl iodides to 1,2,3-triazoles in one pot. *J. Org. Chem.* **2011,** *76* (8), 2613-8.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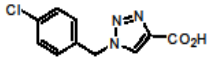
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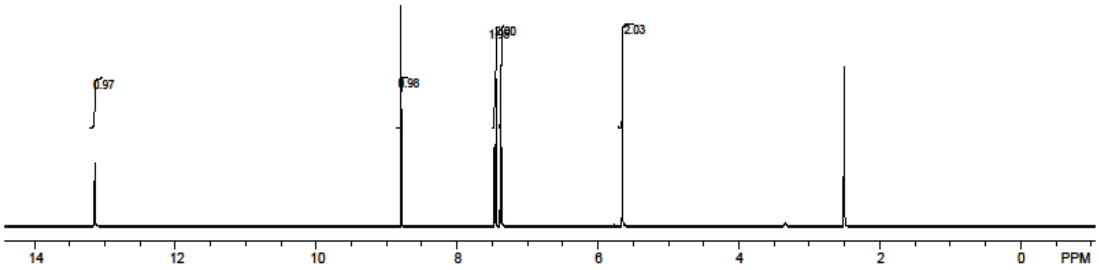
CO2H

7g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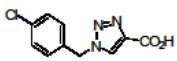
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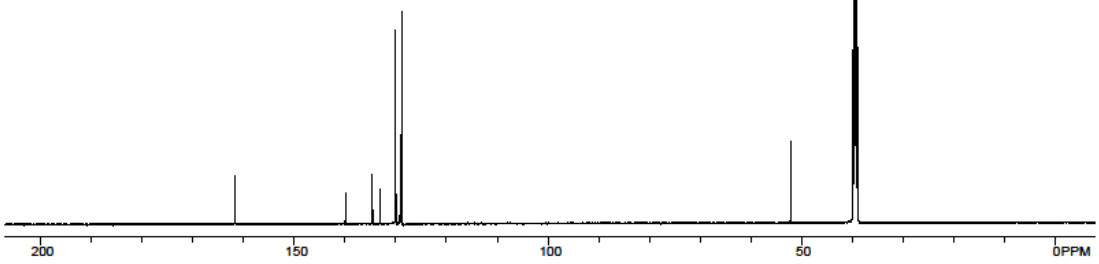
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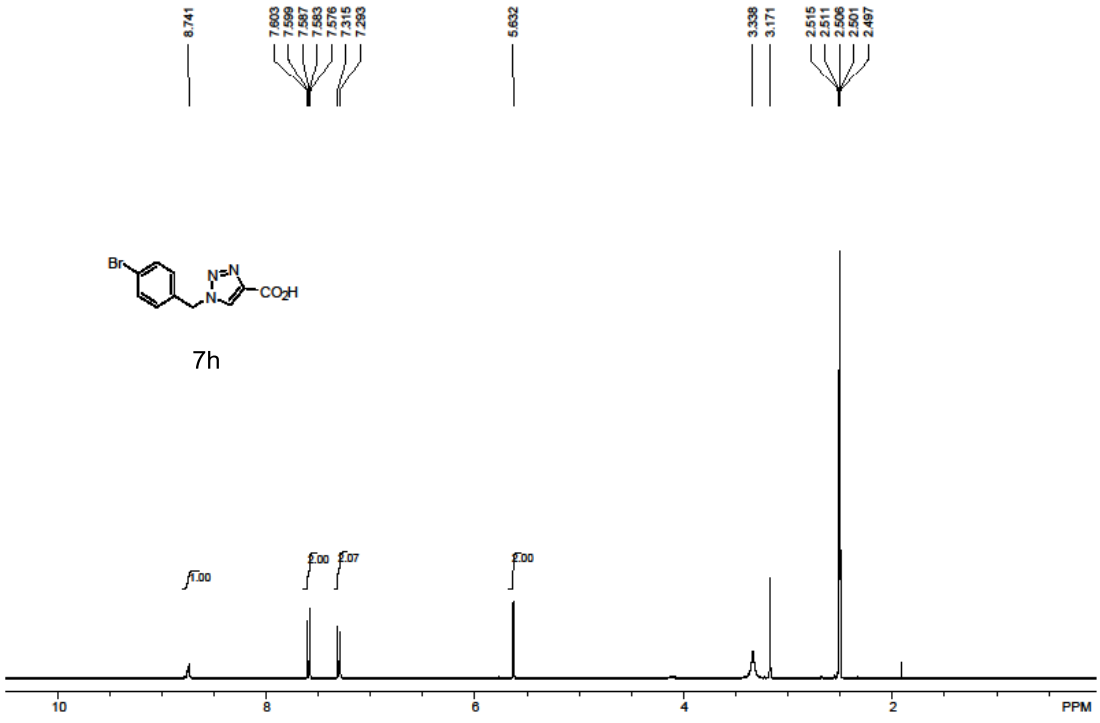
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2.506
2.501
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6
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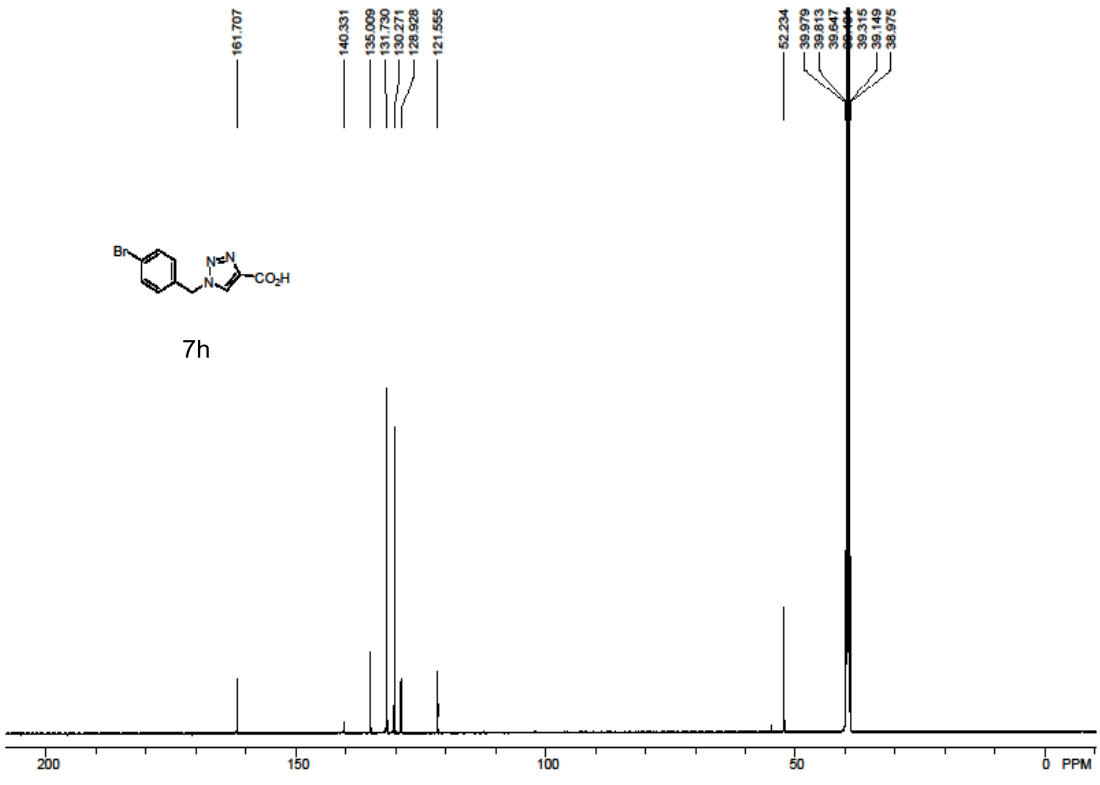
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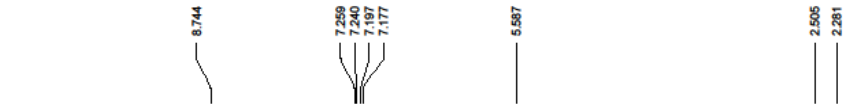
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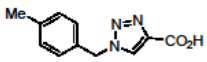
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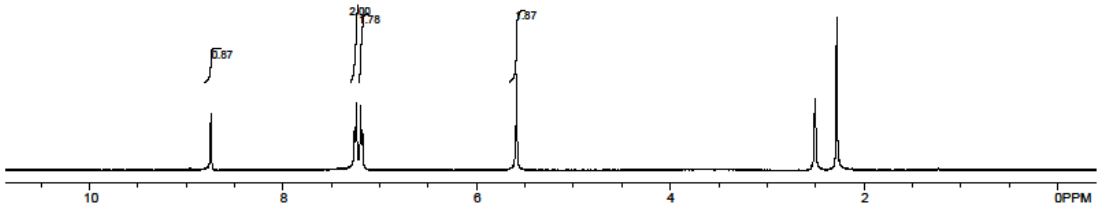
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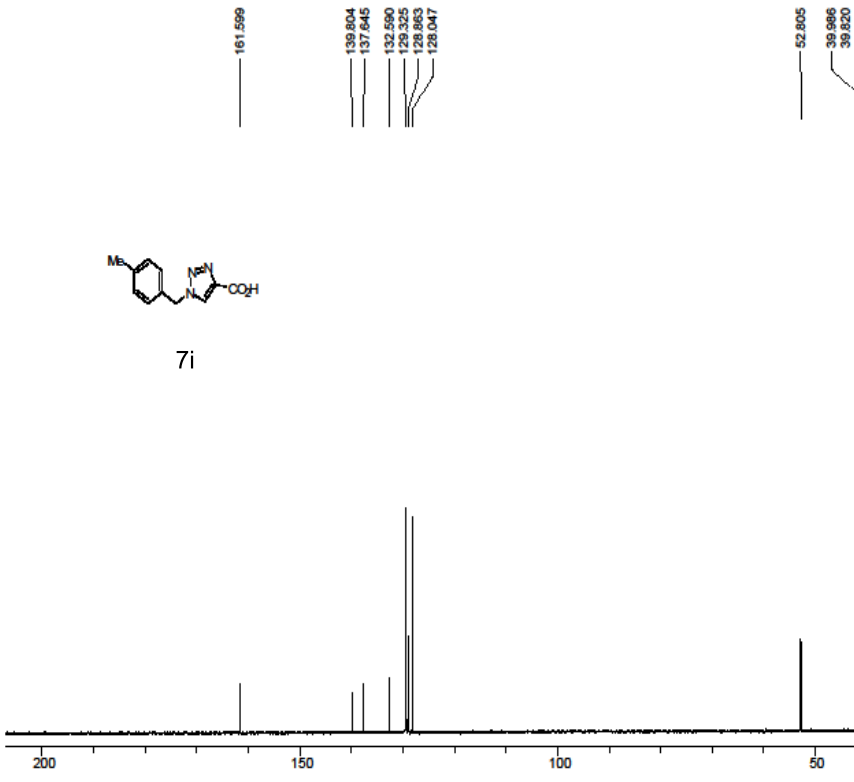
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Me
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CO2H

7i


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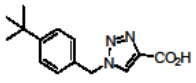
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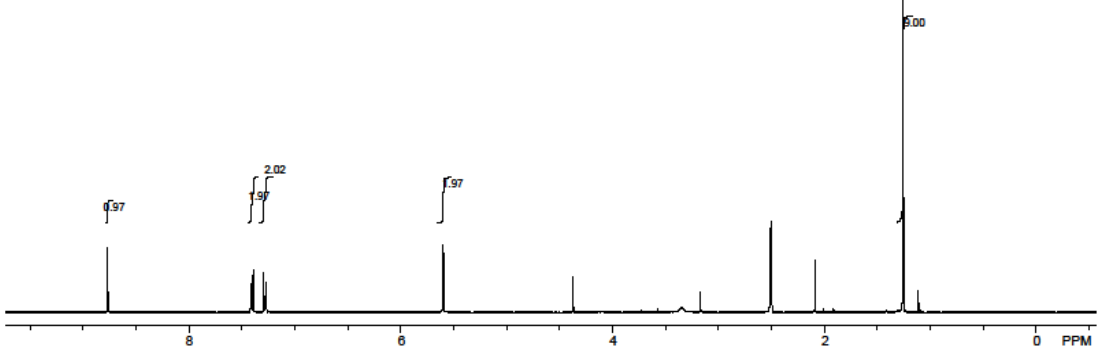
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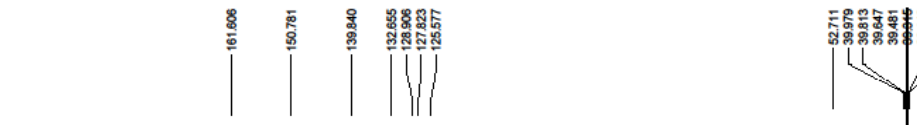
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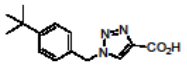
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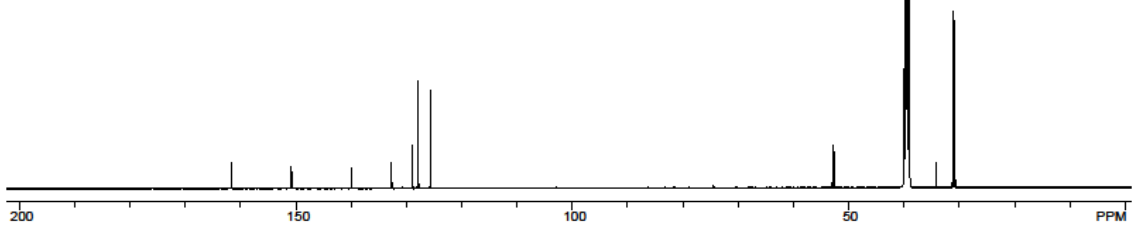
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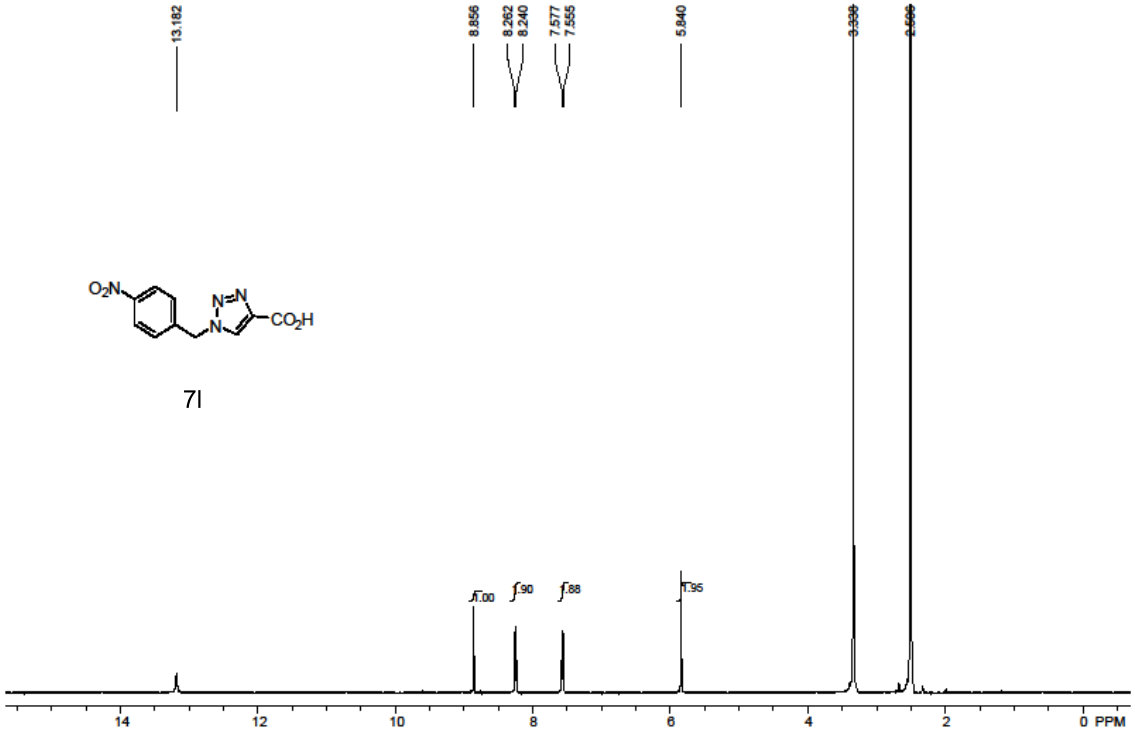
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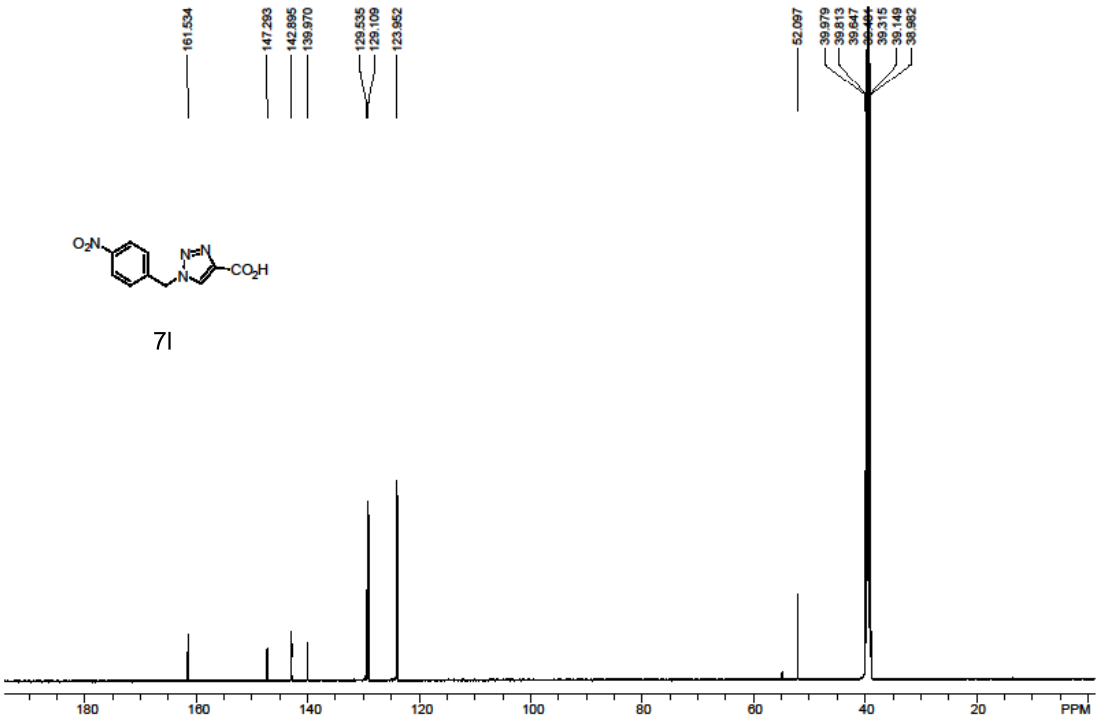
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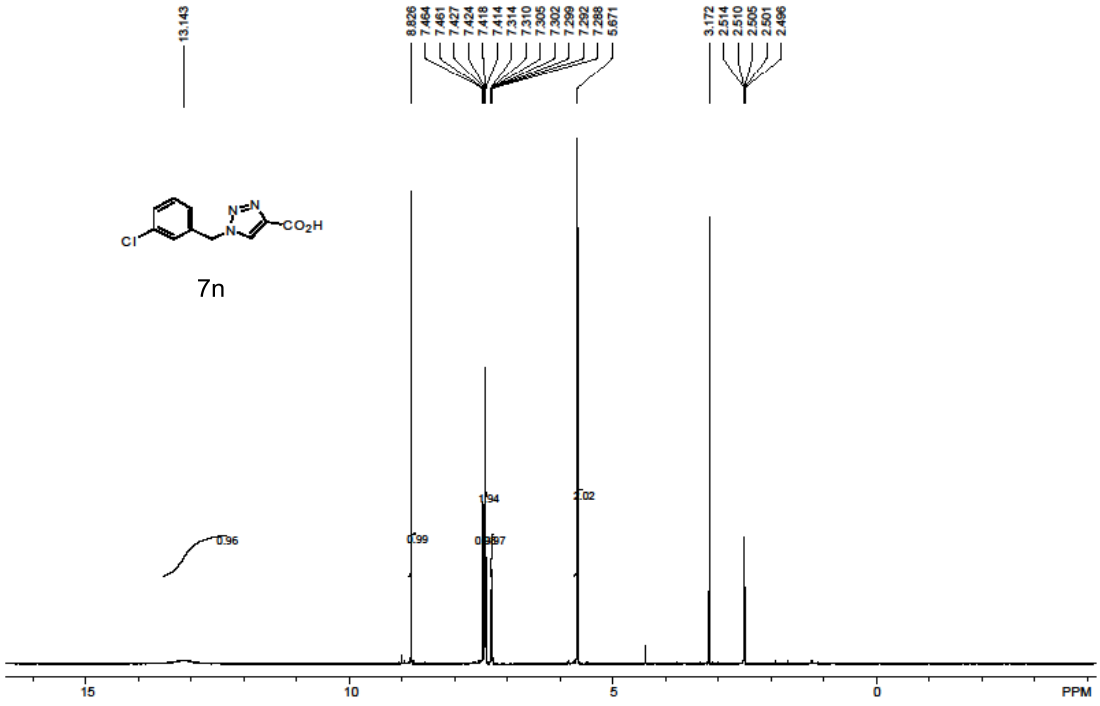
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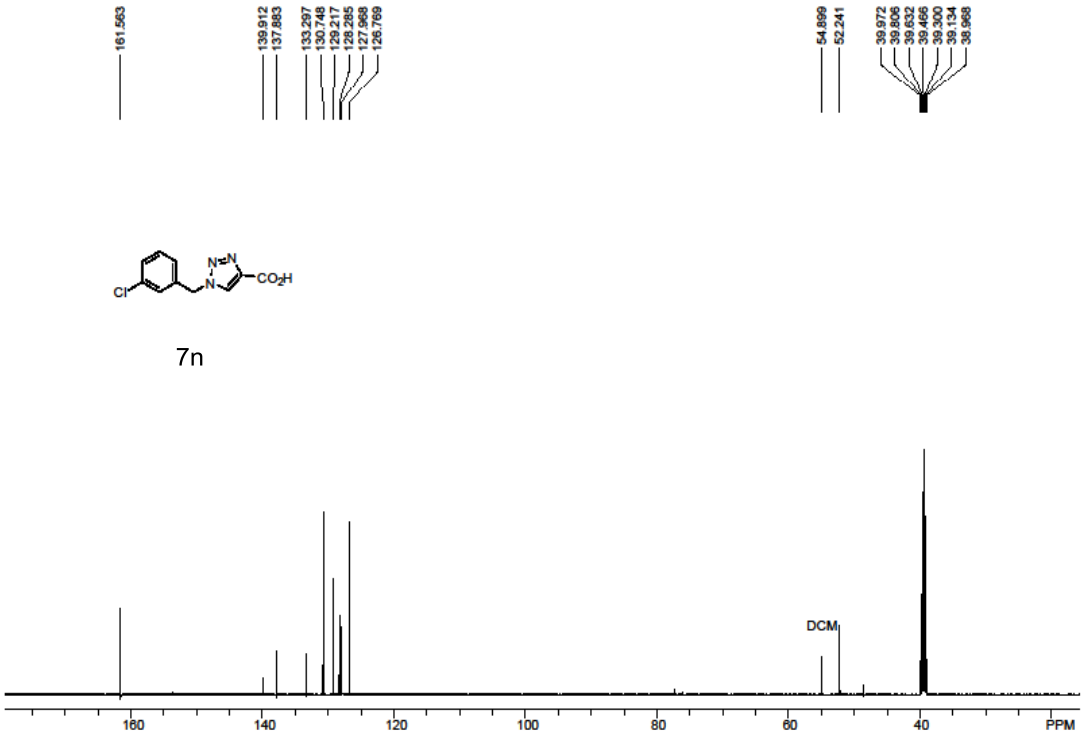
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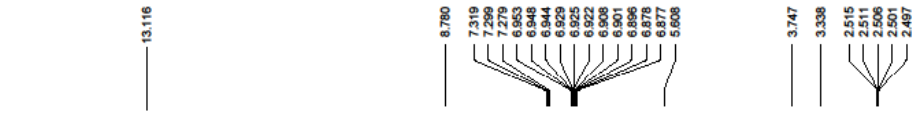
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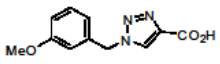
2.501
2.497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N
CO2H

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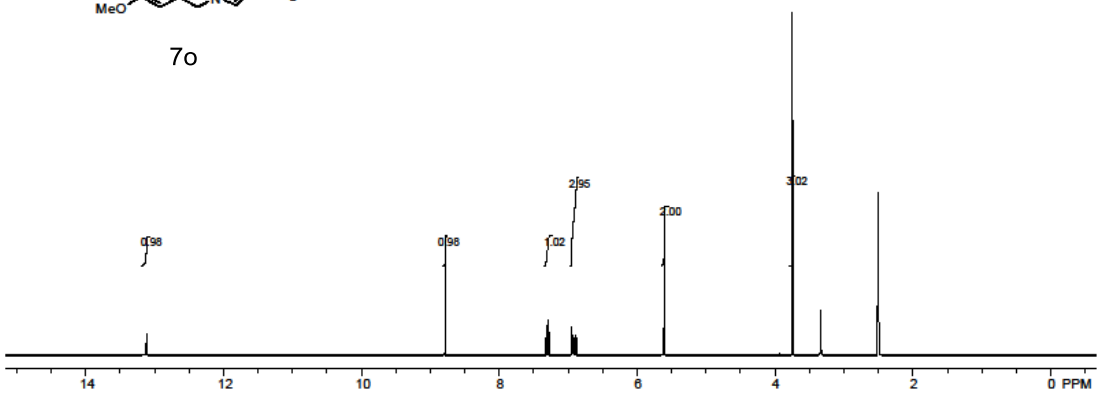
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2
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129.036
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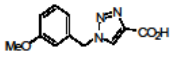
39.149
38.982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CO2H

