

Efficient one-pot synthesis of amino-benzotriazolodiazocinone scaffolds via catalyst-free tandem Ugi-Huisgen reactions

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1. General Information

^1H - 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) ^1H and ^{13}C spectra or two-dimensional (2D) HSQC and COSY spectra. HRMS data was recorded with a Micromass QTOF-micro system. Mass spectra were recorded with a LC-MS triple-quadrupole system. Analytical RP-HPLC was performed on an Agilent 1100 Series system with a Supelco Discovery BIO Wide Pore RP column (25 cm \times 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 100% 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) and KMnO_4 spray. Melting points were determined on a Büchi B-540 apparatus and are uncorrected. All commercial reagents and solvents were used without further purification.

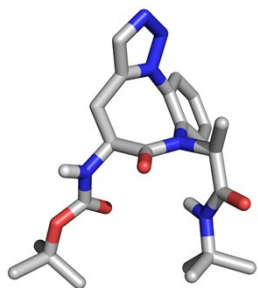
2. Molecular Modelling

In order to study the turn-inducing ability of the synthesized benzo-fused 8-membered lactams, the conformational preferences for **22** and **31** were investigated by molecular modeling using *Molecular Operating Environment* (MOE).¹ The built-in Conformational Search module was used to monitor the conformational preferences of the molecules. The MMFF94x force field was used, which was parameterized for gas phase small organic molecules in medicinal chemistry. This force field was implemented to use the Born solvation model. The LowModeMD method was applied to sample small ring conformations. While the iteration limit was set at 25000, the rejection limit was set at 1000, meaning that if after 1000 iterations no unique conformation was found, the calculation was stopped. The RMSD limit was set at 0.25 kcal/mol/Å, with a maximum energy window of 7 kcal/mol. The figures are represented on the pages that follow.

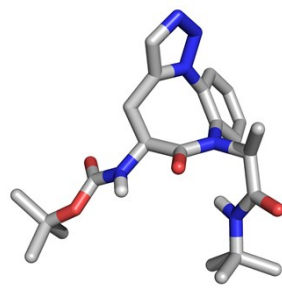
For each structure, the predicted lowest energy conformation is shown first, with two or three additional structures. The lowest energy conformations of all three (*S,S*)-diastereoisomers were turn-like. For the three (*S,R*)-diastereoisomers, the lowest energy conformation was extended. Scanning the higher energy structures showed that a turn-like conformation was adopted at, in each case, less than 1.0 kcal/mol higher than the lowest energy conformation. The first conformation that can adopt a turn structure is shown in boxed.

¹ *Molecular Operating Environment (MOE)*, 2013.08; Chemical Computing Group Inc., 1010 Sherbooke St. West, Suite #910, Montreal, QC, Canada, H3A 2R7, **2015**.

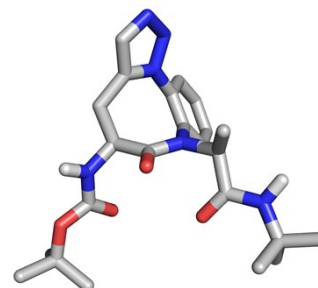
(*S,S*)-**22** - *tert*-butyl ((*S*)-7-((*S*)-1-(*tert*-butylamino)-1-oxopropan-2-yl)-6-oxo-4,5,6,7-tetrahydrobenzo[*b*][1,2,3]triazolo[1,5-*d*][1,4]diazocin-5-yl)carbamate



0.000 kcal/mol

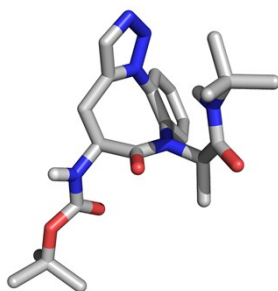


0.350 kcal/mol

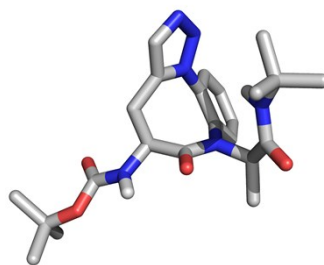


0.966 kcal/mol

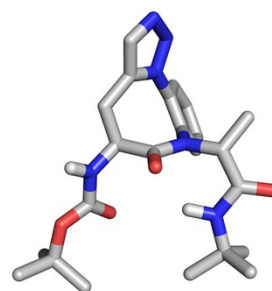
(*S,R*)-**22** - *tert*-butyl ((*S*)-7-((*R*)-1-(*tert*-butylamino)-1-oxopropan-2-yl)-6-oxo-4,5,6,7-tetrahydrobenzo[*b*][1,2,3]triazolo[1,5-*d*][1,4]diazocin-5-yl)carbamate



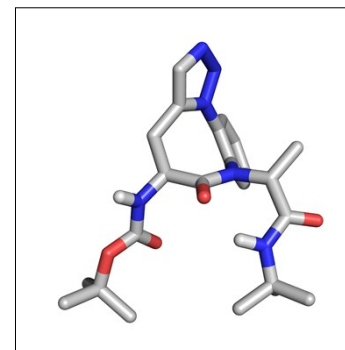
0.000 kcal/mol



0.112 kcal/mol

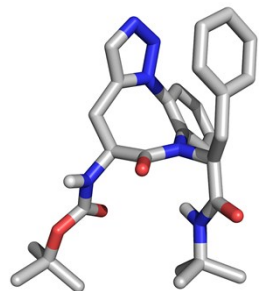


0.670 kcal/mol

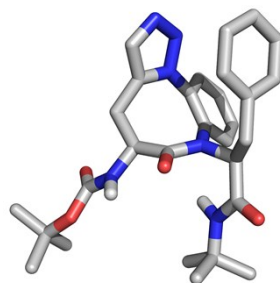


0.905 kcal/mol

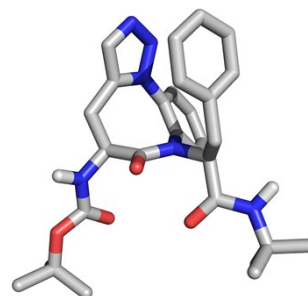
(*S,S*)-**31** - *tert*-butyl ((*S*)-7-((*S*)-1-(*tert*-butylamino)-1-oxo-3-phenylpropan-2-yl)-6-oxo-4,5,6,7-tetrahydrobenzo[*b*][1,2,3]triazolo[1,5-*d*][1,4]diazocin-5-yl)carbamate



0.000 kcal/mol

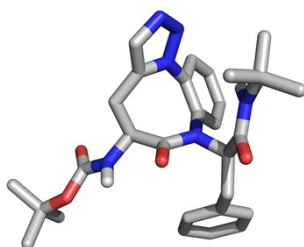


0.129 kcal/mol

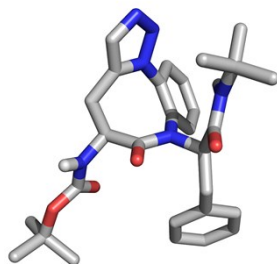


0.372 kcal/mol

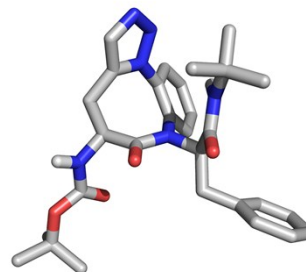
(*S,R*)-**31** - *tert*-butyl ((*S*)-7-((*R*)-1-(*tert*-butylamino)-1-oxo-3-phenylpropan-2-yl)-6-oxo-4,5,6,7-tetrahydrobenzo[*b*][1,2,3]triazolo[1,5-*d*][1,4]diazocin-5-yl)carbamate



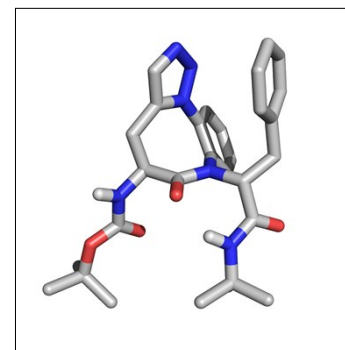
0.000 kcal/mol



0.105 kcal/mol



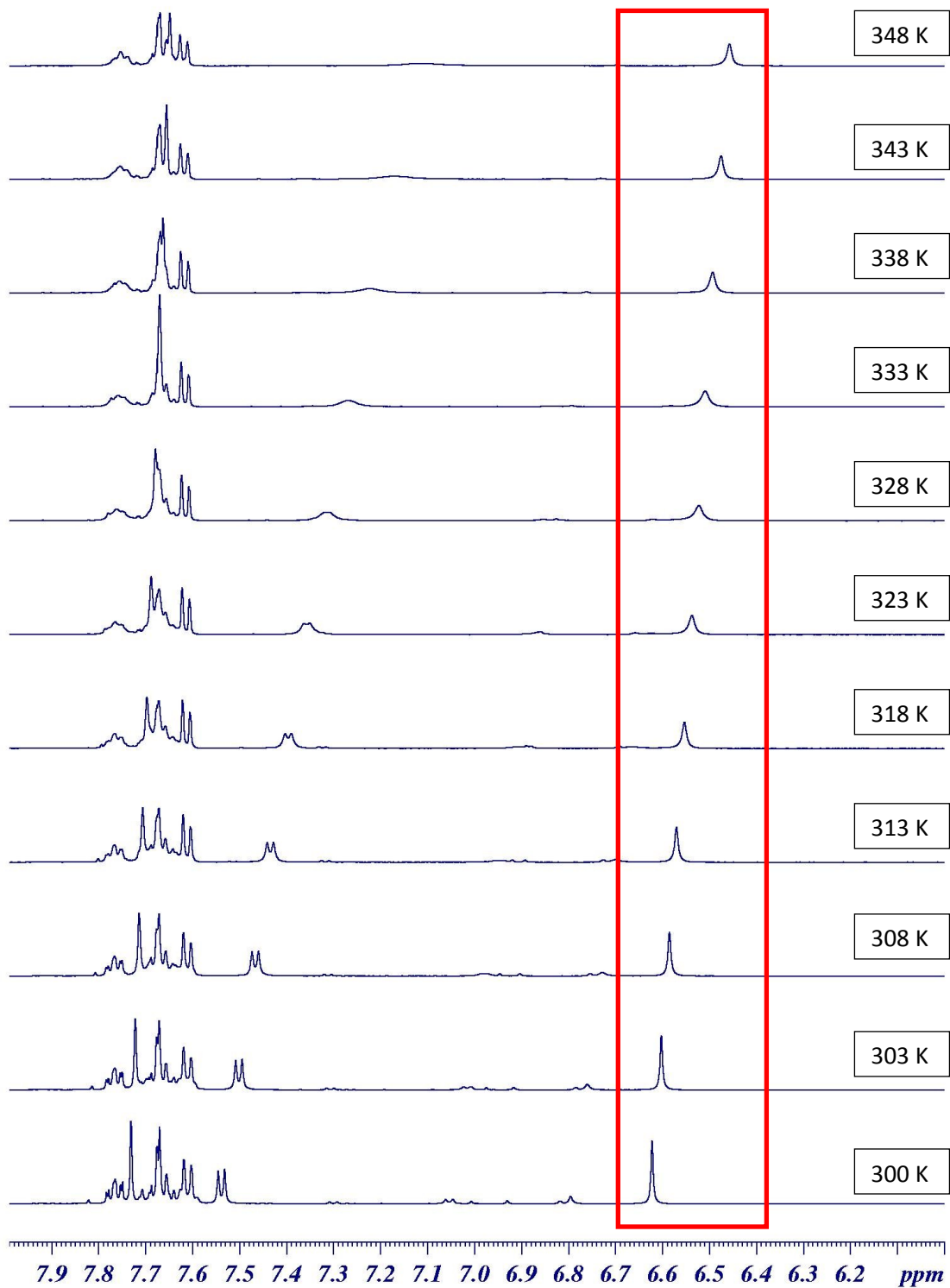
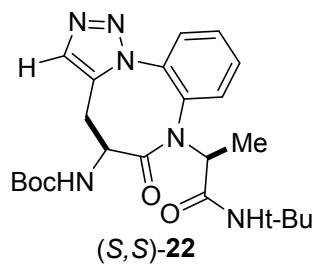
0.176 kcal/mol

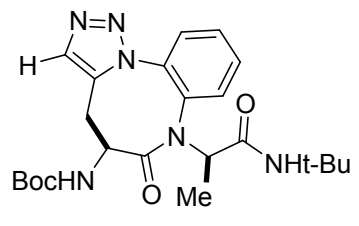


(8th) 0.587 kcal/mol

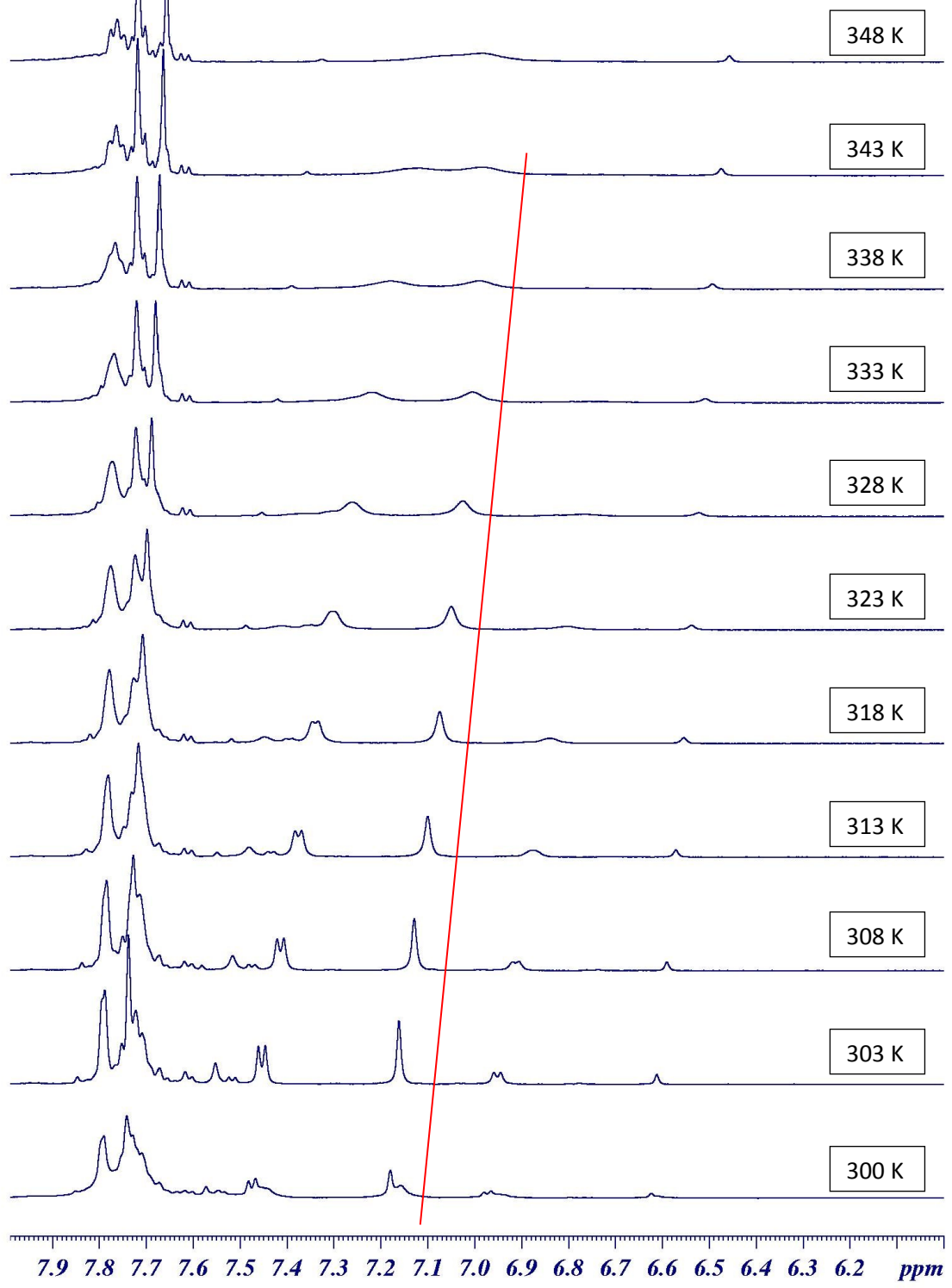
3. Thermal coefficient NMR Data

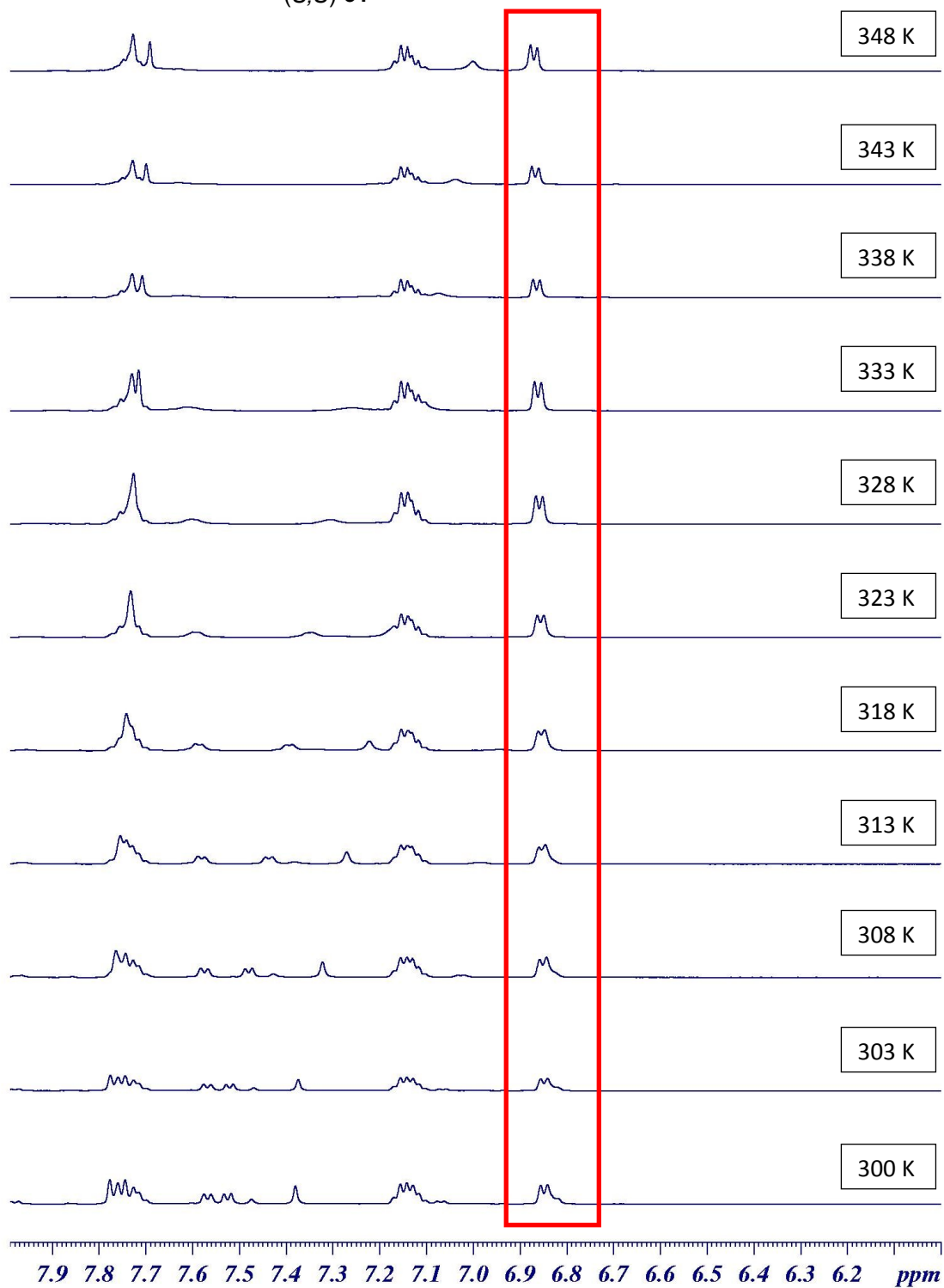
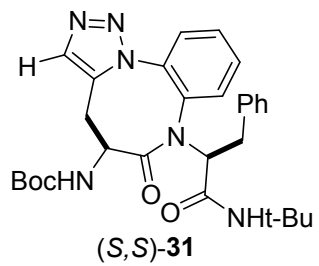
All samples taken in DMSO-*d*₆, 500 MHz

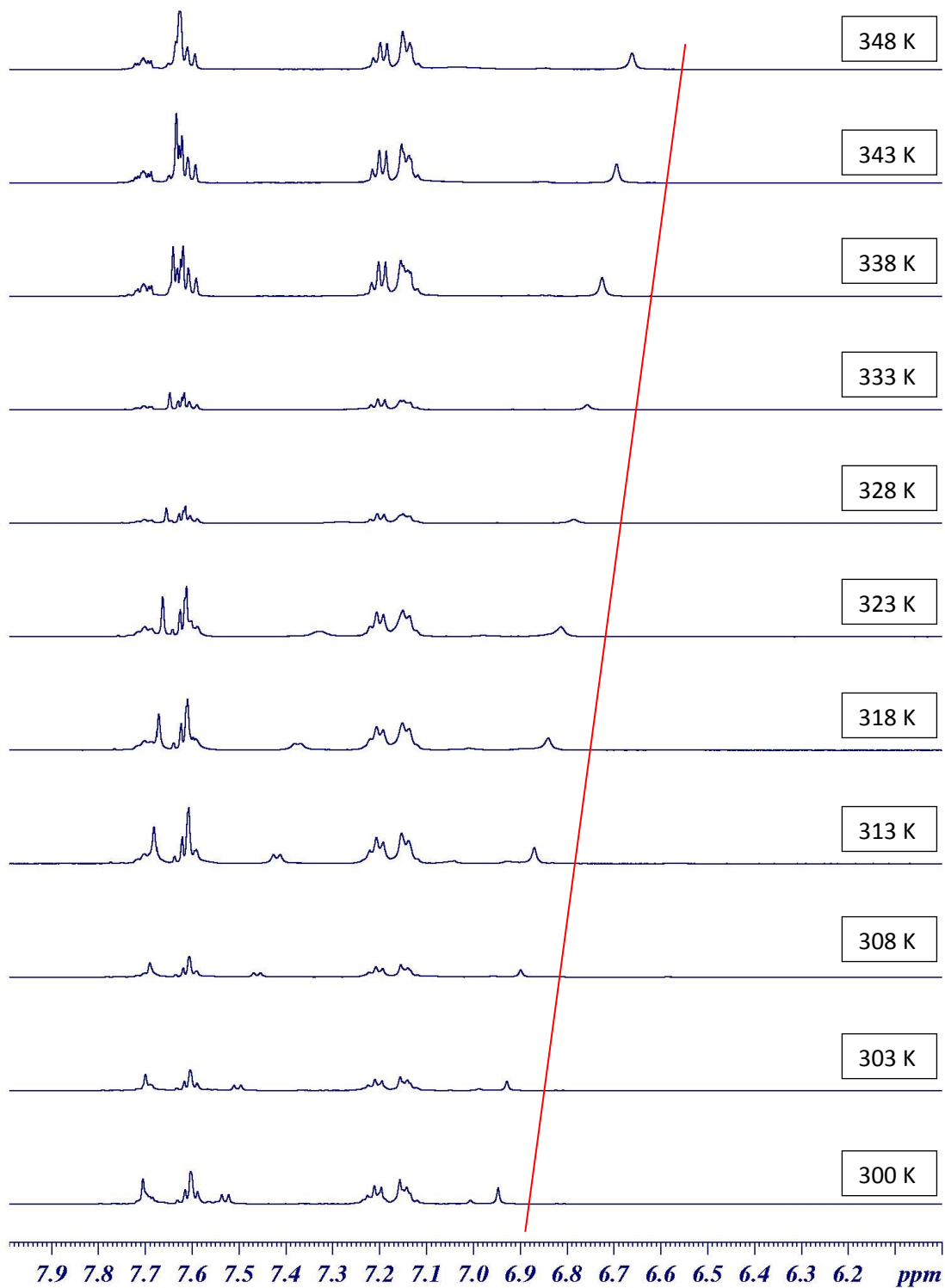
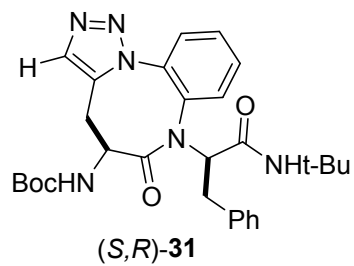




(S,R)-22

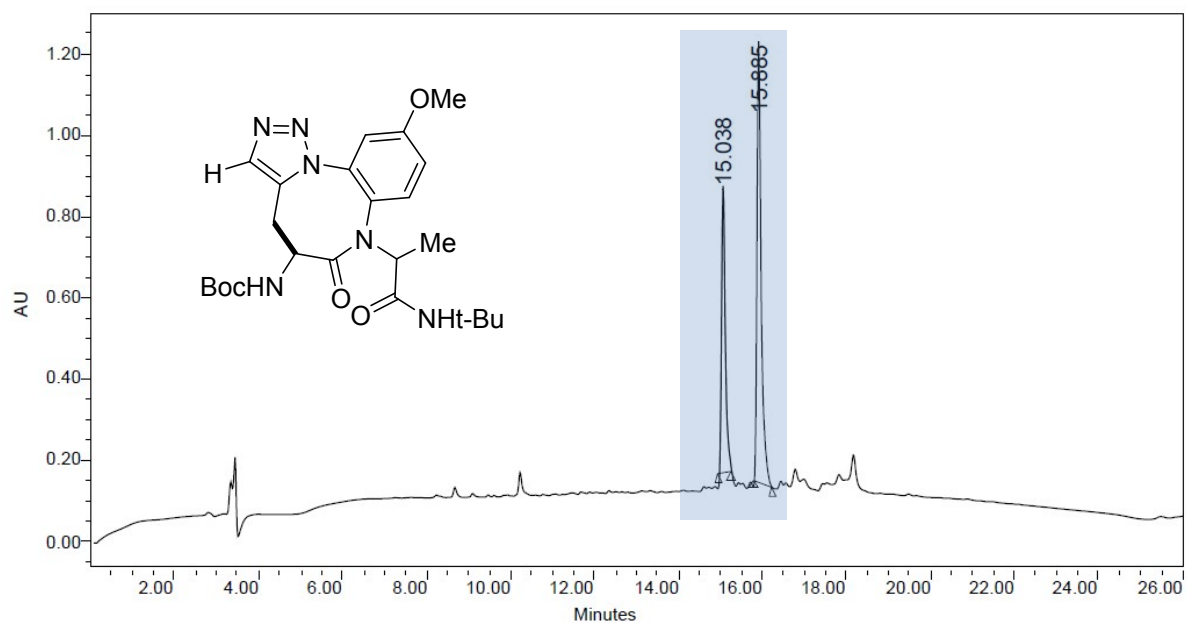




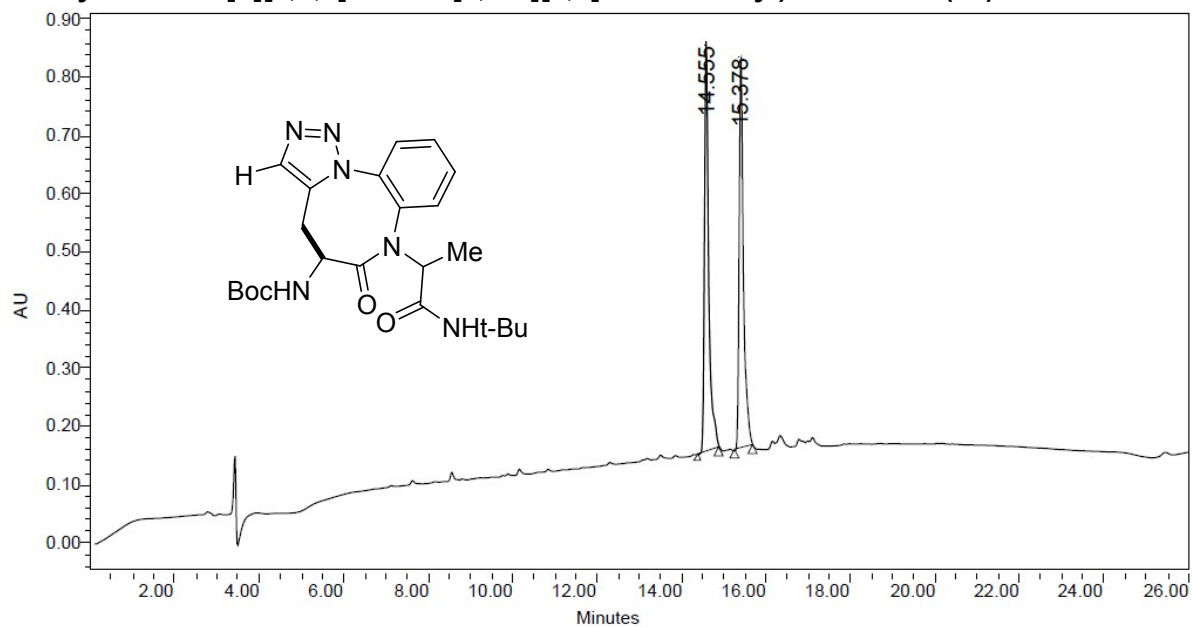


4. HPLC Traces

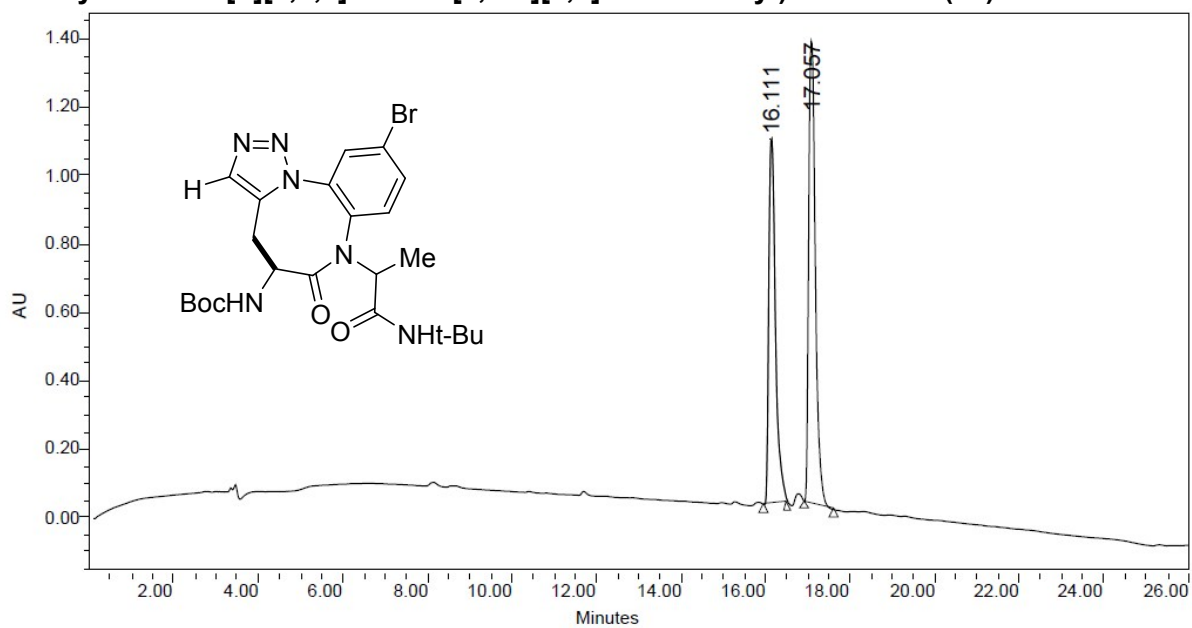
Here we provide an example of an HPLC trace of 26 immediately after 24 hours of heating and prior to purification, showing that the two diastereoisomers (highlighted) are the major product, and that only minor impurities are formed.



