Synthesis, biological evaluation and molecular modeling of a novel series of fused 1,2,3-triazoles as potential anti-coronavirus agents

SUPPORTING INFORMATION

1. General experimental methods

NMR spectra were acquired at room temperature on commercial instruments (Bruker Avance 300 MHz, Bruker AMX 400 MHz or Bruker Avance II+ 600 MHz) and chemical shifts (δ) are reported in parts per million (ppm) referenced to tetramethylsilane (0.00 ppm for ^{1}H), or the internal (NMR) solvent signal (77.16 ppm for ^{13}C). High resolution mass spectra were acquired on a quadrupole orthogonal acceleration time-of-flight mass spectrometer (Synapt G2 HDMS, Waters, Milford, MA). For column chromatography 70-230 mesh silica 60 (E. M. Merck) was used as the stationary phase. Chemicals received from commercial sources were used without further purification. Reaction solvents (toluene) were used as received from commercial sources.

1.1. General procedure for the preparation of substituted 1,2,3-triazoles

To an oven-dried screw-capped reaction tube equipped with a magnetic stirring bar the ketone (1 eq), amine (2.8 eq), 4-nitrophenyl azide (2 eq), acetic acid (10 mol%) and 4 Å molecular sieves (50 mg) were added. The reaction mixture was dissolved in toluene (0.3M) and stirred at 100 °C for 18 hours. The crude reaction mixture was then directly purified by column chromatography (silica gel) at first with dichloromethane (DCM) as eluent to remove all 4-nitroaniline formed during the reaction followed by using a mixture of heptane and ethyl acetate as eluent to afford the corresponding 1,2,3-triazoles as yellow oil.

Ethyl-1,7-dibenzyl-5-phenyl-4,5,6,7-tetrahydro-1*H*-[1,2,3]triazolo[4,5-*c*]pyridine-7-carboxylate (14a): Yellow oil (80%). ^{1}H NMR (300MHz, $CDCl_3$): δ 7.35-7.25 (m, 8H), 7.09-7.00 (m, 6H), 6.93 (t, *J* = 7.3 Hz, 1H), 5.14 (d, *J* = 16.1 Hz, 1H), 4.73 (d, *J* = 16.1 Hz, 1H),4.52 (d, *J* = 14.2 Hz, 1H), 4.40 (d, *J* = 14.2 Hz, 1H), 4.05 (m, 1H), 3.78 (d, *J* = 12.9 Hz, 1H), 3.65 (m, 2H), 3.37 (q, *J* = 13.4 Hz, 2H), 1.04 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (75MHz, $CDCl_3$): δ 171.30, 149.86, 142.41, 135.86, 135.50, 132.04, 130.38, 129.34, 128.63, 128.59, 127.81, 127.51, 127.02, 120.21, 116.00, 61.92, 58.37, 52.08, 50.64, 45.61, 41.39, 13.87. HRMS (ES+): m/z calcd for $C_{28}H_{28}N_4O_2$ $[M+H]^+$: 453.2284, found 453.2284.

Ethyl-7-benzyl-5-phenyl-1-(3,4,5-trimethoxybenzyl)-4,5,6,7-tetrahydro-1*H*-[1,2,3]triazolo[4,5-*c*]pyridine-7-carboxylate (14b): Yellow oil (85%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 – 7.25(m, 6H), 7.02 – 6.99 (m, 3H), 6.91 (t, J = 7.3 Hz, 1H), 6.37 (s, 2H), 5.03 (d, *J* = 15.7 Hz, 1H), 4.70 (d, *J* = 15.7 Hz, 1H), 4.46 (d, *J* = 14.2 Hz, 1H), 4.37

(d, *J* = 14.1 Hz, 1H), 4.10 (dq, *J* = 10.7, 7.1 Hz, 1H), 3.81 – 3.75 (m, 11H), 3.58 (d, *J* = 12.9 Hz, 1H), 3.43 (d, *J* = 13.5 Hz, 1H), 3.33 (d, *J* = 13.5 Hz, 1H), 1.07 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (75MHz, $CDCl_3$): δ 171.43, 153.35, 149.80, 142.47, 137.68, 135.79, 132.01, 130.84, 130.31, 129.33, 128.64, 127.54, 120.25, 116.01, 104.74, 62.03, 60.80, 58.30, 56.24, 56.19, 52.40, 50.67, 45.61, 41.33, 13.94. HRMS (ES+) m/z calcd for $C_{31}H_{34}N_4O_5$ $[M+H]^+$: 543.2601, found 543.2600.

Ethyl-7-benzyl-1-(4-methoxybenzyl)-5-phenyl-4,5,6,7-tetrahydro-1*H*-[1,2,3]triazolo[4,5-*c*]pyridine-7-carboxylate (14c): Yellow oil (65%). ^{1}H NMR (300MHz, $CDCl_3$): δ 7.33-7.23 (m, 5H), 7.05-6.97 (m, 6H), 6.90 (t, *J* = 7.2Hz, 1H), 6.84-6.78 (m, 2H), 5.03 (d, *J* = 15.6 Hz, 1H), 4.75 (d, *J* = 15.6 Hz, 1H), 4.46 (d, *J* = 14.2 Hz, 1H), 4.37 (d, *J* = 14.2 Hz, 1H), 4.09 (dq, *J* = 10.8 Hz, 7.1 Hz, 1H), 3.84-3.73 (m, 5H), 3.56 (d, *J* = 12.9 Hz, 1H), 3.41 (d, *J* = 13.4 Hz, 1H), 3.27 (d, *J* = 13.4 Hz, 1H), 1.08 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (75MHz, $CDCl_3$): δ 171.35, 159.18, 149.82, 142.36, 135.77, 131.84, 130.32, 129.30, 128.61, 128.56, 127.47, 127.42, 120.15, 115.95, 113.94, 62.00, 58.32, 55.27, 51.76, 50.58, 45.56, 41.36, 13.94. HRMS (ES+) m/z calcd for $C_{29}H_{30}N_4O_3$ [M+H]+ : 483.2390, found 483.2386.

Ethyl-7-benzyl-1-(4-fluorobenzyl)-5-phenyl-4,5,6,7-tetrahydro-1*H*-[1,2,3]triazolo[4,5-*c*]pyridine-7-carboxylate (14d): Yellow oil (80%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.33-7.25 (m, 5H), 7.08-6.91 (m, 10H), 4.95 (d, *J* = 15.8 Hz, 1H), 4.63 (d, *J* = 15.8 Hz, 1H), 4.50 (d, *J* = 14.2 Hz, 1H), 4.36 (d, *J* = 14.2 Hz, 1H) , 4.09 (dq, *J* = 10.8Hz, 7.1Hz, 1H), 3.81-3.69 (m, 2H), 3.63 (d, *J* = 12.9 Hz, 1H), 3.39 (q, *J* = 13.2 Hz, 2H), 1.07 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.29, 163.93, 160.66, 149.79, 142.39, 135.85, 131.99, 131.22, 131.17, 130.33, 129.34, 129.08, 128.97, 128.69, 127.56, 120.27, 116.00, 115.60, 115.32, 62.02, 58.41, 51.38, 50.83, 45.57, 41.49, 13.93. HRMS (ES+) m/z calcd for $C_{28}H_{27}N_4O_2F_1$ $[M+H]^+$: 471.2190, found 471.2190.

Ethyl-7-benzyl-1-(3-fluorobenzyl)-5-phenyl-4,5,6,7-tetrahydro-1*H*-[1,2,3]triazolo[4,5-*c*]pyridine-7-carboxylate (14e): Yellow oil (58%) ^{1}H NMR (600MHz, $CDCl_3$): δ 7.34 - 7.21 (m, 6H), 7.04-6.96 (m, 4H), 6.95 - 6.88 (m, 2H), 6.82 (d, *J* = 7.9 Hz, 1H), 6.77 - 6.72 (m, 1H), 4.99 (d, *J* = 16.2 Hz, 1H), 4.59 (d, *J* = 16.2 Hz, 1H), 4.52 (d, *J* = 14.2 Hz, 1H), 4.37 (d, *J* = 14.2 Hz, 1H), 4.07 (dq, *J* = 10.8, 7.2 Hz, 1H), 3.75 - 3.63 (m, 3H), 3.37 (s, 2H), 1.05 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 171.23, 163.68, 162.04, 149.81, 142.42, 138.06, 138.01, 135.89, 132.09, 130.35, 130.12, 130.07, 129.36, 128.71, 127.59, 122.67, 122.65, 120.30, 116.03, 114.83, 114.69, 114.29, 114.14, 62.01, 58.45, 51.40, 51.39, 50.88, 45.60, 41.53, 13.88. HRMS (ES+) m/z calcd for $C_{28}H_{27}N_4O_2F_1$ $[M+H]^+$: 471.2190, found 471.2187.

Ethyl-7-benzyl-1-(3-chlorobenzyl)-5-phenyl-4,5,6,7-tetrahydro-1*H*-[1,2,3]triazolo[4,5-*c*]pyridine-7-carboxylate (14f): Yellow oil (80%) ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.34 - 7.26 (m, 5zH), 7.22 - 7.18 (m, 2H), 7.05 - 6.98 (m, 5H), 6.95 - 6.90 (m, 2H), 4.91 (d, J = 16.2 Hz, 1H), 4.57 - 4.47 (m, 2H), 4.37 (d, J = 14.2 Hz, 1H), 4.08 (dq, J = 10.8, 7.1 Hz, 1H), 3.74 - 3.64 (m, 3H), 3.39 (q, J = 13.2 Hz, 2H), 1.05 (t, J = 7.1 Hz,

1H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 171.24, 149.81, 142.40, 137.48, 135.97, 134.54, 132.09, 130.39, 129.80, 129.38, 128.74, 128.01, 127.61, 127.26, 125.31, 120.32, 116.03, 62.06, 58.51, 51.27, 50.95, 45.61, 41.53, 13.90. HRMS (ES+) m/z calcd for $C_{28}H_{27}N_4O_2Cl_1$ $[M+H]^+$: 487.1895, found 487.1893.

Ethyl-7-benzyl-1-(4-chlorobenzyl)-5-phenyl-4,5,6,7-tetrahydro-1*H*-[1,2,3]triazolo[4,5-*c*]pyridine-7-carboxylate (14g): Yellow oil (67%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36 - 7.22 (m, 8H), 7.05 - 6.97 (m, 6H), 6.92 (t, *J* = 7.2 Hz, 1H), 4.94 (d, *J* = 16.1 Hz, 1H), 4.60 (d, *J* = 16.1 Hz, 1H), 4.51 (d, *J* = 14.2 Hz, 1H), 4.36 (d, *J* = 14.2 Hz, 1H), 4.08 (dq, *J* = 10.8, 7.1 Hz, 1H), 3.78 - 3.68 (m, 2H), 3.64 (d, *J* = 12.9 Hz, 1H), 3.40 - 3.33 (m, 2H), 1.07 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.27, 149.81, 142.43, 135.87, 133.99, 133.75, 132.03, 130.35, 129.36, 128.71, 128.63, 128.60, 127.60, 120.31, 116.03, 62.05, 58.44, 51.38, 50.89, 45.61, 41.56, 13.93. HRMS (ES+) m/z calcd for $C_{28}H_{27}N_4O_2Cl_1$ $[M+H]^+$: 487.1895, found 487.1888.

Ethyl-7-benzyl-1-(2-chlorobenzyl)-5-phenyl-4,5,6,7-tetrahydro-1*H*-[1,2,3]triazolo[4,5-*c*]pyridine-7-carboxylate (14h): Yellow oil (48%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.35 – 7.25 (m, 8H), 7.20 – 7.15 (m, 2H), 7.07 – 7.03 (m, 2H), 7.00 – 6.97 (m, 2H), 6.92 (d, *J* = 7.3 Hz, 1H), 6.74 – 6.71 (m, 1H), 5.30 (d, *J* = 17.2 Hz, 1H), 4.80 (d, *J* = 17.2 Hz, 1H), 4.52 (d, *J* = 14.2 Hz, 1H), 4.41 (d, *J* = 14.2 Hz, 1H), 3.98 (dq, *J* = 10.8, 7.1 Hz, 1H), 3.84 – 3.63 (m, 2H), 3.61 (d, *J* = 12.9 Hz, 1H), 3.36 (d, *J* = 13.3 Hz, 1H), 3.27 (d, *J* = 13.3 Hz, 1H), 1.03 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 170.92, 149.83, 142.60, 135.53, 133.68, 130.20, 129.35, 129.22, 128.84, 128.76, 128.10, 127.67, 127.03, 120.29, 116.04, 61.99, 58.48, 50.83, 49.74, 45.53, 41.48, 13.84. HRMS (ES+) m/z calcd for $C_{28}H_{27}N_4O_2Cl_1$ $[M+H]^+$: 487.1895, found 487.1889.

Ethyl-7-benzyl-1-(3,4-dichlorobenzyl)-5-phenyl-4,5,6,7-tetrahydro-1*H*-[1,2,3]triazolo[4,5-*c*]pyridine-7-carboxylate (14i): Yellow oil (30%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37 - 7.24 (m, 7H), 7.13 (d, *J* = 2.1 Hz, 1H), 7.06 – 6.88 (m, 6H), 4.76 (d, *J* = 16.1 Hz, 1H), 4.55 (d, *J* = 14.2 Hz, 1H), 4.44 (d, *J* = 16.1 Hz, 1H), 4.36 (d, *J* = 14.2 Hz, 1H), 4.14 (dq, *J* = 10.8, 7.1 Hz, 1H), 3.80 (m, 2H), 3.67 (d, *J* = 12.9 Hz, 1H), 3.46 (d, *J* = 13.3 Hz, 1H), 3.37 (d, *J* = 13.3 Hz, 1H), 1.11 (t, *J* = 7.1Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.24, 149.77, 142.42, 135.98, 135.63, 132.70, 132.08, 132.01, 130.43, 130.34, 129.40, 129.33, 128.82, 127.68, 126.75, 120.39, 116.06, 62.17, 58.54, 51.18, 50.79, 45.61, 41.68, 13.96. HRMS (ES+) m/z calcd for $C_{28}H_{26}N_4O_2Cl_2$ $[M+H]^+$: 521.1505, found 521.1483.

Ethyl-7-benzyl-1-(2-chloro-6-fluorobenzyl)-5-phenyl-4,5,6,7-tetrahydro-1*H*-[1,2,3]triazolo[4,5-*c*]pyridine-7-carboxylate (14j): Yellow oil (73%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.35 – 7.21 (m, 8H), 7.11 – 6.98 (m, 5H), 6.94 - 6.85 (m, 1H), 5.46 (dd, *J* = 14.0, 1.6 Hz, 1H), 4.79 (dd, *J* = 14.0, 1.6 Hz, 1H), 4.37 (s, 2H), 4.29 (dq, *J* = 11.5, 7.2 Hz, 2H), 3.89 (d, *J* = 12.9 Hz, 1H), 3.63 (d, *J* = 13.5 Hz, 1H), 3.55 – 3.46 (m, 2H), 1.30 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.49, 163.12, 160.62, 149.89, 142.94,

136.46, 136.41, 135.38, 131.59, 130.71, 130.62, 130.16, 129.27, 128.81, 127.60, 125.52, 125.49, 120.14, 116.04, 114.40, 114.18, 62.32, 58.25, 50.63, 45.61, 45.49, 45.46, 41.01, 14.15. HRMS (ES+) m/z calcd for $C_{28}H_{26}N_4O_2Cl_1F_1$ $[M+H]^+$: 505.1800, found 505.1784.

Ethyl-7-benzyl-1-(furan-2-ylmethyl)-5-phenyl-4,5,6,7-tetrahydro-1*H*-[1,2,3]triazolo[4,5-*c*]pyridine-7-carboxylate (14k): Yellow oil (55%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.33-7.25 (m, 6H), 7.0j-6.97 (m, 4H), 6.90 (t, *J* = 7.3 Hz, 1H), 6.33-6.30 (m, 2H), 5.00 (d, *J* = 16 Hz, 1H), 4.86 (d, *J* = 16 Hz, 1H), 4.42 (d, *J* = 14.2 Hz, 1H), 4.34 (d, *J* = 14.2 Hz, 1H), 4.23 (dq, *J* = 10.8, 7.1 Hz, 1H), 4.09 (m, dq, *J* = 10.8, 7.1 Hz, 1H), 3.80 (d, *J* = 13 Hz, 1H), 3.58 (d, *J* = 13 Hz, 1H), 3.50 (d, *J* = 13.5 Hz, 1H), 3.41 (d, *J* = 13.5 Hz, 1H), 1.20 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.40, 149.81, 148.18, 142.60, 142.34, 135.65, 131.64, 130.21, 129.29, 128.69, 127.52, 120.21, 116.03, 110.73, 109.66, 62.23, 58.27, 50.67, 45.77, 45.52, 41.41, 13.96. HRMS (ES+): m/z calcd for $C_{26}H_{26}N_4O_3$ $[M+H]^+$: 443.2077, found 443.2080.

Ethyl-7-benzyl-1-(2-methoxyphenethyl)-5-phenyl-4,5,6,7-tetrahydro-1*H*-[1,2,3]triazolo[4,5-*c*]pyridine-7-carboxylate (14l): Yellow oil (56%). ^{1}H NMR (300MHz, $CDCl_3$): δ 7.31-7.23 (m, 5H), 7.22-7.19 (m, 3H), 7.09 (dd, *J* = 7.4, 1.7 Hz, 1H), 7.01-6.96 (m, 3H), 6.90-6.87 (m, 2H), 6.83 (d, *J* = 8.1 Hz, 1H), 4.39 (d, *J* = 14.2 Hz, 1H), 4.34 (d, *J* = 14.2 Hz, 1H), 4.27 -4.11 (m, 3H), 4.09-4.01 (m, 1H), 3.87-3.83 (m, 1H), 3.78 (s, 3H), 3.53 (d, *J* = 13.5 Hz, 1H), 3.45 (d, *J* = 13.5 Hz, 1H), 3.32-3.20 (m, 3H), 1.20 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (75MHz, $CDCl_3$): 171.54, 157.61, 149.90, 142.02, 135.53, 131.66, 130.63, 130.15, 129.26, 128.50, 128.24, 127.39, 125.77, 120.68, 120.09, 116.01, 110.21, 62.03, 58.40, 55.15, 50.30, 48.91, 45.53, 40.74, 31.56, 14.05. HRMS (ES+) m/z calcd for $C_{30}H_{32}N_4O_3$ [M+H]+ : 497.2547, found 497.2540.

Ethyl-7-benzyl-1-(4-methoxyphenethyl)-5-phenyl-4,5,6,7-tetrahydro-1*H*-[1,2,3]triazolo[4,5-*c*]pyridine-7-carboxylate (14m): Yellow oil (85%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32 - 7.29 (m, 2H), 7.23 - 7.20 (m, 3H), 7.05 - 6.99 (m, 4H), 6.96 - 6.94 (m, 2H), 6.92 - 6.89 (m, 1H), 6.83 - 6.79 (m, 2H), 4.47 (d, *J* = 14.2 Hz, 1H), 4.35 (d, *J* = 14.2 Hz, 1H), 4.27 (dq, *J* = 10.8, 7.2 Hz, 1H), 4.17 (dq, *J* = 10.8, 7.2 Hz, 1H), 3.78 (s, 3H), 3.77 - 3.63 (m, 4H), 3.40 (s, 2H), 3.18 (ddd, J = 13.7, 11.2, 6.2 Hz, 1H), 3.09 (ddd, J = 13.7, 11.2, 6.2 Hz, 1H), 1.25 (t, *J* = 7.1 Hz, 3H).^{13}C NMR (75 MHz, $CDCl_3$) δ 171.48, 158.37, 149.86, 141.95, 135.83, 131.50, 130.19, 129.72, 129.57, 129.34, 128.65, 127.50, 120.19, 115.99, 113.99, 62.18, 58.51, 55.25, 50.90, 50.63, 45.55, 41.23, 34.59, 14.17. HRMS (ES+) m/z calcd for $C_{30}H_{32}N_4O_3$ [M+H]+ : 497.2547, found 497.2538.

Ethyl-1-(2-(1H-indol-2-yl)ethyl)-7-benzyl-5-phenyl-4,5,6,7-tetrahydro-1*H*-[1,2,3]triazolo[4,5-*c*]pyridine-7-carboxylate (14n): Yellow oil (80%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.02 (s, 1H), 7.54 (d, *J* = 8 Hz, 1H), 7.38-7.26 (m, 3H), 7.22-7.1 (m, 4H), 7.14-7.09 (m, 1H), 7.03 (d, *J* = 8 Hz, 2H), 6.95-6.88 (m, 4H), 4.48 (d, *J* = 14.1 Hz, 1H), 4.36 (d, *J* = 14.1 Hz, 1H), 4.22 (dq, *J* = 10.8 Hz, 7.1 Hz, 1H), 4.10 (dq, *J* = 10.8 Hz, 7.1 Hz, 1H), 3.98-3.80 (m, 2H), 3.73 (d, *J* = 12.8 Hz, 1H), 3.62 (d, *J* = 12.8 Hz, 1H), 3.41-

3.34 (m, 4H), 1.20 (t, *J* = 7.1Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.52,149.90, 141.99, 136.15, 135.84, 131.60, 130.19, 129.33, 128.60, 127.44, 127.18, 122.24, 121.77, 120.19, 119.54, 118.74, 116.01, 112.28, 111.13, 62.18, 58.54, 50.87, 49.70, 45.58, 41.14, 25.53, 14.12. HRMS (ES+) m/z calcd for $C_{31}H_{31}N_5O_2$ [M+H]+: 506.2550, found 506.2543.

Ethyl-7-benzyl-1-(5-hydroxypentyl)-5-phenyl-4,5,6,7-tetrahydro-1*H*-[1,2,3]triazolo[4,5-*c*]pyridine-7-carboxylate (14o): Yellow oil (57%) ^{1}H NMR (400MHz, $CDCl_3$): δ 7.33-7.28 (m, 2H), 7.27-7.22 (m, 3H), 7.02 (d, J = 8.1 Hz, 2H), 6.99-6.95 (m, 2H), 6.91 (t, J = 7.2 Hz, 1H), 4.49 (d, J = 14.1 Hz, 1H), 4.35-4.16 (m, 3H), 3.73-3.66 (m, 2H), 3.62 (t, J = 6.4 Hz, 2H), 3.55 (d, J = 13.4 Hz, 1H), 3.51-3.30 (m, 3H), 1.98-1.86 (m, 1H), 1.84-1.75 (m, 1H), 1.57-1.48 (m, 2H), 1.32-1.23 (m, 5H). ^{13}C NMR (100MHz, $CDCl_3$): δ 171.49, 149.85, 141.82, 136.04, 131.34, 130.28, 129.35, 128.65, 127.42, 120.17, 115.94, 62.46, 62.15, 58.70, 51.04, 49.33, 45.52, 41.28, 32.07, 28.88, 23.15, 14.17. HRMS (ES+) m/z calcd for $C_{26}H_{32}N_4O_3$ [M+H]+ : 449.2547, found 449.2546.

Ethyl-7-benzyl-1-octyl-5-phenyl-4,5,6,7-tetrahydro-1*H*-[1,2,3]triazolo[4,5-*c*]pyridine-7-carboxylate (14p): Yellow oil (51%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.34-7.22 (m, 5H), 7.06-6.94 (m, 4H), 6.91 (t, *J* = 7.3Hz, 1H), 4.49 (d, *J* = 12Hz, 1H), 4.36-4.15 (m, 3H), 3.68 (br s, 2H), 3.59 (d, *J* = 9Hz, 1H), 3.50-3.28 (m, 3H), 1.95-1.63 (m, 2H), 1.30-1.17 (m, 13H), 0.88 (t, *J* = 6.7Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.51, 149.87, 141.77, 136.03, 131.28, 130.30, 129.35, 128.63, 127.41, 120.13, 115.92, 62.12, 58.71, 50.94, 49.47, 45.52, 41.23, 31.75, 29.23, 29.10, 29.05, 26.93, 22.62, 14.16, 14.10. HRMS (ES+): m/z calcd for $C_{29}H_{38}N_4O_2$ $[M+H]^+$: 475.3067, found 475.3068.

Ethyl-1-(3,4-dichlorobenzyl)-7-(4-fluorobenzyl)-5-phenyl-4,5,6,7-tetrahydro-1*H*-[1,2,3]triazolo[4,5-*c*]pyridine-7-carboxylate (14q): Yellow oil (50%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.39 - 7.30 (m, 3H), 7.15 (d, *J* = 2.1 Hz, 1H), 7.04 - 6.91 (m, 8H), 4.94 (d, *J* = 16.0 Hz, 1H), 4.59 - 4.52 (m, 2H), 4.36 (d, *J* = 14.2 Hz, 1H), 4.13 (dq, *J* = 10.8, 7.1 Hz, 1H), 3.78 (dq, *J* = 10.8, 7.1 Hz, 1H), 3.69 (s, 2H), 3.36 (s, 2H), 1.10 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 171.18, 163.12, 161.48, 149.72, 142.53, 135.43, 132.84, 132.21, 131.97, 131.91, 131.63, 131.61, 130.53, 129.44, 129.27, 126.68, 120.52, 116.11, 115.73, 115.59, 62.26, 58.24, 50.95, 50.88, 45.67, 40.77, 13.95. HRMS (ES+) m/z calcd for $C_{28}H_{25}N_4O_2Cl_2F_1$ $[M+H]^+$: 539.1411, found 539.1389.

Ethyl-1-(3-fluorobenzyl)-7-(4-fluorobenzyl)-5-phenyl-4,5,6,7-tetrahydro-1*H*-[1,2,3]triazolo[4,5-*c*]pyridine-7-carboxylate (14r): Yellow oil (60%). ^{1}H NMR (300MHz, $CDCl_3$): δ 7.33-7.20 (m, 3H), 7.04-6.88 (m, 9H), 6.83 (d, *J* = 7.7 Hz, 1H), 6.76 (dt, *J* = 9.6 Hz, 2.1 Hz, 1H), 5.11 (d, *J* = 16.2 Hz, 1H), 4.68 (d, *J* = 16.2 Hz, 1H), 4.51 (d, *J* = 14.2 Hz, 1H), 4.36 (d, *J* = 14.2 Hz, 1H), 4.06 (dq, *J* = 10.9 Hz, 7.1 Hz, 1H), 3.74-3.58 (m, 3H), 3.35 (d, *J* = 13.5 Hz, 1H), 3.28 (d, *J* = 13.5 Hz, 1H), 1.04 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (151 MHz, $CDCl_3$): δ 171.16, 163.72, 163.08, 162.08, 161.44, 149.75, 142.52, 137.87,

137.82, 131.97, 131.91, 131.57, 131.55, 130.23, 130.17, 129.39, 122.64, 122.62, 120.43, 116.08, 115.61, 115.47, 114.98, 114.84, 114.26, 114.11, 62.10, 58.16, 51.55, 50.63, 45.68, 40.62, 13.89. HRMS (ES+) m/z calcd for $C_{28}H_{26}N_4O_2F_2$ $[M+H]^+$: 489.2096, found 489.2092.

1-(4-methoxyphenethyl)-5-phenyl-4,5,6,7-tetrahydro-1*H*-[1,2,3]triazolo[4,5-*c*]pyridine (18a): Yellow oil (85%) ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.26 (t, *J* = 7.9 Hz, 2H), 6.93 – 6.84 (m, 5H), 6.73 (d, *J* = 8.5 Hz, 2H), 4.40-4.37 (m, 4H), 3.74 (s, 3H), 3.44 (t, *J* = 5.6 Hz, 2H), 3.10 (t, J = 6.8 Hz, 2H), 2.23 (t, J = 5.6 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.68, 149.95, 141.30, 131.31, 129.80, 129.39, 129.28, 119.80, 116.40, 114.14, 55.29, 49.79, 47.19, 45.81, 35.97, 20.13. HRMS (ES+) m/z calcd for $C_{20}H_{22}N_4O_1$ $[M+H]^+$: 335.1866, found 335.1868.

1-(2-methoxyphenethyl)-5-phenyl-4,5,6,7-tetrahydro-1*H*-[1,2,3]triazolo[4,5-*c*]pyridine (18b): Yellow oil (74%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.26 (t, *J* = 7.9 Hz, 2H), 7.18 (t, *J* = 7.8 Hz, 1H), 6.92 (d, *J* = 8.0 Hz, 2H), 6.89 – 6.79 (m, 3H), 6.74 (t, *J* = 7.4 Hz, 1H), 4.43 (t, *J* = 6.9 Hz, 2H), 4.38 (s, 2H), 3.80 (s, 3H), 3.45 (t, *J* = 5.6 Hz, 2H), 3.15 (t, *J* = 6.8 Hz, 2H), 2.28 (t, J = 5.6 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.49, 149.97, 141.20, 131.12, 130.71, 129.26, 128.48, 125.58, 120.69, 119.70, 116.32, 110.19, 55.24, 47.83, 47.11, 45.85, 31.98, 20.02. HRMS (ES+) m/z calcd for $C_{20}H_{22}N_4O_1$ $[M+H]^+$: 335.1866, found 335.1869.

1-(cyclopropylmethyl)-5-phenyl-4,5,6,7-tetrahydro-1*H*-[1,2,3]triazolo[4,5-*c*]pyridine (18c): Yellow oil (90%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.32 - 7.23 (m, 2H), 7.03 - 6.95 (m, 2H), 6.92 - 6.82 (m, 1H), 4.43 (s, 2H), 4.12 (d, J = 7.1 Hz, 2H), 3.65 (t, J = 5.7 Hz, 2H), 2.86 (tt, J = 5.6, 1.3 Hz, 2H), 1.29 – 1.22 (m, 1H), 0.68 - 0.59 (m, 2H), 0.43 - 0.38 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 150.12, 141.91, 130.29, 129.32, 119.95, 116.48, 52.82, 47.36, 46.06, 21.06, 11.05, 4.30. HRMS (ES+) m/z calcd for $C_{15}H_{18}N_4$ $[M+H]^+$: 255.1604, found 225.1606.

1-hexyl-5-phenyl-4,5,6,7-tetrahydro-1*H*-[1,2,3]triazolo[4,5-*c*]pyridine (18d): Yellow oil (48%) ^{1}H NMR (300MHz, $CDCl_3$): δ 7.31 - 7.26 (m, 2H), 7.01-6.98 (m, 2H), 6.91 – 6.86 (m, 1H), 4.43 (s, 2H), 4.23 (t, *J* = 7.3 Hz, 2H), 3.65 (t, *J* = 5.6 Hz, 2H), 2.81 (t, *J* = 5.6 Hz, 2H), 1.91-1.82 (m, 2H), 1.32-1.26 (m, 6H), 0.87 (t, *J* = 6.9 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.10, 141.79, 130.43, 129.33, 119.99, 116.53, 48.06, 47.35, 46.05, 31.19, 29.86, 26.23, 22.42, 20.80, 13.95. HRMS (ES+) m/z calcd for $C_{17}H_{24}N_4$ $[M+H]^+$: 285.2073, found 285.2068.

1-(3-methoxyphenethyl)-5-(4-(trifluoromethyl)phenyl)-4,5,6,7-tetrahydro-1*H*-[1,2,3]triazolo[4,5-*c*]pyridine (18e): Yellow oil (90%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.48 (d, *J* = 8.6 Hz, 2H), 7.08 (t, *J* = 7.9 Hz, 1H), 6.90 (d, *J* = 8.8 Hz, 2H), 6.72 (ddd, *J* = 8.3, 2.6, 0.9 Hz, 1H), 6.54 (d, *J* = 7.5, 1H), 6.45 (t, *J* = 2.1 Hz, 1H), 4.48 (s, 2H), 4.43 (t, *J* = 6.7 Hz, 2H), 3.68 (s, 3H), 3.50 (t, *J* = 5.6 Hz, 2H), 3.15 (t, *J* = 6.7 Hz, 2H), 2.17 (t, *J*

= 5.6 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.81, 151.93, 140.59, 138.87, 131.44, 129.76, 126.65, 126.62, 126.58, 126.54, 121.01, 114.60, 114.29, 112.56, 55.12, 49.61, 45.89, 45.19, 36.95, 19.79. HRMS (ES+) m/z calcd for $C_{21}H_{21}N_4O_1F_3$ $[M+H]^+$: 403.1740, found 403.1736.

1-(4-methoxyphenethyl)-5-(4-(trifluoromethyl)phenyl)-4,5,6,7-tetrahydro-1*H*-[1,2,3]triazolo[4,5-*c*]pyridine (18f): Yellow oil (85%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50 – 7.45 (m, 1H), 6.91 (d, *J* = 8.6 Hz, 2H), 6.87 – 6,82 (m, 2H), 6.74 – 6.69 (m, 2H), 4.48 (s, 2H), 4.40 (t, *J* = 6.7 Hz, 2H), 3.72 (s, 3H), 3.52 (t, *J* = 5.6 Hz, 2H), 3.11 (t, *J* = 6.7 Hz, 2H), 2.18 (t, *J* = 5.6 Hz, 2H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 158.72, 151.99, 140.62, 131.29, 129.81, 129.30, 126.63, 126.61, 126.58, 126.56, 114.64, 114.12, 55.26, 49.90, 45.97, 45.17, 36.01, 19.86. HRMS (ES+) m/z calcd for $C_{21}H_{21}N_4O_1F_3$ [M+H]+ : 403.1740, found 403.1737.

1-(2-methoxyphenethyl)-5-(4-(trifluoromethyl)phenyl)-4,5,6,7-tetrahydro-1*H*-[1,2,3]triazolo[4,5-*c*]pyridine (18g): Yellow oil (85%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.49 – 7.45 (m, 2H), 7.16 (ddd, *J* = 8.2, 7.3, 1.9 Hz, 1H), 6.90 (d, *J* = 8.6 Hz, 2H), 6.81 – 6.76 (m, 2H), 6.69 (td, *J* = 7.3, 1.1 Hz, 1H), 4.47 – 4.43 (m, 4H), 3.80 (s, 3H), 3.52 (t, *J* = 5.6 Hz, 2H), 3.15 (t, *J* = 6.7 Hz, 2H), 2.22 (t, J =5.6 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.48, 151.98, 140.51, 131.09, 130.72, 128.54, 126.63, 126.59, 126.55, 126.52, 125.46, 120.66, 114.62, 110.15, 55.25, 47.88, 45.96, 45.20, 32.02, 19.65. HRMS (ES+) m/z calcd for $C_{21}H_{21}N_4O_1F_3$ $[M+H]^+$: 403.1740, found 403.1738.

1-(4-fluorobenzyl)-5-(4-(trifluoromethyl)phenyl)-4,5,6,7-tetrahydro-1*H*-[1,2,3]triazolo[4,5-*c*]pyridine (18h): Yellow oil (89%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50 – 7.47 (m, 2H), 7.22 – 7.18 (m, 2H), 7.07 – 7.01 (m, 2H), 6.95 (d, *J* = 8.7Hz, 2H), 5.45 (s, 2H), 4.50 (br s, 2H), 3.66 (t, J = 5.7 Hz, 2H), 2.64 (t, *J* = 5.7 Hz, 2H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 163.54, 161.90, 152.05, 141.97, 130.62, 130.20, 130.18, 129.47, 129.41, 126.67, 126.65, 126.63, 126.60, 116.20, 116.05, 114.79, 51.47, 46.06, 45.29, 20.65. HRMS (ES+) m/z calcd for $C_{19}H_{16}N_4F_4$ [M+H]+ : 377.1383, found 377.1382.