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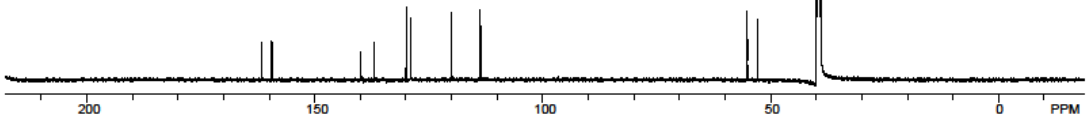
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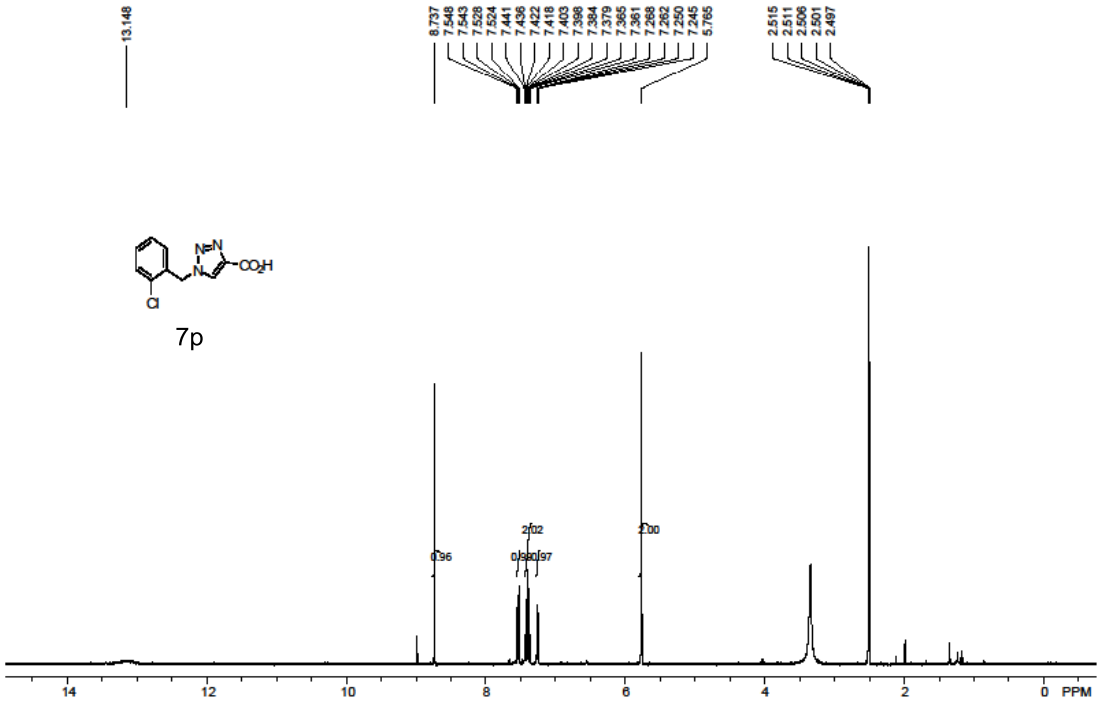
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7.396
7.384
7.379
7.365
7.361
7.268
7.262
7.250
7.245
5.765
2.515
2.511
2.506
2.501
2.497
CO2H
Cl
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2.00
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0.97
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10
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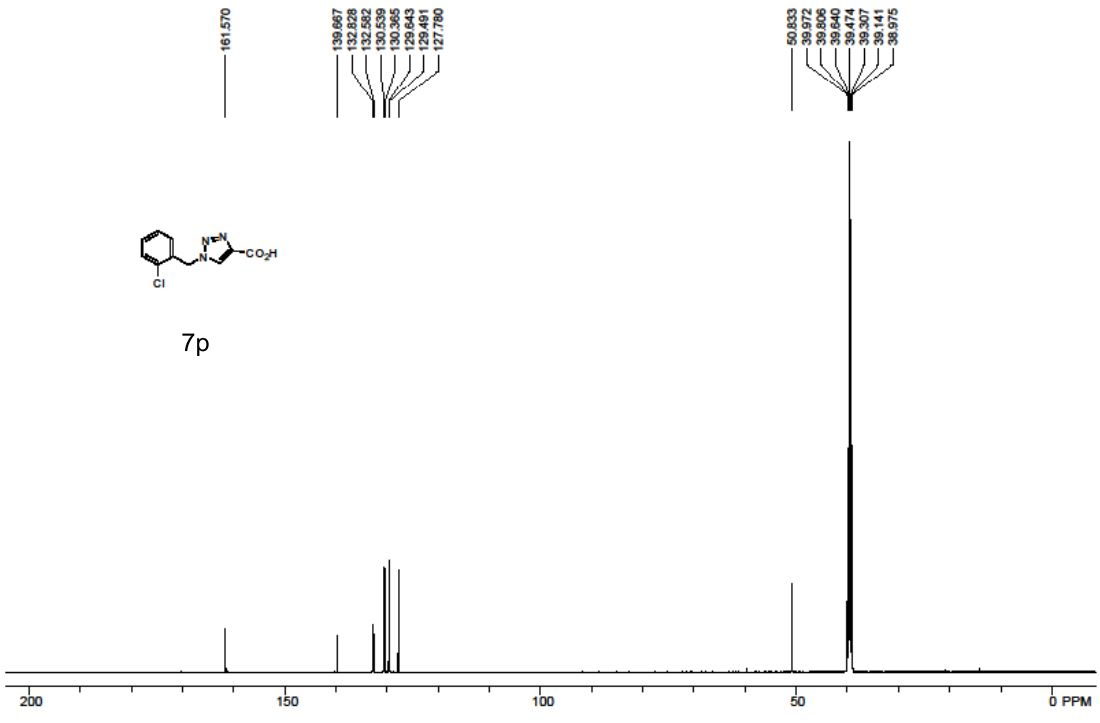
0 PPM

7p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129.491
127.780
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39.474
39.307
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38.975
CO2H
Cl
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50
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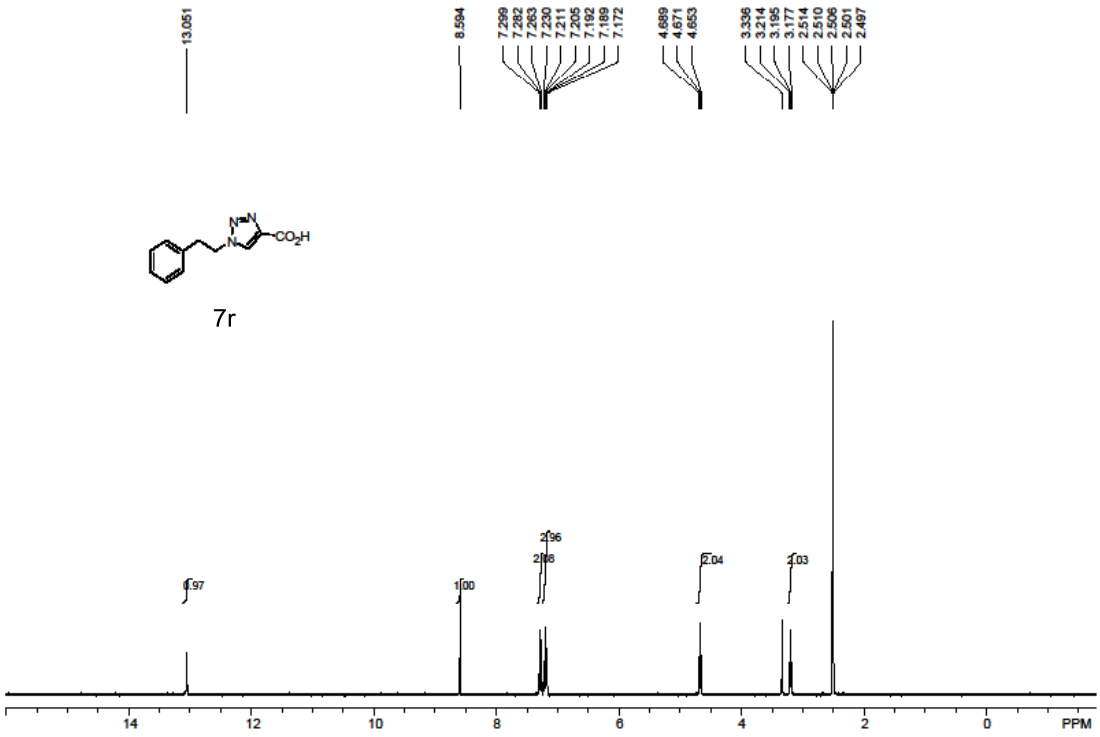
7p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4.671
4.653
3.336
3.214
3.195
3.177
2.514
2.510
2.506
2.501
2.497
CO2H
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2.03
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10
8
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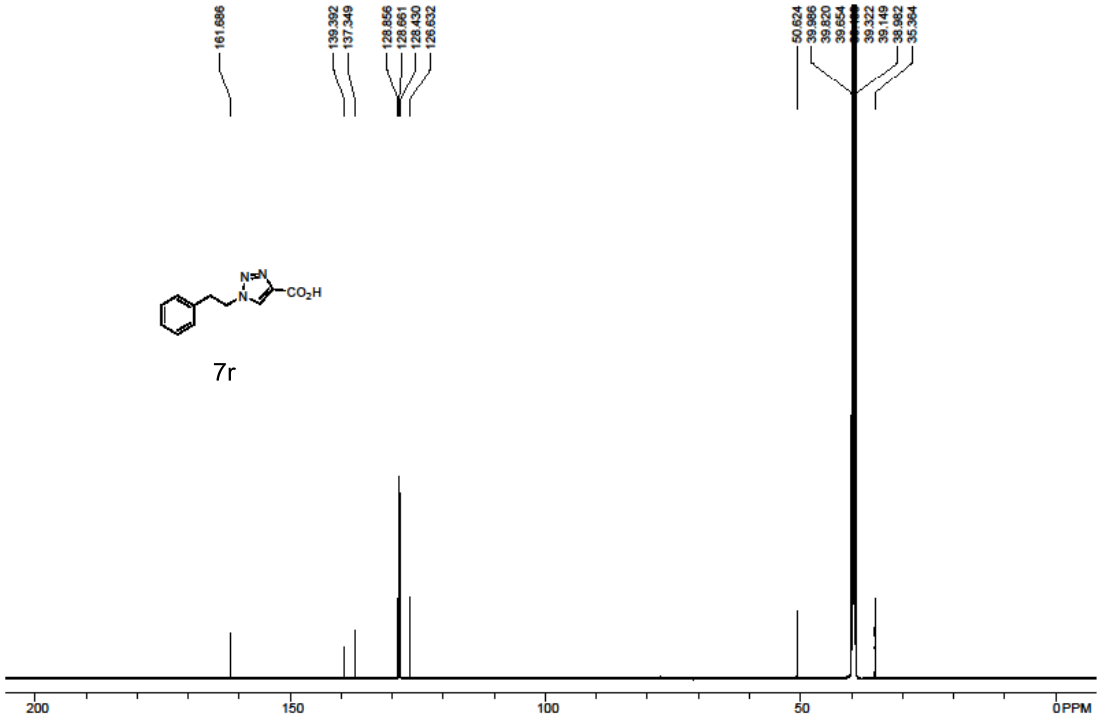
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38.982
35.364
CO2H
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150
100
50
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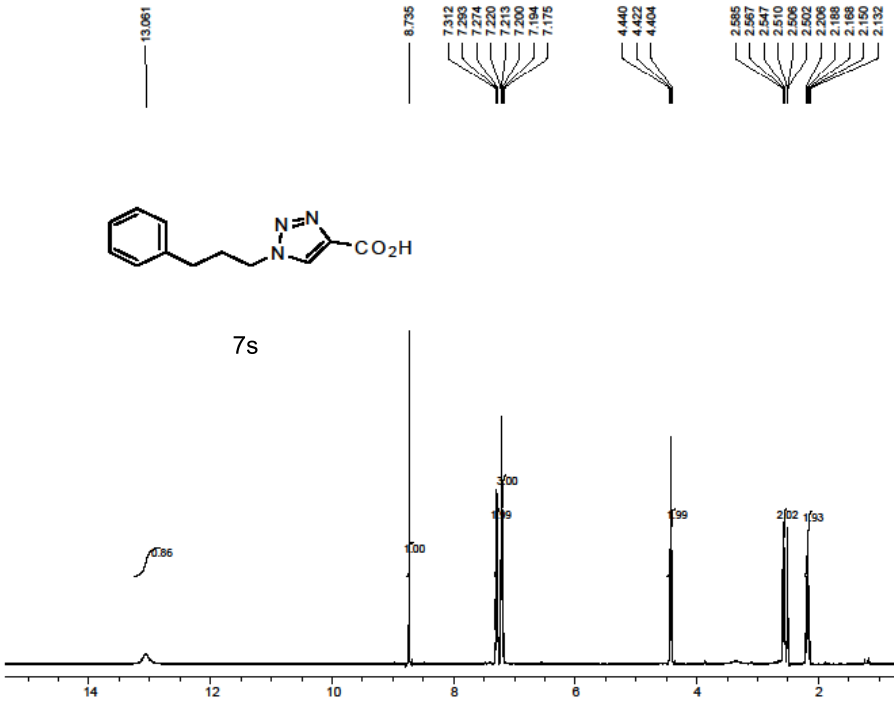
7r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7.213
7.200
7.194
7.175
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4.422
4.404
2.585
2.567
2.547
2.510
2.506
2.502
2.206
2.188
2.168
2.150
2.132
CO2H
7s
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1.99
1.99
2.02
1.93
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12
10
8
6
4
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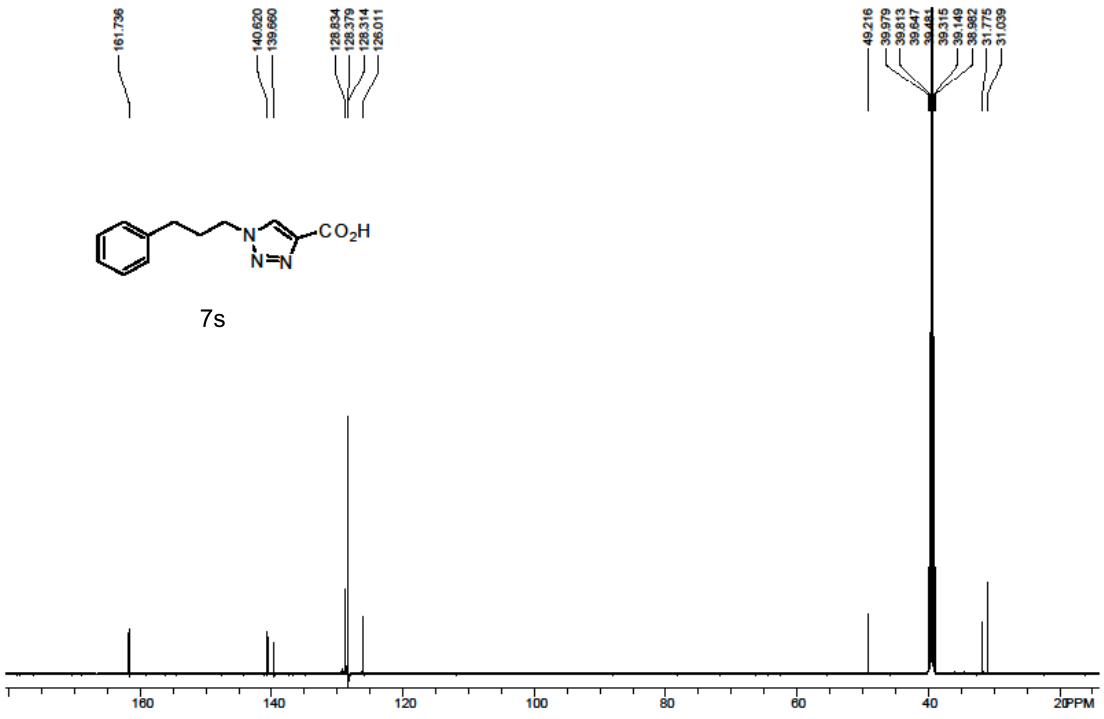
0
PPM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128.379
128.314
126.011
49.216
39.979
39.813
39.647
39.481
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31.039
CO2H
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140
120
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80
60
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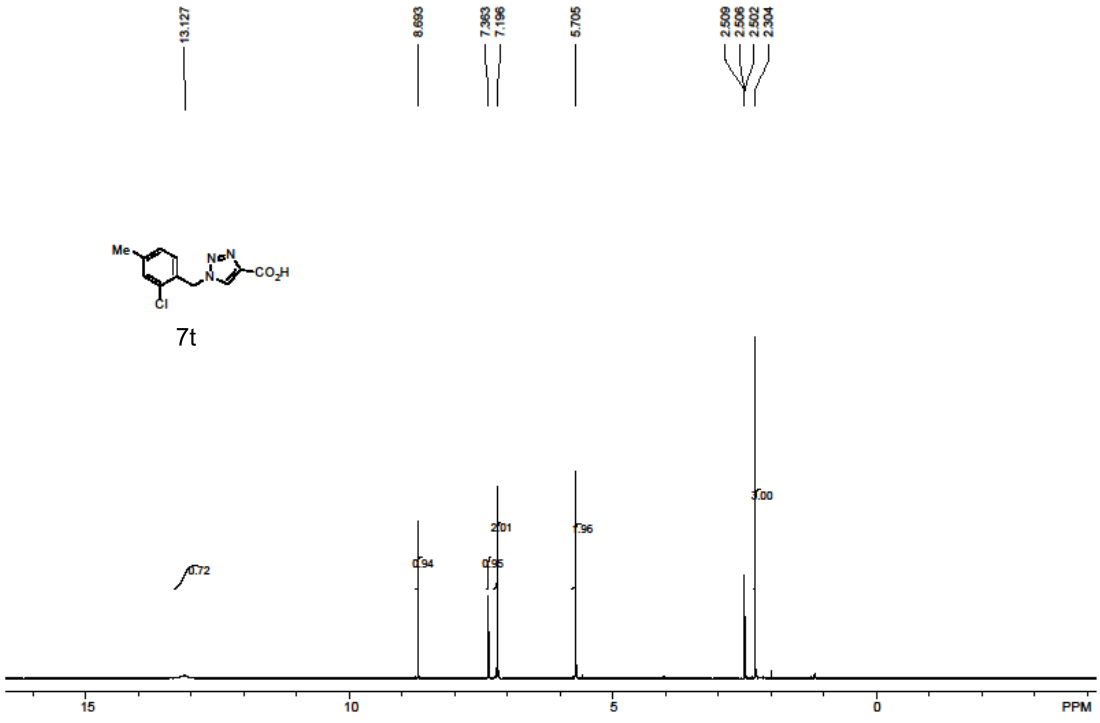
20
PPM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7.196
5.705
2.509
2.506
2.502
2.304
Me
N
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0.95
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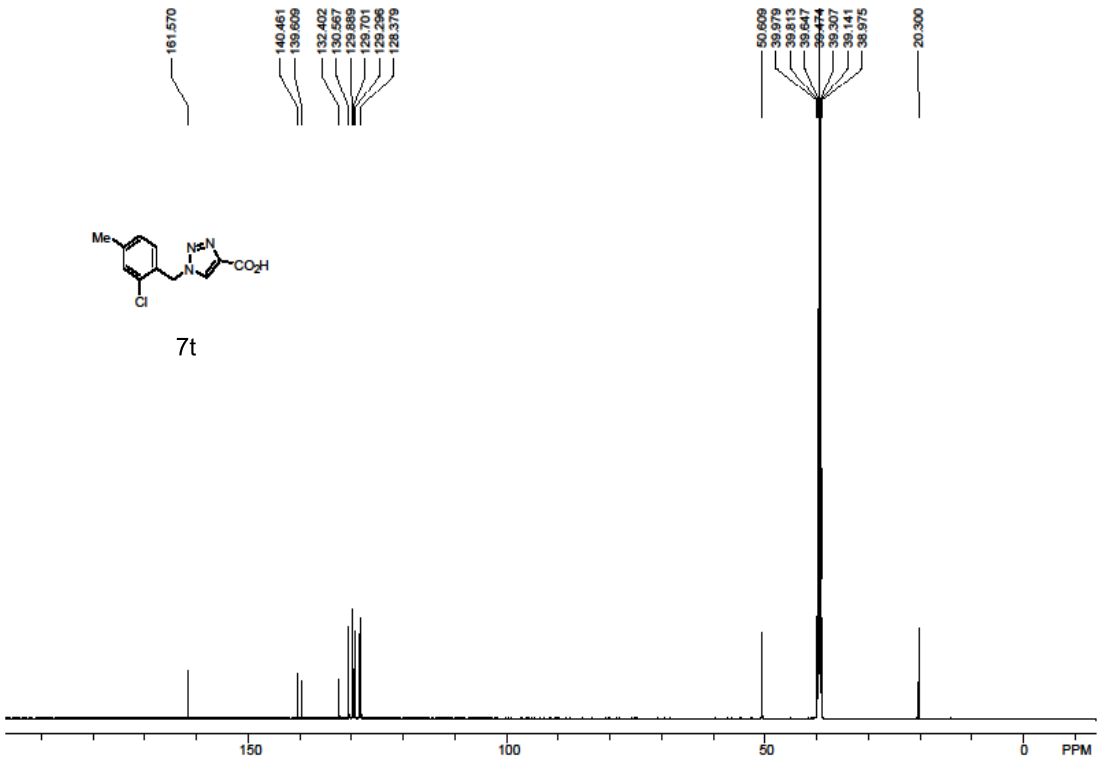
1.96
3.00
15
10
5
0
PPM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129.296
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50.609
39.979
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39.647
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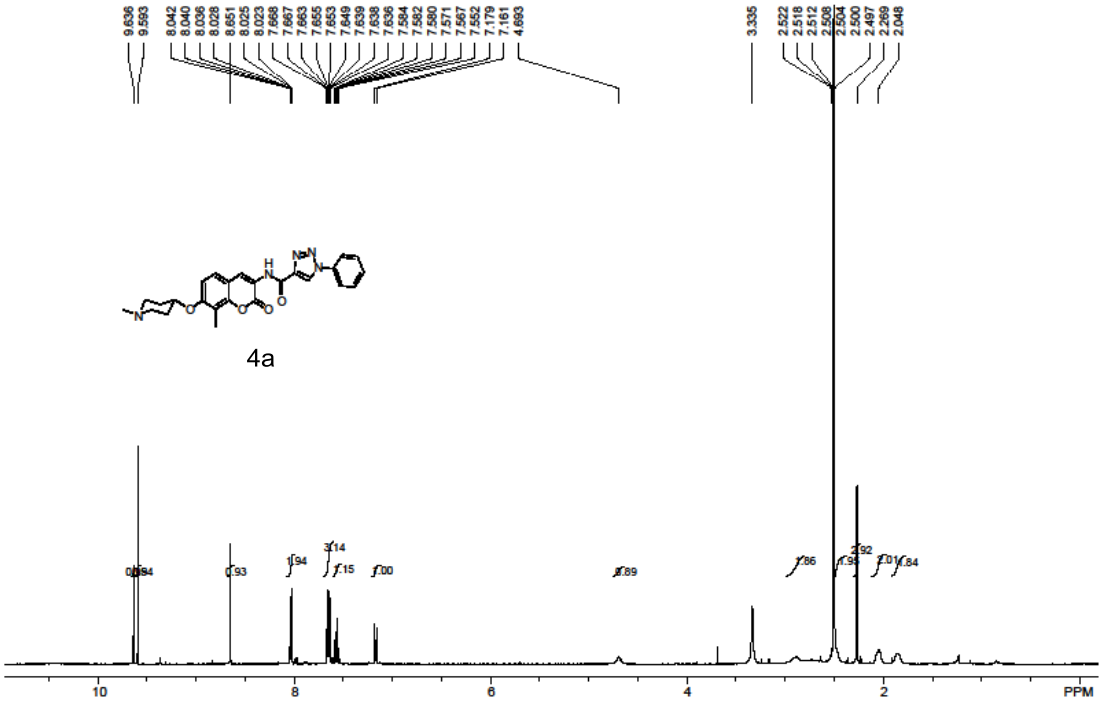
39.307
39.141
38.975
20.300
Me
N
N
CO2H
Cl
7t
150
100
50
0
PPM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7.655
7.653
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7.639
7.638
7.636
7.584
7.582
7.580
7.571
7.567
7.552
7.179
7.161
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3.335
2.522
2.518
2.512
2.508
2.504
2.500
2.497
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2.92
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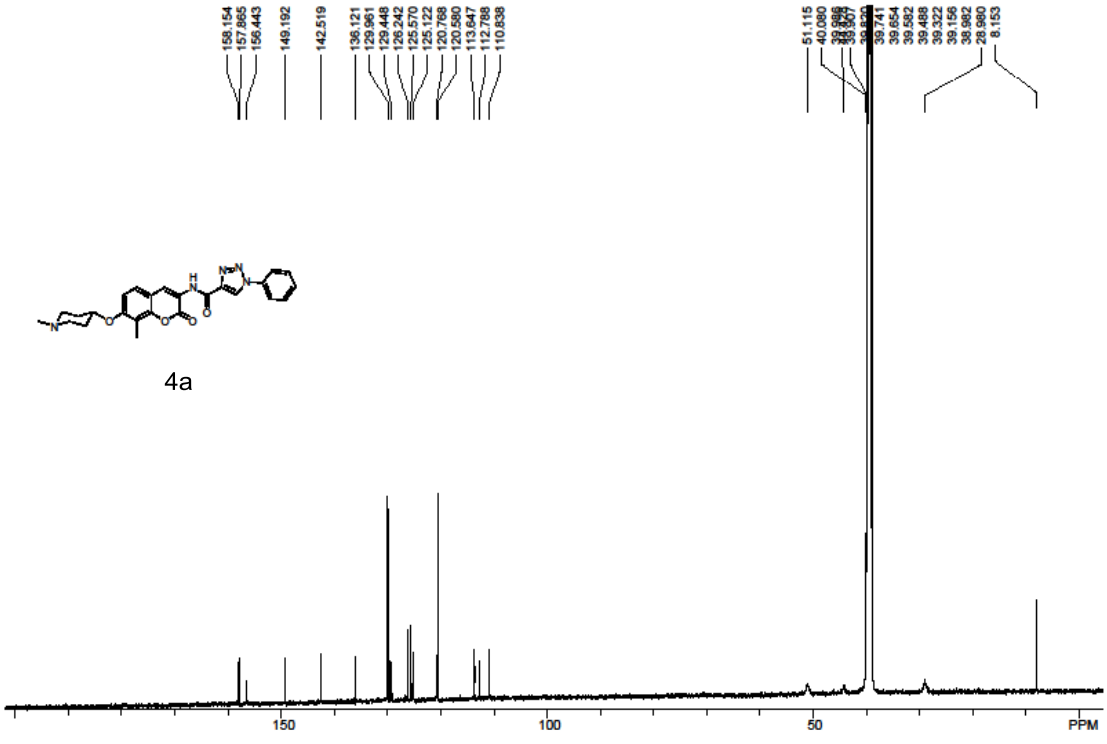
6
4
2
PPM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129.448
126.242
125.570
125.122
120.768
120.580
113.647
112.788
110.838
51.115
40.080
39.741
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39.488
39.322
39.156
38.982
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8.153
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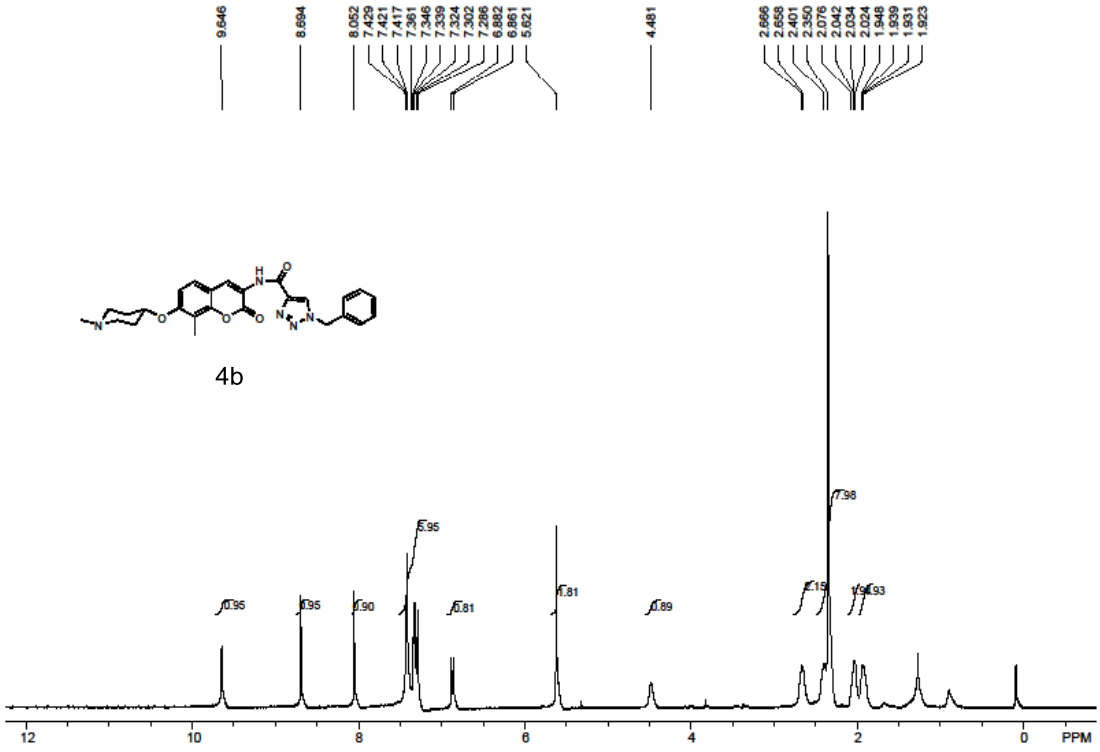
100
50
PPM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7.346
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7.324
7.302
7.286
6.882
6.861
5.521
4.481
2.666
2.658
2.401
2.350
2.076
2.042
2.034
2.024
1.946
1.939
1.931
1.923
4b
0.95
0.95
0.90
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0.81
1.81
0.89
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1.93
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10
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6
4
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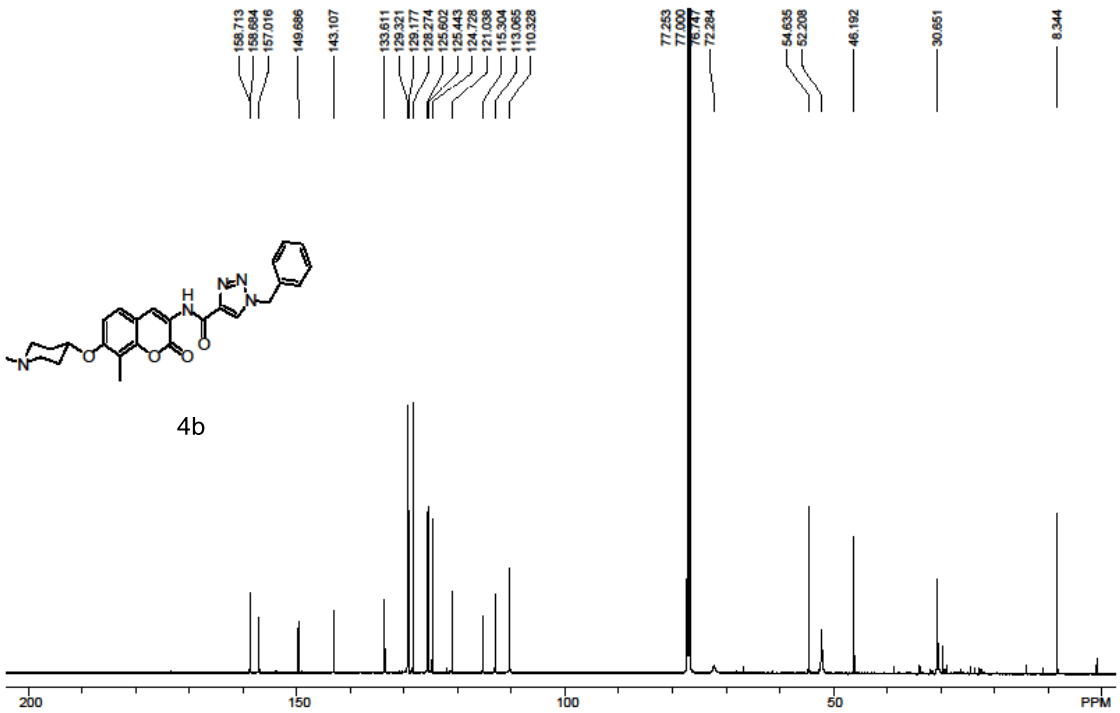
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124.728
121.038
115.304
113.065
110.328
77.253
77.000
76.747
72.284
54.635
52.208
46.192
30.651
8.344
4b
200
150
100
50
PPM


