A Step-Economical Multicomponent Synthesis of 3D-Shaped Aza-Diketopiperazines and Their Drug-like Chemical Space Analysis

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General methods. Reagents were obtained from commercial sources and used without any further purification. Thin-layer chromatography was performed on silica gel 60 F_{254} plates. (Acetylacetonato)dicarbonylrhodium(I) and dry solvents were purchased from Sigma-Aldrich Co. BiPhePhos was prepared as reported previously.[10] All experiments were performed under argon atmosphere except where otherwise noted. Hydroformylation was performed in a reactor from Equilabo® using 1:1 H_2/CO supplied by Airgas, Inc.

Flash chromatography was performed on silica gel pre-packed columns RP18 (30 mm, Interchim) on a PLC 2020 from Gilson. Analytical reverse-phase high-performance liquid chromatography (RP-HPLC) separations were performed on a C18 Ascentis Express column (2.7 μm, 4.6 mm x 75 mm) using a linear gradient (5 % to 95 % of solvent B in solvent A in 7 min, flow rate 1.6 mL/min), detection at 220 nm, solvent A : water/0.1 % trifluoroacetic acid (TFA), solvent B : acetonitrile/0.1 % TFA). Semi-preparative reverse-phase high-performance liquid chromatography (RP-HPLC) separations were performed on a Waters SunFire Prep C18 column (5 μm, 19 mm x 150 mm).

NMR spectra were recorded on Brucker 400 or 500 MHz spectrometers. Conditions are specified for each spectrum (temperature 25 °C unless specified). Chemical shifts are reported in parts per million (ppm) relative to residual solvent and coupling constants (*J*) are reported in hertz (Hz). Signals are described as s (singlet), d (doublet), t (triplet), q (quartet), sx (sextuplet), sp (septuplet), m (multiplet), dd (doublet of doublets), dt (doublet of triplets), ddt (doublet of doublet of triplets), br s (broad singlet) and br dd (broad doublet of doublets). Deutered solvents were purchased from Euriso-top®.

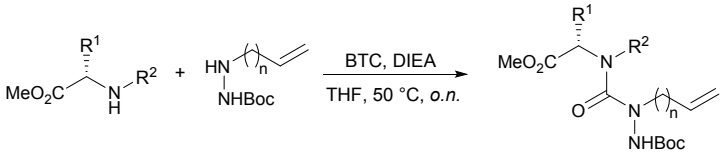
HRMS were obtained on an Agilent Technologie 6520 Accurate-Mass Q.Tof LC/MC apparatus using electrospray ionization mode and time-of flight analyzer (ESI-TOF).

Melting points were determined on a Büchi Melting Point B-540 apparatus in open capillary tubes. Specific rotations were measured with a Perkin-Elmer apparatus using a 10 cm cell with a Na 589 nm filter.

General procedures

General procedure A for the synthesis of semicarbazides. To a solution of BTC (0.335 mmol, 0.335 equiv.) in anhydrous THF (6 mL), under argon, was added dropwise (over 5 minutes) a solution of amino acid derivative (1 mmol, 1 equiv.) and DIEA (1.1 mmol, 1.1 equiv.) in anhydrous THF (2.5 mL). The mixture was stirred at rt for 15 minutes. A solution of *tert*-butyl 2-allylhydrazinecarboxylate or *tert*-butyl 2-(but-3-en-1-yl)hydrazinecarboxylate (1 mmol, 1 equiv.) and DIEA (1.1 mmol, 1.1 equiv.) in anhydrous THF (1.5 mL) was added dropwise. The mixture was heated at 50 °C overnight and evaporated *in vacuo*.

General procedure B for the multicomponent reaction with alcohols. A solution of $Rh(CO)_2(acac)$ (0.02 equiv.) and Biphephos (0.06 equiv.) in anhydrous THF (1 mL), prepared in a Schlenk glassware under an argon atmosphere, was introduced under argon into a stainless steel autoclave containing the semicarbazide (0.35 mmol, 1 equiv.) and camphorsulfonic acid (0.5 equiv.) in MeOH, EtOH, *n*PrOH or *i*PrOH (10 mL). The reactor was purged three times with H_2/CO (1:1, 5 bar) and filled with H_2/CO (1:1, 5 bar). The reactor was heated to 70 °C and stirred for 16 h. The reactor was then cooled to rt and vented to ambient pressure. The solution was quenched with a saturated aqueous solution of $NaHCO_3$ and concentrated *in vacuo*. Water was added to the mixture and the aqueous layer was extracted three times with EtOAc. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated. The crude product was analyzed by ^{1}H NMR to determine the diastereoselectivity of the reaction.



1a-f

***tert*-butyl (*S*)-2-allyl-2-(benzyl(1-methoxy-1-oxopropan-2-yl)carbamoyl)hydrazine-1-carboxylate (1a).** Synthesis was performed following general procedure A starting from (*S*)-*N*-benzyl-1-methoxy-1-oxopropan-2-aminium chloride in CH_2Cl_2/THF (1:1). Purification on silica gel eluting with 20-30% EtOAc in *n*-heptane adding 0.1% of NEt_3 followed by a purification on flash chromatography eluting with 5-100% MeCN in water afforded the title compound as a white solid (926 mg, 2.37 mmol, **82%**). **^{1}H NMR** (500 MHz, DMSO-d_6, 90 °C) δ 8.77 (br s, 1H), 7.36-7.18 (m, 5H), 5.84 (ddt, J = 17.3, 10.3, 6.3 Hz, 1H), 5.18-

5.08 (m, 2H), 4.56 (d, J = 16.6 Hz, 1H), 4.42 (d, J = 16.6 Hz, 1H), 4.06 (q, J = 7.0 Hz, 1H), 3.95 (dd, J = 15.1, 6.6 Hz, 1H), 3.81 (dd, J = 15.1, 6.6 Hz, 1H), 3.60 (s, 3H), 1.33 (s, 9H), 1.28 (d, J = 7.0 Hz, 3H); **^{13}C NMR** (100 MHz, DMSO-d_6) δ 172.5, 161.7, 154.2, 138.7, 133.8, 127.9, 126.8, 126.4, 118.0, 79.3, 55.9, 52.5, 51.9, 51.6, 27.8, 15.3; **HRMS** (ESI-TOF) : calcd. for $C_{20}H_{30}N_3O_5$ $[M+H]^+$: 392.21855, found : 392.21771; **R_f** : 0.28 (30% EtOAc in *n*-heptane + 0.1% NEt_3); **mp** : 99.7 – 101.7 °C; $[\propto]_D^{20} = -10.9$ (c 0.12, $MeOH$).

***tert*-Butyl 2-allyl-2-(benzyl((2*S*,3*S*)-1-methoxy-3-methyl-1-oxopentan-2-yl)carbamoyl)-hydrazine-1-carboxylate (1b)**. Synthesis was performed following general procedure A starting from (2*S*,3*S*)-methyl 2-(benzylamino)-3-methylpentanoate. Purification on silica gel eluting with 20-30% EtOAc in *n*-heptane followed by a purification on flash chromatography eluting with 5-100% MeCN in water afforded the title compound as a white solid (770 mg, 1.78 mmol, **37%**). **^{1}H NMR** (500 MHz, DMSO-d_6, 80 °C) δ 8.81 (br s, 1H), 7.28-7.15 (m, 5H), 5.81 (ddt, J = 17.3, 10.3, 6.2 Hz, 1H), 5.15 (br dd, J = 17.3, 1.8 Hz, 1H), 5.09 (br dd, J = 10.3, 1.8 Hz, 1H), 4.48 (ABq, $\Delta\delta_{AB}$ = 0.082, J_{AB} = 15.9 Hz, 2H), 4.18 (d, J = 9.7 Hz, 1H), 3.96-3.83 (m, 2H), 3.52 (s, 3H), 2.03-1.90 (m, 1H), 1.52-1.41 (m, 1H), 1.39 (s, 9H), 1.06-0.93 (m, 1H), 0.83 (d, J = 6.5 Hz, 3H), 0.74 (t, J = 7.5 Hz, 3H); **^{13}C NMR** (125 MHz, DMSO-d_6, 80 °C) δ 170.8, 161.7, 154.0, 138.5, 133.5, 127.2, 127.0, 125.8, 117.0, 79.2, 64.5, 52.9, 50.6, 48.0, 34.0, 27.6, 24.4, 15.3, 10.3; **HRMS** (ESI-TOF) : calcd. for $C_{23}H_{35}N_3O_5Na$ $[M+Na]^+$: 456.24744, found : 456.24779; **R_f** : 0.38 (25% EtOAc in *n*-heptane); **mp** : 75.8 – 77.8 °C; $[\propto]_D^{20} = -87.5$ (c 0.14, $MeOH$).

***tert*-Butyl (*S*)-2-allyl-2-(isopentyl(1-methoxy-1-oxopropan-2-yl)carbamoyl)hydrazine-1-carboxylate (1c)**. Synthesis was performed following general procedure A starting from (*S*)-methyl 2-(isopentylamino)propanoate. Purification on silica gel eluting with 20-30% EtOAc in *n*-heptane followed by a purification on flash chromatography eluting with 5-100% MeCN in water afforded the title compound as a colorless oil (705 mg, 1.90 mmol, **54%**). **^{1}H NMR** (500 MHz, DMSO-d_6, 80 °C) δ 8.71 (br s, 1H), 5.85 (ddt, J = 17.2, 10.3, 6.2 Hz, 1H), 5.15 (br dd, J = 17.2, 1.7 Hz, 1H), 5.10 (br dd, J = 10.2, 1.7 Hz, 1H), 4.17 (q, J = 7.0 Hz, 1H), 3.96-3.89 (m, 1H), 3.79-3.71 (m, 1H), 3.61 (s, 3H), 3.25-3.16 (m, 1H), 3.08-3.00 (m,

1H), 1.59-1.51 (m, 1H), 1.47-1.34 (m, 2H), 1.41 (s, 9H), 1.31 (d, J = 7.0 Hz, 3H), 0.88 (d, J = 6.7 Hz, 3H), 0.87 (d, J = 6.7 Hz, 3H); **^{13}C NMR** (125 MHz, DMSO-d_6, 80 °C) δ 172.0, 160.4, 153.8, 133.8, 116.8, 79.1, 55.6, 52.7, 51.0, 45.6, 37.2, 27.6, 25.3, 22.1, 21.9, 15.1; **HRMS** (ESI-TOF) : calcd. for $C_{18}H_{33}N_3O_5Na$ $[M+Na]^+$: 394.23179, found : 394.2320; **R_f** : 0.33 (25% EtOAc in *n*-heptane); $[\propto]_D^{20} = -18.6\ (c\ 0.11,\ MeOH)$.

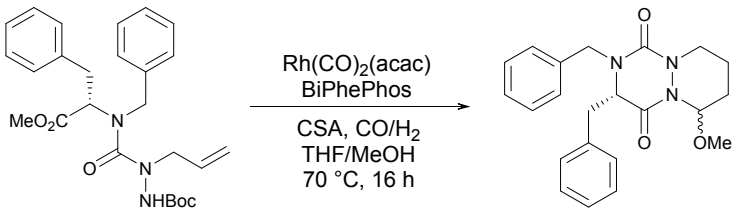
***tert*-Butyl (*S*)-2-allyl-2-(benzyl(1-methoxy-1-oxo-3-phenylpropan-2-yl)carbamoyl)-hydrazine-1-carboxylate (1d)**. Synthesis was performed following general procedure A starting from (*S*)-methyl 2-(benzylamino)-3-phenylpropanoate. Purification on silica gel eluting with 20-30% EtOAc in *n*-heptane followed by a purification on flash chromatography eluting with 5-100% MeCN in water afforded the title compound as a colorless oil (761 mg, 1.63 mmol, **44%**). **^{1}H NMR** (500 MHz, DMSO-d_6, 80 °C) δ 8.78 (br s, 1H), 7.22-7.09 (m, 10 H), 5.83 (ddt, J = 17.3, 10.2, 6.3 Hz, 1H), 5.16 (br dd, J = 17.3, 1.7 Hz, 1H), 5.11 (br dd, J = 10.2, 1.7 Hz, 1H), 4.45 (ABq, $\Delta\delta_{AB}$ = 0.037, J_{AB} = 16.7 Hz, 2H), 4.19-4.10 (m, 1H), 3.95-3.87 (m, 1H), 3.86-3.79 (m, 1H), 3.55 (s, 3H), 3.29 (dd, J = 14.1, 6.8 Hz, 1H), 3.00 (dd, J = 14.1, 6.8 Hz, 1H), 1.34 (s, 9H); **^{13}C NMR** (125 MHz, DMSO-d_6, 80 °C) δ 170.9, 161.1, 154.0, 138.1, 137.6, 133.4, 128.7, 127.6, 127.3, 126.9, 126.0, 125.7, 117.1, 79.2, 61.6, 52.6, 51.4, 51.0, 35.5, 27.6; **HRMS** (ESI-TOF) : calcd. for $C_{26}H_{33}N_3O_5Na$ $[M+Na]^+$: 490.23179, found : 490.23253; **R_f** : 0.29 (25% EtOAc in *n*-heptane); $[\propto]_D^{20} = -103.8\ (c\ 0.11,\ MeOH)$.

tert*-Butyl (*S*)-3-allyl-5-benzyl-6-(methoxycarbonyl)-14,14-dimethyl-4,12-dioxo-13-oxa-2,3,5,11-tetraazapentadecanoate (1e).** Synthesis was performed following general procedure A starting from **(S*)-methyl 2-(benzylamino)-6-((*tert*-butoxycarbonyl)amino)hexanoate. Purification on flash chromatography eluting with 20-40% EtOAc in *n*-heptane adding 0.1% of NEt_3 followed by a purification on flash chromatography eluting with 5-100% MeCN in water afforded the title compound as a white solid (587 mg, 1.07 mmol, **65%**). **^{1}H NMR** (500 MHz, DMSO-d_6, 90 °C) δ 8.78 (br s, 1H), 7.36-7.18 (m, 5H), 6.21 (br s, 1H), 5.84 (ddt, J = 17.2, 10.3, 6.5 Hz, 1H), 5.16 (d, J = 17.2 Hz, 1H), 5.11 (d, J = 10.3 Hz, 1H), 4.46 (s, 2H), 4.05-3.91 (m, 2H), 3.88-3.80 (m, 1H), 3.57 (s, 3H), 2.86-2.79 (m, 2H), 1.91-1.81 (m, 1H), 1.70-1.60 (m, 1H), 1.38 (s, 9H), 1.37 (s, 9H), 1.30-1.12 (m, 4H); **^{13}C NMR** (125 MHz, DMSO-d_6) δ 171.5, 161.3, 155.0,

153.9, 138.1, 133.5, 127.3, 127.2, 126.1, 117.0, 79.2, 76.9, 59.9, 52.6, 50.9, 50.3, 40.1, 29.0, 28.8, 27.8, 27.5, 23.0; **HRMS** (ESI-TOF) : calcd. for $C_{28}H_{44}N_4O_7Na$ $[M+Na]^+$: 571.310770, found : 571.30998; $\mathbf{R_f}$: 0.23 (30% EtOAc in *n*-heptane + 0.1% NEt_3); **mp** : 50.2 – 52.2 °C; $[\propto]_D^{20} = -53.0\ (c\ 0.295, MeOH)$.

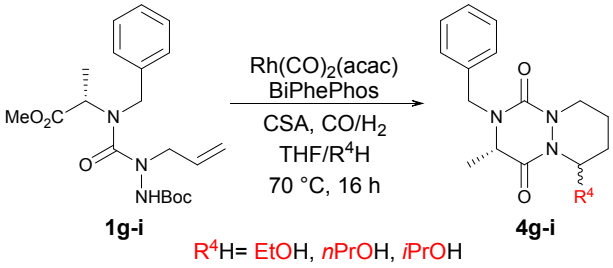
***tert*-Butyl (*S*)-2-(benzyl(1-methoxy-1-oxopropan-2-yl)carbamoyl)-2-(but-3-en-1-yl)hydrazine-1-carboxylate (1f).** Synthesis was performed following general procedure A starting from (*S*)-*N*-benzyl-1-methoxy-1-oxopropan-2-aminium chloride in THF/CH_2Cl_2 (1:1). Purification on silica gel eluting with 20-40% EtOAc in *n*-heptane adding 0.1% of NEt_3 followed by a purification on flash chromatography eluting with 5-100% MeCN in water afforded the title compound as a colorless oil (190 mg, 0.47 mmol, **71%**). **^{1}H NMR** (400 MHz, DMSO-d_6, 100 °C) δ 8.76 (br s, 1H), 7.36-7.16 (m, 5H), 5.80 (ddt, *J* = 17.2, 10.4, 6.7 Hz, 1H), 5.04 (dd, *J* = 17.2, 1.9 Hz, 1H), 4.98 (dd, *J* = 10.4, 1.9 Hz, 1H), 4.55 (d, *J* = 16.5 Hz, 1H), 4.39 (d, *J* = 16.5 Hz, 1H), 4.09 (q, *J* = 7.1 Hz, 1H), 3.61 (s, 3H), 3.48-3.39 (m, 1H), 3.25-3.18 (m 1H), 2.28-2.21 (m, 2H), 1.36 (s, 9H), 1.29 (d, *J* = 7.1 Hz, 3H); **^{13}C NMR** (125 MHz, DMSO-d_6) δ 172.5, 161.8, 154.2, 138.7, 135.9, 127.9, 126.8, 126.5, 116.0, 79.5, 55.8, 51.9, 51.6, 49.1, 30.9, 27.8, 15.3; **HRMS** (ESI-TOF) : calcd. for $C_{21}H_{31}N_3O_5Na$ $[M+Na]^+$: 428.21614, found : 428.21613; $\mathbf{R_f}$: 0.32 (30% EtOAc in *n*-heptane + 0.1% NEt_3); $[\propto]_D^{20} = -8.8\ (c\ 0.25, MeOH)$.

For compounds **4a-c,e-f**, analytical data were in agreement with those previously published.[1]



(3*S*,6*R*)-2,3-dibenzyl-6-methoxyhexahydropyridazino[1,2-*a*][1,2,4]triazine-1,4-dione (4d).

Hydroformylation was performed following general procedure B starting from *tert*-butyl (*S*)-2-allyl-2-(benzyl(1-methoxy-1-oxo-3-phenylpropan-2-yl)carbamoyl)-hydrazine-1-carboxylate (**1d**). Purification on semi-preparative HPLC eluting with 5-100% MeCN in water afforded the title compound as a colorless oil (29 mg, 0.08 mmol, **31%**). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.37-7.12 (m, 10H), 5.62-5.59 (m, 1H), 5.13 (d, *J* = 14.9 Hz, 1H), 4.06-4.02 (m, 1H), 3.99-3.91 (m, 1H), 3.74 (d, *J* = 14.9 Hz, 1H), 3.12 (s, 3H), 3.01 (dd, *J* = 13.9, 4.6 Hz, 1H), 2.90 (dd, *J* = 13.9, 5.7 Hz, 1H), 1.96-1.83 (m, 2H), 1.62 (td, *J* = 12.5, 3.2 Hz, 1H), 1.46-1.27 (m, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 165.4, 154.4, 136.5, 135.4, 130.1, 129.1, 128.5, 128.2, 127.6, 79.4, 60.1, 59.8, 48.9, 44.4, 36.3, 28.3, 18.1; **HRMS** (ESI-TOF): calcd. for $C_{22}H_{26}N_3O_3$ $[M+H]^+$: 380.19742, found : 380.19683; $[\alpha]_D^{20} = +3.5$ (c 0.12, $MeOH$).



