SUPPORTING INFORMATION

Regio- and Stereospecific Synthesis of C-3 Functionalized Proline Derivatives by Palladium Catalyzed Directed C(sp^3)–H Arylation

Dominic P. Affron, Owen A. Davis, James A. Bull*

Department of Chemistry, Imperial College London, South Kensington, London SW7 2AZ, UK

*E-mail: j.bull@imperial.ac.uk

General Experimental Considerations

All non-aqueous reactions were carried out under an inert atmosphere (argon) with flame-dried glassware, using standard techniques. Anhydrous solvents were obtained by filtration through drying columns (toluene, CH_2Cl_2, MeOH, DMF).

Flash column chromatography was performed using 230-400 mesh silica, with the indicated solvent system according to standard techniques. Analytical thin-layer chromatography (TLC) was performed on precoated glass-backed or aluminium-backed silica gel plates. Visualization of the developed chromatogram was performed by UV absorbance (254 nm) and/or stained with aqueous potassium permanganate solution, a ninhydrin solution in ethanol, or a phosphomolybdic acid solution in ethanol.

Infrared spectra (ν_{max}, FTIR ATR) were recorded in reciprocal centimeters (cm^{-1}).

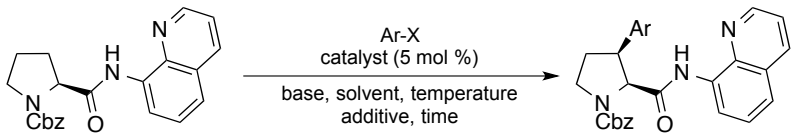
Nuclear magnetic resonance spectra were recorded on 400 or 500 MHz spectrometers. Chemical shifts for ^1H NMR spectra are recorded in parts per million from tetramethylsilane with the solvent resonance as the internal standard (chloroform: δ = 7.27 ppm, methanol: δ = 3.31 ppm, DMSO: δ = 2.50 ppm). Data is reported as follows: chemical shift (multiplicity [s = singlet, d = doublet, t = triplet, m = multiplet and br = broad], coupling constant (in Hz), integration and assignment). ^{13}C NMR spectra were recorded with complete proton decoupling. Chemical shifts are reported in parts per million from tetramethylsilane with the solvent resonance as the internal standard ($^{13}CDCl_3$: 77.0 ppm, $^{13}CD_3OD$: δ = 49.0 ppm, $(^{13}CD_3)_2SO$: δ = 39.5 ppm). ^{19}F NMR spectra were recorded with complete proton decoupling. Chemical shifts are reported in parts per million, referenced to the standard monofluorobenzene at δ = –113.5 ppm. Assignments of ^1H and ^{13}C spectra were based upon the analysis of δ and *J* values, as well as DEPT, COSY and HSQC experiments where appropriate. All Cbz and Boc containing compounds appeared as a mixture of rotamers in the NMR spectra at rt; therefore NMR experiments for these compounds were carried out at 373 K to coalesce the signals, which is indicated in parentheses where appropriate. Even at elevated temperature the Cbz phenyl signals remain broad and can often under-integrate.

Melting points are uncorrected.

Observed rotations (α') were recorded at the indicated temperature (T ºC) and were converted to the corresponding specific rotations $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{T}}$.

Commercial reagents were used as supplied, or purified by standard techniques where necessary.

Optimization of C–H Arylation of *N*-Cbz Proline AQ Amide 1



The following reaction variables were screened during optimization (**Table S1**).

Solvent	toluene, *t*-BuOH, 1,4-dioxane, 1,2-dichloroethane, DMF, (no solvent)
Pd and Ni Source	$PdCl_2$, $Pd(TFA)_2$, $Pd(acac)_2$, $NiCl_2$, $NiCl_2$·glyme, $Pd_2(dba)_3$, $Pd(OAc)_2$
Base	KOAc, K_2CO_3, Ag_2CO_3, AgOAc
Equiv Base	0.5, 1.0, 1.2, 1.5, 1.8, 2.0, 2.2
Additives	PivOH
ArX	Tol-Cl, Tol-Br, Tol-I, Ph-OTf
Equiv ArI	1.2, 1.5, 1.8, 2.0, 3.0, 4.0
Concentration (M, wrt amide 1)	0.1, 0.2, 0.3, 0.4, 0.5, 0.7, 1.0, 2.0, 4.0, (neat)
Scale (mmol)	0.15–0.30, 0.5, 0.7, 1.0
Time (h)	1, 2, 4, 6, 8, 10, 12, 15, 18, 20
Temperature (ºC)	85, 110, 130
Vial Size	0.5–2 mL, 2–10 mL
Miscellaneous	air atmosphere, non-dry toluene

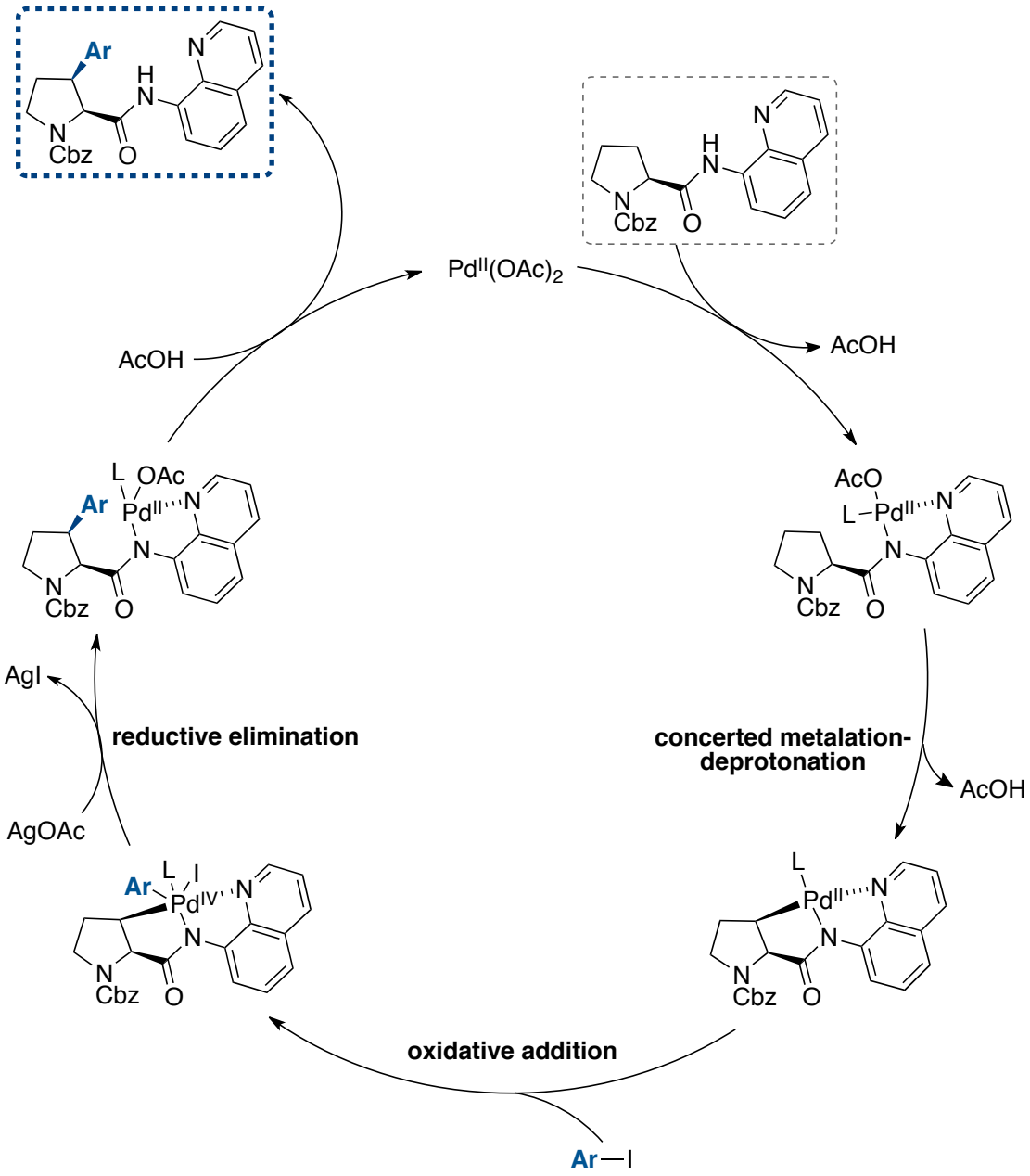
We assessed bases other than AgOAc, to determine whether AgOAc could be substituted with a cheaper alternative. However, alternative bases did not compete with AgOAc. For comparison, when employing iodotoluene (4 equiv), $Pd(OAc)_2$ (5 mol%) and toluene (1.0 M) on a 0.20 mmol scale at 110 ºC for 15 h, the following yields were obtained, using 2.2 equiv of base:

AgOAc 97%
Ag_2CO_3 19%
KOAc 6%
K_2CO_3 0%

Attempts to extend the method to include alkyl iodides were not successful under these conditions.

Proposed Catalytic Cycle for C–H Arylation of Amide 1

We propose the following cycle, in line with that proposed by Daugulis and others,[1] involving a Pd^{II}/Pd^{IV} redox cycle and a concerted metalation-deprotonation step to form chelated palladacyclic intermediates.



(1) (a) Shabashov, D.; Daugulis, O. *J. Am. Chem. Soc.* **2010**, *132*, 3965. (b) Wei, Y.; Tang, H.; Cong, X.; Rao, B.; Wu, C.; Zeng, X. *Org. Lett.* **2014**, *16*, 2248.

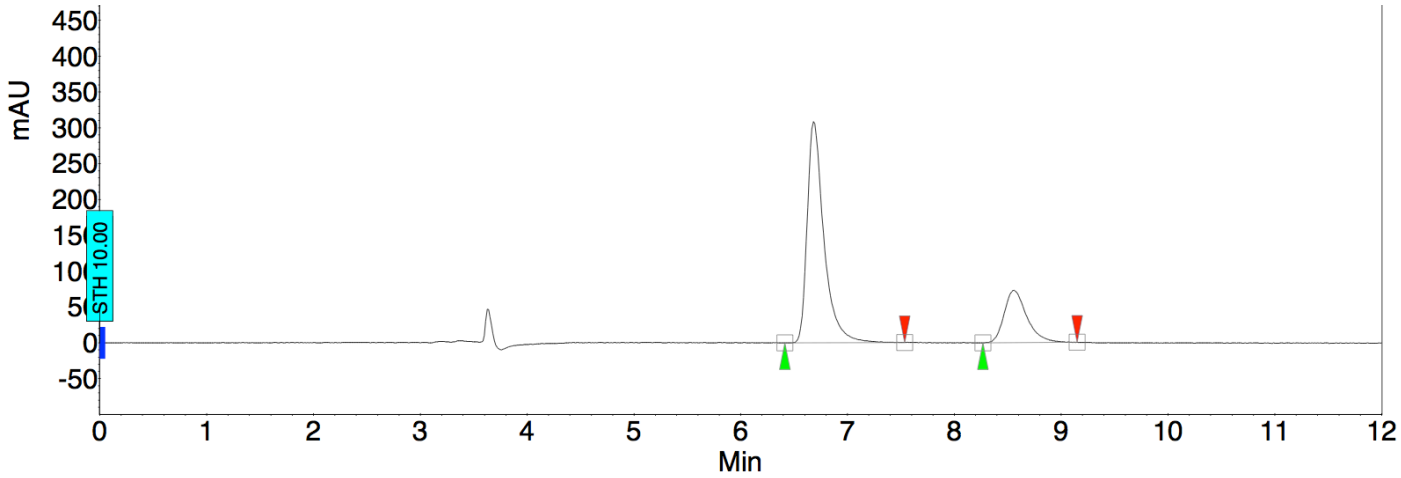
Enantiopurity of Arylated Products: HPLC Traces for 1 and 6a

In order to ensure no loss of enantiopurity in the products from both the amide bond forming reaction and the C–H arylation reaction, both D- and L- enantiomers of **1** and arylated (4-tolyl) 8-aminoquinolyl proline derivative **6a** were examined by chiral HPLC.

Amide Starting Materials

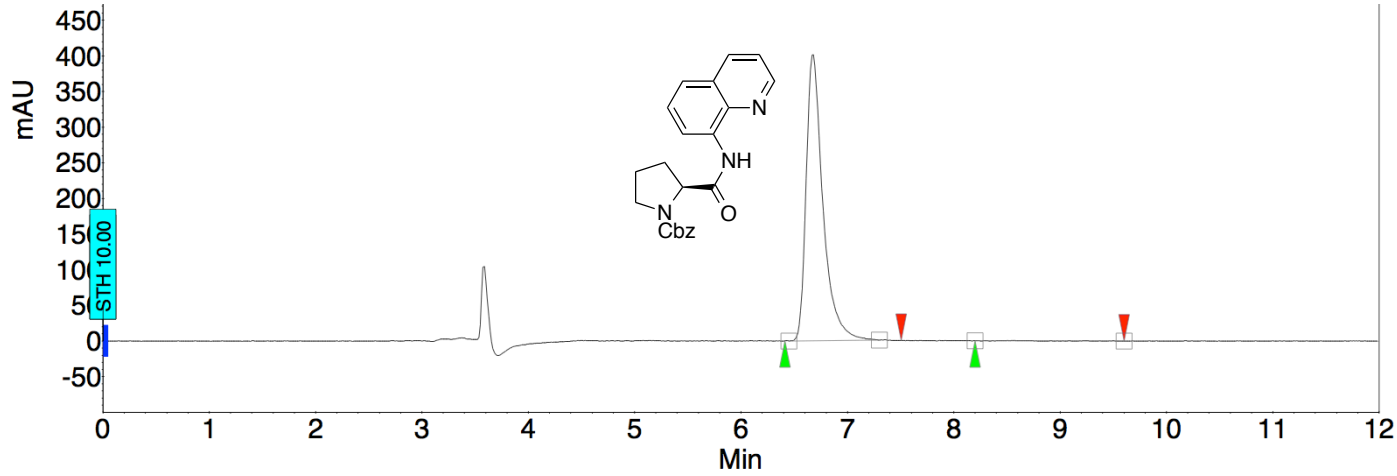
Conditions: Chiralpak IB-3 column, 60:40 *n*-hexane:*i*-PrOH, flow 1 mLmin^{-1}, 25 ºC,wavelength: 224 nm

Scalemic Mixture of Amides 1 and *ent*-1



Index	Name	Time [Min]	Quantity [% Area]	Height [mAU]	Area [mAU.Min]	Area % [%]
1	UNKNOWN	6.680	75.78	308.7	56.0	75.778
2	UNKNOWN	8.560	24.22	73.4	17.9	24.222
Total			100.00	382.1	73.9	100.000

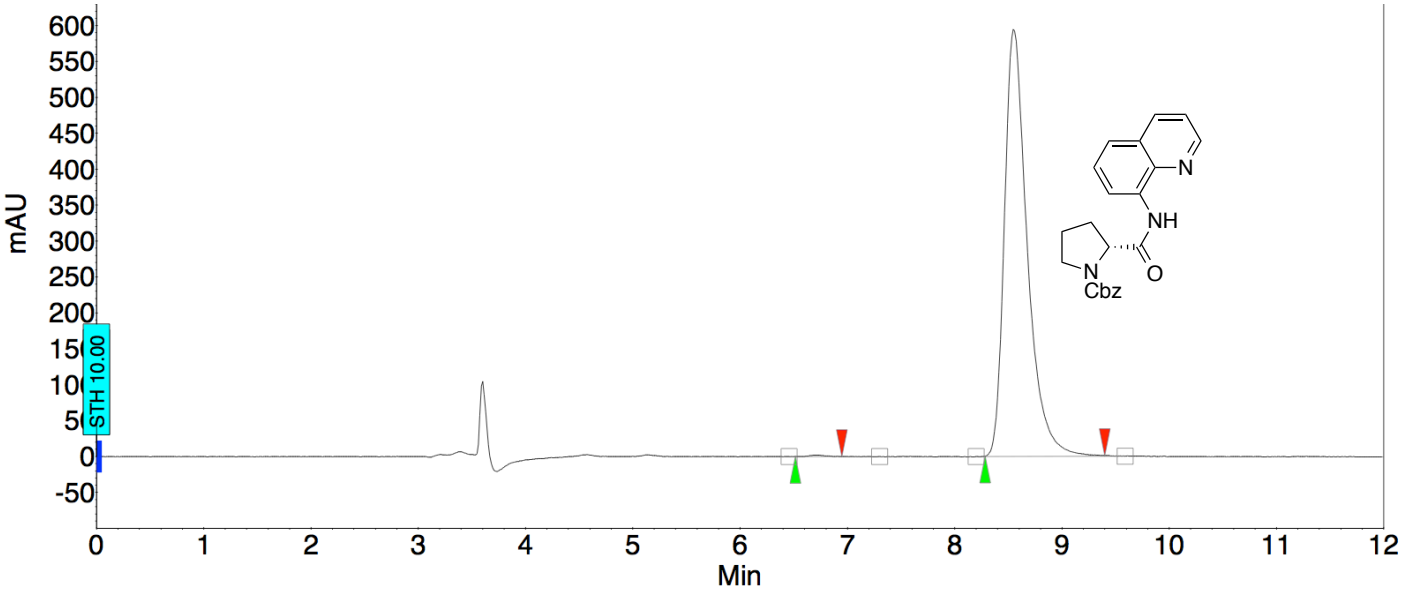
Benzyl (2*S*)-2-[(quinolin-8-yl)carbamoyl]pyrrolidine-1-carboxylate (1)



Index	Name	Time [Min]	Quantity [% Area]	Height [mAU]	Area [mAU.Min]	Area % [%]
1	UNKNOWN	6.680	99.92	401.4	73.3	99.924
2	UNKNOWN	8.573	0.08	0.4	0.1	0.076
Total			100.00	401.8	73.3	100.000

ee = 99.8%

Benzyl (2*R*)-2-[(quinolin-8-yl)carbamoyl]pyrrolidine-1-carboxylate (*ent*-1)



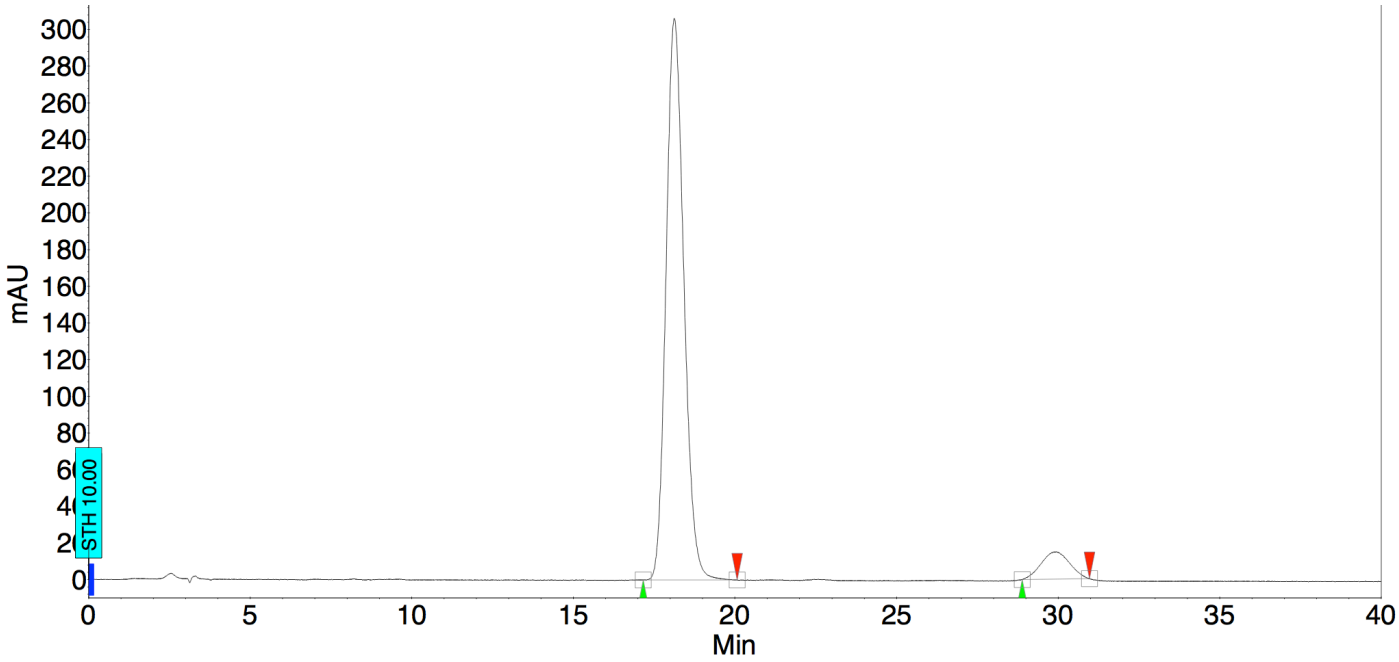
Index	Name	Time [Min]	Quantity [% Area]	Height [mAU]	Area [mAU.Min]	Area % [%]
2	UNKNOWN	6.720	0.25	2.2	0.4	0.254
1	UNKNOWN	8.546	99.75	594.5	146.7	99.746
Total			100.00	596.7	147.1	100.000

ee = 99.5%

Arylated Compounds

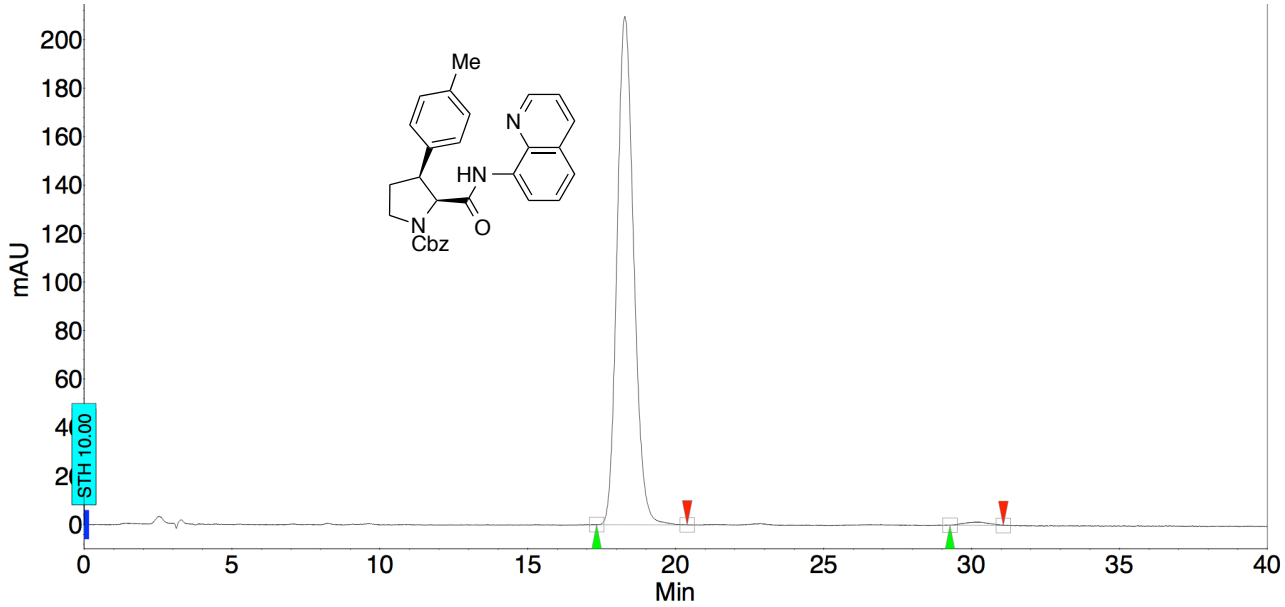
Conditions: Chiralpak IC-3 column, 50:50 *n*-hexane:*i*-PrOH, flow 1 mLmin^{-1}, 25 ºC,wavelength: 244 nm

Scalemic Mixture of Pyrrolidines 6a and *ent*-6a



Index	Name	Time [Min]	Quantity [% Area]	Height [mAU]	Area [mAU.Min]	Area % [%]
1	UNKNOWN	18.119	92.81	306.4	195.6	92.810
2	UNKNOWN	29.904	7.19	14.8	15.2	7.190
Total			100.00	321.2	210.7	100.000

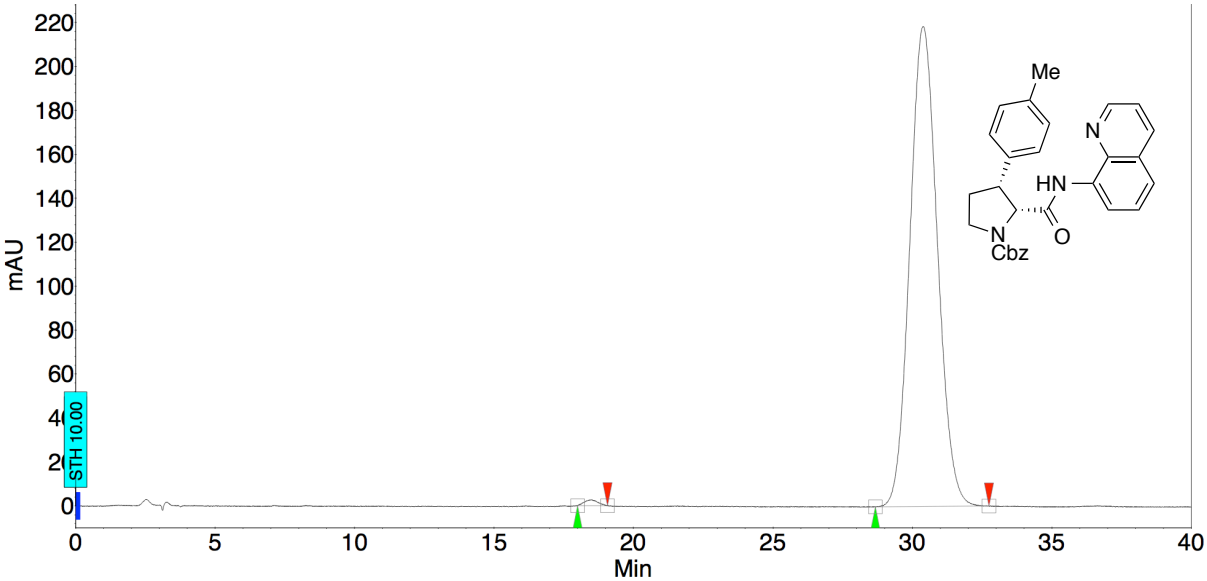
Benzyl (2*S*,3*S*)-3-(4-Methylphenyl)-2-[(quinolin-8-yl)carbamoyl]pyrrolidine-1-carboxylate (6a)



Index	Name	Time [Min]	Quantity [% Area]	Height [mAU]	Area [mAU.Min]	Area % [%]
1	UNKNOWN	18.279	99.06	209.8	136.8	99.063
2	UNKNOWN	30.198	0.94	1.3	1.3	0.937
Total			100.00	211.1	138.1	100.000

ee = 98.1%

Benzyl (2*R*,3*R*)-3-(4-Methylphenyl)-2-[(quinolin-8-yl)carbamoyl]pyrrolidine-1-carboxylate (*ent*-6a)

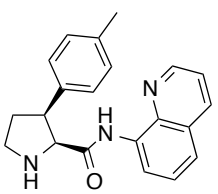


Index	Name	Time [Min]	Quantity [% Area]	Height [mAU]	Area [mAU.Min]	Area % [%]
1	UNKNOWN	18.465	0.58	2.5	1.5	0.580
2	UNKNOWN	30.384	99.42	218.6	250.0	99.420
Total			100.00	221.1	251.4	100.000

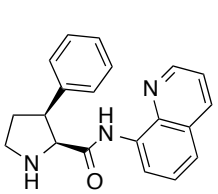
ee = 98.8%

Calculated Molecular Properties of Compounds 9a,b,e,j,l and 13a,b,d

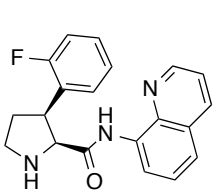
Hughes defines ideal drug-likeness with reduced propensity for toxic side effects as: MW <400 and cLogP <4,[2] which is similar to that used by Churcher,[3] and lower than the Lipinski limits.[4]



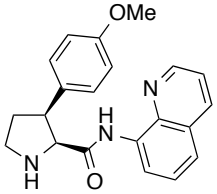
9a
cLogP 3.71 ±0.4
MW 331



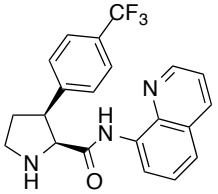
9b
cLogP 3.25 ±0.4
MW 317



9e
cLogP 3.31 ±0.5
MW 335

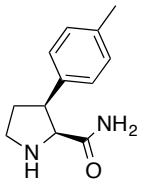
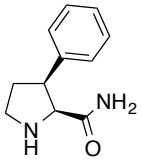
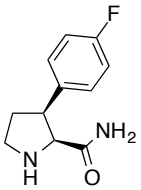


9j
cLogP 3.17 ±0.4
MW 347



9l
cLogP 3.83 ±0.5
MW 385

Fragments targeted to comply with a modified 'rule-of-3', with an increased HBA value: [5]
Molecular weight MW <300
Lipophilicity, as given by cLogP <3
H-bond donors (HBD) ≤3
H-bond donors (HBA) ≤6

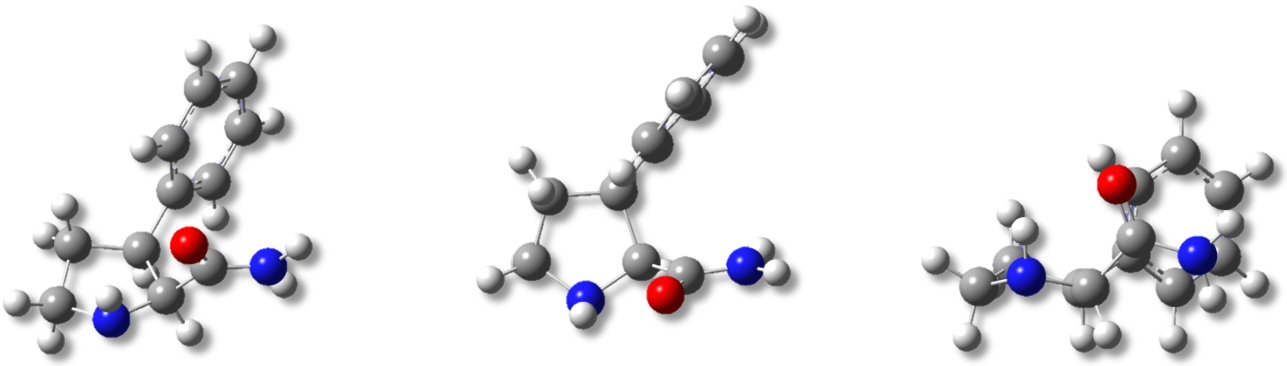
compound	product	MW	cLogP	HBD	HDA	Heavy Atoms	**Fragment like?**
13a		**204**	**0.40 ±0.4**	**3**	**3**	**15**	Y
13b		**190**	**–0.06 ±0.4**	**3**	**3**	**14**	Y
13d		**208**	**–0.01 ±0.5**	**3**	**4**	**15**	Y

cLogP values were determined using ACDlabs LogP calculator
http://www.acdlabs.com/resources/freeware/chemsketch/logp.

(2) Hughes, J. D.; Blagg, J.; Price, D. A; Bailey, S.; Decrescenzo, G. A.; Devraj, R. V; Ellsworth, E.; Fobian, Y. M.; Gibbs, M. E.; Gilles, R. W.; Greene, N.; Huang, E.; Krieger-Burke, T.; Loesel, J.; Wager, T.; Whiteley, L.; Zhang, Y. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 4872.
(3) Nadin, A.; Hattotuwagama, C.; Churcher, I. *Angew. Chem., Int. Ed.* **2012**, *51*, 1114.
(4) Lipinski, C. A.; Lombardo, F.; Dominy, B. W.; Feeney, P. J. *Adv. Drug Deliv. Rev.* **2001**, *46*, 3.
(5) See, (a) Congreve, M.; Carr, R.; Murray, C.; Jhoti, H. *Drug Discov. Today* **2003**, *8*, 876. (b) Köster, H.; Craan, T.; Brass, S.; Herhaus, C.; Zentgraf, M.; Neumann, L.; Heine, A.; Klebe, G. *J. Med. Chem.* **2011**, *54*, 7784. (c) Murray, C. W.; Rees, D. C. *Nat. Chem.* **2009**, *1*, 187.

3D Shape of **13a**

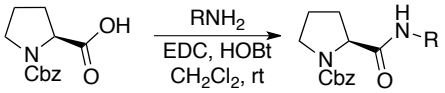
To illustrate the 3D shape of the fragments we calculated the minimum energy structure of **13a** using Gaussian 09 (GaussView 5),[6] up to the B3LYP/6-21G level of theory with default solvation (water; scrf = pcm).



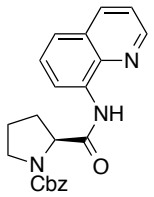
(6) Gaussian 09, Revision **A.1**, M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, B. Mennucci, G. A. Petersson, H. Nakatsuji, M. Caricato, X. Li, H. P. Hratchian, A. F. Izmaylov, J. Bloino, G. Zheng, J. L. Sonnenberg, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, J. A. Montgomery, Jr., J. E. Peralta, F. Ogliaro, M. Bearpark, J. J. Heyd, E. Brothers, K. N. Kudin, V. N. Staroverov, R. Kobayashi, J. Normand, K. Raghavachari, A. Rendell, J. C. Burant, S. S. Iyengar, J. Tomasi, M. Cossi, N. Rega, J. M. Millam, M. Klene, J. E. Knox, J. B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, R. L. Martin, K. Morokuma, V. G. Zakrzewski, G. A. Voth, P. Salvador, J. J. Dannenberg, S. Dapprich, A. D. Daniels, Ö. Farkas, J. B. Foresman, J. V. Ortiz, J. Cioslowski, and D. J. Fox, Gaussian, Inc., Wallingford CT, 2009.

Experimental Details and Characterization Data

Preparation of Amide Substrates 1-5

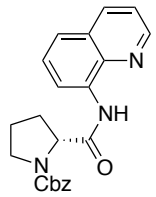


Benzyl (2*S*)-2-[(quinolin-8-yl)carbamoyl]pyrrolidine-1-carboxylate (1)



HOBt hydrate (6.12 g, 45.3 mmol) was added to a solution of *N*-benzyloxycarbonyl-L-proline (7.53 g, 30.2 mmol), 8-aminoquinoline (5.00 g, 34.7 mmol) and EDC·HCl (6.95 g, 36.2 mmol) in CH_2Cl_2 (60 mL) and the resulting solution was stirred at rt for 15 h. The solvent was removed under reduced pressure, a solution of sat. aq. $NaHCO_3$ (100 mL) was added and the aqueous layer was extracted with EtOAc (3 × 250 mL). A solution of sat. aq. NH_4Cl (20 mL) was added after the first EtOAc extraction, to aid the separation of aqueous and organic layers. The combined organic extracts were dried with Na_2SO_4 and filtered. The solvent was removed under reduced pressure, and purification by flash column chromatography (30% Et_2O/hexane grading to 60% Et_2O/hexane) afforded amide **1** (9.28 g, 82%) as a pale yellow oil. R_f 0.08 (40% Et_2O/pentane); $[\alpha]_D^{23}$ –100º (*c* 2.6, $CHCl_3$); ν_{max} (film)/cm^{-1} 3339 (NH br), 2957, 1694 (C=O), 1529, 1487, 1412, 1355, 1325, 1165, 1117, 984, 827, 792, 756, 698; ^{1}H NMR (400 MHz, DMSO-d_6, 373 K) δ 10.25 (br s, 1 H, NH), 8.85 (dd, *J* = 4.2, 1.7 Hz, 1 H, HC_{Ar}), 8.59 (dd, *J* = 7.6, 1.4 Hz, 1 H, HC_{Ar}), 8.37 (dd, *J* = 8.3, 1.7 Hz, 1 H, HC_{Ar}), 7.66 (dd, *J* = 8.3, 1.4 Hz, 1 H, HC_{Ar}), 7.62–7.54 (m, 2 H, 2 × HC_{Ar}), 7.34–7.07 (m, 5 H, 5 × HC_{Ph}), 5.16–5.07 (m, 2 H, OCH_2), 4.63 (dd, *J* = 8.5, 3.9 Hz, 1 H, HCC=O), 3.67–3.55 (m, 2 H, NCH_2), 2.38–2.26 (m, 1 H, NCH(C=O)C*H*H), 2.17–2.09 (m, 1 H, NCH(C=O)CH*H*), 2.04–1.89 (m, 2 H, NCH_2CH_2); ^{13}C NMR (101 MHz, DMSO-d_6, 373 K) δ 170.2 (C=O amide), 153.9 (C=O carbamate), 148.3 (C_{Ar}), 137.8 (C_{Ar} quat.), 136.3 (C_{Ar} quat.), 135.9 (C_{Ar}), 133.6 (C_{Ar} quat.), 127.5 (2 × C_{Ar}), 127.3 (C_{Ar} quat.), 126.9 (C_{Ar}), 126.6 (2 × C_{Ar}), 126.3 (C_{Ar}), 121.5 (C_{Ar}), 121.4 (C_{Ar}), 115.8 (C_{Ar}), 65.8 (OCH_2), 60.9 (H*C*C=O), 46.6 (NCH_2), 29.9 (NCH(C=O)*C*H_2), 23.1 (NCH_2CH_2); HRMS (ESI$^+$) *m/z* Calculated for $C_{22}H_{22}N_3O_3^+$ $[M+H]^+$ 376.1661; Found 376.1656.

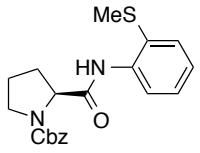
Benzyl (2*R*)-2-[(quinolin-8-yl)carbamoyl]pyrrolidine-1-carboxylate (*ent*-1)



HOBt hydrate (527 mg, 3.90 mmol) was added to a solution of *N*-benzyloxycarbonyl-D-proline (747 mg, 3.00 mmol), 8-aminoquinoline (519 mg, 3.60 mmol) and EDC·HCl (690 mg, 3.60 mmol) in CH_2Cl_2 (12 mL) and the resulting solution was stirred at rt for 36 h. The solvent was removed under reduced pressure, a solution of sat. aq. $NaHCO_3$ (25 mL) was added and the aqueous layer was extracted with EtOAc (3 × 100 mL). A solution of sat. aq. NH_4Cl (10 mL) was added after the first EtOAc extraction, to aid the separation of aqueous and organic layers. The combined organic extracts were dried with Na_2SO_4 and filtered. The solvent was removed under reduced pressure, and purification by flash column chromatography (30% Et_2O/hexane grading to 60% Et_2O/hexane) afforded amide ***ent*-1** (1.00 g, 89%) as a pale yellow oil. $[\alpha]_D^{23}$ +114º (*c* 2.0, $CHCl_3$).

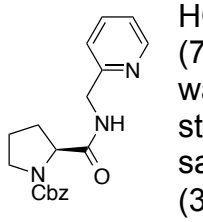
HPLC Conditions: Chiralpak IB-3 column, 60:40 *n*-hexane:*i*-PrOH, flow rate: 1 mLmin^{-1}, 25 ºC, UV detection wavelength: 224 nm. Retention times: 6.7 min (*S* enantiomer), 8.6 min (*R* enantiomer).

Benzyl (2*S*)-2-{[2-(methylsulfanyl)phenyl]carbamoyl}pyrrolidine-1-carboxylate (2)



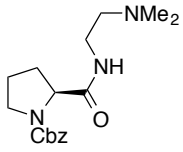
HOBt (446 mg, 3.30 mmol) was added to a solution of *N*-benzyloxycarbonyl-L-proline (748 mg, 3.00 mmol) and 2-(methylthio)aniline (0.56 mL, 4.50 mmol) in CH_2Cl_2 (6 mL) at 0 ºC, and was stirred for 5 min. EDC·HCl (633 mg, 3.30 mmol) was then added and the solution was stirred at 0 ºC for a further 10 min, then at rt for 15 h. The solvent was removed under reduced pressure, then a solution of sat. aq. $NaHCO_3$ (10 mL) was added and the aqueous mixture was extracted with EtOAc (3 × 25 mL). The combined organic extracts were dried with Na_2SO_4 and filtered. The solvent was removed under reduced pressure. Purification by flash column chromatography (50% pentane/Et_2O) afforded amide **2** (952 mg, 86%) as a yellow oil. R_f 0.13 (50% hexane/Et_2O); $[\alpha]_D^{23}$ –82º (*c* 3.0, $CHCl_3$); ν_{max} (film)/cm^{-1} 3315 (NH br), 2953, 1695 (C=O), 1579, 1515, 1436, 1411, 1355, 1174, 1116, 1088, 980, 754, 698; ^{1}H NMR (400 MHz, DMSO-d_6, 373 K) δ 9.07 (br s, 1 H, NH), 7.65 (d, *J* = 7.8 Hz, 1 H, HC_{Ar}), 7.42 (dd, *J* = 7.7, 1.6 Hz, 1 H, HC_{Ar}), 7.38–7.25 (m, 5 H, 5 × HC_{Ph}), 7.24–7.14 (m, 2 H, 2 × HC_{Ar}), 5.14–5.12 (m, 2 H, OCH_2), 4.48 (dd, *J* = 8.6, 3.8 Hz, 1 H, HCC=O), 3.60–3.48 (m, 2 H, NCH_2), 2.36 (s, 3 H, CH_3), 2.32–2.21 (m, 1 H, NCH(C=O)C*H*H), 2.15–2.06 (m, 1 H, NCH(C=O)CH*H*), 2.02–1.85 (m, 2 H, NCH_2CH_2); ^{13}C NMR (101 MHz, DMSO-d_6, 373 K) δ 170.2 (C=O amide), 153.9 (C=O carbamate), 136.4 (C_{Ar} quat.), 136.1 (C_{Ar} quat.), 130.1 (C_{Ar} quat.), 129.1 (C_{Ar}), 127.7 (2 × C_{Ar}), 127.1 (C_{Ar}), 126.8 (2 × C_{Ar}), 126.1 (C_{Ar}), 125.0 (C_{Ar}), 123.3 (C_{Ar}), 65.8 (OCH_2), 60.3 (H*C*C=O), 46.5 (NCH_2), 29.9 (NCH(C=O)*C*H$_2$), 23.0 (NCH_2CH_2), 16.1 (CH_3); HRMS (ESI$^+$) *m/z* Calculated for $C_{20}H_{23}N_2O_3S^+$ $[M+H]^+$ 371.1429; Found 371.1444.

Benzyl (2*S*)-2-[(pyridin-2-ylmethyl)carbamoyl]pyrrolidine-1-carboxylate (3)



HOBt (446 mg, 3.30 mmol) was added to a solution of *N*-benzyloxycarbonyl-L-proline (748 mg, 3.00 mmol) and 2-picolylamine (0.46 mL, 4.50 mmol) in CH_2Cl_2 (6 mL) and was stirred for 5 min. EDC (0.58 mL, 3.30 mmol) was then added and the solution was stirred for 15 h. The solvent was removed under reduced pressure, then a solution of sat. aq. $NaHCO_3$ (10 mL) was added and the aqueous layer was extracted with EtOAc (3 × 25 mL). The combined organic extracts were dried with Na_2SO_4 and filtered. The solvent was removed under reduced pressure. Purification by flash column chromatography (EtOAc/MeOH/NEt_3 100:1:1) afforded amide **3** (614 mg, 60%) as a yellow oil. R_f 0.16 (100:1 EtOAc/NEt_3); $[\alpha]_D^{23}$ –70º (*c* 2.3, $CHCl_3$); ν_{max} (film)/cm^{-1} 3309 (NH br), 3066, 2952, 2880, 1698 (C=O), 1669 (C=O), 1571, 1535, 1416, 1356, 1240, 1209, 1177, 1121, 754, 699; ^{1}H NMR (400 MHz, DMSO-d_6, 373 K) δ 8.49–8.45 (m, 1 H, HC_{pyr}), 8.17 (br s, 1 H, NH), 7.69–7.62 (m, 1 H, HC_{pyr}), 7.37–7.18 (m, 7 H, 5 × HC_{Ar} and 2 × HC_{pyr}), 5.12–5.05 (m, 2 H, OCH_2), 4.44–4.30 (m, 3 H, CH_2C_{pyr} and HCC=O), 3.55–3.43 (m, 2 H, CbzNCH_2), 2.24–2.12 (m, 1 H, NCH(C=O)C*H*H), 1.99–1.78 (m, 3 H, NCH_2CH_2 and NCH(C=O)CH*H*); ^{13}C NMR (101 MHz, DMSO-d_6, 373 K) δ 171.6 (C=O amide), 158.0 (C_{pyr} quat.), 153.7 (C=O carbamate), 148.1 (HC_{pyr}), 136.6 (C_{Ar} quat.), 135.8 (HC_{pyr}), 127.7 (2 × C_{Ar}), 127.0 (C_{Ar}), 126.7 (2 × C_{Ar}), 121.3 (C_{pyr}), 120.3 (C_{pyr}), 65.5 (OCH_2), 59.6 (H*C*C=O), 46.4 (CbzNCH_2), 43.8 ($CH_2C_{pyridine}$), 30.0 (NCH(C=O)*C*H$_2$), 22.9 (NCH_2CH_2); HRMS (ESI$^+$) *m/z* Calculated for $C_{19}H_{22}N_3O_3^+$ $[M+H]^+$ 340.1661; Found 340.1668.

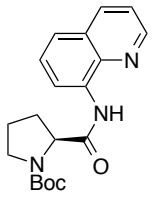
Benzyl (2*S*)-2-{[2-(dimethylamino)ethyl]carbamoyl}pyrrolidine-1-carboxylate (4)



HOBt (446 mg, 3.30 mmol) was added to a solution of *N*-benzyloxycarbonyl-L-proline (748 mg, 3.00 mmol) and *N*,*N*-dimethylethylenediamine (0.49 mL, 4.50 mmol) in CH_2Cl_2 (6 mL) at 0 ºC, and was stirred for 5 min. EDC·HCl (633 mg, 3.30 mmol) was

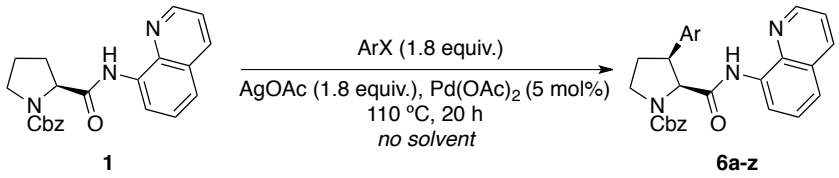
then added and the solution was stirred at 0 ºC for a further 10 min, then at rt for 15 h. The solvent was removed under reduced pressure, then a solution of sat. aq. $NaHCO_3$ (10 mL) was added and the aqueous layer was extracted with EtOAc (3 × 25 mL). The combined organic extracts were dried with Na_2SO_4 and filtered. The solvent was removed under reduced pressure. Purification by flash column chromatography (EtOAc/MeOH/NEt_3 100:5:1), afforded amide **4** (649 mg, 68%) as an off-white solid. mp = 36–38 ºC; R_f 0.05 (100:20:1 EtOAc/MeOH/NEt_3); $[\alpha]_D^{23}$ 68º (*c* 2.1, $CHCl_3$); ν_{max} (film)/cm^{-1} 3317 (NH br), 2950, 2881, 2827, 2781, 1701 (C=O), 1538, 1417, 1357, 1243, 1188, 1121, 769, 698; ^{1}H NMR (400 MHz, DMSO-d_6, 373 K) δ 7.41 (br s, 1 H, NH), 7.38–7.26 (m, 5 H, HC_{Ph}), 5.12–5.01 (m, 2 H, OCH_2), 4.20 (dd, *J* = 8.4, 3.2 Hz, 1 H, HCC=O), 3.51–3.38 (m, 2 H, CbzNCH_2), 3.20–3.08 (m, 2 H, C$H_2CH_2NMe_2$), 2.30 (t, *J* = 6.7 Hz, 2 H, $CH_2CH_2NMe_2$), 2.16 (br s, 6 H, $N(CH_3)_2$), 2.14–2.06 (m, 1 H, NCH(C=O)C*H*H), 1.92–1.77 (m, 3 H, $CbzNCH_2CH_2$ and NCH(C=O)CH*H*); ^{13}C NMR (101 MHz, DMSO-d_6, 373 K) δ 171.3 (C=O amide), 153.6 (C=O carbamate), 136.6 (C_{Ar} quat.), 127.7 (2 × C_{Ar}), 127.0 (C_{Ar}), 126.7 (2 × C_{Ar}), 65.4 (OCH_2), 59.6 (H*C*C=O), 57.5 ($CH_2CH_2NMe_2$), 46.3 (CbzNCH_2), 44.3 (2 × CH_3), 36.2 ($CH_2CH_2NMe_2$), 30.0 (NCH(C=O)CH_2), 22.9 ($CbzNCH_2CH_2$); HRMS (ESI^+) *m/z* Calculated for $C_{17}H_{26}N_3O_3^+$ $[M+H]^+$ 320.1974; Found 320.1988.

tert-Butyl (2*S*)-2-[(quinolin-8-yl)carbamoyl]pyrrolidine-1-carboxylate (5)



HOBt (446 mg, 3.30 mmol) was added to a solution of *N*-Boc-L-proline (748 mg, 3.00 mmol) and 8-aminoquinoline (649 mg, 4.50 mmol) in CH_2Cl_2 (6 mL) at 0 ºC, and was stirred for 5 min. EDC·HCl (633 mg, 3.30 mmol) was then added and the solution was stirred at 0 ºC for a further 10 min, then at rt for 15 h. The solvent was removed under reduced pressure, then a solution of sat. aq. $NaHCO_3$ (10 mL) was added and the aqueous layer was extracted with EtOAc (3 × 25 mL). The combined organic extracts were dried with Na_2SO_4 and filtered. The solvent was removed under reduced pressure. Purification by flash column chromatography (15% Et_2O/hexane) afforded amide **5** (422 mg, 41%) as a yellow solid. mp = 136–139 ºC. R_f 0.23 (20% EtOAc/hexane); $[\alpha]_D^{23}$ –129º (*c* 2.7, $CHCl_3$); ν_{max} (film)/cm^{-1} 3341 (NH br), 2976, 1689 (C=O), 1527, 1488, 1387, 1367, 1324, 1161, 1120, 922, 828, 793, 759; ^{1}H NMR (400 MHz, DMSO-d_6, 373 K) δ 10.25 (br s, 1 H, NH), 8.87 (dd, *J* = 4.3, 1.7 Hz, 1 H, HC_{Ar}), 8.63 (dd, *J* = 7.6, 1.4 Hz, 1 H, HC_{Ar}), 8.36 (dd, *J* = 8.3, 1.7 Hz, 1 H, HC_{Ar}) 7.67–7.54 (m, 3 H, 9 × HC_{Ar}), 4.48 (dd, *J* = 8.5, 4.0 Hz, 1 H, HCC=O), 3.57–3.46 (m, 2 H, NCH_2), 2.32–2.22 (m, 1 H, NCH(C=O)C*H*H), 2.16–2.07 (m, 1 H, NCH(C=O)CH*H*), 1.99–1.85 (m, 2 H, NCH_2CH_2) 1.37 (s, 9 H, 3 × CH_3); ^{13}C NMR (101 MHz, DMSO-d_6, 373 K) δ 170.5 (C=O amide), 153.4 (C=O carbamate), 148.2 (C_{Ar}), 137.7 (C_{Ar} quat.), 135.9 (C_{Ar}), 133.7 (C_{Ar} quat.), 127.3 (C_{Ar} quat.), 126.3 (C_{Ar}), 121.5 (C_{Ar}), 121.3 (C_{Ar}), 115.5 (C_{Ar}), 78.8 ($C(CH_3)_3$ quat.), 60.9 (H*C*C=O), 46.3 (NCH_2), 29.7 (NCH(C=O)CH_2), 27.5 (3 × CH_3), 23.1 (NCH_2CH_2); HRMS (ESI^+) *m/z* Calculated for $C_{19}H_{24}N_3O_3^+$ $[M+H]^+$ 342.1818; Found 342.1808.

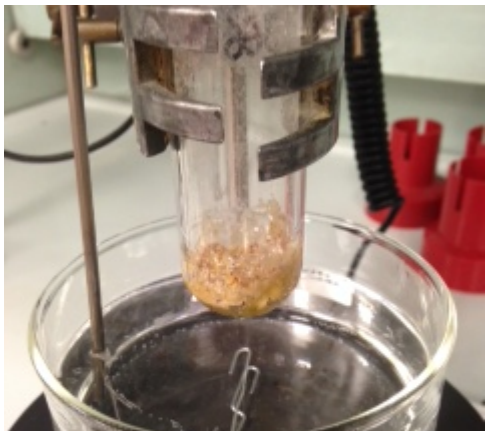
C–H Arylation 6a-z, 7a, 8: Scope of the Aryl Iodides



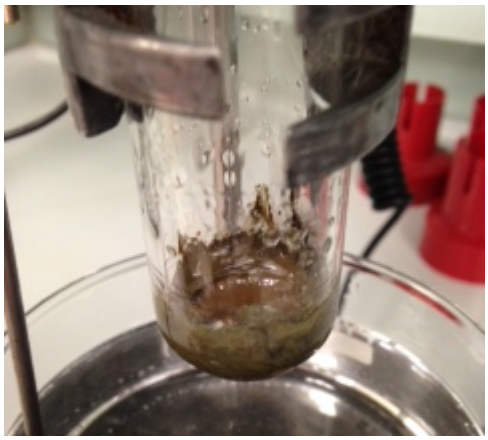
1 **6a-z**

General Procedure for C–H arylation of *N*-Cbz proline derivative 1 – A reaction tube was charged with benzyl (2*S*)-2-[(quinolin-8-yl)carbamoyl]pyrrolidine-1-carboxylate **1** (0.75–1.00 mmol, 1.0 equiv), AgOAc (1.8 equiv), the requisite aryl iodide (1.8 equiv) and $Pd(OAc)_2$ (5 mol%). The reaction vessel was purged with argon and sealed, then placed in an oil bath (preheated to 110 ºC) for 20 h. The reaction mixture was then allowed to cool to rt and EtOAc (10 mL) was added. The resulting solution was filtered through a pad of Celite, eluting with further EtOAc (2 × 10 mL). The solvent was removed under reduced pressure, and the crude material was purified by flash column chromatography under the specified conditions. The product containing fractions were combined and the solvent was removed under reduced pressure. Et_2O (10 mL) was added and the solvent was removed under reduced pressure to afford the arylated proline derivative as a solid.

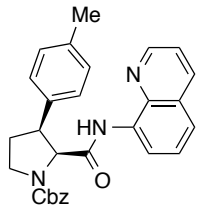
Reaction mixture prior to heating (time = 0 h)



Reaction mixture at time = 20 h

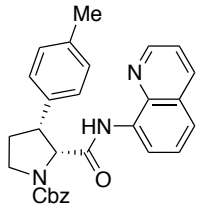


Benzyl (2*S*,3*S*)-3-(4-methylphenyl)-2-[(quinolin-8-yl)carbamoyl]pyrrolidine-1-carboxylate (6a)



Prepared according to the **General Procedure**: amide **1** (308 mg, 0.82 mmol), AgOAc (246 mg, 1.48 mmol), 4-iodotoluene (322 mg, 1.48 mmol) and $Pd(OAc)_2$ (9.2 mg, 41 μmol) were employed. The crude material was purified by flash column chromatography (3% grading to 5% $MeCN/CH_2Cl_2$), affording arylated compound **6a** (348 mg, 91%) as a white solid. mp = 136–139 ºC; R_f 0.68 (10% $MeCN/CH_2Cl_2$); $[\alpha]_D^{23}$ –2º (*c* 1.1, $CHCl_3$); ν_{max} (film)/cm^{-1} 3345 (NH br), 3037, 2872, 1701 (C=O), 1580, 1530, 1487, 1463, 1409, 1348, 1325, 1286, 1275, 1264, 1242, 1231, 1202, 1161, 1121, 1108, 1073, 1062, 983, 950, 915, 895, 845, 827, 797, 764, 730, 696, 672; ^{1}H NMR (400 MHz, DMSO-d_6, 373 K) δ 9.58 (br s, 1 H, NH), 8.77 (dd, *J* = 4.2, 1.7 Hz, 1 H, HC_{Ar}), 8.33 (dd, *J* = 7.6, 1.4 Hz, 1 H, HC_{Ar}), 8.29 (dd, *J* = 8.3, 1.7 Hz, 1 H, HC_{Ar}), 7.58–7.51 (m, 2 H, 2 × HC_{Ar}), 7.46 (t, *J* = 7.9 Hz, 1 H, HC_{Ar}), 7.35–7.05 (m, 7 H, 7 × HC_{Ar}), 6.86 (d, *J* = 7.8 Hz, 2 H, HC_{Ar}), 5.16–5.04 (m, 2 H, OCH_2), 4.90 (d, *J* = 8.4 Hz, 1 H, HCC=O), 3.96–3.89 (m, 1 H, NC*H*H), 3.87–3.78 (m, 1 H, CHC_{Ar}), 3.66–3.57 (m, 1 H, NCH*H*), 2.66–2.53 (m, 1 H, NCH_2CHH), 2.22–2.13 (m, 1 H, NCH_2CHH), 1.98 (s, 3 H, CH_3); ^{13}C NMR (101 MHz, DMSO-d_6, 373 K) δ 168.1 (C=O amide), 153.5 (C=O carbamate), 147.9 (C_{Ar}), 137.4 (C_{Ar} quat.), 136.3 (C_{Ar} quat.), 135.6 (C_{Ar}), 135.2 (C_{Ar} quat.), 133.5 (C_{Ar} quat.), 133.3 (C_{Ar} quat.), 128.0 (2 × C_{Ar}), 127.4 (2 × C_{Ar}), 127.3 (2 × C_{Ar}), 127.0 (C_{Ar} quat.), 126.9 (C_{Ar}), 126.5 (2 × C_{Ar}), 126.1 (C_{Ar}), 121.2 (C_{Ar}), 121.0 (C_{Ar}), 115.3 (C_{Ar}), 65.6 (OCH_2), 65.1 (H*C*C=O), 46.6 (*C*HC_{Ar}), 45.8 (NCH_2), 27.3 (NCH_2CH_2), 19.7 (CH_3); HRMS (ESI^+) *m/z* Calculated for $C_{29}H_{28}N_3O_3^+$ $[M+H]^+$ 466.2131; Found 466.2122.

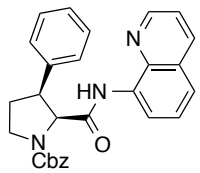
Benzyl (2*R*,3*R*)-3-(4-methylphenyl)-2-[(quinolin-8-yl)carbamoyl]pyrrolidine-1-carboxylate (*ent*-6a)



Prepared according to the **General Procedure**: amide ***ent*-1** (303 mg, 0.81 mmol), AgOAc (244 mg, 1.46 mmol), 4-iodotoluene (318 mg, 1.46 mmol) and $Pd(OAc)_2$ (9.1 mg, 41 μmol) were employed. The crude material was purified by flash column chromatography (3% grading to 5% $MeCN/CH_2Cl_2$), affording arylated compound ***ent*-6a** (301 mg, 80%) as a white solid. $[\alpha]_D^{28}$ +2º (*c* 2.5, $CHCl_3$).

HPLC Conditions: Chiralpak IC-3 column, 50:50 *n*-hexane:*i*-PrOH, flow rate: 1 $mLmin^{-1}$, 25 ºC, UV detection wavelength: 244 nm. Retention times: 18.2 min (2*S*,3*S* enantiomer), 29.9 min (2*R*,3*R* enantiomer).

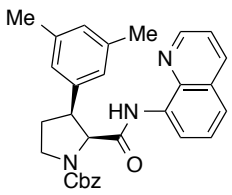
Benzyl (2*S*,3*S*)-3-phenyl-2-[(quinolin-8-yl)carbamoyl]pyrrolidine-1-carboxylate (6b)



Prepared according to the **General Procedure**: amide **1** (355 mg, 0.95 mmol), AgOAc (285 mg, 1.71 mmol), iodobenzene (191 μL, 1.71 mmol) and $Pd(OAc)_2$ (10.7 mg, 48 μmol) were employed. The crude material was purified by flash column chromatography (3% grading to 5% $MeCN/CH_2Cl_2$), affording arylated compound **6b** (370 mg, 86%) as a white solid. mp = 48–50 ºC; R_f 0.69 (10% $MeCN/CH_2Cl_2$); $[\alpha]_D^{23}$ +26º (*c* 2.3, $CHCl_3$); ν_{max} (film)/cm^{-1} 3342 (NH br), 3032, 2943, 2873, 1690 (C=O), 1525, 1486, 1410, 1352, 1324, 1164, 1123, 826, 790, 756, 696; ^{1}H NMR (400 MHz, DMSO-d_6, 373 K) δ 9.63 (br s, 1 H, NH), 8.77 (dd, *J* = 4.2, 1.7 Hz, 1 H, HC_{Ar}), 8.34–8.26 (m, 2 H, 2 × HC_{Ar}), 7.58–7.50 (m, 2 H, 2 × HC_{Ar}), 7.45 (t, *J* = 8.0 Hz, 1 H, HC_{Ar}) 7.37–7.04 (m, 9 H, 9 × HC_{Ar}), 6.98–6.92 (m, 1 H, HC_{Ar}), 5.16–5.04 (m, 2 H, OCH_2), 4.94 (d, *J* = 8.5 Hz, 1 H, *H*CC=O), 3.99–3.83 (m, 2 H, NC*H*H and CHC_{Ar}), 3.68–3.59 (m, 1 H, NCH*H*), 2.70–2.57 (m, 1 H, NCH_2CHH), 2.26–2.17

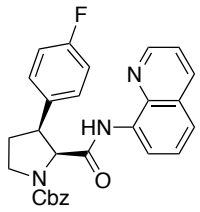
(m, 1 H, $NCH_2CH\mathit{H}$); ^{13}C NMR (101 MHz, DMSO-d_6, 373 K) δ 168.1 (C=O amide), 153.5 (C=O carbamate), 147.9 (C_{Ar}), 137.4 (C_{Ar} quat.), 136.6 (C_{Ar} quat.), 136.3 (C_{Ar} quat.), 135.6 (C_{Ar}), 133.2 (C_{Ar} quat.), 127.5 (2 × C_{Ar}), 127.4 (2 × C_{Ar}), 127.3 (2 × C_{Ar}), 127.1 (C_{Ar} quat.), 126.8 (C_{Ar}), 126.5 (2 × C_{Ar}), 126.11 (C_{Ar}), 126.05 (C_{Ar}), 121.2 (C_{Ar}), 121.0 (C_{Ar}), 115.3 (C_{Ar}), 65.7 (OCH_2), 65.0 ($H\mathit{C}C$=O), 46.8 ($\mathit{C}HC_{Ar}$), 45.8 (NCH_2), 27.3 ($NCH_2\mathit{C}H_2$); HRMS (ESI$^+$) *m/z* Calculated for $C_{28}H_{26}N_3O_3^+$ $[M+H]^+$ 452.1974; Found 452.1971.

Benzyl (2*S*,3*S*)-3-(3,5-dimethylphenyl)-2-[(quinolin-8-yl)carbamoyl]pyrrolidine-1-carboxylate (6c)



Prepared according to the **General Procedure**: amide **1** (382 mg, 1.02 mmol), AgOAc (306 mg, 1.84 mmol), 1-iodo-3,5-dimethylbenzene (265 μL, 1.84 mmol) and $Pd(OAc)_2$ (11.4 mg, 51 μmol) were employed. The crude material was purified by flash column chromatography (3% grading to 5% $MeCN/CH_2Cl_2$), affording arylated compound **6c** (218 mg, 45%) as a white solid. mp = 50–53 ºC; R_f 0.68 (10% $MeCN/CH_2Cl_2$); $[\alpha]_D^{23}$ +11º (*c* 1.8, $CHCl_3$); ν_{max} (film)/cm^{-1} 3340 (NH br), 2952, 1692 (C=O), 1605, 1526, 1486, 1409, 1356, 1323, 1166, 1119, 1065, 994, 898, 825, 791, 754, 695; ^{1}H NMR (400 MHz, DMSO-d_6, 373 K) δ 9.51 (br s, 1 H, NH), 8.78 (dd, *J* = 4.3, 1.7 Hz, 1 H, HC_{Ar}), 8.37 (dd, *J* = 7.6, 1.4 Hz, 1 H, HC_{Ar}), 8.29 (dd, *J* = 8.3, 1.7 Hz, 1 H, HC_{Ar}), 7.58–7.51 (m, 2 H, 2 × HC_{Ar}), 7.46 (t, *J* = 7.9 Hz, 1 H, HC_{Ar}), 7.36–7.08 (m, 5 H, 5 × HC_{Ph}), 6.89 (s, 2 H, 2 × HC_{Ar}), 6.46 (s, 1 H, HC_{Ar}), 5.17–5.06 (m, 2 H, OCH_2), 4.88 (d, *J* = 8.5 Hz, 1 H, HCC=O), 3.97–3.89 (m, 1 H, $NCH\mathit{H}$), 3.83–3.74 (m, 1 H, CHC_{Ar}), 3.65–3.56 (m, 1 H, $NC\mathit{H}H$), 2.63–2.51 (m, 1 H, $NCH_2C\mathit{H}H$), 2.21–2.12 (m, 1 H, $NCH_2CH\mathit{H}$), 1.95 (s, 6 H, 2 × CH_3); ^{13}C NMR (101 MHz, DMSO-d_6, 373 K) δ 168.3 (C=O amide), 153.5 (C=O carbamate), 147.7 (C_{Ar}), 137.4 (C_{Ar} quat.), 136.4 (C_{Ar} quat.), 136.32, (C_{Ar} quat.) 136.27 (C_{Ar} quat.), 135.6 (C_{Ar}), 133.3 (C_{Ar} quat.), 127.50 (2 × C_{Ar}), 127.45 (C_{Ar}), 127.0 (C_{Ar} quat.), 126.8 (C_{Ar}), 126.5 (2 × C_{Ar}), 126.0 (C_{Ar}), 125.2 (2 × C_{Ar}), 121.1 (C_{Ar}), 120.9 (C_{Ar}), 115.1 (C_{Ar}), 65.6 (OCH_2), 65.2 ($H\mathit{C}C$=O), 46.9 ($\mathit{C}HC_{Ar}$), 45.8 (NCH_2), 27.3 ($NCH_2\mathit{C}H_2$), 19.9 (CH_3); HRMS (ESI$^+$) *m/z* Calculated for $C_{30}H_{30}N_3O_3^+$ $[M+H]^+$ 480.2287; Found 480.2287.

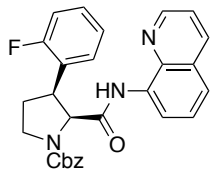
Benzyl (2*S*,3*S*)-3-(4-fluorophenyl)-2-[(quinolin-8-yl)carbamoyl]pyrrolidine-1-carboxylate (6d)



Prepared according to the **General Procedure**: amide **1** (351 mg, 0.94 mmol), AgOAc (280 mg, 1.69 mmol), 4-fluoroiodobenzene (195 μL, 1.69 mmol) and $Pd(OAc)_2$ (10.7 mg, 48 μmol) were employed. The crude material was purified by flash column chromatography (50% hexane/Et_2O), affording arylated compound **6d** (385 mg, 88%) as a white solid. mp = 53–56 ºC; R_f 0.86 (EtOAc); $[\alpha]_D^{21}$ +32º (*c* 2.7, $CHCl_3$); ν_{max} (film)/cm^{-1} 3337 (NH br), 2954, 2883, 1691 (C=O), 1606, 1525, 1486, 1409, 1355, 1324, 1224, 1160, 1122, 1100, 993, 826, 791, 735, 696; ^{1}H NMR (400 MHz, DMSO-d_6, 373 K) δ 9.63 (br s, 1 H, NH), 8.78 (dd, *J* = 4.2, 1.7 Hz, 1 H, HC_{Ar}), 8.33–8.28 (m, 2 H, 2 × HC_{Ar}), 7.59–7.53 (m, 2 H, 2 × HC_{Ar}), 7.49–7.43 (m, 1 H, HC_{Ar}), 7.39–7.33 (m, 2 H, 2 × HC_{Ar}), 7.33–6.98 (m, 5 H, 5 × HC_{Ar}), 6.90–6.82 (m, 2 H, 2 × HC_{Ar}), 5.17–5.03 (m, 2 H, OCH_2), 4.95 (d, *J* = 8.5 Hz, 1 H, HCC=O), 3.98–3.82 (m, 2 H, NCH_2), 3.66–3.57 (m, 1 H, CHC_{Ar}), 2.65–2.52 (m, 1 H, $NCH_2C\mathit{H}H$), 2.25–2.16 (m, 1 H, $NCH_2CH\mathit{H}$); ^{13}C NMR (101 MHz, DMSO-d_6, 373 K) δ 168.1 (C=O amide), 160.7 (d, J_{CF} = 244 Hz, FC_{Ar} quat.), 153.5 (C=O carbamate), 148.0 (C_{Ar}), 137.5 (C_{Ar} quat.), 136.3 (C_{Ar} quat.) 135.7 (C_{Ar}), 133.1 (C_{Ar} quat.), 132.8 (d, J_{CF} = 3 Hz, C_{Ar} quat.), 129.4 (d, J_{CF} = 8 Hz, 2 × C_{Ar}), 127.5 (2 × C_{Ar}), 127.1 (C_{Ar} quat.), 126.9 (C_{Ar}), 126.6 (2 × C_{Ar}), 126.1 (C_{Ar}), 121.3 (C_{Ar}), 121.2 (C_{Ar}), 115.5 (C_{Ar}), 114.0 (d, J_{CF} = 21 Hz, 2 × C_{Ar}), 65.7 (OCH_2), 64.9

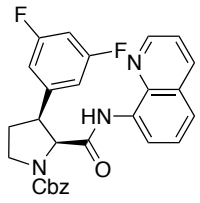
(H*C*C=O), 46.1 (*C*HC$_{Ar}$), 45.8 (NCH$_2$), 27.4 (NCH$_2$*C*H$_2$); ^{19}F NMR (376 MHz, DMSO-d$_6$, 373 K) δ –116.2; HRMS (ESI$^+$) *m/z* Calculated for $C_{28}H_{25}N_3O_3F^+$ [M+H]$^+$ 470.1880; Found 470.1870.