9.710
8.759
8.577
7.780
7.758
7.591
7.569
7.360
7.339
7.283
6.906
6.884
4.518
2.733
2.722
2.705
2.701
2.696
2.487
2.468
2.463
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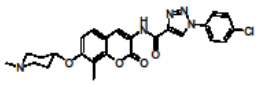
1.972
1.957



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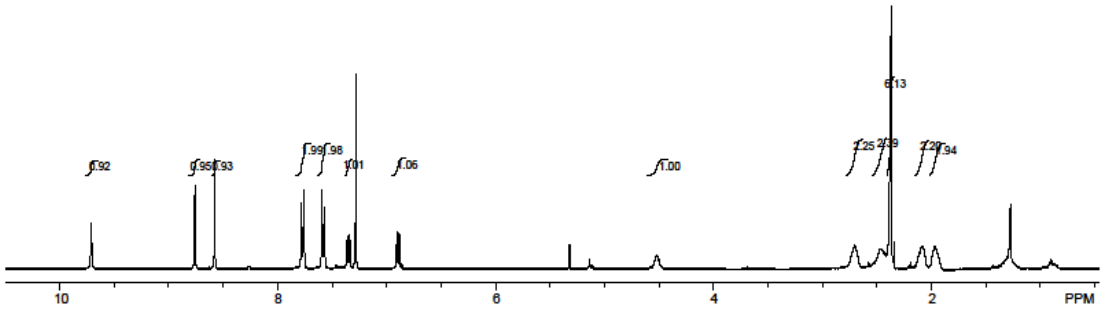
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1.06
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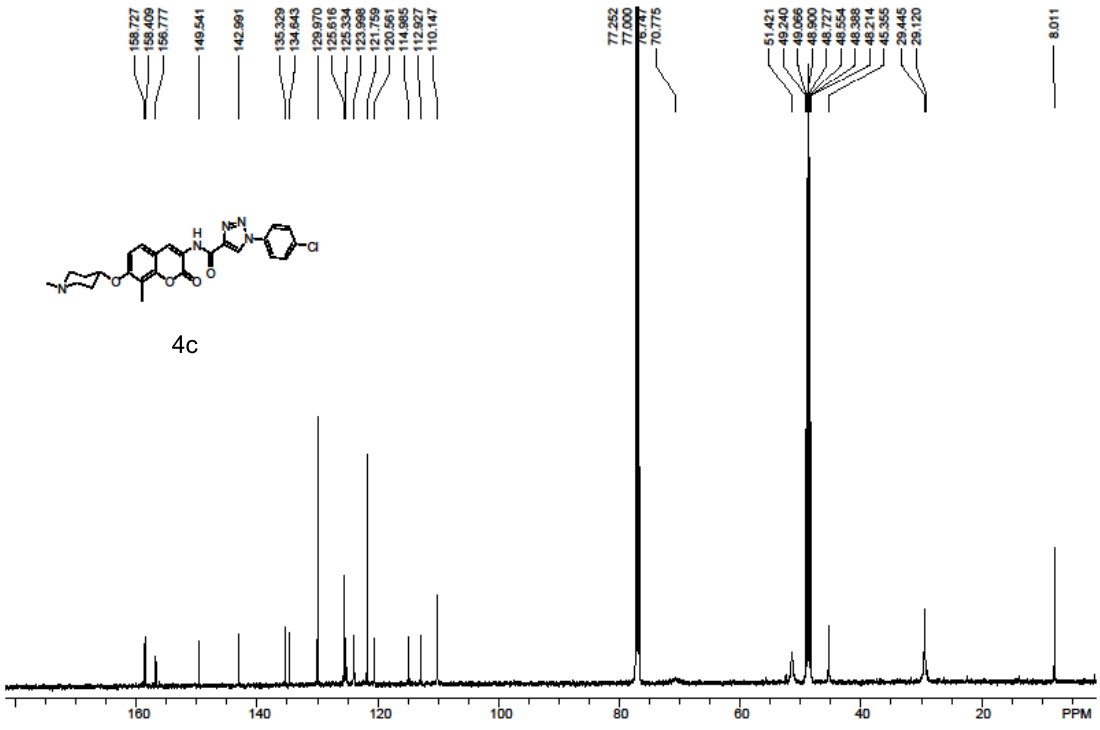
2.29
2.20
1.94
10
8
6
4
2
PPM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120.561
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77.000
76.747
70.775
51.421
49.240
49.066
48.900
48.727
48.554
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29.445
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8.011
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120
100
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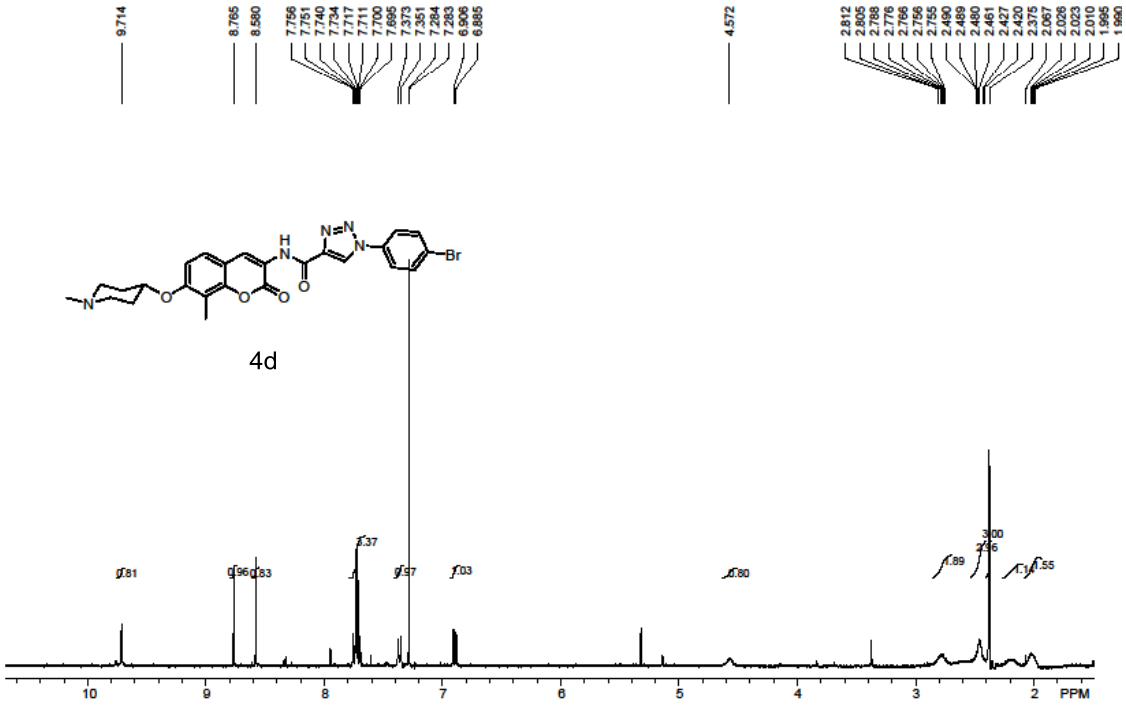
60
40
20
PPM

4c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7.717
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7.700
7.695
7.373
7.351
7.284
7.283
6.906
6.885
4.572
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2.805
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2.776
2.766
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2.755
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2.489
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2.461
2.427
2.420
2.375
2.057
2.026
2.023
2.010
1.966
1.940
Br
4d
0.81
0.96
0.83
1.37
0.97
1.03
0.80
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3.00
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1.55
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9
8
7
6
5
4
3
2
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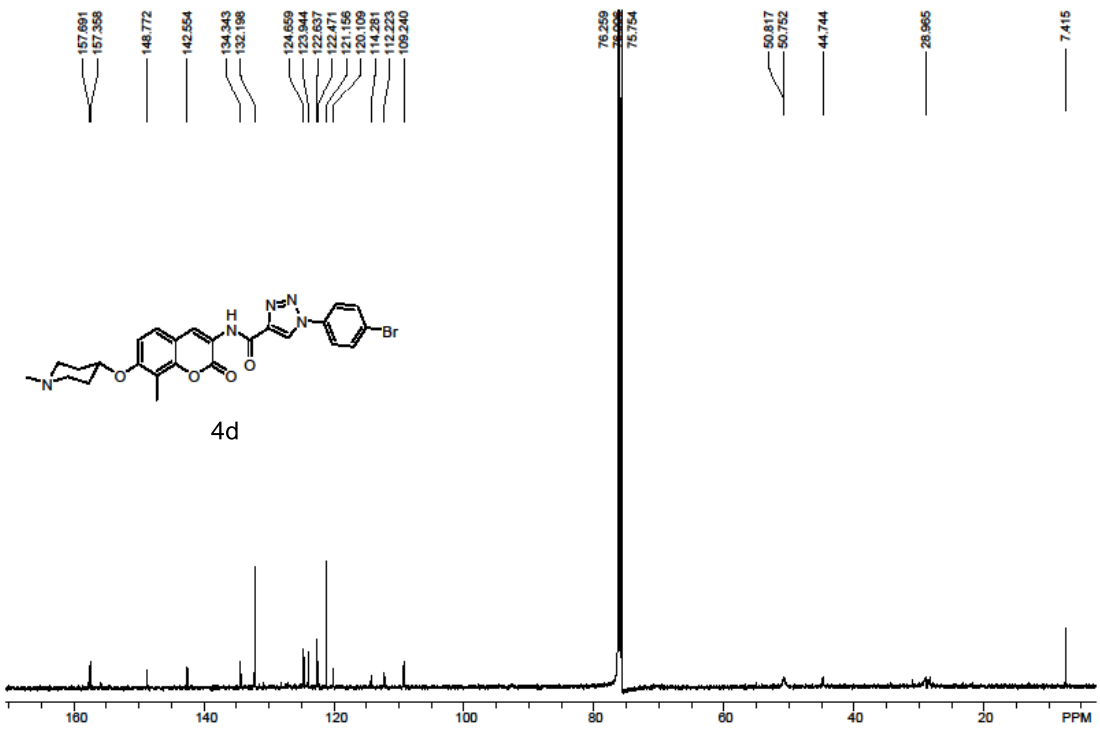
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123.944
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120.109
114.281
112.223
109.240
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75.754
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7.415
Br
4d
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100
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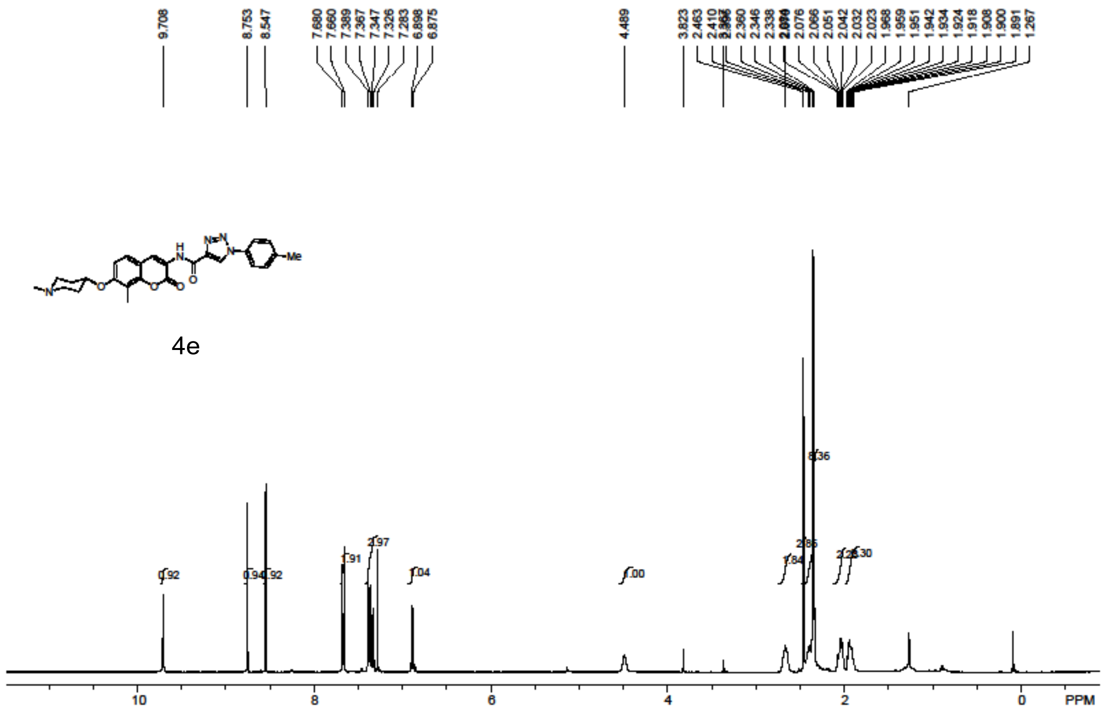
60
40
20
PPM



4e
10
8
6
4
2
0
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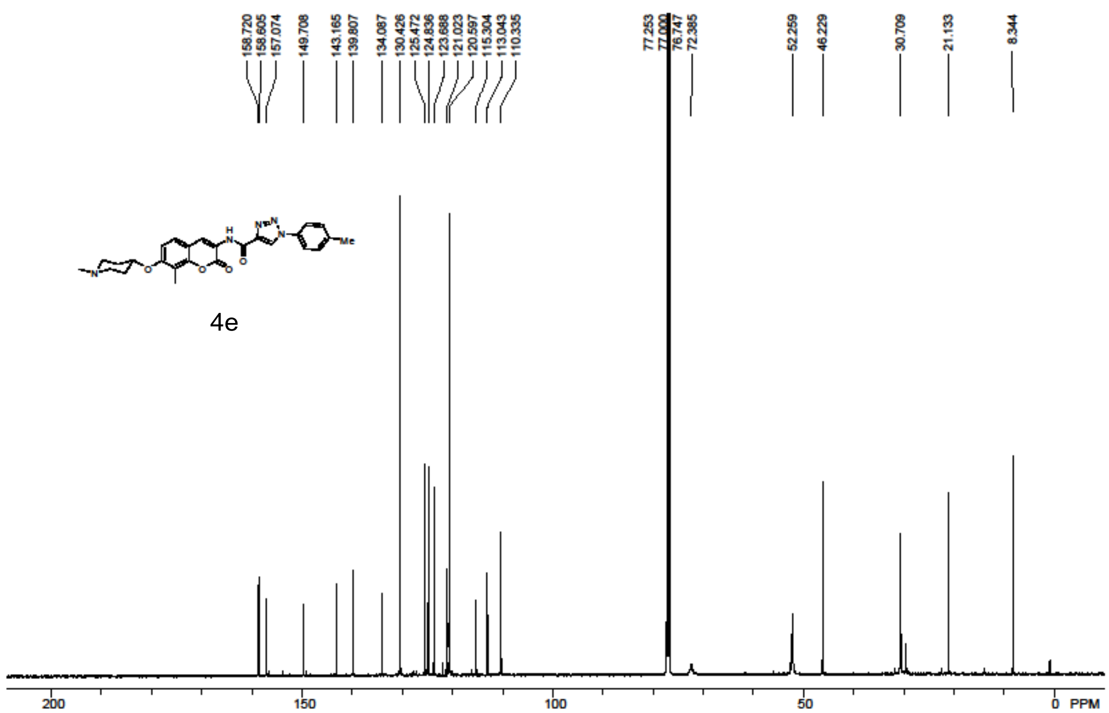

4e
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150
100
50
0
PPM


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7.719
7.700
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7.538
7.519
7.511
7.494
7.490
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7.326
7.283
6.896
6.874
4.498
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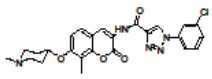
1.932



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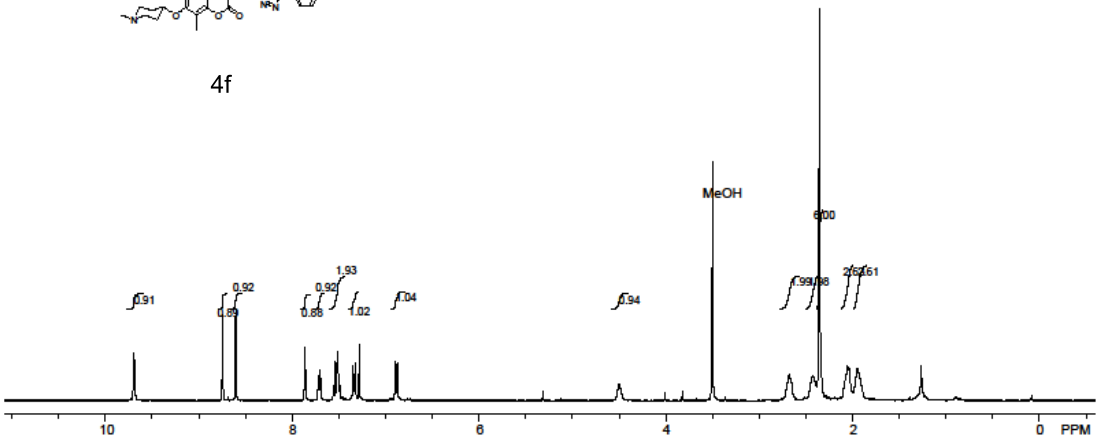
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0.92
0.88
1.93
1.02
1.04
0.94
1.99
1.98
2.61
10
8
6
4
2
0
PPM


