SUPPORTING INFORMATION

Regio and Stereoselective Palladium Catalyzed C(sp^3)–H Arylation of Pyrrolidines and Piperidines with C(3) Directing Groups

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Table of Contents S1
General Experimental Conditions S2
Structures of Pyrrolidine Amide Substrates, and Additional Compounds in SI S3
Further Details on Optimization of C–H Arylation of *N*-Boc Pyrrolidine Amide **1** S4
Optimization of Directing Group Removal from *N*-Boc Amides **20** and **21** to Access Pyrrolidine Derivatives **23**–**25** S10
HPLC Traces for Racemic and Enantioenriched Pyrrolidine Derivatives **1**, **2a** and **4a** ... S12
HPLC Traces for Racemic, Scalemic and Enantioenriched Piperidine Derivatives **13**, **15**–**16d** and **29** S17
NMR Studies on the Stereochemistry of 3,4-Disubstituted Pyrrolidines **2a** and **4a** S25
NMR Studies on the Stereochemistry of 3,4-Disubstituted Piperidine **15a** S30
Spectroscopic Analysis of Pyrrolidine Derivative **2a**: Identification of 2-Arylated Pyrrolidine **3a** S33
Experimental Details and Characterization Data S34–S76
- Pyrrolidine Amide Substrates **1**, **5–8**, **S32, S33** S34
- Piperidine Amide Substrates **13** and **14** S38
- General Procedure A for C–H Arylation of Pyrrolidines and Piperidines S40
- Pyrrolidine C–H Arylation (**2a**, **4a**, **S32**, **S33**): S38
- Pyrrolidine C–H Arylation: Scope of *N*-Protecting Groups **(9a–12a)** S45
- Pyrrolidine C–H Arylation: Scope of Aryl Iodides **(2/9b–x)** S47
- Piperidine C–H Arylation: Scope of *N*-Protecting Groups and Aryl Iodides **(15/16a,c–e,u,y,z and 17/18a,i,x)** S57
- Removal of AQ Directing Group (**19–28**) S66
- Formal Stereocontrolled Synthesis of (–)-Paroxetine: S71

References S74
^{1}H, ^{13}C and ^{19}F NMR Spectra for Selected Compounds S75–S157

General Experimental Conditions

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 and CH_2Cl_2) or used as supplied (α,α,α-trifluorotoluene). Reactions in sealed tubes were run using Biotage microwave vials (2–5 mL) and aluminum caps equipped with molded butyl/PTFE septa, unless otherwise specified. Simple butyl septa led to reproducibility issues due to solvent interaction. Stirring rate (1000 rpm), stir bar size (3 x 10 mm, PTFE), reaction vessel size (2–5 mL) were kept constant throughout optimization process and scope evaluation.

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 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 (FTIR) were recorded in reciprocal centimeters (cm^{-1}) using a FT-IR ATR spectrometer.

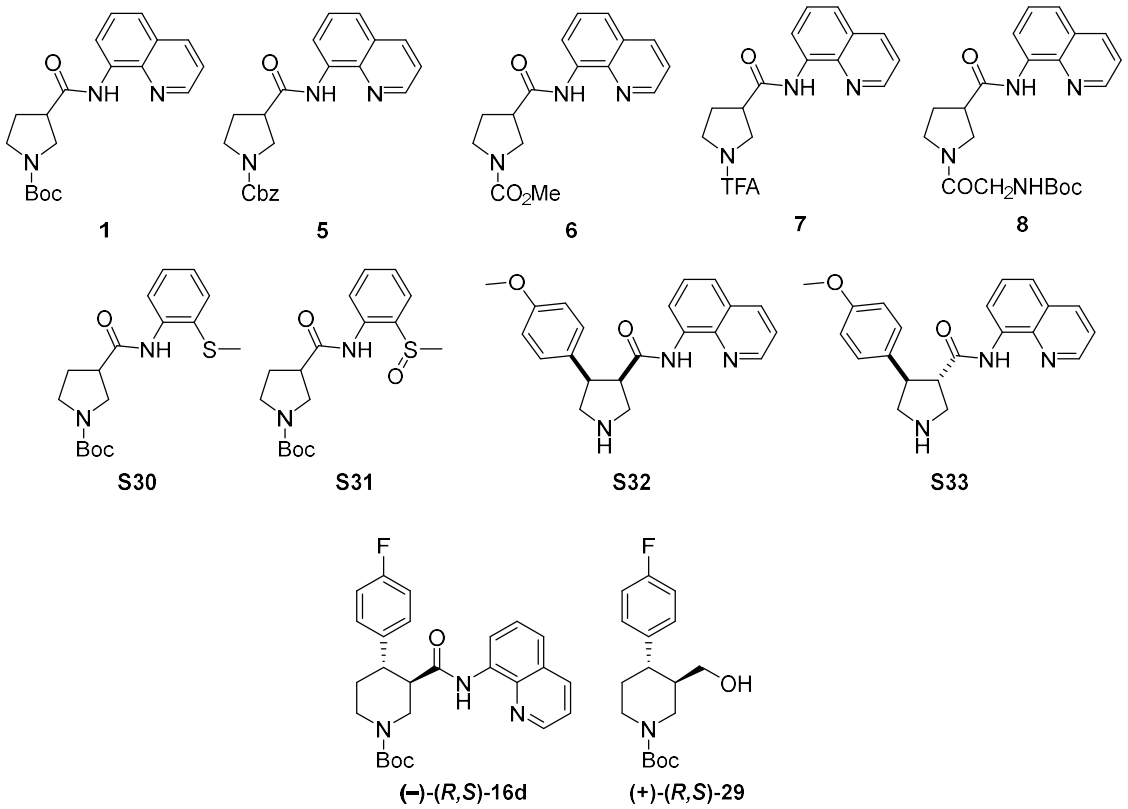
Nuclear magnetic resonance spectra were recorded on 400 or 500 MHz spectrometers. Chemical shifts for ^1H NMR spectra were recorded in parts per million from tetramethylsilane with the residual protonated solvent resonance as the internal standard ($CHCl_3$: δ 7.27 ppm, DMSO: δ 2.50 ppm, MeOD: δ 3.31 ppm). Data was reported as follows: chemical shift (multiplicity [s = singlet, d = doublet, t = triplet, m = multiplet and br = broad], coupling constant, integration and assignment). *J* values are reported in Hz. All multiplet signals were quoted over a chemical shift range. ^{13}C NMR spectra were recorded with complete proton decoupling. Chemical shifts were reported in parts per million from tetramethylsilane with the solvent resonance as the internal standard ($^{13}CDCl_3$: δ 77.0 ppm, $(^{13}CD_3)_2SO$: δ 39.5 ppm, $^{13}CD_3OD$: δ 49.0 ppm). Assignments of ^1H and ^{13}C spectra, as well as *cis*- or *trans*-configuration, were based upon the analysis of δ and *J* values, as well as DEPT, COSY, HMBC, HSQC and NOESY experiments where appropriate.

All Boc, Cbz, methyl carbamate and TFA 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.

Melting points are uncorrected. Observed optical rotation (α') was measured at the indicated temperature (T °C) and were converted to the corresponding specific rotations $[\alpha]_D^T$ in deg cm^2 g^{-1}, concentration (*c*) in g per 100 mL. HPLC analyses were carried out on an Agilent 1260 Infinity Series system, employing Daicel Chiracel columns.

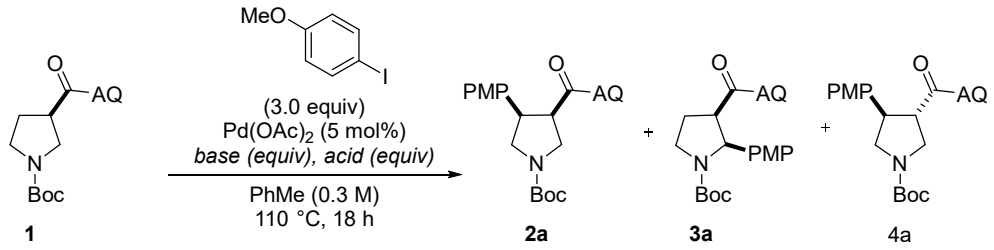
Reagents Commercial reagents were used as supplied or purified by standard techniques where necessary. K_2CO_3 was flame–dried before use as part of reaction set-up. Purity: $Pd(OAc)_2$, >98%; PivOH, 99%; K_2CO_3, ≥98% (powder, –325 mesh).

Structures of Pyrrolidine Amide Substrates, and Additional Compounds in SI



Further Details on Optimization of C–H Arylation of *N*-Boc Pyrrolidine Amide 1

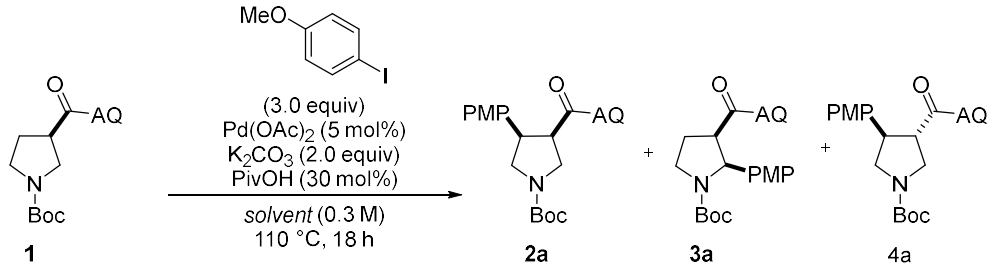
Screening of Bases and Carboxylic Acid Additives (Table S1).



entry	base (equiv)	acid (equiv)	yield[a] (%)				
			2a	**3a**	**4a**	**1**	**tot**
1	AgOAc (2.0)	/	28	9	/	58	95
2	Ag_2CO_3 (1.0)	/	29	4	/	56	89
3	Ag_2CO_3 (1.0)	PivOH (0.3)	37	7	/	44	88
4	CsOAc (2.0)	/	47	11	/	23	81
5	Cs_2CO_3 (2.0)	/	3	/	10	72	85
6	Cs_2CO_3 (2.0)	PivOH (2.0)	51	9	/	28	88
7	K_2CO_3 (2.0)	/	26	4	/	59	89
8	**K_2CO_3 (2.0)**	**PivOH (0.3)**	**36**	**5**	**/**	**53**	**94**
9	PivOK (2.0)	/	31	9	/	50	90
10	K_2CO_3 (2.0)	AcOH (0.3)	20	2	/	69	91
11	K_2CO_3 (2.0)	$EtCO_2H$ (0.3)	22	2	/	67	91
12	K_2CO_3 (2.0)	*i*$PrCO_2H$ (0.3)	37	4	/	47	88
13	K_2CO_3 (2.0)	1-Ad-CO_2H (0.3)	36	4	/	55	95
14	K_2CO_3 (2.0)	2-Mes-CO_2H (0.3)	36	2	/	50	88
15	K_2CO_3 (2.0)	TFA (0.3)	7	/	/	92	99
16	K_2CO_3 (2.0)	$(BnO)_2PO_2H$ (0.3)	15	3	trace	75	93

Table S1. Full screening of bases and carboxylic acids for C–H arylation of *N*-Boc pyrrolidine derivative **1**. Reaction scale: 0.20 mmol. [a] Calculated by ^{1}H NMR spectroscopy using 1,3,5-trimethoxybenzene as internal standard. Ad = adamantyl. Mes = 2,4,6-trimethylphenyl.

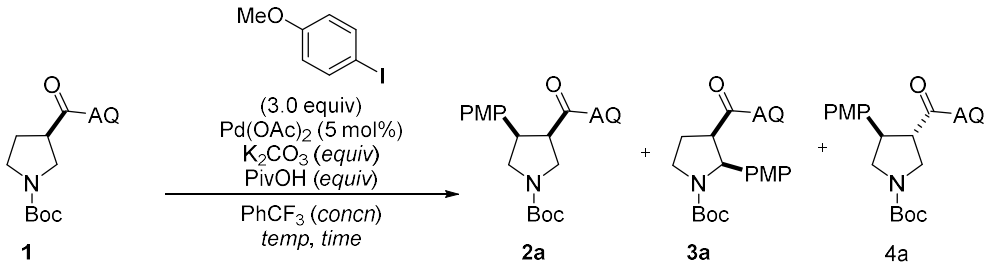
Solvent Screening (Table S2).



entry	solvent	yield (%)[a]				
		2a	**3a**	**4a**	**1**	**tot**
1	PhMe	36	5	/	53	94
2	1,4-dioxane	25	3	/	62	90
3	*t*-amyl-OH	11	/	7	75	93
4	*t*-amyl-OH/H_2O (4:1)	6	/	7	86	99
5	1,2-DCE	38	<3	/	53	94
6	/	29	/	trace	68	97
7	2-Me-THF	12	/	trace	71	83
8	*o*-DCB	24	3	96	69	69
9	DMF	/	/	/	100	100
10	AcCN	18	/	4	88	100
11	**$PhCF_3$**	**46**	**6**	**/**	**42**	**94**
12	*n*-hexane	17	/	93	76	76

Table S2. Full solvent screen for C–H arylation of *N*-Boc pyrrolidine derivative **1**. Reaction scale: 0.20 mmol. [a] Calculated by ^{1}H NMR spectroscopy using 1,3,5-trimethoxybenzene as internal standard.

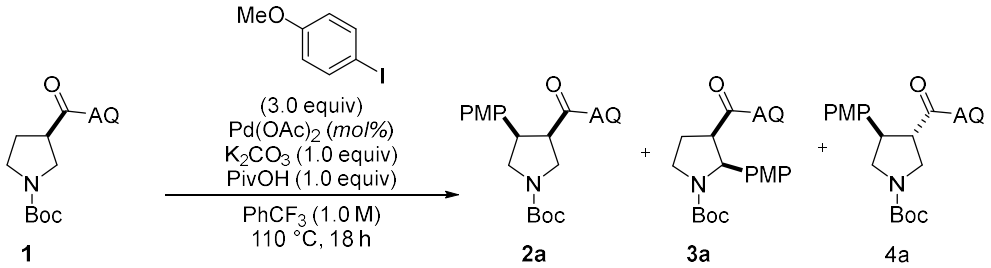
Optimization of Reagent Equivalents, Reaction Concentration, Temperature and Time (Table S3)



entry	equiv K_2CO_3	equiv PivOH	concn. (M)	temp (°C)	time (h)	yield (%)[a] 2a	3a	4a	1	tot
1	2.0	0.3	0.3	110	18	46	6	/	42	94
2	1.0	0.3	0.3	110	18	48	4	/	36	88
3	1.0	1.0	0.3	110	18	49	5	/	44	98
4	1.0	2.0	0.3	110	18	27	9	/	56	92
5	1.0	1.0	0.1	110	18	32	6	/	53	91
6	**1.0**	**1.0**	**1.0**	**110**	**18**	**66**	**3**	**/**	**22**	**91**
7	1.0	1.0	2.0	110	18	65	3	/	24	92
8	2.0	2.0	1.0	110	18	50	3	/	38	91
9	1.0	1.0	1.0	110	24	65	5	5	24	99
10	1.0	1.0	1.0	120	18	61	5	3	20	89
11	1.0	1.0	1.0	130	18	60	6	5	20	91

Table S3. Optimization of continuous factors for C–H arylation of *N*-Boc pyrrolidine derivative **1**. Reaction scale: 0.2 mmol. [a] Calculated by ^{1}H NMR spectroscopy using 1,3,5-trimethoxybenzene as internal standard.

Optimization of Catalyst Loading (Table S4)

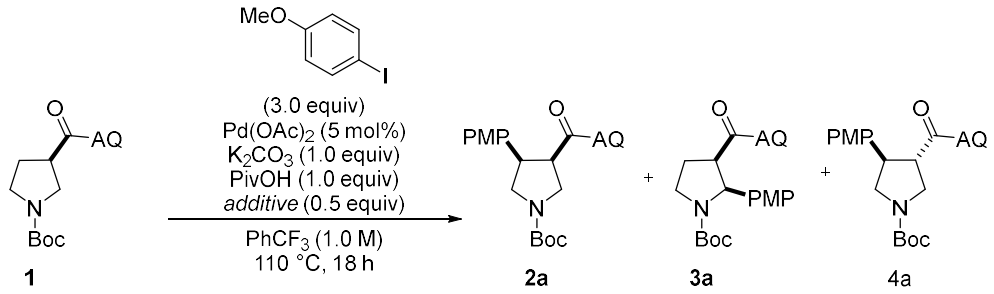


entry	cat. loading (mol%)	yield (%)[a] 2a	3a	4a	1	tot
1	**5.0**	**66**	**3**	**/**	**22**	**91**
2	2.5	45	2	/	47	94
3	10.0	61	5	/	15	81
4[b]	5.0	66	3	/	24	94
5[c]	5.0	62	traces	/	21	84

Table S4. Optimization of catalyst loading for C–H arylation of *N*-Boc pyrrolidine derivative **1**. Reaction scale: 0.2 mmol. [a] Calculated by ^{1}H NMR spectroscopy using 1,3,5-trimethoxybenzene as internal standard. [b] $Pd(TFA)_2$ 5 mol%. [c] $Pd(OPiv)_2$ 5 mol%.

Additive Screening (Table S5)

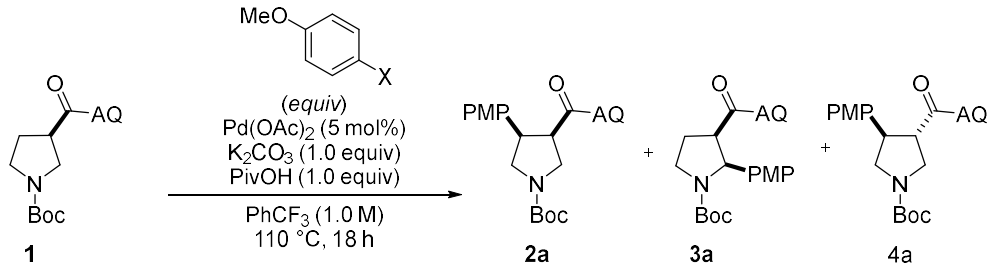
Various additives, which have been reported in the literature to favor the C(sp^3)–H functionalization on different systems, were investigated for effect on yield, but they did not lead to improvements.



entry	additive	yield (%)[a]				
		2a	3a	4a	1	tot
1	**/**	**66**	**4**	/	**24**	**94**
2	DMSO	44	2	/	44	90
3	KF	57	3	/	31	91
4	LiCl	23	/	/	72	95
5	CsF	57	3	/	37	97
6	TBAC	7	/	/	93	100
7	DMF	16	/	/	82	98
8	NMP	46	2	/	47	95
9	benzoquinone	36	/	/	55	91
10	$Mn(OAc)_2$	54	2	/	36	92
11	$Cu(OAc)_2$	45	/	/	45	90
12[b]	HFIP	58	/	5	27	90
13	methyl *p*-tolylsulfide	37	/	/	59	96

Table S5. Additive screen for C–H arylation of *N*-Boc pyrrolidine derivative **1**. Reaction scale: 0.2 mmol. [a] Calculated by ^{1}H NMR spectroscopy using 1,3,5-trimethoxybenzene as internal standard. [b] K_2CO_3 (1.2 equiv).

Optimization of Coupling Partner (Table S6)

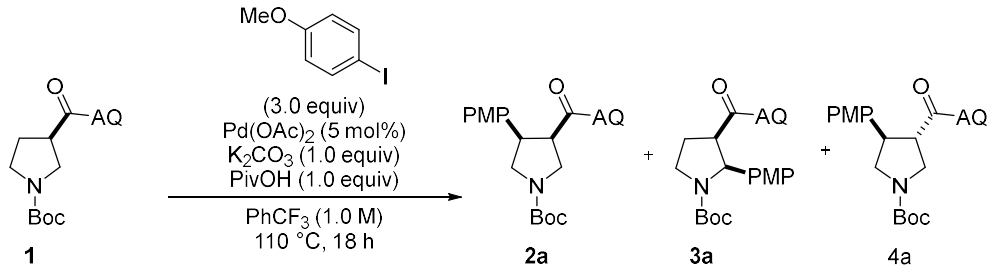


entry	X (equiv)	yield (%)[a]				
		2a	3a	4a	1	tot
1	**I (3.0)**	**66**	**3**	**/**	**22**	**91**
2	I (2.5)	59	4	/	37	100
3	I (2.5)	53	3	/	39	95
4[b]	Br (3.0)	12	/	/	81	93

Table S6. Investigations into coupling partners. Reaction scale: 0.2 mmol. [a] Calculated by ^{1}H NMR spectroscopy using 1,3,5-trimethoxybenzene as internal standard. [b] Concentration = 2.0 M.

Investigations on the Effect of H_2O (Table S7)

Early results showed variable yields, which was ascribed to differences in the level of ambient humidity during the reaction set-up. To systematically investigate the effect of moisture on the reaction outcome, the following experiments were performed, in which different levels of "dry" conditions were compared. These results suggest a detrimental effect of moisture on the reaction yield, which can be avoided by flame-drying K_2CO_3.

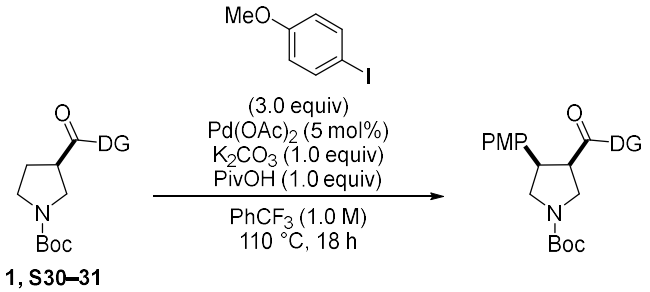


entry	yield (%)[a]				
	2a	**3a**	**4a**	**1**	**tot**
1	**66**	**3**	**/**	**22**	**91**
2	57	3	/	32	92
3	60	3	/	30	93
4	**65**	**3**	**/**	**27**	**93**
5	62	2	/	25	89
6	56	2	/	37	95
7	64	2	/	18	84

Table S7. Effect of ambient humidity on C–H arylation of *N*-Boc pyrrolidine derivative **1**. Reaction scale: 0.2 mmol. Relative humidity: 70%, measured by hygrometer, unless stated. [a] Calculated by ^{1}H NMR spectroscopy using 1,3,5-trimethoxybenzene as internal standard.

Entry 1: Control experiment in non-dried conditions. Relative humidity: 45%.
Entry 2: The yield obtained in the presence of higher external humidity (70% against 45%) was significantly lower.
Entry 3: K_2CO_3 was flame-dried before being added to a flame-dried reaction tube. A slight increase of the yield was observed.
Entry 4: K_2CO_3 was added from the reagent bottle to the reaction tube and then flame-dried before the addition of all the other substances. An improved yield of 65% (comparable to that previously obtained with 45% humidity, entry 1) was observed.
Entry 5: Same of entry 4, but 1.0 equiv of water was added to the reaction. This small amount of water did not seem to affect significantly the yield, although a slight decrease was observed.
Entry 6: Same of entry 4, but 10.0 equiv of water were added to the reaction. The yield was found to be similar to that observed at approximately 70% relative humidity.
Entry 7: Same of entry 4, but 1.2 equiv of K_2CO_3 were used to investigate the effect of flame-drying operation on the mass of the base. It was found that the slight increase in the base loading did not improve the reaction under otherwise equal conditions.

Comparison of Different Directing Groups (Table S8)



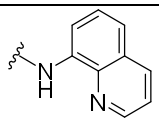
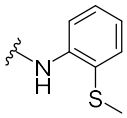
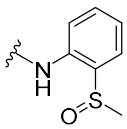
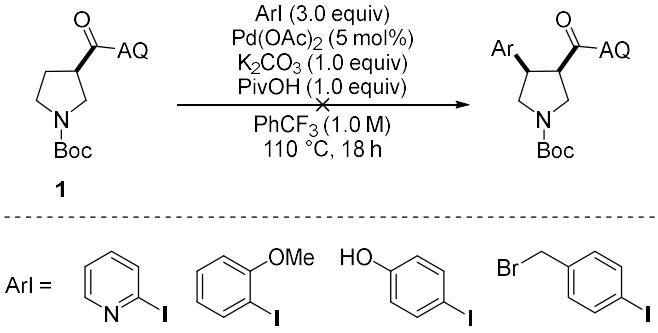
entry	DG	RSM (%)[a]	Product yield (%)[a]
1	 **1**	22	66
2	 **S30**	83	<10
3	 **S31**	96	-

Table S8. Comparison of different bidentate directing groups under optimum conditions. Reaction scale: 0.2 mmol. [a] Calculated by ^{1}H NMR spectroscopy using 1,3,5-trimethoxybenzene as internal standard.

Unsuccessful Aryl Iodides

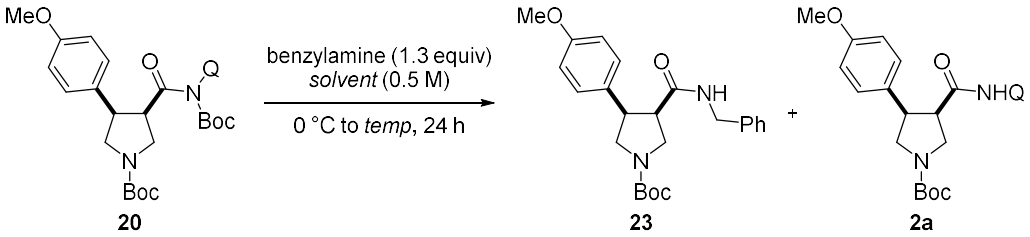
The following aryl iodides were unsuccessful under standard C–H arylation conditions, giving less than 10% conversion.



Optimization of Directing Group Removal from *N*-Boc Amides 20 and 21 to Access Pyrrolidine Derivatives 23–25

Transamidation of *N*-Boc Amide 20 with Benzylamine

Transamidation of activated amide **20** could be achieved using benzylamine. Aminoquinoline amide **2a** was always observed as a minor component of the reaction mixture. The reaction was optimized for solvent and temperature in order to maximise the yield of amide **23**.

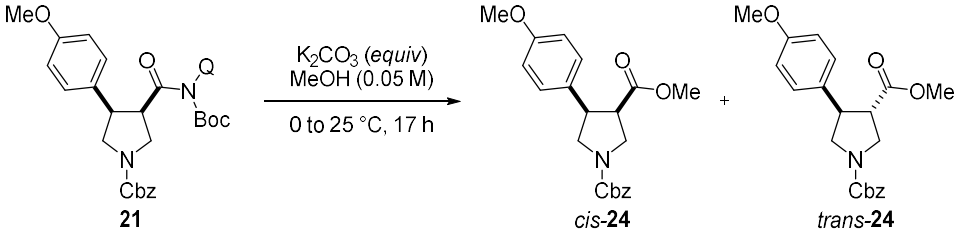


entry	temp (°C)	solvent	20 (%)[a]	23 (%)[a]	2a (%)[a]
1	45	CH_2Cl_2	37	37	25
2	60	CH_2Cl_2	27	44 (44)[b]	29
3[c]	**60**	**toluene**	**3**	**71 (69)[b]**	**26**

Table S9. Optimization of transamidation of *N*-Boc amide **20**. [a] Relative composition calculated by ^{1}H NMR spectroscopy on the crude reaction mixture. [b] Isolated yield. [c] 1.5 equiv of benzylamine.

Esterification of *N*-Boc Amide 21 with MeOH

Formation of ester **24** from activated amide **21** occurred with some epimerization. However, no reaction occurred at 0 °C. Halving the equivalents of K_2CO_3 resulted in reduced conversion and lower *dr* (entry 2).

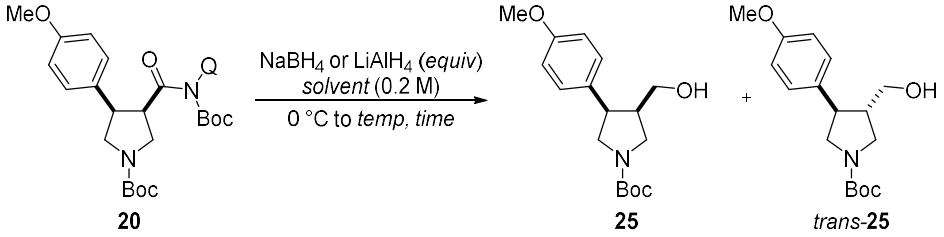


entry	K_2CO_3 equiv	SM conversion (%)[a]	*dr cis:trans* (%)[a]
1	**2.0**	**94 (85)[b]**	**7:3**
2	1.0	51	6:4

Table S10. Esterification of *N*-Boc amide **21**. [a]Calculated by ^{1}H NMR spectroscopy on the crude reaction mixture. [b] Combined isolated yield (56% of *cis*-**24** and 29% of *trans*-**24**).

Reduction of *N*-Boc Amide 20 to alcohol 25

Reduction of *N*-Boc amide **20** could be achieved using nucleophilic hydride reagents. However, reduction with $NaBH_4$ was accompanied by the formation of small amounts of epimerized *trans*-**25**. The reaction was optimized to improve yield and selectivity. Pleasingly, the use of $LiAlH_4$ resulted in the formation of *cis*-alcohol **25** in 76% as a single stereoisomer.



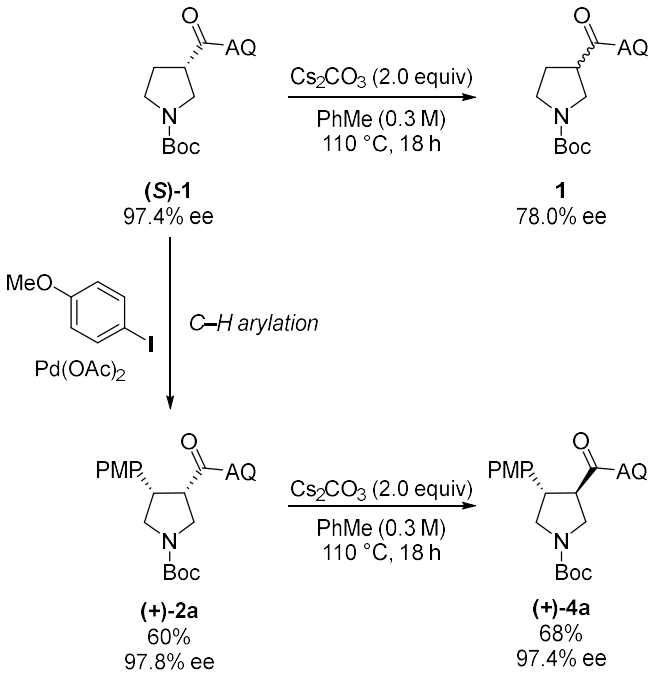
20 **25** *trans*-**25**

entry	reducing agent (equiv)	solvent	temp (°C)	time (h)	25 (%)[a]	*dr cis:trans*[b]
1	$NaBH_4$ (2.0)	EtOH	25	24	20	9:1
2	$NaBH_4$ (5.0)	MeOH	25	24	-	-
3	$NaBH_4$ (2.0)	EtOH	40	24	45	7:3
4	$NaBH_4$ (5.0)	EtOH	40	24	81	8:2
5	**$LiAlH_4$ (4.0)**	**THF**	**25**	**0.5**	**76**	**>50:1**

Table S11. Optimization of reduction of *N*-Boc amide **20**. [a] Isolated yield. [b] Calculated by ^1H NMR spectroscopy on the isolated product. [c]

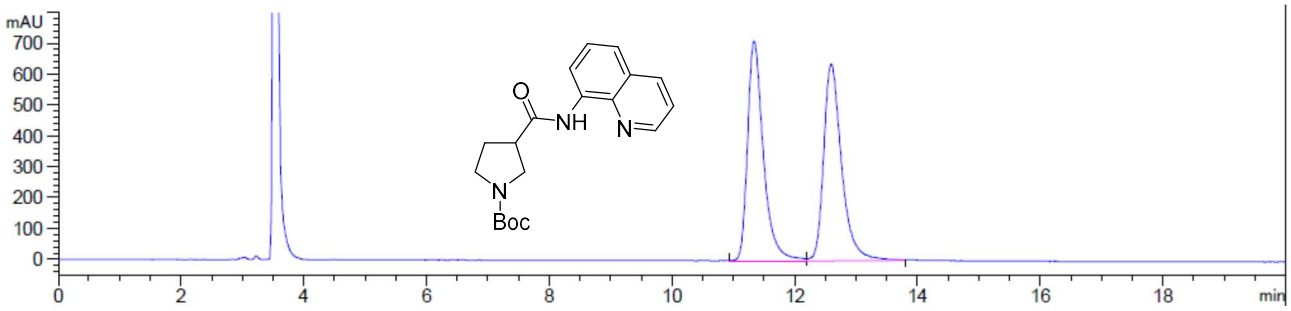
HPLC Traces for Racemic and Enantioenriched Pyrrolidine Derivatives 1, 2a and 4a

In order to ensure there was no loss of enantiopurity in the products during the C–H arylation reaction, as well as to investigate the base-mediated epimerisation of arylated pyrrolidine derivates, the ee of enantioenriched amide **(*S*)-1** and both enantioenriched *cis*- and *trans*-arylated (4-methoxyphenyl)pyrrolidine derivatives **(+)-2a** and **(+)-4a** were determined by chiral HPLC.



tert-Butyl (±)-3-(quinolin-8-ylcarbamoyl)pyrrolidine-1-carboxylate (1)

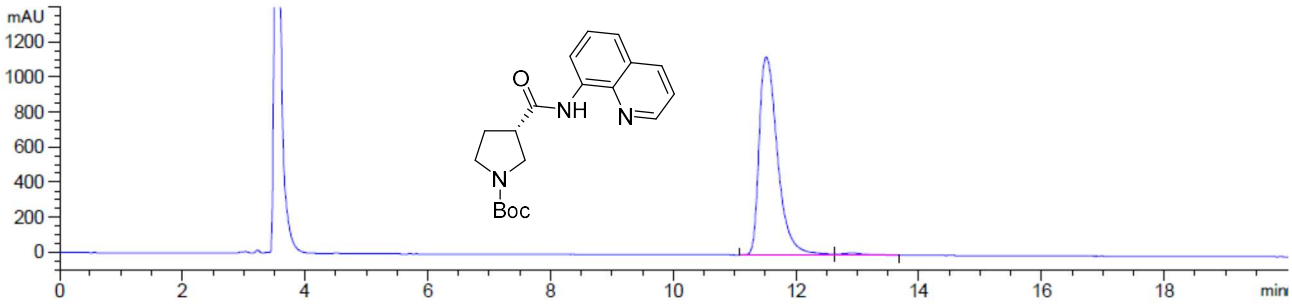
Conditions: Chiralpak IA 3-column, 90:10 *n*-hexane:*i*-PrOH, flow rate: 1 mL·min^{-1}, 35 ºC. UV detection wavelength: 210.4 nm.



Signal 3: DAD1 C, Sig=210,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.338	VV	0.2693	1.27653e4	711.69177	49.5007
2	12.595	VB	0.3081	1.30228e4	638.10852	50.4993
Totals :				2.57880e4	1349.80029	

tert-Butyl (–)-(*S*)-3-(quinolin-8-ylcarbamoyl)pyrrolidine-1-carboxylate ((*S*)-1)

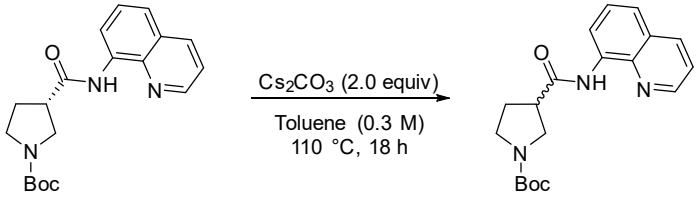


Signal 3: DAD1 C, Sig=210,4 Ref=off

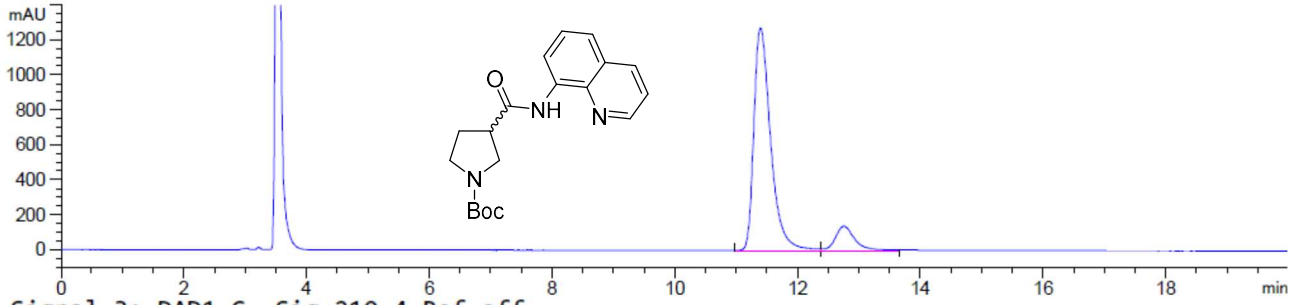
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.513	MM	0.3493	2.38111e4	1136.07556	98.7011
2	12.910	MM	0.4232	313.34824	12.34031	1.2989
Totals :				2.41244e4	1148.41587	

***ee* = 97.4%**

Racemization of *tert*-butyl (*S*)-3-(quinolin-8-ylcarbamoyl)pyrrolidine-1-carboxylate ((*S*)-1)



A flame-dried reaction tube was charged with enantioenriched amide **(*S*)-1** (68.3 mg, 0.20 mmol) and Cs_2CO_3 (130 mg, 0.40 mmol). The reaction vessel was sealed and purged with argon, then toluene (670 μL, 0.3 M) was added by syringe. The reaction tube was then placed in a preheated oil bath and stirred at 110 ºC for 18 h. The reaction mixture was then allowed to cool to rt and EtOAc (5 mL) was added. The resulting mixture was filtered through a pad of Celite, eluting with further EtOAc (2 × 5 mL). The solvent was removed under reduced pressure and the crude material was purified by flash column chromatography (20% acetone/hexane). The product containing fractions were combined and the solvent was removed under reduced pressure. Et_2O (5 mL) and pentane (5 mL) were added and the solvent was removed under reduced pressure to afford amide **1** as a white solid (67.9 mg, quant., 78% *ee*).