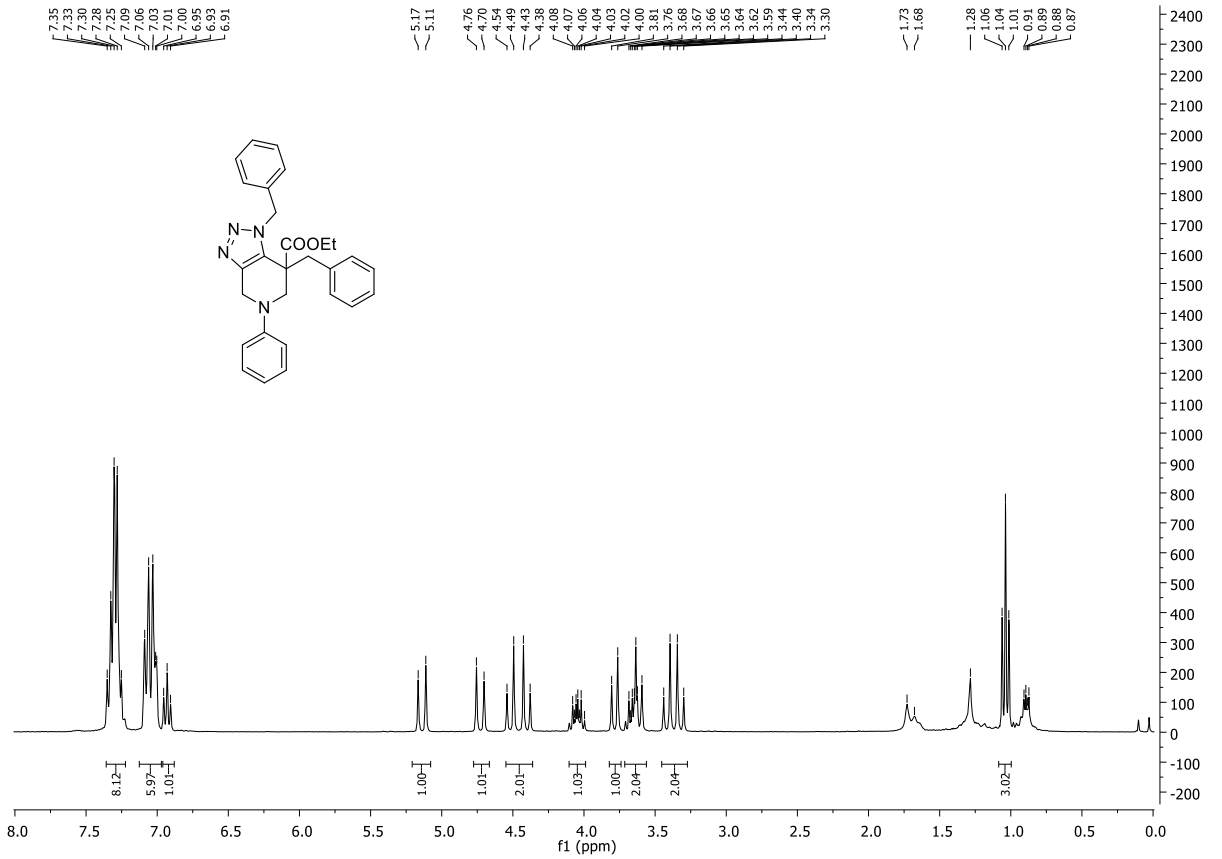
1-(3-fluorobenzyl)-5-(4-(trifluoromethyl)phenyl)-4,5,6,7-tetrahydro-1*H*-[1,2,3]triazolo[4,5-*c*]pyridine (18i): Yellow oil (85%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.49 (d, *J* = 8.6 Hz, 2H), 7.36 – 7.29 (m, 1H), 7.06 – 6.87 (m, 5H), 5.47 (s, 2H), 4.51 (s, 2H), 3.67 (t, *J* = 5.7 Hz, 2H), 2.65 (t, *J* = 5.7 Hz, 2H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 163.85, 162.21, 152.06, 141.98, 136.82, 136.77, 130.80, 130.75, 126.67, 126.65, 126.62, 126.60, 123.07, 123.05, 115.72, 115.58, 114.81, 114.64, 114.49, 51.47, 46.04, 45.27, 20.57. HRMS (ES+) m/z calcd for $C_{19}H_{16}N_4F_4$ [M+H]+ : 377.1383, found 377.1371.

1-hexyl-5-(4-(trifluoromethyl)phenyl)-4,5,6,7-tetrahydro-1*H*-[1,2,3]triazolo[4,5-*c*]pyridine (18j): Yellow oil (89%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50 (d, *J* = 8.7 Hz, 2H), 6.99 (d, *J* = 8.7 Hz, 2H), 4.51 (s, 2H), 4.23 (t, *J* = 7.3 Hz, 2H), 3.75 (t, *J* = 5.6 Hz, 2H), 2.83 (t, *J* = 5.6 Hz, 2H), 1.90 – 1.83 (m, 2H), 1.33 – 1.26 (m, 6H), 0.89-0.85 (m, 3H).^{13}C

NMR (151 MHz, $CDCl_3$): δ 152.14, 141.15, 130.30, 126.64 (q, 4 Hz), 125.52, 123.73, 120.87, 120.65, 114.78, 48.13, 46.14, 45.33, 31.17, 29.86, 26.22, 22.42, 20.55, 13.93. HRMS (ES+) m/z calcd for $C_{18}H_{23}N_4F_3$ $[M+H]^+$: 353.1947, found 353.1941.

5-(4-fluorophenyl)-1-hexyl-4,5,6,7-tetrahydro-1*H*-[1,2,3]triazolo[4,5-*c*]pyridine (18k): Yellow oil (91%) ^1H NMR (300 MHz, $CDCl_3$): δ 7.01-6.91 (m, 4H), 4.35 (br s, 2H), 4.23 (t, *J* = 7.3 Hz, 2H), 3.57 (t, *J* = 5.7 Hz, 2H), 2.80 (t, *J* = 5.7 Hz, 2H), 1.89-1.84 (m, 2H), 1.44 – 1.13 (m, 6H), 0.87 (t, *J* = 5.7 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.90, 155.73, 146.72, 146.69, 141.63, 130.27, 118.59, 118.49, 115.90, 115.60, 48.37, 48.08, 46.94, 31.18, 29.85, 26.21, 22.42, 20.77, 13.95. HRMS (ES+) m/z calcd for $C_{17}H_{23}N_4F_1$ [M+H]+ : 303.1979, found 303.1983.