158.147
157.685
156.688
149.221
142.577
137.139
134.236
131.658
129.246
126.213
125.873
125.288
120.602
120.464
119.208
113.553
112.578
110.896
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39.741
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39.481
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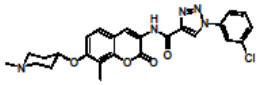
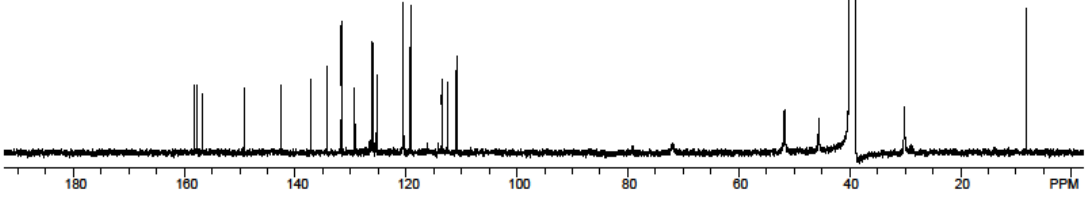
39.149
38.982
30.121
8.124



4f


180
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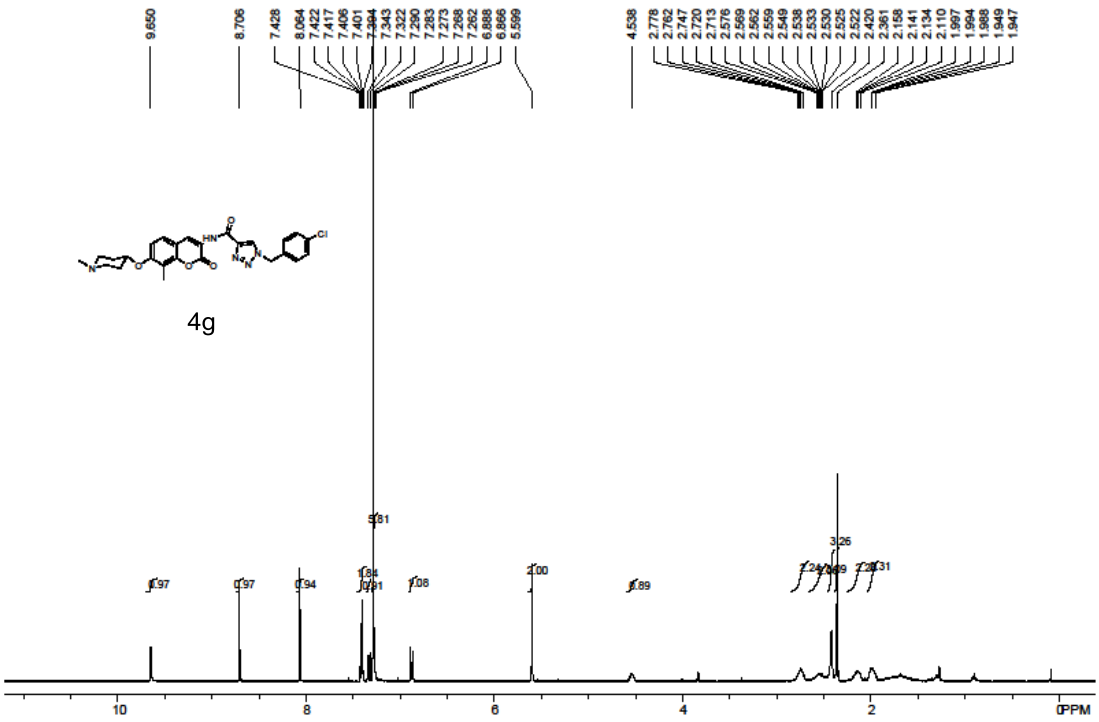
120
100
80
60
40
20
PPM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2.134
2.110
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1.994
1.988
1.949
1.947
5.31
3.26
0.97
0.97
0.94
1.84
1.91
1.08
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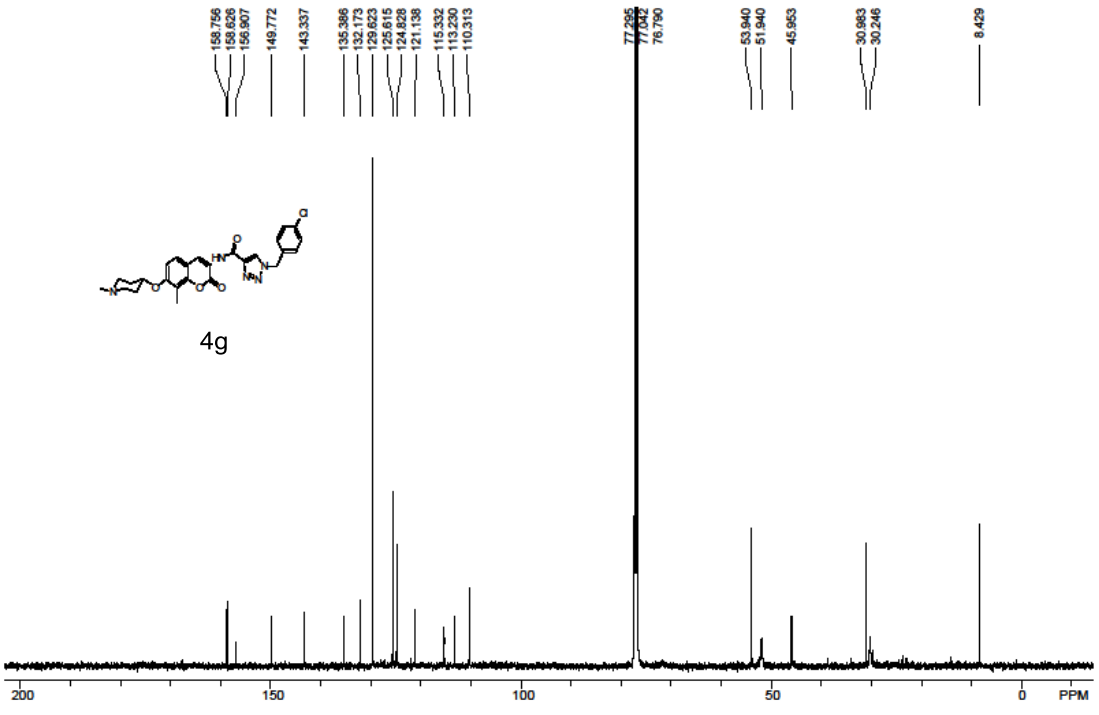
0.89
7.24
7.09
7.31
10
8
6
4
2
0
PPM

4g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113.230
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77.295
77.042
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51.940
45.953
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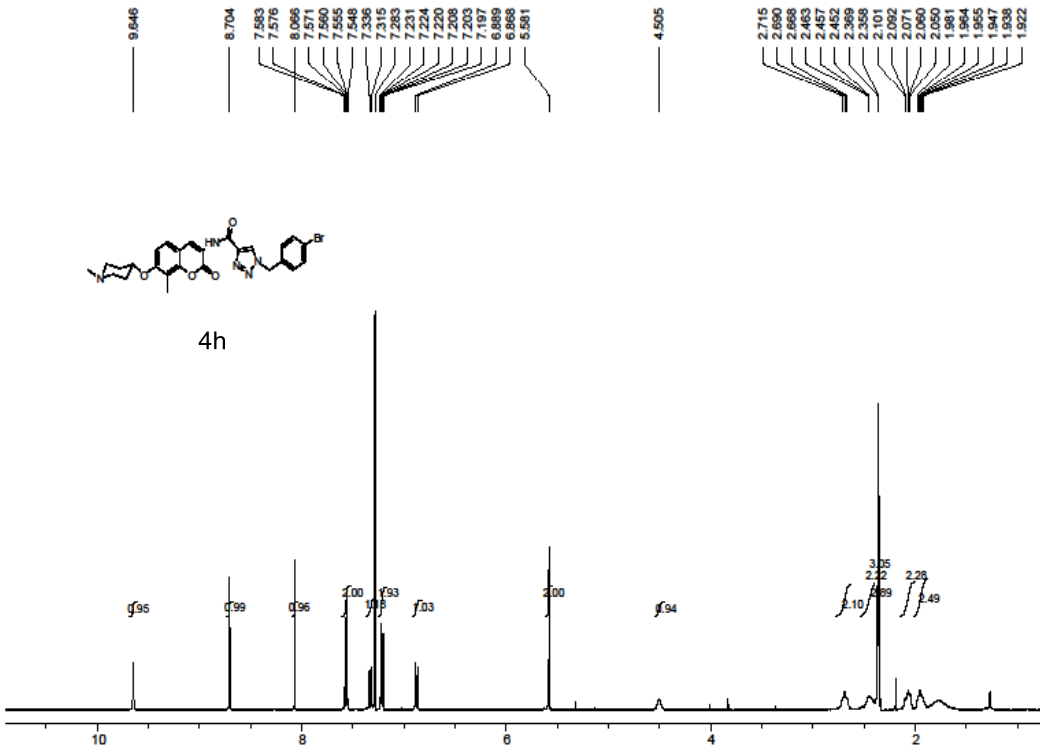
PPM

4g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7.571
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7.555
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7.336
7.315
7.283
7.231
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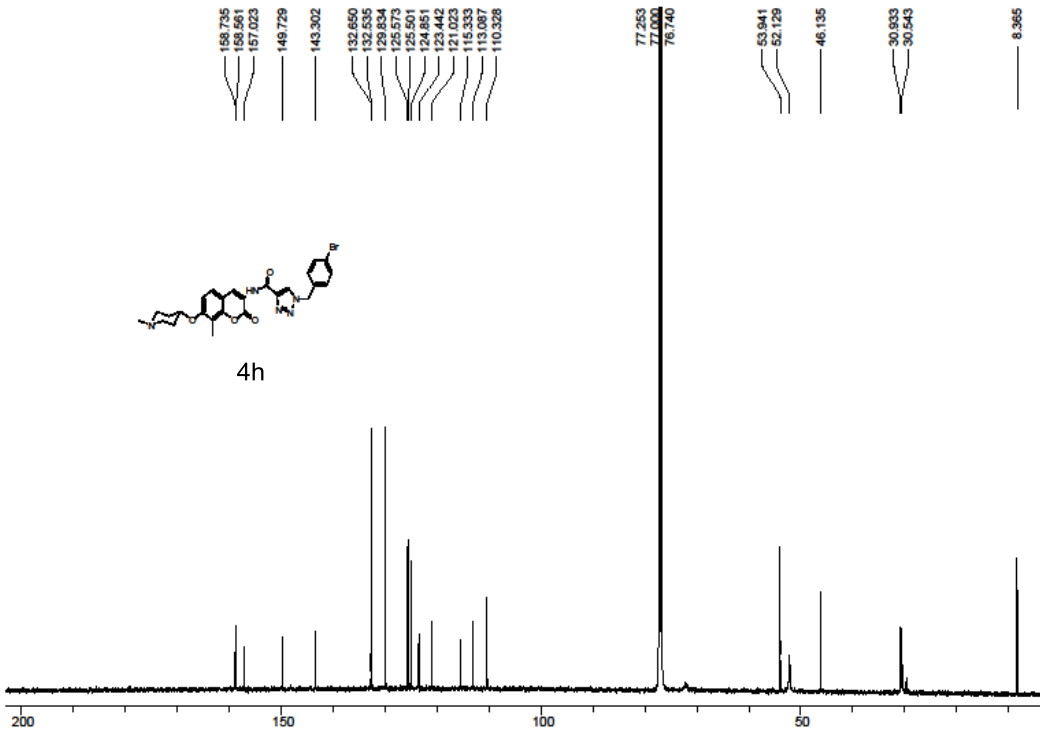
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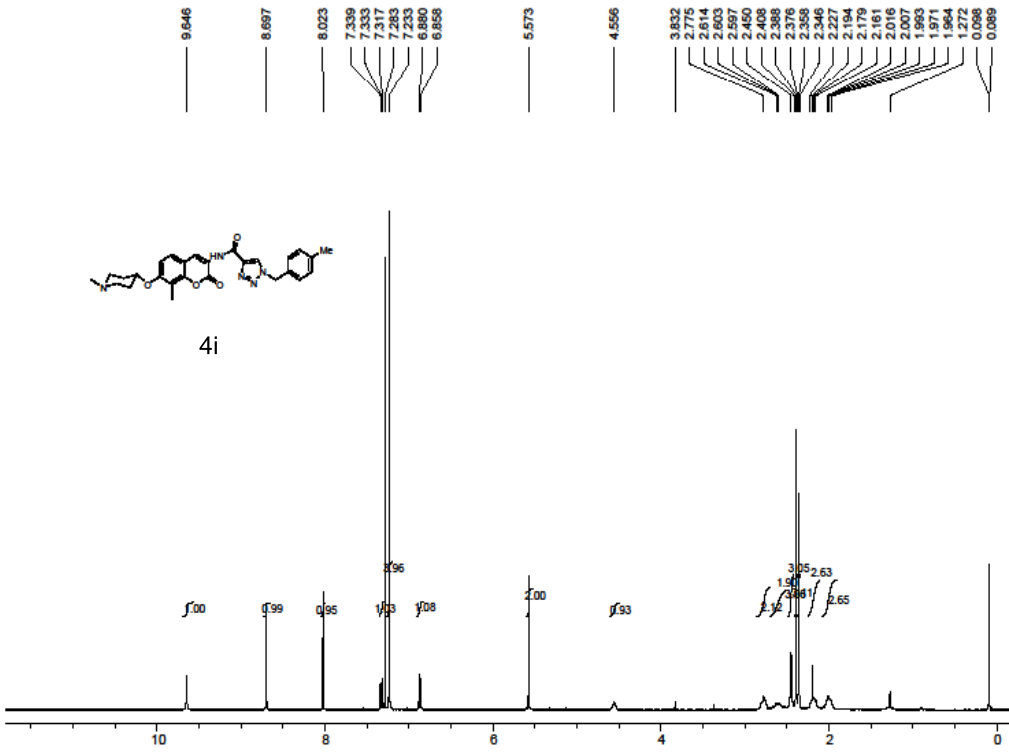
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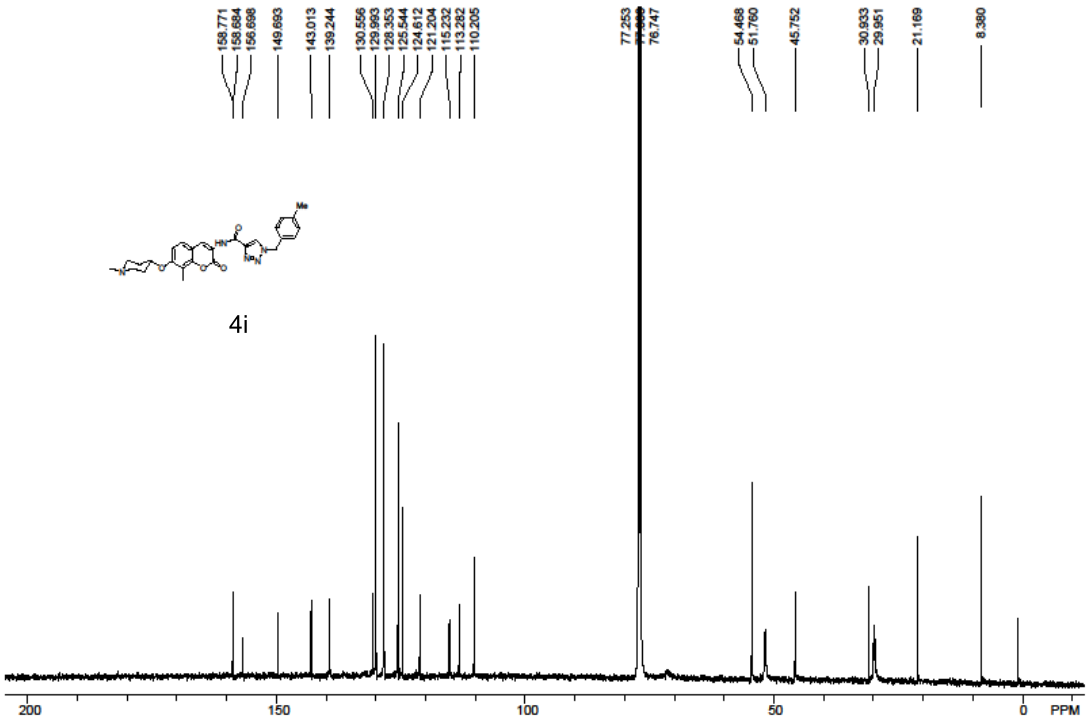
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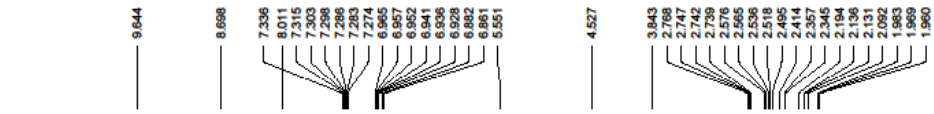
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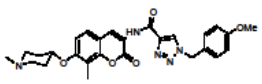

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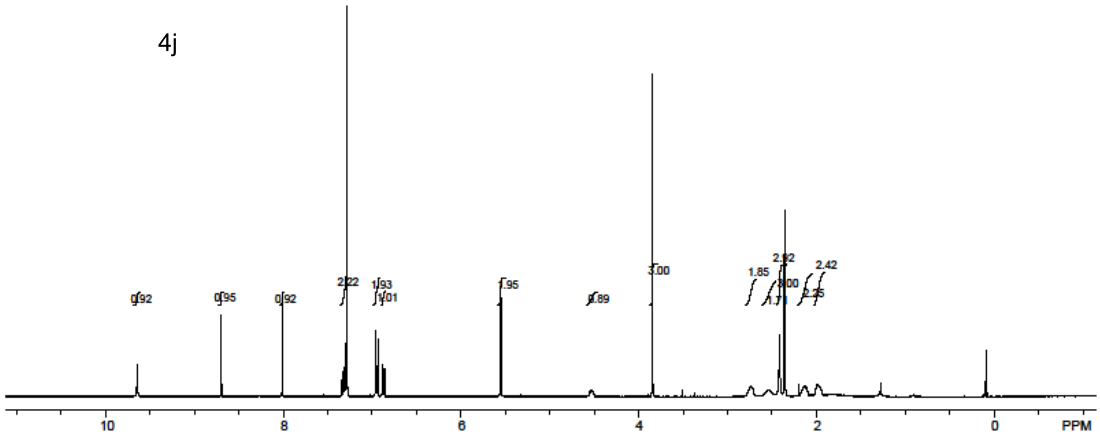
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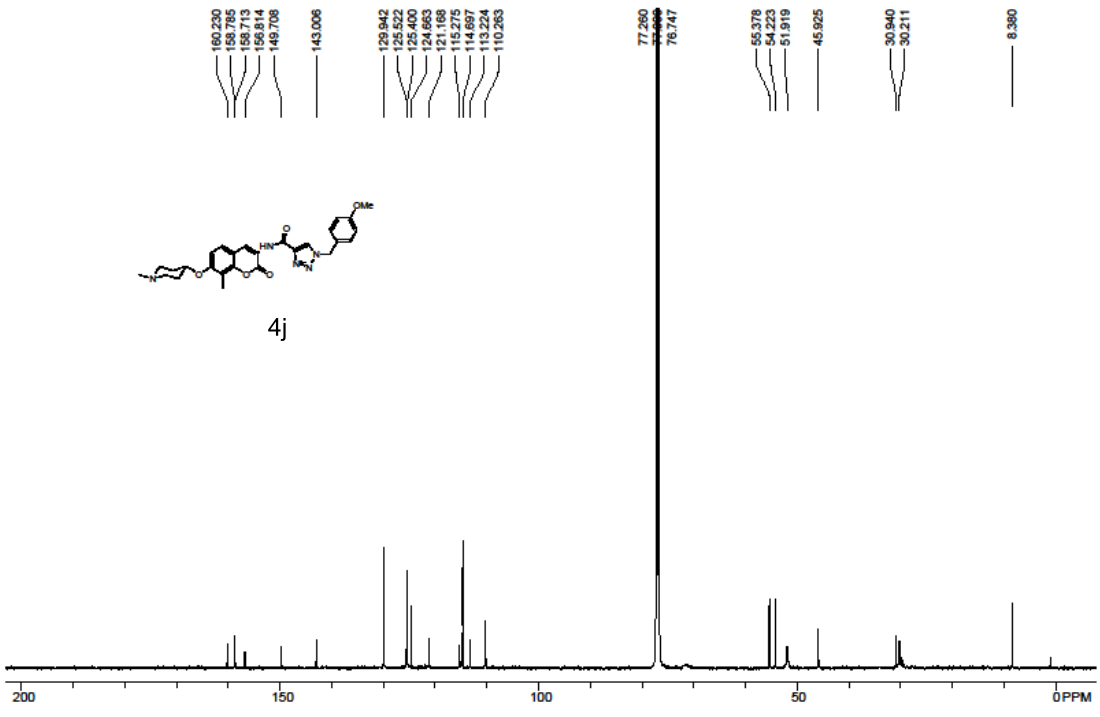
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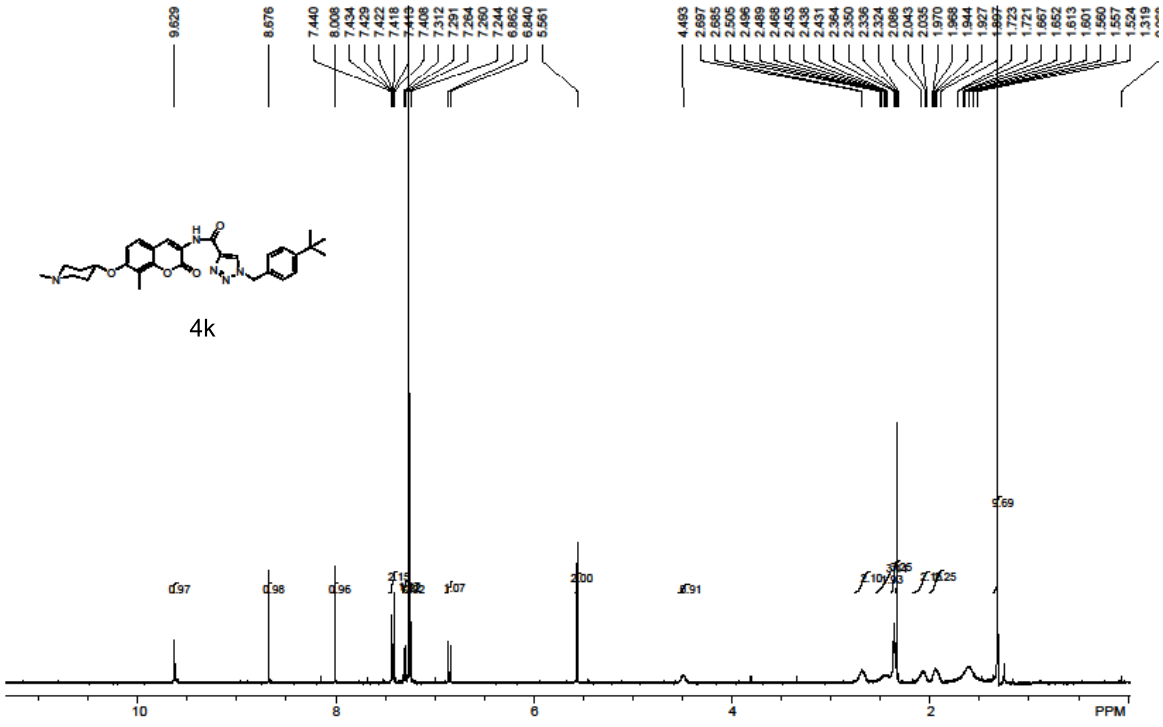
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7.260
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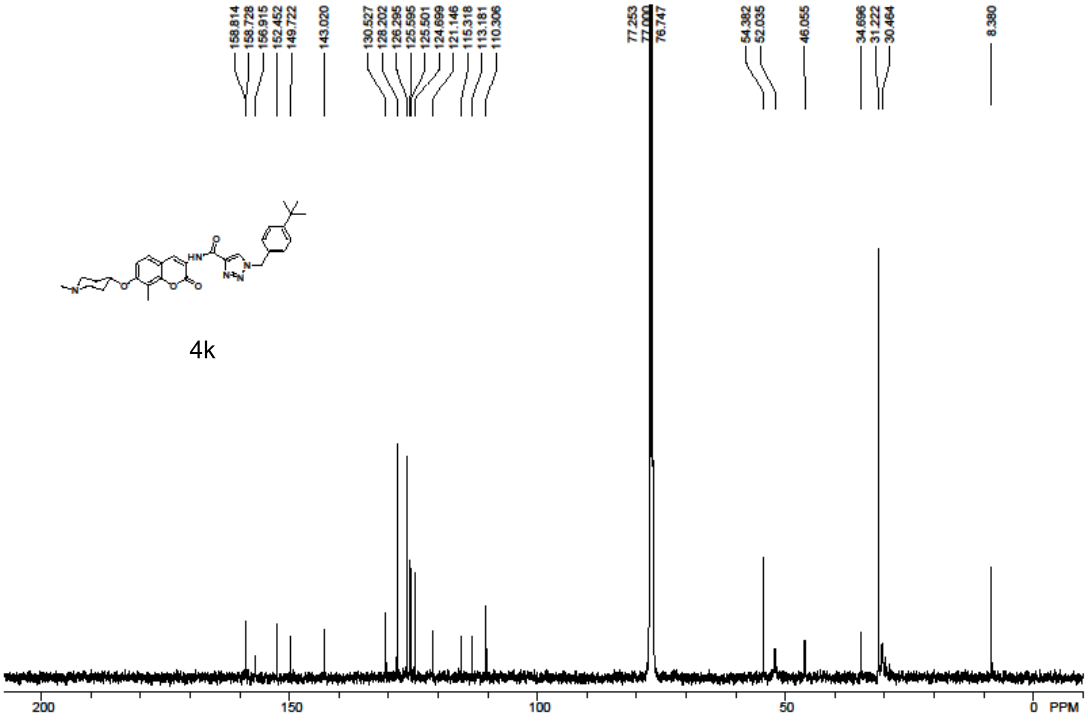
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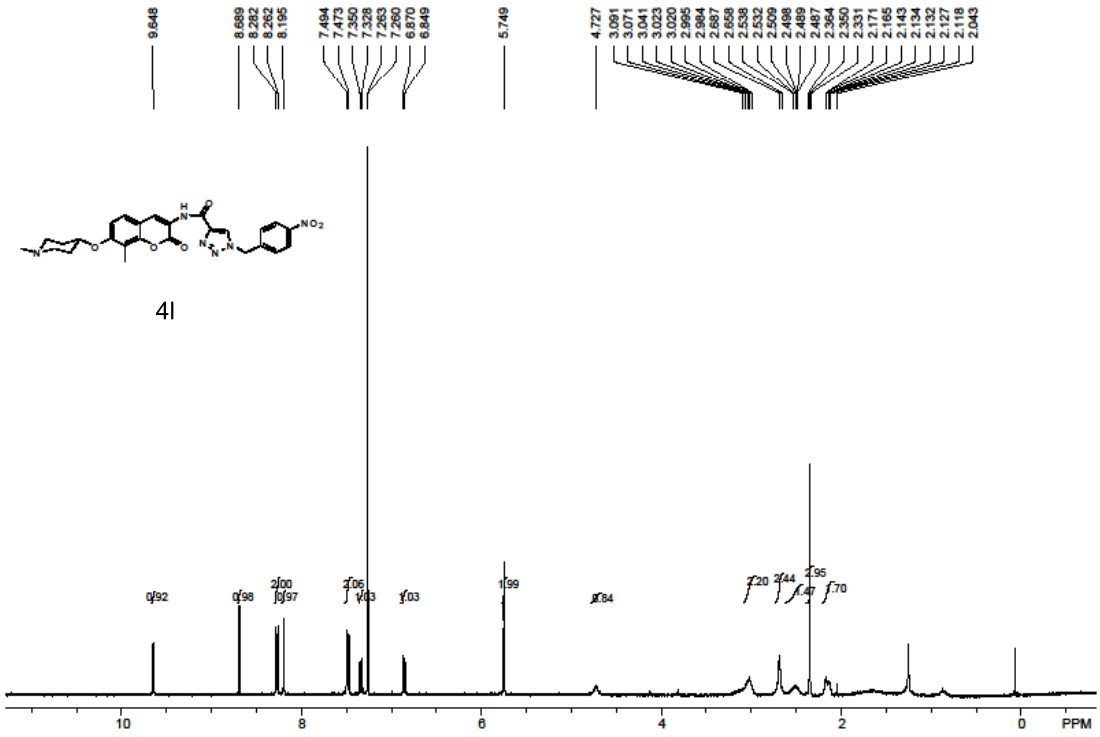
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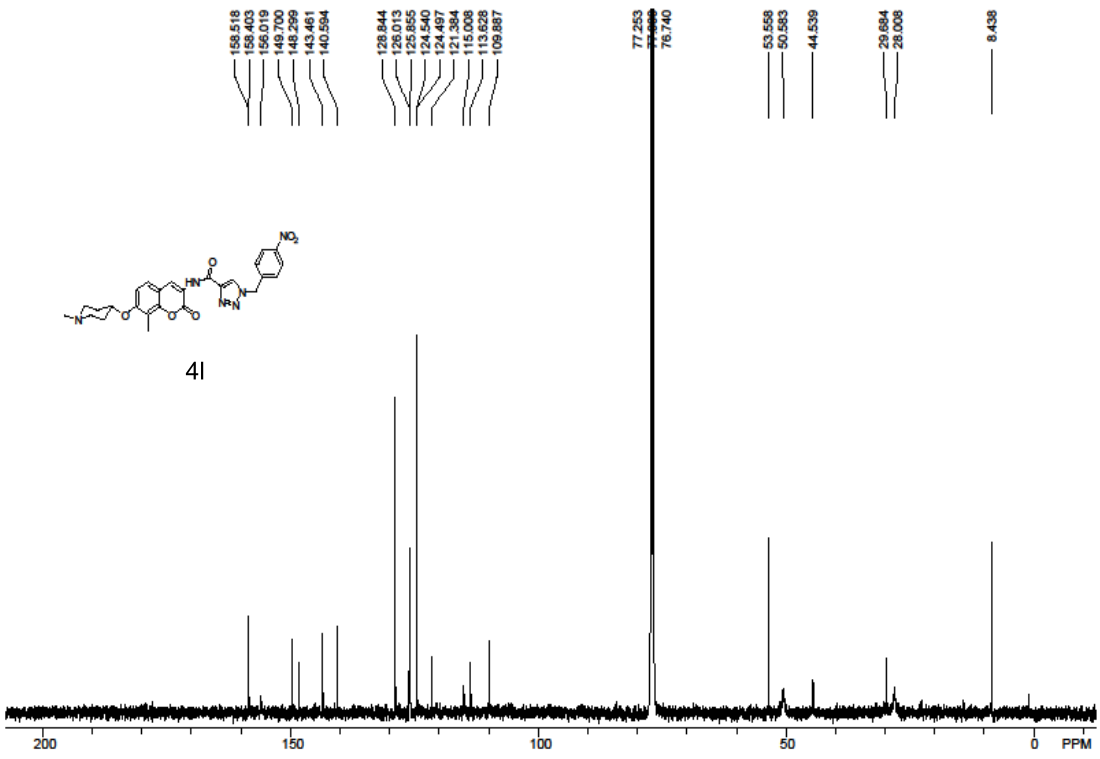
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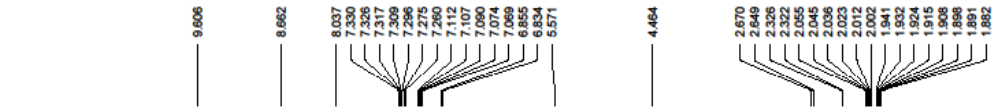
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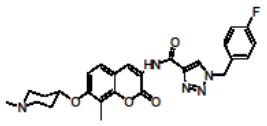