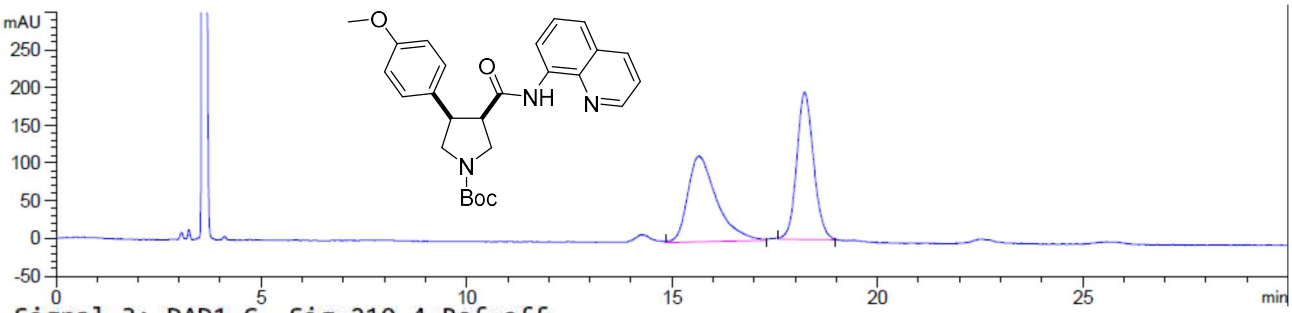
Signal 3: DAD1 C, Sig=210,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.402	VV	0.2850	2.41145e4	1272.72388	88.9699
2	12.757	VV	0.3187	2989.60229	138.00783	11.0301
Totals :				2.71041e4	1410.73170	

***ee* = 78.0%**

tert-Butyl _cis_-(±)-3-(4-methoxyphenyl)-4-(quinolin-8-ylcarbamoyl)pyrrolidine-1-carboxylate (2a)

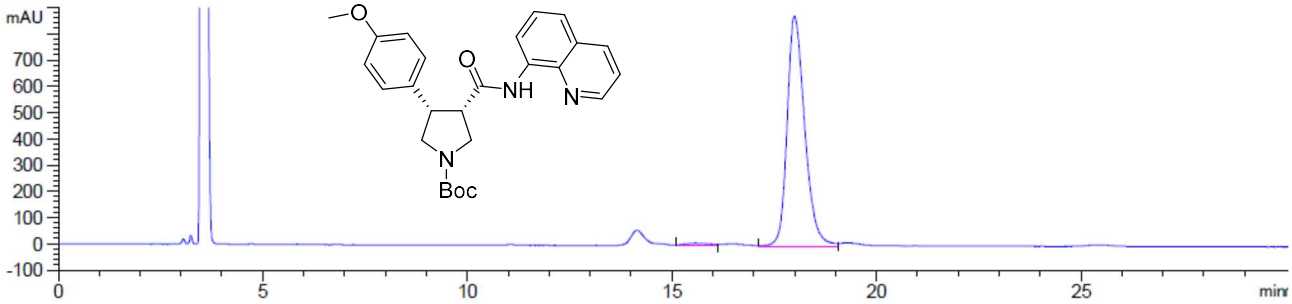
Conditions: Chiralpak IF 3-column, 80:20 *n*-hexane:*i*-PrOH, flow rate: 1 mL·min^{-1}, 35 ºC, UV detection wavelength: 210.4 nm.



Signal 3: DAD1 C, Sig=210,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	15.663	MM	0.8146	5550.24023	113.55860	49.9652
2	18.226	MM	0.4739	5557.96191	195.46326	50.0348
Totals :				1.11082e4	309.02186	

tert-Butyl (+)-(3*S*,4*S*)-3-(4-methoxyphenyl)-4-(quinolin-8-ylcarbamoyl)pyrrolidine-1-carboxylate ((+)-2a)



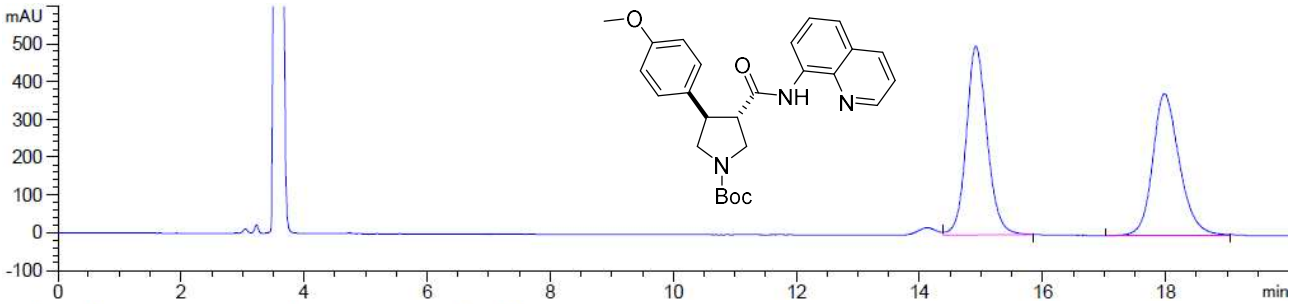
Signal 3: DAD1 C, Sig=210,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	15.569	MM	0.6005	279.84583	7.76737	1.0602
2	17.995	VV	0.4379	2.61167e4	875.85565	98.9398
Totals :				2.63966e4	883.62302	

***ee* = 97.8%**

tert-Butyl _trans_-(±)-3-(4-methoxyphenyl)-4-(quinolin-8-ylcarbamoyl)pyrrolidine-1-carboxylate (4a)

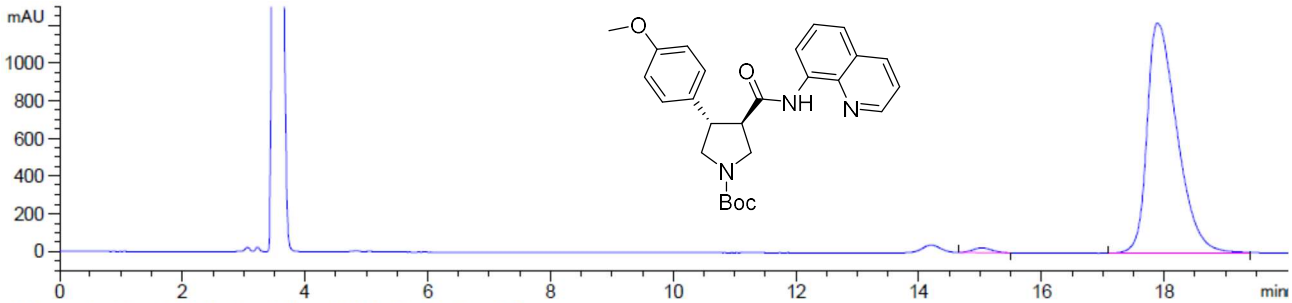
Conditions: Chiralpak IF 3-column, 80:20 *n*-hexane:*i*-PrOH, flow rate: 1 mL·min^{-1}, 35 ºC, UV detection wavelength: 210.4 nm.



Signal 3: DAD1 C, Sig=210,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	14.919	VB	0.3628	1.17787e4	500.01050	50.7780
2	17.982	VV	0.4441	1.14178e4	376.20358	49.2220
Totals :				2.31966e4	876.21408	

tert-Butyl (+)-(3_S_,4_R_)-3-(4-methoxyphenyl)-4-(quinolin-8-ylcarbamoyl)pyrrolidine-1-carboxylate ((+)-4a)



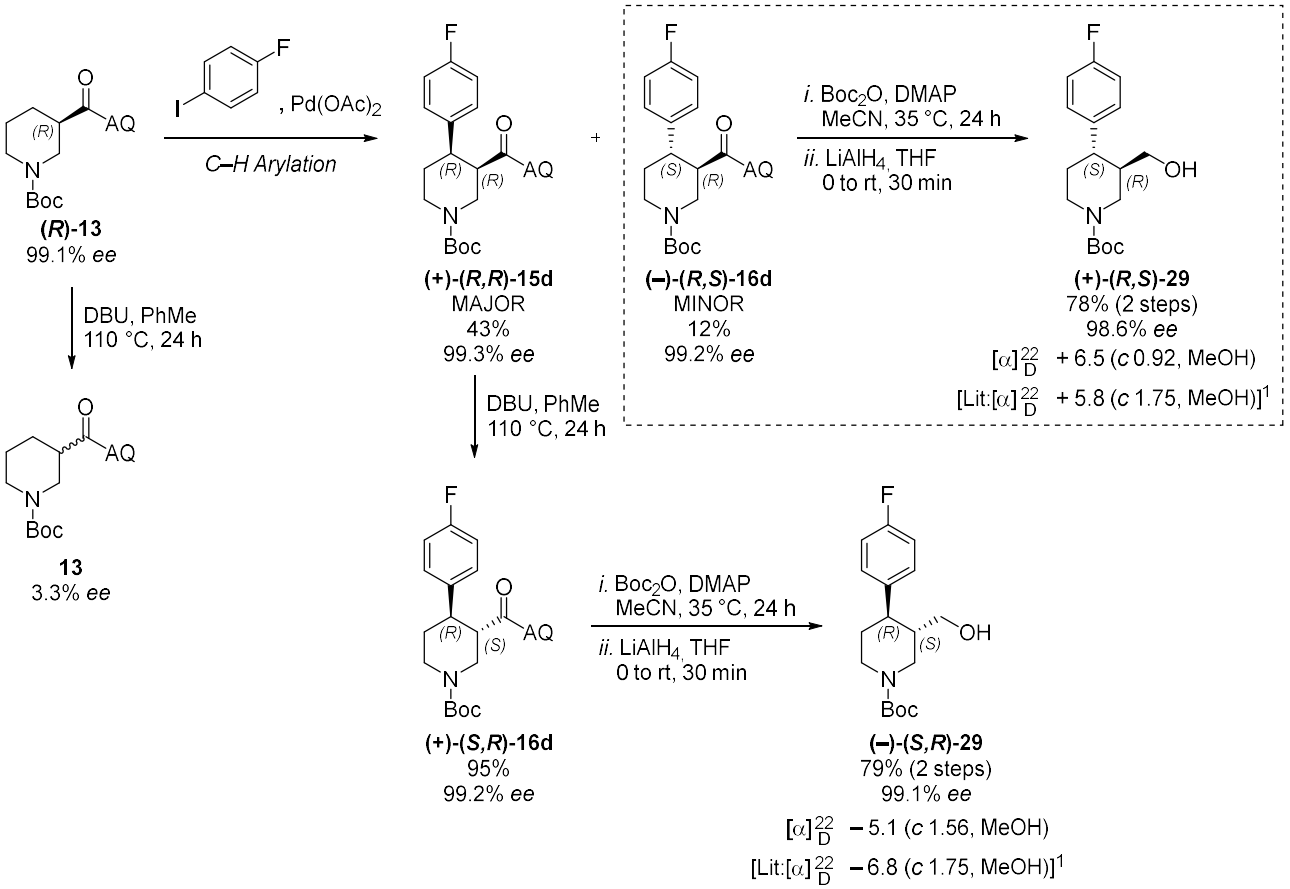
Signal 3: DAD1 C, Sig=210,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	15.035	MM	0.3622	552.23920	25.41263	1.3099
2	17.889	VV	0.4751	4.16078e4	1222.52466	98.6901
Totals :				4.21601e4	1247.93728	

***ee* = 97.4%**

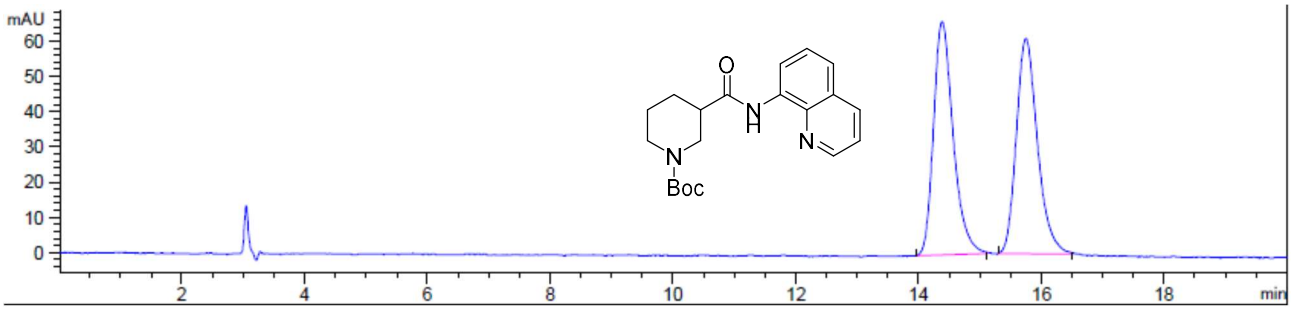
HPLC Traces for Racemic, Scalemic and Enantioenriched Piperidine Derivatives 13, 15–16d and 29

Enantioenriched piperidine derivatives **(*R*)-13**, **(+)-(*R*,*R*)-15d**, **(+)-(*S*,*R*)-16d** and **(–)-(*S*,*R*)-29**, isolated as intermediates in the formal stereocontrolled synthesis of (–)-paroxetine, were examined by chiral HPLC. These investigations also offered the opportunity to gain insight into the stereochemical outcome of the C–H arylation on the piperidine system, supporting the proposed formation of a *trans*-palladacycle.



tert-Butyl (±)-3-(quinolin-8-ylcarbamoyl)piperidine-1-carboxylate (13)

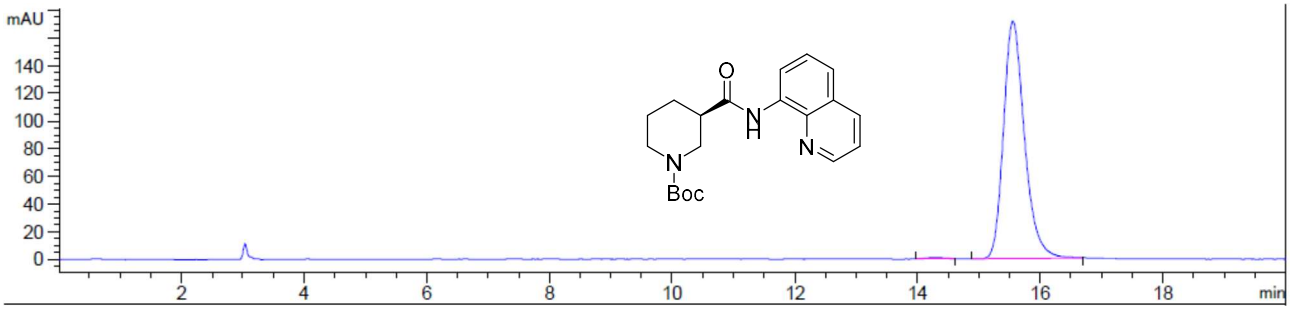
Conditions: Chiralpak IA 3-column, 95:5 *n*-hexane:*i*-PrOH, flow rate: 1 mL·min^{-1}, 35 ºC, UV detection wavelength: 210.4 nm.



Signal 3: DAD1 C, Sig=210,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	14.385	BB	0.3397	1472.82434	66.16891	50.1480
2	15.749	BB	0.3594	1464.13306	61.12620	49.8520
Totals :				2936.95740	127.29512	

tert-Butyl (–)-(*R*)-3-(quinolin-8-ylcarbamoyl)piperidine-1-carboxylate ((*R*)-13)

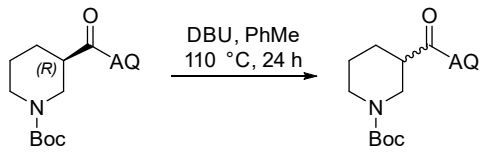


Signal 3: DAD1 C, Sig=210,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	14.276	MM	0.3115	19.52340	1.04475	0.4743
2	15.555	VB	0.3643	4096.96484	171.74301	99.5257
Totals :				4116.48825	172.78776	

_ee_ = 99.1%

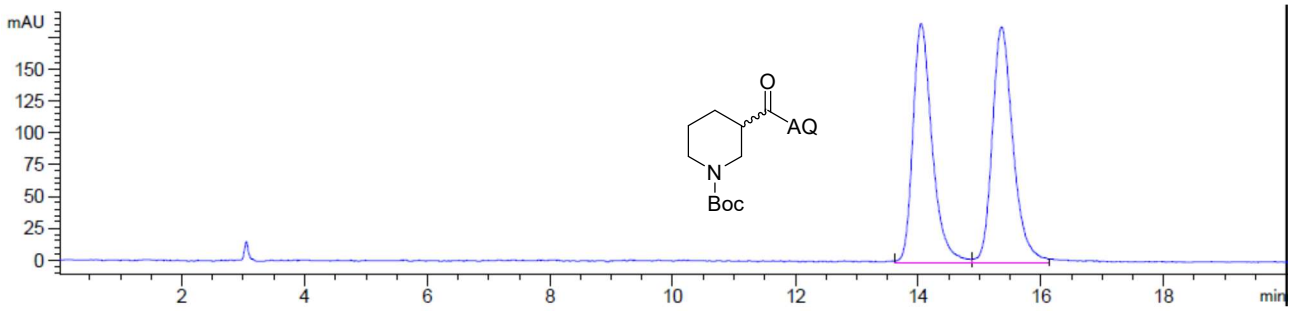
Racemization of (–)-(*R*)-3-(quinolin-8-ylcarbamoyl)piperidine-1-carboxylate ((*R*)-13)



(*R*)-13
99.1% *ee*

13
quant.
3.3% *ee*

A flame-dried reaction tube was charged with enantioenriched amide **(*R*)-13** (35.5 mg, 0.10 mmol) and 1,8-diazabicyclo(5.4.0)undec-7-ene (DBU, 45 μL, 0.30 mmol). The reaction vessel was sealed and purged with argon, then toluene (100 μL, 1.0 M) was added by syringe. The reaction tube was then placed in a preheated oil bath and stirred at 110 ºC for 24 h. The reaction mixture was then allowed to cool to rt and EtOAc (3 mL) and sat. aq. NH_4Cl (3 mL) were added. The phases were separated and the aqueous layer was extracted with EtOAc (3 × 5 mL). The combined organic extracts were dried with Na_2SO_4 and filtered. The solvent was removed under reduced pressure. Et_2O (3 mL) and pentane (3 mL) were added and the solvent was removed under reduced pressure to afford amide **13** as a pale brown solid (35.9 mg, quant., 3.3% *ee*).



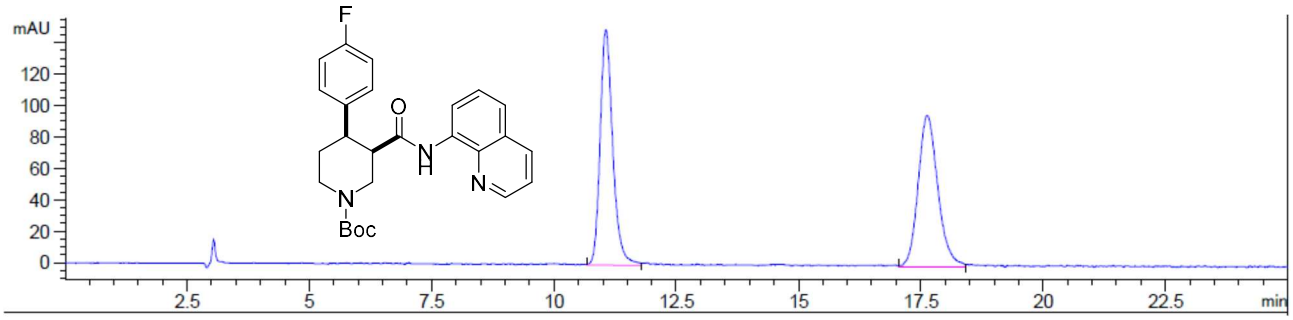
Signal 3: DAD1 C, Sig=210,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	14.049	VV	0.3310	4064.87427	187.46590	48.3355
2	15.361	VV	0.3442	4344.82520	184.89185	51.6645
Totals :				8409.69946	372.35774	

***ee* = 3.3%**

tert-Butyl _cis_-(±)-4-(4-fluorophenyl)-3-(quinolin-8-ylcarbamoyl)piperidine-1-carboxylate (15d)

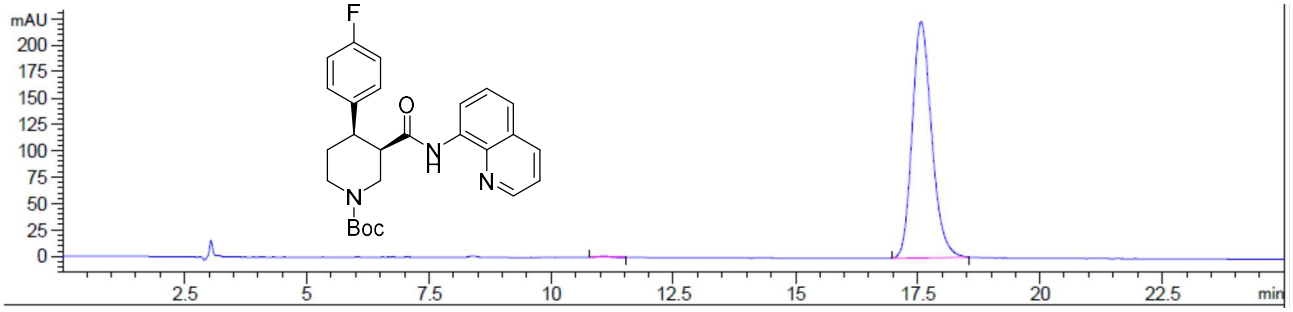
Conditions: Chiralpak IA 3-column, 85:15 *n*-hexane:*i*-PrOH, flow rate: 1 mL·min^{-1}, 35 ºC, UV detection wavelength: 210.4 nm.



Signal 3: DAD1 C, Sig=210,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.062	VV	0.2717	2695.62085	149.96115	49.9461
2	17.630	VV	0.3917	2701.43848	96.16893	50.0539
Totals :				5397.05933	246.13008	

tert-Butyl (+)-(_3R,4R_)-4-(4-fluorophenyl)-3-(quinolin-8-ylcarbamoyl)piperidine-1-carboxylate ((+)-15d)



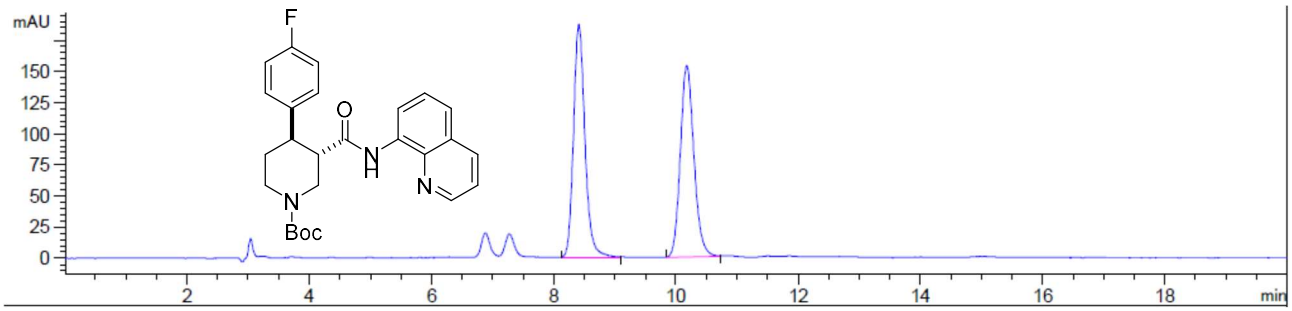
Signal 3: DAD1 C, Sig=210,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.088	BB	0.1912	20.81451	1.37068	0.3333
2	17.567	BB	0.4261	6223.61230	224.00349	99.6667
Totals :				6244.42682	225.37417	

***ee* = 99.3%**

tert-Butyl _trans_-(±)-4-(4-fluorophenyl)-3-(quinolin-8-ylcarbamoyl)piperidine-1-carboxylate (16d)

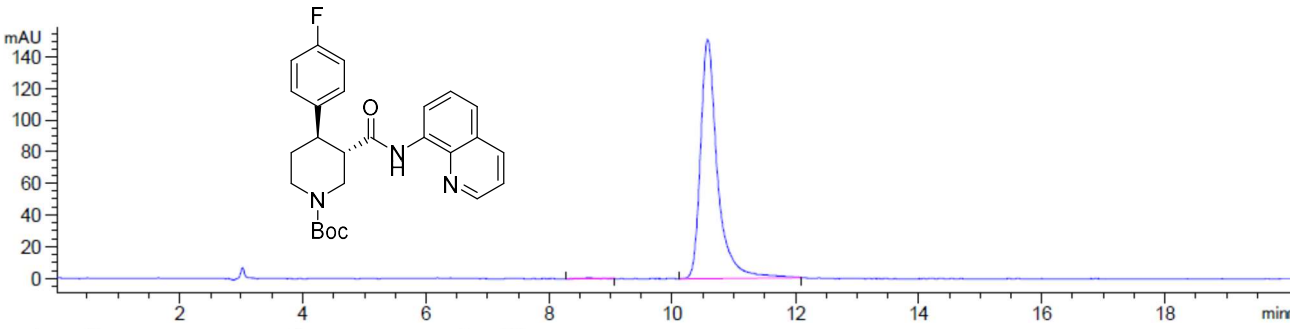
Conditions: Chiralpak IA 3-column, 85:15 *n*-hexane:*i*-PrOH, flow rate: 1 mL·min^{-1}, 35 ºC, UV detection wavelength: 210.4 nm.



Signal 3: DAD1 C, Sig=210,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.411	BB	0.1977	2434.44775	187.19498	50.7214
2	10.177	BB	0.2379	2365.19409	153.38963	49.2786
Totals :				4799.64185	340.58461	

tert-Butyl (+)-(*3S,4R*)-4-(4-fluorophenyl)-3-(quinoline-8-ylcarbamoyl)piperidine-1-carboxylate ((+)-16d)

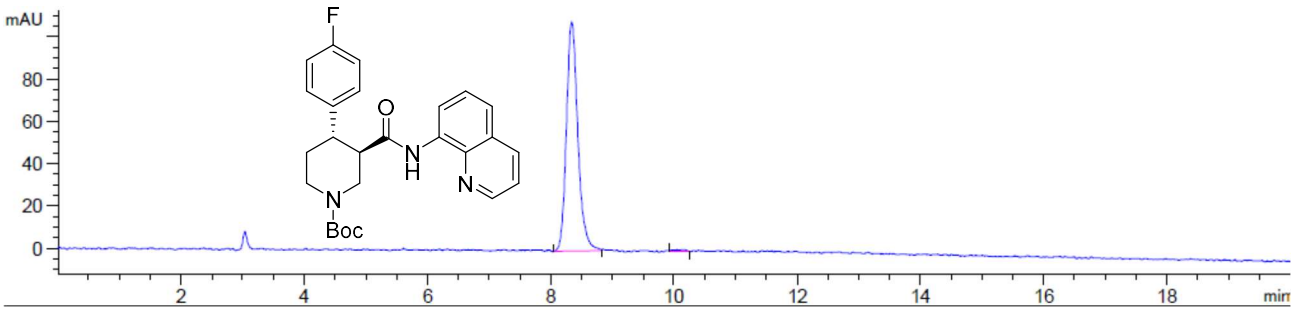


Signal 3: DAD1 C, Sig=210,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.651	MM	0.2176	9.08455	6.95668e-1	0.3108
2	10.575	MM	0.3204	2913.55933	151.54610	99.6892
Totals :				2922.64387	152.24176	

_ee_ = 99.4%

tert-Butyl (–)-(_3R,4S_)-4-(4-fluorophenyl)-3-(quinoline-8-ylcarbamoyl)piperidine-1-carboxylate ((–)-16d)



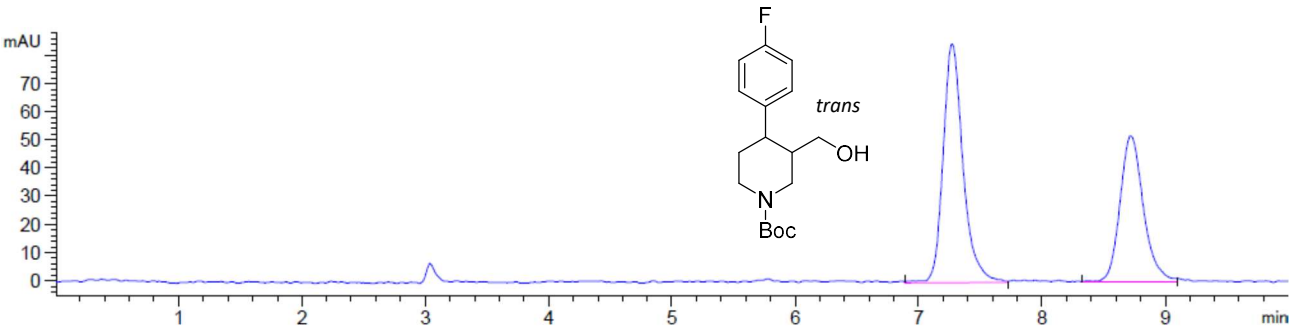
Signal 3: DAD1 C, Sig=210,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.342	MM	0.2150	1397.42517	108.34052	99.5792
2	10.147	MM	0.1757	5.90466	5.60225e-1	0.4208
Totals :				1403.32983	108.90075	

***ee* = 99.2%**

Scalemic Mixture of Enantioenriched Piperidines (–)-29 and (+)-29

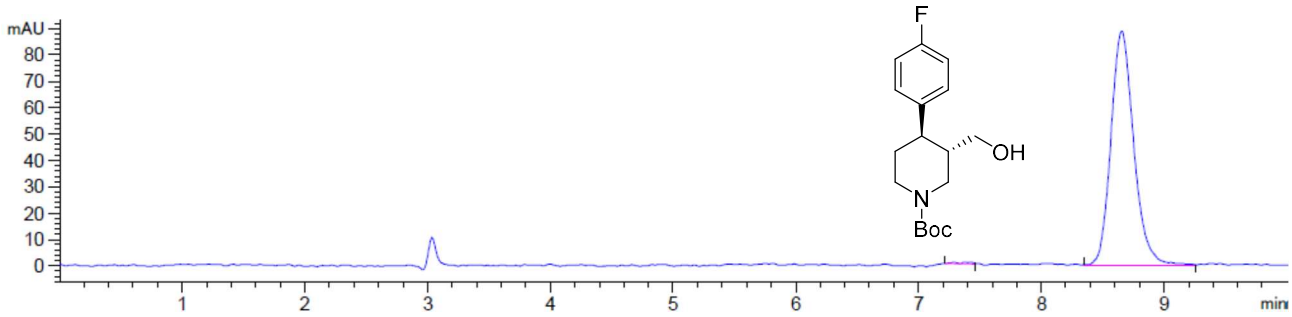
Conditions: Chiralpak IA 3-column, 90:10 *n*-hexane:*i*-PrOH, flow rate: 1 mL·min^{-1}, 35 ºC, UV detection wavelength: 210.4 nm.



Signal 3: DAD1 C, Sig=210,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.273	VV	0.1694	958.86566	85.10578	57.8307
2	8.721	VB	0.2040	699.19006	52.29891	42.1693
Totals :				1658.05573	137.40469	

***tert*-Butyl (–)-(*3S,4R*)-4-(4-fluorophenyl)-3-(hydroxymethyl)piperidine-1-carboxylate ((–)-29)**

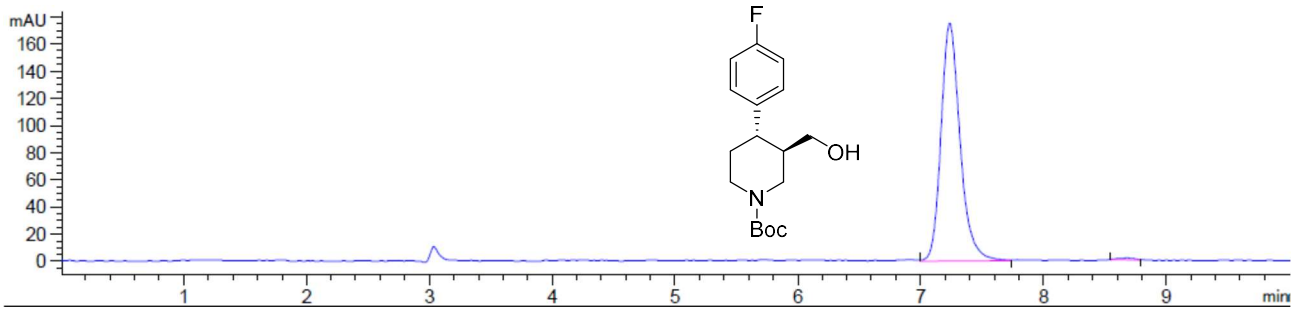


Signal 3: DAD1 C, Sig=210,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.429	MM	0.1304	5.20992	6.65965e-1	0.4498
2	8.655	MM	0.2161	1153.14832	88.92207	99.5502
Totals :				1158.35824	89.58804	

***ee* = 99.1%**

tert-Butyl (+)-(*3R,4S*)-4-(4-fluorophenyl)-3-(hydroxymethyl)piperidine-1-carboxylate ((+)-29)



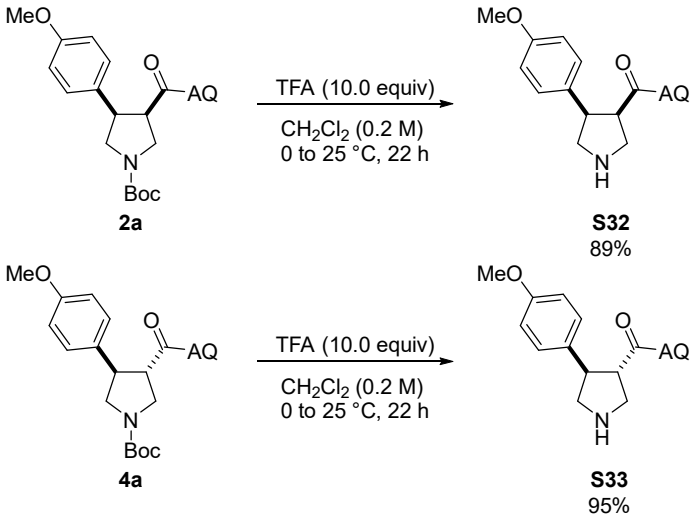
Signal 3: DAD1 C, Sig=210,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.237	VB	0.1638	1890.05115	175.22661	99.3085
2	8.678	MM	0.1633	13.16094	1.34361	0.6915
Totals :				1903.21209	176.57022	

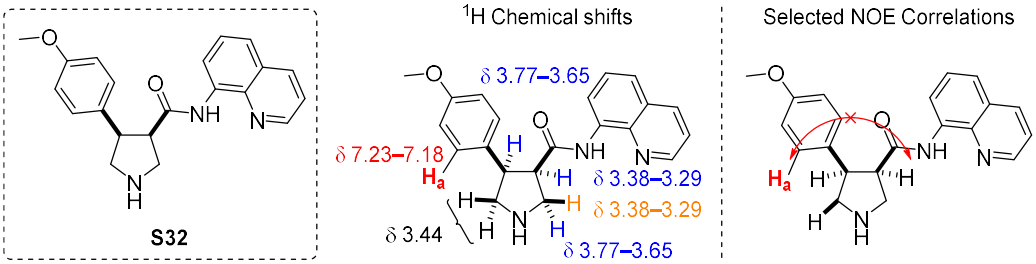
***ee* = 98.6%**

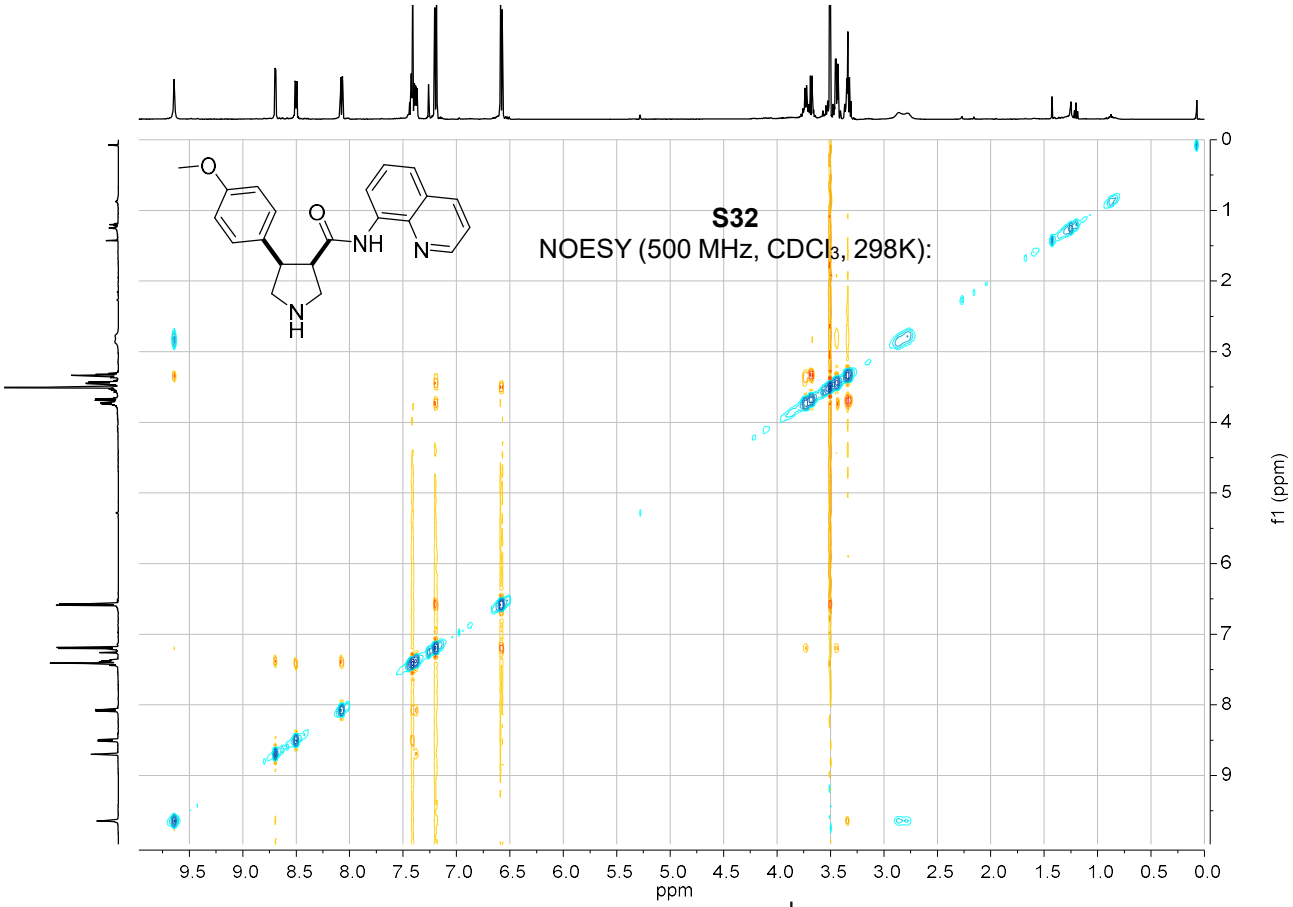
NMR Studies on the Stereochemistry of 3,4-Disubstituted Pyrrolidines 2a and 4a

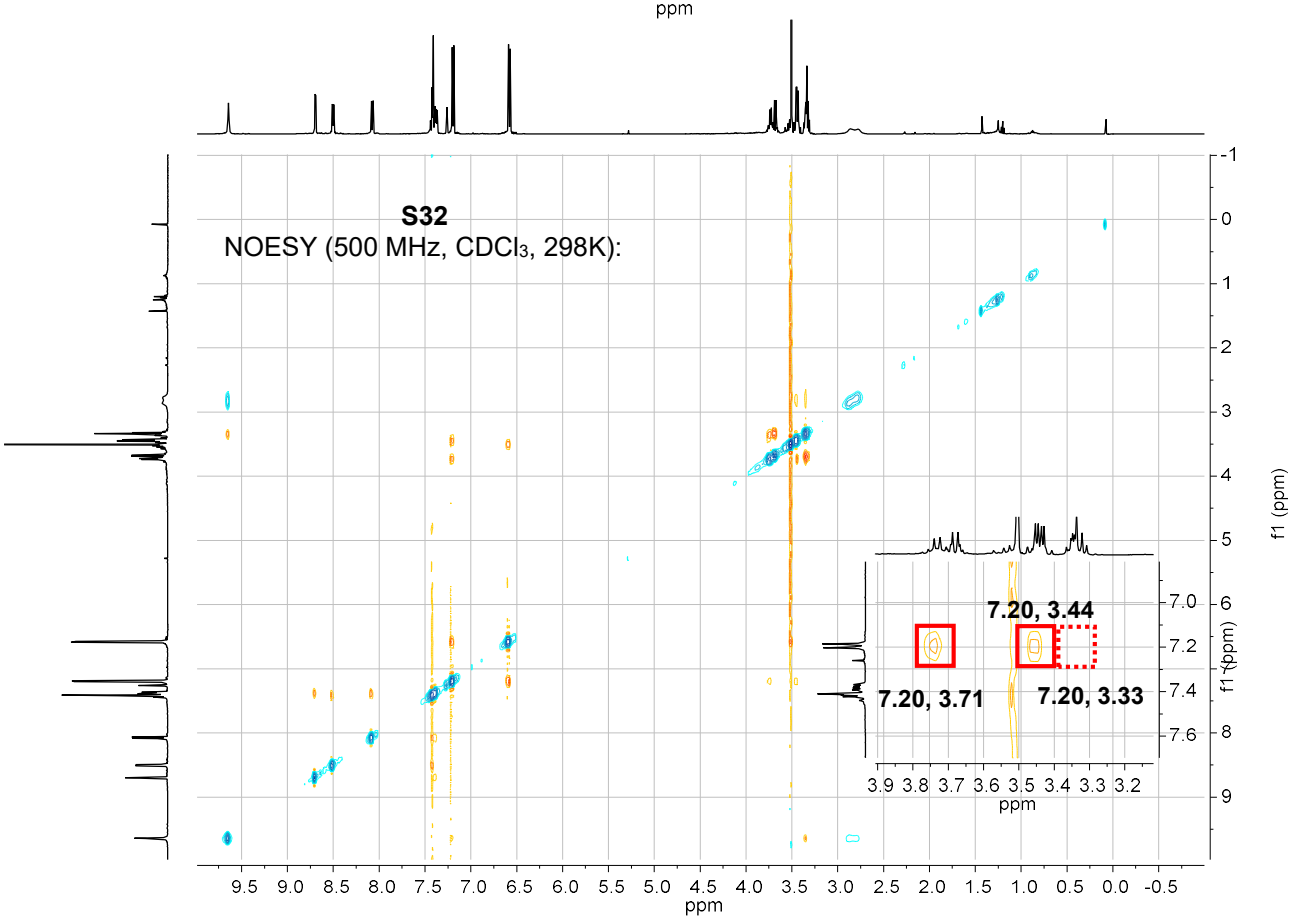
The relative configuration of 3,4-disubstituted pyrrolidine derivatives **2a** and **4a** was assigned on the basis of selective NOE experiments after Boc deprotection to give compounds **S32** and **S33** respectively.



