SUPPORTING INFORMATION FOR

Discovery of novel theophylline derivatives bearing tetrazole scaffold for the treatment of Alzheimer's disease

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MACHINE LEARNING RESULTS

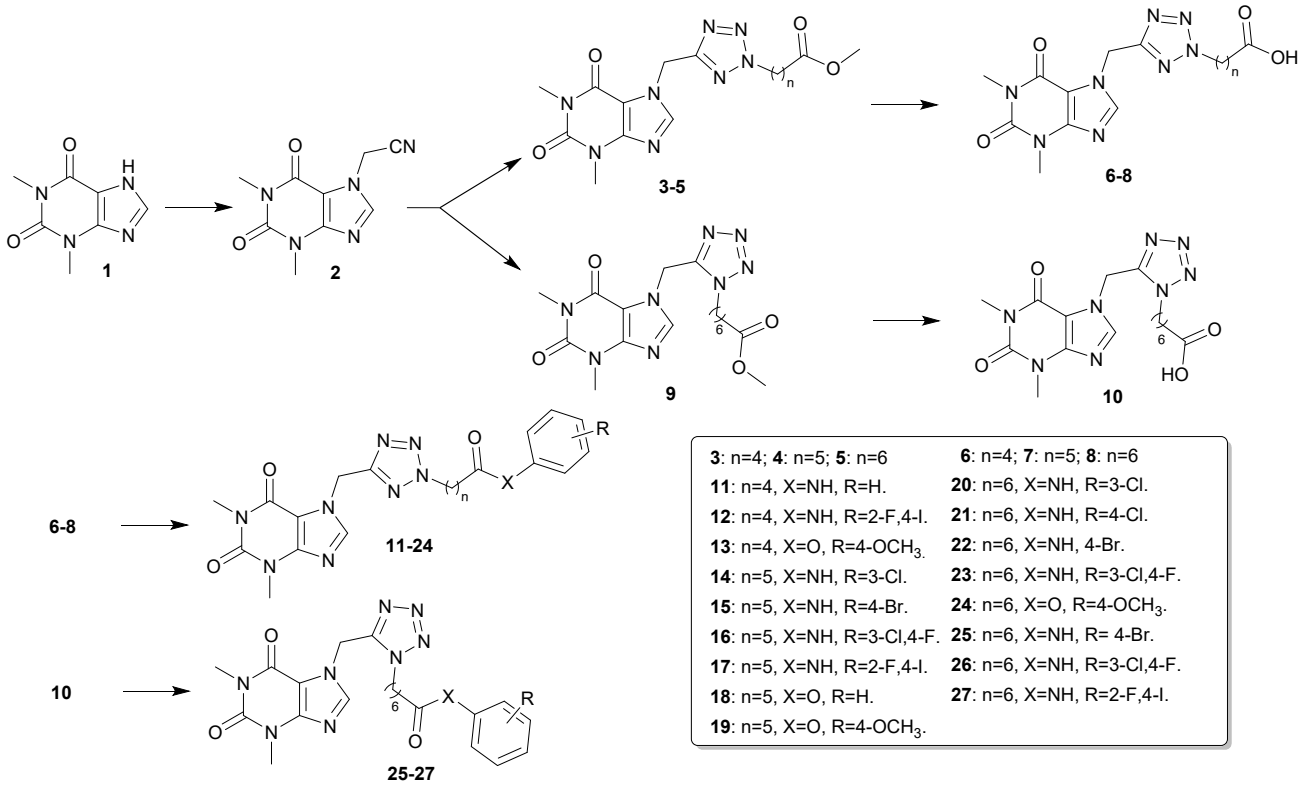
Table S1. Binding energy caculated by Machine learning approach

Smiles	ΔG_{ML}^{AChE}	ΔG_{ML}^{BACE-1}
O=C1C2=C(N=CN2CC3=NN(CCCCCC(NC4=CC=C(I)C=C4F)=O)N=N3)N(C)C(N1C)=O	-10.409693	-10.068348
O=C1C2=C(N=CN2CC3=NN=NN3CCCCCC(NC4=CC=C(I)C=C4F)=O)N(C)C(N1C)=O	-10.4689455	-9.965019
O=C1C2=C(N=CN2CC3=NN(CCCCCCC(NC4=CC=C(I)C=C4F)=O)N=N3)N(C)C(N1C)=O	-10.293982	-10.011011
O=C1C2=C(N=CN2CC3=NN=NN3CCCCCCCC(NC4=CC=C(I)C=C4F)=O)N(C)C(N1C)=O	-10.3300085	-9.90273
O=C1C2=C(N=CN2CC3=NN=NN3CCCCCCCC(NC4=CC=C(F)C(Cl)=C4)=O)N(C)C(N1C)=O	-10.247373	-9.609058
O=C1C2=C(N=CN2CC3=NN=NN3CCCCCCCC(NC4=CC=C(Br)C=C4)=O)N(C)C(N1C)=O	-10.555878	-9.291848
O=C1C2=C(N=CN2CC3=NN=NN3CCCCCCCC(NC4=CC=C(Cl)C=C4)=O)N(C)C(N1C)=O	-10.514137	-9.29776
O=C1C2=C(N=CN2CC3=NN=NN3CCCCCCCC(NC4=CC=C([N+]([O-])=O)C=C4)=O)N(C)C(N1C)=O	-10.271304	-9.487595
O=C1C2=C(N=CN2CC3=NN(CCCCC(NC4=CC=C(I)C=C4F)=O)N=N3)N(C)C(N1C)=O	-9.712008	-10.040927
O=C1C2=C(N=CN2CC3=NN=NN3CCCCCCCC(NC4=CC=CC(Cl)=C4)=O)N(C)C(N1C)=O	-10.442992	-9.272117
O=C1C2=C(N=CN2CC3=NN(CCCCCCC(NC4=CC=C(Br)C=C4)=O)N=N3)N(C)C(N1C)=O	-10.146721	-9.50038
O=C1C2=C(N=CN2CC3=NN=NN3CCCCCCCC(NC4=CC=CC=C4Cl)=O)N(C)C(N1C)=O	-10.513418	-9.109821
O=C1C2=C(N=CN2CC3=NN(CCCCCCC(NC4=CC=C(F)C(Cl)=C4)=O)N=N3)N(C)C(N1C)=O	-10.171043	-9.432928
O=C1C2=C(N=CN2CC3=NN=NN3CCCCCCCC(NC4=CC=C(OC)C=C4)=O)N(C)C(N1C)=O	-9.823613	-9.704937
O=C1C2=C(N=CN2CC3=NN=NN3CCCCCC(NC4=CC=C(Br)C=C4)=O)N(C)C(N1C)=O	-10.400115	-9.093646
O=C1C2=C(N=CN2CC3=NN=NN3CCCCCC(NC4=CC=CC(Cl)=C4)=O)N(C)C(N1C)=O	-10.210088	-9.265701
O=C1C2=C(N=CN2CC3=NN=NN3CCCCCC(NC4=CC=C(F)C(Cl)=C4)=O)N(C)C(N1C)=O	-9.872982	-9.576952
O=C1C2=C(N=CN2CC3=NN(CCCCCCC(NC4=CC=C(Cl)C=C4)=O)N=N3)N(C)C(N1C)=O	-9.960075	-9.485219
O=C1C2=C(N=CN2CC3=NN=NN3CCCCCC(NC4=CC=CC=C4Cl)=O)N(C)C(N1C)=O	-10.272831	-9.135108
O=C1C2=C(N=CN2CC3=NN(CCCCCCC(NC4=CC=C([N+]([O-])=O)C=C4)=O)N=N3)N(C)C(N1C)=O	-9.940655	-9.465313
O=C1C2=C(N=CN2CC3=NN=NN3CCCCCC(NC4=CC=C([N+]([O-])=O)C=C4)=O)N(C)C(N1C)=O	-9.903742	-9.477954
O=C1C2=C(N=CN2CC3=NN=NN3CCCCCC(NC4=CC=C(Cl)C=C4)=O)N(C)C(N1C)=O	-10.233639	-9.105392
O=C1C2=C(N=CN2CC3=NN(CCCCCC(NC4=CC=C(F)C(Cl)=C4)=O)N=N3)N(C)C(N1C)=O	-9.896478	-9.413058
O=C1C2=C(N=CN2CC3=NN=NN3CCCCCC(NC4=CC=C(OC)C=C4)=O)N(C)C(N1C)=O	-9.806946	-9.49427
O=C1C2=C(N=CN2CC3=NN(CCCCCCC(NC4=CC=CC(Cl)=C4)=O)N=N3)N(C)C(N1C)=O	-9.971409	-9.307013
O=C1C2=C(N=CN2CC3=NN=NN3CCCCCCCC(NC4=CC=C(F)C=C4)=O)N(C)C(N1C)=O	-9.841448	-9.420293
O=C1C2=C(N=CN2CC3=NN(CCCCCCC(NC4=CC=C(F)C=C4)=O)N=N3)N(C)C(N1C)=O	-9.65381	-9.602494
O=C1C2=C(N=CN2CC3=NN=NN3CCCCCCCC(NC4=CC=C(OC)C=C4OC)=O)N(C)C(N1C)=O	-9.937963	-9.318114
O=C1C2=C(N=CN2CC3=NN(CCCCCCC(NC4=CC=CC=C4F)=O)N=N3)N(C)C(N1C)=O	-9.661625	-9.580032
O=C1C2=C(N=CN2CC3=NN=NN3CCCCCCCC(NC4=CC=CC5=C4C=CC=C5)=O)N(C)C(N1C)=O	-9.926688	-9.291291
O=C1C2=C(N=CN2CC3=NN(CCCCCCC(NC4=CC=CC=C4Cl)=O)N=N3)N(C)C(N1C)=O	-10.036669	-9.180031
O=C1C2=C(N=CN2CC3=NN=NN3CCCCCC(NC4=CC=CC=C4F)=O)N(C)C(N1C)=O	-9.723577	-9.491406
O=C1C2=C(N=CN2CC3=NN(CCCCCC(NC4=CC=C(Br)C=C4)=O)N=N3)N(C)C(N1C)=O	-9.914809	-9.293579
O=C1C2=C(N=CN2CC3=NN=NN3CCCCCCCC(NC4=CC=CC(F)=C4)=O)N(C)C(N1C)=O	-9.753476	-9.43736
O=C1C2=C(N=CN2CC3=NN=NN3CCCCCCCC(NC4=CC=CC=C4F)=O)N(C)C(N1C)=O	-9.646044	-9.5428915
O=C1C2=C(N=CN2CC3=NN(CCCCCCC(NC4=CC=CC(F)=C4)=O)N=N3)N(C)C(N1C)=O	-9.598281	-9.569607
O=C1C2=C(N=CN2CC3=NN(CCCCCC(NC4=CC=CC=C4F)=O)N=N3)N(C)C(N1C)=O	-9.702657	-9.363819
O=C1C2=C(N=CN2CC3=NN(CCCCCC(NC4=CC=CC(Cl)=C4)=O)N=N3)N(C)C(N1C)=O	-9.755661	-9.306952
O=C1C2=C(N=CN2CC3=NN(CCCCCC(NC4=CC=CC(F)=C4)=O)N=N3)N(C)C(N1C)=O	-9.5940485	-9.454989
O=C1C2=C(N=CN2CC3=NN=NN3CCCCCC(NC4=CC=C(OC)C=C4OC)=O)N(C)C(N1C)=O	-9.763484	-9.238015
O=C1C2=C(N=CN2CC3=NN(CCCCCC(NC4=CC=CC=C4Cl)=O)N=N3)N(C)C(N1C)=O	-9.83854	-9.161812
O=C1C2=C(N=CN2CC3=NN=NN3CCCCCC(NC4=CC=CC5=C4C=CC=C5)=O)N(C)C(N1C)=O	-9.739863	-9.246615
O=C1C2=C(N=CN2CC3=NN(CCCCCC(NC4=CC=C(F)C=C4)=O)N=N3)N(C)C(N1C)=O	-9.627663	-9.353492
O=C1C2=C(N(C(N1C)=O)C)N=CN2CC3=NN(N=N3)CCCCCCC(NC4=CC=CC5=C4C=CC=C5)=O	-9.423247	-9.548932

O=C1C2=C(N=CN2CC3=NN=NN3CCCCCC(NC4=CC=C(F)C=C4)=O)N(C)C(N1C)=O	-9.805064	-9.129618
O=C1C2=C(N=CN2CC3=NN(CCCCCC(NC4=CC=C([N+]([O-])=O)C=C4)=O)N=N3)N(C)C(N1C)=O	-9.50172	-9.42738
O=C1C2=C(N=CN2CC3=NN(CCCCCC(NC4=CC=C(Cl)C=C4)=O)N=N3)N(C)C(N1C)=O	-9.684119	-9.243118
O=C1C2=C(N=CN2CC3=NN(CCCCCCC(NC4=CC=C(OC)C=C4OC)=O)N=N3)N(C)C(N1C)=O	-9.500409	-9.411681
O=C1C2=C(N=CN2CC3=NN=NN3CCCCCC(NC4=CC=CC(F)=C4)=O)N(C)C(N1C)=O	-9.707659	-9.196531
O=C1C2=C(N=CN2CC3=NN(CCCCCCC(NC4=CC=C(OC)C=C4)=O)N=N3)N(C)C(N1C)=O	-9.241608	-9.577578
O=C1C2=C(N=CN2CC3=NN(CCCCCC(NC4=CC=C(OC)C=C4OC)=O)N=N3)N(C)C(N1C)=O	-9.39806	-9.407064
O=C1C2=C(N(C(N1C)=O)C)N=CN2CC3=NN(N=N3)CCCCCC(NC4=CC=CC5=C4C=CC=C5)=O	-9.231118	-9.521998
O=C1C2=C(N=CN2CC3=NN=NN3CCCCCCC(NC4=CC=CC=C4)=O)N(C)C(N1C)=O	-9.670733	-9.074527
O=C1C2=C(N=CN2CC3=NN(CCCCC(NC4=CC=C(F)C(Cl)=C4)=O)N=N3)N(C)C(N1C)=O	-9.268599	-9.411899
O=C1C2=C(N=CN2CC3=NN=NN3CCCCCC(NC4=CC=CC=C4)=O)N(C)C(N1C)=O	-9.682138	-8.986335
O=C1C2=C(N=CN2CC3=NN(CCCCCC(NC4=CC=C(OC)C=C4)=O)N=N3)N(C)C(N1C)=O	-9.213857	-9.4022045
O=C1C2=C(N=CN2CC3=NN(CCCCC(NC4=CC=C(Br)C=C4)=O)N=N3)N(C)C(N1C)=O	-9.250253	-9.343806
O=C1C2=C(N=CN2CC3=NN=NN3CCCCCC(NC4=CC=CC=N4)=O)N(C)C(N1C)=O	-9.6973295	-8.875869
O=C1C2=C(N(C(N1C)=O)C)N=CN2CC3=NN(N=N3)CCCCC(NC4=CC=CC5=C4C=CC=C5)=O	-9.061124	-9.488653
O=C1C2=C(N=CN2CC3=NN=NN3CCCCCCC(NC4=CC=CC=N4)=O)N(C)C(N1C)=O	-9.628928	-8.899093
O=C1C2=C(N=CN2CC3=NN(CCCCC(NC4=CC=C(OC)C=C4)=O)N=N3)N(C)C(N1C)=O	-9.240488	-9.225705
O=C1C2=C(N=CN2CC3=NN(CCCCC(NC4=CC=C(F)C=C4)=O)N=N3)N(C)C(N1C)=O	-9.111293	-9.3255
O=C1C2=C(N=CN2CC3=NN(CCCCC(NC4=CC=CC(F)=C4)=O)N=N3)N(C)C(N1C)=O	-9.066723	-9.36249
O=C1C2=C(N=CN2CC3=NN(CCCCC(NC4=CC=C(OC)C=C4OC)=O)N=N3)N(C)C(N1C)=O	-9.020803	-9.37702
O=C1C2=C(N=CN2CC3=NN(CCCCC(NC4=CC=C(Cl)C=C4)=O)N=N3)N(C)C(N1C)=O	-9.137405	-9.220517
O=C1C2=C(N=CN2CC3=NN(CCCCC(NC4=CC=CC(Cl)=C4)=O)N=N3)N(C)C(N1C)=O	-9.119699	-9.222841
O=C1C2=C(N=CN2CC3=NN(CCCCC(NC4=CC=CC=C4F)=O)N=N3)N(C)C(N1C)=O	-9.052198	-9.27806
O=C1C2=C(N=CN2CC3=NN(CCCCC(NC4=CC=C([N+]([O-])=O)C=C4)=O)N=N3)N(C)C(N1C)=O	-9.101535	-9.223135
O=C1C2=C(N=CN2CC3=NN(CCCCC(NC4=CC=CC=C4Cl)=O)N=N3)N(C)C(N1C)=O	-9.252419	-8.997787
O=C1C2=C(N=CN2CC3=NN(CCCCCCC(NC4=CC=CC=N4)=O)N=N3)N(C)C(N1C)=O	-9.148231	-9.059104
O=C1C2=C(N=CN2CC3=NN(CCCCCC(NC4=CC=CC=N4)=O)N=N3)N(C)C(N1C)=O	-9.124372	-9.056039
O=C1C2=C(N=CN2CC3=NN(CCCCCC(NC4=CC=CC=C4)=O)N=N3)N(C)C(N1C)=O	-9.015229	-9.076412
O=C1C2=C(N=CN2CC3=NN(CCCCCCC(NC4=CC=CC=C4)=O)N=N3)N(C)C(N1C)=O	-8.969881	-9.117786
O=C1C2=C(N=CN2CC3=NN(CCCCC(NC4=CC=CC=N4)=O)N=N3)N(C)C(N1C)=O	-8.980835	-9.083343
O=C1C2=C(N=CN2CC3=NN(CCCCC(NC4=CC=CC=C4)=O)N=N3)N(C)C(N1C)=O	-8.820724	-9.052842
O=C1C2=C(N(C(N1C)=O)C)N=CN2CC3=NN(N=N3)CCCCCC(OC4=CC=CC=C4)=O	-8.85575	-9.355982
O=C1C2=C(N(C(N1C)=O)C)N=CN2CC3=NN(N=N3)CCCCC(OC4=CC=C(OC)C=C4)=O	-8.806358	-9.129724
O=C1C2=C(N(C(N1C)=O)C)N=CN2CC3=NN(N=N3)CCCCCCC(OC4=CC=C(OC)C=C4)=O	-8.927311	-9.225198
O=C1C2=C(N(C(N1C)=O)C)N=CN2CC3=NN(N=N3)CCCCCCCC(OC4=CC=C(OC)C=C4)=O	-8.86567	-9.398321

CHEMISTRY RESULTS

Detailed synthetic protocol



3: n=4; **4**: n=5; **5**: n=6
6: n=4; **7**: n=5; **8**: n=6
11: n=4, X=NH, R=H.
12: n=4, X=NH, R=2-F,4-I.
13: n=4, X=O, R=4-OCH_3.
14: n=5, X=NH, R=3-Cl.
15: n=5, X=NH, R=4-Br.
16: n=5, X=NH, R=3-Cl,4-F.
17: n=5, X=NH, R=2-F,4-I.
18: n=5, X=O, R=H.
19: n=5, X=O, R=4-OCH_3.
20: n=6, X=NH, R=3-Cl.
21: n=6, X=NH, R=4-Cl.
22: n=6, X=NH, 4-Br.
23: n=6, X=NH, R=3-Cl,4-F.
24: n=6, X=O, R=4-OCH_3.
25: n=6, X=NH, R= 4-Br.
26: n=6, X=NH, R=3-Cl,4-F.
27: n=6, X=NH, R=2-F,4-I.

5-(5-((1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydro-7H-purin-7-yl)methyl)-2H-tetrazol-2-yl)-N phenylpentanamide (11). Prepared from acid (**7**) and aniline following general procedure (d) to afford a off-white solid, yield: 60%. ^{1}H NMR (500 MHz, $CDCl_3$) *δ* ppm: 7.76 (s, 1H, H2''), 7.50 (m, 3H, CO-NH, H2', H6'), 7.31 (t, 2H, H3', H5', *J* = 8.0Hz), 7.10 (t, 1H, H4', *J* = 7.5 Hz), 5.82 (s, 2H, N1''-CH_2), 4.65 (t, 2H, H5, *J* = 7.0 Hz), 3.60 (s, 3H, N5''-CH_3), 3.36 (s, 3H, N7''-CH_3), 2.32 (t, 2H, H2, *J* = 7.0 Hz), 2.11 (quint, 2H, H4, *J* = 7.0 Hz), 1.77 (quint, 2H, H3, *J* = 7.5 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.130 (C=O), 161.523 (N=C-N), 155.286 (C8''), 151.620 (C6''), 148.853 (C4''), 141.653 (C2''), 137.845 (C1'), 129.034 (C3', C5'), 124.348 (C4'), 119.780 (C2', C6'), 106.934 (C9''), 53.198 (C5), 41.383 (N1''-CH_2), 36.226 (C2), 29.883 (N5''-CH_3), 28.396 (N7''-CH_3), 28.042 (C4), 22.063 (C3). HRMS (ESI) m/z calc. for $C_{20}H_{23}N_9O_3$ $[M+H]^+$ 438.1997, **found 438.1951; 301.1392**

***5-(5-((1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydro-7H-purin-7-yl)methyl)-2H-tetrazol-2-yl)-N-(2-fluoro-4-iodophenyl)pentanamide* (*12*).** Prepared from acid (**7**) and 2-flouro-4-iodoaniline following general procedure (d) to afford a off-white solid, yield: 56.1%. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 8.06 (s, 1H, H3'), 7.76 (s, 1H, H2''), 7.44 (m, 3H, CO-NH,', H5', H6'), 5.84 (s, 2H, N1''-CH_2), 4.65 (t, 2H, H5, *J* = 7.0 Hz), 3.60 (s, 3H, N5''-CH_3), 3.37 (s, 3H, N7''-CH_3), 2.41 (t, 2H, H2, *J* = 7.0 Hz), 2.11 (quint, 2H, H4, *J* = 7.0 Hz), 1.76 (quint, 2H, H3, *J* = 7.5 Hz). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 170.106 (C=O), 161.513 (N=C-N), 155.203 (C8''), 151,626 (C6''), 152.763-150.792 (C2', $^{1}J_{C\text{-}F}$ = 246.48 Hz), 148.741 (C4''), 141.526 (C2''), 133.829-133.800 (C4', $^{3}J_{C\text{-}F}$ = 3.63 Hz), 126.150 (C1'), 124.049-123.878 (C3', $^{2}J_{C\text{-}F}$ = 21.38 Hz), 123.115 (C5'), 123.115 (C6'), 106.903 (C9''), 53.095 (C5), 41.247 (N1'-CH_2), 36.220 (C2), 29.848 (N5''-CH_3), 28.393 (N7''-CH_3), 27.986 (C4), 21.822 (C3). HRMS (ESI) m/z calc. for $C_{20}H_{21}FIN_9O_3$ $[M+Na]^+$ 604.0688, found 604.0682.

4-methoxyphenyl 5-(5-((1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydro-7H-purin-7-yl)methyl)-2H-tetrazol-2-yl)pentanoate (13). Prepared from acid (**7**) and 4-methoxyphenol following general procedure (d) to afford a off-white solid, **yield: 63.1%** ^{1}H NMR (600 MHz, $CDCl_3$) δ ppm: 7.74 (s, 1H, H2''), 6.97 (dd, 2H, H2', H6', J_1 = 7.2 Hz, J_2 = 1.8 Hz), 6.88 (dd, 2H, H3', H5', J_1 = 5 Hz, J_2 = 2.4 Hz), 5.85 (s, 2H, N1''-CH_2), 4.66 (t, 2H, H5, *J* = 7.2 Hz), 3.80 (s, 3H, OCH_3), 3.59 (s, 3H, N5''-CH_3), 3.39 (s, 3H, N7''-CH_3), 2.58 (t, 2H, H2, *J* = 7.2 Hz), 2.13 (m, 2H, H4), 1.77 (m, 2H, H3). ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.564 (C=O), 161.510 (N=C-N), 157.338 (C4'), 155.218 (C8''), 151.662 (C6''), 148.690 (C4''), 144.023 (C2''), 141.441 (C1'), 122.168 (C2', C6'), 114.495 (C3', C5'), 106.915 (C9''), 55.601 (OCH_3), 53.009 (C5), 41.112 (N1''-CH_2), 33.257 (C2), 29.793 (N5''-CH_3), 28.451 (N7''-CH_3), 27.958 (C4), 21.627 (C3). HRMS (ESI) m/z calc. for $C_{21}H_{24}N_8O_5$ $[M+Na]^+$ 491.1762, found 491.1723.

N-(3-chlorophenyl)-6-(5-((1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydro-7H-purin-7-yl)methyl)-2H-tetrazol-2-yl)hexanamide (14). Prepared from acid (**8**) and 3-chloroaniline following general procedure (d) to afford a off-white solid, yield: 50.2%. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.79 (s, 1H, H2''), 7.68 (s, 1H, H2'), 7.58 (s, 1H, CO-NH), 7.40 (d, 1H, H6', *J* = 8.0 Hz), 7.26 (t, 1H, H5', *J* = 8.0 Hz), 7.10 (d, 1H, H4', *J* = 7.0 Hz), 5.85 (s, 2H, N1''-CH_2), 4.63 (t, 2H, H6, *J* = 7.0 Hz), 3.63 (s, 3H, N5''-CH_3), 3.41 (s, 3H, N7''-CH_3), 2.32 (t, 2H, H2, *J* = 7.5 Hz), 2.05 (quint, 2H, H5, J_1 = 7.5 Hz, J_2 = 7.5 Hz), 1.76 (quint, 2H, H4, *J* = 7.5 Hz), 1.38 (quint, 2H, H3, *J* = 7.5 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.800 (C=O), 161.440 (N=C-N), 155.282 (C8''), 151.652 (C6''), 148.816 (C4''), 141.658 (C2''), 139.105 (C1), 134.663 (C3'), 130.001 (C5'), 124.268 (C4'), 119.815 (C2'), 117.626 (C6'), 106.914 (C9''), 53.159 (C6), 41.283 (N1''-CH_2), 37.106 (C2), 29.893 (N5''-CH_3), 28.766 (N7''-CH_3), 28.061 (C4), 25.816 (C5), 24.315 (C3). HRMS (ESI) m/z calc. for $C_{21}H_{24}{}^{35}ClN_9O_3$ $[M+Na]^+$ 508.1583, found 508.1579; calc. for $C_{21}H_{24}{}^{37}ClN_9O_3$ $[M+Na]^+$ 510.1553, found 510.1563.

N-(4-bromophenyl)-6-(5-((1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydro-7H-purin-7-yl)methyl)-2H-tetrazol-2-yl)hexanamide (15). Prepared from acid (**8**) and 4-bromoaniline following general procedure (d) to afford a off-white solid, yield: 54.1%. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.76 (s, 1H, H2''), 7.505 (s, 1H, CO-NH), 7.43 (m, 4H, H2', H3', H5', H6'), 5.83 (s, 2H, N1''-CH_2), 4.61 (t, 2H, H6, *J* = 7.0 Hz), 3.60 (s, 3H, N5''-CH_3), 3.39 (s, 3H, N7''-CH_3), 2.29 (t, 2H, H2, *J* = 7.5 Hz), 2.03 (quint, 2H, H5, J_1= 7.5 Hz, J_2= 7.0 Hz), 1.74 (quint, 2H, H4, *J* = 7.5 Hz), 1.36 (t, 2H, H3, *J* = 7.5 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.691 (C=O), 161.439 (N=C-N), 155.275 (C8''), 151.650 (C6''), 148.810 (C48''), 141.632 (C2''), 137.035 (C1'), 131.974 (C3', C5'), 121.282 (C2', C6'), 116.778 (C4'), 106.909 (C9''), 53.157 (C6), 41.267 (N1''-C), 37.106 (C2), 29.886 (N5''-CH_3), 28.765 (N7''-CH_3), 28.052 (C5), 25.829 (C4), 24.323 (C3). HRMS (ESI) m/z calc. for $C_{21}H_{24}{}^{79}BrN_9O_3$ $[M+Na]^+$ 552.1078, found 552.1069; calc. for $C_{21}H_{24}{}^{81}BrN_9O_3$ $[M+Na]^+$ 554.1057, found 554.1058.

N-(3-chloro-4-fluorophenyl)-6-(5-((1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydro-7H-purin-7-yl)methyl)-2H-tetrazol-2-yl)hexanamide (16). Prepared from acid (**8**) and 3-chloro-4-fluoro-bromoaniline following general procedure (d) to afford a off-white solid, yield: 61.6%. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.77 (s, 1H, H2''), 7.73 (dd, 1H, H2', J_1 = 6.5 Hz, J_2 = 2.5 Hz), 7.63 (s, 1H, CO-NH'), 7.35 (t, 1H, H5'), 7.08 (t, 1H, H6', *J* = 8.5 Hz) 5.83 (s, 2H, N1''-CH_2), 4.61 (t, 2H, H6, *J* = 7.0 Hz), 3.61 (s, 3H, N5''-CH_3), 3.39 (s, 3H, N7''-CH_3), 2.29 (t, 2H, H2, *J* = 7.5 Hz), 2.03 (m, 2H, H5), 1.73 (quint, 2H, H4, *J* = 7.5 Hz), 1.34 (quint, 2H, H3, *J* = 7.5 Hz).^{13}C NMR (125 MHz, $CDCl_3$) δ 170.770 (C=O), 161.451 (N=C-N), 155.668-153.709 (C4', $^{1}J_{C\text{-}F}$ = 244.88 Hz) 155.297 (C8''), 151.641 (C6''), 148.852 (C4''), 141.689 (C2''), 134.621 (C1'), 122.017 (C6'), 121.028 (C3'), 119.430-119.375 (C2', $^{3}J_{C\text{-}F}$ = 6,88 Hz), 116.678-116.504 (C5', $^{2}J_{C\text{-}F}$ = 21.75 Hz), 106.906 (C9''), 53.152 (C6), 41.308 (N1''-C), 36.966 (C2), 29.705 (N5''-CH_3), 28.733 (N7''-CH_3), 28.067 (C4), 25.817 (C5), 24.294 (C3). HRMS (ESI) m/z calc. for $C_{21}H_{23}{}^{35}ClFN_9O_3$ $[M+Na]^+$ 526.1489 , found 526.1482; calc. for $C_{21}H_{23}{}^{37}ClFN_9O_3$ $[M+Na]^+$ 528.1459 , found 528.1483.

6-(5-((1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydro-7H-purin-7-yl)methyl)-2H-tetrazol-2-yl)-N-(2-fluoro-4-iodophenyl)hexanamide (17). Prepared from acid (**8**) and 2-fluoro-4-iodo-bromoaniline following general procedure (d) to afford a off-white solid, yield: 44.3%. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 8.08 (s, 1H, H3'), 7.75 (s, 1H, H2''), 7.42 (m, 3H, CO-NH, H5', H6'), 5.84 (s, 2H, N1''-CH_2), 4.61 (t, 2H, H6, *J* = 7.0Hz), 3.59 (s, 3H, N5''-CH_3), 3.39 (s, 3H, N7''-CH_3), 2.38 (t, 2H, H2, *J* = 7.5Hz), 2.04 (quint, 2H, H5, J_1 = 7.5Hz, J_2= 7.0Hz), 1.75 (quint, 2H, H3, J_1 = 8.0Hz, J_2= 7.5Hz), 1.39 (quint, 2H, H4, J_1 = 8.0Hz, J_2 = 7.5Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.674 (C=O), 161.433 (N=C-N), 155.225 (C8''), 151.661 (C6''), 148.710 (C4''), 141.511 (C2', C2''), 133.836 (C3'), 133.806 (C1'), 124.033 (C5') 123.856 (C4'), 123.091 (C6'), 106.915 (C9''), 53.157 (C6), 41.165 (N1''-CH_2), 37.090 (C2), 29.848 (N5''-CH_3), 28.871 (N7''-CH_3), 28.008 (C5), 25.817 (C4), 24.322 (C3). HRMS (ESI) m/z calc. for $C_{21}H_{23}FIN_9O_3$ $[M+H]^+$ 618.0845, found 618.0848.

Phenyl 6-(5-((1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydro-7H-purin-7-yl)methyl)-2H-tetrazol-2-yl)hexanoate (18). Prepared from acid (8) and phenol following general procedure (d) to afford a off-white solid, yield: 35.3%. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 8.24 (s, 1H, H2''), 7.41 (t, 2H, H3', H5', *J* = 8.0Hz), 7.25 (t, 1H, H4', *J* =7.5Hz), 7.09 (d, 2H, H2', H6', *J* = 7.5Hz), 5.85 (s, 2H, N1''-CH_2), 4.67 (t, 2H, H6, *J* = 7.0Hz), 3.44 (s, 3H, N5''-CH_3), 3.17 (s, 3H, N7''-CH_3), 2.54 (t, 2H, H2, *J* = 7.5Hz), 1.92 (quint, 2H, H5, J_1 = 7.5Hz, J_2 = 7.0Hz), 1.64 (quint, 2H, H3, J_1 = 7.5Hz, J_2 = 7.0Hz), 1.30 (quint, 2H, H4, J_1 = 7.5Hz, J_2 = 7.0Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.084 (C=O), 162.589 (N=C-N), 154.672 (C8''), 151.457-150.921 (C6''), 148.737 (C4''), 143.630 (C2''), 129.926 (C3', C5'), 126.215 (C4'), 122.246 (C2', C6'), 106.570 (C9''), 53.008 (C6), 41.648 (N1''-CH_2), 33.682 (C2), 29.951 (N5''-CH_3), 28.788 (N7''-CH_3), 27.934 (C4), 25.477 (C5), 24.047 (C3). HRMS (ESI) m/z calc. for $C_{21}H_{24}N_8O_4$ $[M+Na]^+$ 475.1813 , found 475.1876.

4-methoxyphenyl 6-(5-((1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydro-7H-purin-7-yl)methyl)-2H-tetrazol-2-yl)hexanoate (19). Prepared from acid (**8**) and 4-methoxyphenol following general procedure (d) to afford a off-white solid, yield: 44.2% ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.76 (s, 1H, H2''), 6.99 (m, 2H, H2', H6'), 6.90 (m, 2H, H3', H5'), 5.87 (s, 2H, N1''-CH_2), 4.65 (t, 2H, H6, *J* = 7.0Hz), 3.82 (s, 3H, OCH_3), 3.62 (s, 3H, N5''-CH_3), 3.42 (s, 3H, N7''-CH_3), 2.56 (t, 2H, H2, *J* = 7.5Hz), 2.08 (quint, 2H, H5, *J* = 7.0Hz), 1.80 (quint, 2H, H4, *J* = 7.5Hz), 1.46 (quint, 2H, H3, *J* = 7.0Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.083 (C=O), 161.455 (N=C-N), 157.277 (C4'), 155.222 (C8''), 151.676 (C6''), 148.681 (C4''), 144.081 (C2''), 141.461 (C1'), 122.235 (2C, C2',C6'), 114.477 (2C, C3', C5'), 106.919 (C9'')55.609 (OCH_3), 53.198 (C6), 41.130 (N1''-CH_2), 33.833 (C5), 29.826 (N5''-CH_3), 28.863 (N7''-CH_3), 27.990 (C2), 25.751 (C4), 24.082 (C3). HRMS (ESI) m/z calc. for $C_{22}H_{26}N_8O_5$ $[M+Na]^+$ 483.2099 , found 483.2080.

N-(3-chlorophenyl)-7-(5-((1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydro-7H-purin-7-yl)methyl)-2H-tetrazol-2-yl)heptanamide (20). Prepared from acid (9) and 3-chloroaniline following general procedure (d) to afford a off-white solid off-white solid, yield: 50.2%. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.79 (s, 1H, H2''), 7.68 (s, 2H, H2', CO-NH), 7.40 (d, 1H, H6', *J* = 8.0Hz), 7.24 (t, 1H, H5', *J* = 8.0Hz), 7.09 (d, 1H, H4', *J* = 7.5Hz), 5.87 (s, 2H, N1''-CH_2), 4.62 (t, 2H, H7, *J* = 7.0Hz), 3.62 (s, 3H, N5''-CH_3), 3.41 (s, 3H, N7''-CH_3), 2.32 (t, 2H, H2, *J* = 7.0Hz), 2.02 (quint, 2H, H6, *J* = 7.0Hz), 1.72 (quint, 2H, H3, *J* = 7.5Hz), 1.36 (m, 4H, H4, H5). ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.124 (C=O), 161.432 (N=C-N), 155.301 (C8''), 151.630 (C6''), 148.783 (C4''), 141.607 (C2''), 139.234 (C1'), 134.635 (C3'), 129.979 (C5'), 124.164 (C4'), 119.769 (C2'), 117.586 (C6'), 106.916 (C9''), 53.244 (C7), 41.254 (N1''-C), 36.930 (C2), 29.886 (N5''-CH_3), 28.821 (N7''-CH_3), 28.055 (C4), 27.987 (C6), 25.666 (C5), 24.759 (C3). HRMS (ESI) m/z calc. for $C_{22}H_{26}{}^{35}ClN_9O_5$ $[M+Na]^+$ 522.1739 , found 522.1722; calc. for $C_{22}H_{26}{}^{37}ClN_9O_5$ $[M+Na]^+$ 524.1719 , found 524.1725.