Benzyl (2*S*,3*S*)-3-(2-fluorophenyl)-2-[(quinolin-8-yl)carbamoyl]pyrrolidine-1-carboxylate (6e)



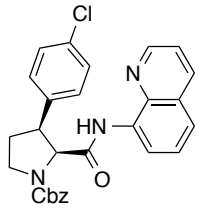
Prepared according to the **General Procedure**: amide **1** (302 mg, 0.80 mmol), AgOAc (240 mg, 1.44 mmol), 2-fluoroiodobenzene (168 μL, 1.44 mmol) and Pd(OAc)$_2$ (9.0 mg, 40 μmol) were employed and the reaction was heated for **60 h**. The crude material was purified by flash column chromatography (3% grading to 5% MeCN/CH$_2$Cl$_2$), affording arylated compound **6e** (166 mg, 44%) as a pale yellow solid. mp = 47–50 ºC; R_f 0.54 (10% MeCN/CH$_2$Cl$_2$); $[\alpha]_D^{21}$ +22º (*c* 0.9, CHCl$_3$); ν$_{max}$ (film)/cm^{-1} 3336 (NH br), 2953, 2881, 1690 (C=O), 1526, 1486, 1455, 1408, 1354, 1324, 1215, 1165, 1125, 1099, 992, 826, 791, 754, 696; ^{1}H NMR (400 MHz, DMSO-*d*$_6$, 373 K) δ 9.78 (br s, 1 H, NH), 8.81 (dd, *J* = 4.2, 1.7 Hz, 1 H, HC$_{Ar}$), 8.31 (dd, *J* = 8.3, 1.7 Hz, 1 H, HC$_{Ar}$), 8.25 (dd, *J* = 7.7, 1.3 Hz, 1 H, HC$_{Ar}$), 7.59–7.54 (m, 2 H, 2 × HC$_{Ar}$), 7.47–7.41 (m, 1 H, HC$_{Ar}$), 7.34–7.02 (m, 7 H, 7 × HC$_{Ar}$), 7.01–6.95 (m, 1 H, HC$_{Ar}$), 6.94–6.88 (m, 1 H, HC$_{Ar}$), 5.17–5.04 (m, 2 H, OCH$_2$), 4.87 (dd, *J* = 8.5, 1.2 Hz, 1 H, HCC=O), 4.10–4.01 (m, 1 H, CHC$_{Ar}$), 3.99–3.91 (m, 1 H, NC*H*H), 3.70–3.60 (m, 1 H, NCH*H*), 2.73–2.60 (m, 1 H, NCH$_2$C*H*H), 2.27–2.19 (m, 1 H, NCH$_2$CH*H*); ^{13}C NMR (101 MHz, DMSO-*d*$_6$, 373 K) δ 167.6 (C=O amide), 160.3 (d, J_{CF} = 224 Hz, FC$_{Ar}$ quat.), 153.5 (C=O carbamate), 148.1 (C$_{Ar}$), 137.4 (C$_{Ar}$ quat.), 136.2 (C$_{Ar}$ quat.), 135.7 (C$_{Ar}$), 132.9 (C$_{Ar}$ quat.), 128.2 (d, J_{CF} = 8 Hz, C$_{Ar}$), 127.9 (d, J_{CF} = 4 Hz, C$_{Ar}$), 127.5 (2 × C$_{Ar}$), 127.1 (C$_{Ar}$ quat.), 126.9 (C$_{Ar}$), 126.6 (2 × C$_{Ar}$), 126.1 (C$_{Ar}$), 123.7 (d, J_{CF} = 15 Hz, C$_{Ar}$ quat.), 123.4 (d, J_{CF} = 3 Hz, C$_{Ar}$), 121.4 (C$_{Ar}$), 121.2 (C$_{Ar}$), 115.2 (C$_{Ar}$), 114.3 (d, J_{CF} = 22 Hz, C$_{Ar}$), 65.8 (OCH$_2$), 63.7 (H*C*C=O), 45.3 (NCH$_2$), 40.1 (*C*HC$_{Ar}$), 26.3 (NCH$_2$*C*H$_2$); ^{19}F NMR (376 MHz, DMSO-d$_6$, 373 K) δ –115.4; HRMS (ESI$^+$) *m/z* Calculated for $C_{28}H_{25}N_3O_3F^+$ [M+H]$^+$ 470.1874; Found 470.1865.

Benzyl (2*S*,3*S*)-3-(3,5-difluorophenyl)-2-[(quinolin-8-yl)carbamoyl]pyrrolidine-1-carboxylate (6f)



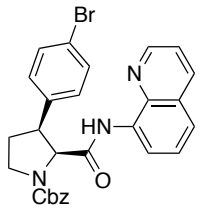
Prepared according to the **General Procedure**: amide **1** (288 mg, 0.77 mmol), AgOAc (230 mg, 1.38 mmol), 3,5-difluoroiodobenzene (166 μL, 1.38 mmol) and Pd(OAc)$_2$ (8.7 mg, 39 μmol) were employed. The crude material was purified by flash column chromatography (3% grading to 5% MeCN/CH$_2$Cl$_2$), affording arylated compound **6f** (224 mg, 60%) as a white solid. mp = 51–54 ºC; R_f 0.59 (10% MeCN/CH$_2$Cl$_2$); $[\alpha]_D^{21}$ +6º (*c* 2.6, CHCl$_3$); ν$_{max}$ (film)/cm^{-1} 3337 (NH br), 2955, 2882, 1691 (C=O), 1625, 1596, 1526, 1486, 1456, 1411, 1348, 1323, 1290, 1166, 1117, 983, 855, 826, 791, 755, 696, 673; ^{1}H NMR (400 MHz, DMSO-*d*$_6$, 373 K) δ 9.71 (br s, 1 H, NH), 8.79 (dd, *J* = 4.2, 1.7 Hz, 1 H, HC$_{Ar}$), 8.34–8.29 (m, 2 H, 2 × HC$_{Ar}$), 7.61–7.54 (m, 2 H, 2 × HC$_{Ar}$), 7.50–7.43 (m, 1 H, HC$_{Ar}$), 7.38–7.07 (m, 5 H, 5 × HC$_{Ar}$), 7.07–7.00 (m, 2 H, 2 × HC$_{Ar}$), 6.68–6.61 (m, 1 H, HC$_{Ar}$), 5.17–5.08 (m, 2 H, OCH$_2$), 5.06 (d, *J* = 8.5 Hz, 1 H, HCC=O), 3.97–3.87 (m, 2 H, NCH$_2$), 3.66–3.56 (m, 1 H, CHC$_{Ar}$), 2.62–2.52 (m, 1 H, NCH$_2$C*H*H), 2.27–2.18 (m, 1 H, NCH$_2$CH*H*), ^{13}C NMR (101 MHz, DMSO-*d*$_6$, 373 K) δ 167.9 (C=O amide), 161.7 (d, J_{CF} = 246 Hz, FC$_{Ar}$ quat.), 161.6 (d, J_{CF} = 246 Hz, FC$_{Ar}$ quat.), 153.4 (C=O carbamate), 148.0 (C$_{Ar}$), 141.5 (t, J_{CF} = 9 Hz, C$_{Ar}$ quat.), 137.5 (C$_{Ar}$ quat.), 136.2 (C$_{Ar}$ quat.), 135.7 (C$_{Ar}$), 133.1 (C$_{Ar}$ quat.), 127.5 (2 × C$_{Ar}$), 127.1 (C$_{Ar}$ quat.), 126.9 (C$_{Ar}$), 126.6 (2 × C$_{Ar}$), 126.0 (C$_{Ar}$), 121.31 (C$_{Ar}$), 121.29 (C$_{Ar}$), 115.6 (C$_{Ar}$), 110.8 (d, J_{CF} = 18 Hz, C$_{Ar}$), 110.7 (d, J_{CF} = 18 Hz, C$_{Ar}$), 101.4 (t, J_{CF} = 26 Hz, C$_{Ar}$), 65.7 (OCH$_2$), 64.5 (H*C*C=O), 46.2 (*C*HC$_{Ar}$), 45.6 (NCH$_2$), 26.8 (NCH$_2$*C*H$_2$); ^{19}F NMR (376 MHz, DMSO-d$_6$, 373 K) δ –110.7; HRMS (ESI$^+$) *m/z* Calculated for $C_{28}H_{24}N_3O_3F_2^+$ [M+H]$^+$ 488.1780; Found 488.1771.

Benzyl (2*S*,3*S*)-3-(4-chlorophenyl)-2-[(quinolin-8-yl)carbamoyl]pyrrolidine-1-carboxylate (6g)



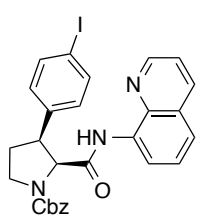
Prepared according to the **General Procedure**: amide **1** (321 mg, 0.86 mmol), AgOAc (259 mg, 1.55 mmol), 1-chloro-4-iodobenzene (369 mg, 1.55 mmol) and $Pd(OAc)_2$ (9.7 mg, 43 μmol) were employed. The crude material was purified by flash column chromatography (3% grading to 5% $MeCN/CH_2Cl_2$), affording arylated compound **6g** (324 mg, 78%) as a white solid. mp = 53–55 ºC; R_f 0.65 (10% $MeCN/CH_2Cl_2$); $[\alpha]_D^{23}$ –2º (*c* 1.1, $CHCl_3$); ν_{max} (film)/cm^{-1} 3330 (NH br), 2947, 2885, 1690 (C=O), 1525, 1486, 1409, 1355, 1324, 1164, 1125, 1091, 1014, 825, 754, 696; ^{1}H NMR (400 MHz, DMSO-d_6, 373 K) δ 9.65 (br s, 1 H, NH), 8.78 (dd, *J* = 4.2, 1.7 Hz, 1 H, HC_{Ar}), 8.33–8.28 (m, 2 H, 2 × HC_{Ar}), 7.60–7.52 (m, 2 H, 2 × HC_{Ar}), 7.46 (t, *J* = 8.0 Hz, 1 H, HC_{Ar}), 7.38–7.06 (m, 9 H, 9 × HC_{Ar}), 5.17–5.04 (m, 2 H, OCH_2), 4.97 (d, *J* = 8.5 Hz, 1 H, HCC=O), 3.97–3.83 (m, 2 H, NC*H*H and CHC_{Ar}), 3.67–3.58 (m, 1 H, NCH*H*), 2.64–2.52 (m, 1 H, NCH_2CHH), 2.25 (m, 1 H, NCH_2CHH); ^{13}C NMR (101 MHz, DMSO-d_6, 373 K) δ 167.9 (C=O amide), 153.5 (C=O carbamate), 148.0 (C_{Ar}), 137.5 (C_{Ar} quat.), 136.3 (C_{Ar} quat.), 135.7 (C_{Ar} quat.), 135.6 (C_{Ar}), 133.1 (C_{Ar} quat.), 131.1 (C_{Ar} quat.), 129.3 (2 × C_{Ar}), 127.4 (2 × C_{Ar}), 127.3 (2 × C_{Ar}), 127.1 (C_{Ar} quat.), 126.9 (C_{Ar}), 126.6 (2 × C_{Ar}), 126.0 (C_{Ar}), 121.23 (C_{Ar}), 121.19 (C_{Ar}), 115.5 (C_{Ar}), 65.7 (OCH_2), 64.8 (H*C*C=O), 46.1 (*C*HC_{Ar}), 45.7 (NCH_2), 27.2 (NCH_2CH_2); HRMS (ESI^+) *m/z* Calculated for $C_{28}H_{25}N_3O_3Cl^+$ $[M+H]^+$ 486.1584; Found 486.1581.

Benzyl (2*S*,3*S*)-3-[4-bromophenyl]-2-[(quinolin-8-yl)carbamoyl]pyrrolidine-1-carboxylate (6h)



Prepared according to the **General Procedure**: amide **1** (284 mg, 0.76 mmol), AgOAc (227 mg, 1.36 mmol), 1-bromo-4-iodobenzene (384 mg, 1.36 mmol) and $Pd(OAc)_2$ (8.5 mg, 38 μmol) were employed. The crude material was purified by flash column chromatography (3% grading to 5% $MeCN/CH_2Cl_2$), affording arylated compound **6h** (272 mg, 68%) as a white solid, followed by dimer **S14** as a brown solid (18 mg, 6%; *vide infra*). mp = 62–65 ºC; R_f 0.67 (10% $MeCN/CH_2Cl_2$); $[\alpha]_D^{22}$ –10º (*c* 2.7, $CHCl_3$); ν_{max} (film)/cm^{-1} 3338 (NH br), 2946, 2885, 1690 (C=O), 1525, 1486, 1407, 1354, 1323, 1192, 1164, 1125, 1010, 825, 790, 752, 696, 673; ^{1}H NMR (400 MHz, DMSO-d_6, 373 K) δ 9.64 (br s, 1 H, NH), 8.78 (dd, *J* = 4.2, 1.7 Hz, 1 H, HC_{Ar}), 8.32–8.31 (m, 1 H, HC_{Ar}), 8.30–8.29 (m, 1 H, HC_{Ar}), 7.58 (dd, *J* = 8.3, 1.3 Hz, 1 H, HC_{Ar}), 7.56 (dd, *J* = 8.3, 4.2 Hz, 1 H, HC_{Ar}), 7.48–7.44 (m, 1 H, HC_{Ar}), 7.38–6.99 (m, 9 H, 9 × HC_{Ar}), 5.15–5.06 (m, 2 H, OCH_2), 4.97 (d, *J* = 8.5 Hz, 1 H, HCC=O), 3.95–3.83 (m, 2 H, NCH_2), 3.65–3.59 (m, 1 H, CHC_{Ar}), 2.62–2.53 (m, 1 H, NCH_2CHH), 2.24–2.17 (m, 1 H, NCH_2CHH); ^{13}C NMR (126 MHz, DMSO-d_6, 373 K) δ 168.0 (C=O amide), 153.5 (C=O carbamate), 148.0 (C_{Ar}), 137.5 (C_{Ar} quat.), 136.3 (C_{Ar} quat.), 136.2 (C_{Ar} quat.), 135.7 (C_{Ar}), 133.1 (C_{Ar} quat.), 130.3 (2 × C_{Ar}), 129.7 (2 × C_{Ar}), 127.5 (2 × C_{Ar}), 127.1 (C_{Ar} quat.), 126.9 (C_{Ar}), 126.6 (2 × C_{Ar}), 126.0 (C_{Ar}), 121.3 (C_{Ar}), 121.2 (C_{Ar}), 119.5 (C_{Ar} quat.), 115.6 (C_{Ar}), 65.7 (OCH_2), 64.7 (H*C*C=O), 46.2 (*C*HC_{Ar}), 45.7 (NCH_2), 27.1 (NCH_2CH_2); HRMS (ESI^+) *m/z* Calculated for $C_{28}H_{25}N_3O_3Br^+$ $[M+H]^+$ 530.1079; Found 530.1101.

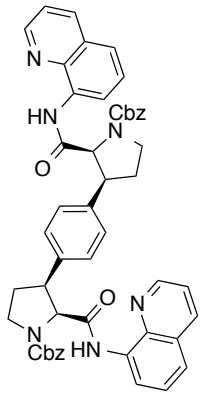
Benzyl (2*S*,3*S*)-3-(4-iodophenyl)-2-[(quinolin-8-yl)carbamoyl]pyrrolidine-1-carboxylate (6i)



Prepared according to the **General Procedure**: amide **1** (290 mg, 0.77 mmol), AgOAc (231 mg, 1.39 mmol), 1,4-diiodobenzene (457 mg, 1.55 mmol) and $Pd(OAc)_2$ (8.6 mg, 0.39 μmol) were employed. The crude material was purified by flash column chromatography (3% grading to 5% $MeCN/CH_2Cl_2$), affording arylated compound **6i** (284 mg, 64%) as a white solid. Eluting further (20% $MeCN/CH_2Cl_2$) also afforded dimer **S14** (vide infra). mp = 135–138 ºC; R_f 0.73 (10%

MeCN/CH_2Cl_2); $[\alpha]_D^{23}$ –24º (*c* 2.4, $CHCl_3$); ν_{max} (film)/cm^{-1} 3341 (NH br), 2950, 2877, 1690 (C=O), 1595, 1525, 1485, 1407, 1323, 1350, 1445, 1260, 1203, 1164, 1125, 1104, 1062, 1005, 946, 913, 825, 791, 769, 739, 752, 697, 675; ^{1}H NMR (500 MHz, DMSO-d_6, 373 K) δ 9.63 (br s, 1 H, NH), 8.78 (dd, *J* = 4.2, 1.7 Hz, 1 H, HC_{Ar}), 8.32–8.28 (m, 2 H, 2 × HC_{Ar}), 7.60–7.54 (m, 2 H, 2 × HC_{Ar}), 7.46 (t, *J* = 8.0 Hz, 1 H, HC_{Ar}), 7.43–7.39 (m, 2 H, 2 × HC_{Ar}), 7.34–7.06 (m, 7 H, 7 × HC_{Ar}), 5.16–5.04 (m, 2 H, OCH_2), 4.96 (d, *J* = 8.5 Hz, 1 H, HCC=O), 3.95–3.89 (m, 1 H, NC*H*H), 3.87–3.80 (m, 1 H, CHC_{Ar}), 3.65–3.57 (m, 1 H, NCH*H*), 2.60–2.51 (m, 1 H, NCH_2CHH), 2.23–2.16 (m, 1 H, NCH_2CHH); ^{13}C NMR (126 MHz, DMSO-d_6, 373 K) δ 167.9 (C=O amide), 153.5 (C=O carbamate), 148.0 (C_{Ar}), 137.5 (C_{Ar} quat.), 136.6 (C_{Ar} quat.), 136.3 (C_{Ar} quat.), 136.2 (2 × C_{Ar}), 135.7 (C_{Ar}), 133.1 (C_{Ar} quat.), 129.8 (2 × C_{Ar}), 127.5 (2 × C_{Ar}), 127.1 (C_{Ar} quat.), 126.9 (C_{Ar}), 126.6 (2 × C_{Ar}), 126.0 (C_{Ar}), 121.3 (C_{Ar}), 121.2 (C_{Ar}), 115.5 (C_{Ar}), 91.7 (IC_{Ar} quat.), 65.7 (OCH_2), 64.8 (H*C*C=O), 46.3 (*C*HC_{Ar}), 45.7 (NCH_2), 27.0 (NCH_2CH_2); HRMS (ESI$^+$) *m/z* Calculated for $C_{28}H_{25}N_3O_3I^+$ $[M+H]^+$ 578.0937; Found 578.0941.

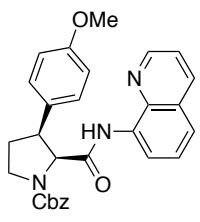
Benzyl (2*S*,3*S*)-3-{4-[(2*S*,3*S*)-1-[(benzyloxy)carbonyl]-2-[(quinolin-8-yl)carbamoyl]pyrrolidin-3-yl]phenyl}-2-[(quinolin-8-yl)carbamoyl]pyrrolidine-1-carboxylate (S14)



From reaction with 1,4-diiodobenzene

Eluting further (20% MeCN/CH_2Cl_2) gave dimer **S14** (104 mg, 33%) as an off-white solid. mp = 166–169 ºC; R_f 0.41 (20% MeCN/CH_2Cl_2); $[\alpha]_D^{23}$ –25º (*c* 3.3, $CHCl_3$); ν_{max} (film)/cm^{-1} 3345 (NH br), 3033, 2956, 2879, 1698 (C=O), 1596, 1580, 1526, 1486, 1464, 1413, 1379, 1351, 1323, 1292, 1283, 1258, 1228, 1210, 1121, 990, 824, 791, 747, 737, 694, 666; ^{1}H NMR (500 MHz, DMSO-d_6, 373 K) δ 9.48 (br s, 2 H, 2 × NH), 8.74 (dd, *J* = 4.2, 1.7 Hz, 2 H, 2 × HC_{Ar}), 8.28 (dd, *J* = 8.3, 1.7 Hz, 2 H, 2 × HC_{Ar}), 8.20 (dd, *J* = 7.7, 1.3 Hz, 2 H, 2 × HC_{Ar}), 7.56–7.51 (m, 4 H, 4 × HC_{Ar}), 7.39 (t, *J* = 7.9 Hz, 2 H, 2 × HC_{Ar}), 7.30–7.02 (m, 10 H, 10 × HC_{Ar}), 7.00 (s, 4 H, 4 × HC_{Ar}), 5.11–5.00 (m, 4 H, 2 × OCH_2), 4.79 (d, *J* = 8.4 Hz, 2 H, 2 × *H*CC=O), 3.80–3.73 (m, 2 H, 2 × NC*H*H), 3.56–3.42 (m, 4 H, 2 × NCH*H* and 2 × CHC_{Ar}), 2.28–2.16 (m, 2 H, 2 × NCH_2CHH), 1.72–1.64 (m, 2 H, 2 × NCH_2CHH); ^{13}C NMR (126 MHz, DMSO-d_6, 373 K) δ 167.9 (2 × C=O amide), 153.4 (2 × C=O carbamate), 147.8 (2 × C_{Ar}), 137.4 (2 × C_{Ar} quat.), 136.3 (2 × C_{Ar} quat.), 135.6 (2 × C_{Ar}), 135.1 (2 × C_{Ar} quat.), 133.2 (2 × C_{Ar} quat.), 127.4 (4 × C_{Ar}), 127.1 (4 × C_{Ar}), 127.0 (2 × C_{Ar} quat.), 126.9 (2 × C_{Ar}), 126.5 (4 × C_{Ar}), 126.0 (2 × C_{Ar}), 121.2 (2 × C_{Ar}), 121.0 (2 × C_{Ar}), 115.3 (2 × C_{Ar}), 65.6 (2 × OCH_2), 64.8 (2 × H*C*C=O), 46.3 (2 × *C*HC_{Ar}), 45.6 (2 × NCH_2), 27.0 (2 × NCH_2CH_2); HRMS (ESI$^+$) *m/z* Calculated for $C_{50}H_{45}N_6O_6^+$ $[M+H]^+$ 825.3401; Found 825.3361.

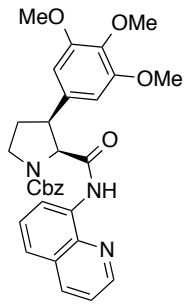
Benzyl (2*S*,3*S*)-3-(4-methoxyphenyl)-2-[(quinolin-8-yl)carbamoyl]pyrrolidine-1-carboxylate (6j)



Prepared according to the **General Procedure**: amide **1** (286 mg, 0.76 mmol), AgOAc (229 mg, 1.37 mmol), 4-iodoanisole (323 mg, 1.37 mmol) and $Pd(OAc)_2$ (8.4 mg, 37 μmol) were employed. The crude material was purified by flash column chromatography (70% Et_2O/hexane), affording arylated compound **6j** (313 mg, 85%) as a white solid. mp = 115–117 ºC; R_f 0.85 (EtOAc); $[\alpha]_D^{22}$ –1º (*c* 2.0, $CHCl_3$); ν_{max} (film)/cm^{-1} 3346 (NH br), 2946, 2871, 1689 (C=O), 1612, 1529, 1487, 1410, 1347,1326, 1248, 1206, 1161, 1123, 1109, 1035, 984, 825, 795, 767, 738, 697, 669; ^{1}H NMR (500 MHz, DMSO-d_6, 373 K) δ 9.57 (br s, 1 H, NH), 8.77 (dd, *J* = 4.0, 1.5 Hz, 1 H, HC_{Ar}), 8.33 (dd, *J* = 7.6, 1.0 Hz, 1 H, HC_{Ar}), 8.30 (dd, *J* = 8.2, 1.5 Hz, 1 H, HC_{Ar}), 7.62–7.51 (m, 2 H, 2 × HC_{Ar}),

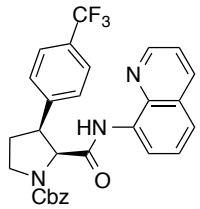
7.51–7.42 (m, 1 H, HC_{Ar}), 7.36–6.91 (m, 7 H, HC_{Ar}), 6.62 (d, *J* = 8.7 Hz, 2 H, 2 × HC_{Ar}), 5.19–5.02 (m, 2 H, OCH_2), 4.88 (d, *J* = 8.5 Hz, 1 H, HCC=O), 3.97–3.88 (m, 1 H, NC*H*H), 3.87–3.77 (m, 1 H, CHC_{Ar}), 3.68–3.56 (m, 1 H, NCH*H*), 3.47 (s, 3 H, CH_3), 2.62–2.52 (m, 1 H, NCH_2CHH), 2.23–2.12 (m, 1 H, NCH_2CHH); ^{13}C NMR (126 MHz, DMSO-d_6, 373 K) δ 168.2 (C=O amide), 157.8 (C_{Ar} quat.), 153.5 (C=O carbamate), 147.9 (C_{Ar}), 137.4 (C_{Ar} quat.), 136.3 (C_{Ar} quat.), 135.6 (C_{Ar}), 133.3 (C_{Ar} quat.), 128.6 (C_{Ar} quat.), 128.4 (2 × C_{Ar}), 127.5 (2 × C_{Ar}), 127.1 (C_{Ar} quat.), 126.9 (C_{Ar}), 126.5 (2 × C_{Ar}), 126.1 (C_{Ar}), 121.2 (C_{Ar}), 121.0 (C_{Ar}), 115.3 (C_{Ar}), 113.2 (2 × C_{Ar}), 65.6 (OCH_2), 65.1 (H*C*C=O), 54.4 (CH_3), 46.2 (CHC_{Ar}), 45.8 (NCH_2), 27.5 (NCH_2CH_2); HRMS (ESI^+) *m/z* Calculated for $C_{29}H_{28}N_3O_4^+$ $[M+H]^+$ 482.2080; Found 482.2076.

Benzyl (2*S*,3*S*)-2-[(quinolin-8-yl)carbamoyl]-3-(3,4,5-trimethoxyphenyl)pyrrolidine-1-carboxylate (6k)



Prepared according to the **General Procedure**: amide **1** (284 mg, 0.76 mmol), AgOAc (229 mg, 1.37 mmol), 5-iodo-1,2,3-trimethoxybenzene[7] (403 mg, 1.37 mmol) and $Pd(OAc)_2$ (8.5 mg, 38 μmol) were employed. The crude material was purified by flash column chromatography (5% grading to 10% $MeCN/CH_2Cl_2$), affording arylated compound **6k** (142 mg, 34%) as a pale orange solid. mp = 64–67 ºC; R_f 0.29 (10% $MeCN/CH_2Cl_2$); $[\alpha]_D^{22}$ +6º (*c* 3.3, $CHCl_3$); ν_{max} (film)/cm^{-1} 3345 (NH br), 2942, 2839, 1692 (C=O), 1591, 1528, 1487, 1456, 1412, 1359, 1325, 1239, 1191, 1120, 827, 792, 749, 698, 666; ^{1}H NMR (500 MHz, DMSO-d_6, 373 K) δ 9.49 (br s, 1 H, NH), 8.76 (dd, *J* = 4.2, 1.7 Hz, 1 H, HC_{Ar}), 8.42 (dd, *J* = 7.7, 1.3 Hz, 1 H, HC_{Ar}), 8.28 (dd, *J* = 8.3, 1.7 Hz, 1 H, HC_{Ar}), 7.57–7.52 (m, 2 H, 2 × HC_{Ar}), 7.46 (t, *J* = 7.9 Hz, 1 H, HC_{Ar}), 7.36–7.08 (m, 5 H, 5 × HC_{Ar}), 6.62 (s, 2 H, 2 × HC_{Ar}), 5.17–5.03 (m, 2 H, OCH_2), 4.96 (d, *J* = 8.5 Hz, 1 H, HCC=O), 3.95–3.89 (m, 1 H, NC*H*H), 3.86–3.79 (m, 1 H, CHC_{Ar}), 3.64–3.59 (m, 1 H, NCH*H*), 3.58 (s, 6 H, 2 × *m*-OCH_3), 3.13 (s, 3 H, *p*-OCH_3), 2.62–2.51 (m, 1 H, NCH_2CHH), 2.22–2.13 (m, 1 H, NCH_2CHH); ^{13}C NMR (126 MHz, DMSO-d_6, 373 K) δ 168.3 (C=O amide), 153.5 (C=O carbamate), 152.2 (C_{Ar} quat.), 147.8 (C_{Ar}), 137.3 (C_{Ar} quat.), 137.0 (C_{Ar} quat.), 136.4 (C_{Ar} quat.), 135.6 (C_{Ar}), 133.4 (C_{Ar} quat.), 131.9 (C_{Ar} quat.), 127.5 (2 × C_{Ar}), 127.1 (C_{Ar} quat.), 126.9 (C_{Ar}), 126.6 (2 × C_{Ar}), 126.1 (C_{Ar}), 121.3 (C_{Ar}), 120.9 (C_{Ar}), 115.0 (C_{Ar}), 106.1 (2 × C_{Ar}), 65.6 (OCH_2), 65.1 (H*C*C=O), 58.8 (*p*-OCH_3), 55.5 (2 × *m*-OCH_3), 47.0 (CHC_{Ar}), 45.8 (NCH_2), 26.9 (NCH_2CH_2); HRMS (ESI^+) *m/z* Calculated for $C_{31}H_{32}N_3O_6^+$ $[M+H]^+$ 542.2291; Found 542.2286.

Benzyl (2*S*,3*S*)-2-[(quinolin-8-yl)carbamoyl]-3-[4-(trifluoromethyl)phenyl]pyrrolidine-1-carboxylate (6l)

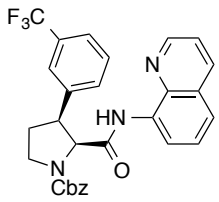


Prepared according to the **General Procedure**: amide **1** (333 mg, 0.89 mmol), AgOAc (267 mg, 1.60 mmol), 4-iodobenzotrifluoride (236 μL, 1.60 mmol) and $Pd(OAc)_2$ (10.0 mg, 45 μmol) were employed. The crude material was purified by flash column chromatography (3% grading to 5% $MeCN/CH_2Cl_2$), affording arylated compound **6l** (388 mg, 84%) as a white solid. mp = 135–137 ºC; R_f 0.62 (10% $MeCN/CH_2Cl_2$); $[\alpha]_D^{23}$ –11º (*c* 1.1, $CHCl_3$); ν_{max} (film)/cm^{-1} 3322 (NH br), 3067, 2947, 2877, 1711 (C=O), 1688 (C=O), 1529, 1487, 1444, 1405, 1324, 1192, 1150, 1115, 1103, 1064, 1018, 995, 851; ^{1}H NMR (500 MHz, DMSO-d_6, 373 K) δ 9.64 (br s, 1 H, NH), 8.75 (dd, *J* = 4.2, 1.7

(7) Barbosa, E. G.; Bega, L. A. S.; Beatriz, A.; Sarkar, T.; Hamel, E.; do Amaral, M. S.; de Lima, D. P. *Eur. J. Med. Chem.* **2009**, *44*, 2685.

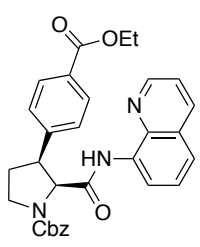
Hz, 1 H, HC_{Ar}), 8.30–8.25 (m, 2 H, 2 × HC_{Ar}), 7.58–7.50 (m, 4 H, 4 × HC_{Ar}), 7.44 (t, *J* = 7.9 Hz, 1 H, HC_{Ar}), 7.40–7.35 (m, 2 H, 2 × HC_{Ar}), 7.34–7.07 (m, 5 H, 5 × HC_{Ar}), 5.17–5.07 (m, 2 H, OCH_2), 5.06 (d, *J* = 8.5 Hz, 1 H, HCC=O), 4.03–3.93 (m, 2 H, CHC_{Ar} and NC*H*H), 3.69–3.61 (m, 1 H, NCH*H*), 2.69–2.58 (m, 1 H, NCH_2CHH), 2.28–2.22 (m, 1 H, NCH_2CHH); ^{13}C NMR (126 MHz, DMSO-d_6, 373 K) δ 167.9 (C=O amide), 153.5 (C=O carbamate), 147.9 (C_{Ar}), 141.6 (C_{Ar} quat), 137.4 (C_{Ar} quat), 136.3 (C_{Ar} quat), 135.6 (C_{Ar}), 133.0 (C_{Ar} quat), 128.3 (2 × C_{Ar}), 127.5 (2 × C_{Ar}), 127.2 (q, J_{CF} = 32 Hz, F_3CC_{Ar} quat), 127.1 (C_{Ar} quat), 126.9 (C_{Ar}), 126.6 (2 × C_{Ar}), 126.0 (C_{Ar}), 124.1 (q, J_{CF} = 4.1 Hz, 2 × C_{Ar}), 123.5 (q, J_{CF} = 273 Hz, CF_3 quat), 121.21 (C_{Ar}), 121.19 (C_{Ar}), 115.5 (C_{Ar}), 65.7 (OCH_2), 64.8 (H*C*C=O), 46.5 (*C*HC_{Ar}), 45.8 (NCH_2), 27.0 (NCH_2CH_2); ^{19}F NMR (470 MHz, DMSO-d_6, 373 K) δ –61.4; HRMS (ESI$^+$) *m/z* Calculated for $C_{29}H_{25}N_3O_3F_3^+$ $[M+H]^+$ 520.1848; Found 520.1838.

Benzyl (2*S*,3*S*)-2-[(quinolin-8-yl)carbamoyl]-3-[3-(trifluoromethyl)phenyl]pyrrolidine-1-carboxylate (6m)



Prepared according to the **General Procedure**: amide **1** (385 mg, 1.03 mmol), AgOAc (309 mg, 1.85 mmol), 3-iodobenzotrifluoride (267 μL, 1.85 mmol) and $Pd(OAc)_2$ (11.6 mg, 52 μmol) were employed. The crude material was purified by flash column chromatography (3% grading to 5% $MeCN/CH_2Cl_2$), affording arylated compound **6m** (408 mg, 76%) as a white solid. mp = 47–49 ºC; R_f 0.82 (10% $MeCN/CH_2Cl_2$); $[\alpha]_D^{23}$ +16º (*c* 2.5, $CHCl_3$); ν_{max} (film)/cm^{-1} 3334 (NH br), 3051, 2954, 2889, 1692 (C=O), 1529, 1487, 1413, 1324, 1119, 1099, 1072, 999, 960, 898, 824, 789, 696; ^{1}H NMR (500 MHz, DMSO-d_6, 373 K) δ 9.68 (br s, 1 H, NH), 8.74 (dd, *J* = 4.2, 1.7 Hz, 1 H, HC_{Ar}), 8.30 (d, *J* = 1.5 Hz, 1 H, HC_{Ar}), 8.28 (d, *J* = 1.5 Hz, 1 H, HC_{Ar}), 7.68–7.64 (m, 1 H, HC_{Ar}), 7.63–7.60 (m, 1 H, HC_{Ar}), 7.56 (dd, *J* = 8.3, 1.3 Hz, 1 H, HC_{Ar}), 7.54 (dd, *J* = 8.3, 4.2 Hz, 1 H, HC_{Ar}), 7.44 (t, *J* = 8.0 Hz, 1 H, HC_{Ar}), 7.34–7.08 (m, 7 H, 7 × HC_{Ar}), 5.16–5.03 (m, 3 H, OCH_2 and HCC=O), 4.04–3.92 (m, 2 H, CHC_{Ar} and NC*H*H), 3.68–3.60 (m, 1 H, NCH*H*), 2.70–2.58 (m, 1 H, NCH_2CHH), 2.30–2.22 (m, 1 H, NCH_2CHH); ^{13}C NMR (126 MHz, DMSO-d_6, 373 K) δ 168.0 (C=O amide), 153.5 (C=O carbamate), 147.9 (C_{Ar}), 138.2 (C_{Ar} quat), 137.5 (C_{Ar} quat), 136.3 (C_{Ar} quat), 135.6 (C_{Ar}), 133.0 (C_{Ar} quat), 131.6 (C_{Ar}), 128.6 (q, J_{CF} = 32 Hz, F_3CC_{Ar} quat), 128.3 (C_{Ar}), 127.5 (2 × C_{Ar}), 127.1 (C_{Ar} quat), 126.9 (C_{Ar}), 126.6 (2 × C_{Ar}), 126.0 (C_{Ar}), 125.7 (q, J_{CF} = 273 Hz, F_3CC_{Ar} quat), 124.2 (q, J_{CF} = 4 Hz, C_{Ar}), 122.9 (q, J_{CF} = 4 Hz, C_{Ar}), 121.22 (C_{Ar}), 121.19 (C_{Ar}), 115.5 (C_{Ar}), 65.7 (OCH_2), 64.8 (H*C*C=O), 46.5 (*C*HC_{Ar}), 45.8 (NCH_2), 27.3 (NCH_2CH_2); ^{19}F NMR (470 MHz, DMSO-d_6, 373 K) δ –61.5; HRMS (ESI$^+$) *m/z* Calculated for $C_{29}H_{25}N_3O_3F_3^+$ $[M+H]^+$ 520.1848; Found 520.1848.

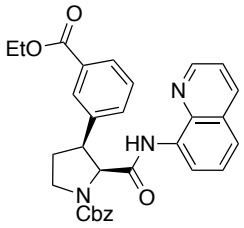
Benzyl (2*S*,3*S*)-3-[4-(ethoxycarbonyl)phenyl]-2-[(quinolin-8-yl)carbamoyl]pyrrolidine-1-carboxylate (6n)



Prepared according to the **General Procedure**: amide **1** (289 mg, 0.77 mmol), AgOAc (233 mg, 1.39 mmol), ethyl 4-iodobenzoate (234 μL, 1.39 mmol) and $Pd(OAc)_2$ (8.7 mg, 39 μmol) were employed. The crude material was purified by flash column chromatography (40% grading to 80% Et_2O/hexane), affording arylated compound **6n** (363 mg, 90%) as a white solid. mp = 55–56 ºC; R_f 0.26 (80% Et_2O/hexane); $[\alpha]_D^{22}$ +4º (*c* 2.3, $CHCl_3$); ν_{max} (film)/cm^{-1} 3338 (NH br), 2976, 2885, 1701 (C=O), 1525, 1486, 1409, 1357, 1323, 1272, 1184, 1165, 1103, 1021, 859, 826, 790, 766, 697; ^{1}H NMR (400 MHz, DMSO-d_6, 373 K) δ 9.62 (br s, 1 H, NH), 8.74 (dd, *J* = 4.2, 1.6 Hz, 1 H, HC_{Ar}), 8.31–8.29 (m, 1 H, HC_{Ar}), 8.27 (dd, *J* = 2.6, 1.3 Hz, 1 H, HC_{Ar}), 7.67–7.65 (m, 1 H, HC_{Ar}), 7.65–7.63 (m, 1 H, HC_{Ar}), 7.55 (dd, *J* = 8.3, 1.3 Hz, 1 H, HC_{Ar}), 7.52 (dd, *J* = 8.3,

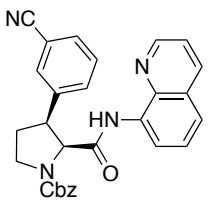
4.2 Hz, 1 H, HC_{Ar}), 7.48–7.41 (m, 3 H, 3 × HC_{Ar}), 7.39–7.00 (m, 5 H, 5 × HC_{Ar}), 5.18–5.05 (m, 2 H, OCH_2Ph), 5.02 (d, *J* = 8.5 Hz, 1 H, HCC=O), 4.18 (q, *J* = 7.1 Hz, 2 H, OCH_2CH_3), 4.01–3.91 (m, 2 H, NCH_2), 3.69–3.60 (m, 1 H, CHC_{Ar}), 2.71–2.57 (m, 1 H, NCH_2CHH), 2.29–2.20 (m, 1 H, NCH_2CHH), 1.23 (t, *J* = 7.1 Hz, 3 H, OCH_2CH_3); ^{13}C NMR (101 MHz, DMSO-d_6, 373 K) δ 167.9 (C=O amide), 164.8 (C=O ester), 153.5 (C=O carbamate), 147.9 (C_{Ar}), 142.1 (C_{Ar} quat.), 137.4 (C_{Ar} quat.), 136.3 (C_{Ar} quat.), 135.6 (C_{Ar}), 133.1 (C_{Ar} quat.), 128.3 (C_{Ar} quat.), 128.2 (2 × C_{Ar}), 127.7 (2 × C_{Ar}), 127.5 (2 × C_{Ar}), 127.1 (C_{Ar} quat.), 126.9 (C_{Ar}), 126.6 (2 × C_{Ar}), 126.0 (C_{Ar}), 121.2 (2 × C_{Ar}), 115.5 (C_{Ar}), 65.7 (OCH_2Ph), 64.8 (HCC=O), 59.7 (OCH_2CH_3), 46.7 (CHC_{Ar}), 45.8 (NCH_2), 27.0 (NCH_2CH_2), 13.4 (OCH_2CH_3); HRMS (ESI^+) *m/z* Calculated for $C_{31}H_{30}N_3O_5^+$ $[M+H]^+$ 524.2185; Found 524.2191.

Benzyl (2*S*,3*S*)-3-[3-(ethoxycarbonyl)phenyl]-2-[(quinolin-8-yl)carbamoyl]pyrrolidine-1-carboxylate (6o)



Prepared according to the **General Procedure**: amide **1** (298 mg, 0.79 mmol), AgOAc (238 mg, 1.43 mmol), ethyl 3-iodobenzoate (240 μL, 1.43 mmol) and $Pd(OAc)_2$ (8.8 mg, 40 μmol) were employed. The crude material was purified by flash column chromatography (3% grading to 10% $MeCN/CH_2Cl_2$), affording arylated compound **6o** (344 mg, 83%) as a white solid. mp = 53–55 ºC; R_f 0.81 (EtOAc); $[\alpha]_D^{22}$ +43º (*c* 2.7, $CHCl_3$); ν_{max} (film)/cm^{-1} 3339 (NH br), 2977, 2891, 1690 (C=O), 1525, 1426, 1410, 1356, 1324, 1286, 1191, 1164, 1107, 1023, 991, 826, 791, 754, 693; ^{1}H NMR (500 MHz, DMSO-d_6, 373 K) δ 9.64 (br s, 1 H, NH), 8.72 (dd, *J* = 4.2, 1.7 Hz, 1 H, HC_{Ar}), 8.30–8.28 (m, 1 H, HC_{Ar}), 8.28–8.26 (m, 1 H, HC_{Ar}), 7.94 (dd, *J* = 1.8, 1.7 Hz, 1 H, HC_{Ar}), 7.60–7.50 (m, 4 H, 4 × HC_{Ar}), 7.46–7.41 (m, 1 H, HC_{Ar}), 7.34–6.99 (m, 6 H, 6 × HC_{Ar}), 5.17–5.06 (m, 2 H, OCH_2Ph), 5.01 (d, *J* = 8.5 Hz, 1 H, HCC=O), 4.19 (q, *J* = 7.1 Hz, 2 H, OCH_2CH_3), 4.01–3.92 (m, 2 H, NCH_2), 3.69–3.60 (m, 1 H, CHC_{Ar}), 2.68–2.57 (m, 1 H, NCH_2CHH), 2.29–2.20 (m, 1 H, NCH_2CHH), 1.21 (t, *J* = 7.1 Hz, 3 H, OCH_2CH_3); ^{13}C NMR (126 MHz, DMSO-d_6, 373 K) δ 168.0 (C=O amide), 164.9 (C=O ester), 153.5 (C=O carbamate), 147.9 (C_{Ar}), 137.42 (C_{Ar} quat.), 137.38 (C_{Ar} quat.), 136.3 (C_{Ar} quat.), 135.6 (C_{Ar}), 133.0 (C_{Ar} quat.), 132.2 (C_{Ar}), 129.5 (C_{Ar} quat.), 128.2 (C_{Ar}), 127.6 (C_{Ar}), 127.5 (2 × C_{Ar}), 127.04 (C_{Ar}), 126.99 (C_{Ar}), 126.9 (C_{Ar} quat.), 126.6 (2 × C_{Ar}), 126.0 (C_{Ar}), 121.2 (C_{Ar}), 121.1 (C_{Ar}), 115.5 (C_{Ar}), 65.7 (OCH_2Ph), 64.9 (HCC=O), 59.8 (OCH_2CH_3), 46.6 (CHC_{Ar}), 45.8 (NCH_2), 27.4 (NCH_2CH_2), 13.4 (OCH_2CH_3); HRMS (ESI^+) *m/z* Calculated for $C_{31}H_{30}N_3O_5^+$ $[M+H]^+$ 524.2185; Found 524.2189.

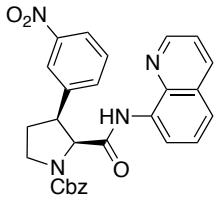
Benzyl (2*S*,3*S*)-3-(3-cyanophenyl)-2-[(quinolin-8-yl)carbamoyl]pyrrolidine-1-carboxylate (6p)



Prepared according to the **General Procedure**: amide **1** (293 mg, 0.78 mmol), AgOAc (235 mg, 1.41 mmol), 3-iodobenzonitrile (322 mg, 1.40 mmol) and $Pd(OAc)_2$ (8.8 mg, 39 μmol) were employed. The crude material was purified by flash column chromatography (80% Et_2O/hexane grading to 100% Et_2O), affording arylated compound **6p** (221 mg, 59%) as a white solid. mp = 61–63 ºC; R_f 0.17 (80% Et_2O/hexane); $[\alpha]_D^{22}$ +41º (*c* 1.7, $CHCl_3$); ν_{max} (film)/cm^{-1} 3338 (NH br), 2953, 2229 (CN), 1689 (C=O), 1526, 1486, 1410, 1356, 1323, 1165, 1122, 826, 792, 756, 690; ^{1}H NMR (500 MHz, DMSO-d_6, 373 K) δ 9.69 (br s, 1 H, NH), 8.80 (dd, *J* = 4.2, 1.7 Hz, 1 H, HC_{Ar}), 8.31 (dd, *J* = 8.3, 1.7 Hz, 1 H, HC_{Ar}), 8.27 (dd, *J* = 7.7, 1.3 Hz, 1 H, HC_{Ar}), 7.80–7.77 (m, 1 H, HC_{Ar}), 7.65–7.61 (m, 1 H, HC_{Ar}), 7.60–7.54 (m, 2 H, 2 × HC_{Ar}), 7.48–7.43 (m, 1 H, HC_{Ar}), 7.36–7.32 (m, 1 H, HC_{Ar}), 7.32–7.00 (m, 6 H, 6 × HC_{Ar}), 5.16–5.04 (m, 3 H, OCH_2 and HCC=O), 4.00–3.90 (m, 2 H, $NCHH$ and CHC_{Ar}), 3.69–3.58 (m, 1 H, NCH*H*), 2.68–2.57 (m, 1 H, NCH_2CHH), 2.29–2.19 (m, 1 H, NCH_2CHH); ^{13}C NMR (126 MHz, DMSO-d_6, 373 K) δ 167.9 (C=O amide), 153.4 (C=O carbamate),

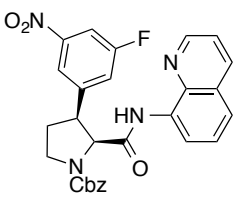
148.0 (C_{Ar}), 138.6 (C_{Ar} quat.), 137.5 (C_{Ar} quat.), 136.3 (C_{Ar} quat.), 135.7 (C_{Ar}), 133.0 (C_{Ar} quat.), 132.1 (C_{Ar}), 131.5 (C_{Ar}), 129.8 (C_{Ar}), 128.5 (C_{Ar}), 127.5 (2 × C_{Ar}), 127.1 (C_{Ar} quat.), 126.9 (C_{Ar}), 126.6 (2 × C_{Ar}), 126.0 (C_{Ar}), 121.33 (C_{Ar}), 121.27 (C_{Ar}), 117.8 (C≡N quat.), 115.7 (C_{Ar}), 110.8 (C_{Ar} quat.), 65.7 (OCH_2), 64.5 (H*C*C=O), 46.1 (*C*HC$_{Ar}$), 45.7 (NCH_2), 26.8 (NCH_2CH_2); HRMS (ESI^+) *m/z* Calculated for $C_{29}H_{25}N_4O_3^+$ $[M+H]^+$ 477.1927; Found 477.1925.

Benzyl (2*S*,3*S*)-3-(3-nitrophenyl)-2-[(quinolin-8-yl)carbamoyl]pyrrolidine-1-carboxylate (6q)



Prepared according to the **General Procedure**: amide **1** (317 mg, 0.84 mmol), AgOAc (253 mg, 1.51 mmol), 1-iodo-3-nitrobenzene (378 mg, 1.51 mmol) and $Pd(OAc)_2$ (9.5 mg, 42 μmol) were employed. The crude material was purified by flash column chromatography (80% Et_2O/hexane), affording arylated compound **6q** (310 mg, 74%) as a white solid. mp = 65–68 ºC; R_f 0.18 (80% Et_2O/hexane); $[\alpha]_D^{22}$ +34º (*c* 2.2, $CHCl_3$); ν_{max} (film)/cm^{-1} 3327 (NH br), 2959, 2892, 1689 (C=O), 1524, 1485, 1410, 1346, 1323, 1164, 1123, 825, 791, 730, 695; ^{1}H NMR (400 MHz, DMSO-d_6, 373 K) δ 9.70 (br s, 1 H, NH), 8.71 (dd, *J* = 4.2, 1.7 Hz, 1 H, HC$_{Ar}$), 8.28 (dd, *J* = 8.2, 1.6 Hz, 1 H, HC$_{Ar}$), 8.26 (dd, *J* = 7.7, 1.3 Hz, 1 H, HC$_{Ar}$), 8.23–8.21 (m, 1 H, HC$_{Ar}$), 7.77–7.75 (m, 1 H, HC$_{Ar}$), 7.75–7.72 (m, 1 H, HC$_{Ar}$), 7.58–7.51 (m, 2 H, 2 × HC$_{Ar}$), 7.45–7.40 (m, 1 H, HC$_{Ar}$), 7.38–7.03 (m, 6 H, 6 × HC$_{Ar}$), 5.18–5.07 (m, 3 H, OCH_2 and HCC=O), 4.11–4.01 (m, 1 H, NC*H*H), 4.01–3.91 (m, 1 H, NCH*H*), 3.71–3.61 (m, 1 H, CHC$_{Ar}$), 2.71–2.57 (m, 1 H, NCH_2CHH), 2.34–2.24 (m, 1 H, NCH_2CHH); ^{13}C NMR (101 MHz, DMSO-d_6, 373 K) δ 168.0 (C=O amide), 153.4 (C=O carbamate), 147.9 (C_{Ar}), 147.3 (C_{Ar} quat.), 139.2 (C_{Ar} quat.), 137.5 (C_{Ar} quat.), 136.3 (C_{Ar} quat.), 135.7 (C_{Ar}), 134.0 (C_{Ar}), 132.9 (C_{Ar} quat.), 128.7 (C_{Ar}), 127.5 (2 × C_{Ar}), 127.1 (C_{Ar} quat.), 126.9 (C_{Ar}), 126.6 (2 × C_{Ar}), 126.0 (C_{Ar}), 122.5 (C_{Ar}), 121.3 (C_{Ar}), 121.2 (C_{Ar}), 121.0 (C_{Ar}), 115.7 (C_{Ar}), 65.7 (OCH_2), 64.6 (H*C*C=O), 46.2 (*C*HC$_{Ar}$), 45.8 (NCH_2), 27.2 (NCH_2CH_2); HRMS (ESI^+) *m/z* Calculated for $C_{28}H_{25}N_4O_5^+$ $[M+H]^+$ 497.1825; Found 497.1800.

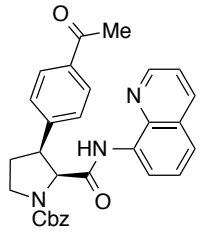
Benzyl (2*S*,3*S*)-3-(3-fluoro-5-nitrophenyl)-2-[(quinolin-8-yl)carbamoyl]pyrrolidine-1-carboxylate (6r)



Prepared according to the **General Procedure**: amide **1** (311 mg, 0.83 mmol), AgOAc (249 mg, 1.49 mmol), 1-fluoro-3-iodo-5-nitrobenzene (398 mg, 1.49 mmol) and $Pd(OAc)_2$ (9.3 mg, 42 μmol) were employed. The crude material was purified by flash column chromatography (3% grading to 5% MeCN/CH_2Cl_2), affording arylated compound **6r** (297 mg, 70%) as a white solid. mp = 62–65 ºC; R_f 0.63 (10% MeCN/CH_2Cl_2); $[\alpha]_D^{23}$ +25º (*c* 2.1, $CHCl_3$); ν_{max} (film)/cm^{-1} 3332 (NH br), 3094, 2954, 2886, 1692 (C=O), 1595, 1530, 1487, 1448, 1412, 1351, 1323, 1280, 1216, 1166, 1148, 1124, 1084, 1073, 995, 885, 827, 792, 747, 697, 665; ^{1}H NMR (400 MHz, DMSO-d_6, 373 K) δ 9.74 (br s, 1 H, NH), 8.72 (dd, *J* = 4.2, 1.7 Hz, 1 H, HC$_{Ar}$), 8.30 (dd, *J* = 8.3, 1.7 Hz, 1 H, HC$_{Ar}$), 8.26 (dd, *J* = 7.7, 1.3 Hz, 1 H, HC$_{Ar}$), 8.08–8.04 (m, 1 H, HC$_{Ar}$), 7.66–7.60 (m, 1 H, HC$_{Ar}$), 7.60–7.51 (m, 3 H, 3 × HC$_{Ar}$), 7.44 (t, *J* = 8.0 Hz, 1 H, HC$_{Ar}$), 7.42–7.04 (m, 5 H, 5 × HC$_{Ar}$), 5.20–5.06 (m, 3 H, OCH_2 and HCC=O), 4.12–4.02 (m, 1 H, CHC$_{Ar}$), 3.99–3.91 (m, 1 H, NC*H*H), 3.69 (m, 1 H, NCH*H*), 2.68–2.54 (m, 1 H, NCH_2CHH), 2.34–2.24 (m, 1 H, NCH_2CHH); ^{13}C NMR (101 MHz, DMSO-d_6, 373 K) δ 167.9 (C=O amide), 160.9 (d, J_{CF} = 248 Hz, FC$_{Ar}$ quat), 153.4 (C=O carbamate), 148.0 (d, J_{CF} = 8 Hz, C$_{Ar}$ quat.), 147.9 (C$_{Ar}$), 141.8 (d, J_{CF} = 8 Hz, C$_{Ar}$ quat.), 137.5 (C$_{Ar}$ quat), 136.2 (C$_{Ar}$ quat.), 135.7 (C$_{Ar}$), 132.9 (C$_{Ar}$ quat.), 127.5 (2 × C$_{Ar}$), 127.1 (C$_{Ar}$ quat.), 126.9 (C$_{Ar}$), 126.6 (2 × C$_{Ar}$), 126.0 (C$_{Ar}$), 121.4 (d, J_{CF} = 22 Hz, C$_{Ar}$), 121.3 (d, J_{CF} = 22 Hz, C$_{Ar}$), 118.8 (d, J_{CF} = 3 Hz, C$_{Ar}$), 115.9 (C$_{Ar}$), 108.7 (C$_{Ar}$), 108.5 (C$_{Ar}$), 65.8 (OCH_2), 64.4 (H*C*C=O), 46.0 (*C*HC$_{Ar}$), 45.7

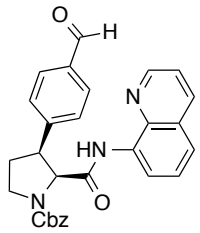
(NCH_2), 27.0 (NCH_2CH_2); ^{19}F NMR (376 MHz, DMSO-d_6, 373 K) δ –110.4; HRMS (ESI^+) *m/z* Calculated for $C_{28}H_{24}FN_4O_5^+$ $[M+H]^+$ 515.1731; Found 515.1723.

Benzyl (2*S*,3*S*)-3-(4-acetylphenyl)-2-[(quinolin-8-yl)carbamoyl]pyrrolidine-1-carboxylate (6s)



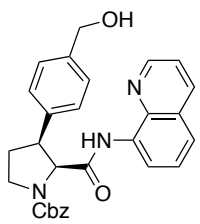
Prepared according to the **General Procedure**: amide **1** (338 mg, 0.90 mmol), AgOAc (270 mg, 1.62 mmol), 4'-iodoacetophenone (399 mg, 1.62 mmol) and $Pd(OAc)_2$ (10.1 mg, 0.45 μmol) were employed. The crude material was purified by flash column chromatography (5% grading to 10% $MeCN/CH_2Cl_2$), affording arylated compound **6s** (330 mg, 74%) as a white solid. mp = 58–61 ºC; R_f 0.27 (10% $MeCN/CH_2Cl_2$); $[\alpha]_D^{24}$ –4º (*c* 2.7, $CHCl_3$); ν_{max} (film)/cm^{-1} 3327 (NH br), 2950, 2881, 1678 (C=O), 1608, 1525, 1486, 1447, 1409, 1355, 1324, 1267, 1188, 1165, 1128, 1111, 1062, 1017, 957, 913, 848, 826, 791, 755, 696; ^1H NMR (400 MHz, DMSO-d_6, 373 K) δ 9.64 (br s, 1 H, NH), 8.75 (dd, *J* = 4.2, 1.7 Hz, 1 H, HC_{Ar}), 8.31–8.25 (m, 2 H, 2 × HC_{Ar}), 7.65–7.60 (m, 2 H, 2 × HC_{Ar}), 7.57–7.50 (m, 2 H, 2 × HC_{Ar}), 7.48–7.41 (m, 3 H, 3 × HC_{Ar}), 7.36–7.08 (m, 5 H, 5 × HC_{Ar}), 5.17–5.06 (m, 2 H, OCH_2), 5.03 (d, *J* = 8.5 Hz, 1 H, HCC=O), 4.01–3.91 (m, 2 H, NC*H*H and CHC_{Ar}), 3.69–3.60 (m, 1 H, NCH*H*), 2.70 (m, 1 H, NCH_2CHH), 2.28 (s, 3 H, CH_3), 2.27–2.20 (m, 1 H, NCH_2CHH); ^{13}C NMR (101 MHz, DMSO-d_6, 373 K) δ 196.3 (C=O ketone), 167.9 (C=O amide), 153.5 (C=O carbamate), 147.9 (C_{Ar}), 142.1 (C_{Ar} quat.), 137.4 (C_{Ar} quat.), 136.3 (C_{Ar} quat.), 135.6 (C_{Ar}), 135.3 (C_{Ar} quat.), 133.1 (C_{Ar} quat.), 127.8 (2 × C_{Ar}), 127.5 (2 × C_{Ar}), 127.1 (2 × C_{Ar}), 127.0 (C_{Ar} quat.), 126.9 (C_{Ar}), 126.6 (2 × C_{Ar}), 126.0 (C_{Ar}), 121.2 (C_{Ar}), 121.1 (C_{Ar}), 115.5 (C_{Ar}), 65.7 (OCH_2), 64.8 (H*C*C=O), 46.7 (*C*HC_{Ar}), 45.8 (NCH_2), 27.1 (NCH_2CH_2), 25.5 (CH_3); HRMS (ESI^+) *m/z* Calculated for $C_{30}H_{28}N_3O_4^+$ $[M+H]^+$ 494.2080; Found 494.2088.

Benzyl (2*S*,3*S*)-3-(4-formylphenyl)-2-[(quinolin-8-yl)carbamoyl]pyrrolidine-1-carboxylate (6t)



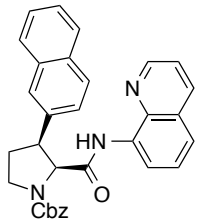
Prepared according to the **General Procedure**: amide **1** (301 mg, 0.80 mmol), AgOAc (240 mg, 1.44 mmol), 4-iodobenzaldehyde (334 mg, 1.44 mmol) and $Pd(OAc)_2$ (9.0 mg, 40 μmol) were employed. The crude material was purified by flash column chromatography (3% grading to 5% $MeCN/CH_2Cl_2$), affording arylated compound **6t** (110 mg, 29%) as a white solid. mp = 58–60 ºC; R_f 0.59 (10% $MeCN/CH_2Cl_2$); $[\alpha]_D^{23}$ –1º (*c* 1.6, $CHCl_3$); ν_{max} (film)/cm^{-1} 3329 (NH br), 2951, 1690 (C=O), 1663, 1608, 1577, 1525, 1486, 1447, 1409, 1355, 1285, 1212, 1169, 1124, 1029, 1007, 993, 914, 827, 791, 737, 696, 662; ^1H NMR (400 MHz, DMSO-d_6, 373 K) δ 9.73 (s, 1 H, CHO), 9.67 (br s, 1 H, NH), 8.75 (dd, *J* = 4.2, 1.7 Hz, 1 H, HC_{Ar}), 8.28 (dd, *J* = 5.1, 1.5 Hz, 1 H, HC_{Ar}), 8.26 (dd, *J* = 4.4, 1.5 Hz, 1 H, HC_{Ar}), 7.63–7.58 (m, 2 H, 2 × HC_{Ar}), 7.58–7.50 (m, 4 H, 4 × HC_{Ar}), 7.44 (t, *J* = 8.0 Hz, 1 H, HC_{Ar}), 7.36–7.05 (m, 5 H, 5 × HC_{Ar}), 5.17–5.02 (m, 3 H, OCH_2 and HCC=O), 4.04–3.91 (m, 2 H, NC*H*H and CHC_{Ar}), 3.70–3.60 (m, 1 H, NCH*H*), 2.72–2.58 (m, 1 H, NCH_2CHH), 2.31–2.22 (m, 1 H, NCH_2CHH); ^{13}C NMR (101 MHz, DMSO-d_6, 373 K) δ 191.3 (C=O aldehyde), 167.9 (C=O amide), 153.5 (C=O carbamate), 147.9 (C_{Ar}), 143.8 (C_{Ar} quat.), 137.5 (C_{Ar} quat.), 136.3 (C_{Ar} quat.), 135.6 (C_{Ar}), 134.7 (C_{Ar} quat.), 133.0 (C_{Ar} quat.), 128.4 (2 × C_{Ar}), 128.3 (2 × C_{Ar}), 127.5 (2 × C_{Ar}), 127.1 (C_{Ar} quat.), 126.9 (C_{Ar}), 126.6 (2 × C_{Ar}), 126.0 (C_{Ar}), 121.2 (2 × C_{Ar}), 115.6 (C_{Ar}), 65.7 (OCH_2), 64.8 (H*C*C=O), 46.8 (*C*HC_{Ar}), 45.8 (NCH_2), 27.1 (NCH_2CH_2); HRMS (ESI^+) *m/z* Calculated for $C_{29}H_{26}N_3O_4^+$ $[M+H]^+$ 480.1923; Found 480.1912.

Benzyl (2*S*,3*S*)-3-[4-(hydroxymethyl)phenyl]-2-[(quinolin-8-yl)carbamoyl]pyrrolidine-1-carboxylate (6u)



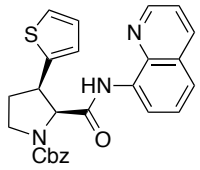
Prepared according to the **General Procedure**: amide **1** (299 mg, 0.80 mmol), AgOAc (239 mg, 1.43 mmol), 4-iodobenzyl alcohol (336 mg, 1.43 mmol) and $Pd(OAc)_2$ (9.0 mg, 40 μmol) were employed. The crude material was purified by flash column chromatography (3% grading to 20% $MeCN/CH_2Cl_2$), affording arylated compound **6u** (84 mg, 22%) as a pale yellow solid. mp = 67–70 ºC; R_f 0.05 (10% $MeCN/CH_2Cl_2$); $[\alpha]_D^{22}$ +1º (*c* 1.6, $CHCl_3$); ν_{max} (film)/cm^{-1} 3418 (OH br), 3337 (NH), 2946, 2880, 1685 (C=O), 1526, 1486, 1411, 1354, 1323, 1194, 1165, 1126, 1110, 825, 791, 734, 696; ^{1}H NMR (500 MHz, DMSO-d_6, 373 K) δ 9.66 (br s, 1 H, NH), 8.78 (dd, *J* = 4.2, 1.6 Hz, 1 H, HC_{Ar}), 8.39–8.21 (m, 2 H, 2 × HC_{Ar}), 7.60–7.52 (m, 2 H, 2 × HC_{Ar}), 7.49–7.43 (m, 1 H, HC_{Ar}), 7.38–6.91 (m, 9 H, 9 × HC_{Ar}), 5.17–5.02 (m, 2 H, OCH_2), 4.91 (d, *J* = 8.5 Hz, 1 H, HCC=O), 4.23 (s, 2 H, C*H*$_2$OH), 3.96–3.90 (m, 1 H, NC*H*H), 3.90–3.81 (m, 1 H, CHC_{Ar}), 3.67–3.58 (m, 1 H, NCH*H*), 3.12 (br s, 1 H, OH), 2.68–2.56 (m, 1 H, NCH_2CHH), 2.25–2.17 (m, 1 H, NCH_2CHH); ^{13}C NMR (126 MHz, DMSO-d_6, 373 K) δ 168.1 (C=O amide), 153.5 (C=O carbamate), 148.0 (C_{Ar}), 140.6 (C_{Ar} quat.), 137.4 (C_{Ar} quat.), 136.3 (C_{Ar} quat.), 135.7 (C_{Ar}), 134.9 (C_{Ar} quat.), 133.2 (C_{Ar} quat.), 127.4 (2 × C_{Ar}), 127.2 (2 × C_{Ar}), 127.1 (C_{Ar} quat.), 126.9 (C_{Ar}), 126.5 (2 × C_{Ar}) 126.1 (C_{Ar}), 125.5 (2 × C_{Ar}), 121.3 (C_{Ar}), 121.1 (C_{Ar}), 115.4 (C_{Ar}), 65.7 (OCH_2), 65.0 (H*C*C=O), 62.1 (CH_2OH), 46.7 (*C*HC_{Ar}), 45.7 (NCH_2), 27.5 (NCH_2CH_2); HRMS (ESI$^+$) *m/z* Calculated for $C_{29}H_{28}N_3O_4^+$ $[M+H]^+$ 482.2080; Found 482.2078.

Benzyl (2*S*,3*S*)-3-(naphthalen-2-yl)-2-[(quinolin-8-yl)carbamoyl]pyrrolidine-1-carboxylate (6v)



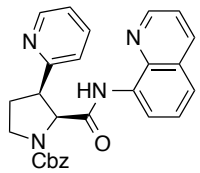
A sealable reaction tube was charged with benzyl (2*S*)-2-[(quinolin-8-yl)carbamoyl]pyrrolidine-1-carboxylate **1** (294 mg, 0.78 mmol), AgOAc (286 mg, 1.72 mmol), 2-iodonaphthalene (574 mg, 2.34 mmol), $Pd(OAc)_2$ (8.8 mg, 39 μmol) and toluene (0.39 mL). The reaction vessel was purged with argon and sealed, then placed in an oil bath (preheated to 110 ºC) for 20 h. The reaction mixture was then allowed to cool to rt and EtOAc (10 mL) was added. The resulting solution was filtered through a pad of Celite, eluting with further EtOAc (2 × 10 mL). The solvent was removed under reduced pressure, and the crude material was purified by flash column chromatography (3% grading to 5% $MeCN/CH_2Cl_2$). The product containing fractions were combined and the solvent was removed under reduced pressure. Et_2O (10 mL) was added and the solvent was removed under reduced pressure to afford the arylated compound **6v** (287 mg, 73%) as a white solid. mp = 64–67 ºC; R_f 0.76 (10% $MeCN/CH_2Cl_2$); $[\alpha]_D^{28}$ –11º (*c* 2.6, $CHCl_3$); ν_{max} (film)/cm^{-1} 3342 (NH br), 3012, 2952, 2886, 1689 (C=O), 1525, 1486, 1409, 1352, 1324, 1216, 1164, 1116, 1064, 895, 858, 823, 791, 746, 697; ^{1}H NMR (500 MHz, DMSO-d_6, 373 K) δ 9.64 (br s, 1 H, NH), 8.58 (dd, *J* = 4.0, 1.3 Hz, 1 H, HC_{Ar}), 8.27–8.23 (m, 1 H, HC_{Ar}), 8.19 (dd, *J* = 8.3, 1.4 Hz, 1 H, HC_{Ar}), 7.82 (s, 1 H, HC_{Ar}), 7.67 (d, *J* = 8.0 Hz, 1 H, HC_{Ar}), 7.61–7.56 (m, 2 H, 2 × HC_{Ar}), 7.51–7.45 (m, 2 H, 2 × HC_{Ar}), 7.43 (dd, *J* = 8.3, 4.2 Hz, 1 H, HC_{Ar}), 7.39–7.03 (m, 8 H, HC_{Ar}), 5.18–5.08 (m, 2 H, OCH_2), 5.06 (d, *J* = 8.4 Hz, 1 H, HCC=O), 4.10–3.97 (m, 2 H, NC*H*H and CHC_{Ar}), 3.73–3.63 (m, 1 H, NCH*H*), 2.81–2.70 (m, 1 H, NCH_2CHH), 2.35–2.26 (m, 1 H, NCH_2CHH); ^{13}C NMR (126 MHz, DMSO-d_6, 373 K) δ 168.1 (C=O amide), 153.5 (C=O carbamate), 147.7 (C_{Ar}), 137.3 (C_{Ar} quat.), 136.3 (C_{Ar} quat.), 135.5 (C_{Ar}), 134.3 (C_{Ar} quat.), 133.1 (C_{Ar} quat.), 132.4 (C_{Ar} quat.), 131.6 (C_{Ar} quat.), 127.5 (2 × C_{Ar}), 126.92 (C_{Ar} quat.), 126.87 (C_{Ar}), 126.8 (C_{Ar}), 126.7 (C_{Ar}), 126.6 (2 × C_{Ar}), 126.5 (C_{Ar}), 126.1 (C_{Ar}), 125.9 (C_{Ar}), 125.8 (C_{Ar}), 125.1 (C_{Ar}), 124.7 (C_{Ar}), 121.1 (C_{Ar}), 121.0 (C_{Ar}), 115.4 (C_{Ar}), 65.7 (OCH_2), 65.0 (H*C*C=O), 47.0 (*C*HC_{Ar}), 45.8 (NCH_2), 27.4 (NCH_2CH_2); HRMS (ESI$^+$) *m/z* Calculated for $C_{32}H_{28}N_3O_3^+$ $[M+H]^+$ 502.2131; Found 502.2140.

Benzyl (2*S*,3*R*)-2-[(quinolin-8-yl)carbamoyl]-3-(thiophen-2-yl)pyrrolidine-1-carboxylate (6w)



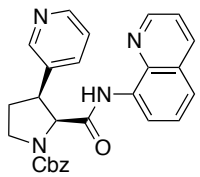
Prepared according to the **General Procedure**: amide **1** (296 mg, 0.79 mmol), AgOAc (237 mg, 1.42 mmol), 2-iodothiophene (160 μL, 1.42 mmol) and $Pd(OAc)_2$ (9.0 mg, 40 μmol) were employed. The crude material was purified by flash column chromatography (50% grading to 70% hexane/Et_2O), affording arylated compound **6w** (313 mg, 87%) as a yellow solid. mp = 52–55 ºC; R_f 0.14 (70% Et_2O/hexane); $[\alpha]_D^{22}$ +58º (*c* 3.0, $CHCl_3$); ν_{max} (film)/cm^{-1} 3337 (NH), 2949, 2890, 1690 (C=O), 1525, 1485, 1407, 1353, 1323, 1163, 1114, 823, 791, 754, 695; ^{1}H NMR (400 MHz, DMSO-d_6, 373 K) δ 9.77 (br s, 1 H, NH), 8.81 (dd, *J* = 4.2, 1.7 Hz, 1 H, HC_{Ar}), 8.39 (dd, *J* = 7.7, 1.3 Hz, 1 H, HC_{Ar}), 8.31 (dd, *J* = 8.3, 1.7 Hz, 1 H, HC_{Ar}), 7.61–7.53 (m, 2 H, 2 × HC_{Ar}), 7.51–7.44 (m, 1 H, HC_{Ar}), 7.35–7.05 (m, 6 H, 6 × HC_{Ar}), 7.05–7.00 (m, 1 H, HC_{Ar}), 6.75 (dd, *J* = 5.1, 3.5 Hz, 1 H, HC_{Ar}), 5.16–5.03 (m, 2 H, OCH_2), 4.91 (d, *J* = 8.3 Hz, 1 H, HCC=O), 4.21–4.10 (m, 1 H, NC*H*H), 3.94–3.86 (m, 1 H, NCH*H*), 3.68–3.57 (m, 1 H, CHC_{Ar}), 2.62–2.51 (m, 1 H, NCH_2CHH), 2.41–2.31 (m, 1 H, NCH_2CHH); ^{13}C NMR (101 MHz, DMSO-d_6, 373 K) δ 167.9 (C=O amide), 153.5 (C=O carbamate), 148.0 (HC_{Ar}), 139.7 (C_{Ar} quat.), 137.5 (C_{Ar} quat.), 136.2 (C_{Ar} quat.), 135.7 (HC_{Ar}), 133.3 (C_{Ar} quat.), 127.4 (2 × HC_{Ar}), 127.1 (C_{Ar} quat.), 126.9 (HC_{Ar}), 126.6 (2 × HC_{Ar}), 126.1 (HC_{Ar}), 125.9 (HC_{Ar}), 125.3 (HC_{Ar}), 123.7 (HC_{Ar}), 121.3 (HC_{Ar}), 121.1 (HC_{Ar}), 115.5 (HC_{Ar}), 65.7 (OCH_2), 65.0 (H*C*C=O), 45.6 (NCH_2), 42.2 (*C*HC_{Ar}), 29.8 (NCH_2CH_2); HRMS (ESI$^+$) *m/z* Calculated for $C_{26}H_{24}N_3O_3S^+$ $[M+H]^+$ 458.1538; Found 458.1548.