(3*S*)-2-benzyl-6-ethoxy-3-methylhexahydropyridazino[1,2-*a*][1,2,4]triazine-1,4-dione (4g).

Hydroformylation was performed following general procedure B starting from *tert*-butyl (*S*)-2-allyl-2-(benzyl(1-methoxy-1-oxopropan-2-yl)carbamoyl)hydrazine-1-carboxylate (**1a**) using EtOH instead of MeOH. Purification on silica gel column eluting with 30-60% EtOAc in *n*-heptane afforded the desired product as a colorless oil (73 mg, 0.23 mmol, **65%**). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.29-7.15 (m, 5H),

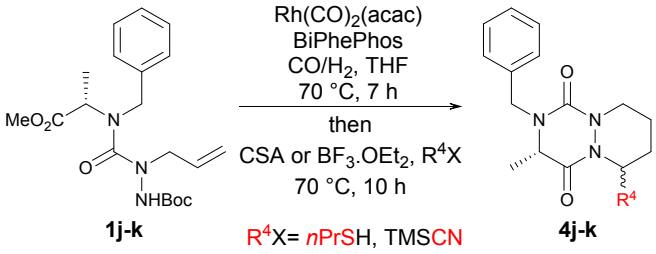
[1] P. Regenass, J. F. Margathe, A. Mann, J. Suffert, M. Hibert, N. Girard and D. Bonnet, *Chem. Commun.*, 2014, **50**, 9657-9660.

5.68-5.62 (m, 1H), 4.89 (d, *J* = 14.9 Hz, 1H), 4.47-4.38 (m, 1H), 3.90 (d, *J* = 14.9 Hz, 1H), 3.69 (q, *J* = 7.0 Hz, 1H), 3.31 (q, *J* = 7.1 Hz, 2H), 2.92 (td, *J* = 12.7, 3.0 Hz, 1H), 2.18-2.03 (m, 1H), 2.00-1.90 (m, 1H), 1.66-1.48 (m, 2H), 1.17 (d, *J* = 7.0 Hz, 3H), 1.08 (t, *J* = 3.0 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 167.3, 155.1, 136.9, 129.0, 128.4, 128.1, 78.1, 64.0, 55.0, 48.6, 44.4, 28.6, 18.5, 15.4, 15.1; **HRMS** (ESI-TOF) : calcd. for $C_{17}H_{24}N_3O_3$ $[M+H]^+$: 318.18177, found : 318.1813; **R_f** : 0.31 (50% EtOAc in *n*-heptane); $[\propto]_D^{20} = -62.5$ (c 0.40, $MeOH$).

(3*S*,6*R*)-2-benzyl-3-methyl-6-propoxyhexahydropyridazino[1,2-*a*][1,2,4]triazine-1,4-dione (4h). Hydroformylation was performed following general procedure B starting from *tert*-butyl (*S*)-2-allyl-2-(benzyl(1-methoxy-1-oxopropan-2-yl)carbamoyl)hydrazine-1-carboxylate (**1a**) in *n*PrOH (14.2 mL)/THF (2 mL) using 1 equiv. of CSA. Purification silica gel column eluting with 20-70% EtOAc in *n*-heptane afforded the major isomer as a colorless oil (215 mg, 0.65 mmol, **47%**). **^{1}H NMR** (400 MHz, DMSO-d_6) δ 7.36-7.25 (m, 5H), 5.62-5.59 (m, 1H), 4.74 (d, *J* = 15.0 Hz, 1H), 4.26-4.19 (m, 1H), 4.06 (d, *J* = 15.0 Hz, 1H), 3.83 (q, *J* = 7.0 Hz, 1H), 3.23 (dt, *J* = 9.2, 6.4 Hz, 1H), 3.17 (dt, *J* = 9.2, 6.9 Hz, 1H), 3.02 (td, *J* = 12.5, 3.2 Hz, 1H), 1.93-1.79 (m, 2H), 1.71-1.50 (m, 2H), 1.44 (sx, *J* = 7.0 Hz, 2H), 1.17 (d, *J* = 7.0 Hz, 3H), 0.78 (t, *J* = 7.4 Hz, 3H); **^{13}C NMR** (100 MHz, DMSO-d_6) δ 166.5, 154.2, 137.7, 128.4, 127.8, 127.4, 77.2, 68.9, 54.9, 47.4, 43.4, 27.6, 22.1, 18.0, 15.0, 10.3; **HRMS** (ESI-TOF) : calcd. for $C_{18}H_{26}N_3O_3$ $[M+H]^+$: 332.19742, found : 332.19662; **R_f** : 0.38 (60% EtOAc in *n*-heptane); $[\propto]_D^{20} = -14.6$ (c 0.24, $MeOH$).

(3*S*,6*R*)-2-benzyl-6-isopropoxy-3-methylhexahydropyridazino[1,2-*a*][1,2,4]triazine-1,4-dione (4i). Hydroformylation was performed following general procedure B starting from *tert*-butyl (*S*)-2-allyl-2-(benzyl(1-methoxy-1-oxopropan-2-yl)carbamoyl)hydrazine-1-carboxylate (**1a**) in *i*PrOH (13.2 mL)/THF (1.85 mL) using 1 equiv. of CSA. Purification on semi-preparative HPLC eluting with 5-60% MeCN in water and freeze-drying afforded the major isomer as a colourless oil (196 mg, 0.59 mmol, **46%**). **^{1}H NMR** (400 MHz, DMSO-d_6) 7.36-7.24 (m, 5H), 5.72-5.69 (m, 1H), 4.74 (d, *J* = 15.1 Hz, 1H), 4.26-4.19 (m, 1H), 4.06 (d, *J* = 15.1 Hz, 1H), 3.81 (q, *J* = 7.1 Hz, 1H), 3.49 (sp, *J* = 6.1 Hz, 1H), 3.02 (td, *J* = 12.6, 3.0 Hz, 1H), 1.94-1.69 (m, 2H), 1.73-1.60 (m, 1H), 1.58-1.49 (m, 1H), 1.17 (d, *J* = 7.0 Hz, 3H), 1.07 (d, *J* = 7.0 Hz, 3H),

0.99 (d, J = 7.0 Hz, 3H); **^{13}C NMR** (100 MHz, DMSO-d_6) δ 166.4, 154.3, 137.7, 128.4, 127.7, 127.3, 74.8, 68.1, 54.9, 47.4, 43.5, 28.1, 22.8, 21.1, 17.9, 15.1; **HRMS** (ESI-TOF) : calcd. for $C_{18}H_{25}N_3O_3Na$ $[M+Na]^+$: 354.17936, found : 354.17956; **R_f** : 0.38 (60% EtOAc in *n*-heptane); $[\propto]_D^{20} = -3.2$ (c 0.125, $MeOH$).



(3*S*)-2-Benzyl-3-methyl-6-(propylthio)hexahydropyridazino[1,2-*a*][1,2,4]triazine-1,4-dione (4j). A solution of $Rh(CO)_2(acac)$ (2.2 mg, 0.01 mmol, 0.02 equiv.) and Biphephos (20 mg, 0.03 mmol, 0.06 equiv.) in anhydrous THF (1 mL), prepared in a Schlenk glassware under an argon atmosphere, was introduced under argon into a stainless steel autoclave containing *tert*-butyl (*S*)-2-allyl-2-(benzyl(1-methoxy-1-oxopropan-2-yl)carbamoyl)hydrazine-1-carboxylate (**1a**, 164 mg, 0.42 mmol, 1 equiv.) in anhydrous THF (2.7 mL). The reactor was purged three time with H_2/CO (5 bar, 1:1), filled with H_2/CO (5 bar, 1:1), heated to 70 °C and the mixture was stirred for 7 h. The reactor was then cooled to ambient temperature and vented to ambient pressure. *n*PrSH (3.7 mL), then CSA (97 mg, 0.42 mmol, 1 equiv.) were added. The reactor was filled with H_2/CO (1:1, 5 bar), heated to 70 °C and stirred for 10 h. The reactor was then cooled to ambient temperature and vented to ambient pressure. The solution was quenched with a saturated aqueous solution of $NaHCO_3$ and concentrated *in vacuo*. Water was added to the mixture and the aqueous layer was extracted three times with EtOAc. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated. The crude product was analyzed by ^{1}H NMR to determine the diastereoselectivity of the reaction. Purification on silica gel column eluting with 30-70% EtOAc in *n*-heptane afforded the major isomer (75 mg, 0.22 mmol, **52%**) and the minor isomer (28 mg, 0.08 mmol, **19%**) as colorless oils.

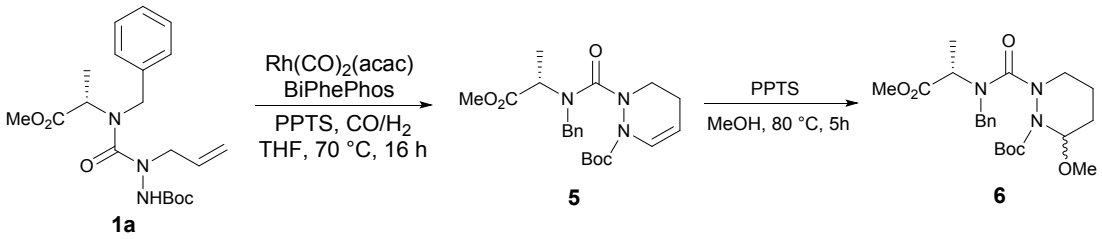
***Trans*-isomer (3*S*,6*R*) : ^{1}H NMR** (400 MHz, $CHCl_3$) δ 7.26-7.18 (m, 5H), 5.85-5.78 (m, 1H), 4.93 (d, J = 15.0 Hz, 1H), 4.50-4.43 (m, 1H), 3.89 (d, J = 15.0 Hz, 1H), 3.66 (q, J = 7.1 Hz, 1H), 2.89 (td, J = 12.6, 3.1 Hz, 1H), 2.46 (ddd, J = 12.6, 8.2, 6.2 Hz, 1H), 2.32 (ddd, J = 12.5, 8.4, 6.6 Hz, 1H), 2.07-1.87 (m, 3H), 1.61-1.43 (m, 3H), 1.17 (d, J = 7.0 Hz, 3H), 0.83 (t, J = 7.4 Hz, 3H); **^{13}C NMR** (100 MHz, $CHCl_3$) δ 166.2,

155.3, 136.6, 128.9, 128.4, 128.1, 57.0, 54.7, 48.5, 44.8, 33.7, 29.4, 23.3, 19.9, 15.7, 13.7; **HRMS** (ESI-TOF): calcd. for $C_{18}H_{25}N_3O_2SNa$ $[M+Na]^+$: 370.15652, found : 370.15578; $\mathbf{R_f}$: 0.32 (50% AcOEt in *n*-heptane); $[\propto]_D^{20} = -22.7\ (c\ 0.235, CDCl_3)$.

***Cis*-isomer (3*S*,6*S*) : ^{1}H NMR** (400 MHz, $CHCl_3$) δ 7.24-7.14 (m, 5H), 5.88-5.79 (m, 1H), 4.69 (d, *J* = 16.1 Hz, 1H), 4.50-4.39 (m, 2H), 3.84 (q, *J* = 7.0 Hz, 1H), 3.08-2.98 (m, 1H), 2.56 (ddd, *J* = 12.6, 8.1, 6.1 Hz, 1H), 2.38 (ddd, *J* = 12.8, 8.3, 6.7 Hz, 1H), 2.07-1.92 (m, 3H), 1.64-1.42 (m, 3H), 1.30 (d, *J* = 6.9 Hz, 3H), 0.86 (t, *J* = 7.3 Hz, 3H); **^{13}C NMR** (100 MHz, $CHCl_3$) δ 167.3, 157.8, 138.3, 128.8, 127.4, 127.4, 58.6, 53.2, 46.9, 43.9, 34.2, 29.6, 23.4, 19.7, 13.8, 13.7; **HRMS** (ESI-TOF): calcd. for $C_{18}H_{25}N_3O_2SNa$ $[M+Na]^+$: 370.15652, found : 370.15584; $\mathbf{R_f}$: 0.38 (50% AcOEt in *n*-heptane); $[\propto]_D^{20} = +8.4\ (c\ 0.11, CDCl_3)$.

(3*S*)-2-Benzyl-3-methyl-1,4-dioxooctahydropyridazino[1,2-*a*][1,2,4]triazine-6-carbonitrile (4k). A solution of $Rh(CO)_2(acac)$ (0.02 equiv.) and BiPhePhos (0.06 equiv.) in anhydrous THF (1 mL), prepared in a Schlenk glassware under an argon atmosphere, was introduced under argon into a stainless steel autoclave containing *tert*-butyl (*S*)-2-allyl-2-(benzyl(1-methoxy-1-oxopropan-2-yl)carbamoyl)hydrazine-1-carboxylate (140 mg, 0.36 mmol, 1 equiv.) in anhydrous THF (3.2 mL). The reactor was purged three time with H_2/CO (5 bar, 1:1), filled with H_2/CO (5 bar, 1:1), heated to 70 °C and the mixture was stirred for 7 h. The reactor was then cooled to ambient temperature and vented to ambient pressure. TMSCN (95 µL, 0.72 mmol, 2 equiv.) and $BF_3.OEt_2$ (91 µL, 0.72 mmol, 2 equiv.) were added. The reactor was purged three time with H_2/CO (5 bar, 1:1), filled with H_2/CO (5 bar, 1:1), heated to 70 °C and the mixture was stirred for 10 h. The reactor was then cooled to ambient temperature and vented to ambient pressure. The reaction mixture was quenched with a saturated solution of $NaHCO_3$ and evaporated to a slurry. Water was added to the mixture and the aqueous layers was extracted three times with EtOAc. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated. The crude product was analyzed by NMR to determine the diastereoselectivity of the reaction. Purification on silica gel eluting with 30-50% EtOAc in *n*-heptane afforded a white solid containing the mixture of two diastereoisomers (84 mg, 0.28 mmol, dr : 55:45, **79%**). **Major isomer (3*S*,6*S*): ^{1}H NMR** (400 MHz, MeOD-d_4) δ 7.31-7.18 (m, 5H), 5.55-

5.50 (m, 1H), 4.77 (d, J = 15.4 Hz, 1H), 4.40-4.33 (m, 1H), 4.16 (d, J = 15.4 Hz, 1H), 3.78 (q, J = 7.0 Hz, 1H), 3.06-2.97 (m, 1H), 2.15-2.04 (m, 1H), 1.99-1.77 (m, 3H), 1.17 (d, J = 7.0 Hz, 3H); **^{13}C NMR** (100 MHz, MeOD-d_4) δ 166.8, 156.0, 138.0, 130.0, 129.1, 117.4, 56.3, 49.9, 45.5, 44.3, 27.2, 21.8, 16.2; **HRMS** (ESI-TOF): calcd. for $C_{16}H_{18}N_4O_2Na$ $[M+Na]^+$: 321.13275, found: 321.13206; **R_f** : 0.25 (50% EtOAc in *n*-heptane); **mp** : 131.7 – 133.7 °C; $[\propto]_D^{20} = -129.8\ (c\ 0.10, MeOH)$. **Minor isomer (3*S*,6*R*): ^{1}H NMR** (400 MHz, MeOD-d_4) δ 7.35-7.21 (m, 5H), 5.59-5.42 (m, 1H), 4.70 (d, J = 16.6 Hz, 1H), 4.59 (d, J = 16.6 Hz, 1H), 4.47-4.38 (m, 1H), 4.15 (q, J = 7.0 Hz, 1H), 3.22-3.12 (m, 1H), 2.22-2.11 (m, 1H), 2.06-1.83 (m, 3H), 1.33 (d, J = 7.0 Hz, 3H); **^{13}C NMR** (400 MHz, MeOD-d_4) δ 168.4, 158.7, 139.4, 129.9, 128.4, 127.9, 117.6, 54.0, 47.5, 45.3, 44.9, 27.2, 21.5, 13.0; **HRMS** (ESI-TOF): calcd. for $C_{16}H_{18}N_4O_2Na$ $[M+Na]^+$: 321.13275, found: 321.13166; **R_f** : 0.25 (50% EtOAc in *n*-heptane); **mp** : 67.9 – 69.9 °C; $[\propto]_D^{20} = +123.9\ (c\ 0.12, MeOH)$.