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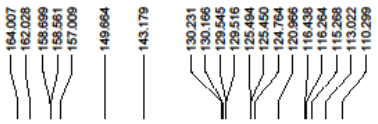
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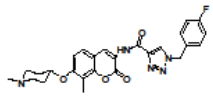

4m

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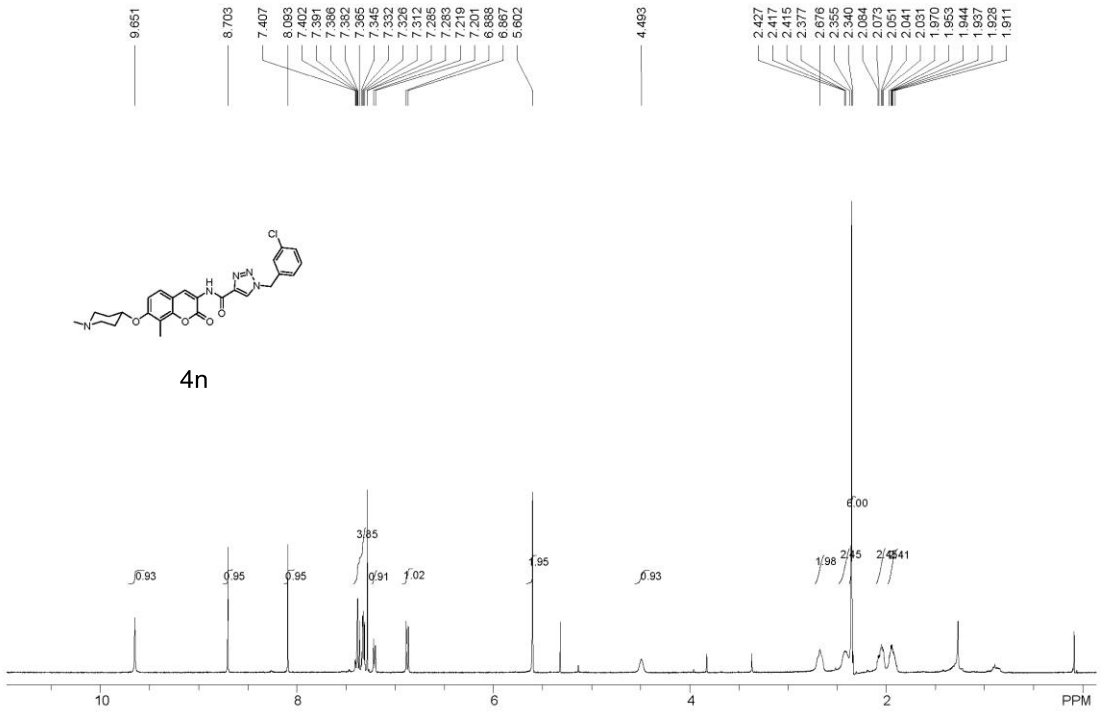
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O
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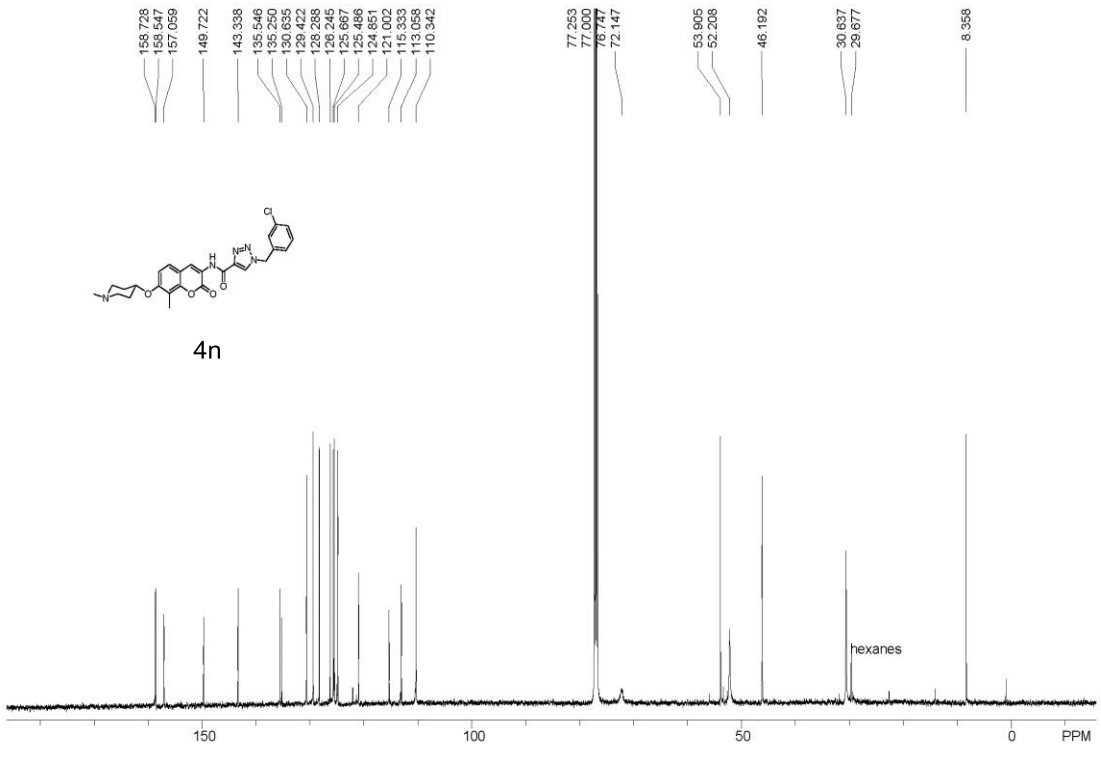
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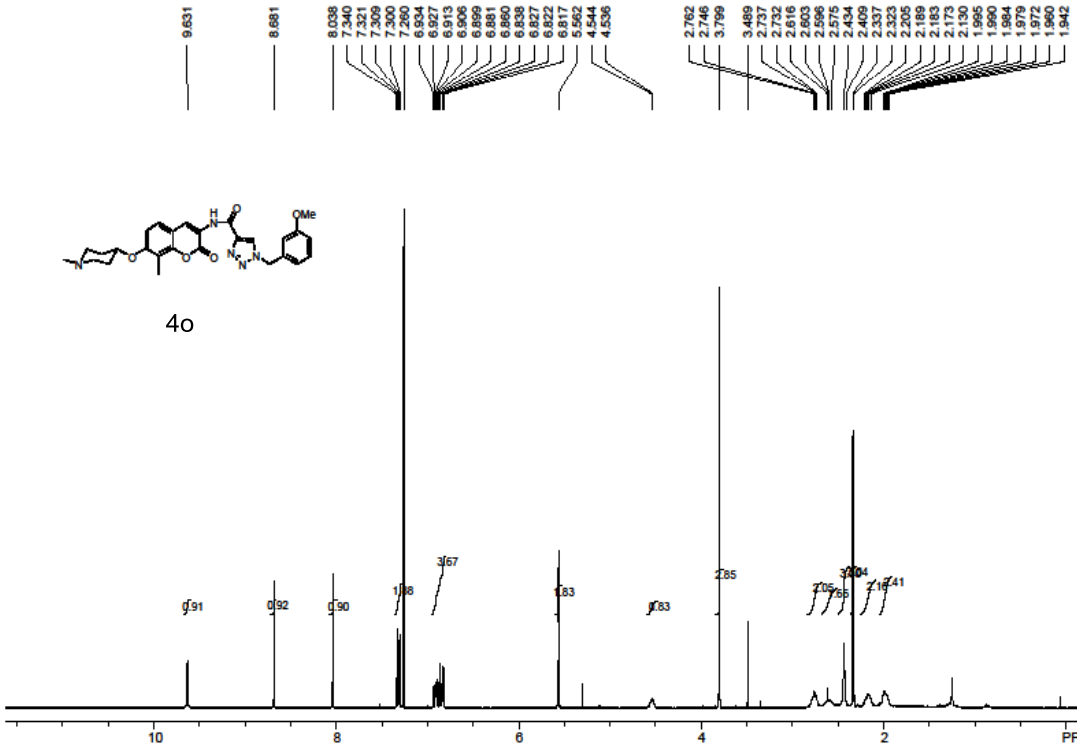
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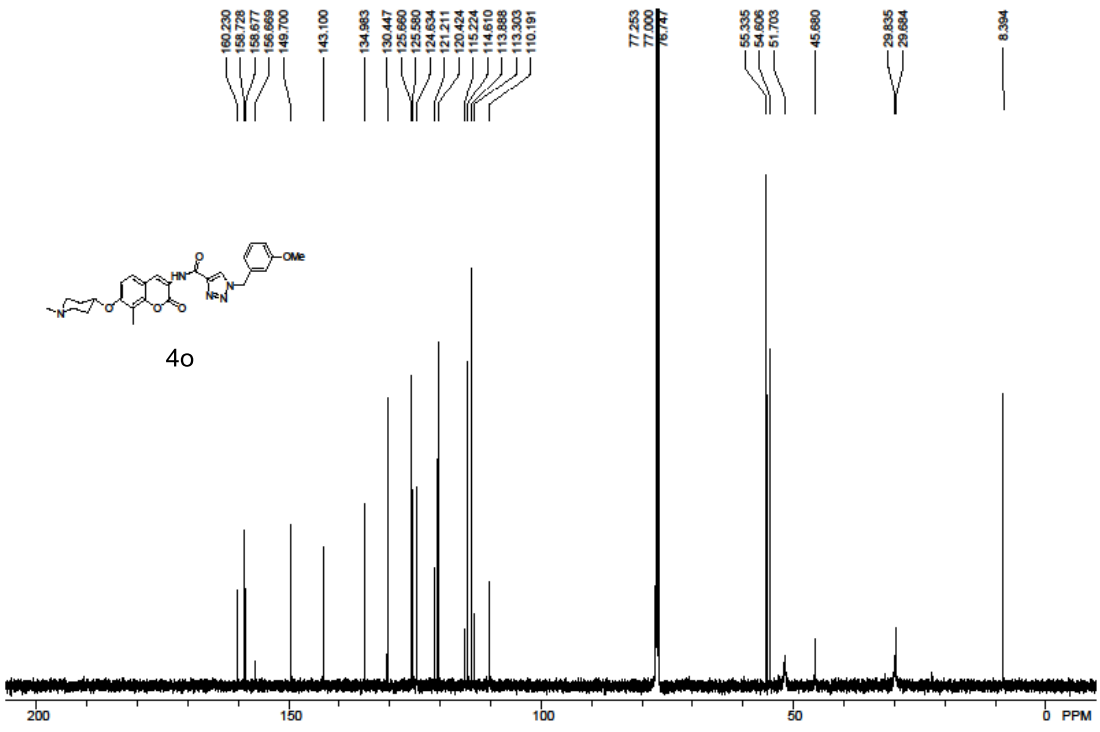
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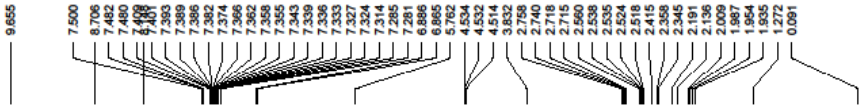
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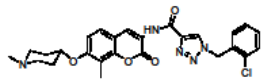

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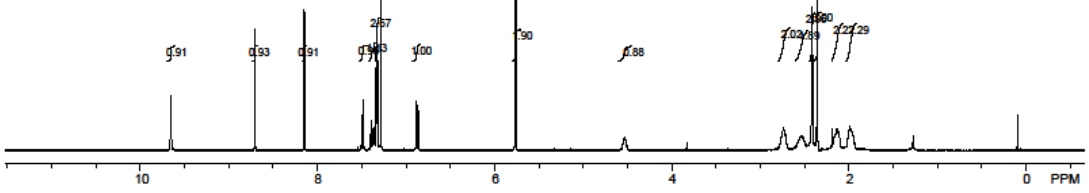
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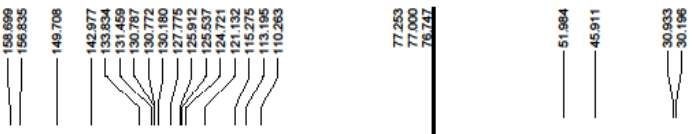
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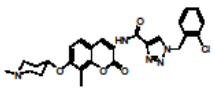

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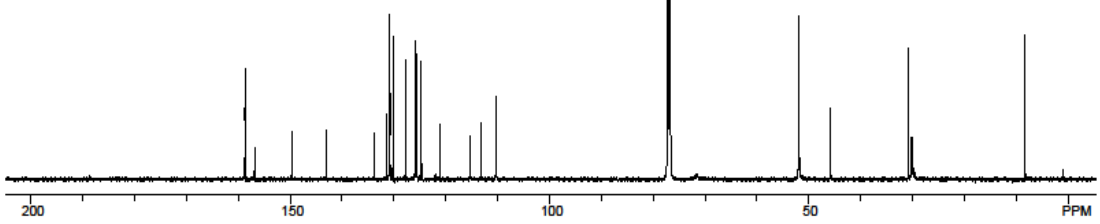
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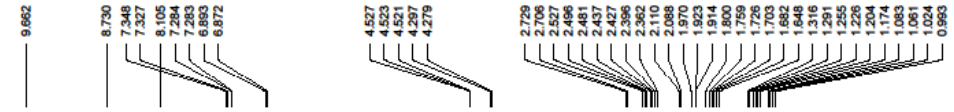
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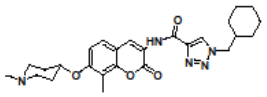

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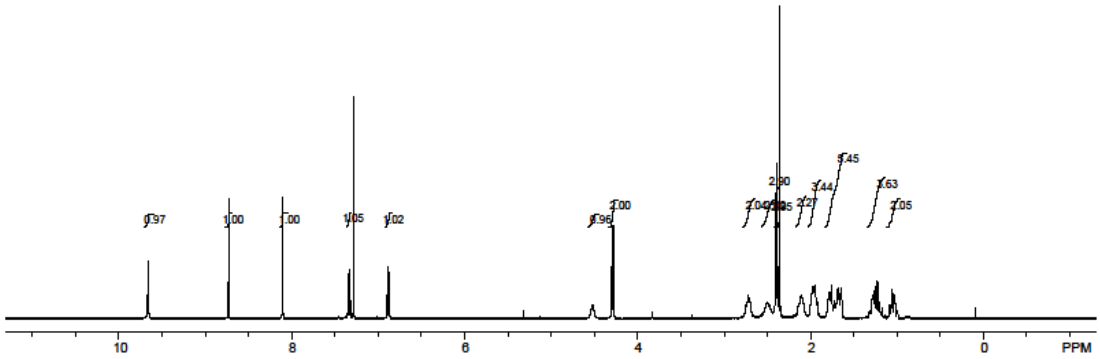
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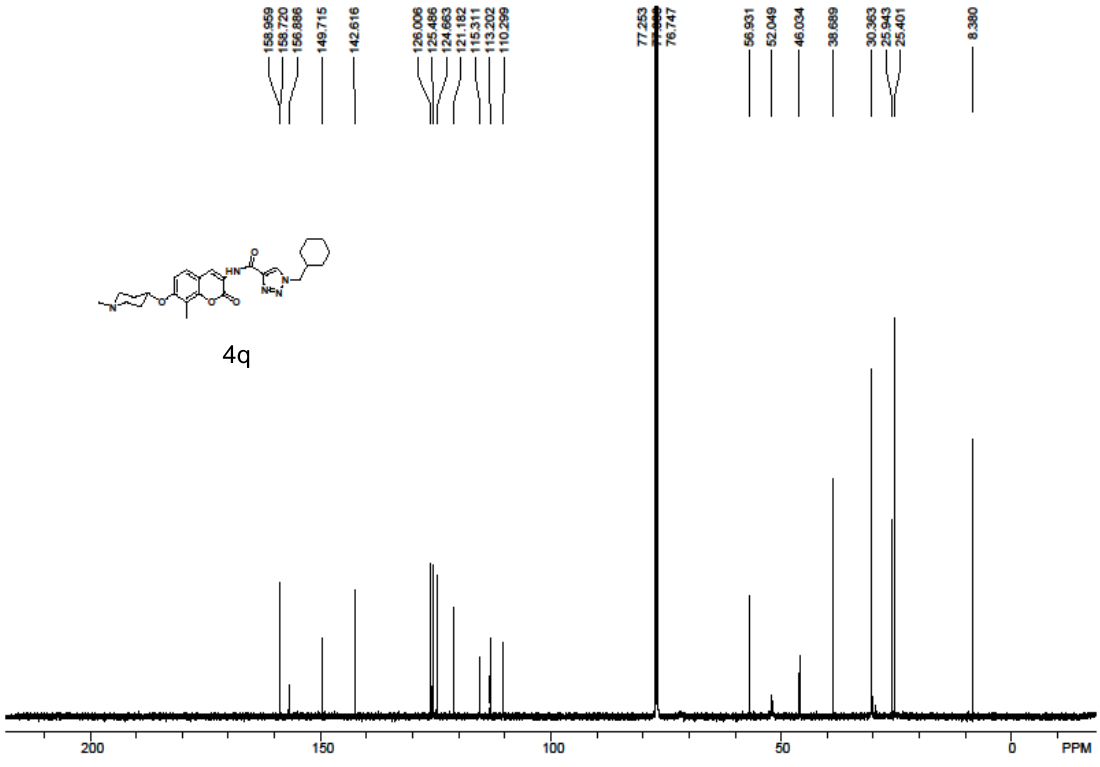
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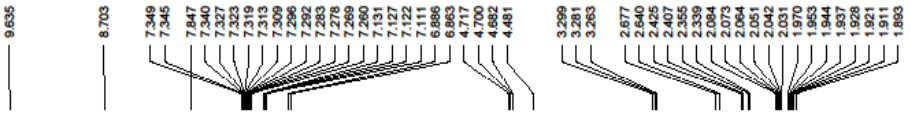
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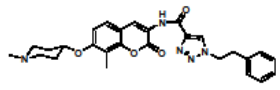