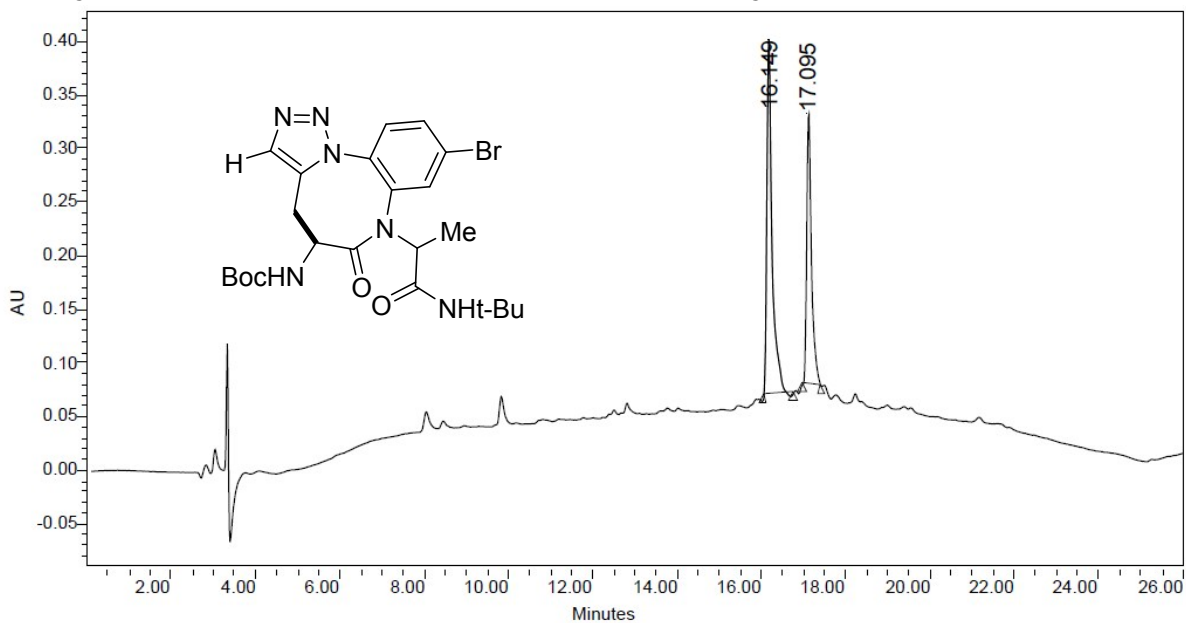
***tert*-butyl ((5*S*)-7-(1-(*tert*-butylamino)-1-oxopropan-2-yl)-6-oxo-4,5,6,7-tetrahydrobenzo[*b*][1,2,3]triazolo[1,5-*d*][1,4]diazocin-5-yl)carbamate (22)**



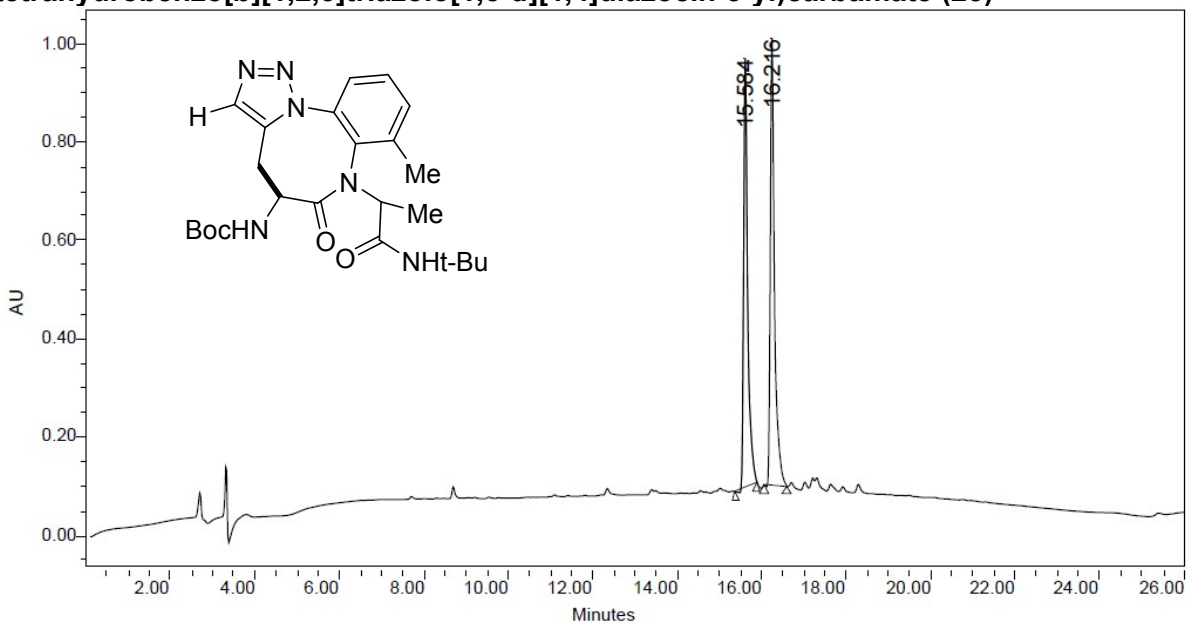
***tert*-butyl ((5*S*)-10-bromo-7-(1-(*tert*-butylamino)-1-oxopropan-2-yl)-6-oxo-4,5,6,7-tetrahydrobenzo[*b*][1,2,3]triazolo[1,5-*d*][1,4]diazocin-5-yl)carbamate (23)**



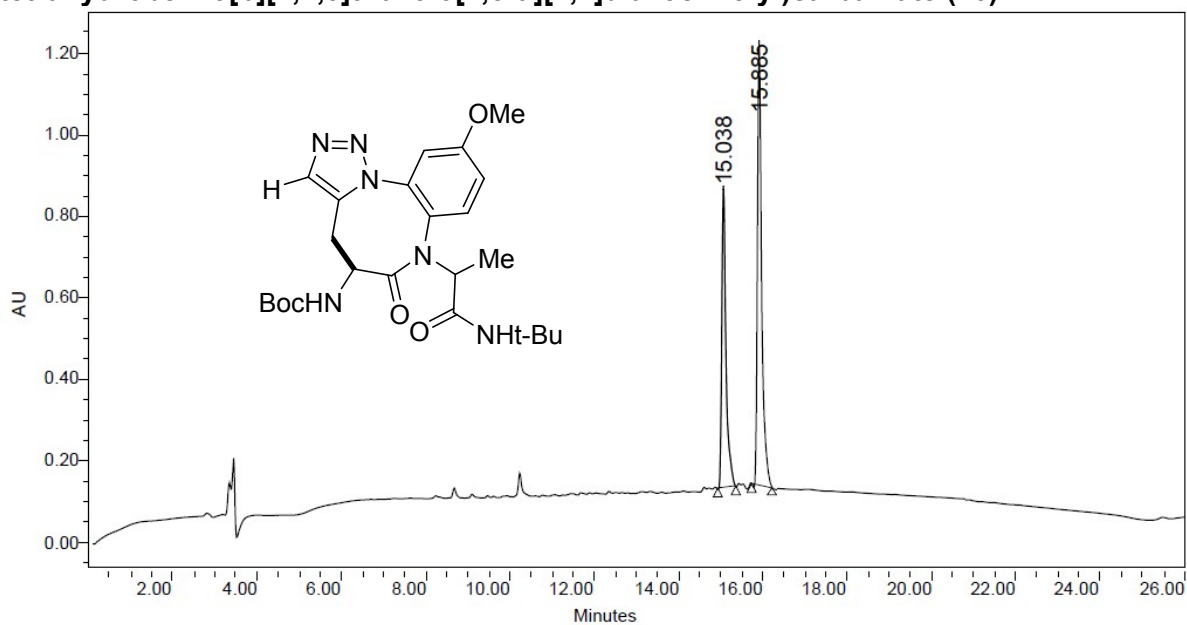
***tert*-butyl ((5*S*)-9-bromo-7-(1-(*tert*-butylamino)-1-oxopropan-2-yl)-6-oxo-4,5,6,7-tetrahydrobenzo[*b*][1,2,3]triazolo[1,5-*d*][1,4]diazocin-5-yl)carbamate (24)**



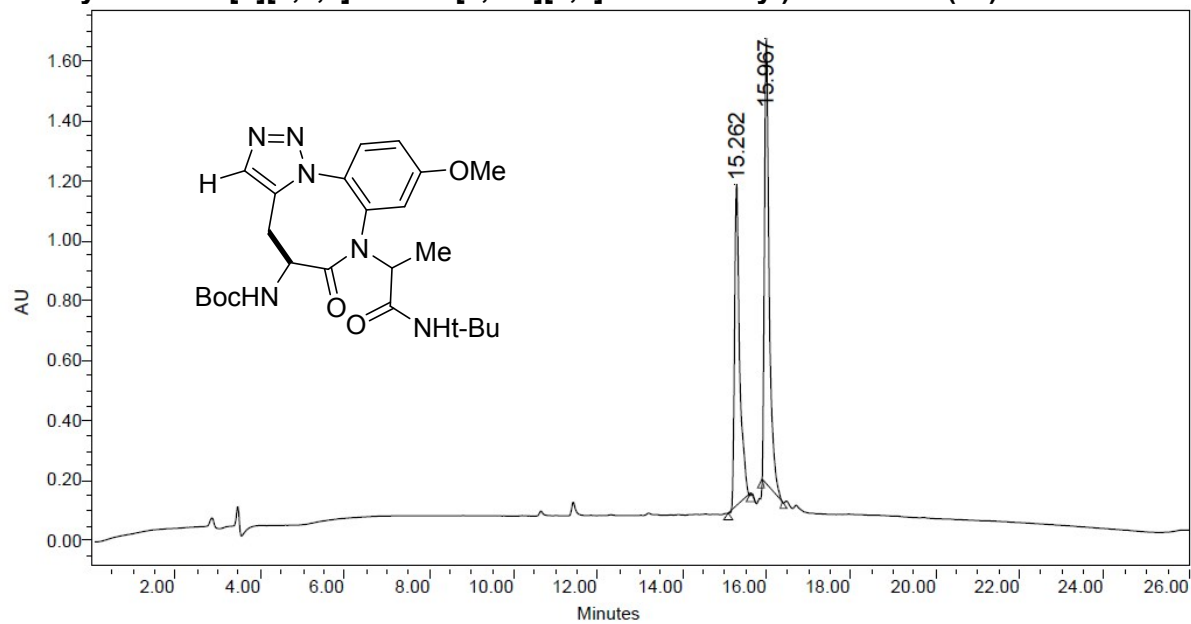
***tert*-butyl ((5*S*)-7-(1-(*tert*-butylamino)-1-oxopropan-2-yl)-8-methyl-6-oxo-4,5,6,7-tetrahydrobenzo[*b*][1,2,3]triazolo[1,5-*d*][1,4]diazocin-5-yl)carbamate (25)**



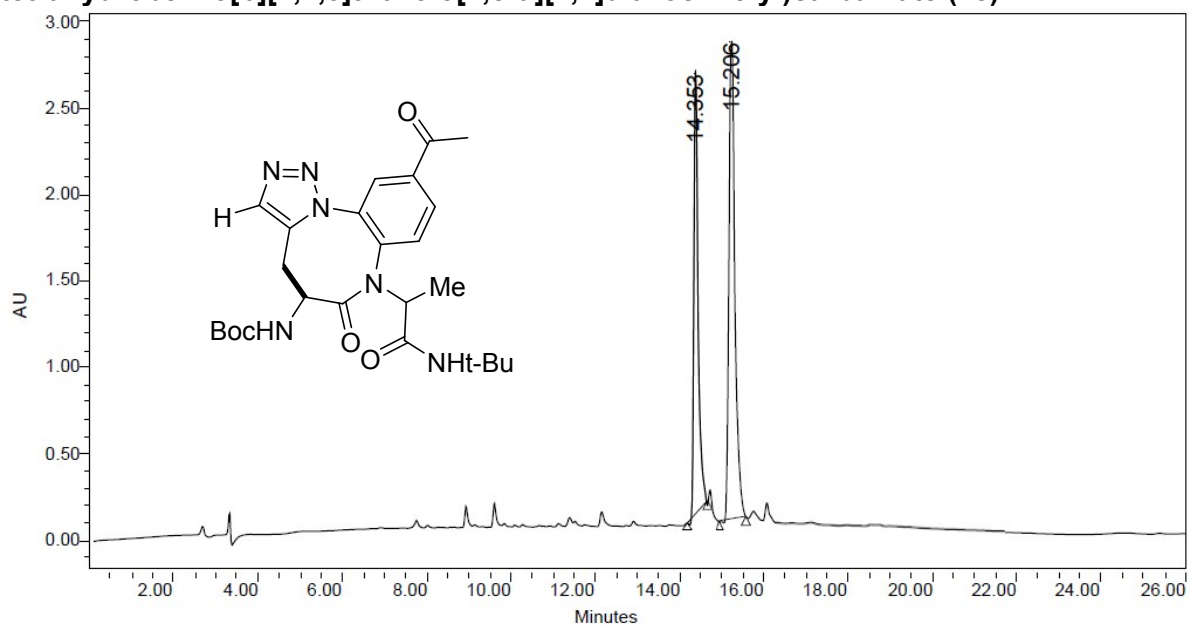
***tert*-butyl ((5*S*)-7-(1-(*tert*-butylamino)-1-oxopropan-2-yl)-10-methoxy-6-oxo-4,5,6,7-tetrahydrobenzo[*b*][1,2,3]triazolo[1,5-*d*][1,4]diazocin-5-yl)carbamate (26)**



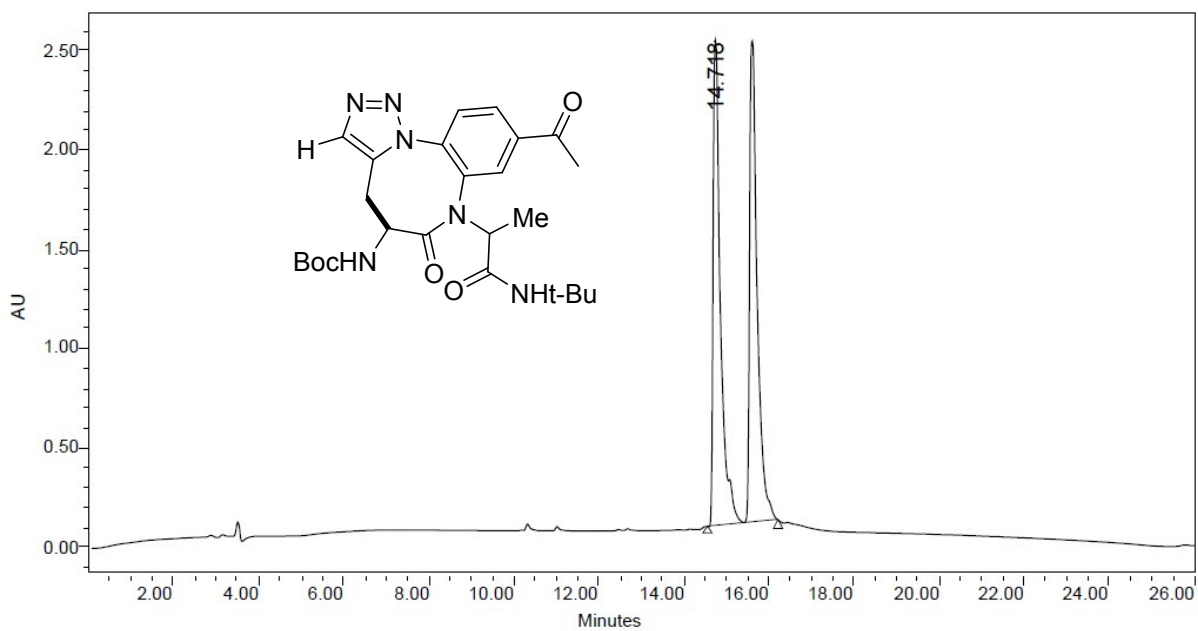
***tert*-butyl ((5*S*)-7-(1-(*tert*-butylamino)-1-oxopropan-2-yl)-9-methoxy-6-oxo-4,5,6,7-tetrahydrobenzo[*b*][1,2,3]triazolo[1,5-*d*][1,4]diazocin-5-yl)carbamate (27)**



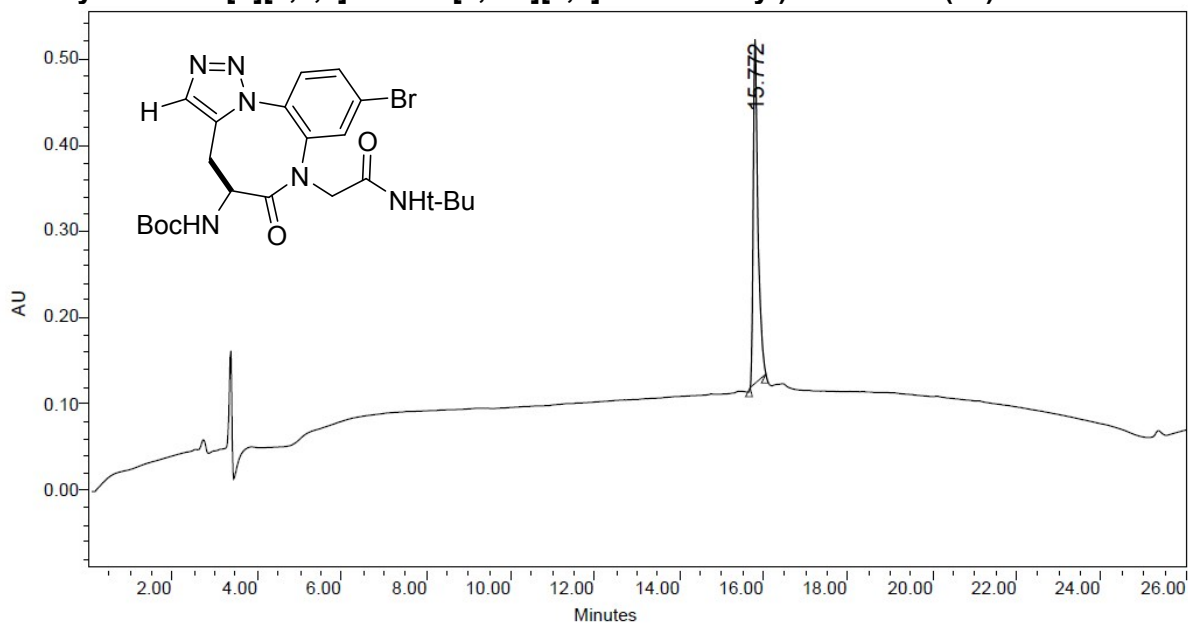
***tert*-butyl ((5*S*)-10-acetyl-7-(1-(*tert*-butylamino)-1-oxopropan-2-yl)-6-oxo-4,5,6,7-tetrahydrobenzo[*b*][1,2,3]triazolo[1,5-*d*][1,4]diazocin-5-yl)carbamate (28)**



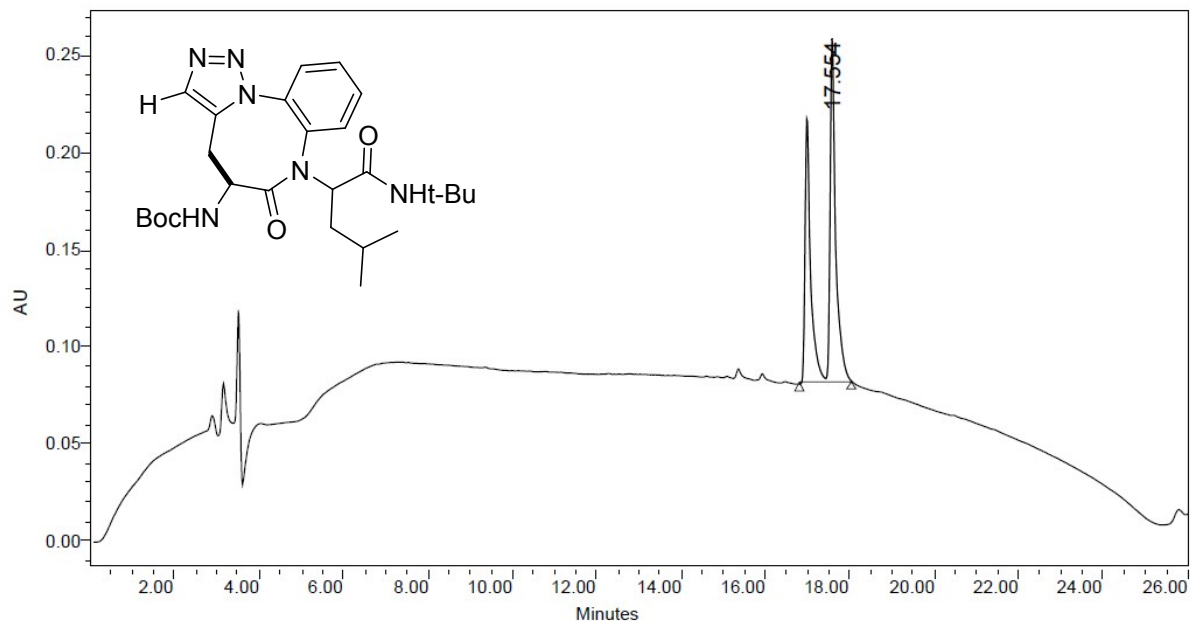
***tert*-butyl ((5*S*)-9-acetyl-7-(1-(*tert*-butylamino)-1-oxopropan-2-yl)-6-oxo-4,5,6,7-tetrahydrobenzo[*b*][1,2,3]triazolo[1,5-*d*][1,4]diazocin-5-yl)carbamate (29)**



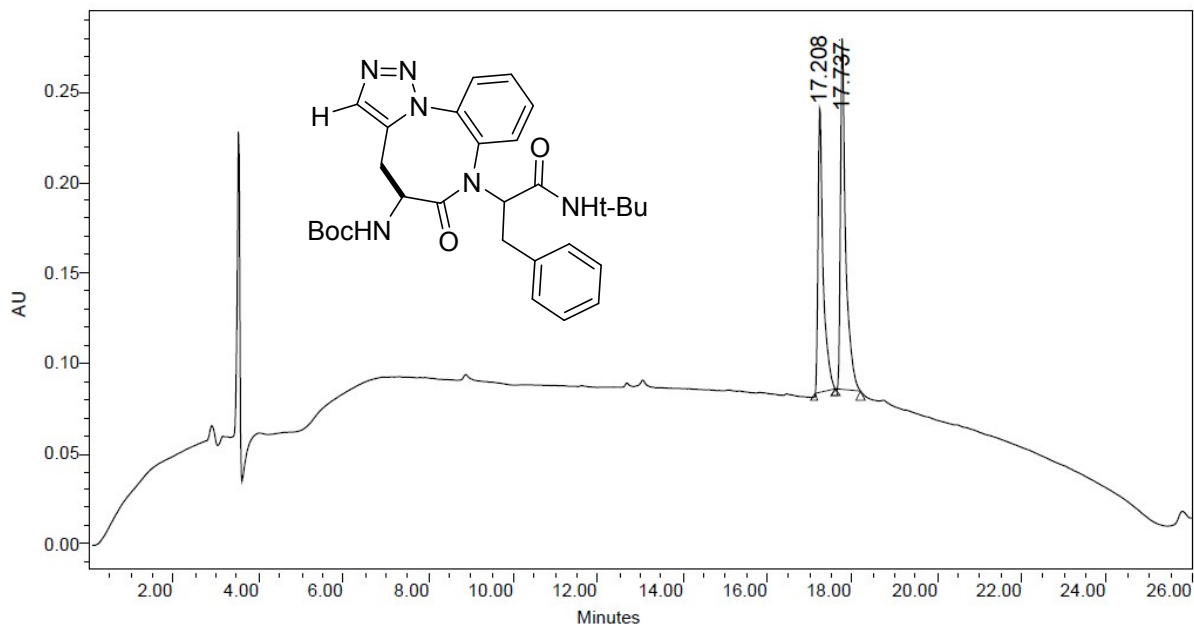
***tert*-butyl (S)-(9-bromo-7-(2-(*tert*-butylamino)-2-oxoethyl)-6-oxo-4,5,6,7-tetrahydrobenzo[*b*][1,2,3]triazolo[1,5-*d*][1,4]diazocin-5-yl)carbamate (30)**



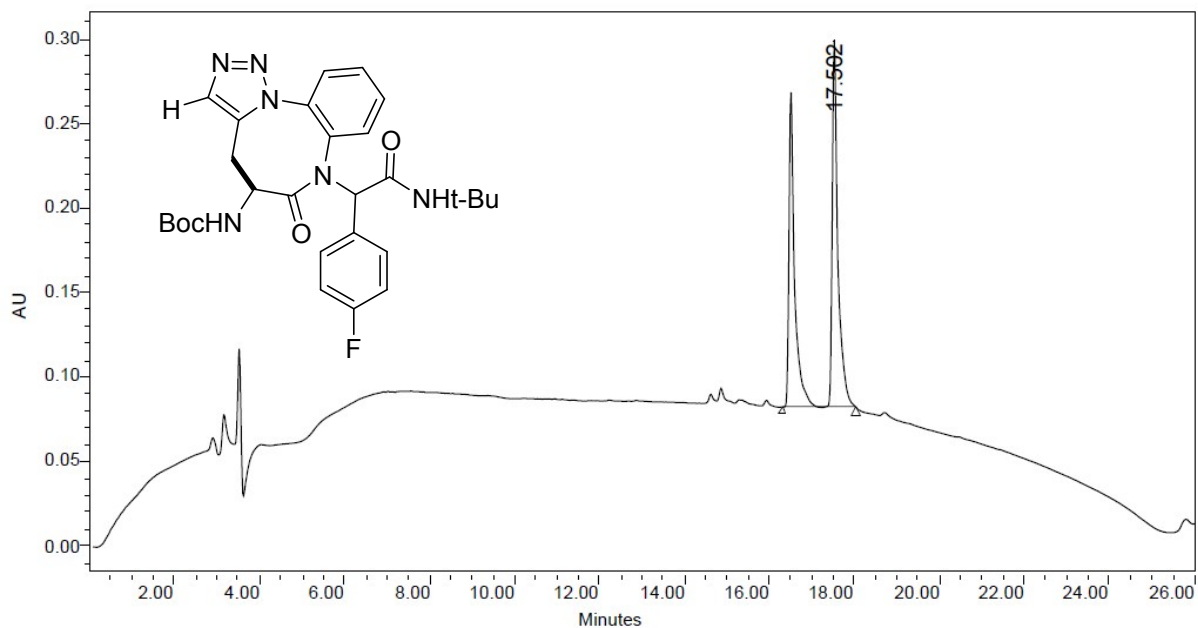
***tert*-butyl ((5*S*)-7-(1-(*tert*-butylamino)-4-methyl-1-oxopentan-2-yl)-6-oxo-4,5,6,7-tetrahydrobenzo[*b*][1,2,3]triazolo[1,5-*d*][1,4]diazocin-5-yl)carbamate (31)**



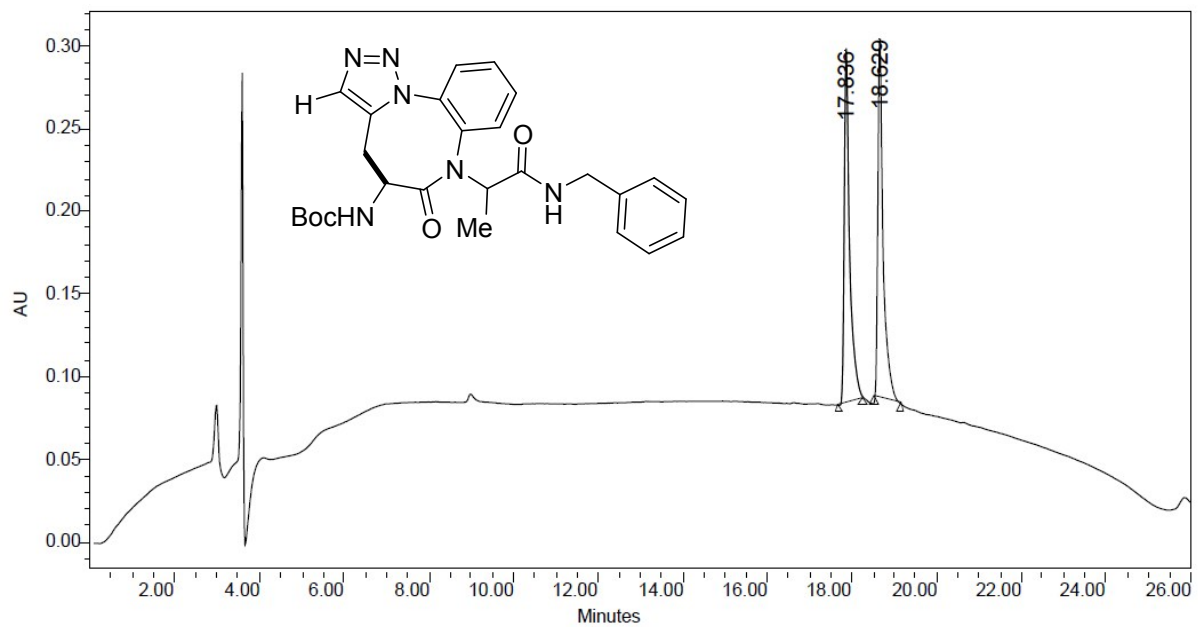
***tert*-butyl ((5*S*)-7-(1-(*tert*-butylamino)-4-methyl-1-oxopentan-2-yl)-6-oxo-4,5,6,7-tetrahydrobenzo[*b*][1,2,3]triazolo[1,5-*d*][1,4]diazocin-5-yl)carbamate (32)**



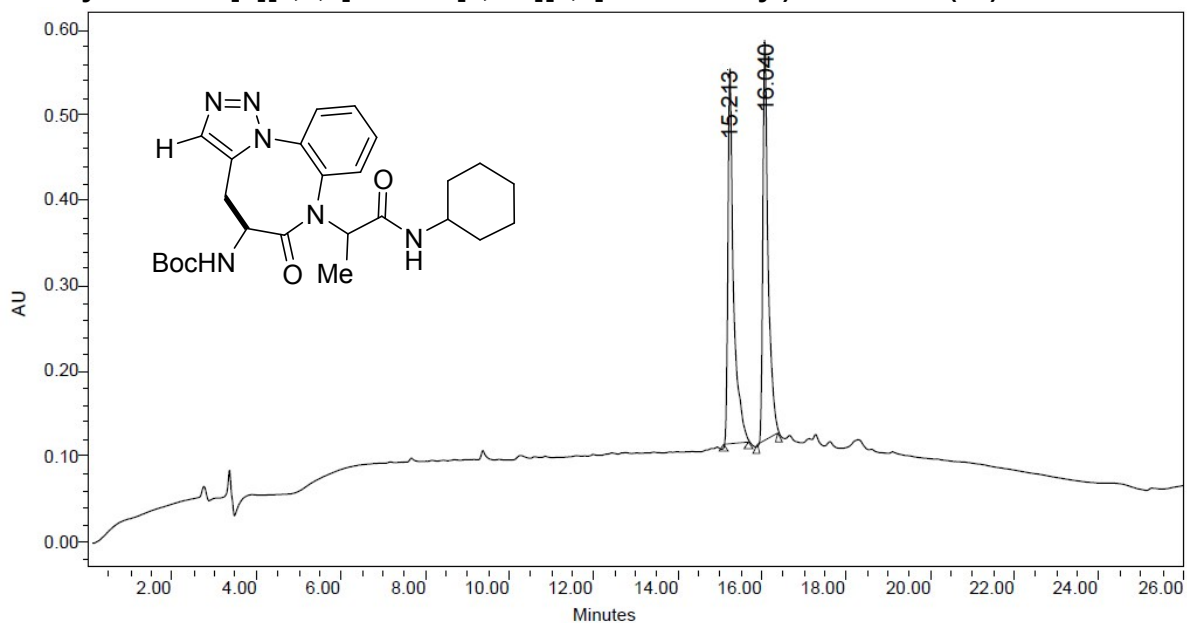
***tert*-butyl ((5*S*)-7-(2-(*tert*-butylamino)-1-(4-fluorophenyl)-2-oxoethyl)-6-oxo-4,5,6,7-tetrahydrobenzo[*b*][1,2,3]triazolo[1,5-*d*][1,4]diazocin-5-yl)carbamate (33)**