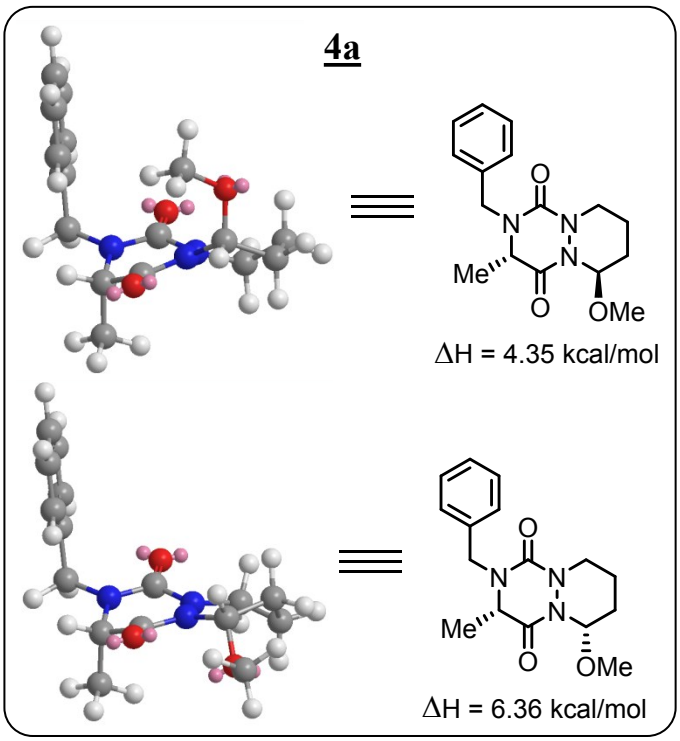
***tert*-Butyl (*S*)-2-(benzyl(1-methoxy-1-oxopropan-2-yl)carbamoyl)-3,4-dihydropyridazine-1(2*H*)-carboxylate (5)**. A solution of $Rh(CO)_2(acac)$ (1.6 mg, 0.01 mmol, 0.02 equiv.) and BiPhePhos (15 mg, 0.02 mmol, 0.06 equiv.) in anhydrous THF (2 mL), prepared in a Schlenk glassware under an argon atmosphere, was introduced under argon into a stainless steel autoclave containing *tert*-butyl (*S*)-2-allyl-2-(benzyl(1-methoxy-1-oxopropan-2-yl)carbamoyl)hydrazine-1-carboxylate (**1a**, 125 mg, 0.32 mmol, 1 equiv.) and pyridinium *p*-toluenesulfonate (8 mg, 0.03 mmol, 0.1 equiv.) in anhydrous THF (8 mL). The reactor was purged three time with H_2/CO (1:1, 5 bar) and filled with H_2/CO (1:1, 5 bar). The reactor was heated to 70 °C and stirred for 16 h. The reactor was then cooled to rt and vented to ambient pressure. The reaction mixture was evaporated. Purification on silica gel eluting with 20% EtOAc in *n*-heptane afforded the title compound as a colorless oil (116 mg, 0.29 mmol, **90%**). **^{1}H NMR** (500 MHz, DMSO-d_6, 100 °C) δ 7.37-7.22 (m, 5H), 6.76 (dt, J = 8.3, 2.0 Hz, 1H), 5.04 (dt, J = 8.3, 3.9 Hz, 1H), 4.65 (d, J = 26.7 Hz, 1H), 4.53 (d, J = 16.7 Hz, 1H), 4.15 (q, J = 7.0 Hz, 1H), 3.63 (s, 3H), 3.55-3.42 (m, 2H), 2.11-1.96 (m, 2H), 1.39

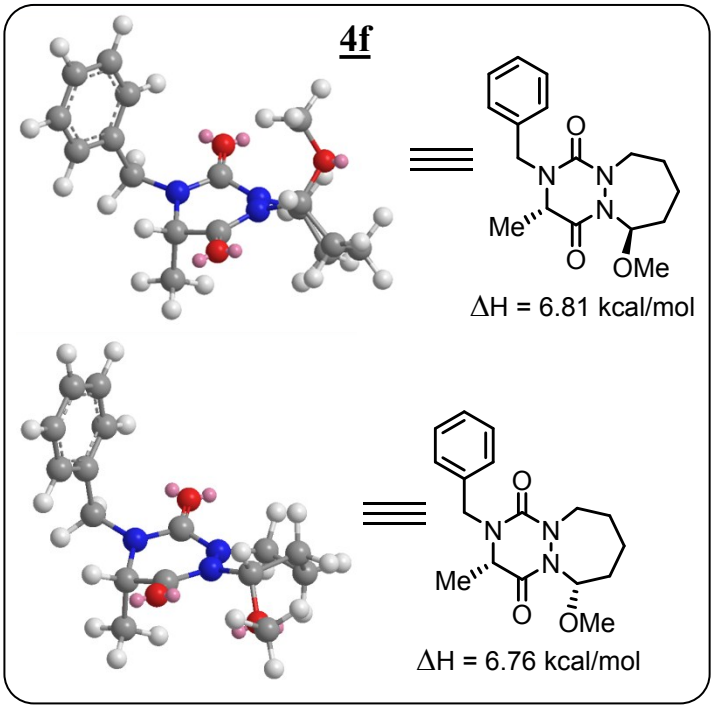
(s, 9H), 1.37 (d, J = 7.0 Hz, 3H); **^{13}C NMR** (125 MHz, DMSO-d_6, 80 °C) δ 171.2, 160.6, 150.8, 137.6, 127.9, 126.5, 126.4, 125.6, 105.5, 80.9, 55.7, 51.2, 50.7, 45.7, 27.4, 20.0, 14.4; **HRMS** (ESI-TOF) : calcd. for $C_{21}H_{29}N_3O_5Na$ $[M+Na]^+$: 426.20049, found : 426.20069; **R_f** : 0.19 (20% EtOAc in *n*-heptane); $[\propto]_D^{20} = -53.4\ (c\ 0.13, MeOH)$.

***tert*-Butyl 2-(benzyl((*S*)-1-methoxy-1-oxopropan-2-yl)carbamoyl)-6-methoxytetrahydropyridazine-1(2*H*)-carboxylate (6)**. To a solution of (*S*)-*tert*-butyl 2-((1-methoxy-1-oxopropan-2-yl)(phenyl)carbamoyl)-3,4-dihydropyridazine-1(2H)-carboxylate (**5**, 118 mg, 0.29 mmol, 1 equiv.) in methanol (9.9 mL) was added pyridinium *p*-toluenesulfonate (68 mg, 0.15 mmol, 0.5 equiv.). The mixture was heated to 80 °C for 5 h, cooled to rt, quenched with a satured solution of $NaHCO_3$ and evaporated to a slurry. Water was added to the mixture and the aqueous layer was extracted three times with EtOAc. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated. Analysis of the crude product by NMR showed a diastereoselectivity of 60:40. The residue was purified on semi-preparative HPLC eluting with 20-80% MeCN in water and freeze-drying to obtain a colorless oil (99 mg, 0.23 mmol, **78%**). **^{1}H NMR** (500 MHz, DMSO-d_6, 50 °C) δ 7.41-7.18 (m, 5H), 5.06-4.98 (m, 1H), 4.80-4.68 (m, 0.6H), 4.60 (d, J = 16.1 Hz, 0.4H), 4.49 (d, J = 16.2 Hz, 0.6H), 4.37 (d, J = 16.1 Hz, 0.4H), 4.16 (q, J = 7.1 Hz, 0.4H), 3.94 (q, J = 7.1 Hz, 0.6H), 3.66-3.52 (m, 3.4H), 3.44-3.38 (m, 0.6H), 3.19-3.12 (m, 1.8H), 3.05-2.95 (m, 2.2H), 1.97-1.10 (m, 16H); **^{13}C NMR** (125 MHz, DMSO-d_6, 50 °C) δ 172.3, 172.0, 160.9, 160.1, 155.0, 154.5, 138.6, 138.5, 127.9, 127.7, 127.3, 126.7, 126.5, 126.4, 88.5, 87.1, 81.7, 81.4, 56.3, 56.2, 51.8, 51.8, 51.3, 51.3, 50.1, 44.4, 44.0, 27.5, 27.4, 26.5, 26.3, 17.1, 16.7, 15.6, 14.5; **HRMS** (ESI-TOF) : calcd. for $C_{22}H_{33}N_3O_6Na$ $[M+Na]^+$: 458.22671, found : 458.22586; **R_f** : 0.22 (50% EtOAc in *n*-heptane).

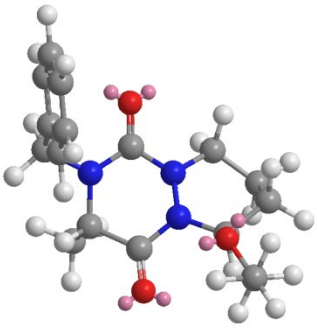
Minimized structure of compounds 4a,f-j and 6 based on dynamic molecular calculations.

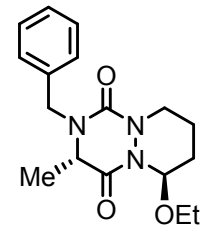
Heat of formations (ΔH) are calculated based on MM2 calculations in CS Chem3D Ultra with minimization energy to minimum RMS Gradient of 0.010.