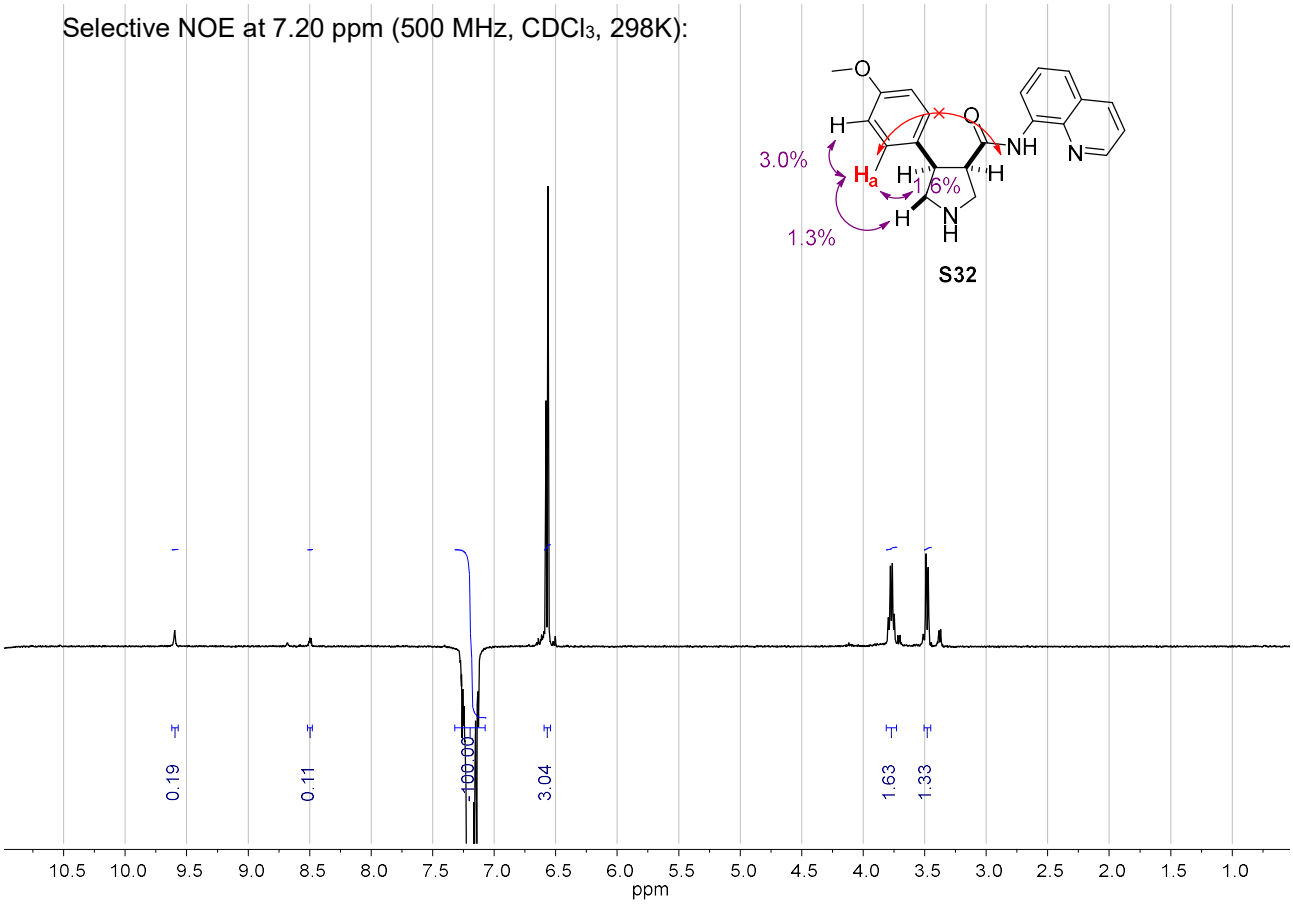
In the NOESY spectrum of N-H pyrrolidine derivative **S32**, the aromatic proton H_a (δ 7.20) correlates to nearby protons on the pyrrolidine ring, but no interaction was observed between this proton and the CHCO (δ 3.38–3.29). This is consistent with a *cis*-configuration. On the other hand for compound **S33**, a significant correlation was found between the same aromatic proton (δ 7.27) and the CHCO proton (δ 3.21–3.14), thus supporting a *trans*-configuration. These findings were further confirmed by selective NOE experiments in which the aromatic H_a proton was irradiated selectively, confirming the hypothesised *cis*- and *trans*-configuration of **S32** and **S33** respectively.

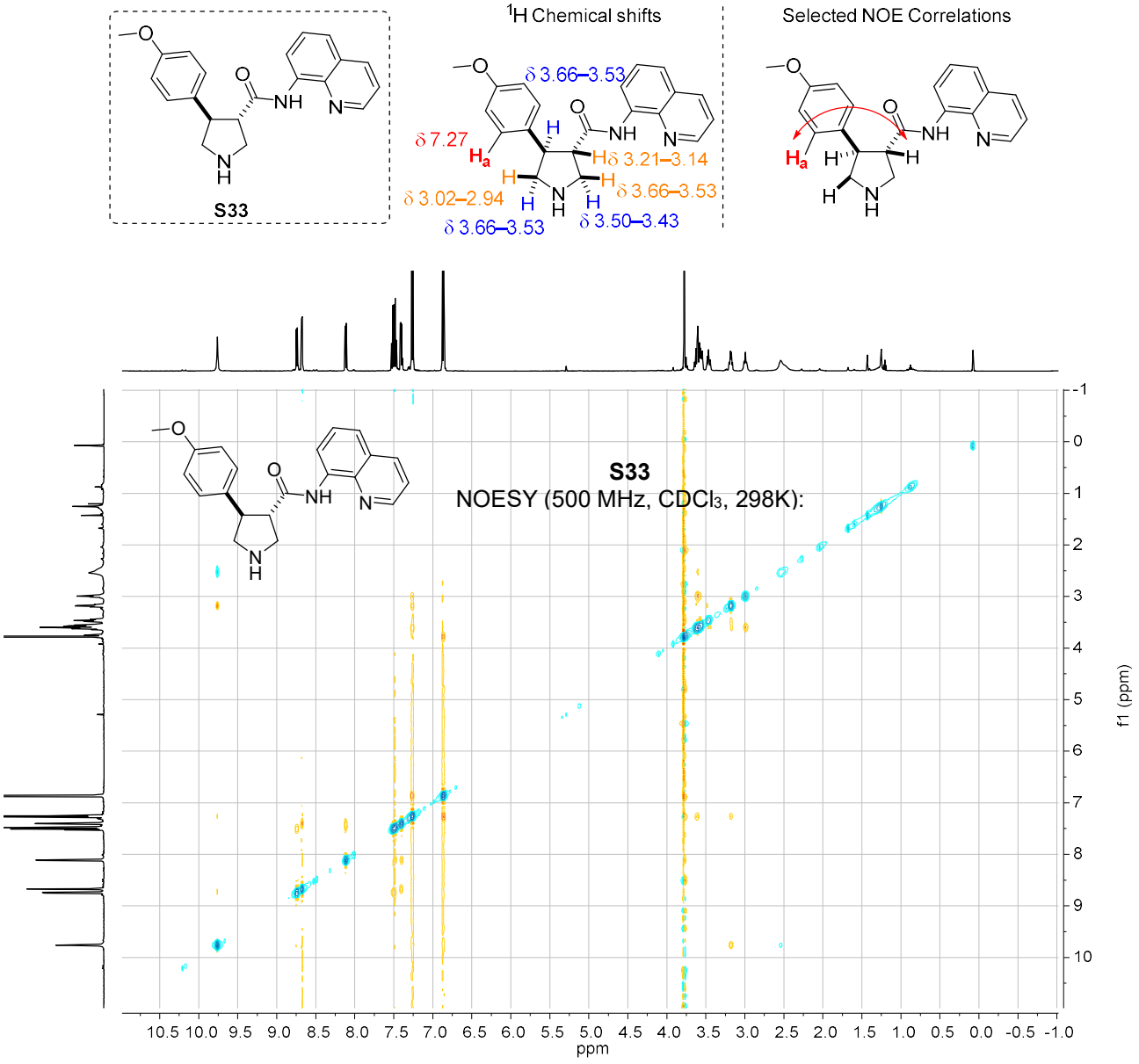



S32
NOESY (500 MHz, CDCl3, 298K):
NH
N
O
N
H
ppm
f1 (ppm)


S32
NOESY (500 MHz, CDCl3, 298K):
7.20, 3.44
7.20, 3.71
7.20, 3.33
ppm
f1 (ppm)

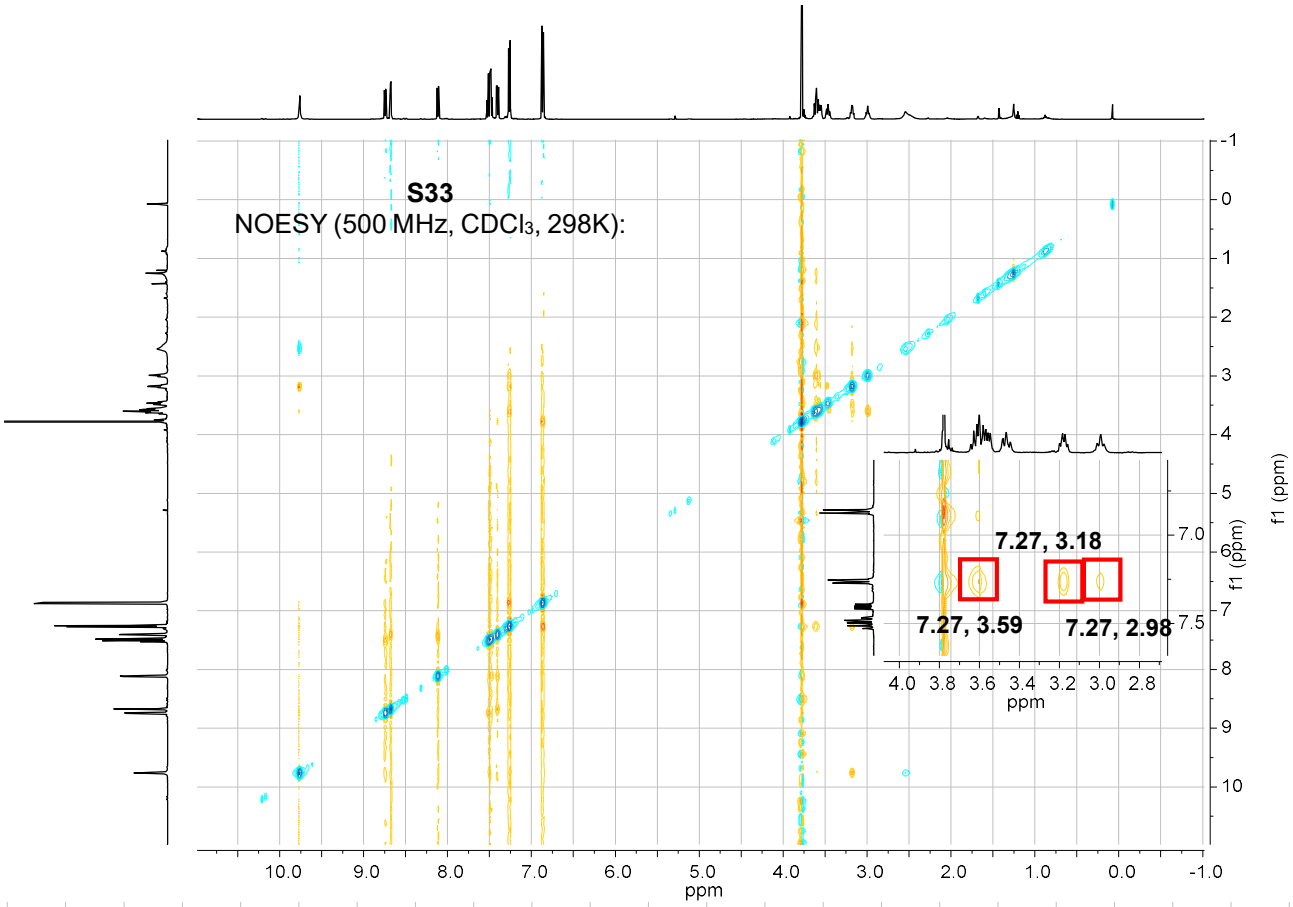
Selective NOE at 7.20 ppm (500 MHz, $CDCl_3$, 298K):



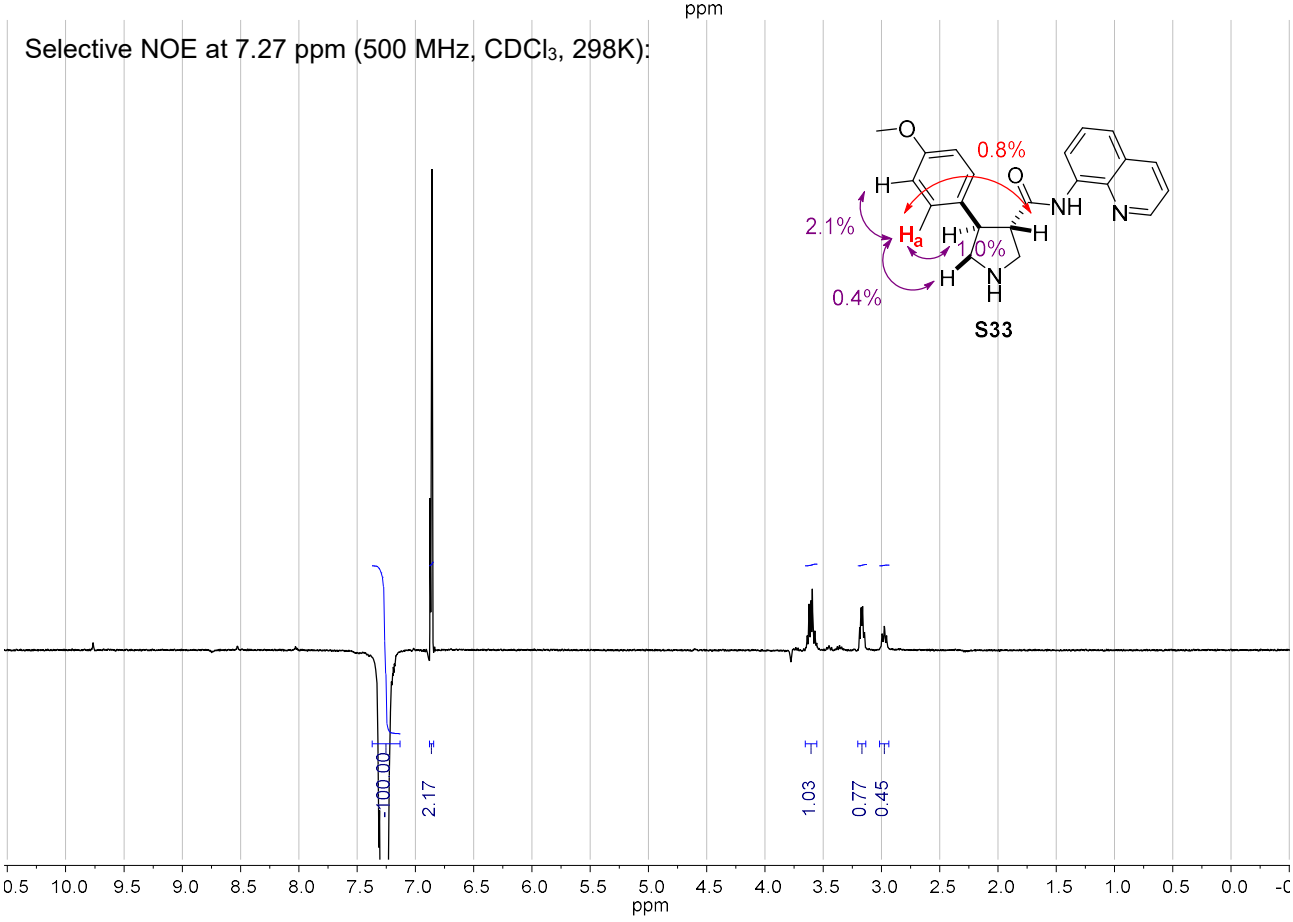

S33
^{1}H Chemical shifts
δ 3.66–3.53
δ 7.27
Ha
Hδ 3.21–3.14
δ 3.02–2.94
δ 3.66–3.53
δ 3.50–3.43
Selected NOE Correlations
S33
NOESY (500 MHz, CDCl3, 298K):
f1 (ppm)
ppm

S33

NOESY (500 MHz, $CDCl_3$, 298K):

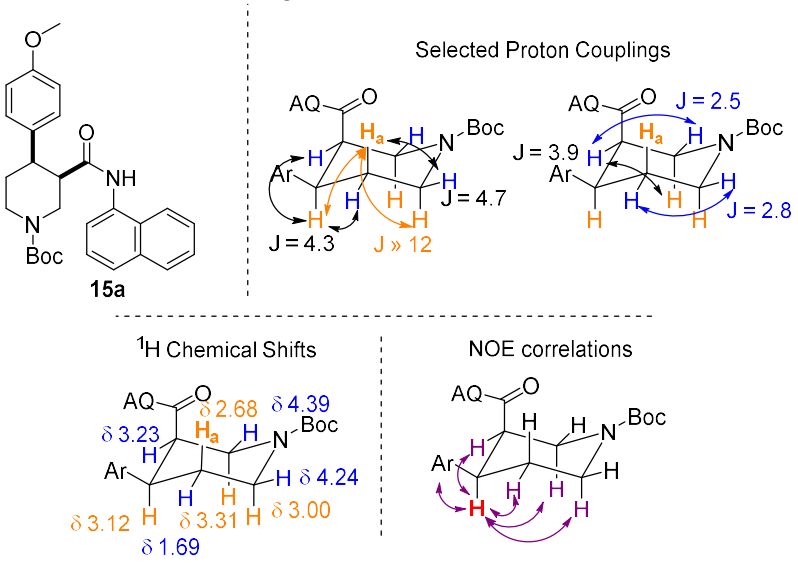


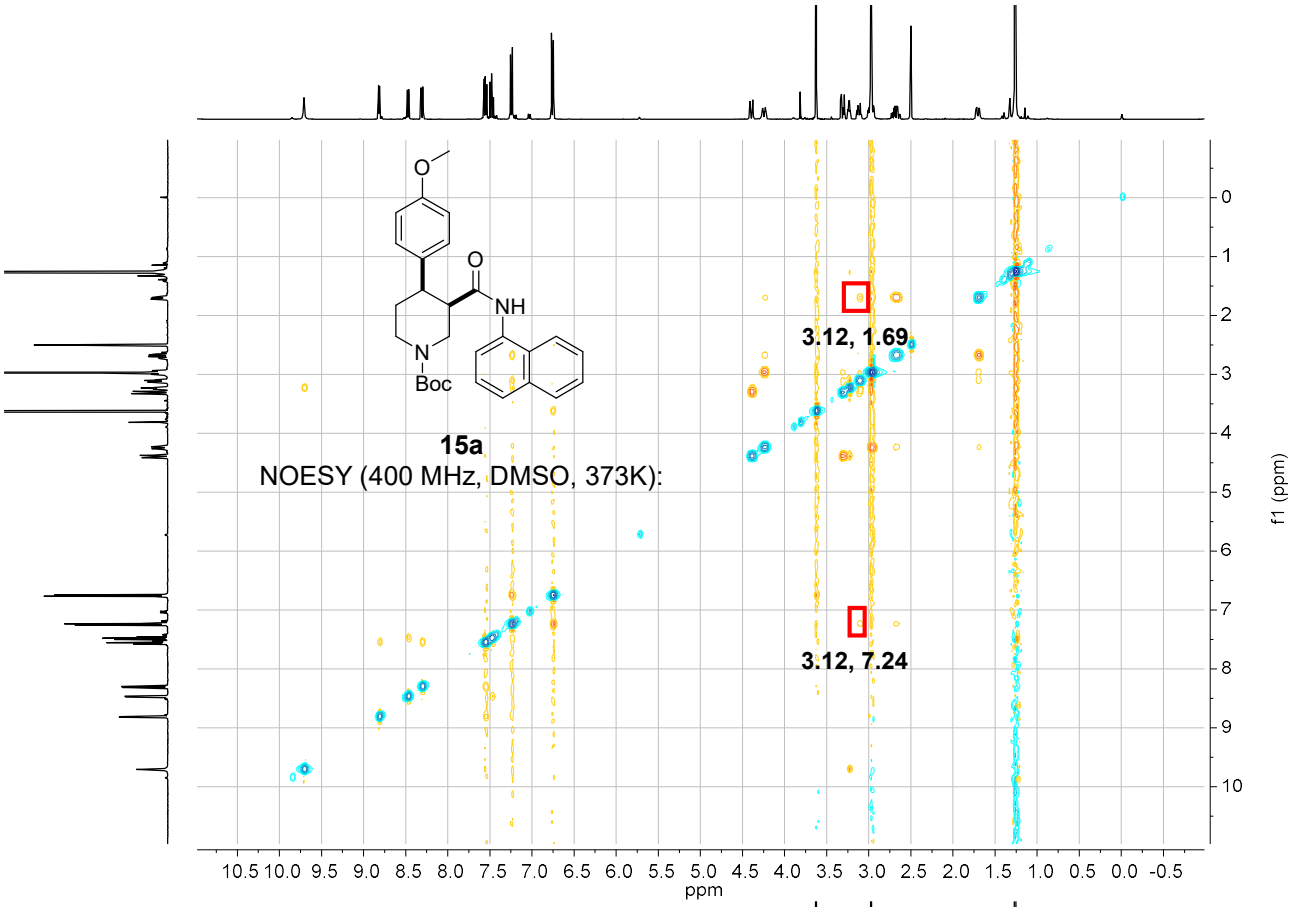
Selective NOE at 7.27 ppm (500 MHz, $CDCl_3$, 298K):

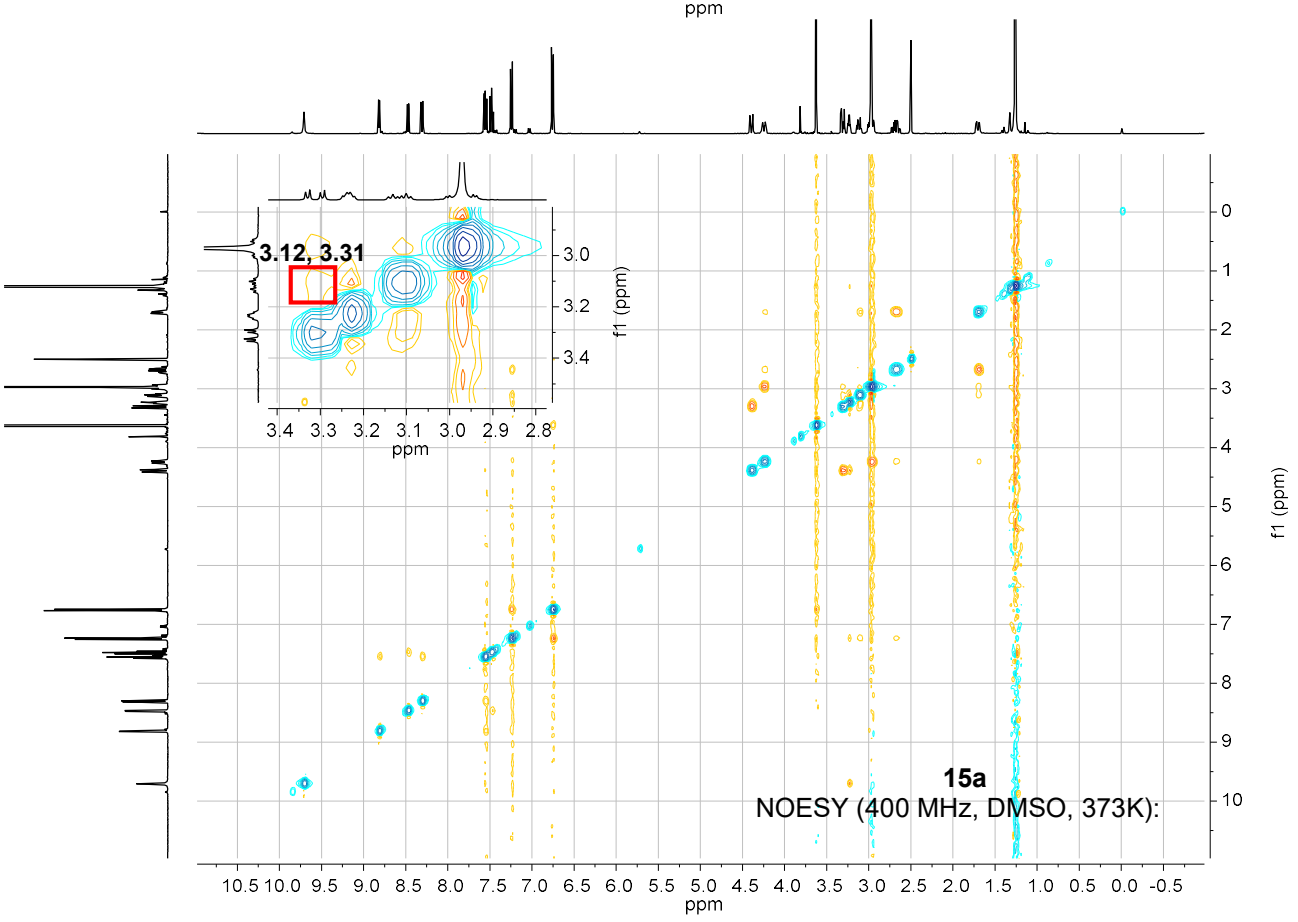


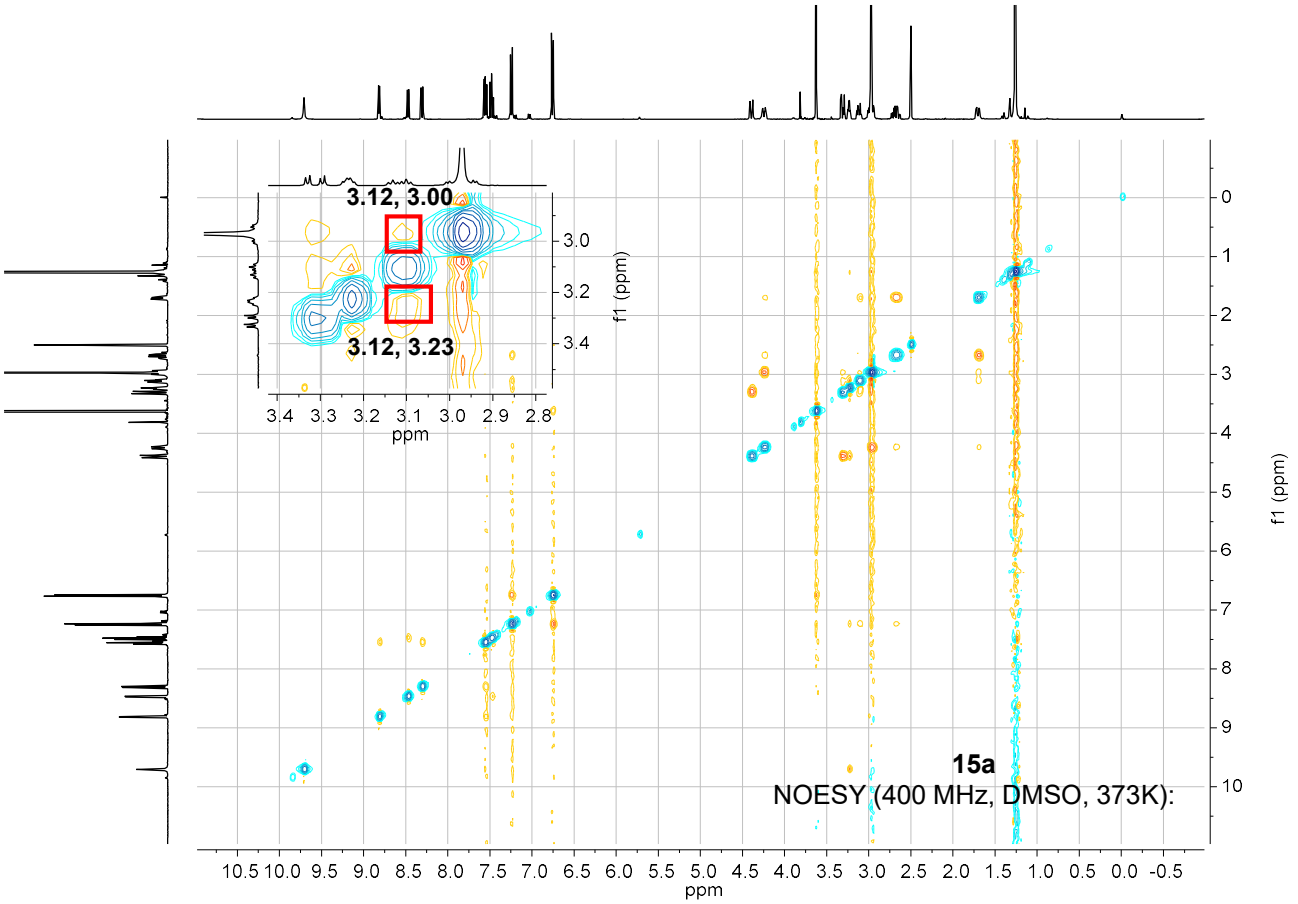
NMR Studies on the Stereochemistry of 3,4-Disubstituted Piperidine 15a

The relative configuration of 3,4-disubstitued piperidine derivative **15a** was assigned on the basis of ^{1}H NMR coupling constants and NOE experiments. Chemical shifts and proton coupling constants in the ^{1}H NMR spectrum, indicated a well-defined chair conformation with the amide functionality in the axial position, with clear axial-axial couplings (J ~ 12 Hz), as well as axial-equatorial (J ~ 3–5 Hz) and equatorial-equatorial (J ~ 3 Hz) present around the ring. In particular, proton H_a was found at a higher chemical shift (δ 2.68) than expected, likely due to the deshielding effect of the carbonyl function in the axial position. Additionally, from the NOESY spectrum, the CHAr proton correlates to nearby protons on the same face of the ring only. This, together with all the proton couplings constants observed, supports a *cis*-configuration.



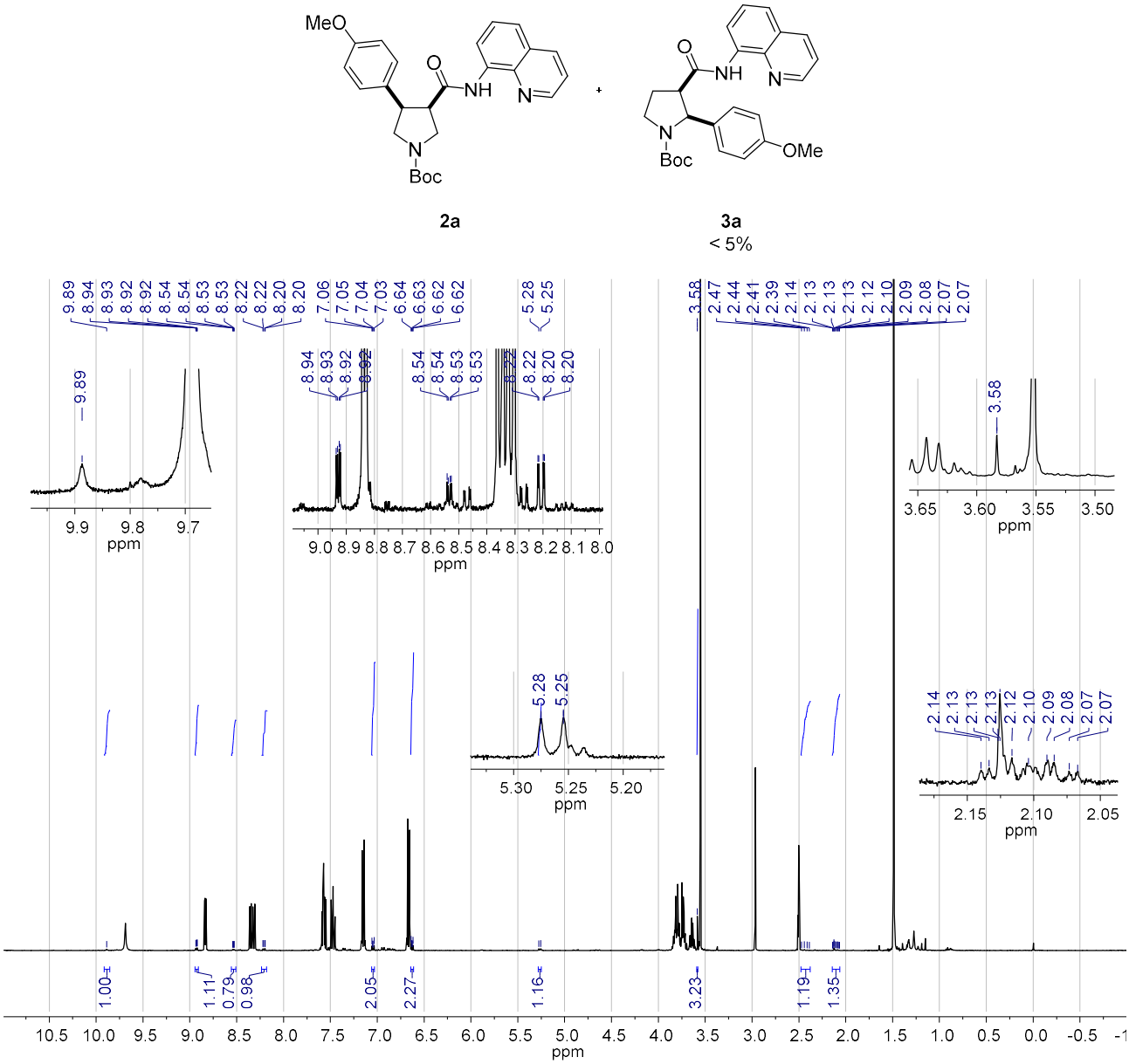

O
O
NH
N
Boc
15a
NOESY (400 MHz, DMSO, 373K):
3.12, 1.69
3.12, 7.24
f1 (ppm)
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
ppm


3.12, 3.31
3.0
3.2
3.4
f1 (ppm)
3.4 3.3 3.2 3.1 3.0 2.9 2.8
ppm
15a
NOESY (400 MHz, DMSO, 373K):
f1 (ppm)
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
ppm


3.12, 3.00
3.12, 3.23
ppm
f1 (ppm)
15a
NOESY (400 MHz, DMSO, 373K):

Spectroscopic Analysis of Pyrrolidine Derivative 2a: Identification of 2-Arylated Pyrrolidine 3a

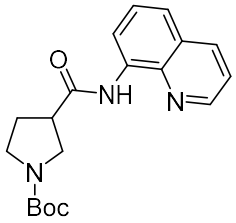
The ^{1}H NMR spectrum (400 MHz, DMSO-d_6, 373 K) of the purified product **2a** revealed the presence of an inseparable impurity (<5%). This is assigned as the C2-arylated product **3a** as it is consistent with the integral ratio between the broad singlet observed at δ 9.89 (CONH), the aromatic protons at δ 8.93, 8.54, 8.21, 7.05 and 6.65, the doublet centred at δ 5.33 (the NC*H*Ar proton)[2] and the signal at δ 3.58 (OCH_3), as well as with the presence of two multiplets below δ 2.5 (NCH_2CH_2 protons). Moreover, the coupling constant observed for the doublet at δ 5.33 (J = 8.2 Hz) is consistent with a *cis* configuration of the 2,3-disubstituted product **3a**. This is in accordance with values reported by Holladay for *N*-acetyl-3-propylproline derivatives, with values for *cis* isomer of J = 8.1–8.5 Hz and for *trans* isomers of J = 4.4–6.2 Hz (confirmed by single-crystal X-ray analysis of a *trans*-derivative).[2b]



Experimental Details and Characterisation Data

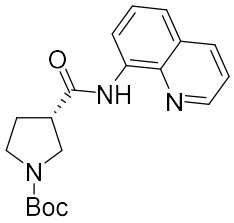
Pyrrolidine Amide Substrates **1**, **5–8**, **S32**, **S33**

tert-Butyl (±)-3-(quinolin-8-ylcarbamoyl)pyrrolidine-1-carboxylate (1)



HOBt hydrate (2.56 g, 16.7 mmol) was added to a solution of *N*-Boc-pyrrolidine-3-carboxylic acid (3.00 g, 14.0 mmol) and 8-aminoquinoline (2.41 g, 16.8 mmol) in dry CH_2Cl_2 (55 mL) at 25 °C, and was stirred for 5 min. EDC·HCl (3.20 g, 16.8 mmol) was then added and the solution was stirred for 5 days. The reaction was diluted with CH_2Cl_2 (75 mL), then a solution of sat. aq. $NaHCO_3$ (75 mL) was added and the aqueous layer was extracted with CH_2Cl_2 (3 × 150 mL). The combined organic extracts were dried over Na_2SO_4 and filtered. The solvent was removed under reduced pressure. The crude material was purified by flash column chromatography (15% to 50% EtOAc/pentane), the product containing fractions were combined and the solvent was removed under reduced pressure. Et_2O (20 mL) and pentane (20 mL) were added and the solvent was removed under reduced pressure to afford amide **1** as a white solid (4.30 g, 91%). R_f 0.23 (25% EtOAc/pentane); mp = 110–113 °C (from Et_2O/pentane); ν_{max} (film)/cm^{-1} 3343 (NH), 2972, 1738, 1693 (C=O carbamate), 1672 (C=O amide), 1536, 1487, 1398, 1362, 1223, 1164, 1125, 1082, 986, 874, 821, 782, 686; ^{1}H NMR (400 MHz, DMSO-d_6, 373 K) δ 10.02 (br s, 1 H, NH), 8.91 (dd, *J* = 4.2, 1.7 Hz, 1 H, HC_{Ar}), 8.58 (dd, *J* = 7.7, 1.3 Hz, 1 H, HC_{Ar}), 8.36 (dd, *J* = 8.3, 1.7 Hz, 1 H, HC_{Ar}), 7.65 (dd, *J* = 8.2, 1.3 Hz, 1 H, HC_{Ar}), 7.60 (dd, *J* = 8.3, 4.2 Hz, 1 H, HC_{Ar}), 7.56 (t, *J* = 7.9 Hz, 1 H, HC_{Ar}), 3.63 (dd, *J* = 10.4, 7.5 Hz, 1 H, NC*H*HCHCO), 3.55–3.44 (m, 3 H, NCH*H*CHCO, CHCO, NC*H*HCH_2), 3.34 (dt, *J* = 10.5, 7.5 Hz, 1 H, NCH*H*CH_2), 2.27–2.19 (m, 1 H, NCH_2CHH), 2.18–2.09 (m, 1 H, NCH_2CH*H*), 1.43 (s, 9 H, $C(CH_3)_3$); ^{13}C NMR (101 MHz, DMSO-d_6, 373 K) δ 171.0 (C=O amide), 153.2 (C=O carbamate), 148.4 (C_{Ar}), 138.0 (C_{Ar} quat), 136.0 (C_{Ar}), 133.9 (C_{Ar} quat), 127.5 (C_{Ar} quat), 126.4 (C_{Ar}), 121.6 (C_{Ar}), 121.5 (C_{Ar}), 116.5 (C_{Ar}), 78.0 (*C*$(CH_3)_3$), 48.1 (N*C*H_2CHCO), 44.9 (N*C*H_2CH_2), 44.1 (*C*HCO), 28.5 (NCH_2*C*H_2), 27.8 (C(*C*$H_3)_3$); HRMS (ESI$^+$) m/z Calculated for $C_{19}H_{24}N_3O_3^+$ $[M+H]^+$ 342.1818; Found 342.1829.