N-(4-chlorophenyl)-7-(5-((1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydro-7H-purin-7-yl)methyl)-2H-tetrazol-2-yl)heptanamide (21). Prepared from acid (**9**) and 4-chloroaniline following general procedure (d) to afford a off-white solid off-white solid, yield: 46.2%. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.78 (s, 1H, H2''), 7.61 (s, 1H, CO-NH), 7.52 (d, 2H, H2', H6', *J* = 9.0Hz), 7.29 (t, 2H, H3', H5', *J* = 5.0 Hz), 5.86 (s, 2H, N1''-CH_2), 4.62 (t, 2H, H7, *J* = 7.0Hz), 3.62 (s, 3H, N5''-CH_3), 3.41 (s, 3H, N7''-CH_3), 2.32 (t, 2H, H2, *J* = 7.0Hz), 2.02 (quint, 2H, H6, *J* = 7.0Hz), 1.72 (t, 2H, H3, *J* = 7.5Hz), 1.40 (m, 4H, H4, H5). ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.042 (C=O), 161.429 (N=C-N), 155.289 (C8''), 151.631 (C6''), 148.771 (C4''), 141.600 (C2''), 136.650 (C1'), 128.991 (C2', C6'), 128.991 (C3', C5'), 120.936 (C4'), 106.915 (C9''), 53.254 (C7), 41.247 (N1''-CH_2), 36.950 (C2), 29.883 (N5''-CH_3), 28.822 (N7''-CH_3), 28.048 (C4), 28.029 (C6), 25.686 (C5), 24.805 (C3). HRMS (ESI) m/z calc. for $C_{22}H_{26}{}^{35}ClN_9O_5$ $[M+Na]^+$ 522.1739 , found 522.1718; calc. for $C_{22}H_{26}{}^{37}ClN_9O_5$ $[M+Na]^+$ 524.1719, found 524.1724.

***N-(4-bromophenyl)-7-(5-((1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydro-7H-purin-7-yl)methyl)-2H-tetrazol-2-yl)heptanamide* (22).** Prepared from acid (9) and 4-bromoaniline following general procedure (d) to afford a off-white solid off-white solid, yield: 40.6%. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.76 (s, 1H, H2''), 7.57 (s, 1H, CO-NH), 7.43 (m, 4H, H2', H3', H5', H6'), 5.84 (s, 2H, N1''-CH_2), 4.60 (t, 2H, H7, *J* = 7.0Hz), 3.60 (s, 3H, N5''-CH_3), 3.39 (s, 3H, N7''-CH_3), 2.30 (t, 2H, H2, *J* = 7.5Hz), 2.00 (quint, 2H, H6, *J* = 7.0Hz), 1.70 (quint, 2H, H3, *J* = 7.0Hz), 1.34 (m, 4H, H4, H5). ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.996 (C=O), 161.425 (N=C-N), 155.298 (C8''), 151.632 (C6''), 148.776 (C4''), 141.582 (C2''), 137.133 (C1'), 131.957 (C2', C6'), 121.237 (C3', C5'), 116.680 (C4'), 106.914 (C9''), 53.245 (C7), 41.247 (N1''- CH_2), 36.969 (C2), 29.883 (N5''-CH_3), 28.812 (N7''-CH_3), 28.048 (C6), 27.999 (C3), 25.661 (C5), 24.763 (C4). HRMS (ESI) m/z calc. for $C_{22}H_{26}{}^{79}BrN_9O_5$ $[M+Na]^+$ 566.1234 , found 566.1231 ; calc. for $C_{22}H_{26}{}^{81}BrN_9O_5$ $[M+Na]^+$ 568.1214 , found 568.1207.

N-(3-chloro-4-fluorophenyl)-7-(5-((1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydro-7H-purin-7-yl)methyl)-2H-tetrazol-2-yl)heptanamide (23). Prepared from acid (**9**) and 3-chloro-4-fluoroaniline following general procedure (d) to afford a off-white solid off-white solid, yield: 60.9%. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.77 (s, 1H, H2'') 7.73 (d, 1H, H2', J = 3.5Hz), 7.65 (s, 1H, CO-NH) 7.35 (d, 1H, H5', *J* = 8.5Hz), 7.07 (t, 1H, H6', *J* = 8.5Hz), 5.85 (s, 2H, N1''-CH_2), 4.61 (t, 2H, H7, *J* = 7.0Hz), 3.60 (s, 3H, N5''-CH_3), 3.39 (s, 3H, N7''-CH_3), 2,29 (t, 2H, H2, *J* = 7.5Hz), 2.00 (m, 2H, H6), 1.70 (m, 2H, H3), 1.38 (m, 2H, H5), 1.31 (m, 2H,H4). ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.042 (C=O), 161.436 (N=C-N), 155.318 (C8''), 153.655 (C4'), 151.619 (C6''), 148.805 (C4''), 141.625 (C2''), 134.697 (C1'), 121.955 (C6'), 119.302 (C3'), 116.654 (C2'), 116.479(C5'), 106.910 (C9''), 53.229 (C7), 41.276 (N1''-CH_2), 36.755 (C2), 29.895(N5''-CH_3), 28.787 (N7''-CH_3), 28.060 (C4), 27.391 (C6), 25.604 (C5), 24.717 (C3). HRMS (ESI) m/z calc. for $C_{22}H_{25}{}^{35}ClFN_9O_5$ $[M+Na]^+$ 540.1645 , found 540.1605 ; calc. for $C_{22}H_{25}{}^{37}ClFN_9O_5$ $[M+Na]^+$ 542.1616 , found 542.1601.

4-methoxyphenyl 7-(5-((1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydro-7H-purin-7-yl)methyl)-2H-tetrazol-2-yl)heptanoate (24). Prepared from acid (**9**) and 4-methoxyphenol following general procedure (d) to afford a off-white solid off-white, yield: 48.7%. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.76 (s, 1H, H2''), 7.01 (d, 2H, H2', H6', *J* = 9.0Hz), 6.90 (d, 2H, H3', H5', *J* = 9.0Hz), 5.87 (s, 2H, N1''-CH_2), 4.63 (t, 2H, H7, *J* = 7.0Hz), 3.82 (s, 3H, OCH_3), 3.62 (s, 3H, N5''-CH_3), 3.42 (s, 3H, N7''-CH_3), 2.55 (t, 2H, H2, *J* = 7.5Hz), 2.05 (quint, 2H, H6, *J* = 7.5Hz), 1.75 (quint, 2H, H3, *J* = 7.5Hz), 1.47 (m, 2H, H5), 1.41 (m, 2H, H4). ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.360 (C=O), 157.239 (C4'), 155.222 (C8''), 151.676 (C6''), 144.135 (C2'') 141.453 (C1'), 122.268 (C2', C6'), 114.464 (C3', C5'), 106.923 (C9''), 55.606 (OCH_3), 53.338 (C7), 41.130 (N1''-CH_2), 34.016 (C2), 29.829 (N5''-CH_3), 28.977 (N7''-CH_3), 28.253 (C4), 27.992 (C6), 25.958 (C5), 24.536 (C3). HRMS (ESI) m/z calc. for $C_{23}H_{28}N_8O_5$ $[M+Na]^+$ 497.2255 , found 497.2240.

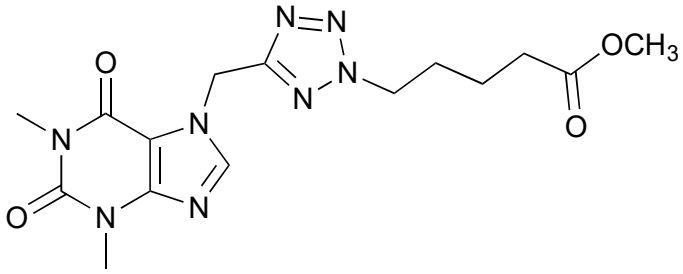
N-(4-bromophenyl)-7-(5-((1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydro-7H-purin-7-yl)methyl)-1H-tetrazol-1-yl)heptanamide (25). Prepared from acid (**10**) and 4-bromoaniline following general procedure (d) to afford a off-white solid off-white, yield: 64.5%. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.91 (s, 1H, H2''), 7.43 (m, 5H, CO-NH, H2', H3', H5', H6', *J* = 7.5Hz), 5.88 (s, 2H, N1''-CH_2), 4.55 (t, 2H, H7, *J* = 7.0Hz), 3.62 (s, 3H, N5''-CH_3), 3.39 (s, 3H, N7''-CH_3), 2,34 (t, 2H, H2, *J* = 7.0Hz), 1.94 (quint, 2H, H6, *J* = 7.0Hz), 1.73 (quint, 2H, H3, *J* = 7.5Hz), 1.40 (m, 4H, H4, H5). ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.965 (C=O), 155.606 (N=C-N), 151.426 (C8''), 150.251 (C6''), 148.813 (C4''), 142.139 (C2''), 136.987 (C1'), 131.948 (C2', C6'), 121.206 (C3', C5'), 116.762 (C4'), 106.217 (C9''), 47.639 (C7), 37.908 (N1''-C), 37.068 (C2), 29.990 (N5''-CH_3), 29.713 (N7''-CH_3), 29.565 (C6), 28.059 (C3), 25.748 (C5), 24.743 (C4). HRMS (ESI) m/z calc. for $C_{22}H_{26}{}^{79}BrN_9O_5$ $[M+Na]^+$ 566.1234 , found 566.1241 ; calc. for $C_{22}H_{26}{}^{81}BrN_9O_5$ $[M+Na]^+$ 568.1214 , found 568.1228.

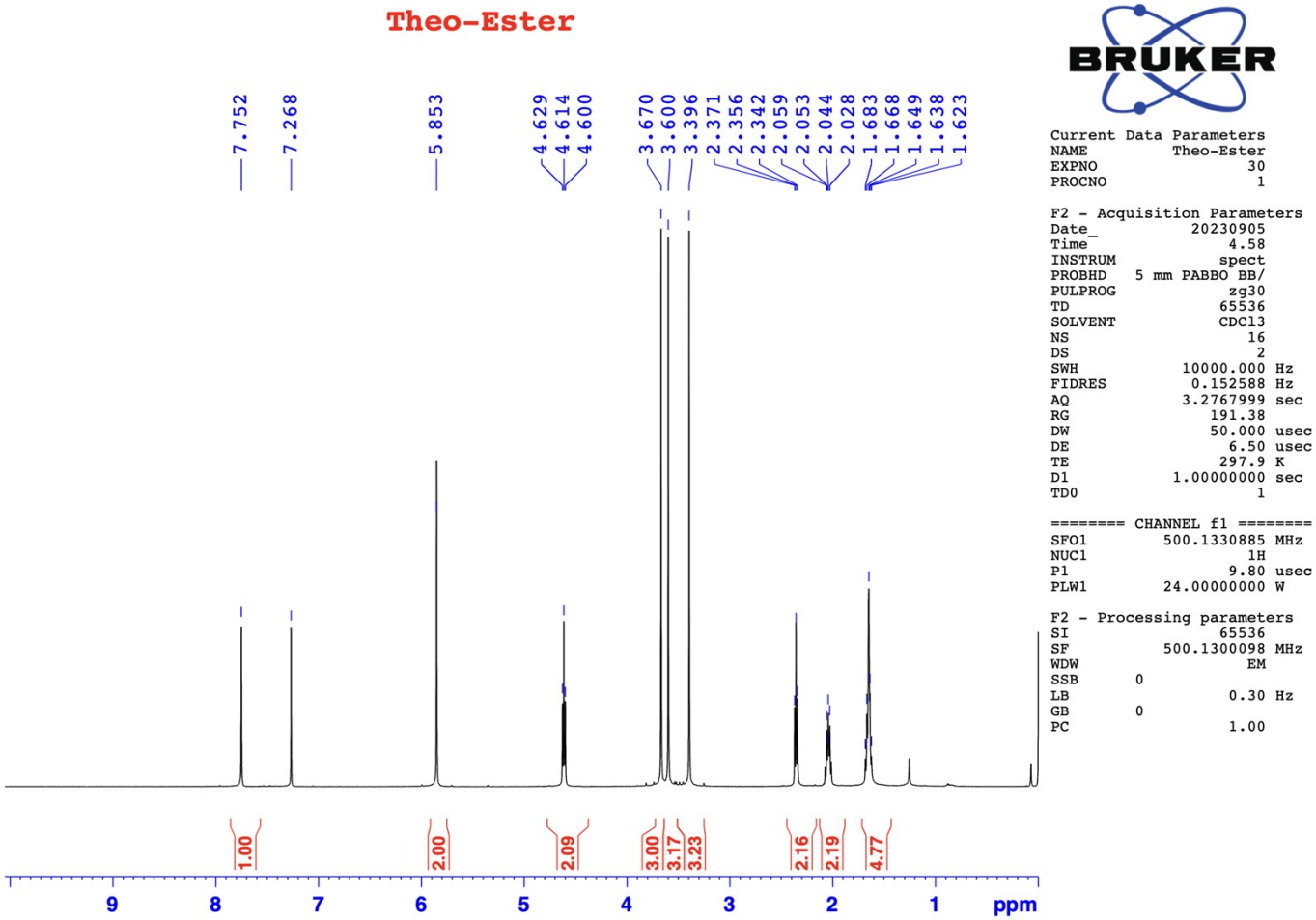
N-(3-chloro-4-fluorophenyl)-7-(5-((1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydro-7H-purin-7-yl)methyl)-1H-tetrazol-1-yl)heptanamide (26). Prepared from acid (**10**) and 3-chloro-4-fluoroaniline following general procedure (d) to afford a off-white solid, yield: 72.4%. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.91 (s, 1H, H2''), 7.74 (m, 1H, CO-NH), 7.56 (brs, 1H, H2'), 7.34 (m, 1H, H5'), 7.08 (t, 1H, H6', *J* = 8.5Hz), 5.89 (s, 2H, N1''-CH_2), 4.55 (t, 2H, H6, *J* = 7.0Hz), 3.61 (s, 3H, N5''-CH_3), 3.39 (s, 3H, N7''-CH_3), 2,33 (t, 2H, H2, *J* = 7.5Hz), 1.92 (quint, 2H, H6, *J* = 7.0Hz), 1.36 (m, 6H, H3, H4, H5). ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.022 (C=O), 155.608 (N=C-N), 151.433 (C8''), 150.292 (C6''), 148.828 (C4''), 142.165 (C2''), 134.556 (C1'), 121.934 (C6'), 119.343 (C2'), 116.664-116.489 (C3'), 116.486 (C5'), 106.223 (C9''), 47.650 (C7), 37.947 (N1''-CH_2), 36.882 (C2), 29.977 (N5''-CH_3), 29.542 (N7''-CH_3), 28.136 (C6), 28.059 (C3), 25.738 (C5), 24.741 (C4). HRMS (ESI) m/z calc. for $C_{22}H_{25}{}^{35}ClFN_9O_5$ $[M+H]^+$ 518.1826 , found 518.1997 ; calc. for $C_{22}H_{25}{}^{37}ClFN_9O_5$ $[M+H]^+$ 520.1796 , found 520.1942; calc. for $[M+Na]^+$ 540.1645 , found 540.11803 ; calc. for $C_{22}H_{25}{}^{37}ClFN_9O_5$ $[M+Na]^+$ 542.1616, found 542.1795.

7-(5-((1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydro-7H-purin-7-yl)methyl)-1H-tetrazol-1-yl)-N-(2-fluoro-4-iodophenyl)heptanamide (27). Prepared from acid (**10**) and 3-chloro-4-fluoroaniline following general procedure (d) to afford a off-white solid, yield: 68.3%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.08 (t, 1H, H3', *J* =7.5Hz), 7.89 (s, 1H, H2''), 7.41 (m, 2H, H5', H6'), 7.38 (s, 1H, CO-NH), 5.86 (s, 2H, N1''-CH_2), 4.546 (t, 2H, H7, *J* = 7.0Hz), 3.60 (s, 3H, N5''-CH_3), 3.37 (s, 3H, N7''-CH_3), 2.39 (t, 2H, H2, *J* = 7.5Hz), 1.92 (quint, 2H, H6, *J* = 7.5Hz), 1.72 (quint, 2H, H3, *J* = 7.5Hz), 1.40 (m, 4H, H4, H5). ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.954 (C=O), 155.593 (N=C-N), 151.381 (C8''), 150.168 (C6''), 148.788 (C4''), 142.086 (C2''), 133.785 (C2'), 123.991 (C5') 123.815 (C1'), 122.967 (C3',C6'), 106.168 (C9''), 47.639 (C7), 37.831 (N1''-CH_2), 37.197 (C2), 29.960 (N5''-CH_3), 29.702 (N7''-CH_3), 29.626 (C6), 28.185 (C3), 25.876 (C5), 24.700 (C4). HRMS (ESI) m/z calc. for $C_{22}H_{25}FIN_9O_5$ $[M+Na]^+$ 632.1001 , found 632.1000.

2D SPECTRA

Ester 3:



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PROCNO                 1

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INSTRUM           spect
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PULPROG            zg30
TD                65536
SOLVENT           CDCl3
NS                   16
DS                    2
SWH           10000.000 Hz
FIDRES            0.152588 Hz
AQ              3.2767999 sec
RG                 191.38
DW                 50.000 usec
DE                  6.50 usec
TE                297.9 K
D1            1.00000000 sec
TD0                    1

======== CHANNEL f1 ========
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NUC1                1H
P1                 9.80 usec
PLW1        24.00000000 W

F2 - Processing parameters
SI                65536
SF           500.1300098 MHz
WDW                EM
SSB       0
LB                 0.30 Hz
GB        0
PC                 1.00
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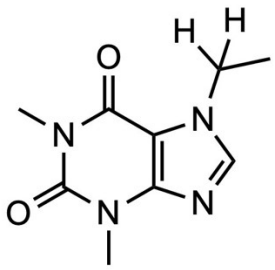
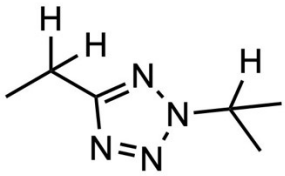
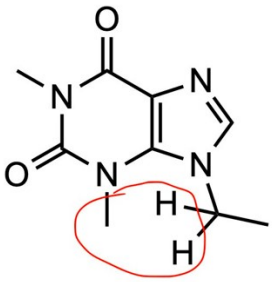
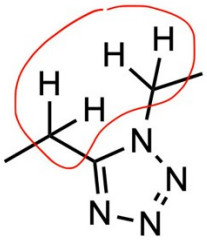
No interaction between N-C<u>H</u>$_2$-tetrazole and N-C<u>H</u>$_3$

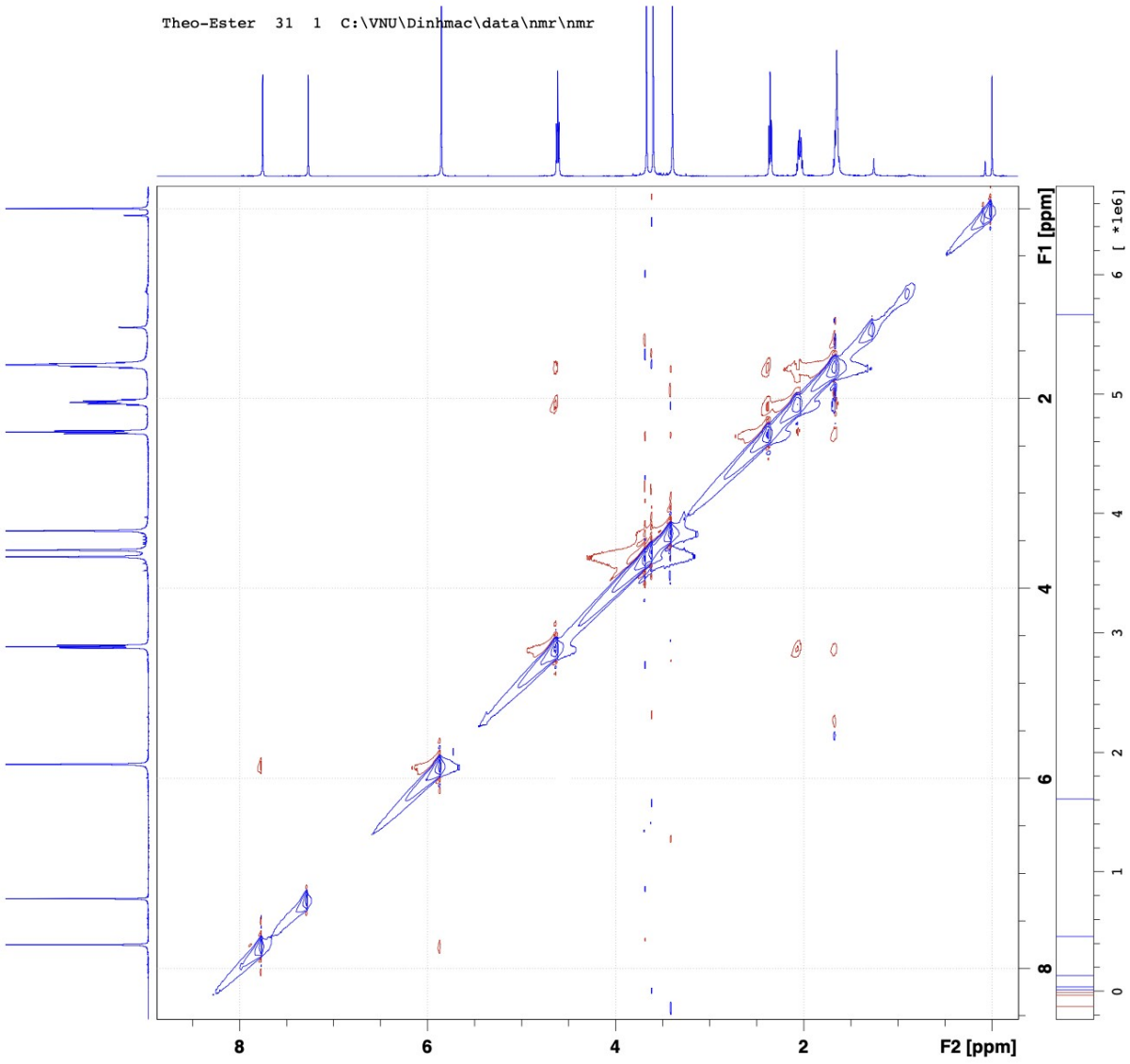
No interaction between N-C<u>H</u>$_2$-tetrazole and N-C<u>H</u>$_2$-…-COOMe







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F2 [ppm]
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6
4
2
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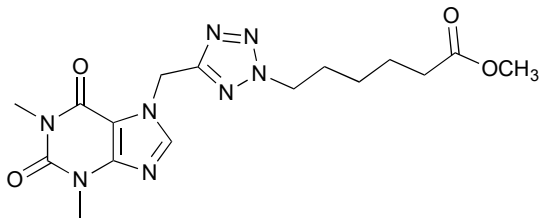
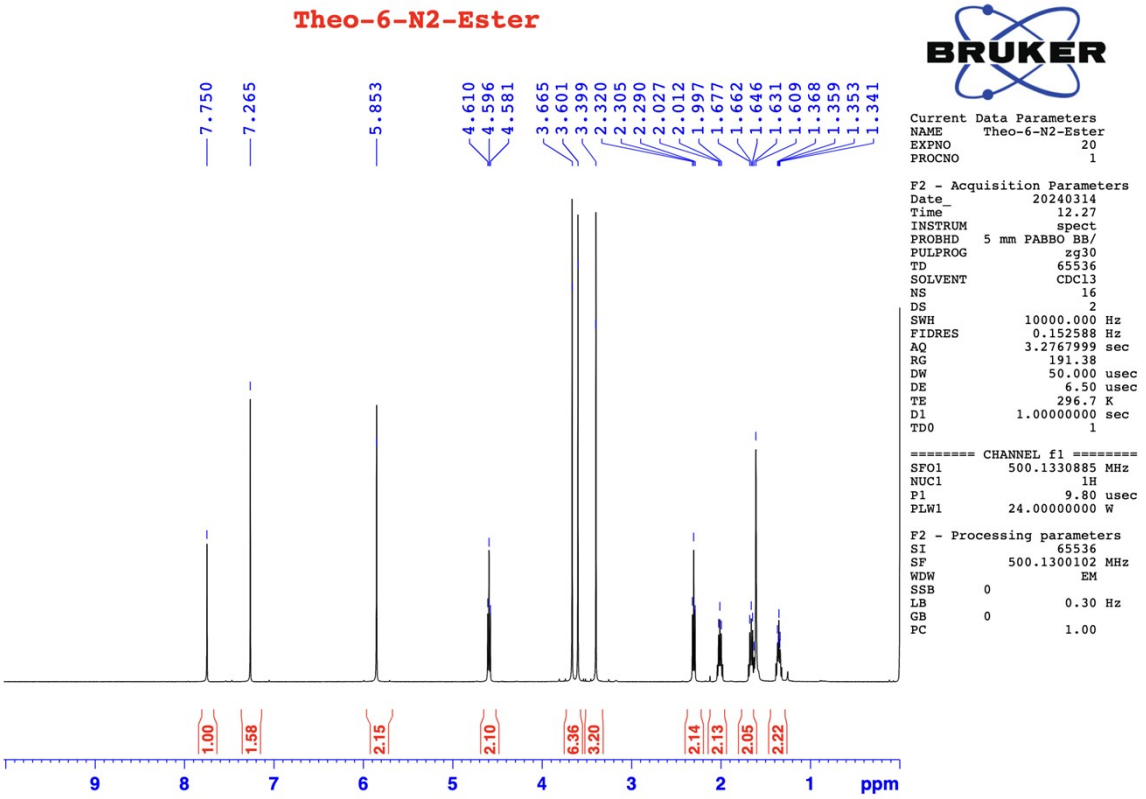
Ester 4



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EXPNO                 20
PROCNO                 1

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PULPROG           zg30
TD               65536
SOLVENT          CDCl3
NS                  16
DS                   2
SWH          10000.000 Hz
FIDRES        0.152588 Hz
AQ            3.2767999 sec
RG               191.38
DW               50.000 usec
DE                6.50 usec
TE               296.7 K
D1           1.00000000 sec
TD0                  1

======== CHANNEL f1 ========
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NUC1               1H
P1                9.80 usec
PLW1       24.00000000 W

F2 - Processing parameters
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SF          500.1300102 MHz
WDW                EM
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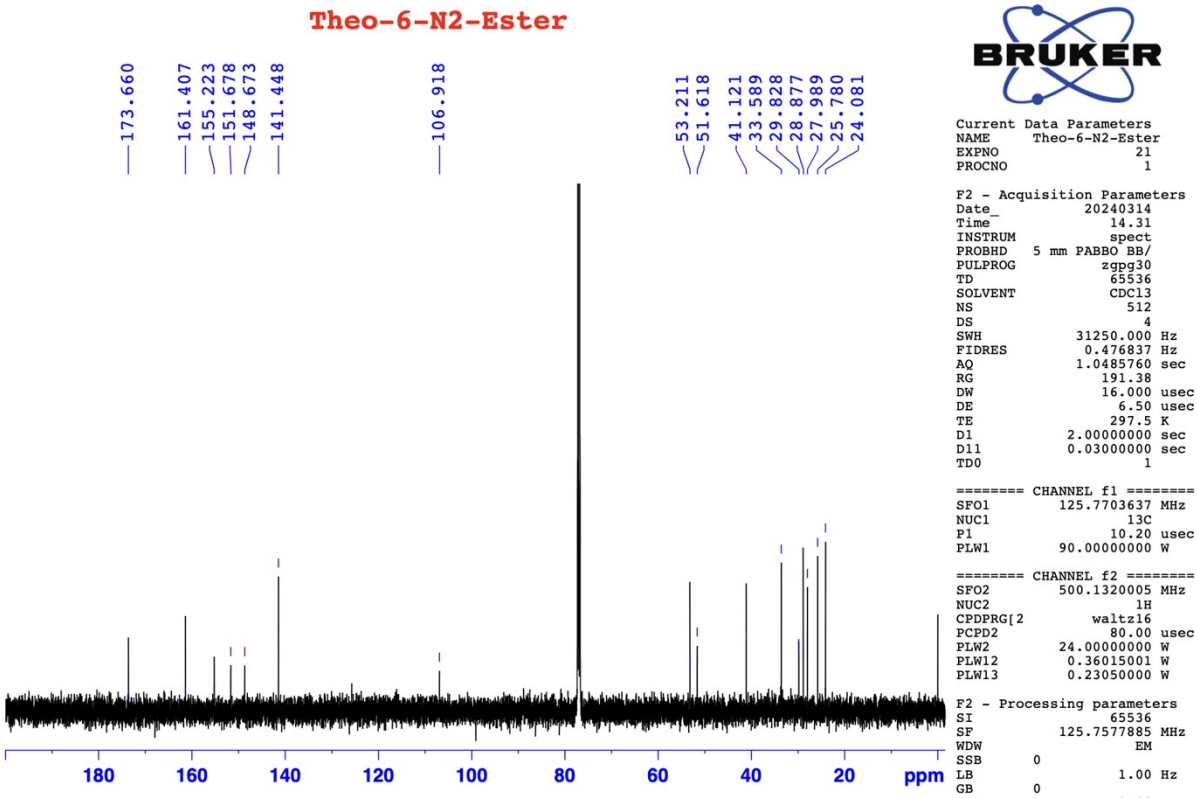


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Current Data Parameters
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EXPNO                 21
PROCNO                 1

F2 - Acquisition Parameters
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Time              14.31
INSTRUM           spect
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PULPROG         zgpg30
TD               65536
SOLVENT          CDCl3
NS                 512
DS                   4
SWH          31250.000 Hz
FIDRES        0.476837 Hz
AQ            1.0485760 sec
RG               191.38
DW               16.000 usec
DE                6.50 usec
TE               297.5 K
D1           2.00000000 sec
D11          0.03000000 sec
TD0                  1

======== CHANNEL f1 ========
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NUC1               13C
P1               10.20 usec
PLW1       90.00000000 W

======== CHANNEL f2 ========
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NUC2               1H
CPDPRG[2         waltz16
PCPD2             80.00 usec
PLW2       24.00000000 W
PLW12       0.36015001 W
PLW13       0.23050000 W

F2 - Processing parameters
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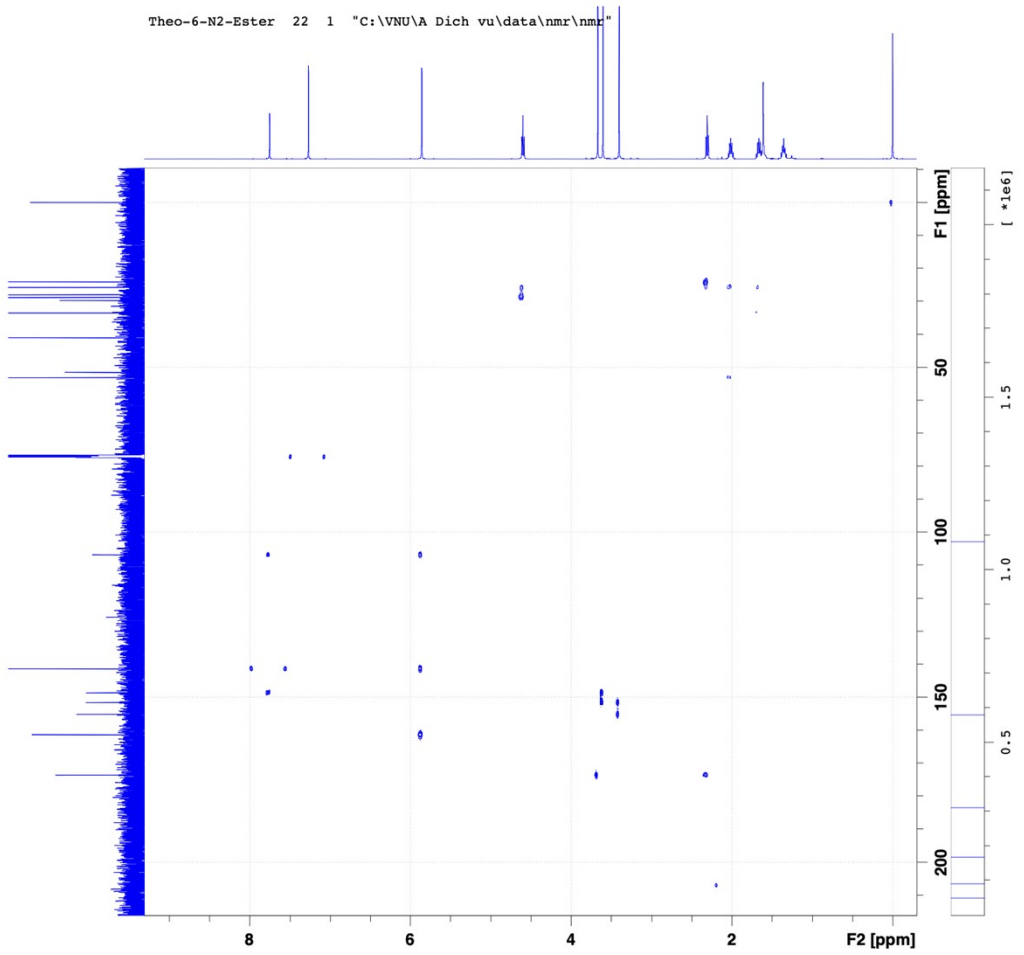
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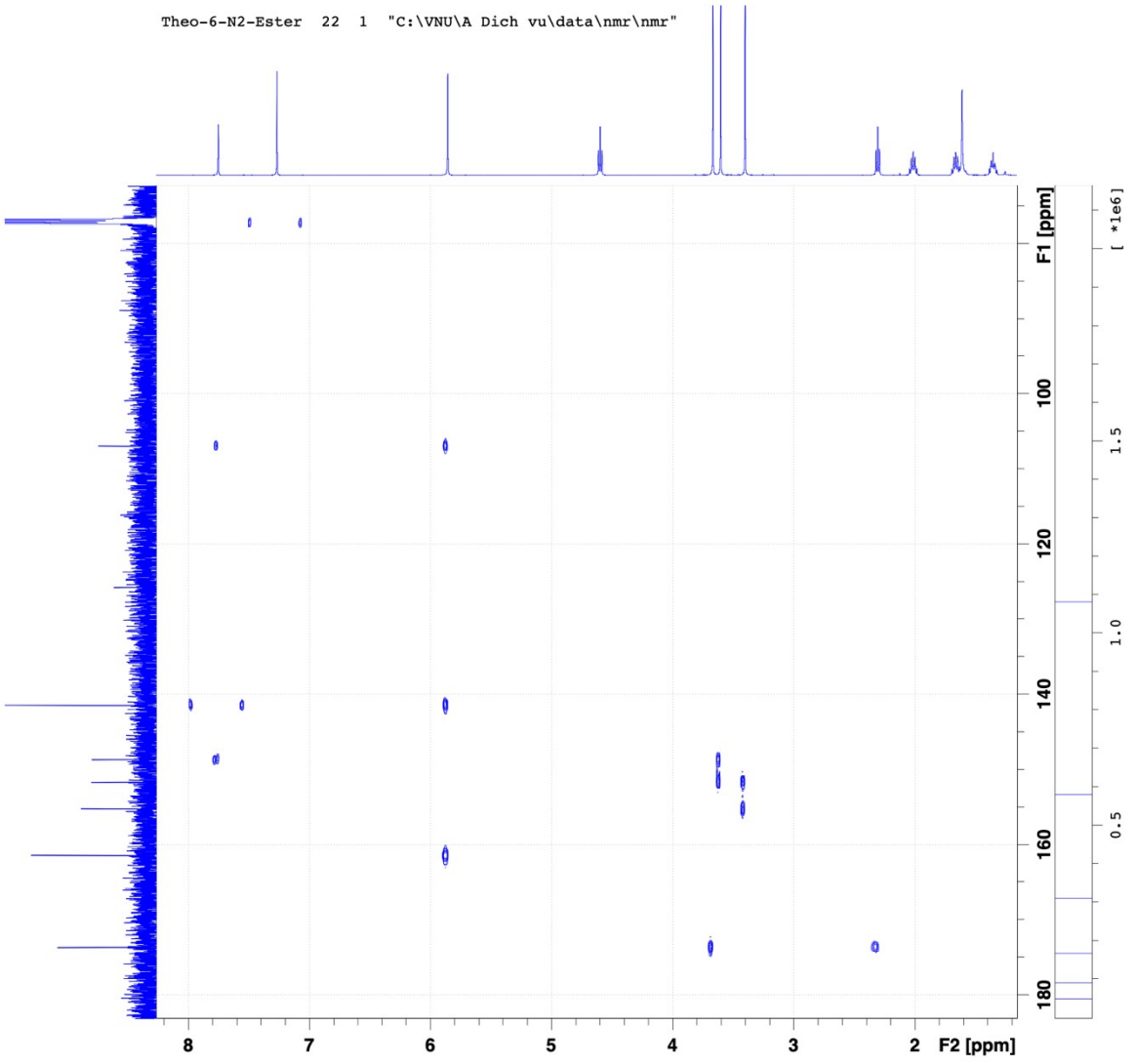
F1 [ppm]
F2 [ppm]
[*1e6]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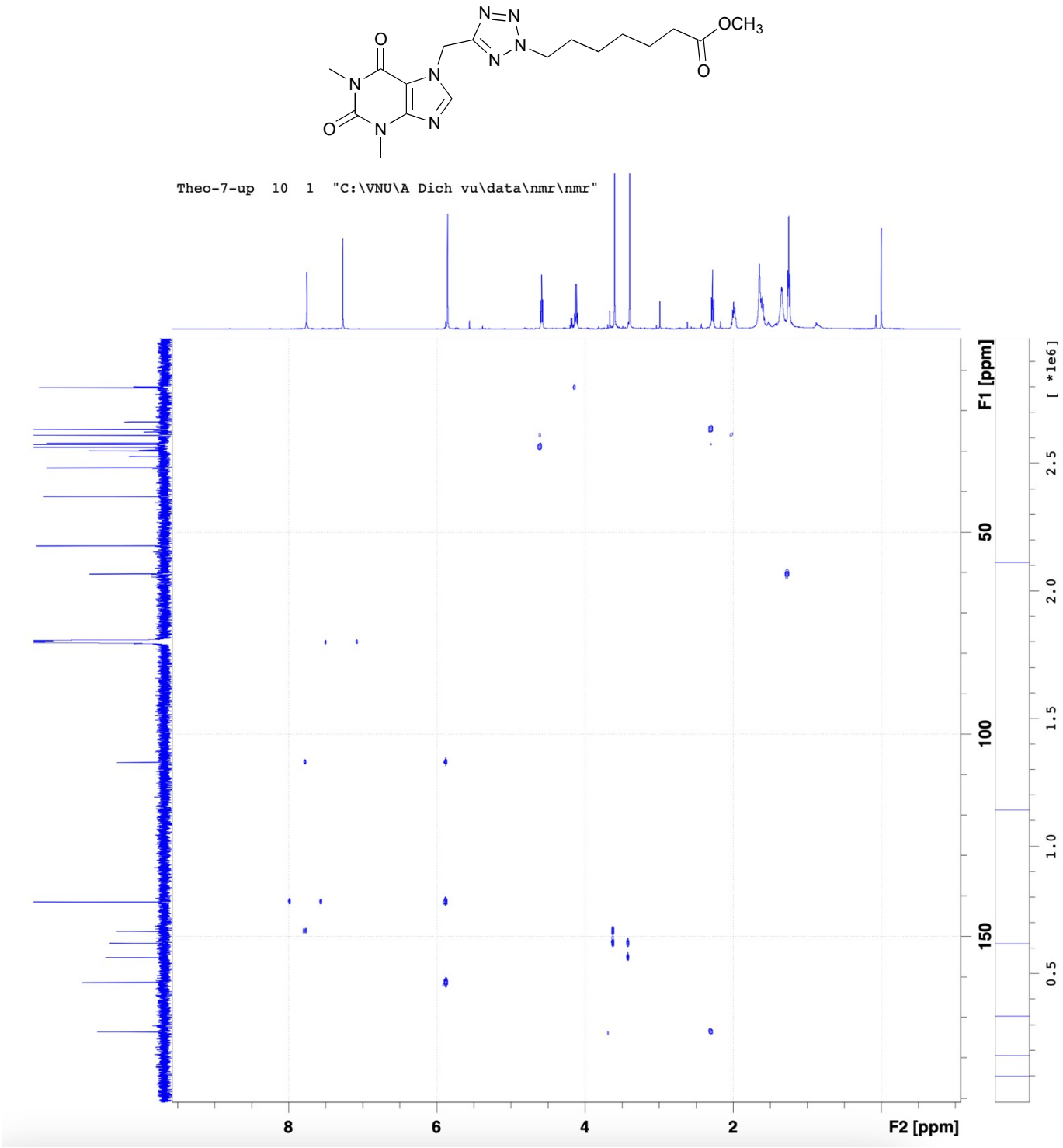
F1 [ppm]
F2 [ppm]
[*1e6]