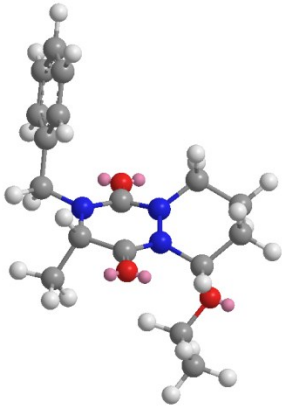


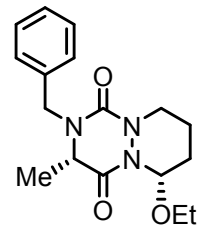
4g





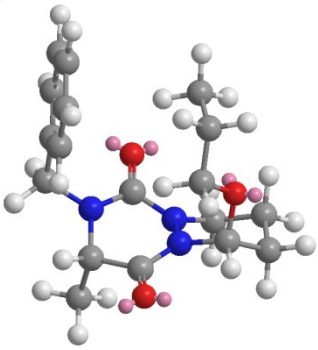
ΔH = 5.87 kcal/mol

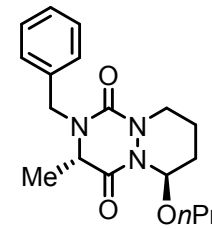




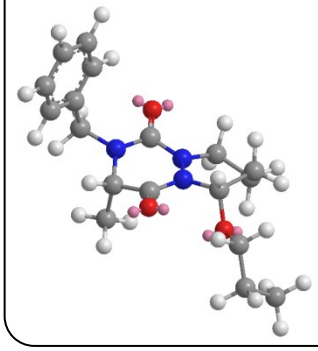
ΔH = 8.00 kcal/mol

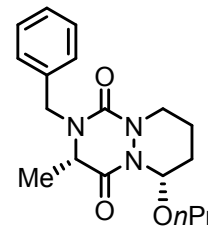
4h





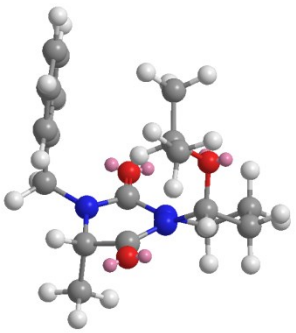
ΔH = 3.91 kcal/mol

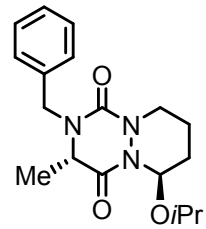




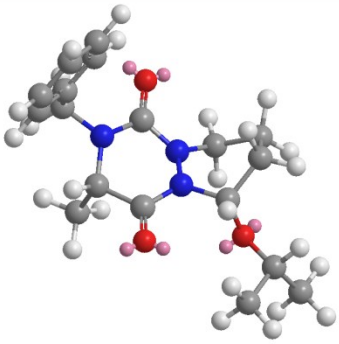
ΔH = 7.74 kcal/mol

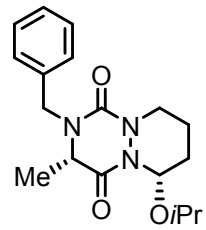
4i





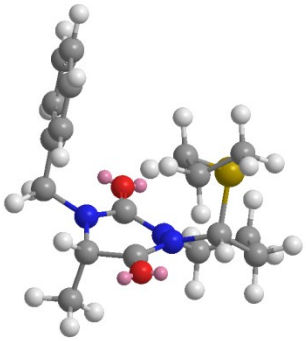
ΔH = 6.12 kcal/mol

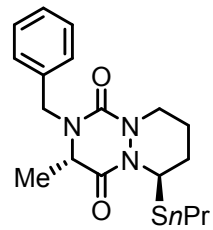




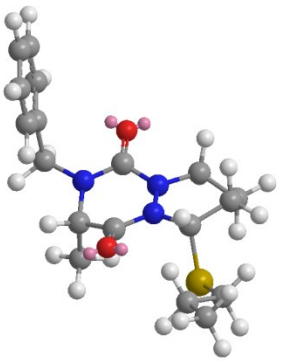
ΔH = 10.77 kcal/mol

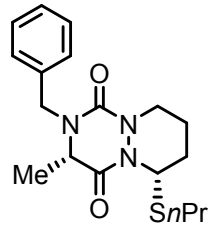
4j





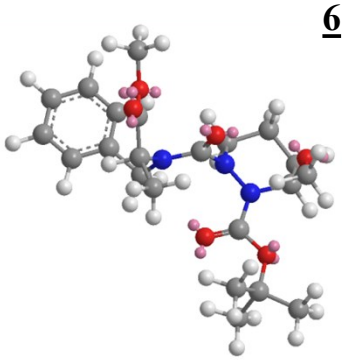
ΔH = 1.11 kcal/mol

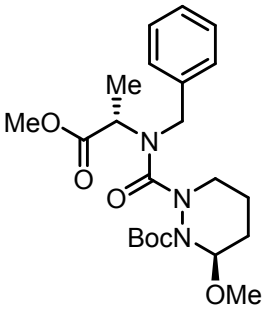




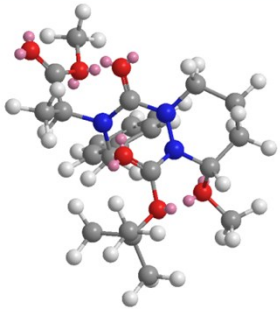
ΔH = 2.91 kcal/mol

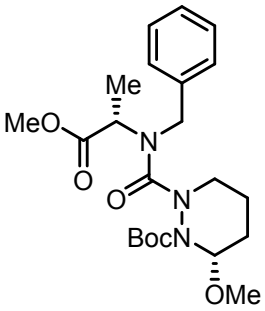
6





ΔH = 18.38 kcal/mol

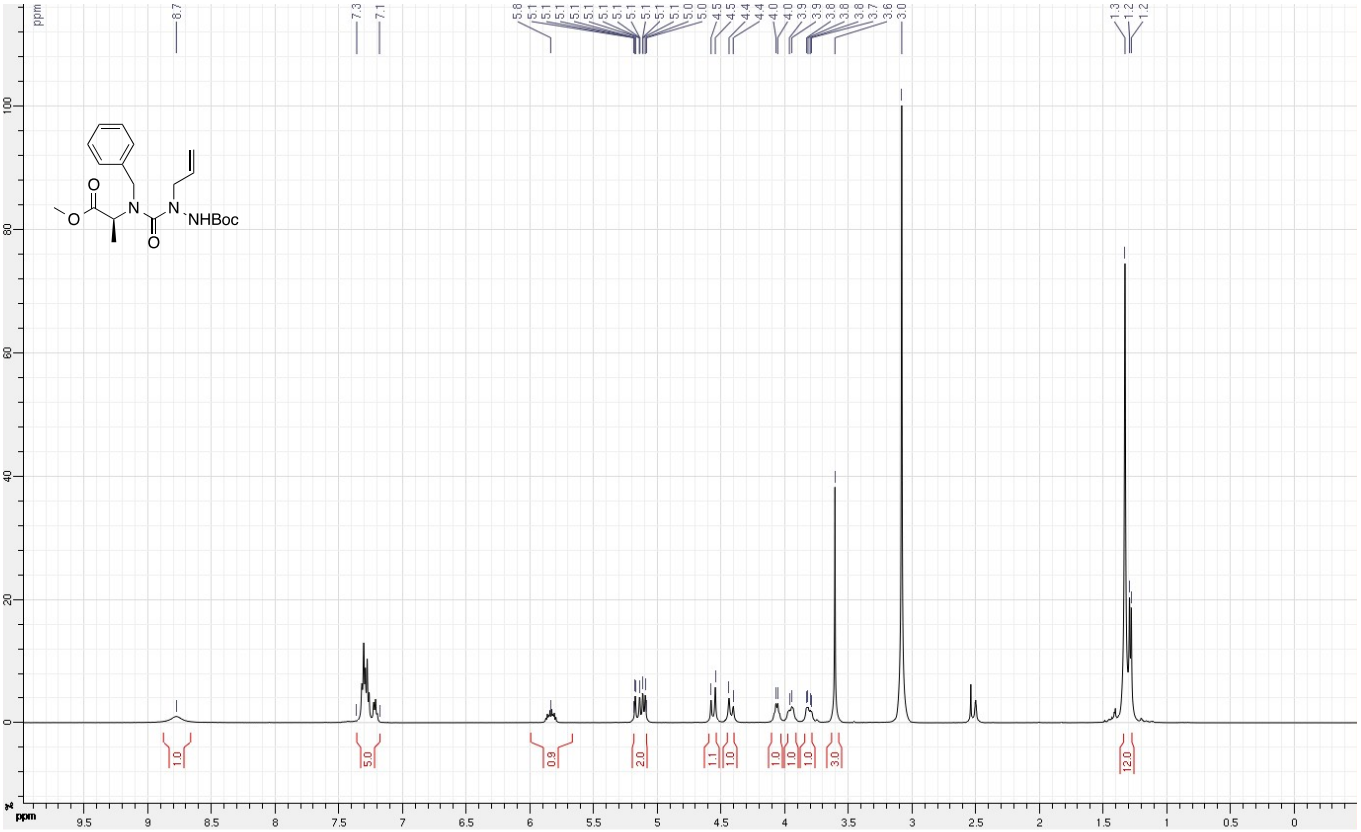




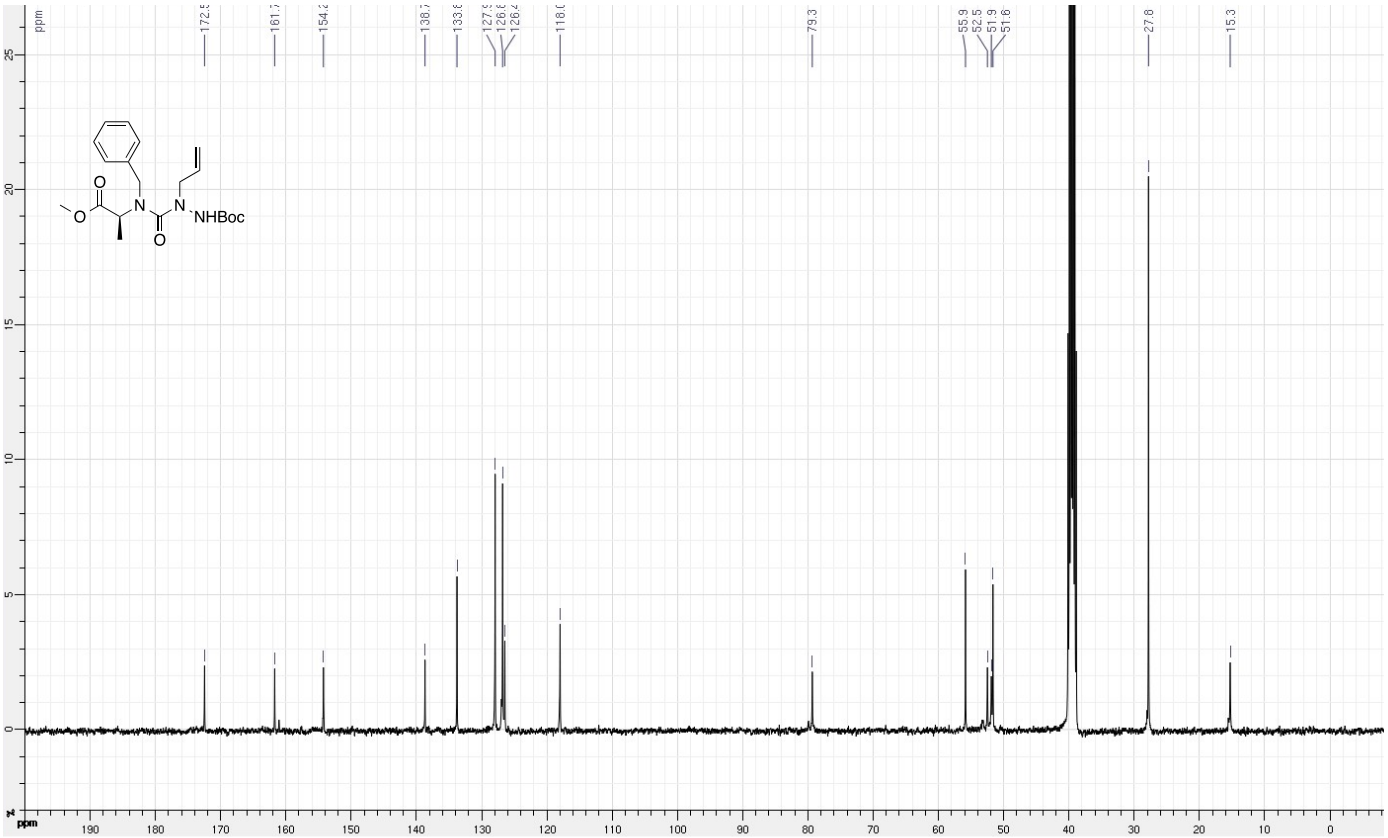
ΔH = 19.77 kcal/mol

[1]H and [13]C NMR spectrum of compounds 1a-f, 4d,g-j, 5 and 6

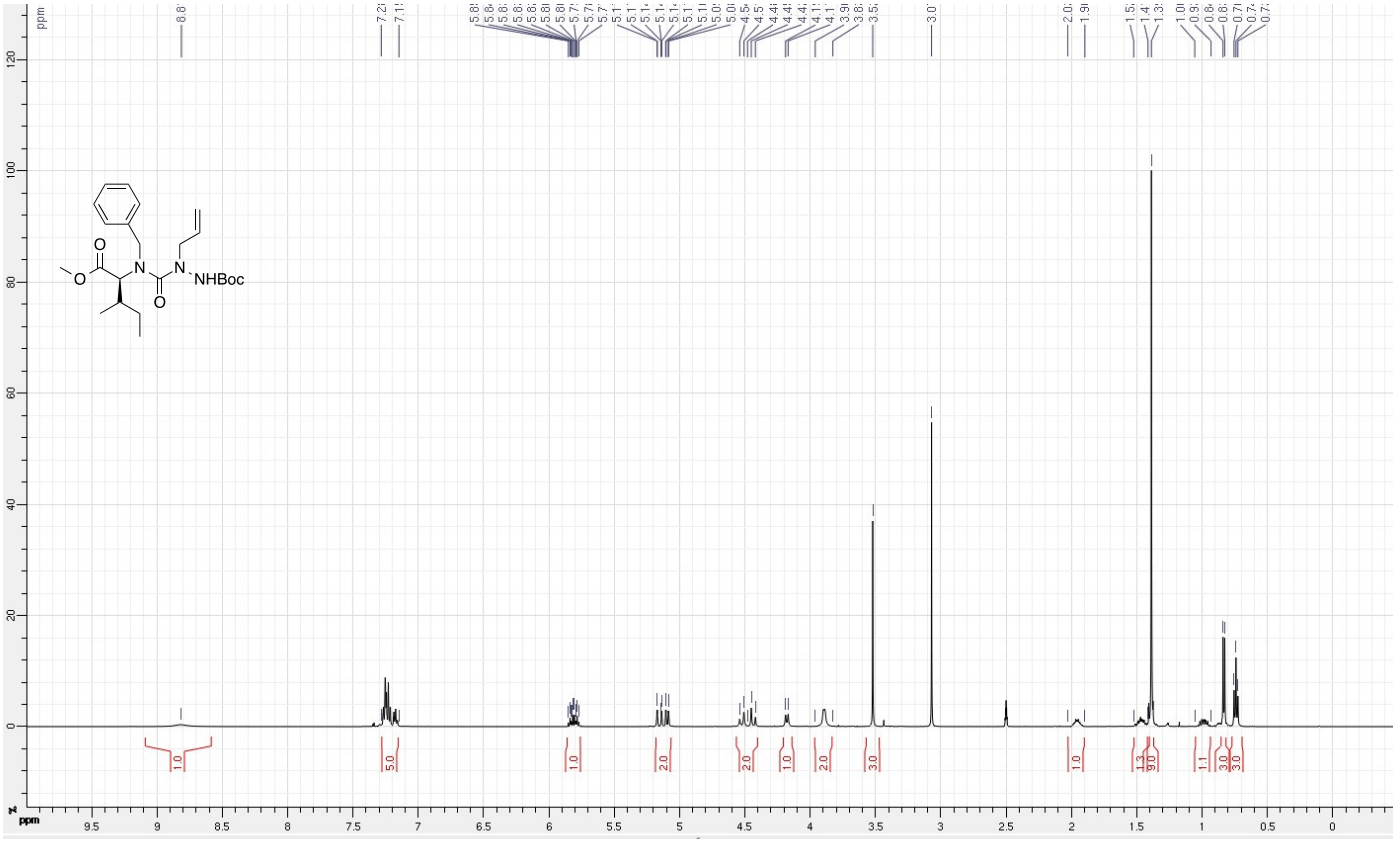
[1]H NMR of compound **1a** (500 MHz, DMSO-d_6, 90 °C) :



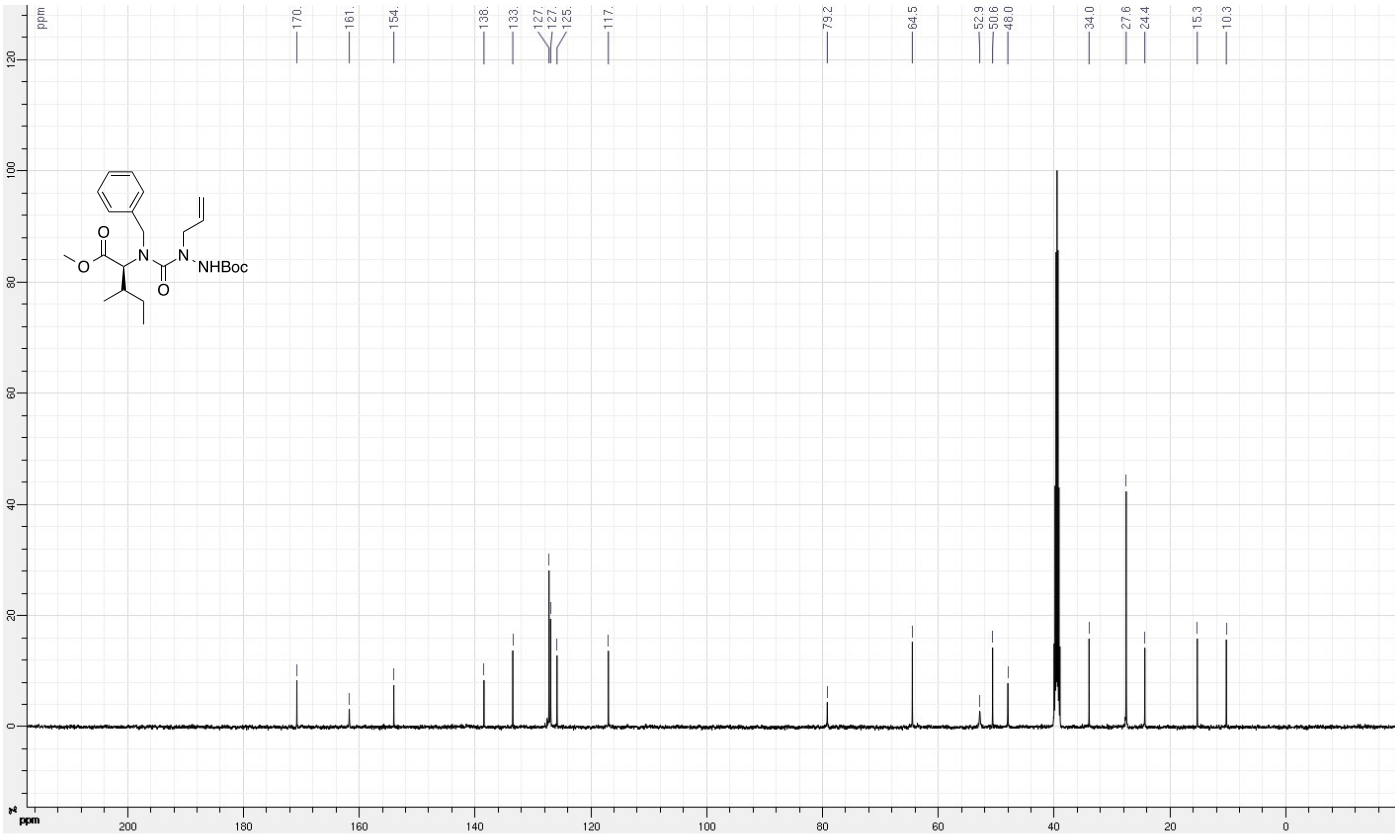
[13]C NMR of compound **1a** (100 MHz, DMSO-d_6) :



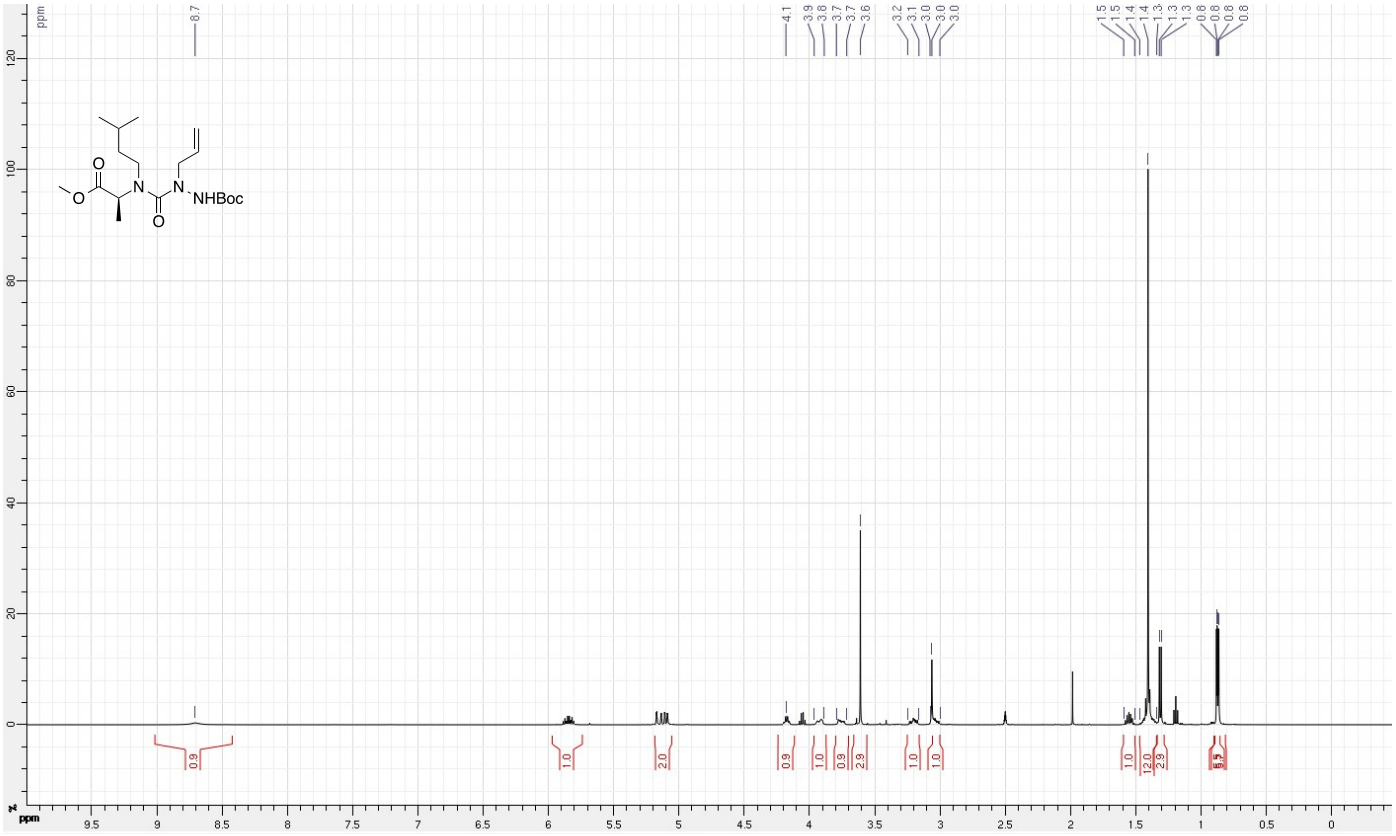
^{1}H NMR of compound **1b** (500 MHz, DMSO-d_6, 80 °C) :



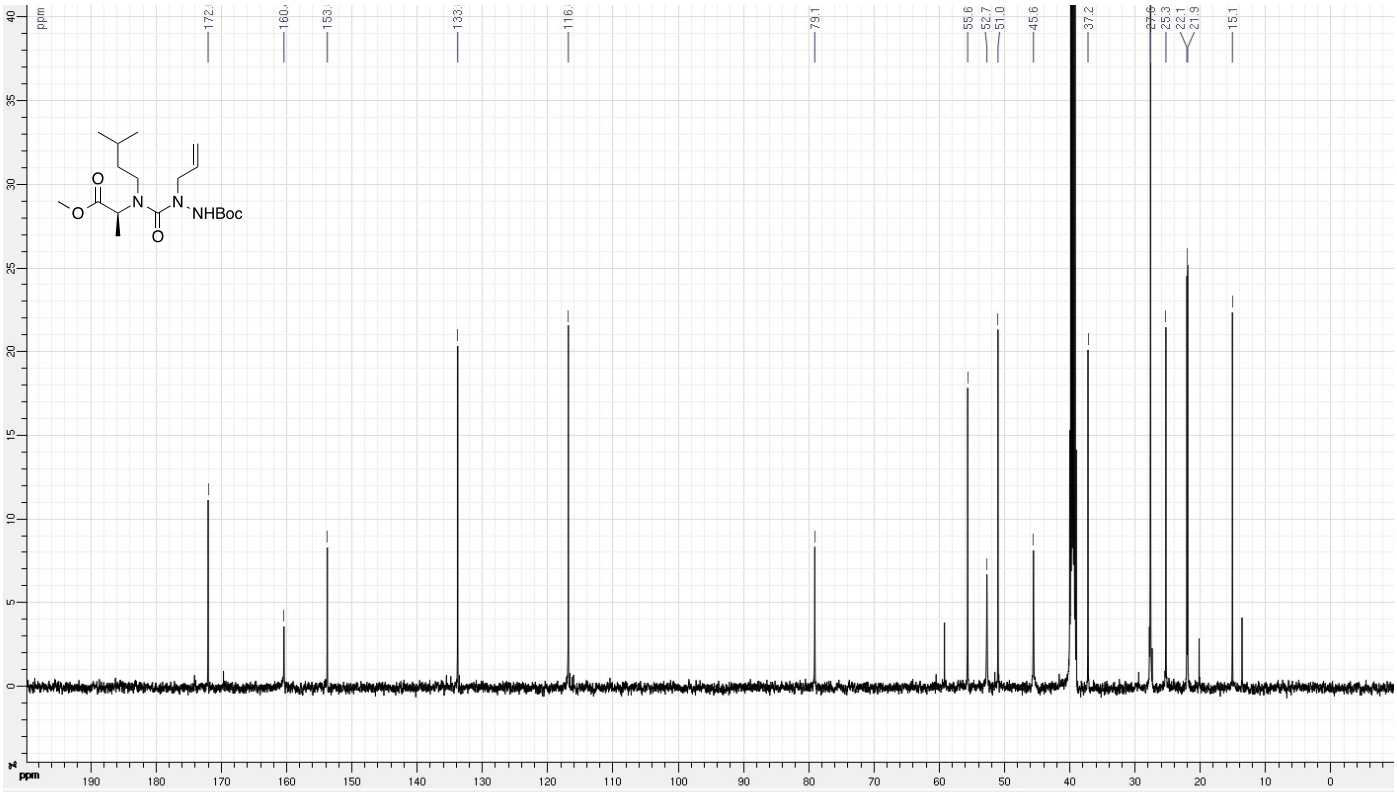
^{13}C NMR of compound **1b** (125 MHz, DMSO-d_6, 80 °C) :



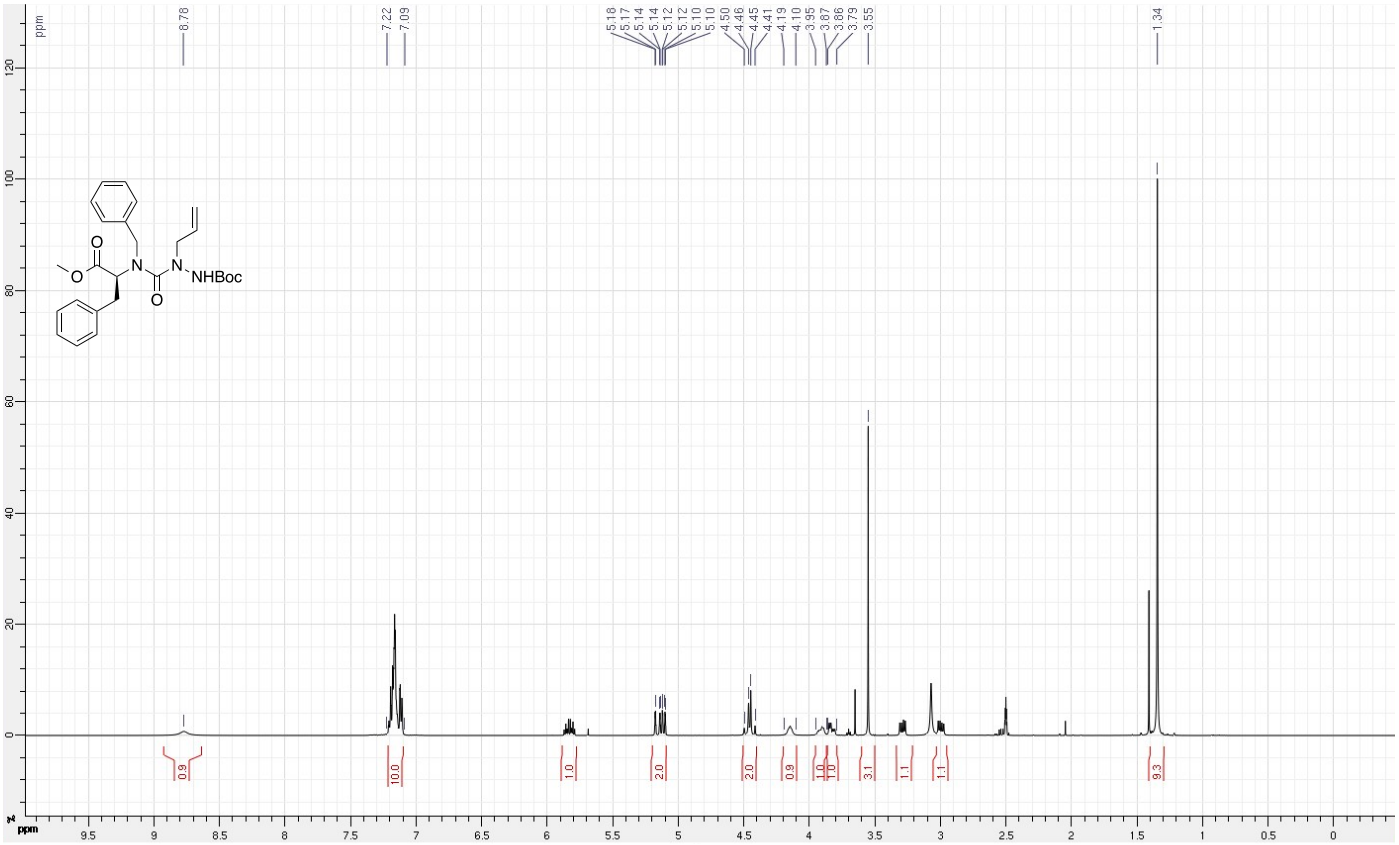
^{1}H NMR of compound **1c** (500 MHz, DMSO-d_6, 80 °C) :