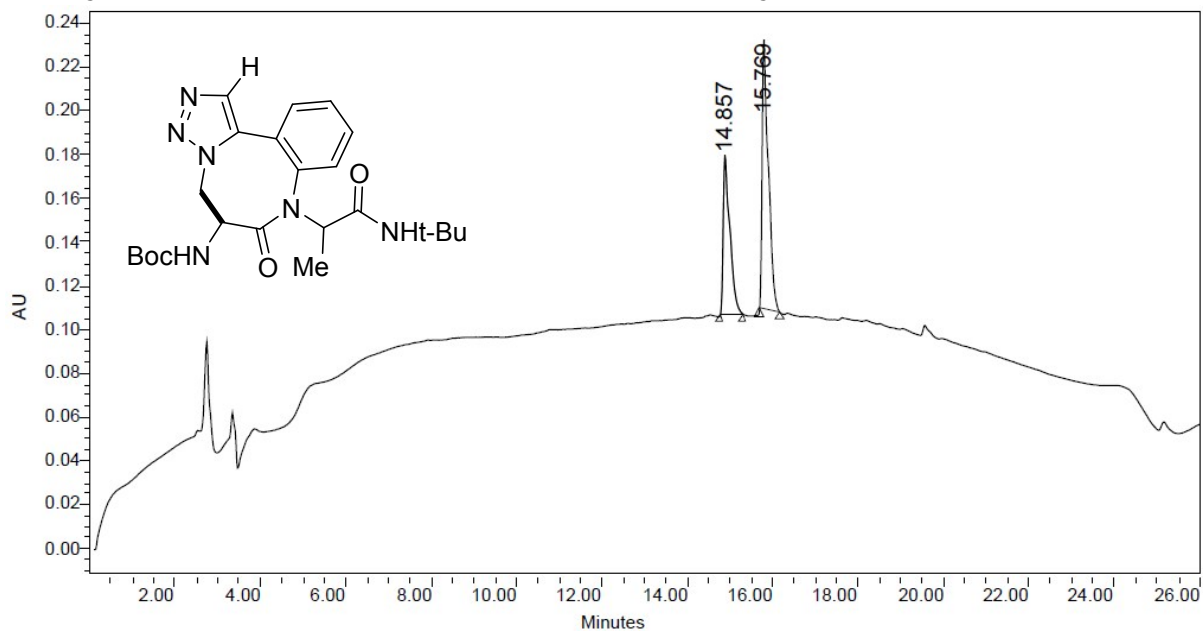
***tert*-butyl ((5*S*)-7-(1-(benzylamino)-1-oxopropan-2-yl)-6-oxo-4,5,6,7-tetrahydrobenzo[*b*][1,2,3]triazolo[1,5-*d*][1,4]diazocin-5-yl)carbamate (34)**



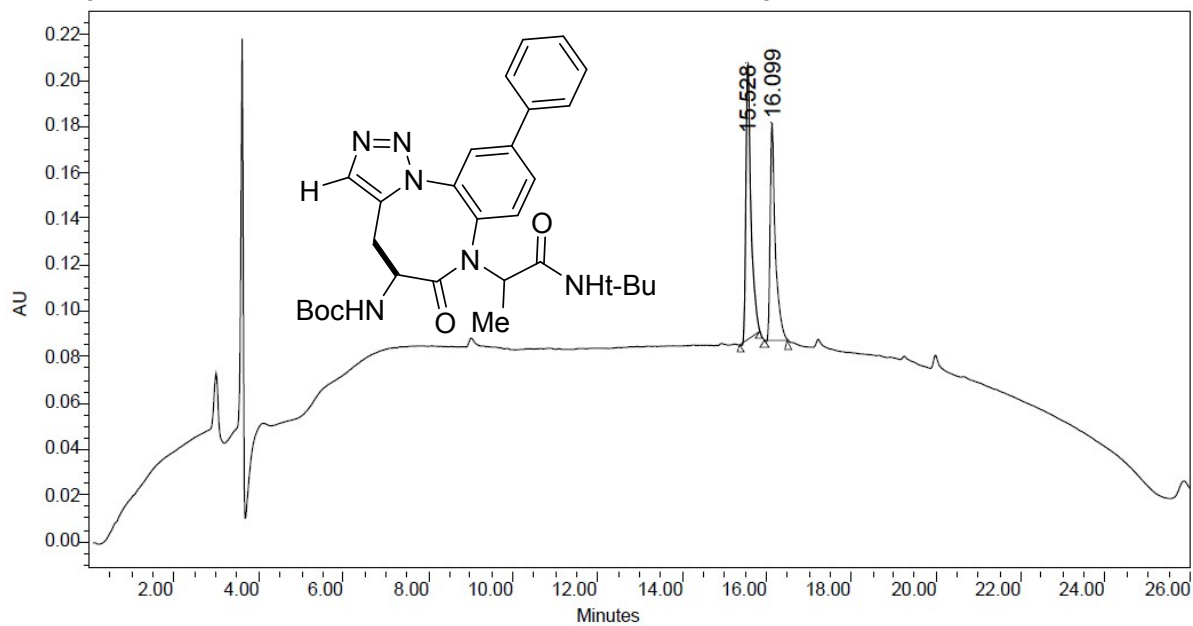
***tert*-butyl ((5*S*)-7-(1-(cyclohexylamino)-1-oxopropan-2-yl)-6-oxo-4,5,6,7-tetrahydrobenzo[*b*][1,2,3]triazolo[1,5-*d*][1,4]diazocin-5-yl)carbamate (35)**



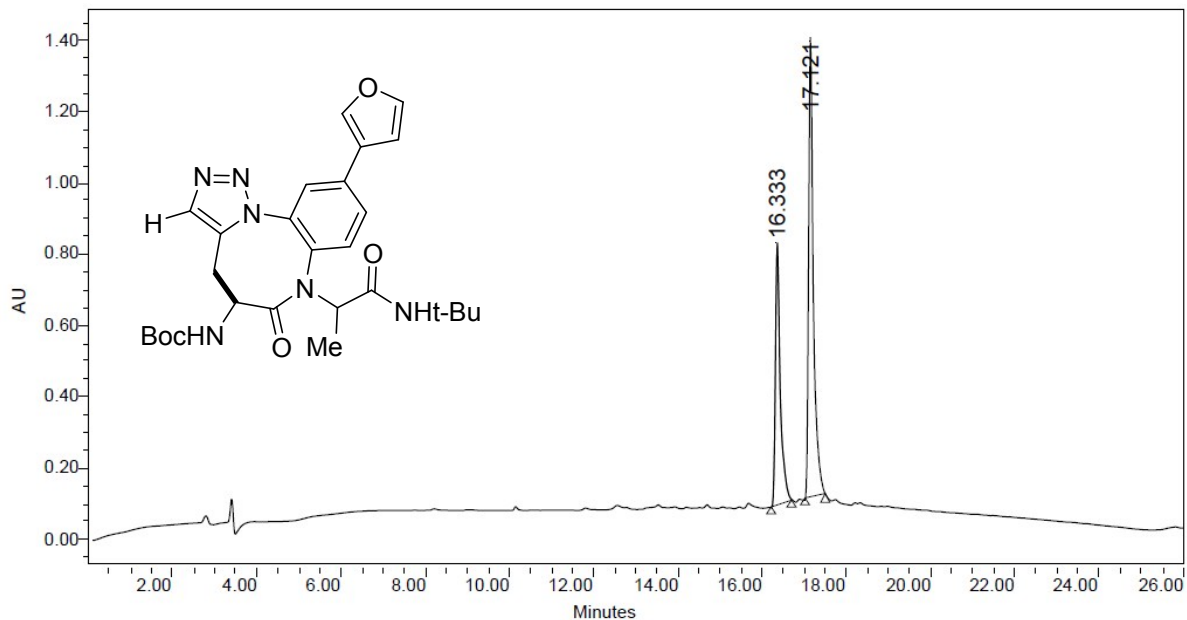
***tert*-butyl ((6*S*)-8-(1-(*tert*-butylamino)-1-oxopropan-2-yl)-7-oxo-5,6,7,8-tetrahydrobenzo[*c*][1,2,3]triazolo[1,5-*a*][1,5]diazocin-6-yl)carbamate (37)**



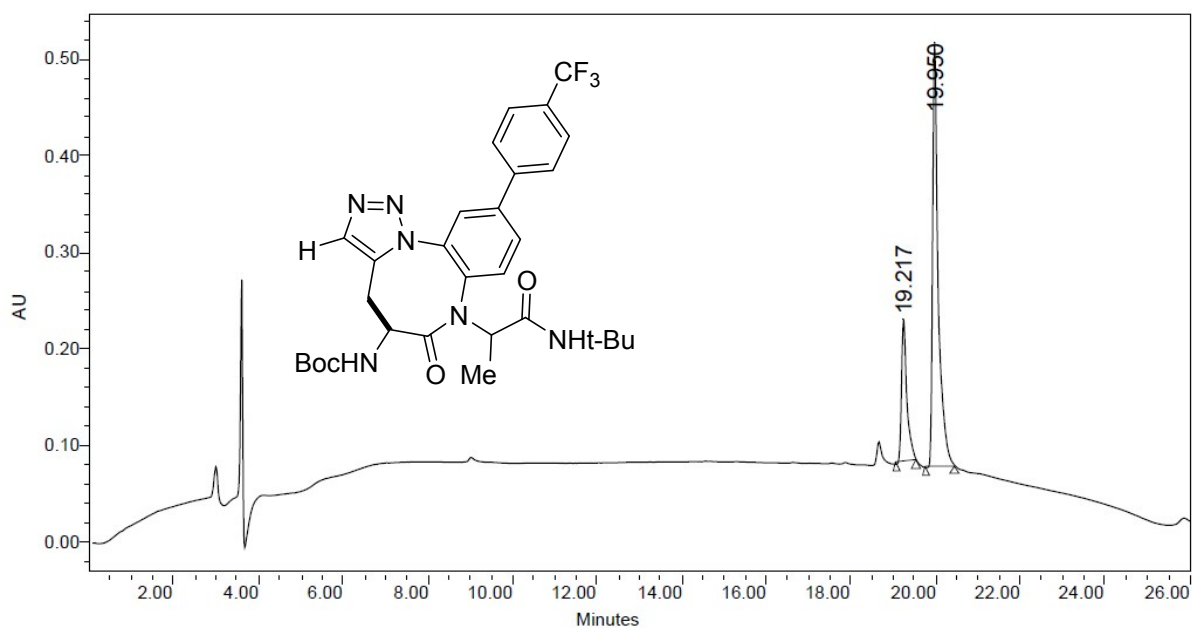
***tert*-butyl ((5*S*)-7-(1-(*tert*-butylamino)-1-oxopropan-2-yl)-6-oxo-10-phenyl-4,5,6,7-tetrahydrobenzo[*b*][1,2,3]triazolo[1,5-*d*][1,4]diazocin-5-yl)carbamate (38)**



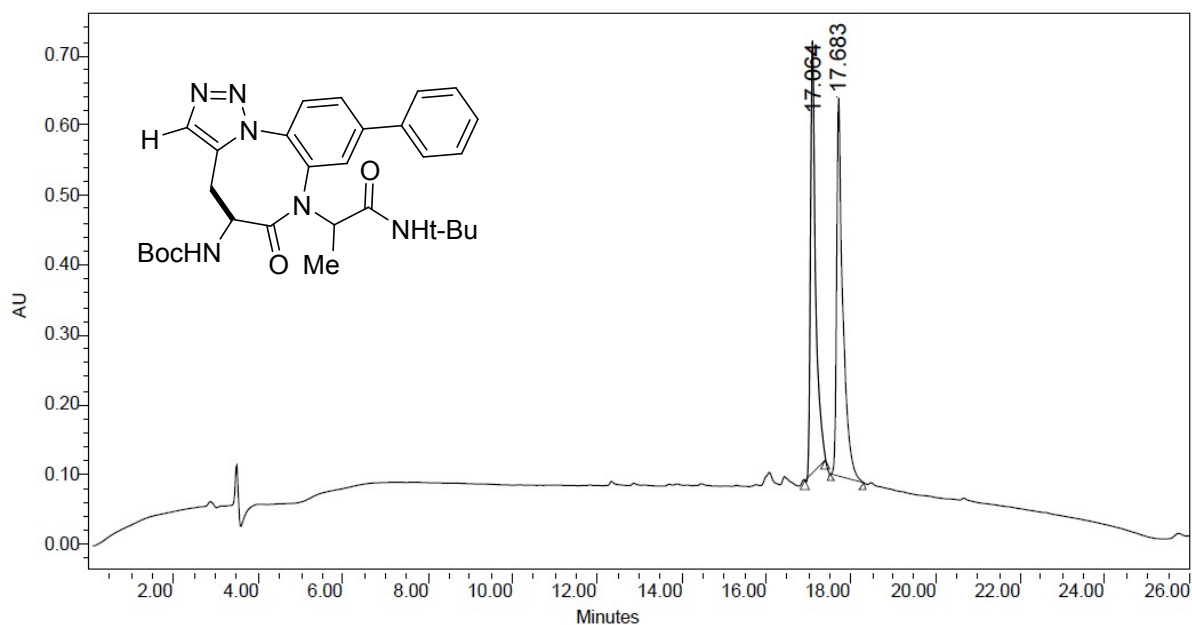
***tert*-butyl ((5*S*)-7-(1-(*tert*-butylamino)-1-oxopropan-2-yl)-10-(furan-3-yl)-6-oxo-4,5,6,7-tetrahydrobenzo[*b*][1,2,3]triazolo[1,5-*d*][1,4]diazocin-5-yl)carbamate (39)**



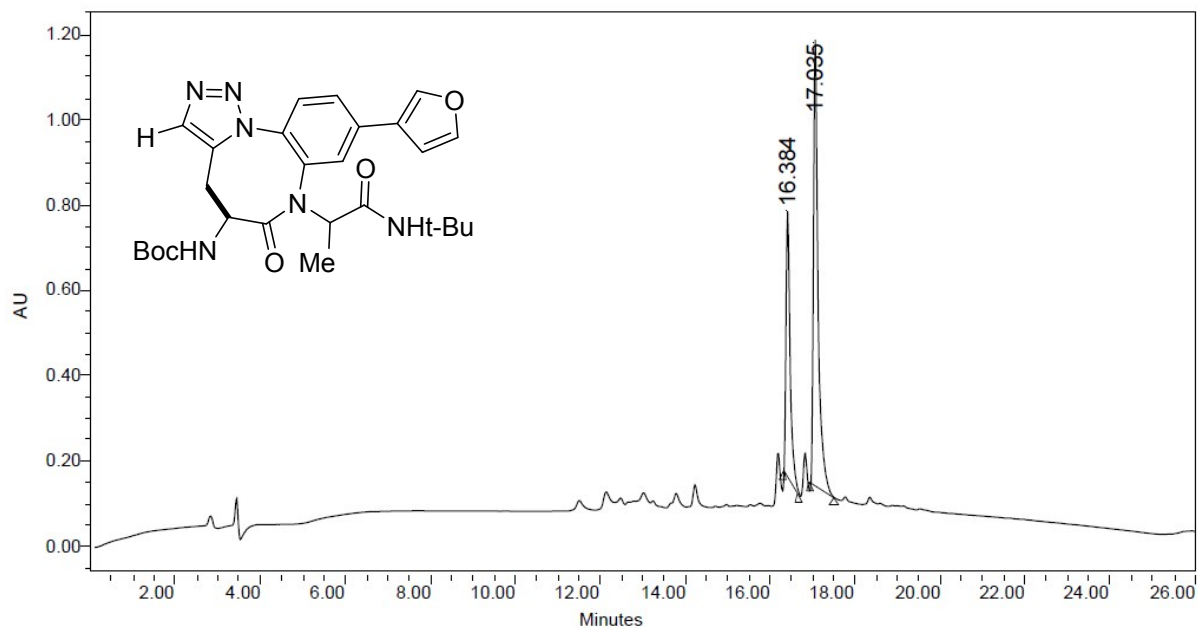
***tert*-butyl ((5*S*)-7-(1-(*tert*-butylamino)-1-oxopropan-2-yl)-6-oxo-10-(4-(trifluoromethyl)phenyl)-4,5,6,7-tetrahydrobenzo[*b*][1,2,3]triazolo[1,5-*d*][1,4]diazocin-5-yl)carbamate (40)**



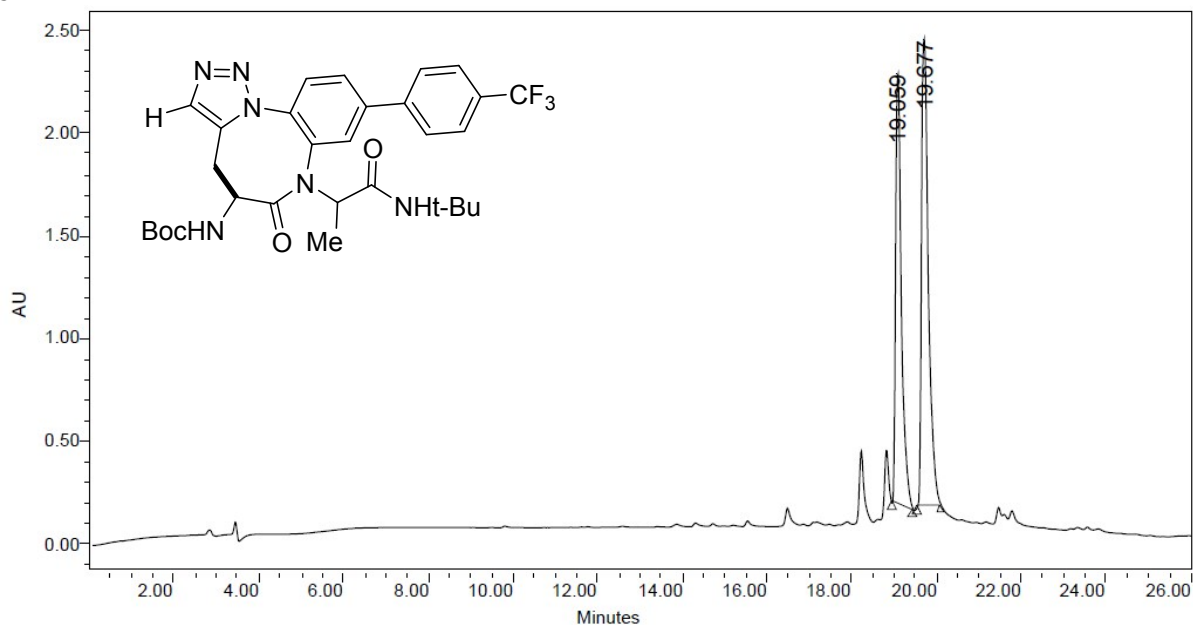
***tert*-butyl ((5*S*)-7-(1-(*tert*-butylamino)-1-oxopropan-2-yl)-6-oxo-9-phenyl-4,5,6,7-tetrahydrobenzo[*b*][1,2,3]triazolo[1,5-*d*][1,4]diazocin-5-yl)carbamate (41)**



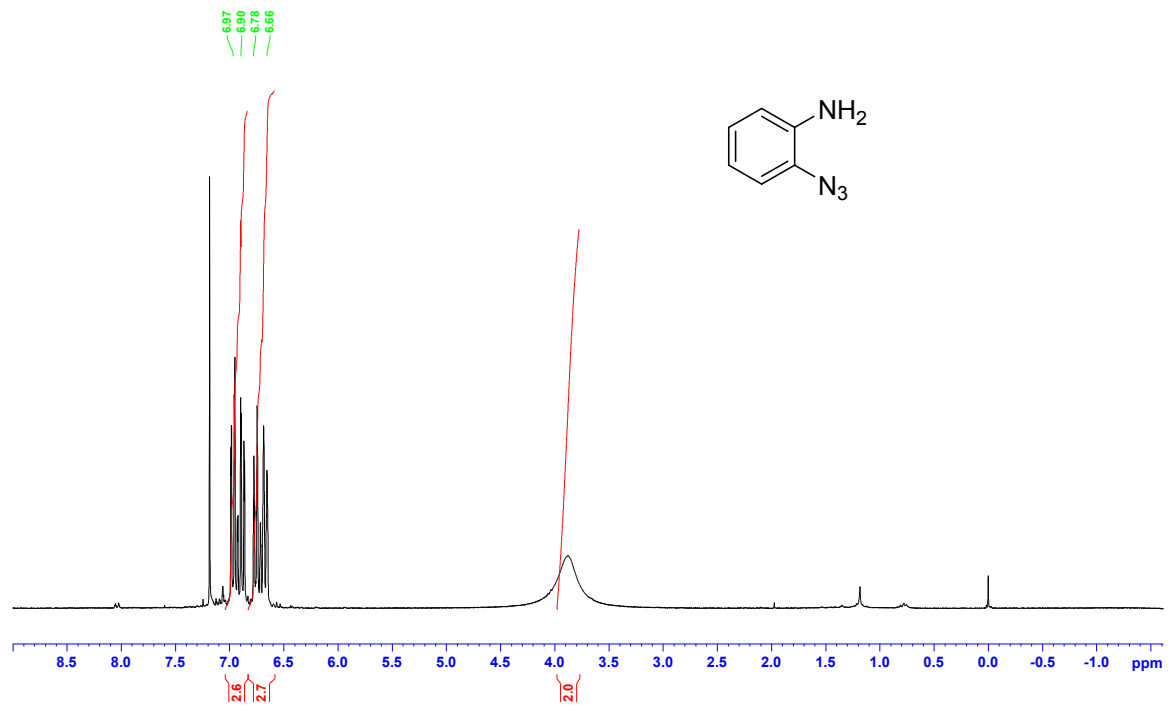
***tert*-butyl ((5*S*)-7-(1-(*tert*-butylamino)-1-oxopropan-2-yl)-9-(furan-3-yl)-6-oxo-4,5,6,7-tetrahydrobenzo[*b*][1,2,3]triazolo[1,5-*d*][1,4]diazocin-5-yl)carbamate (42)**



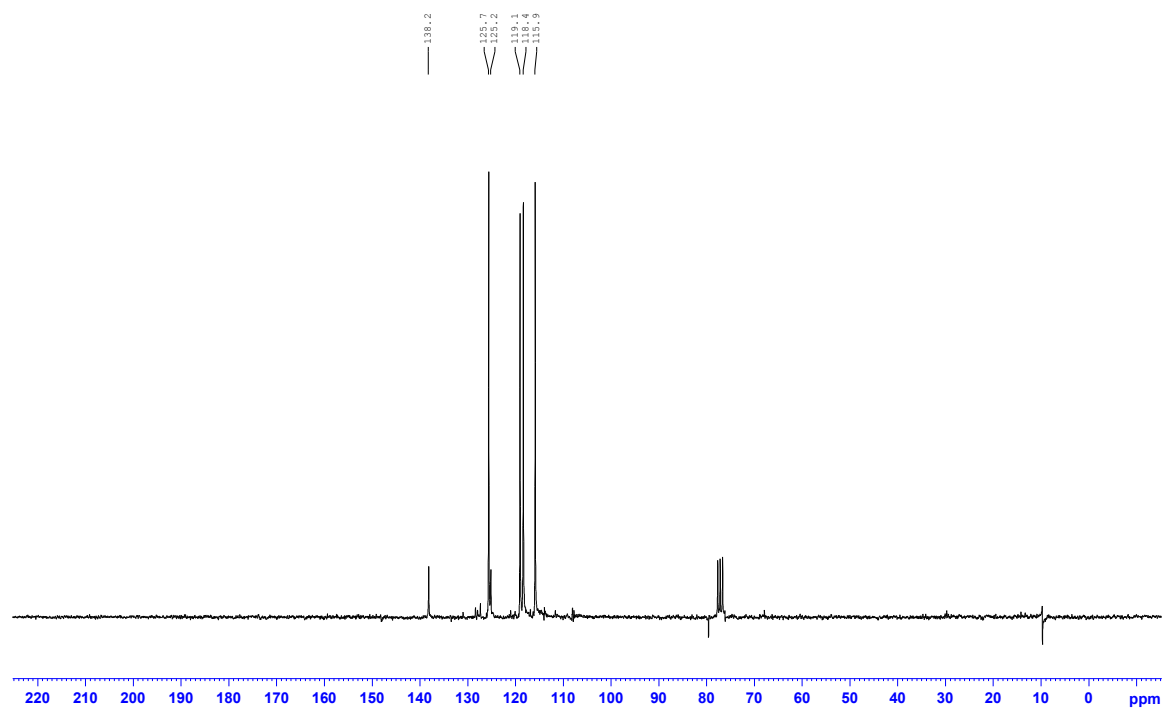
***tert*-butyl ((5*S*)-7-(1-(*tert*-butylamino)-1-oxopropan-2-yl)-6-oxo-9-(4-(trifluoromethyl)phenyl)-4,5,6,7-tetrahydrobenzo[*b*][1,2,3]triazolo[1,5-*d*][1,4]diazocin-5-yl)carbamate (43)**



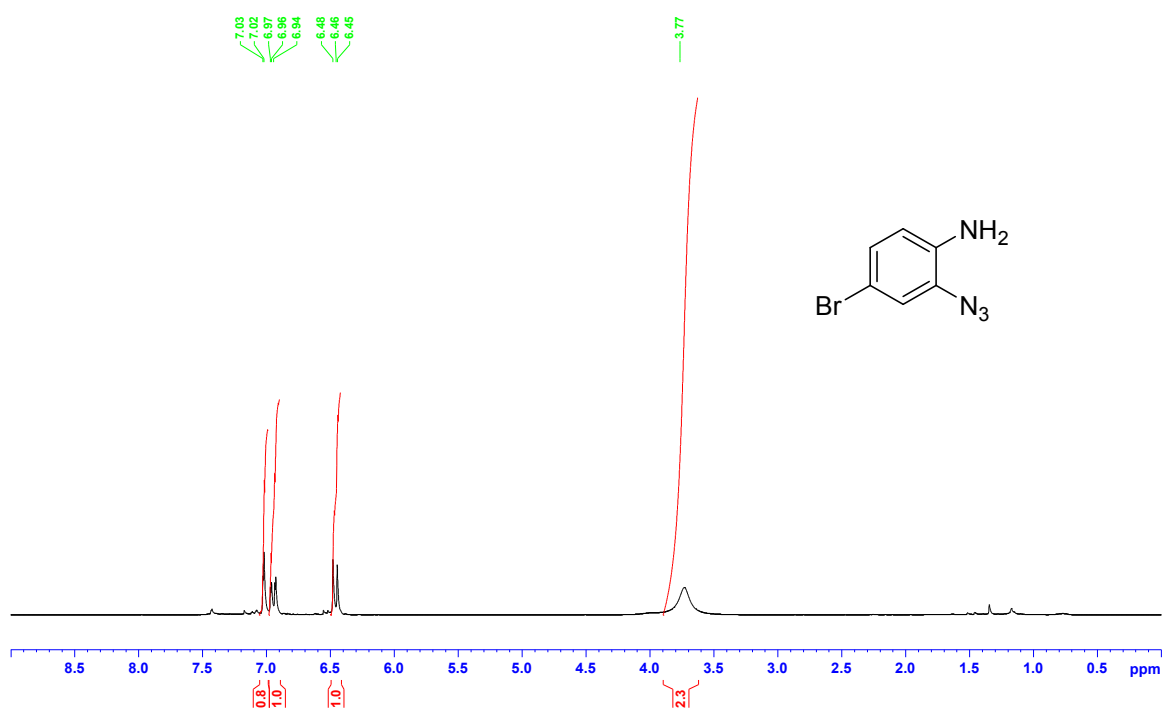
5. NMR Spectra
14 – ¹H-NMR (250 MHz, CDCl₃)



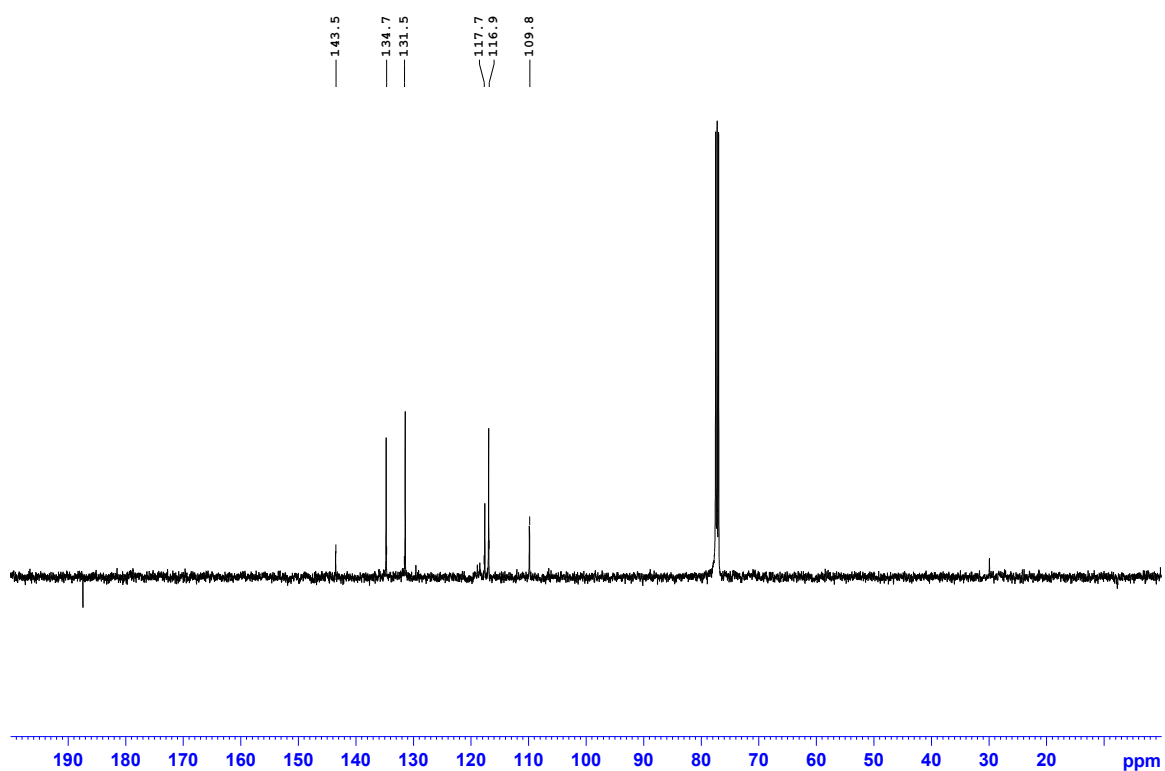
14 – ¹³C-NMR (63 MHz, CDCl₃)