Ester 5:


Theo-7-up 10 1 "C:\VNU\A Dich vu\data\nmr\nmr"
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F2 [ppm]
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6
4
2
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100
150
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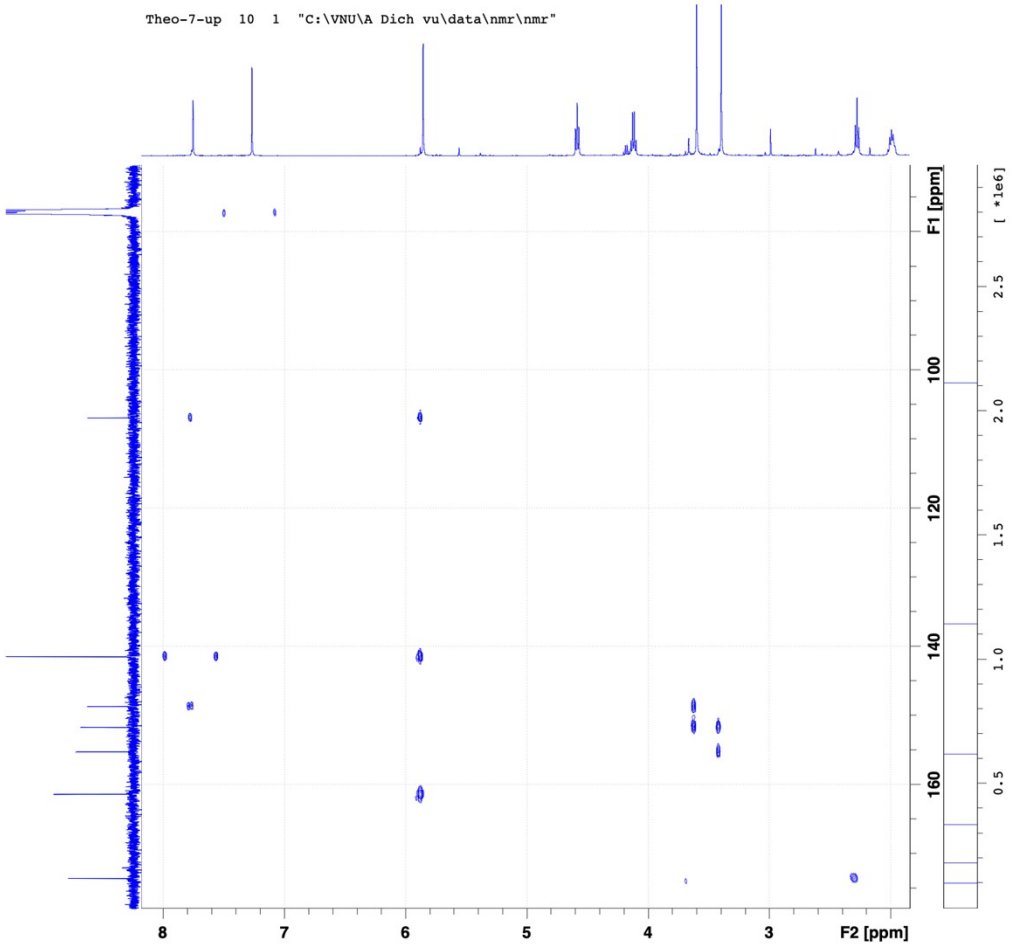
2.0
1.5
1.0
0.5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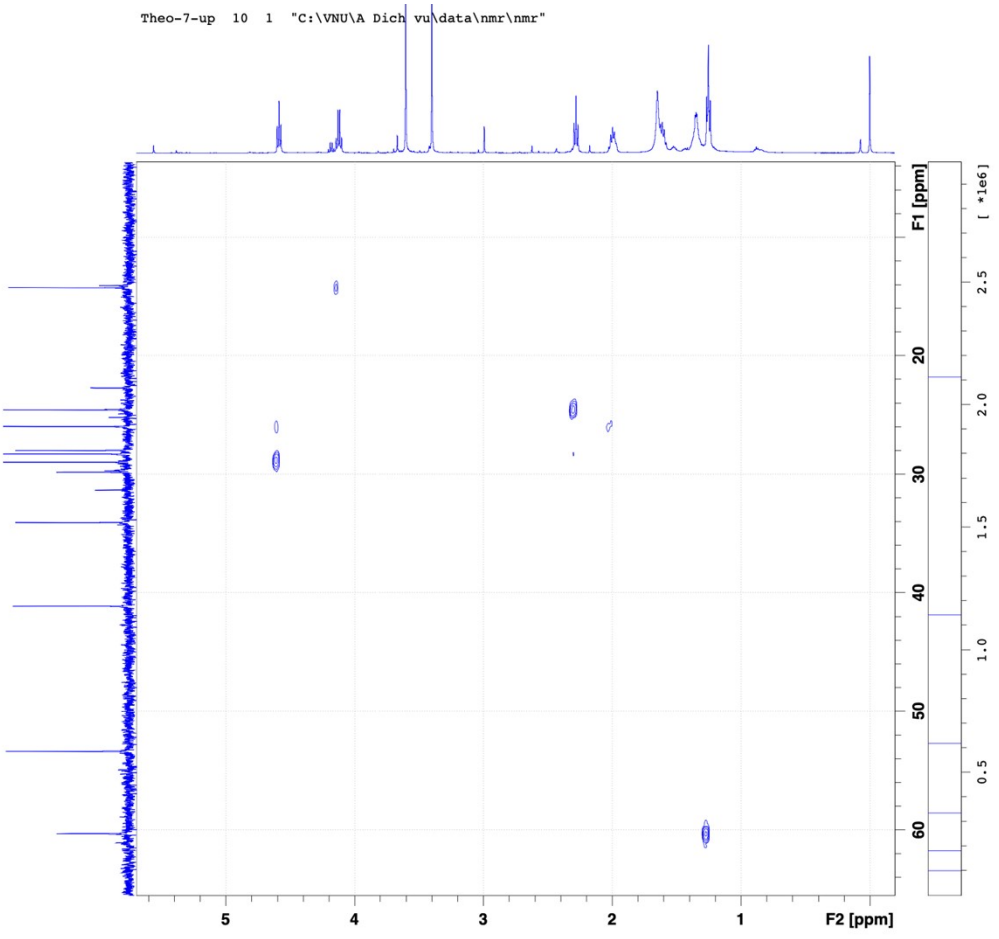
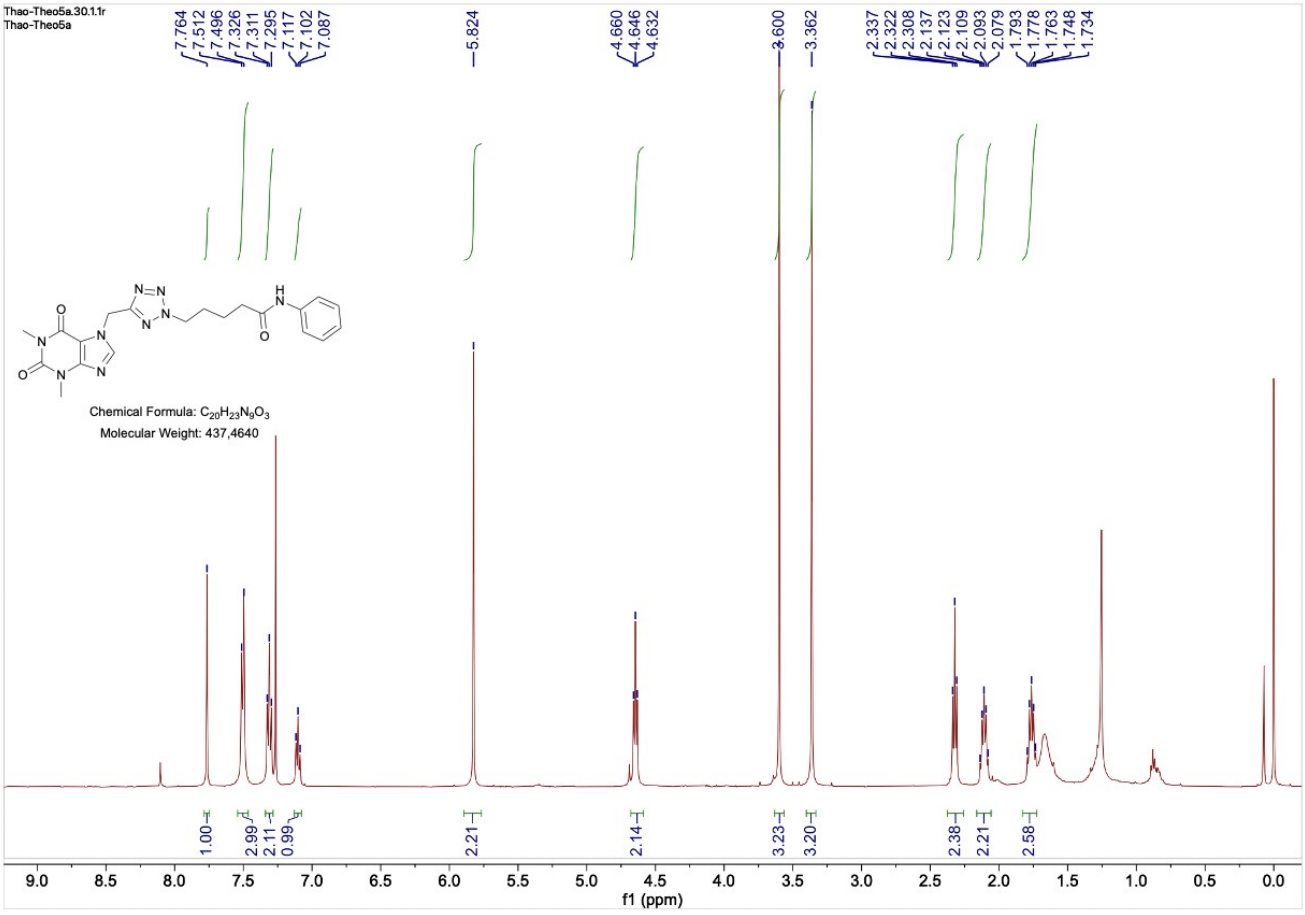
F1 [ppm]
F2 [ppm]
[*1e6]

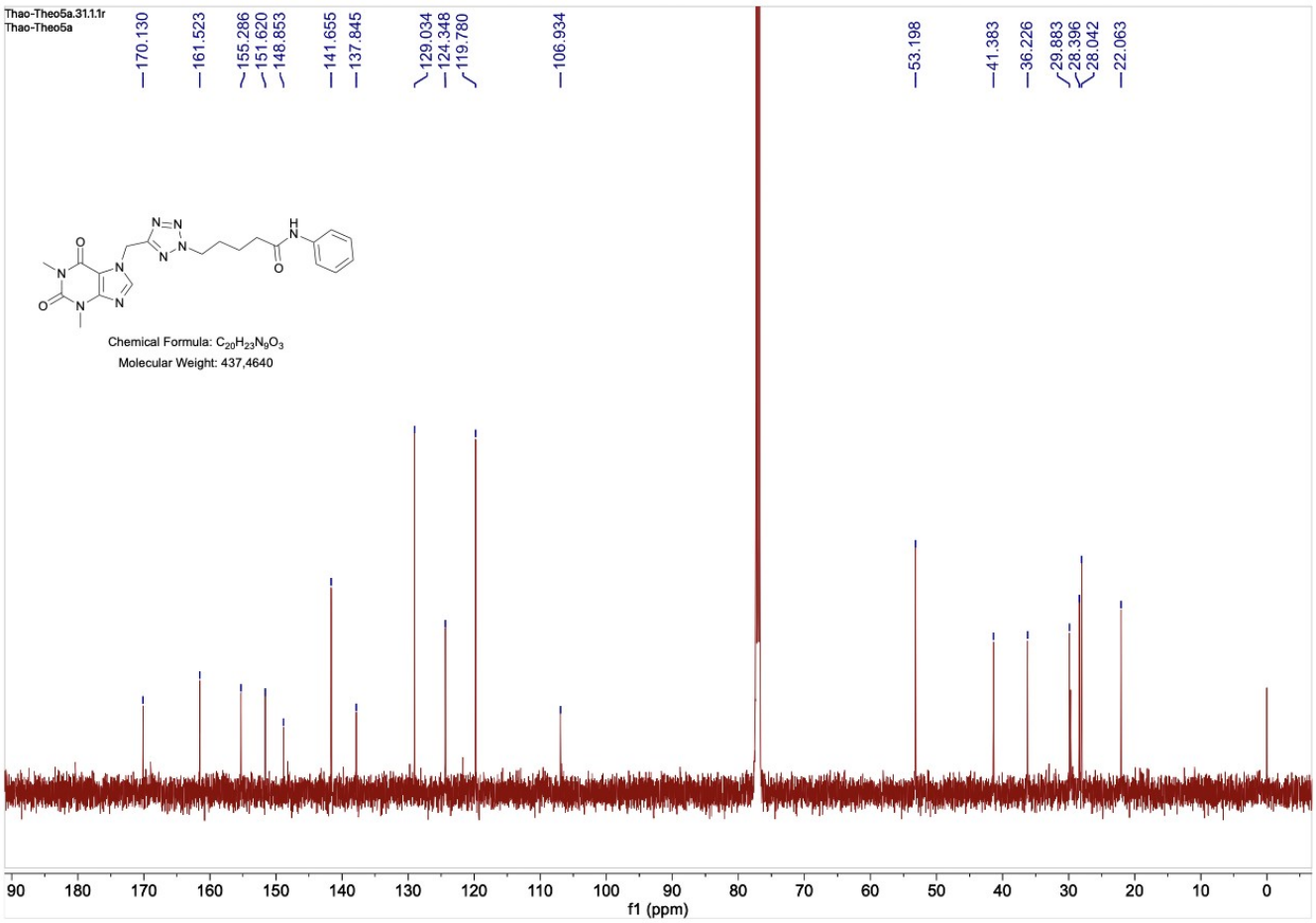

Theo-7-up 10 1 "C:\VNU\A Dich vu\data\nmr\nmr"
F1 [ppm]
F2 [ppm]
[*1e6]

ALL ^{1}H-NMR, ^{13}C-NMR & MS SPECTRA OF THE FINAL COMPOUNDS (11-27)

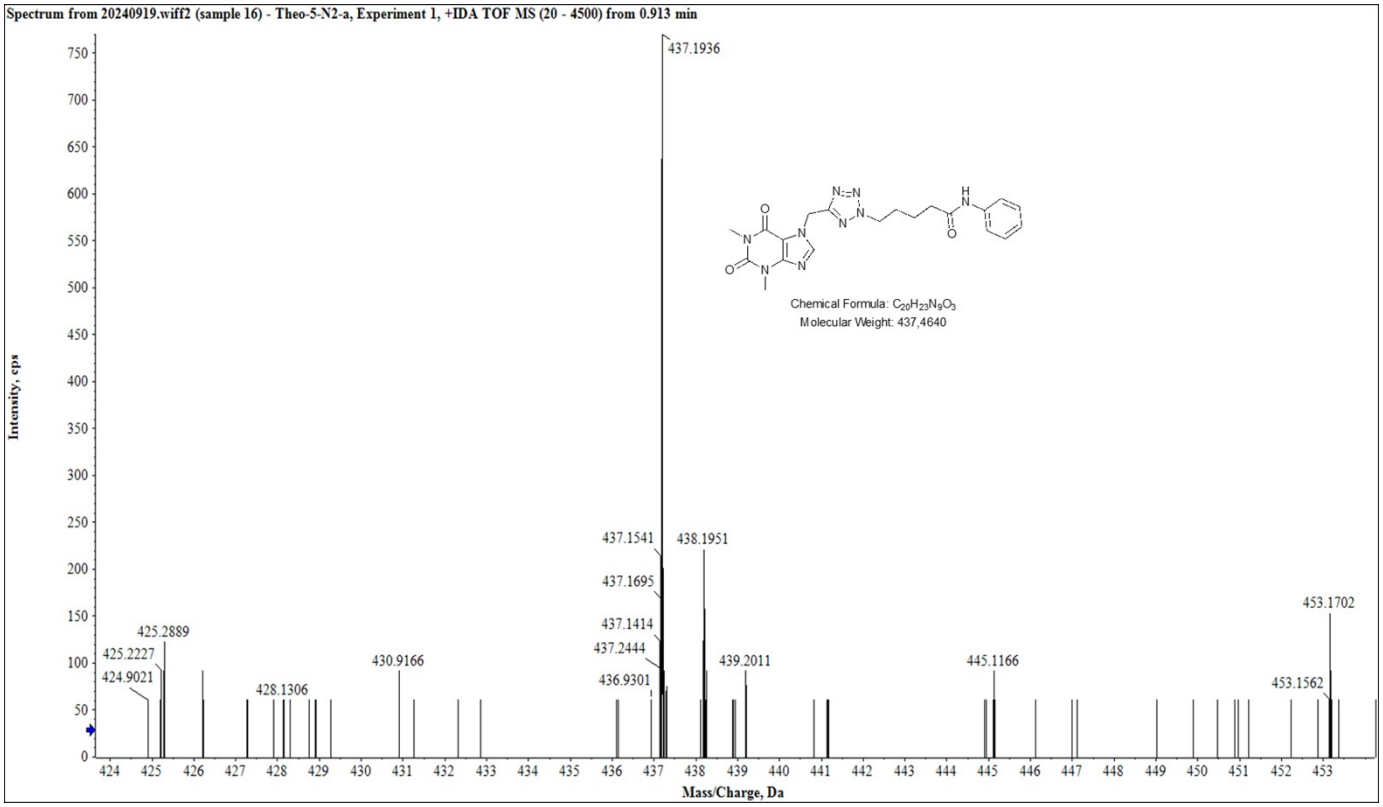
^{1}H-NMR of compound 11



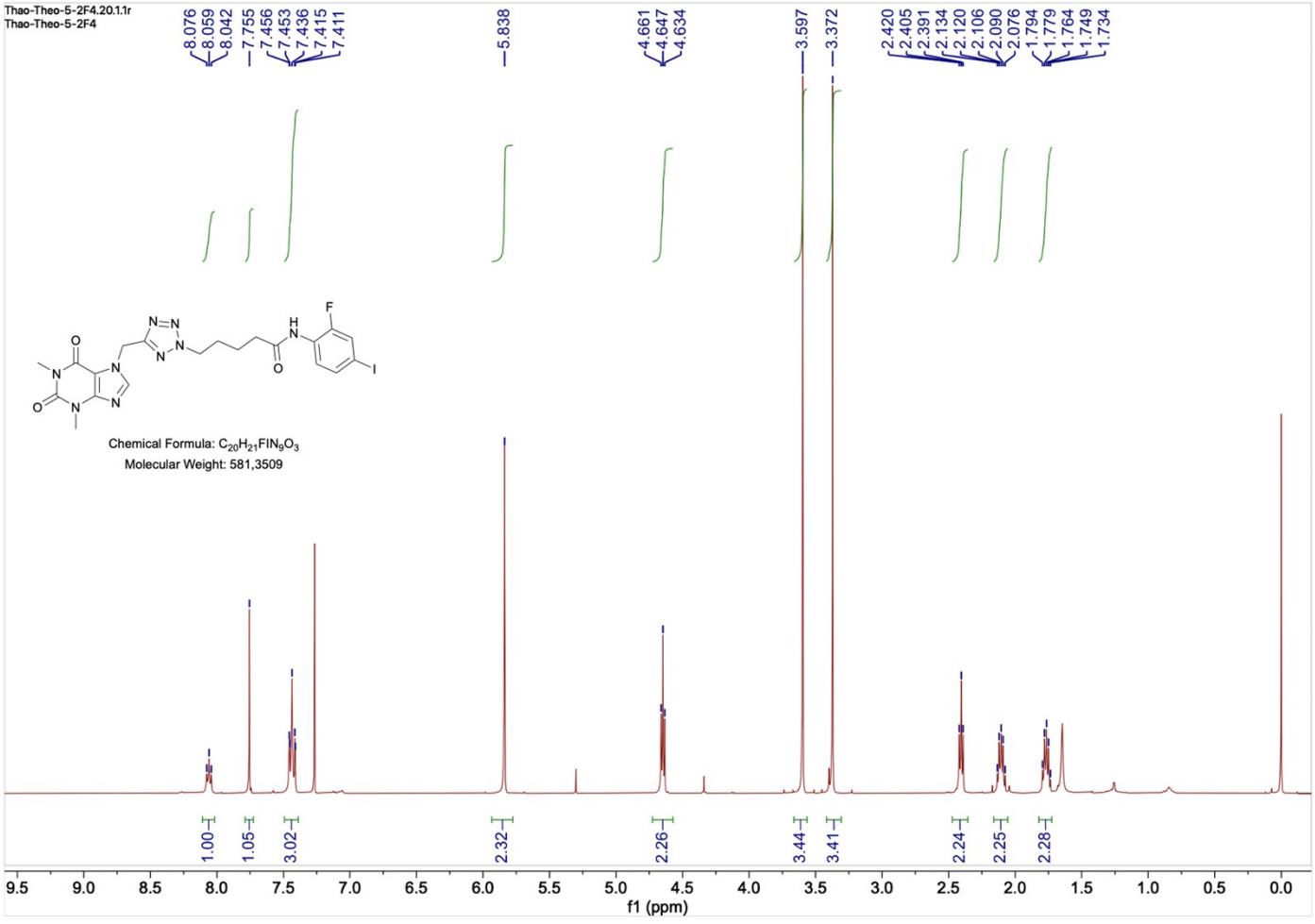
^{13}C-NMR of compound 11



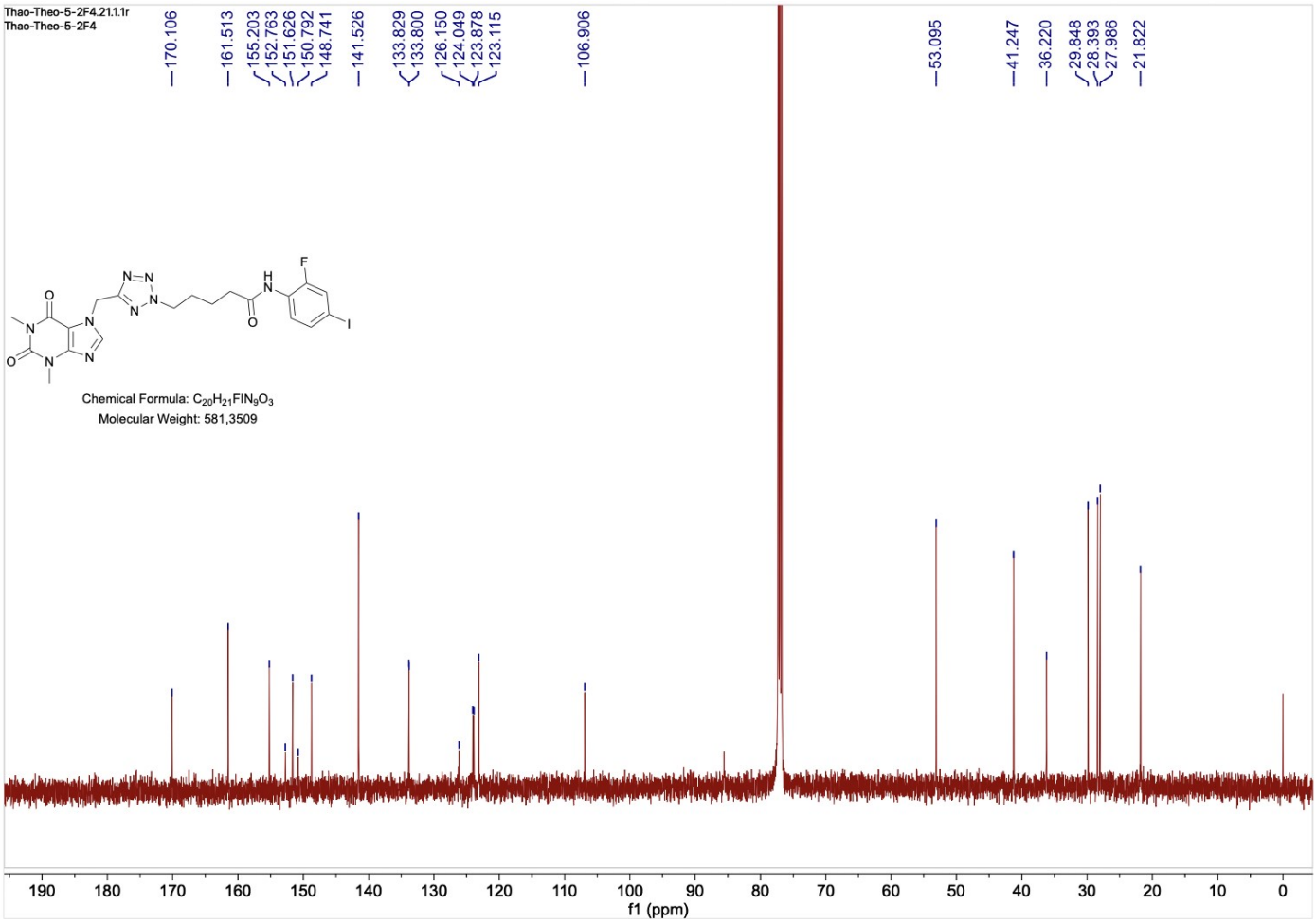
HR-MS of compound 11



^{1}H-NMR of compound 12



^{13}C-NMR of compound 12



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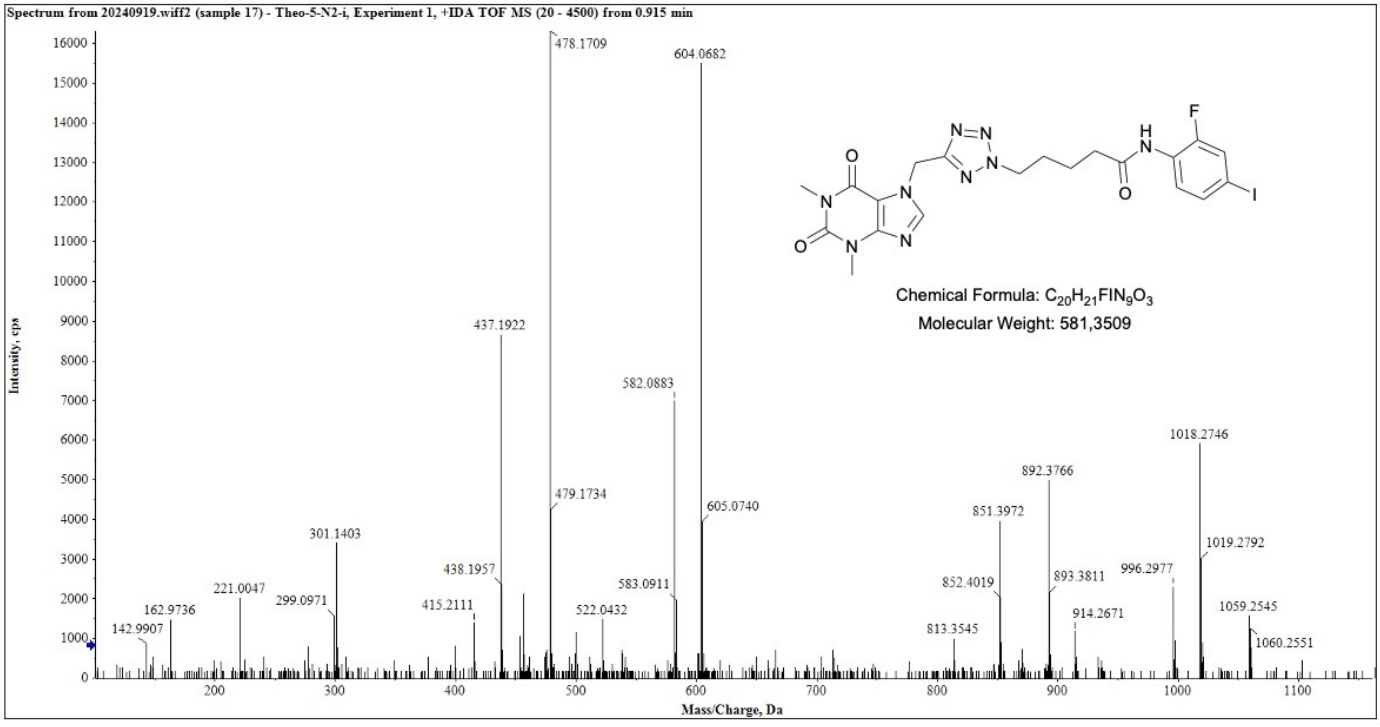

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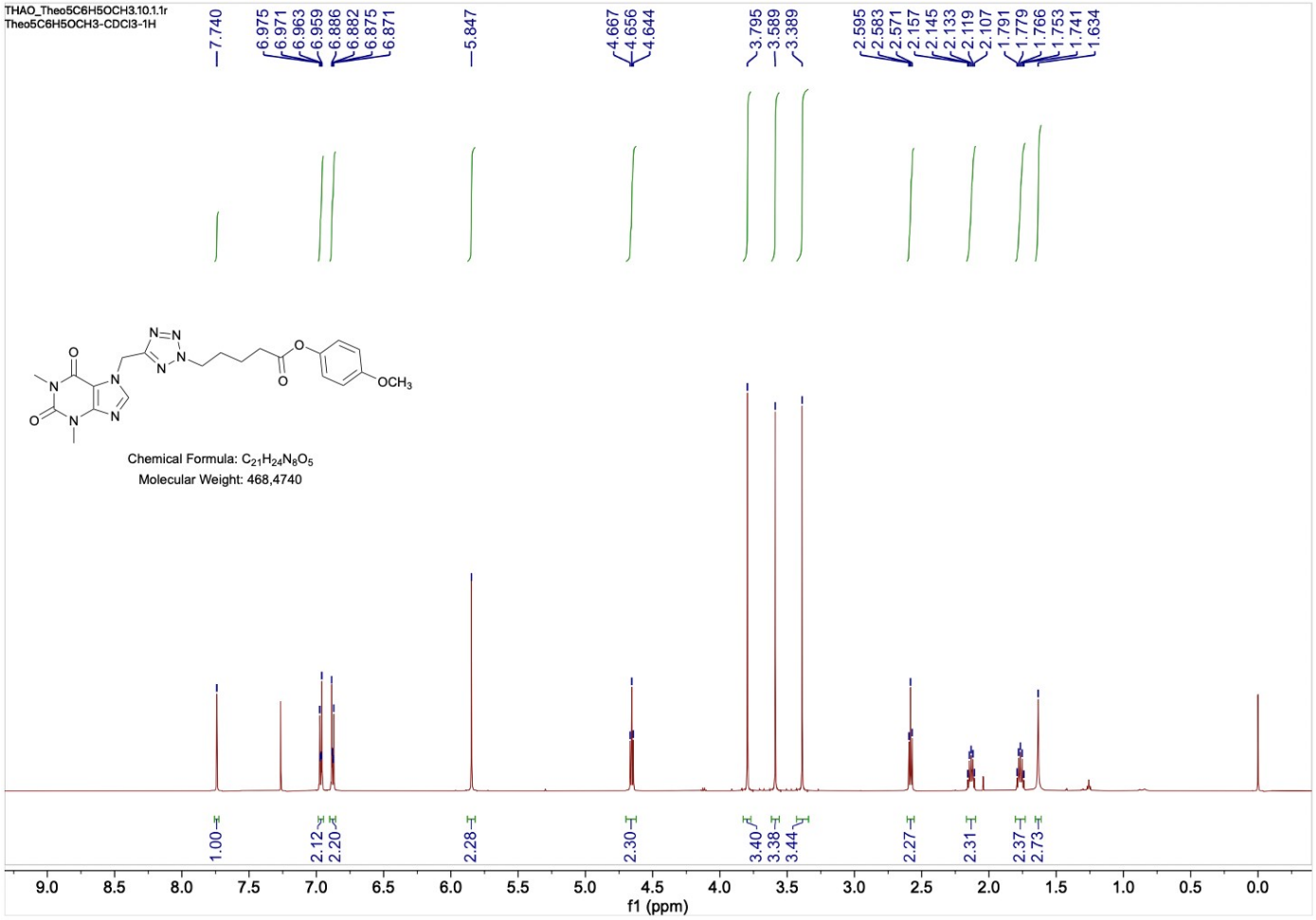