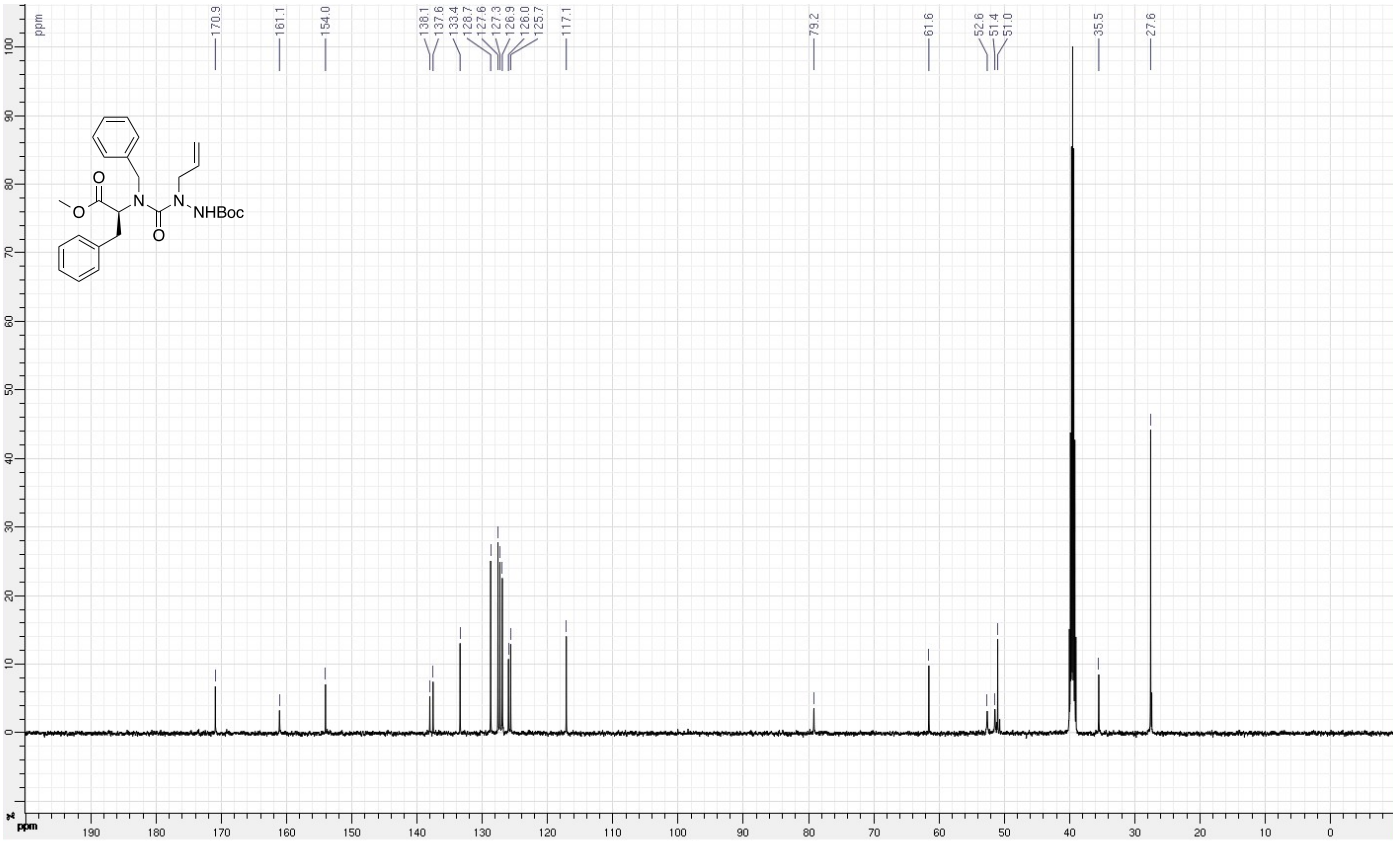
^{13}C NMR of compound **1c** (125 MHz, DMSO-d_6, 80 °C) :



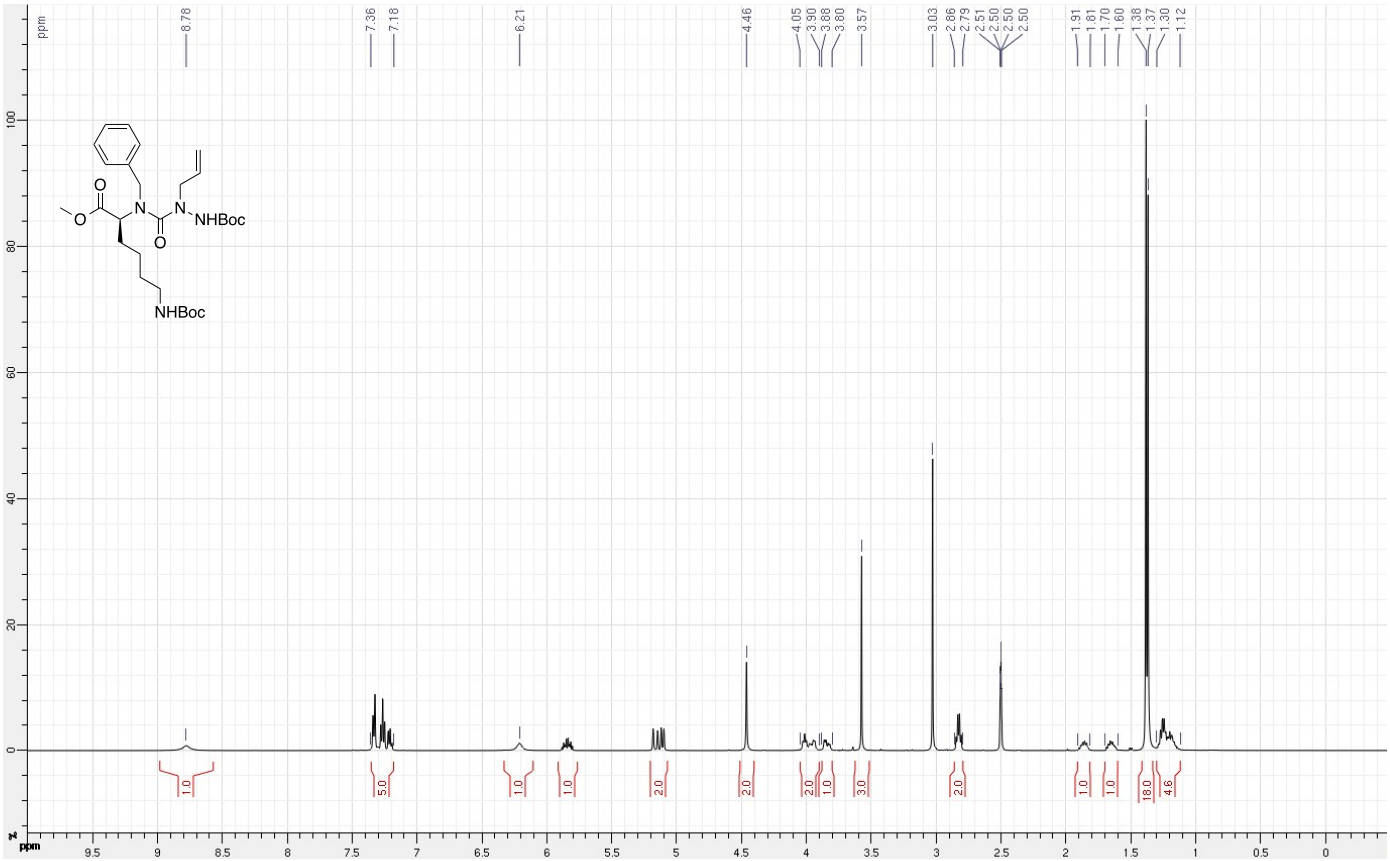
^{1}H NMR of compound **1d** (500 MHz, DMSO-d_6, 80 °C) :



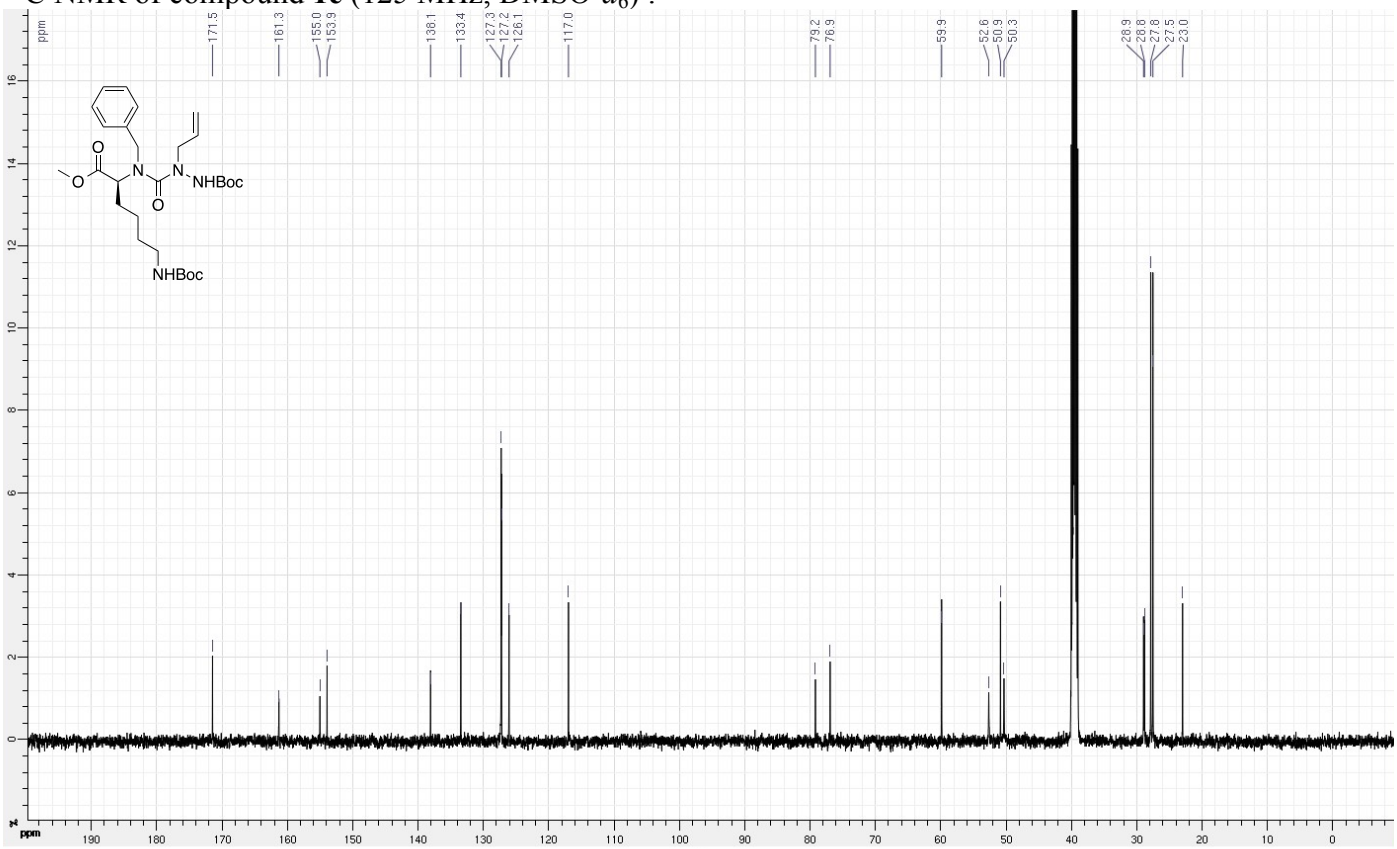
^{13}C NMR of compound **1d** (125 MHz, DMSO-d_6, 80 °C) :



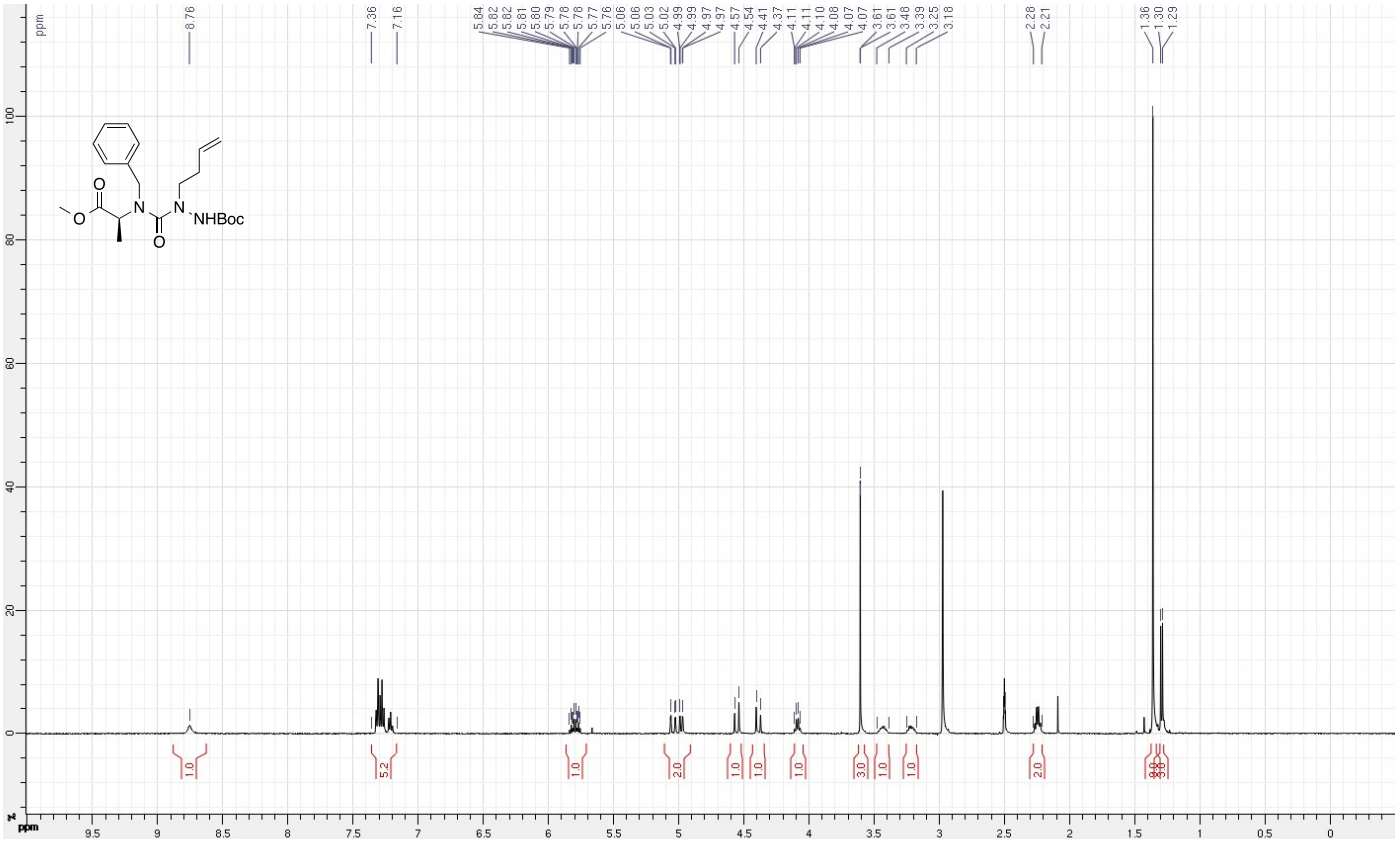
^{1}H NMR of compound **1e** (500 MHz, DMSO-d_6, 90 °C) :



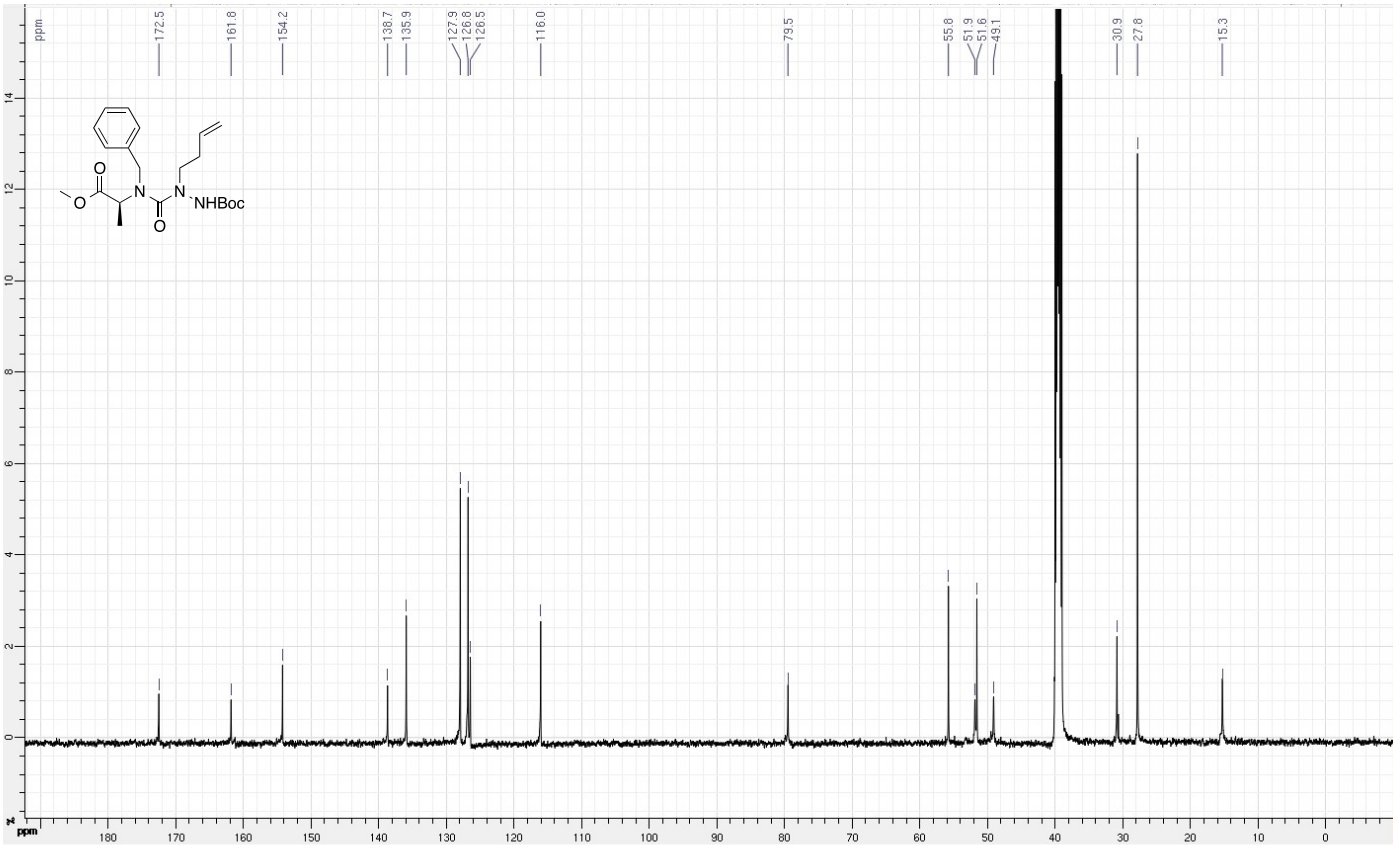
^{13}C NMR of compound **1e** (125 MHz, DMSO-d_6) :