Benzyl (2*S*,3*R*)-3-(pyridin-2-yl)-2-[(quinolin-8-yl)carbamoyl]pyrrolidine-1-carboxylate (6x)



Prepared according to the **General Procedure**: amide **1** (287 mg, 0.76 mmol), AgOAc (228 mg, 1.37 mmol), 2-iodopyridine (145 μL, 1.37 mmol) and $Pd(OAc)_2$ (8.5 mg, 38 μmol) were employed. The crude material was purified by flash column chromatography (10% grading to 20% MeCN/CH_2Cl_2), affording arylated compound **6x** (116 mg, 34%) as a white solid. mp = 175–178 ºC; R_f 0.25 (10% MeCN/CH_2Cl_2); $[\alpha]_D^{23}$ –16º (*c* 1.6, $CHCl_3$); ν_{max} (film)/cm^{-1} 3236 (NH), 2880, 1701 (C=O), 1681 (C=O), 1591, 1525, 1488, 1469, 1424, 1350, 1284, 1224, 1177, 1117, 981, 964, 827, 792, 765, 752, 698; ^{1}H NMR (400 MHz, DMSO-d_6, 373 K) δ 10.58 (br s, 1 H, NH), 8.84 (d, *J* = 4.2, 1.7 Hz, 1 H, HC_{Ar}), 8.67–8.60 (m, 2 H, 2 × HC_{Ar}), 8.35 (dd, *J* = 8.3, 1.7 Hz, 1 H, HC_{Ar}), 7.76 (td, *J* = 7.7, 1.9 Hz, 1 H, HC_{Ar}), 7.64 (dd, *J* = 8.3, 1.4 Hz, 1 H, 4 × HC_{Ar}), 7.61–7.53 (m, 2 H, 2 × HC_{Ar}), 7.42–7.38 (m, 1 H, HC_{Ar}), 7.33–7.06 (m, 6 H, HC_{Ar}), 5.18–5.08 (m, 2 H, OCH_2), 5.03 (d, *J* = 5.9 Hz, 1 H, HCC=O), 3.90–3.82 (m, 2 H, NC*H*H and CHC_{Ar}), 3.70–3.62 (m, 1 H, NCH*H*), 2.48–2.42 (m, 1 H, NCH_2CHH), 2.21–2.11 (m, 1 H, NCH_2CHH); ^{13}C NMR (101 MHz, DMSO-d_6, 373 K) δ 169.4 (C=O amide), 159.4 (C_{Ar} quat.), 153.8 (C=O carbamate), 148.5 (C_{Ar}), 148.3 (C_{Ar}), 137.7 (C_{Ar} quat.), 136.4 (C_{Ar}), 136.3 (C_{Ar} quat.), 135.8 (C_{Ar}), 133.7 (C_{Ar} quat.), 127.5 (2 × C_{Ar}), 127.3 (C_{Ar} quat.), 126.9 (C_{Ar}), 126.6 (2 × C_{Ar}), 126.3 (C_{Ar}), 121.8 (C_{Ar}), 121.6 (C_{Ar}), 121.4 (C_{Ar}), 121.3 (C_{Ar}), 115.6 (C_{Ar}), 65.8 (OCH_2), 65.0 (H*C*C=O), 49.6 (*C*HC_{Ar}), 46.3 (NCH_2), 30.6 (NCH_2CH_2); HRMS (ESI$^+$) *m/z* Calculated for $C_{27}H_{25}N_4O_3^+$ $[M+H]^+$ 453.1927; Found 453.1909.

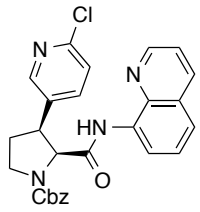
Benzyl (2*S*,3*S*)-3-(pyridin-3-yl)-2-[(quinolin-8-yl)carbamoyl]pyrrolidine-1-carboxylate (6y)



Prepared according to the **General Procedure**: amide **1** (288 mg, 0.77 mmol), AgOAc (231 mg, 1.39 mmol), 3-iodopyridine (283 mg, 1.39 mmol) and $Pd(OAc)_2$ (8.8 mg, 39 μmol) were employed. The crude material was purified by flash column chromatography (3% grading to 40% MeCN/CH_2Cl_2), affording arylated compound **6y** (99 mg, 28%) as a pale yellow solid. mp = 62–64 ºC; R_f 0.21 (50%

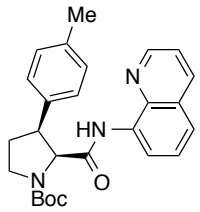
MeCN/CH_2Cl_2); $[\alpha]_D^{22}$ +50º (*c* 1.7, $CHCl_3$); ν_{max} (film)/cm^{-1} 3326 (NH), 2953, 2888, 1690, 1525, 1486, 1410, 1353, 1323, 1165, 1119, 826, 792, 754, 697; ^{1}H NMR (400 MHz, DMSO-d_6, 373 K) δ 9.79 (br s, 1 H, NH), 8.79 (dd, *J* = 4.2, 1.7 Hz, 1 H, HC_{Ar}), 8.56 (d, *J* = 2.3 Hz, 1 H, HC_{Ar}), 8.31 (dd, *J* = 8.3, 1.6 Hz, 1 H, HC_{Ar}), 8.28 (dd, *J* = 7.7, 1.3 Hz, 1 H, HC_{Ar}), 8.19 (dd, *J* = 4.7, 1.6 Hz, 1 H, HC_{Ar}), 7.72–7.66 (m, 1 H, HC_{Ar}), 7.59 (dd, *J* = 8.3, 1.3 Hz, 1 H, HC_{Ar}), 7.56 (dd, *J* = 8.3, 4.2 Hz, 1 H, HC_{Ar}), 7.49–7.43 (m, 1 H, HC_{Ar}), 7.33–6.99 (m, 6 H, HC_{Ar}), 5.16–5.05 (m, 2 H, OCH_2), 5.03 (d, *J* = 8.5 Hz, 1 H, HCC=O), 3.99–3.86 (m, 2 H, NCH_2), 3.70–3.59 (m, 1 H, CHC_{Ar}), 2.70–2.57 (m, 1 H, NCH_2CHH), 2.31–2.21 (m, 1 H, NCH_2CHH); ^{13}C NMR (101 MHz, DMSO-d_6, 373 K) δ 168.0 (C=O amide), 153.5 (C=O carbamate), 149.1 (C_{Ar}), 148.1 (C_{Ar}), 147.4 (C_{Ar}), 137.5 (C_{Ar} quat.), 136.2 (C_{Ar} quat.), 135.7 (C_{Ar}), 134.7 (C_{Ar}), 133.0 (C_{Ar} quat.), 132.3 (C_{Ar} quat.), 127.5 (2 × C_{Ar}), 127.1 (C_{Ar} quat.), 126.9 (C_{Ar}), 126.6 (2 × C_{Ar}), 126.1 (C_{Ar}), 122.2 (C_{Ar}), 121.32 (C_{Ar}), 121.29 (C_{Ar}), 115.7 (C_{Ar}), 65.7 (OCH_2), 64.6 (H*C*C=O), 45.8 (NCH_2), 44.4 (*C*HC_{Ar}), 27.1 (NCH_2CH_2); HRMS (ESI^+) *m/z* Calculated for $C_{27}H_{25}N_4O_3^+$ $[M+H]^+$ 453.1927; Found 453.1924.

Benzyl (2*S*,3*S*)-3-(6-chloropyridin-3-yl)-2-[(quinolin-8-yl)carbamoyl]pyrrolidine-1-carboxylate (6z)



Prepared according to the **General Procedure**: amide **1** (283 mg, 0.75 mmol), AgOAc (225 mg, 1.35 mmol), 2-chloro-5-iodopyridine (323 mg, 1.35 mmol) and $Pd(OAc)_2$ (8.4 mg, 38 μmol) were employed. The crude material was purified by flash column chromatography (5% grading to 20% MeCN/CH_2Cl_2), affording arylated compound **6z** (198 mg, 54%) as a white solid. mp = 59–62 ºC; R_f 0.27 (10% MeCN/CH_2Cl_2); $[\alpha]_D^{23}$ +14º (*c* 1.8, $CHCl_3$); ν_{max} (film)/cm^{-1} 3325 (NH), 2891, 1685 (C=O), 1525, 1486, 1459, 1412, 1103, 1024, 826, 790, 742, 696; ^{1}H NMR (400 MHz, DMSO-d_6, 373 K) δ 9.81 (br s, 1 H, NH), 8.79 (dd, *J* = 4.2, 1.7 Hz, 1 H, HC_{Ar}), 8.37 (d, *J* = 2.5 Hz, 1 H, HC_{Ar}), 8.32 (dd, *J* = 8.3, 1.7 Hz, 1 H, HC_{Ar}), 8.28 (dd, *J* = 7.7, 1.3 Hz, 1 H, HC_{Ar}), 7.74 (dd, *J* = 8.2, 2.5 Hz, 1 H, HC_{Ar}), 7.61 (dd, *J* = 8.3, 1.3 Hz, 1 H, HC_{Ar}), 7.57 (dd, *J* = 8.3, 4.2 Hz, 1 H, HC_{Ar}), 7.48 (t, *J* = 7.9 Hz, 1 H, HC_{Ar}), 7.36–7.04 (m, 6 H, 6 × HC_{Ar}) 5.18–5.02 (m, 3 H, OCH_2 and HCC=O), 3.98–3.87 (m, 2 H, NC*H*H and CHC_{Ar}), 3.69–3.59 (m, 1 H, NCH*H*), 2.66–2.52 (m, 1 H, NCH_2CHH), 2.30–2.20 (m, 1 H, NCH_2CHH); ^{13}C NMR (101 MHz, DMSO-d_6, 373 K) δ 167.9 (C=O amide), 153.5 (C=O carbamate), 149.1 (C_{Ar}), 148.4 (C_{Ar} quat.), 148.1 (C_{Ar}), 138.4 (C_{Ar}), 137.6 (C_{Ar} quat.), 136.2 (C_{Ar} quat.), 135.7 (C_{Ar}), 132.9 (C_{Ar} quat.), 132.0 (C_{Ar} quat.), 127.5 (2 × C_{Ar}), 127.2 (C_{Ar} quat.), 126.9 (C_{Ar}), 126.6 (2 × C_{Ar}), 126.0 (C_{Ar}), 122.7 (C_{Ar}), 121.5 (C_{Ar}), 121.3 (C_{Ar}), 116.0 (C_{Ar}), 65.8 (OCH_2), 64.4 (H*C*C=O), 45.7 (NCH_2), 43.6 (*C*HC_{Ar}), 27.1 (NCH_2CH_2); HRMS (ESI^+) *m/z* Calculated for $C_{27}H_{24}ClN_4O_3^+$ $[M+H]^+$ 487.1537; Found 487.1542.

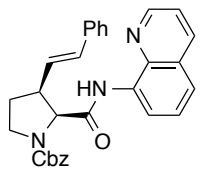
***tert*-Butyl (2*S*,3*S*)-3-(4-methylphenyl)-2-[(quinolin-8-yl)carbamoyl]pyrrolidine-1-carboxylate (7a)**



A sealable reaction tube was charged with amide **5** (256 mg, 0.75 mmol), AgOAc (250 mg, 1.50 mmol), 4-iodotoluene (491 mg, 2.25 mmol), $Pd(OAc)_2$ (8.4 mg, 38 μmol) and toluene (0.38 mL). The reaction vessel was purged with argon and sealed, then placed in an oil bath (preheated to 110 ºC) for 20 h. The reaction mixture was then allowed to cool to rt and EtOAc (10 mL) was added. The resulting solution was filtered through a pad of Celite, eluting with further EtOAc (2 × 10 mL). The solvent was removed under reduced pressure, and the crude material was purified by flash column chromatography (3% grading to 5% MeCN/CH_2Cl_2). The product containing fractions were combined and the solvent was removed under reduced pressure. Et_2O (10 mL) was added and the solvent was removed under reduced pressure to afford the arylated compound **7a** (68 mg, 21%) as

an amorphous solid. R_f 0.69 (10% MeCN/CH_2Cl_2); $[\alpha]_D^{21}$ +20º (*c* 1.5, $CHCl_3$); ν_{max} (film)/cm^{-1} 3349 (NH), 2975, 2248, 1689 (C=O), 1524, 1486, 1455, 1425, 1388, 1366, 1324, 1164, 1131, 910, 825, 792, 758, 731; ^{1}H NMR (400 MHz, DMSO-d_6, 373 K) δ 9.57 (br s, 1 H, NH), 8.80 (dd, *J* = 4.2, 1.7 Hz, 1 H, HC_{Ar}), 8.34–8.27 (m, 2 H, 2 × HC_{Ar}), 7.58–7.53 (m, 2 H, 2 × HC_{Ar}), 7.46 (t, *J* = 8.0 Hz, 1 H, HC_{Ar}), 7.17 (d, *J* = 8.0 Hz, 2 H, 2 × HC_{Ar}), 6.87 (d, *J* = 8.0 Hz, 2 H, 2 × HC_{Ar}), 4.72 (d, *J* = 8.5 Hz, 1 H, HCC=O), 3.87–3.74 (m, 2 H, CHC_{Ar} and NC*H*H), 3.55–3.46 (m, 1 H, NCH*H*), 2.60–2.48 (m, 1 H, NCH_2CH*H*), 2.18–2.10 (m, 1 H, NCH_2CH*H*), 2.00 (s, 3 H, $C_{Ar}CH_3$), 1.34 (s, 9 H, $C(CH_3)_3$); ^{13}C NMR (101 MHz, DMSO-d_6, 373 K) δ 168.5 (C=O amide), 153.0 (C=O carbamate), 147.9 (C_{Ar}), 137.4 (C_{Ar} quat.), 135.7 (C_{Ar}), 135.2 (C_{Ar} quat.), 133.8 (C_{Ar} quat.), 133.4 (C_{Ar} quat.), 127.9 (2 × C_{Ar}), 127.3 (2 × C_{Ar}), 127.1 (C_{Ar} quat.), 126.2 (C_{Ar}), 121.3 (C_{Ar}), 120.9 (C_{Ar}), 115.2 (C_{Ar}), 78.6 (*C*$(CH_3)_3$ quat.), 65.2 (H*C*C=O), 46.6 (*C*HC_{Ar}), 45.5 (NCH_2), 27.54 (C(*C*$H_3)_3$), 27.45 (NCH_2*C*H_2), 19.7 (C_{Ar}*C*H_3); HRMS (ESI^+) *m/z* Calculated for $C_{26}H_{30}N_3O_3^+$ $[M+H]^+$ 432.2287; Found 432.2285.

Benzyl (2*S*,3*S*)-3-[(*E*)-2-phenylethenyl]-2-[(quinolin-8-yl)carbamoyl]pyrrolidine-1-carboxylate (8)

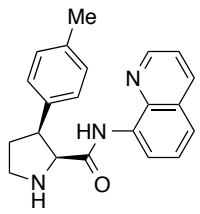


Prepared according to the **General Procedure**: amide **1** (354 mg, 0.94 mmol), AgOAc (282 mg, 1.69 mmol), [(*E*)-2-iodoethenyl]benzene[8] (389 mg, 1.69 mmol) and $Pd(OAc)_2$ (10.6 mg, 47 μmol) were employed. The crude material was purified by flash column chromatography (3% grading to 5% MeCN/CH_2Cl_2), affording arylated compound **8** (230 mg, 51%, 95:5 *E*:*Z*) as a yellow solid. mp = 47–50 ºC; R_f 0.63 (10% MeCN/CH_2Cl_2); $[\alpha]_D^{23}$ –40º (*c* 1.9, $CHCl_3$); ν_{max} (film)/cm^{-1} 3337 (NH br), 3028, 2949, 2883, 1686 (C=O), 1597, 1578, 1524, 1486, 1448, 1353, 1323, 1260, 1239, 1164, 1116, 1028, 966, 914, 826, 791, 749, 693; ^{1}H NMR (400 MHz, DMSO-d_6, 373 K) δ 10.10 (br s, 1 H, NH), 8.77 (dd, *J* = 4.2, 1.7 Hz, 1 H, HC_{Ar}), 8.52 (dd, *J* = 7.6, 1.4 Hz, 1 H, HC_{Ar}), 8.33 (dd, *J* = 8.3, 1.7 Hz, 1 H, HC_{Ar}), 7.62 (dd, *J* = 8.3, 1.4 Hz, 1 H, HC_{Ar}), 7.57–7.49 (m, 2 H, 2 × HC_{Ar}), 7.33–7.05 (m, 11 H, 11 × HC_{Ar}), 6.57 (dd, *J* = 15.9, 1.2 Hz, 1 H, CH=C*H*Ph), 6.19 (dd, *J* = 15.9, 7.8 Hz, 1 H, C*H*=CHPh), 5.16–5.04 (m, 2 H, OCH_2), 4.82 (d, *J* = 8.4 Hz, 1 H, HCC=O), 3.88–3.80 (m, 1 H, NC*H*H), 3.64–3.54 (m, 1 H, NCH*H*), 3.50–3.38 (m, 1 H, C*H*CH=CH), 2.21–2.12 (m, 2 H, NCH_2CH_2); ^{13}C NMR (101 MHz, DMSO-d_6, 373 K) δ 168.4 (C=O amide), 152.6 (C=O carbamate), 148.2 (C_{Ar}), 137.8 (C_{Ar} quat.), 136.4 (C_{Ar} quat.), 136.3 (C_{Ar} quat.), 135.8 (C_{Ar}), 133.3 (C_{Ar} quat.), 131.1 (CH=*C*HPh), 127.6 (2 × C_{Ar}), 127.5 (*C*H=CHPh), 127.3 (C_{Ar} quat.), 126.9 (C_{Ar}), 126.7 (C_{Ar}), 126.6 (C_{Ar}), 126.5 (C_{Ar}), 126.2 (C_{Ar}), 125.4 (2 × C_{Ar}), 121.4 (C_{Ar}), 121.3 (C_{Ar}), 116.0 (C_{Ar}), 65.7 (OCH_2), 64.2 (H*C*C=O), 45.8 (NCH_2), 44.4 (*C*HCH=CH), 28.6 (NCH_2CH_2); HRMS (ESI^+) *m/z* Calculated for $C_{30}H_{28}N_3O_3^+$ $[M+H]^+$ 478.2131; Found 478.2128.

(8) Bull, J. A.; Mousseau, J. J.; Charette, A. B. *Org. Lett.* **2008**, *10*, 5485.

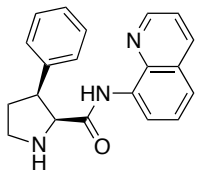
Cbz Deprotection of Selected 3-Arylated Proline Derivatives (9a,b,e,j,l)

(2*S*,3*S*)-3-(4-Methylphenyl)-*N*-(quinolin-8-yl)pyrrolidine-2-carboxamide (9a)



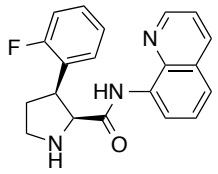
Pd/C (12 mg, 10 wt. %) was added to a solution of benzyl (2*S*,3*S*)-3-(4-methylphenyl)-2-[(quinolin-8-yl)carbamoyl]pyrrolidine-1-carboxylate **6a** (49 mg, 0.11 mmol) in EtOH (1.5 mL). The reaction vessel was evacuated and backfilled with Ar three times, followed by evacuation and backfilling with H_2 (balloon). The resulting solution was stirred vigorously at rt for 1 h, then filtered through Celite, washing with MeOH (10 mL). The crude material was purified by flash column chromatography (3% grading to 5% MeOH/CH_2Cl_2), affording pyrrolidine **9a** (34 mg, 94%) as a white solid. mp = 104–107 ºC; R_f 0.62 (10% MeOH/CH_2Cl_2); $[\alpha]_D^{28}$ +112º (*c* 2.8, $CHCl_3$); ν_{max} (film)/cm^{-1} 3296 (NH br), 2940, 2868, 1679 (C=O), 1515, 1484, 1459, 1425, 1384, 1325, 1104, 896, 826, 792, 756; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.98 (br s, 1 H, NH), 8.85 (dd, *J* = 4.2, 1.7 Hz, 1 H, HC_{Ar}), 8.48 (dd, *J* = 6.3, 2.7 Hz, 1 H, HC_{Ar}), 8.11 (dd, *J* = 8.3, 1.7 Hz, 1 H, HC_{Ar}), 7.46–7.40 (m, 3 H, 3 × HC_{Ar}), 7.16 (d, *J* = 8.0 Hz, 2 H, 2 × HC_{Ar}), 6.89 (d, *J* = 8.0 Hz, 2 H, 2 × HC_{Ar}), 4.23 (d, *J* = 8.8 Hz, 1 H, HCC=O), 3.75 (q, *J* = 8.1 Hz, 1 H, CHC_{Ar}), 3.59 (ddd, *J* = 9.5, 7.2, 4.0 Hz, 1 H, NC*H*H), 3.30–3.21 (m, 1 H, NCH*H*), 2.48 (s, 1 H, CH_2NH), 2.33–2.14 (m, 2 H, NCH_2CH_2), 2.10 (s, 3 H, CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.4 (C=O), 148.2 (C_{Ar}), 138.9 (C_{Ar} quat.), 137.4 (C_{Ar} quat.), 135.9 (C_{Ar}), 135.8 (C_{Ar} quat.), 134.0 (C_{Ar} quat.), 128.7 (2 × C_{Ar}), 128.0 (2 × C_{Ar}), 127.8 (C_{Ar} quat.), 127.1 (C_{Ar}), 121.2 (2 × C_{Ar}), 116.3 (C_{Ar}), 67.0 (H*C*C=O), 48.5 (*C*HC_{Ar}), 46.3 (NCH_2), 32.7 (NCH_2CH_2), 20.8 (CH_3); HRMS (ESI$^+$) *m/z* Calculated for $C_{21}H_{22}N_3O^+$ $[M+H]^+$ 332.1763; Found 332.1774.

(2*S*,3*S*)-3-Phenyl-*N*-(quinolin-8-yl)pyrrolidine-2-carboxamide (9b)



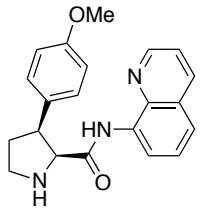
Pd/C (12 mg, 10 wt. %) was added to a solution of benzyl (2*S*,3*S*)-3-phenyl-2-[(quinolin-8-yl)carbamoyl]pyrrolidine-1-carboxylate **6b** (50 mg, 0.11 mmol) in EtOH (1.5 mL). The reaction vessel was evacuated and backfilled with Ar three times, followed by evacuation and backfilling with H_2 (balloon). The resulting solution was stirred vigorously at rt for 1 h, then filtered through Celite, washing with MeOH (10 mL). The crude material was purified by flash column chromatography (3% MeOH/CH_2Cl_2), affording pyrrolidine **9b** (30 mg, 86%) as a white solid. mp = 116–119 ºC; R_f 0.37 (5% MeOH/CH_2Cl_2); $[\alpha]_D^{25}$ +87º (*c* 0.6, $CHCl_3$); ν_{max} (film)/cm^{-1} 3288 (NH br), 2940, 1679 (C=O), 1518, 1485, 1456, 1425, 1385, 1325, 826, 792, 758, 700; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.94 (br s, 1 H, CONH), 8.85 (dd, *J* = 4.2, 1.7 Hz, 1 H, HC_{Ar}), 8.44 (dd, *J* = 6.8, 2.2 Hz, 1 H, HC_{Ar}), 8.11 (dd, *J* = 8.3, 1.7 Hz, 1 H, HC_{Ar}), 7.46–7.38 (m, 3 H, 3 × HC_{Ar}), 7.32–7.26 (m, 2 H, 2 × HC_{Ar}), 7.12–7.07 (m, 2 H, 2 × HC_{Ar}), 7.02–6.96 (m, 1 H, HC_{Ar}), 4.26 (d, *J* = 8.8 Hz, 1 H, HCC=O), 3.78 (q, *J* = 7.7 Hz, 1 H, CHC_{Ar}), 3.64–3.57 (m, 1 H, NC*H*H), 3.32–3.23 (m, 1 H, NCH*H*), 2.51 (br s, 1 H, NH), 2.36–2.16 (m, 2 H, NCH_2CH_2); ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.2 (C=O), 148.3 (C_{Ar}), 140.6 (C_{Ar} quat), 138.9 (C_{Ar} quat), 136.0 (C_{Ar}), 134.0 (C_{Ar} quat), 128.2 (2 × C_{Ar}), 127.9 (2 × C_{Ar}), 127.8 (C_{Ar} quat), 127.1 (C_{Ar}), 126.5 (C_{Ar}), 121.3 (C_{Ar}), 121.2 (C_{Ar}), 116.4 (C_{Ar}), 67.1 (H*C*C=O), 48.8 (*C*HC_{Ar}), 46.3 (NCH_2), 32.6 (NCH_2CH_2); HRMS (ESI$^+$) *m/z* Calculated for $C_{20}H_{20}N_3O^+$ $[M+H]^+$ 318.1606; Found 318.1616.

(2*S*,3*S*)-3-(2-Fluorophenyl)-*N*-(quinolin-8-yl)pyrrolidine-2-carboxamide (9e)



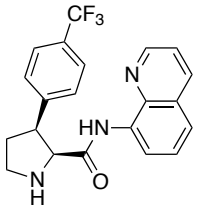
Pd/C (1.4 mg, 10 wt. %) was added to a solution of benzyl (2*S*,3*S*)-3-(2-fluorophenyl)-2-[(quinolin-8-yl)carbamoyl]pyrrolidine-1-carboxylate **6e** (61 mg, 0.13 mmol) in MeOH (2.5 mL) and EtOAc (1.0 mL). The reaction vessel was evacuated and backfilled with Ar three times, followed by evacuation and backfilling with H_2 (balloon). The resulting solution was stirred vigorously at rt for 36 h, then filtered through Celite, washing with MeOH (25 mL). The crude material was purified by flash column chromatography (1:1:100 MeOH/NEt_3/CH_2Cl_2), affording pyrrolidine **9e** (20 mg, 46%) as an off-white solid. mp = 118–121 ºC; R_f 0.64 (10% MeOH/CH_2Cl_2); $[\alpha]_D^{25}$ +126º (*c* 1.3, $CHCl_3$); ν_{max} (film)/cm^{-1} 3278 (NH br), 2876, 1683 (C=O), 1577, 1518, 1487, 1457, 1425, 1385, 1325, 1229, 1098, 826, 792, 756; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.03 (br s, 1 H, CONH), 8.90–8.83 (m, 1 H, HC_{Ar}), 846–8.40 (m, 1 H, HC_{Ar}), 8.16–8.08 (m, 1 H, HC_{Ar}), 7.48–7.36 (m, 3 H, 3 × HC_{Ar}), 7.22 (t, *J* = 7.5 Hz, 1 H, HC_{Ar}), 7.08–7.00 (m, 1 H, HC_{Ar}), 6.99–6.92 (m, 1 H, HC_{Ar}), 6.84 (t, *J* = 7.5 Hz, 1 H, HC_{Ar}), 4.35 (d, *J* = 9.1 Hz, 1 H, HCC=O), 4.12–4.03 (m, 1 H, CHC_{Ar}), 3.66–3.57 (m, 1 H, NC*H*H), 3.33–3.24 (m, 1 H, NCH*H*), 2.64 (br s, 1 H, CH_2NH), 2.32–2.16 (m, 2 H, NCH_2CH_2); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.8 (C=O amide), 161.1 (d, J_{CF} = 245 Hz, FC_{Ar} quat.), 148.4 (C_{Ar}), 138.9 (C_{Ar} quat.), 136.1 (C_{Ar}), 134.0 (C_{Ar} quat.), 128.4 (d, J_{CF} = 4.1 Hz, C_{Ar}), 128.1 (d, J_{CF} = 8.5 Hz, C_{Ar}), 127.9 (C_{Ar} quat.), 127.2 (C_{Ar}), 126.9 (d, J_{CF} = 15 Hz, C_{Ar} quat.), 123.6 (d, J_{CF} = 3.2 Hz, C_{Ar}), 121.4 (C_{Ar}), 121.3 (C_{Ar}), 116.4 (C_{Ar}), 114.9 (d, J_{CF} = 23 Hz, C_{Ar}), 65.1 (H*C*C=O), 46.3 (NCH_2), 41.1 (d, J_{CF} = 2.8 Hz, *C*HC_{Ar}), 30.5 (NCH_2CH_2); ^{19}F NMR (376 MHz, DMSO-d_6, 373 K) δ –116.7; HRMS (ESI$^+$) *m/z* Calculated for $C_{20}H_{19}N_3OF^+$ $[M+H]^+$ 336.1507; Found 336.1510.

(2*S*,3*S*)-3-(4-Methoxyphenyl)-*N*-(quinolin-8-yl)pyrrolidine-2-carboxamide (9j)



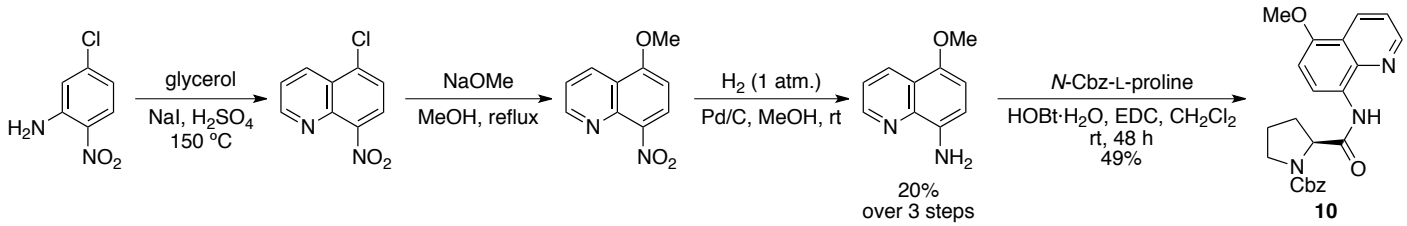
Pd/C (11 mg, 10 wt. %) was added to a solution of benzyl (2*S*,3*S*)-3-(4-methoxyphenyl)-2-[(quinolin-8-yl)carbamoyl]pyrrolidine-1-carboxylate **6j** (48 mg, 0.10 mmol) in EtOH (1.5 mL) and EtOAc (0.5 mL). The reaction vessel was evacuated and backfilled with Ar three times, followed by evacuation and backfilling with H_2 (balloon). The resulting solution was stirred vigorously at rt for 1 h, then filtered through Celite, washing with EtOH (10 mL). The crude material was purified by flash column chromatography (3% grading to 5% MeOH/CH_2Cl_2), affording pyrrolidine **9j** (26 mg, 75%) as a white solid. mp = 90–93 ºC; R_f 0.43 (5% MeOH/CH_2Cl_2); $[\alpha]_D^{28}$ +108º (*c* 0.5, $CHCl_3$); ν_{max} (film)/cm^{-1} 3295 (NH br), 2935, 2836, 1679 (C=O), 1513, 1485, 1325, 1247, 1035, 826, 792; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.90 (br s, 1 H, CONH), 8.84 (dd, *J* = 4.2, 1.7 Hz, 1 H, HC_{Ar}), 8.46 (dd, *J* = 6.7, 2.3 Hz, 1 H, HC_{Ar}), 8.11 (dd, *J* = 8.3, 1.7 Hz, 1 H, HC_{Ar}), 7.46–7.38 (m, 3 H, 3 × HC_{Ar}), 7.22–7.16 (m, 2 H, 2 × HC_{Ar}), 6.64–6.58 (m, 2 H, 2 × HC_{Ar}), 4.21 (d, *J* = 8.8 Hz, 1 H, HCC=O), 3.74 (q, *J* = 8.0 Hz, 1 H, CHC_{Ar}), 3.63–3.54 (m, 4 H, NC*H*H and CH_3), 3.31–3.21 (m, 1 H, NCH*H*), 2.45 (br s, 1 H, CH_2NH), 2.33–2.23 (m, 1 H, NCH_2CHH), 2.22–2.11 (m, 1 H, NCH_2CHH); ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.4 (C=O), 158.1 (C_{Ar} quat), 148.3 (C_{Ar}), 138.9 (C_{Ar} quat), 136.0 (C_{Ar}), 134.0 (C_{Ar} quat), 132.6 (C_{Ar} quat), 129.1 (2 × C_{Ar}), 127.9 (C_{Ar} quat), 127.2 (C_{Ar}), 121.32 (C_{Ar}), 121.26 (C_{Ar}), 116.4 (C_{Ar}), 113.4 (2 × C_{Ar}), 67.0 (H*C*C=O), 54.9 (OCH_3), 48.0 (*C*HC_{Ar}), 46.3 (N*C*H$_2$), 32.7 (NCH_2CH_2); HRMS (ESI$^+$) *m/z* Calculated for $C_{21}H_{22}N_3O_2^+$ $[M+H]^+$ 348.1712; Found 348.1724.

(2*S*,3*S*)-*N*-(Quinolin-8-yl)-3-[4-(trifluoromethyl)phenyl]pyrrolidine-2-carboxamide (9l)



Pd/C (11 mg, 10 wt. %) was added to a solution of benzyl (2*S*,3*S*)-2-[(quinolin-8-yl)carbamoyl]-3-[4-(trifluoromethyl)phenyl]pyrrolidine-1-carboxylate **6l** (52 mg, 0.10 mmol) in EtOH (1.5 mL). The reaction vessel was evacuated and backfilled with Ar three times, followed by evacuation and backfilling with H_2 (balloon). The resulting solution was stirred vigorously at rt for 1 h, then filtered through Celite, washing with EtOH (10 mL). The crude material was purified by flash column chromatography (EtOAc grading to 5% MeOH/EtOAc), affording pyrrolidine **9l** (36 mg, 93%) as an off-white solid. mp = 121–124 ºC; R_f 0.15 (5% MeOH/CH_2Cl_2); $[\alpha]_D^{28}$ +77º (*c* 0.7, $CHCl_3$); ν_{max} (film)/cm^{-1} 3296 (NH br), 2927, 1678 (C=O), 1619, 1577, 1518, 1486, 1460, 1424, 1385, 1324, 1161, 1113, 1069, 1017, 906, 825, 791, 757, 734; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.82 (br s, 1 H, CONH), 8.82 (dd, *J* = 4.2, 1.7 Hz, 1 H, HC_{Ar}), 8.39 (dd, *J* = 7.3, 1.7 Hz, 1 H, HC_{Ar}), 8.11 (dd, *J* = 8.3, 1.7 Hz, 1 H, HC_{Ar}), 7.47–7.35 (m, 5 H, 5 × HC_{Ar}), 7.29 (d, *J* = 8.2 Hz, 2 H, 2 × HC_{Ar}), 4.30 (d, *J* = 8.6 Hz, 1 H, HCC=O), 3.84 (q, *J* = 7.7 Hz, 1 H, CHC_{Ar}), 3.65–3.58 (m, 1 H, NC*H*H), 3.35–3.26 (m, 1 H, NCH*H*), 2.85 (br s, 1 H, CH_2NH), 2.39–2.29 (m, 1 H, NCH_2CHH), 2.24–2.14 (m, 1 H, NCH_2CHH); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.6 (C=O), 148.3 (C_{Ar}), 144.7 (C_{Ar} quat), 138.7 (C_{Ar} quat), 136.1 (C_{Ar}), 133.6 (C_{Ar} quat), 128.6 (q, J_{CF} = 32 Hz, F_3CC_{Ar} quat), 128.5 (2 × C_{Ar}), 127.9 (C_{Ar} quat), 127.1 (C_{Ar}), 124.9 (q, J_{CF} = 3.8 Hz, 2 × C_{Ar}), 124.0 (q, J_{CF} = 271 Hz, F_3CC_{Ar} quat), 121.7 (C_{Ar}), 121.4 (C_{Ar}), 116.4 (C_{Ar}), 67.0 (H*C*C=O), 48.4 (*C*HC_{Ar}), 46.2 (NCH_2), 32.3 (NCH_2CH_2); ^{19}F NMR (376 MHz, DMSO-d_6, 373 K) δ –62.6; HRMS (ESI$^+$) *m/z* Calculated for $C_{21}H_{19}N_3F_3O^+$ $[M+H]^+$ 386.1480; Found 386.1488.

Synthesis of *N*-Cbz Proline 5-MeO-8-AQ Amide 10



5-Methoxyquinolin-8-amine
Prepared according to the procedure of Chen.[9]

Glycerol (14.4 g, 157 mmol) was heated to 160 ºC for 1 h, then cooled to 110 ºC. NaI (170 mg, 1.20 mmol) and 5-chloro-2-nitroaniline (10.0 g, 57.9 mmol) were added and the reaction was heated to 150 ºC. Concentrated H_2SO_4 (7.1 mL, 133 mmol) was added dropwise, then the reaction was stirred vigorously for 45 min at the same temperature. The reaction was cooled to rt, diluted with H_2O (250 mL) and extracted with CH_2Cl_2 (3 × 250 mL), then washed with brine (100 mL). The combined organic extracts were dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure. The crude reaction material was used in the next step without further purification.

The residue was dissolved in MeOH (100 mL) and small pieces of sodium (2.44 g, 106 mmol) were added carefully and allowed to completely react. The reaction mixture was heated to reflux for 3 h then allowed to cool to rt. H_2O (250 mL) was added and the mixture was extracted with CH_2Cl_2 (4 × 250 mL). The combined organic extracts were dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure. The crude material was used in the next step without further purification.

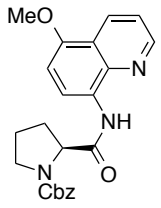
The mixture was dissolved in MeOH (200 mL). Pd/C (10 wt. % loading, 500 mg) was added and the flask was evacuated and backfilled with Ar three times, followed by evacuation and backfilling with H_2 (balloon). The reaction mixture was stirred vigorously for 4 h at rt then filtered through Celite, washing with MeOH (500 mL). The solvent was removed under reduced pressure and purification by flash column chromatography (5% grading to 10%, 15% to 20% EtOAc/hexane) afforded 5-methoxyquinolin-8-amine (2.02 g, 20% over 3 steps) as a brown solid that was sufficiently pure to use in the next step. mp = 113–116 ºC (lit.[10] 89.5–91 ºC); R_f 0.46 (50% hexane/EtOAc); ν_{max} (film)/cm^{-1} 3452, 3347, 2936, 2830, 1620, 1587, 1478, 1399, 1375, 1274, 1241, 1147, 1090, 813, 786; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.81 (dd, J = 4.2, 1.7 Hz, 1 H, HC_{Ar}), 8.51 (dd, J = 8.5, 1.7 Hz, 1 H, HC_{Ar}), 7.38 (dd, J = 8.5, 4.2 Hz, 1 H, HC_{Ar}), 6.87 (d, J = 8.2 Hz, 1 H, HC_{Ar}), 6.73 (d, J = 8.2 Hz, 1 H, HC_{Ar}), 4.39 (br s, 2 H, NH_2), 3.93 (s, 3 H, CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 148.0 (C_{Ar}), 147.0 (C_{Ar} quat.), 139.0 (C_{Ar} quat.), 137.3 (C_{Ar} quat.), 130.8 (C_{Ar}), 121.1 (C_{Ar} quat.), 120.4 (C_{Ar}), 109.7 (C_{Ar}), 105.3 (C_{Ar}), 55.9 (CH_3).

^{1}H and ^{13}C NMR spectral data consistent with those described in the literature.[9]

(9) He, G.; Zhang, S.-Y.; Nack, W. A.; Li, Q.; Chen, G. *Angew. Chem., Int. Ed.* **2013**, *52*, 11124.

(10) Elderfield, R. C.; Gensler, W. J.; Head, J. D.; Hageman, H. A.; Kremer, C. B.; Wright, J. B.; Holley, A. D.; Williamson, B.; Galbreath, J.; Wiederhold, L.; Frohardt, R.; Kupchan, S. M.; Williamson, T. A.; Birstein, O. *J. Am. Chem. Soc.* **1946**, *68*, 1524.

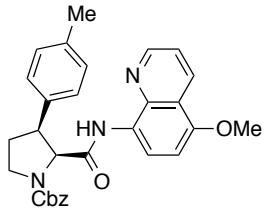
Benzyl (2*S*)-2-[(5-methoxyquinolin-8-yl)carbamoyl]pyrrolidine-1-carboxylate (10)



HOBt hydrate (822 mg, 6.08 mmol) was added to a solution of *N*-Cbz-L-proline (910 mg, 3.65 mmol) and 5-methoxyquinolin-8-amine (529 mg, 3.04 mmol) in CH_2Cl_2 (10 mL). EDC (1.07 mL, 6.08 mmol) was then added and the solution was stirred at rt for 48 h. The solvent was removed under reduced pressure, a solution of sat. aq. $NaHCO_3$ (25 mL) was added and the aqueous layer was extracted with EtOAc (3 × 50 mL). The combined organic extracts were dried with Na_2SO_4 and filtered. The solvent was removed under reduced pressure, and the crude oil was purified by flash column chromatography (60% Et_2O/hexane), affording the desired amide **10** (610 mg, 49%) as a yellow/brown oil. R_f 0.26 (75% Et_2O/hexane); $[\alpha]_D^{23}$ –102º (*c* 2.7, $CHCl_3$); ν_{max} (film)/cm^{-1} 3347 (NH br), 2954, 2882, 2246, 1681 (C=O), 1622, 1595, 1526, 1494, 1442, 1399, 1354, 1269, 1244, 1192, 1158, 1115, 1089, 1029, 984, 917, 819, 789, 770, 731, 697; ^{1}H NMR (400 MHz, DMSO-d_6, 373 K) δ 9.98 (br s, 1 H, NH), 8.86 (dd, *J* = 4.2, 1.7 Hz, 1 H, HC_{Ar}), 8.56 (dd, *J* = 8.5, 1.7 Hz, 1 H, HC_{Ar}), 8.50 (d, *J* = 8.6 Hz, 1 H, HC_{Ar}), 7.58 (dd, *J* = 8.5, 4.2 Hz, 1 H, HC_{Ar}), 7.34–7.09 (m, 5 H, 5 × HC_{Ar}), 7.03 (d, *J* = 8.5 Hz, 1 H, HC_{Ar}), 5.16–5.06 (m, 2 H, OCH_2), 4.60 (dd, *J* = 8.5, 3.8 Hz, 1 H, HCC=O), 4.00 (s, 3 H, OCH_3), 3.66–3.54 (m, 2 H, NCH_2), 2.36–2.24 (m, 1 H, NCH(C=O)C*H*H), 2.17–2.08 (m, 1 H, NCH(C=O)CH*H*), 2.04–1.88 (m, 2 H, NCH_2CH_2); ^{13}C NMR (101 MHz, DMSO-d_6, 373 K) δ 169.7 (C=O amide), 153.9 (C=O carbamate), 149.7 (C_{Ar} quat.), 148.7 (C_{Ar}), 138.6 (C_{Ar} quat.), 136.3 (C_{Ar} quat.), 130.2 (C_{Ar}), 127.5 (2 × C_{Ar}), 127.1 (C_{Ar} quat.), 126.9 (C_{Ar}), 126.6 (2 × C_{Ar}), 120.6 (C_{Ar}), 119.5 (C_{Ar} quat.), 116.4 (C_{Ar}), 104.6 (C_{Ar}), 65.7 (OCH_2), 60.8 (H*C*C=O), 55.6 (OCH_3), 46.5 (NCH_2), 29.8 (NCH(C=O)*C*H$_2$), 23.1 (NCH_2CH_2); HRMS (ESI$^+$) *m/z* Calculated for $C_{23}H_{24}N_3O_4^+$ $[M+H]^+$ 406.1767; Found 406.1762.

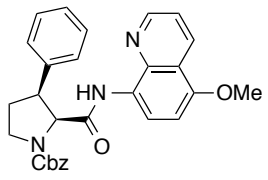
C–H Arylation of 5-MeO-8-AQ Amide 10 (11a, 11b, 11d)

Benzyl (2*S*,3*S*)-2-[(5-methoxyquinolin-8-yl)carbamoyl]-3-(4-methylphenyl)pyrrolidine-1-carboxylate (11a)



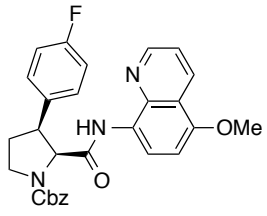
Prepared according to the **General Procedure**, using amide **10** in place of amide **1**: amide **10** (387 mg, 0.95 mmol), AgOAc (285 mg, 1.71 mmol), 4-iodotoluene (373 mg, 1.71 mmol) and $Pd(OAc)_2$ (10.7 mg, 48 μmol) were employed. The crude material was purified by flash column chromatography (3% grading to 5% $MeCN/CH_2Cl_2$), affording arylated compound **11a** (384 mg, 82%) as a yellow solid. mp = 61–64 ºC; R_f 0.54 (10% $MeCN/CH_2Cl_2$); $[\alpha]_D^{28}$ +12º (*c* 1.2, $CHCl_3$); ν_{max} (film)/cm^{-1} 3349 (NH br), 2947, 1704 (C=O), 1596, 1530, 1495, 1443, 1356, 1271, 1159, 1123, 1111, 1092, 820, 790, 751, 697; ^1H NMR (500 MHz, DMSO-d_6, 373 K) δ 9.33 (br s, 1 H, NH), 8.77 (dd, *J* = 4.2, 1.7 Hz, 1 H, HC_{Ar}), 8.50 (dd, *J* = 8.4, 1.7 Hz, 1 H, HC_{Ar}), 8.24 (d, *J* = 8.5 Hz, 1 H, HC_{Ar}), 7.53 (dd, *J* = 8.4, 4.2 Hz, 1 H, HC_{Ar}), 7.33–7.05 (m, 5 H, 5 × HC_{Ar}), 7.19 (d, *J* = 8.1 Hz, 2 H, 2 × HC_{Ar}), 6.93 (d, *J* = 8.5 Hz, 1 H, HC_{Ar}), 6.88 (d, *J* = 7.9 Hz, 2 H, 2 × HC_{Ar}), 5.15–5.05 (m, 2 H, OCH_2), 4.85 (d, *J* = 8.4 Hz, 1 H, HCC=O), 3.96 (s, 3 H, OCH_3), 3.93–3.88 (m, 1 H, NC*H*H), 3.83–3.76 (m, 1 H, CHC_{Ar}), 3.64–3.57 (m, 1 H, NCH*H*), 2.64–2.54 (m, 1 H, NCH_2CHH), 2.20–2.13 (m, 1 H, NCH_2CHH), 2.00 (s, 3 H, $C_{Ar}CH_3$); ^{13}C NMR (126 MHz, DMSO-d_6, 373 K) δ 167.6 (C=O amide), 153.5 (C=O carbamate), 149.4 (C_{Ar} quat.), 148.3 (C_{Ar}), 138.2 (C_{Ar} quat.), 136.3 (C_{Ar} quat.), 135.2 (C_{Ar} quat.), 133.6 (C_{Ar} quat.), 129.2 (C_{Ar}), 127.9 (2 × C_{Ar}), 127.5 (2 × C_{Ar}), 127.3 (2 × C_{Ar}), 126.9 (C_{Ar}), 126.8 (C_{Ar} quat.), 126.5 (2 × C_{Ar}), 120.4 (C_{Ar}), 119.3 (C_{Ar} quat.), 115.9 (C_{Ar}), 104.4 (C_{Ar}), 65.6 (OCH_2), 65.0 (H*C*C=O), 55.6 (OCH_3), 46.6 (CHC_{Ar}), 45.7 (NCH_2), 27.4 (NCH_2CH_2), 19.7 ($C_{Ar}CH_3$); HRMS (ESI^+) ***m/z*** Calculated for $C_{30}H_{30}N_3O_4^+$ $[M+H]^+$ 496.2236; Found 496.2216.

Benzyl (2*S*,3*S*)-2-[(5-methoxyquinolin-8-yl)carbamoyl]-3-phenylpyrrolidine-1-carboxylate (11b)



Prepared according to the **General Procedure**, using amide **10** in place of amide **1**: amide **10** (325 mg, 0.80 mmol), AgOAc (240 mg, 1.44 mmol), iodobenzene (161 μL, 1.44 mmol) and $Pd(OAc)_2$ (9.0 mg, 40 μmol) were employed. The crude material was purified by flash column chromatography (3% grading to 5% $MeCN/CH_2Cl_2$), affording arylated compound **11b** (289 mg, 75%) as a a pale yellow solid. mp = 53–56 ºC; R_f 0.64 (10% $MeCN/CH_2Cl_2$); $[\alpha]_D^{25}$ +35º (*c* 1.6, $CHCl_3$); ν_{max} (film)/cm^{-1} 3349 (NH br), 2950, 2892, 1703 (C=O), 1686, 1596, 1529, 1496, 1455, 1442, 1402, 1353, 1271, 1208, 1158, 1124, 1090, 823, 789, 752, 697; ^1H NMR (400 MHz, DMSO-d_6, 373 K) δ 9.38 (br s, 1 H, NH), 8.78 (dd, *J* = 4.2, 1.7 Hz, 1 H, HC_{Ar}), 8.49 (dd, *J* = 8.4, 1.7 Hz, 1 H, HC_{Ar}), 8.22 (d, *J* = 8.5 Hz, 1 H, HC_{Ar}), 7.53 (dd, *J* = 8.4, 4.2 Hz, 1 H, HC_{Ar}), 7.37–7.05 (m, 9 H, 9 × HC_{Ar}), 6.99–6.94 (m, 1 H, HC_{Ar}), 6.92 (d, *J* = 8.6 Hz, 1 H, HC_{Ar}), 5.15–5.04 (m, 2 H, OCH_2), 4.90 (d, *J* = 8.4 Hz, 1 H, HCC=O), 3.95 (s, 3 H, CH_3), 3.95–3.89 (m, 1 H, NC*H*H), 3.89–3.81 (m, 1 H, CHC_{Ar}), 3.66–3.56 (m, 1 H, NCH*H*), 2.70–2.57 (m, 1 H, NCH_2CHH), 2.25–2.16 (m, 1 H, NCH_2CHH); ^{13}C NMR (101 MHz, DMSO-d_6, 373 K) δ 167.5 (C=O amide), 153.5 (C=O carbamate), 149.4 (C_{Ar} quat.), 148.3 (C_{Ar}), 138.2 (C_{Ar} quat.), 136.8 (C_{Ar} quat.), 136.3 (C_{Ar} quat.), 130.0 (C_{Ar}), 127.49 (2 × C_{Ar}), 127.45 (2 × C_{Ar}), 127.3 (2 × C_{Ar}), 126.8 (C_{Ar}), 126.7 (C_{Ar} quat.), 126.5 (2 × C_{Ar}), 126.1 (C_{Ar}), 120.4 (C_{Ar}), 119.3 (C_{Ar} quat.), 115.9 (C_{Ar}), 104.4 (C_{Ar}), 65.6 (OCH_2), 64.9 (H*C*C=O), 55.5 (CH_3), 46.9 (*C*HC_{Ar}), 45.8 (NCH_2), 27.3 (NCH_2CH_2); HRMS (ESI^+) ***m/z*** Calculated for $C_{29}H_{28}N_3O_4^+$ $[M+H]^+$ 482.2080; Found 482.2080.

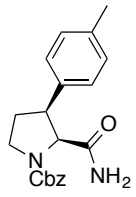
Benzyl (2*S*,3*S*)-3-(4-fluorophenyl)-2-[(5-methoxyquinolin-8-yl)carbamoyl]pyrrolidine-1-carboxylate (11d)



Prepared according to the **General Procedure**, using amide **10** in place of amide **1**: amide **10** (310 mg, 0.76 mmol), AgOAc (229 mg, 1.37 mmol), 4-fluoroiodobenzene (158 μL, 1.37 mmol) and $Pd(OAc)_2$ (8.5 mg, 38 μmol) were employed. The crude material was purified by flash column chromatography (3% grading to 5% $MeCN/CH_2Cl_2$), affording arylated compound **11d** (286 mg, 75%) as a white solid. mp = 58–60 ºC; R_f 0.68 (10% $MeCN/CH_2Cl_2$); $[\alpha]_D^{25}$ +40º (*c* 1.0, $CHCl_3$); ν_{max} (film)/cm^{-1} 3344, 2954, 1704, 1596, 1531, 1513, 1496, 1403, 1271, 1160, 1124, 1093, 837, 789, 752, 698; ^1H NMR (400 MHz, DMSO-d_6, 373 K) δ 9.38 (br s, 1 H, NH), 8.79 (dd, *J* = 4.2, 1.7 Hz, 1 H, HC_{Ar}), 8.50 (dd, *J* = 8.4, 1.7 Hz, 1 H, HC_{Ar}), 8.22 (d, *J* = 8.5 Hz, 1 H, HC_{Ar}), 7.54 (dd, *J* = 8.4, 4.2 Hz, 1 H, HC_{Ar}), 7.39–7.32 (m, 2 H, HC_{Ar}), 7.32–7.04 (m, 5 H, HC_{Ar}), 6.93 (d, *J* = 8.6 Hz, 1 H, HC_{Ar}), 6.91–6.84 (m, 2 H, HC_{Ar}), 5.16–5.04 (m, 2 H, OCH_2), 4.91 (d, *J* = 8.4 Hz, 1 H, HCC=O), 3.96 (s, 3 H, CH_3), 3.95–3.81 (m, 2 H, CHC_{Ar} and NC*H*H), 3.65–3.56 (m, 1 H, NCH*H*), 2.65–2.52 (m, 1 H, NCH_2CHH), 2.25–2.15 (m, 1 H, NCH_2CHH); ^{13}C NMR (101 MHz, DMSO-d_6, 373 K) δ 167.5 (C=O amide), 160.7 (d, J_{CF} = 243 Hz, C_{Ar} quat.), 153.5 (C_{Ar} quat.), 149.5 (C_{Ar} quat.), 148.3 (C_{Ar}), 138.3 (C_{Ar} quat.), 136.3 (C_{Ar} quat.), 132.9 (d, J_{CF} = 3 Hz, C_{Ar} quat.), 130.0 (C_{Ar}), 129.4 (d, J_{CF} = 8 Hz, 2 × C_{Ar}), 127.5 (2 × C_{Ar}), 126.9 (C_{Ar}), 126.7 (C_{Ar} quat.), 126.6 (2 × C_{Ar}), 120.4 (C_{Ar}), 119.3 (C_{Ar} quat.), 116.1 (C_{Ar}), 114.0 (d, J_{CF} = 21 Hz, 2 × C_{Ar}), 104.4 (C_{Ar}), 65.6 (OCH_2), 64.8 (H*C*C=O), 55.6 (CH_3), 46.1 (*C*HC_{Ar}), 45.7 (NCH_2), 27.4 (NCH_2CH_2); ^{19}F NMR (376 MHz, DMSO-d_6, 373 K) δ –116.7; HRMS (ESI^+) *m/z* Calculated for $C_{29}H_{27}N_3O_4F^+$ $[M+H]^+$ 500.1986; Found 500.1979.

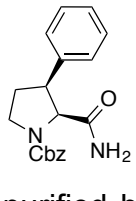
Oxidative Removal of 5-Methoxy-8-aminoquinolyl Directing Group (12a, 12b, 12d)

Benzyl (2*S*,3*S*)-2-carbamoyl-3-(4-methylphenyl)pyrrolidine-1-carboxylate (12a)



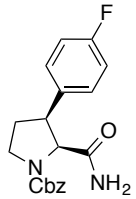
Ceric (IV) ammonium nitrate (1.45 g, 2.64 mmol) was added to a solution of secondary amide **11a** (435 mg, 0.88 mmol) in MeCN (7.3 mL) and H_2O (1.5 mL). The resulting solution was stirred at rt for 5 h. EtOAc (100 mL) was then added, and the organic layer was washed with H_2O (50 mL) and then brine (50 mL). The organic layer was dried over Na_2SO_4 and the solvent was removed under reduced pressure. The crude material was purified by flash column chromatography (20% grading to 30% MeCN/CH_2Cl_2), affording primary amide **12a** (235 mg, 79%) as a white solid. mp = 55–58 ºC; R_f 0.42 (20% MeCN/CH_2Cl_2); $[\alpha]_D^{23}$ +90º (*c* 1.4, $CHCl_3$); ν_{max} (film)/cm^{-1} 3330 (NH br), 3190, 2951, 2889, 2243, 1675 (C=O), 1614, 1517, 1416, 1408, 1258, 1303, 1282, 1201, 1173, 1129, 1113, 1077, 1052, 1030, 997, 911, 819, 770, 731, 698; ^{1}H NMR (500 MHz, DMSO-d_6, 373 K) δ 7.39–7.27 (m, 5 H, 5 × HC_{Ar}), 7.19 (d, *J* = 8.1 Hz, 2 H, 2 × HC_{Ar}), 7.08 (d, *J* = 8.1 Hz, 2 H, 2 × HC_{Ar}), 6.48 (br s, 2 H, NH_2), 5.10 (s, 2 H, OCH_2), 4.45 (d, *J* = 8.4 Hz, HCC=O), 3.79–3.72 (m, 1 H, NC*H*H), 3.63–3.55 (m, 1 H, CHC_{Ar}), 3.50–3.42 (m, 1 H, NCH*H*), 2.56–2.45 (m, 1 H, NCH_2CHH), 2.28 (s, 3 H, CH_3), 2.08–2.01 (m, 1 H, NCH_2CHH);^{13}C NMR (126 MHz, DMSO-d_6, 373 K) δ 170.9 (C=O amide), 153.3 (C=O carbamate), 136.6 (C_{Ar} quat.), 135.1 (C_{Ar} quat.), 134.2 (C_{Ar} quat.), 127.9 (2 × C_{Ar}), 127.67 (2 × C_{Ar}), 127.65 (2 × C_{Ar}), 126.9 (C_{Ar}), 126.6 (2 × C_{Ar}), 65.4 (OCH_2), 63.3 (H*C*C=O), 46.2 (*C*HC_{Ar}), 45.5 (NCH_2), 27.5 (NCH_2CH_2), 19.9 (CH_3); HRMS (ESI$^+$) *m/z* Calculated for $C_{20}H_{23}N_2O_3^+$ $[M+H]^+$ 339.1707; Found 339.1701.

Benzyl (2*S*,3*S*)-2-carbamoyl-3-phenylpyrrolidine-1-carboxylate (12b)



Ceric (IV) ammonium nitrate (345 mg, 0.63 mmol) was added to a solution of secondary amide **11b** (100 mg, 0.21 mmol) in MeCN (1.75 mL) and H_2O (0.35 mL). The resulting solution was stirred at rt for 4 h. EtOAc (25 mL) was then added, and the organic layer was washed with H_2O (20 mL) and then brine (20 mL). The organic layer was dried over Na_2SO_4 and the solvent was removed under reduced pressure. The crude material was purified by flash column chromatography (20% grading to 30% MeCN/CH_2Cl_2), affording primary amide **12b** (51 mg, 75%) as a white solid. mp = 41–44 ºC; R_f 0.35 (20% MeCN/CH_2Cl_2); $[\alpha]_D^{28}$ +72º (*c* 1.0, $CHCl_3$); ν_{max} (film)/cm^{-1} 3334 (NH br), 2955, 1682 (C=O), 1498, 1417, 1357, 1205, 1127, 1089, 769, 698; ^{1}H NMR (400 MHz, DMSO-d_6, 373 K) δ 7.40–7.18 (m, 10 H, 10 × HC_{Ar}), 6.50 (br s, 2 H, NH_2), 5.10 (s, 2 H, OCH_2), 4.48 (d, *J* = 8.4 Hz, 1 H, HCC=O), 3.80–3.73 (m, 1 H, NC*H*H), 3.69 (m, 1 H, CHC_{Ar}), 3.48 (td, *J* = 10.1, 6.7 Hz, 1 H, NCH*H*), 2.60–2.48 (m, 1 H, NCH_2CHH), 2.12–2.03 (m, 1 H, NCH_2CHH); ^{13}C NMR (101 MHz, DMSO-d_6, 373 K) δ 170.9 (C=O amide), 153.3 (C=O carbamate), 137.3 (C_{Ar} quat.), 136.6 (C_{Ar} quat.), 127.8 (2 × C_{Ar}), 127.7 (2 × C_{Ar}), 127.2 (2 × C_{Ar}), 126.9 (C_{Ar}), 126.6 (2 × C_{Ar}), 126.1 (C_{Ar}), 65.4 (OCH_2), 63.3 (H*C*C=O), 46.5 (*C*HC_{Ar}), 45.5 (NCH_2), 27.5 (NCH_2CH_2); HRMS (ESI$^+$) *m/z* Calculated for $C_{19}H_{21}N_2O_3^+$ $[M+H]^+$ 325.1552; Found 325.1544.

Benzyl (2*S*,3*S*)-2-carbamoyl-3-(4-fluorophenyl)pyrrolidine-1-carboxylate (12d)

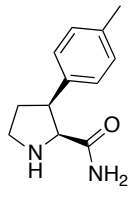


Ceric (IV) ammonium nitrate (329 mg, 0.60 mmol) was added to a solution of secondary amide **11d** (100 mg, 0.20 mmol) in MeCN (1.66 mL) and H_2O (0.34 mL). The resulting solution was stirred at rt for 4 h. EtOAc (25 mL) was then added, and the organic layer was washed with H_2O (20 mL) and then brine (20 mL). The organic layer was dried over Na_2SO_4 and the solvent was removed under reduced pressure. The crude material was purified by flash column chromatography (20% grading to 30% MeCN/CH_2Cl_2), affording

primary amide **12d** (44 mg, 64%) as a colourless oil. R_f 0.33 (20% MeCN/CH_2Cl_2); $[\alpha]_D^{28}$ +67º (*c* 0.9, $CHCl_3$); ν_{max} (film)/cm^{-1} 3329 (NH br), 3194, 2954, 2890, 1678 (C=O), 1607, 1513, 1415, 1359, 1305, 1226, 1161, 1127, 1102, 836, 751, 698; ^{1}H NMR (400 MHz, DMSO-d_6, 373 K) δ 7.40–7.26 (m, 7 H, 7 × HC_{Ar}), 7.09–7.02 (m, 2 H, 2 × HC_{Ar}), 6.53 (br s, 2 H, NH_2), 5.10 (s, 2 H, OCH_2), 4.46 (d, *J* = 8.4 Hz, 1 H, HCC=O), 3.80–3.72 (m, 1 H, NC*H*H), 3.70–3.59 (m, 1 H, CHC_{Ar}), 3.51–3.42 (m, 1 H, NH*H*), 2.55–2.42 (m, 1 H, NCH_2CHH), 2.12–2.03 (m, 1 H, NCH_2CHH); ^{13}C NMR (101 MHz, DMSO-d_6, 373 K) δ 170.9 (C=O amide), 160.8 (d, J_{CF} = 243 Hz, C_{Ar} quat.), 153.3 (C=O carbamate), 136.6 (C_{Ar} quat.), 133.4 (d, J_{CF} = 3 Hz, C_{Ar} quat.) 129.6 (d, J_{CF} = 8 Hz, 2 × C_{Ar}), 127.7 (2 × C_{Ar}), 127.0 (C_{Ar}), 126.6 (2 × C_{Ar}), 113.9 (d, J_{CF} = 21 Hz, 2 × C_{Ar}), 65.4 (OCH_2), 63.3 (H*C*C=O), 45.7 (*C*HC_{Ar}), 45.5 (NCH_2), 27.6 (NCH_2CH_2); ^{19}F NMR (376 MHz, DMSO-d_6, 373 K) δ –116.5; HRMS (ESI^+) *m/z* Calculated for $C_{19}H_{20}N_2O_3F^+$ $[M+H]^+$ 343.1458; Found 343.1448.

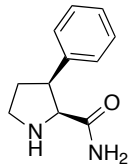
Cbz Deprotection to Primary Amide Fragments 13a, 13b, 13d

(2*S*,3*S*)-3-(4-Methylphenyl)pyrrolidine-2-carboxamide (13a)



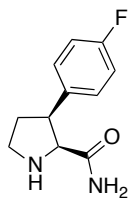
Pd/C (22 mg, 10 wt. %) was added to a solution of benzyl (2*S*,3*S*)-2-carbamoyl-3-(4-methylphenyl)pyrrolidine-1-carboxylate **12a** (70 mg, 0.21 mmol) in MeOH (1.5 mL). The reaction vessel was evacuated and backfilled with Ar three times, followed by evacuation and backfilling with H_2 (balloon). The resulting solution was stirred vigorously at rt for 48 h, then filtered through Celite, washing with MeOH (10 mL). The crude material was purified by flash column chromatography (10% MeOH/CH_2Cl_2), affording pyrrolidine **13a** (43 mg, 99%) as a white solid. mp = 170–172 ºC; R_f 0.12 (10% MeOH/CH_2Cl_2); $[\alpha]_D^{28}$ +34º (*c* 2.9, MeOH); ν_{max} (film)/cm^{-1} 3321 (NH br), 3182, 2945, 1674 (C=O), 1517, 1407, 818; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.18 (br s, 1 H, CON*H*H), 7.08 (d, *J* = 8.0 Hz, 2 H, 2 × HC_{Ar}), 7.01 (d, *J* = 8.0 Hz, 2 H, 2 × HC_{Ar}), 6.81 (br s, 1 H, CONH*H*), 3.82 (d, *J* = 8.1 Hz, 1 H, HCC=O), 3.47 (q, *J* = 7.6 Hz, 1 H, CHC_{Ar}), 3.30–3.21 (m, 1 H, NC*H*H), 2.98–2.89 (m, 1 H, NCH*H*), 2.23 (s, 3 H, CH_3), 2.17–2.06 (m, 1 H, NCH_2CHH), 1.96–1.84 (m, 1 H, NCH_2CHH); ^{13}C NMR (101 MHz, DMSO-d_6) δ 172.5 (C=O), 138.2 (C_{Ar} quat), 135.0 (C_{Ar} quat), 128.3 (2 × C_{Ar}), 128.2 (2 × C_{Ar}), 65.1 (H*C*C=O), 47.1 (*C*HC_{Ar}), 45.4 (NCH_2), 32.9 (NCH_2CH_2), 20.6 (CH_3); HRMS (ESI$^+$) *m/z* Calculated for $C_{12}H_{17}N_2O^+$ $[M+H]^+$ 205.1341; Found 205.1340.

(2*S*,3*S*)-3-Phenylpyrrolidine-2-carboxamide (13b)



Pd/C (16 mg, 10 wt. %) was added to a solution of benzyl (2*S*,3*S*)-2-carbamoyl-3-phenylpyrrolidine-1-carboxylate **12b** (47 mg, 0.15 mmol) in EtOH (1.5 mL). The reaction vessel was evacuated and backfilled with Ar three times, followed by evacuation and backfilling with H_2 (balloon). The resulting solution was stirred vigorously at rt for 1 h, then filtered through Celite, washing with EtOH (10 mL). The crude material was purified by flash column chromatography (10% MeOH/CH_2Cl_2), affording pyrrolidine **13b** (29 mg, 99%) as a white solid. mp = 116–119 ºC; R_f 0.11 (10% MeOH/CH_2Cl_2); $[\alpha]_D^{28}$ +33º (*c* 0.6, MeOH); ν_{max} (film)/cm^{-1} 3316 (NH br), 3176, 2966, 2876, 1667 (C=O), 1494, 1453, 1392, 1342, 1088, 1032, 769, 699, 635; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.29–7.11 (m, 6 H, HC_{Ar} and CON*H*H), 6.79 (br s, 1 H, CONH*H*), 3.89–3.72 (m, 1 H, CH_2NH), 3.80 (d, *J* = 8.2 Hz, 1 H, HCC=O), 3.49 (q, *J* = 7.6 Hz, 1 H, CHC_{Ar}), 3.29–3.21 (m, 1 H, NC*H*H), 2.97–2.88 (m, 1 H, NCH*H*), 2.19–2.08 (m, 1 H, NCH_2CHH), 1.97–1.86 (m, 1 H, NCH_2CHH); ^{13}C NMR (101 MHz, DMSO-d_6) δ 172.8 (C=O), 141.5 (C_{Ar} quat), 128.3 (2 × C_{Ar}), 127.7 (2 × C_{Ar}), 126.1 (C_{Ar}), 65.3 (H*C*C=O), 47.6 (*C*HC_{Ar}), 45.5 (NCH_2), 33.0 (NCH_2CH_2); HRMS (ESI$^+$) *m/z* Calculated for $C_{11}H_{15}N_2O^+$ $[M+H]^+$ 191.1184; Found 191.1179.