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

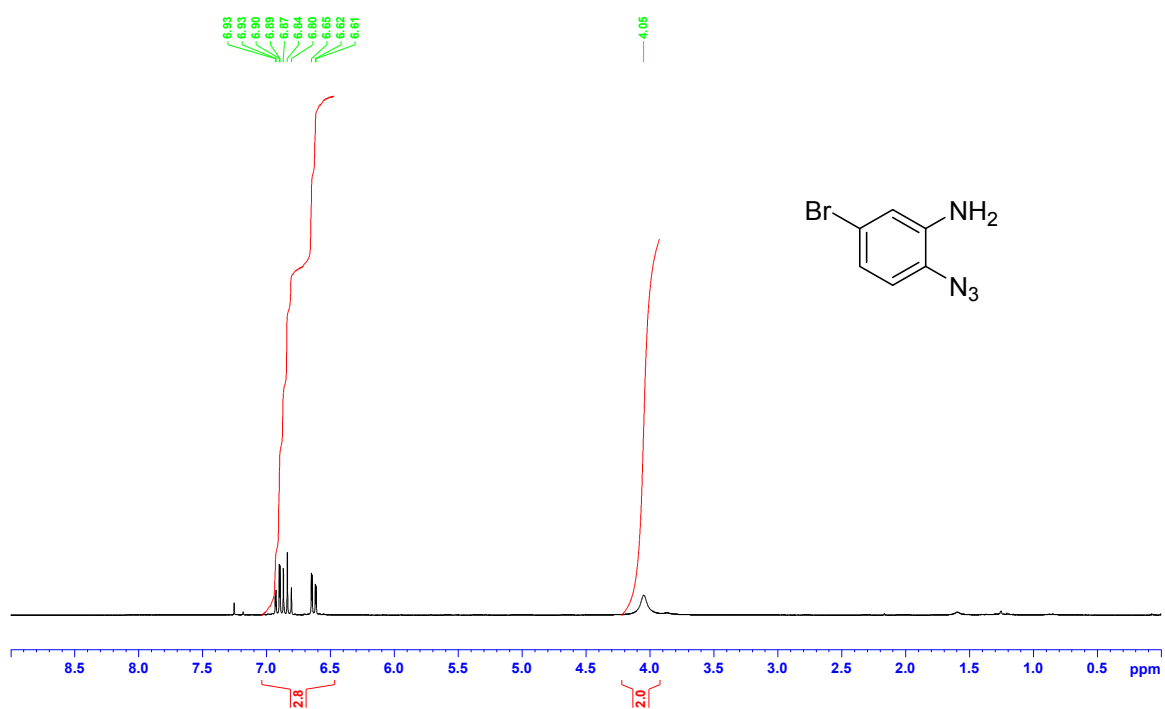


15 – $^{13}\text{C-NMR}$ (63 MHz, CDCl_3)

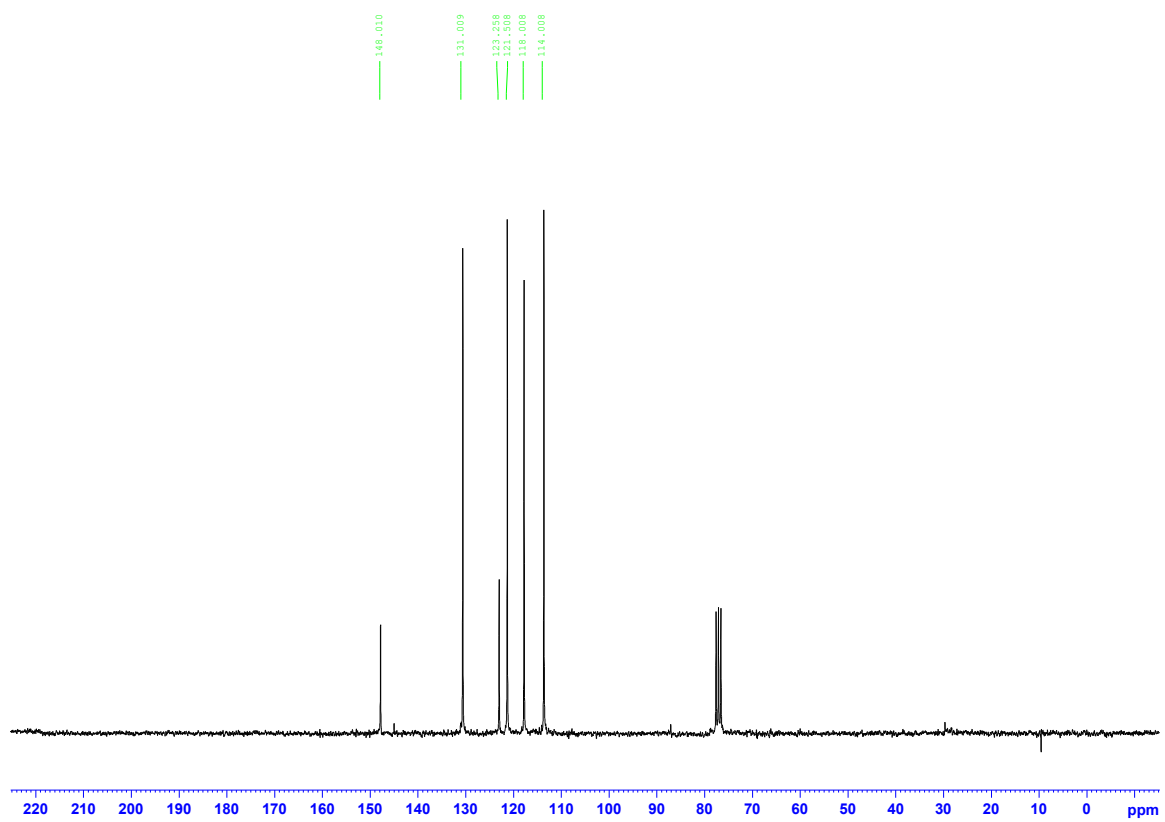


The small peak at 186 ppm is an artefact of our spectrometer and not due to the sample

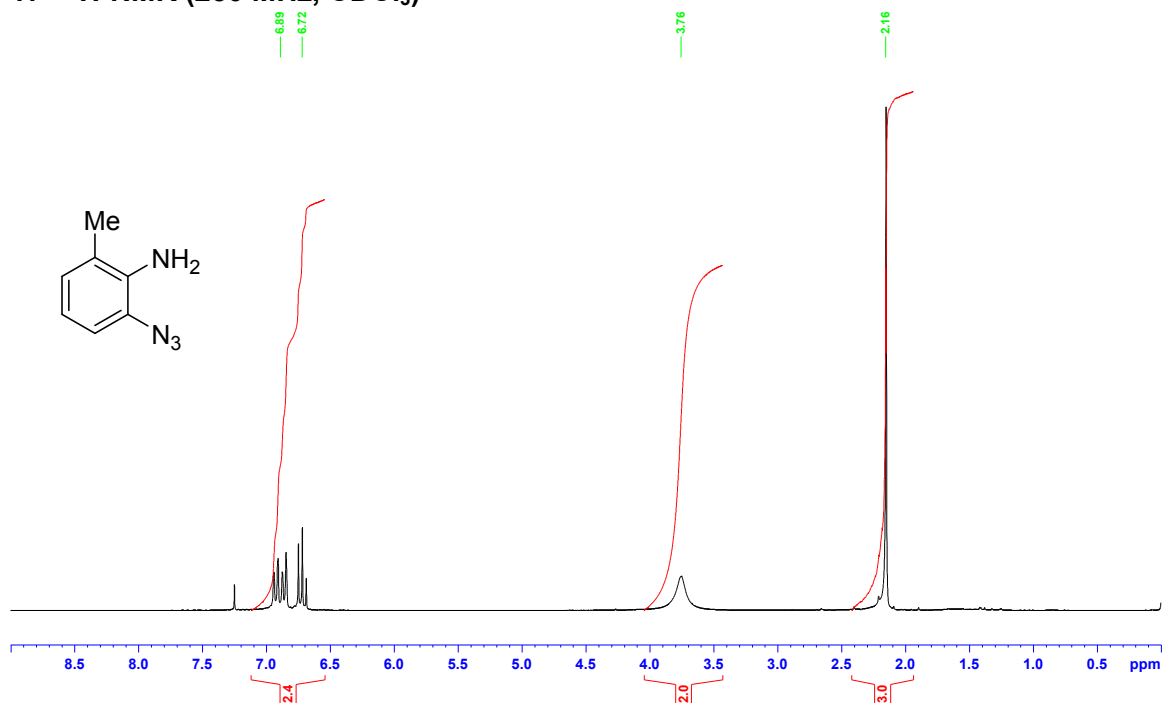
16 – ¹H-NMR (250 MHz, CDCl₃)



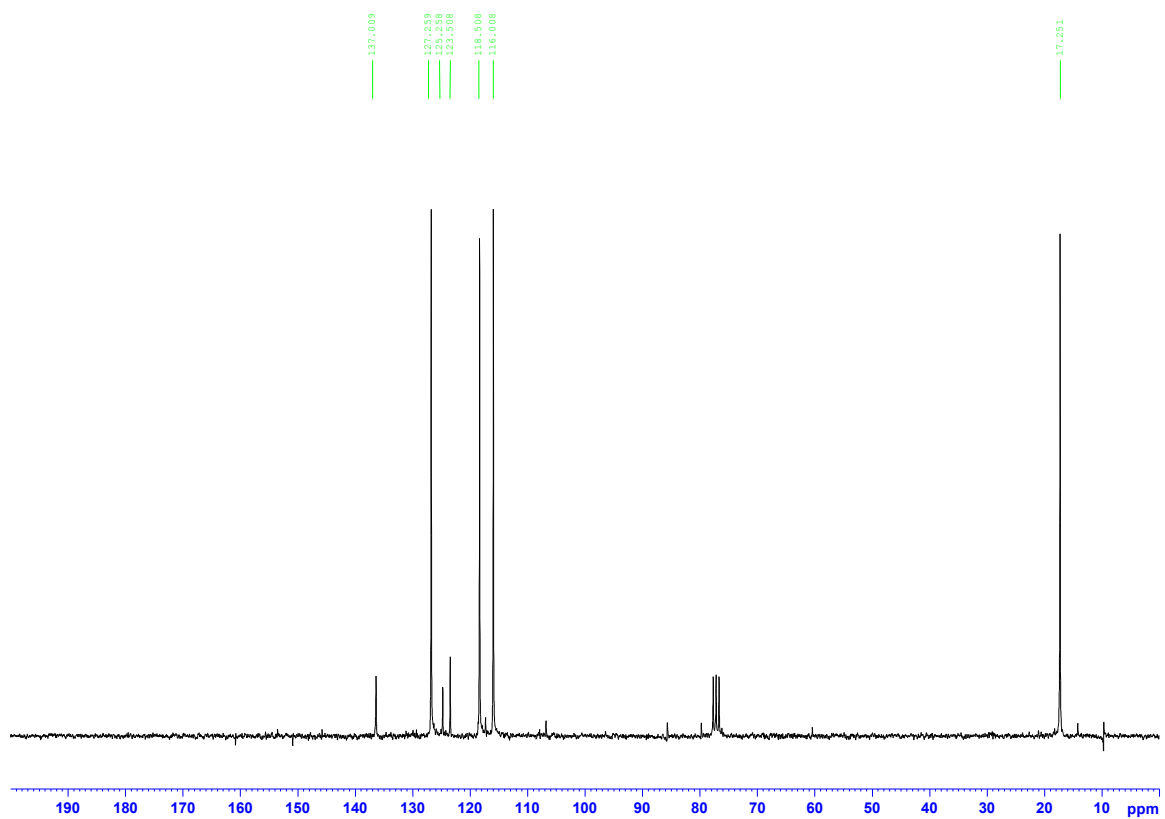
16 – ¹³C-NMR (125 MHz, CDCl₃)



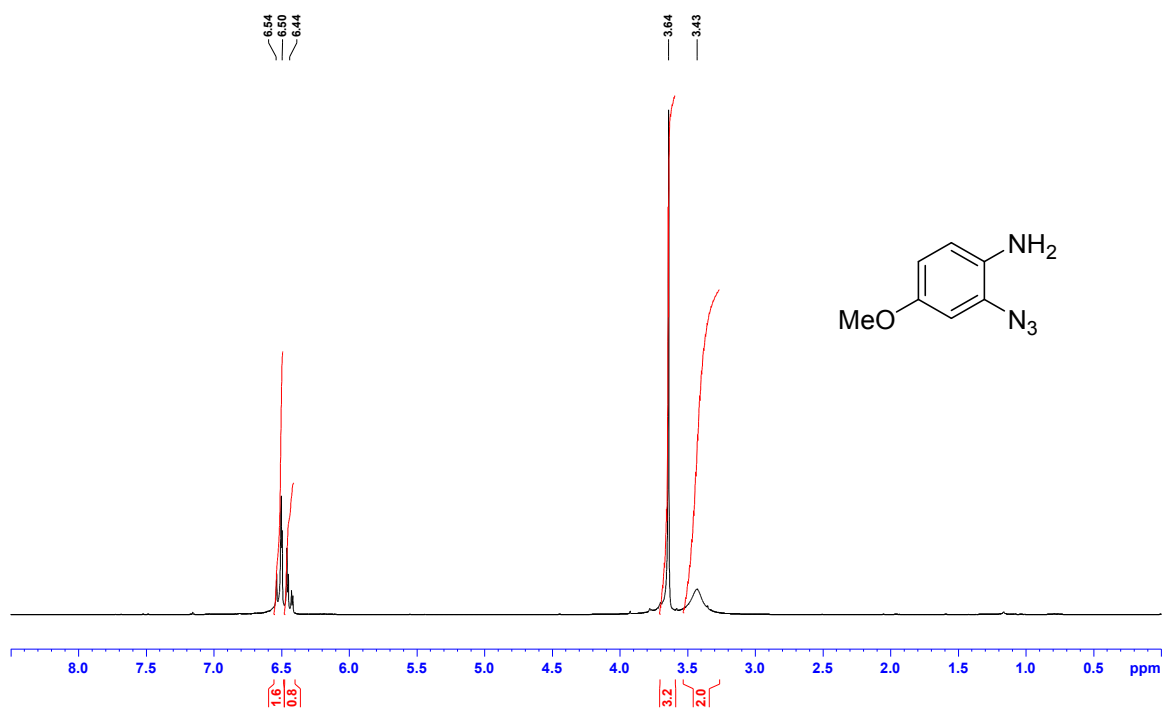
17 - ¹H-NMR (250 MHz, CDCl₃)



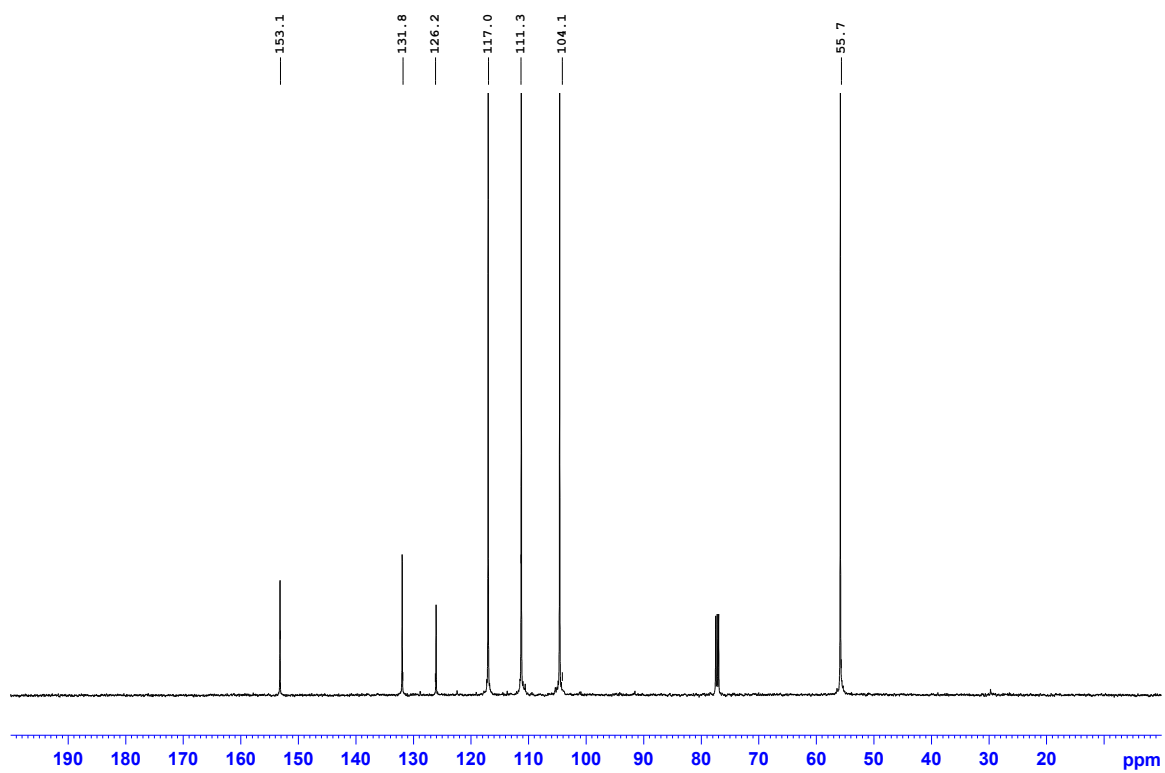
17 - ¹³C-NMR (63 MHz, CDCl₃)



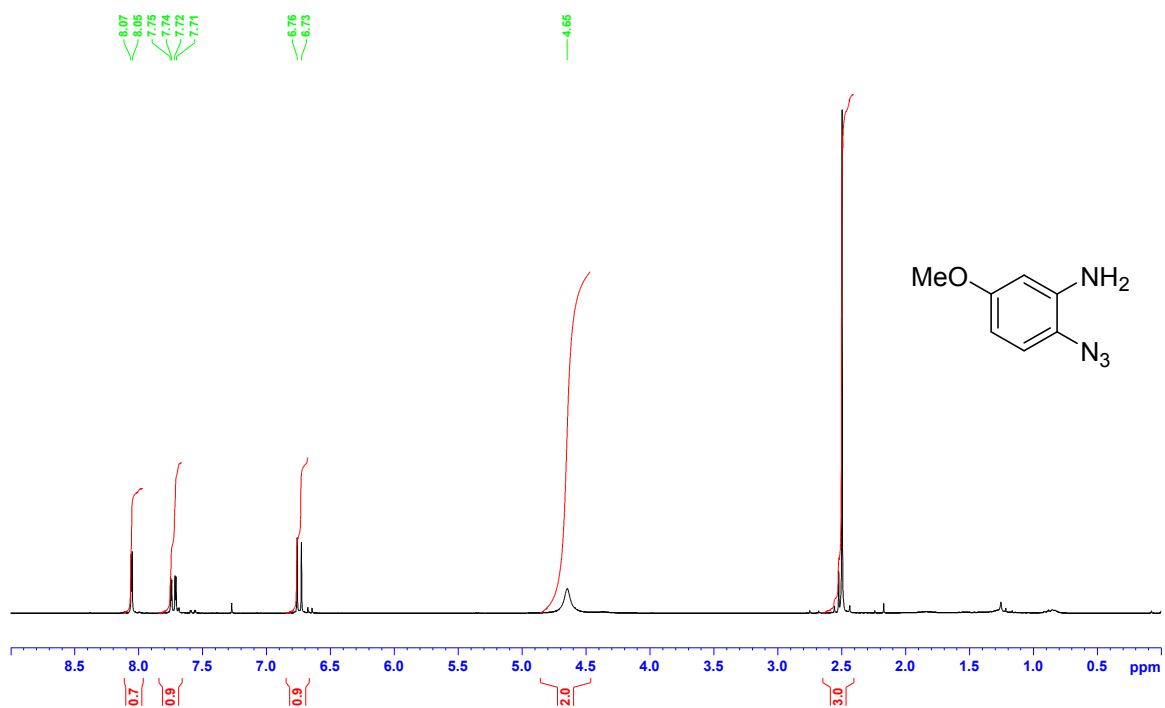
18 - ¹H-NMR (250 MHz, CDCl₃)



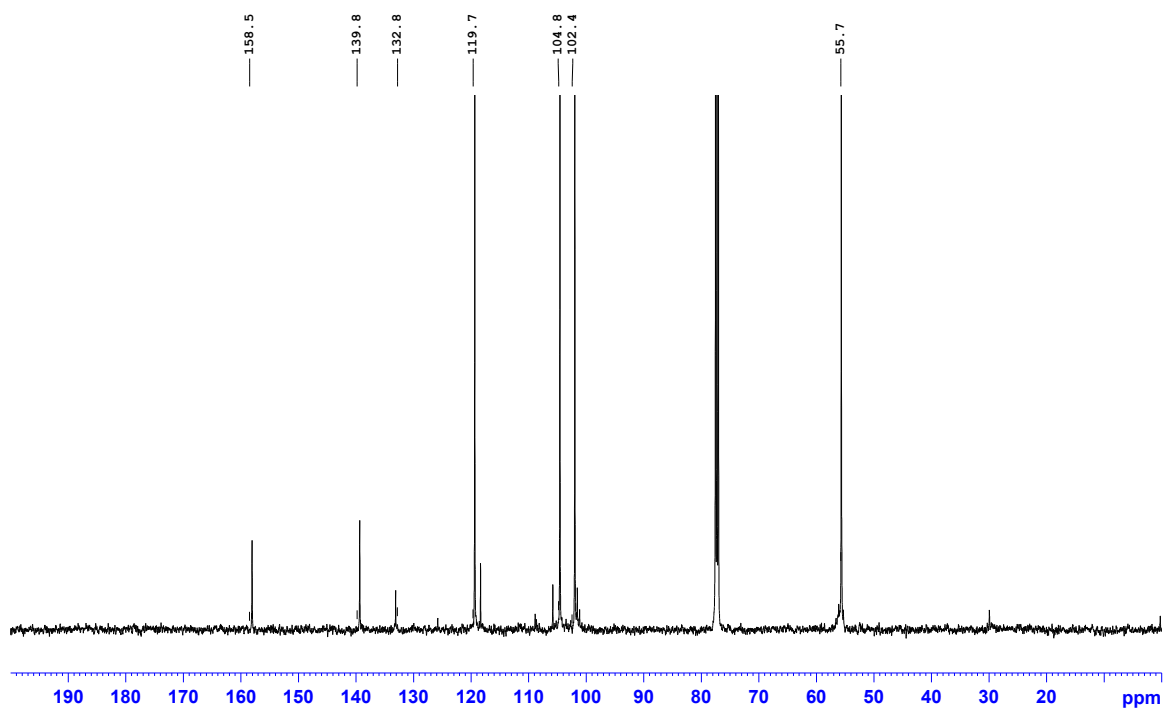
18 - ¹³C-NMR (125 MHz, CDCl₃)



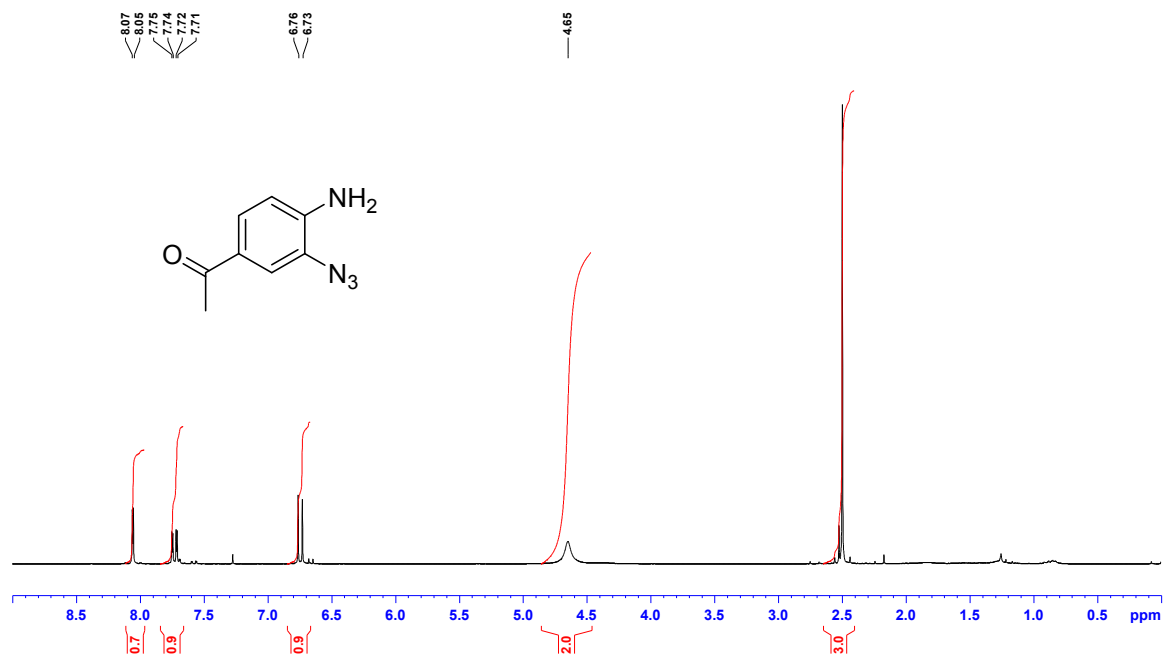
19 - ¹H-NMR (250 MHz, CDCl₃)



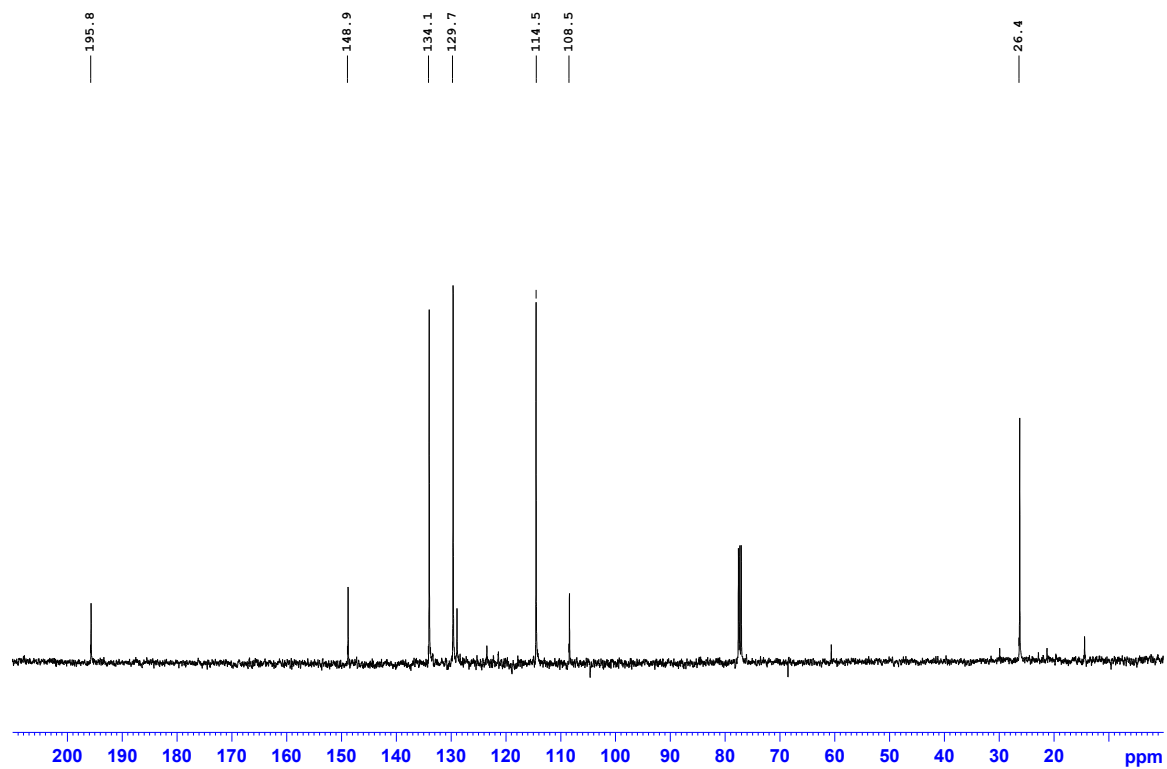
19 - ¹³C-NMR (125 MHz, CDCl₃)



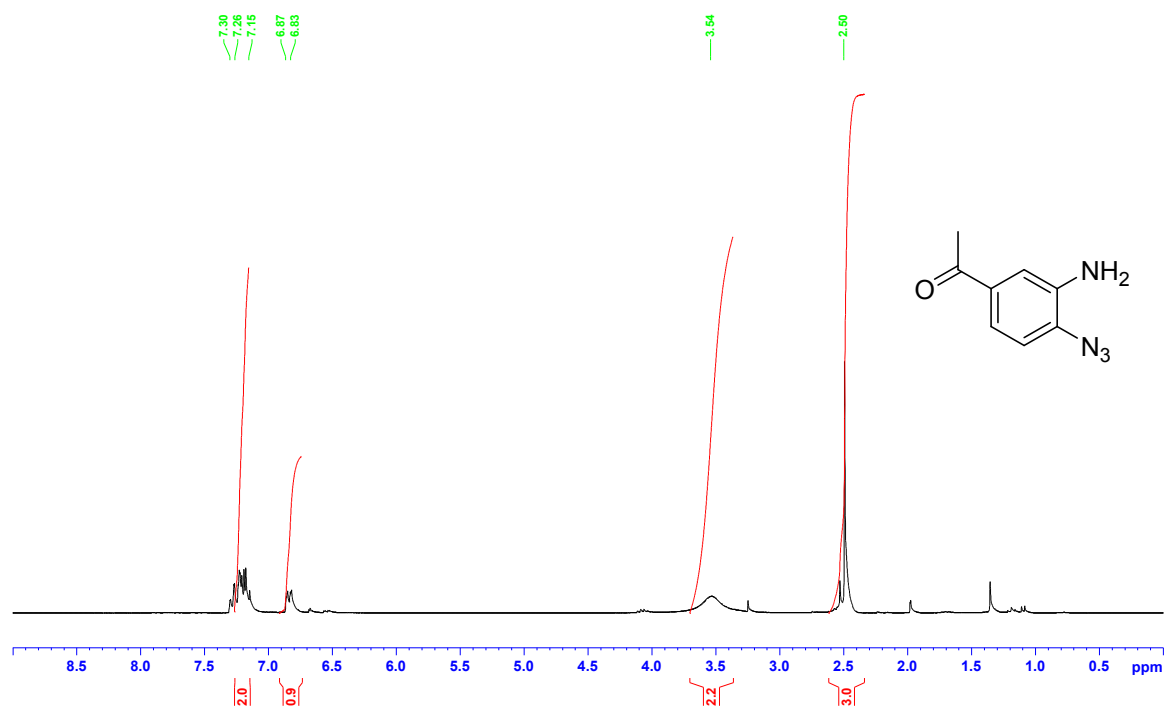
20 - $^1\text{H-NMR}$ (250 MHz, CDCl_3)