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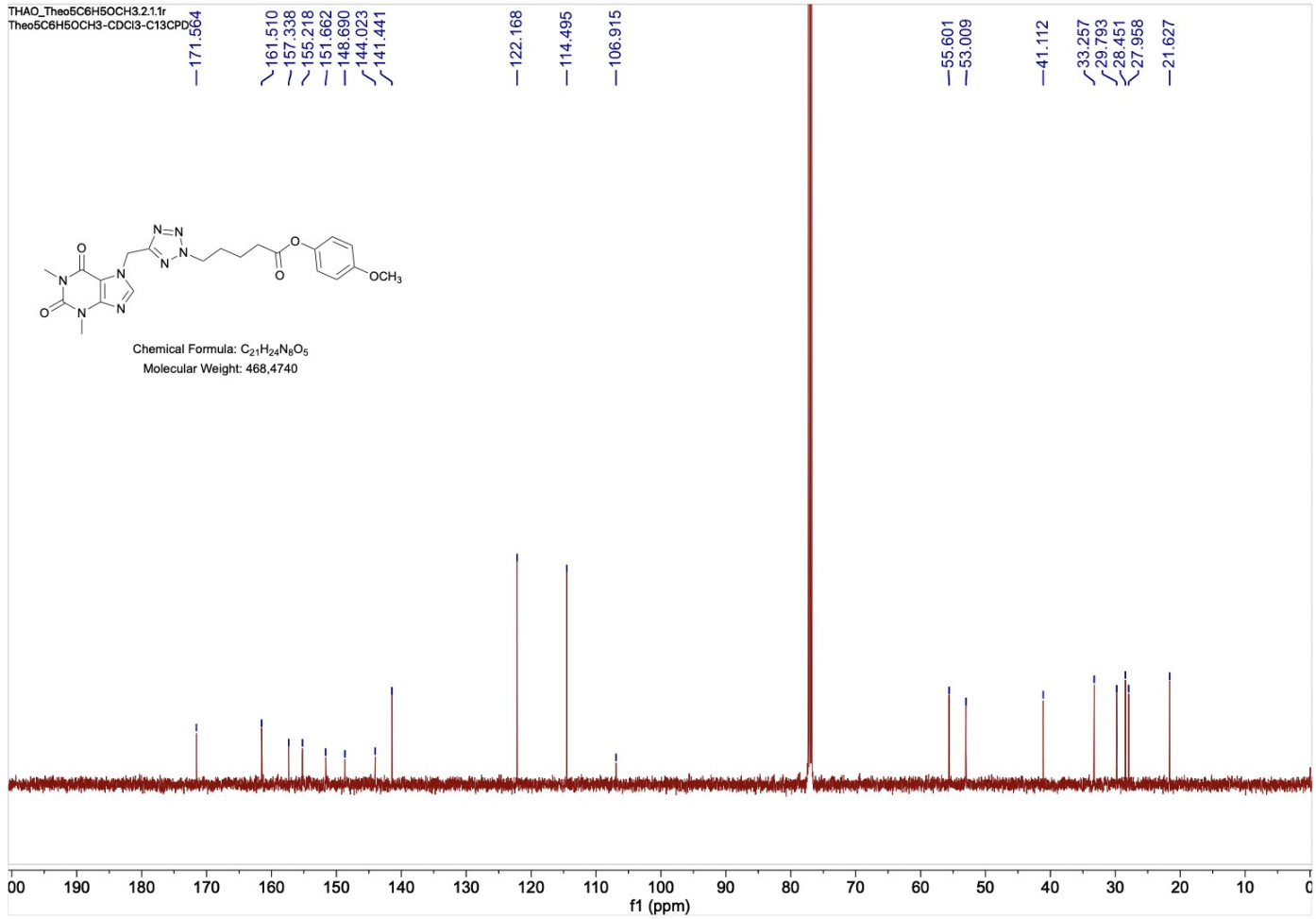
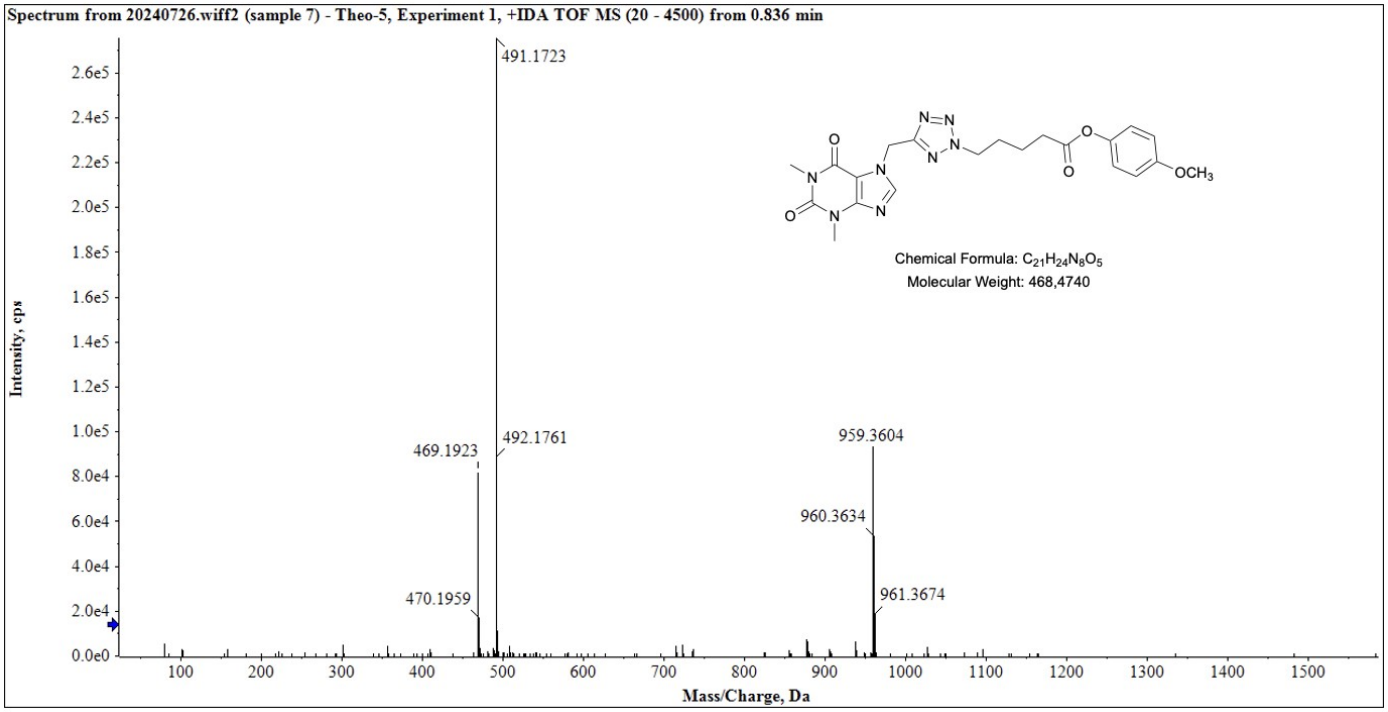
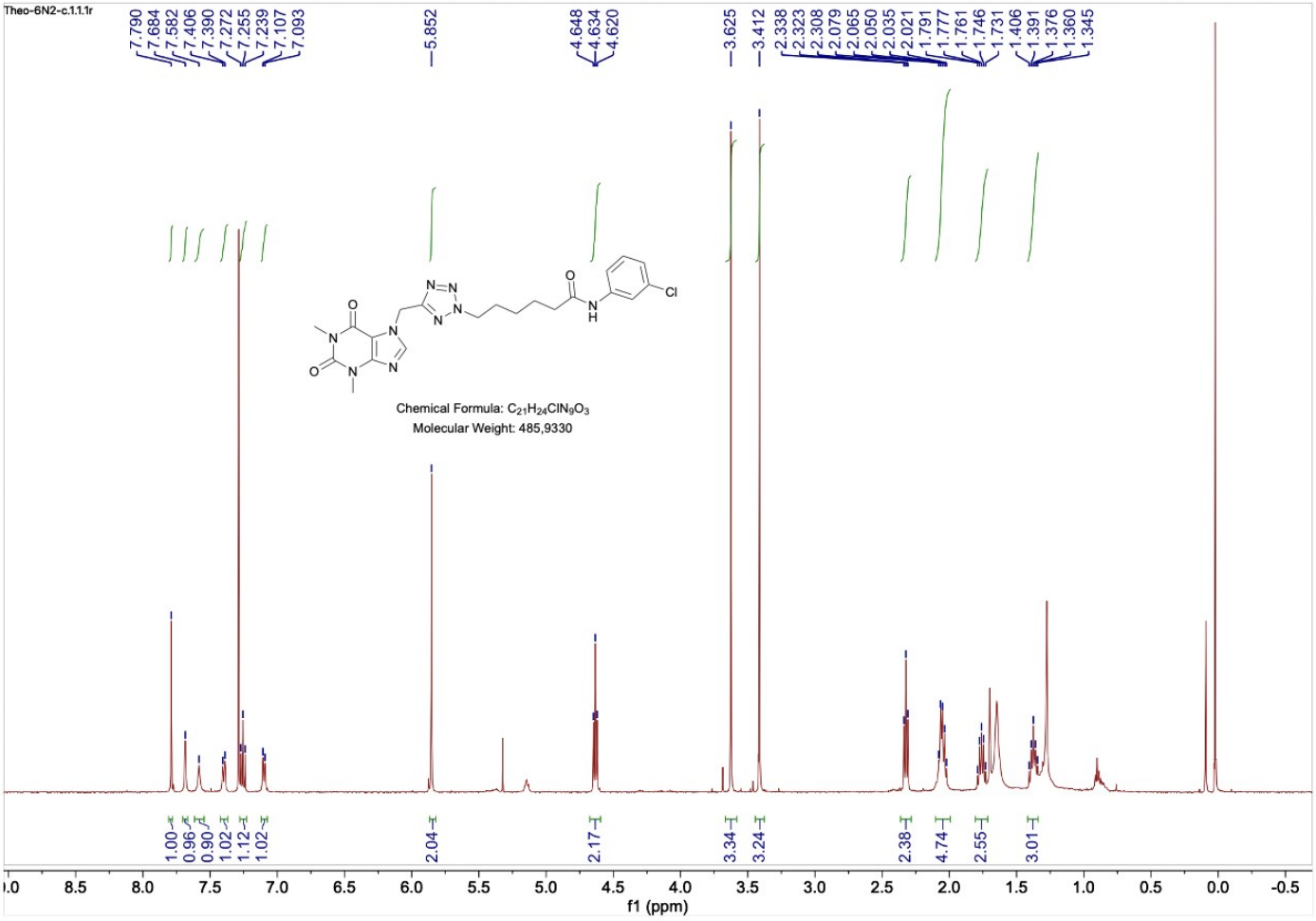