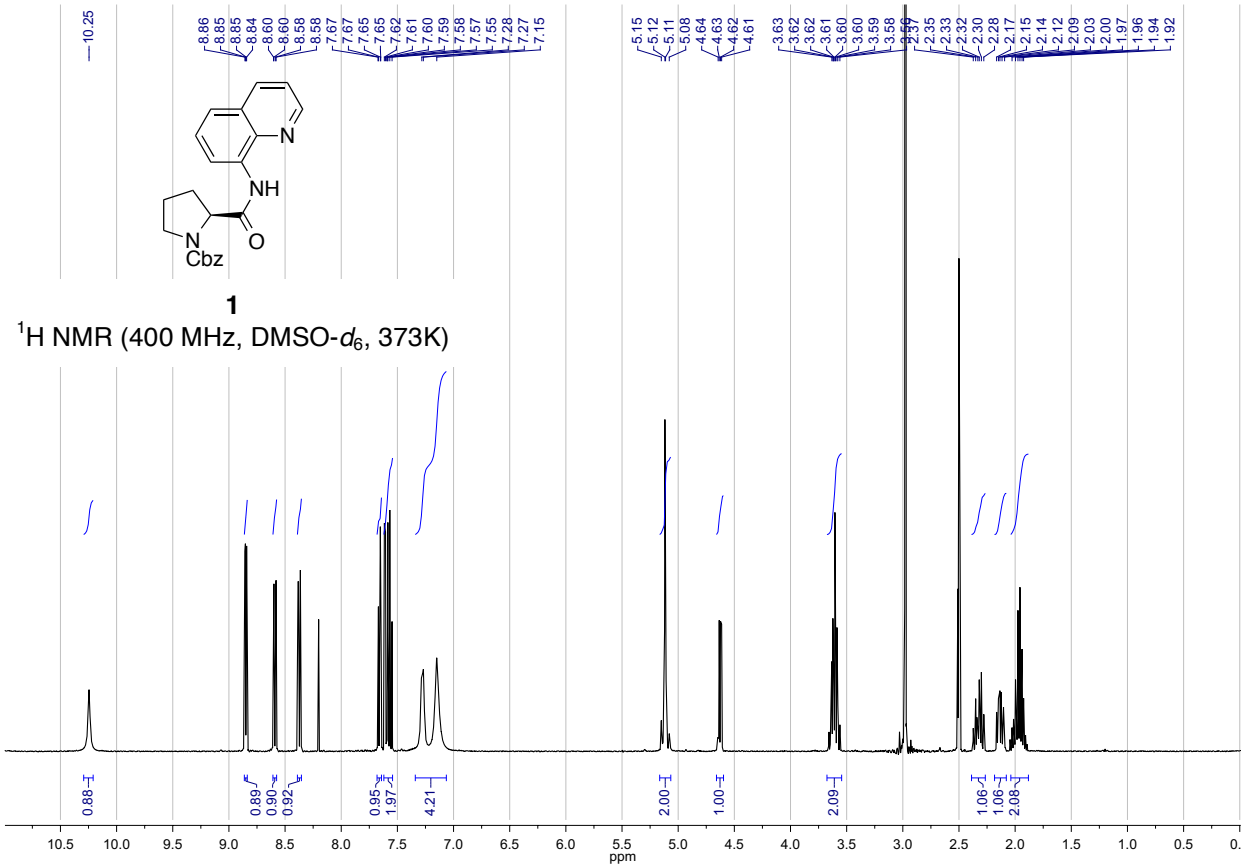
(2*S*,3*S*)-3-(4-Fluorophenyl)pyrrolidine-2-carboxamide (13d)



Pd/C (9 mg, 10 wt. %) was added to a solution of benzyl (2*S*,3*S*)-2-carbamoyl-3-(4-fluorophenyl)pyrrolidine-1-carboxylate **12d** (26 mg, 76 μmol) in EtOH (1.5 mL). The reaction vessel was evacuated and backfilled with Ar three times, followed by evacuation and backfilling with H_2 (balloon). The resulting solution was stirred vigorously at rt for 1 h, then filtered through Celite, washing with EtOH (10 mL). The crude material was purified by flash column chromatography (10% MeOH/CH_2Cl_2), affording pyrrolidine **13d** (17 mg, 99%) as a white solid. mp = 131–134 ºC; R_f 0.11 (10% MeOH/CH_2Cl_2); $[\alpha]_D^{27}$ +20º (*c* 0.5, MeOH); ν_{max} (film)/cm^{-1} 3347 (NH br), 1672 (C=O), 1605, 1512, 1428, 1309, 1222, 1160, 835, 673; ^{1}H NMR (400 MHz, CD_3OD) δ 7.29–7.21 (m, 2 H, HC_{Ar}), 7.00–6.93 (m, 2 H, HC_{Ar}), 3.90 (d, *J* = 8.6 Hz, 1 H, HCC=O), 3.62 (q, *J* = 8.2 Hz, 1 H, CHC_{Ar}), 3.45–3.37 (m, 1 H, NC*H*H), 3.05–

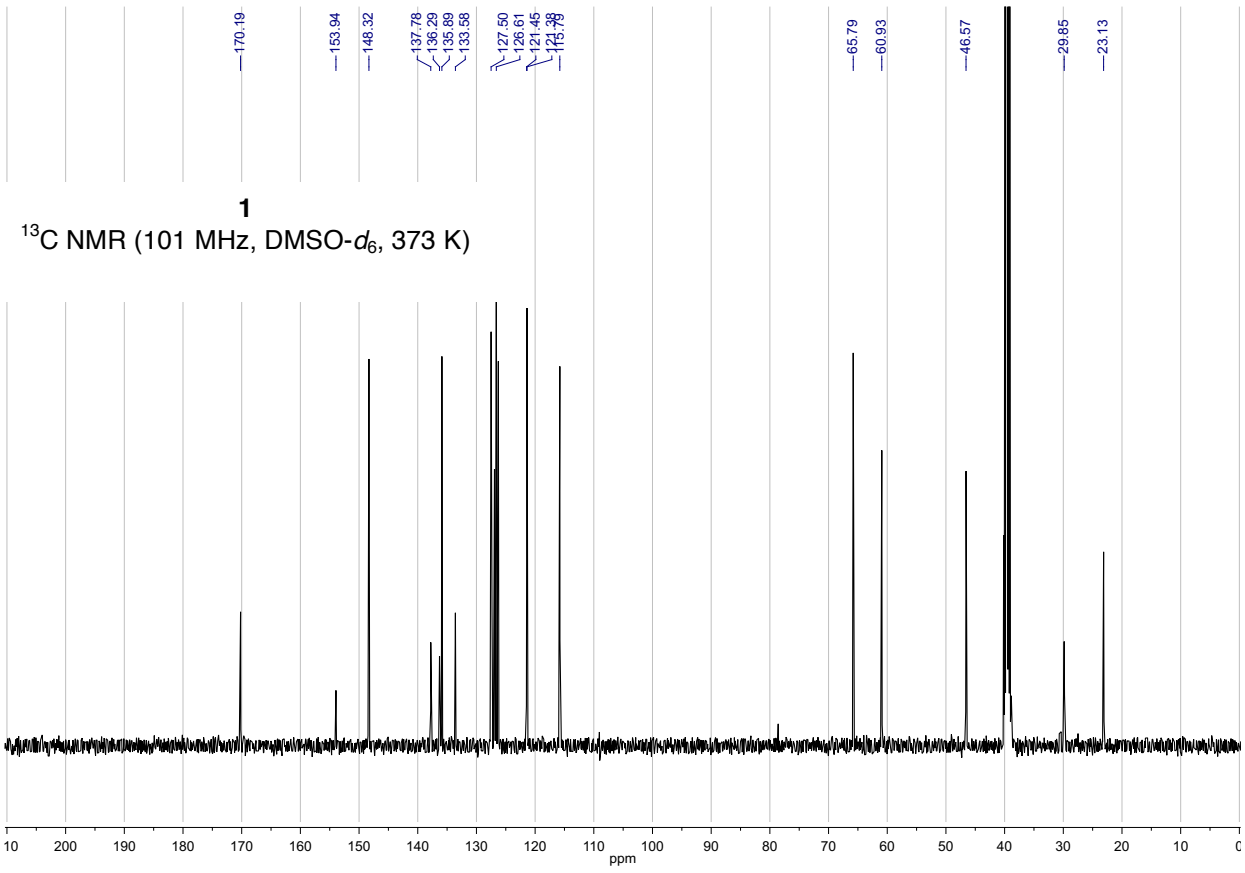
2.96 (m, 1 H, NCH*H*), 2.29–2.19 (m, 1 H, NCH_2CHH), 2.13–2.02 (m, 1 H, NCH_2CHH); ^{13}C NMR (101 MHz, CD_3OD) δ 176.2 (C=O), 163.2 (d, J_{CF} = 243 Hz, C_{Ar} quat.), 137.7 (d, J_{CF} = 3 Hz, C_{Ar} quat.), 131.2 (d, J_{CF} = 8 Hz, 2 × C_{Ar}), 115.6 (d, J_{CF} = 21 Hz, 2 × C_{Ar}), 66.6 (H*C*C=O), 49.2 (*C*HCAr), 47.1 (NCH_2), 34.1 (NCH_2CH_2); ^{19}F NMR (376 MHz, CD_3OD) δ –118.8; HRMS (ESI^+) *m/z* Calculated for $C_{11}H_{14}N_2OF^+$ $[M+H]^+$ 209.1090; Found 209.1087.

^{1}H and ^{13}C NMR Spectra of Selected Compounds



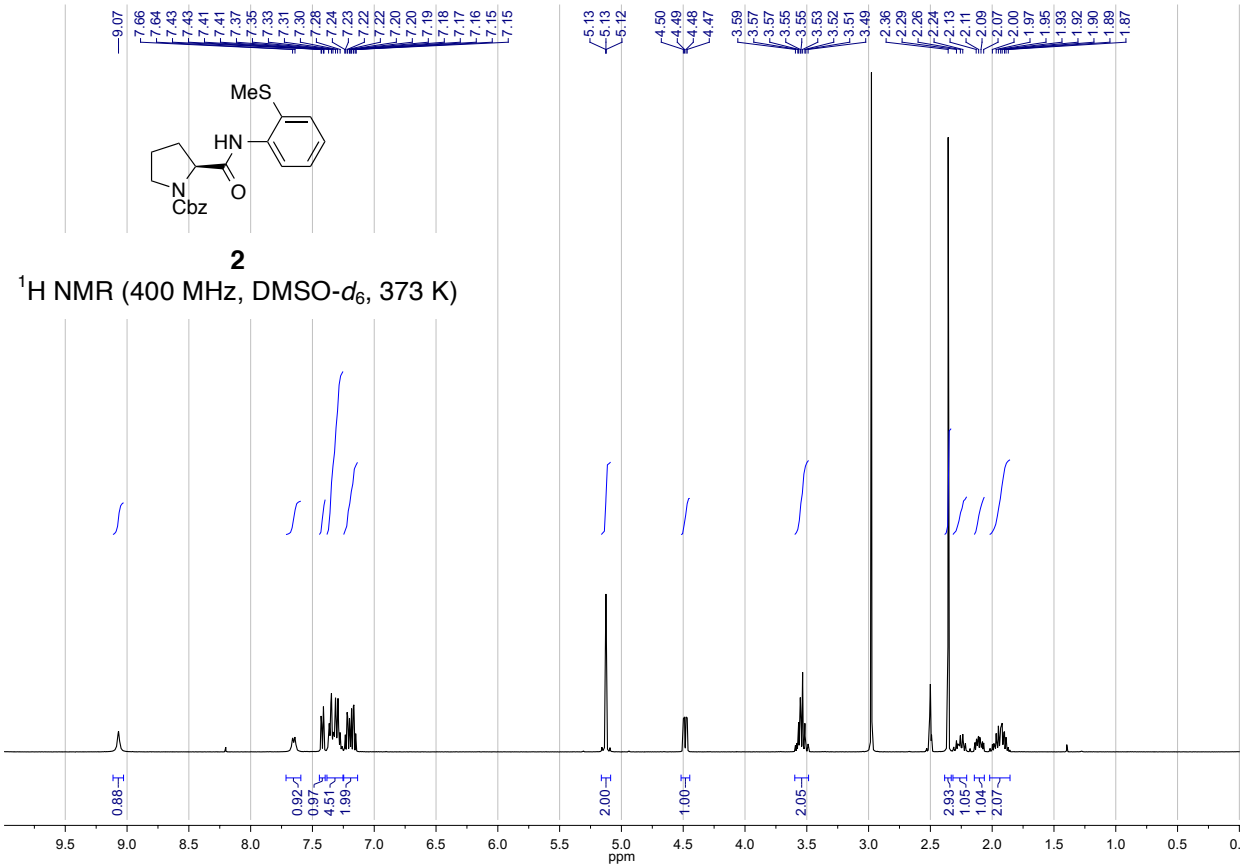
1

^{1}H NMR (400 MHz, DMSO-d_6, 373K)



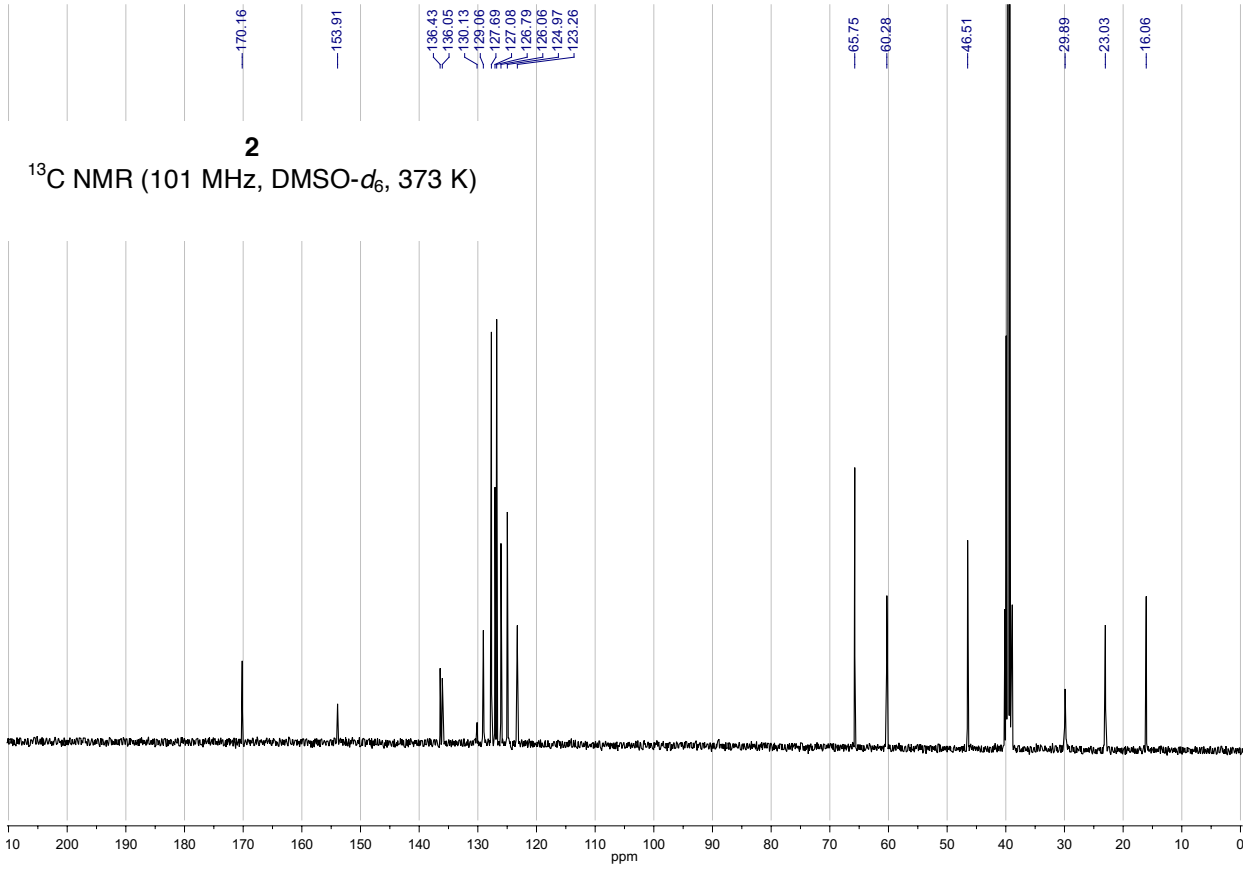
1

^{13}C NMR (101 MHz, DMSO-d_6, 373 K)



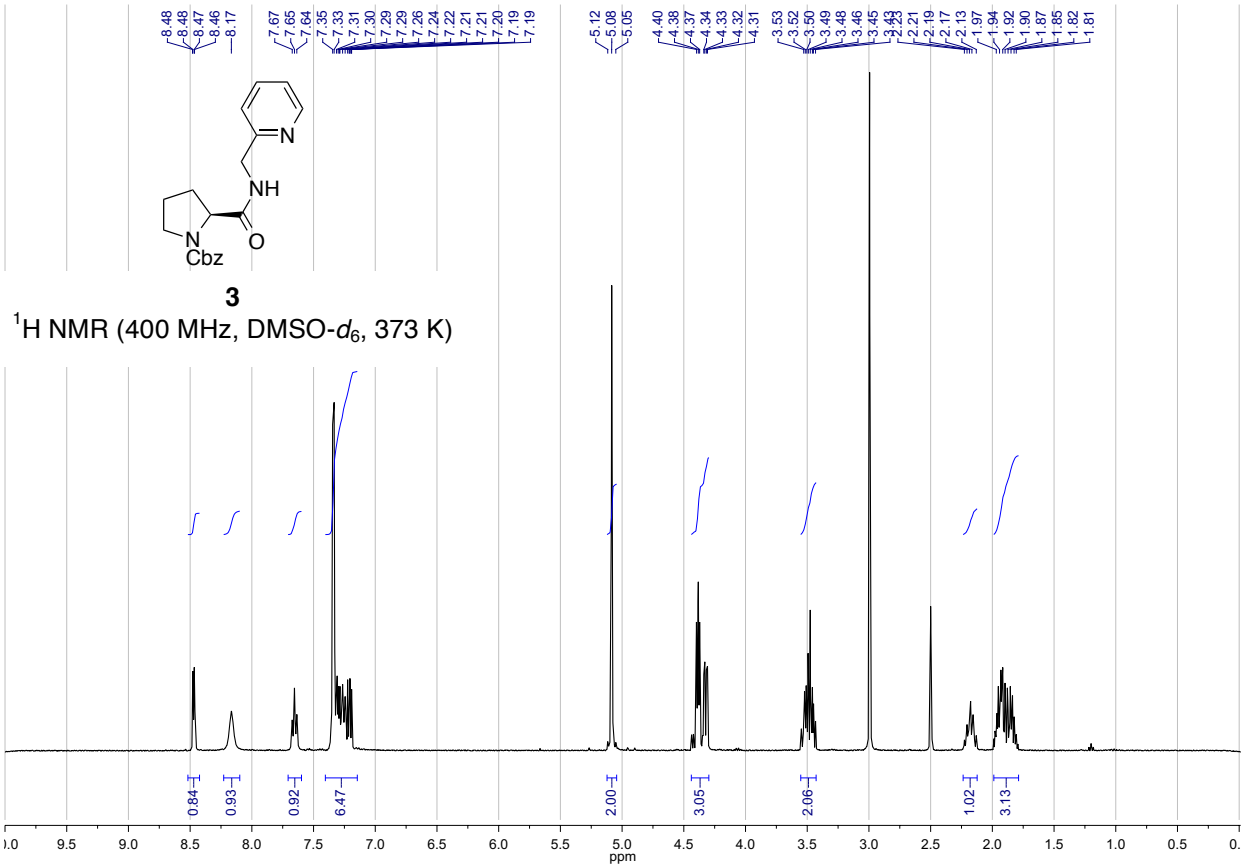
2

^{1}H NMR (400 MHz, DMSO-d_6, 373 K)



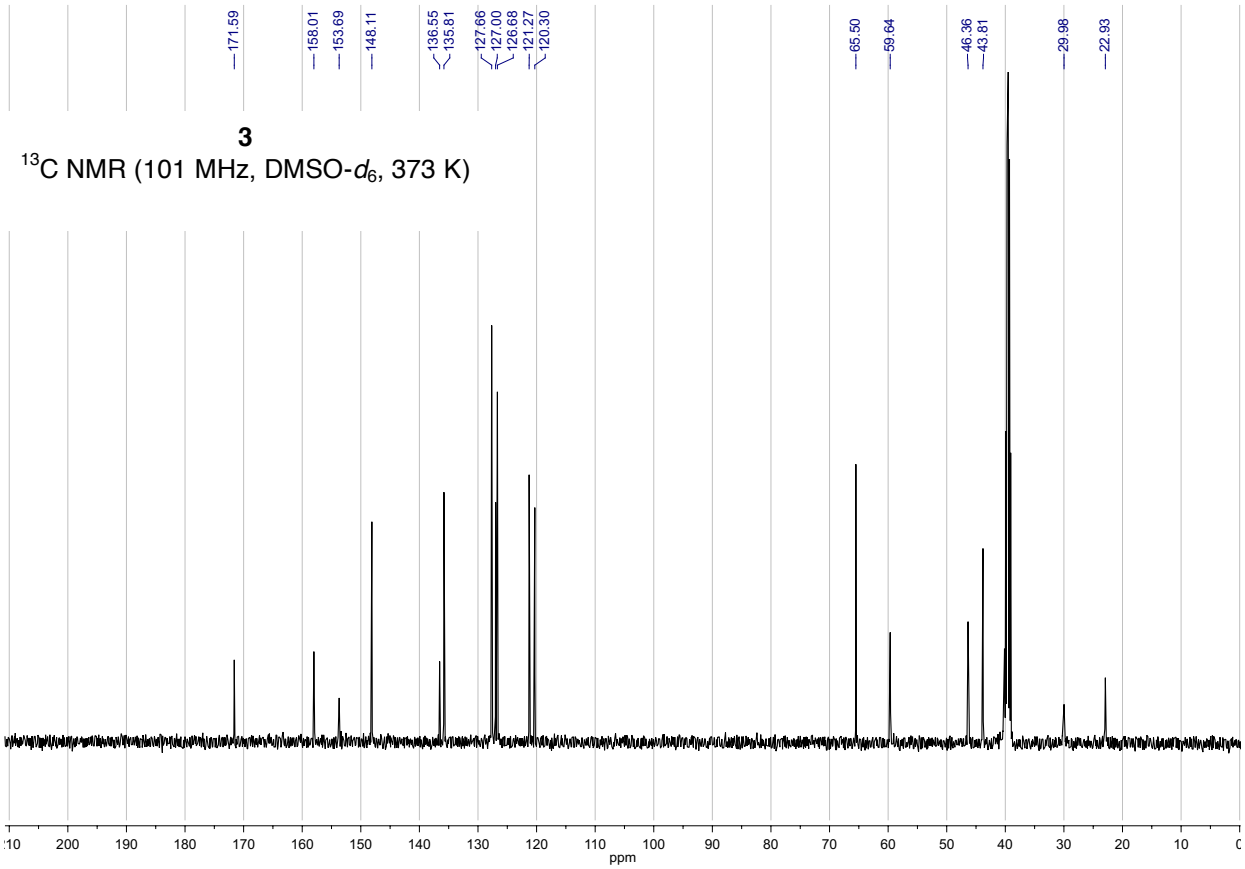
2

^{13}C NMR (101 MHz, DMSO-d_6, 373 K)



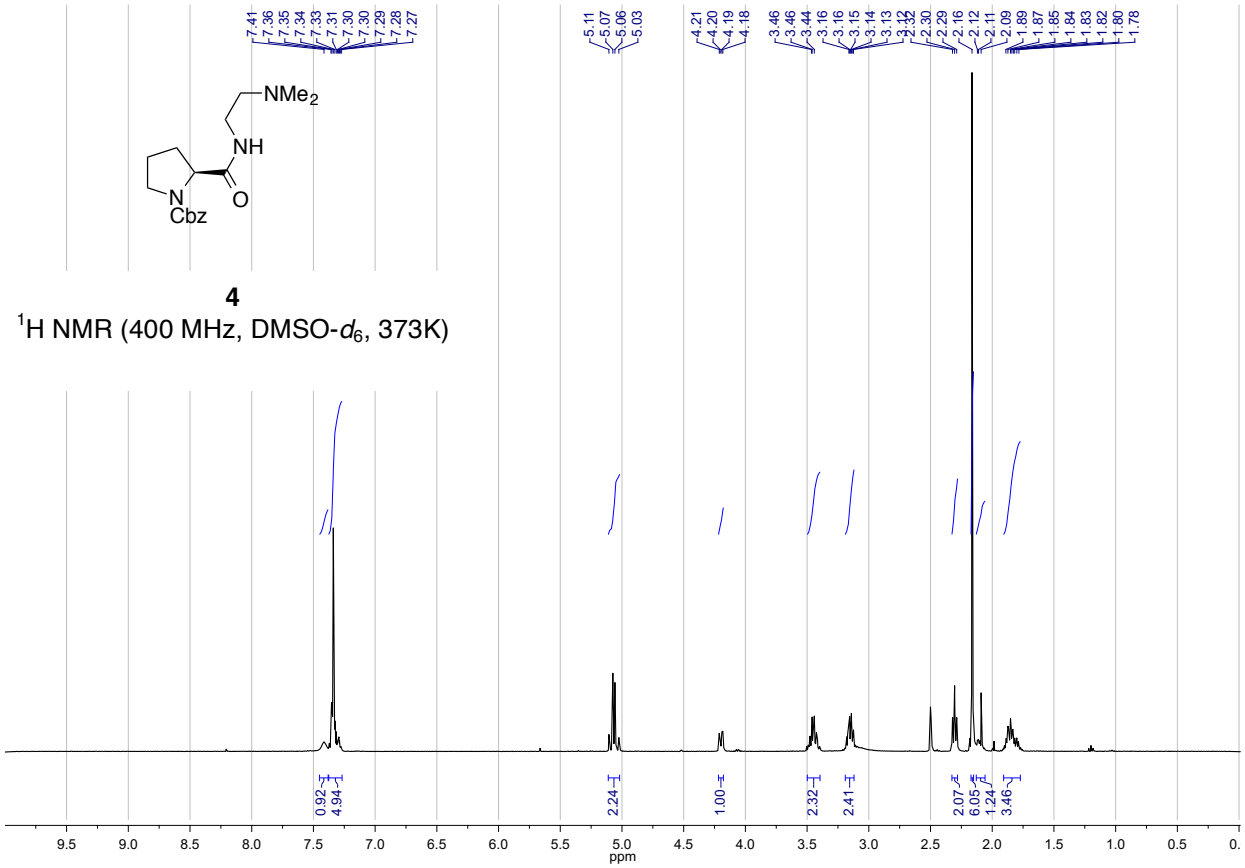
3

^{1}H NMR (400 MHz, DMSO-d_6, 373 K)



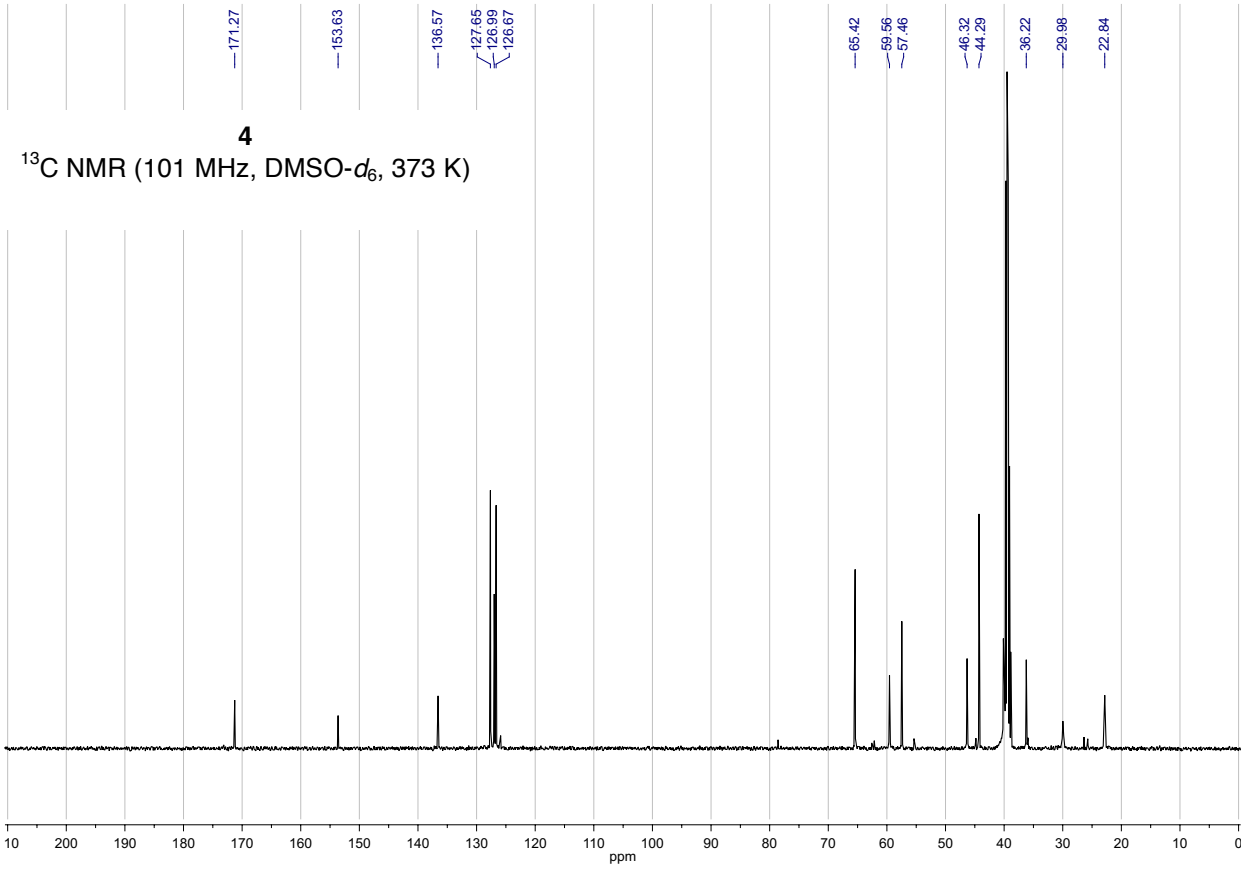
3

^{13}C NMR (101 MHz, DMSO-d_6, 373 K)



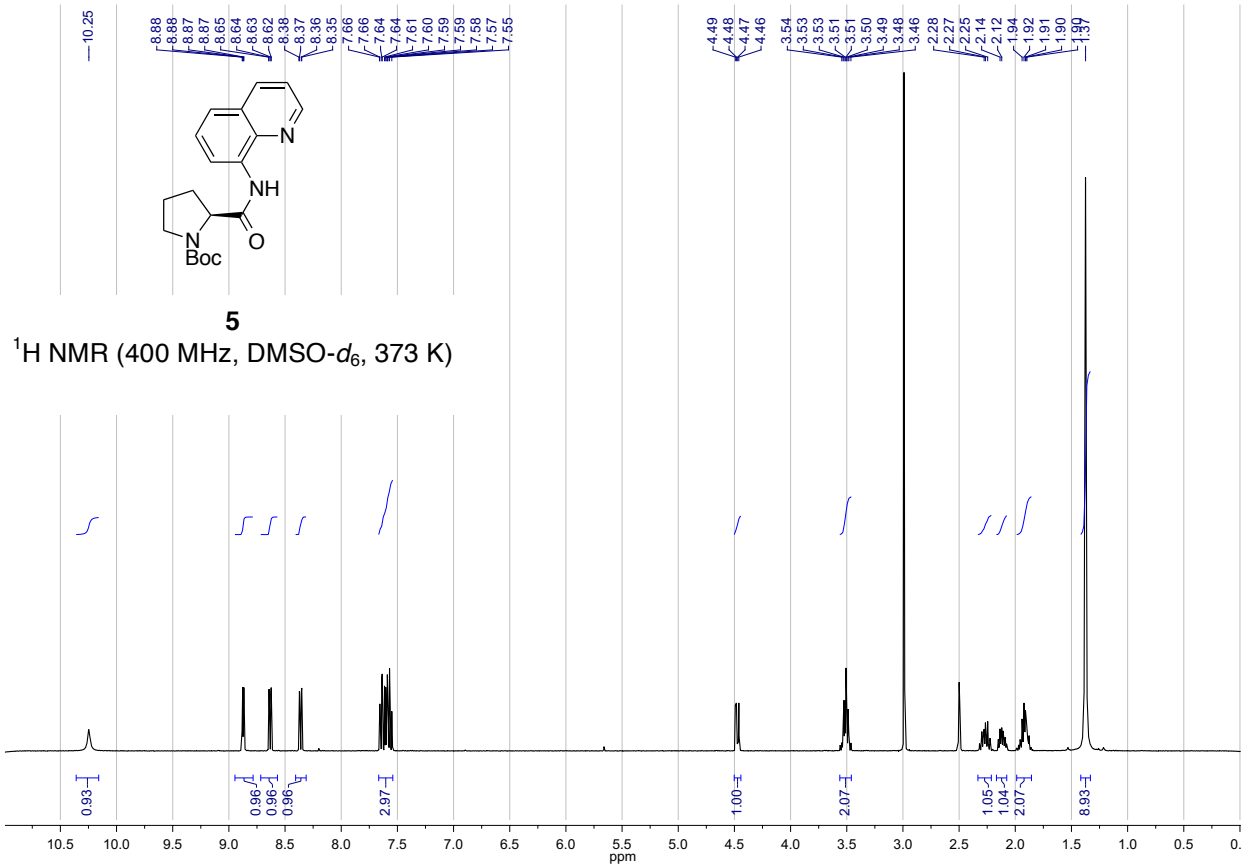
4

^{1}H NMR (400 MHz, DMSO-d_6, 373K)



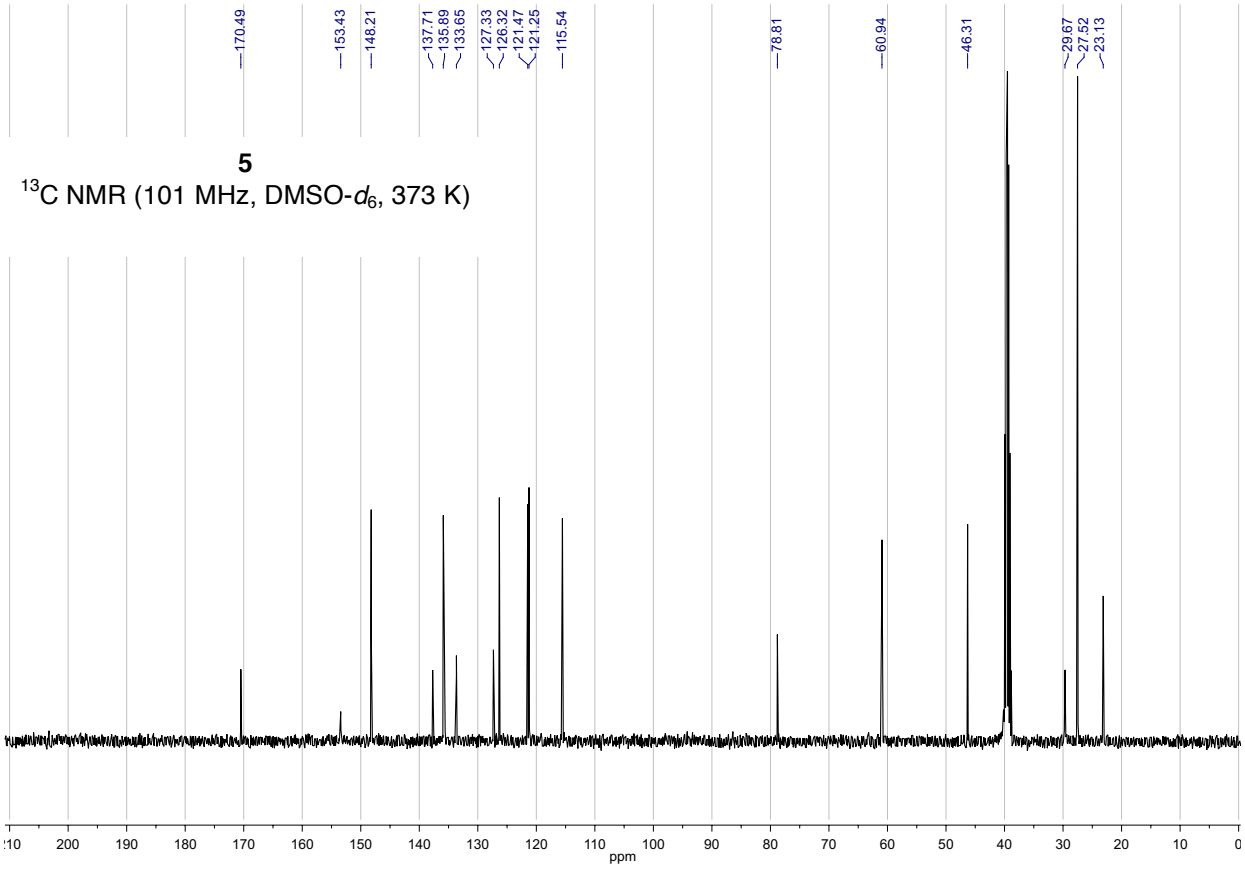
4

^{13}C NMR (101 MHz, DMSO-d_6, 373 K)



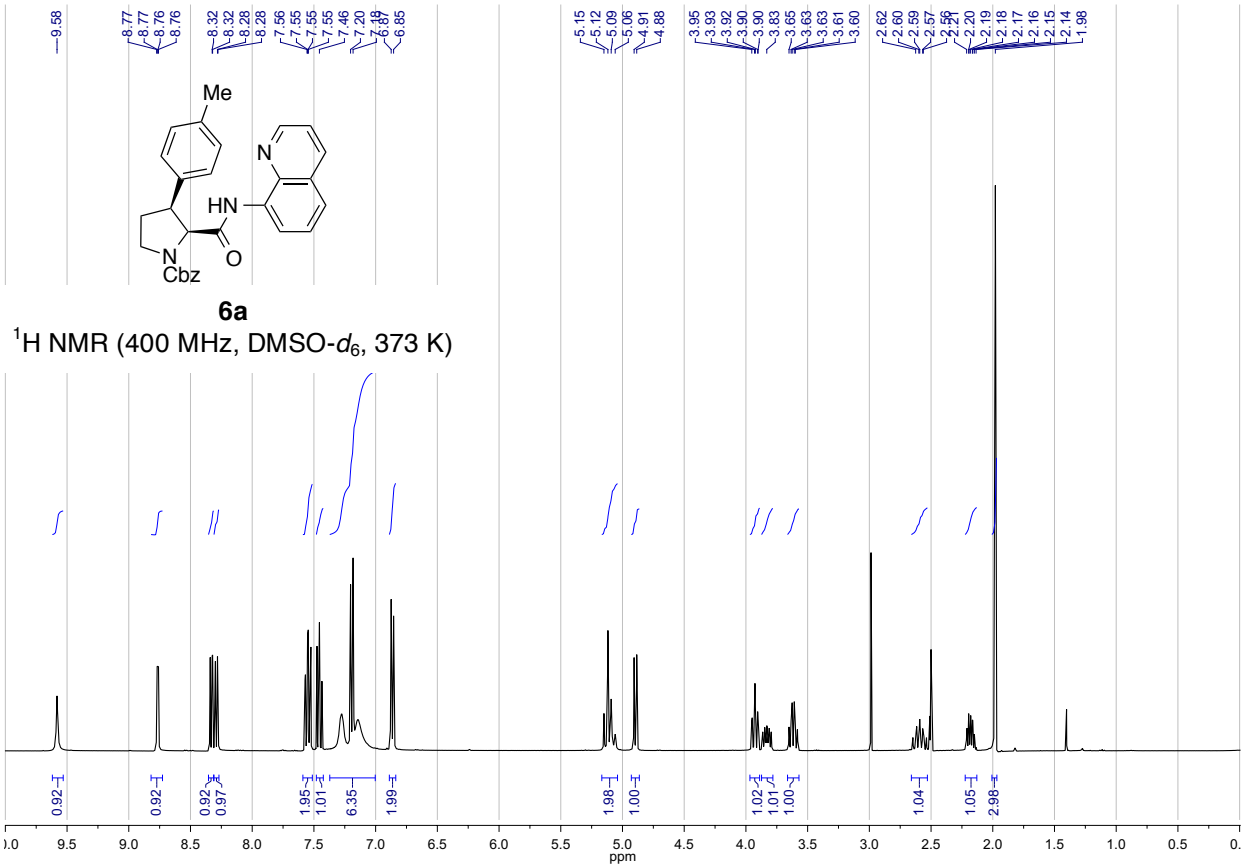
5

^{1}H NMR (400 MHz, DMSO-d_6, 373 K)



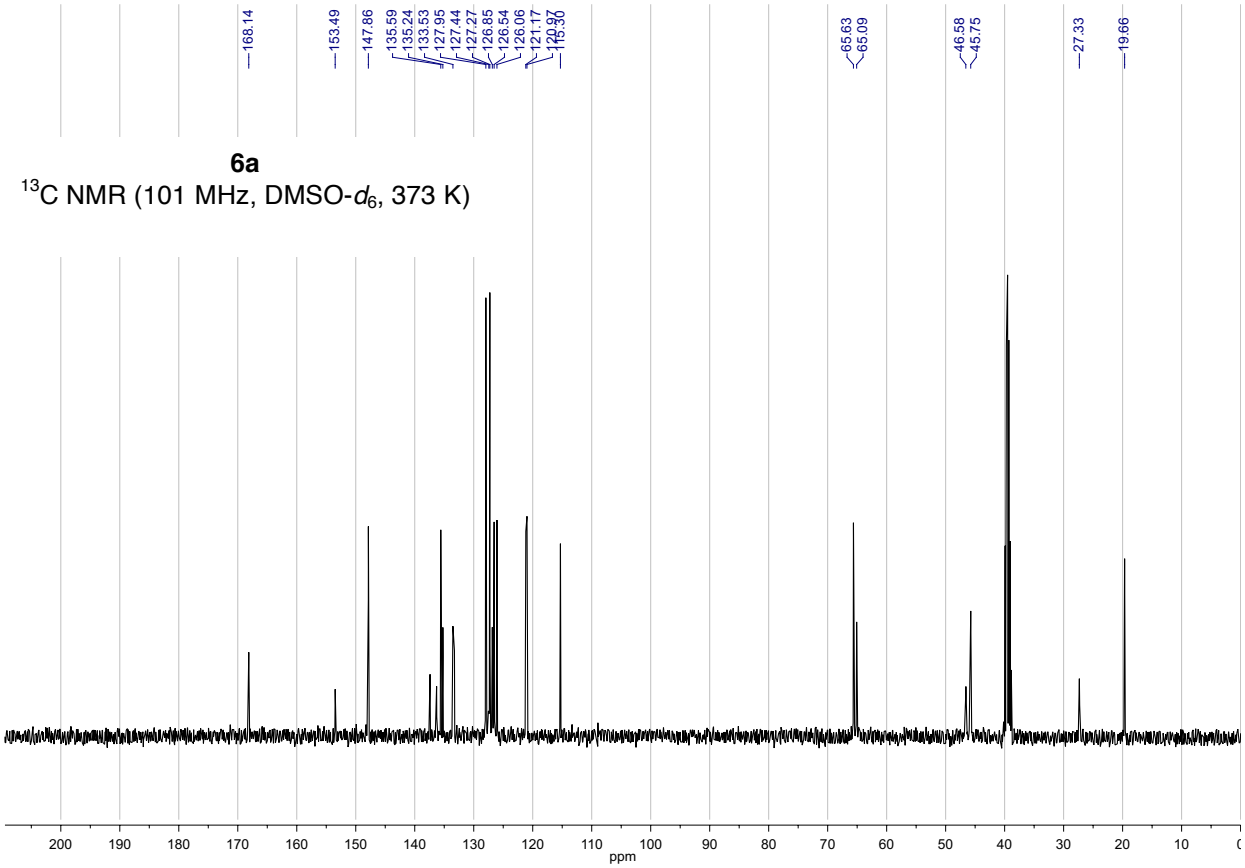
5

^{13}C NMR (101 MHz, DMSO-d_6, 373 K)



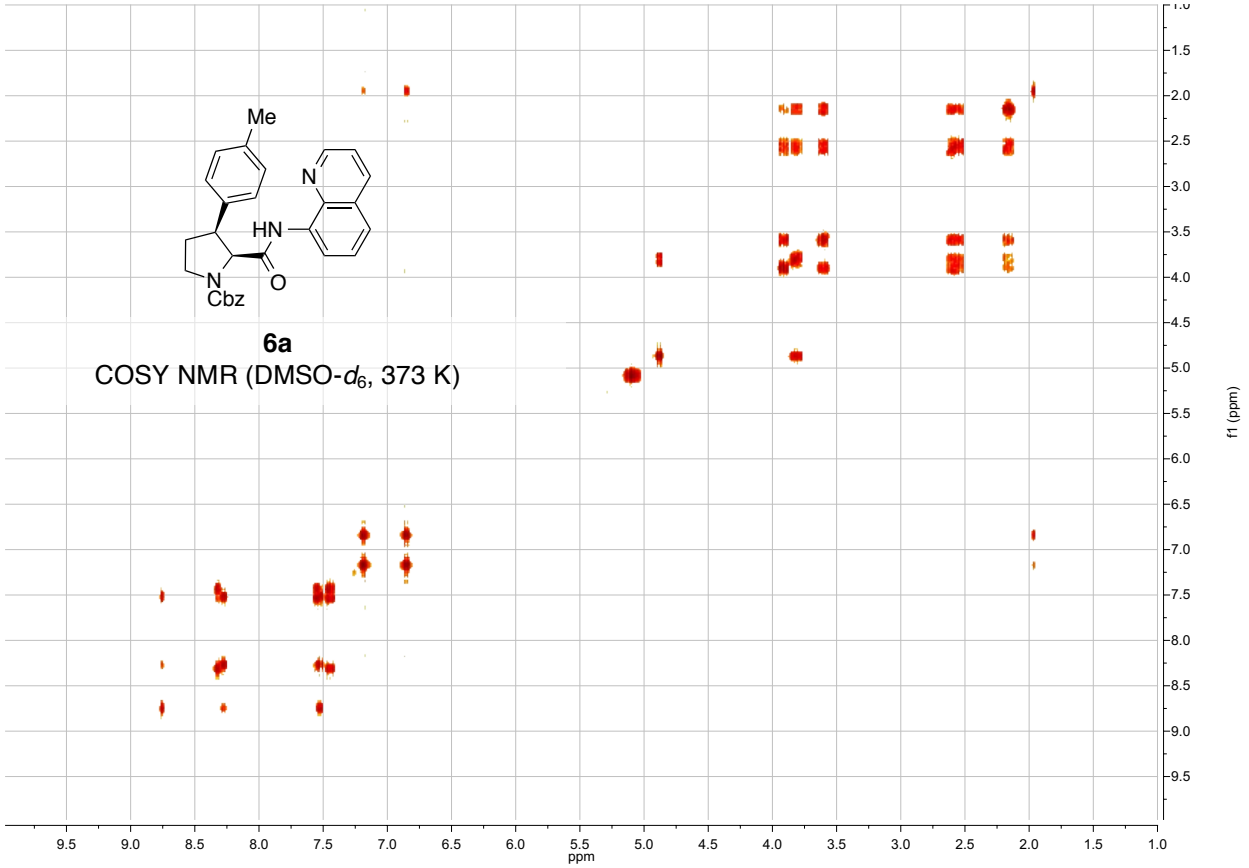
6a

^{1}H NMR (400 MHz, DMSO-d_6, 373 K)



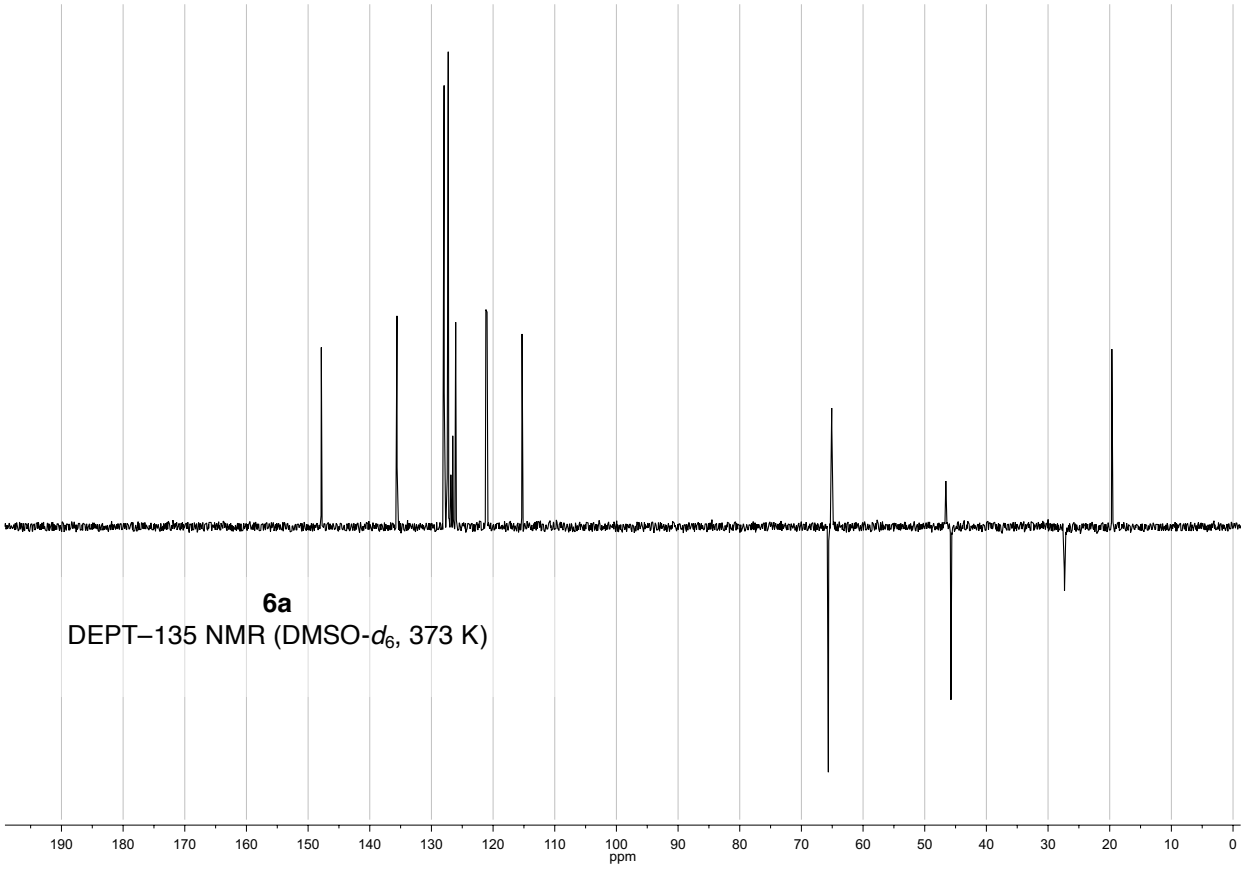
6a

^{13}C NMR (101 MHz, DMSO-d_6, 373 K)



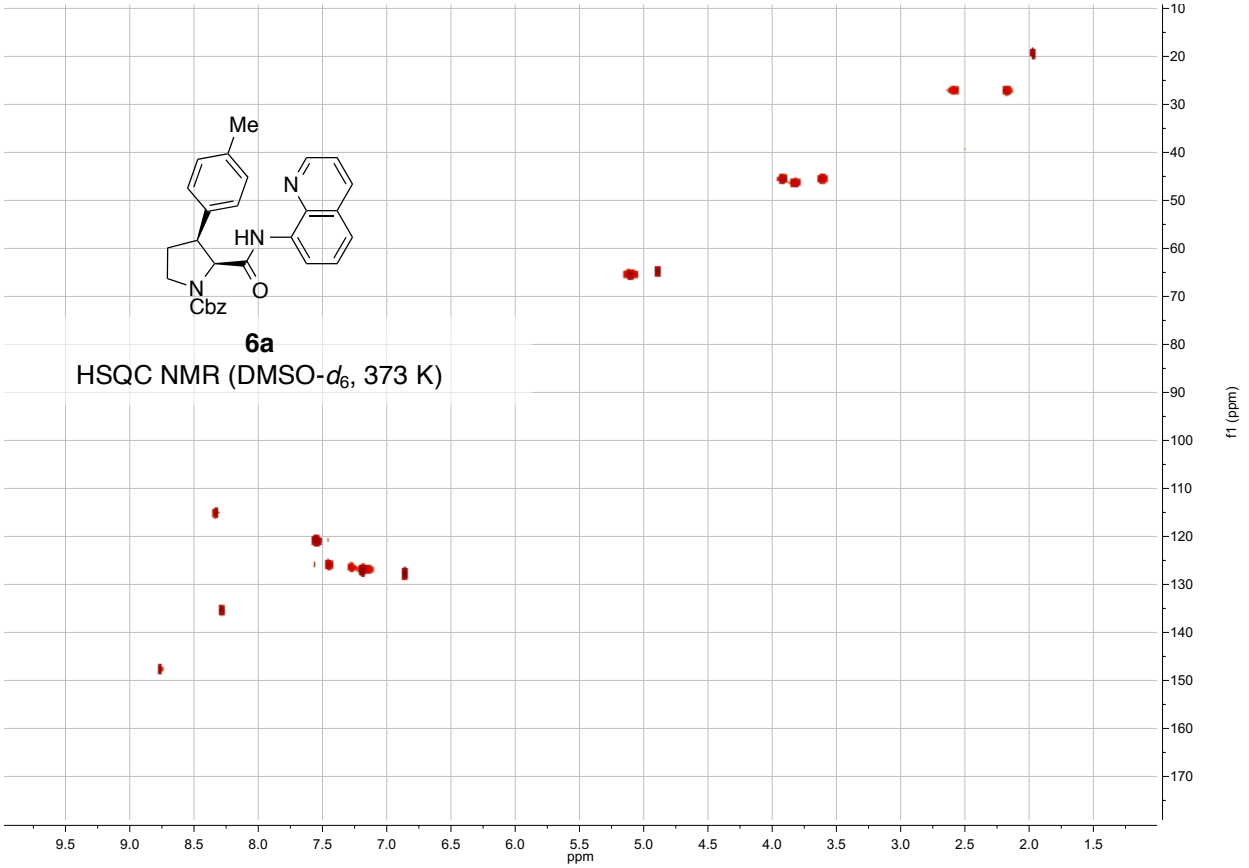
6a

COSY NMR (DMSO-d_6, 373 K)

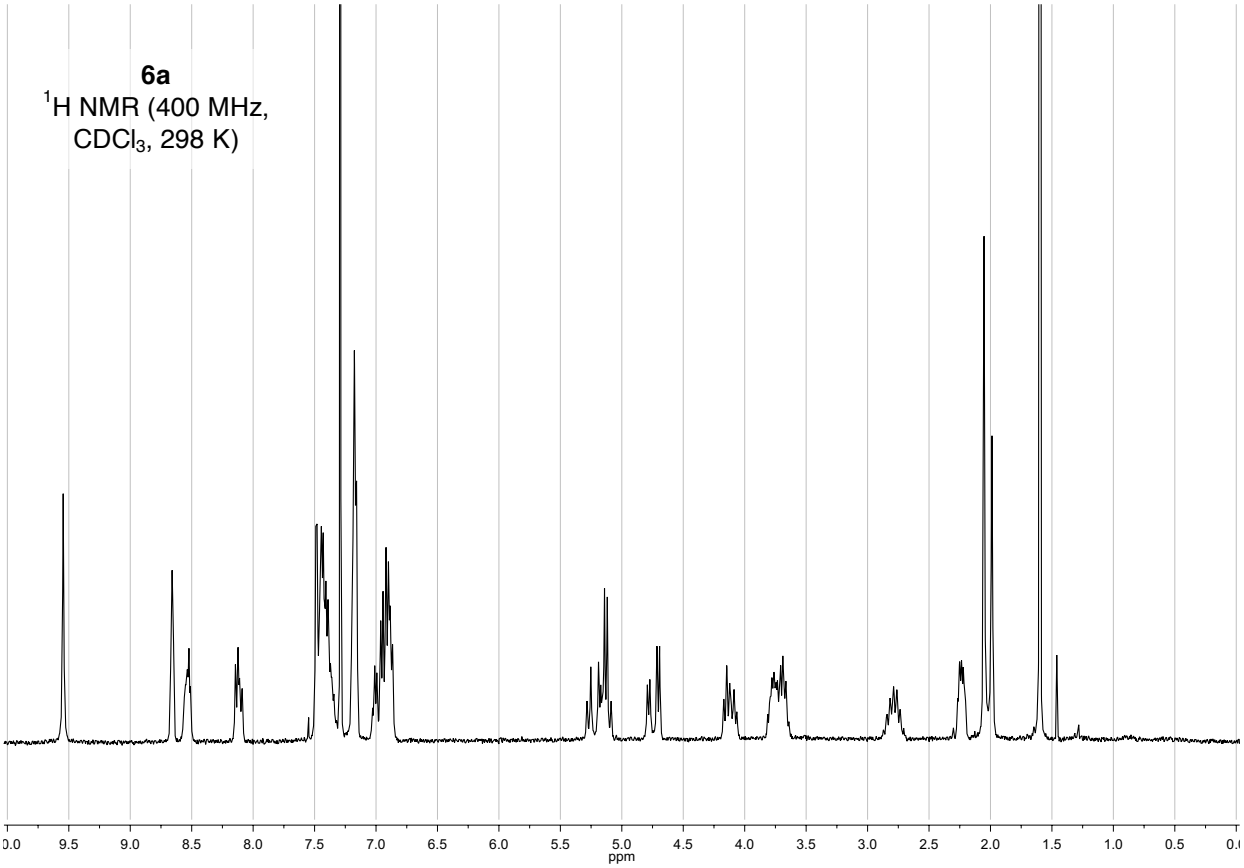


6a

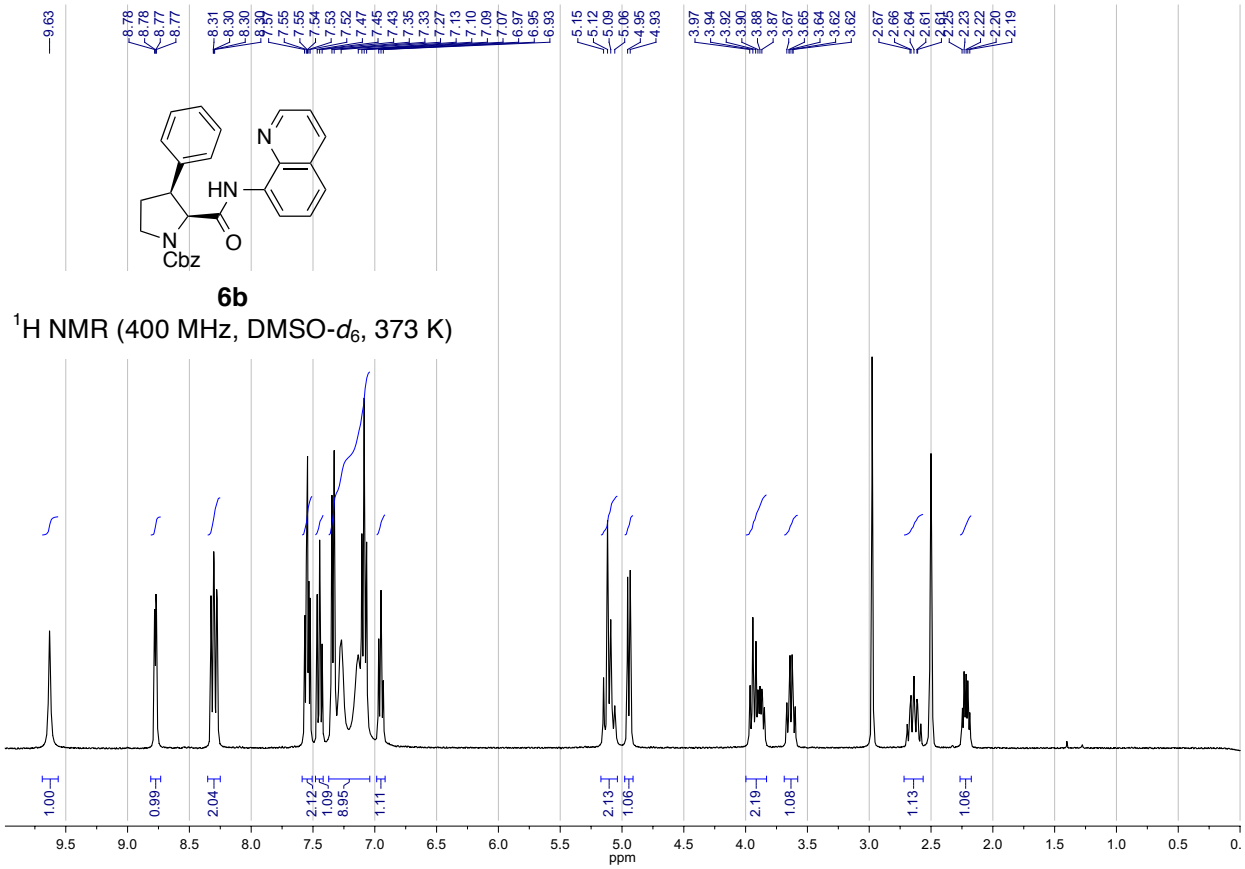
DEPT–135 NMR (DMSO-d_6, 373 K)



6a
HSQC NMR (DMSO-d_6, 373 K)

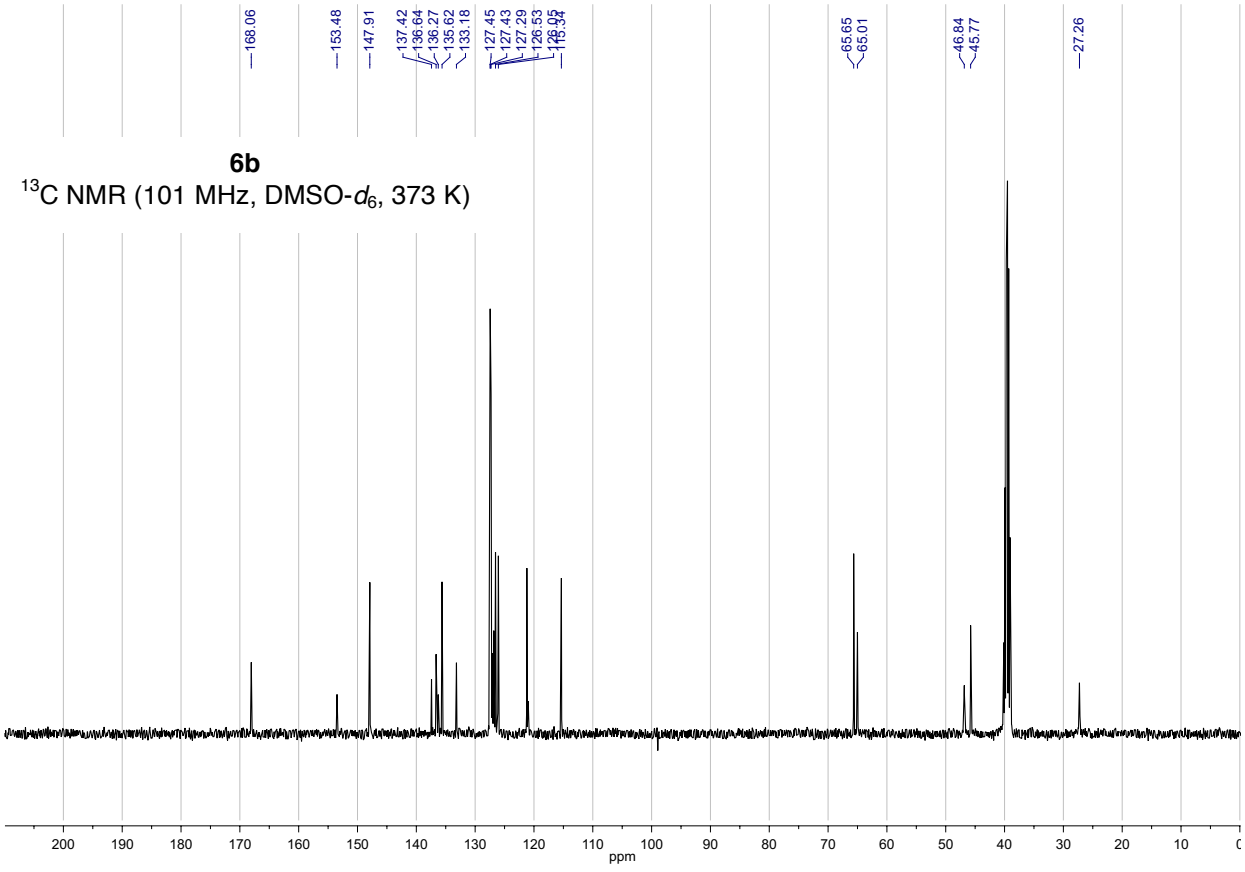


6a
^{1}H NMR (400 MHz, $CDCl_3$, 298 K)



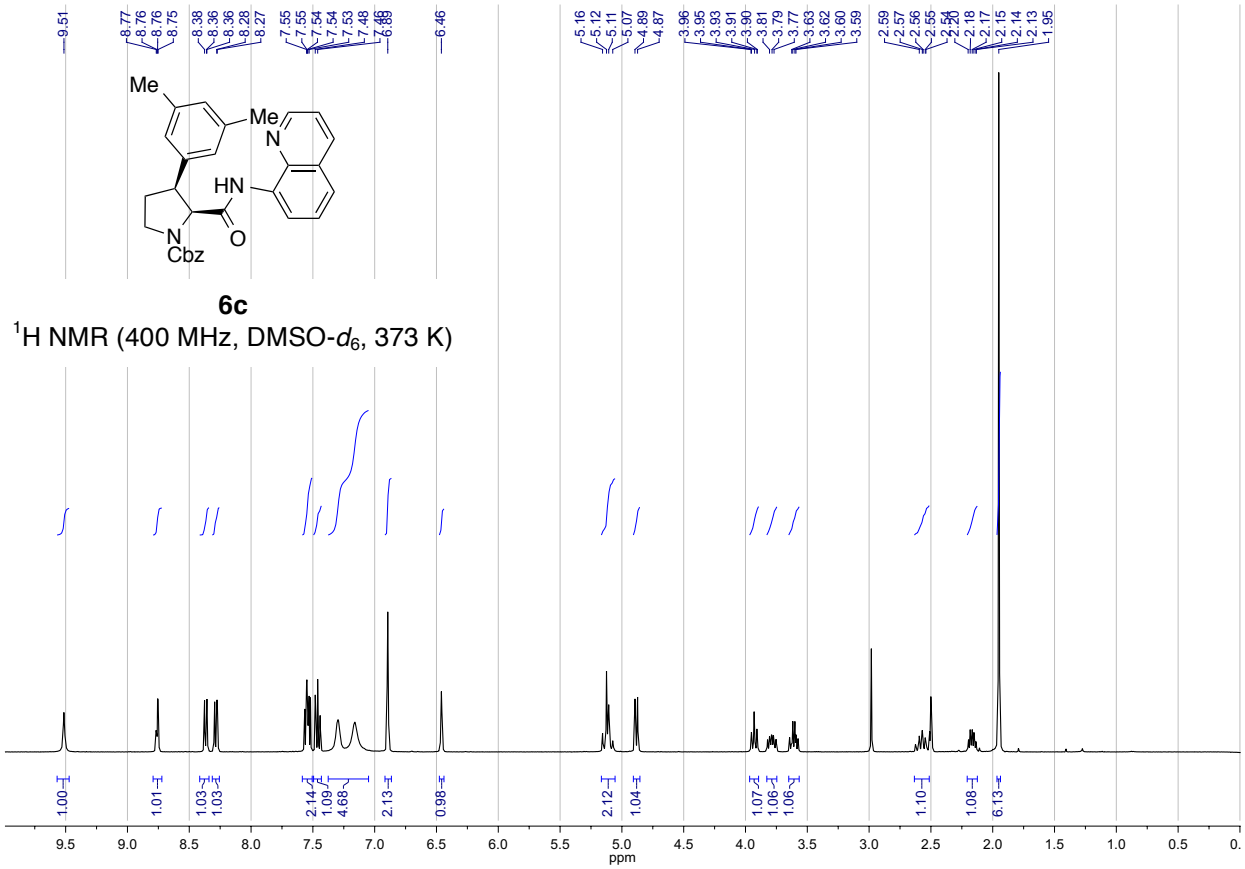
6b

^{1}H NMR (400 MHz, DMSO-d_6, 373 K)



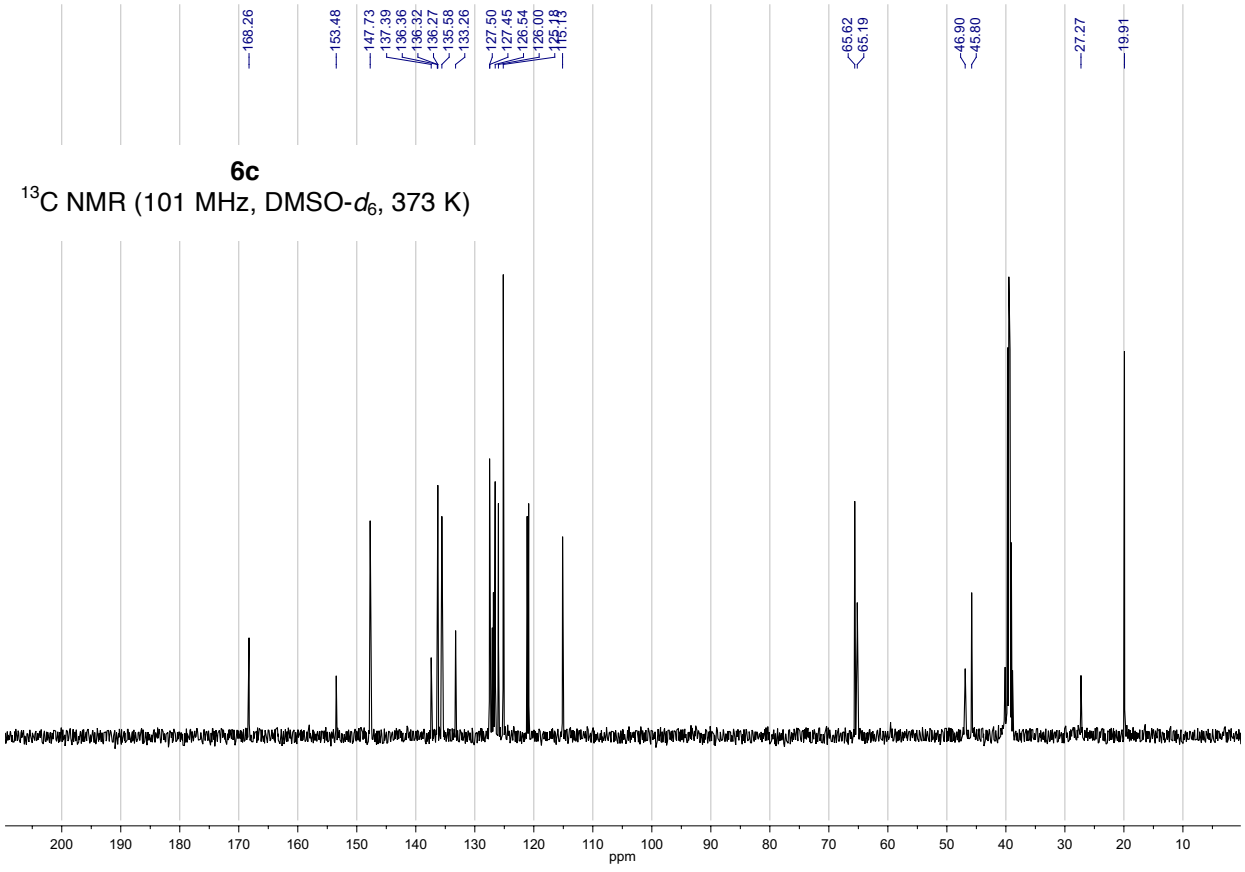
6b

^{13}C NMR (101 MHz, DMSO-d_6, 373 K)



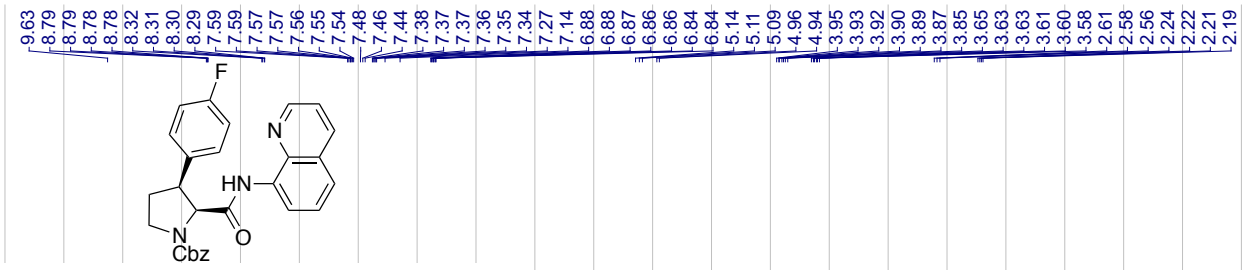
6c

^{1}H NMR (400 MHz, DMSO-d_6, 373 K)