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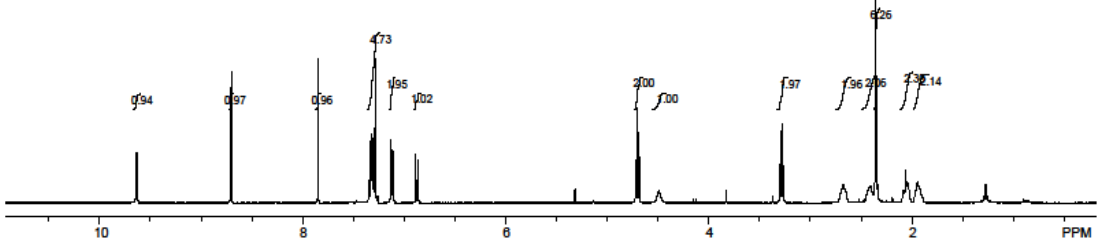
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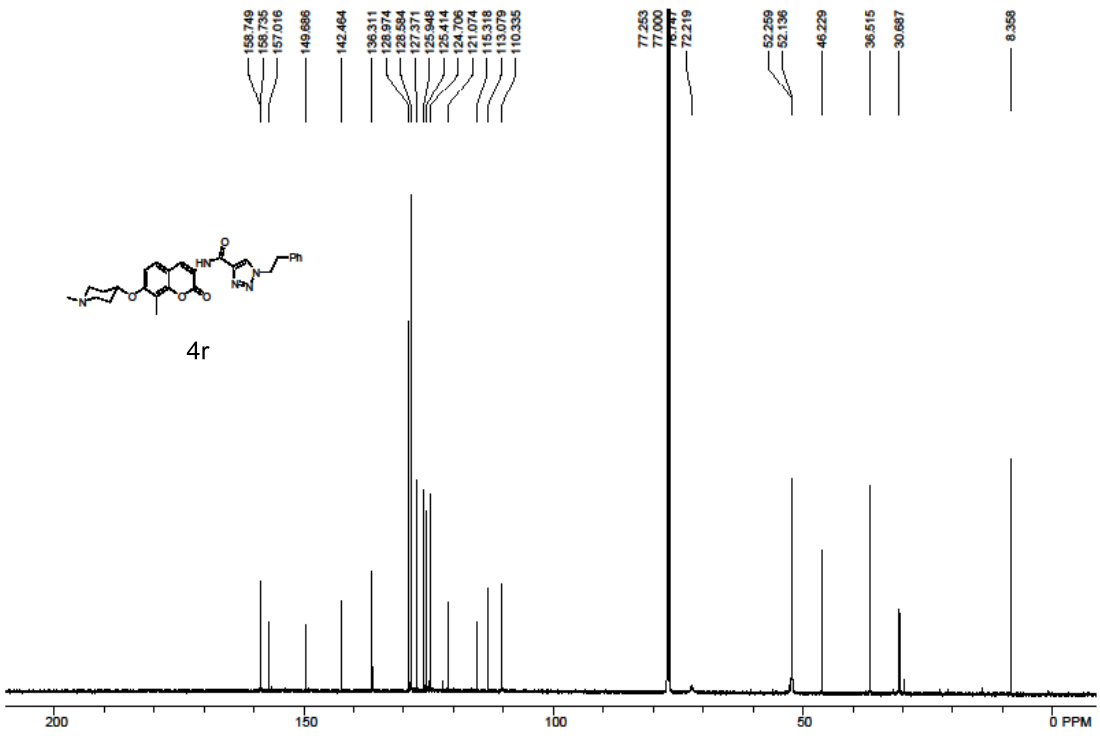
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77.000
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50
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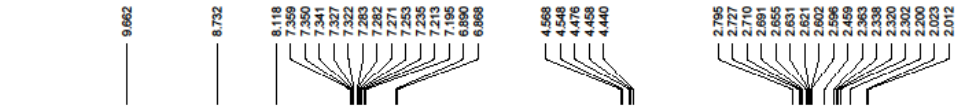
4r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7.213
7.195
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6.868
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4.476
4.458
4.440
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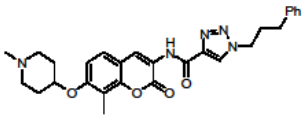
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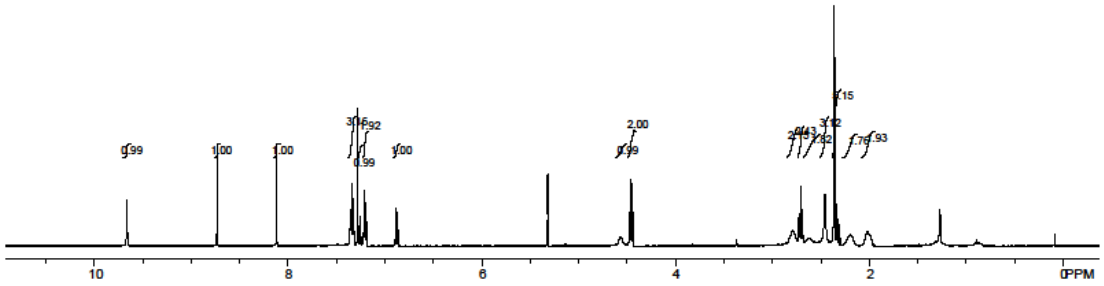
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10
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6
4
2
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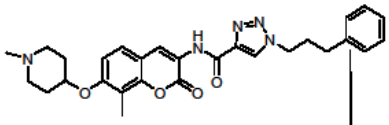

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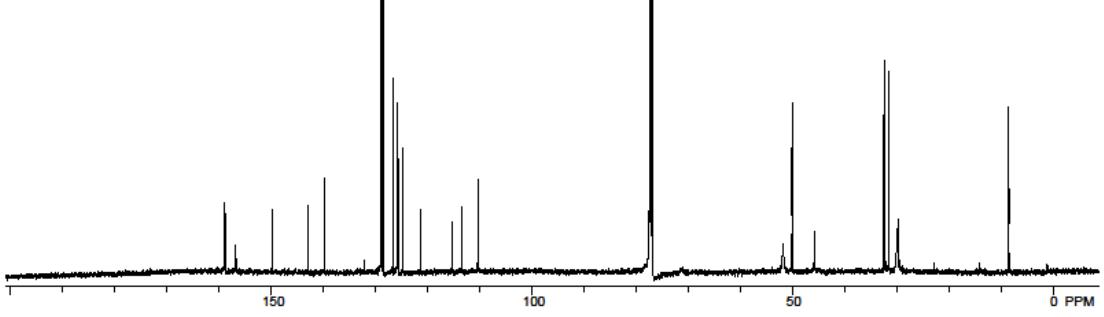
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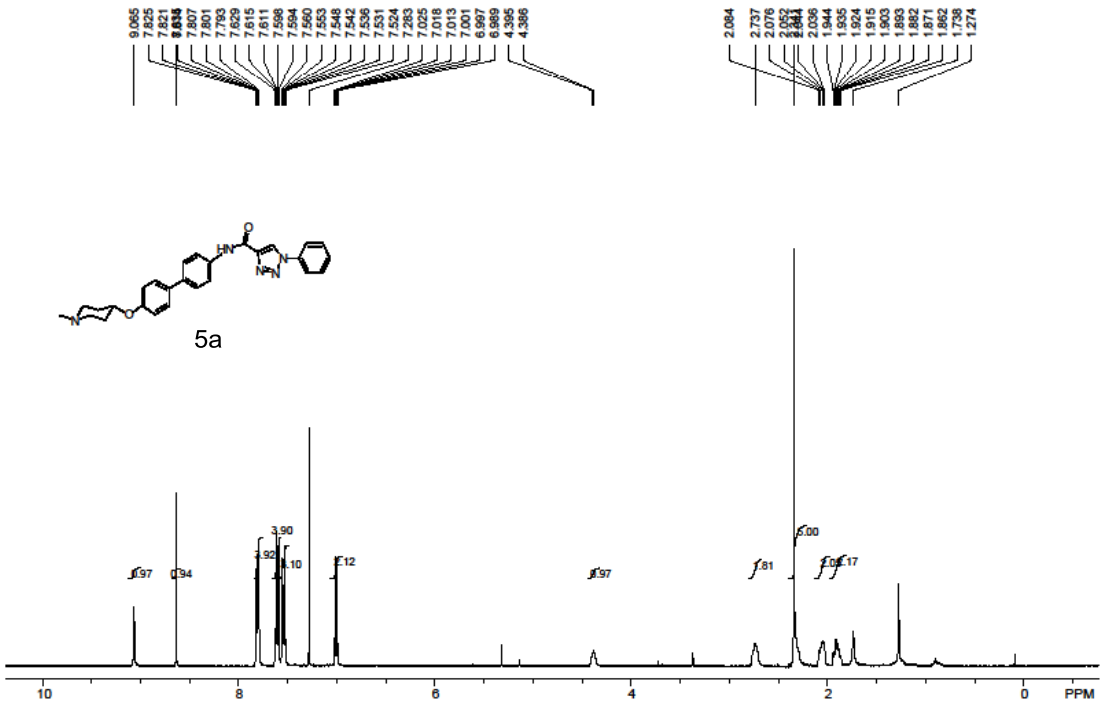
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7.548
7.542
7.536
7.531
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7.283
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7.013
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4.386
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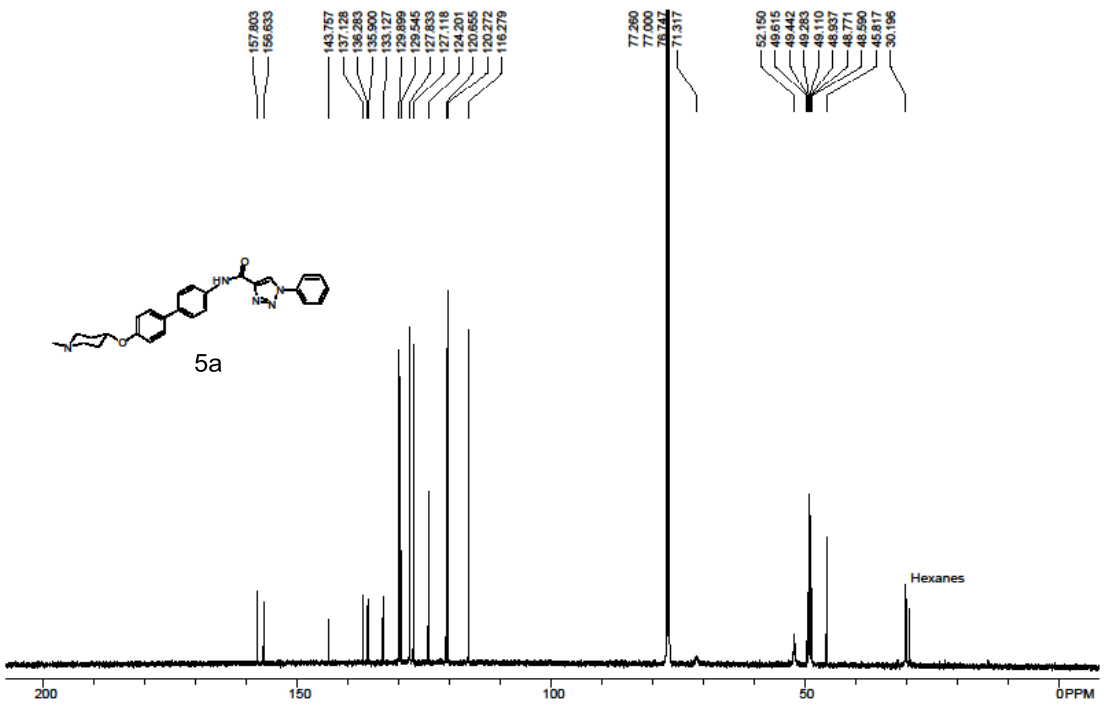
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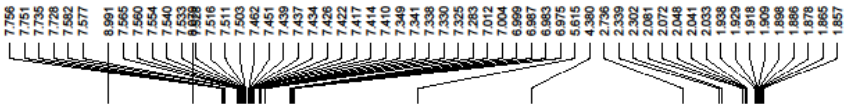
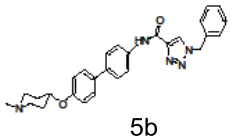
Hexanes
PPM





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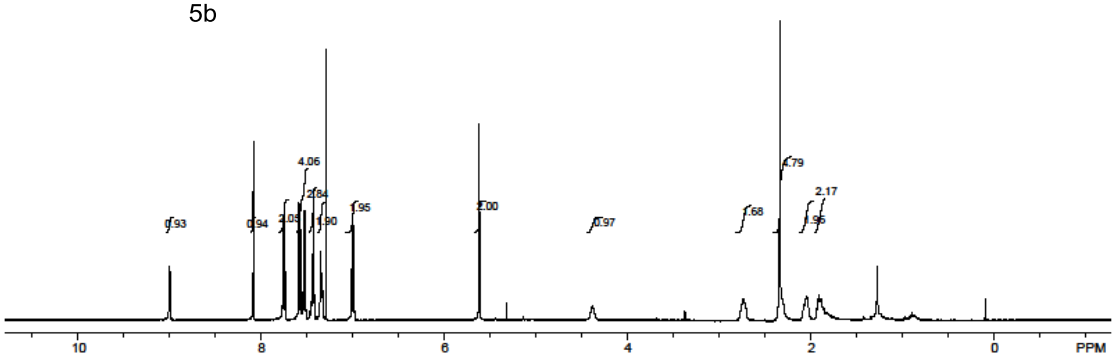
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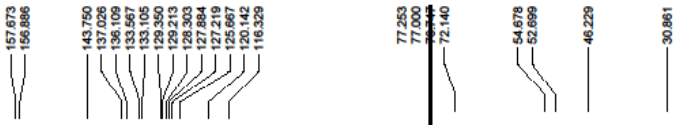

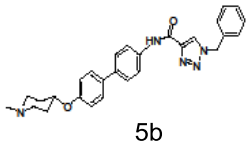

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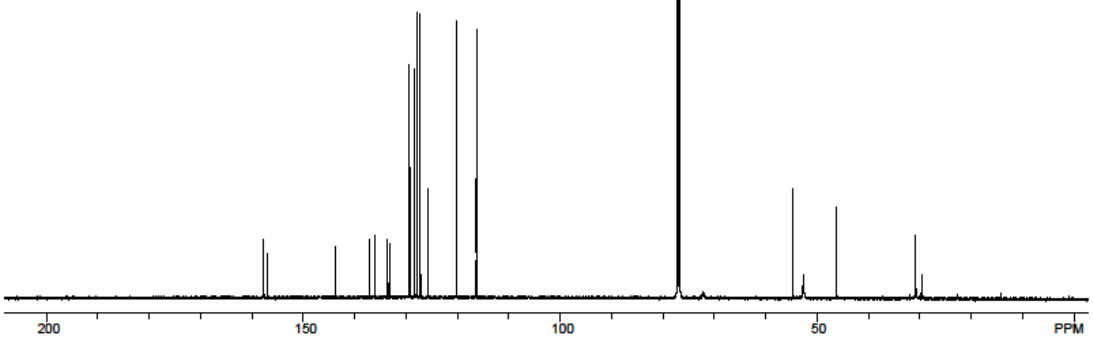
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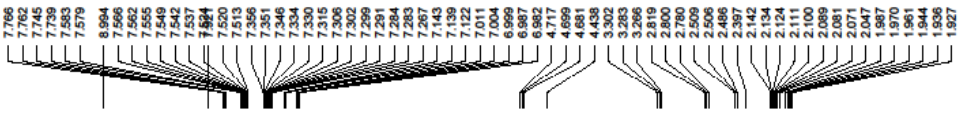

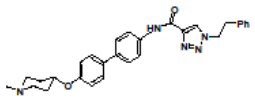

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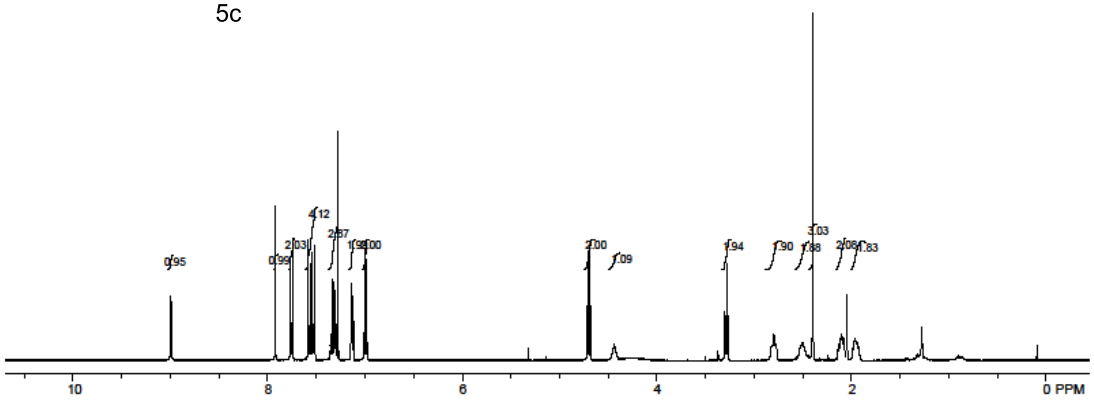

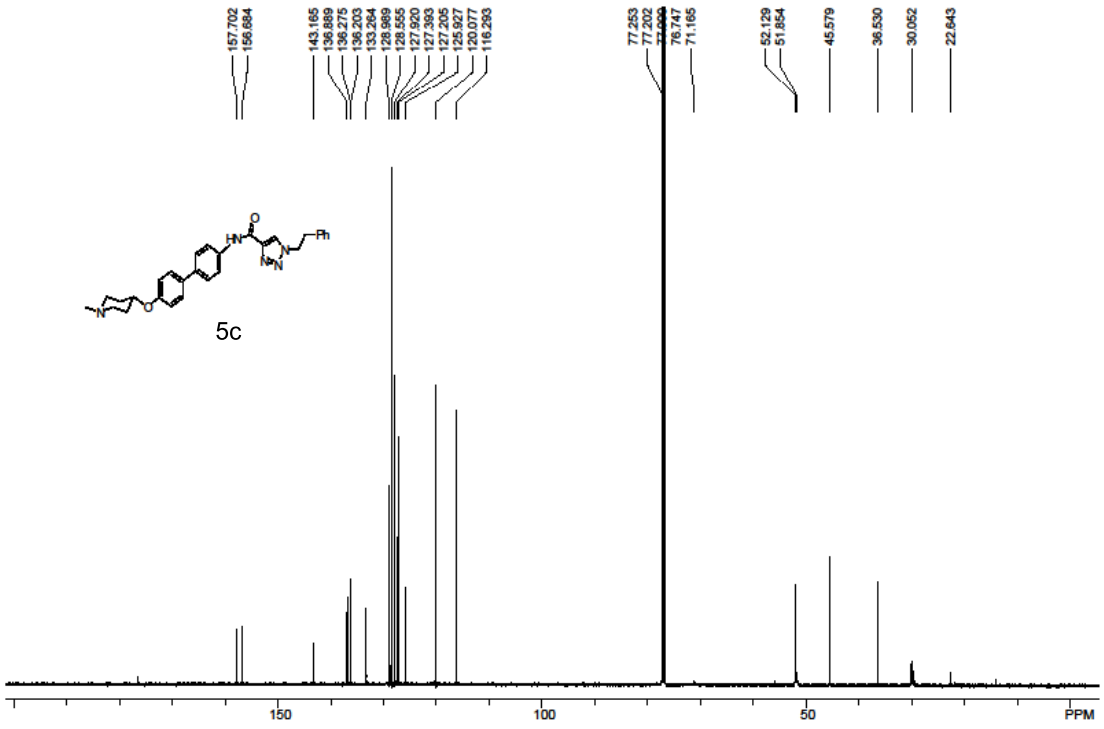

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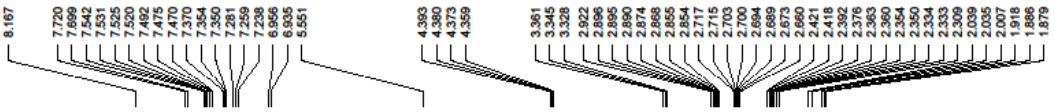
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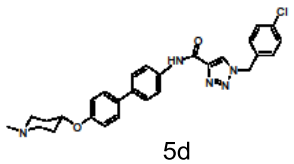

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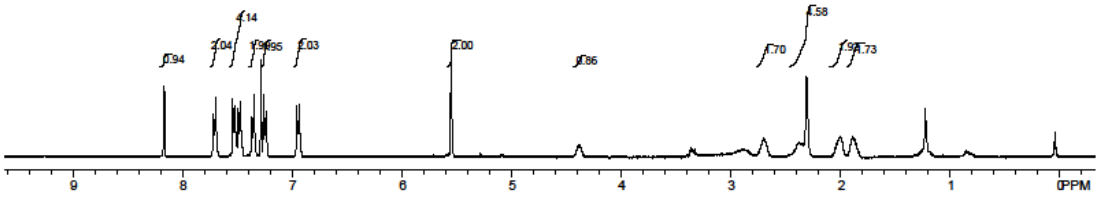
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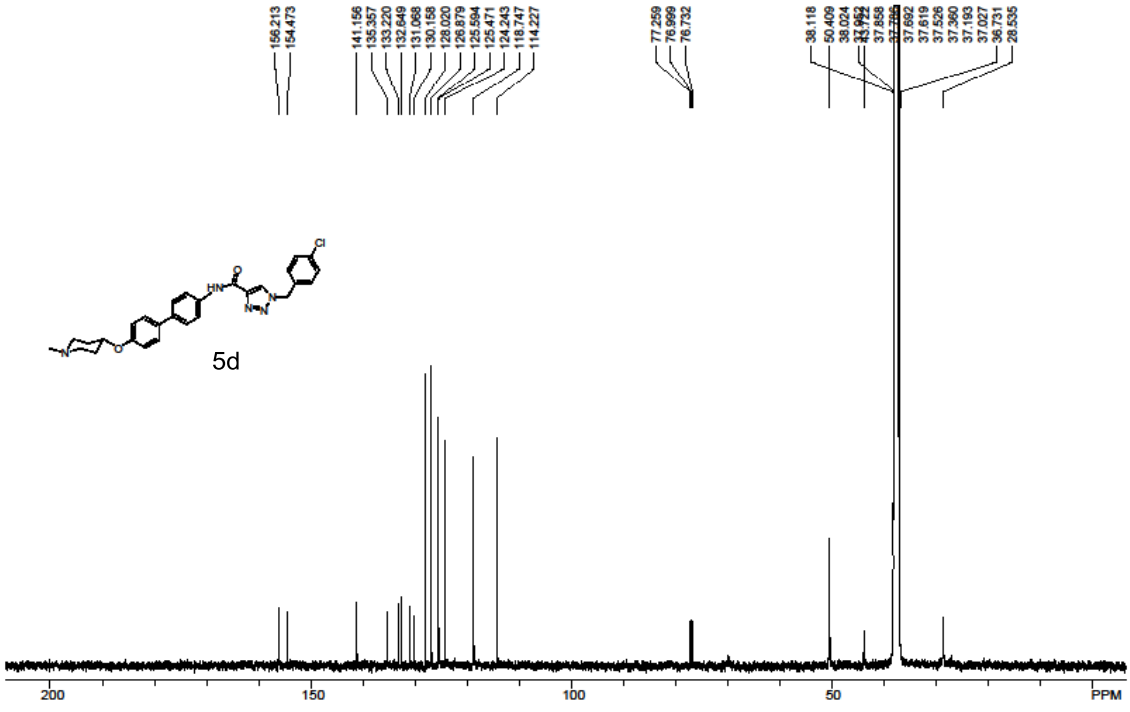
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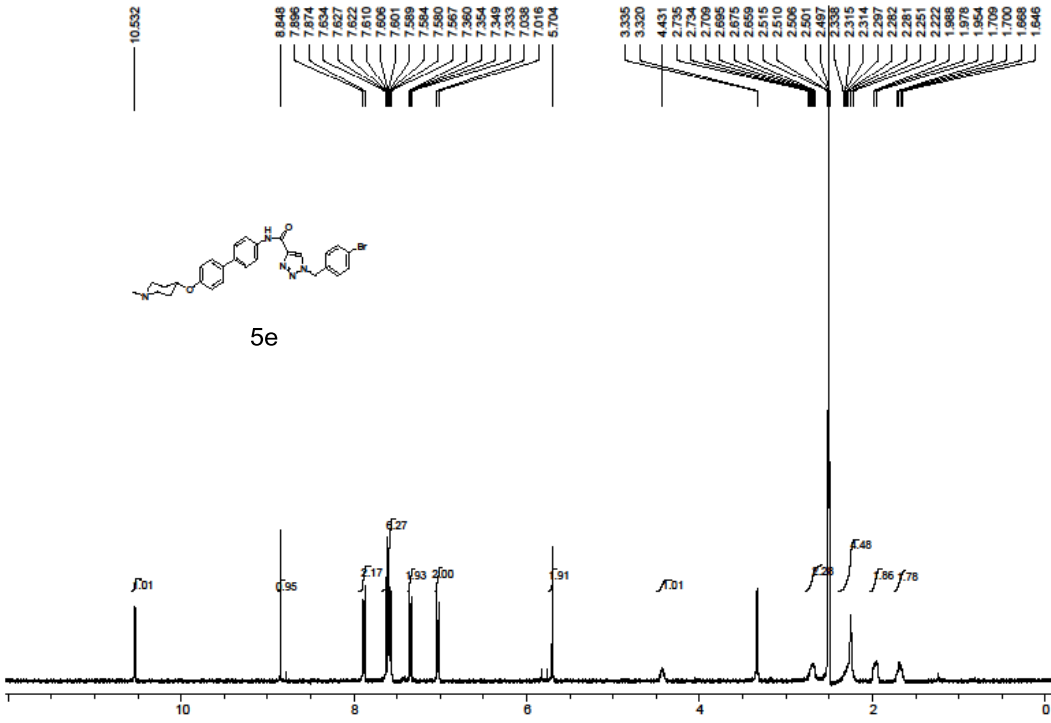
5d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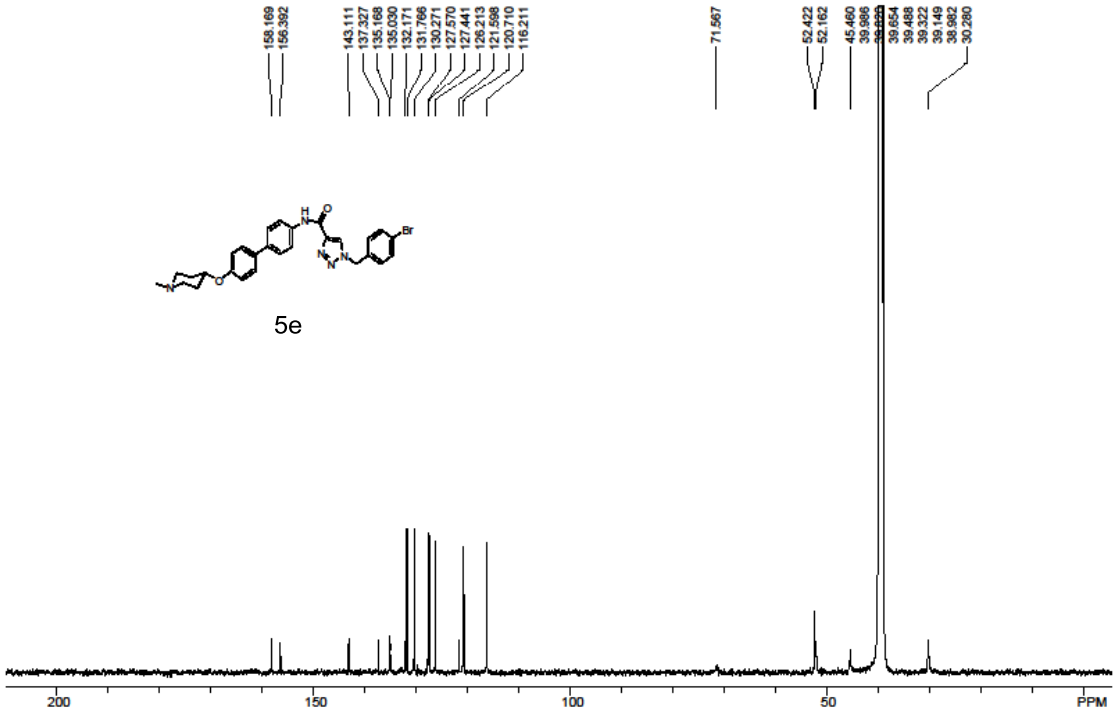
5e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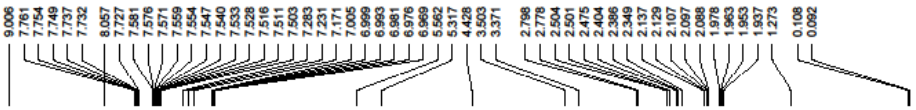
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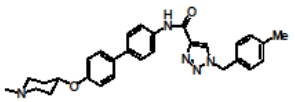
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N
N
Me
O
N

