Electronic Supplementary Information

Efficient Synthesis of Conformationally Constrained, Aminotriazoloazepinone-containing Di- and Tripeptides via a One-Pot Ugi-Huisgen tandem Reaction

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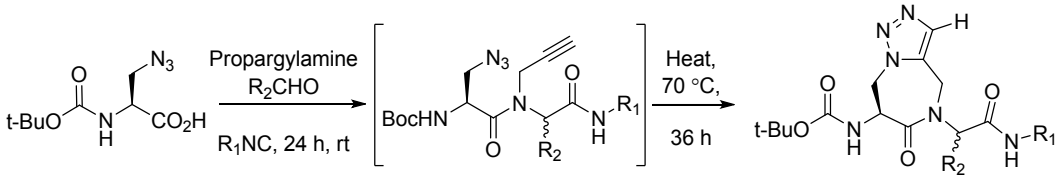


1. General Information

^{1}H and ^{13}C NMR spectra (25°C) were recorded at 250 MHz and 63 MHz on a Bruker Avance DRX 250 spectrometer or at 500 MHz and 126 MHz respectively on a Bruker Avance II 500 spectrometer. Chemical shifts are in parts per million (ppm). The assignments were made using one dimensional (1D) ^{1}H and ^{13}C spectra. HRMS data was recorded with a Micromass QTOF-micro system. Mass spectra were recorded with a LCMS-MS triple-quadrupole system. Analytical HPLC was performed on an Agilent 1100 Series system with a Supelco Disovery BIO Wide Pore RP column (25 cm × 4.6 mm, 5 μm). Flow rates of 1 ml/min were used and detection was done at 215 nm. The solvent system consisted of 0.1% TFA in water (A) and 0.1% TFA in acetonitrile (B). The gradient consisted of a 20 min. run from 3% B to 97% B. Flash chromatography was performed with silica gel 60 (Davisil, 0.040-0.063 mm) from Merck. Glass plates with silica gel 60 F254 (Merck) were used for thin layer chromatography. Visualization of the products on TLC plates was realized using UV light (254 nm), $KMnO_4$ spray. Melting points were determined on a Büchi B-540 apparatus and are uncorrected. Reactions were performed using a Biotage® Initiator^{+} Microwave Synthesiser. All commercial

reagents and solvents were used without further purification. Diastereomeric ratios were calculated based on the integration of the Boc-proton resonances for all compounds except where noted in the manuscript.

2. General Procedure for synthesis of *N*-Boc-2-amino-3-azidopropanoic acid (12)

To a mixture of sodium azide (9.6 eq.) in water-methanol (5:8 v/v) at 0 °C was added triflic anhydride (1.86 eq., max. 2.5 ml) dropwise. The mixture was stirred at 0 °C for a further 2 hours after which time the layers were partitioned, and the aqueous layer was washed with dichloromethane. Combined organics were washed with a 10% solution of sodium bicarbonate.

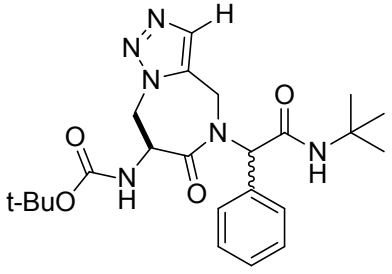
To a mixture of Boc-diaminopropanoic acid (1.0 eq.) in water-methanol (1:2 v/v) was added sodium bicarbonate (10 eq.) and copper(ii) sulfate pentahydrate (0.013 eq.). The crude triflic azide mixture was then added dropwise at room temperature and the mixture allowed to stir overnight. Methanol was then removed under reduced pressure and the mixture acidified to pH 6 with HCl 1 N. Phosphate buffer (pH 6.2 was then added) and the resulting mixture was extracted with ethyl acetate. The resulting aqueous layers were further acidified to pH 2 and extracted again with ethyl acetate. Combined organics were washed with brine, dried over anhydrous magnesium sulfate and concentrated in vacuo to give product as a viscous yellow-green oil.

3. General Procedure for Ugi reaction under heating in a sealed vial

In a microwave vial was combined *N*-Boc-2-Amino-3-azidopropanoic acid (0.4 mmol), propargylamine (0.4 mmol), aldehyde (0.4 mmol) and isocyanide (0.4 mmol) in MeOH (4 ml). The vial was sealed and the mixture was stirred at room temperature for 24 hours. Reaction conversion was monitored by HPLC analysis and after full conversion the vial was heated at 70 °C in an oil bath for 36 h. Upon reaction completion the methanol was removed from the mixture under reduced pressure. The crude products were purified either by precipitation from apolar solvents (hexane or heptane) with sonication or were purified directly by flash chromatography. Purity was determined by reversed phase HPLC, using UV detection (215 nM).

4. Characterisation of Compounds

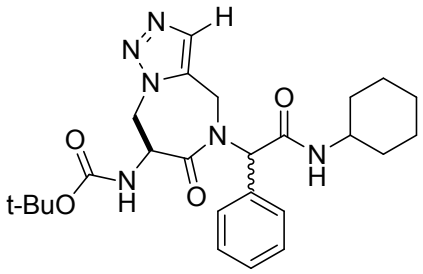
(*S*)-*tert*-Butyl (5-(2-(tert-Butylamino)-2-oxo-1-phenylethyl)-6-oxo-5,6,7,8-tetrahydro-4*H*-[1,2,3]triazolo[1,5-a][1,4]diazepin-7-yl)carbamate (14)



Chemical Formula: $C_{23}H_{32}N_6O_4$
Exact Mass: 456.2485

Yield: 160 mg (81%). White solid, mp: 155-157 °C. Purification: precipitation from hexane; dr: 55/45. HPLC R_T: 15.5 min; ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.59-7.40 (5H, m), 7.39-7.29 (4H, m), 7.26-7.21 (1H, m), 7.11 (2H, d, *J* = 11.0 Hz), 6.13 (2H, d, *J* = 13.8 Hz), 6.00 (2H, d, *J* = 8.3 Hz), 5.63-5.50 (2H, m), 5.30-5.13 (2H, m), 4.97 (2H, dt, *J* = 5.5, 13.8 Hz), 4.76-4.56 (3H, m), 4.40-4.10 (3H, m), 1.48 (18H, s), 1.45 (9H, s), 1.40 (9H, s); ^{13}C NMR (125 MHz, $CDCl_3$): δ 172.9, 170.6, 170.3, 168.1, 166.8, 154.9, 134.2, 131.8, 131.6, 130.4, 129.5, 129.3, 128.8, 81.0, 80.9, 61.3, 61.2, 52.4, 52.0, 50.2, 49.0, 48.9, 37.9, 37.5, 28.8, 28.6, 28.4; HRMS (m/z) calcd. for $C_{23}H_{32}N_6O_4$ $(M+H)^+$: 457.2558, found: 457.2540.

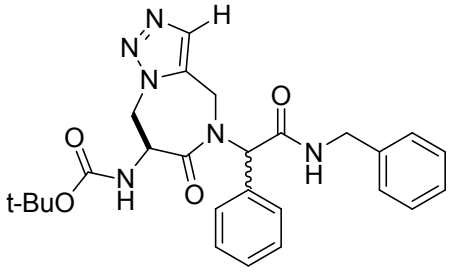
(*S*)-*tert*-Butyl (5-(2-(cyclohexylamino)-2-oxo-1-phenylethyl)-6-oxo-5,6,7,8-tetrahydro-4*H*-[1,2,3] triazolo[1,5-a][1,4]diazepin-7-yl)carbamate (15)



Chemical Formula: $C_{25}H_{34}N_6O_4$
Exact Mass: 482.2642

Yield: 238 mg (78%). Light-brown solid, mp: 122-123 °C. Purification: precipitation from cyclohexane; dr: 52/48. HPLC R_T: 16.4, 16.6 min; ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.46-7.4/2 (5H, m), 7.35-7.31 (3H, m), 7.25-7.21 (2H, m), 7.09 (2H, d, *J* = 6.8 Hz), 6.21 (2H, d, *J* = 3.0 Hz), 5.99 (2H, d, *J* = 6.5 Hz), 5.84 (1H, d, *J* = 9.3 Hz), 5.66 (1H, d, *J* = 9.3 Hz), 5.30-5.10 (2H, m), 4.97 (2H, dd, *J* = 8.5, 11.5 Hz), 4.83-4.52 (3H, m), 4.36-4.10 (3H, m), 1.95-1.84 (4H, m), 1.73-1.60 (8H, m), 1.47 (18H, s), 1.42 (2H, m), 1.26 (4H, m), 1.11 (2H, m), 0.99-0.88 (2H, m); ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.5, 170.3, 167.5, 166.6, 154.7, 133.9, 133.7, 133.4, 131.7, 131.5, 130.9, 130.4, 129.4, 129.2, 129.0, 128.8, 128.7, 127.6, 127.3, 126.1, 125.180.8, 80.7, 61.0, 60.9, 50.1, 50.0, 49.0, 48.9, 37.8, 37.5, 35.4, 34.7, 32.8, 32.6, 29.7, 28.3, 25.4, 25.3, 24.7, 24.6; HRMS (m/z) calcd. for $C_{23}H_{34}N_6O_4$ $(M+H)^+$: 483.2714, found: 483.2719.

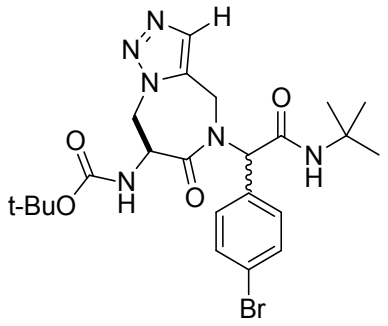
(*S*)-*tert*-Butyl (5-(2-(benzylamino)-2-oxo-1-phenylethyl)-6-oxo-5,6,7,8-tetrahydro-4*H*-[1,2,3]triazolo[1,5-a][1,4]diazepin-7-yl)carbamate (16)



Chemical Formula: $C_{26}H_{30}N_6O_4$
Exact Mass: 490.2329

Yield: 237 mg (76%). Brown solid, mp: 132-133 °C. Purification: column 30% EtOAc in cyclohexane; dr: 50/50. HPLC R_T: 15.5 min; ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.50-7.40 (4H, m), 7.38-7.27 (12H, m), 7.25-7.06 (6H, m), 6.72 (1H, s), 6.26 (2H, s), 6.04 (4H, dt, *J* = 7.1, 34.8 Hz), 5.31-5.12 (2H, m), 4.97 (2H, dd, *J* = 4.2, 14.4 Hz), 4.78 (1H, t, *J* = 17.2 Hz), 4.67 (1H, d, *J* = 4.2 Hz), 4.60-4.51 (2H, m), 4.41-4.33 (3H, m), 4.18 (2H, q, *J* = 14.4 Hz). 1.49 (9H, s), 1.48 (9H, s); ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.6, 170.4, 168.9, 168.1, 155.0, 137.7, 133.9, 133.8, 129.8, 127.9, 125.1, 81.0, 61.2, 61.1, 60.58, 50.1, 50.0, 49.0, 43.8, 43.6, 37.8, 37.5, 28.4, 21.1, 14.3; HRMS (m/z) calcd. for $C_{26}H_{30}N_6O_4$ $(M+H)^+$: 491.2401, found: 491.2410.

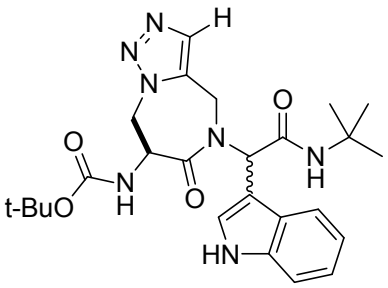
(*S*)-*tert*-Butyl (5-(1-(4-bromophenyl)-2-(*tert*-Butylamino)-2-oxoethyl)-6-oxo-5,6,7,8-tetrahydro-4*H*-[1,2,3]triazolo[1,5-a][1,4]diazepin-7-yl)carbamate (17)



Chemical Formula: $C_{23}H_{31}BrN_6O_4$
Exact Mass: 534.1590

Yield: 171 mg (74%). white solid, mp: 152-154 °C. Purification: 30% EtOAc in cyclohexane; dr: 53/47. HPLC R_T: 16.9, 17.1 min; ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.57 (2H, d, *J* = 8.3 Hz), 7.49 (1H, s), 7.43 (2H, d, *J* = 8.3 Hz), 7.25-7.22 (2H, s), 7.01 (2H, d, *J* = 8.3 Hz), 6.81 (1H, s), 6.07 (2H, d, *J* = 8.3 Hz), 5.94 (2H, t, *J* = 8.3 Hz), 5.48 (2H, d, *J* = 13.5 Hz), 5.31-5.12 (2H, m), 5.04-4.98 (2H, dd, *J* = 8.3, 16.5 Hz), 4.81 (1H, d, *J* = 16.5 Hz), 4.72 (1H, d, *J* = 8.3 Hz), 4.60 (1H, d, *J* = 8.3 Hz), 4.39 (1H, d, 16.5 Hz), 4.29-4.11 (2H, m), 1.48 (18H, s), 1.39 (9H, s), 1.19 (9H, s); ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.6, 170.3, 167.5, 166.2, 154.7, 133.1, 132.9, 132.5, 132.4, 131.9, 131.5, 131.2, 130.4, 130.4, 130.3, 123.6, 123.3, 81.0, 80.9, 60.4, 60.1, 52.4, 52.0, 50.1, 50.0, 48.9, 37.8, 37.3, 29.7, 28.7, 28.4, 28.3, 26.9; HRMS (m/z) calcd. for $C_{23}H_{31}BrN_6O_4$ $(M+H)^+$: 535.1663, 537.1646, found: 535.1650.

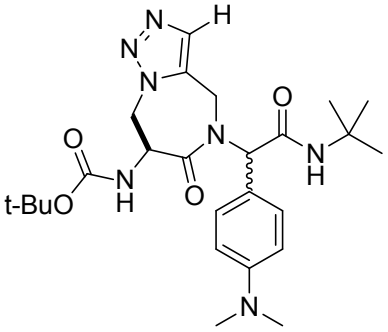
(*S*)-*tert*-Butyl (5-(2-(*tert*-Butylamino)-1-(1H-indol-3-yl)-2-oxoethyl)-6-oxo-5,6,7,8-tetrahydro-4*H*-[1,2,3]triazolo[1,5-a][1,4]diazepin-7-yl)carbamate (18)



Chemical Formula: $C_{25}H_{33}N_7O_4$
Exact Mass: 495.2594

Yield: 87 mg (40%). Orange solid, mp: 143-145 °C. Purification: 90% EtOAc in cyclohexane; dr: 58/42; HPLC R_T: 15.2 min; ^{1}H NMR (250 MHz, $CDCl_3$): δ 8.96 (2H, d, *J* = 6.1 Hz), 10.9, 11.1 (1H, m), 7.48-7.41 (4H, m), 7.30-7.27 (1H, m), 7.24-7.23 (2H, m), 7.20-7.14 (1H, m), 7.09-7.04 (2H, m), 6.89 (1H, t, *J* = 8.3 Hz), 6.44 (1H, s), 6.38 (1H, s), 6.07 (1H, s), 6.05 (1H, s), 5.90 (1H, s), 5.68 (1H, s), 5.28-5.05 (2H, m), 4.99-4.89 (2H, dd, *J* = 5.5, 22.0 Hz), 4.82-4.62 (4H, dd, 5.5, 22.0 Hz), 4.28-4.18 (1H, m), 4.13-4.00 (1H, m), 1.49 (18H, s), 1.40 (9H, s), 1.17 (9H, s); ^{13}C NMR (125 MHz, $CDCl_3$): δ 172.0, 170.4, 170.2, 168.7, 167.6, 155.2, 136.6, 136.3, 132.1, 131.9, 130.1, 130.0, 126.7, 126.6, 126.2, 125.3, 125.2, 123.6, 121.1, 120.9, 119.0, 118.8, 117.7, 112.2, 112.1, 109.5, 108.3, 81.3, 81.2, 55.4,, 55.1, 53.8, 52.4, 52.0, 50.4, 49.3, 49.2, 37.6, 36.6, 28.8, 28.7; HRMS (m/z) calcd. for $C_{25}H_{33}N_7O_4$ $(M+H)^+$: 496.2667, found: 496.2646.

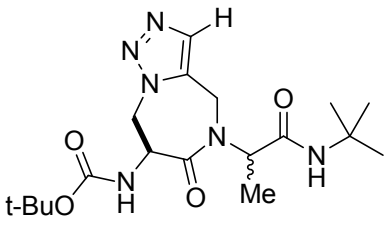
(*S*)-*tert*-Butyl (5-(2-(*tert*-Butylamino)-1-(4-(dimethylamino)phenyl)-2-oxoethyl)-6-oxo-5,6,7,8-tetrahydro-4*H*-[1,2,3]triazolo[1,5-a][1,4]diazepin-7-yl)carbamate (19)



Chemical Formula: $C_{25}H_{37}N_7O_4$
Exact Mass: 499.2907

Yield: 237 mg (76%). Yellow solid, mp: 145-146 °C. Purification: 40% EtOAc in cyclohexane; dr: 52/48; HPLC R_T: 11.9, 12.6 min, 12.507 min; ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.44 (1H, s), 7.18 (2H, d, *J* = 11.0 Hz), 6.95 (2H, d, *J* = 8.3 Hz), 6.74 (3H, t, *J* = 8.3 Hz), 6.54 (2H, d, *J* = 8.3 Hz), 6.04 (1H, s), 5.97 (1H, s), 5.46 (1H, s), 5.33 (1H, s), 5.27-5.06 (2H, m), 5.01-4.94 (2H, dd, *J* = 8.3, 19.3 Hz), 4.78-4.58 (4H, dd, *J* = 8.3, 19.3 Hz), 4.32-4.08 (4H, m), 3.00 (6H, s), 2.93 (6H, s), 1.48 (18H, s), 1.39 (9H, s), 1.22 (9H, s); ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.3, 169.9, 168.6, 167.3, 154.8, 150.8, 131.8, 131.7, 131.5, 130.4, 130.1, 129.8, 120.5, 120.2, 112.5, 112.2, 80.7, 61.8, 61.2, 52.0, 51.8, 50.1, 50.1, 48.9, 40.3, 40.2, 37.5, 37.0, 28.7, 28.5, 28.3; HRMS (m/z) calcd. for $C_{25}H_{37}N_7O_4$ $(M+H)^+$: 500.2980, found: 500.2963.

***tert*-Butyl ((7S)-5-(1-(*tert*-Butylamino)-1-oxopropan-2-yl)-6-oxo-5,6,7,8-tetrahydro-4*H*-[1,2,3]triazolo[1,5-a][1,4]diazepin-7-yl)carbamate (20)**

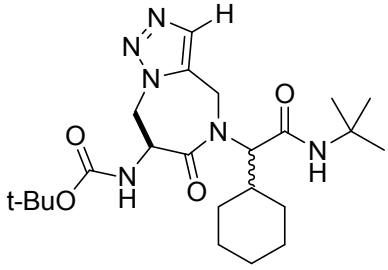


Chemical Formula: $C_{18}H_{30}N_6O_4$
Exact Mass: 394.2

A) Yield: 22 mg (26%) White powder? mp: 79-80 °C. Purification: preparative-HPLC; dr: 58/48. HPLC R_T: 13.2 min; ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.55 (1H, s), 5.90 (1H, d, *J* = 6.5 Hz), 5.44 (1H, s), 5.26-5.16 (1H, m), 5.10-5.07 (1H, m), 5.00 (1H, dd, *J* = 2.8, 8.5), 4.84 (1H, d, *J* = 19.0 Hz), 4.61 (1H, d, *J* = 19.0 Hz), 4.16 (1H, t, *J* = 12.5), 1.48 (9H, s), 1.37 (3H, d, *J* = 7.5 Hz), 1.03 (9H, s); ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.44, 168.1, 155.13, 132.3, 131.1, 81.2, 52.6, 51.6, 50.2, 48.6, 35.4, 28.4, 13.7; HRMS (m/z) calcd. for $C_{18}H_{31}N_6O_4$ $(M+H)^+$: 395.2401, found: 395.2408.

B) Yield: 24 mg (28%). White powder, mp: 100-102 °C. Purification: preparative-HPLC; dr: 58/48. HPLC R_T: 13.8 min; ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.56 (1H, s), 5.92 (1H, d, *J* = 6.5 Hz), 5.65 (1H, s), 5.25-5.15 (1H, m), 5.05-4.98 (2H, m), 4.91 (1H, d, *J* = 16 Hz), 4.65 (1H, d, *J* = 19.3 Hz), 4.179 (1H, t, *J* = 12 Hz), 1.49 (9H, s), 1.36 (9H, s), 1.25 (3H, d, *J* = 7.8 Hz); ^{13}C NMR (125 MHz, MeOH-d_4): δ 171.3, 170.9, 156.0, 80.2, 53.7, 51.1, 49.6, 19.1, 36.0, 27.6, 27.4, 14.6; HRMS (m/z) calcd. for $C_{18}H_{31}N_6O_4$ $(M+H)^+$: 395.2401, found: 395.2414.

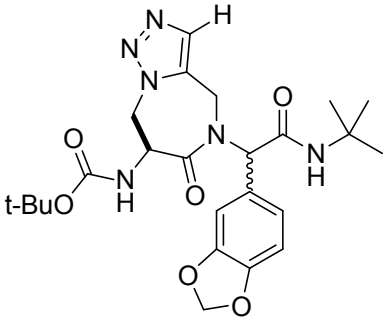
***tert*-Butyl ((7S)-5-(2-(*tert*-Butylamino)-1-cyclohexyl-2-oxoethyl)-6-oxo-5,6,7,8-tetrahydro-4*H*-[1,2,3]triazolo[1,5-a][1,4]diazepin-7-yl)carbamate (21)**



Chemical Formula: $C_{23}H_{38}N_6O_4$
Exact Mass: 462.2955

Yield: 89 mg (44%). brown oil. Purification: preparative-HPLC; dr: 64/36. HPLC R_T: 11.9, 12.2 min; ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.55 (1H, s), 5.91 (1H, d, *J* = 8.3 Hz), 5.56 (1H, s), 5.26-5.16 (1H, m), 5.10-4.94 (4H, m), 4.84 (1H, d, *J* = 17.3 Hz), 4.69-4.58 (1H, m), 4.16 (1H, t, *J* = 13.0 Hz), 1.48 (9H, s), 1.39 (1H, s), 1.36 (1H, s), 1.35 (4H, s), 1.25 (4H, s), 1.04 (8H, s); ^{13}C NMR (125 MHz, $CDCl_3$): δ 173.6, 170.3, 169.6, 154.9, 132.2, 132.1, 131.2, 81.2, 53.4, 52.7, 51.6, 50.4, 50.3, 48.7, 48.6, 36.3, 35.4, 28.8, 28.5, 28.4, 15.2, 13.8; HRMS (m/z) calcd. for $C_{23}H_{38}N_6O_4$ $(M+H)^+$: 463.3027, found: 463.3027.