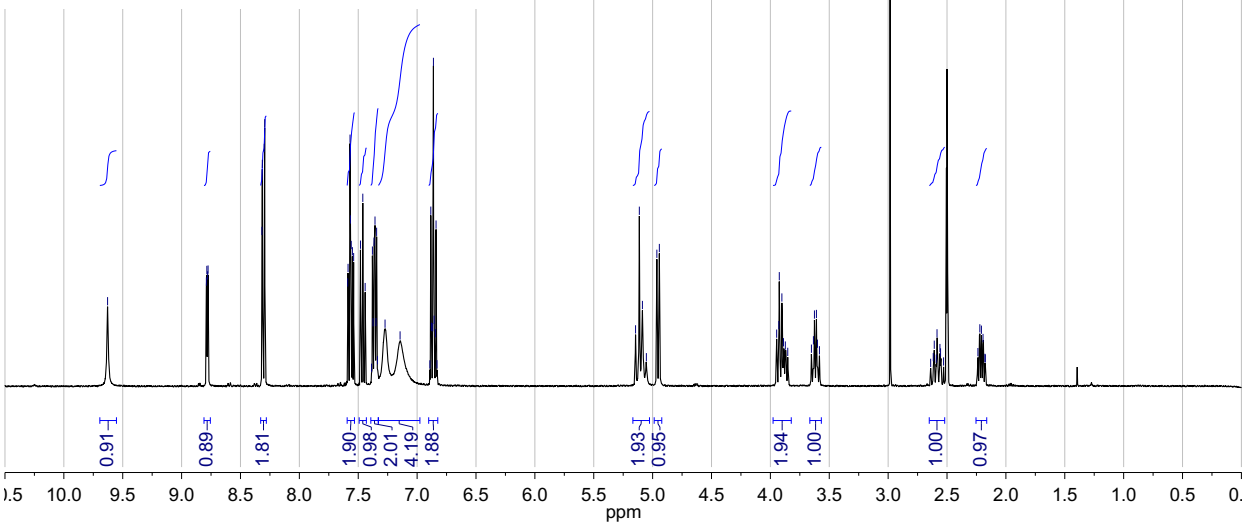
6c

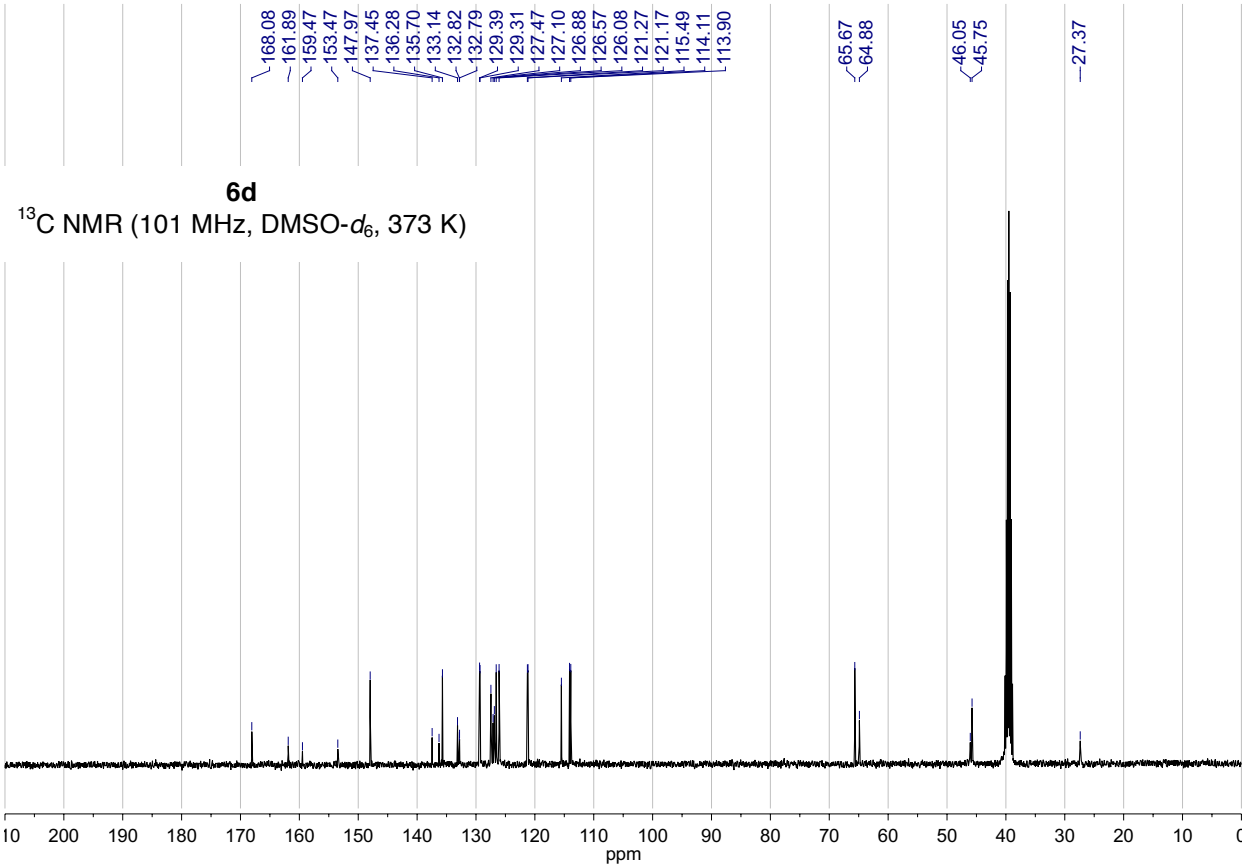
^{13}C NMR (101 MHz, DMSO-d_6, 373 K)



6d

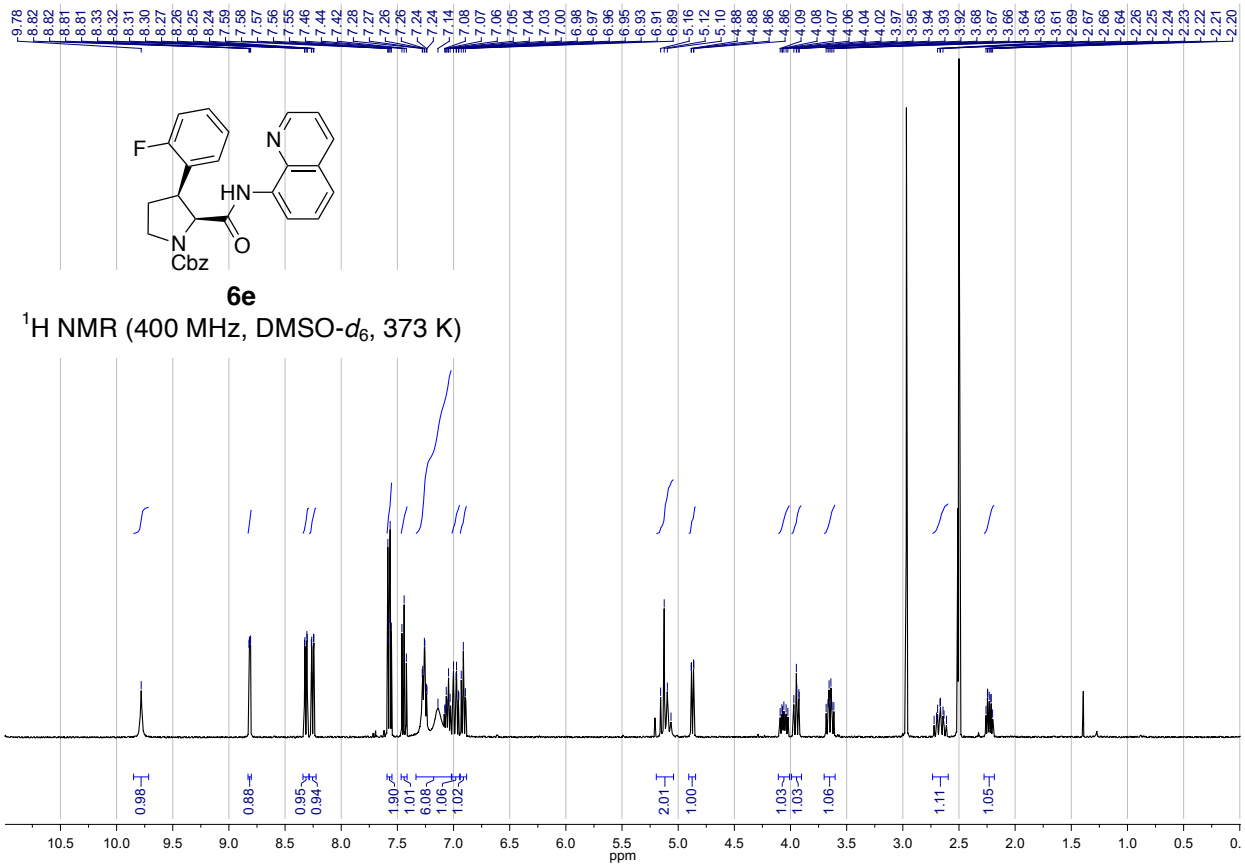
^{1}H NMR (400 MHz, DMSO-d_6, 373 K)





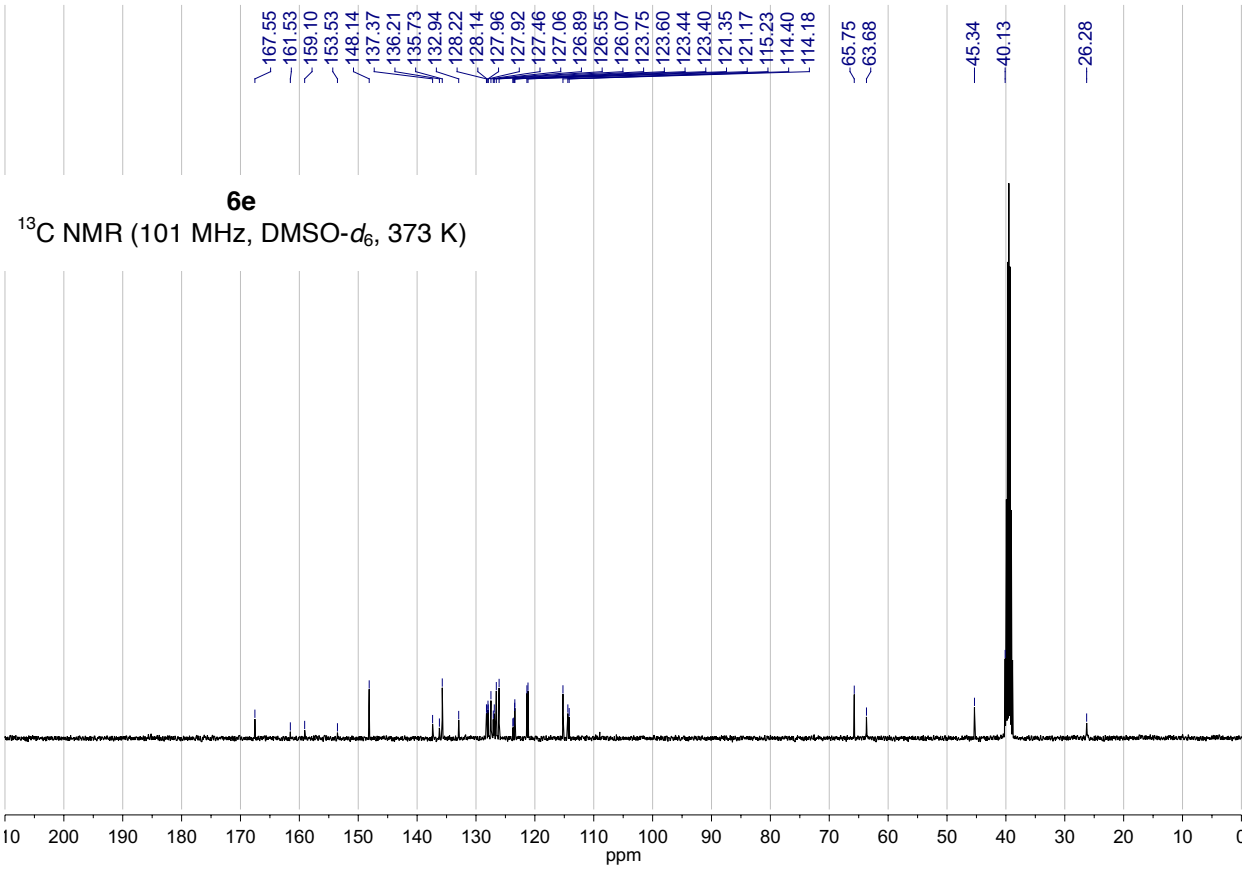
6d

^{13}C NMR (101 MHz, DMSO-d_6, 373 K)



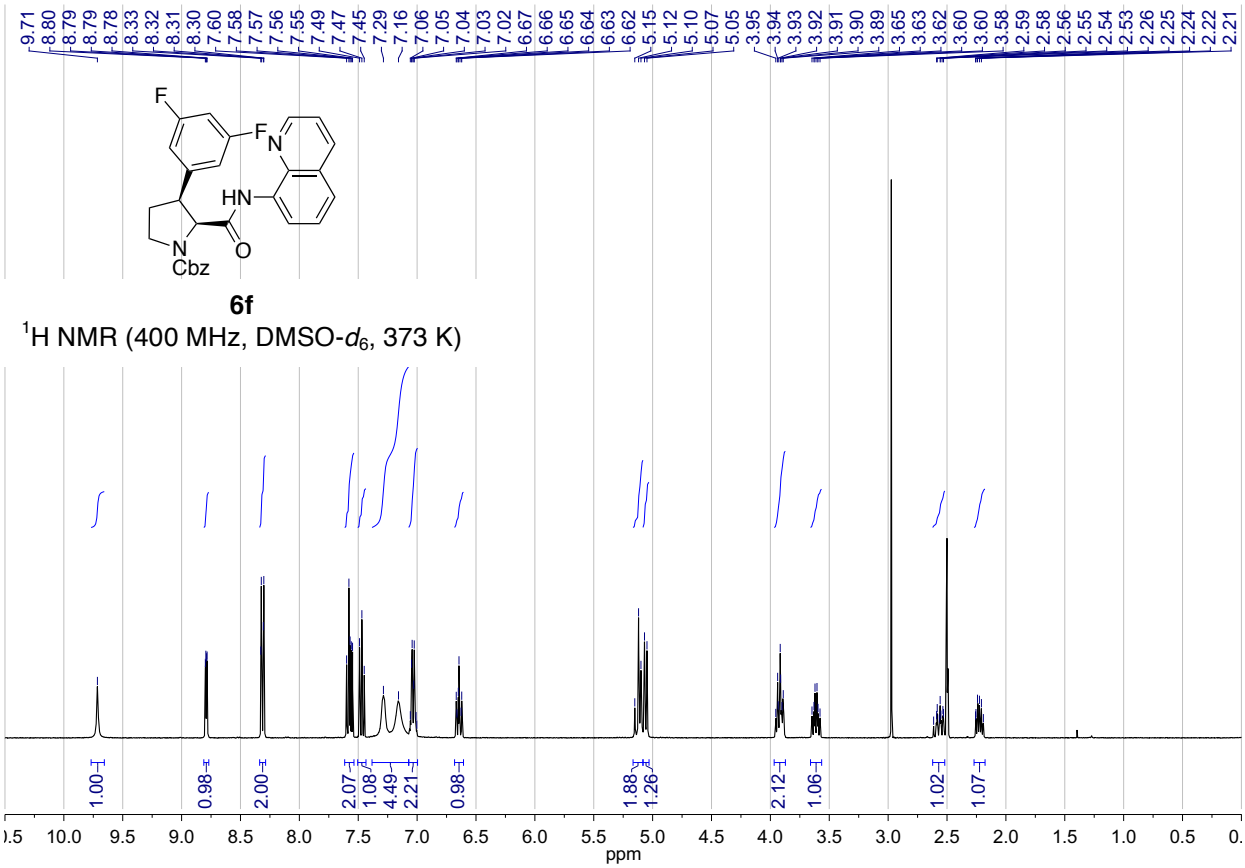
6e

^{1}H NMR (400 MHz, DMSO-d_6, 373 K)



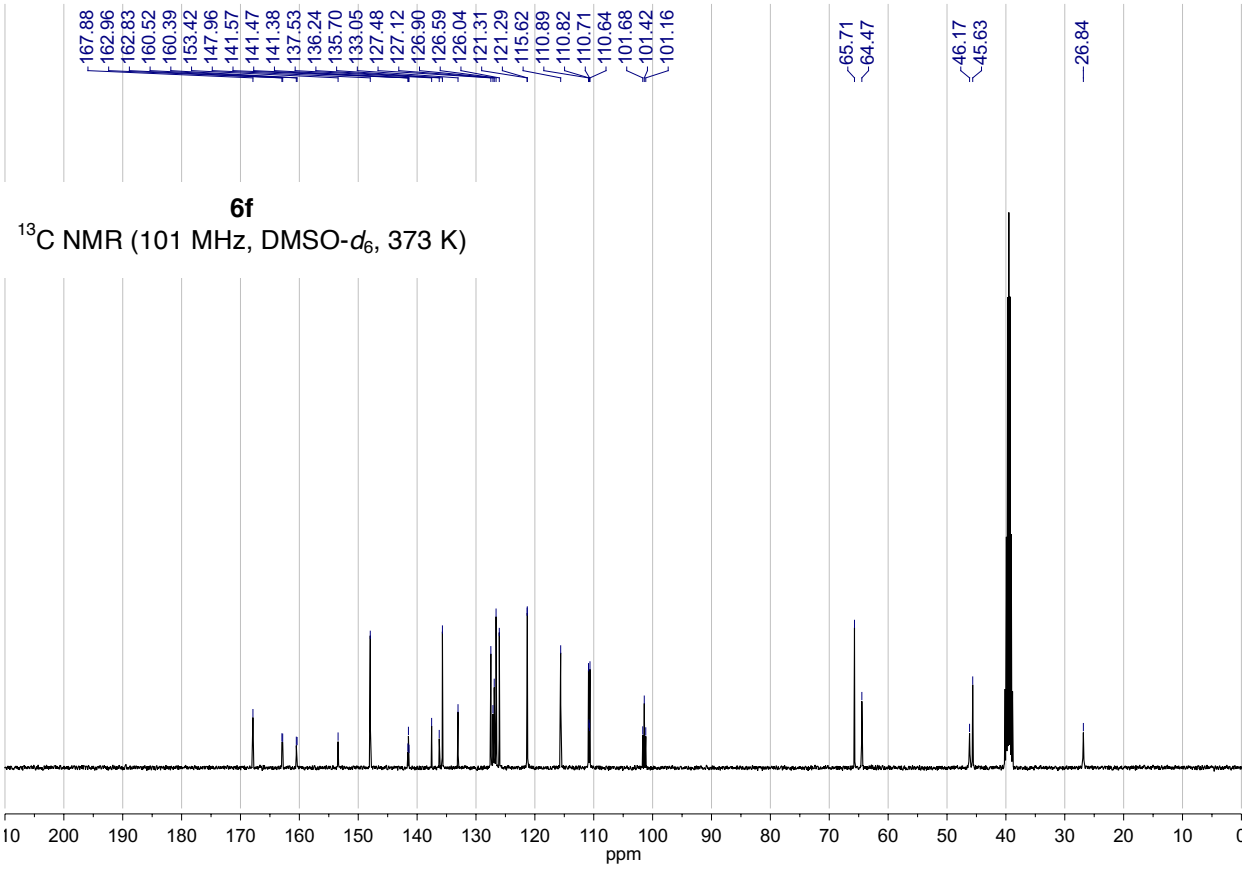
6e

^{13}C NMR (101 MHz, DMSO-d_6, 373 K)



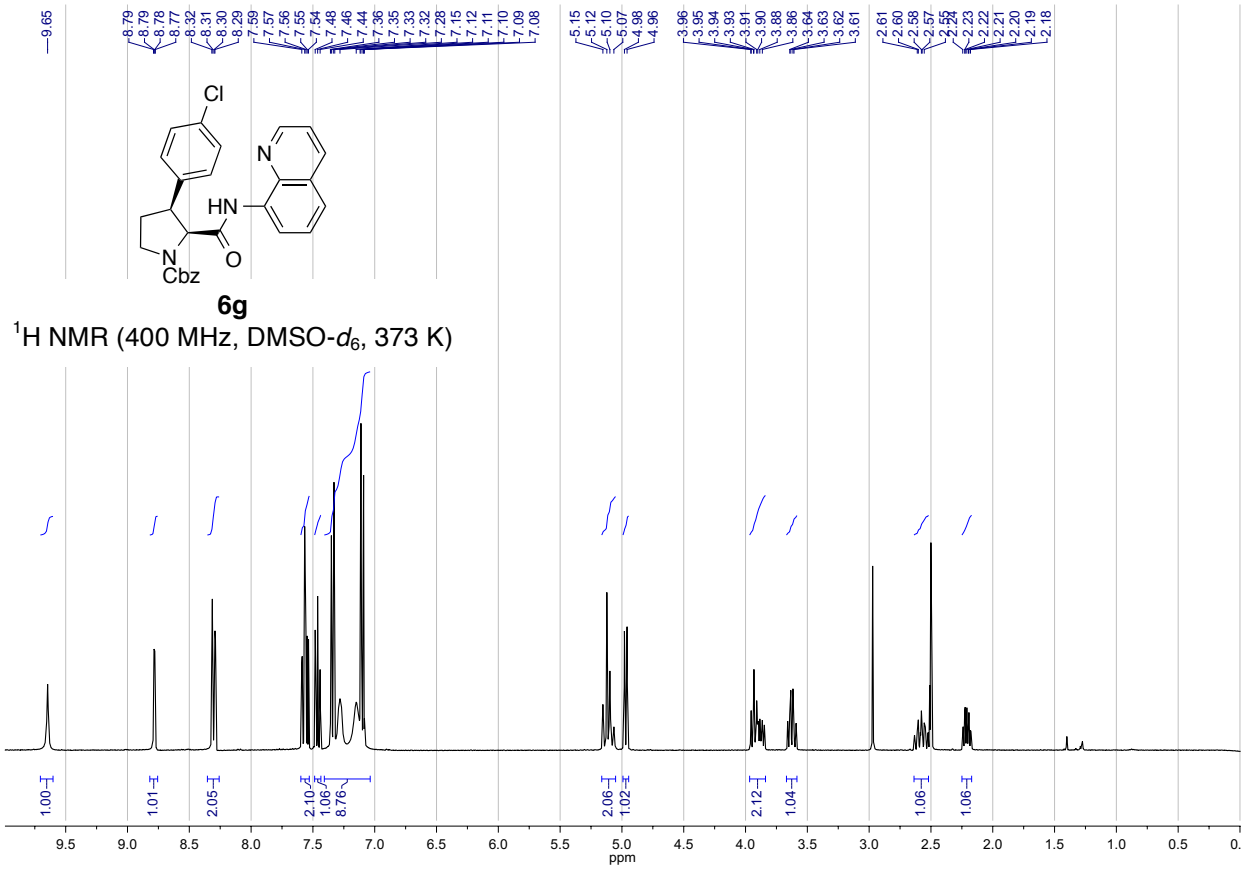
6f

^{1}H NMR (400 MHz, DMSO-d_6, 373 K)



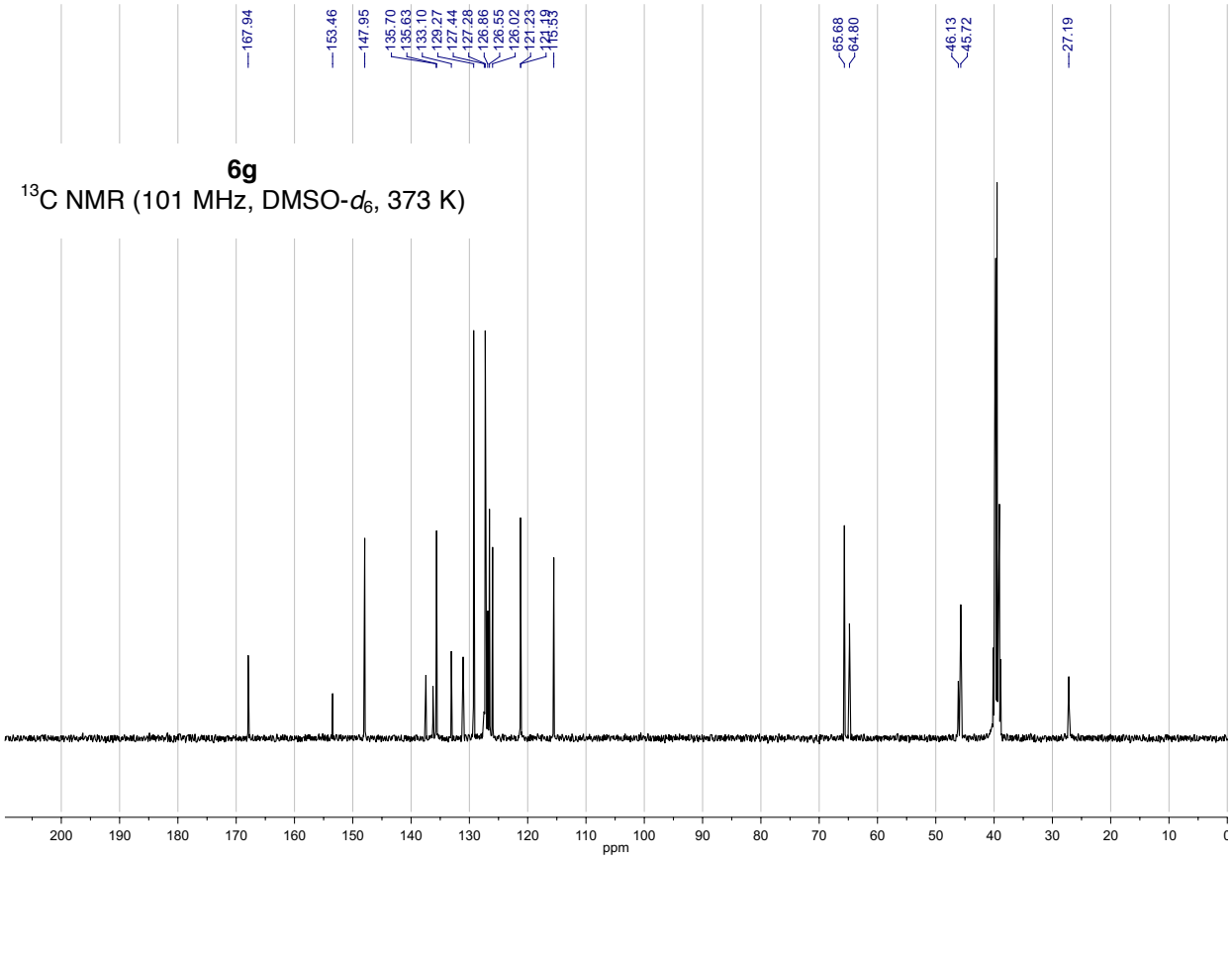
6f

^{13}C NMR (101 MHz, DMSO-d_6, 373 K)



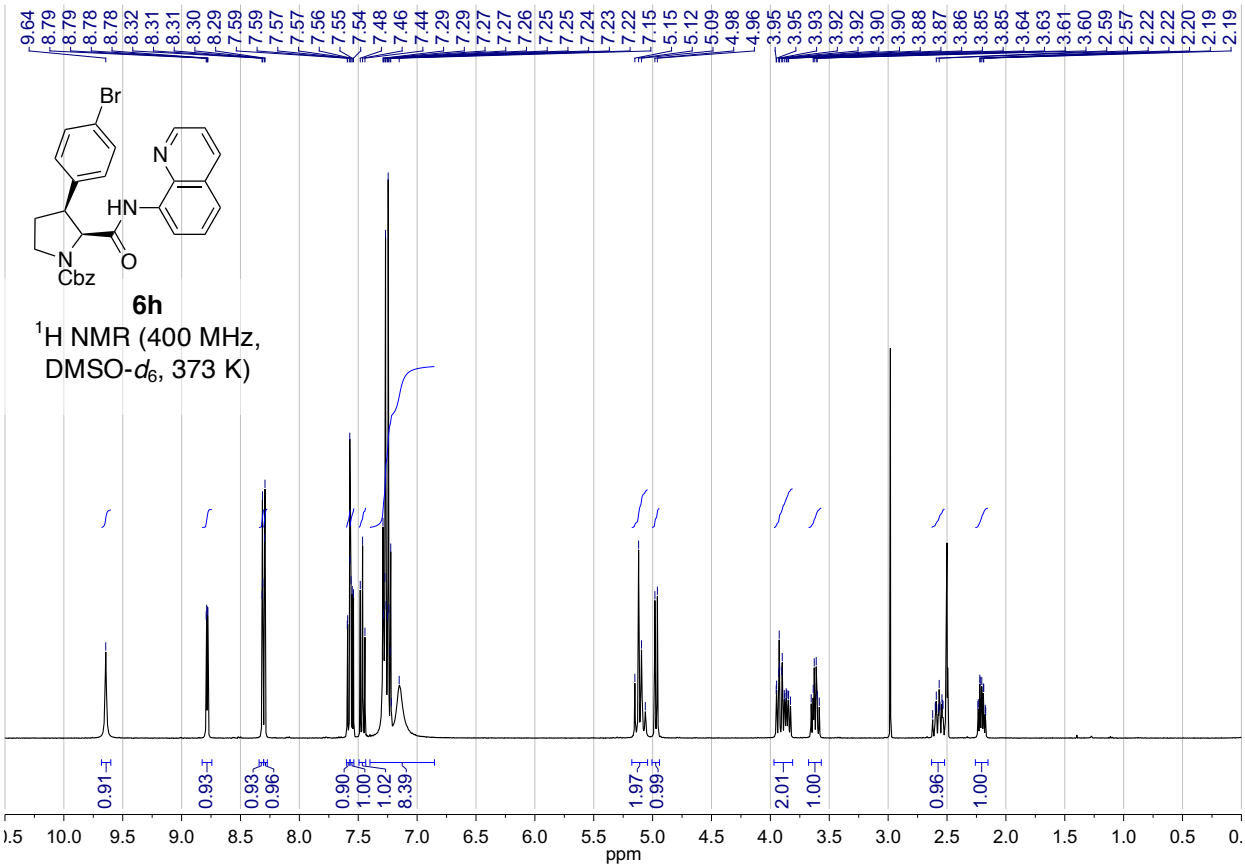
6g

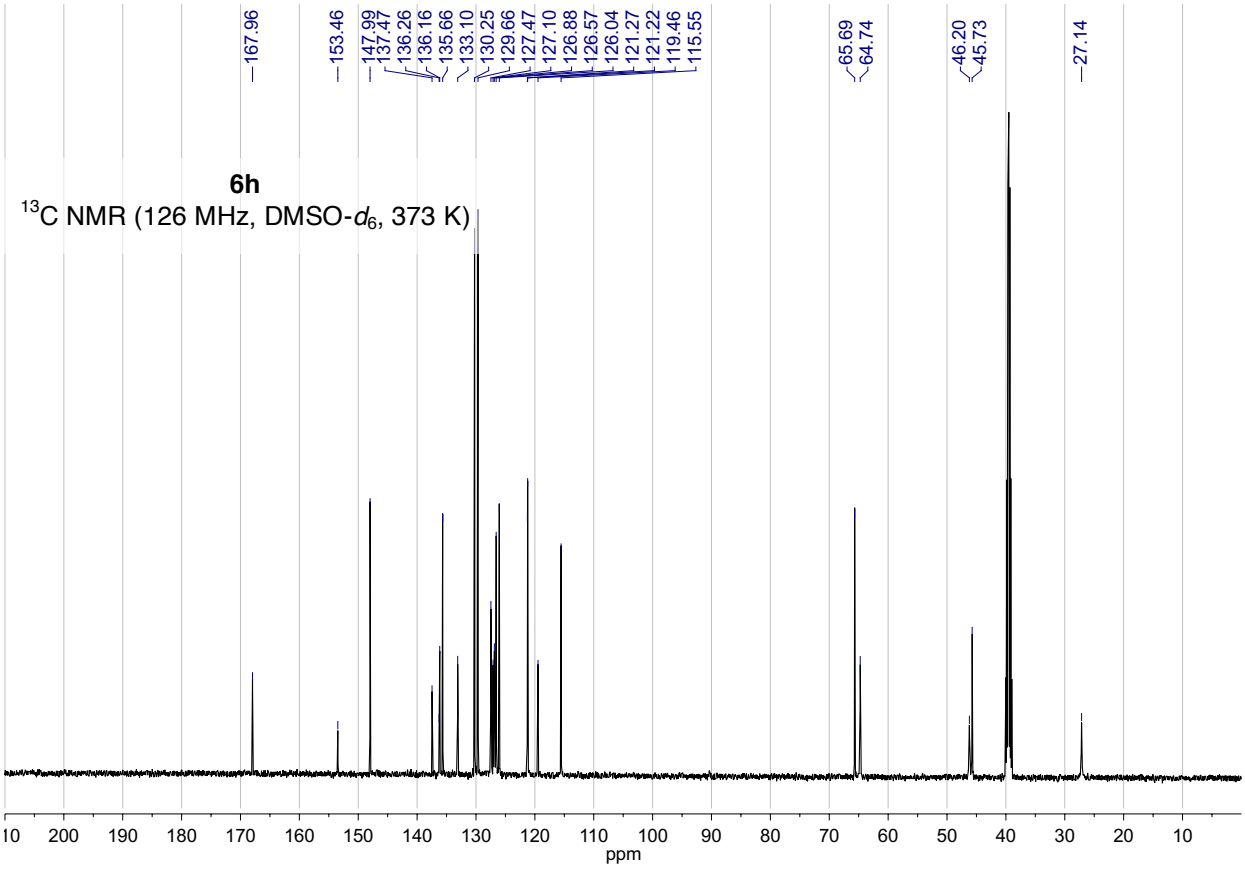
^{1}H NMR (400 MHz, DMSO-d_6, 373 K)

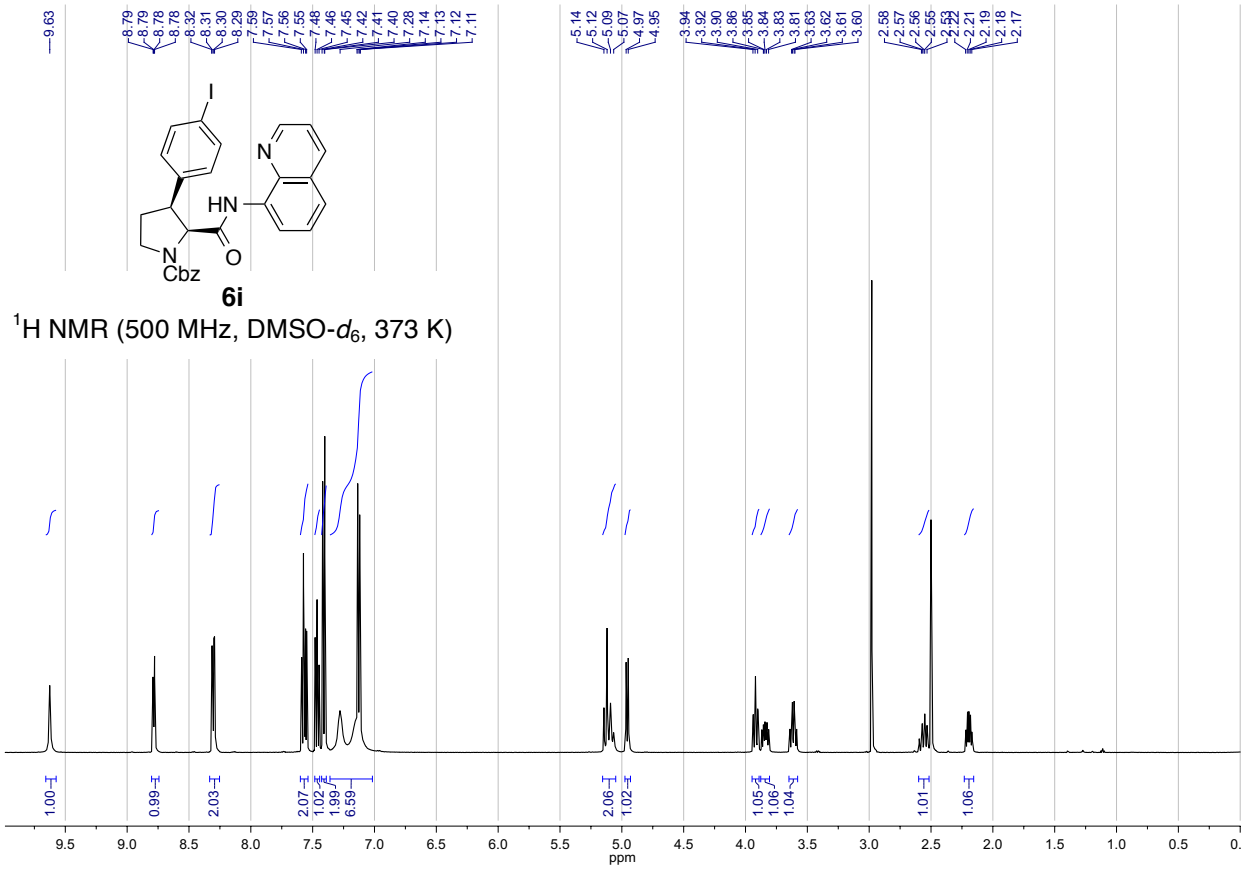


6g

^{13}C NMR (101 MHz, DMSO-d_6, 373 K)

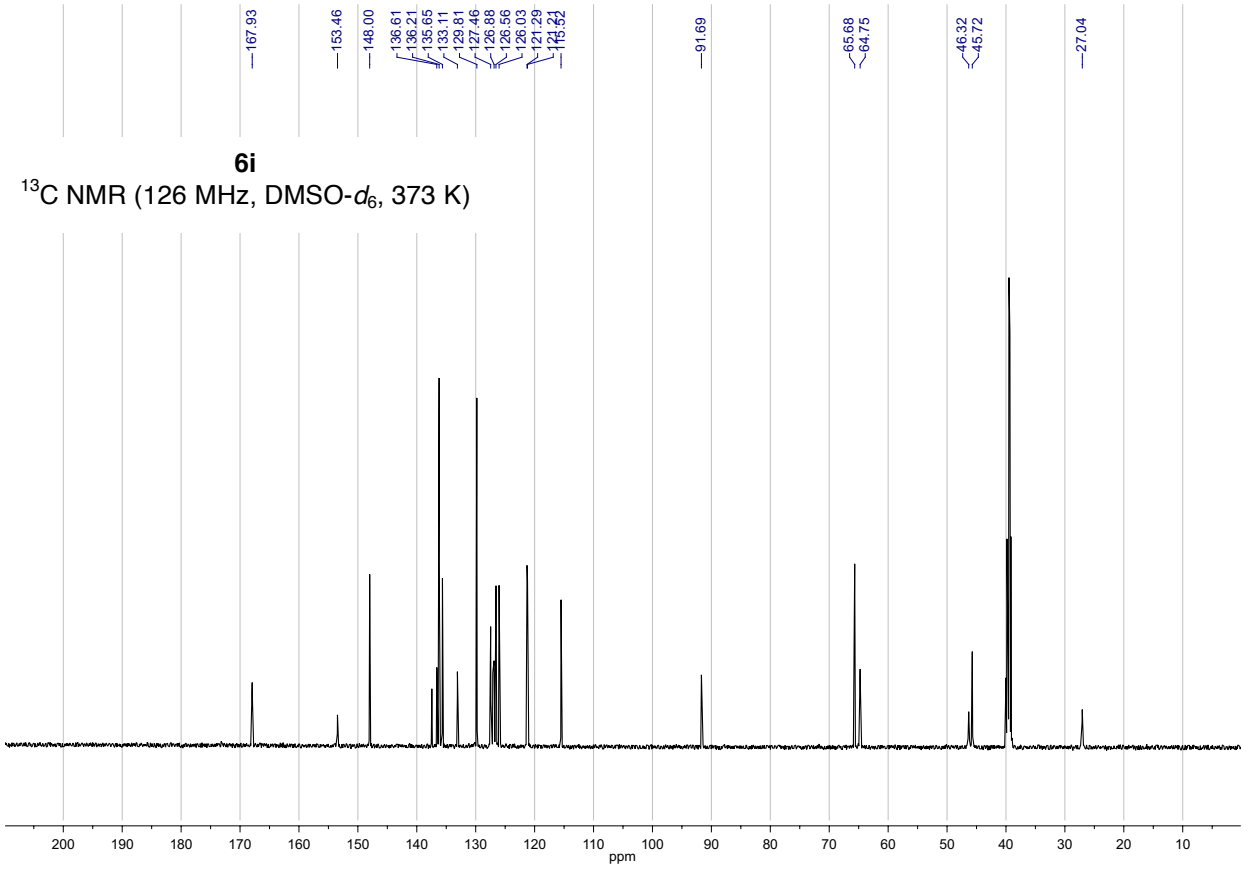

Br
N
HN
O
N
Cbz
6h
^{1}H NMR (400 MHz,
DMSO-d_6, 373 K)
ppm


6h
^{13}C NMR (126 MHz, DMSO-d_6, 373 K)
ppm



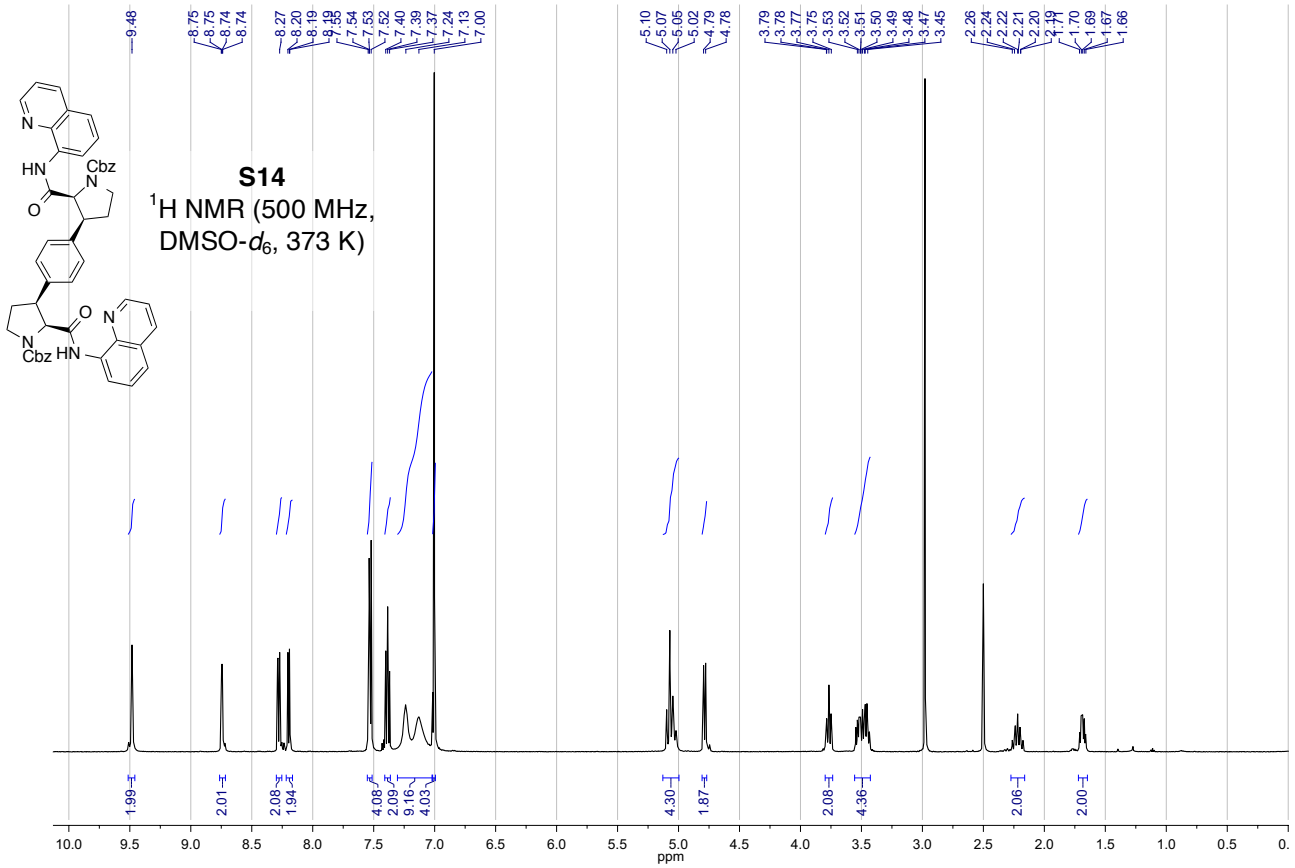
6i

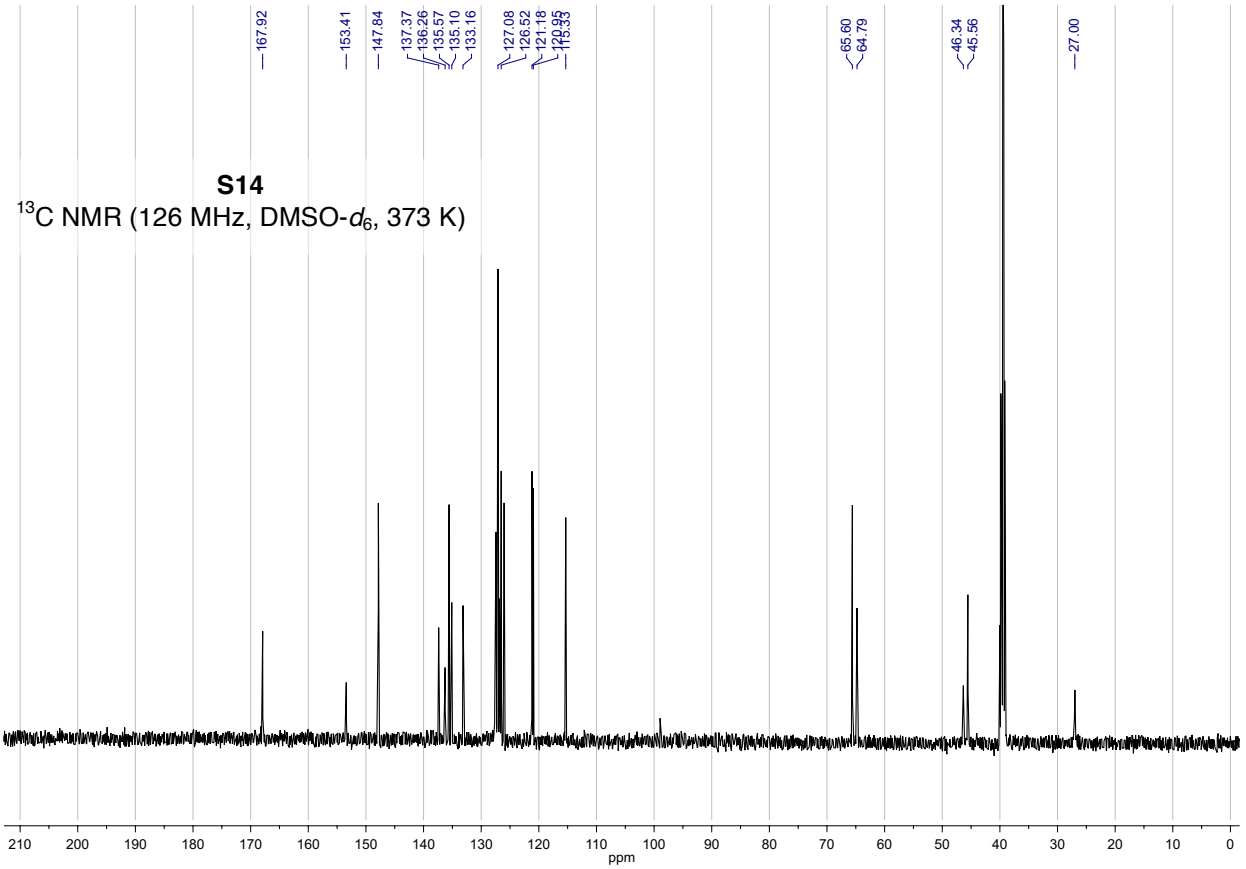
^{1}H NMR (500 MHz, DMSO-d_6, 373 K)

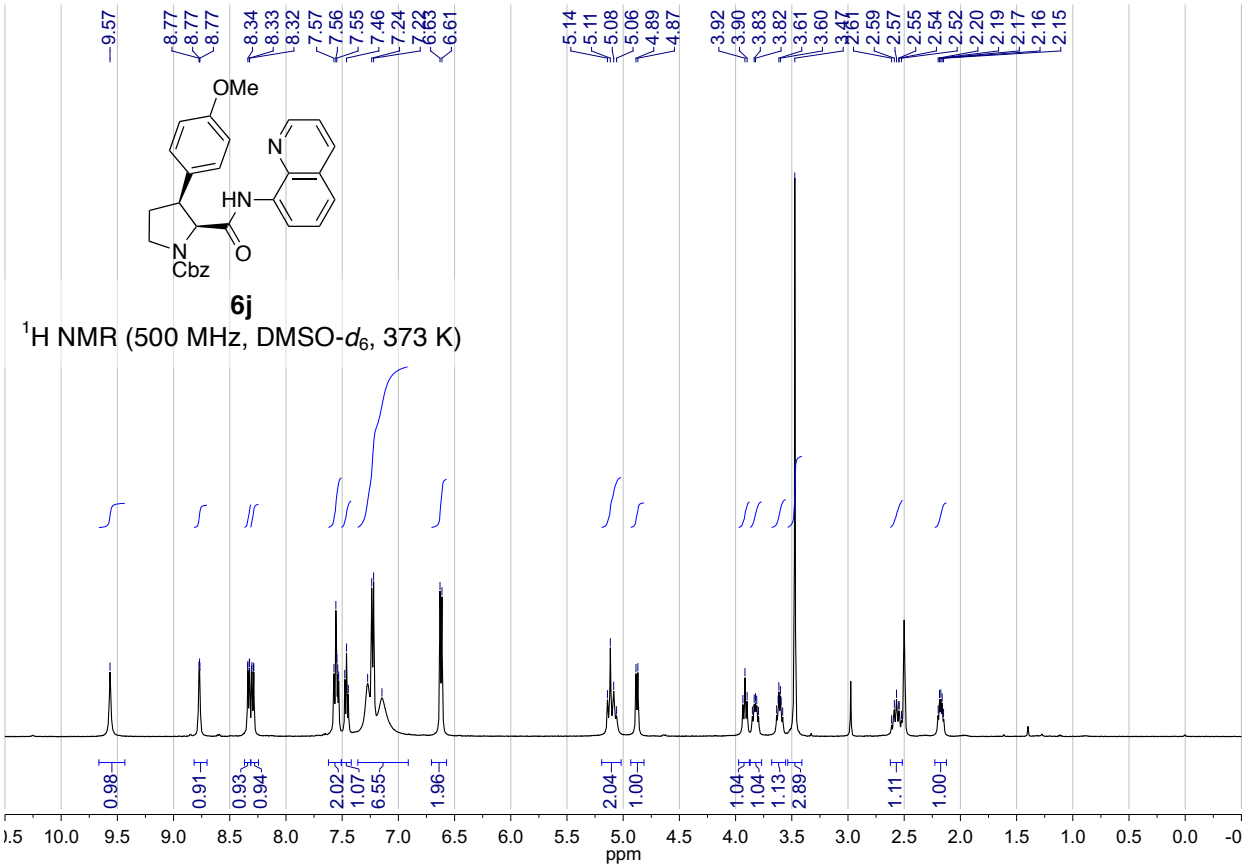


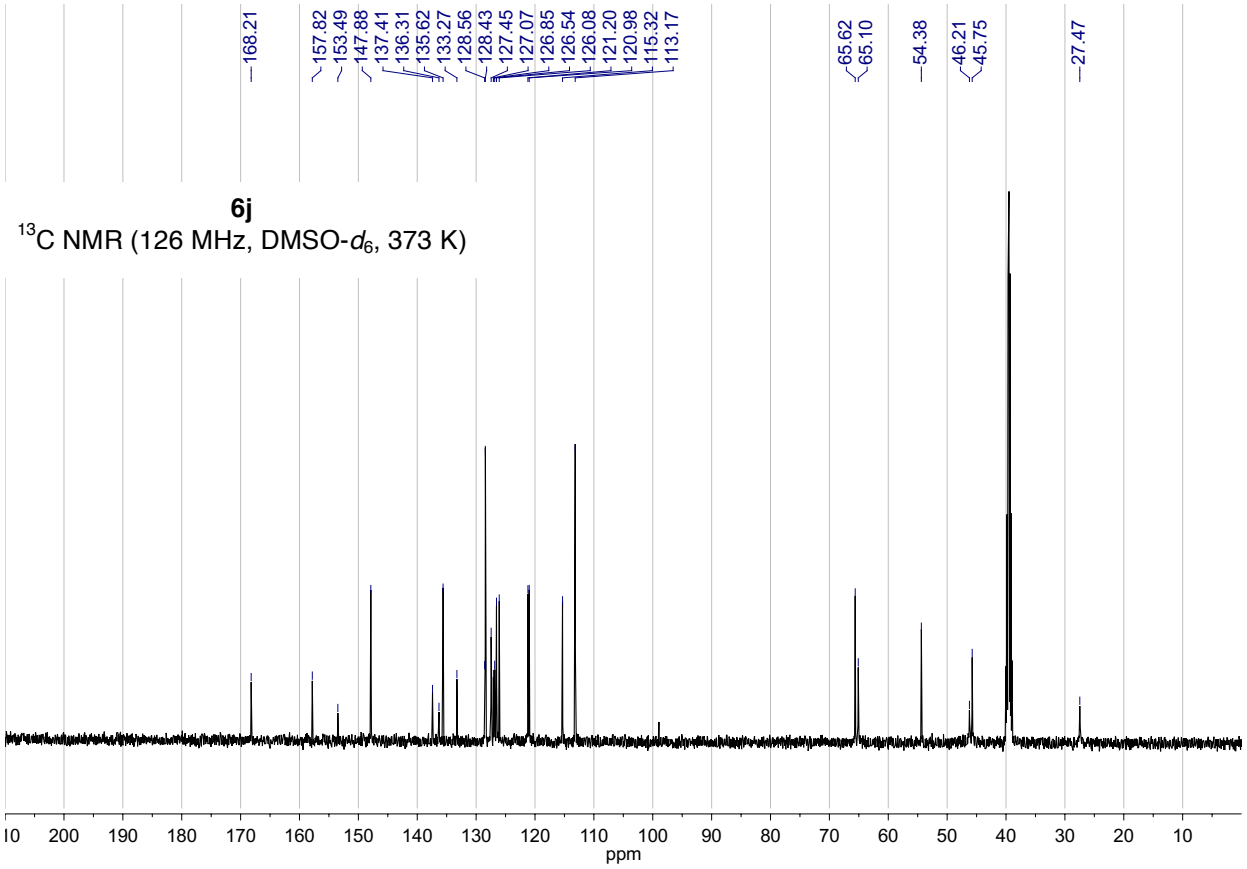
6i

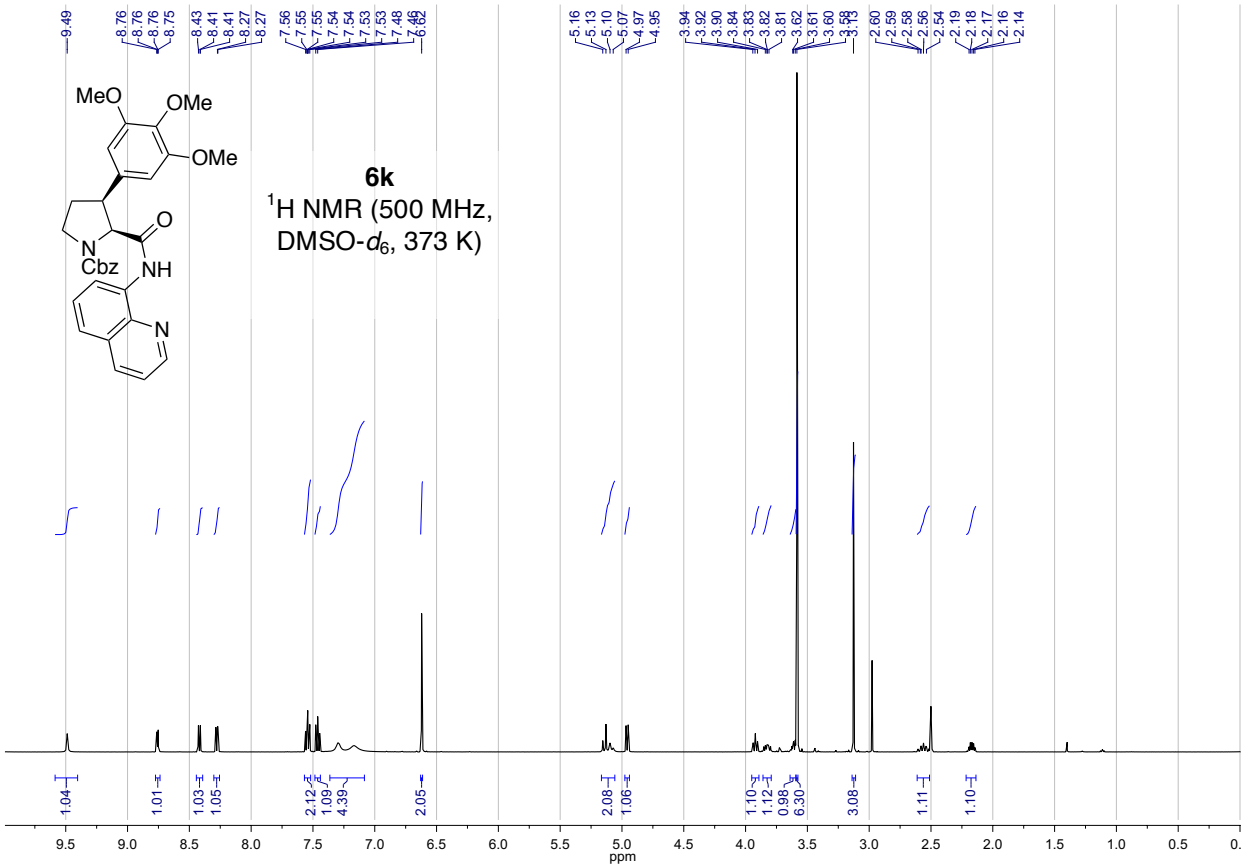
^{13}C NMR (126 MHz, DMSO-d_6, 373 K)

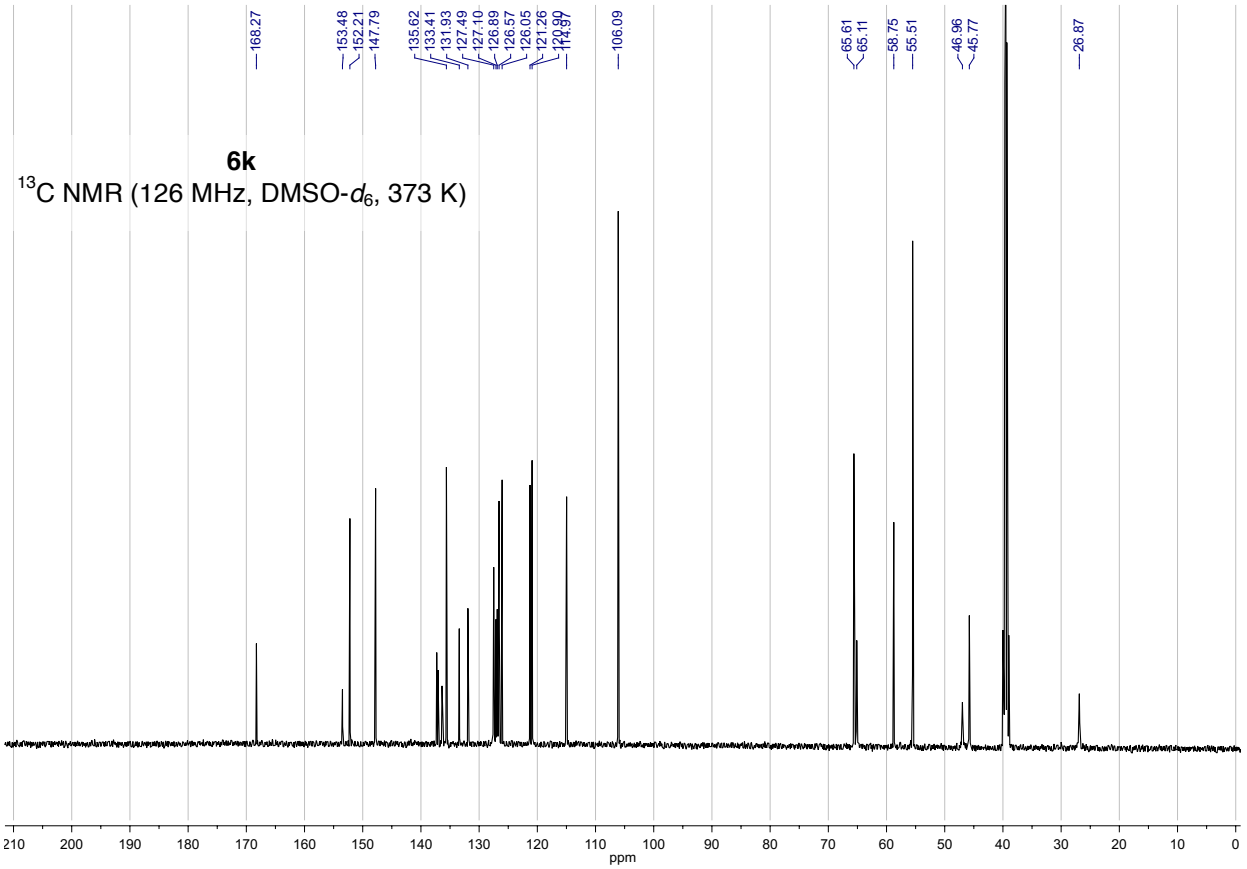

S14
1H NMR (500 MHz, DMSO-d6, 373 K)
ppm

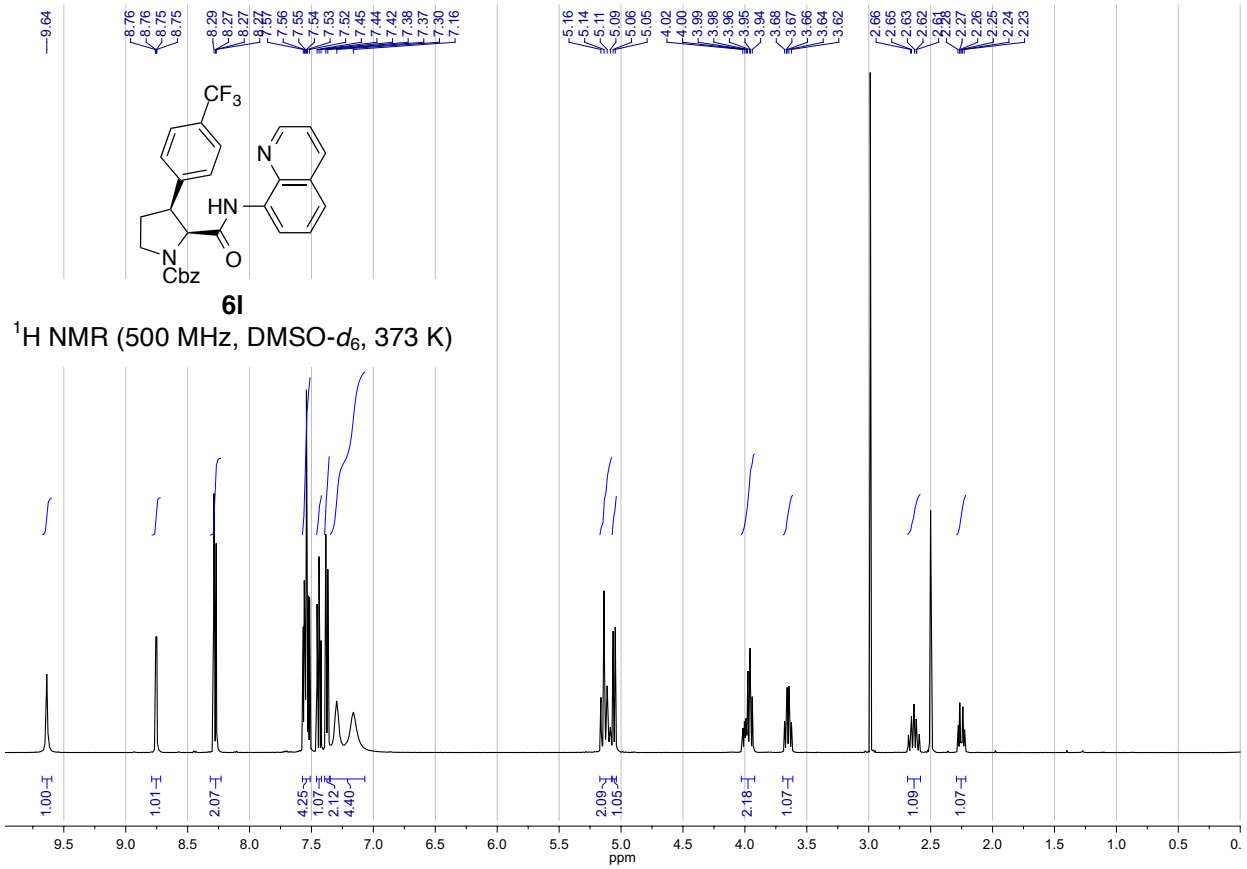

S14
13C NMR (126 MHz, DMSO-d6, 373 K)
ppm


OMe
N
HN
O
N
Cbz
6j
^{1}H NMR (500 MHz, DMSO-d_6, 373 K)
ppm


6j
^{13}C NMR (126 MHz, DMSO-d_6, 373 K)
ppm

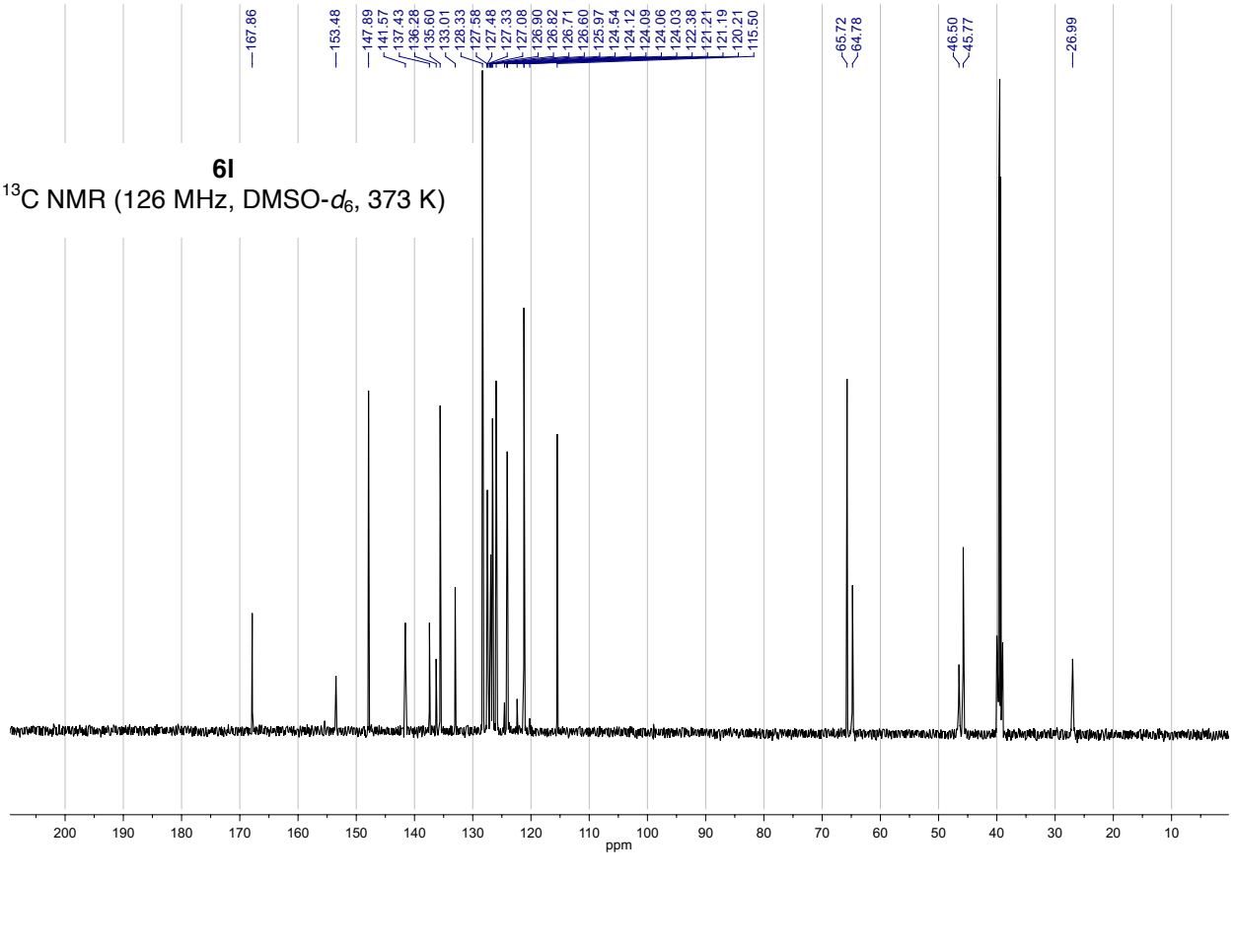

MeO
OMe
OMe
O
N
Cbz
NH
N
6k
1H NMR (500 MHz,
DMSO-d6, 373 K)
ppm


6k
13C NMR (126 MHz, DMSO-d6, 373 K)
ppm



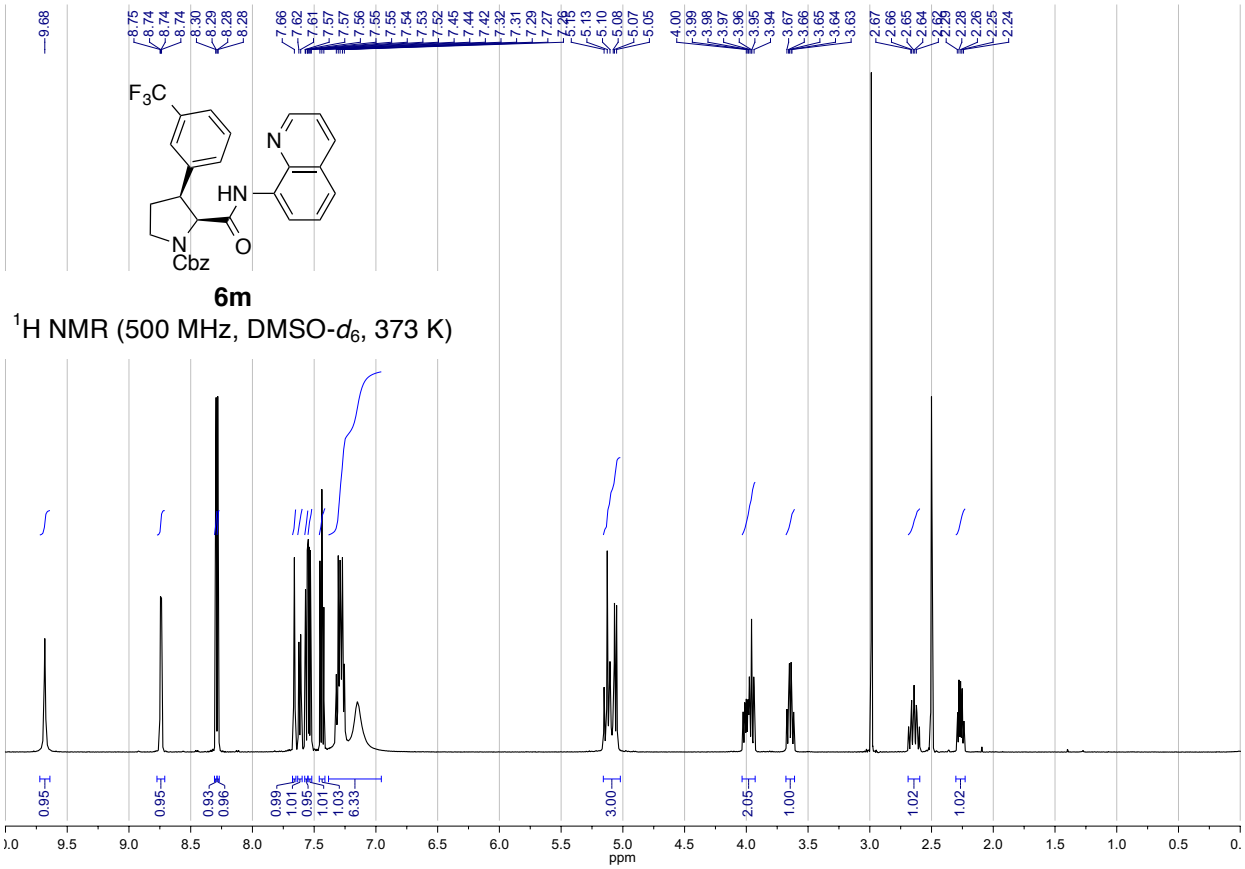
6l

^{1}H NMR (500 MHz, DMSO-d_6, 373 K)