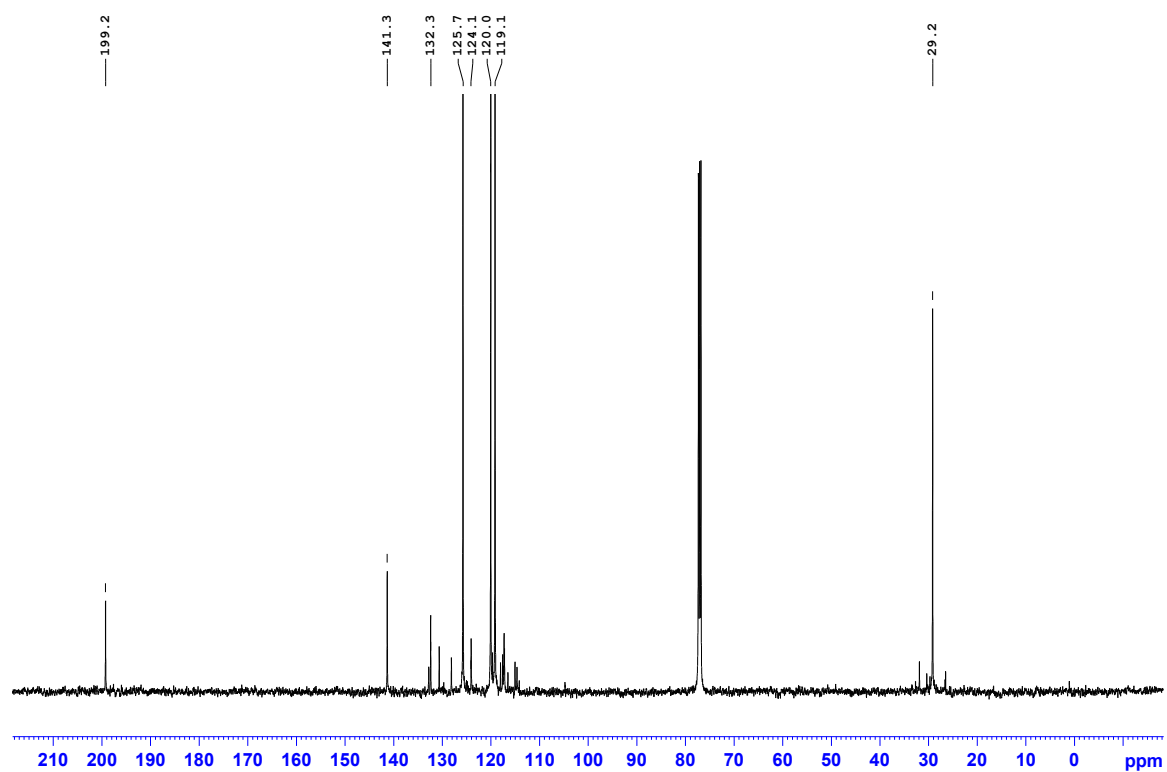
20 - $^{13}\text{C-NMR}$ (63 MHz, CDCl_3)



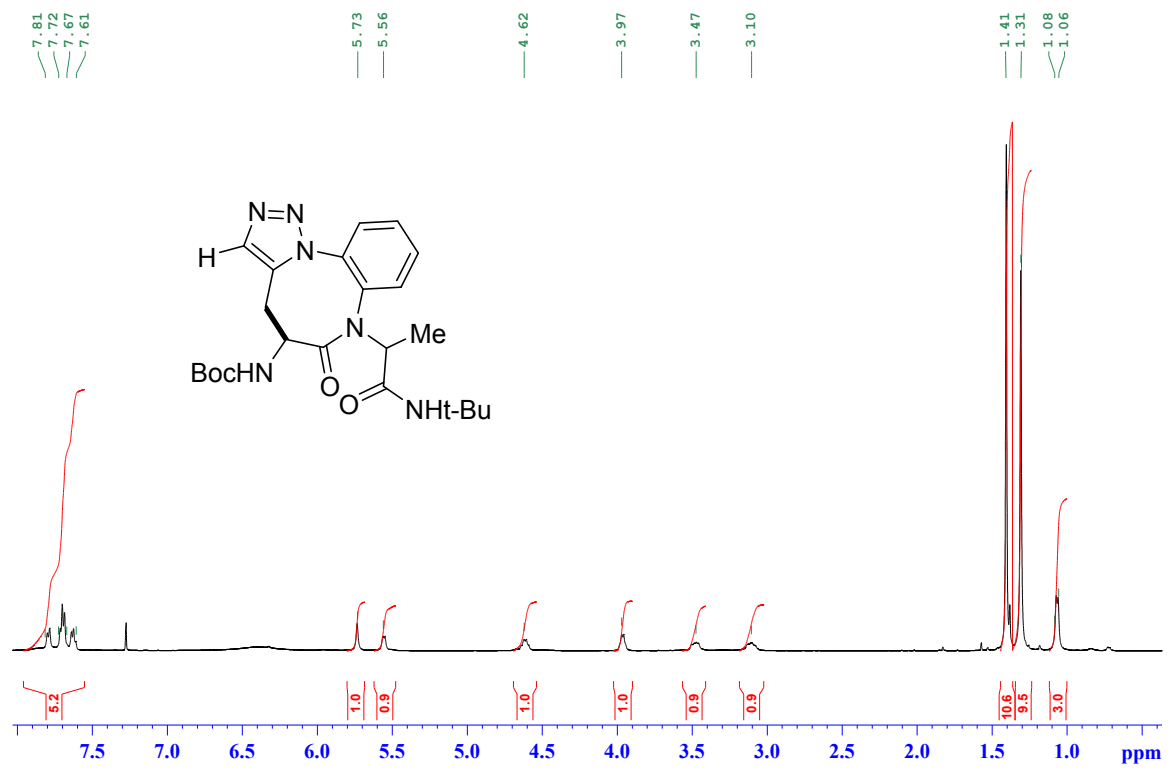
21 - ¹H-NMR (250 MHz, CDCl₃)



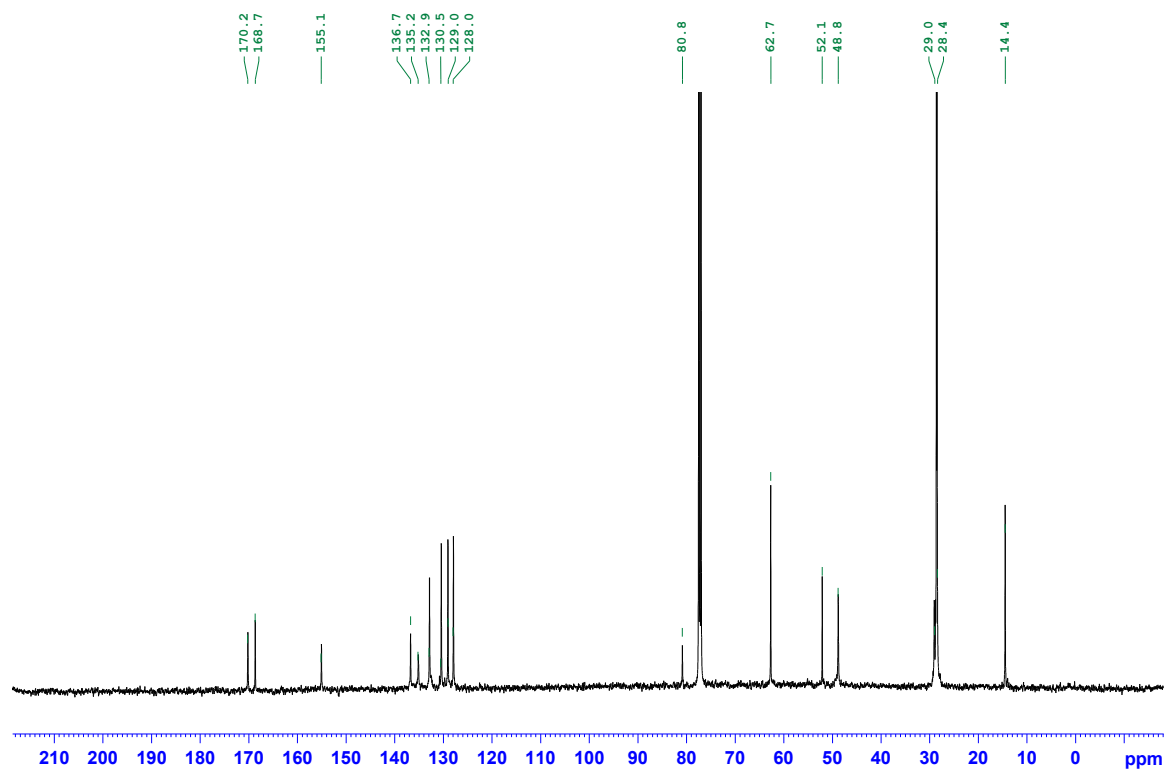
21 - ¹³C-NMR (125 MHz, CDCl₃)



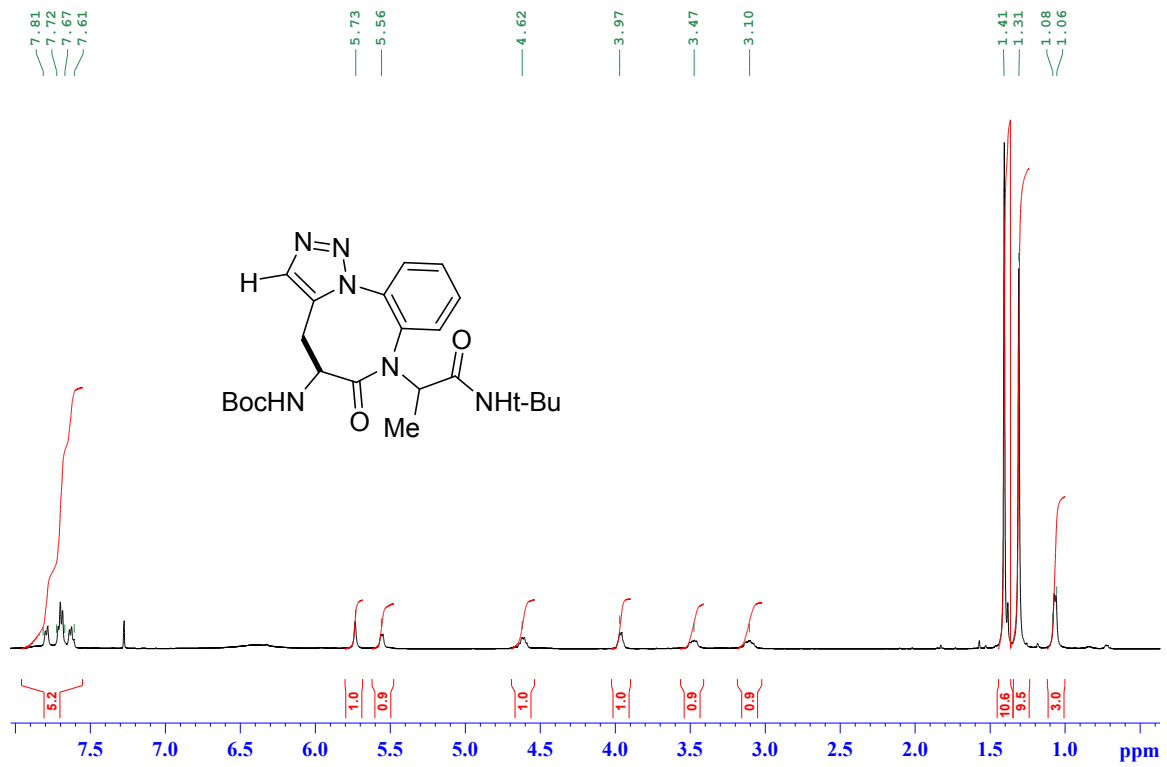
22a - ¹H-NMR (250 MHz, CDCl₃)



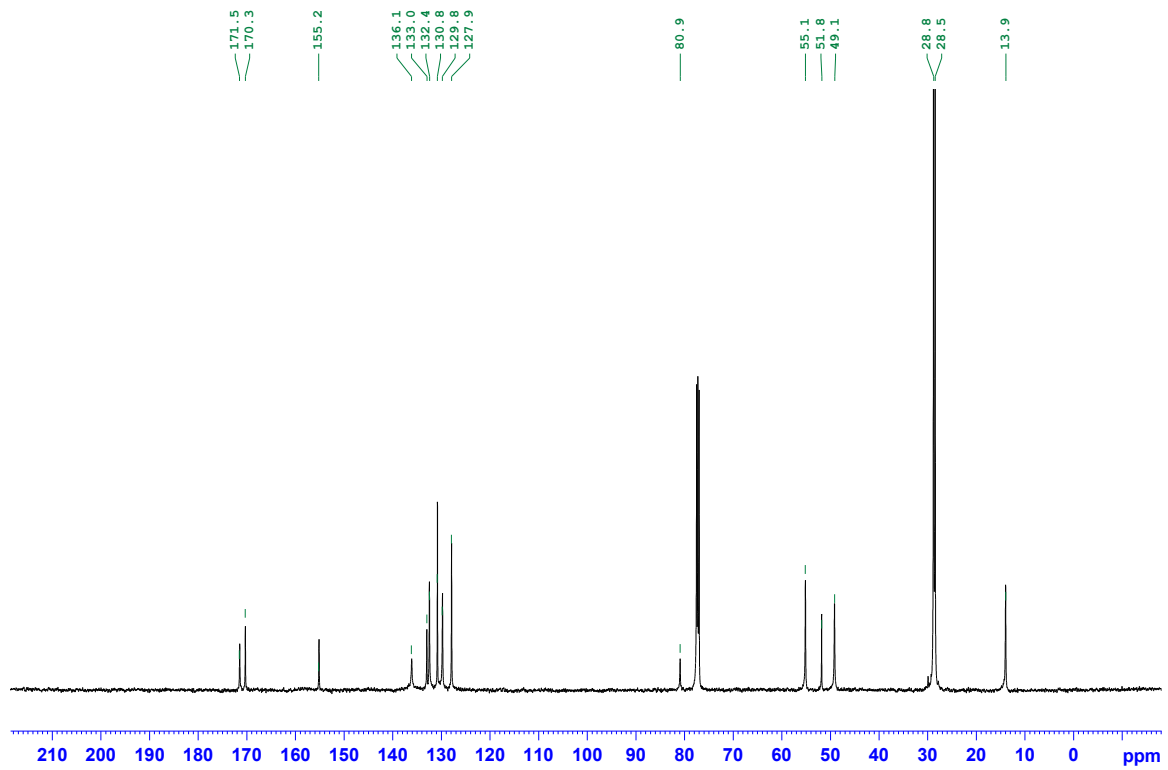
22a - ¹³C-NMR (125 MHz, CDCl₃)



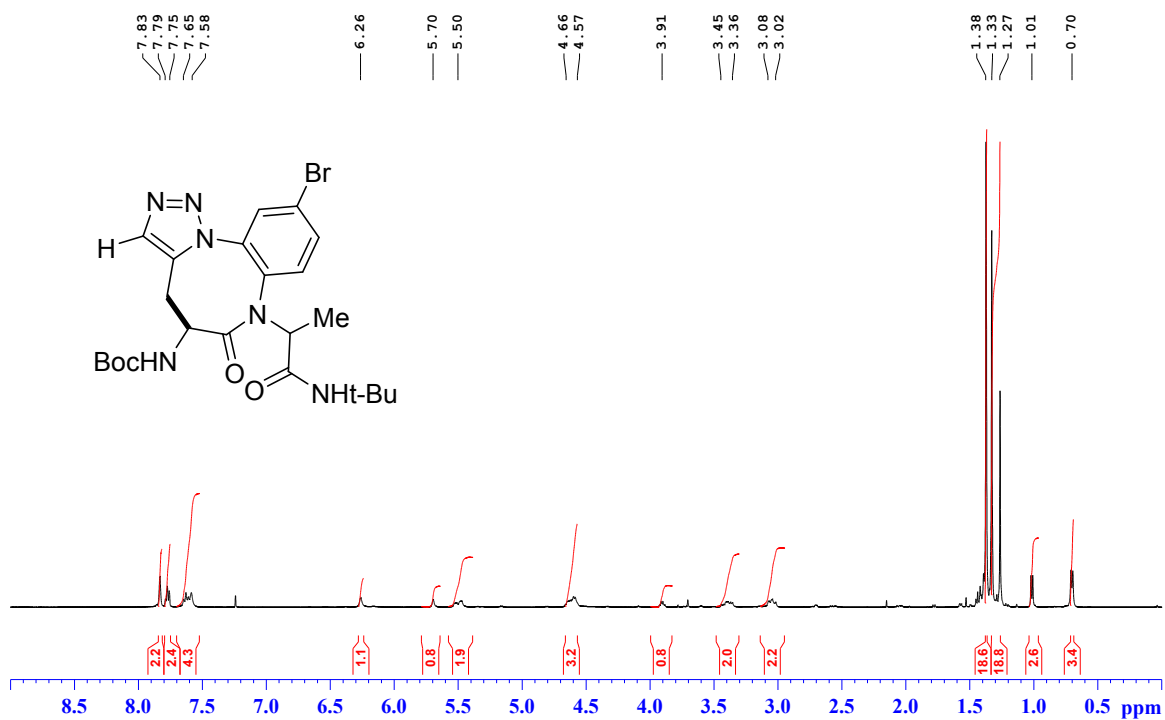
22b - ¹H-NMR (250 MHz, CDCl₃)



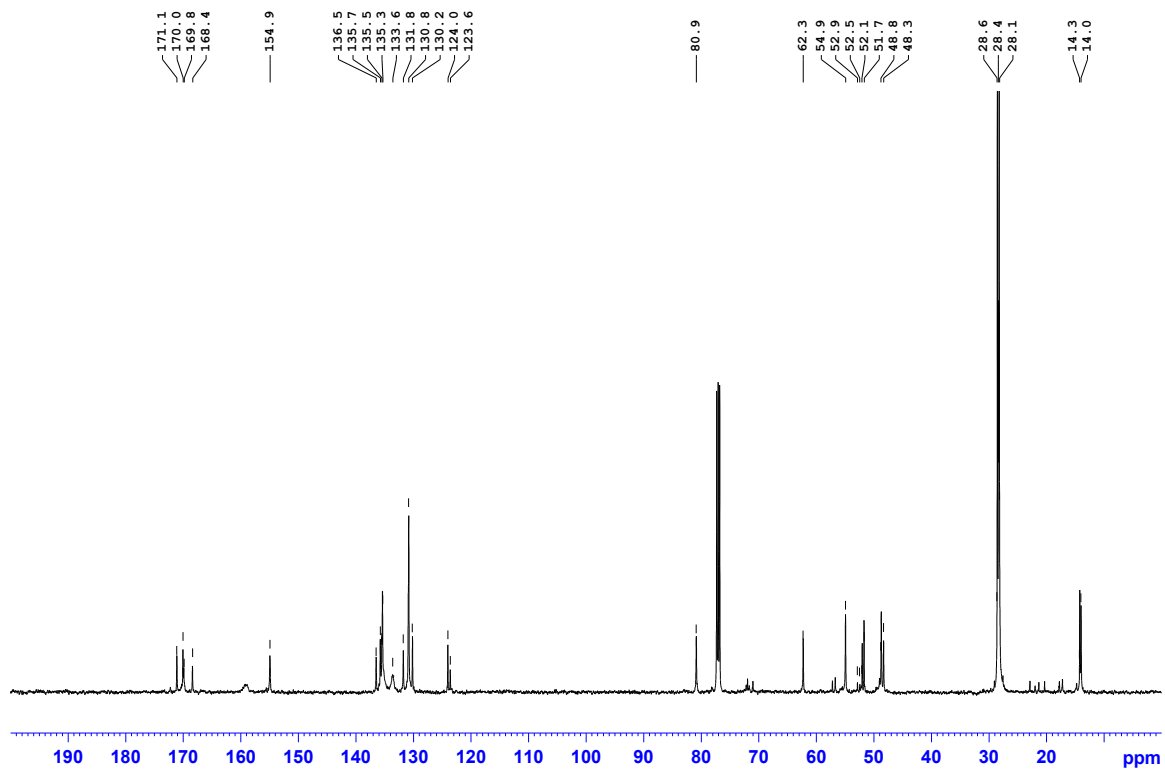
22b - ¹³C-NMR (125 MHz, CDCl₃)



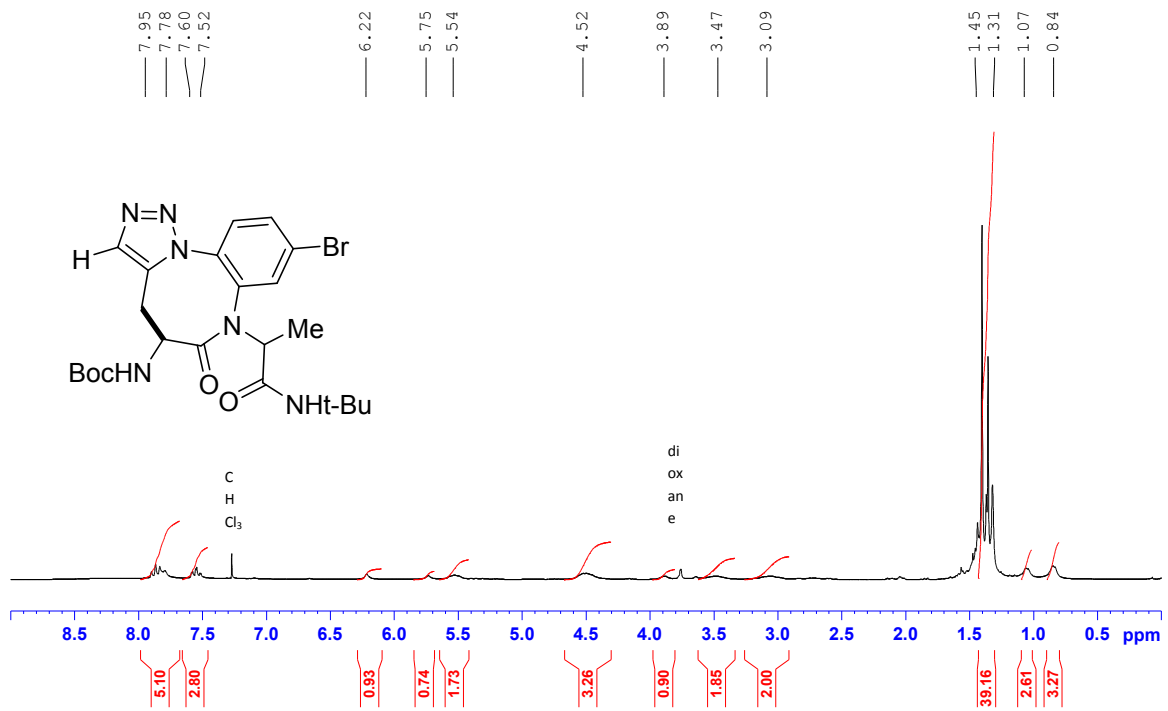
23 - ¹H-NMR (250 MHz, CDCl₃)



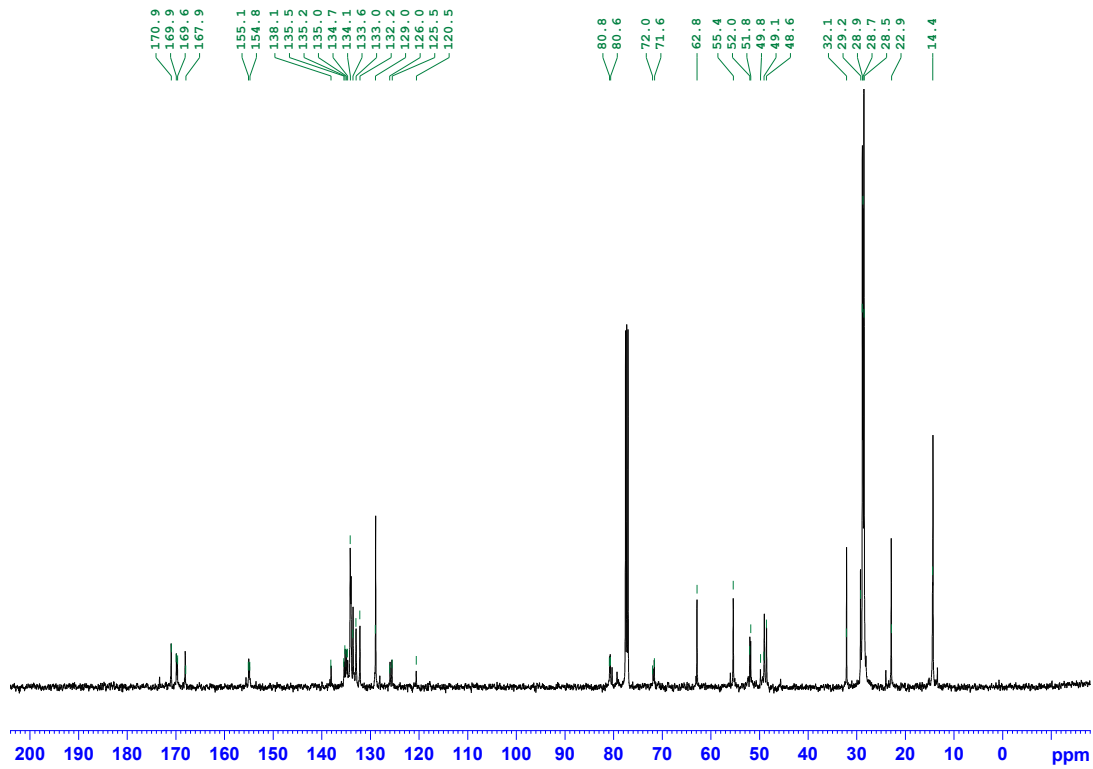
23 - ¹³CNMR (125 MHz, CDCl₃)



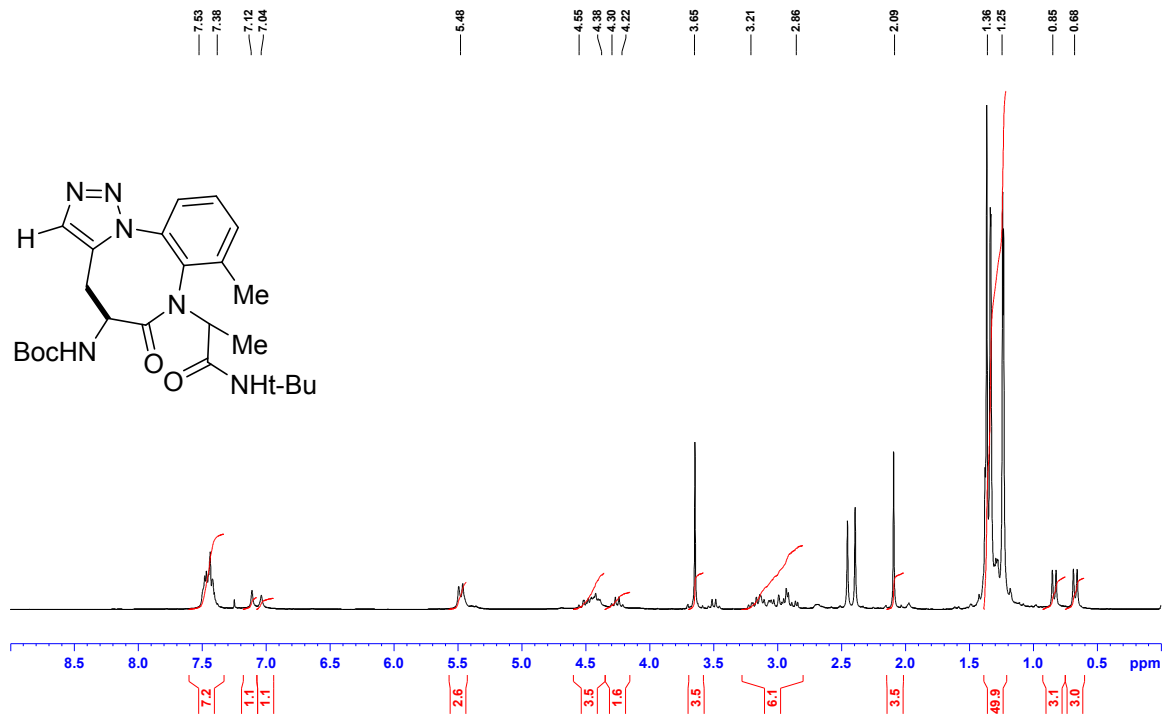
24 - ¹H-NMR (250 MHz, CDCl₃)



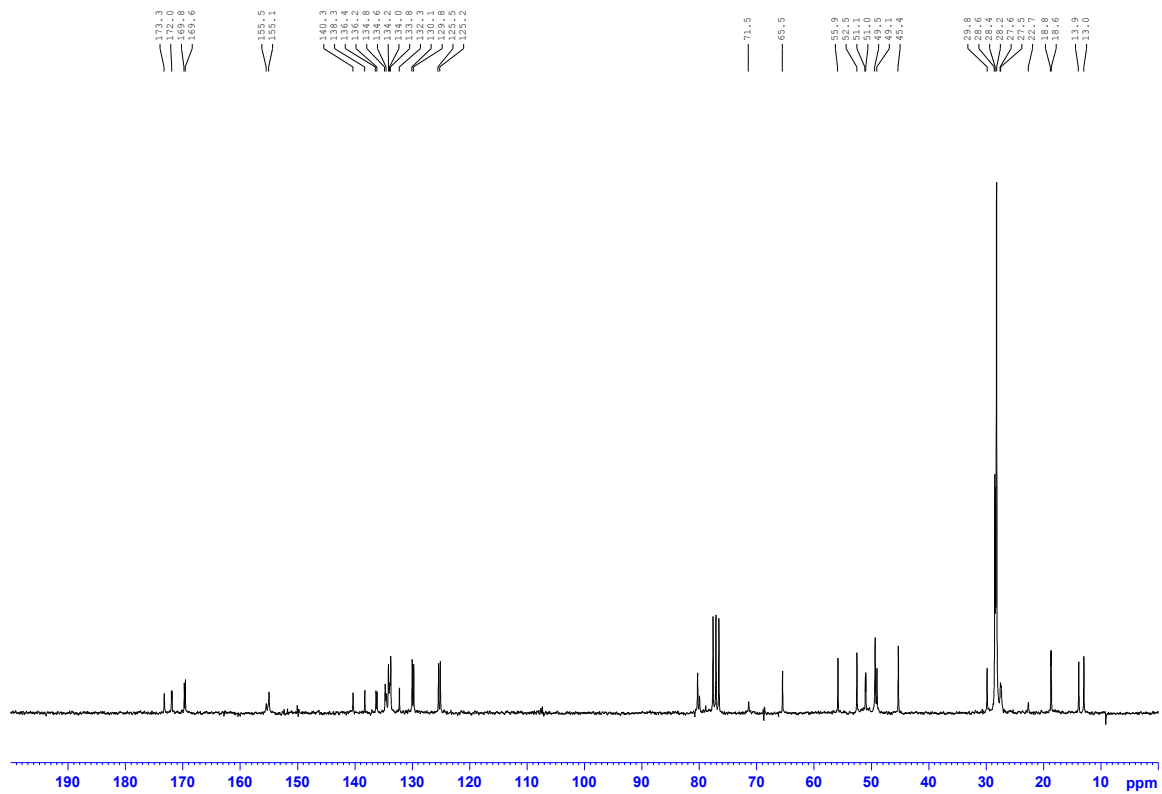
24 - ¹³C-NMR (125 MHz, CDCl₃)