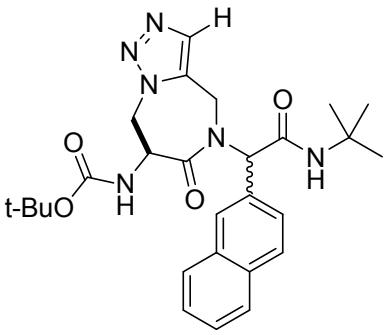
(*S*)-*tert*-Butyl (5-(1-(benzo[d][1,3]dioxol-5-yl)-2-(*tert*-Butylamino)-2-oxoethyl)-6-oxo-5,6,7,8-tetrahydro-4*H*-[1,2,3]triazolo[1,5-a][1,4]diazepin-7-yl)carbamate (22)



Chemical Formula: $C_{24}H_{32}N_6O_6$
Exact Mass: 500.2383

Yield: 146 mg (67%). Brown oil. Purification: 2% MeOH in dichloromethane; dr: 45/55. HPLC R_T: 15.6, 15.8 min; ^{1}H NMR (250 MHz, $CDCl_3$): δ 77.48 (1H, s), 7.27 (1H, s), 6.84 (3H, t, *J* = 7.5 Hz), 6.72-6.52 (3H, m), 6.05-5.92 (8H, m), 5.58 (1H, s), 5.48 (1H, s), 5.29-5.09 (2H, m), 5.02-4.99 (2H, dd, *J* = 7.5, 17.5 Hz), 4.78-4.65 (2H, m), 4.39-4.08 (4H, m), 1.48 (9H, s), 1.42 (9H, s), 1.39 (9H, s), 1.21 (9H, s); ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.5, 170.2, 168.2, 166.9, 154.9, 148.6, 148.4, 132.0, 131.8, 130.4, 127.9, 127.8, 122.7, 122.6, 109.1, 109.1, 108.9, 108.7, 101.7, 80.9, 61.0, 60.7, 52.2, 51.9, 50.2, 50.1, 49.0, 48.9, 37.6, 37.3, 29.8, 28.7, 28.5, 28.4, 27.0; HRMS (m/z) calcd. for $C_{24}H_{32}N_6O_6$ $(M+H)^+$: 501.2456, found: 501.2439.

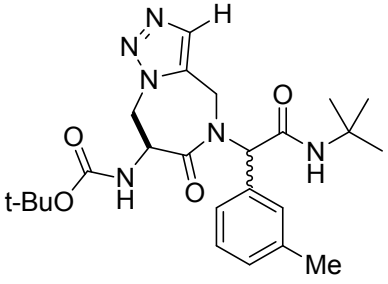
(*S*)-*tert*-Butyl (5-(2-(*tert*-Butylamino)-1-(naphthalen-2-yl)-2-oxoethyl)-6-oxo-5,6,7,8-tetrahydro-4*H*-[1,2,3]triazolo[1,5-a][1,4]diazepin-7-yl)carbamate (23)



Chemical Formula: $C_{27}H_{34}N_6O_4$
Exact Mass: 506.2642

Yield: 152 mg (69%). Light brown solid, mp: 184-186 °C. Purification: precipitation from hexane; dr: 53/47. HPLC R_T: 16.9 min; ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.96-7.86 (2H, m), 7.81-7.73 (4H, m), 7.68-7.65 (2H, m), 7.60 (2H, d, *J* =7.8 Hz), 7.59-7.51 (4H, m), 7.7.38 (1H, s), 7.35 (1H, d, *J* = 11.0 Hz), 6.99 (1H, dd, 2.8, 11.0 Hz), 6.49 (1H, s), 6.29 (2H, d, *J* = 5.5 Hz), 6.02 (2H, d, *J* = 5.5 Hz), 5.52 (2H, m), 5.32-5.14 (2H, m), 5.00 (2H, dd, *J* = 5.5, 13.8 Hz), 4.80-4.66 (2H, m), 4.34-4.20 (2H, m), 1.50 (18H, s), 1.44 (9H, s), 1.25 (9H, s); ^{13}C NMR (125 MHz, $CDCl_3$): δ 171.1, 171.0, 168.5, 166.6,155.0, 133.3, 132.0, 131.9, 131.7, 131.6, 131.5, 131.3, 130.6, 129.8, 129.4, 128.6, 128.4, 128.1, 128.0, 127.9, 127.4, 127.3, 127.1, 125.8, 125.7, 122.6, 81.1, 80.9, 61.6, 52.5, 52.1, 50.3, 50.2, 49.0, 38.0, 37.6, 28.9, 28.6, 28.4; HRMS (m/z) calcd. for $C_{27}H_{34}N_6O_4$ $(M+H)^+$: 507.2714, found: 507.2715.

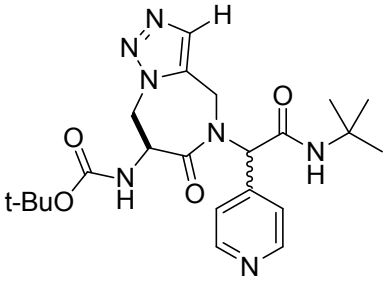
(*S*)-*tert*-Butyl (5-(2-(*tert*-Butylamino)-2-oxo-1-(m-tolyl)ethyl)-6-oxo-5,6,7,8-tetrahydro-4*H*-[1,2,3]triazolo[1,5-a][1,4]diazepin-7-yl)carbamate (24)



Chemical Formula: $C_{24}H_{34}N_6O_4$
Exact Mass: 470.2642

Yield: 154 mg (75%). Light brown solid, mp: 126-128 °C; Purification: precipitation from heptane; dr: 51/49. HPLC R_T: 16.5 min; ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.47 (1H, s), 7.35-7.16 (6H, m), 6.93-6.87 (2H, m), 6.68 (1H, s), 6.04 (4H, dd, *J* = 11, 27.5 Hz), 5.64 (1H, s), 5.49 (1H, s), 5.32-5.10 (2H, m), .02-4.93 (2H, m), 4.83-4.56 (3H, m), 4.39-4.10 (3H, m), 2.40 (3H, s), 2.23 (3H, s), 1.48 (18H, s), 1.41 (9H, s), 1.26 (9H, s); ^{13}C NMR (125 MHz, $CDCl_3$): δ 172.2, 170.9, 170.8, 168.7, 168.1, 139.2, 138.9, 135.6, 133.3, 133.1, 131.6, 130.4, 129.9, 129.8, 129.6, 129.4, 129.2, 128.9, 126.3, 80.2, 63.5, 61.7, 61.2, 54.5, 52.7, 51.7, 51.5, 49.8, 49.5, 49.3, 37.8, 37.5, 28.2, 28.1, 27.9, 25.0, 20.9, 20.7; HRMS (m/z) calcd. for $C_{24}H_{34}N_6O_4$ $(M+H)^+$: 471.2714, found: 471.2714.

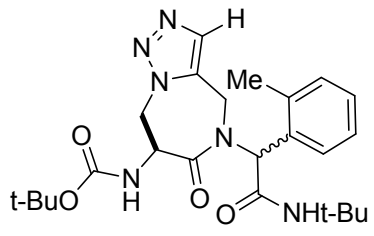
***tert*-Butyl ((7*S*)-5-(2-(*tert*-Butylamino)-2-oxo-1-(pyridin-4-yl)ethyl)-6-oxo-5,6,7,8-tetrahydro-4*H*-[1,2,3]triazolo[1,5-a][1,4]diazepin-7-yl)carbamate (25)**



Chemical Formula: $C_{22}H_{31}N_7O_4$
Exact Mass: 457.2438

Yield: 169 mg (85%). Off-white solid, mp: 128-129 °C; Purification: 10% MeOH in dichloromethane; dr: 54/46; HPLC R_T: 11.3, 12.1 min; ^{1}H NMR (250 MHz, $CDCl_3$): δ 8.63 (2H, s), 8.47 (2H, s), 7.47 (1H, s), 7.26-7.22 (1H, m), 7.12 (1H, d, *J* = 5.6 Hz), 6.97 (2H, d, *J* = 4.9 Hz), 6.78-6.74 (1H, m), 6.03 (2H, s), 5.88 (2H, t, *J* = 5.6 Hz), 5.68 (2H, d, *J* = 17.8 Hz), 5.26-5.14 (2H, m), 4.95 (2H, dd, *J* = 4.6, 13.6 Hz), 4.76 (2H, dd, *J* = 7.3, 18.2 Hz), 4.63-4.43 (2H, m), 4.23-4.09 (2H, m), 1.41 (18H, s), 1.35 (18H, s); ^{13}C NMR (125 MHz, $CDCl_3$): δ170.9, 166.9, 154.9, 150.4, 150.0, 149.7, 144.0, 143.6, 132.3, 131.7, 131.4, 130.9, 130.6, 123.5, 123.2, 121.6, 81.1, 59.9, 52.6, 50.3, 49.1, 38.4, 28.8, 28.5; HRMS (m/z) calcd. for $C_{22}H_{31}N_7O_4$ $(M+H)^+$: 458.2510, found: 458.2511.

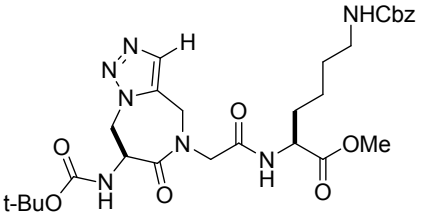
***tert*-Butyl ((7*S*)-5-(2-(*tert*-Butylamino)-2-oxo-1-(o-tolyl)ethyl)-6-oxo-5,6,7,8-tetrahydro-4*H*-[1,2,3]triazolo[1,5-a][1,4]diazepin-7-yl)carbamate (26)**



Chemical Formula: $C_{24}H_{34}N_6O_4$
Exact Mass: 470.2642

Yield: 191 mg (93%). Light brown solid, mp: 123-125 °C; Purification: precipitation from hexane; dr: 52/48. HPLC R_T: 16.0 min; ^{1}H NMR (250 MHz, MeCN-d_3): δ 7.38-7.03 (10H, m), 6.52 (2H, d, *J* = 12.3 Hz), 5.99 (2H, dd, *J* = 5.8, 12.8 Hz), 5.61 (1H, s), 5.32 (1H, m), 5.23-5.09 (2H, m), 5.08-4.94 (2H, m), 4.80 (1H, d, *J* = 17.0 Hz), 4.47 (1H, d, *J* = 17.0 Hz), 4.29 (2H, t, *J* = 12.5 Hz), 4.11 (2H, t, *J* = 12.5 Hz), 2.27 (3H, s), 1.74 (3H, s), 1.50 (18H, s), 1.40 (9H, s), 1.25 (9H, s); ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.7, 169.1, 167.2, 154.9, 154.9, 138.3, 133.8, 132.3, 132.0, 131.8,131.8, 131.6, 131.3, 131.2, 130.6, 130.2, 130.1, 129.6, 129.6, 129.4, 129.0, 128.5, 128.4, 127.0, 126.6, 125.5, 101.8, 80.8, 60.6, 59.3, 53.1, 52.8, 52.2, 51.9, 50.2, 50.0, 49.1, 48.9, 37.6, 36.9, 28.8, 28.6, 28.4; HRMS (m/z) calcd. for $C_{24}H_{34}N_6O_4$ $(M+H)^+$: 471.2714, found: 471.2716.

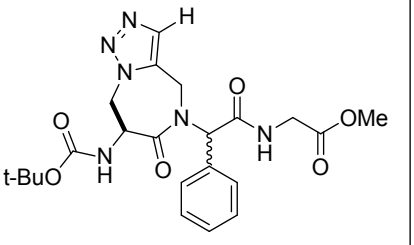
(*S*)-methyl 6-(((benzyloxy)carbonyl)amino)-2-(2-((*S*)-7-((*tert*-butoxycarbonyl)amino)-6-oxo-7,8-dihydro-4*H*-[1,2,3]triazolo[1,5-a][1,4]diazepin-5(6*H*)-yl)acetamido)hexanoate (28)



Chemical Formula: $C_{28}H_{39}N_7O_8$
Exact Mass: 601.2860

Yield: 66 mg (51%). White powder, mp: 71-72 °C; Purification: Preparative HPLC (5-100% MeCN in 20 mins); HPLC R_T: 15.1 min; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.05 (1H, s), 7.58 (1H, s), 7.33 (5H, s), 6.84-6.82 (1H, m), 6.00-5.99 (1H, m),5.24-5.14 (2H, m),5.09 (2H, m), 5.01-4.93 (2H, m), 4.51-4.45 (2H, m) 4.27-4.20 (2H, m), 4.19-4.06 (1H, d, *J* = 16 Hz), 3.70-3.69 (3H, s), 3.16-3.15 (2H, m), 1.82-1.75 (1H, m),1.67-1.58 (1H, m),1.46 (9H, s), 1.25 (2H, m); ^{13}C NMR (125 MHz, $CDCl_3$): δ 172.6, 170.6, 167.2, 156.9, 156.9, 155.0, 136.7, 131.5, 130.9, 128.7, 128.3, 128.1, 81.1, 66.8, 52.7, 52.3, 51.8, 50.2, 48.8, 42.3, 40.4, 31.4, 29.3, 28.4, 22.1; HRMS (m/z) calcd. for $C_{28}H_{39}N_7O_8Na$ $(M+Na)^+$: 624.2752, found: 624.2747

Methyl-2-(2-((*S*)-7-((*tert*-butoxycarbonyl)amino)-6-oxo-7,8-dihydro-4*H*-[1,2,3]triazolo[1,5-a][1,4]diazepin-5(6*H*)-yl)-2-phenylacetamido)acetate (30)

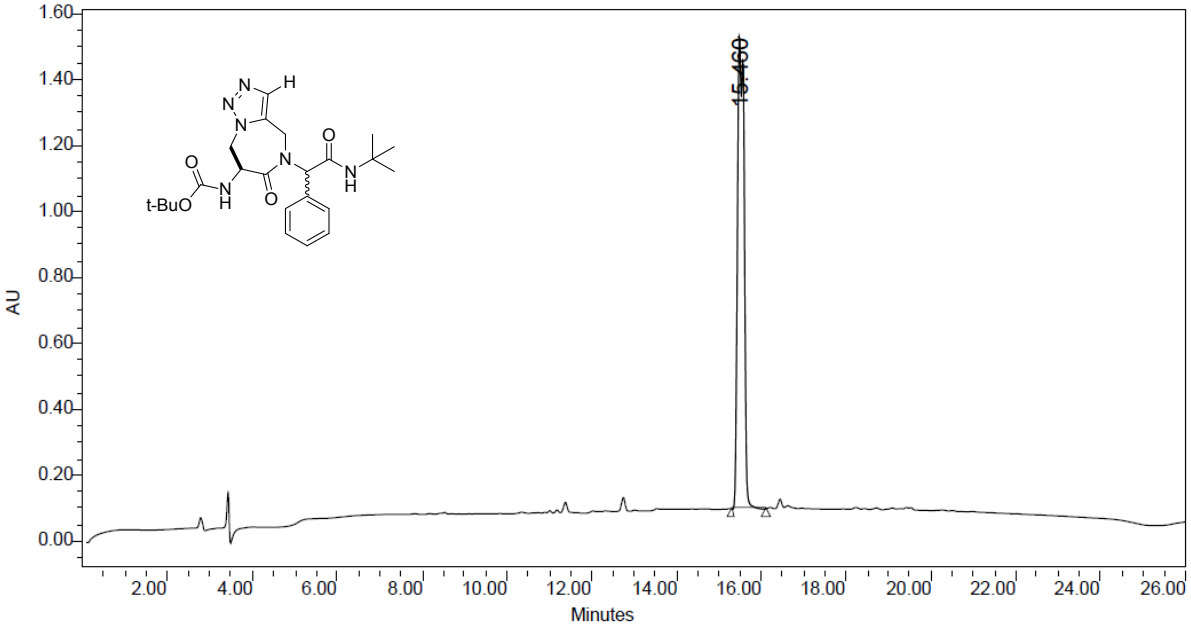


Chemical Formula: $C_{22}H_{28}N_6O_6$
Exact Mass: 472.2

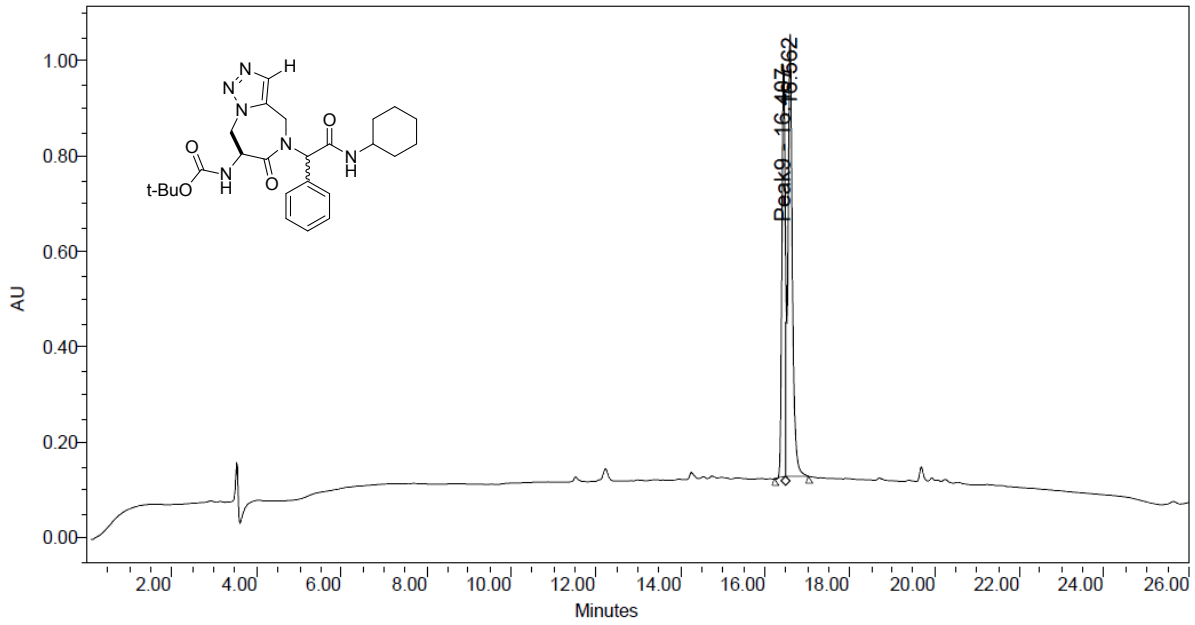
Yield: 43% (over four steps). Brown powder, mp: 91-92 °C; Purification: Preparative HPLC (5-100% MeCN in 20 mins); HPLC R_T: 13.2, 13.7 min; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.48-7.28 (10H, m), 7.18 (2H, d, *J* = 9.3 Hz), 6.78 (1H, s), 6.37 (2H, s), 6.22 (1H, s), 5.98 (2H, s), 5.29-5.16 (2H, m), 4.99 (1H, d, *J* = 18.0 Hz), 4.82 (1H, d, *J* = 18.0 Hz), 4.61 (2H, t, *J* = 18.0 Hz), 4.42 (2H, t, *J* = 18.0 Hz), 4.38-4.28 (1H, m), 4.24-4.19 (2H, m), 4.07-3.88 (3H, m), 3.79 (3H, s), 3.71 (3H, s), 1.49 (18 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.6, 169.8, 169.1, 168.2, 155.0, 133.3, 133.0, 131.8, 131.4, 130.4, 129.7, 129.4, 129.1, 81.3, 81.1, 61.3, 61.1, 52.7, 50.3, 49.0, 48.9, 48.9, 41.5, 41.3, 37.9, 37.6, 28.4; HRMS (m/z) calcd. for $C_{22}H_{29}N_6O_6$ $(M+H)^+$: 473.2143, found: 473.2132

5. HPLC Chromatograms

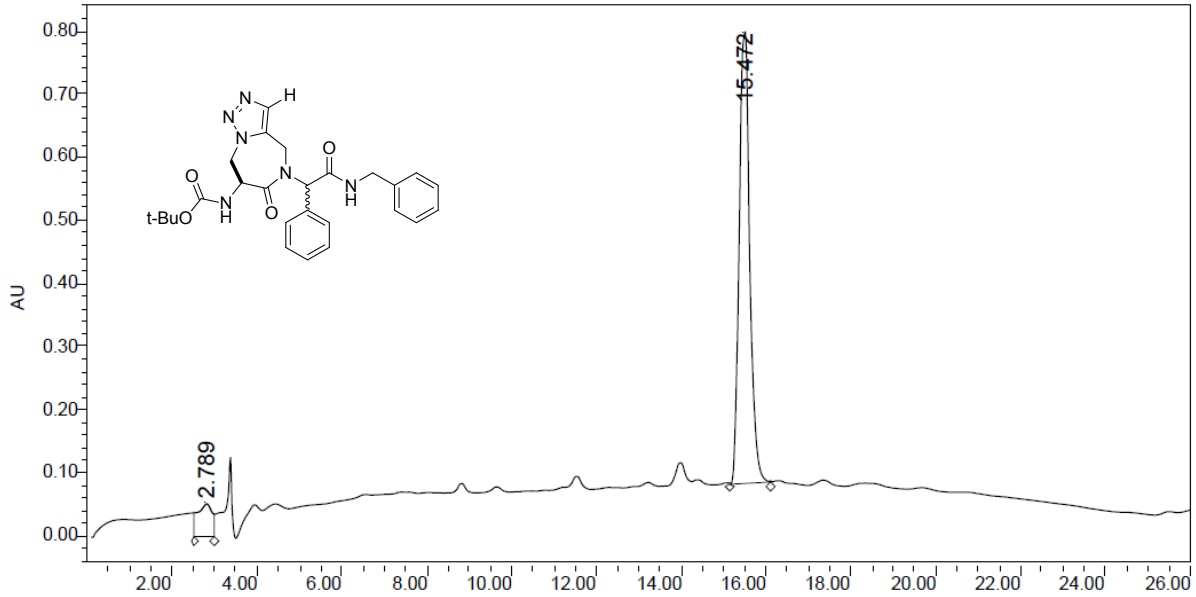
(*S*)-*tert*-Butyl (5-(2-(tert-Butylamino)-2-oxo-1-phenylethyl)-6-oxo-5,6,7,8-tetrahydro-4*H*-[1,2,3]triazolo[1,5-a][1,4]diazepin-7-yl)carbamate (14)