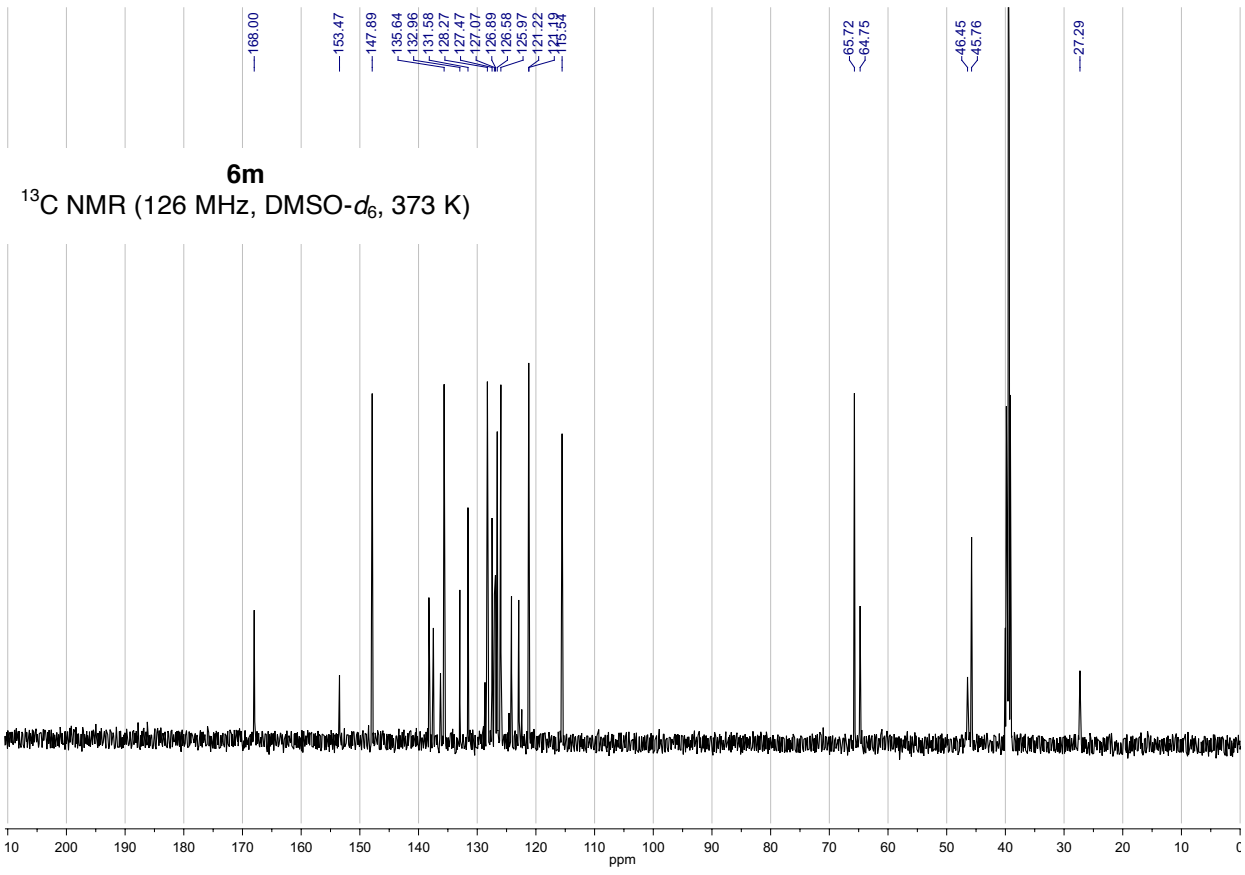
6l

^{13}C NMR (126 MHz, DMSO-d_6, 373 K)



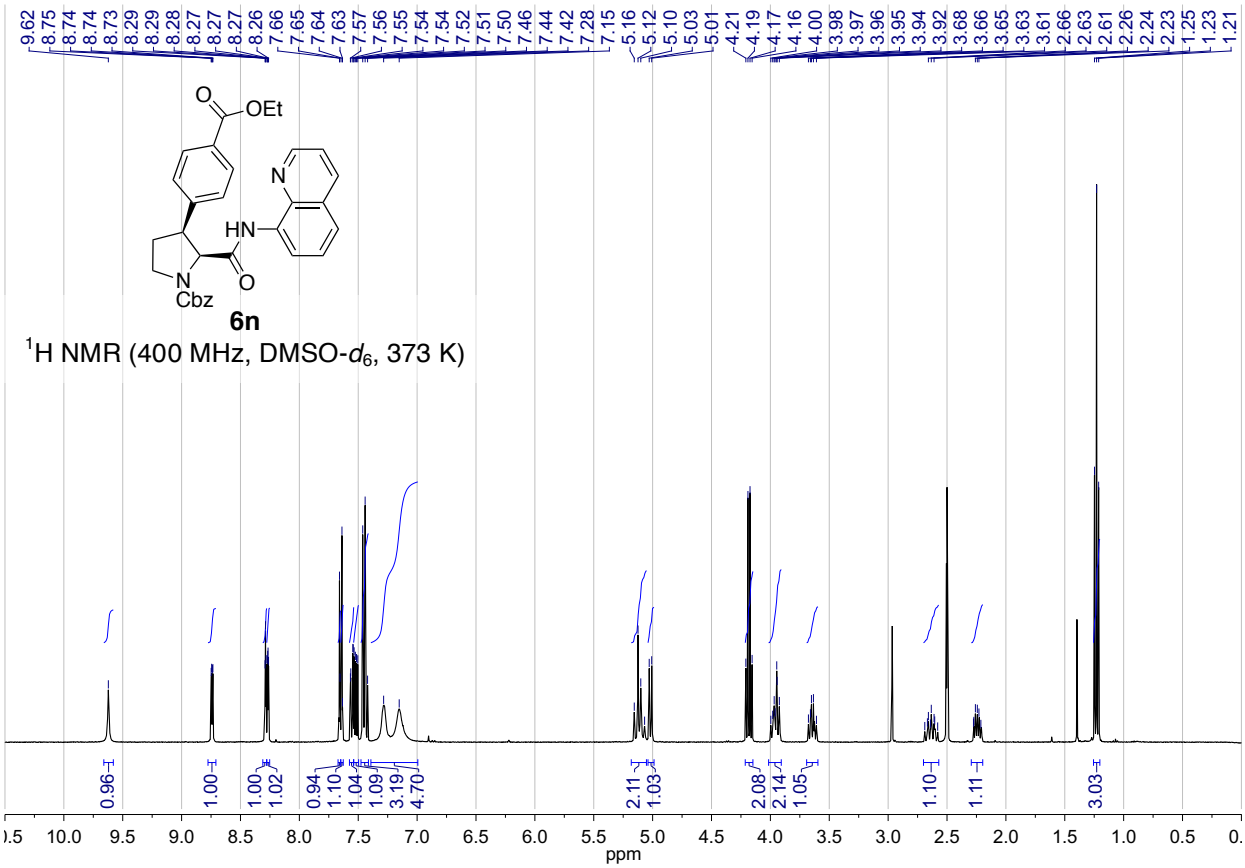
6m

^{1}H NMR (500 MHz, DMSO-d_6, 373 K)



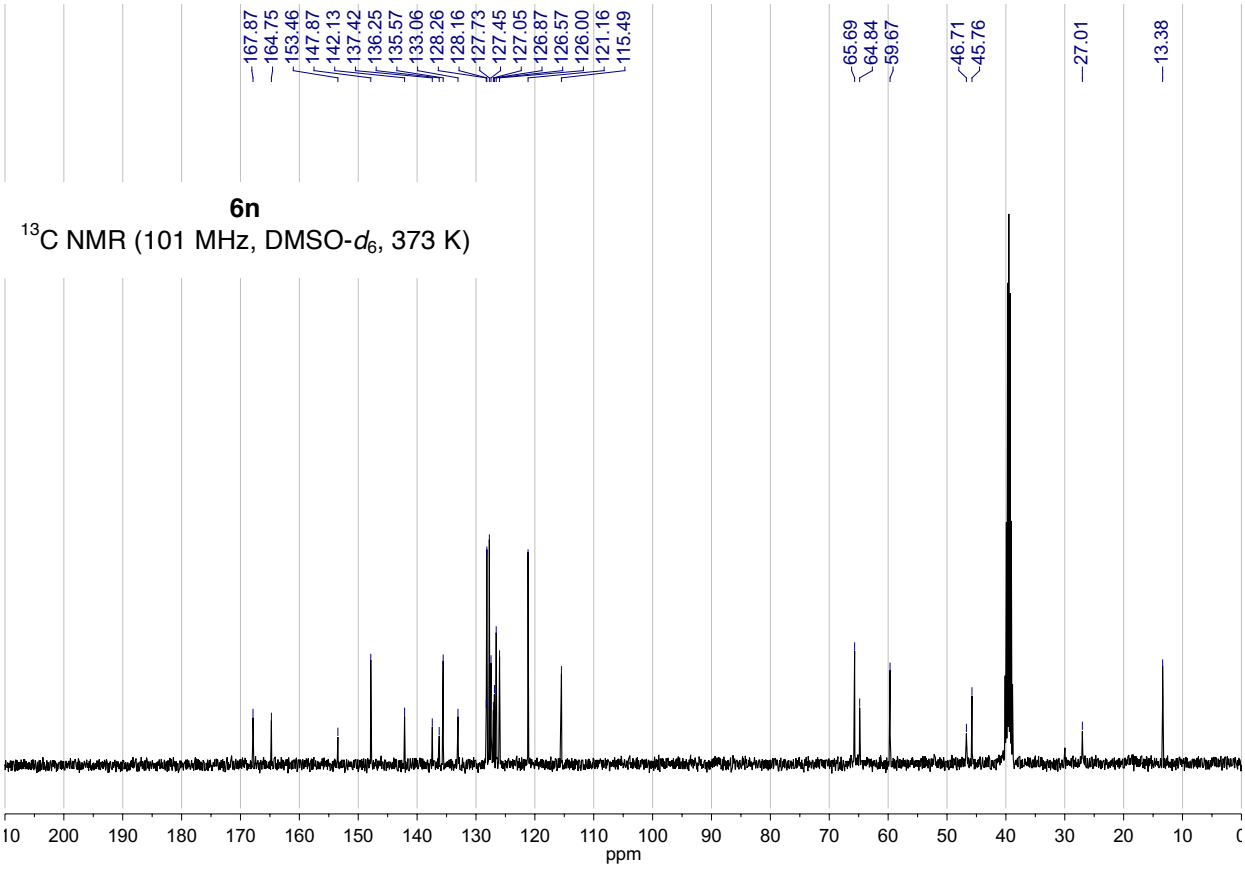
6m

^{13}C NMR (126 MHz, DMSO-d_6, 373 K)



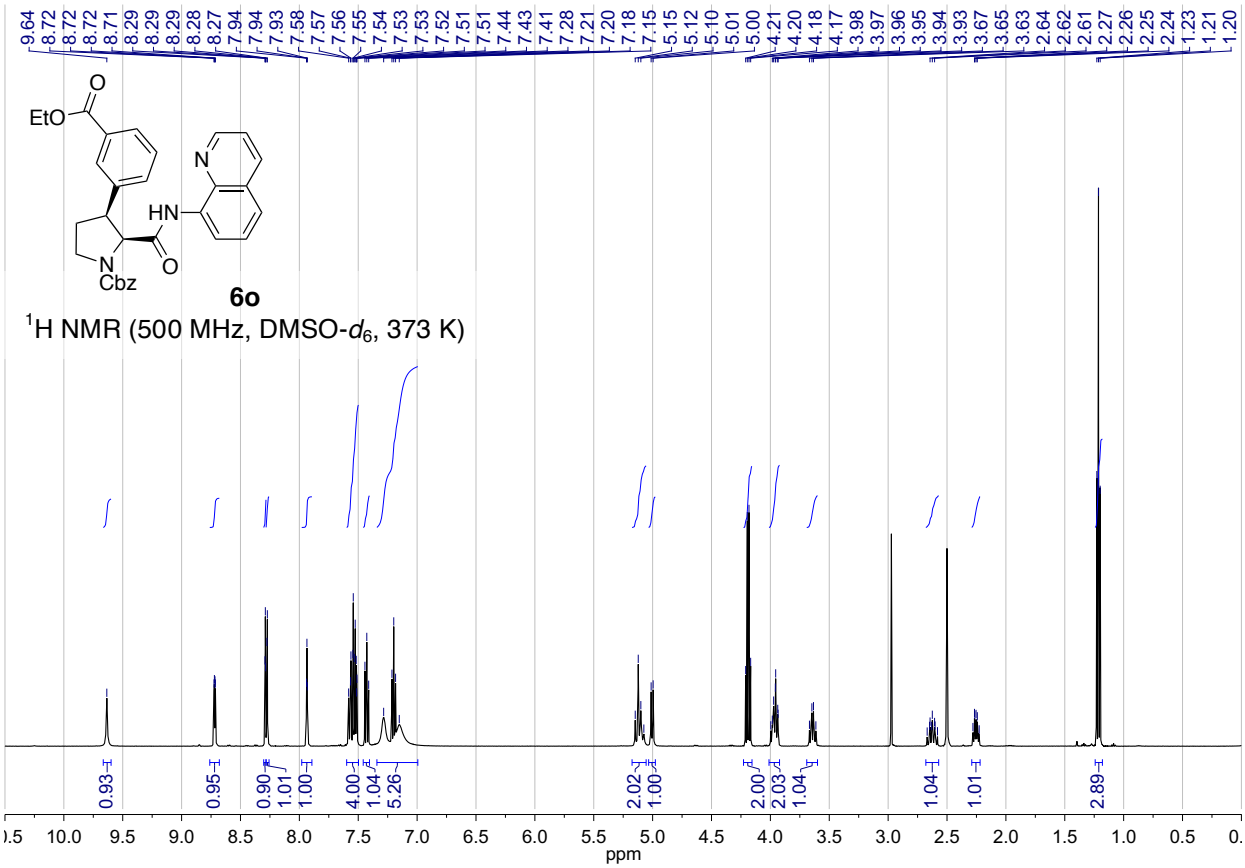
6n

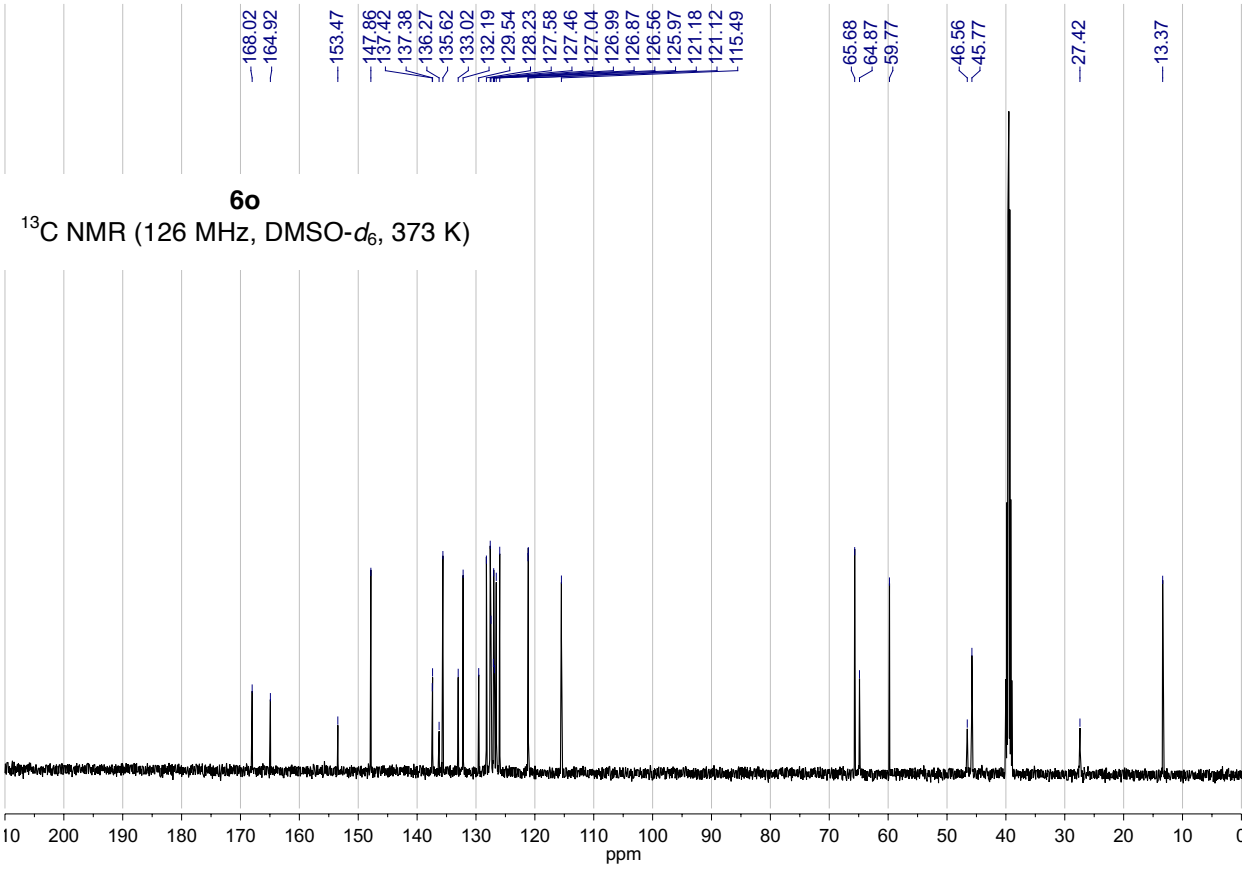
^{1}H NMR (400 MHz, DMSO-d_6, 373 K)

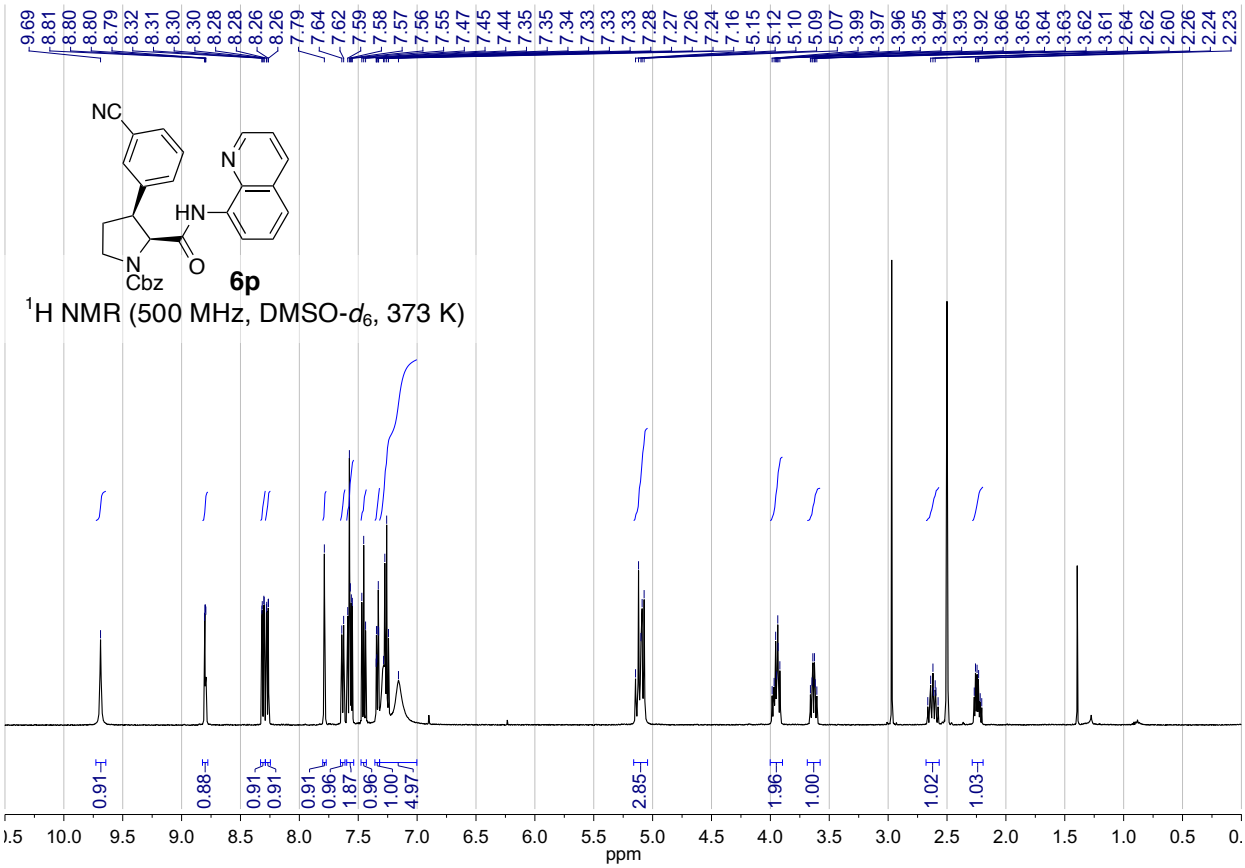


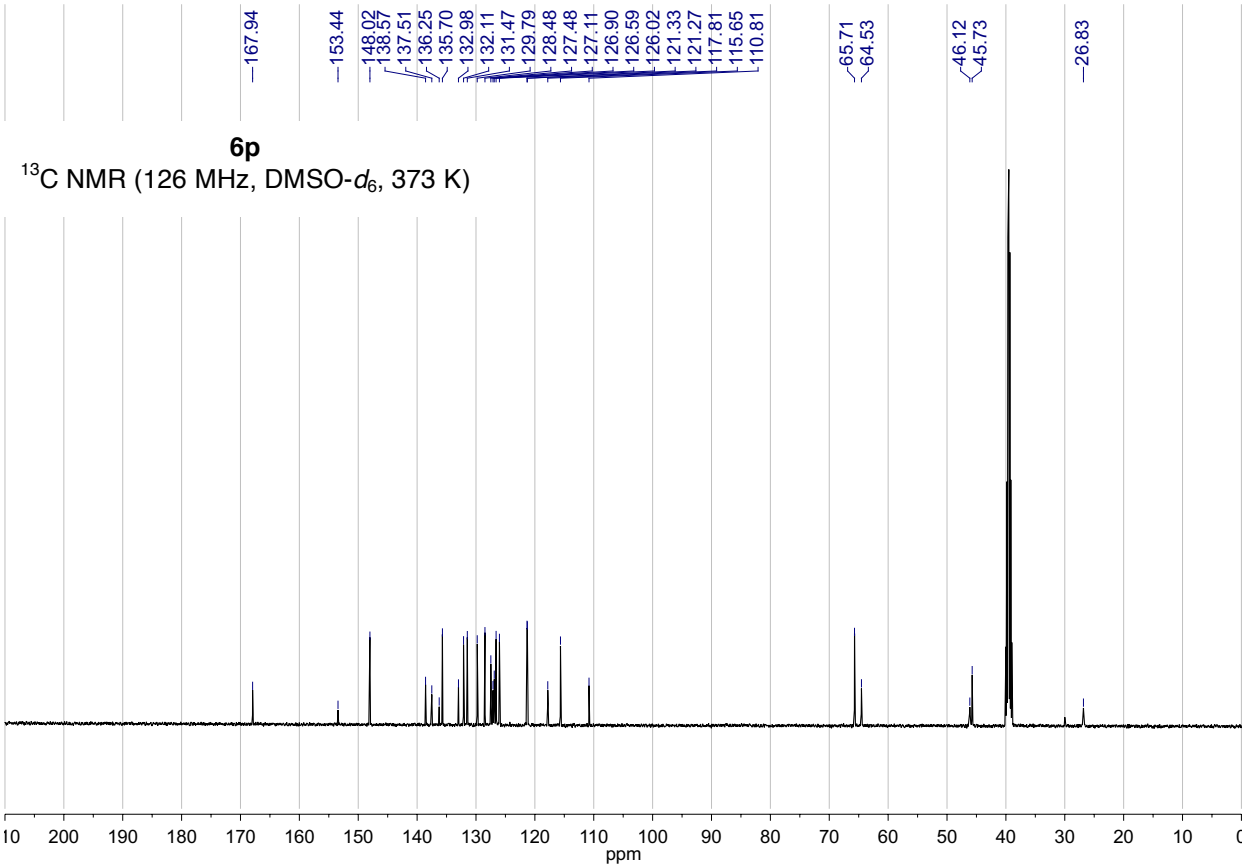
6n

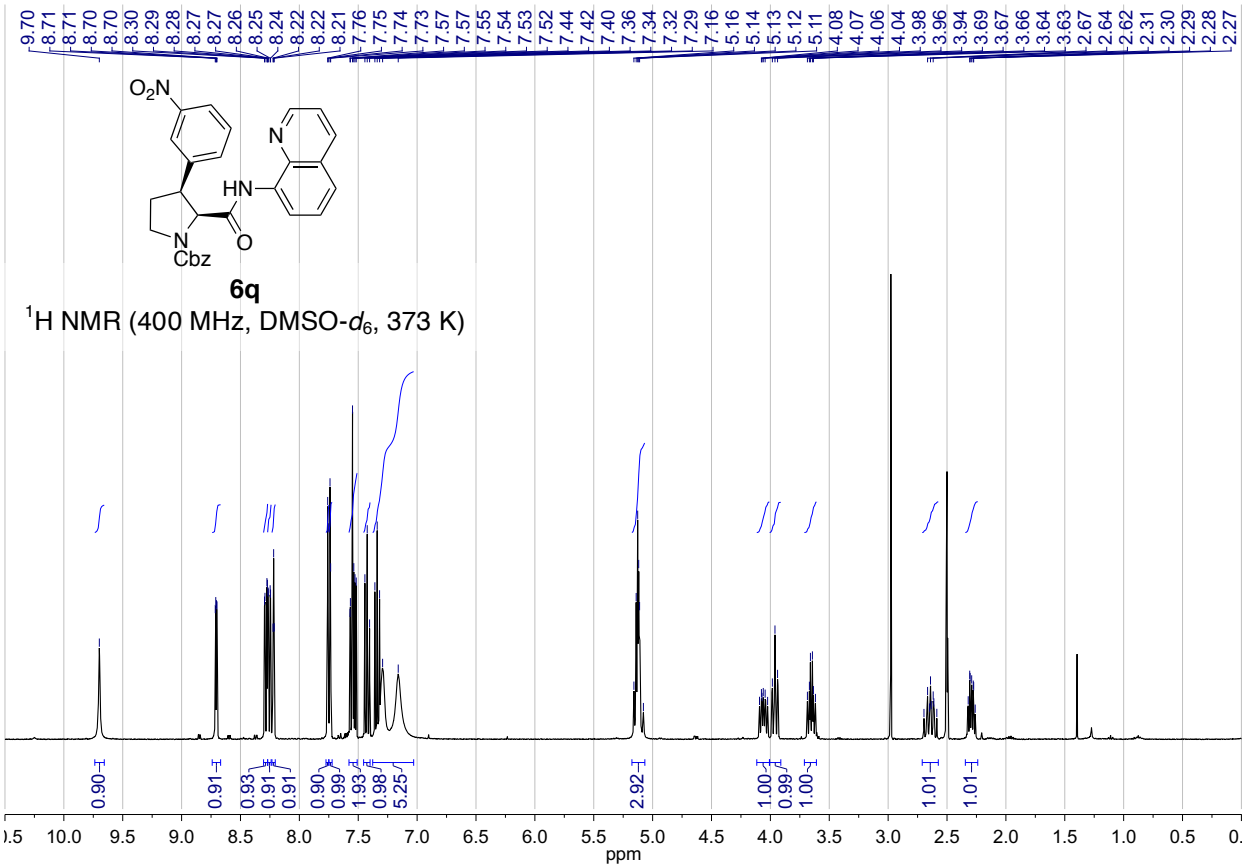
^{13}C NMR (101 MHz, DMSO-d_6, 373 K)

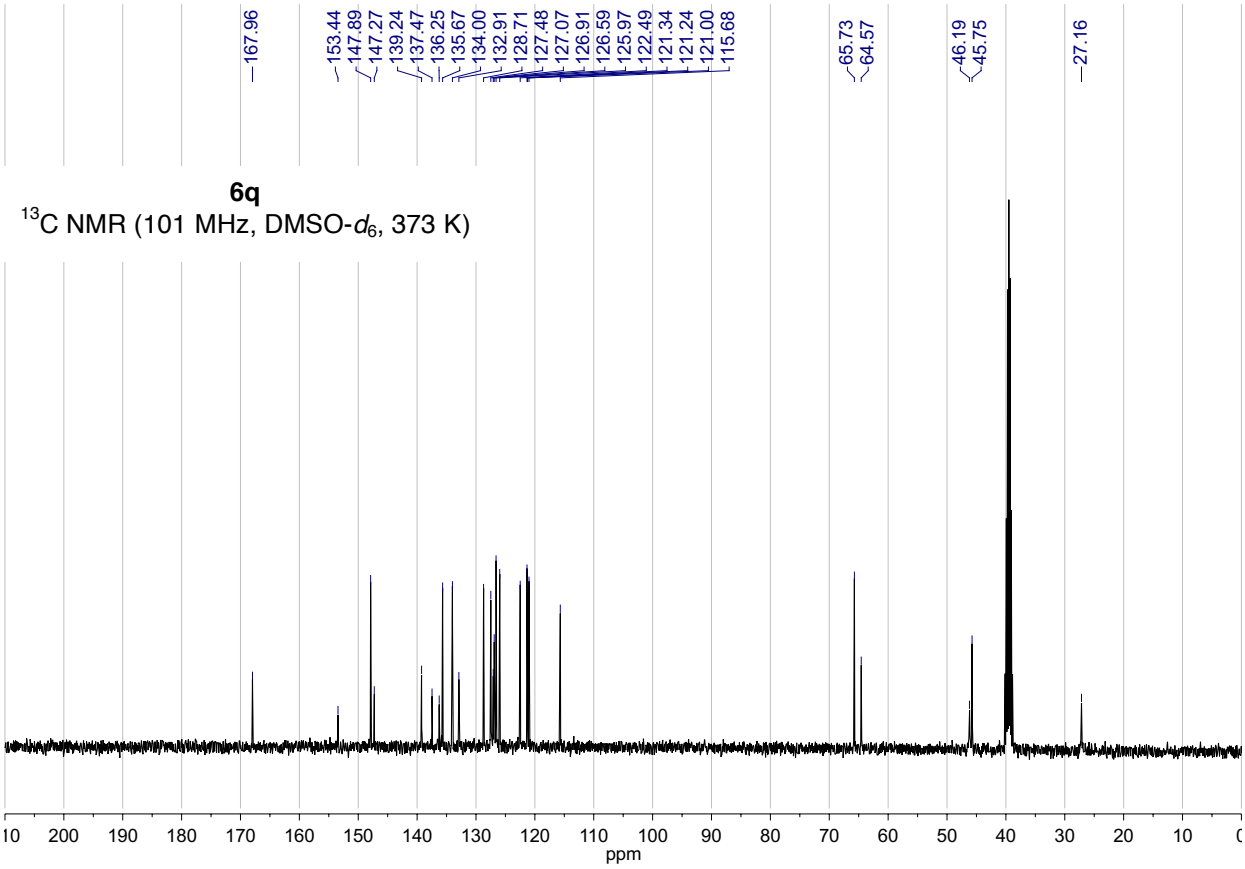

EtO
O
HN
N
O
N
Cbz
6o
^{1}H NMR (500 MHz, DMSO-d_6, 373 K)
ppm

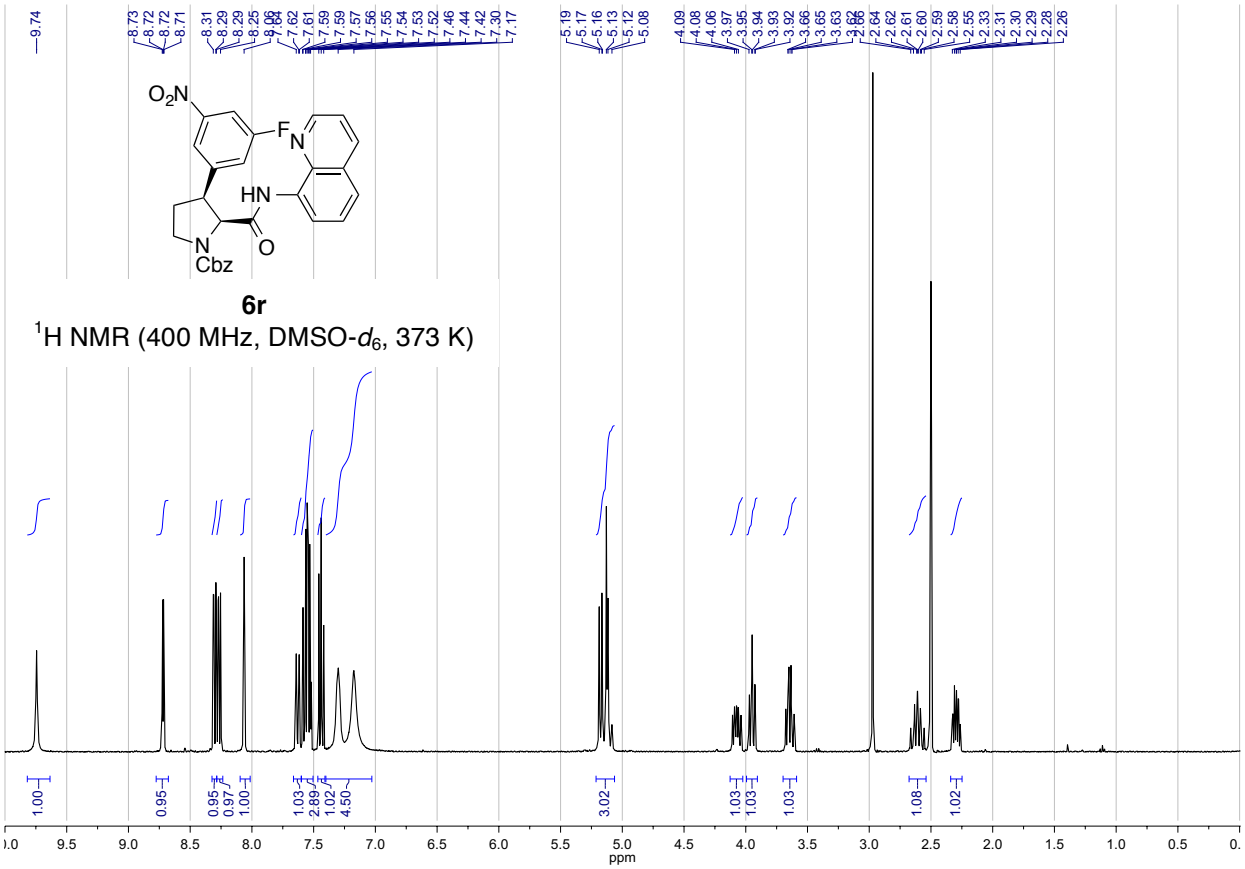

6o
^{13}C NMR (126 MHz, DMSO-d_6, 373 K)
ppm

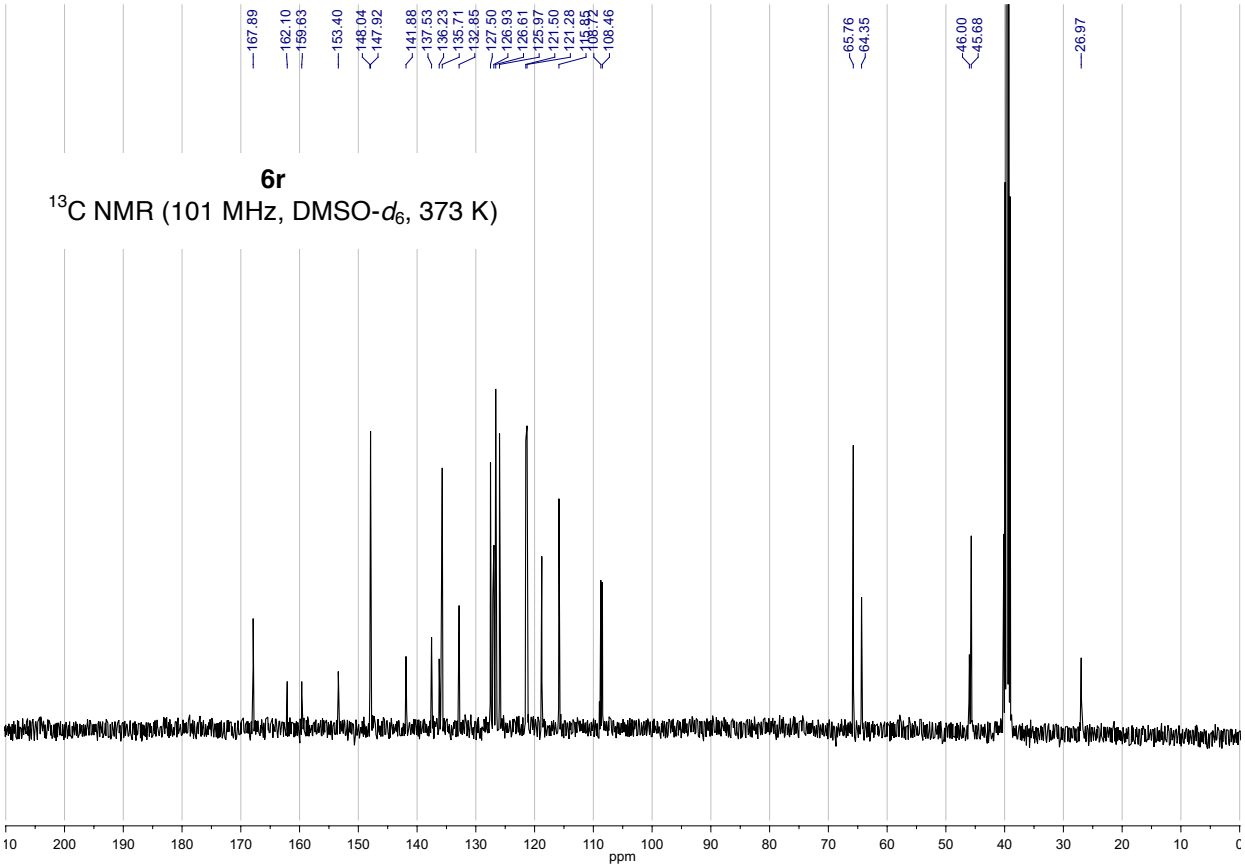

NC
N
HN
O
N
Cbz
6p
^{1}H NMR (500 MHz, DMSO-d_6, 373 K)
ppm

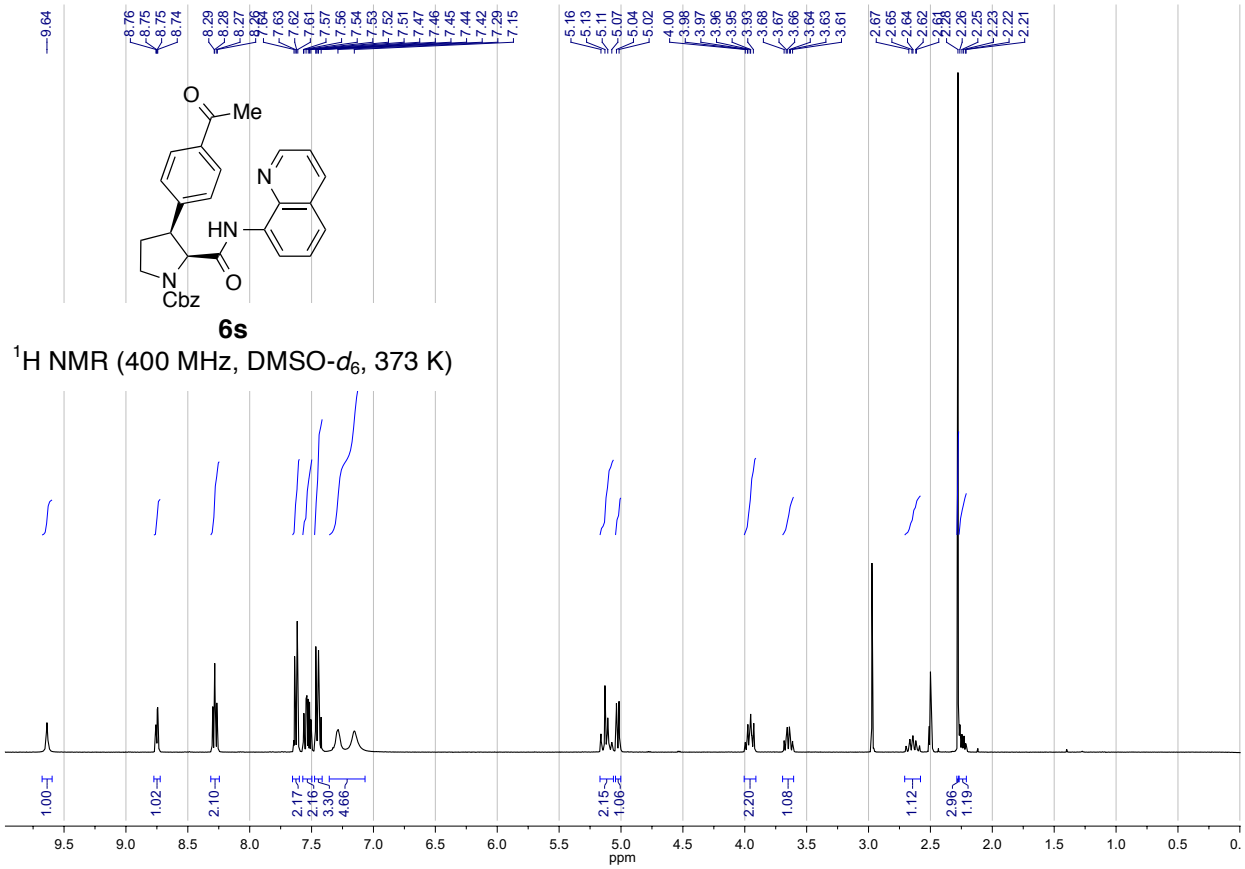

6p
^{13}C NMR (126 MHz, DMSO-d_6, 373 K)
ppm


O2N
N
HN
O
N
Cbz
6q
1H NMR (400 MHz, DMSO-d6, 373 K)
ppm


6q
13C NMR (101 MHz, DMSO-d6, 373 K)
ppm

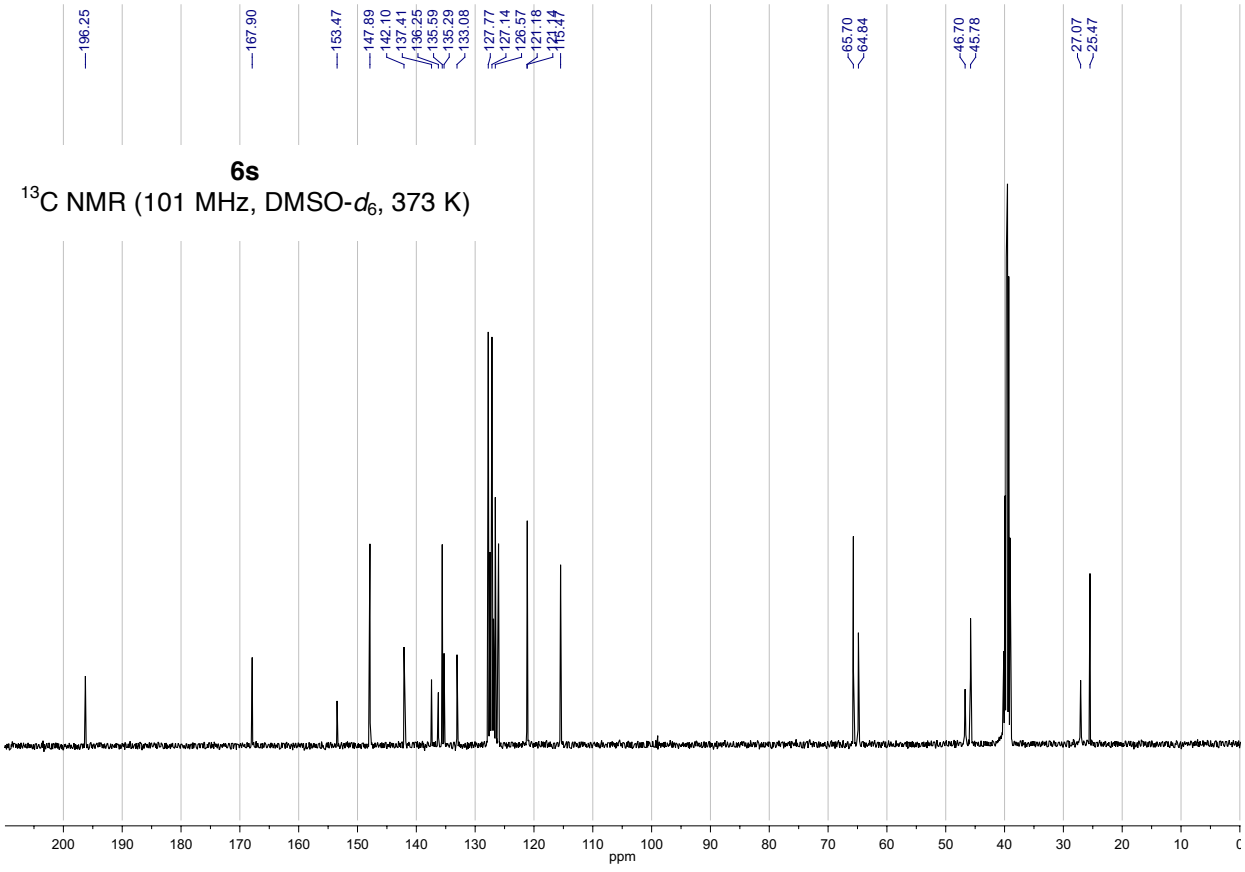

O2N
F
N
HN
O
N
Cbz
6r
1H NMR (400 MHz, DMSO-d6, 373 K)
ppm


6r
13C NMR (101 MHz, DMSO-d6, 373 K)
ppm



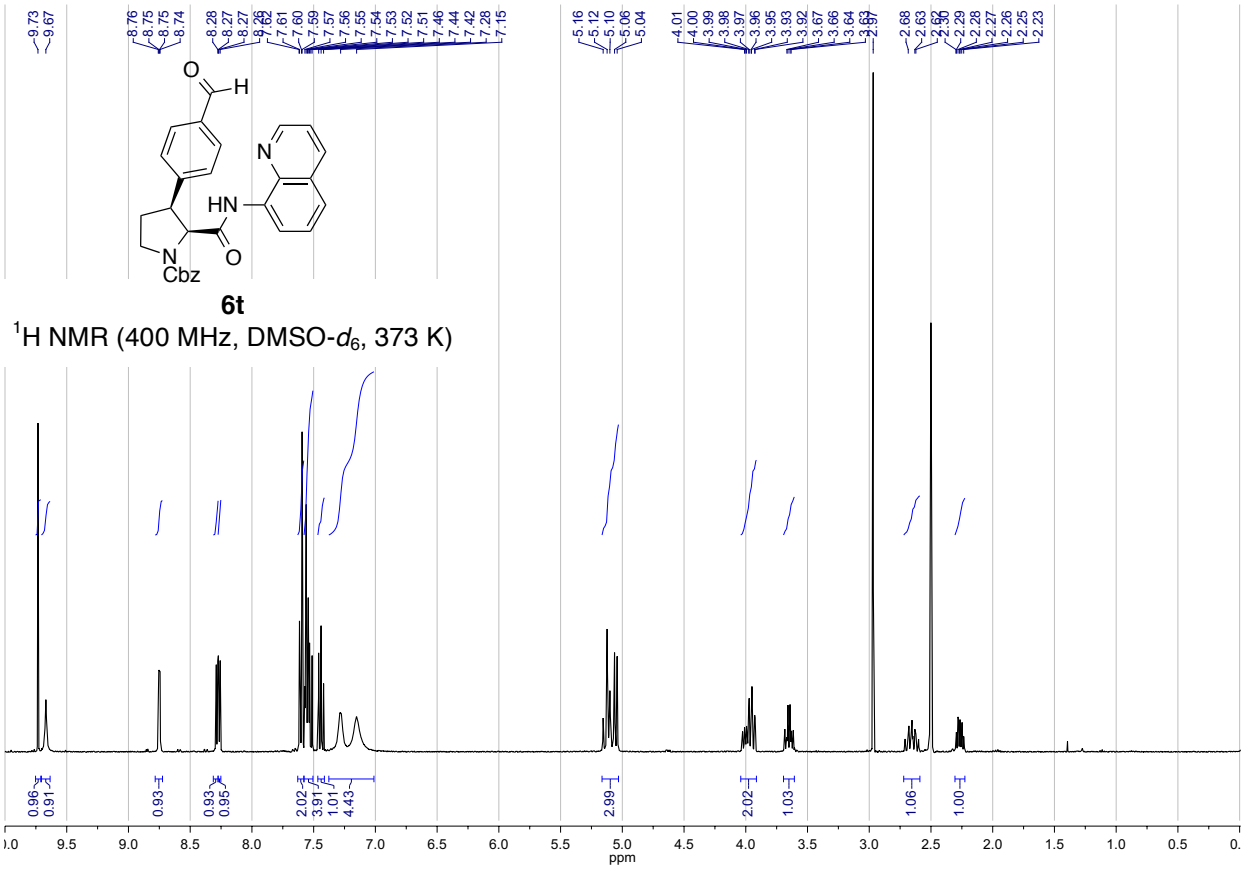
6s

^{1}H NMR (400 MHz, DMSO-d_6, 373 K)



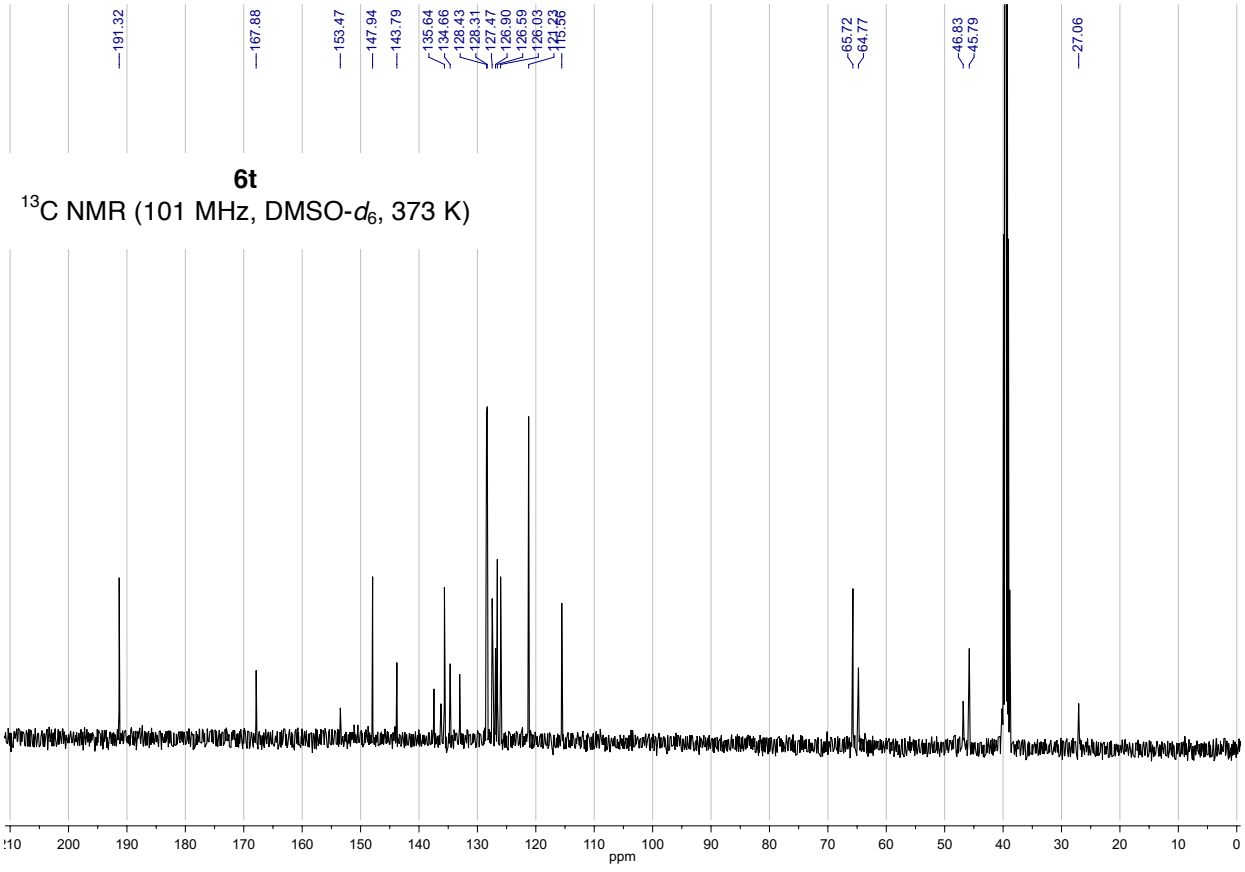
6s

^{13}C NMR (101 MHz, DMSO-d_6, 373 K)



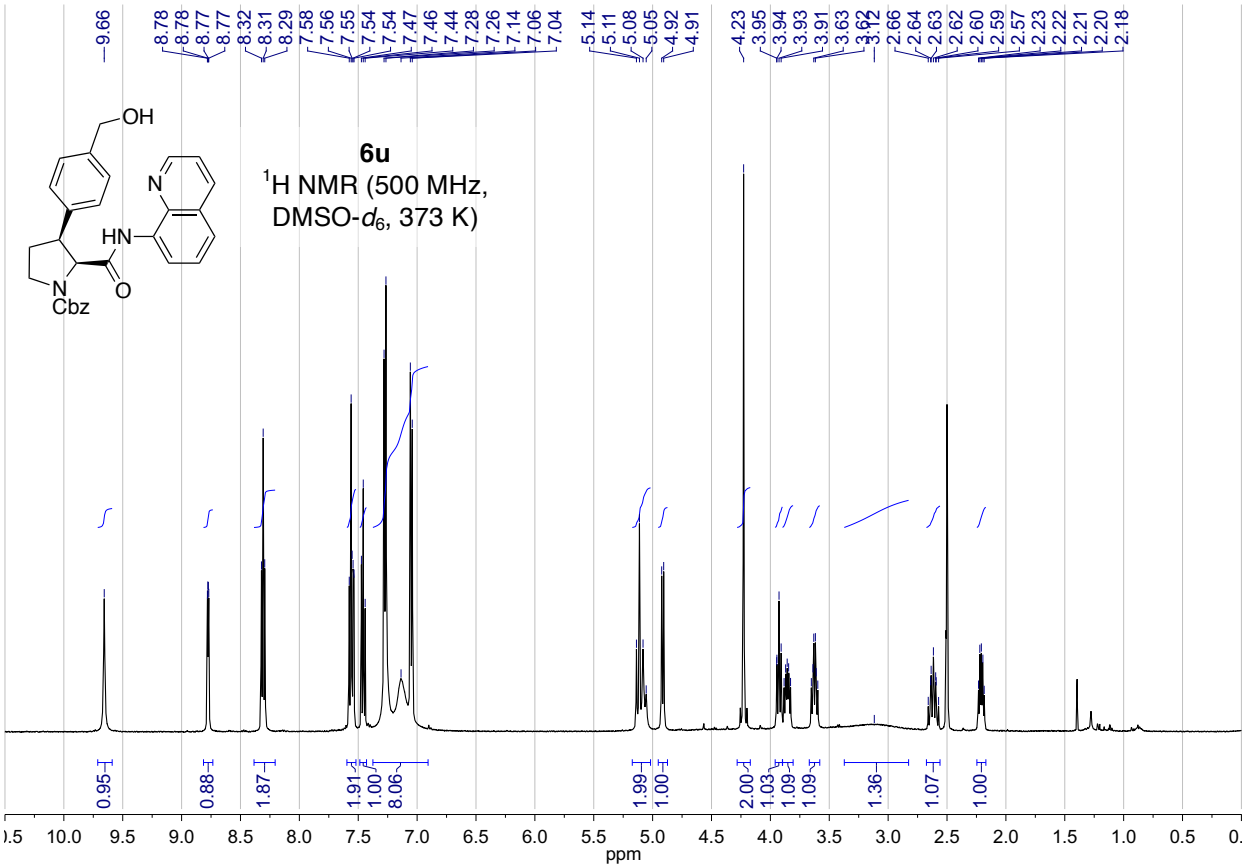
6t

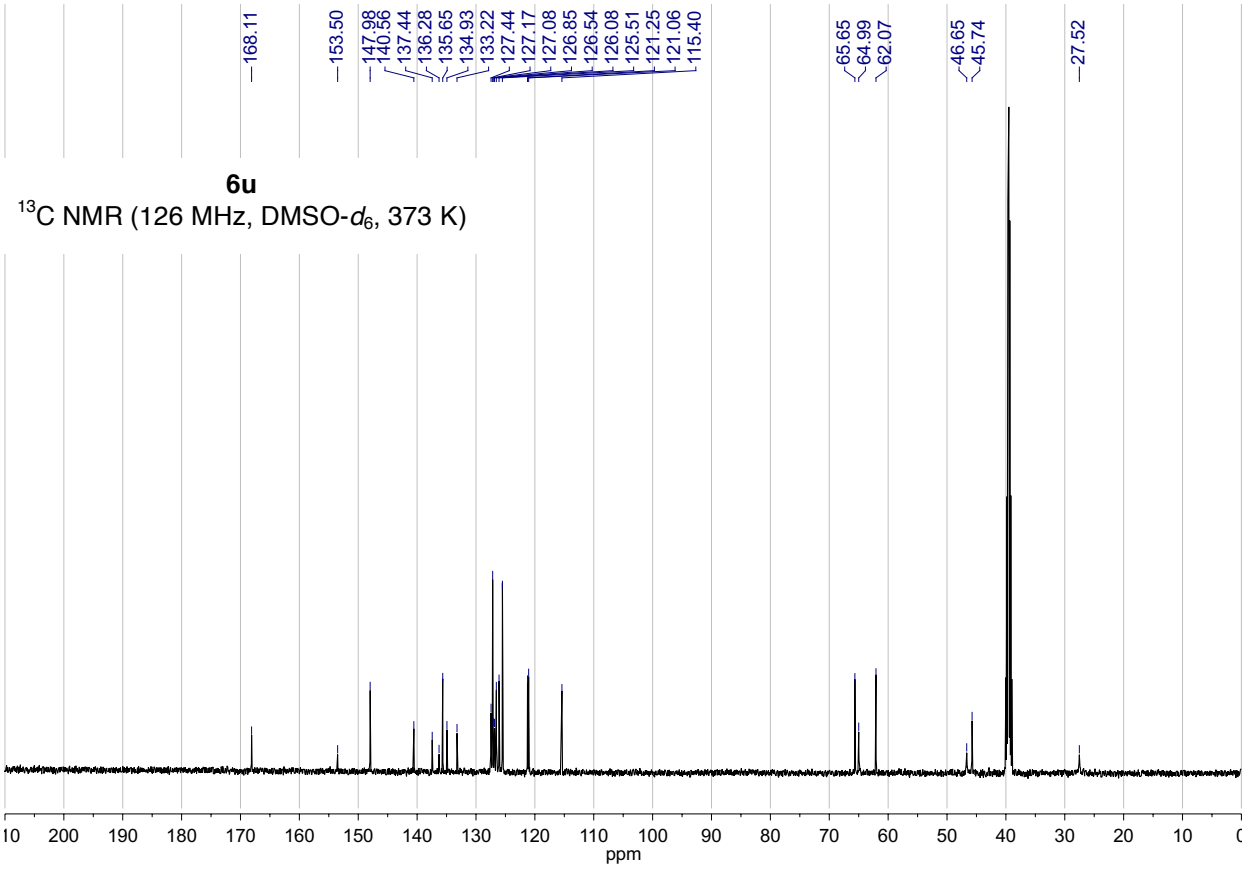
^{1}H NMR (400 MHz, DMSO-d_6, 373 K)

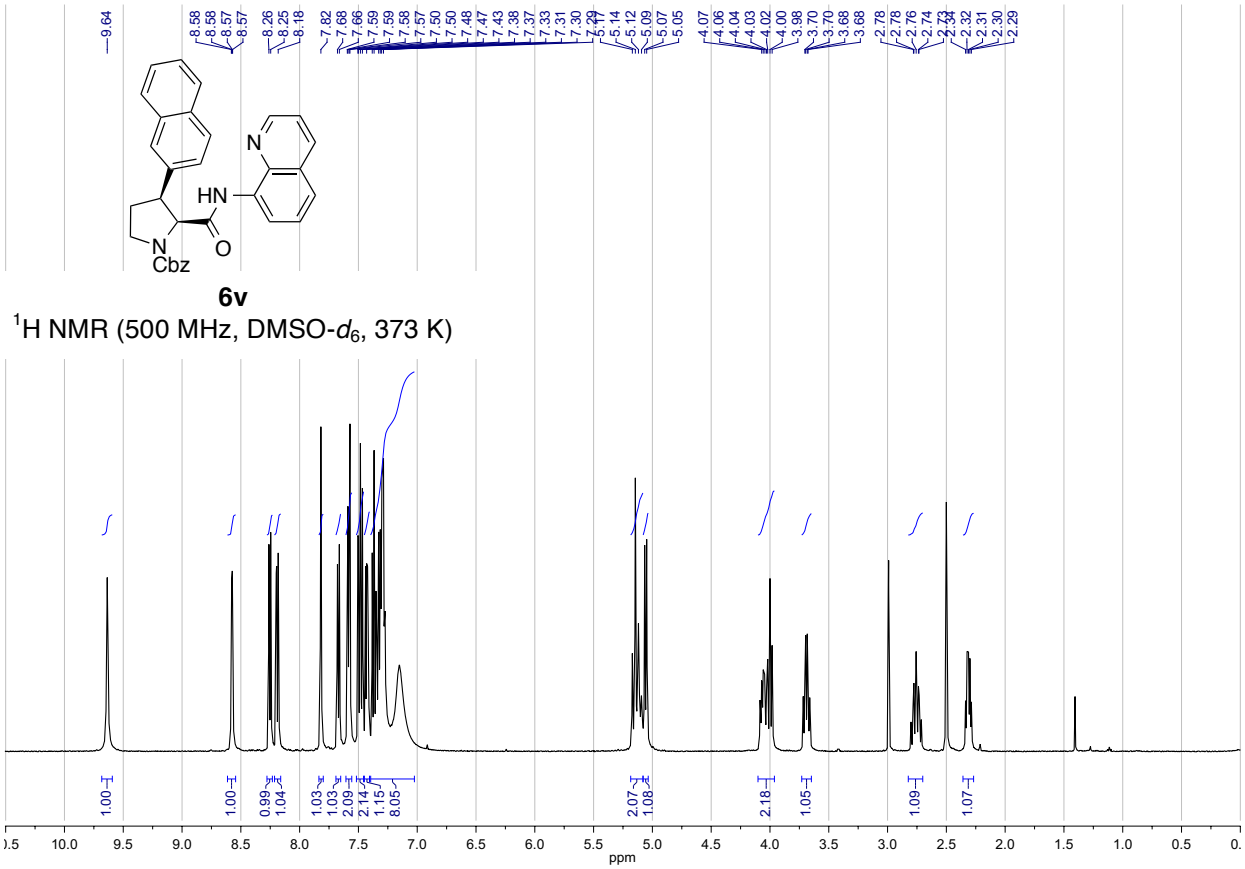


6t

^{13}C NMR (101 MHz, DMSO-d_6, 373 K)

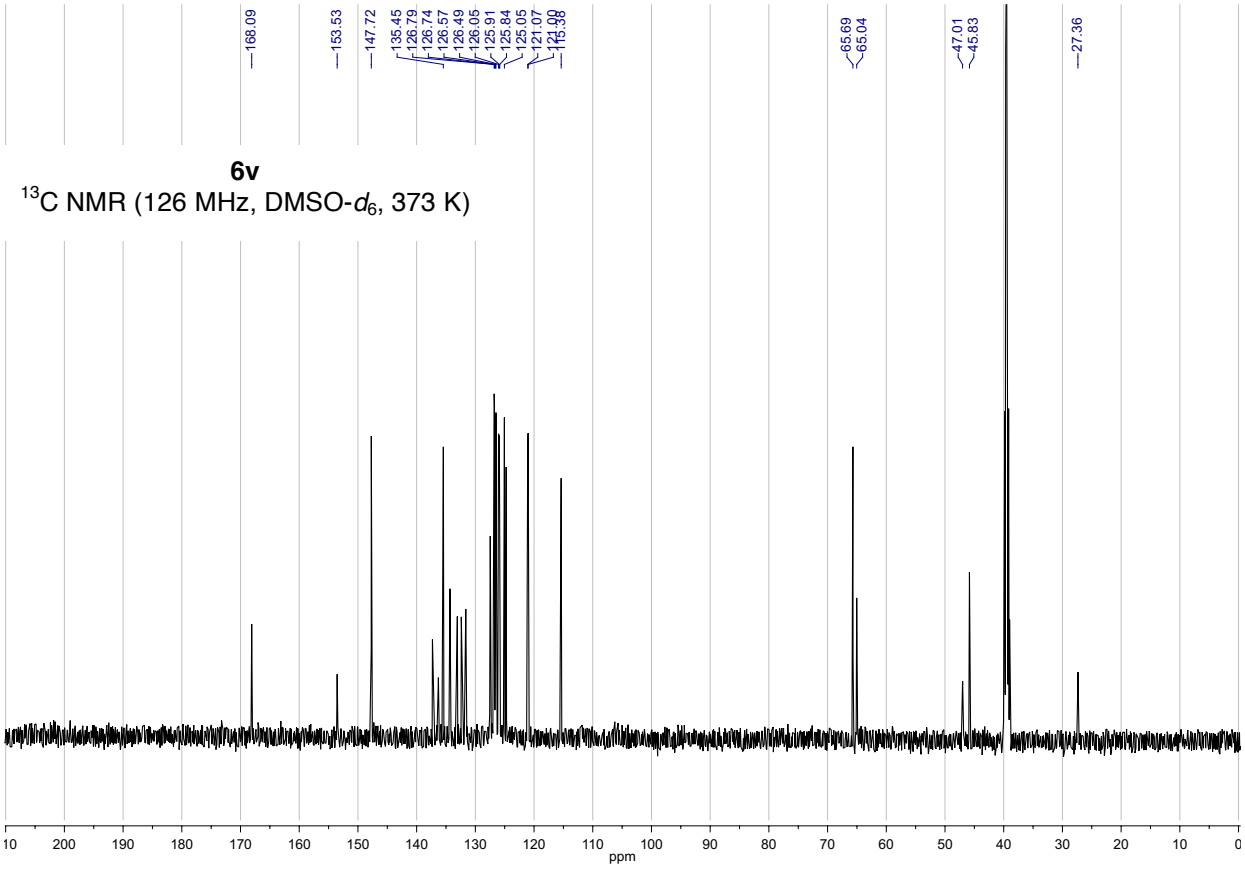

OH
N
HN
O
N
Cbz
6u
1H NMR (500 MHz,
DMSO-d6, 373 K)
ppm


6u
13C NMR (126 MHz, DMSO-d6, 373 K)
ppm



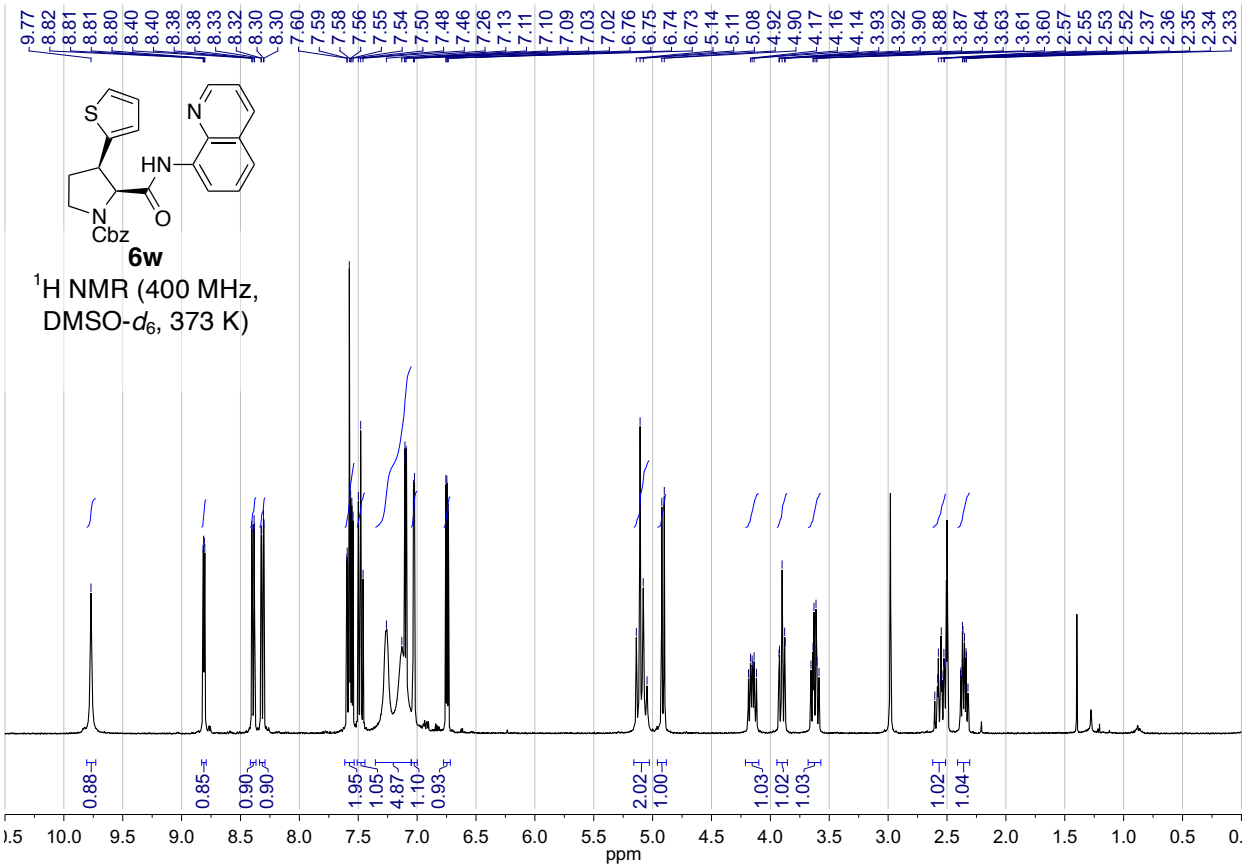
6v

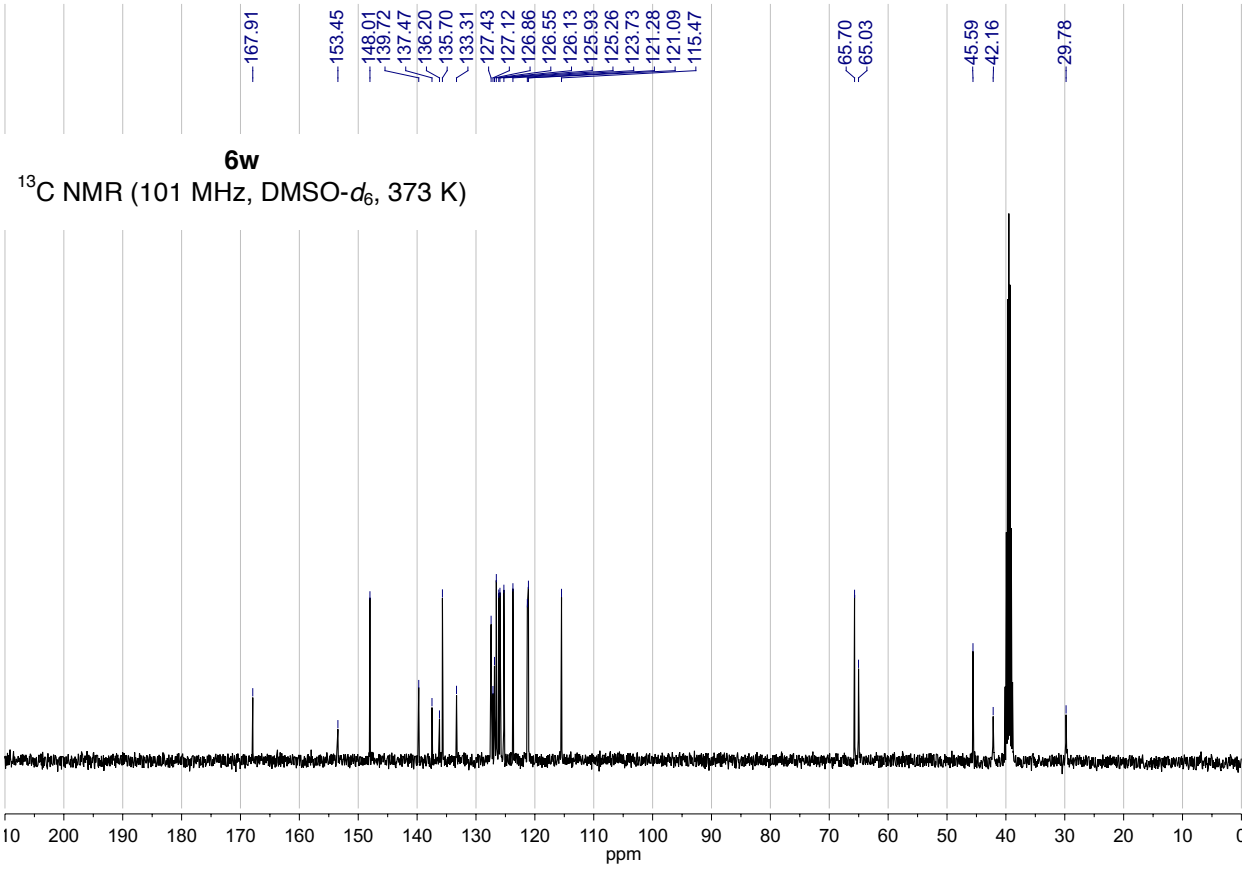
^{1}H NMR (500 MHz, DMSO-d_6, 373 K)