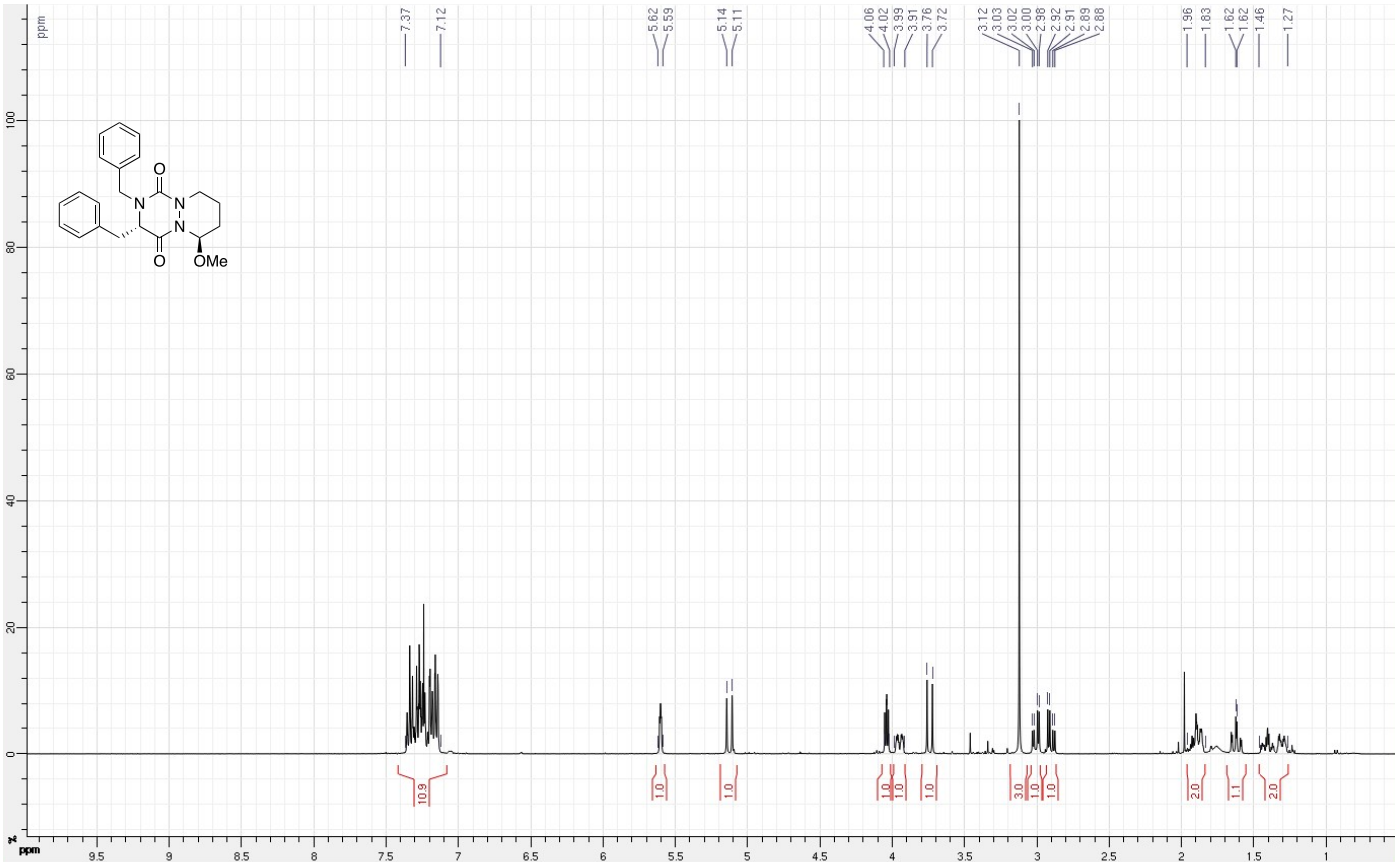
^{1}H NMR of compound **1f** (500 MHz, DMSO-d_6, 100 °C) :



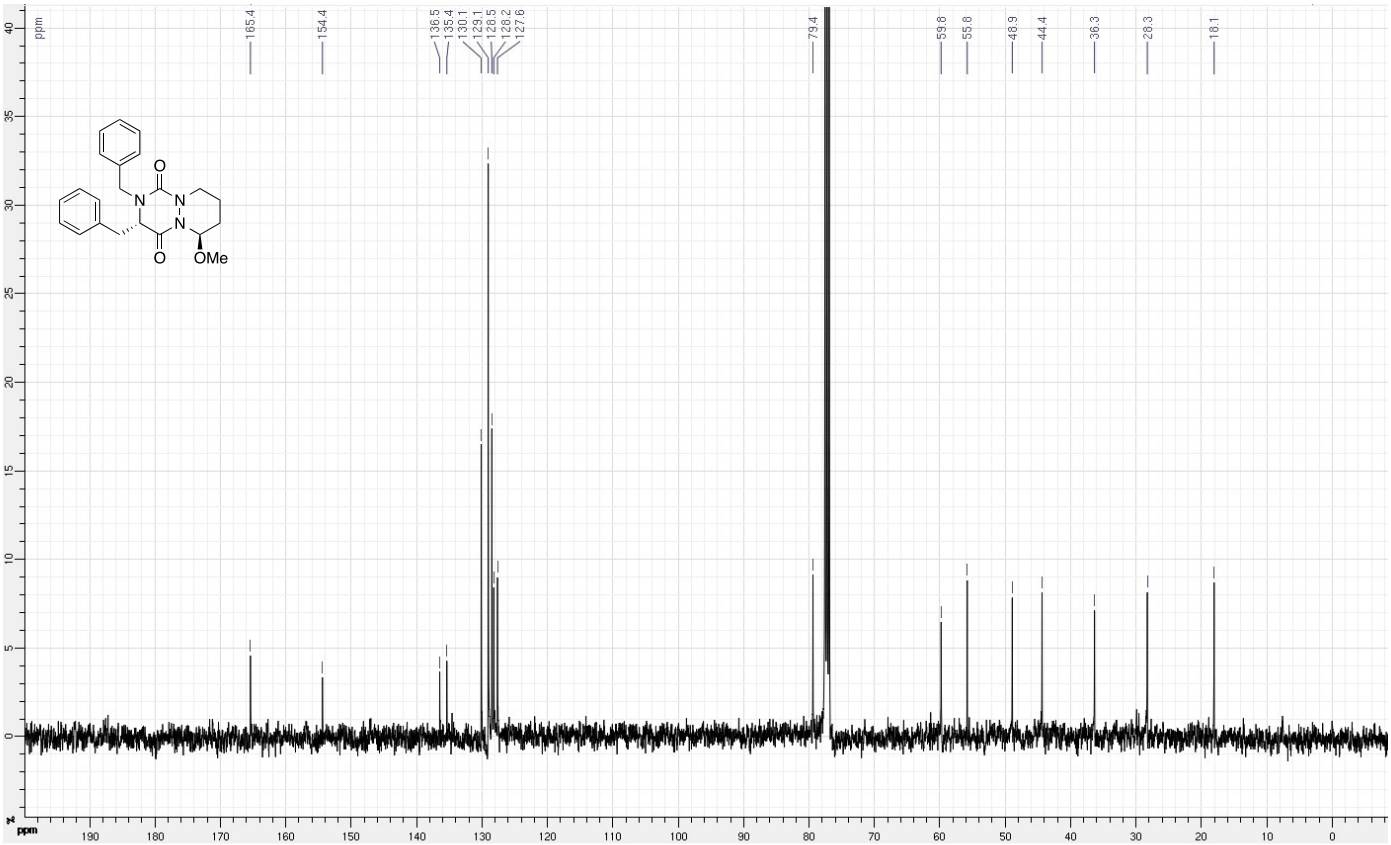
^{13}C NMR of compound **1f** (125 MHz, DMSO-d_6) :



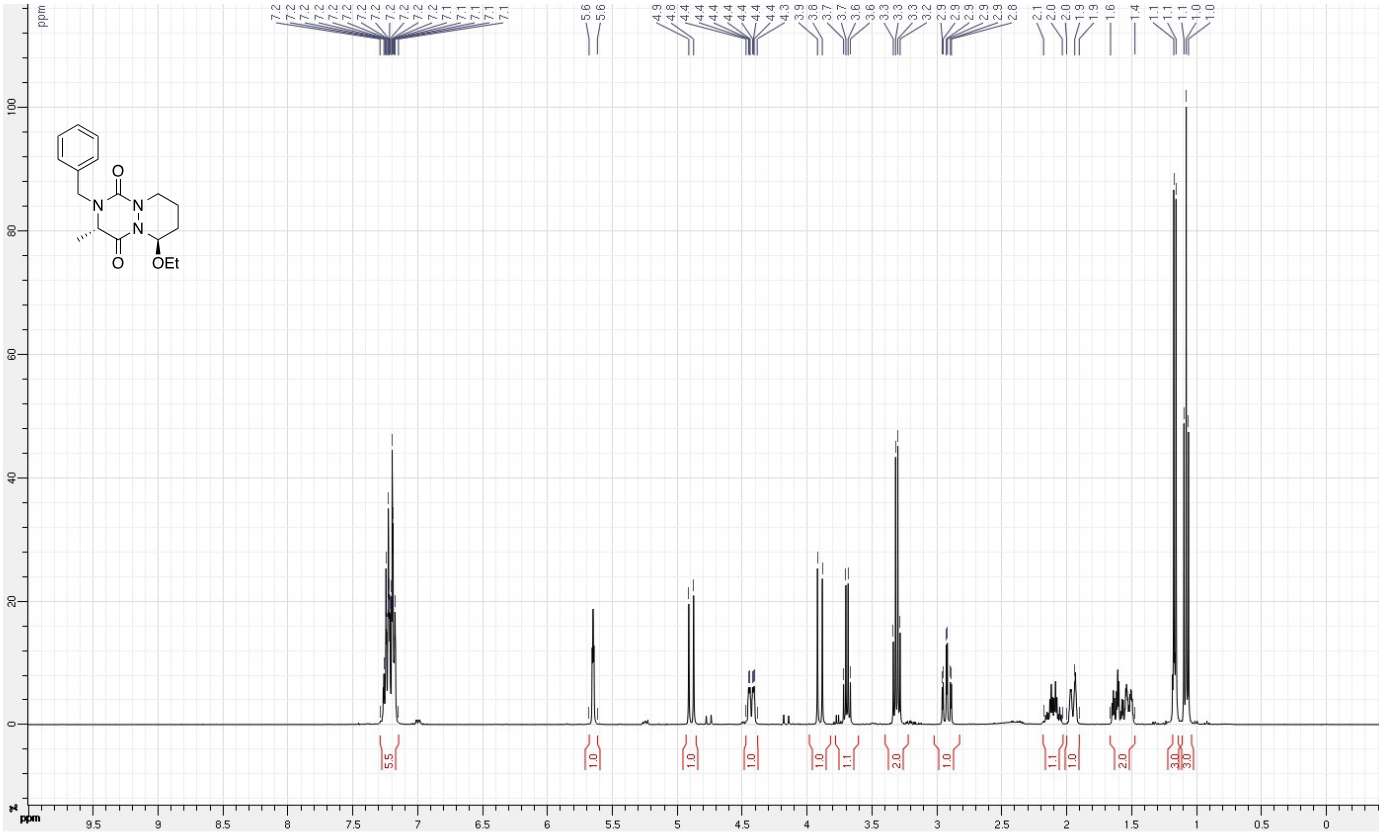
^{1}H NMR of compound **4d** (400 MHz, $CDCl_3$) :



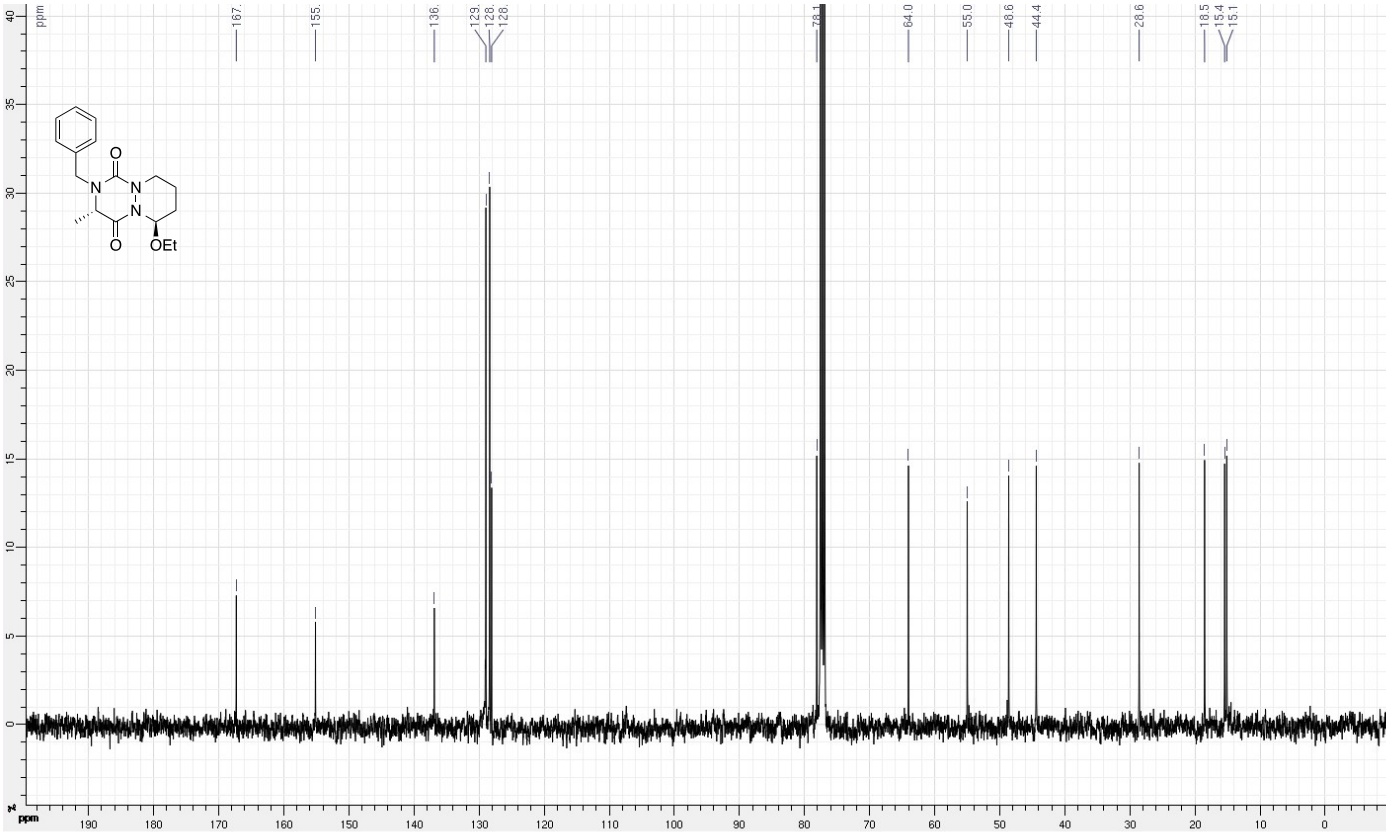
^{13}C NMR of compound **4d** (100 MHz, $CDCl_3$) :



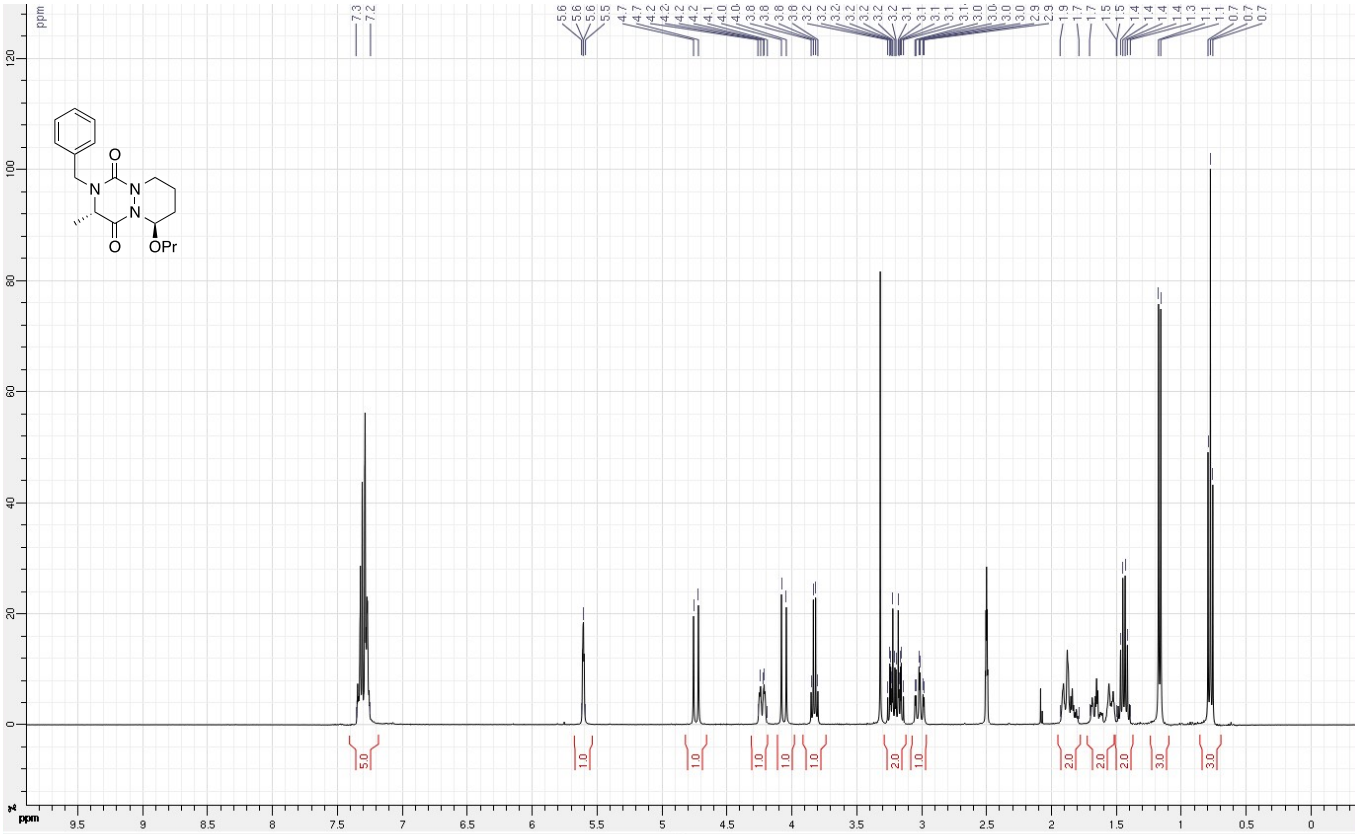
^{1}H NMR of compound **4g** (400 MHz, $CDCl_3$) :