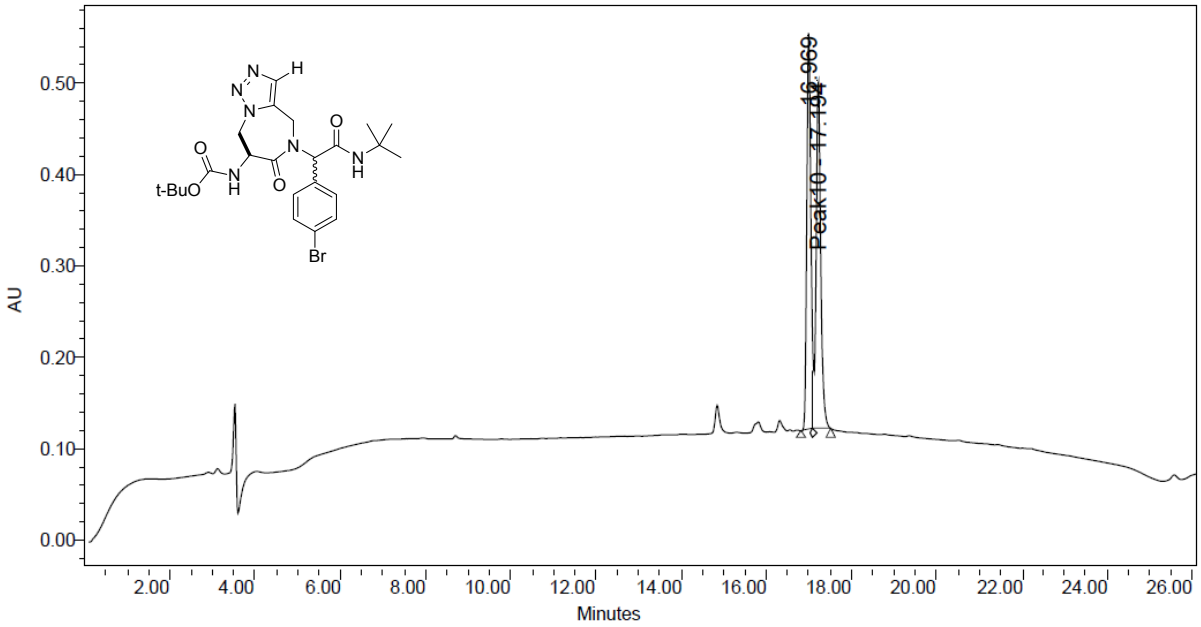
(*S*)-*tert*-Butyl (5-(2-(cyclohexylamino)-2-oxo-1-phenylethyl)-6-oxo-5,6,7,8-tetrahydro-4*H*-[1,2,3]triazolo[1,5-a][1,4]diazepin-7-yl)carbamate (15)



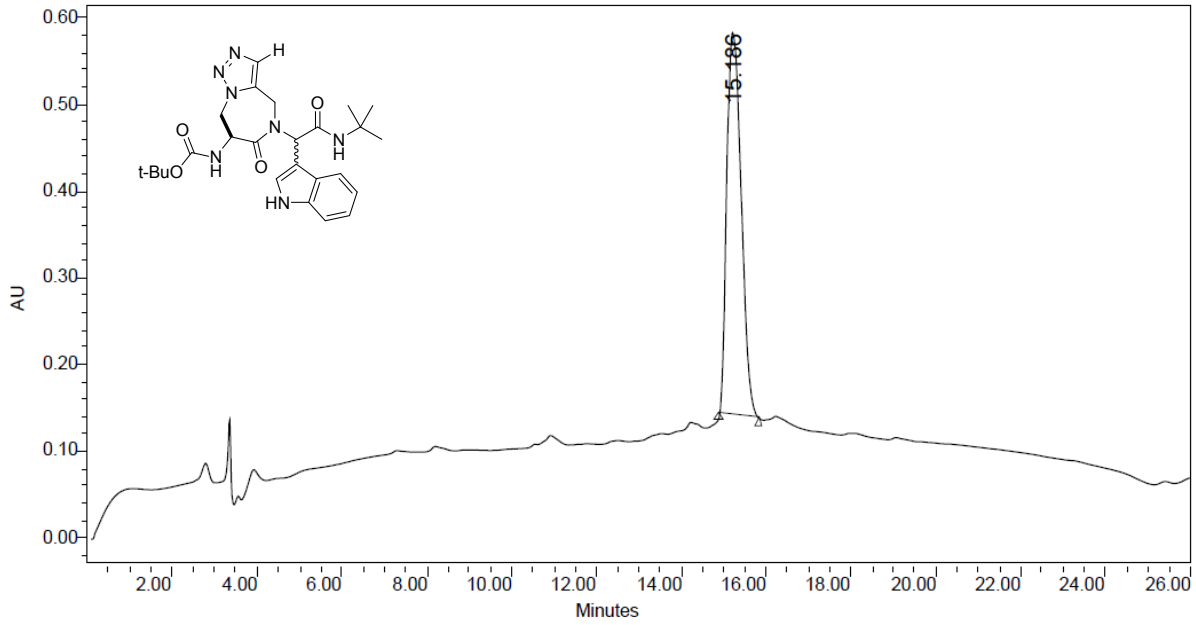
(*S*)-*tert*-Butyl (5-(2-(benzylamino)-2-oxo-1-phenylethyl)-6-oxo-5,6,7,8-tetrahydro-4*H*-[1,2,3]triazolo[1,5-a][1,4]diazepin-7-yl)carbamate (16)



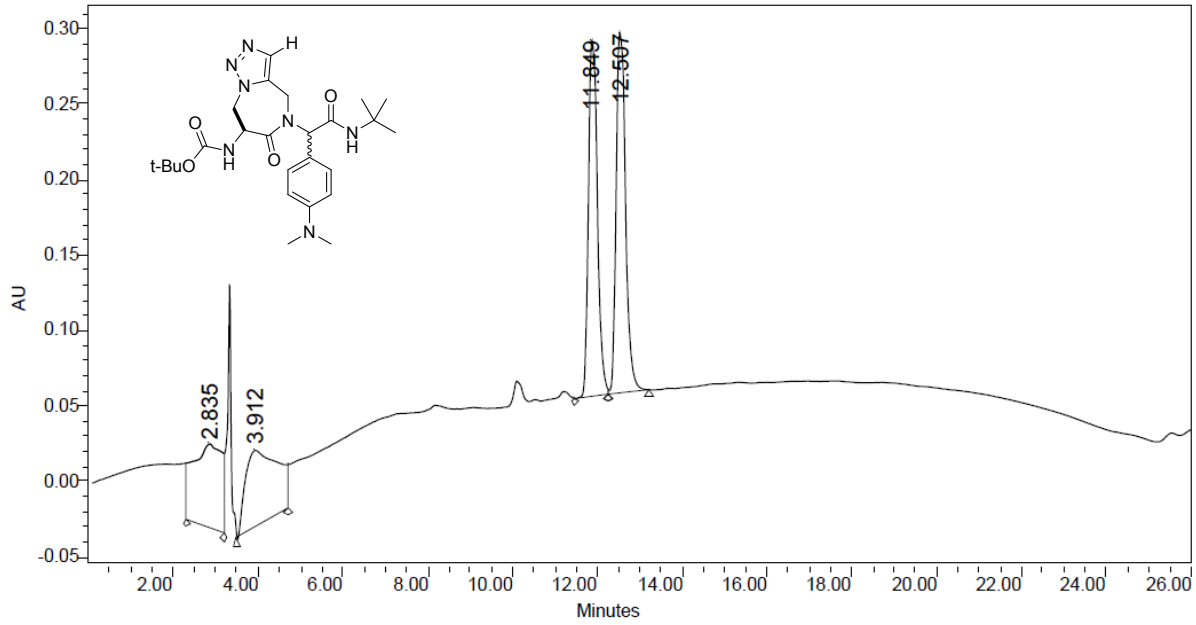
(*S*)-*tert*-Butyl (5-(1-(4-bromophenyl)-2-(*tert*-Butylamino)-2-oxoethyl)-6-oxo-5,6,7,8-tetrahydro-4*H*-[1,2,3]triazolo[1,5-a][1,4]diazepin-7-yl)carbamate (17)



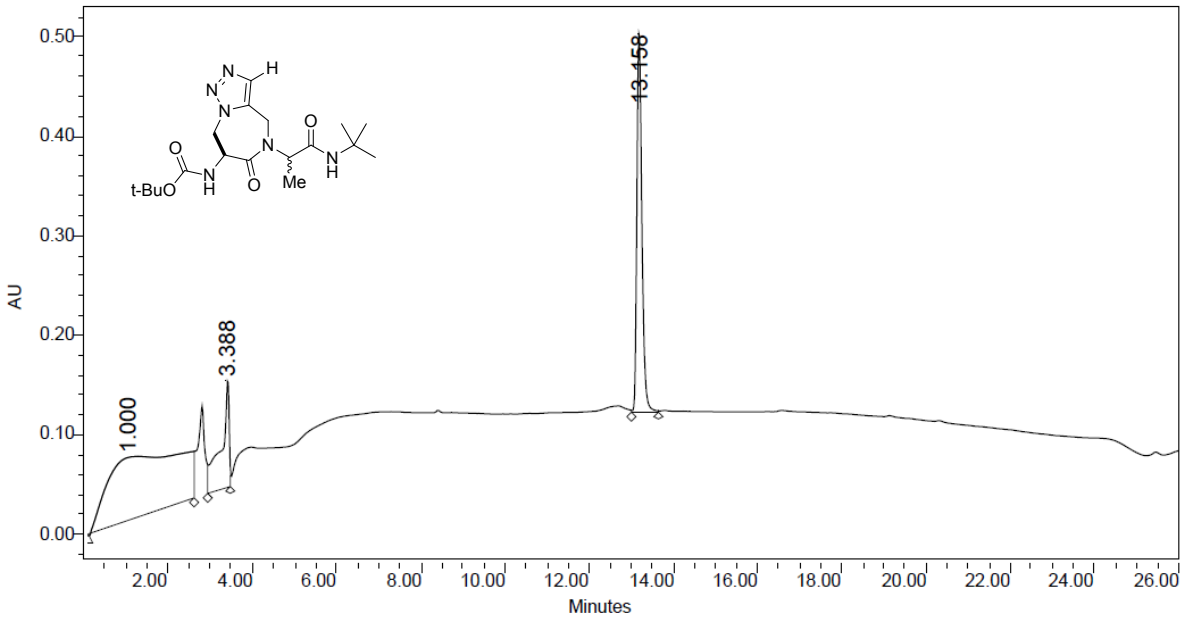
(*S*)-*tert*-Butyl (5-(2-(*tert*-Butylamino)-1-(1H-indol-3-yl)-2-oxoethyl)-6-oxo-5,6,7,8-tetrahydro-4*H*-[1,2,3]triazolo[1,5-a][1,4]diazepin-7-yl)carbamate (18)



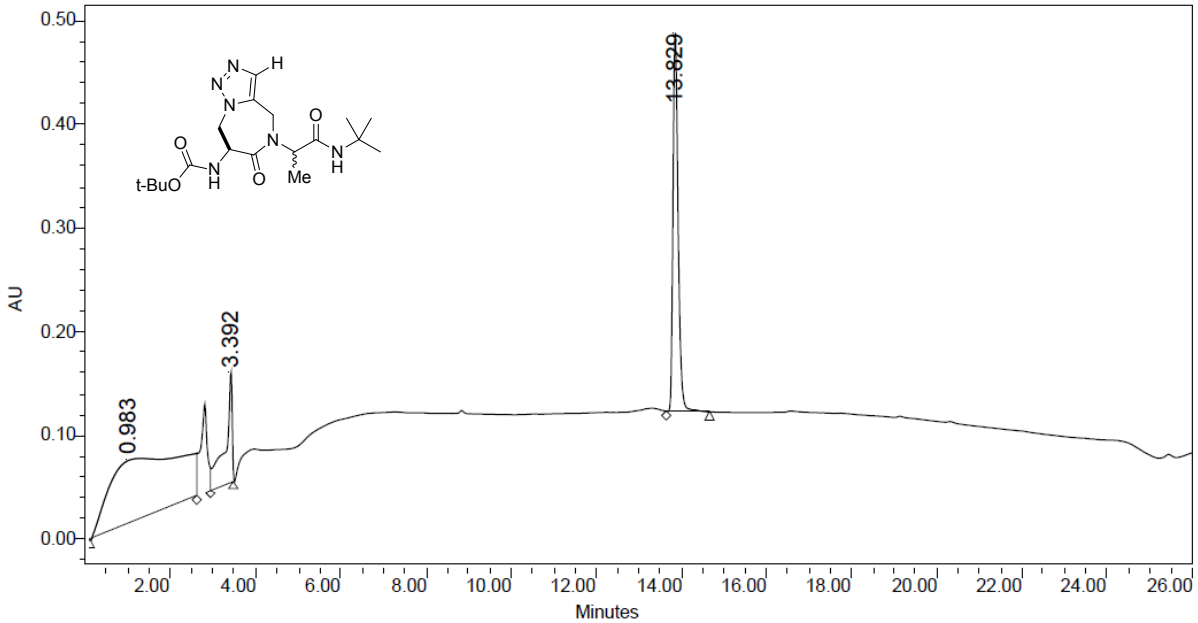
(*S*)-*tert*-Butyl (5-(2-(*tert*-Butylamino)-1-(4-(dimethylamino)phenyl)-2-oxoethyl)-6-oxo-5,6,7,8-tetrahydro-4*H*-[1,2,3]triazolo[1,5-a][1,4]diazepin-7-yl)carbamate (19)



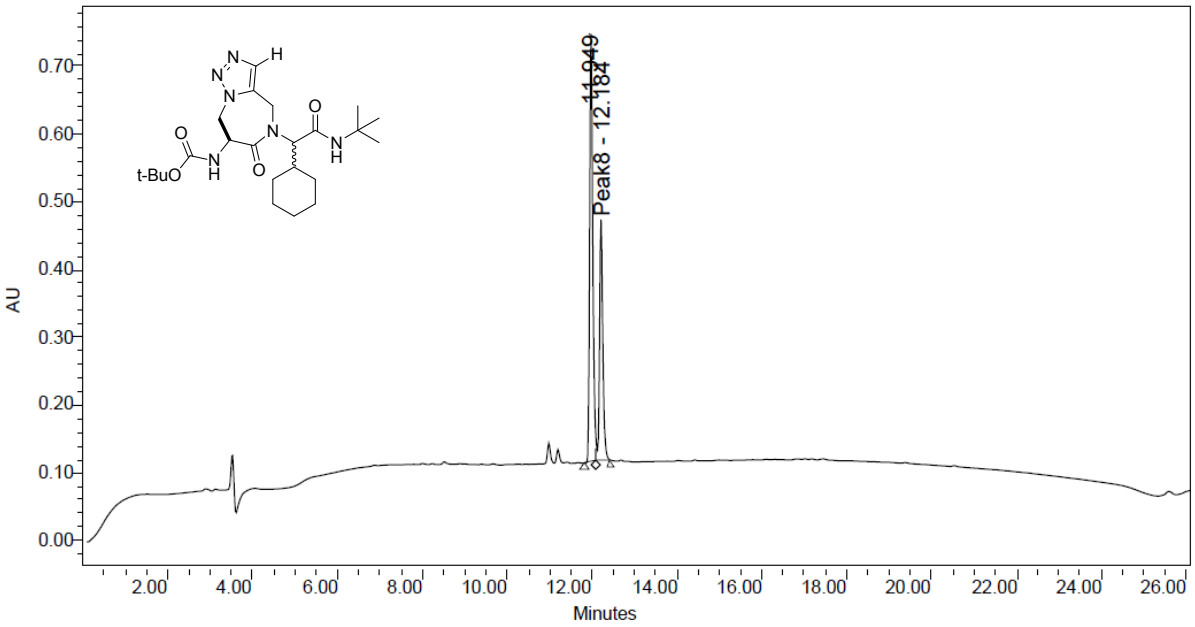
First diastereoisomer of ***tert*-Butyl ((7S)-5-(1-(*tert*-Butylamino)-1-oxopropan-2-yl)-6-oxo-5,6,7,8-tetrahydro-4*H*-[1,2,3]triazolo[1,5-a][1,4]diazepin-7-yl)carbamate (20)**



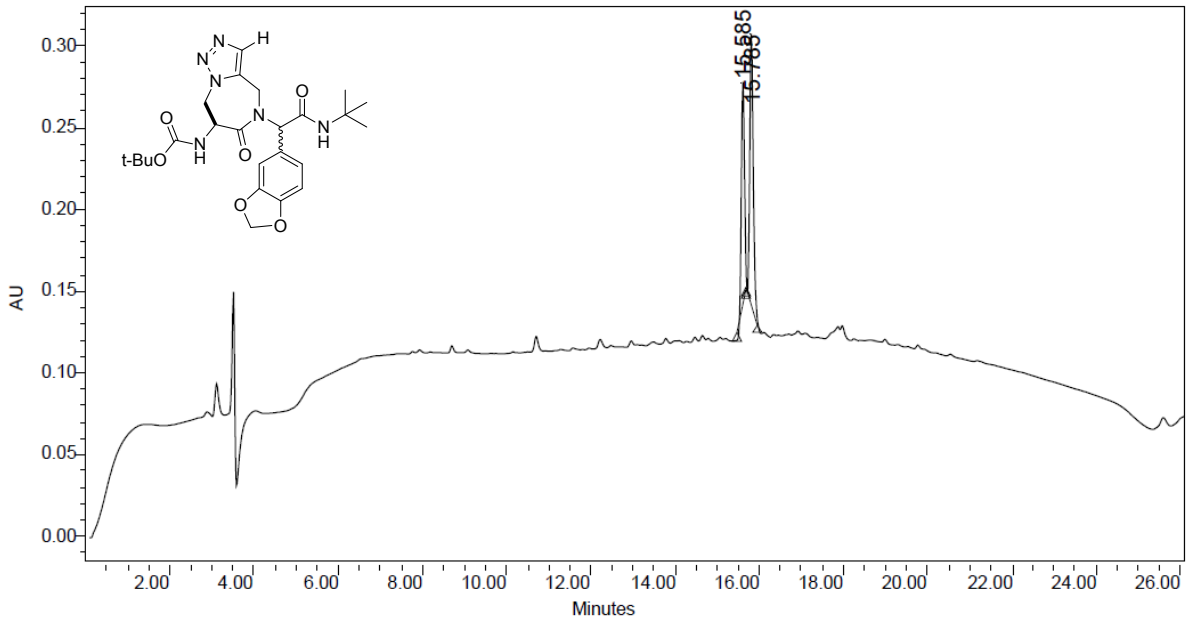
Second diastereoisomer of ***tert*-Butyl ((7S)-5-(1-(*tert*-Butylamino)-1-oxopropan-2-yl)-6-oxo-5,6,7,8-tetrahydro-4*H*-[1,2,3]triazolo[1,5-a][1,4]diazepin-7-yl)carbamate (20)**



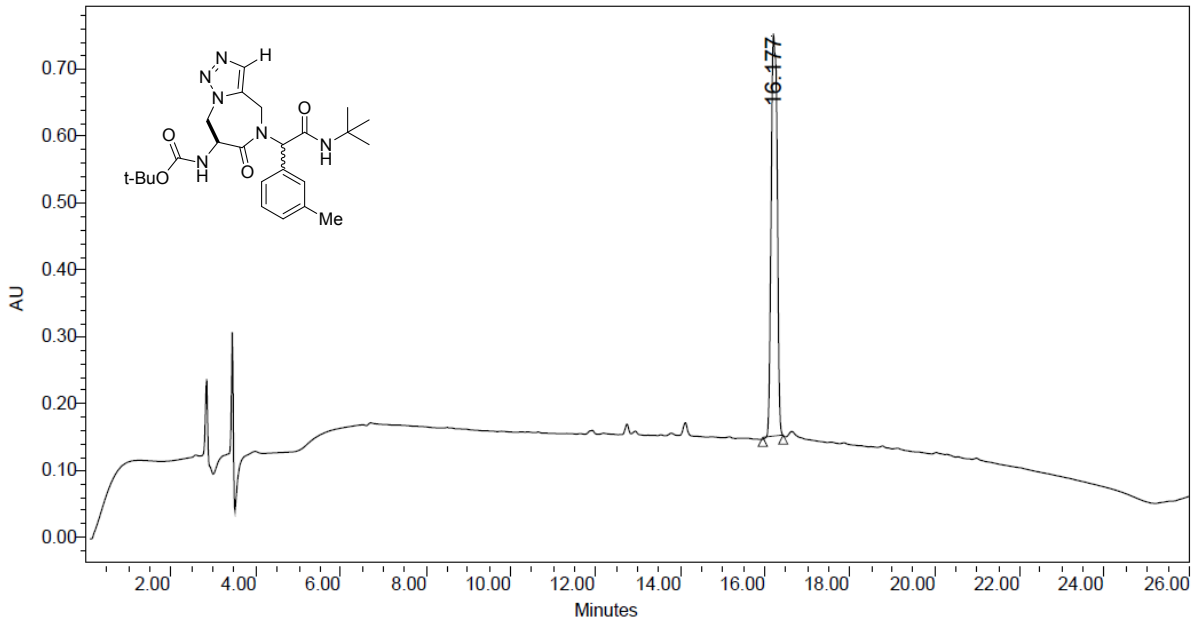
***tert*-Butyl ((7S)-5-(2-(*tert*-Butylamino)-1-cyclohexyl-2-oxoethyl)-6-oxo-5,6,7,8-tetrahydro-4*H*-[1,2,3]triazolo[1,5-a][1,4]diazepin-7-yl)carbamate (21)**