1-(2,2-diphenylethyl)-5-(4-fluorophenyl)-4,5,6,7-tetrahydro-1*H*-[1,2,3]triazolo[4,5-*c*]pyridine (18l): Yellow oil (57%). ^1H NMR (300 MHz, $CDCl_3$): δ 7.28-7.19 (m, 7H), 7.13 – 7.10 (m, 4H), 6.97-6.91 (m, 2H), 6.83-6.79 (m, 2H), 4.81 – 4.77 (m, 2H), 4.67 – 4.62 (m, 1H), 4.28 (s, 2H), 3.25 (t, *J* = 5.6 Hz, 2H), 1.97 (t, *J* = 5.6, 2H). ^{13}C NMR (101 MHz, CDCl3): δ 158.34, 146.37, 140.81, 140.70, 131.55, 128.74, 127.95, 127.25, 118.27, 118.20, 115.77, 115.55, 52.96, 51.71, 48.02, 46.54, 19.83. HRMS (ES+) m/z calcd for $C_{25}H_{23}N_4F_1$ $[M+H]^+$: 399.1979, found 399.1976.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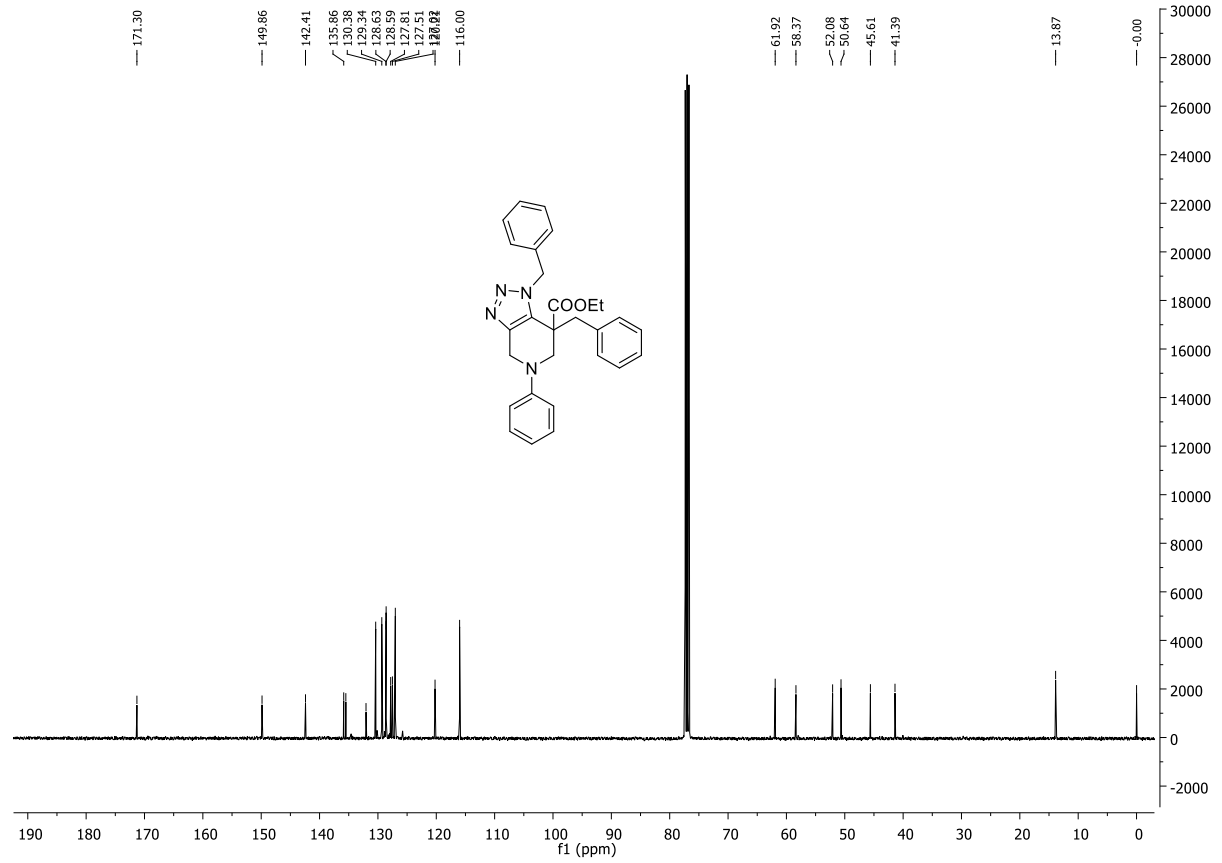
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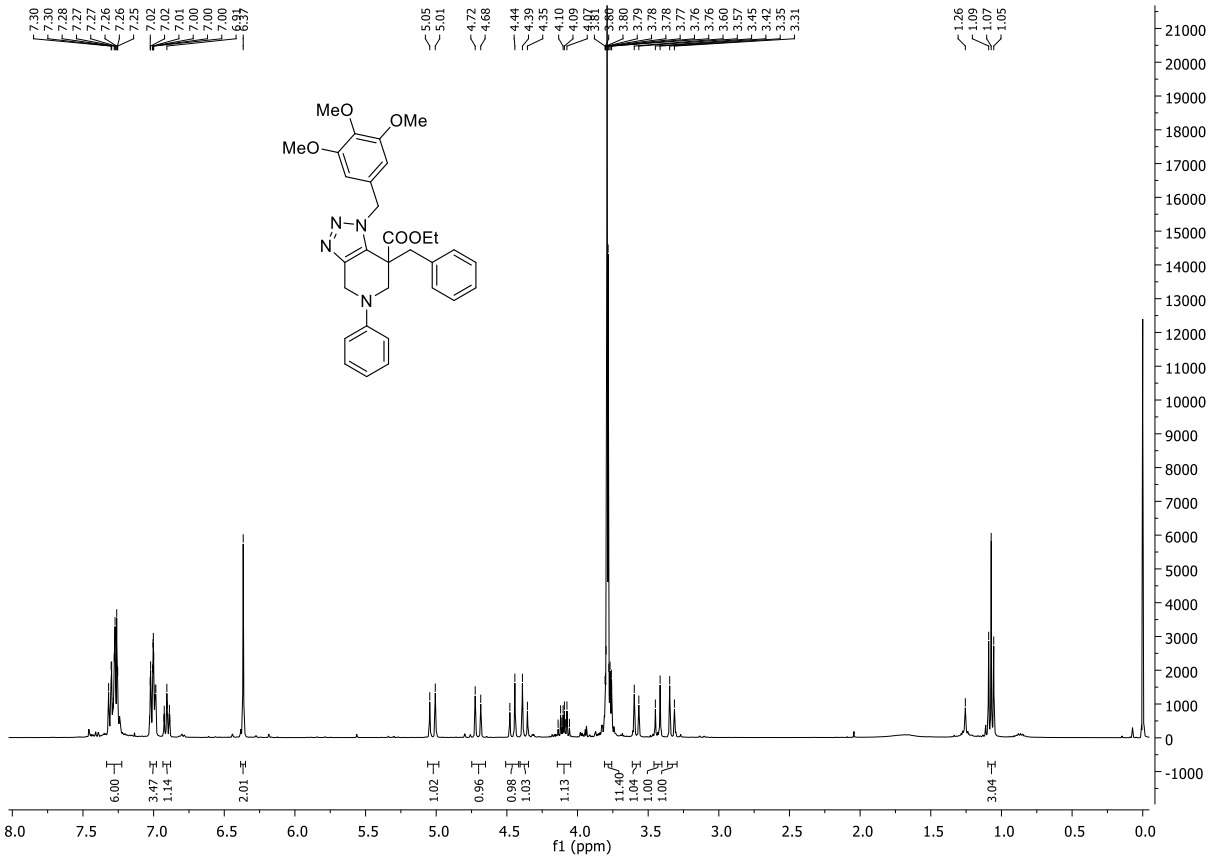
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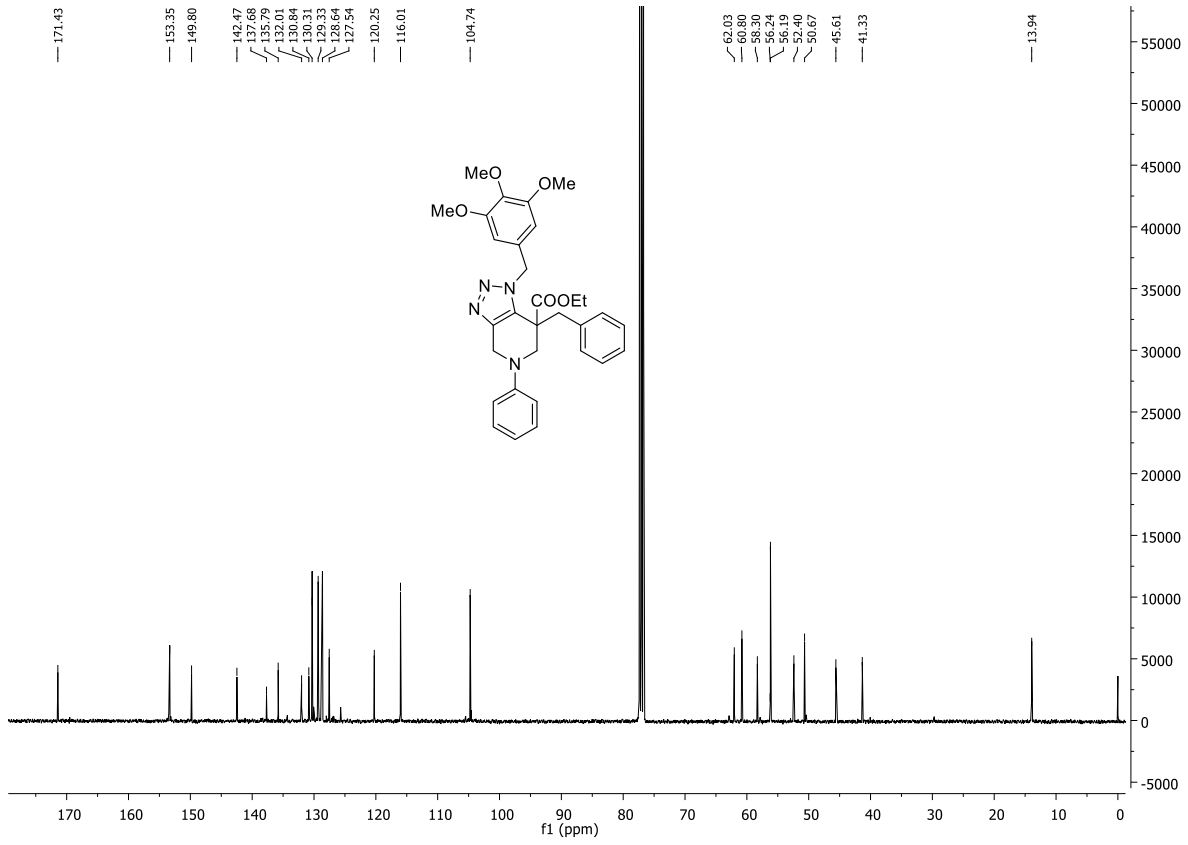
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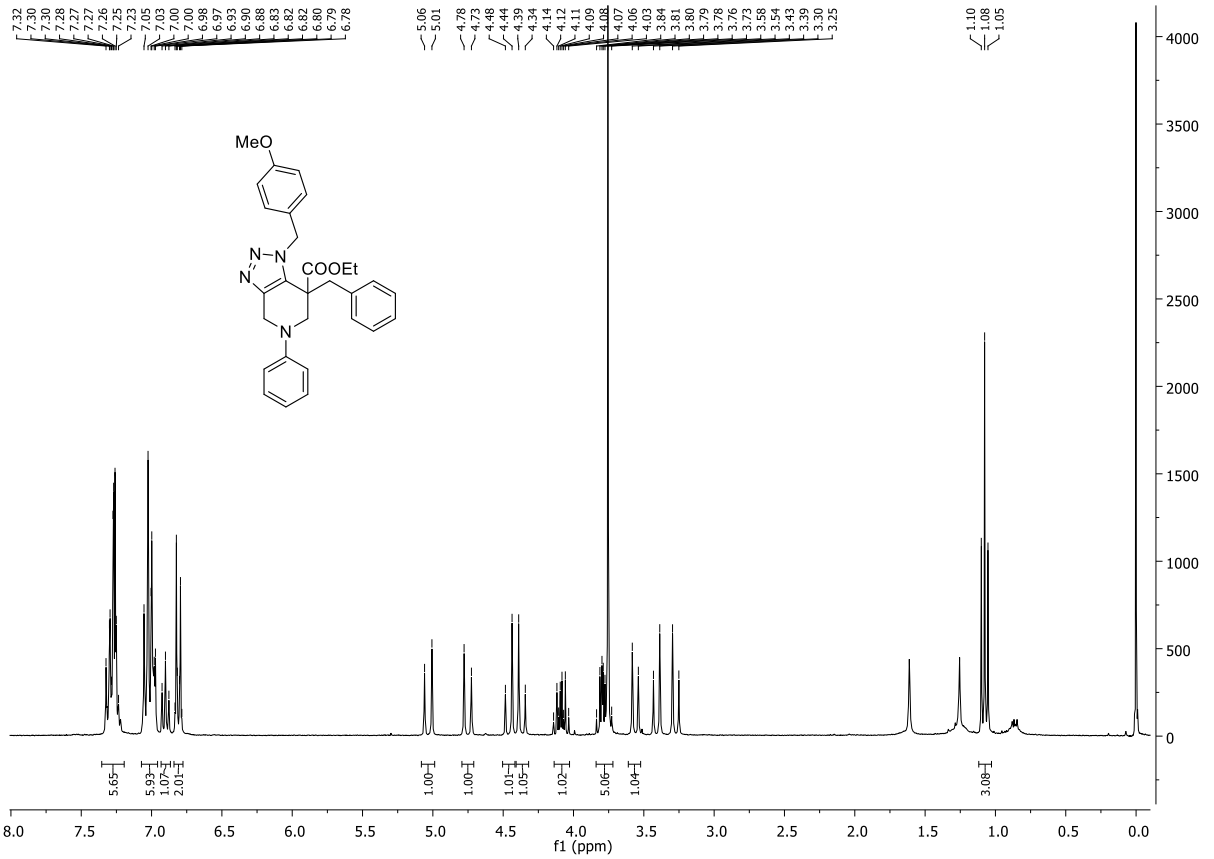
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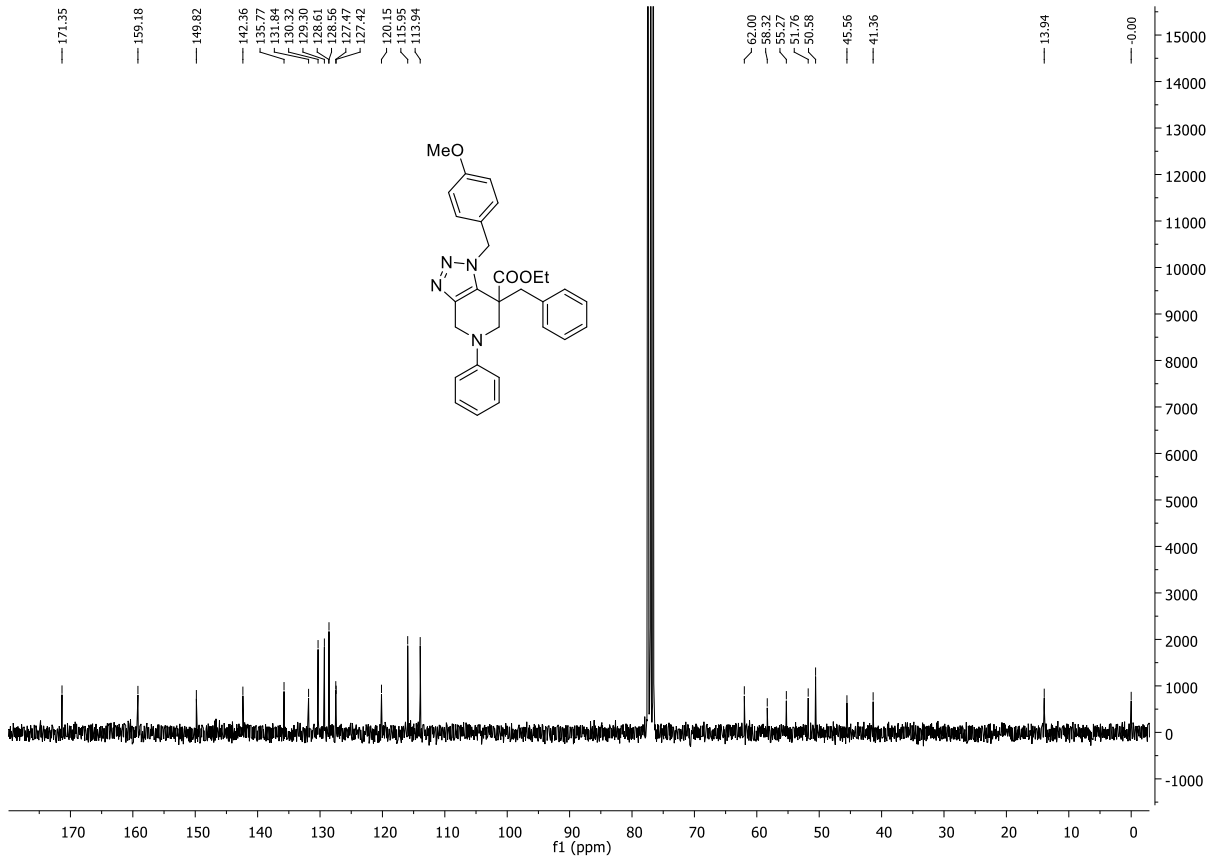
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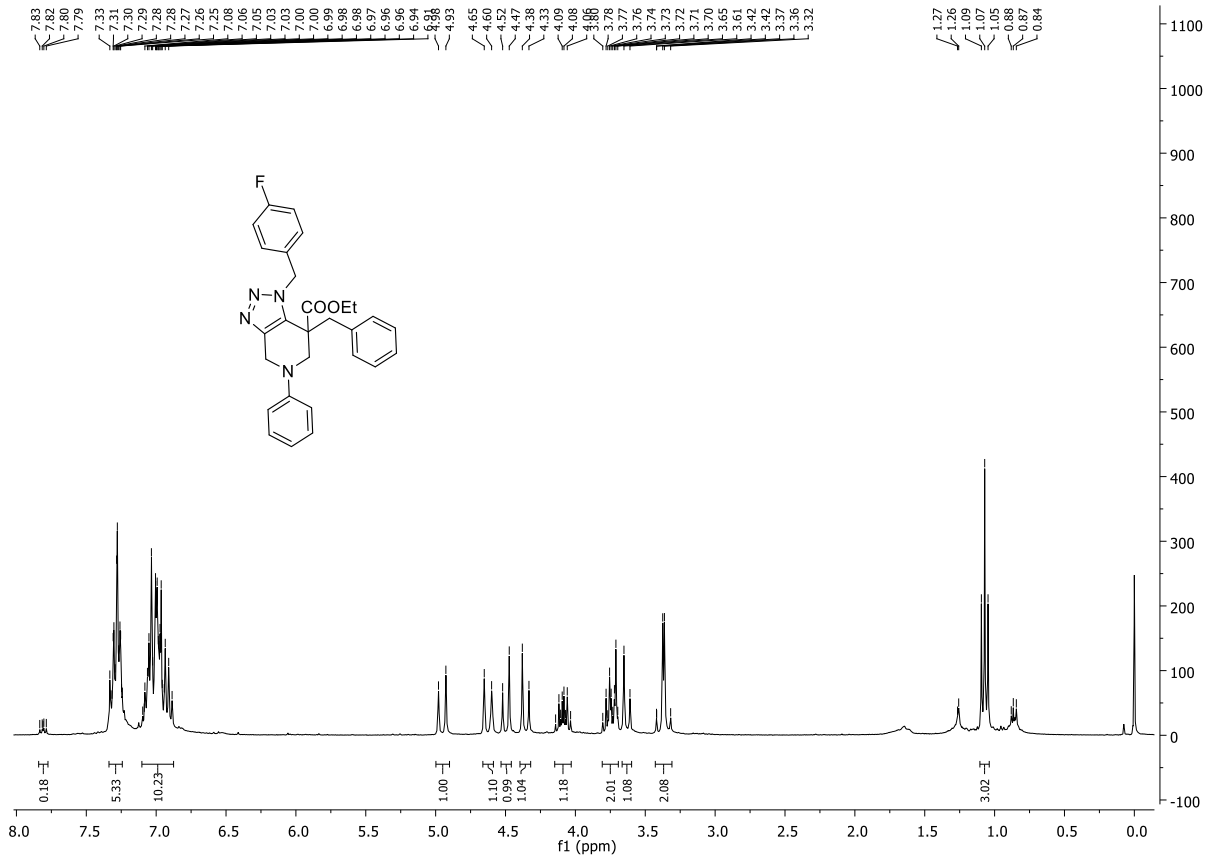
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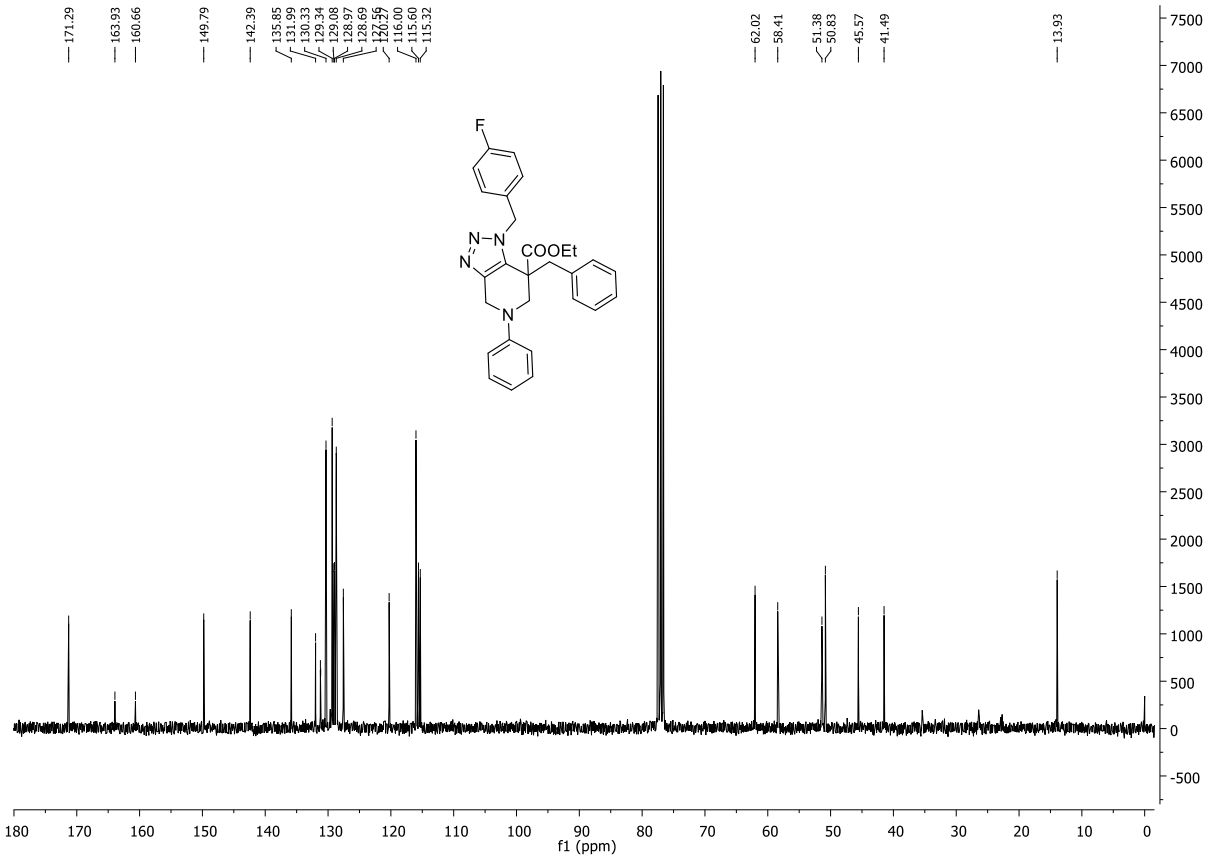
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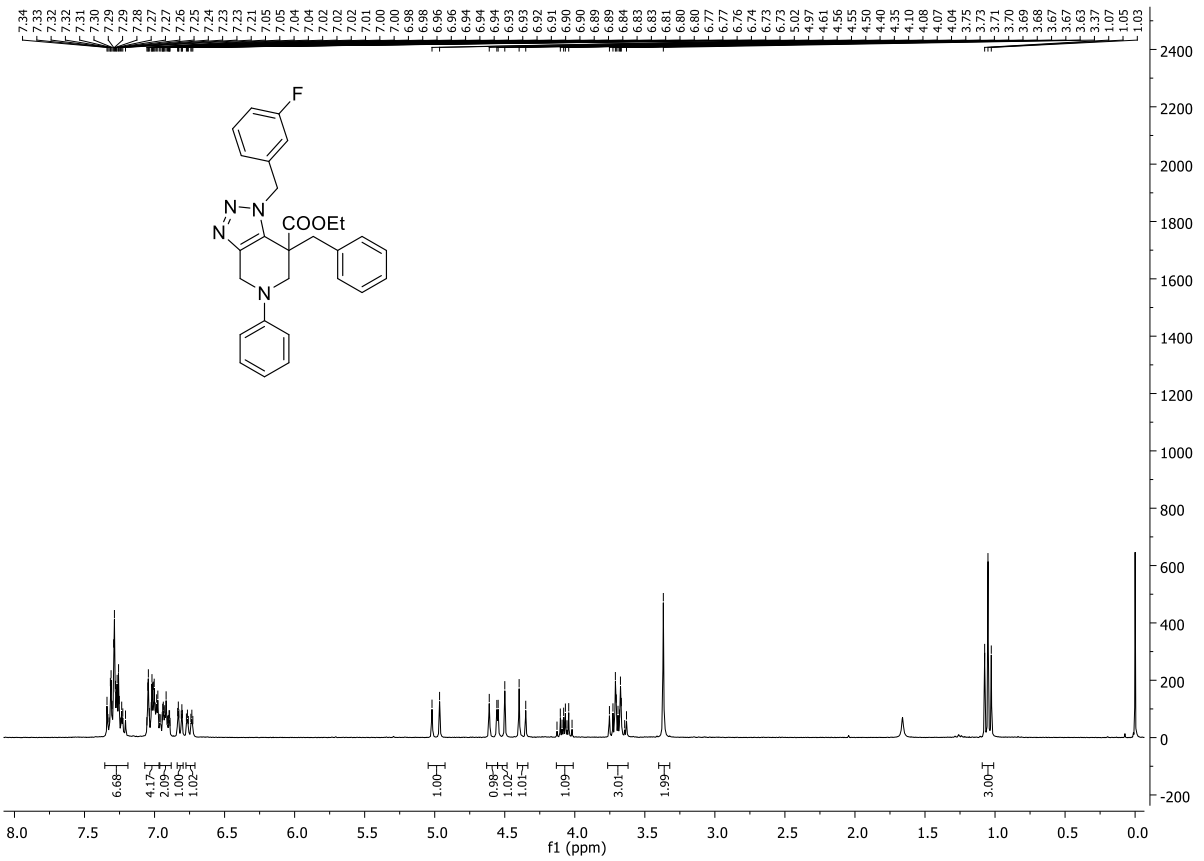
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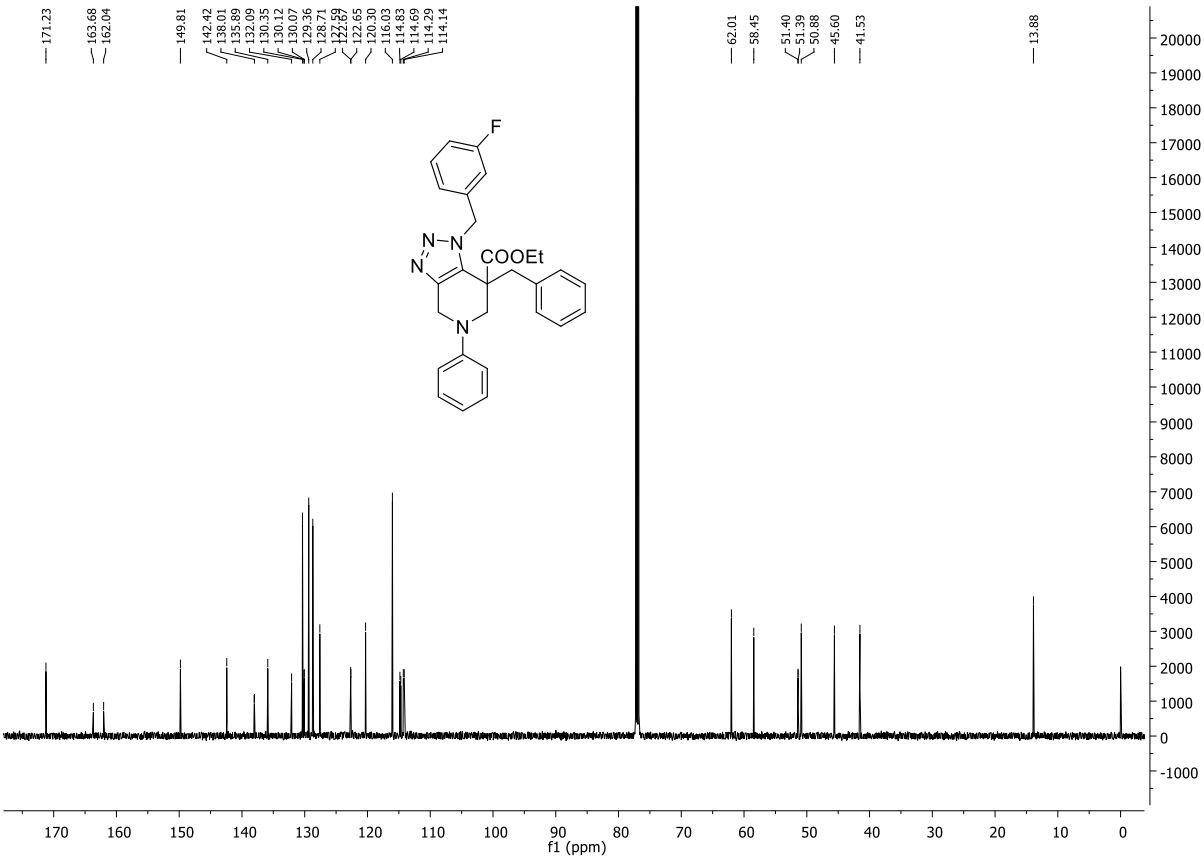
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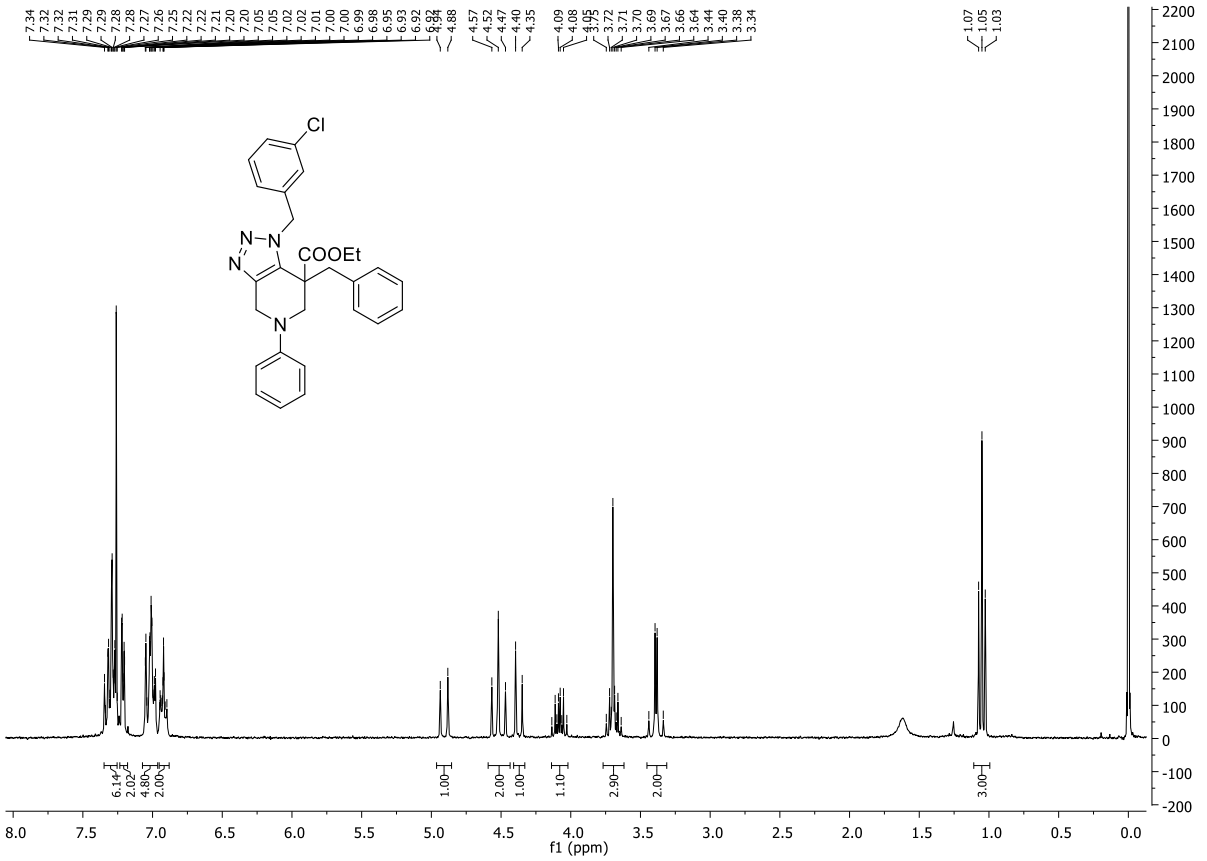
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1.05
1.03
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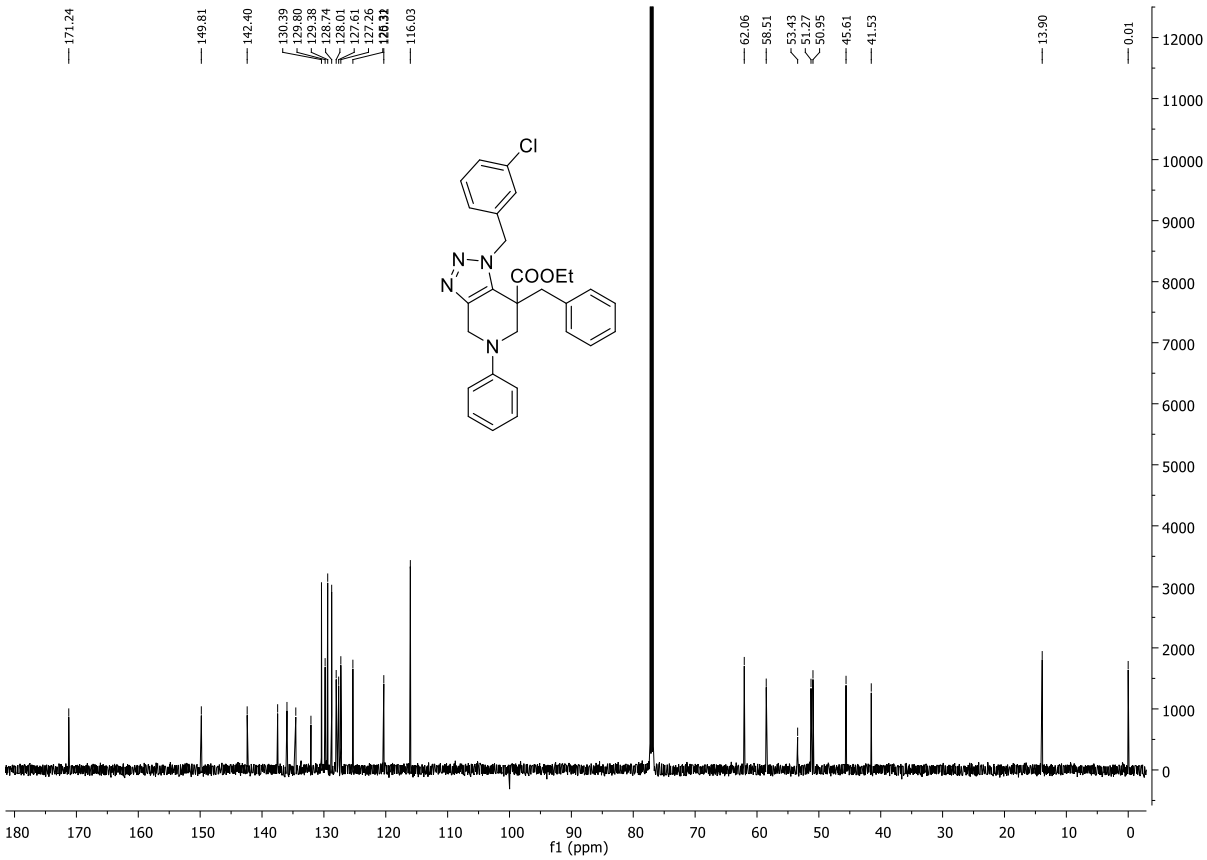
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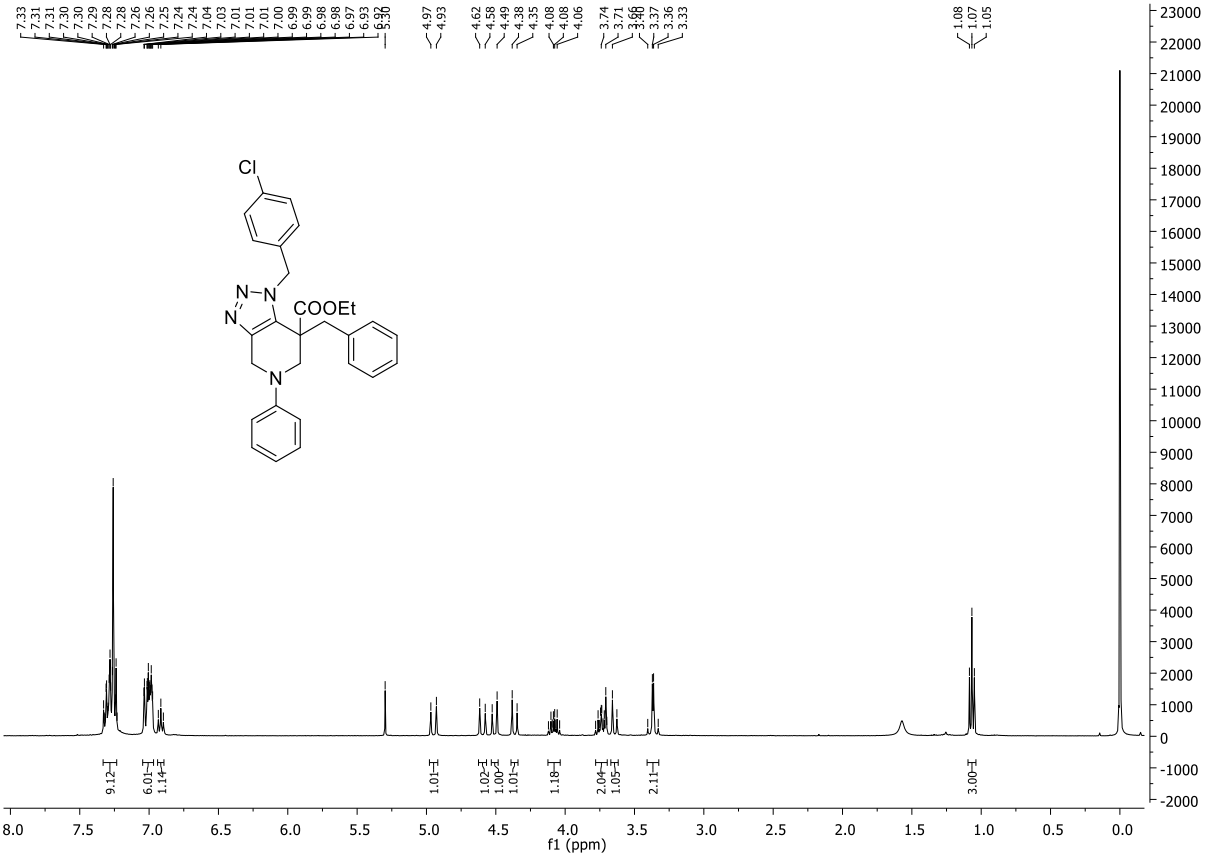
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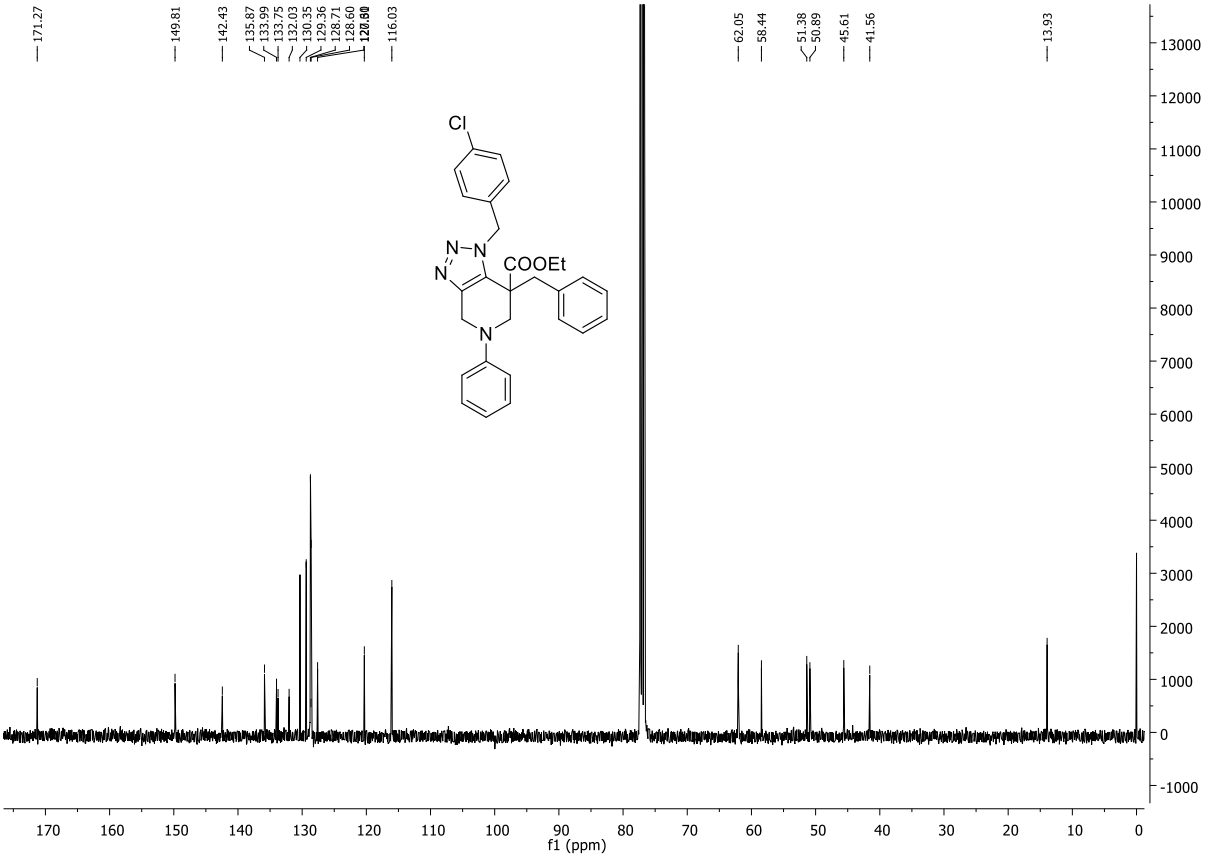