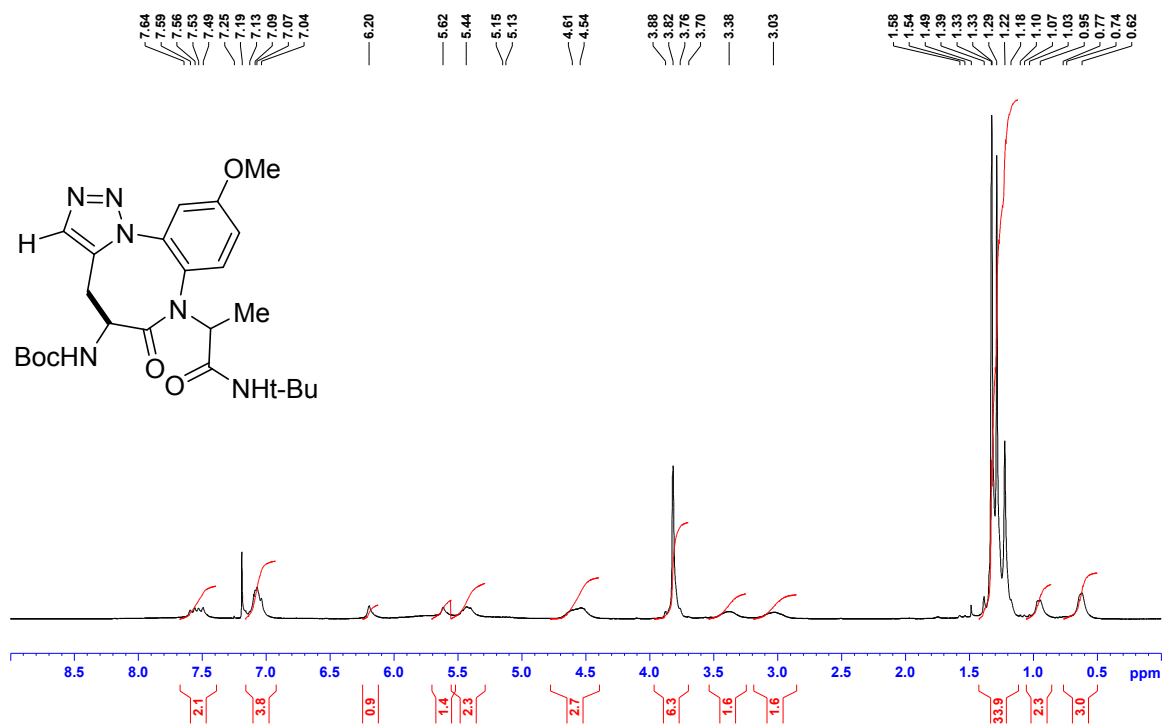
25 - ¹H-NMR (250 MHz, CDCl₃)



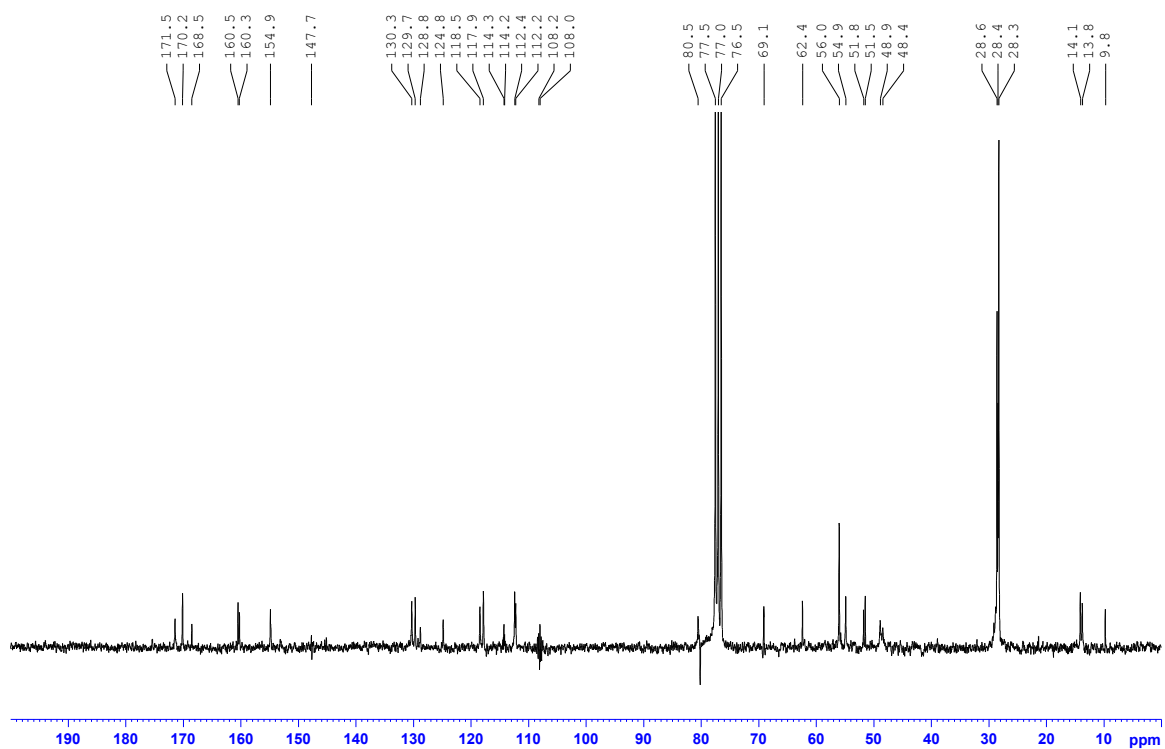
25 - ¹³C-NMR (63 MHz, CDCl₃)



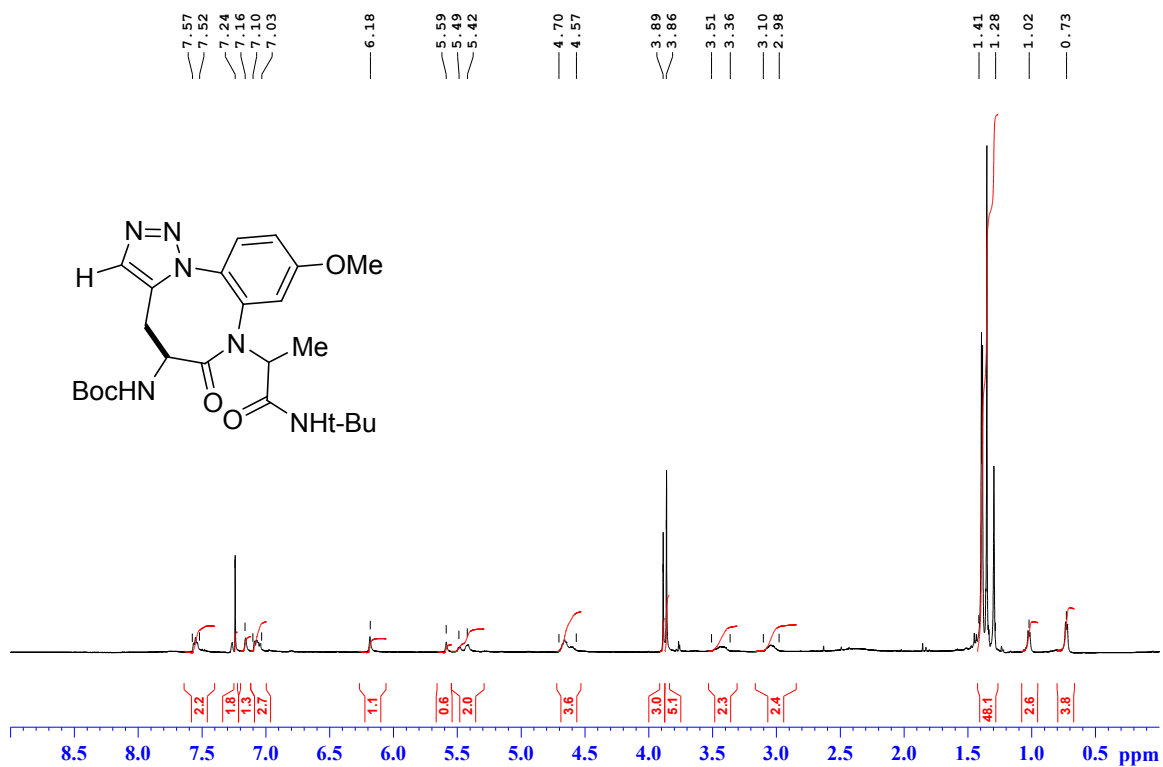
26 - ¹H-NMR (250 MHz, CDCl₃)



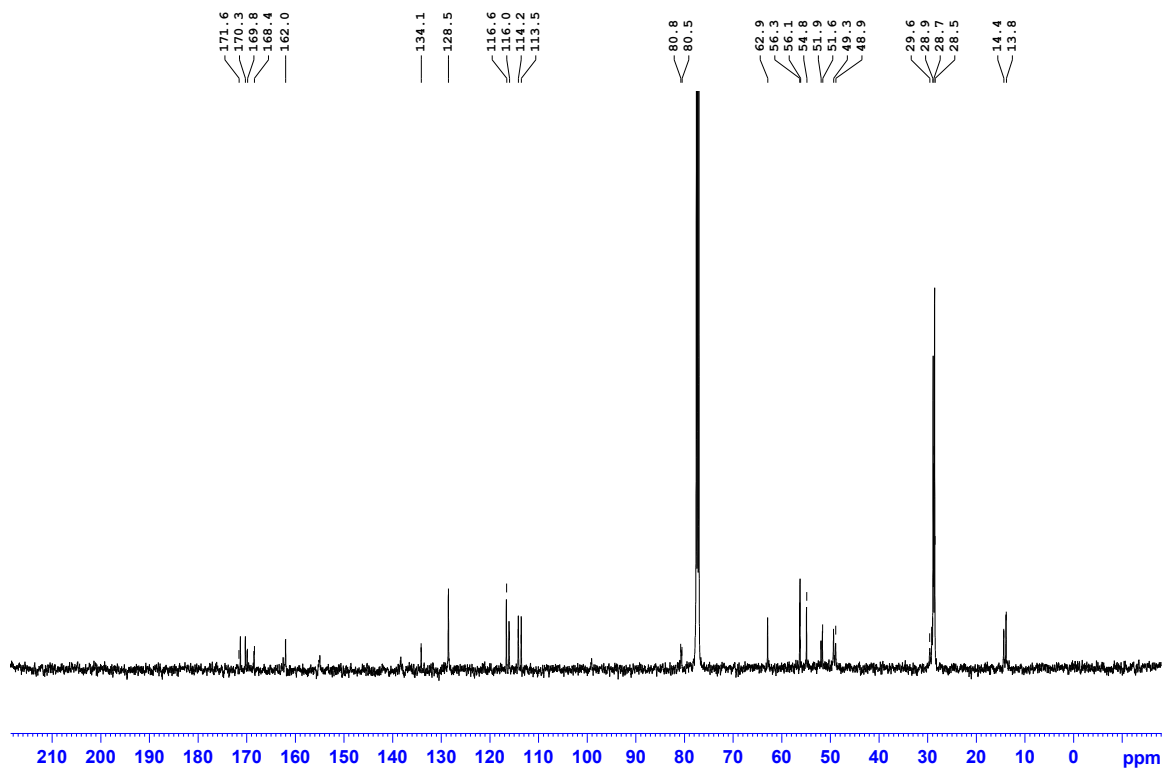
26 - ¹³C-NMR (63 MHz, CDCl₃)



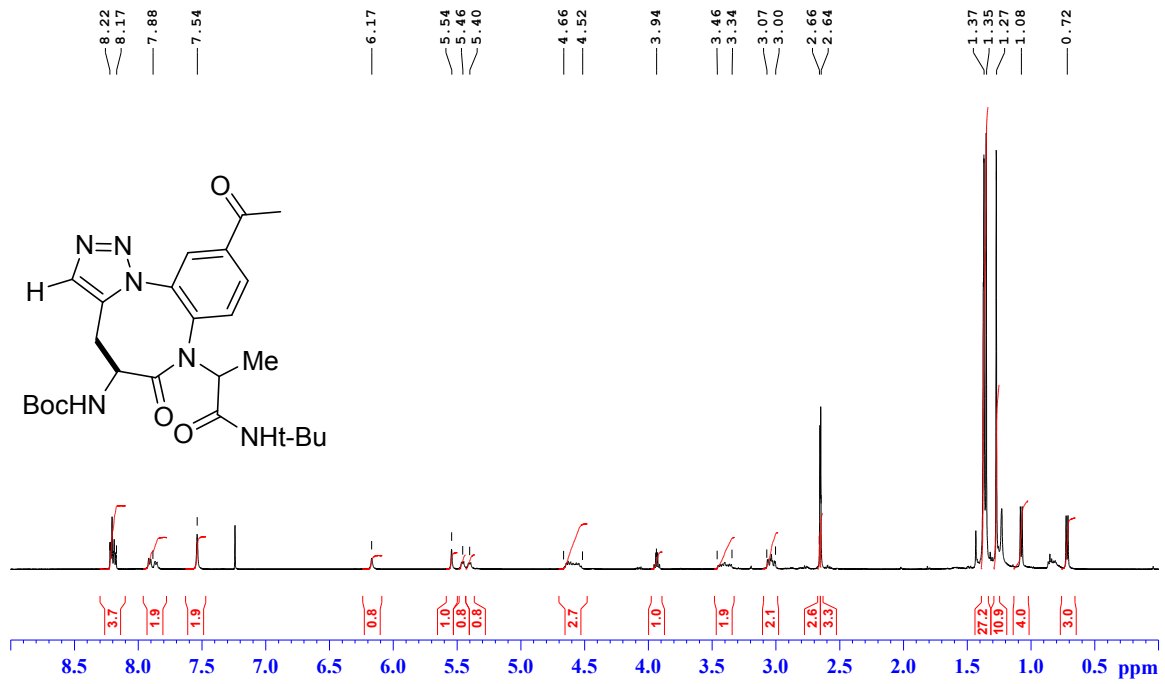
27 - ¹H-NMR (250 MHz, CDCl₃)



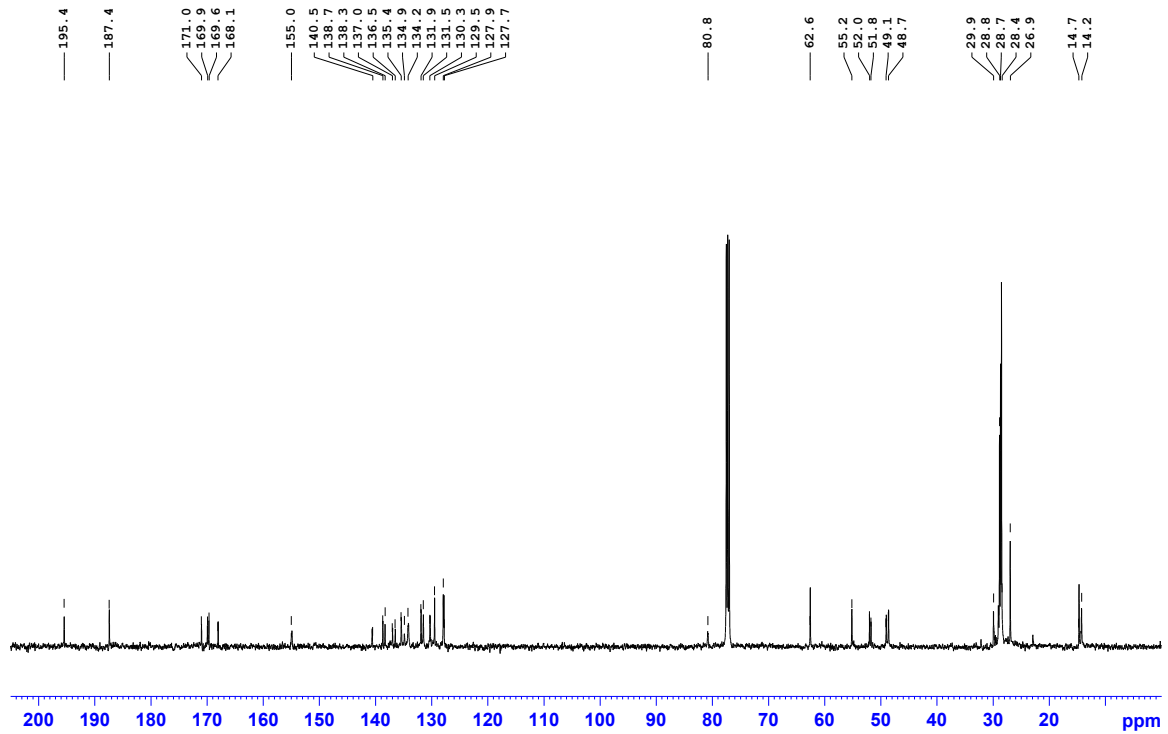
27 - ¹³C-NMR (125 MHz, CDCl₃)



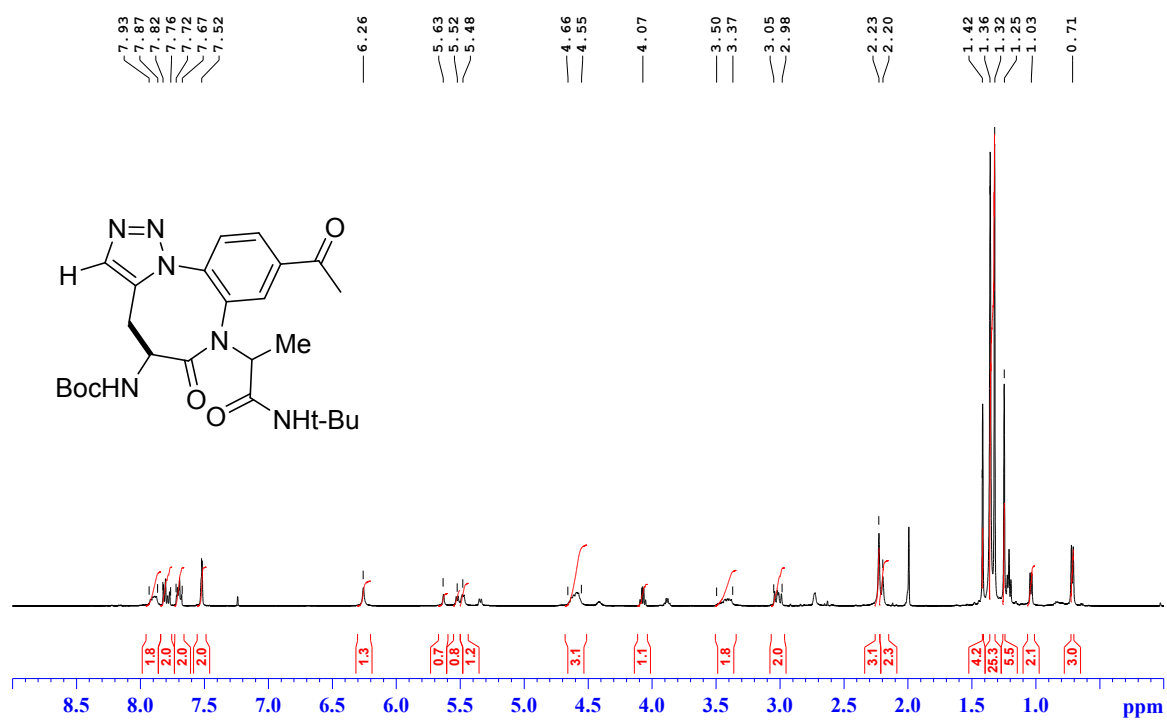
28 - ¹H-NMR (250 MHz, CDCl₃)



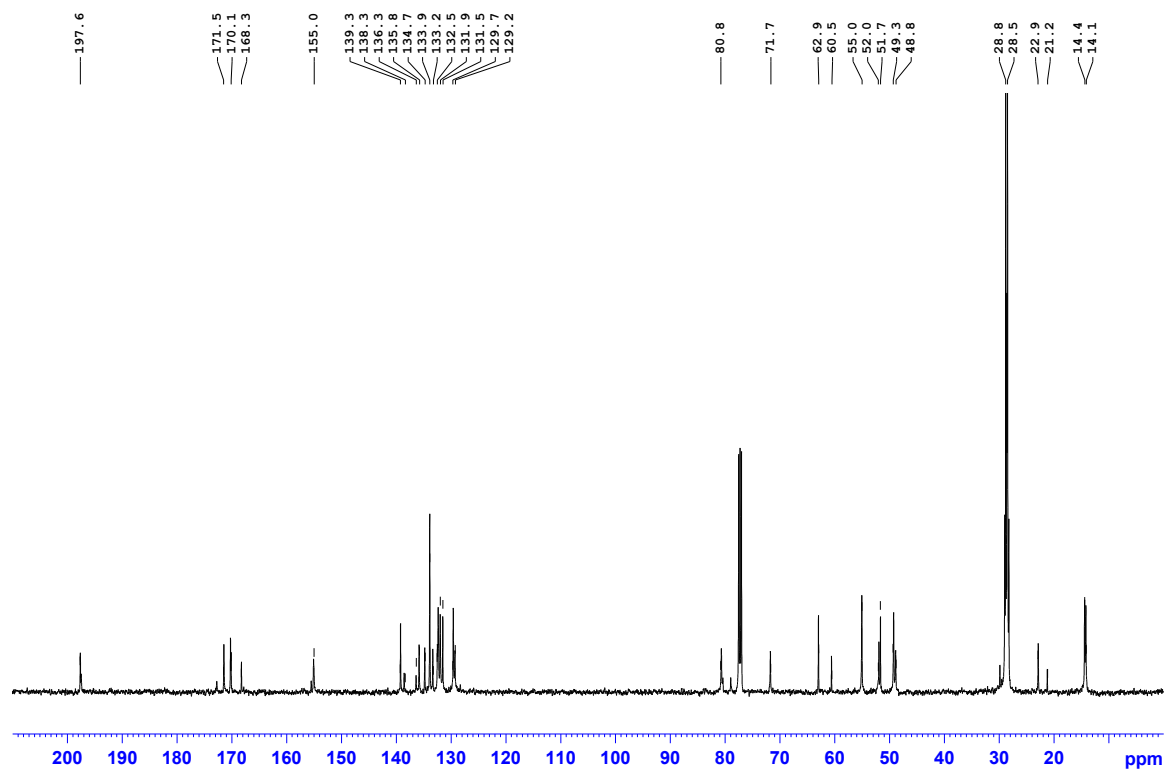
28 - ¹³C-NMR (125 MHz, CDCl₃)



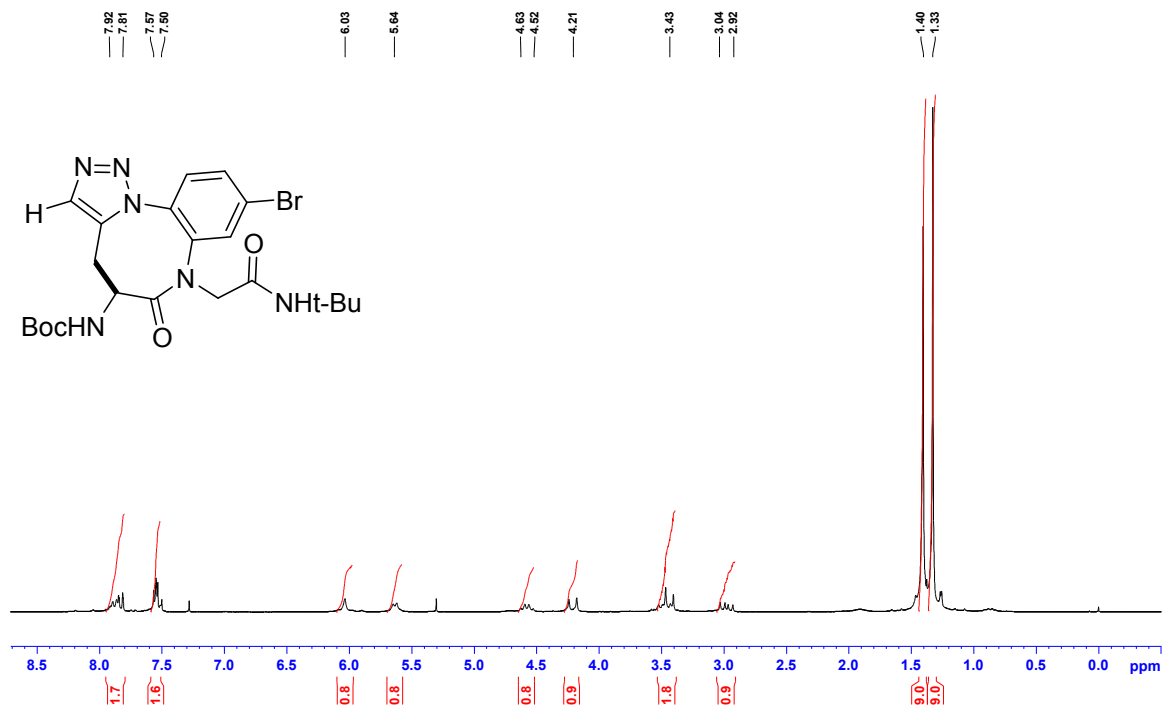
29 -¹H-NMR (250 MHz, CDCl₃)



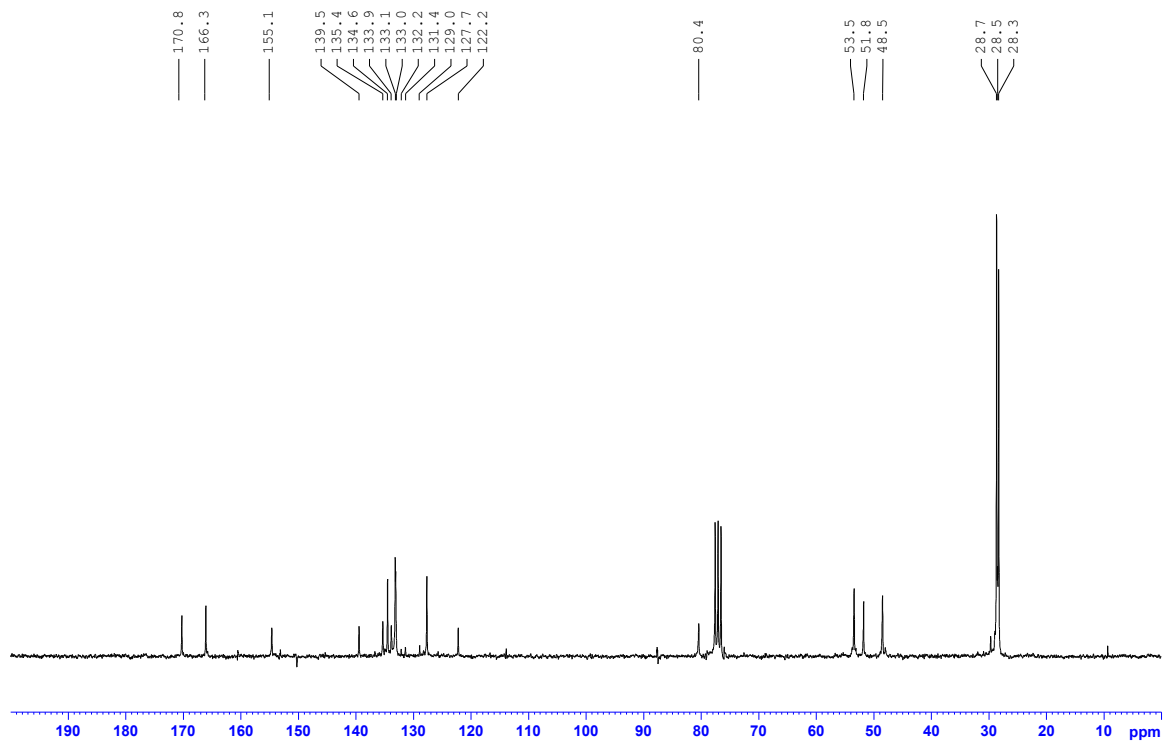
29 -¹³C-NMR (125 MHz, CDCl₃)



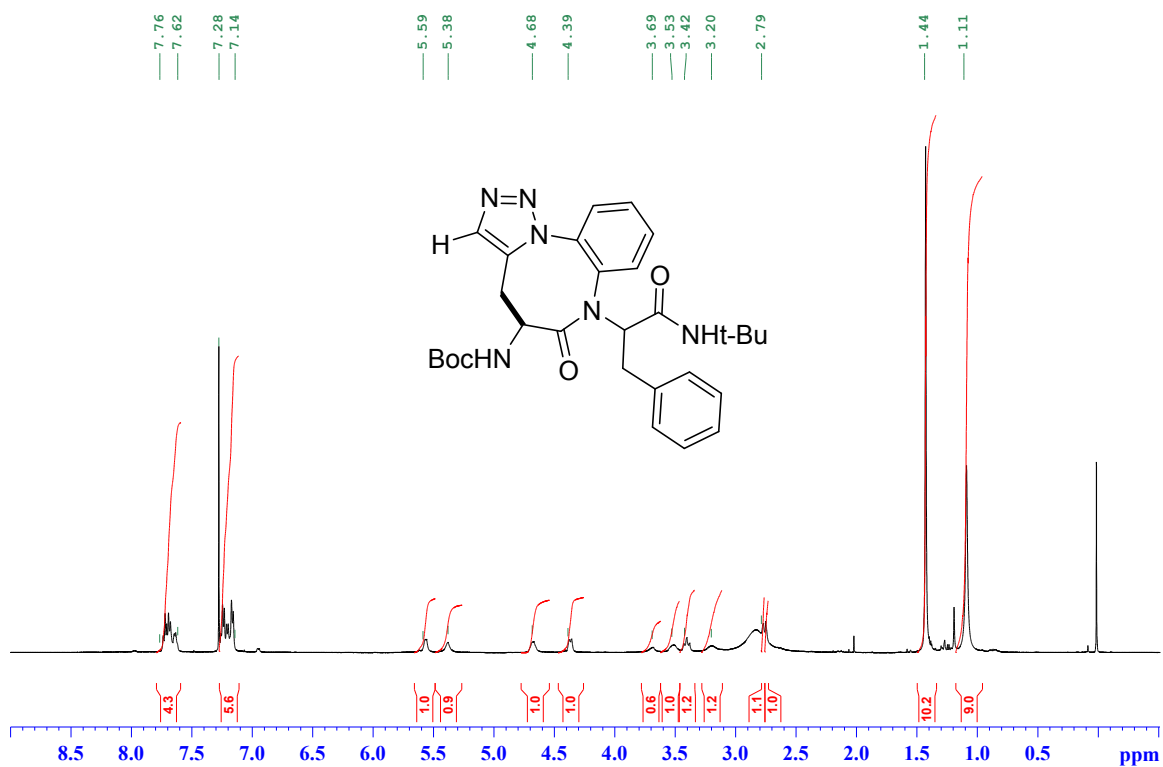
30 - ¹H-NMR (250 MHz, CDCl₃)



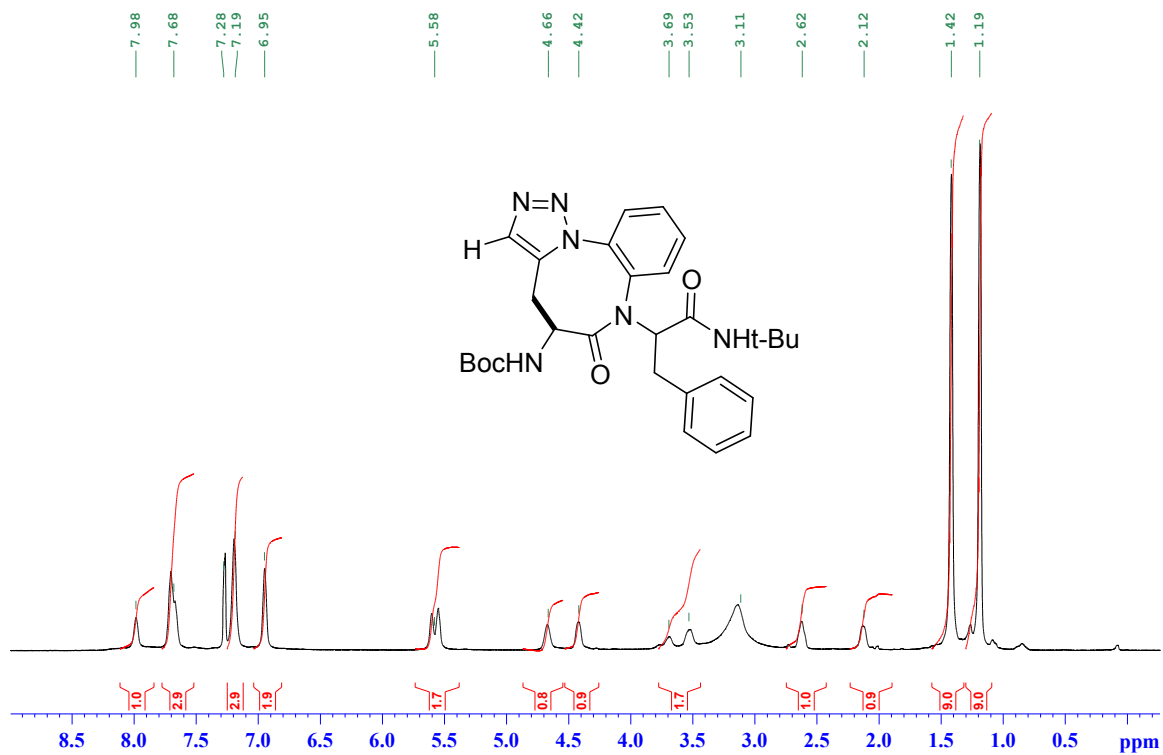
30 - ¹³C-NMR (125 MHz, CDCl₃)