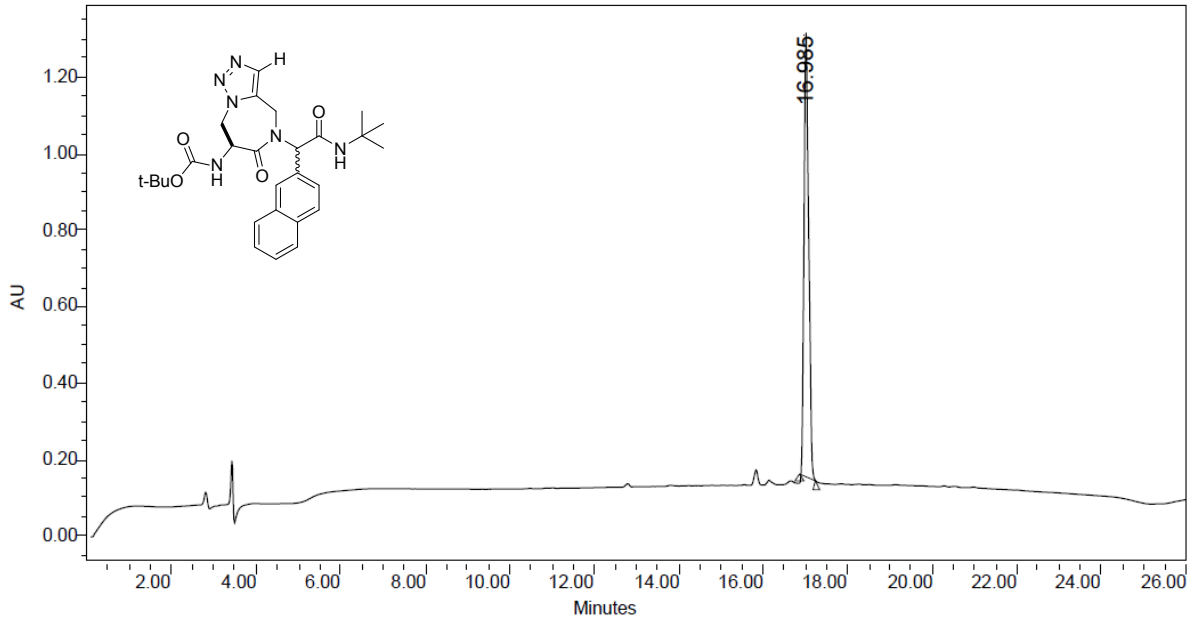
(*S*)-*tert*-Butyl (5-(1-(benzo[d][1,3]dioxol-5-yl)-2-(*tert*-Butylamino)-2-oxoethyl)-6-oxo-5,6,7,8-tetrahydro-4*H*-[1,2,3]triazolo[1,5-a][1,4]diazepin-7-yl)carbamate (22)



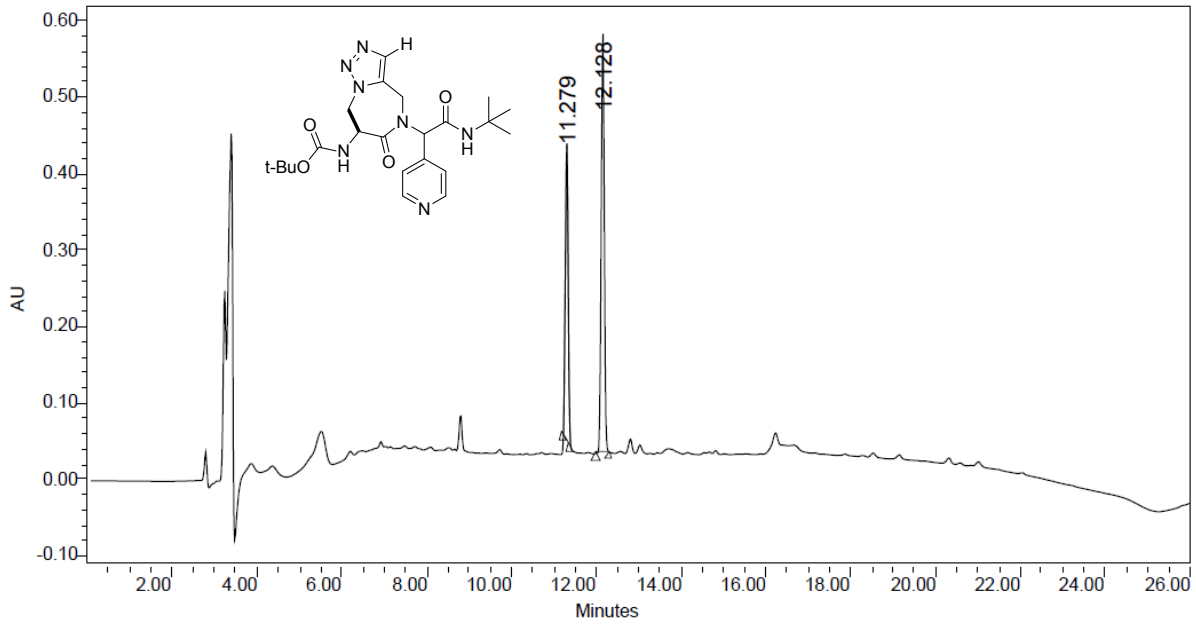
(*S*)-*tert*-Butyl (5-(2-(*tert*-Butylamino)-2-oxo-1-(m-tolyl)ethyl)-6-oxo-5,6,7,8-tetrahydro-4*H*-[1,2,3]triazolo[1,5-a][1,4]diazepin-7-yl)carbamate (24)



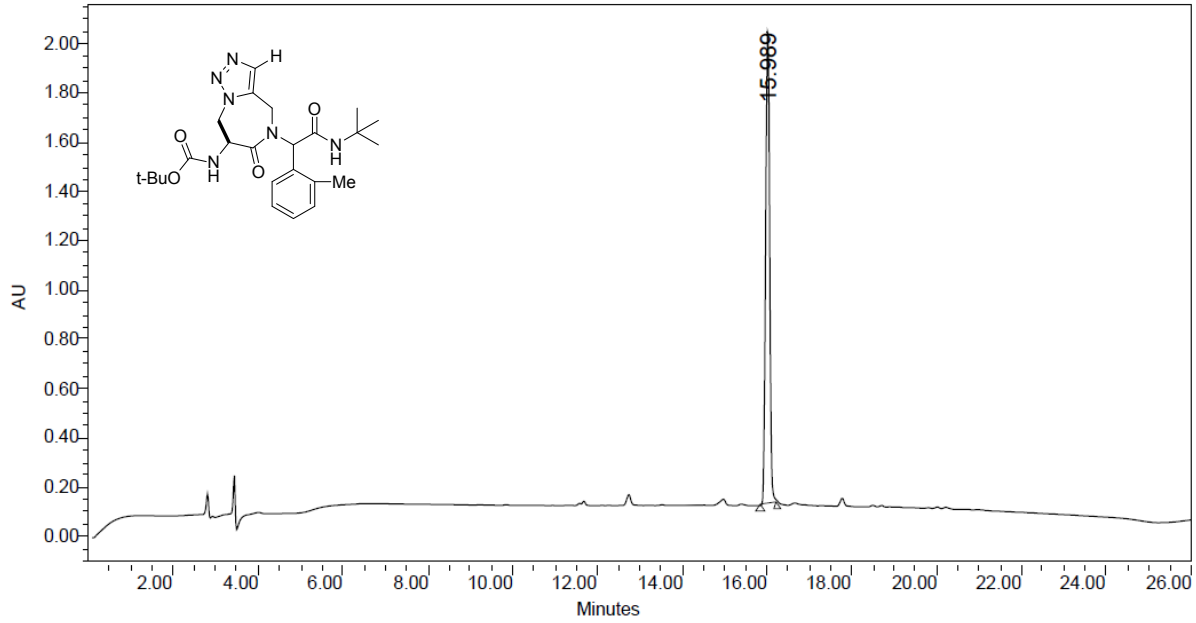
(*S*)-*tert*-Butyl (5-(2-(*tert*-Butylamino)-1-(naphthalen-2-yl)-2-oxoethyl)-6-oxo-5,6,7,8-tetrahydro-4*H*-[1,2,3]triazolo[1,5-a][1,4]diazepin-7-yl)carbamate (23)



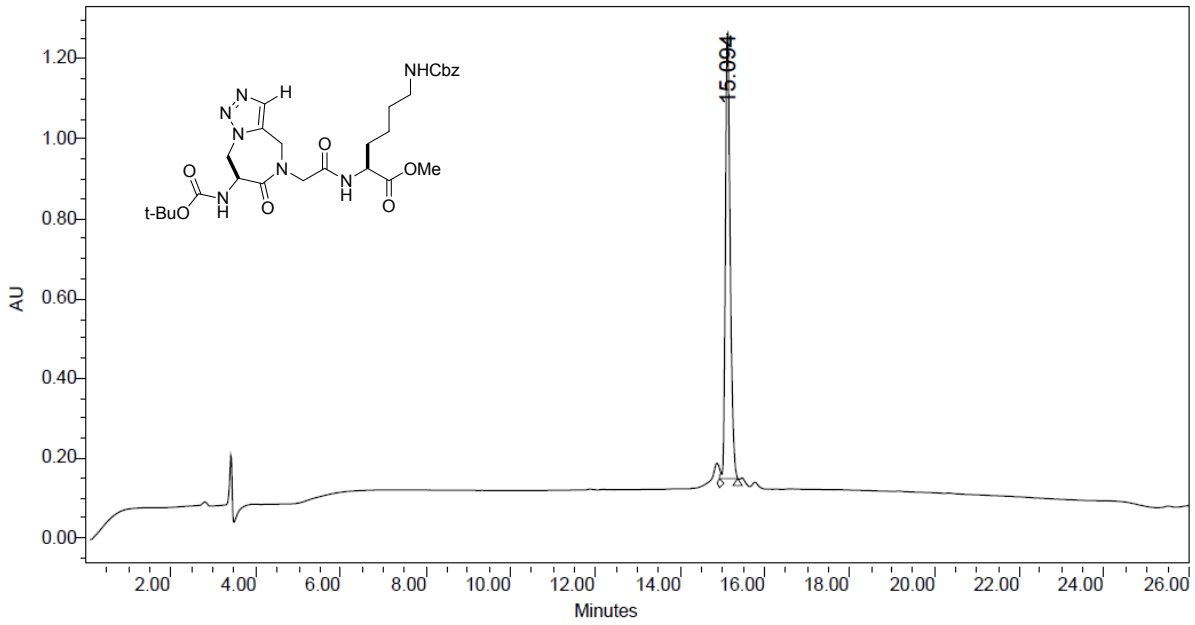
***tert*-Butyl ((7*S*)-5-(2-(*tert*-Butylamino)-2-oxo-1-(pyridin-4-yl)ethyl)-6-oxo-5,6,7,8-tetrahydro-4*H*-[1,2,3]triazolo[1,5-a][1,4]diazepin-7-yl)carbamate (25)**



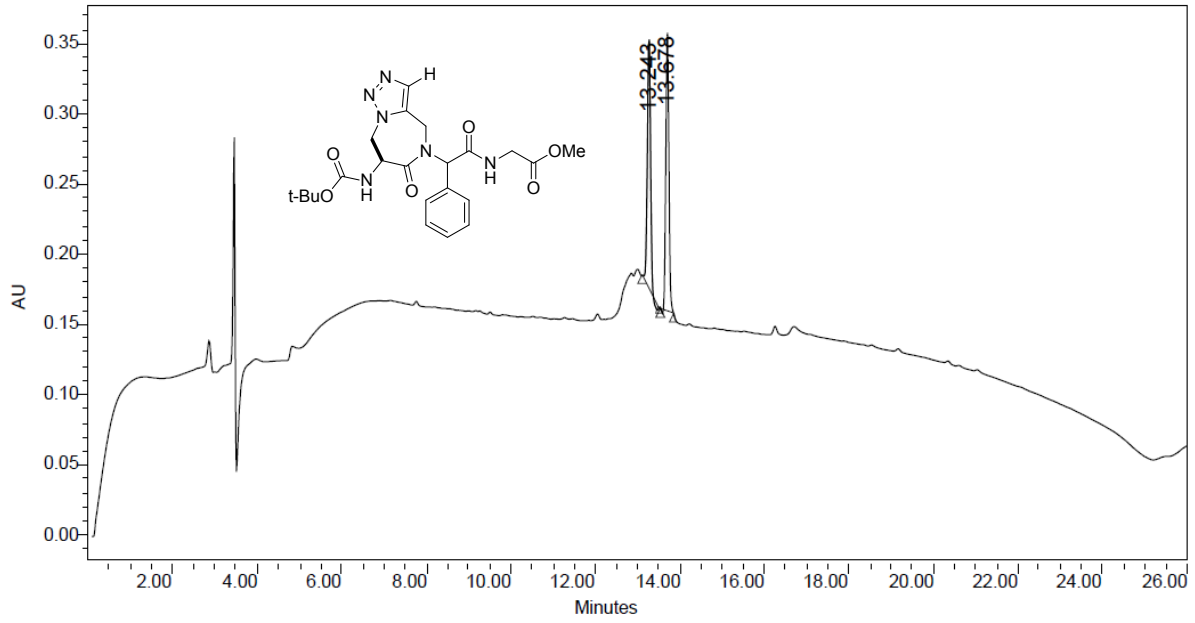
***tert*-Butyl ((7*S*)-5-(2-(*tert*-Butylamino)-2-oxo-1-(o-tolyl)ethyl)-6-oxo-5,6,7,8-tetrahydro-4*H*-[1,2,3]triazolo[1,5-a][1,4]diazepin-7-yl)carbamate (26)**



(*S*)-methyl 6-(((benzyloxy)carbonyl)amino)-2-(2-((*S*)-7-((*tert*-butoxycarbonyl)amino)-6-oxo-7,8-dihydro-4*H*-[1,2,3]triazolo[1,5-a][1,4]diazepin-5(6*H*)-yl)acetamido)hexanoate (28)

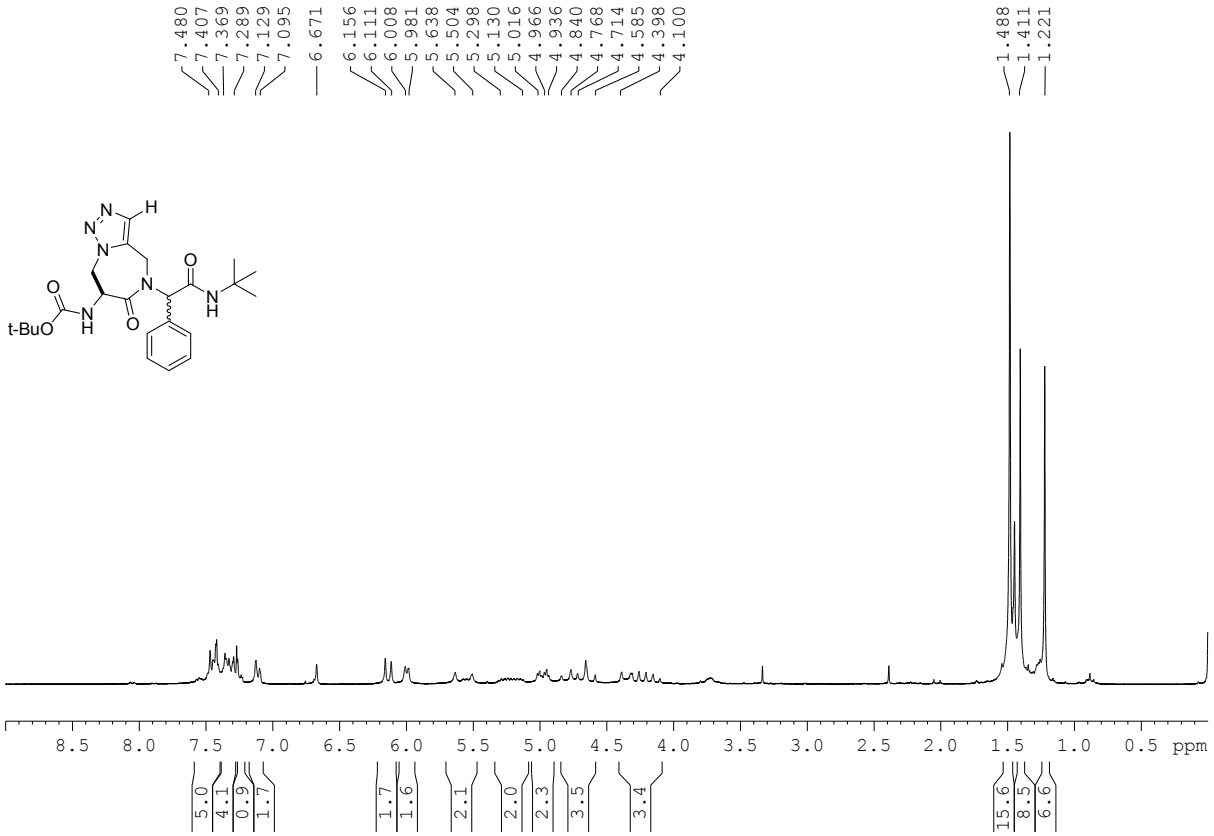


Methyl-2-(2-((*S*)-7-((*tert*-butoxycarbonyl)amino)-6-oxo-7,8-dihydro-4*H*-[1,2,3]triazolo[1,5-a][1,4]diazepin-5(6*H*)-yl)-2-phenylacetamido)acetate (30)

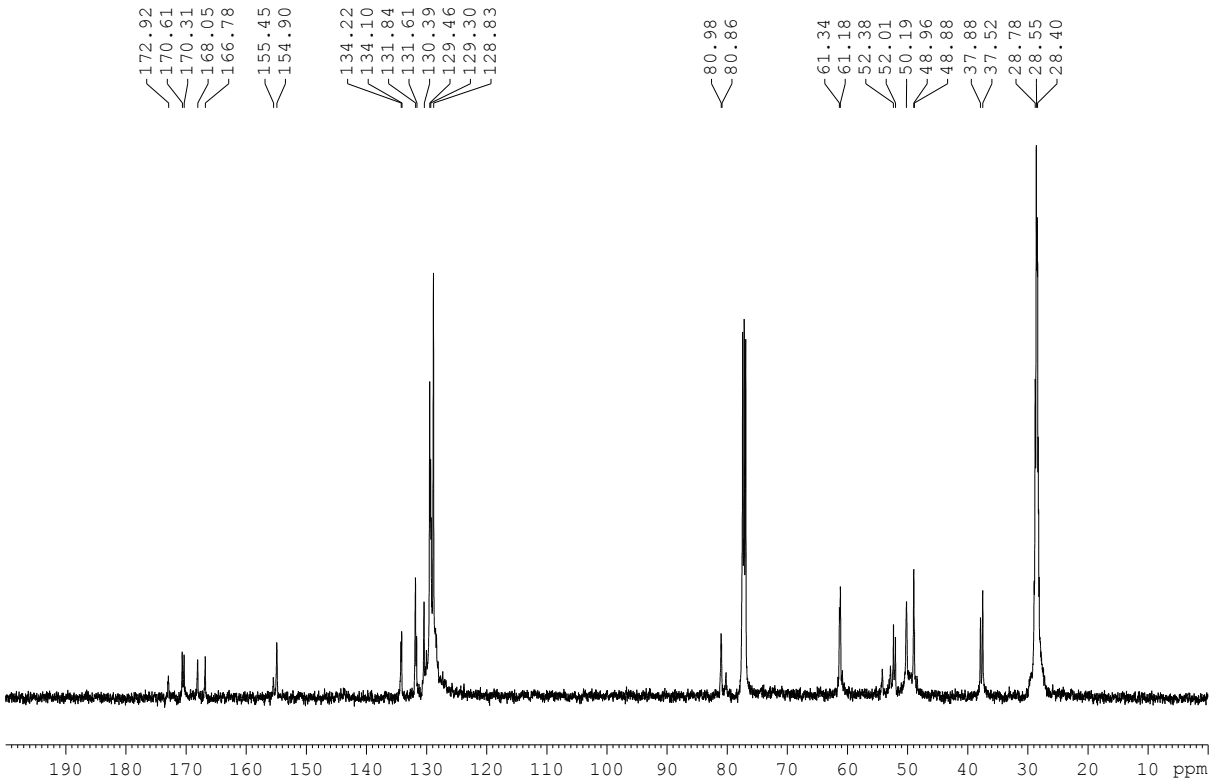


6. NMR Spectral Data

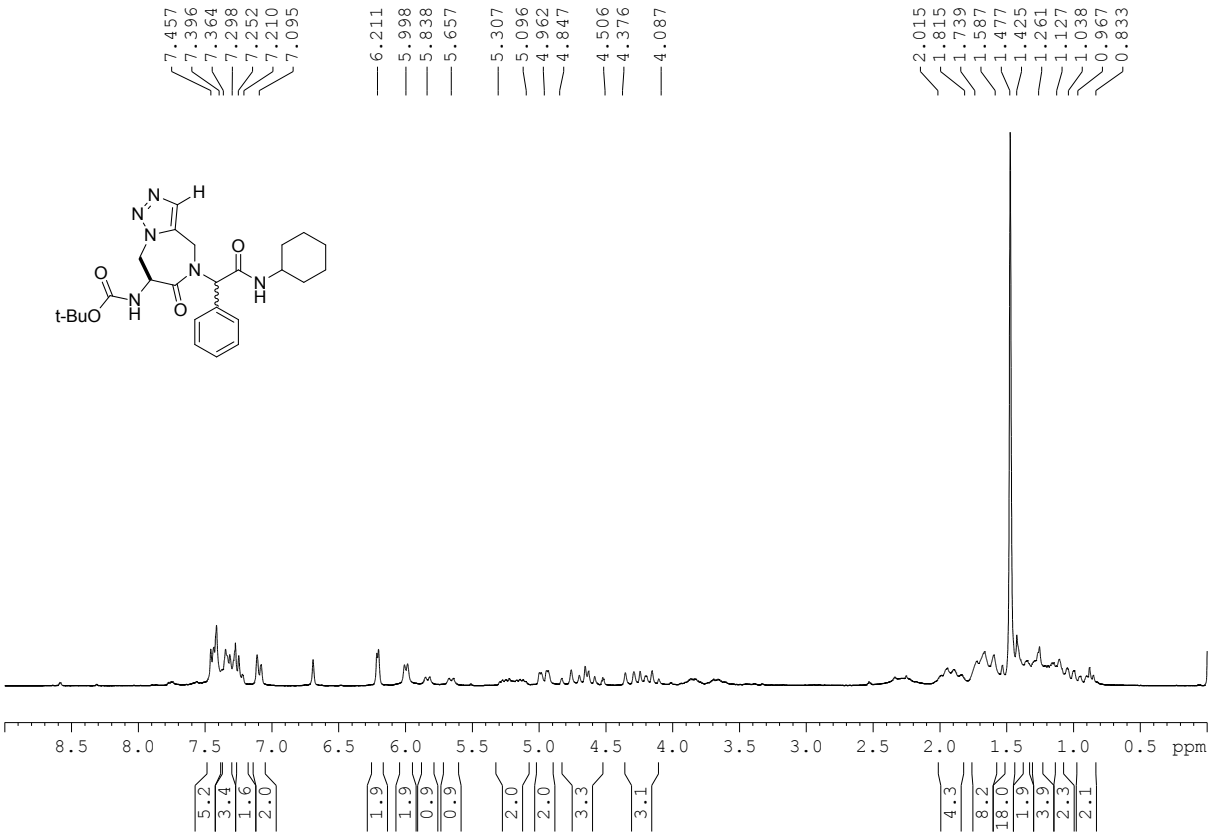
14 - ^{1}H NMR (250 MHz, $CDCl_3$)