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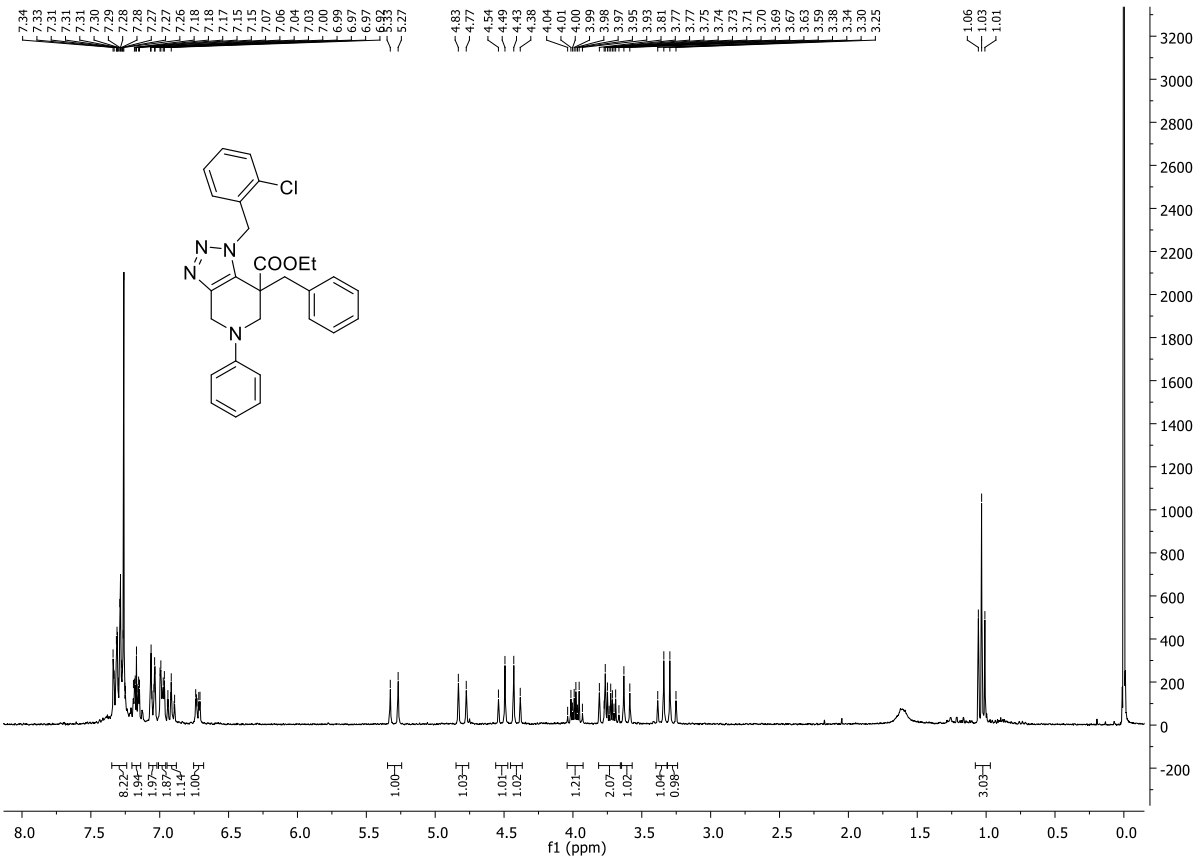
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4.83 4.77 4.54 4.49 4.43 4.38 4.04 4.01 4.00 3.99 3.98 3.97 3.95 3.93 3.81 3.77 3.77 3.75 3.74 3.73 3.71 3.70 3.69 3.67 3.63 3.59 3.38 3.34 3.30 3.25
1.06 1.03 1.01
Cl
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N
N
COOEt
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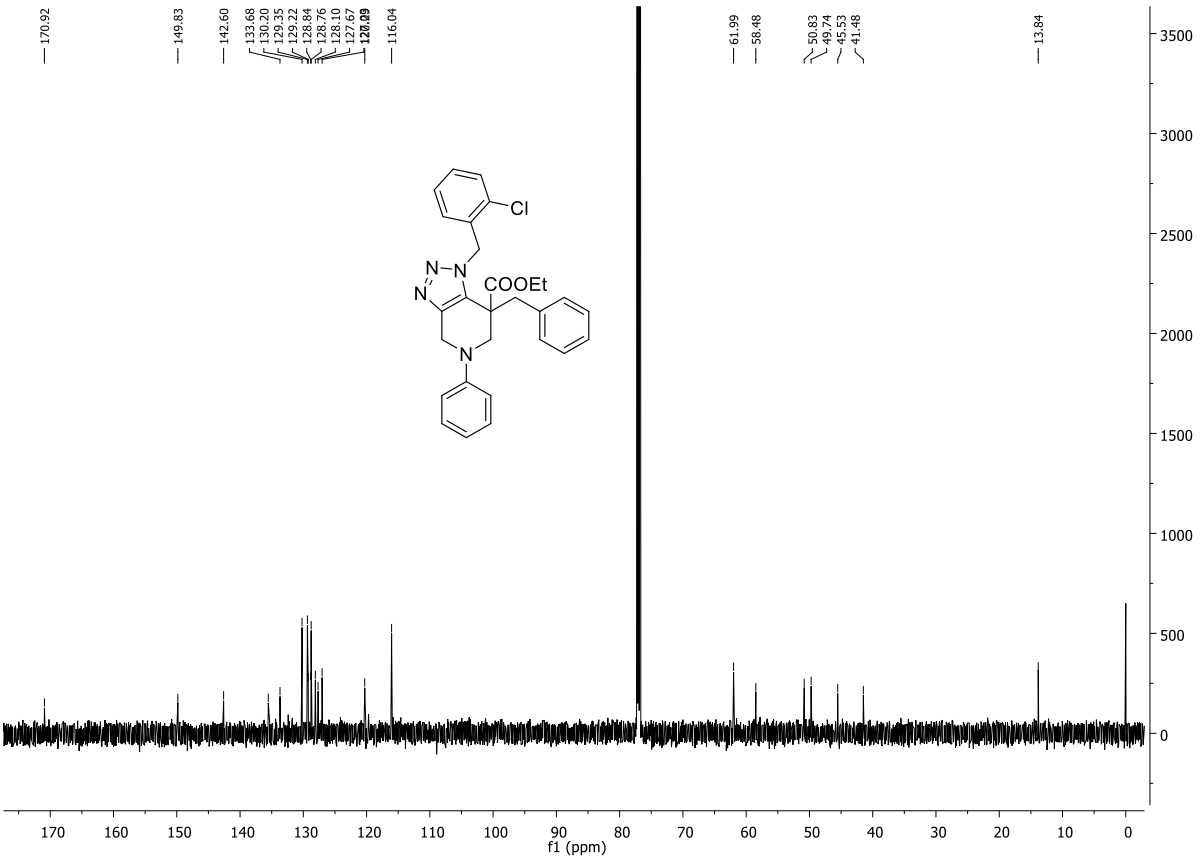
f1 (ppm)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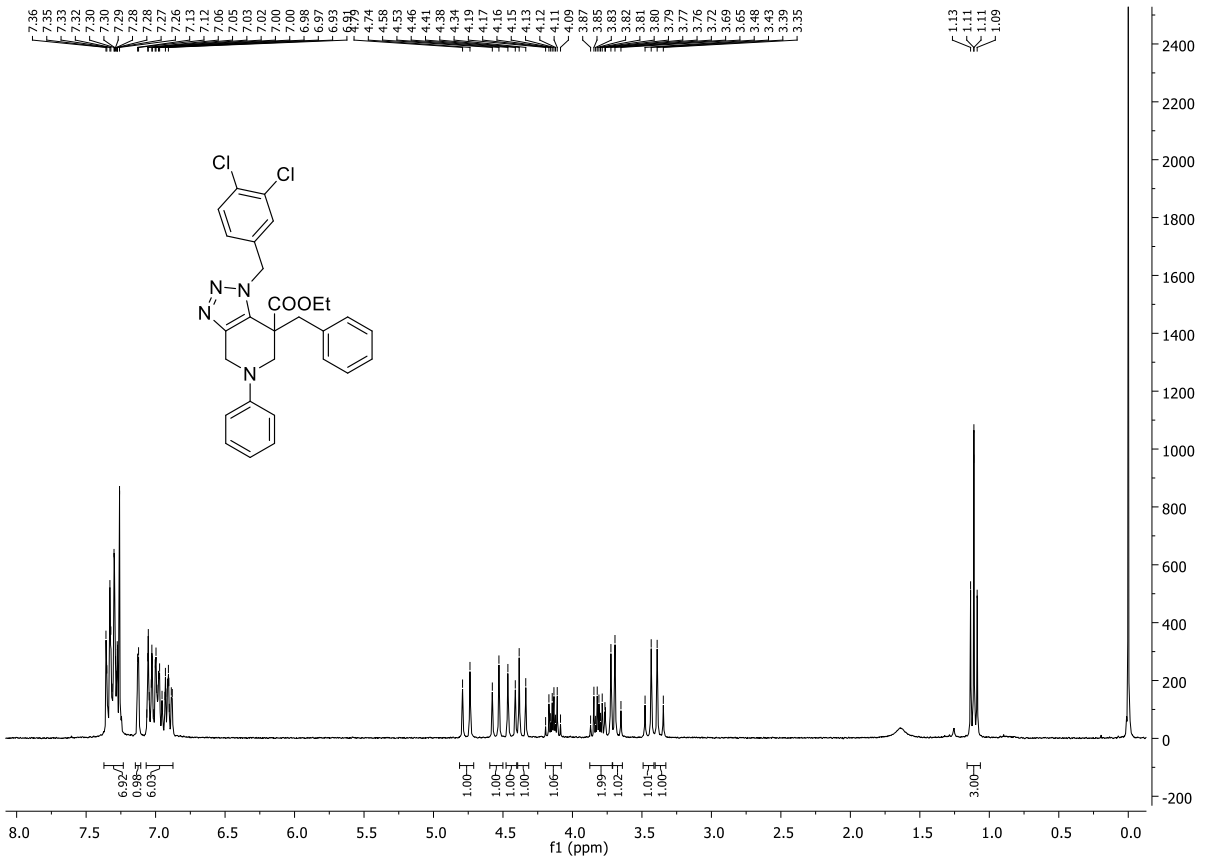
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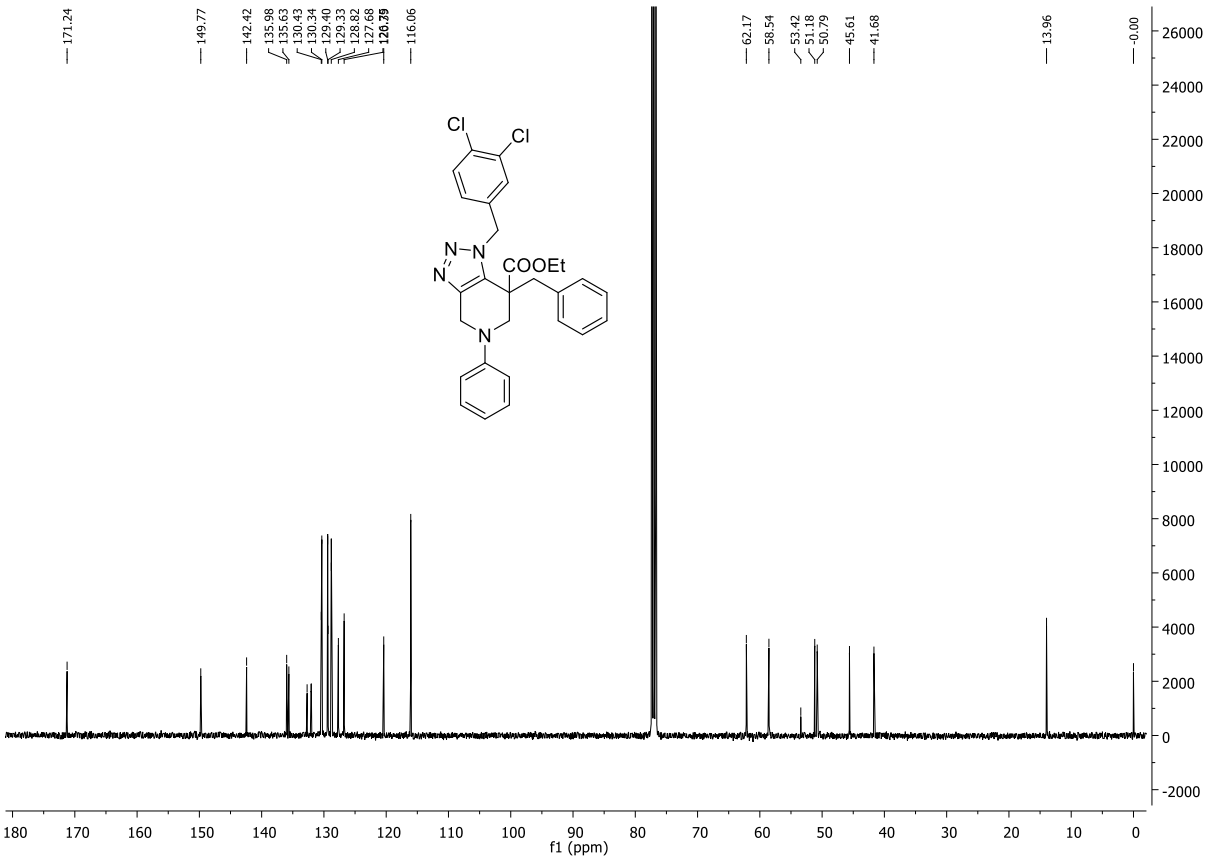
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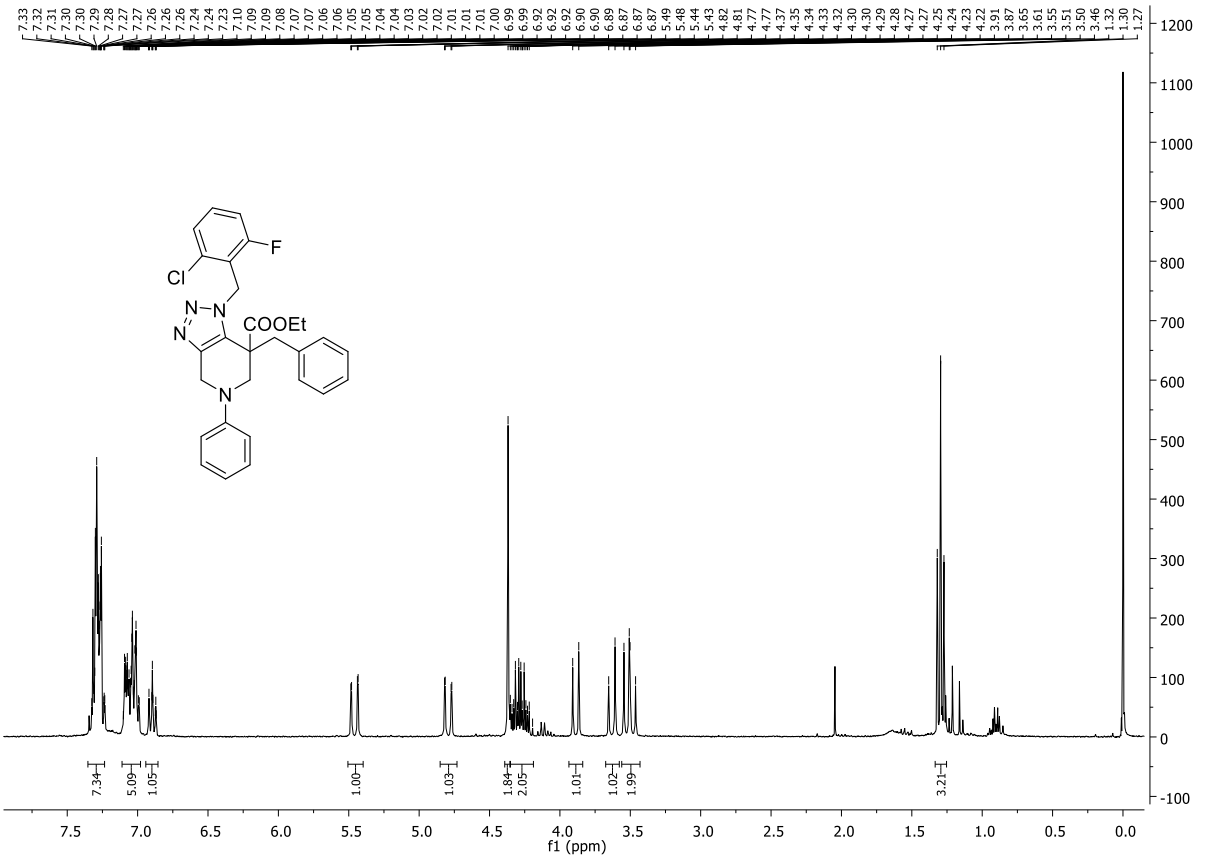
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1.02
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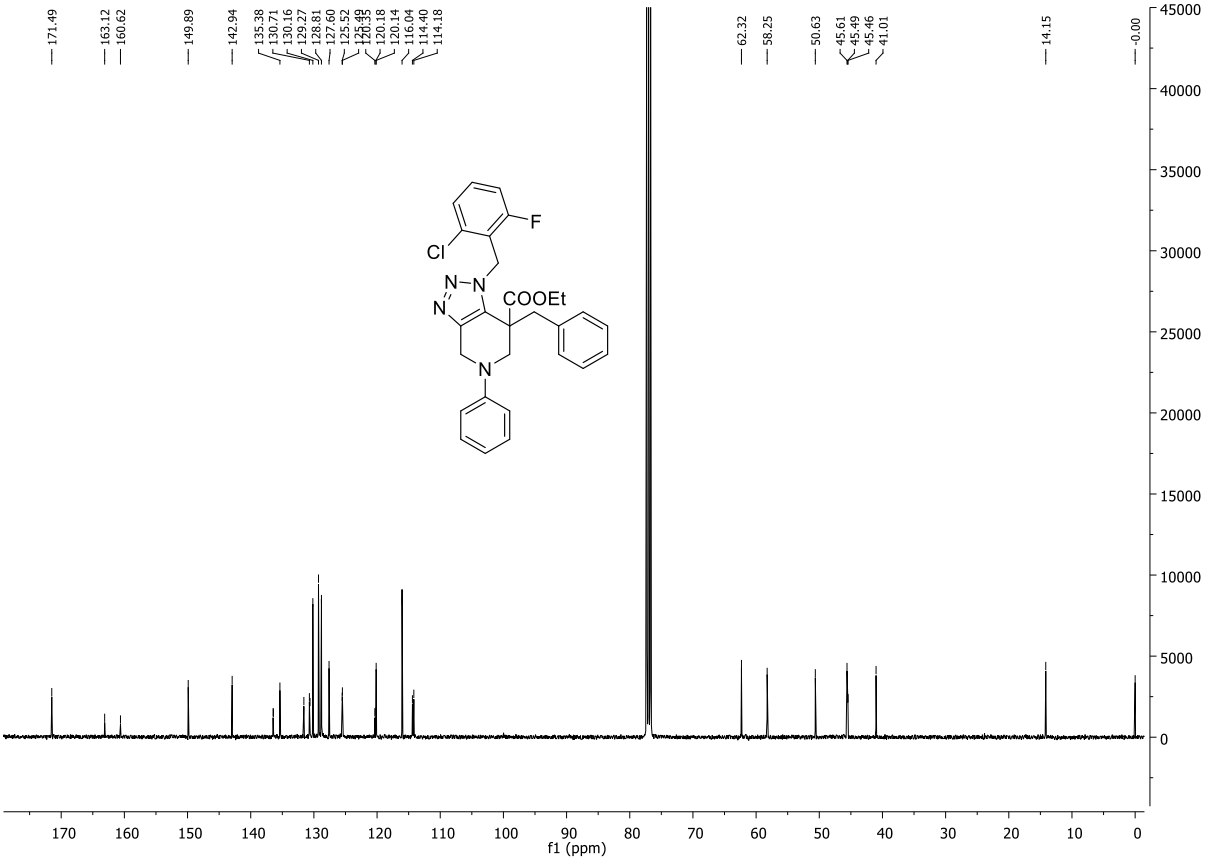
3.21
f1 (ppm)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114.18
62.32
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COOEt
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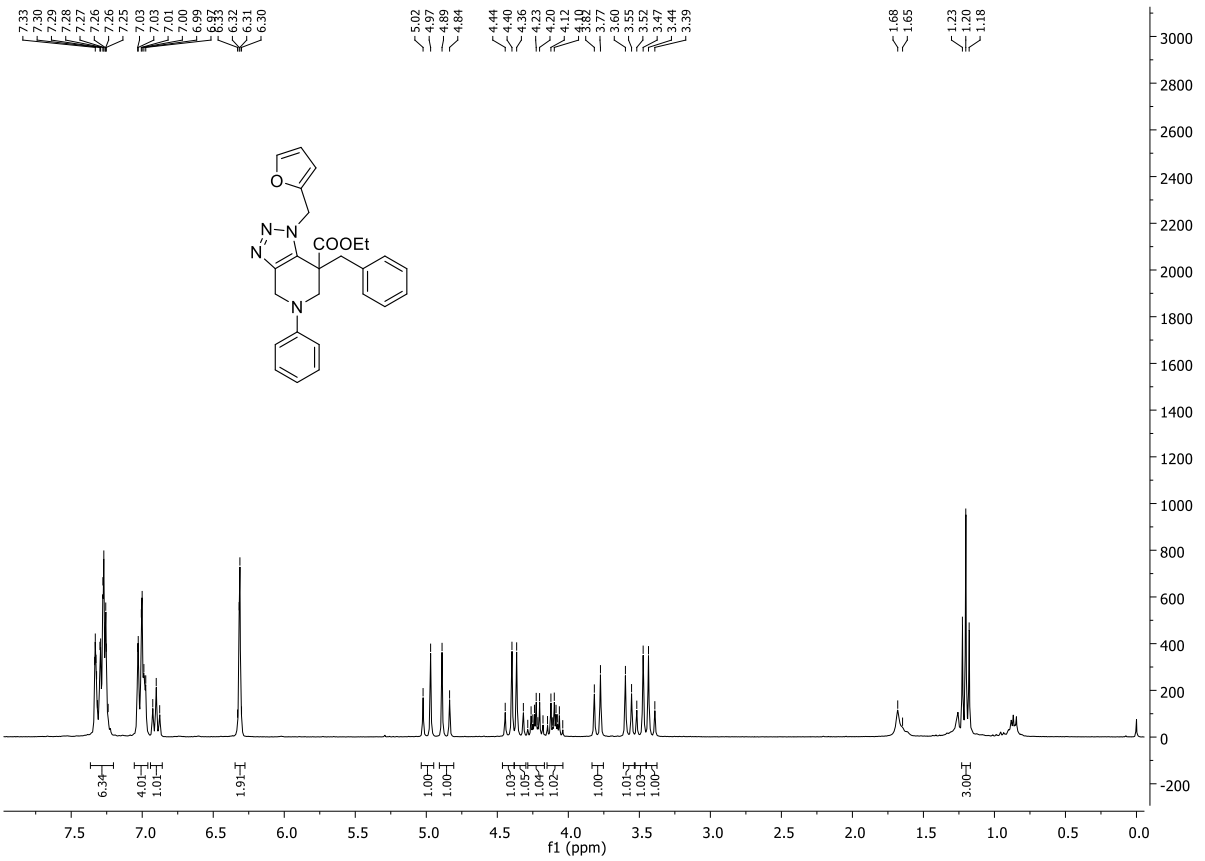
f1 (ppm)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6.33
6.32
6.31
6.30
5.02
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4.20
4.12
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3.52
3.47
3.44
3.39
1.68
1.65
1.23
1.20
1.18
COOEt
6.34
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1.01
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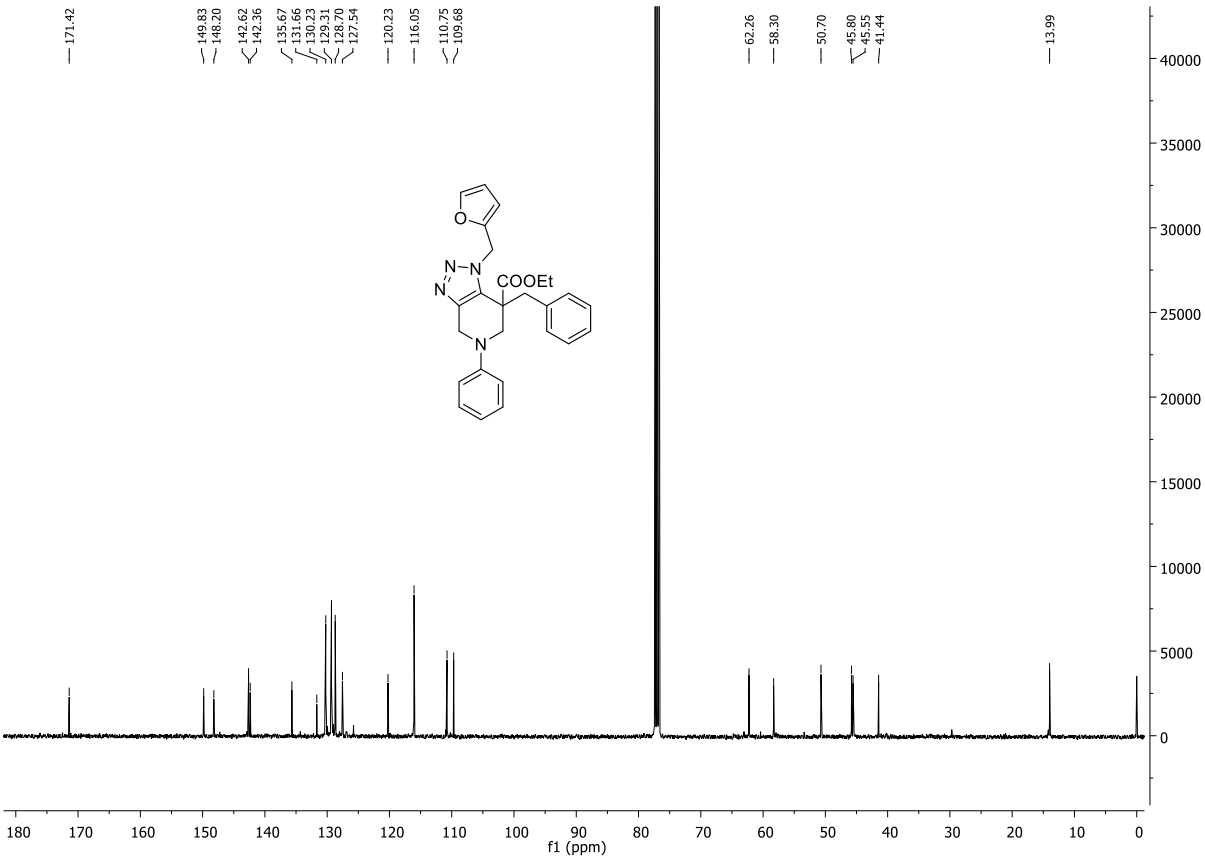
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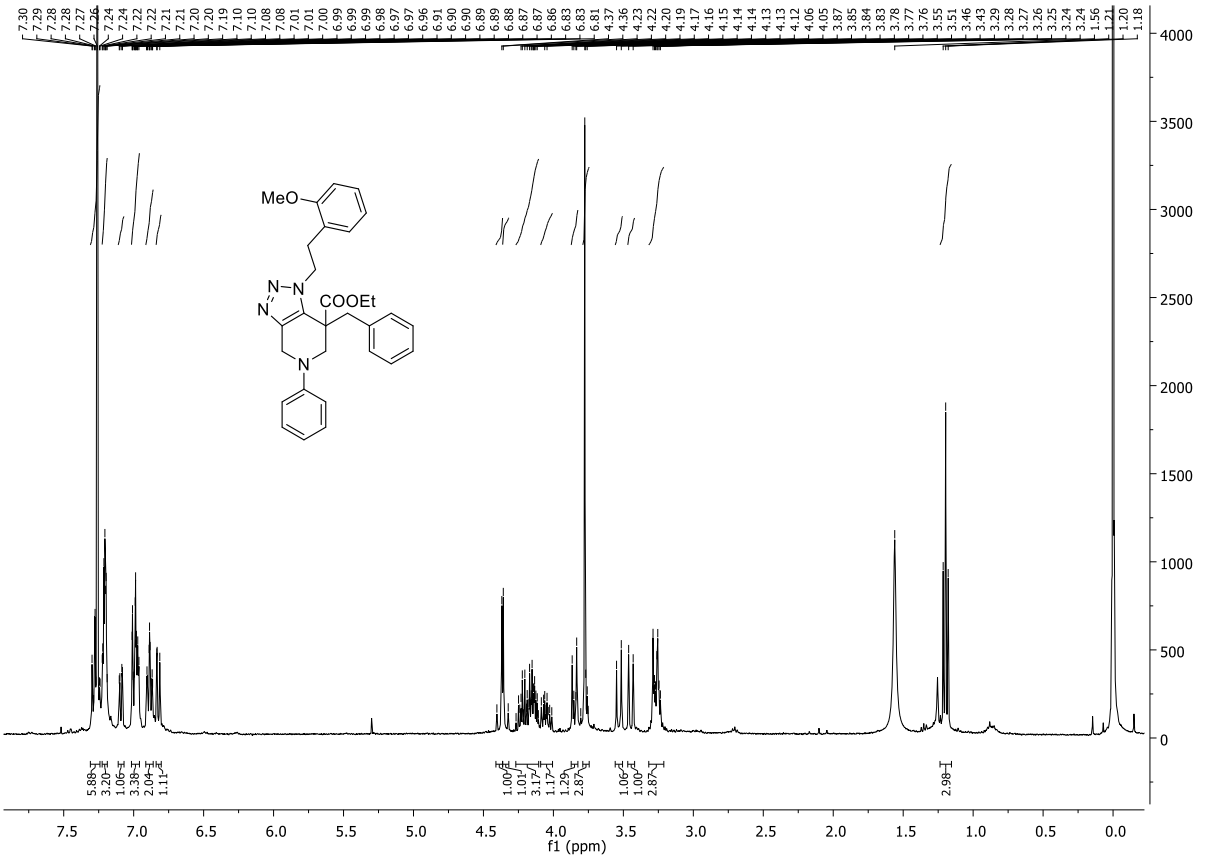
41.44
13.99
COOEt
f1 (ppm)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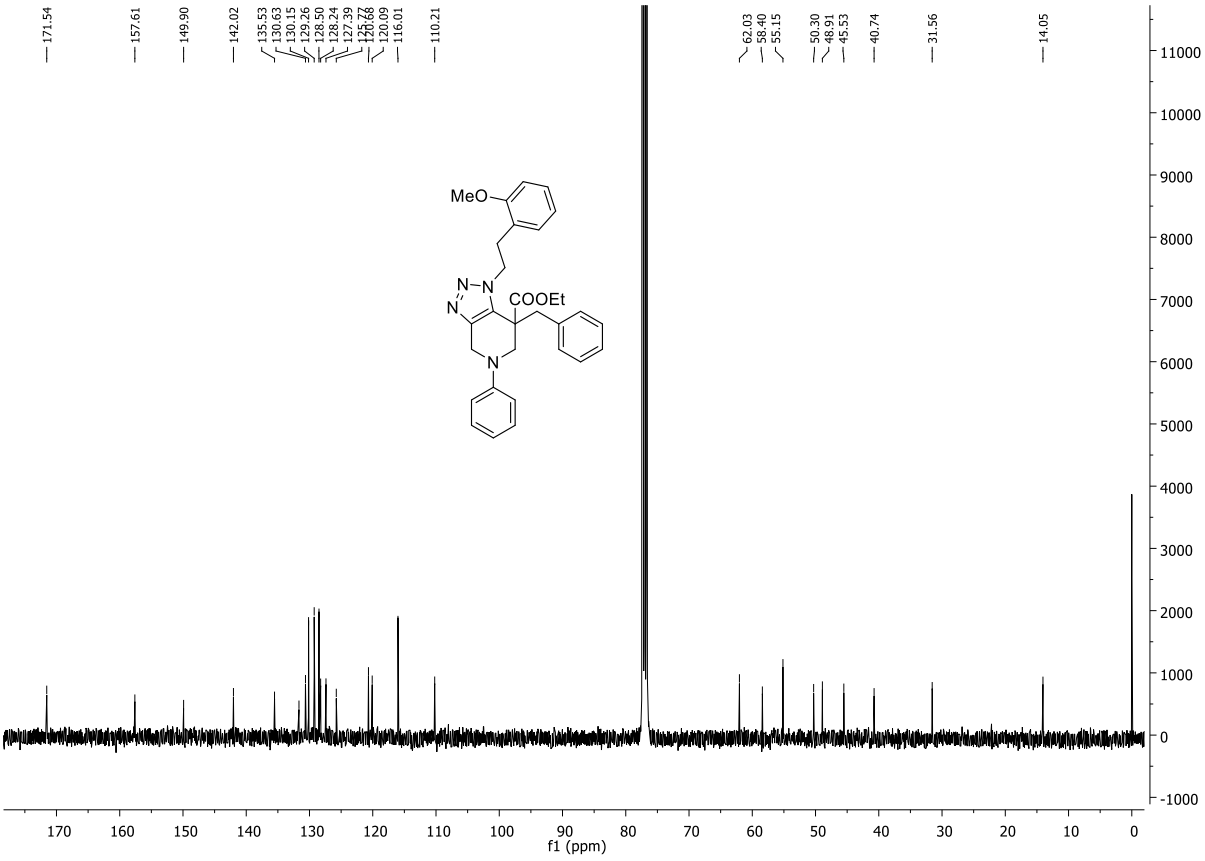