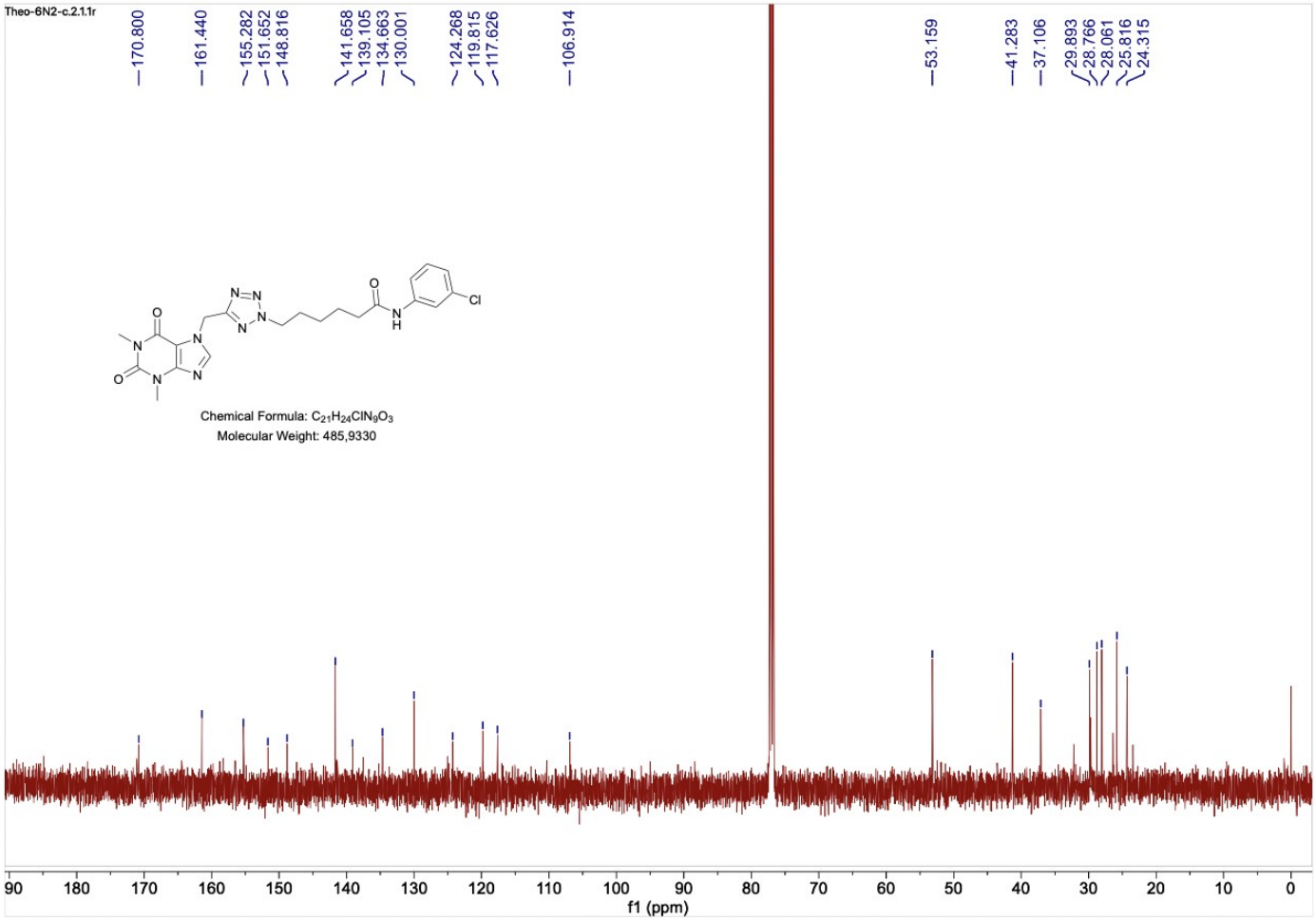
HR-MS of compound 13



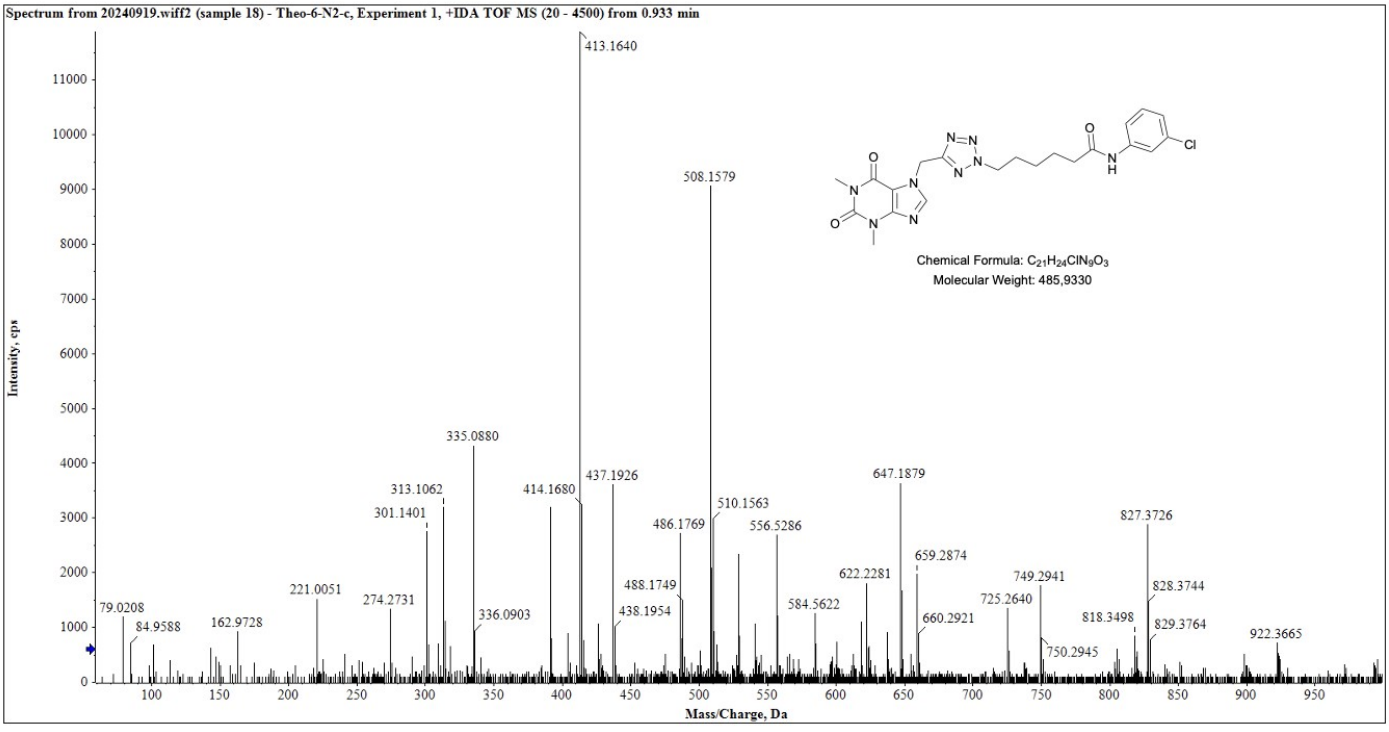
^{1}H-NMR of compound 14



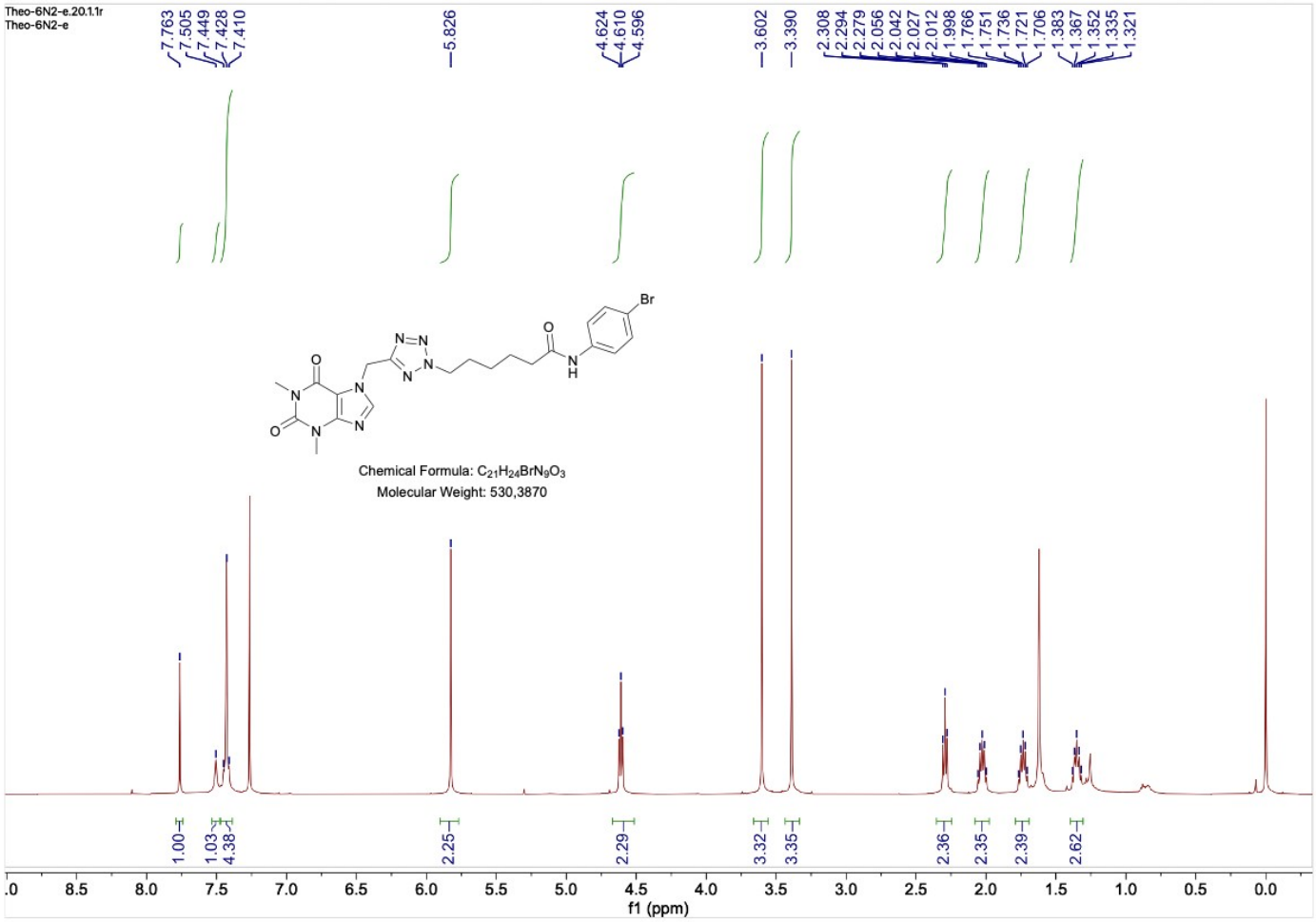
^{13}C-NMR of compound 14



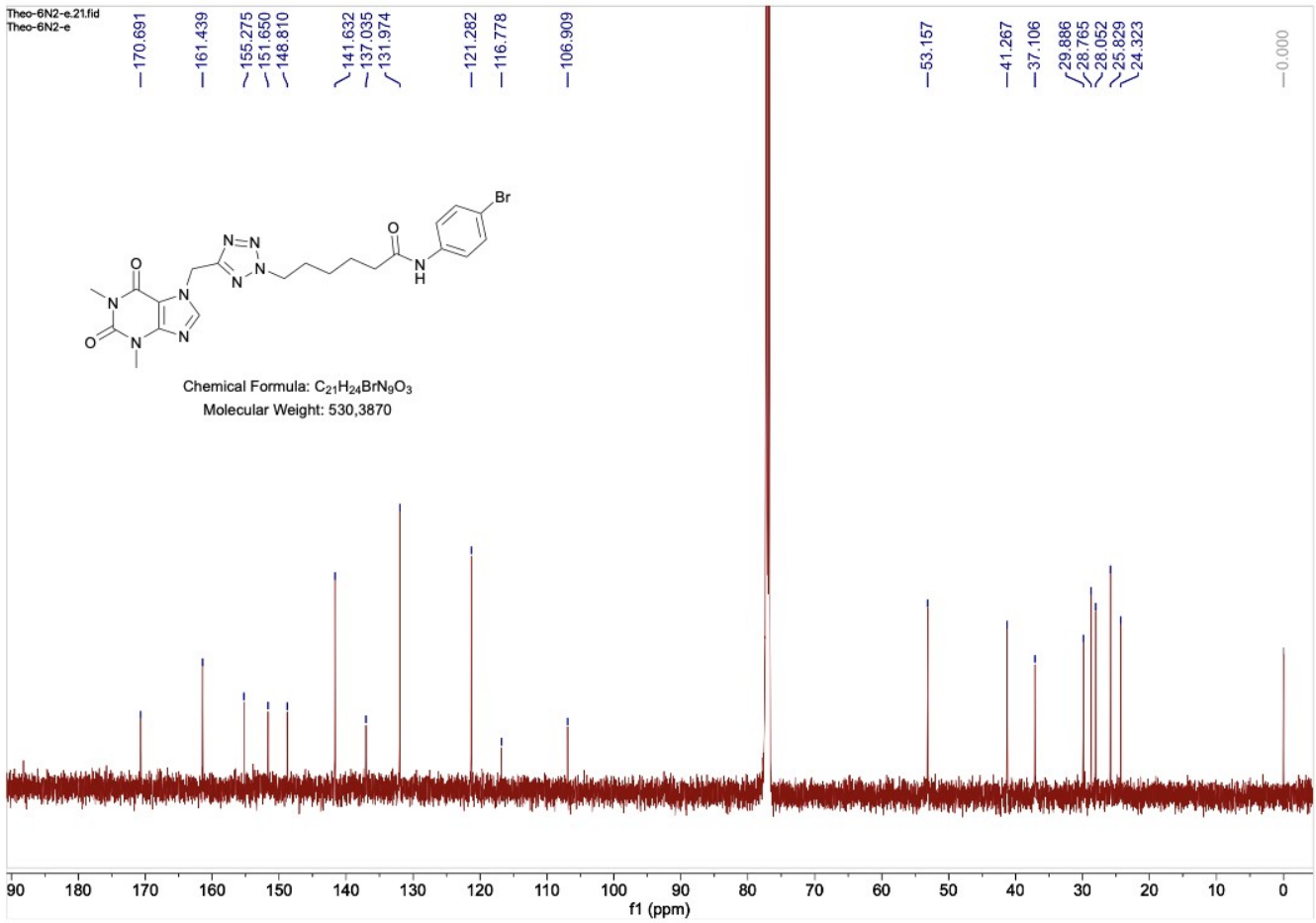
HR-MS of compound 14



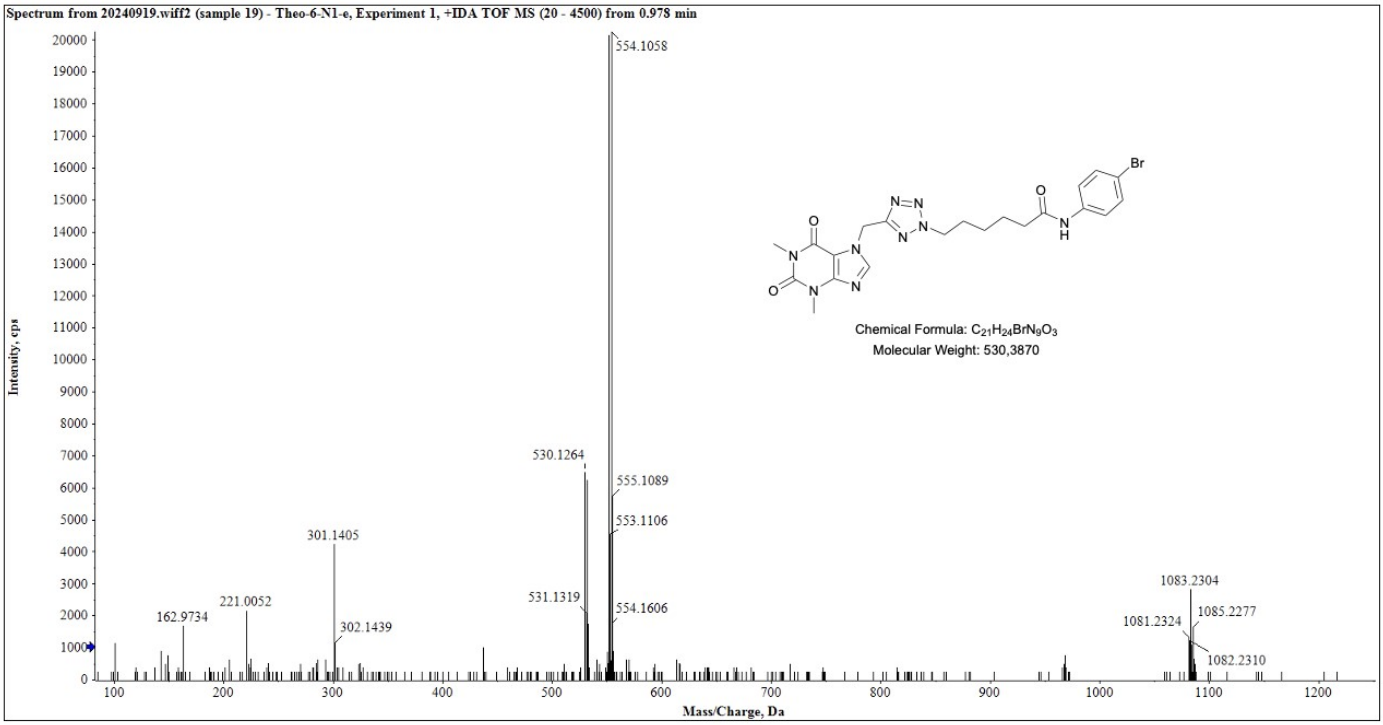
^{1}H-NMR of compound 15

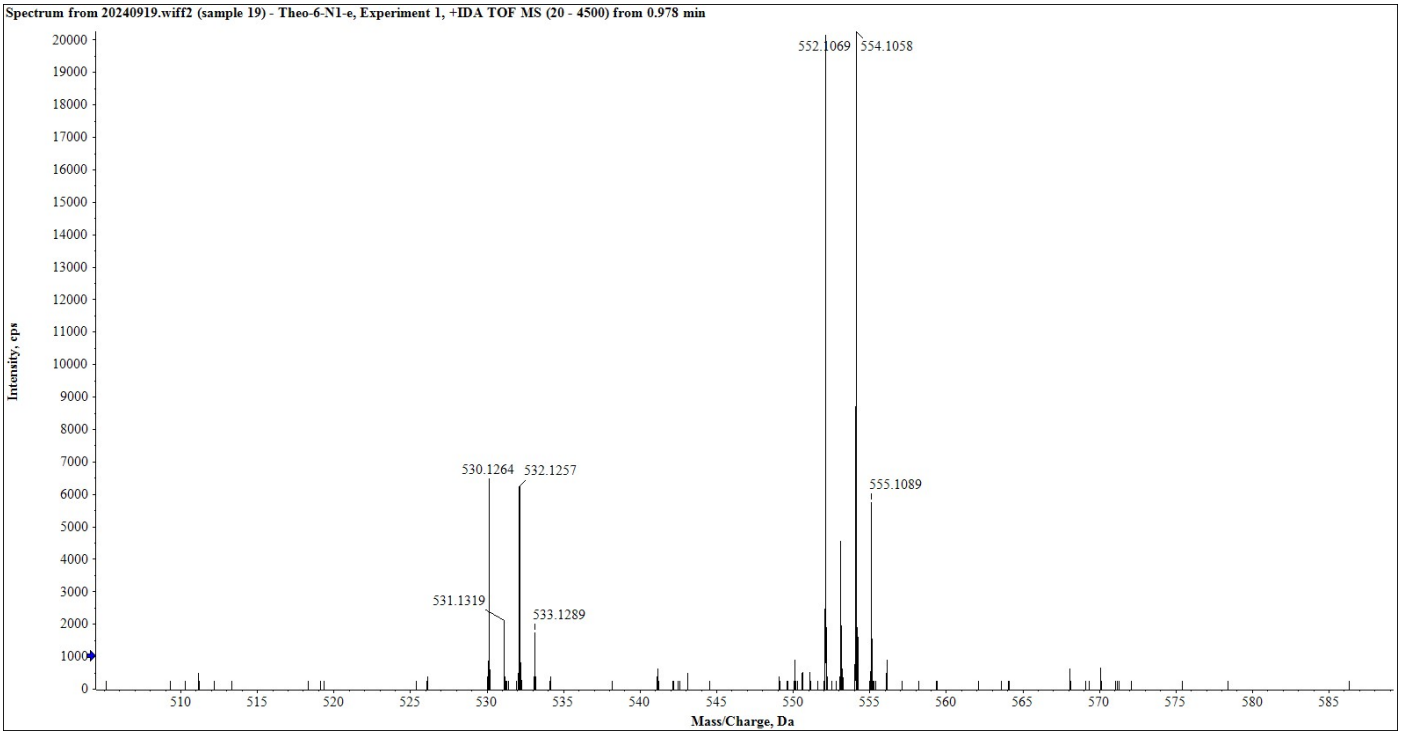


^{13}C-NMR of compound 15

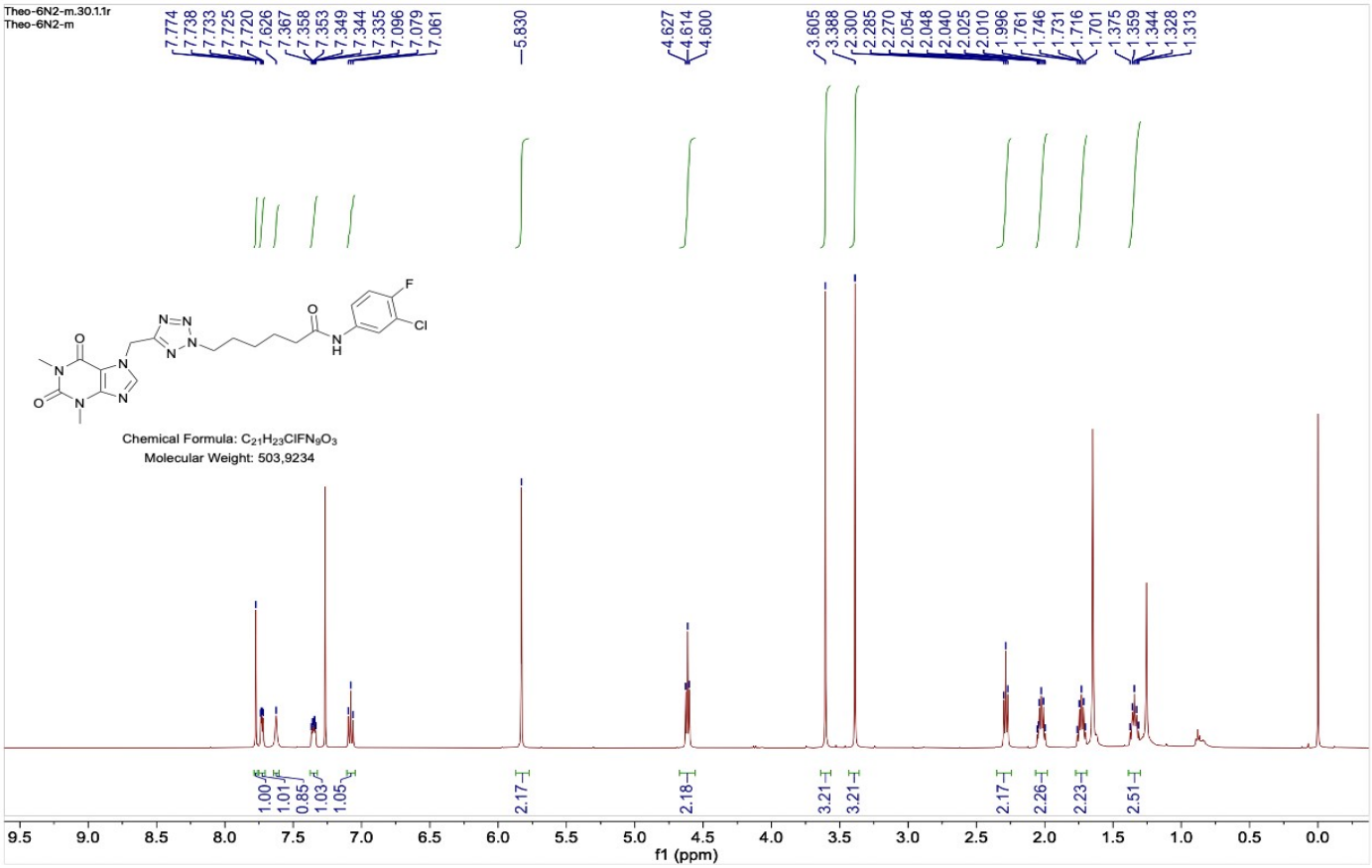


HR-MS of compound 15

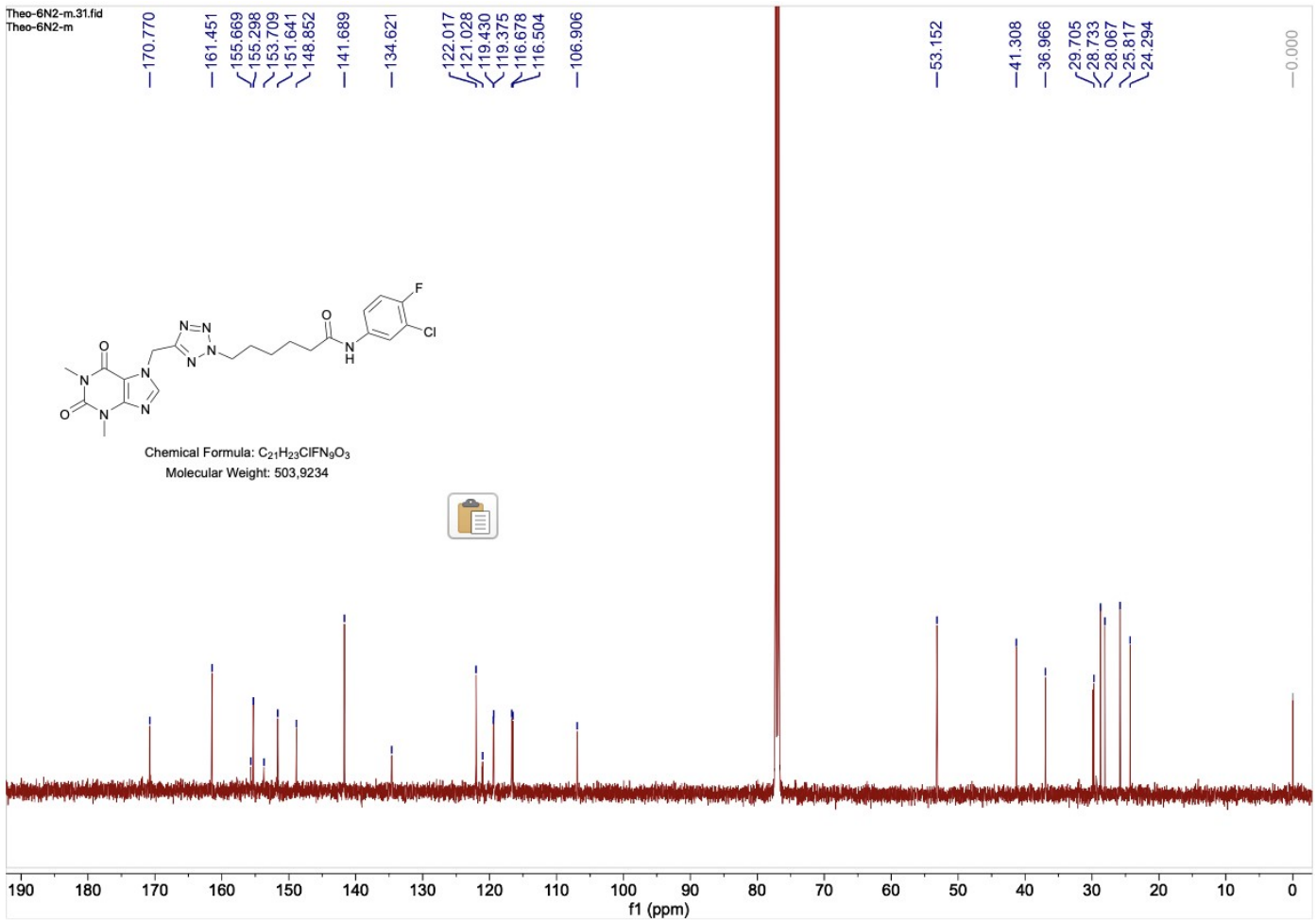




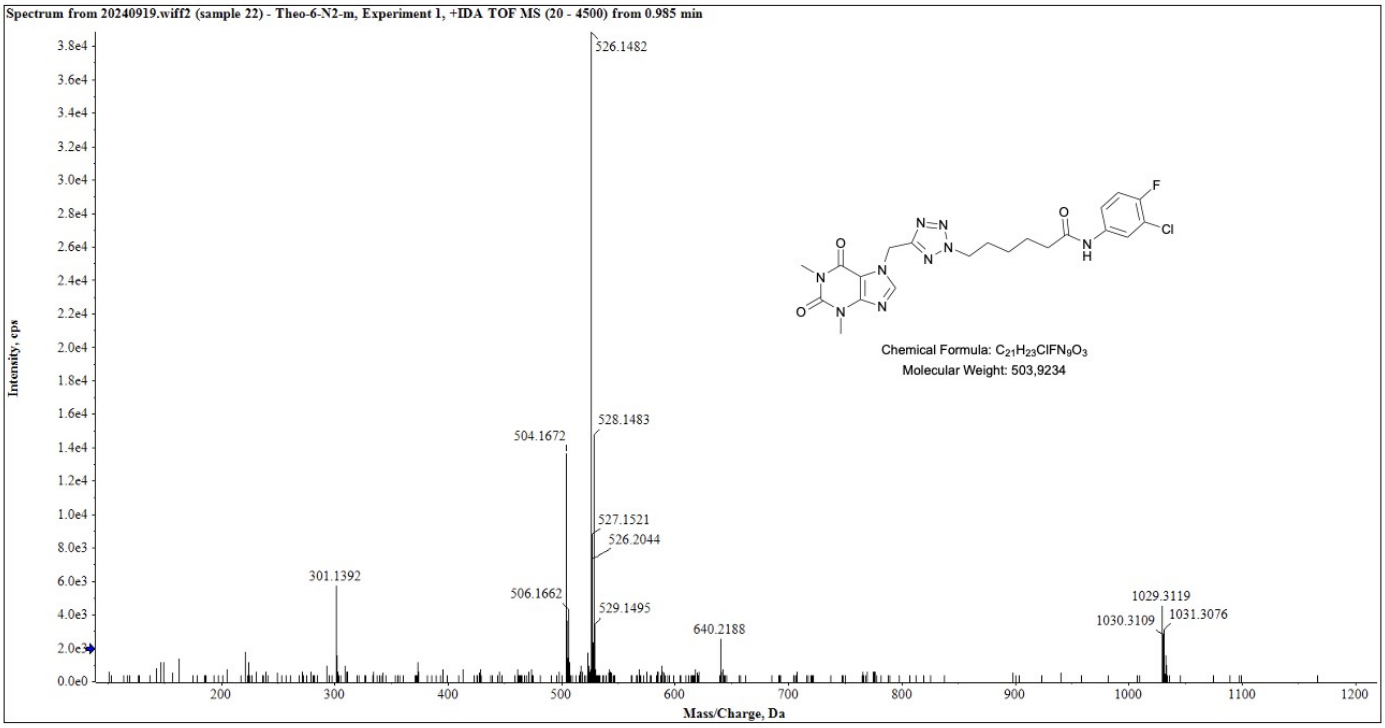
^{1}H-NMR of compound 16



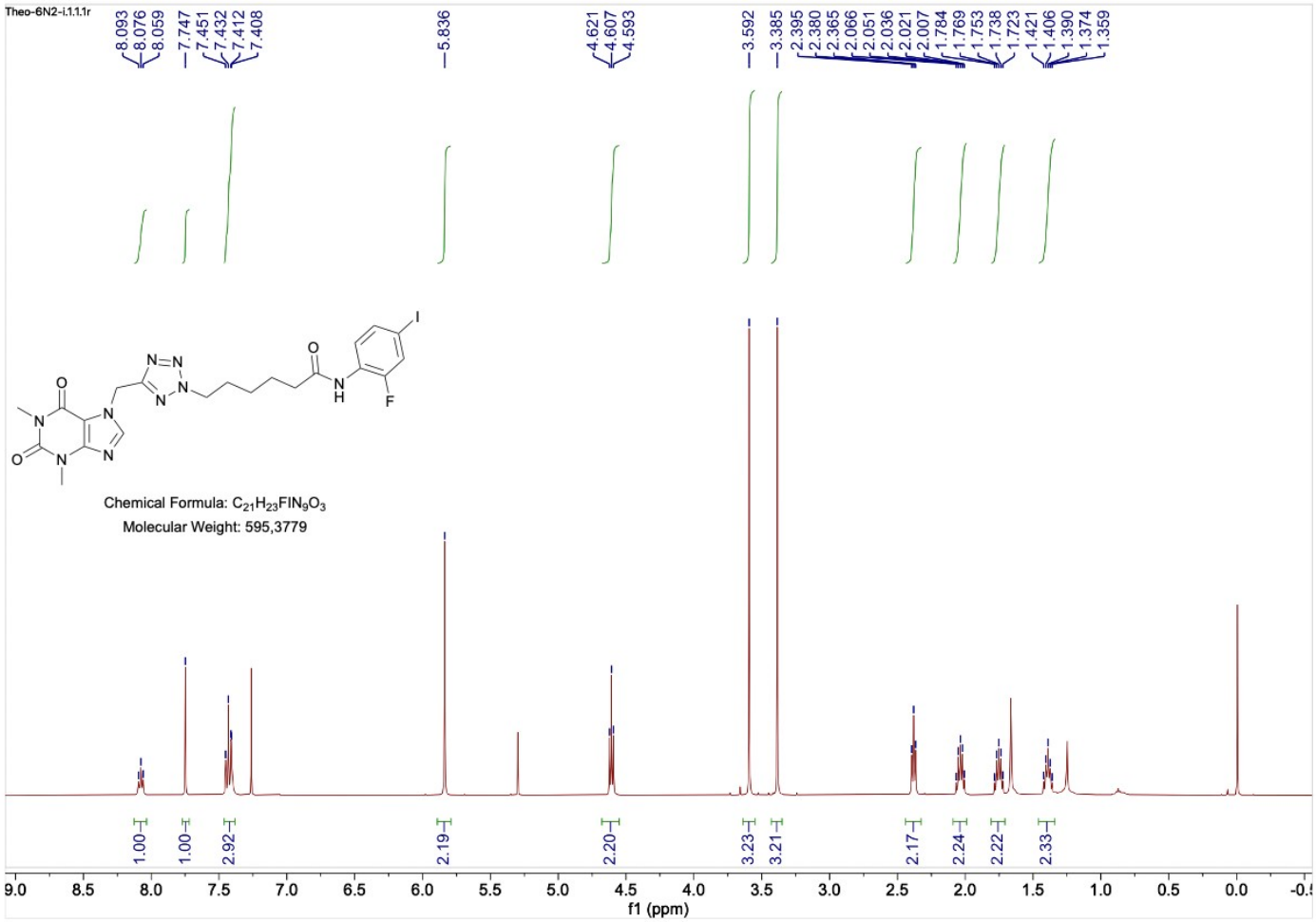
^{13}C-NMR of compound 16



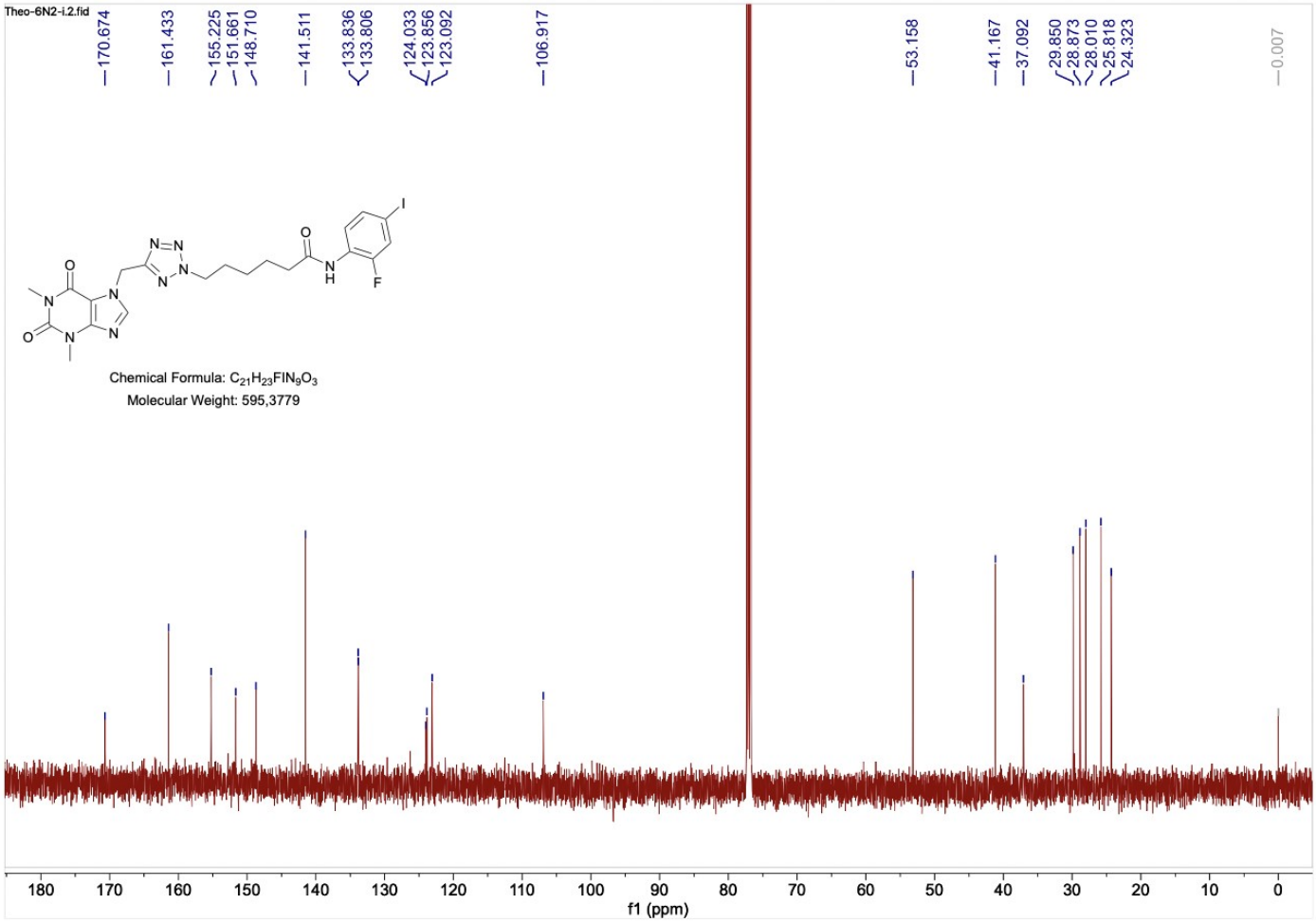
HR-MS of compound 16



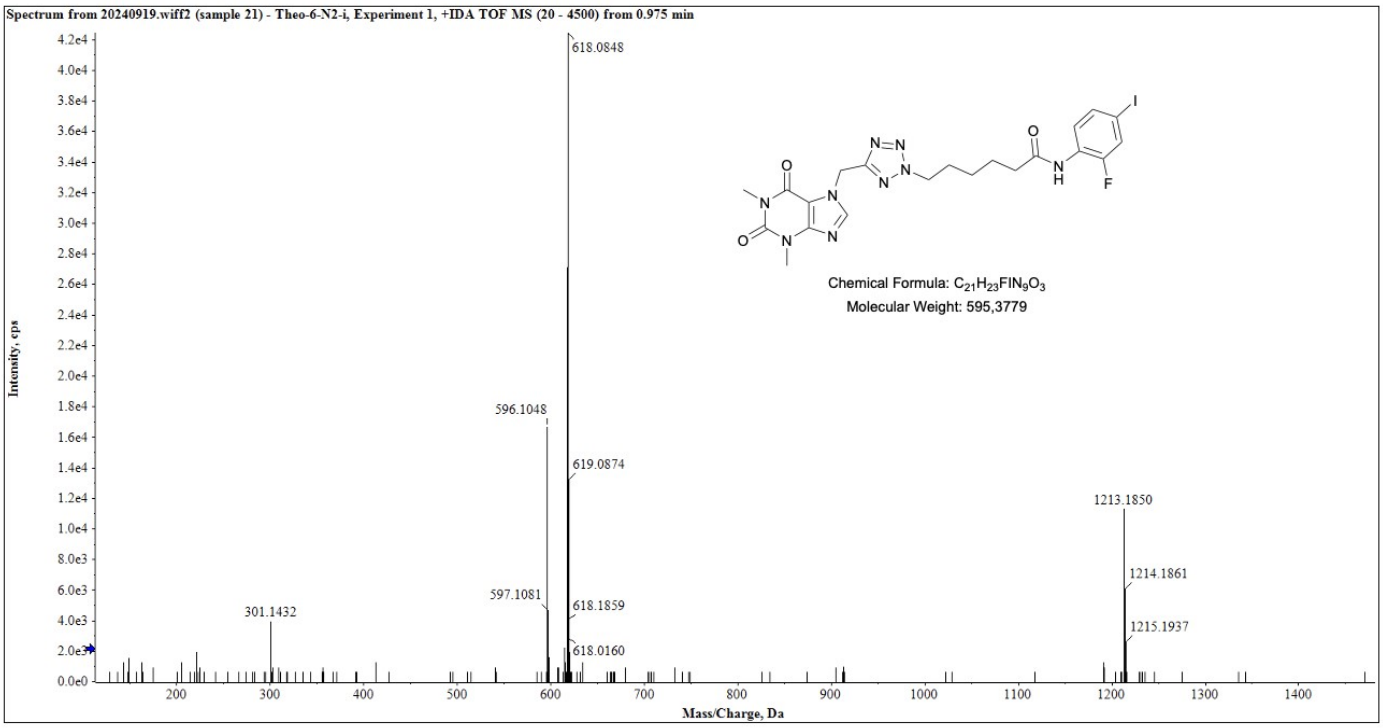
^{1}H-NMR of compound 17



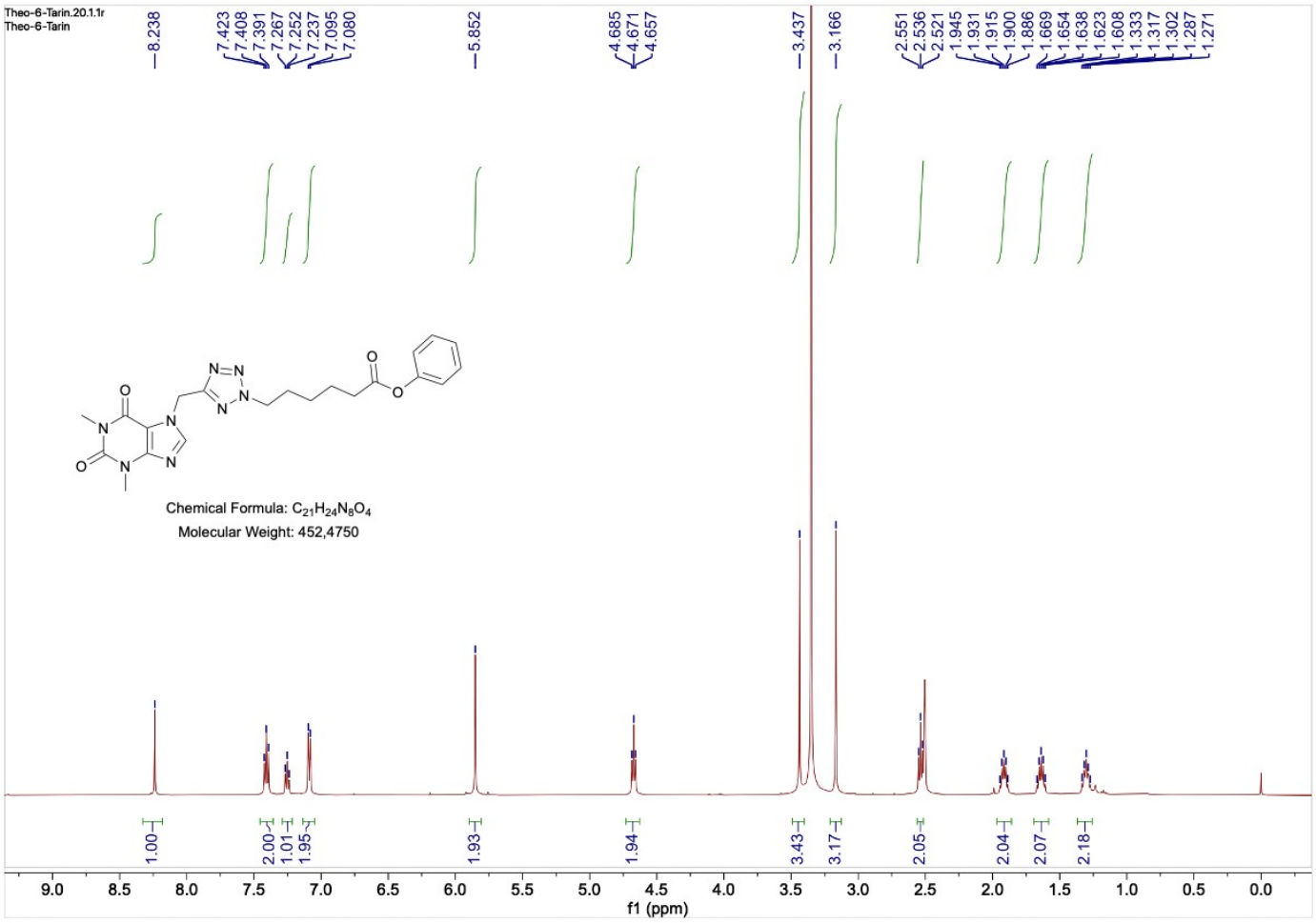
^{13}C-NMR of compound 17



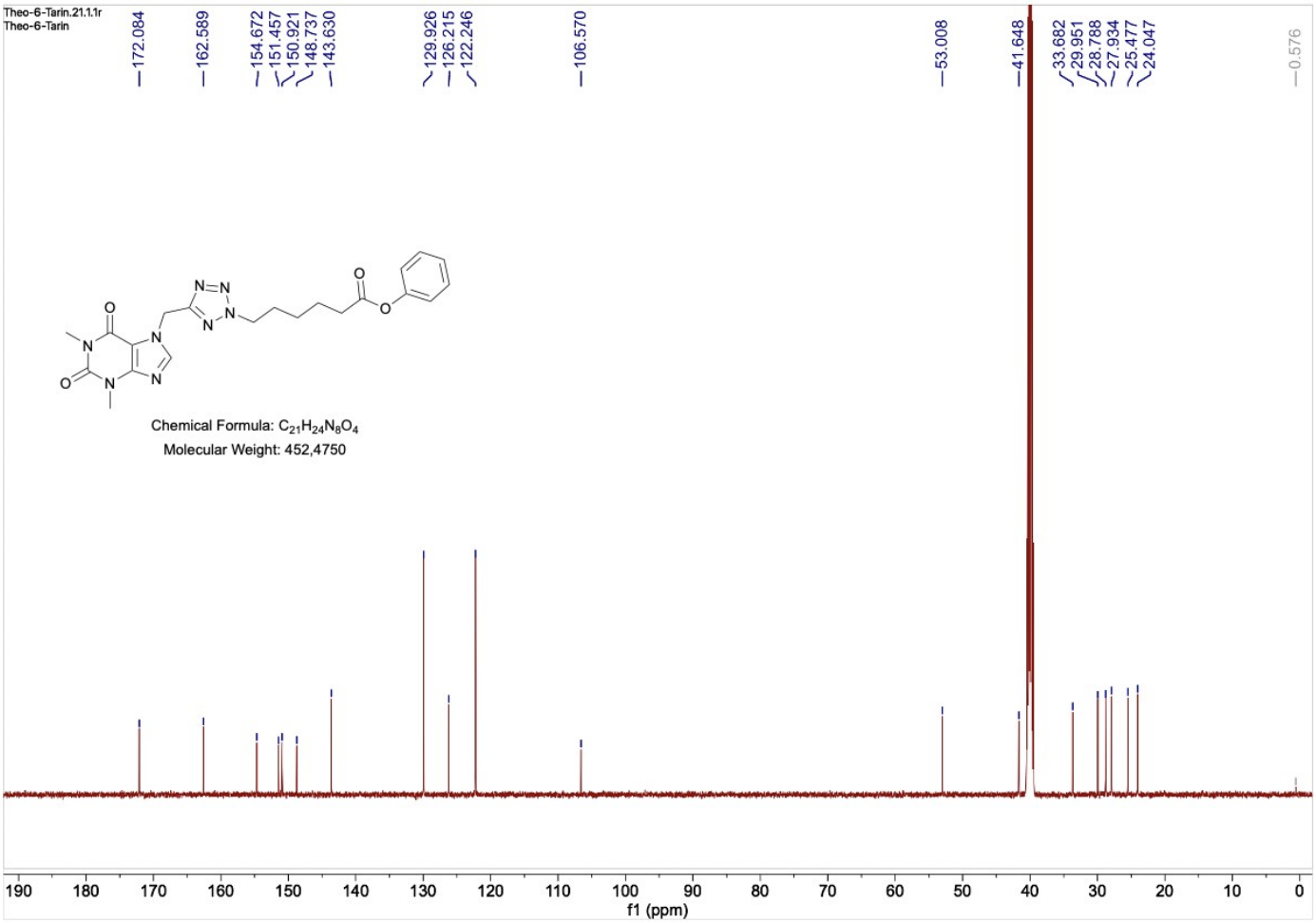
HR-MS of compound 17



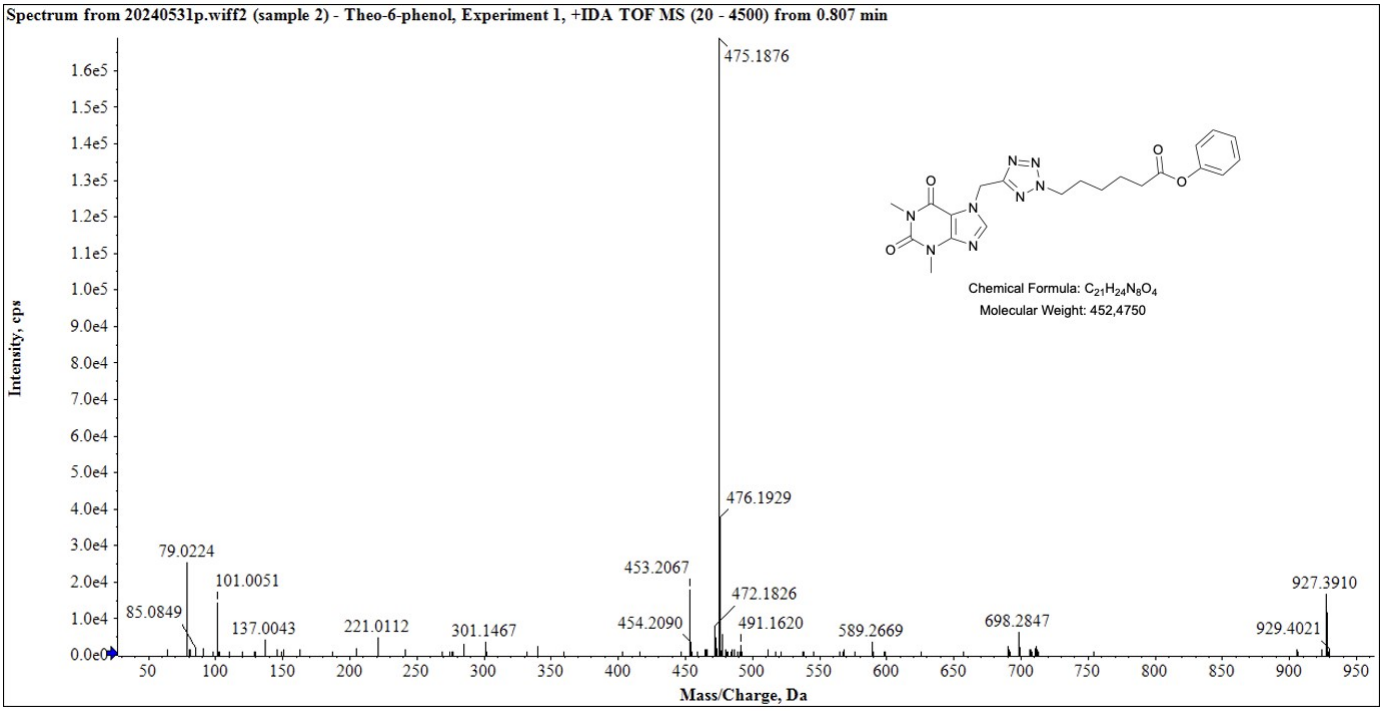
^{1}H-NMR of compound 18



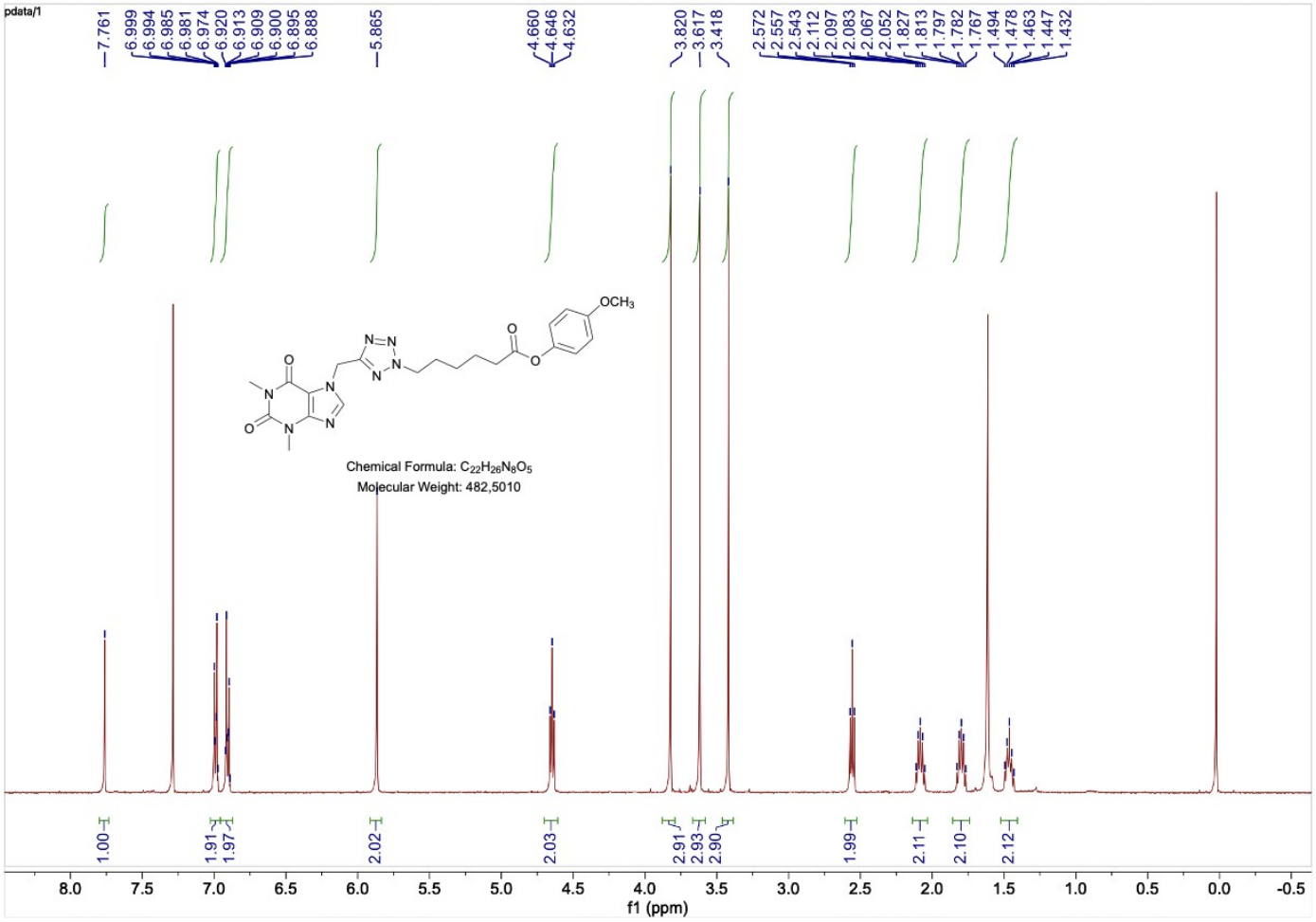
^{13}C-NMR of compound 18



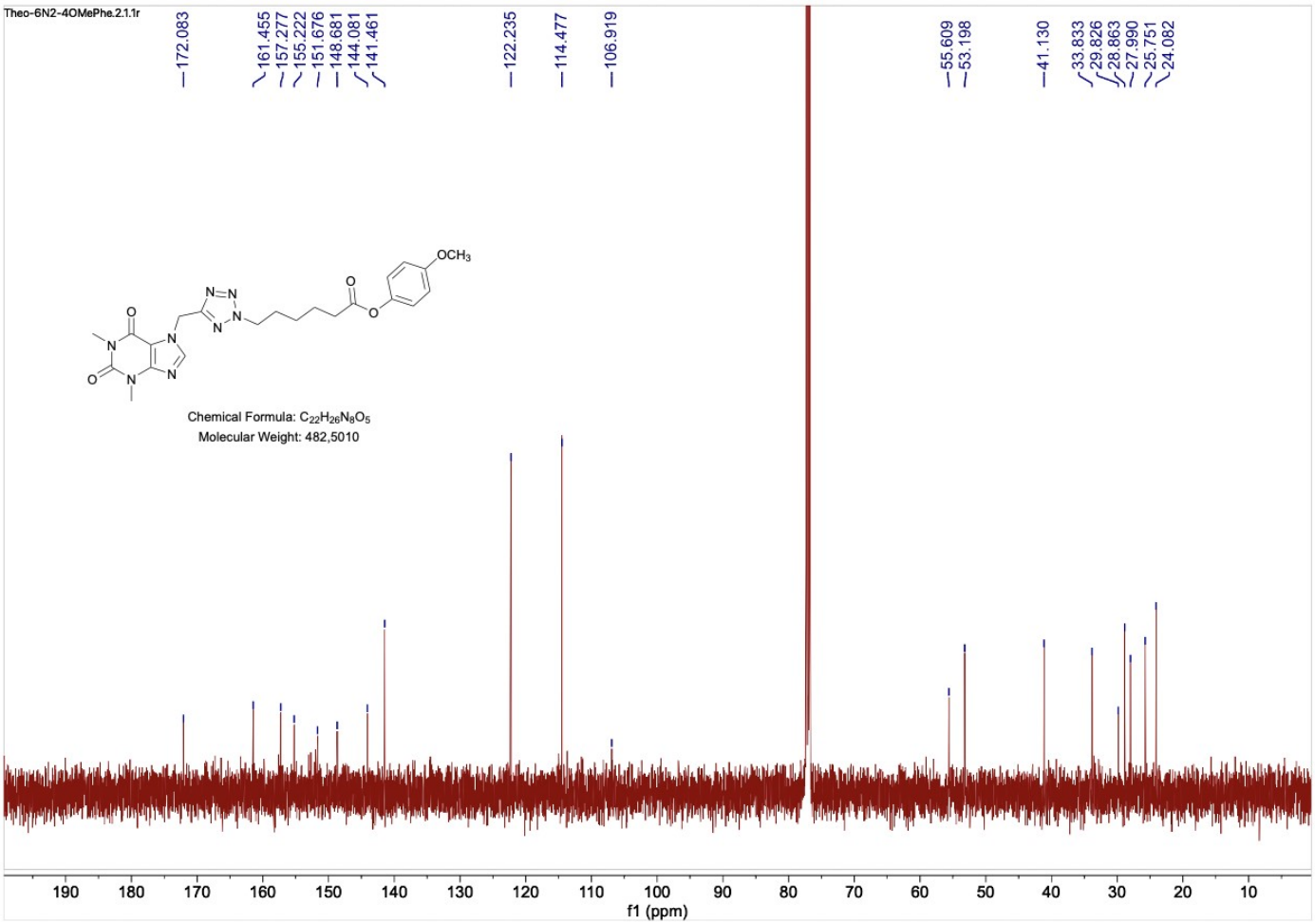
HR-MS of compound 18



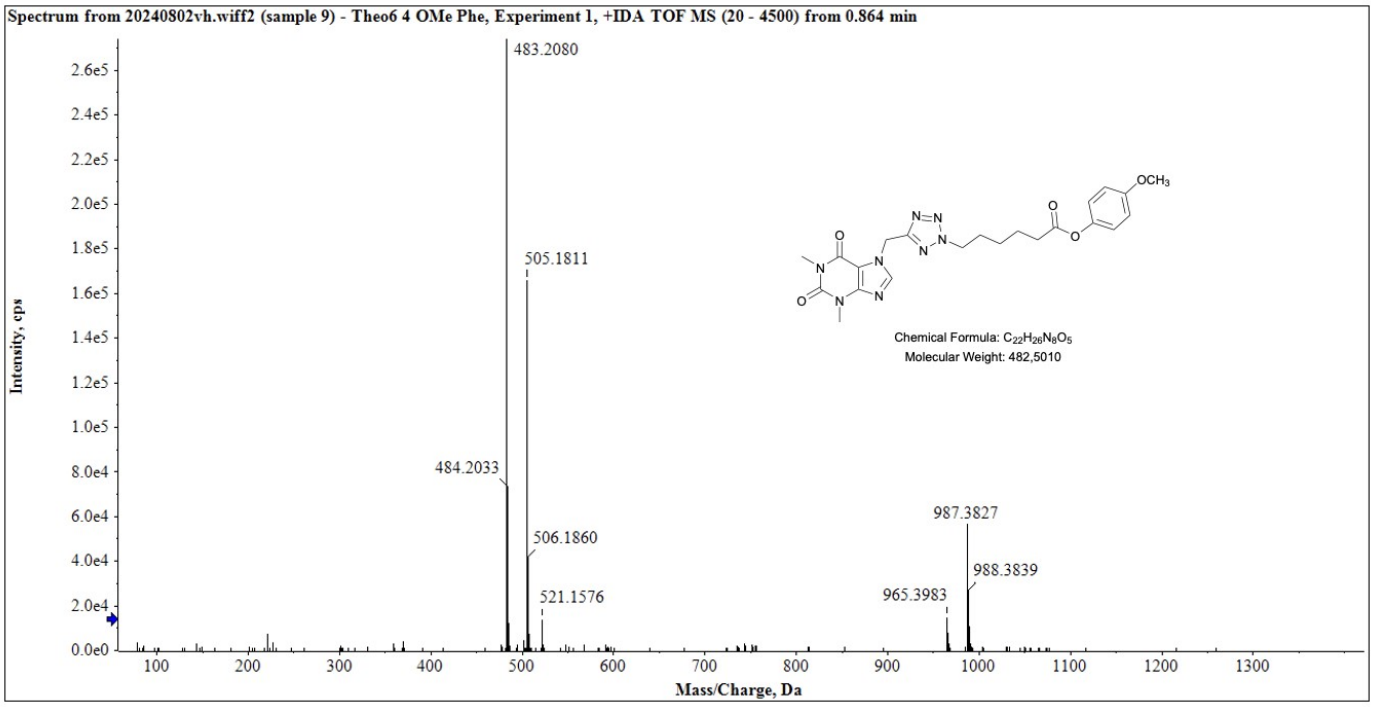
^{1}H-NMR of compound 19



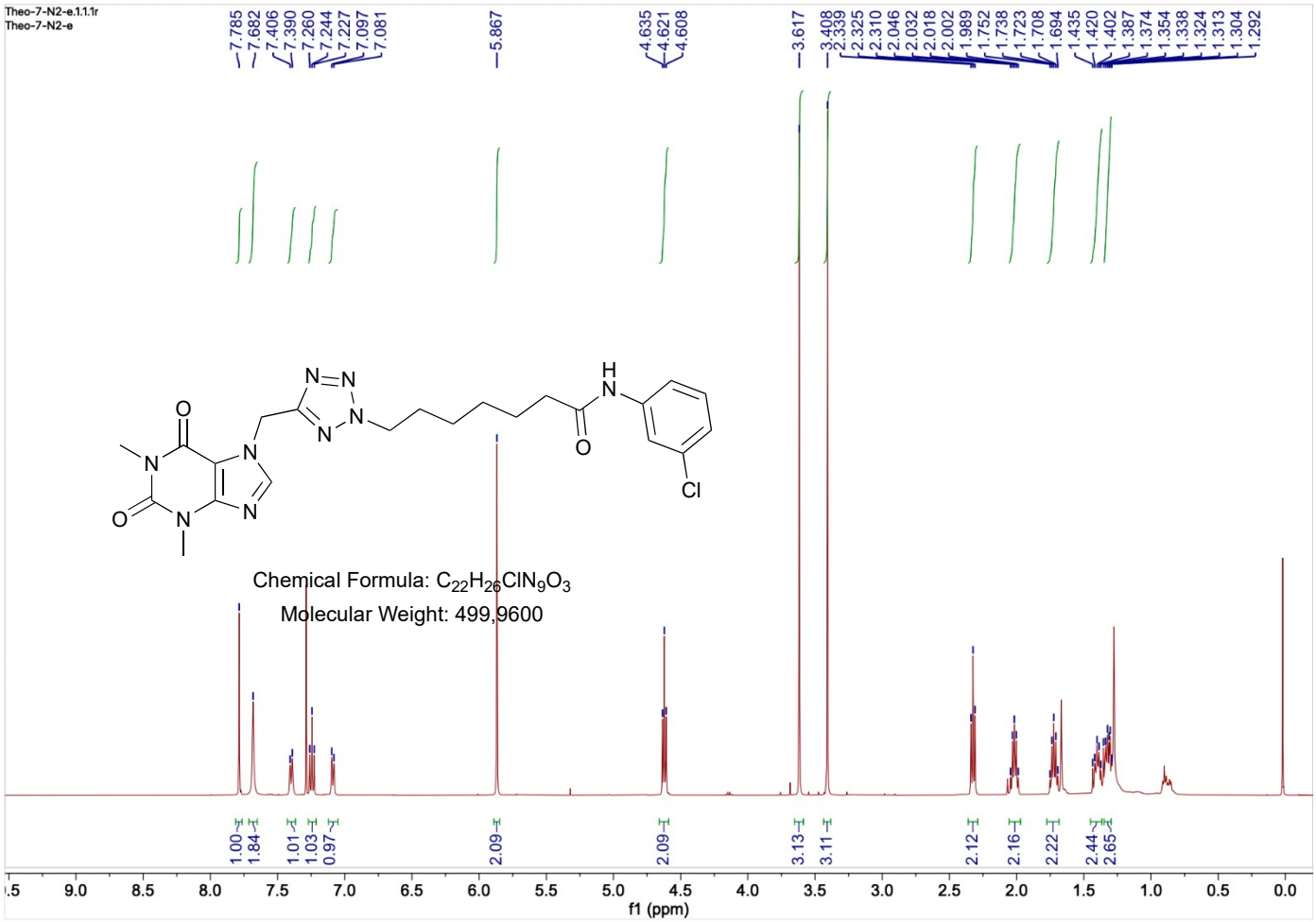
^{13}C-NMR of compound 19



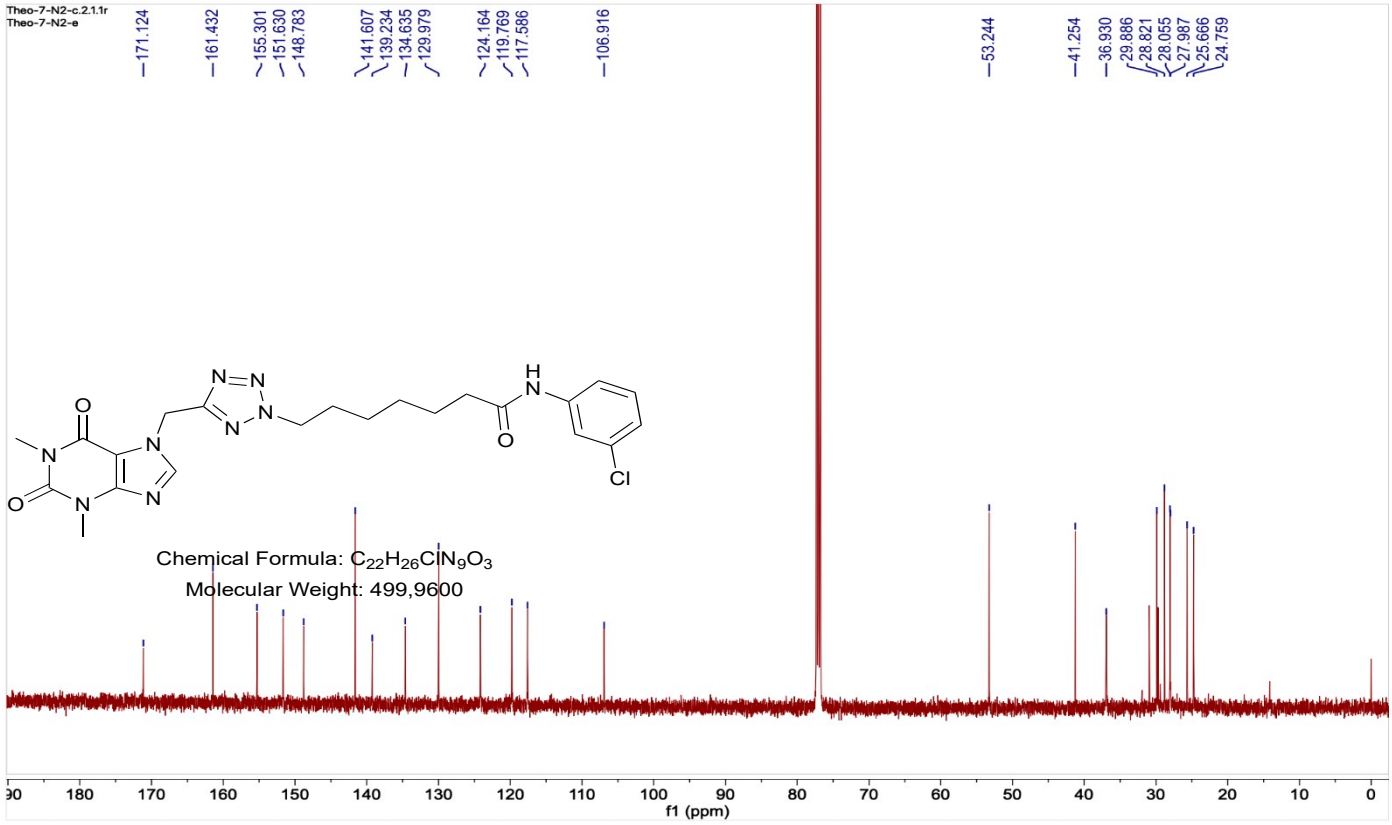
HR-MS of compound 19



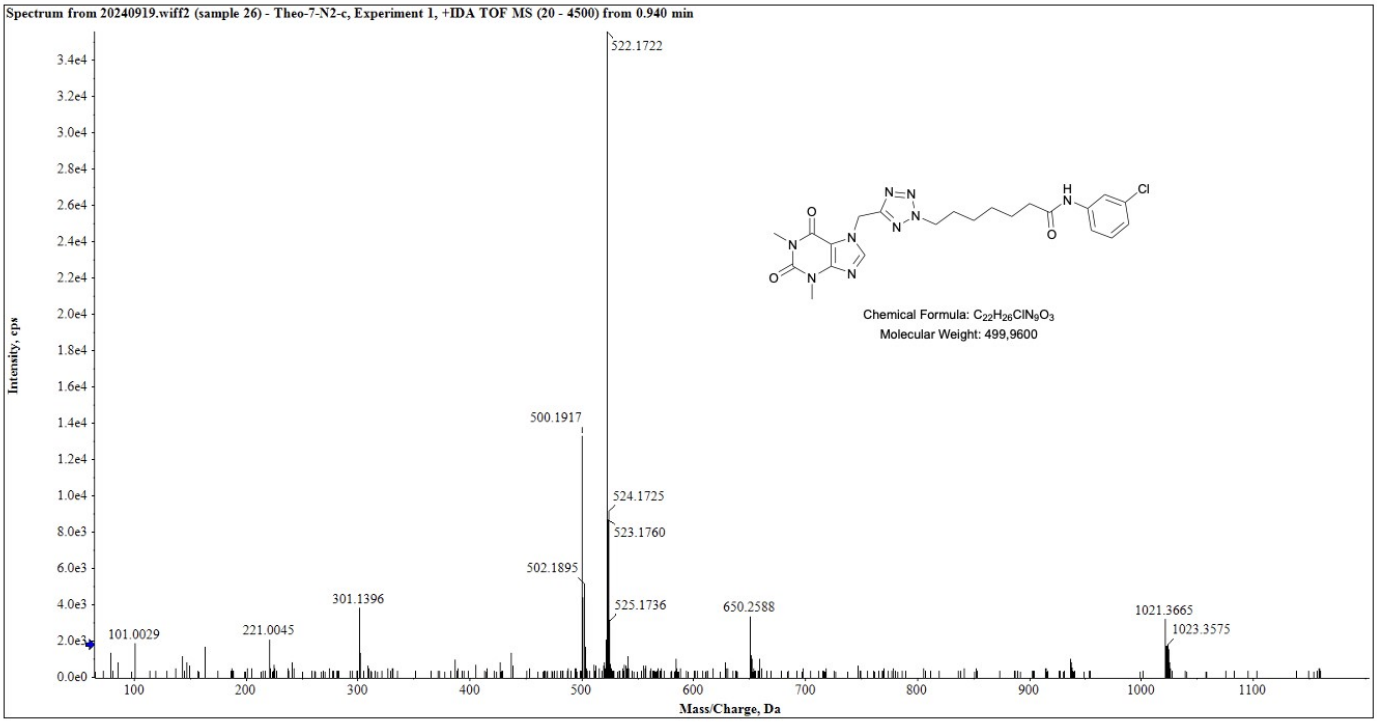
^{1}H-NMR of compound 20



