Electronic Supplementary Material (ESI) for ChemComm.

'Atypical Ugi' Tetrazoles

Eman M.M. Abdelraheem[a,b], Imogen Goodwin[a], Shabnam Shaabani[a], Michel P. de Haan[a], Katarzyna Kurpiewska[c], Justyna Kalinowska-Tłuścik[c], and Alexander Dömling[a*]

[a]Department of Drug Design, University of Groningen, A. Deusinglaan 1, 9713 AV Groningen, The Netherlands.

[b]Chemistry Department, Faculty of Science, Sohag University, Sohag 82524, Egypt.

[c]Faculty of Chemistry, Jagiellonian University, 3 Ingardena Street, 30-060 Krakow, Poland.

Supporting Information

Contents

Experimental section

General information:

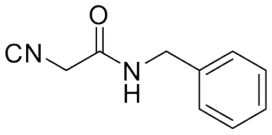
Nuclear magnetic resonance spectra (NMR) were recorded on a Bruker Avance 500 spectrometer (^{1}H NMR (500 MHz), ^{13}C NMR (126 MHz)). Chemical shifts for ^{1}H NMR were reported as δ values and coupling constants were in hertz (Hz). The following abbreviations were used for spin multiplicity: s = singlet, d = doublet, t = triplet, dd = double doublet, m = multiplet, bs = broad singlet. Chemical shifts for ^{13}C NMR reported in ppm relative to the solvent peak. Thin layer chromatography was performed on Fluka precoated silica gel plates (0.20 mm thick, particle size 25 µm). Flash chromatography was performed on a Teledyne ISCO Combiflash Rf, using RediSep Rf Normal-phase Silica Flash Columns (Silica Gel 60 Å, 230 - 400 mesh). Reagents were available from commercial suppliers and used without any purification unless otherwise noted. All isocyanides were made in house by either performing the Hoffman or Ugi procedure. Other reagents were purchased from Sigma Aldrich, ABCR, Acros and AK Scientific and were used without further purification. Mass spectra were measured on a Waters Investigator Supercritical Fluid Chromatograph with a 3100 MS Detector (ESI) using a solvent system of methanol and CO_2 on a Viridis silica gel column (4.6 × 250 mm, 5 µm particle size) and reported as (m/z). High resolution mass spectra (HRMS) were recorded using a LTQ-Orbitrap-XL (Thermo Fisher Scientific; ESI pos. mode) at a resolution of 60000@m/z400. Electrospray ionization mass spectra (ESI-MS) were recorded on a Waters Investigator Semi-prep 15 SFC-MS instrument. Yields given refer to chromatographically purified and spectroscopically pure compounds unless otherwise stated.

General experimental

General procedure and analytical data for synthesis of isocyanoacetamides:

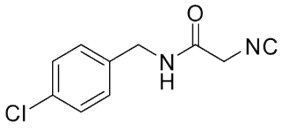
10 mmol of isocyano methyl ester was added to 10 mmol of amine and the mixture was stirred at room temperature overnight. In case of precipitation, it was filtered off, washed with cold diethyl ether, and dried under vacuum. Otherwise, cold diethyl ether was added to the reaction mixture, and the product was allowed to crystallize at -20 °C. In case of no precipitaiton, the product was purified by preparative chromatography using silica gel and ethyl acetate as eluent.

***N*-benzyl-2-isocyanoacetamide 3a:**



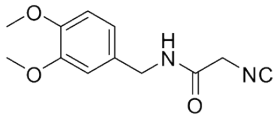
White solid (1.7g, 98%); ^{1}H NMR (500 MHz, Chloroform-d) δ 7.43 – 7.38 (m, 2H), 7.38 – 7.31 (m, 3H), 6.73 (s, 1H), 4.54 (d, J = 5.8 Hz, 2H), 4.24 (s, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 178.9, 162.1, 136.8, 128.8, 128.1, 127.9, 45.3, 44.01.

***N*-(4-chlorobenzyl-2-cyanoacetamide 3b:**



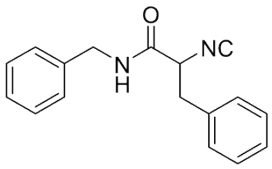
Cream solid (0.6g, 88%); ^{1}H NMR (500 MHz, Chloroform-d) δ 7.33 (d, J = 8.3 Hz, 2H), 7.23 (d, J = 8.2 Hz, 2H), 6.77 (s, 1H), 4.46 (d, J = 5.9 Hz, 2H), 4.21 (s, 2H). ^{13}C NMR (126 MHz, Chloroform-d) δ 172.4, 162.3, 135.4, 129.3, 129.1, 45.3, 43.3.

***N*-(3,4-dimethxylbenzyl)-2-isocyanoacetamide 3c:**



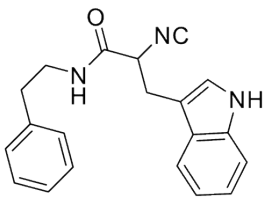
Yellow Solid (0.5g ,99%); ^{1}H NMR (500 MHz, Chloroform-d) δ 6.86 (d, J = 8.1 Hz, 1H), 6.80 – 6.74 (m, 2H), 6.45 (s, 1H), 4.17 (s, 2H), 3.92 (s,3H), 3.90 (s, 3H), 3.60 (d, J = 7.0, 5.7 Hz, 2H). ^{13}C NMR (126 MHz, Chloroform-d) δ 170.2, 162.2, 149.2, 130.4, 120.6, 111.8, 111.6, 56.0, 41.2, 35.0.

***N*-benzyl-2-isocyano-3-phenylpropanamide 3d:**



White solid (1.2g, 94%), ^{1}H NMR (500 MHz, Chloroform-d) δ 7.37 – 7.31 (m, 6H), 7.31 – 7.26 (m, 2H), 7.23 – 7.08 (m, 2H), 6.64 (t, J = 6.0 Hz, 1H), 4.53 – 4.45 (m, 2H), 4.40 (dd, J = 14.7, 5.5 Hz, 1H), 3.32 (dd, J = 13.9, 4.4 Hz, 1H), 3.23 (dd, J = 13.9, 7.2 Hz, 1H). ^{13}C NMR (126 MHz, Chloroform-d) δ 164.7, 162.4, 136.9, 134.5, 129.7, 128.8, 128.7, 127.9, 127.8, 127.7, 43.9, 38.6.

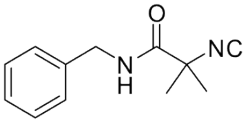
3-(1*H*-indol-3-yl)-2-isocyano-*N*-phenethylpropanamide 3e:



White Solid (1.5g, 97%), ^{1}H NMR (500 MHz, Chloroform-d) δ 8.24 (s, 1H), 7.69 (dd, J = 7.9, 1.1 Hz, 1H), 7.48 – 7.36 (m, 1H), 7.34 – 7.14 (m, 7H), 7.02 – 6.89 (m, 2H), 6.17 (t, J = 5.9 Hz, 1H), 4.47 (dd, J = 6.3, 4.6 Hz, 1H), 3.55 – 3.32 (m, 4H), 2.62 (dt, J = 13.6, 6.8 Hz, 1H), 2.51 (dt, J

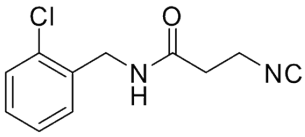
= 13.9, 7.2 Hz, 1H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 165.3, 161.7, 138.1, 136.1, 128.7, 126.7, 124.0, 123.9, 122.5, 119.9, 119.0, 118.8, 111.3, 108.8, 59.5, 40.9, 35.2, 29.3.

_N_-benzyl-2-isocyano-2-methylpropanamide 3f:



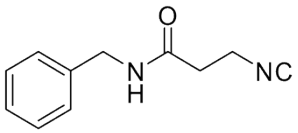
White Solid (0.6g, 90%); ^{1}H NMR (500 MHz, Chloroform-d) δ 7.48 – 7.42 (m, 2H), 7.41 – 7.37 (m, 1H), 7.36 – 7.33 (m, 2H), 6.90 (s, 1H), 4.55 (d, J = 5.8 Hz, 2H), 1.73 – 1.70 (m, 6H). ^{13}C NMR (126 MHz, Chloroform-d) δ 171.8, 168.9, 137.2, 129.0, 127.9, 127.7, 61.4, 44.1, 27.9, 27.7.

_N_-(2-chlorobenzyl)-3-isocyanopropanamide 3g:



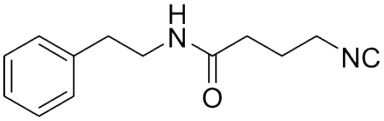
Brown Solid (0.8g, 79%); ^{1}H NMR (500 MHz, Chloroform-d) δ 7.32 (m, 2H), 7.24 – 7.13 (m, 2H), 4.47 (m, 1H), 3.87 (m, 2H), 3.70 (d, J = 5.3 Hz, 2H), 3.64 (m, 2H). ^{13}C NMR (126 MHz, Chloroform-d) δ 169.9, 159.5, 140.4, 129.5, 128.9, 128.2, 127.1, 44.5, 36.9, 33.7.

_N_-benzyl-3-cyanopropanamide 3h:



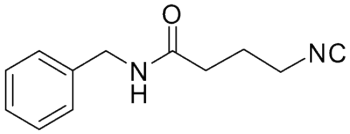
White Solid (0.3g, 85%); ^{1}H NMR (500 MHz, Chloroform-d) δ 7.49 – 7.18 (m, 5H), 5.95 (s, 1H), 4.50 (d, J = 5.7 Hz, 2H), 3.78 (tt, J = 6.9, 1.8 Hz, 2H), 2.61 (tt, J = 6.8, 2.0 Hz, 2H). ^{13}C NMR (126 MHz, Chloroform-d) δ 168.1, 158.5, 137.5, 128.9, 127.9, 127.8, 43.9, 39.4, 36.1.

4-isocyano-_N_-phenethylbutanamide 3i:



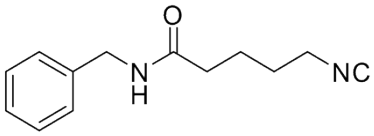
White Solid (0.6g, 50%); ^{1}H NMR (500 MHz, Chloroform-d) δ 7.6 – 7.5 (m, 5H), 5.7 (s, 1H), 4.5 (d, J = 5.7 Hz, 2H), 3.4 (tt, J = 6.3, 1.9 Hz, 2H), 2.3 (t, J = 7.1 Hz, 2H), 1.7 (t, J = 8.5, 6.8, 4.1 Hz, 2H), 1.7 (t, J = 6.5, 2.1 Hz, 2H). ^{13}C NMR (126 MHz, Chloroform-d) δ 171.3, 155.1, 136.7, 128.8, 127.9, 127.7, 43.7, 41.4, 37.4, 28.6, 22.4.

_N_-benzyl-4-isocyanobutanamide 3j:



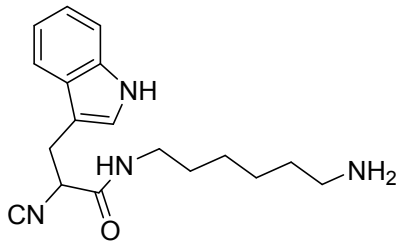
White Solid (1.4g, 70%); ^{1}H NMR (500 MHz, Chloroform-d) δ 7.36 – 7.26 (m, 5H), 6.22 (s, 1H), 4.48 – 4.38 (m, 2H), 3.48 (ddd, J = 8.3, 5.1, 1.9 Hz, 2H), 2.39 (t, J = 7.1 Hz, 2H), 2.07 – 1.97 (m, 2H). ^{13}C NMR (126 MHz, Chloroform-d) δ 170.9, 156.6, 129.9, 126.5, 43.6, 41.4, 32.2, 24.6.

***N*-benzyl-5-isocyanopentanamide 3k:**



White Solid (0.7g, 65%); ^{1}H NMR (500 MHz, Chloroform-d) δ 7.39 – 7.28 (m, 5H), 5.79 (s, 1H), 4.47 (d, J = 5.7 Hz, 2H), 3.44 (tt, J = 6.3, 1.9 Hz, 2H), 2.30 (t, J = 7.1 Hz, 2H), 1.87 – 1.85 (m, 2H), 1.77– 1.76 (m, 2H). ^{13}C NMR (126 MHz, Chloroform-d) δ 171.7, 156.2, 138.1, 128.8, 127.9, 127.7, 43.7, 41.4, 35.4, 28.6, 22.4.

***N*-(6-aminohexyl)-3-(1H-indol-3-yl)-2-isocyanopropanamide 3l:**

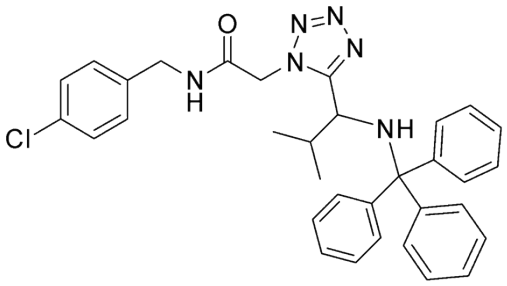


Orange oil (2.9g, 95%). ^{1}H NMR (500 MHz, Methanol-d4) δ 7.61 (d, J = 8 Hz, 1H), 7.38 (d, J = 8.0 Hz, 1H), 7.20 (s, 1H), 7.17 – 7.09 (m, 1H), 7.09 – 6.95 (m, 1H), 4.55 (t, 1H), 3.46 – 3.36 (m, 2H), 3.14 (dt, 1H), 3.08 – 2.95 (m, 1H), 2.61 (t, 1H), 1.46 – 1.34 (m, 2H), 1.34 – 1.18 (m, 4H), 1.11 (m, 2H). ^{13}C NMR (126 MHz, Methanol-d4) δ 166.9, 158.0, 136.6, 127.1, 123.9, 121.2, 118.6, 117.9, 111.0, 107.8, 40.9, 39.3, 31.8, 29.8, 29.5, 28.4, 26.7, 26.1.

General procedure and analytical data for the synthesis of Ugi products:

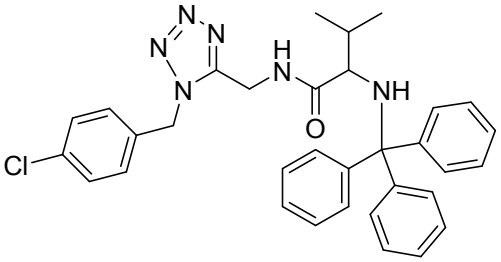
Aldehyde (1 equiv) was added to the appropriate amine (1 equiv) in methanol (1M solution) and it was allowed to stir for an hour to form the Schiff base. Then, isocyanoacetamides (1 equiv) and $TMSN_3$ (1 equiv) were added, and the reaction mixture was stirred overnight. The following day the crude mixture was tested by TLC before being adsorbed onto silica and being purified via column chromatography using ethyl acetate and petroleum ether as the eluent.

***N*-(4-chlorobenzyl)-2-(5-(2-methyl-1-(tritylamino)propyl)-1*H*-tetrazol-1-yl)acetamide 6a:**



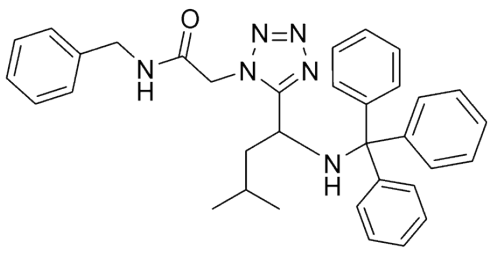
White Solid (0.14g, 24%); the rotamers was observed; ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.40 – 7.37 (m, 5H), 7.32 (d, *J* = 8.4 Hz, 1H), 7.29 – 7.25 (m, 2H), 7.23 – 7.19 (m, 7H), 7.17 – 7.13 (m, 2H), 7.13 – 7.10 (m, 2H), 6.65 (s, 1H), 6.56 (t, *J* = 6.0 Hz, 1H), 5.33 (d, *J* = 16.0 Hz, 1H), 5.24 (d, *J* = 16.0 Hz, 1H), 4.89 (dd, *J* = 6.6, 5.1 Hz, 1H), 4.58 (d, *J* = 16.8 Hz, 1H), 4.44 (d, *J* = 5.9 Hz, 1H), 4.32 (d, *J* = 6.0 Hz, 2H), 4.25 (d, *J* = 16.8 Hz, 1H), 3.86 – 3.83 (m, 1H), 3.82 (d, *J* = 5.5 Hz, 1H), 3.05 (d, *J* = 8.8 Hz, 1H), 2.47 – 2.37 (m, 1H), 2.33– 2.30 (m, 1H), 1.05 (d, *J* = 6.7 Hz, 2H), 0.99 (d, *J* = 6.8 Hz, 3H), 0.94 (d, *J* = 6.8 Hz, 2H), 0.62 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 163.8, 156.8, 144.9, 135.5, 133.7, 129.2, 128.9, 128.5, 127.9, 126.8, 71.3, 70.8, 60.5, 53.1, 50.6, 50.2, 43.2, 43.0, 34.8, 33.4, 19.3, 18.6, 17.5, 16.9. HRMS calculated for $C_{33}H_{33}N_6OClNa$: 587.22966; found $[M+Na]^+$: 587.23041.

_N_-((1-(4-chlorobenzyl)-1_H_-tetrazol-5-yl)methyl)-3-methyl-2-(tritylamino)butanamide 7a:



White Solid (0.1g, 16%); ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.33 (dd, *J* = 8.1, 3.6 Hz, 7H), 7.24 (d, *J* = 8.3 Hz, 2H), 7.19 (t, *J* = 7.5 Hz, 6H), 7.13 (t, *J* = 7.2 Hz, 3H), 7.08 (t, *J* = 6.2 Hz, 1H), 5.59 (s, 2H), 4.09 (dd, *J* = 15.6, 6.1 Hz, 1H), 3.95 (dd, *J* = 15.6, 6.2 Hz, 1H), 3.23 (t, *J* = 4.1 Hz, 1H), 2.75 (d, *J* = 4.6 Hz, 1H), 1.89 (m, 1H), 0.88 (t, *J* = 7.3 Hz, 6H). ^{13}C NMR (126 MHz, Chloroform-d) δ 174.0, 152.1, 145.3, 135.0, 129.4, 129.4, 128.9, 127.9, 126.8, 71.5, 62.2, 50.1, 34.1, 31.1, 20.2, 17.8. HRMS calculated for $C_{33}H_{33}N_6OClNa$: 587.22966; found $[M+Na]^+$: 587.23029.

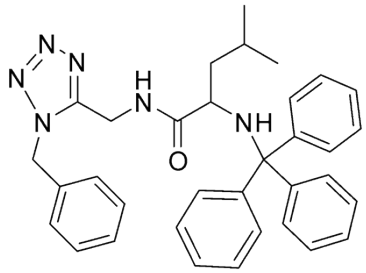
_N_-benzyl-2-(5-(3-methyl-1-(tritylamino)butyl)-1_H_-tetrazol-1-yl)acetamide 6b:



White Solid (0.16g, 29%); ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.36 – 7.32 (m, 7H), 7.32 – 7.29 (m, 2H), 7.22 (dd, *J* = 8.3, 6.4 Hz, 6H), 7.18 (dd, *J* = 7.4, 2.3 Hz, 5H), 6.28 (t, *J* = 5.9 Hz, 1H), 4.45 – 4.33 (m, 2H), 4.22 – 4.12 (m, 2H), 2.80 (d, *J* = 6.1 Hz, 1H), 1.81 – 1.74 (m, 1H), 1.62 – 1.57 (m, 1H), 1.05 – 0.99 (m, 2H), 0.75 (d, *J* = 6.5 Hz, 3H), 0.70 (d, *J* = 6.6

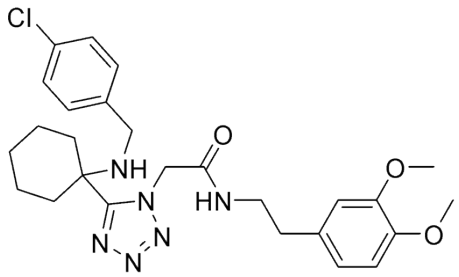
Hz, 3H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 164.0, 158.5, 153.7, 144.8, 128.8, 128.5, 128.0, 127.8, 126.9, 71.7, 50.2, 47.4, 47.04, 43.9, 24.5, 23.2, 21.8. HRMS calculated for $C_{34}H_{36}N_6ONa$: 567.28428; found $[M+Na]^+$: 567.28442.

***N*-((1-benzyl-1H-tetrazol-5-yl)methyl)-4-methyl-2-(tritylamino)pentanamide 7b:**



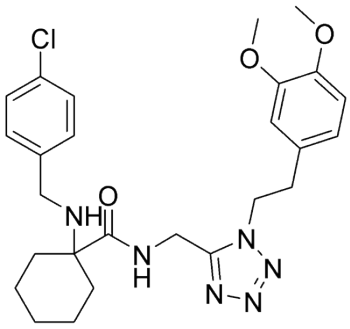
White Solid (0.11g, 21%); ^{1}H NMR (500 MHz, Chloroform-d) δ 7.38 (m, 3H), 7.34 (d, J = 7.3 Hz, 6H), 7.30 (d, J = 2.5 Hz, 1H), 7.25 (t, J = 7.6 Hz, 6H), 7.18 (t, J = 7.2 Hz, 3H), 7.03 (t, J = 6.2 Hz, 1H), 5.61 (d, J = 3.7 Hz, 2H), 4.22 – 4.10 (m, 1H), 3.99 (dd, J = 15.8, 6.1 Hz, 1H), 3.35 (dd, J = 7.9, 5.7 Hz, 1H), 2.72 (s, 1H), 1.67 (s, 1H), 1.62 (m, 1H), 1.49 – 1.41 (m, 2H), 0.82 (dd, J = 6.5, 4.2 Hz, 6H).^{13}C NMR (126 MHz, Chloroform-*d*) δ 176.0, 152.0, 145.2, 133.6, 129.2, 129.0, 128.9, 127.9, 127.8, 126.9, 71.6, 56.4, 50.8, 45.5, 31.5, 24.7, 23.4, 22.3. HRMS calculated for $C_{34}H_{36}N_6ONa$: 567.28428; found $[M+Na]^+$: 567.2851.

2-(5-(1-((4-chlorobenzyl)amino)cyclohexyl)-1*H*-tetrazol-1-yl)-*N*-(3,4-dimethoxybenzyl) acetamide 6c:



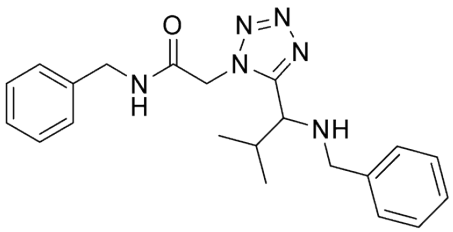
Brown oil (0.22 g, 44%); ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.07 (t, *J* = 6.3 Hz, 1H), 7.35 – 7.32 (m, 2H), 7.28 – 7.25 (m, 2H), 6.78 (d, *J* = 8.1 Hz, 1H), 6.58 (dd, *J* = 8.2, 2.1 Hz, 1H), 6.48 (d, *J* = 2.0 Hz, 1H), 4.69 (t, *J* = 6.7 Hz, 2H), 4.09 (d, *J* = 6.2 Hz, 2H), 3.86 (s, 3H), 3.81 (s, 3H), 3.44 (s, 2H), 3.15 (t, *J* = 6.7 Hz, 2H), 1.81 (d, *J* = 13.6 Hz, 2H), 1.67 (d, *J* = 13.0 Hz, 5H), 1.34 – 1.27 (m, 3H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 177.3, 153.04, 149.1, 148.2, 137.9, 133.2, 129.5, 128.8, 128.6, 120.8, 111.6, 111.5, 61.1, 55.9, 55.8, 49.1, 46.4, 36.0, 31.7, 31.3, 25.0, 21.3. HRMS calculated for $C_{26}H_{34}N_6O_3Cl$: 513.23754; found $[M+H]^+$: 513.23834.

1-((4-chlorobenzyl)amino)-*N*-((1-(3,4-dimethoxybenzyl)-1*H*-tetrazol-5-yl)methyl)cyclo hexanecarboxamide 7c:



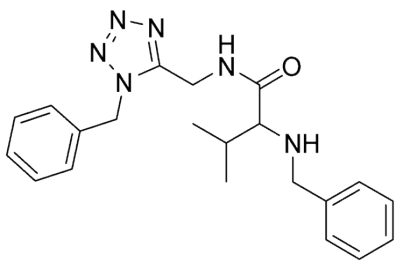
Brown oil (0.1 g, 17%); ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.28 (d, *J* = 8.4 Hz, 2H), 7.11 (d, *J* = 8.3 Hz, 2H), 6.78 (d, *J* = 8.1 Hz, 1H), 6.62 – 6.55 (m, 2H), 5.75 (s, 1H), 5.46 (s, 2H), 3.88 (s, 3H), 3.86 (s, 3H), 3.44 (q, *J* = 6.7 Hz, 2H), 3.31 (s, 2H), 2.68 (t, *J* = 6.9 Hz, 2H), 2.07 (m, 2H), 1.97 (m, 2H), 1.60 (m, 2H), 1.50 (m, 2H), 1.43 (m, 1H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 165.2, 159.1, 149.5, 148.2, 137.9, 133.5, 130.7, 129.6, 129.1, 120.8, 111.7, 56.5, 56.3, 55.9, 51.5, 46.3, 41.4, 35.0, 34.8, 25.3, 21.8. HRMS calculated for $C_{26}H_{34}N_6O_3Cl$: 513.23754; found $[M+H]^+$: 513.23828.

***N*-benzyl-2-(5-(1-(benzylamino)-2-methylpropyl)-1*H*-tetrazol-1-yl)acetamide 6d:**



Orange oil (0.2 g ,53%); ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.34 – 7.30 (m, 7H), 7.26 – 7.14 (m, 3H), 6.35 (s, 1H), 5.35 (d, *J* = 16.3 Hz, 1H), 5.10 (d, *J* = 16.4 Hz, 1H), 4.41 (t, *J* = 5.2 Hz, 1H), 3.93 (d, *J* = 8.3 Hz, 1H), 3.63 (d, *J* = 13.3 Hz, 1H), 3.50 (d, *J* = 13.3 Hz, 1H), 2.13 – 2.08 (m, 1H), 1.66 (s, 1H), 1.05 (d, *J* = 6.6 Hz, 3H), 0.78 (d, *J* = 6.7 Hz, 3H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 164.2, 156.5, 138.7, 136.9, 128.8, 128.6, 128.1, 127.9, 127.8, 127.5, 59.4, 51.8, 50.2, 43.9, 32.2, 19.6. HRMS calculated for $C_{21}H_{27}N_6O$: 379.22409; found $[M+H]^+$: 379.22440.

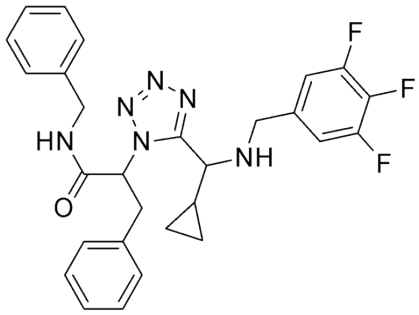
***N*-((1-benzyl-1*H*-tetrazol-5-yl)methyl)-2-(benzylamino)-3-methylbutanamide 7d:**



Orange oil (0.07g ,19%), Melting Point: N/A, ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.09 (t, *J* = 6.4 Hz, 1H), 7.40 – 7.38 (m, 3H), 7.39 – 7.29 (m, 5H), 7.28 – 7.25 (m, 2H), 5.69 (d, *J* = 3.5 Hz, 2H), 4.64 (dd, *J* = 15.8, 6.6 Hz, 1H), 4.56 (dd, *J* = 15.8, 5.7 Hz, 1H), 3.71 – 3.58 (m, 2H), 3.03 (d, *J* = 4.4 Hz, 1H), 2.13 – 2.10 (m, 1H), 1.71 (s, 1H), 0.95 (d, *J* = 6.9 Hz, 3H), 0.85 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 174.6, 152.4, 139.1, 133.5, 129.2, 128.9, 128.6, 128.3, 127.8,

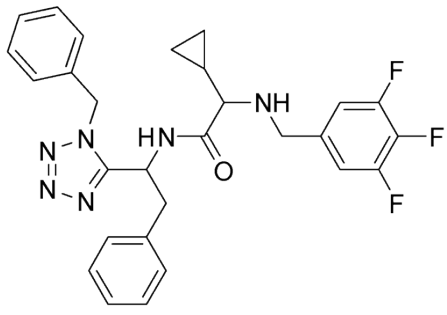
127.4, 67.6, 53.7, 50.9, 31.6, 31.4, 19.5, 17.7. HRMS calculated for $C_{21}H_{27}N_6O$: 379.22409; found $[M+H]^+$: 379.22458.

***N*-benzyl-2-(5-(cyclopropyl((3,4,5-trifluorobenzyl)amino)methyl)-1*H*-tetrazol-1-yl)-3-phenylpropanamide 6e**:



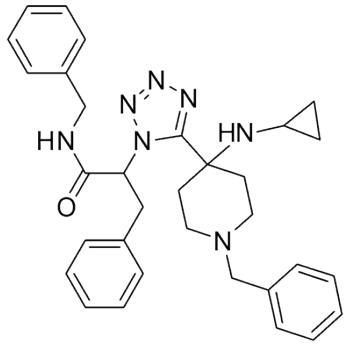
Yellow solid (0.3g, 65%); two diastomers in ratio (1:1); ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.54 – 7.45 (m, 7H), 7.43 – 7.37 (m, 9H), 7.35 – 7.30 (m, 4H), 7.26 – 7.21 (m, 3H), 7.18 (dt, *J* = 7.1, 2.3 Hz, 3H), 7.05 (dd, *J* = 8.1, 6.4 Hz, 2H), 6.98 (dd, *J* = 8.1, 6.4 Hz, 2H), 6.08 (dd, *J* = 11.5, 3.9 Hz, 1H), 6.04 (dd, *J* = 11.1, 4.4 Hz, 1H), 4.76 – 4.70 (m, 3H), 4.65 (dd, *J* = 14.7, 5.7 Hz, 1H), 4.00 – 3.85 (m, 4H), 3.51 (dd, *J* = 14.1, 11.5 Hz, 2H), 3.40 (d, *J* = 8.4 Hz, 2H), 3.37 (t, *J* = 4.3 Hz, 1H), 3.07 (d, *J* = 9.6 Hz, 1H), 1.38 – 1.25 (m, 1H), 0.87 – 0.79 (m, 1H), 0.69 – 0.62 (m, 1H), 0.58 – 0.0.56 (m, 1H), 0.43 – 0.37 (m, 1H), 0.34 – 0.30 (m, 1H), 0.31 – 0.24 (m, 1H), 0.18 – 0.11 (m, 1H), 0.08 – 0.05 (m, 1H), 0.03 – -0.04 (m, 1H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 166.8, 156.9, 152.1, 150.1, 139.7, 137.7, 137.4, 135.8, 135.1, 129.1, 128.9, 128.8, 128.7, 128.6, 127.7, 127.5, 127.4, 111.8, 111.6, 111.6, 65.1, 58.3, 50.2, 43.7, 38.9,15.0, 13.7, 5.8, 2.2. HRMS calculated for $C_{28}H_{28}N_6OF_3$: 521.22712; found $[M+H]^+$: 521.22778.

***N*-(1-(1-benzyl-1*H*-tetrazol-5-yl)-2-phenylethyl)-2-cyclopropyl-2-((3,4,5-trifluorobenzyl) amino)acetamide 7e:**



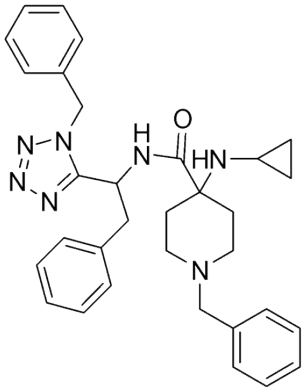
Yellow solid (0.07g, 14%); ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.39 – 7.28 (m, 4H), 7.25 – 7.12 (m, 5H), 6.97 – 6.94 (m, 2H), 6.92 – 6.83 (m, 1H), 6.79– 6.74 (m, 1H), 5.61 (s, 1H), 5.50 (s, 1H), 3.47 (d, *J* = 13.6 Hz, 1H), 5.41 (s, 1H), 3.41 – 3.30 (m, 1H), 3.28 – 3.21 (m, 1H), 3.06 – 3.02 (m, 1H), 2.27 (dd, *J* = 12.8, 9.1 Hz, 1H), 1.39 – 1.14 (m, 1H), 0.97 – 0.67 (m, 2H), 0.57 – 0.38 (m, 3H), 0.17 – 0.04 (m, 1H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 173.2, 155.4, 152.2, 150.1, 139.8, 137.8, 135.3, 133.7, 129.3, 129.1, 128.9, 128.8, 127.7, 127.6, 127.3, 111.9, 111.5, 66.6, 50.9, 44.1, 39.9, 15.2, 3.8, 3.2, 3.1. HRMS calculated for $C_{28}H_{28}N_6OF_3$: 521.22712; found $[M+H]^+$: 521.22797.

***N*-benzyl-2-(5-(1-benzyl-4-(cyclopropylamino)piperidin-4-yl)-1*H*-tetrazol-1-yl)-3-phenylpropanamide 6f:**



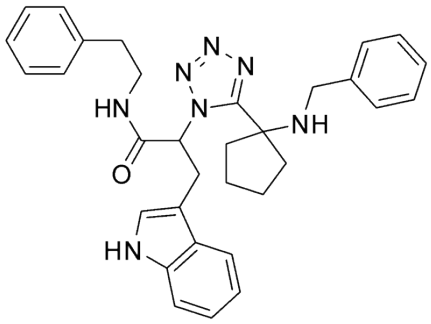
White solid (0.2g, 44%); ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.34 – 7.31 (m, 2H), 7.30 (q, *J* = 3.2, 2.7 Hz, 2H), 7.28 (q, *J* = 2.0, 1.5 Hz, 1H), 7.27 – 7.23 (m, 3H), 7.21 – 7.16 (m, 5H), 7.05 – 7.01 (m, 2H), 6.78 (t, *J* = 5.9 Hz, 1H), 5.87 (dd, *J* = 11.2, 4.3 Hz, 1H), 4.46 (dd, *J* = 14.7, 5.9 Hz, 1H), 4.39 (dd, *J* = 14.7, 5.7 Hz, 1H), 3.72 (dd, *J* = 14.0, 11.2 Hz, 1H), 3.60 (dd, *J* = 14.0, 4.3 Hz, 1H), 3.42 (d, *J* = 13.0 Hz, 1H), 3.31 (d, *J* = 13.0 Hz, 1H), 2.43 (s, 2H), 2.31 – 2.29 (m, 1H), 2.19 – 2.14(m, 1H), 2.06 – 2.01 (m, 1H), 1.78– 1.76 (m, 1H), 1.73 (s, 2H), 1.66 (d, *J* = 5.8 Hz, 2H), 0.24 – 0.20 (m, 1H), 0.17 – 0.15 (m, 1H), 0.14 – 0.12 (m, 1H), 0.25 – 0.36 (m, 1H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 167.2, 159.7, 138.1, 137.2, 135.5, 129.4, 129.3, 129.1, 128.9, 128.8, 128.2, 127.8, 127.7, 127.5, 127.1, 65.4, 62.8, 54.5, 49.5, 49.1, 43.8, 39.4, 34.7, 34.3, 24.6, 6.4, 5.8. HRMS calculated for $C_{32}H_{38}N_7O$: 536.31324; found $[M+H]^+$: 536.31396.

1-benzyl-*N*-(1-(1-benzyl-1*H*-tetrazol-5-yl)-2-phenylethyl)-4-(cyclopropylamino) piperidine-4-carboxamide 7f:



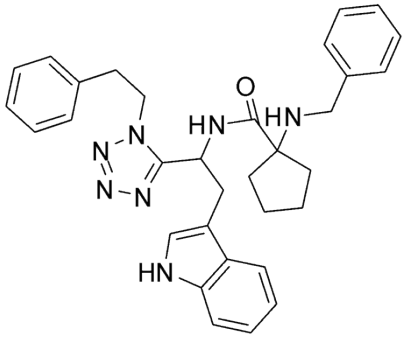
Yellow solid (0.1g, 14%); ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.66 (d, *J* = 8.4 Hz, 1H), 7.35 – 7.30 (m, 7H), 7.29 – 7.25 (m, 1H), 7.20 – 7.17 (m, 3H), 7.16 – 7.13 (m, 2H), 6.95 (dd, *J* = 6.5, 2.9 Hz, 2H), 5.58 (d, *J* = 15.4 Hz, 1H), 5.48 (d, *J* = 15.4 Hz, 1H), 5.41 (q, *J* = 8.1 Hz, 1H), 3.48 (s, 2H), 3.21 (dd, *J* = 13.7, 8.2 Hz, 1H), 3.05 (dd, *J* = 13.6, 7.8 Hz, 1H), 2.68 – 2.52 (m, 2H), 2.21 (q, *J* = 10.4 Hz, 2H), 2.06 – 1.90 (m, 2H), 1.90 – 1.79 (m, 1H), 1.67 – 1.53 (m, 2H), 1.28 (s, 1H), 0.34 – 0.27 (m, 1H), 0.26 – 0.16 (m, 2H), 0.12 – 0.05 (m, 1H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 177.4, 155.3, 138.3, 135.5, 133.7, 129.2, 129.1, 128.9, 128.7, 128.2, 127.7, 127.6, 127.2, 127.1, 63.00, 59.4, 50.8, 49.3, 44.3, 39.6, 32.4, 31.9, 29.7, 25.1, 6.1. HRMS calculated for $C_{32}H_{38}N_7O$: 536.31324; found $[M+H]^+$: 536.31396.

2-(5-(1-(benzylamino)cyclopentyl)-1*H*-tetrazol-1-yl)-3-(1*H*-indol-3-yl)-*N*-phenethyl propanamide 6g:



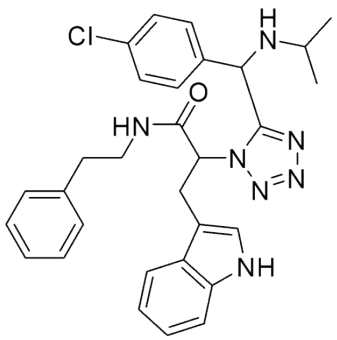
Yellow solid (0.3g, 62%); ^{1}H NMR (500 MHz, Chloroform-d) δ 8.13 – 8.12 (m, 1H), 7.59 – 7.54 (m, 1H), 7.29 (t, J = 4.0 Hz, 1H), 7.30 – 7.28 (m, 1H), 7.26 – 7.25 (m, 1H), 7.25 – 7.23 (m, 2H), 7.23 – 7.22 (m, 1H), 7.21 – 7.20 (m, 1H), 7.19 – 7.17 (m, 1H), 7.14 – 7.12 (m, 1H), 6.99 (dd, J = 7.4, 2.1 Hz, 2H), 6.91 – 6.86 (m, 2H), 6.69 (d, J = 2.4 Hz, 1H), 6.30 (t, J = 5.7 Hz, 1H), 5.94 (dd, J = 10.4, 4.9 Hz, 1H), 3.89 – 3.74 (m, 2H), 3.43 – 3.40 (m, 1H), 3.22 – 3.11 (m, 2H), 3.00 (d, J = 12.6 Hz, 1H), 2.63– 2.54 (m, 2H), 2.35– 3.29 (m, 1H), 1.94 – 1.88 (m, 1H), 1.66 – 1.56 (m, 2H), 1.50 –1.45 (m, 1H), 1.43 – 1.31 (m, 2H), 1.23 – 1.19 (m, 1H), 1.16 – 1.07 (m, 1H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 167.4, 159.5, 138.8, 138.2, 135.9, 128.7, 128.6, 128.5, 127.7, 127.2, 126.8, 126.5, 123.5, 123.4, 122.4, 119.9, 118.2, 111.3, 109.7, 63.9, 47.9, 40.8, 36.9, 36.3, 34.9, 28.8, 22.9. HRMS calculated for $C_{32}H_{36}N_7O$: 534.29759; found $[M+H]^+$: 534.29828.