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116.01
110.21
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31.56
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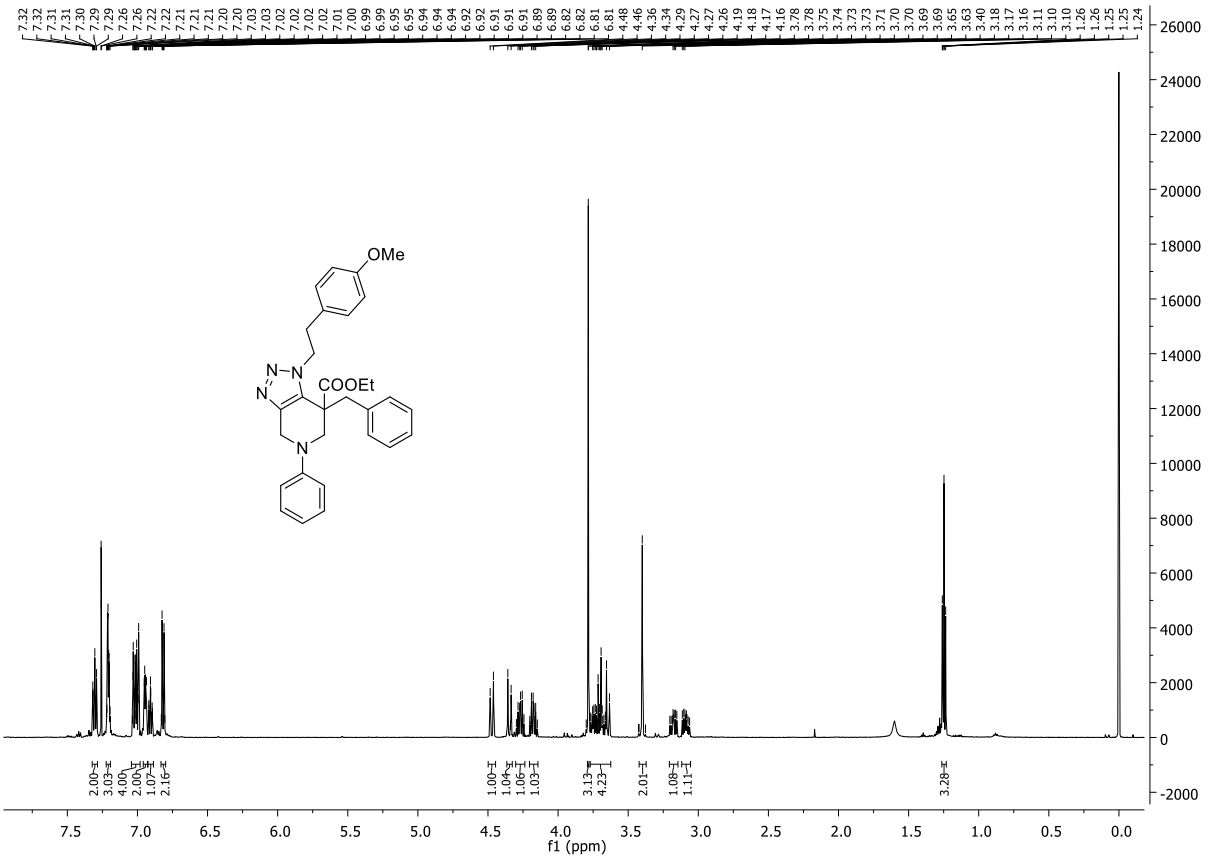
f1 (ppm)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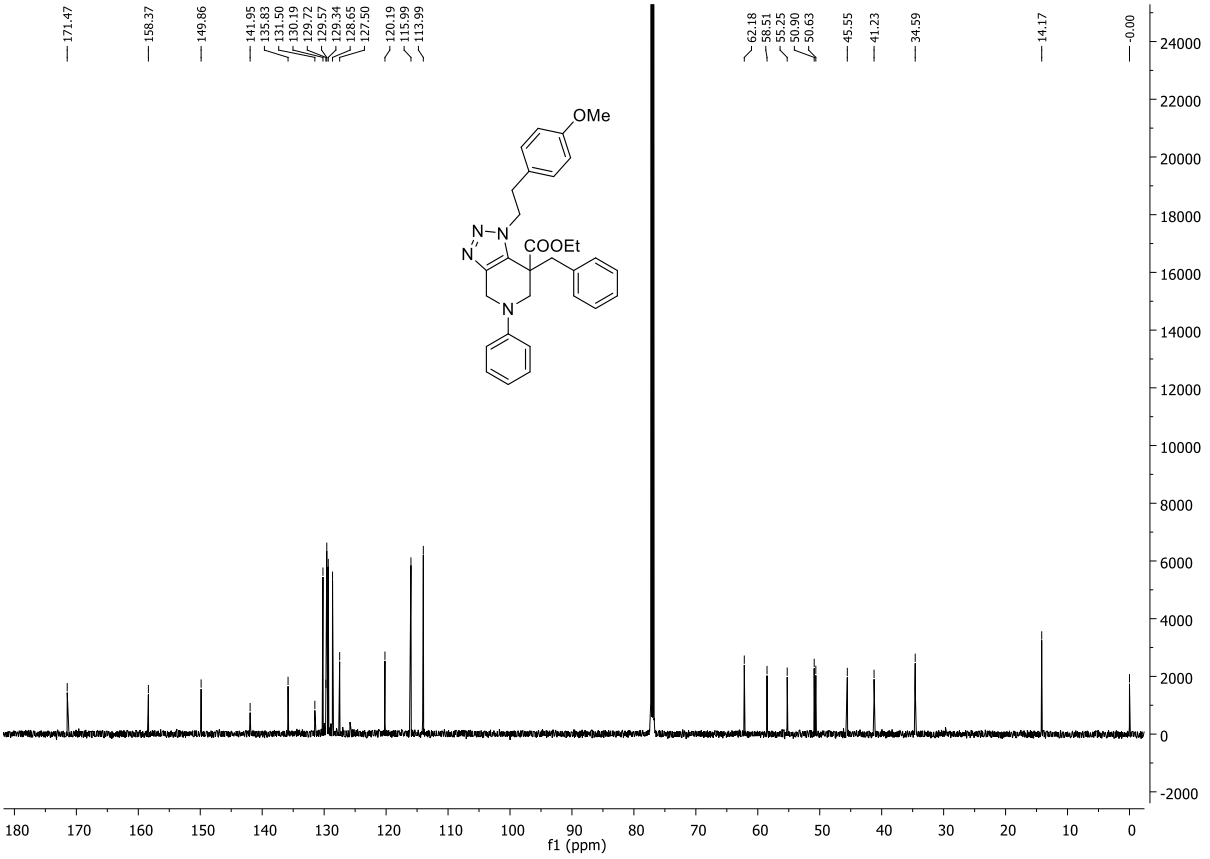
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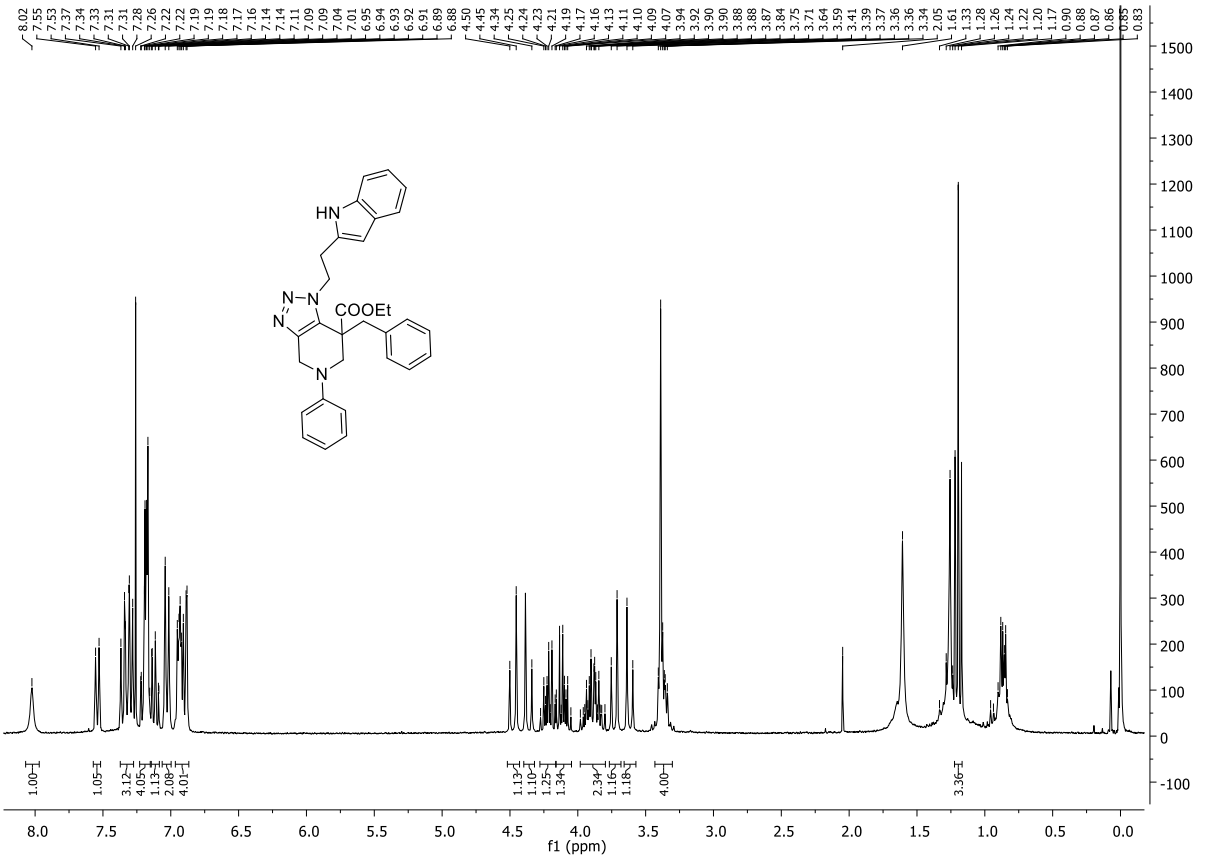
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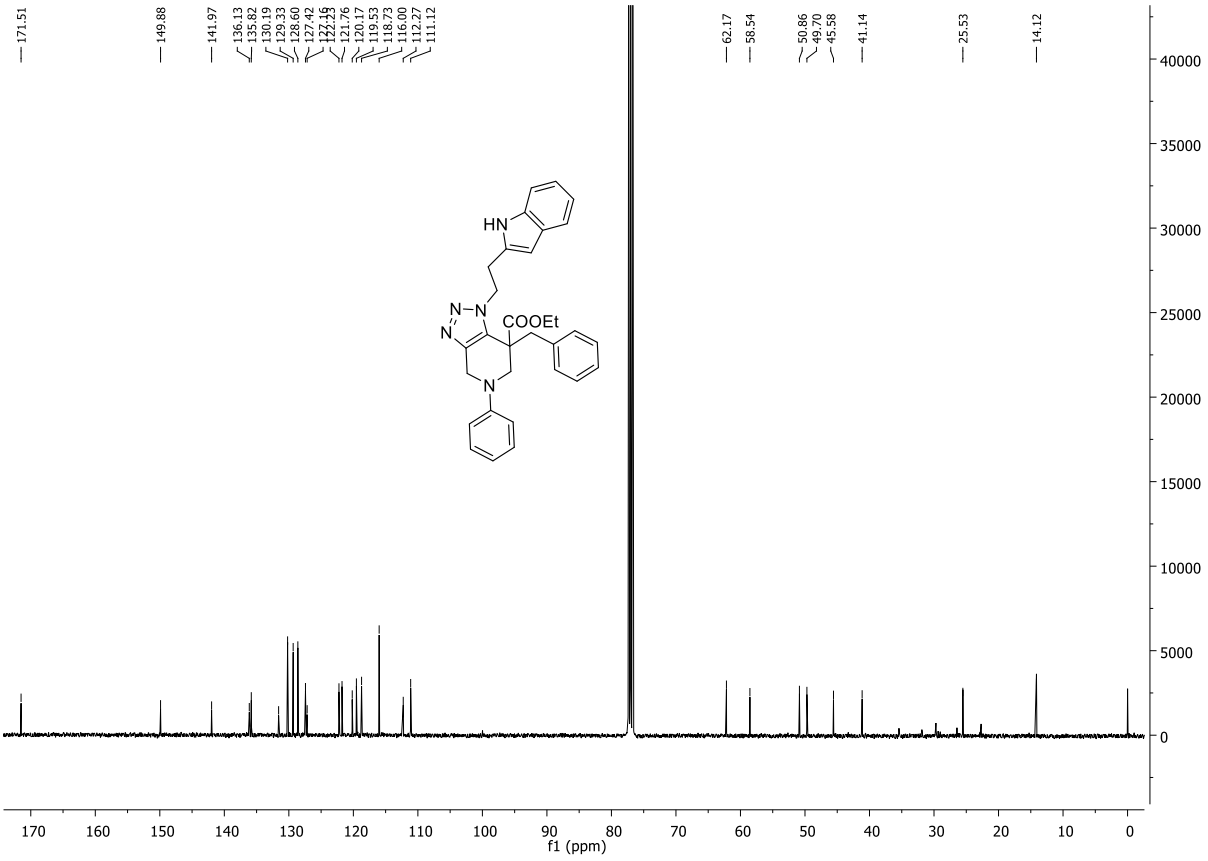
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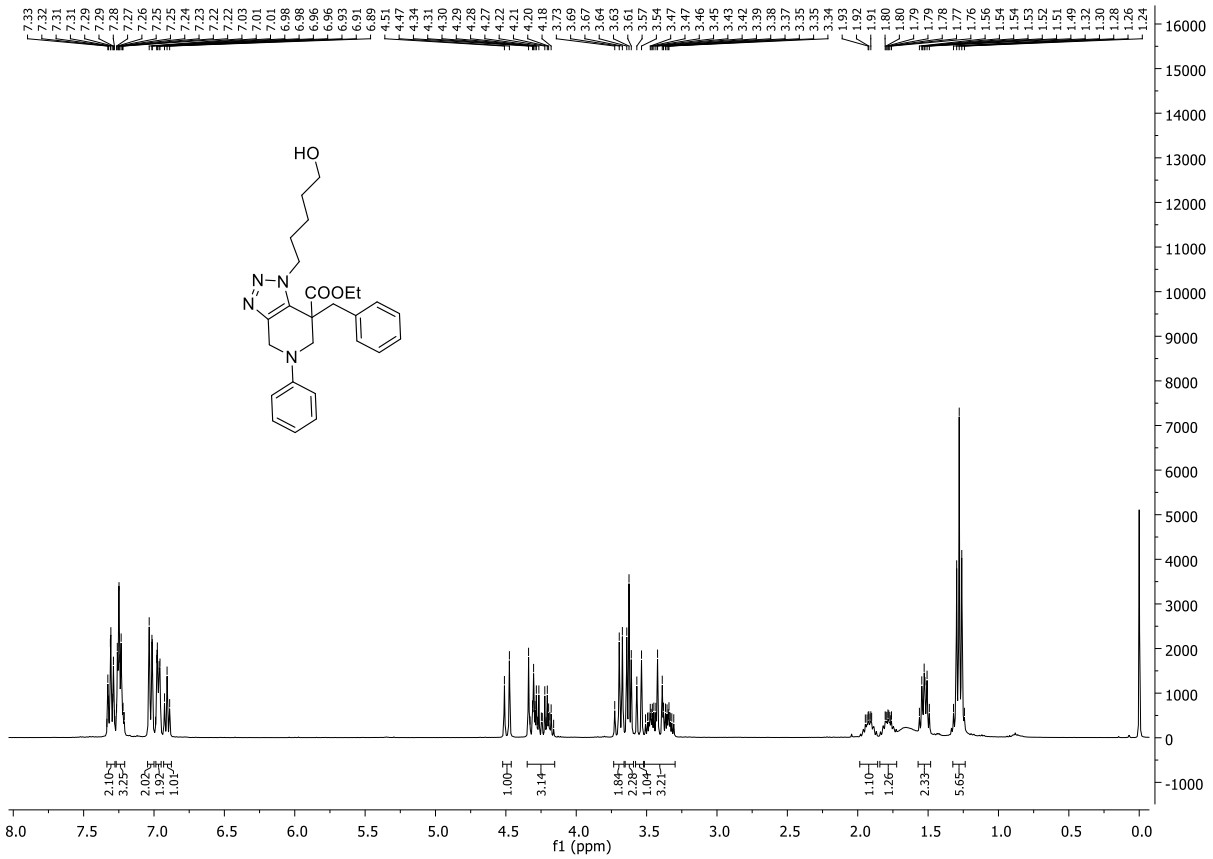
f1 (ppm)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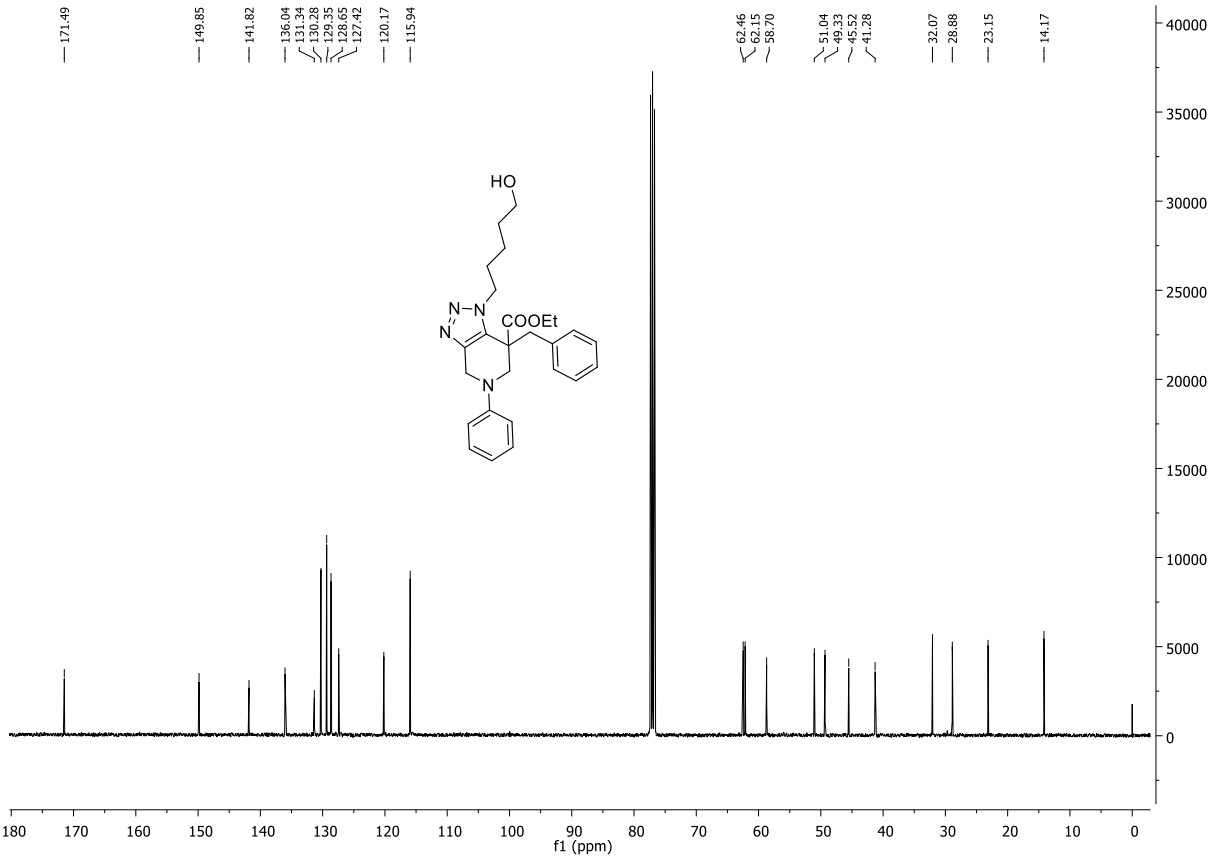
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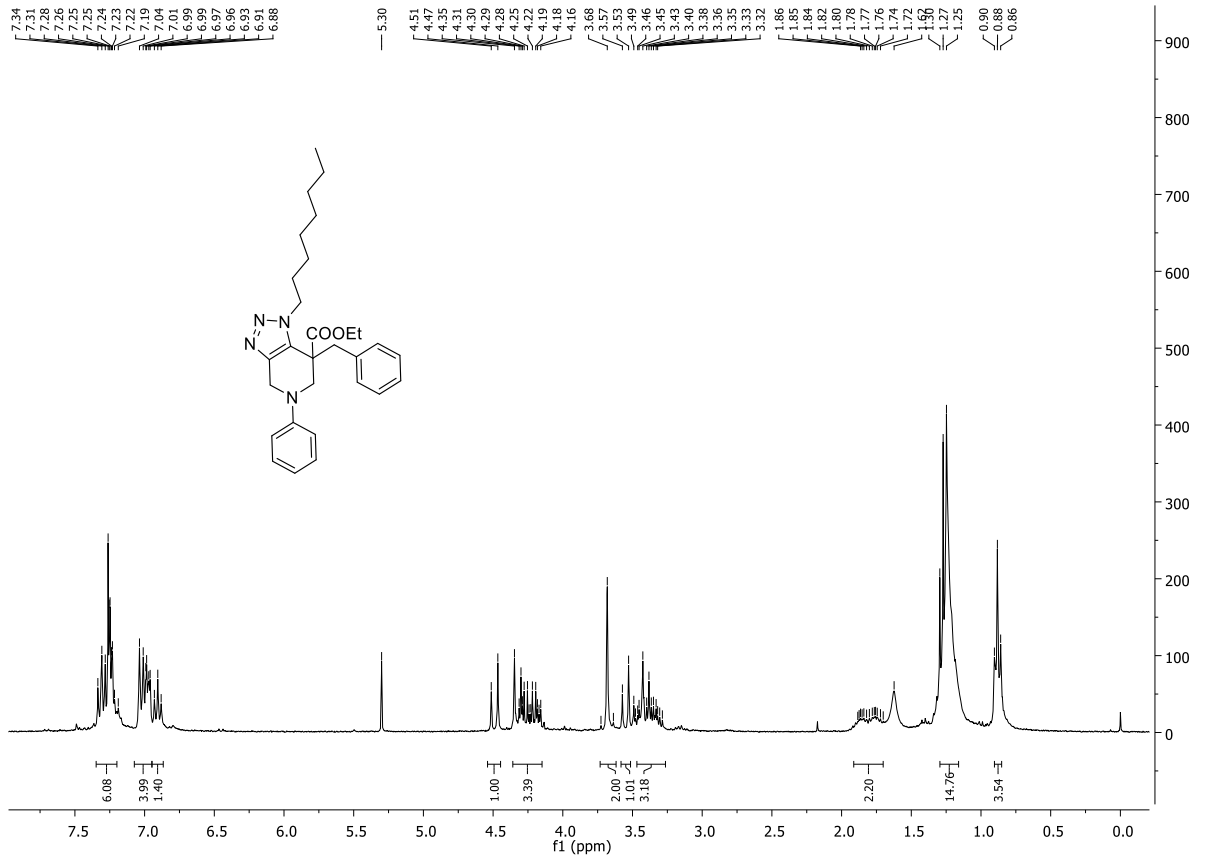
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0.88
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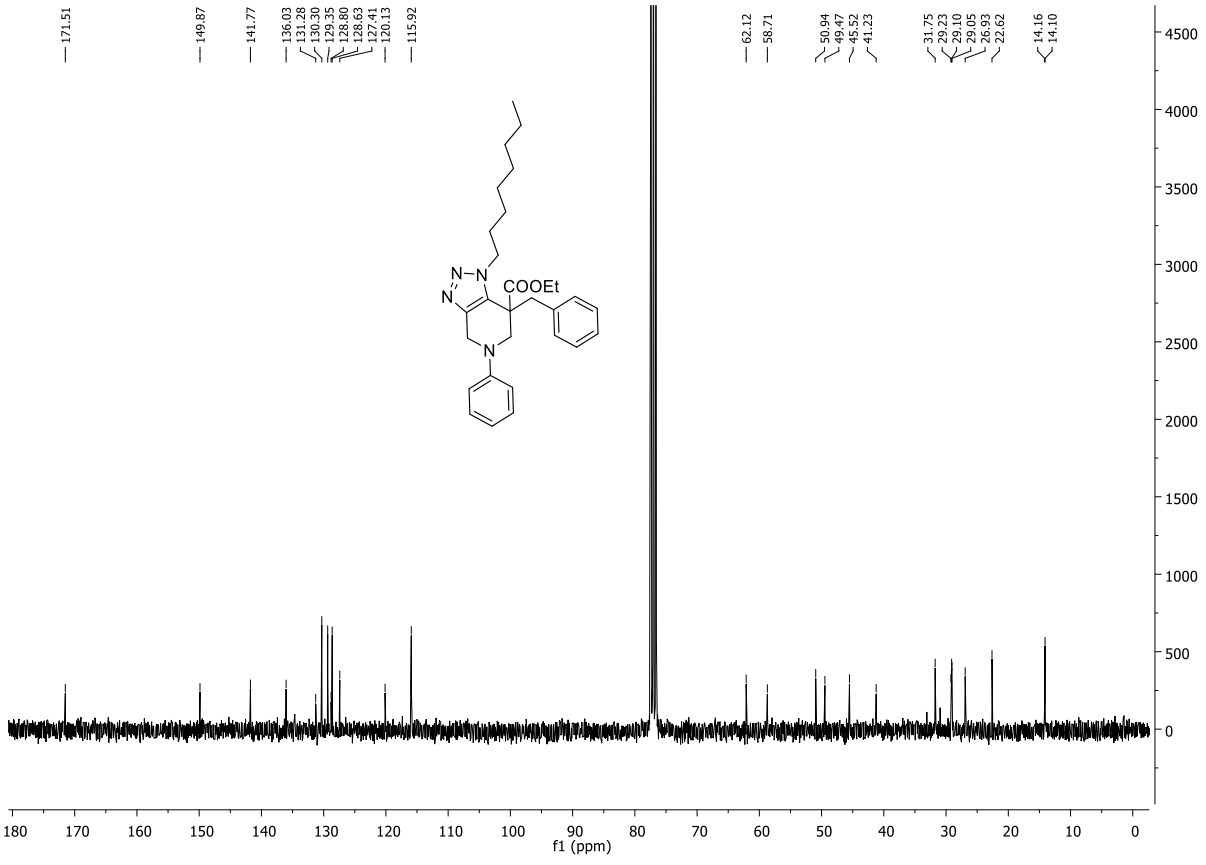
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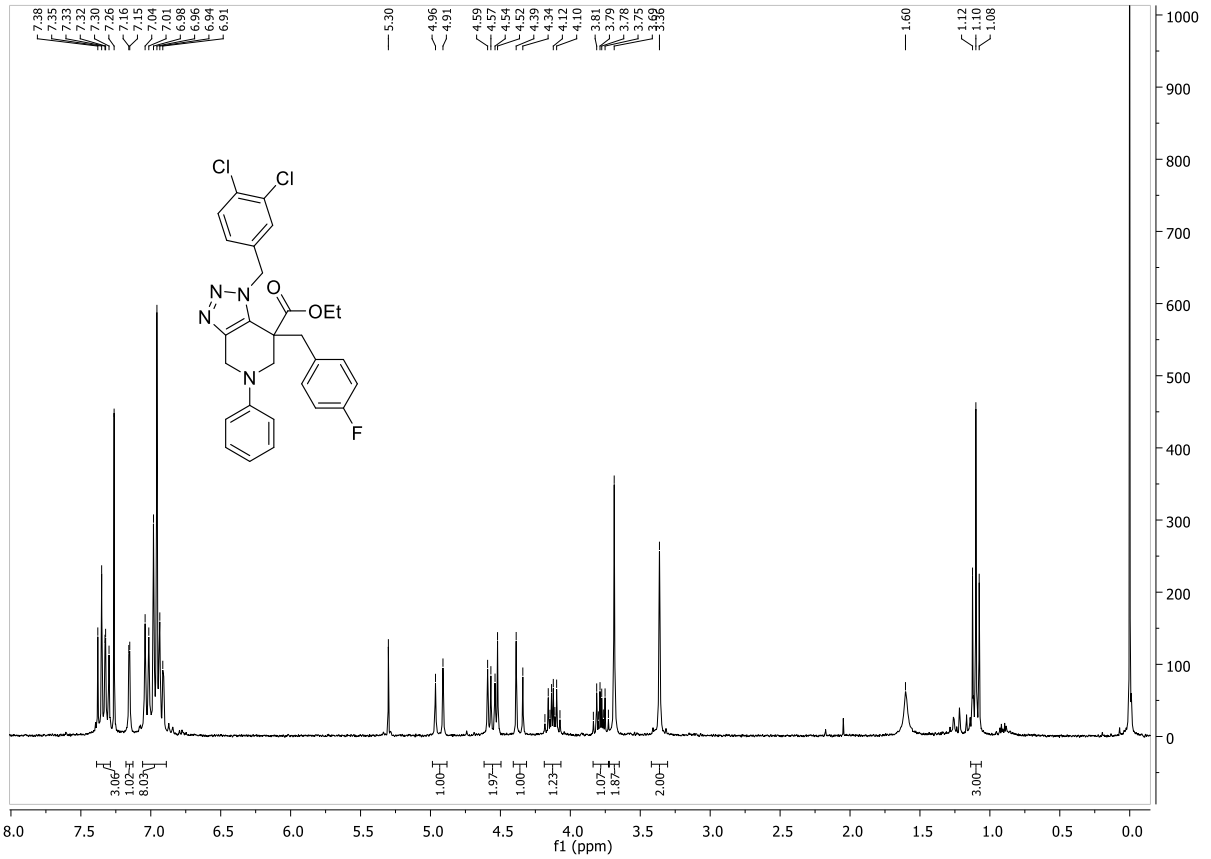
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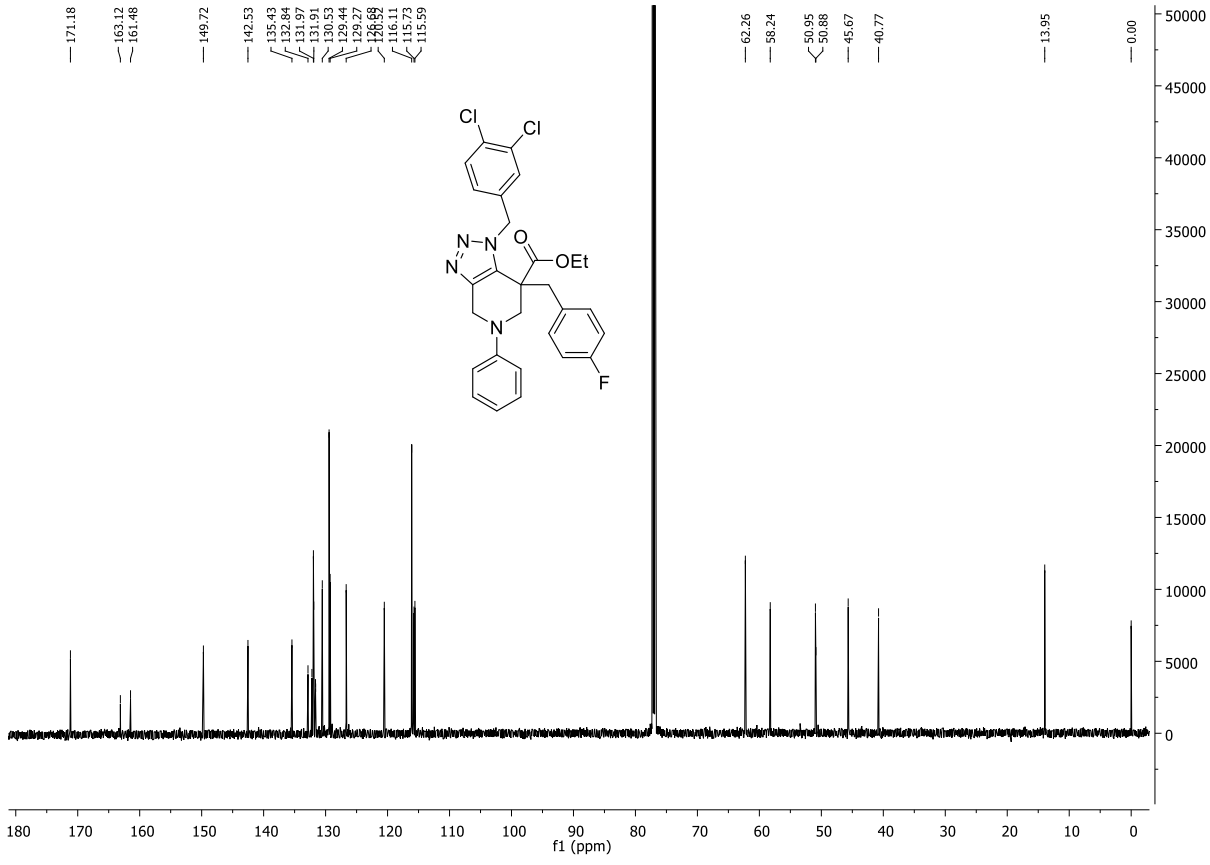
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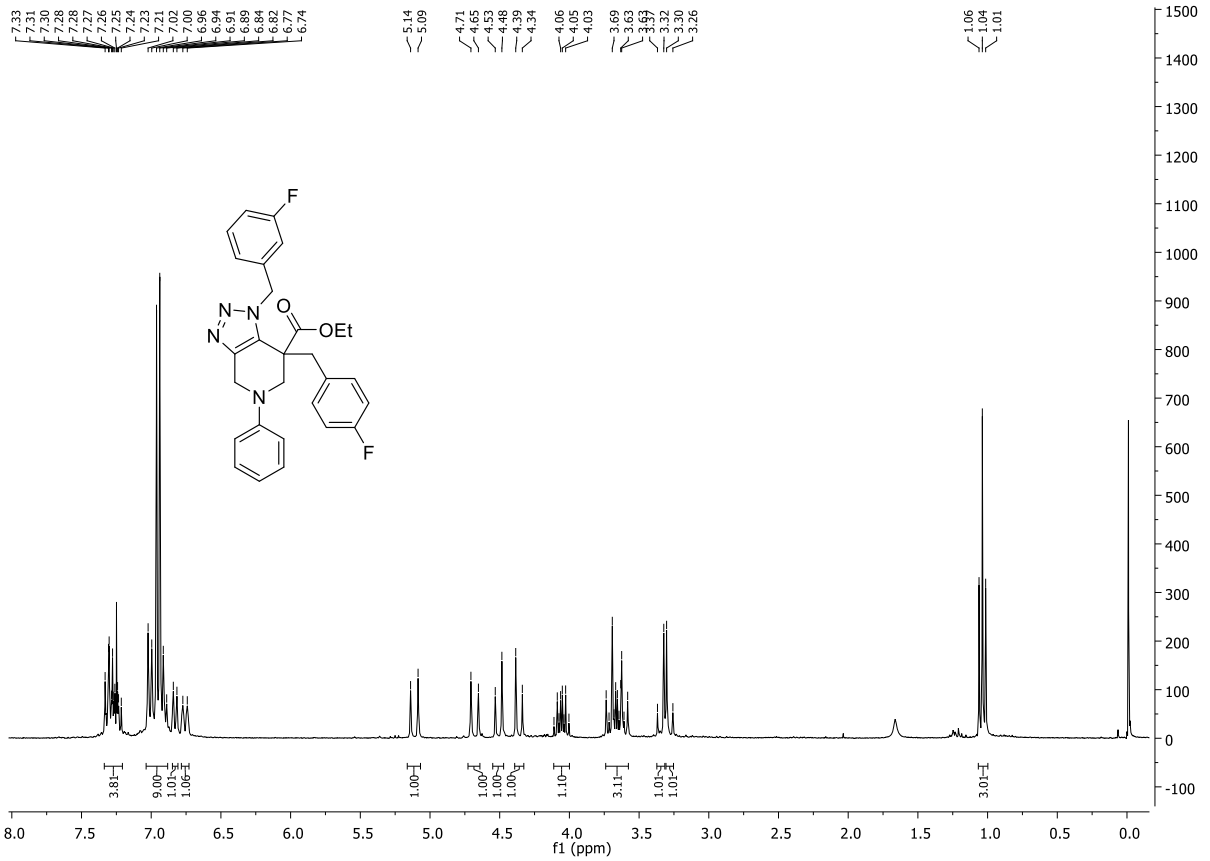
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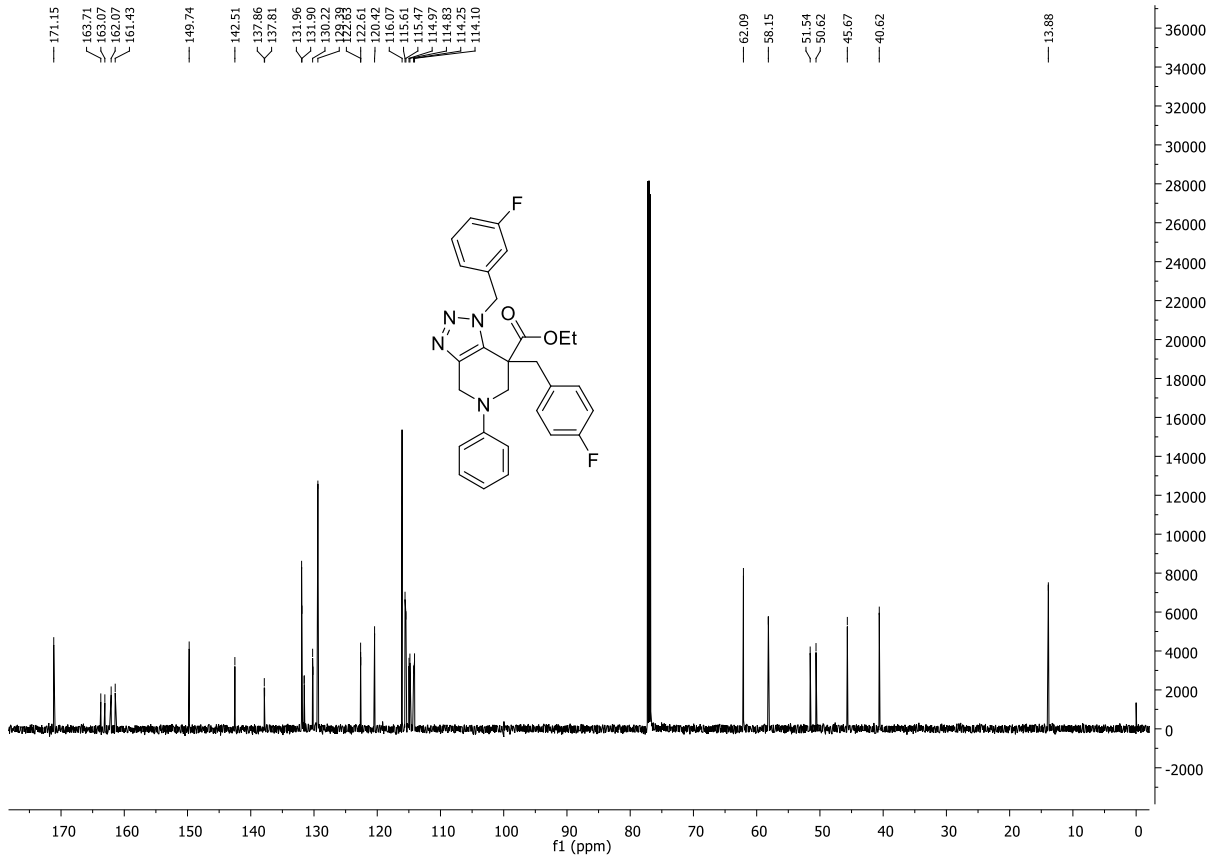
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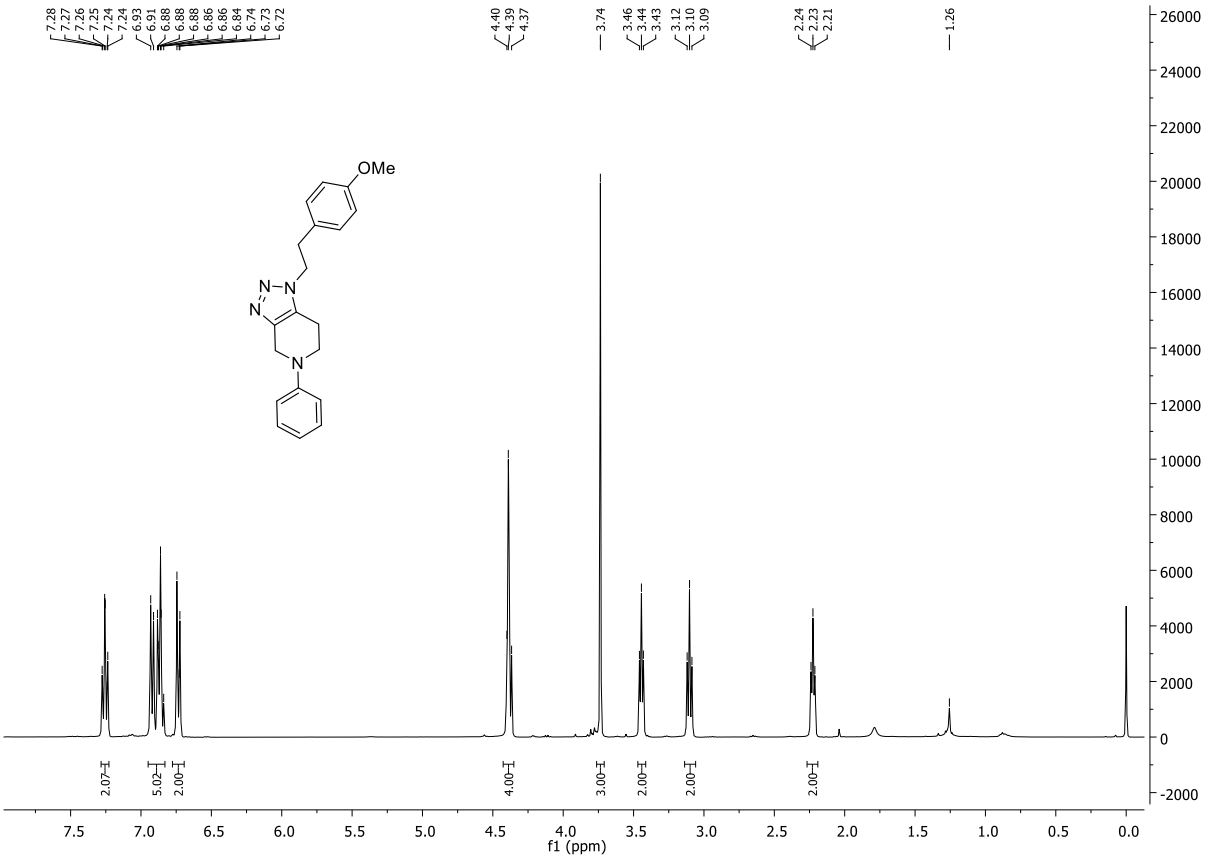
f1 (ppm)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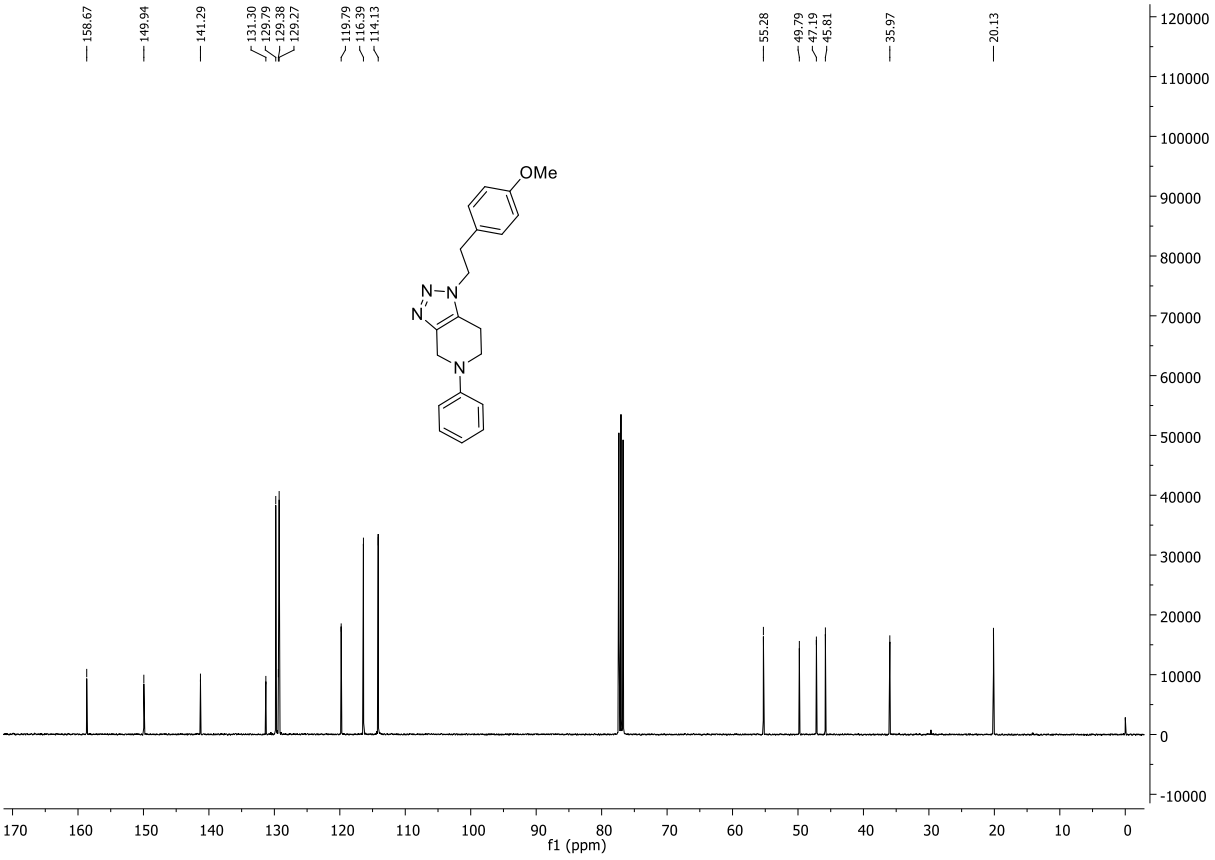
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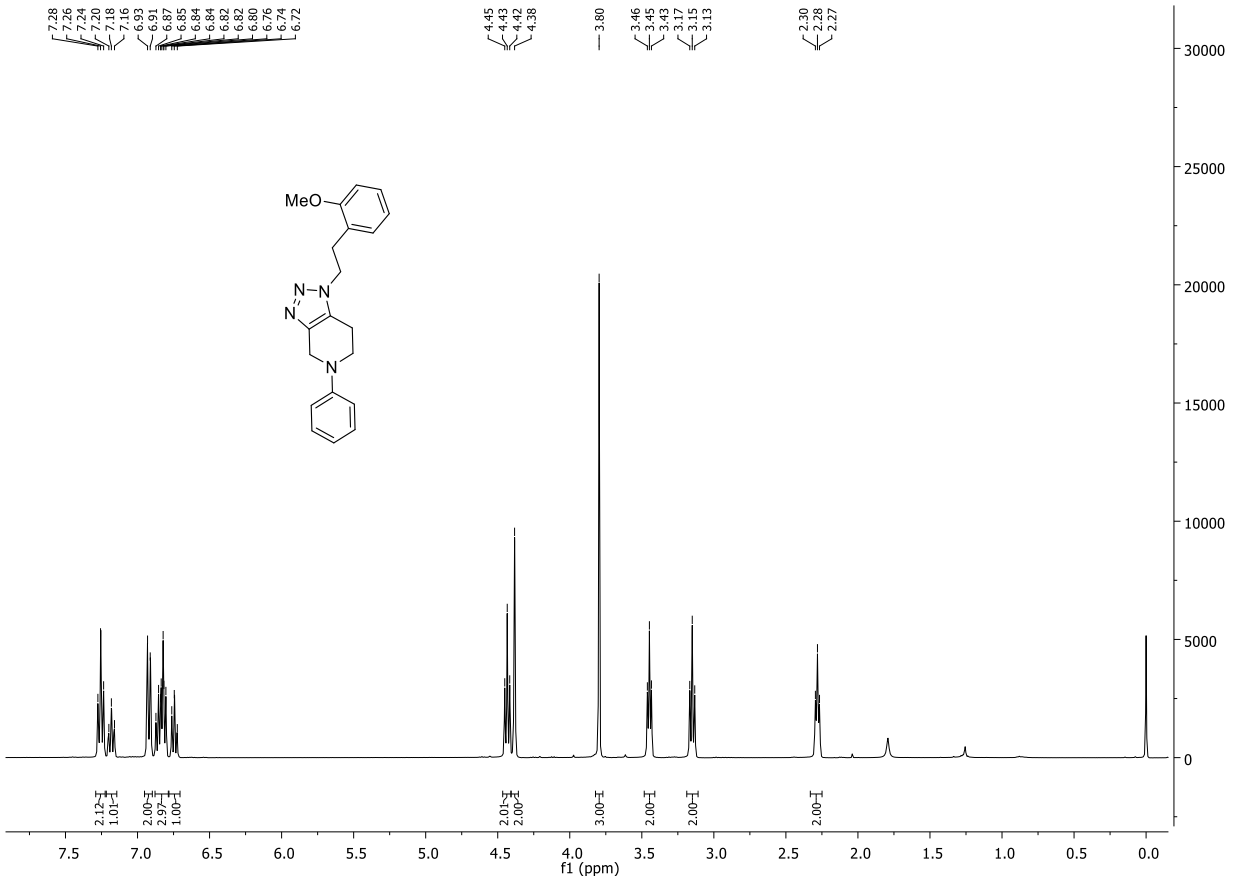
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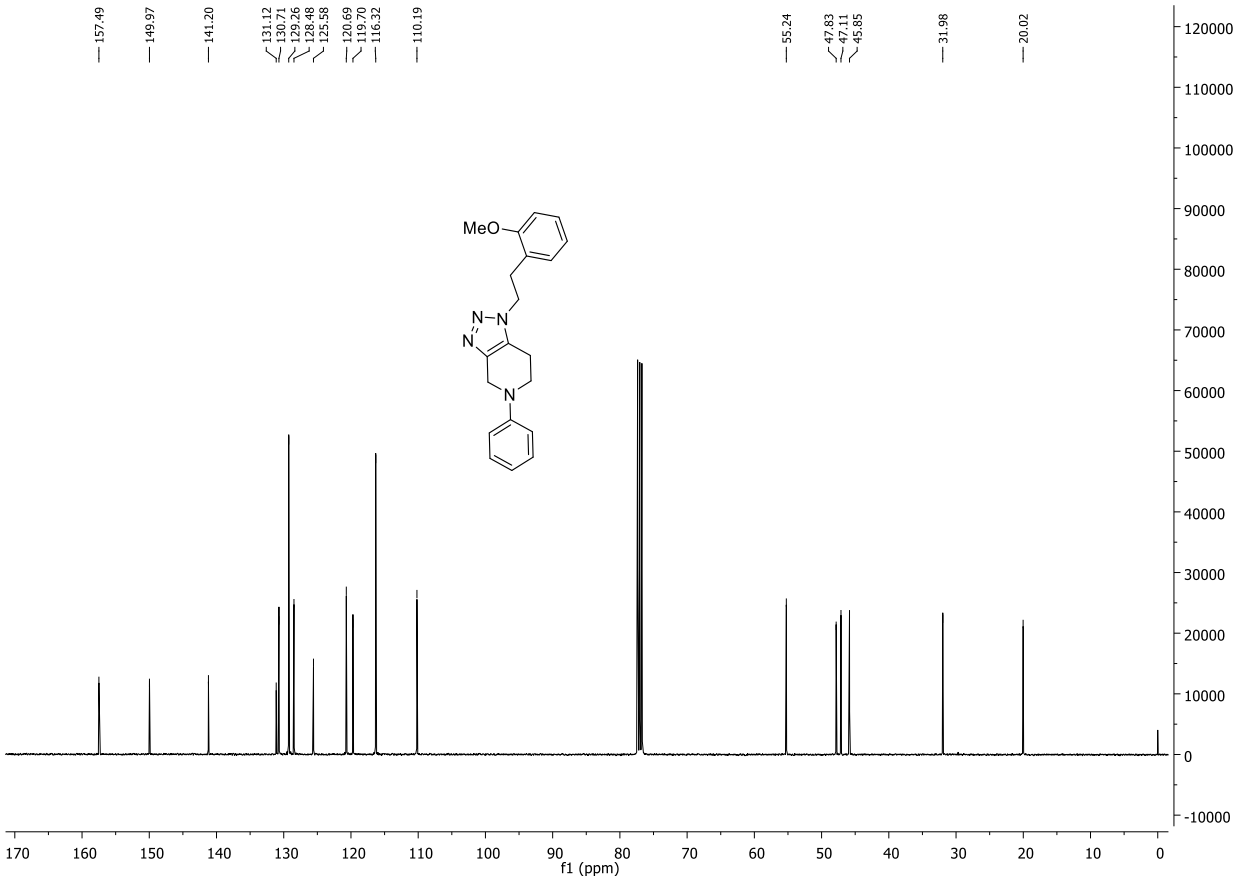
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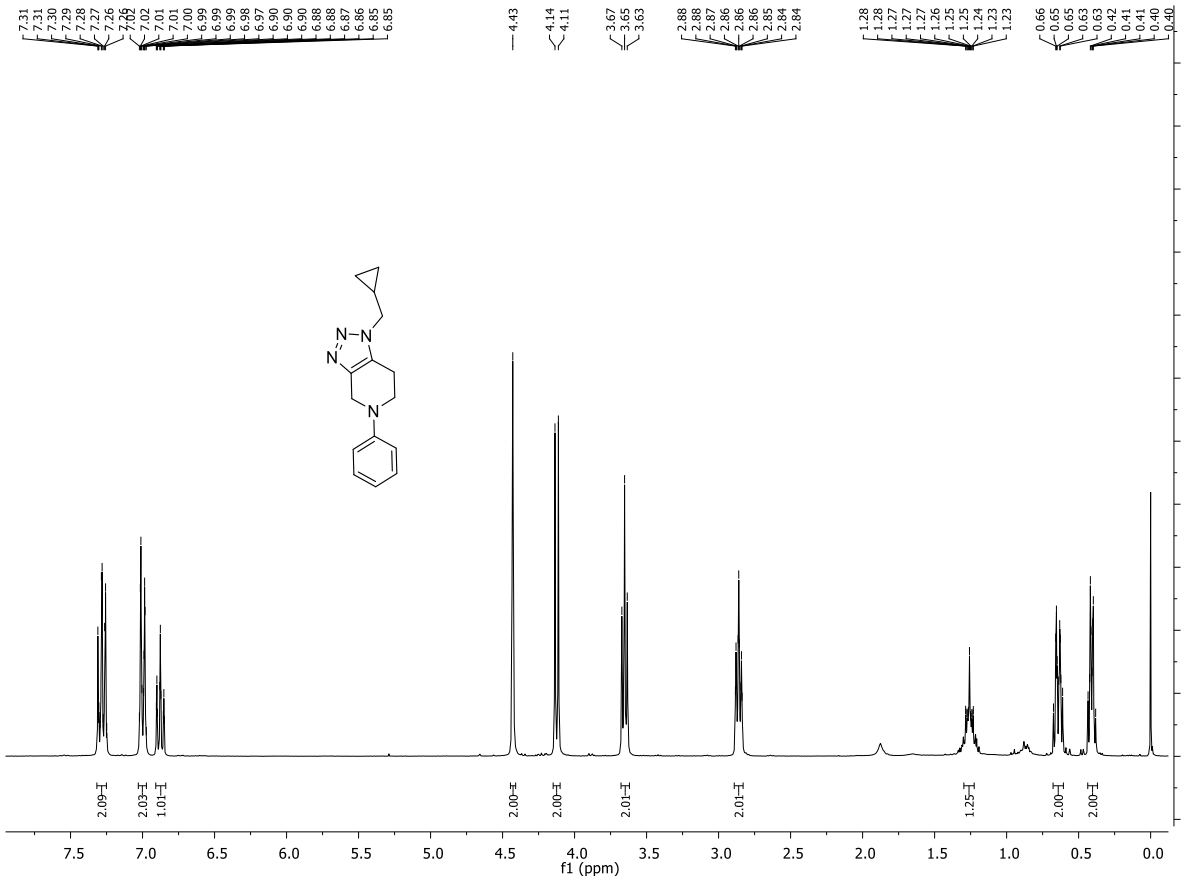