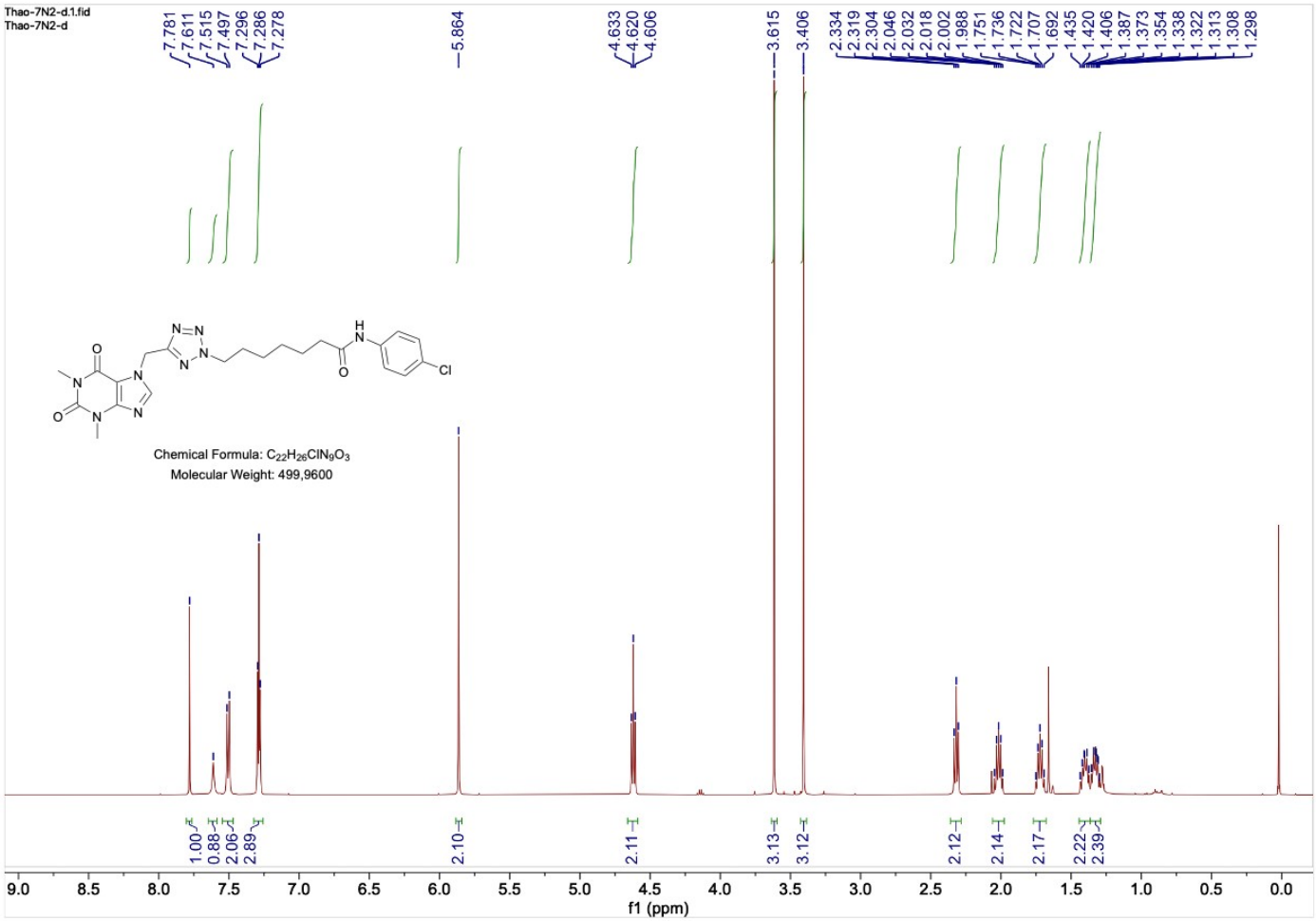
^{13}C-NMR of compound 20



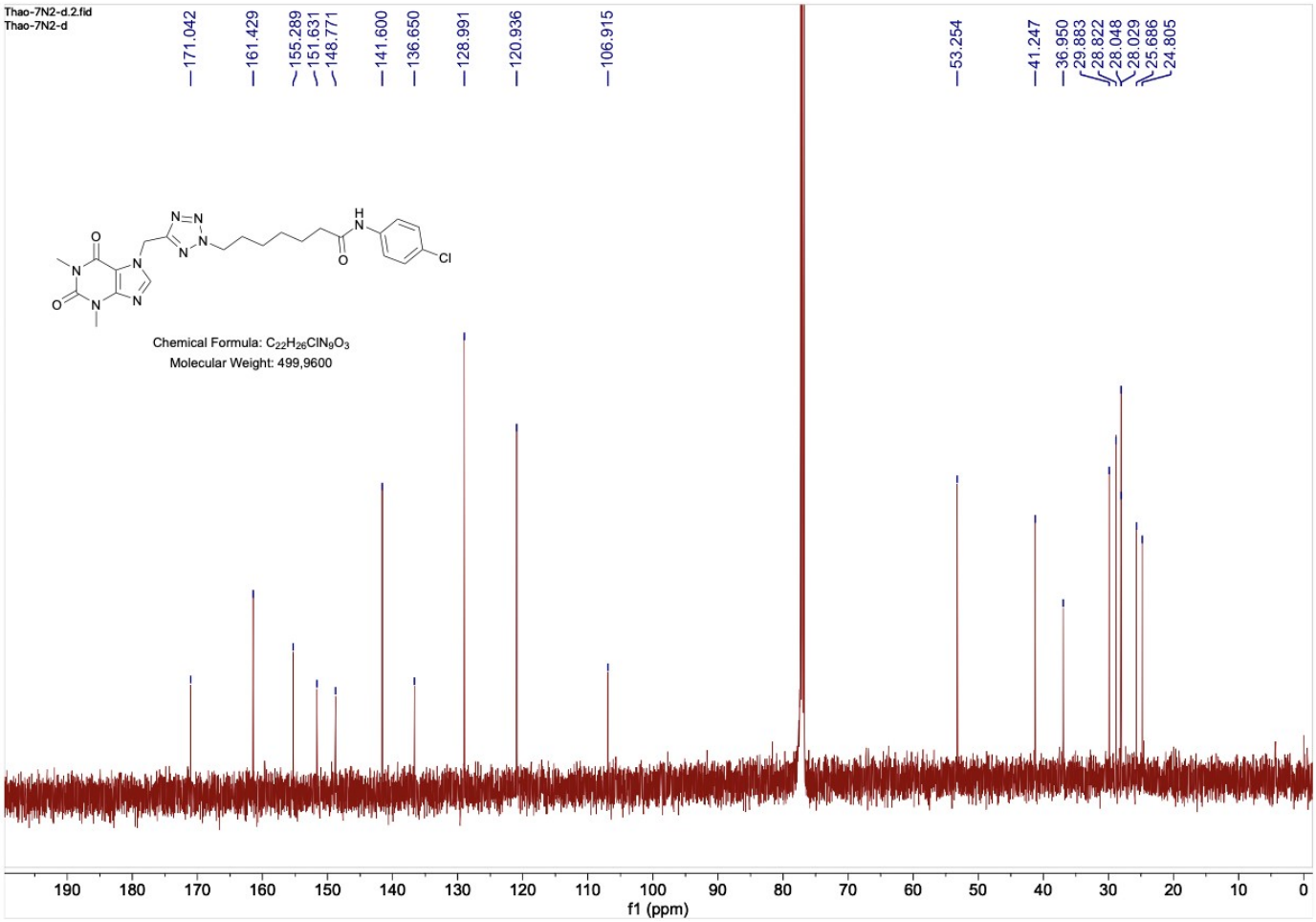
HR-MS of compound 20



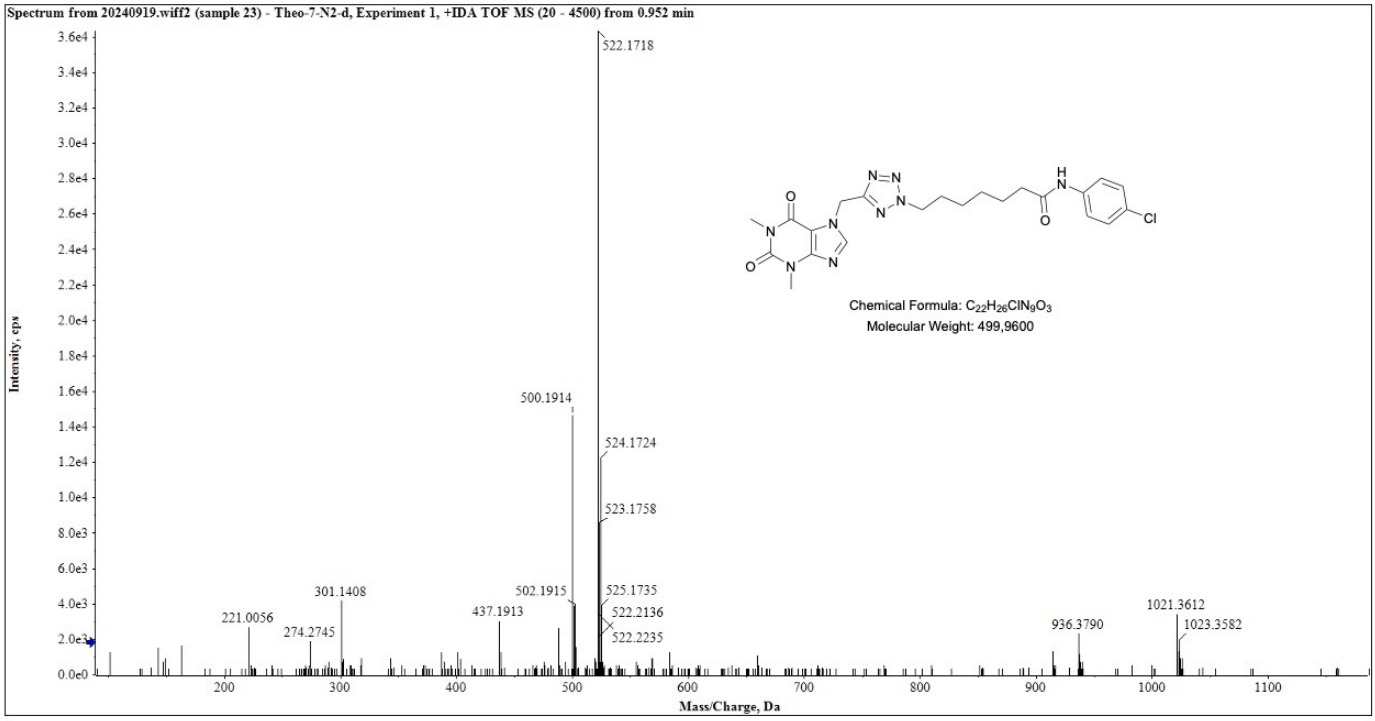
^{1}H-NMR of compound 21



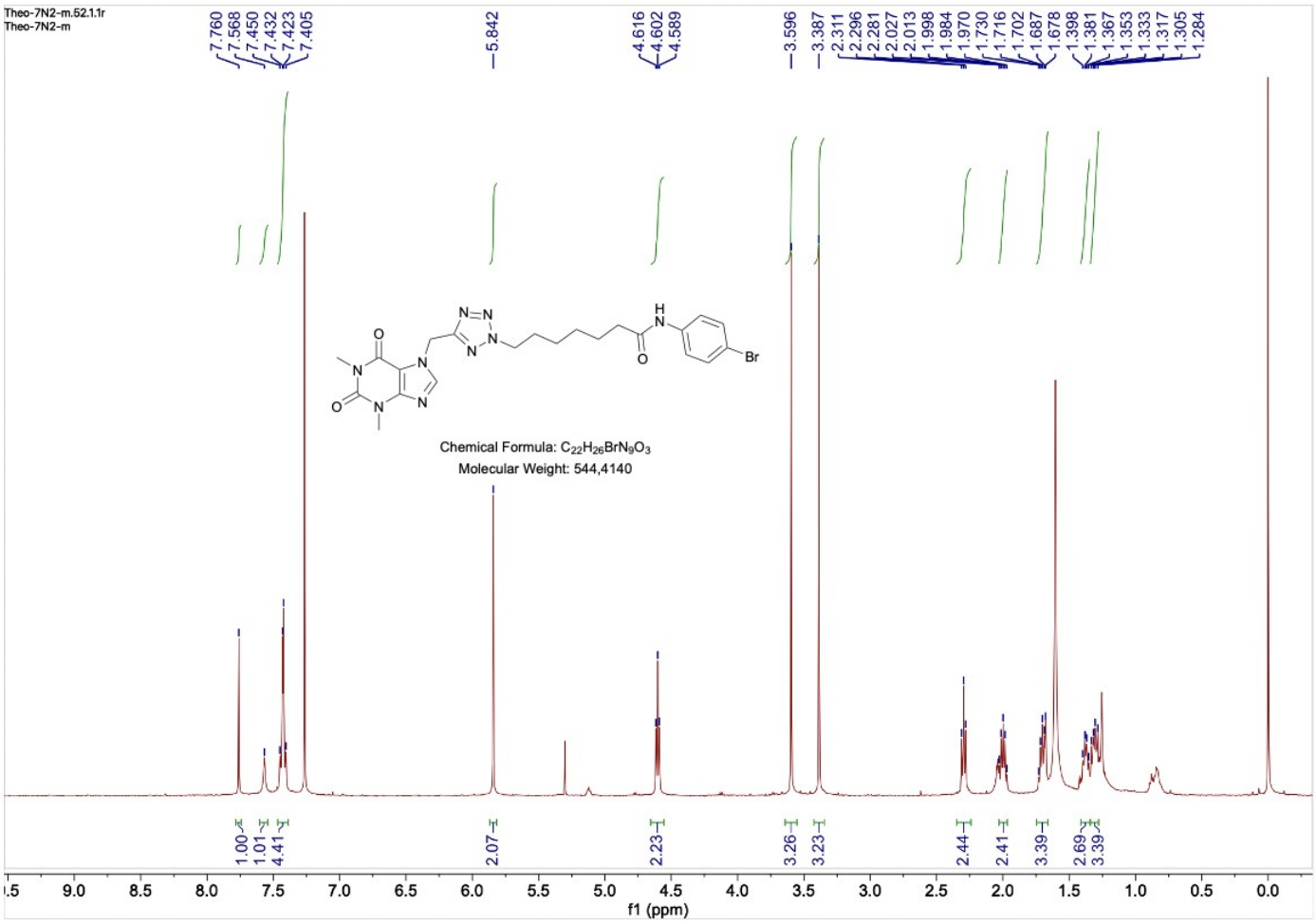
^{13}C-NMR of compound 21



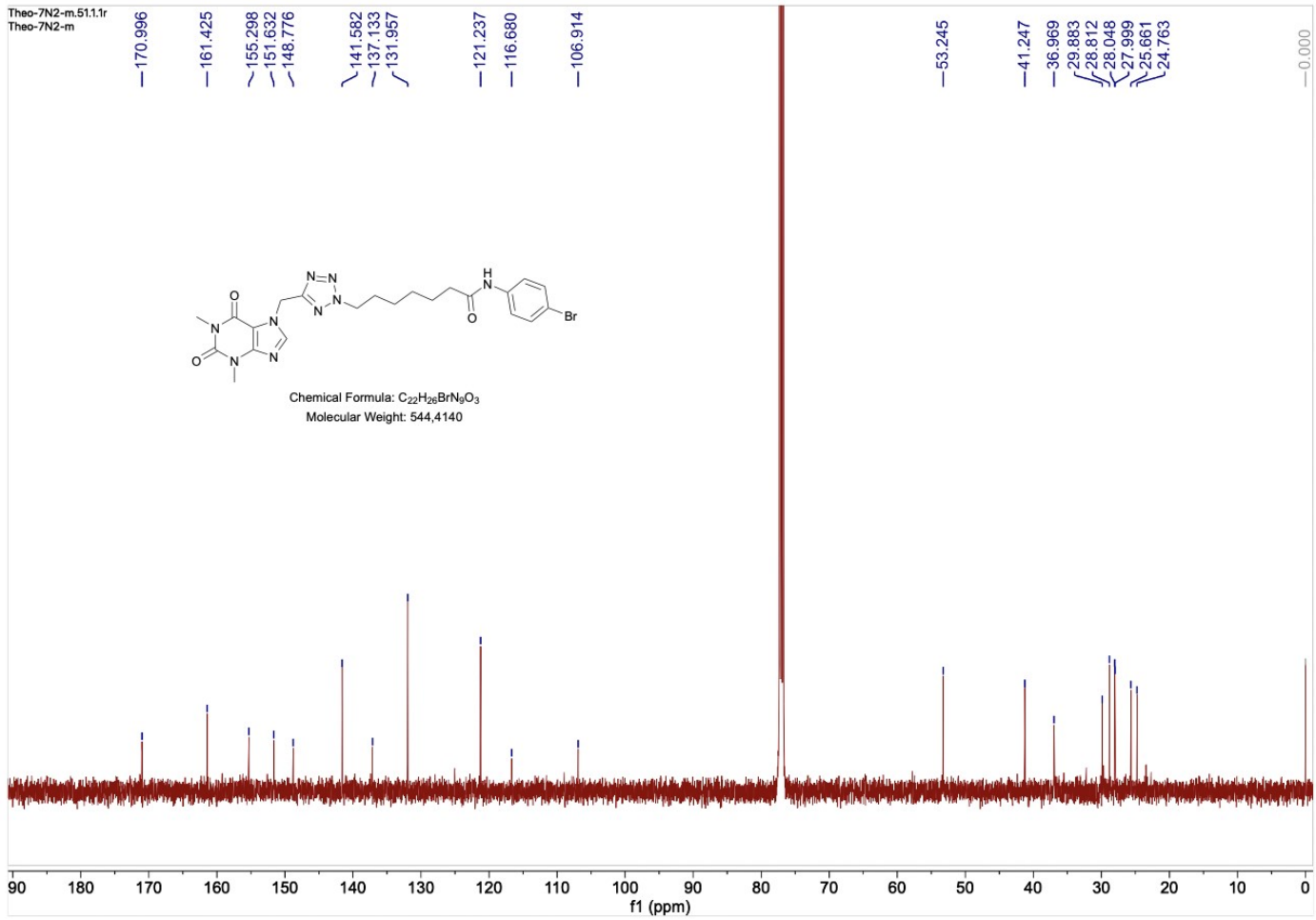
HR-MS of compound 21



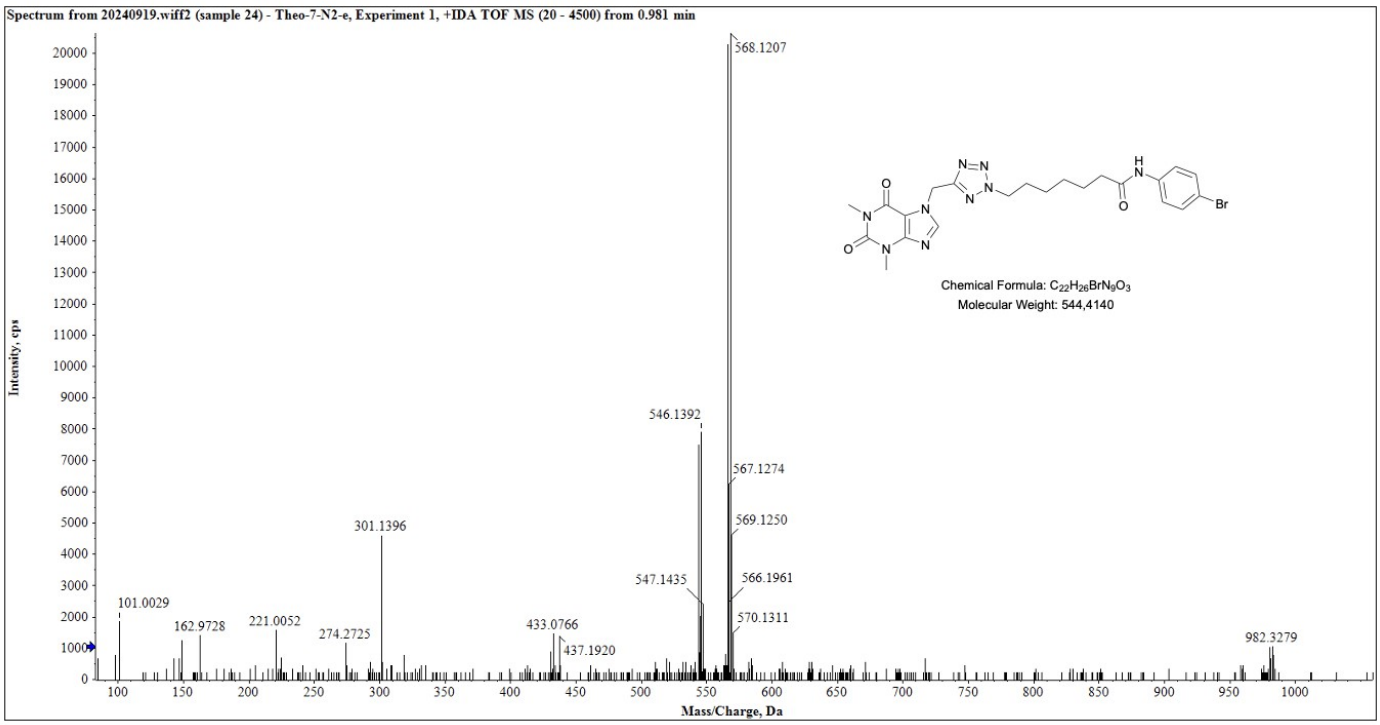
[1]H-NMR of compound 22

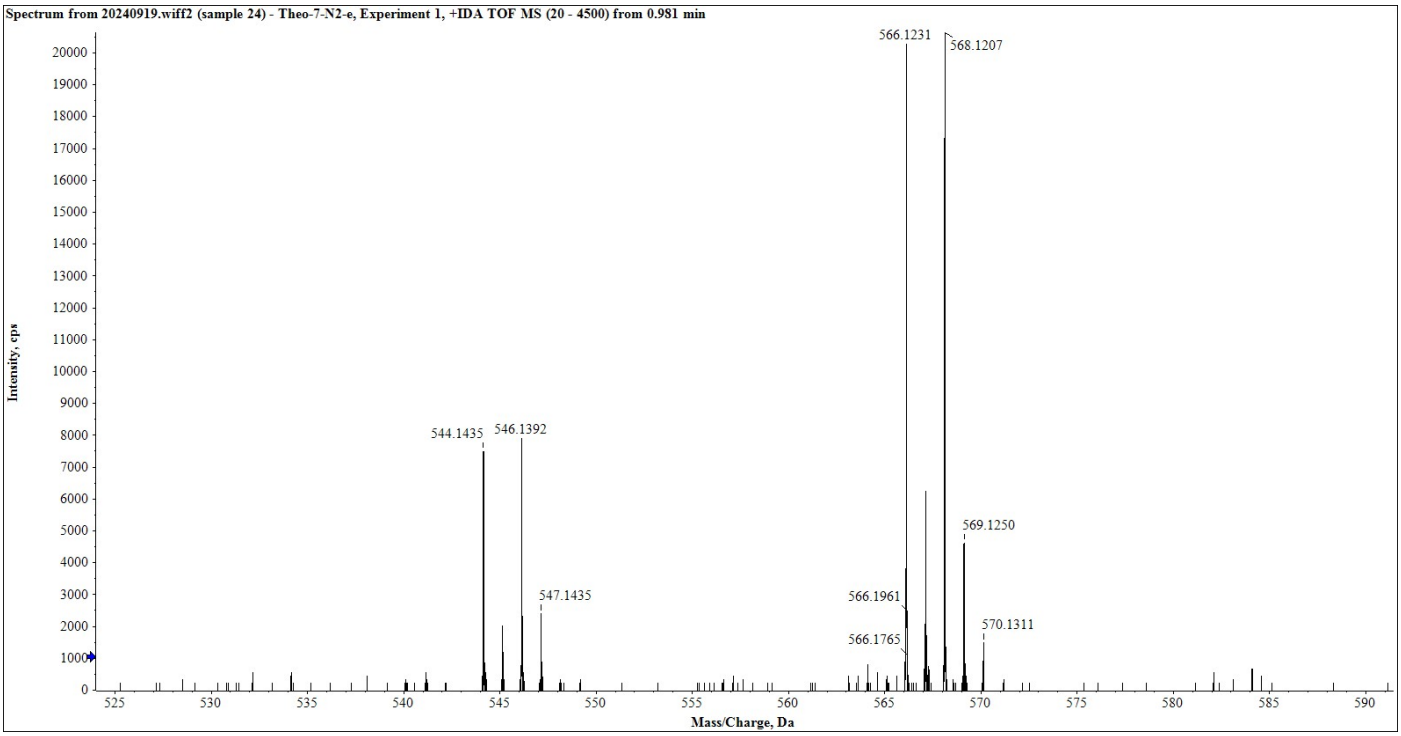


[13]C-NMR of compound 22

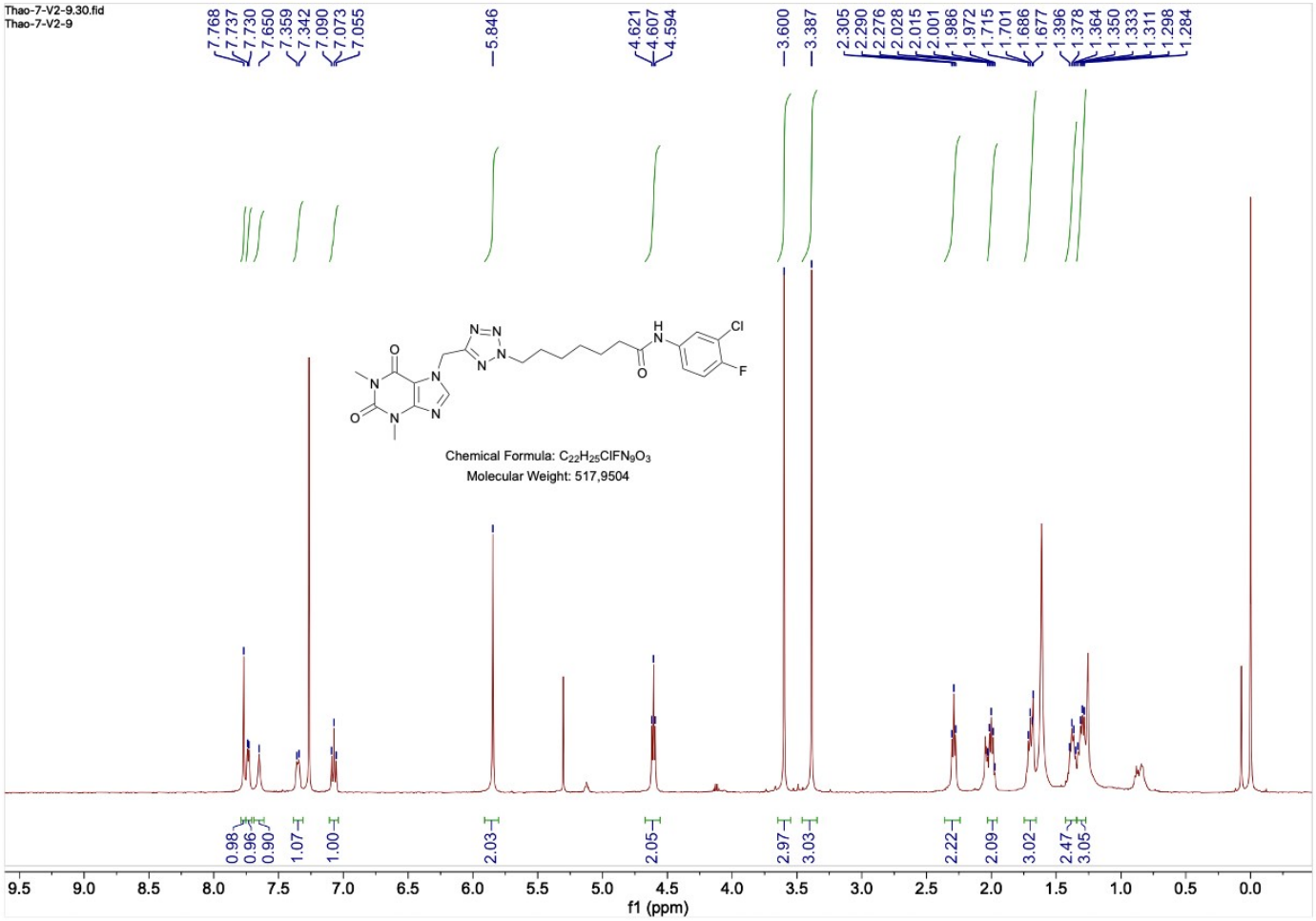


HR-MS of compound 22

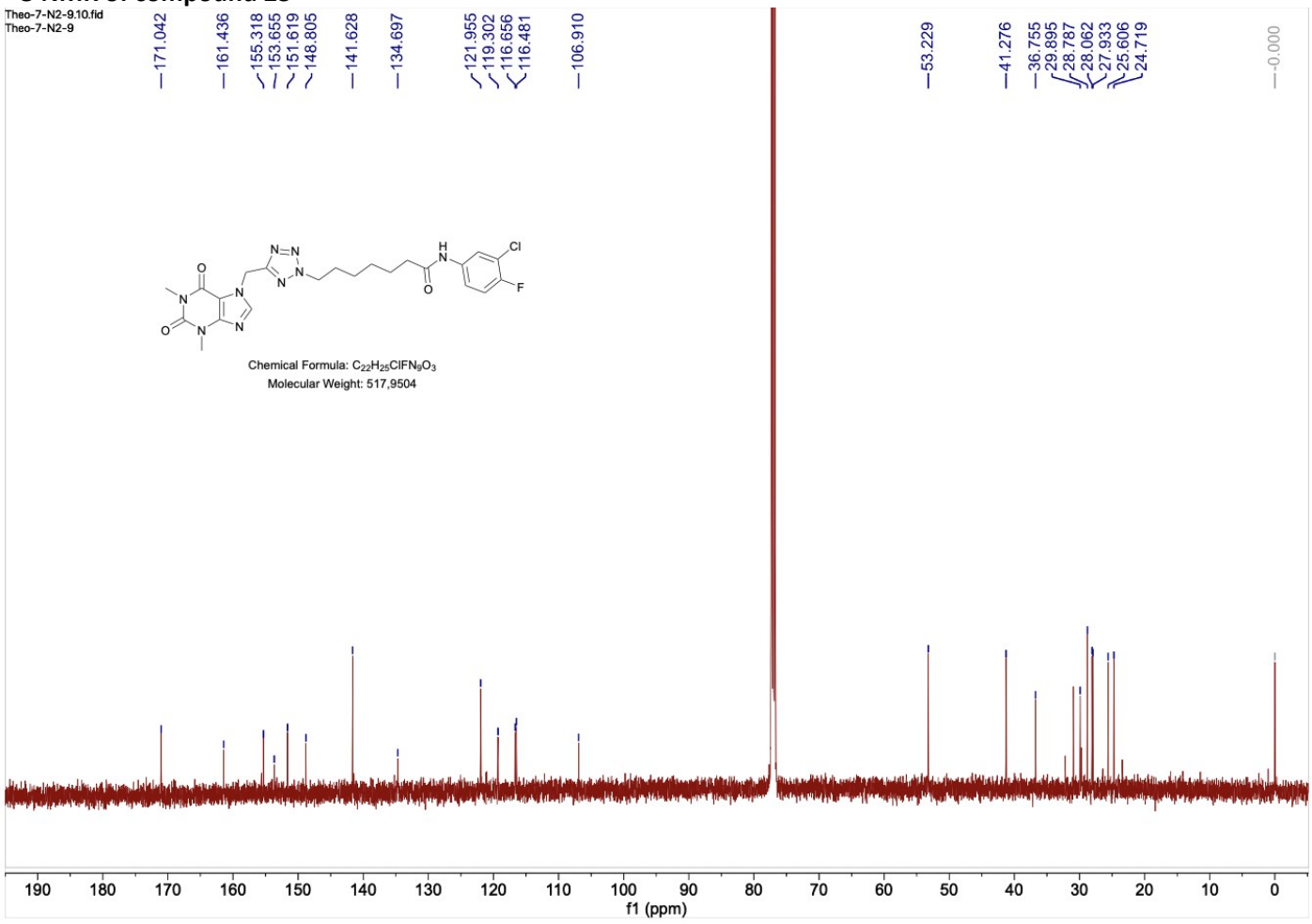




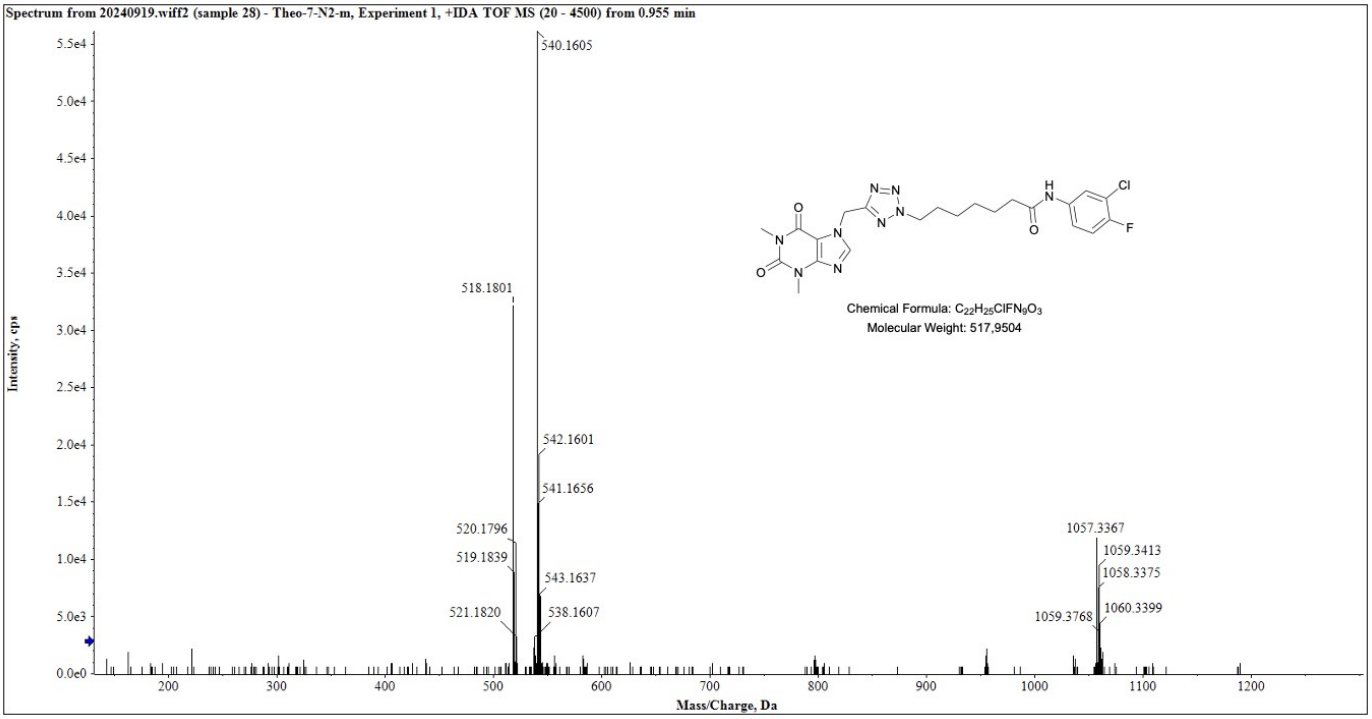
^{1}H-NMR of compound 23



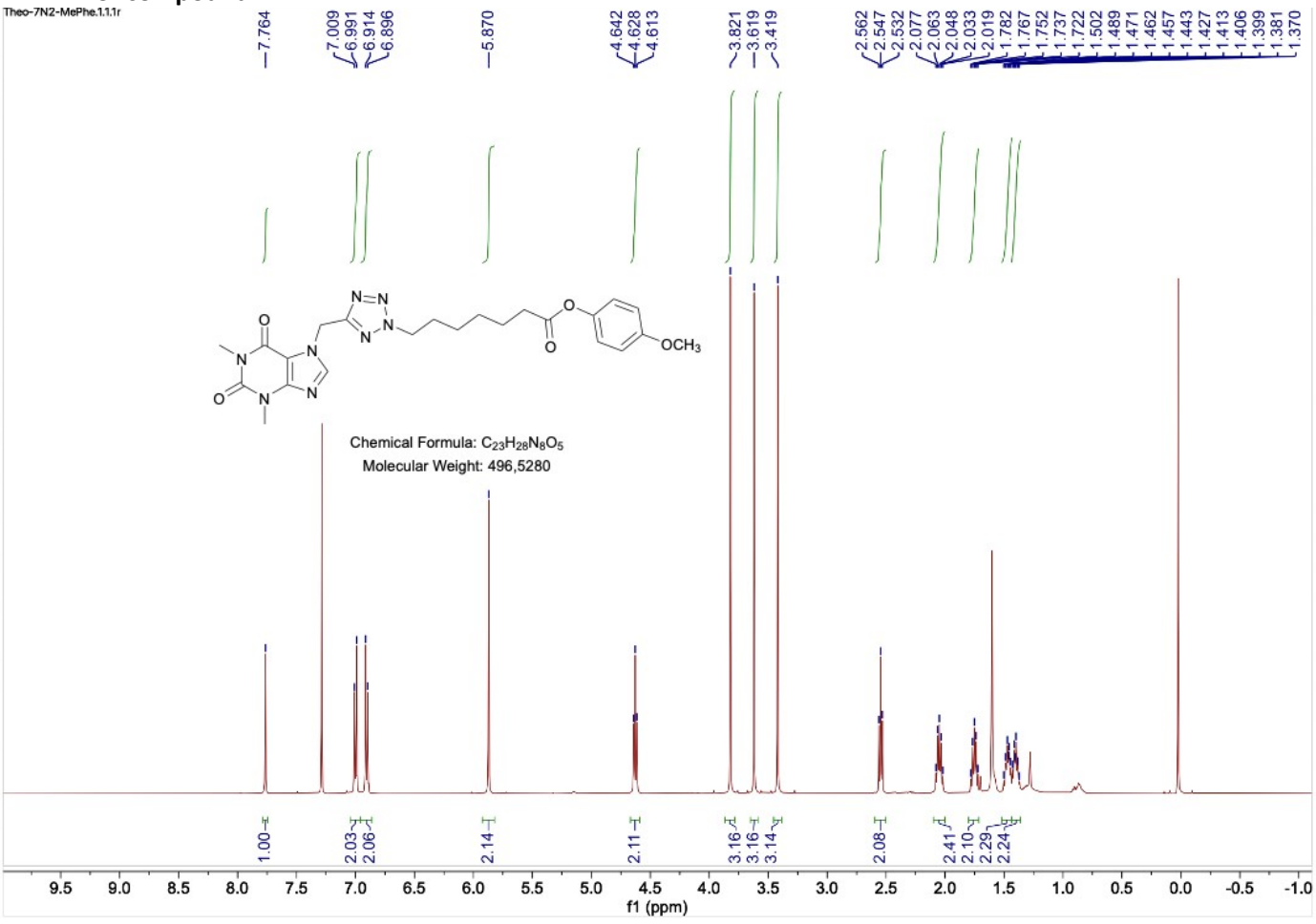
^{13}C-NMR of compound 23



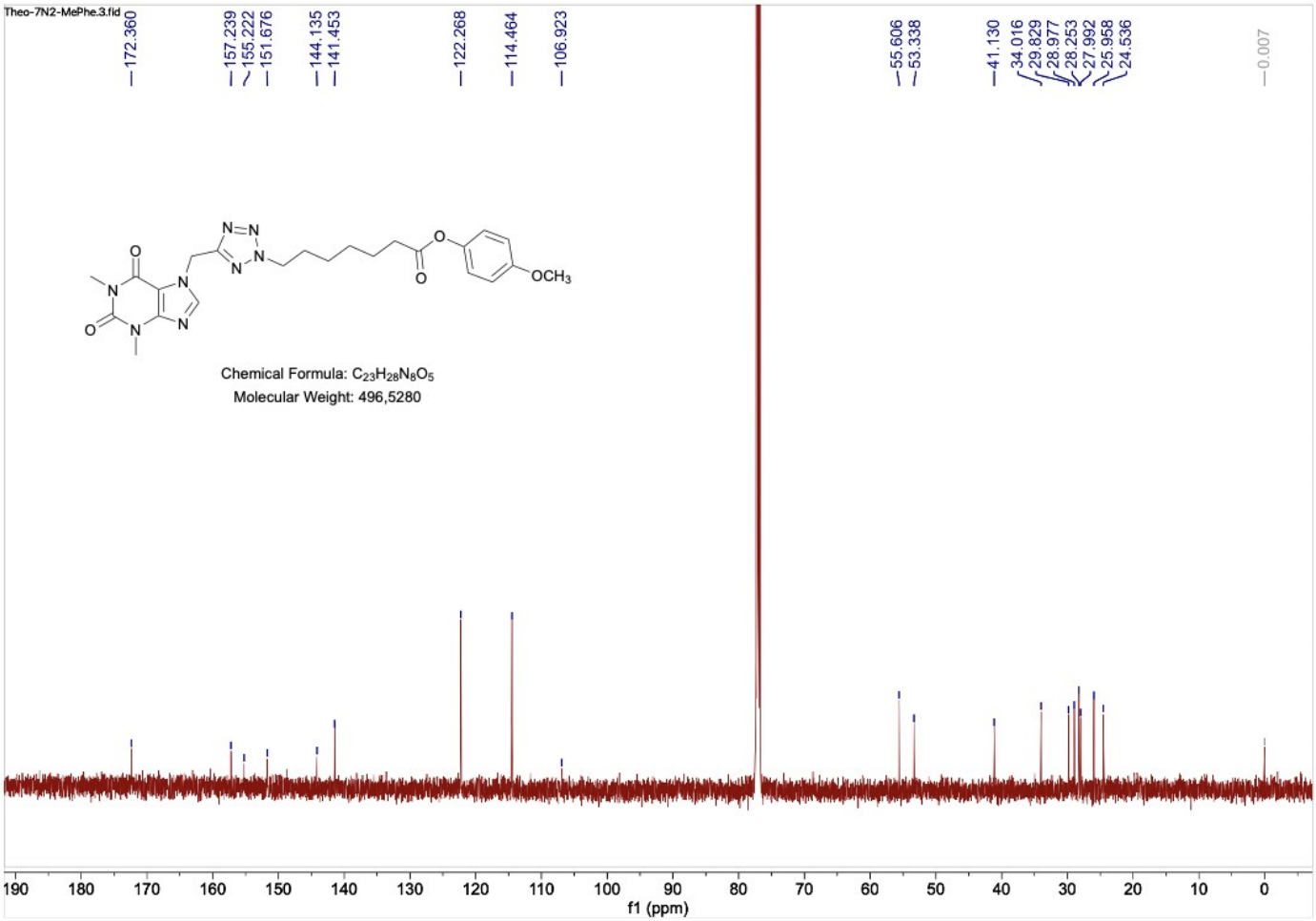
HR-MS of compound 23



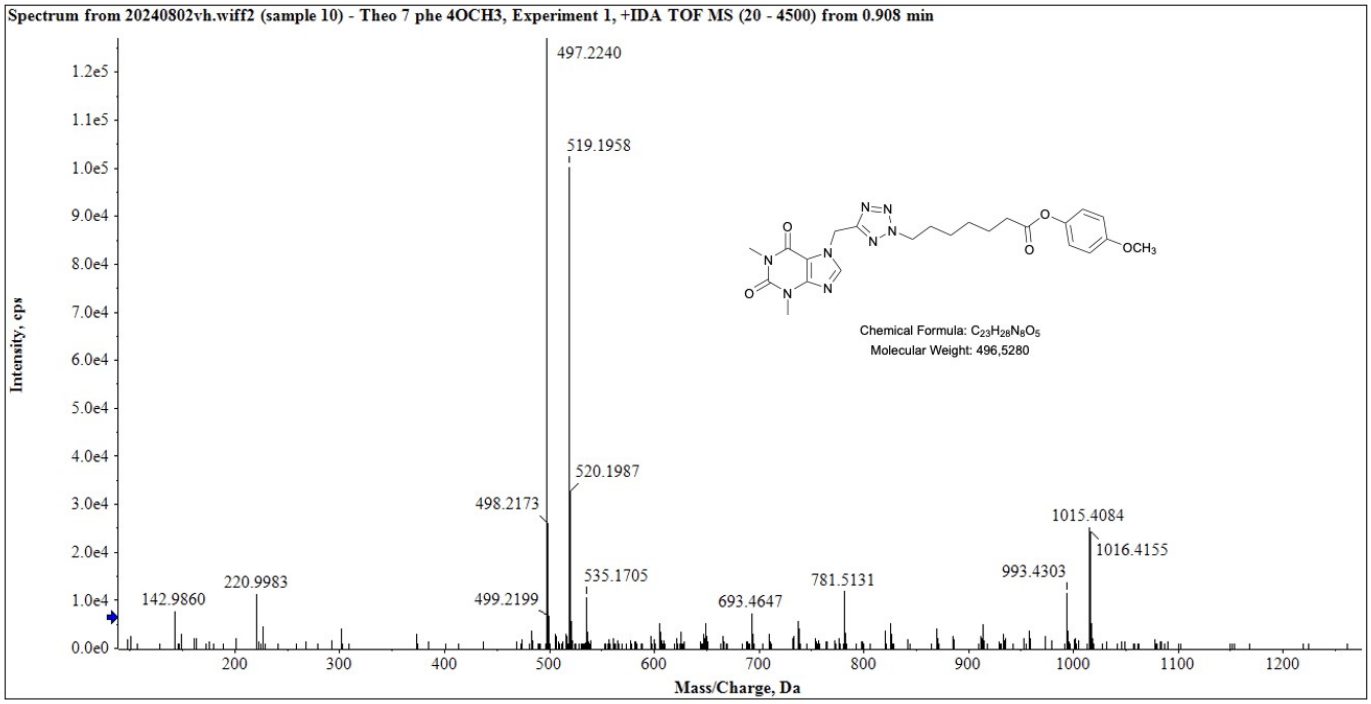
^{1}H-NMR of compound 24



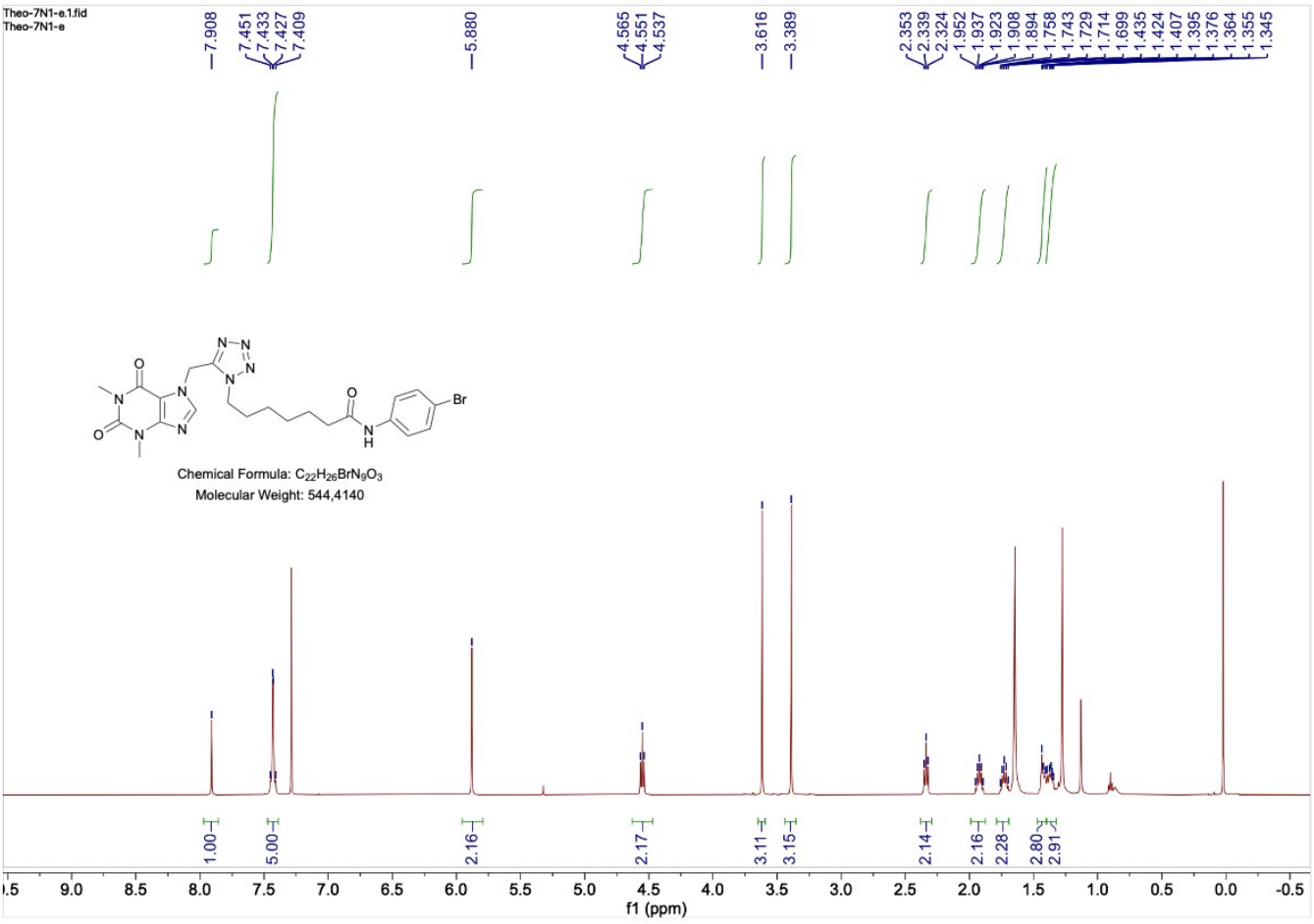
^{13}C-NMR of compound 24



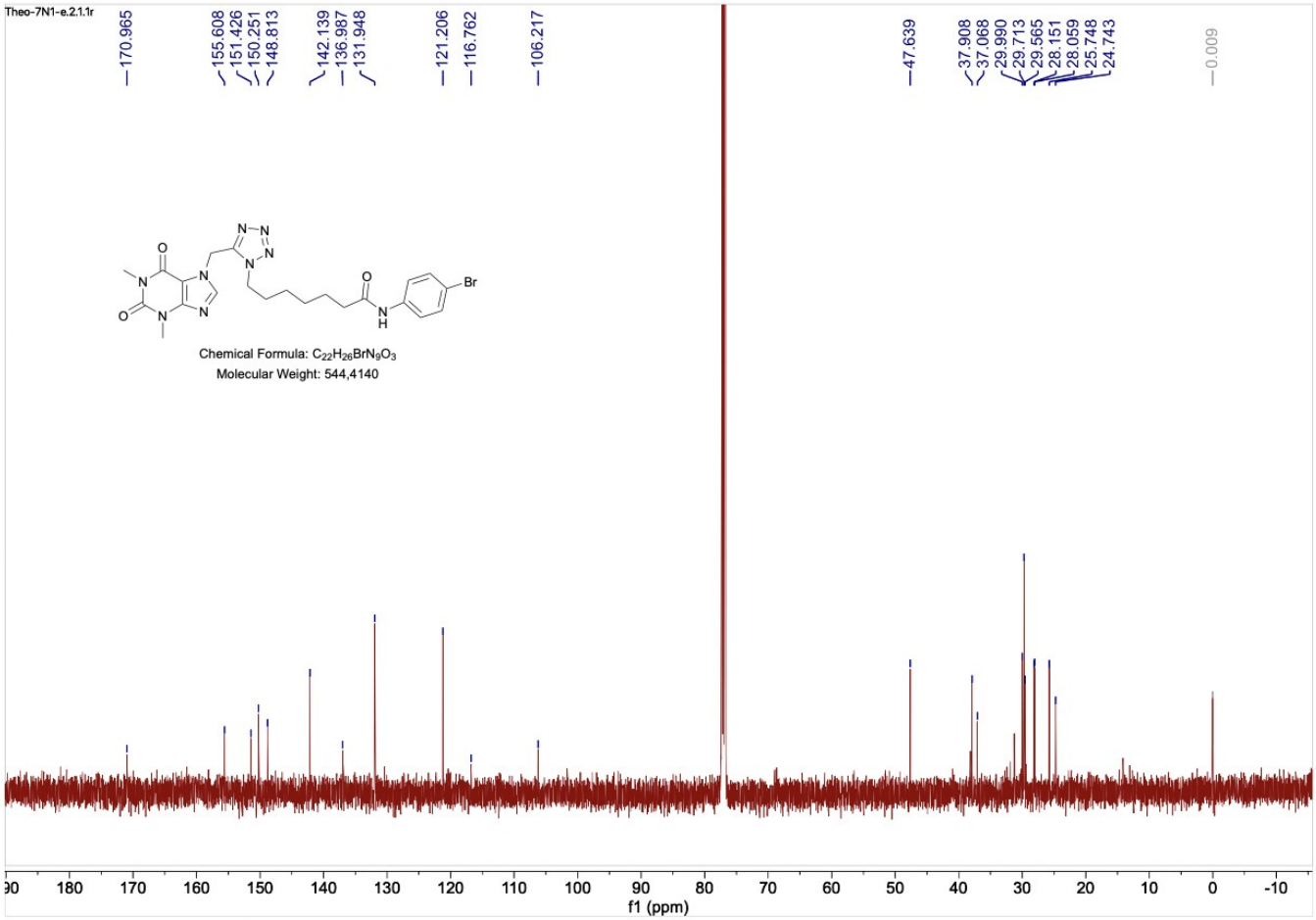
HR-MS of compound 24



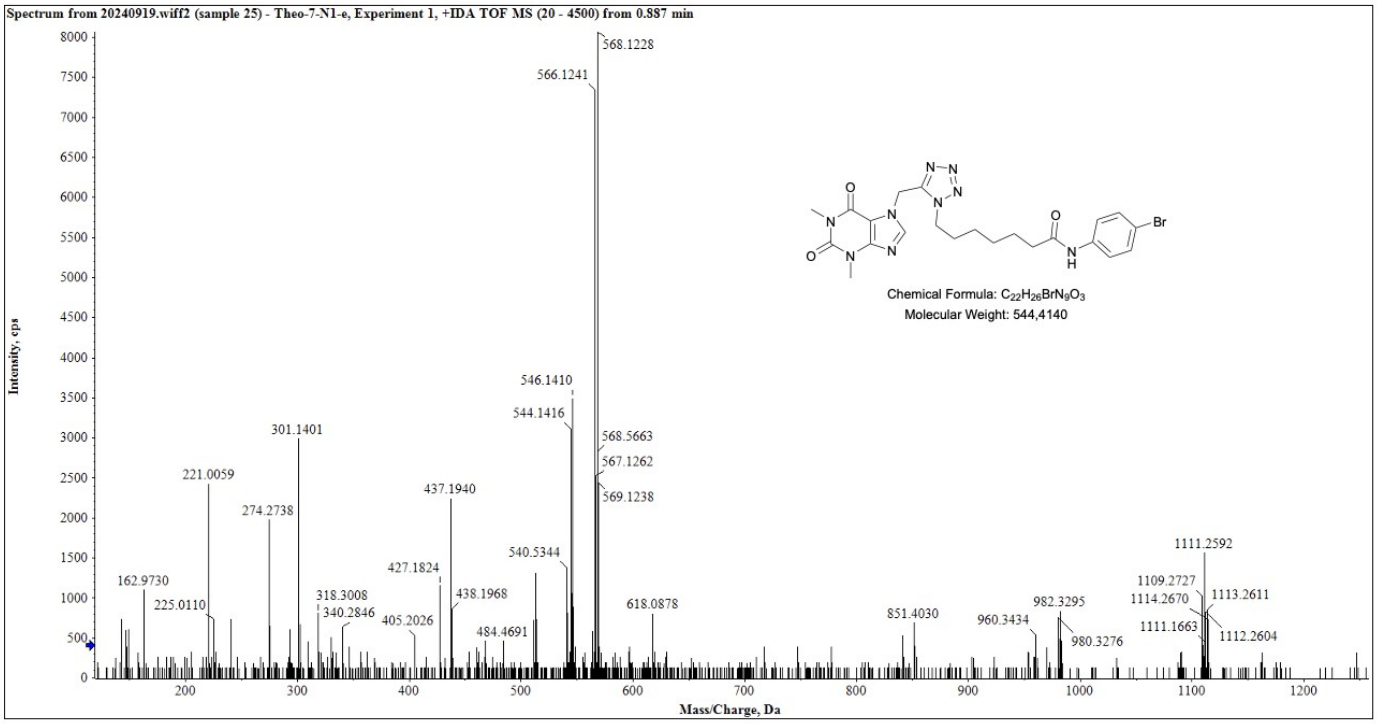
^{1}H-NMR of compound 25



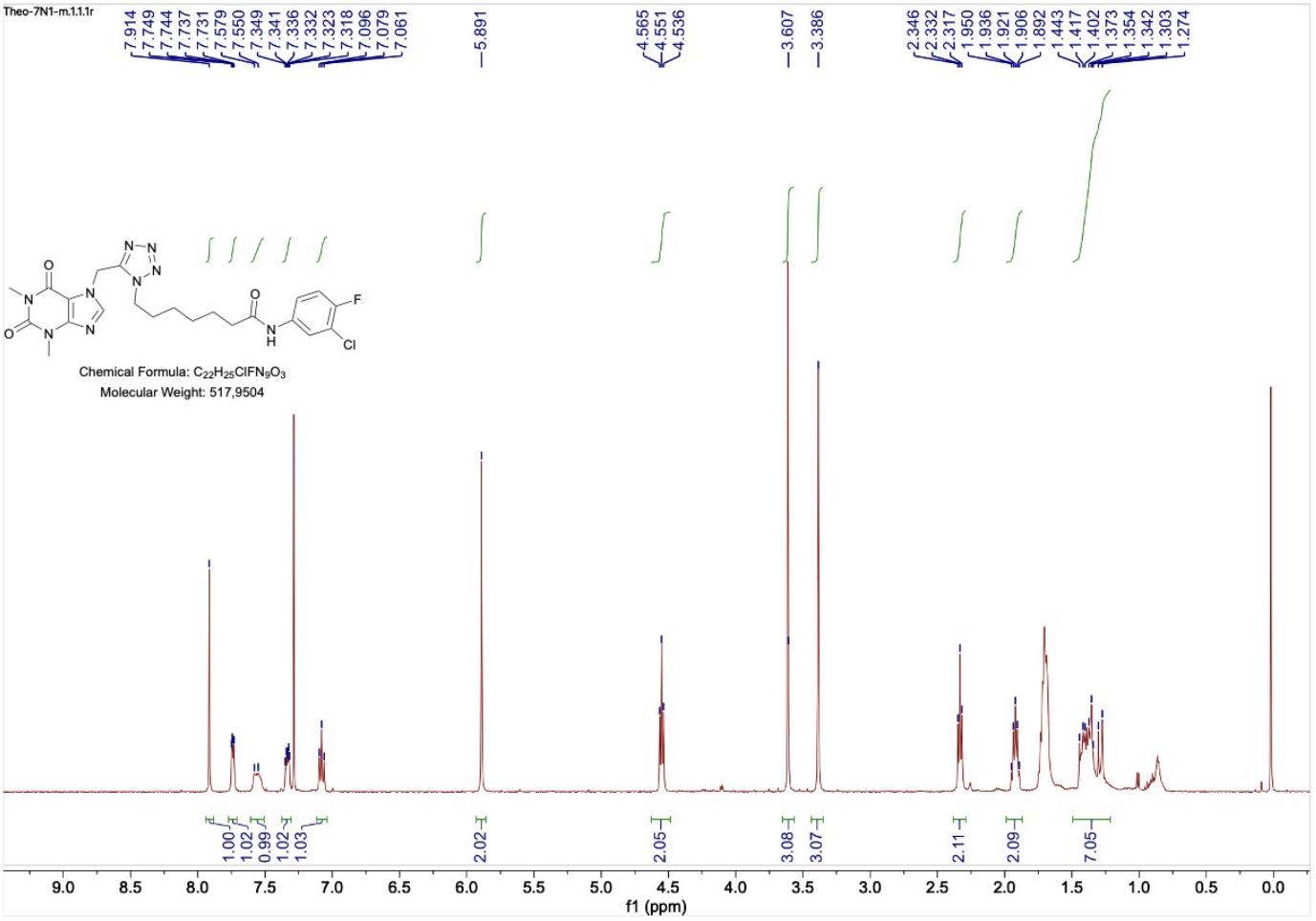
^{13}C-NMR of compound 25



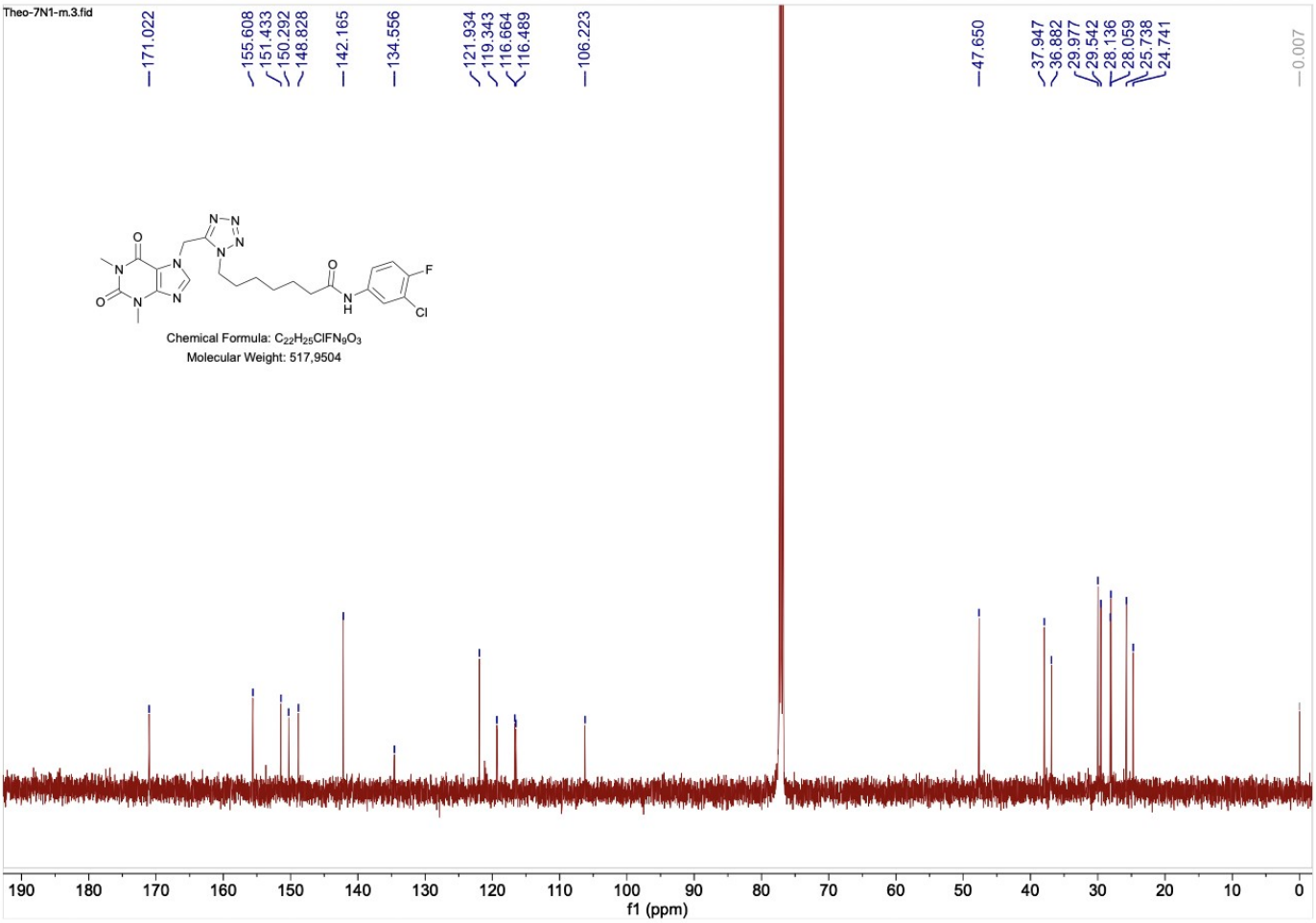
HR-MS of compound 25



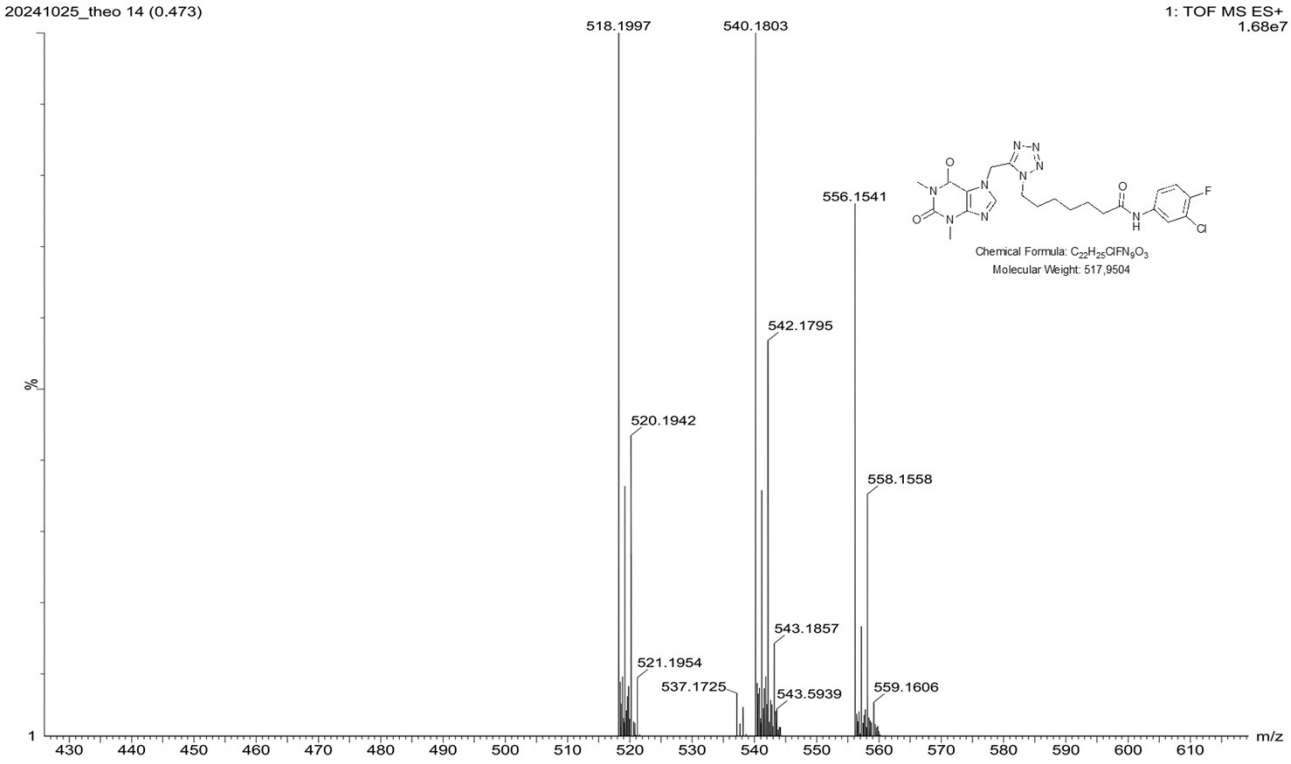
^{1}H-NMR of compound 26



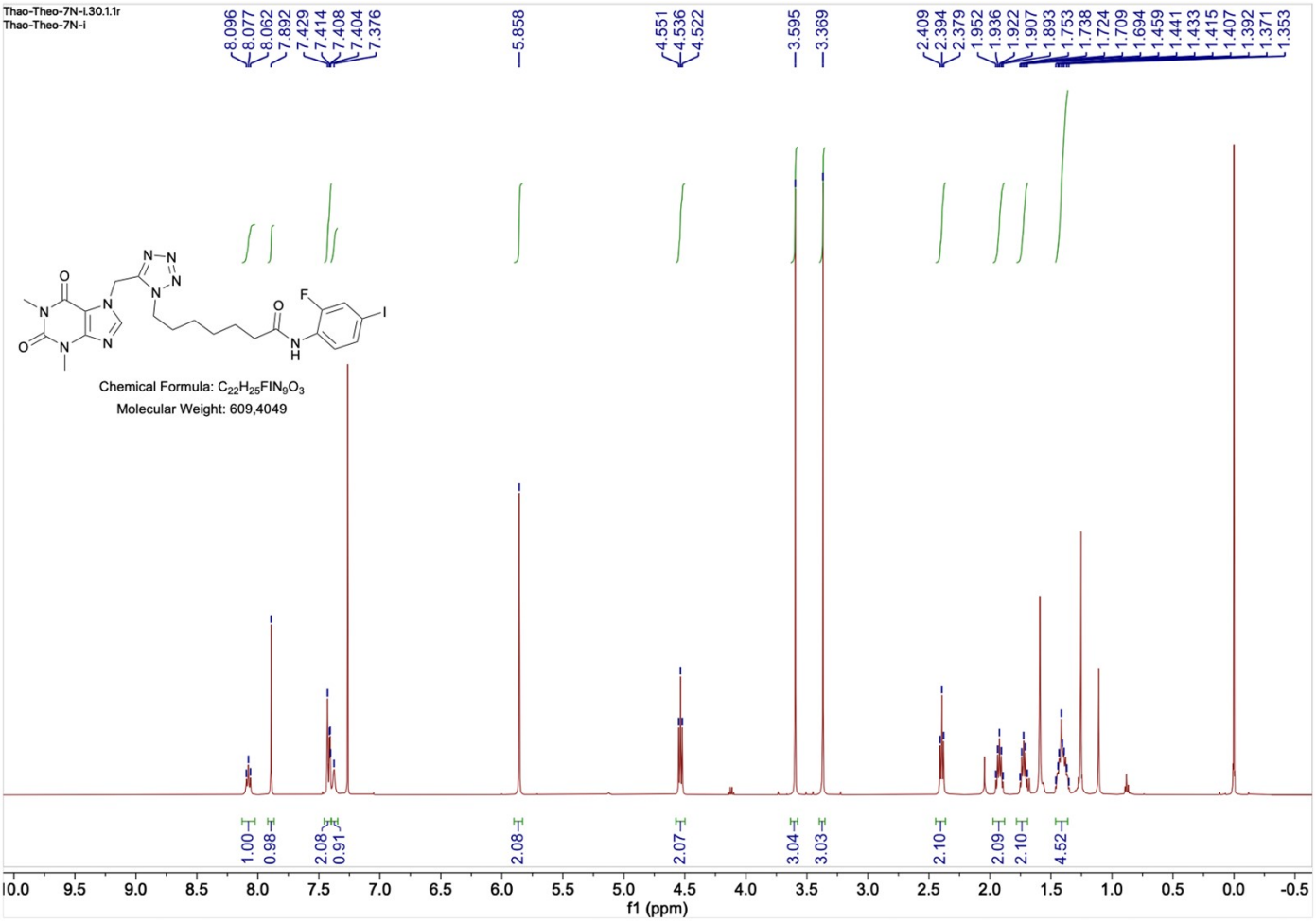
^{13}C-NMR of compound 26



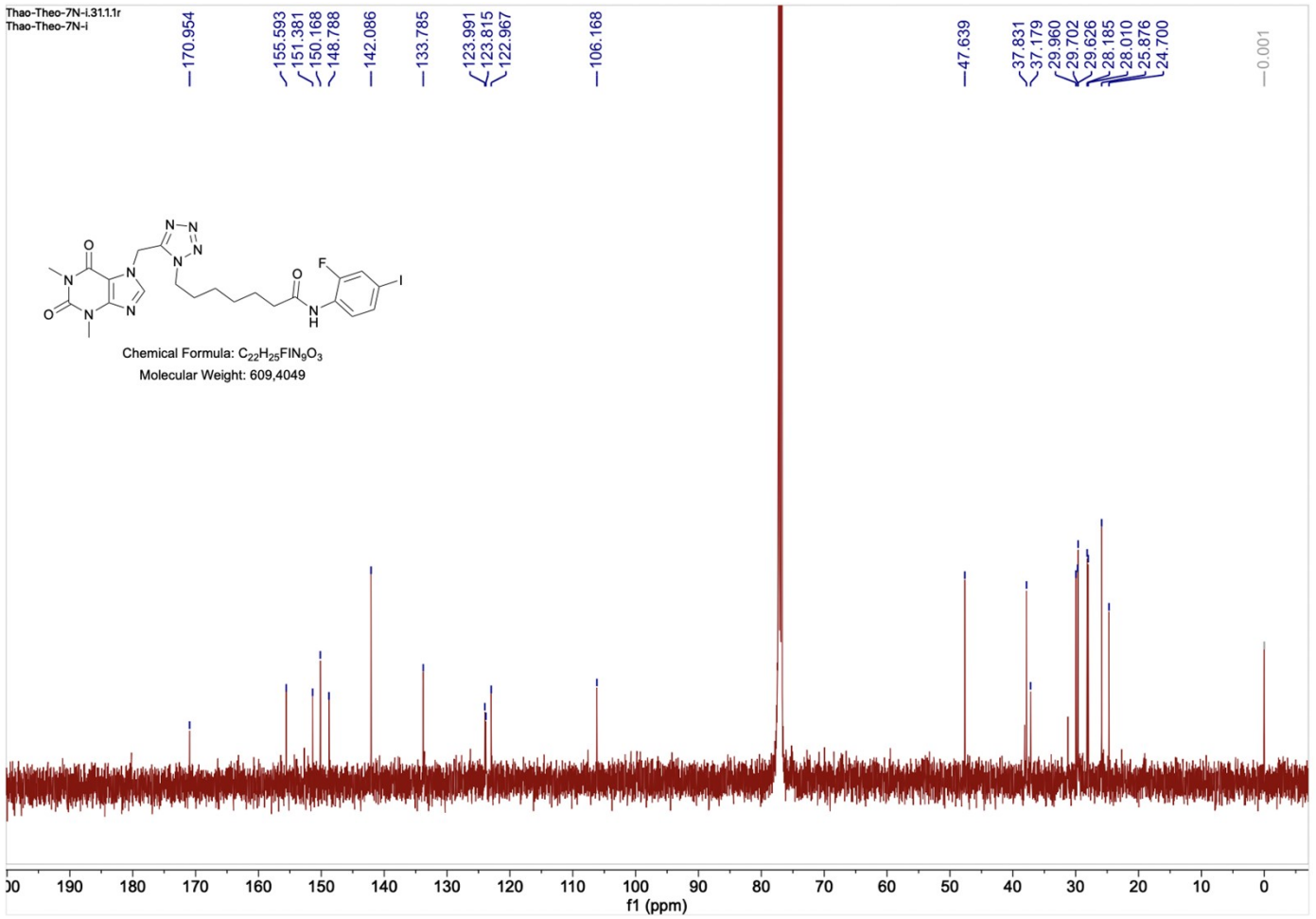