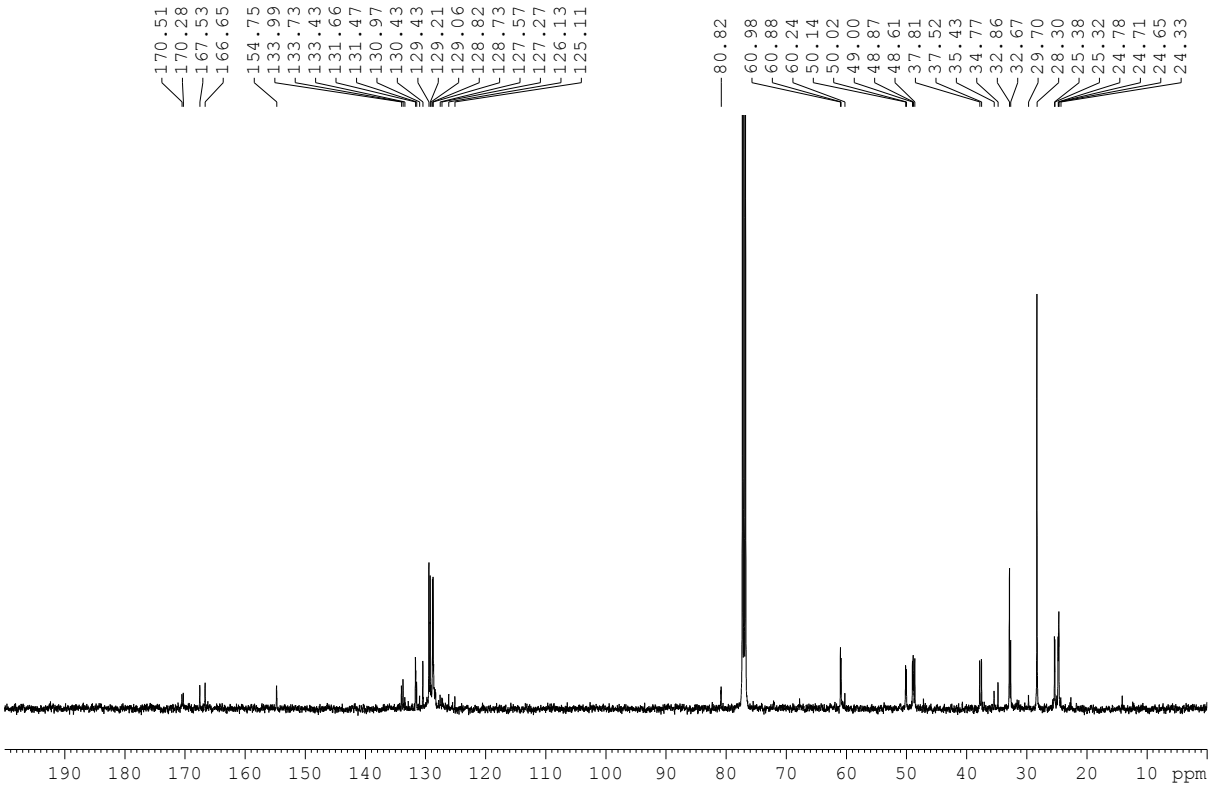
14 - ^{13}C NMR (125 MHz, $CDCl_3$)



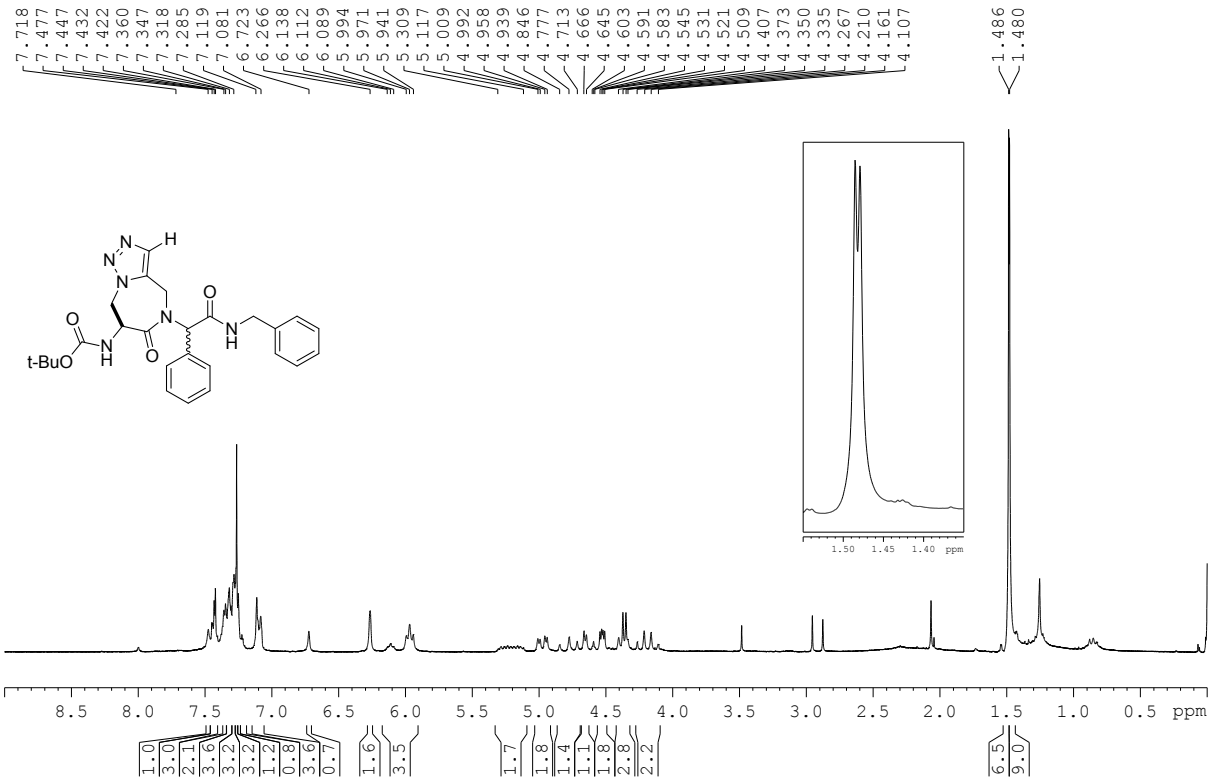
15 - ^{1}H NMR (250 MHz, $CDCl_3$)



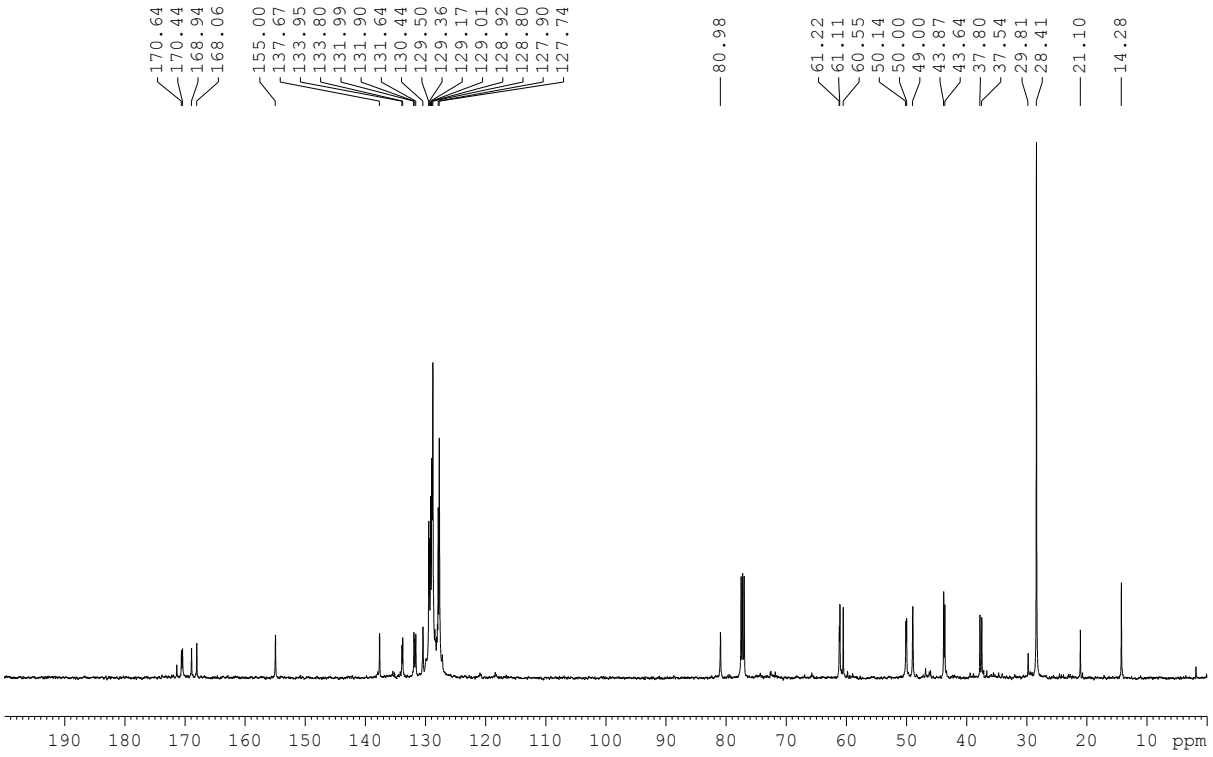
15 - ^{13}C NMR (125 MHz, $CDCl_3$)



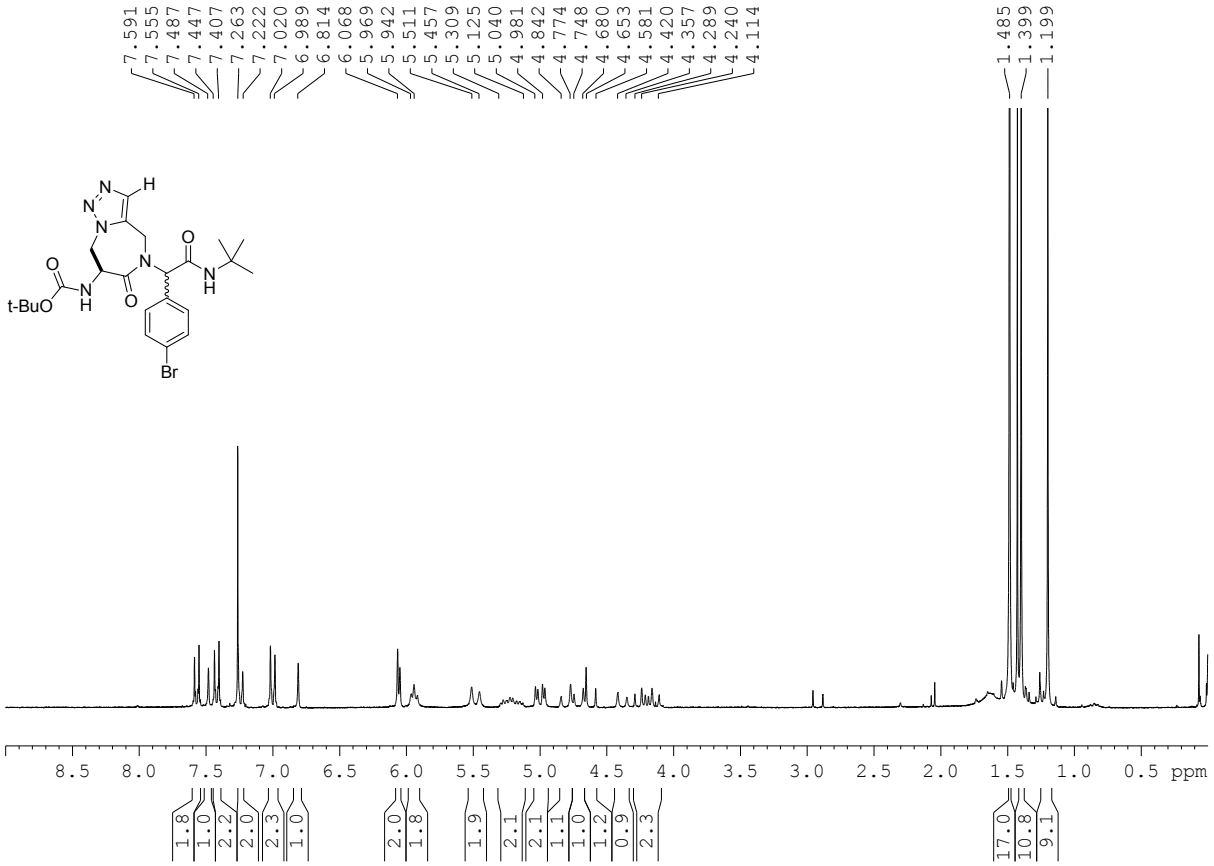
16 - ^{1}H NMR (250 MHz, $CDCl_3$)



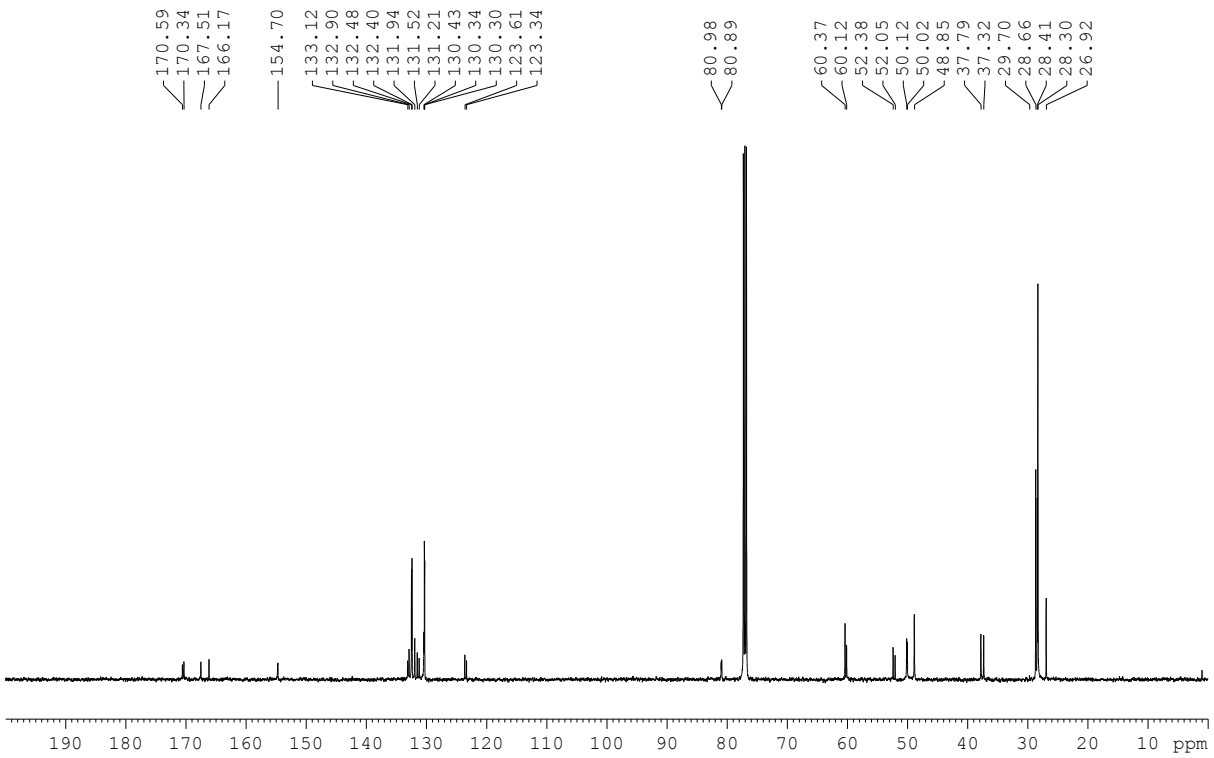
16 - ^{13}C NMR (125 MHz, $CDCl_3$)



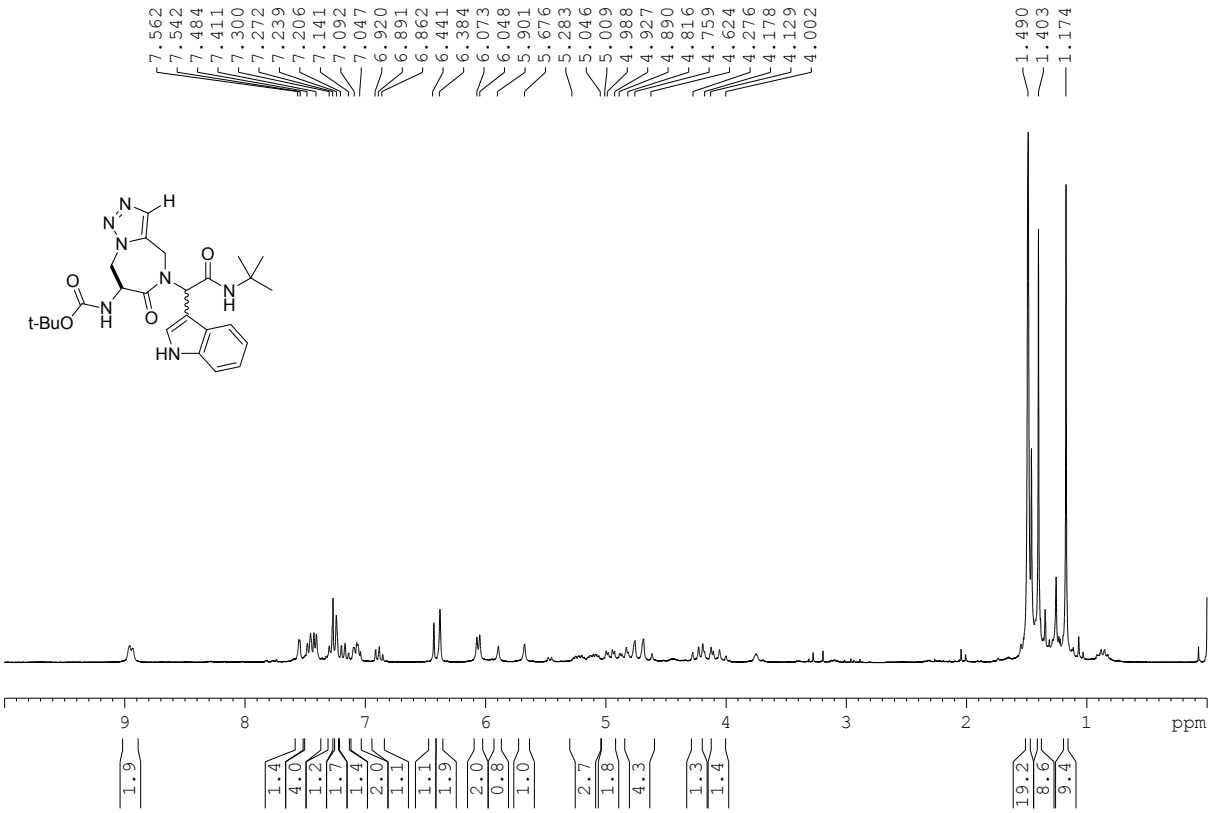
17 - ^{1}H NMR (250 MHz, $CDCl_3$)



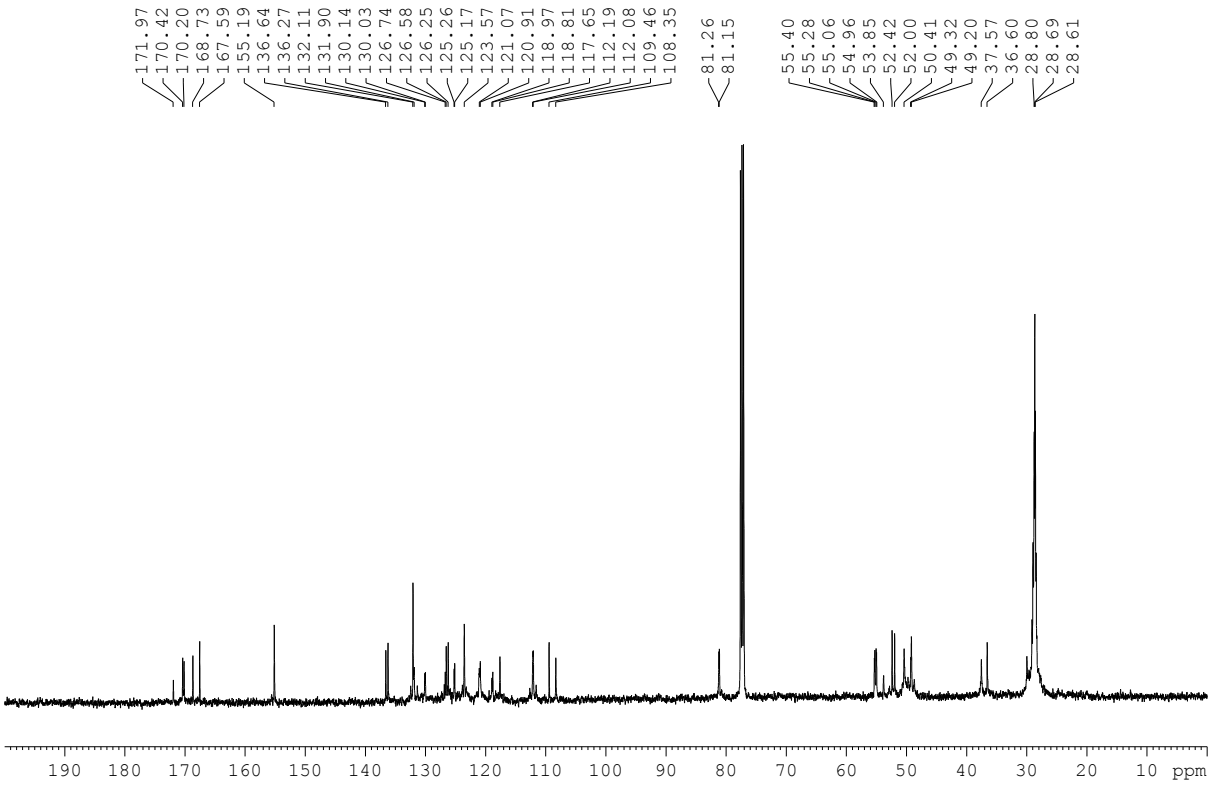
17 - ^{13}C NMR (125 MHz, $CDCl_3$)