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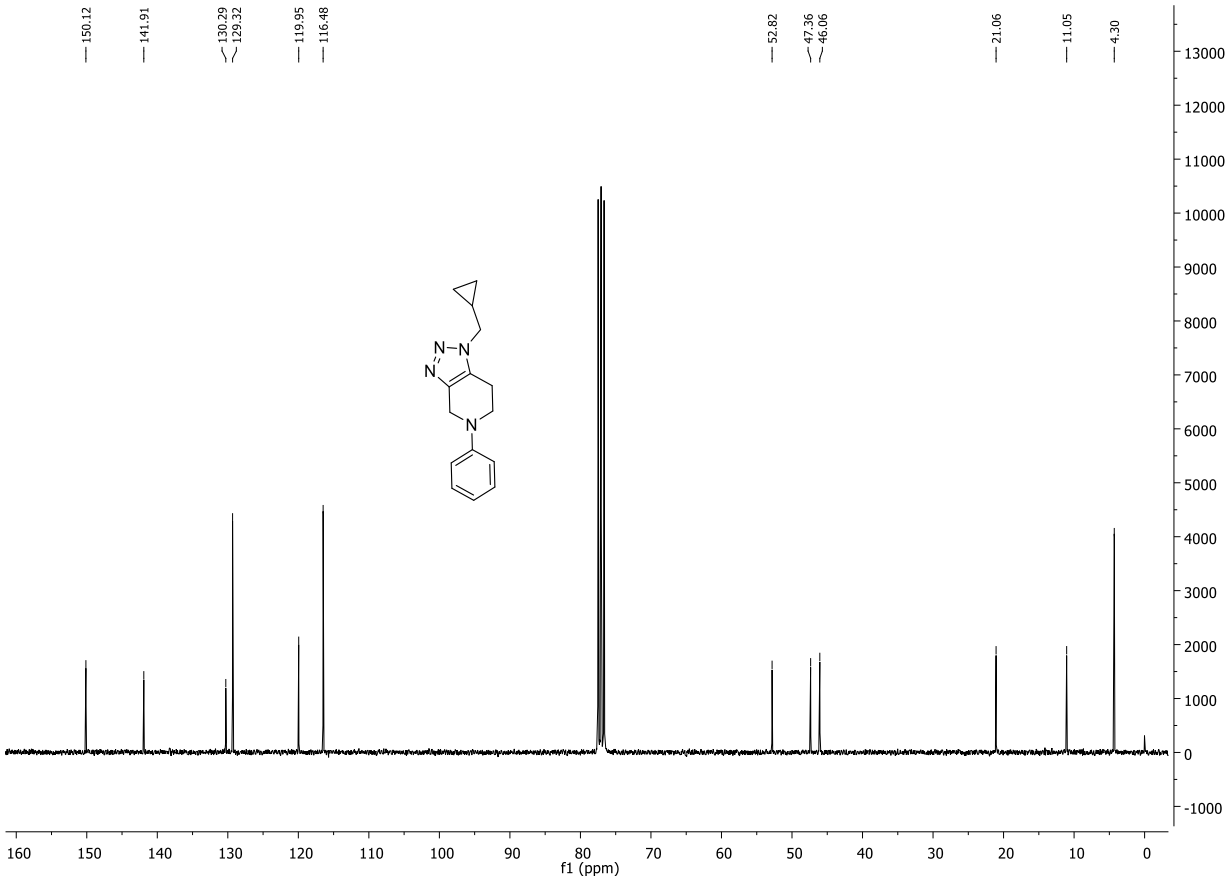
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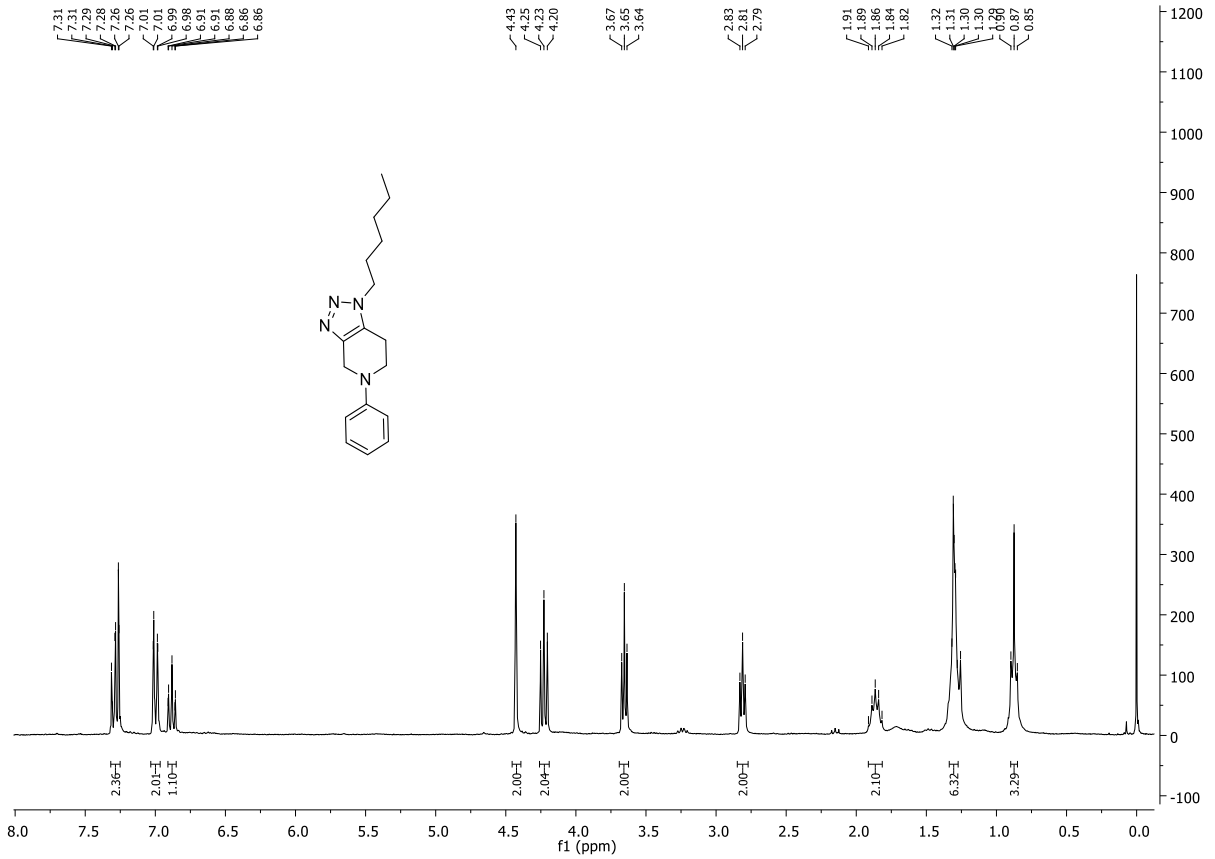
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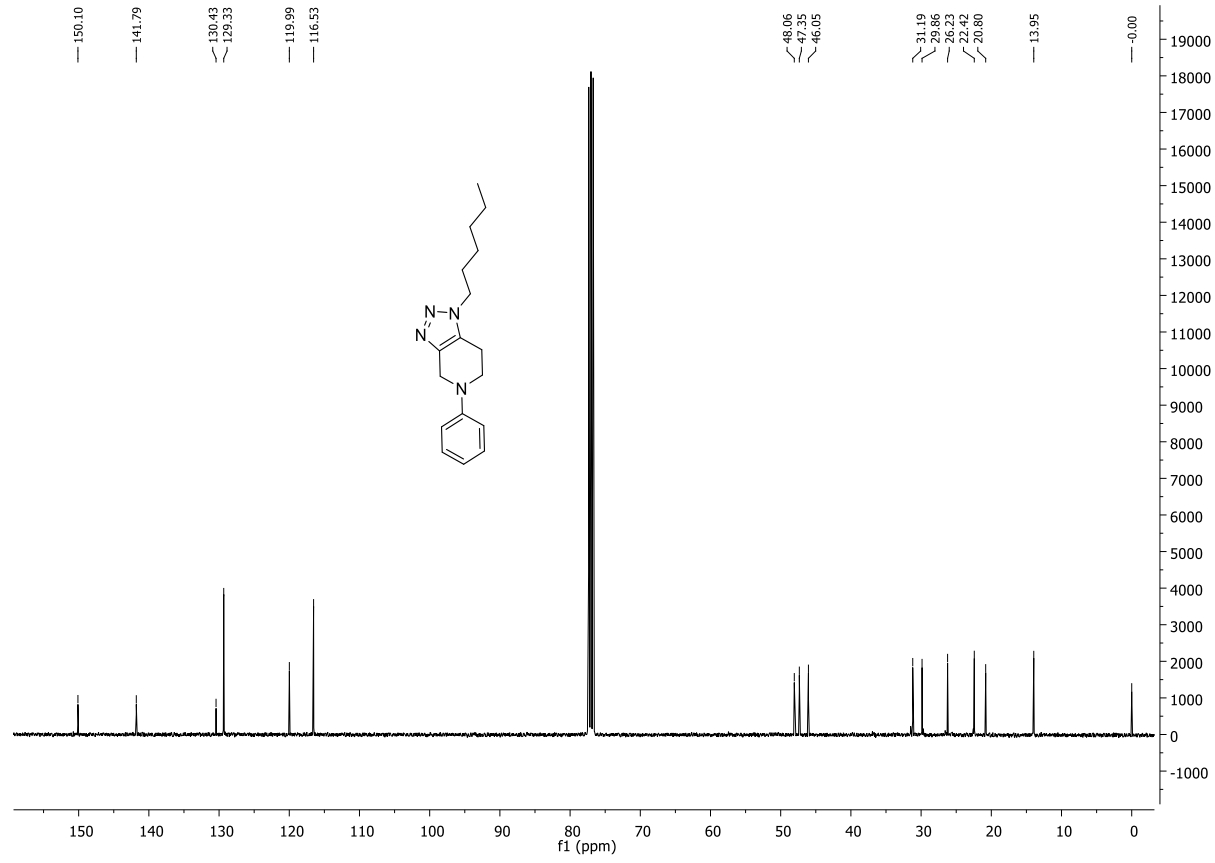
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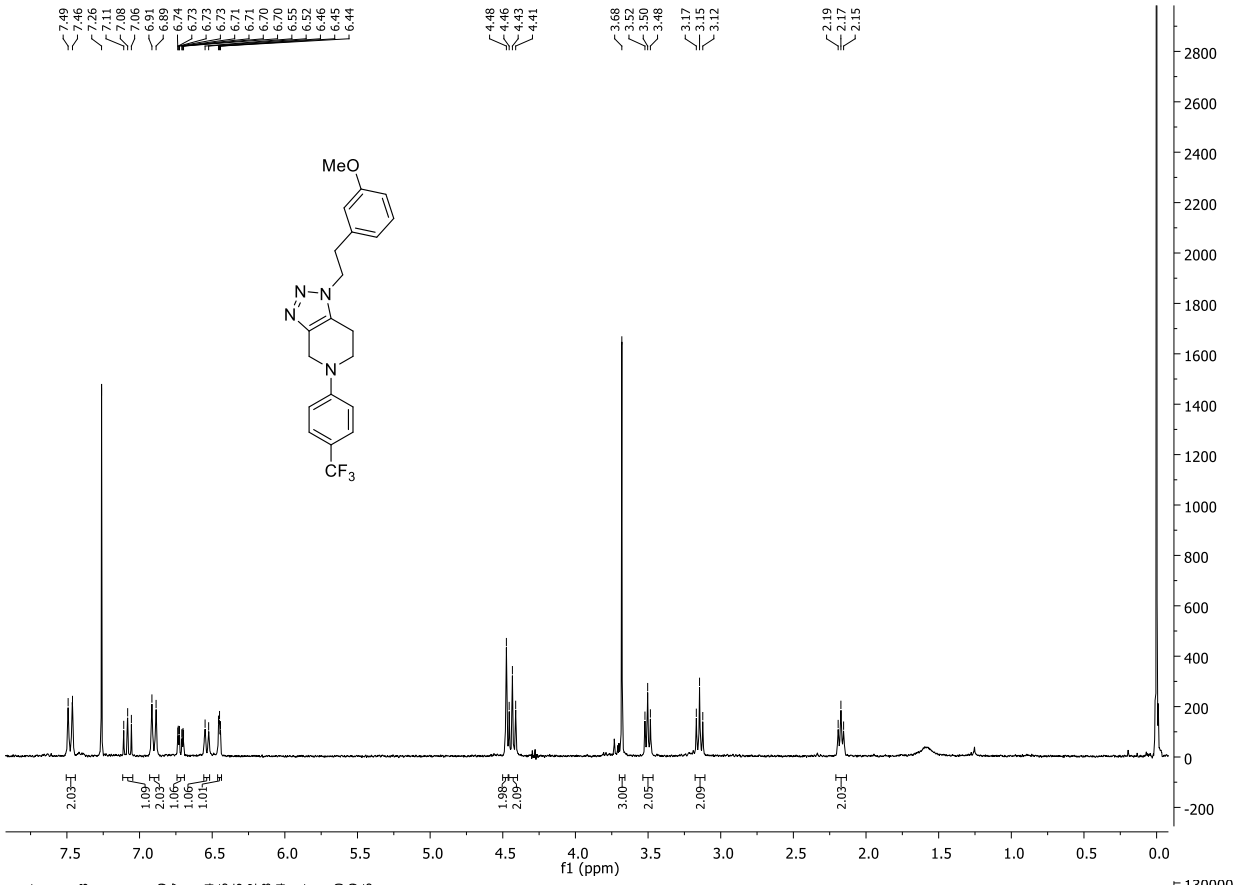
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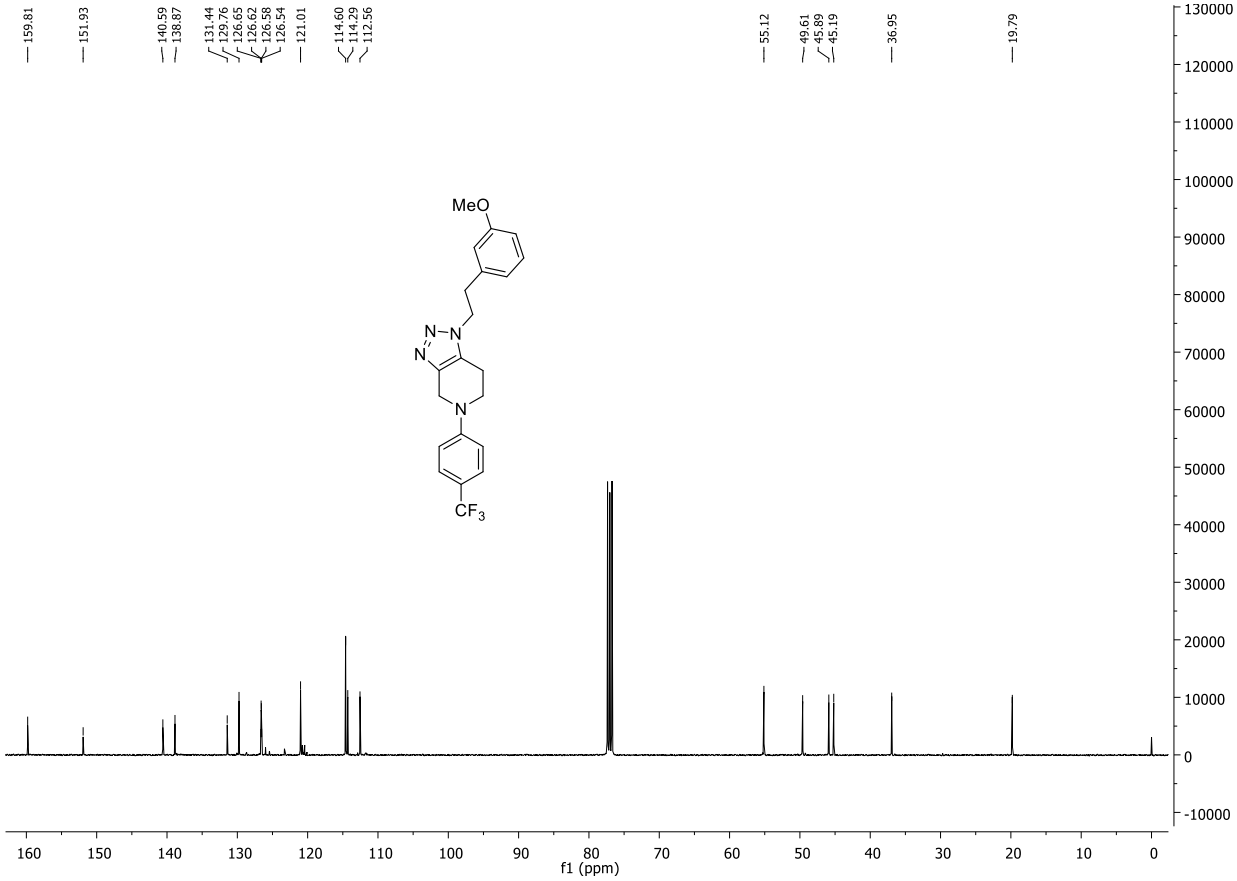
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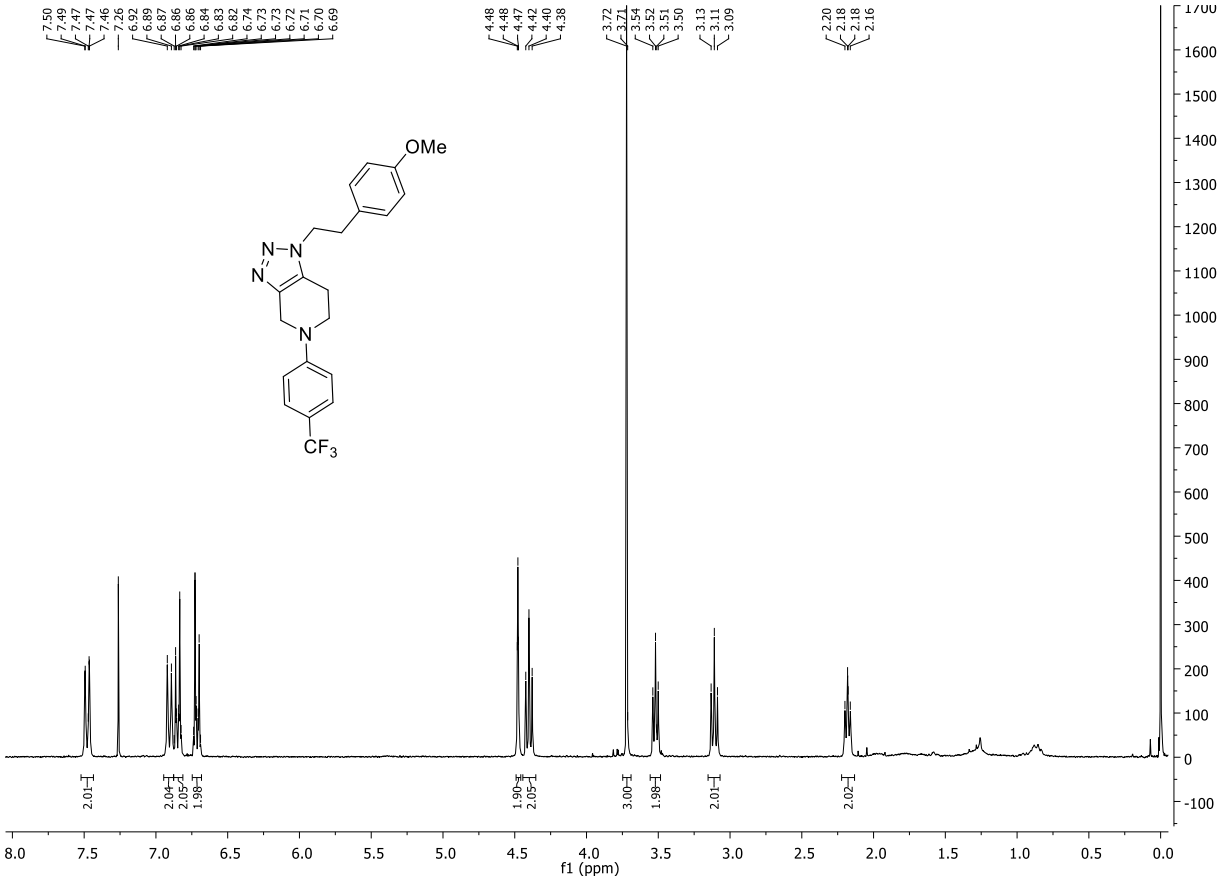
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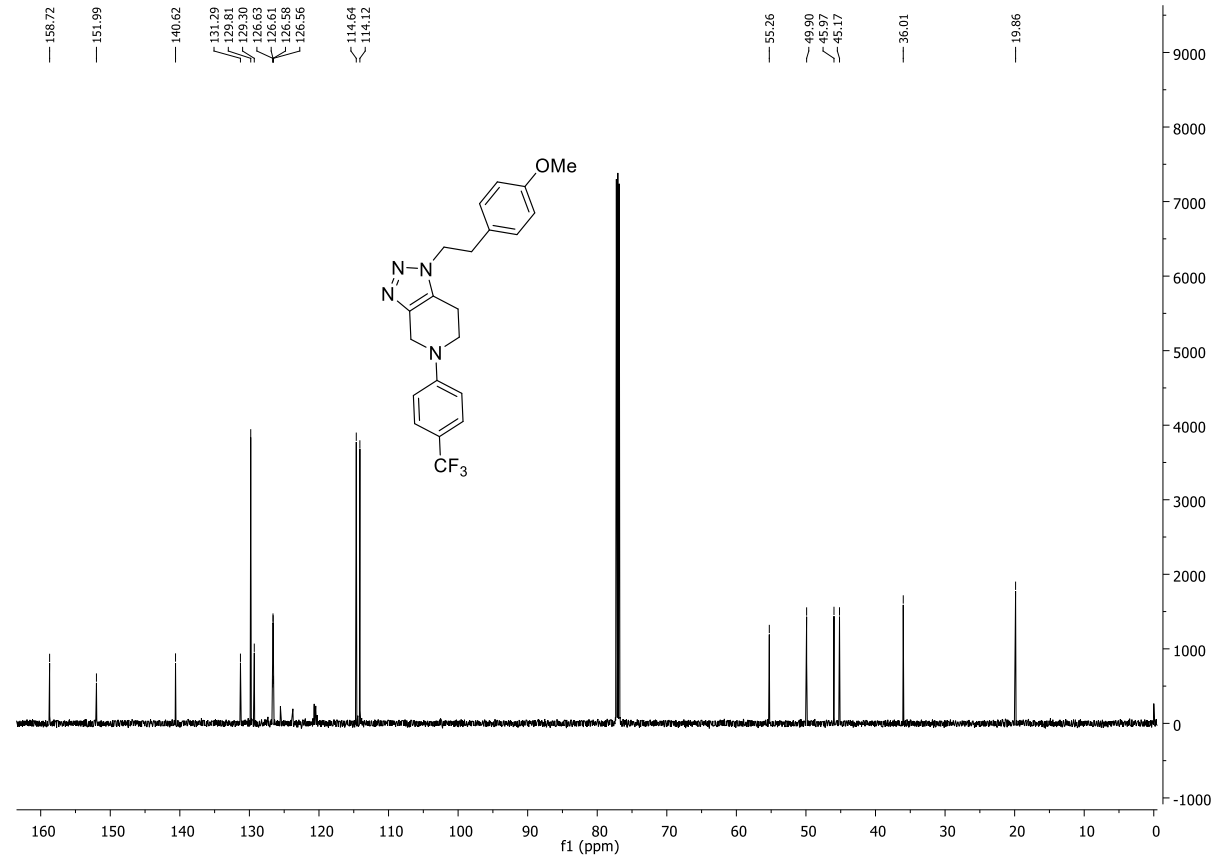
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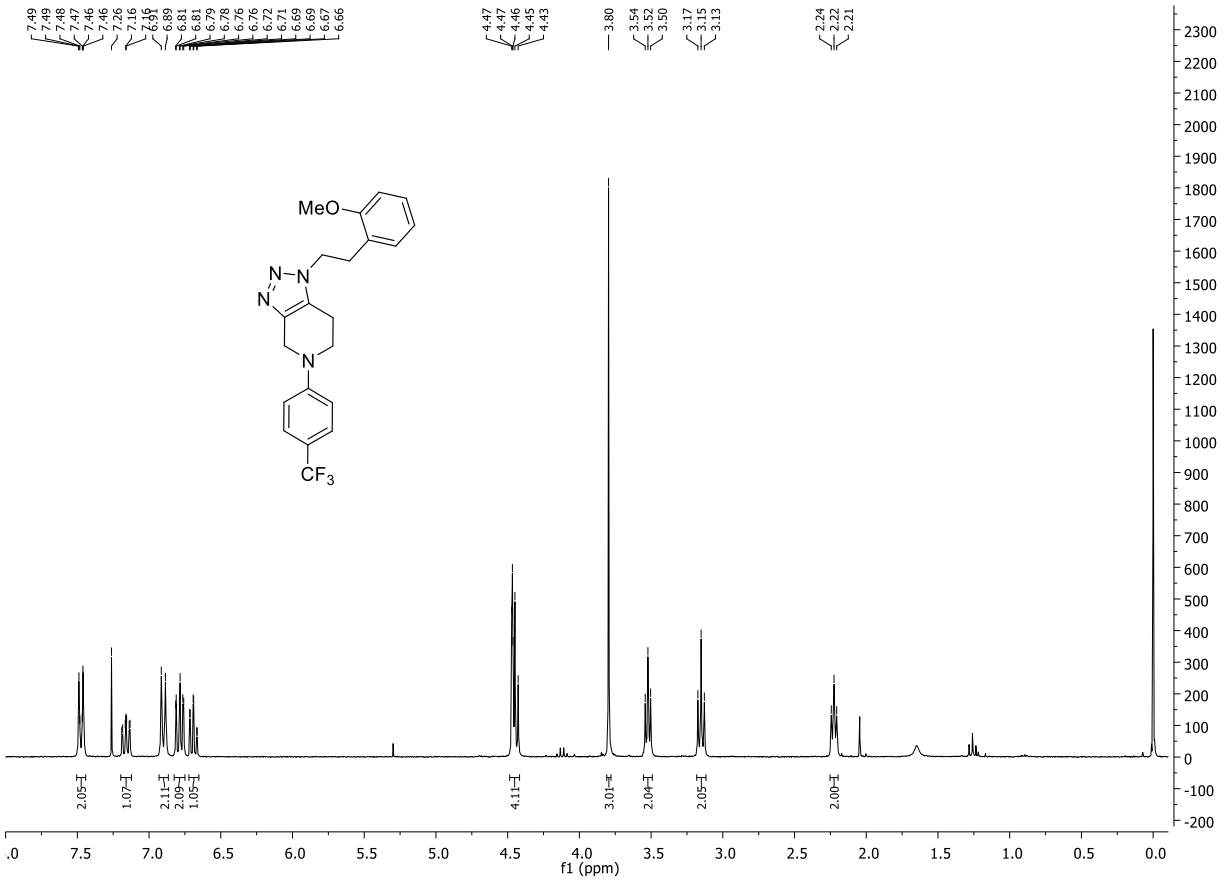
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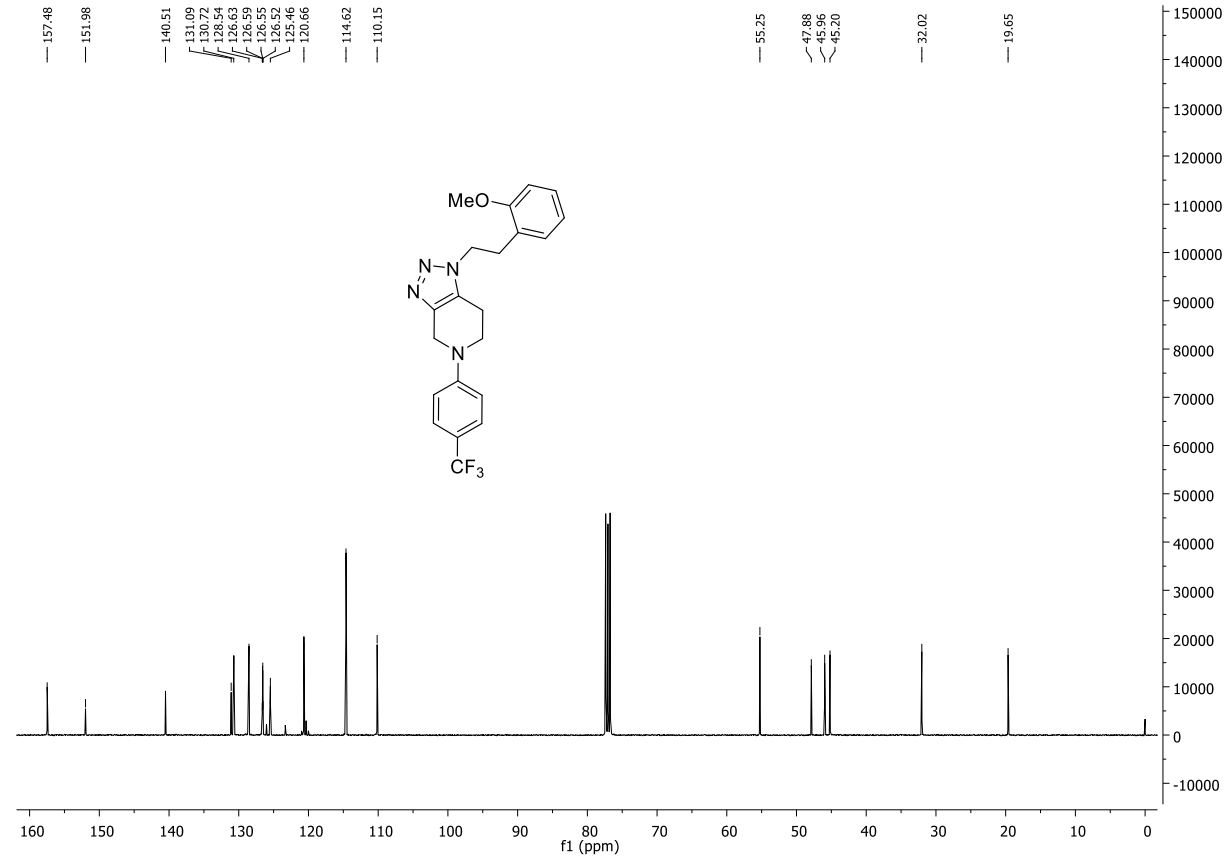
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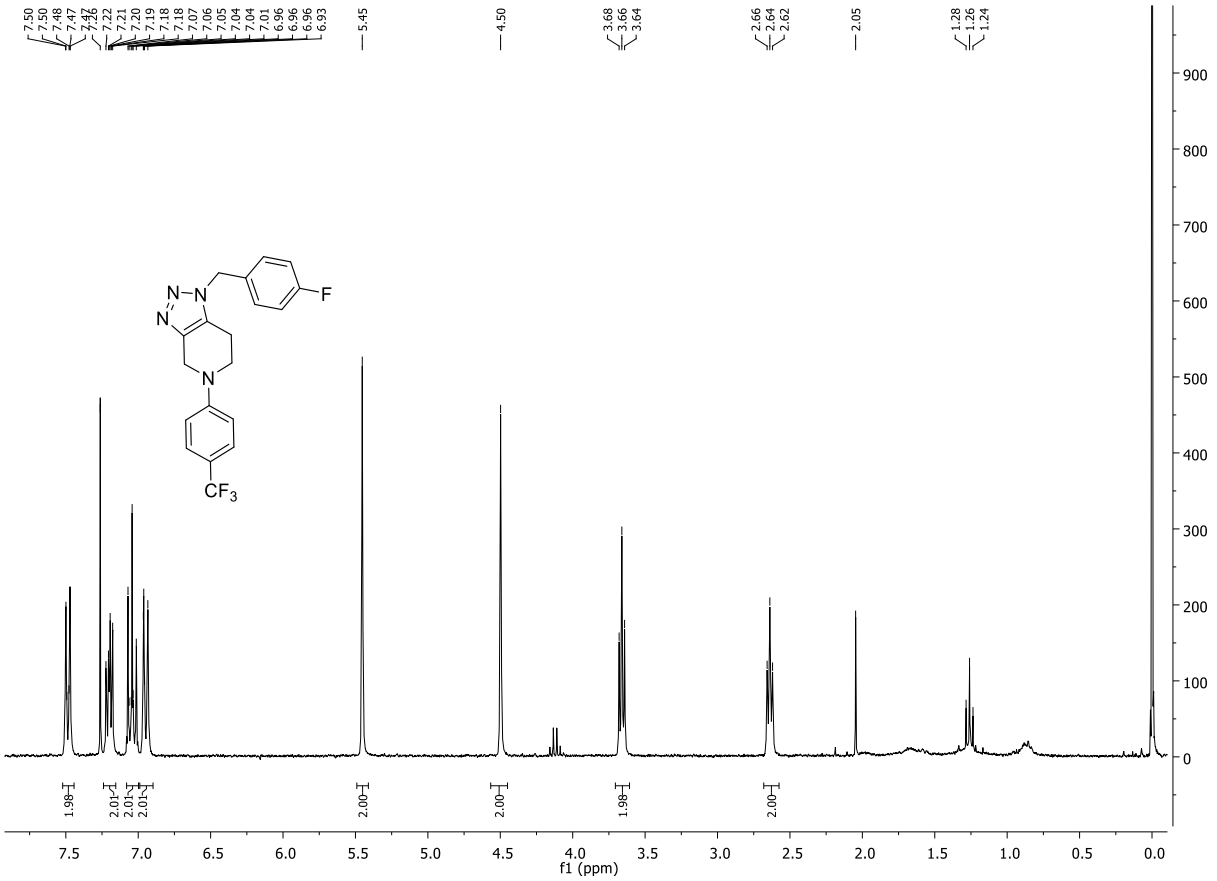
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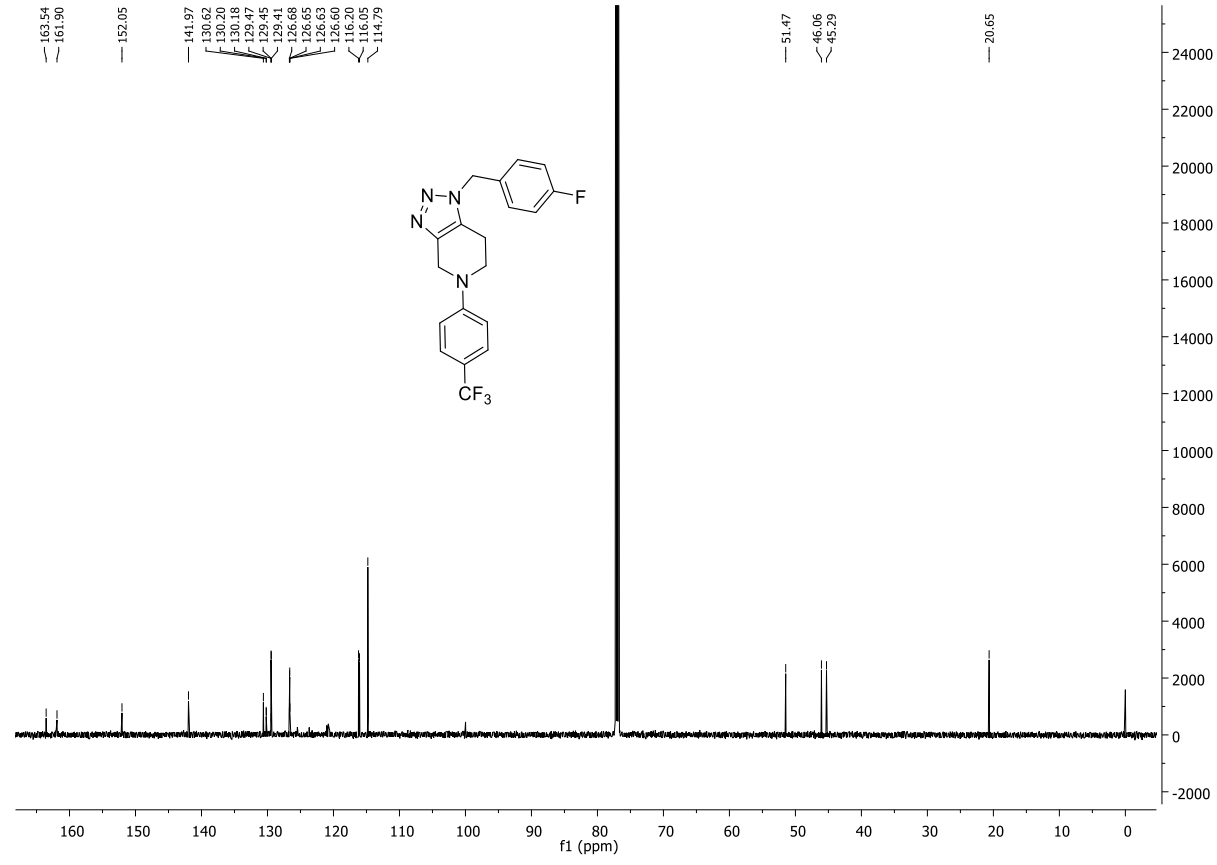
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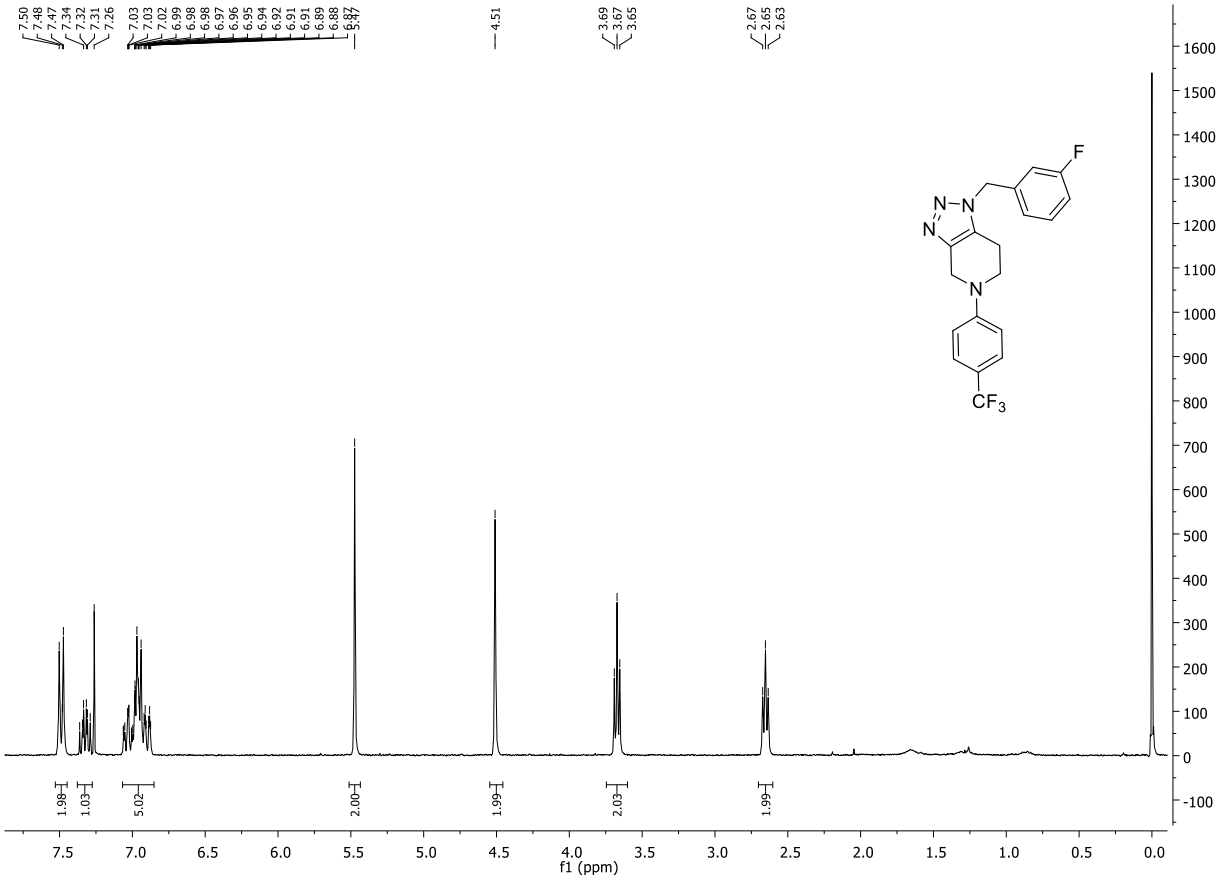
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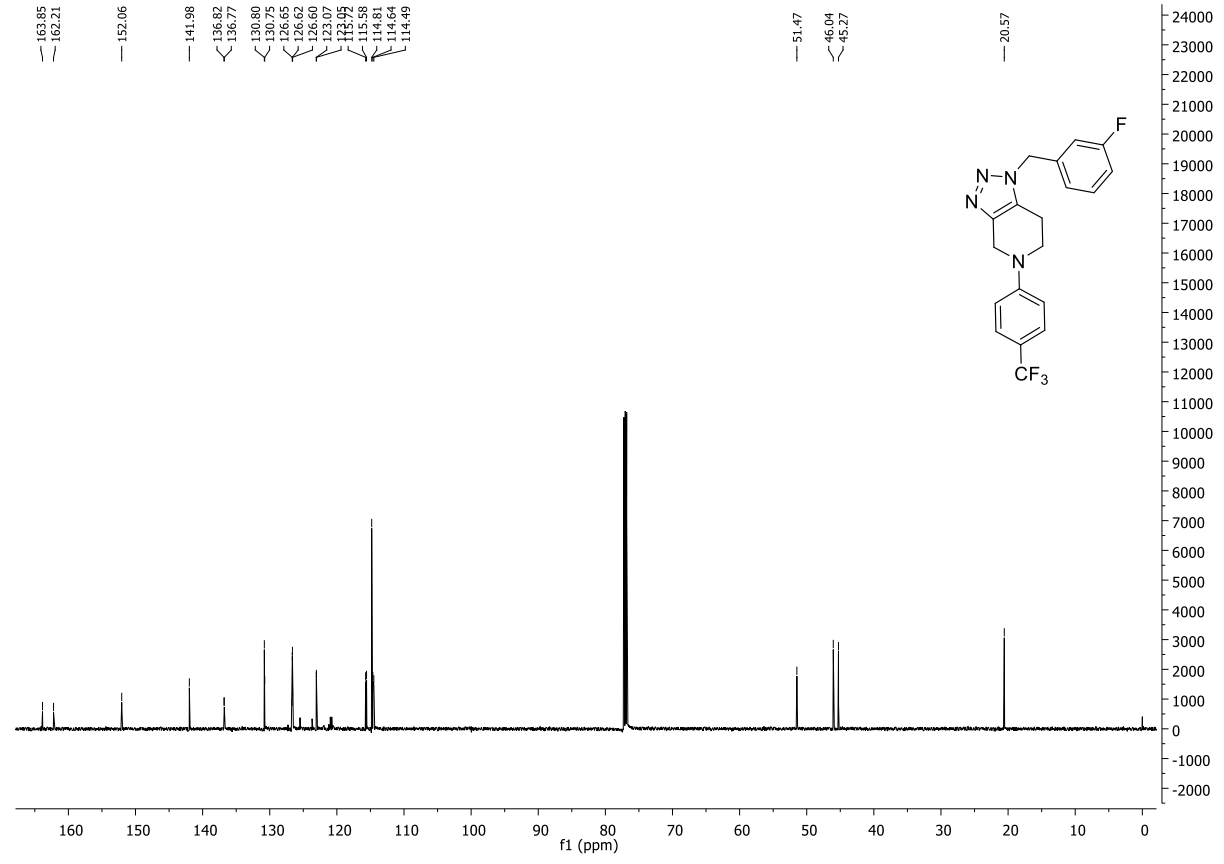
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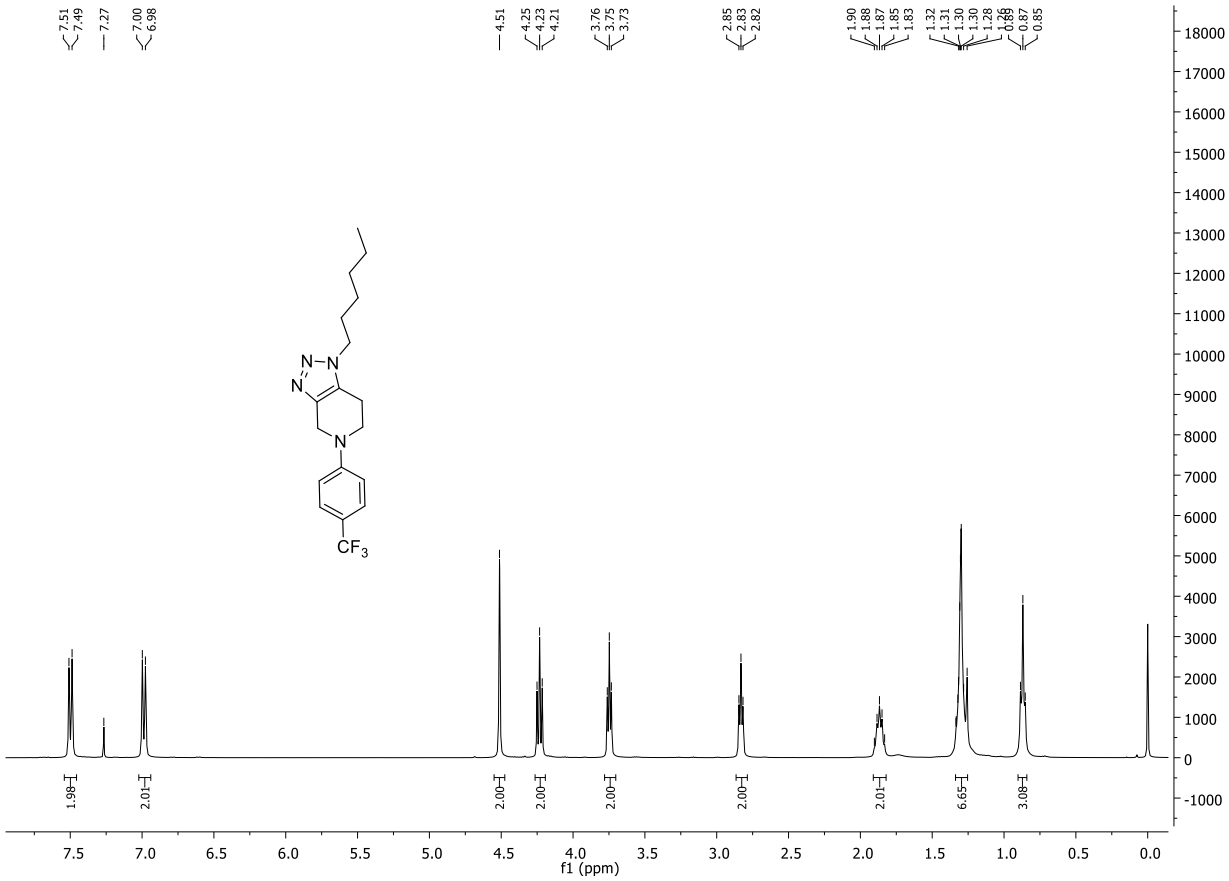
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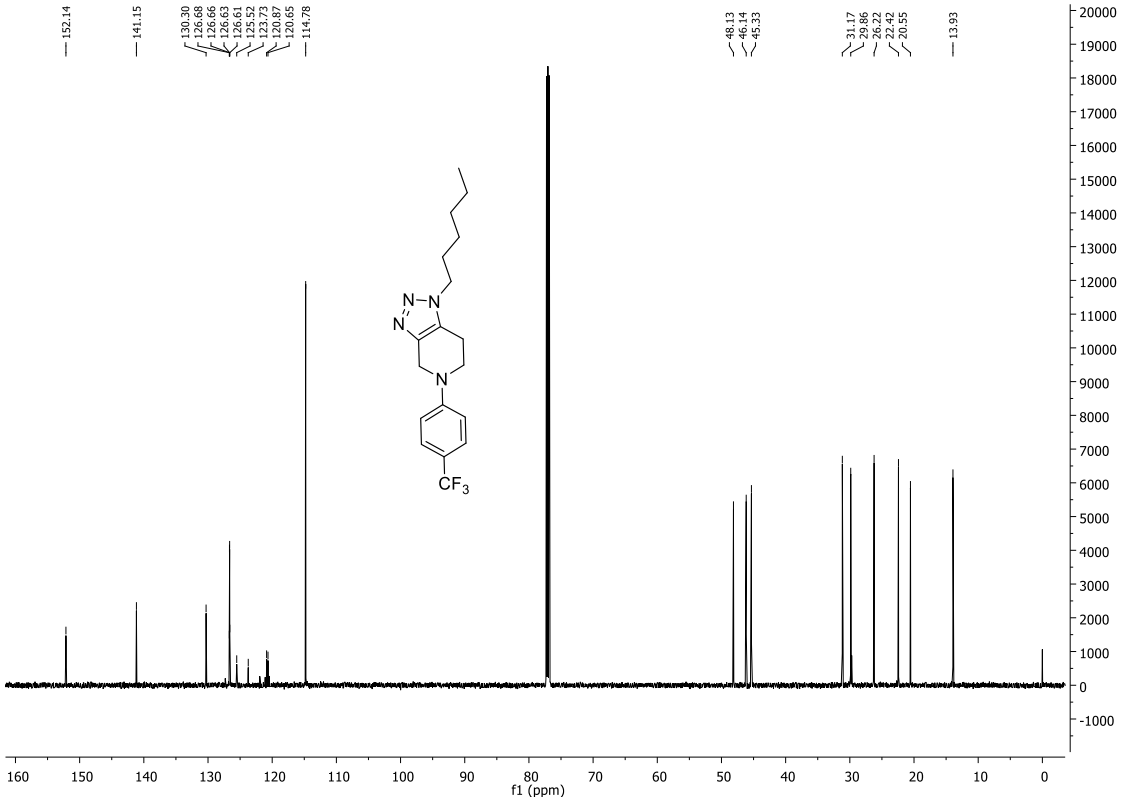
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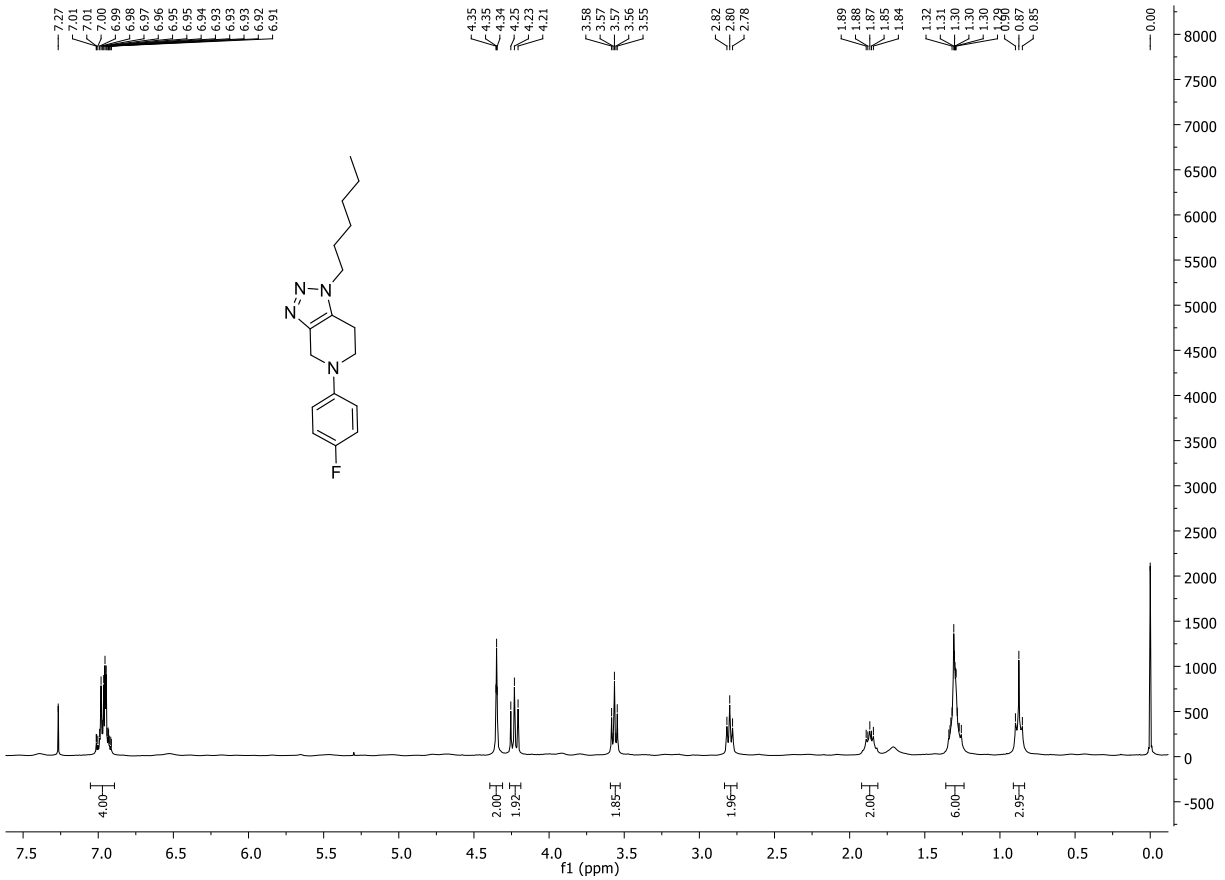
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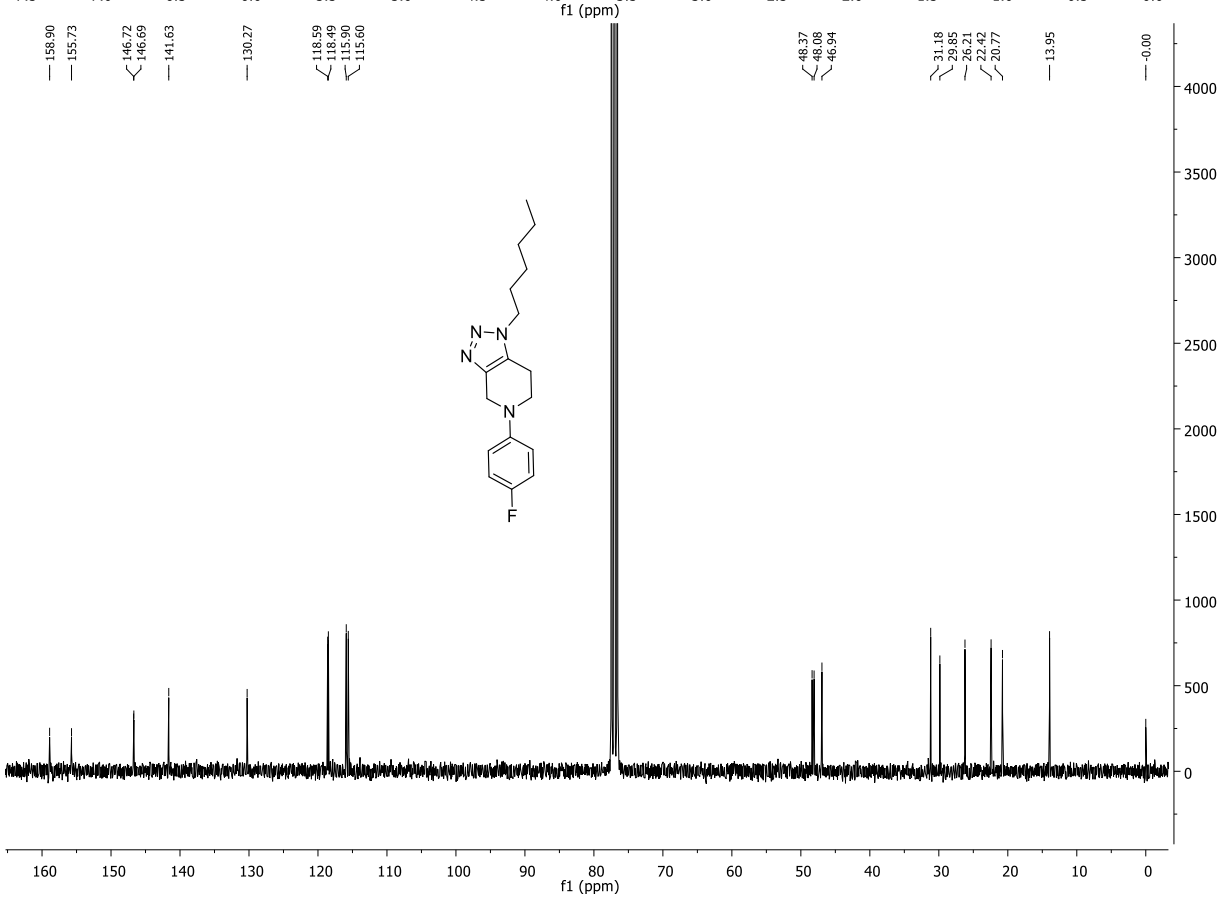
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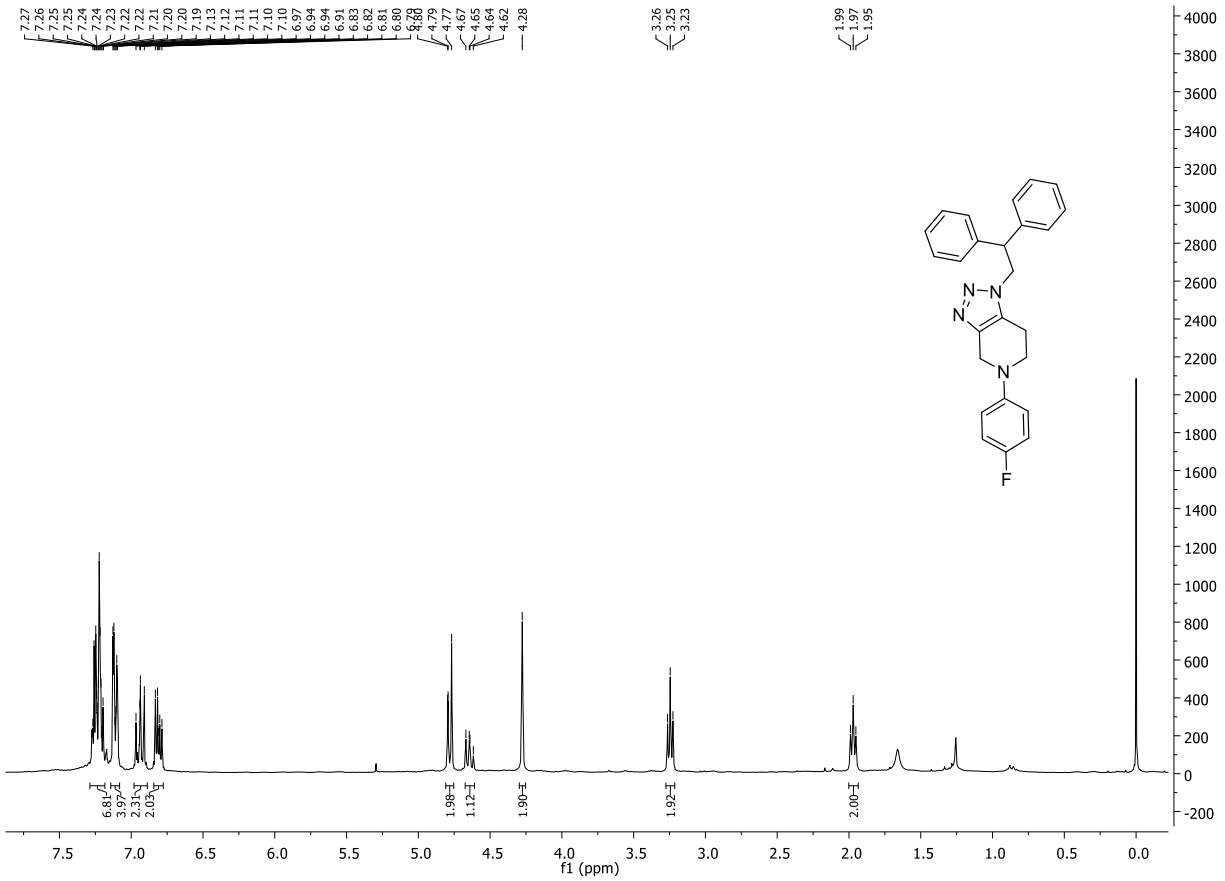
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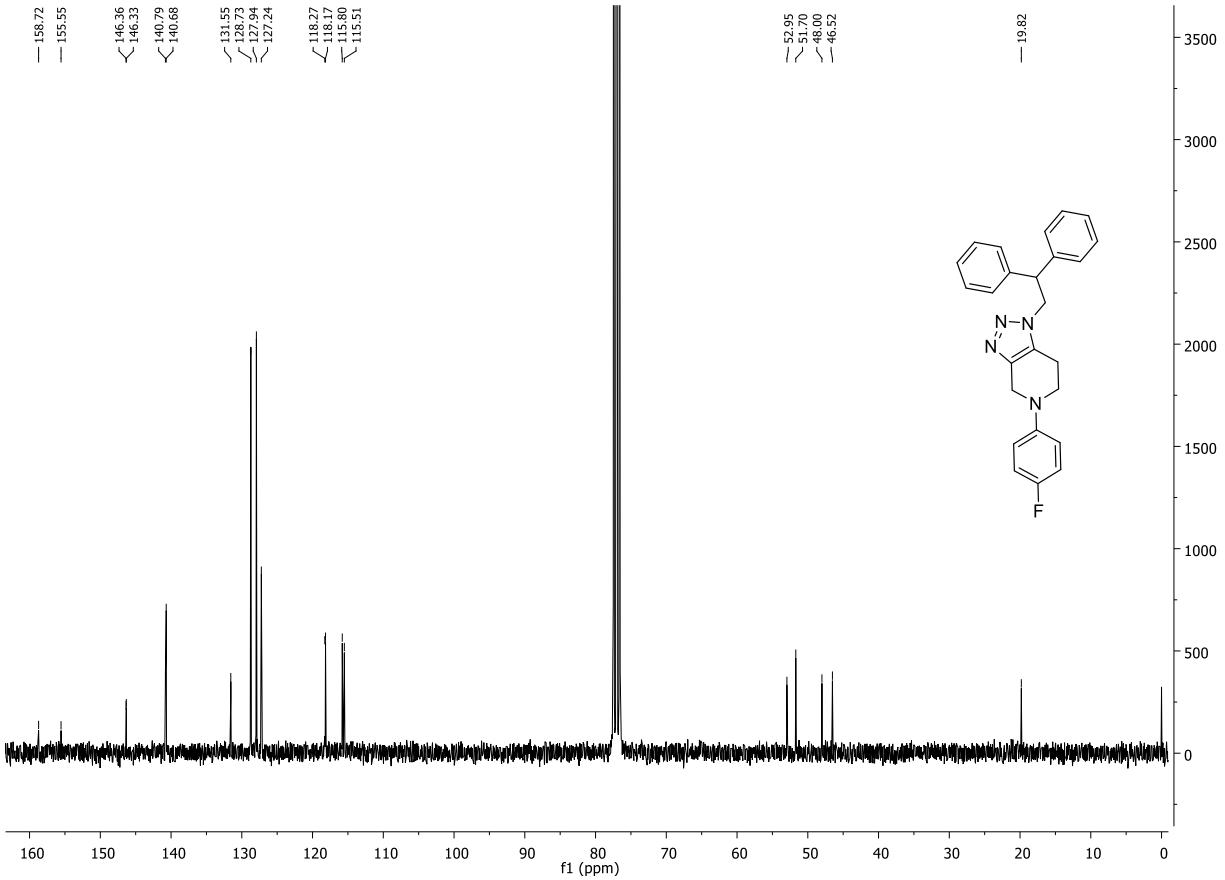
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19.82
f1 (ppm)
F