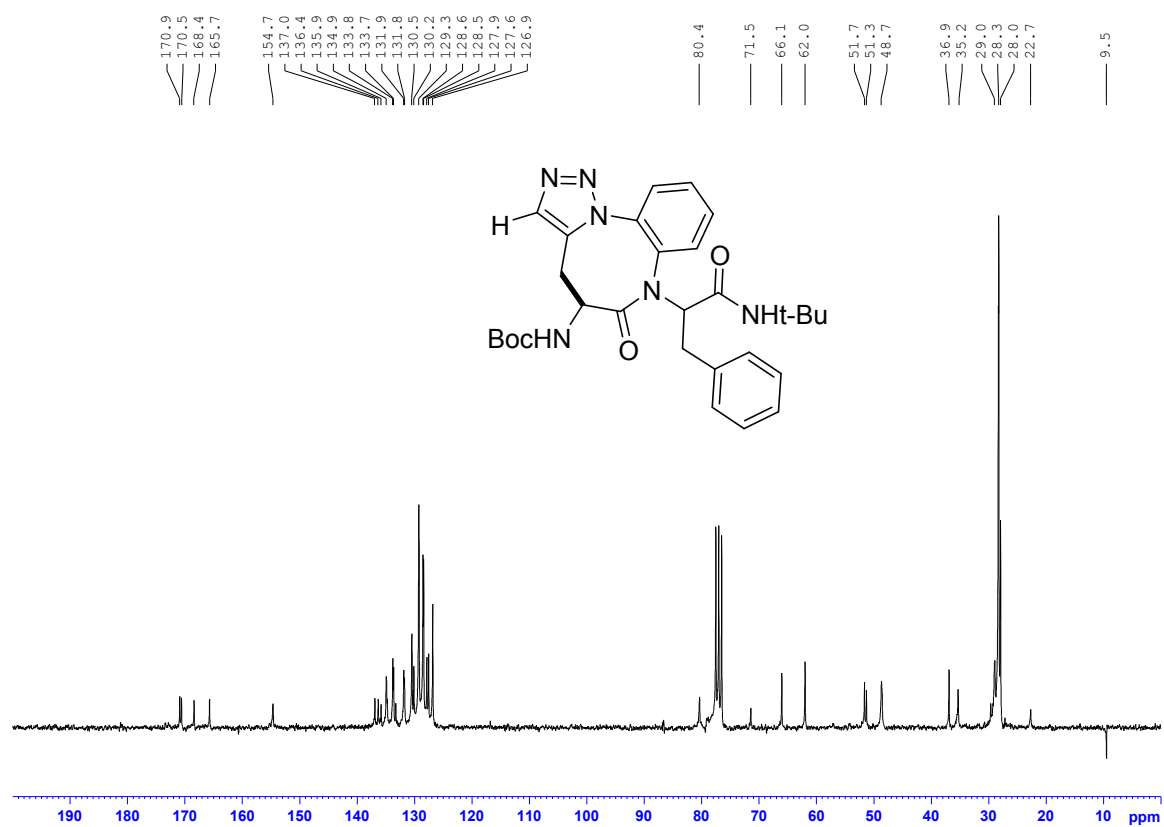
31a - ¹H-NMR (250 MHz, CDCl₃): First diastereomer



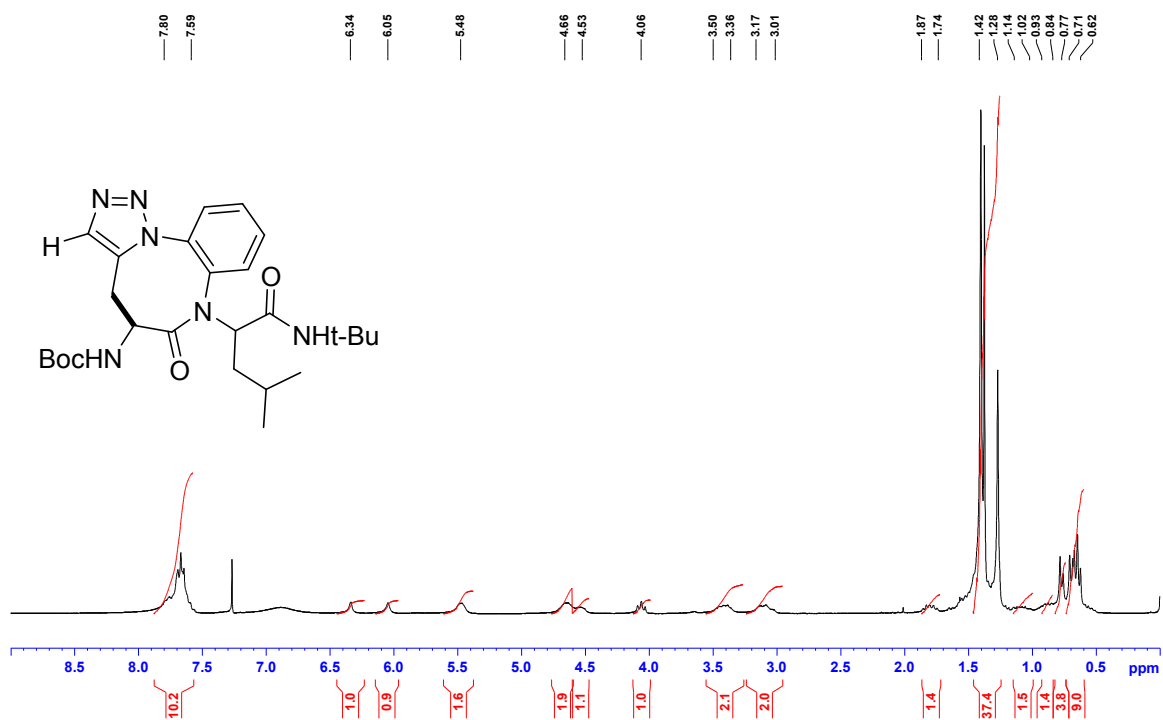
31b - ¹H-NMR (250 MHz, CDCl₃): Second diastereomer



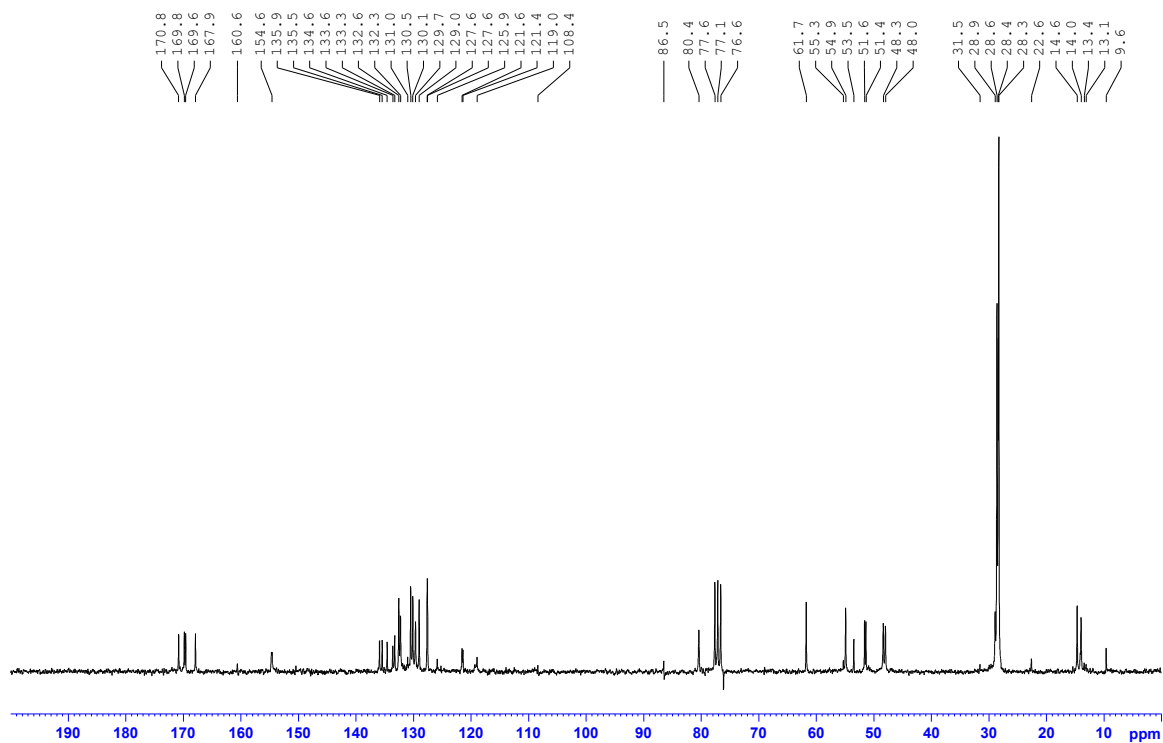
31 – ¹³C-NMR (125 MHz, CDCl₃): Diastereomeric mix



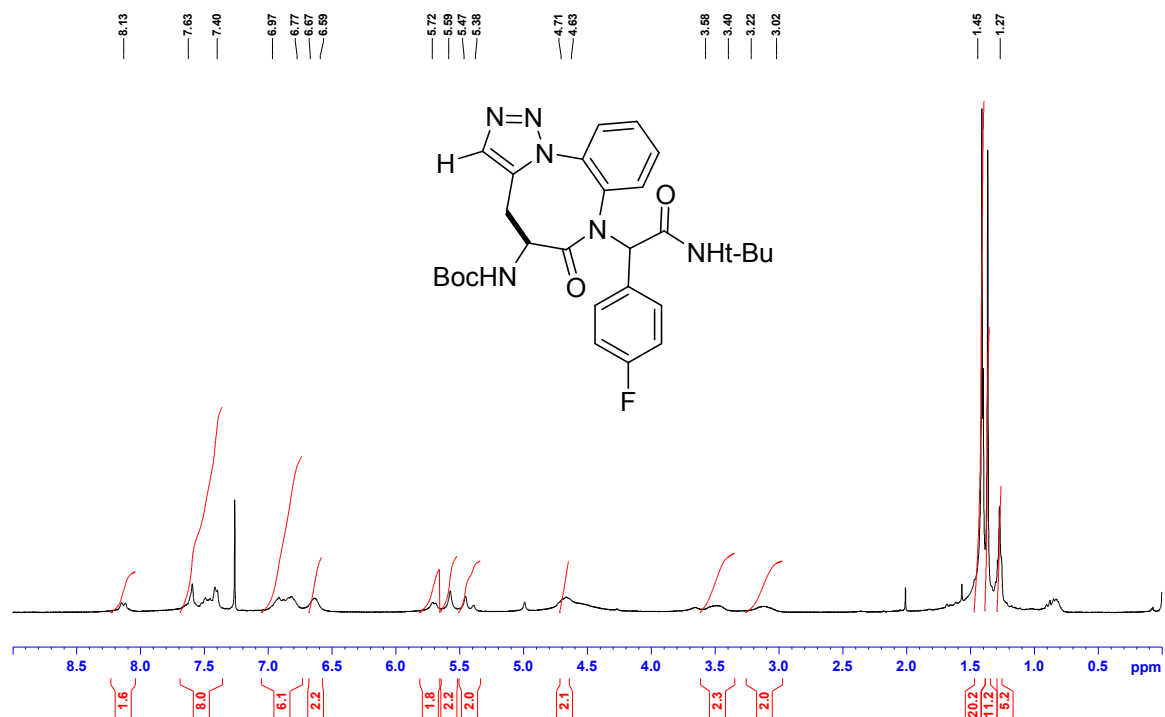
32 - ¹H-NMR (250 MHz, CDCl₃)



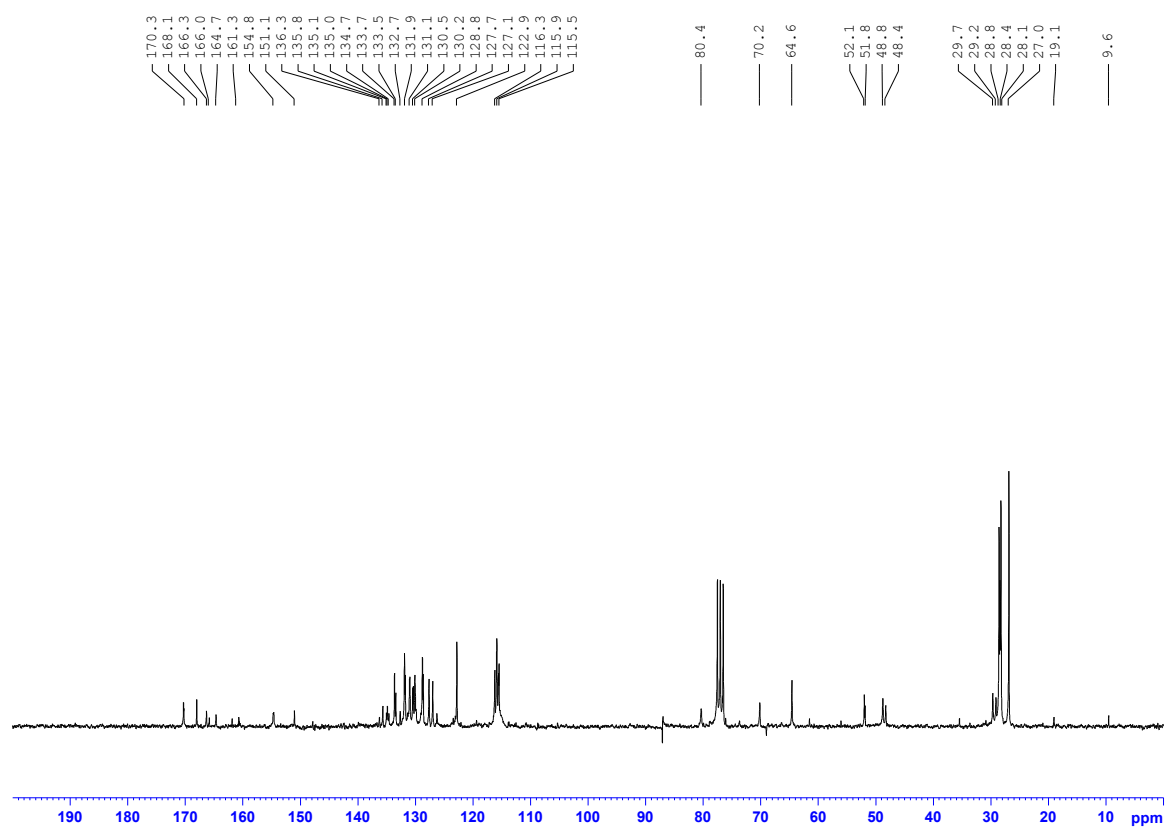
32 - ¹³C-NMR (125 MHz, CDCl₃)



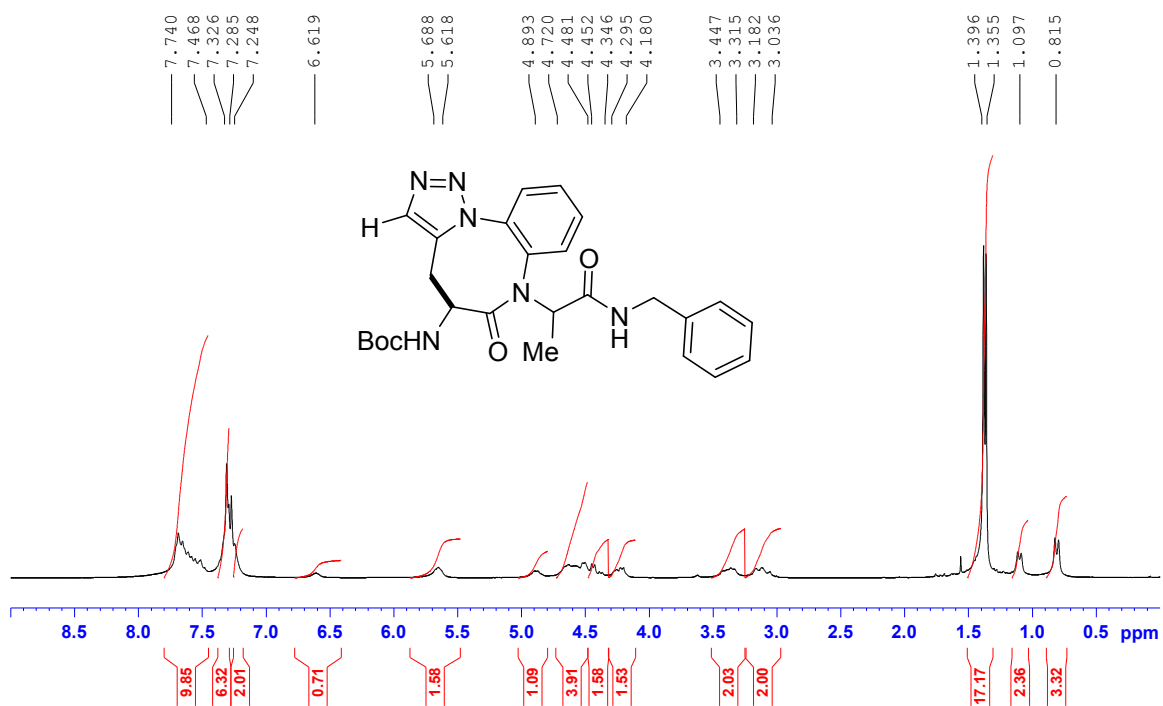
33 – ¹H-NMR (250 MHz, CDCl₃)



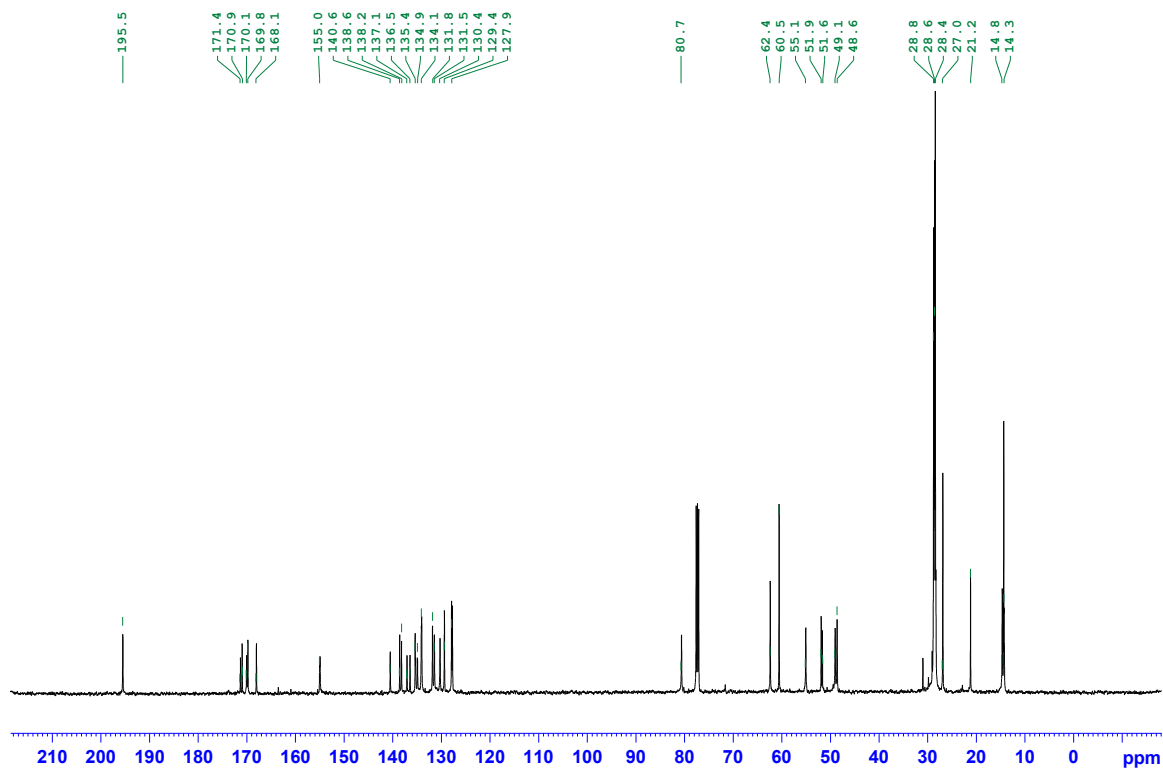
33 – ¹³C-NMR (125 MHz, CDCl₃)



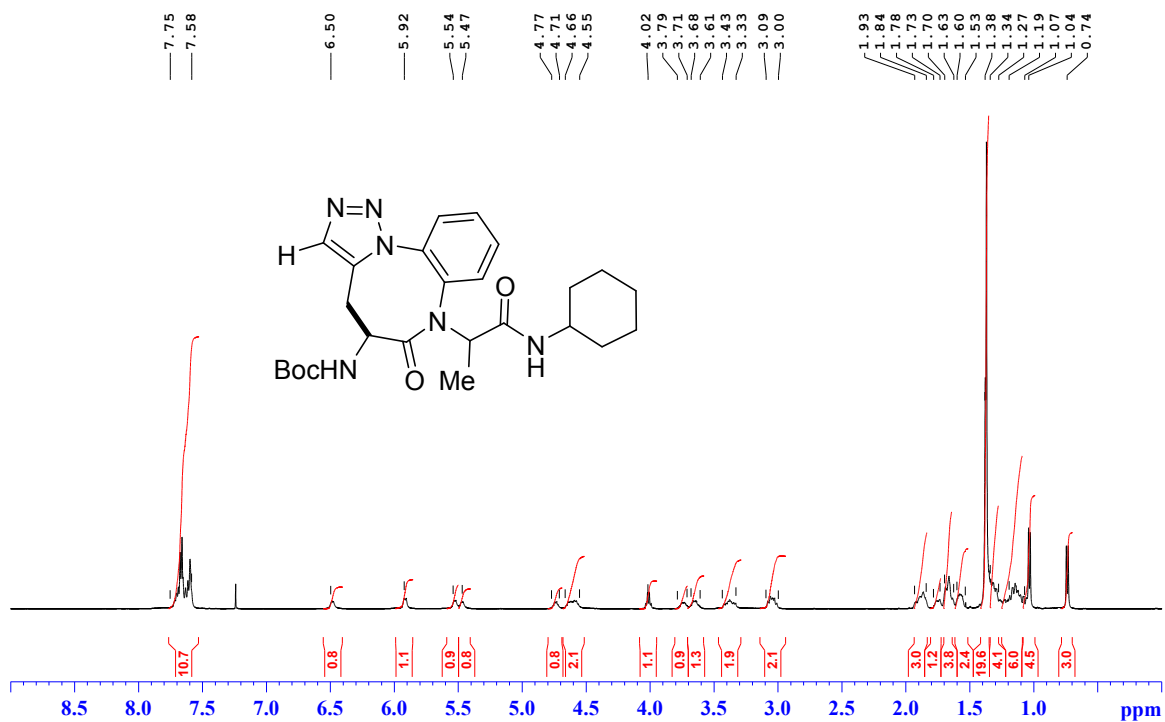
34 - ¹H-NMR (250 MHz, CDCl₃)



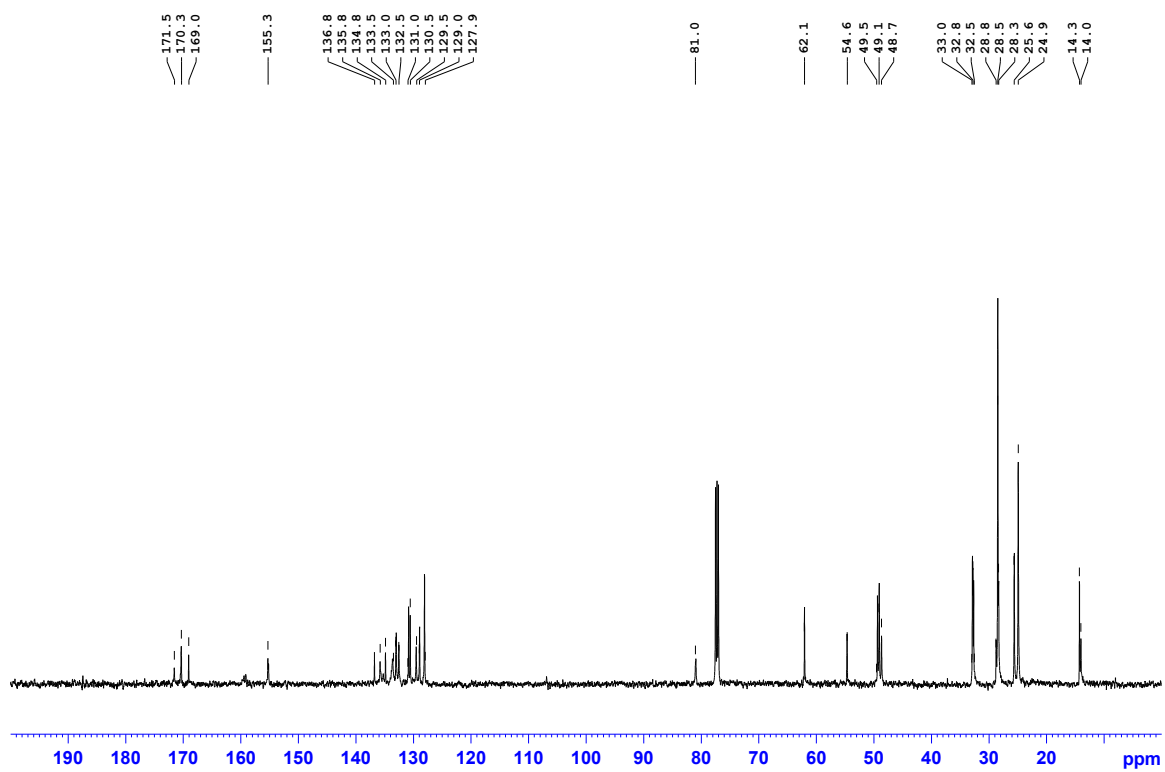
34 - ¹³C-NMR (125 MHz, CDCl₃)



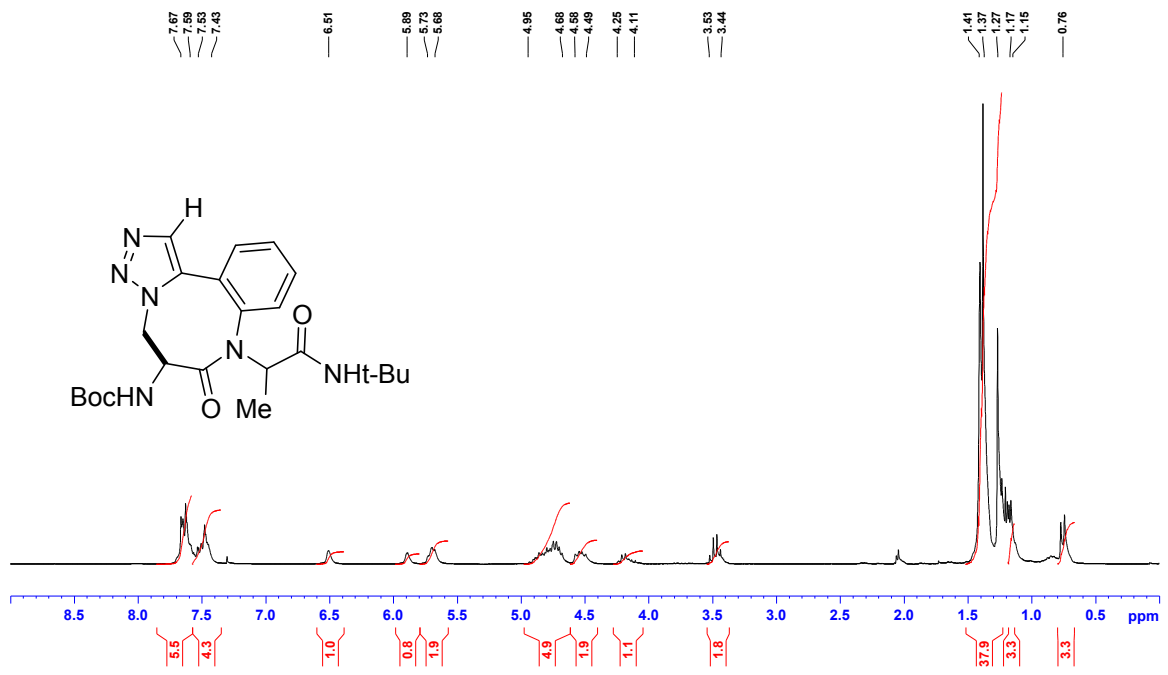
35 – ¹H-NMR (250 MHz, CDCl₃)



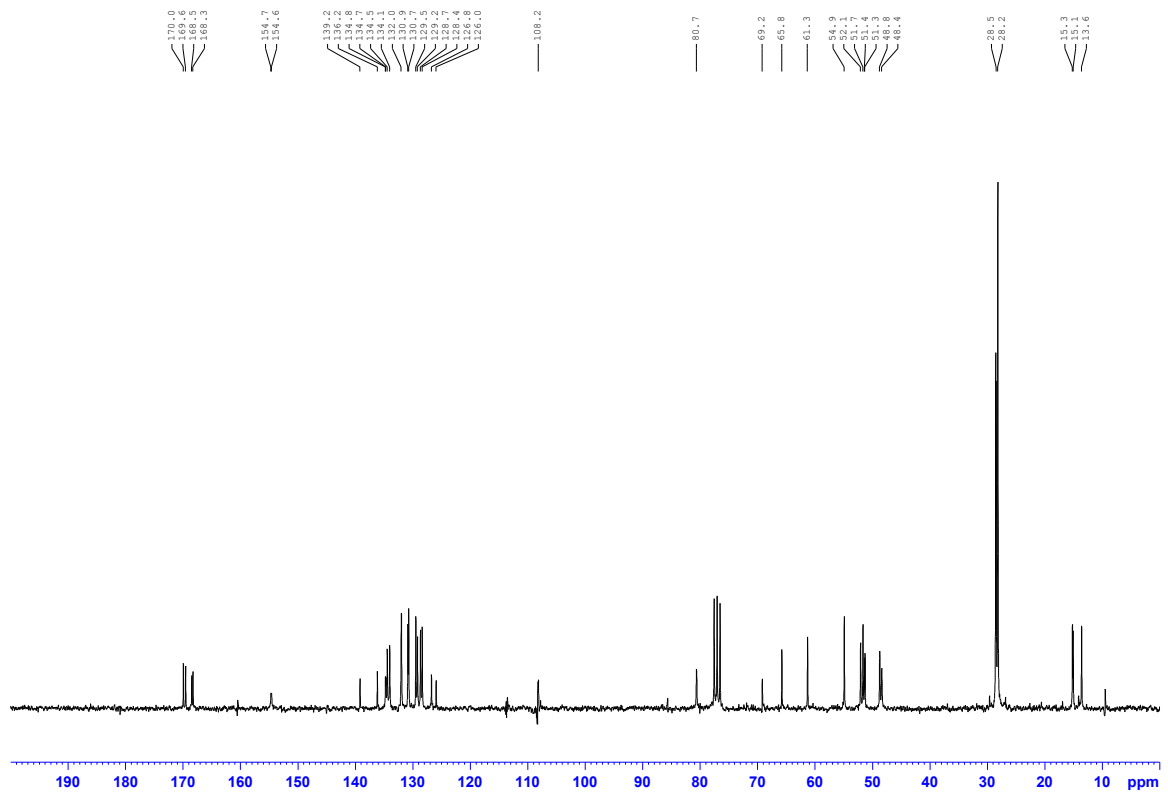
35 - ¹³C-NMR (125 MHz, CDCl₃)