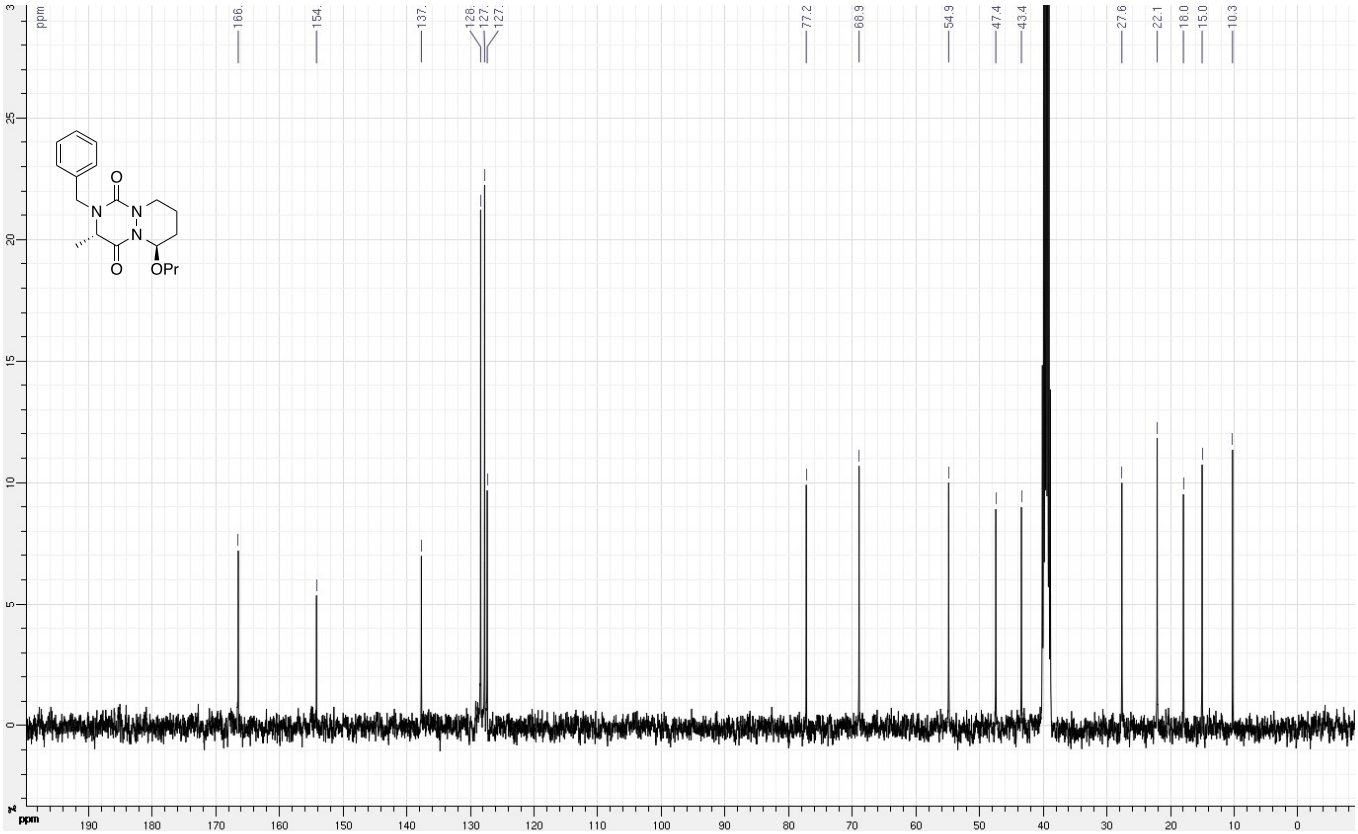
^{13}C NMR of compound **4g** (100 MHz, $CDCl_3$) :



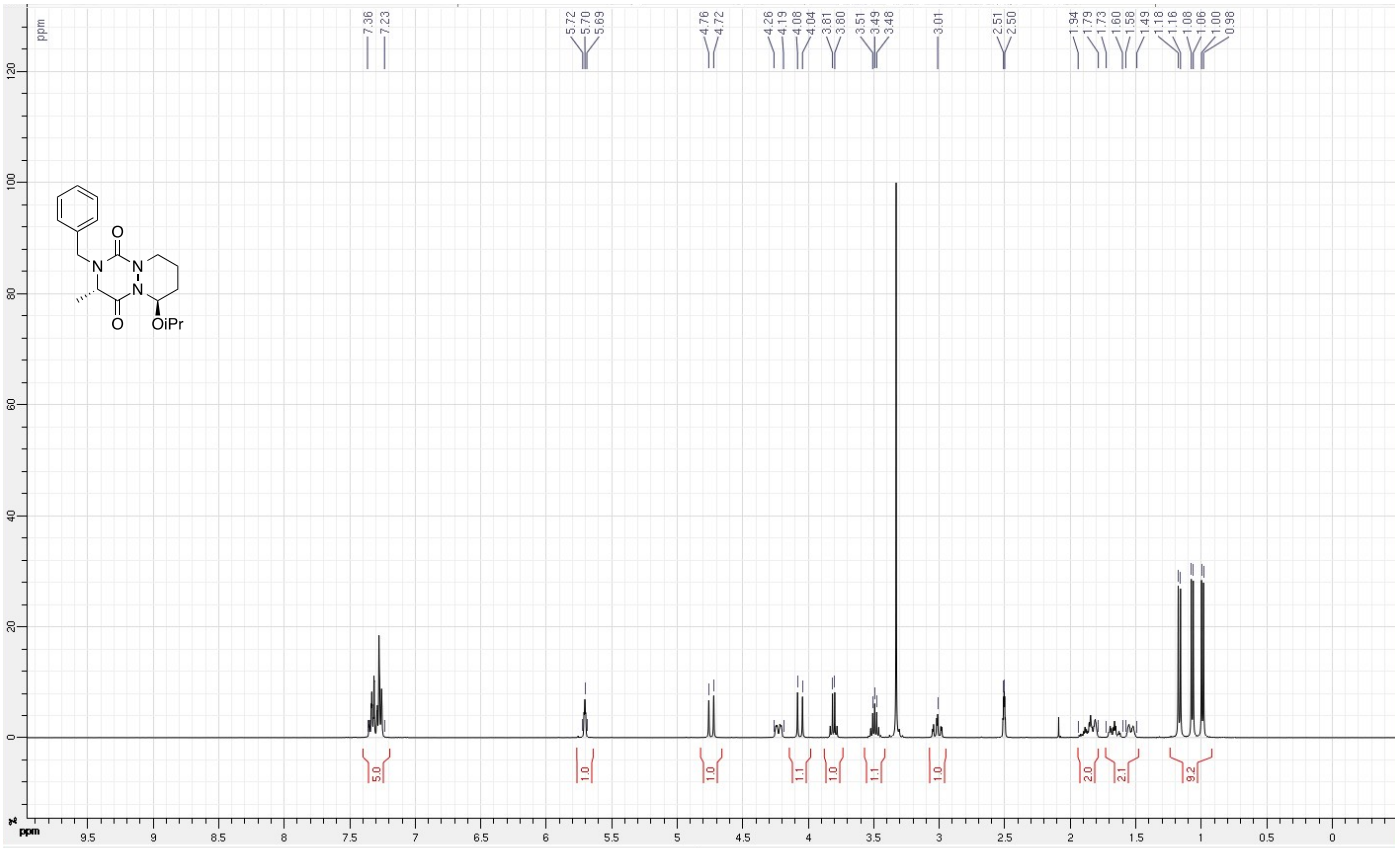
^{1}H NMR of compound **4h** (400 MHz, DMSO-d_6) :



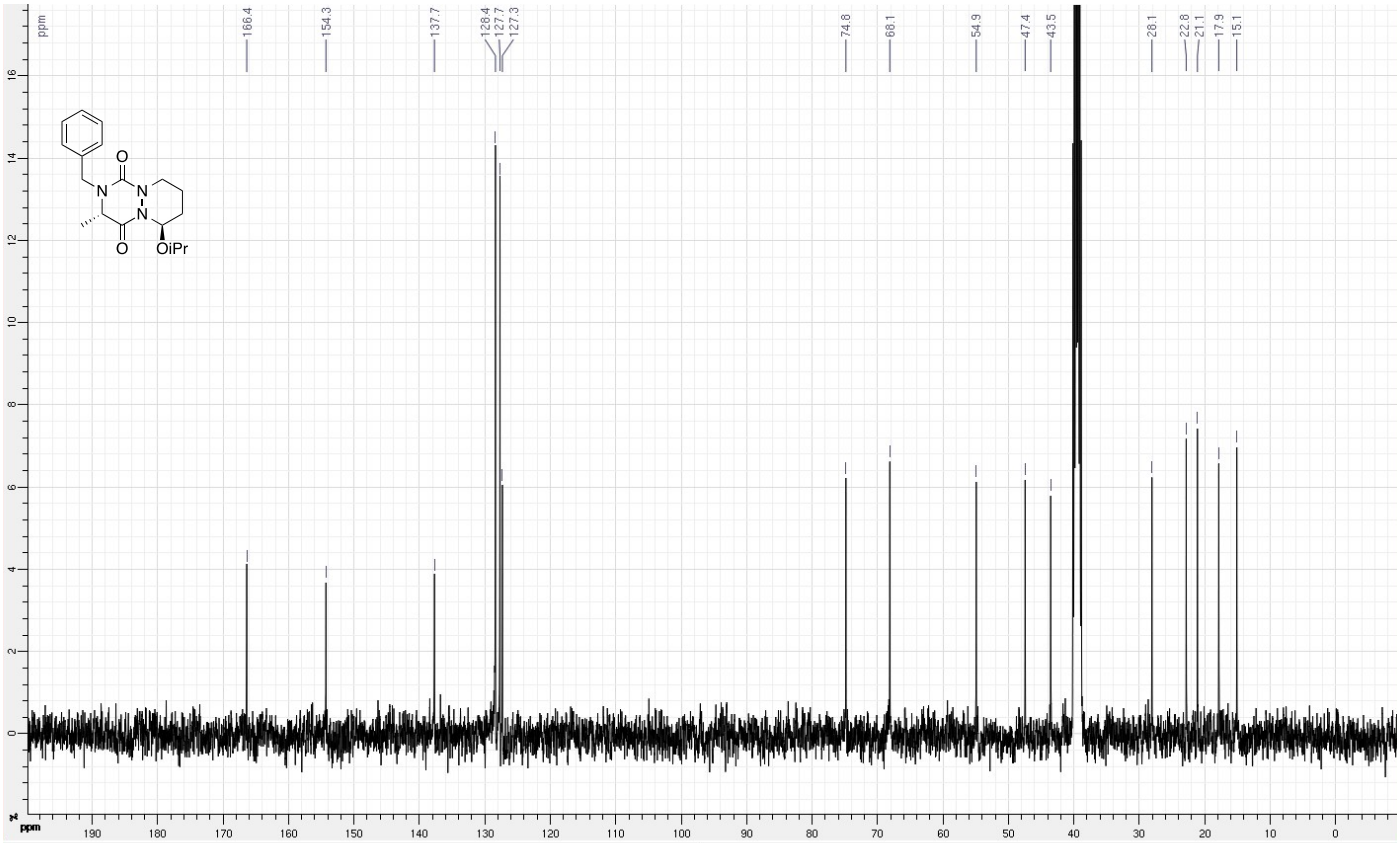
^{13}C NMR of compound **4h** (100 MHz, DMSO-d_6) :



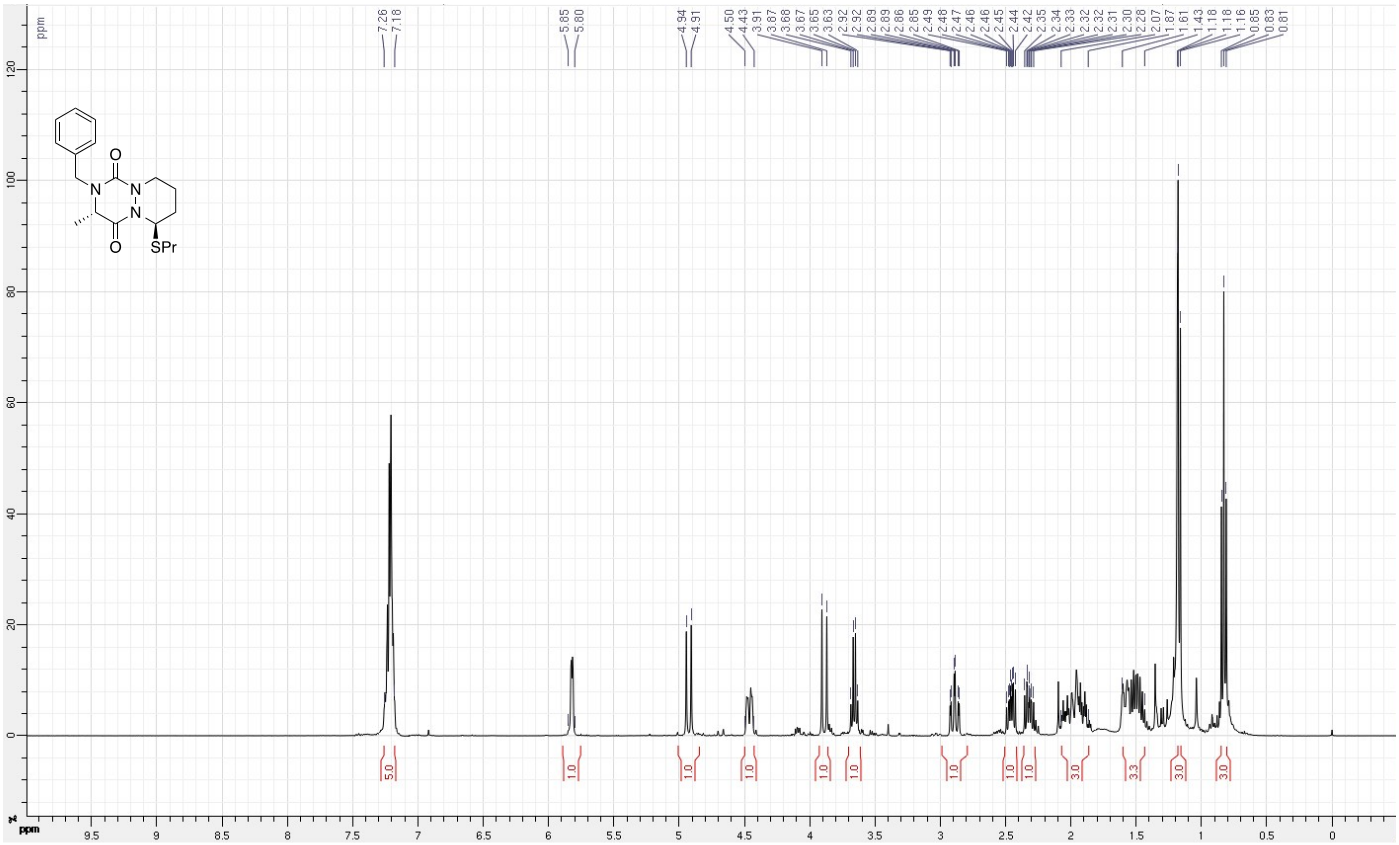
^{1}H NMR of compound **4i** (400 MHz, DMSO-d_6) :



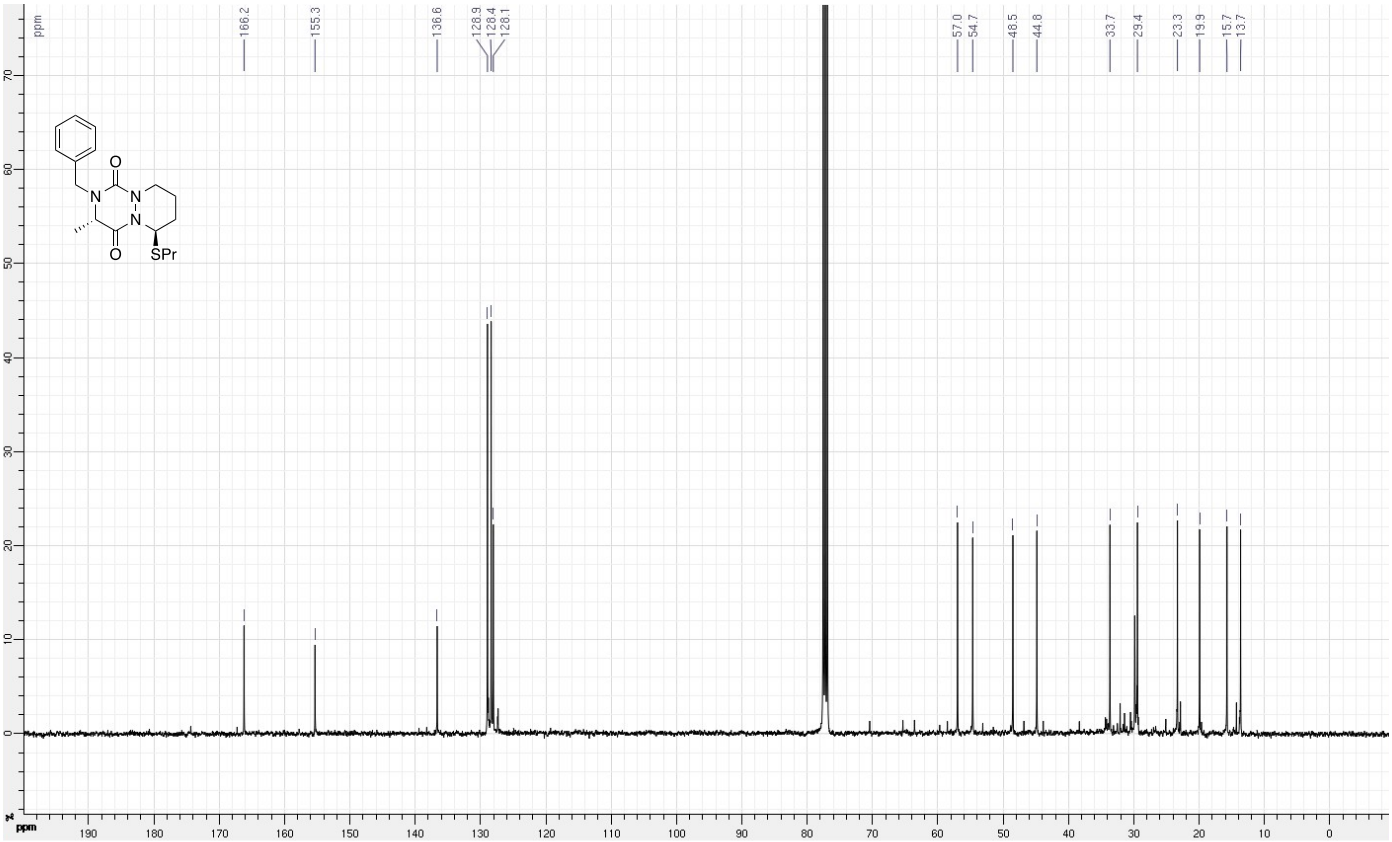
^{13}C NMR of compound **4i** (100 MHz, DMSO-d_6) :