1.2 Antiviral screening

Antiviral activity against HIV-1 (III_B), HIV-2 (ROD), herpes simplex virus type 1 (KOS), herpes simplex virus type 2 (G), herpes simplex virus 1 TK- (KOS) ACV^{res}, vaccinia virus, adeno virus 2 and human coronavirus (229E) was determined essentially as described previousl.[1,2,3] After a 2 hours incubation period, residual virus was removed and the infected cells were further incubated with the medium containing different concentrations of the test compounds. After incubation for 3 days at 37°C, virus-induced cytopathogenicity was monitored microscopically. Antiviral activity was expressed as the concentration required to reduce virus-induced cytopathogenicity by 50% (EC_{50}). The cytotoxicity was assessed in parallel based on the inhibition of the HEL cell growth. Cells were seeded at 5 x 10^3 cells/well in 96 well microtiter plates. Subsequently medium containing different concentrations of test compounds was added. After 3 days of incubation at 37°C, the alterations of the cell morphology was recorded light microscopically. Cytotoxicity was expressed as minimum cytotoxic concentration (MCC).

Compound	Concentration unit	Minimum cytotoxic concentration[a]	EC_{50}[b]					
			Herpes simplex virus-1 (KOS)	Herpes simplex virus-2 (G)	Herpes simplex virus-1 TK- KOS ACV^r	Vaccinia virus	Adeno virus-2	Human Coronavirus (229E)
14a	µM	≥20	>100	>100	>100	>100	>100	>100
14b	µM	≥100	>100	>100	>100	>100	>100	>100
14c	µM	>100	>100	>100	>100	>100	>100	>100
14d	µM	≥100	>100	>100	>100	>100	>100	**8,95**
14e	µM	≥100	>100	>100	>100	>100	>100	>100
14f	µM	>100	>100	>100	>100	>100	>100	>100
14g	µM	>100	>100	>100	>100	>100	>100	>100
14h	µM	>100	>100	>100	>100	>100	>100	>100
14i	µM	>100	>100	>100	>100	>100	>100	>100
14j	µM	>100	>100	>100	>100	>100	>100	>100
14k	µM	100	>100	>100	>100	>100	>100	>100
14l	µM	≥100	>100	>100	>100	>100	>100	>100
14m	µM	≥20	>100	>100	>100	>100	>100	>100
14n	µM	>100	>100	>100	>100	>100	>100	**9,45**
14o	µM	>100	>100	>100	>100	>100	>100	>100
14p	µM	≥20	>100	>100	>100	>100	>100	>100
14q	µM	>100	>100	>100	>100	>100	>100	**9,45**
14r	µM	>100	>100	>100	>100	>100	>100	>100
18a	µM	>100	>100	>100	>100	>100	>100	>100
18d	µM	≥100	>100	>100	>100	>100	>100	>100
18c	µM	>100	>100	>100	>100	>100	>100	>100
18b	µM	>100	>100	>100	>100	>100	>100	>100

18e	µM	>100	>100	>100	>100	>100	**16**	**45**
18f	µM	>100	>100	>100	>100	>100	>100	**8,9**
18g	µM	>100	>100	>100	>100	>100	>100	>100
18h	µM	100	>100	>100	>100	>100	>100	>100
18i	µM	100	>100	>100	>100	>100	>100	**11,95**
18j	µM	>100	>100	>100	>100	>100	>100	>100
18k	µM	>100	>100	>100	>100	>100	>100	>100
18l	µM	≥100	>100	>100	>100	>100	>100	>100
Brivudin	µM	>250	0,01	250	0,1	3,8	-	-
Cidofovir	µM	>250	4,5	3,4	2,8	85	22	-
Acyclovir	µM	>250	0,6	0,6	2	>250	-	-
Ganciclovir	µM	>100	0,01	0,01	0,2	>100	-	-
Zalcitabine	µM	>250	-	-	-	-	50	-
Alovudine	µM	>250	-	-	-	-	22	-
UDA	µg/ml	>100	-	-	-	-	-	1,8

[a] Required to cause a microscopically detectable alteration of normal cell morphology.

[b] Required to reduce virus-induced cytopathogenicity by 50 %.
Data indicating antiviral activity are shown in red font, and marked in yellow if the SI (ratio of MCC to EC50) is five or higher.
Note that the SI cannot be accurately calculated for compounds showing no cytotoxicity at the highest concentration tested (100µM).

1.2. Molecular modeling studies

The initial structures of the modeled structures were constructed using MarvinSketch v.16.2.15 developed by ChemAxon Ltd. [4], energy minimized by applying a semi-empirical (AM1) and *ab initio* (HF/6-311 +G*) methods as implemented in the Gaussian03 software.[5] Prior to docking analyses, all ligands were subjected to conformational enumeration using the OMEGA software developed by OpenEye Scientific Software,[6] applying an energy threshold of 1k kcal/mol. The corresponding biological activity data for the training set was retrieved from the ChEMBL database (Doc IDs: CHEMBL2439951 and CHEMBL2311314).[7,8]

In order to perform molecular docking studies, crystallographic structures of $3CL^{pro}$ in complex with the corresponding ligands were retrieved from Protein Data Bank (PDB codes: 3V3M and 4MDS, respectively). Ionization states of side chains in the receptor were assigned using the ProteinPlus Server, from the University of Hamburg.[9] With the purpose of exhaustively exploring the surface energy landscape associated to the binding to the $3CL^{pro}$ catalytic site, all molecular docking assays were performed using identically parameterized receptor structures and two different docking engines: FRED3 and AutodockVina.[10] In the first case, a fast rigid exhaustive docking approach was used based on the ligands conformers libraries previously generated, and ranking the ligands bound poses using the ChemGauss3 scoring function. When using AutodockVina, individual runs were performed for each ligand conformer, ranking the

resulting docked poses using the AutoDock built-in scoring function. In all cases, the cubic search space was placed on the geometrical center of ligand bound to $3CL^{pro}$ (pdb code: 3V3M or 4MDS), with the length, width and height being set to extend 30% from the bound ligand. In order to identify the lowest energy binding mode for each ligand, a free energy of binding analysis was performed on the corresponding docked structures obtained by using both software packages, applying the molecular mechanics Poisson-Boltzmann surface area (MMPBSA) approach as implemented in the MMPBSA.py tool.[11] The lowest total interaction energy was extracted for further MD analysis. Intermolecular interaction analyses were performed on the resulting complexes using the VIDA [12] and LigPot+ [13] software packages.

Molecular dynamics simulations were performed using the Amber18 software package.[14] Starting from the lowest energy binding modes predicted by molecular docking, the *ff14SB* and GAFF force fields implemented were used to parameterize $3CL^{pro}$ and the corresponding ligands, respectively.[15,16] Complexes were solvated using a pre-equilibrated TIP3P explicit water model, applying a solvent box with boundaries at a minimum distance from the solute of 10 Å in each direction. After standard minimization procedures (5000 steps, first stage: solute restrained; 5000 steps, second stage: unrestrained system), the minimized complexes were heated under constant volume conditions from 0 to 300 K in a 0.5 ns timeframe, applying restraints on the solute. Next, the systems were equilibrated during 1 ns, after which the production phase under constant pressure and temperature conditions was performed for additional 10 ns. The trajectories were obtained applying restraints to the backbone of $3CL^{pro}$. In all cases, a 2 fs time step was used, with the SHAKE algorithm being applied to constrain all covalent bonds involving hydrogen atoms. A 10 Å cutoff value was used to calculate non-bonded interactions. The cpptraj module of Amber16 was used to analyze the hydrogen bond interaction on the $3CL^{pro}$-ligand complexes during the 10 ns of production stage.

MD trajectories were generated using CUDA designed code (*pmemd.cuda*), and computed using computational resources provided by the CCAD – Universidad Nacional de Córdoba (http://ccad.unc.edu.ar/). In particular, the Mendieta cluster was used which is part of SNCAD – MinCyT, República Argentina. In addition, GPU infrastructure was provided by NVIDIA Corporation, specifically through the donation of the Titan Xp GPU used for this research.

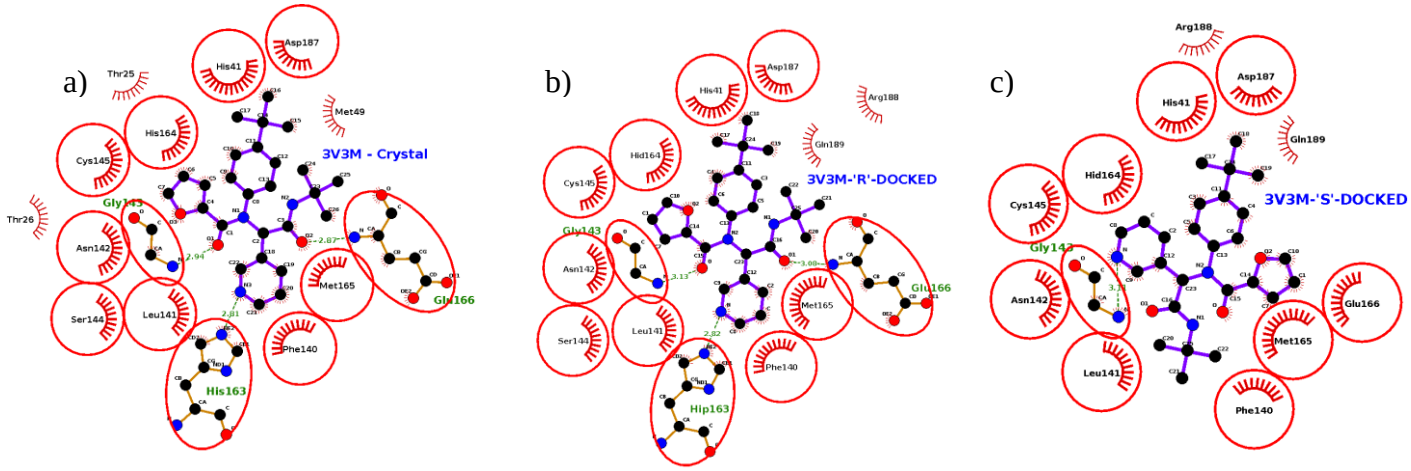


Figure S1. Intermolecular interactions observed in a) the crystallographic structure deposited under pdb code: 3V3M; b) docked position of the R enantiomer; c) docked position of the S enantiomer.

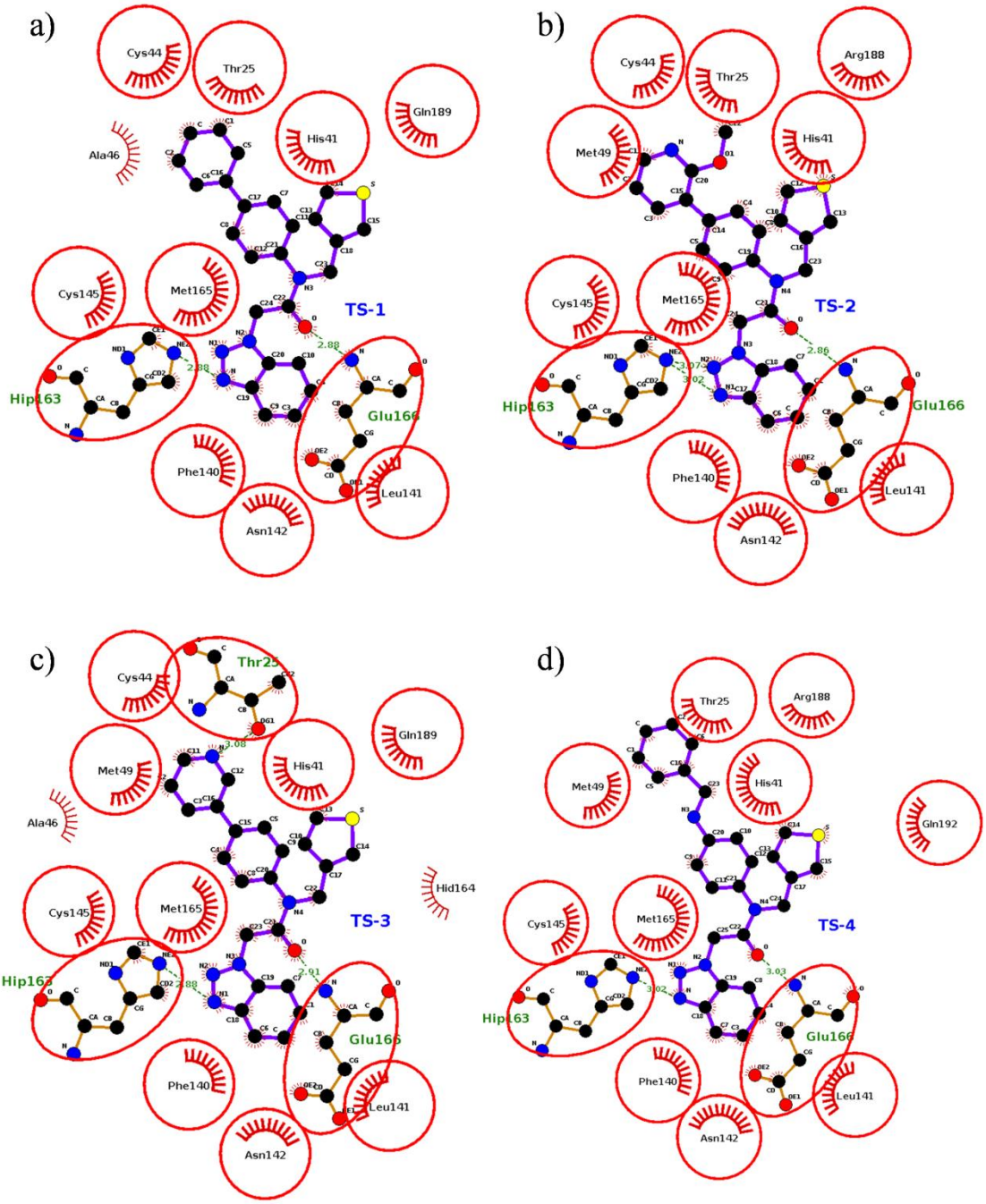


Figure S2. Intermolecular interaction pattern obtained from the molecular docking of compounds 1-4 of the training set (TS-1 - TS-4). Crystal structure template pdb code: 4MDS.

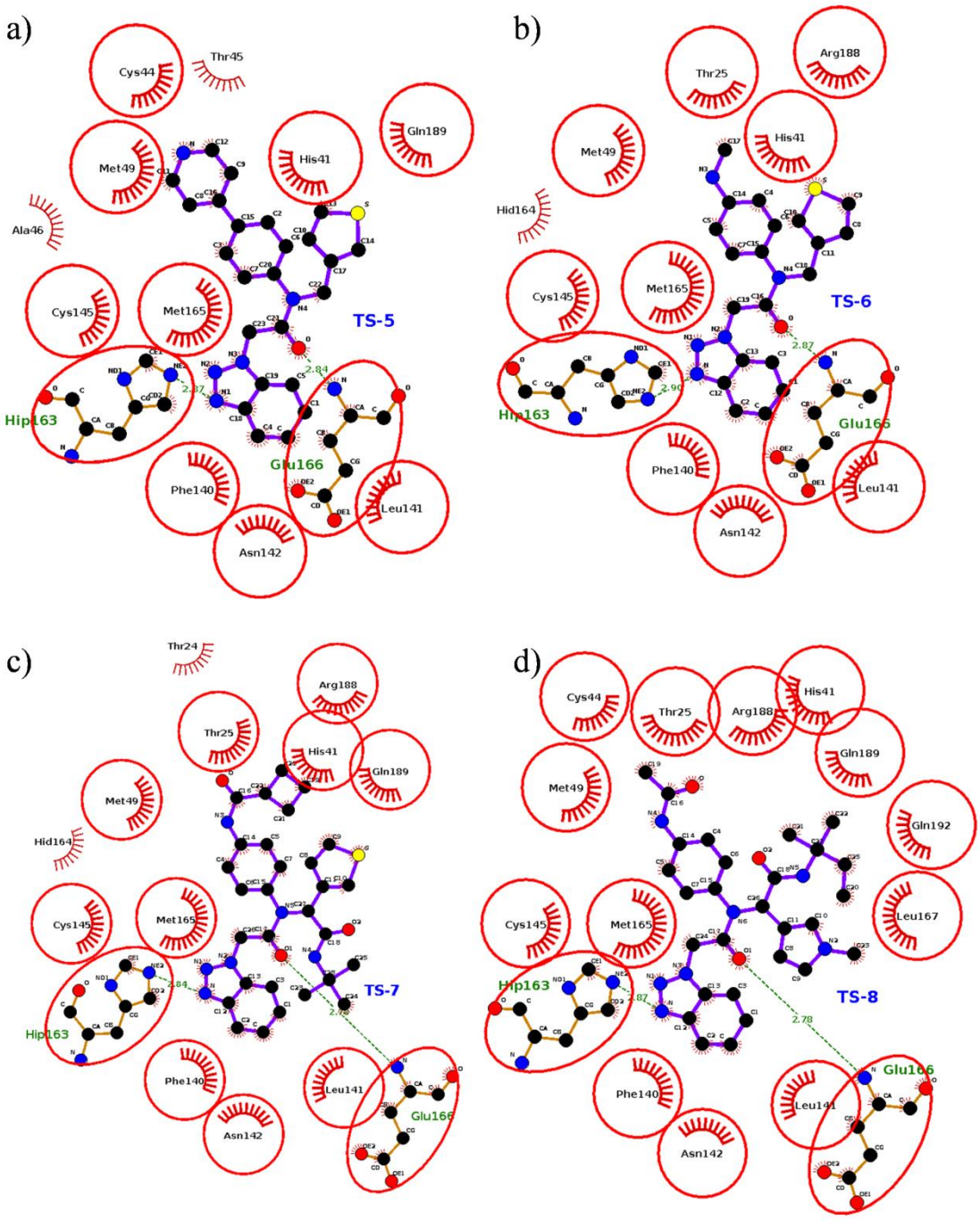


Figure S3. Intermolecular interaction pattern obtained from the molecular docking of compounds 5-8 of the training set (TS-5 - TS-8). Crystal structure template pdb code: 4MDS.

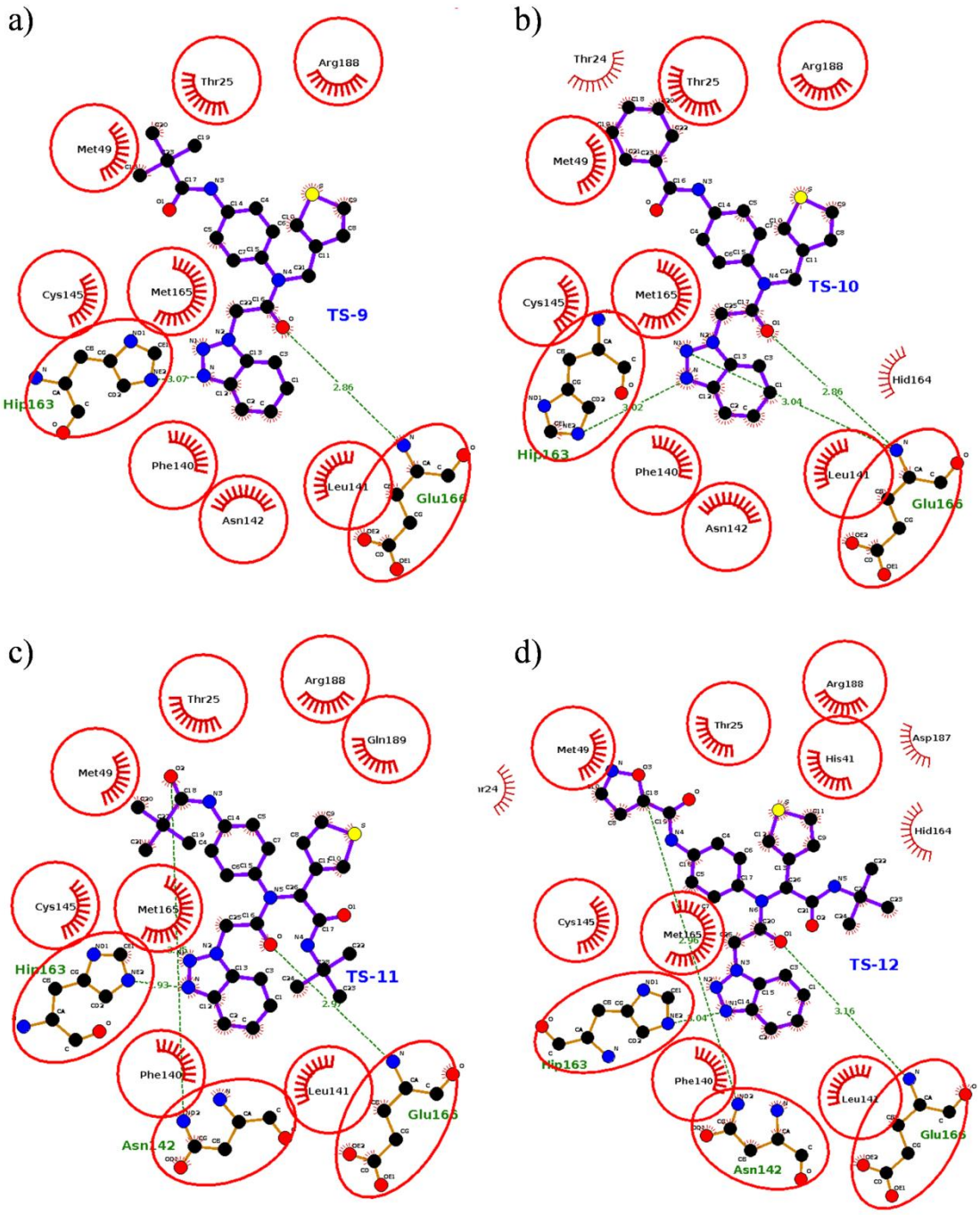


Figure S4. Intermolecular interaction pattern obtained from the molecular docking of compounds 9-12 of the training set (TS-9 - TS-12). Crystal structure template pdb code: 4MDS.