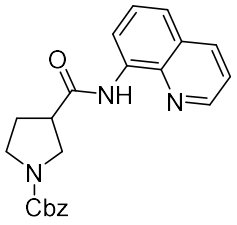
tert-Butyl (–)-(*S*)-3-(quinolin-8-ylcarbamoyl)pyrrolidine-1-carboxylate ((*S*)-1)



HOBt hydrate (430 mg, 2.80 mmol) was added to a solution of (*S*)-*N*-Boc-pyrrolidine-3-carboxylic acid (500 mg, 2.33 mmol) and 8-aminoquinoline (404 mg, 2.80 mmol) in dry CH_2Cl_2 (9.0 mL) at 25 °C, and was stirred for 5 min. EDC·HCl (537 mg, 2.80 mmol) was then added and the solution was stirred for 5 days. The reaction was diluted with CH_2Cl_2 (12 mL), then a solution of sat. aq. $NaHCO_3$ (12 mL) was added and the aqueous layer was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic extracts were dried over Na_2SO_4 and filtered. The solvent was removed under reduced pressure. The crude material was purified by flash column chromatography (15% to 40% EtOAc/hexane), the product containing fractions were combined and the solvent was removed under reduced pressure. Et_2O (10 mL) and pentane (10 mL) were added and the solvent was removed under reduced pressure to afford amide **(*S*)-1** as a white solid (684 mg, 86%, 97.4% *ee*). $[\alpha]_D^{25}$ –7.7 (*c* 1.00, $CHCl_3$).
Characterisation data identical to that reported for racemic amide **1**.

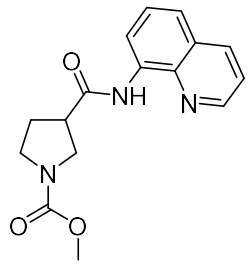
HPLC Conditions: Chiralpak IA 3-column, 90:10 *n*-hexane:*i*-PrOH, flow rate: 1 mL·min^{-1}, 35 ºC. UV detection wavelength: 210.4 nm. Retention times: 11.5 min (*S* enantiomer), 12.6 min (*R* enantiomer).

Benzyl (±)-3-(quinolin-8-ylcarbamoyl)pyrrolidine-1-carboxylate (5)



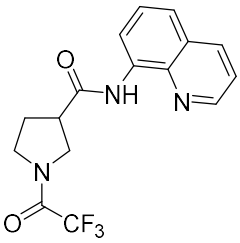
HOBt hydrate (739 mg, 4.80 mmol) was added to a solution of *N*-Cbz-pyrrolidine-3-carboxylic acid (1.00 g, 4.00 mmol) and 8-aminoquinoline (694 mg, 4.80 mmol) in dry CH_2Cl_2 (16 mL) at 25 °C, and was stirred for 5 min. EDC·HCl (923 mg, 4.80 mmol) was then added and the solution was stirred for 3 days. The reaction was diluted with CH_2Cl_2 (25 mL), then a solution of sat. aq. $NaHCO_3$ (25 mL) was added and the aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic extracts were dried over Na_2SO_4 and filtered. The crude material was purified by flash column chromatography (15% to 50% EtOAc/hexane), the product containing fractions were combined and the solvent was removed under reduced pressure. Et_2O (10 mL) and pentane (10 mL) were added and the solvent was removed under reduced pressure to afford amide **5** as a white solid (1.44 g, 96%). R_f 0.10 (25% EtOAc/hexane); mp = 124–125 °C (from Et_2O/pentane); ν_{max} (film)/cm^{-1} 3342 (NH), 2888, 1685 (C=O), 1524, 1484, 1422, 1365, 1335, 1181, 1133, 956, 877, 823, 786, 727, 686; ^{1}H NMR (400 MHz, DMSO-d_6, 373 K) δ 10.06 (br s, 1 H, NH), 8.91 (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}), 7.61 (dd, *J* = 8.3, 4.2 Hz, 1 H, HC_{Ar}), 7.57 (t, *J* = 8.0 Hz, 1 H, HC_{Ar}), 7.40–7.33 (m, 4 H, HC_{Ar}), 7.33–7.28 (m, 1 H, HC_{Ar}), 5.12 (s, 2 H, OCH_2Ph), 3.73 (dd, *J* = 10.6, 7.8 Hz, 1 H, NC*H*HCHCO), 3.63 (dd, *J* = 10.6, 6.5 Hz, 1 H, NCH*H*CHCO), 3.61–3.50 (m, 2 H, CHCO, NC*H*HCH_2), 3.44 (dt, *J* = 10.5, 7.5 Hz, 1 H, NCH*H*CH_2), 2.32–2.23 (m, 1 H, NCH_2CHH), 2.23–2.13 (m, 1 H, NCH_2CH*H)*; ^{13}C NMR (101 MHz, DMSO-d_6, 373 K) δ 170.8 (C=O amide), 153.5 (C=O carbamate), 148.3 (C_{Ar}), 137.9 (C_{Ar} quat), 136.7 (C_{Ar} quat), 135.9 (C_{Ar}) 133.9 (C_{Ar} quat), 127.8 (2 × C_{Ar}), 127.4 (C_{Ar} quat), 127.1 (C_{Ar}), 126.8 (2 × C_{Ar}), 126.3 (C_{Ar}), 121.5 (C_{Ar}), 121.4 (C_{Ar}), 116.5 (C_{Ar}), 65.4 (OCH_2Ph), 48.1 (NCH_2CHCO), 45.1 (NCH_2CH_2), 44.0 (*C*HCO), 28.4 (NCH_2CH_2); HRMS (ESI$^+$) m/z Calculated for $C_{22}H_{22}N_3O_3^+$ $[M+H]^+$ 376.1661; Found 376.1662.

Methyl (±)-3-(quinolin-8-ylcarbamoyl)pyrrolidine-1-carboxylate (6)



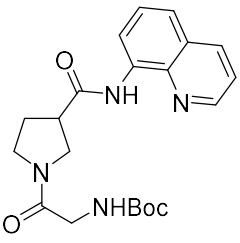
Trifluoroacetic acid (6.5 mL) was added dropwise to a solution of Boc-protected pyrrolidine **1** (3.00 g, 8.79 mmol) in dry CH_2Cl_2 (43 mL) at 0 °C. The reaction was allowed to warm up and stirred at 25 °C for 24 h. The reaction mixture was then diluted with CH_2Cl_2 (15 mL), and quenched with sat. aq. $NaHCO_3$ (30 mL). The organic and aqueous phases were separated and the aqueous layer was extracted with CH_2Cl_2 (4 × 60 mL). The combined organic layers were dried over Na_2SO_4 and the solvent was removed under reduced pressure, affording *N*-(quinolin-8-yl)pyrrolidine-3-carboxamide (2.40 g), which was used in the next step without further purification. A portion of *N*-(quinolin-8-yl)pyrrolidine-3-carboxamide (362 mg, 1.5 mmol) was solubilised in THF (2.0 mL), and sat. aq. $NaHCO_3$ (2.0 mL) was added. The resulting solution was stirred for 5 min at 0 °C. Methyl chloroformate (232 μL, 3.00 mmol) was then added and the solution was stirred at 25 °C for 20 h. The reaction was diluted with EtOAc (5 mL) and sat. aq. $NaHCO_3$ (2 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (3 × 15 mL). The combined organic extracts were dried over Na_2SO_4 and filtered. The solvent was removed under reduced pressure. Purification by flash column chromatography (30% to 60% EtOAc/pentane) afforded amide **6** as a white paste (360 mg, 80% over two steps). R_f 0.09 (40% EtOAc/hexane); ν_{max} (film)/cm^{-1} 3340 (NH), 2953, 2883, 1678 (C=O), 1523, 1485, 1448, 1425, 1383, 1323, 1259, 1187, 1164, 1119, 826, 791, 767; ^{1}H NMR (400 MHz, DMSO-d_6, 373 K) δ 10.05 (br s, 1 H, NH), 8.92 (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}), 7.61 (dd, *J* = 8.3, 4.2 Hz, 1 H, HC_{Ar}), 7.56 (t, *J* = 7.9 Hz, 1 H, HC_{Ar}), 3.68 (dd, *J* = 10.3, 7.6 Hz, 1 H, NC*H*HCHCO), 3.64 (s, 3 H, OCH_3), 3.61–3.48 (m, 3 H, NCH*H*CHCO, CHCO, NC*H*HCH_2), 3.39 (dt, *J* = 10.4, 7.4 Hz, 1 H, NCH*H*CH_2), 2.31–2.21 (m, 1 H, NCH_2CHH), 2.21–2.11 (m, 1 H, NCH_2CH*H*); ^{13}C NMR (101 MHz, DMSO-d_6, 373 K) δ 170.8 (C=O amide), 154.0 (C=O carbamate), 148.2 (C_{Ar}), 137.9 (C_{Ar} quat), 135.9 (C_{Ar}), 133.9 (C_{Ar} quat), 127.4 (C_{Ar} quat), 126.2 (C_{Ar}), 121.43 (C_{Ar}), 121.41 (C_{Ar}), 116.4 (C_{Ar}), 51.3 (OCH_3), 48.0 (NCH_2CHCO), 45.0 (NCH_2CH_2), 44.0 (*C*HCO), 28.4 (NCH_2CH_2); HRMS (ESI$^+$) *m/z* Calculated for $C_{16}H_{18}N_3O_3^+$ $[M+H]^+$ 300.1348; Found 300.1342.

(±)-*N*-(Quinolin-8-yl)-1-(2,2,2-trifluoroacetyl)pyrrolidine-3-carboxamide (7)



Trifluoroacetic acid (6.5 mL) was added dropwise to a solution of Boc-protected pyrrolidine **1** (3.00 g, 8.79 mmol) in dry CH_2Cl_2 (43 mL) at 0 °C. The reaction was allowed to warm up and stirred at 25 °C for 24 h. The reaction mixture was then diluted with CH_2Cl_2 (15 mL), and quenched with sat. aq. $NaHCO_3$ (30 mL). The organic and aqueous phases were separated and the aqueous layer was extracted with CH_2Cl_2 (4 × 60 mL). The combined organic layers were dried over Na_2SO_4 and the solvent was removed under reduced pressure, affording *N*-(quinolin-8-yl)pyrrolidine-3-carboxamide (2.40 g), which was used in the next step without further purification. A portion of *N*-(quinolin-8-yl)pyrrolidine-3-carboxamide (724 mg, 3.0 mmol) was dissolved in dry CH_2Cl_2 (10 mL), and *N*-ethyl-*N*-isopropylpropan-2-amine (1.50 mL, 8.76 mmol) was added. This solution was stirred for 5 min at 25 °C and then cooled at 0 °C. Trifluoroacetic anhydride (542 μL, 3.90 mmol) was then added and the solution was stirred at 0 °C for 30 min, warmed to 25 °C and stirred for 1 h. The reaction was diluted with CH_2Cl_2 (5 mL) and acidified with 1 M HCl to pH ~ 2. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic extracts were dried over Na_2SO_4 and filtered. The solvent was removed under reduced pressure. The crude material was purified by flash column chromatography (30% EtOAc/hexane), the product containing fractions were combined and the solvent was removed under reduced pressure. Et_2O (10 mL) and pentane (10 mL) were added and the solvent was removed under reduced pressure to afford amide **7** as a white solid (863 mg, 85% over two steps). R_f 0.18 (30% EtOAc/hexane); mp = 84–87 °C (from Et_2O/pentane); ν_{max} (film)/cm^{-1} 3348 (NH), 1690 (C=O), 1671 (C=O), 1523, 1485, 1427, 1380, 1321, 1238, 1201, 1143, 863, 830, 800, 755, 703, 676; ^{1}H NMR (400 MHz, DMSO-d_6, 373 K, observed as a mixture of rotamers) δ 10.14 (br s, 1 H, NH), 8.93 (dd, *J* = 4.2, 1.7 Hz, 1 H, HC_{Ar}), 8.58 (dd, *J* = 7.6, 1.4 Hz, 1 H, HC_{Ar}), 8.38 (dd, *J* = 8.3, 1.7 Hz, 1 H, HC_{Ar}), 7.67 (dd, *J* = 8.3, 1.4 Hz, 1 H, HC_{Ar}), 7.61 (dd, *J* = 8.3, 4.2 Hz, 1 H, HC_{Ar}), 7.57 (t, *J* = 7.9 Hz, 1 H, HC_{Ar}), 4.04–3.66 (m, 4 H, NCH_2CHCO, CHCO, NC*H*HCH_2), 3.65–3.54 (m, 1 H, NCH*H*CH_2), 2.48–2.14 (m, 2 H, NCH_2CH_2); ^{13}C NMR (101 MHz, DMSO-d_6, 373 K, observed as a mixture of rotamers) δ 170.4 and 170.0 (C=O amide), 153.7 (q, J_{CF} = 35.6 Hz, CF_3*C*=O), 148.3 (C_{Ar}), 138.0 (C_{Ar} quat), 135.9 (C_{Ar}), 133.8 (C_{Ar} quat), 127.4 (C_{Ar} quat), 126.2 (C_{Ar}), 121.6 (C_{Ar}), 121.4 (C_{Ar}), 116.7 (C_{Ar}), 115.7 (q, J_{CF} = 288.4 Hz, CF_3), 49.4 and 46.4 (NCH_2CHCO), 48.2 and 45.5 (NCH_2CH_2), 44.6 and 41.9 (*C*HCO), 29.4 and 26.7 (NCH_2CH_2) ^{19}F NMR (376 MHz, DMSO-d_6, 373 K) δ –71.3; HRMS (ESI$^+$) *m/z* Calculated for $C_{16}H_{15}N_3O_2F_3^+$ [M+H]$^+$ 338.1116; Found 338.1105.

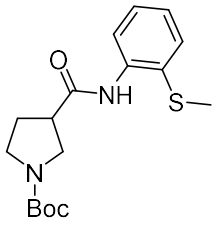
***tert*-Butyl (±)-(2-oxo-2-(3-(quinolin-8-ylcarbamoyl)pyrrolidin-1-yl)ethyl)carbamate (8)**



Trifluoroacetic acid (6.5 mL) was added dropwise to a solution of Boc-protected pyrrolidine **1** (3.00 g, 8.79 mmol) in dry CH_2Cl_2 (43 mL) at 0 °C. The reaction was allowed to warm up and stirred at 25 °C for 24 h. The reaction mixture was then diluted with CH_2Cl_2 (15 mL), and quenched with sat. aq. $NaHCO_3$ (30 mL). The organic and aqueous phases were separated and the aqueous layer was extracted with CH_2Cl_2 (4 × 60 mL). The combined organic layers were dried over Na_2SO_4 and the solvent was removed under reduced pressure, affording *N*-(quinolin-8-yl)pyrrolidine-3-carboxamide (2.40 g), which was used in the next step without further purification. A portion of *N*-(quinolin-8-yl)pyrrolidine-3-carboxamide (362 mg, 1.50 mmol) was solubilised in dry CH_2Cl_2 (6.0 mL) and HOBt hydrate (276 mg, 1.80 mmol) and *N*-(*tert*-butoxycarbonyl)glycine (315 mg, 1.80 mmol) were added. The resulting solution was stirred for 5 min at 25 °C. EDC·HCl (345 mg, 1.80 mmol) was then added and the solution was stirred for 24 h. The reaction was diluted with CH_2Cl_2 (10 mL), then a solution of sat. aq. $NaHCO_3$ (10 mL) was added and the aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were dried over Na_2SO_4 and filtered. The crude material was purified by flash column chromatography (3% MeOH/CH_2Cl_2), the product containing fractions were combined and the solvent was removed under reduced pressure. Et_2O (10 mL) and pentane (10 mL) were added and the solvent was removed under reduced pressure to afford amide **8** as a white solid (4.88 mg, 82%). R_f 0.44 (5% MeOH/CH_2Cl_2); mp = 62–67 °C (from Et_2O/pentane); ν_{max} (film)/cm^{-1} 3339 (NH), 2974, 1686 (C=O), 1648 (C=O), 1525, 1486, 1439, 1425, 1390, 1365, 1324, 1246, 1162, 1053, 865, 827, 792, 760; ^{1}H

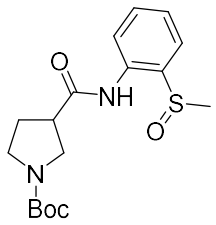
NMR (400 MHz, CDCl3, 298 K, observed as a mixture of rotamers) δ 9.98 and 9.96 (2 × br s, 1 H, NH_{AQ}), 8.81 and 8.80 (2 × dd, *J* = 4.4, 1.7 Hz, 1 H, HC_{Ar}), 8.76–8.69 (m, 1 H, HC_{Ar}), 8.19 and 8.17 (2 × dd, *J* = 3.9, 1.7 Hz, 1 H, HC_{Ar}), 7.58–7.51 (m, 2 H, HC_{Ar}), 7.48 and 7.47 (2 × dd, *J* = 8.3, 4.2 Hz, 1 H, HC_{Ar}), 5.51 and 5.49 (2 × br s, 1 H, NHBoc), 4.05–3.65 (m, 5 H, C*H*$_2$NHBoc, NC*H*$_2$CHCO, NC*H*HCH$_2$), 3.64–3.46 (m, 1 H, NCH*H*CH$_2$), 3.40 and 3.28 (2 × p, *J* = 7.5 Hz, 1 H, CHCO), 2.55–2.26 (m, 2 H, NCH$_2$C*H*$_2$), 1.46 and 1.45 (2 × s, 9 H, C(CH_3)$_3$); ^{13}C NMR (101 MHz, CDCl3, 298 K, observed as a mixture of rotamers) δ 170.4 and 169.8 (CH*C*=O amide), 166.9 (CH$_2$*C*=O amide), 155.8 (C=O carbamate), 148.31 and 148.27 (C_{Ar}), 138.3 (C_{Ar} quat), 136.44 and 136.40 (C_{Ar}), 134.0 and 133.9 (C_{Ar} quat), 127.9 (C_{Ar} quat), 127.3 (C_{Ar}), 122.0 and 121.9 (C_{Ar}), 121.74 and 121.71 (C_{Ar}), 116.70 and 116.67 (C_{Ar}), 79.6 (*C*(CH_3)$_3$), 48.9 and 47.8 (N*C*H$_2$CHCO), 46.4 and 44.4 (*C*HCO), 45.6 and 44.9 (N*C*H$_2$CH$_2$), 43.1 and 43.0 (*C*H$_2$NHBoc), 29.8 and 28.5 (NCH$_2$*C*H$_2$), 28.3 (C(*C*H$_3$)$_3$); HRMS (ESI$^+$) *m/z* Calculated for $C_{21}H_{27}N_4O_4^+$ [M+H]$^+$ 399.2032; Found 399.2052.

tert-Butyl (±)-3-((2-(methylthio)phenyl)carbamoyl)pyrrolidine-1-carboxylate (S30)



HOBt hydrate (2.60 g, 16.8 mmol) was added to a solution of *N*-Boc-pyrrolidine-3-carboxylic acid (3.00 g, 14.0 mmol) and 2-(methylthio)aniline (2.1 mL, 16.8 mmol) in dry CH_2Cl_2 (55 mL) at rt, and was stirred for 5 min. EDC·HCl (3.20 g, 16.8 mmol) was then added and the solution was stirred for 5 days. The reaction was diluted with CH_2Cl_2 (70 mL), then a solution of sat. aq. $NaHCO_3$ (70 mL) was added and the aqueous layer was extracted with CH_2Cl_2 (3 × 150 mL). The combined organic extracts were dried over Na_2SO_4 and filtered. The solvent was removed under reduced pressure. Purification by flash column chromatography (30% EtOAc/hexane) afforded amide **S30** as an orange oil (3.17 g, 67%). R_f 0.17 (30% EtOAc/hexane); ν_{max} (film)/cm^{-1} 3260 (NH), 2975, 2881, 1687 (C=O), 1661 (C=O), 1579, 1513, 1402, 1364, 1163, 1118, 1072, 879, 745; ^{1}H NMR (400 MHz, DMSO-d_6, 373 K) δ 9.05 (br s, 1 H, NH), 7.54–7.47 (m, 1 H, HC_{Ar}), 7.43–7.36 (m, 1 H, HC_{Ar}), 7.24–7.16 (m, 2 H, HC_{Ar}), 3.57 (dd, *J* = 10.8, 8.0 Hz, 1 H, NC*H*HCHCO), 3.52–3.38 (m, 2 H, NCH*H*CHCO, NC*H*HCH$_2$), 3.30 (dt, *J* = 10.5, 7.5 Hz, 1 H, NCH*H*CH$_2$), 3.23 (p, *J* = 7.5 Hz, 1 H, CHCO), 2.42 (s, 3 H, CH_3), 2.18–2.04 (m, 2 H, NCH$_2$C*H*$_2$), 1.44 (s, 9 H, C(CH_3)$_3$); ^{13}C NMR (101 MHz, DMSO-d_6, 373 K) δ 170.7 (C=O amide), 153.0 (C=O carbamate), 135.7 (C_{Ar} quat), 132.2 (SC_{Ar} quat), 127.8 (C_{Ar}), 125.5 (C_{Ar}), 125.4 (C_{Ar}), 125.0 (C_{Ar}), 77.8 (*C*(CH_3)$_3$), 47.9 (N*C*H$_2$CHCO), 44.8 (N*C*H$_2$CH$_2$), 43.0 (*C*HCO), 28.2 (NCH$_2$*C*H$_2$), 27.7 (C(*C*H$_3$)$_3$), 15.5 (SCH_3); HRMS (ESI$^+$) m/z Calculated for $C_{17}H_{25}N_2O_3S^+$ [M+H]$^+$ 337.1586; Found 337.1588.

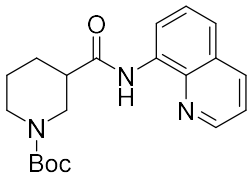
tert-Butyl (±)-3-((2-(methylsulfinyl)phenyl)carbamoyl)pyrrolidine-1-carboxylate (S31)



A solution of *m*-CPBA (256 mg, 1.49 mmol) in CH_2Cl_2 (3.0 mL) was added dropwise to a solution of starting carboxamide **S30** (500 mg, 1.49 mmol) in CH_2Cl_2 (6.0 mL) at –30 °C. The reaction mixture was stirred at –30 °C for 3 h, then sat. aq. $NaHCO_3$ (10 mL) was added and the reaction mixture was stirred at 25 °C for 30 min. The phases were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 25 mL). The combined organic extracts were dried over Na_2SO_4 and filtered. The solvent was removed under reduced pressure. Purification by flash column chromatography (EtOAc) afforded amide **S31** as a colourless oil (305 mg, 58%, 1:1 *dr*). R_f 0.11 (EtOAc); ν_{max} (film)/cm^{-1} 3242 (NH), 2976, 2884, 1685 (C=O), 1587, 1525, 1475, 1403, 1163, 1120, 1014, 955, 879, 756; ^{1}H NMR (400 MHz, DMSO-d_6, 373 K) δ 9.96 (br s, 1 H, NH), 7.77 (dd, *J* = 7.8, 1.6 Hz, 1 H, HC_{Ar}), 7.59 (dd, *J* = 8.0, 1.3 Hz, 1 H, HC_{Ar}), 7.52 (ddd, *J* = 8.0, 7.3, 1.6, Hz, 1 H, HC_{Ar}), 7.43 (ddd, *J* = 7.8, 7.3, 1.4, Hz, 1 H, HC_{Ar}), 3.57 and 3.55 (2 × dd, *J* = 10.9, 7.9 Hz, 1 H, NC*H*HCHCO), 3.52–3.38 (m, 2 H, NCH*H*CHCO, NC*H*HCH$_2$), 3.305 and 3.301 (2 × dt, *J* = 10.5, 7.5 Hz, 1 H, NCH*H*CH$_2$), 3.17 (p, *J* = 7.4 Hz, 1 H, CHCO), 2.774 and 2.771 (2 × s, 3 H, SCH_3), 2.22–2.03 (m, 2 H, NCH$_2$C*H*$_2$), 1.44 and 1.43 (2 × s, 9 H, C(CH_3)$_3$); ^{13}C NMR (101 MHz, DMSO-d_6, 373 K) δ 171.3 and 171.2 (C=O amide), 153.0 (C=O carbamate), 138.6 (SC_{Ar} quat), 135.1 (C_{Ar} quat), 130.8 (C_{Ar}), 125.8 (C_{Ar}), 125.0 and 124.9 (C_{Ar}), 124.0 (C_{Ar}), 77.8 (*C*(CH_3)$_3$), 47.7 and 47.6 (N*C*H$_2$CHCO), 44.7 (N*C*H$_2$CH$_2$), 43.2 (*C*HCO), 41.6 (SCH_3), 28.1 and 27.9 (NCH$_2$*C*H$_2$), 27.7 (C(*C*H$_3$)$_3$); HRMS (ESI$^+$) m/z Calculated for $C_{17}H_{25}N_2O_4S^+$ [M+H]$^+$ 353.1535; Found 353.1523.

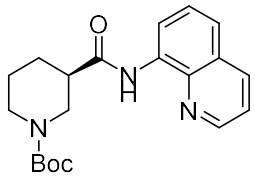
Piperidine Amide Substrates **13** and **14**

***tert*-Butyl (±)-3-(quinoline-8-ylcarbamoyl)piperidine-1-carboxylate (13)**



N-Ethyl-*N*-isopropylpropan-2-amine (3.0 mL, 17.4 mmol) was added to a solution of *N*-Boc-piperidine-3-carboxylic acid (2.00 g, 8.70 mmol) and HATU (3.97 g, 10.4 mmol) in CH_2Cl_2 (40 mL) at 0 °C, and was stirred for 5 min. 8-Aminoquinoline (1.50 g, 10.4 mmol) was then added and the solution was stirred for 24 h at 25 °C. The reaction was diluted with CH_2Cl_2 (40 mL), then a solution of sat. aq. $NaHCO_3$ (40 mL) was added and the aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic extracts were dried over Na_2SO_4 and filtered. The solvent was removed under reduced pressure. The crude material was purified by flash column chromatography (10% to 20% EtOAc/pentane), the product containing fractions were combined and the solvent was removed under reduced pressure. Et_2O (20 mL) and pentane (20 mL) were added and the solvent was removed under reduced pressure to afford amide **13** as a pale brown solid (2.73 g, 87%). R_f 0.14 (15% EtOAc/pentane); mp = 124–128 °C (from Et_2O/pentane); ν_{max} (film)/cm^{-1} 3350 (NH), 2936, 1682 (C=O), 1525, 1486, 1423, 1389, 1366, 1327, 1257, 1241, 1163, 1147, 826, 792, 760; ^{1}H NMR (400 MHz, DMSO-d_6, 373 K) δ 10.00 (br s, 1 H, NH), 8.91 (dd, J = 4.2, 1.7 Hz, 1 H, HC_{Ar}), 8.60 (dd, J = 7.6, 1.4 Hz, 1 H, HC_{Ar}), 8.36 (dd, J = 8.3, 1.7 Hz, 1 H, HC_{Ar}), 7.64 (dd, J = 8.3, 1.4 Hz, 1 H, HC_{Ar}), 7.60 (dd, J = 8.3, 4.2 Hz, 1 H, HC_{Ar}), 7.56 (t, J = 7.9 Hz, 1 H, HC_{Ar}), 4.15–4.06 (m, 1 H, NC*H*HCHCO), 3.88–3.80 (m, 1 H, NC*H*HCH$_2$), 3.11 (dd, J = 13.1, 10.1 Hz, 1 H, NCH*H*CHCO), 2.94–2.86 (m, 1 H, NCH*H*CH$_2$), 2.84–2.75 (m, 1 H, CHCO), 2.12–2.04 (m, 1 H, N(CH$_2$)$_2$C*H*H), 1.81–1.70 (m, 2 H, N(CH$_2$)$_2$CH*H*, NCH$_2$C*H*H), 1.53–1.46 (m, 1 H, NCH$_2$CH*H*), 1.42 (s, 9 H, C(CH$_3$)$_3$); ^{13}C NMR (101 MHz, DMSO-d_6, 373 K) δ 171.2 (C=O amide), 153.5 (C=O carbamate), 148.2 (C_{Ar}), 137.8 (C_{Ar} quat), 135.9 (C_{Ar}), 133.9 (C_{Ar} quat), 127.3 (C_{Ar} quat), 126.3 (C_{Ar}), 121.4 (C_{Ar}), 121.2 (C_{Ar}), 116.1 (C_{Ar}), 78.3 (*C*(CH$_3$)$_3$), 45.7 (N*C*H$_2$CHCO), 43.3 (N*C*H$_2$CH$_2$), 42.7 (*C*HCO), 27.6 (C(*C*H$_3$)$_3$), 26.9 (N(CH$_2$)$_2$*C*H$_2$), 23.3 (NCH$_2$*C*H$_2$); HRMS (ESI$^+$) *m/z* Calculated for $C_{20}H_{26}N_3O_3^+$ $[M+H]^+$ 356.1974; Found 356.1986.

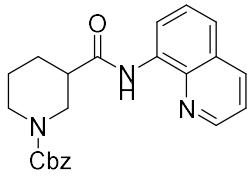
***tert*-Butyl (–)-(*R*)-3-(quinolin-8-ylcarbamoyl)piperidine-1-carboxylate ((*R*)-13)**



N-Ethyl-*N*-isopropylpropan-2-amine (6.0 mL, 34.9 mmol) was added to a solution of *(R)*-1-(*tert*-butoxycarbonyl)piperidine-3-carboxylic acid (4.0 g, 17.4 mmol) and HATU (8.00 g, 20.9 mmol) in CH_2Cl_2 (90 mL) at 0 °C, and was stirred for 5 min. 8-Aminoquinoline (3.0 g, 20.9 mmol) was then added and the solution was stirred for 24 h at 25 °C. The reaction was diluted with CH_2Cl_2 (90 mL), then a solution of sat. aq. $NaHCO_3$ (90 mL) was added and the aqueous layer was extracted with CH_2Cl_2 (3 × 150 mL). The combined organic extracts were dried over Na_2SO_4 and filtered. The solvent was removed under reduced pressure. The crude material was purified by flash column chromatography (10% to 20% EtOAc/pentane), the product containing fractions were combined and the solvent was removed under reduced pressure. Et_2O (30 mL) and pentane (30 mL) were added and the solvent was removed under reduced pressure to afford amide **(*R*)-13** as a pale brown solid (5.49 g, 89%, 99.1% *ee*). $[\alpha]_D^{25}$ –8.5 (*c* 1.41, $CHCl_3$).
Characterisation data identical to that reported for racemic amide **13**.

HPLC Conditions: Chiralpak IA 3-column, 95:5 *n*-hexane:*i*-PrOH, flow rate: 1 mL·min^{-1}, 35 ºC. UV detection wavelength: 210.4 nm. Retention times: 14.4 min (*S* enantiomer), 15.7 min (*R* enantiomer).

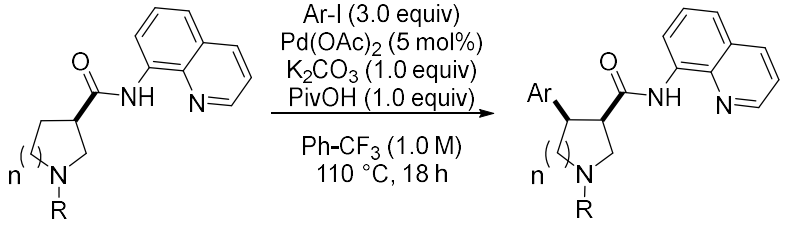
Benzyl (±)-3-(quinolin-8-ylcarbamoyl)piperidine-1-carboxylate (14)



HOBt hydrate (670 mg, 4.60 mmol) was added to a solution of *N*-Cbz-piperidine-3-carboxylic acid (1.00 g, 3.80 mmol) and 8-aminoquinoline (657 mg, 4.60 mmol) in CH_2Cl_2 (15.0 mL) at 25 °C, and was stirred for 5 min. EDC·HCl (874 mg, 4.60 mmol) was then added and the solution was stirred for 3 days. The reaction was diluted with CH_2Cl_2 (20 mL), then a solution of sat. aq. $NaHCO_3$ (20 mL) was added and the aqueous layer was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic extracts were dried over Na_2SO_4 and filtered. The solvent

was removed under reduced pressure. The crude material was purified by flash column chromatography (15% to 40% EtOAc/pentane), the product containing fractions were combined and the solvent was removed under reduced pressure. Et_2O (10 mL) and pentane (10 mL) were added and the solvent was removed under reduced pressure to afford amide **14** as a white solid (1.20 g, 84%). R_f 0.08 (20% EtOAc/hexane); mp = 110–111 °C (from Et_2O/pentane); ν_{max} (film)/cm^{-1} 3347 (NH), 2936, 2858, 1679 (C=O), 1522, 1485, 1423, 1383, 1326, 1234, 1136, 949, 825, 790, 756, 696; ^{1}H NMR (400 MHz, DMSO-d_6, 373 K) δ 10.02 (br s, 1 H, NH), 8.89 (dd, J = 4.2, 1.7 Hz, 1 H, HC_{Ar}), 8.59 (dd, J = 7.6, 1.4 Hz, 1 H, HC_{Ar}), 8.36 (dd, J = 8.3, 1.7 Hz, 1 H, HC_{Ar}), 7.65 (dd, J = 8.3, 1.4 Hz, 1 H, HC_{Ar}), 7.60 (dd, J = 8.3, 4.2 Hz, 1 H, HC_{Ar}), 7.56 (t, J = 7.9 Hz, 1 H, HC_{Ar}), 7.38–7.26 (m, 5 H, HC_{Ar}), 5.12 (s, 2 H, O*C*H$_2$Ph), 4.17 (ddt, J = 13.2, 4.2, 1.5 Hz, 1 H, NC*H*HCHCO), 3.94–3.87 (m, 1 H, NC*H*HCH$_2$), 3.23 (dd, J = 13.2, 10.0 Hz, 1 H, NCH*H*CHCO), 3.02 (ddd, J = 13.3, 11.2, 3.2 Hz, 1 H, NCH*H*CH$_2$), 2.90–2.81 (m, 1 H, CHCO), 2.15–2.05 (m, 1 H, N(CH$_2$)$_2$C*H*H), 1.86–1.75 (m, 2 H, N(CH$_2$)$_2$CH*H*, NCH$_2$C*H*H), 1.62–1.47 (m, 1 H, NCH$_2$CH*H*); ^{13}C NMR (101 MHz, DMSO-d_6, 373 K) δ 171.1 (C=O amide), 154.1 (C=O carbamate), 148.2 (C_{Ar}), 137.9 (C_{Ar} quat), 136.6 (C_{Ar} quat), 135.9 (C_{Ar}), 133.8 (C_{Ar} quat), 127.7 (2 × C_{Ar}), 127.3 (C_{Ar} quat), 127.1 (C_{Ar}), 126.8 (2 × C_{Ar}), 126.2 (C_{Ar}), 121.4 (C_{Ar}), 121.3 (C_{Ar}), 116.2 (C_{Ar}), 65.8 (O*C*H$_2$Ph), 45.6 (N*C*H$_2$CHCO), 43.4 (N*C*H$_2$CH$_2$), 42.5 (C*H*CO), 26.8 (N(CH$_2$)$_2$*C*H$_2$), 23.2 (NCH$_2$*C*H$_2$); HRMS (ESI$^+$) *m/z* Calculated for $C_{23}H_{24}N_3O_3^+$ $[M+H]^+$ 390.1818; Found 390.1816.