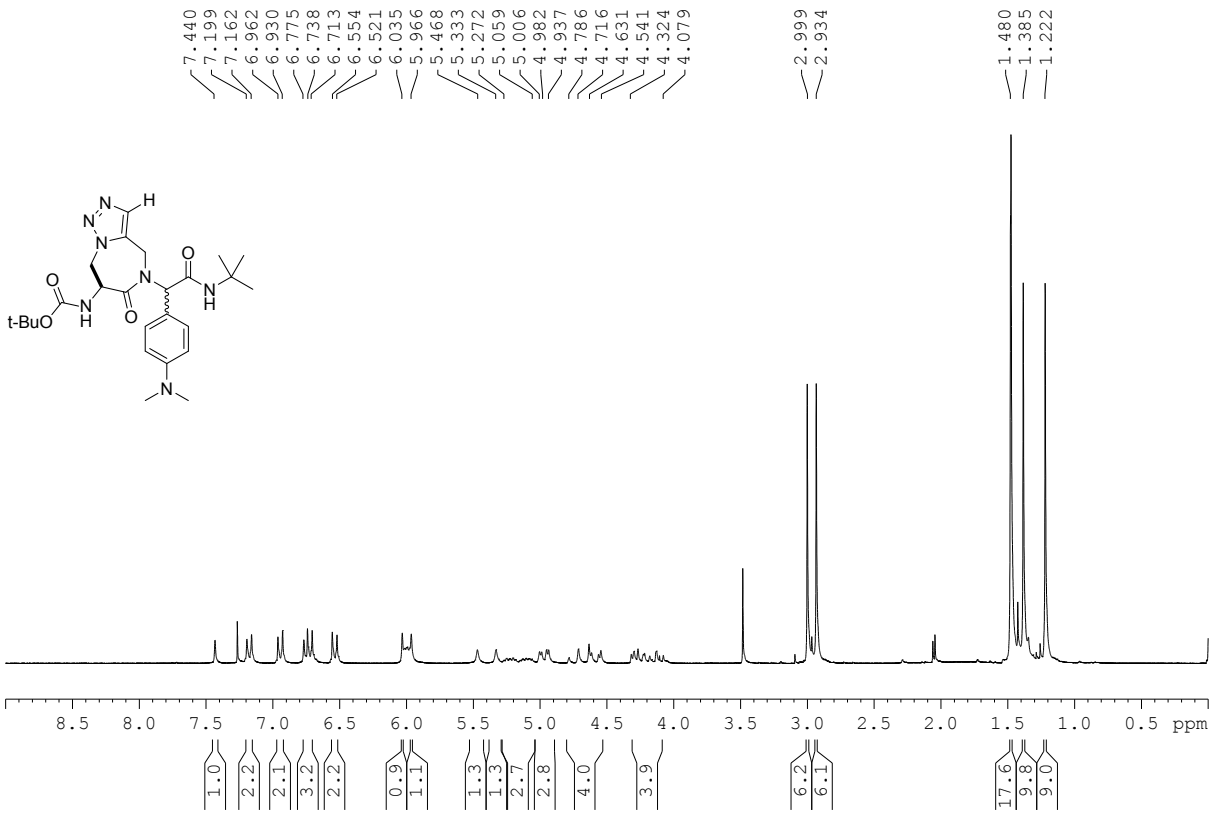
18 - ^{1}H NMR (250 MHz, $CDCl_3$)



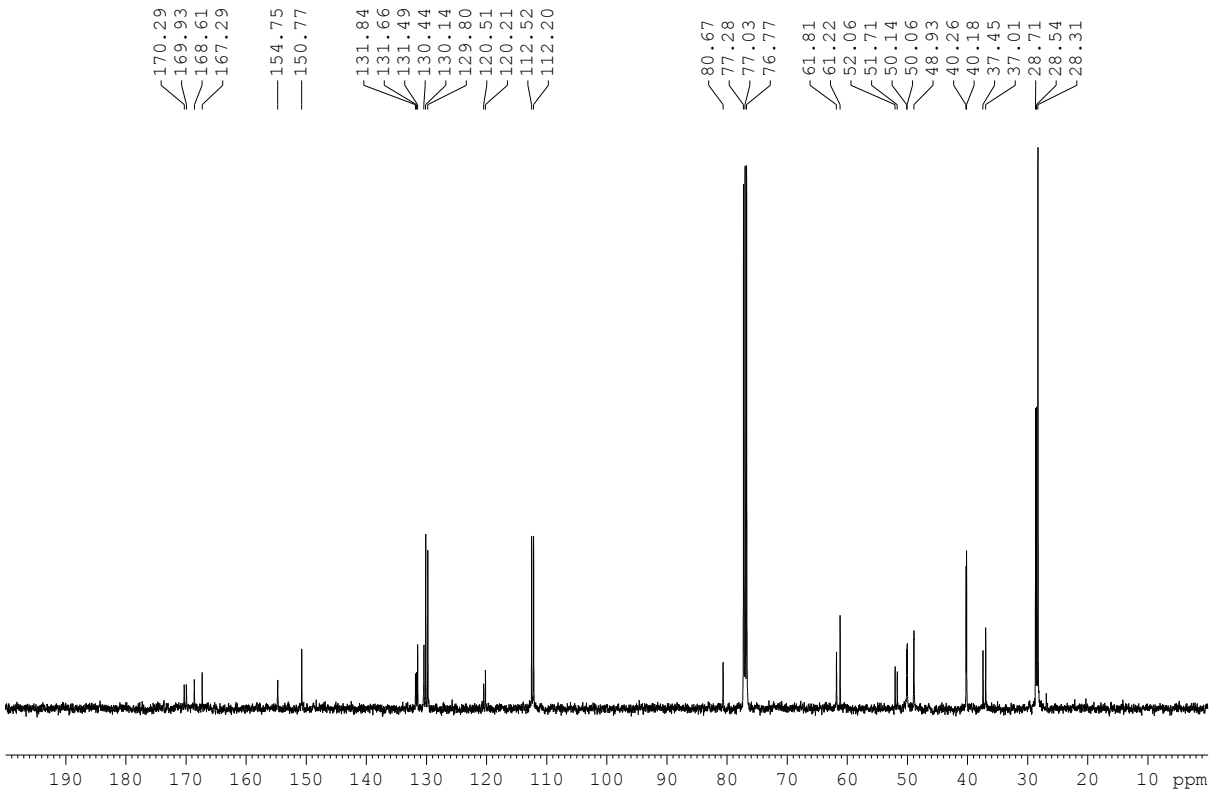
18 - ^{13}C NMR (125 MHz, $CDCl_3$)



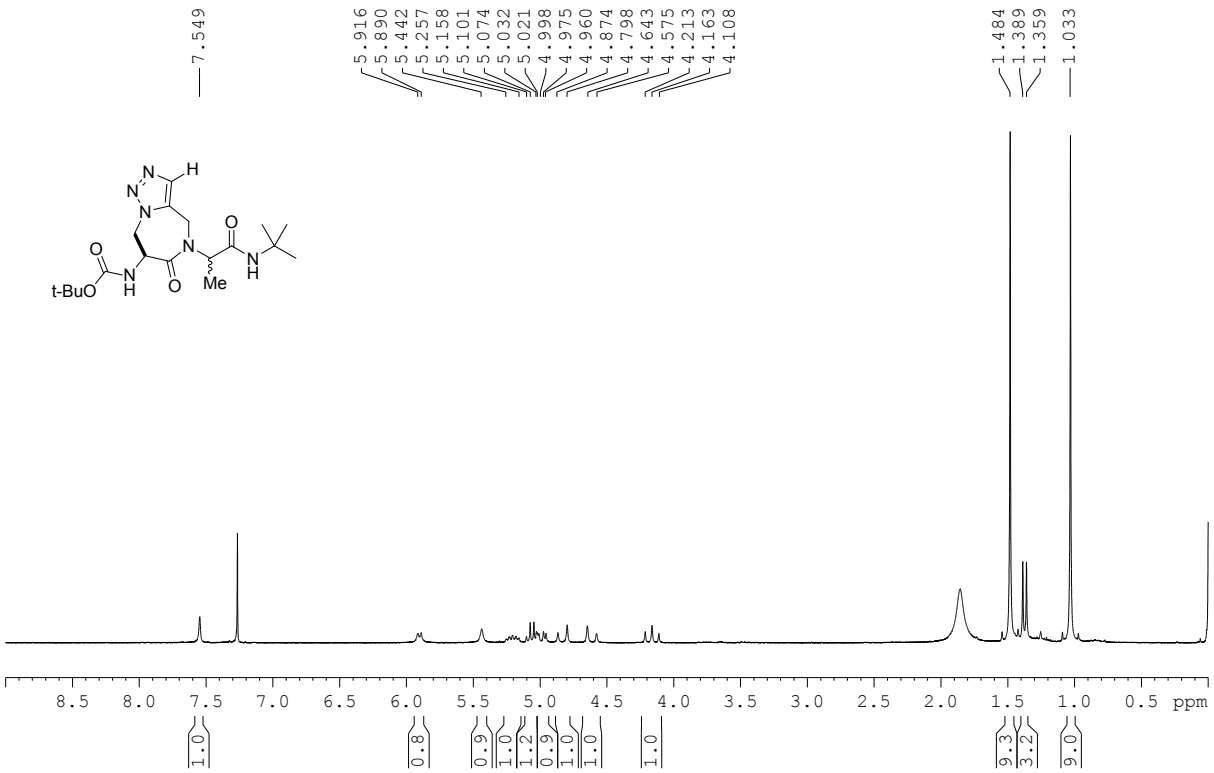
19 - ^{1}H NMR (250 MHz, $CDCl_3$)



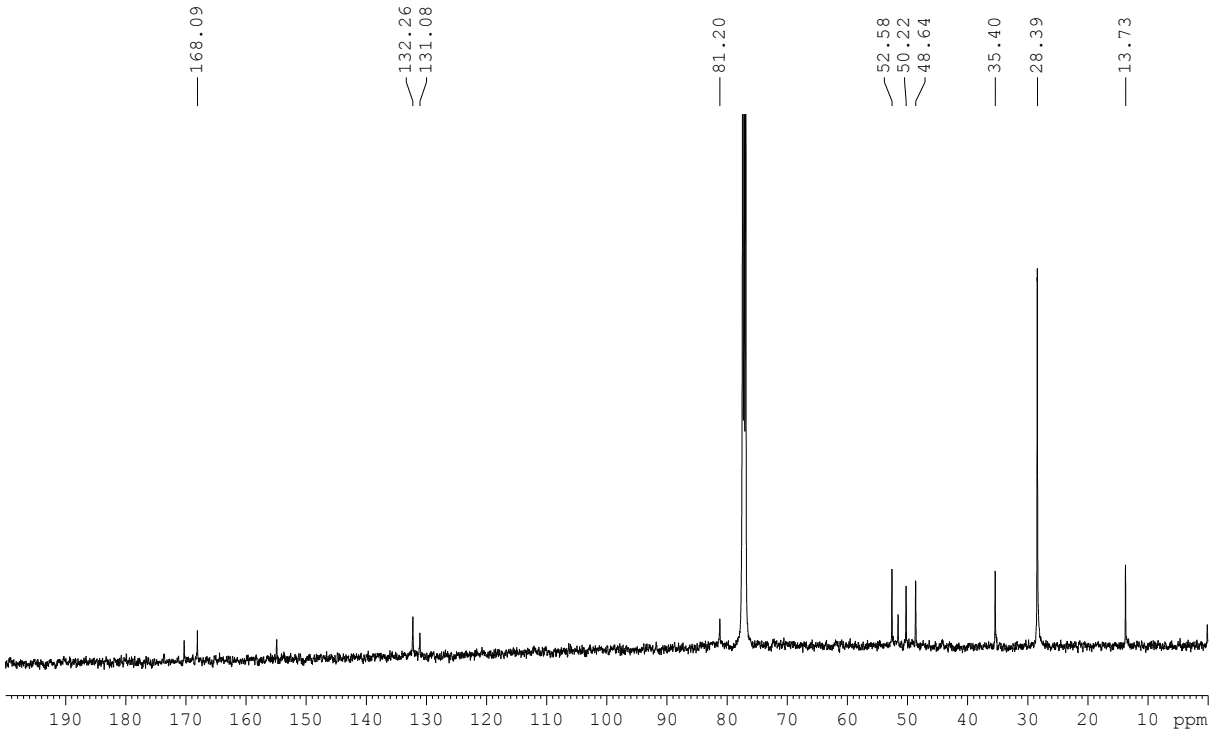
19 - ^{13}C NMR (125 MHz, $CDCl_3$)



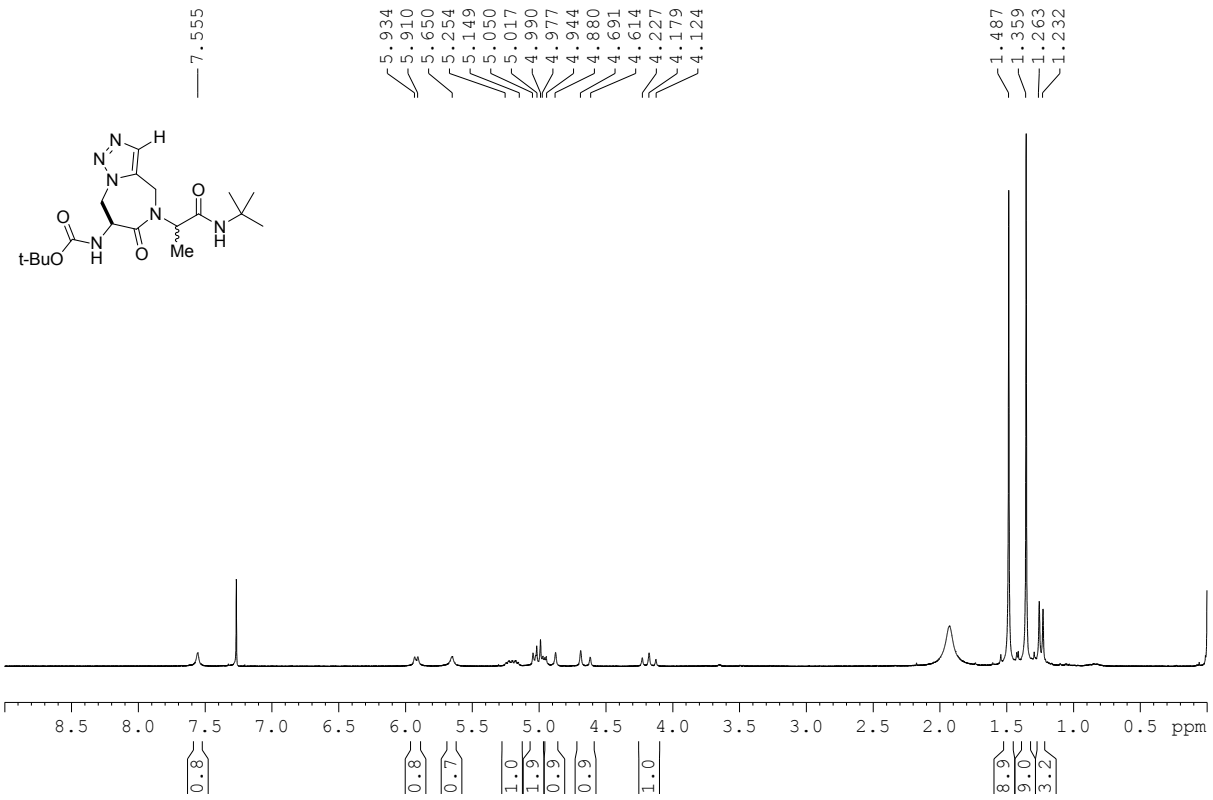
19A - ^{1}H NMR (250 MHz, $CDCl_3$)



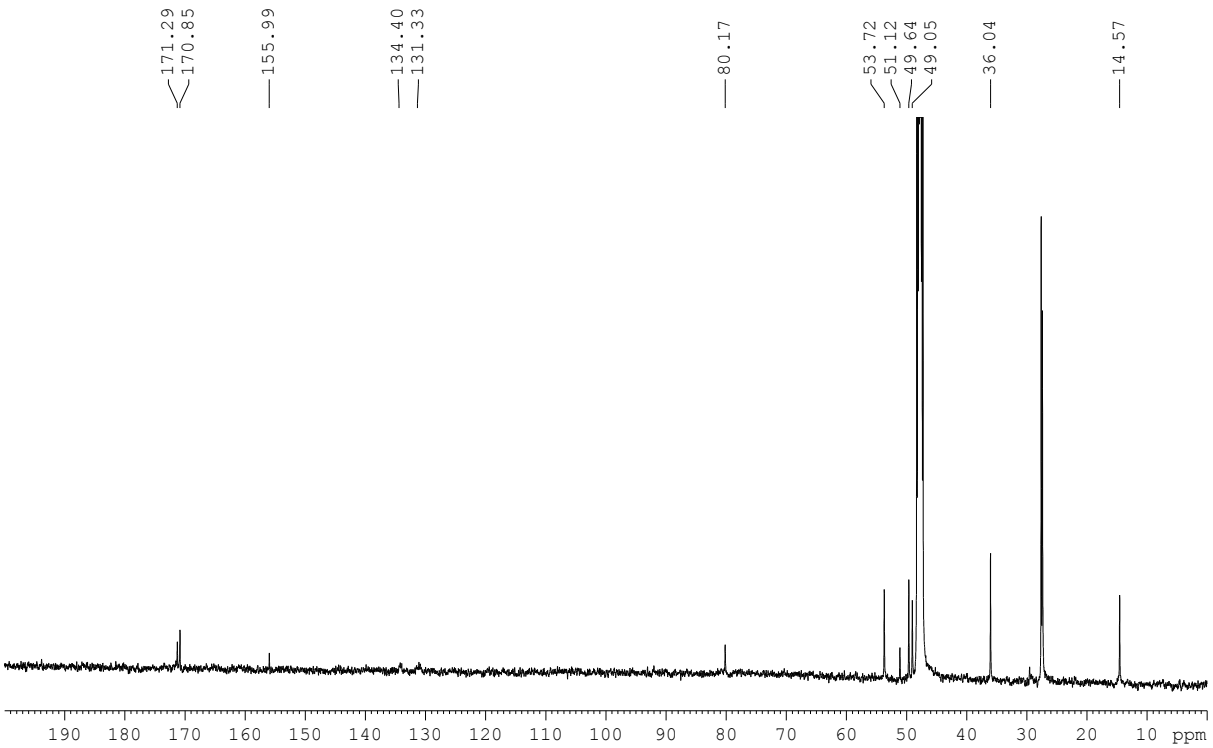
19A - ^{13}C NMR (125 MHz, $CDCl_3$)



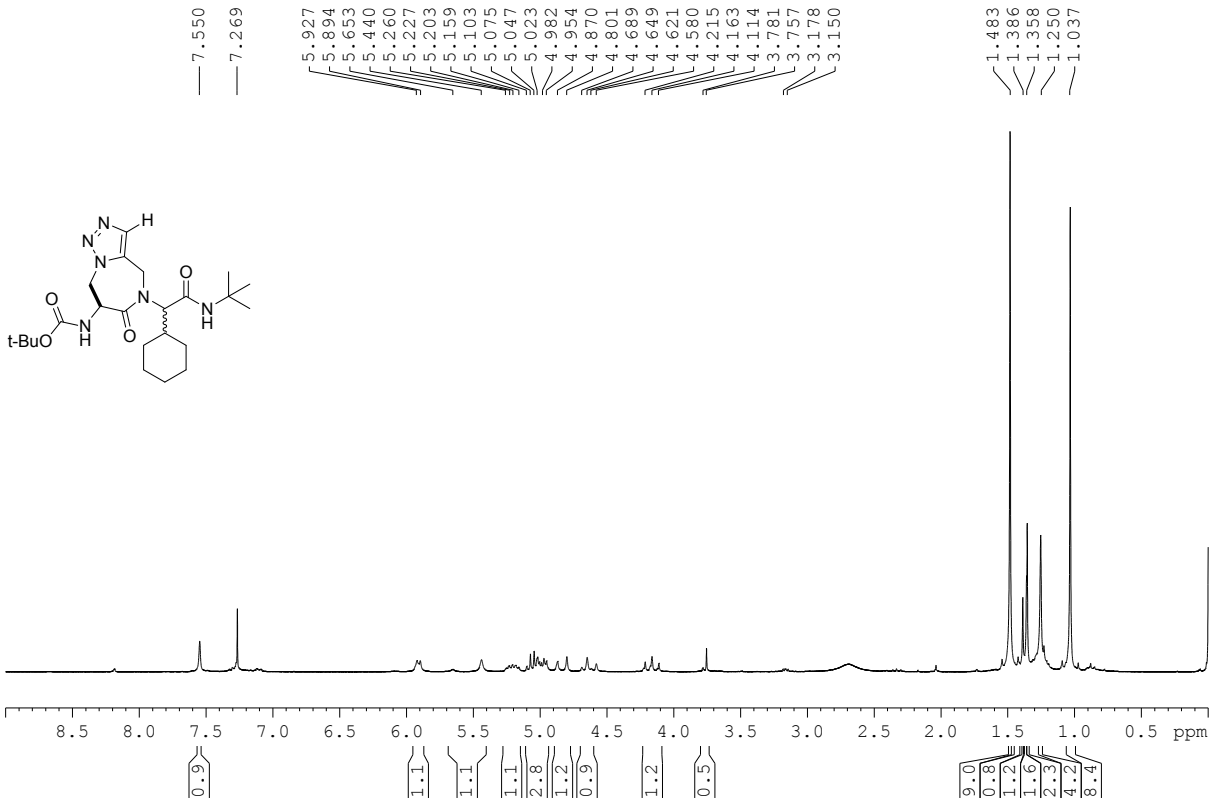
19B - ^{1}H NMR (250 MHz, $CDCl_3$)