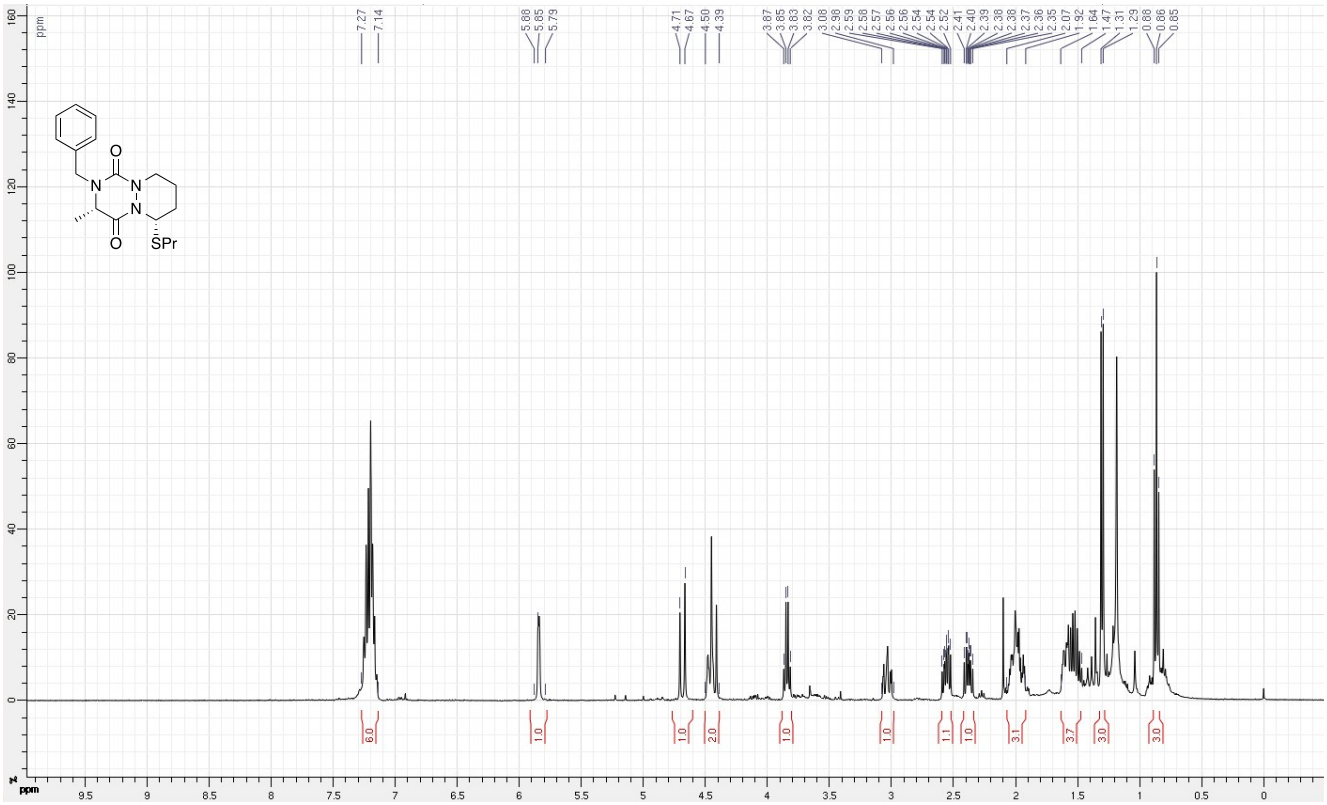
^{1}H NMR of compound **4j - *trans*** (400 MHz, $CDCl_3$) :



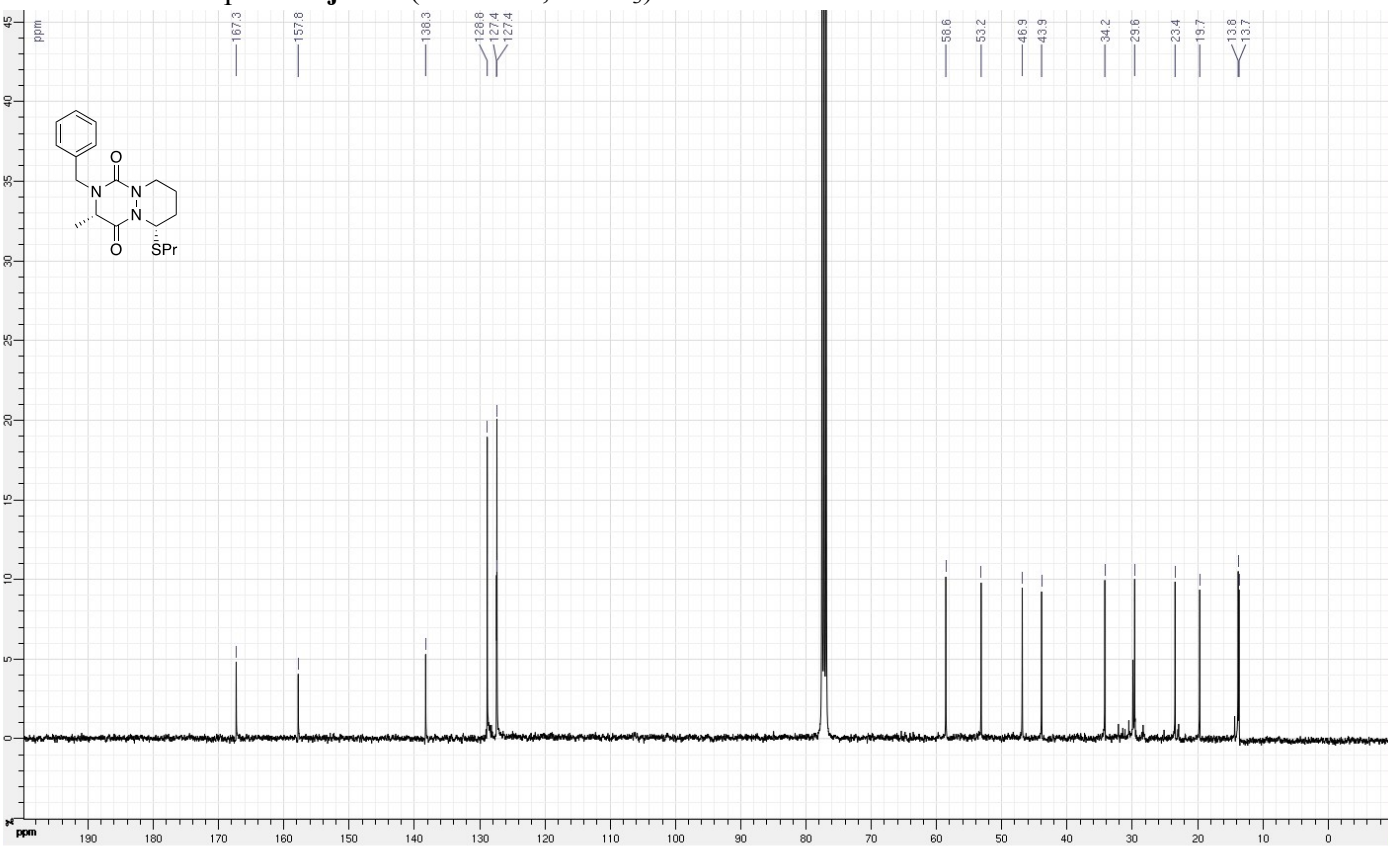
^{13}C NMR of compound **4j - *trans*** (100 MHz, $CDCl_3$) :



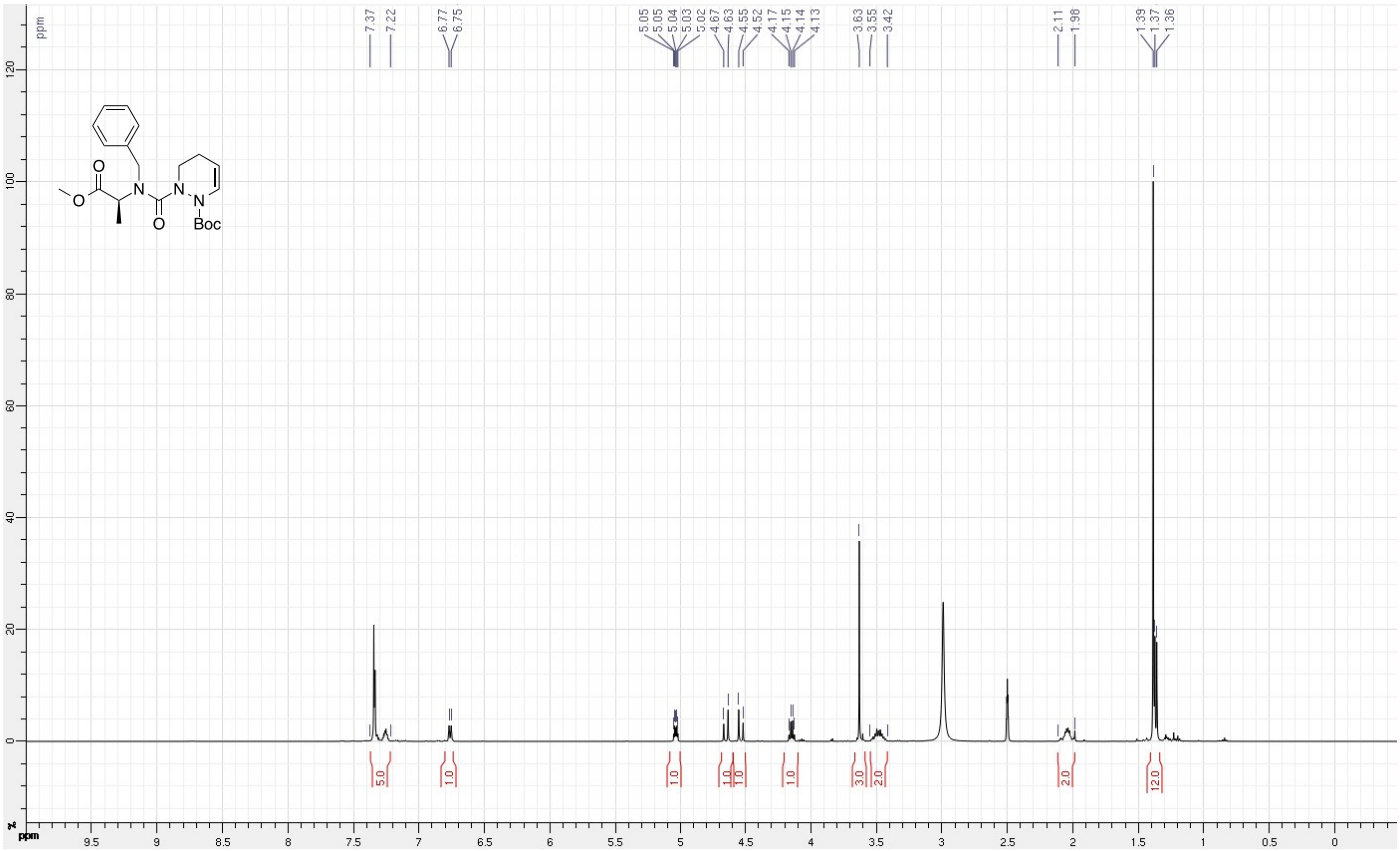
^{1}H NMR of compound **4j - *cis*** (400 MHz, $CDCl_3$) :



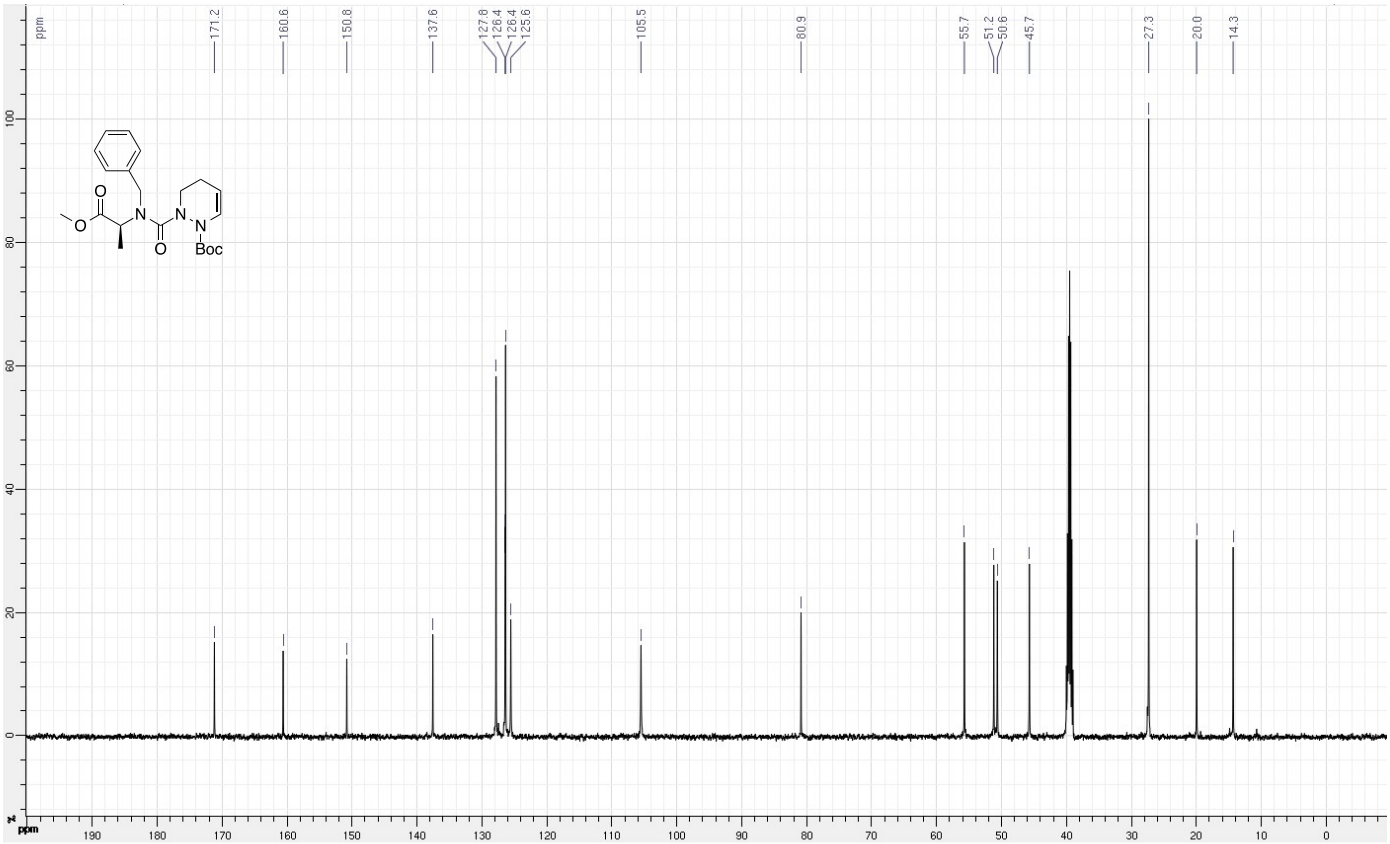
^{13}C NMR of compound **4j - *cis*** (100 MHz, $CDCl_3$) :



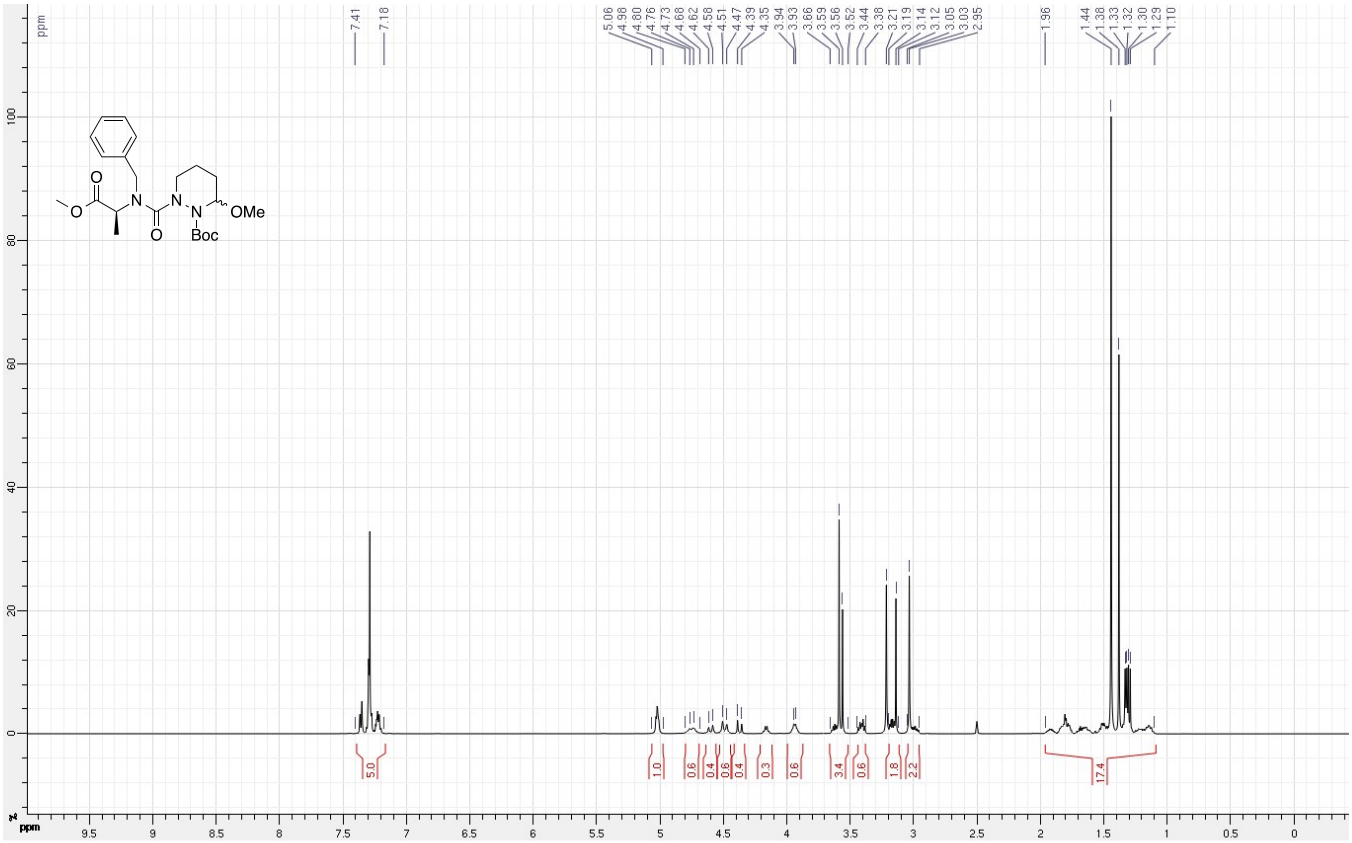
^{1}H NMR of compound **5** (500 MHz, DMSO-d_6, 100 °C) :



^{13}C NMR of compound **5** (125 MHz, DMSO-d_6, 80 °C) :



^{1}H NMR of compound **6** (500 MHz, DMSO-d_6, 50 °C) :



^{13}C NMR of compound **6** (125 MHz, DMSO-d_6, 50 °C) :