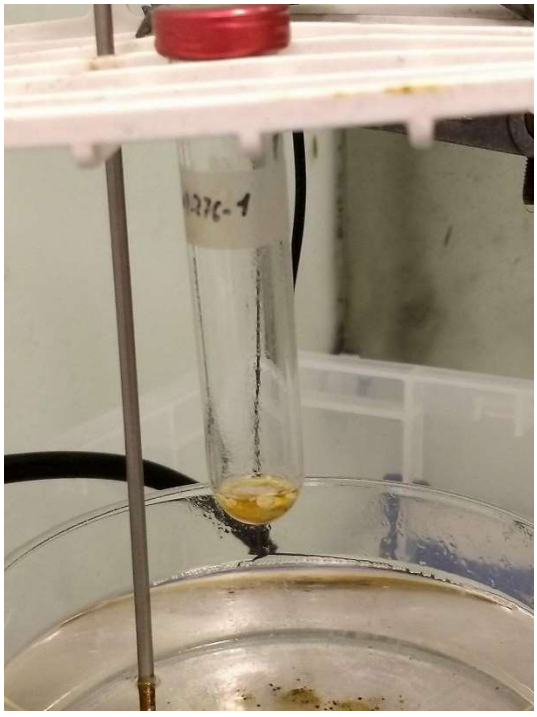
General Procedure A for C–H Arylation of *N*-Protected Pyrrolidines and Piperidines



n = 1, 2
R = Boc, Cbz, CO_2Me, TFA, $COCH_2NHBoc$

A reaction tube was charged with K_2CO_3 (69.1 mg, 0.50 mmol), flame-dried, and allowed to cool under argon. The starting carboxamide (0.50 mmol), the requisite aryl iodide (1.50 mmol), $Pd(OAc)_2$ (5.60 mg, 25.0 μmol) and PivOH (51.2 mg, 0.50 mmol) were added sequentially. The reaction vessel was sealed and purged with argon, then $PhCF_3$ (500 μL, 1.0 M) was added by syringe. The reaction tube was then placed in a preheated oil bath and stirred at 110 ºC for 18 h. The reaction mixture was then allowed to cool to rt and EtOAc (10 mL) was added. The resulting mixture 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 (5 mL) and pentane (5 mL) were added and the solvent was removed under reduced pressure to afford the 3-arylated derivative.

Reaction mixture before heating (time = 0)

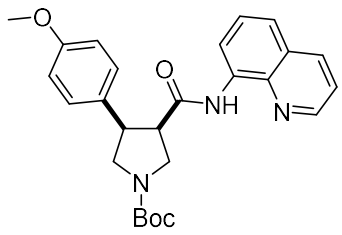


Reaction mixture at time = 18 h



Pyrrolidine C–H Arylation **(2a, 4a, S32, S33):**

***tert*-Butyl *cis*-(±)-3-(4-methoxyphenyl)-4-(quinolin-8-ylcarbamoyl)pyrrolidine-1-carboxylate (2a)**

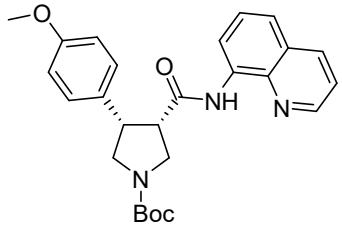


Prepared according to **General Procedure A** using *tert*-butyl 3-(quinoline-8-ylcarbamoyl)pyrrolidine-1-carboxylate **1** (171 mg) and 4-iodoanisole (351 mg). Purification by flash column chromatography (5% to 20% acetone/pentane) afforded arylated pyrrolidine **2a** as a yellow solid (143 mg, 64%). R_f 0.20 (20% acetone/pentane); mp = 62–65 °C (from Et_2O/pentane); ν_{max} (film)/cm^{-1} 3346 (NH br), 2976, 1681 (C=O), 1525, 1515, 1486, 1402, 1365, 1324, 1248, 1163, 1114, 1033, 912, 791, 758, 729; ^{1}H NMR (400 MHz, DMSO-d_6, 373 K) δ 9.69 (br s, 1 H, NH), 8.83 (dd, *J* = 4.2, 1.7 Hz, 1 H, HC_{Ar}), 8.35 (dd, *J* = 7.6, 1.4 Hz, 1 H, HC_{Ar}), 8.31 (dd, *J* = 8.3, 1.7 Hz, 1 H, HC_{Ar}), 7.60–7.55 (m, 2 H, HC_{Ar}), 7.47 (t, *J* = 7.9 Hz, 1 H, HC_{Ar}), 7.19–7.11 (m, 2 H, HC_{Ar}), 6.71–6.64 (m, 2 H, HC_{Ar}), 3.86–3.76 (m, 3 H, CHCO, CHAr, NC*H*HCHCO), 3.76–3.71 (m, 2 H, NCH_2CHAr), 3.67–3.60 (m, 1 H, NCH*H*CHCO), 3.55 (s, 3 H, OCH_3), 1.49 (s, 9 H, $C(CH_3)_3$); ^{13}C NMR (101 MHz, DMSO-d_6, 373 K) δ 169.4 (C=O amide), 157.7 (OC_{Ar} quat), 153.2 (C=O carbamate), 147.9 (C_{Ar}), 137.6 (C_{Ar} quat), 135.7 (C_{Ar}), 133.6 (C_{Ar} quat), 129.9 (C_{Ar} quat), 128.0 (2 × C_{Ar}), 127.2 (C_{Ar} quat), 126.1 (C_{Ar}), 121.2 (C_{Ar}), 121.1 (C_{Ar}), 116.0 (C_{Ar}), 113.3 (2 × C_{Ar}), 78.0 ($C(CH_3)_3$), 54.4 (OCH_3), 49.8 (NCH_2CHAr), 49.2 (*C*HCO), 47.4 (NCH_2CHCO), 44.8 (*C*HAr), 27.8 ($C(CH_3)_3$); HRMS (ESI$^+$) m/z Calculated for $C_{26}H_{30}N_3O_4^+$ $[M+H]^+$ 448.2236; Found 448.2238.

Gram scale C–H Arylation for the Preparation of Pyrrolidine Derivative 2a

A large microwave vial (10–20 mL recommended volume) was charged with K_2CO_3 (553 mg, 4.0 mmol), flame-dried, and allowed to cool under argon. *tert*-butyl 3-(quinolin-8-ylcarbamoyl)pyrrolidine-1-carboxylate **1** (1.37 g, 4.0 mmol), 4-iodoanisole (2.81 g, 12.0 mmol), $Pd(OAc)_2$ (45.1 mg, 0.2 mmol) and PivOH (409 mg, 4.0 mmol) were added sequentially. The reaction vessel was sealed and purged with argon, then $PhCF_3$ (2.0 mL, 2.00 M) was added by syringe. The reaction tube was then placed in a preheated oil bath and stirred at 110 ºC for 18 h. The reaction mixture was then allowed to cool to rt and EtOAc (20 mL) was added. The resulting mixture was filtered through a pad of Celite, eluting with further EtOAc (2 × 50 mL). The solvent was removed under reduced pressure. The reaction mixture was purified by flash column chromatography (20% acetone/hexane). The product containing fractions were combined and the solvent was removed under reduced pressure. Et_2O (20 mL) and pentane (20 mL) were added and the solvent was removed under reduced pressure to afford arylated pyrrolidine **2a** as a yellow solid (1.20 g, 67%).

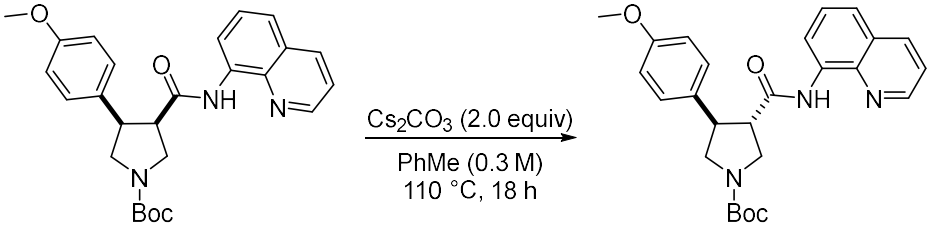
***tert*-Butyl (+)-(3*S*,4*S*)-3-(4-methoxyphenyl)-4-(quinolin-8-ylcarbamoyl)pyrrolidine-1-carboxylate ((+)-2a)**



A reaction tube was charged with K_2CO_3 (69.1 mg, 0.50 mmol), flame-dried, and allowed to cool under argon. Amide (*S*)-**1** (171 mg, 0.50 mmol), 4-iodoanisole (1.50 mmol), $Pd(OAc)_2$ (5.60 mg, 25.0 μmol) and PivOH (51.2 mg, 0.50 mmol) were added sequentially. The reaction vessel was sealed and purged with argon, then $PhCF_3$ (500 μL, 1.00 M) was added by syringe. The reaction tube was then placed in a preheated oil bath and stirred at 110 ºC for 18 h. The reaction mixture was then allowed to cool to rt and EtOAc (10 mL) was added. The resulting mixture 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 (5% to 20% acetone/pentane). The product containing fractions were combined and the solvent was removed under reduced pressure. Et_2O (5 mL) and pentane (5 mL) were added and the solvent was removed under reduced pressure to afford the arylated pyrrolidine **(+)-2a** as a yellow solid (134 mg, 60%, 97.8% *ee*). $[\alpha]_D^{25}$ +92 (*c* 0.40, $CHCl_3$).
Characterisation data identical to that reported for racemic pyrrolidine **2a**.

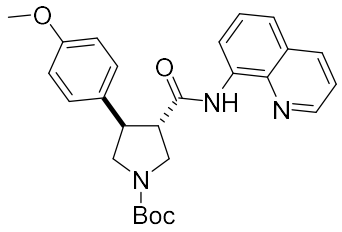
HPLC Conditions: Chiralpak IF 3-column, 80:20 *n*-hexane:*i*-PrOH, flow rate: 1 mL·min^{-1}, 35 ºC. UV detection wavelength: 210.4 nm. Retention times: 15.7 min (3*R*,4*R* enantiomer), 18.2 min (3*S*,4*S* enantiomer).

Epimerization of *cis*-3,4-Disubstituted Pyrrolidine 2a



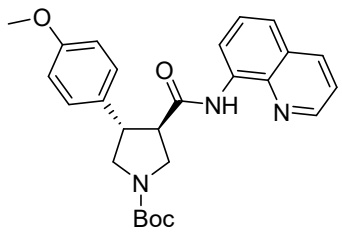
2a **4a** 85%

***tert*-Butyl *trans*-(±)-3-(4-methoxyphenyl)-4-(quinolin-8–ylcarbamoyl)pyrrolidine-1-carboxylate (4a)**



A flame-dried reaction tube was charged with 3-aryl pyrrolidine **2a** (89.5 mg, 0.20 mmol) and Cs_2CO_3 (130 mg, 0.40 mmol). The reaction vessel was sealed and purged with argon, then toluene (667 μL, 0.3 M) was added by syringe. The reaction tube was then placed in a preheated oil bath and stirred at 110 ºC for 18 h. The reaction mixture was then allowed to cool to rt and EtOAc (5 mL) was added. The resulting mixture was filtered through a pad of Celite, eluting with further EtOAc (2 × 5 mL). The solvent was removed under reduced pressure and the crude material was purified by flash column chromatography (0% to 20% acetone/hexane). The product containing fractions were combined and the solvent was removed under reduced pressure. Et_2O (5 mL) and pentane (5 mL) were added and the solvent was removed under reduced pressure to afford arylated pyrrolidine **4a** as a white solid (78.0 mg, 85%). R_f 0.20 (20% acetone/hexane); mp = 145–150 °C (from Et_2O/pentane); ν_{max} (film)/cm^{-1} 3341 (NH br), 2973, 1684 (C=O), 1526, 1485, 1387, 1325, 1246, 1161, 1125, 1033, 881, 826, 791, 770; ^{1}H NMR (400 MHz, DMSO-d_6, 373 K) δ 9.81 (br s, 1 H, NH), 8.77 (dd, *J* = 4.2, 1.7 Hz, 1 H, HC_{Ar}), 8.55 (dd, *J* = 7.6, 1.4 Hz, 1 H, HC_{Ar}), 8.32 (dd, *J* = 8.3, 1.7 Hz, 1 H, HC_{Ar}), 7.61 (dd, *J* = 8.3, 1.4 Hz, 1 H, HC_{Ar}), 7.58–7.49 (m, 2 H, HC_{Ar}), 7.37–7.30 (m, 2 H, HC_{Ar}), 6.91–6.86 (m, 2 H, HC_{Ar}), 3.92–3.87 (m, 1 H, NC*H*HCHCO), 3.87–3.82 (m, 1 H, NC*H*HCHAr), 3.72 (s, 3 H, OCH_3), 3.71–3.57 (m, 3 H, NCH*H*CHCO, CHCO, CHAr), 3.38–3.26 (m, 1 H, NCH*H*CHAr), 1.46 (s, 9 H, $C(CH_3)_3$); ^{13}C NMR (101 MHz, DMSO-d_6, 373 K) δ 169.4 (C=O amide), 158.2 (OC_{Ar} quat), 152.9 (C=O carbamate), 148.0 (C_{Ar}), 137.7 (C_{Ar} quat), 135.8 (C_{Ar}), 133.7 (C_{Ar} quat), 130.9 (C_{Ar} quat), 128.0 (2 × C_{Ar}), 127.3 (C_{Ar} quat), 126.2 (C_{Ar}), 121.44 (C_{Ar}), 121.37 (C_{Ar}), 116.2 (C_{Ar}), 113.9 (2 × C_{Ar}), 78.2 (*C*$(CH_3)_3$), 54.7 (OCH_3), 52.6 (N*C*H_2CHAr), 51.0 (*C*HCO), 48.6 (N*C*H_2CHCO), 46.2 (*C*HAr), 27.8 (C(*C*$H_3)_3$); HRMS (ESI$^+$) m/z Calculated for $C_{26}H_{30}N_3O_4^+$ $[M+H]^+$ 448.2236; Found 448.2224.

***tert*-Butyl (+)-(3*S*,4*R*)-3-(4-methoxyphenyl)-4-(quinolin-8-ylcarbamoyl)pyrrolidine-1-carboxylate ((+)-4a)**

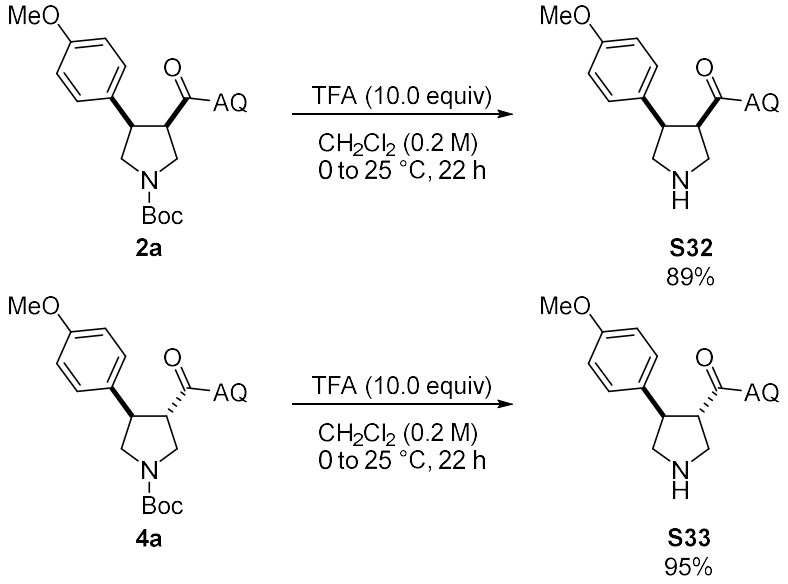


A flame-dried reaction tube was charged with 3-aryl pyrrolidine **(+)-2a** (89.5 mg, 0.20 mmol) and Cs_2CO_3 (130 mg, 0.40 mmol). The reaction vessel was sealed and purged with argon, then toluene (667 μL, 0.3 M) was added by syringe. The reaction tube was then placed in a preheated oil bath and stirred at 110 ºC for 18 h. The reaction mixture was then allowed to cool to rt and EtOAc (5 mL) was added. The resulting mixture was filtered through a pad of Celite, eluting with further EtOAc (2 × 5 mL). The solvent was removed under reduced pressure and the crude material was purified by flash column chromatography (20% acetone/hexane). The product containing fractions were combined and the solvent was removed under reduced pressure. Et_2O (5 mL) and pentane (5 mL) were added and the solvent was removed under reduced pressure to

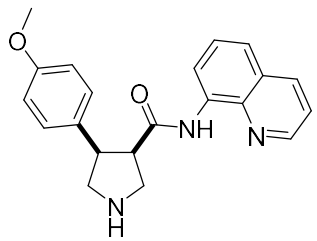
afford arylated pyrrolidine **(+)-4a** as a white solid (61.1 mg, 68%, 97.4% *ee*). $[\alpha]_D^{25}$ +11.4 (*c* 0.90, $CHCl_3$).
Characterisation data identical to that reported for racemic pyrrolidine **4a**.

HPLC Conditions: Chiralpak IF 3-column, 80:20 *n*-hexane:*i*-PrOH, flow rate: 1 mL·min^{-1}, 35 ºC. UV detection wavelength: 210.4 nm. Retention times: 14.9 min (3*R*,4*S* enantiomer), 18.0 min (3*S*,4*R* enantiomer).

Boc-Deprotection of Pyrrolidine Derivatives 2a and 4a

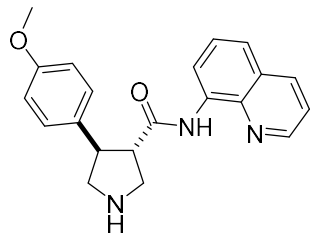


***cis*-(±)-4-(4–methoxyphenyl)-*N*-(quinolin-8-yl)pyrrolidine-3-carboxamide (S32)**



Freshly-distilled trifluoroacetic acid (149 μL) was added dropwise to a solution of Boc-protected *cis*-pyrrolidine **2a** (89.5 mg, 0.20 mmol) in CH_2Cl_2 (1.0 mL) at 0 °C. The reaction was allowed to warm up and stirred at rt for 22 h. The reaction mixture was then diluted with H_2O (3 mL), and quenched with $NaHCO_3$ (250 mg). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (4 × 5 mL). The combined organic layers were dried over Na_2SO_4 and the solvent was removed under reduced pressure. The resulting crude material was purified by flash column chromatography (98:2:1, CH_2Cl_2/MeOH/Et_3N), which afforded *cis*-pyrrolidine **S32** as a yellow paste (62 mg, 89%). R_f 0.27 (95:5:1, CH_2Cl_2/MeOH/Et_3N); ν_{max} (film)/cm^{-1} 3344 (NH br), 2933, 1675 (C=O), 1526, 1487, 1425, 1379, 1324, 1249, 1181, 1036, 905, 826, 792, 727; ^{1}H NMR (400 MHz, $CDCl_3$, 298 K) δ 9.67 (br s, 1 H, CONH), 8.71 (dd, *J* = 4.3, 1.6 Hz, 1 H, HC_{Ar}), 8.51 (dd, *J* = 6.1, 2.9 Hz, 1 H, HC_{Ar}), 8.09 (d, *J* = 8.1 Hz, 1 H, HC_{Ar}), 7.46–7.38 (m, 3 H, HC_{Ar}), 7.23–7.18 (m, 2 H, HC_{Ar}), 7.61–7.56 (m, 2 H, HC_{Ar}), 3.77–3.65 (m, 2 H, CHAr, NC*H*HCHCO), 3.52 (s, 3 H, OCH_3), 3.44 (dd, 2 H, *J* = 8.4, 3.2 Hz, N*CH*$_2$CHAr), 3.38–3.29 (m, 2 H, CHCO, NCH*H*CHCO), 2.52 (br s, 1 H, NH); ^{13}C NMR (101 MHz, $CDCl_3$, 298 K) δ 171.6 (C=O amide), 158.2 (OC_{Ar} quat), 147.9 (C_{Ar}), 138.3 (C_{Ar} quat), 136.0 (C_{Ar}), 134.3 (C_{Ar} quat), 130.8 (C_{Ar} quat), 129.0 (2 × C_{Ar}), 127.7 (C_{Ar} quat), 127.1 (C_{Ar}), 121.3 (C_{Ar}), 121.2 (C_{Ar}), 116.3 (C_{Ar}), 113.6 (2 × C_{Ar}), 54.9 (OCH_3), 53.1 (*C*HCO), 52.0 (N*C*H$_2$CHAr), 50.7 (N*C*H$_2$CHCO), 49.2 (*C*HAr); HRMS (ESI$^+$) m/z Calculated for $C_{21}H_{22}N_3O_2^+$ $[M+H]^+$ 348.1712; Found 348.1716.

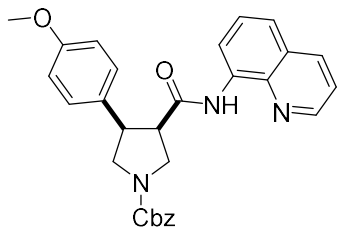
trans-(±)-4-(4-methoxyphenyl)-_N_-(quinolin-8-yl)pyrrolidine-3-carboxamide (S33)



Freshly-distilled trifluoroacetic acid (119 μL) was added dropwise to a solution of Boc-protected *trans*-pyrrolidine **4a** (71.0 mg, 0.16 mmol) in CH_2Cl_2 (800 μL) at 0 °C. The reaction was allowed to warm up and stirred at rt for 22 h. The reaction mixture was then diluted with H_2O (3 mL), and quenched with $NaHCO_3$ (250 mg). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (4 × 5 mL). The combined organic layers were dried over Na_2SO_4 and the solvent was removed under reduced pressure, affording *trans*-pyrrolidine **S33** as a pale orange oil (65.9 mg, 95%). R_f 0.27 (95:5:1, CH_2Cl_2/MeOH/Et_3N); ν_{max} (film)/cm^{-1} 3302 (NH br), 2929, 1676 (C=O), 1522, 1513, 1484, 1462, 1424, 1385, 1323, 1244, 1179, 1032, 824, 790; ^{1}H NMR (400 MHz, $CDCl_3$, 298 K) δ 9.78 (br s, 1 H, CONH), 8.76 (dd, *J* = 7.3, 1.7 Hz, 1 H, HC_{Ar}), 8.69 (dd, *J* = 4.3, 1.7 Hz, 1 H, HC_{Ar}), 8.13 (dd, *J* = 8.2, 1,7 Hz, 1 H, HC_{Ar}), 7.58–7.47 (m, 2 H, HC_{Ar}), 7.42 (dd, *J* = 8.3, 4.2 Hz, 1 H, HC_{Ar}), 7.27 (d, *J* = 8.7 Hz, 2 H, HC_{Ar}), 7.68 (d, *J* = 8.7 Hz, 2 H, HC_{Ar}), 3.79 (s, 3 H, OCH_3), 3.66–3.53 (m, 3 H, CHAr, NC*H*HCHCO, NC*H*HCHAr), 3.50–3.43 (m, 1 H, NCH*H*CHCO), 3.21–3.14 (m, 1 H, CHCO), 3.02–2.94 (m, 1 H, NCH*H*CHAr), 2.31 (br s, 1 H, NH); ^{13}C NMR (101 MHz, $CDCl_3$, 298 K) δ 173.0 (C=O amide), 158.4 (OC_{Ar} quat), 148.0 (C_{Ar}), 138.2 (C_{Ar} quat), 136.2 (C_{Ar}), 134.4 (C_{Ar} quat), 134.1 (C_{Ar} quat), 128.5 (2 × C_{Ar}), 127.8 (C_{Ar} quat), 127.3 (C_{Ar}), 121.5 (2 × C_{Ar}), 116.4 (C_{Ar}), 114.2 (2 × C_{Ar}), 56.7 (N*C*H_2CHAr), 56.5 (*C*HCO), 55.2 (OCH_3), 52.5 (N*C*H_2CHCO), 50.8 (*C*HAr); HRMS (ESI$^+$) m/z Calculated for $C_{21}H_{22}N_3O_2^+$ $[M+H]^+$ 348.1712; Found 348.1708.

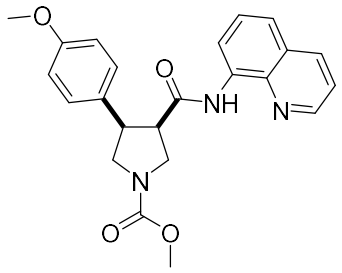
Pyrrolidine C–H Arylation: Scope of *N*-Protecting Groups **(9–12a)**

Benzyl *cis*-(±)-3-(4-methoxyphenyl)-4-(quinolin-8-ylcarbamoyl)pyrrolidine-1-carboxylate (9a)



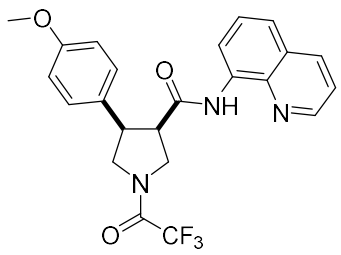
A reaction tube was charged with K_2CO_3 (27.6 mg, 0.20 mmol), flame-dried, and allowed to cool under argon. Amide **5** (75.1 mg, 0.20 mmol), 4-iodoanisole (140 mg, 0.6 mmol), $Pd(OAc)_2$ (2.20 mg, 10.0 μmol) and PivOH (20.5 mg, 0.20 mmol) were added sequentially. The reaction vessel was sealed and purged with argon, then $PhCF_3$ (1.00 M, 200 μL) was added by syringe. The reaction tube was then placed in a preheated oil bath and stirred at 110 ºC for 18 h. The reaction mixture was then allowed to cool to rt and EtOAc (5 mL) was added. The resulting mixture was filtered through a pad of Celite, eluting with further EtOAc (2 × 5 mL). The solvent was removed under reduced pressure and the crude material was purified by flash column chromatography (0% to 20% acetone/hexane). The product containing fractions were combined and the solvent was removed under reduced pressure. Et_2O (5 mL) and pentane (5 mL) were added and the solvent was removed under reduced pressure to afford arylated pyrrolidine **9a** as a yellow solid (65.1 mg, 67%). R_f 0.10 (20% acetone/hexane); mp = 54–60 °C (from Et_2O/pentane); ν_{max} (film)/cm^{-1} 3342 (NH br), 2955, 1685 (C=O), 1525, 1417, 1324, 1248, 1181, 1110, 1030, 826, 756, 697; ^{1}H NMR (400 MHz, DMSO-d_6, 373 K): δ 9.70 (br s, 1 H, NH), 8.82 (dd, *J* = 4.2, 1.7 Hz, 1 H, HC_{Ar}), 8.35 (dd, *J* = 7.7, 1.4 Hz, 1 H, HC_{Ar}), 8.31 (dd, *J* = 8.3, 1.7 Hz, 1 H, HC_{Ar}), 7.54–7.48 (m, 2 H, HC_{Ar}), 7.47 (t, *J* = 8.0 Hz, 1 H, HC_{Ar}), 7.44–7.35 (m, 4 H, HC_{Ar}), 7.35–7.29 (m, 1 H, HC_{Ar}), 7.18–7.14 (m, 2 H, HC_{Ar}), 6.69–6.63 (m, 2 H, HC_{Ar}), 5.18 (s, 2H, OCH_2Ph), 3.90 (dd, *J* = 10.5, 3.8 Hz, 1 H, NC*H*HCHCO), 3.88–3.80 (m, 4 H, CHCO, CHAr, NCH_2CHAr), 3.76–3.70 (m, 1 H, NCH*H*CHCO), 3.55 (s, 3 H, OCH_3);^{13}C NMR (101 MHz, DMSO-d_6, 373 K) δ 169.3 (C=O amide), 157.8 (OC_{Ar} quat), 153.6 (C=O carbamate), 147.9 (C_{Ar}), 137.7 (C_{Ar} quat), 136.8 (C_{Ar}, quat), 135.7 (C_{Ar}), 133.6 (C_{Ar} quat), 129.7 (C_{Ar} quat), 128.0 (2 × C_{Ar}), 127.8 (2 × C_{Ar}), 127.2 (C_{Ar} quat), 127.1 (C_{Ar}), 126.8 (2 × C_{Ar}), 126.1 (C_{Ar}), 121.2 (C_{Ar}), 121.1 (C_{Ar}), 116.0 (C_{Ar}), 113.3 (2 × C_{Ar}), 65.5 (O*C*H_2Ph), 54.4 (OCH_3), 49.8 (N*C*H_2CHAr), 49.1 (*C*HCO), 47.7 (N*C*H_2CHCO), 44.9 (*C*HAr); HRMS (ESI$^+$) m/z Calculated for $C_{29}H_{28}N_3O_4^+$ $[M+H]^+$ 482.2080; Found 482.2072.

Methyl *cis*-(±)-3-(4-methoxyphenyl)-4-(quinolin-8-ylcarbamoyl)pyrrolidine-1-carboxylate (10a)



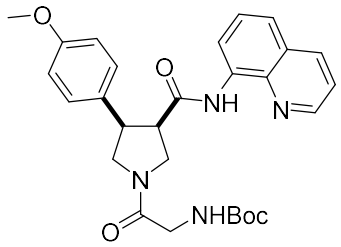
Prepared according to **General Procedure A** using methyl 3-(quinolin-8-ylcarbamoyl)pyrrolidine-1-carboxylate **6** (154 mg) and 4-iodoanisole (351 mg). Purification by flash column chromatography (30% to 35% acetone/hexane) afforded arylated pyrrolidine **10a** as a pale pink solid (118 mg, 57%). R_f 0.18 (30% acetone/hexane); mp = 60–65 °C (from Et_2O/pentane); ν_{max} (film)/cm^{-1} 3336 (NH br), 2954, 1683 (C=O), 1525, 1486, 1451, 1386, 1324, 1248, 1182, 1116, 1032, 827, 792, 769; ^{1}H NMR (400 MHz, DMSO-d_6, 373 K) δ 9.70 (br s, 1 H, NH), 8.83 (dd, *J* = 4.2, 1.7 Hz, 1 H, HC_{Ar}), 8.35 (dd, *J* = 7.7, 1.4 Hz, 1 H, HC_{Ar}), 8.31 (dd, *J* = 8.3, 1.7 Hz, 1 H, HC_{Ar}), 7.60–7.54 (m, 2 H, HC_{Ar}), 7.47 (t, *J* = 8.0 Hz, 1 H, HC_{Ar}), 7.19–7.13 (m, 2 H, HC_{Ar}), 6.70–6.65 (m, 2 H, HC_{Ar}), 3.88–3.76 (m, 5 H, CHCO, CHAr, NC*H*HCHCO, NCH_2CHAr), 3.72–3.7 (m, 4 H, NCH*H*CHCO, $COOCH_3$), 3.55 (s, 3 H, OCH_3); ^{13}C NMR (101 MHz, DMSO-d_6, 373 K) δ 169.4 (C=O amide), 157.7 (OC_{Ar} quat), 154.2 (C=O carbamate), 147.9 (C_{Ar}), 137.7 (C_{Ar} quat), 135.7 (C_{Ar}), 133.6 (C_{Ar} quat), 129.7 (C_{Ar} quat), 128.0 (2 × C_{Ar}), 127.2 (C_{Ar} quat), 126.1 (C_{Ar}), 121.3 (C_{Ar}), 121.1 (C_{Ar}), 116.0 (C_{Ar}), 113.3 (2 × C_{Ar}), 54.4 (OCH_3), 51.4 ($COOCH_3$), 49.7 (N*C*H_2CHAr), 49.1 (*C*HCO), 47.6 (N*C*H_2CHCO), 44.9 (*C*HAr); HRMS (ESI$^+$) m/z Calculated for $C_{23}H_{24}N_3O_4^+$ $[M+H]^+$ 406.1767; Found 406.1771.

cis-(±)-4-(4-Methoxyphenyl)-_N_-(quinolin-8-yl)-1-(2,2,2-trifluoroacetyl)pyrrolidine-3-carboxamide (11a)



Prepared according to **General Procedure A** using *N*-(quinolin-8-yl)-1-(2,2,2-trifluoroacetyl) pyrrolidine-3-carboxamide **7** (189 mg) and 4-iodoanisole (351 mg). Purification by flash column chromatography (20% to 30% acetone/hexane) afforded arylated pyrrolidine **11a** as a pale yellow solid (43.0 mg, 19%, containing 6% of inseparable impurity). R_f 0.26 (30% acetone/pentane); mp = 111–115 °C (from Et_2O/pentane); ν_{max} (film)/cm^{-1} 3332 (NH br), 1681 (C=O), 1531, 1515, 1488, 1456, 1424, 1325, 1245, 1197, 1127, 1035, 940, 826, 788, 755, 689; ^{1}H NMR (400 MHz, DMSO-d_6, 373 K, observed as a mixture of rotamers) δ 9.74 (br s, 1 H, NH), 8.83 (dd, J = 4.2, 1.7 Hz, 1 H, HC_{Ar}), 8.39–8.29 (m, 2 H, HC_{Ar}), 7.60 (dd, J = 8.3, 1.4 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}), 7.21–7.16 (m, 2 H, HC_{Ar}), 6.71–6.66 (m, 2 H, HC_{Ar}), 4.21–3.82 (br m, 6 H, CHCO, CHAr, NCH_2CHCO, NCH_2CHAr), 3.55 (s, 3 H, OCH_3); ^{13}C NMR (101 MHz, DMSO-d_6, 373 K, observed as a mixture of rotamers) δ 169.3 and 168.8 (C=O amide), 158.0 (C_{Ar} quat), 153.8 (q, J_{CF} = 35.5 Hz, CF_3C=O), 148.0 (C_{Ar}), 137.7 (C_{Ar} quat), 135.7 (C_{Ar}), 133.5 (C_{Ar} quat), 128.6 and 128.4 (C_{Ar} quat), 128.0 (2 × C_{Ar}), 127.2 (C_{Ar} quat), 126.1 (C_{Ar}), 121.4 (C_{Ar}), 121.3 (C_{Ar}), 116.3 and 116.2 (C_{Ar}), 115.8 (q, J_{CF} = 287.7 Hz, CF_3), 113.4 (2 × C_{Ar}), 54.5 (OCH_3), 50.7 and 49.4 (NCH$_2$CHAr), 49.60 and 47.0 (*C*HCO), 49.55 and 48.1 (NCH$_2$CH$_2$), 45.6 and 43.0 (*C*HAr); ^{19}F NMR (376 MHz, DMSO-d_6, 373 K, observed as a mixture of rotamers) δ –71.16, –71.21; HRMS (ESI$^+$) m/z Calculated for $C_{23}H_{21}N_3O_3F_3^+$ $[M+H]^+$ 444.1535; Found 444.1543.

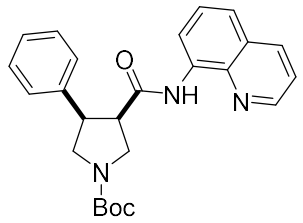
***tert*-Butyl *cis*-(±)-(2-(3-(4-methoxyphenyl)-4-(quinolin-8-ylcarbamoyl)pyrrolidin-1-yl)-2-oxoethyl)carbamate (12a)**



Prepared according to **General Procedure A** using *tert*-butyl (±)-(2-oxo-2-(3-(quinolin-8-ylcarbamoyl)pyrrolidin-1-yl)ethyl)carbamate **8** (199 mg) and 4-iodoanisole (585 mg, **2.50 mmol**). The reaction was stirred at 110 °C for **48 h**. Purification by flash column chromatography (2% MeOH/CH_2Cl_2) afforded arylated pyrrolidine **12a** as a pale yellow solid (44.3 mg, 18%). R_f 0.47 (5% MeOH/ CH_2Cl_2); mp = 155–160 °C (from Et_2O/pentane); ν_{max} (film)/cm^{-1} 3407 (NH), 3325 (NH), 2974, 1706 (C=O), 1685 (C=O), 1645 (C=O), 1529, 1488, 1440, 1326, 1246, 1163, 1035, 826, 789, 705; ^{1}H NMR (400 MHz, CDCl3, 298 K, observed as a mixture of rotamers) δ 9.48 and 9.46 (2 × br s, 1 H, NH_{AQ}), 8.68 and 8.67 (2 × dd, J = 4.2, 2.1 Hz, 1 H, HC_{Ar}), 8.58–8.45 (m, 1 H, HC_{Ar}), 8.12 and 8.10 (2 × dd, J = 3.4, 1.7 Hz, 1 H, HC_{Ar}), 7.49–7.43 (m, 2 H, HC_{Ar}), 7.42 and 7.41 (2 × dd, J = 8.5, 4.4 Hz, 1 H, HC_{Ar}), 7.19–7.10 (m, 2 H, HC_{Ar}), 6.67–6.59 (m, 2 H, HC_{Ar}), 5.57 (br t, J = 4.3 Hz, 1 H, NHBoc), 4.22 (dd, J = 12.4, 3.2 Hz, 0.6 H, NC*H*HCHCO), 4.12–3.96 (m, 4 H, NC*H*HCHCO, CH_2NHBoc, NC*H*HCH$_2$), 3.91–3.72 (m, 3 H, NCH*H*CH$_2$, CHAr, NCH*H*CHCO), 3.63–3.56 (m, 0.6 H, CHCO), 3.54 and 3.53 (2 × s, 3 H, OCH_3), 3.50–3.44 (m, 0.6 H, CHCO), 1.48 (s, 9 H, C(CH_3)$_3$); ^{13}C NMR (101 MHz, CDCl3, 298 K, observed as a mixture of rotamers) δ 169.4 and 168.7 (CH*C*=O amide), 167.1 (CH$_2$*C*=O amide), 158.9 and 158.8 (OC_{Ar} quat), 155.8 (C=O carbamate), 148.0 (C_{Ar}), 138.2 and 138.1 (C_{Ar} quat), 136.1 (C_{Ar}), 133.8 and 133.7 (C_{Ar} quat), 128.6 and 128.5 (2 × C_{Ar}), 128.1 (C_{Ar} quat), 127.7 (C_{Ar} quat), 127.2 (C_{Ar}), 121.7 (C_{Ar}), 121.5 (C_{Ar}), 116.5 and 116.4 (C_{Ar}), 114.1 and 114.0 (2 × C_{Ar}), 79.6 (*C*(CH_3)$_3$), 55.0 and 54.9 (OCH_3), 51.6 and 50.0 (*C*HCO), 49.8 and 49.1 (NCH$_2$CHAr), 48.5 and 47.21 (NCH$_2$CHCO), 47.15 and 45.2 (*C*HAr), 43.2 and 43.0 (*C*H$_2$NHBoc), 28.4 (C(*C*H$_3$)$_3$); HRMS (ESI$^+$) m/z Calculated for $C_{28}H_{33}N_4O_5^+$ $[M+H]^+$ 505.2451; Found 505.2457.