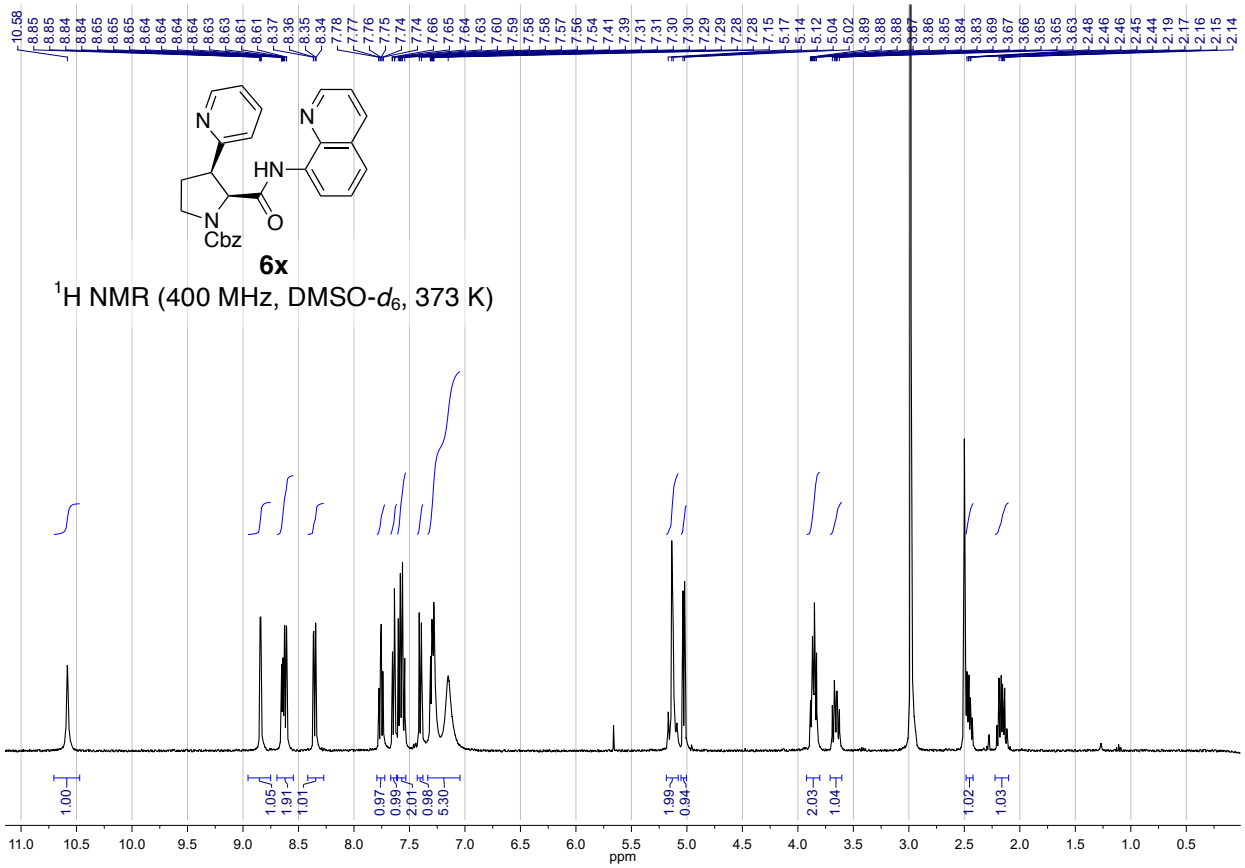


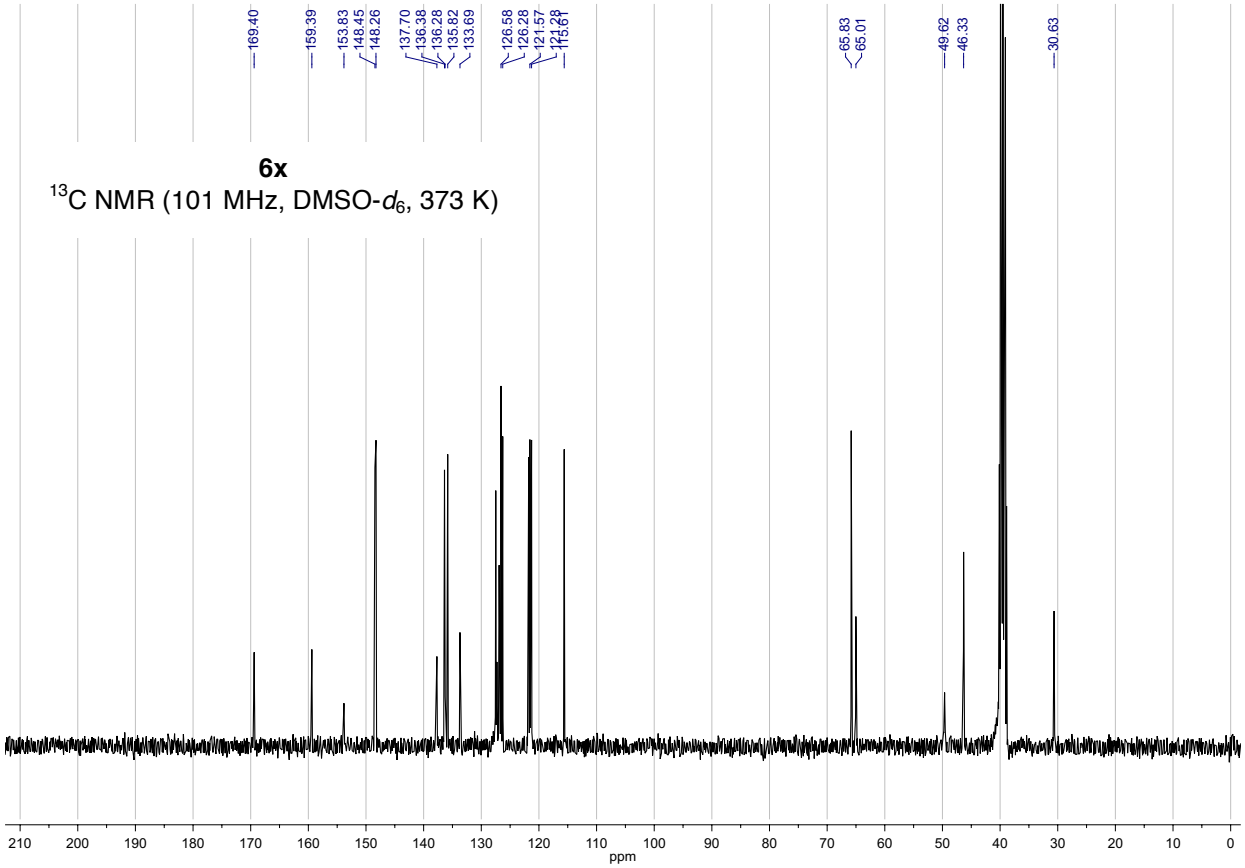
6v

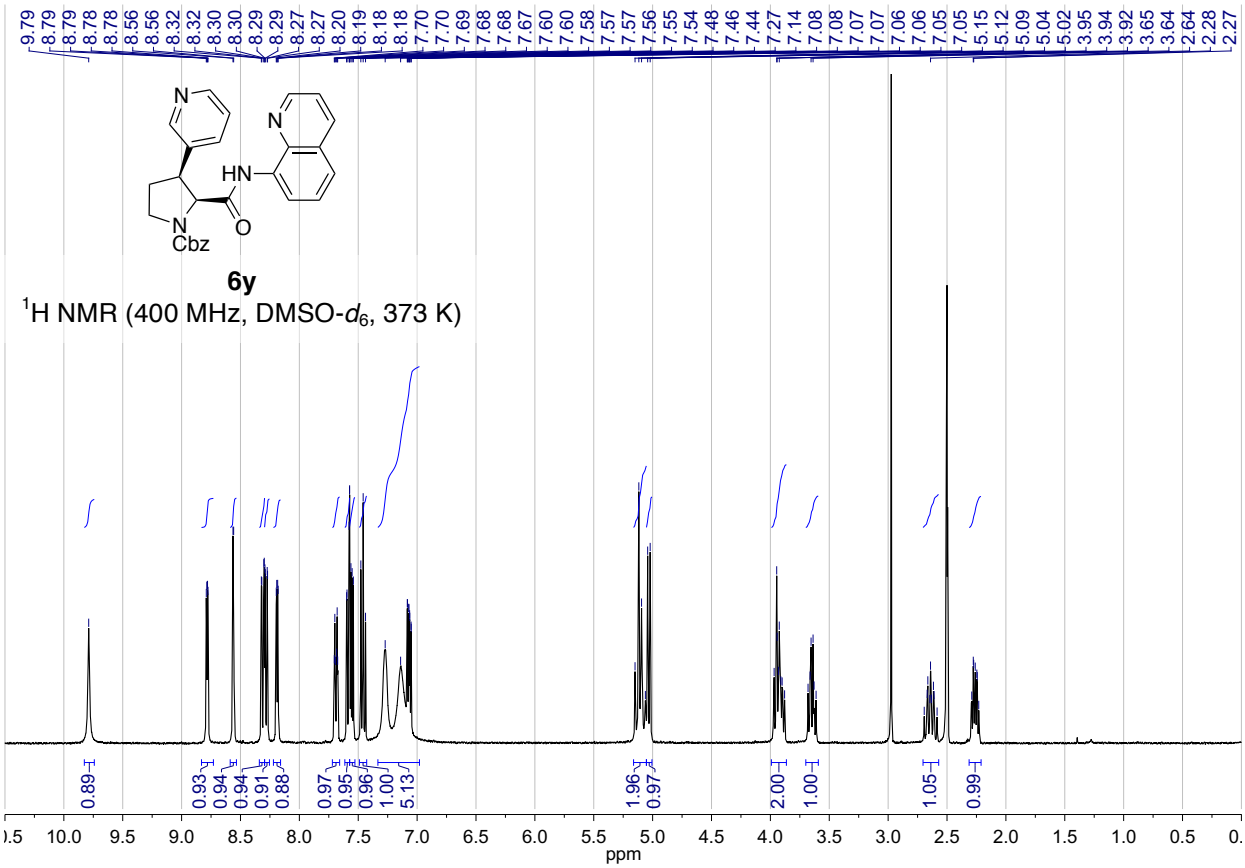
^{13}C NMR (126 MHz, DMSO-d_6, 373 K)


S
N
HN
O
N
Cbz
6w
1H NMR (400 MHz,
DMSO-d6, 373 K)
ppm


6w
13C NMR (101 MHz, DMSO-d6, 373 K)
ppm

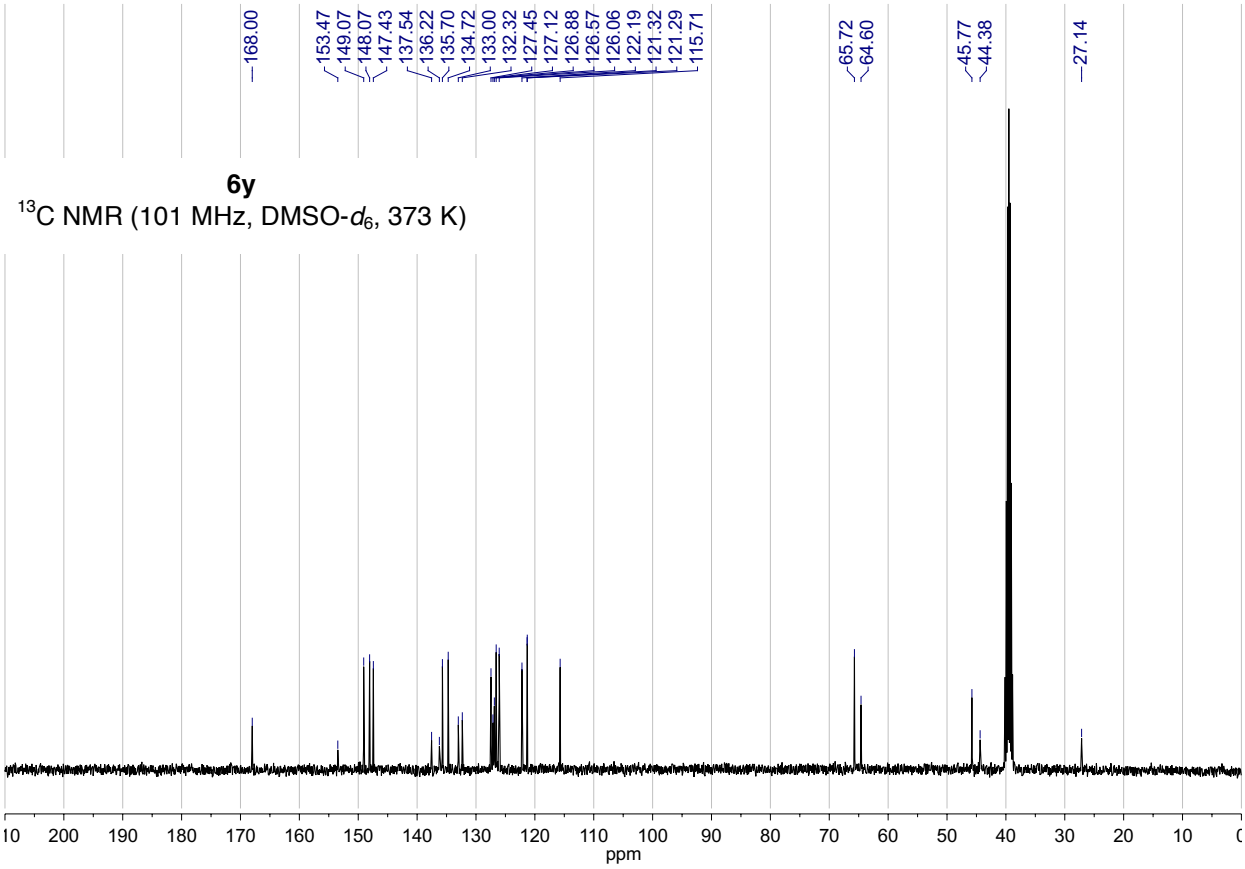

N
N
HN
O
N
Cbz
6x
^{1}H NMR (400 MHz, DMSO-d_6, 373 K)
ppm


6x
^{13}C NMR (101 MHz, DMSO-d_6, 373 K)
ppm



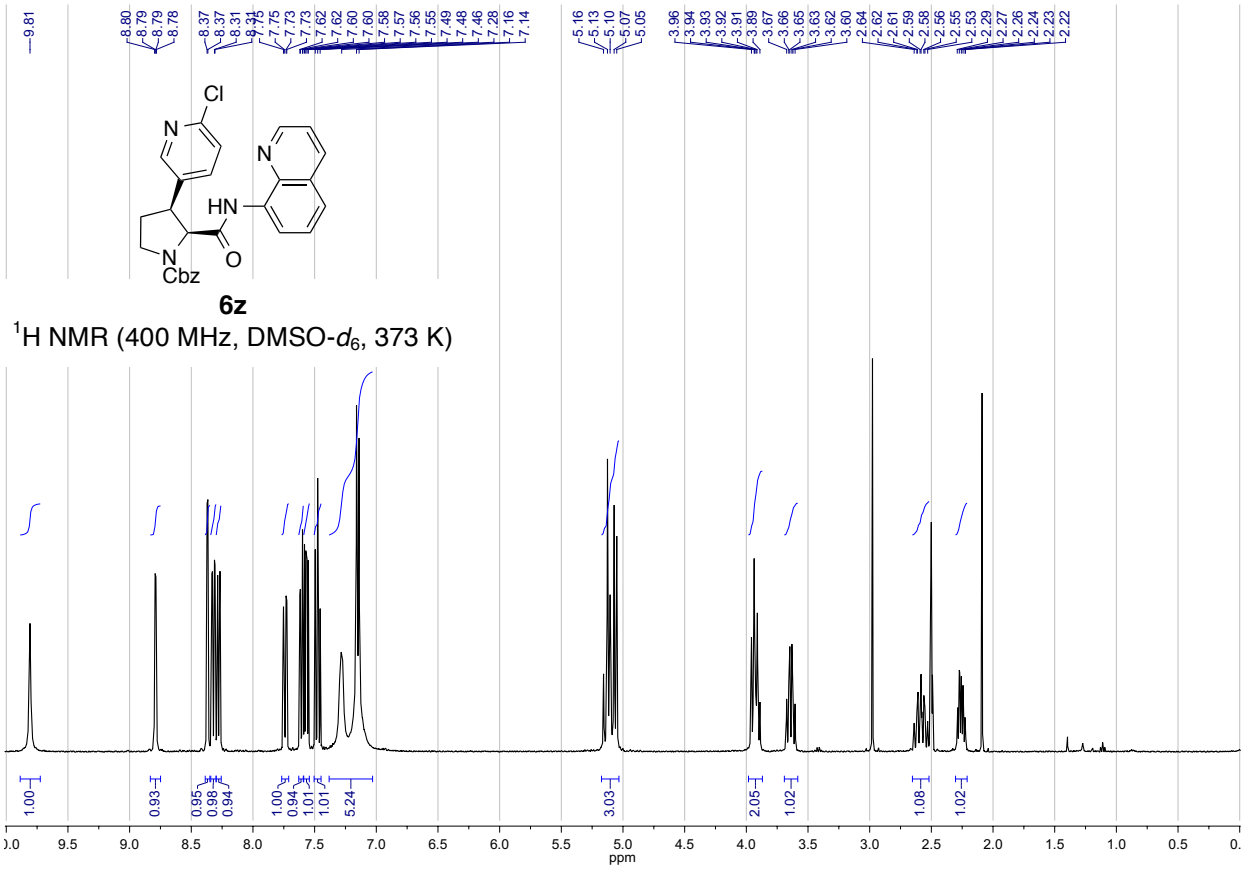
6y

^{1}H NMR (400 MHz, DMSO-d_6, 373 K)



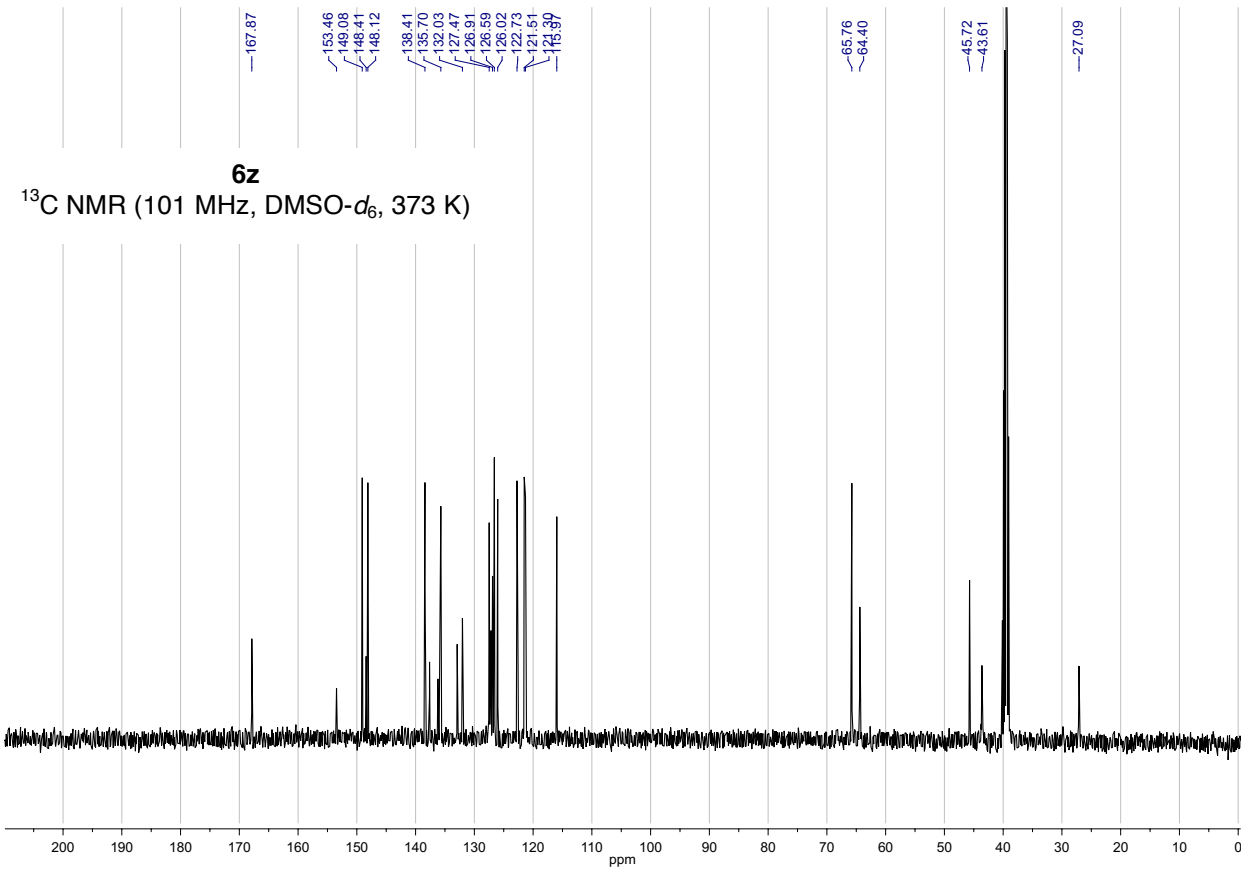
6y

^{13}C NMR (101 MHz, DMSO-d_6, 373 K)



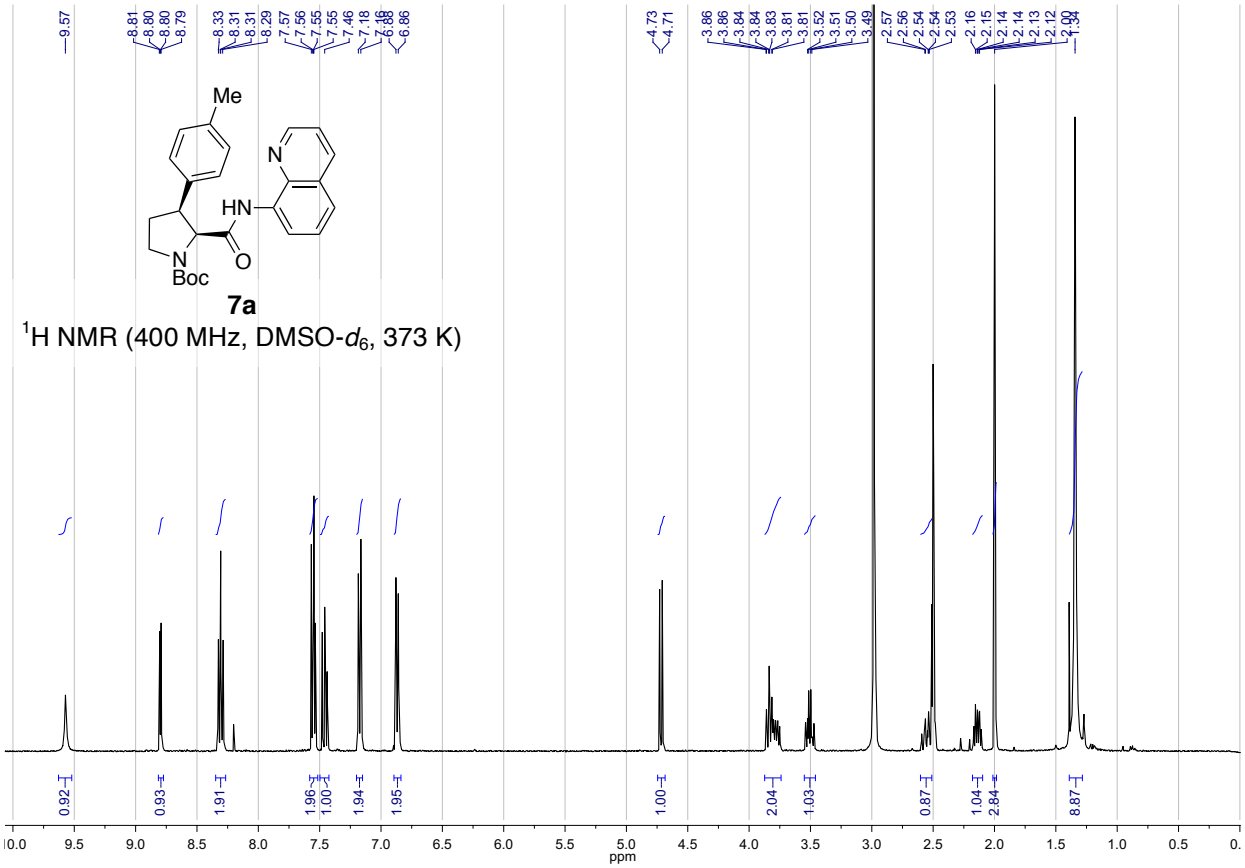
6z

^{1}H NMR (400 MHz, DMSO-d_6, 373 K)



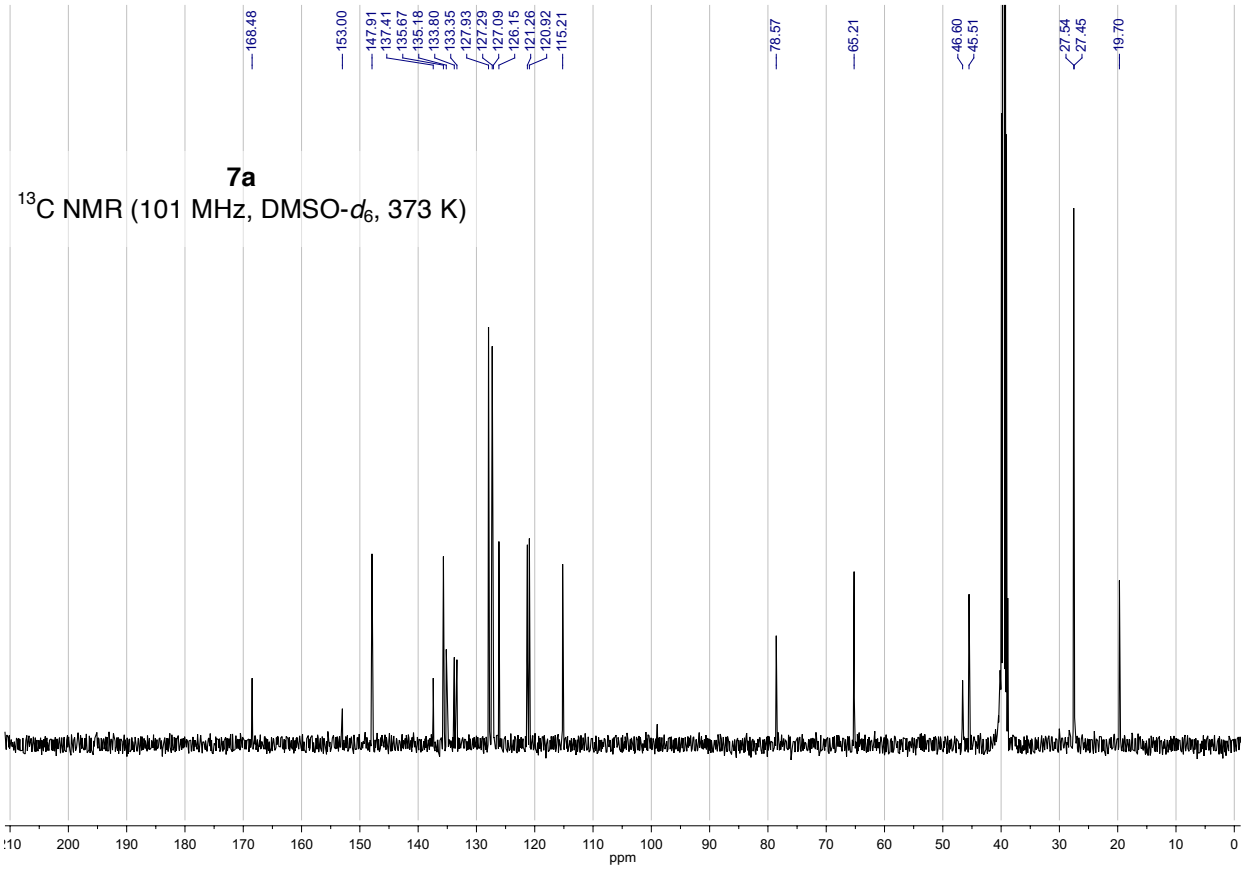
6z

^{13}C NMR (101 MHz, DMSO-d_6, 373 K)



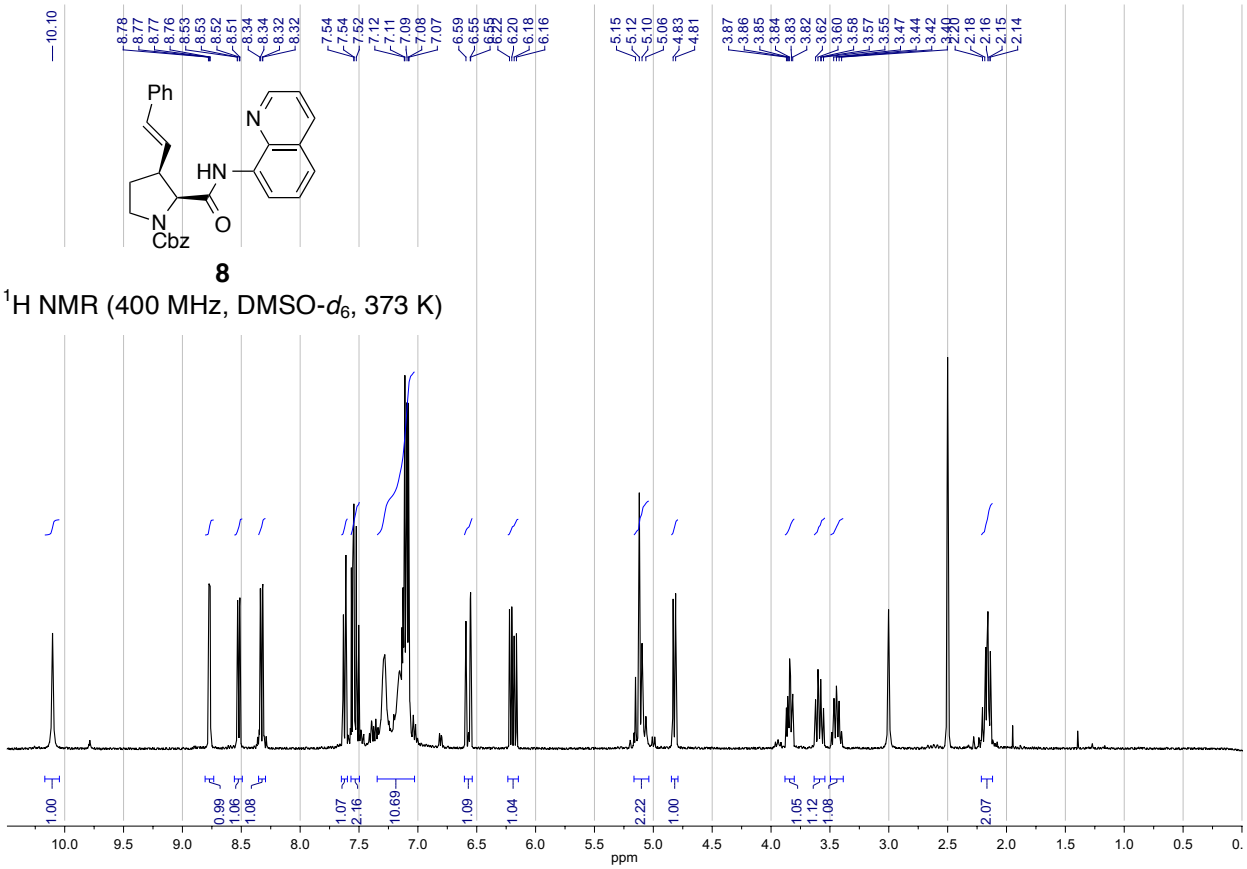
7a

^{1}H NMR (400 MHz, DMSO-d_6, 373 K)



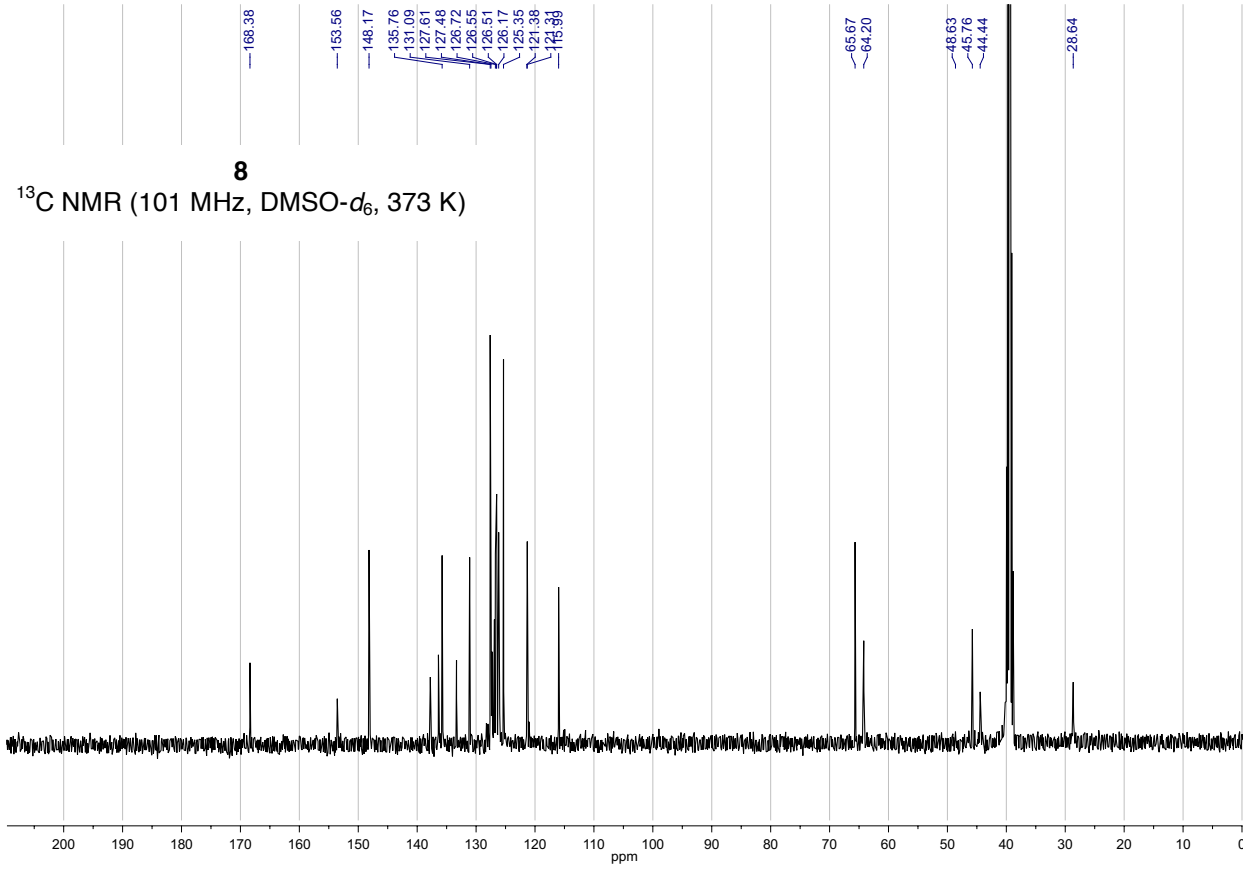
7a

^{13}C NMR (101 MHz, DMSO-d_6, 373 K)



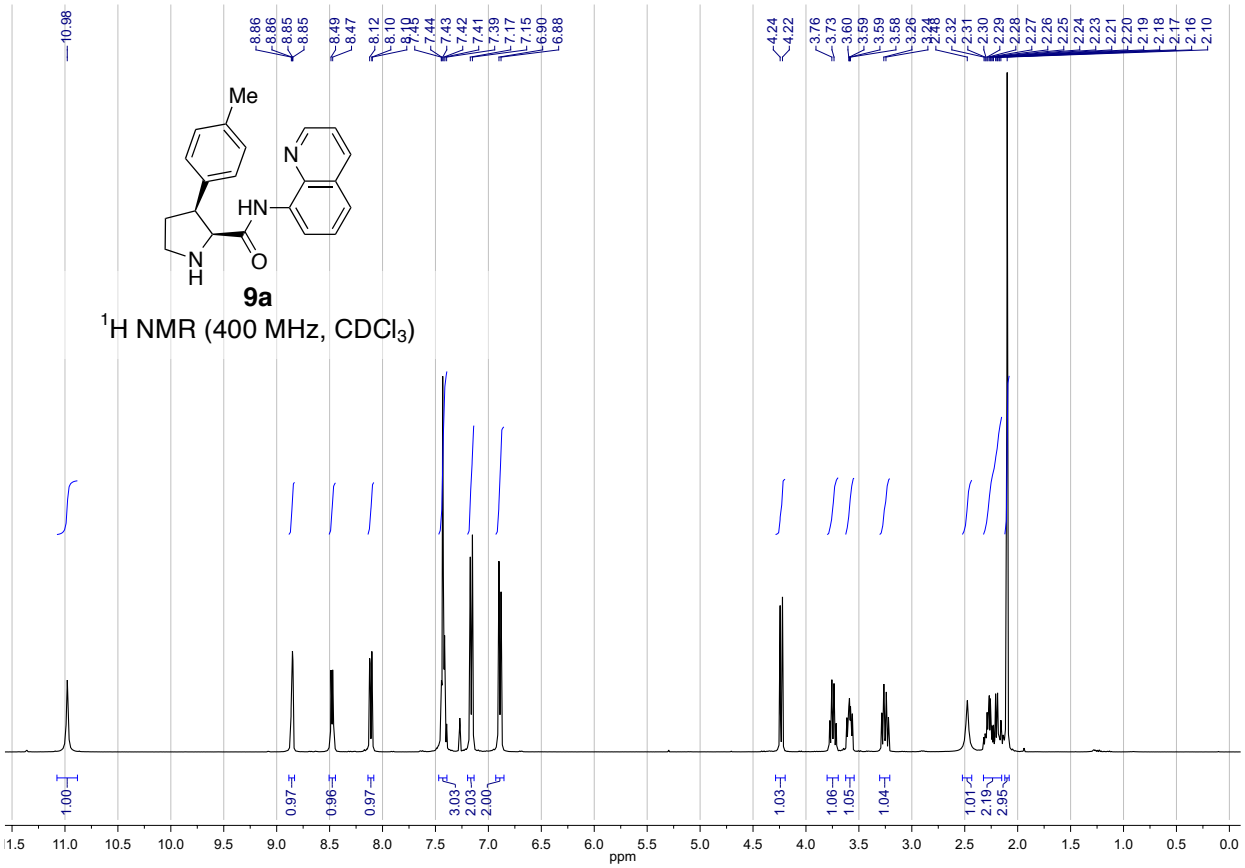
8

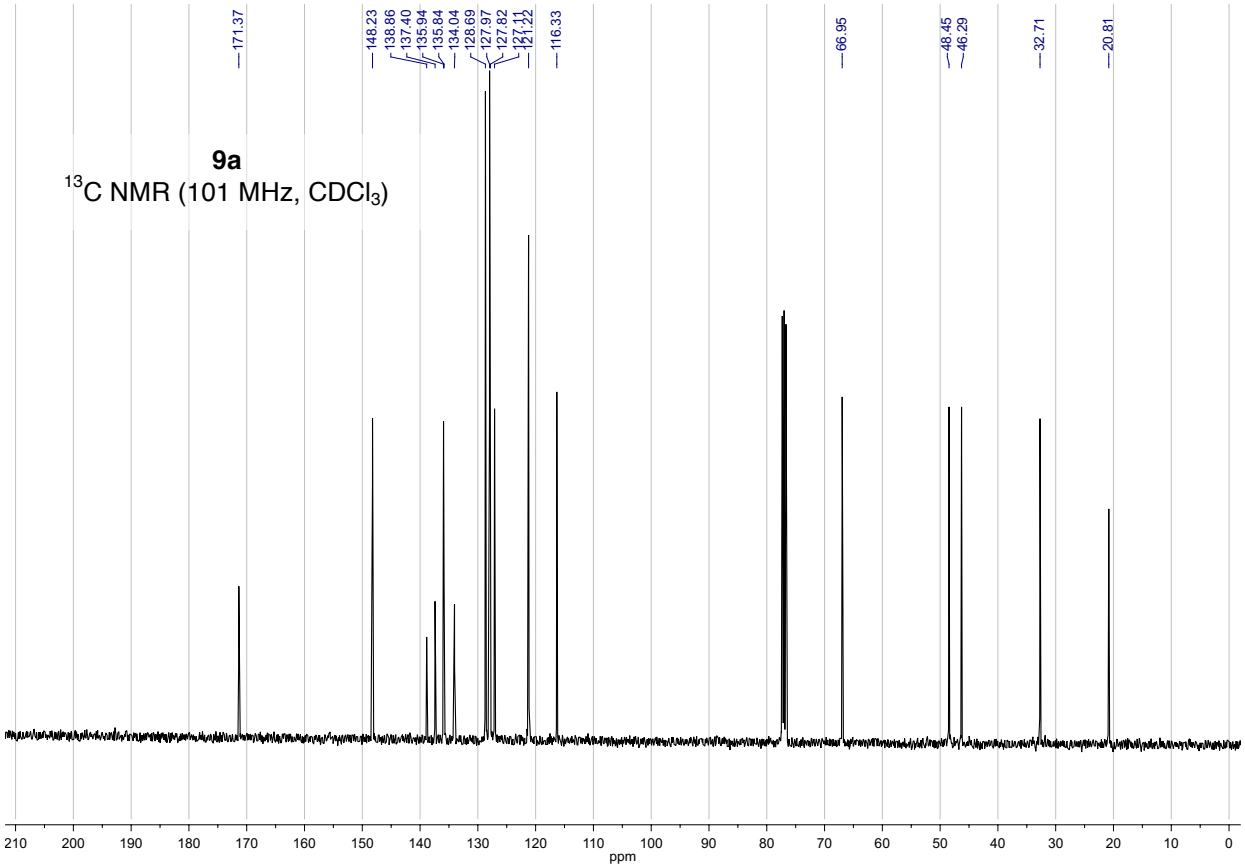
^{1}H NMR (400 MHz, DMSO-d_6, 373 K)

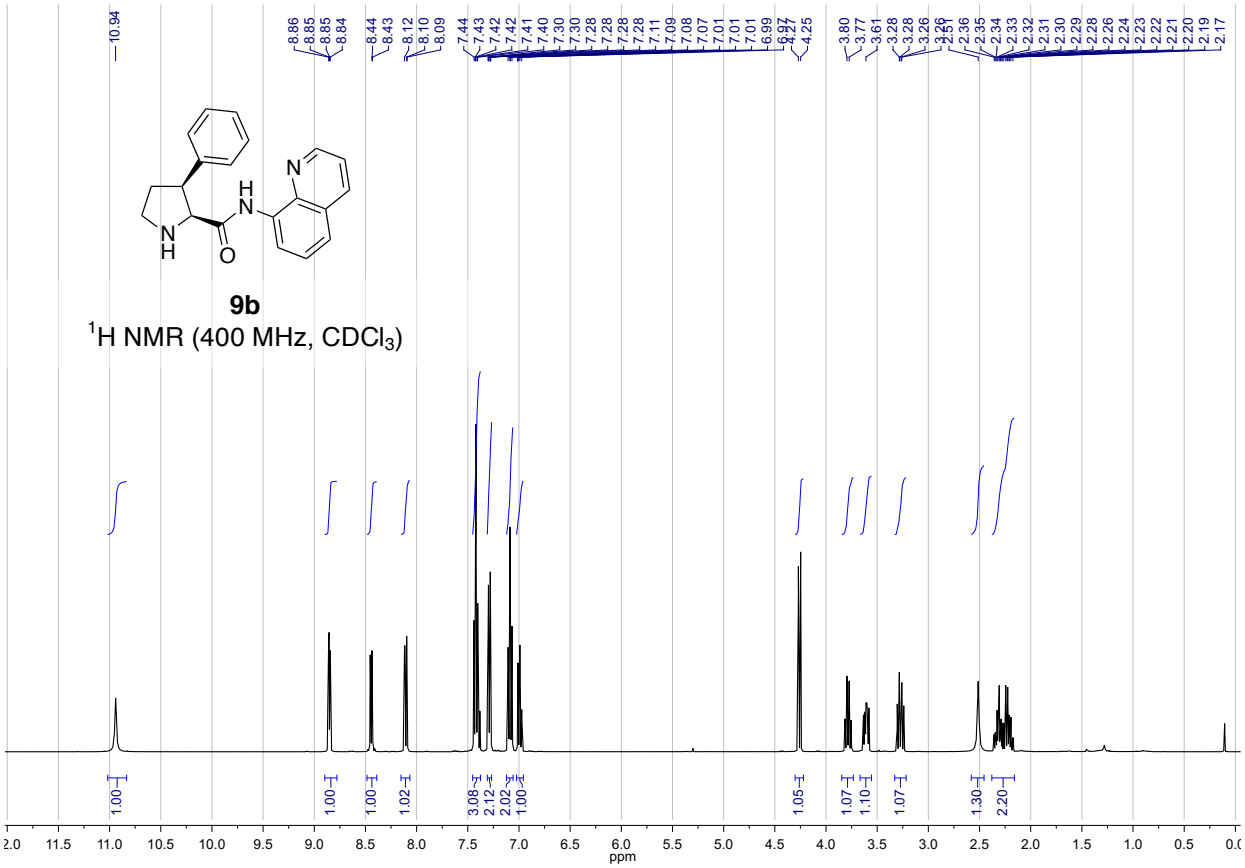


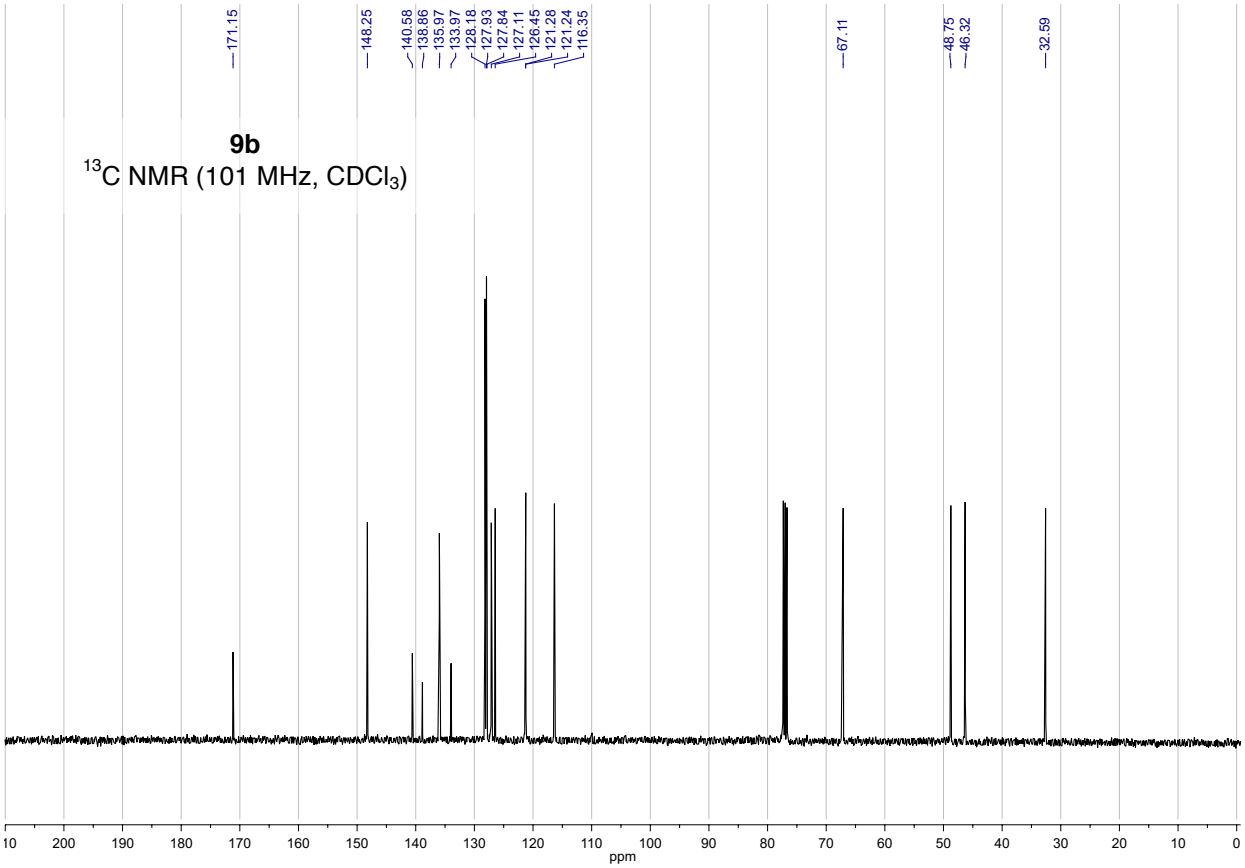
8

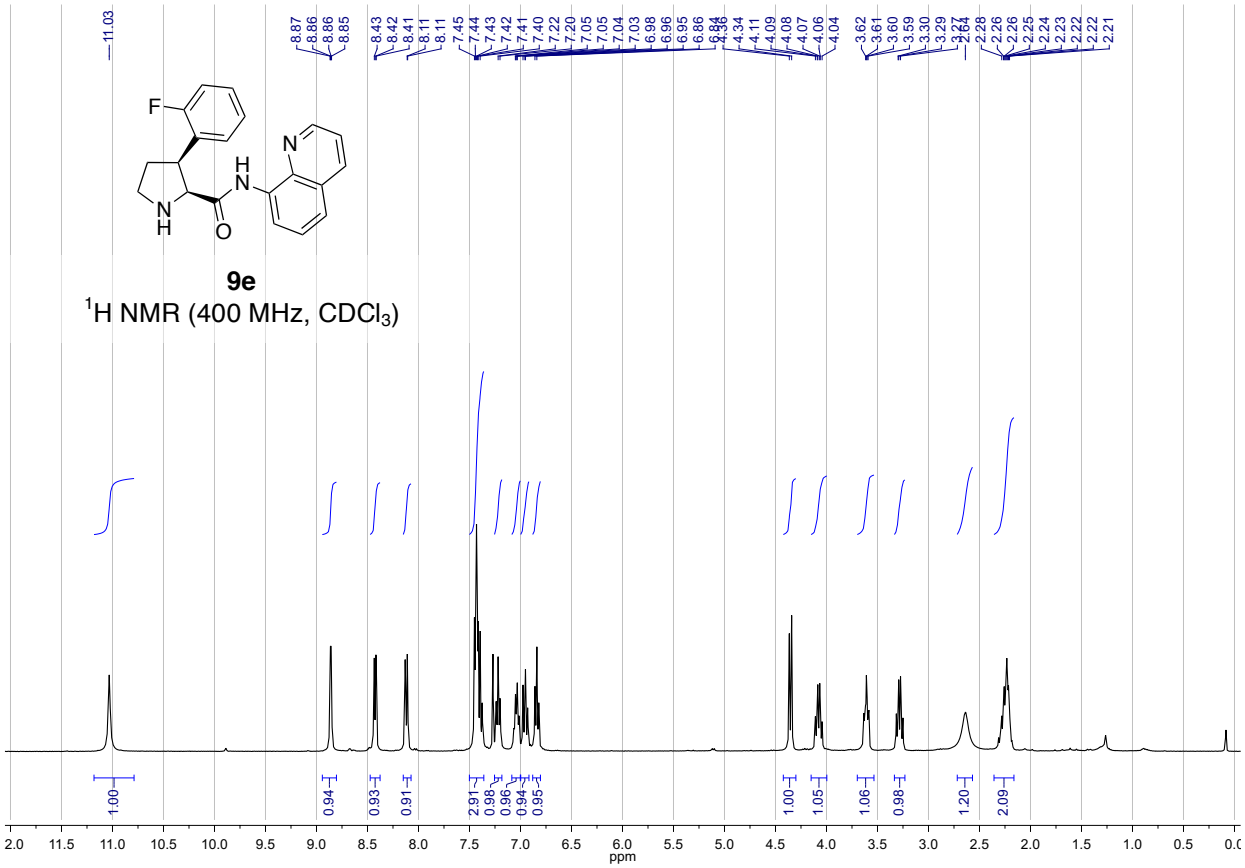
^{13}C NMR (101 MHz, DMSO-d_6, 373 K)

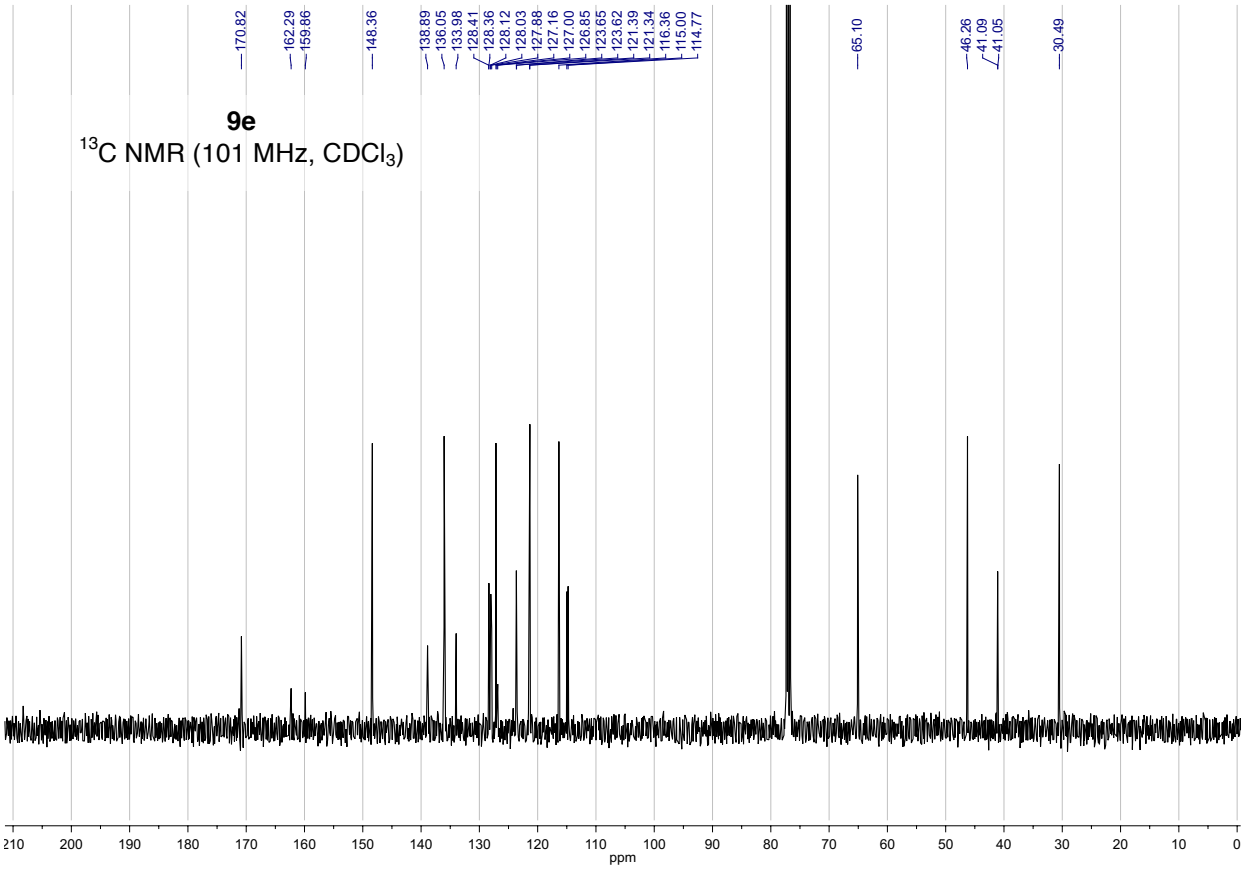

Me
N
HN
N
H
O
9a
^{1}H NMR (400 MHz, $CDCl_3$)
ppm

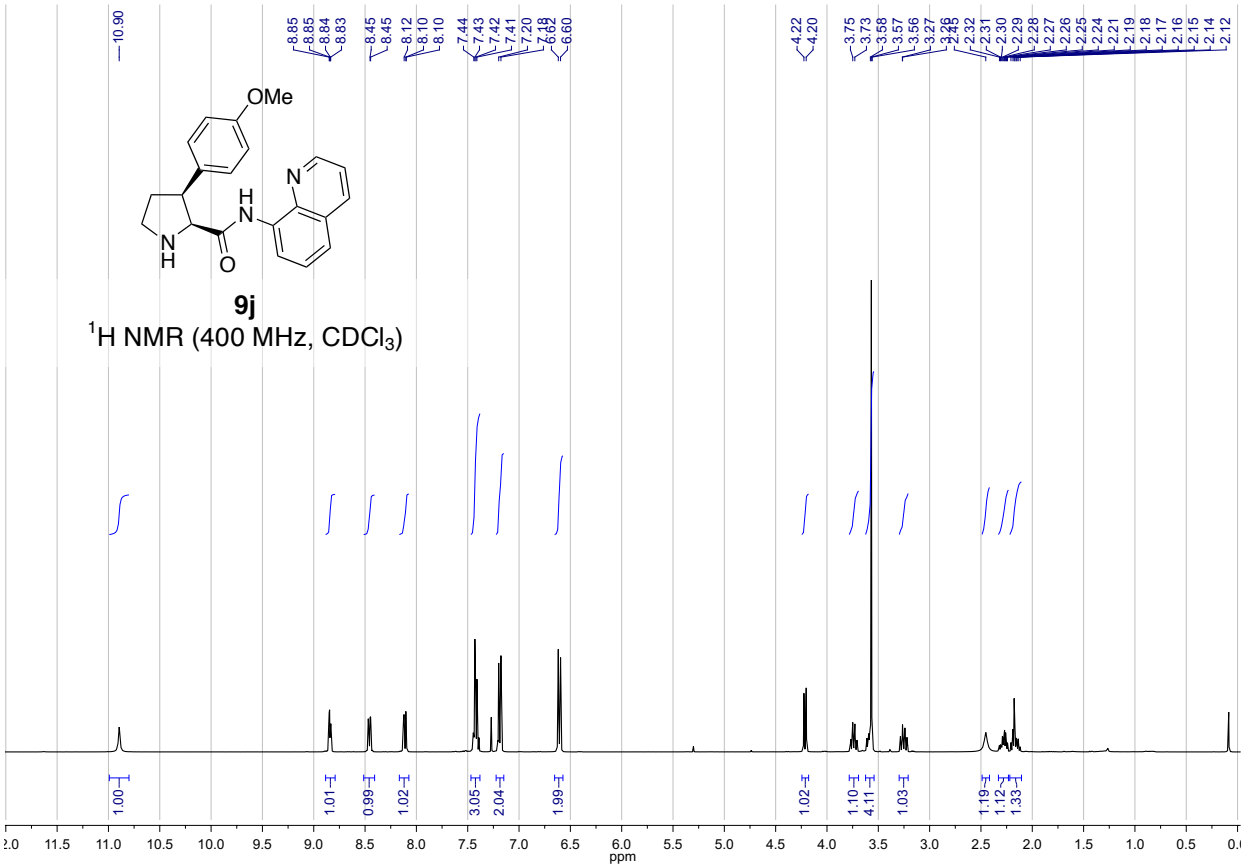

9a
^{13}C NMR (101 MHz, $CDCl_3$)
ppm

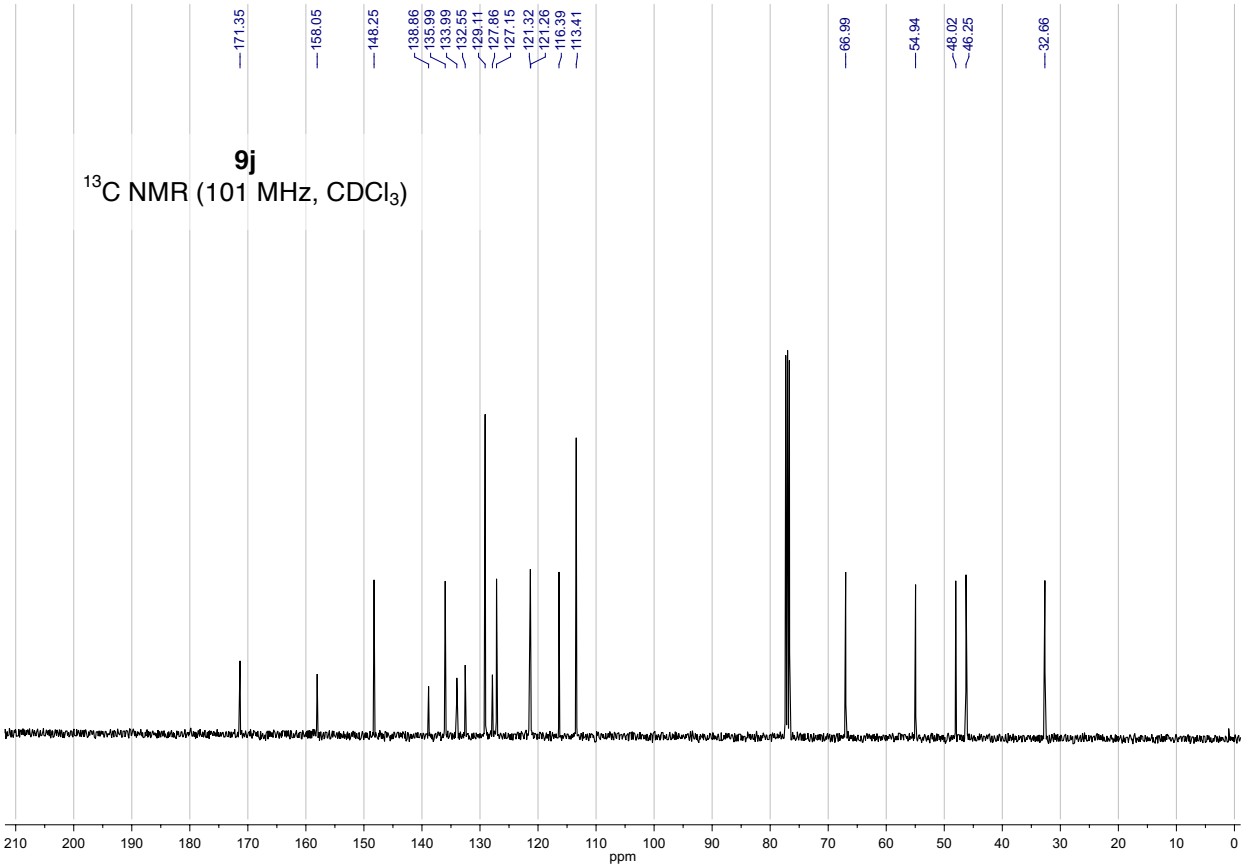

10.94
8.86
8.85
8.85
8.84
8.44
8.43
8.12
8.10
8.09
7.44
7.43
7.42
7.42
7.41
7.40
7.30
7.30
7.28
7.28
7.28
7.11
7.09
7.08
7.07
7.01
7.01
7.01
6.99
6.97
4.27
4.25
3.80
3.77
3.61
3.28
3.28
3.26
2.36
2.35
2.34
2.33
2.32
2.31
2.30
2.29
2.28
2.26
2.24
2.23
2.22
2.21
2.20
2.19
2.17
N
H
N
N
H
O
9b
1H NMR (400 MHz, CDCl3)
1.00
1.00
1.00
1.02
3.08
2.12
2.02
1.00
1.05
1.07
1.10
1.07
1.30
2.20
ppm

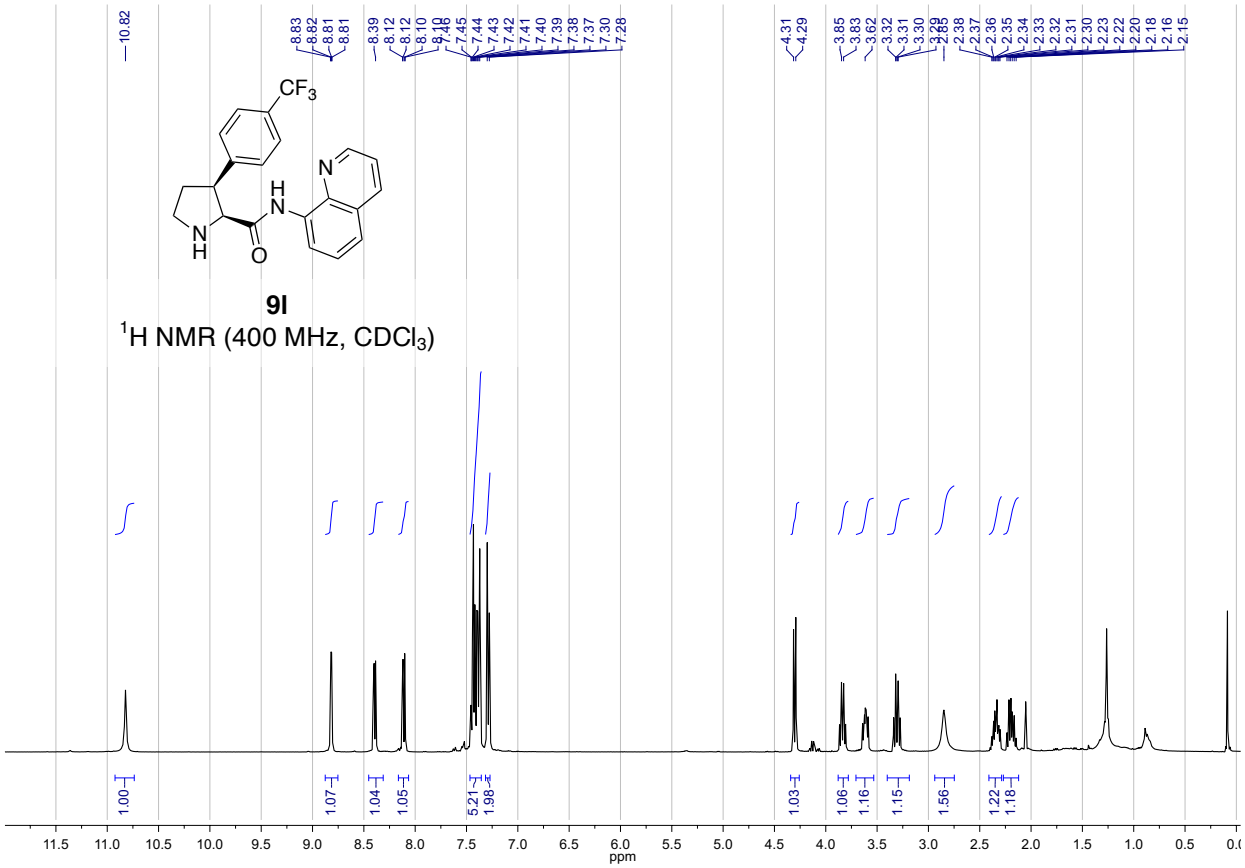

171.15
148.25
140.58
138.86
135.97
133.97
128.18
127.93
127.84
127.11
126.45
121.28
121.24
116.35
67.11
48.75
46.32
32.59
9b
13C NMR (101 MHz, CDCl3)
ppm