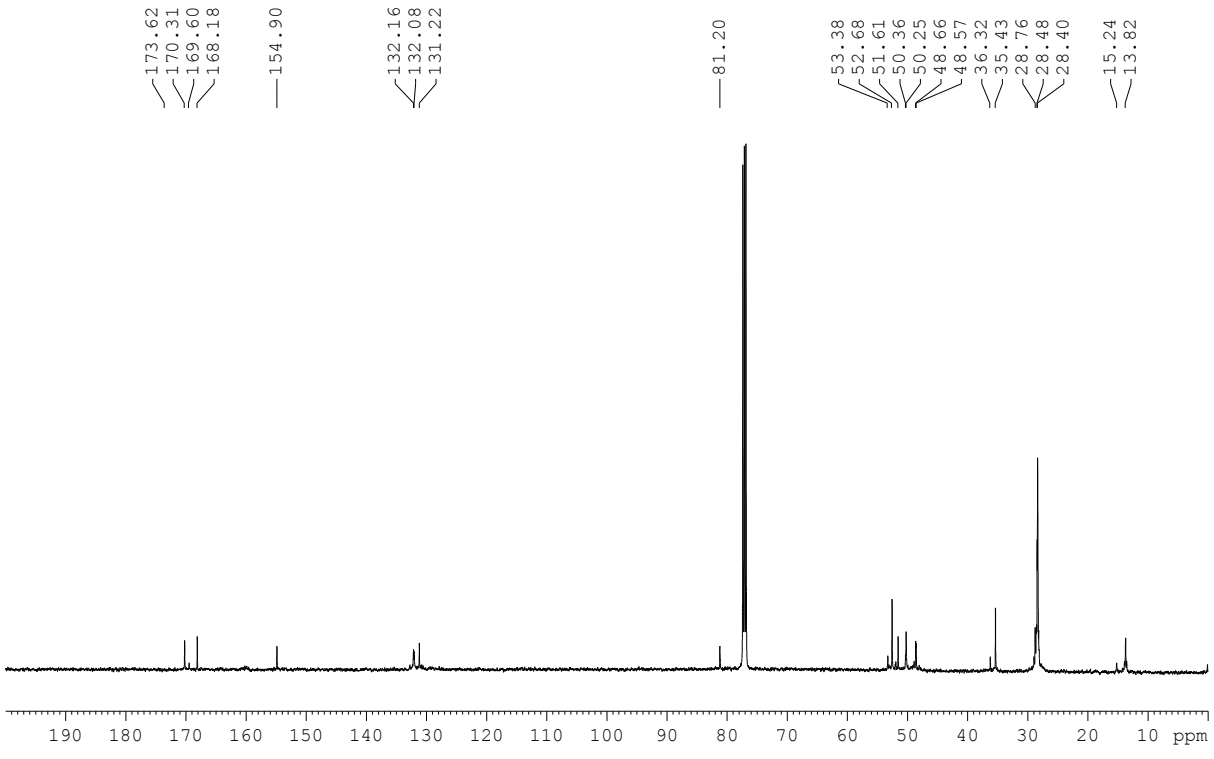
19B - ^{13}C NMR (125 MHz, MeOH-d_4)



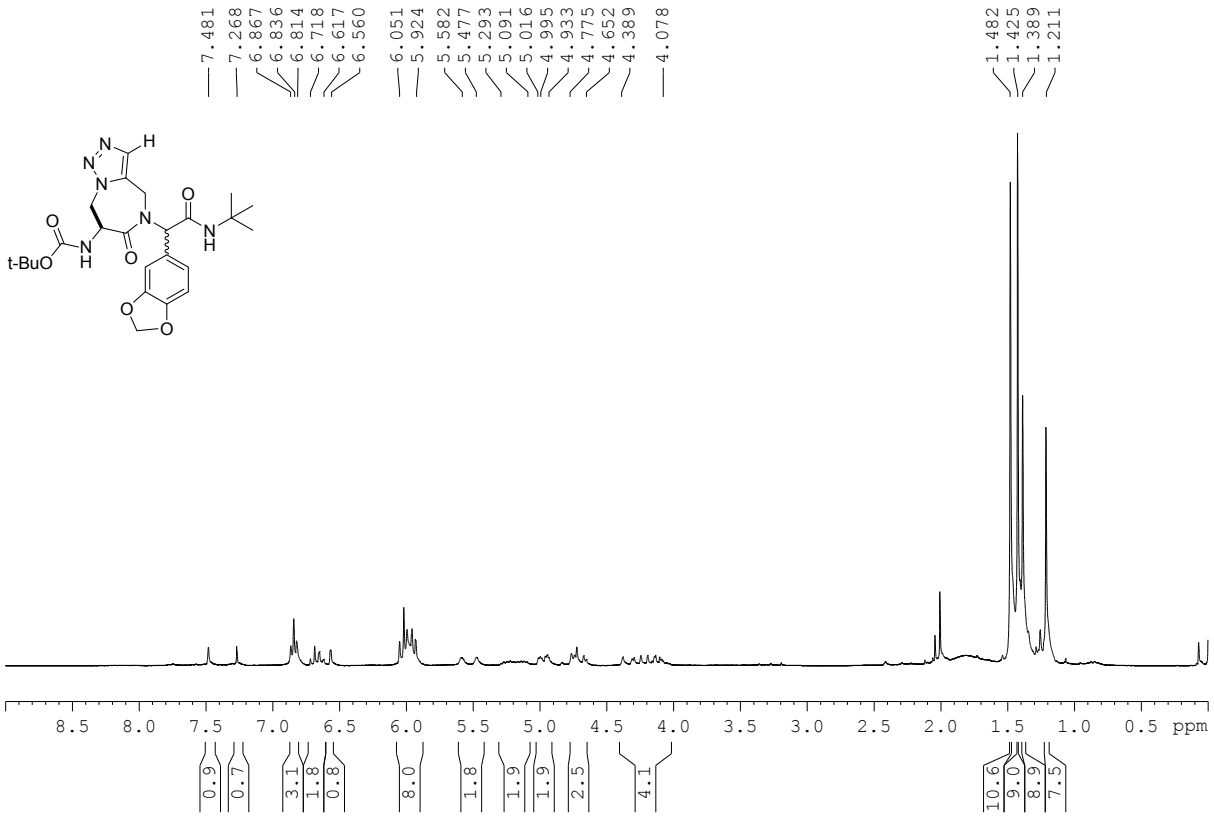
21 - ^{1}H NMR (250 MHz, $CDCl_3$)



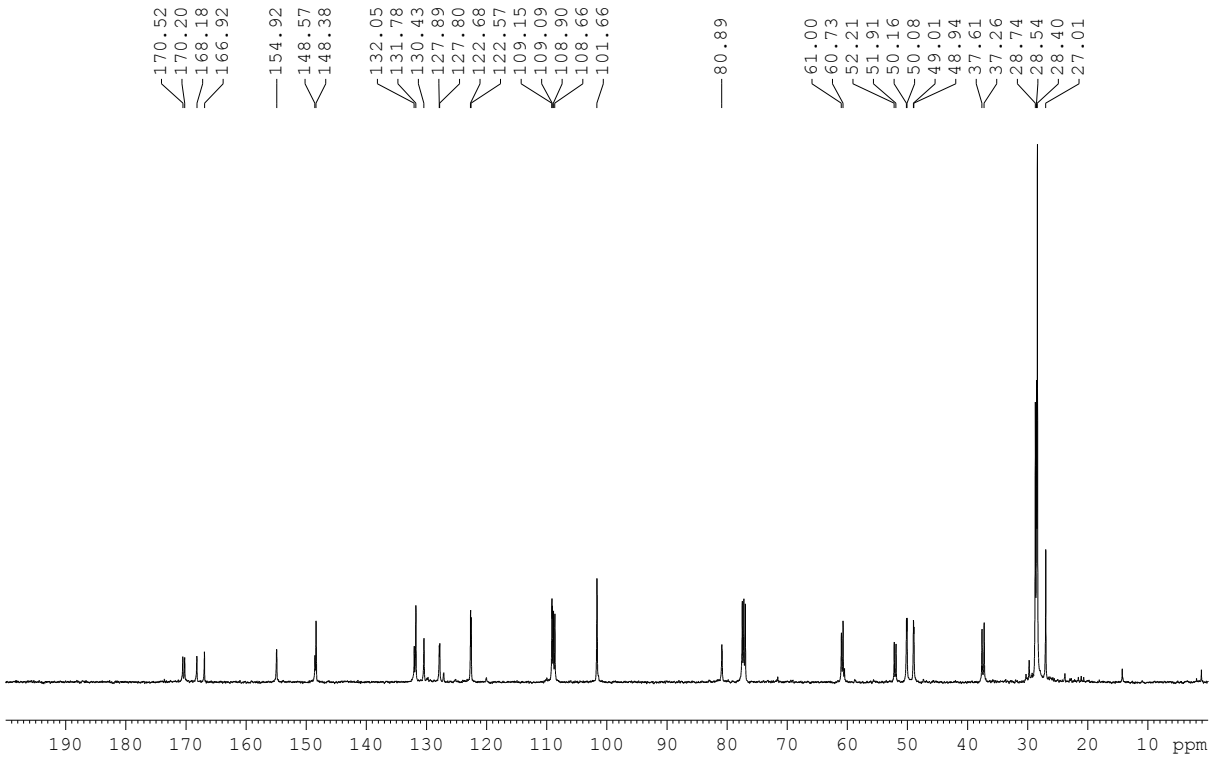
21 - ^{13}C NMR (125 MHz, $CDCl_3$)



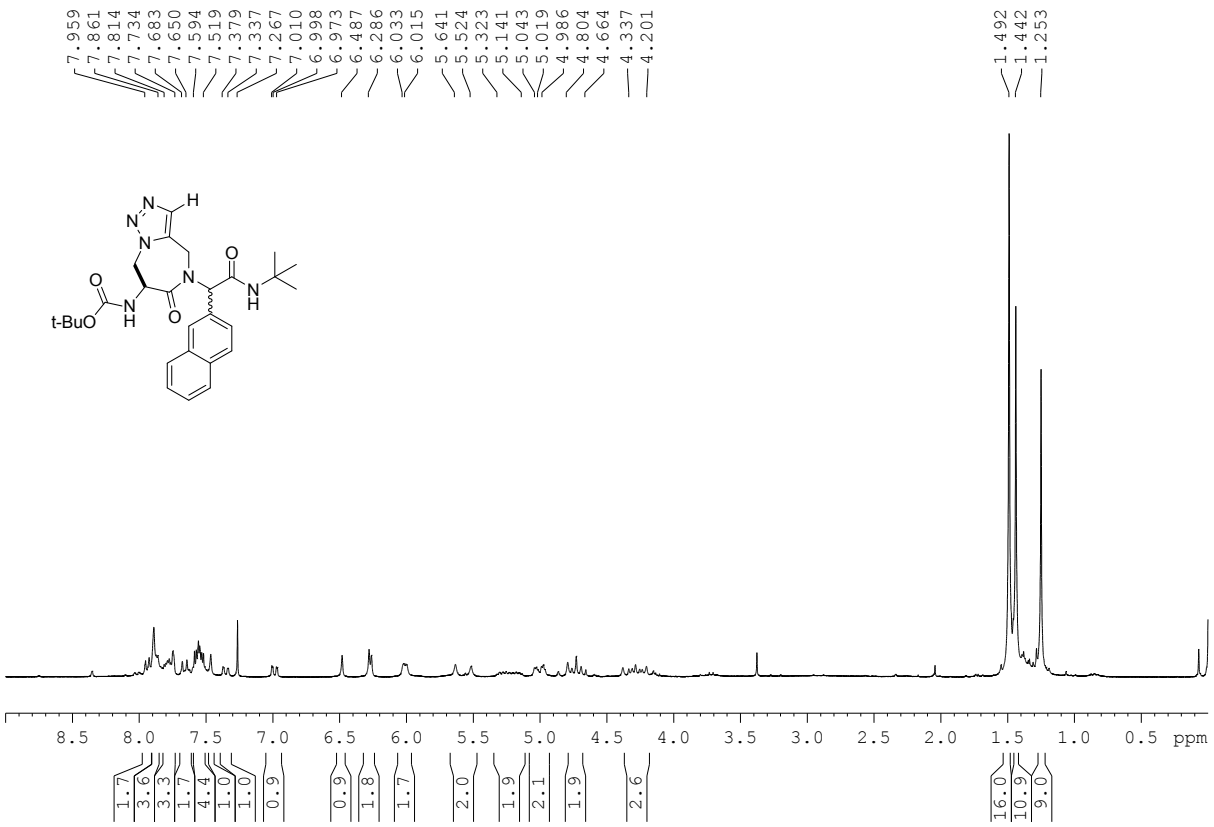
22 - ^{1}H NMR (250 MHz, $CDCl_3$)



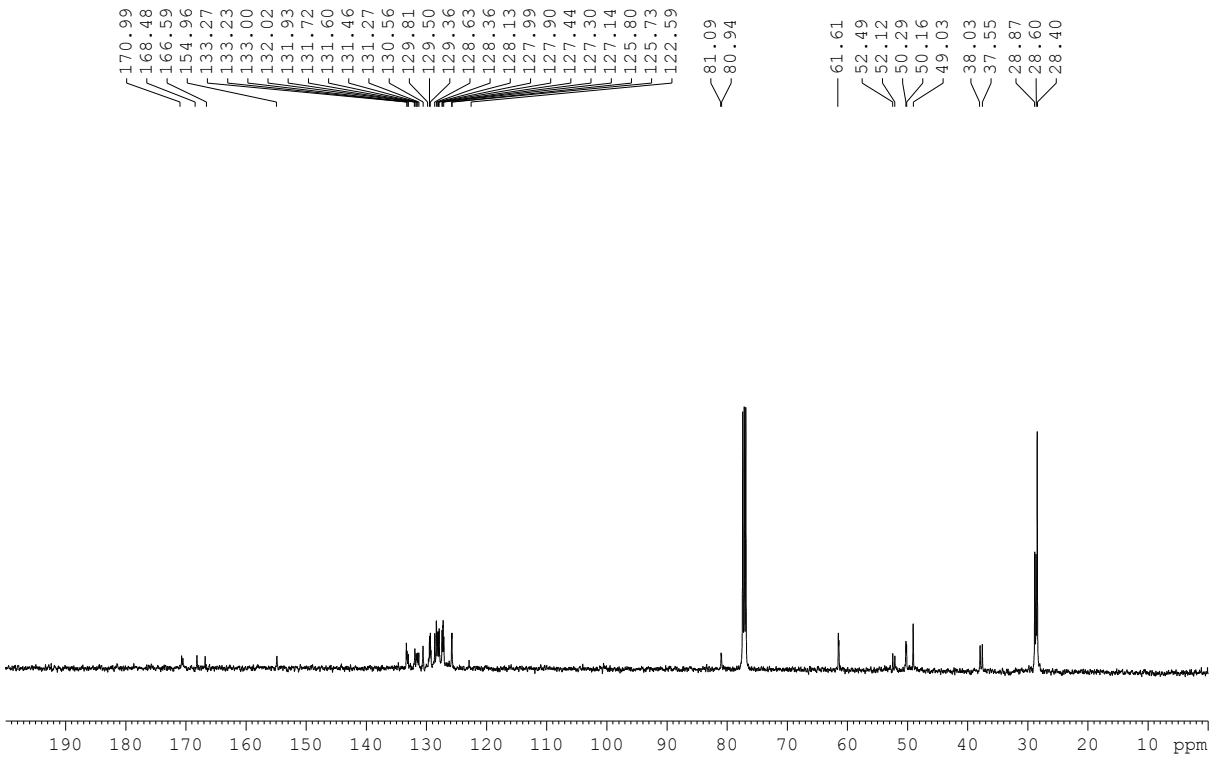
22 - ^{13}C NMR (125 MHz, $CDCl_3$)



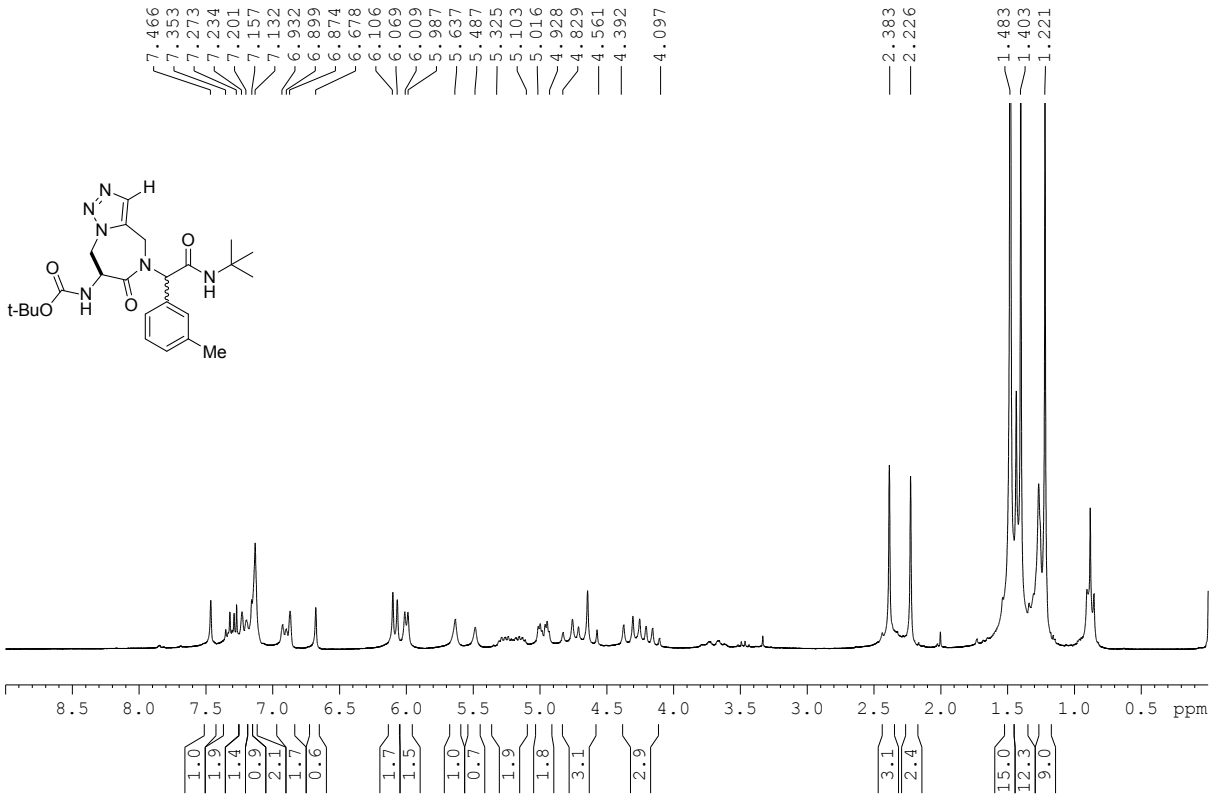
23 - ^{1}H NMR (250 MHz, $CDCl_3$)



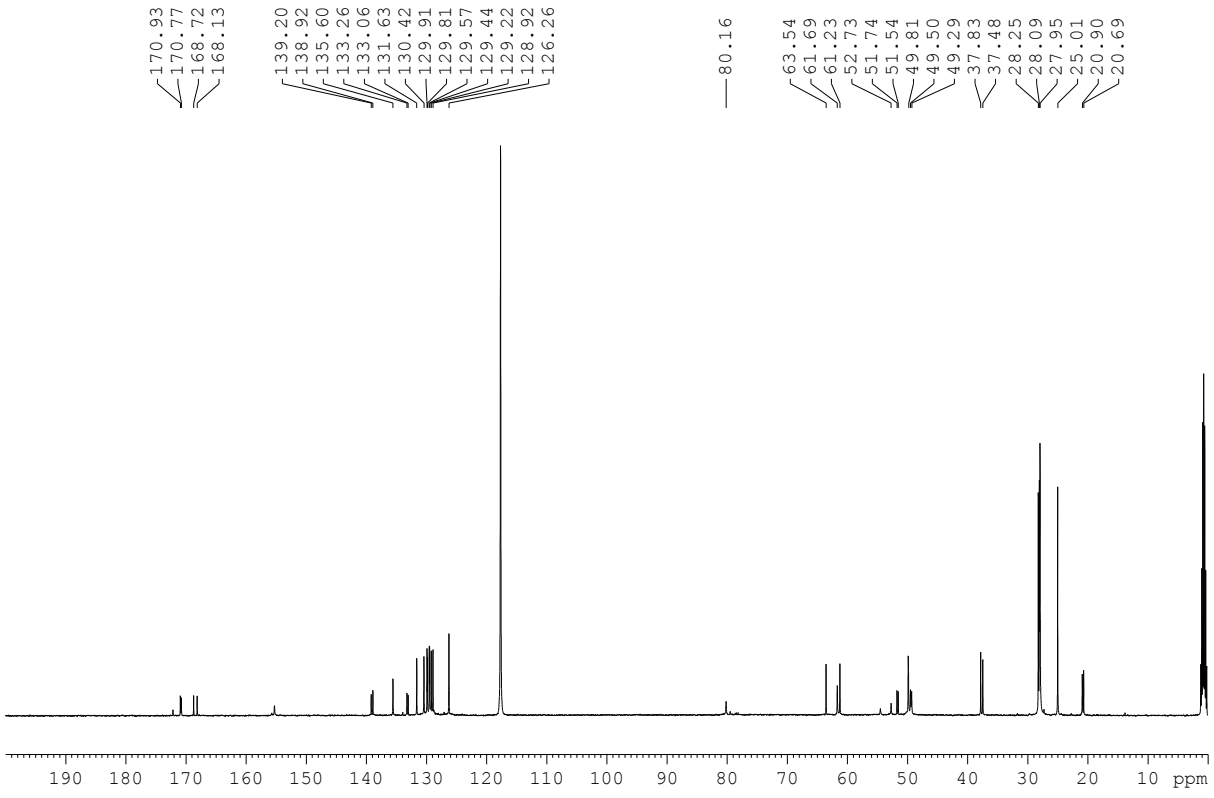
23 - ^{13}C NMR (125 MHz, $CDCl_3$)