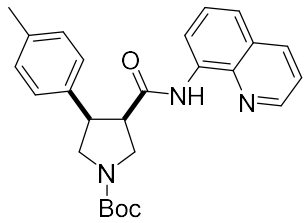
Pyrrolidine C–H Arylation: Scope of Aryl Iodides **(2/9b–x)**

tert-Butyl *cis*-(±)-3-phenyl-4-(quinolin-8-ylcarbamoyl)pyrrolidine-1-carboxylate (2b)



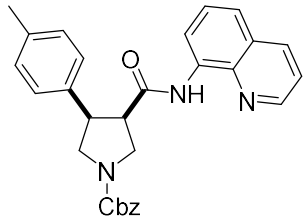
Prepared according to **General Procedure A** using *tert*-butyl 3-(quinolin-8-ylcarbamoyl)pyrrolidine-1-carboxylate **1** (171 mg) and iodobenzene (306 mg). Purification by flash column chromatography (10% $MeCN/CH_2Cl_2$) afforded arylated pyrrolidine **2b** as a white solid (89.6 mg, 43%). R_f 0.42 (10% $MeCN/CH_2Cl_2$); mp = 65–68 °C (from Et_2O/pentane); ν_{max} (film)/cm^{-1} 3341 (NH br), 2976, 1682 (C=O), 1524, 1485, 1390, 1365, 1325, 1256, 1162, 1116, 874, 826, 790, 755, 698; ^{1}H NMR (400 MHz, DMSO-d_6, 373 K) δ 9.75 (br s, 1 H, NH), 8.85 (dd, *J* = 4.2, 1.7 Hz, 1 H, HC_{Ar}), 8.33 (dd, *J* = 3.8, 1.5 Hz, 1 H, HC_{Ar}), 8.31 (dd, *J* = 4.5, 1.5 Hz, 1 H, HC_{Ar}), 7.60–7.54 (m, 2 H, HC_{Ar}), 7.46 (t, *J* = 8.0 Hz, 1 H, HC_{Ar}), 7.27–7.22 (m, 2 H, HC_{Ar}), 7.15–7.09 (m, 2 H, HC_{Ar}), 7.05–7.00 (m, 1 H, HC_{Ar}), 3.92–3.85 (m, 2 H, CHCO, CHAr), 3.85–3.77 (m, 3 H, NC*H*HCHCO, NCH_2CHAr), 3.69–3.64 (m, 1 H, NCH*H*CHCO), 1.49 (s, 9 H, $C(CH_3)_3$); ^{13}C NMR (101 MHz, DMSO-d_6, 373 K) δ 169.3 (C=O amide), 153.2 (C=O carbamate), 148.0 (C_{Ar}), 138.1 (C_{Ar} quat), 137.7 (C_{Ar} quat), 135.7 (C_{Ar}), 133.6 (C_{Ar} quat), 127.5 (2 × C_{Ar}), 127.2 (C_{Ar} quat), 127.0 (2 × C_{Ar}), 126.1 (C_{Ar}), 126.0 (C_{Ar}), 121.3 (C_{Ar}), 121.1 (C_{Ar}), 116.0 (C_{Ar}), 78.0 (*C*$(CH_3)_3$), 49.7 (N*C*H_2CHAr), 49.0 (*C*HCO), 47.5 (N*C*H_2CHCO), 45.4 (*C*HAr), 27.8 (C(*C*$H_3)_3$); HRMS (ESI$^+$) m/z Calculated for $C_{25}H_{28}N_3O_3^+$ $[M+H]^+$ 418.2131; Found 418.2136.

tert-Butyl *cis*-(±)-3-(quinolin-8-ylcarbamoyl)-4-(*p*-tolyl)pyrrolidine-1-carboxylate (2c)



Prepared according to **General Procedure A** using *tert*-butyl 3-(quinolin-8-ylcarbamoyl)pyrrolidine-1-carboxylate **1** (171 mg) and 4-iodotoluene (327 mg). Purification by flash column chromatography (5% to 10% $MeCN/CH_2Cl_2$) afforded arylated pyrrolidine **2c** as a white solid (118 mg, 55%). *R*$_f$ 0.22 (5% $MeCN/CH_2Cl_2$); mp = 60–64 °C (from Et_2O/pentane); ν_{max} (film)/cm^{-1} 3345 (NH br), 2974, 1685 (C=O), 1525, 1485, 1391, 1324, 1163, 1115, 874, 824, 791, 758; ^{1}H NMR (400 MHz, DMSO-d_6, 373 K) δ 9.71 (br s, 1 H, NH), 8.84 (dd, *J* = 4.2, 1.7 Hz, 1 H, HC_{Ar}), 8.34 (dd, *J* = 7.7, 1.4 Hz, 1 H, HC_{Ar}), 8.31 (dd, *J* = 8.3, 1.7 Hz, 1 H, HC_{Ar}), 7.60–7.53 (m, 2 H, HC_{Ar}), 7.47 (t, *J* = 8.0 Hz, 1 H, HC_{Ar}), 7.14–7.08 (m, 2 H, HC_{Ar}), 6.94–6.88 (m, 2 H, HC_{Ar}), 3.87–3.78 (m, 3 H, CHCO, CHAr, NC*H*HCHCO), 3.78–3.72 (m, 2 H, NCH_2CHAr), 3.69–3.61 (m, 1 H, NCH*H*CHCO), 2.07 (s, 3 H, CH_3), 1.49 (s, 9 H, $C(CH_3)_3$); ^{13}C NMR (101 MHz, DMSO-d_6, 373 K) δ 169.3 (C=O amide), 153.2 (C=O carbamate), 147.9 (C_{Ar}), 137.6 (C_{Ar} quat), 135.7 (C_{Ar}), 135.1 (C_{Ar} quat), 135.0 (C_{Ar} quat), 133.6 (C_{Ar} quat), 128.1 (2 × C_{Ar}), 127.2 (C_{Ar} quat), 126.8 (2 × C_{Ar}), 126.1 (C_{Ar}), 121.2 (C_{Ar}), 121.1 (C_{Ar}), 116.0 (C_{Ar}), 78.0 (*C*$(CH_3)_3$), 49.7 (N*C*H_2CHAr), 49.1 (*C*HCO), 47.5 (N*C*H_2CHCO), 45.2 (*C*HAr), 27.8 (C(*C*$H_3)_3$), 19.7 (CH_3); HRMS (ESI$^+$) m/z Calculated for $C_{26}H_{30}N_3O_3^+$ $[M+H]^+$ 432.2287; Found 432.2304.

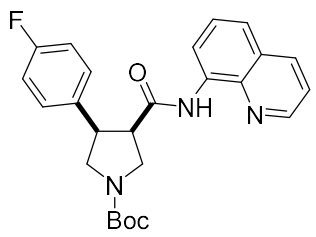
Benzyl *cis*-(±)-3-(quinolin-8-ylcarbamoyl)-4-(*p*-tolyl)pyrrolidine-1-carboxylate (9c)



Prepared according to **General Procedure A** using benzyl 3-(quinolin-8-ylcarbamoyl)pyrrolidine-1-carboxylate **5** (187 mg) and 4-iodotoluene (327 mg). Purification by flash column chromatography (5% to 10% $MeCN/CH_2Cl_2$) afforded arylated pyrrolidine **9c** as a spale brown solid (123 mg, 53%). *R*$_f$ 0.53 (10% $MeCN/CH_2Cl_2$); mp = 56–59 °C (from Et_2O/pentane); ν_{max} (film)/cm^{-1} 3347 (NH br), 1694 (C=O), 1523, 1485, 1415, 1358, 1324, 1167, 1112, 824, 790, 765, 732, 696; ^{1}H NMR (400 MHz, DMSO-d_6, 373 K): δ 9.73 (br s, 1 H, NH), 8.82 (dd, *J* = 4.2, 1.7 Hz, 1 H, HC_{Ar}), 8.34 (dd, *J* = 7.7, 1.4 Hz, 1 H, HC_{Ar}), 8.31 (dd, *J* = 8.3, 1.7 Hz, 1 H, HC_{Ar}), 7.62–7.52 (m, 2 H, HC_{Ar}), 7.47 (t, *J* = 8.0 Hz, 1 H, HC_{Ar}), 7.46–7.33 (m, 4 H, HC_{Ar}), 7.36–7.27 (m, 1 H, HC_{Ar}), 7.17–7.09 (m, 2 H, HC_{Ar}), 6.95–6.87 (m, 2 H, HC_{Ar}), 5.18 (s, 2 H, OCH_2Ph), 3.94–3.82 (br m, 5 H, NC*H*HCHCO, CHCO, CHAr, NCH_2CHAr), 3.74 (dd, *J* = 10.3, 5.9 Hz, 1 H, NCH*H*CHCO), 2.07 (s, 3 H, CH_3);^{13}C NMR (101 MHz, DMSO-d_6, 373 K) δ 169.3 (C=O amide), 153.6 (C=O carbamate),

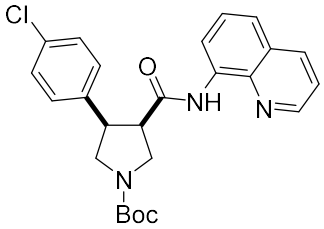
147.9 (C_{Ar}), 137.7 (C_{Ar} quat), 136.7 (C_{Ar}, quat), 135.7 (C_{Ar}), 135.2 (C_{Ar} quat), 134.7 (C_{Ar} quat), 133.6 (C_{Ar} quat), 128.1 (2 × C_{Ar}), 127.7 (2 × C_{Ar}), 127.2 (C_{Ar} quat), 127.1 (C_{Ar}), 126.83 (2 × C_{Ar}), 126.80 (2 × C_{Ar}), 126.1 (C_{Ar}), 121.2 (C_{Ar}), 121.1 (C_{Ar}), 116.0 (C_{Ar}), 65.5 (O*C*H_2Ph), 49.7 (N*C*H_2CHAr), 49.0 (*C*HCO), 47.7 (N*C*H_2CHCO), 45.2 (*C*HAr), 19.7 (CH_3); HRMS (ESI$^+$) m/z Calculated for $C_{29}H_{28}N_3O_3^+$ $[M+H]^+$ 466.2131; Found 466.2123.

tert-Butyl _cis_-(±)-3-(4-fluorophenyl)-4-(quinolin-8-ylcarbamoyl)pyrrolidine-1-carboxylate (2d)



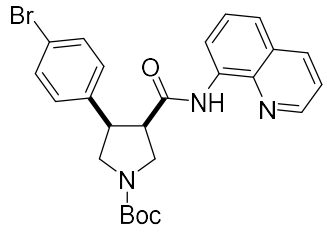
Prepared according to **General Procedure A** using *tert*-butyl 3-(quinolin-8-ylcarbamoyl)pyrrolidine-1-carboxylate **1** (171 mg) and 4-fluoroiodobenzene (333 mg). Purification by flash column chromatography (5% to 15% acetone/pentane) afforded arylated pyrrolidine **2d** as a white solid (95.8 mg, 44%). R_f 0.12 (10% acetone/pentane); mp = 94–97 °C (from Et_2O/pentane); ν_{max} (film)/cm^{-1} 3334 (NH br), 2973, 1678 (C=O), 1526, 1486, 1391, 1324, 1226, 1164, 1119, 827, 791, 769; ^{1}H NMR (400 MHz, DMSO-d_6, 373 K) δ 9.73 (br s, 1 H, NH), 8.85 (dd, J = 4.2, 1.7 Hz, 1 H, HC_{Ar}), 8.33 (m, 1 H, HC_{Ar}), 8.31 (m, 1 H, HC_{Ar}), 7.61–7.55 (m, 2 H, HC_{Ar}), 7.47 (t, J = 8.0 Hz, 1 H, HC_{Ar}), 7.30–7.24 (m, 2 H, HC_{Ar}), 6.94–6.87 (m, 2 H, HC_{Ar}), 3.93–3.84 (m, 2 H, CHCO, CHAr), 3.84–3.71 (m, 3 H, NC*H*HCHCO, NCH_2CHAr), 3.66 (dd, J = 10.9, 6.7 Hz, 1 H, NCH*H*CHCO), 1.49 (s, 9 H, C(CH_3)$_3$); ^{13}C NMR (101 MHz, DMSO-d_6, 373 K) δ 169.3 (C=O amide), 160.4 (d, J_{CF} = 243.4 Hz, FC_{Ar} quat), 153.2 (C=O carbamate), 148.0 (C_{Ar}), 137.7 (C_{Ar} quat), 135.8 (C_{Ar}), 134.2 (d, J_{CF} = 3.3 Hz, F-*p*-C_{Ar} quat), 133.5 (C_{Ar} quat), 128.9 (d, J_{CF} = 8.1 Hz, 2 × F-*m*-C_{Ar}), 127.2 (C_{Ar} quat), 126.1 (C_{Ar}), 121.3 (C_{Ar}), 121.2 (C_{Ar}), 116.2 (C_{Ar}), 114.2 (d, J_{CF} = 21.0 Hz, 2 × F-*o*-C_{Ar}), 78.1 (*C*(CH_3)$_3$), 49.7 (N*C*H_2CHAr), 49.0 (*C*HCO), 47.4 (N*C*H_2CHCO), 44.8 (*C*HAr), 27.8 (C(*C*H_3)$_3$); ^{19}F NMR (471 MHz, DMSO-d_6, 373 K) δ –116.3 (tt, J_{HF} = 8.6, 5.8 Hz); HRMS (ESI$^+$) m/z Calculated for $C_{25}H_{27}N_3O_3F^+$ $[M+H]^+$ 436.2036; Found 436.2053.

tert-Butyl _cis_-(±)-3-(4-chlorophenyl)-4-(quinolin-8-ylcarbamoyl)pyrrolidine-1-carboxylate (2e)



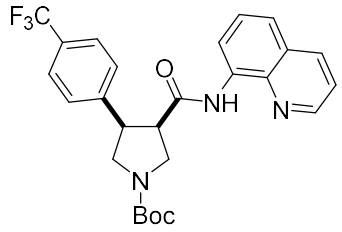
Prepared according to **General Procedure A** using *tert*-butyl 3-(quinolin-8-ylcarbamoyl)pyrrolidine-1-carboxylate **1** (171 mg) and 1-chloro-4-iodobenzene (358 mg). Purification by flash column chromatography (5% to 10% MeCN/CH_2Cl_2) afforded arylated pyrrolidine **2e** as a white solid (97.2 mg, 43%). R_f 0.17 (5% MeCN/CH_2Cl_2); mp = 152–155 °C (from Et_2O/pentane); ν_{max} (film)/cm^{-1} 3267 (NH br), 2982, 1674 (C=O), 1534, 1489, 1407, 1390, 1322, 1161, 1116, 1016, 871, 829, 799, 767; ^{1}H NMR (400 MHz, DMSO-d_6, 373 K) δ 9.75 (br s, 1 H, NH), 8.85 (dd, J = 4.2, 1.7 Hz, 1 H, HC_{Ar}), 8.35–8.29 (m, 2 H, HC_{Ar}), 7.62–7.55 (m, 2 H, HC_{Ar}), 7.47 (t, J = 8.0 Hz, 1 H, HC_{Ar}), 7.28–7.23 (m, 2 H, HC_{Ar}), 7.18–7.12 (m, 2 H, HC_{Ar}), 3.93–3.84 (m, 2 H, CHCO, CHAr), 3.84–3.71 (m, 3 H, NC*H*HCHCO, NCH_2CHAr), 3.70–3.62 (m, 1 H, NCH*H*CHCO), 1.48 (s, 9 H, C(CH_3)$_3$); ^{13}C NMR (101 MHz, DMSO-d_6, 373 K) δ 169.2 (C=O amide), 153.1 (C=O carbamate), 148.0 (C_{Ar}), 137.7 (C_{Ar} quat), 137.1 (C_{Ar} quat), 135.7 (C_{Ar}), 133.5 (C_{Ar} quat), 130.9 (C_{Ar} quat), 128.8 (2 × C_{Ar}), 127.4 (2 × C_{Ar}), 127.2 (C_{Ar} quat), 126.1 (C_{Ar}), 121.3 (2 × C_{Ar}), 116.2 (C_{Ar}), 78.1 (*C*(CH_3)$_3$), 49.5 (N*C*H_2CHAr), 48.9 (*C*HCO), 47.5 (N*C*H_2CHCO), 44.8 (*C*HAr), 27.8 (C(*C*H_3)$_3$); HRMS (ESI$^+$) m/z Calculated for $C_{25}H_{27}N_3O_3Cl^+$ $[M+H]^+$ 452.1741; Found 452.1750.

tert-Butyl _cis_-(±)-3-(4-bromophenyl)-4-(quinolin-8-ylcarbamoyl)pyrrolidine-1-carboxylate (2f)



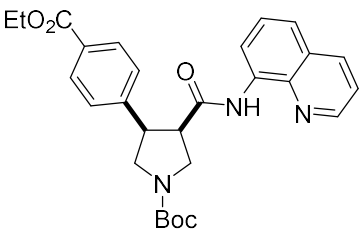
Prepared according to **General Procedure A** using *tert*-butyl 3-(quinolin-8-ylcarbamoyl)pyrrolidine-1-carboxylate **1** (171 mg) and 1-bromo-4-iodobenzene (424 mg). Purification by flash column chromatography (10% MeCN/CH_2Cl_2) afforded arylated pyrrolidine **2f** as a pale pink solid (112 mg, 45%). R_f 0.34 (10% MeCN/CH_2Cl_2); mp = 159–161°C; ν_{max} (film)/cm^{-1} 3273 (NH br), 2980, 1674 (C=O), 1533, 1488, 1409, 1389, 1321, 1161, 1115, 1011, 870, 828, 798, 767; ^{1}H NMR (400 MHz, DMSO-d_6, 373 K) δ 9.75 (br s, 1 H, NH), 8.85 (dd, J = 4.2, 1.7 Hz, 1 H, HC_{Ar}), 8.33 (dd, J = 2.7, 1.5 Hz, 1 H, HC_{Ar}), 8.31 (t, J = 1.8 Hz, 1 H, HC_{Ar}), 7.61–7.56 (m, 2 H, HC_{Ar}), 7.47 (t, J = 8.0 Hz, 1 H, HC_{Ar}), 7.31–7.27 (m, 2 H, HC_{Ar}), 7.21–7.17 (m, 2 H, HC_{Ar}), 3.91–3.83 (m, 2 H, CHCO, CHAr), 3.83–3.71 (m, 3 H, NC*H*HCHCO, NCH_2CHAr), 3.69–3.63 (m, 1 H, NCH*H*CHCO), 1.48 (s, 9 H, $C(CH_3)_3$); ^{13}C NMR (101 MHz, DMSO-d_6, 373 K) δ 169.1 (C=O amide), 153.1 (C=O carbamate), 148.0 (C_{Ar}), 137.7 (C_{Ar} quat), 137.6 (C_{Ar} quat), 135.7 (C_{Ar}), 133.5 (C_{Ar} quat), 130.4 (2 × C_{Ar}), 129.2 (2 × C_{Ar}), 127.2 (C_{Ar} quat), 126.1 (C_{Ar}), 121.3 (2 × C_{Ar}), 119.3 (C_{Ar} quat), 116.2 (C_{Ar}), 78.1 (*C*$(CH_3)_3$), 49.4 (N*C*H_2CHAr), 48.8 (*C*HCO), 47.5 (N*C*H_2CHCO), 44.9 (*C*HAr), 27.8 (C(*C*$H_3)_3$); HRMS (ESI$^+$) m/z Calculated for $C_{25}H_{27}N_3O_3Br^+$ [M+H]$^+$ 496.1236; Found 496.1239.

tert-Butyl _cis_-(±)-3-(quinolin-8-ylcarbamoyl)-4-(4-(trifluoromethyl)phenyl)pyrrolidine-1-carboxylate (2g)



Prepared according to **General Procedure A** using *tert*-butyl 3-(quinolin-8-ylcarbamoyl)pyrrolidine-1-carboxylate **1** (171 mg) and 1-iodo-4-(trifluoromethyl)benzene (408 mg). Purification by flash column chromatography (5% to 10% MeCN/CH_2Cl_2) afforded arylated pyrrolidine **2g** as a pale brown solid (59.0 mg, 24%). R_f 0.43 (10% MeCN/CH_2Cl_2); mp = 143–145 °C (from Et_2O/pentane); ν_{max} (film)/cm^{-1} 3274 (NH br), 2978, 1674 (C=O), 1532, 1488, 1408, 1369, 1328, 1161, 1117, 1070, 1019, 872, 841, 797, 765; ^{1}H NMR (400 MHz, DMSO-d_6, 373 K) δ 9.75 (br s, 1 H, NH), 8.83 (dd, J = 4.2, 1.7 Hz, 1 H, HC_{Ar}), 8.31 (dd, J = 8.3, 1.7 Hz, 1 H, HC_{Ar}), 8.28 (dd, J = 7.7, 1.3 Hz, 1 H, HC_{Ar}), 7.60–7.54 (m, 2 H, HC_{Ar}), 7.49–7.41 (m, 5 H, HC_{Ar}), 4.03–3.91 (m, 2 H, CHCO, CHAr), 3.86–3.78 (m, 3 H, N*C*HHCHCO, NCH_2CHAr), 3.69 (dd, J = 11.2, 7.0 Hz, 1 H, NCH*H*CHCO), 1.49 (s, 9 H, $C(CH_3)_3$); ^{13}C NMR (101 MHz, DMSO-d_6, 373 K) δ 169.1 (C=O amide), 153.1 (C=O carbamate), 148.0 (C_{Ar}), 143.0 (C_{Ar} quat), 137.7 (C_{Ar} quat), 135.7 (C_{Ar}), 133.4 (C_{Ar} quat), 127.9 (2 × C_{Ar}), 127.2 (C_{Ar} quat), 127.1 (q, J_{CF} = 30.1 Hz, F_3CC_{Ar} quat), 126.0 (C_{Ar}), 124.3 (q, J_{CF} = 3.9 Hz, 2 × C_{Ar}), 123.6 (q, J_{CF} = 271.9 Hz, CF_3 quat), 121.3 (C_{Ar}), 121.2 (C_{Ar}), 116.2 (C_{Ar}), 78.2 (*C*$(CH_3)_3$), 49.2 (N*C*H_2CHAr), 48.8 (*C*HCO), 47.6 (N*C*H_2CHCO), 45.2 (*C*HAr), 27.8 (C(*C*$H_3)_3$); ^{19}F NMR (376 MHz, DMSO-d_6, 373 K) δ –61.3; HRMS (ESI$^+$) m/z Calculated for $C_{26}H_{27}N_3O_3F_3^+$ [M+H]$^+$ 486.2005; Found 486.2003.

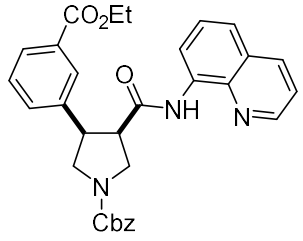
tert-Butyl _cis_-(±)-3-(4-(ethoxycarbonyl)phenyl)-4-(quinolin-8-ylcarbamoyl)pyrrolidine-1-carboxylate (2h)



Prepared according to **General Procedure A** using *tert*-butyl 3-(quinolin-8-ylcarbamoyl)pyrrolidine-1-carboxylate **1** (171 mg) and ethyl 4-iodobenzoate (552 mg, **2.0 mmol**). The reaction was stirred at 110 °C for **48 h**. Purification by flash column chromatography (20% acetone/hexane) afforded arylated pyrrolidine **2h** as a white solid (76.3 mg, 38%). R_f 0.12 (20% acetone/hexane); mp = 69–71 °C (from Et_2O/pentane); ν_{max} (film)/cm^{-1} 3323 (NH br), 1689 (C=O), 1525, 1486, 1392, 1324, 1276, 1164, 1105, 826, 791, 759; ^{1}H NMR (400 MHz, DMSO-d_6, 373 K) δ 9.74 (br s, 1 H, NH), 8.82 (dd, J = 4.2, 1.7 Hz, 1 H, HC_{Ar}), 8.32–8.28 (m, 2 H, HC_{Ar}), 7.72–7.68 (m, 2 H, HC_{Ar}), 7.59–7.53 (m, 2 H, HC_{Ar}), 7.45 (t, J = 7.9 Hz, 1 H, HC_{Ar}), 7.40–7.35 (m, 2 H, HC_{Ar}), 4.22 (q, J = 7.1 Hz, 2 H, OCH_2CH_3), 4.02–3.88 (m, 2 H, CHCO, CHAr), 3.85–3.79 (m, 3 H, N*C*HHCHCO, NCH_2CHAr), 3.68 (dd, J = 11.2, 6.9 Hz, 1 H, NCH*H*CHCO), 1.49 (s, 9 H, $C(CH_3)_3$), 1.25 (t, J = 7.1 Hz, 3 H, OCH_2CH_3); ^{13}C NMR (101 MHz, DMSO-d_6, 373 K) δ 169.1 (C=O amide), 164.8 (C=O ester), 153.2 (C=O carbamate), 147.9 (C_{Ar}), 143.6 (C_{Ar} quat), 137.7 (C_{Ar} quat),

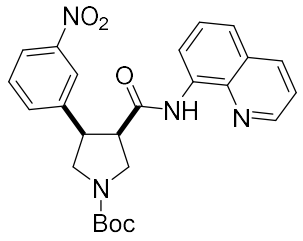
135.7 (C_{Ar}), 133.5 (C_{Ar} quat), 128.3 (2 × C_{Ar}), 128.2 (C_{Ar} quat), 127.3 (2 × C_{Ar}), 127.2 (C_{Ar} quat), 126.1 (C_{Ar}), 121.3 (C_{Ar}), 121.2(C_{Ar}), 116.2 (C_{Ar}), 78.1 (*C*(CH_3)$_3$), 59.8 (O*C*H_2CH$_3$), 49.3 (N*C*H_2CHAr), 48.9 (*C*HCO), 47.5 (N*C*H_2CHCO), 45.4 (*C*HAr), 27.8 (C(*C*H_3)$_3$), 13.4 (OCH$_2$*C*H_3); HRMS (ESI$^+$) m/z Calculated for $C_{28}H_{32}N_3O_5^+$ $[M+H]^+$ 490.2342; Found 490.2346.

Benzyl *cis*-(±)-3-(3-(ethoxycarbonyl)phenyl)-4-(quinolin-8-ylcarbamoyl)pyrrolidine-1-carboxylate (9i)



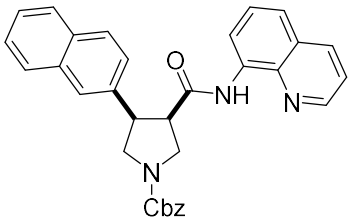
Prepared according to **General Procedure A** using benzyl 3-(quinolin-8-ylcarbamoyl)pyrrolidine-1-carboxylate **5** (187 mg) and ethyl 3-iodobenzoate (414 mg). Purification by flash column chromatography (30% acetone/hexane) afforded arylated pyrrolidine **9i** as a pale yellow solid (84.3 mg, 32%). R_f 0.24 (30% acetone/hexane); mp = 47–53 °C (from Et_2O/pentane); ν_{max} (film)/cm^{-1} 3332 (NH br), 2979, 1697 (C=O), 1524, 1486, 1416, 1324, 1275, 1193, 1108, 1021, 826, 791, 751, 695; ^{1}H NMR (400 MHz, DMSO-d_6, 373 K): δ 9.78 (br s, 1 H, NH), 8.79 (dd, *J* = 4.2, 1.7 Hz, 1 H, HC_{Ar}), 8.32–8.30 (m, 1 H, HC_{Ar}), 8.30–8.28 (m, 1 H, HC_{Ar}), 7.89–7.87 (m, 1 H, HC_{Ar}), 7.62–7.59 (m, 1 H, HC_{Ar}), 7.58–7.52 (m, 2 H, HC_{Ar}), 7.52–7.48 (m, 1 H, HC_{Ar}), 7.47–7.35 (m, 5 H, HC_{Ar}), 7.34–7.29 (m, 1 H, HC_{Ar}), 7.25 (t, *J* = 7.7 Hz, 1 H, HC_{Ar}), 5.20 (s, 2 H, OCH_2Ph), 4.16 (qd, *J* = 7.1, 1.6 Hz, 2 H, O*C*H_2CH$_3$), 4.03 (q, *J* = 7.4 Hz, 1 H, CHAr), 3.99–3.88 (m, 4 H, CHCO, NC*H*HCHCO, N*C*H_2Ar), 3.81–3.74 (m, 1 H, NCH*H*CHCO), 1.17 (t, *J* = 7.1 Hz, 3 H, OCH$_2$C*H*$_3$);^{13}C NMR (101 MHz, DMSO-d_6, 373 K) δ 169.1 (C=O amide), 164.9 (C=O ester), 153.6 (C=O carbamate), 147.9 (C_{Ar}), 138.4 (C_{Ar} quat), 137.7 (C_{Ar} quat), 136.7 (C_{Ar} quat), 135.7 (C_{Ar}), 133.4 (C_{Ar} quat), 131.6 (C_{Ar}), 129.7 (C_{Ar} quat), 127.9 (C_{Ar}), 127.81 (C_{Ar}), 127.75 (2 × C_{Ar}), 127.2 (C_{Ar} quat), 127.1 (C_{Ar}), 126.9 (C_{Ar}), 126.8 (2 × C_{Ar}), 126.0 (C_{Ar}), 121.25 (C_{Ar}), 121.21 (C_{Ar}), 116.2 (C_{Ar}), 65.6 (O*C*H$_2$Ph), 59.8 (O*C*H_2CH$_3$), 49.6 (N*C*H_2CHAr), 48.9 (*C*HCO), 47.7 (N*C*H_2CHCO), 45.3 (*C*HAr), 13.3 (OCH$_2$*C*H_3); HRMS (ESI$^+$) m/z Calculated for $C_{31}H_{30}N_3O_5^+$ $[M+H]^+$ 524.2185; Found 524.2196.

***tert*-Butyl *cis*-(±)-3-(3-nitrophenyl)-4-(quinolin-8-ylcarbamoyl)pyrrolidine-1-carboxylate (2j)**



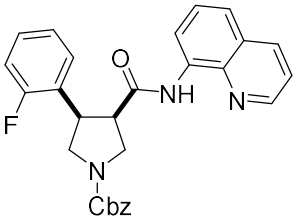
Prepared according to **General Procedure A** using *tert*-butyl 3-(quinolin-8-ylcarbamoyl)pyrrolidine-1-carboxylate **1** (171 mg) and 1-iodo-3-nitrobenzene (374 mg). Purification by flash column chromatography (10% to 20% acetone/pentane) afforded arylated pyrrolidine **2j** as a white solid (70.5 mg, 30%). R_f 0.24 (20% acetone/pentane); mp = 76–79 °C (from Et_2O/pentane); ν_{max} (film)/cm^{-1} 3340 (NH br), 2974, 1682 (C=O), 1525 (NO_2), 1485, 1392, 1346 (NO_2), 1324, 1163, 1120, 873, 827, 792, 730, 681; ^{1}H NMR (400 MHz, DMSO-d_6, 373 K) δ 9.81 (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}), 8.25 (dd, *J* = 7.7, 1.3 Hz, 1 H, HC_{Ar}), 8.10 (t, *J* = 2.1 Hz, 1 H, HC_{Ar}), 7.84 (ddd, *J* = 8.2, 2.4, 1.0 Hz, 1 H, HC_{Ar}), 7.70–7.63 (m, 1 H, HC_{Ar}), 7.61–7.54 (m, 2 H, HC_{Ar}), 7.42 (dt, *J* = 16.0, 7.9 Hz, 2 H, HC_{Ar}), 4.07 (q, *J* = 7.3 Hz, 1 H, CHAr), 4.00 (td, *J* = 7.3, 4.5 Hz, 1 H, CHCO), 3.88–3.78 (m, 3 H, N*CH*HCHCO, NC*H*$_2$CHAr), 3.69 (dd, *J* = 11.2, 7.3 Hz, 1 H, NCH*H*CHCO), 1.50 (s, 9 H, C(CH$_3$)$_3$); ^{13}C NMR (101 MHz, DMSO-d_6, 373 K) δ 169.0 (C=O amide), 153.1 (C=O carbamate), 148.0 (C_{Ar}), 147.4 (O_2NC_{Ar} quat), 140.5 (C_{Ar} quat), 137.8 (C_{Ar} quat), 135.7 (C_{Ar}), 133.6 (C_{Ar}), 133.3 (C_{Ar} quat), 128.9 (C_{Ar}), 127.2 (C_{Ar} quat), 126.0 (C_{Ar}), 121.9 (C_{Ar}), 121.4 (C_{Ar}), 121.3 (C_{Ar}), 120.9 (C_{Ar}), 116.4 (C_{Ar}), 78.3 (*C*(CH$_3$)$_3$), 49.3 (N*C*H$_2$CHAr), 48.8 (*C*HCO), 47.3 (N*C*H$_2$CHCO), 45.0 (*C*HAr), 27.8 (C(*C*H$_3$)$_3$); HRMS (ESI$^+$) m/z Calculated for $C_{25}H_{27}N_4O_5^+$ $[M+H]^+$ 463.1981; Found 463.1980.

Benzyl *cis*-(±)-3-(naphthalen-2-yl)-4-(quinolin-8-ylcarbamoyl)pyrrolidine-1-carboxylate (9k)



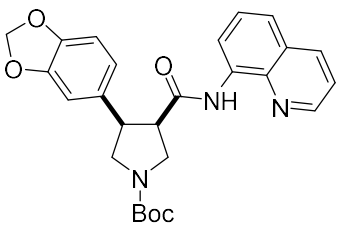
Prepared according to **General Procedure A** using benzyl 3-(quinolin-8-ylcarbamoyl)pyrrolidine-1-carboxylate **5** (187 mg) and 2-iodonaphthalene (381 mg). Purification by flash column chromatography (5% to 10% MeCN/CH_2Cl_2) afforded arylated pyrrolidine **9k** as a pale orange solid (131 mg, 52%). R_f 0.34 (5% MeCN/CH_2Cl_2); mp = 59–64 °C (from Et_2O/pentane); ν_{max} (film)/cm^{-1} 3333 (NH br), 2951, 1681 (C=O), 1524, 1485, 1416, 1359, 1324, 1209, 1166, 1111, 824, 791, 746; ^{1}H NMR (400 MHz, DMSO-d_6, 373 K): δ 9.76 (br s, 1 H, NH), 8.67 (dd, J = 4.2, 1.7 Hz, 1 H, HC_{Ar}), 8.29–8.22 (m, 2 H, HC_{Ar}), 7.76–7.73 (m, 1 H, HC_{Ar}), 7.69–7.58 (m, 3 H, HC_{Ar}), 7.52 (dd, J = 8.3, 1.3 Hz, 1 H, HC_{Ar}), 7.48 (dd, J = 8.3, 4.2 Hz, 1 H, HC_{Ar}), 7.48–7.34 (m, 6 H, HC_{Ar}), 7.37–7.28 (m, 3 H, HC_{Ar}), 5.21 (s, 2 H, OCH_2Ph), 4.12 (q, J = 7.3 Hz, 1 H, CHAr), 4.07–3.94 (m, 4 H, CHCO, NC*H*HCHCO, NCH_2Ar), 3.86–3.76 (m, 1 H, NCH*H*CHCO);^{13}C NMR (101 MHz, DMSO-d_6, 373 K) δ 169.3 (C=O amide), 153.6 (C=O carbamate), 147.8 (C_{Ar}), 137.6 (C_{Ar} quat), 136.8 (C_{Ar} quat), 135.6 (C_{Ar}), 135.4 (C_{Ar} quat), 133.5 (C_{Ar} quat), 132.4 (C_{Ar} quat), 131.5 (C_{Ar} quat), 127.8 (2 × C_{Ar}), 127.1 (C_{Ar} quat, C_{Ar}), 127.0 (C_{Ar}), 126.83 (2 × C_{Ar}), 126.78 (C_{Ar}), 126.6 (C_{Ar}), 126.0 (C_{Ar}), 125.5 (C_{Ar}), 125.4 (C_{Ar}), 125.2 (C_{Ar}), 124.8 (C_{Ar}), 121.2 (2 × C_{Ar}), 116.1 (C_{Ar}), 65.5 (OCH_2Ph), 49.6 (NCH_2CHAr), 49.0 (*C*HCO), 47.9 (NCH_2CHCO), 45.6 (*C*HAr); HRMS (ESI$^+$) m/z Calculated for $C_{32}H_{28}N_3O_3^+$ $[M+H]^+$ 502.2131; Found 502.2140.

Benzyl *cis*-(±)-3-(2-fluorophenyl)-4-(quinolin-8-ylcarbamoyl)pyrrolidine-1-carboxylate (9l)



Prepared according to **General Procedure A** using benzyl 3-(quinolin-8-ylcarbamoyl)pyrrolidine-1-carboxylate **5** (187 mg) and 2-fluoroiodobenzene (444 mg, **2.0 mmol**). The reaction was stirred at 110 °C for **72 h**. Purification by flash column chromatography (5% to 10% MeCN/CH_2Cl_2) afforded arylated pyrrolidine **9l** as a brown solid (36.2 mg, 15%). R_f 0.54 (10% MeCN/CH_2Cl_2); mp = 50–54 °C; ν_{max} (film)/cm^{-1} 3345 (NH br), 2953, 1683 (C=O), 1524, 1486, 1416, 1380, 1324, 1210, 1103, 825, 791, 752, 696; ^{1}H NMR (400 MHz, DMSO-d_6, 373 K): δ 9.80 (br s, 1 H, NH), 8.83 (dd, J = 4.2, 1.7 Hz, 1 H, HC_{Ar}), 8.31 (td, J = 8.2, 1.5 Hz, 2 H, HC_{Ar}), 7.59–7.54 (m, 2 H, HC_{Ar}), 7.48–7.36 (m, 5 H, HC_{Ar}), 7.34–7.29 (m, 1 H, HC_{Ar}), 7.25 (td, J = 7.7, 1.5 Hz, 1 H, HC_{Ar}) 7.12–7.05 (m, 1 H, HC_{Ar}), 7.01–6.92 (m, 2 H, HC_{Ar}), 5.19 (s, 2 H, OCH_2Ph), 4.13 (q, J = 7.5 Hz, 1 H, CHAr), 3.95–3.88 (m, 4 H, NC*H*HCHCO, CHCO, NCH_2CHAr), 3.80 (dd, J = 12.1, 8.3 Hz, 1 H, NCH*H*CHCO);^{13}C NMR (101 MHz, DMSO-d_6, 373 K) δ 169.1 (C=O amide), 160.0 (d, J_{CF} = 244.6 Hz, FC_{Ar} quat), 153.6 (C=O carbamate), 148.0 (C_{Ar}), 137.6 (C_{Ar} quat), 136.7 (C_{Ar}, quat), 135.7 (C_{Ar}), 133.5 (C_{Ar} quat), 128.0 (d, J_{CF} = 8.6 Hz, F-*m*-C_{Ar}), 127.9 (d, J_{CF} = 4.4 Hz, F-*m*-C_{Ar}), 127.8 (2 × C_{Ar}), 127.15 (C_{Ar} quat), 127.09 (C_{Ar}), 126.8 (2 × C_{Ar}), 126.1 (C_{Ar}), 124.7 (d, J_{CF} = 14.2 Hz, F-*o*-C_{Ar} quat.), 123.5 (d, J_{CF} = 3.6 Hz, F-*p*-C_{Ar}), 121.3 (C_{Ar}), 121.2 (C_{Ar}), 115.9 (C_{Ar}), 114.5 (d, J_{CF} = 22.6 Hz, F-*o*-C_{Ar}), 65.5 (OCH_2Ph), 48.8 (NCH_2CHAr), 47.9 (*C*HCO, NCH_2CHCO), 38.8 (*C*HAr); ^{19}F NMR (471 MHz, DMSO-d_6, 373 K) δ –116.0 (m); HRMS (ESI$^+$) m/z Calculated for $C_{28}H_{25}N_3O_3F^+$ $[M+H]^+$ 470.1880; Found 470.1893.