***N*-(2-(1H-indol-3-yl)-1-(1-phenethyl-1*H*-tetrazol-5-yl)ethyl)-1-(benzylamino) cyclopentane carboxamide 7g:**



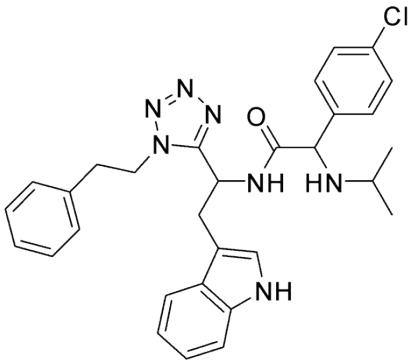
Yellow oil (0.1g, 13%); ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.35 (d, *J* = 8.3 Hz, 1H), 8.10 (d, *J* = 2.5 Hz, 1H), 7.62 (d, *J* = 7.7 Hz, 1H), 7.38 – 7.32 (m, 2H), 7.31 (s, 1H), 7.30 – 7.25 (m, 3H), 7.24 – 7.12 (m, 5H), 6.81 – 6.69 (m, 3H), 5.36 – 5.31 (m, 1H), 4.28 – 4.06 (m, 2H), 3.50 (dd, *J* = 14.1, 6.3 Hz, 1H), 3.46 – 3.37 (m, 2H), 3.16 (dd, *J* = 14.2, 9.3 Hz, 1H), 2.94 – 2.88 (m, 1H), 2.51– 2.45 (m, 1H), 2.13 – 2.04 (m, 1H), 2.04 – 1.96 (m, 1H), 1.81 – 1.79 (m, 2H), 1.73 – 1.62 (m, 4H), 1.33 – 1.26 (m, 1H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 176.4, 155.8, 139.6, 136.2, 128.7, 128.6, 128.5, 128.1, 127.3, 127.1, 127.0, 126.9, 123.1, 123.0, 122.6, 120.1, 118.5, 118.4, 111.5, 109.7, 69.9, 48.4, 48.2, 43.9, 35.9, 35.8, 35.67, 30.6, 24.3. HRMS calculated for $C_{32}H_{36}N_7O$: 534.29759; found $[M+H]^+$: 534.29816.

***N*-benzyl-2-(5-((4-chlorophenyl)(isopropylamino)methyl)-1*H*-tetrazol-1-yl)-3-(1*H*-indol-3-yl)propanamide 6h:**



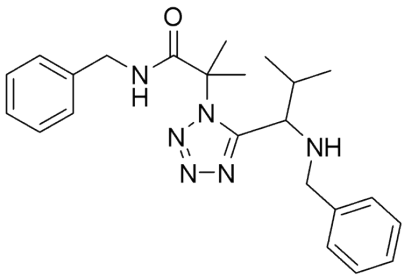
Orange oil (0.3g, 49%); ^{1}H NMR (500 MHz, Chloroform-d) δ 7.57 (d, J = 7.9 Hz, 1H), 7.42– 7.40 (m, 1H), 7.28 (s, 1H), 7.26 (s, 1H), 7.24– 7.22 (m, 3H), 7.20 – 7.18 (m, 1H), 7.17 (s, 1H), 7.15 (s, 1H), 6.97 – 6.95 (m, 1H), 6.84 – 6.74 (m, 2H), 6.43 – 6.41 (m, 2H), 5.37 (dd, J = 11.9, 4.1 Hz, 1H), 4.11 (s, 1H), 3.99 – 3.91 (m, 1H), 3.87 – 3.82 (m, 1H), 3.76 – 3.71 (m, 1H), 3.50 – 3.33 (m, 2H), 3.11 – 3.09 (m, 1H), 2.76– 2.71 (m, 1H), 2.68– 2.55 (m, 1H), 2.22– 2.19 (m, 1H), 0.83 (d, J = 6.5 Hz, 3H). 0.63 (d, J = 6.3 Hz, 3H). ^{13}C NMR (126 MHz, Chloroform-d) δ 165.9, 155.9, 139.1, 136.3, 133.8, 129.0, 128.9, 128.7, 128.6, 126.1, 123.9, 122.4, 119.9, 117.8, 112.0, 108.7, 60.7, 52.4, 44.9, 35.3, 29.3, 27.3, 23.6. HRMS calculated for $C_{30}H_{33}N_7OCl$: 542.24296; found $[M+H]^+$: 542.24371.

***N*-((1-(1-(1*H*-indol-2-yl)-2-phenylethyl)-1*H*-tetrazol-5-yl)methyl)-2-(4-chlorophenyl)-2-(isopropylamino)acetamide 7h:**



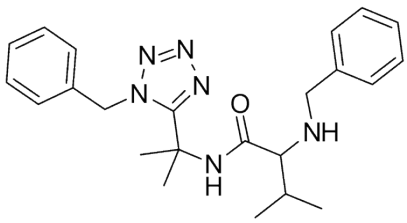
Yellow solid (0.1g, 17%); ^{1}H NMR (500 MHz, Chloroform-d) δ 8.47 (s, 1H), 7.45 (d, J = 7.9 Hz, 1H), 7.37 (d, J = 8.1 Hz, 1H), 7.29 (d, J = 5.1 Hz, 1H), 7.29 – 7.26 (m, 2H), 7.24 (dt, J = 8.4, 4.2 Hz, 2H), 7.18 (t, J = 7.5 Hz, 1H), 7.08 – 6.95 (m, 4H), 6.85 (d, J = 8.4 Hz, 2H), 6.56 (d, J = 2.3 Hz, 1H), 6.03 – 5.93 (m, 1H), 5.29 – 5.25 (m, 1H), 4.71 (d, J = 3.4 Hz, 1H), 3.77 (dd, J = 14.9, 4.4 Hz, 1H), 3.61– 3.55 (m, 1H), 3.53 – 3.45 (m, 1H), 3.35 – 3.27 (m, 1H), 2.75 – 2.60 (m, 2H), 2.21 (dd, J = 7.5, 5.0 Hz, 1H), 0.76 (d, J = 6.2 Hz, 3H), 0.72 (d, J = 6.2 Hz, 3H). ^{13}C NMR (126 MHz, Chloroform-d) δ 156.9, 138.2, 136.2, 135.8, 134.4, 129.3, 128.8, 128.7, 128.2, 126.7, 126.3, 123.6, 122.6, 120.1, 117.71, 111.9, 63.1, 53.9, 46.3, 41.1, 35.1, 22.3, 21.9. HRMS calculated for $C_{30}H_{33}N_7OCl$: 542.24296; found $[M+H]^+$: 542.24377.

***N*-benzyl-2-(5-(1-(benzylamino)-2-methylpropyl)-1*H*-tetrazol-1-yl)-2-methyl propanamide 6i:**



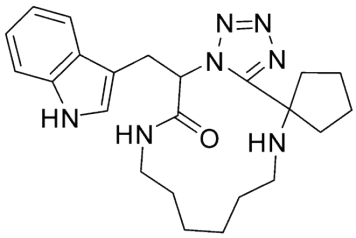
White solid (0.13g, 31%); ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.31 – 7.07 (m, 10H), 6.56 (t, *J* = 5.9 Hz, 1H), 4.35 (dd, *J* = 14.6, 6.0 Hz, 1H), 4.24 (dd, *J* = 14.6, 5.6 Hz, 1H), 3.83 (d, *J* = 5.5 Hz, 1H), 3.64 (d, *J* = 12.8 Hz, 1H), 3.46 (d, *J* = 12.9 Hz, 1H), 2.10 (m, 1H), 1.89 (d, *J* = 7.0 Hz, 7H), 0.95 (dt, *J* = 6.8, 1.7 Hz, 6H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 170.11, 157.47, 139.73, 137.24, 128.79, 128.38, 128.07, 127.79, 127.75, 127.14, 65.68, 57.88, 57.81, 50.31, 44.11, 44.07, 44.04, 31.52, 27.23, 27.16, 26.57, 26.49, 20.40, 20.32, 16.88, 16.81. HRMS calculated for $C_{23}H_{31}N_6O$: 407.25539; found $[M+H]^+$: 407.25586.

***N*-(2-(1-benzyl-1*H*-tetrazol-5-yl)propan-2-yl)-2-(benzylamino)-3-methylbutanamide 7i:**



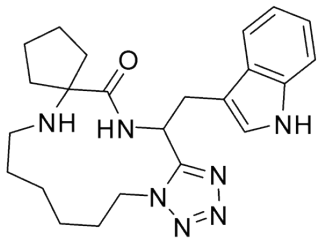
White solid (0.09 g, 23%); ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.03 (s, 1H), 7.42 – 7.23 (m, 8H), 7.15 – 7.05 (m, 2H), 5.71 (d, *J* = 15.8 Hz, 1H), 5.64 (d, *J* = 15.8 Hz, 1H), 3.72 (d, *J* = 2.0 Hz, 2H), 2.91 (d, *J* = 4.4 Hz, 1H), 2.17 (m, 1H), 1.75 (s, 3H), 1.64 (s, 3H), 0.98 (d, *J* = 7.0 Hz, 3H), 0.89 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 173.84, 158.16, 139.34, 134.36, 129.04, 128.72, 128.47, 128.18, 127.54, 127.04, 67.70, 53.88, 51.70, 50.49, 31.23, 27.60, 27.32, 27.30, 19.63, 19.58, 17.65, 17.62. HRMS calculated for $C_{23}H_{31}N_6O$: 407.25539; found $[M+H]^+$: 407.25601.

5'-((1*H*-indol-3-yl)methyl)-7',8',9',10',11',12',13',14'-octahydrospiro[cyclopentane-1,15'-tetrazolo[5,1-c][1,4,7]triazacyclotridecin]-6'(5'*H*)-one 6j:



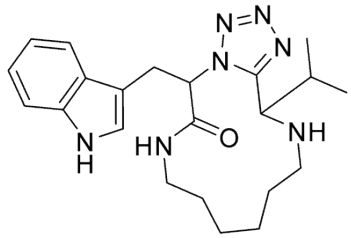
White solid (0.1 g, 25%); ^{1}H NMR (500 MHz, Chloroform-d) δ 7.38 – 7.32 (m, 3H), 7.13 – 7.08 (m, 1H), 6.63 (s, 1H), 4.22 – 4.06 (m, 1H), 3.69 (s, 1H), 2.59 – 2.52 (m, 2H), 2.04 (q, J = 7.7 Hz, 1H), 1.64 (s, 1H), 1.31 (s, 1H), 1.28 (d, J = 4.2 Hz, 2H), 0.91 – 0.85 (m, 1H). ^{13}C NMR (126 MHz, Chloroform-d) δ 176.1, 136.5, 129.2, 128.8, 128.7, 128.7, 127.1, 65.6, 64.4, 62.5, 58.2, 48.9, 39.9, 35.0, 30.7, 29.7, 28.3, 27.9, 19.9, 18.9. HRMS calculated for $C_{23}H_{32}N_7O$: 422.26629; found $[M+H]^+$: 422.2660.

15'-((1*H*-indol-3-yl)methyl)-6',7',*8*',9',10',11',14',15'-octahydro-5'*H*,13'*H*-spiro [cyclopentane-1,12'-tetrazolo[1,5-*a*][1,4,7]triazacyclotridecin]-13'-one 7j:



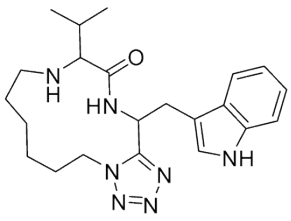
Yellow oil (0.06 g, 15%); ^{1}H NMR (500 MHz, Chloroform-d) δ 8.10 (s, 1H), 7.84 (d, J = 8.7 Hz, 1H), 7.73 (d, J = 7.8 Hz, 1H), 7.35 (d, J = 8.0 Hz, 1H), 7.24 – 7.18 (m, 1H), 7.18 – 7.13 (m, 1H), 6.98 (d, J = 2.3 Hz, 1H), 5.97 – 5.79 (m, 1H), 4.11 – 4.02 (m, 1H), 3.90 – 3.82 (m, 1H), 3.58 (dd, J = 7.3, 4.3 Hz, 2H), 2.72 – 2.56 (m, 1H), 2.26 – 2.15 (m, 2H), 2.14 – 2.04 (m, 1H), 2.00 – 1.90 (m, 1H), 1.85 – 1.76 (m, 3H), 1.72 – 1.59 (m, 3H), 1.46 – 1.38 (m, 1H), 1.33 – 1.20 (m, 5H), 1.15 – 1.07 (m, 1H), 1.03 – 0.94 (m, 1H). ^{13}C NMR (126 MHz, Chloroform-d) δ 176.9, 127.2, 123.3, 122.3, 119.9, 118.6, 111.2, 70.1, 47.4, 44.5, 41.7, 40.3, 30.1, 29.9, 29.3, 27.7, 24.9, 24.2, 24.0, 23.5. HRMS calculated for $C_{23}H_{32}N_7O$: 422.26629; found $[M+H]^+$: 422.26678.

5-((1*H*-indol-3-yl)methyl)-15-isopropyl-8,9,10,11,12,13,14,15-octahydro-5*H*-tetrazolo[5,1-c][1,4,7]triazacyclotridecin-6(7*H*)-one 6k:



White solid (0.18 g, 43%); ^{1}H NMR (500 MHz, Chloroform-d) δ 8.11 – 7.99 (m, 2H), 7.70 (d, J = 7.9 Hz, 1H), 7.40 – 7.33 (m, 1H), 7.26 – 7.20 (m, 1H), 7.20 – 7.14 (m, 1H), 7.07 – 7.00 (m, 1H), 5.94 – 5.82 (m, 1H), 4.02 – 3.94 (m, 1H), 3.89 – 3.81 (m, 1H), 3.67 – 3.60 (m, 1H), 3.58 – 3.49 (m, 1H), 2.90 – 2.78 (m, 2H), 2.51 – 2.42 (m, 1H), 2.17 – 2.09 (m, 1H), 1.60 (s, 3H), 1.37 – 1.17 (m, 5H), 0.98 (d, J = 7.0 Hz, 3H), 0.95 – 0.85 (m, 1H), 0.82 (d, J = 6.9 Hz, 3H). ^{13}C NMR (126 MHz, CDCl3) δ 174.5, 154.7, 127.3, 123.4, 122.4, 119.9, 118.6, 111.2, 110.2, 69.4, 49.3, 46.7, 44.3, 30.2, 28.9, 26.6, 24.4, 19.5, 17.5. HRMS calculated for $C_{22}H_{32}N_7O$: 410.26629; found $[M+H]^+$: 410.26669.

15-((1*H*-indol-3-yl)methyl)-12-isopropyl-5,6,7,8,9,10,11,12,14,15-decahydro-13*H*-tetrazolo[1,5-a][1,4,7]triazacyclotridecin-13-one 7k:

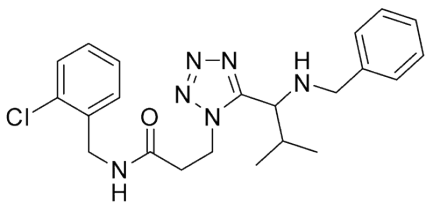


White solid (0.08 g, 19%); 1H NMR (500 MHz, Chloroform-d) δ 7.37 (s, 1H), 7.37 – 7.33 (m, 3H), 7.30 (d, J = 6.9 Hz, 1H), 7.18 (d, J = 5.9 Hz, 1H), 5.56 (t, J = 6.4 Hz, 1H), 4.26 (s, 1H), 3.83 (d, J = 5.9 Hz, 2H), 3.58 (dt, J = 14.5, 5.9 Hz, 2H), 3.32 (q, J = 5.3 Hz, 2H), 3.14 (td, J = 9.3, 8.9, 4.4 Hz, 1H), 3.08 – 2.99 (m, 1H), 2.37 (ddd, J = 15.0, 8.1, 2.9 Hz, 1H), 2.21 (ddd, J = 15.1, 9.9, 2.8 Hz, 1H), 1.88 (d, J = 7.3 Hz, 2H), 1.83 – 1.75 (m, 1H), 1.54 – 1.48 (m, 3H), 1.34 (dq,

J = 11.4, 3.7 Hz, 1H), 1.23 (d, J = 6.0 Hz, 1H), 0.91 (t, J = 6.2 Hz, 8H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 173.2, 151.2, 134.9, 128.9, 128.7, 126.99, 115.0, 109.5, 60.9, 48.9, 41.5, 40.7, 37.5, 35.2, 29.1, 28.6, 24.9, 22.9, 22.1.

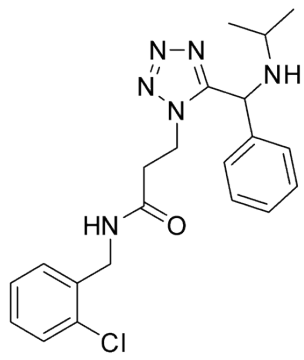
HRMS calculated for $C_{22}H_{32}N_7O$: 410.26629; found $[M+H]^+$: 410.26678.

3-(5-(1-(benzylamino)-2-methylpropyl)-1*H*-tetrazol-1-yl)-*N*-(2-chlorobenzyl) propanamide 6l:



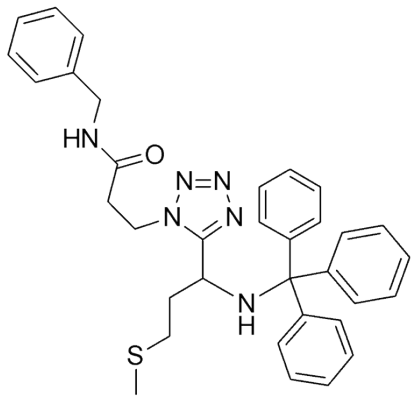
Yellow solid (0.3g, 66%); ^{1}H NMR (500 MHz, Chloroform-d) δ 7.37 – 7.32 (m, 1H), 7.30 – 7.27 (m, 2H), 7.26 – 7.18 (m, 6H), 6.49 (t, J = 6.0 Hz, 1H), 4.63 – 4.52 (m, 2H), 4.47 (d, J = 6.0 Hz, 2H), 3.89 (d, J = 7.7 Hz, 1H), 3.61 (d, J = 3.9 Hz, 1H), 3.49 (d, J = 13.4 Hz, 1H), 2.92 – 2.90 (m, 2H), 2.20 – 2.07 (m, J = 6.7 Hz, 1H), 2.03 (s, 1H), 1.06 (d, J = 6.6 Hz, 3H), 0.83 (d, J = 6.8 Hz, 3H). ^{13}C NMR (126 MHz, Chloroform-d) δ 168.8, 156.6, 139.4, 135.2, 133.3, 129.5, 128.9, 128.4, 128.1, 127.2, 127.0, 58.4, 51.5, 43.4, 41.5, 35.2, 32.5, 19.3, 19.1. HRMS calculated for $C_{22}H_{28}N_6OCl$: 427.1948; found $[M+H]^+$: 427.1950.

***N*-(2-chlorobenzyl)-3-(5-((isopropylamino)(phenyl)methyl)-1*H*-tetrazol-1-yl) propanamide 6m:**



Yellow solid (0.2g, 52%); ^{1}H NMR (500 MHz, Chloroform-d) δ 7.38 – 7.33 (m, 5H), 7.33 – 7.28 (m, 2H), 7.24 – 7.19 (m, 3H), 6.37 (t, J = 5.9 Hz, 1H), 5.47 (s, 1H), 4.56 – 4.53 (m, 1H), 4.48 – 4.45 (m, 2H), 2.80 – 2.74 (m, 1H), 2.74 – 2.67 (m, 2H), 2.30 (s, 1H), 1.11 (d, J = 2.7 Hz, 3H), 1.09 (d, J = 2.7 Hz, 3H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 168.8, 156.5, 138.2, 135.2, 133.4, 129.5, 129.1, 128.9, 128.4, 127.4, 127.1, 54.4, 46.1, 43.3, 41.5, 35.2, 22.92, 22.5. HRMS calculated for $C_{21}H_{26}N_6OCl$: 413.18511; found $[M+H]^+$: 413.18552.

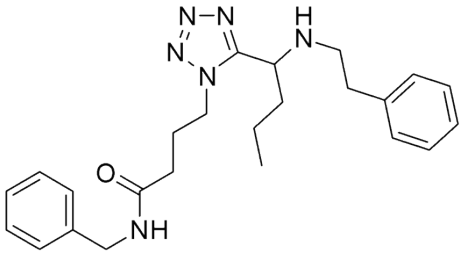
***N*-benzyl-5-(3-(methylthio)-1-(tritylamino)propyl)-1*H*-tetrazole-1-carboxamide 6n:**



White solid (0.3g, 46%); ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.44 – 7.38 (m, 6H), 7.34 – 7.28 (m, 2H), 7.29 – 7.25 (m, 1H), 7.24 – 7.18 (m, 7H), 7.19 – 7.14 (m, 4H), 6.29 (s, 1H), 4.42 – 4.31 (m, 2H), 4.21 – 4.15 (m, 1H), 3.88– 3.86 (m, 1H), 3.05 (d, *J* = 9.0 Hz, 1H), 2.78 – 2.60 (m, 2H), 2.60 –

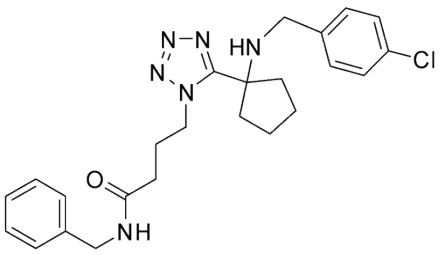
2.47 (m, 1H), 2.29 – 2.16 (m, 2H), 2.09 – 2.05 (m, 1H), 2.06 (s, 3H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 168.5, 157.6, 145.2, 137.7, 128.7, 128.53, 127.9, 127.7, 127.6, 126.7, 71.5, 47.1, 43.6, 43.2, 36.6, 34.9, 29.5, 15.3. HRMS calculated for $C_{34}H_{36}N_6OSNa$: 599.25635; found $[M+Na]^+$: 599.25684.

_N_-benzyl-4-(5-(1-(phenethylamino)butyl)-1_H_-tetrazol-1-yl)butanamide 6o:



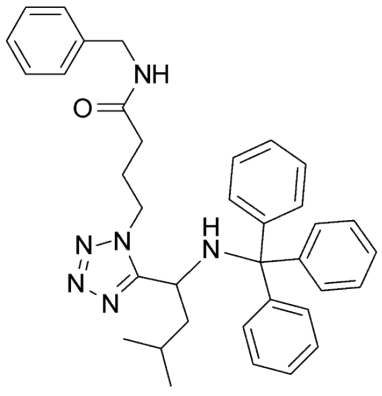
Yellow oil (0.36g, 70%); ^{1}H NMR (500 MHz, Chloroform-d) δ 7.35 – 7.29 (m, 3H), 7.26 (dd, J = 7.0, 5.1 Hz, 4H), 7.22 – 7.17 (m, 1H), 7.14 – 7.10 (m, 2H), 6.63 (t, J = 5.9 Hz, 1H), 4.47 – 4.32 (m, 4H), 4.13 (t, J = 7.2 Hz, 1H), 4.03 (m, 1H), 2.78 – 2.69 (m, 3H), 2.69 – 2.60 (m, 1H), 2.28 (t, J = 7.1 Hz, 2H), 2.24 – 2.15 (m, 2H), 2.13 (s, 1H), 1.78 (m, 2H), 1.34 – 1.24 (m, 3H), 1.21 – 1.09 (m, 1H), 0.89 (t, J = 7.3 Hz, 3H). ^{13}C NMR (126 MHz, Chloroform-d) δ 171.4, 156.4, 139.5, 138.4, 128.7, 128.6, 128.5, 127.7, 127.4, 126.3, 62.4, 62.4, 53.2, 53.1, 48.4, 46.6, 43.5, 36.2, 36.1, 32.4, 25.4, 19.2, 13.8, 13.9. HRMS calculated for $C_{24}H_{33}N_6O$: 421.27104; found $[M+H]^+$: 421.27148.

_N_-benzyl-4-(5-(1-((4-chlorobenzyl)amino)cyclopentyl)-1_H_-tetrazol-1-yl)butanamide 6p:



Yellow solid (0.3g, 60%); ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.33 – 7.28 (m, 2H), 7.28 – 7.22 (m, 5H), 7.12 (d, *J* = 8.2 Hz, 2H), 6.42 (d, *J* = 6.0 Hz, 1H), 4.67 (t, *J* = 6.9 Hz, 2H), 4.41 (d, *J* = 5.8 Hz, 2H), 3.38 (s, 2H), 2.35 (m, 4H), 2.27 (q, *J* = 6.9 Hz, 2H), 2.18 – 2.10 (m, 2H), 1.87 – 1.76 (m, 4H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 171.3, 158.1, 138.2, 138.0, 132.8, 129.2, 129.1, 128.7, 128.6, 127.8, 127.5, 63.6, 47.6, 47.4, 43.6, 43.6, 37.3, 32.7, 25.4, 23.4. HRMS calculated for $C_{24}H_{30}N_6OCl$: 453.21641; found $[M+H]^+$: 453.21698.

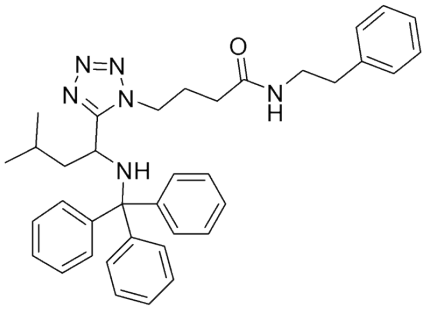
_N_-benzyl-4-(5-(3-methyl-1-(tritylamino)butyl)-1_H_-tetrazol-1-yl)butanamide 6q:



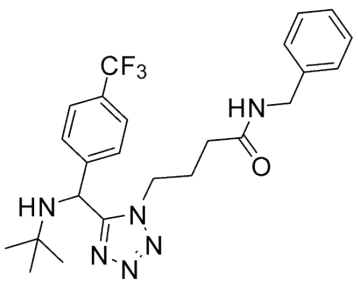
White Solid (0.4g, 77%); ^{1}H NMR (500 MHz, Chloroform-d) δ 7.38 – 7.34 (m, 7H), 7.34 – 7.30 (m, 2H), 7.28 (td, J = 7.6, 7.2, 1.6 Hz, 4H), 7.19 (dd, J = 8.4, 6.7 Hz, 6H), 7.16 – 7.11 (m, 3H), 5.96 (d, J = 6.5 Hz, 1H), 4.54 – 4.32 (m, 2H),

4.05 (dd, J = 11.7, 5.5 Hz, 2H), 3.90 (m, 1H), 2.75 (d, J = 7.0 Hz, 1H), 2.24 (t, J = 6.9 Hz, 2H), 2.04 (m, 2H), 1.73 (m, 1H), 1.65 (s, 1H), 1.51 (m, 1H), 1.18 – 1.05 (m, 1H), 0.74 (dd, J = 6.6, 1.5 Hz, 6H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 171.0, 157.9, 145.2, 138.1, 128.78, 128.59, 127.93, 127.83, 127.64, 126.74, 71.74, 47.26, 46.99, 46.27, 43.71, 32.68, 25.02, 24.46, 23.27, 22.12. HRMS calculated for $C_{36}H_{40}N_6ONa$: 595.31558; found $[M+Na]^+$: 595.31604.

4-(5-(2-methyl-1-(tritlyamino)propyl)-1*H*-tetrazol-1-yl)-N-phenylbutanamide 6x:



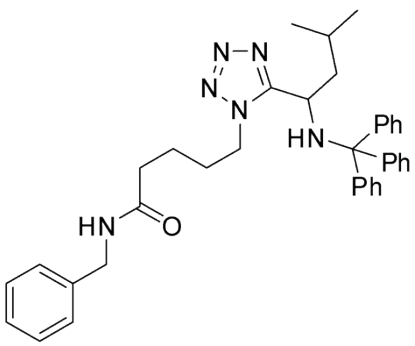
White solid (0.3g, 53%); ^{1}H NMR (500 MHz, Chloroform-d) δ 7.41 – 7.36 (m, 6H), 7.33 (dd, J = 8.1, 6.8 Hz, 2H), 7.28 – 7.25 (m, 1H), 7.22 (t, J = 7.5 Hz, 8H), 7.19 – 7.14 (m, 3H), 5.62 (s, 1H), 4.07 – 4.03 (m, 1H), 3.93 – 3.84 (m, 1H), 3.55 (q, J = 6.7 Hz, 2H), 2.84 (t, J = 7.0 Hz, 2H), 2.23 – 2.12 (m, 2H), 2.02 – 1.98 (m, 2H), 1.75 – 1.72 (m, 1H), 1.55 – 1.51(m, 1H), 1.21 – 1.06 (m, 1H), 0.76 (d, J = 6.6 Hz, 6H). ^{13}C NMR (126 MHz, Chloroform-d) δ 171.1, 156.4, 139.4, 128.7, 128.6, 128.5, 128.4, 126.6, 126.4, 51.7, 48.6, 46.3, 43.2, 40.6, 36.2, 35.6, 32.5, 25.3, 24.9, 22.6, 22.4. HRMS calculated for $C_{37}H_{42}N_6ONa$: 609.33123; found $[M+Na]^+$: 609.33173.



***N*-benzyl-4-(5-((tert-butylamino)(4-(trifluoromethyl)phenyl)methyl)-1*H*-tetrazol-1-yl)butanamide6y:**

Orange solid (0.2 g, 42%); ^{1}H NMR (500 MHz, Chloroform-d) δ 7.61 (d, J = 8.1 Hz, 2H), 7.53 (d, J = 8.1 Hz, 2H), 7.38 – 7.35 (m, 2H), 7.34 – 7.32 (m, 1H), 7.31 (d, J = 1.7 Hz, 2H), 5.84 (s, 1H), 5.59 (s, 1H), 4.47 (d, J = 5.9 Hz, 2H), 2.30 – 2.24 (m, 2H), 2.16 (m, 2H), 2.07 (s, 1H), 1.30 – 1.25 (m, 2H), 1.12 (s, 9H); ^{13}C NMR (126 MHz, Chloroform-d) δ 170.9 , 158.7 , 157.1, 144.4, 137.9, 130.3, 128.8, 127.8 , 126.1, 52.1, 51.5, 46.5, 43.8, 31.9, 29.7, 29.6, 24.9. HRMS calculated for $C_{24}H_{30}N_6OF_3$: 475.24277; found $[M+H]^+$: 475.24319.

***N*-benzyl-5-(5-(3-methyl-1-(tritylamino)butyl)-1*H*-tetrazol-1-yl)pentanamide 6z:**



White solid (0.2g, 35%); ^{1}H NMR (500 MHz, Chloroform-d) δ 7.41 – 7.36 (m, 6H), 7.36 – 7.34 (m, 2H), 7.32 – 7.26

(m, 4H), 7.23 (dd, J = 8.5, 6.6 Hz, 5H), 7.19 – 7.15 (m, 3H), 5.82 (s, 1H), 4.45 (d, J = 5.7 Hz, 2H), 4.03 (m, 1H), 3.87 (m, 1H), 3.82 – 3.67 (m, 1H), 2.78 (d, J = 7.3 Hz, 1H), 2.24 (t, J = 7.2 Hz, 2H), 1.81– 1.77 (m, 2H), 1.72–1.67 (m, 2H), 1.59 –1.54 (m, 1H), 1.28 (s, 1H), 1.16 – 1.07 (m, 1H), 0.77 (d, J = 6.5 Hz, 6H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 171.6, 157.9, 145.2, 138.1, 128.8, 128.6, 127.9, 127.8, 127.6, 126.8, 71.7, 47.4, 46.9, 43.7, 35.6, 28.8, 24.4, 23.3, 22.6, 22.1. HRMS calculated for $C_{37}H_{42}N_6ONa$: 609.33123; found $[M+H]^+$: 609.3316.

^{1}H, ^{13}C NMR, chromatograms of the novel synthesized compounds:

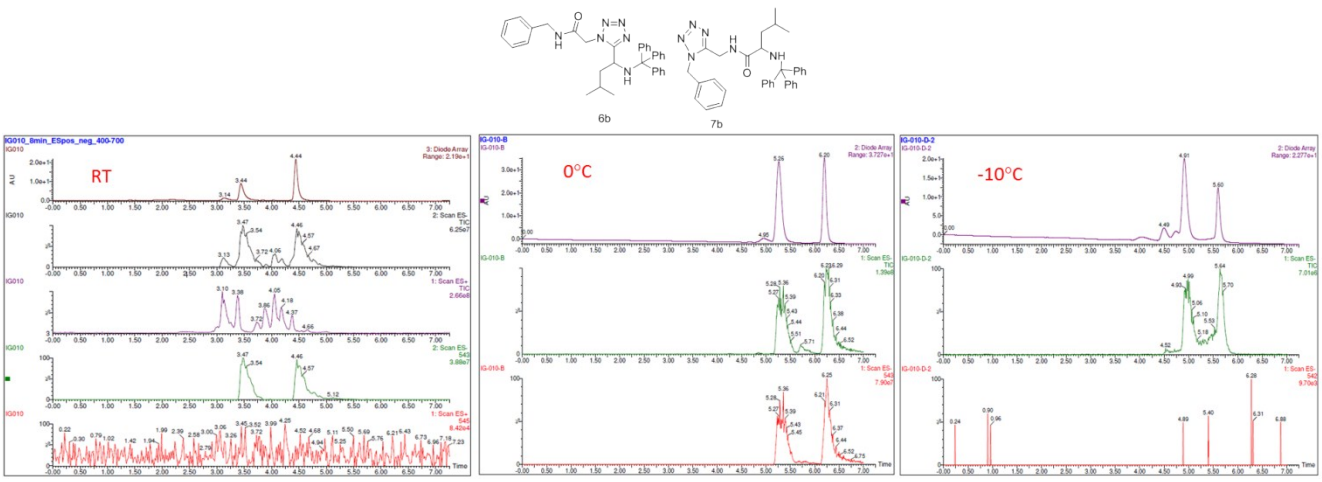
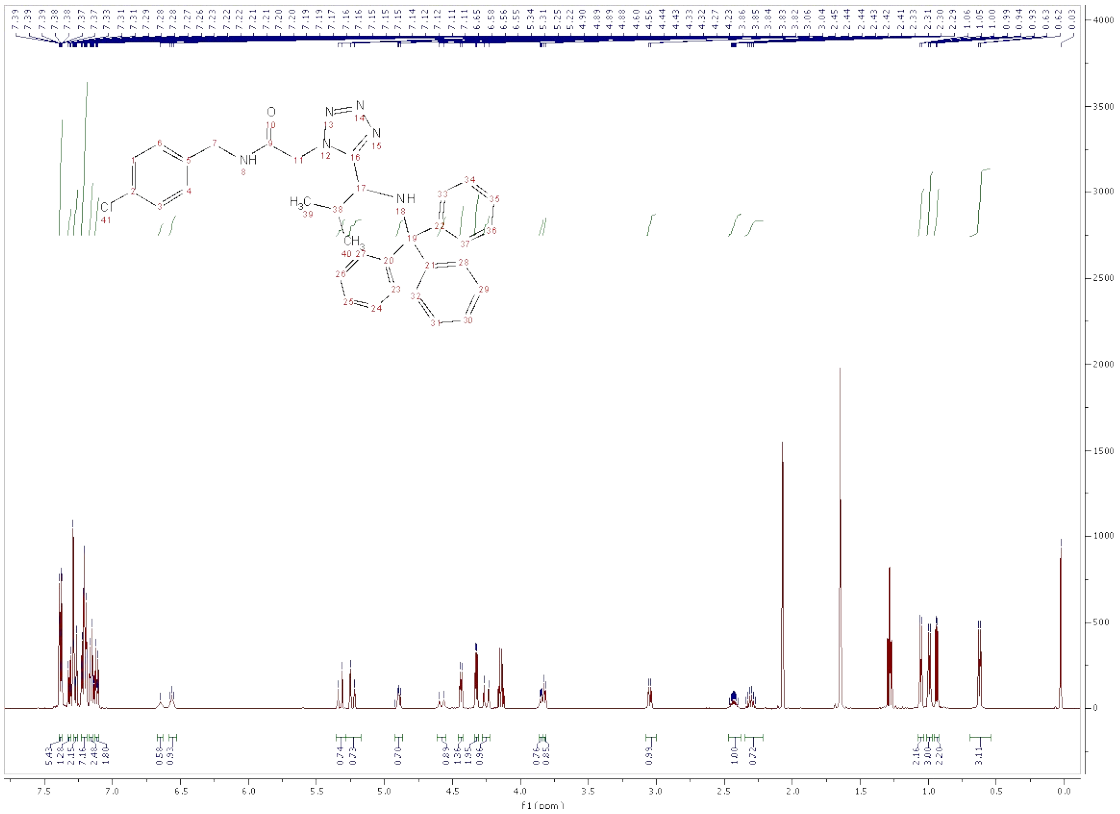
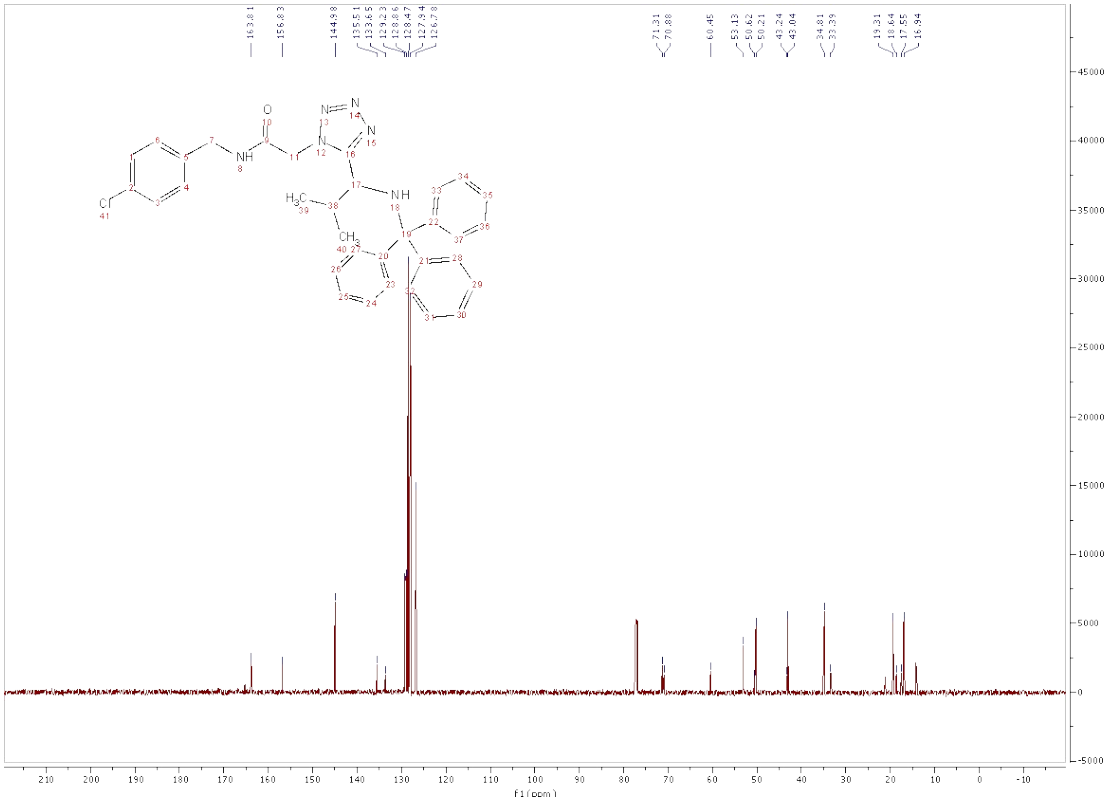
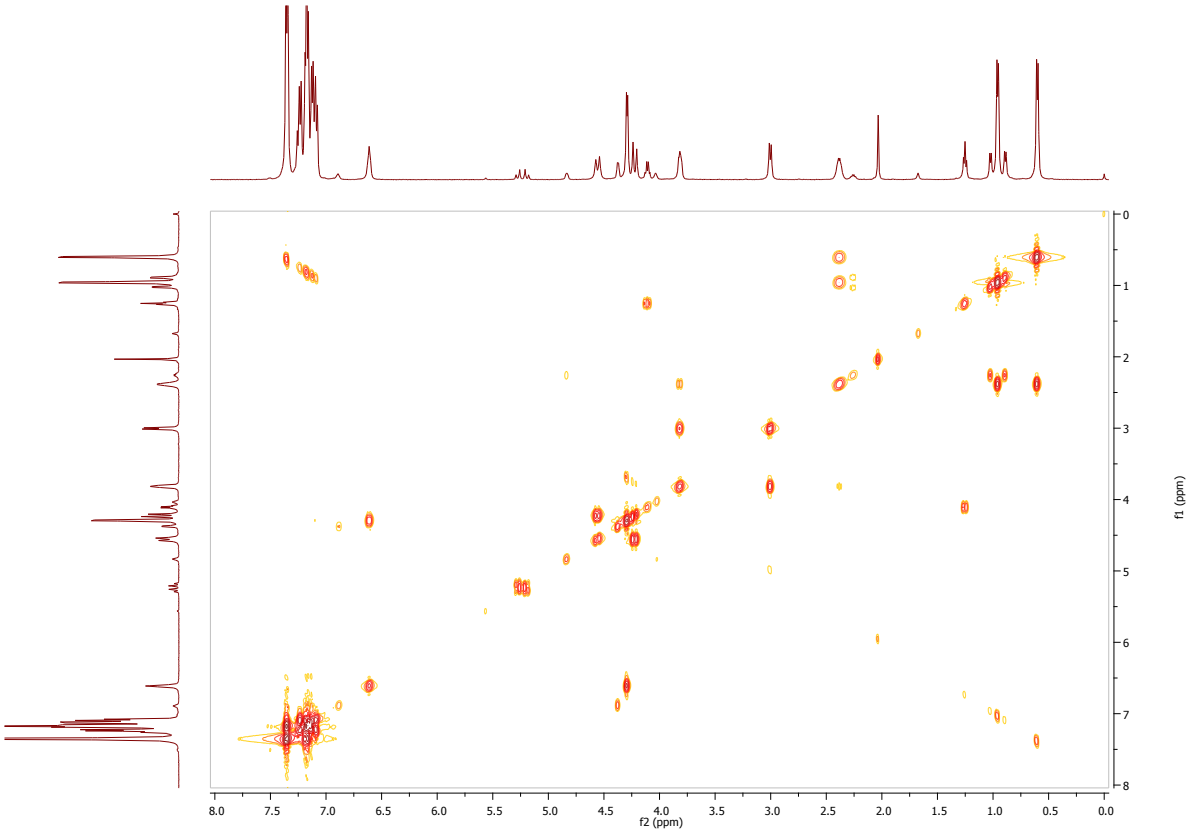


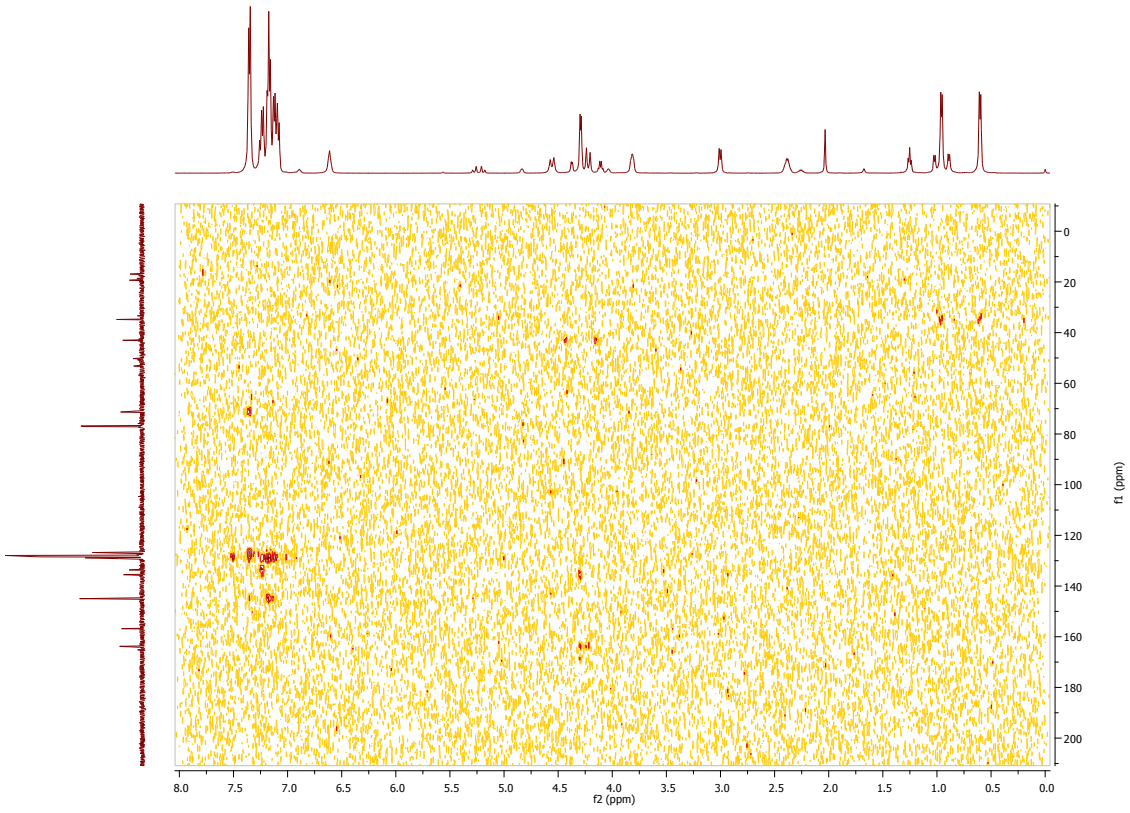
Figure 1. The change of the temperature of the reaction from room temperature to 0°C and -10 °C showed a slight increase in the formation of the minor product B.