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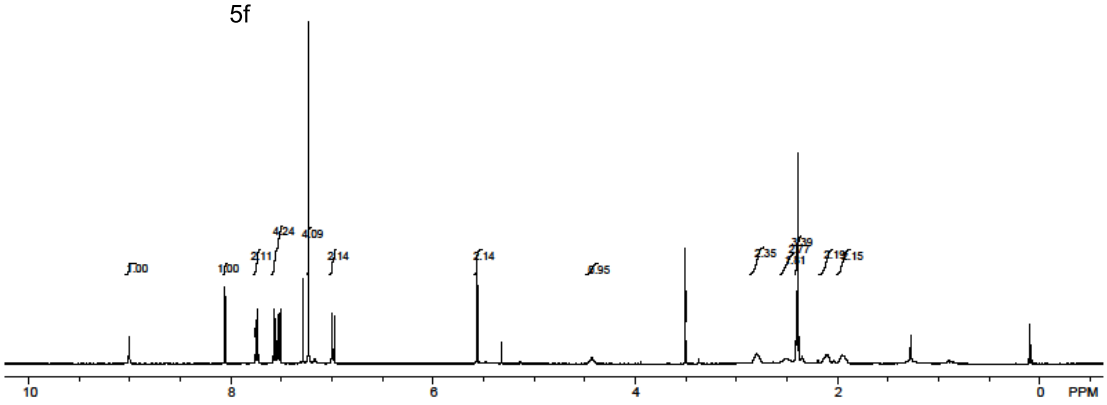
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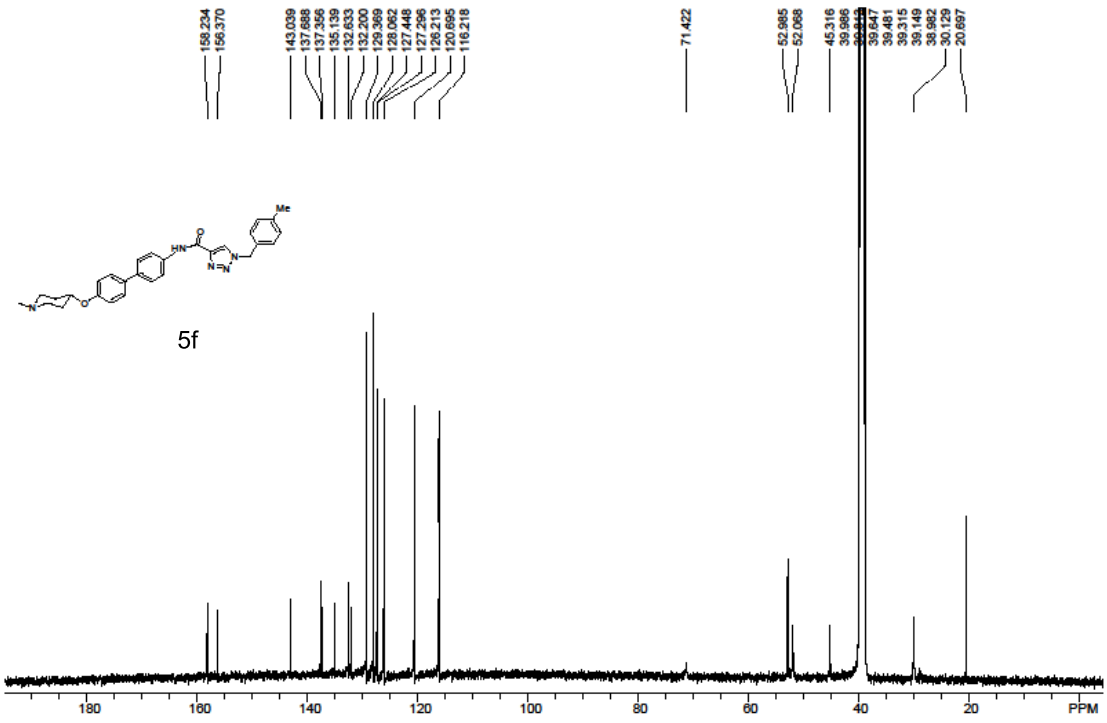
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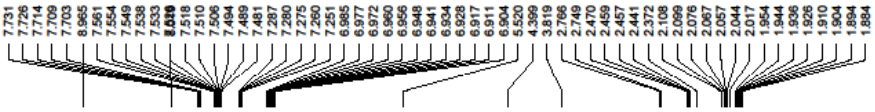
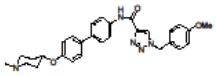
5f





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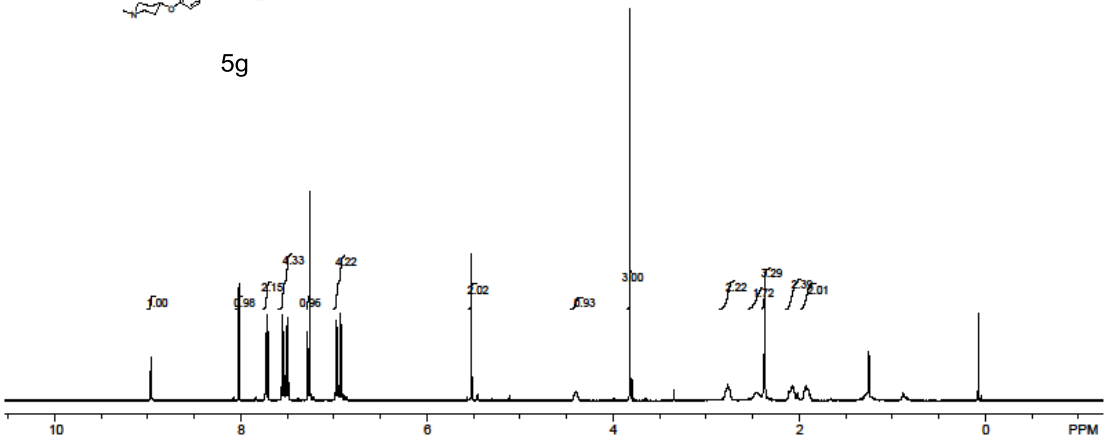
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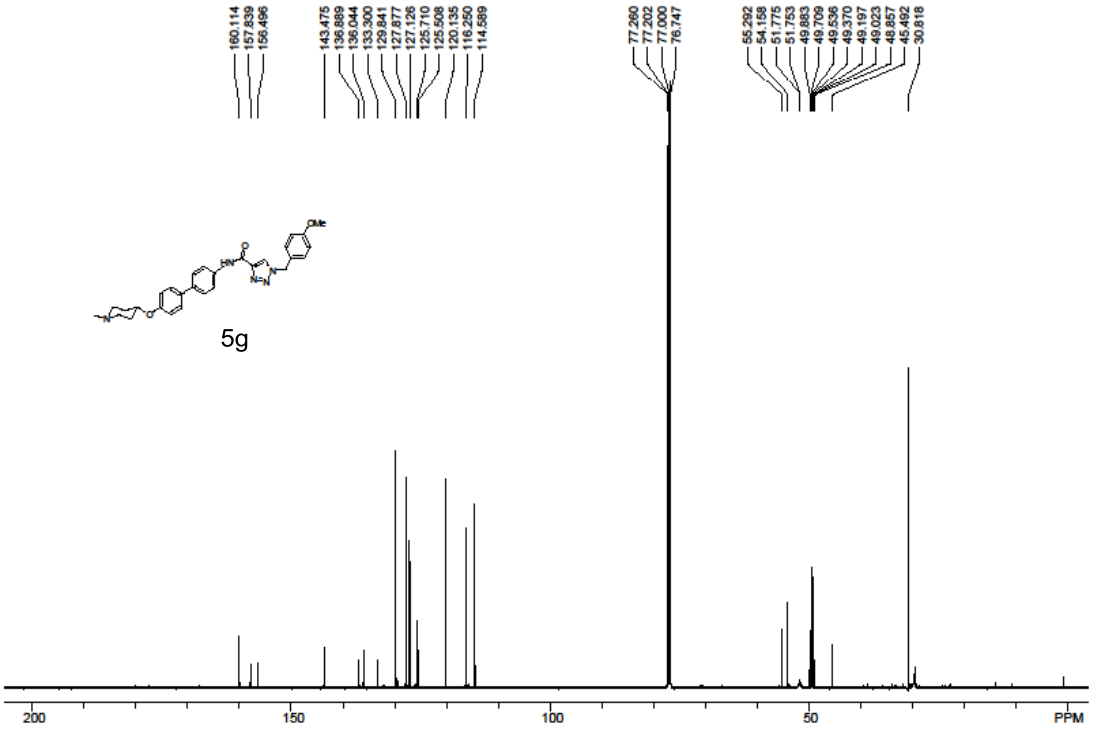
PPM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51.775
51.753
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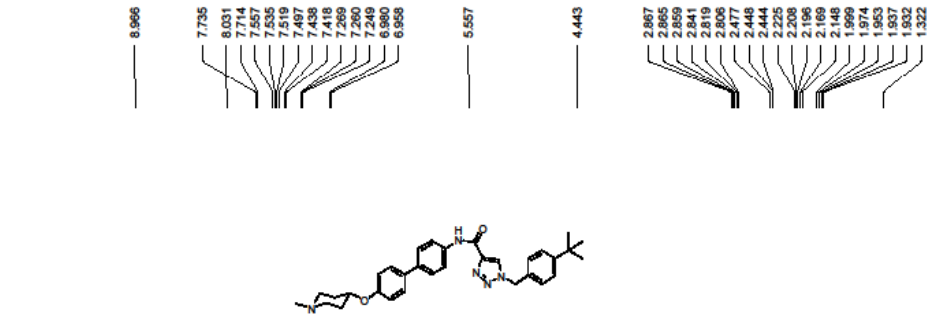
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7.249
6.980
6.958
5.557
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2.865
2.859
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2.819
2.806
2.477
2.448
2.444
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1.953
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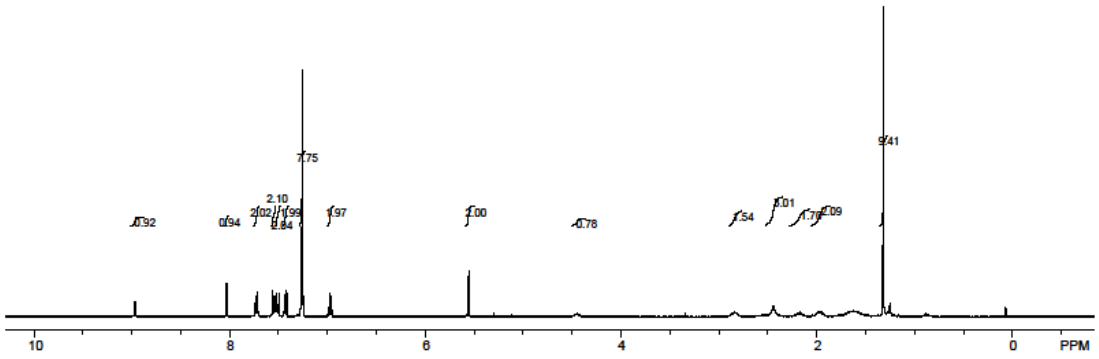
1.932
1.322

5h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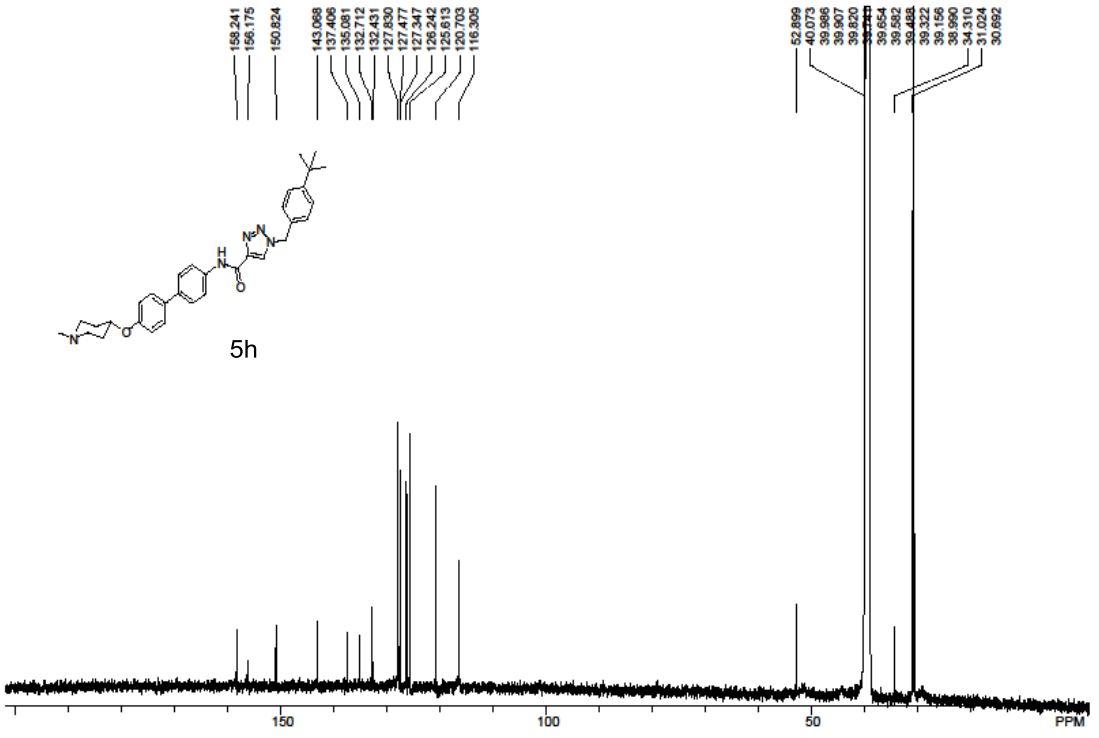
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125.613
120.703
116.305
52.899
40.073
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39.820
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38.990
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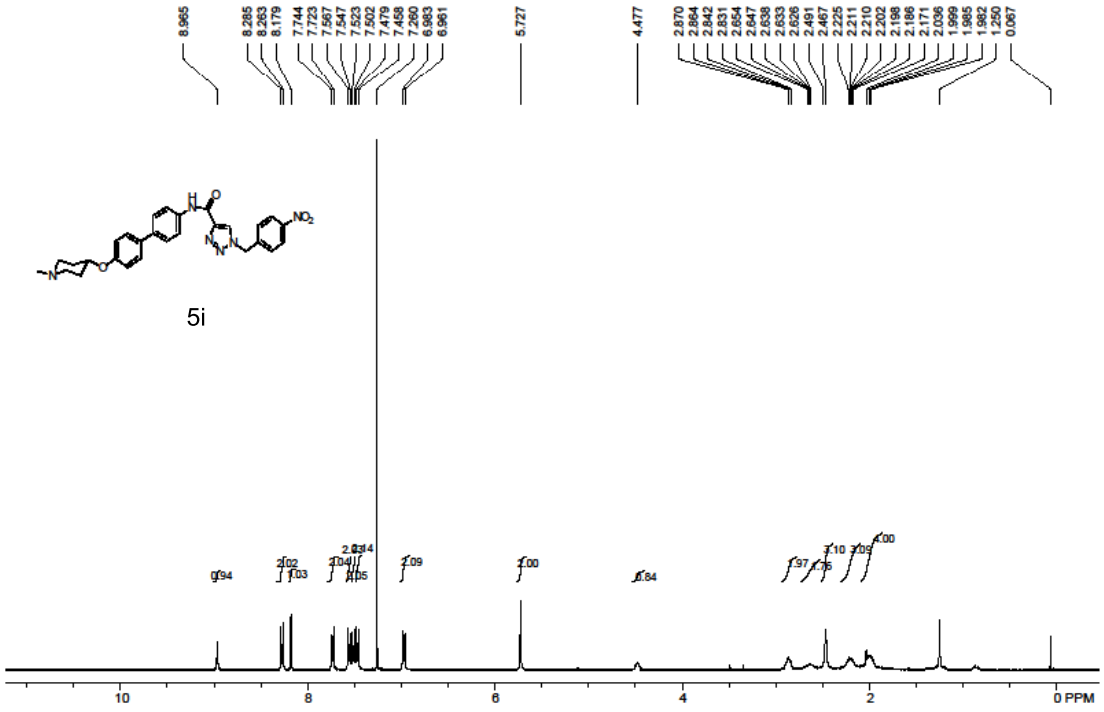
5h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7.260
6.983
6.961
5.727
4.477
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2.842
2.831
2.654
2.647
2.638
2.633
2.626
2.491
2.467
2.225
2.211
2.210
2.202
2.198
2.186
2.171
2.036
1.999
1.985
1.982
1.250
0.067
5i
0.94
2.02
2.03
2.04
2.05
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1.97
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2.09
4.00
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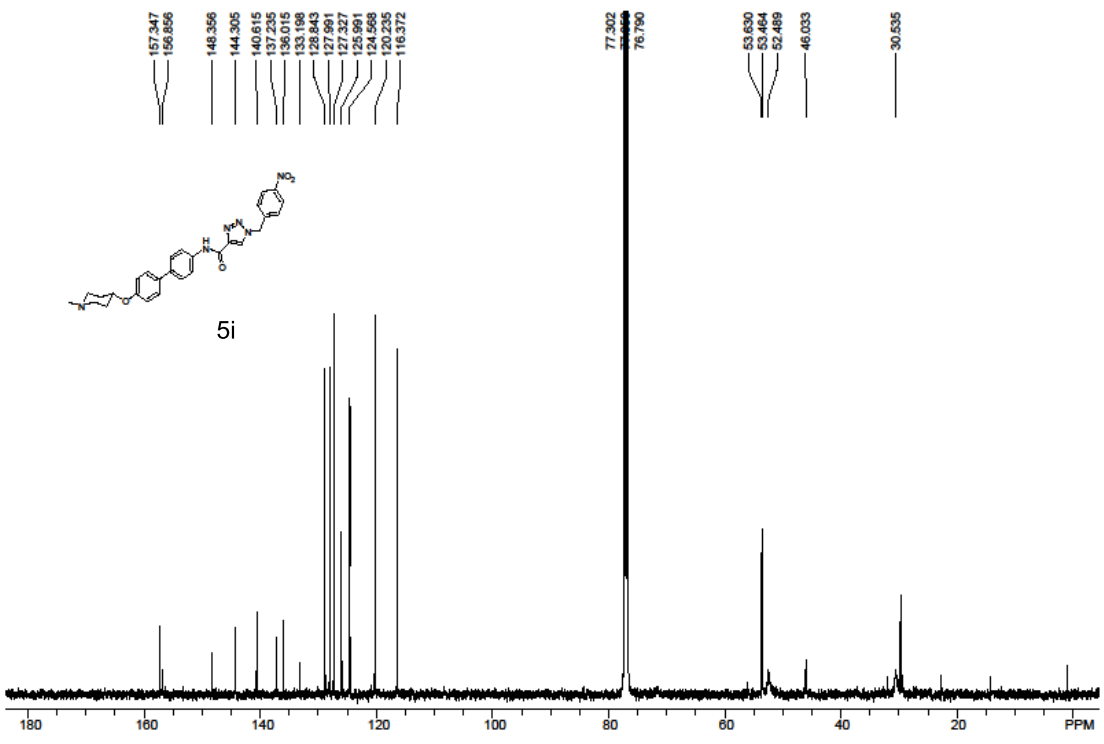
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133.198
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127.327
125.991
124.568
120.235
116.372
77.302
76.790
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46.033
30.535
5i
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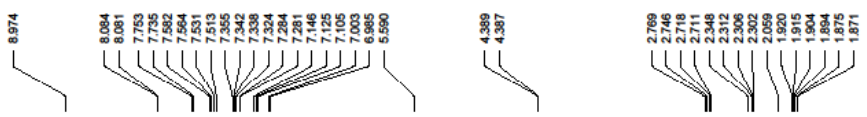
160
140
120
100
80
60
40
20
PPM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7.531
7.513
7.355
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7.338
7.324
7.284
7.281
7.146
7.125
7.105
7.003
6.985
5.590
4.389
4.387
2.769
2.746
2.716
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2.306
2.302
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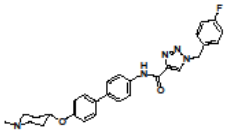
1.915
1.904
1.894
1.875
1.871



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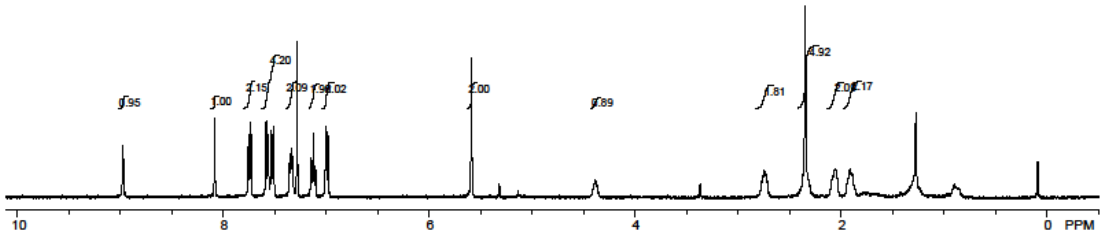
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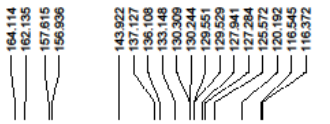
0.81
4.92
1.08
2.17
10
8
6
4
2
0
PPM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162.135
157.615
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133.148
130.309
130.244
129.551
129.529
127.941
127.284
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77.042
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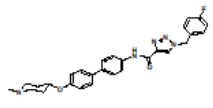
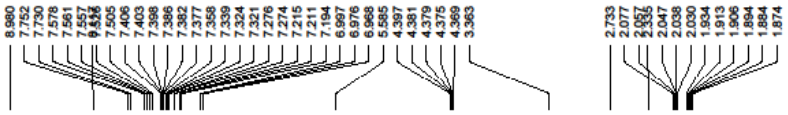
29.726



5j

Hexanes
200
150
100
50
PPM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7.382
7.377
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7.339
7.324
7.321
7.276
7.274
7.215
7.211
7.194
6.997
6.976
6.968
5.585
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4.381
4.379
4.375
4.369
3.363
2.733
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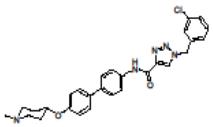
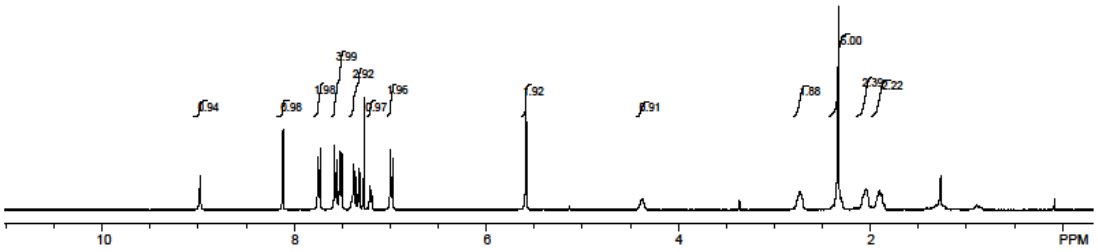
1.884
1.874