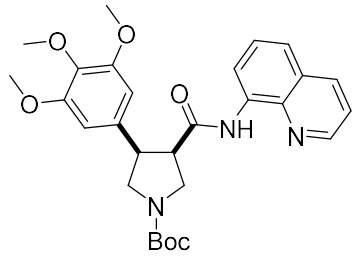
***tert*-Butyl *cis*-(±)-3-(benzo[*d*][1,3]dioxol-5-yl)-4-(quinolin-8-ylcarbamoyl)pyrrolidine-1-carboxylate (2m)**



Prepared according to **General Procedure A** using *tert*-butyl 3-(quinolin-8-ylcarbamoyl)pyrrolidine-1-carboxylate **1** (171 mg) and 5-iodo-1,3-benzodioxole (372 mg). Purification by flash column chromatography (20% acetone/pentane) afforded arylated pyrrolidine **2m** as a pale yellow solid (137 mg, 59%). R_f 0.18 (20% acetone/pentane); mp = 75–80 °C (from Et_2O/pentane); ν_{max} (film)/cm^{-1} 3328 (NH br), 2975, 1684 (C=O), 1526, 1486, 1400, 1324, 1240, 1164, 1120, 1039, 934, 874, 826, 791, 770; ^{1}H NMR (400 MHz, DMSO-d_6, 373 K) δ 9.69 (br s, 1 H, NH), 8.84 (dd, J = 4.2, 1.7 Hz, 1 H, HC_{Ar}), 8.37 (dd, J = 7.7, 1.3 Hz, 1 H, HC_{Ar}), 8.32 (dd, J = 8.3, 1.7 Hz, 1 H, HC_{Ar}), 7.61–7.55 (m, 2 H, HC_{Ar}), 7.48 (t, J = 7.9 Hz, 1 H, HC_{Ar}), 6.77 (d, J = 1.8 Hz, 1 H, HC_{Ar}), 6.70 (dd, J = 8.0, 1.8 Hz, 1 H, HC_{Ar}), 6.59 (d, J = 8.0 Hz, 1 H, HC_{Ar}),

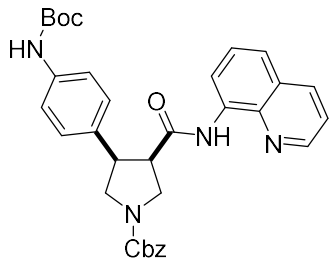
5.75 (d, *J* = 1.0 Hz, 1 H, OC*H*HO), 5.71 (d, *J* = 1.0 Hz, 1 H, OCH*H*O), 3.84–3.76 (m, 3 H, CHCO, CHAr, NC*H*HCHCO), 3.76–3.66 (m, 2H, NCH_2CHAr), 3.66–3.59 (m, 1 H, NC*H*HCHCO), 1.48 (s, 9 H, C(CH_3)$_3$); ^{13}C NMR (101 MHz, DMSO-d_6, 373 K) δ 169.4 (C=O amide), 153.2 (C=O carbamate), 147.9 (C_{Ar}), 146.7 (OC_{Ar} quat), 145.4 (OC_{Ar} quat), 137.7 (C_{Ar} quat), 135.7 (C_{Ar}), 133.6 (C_{Ar} quat), 131.7 (C_{Ar} quat), 127.2 (C_{Ar} quat), 126.1 (C_{Ar}), 121.3 (C_{Ar}), 121.1 (C_{Ar}), 120.1 (C_{Ar}), 116.0 (C_{Ar}), 107.4 (C_{Ar}), 107.2 (C_{Ar}), 100.0 (OCH_2O), 78.0 (*C*(CH_3)$_3$), 49.6 (NCH_2CHAr), 49.2 (*C*HCO), 47.4 (NCH_2CHCO), 45.3 (*C*HAr), 27.8 (C(*C*H_3)$_3$); HRMS (ESI$^+$) m/z Calculated for $C_{26}H_{28}N_3O_5^+$ [M+H]$^+$ 462.2029; Found 462.2032.

tert-Butyl _cis_-(±)-3-(quinolin-8-ylcarbamoyl)-4-(3,4,5-trimethoxyphenyl)pyrrolidine-1-carboxylate (2n)



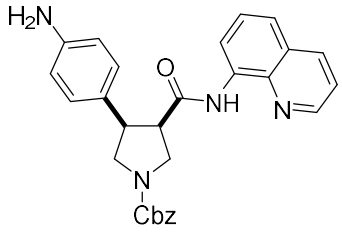
Prepared according to **General Procedure A** using *tert*-butyl 3-(quinolin-8-ylcarbamoyl)pyrrolidine-1-carboxylate **1** (171 mg) and 1,3,5-trimethoxybenzene (441 mg). Purification by flash column chromatography (30% acetone/hexane) afforded arylated pyrrolidine **2n** as a yellow solid (147 mg, 58%). R_f 0.20 (30% acetone/hexane); mp = 156–161 °C (from Et_2O/pentane); ν_{max} (film)/cm^{-1} 3357 (NH br), 2971, 1692 (C=O), 1671 (C=O), 1589, 1521, 1485, 1464, 1406, 1366, 1323, 1239, 1169, 1120, 1015, 845, 828, 794; ^{1}H NMR (400 MHz, DMSO-d_6, 373 K) δ 9.66 (br s, 1 H, NH), 8.82 (dd, *J* = 4.2, 1.7 Hz, 1 H, HC_{Ar}), 8.42 (dd, *J* = 7.6, 1.4 Hz, 1 H, HC_{Ar}), 8.31 (dd, *J* = 8.3, 1.7 Hz, 1 H, HC_{Ar}), 7.59–7.53 (m, 2 H, HC_{Ar}), 7.48 (t, *J* = 7.9 Hz, 1 H, HC_{Ar}), 6.51 (s, 2 H, HC_{Ar}), 3.85–3.80 (m, 3 H, CHCO, CHAr, NC*H*HCHCO), 3.76–3.71 (m, 2H, NCH_2CHAr), 3.65–3.58 (m, 1 H, NCH*H*CHCO), 3.51 (s, 6 H, OCH_3), 3.31 (s, 3 H, OCH_3), 1.49 (s, 9 H, C(CH_3)$_3$); ^{13}C NMR (101 MHz, DMSO-d_6, 373 K) δ 169.4 (C=O amide), 153.1 (C=O carbamate), 152.2 (2 × OC_{Ar} quat), 147.9 (C_{Ar}), 137.5 (C_{Ar} quat), 136.9 (OC_{Ar} quat), 135.7 (C_{Ar}), 133.7 (C_{Ar} quat), 133.1 (C_{Ar} quat), 127.2 (C_{Ar} quat), 126.1 (C_{Ar}), 121.3 (C_{Ar}), 121.0 (C_{Ar}), 115.6 (C_{Ar}), 105.7 (2 × C_{Ar}), 78.0 (*C*(CH_3)$_3$), 59.0 (OCH_3), 55.4 (2 × OCH_3), 49.4 (*C*HCO), 49.2 (NCH_2CHAr), 47.2 (NCH_2CHCO), 45.7 (*C*HAr), 27.8 (C(*C*H_3)$_3$); HRMS (ESI$^+$) m/z Calculated for $C_{28}H_{34}N_3O_6^+$ [M+H]$^+$ 508.2448; Found 508.2458.

Benzyl _cis_-(±)-3-(4-((tert-butoxycarbonyl)amino)phenyl)-4-(quinolin-8-ylcarbamoyl)-pyrrolidine-1-carboxylate (9o)



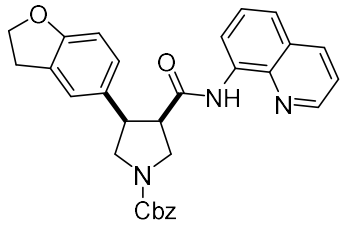
Prepared according to **General Procedure A** using benzyl 3-(quinolin-8-ylcarbamoyl)pyrrolidine-1-carboxylate **5** (187 mg) and *tert*-butyl (4-iodophenyl)carbamate (479 mg). The crude material was purified by flash column chromatography (20% to 30% acetone/hexane), the product containing fractions were combined and the solvent was removed under reduced pressure. CH_2Cl_2 (5 mL) and pentane (5 mL) were added and the solvent was removed under reduced pressure to afford arylated compound **9o** as a yellow solid (153 mg, 54%). R_f 0.30 (30% acetone/hexane); mp = 92–97 °C (from CH_2Cl_2/pentane); ν_{max} (film)/cm^{-1} 3280 (NH br), 1674 (C=O), 1537, 1419, 1315, 1196, 1156, 1113, 1047, 1031, 789, 754, 695; ^{1}H NMR (400 MHz, $CDCl_3$, 298 K, observed as a mixture of rotamers): δ 9.57 and 9.54 (2 × br s, 1 H, NH amide), 8.70 and 8.67 (2 × dd, *J* = 4.2, 1.7 Hz, 1 H, HC_{Ar}), 8.58–8.49 (m, 1 H, HC_{Ar}), 8.12 and 8.10 (2 × dd, *J* = 4.1, 1.7 Hz, 1 H, HC_{Ar}), 7.49–7.29 (m, 8 H, HC_{Ar}), 7.16 (dd, *J* = 8.6, 1.9 Hz, 2 H, HC_{Ar}), 7.11 (d, *J* = 8.4 Hz, 2 H, HC_{Ar}), 6.28 (br s, 1 H, NH carbamate), 5.30–5.15 (m, 2 H, OCH_2Ph), 4.15–4.06 (m, 1 H, NC*H*HCHCO), 4.06–3.89 (m, 2 H, NCH_2CHAr), 3.89–3.76 (m, 2 H, NCH*H*CHCO, CHAr), 3.57–3.46 (m 1 H, CHCO), 1.45 (br s, 9 H, C(CH_3)$_3$);^{13}C NMR (101 MHz, $CDCl_3$, 298 K, observed as a mixture of rotamers) δ 169.4 and 169.1 (C=O amide), 154.8 and 154.7 (C=O Cbz), 152.4 (C=O Boc), 148.1 and 148.0 (C_{Ar}), 138.1 (C_{Ar} quat), 137.5 (C_{Ar} quat), 136.8 (C_{Ar} quat), 136.1 (C_{Ar}), 133.8 (C_{Ar} quat), 131.7 and 131.5 (C_{Ar} quat), 128.4 (2 × C_{Ar}), 128.2 (2 × C_{Ar}), 127.9 (2 × C_{Ar}), 127.8 (C_{Ar}), 127.7 (C_{Ar} quat), 127.2 (C_{Ar}), 121.6 (C_{Ar}), 121.5 and 121.4 (C_{Ar}), 118.3 (2 × C_{Ar}), 116.5 and 116.4 (C_{Ar}), 80.3 (*C*(CH_3)$_3$), 66.9 (OCH_2Ph), 51.4 and 50.6 (*C*HCO), 50.4 and 49.9 (NCH_2CHAr), 48.4 and 47.7 (NCH_2CHCO), 46.9 and 46.0 (*C*HAr), 28.2 (C(*C*H_3)$_3$); HRMS (ESI$^+$) m/z Calculated for $C_{33}H_{35}N_4O_5^+$ [M+H]$^+$ 567.2607; Found 567.2617.

Benzyl *cis*-(±)-3-(4-aminophenyl)-4-(quinolin-8-ylcarbamoyl)pyrrolidine-1-carboxylate (9p)



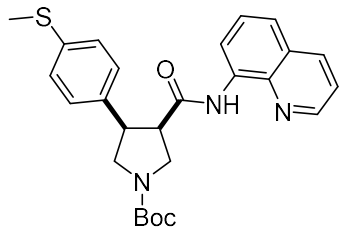
Prepared according to **General Procedure A** using benzyl 3-(quinolin-8-ylcarbamoyl)pyrrolidine-1-carboxylate **5** (187 mg) and 4-iodoaniline (329 mg). The crude material was purified by flash column chromatography (30% to 40% acetone/hexane), the product containing fractions were combined and the solvent was removed under reduced pressure. CH_2Cl_2 (5 mL) and pentane (5 mL) were added and the solvent was removed under reduced pressure to arylated pyrrolidine **9p** as a pale orange solid (57.9 mg, 25%). R_f 0.28 (40% acetone/hexane); mp = 75–78 °C (from CH_2Cl_2/pentane); ν_{max} (film)/cm^{-1} 3347 (NH br), 2944, 1683 (C=O), 1624, 1521, 1485, 1419, 1358, 1324, 1166, 1114, 826, 791, 755, 697; ^{1}H NMR (500 MHz, DMSO-d_6, 373 K): δ 9.73 (br s, 1 H, NH amide), 8.84 (dd, J = 4.2, 1.7 Hz, 1 H, HC_{Ar}), 8.39 (dd, J = 7.7, 1.3 Hz, 1 H, HC_{Ar}), 8.32 (dd, J = 8.3, 1.8 Hz, 1 H, HC_{Ar}), 7.61–7.54 (m, 2 H, HC_{Ar}), 7.48 (t, J = 7.9 Hz, 1 H, HC_{Ar}), 7.43–7.35 (m, 4 H, HC_{Ar}), 7.34–7.29 (m, 1 H, HC_{Ar}), 6.97–6.86 (m, 2 H, HC_{Ar}), 6.39–6.32 (m, 2 H, HC_{Ar}), 5.17 (s, 2 H, OCH_2Ph), 4.49 (br s, 2 H, $ArNH_2$), 3.87 (dd, J = 10.8, 3.2 Hz, 1 H, NC*H*HCHCO), 3.83–3.66 (m, 5 H, NCH*H*CHCO, CHCO, CHAr, NCH_2CHAr);^{13}C NMR (126 MHz, DMSO-d_6, 373 K) δ 169.4 (C=O amide), 153.6 (C=O carbamate), 148.0 (C_{Ar}), 146.5 ($C_{Ar}NH_2$ quat), 137.6 (C_{Ar} quat), 136.8 (C_{Ar} quat), 135.7 (C_{Ar}), 133.7 (C_{Ar} quat), 127.7 (2 × C_{Ar}), 127.4 (2 × C_{Ar}), 127.2 (C_{Ar} quat), 127.1 (C_{Ar}), 126.8 (2 × C_{Ar}), 126.1 (C_{Ar}), 124.9 (C_{Ar} quat), 121.3 (C_{Ar}), 121.0 (C_{Ar}), 115.9 (C_{Ar}), 113.5 (2 × C_{Ar}), 65.4 (O*C*H_2Ph), 50.1 (N*C*H_2CHAr), 49.2 (*C*HCO), 47.7 (N*C*H_2CHCO), 45.0 (*C*HAr); HRMS (ESI$^+$) m/z Calculated for $C_{28}H_{27}N_4O_3^+$ [M+H]$^+$ 467.2083; Found 467.2090.

Benzyl *cis*-(±)-3-(2,3-dihydrobenzofuran-5-yl)-4-(quinolin-8-ylcarbamoyl)pyrrolidine-1-carboxylate (9q)



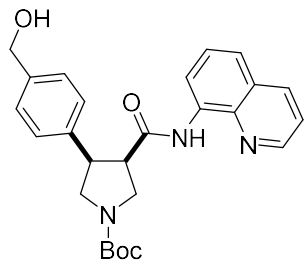
Prepared according to **General Procedure A** using benzyl 3-(quinolin-8-ylcarbamoyl)pyrrolidine-1-carboxylate **5** (187 mg) and 5-iodo-2,3-dihydrobenzofuran (369 mg). Purification by flash column chromatography (20% to 30% acetone/hexane) afforded arylated pyrrolidine **9q** as a pale yellow solid (156 mg, 63%). R_f 0.20 (30% acetone/hexane); mp = 58–65 °C (from Et_2O/pentane); ν_{max} (film)/cm^{-1} 3343 (NH br), 2891, 1683 (C=O), 1523, 1486, 1416, 1357, 1324, 1239, 1212, 1165, 1104, 982, 941, 825, 791, 758, 697; ^{1}H NMR (400 MHz, DMSO-d_6, 373 K): δ 9.64 (br s, 1 H, NH), 8.81 (dd, J = 4.2, 1.7 Hz, 1 H, HC_{Ar}), 8.37 (dd, J = 7.7, 1.4 Hz, 1 H, HC_{Ar}), 8.32 (dd, J = 8.3, 1.7 Hz, 1 H, HC_{Ar}), 7.62–7.52 (m, 2 H, HC_{Ar}), 7.48 (t, J = 8.0 Hz, 1 H, HC_{Ar}), 7.45–7.35 (m, 4 H, HC_{Ar}), 7.34–7.29 (m, 1 H, HC_{Ar}), 7.08–7.05 (m, 1 H, HC_{Ar}), 6.96 (dd, J = 8.2, 2.0 Hz, 1 H, HC_{Ar}), 6.45 (d, J = 8.2 Hz, 1 H, HC_{Ar}), 5.18 (s, 2 H, OCH_2Ph), 4.30–4.15 (m, 2 H, CH_2CH_2O), 3.91 (dd, J = 10.7, 3.7 Hz, 1 H, NC*H*HCHCO), 3.90–3.75 (m, 4 H, CHAr, CHCO, NCH_2Ar), 3.71 (dd, J = 10.7, 6.8, 1 H, NCH*H*CHCO), 2.91–2.81 (m, 1 H, C*H*HCH$_2$O), 2.79–2.69 (m, 1 H, CH*H*CH$_2$O);^{13}C NMR (101 MHz, DMSO-d_6, 373 K) δ 169.5 (C=O amide), 158.1 (OC_{Ar} quat), 153.6 (C=O carbamate), 147.9 (C_{Ar}), 137.6 (C_{Ar} quat), 136.8 (C_{Ar} quat), 135.7 (C_{Ar}), 133.6 (C_{Ar} quat), 129.2 (C_{Ar} quat), 127.7 (2 × C_{Ar}), 127.2 (C_{Ar} quat), 127.1 (C_{Ar}), 126.8 (2 × C_{Ar}), 126.51 (C_{Ar}), 126.47 (C_{Ar} quat), 126.1 (C_{Ar}), 123.6 (C_{Ar}), 121.2 (C_{Ar}), 121.1 (C_{Ar}), 115.9 (C_{Ar}), 107.8 (C_{Ar}), 70.0 (CH_2CH_2O), 65.5 (O*C*H_2Ph), 49.7 (N*C*H_2CHAr), 49.3 (*C*HCO), 47.6 (N*C*H_2CHCO), 45.3 (*C*HAr), 28.4 (CH_2CH_2O); HRMS (ESI$^+$) m/z Calculated for $C_{30}H_{28}N_3O_4^+$ [M+H]$^+$ 494.2080; Found 494.2079.

tert-Butyl _cis_-(±)-3-(4-(methylthio)phenyl)-4-(quinolin-8-ylcarbamoyl)pyrrolidine-1-carboxylate (2r)



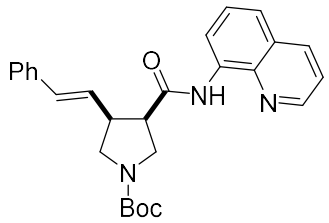
Prepared according to **General Procedure A** using *tert*-butyl 3-(quinolin-8-ylcarbamoyl)pyrrolidine-1-carboxylate **1** (171 mg) and 4-iodophenyl methyl sulfide (375 mg). Purification by flash column chromatography (20% acetone/hexane) afforded arylated pyrrolidine **2r** as a pale yellow solid (127 mg, 55%). R_f 0.19 (20% acetone/hexane); mp = 61–67 °C (from Et_2O/pentane); ν_{max} (film)/cm^{-1} 3341 (NH br), 2974, 1682 (C=O), 1524, 1486, 1392, 1324, 1256, 1163, 1117, 875, 825, 791, 758; ^{1}H NMR (400 MHz, DMSO-d_6, 373 K) δ 9.72 (br s, 1 H, NH), 8.84 (dd, J = 4.2, 1.7 Hz, 1 H, HC_{Ar}), 8.36–8.28 (m, 2 H, HC_{Ar}), 7.62–7.54 (m, 2 H, HC_{Ar}), 7.47 (t, J = 8.0 Hz, 1 H, HC_{Ar}), 7.20–7.15 (m, 2 H, HC_{Ar}), 7.06–7.00 (m, 2 H, HC_{Ar}), 3.88–3.78 (m, 3 H, CHCO, CHAr, NC*H*HCHCO), 3.78–3.72 (m, 2 H, NCH_2CHAr), 3.70–3.62 (m, 1 H, NCH*H*CHCO), 2.25 (s, 3 H, SCH_3), 1.49 (s, 9 H, $C(CH_3)_3$); ^{13}C NMR (101 MHz, DMSO-d_6, 373 K) δ 169.3 (C=O amide), 153.2 (C=O carbamate), 148.0 (C_{Ar}), 137.7 (C_{Ar} quat), 135.8 (SC_{Ar} quat), 135.7 (C_{Ar}), 135.1 (C_{Ar} quat), 133.6 (C_{Ar} quat), 127.6 (2 × C_{Ar}), 127.2 (C_{Ar} quat), 126.12 (C_{Ar}), 126.09 (2 × C_{Ar}), 121.3 (C_{Ar}), 121.2 (C_{Ar}), 116.1 (C_{Ar}), 78.1 ($C(CH_3)_3$), 49.5 (NCH_2CHAr), 49.0 (*C*HCO), 47.5 (NCH_2CHCO), 45.0 (*C*HAr), 27.8 (C(CH_3)$_3$), 14.7 (SCH_3); HRMS (ESI$^+$) m/z Calculated for $C_{26}H_{30}N_3O_3S^+$ $[M+H]^+$ 464.2008; Found 464.2001.

tert-Butyl _cis_-(±)-3-(4-(hydroxymethyl)phenyl)-4-(quinolin-8-ylcarbamoyl)pyrrolidine-1-carboxylate (2s)



Prepared according to **General Procedure A** using *tert*-butyl 3-(quinolin-8-ylcarbamoyl)pyrrolidine-1-carboxylate **1** (171 mg) and 4-iodobenzyl alcohol (351 mg). Purification by flash column chromatography (10% to 20% MeCN/CH_2Cl_2) afforded arylated pyrrolidine **2s** as a white solid (78.2 mg, 35%). R_f 0.23 (20% MeCN/CH_2Cl_2); mp = 82–86 °C (from Et_2O/pentane); ν_{max} (film)/cm^{-1} 3346 (OH, NH br), 2973, 1671 (C=O), 1525, 1486, 1404, 1324, 1163, 1117, 826, 791, 758; ^{1}H NMR (400 MHz, DMSO-d_6, 373 K) δ 9.78 (br s, 1 H, NH), 8.85 (dd, J = 4.2, 1.7 Hz, 1 H, HC_{Ar}), 8.35–8.30 (m, 2 H, HC_{Ar}), 7.60–7.55 (m, 2 H, HC_{Ar}), 7.47 (t, J = 8.0 Hz, 1 H, HC_{Ar}), 7.21–7.17 (m, 2 H, HC_{Ar}), 7.10–7.07 (m, 2 H, HC_{Ar}), 4.64–4.57 (m, 1 H, OH), 4.33–4.28 (m, 2 H, CH_2OH), 3.90–3.75 (m, 5 H, CHCO, CHAr, NC*H*HCHCO, NCH_2CHAr), 3.69–3.63 (m, 1 H, NCH*H*CHCO), 1.49 (s, 9 H, $C(CH_3)_3$); ^{13}C NMR (101 MHz, DMSO-d_6, 373 K) δ 169.3 (C=O amide), 153.2 (C=O carbamate), 148.0 (C_{Ar}), 140.4 (C_{Ar} quat), 137.7 (C_{Ar} quat), 136.5 (C_{Ar} quat), 135.7 (C_{Ar}), 133.6 (C_{Ar} quat), 127.2 (C_{Ar} quat), 126.7 (2 × C_{Ar}), 126.1 (C_{Ar}), 125.7 (2 × C_{Ar}), 121.3 (C_{Ar}), 121.1 (C_{Ar}), 116.1 (C_{Ar}), 78.0 ($C(CH_3)_3$), 62.1 (CH_2OH) 49.9 (NCH_2CHAr), 49.0 (*C*HCO), 47.5 (NCH_2CHCO), 45.2 (*C*HAr), 27.8 (C(CH_3)$_3$); HRMS (ESI$^+$) m/z Calculated for $C_{26}H_{30}N_3O_4^+$ $[M+H]^+$ 448.2236; Found 448.2243.

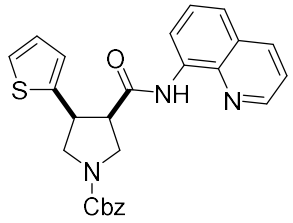
tert-Butyl _cis_-(±)-3-(quinolin-8-ylcarbamoyl)-4-((_E_)-styryl)pyrrolidine-1-carboxylate (2t)



Prepared according to **General Procedure A** using *tert*-butyl 3-(quinolin-8-ylcarbamoyl)pyrrolidine-1-carboxylate **1** (171 mg) and ((*E*)-2-iodoethenyl)benzene[3] (460 mg, **2.0 mmol**). The reaction was stirred at 110 °C for **48 h**. Purification by flash column chromatography (10% MeCN/CH_2Cl_2) afforded arylated pyrrolidine **2t** as a yellow solid (45.0 mg, 20%). R_f 0.34 (10% MeCN/CH_2Cl_2); mp = 63–69 °C (from Et_2O/pentane); ν_{max} (film)/cm^{-1} 3337 (NH br), 2973, 1683 (C=O), 1524, 1485, 1391, 1324, 1257, 1163, 1115, 966, 876, 826, 791, 750, 693; ^{1}H NMR (400 MHz, DMSO-d_6, 373 K) δ 10.00 (br s, 1 H, NH), 8.81 (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}), 7.56 (dd, J = 8.3, 4.2 Hz, 1 H, HC_{Ar}), 7.52 (t, J = 7.9 Hz, 1 H, HC_{Ar}), 7.18–7.09 (m, 5 H, HC_{Ar}), 6.56 (dd, J = 16.0, 0.9 Hz, 1 H, CH=C*H*Ph), 6.23 (dd, J = 15.9, 7.8 Hz, 1 H, C*H*=CHPh), 3.78 (dd, J = 10.7, 4.6 Hz, 1 H, NC*H*HCHCO), 3.69 (td, J = 6.8, 4.6 Hz, 1 H, CHCO), 3.65–3.56 (m, 2 H, NC*H*HCHCH=CH, NCH*H*CHCO), 3.50–3.41 (m, 2 H, NCH*H*CHCH=CH, C*H*CH=CH), 1.47 (s, 9 H,

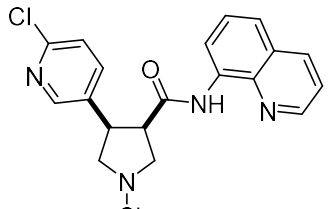
$C(CH_3)_3$); ^{13}C NMR (101 MHz, DMSO-d_6, 373 K) δ 169.6 (C=O amide), 153.2 (C=O carbamate), 148.1 (C_{Ar}), 137.9 (C_{Ar} quat), 136.4 (C_{Ar} quat), 135.8 (C_{Ar}), 133.7 (C_{Ar} quat), 131.3 (CH=*C*HPh), 127.7 (2 × C_{Ar}), 127.3 (C_{Ar} quat), 126.64 (*C*H=CHPh), 126.58 (C_{Ar}), 126.2 (C_{Ar}), 125.4 (2 × C_{Ar}), 121.4 (C_{Ar}), 121.3 (C_{Ar}), 116.4 (C_{Ar}), 78.0 (*C*(CH_3)$_3$), 49.8 (N*C*H_2CHAr), 48.4 (*C*HCO), 47.2 (N*C*H_2CHCO), 43.5 (*C*HCH=CH), 27.8 (C(*C*H_3)$_3$); HRMS (ESI$^+$) m/z Calculated for $C_{27}H_{30}N_3O_3^+$ [M+H]$^+$ 444.2287; Found 444.2282.

Benzyl *cis*-(±)-3-(quinolin-8-ylcarbamoyl)-4-(thiophen-2-yl)pyrrolidine-1-carboxylate (9u)



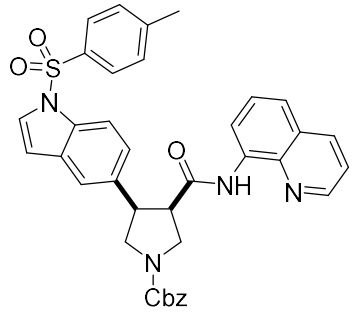
Prepared according to **General Procedure A** using benzyl 3-(quinolin-8-ylcarbamoyl)pyrrolidine-1-carboxylate **5** (187 mg) and 2-iodothiophene (315 mg). Purification by flash column chromatography (10% MeCN/CH_2Cl_2) afforded arylated pyrrolidine **9u** as a white solid (128 mg, 56%). R_f 0.41 (10% MeCN/CH_2Cl_2); mp = 48–51 °C (from Et_2O/pentane); ν_{max} (film)/cm^{-1} 3328 (NH br), 3031, 2883, 1682 (C=O), 1524, 1485, 1415, 1358, 1323, 1167, 1112, 825, 791, 755, 695; ^1H NMR (400 MHz, DMSO-d_6, 373 K): δ 9.90 (br s, 1 H, NH), 8.87 (dd, *J* = 4.2, 1.7 Hz, 1 H, HC_{Ar}), 8.41 (dd, *J* = 7.7, 1.4 Hz, 1 H, HC_{Ar}), 8.33 (dd, *J* = 8.3, 1.7 Hz, 1 H, HC_{Ar}), 7.62–7.56 (m, 2 H, HC_{Ar}), 7.49 (t, *J* = 7.9 Hz, 1 H, HC_{Ar}), 7.45–7.33 (m, 4 H, HC_{Ar}), 7.36–7.27 (m, 1 H, HC_{Ar}), 7.17 (dd, *J* = 5.1, 1.2 Hz, 1 H, SCH), 6.93 (ddd, *J* = 3.5, 1.2, 0.8 Hz, 1 H, SCHCHC*H*), 6.78 (dd, *J* = 5.1, 3.5 Hz, 1 H, SCHC*H*), 5.18 (s, 2 H, OCH_2Ph), 4.23 (m, 1 H, CHAr), 3.95–3.85 (m, 3 H, NC*H*HCHCO, NC*H*HCHAr, CHCO), 3.81 (dd, *J* = 10.3, 6.9 Hz, 1 H, NCH*H*CHAr), 3.77–3.71 (m, 1 H, NCH*H*CHCO);^{13}C NMR (101 MHz, DMSO-d_6, 373 K) δ 168.7 (C=O amide), 153.5 (C=O carbamate), 148.1 (C_{Ar}), 140.2 (SC_{Ar} quat), 137.7 (C_{Ar} quat), 136.7 (C_{Ar} quat), 135.8 (C_{Ar}), 133.7 (C_{Ar} quat), 127.7 (2 × C_{Ar}), 127.2 (C_{Ar} quat), 127.1 (SCH*C*H_{Ar}), 126.8 (2 × C_{Ar}), 126.2 (C_{Ar}), 125.9 (SCHCH*C*H_{Ar}), 124.8 (S*C*H_{Ar}), 123.8 (C_{Ar}), 121.3 (C_{Ar}), 121.2 (C_{Ar}), 116.2 (C_{Ar}), 65.5 (O*C*H_2Ph), 51.4 (N*C*H_2CHAr), 49.2 (*C*HCO), 47.1 (N*C*H_2CHCO), 41.3 (*C*HAr); HRMS (ESI$^+$) m/z Calculated for $C_{26}H_{24}N_3O_3S^+$ [M+H]$^+$ 458.1538; Found 458.1550.

Benzyl *cis*-(±)-3-(6-chloropyridin-3-yl)-4-(quinolin-8-ylcarbamoyl)pyrrolidine-1-carboxylate (9v)



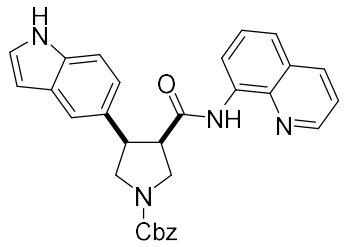
Prepared according to **General Procedure A** using benzyl 3-(quinolin-8-ylcarbamoyl)pyrrolidine-1-carboxylate **5** (187 mg) and 2-chloro-5-iodopyridine (359 mg). Purification by flash column chromatography (20% MeCN/CH_2Cl_2) afforded arylated pyrrolidine **9v** as a pale orange solid (54.9 mg, 23%). R_f 0.33 (20% MeCN/CH_2Cl_2); mp = 63–67 °C (from Et_2O/pentane); ν_{max} (film)/cm^{-1} 3330 (NH br), 2887, 1685 (C=O), 1525, 1486, 1459, 1420, 1359, 1324, 1106, 826, 791, 756, 697; ^1H NMR (400 MHz, DMSO-d_6, 373 K): δ 9.87 (br s, 1 H, NH), 8.85 (dd, *J* = 4.2, 1.7 Hz, 1 H, HC_{Ar}), 8.33 (dd, *J* = 8.3, 1.7 Hz, 1 H, HC_{Ar}), 8.31–8.28 (m, 2 H, HC_{Ar}, NHC_{Pyr}), 7.67 (dd, *J* = 8.3, 2.6 Hz, 1 H, HC_{Ar}), 7.62 (dd, *J* = 8.3, 1.3 Hz, 1 H, HC_{Pyr}), 7.58 (dd, *J* = 8.3, 4.2 Hz, 1 H, HC_{Ar}), 7.48 (t, *J* = 8.0 Hz, 1 H, HC_{Ar}), 7.44–7.35 (m, 4 H, HC_{Ar}), 7.35–7.29 (m, 1 H, HC_{Ar}), 7.21 (dd, *J* = 8.3, 0.7 Hz, 1 H, Cl-*o*-HC_{pyr}), 5.18 (s, 2 H, OCH_2Ph), 4.03–3.95 (m, 2 H, CHAr, CHCO), 3.95–3.82 (m, 3 H, NC*H*HCHCO, NC*H*$_2$Ar), 3.78 (m, 1 H, NCH*H*CHCO);^{13}C NMR (101 MHz, DMSO-d_6, 373 K) δ 169.0 (C=O amide), 153.5 (C=O carbamate), 148.6 (N*C*H_{Pyr}), 148.3 (ClC_{Pyr} quat), 148.1 (C_{Ar}), 138.0 (C_{Pyr}), 137.9 (C_{Ar} quat), 136.6 (C_{Ar} quat), 135.8 (C_{Ar}), 133.3 (C_{Ar} quat), 133.2 (C_{Pyr} quat), 127.8 (2 × C_{Ar}), 127.3 (C_{Ar} quat), 127.1 (C_{Ar}), 126.8 (2 × C_{Ar}), 126.1 (C_{Ar}), 123.0 (Cl-*o*-C_{Pyr}), 121.6 (C_{Ar}), 121.3 (C_{Ar}), 116.7 (C_{Ar}), 65.6 (O*C*H_2Ph), 49.3 (N*C*H_2CHAr), 48.5 (*C*HCO), 47.7 (N*C*H_2CHCO), 42.4 (*C*HAr); HRMS (ESI$^+$) m/z Calculated for $C_{27}H_{24}N_4O_3Cl^+$ [M+H]$^+$ 487.1537; Found 487.1526.

Benzyl *cis*-(±)-3-(quinolin-8-ylcarbamoyl)-4-(1-tosyl-1H-indol-5-yl)pyrrolidine-1-carboxylate (9w)



Prepared according to **General Procedure A** using benzyl 3-(quinolin-8-ylcarbamoyl)pyrrolidine-1-carboxylate **5** (187 mg) and 5-iodo-1-tosyl-1H-indole (596 mg) Purification by flash column chromatography (30% acetone/hexane) afforded arylated pyrrolidine **9w** as a white solid (190 mg, 59%). R_f 0.20 (30% acetone/hexane); mp = 96–100 °C (from Et_2O/pentane); ν_{max} (film)/cm^{-1} 3331 (NH br), 2948, 1686 (C=O), 1524, 1486, 1416, 1360, 1324, 1169, 1120, 996, 825, 791, 765, 731, 673; ^{1}H NMR (400 MHz, DMSO-d_6, 373 K): δ 9.67 (br s, 1 H, NH), 8.70 (dd, J = 4.2, 1.7 Hz, 1 H, HC_{Ar}), 8.29 (dd, J = 8.3, 1.7 Hz, 1 H, HC_{Ar}), 8.22 (dd, J = 7.7, 1.3 Hz, 1 H, HC_{Ar}), 7.67–7.51 (m, 3 H, 2 × HC_{Ar}, NCHCH_{Indole}), 7.56 (dd, J = 8.3, 1.3 Hz, 1 H, HC_{Ar}), 7.53–7.49 (m, 2 H, HC_{Ar}), 7.47–7.45 (m, 1 H, HC_{Ar}), 7.44–7.35 (m, 5 H, HC_{Ar}), 7.35–7.29 (m, 1 H, HC_{Ar}), 7.26 (dd, J = 8.6, 1.8 Hz, 1 H, HC_{Ar}), 7.23–7.19 (m, 2 H, HC_{Ar}), 6.55 (dd, J = 3.7, 0.8 Hz, 1 H, NCH_{Indole}), 5.18 (s, 2 H, OCH_2Ph), 4.04–3.97 (m, 1 H, CHAr), 3.95–3.85 (m, 4 H, NCHHCHCO, NCH_2Ar, CHCO), 3.78–3.72 (m, 1 H, NCHHCHCO), 2.28 (s, 3 H, CH_3);^{13}C NMR (101 MHz, DMSO-d_6, 373 K) δ 170.3 (C=O amide), 154.6 (C=O carbamate), 148.8 (C_{Ar}), 145.5 (C_{Ar} quat), 138.7 (C_{Ar} quat), 137.7 (C_{Ar} quat), 136.6 (C_{Ar}), 135.3 (C_{Ar} quat), 134.4 (C_{Ar} quat), 133.95 (C_{Ar} quat), 133.90 (C_{Ar} quat), 131.0 (C_{Ar} quat), 130.4 (2 × C_{Ar}), 128.7 (2 × C_{Ar}), 128.12 (C_{Ar} quat), 128.07 (C_{Ar}), 127.8 (2 × C_{Ar}), 127.2 (C_{Ar}), 127.0 (C_{Ar}), 126.7 (2 × C_{Ar}), 125.0 (C_{Ar}), 122.21 (C_{Ar}), 122.16 (C_{Ar}), 120.8 (C_{Ar}), 117.2 (C_{Ar}), 113.2 (NCHCH$_{Indole}$), 109.5 (NCH$_{Indole}$), 66.5 (OCH$_2$Ph), 50.7 (NCH$_2$CHAr), 50.0 (CHCO), 48.8 (NCH$_2$CHCO), 46.4 (CHAr), 21.3 (CH_3); HRMS (ESI$^+$) m/z Calculated for $C_{37}H_{33}N_4O_5S^+$ [M+H]$^+$ 645.2172; Found 645.2183.