Compound 6a:

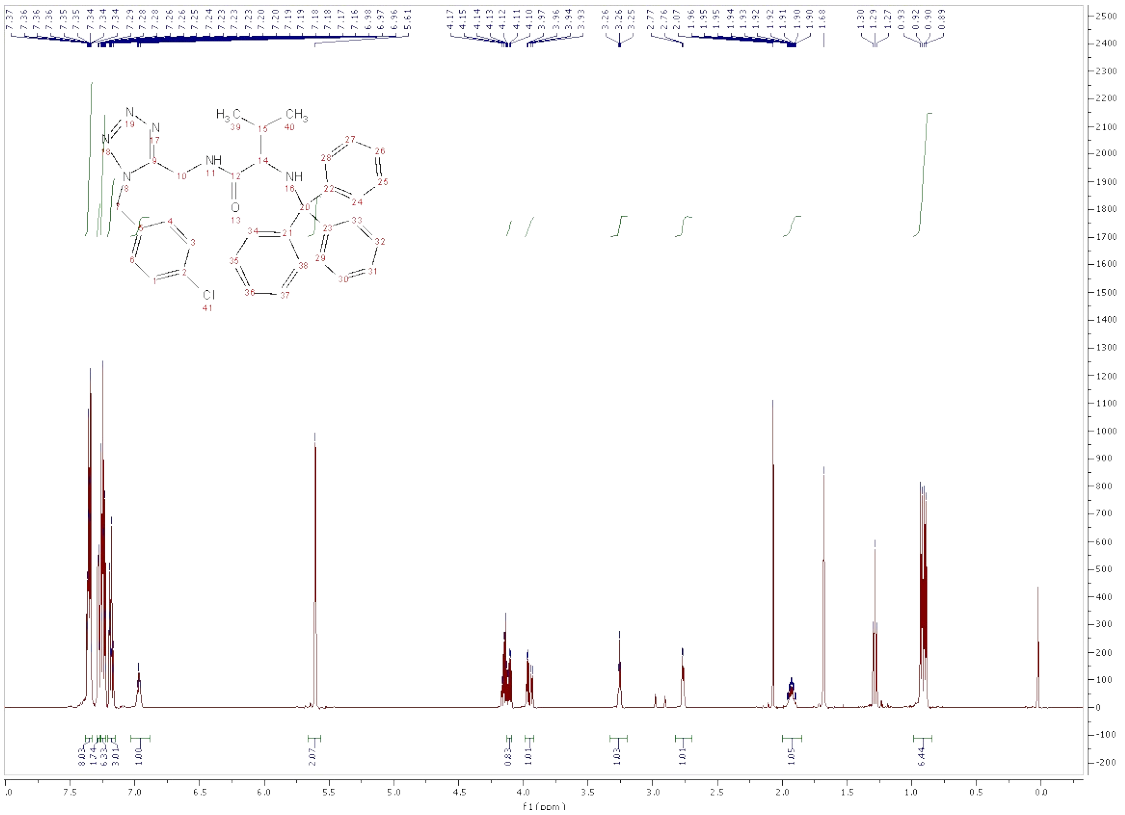


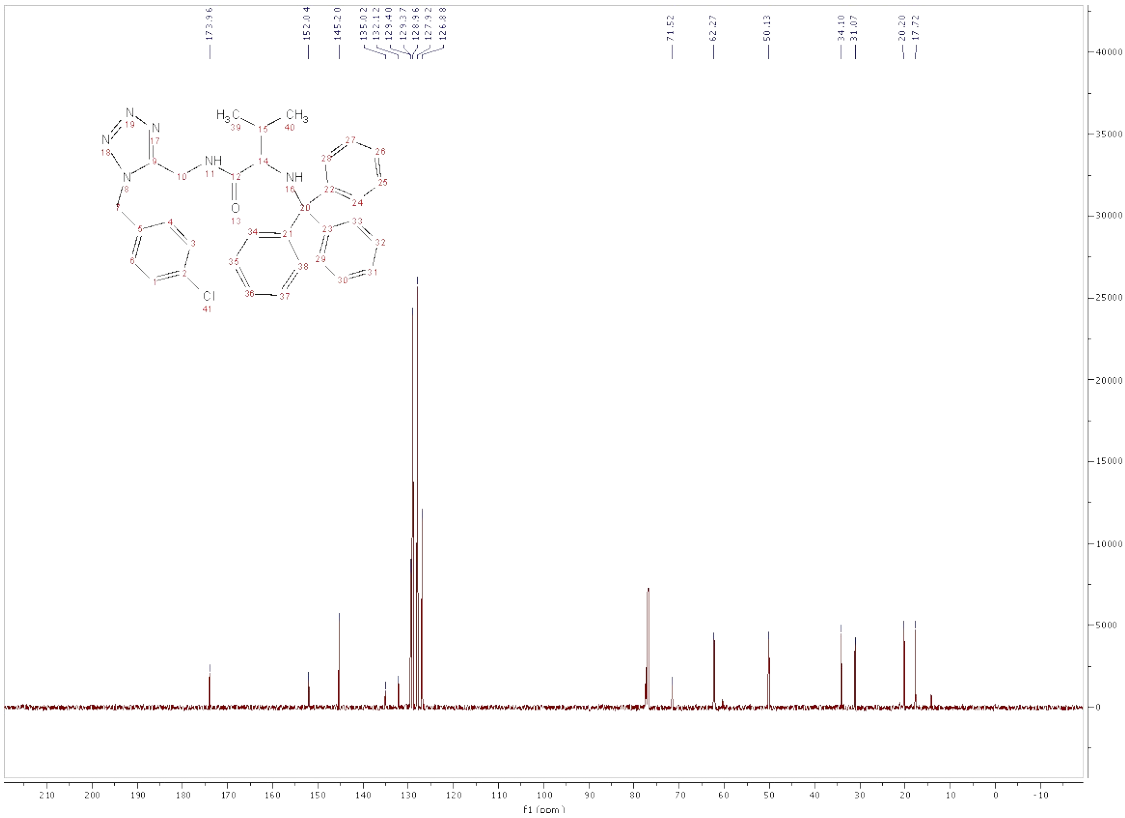


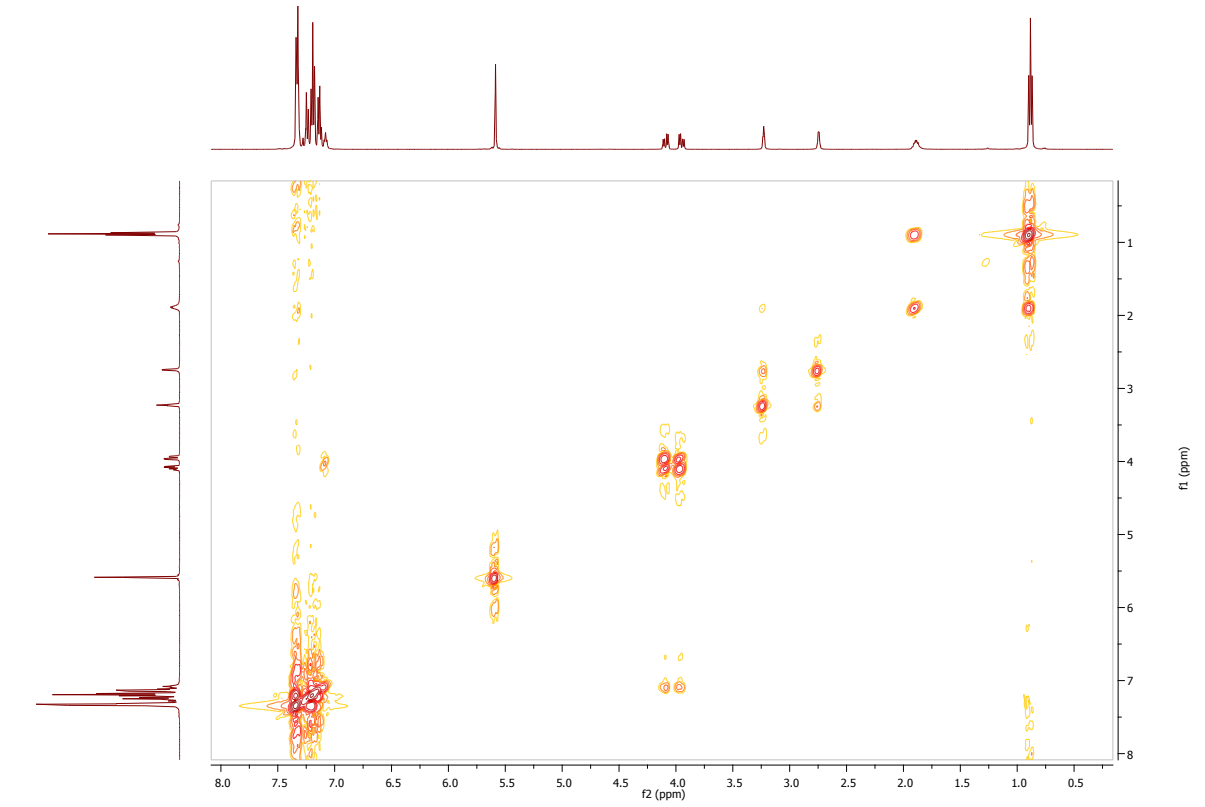

f2 (ppm)
f1 (ppm)

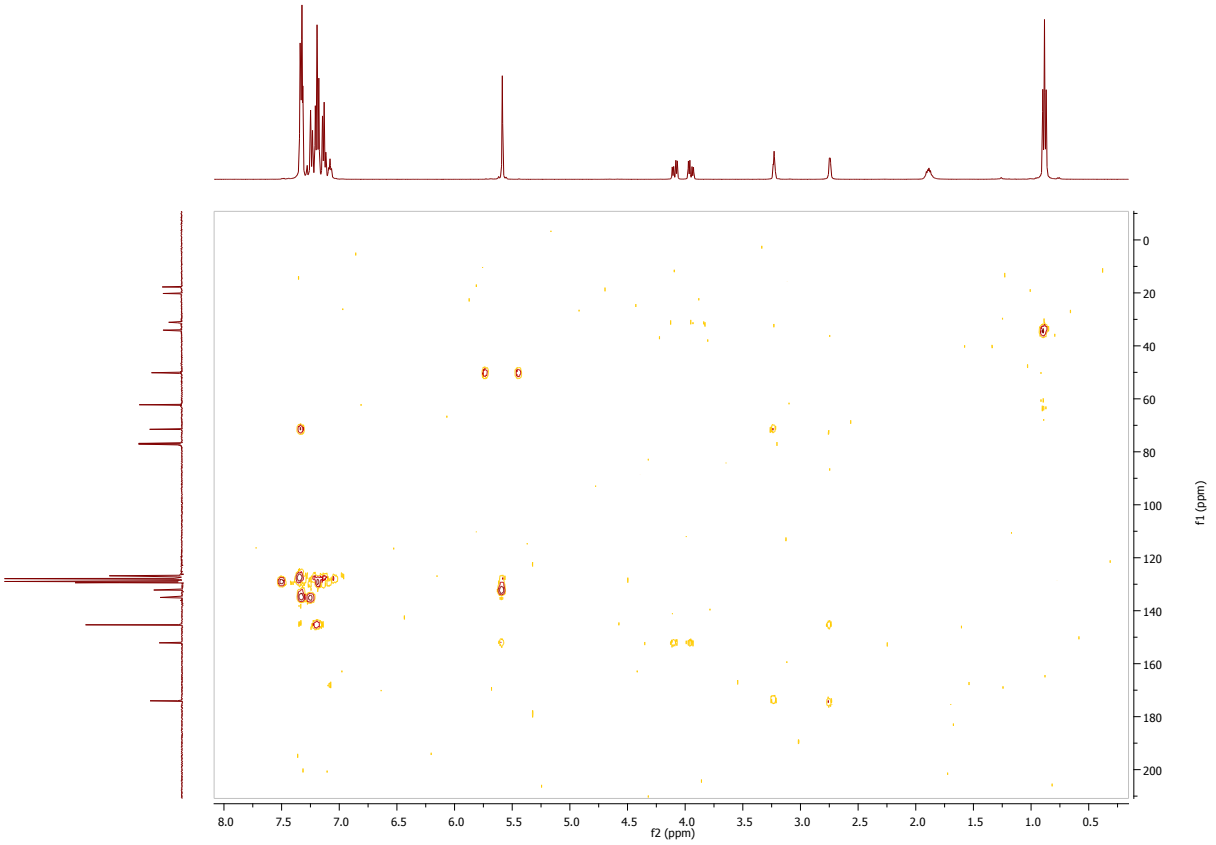

f2 (ppm)
f1 (ppm)

Compound 7a:

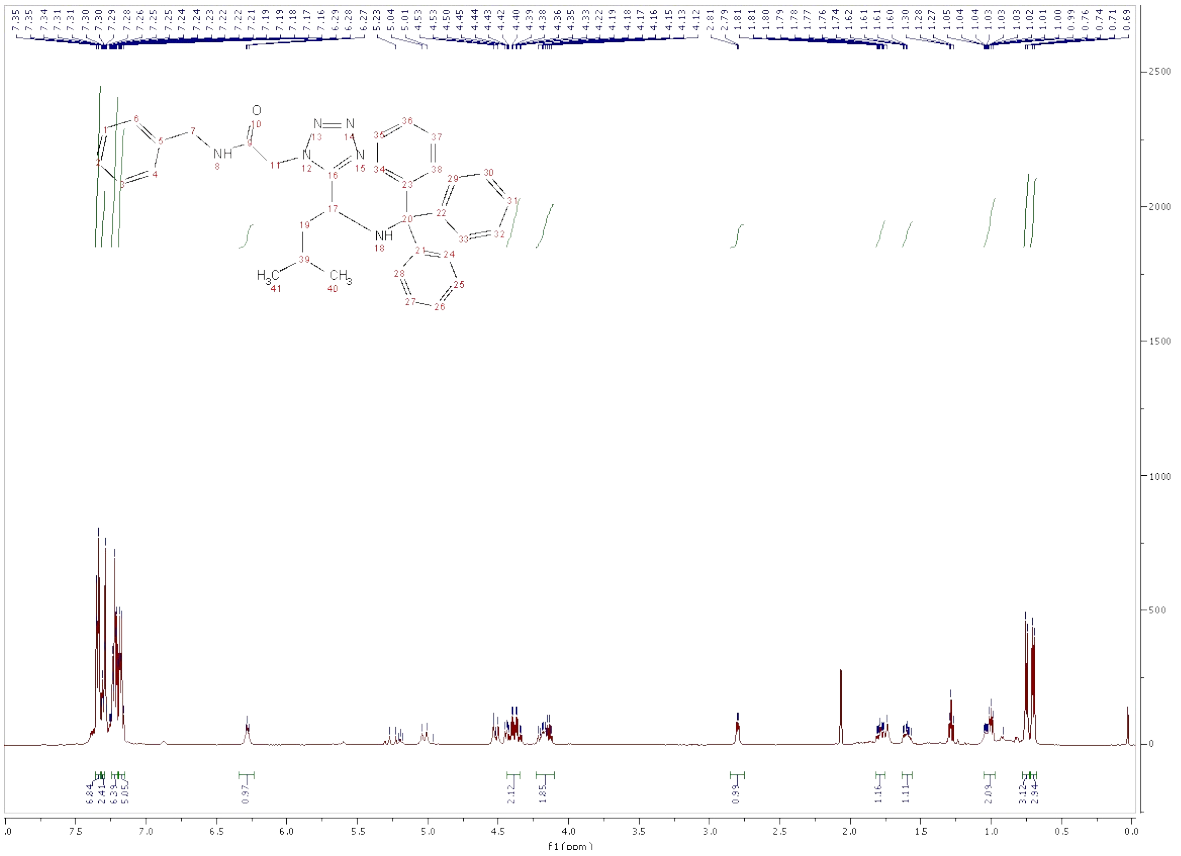


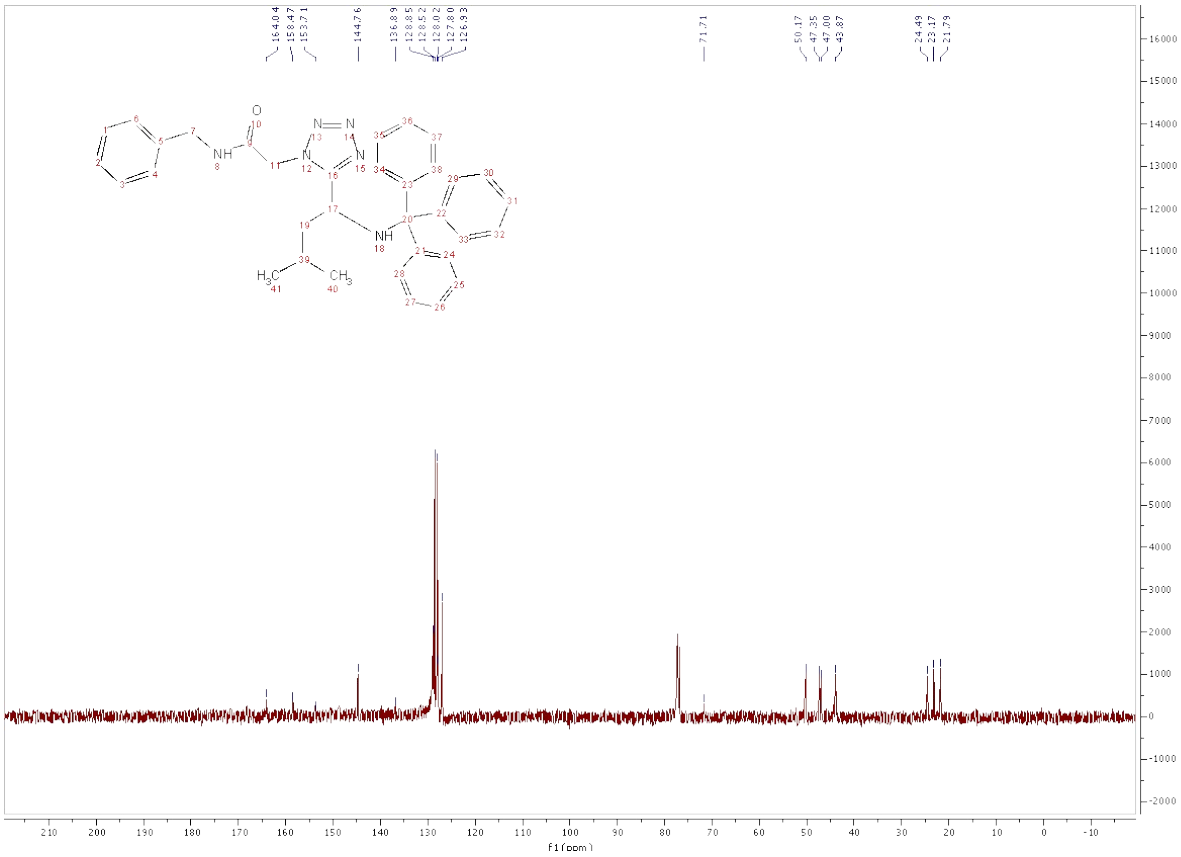



f2 (ppm)
f1 (ppm)

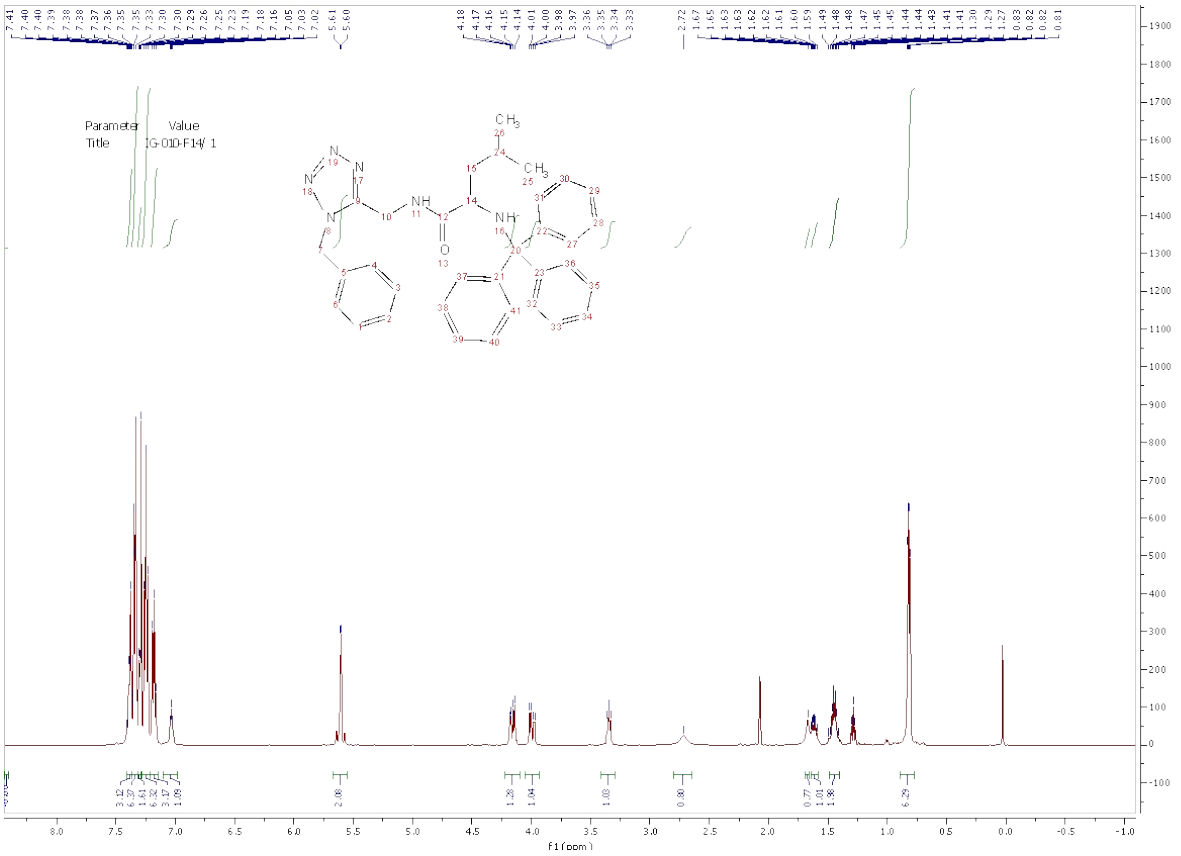

f2 (ppm)
f1 (ppm)

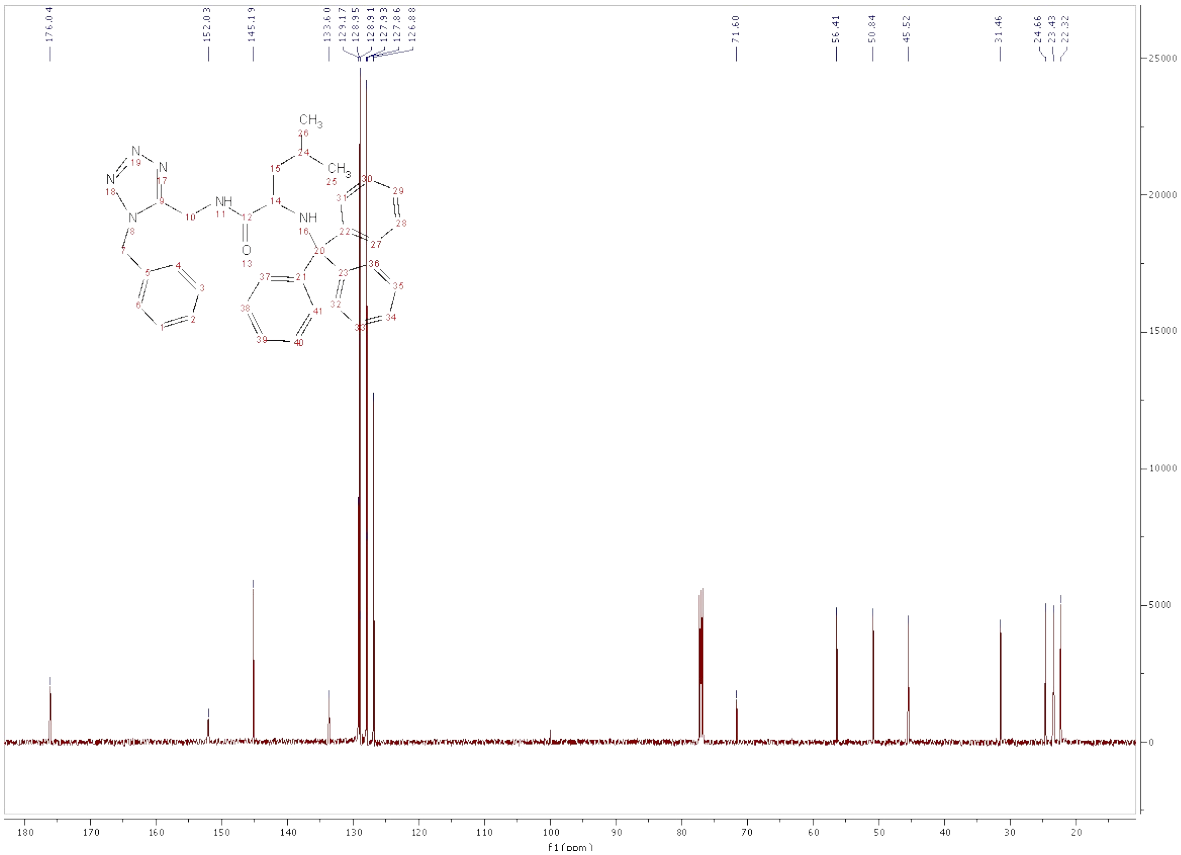
Compound 6b:



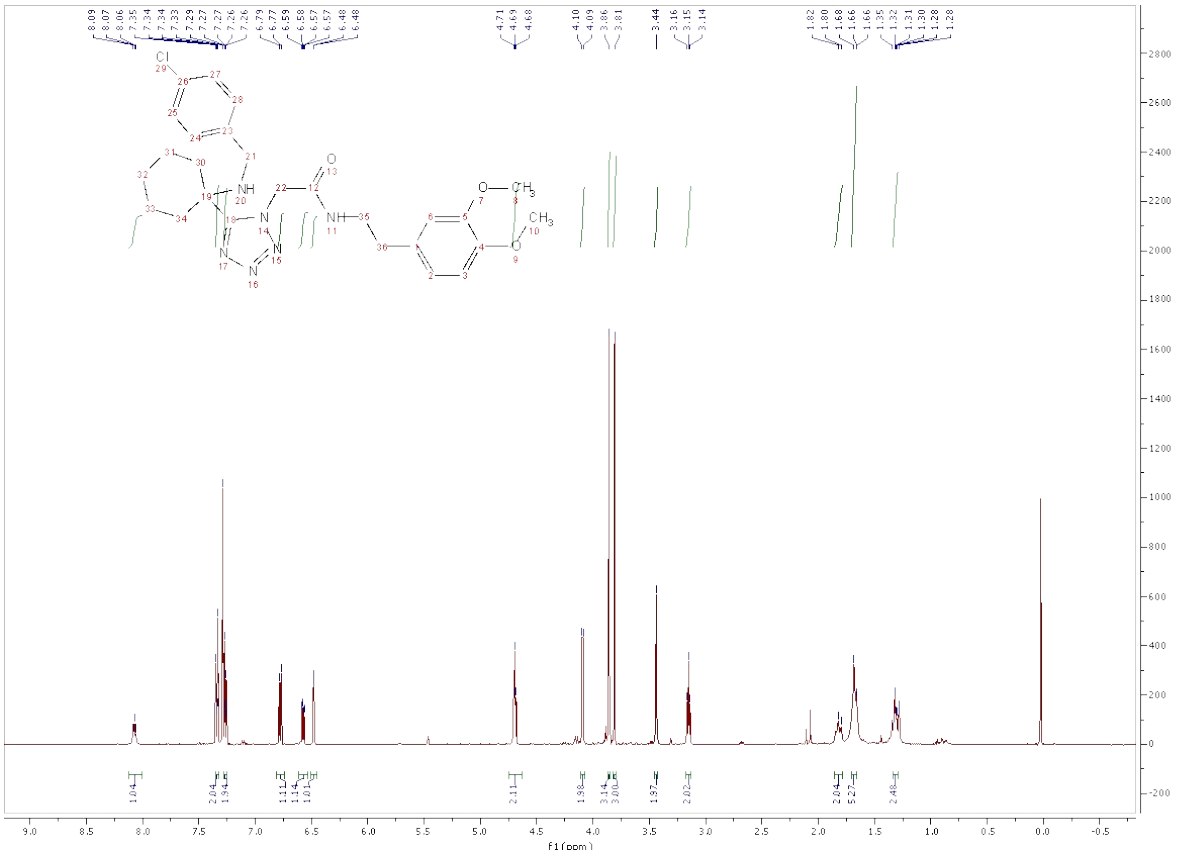


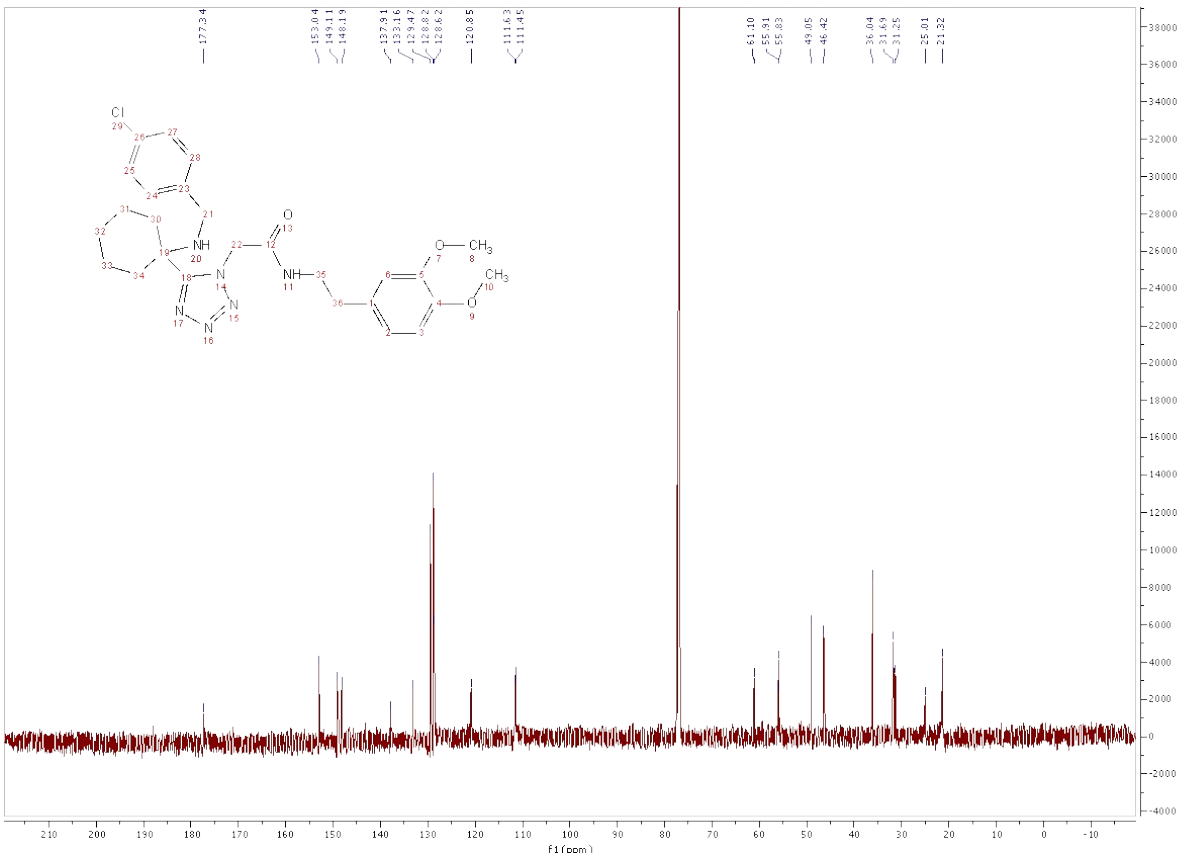
Compound 7b:



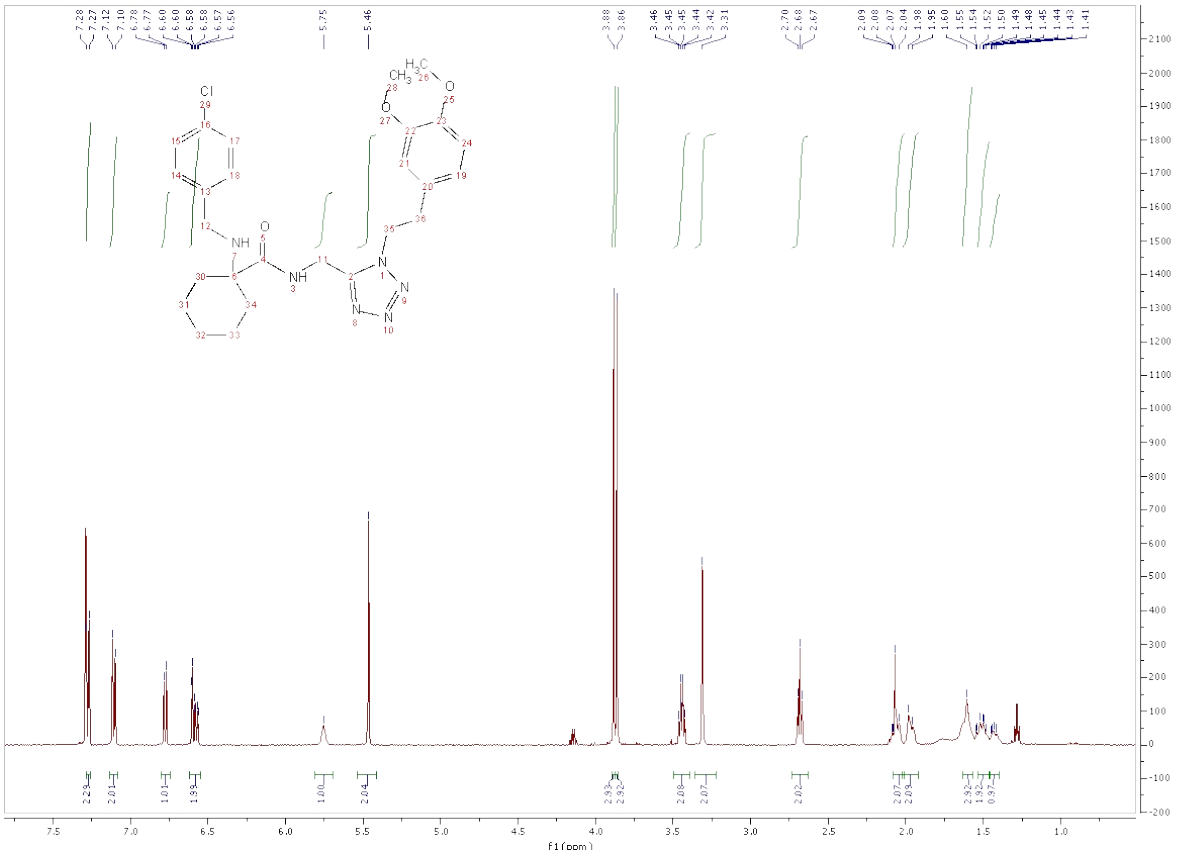


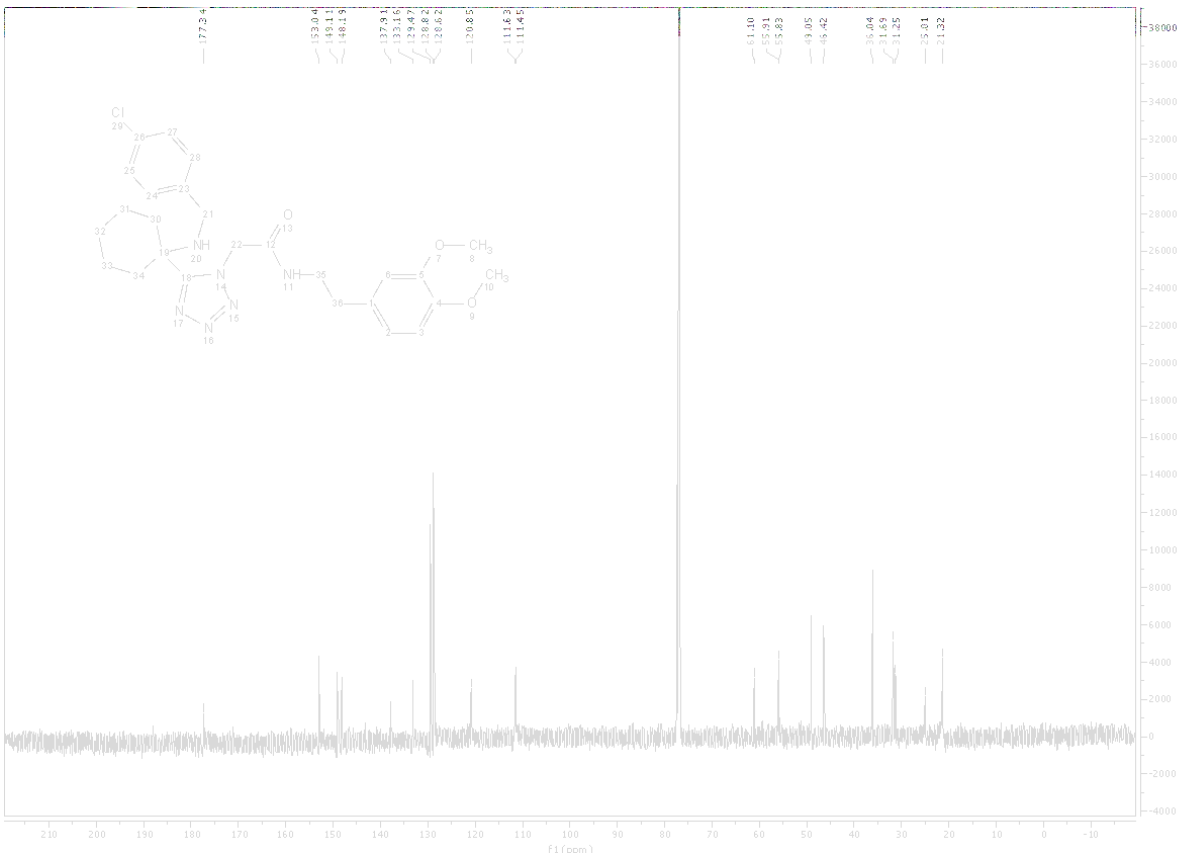
Compound 6c:



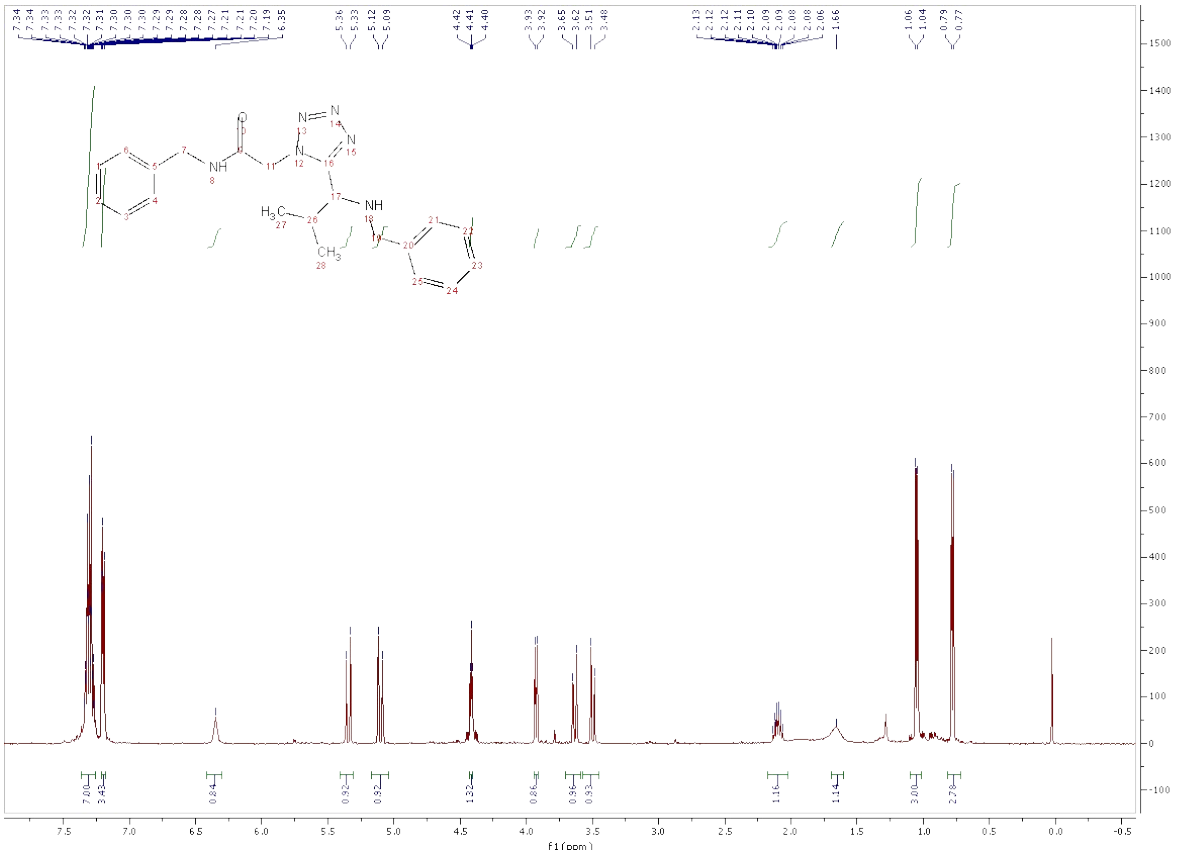


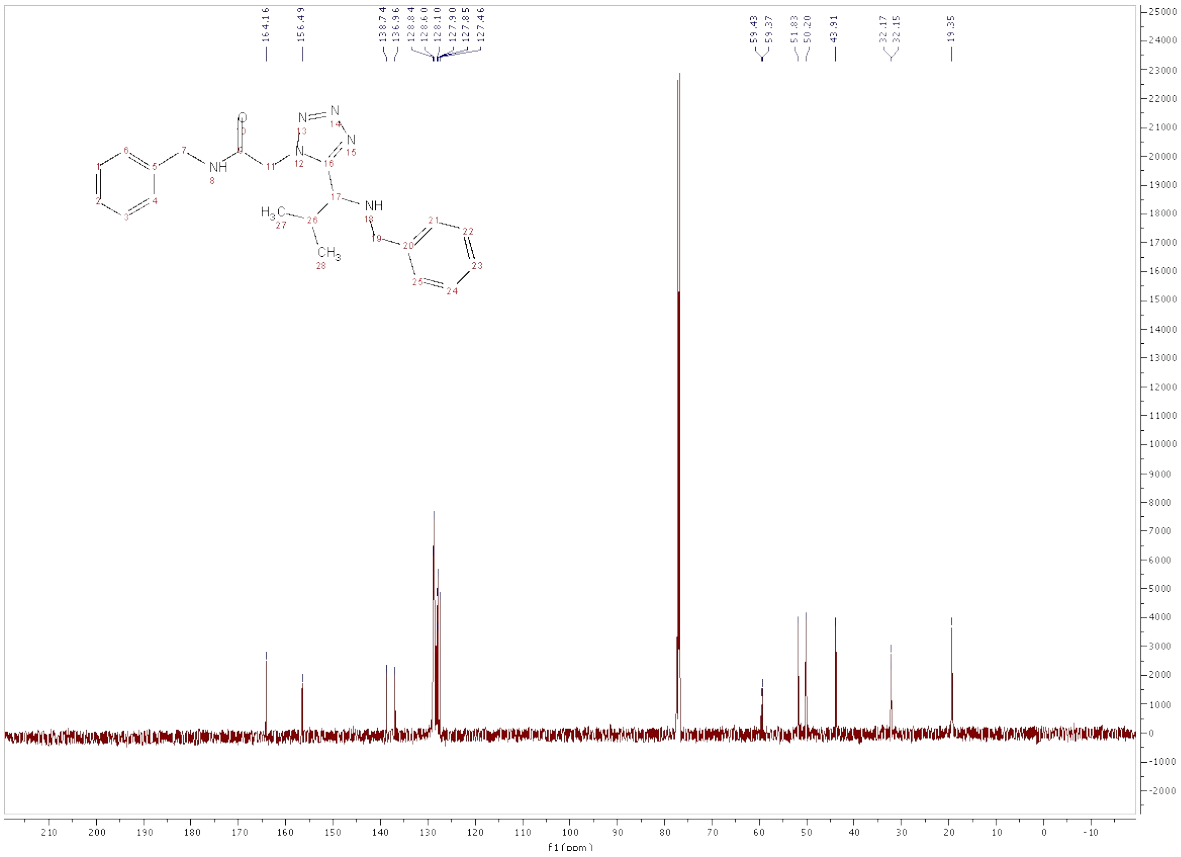
Compound 7c:



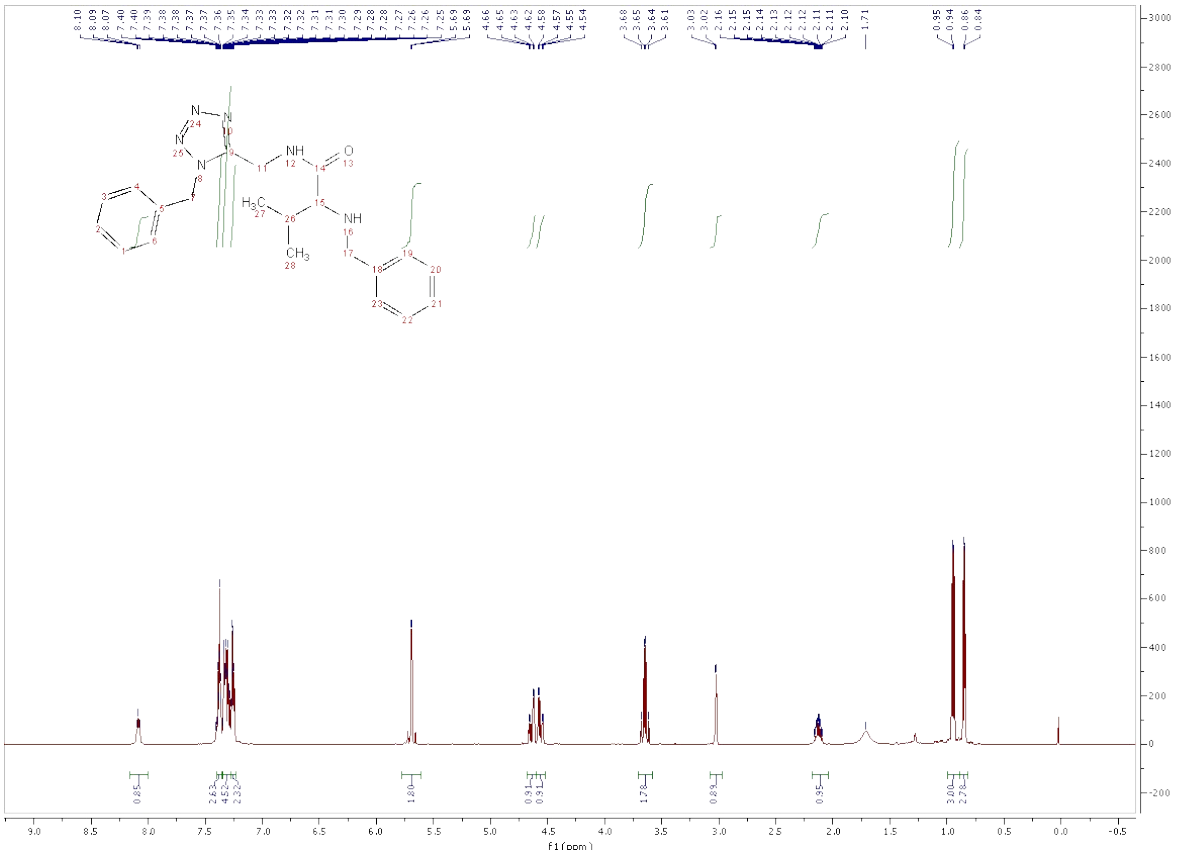


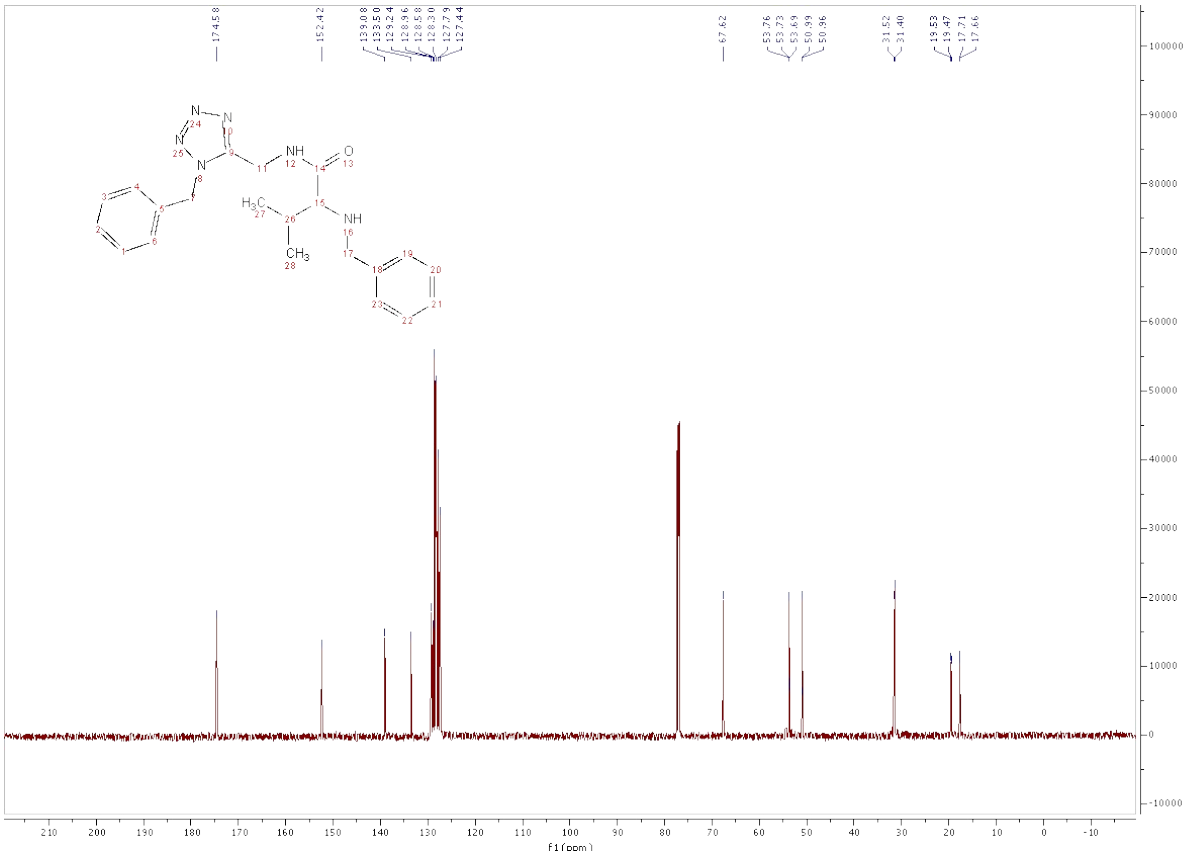
Compound 6d:



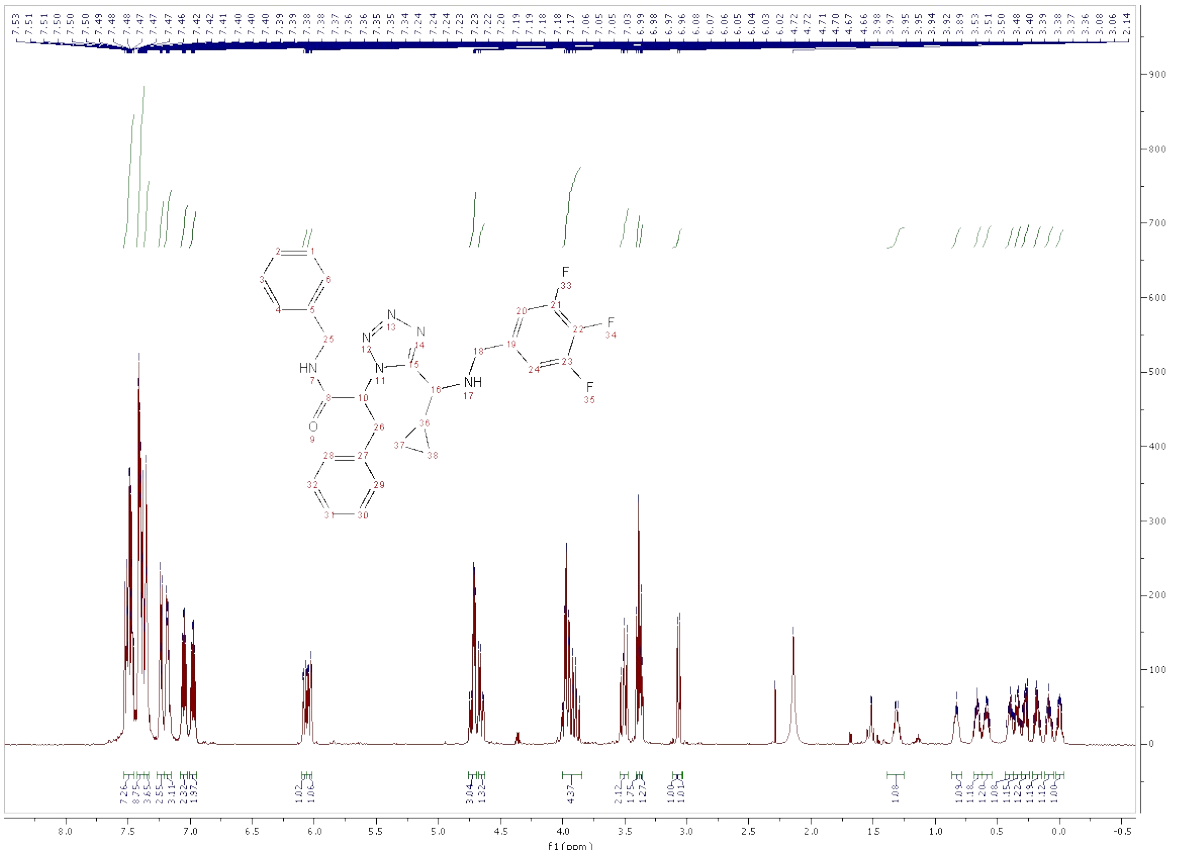


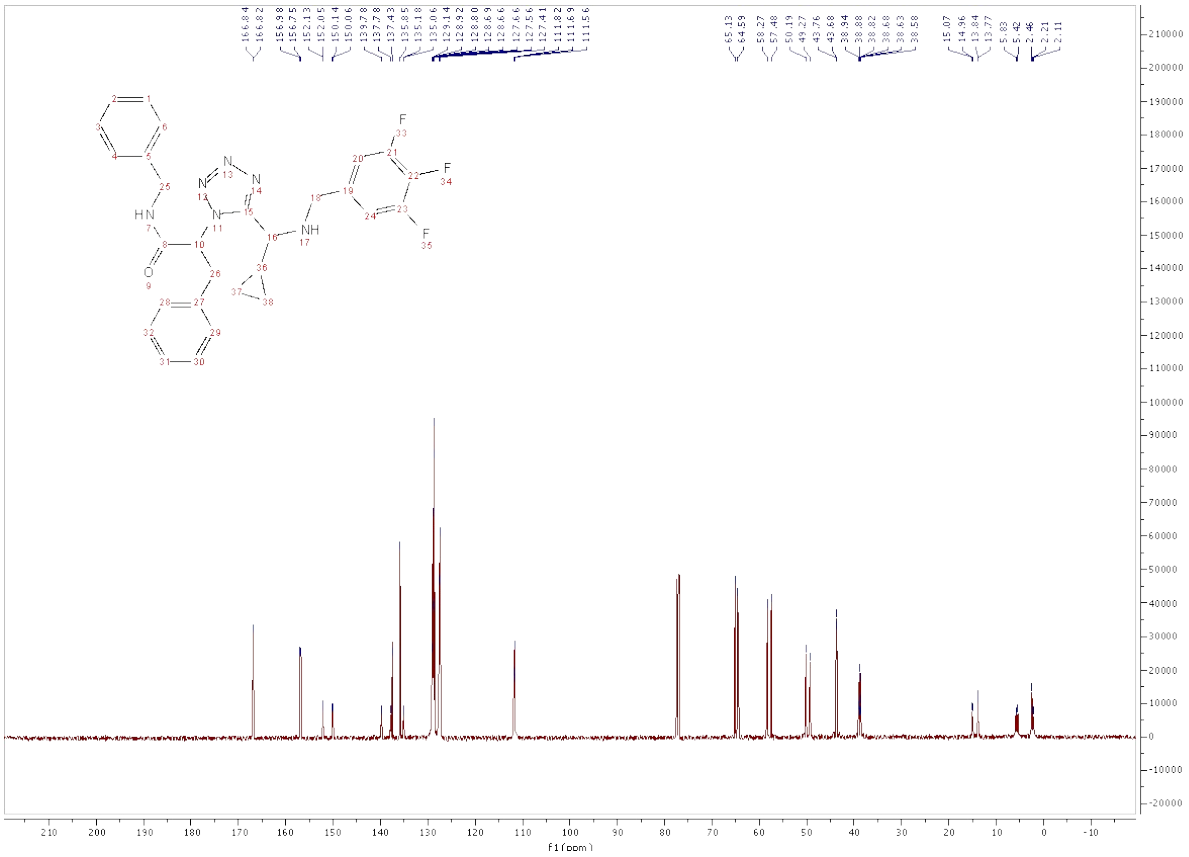
Compound 7d:



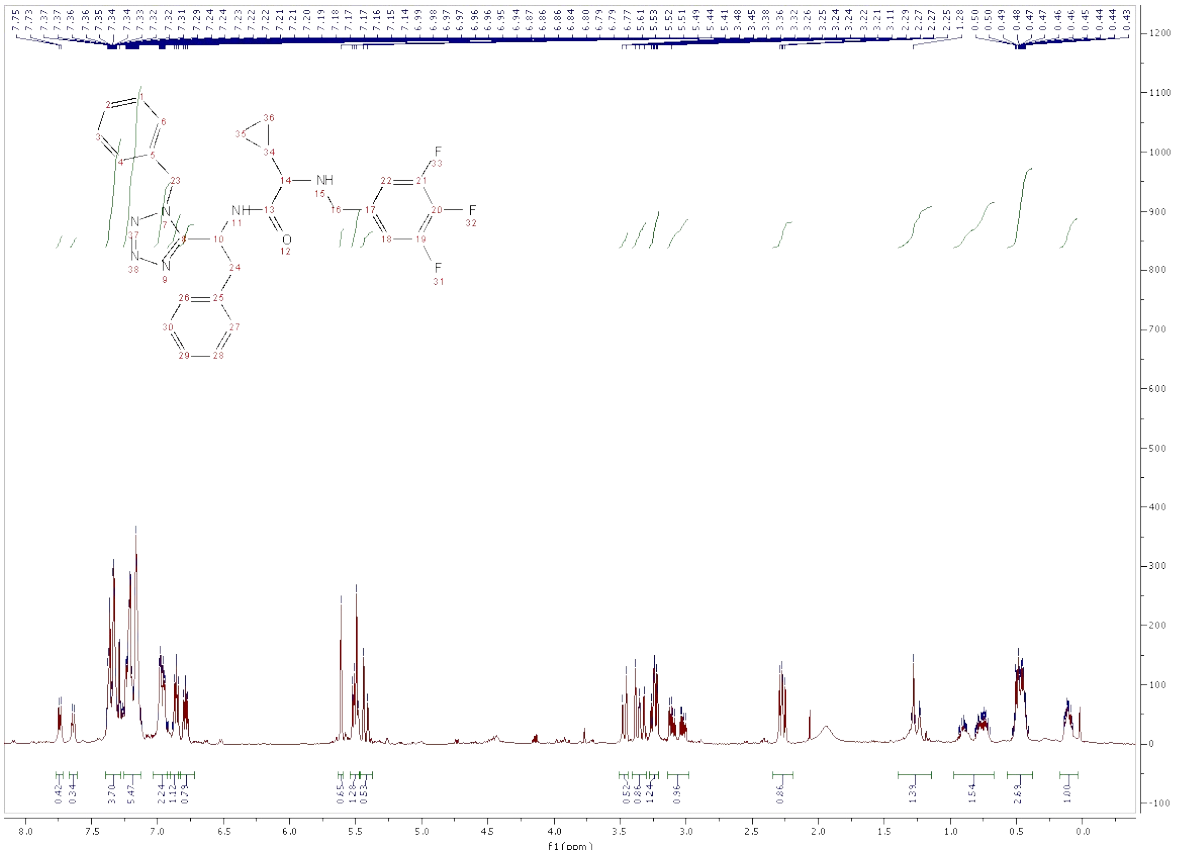


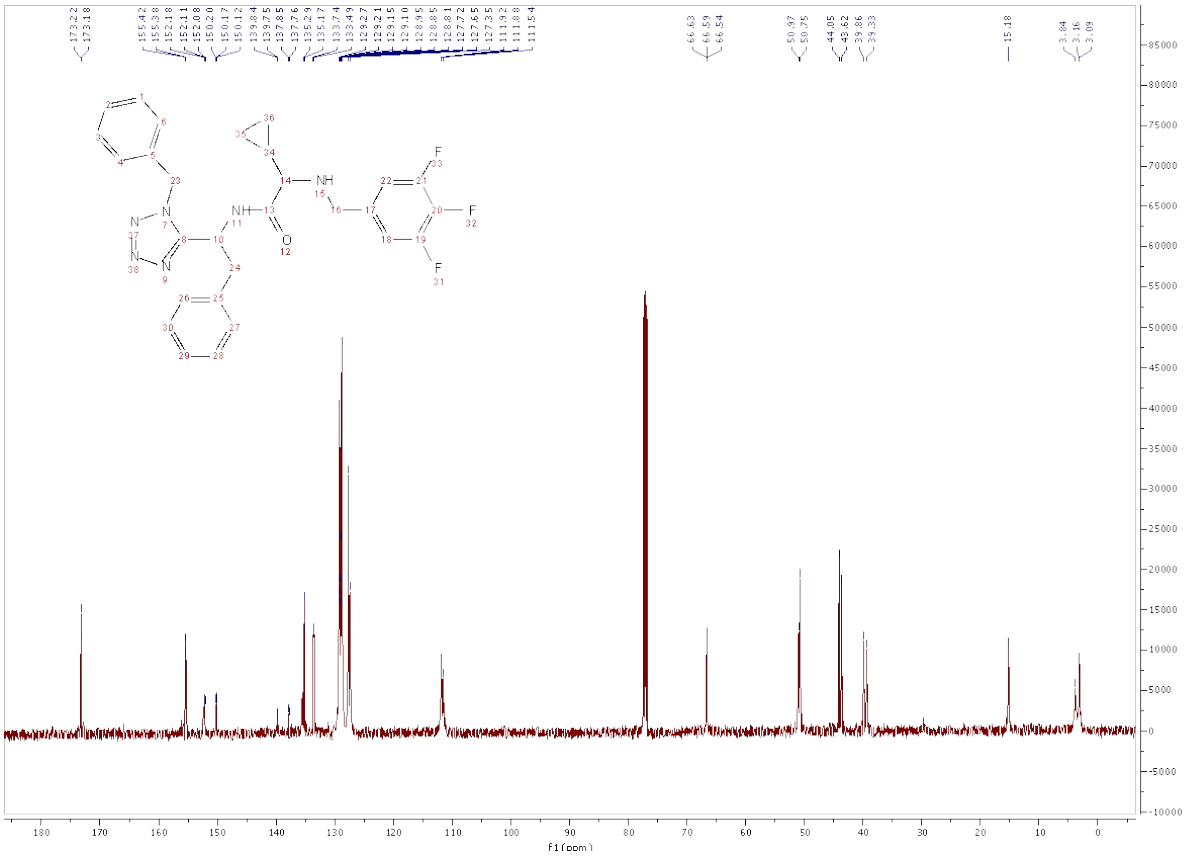
Compound 6e:



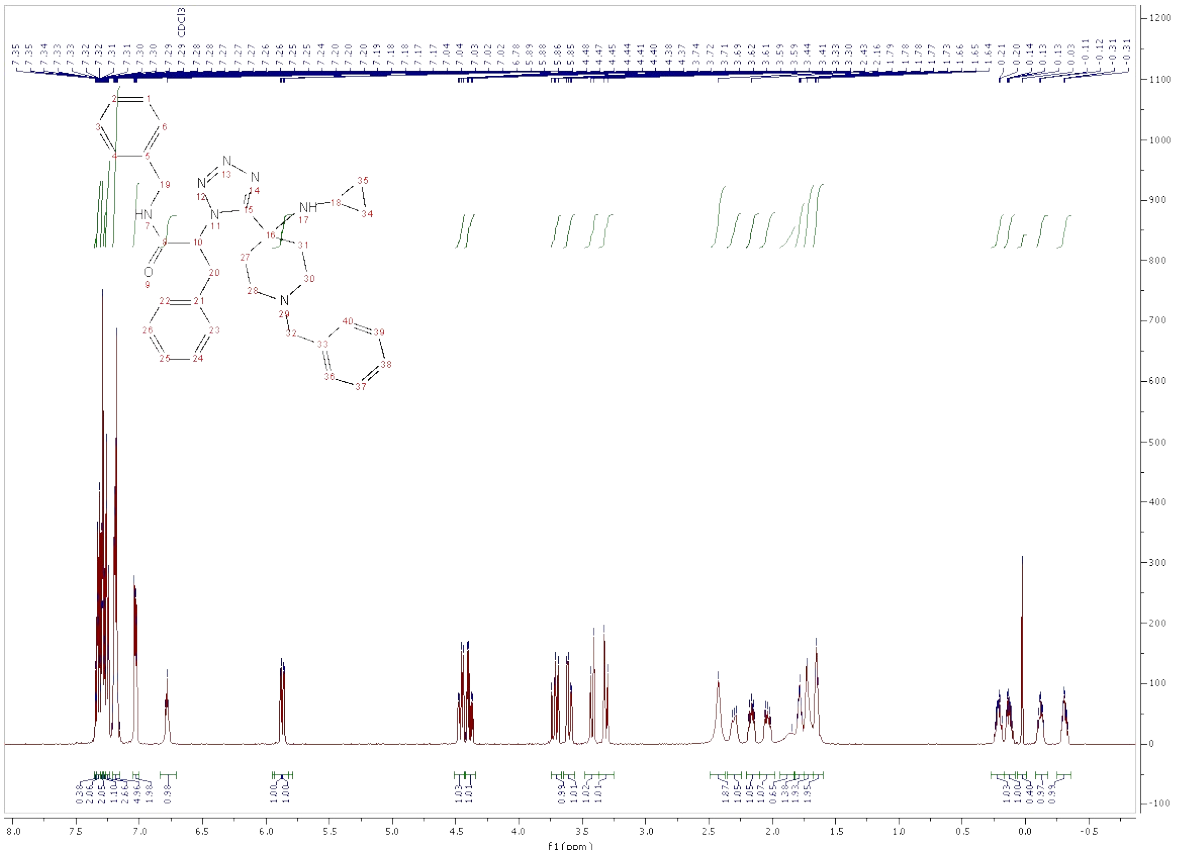


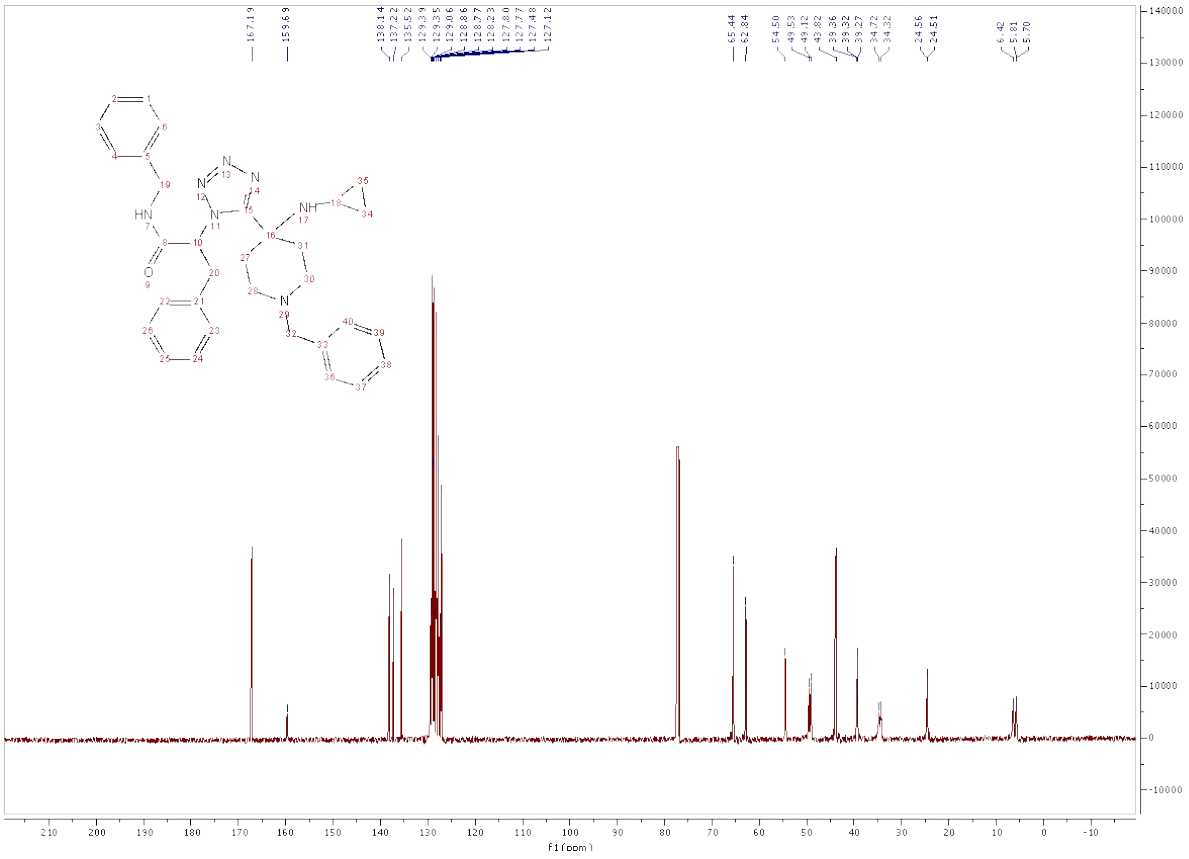
Compound 7e:



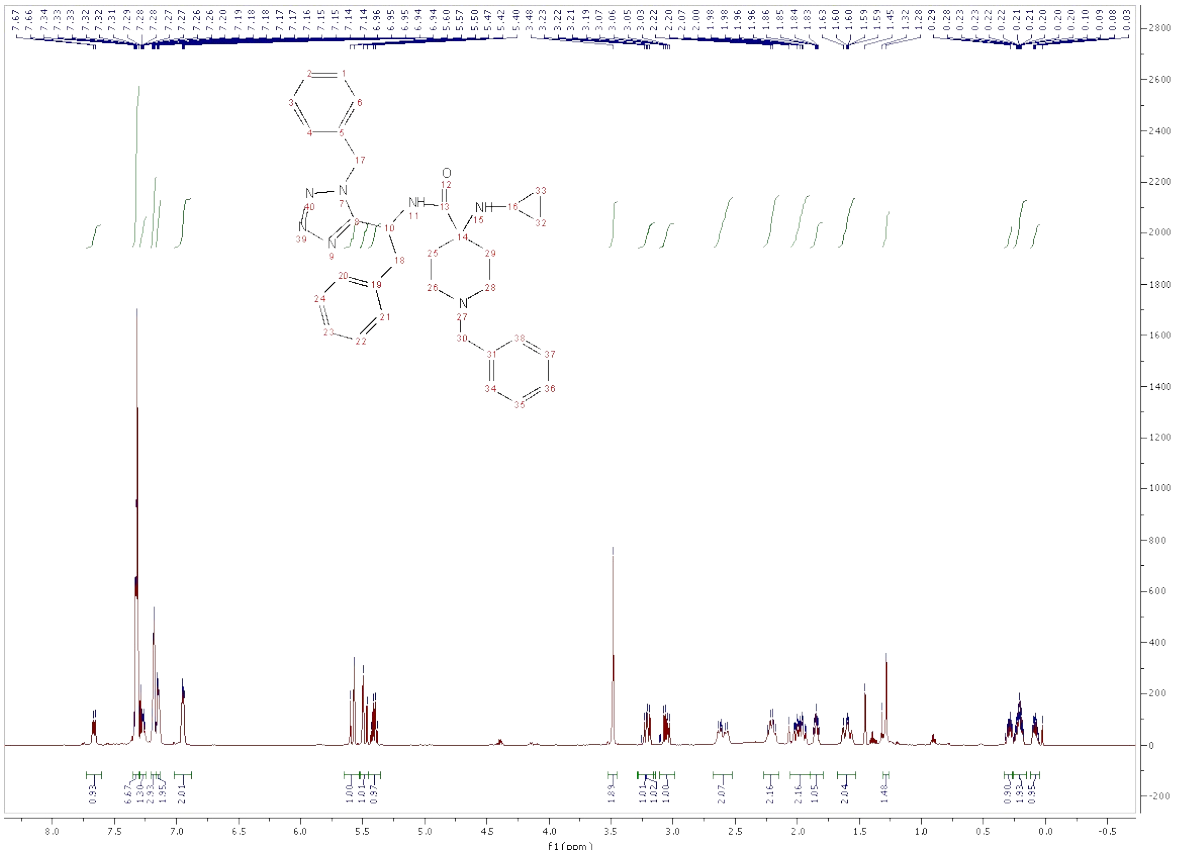


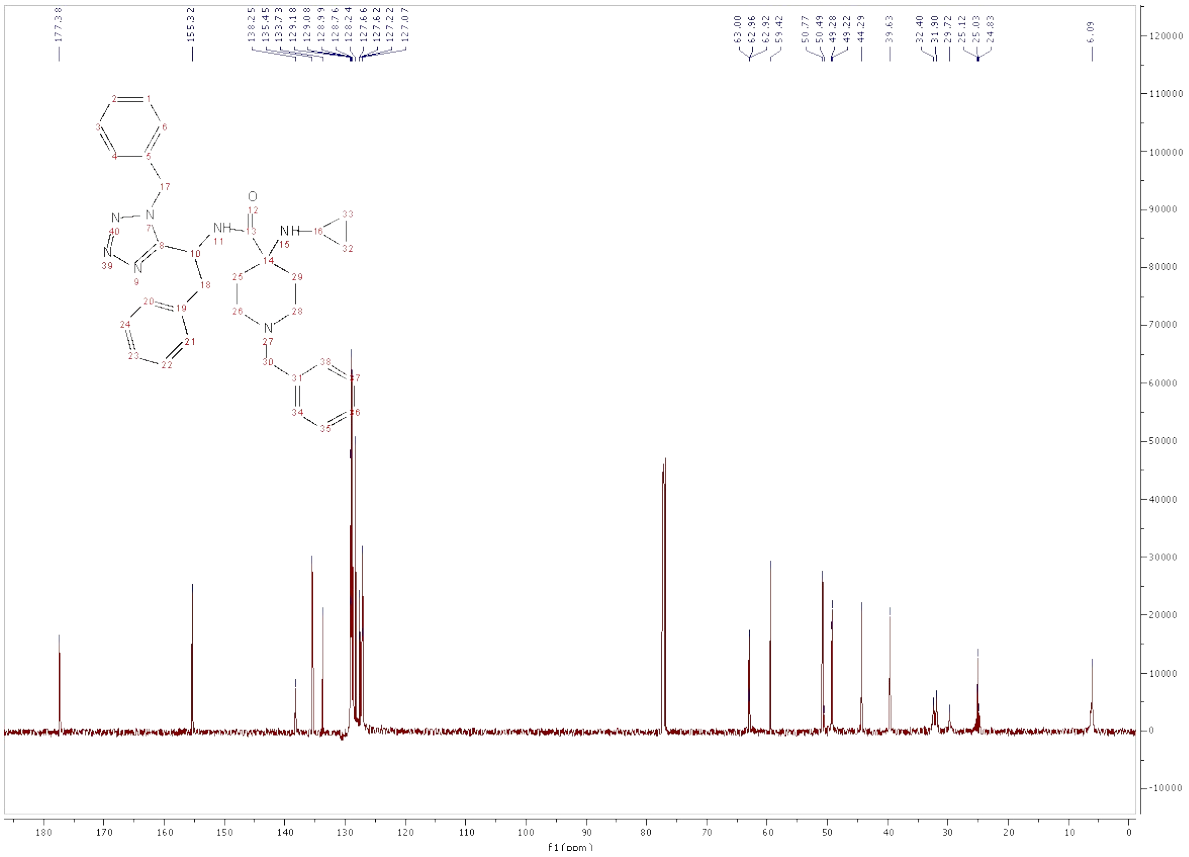
Compound 6f:



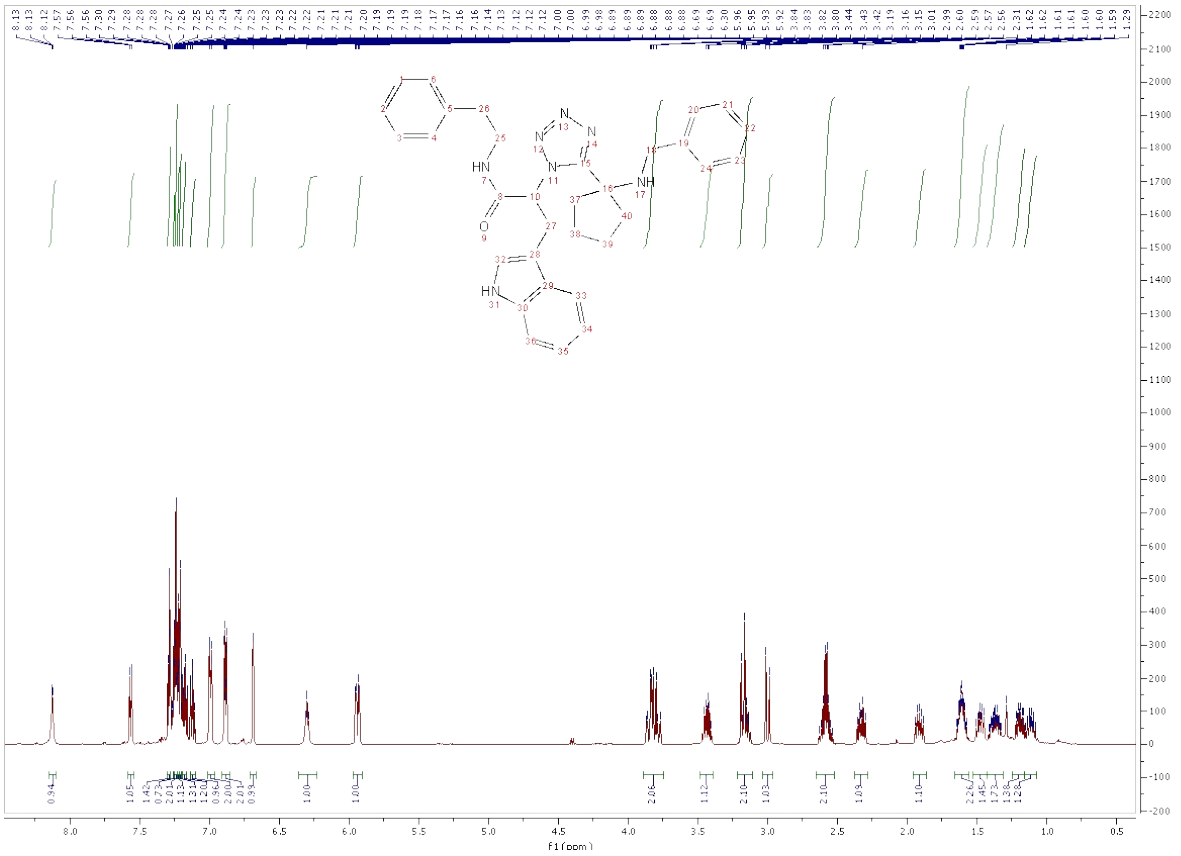


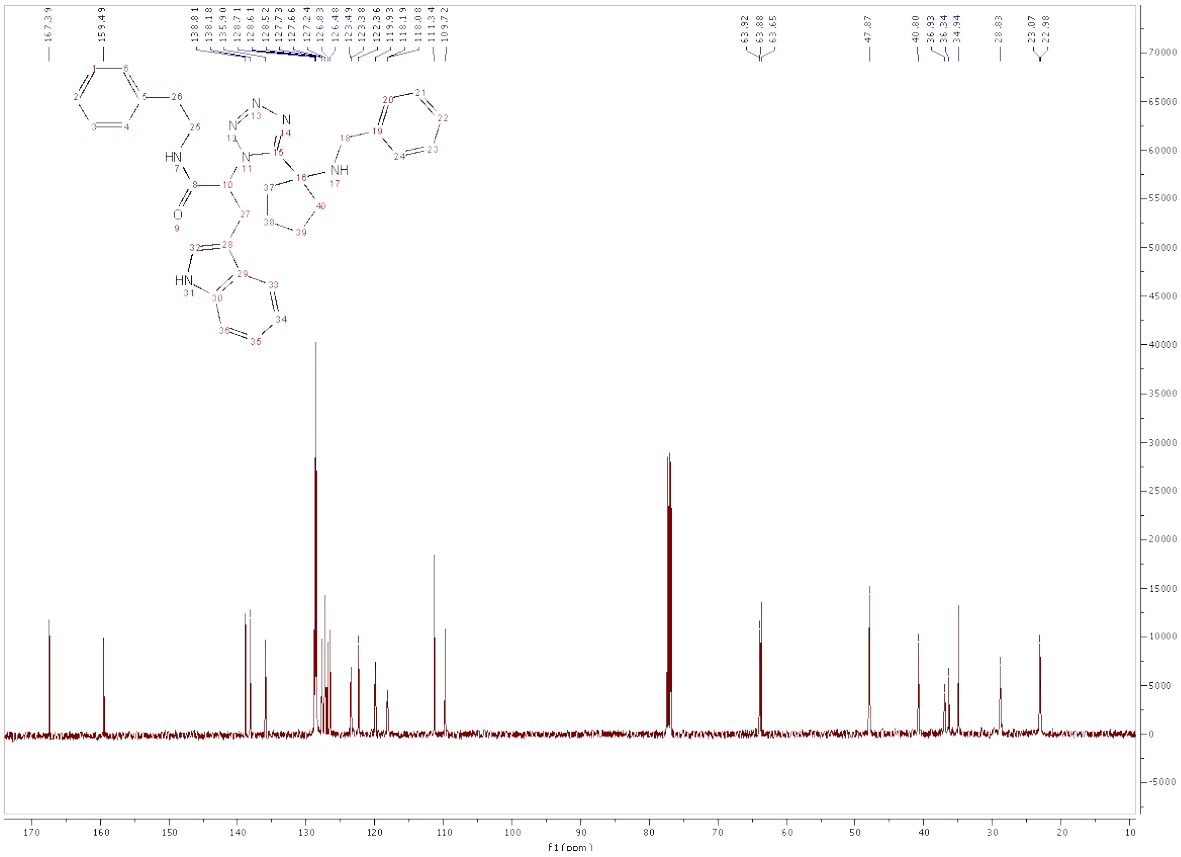
Compound 7f:



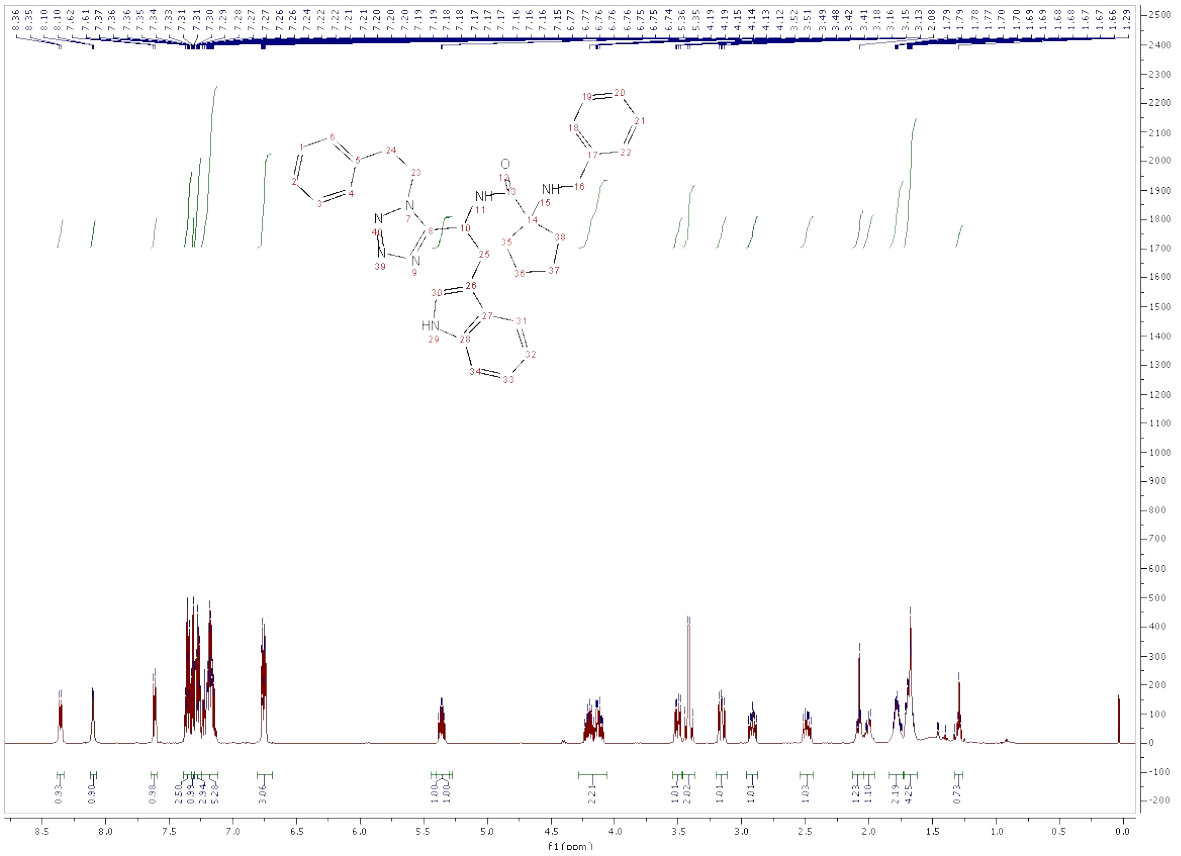


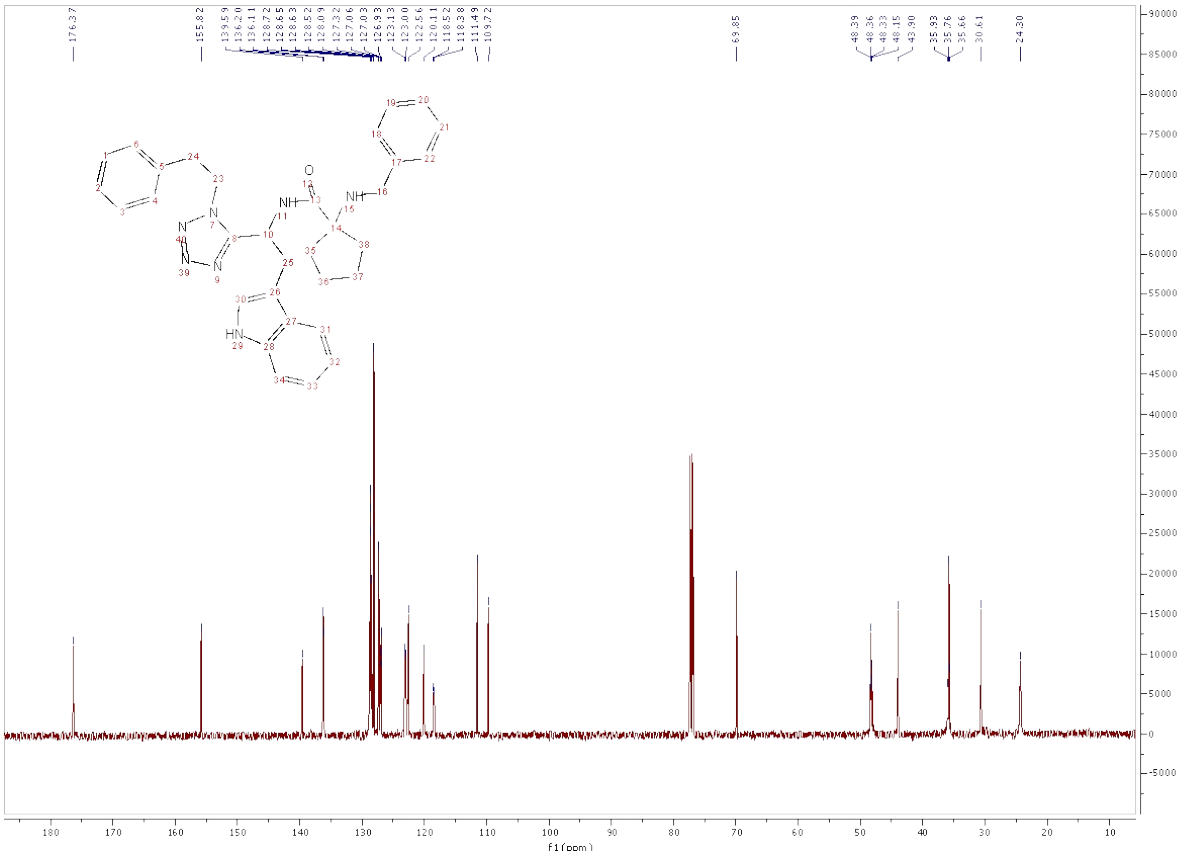
Compound 6g:



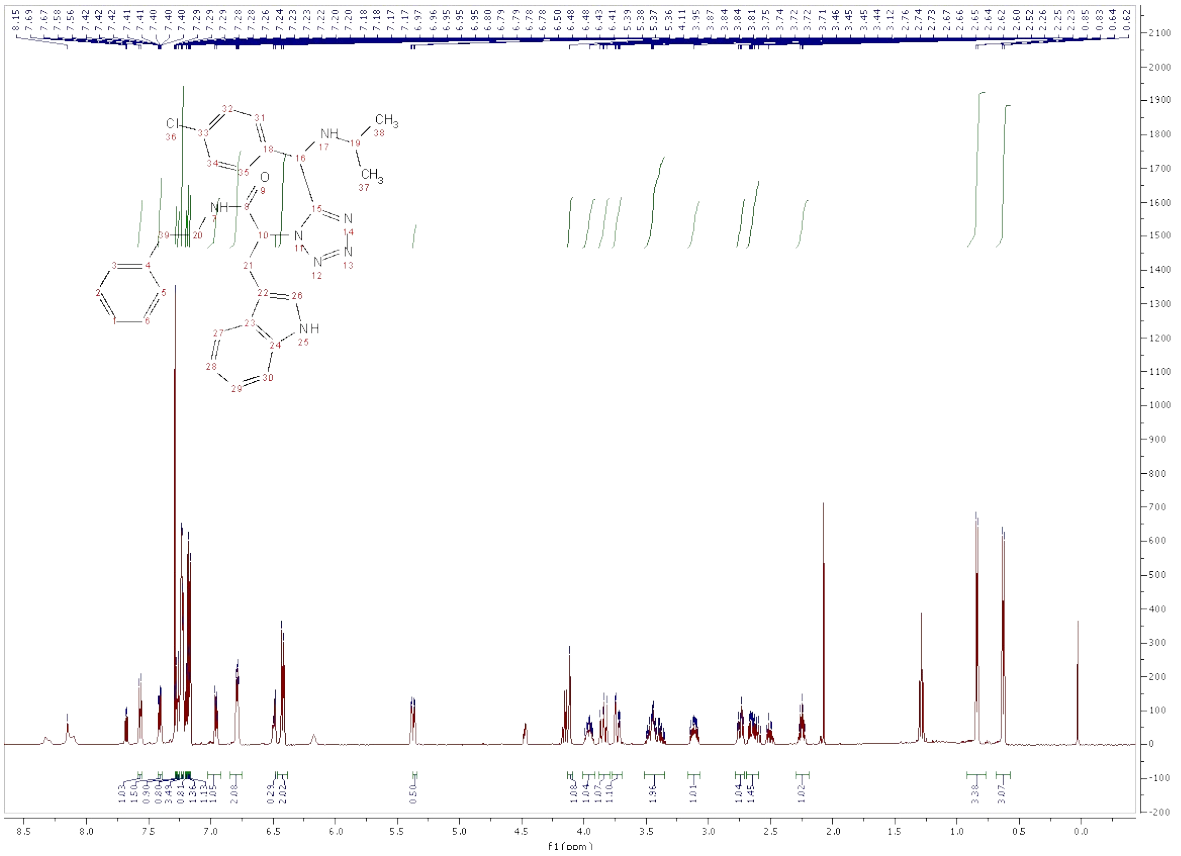


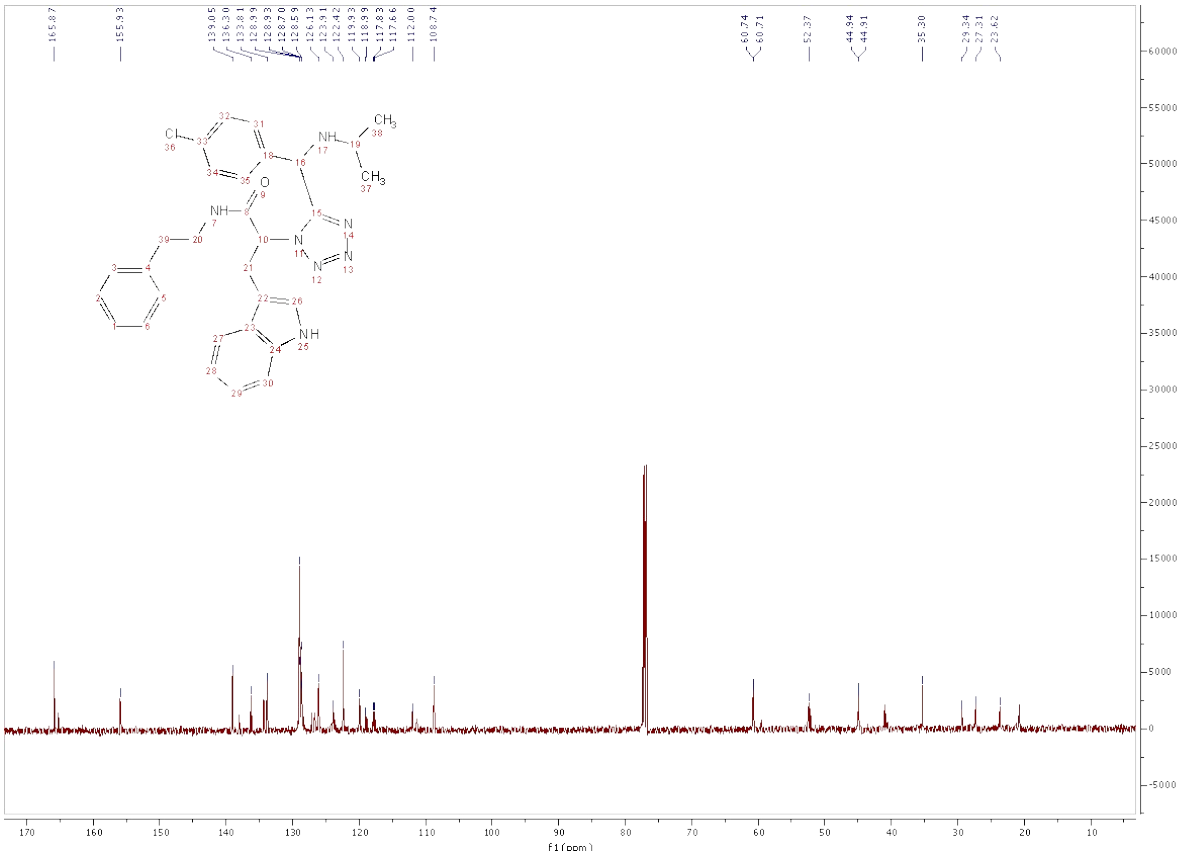
Compound 7g:



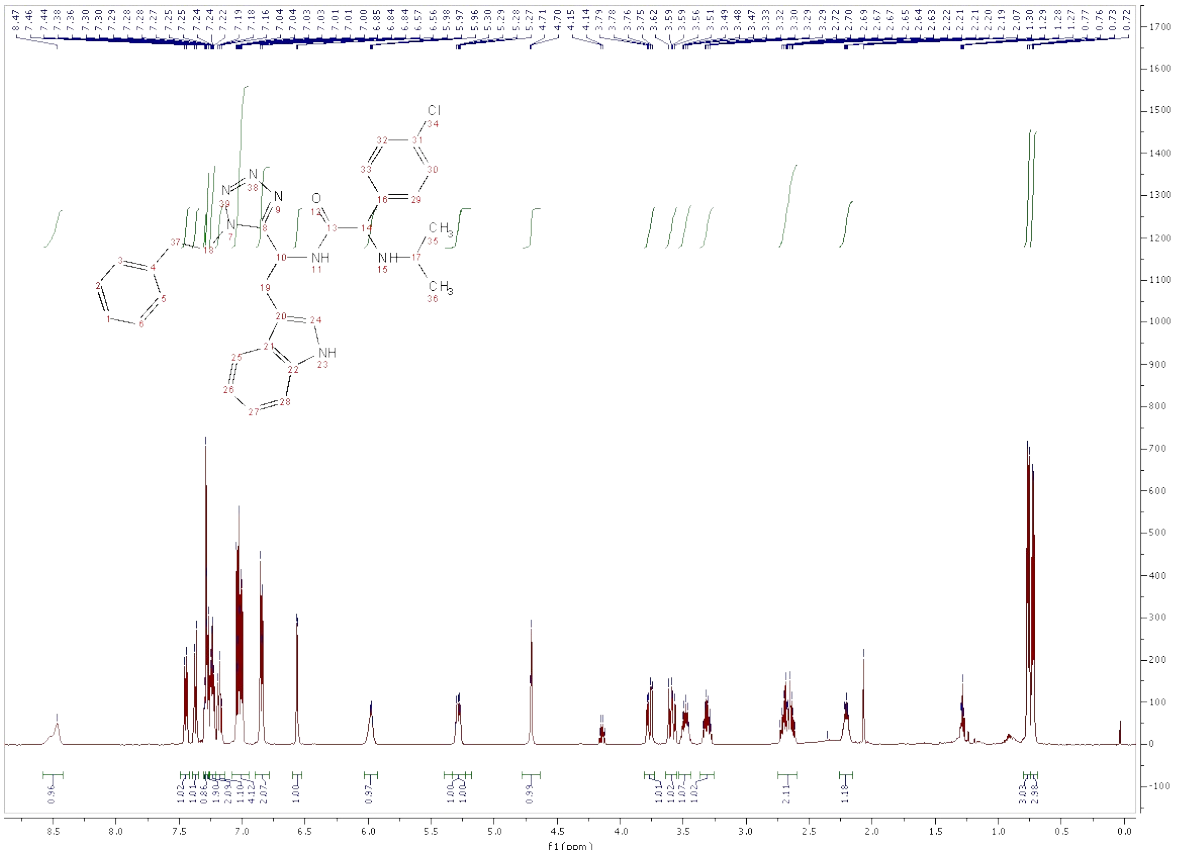


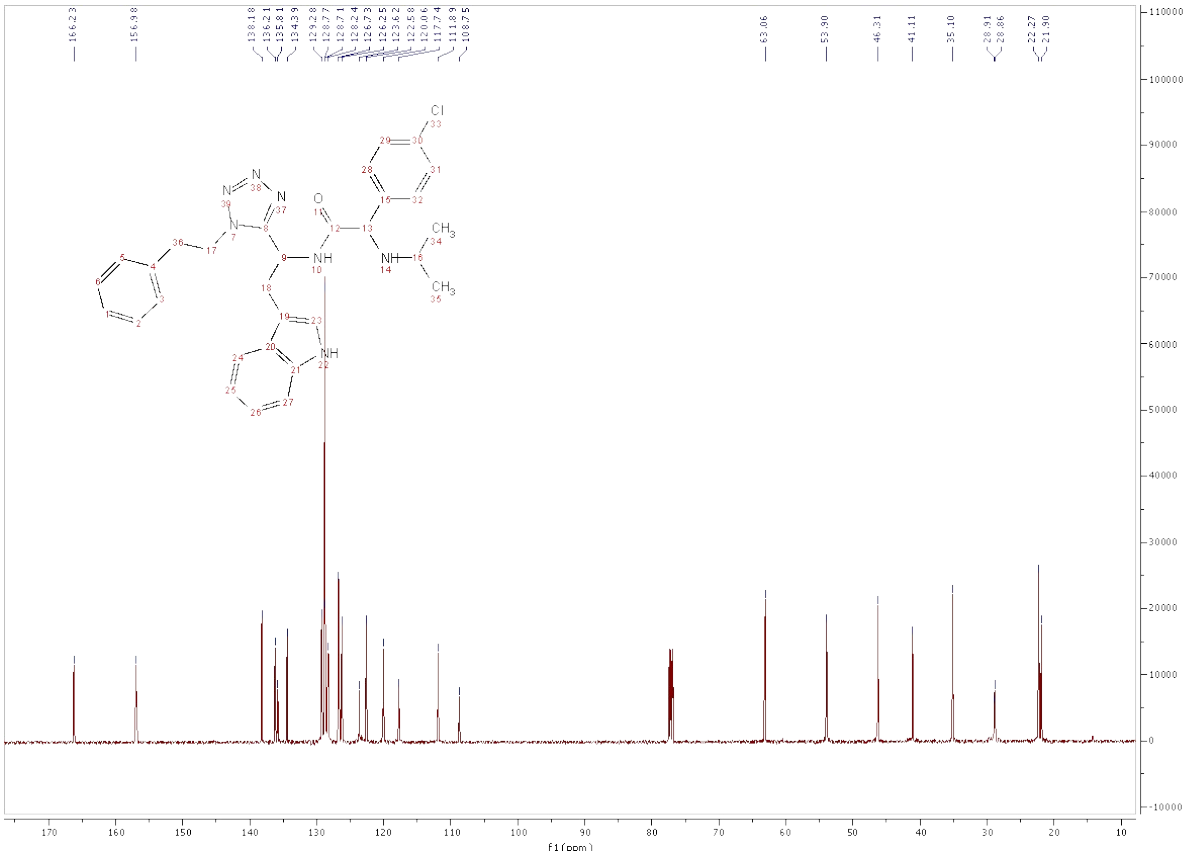
Compound 6h:



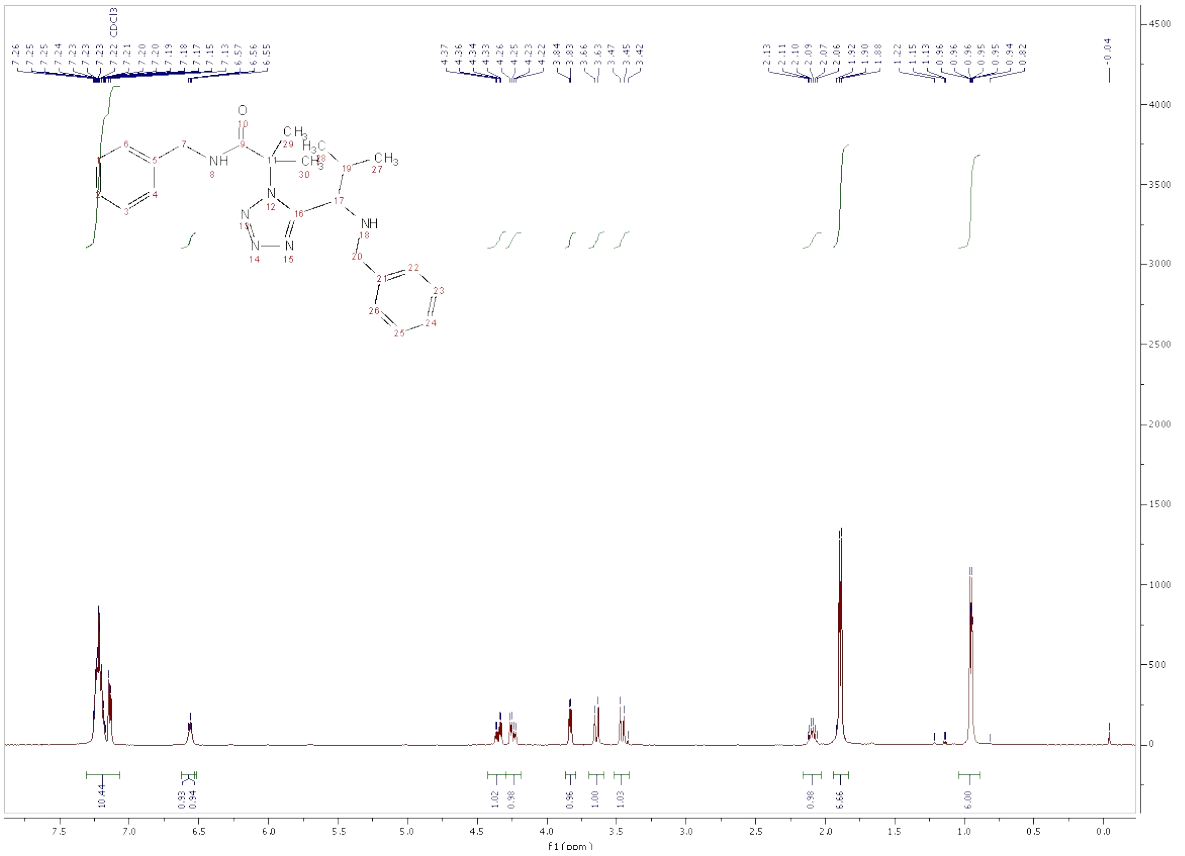


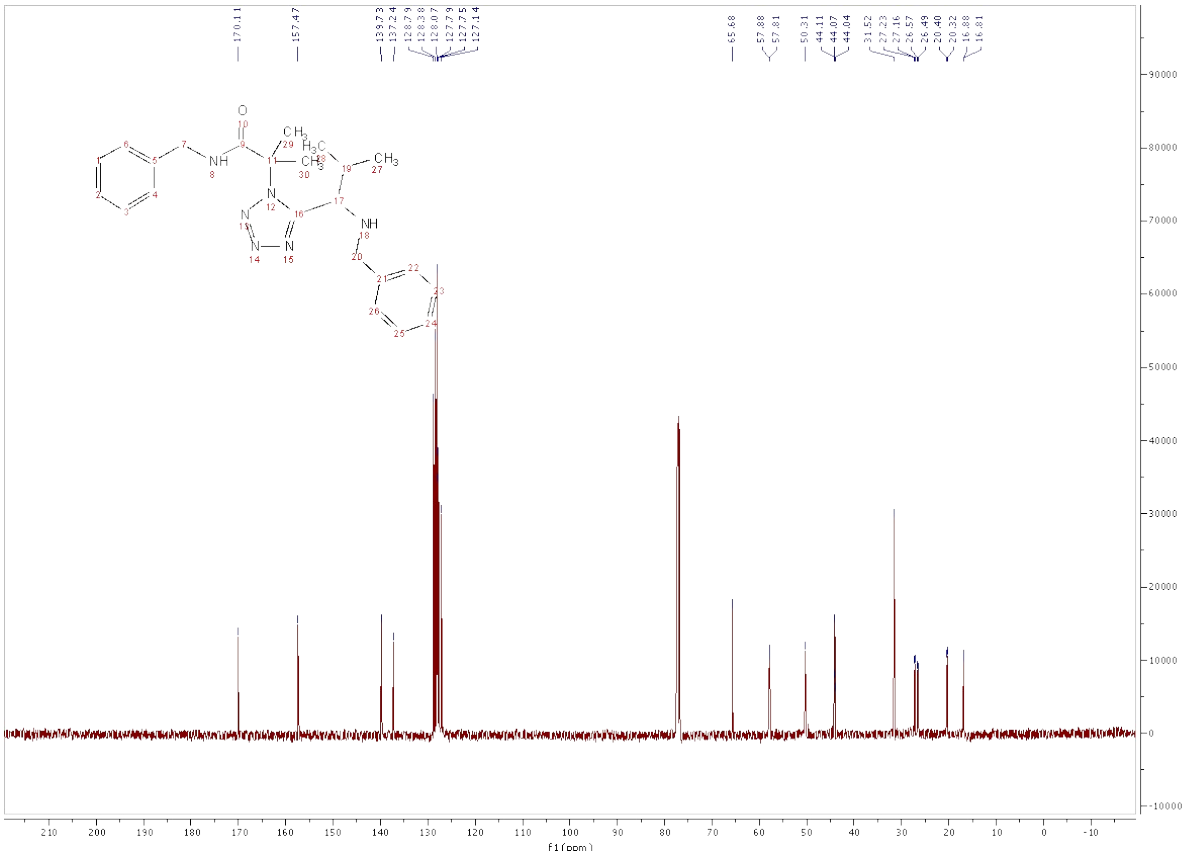
Compound 7h:

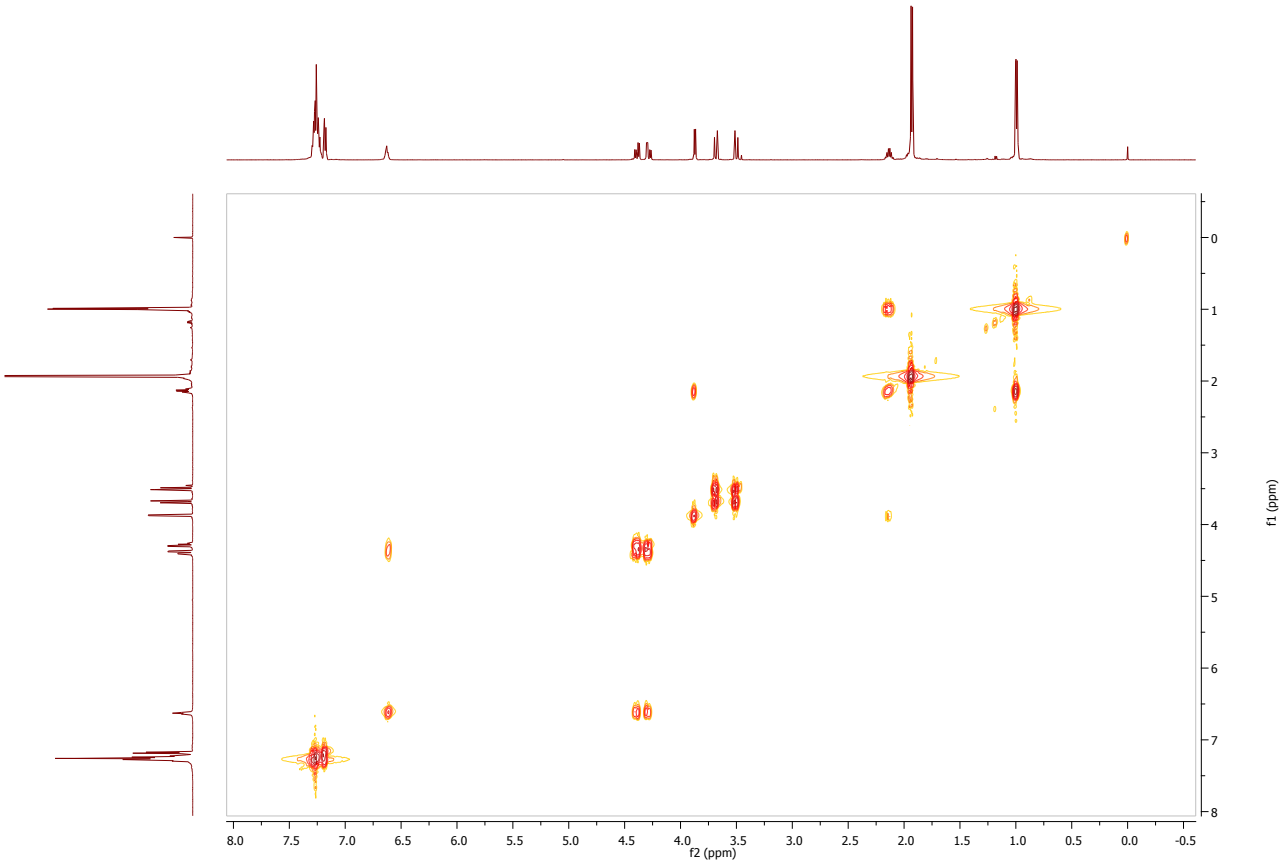




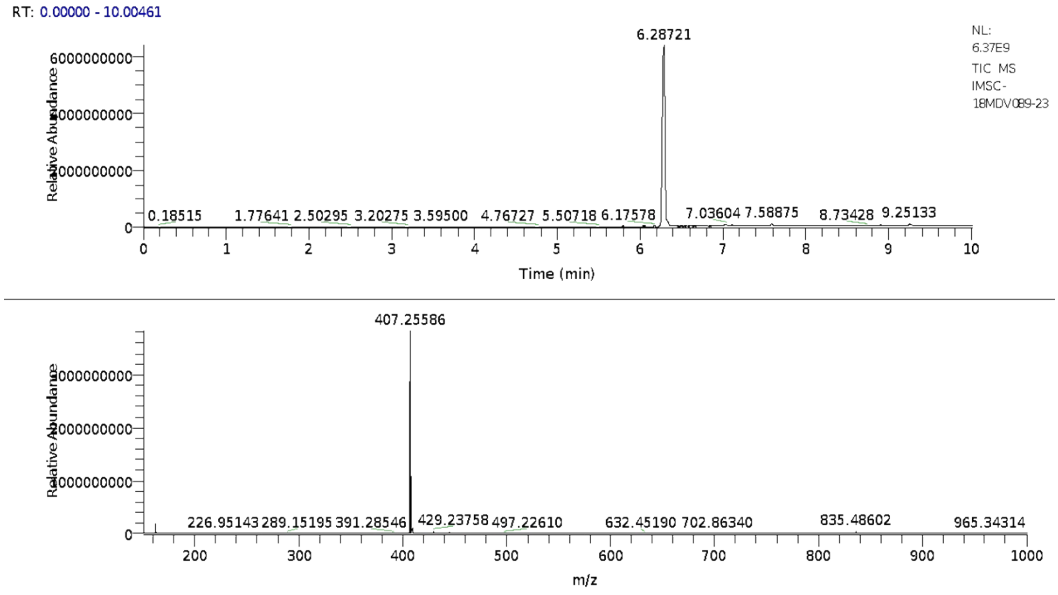
Compound 6i:



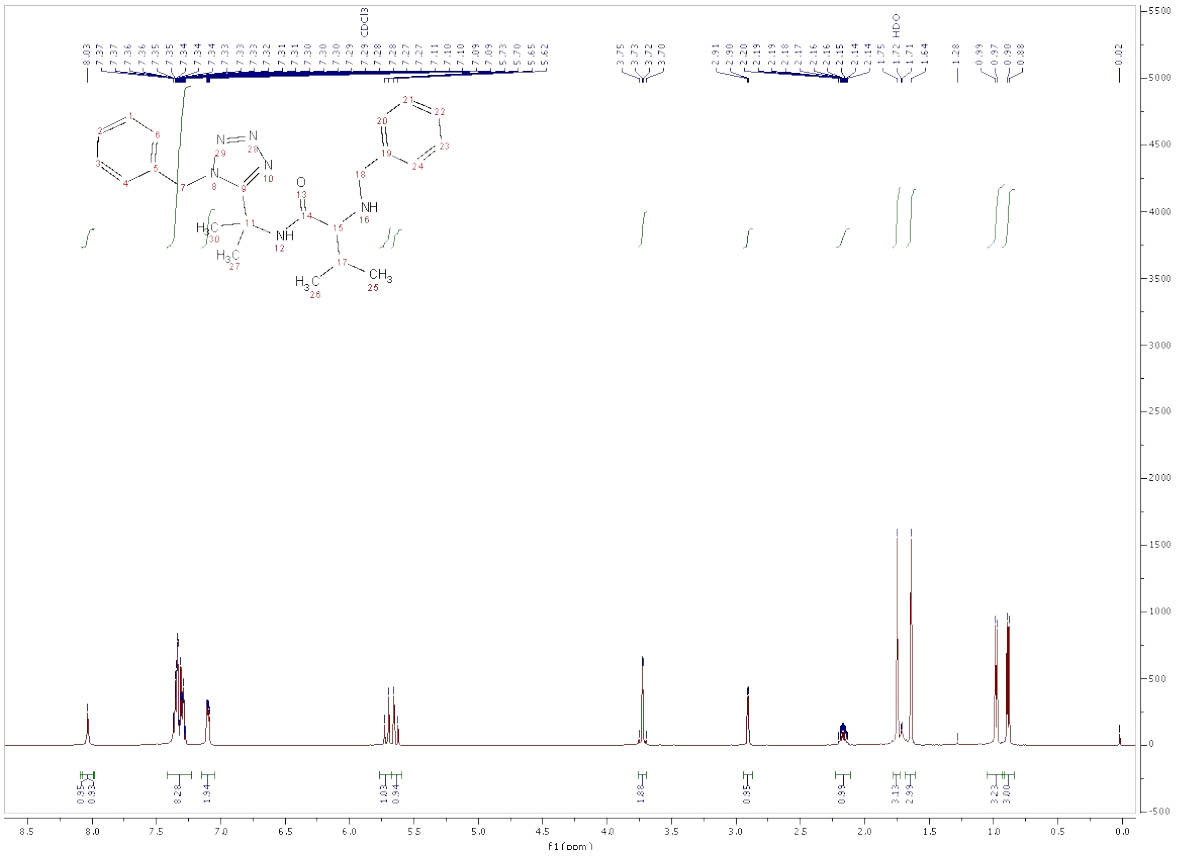


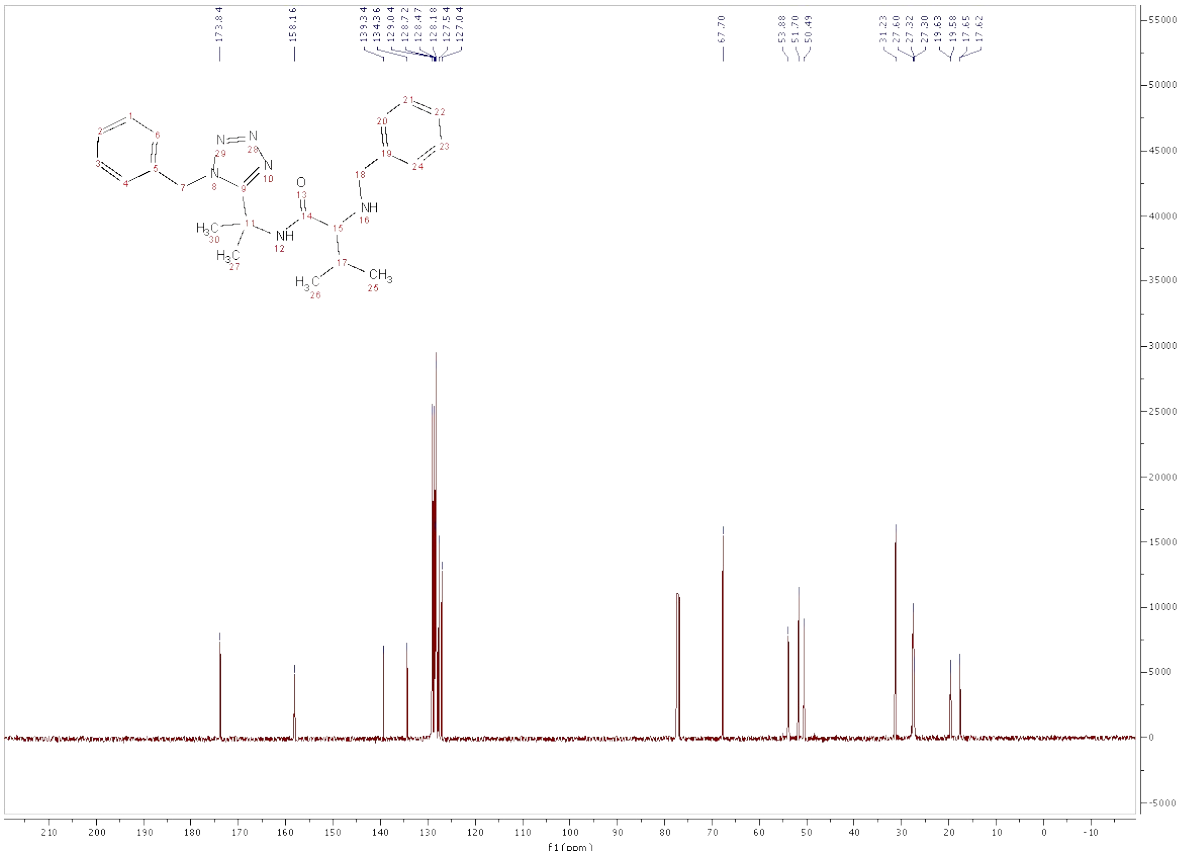


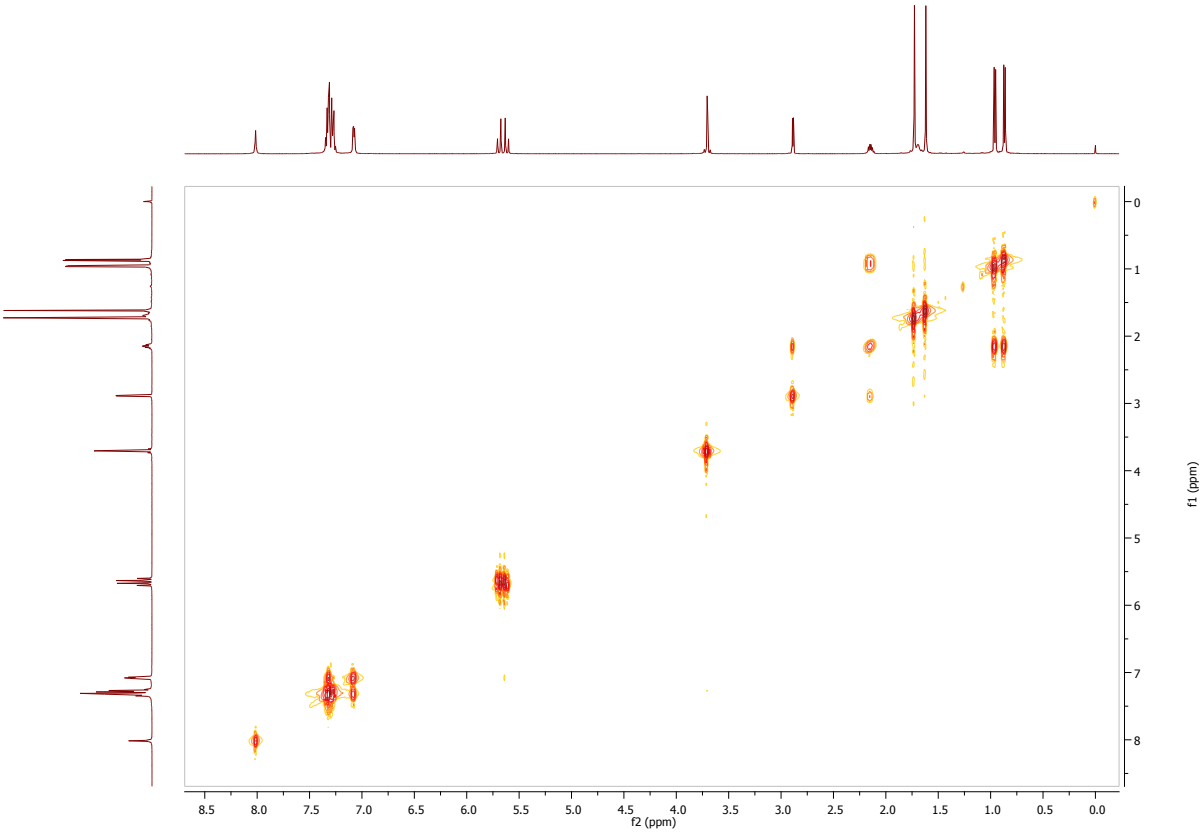
IMSC-18MDV089-23 03/15/18 17:06:27

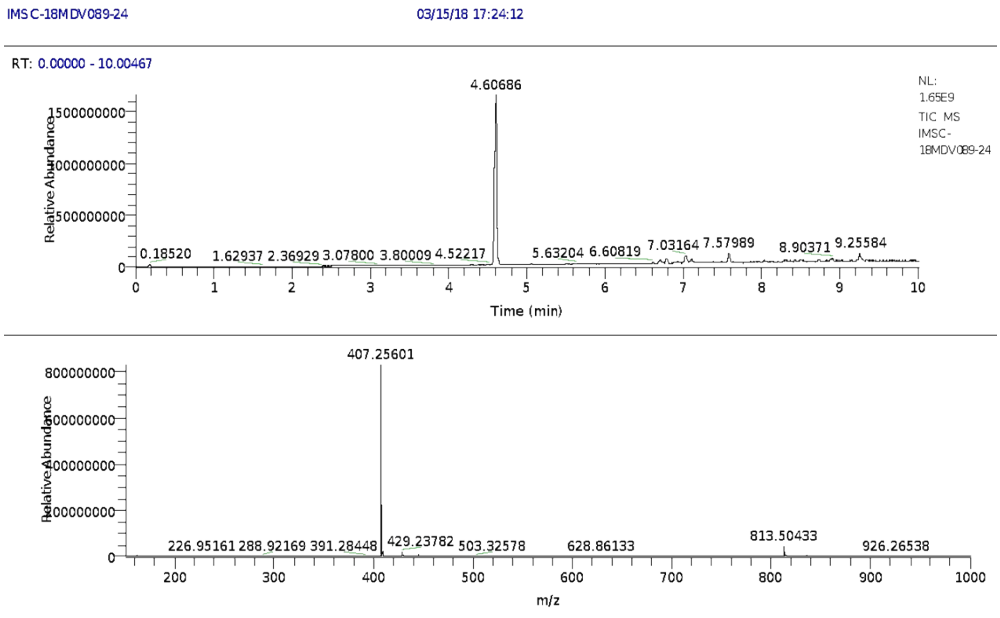


Compound 7i:

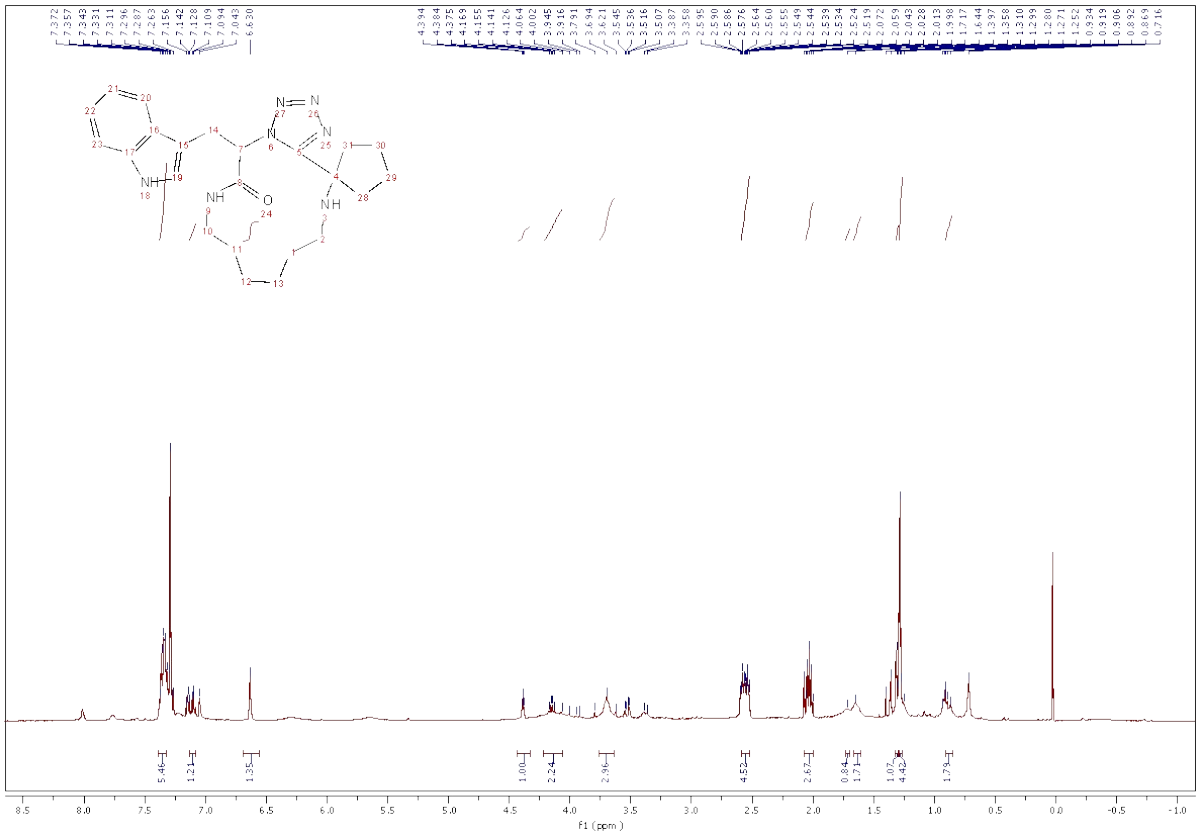




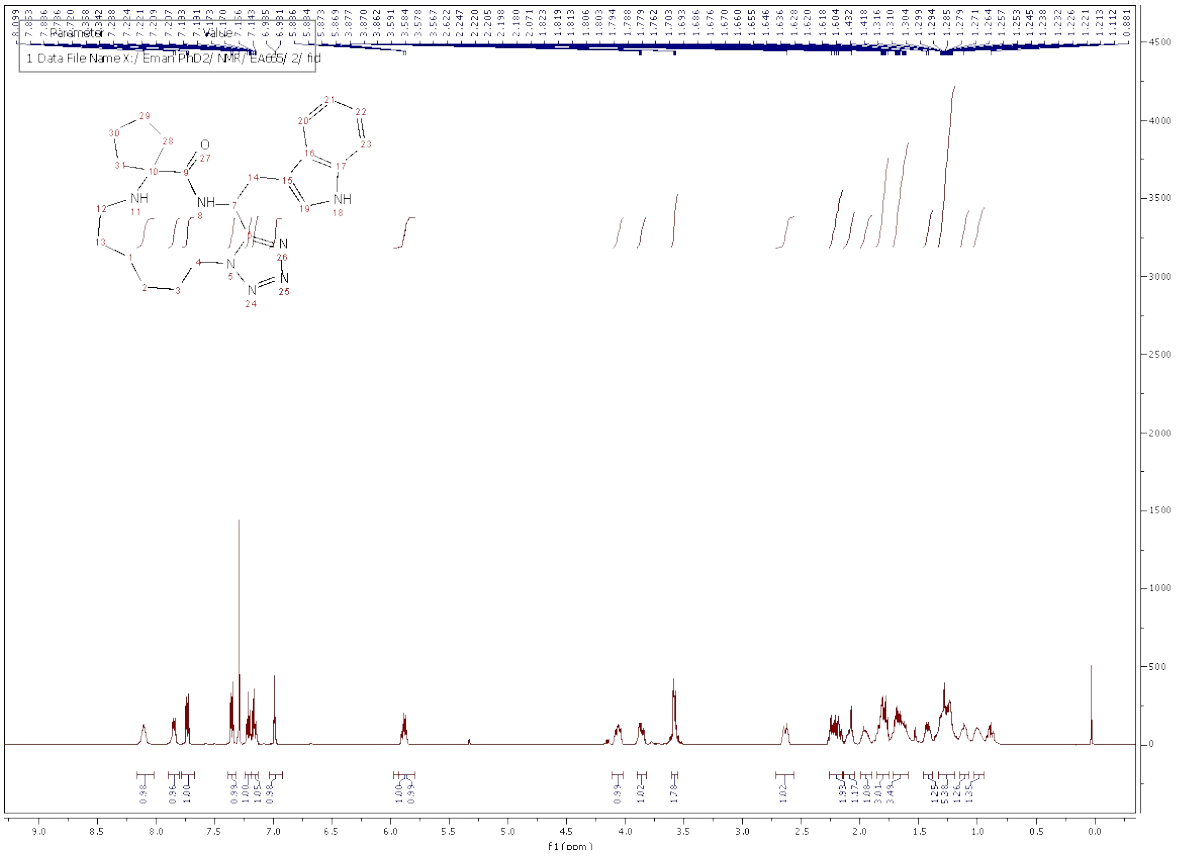

f2 (ppm)
f1 (ppm)

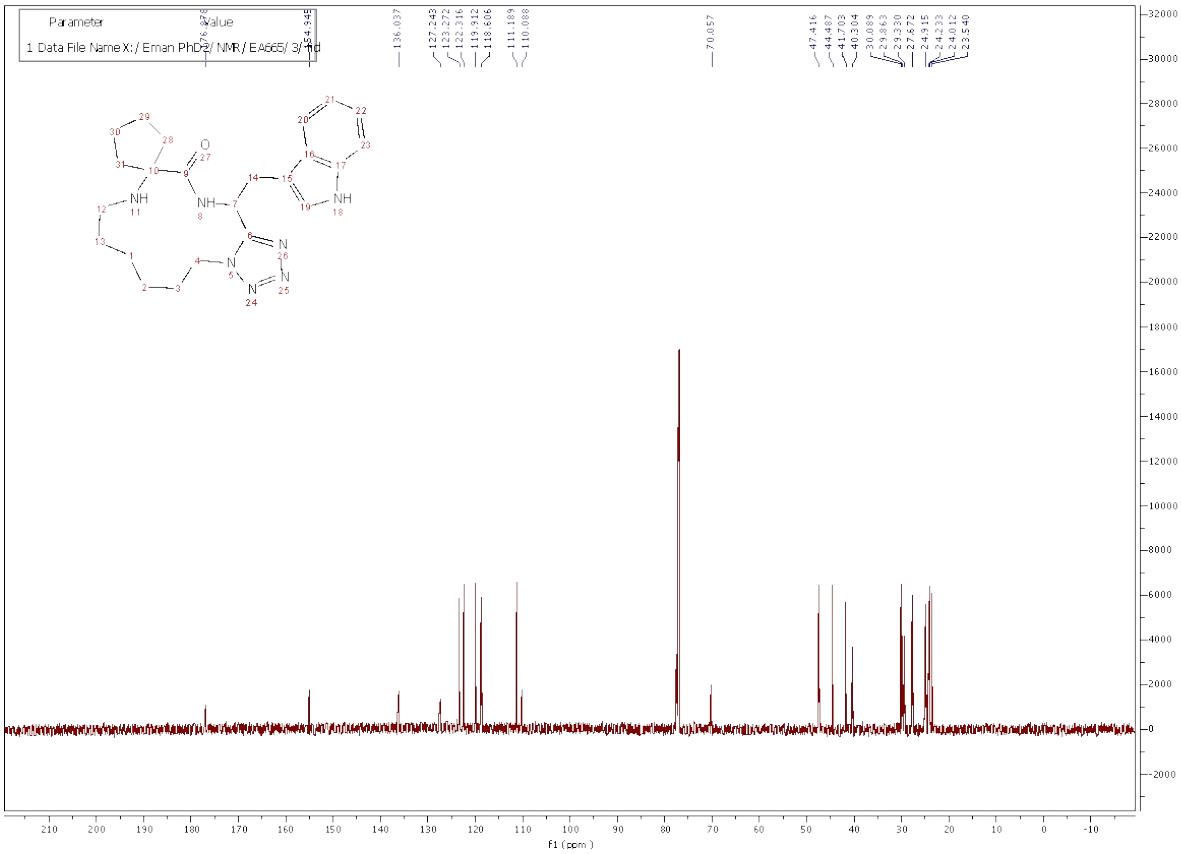

IMSC-18MDV089-24
03/15/18 17:24:12
RT: 0.00000 - 10.00467
NL:
1.65E9
TIC MS
IMSC-
18MDV089-24
Relative Abundance
Time (min)
4.60686
0.18520
1.62937
2.36929
3.07800
3.80009
4.52217
5.63204
6.60819
7.03164
7.57989
8.90371
9.25584
407.25601
226.95161
288.92169
391.28448
429.23782
503.32578
628.86133
813.50433
926.26538
m/z

Compound 6j:

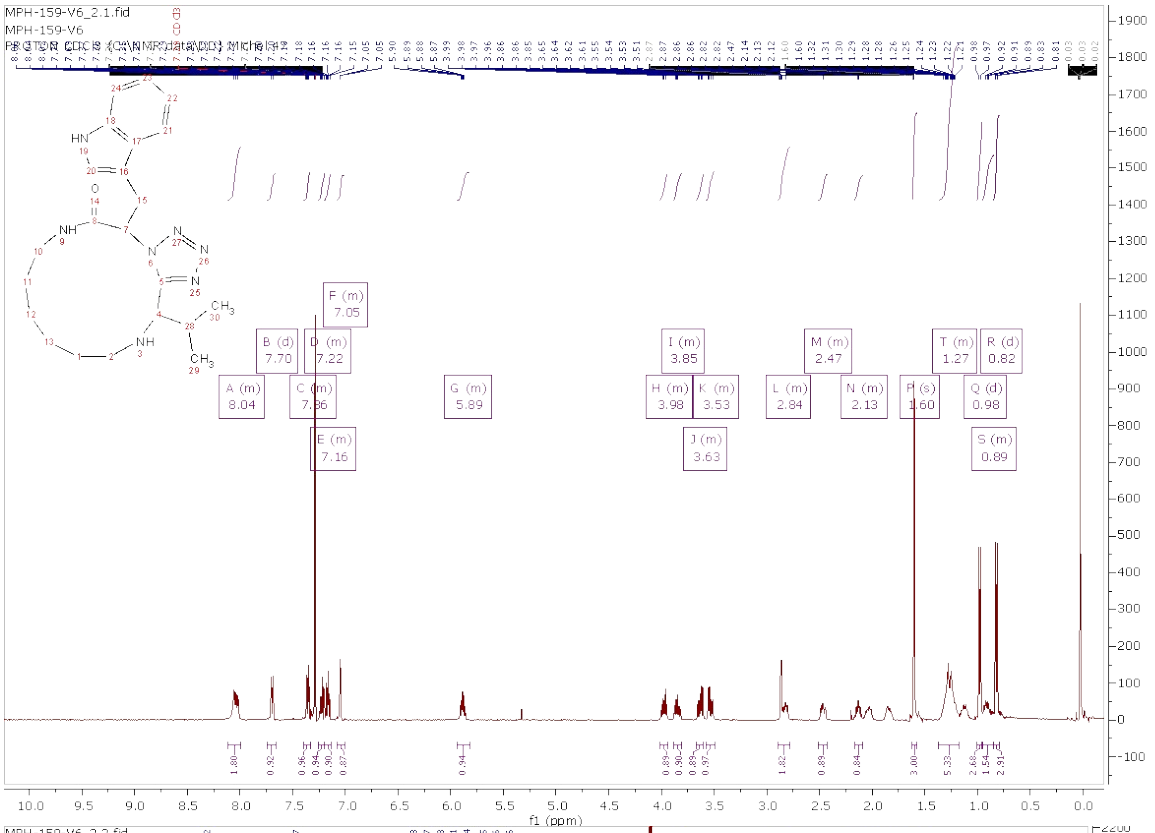


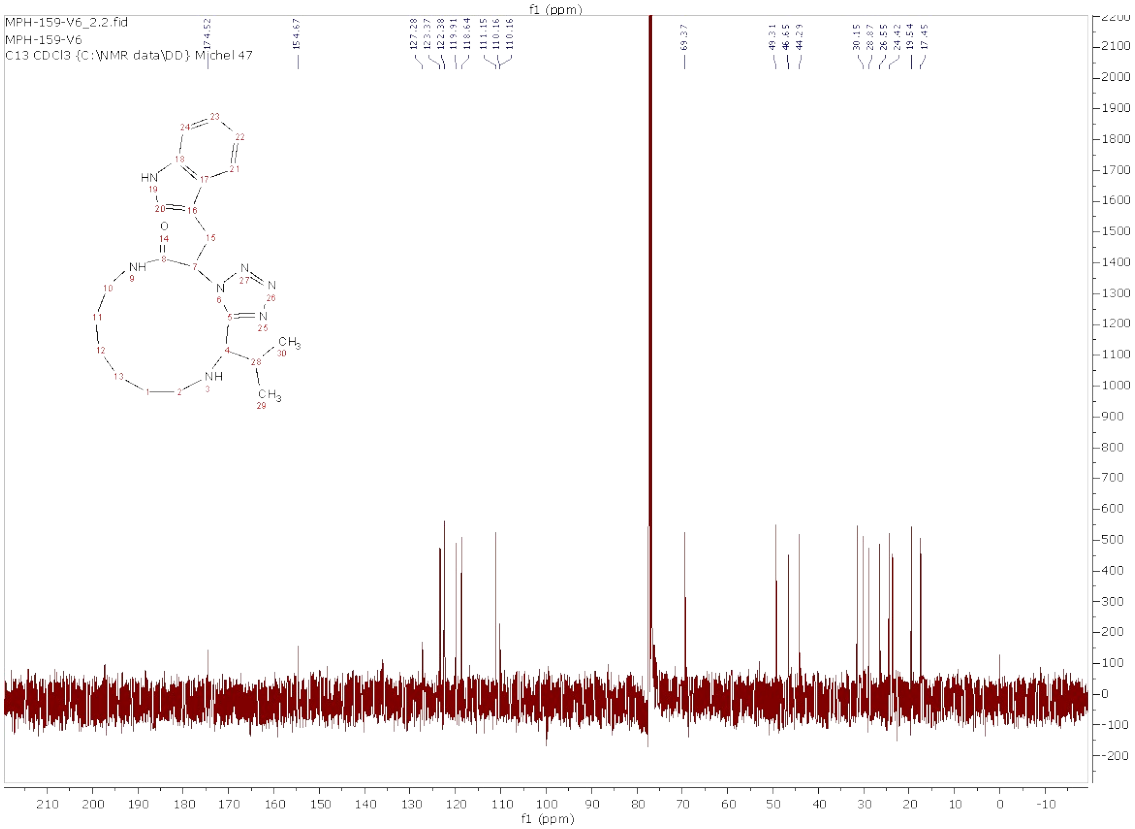
Compound 7j:


Parameter
Value
1 Data File Name X:/ Eman PhD2/ NMR/ EA665/ 2/ fid
f1 (ppm)

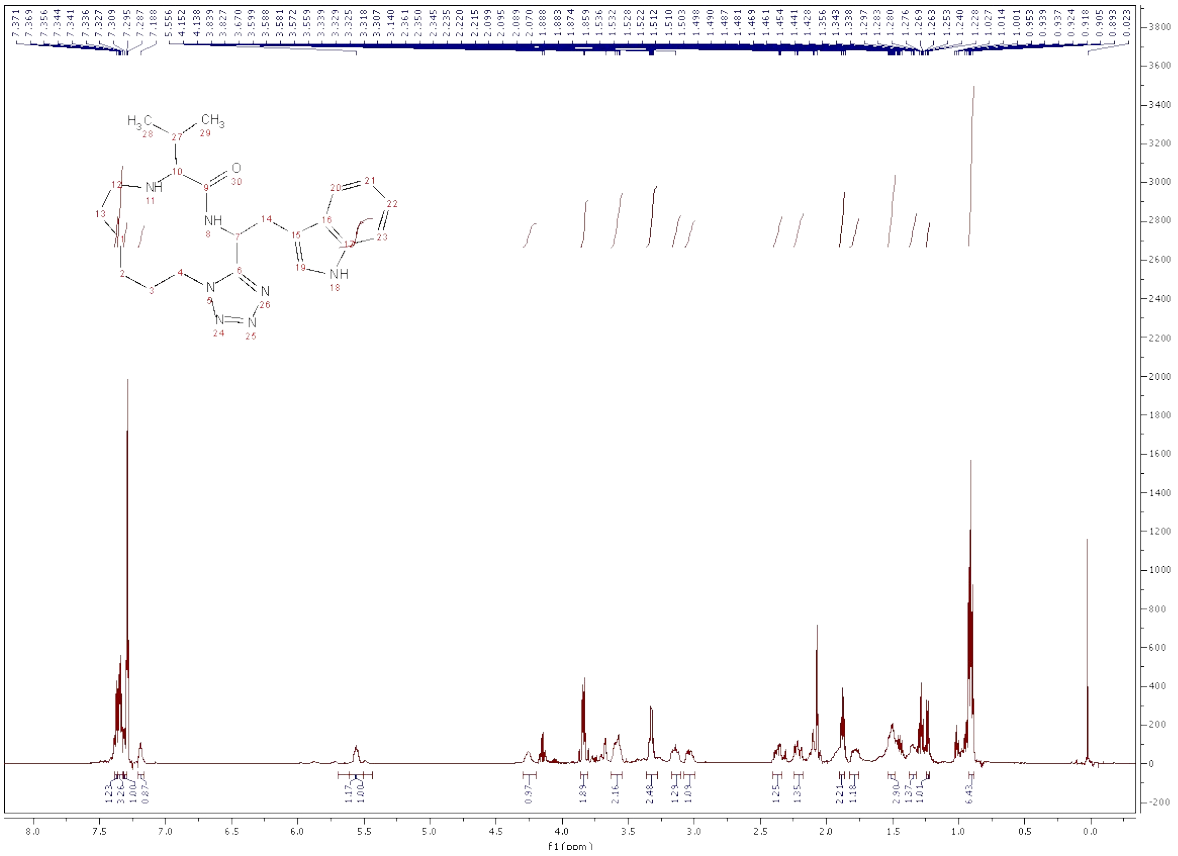

Parameter
Value
1 Data File Name X:/ Eman PhD2/ NMR/ EA665/ 3/ fid
f1 (ppm)

Compound 6k:

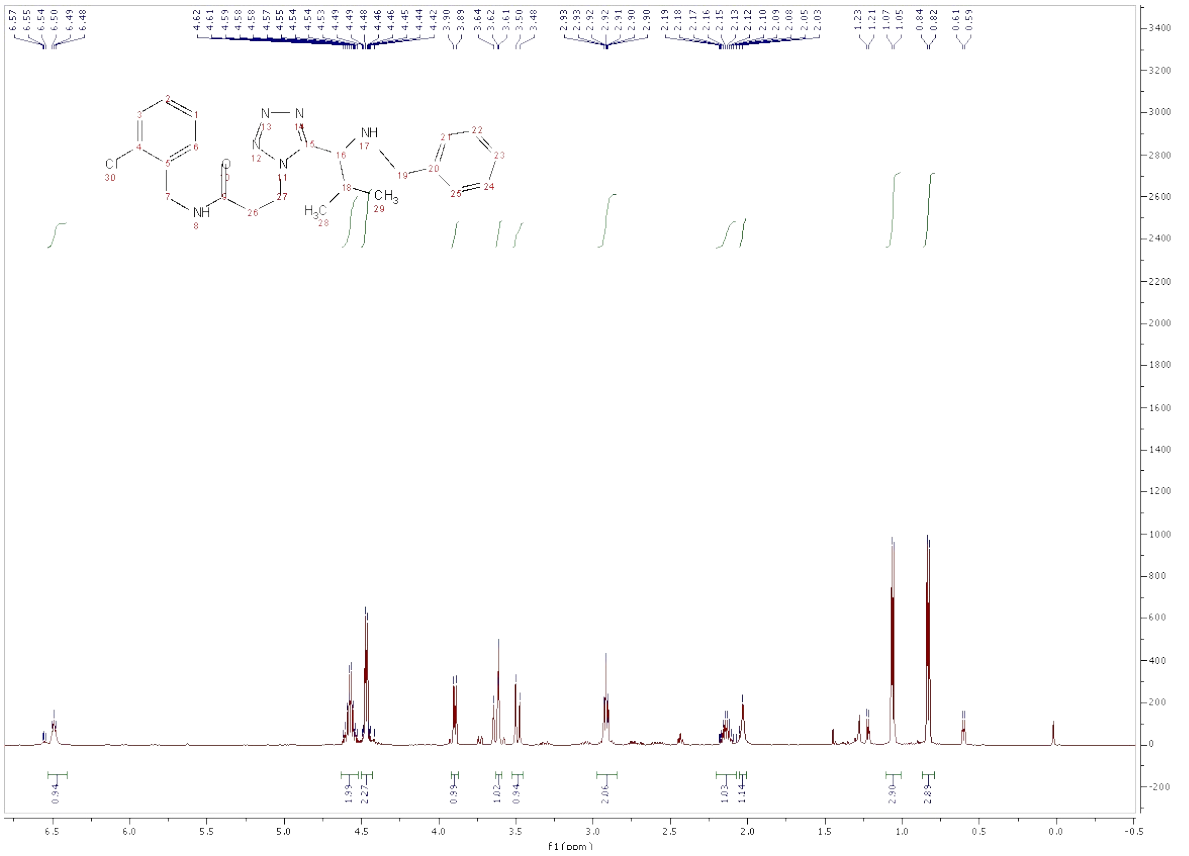

MPH-159-V6_2.1.fid
MPH-159-V6
A (m) 8.04
B (d) 7.70
C (m) 7.36
D (m) 7.22
E (m) 7.16
F (m) 7.05
G (m) 5.89
H (m) 3.98
I (m) 3.85
J (m) 3.63
K (m) 3.53
L (m) 2.84
M (m) 2.47
N (m) 2.13
P (s) 1.60
Q (d) 0.98
R (d) 0.82
S (m) 0.89
f1 (ppm)

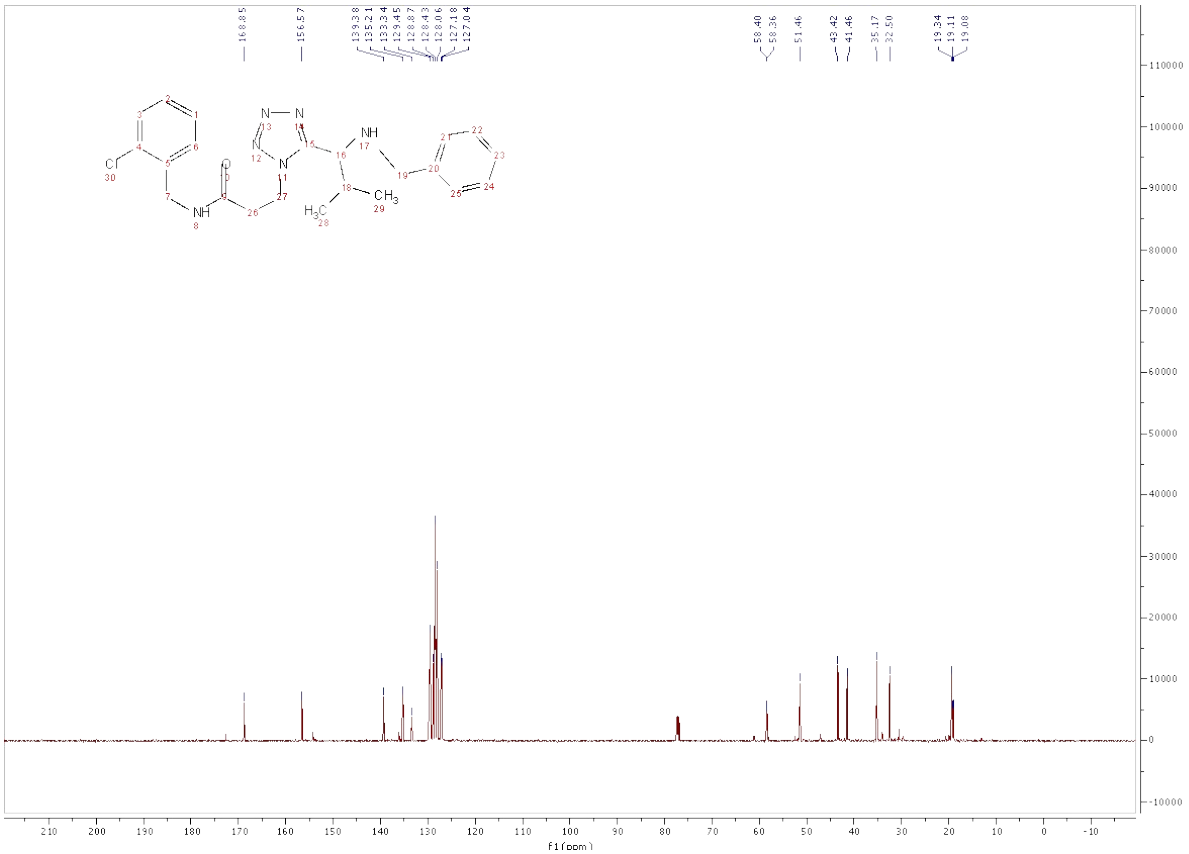

MPH-159-V6_2.2.fid
MPH-159-V6
C13 CDCl3 {C:\NMR data\DD} Michel 47
f1 (ppm)

Compound 7k:

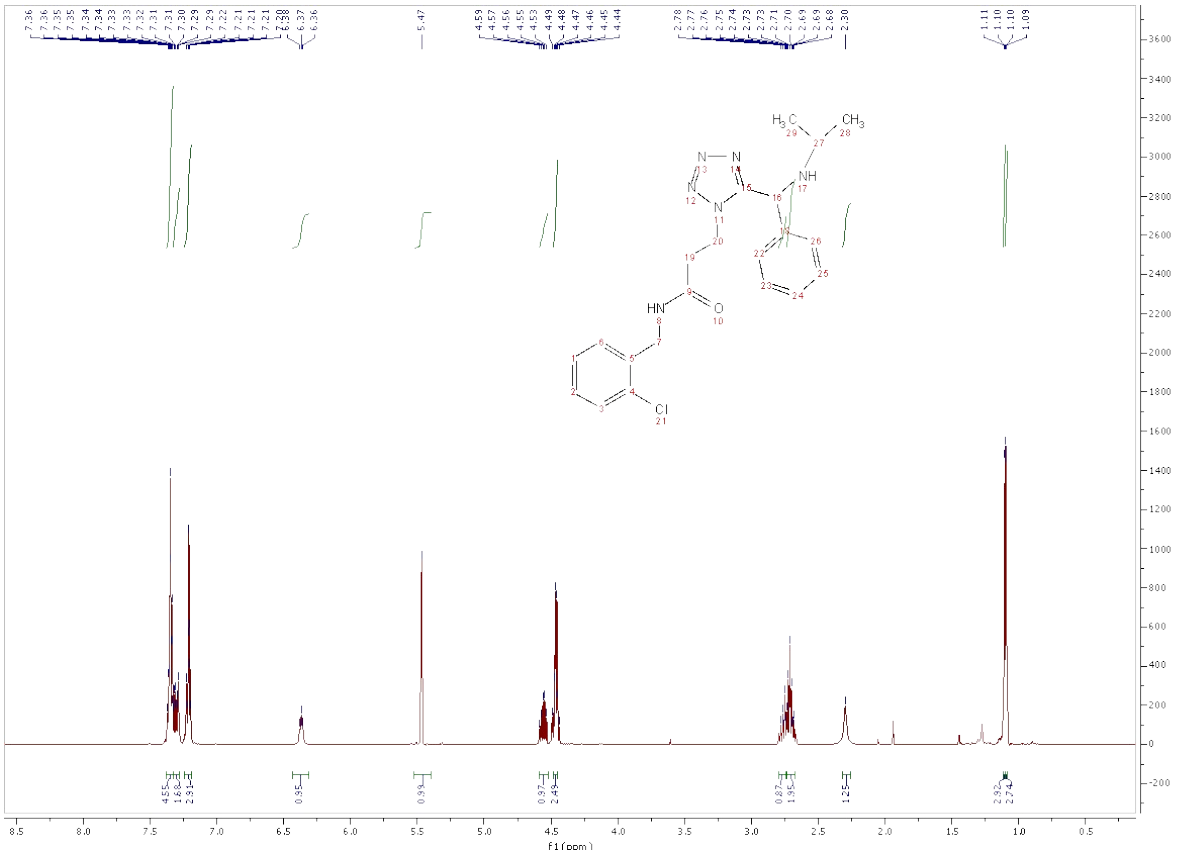


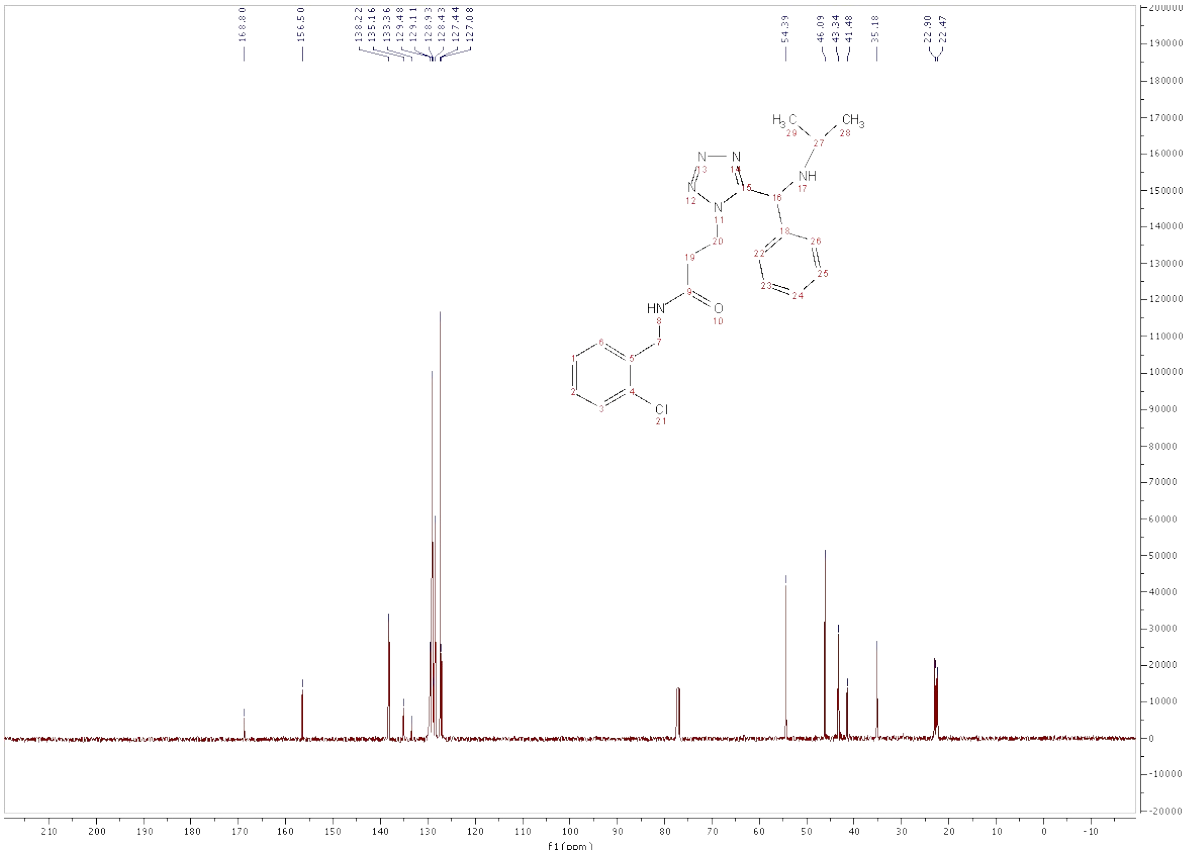
Compound 6l:



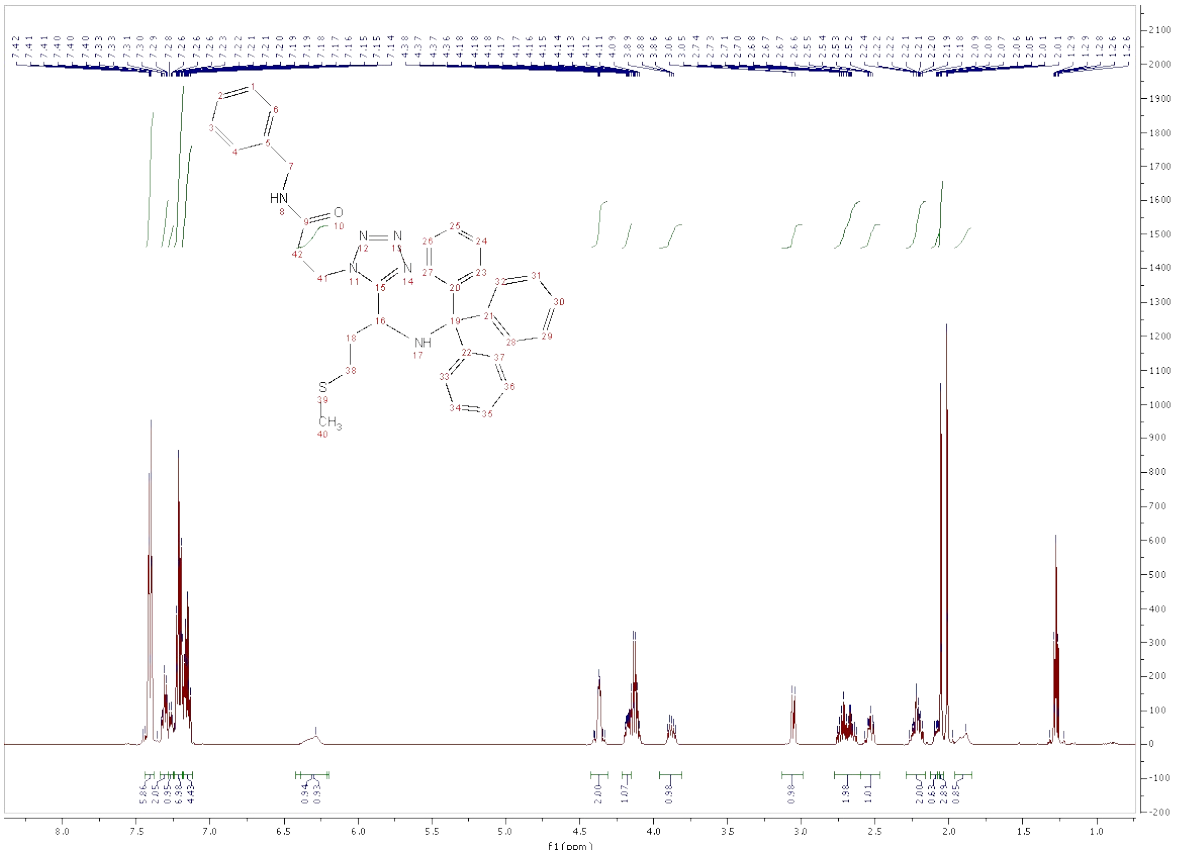


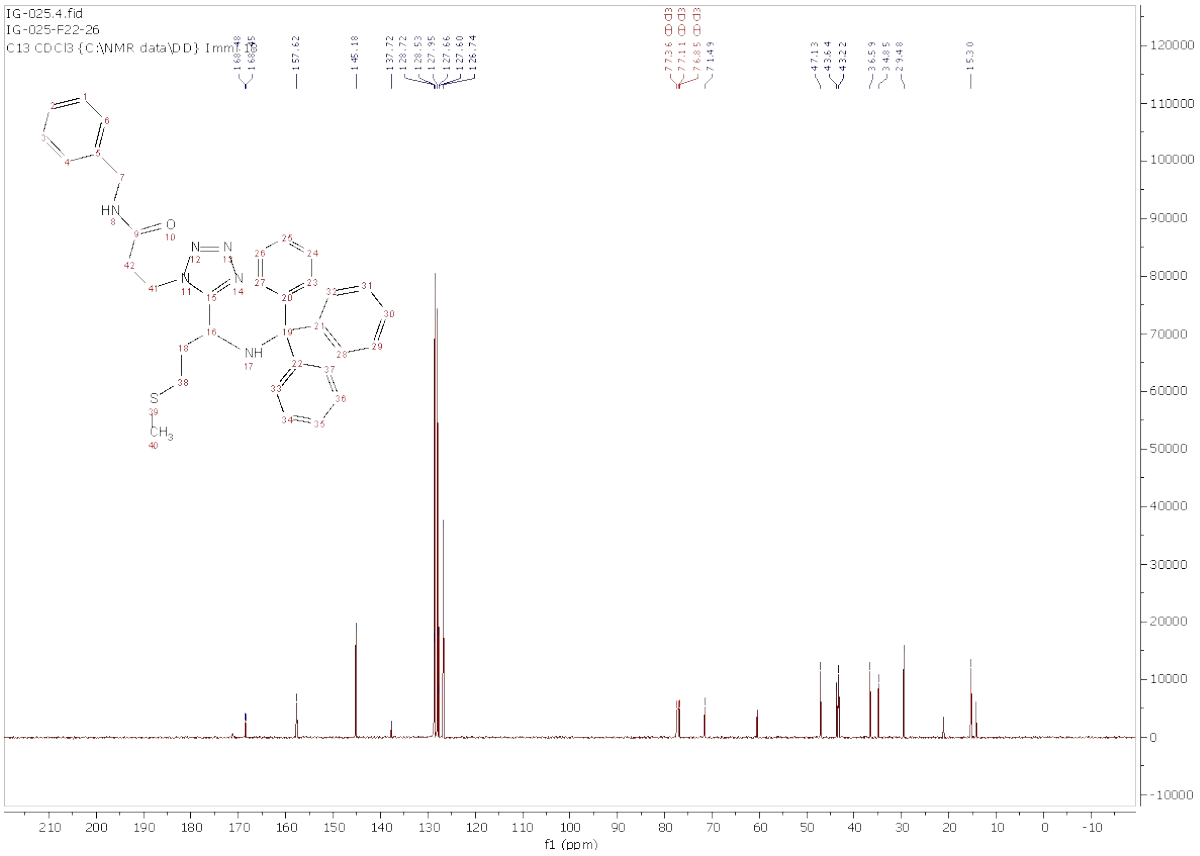
Compound 6m:



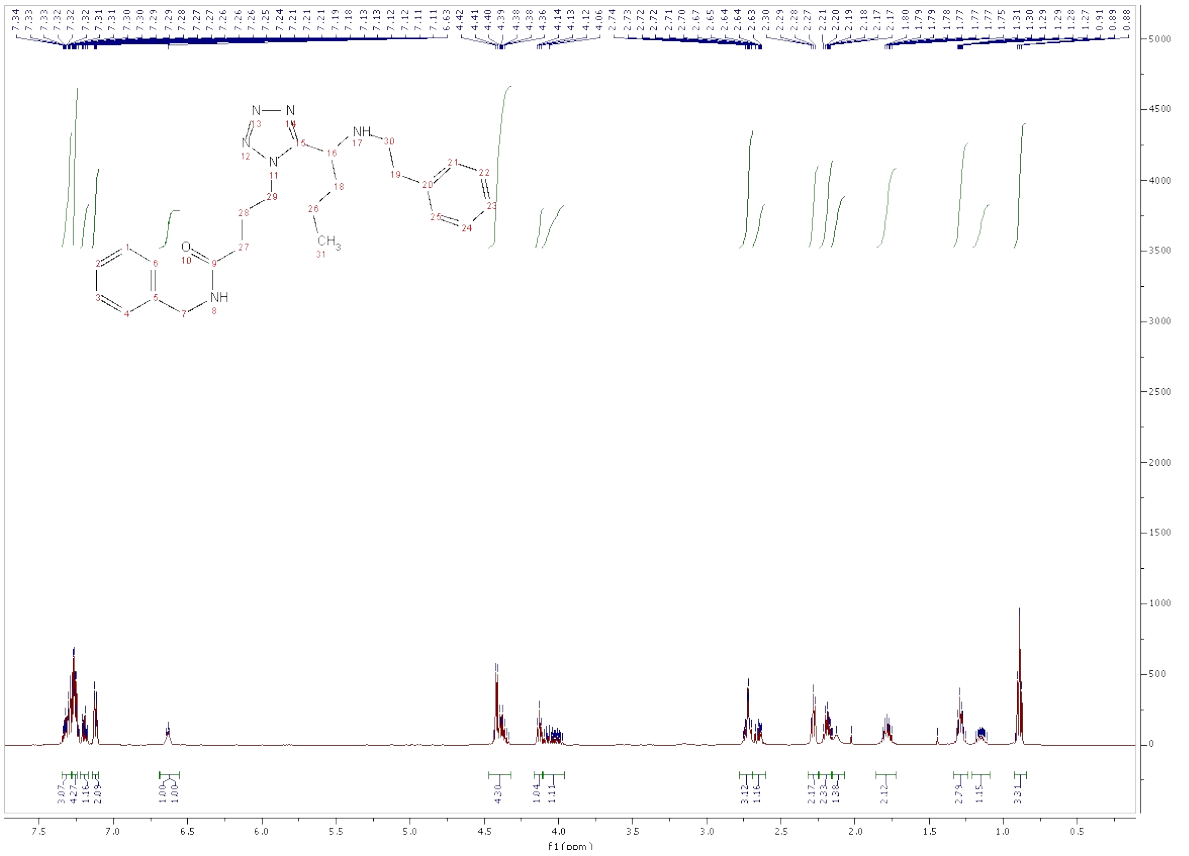


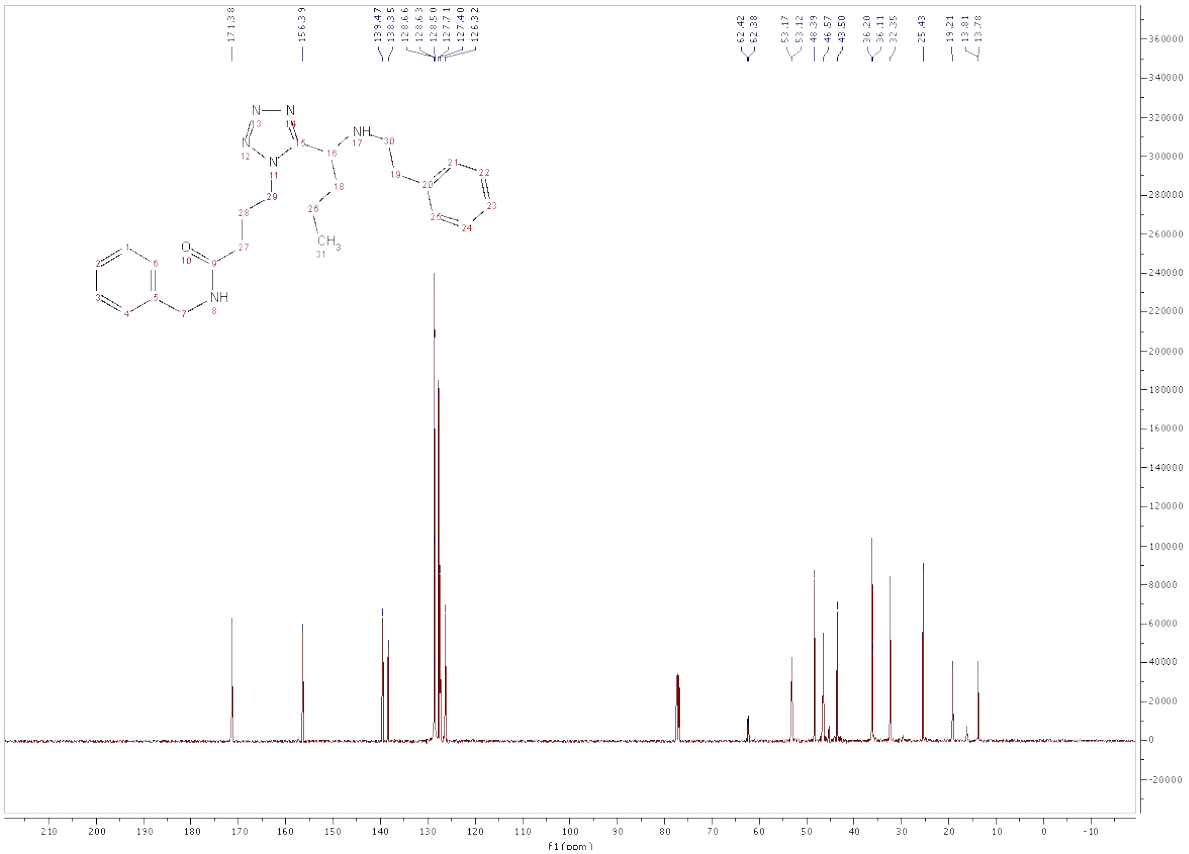
Compound 6n:

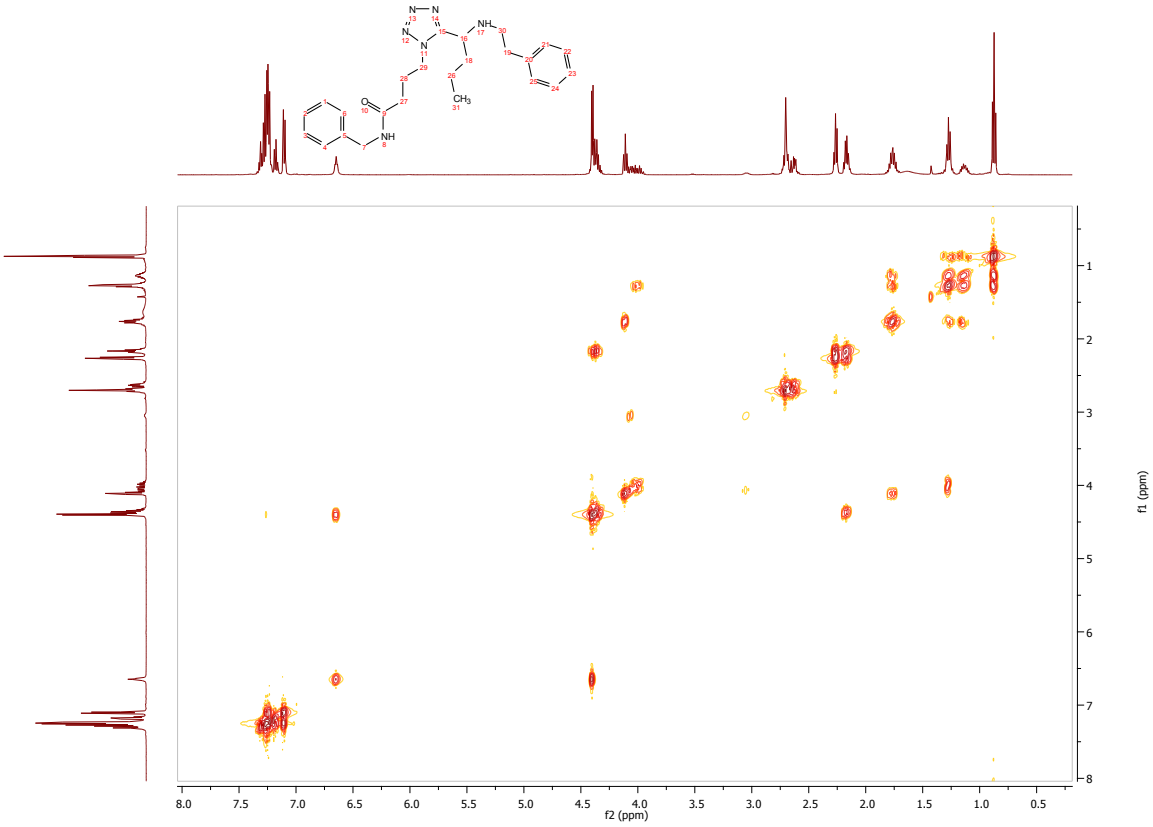


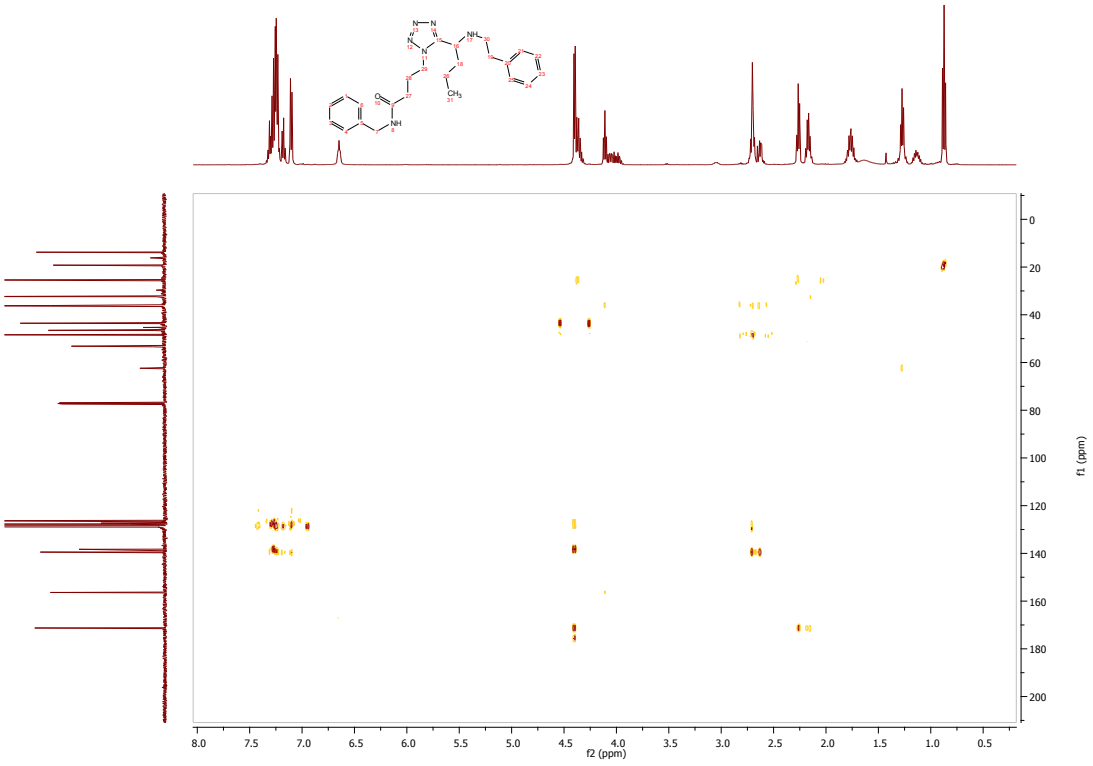


Compound 6o:

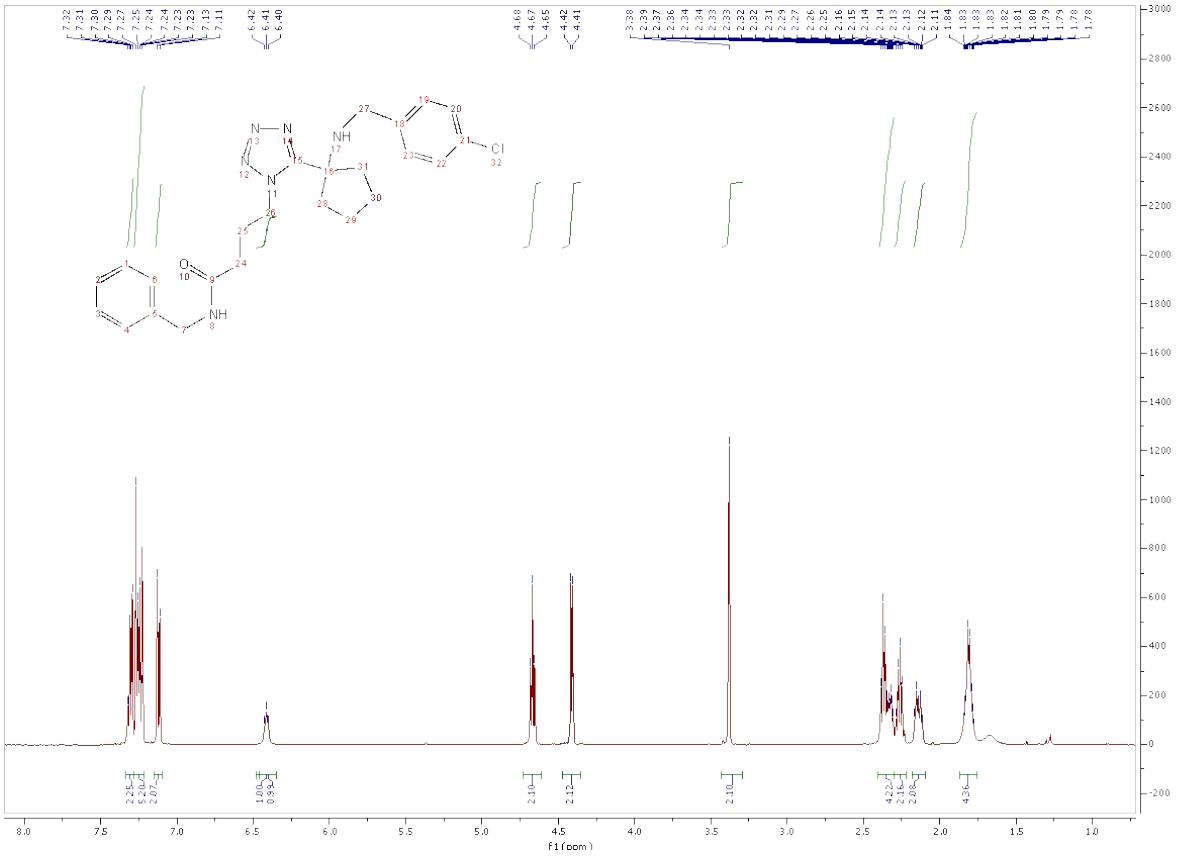


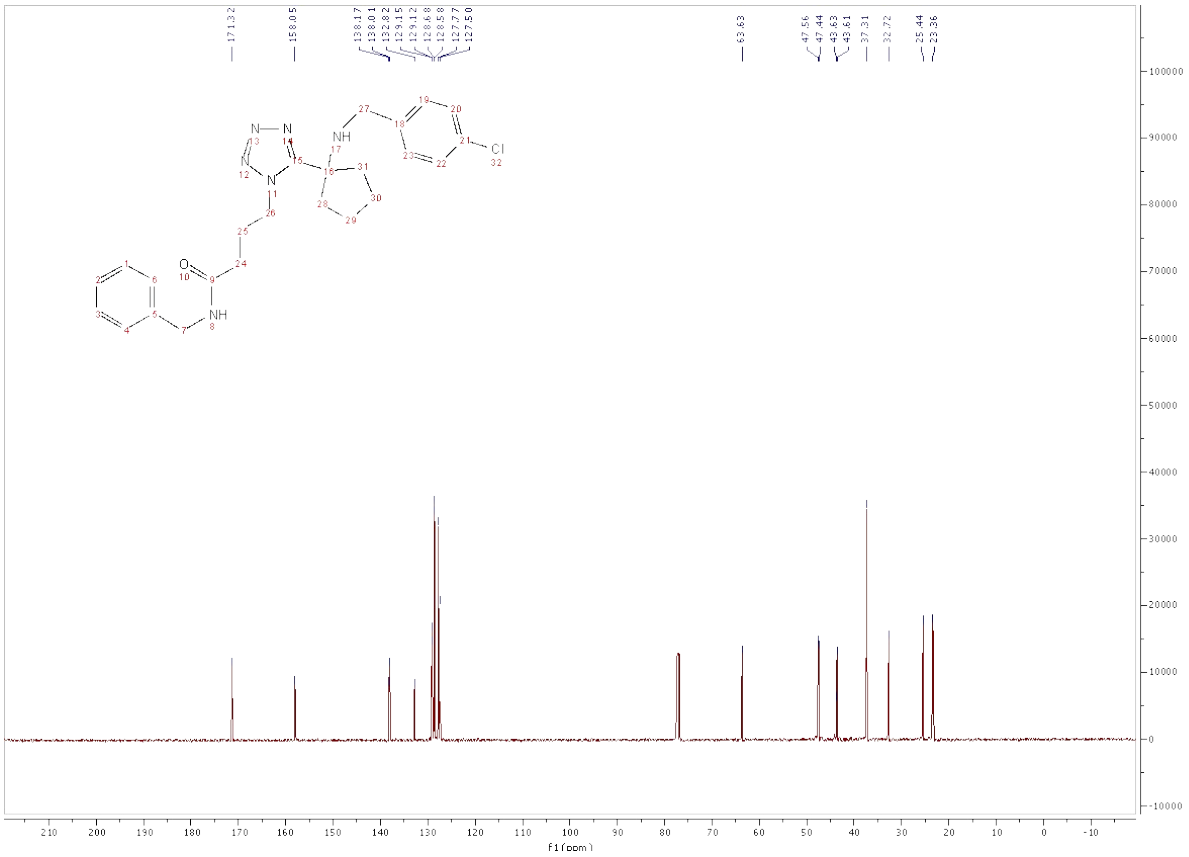



f2 (ppm)
f1 (ppm)

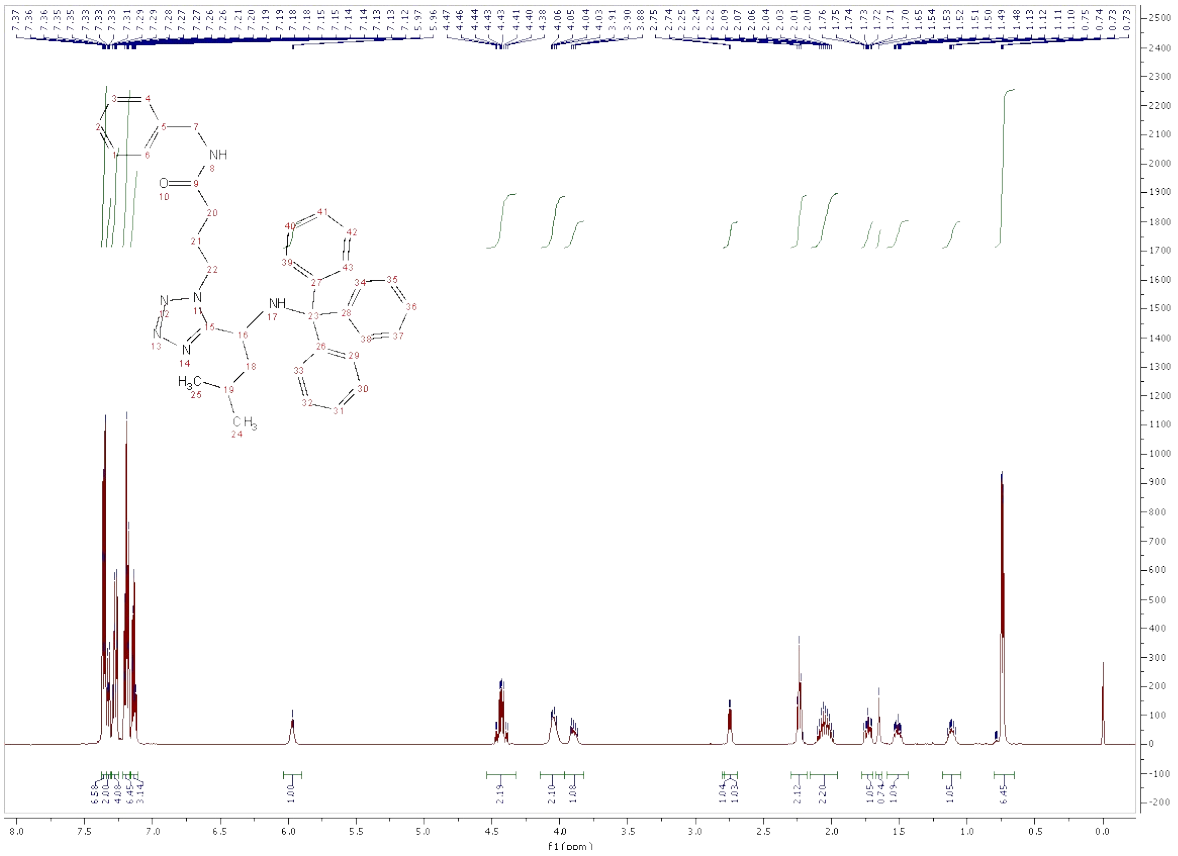

f2 (ppm)
f1 (ppm)

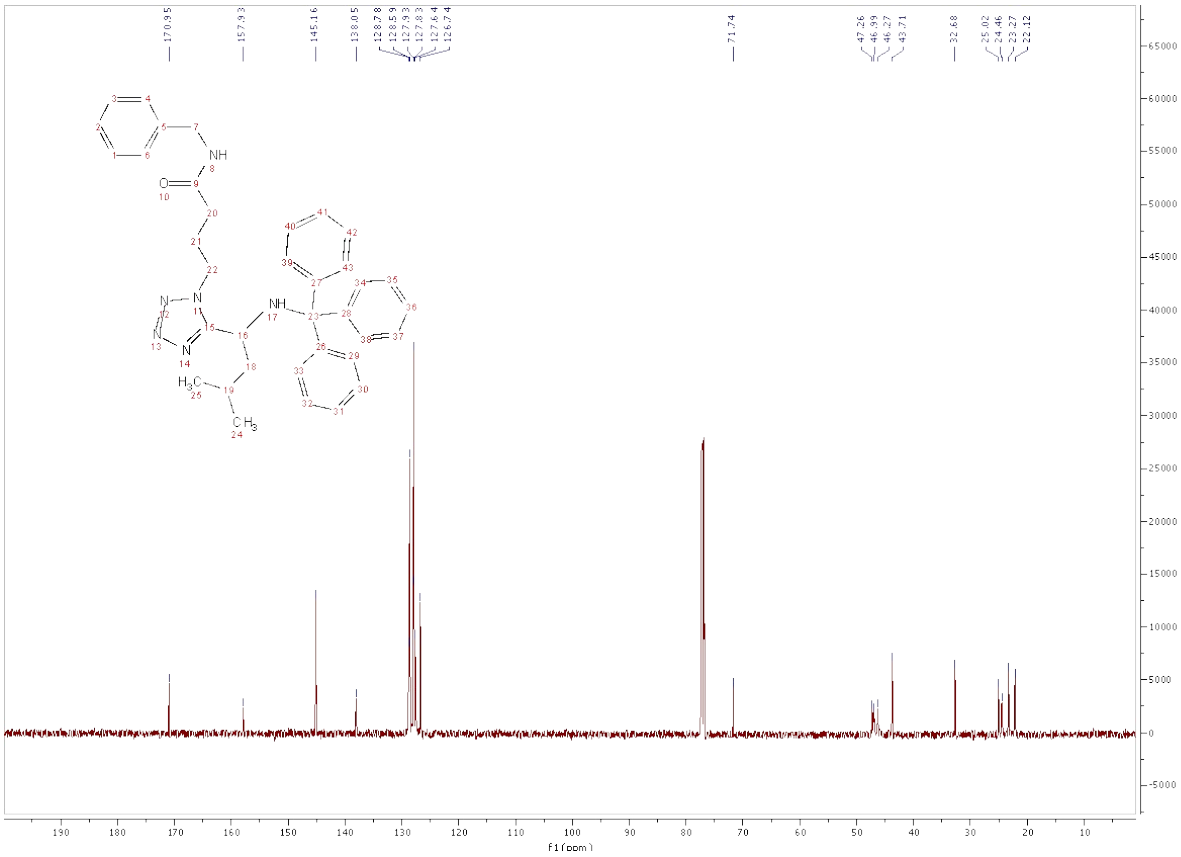
Compound 6p:

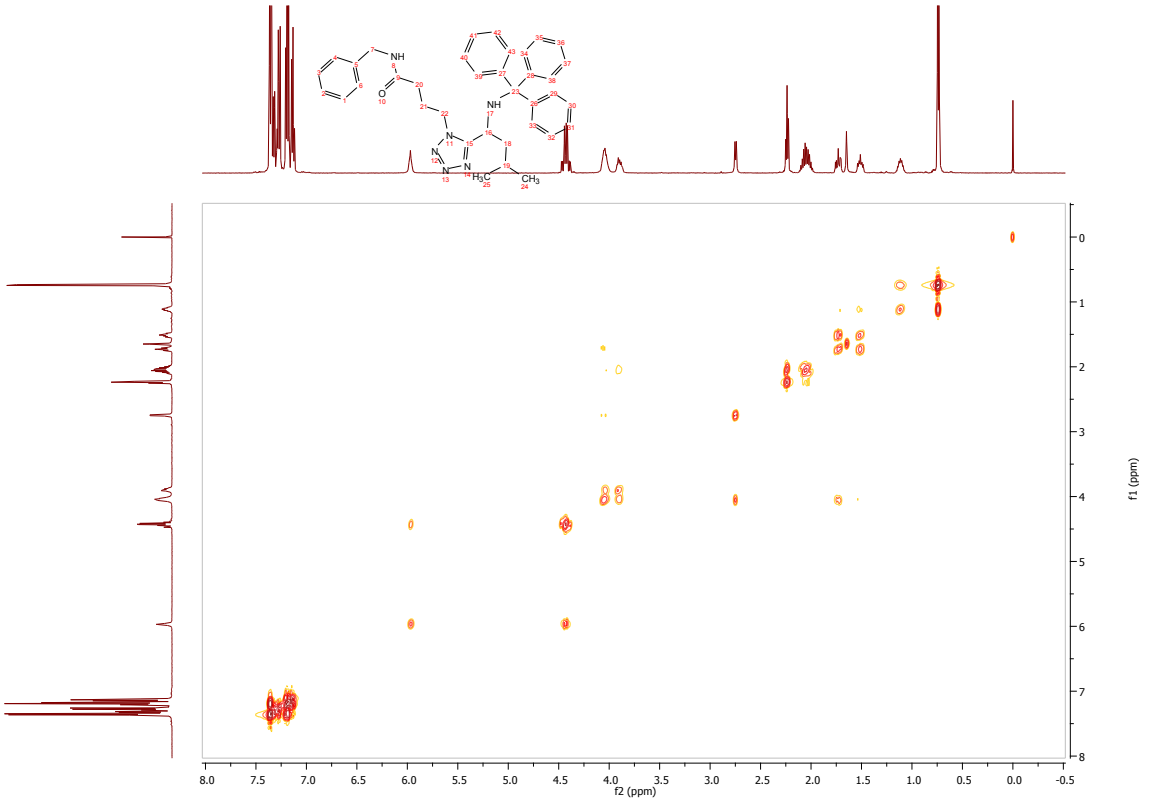


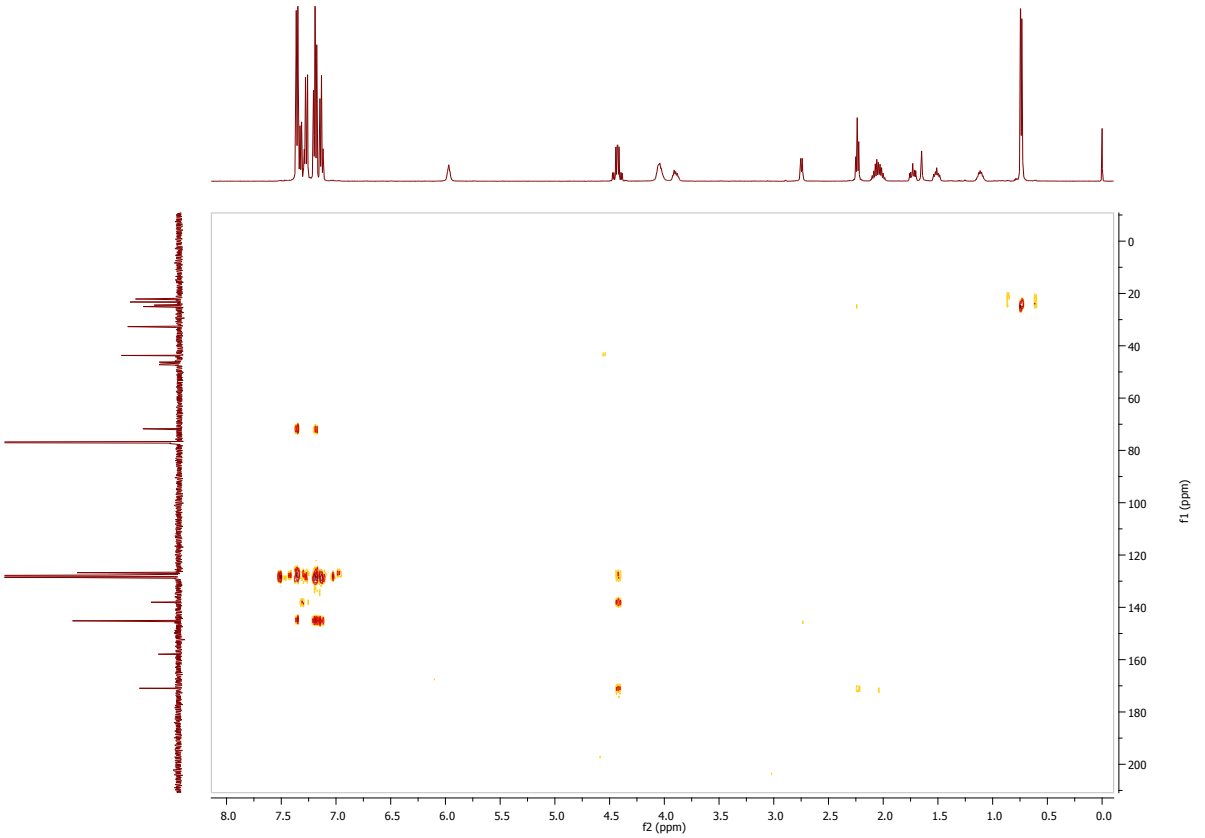


Compound 6q:

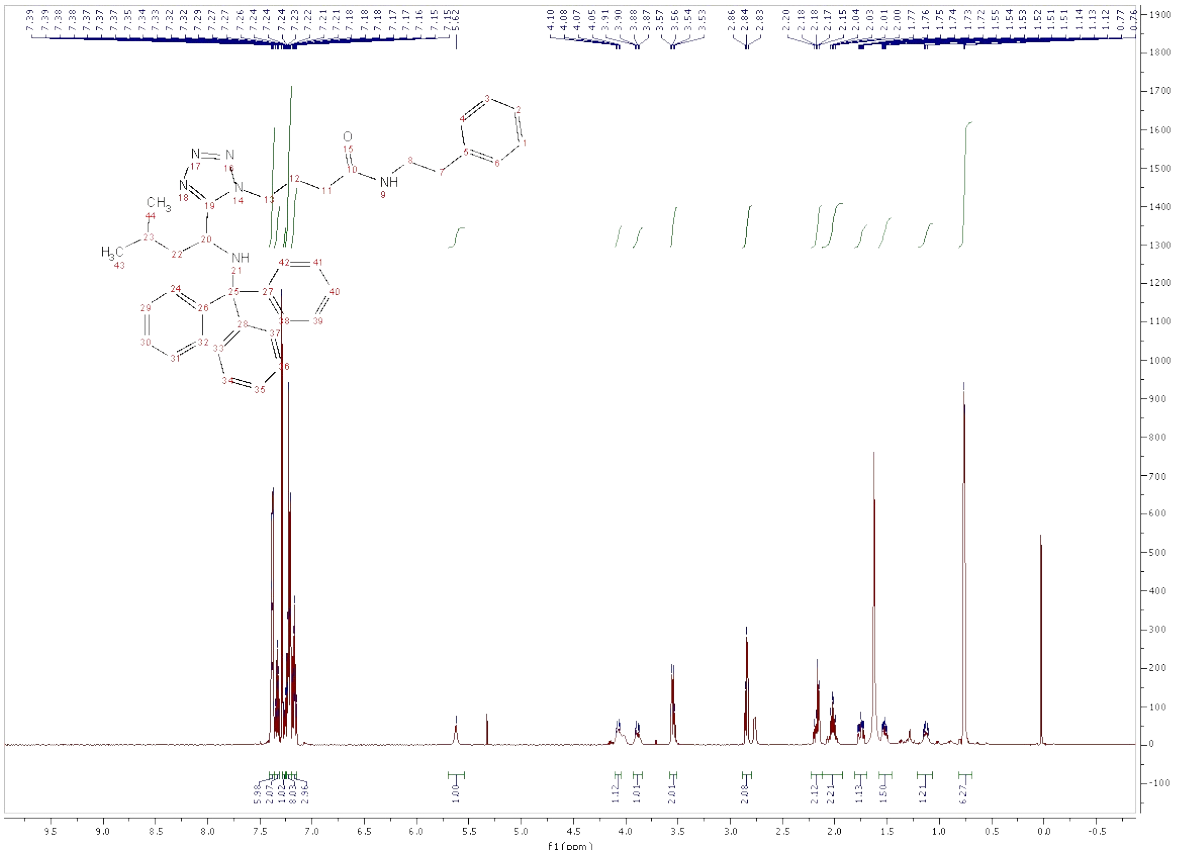


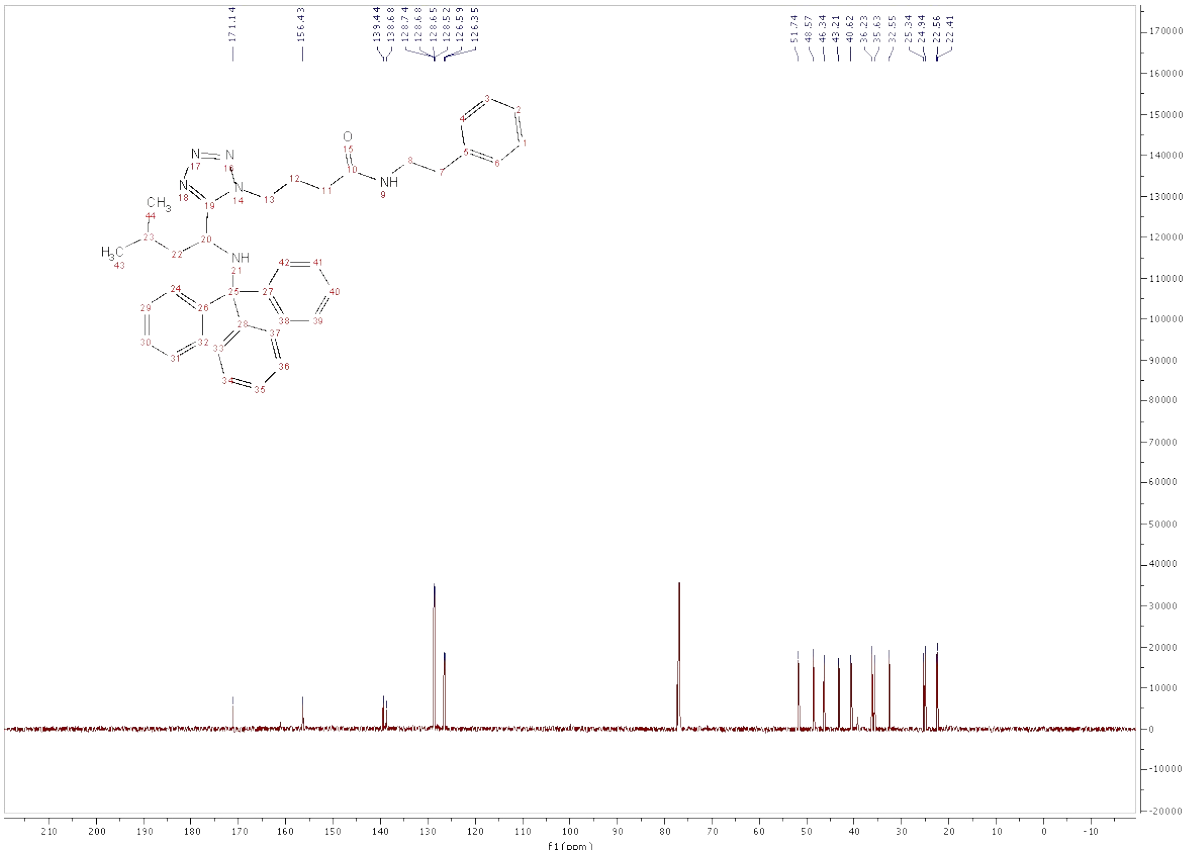



f2 (ppm)
f1 (ppm)

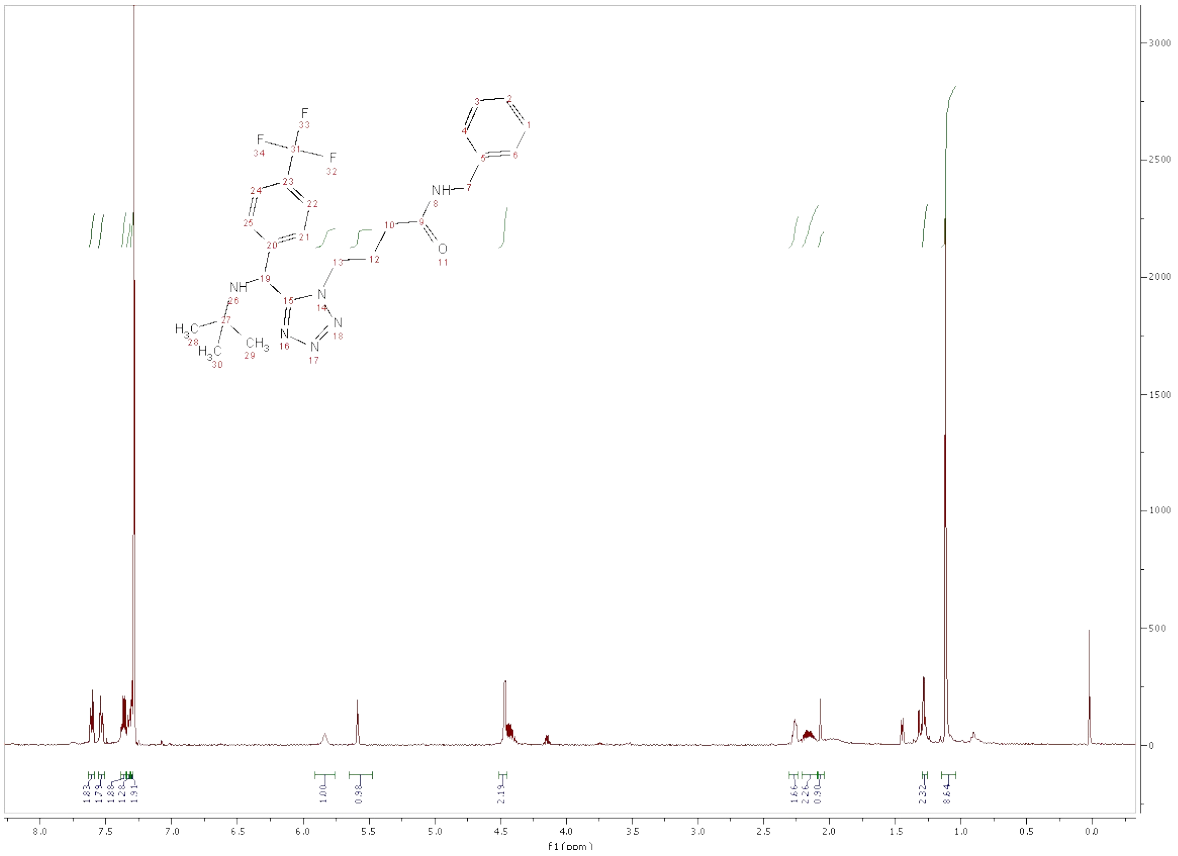

f2 (ppm)
f1 (ppm)

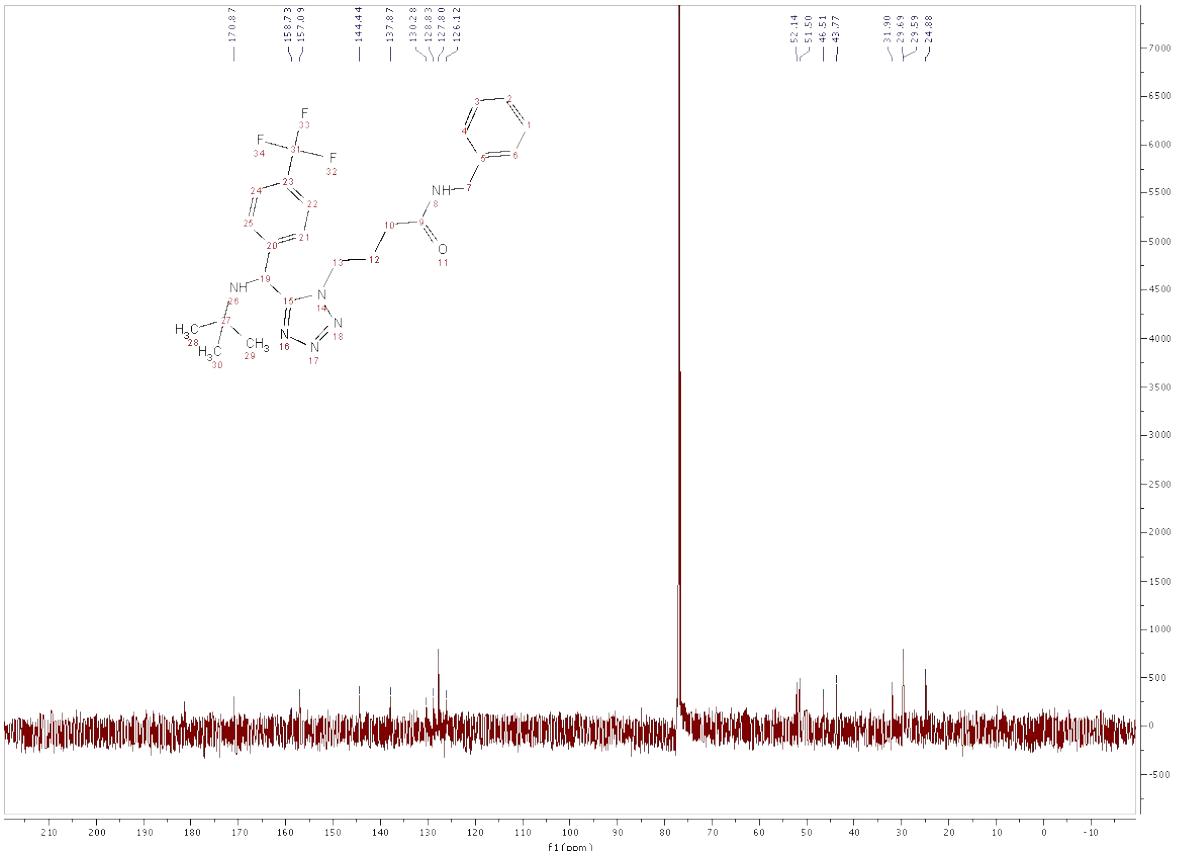
Compound 6x:



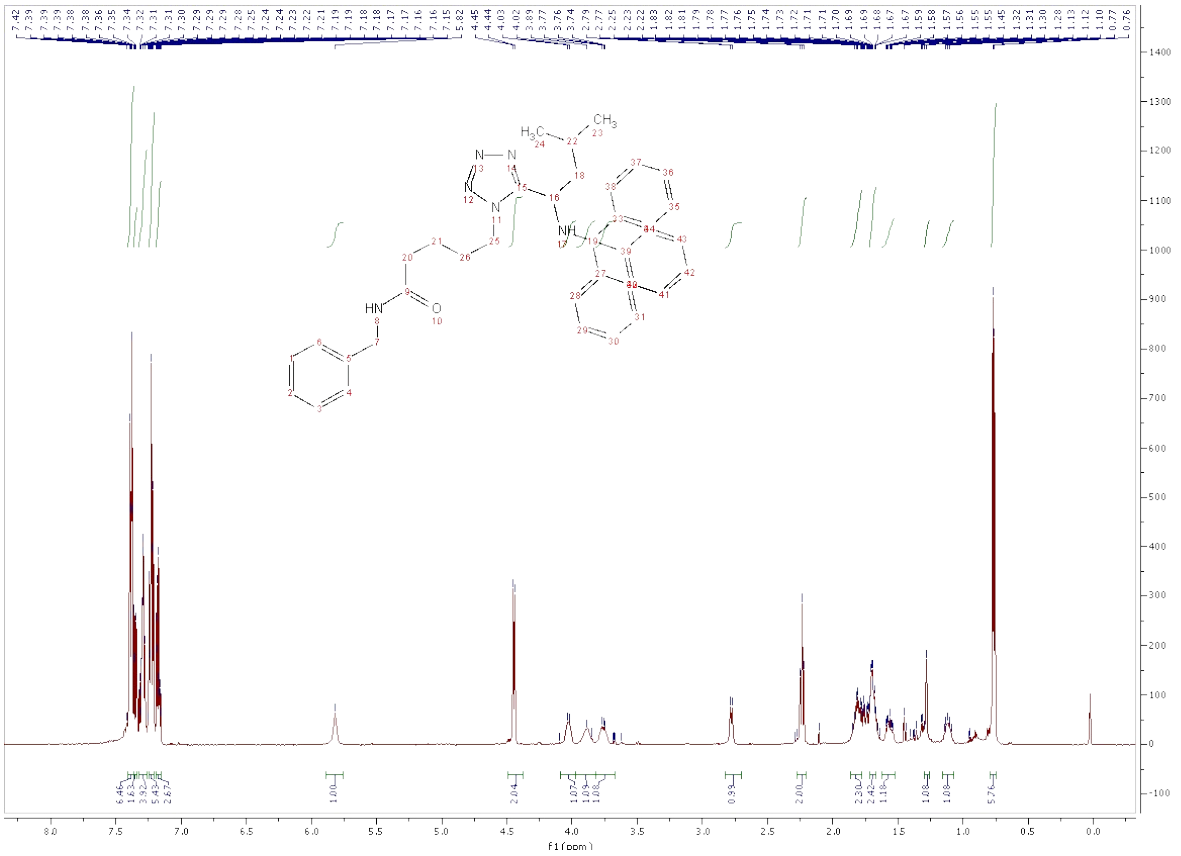


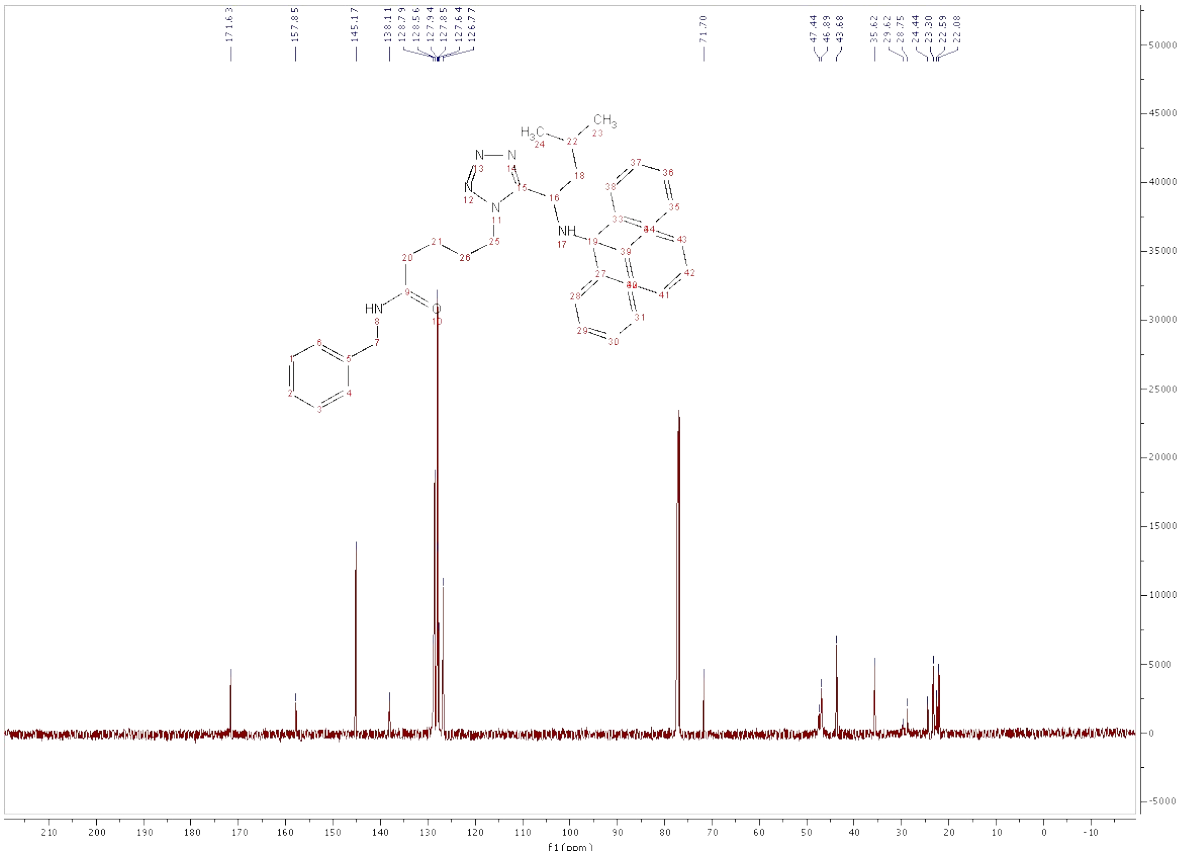
Compound 6y:





Compound 6z:





Crystal structure determination

X-ray diffraction data for single crystals of compounds **6f, 6p, 6l, 6g, 6e, 6h, 7a, 6a, 6b, 7j,** and **7k** was collected using SuperNova (Rigaku - Oxford Diffraction) four circle diffractometer with a mirror monochromator and a microfocus MoKα radiation source (λ = 0.71073 Å, used for monocrystals of **6f**, **6p, 6g, 7a, 6a, 6b, 7j** and **7k**) and CuKα radiation source (λ = 1.5418 Å used for **6l, 6e** and **6h**). The diffractometer was equipped with a CryoJet HT cryostat system (Oxford Instruments) allowing low temperature experiments, performed at 130(2)-132(4) K. The obtained data sets were processed with CrysAlisPro software [S1]. The phase problem was solved with direct methods using SIR2004 [S2] or SUPERFLIP [S3]. Parameters of obtained models were refined by full-matrix least-squares on F^2 using SHELXL-2014/6 [S4]. Calculations were performed using WinGX integrated system (ver. 2014.1) [S5]. Figure was prepared with Mercury 3.7 software [S6].

All non-hydrogen atoms were refined anisotropically. All hydrogen atoms attached to carbon atoms were positioned with the idealised geometry and refined using the riding model with the isotropic displacement parameter $U_{iso}[H] = 1.2$ (or 1.5 (methyl groups only)) $U_{eq}[C]$. Hydrogen atoms bound to nitrogen atoms were positioned on the difference Fourier map and refined with no restrains on the isotropic displacement parameters. Crystal data and structure refinement results for presented crystal structures are shown in Table S1. The molecular geometry observed in the crystal structures are shown in Figure S1.

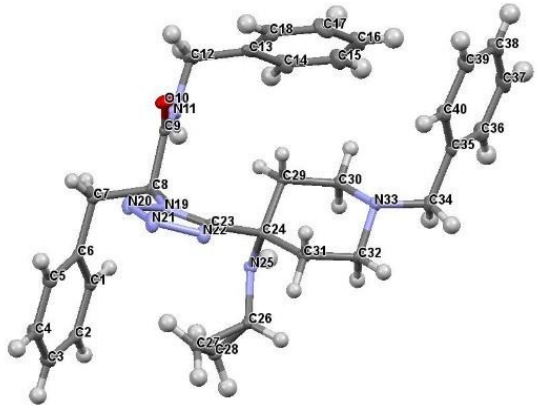
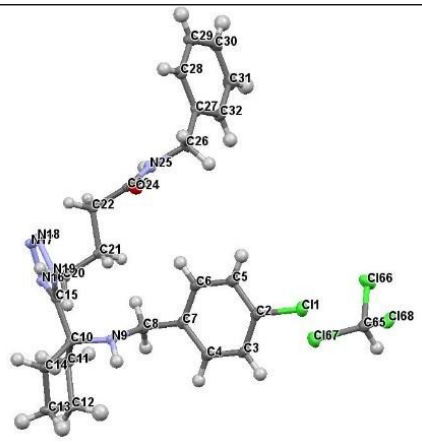
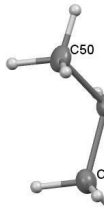
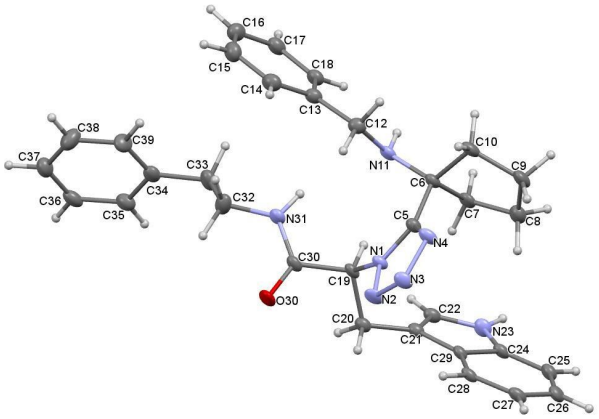
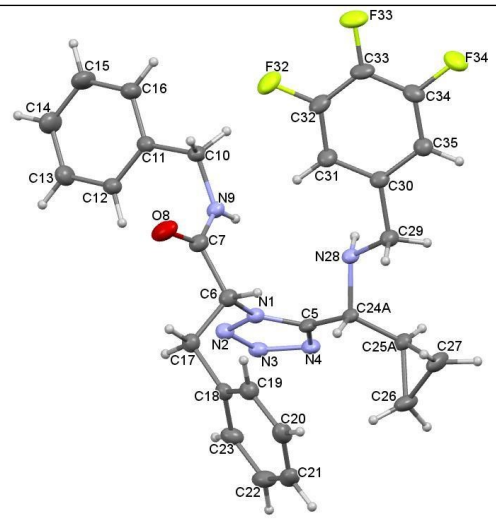
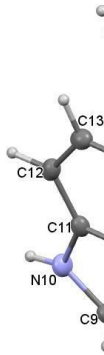
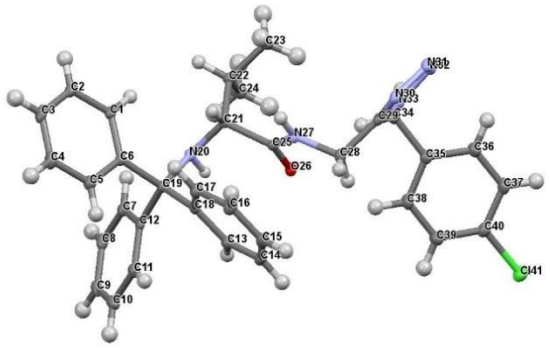
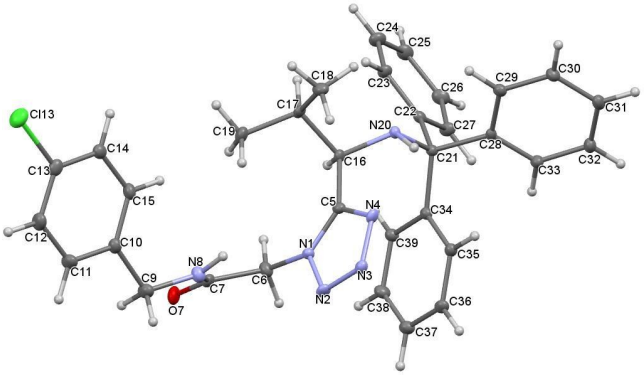
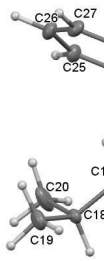
In the asymmetric units of **6p**, **6l** and **6e** two independent molecules are observed. Compound **6p** crystallised as a solvate, with the chloroform molecule forming several interactions with the main compound atoms and additionally stabilising the crystal lattice. In structures **6l** and **6e**, a conformational disorder was observed. In the case of **6l** one of two molecules of the asymmetric units exhibits disorder within the benzylamine fragment of the molecule. Two alternative conformers were modelled (refined site occupancies: 84.5% and 15.4%, respectively) based on the difference Fourier maps interpretation. To guarantee the reliable geometry of the modelled fragment for the less abundant conformer, several geometrical constraints were applied. In the crystal structure of compound **6e**, the two independent molecules of the asymmetric units show different orientations of the aromatic rings. Additionally, a conformational disorder in the cyclopropyl fragment orientation for both

molecules was observed, with the refined site occupancies 55:45 and 60:40, for molecule 1 and 2, respectively. Crystals of **6a** were poor quality plates. In the asymmetric unit of **7j** there are two independent molecules of the macrocyclic compound (here only one of them is presented) and chloroform molecules. The data processing revealed the twinning phenomena, with two components of 55% and 45% ratio. Data was processed with TWIN option of the CrysAlisPro software [S1]. The obtained model was refined against HKLF4.

Crystallographic data have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos.: CCDC 1842386 (**6f**), CCDC 1842385 (**6p**), CCDC 1844783 (**6l**), CCDC 1844786 (**6g**), CCDC 1844784 (**6e**), CCDC 1844787 (**6h**), CCDC 1842390 (**7a**), CCDC 1844788 (**6a**) and CCDC 1844785 (**6b**). CCDC 1548702 (**7j**), CCDC 1548703 (**7k**), Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, (fax: +44-(0)1223-336033 or e-mail: deposit@ccdc.cam.ac.uk).

Acknowledgements

The research was carried out with the equipment purchased thanks to the financial support of the European Regional Development Fund in the framework of the Polish Innovation Economy Operational Program (contract no. POIG.02.01.00-12-023/08).

		
6f	**6p**	**6l**
		
6g	**6e**	**6h**
		
7a	**6a**	**6b**

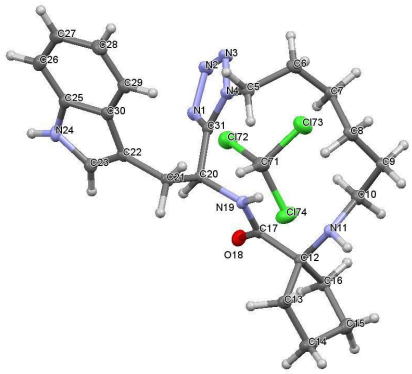
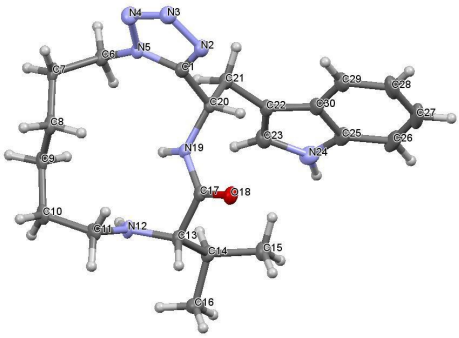
		
7j	**7k**	

Figure S1. Molecular geometry observed in the crystal structures of compounds **6f, 6p, 6l, 6g, 6e, 6h, 7a, 6a, 6b, 7j,** and **7k** showing the atom labelling scheme (here asymmetric units are presented except for **6p**, **6l** and **6e**, for which two independent molecules are observed in the asymmetric unit). Additionally, a partial, conformational disorder was observed in structures **6l** and **6e** - here only one of alternative conformers are presented. Displacement ellipsoids of non-hydrogen atoms are drawn at the 30% probability level. H atoms are presented as small spheres with an arbitrary radius. In the asymmetric unit of **7j** there are two independent molecules of the macrocyclic compound (here only one of them is presented) and chloroform molecules.

Table S1. Crystal data and structure refinement results for compounds **6f, 6p, 6l, 6g, 6e, 6h, 7a, 6a, 6b, 7j,** and **7k**.

	6f	**6p**	**6l**	**6g**	**6e**
Empirical moiety formula	$C_{32}\ H_{37}\ N_7\ O$	2 ($C_{24}\ H_{29}\ N_6\ Cl$, $C\ H\ Cl_3$)	2 ($C_{22}\ H_{27}\ Cl\ N_6\ O$)	$C_{32}\ H_{35}\ N_7\ O$	2 ($C_{28}\ H_{27}\ F_3\ N_6\ O$)
Formula weight [g/mol]	535.7	1144.7	853.89	533.67	1041.11
Crystal system	Triclinic	Triclinic	Triclinic	Monoclinic	Triclinic
Space group	$P\bar{1}$	$P\bar{1}$	$P\bar{1}$	$P2_1$	$P\bar{1}$
Unite cell dimensions	a = 6.3741(8) Å b = 9.3723(12) Å c = 24.838(2) Å α= 83.121(9)° β=85.819(9)° γ=79.949(10)°	a = 10.3164(4) Å b = 15.7661(6) Å c = 18.2979(6) Å α=68.115(3)° β=89.376(3)° γ=87.542(3)°	a = 10.764(6) Å b = 14.0058(6) Å c = 15.9242(8) Å α=89.704(4)° β=78.054(4)° γ=67.659(5)°	a = 6.7885(4) Å b = 7.9643(4) Å c = 26.039(2) Å β=94.113(6)°	a = 10.8092(4) Å b = 14.1679(6) Å c = 17.2034(7) Å α=78.408(4)° β=86.646(3)° γ=86.284(3)°
Volume [$Å^3$]	1448.5(3)	2759.08(17)	2165.3(2)	1404.17(17)	2572.64(18)
Z	2	2	2	2	2
D_{calc} [Mg/m^3]	1.228	1.378	1.310	1.262	1.344
μ [mm^{-1}]	0.077	0.459	1.769	0.080	0.835
F(000)	572	1192	904	568	1088
Crystal size [mm^3]	0.2 x 0.15 x 0.10	0.2 x 0.2 x 0.15	0.6 x 0.4 x 0.1	0.4 x 0.4 x 0.02	0.4 x 0.3 x 0.1

Θ range	3.14° to 28.52°	2.87° to 28.67°	3.42° to 71.39°	3.01° to 28.73°	3.19° to 71.30°
Index ranges	-8 ≤ h ≤ 7, -9 ≤ k ≤ 12, -31 ≤ l ≤ 33	-13 ≤ h ≤ 13, -20 ≤ k ≤ 20, -24 ≤ l ≤ 24	-13 ≤ h ≤ 12, -16 ≤ k ≤ 17, -19 ≤ l ≤ 16	-9 ≤ h ≤ 9, -10 ≤ k ≤ 10, -32 ≤ l ≤ 34	-13 ≤ h ≤ 11, -17 ≤ k ≤ 15, -21 ≤ l ≤ 20
Refl. collected	8886	25215	13358	19388	16985
Independent reflections	6321 [R(int) = 0.0327]	12499 [R(int) = 0.0350]	7978 [R(int) = 0.0358]	6631 [R(int) = 0.0681]	9771 [R(int) = 0.0317]
Completeness [%] to Θ	98.6 (Θ 26.3°)	99.9 (Θ 26.3°)	96.4 (Θ 67.7°)	99.8 (Θ 25.2°)	99.9 (Θ 67.7°)
Absorption correction	Multi-scan	Multi-scan	Multi-scan	Multi-scan	Multi-scan
Tmin. and Tmax.	0.428 and 1.000	0.428 and 1.000	0.427 and 1.000	0.621 and 1.000	0.695 and 1.000
Data/ restraints/ parameters	6321 / 0 / 2370	12499 / 0 / 661	7978 / 10 / 620	6631 / 1 / 373	9771 / 3 / 739
GooF on F2	1.086	1.052	1.020	1.068	1.024
Final R indices [I>2sigma(I)]	R1= 0.0658, wR2= 0.1458	R1= 0.0461, wR2= 0.1131	R1= 0.0511, wR2= 0.1380	R1= 0.0799, wR2= 0.1706	R1= 0.0566, wR2= 0.1514
R indices (all data)	R1= 0.0984, wR2= 0.1622	R1= 0.0659, wR2= 0.1310	R1= 0.0599, wR2= 0.1493	R1= 0.1017, wR2= 0.1845	R1= 0.0764, wR2= 0.1705
$\Delta\rho_{max}$, $\Delta\rho_{min}$ [e·Å^{-3}]	0.28 and -0.27	0.59 and -0.46	0.44 and -0.47	0.34 and -0.25	0.43 and -0.48

	6h	**7a**	**6a**	**6b**
Empirical moiety formula	C_{30} H_{32} Cl N_7 O	C_{33} H_{33} Cl N_6 O	C_{33} H_{33} Cl N_6 O	C_{34} H_{36} N_6 O
Formula weight [g/mol]	542.07	565.1	565.10	544.69
Crystal system	Monoclinic	Triclinic	Monoclinic	Triclinic
Space group	$P2_1/n$	P-1	$P2_1/n$	$P\underline{1}$
Unite cell dimensions	a = 9.8002(3) Å b = 15.1210(5) Å c = 18.4804(7) Å β=90.374(3)°	a = 9.1544(3) Å b = 10.8644(4) Å c = 15.5035(5) Å α= 72.725(3)° β= 84.894(3)° γ= 83.984(3)	a = 9.0985(3) Å b = 10.3538(3) Å c = 30.3383(10) Å β=97.525(3)°	a = 11.2953(14) Å b = 11.4120(10) Å c = 13.0664(13) Å α=70.404(9)° β=73.213(10)° γ=70.603(10)°
Volume [$Å^3$]	2886.72(17)	1461.55(9)	2833.38(16)	1466.5(3)
Z	4	2	4	2

D_{calc} [Mg/m^3]	1.247	1.284	1.325	1.233
μ [mm^{-1}]	1.451	0.168	0.173	0.077
F(000)	1144	596	1192	580
Crystal size [mm^3]	0.6 x 0.6 x 0.4	0.2 x 0.2 x 0.15	0.4 x 0.2 x 0.05	0.2 x 0.2 x 0.1
Θ range	3.70° to 71.92°	2.84° to 28.50°	3.00° to 30.33°	3.11° to 30.36°
Index ranges	-9 ≤ h ≤ 11, -18 ≤ k ≤ 18, -21 ≤ l ≤ 23	-11 ≤ h ≤ 11, -14 ≤ k ≤ 13, -20 ≤ l ≤ 19	-12 ≤ h ≤ 12, -13 ≤ k ≤ 12, -36 ≤ l ≤ 40	-15 ≤ h ≤ 15, -15 ≤ k ≤ 15, -16 ≤ l ≤ 18
Refl. collected	18364	20432	27066	12639
Independent reflections	5568 [R(int) = 0.0477]	6744 [R(int) = 0.0295]	7892 [R(int) = 0.0784]	7920 [R(int) = 0.0676]
Completeness [%] to Θ	100.0 (Θ 67.7°)	99.8 (Θ 26.3°)	99.8 (Θ 25.2°)	99.8 (Θ 25.2°)
Absorption correction	Multi-scan	Multi-scan	Multi-scan	Multi-scan
Tmin. and Tmax.	0.152 and 1.000	0.873 and 1.000	0.808 and 1.000	0.817 and 1.000
Data/ restraints/ parameters	5568 / 0 / 367	6744 / 0 / 376	7892 / 1 / 379	7920 / 0 / 380
GooF on F2	1.037	1.039	1.439	1.042
Final R indices [I>2sigma(I)]	R1= 0.0444, wR2= 0.1221	R1= 0.0414, wR2= 0.0886	R1= 0.1130, wR2= 0.3278	R1= 0.0717, wR2= 0.1428

R indices (all data)	R1= 0.0496, wR2= 0.1270	R1= 0.0586, wR2= 0.0982	R1= 0.1223, wR2= 0.3461	R1= 0.1305, wR2= 0.1931
$\Delta\rho_{max}$, $\Delta\rho_{min}$ [e·Å^{-3}]	0.29 and -0.49	0.29 and -0.26	0.68 and -0.53	0.32 and -0.32
	7j	**7k**		
Empirical moiety formula	2(C_{23} H_{31} N_7 O), 3$CHCl_3$	C_{22} H_{31} N_7 O		
Formula weight [g/mol]	1201.20	409.54		
Crystal system	Triclinic	Orthorhombic		
Space group	P-1	P*bca*		
Unite cell dimensions	a = 12.9113(4) Å b = 13.8869(4) Å c = 16.5533(3) Å α = 102.178(2)° β = 91.521(2)° γ = 97.504(2)°	a = 9.8856(6) Å b = 10.4180(5) Å c = 42.5525(16) Å α = 90.0° β = 90.0° γ = 90.0°		
Volume [Å^3]	2871.85(13)	4382.4(4)		
Z	2	8		
D_{calc}	1.389	1.241		

[Mg/m^3]				
μ [mm^{-1}]	0.491	0.081		
F(000)	1252	1760		
Crystal size [mm^3]	0.4 x 0.4 x 0.2	0.6 x 0.1 x 0.4		
Θ range	3.05 to 28.67°	3.00° to 28.57°		
Index ranges	-17 ≤ h ≤ 16, -18 ≤ k ≤ 18, -21 ≤ l ≤ 20	-12 ≤ h ≤ 9, -8 ≤ k ≤ 13, -34 ≤ l ≤ 56		
Refl. collected	40860	13478		
Independent reflections	13393 [R(int) = 0.0474]	5024 [R(int)=0.1206]		
Completeness [%] (Θ 25.24°)	99.8	99.4		
Absorption correction	Multi-scan	Multi-scan		
Max. and min. transmission	0.715 and 1.000	0.2818 and 1.000		
Refinement method	Full-matrix least-squares on F^2	Full-matrix least-squares on F^2		
Data/ restraints/ parameters	13393 / 0 /695	5024 / 0 / 276		
GooF on F2	1.030	0.981		

Final R indices [I>2sigma(I)]	R1= 0.0662, wR2= 0.1639	R1= 0.0836, wR2= 0.1581		
R indices (all data)	R1= 0.1015, wR2= 0.1928	R1= 0.2098, wR2= 0.2206		
$\Delta\rho_{max}$, $\Delta\rho_{min}$ [e·Å^{-3}]	0.79 and -0.70	0.39 and -0.38		

References:

[S1] Rigaku-Oxford Diffraction; CrysAlisPro Oxford Diffraction Ltd, Abingdon, England V 1. 171. 36. 2.
(release 27-06-2012 CN) 2006.

[S2] Burla M.C., Caliandro R., Camalli M., Carrozzini B., Cascarano G.L., De Caro L., Giacovazzo C., Polidori G. and Spagna R., J. Appl.Cryst. 2005, 38(2), 381–388.

[S3] Palatinus L., Chapuis G., J. App. Cryst. 2007, 40, 786-790.

[S4] Sheldrick G. M., ActaCryst. 2008, A64, 112-122.

[S5] Farrugia L.J., J. Appl. Cryst. 1999, 32, 837-838.

[S6] Macrae C. F., Edgington P.R., McCabe P., Pidcock E., Shields G.P., Taylor R., Towler M. and van de Streek J., J. Appl. Cryst. 2006, 39, 453-457.