5k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1.98
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0.92
0.91
0.88
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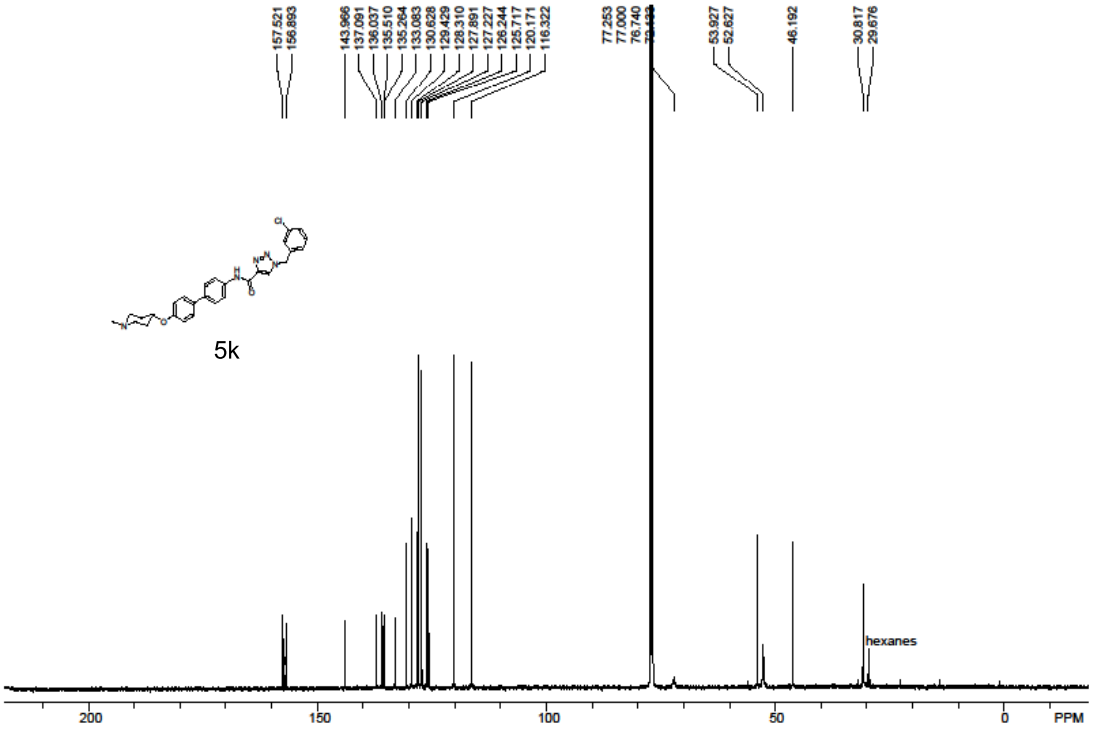
2.22
10
8
6
4
2
PPM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127.891
127.227
126.244
125.717
120.171
116.322
77.253
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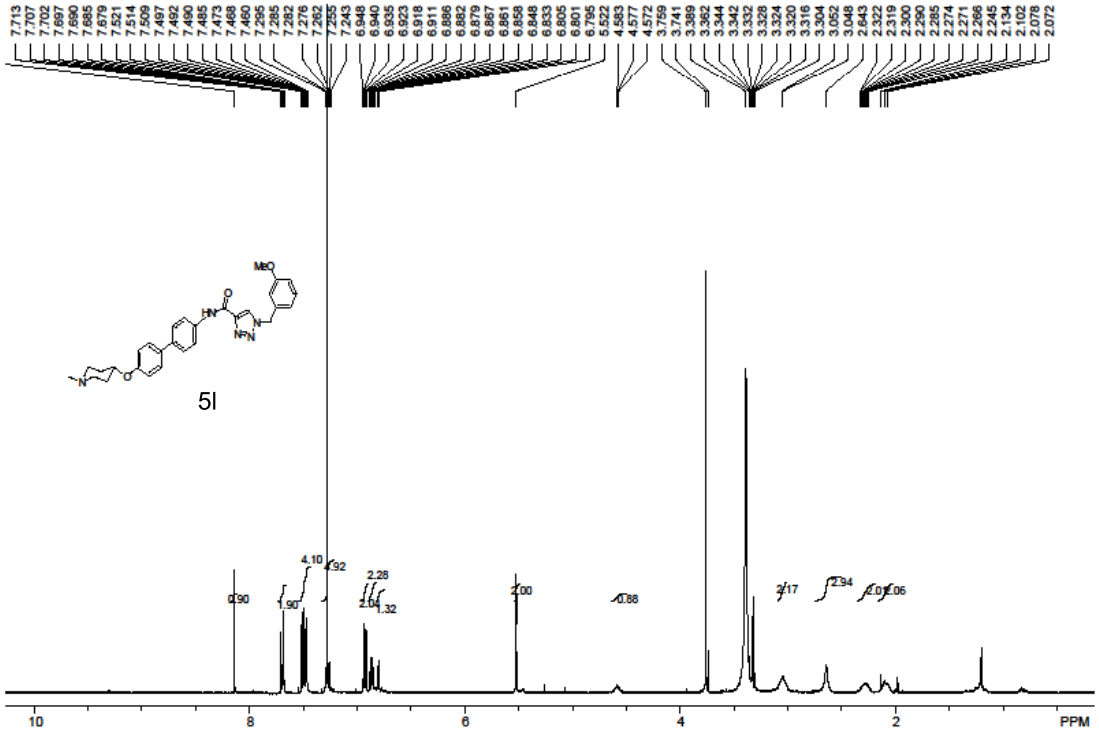
52.627
46.192
30.817
29.676
hexanes
200
150
100
50
0
PPM

5k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7.679
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7.509
7.497
7.492
7.490
7.485
7.473
7.468
7.460
7.295
7.285
7.282
7.276
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7.255
7.243
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6.840
6.835
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6.911
6.886
6.882
6.879
6.867
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4.572
3.759
3.741
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3.344
3.342
3.332
3.328
3.324
3.320
3.316
3.304
3.052
3.048
2.643
2.322
2.319
2.300
2.290
2.285
2.274
2.271
2.266
2.245
2.134
2.102
2.078
2.072
MeO
HN
O
N
NH
N
N
O
5l
0.90
1.90
4.10
4.32
2.28
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2.00
0.88
2.17
2.94
2.01
2.06
10
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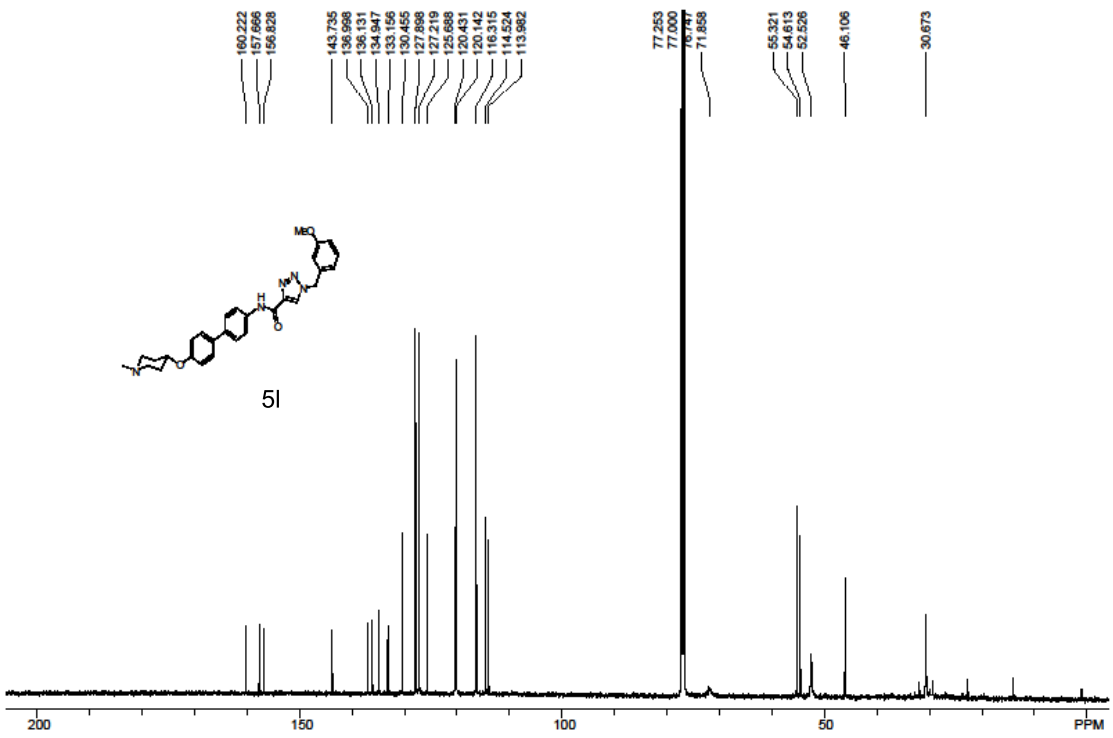
6
4
2
PPM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76.747
71.858
55.321
54.613
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MeO
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N
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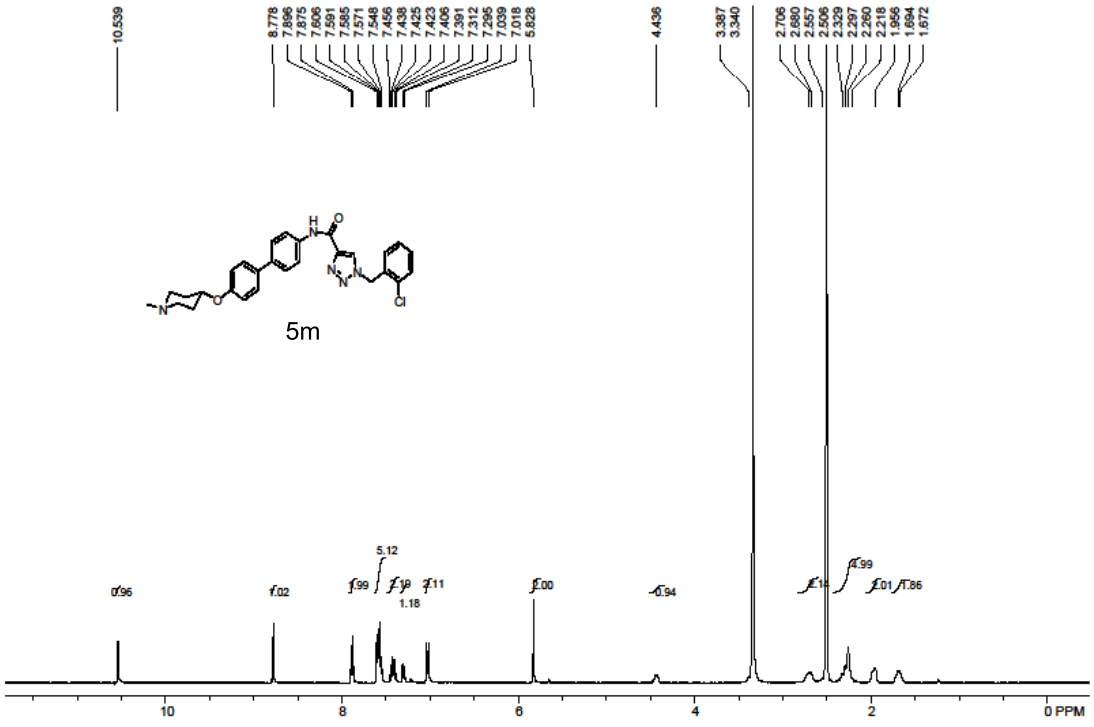
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7.423
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7.018
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3.340
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2.506
2.329
2.297
2.260
2.218
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1.694
1.672
5m
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1.02
0.99
5.12
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0.94
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4
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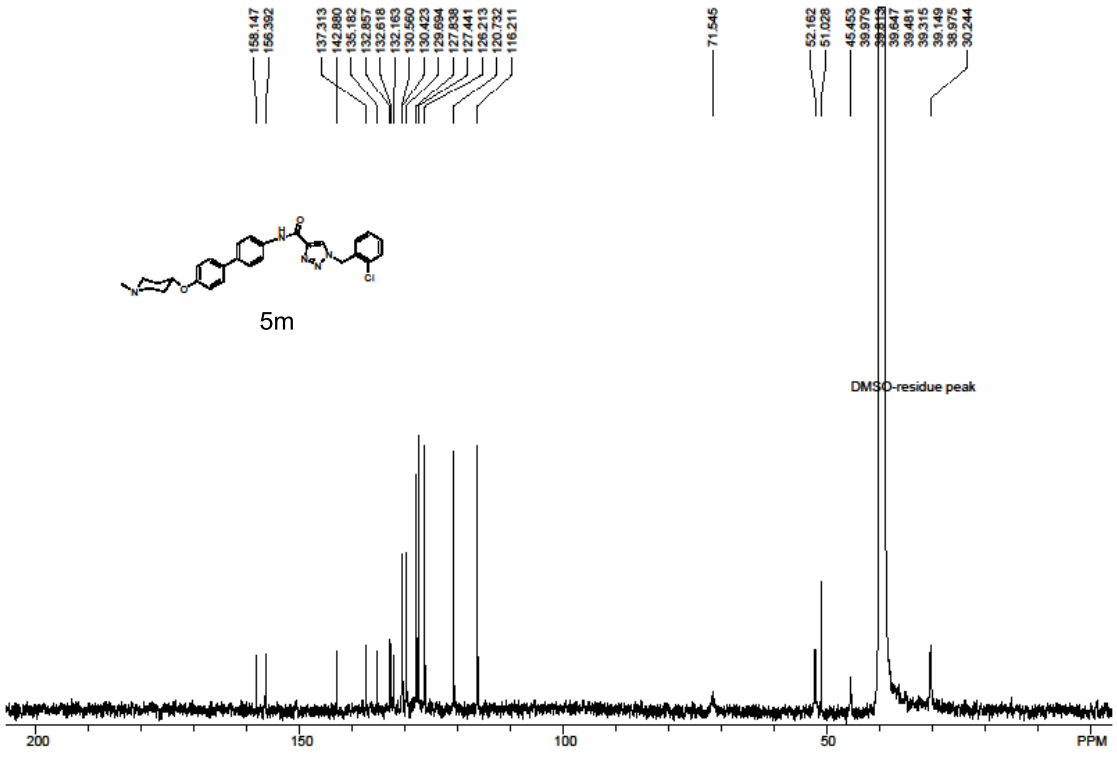
0 PPM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132.163
130.560
130.423
129.694
127.838
127.441
126.213
120.732
116.211
71.545
52.162
51.028
45.453
39.979
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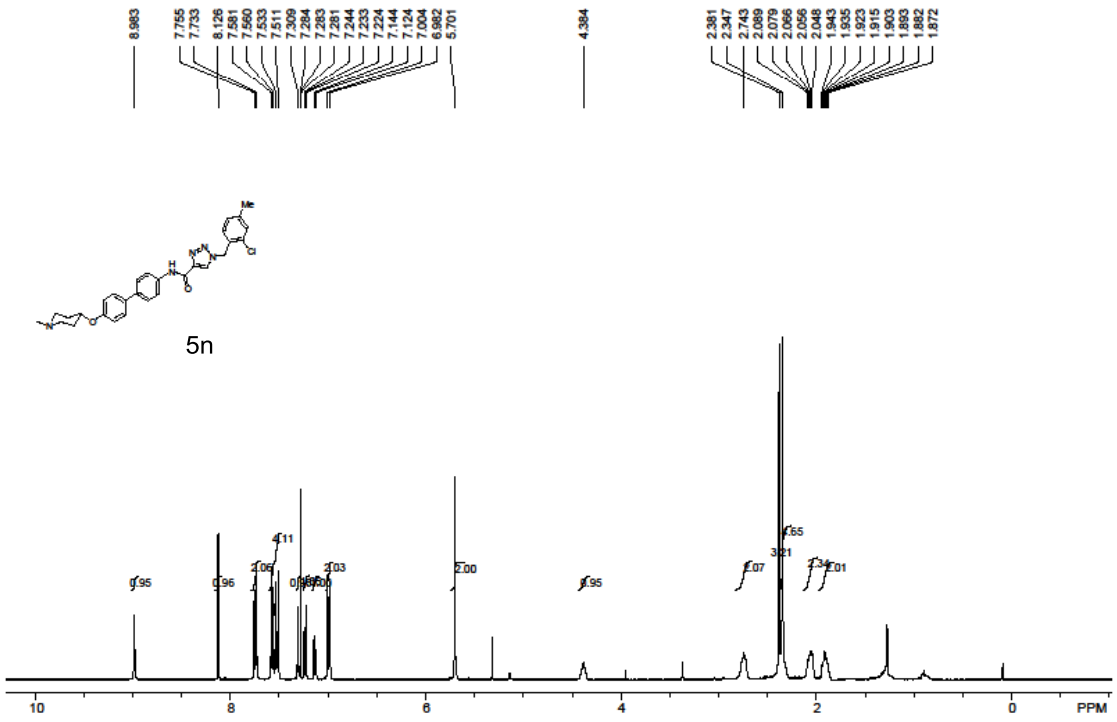
39.315
39.149
38.975
30.244
5m
DMSO-residue peak
200
150
100
50
PPM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7.284
7.283
7.281
7.244
7.233
7.224
7.144
7.124
7.004
6.982
5.701
4.384
2.381
2.347
2.743
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2.079
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2.056
2.048
1.943
1.935
1.923
1.915
1.903
1.893
1.882
1.872
5n
0.95
0.96
2.06
4.11
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10
8
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4
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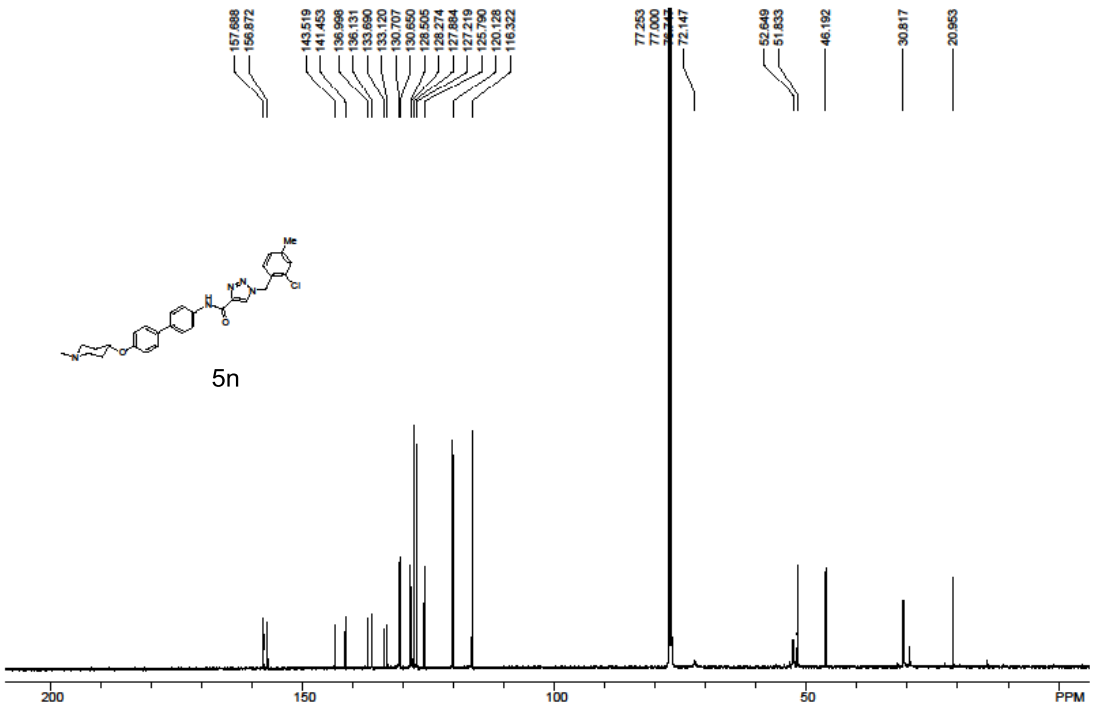
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125.790
120.128
116.322
77.253
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30.817
20.953
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100
50
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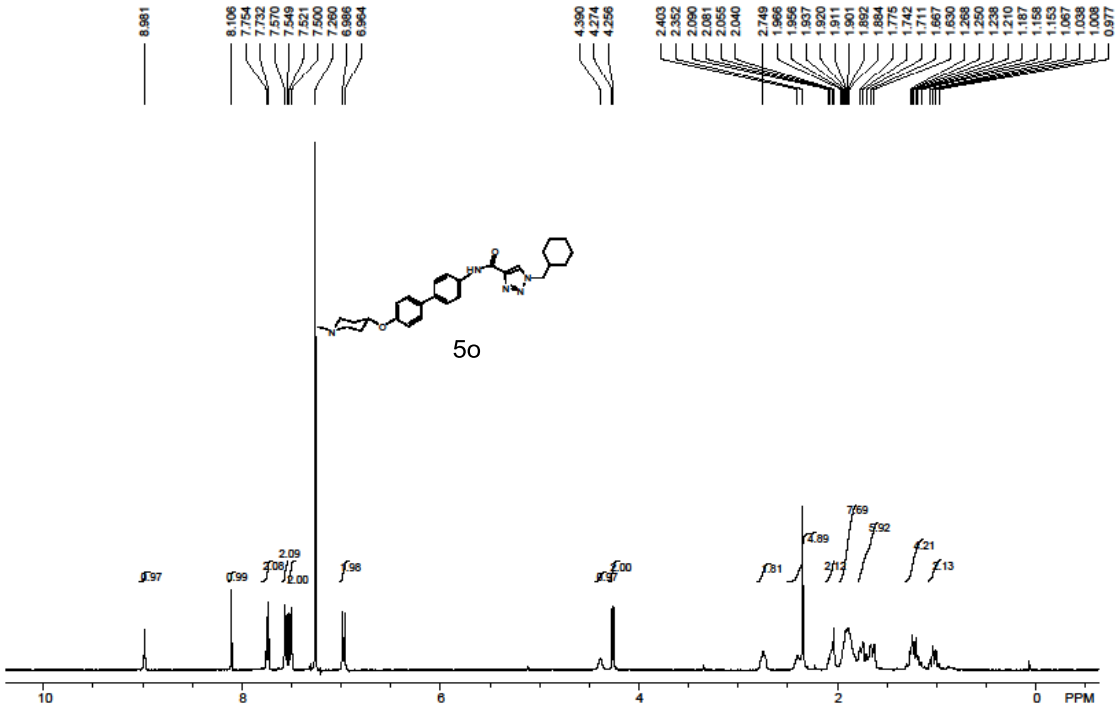
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4.256
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2.352
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1.937
1.920
1.911
1.901
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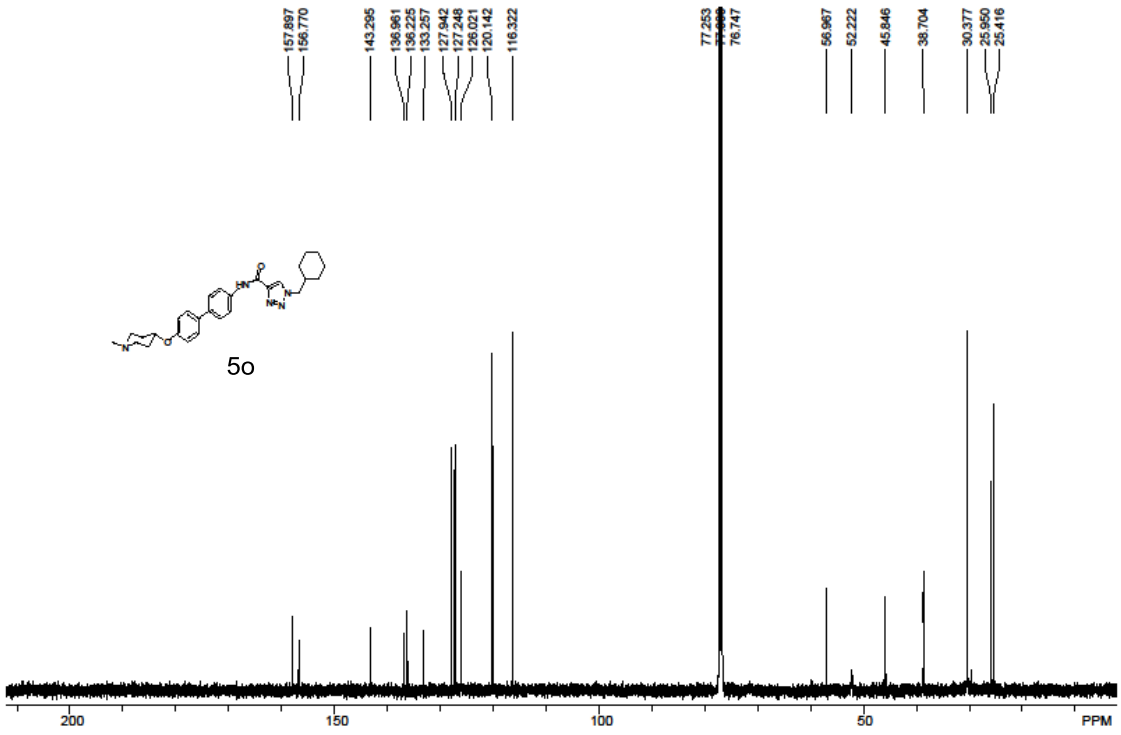
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56.967
52.222
45.846
38.704
30.377
25.950
25.416
5o
200
150
100
50
PPM