HR-MS of compound 26



^{1}H-NMR of compound 27



^{13}C-NMR of compound 27



HR-MS of compound 27

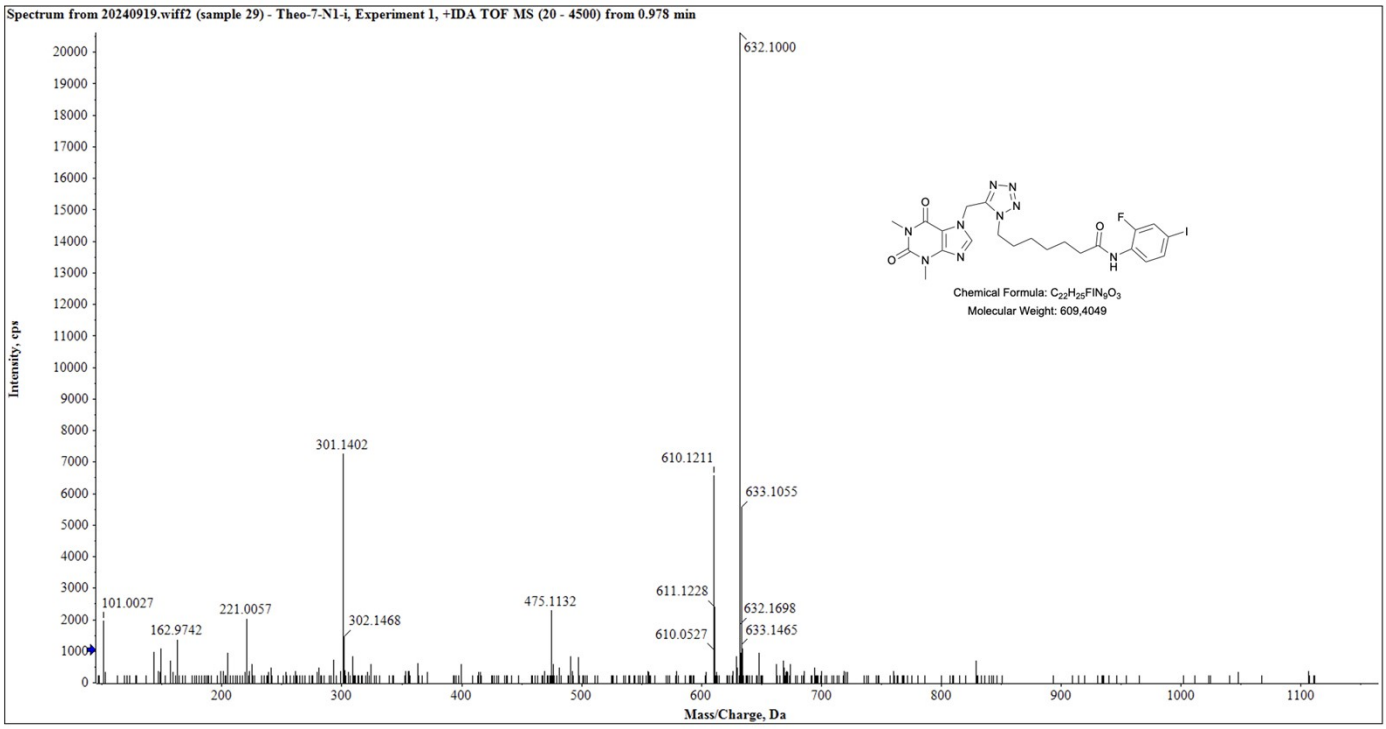
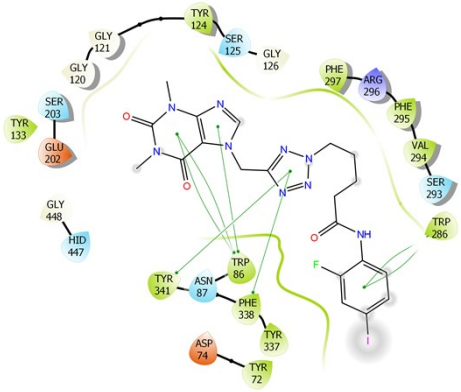
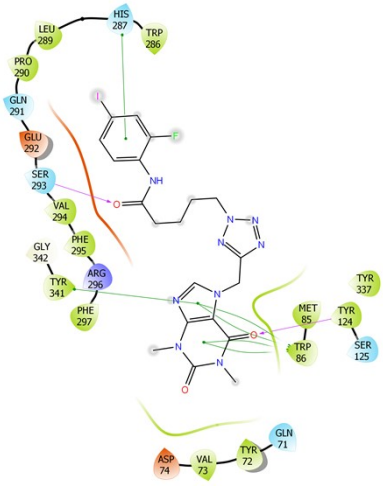
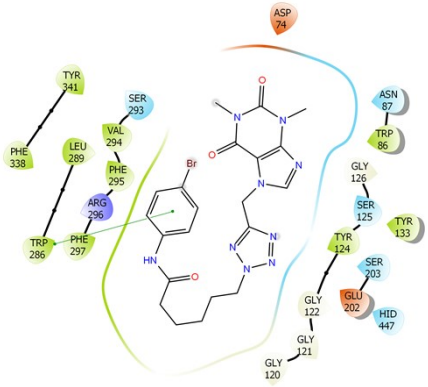
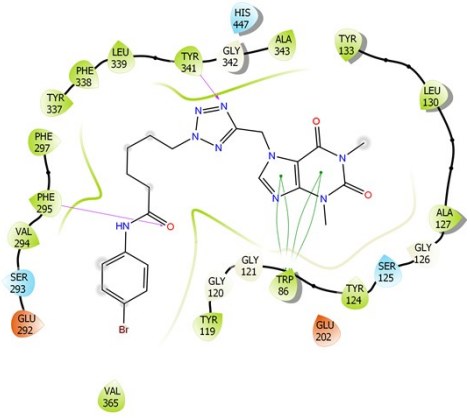
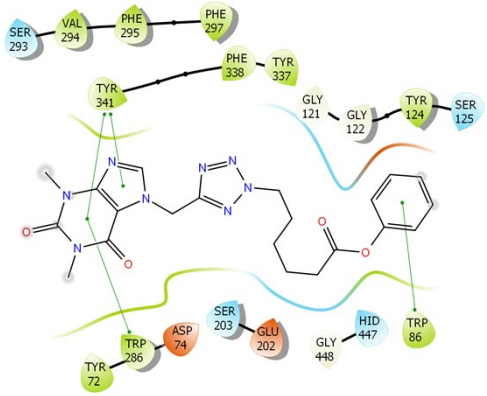
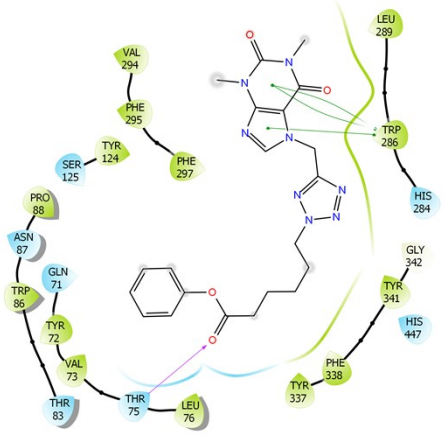


Table S2: 2D Chemical Structures and 3D diagrams representing the binding pose and protein-ligand interactions of six compounds **12, 15, 18, 22, 25, 26**

Nº.	Code	2D Structure	3D Structure
1	12		
2	15		
3	18		

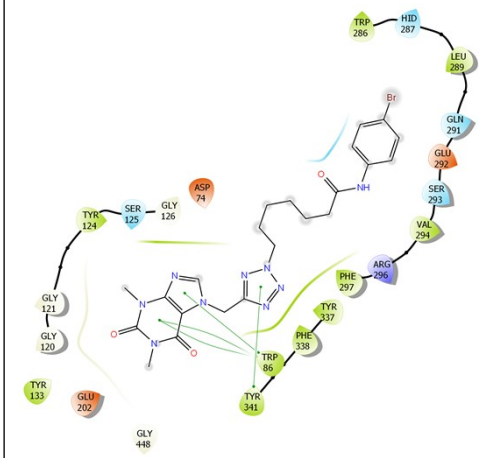
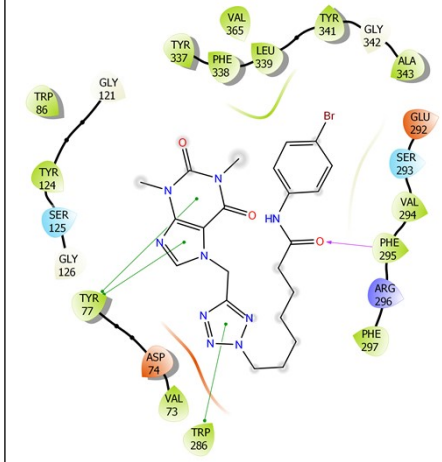
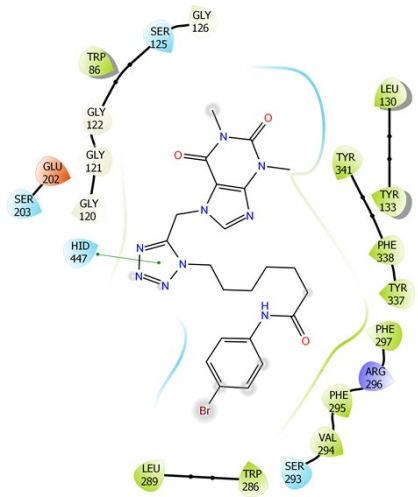
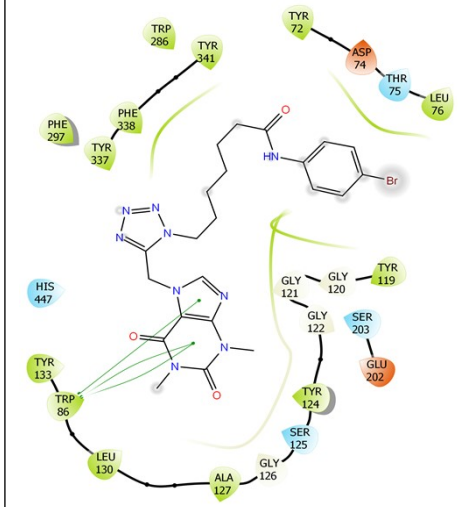
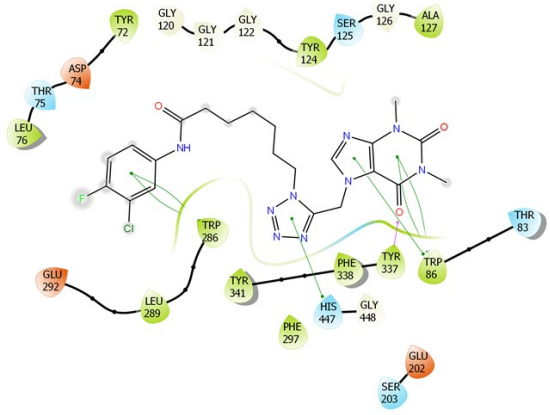
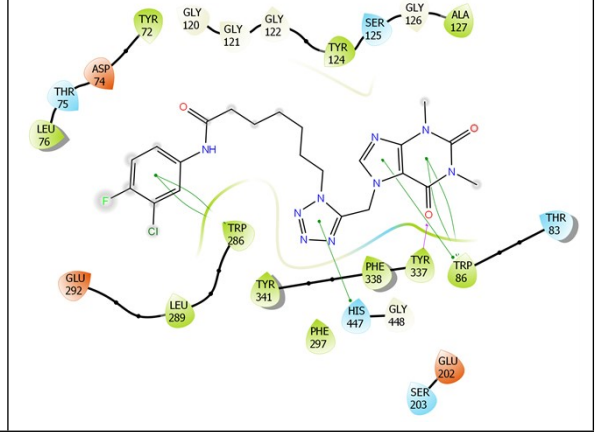
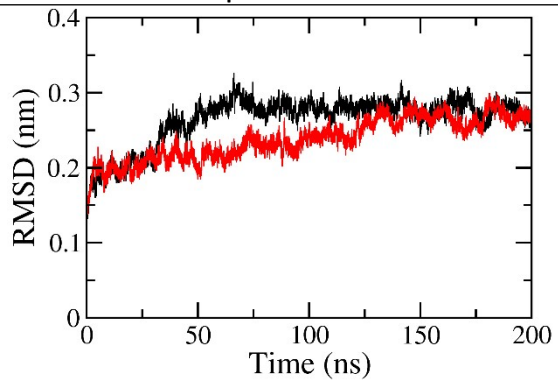
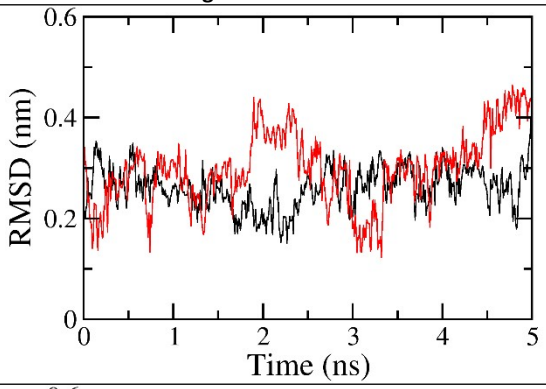
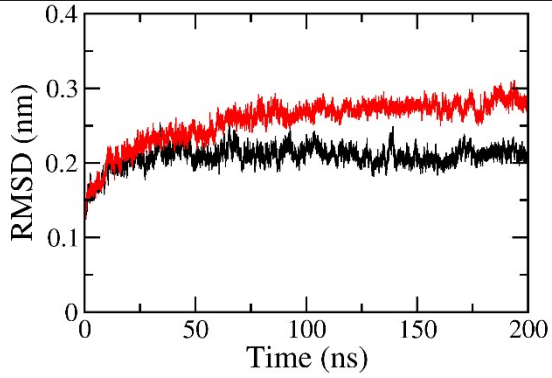
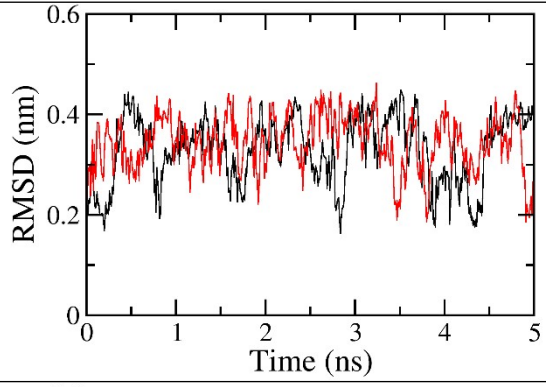
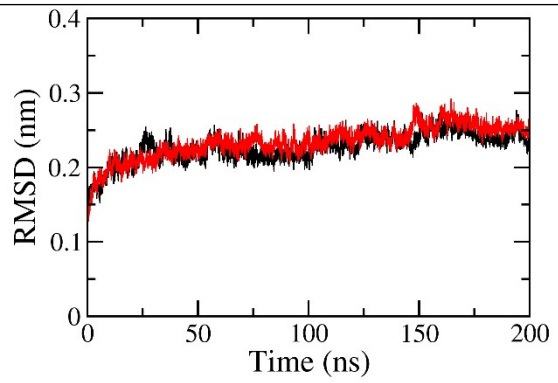
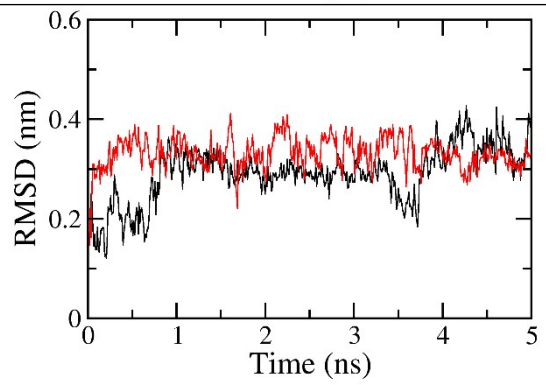
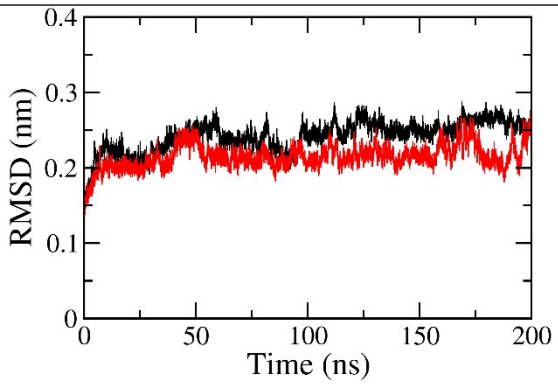
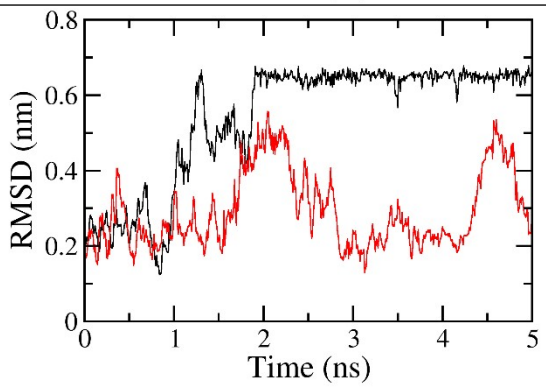
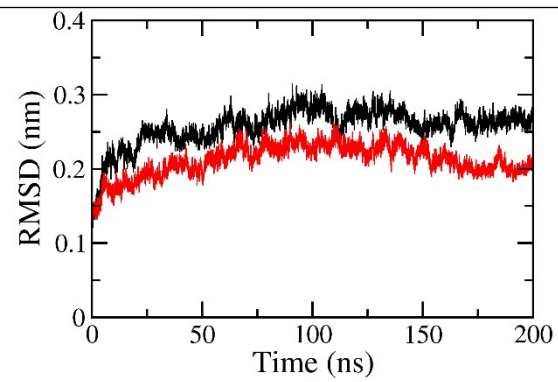
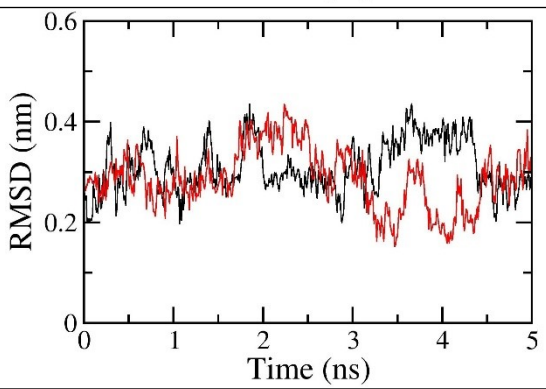
4	**22**		
5	**25**		
6	**26**		

Table S3: All-atom RMSD of available AChE complexes and inhibitor in solution systems