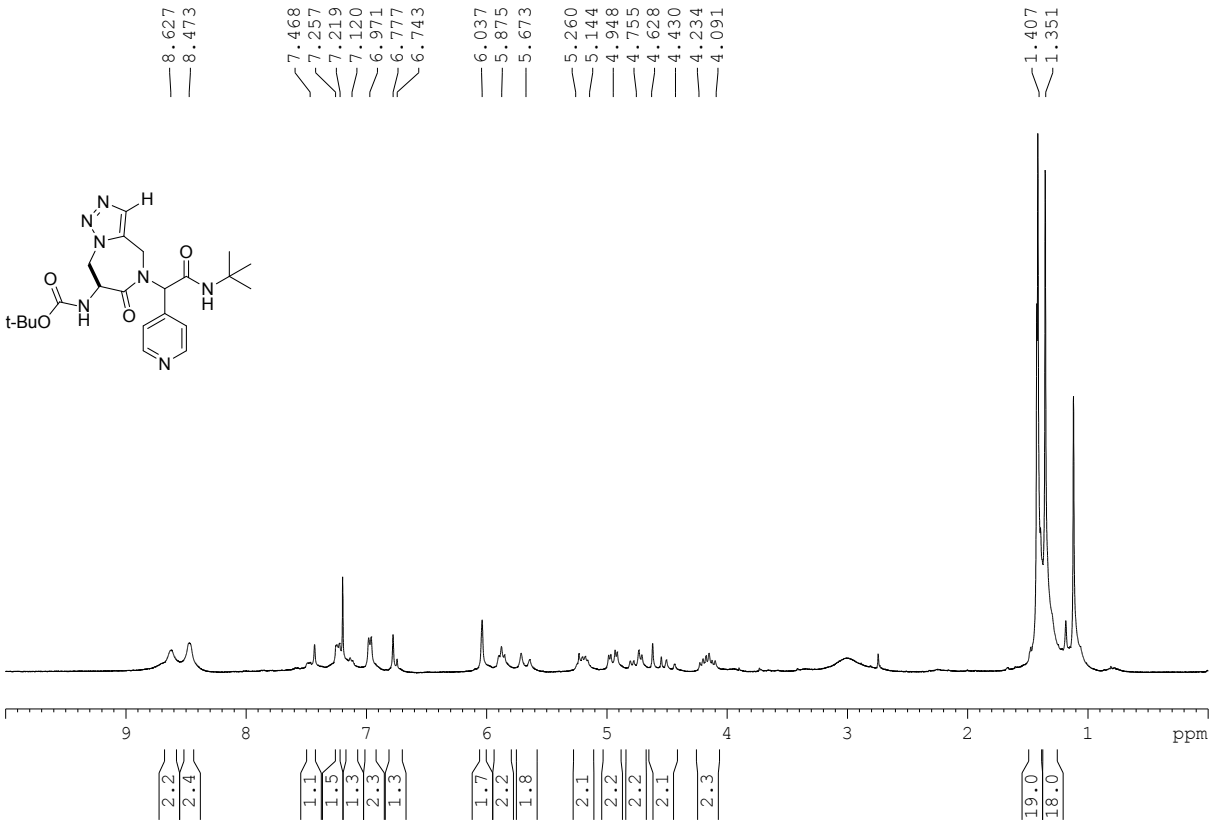
24 - ^{1}H NMR (250 MHz, $CDCl_3$)



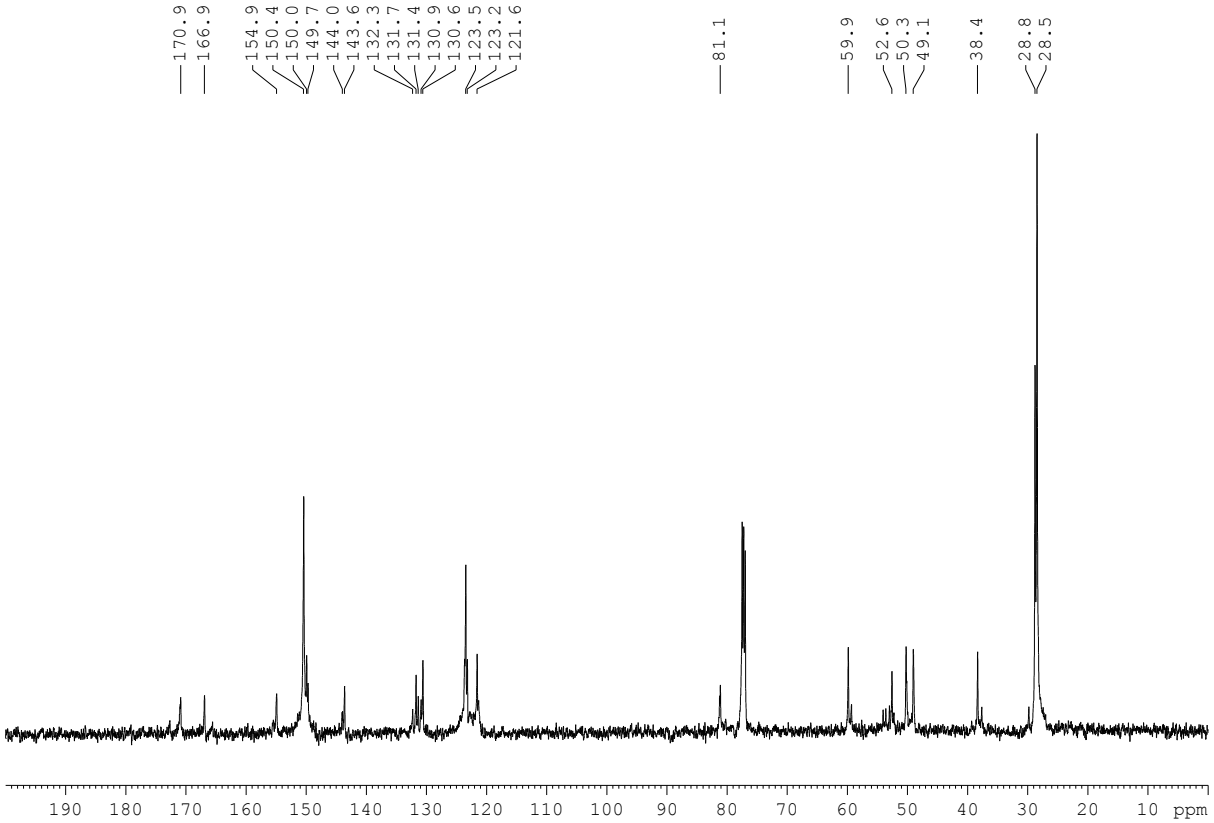
24 - ^{13}C NMR (125 MHz, CD_3CN)



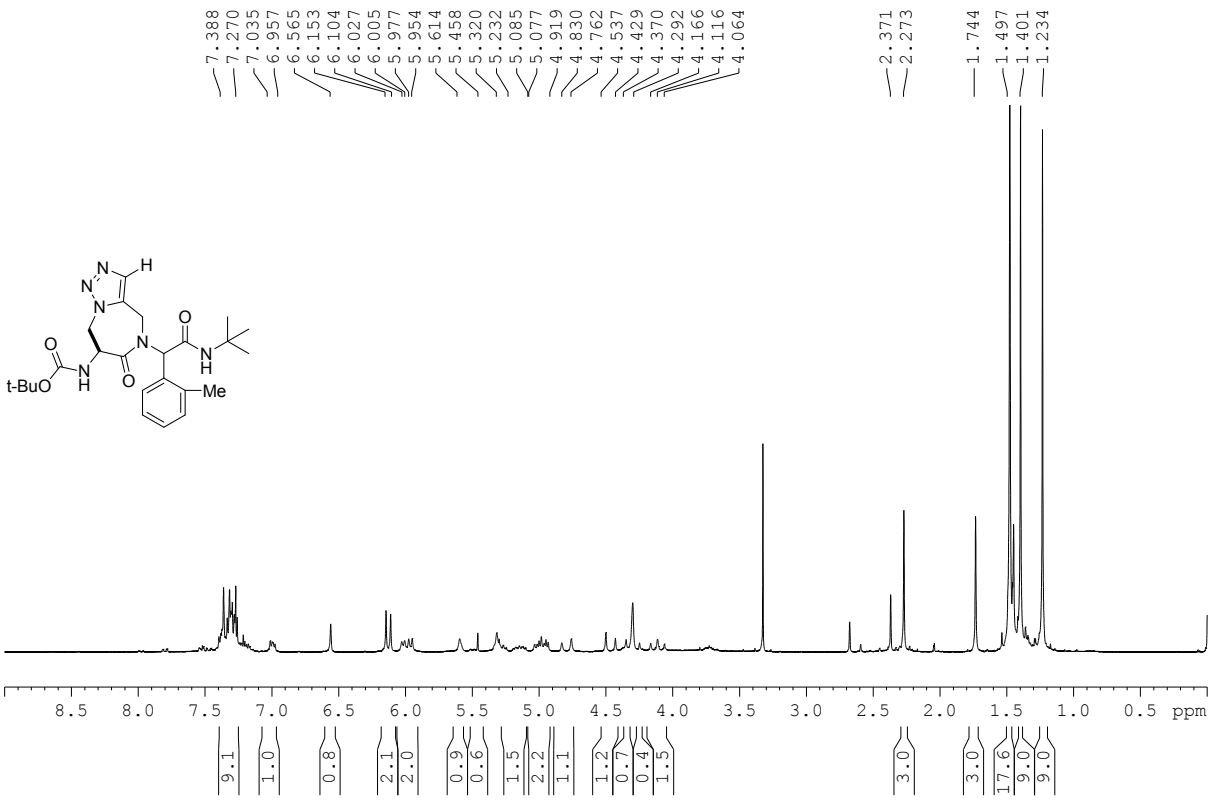
25 - ^{1}H NMR (250 MHz, $CDCl_3$)



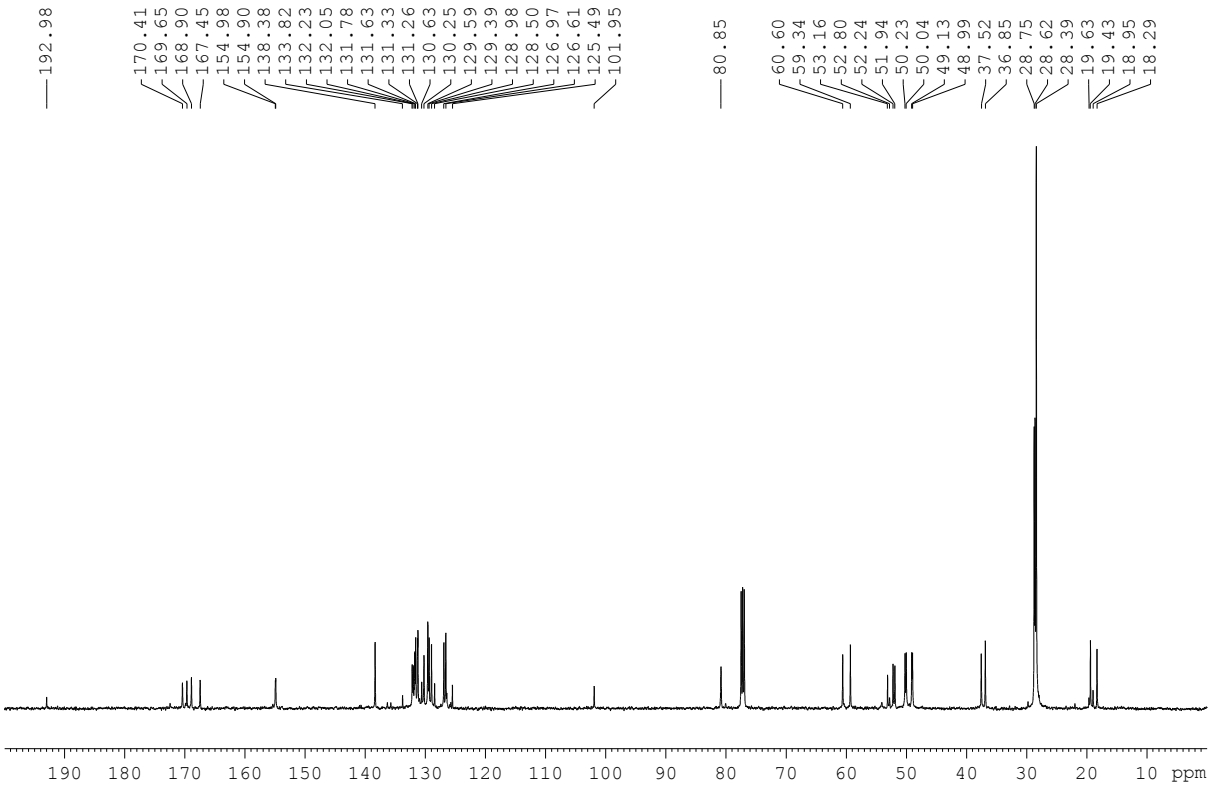
25 - ^{13}C NMR (125 MHz, $CDCl_3$)



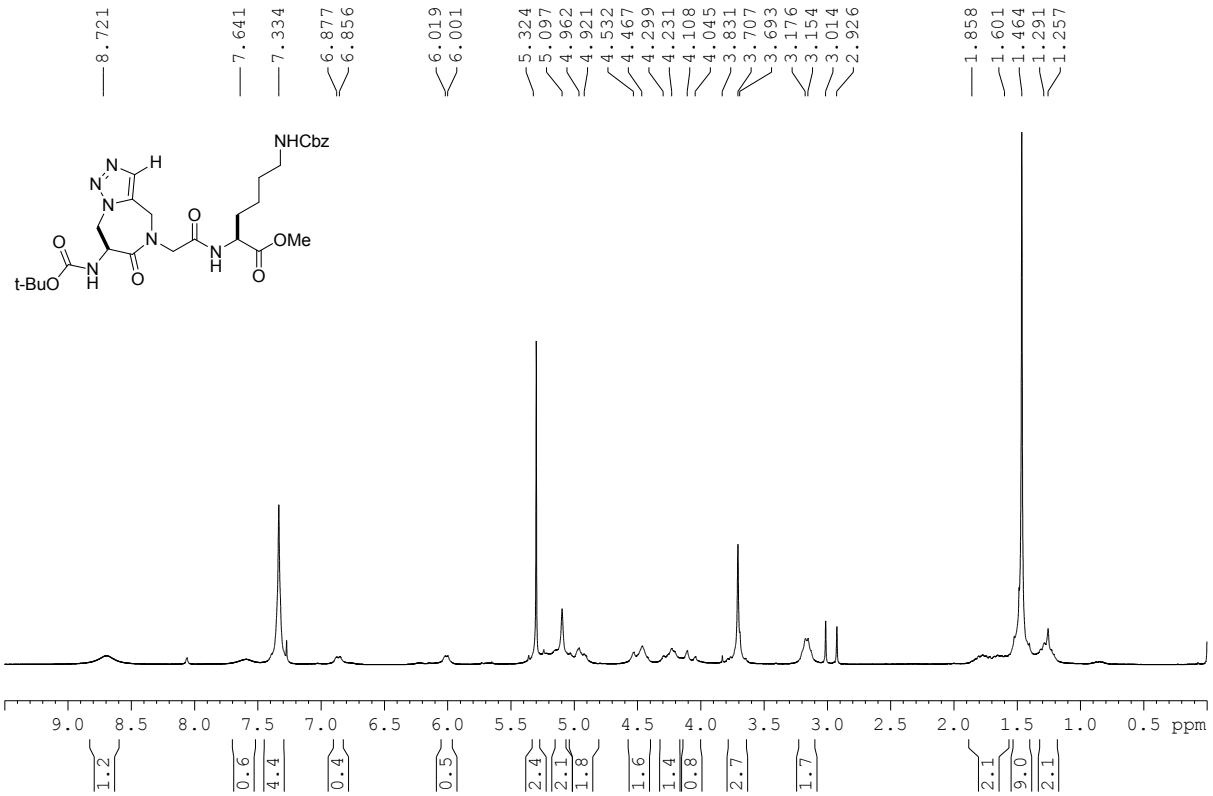
26 - ^{1}H NMR (250 MHz, MeCN-d_4)



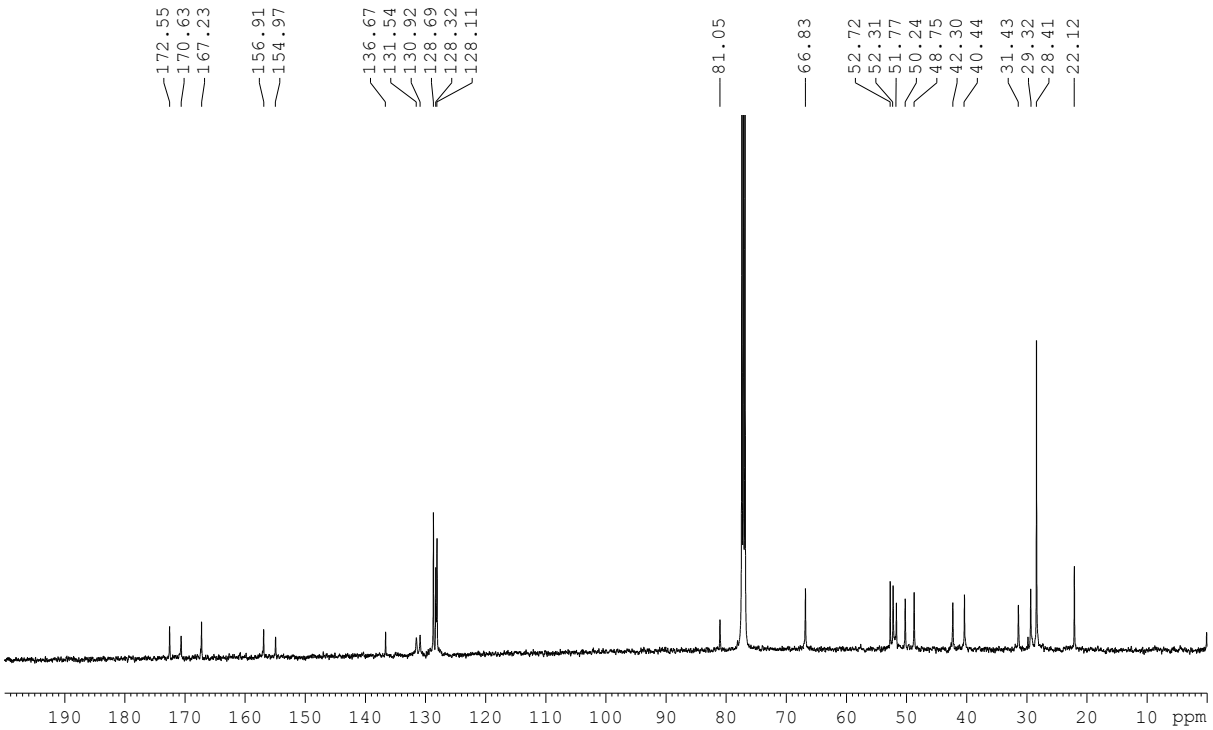
26 - ^{13}C NMR (125 MHz, $CDCl_3$)



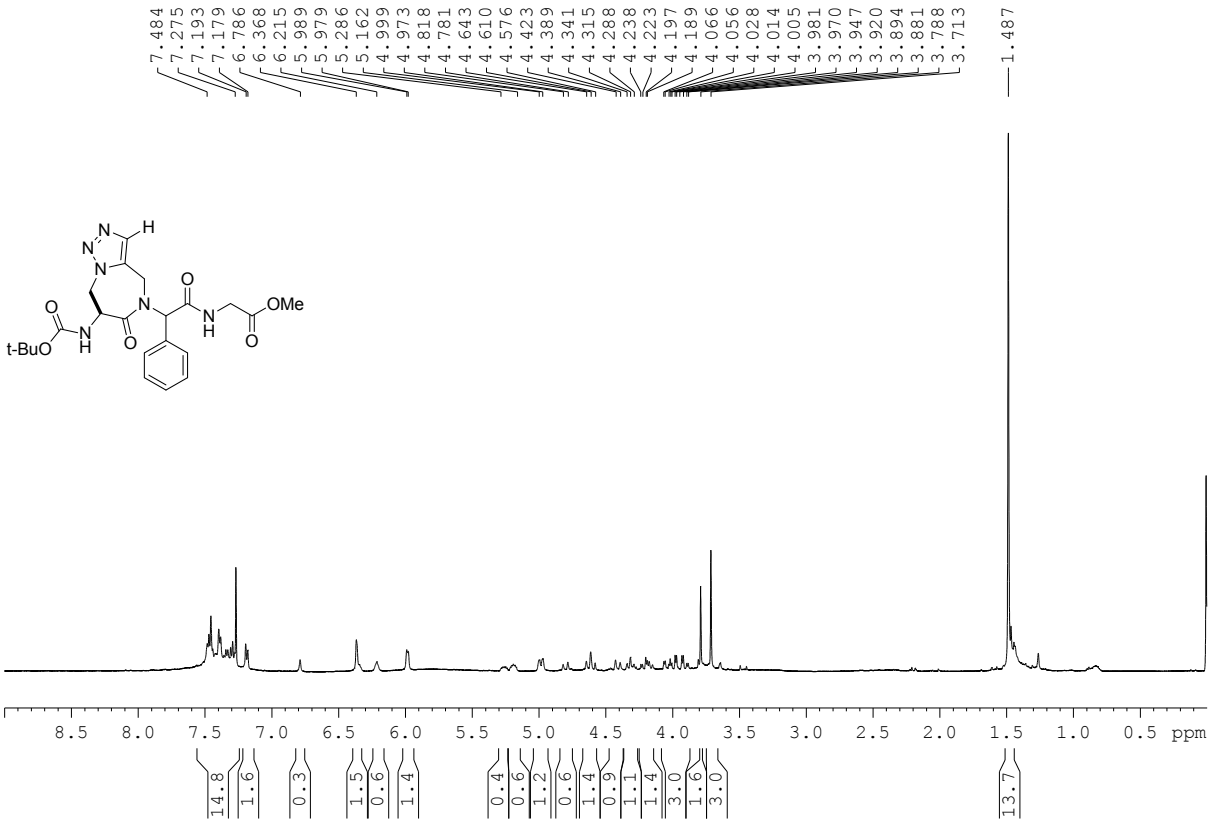
28 - ^{1}H NMR (500 MHz, $CDCl_3$)



31 - ^{13}C NMR (125 MHz, $CDCl_3$)



30 - ^{1}H NMR (500 MHz, $CDCl_3$)



31 - ^{13}C NMR (125 MHz, $CDCl_3$)