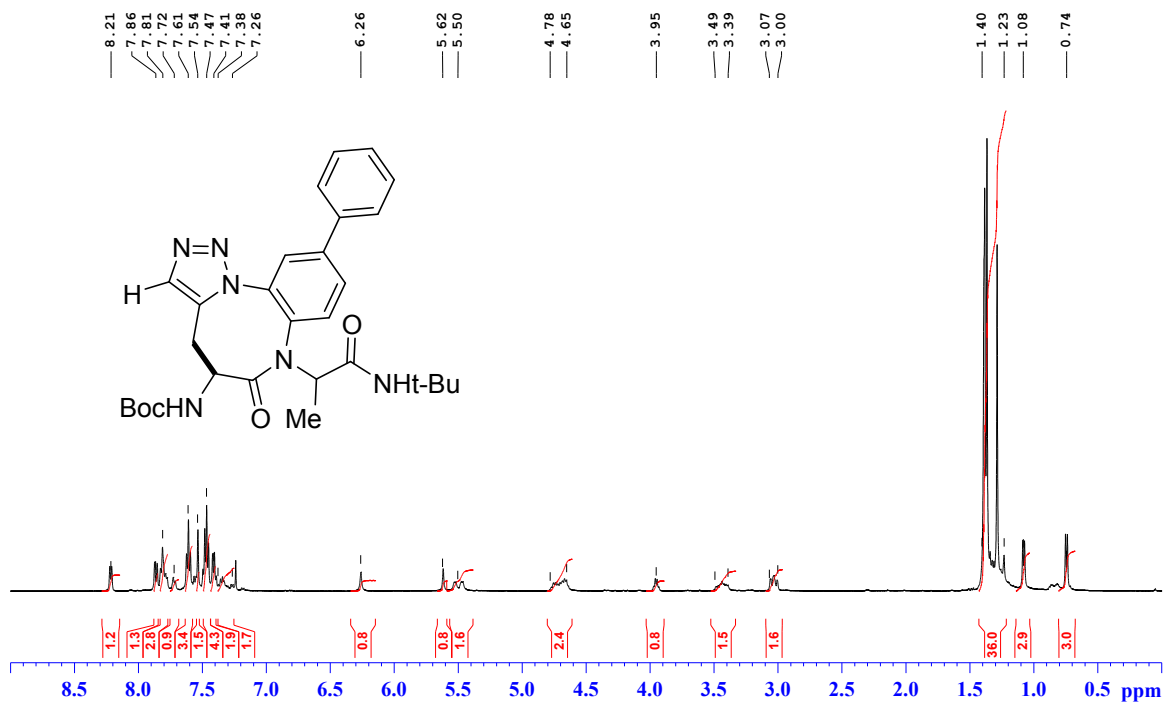
37 – ¹H-NMR (250 MHz, CDCl₃)



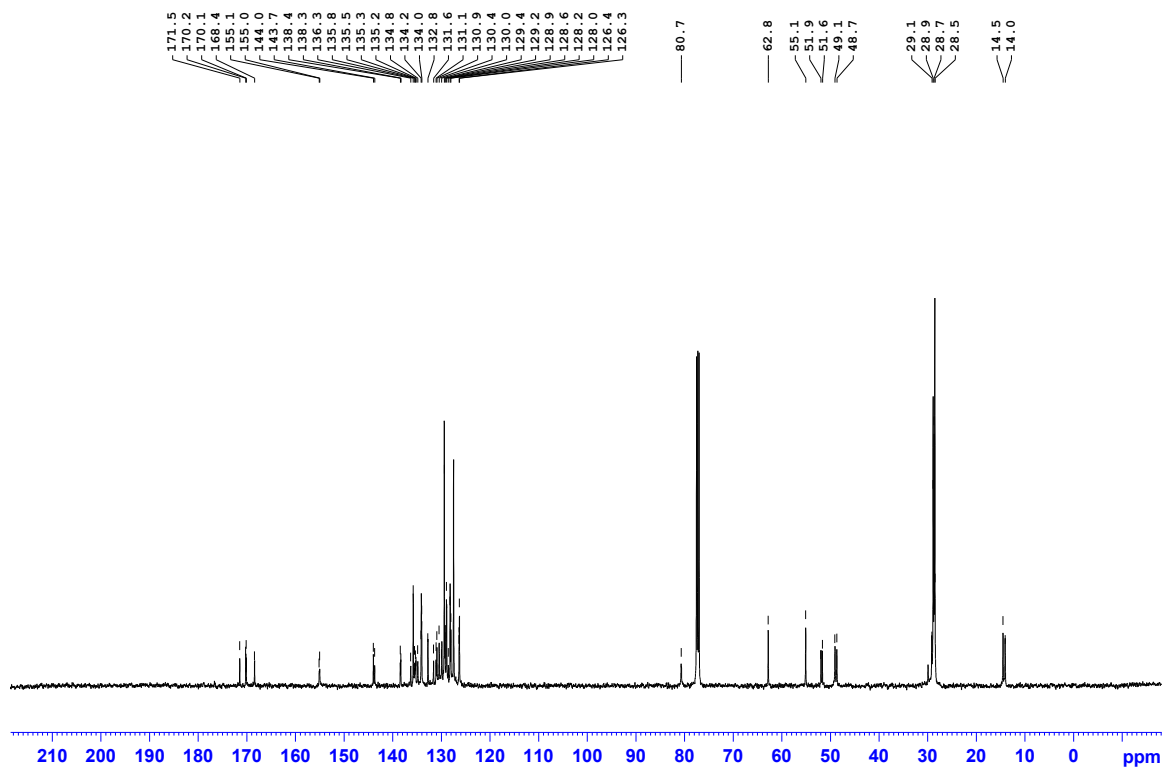
37 – ¹³C-NMR (63 MHz, CDCl₃)



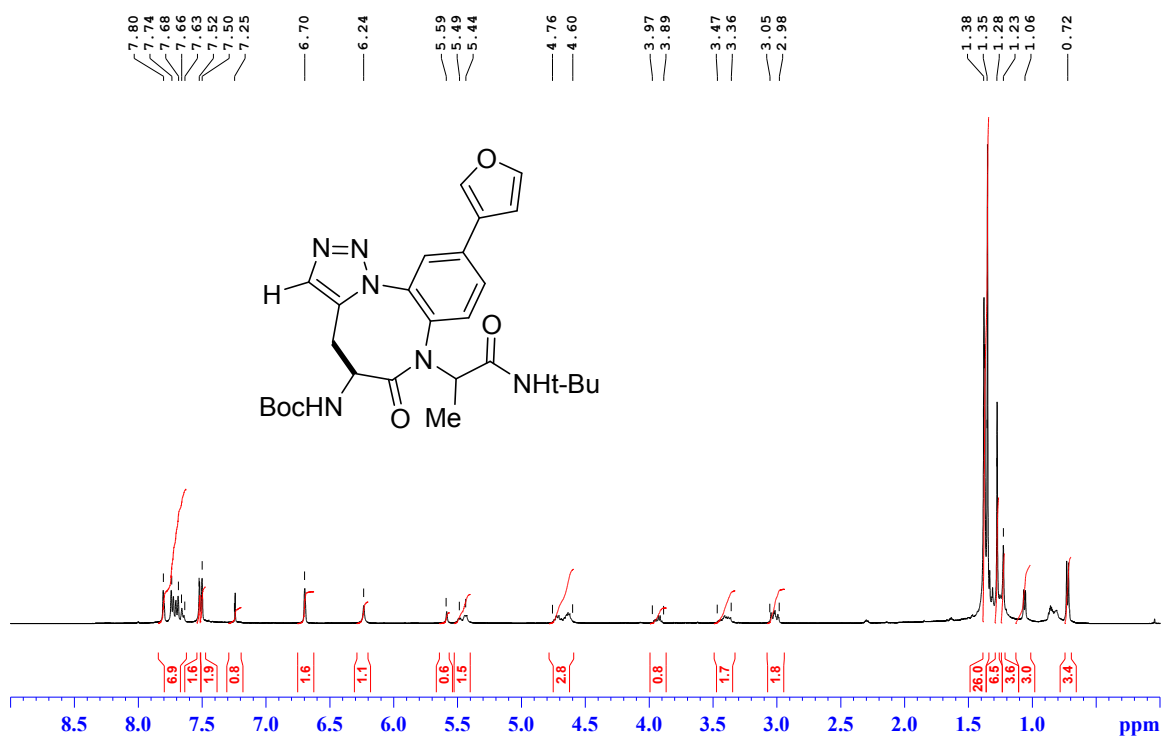
38 - $^1\text{H-NMR}$ (500 MHz, CDCl_3)



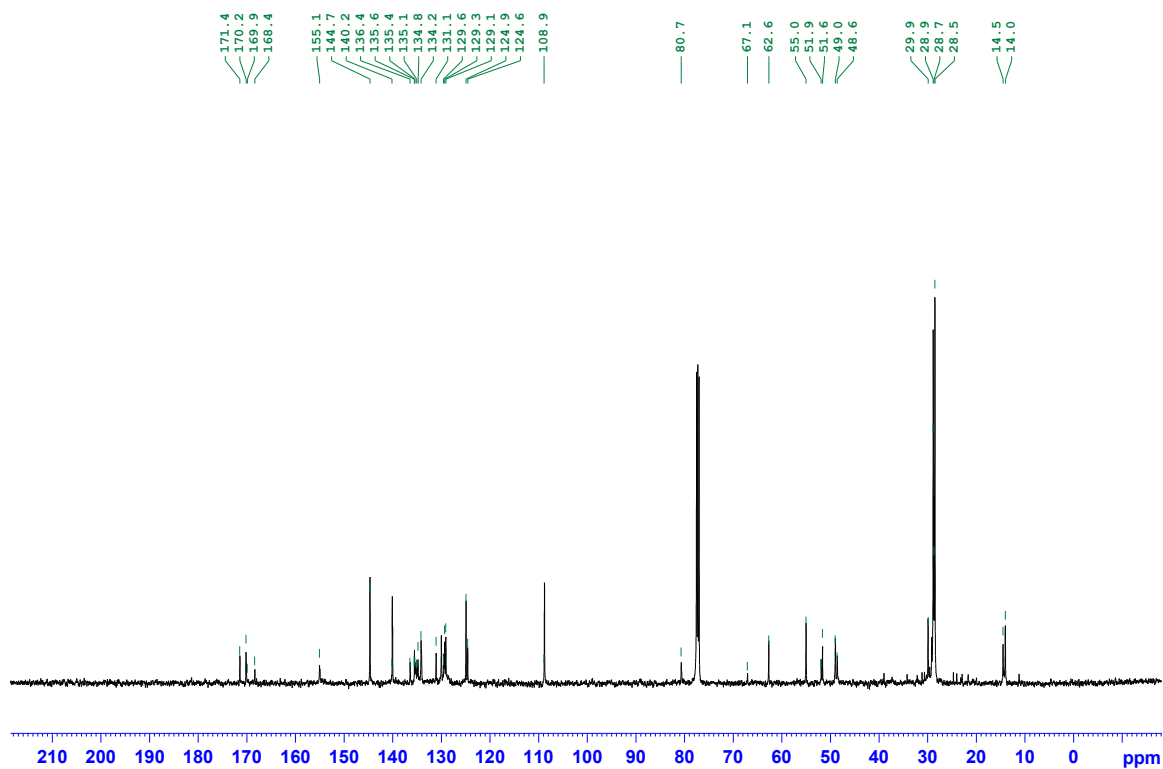
38 - $^{13}\text{C-NMR}$ (125 MHz, CDCl_3)



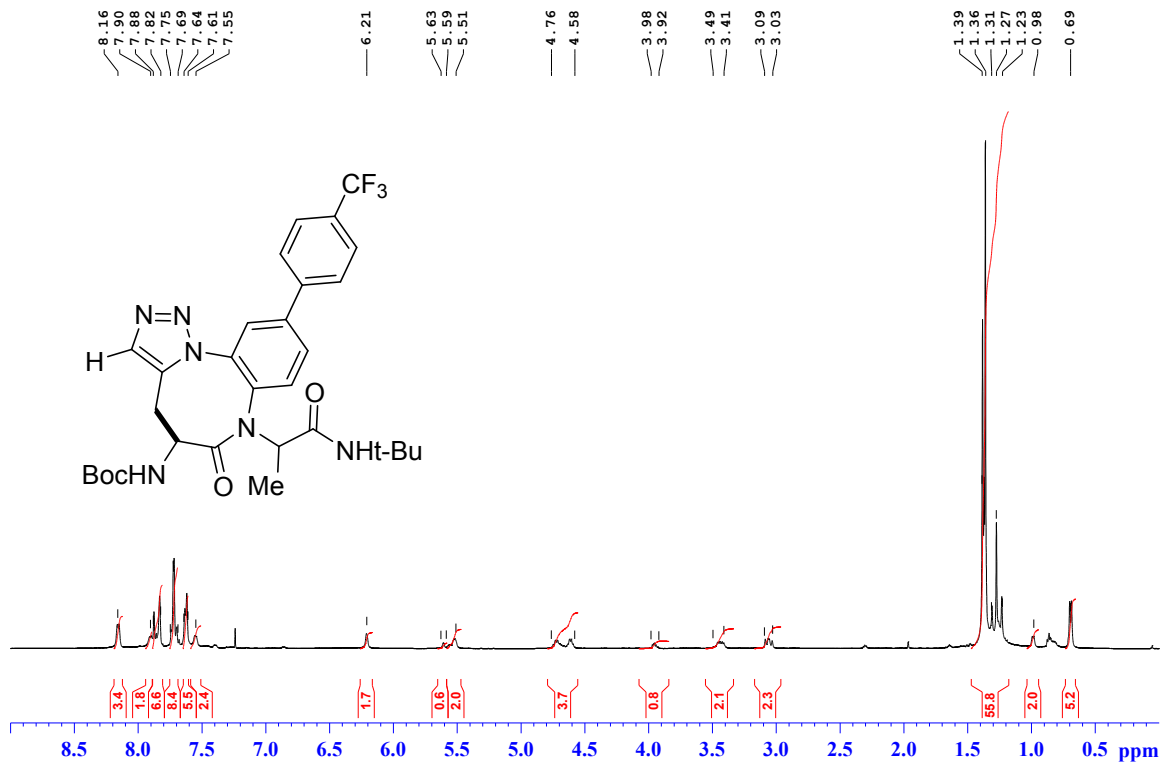
39 - ¹H-NMR (500 MHz, CDCl₃)



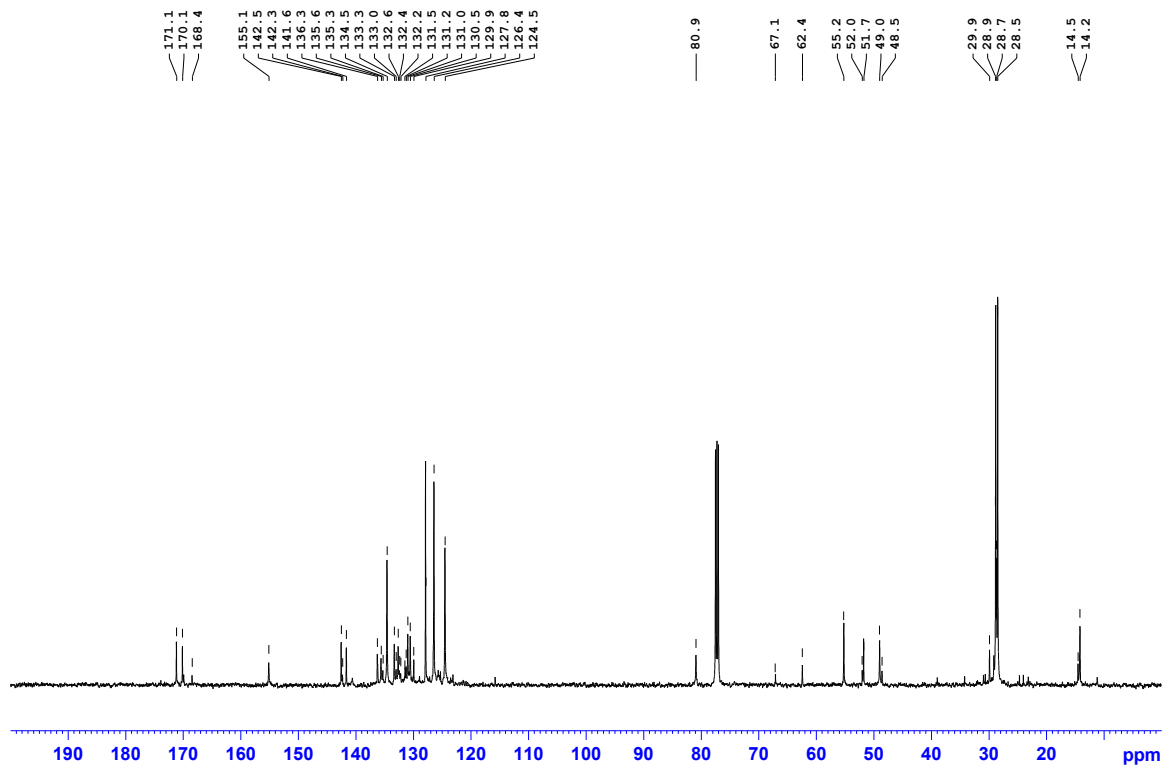
39 - ¹³C-NMR (125 MHz, CDCl₃)



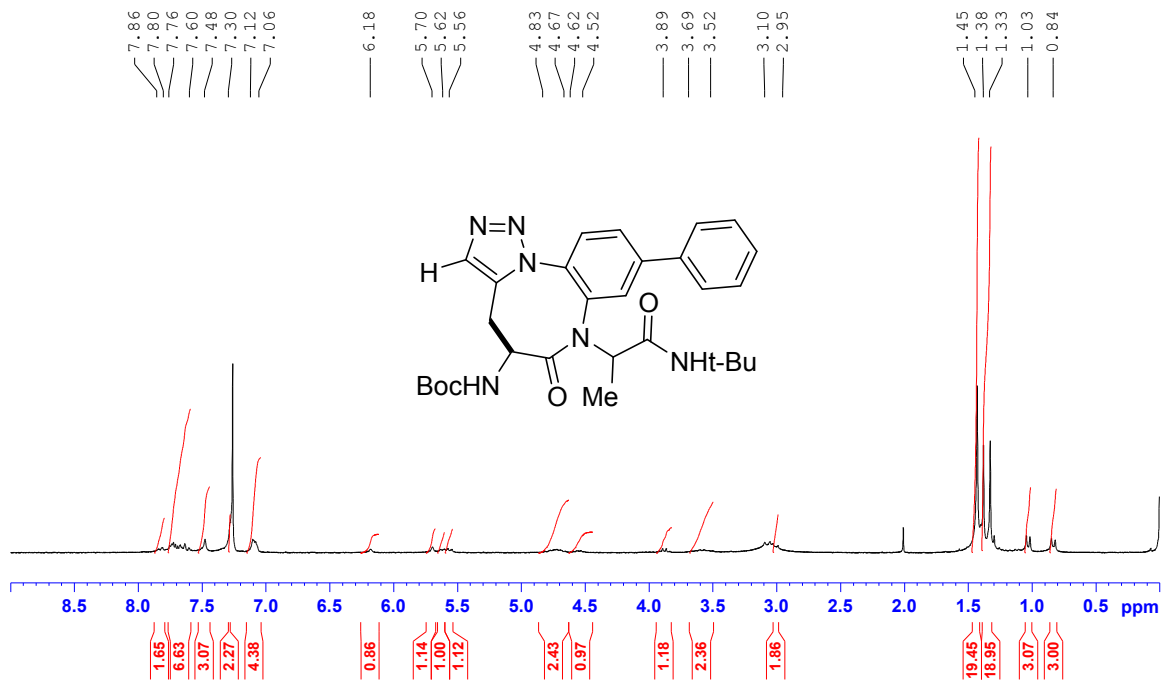
40 - ¹H-NMR (500 MHz, CDCl₃)



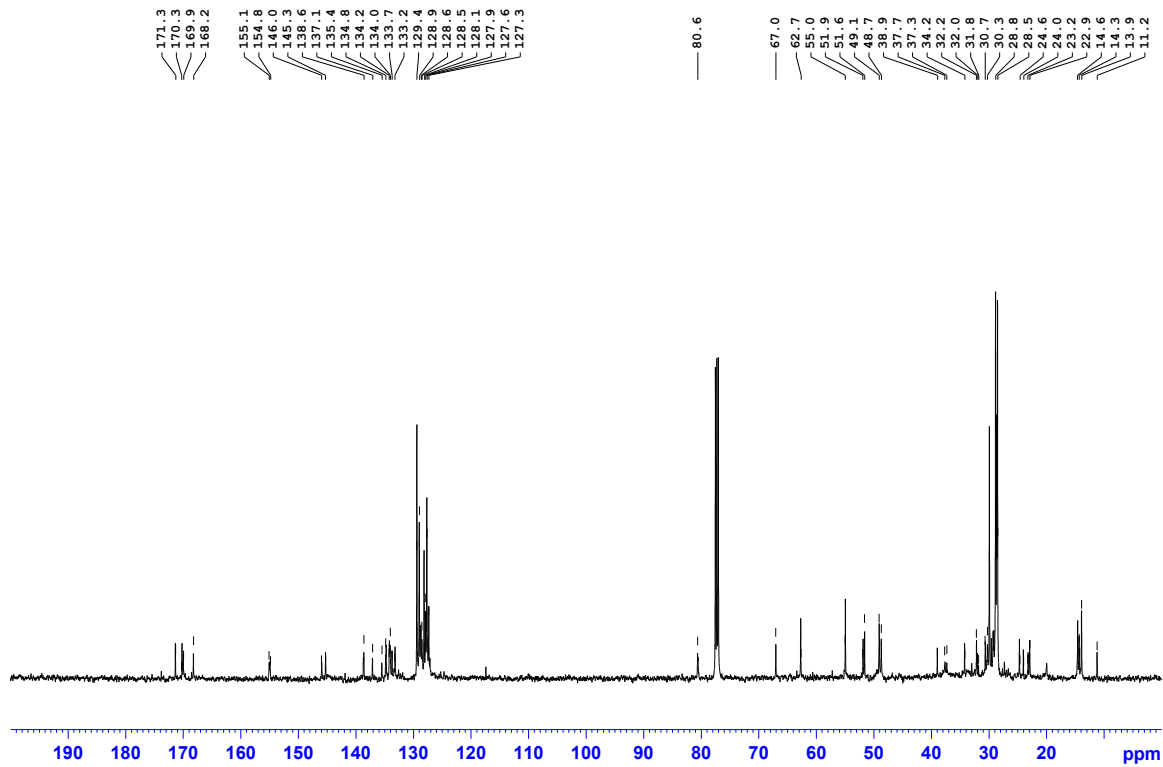
40 - ¹³C-NMR (125 MHz, CDCl₃)



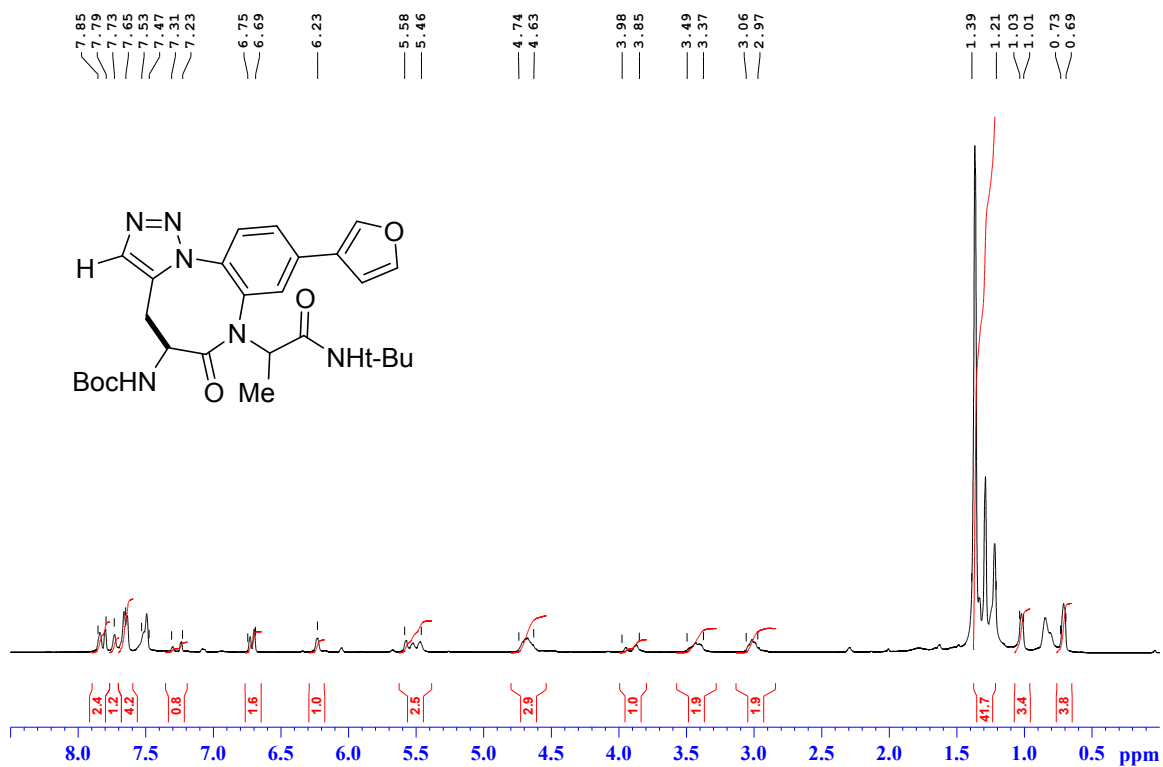
41 - ¹H-NMR (250 MHz, CDCl₃)



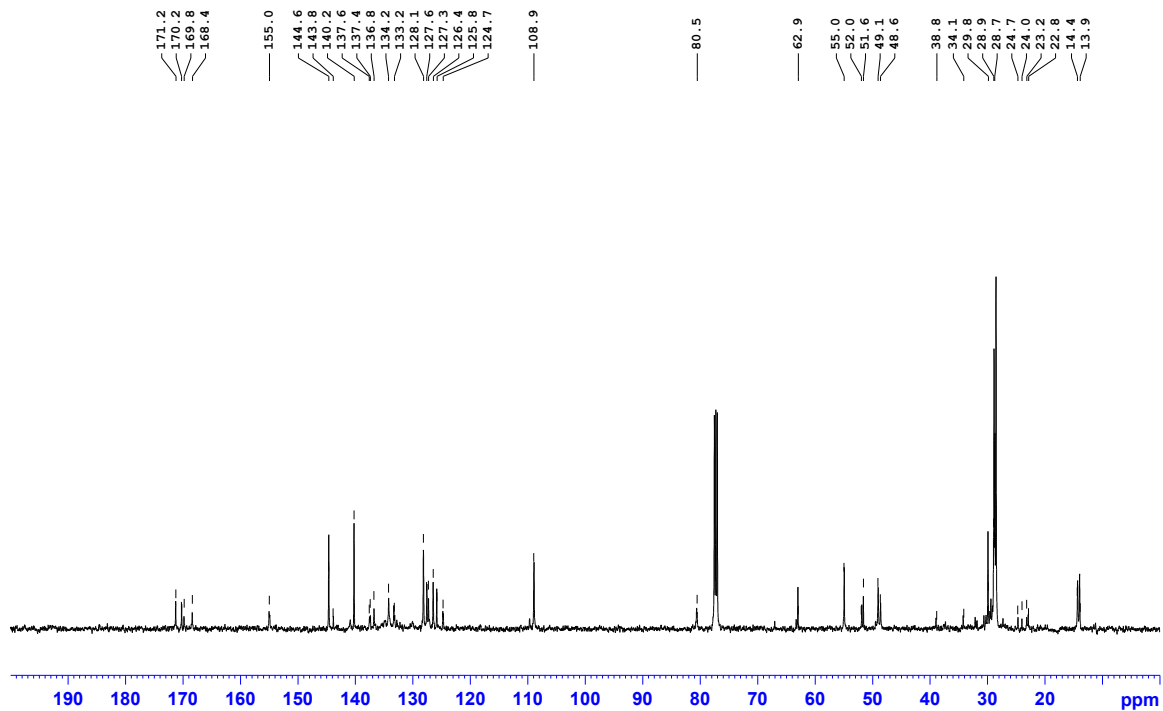
41 - ¹³C-NMR (125 MHz, CDCl₃)



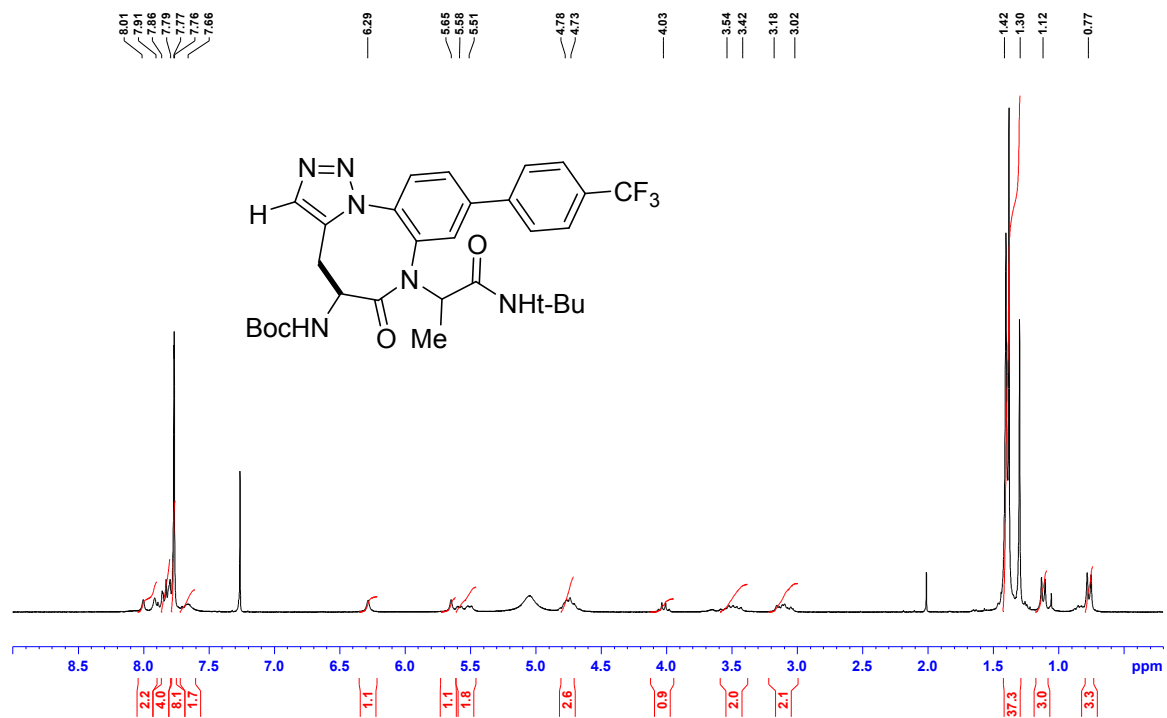
42 – ¹H-NMR (250 MHz, CDCl₃)



42 – ¹³C-NMR (125 MHz, CDCl₃)



43 - ¹H-NMR (250 MHz, CDCl₃)



43 - ¹³C-NMR (125 MHz, CDCl₃)