N^0	Compound	Complex in Solution	Ligand in Solution
1	**12**		
2	**15**		
3	**18**		
4	**22**		
5	**25**		

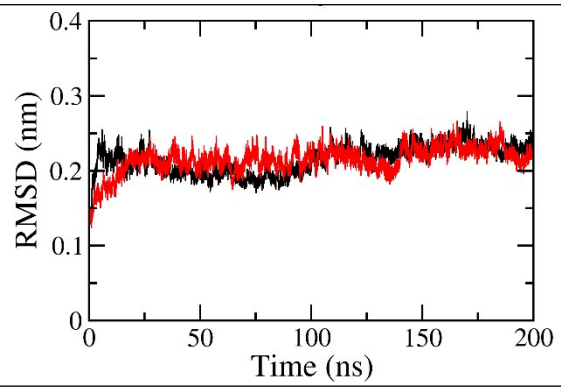
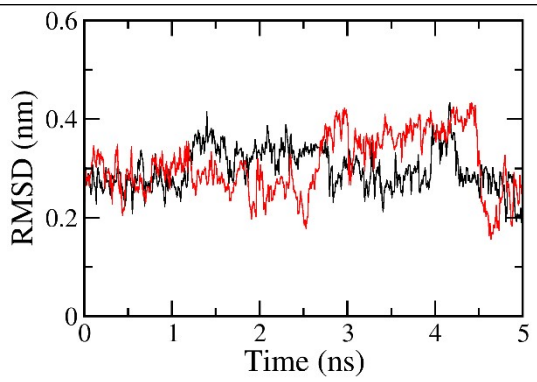
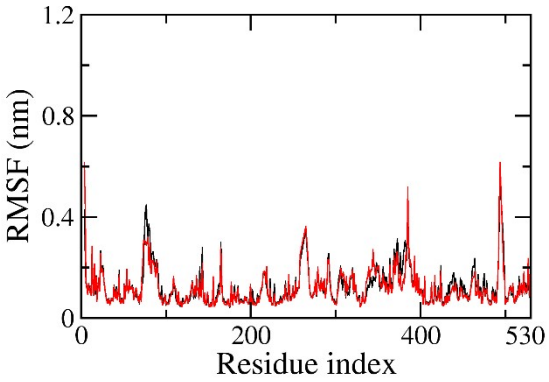
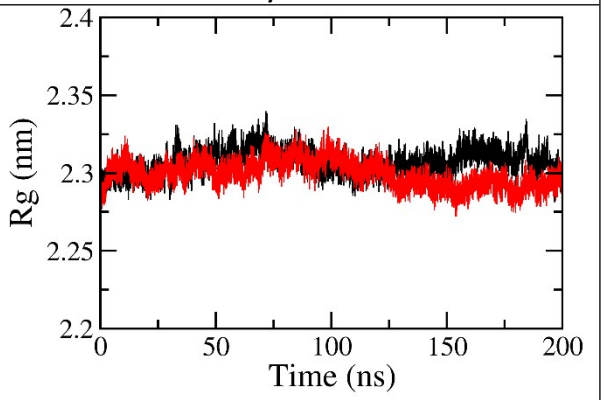
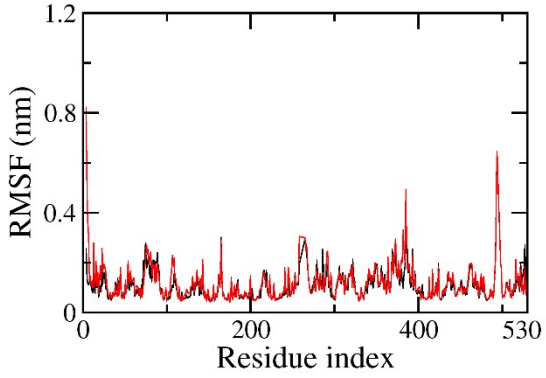
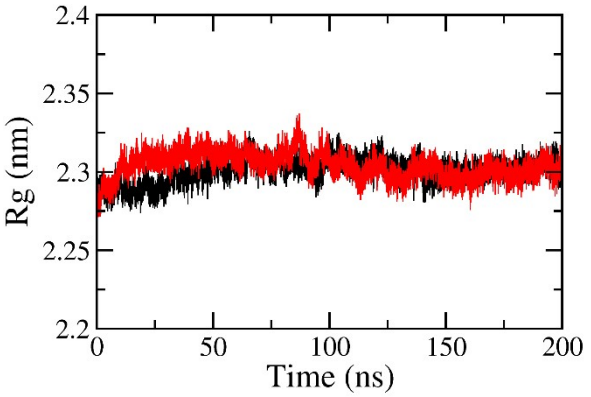
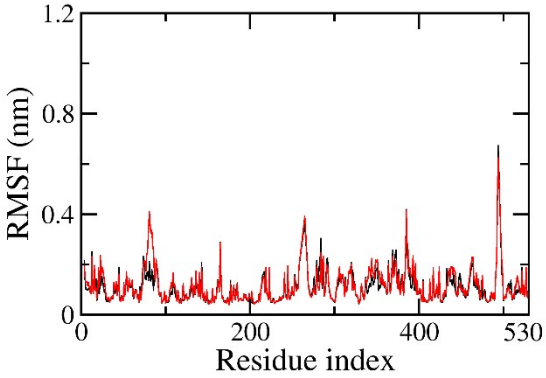
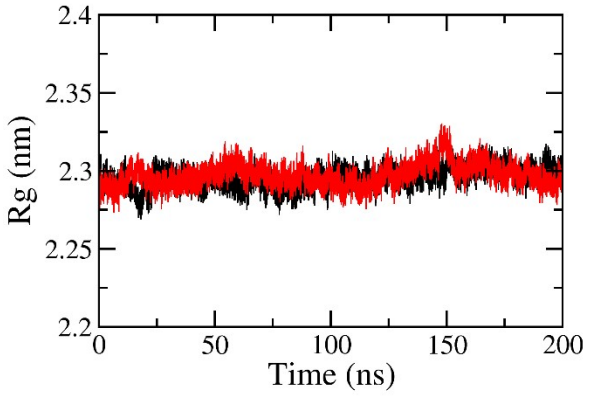
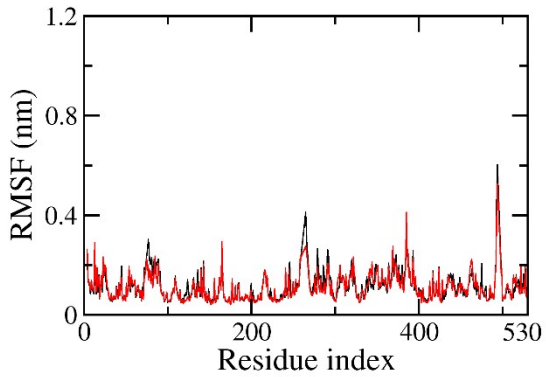
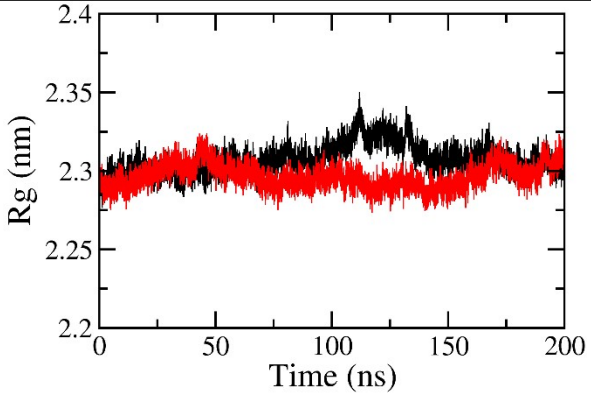
6	**26**	 RMSD (nm) 0 0.1 0.2 0.3 0.4 0 50 100 150 200 Time (ns)	 RMSD (nm) 0 0.2 0.4 0.6 0 1 2 3 4 5 Time (ns)

Table S4: RMSF and Radius of Gyration (Rg) of all residues over 200 ns MD simulation

N⁰	Compound	RMSF	Gyration
1	**12**		
2	**15**		
3	**18**		
4	**22**		

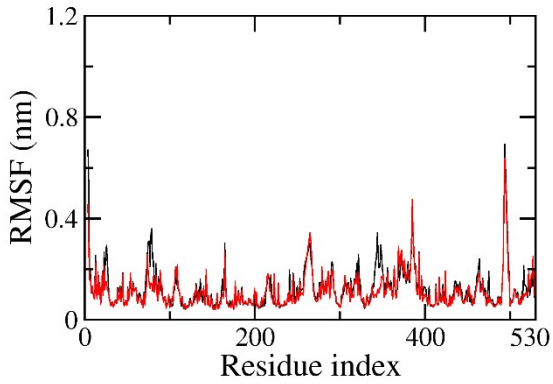
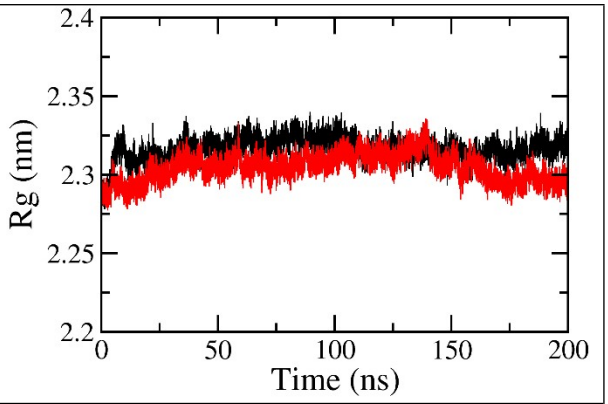
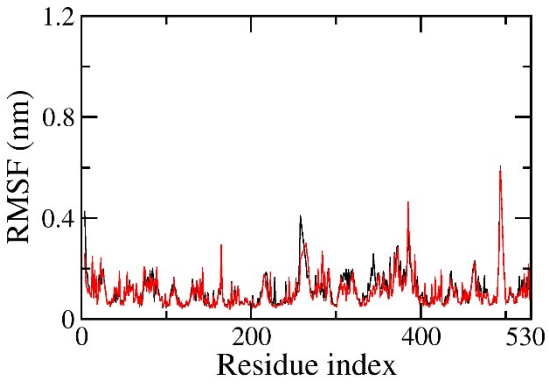
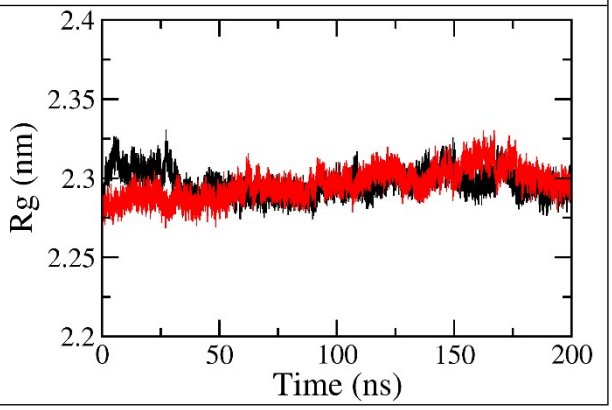
5	**25**		
6	**26**		

Table S5: Some ADMET values of compounds **12** and Galantamine caculated by PreADMET web-server

Compounds/Values	BBB	logBB	HIA (%)	Caco2	algae_at	Carcino_Mouse
Compound 12	0.107584	-0.968252	97.155198	20.7634	0.022619	negative
Galantamine	0.306811	-0.513129	96.172755	21.0629	0.342056	positive

BBB: Blood-Brain Barrier (BBB) penetration; logBB: log of BBB; HIA: Human Intestinal Absorption; algae_at: Acute algae toxicity