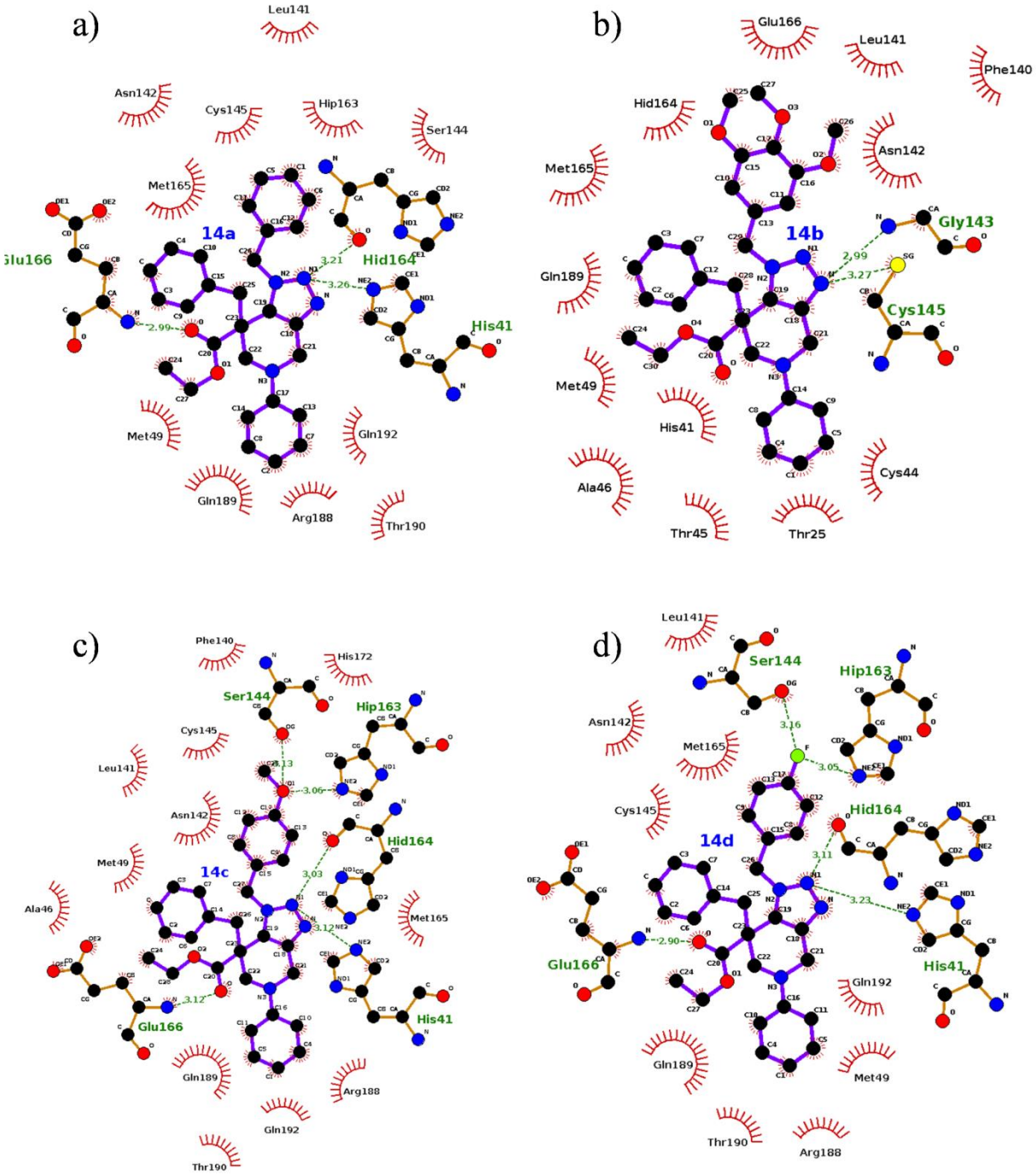


Figure S5. Lowest energy binding modes obtained by molecular docking simulation between $3CL^{pro}$ (pdb code: 4MDS) and compounds **14a-14d**.

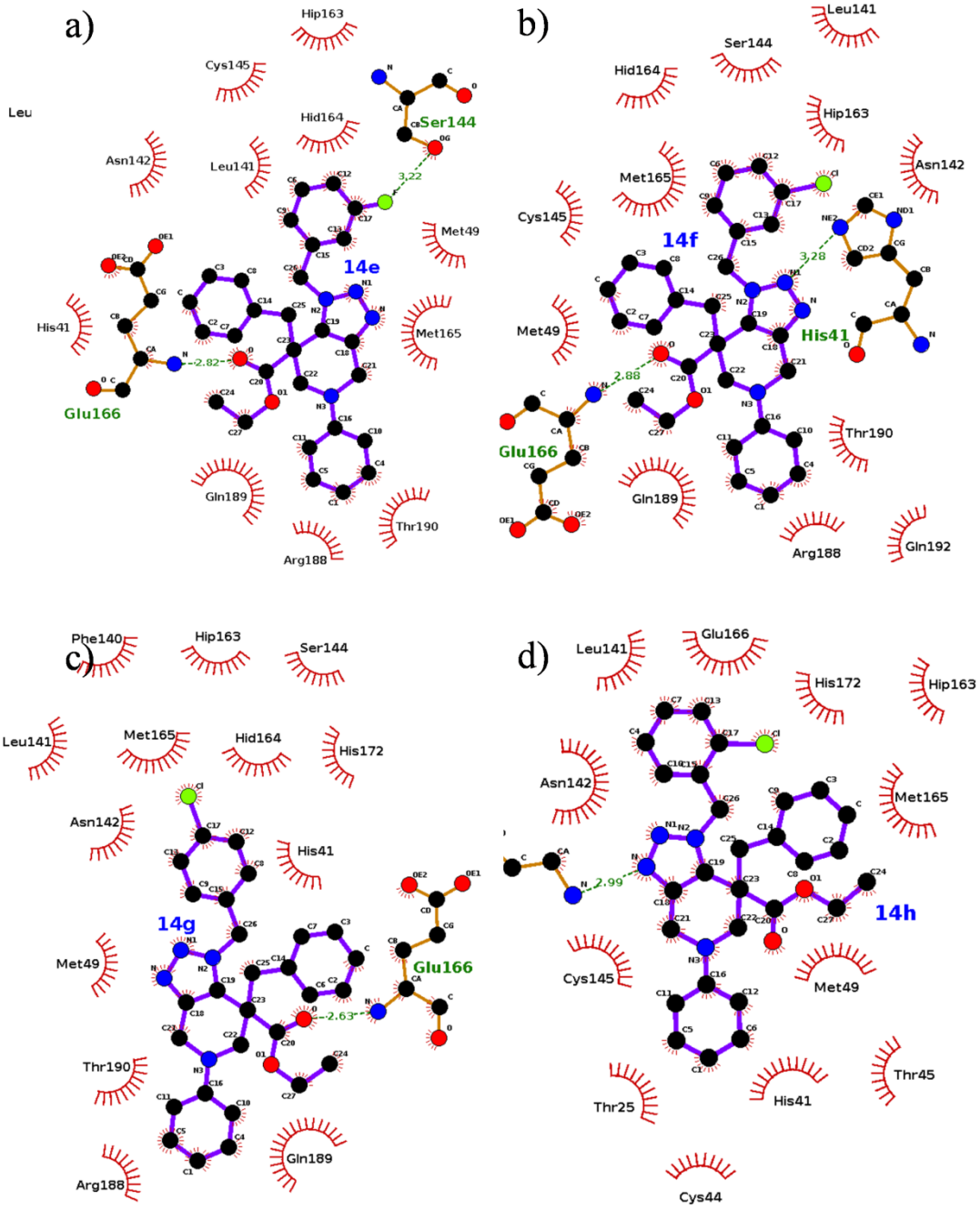


Figure S6. Lowest energy binding modes obtained by molecular docking simulation between $3CL^{pro}$ (pdb code: 4MDS) and compounds **14e-14h**.

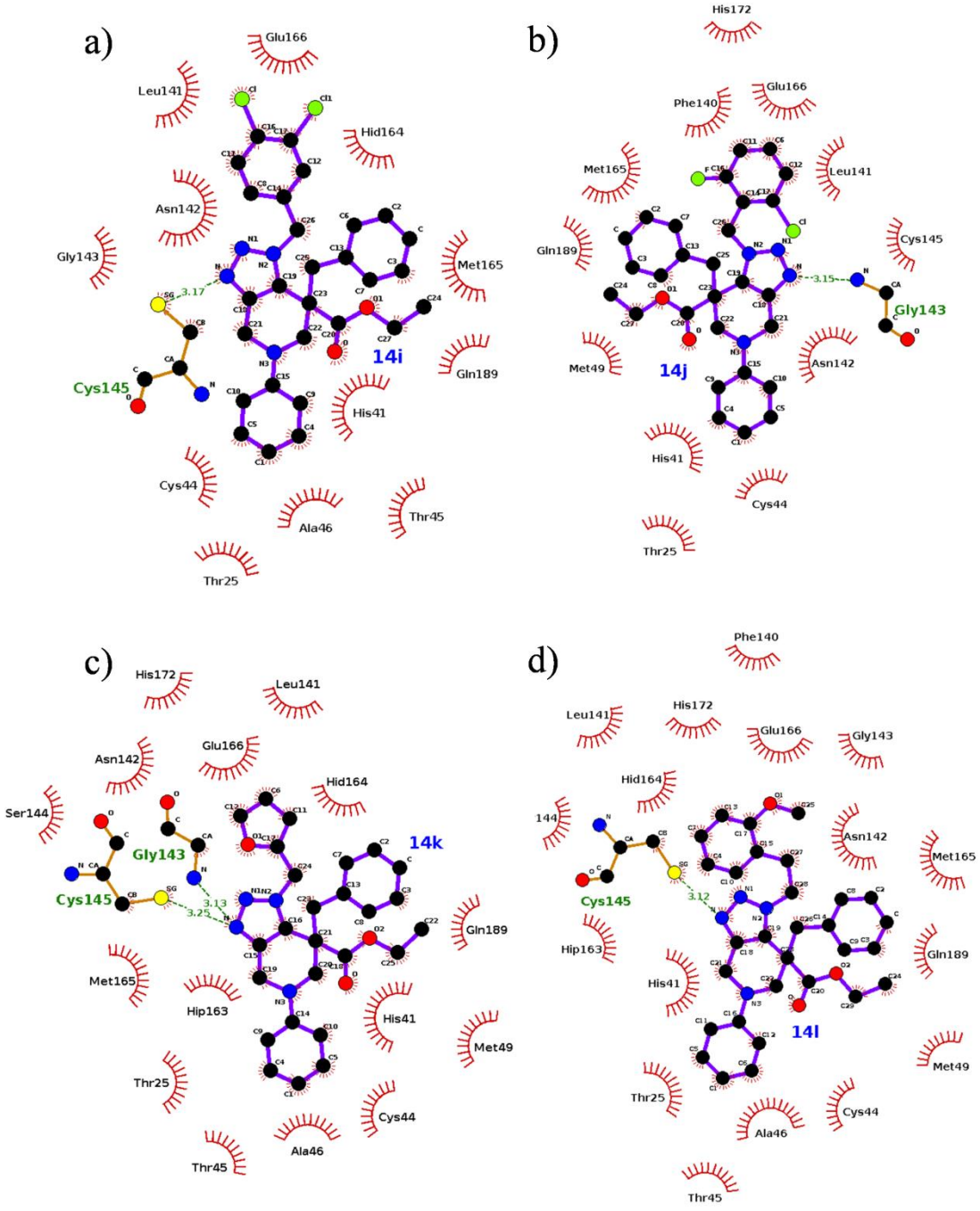


Figure S7. Lowest energy binding modes obtained by molecular docking simulation between $3CL^{pro}$ (pdb code: 4MDS) and compounds **14i-14l**.

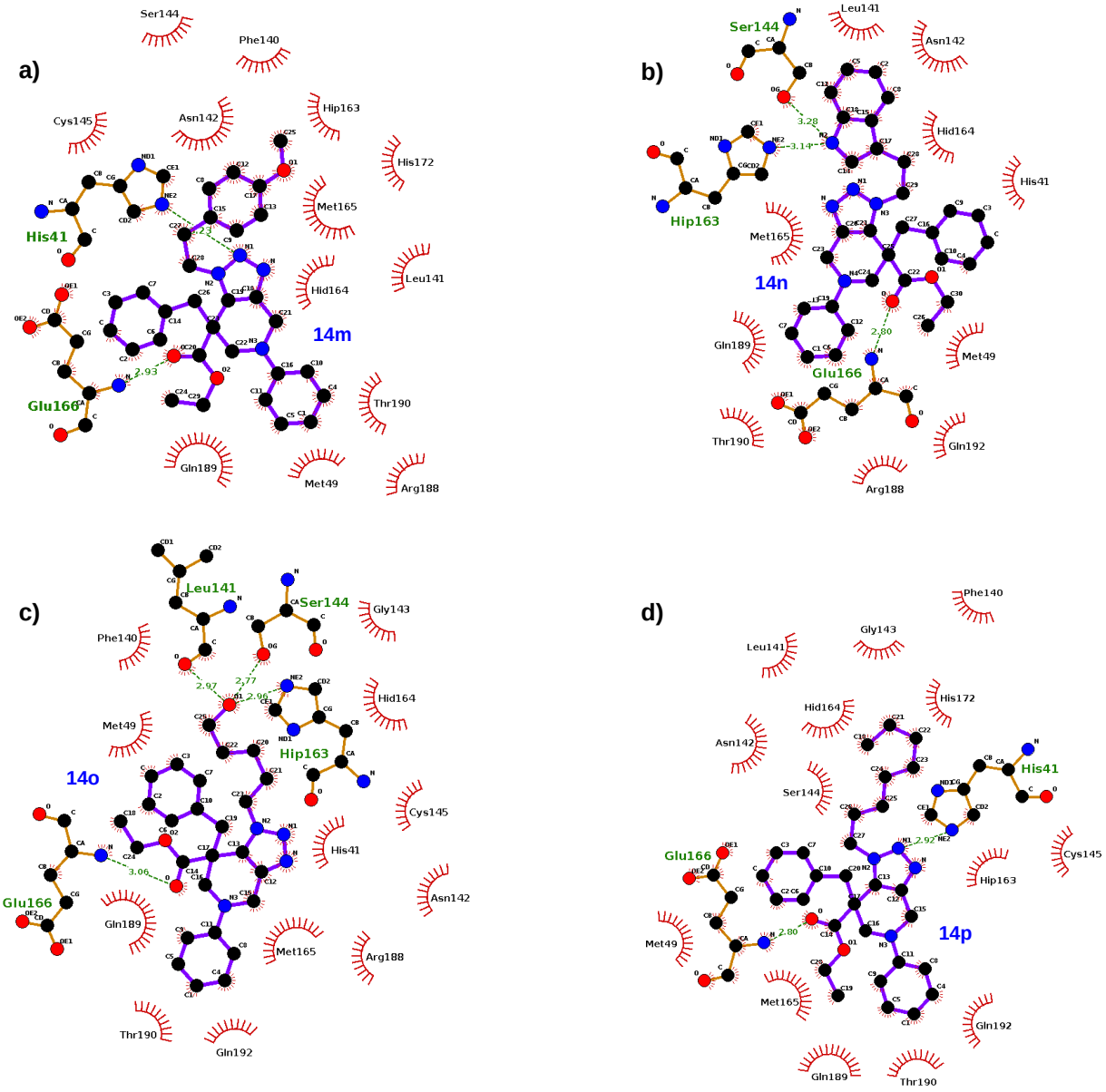


Figure S8. Lowest energy binding modes obtained by molecular docking simulation between 3CL^{pro} (pdb code: 4MDS) and compounds **14m-14p**.

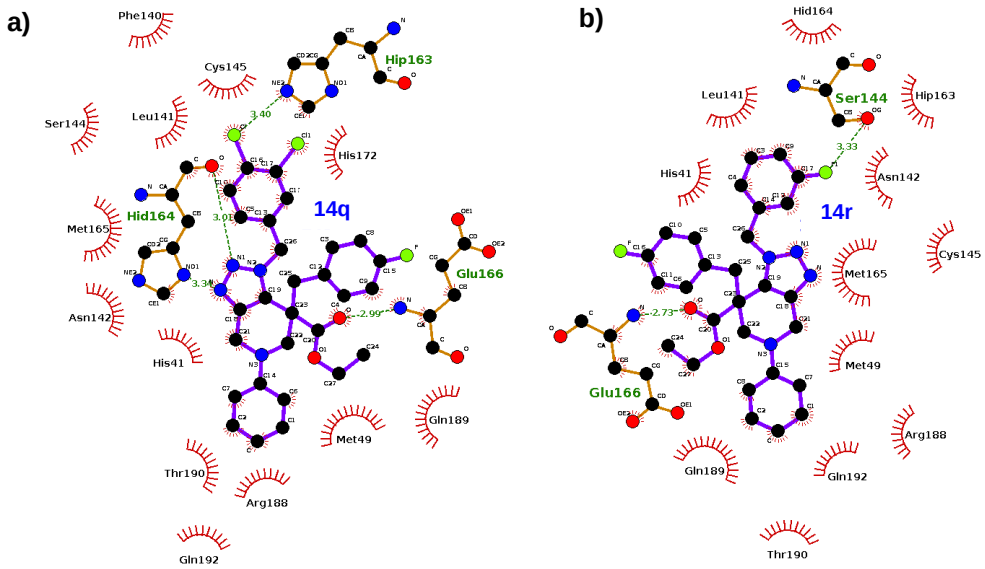


Figure S9. Lowest energy binding modes obtained by molecular docking simulation between $3CL^{pro}$ (pdb code: 4MDS) and compounds **14q-14r**.

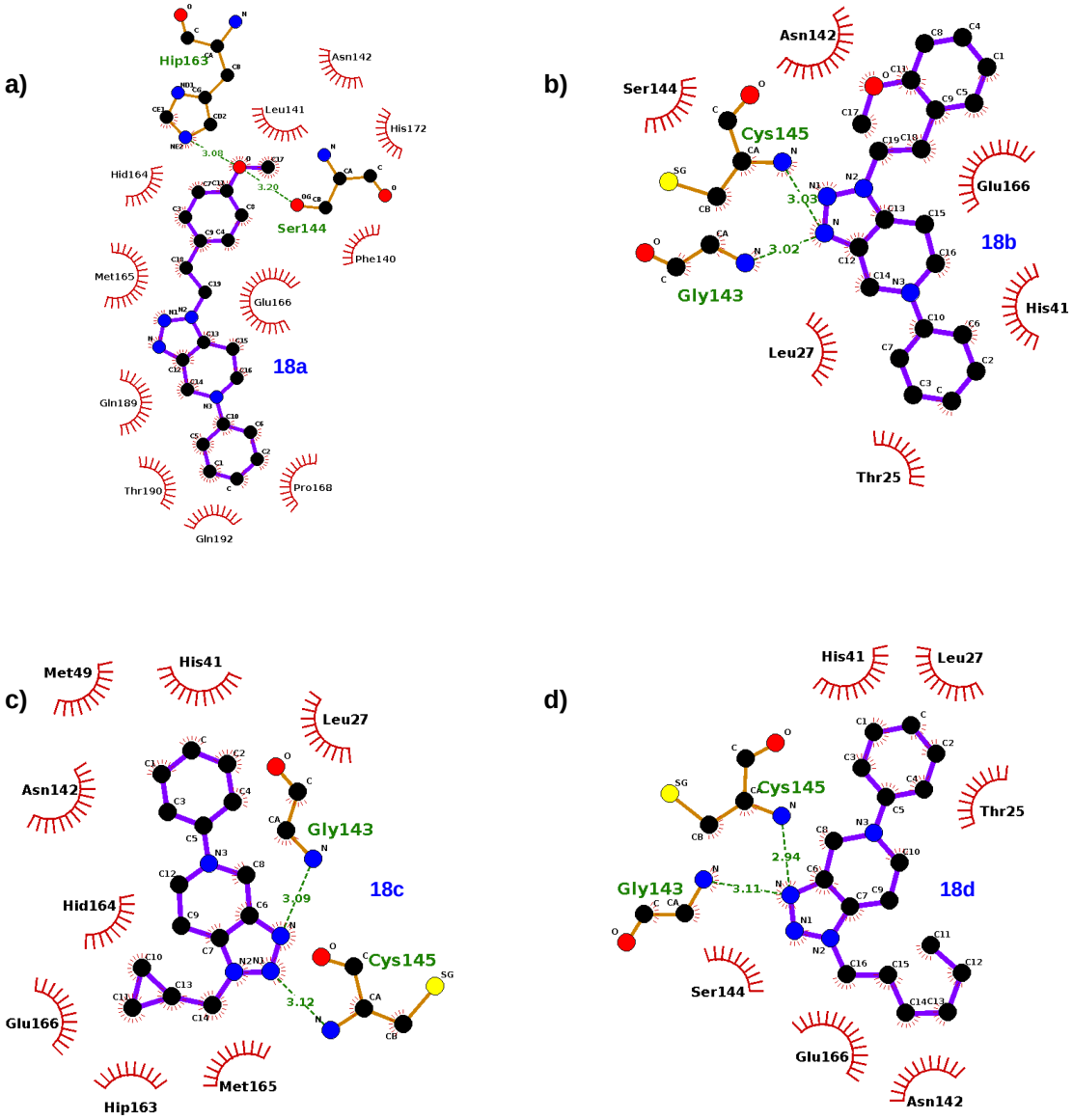


Figure S10. Lowest energy binding modes obtained by molecular docking simulation between 3CL^{pro} (pdb code: 4MDS) and compounds **18a-18d**.

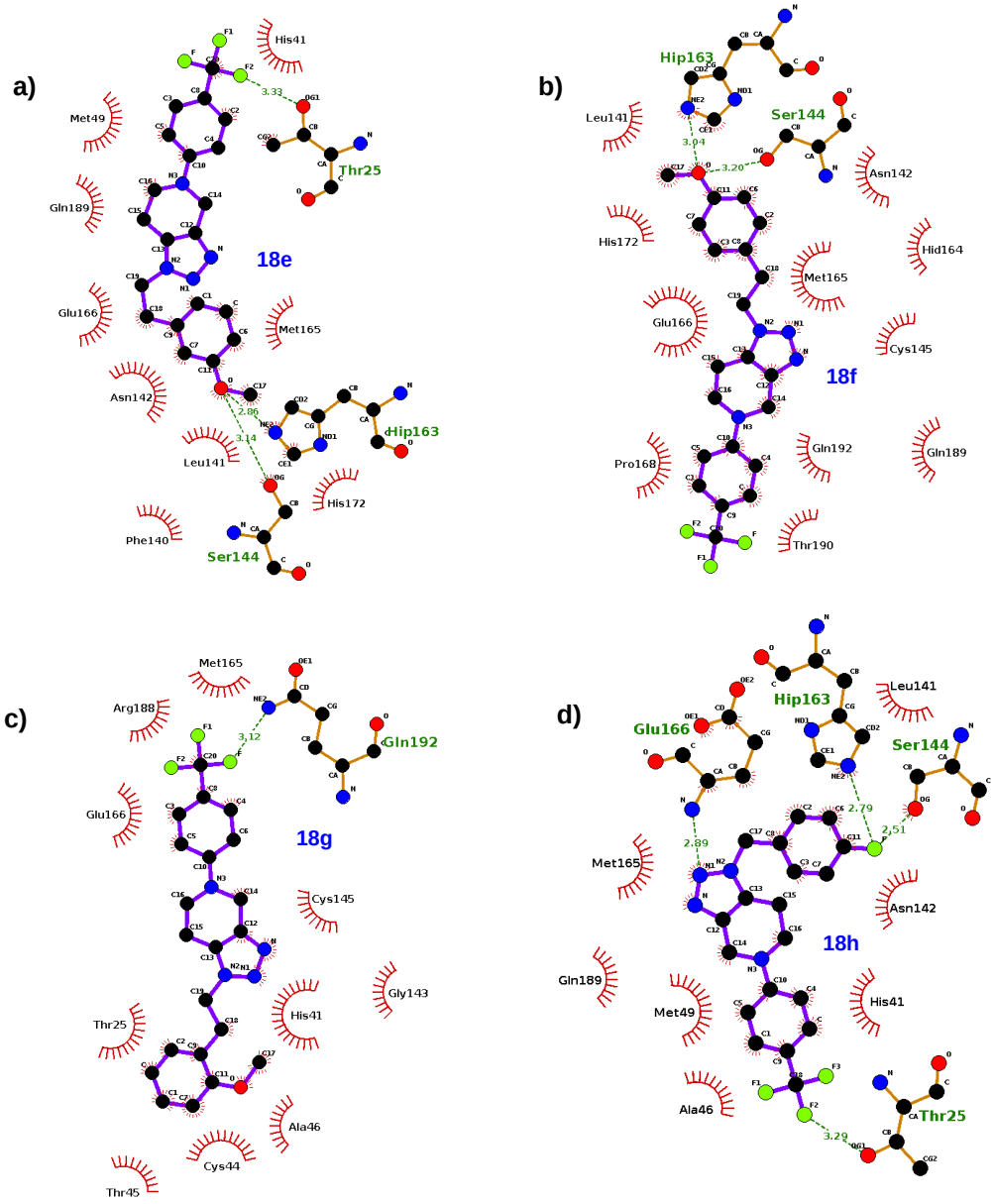


Figure S11. Lowest energy binding modes obtained by molecular docking simulation between 3CL^{pro} (pdb code: 4MDS) and compounds **18e-18h**.

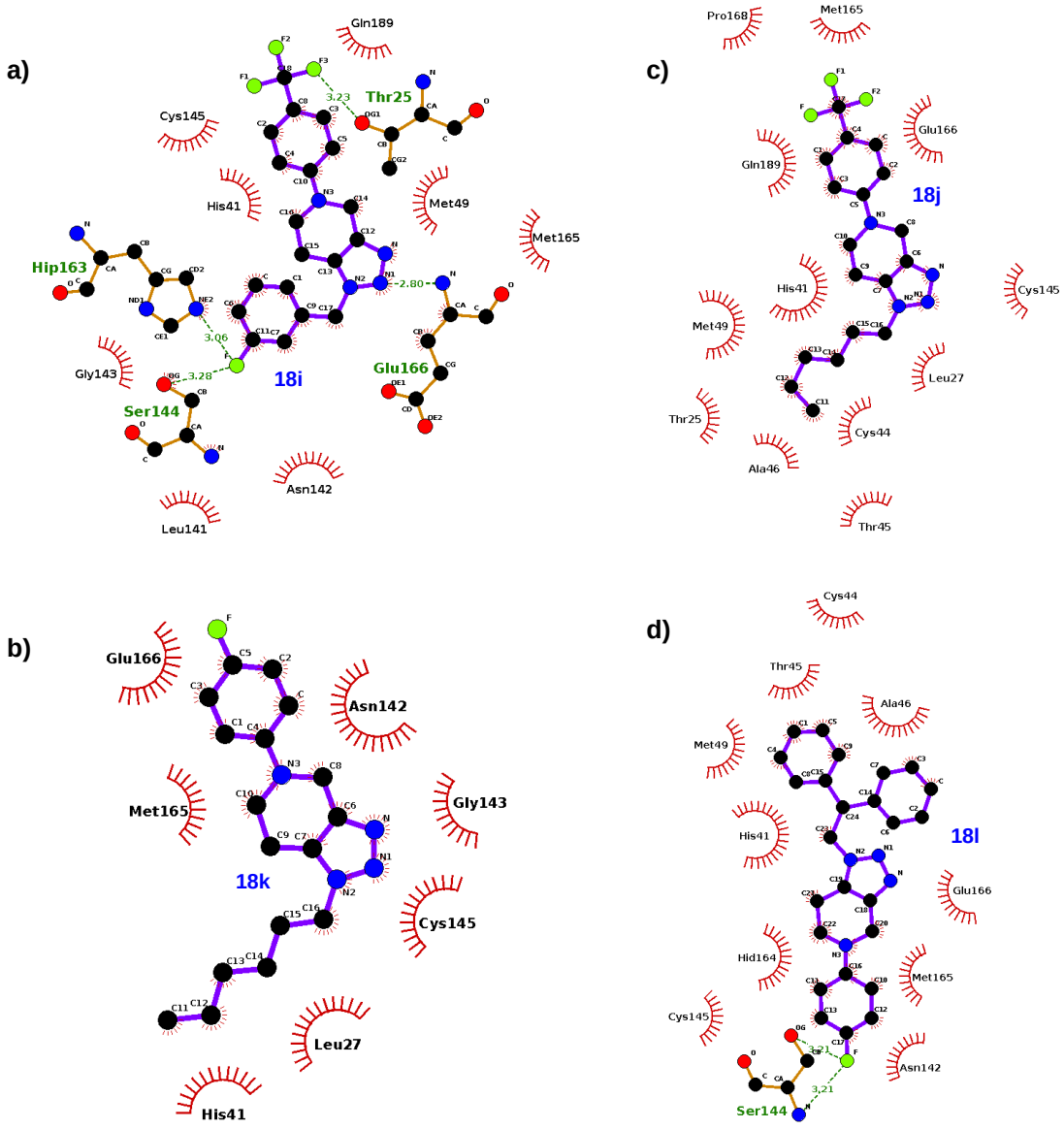


Figure S12. Lowest energy binding modes obtained by molecular docking simulation between $3CL^{pro}$ (pdb code: 4MDS) and compounds **18i-18l**.

Table S1. HB persistence value (%) for the training set.

Entry	Glu166 (% HB)	His163 (% HB)	Gly143(% HB)	Asn142(% HB)
1- 3V3M-*R*	82	39	96	-
2- 3V3M-*S*	60	0	0	-
3- TS-1	99	36	-	-
4- TS-2	99	34	-	-
5- TS-3	99	13	-	-
6- TS-4	99	25	-	-
7- TS-5	99	25	-	-
8- TS-6	99	32	-	-
9- TS-7 (*R*)	82	15	-	46
10- TS-8 (*R*)	99	48	-	-
11- TS-9	99	28	-	40
12- TS-10	99	10	-	-
13- TS-11 (*R*)	99	21	-	41
14- TS-12 (*R*)	49	10	-	72

Table S2. HB persistence value (%) for the fused 1,2,3-triazole derivatives**.**

Entry	Compound	Glu166 (% HB)	His163 (% HB)	Gln189 (% HB)	Thr25 (% HB)	Active
1	**14a**	37	-	-	-	
2	**14b**	-	-	-	-	
3	**14c**	99	88	-	-	
4	**14d**	99	57			
5	**14e**	99	-	-	-	
6	**14f**	41	-	-	-	
7	**14g**	98	7	-	-	
8	**14h**	-	71	-	-	
9	**14i**	63	56	-	-	
10	**14j**	-	46			
11	**14k**	-	3	-	-	
12	**14l**	99	-	-	-	
13	**14m**	94	70	-	-	
14	**14n**	97	69	-	-	
15	**14o**	79	50	-	-	
16	**14p**	92	-	-	-	
17	**14q**	90	47	-		
18	**14r**	61	-	-	-	
19	**18a**	-	12	35	-	
20	**18b**	-	-	-	-	
21	**18c**	-	-	-	-	
22	**18d**	-	-	-	-	
23	**18e**	-	46	-	-	
24	**18f**	40	94	-	55	
25	**18g**	-	-	-	-	
26	**18h**	98	-	-	-	
27	**18i**	99	97	52	-	
28	**18j**	-	-	-	-	
29	**18k**	-	-	-	-	
30	**18l**	48	-	-	-	

Table S3. Molecular structures of training set (TS1-TS4).

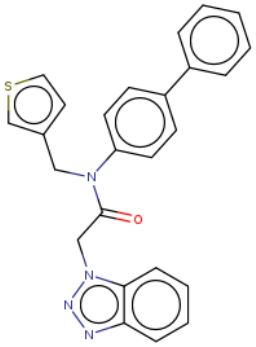
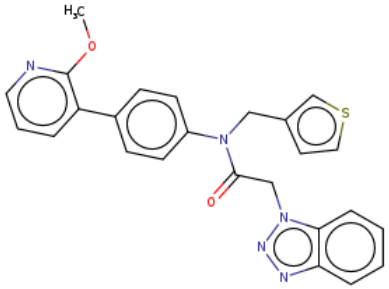
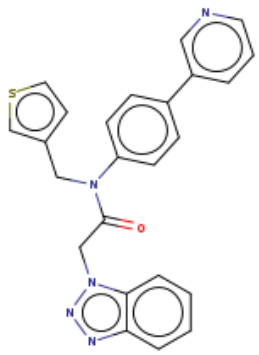
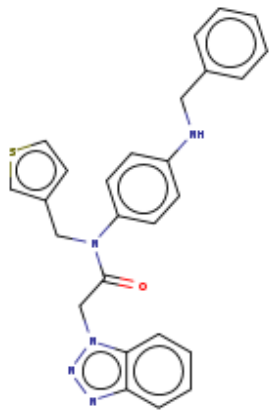
Compound	Structure	IC50 (nM)	Ref.
TS-1		51	7
TS-2		700	7
TS-3		970	7
TS-4		1500	7

Table S4. Molecular structures of training set (TS5-TS8).

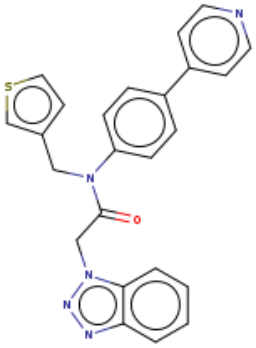
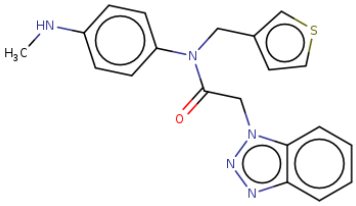
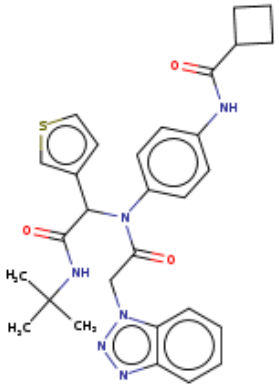
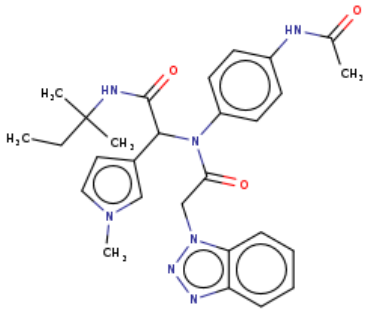
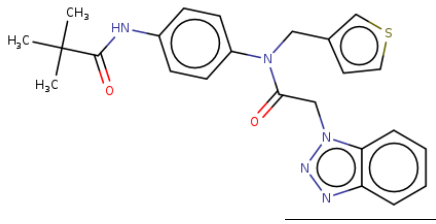
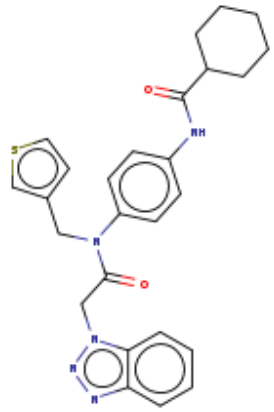
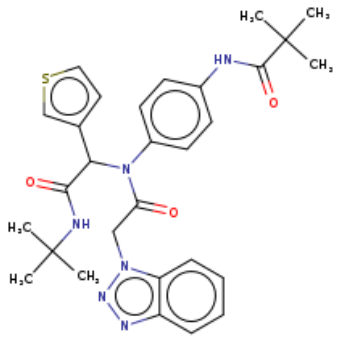
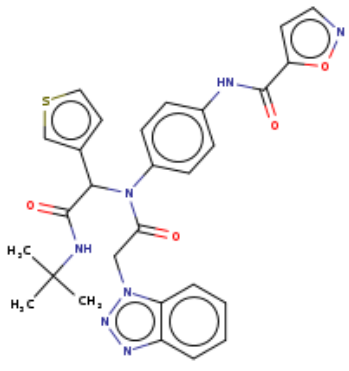
Compound	Structure	IC50 (nM)	Ref.
TS-5		2000	7
TS-6		2100	7
TS-7		3800	7
TS-8		6200	7

Table S5. Molecular structures of training set (TS9-TS12).

Compound	Structure	IC50 (nM)	Ref.
TS-9		13300	7
TS-10		22100	7
TS-11		22500	7
TS-12		26000	7

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