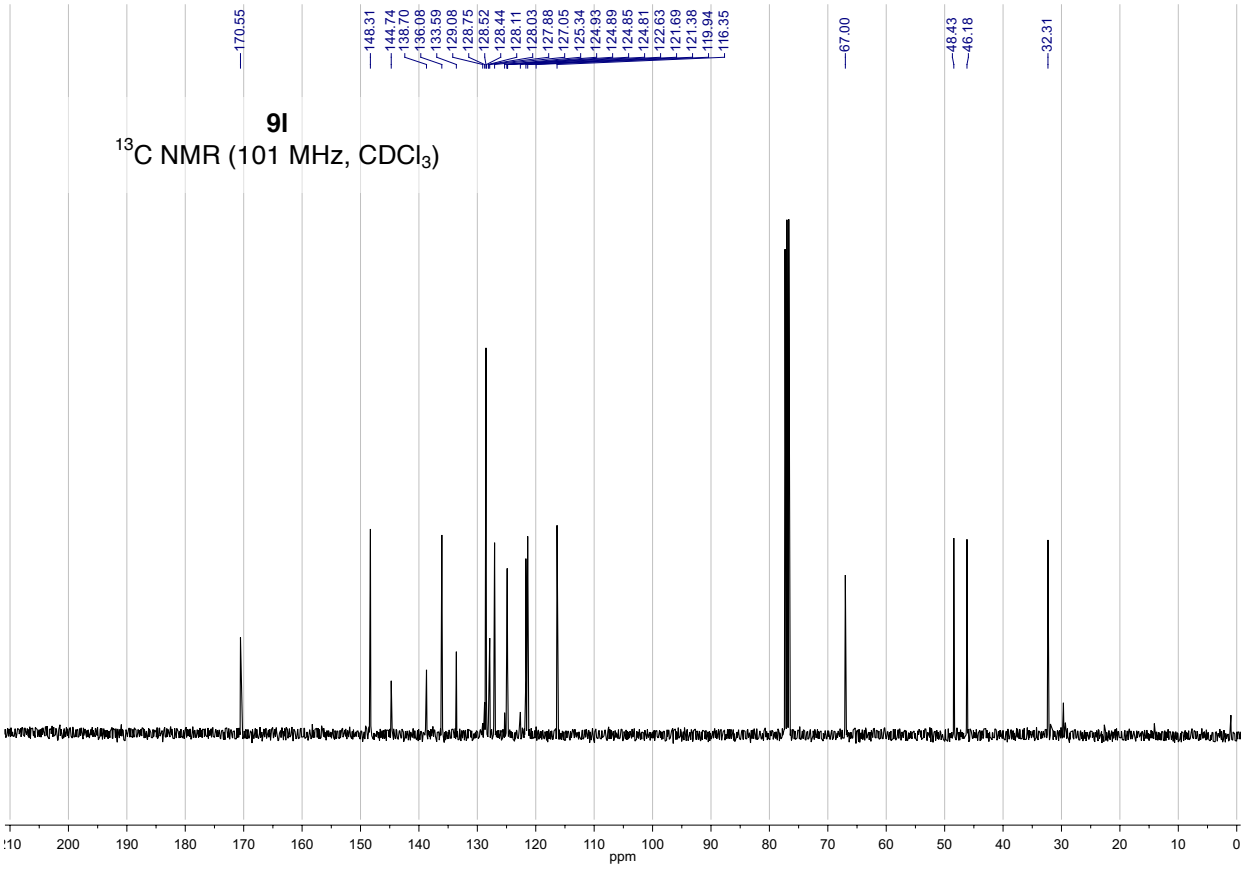

F
N
H
N
N
H
O
9e
^{1}H NMR (400 MHz, $CDCl_3$)
ppm

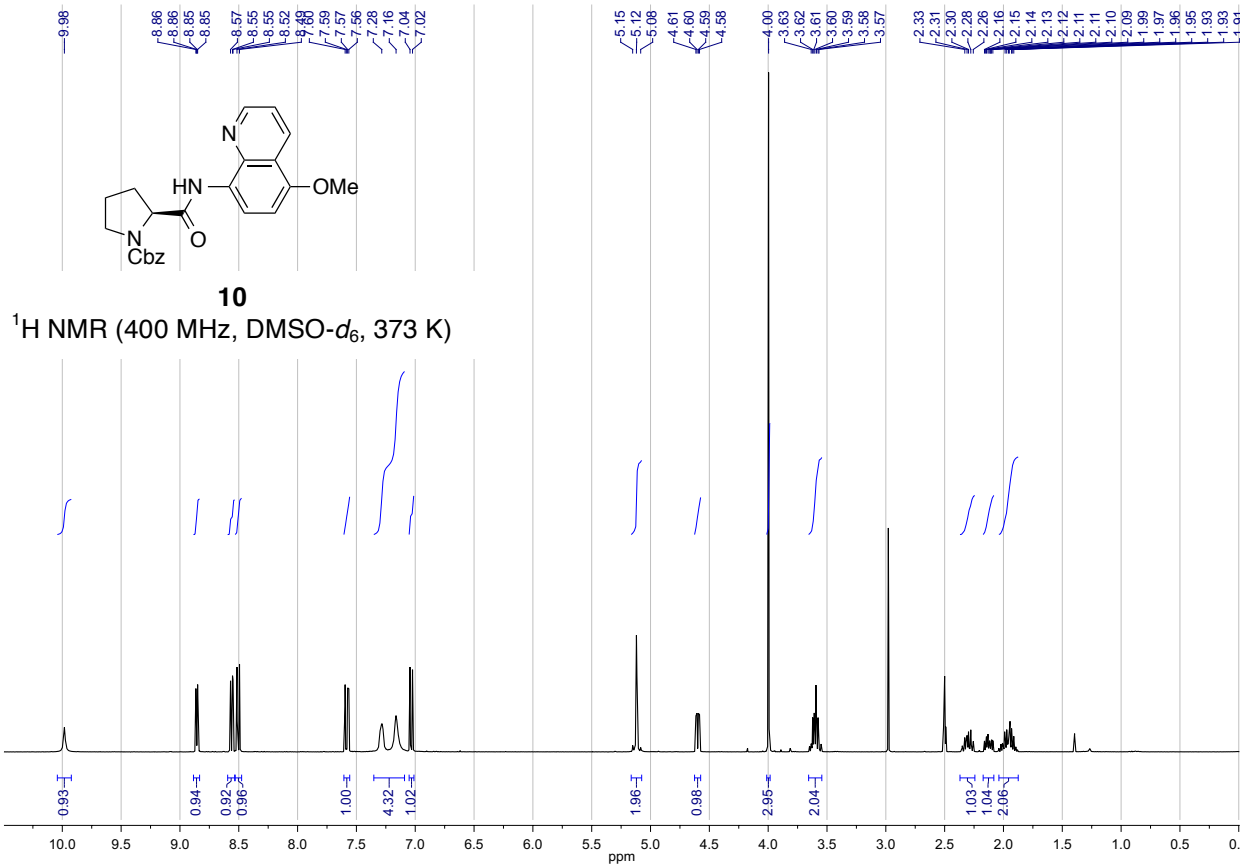

9e
^{13}C NMR (101 MHz, $CDCl_3$)
ppm


OMe
N
H
N
N
H
O
9j
^{1}H NMR (400 MHz, $CDCl_3$)
ppm


9j
^{13}C NMR (101 MHz, $CDCl_3$)
ppm

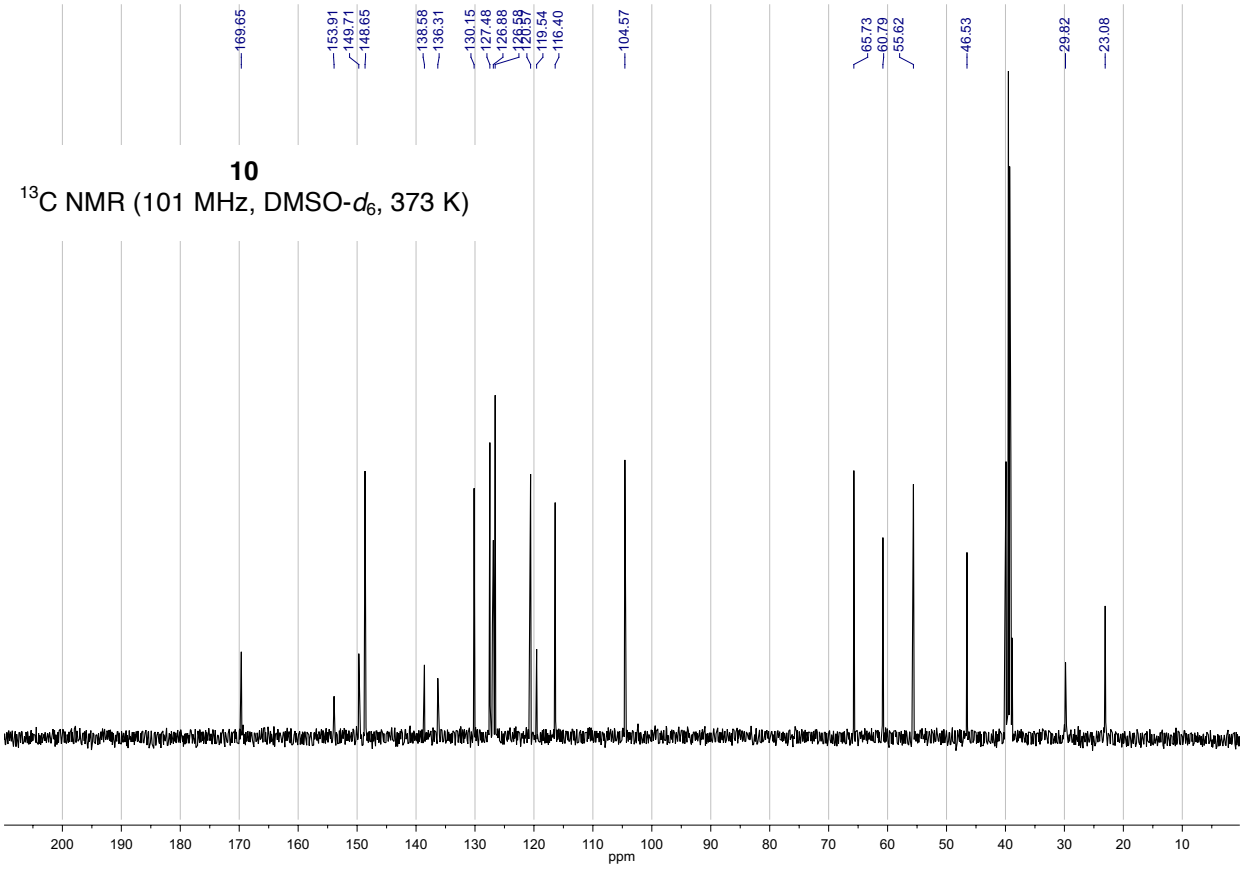

CF3
H
N
N
N
H
O
9l
1H NMR (400 MHz, CDCl3)
ppm


9l
13C NMR (101 MHz, CDCl3)
ppm



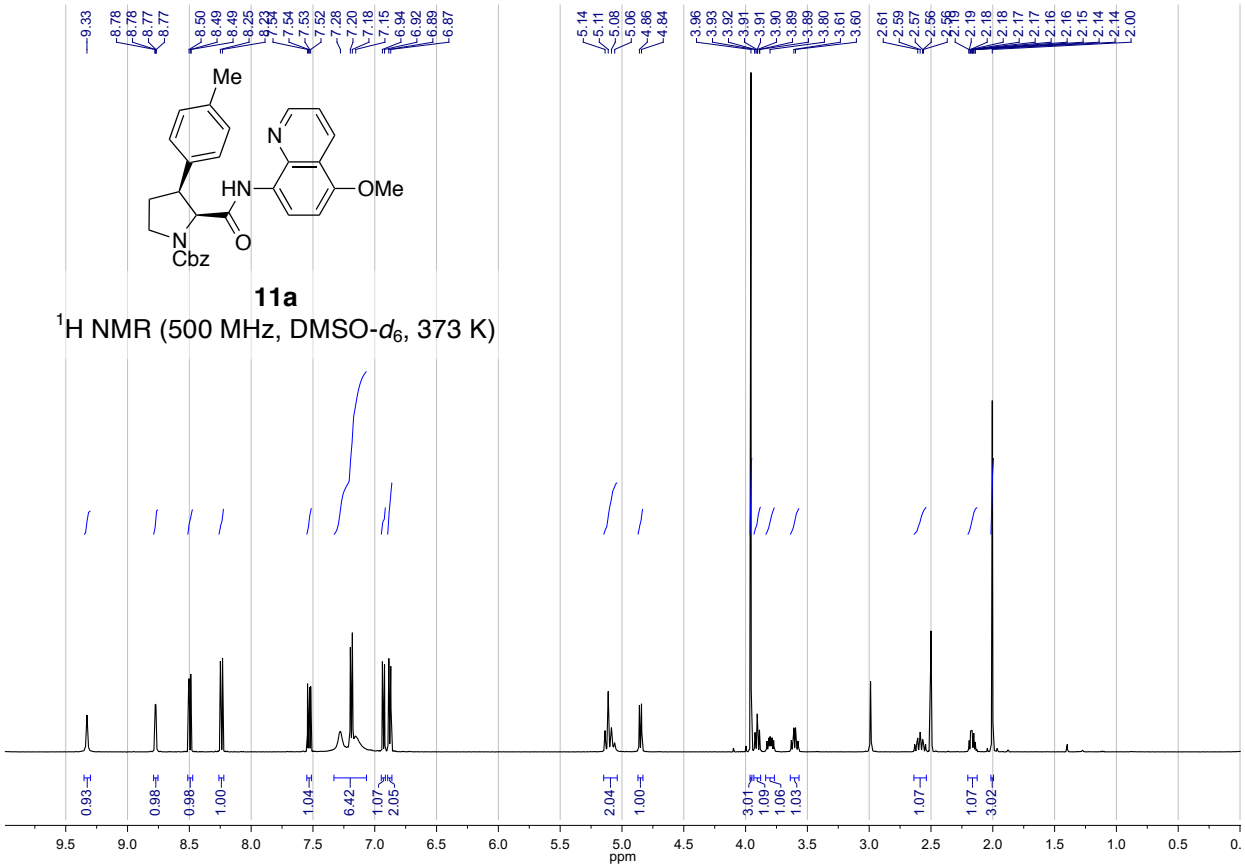
10

^{1}H NMR (400 MHz, DMSO-d_6, 373 K)



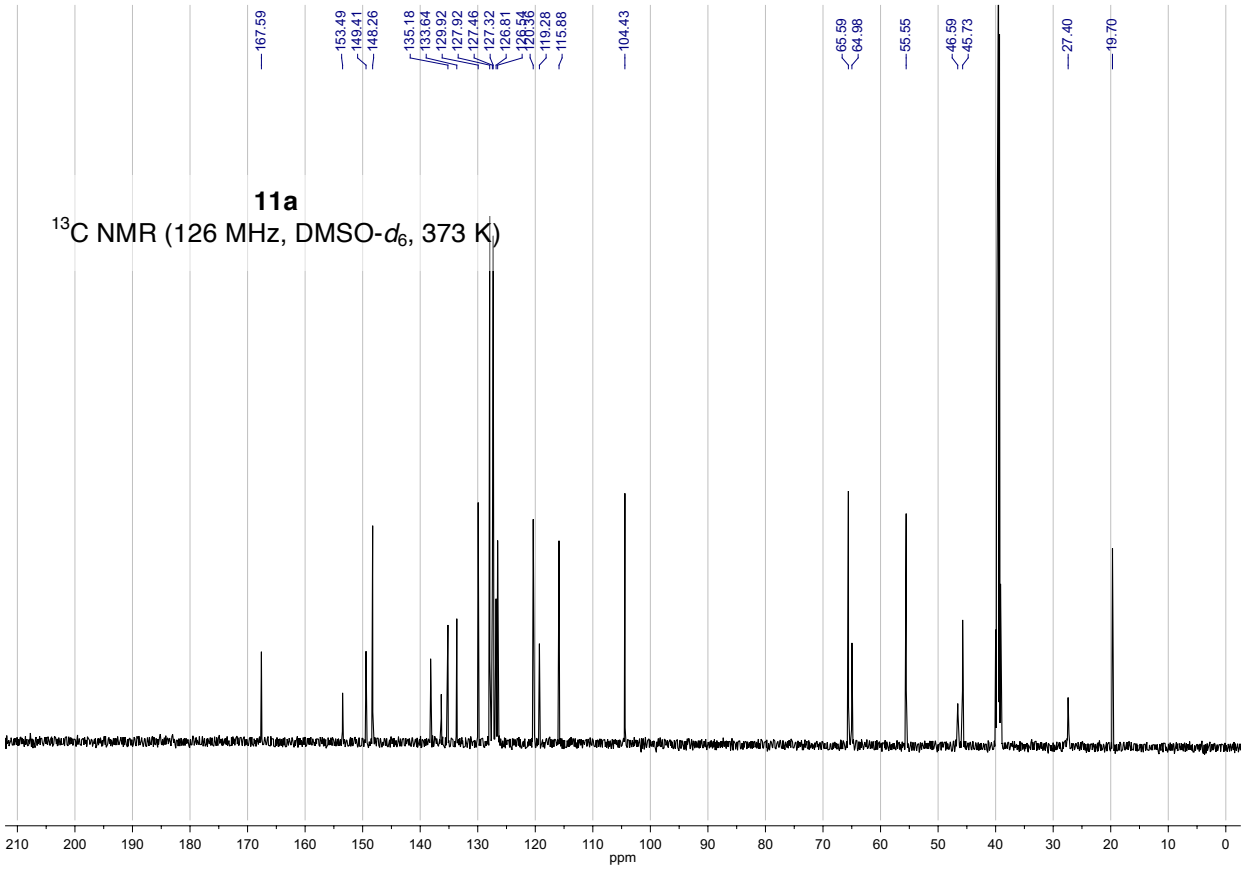
10

^{13}C NMR (101 MHz, DMSO-d_6, 373 K)



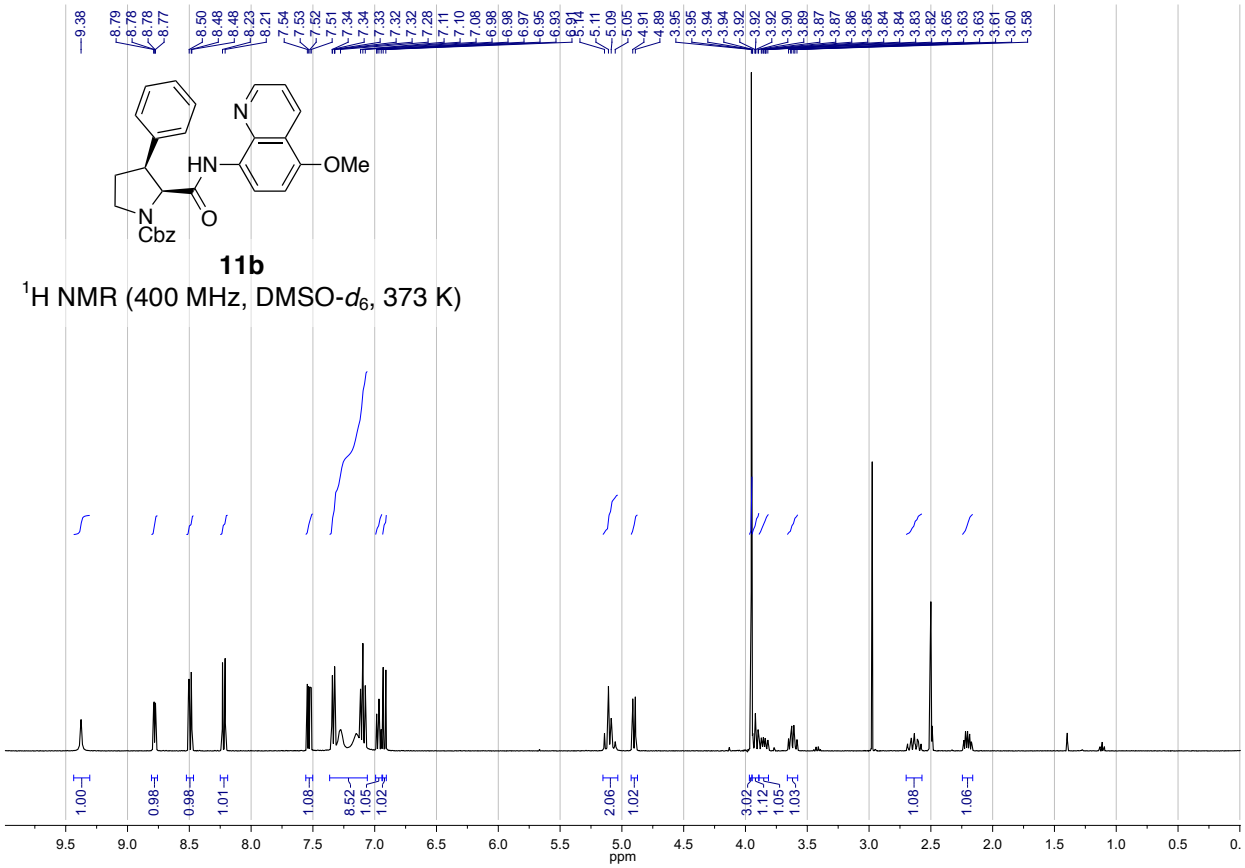
11a

^{1}H NMR (500 MHz, DMSO-d_6, 373 K)



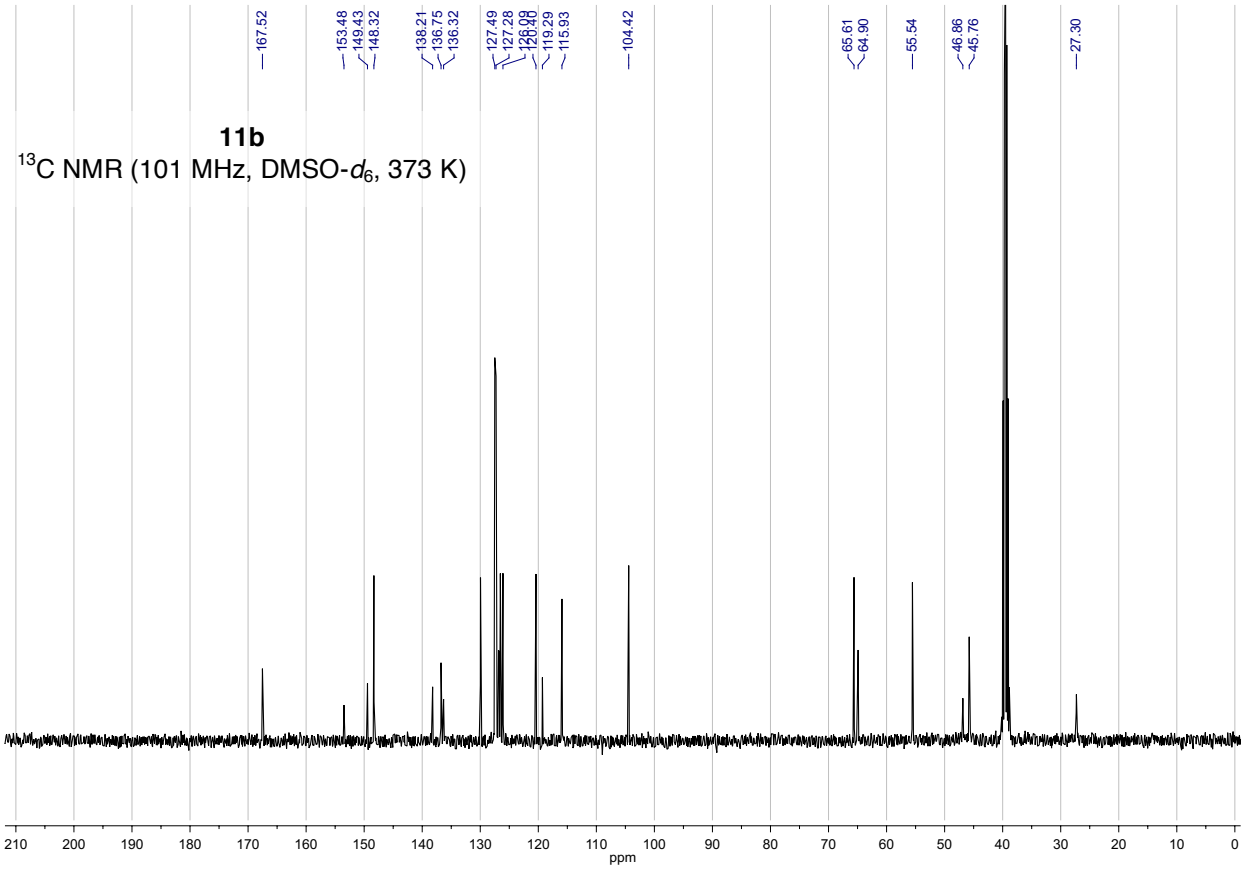
11a

^{13}C NMR (126 MHz, DMSO-d_6, 373 K)



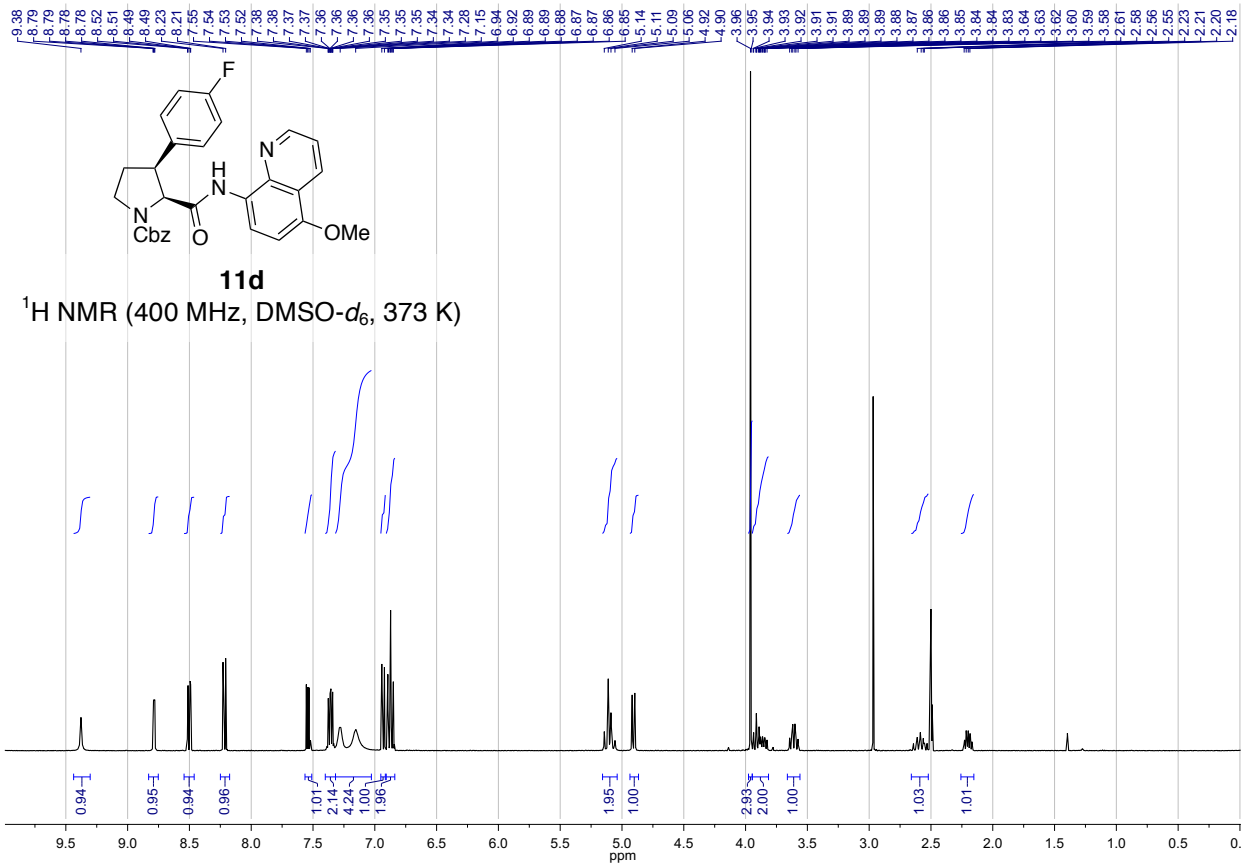
11b

^{1}H NMR (400 MHz, DMSO-d_6, 373 K)



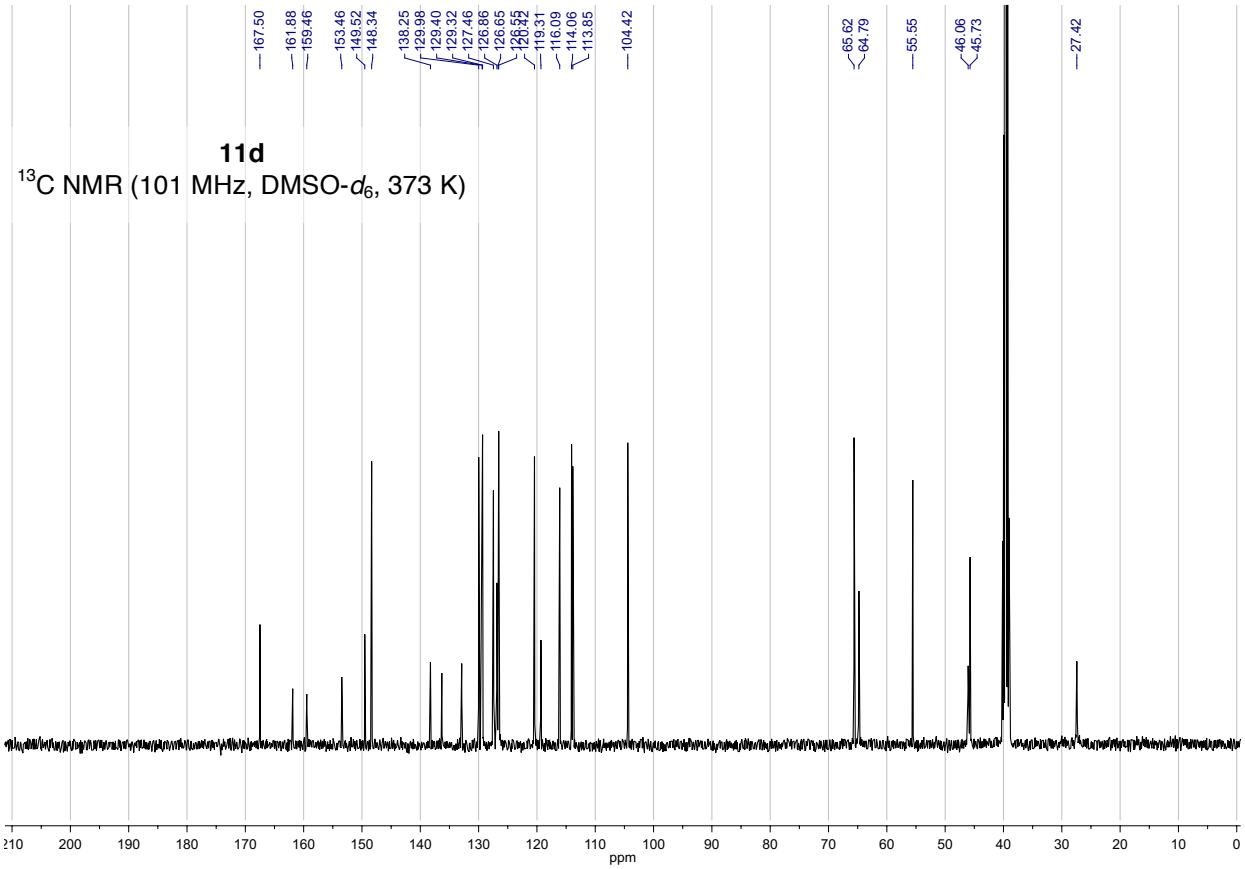
11b

^{13}C NMR (101 MHz, DMSO-d_6, 373 K)



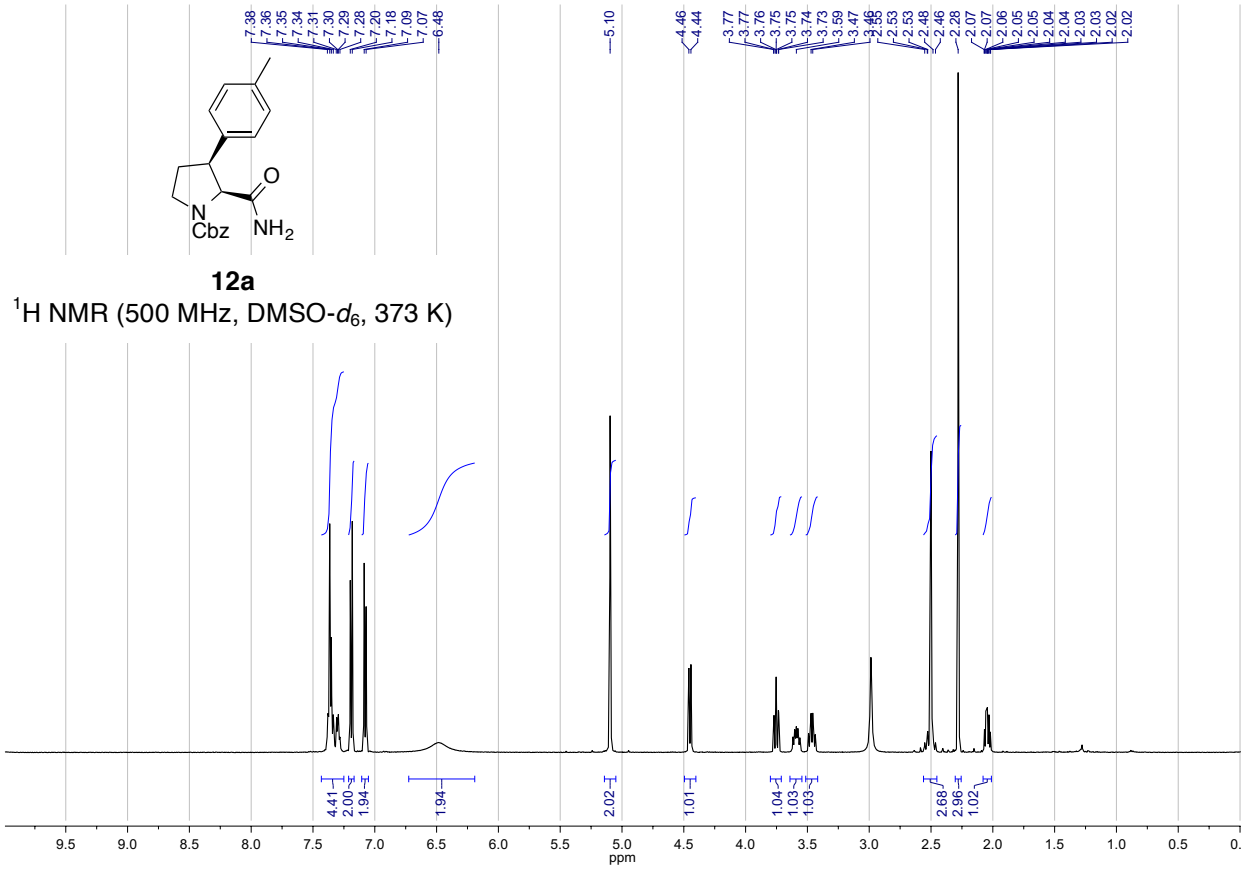
11d

^{1}H NMR (400 MHz, DMSO-d_6, 373 K)



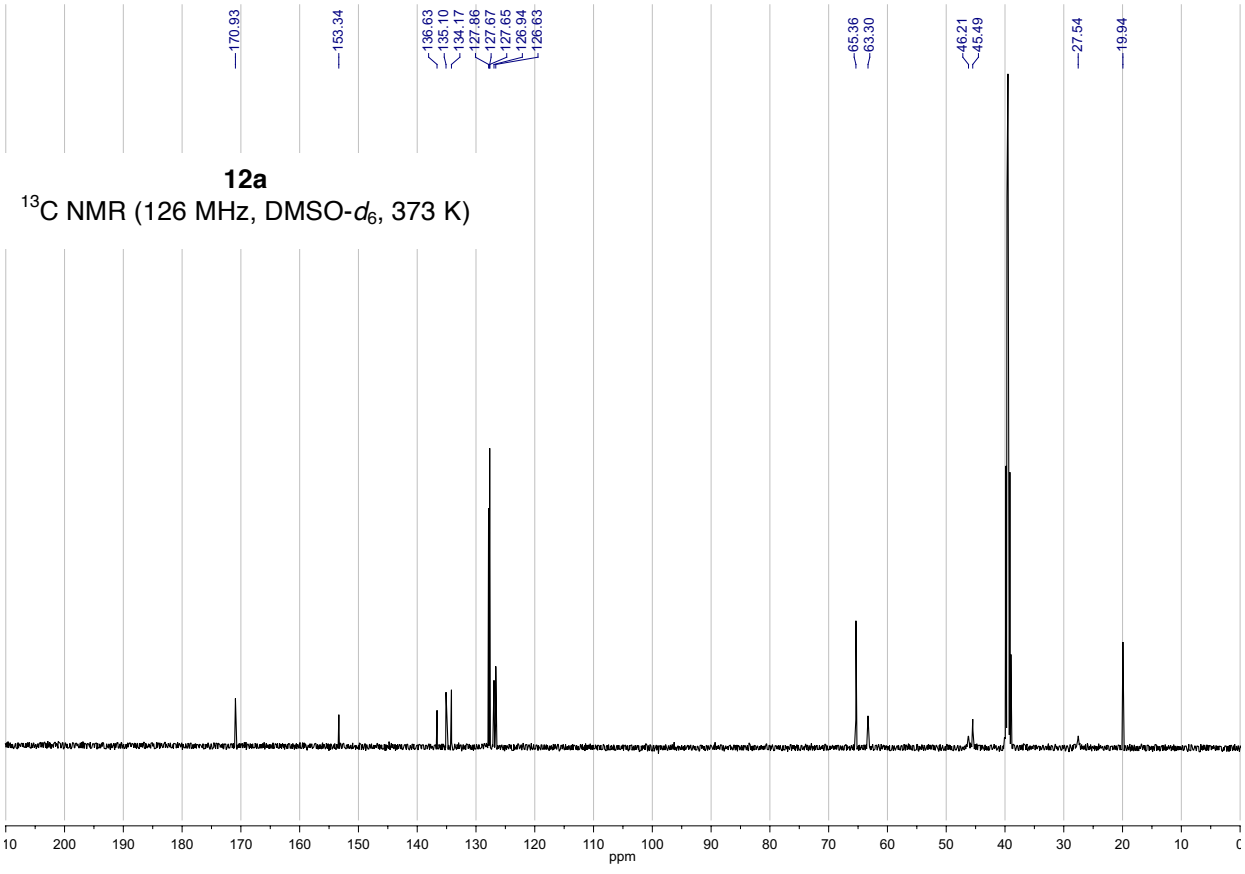
11d

^{13}C NMR (101 MHz, DMSO-d_6, 373 K)



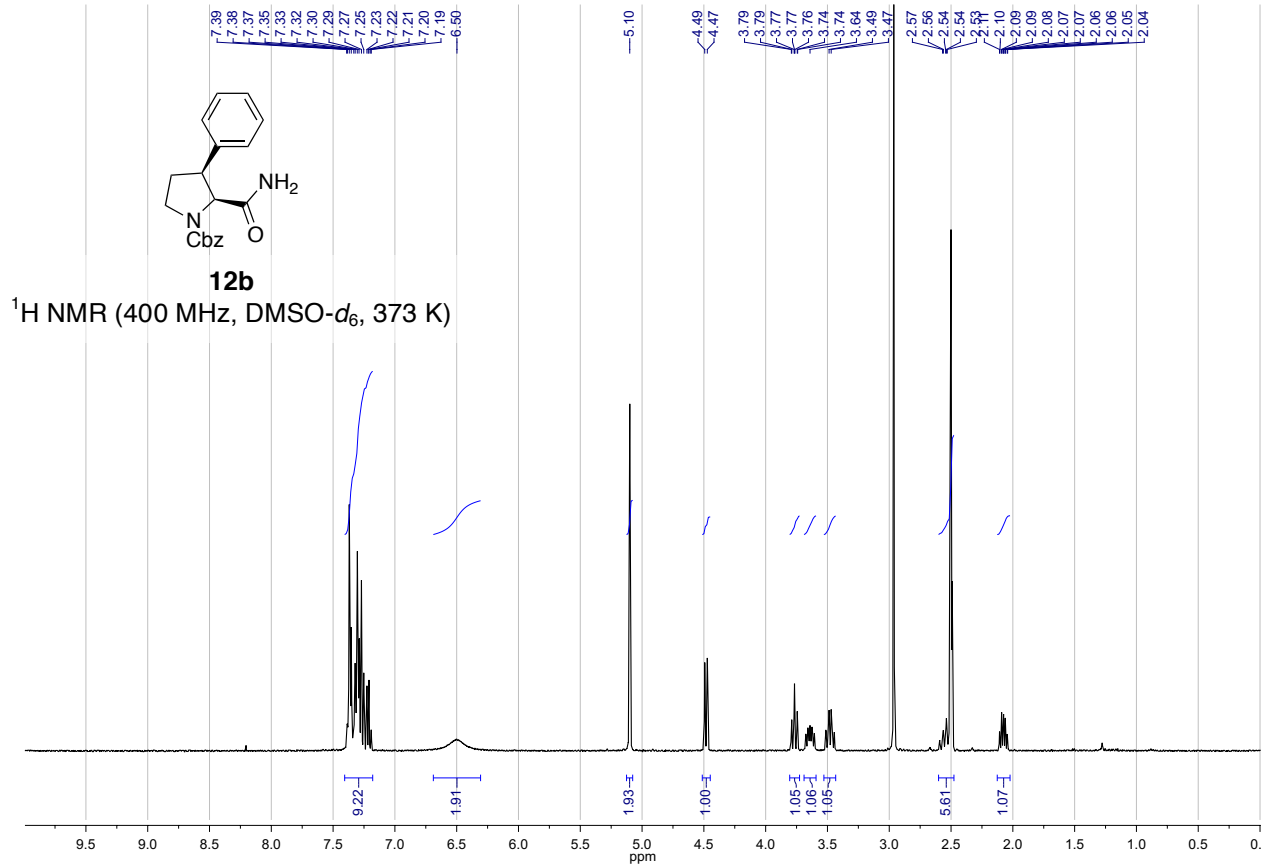
12a

^{1}H NMR (500 MHz, DMSO-d_6, 373 K)



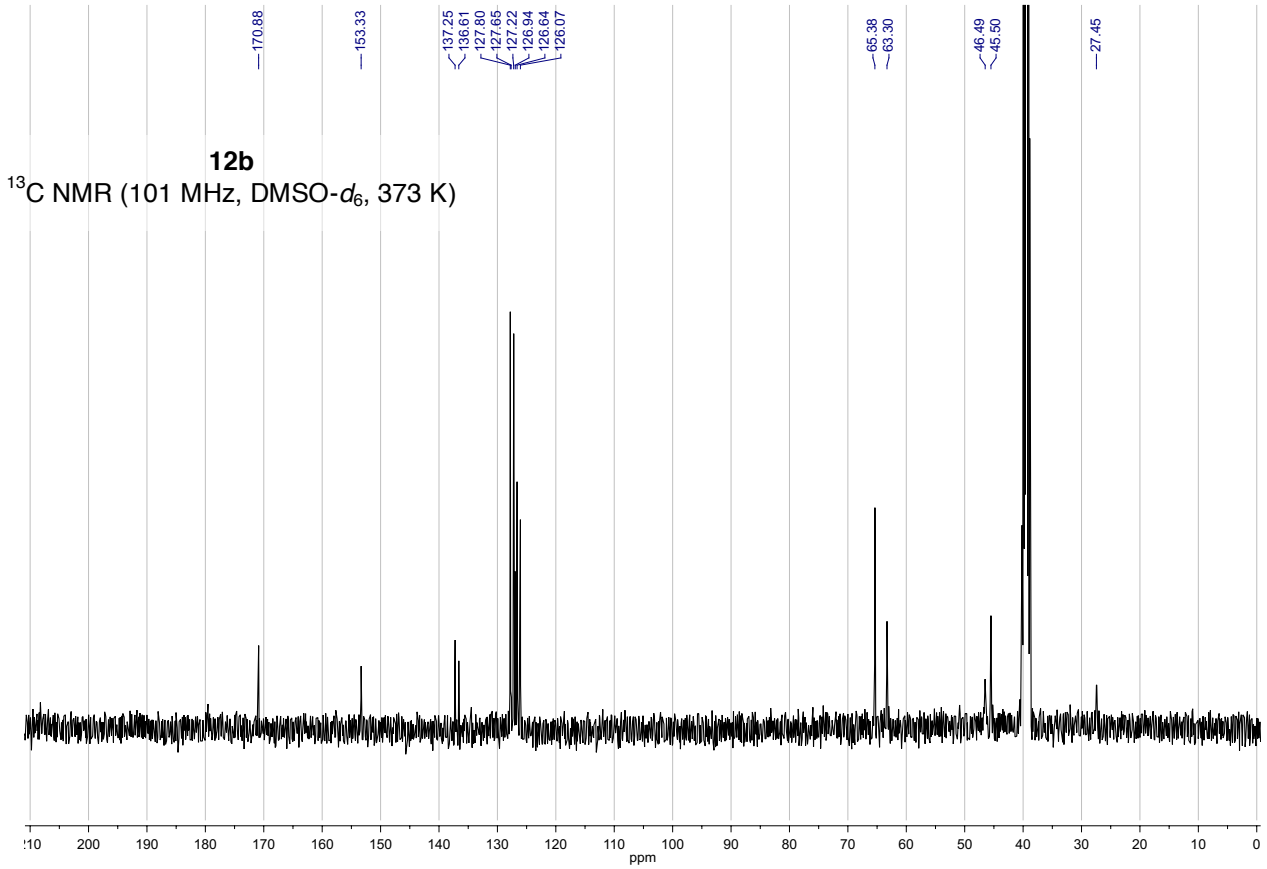
12a

^{13}C NMR (126 MHz, DMSO-d_6, 373 K)



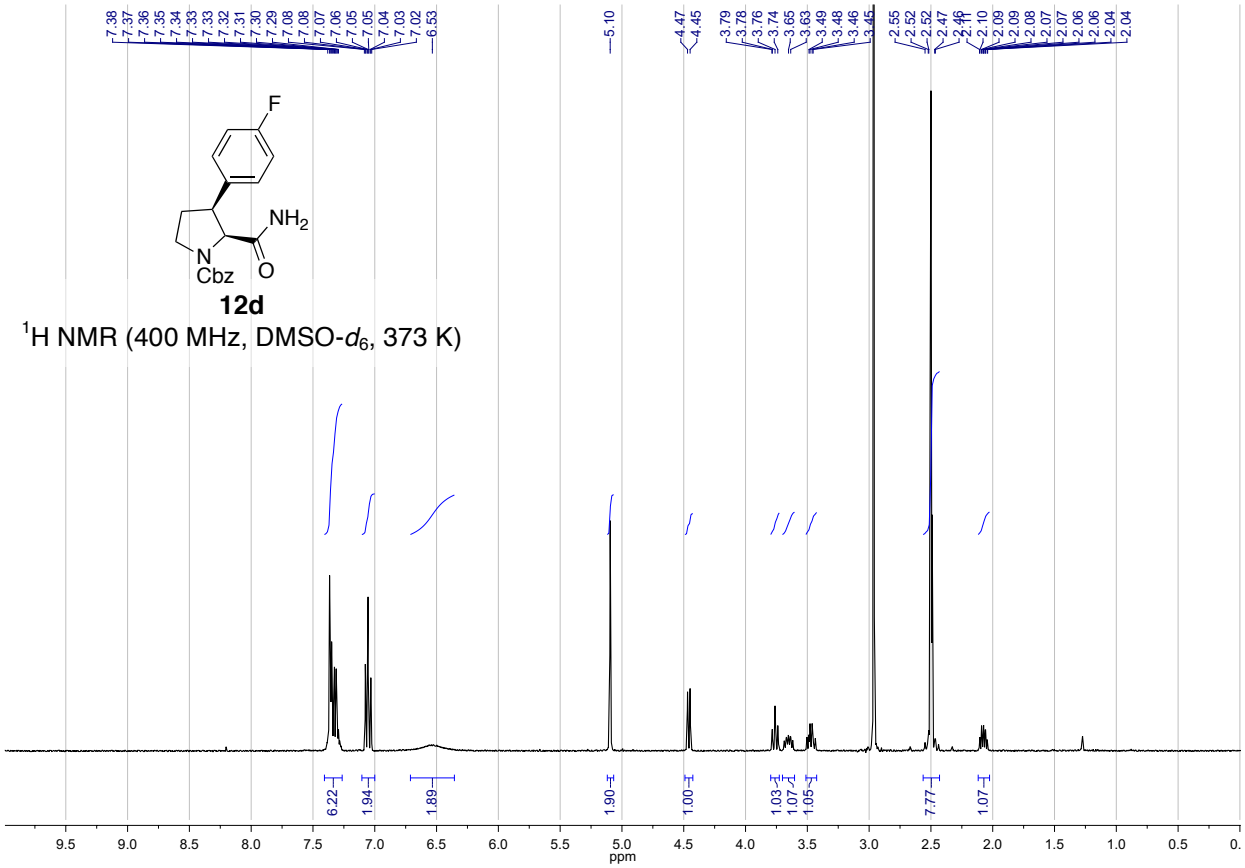
12b

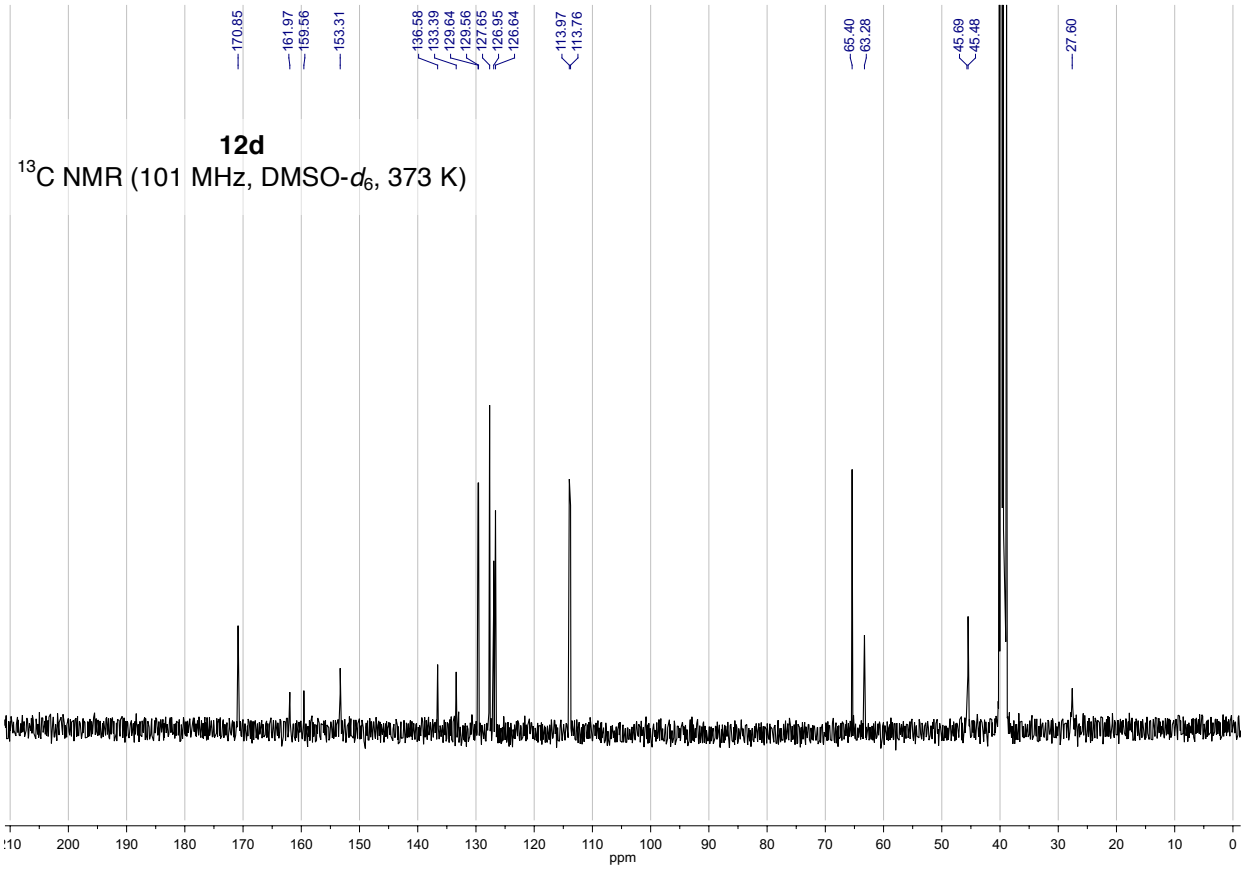
^{1}H NMR (400 MHz, DMSO-d_6, 373 K)

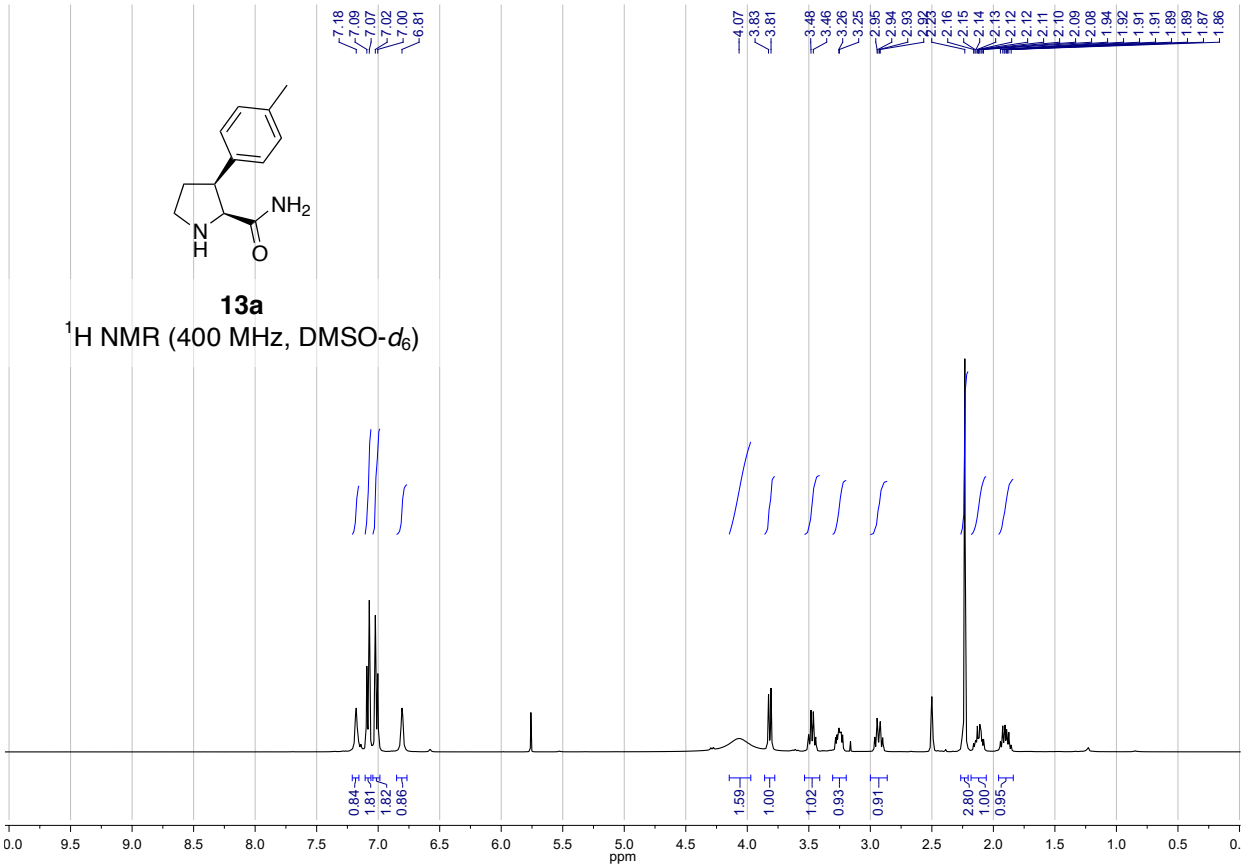


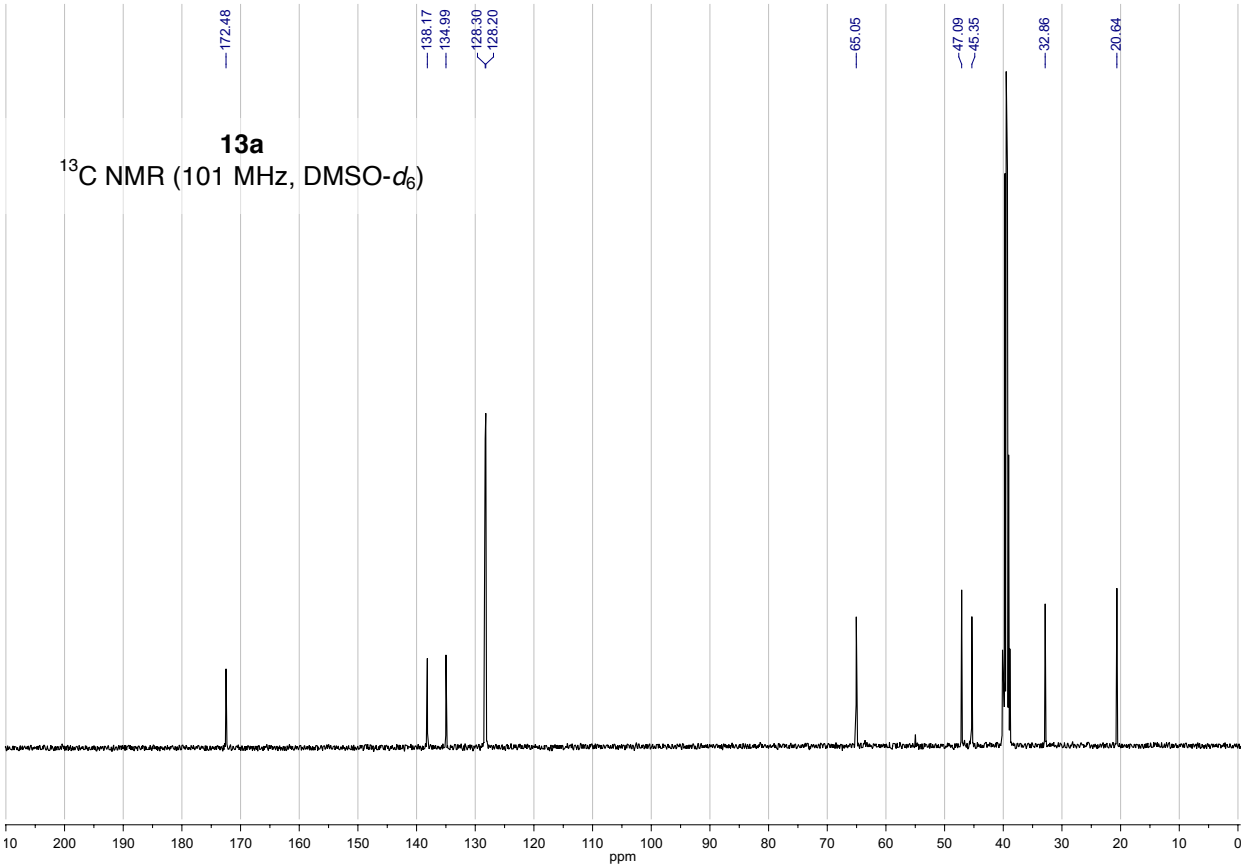
12b

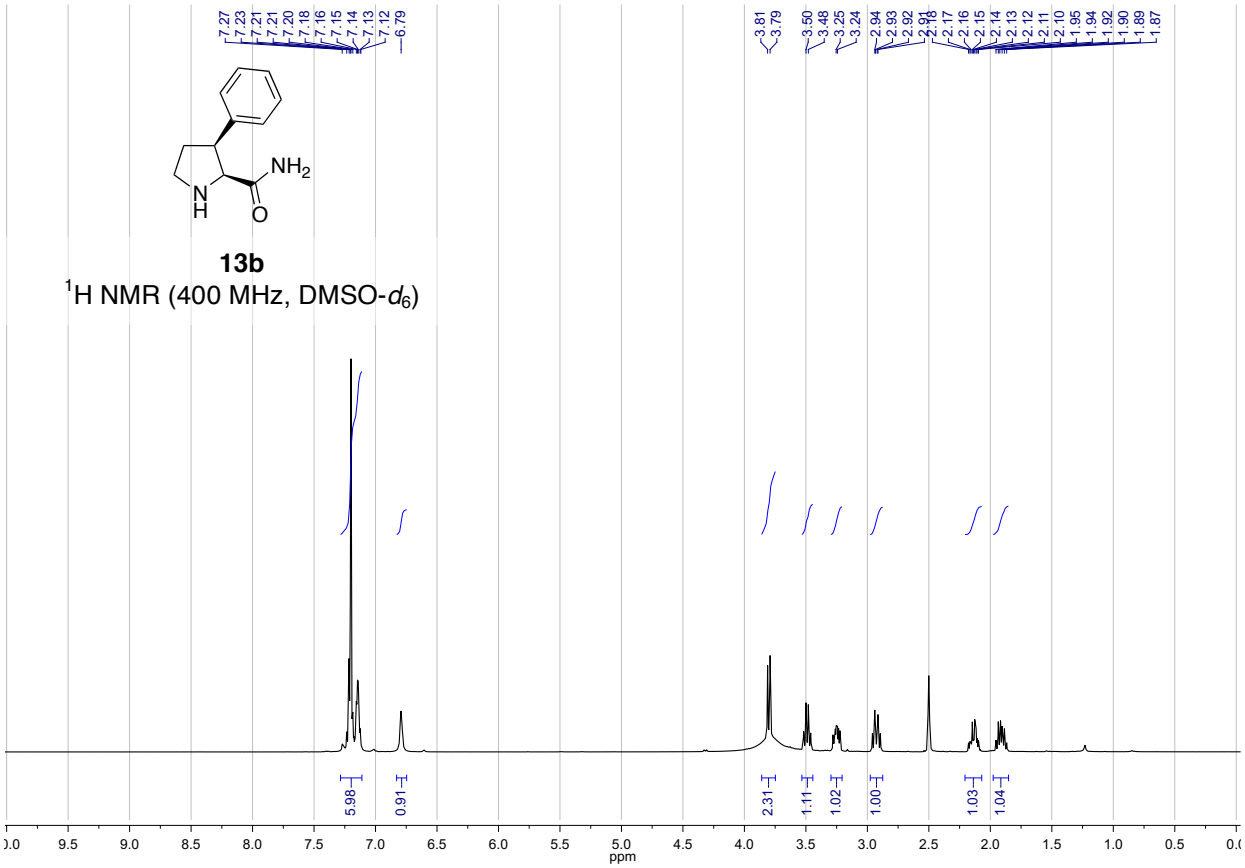
^{13}C NMR (101 MHz, DMSO-d_6, 373 K)


F
NH2
N
Cbz
O
12d
1H NMR (400 MHz, DMSO-d6, 373 K)
ppm


12d
13C NMR (101 MHz, DMSO-d6, 373 K)
ppm

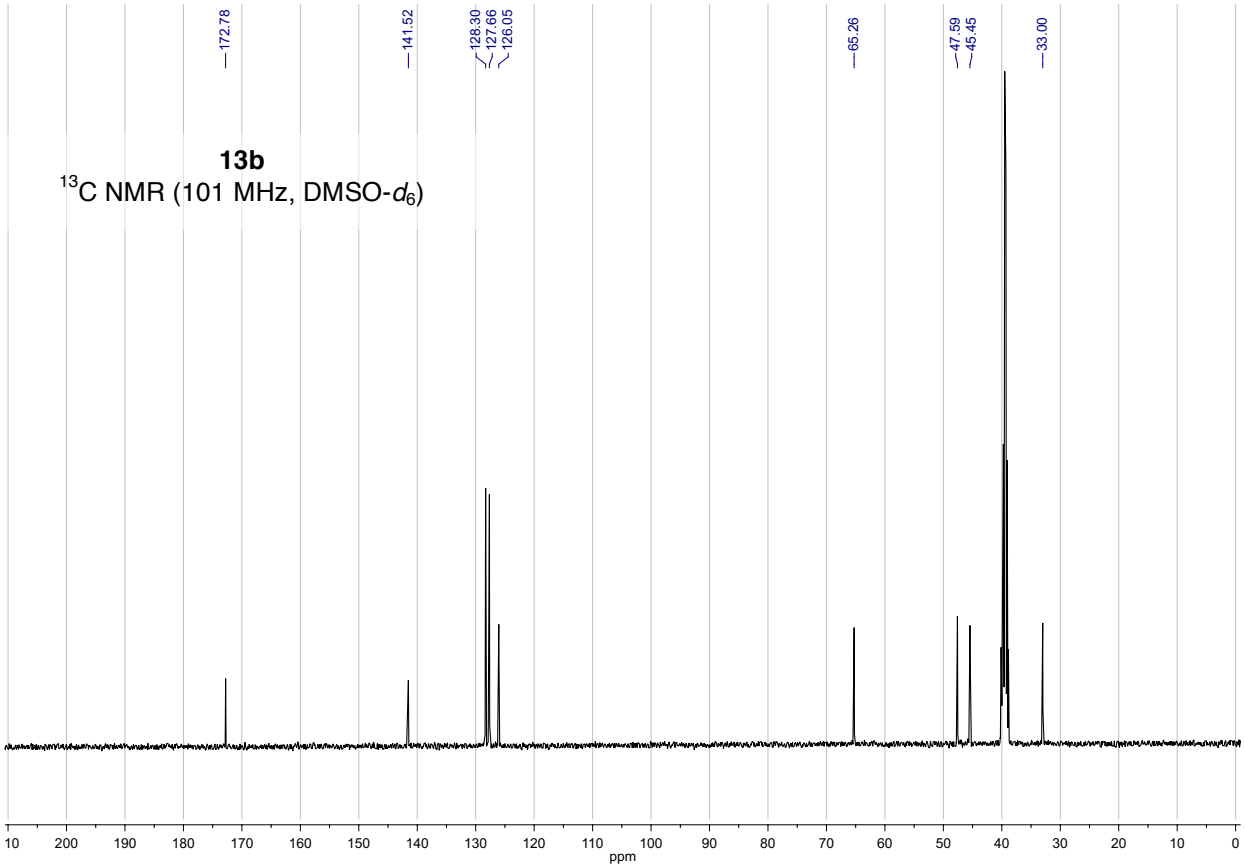

NH2
N
H
O
13a
1H NMR (400 MHz, DMSO-d6)
7.18
7.09
7.07
7.02
7.00
6.81
4.07
3.83
3.81
3.48
3.46
3.26
3.25
2.95
2.94
2.93
2.92
2.23
2.16
2.15
2.14
2.13
2.12
2.12
2.11
2.10
2.09
2.08
1.94
1.92
1.91
1.91
1.89
1.89
1.87
1.86
0.84
1.81
1.82
0.86
1.59
1.00
1.02
0.93
0.91
2.80
1.00
0.95
ppm


13a
13C NMR (101 MHz, DMSO-d6)
172.48
138.17
134.99
128.30
128.20
65.05
47.09
45.35
32.86
20.64
ppm



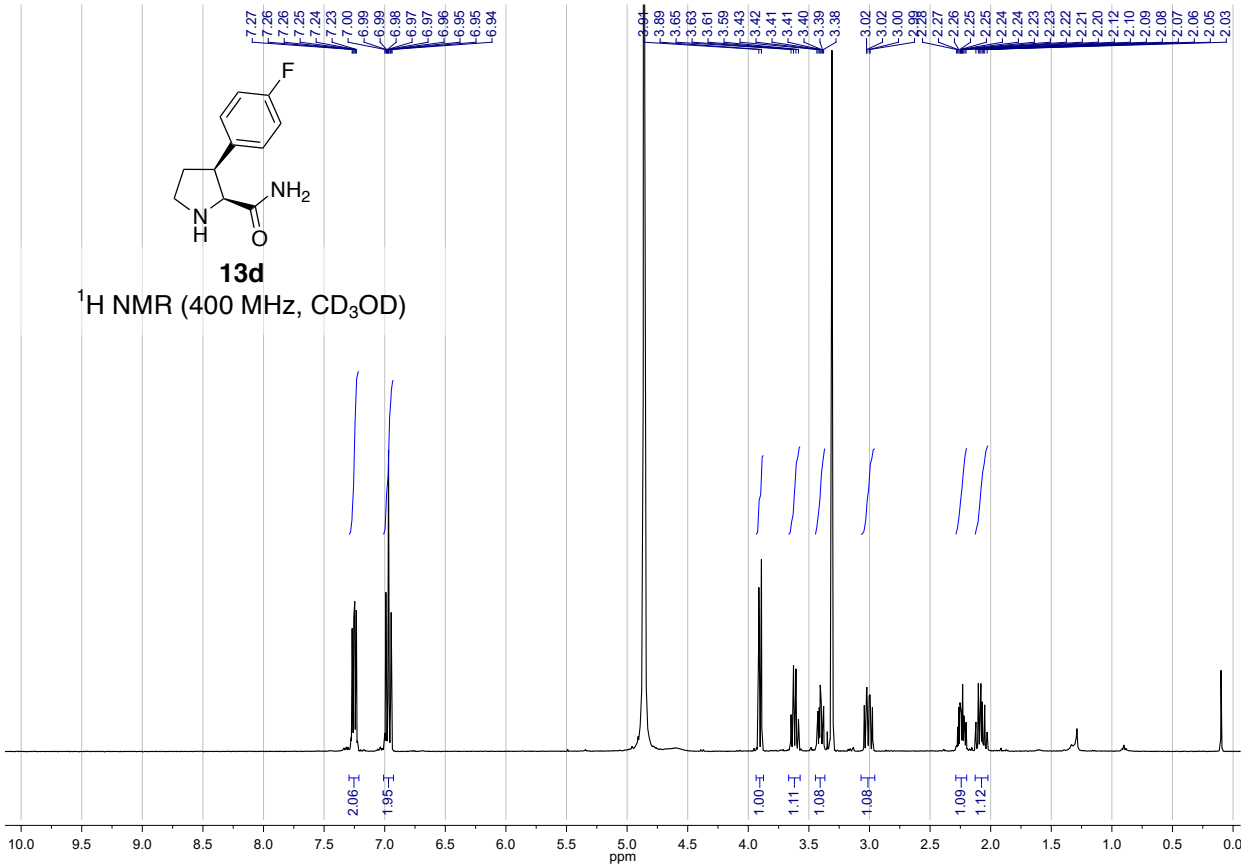
13b

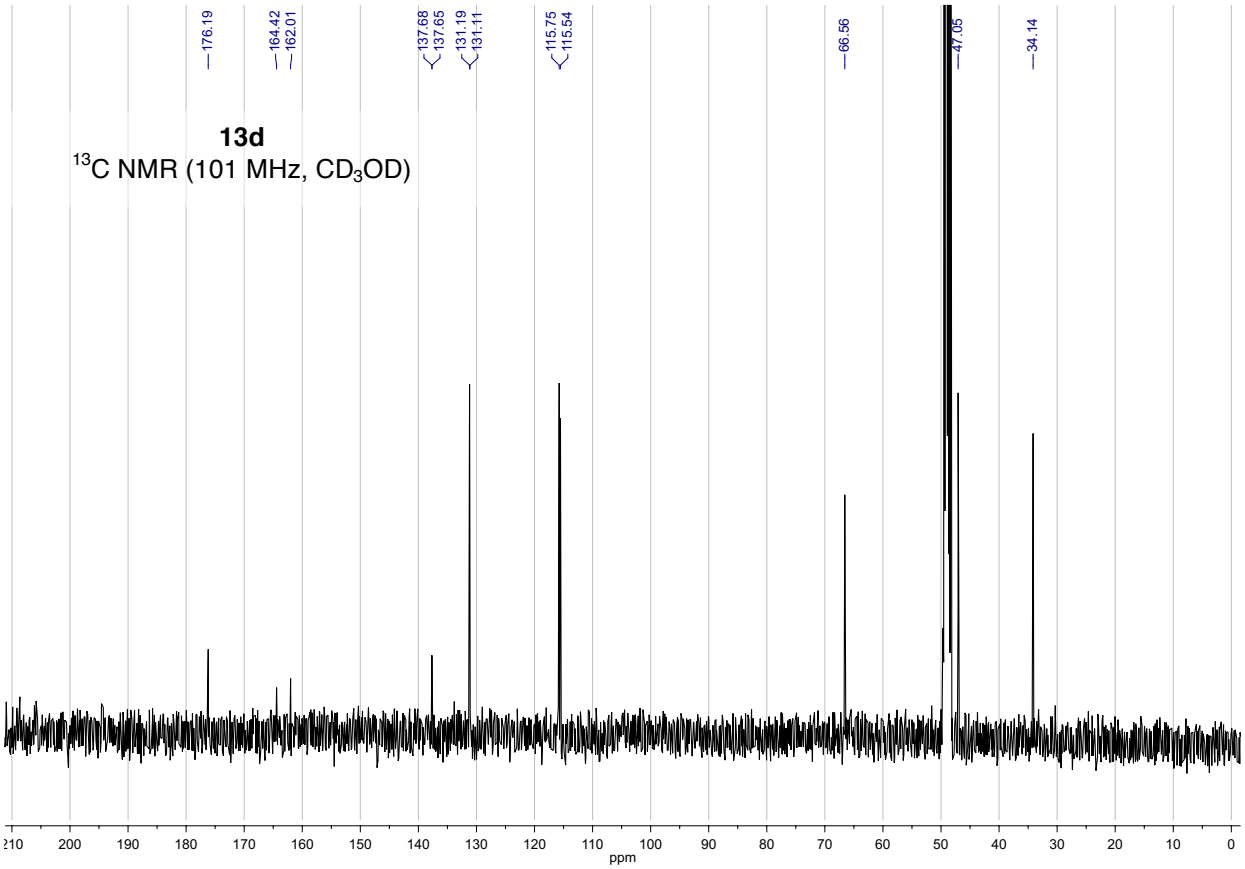
^{1}H NMR (400 MHz, DMSO-d_6)



13b

^{13}C NMR (101 MHz, DMSO-d_6)


F
NH2
N
H
O
13d
1H NMR (400 MHz, CD3OD)
ppm


13d
13C NMR (101 MHz, CD3OD)
ppm