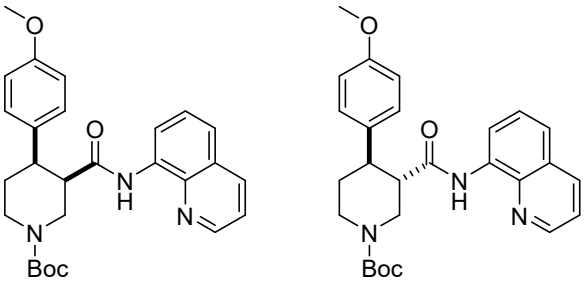
Benzyl *cis*-(±)-3-(1H-indol-5-yl)-4-(quinolin-8-ylcarbamoyl)pyrrolidine-1–carboxylate (9x)



Prepared according to **General Procedure A** using benzyl 3-(quinolin-8-ylcarbamoyl)pyrrolidine-1-carboxylate **5** (187 mg) and 5-iodo-1H-indole (365 mg). The crude material was purified by flash column chromatography (30% to 40% acetone/hexane), the product containing fractions were combined and the solvent was removed under reduced pressure. CH_2Cl_2 (5 mL) and pentane (5 mL) were added and the solvent was removed under reduced pressure to afford arylated pyrrolidine **9x** as a white solid (146 mg, 60%, containing <6% inseparable impurity). R_f 0.33 (40% acetone/hexane); mp = 87–93 °C (from CH_2Cl_2/pentane); ν_{max} (film)/cm^{-1} 3322 (NH br), 1678 (C=O), 1523, 1485, 1417, 1356, 1324, 1210, 1112, 825, 790, 763, 732, 696; ^{1}H NMR (400 MHz, DMSO-d_6, 373 K): δ 10.51 (br s, 1 H, HN_{Indole}), 9.70 (br s, 1 H, CONH), 8.71 (dd, J = 4.2, 1.7 Hz, 1 H, HC_{Ar}), 8.32 (dd, J = 7.7, 1.4 Hz, 1 H, HC_{Ar}), 8.26 (dd, J = 8.3, 1.7 Hz, 1 H, HC_{Ar}), 7.55–7.49 (m, 2 H, HC_{Ar}), 7.46–7.36 (m, 6 H, 5 × HC_{Ar}, HC_{Indole}), 7.35–7.30 (m, 1 H, HC_{Ar}), 7.15–7.10 (m, 2 H, HC_{Indole}), 7.00 (dd, J = 8.4, 1.8 Hz, 1 H, HC_{Indole}), 6.20 (ddd, J = 3.0, 1.9, 0.9 Hz, 1 H, NHCHCH_{Indole}), 5.20 (s, 2 H, OCH_2Ph), 4.04–3.90 (m, 4 H, CHAr, NCHHCHCO, NCH_2Ar), 3.87 (td, J = 6.9, 4.3 Hz, 1 H, CHCO), 3.76 (dd, J = 10.7, 7.0 Hz, 1 H, NCHHCHCO);^{13}C NMR (101 MHz, DMSO-d_6, 373 K) δ 169.4 (C=O amide), 153.6 (C=O carbamate), 147.8 (C_{Ar}), 137.6 (C_{Ar} quat), 136.8 (C_{Ar} quat), 135.6 (C_{Ar}), 134.6 (C_{Indole} quat), 133.6 (C_{Ar} quat), 127.82 (C_{Indole} quat), 127.75 (2 × C_{Ar}), 127.3 (C_{Ar} quat), 127.11 (C_{Indole} quat), 127.05 (C_{Ar}), 126.8 (2 × C_{Ar}), 126.0 (C_{Ar}), 124.5 (NHCH$_{Indole}$), 121.1 (C_{Ar}), 121.0 (C_{Ar}), 120.3 (CH_{Indole}), 118.3 (CH_{Indole}), 115.9 (C_{Ar}), 110.4 (CH_{Indole}), 100.3 (NHCHCH$_{Indole}$), 66.5 (OCH$_2$Ph), 50.3 (NCH$_2$CHAr), 49.4 (CHCO), 47.8 (NCH$_2$CHCO), 45.8 (CHAr); HRMS (ESI$^+$) m/z Calculated for $C_{30}H_{27}N_4O_3^+$ [M+H]$^+$ 491.2083; Found 491.2086.

Piperidine C–H Arylation: Scope of *N*-Protecting Groups and Aryl Iodides **(15/16a,c–e,u,y and 17/18a,i,x)**

***tert*-Butyl *cis*-(±)-4-(4-methoxyphenyl)-3-(quinolin-8-ylcarbamoyl)piperidine-1-carboxylate (15a)** and ***tert*-butyl *trans*-(±)-4-(4-methoxyphenyl)-3-(quinolin-8-ylcarbamoyl)piperidine-1-carboxylate (16a):**



Prepared according to **General Procedure A** using amide **13** (178 mg) and 4-iodoanisole (351 mg). Purification by flash column chromatography (5% to 15% acetone/pentane) afforded the minor product *tert*-butyl *trans*-(±)-4-(4-methoxyphenyl)-3-(quinolin-8-ylcarbamoyl) piperidine-1-carboxylate **16a** as a white solid (46.2 mg, 20%) followed by the major product *tert*-butyl *cis*-(±)-4-(4-methoxyphenyl)-3-(quinolin-8-ylcarbamoyl)piperidine-1-carboxylate **15a** as a white solid (102 mg, 44%).

Major (**15a**): R_f 0.20 (15% acetone/pentane); mp = 68–72 °C (from Et_2O/pentane); ν_{max} (film)/cm^{-1} 3355 (NH), 2971, 1684 (C=O), 1522, 1485, 1424, 1324, 1246, 1162, 1120, 1035, 1004, 827, 792, 759; ^{1}H NMR (400 MHz, DMSO-d_6, 373 K) δ 9.71 (br s, 1 H, NH), 8.82 (dd, J = 4.2, 1.7 Hz, 1 H, HC_{Ar}), 8.47 (dd, J = 7.6, 1.4 Hz, 1 H, HC_{Ar}), 8.31 (dd, J = 8.3, 1.7 Hz, 1 H, HC_{Ar}), 7.58–7.54 (m, 2 H, HC_{Ar}), 7.48 (t, J = 7.9 Hz, 1 H, HC_{Ar}), 7.27–7.22 (m, 2 H, HC_{Ar}), 6.78–6.74 (m, 2 H, HC_{Ar}), 4.39 (ddd, J = 13.7, 2.5, 1.8 Hz, 1 H, NC*H*HCHCO), 4.24 (dddd, J = 13.1, 4.7, 2.8, 1.8 Hz, 1 H, NC*H*HCH$_2$), 3.63 (s, 3 H, OCH_3), 3.31 (dd, J = 13.7, 3.9 Hz, 1 H, NCH*H*CHCO), 3.26–3.21 (m, 1 H, CHCO), 3.12 (ddd, J = 12.3, 4.3, 4.3 Hz, 1 H, CHAr), 3.01–2.93 (m, 1 H, NCH*H*CH$_2$), 2.68 (dddd, J = 12.2, 12.2, 12.2, 4.7, 1 H, NCH$_2$C*H*H), 1.74–1.67 (m, 1 H, NCH$_2$CH*H*), 1.26 (s, 9 H, C(CH$_3$)$_3$); ^{13}C NMR (101 MHz, DMSO-d_6, 373 K) δ 170.1 (C=O amide), 157.3 (OC_{Ar} quat), 153.4 (C=O carbamate), 147.8 (C_{Ar}), 137.6 (C_{Ar} quat), 135.7 (C_{Ar}), 134.6 (C_{Ar} quat), 134.1 (C_{Ar} quat), 127.8 (2 × C_{Ar}), 127.2 (C_{Ar} quat), 126.2 (C_{Ar}), 121.2 (C_{Ar}), 120.7 (C_{Ar}), 115.6 (C_{Ar}), 113.2 (2 × C_{Ar}), 77.9 (*C*(CH$_3$)$_3$), 54.5 (OCH_3), 46.2 (N*C*H$_2$CHCO), 46.1 (*C*HCO), 43.1 (N*C*H$_2$CH$_2$), 41.6 (*C*HAr), 27.4 (C(*C*H$_3$)$_3$), 25.5 (NCH$_2$*C*H$_2$); HRMS (ESI$^+$) *m/z* Calculated for $C_{27}H_{32}N_3O_4^+$ [M+H]$^+$ 462.2393; Found 462.2386.

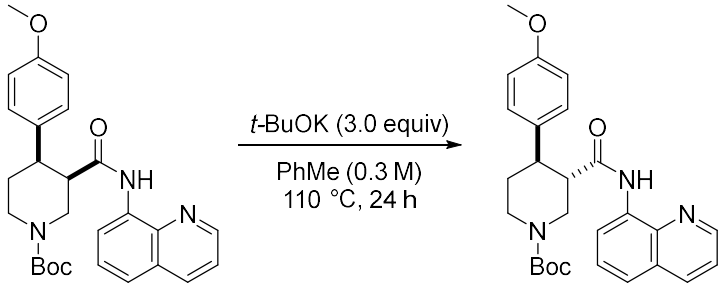
Minor (**16a**): R_f 0.27 (15% acetone/pentane); mp = 59–63 °C (from Et_2O/pentane); ν_{max} (film)/cm^{-1} 3348 (NH), 2931, 1681 (C=O), 1525, 1514, 1486, 1424, 1366, 1284, 1233, 1158, 1126, 1034, 826, 791, 762; ^{1}H NMR (500 MHz, DMSO-d_6, 373 K) δ 9.69 (br s, 1 H, NH), 8.84 (dd, J = 4.2, 1.7 Hz, 1 H, HC_{Ar}), 8.41 (dd, J = 7.7, 1.3 Hz, 1 H, HC_{Ar}), 8.31 (dd, J = 8.3, 1.7 Hz, 1 H, HC_{Ar}), 7.59–7.54 (m, 2 H, HC_{Ar}), 7.47 (t, J = 7.9 Hz, 1 H, HC_{Ar}), 7.26–7.23 (m, 2 H, HC_{Ar}), 6.76–6.63 (m, 2 H, HC_{Ar}), 4.37–4.30 (m, 1 H, NC*H*HCHCO), 4.12 (ddt, J = 13.2, 4.4, 2.2 Hz, 1 H, NC*H*HCH$_2$), 3.59 (s, 3 H, OCH_3), 3.07–3.01 (m, 3 H, NCH*H*CHCO, CHCO, CHAr), 2.97–2.90 (m, 1 H, NCH*H*CH$_2$), 1.81–1.76 (m, 1 H, NCH$_2$C*H*H), 1.71–1.60 (m, 1 H, NCH$_2$CH*H*), 1.48 (s, 9 H, C(CH$_3$)$_3$); ^{13}C NMR (126 MHz, DMSO-d_6, 373 K) δ 170.0 (C=O amide), 157.5 (OC_{Ar} quat), 153.4 (C=O carbamate), 148.0 (C_{Ar}), 137.6 (C_{Ar} quat), 135.7 (C_{Ar}), 135.0 (C_{Ar} quat), 133.6 (C_{Ar} quat), 127.7 (2 × C_{Ar}), 127.2 (C_{Ar} quat), 126.1 (C_{Ar}), 121.3 (C_{Ar}), 121.2 (C_{Ar}), 116.1 (C_{Ar}), 113.5 (2 × C_{Ar}), 78.5 (*C*(CH$_3$)$_3$), 54.5 (OCH_3), 49.8 (*C*HCO), 46.3 (N*C*H$_2$CHCO), 43.6 (*C*HAr), 43.5 (N*C*H$_2$CH$_2$), 32.4 (NCH$_2$*C*H$_2$), 27.7 (C(*C*H$_3$)$_3$); HRMS (ESI$^+$) *m/z* Calculated for $C_{27}H_{32}N_3O_4^+$ [M+H]$^+$ 462.2393; Found 462.2403.

Larger scale C–H Arylation of Piperidine Amide 13

A large microwave vial (10–20 mL recommended volume) was charged with K_2CO_3 (470 mg, 3.4 mmol), flame-dried, and allowed to cool under argon. *tert*-butyl (±)-3-(quinoline-8-ylcarbamoyl)piperidine-1-carboxylate **13** (1.22 g, 3.4 mmol), 4-iodoanisole (2.41 g, 10.3 mmol), $Pd(OAc)_2$ (38.3 mg, 0.17 mmol) and PivOH (348 mg, 3.4 mmol) were added sequentially. The reaction vessel was sealed and purged with argon, then $PhCF_3$ (1.7 mL, 2.00 M) was added by syringe. The reaction tube was then placed in a preheated oil bath and stirred at 110 ºC for 18 h. The reaction mixture was then allowed to cool to rt and EtOAc (20 mL) was added. The resulting mixture was filtered through a pad of Celite, eluting with further EtOAc (2 × 50 mL). The solvent was removed under reduced pressure. The reaction mixture was purified by flash column chromatography (5% to 15% acetone/pentane). The product containing fractions were combined

and the solvent was removed under reduced pressure. Et_2O (20 mL) and pentane (20 mL) were added and the solvent was removed under reduced pressure to afford the minor product *tert*-butyl *trans*-(±)-4-(4-methoxyphenyl)-3-(quinolin-8-ylcarbamoyl) piperidine-1-carboxylate **16a** as a white solid (253 mg, 16%) and the major product *tert*-butyl *cis*-(±)-4-(4-methoxyphenyl)-3-(quinolin-8-ylcarbamoyl)piperidine-1-carboxylate **15a** as a white solid (821 mg, 52%).

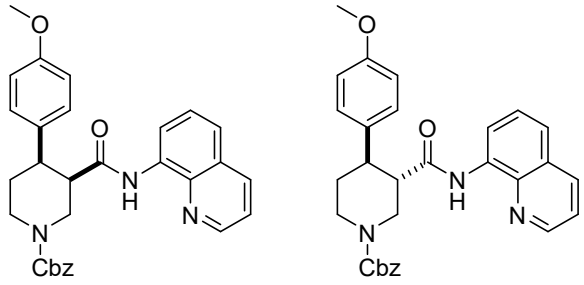
Epimerization of *cis*-3,4-Disubstituted Piperidine 15a



15a **16a** 97%

A flame-dried reaction tube was charged with *cis*-3,4-disubstituted piperidine **15a** (92.3 mg, 0.20 mmol) and potassium *tert*-butoxide (67.3 mg, 0.60 mmol). The reaction vessel was sealed and purged with argon, then dry toluene (667 μL, 0.3 M) was added by syringe. The reaction tube was then placed in a preheated oil bath and stirred at 110 ºC for 18 h. The reaction mixture was then allowed to cool to rt and EtOAc (2 mL) and sat. aq. NH_4Cl (2 mL) were added. The phases were separated and the aqueous layer was extracted with EtOAc (3 × 5 mL). The combined organic extracts were dried over Na_2SO_4 and filtered. The solvent was removed under reduced pressure. Et_2O (3 mL) and pentane (3 mL) were added and the solvent was removed under reduced pressure to afford pure *trans*-3,4-disubstituted piperidine **16a** as a white solid (89.9 mg, 97%).

Benzyl *cis*-(±)-4-(4-methoxyphenyl)-3-(quinolin-8-ylcarbamoyl)piperidine-1-carboxylate (17a) and **benzyl *trans*-(±)-4-(4-methoxyphenyl)-3-(quinolin-8-ylcarbamoyl)piperidine-1-carboxylate (18a):**

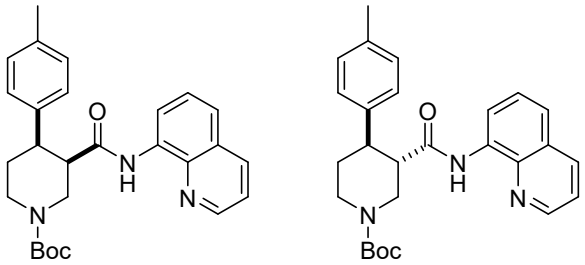


Prepared according to **General Procedure A** using amide **14** (195 mg) and 4-iodoanisole (351 mg). Purification by flash column chromatography (10% to 20% acetone/pentane) afforded the minor product *trans*-(±)-4-(4-methoxyphenyl)-3-(quinolin-8-ylcarbamoyl) piperidine-1-carboxylate **18a** as a white solid (46.1 mg, 19%) followed by the major product benzyl *cis*-(±)-4-(4-methoxyphenyl)-3-(quinolin-8–ylcarbamoyl)piperidine-1-carboxylate **17a** as a white solid (125 mg, 50%).

Major (**17a**): R_f 0.21 (20% acetone/pentane); mp = 56–61 °C(from Et_2O/pentane); ν_{max} (film)/cm^{-1} 3339 (NH), 2912, 1684 (C=O), 1521, 1484, 1424, 1379, 1323, 1286, 1235, 1180, 1116, 1030, 1004, 826, 791, 758, 697; ^{1}H NMR (400 MHz, DMSO-d_6, 373 K) δ 9.68 (br s, 1 H, NH), 8.77 (dd, *J* = 4.2, 1.7 Hz, 1 H, HC_{Ar}), 8.45 (dd, *J* = 7.6, 1.4 Hz, 1 H, HC_{Ar}), 8.30 (dd, *J* = 8.3, 1.7 Hz, 1 H, HC_{Ar}), 7.60–7.50 (m, 2 H, HC_{Ar}), 7.48 (t, *J* = 7.9 Hz, 1 H, HC_{Ar}), 7.28–7.11 (m, 7 H, HC_{Ar}), 6.80-6.71 (m, 2 H, HC_{Ar}), 5.09–4.96 (m, 2 H, OCH_2Ph), 4.47 (ddd, *J* = 13.8, 2.5, 1.8 Hz, 1 H, NC*H*HCHCO), 4.32 (dddd, *J* = 13.0, 4.4, 2.7, 1.8 Hz, 1 H, NC*H*HCH_2), 3.61 (s, 3 H, OCH_3), 3.39 (dd, *J* = 13.8, 3.9 Hz, 1 H, NCH*H*CHCO), 3.26 (q, *J* = 4.0 Hz, 1 H, CHCO), 3.17 (ddd, *J* = 12.3, 4.3, 4.3 Hz, 1 H, CHAr), 3.08 (ddd, *J* = 12.7, 12.7, 3.3, 1 H, NCH*H*CH_2), 2.67 (dddd, *J* = 12.4, 12.4, 12.4, 4.6, 1 H, NCH_2C*H*H), 1.74 (dddd, *J* = 13.1, 3.2, 3.2, 3.2, 1 H, NCH_2CH*H*); ^{13}C NMR (101 MHz, DMSO-d_6, 373 K) δ 170.1 (C=O amide), 157.4 (OC_{Ar} quat), 154.2 (C=O carbamate), 147.8 (C_{Ar}), 137.5 (C_{Ar} quat), 136.5 (C_{Ar} quat), 135.7 (C_{Ar}), 134.4 (C_{Ar} quat), 133.9 (C_{Ar} quat), 127.7 (2 × C_{Ar}), 127.4 (2 × C_{Ar}), 127.2 (C_{Ar} quat), 126.8 (C_{Ar}), 126.6 (2 × C_{Ar}), 126.2 (C_{Ar}), 121.2 (C_{Ar}), 120.8 (C_{Ar}), 115.7 (C_{Ar}), 113.3 (2 × C_{Ar}), 65.6

(O*C*H$_2$Ph), 54.5 (OCH$_3$), 46.00 (N*C*H$_2$CHCO), 45.96 (*C*HCO), 43.4 (N*C*H$_2$CH$_2$), 41.6 (*C*HAr), 25.5 (NCH$_2$*C*H$_2$); HRMS (ESI$^+$) ***m/z*** Calculated for $C_{30}H_{30}N_3O_4^+$ [M+H]$^+$ 496.2236; Found 496.2225.
Minor (**18a**): R_f 0.28 (20% acetone/pentane); mp = 56–62 °C (from Et$_2$O/pentane); ν_{max} (film)/cm^{-1} 3344 (NH), 2936, 1678 (C=O), 1524, 1514, 1486, 1466, 1424, 1325, 1281, 1220, 1124, 1032, 997, 950, 825, 791, 759, 697; ^{1}H NMR (400 MHz, DMSO-*d*$_6$, 373 K) δ 9.68 (br s, 1 H, NH), 8.83 (dd, *J* = 4.2, 1.7 Hz, 1 H, HC$_{Ar}$), 8.41 (dd, *J* = 7.6, 1.4 Hz, 1 H, HC$_{Ar}$), 8.29 (dd, *J* = 8.3, 1.7 Hz, 1 H, HC$_{Ar}$), 7.61–7.51 (m, 2 H, HC$_{Ar}$), 7.46 (t, *J* = 8.0 Hz, 1 H, HC$_{Ar}$), 7.46–7.29 (m, 5 H, HC$_{Ar}$), 7.28–7.20 (m, 2 H, HC$_{Ar}$), 6.78–6.70 (m, 2 H, HC$_{Ar}$), 5.18 (s, 2 H, OCH$_2$Ph), 4.45–4.38 (m, 1 H, NC*H*HCHCO), 4.20 (ddt, *J* = 13.3, 4.3, 2.1 Hz, 1 H, NC*H*HCH$_2$), 3.59 (s, 3 H, OCH$_3$), 3.20–2.97 (m, 4 H, NCH*H*CHCO, CHCO, CHAr, NCH*H*CH$_2$), 1.85–1.77 (m, 1 H, NCH$_2$C*H*H), 1.76–1.64 (m, 1 H, NCH$_2$CH*H*); ^{13}C NMR (101 MHz, DMSO-*d*$_6$, 373 K) δ 169.9 (C=O amide), 157.5 (C$_{Ar}$ quat), 154.1 (C=O carbamate), 148.0 (C$_{Ar}$), 137.6 (C$_{Ar}$ quat), 136.5 (C$_{Ar}$ quat), 135.7 (C$_{Ar}$), 134.8 (C$_{Ar}$ quat), 133.5 (C$_{Ar}$ quat), 127.8 (2 × C$_{Ar}$), 127.7 (2 × C$_{Ar}$), 127.2 (C$_{Ar,}$ C$_{Ar}$ quat), 127.0 (2 × C$_{Ar}$), 126.1 (C$_{Ar}$), 121.27 (C$_{Ar}$), 121.25 (C$_{Ar}$), 116.1 (C$_{Ar}$), 113.5 (2 × C$_{Ar}$), 65.9 (O*C*H$_2$Ph), 54.5 (OCH$_3$), 49.8 (*C*HCO), 46.4 (N*C*H$_2$CHCO), 43.63 (N*C*H$_2$CH$_2$), 43.56 (*C*HAr), 32.3 (NCH$_2$*C*H$_2$); HRMS (ESI$^+$) ***m/z*** Calculated for $C_{30}H_{30}N_3O_4^+$ [M+H]$^+$ 496.2236; Found 496.2253.

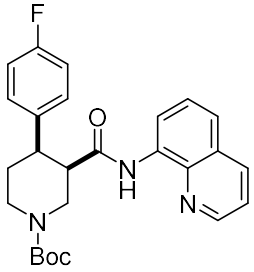
***tert*-Butyl *cis*-(±)-3-(quinolin-8-ylcarbamoyl)-4-(*p*-tolyl)piperidine-1-carboxylate (15c)** and ***tert*-butyl *trans*-(±)-3-(quinolin-8-ylcarbamoyl)-4-(*p*-tolyl)piperidine-1-carboxylate (16c):**

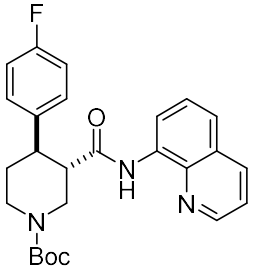


Prepared according to **General Procedure A** using amide **13** (178 mg) and 4-iodotoluene (327 mg). Purification by flash column chromatography (0% to 5% MeCN/CH$_2$Cl$_2$) afforded the minor product *tert*-butyl *trans*-(±)-3-(quinolin-8-ylcarbamoyl)-4-(*p*-tolyl) piperidine-1-carboxylate **15c** as a white solid (46.0 mg, 20%) followed by the major product *tert*–butyl *cis*-(±)-3-(quinolin-8-ylcarbamoyl)-4-(*p*-tolyl) piperidine-1-carboxylate **16c** as a white solid (79.3 mg, 35%).
Major (**15c**): R_f 0.42 (3% MeCN/CH$_2$Cl$_2$); mp = 60–66 °C (from Et$_2$O/pentane); ν_{max} (film)/cm^{-1} 3357 (NH), 2924, 1685 (C=O), 1522, 1484, 1424, 1365, 1324, 1243, 1160, 1121, 1006, 823, 791, 759; ^{1}H NMR (400 MHz, DMSO-*d*$_6$, 373 K) δ 9.72 (br s, 1 H, NH), 8.82 (dd, *J* = 4.2, 1.7 Hz, 1 H, HC$_{Ar}$), 8.46 (dd, *J* = 7.7, 1.4 Hz, 1 H, HC$_{Ar}$), 8.31 (dd, *J* = 8.3, 1.7 Hz, 1 H, HC$_{Ar}$), 7.59–7.53 (m, 2 H, HC$_{Ar}$), 7.48 (t, *J* = 7.9 Hz, 1 H, HC$_{Ar}$), 7.24–7.19 (m, 2 H, HC$_{Ar}$), 7.02–6.97 (m, 2 H, HC$_{Ar}$), 4.40 (ddd, *J* = 13.2, 2.2, 2.2 Hz, 1 H, NC*H*HCHCO), 4.24 (dddd, *J* = 13.1, 4.7, 2.6, 2.6 Hz, 1 H, NC*H*HCH$_2$), 3.32 (dd, *J* = 13.7, 3.9 Hz, 1 H, NCH*H*CHCO), 3.28–3.24 (m, 1 H, CHCO), 3.12 (ddd, *J* = 12.3, 4.3, 4.3 Hz, 1 H, CHAr), 3.02–2.93 (m, 1 H, NCH*H*CH$_2$), 2.70 (dddd, *J* = 12.3, 12.3, 12.3, 4.6, 1 H, NCH$_2$C*H*H), 2.15 (s, 3 H, CH$_3$), 1.75–1.68 (m, 1 H, NCH$_2$CH*H*), 1.26 (s, 9 H, C(CH$_3$)$_3$); ^{13}C NMR (101 MHz, DMSO-*d*$_6$, 373 K) δ 170.1 (C=O amide), 153.4 (C=O carbamate), 147.9 (C$_{Ar}$), 139.5 (C$_{Ar}$ quat), 137.5 (C$_{Ar}$ quat), 135.7 (C$_{Ar}$), 134.5 (C$_{Ar}$ quat), 134.1 (C$_{Ar}$ quat), 128.0 (2 × C$_{Ar}$), 127.2 (C$_{Ar}$ quat), 126.7 (2 × C$_{Ar}$), 126.2 (C$_{Ar}$), 121.2 (C$_{Ar}$), 120.7 (C$_{Ar}$), 115.6 (C$_{Ar}$), 77.9 (*C*(CH$_3$)$_3$), 46.3 (N*C*H$_2$CHCO), 46.0 (*C*HCO), 43.1 (N*C*H$_2$CH$_2$), 41.9 (*C*HAr), 27.4 (C(*C*H$_3$)$_3$), 25.4 (NCH$_2$*C*H$_2$), 19.8 (CH$_3$); HRMS (ESI$^+$) ***m/z*** Calculated for $C_{27}H_{32}N_3O_3^+$ [M+H]$^+$ 446.2444; Found 446.2466.
Minor (**16c**): *Rf* 0.53 (3% MeCN/CH$_2$Cl$_2$); mp = 57–63 °C (from Et$_2$O/pentane); ν_{max} (film)/cm^{-1} 3347 (NH), 2923, 1682 (C=O), 1524, 1486, 1423, 1365, 1324, 1234, 1155, 1126, 825, 790, 759; ^{1}H NMR (400 MHz, DMSO-*d*$_6$, 373 K) δ 9.71 (br s, 1 H, NH), 8.84 (dd, *J* = 4.2, 1.7 Hz, 1 H, HC$_{Ar}$), 8.41 (dd, *J* = 7.7, 1.4 Hz, 1 H, HC$_{Ar}$), 8.30 (dd, *J* = 8.3, 1.7 Hz, 1 H, HC$_{Ar}$), 7.59–7.54 (m, 2 H, HC$_{Ar}$), 7.46 (t, *J* = 8.0 Hz, 1 H, HC$_{Ar}$), 7.23-7.18 (m, 2 H, HC$_{Ar}$), 7.02-6.96 (m, 2 H, HC$_{Ar}$), 4.39-4.32 (m, 1 H, NC*H*HCHCO), 4.12 (ddt, *J* = 13.3, 4.3, 2.1 Hz, 1 H, NC*H*HCH$_2$), 3.10–3.03 (m, 3 H, NCH*H*CHCO, CHCO, CHAr), 2.99–2.89 (m, 1 H, NCH*H*CH$_2$), 2.12 (s, 3 H, CH$_3$), 1.79 (dq, *J* = 13.3, 2.0 Hz, 1 H, NCH$_2$C*H*H), 1.72–1.63 (m, 1 H, NCH$_2$CH*H*), 1.49 (s, 9 H, C(CH$_3$)$_3$); ^{13}C NMR (101 MHz, DMSO-*d*$_6$, 373 K) δ 170.0 (C=O amide), 153.4 (C=O carbamate), 148.0 (C$_{Ar}$), 139.9 (C$_{Ar}$ quat), 137.6 (C$_{Ar}$ quat), 135.7 (C$_{Ar}$), 134.7 (C$_{Ar}$ quat), 133.6 (C$_{Ar}$ quat), 128.3 (2 × C$_{Ar}$), 127.2 (C$_{Ar}$ quat), 126.6 (2 × C$_{Ar}$), 126.1 (C$_{Ar}$), 121.3 (C$_{Ar}$), 121.2 (C$_{Ar}$), 116.0 (C$_{Ar}$), 78.5 (*C*(CH$_3$)$_3$), 49.6 (*C*HCO), 46.3

(N*C*H$_2$CHCO), 44.0 (*C*HAr), 43.5 (N*C*H$_2$CH$_2$), 32.4 (NCH$_2$*C*H$_2$), 27.7 (C(*C*H$_3$)$_3$), 19.8 (CH$_3$); HRMS (ESI$^+$) *m/z* Calculated for $C_{27}H_{32}N_3O_3^+$ [M+H]$^+$ 446.2444; Found 446.2459.

***tert*-butyl *cis*-(±)-4-(4-fluorophenyl)-3-(quinolin-8-ylcarbamoyl)piperidine-1-carboxylate (15d)** and ***tert*-butyl *trans*-(±)-4-(4-fluorophenyl)-3-(quinolin-8-ylcarbamoyl)piperidine-1-carboxylate (16d):**



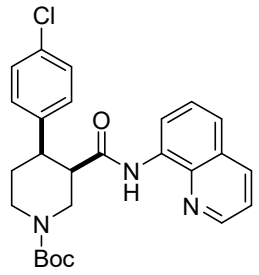


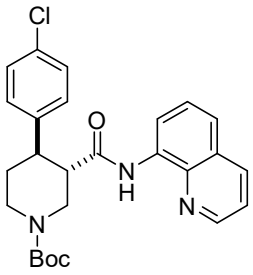
Prepared according to **General Procedure A** using amide **13** (178 mg) and 4-fluoroiodobenzene (333 mg). Purification by flash column chromatography (5% to 10% acetone/pentane) afforded the minor product *tert*-butyl *trans*-(±)-4-(4-fluorophenyl)-3-(quinolin-8-ylcarbamoyl) piperidine-1-carboxylate **16d** as a white solid (35.0 mg, 16%) followed by the major product *tert*-butyl *cis*-(±)-4-(4-fluorophenyl)-3-(quinolin-8-ylcarbamoyl)piperidine-1-carboxylate **15d** as a white solid (42.4 mg, 42%).

Major (**15d**): R_f 0.18 (10% acetone/pentane); mp = 66–72 °C (from Et$_2$O/pentane); ν_{max} (film)/cm^{-1} 3343 (NH), 2976, 1680 (C=O), 1522, 1485, 1424, 1365, 1324, 1223, 1158, 1122, 1005, 826, 791, 758, 671; ^{1}H NMR (400 MHz, DMSO-d_6, 373 K) δ 9.73 (br s, 1 H, NH), 8.82 (dd, J = 4.2, 1.7 Hz, 1 H, HC$_{Ar}$), 8.45 (dd, J = 7.7, 1.4 Hz, 1 H, HC$_{Ar}$), 8.31 (dd, J = 8.3, 1.6 Hz, 1 H, HC$_{Ar}$), 7.61–7.52 (m, 2 H, HC$_{Ar}$), 7.48 (t, J = 8.0 Hz, 1 H, HC$_{Ar}$), 7.41–7.32 (m, 2 H, HC$_{Ar}$), 7.01–6.93 (m, 2 H, HC$_{Ar}$), 4.41 (ddd, J = 13.3, 1.8, 1.8 Hz, 1 H, NC*H*HCHCO), 4.26 (dddd, J = 13.1, 4.6, 2.4, 2.4 Hz, 1 H, NC*H*HCH$_2$), 3.36–3.27 (m, 2 H, NCH*H*CHCO, CHCO), 3.18 (ddd, J = 12.4, 4.1, 4.1 Hz, 1 H, CHAr), 3.02–2.93 (m, 1 H, NCH*H*CH$_2$), 2.70 (dddd, J = 12.4, 12.4, 12.4, 4.6, 1 H, NCH$_2$C*H*H), 1.72 (dddd, J = 13.0, 3.4, 3.4, 3.4, 1 H, NCH$_2$CH*H*), 1.26 (s, 9 H, C(CH$_3$)$_3$); ^{13}C NMR (101 MHz, DMSO-d_6, 373 K) δ 169.9 (C=O amide), 160.3 (d, J_{CF} = 242.3 Hz, FC$_{Ar}$ quat), 153.4 (C=O carbamate), 147.9 (C$_{Ar}$), 138.7 (d, J_{CF} = 3.4 Hz, F-*p*-C$_{Ar}$ quat), 137.6 (C$_{Ar}$ quat), 135.7 (C$_{Ar}$), 134.0 (C$_{Ar}$ quat), 128.6 (d, J_{CF} = 7.9 Hz, 2 × F-*m*-C$_{Ar}$), 127.2 (C$_{Ar}$ quat), 126.1 (C$_{Ar}$), 121.2 (C$_{Ar}$), 120.8 (C$_{Ar}$), 115.7 (C$_{Ar}$), 114.0 (d, J_{CF} = 20.9 Hz, 2 × F-*o*-C$_{Ar}$), 77.9 (*C*(CH$_3$)$_3$), 46.2 (N*C*H$_2$CHCO), 45.9 (*C*HCO), 43.0 (N*C*H$_2$CH$_2$), 41.6 (*C*HAr), 27.4 (C(*C*H$_3$)$_3$), 25.3 (NCH$_2$*C*H$_2$); ^{19}F NMR (376 MHz, DMSO-d_6, 373 K) δ –117.2 (ddd, J_{HF} = 14.6, 9.1, 5.5 Hz); HRMS (ESI$^+$) *m/z* Calculated for $C_{26}H_{29}N_3O_3F^+$ [M+H]$^+$ 450.2193; Found 450.2207.

Minor (**16d**): R_f 0.24 (10% acetone/pentane); mp = 62–68 °C (from Et$_2$O/pentane); ν_{max} (film)/cm^{-1} 3345 (NH), 2976, 1681 (C=O), 1525, 1486, 1424, 1389, 1366, 1325, 1227, 1158, 1124, 826, 791, 760; ^{1}H NMR (400 MHz, DMSO-d_6, 373 K) δ 9.71 (br s, 1 H, NH), 8.84 (dd, J = 4.2, 1.7 Hz, 1 H, HC$_{Ar}$), 8.39 (dd, J = 7.6, 1.3 Hz, 1 H, HC$_{Ar}$), 8.31 (dd, J = 8.3, 1.7 Hz, 1 H, HC$_{Ar}$), 7.62–7.52 (m, 2 H, HC$_{Ar}$), 7.47 (t, J = 8.0 Hz, 1 H, HC$_{Ar}$), 7.43–7.32 (m, 2 H, HC$_{Ar}$), 7.02–6.91 (m, 2 H, HC$_{Ar}$), 4.40–4.31 (m, 1 H, NC*H*HCHCO), 4.13 (ddt, J = 13.3, 4.4, 2.2 Hz, 1 H, NC*H*HCH$_2$), 3.15–2.99 (m, 3 H, NCH*H*CHCO, CHCO, CHAr), 2.99–2.90 (m, 1 H, NCH*H*CH$_2$), 1.81 (dq, J = 13.8, 3.2 Hz, 1 H, NCH$_2$C*H*H), 1.73–1.61 (m, 1 H, NCH$_2$CH*H*), 1.49 (s, 9 H, C(CH$_3$)$_3$); ^{13}C NMR (101 MHz, DMSO-d_6, 373 K) δ 169.9 (C=O amide), 160.4 (d, J_{CF} = 242.2 Hz, FC$_{Ar}$ quat), 153.4 (C=O carbamate), 148.0 (C$_{Ar}$), 139.0 (d, J_{CF} = 3.2 Hz, F-*p*-C$_{Ar}$ quat), 137.7 (C$_{Ar}$ quat), 135.7 (C$_{Ar}$), 133.5 (C$_{Ar}$ quat), 128.6 (d, J_{CF} = 8.0 Hz, 2 × F-*m*-C$_{Ar}$), 127.2 (C$_{Ar}$ quat), 126.1 (C$_{Ar}$), 121.4 (C$_{Ar}$), 121.3 (C$_{Ar}$), 116.3 (C$_{Ar}$), 114.3 (d, J_{CF} = 21.0 Hz, 2 × F-*o*-C$_{Ar}$), 78.6 (*C*(CH$_3$)$_3$), 49.6 (*C*HCO), 46.2 (N*C*H$_2$CHCO), 43.7 (*C*HAr), 43.4 (N*C*H$_2$CH$_2$), 32.2 (NCH$_2$*C*H$_2$), 27.7 (C(*C*H$_3$)$_3$); ^{19}F NMR (376 MHz, DMSO-d_6, 373 K) δ –116.8 (ddd, J_{HF} = 14.1, 9.1, 5.2 Hz); HRMS (ESI$^+$) *m/z* Calculated for $C_{26}H_{29}N_3O_3F^+$ [M+H]$^+$ 450.2193; Found 450.2216.

tert-Butyl _cis_-(±)-4-(4-chlorophenyl)-3-(quinolin-8-ylcarbamoyl)piperidine-1-carboxylate (15e) and **_tert_-butyl _trans_-(±)-4-(4-chlorophenyl)-3-(quinolin-8-ylcarbamoyl)piperidine-1-carboxylate (16e):**



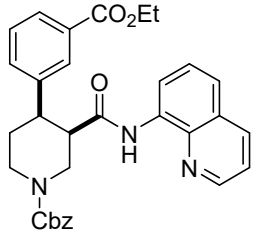


Prepared according to **General Procedure A** using amide **13** (178 mg) and 4-chloroiodobenzene (358 mg). Purification by flash column chromatography (0% to 5% MeCN/CH_2Cl_2) afforded the minor product *tert*–butyl *trans*-(±)-4-(4-chlorophenyl)-3-(quinolin-8-ylcarbamoyl) piperidine-1-carboxylate **16e** as a white solid (33.1 mg, 14%) followed by the major product *tert*-butyl *cis*-(±)-4-(4-chlorophenyl)-3-(quinolin-8-ylcarbamoyl)piperidine-1-carboxylate **15e** as a pale pink solid (71.0 mg, 30%).

Major (**15e**): R_f 0.34 (3% MeCN/CH_2Cl_2); mp = 64–70 °C (from Et_2O/pentane); ν_{max} (film)/cm^{-1} 3335 (NH), 2976, 1685 (C=O), 1522, 1485, 1424, 1365, 1324, 1244, 1161, 1121, 1092, 1005, 826, 791, 758; ^{1}H NMR (400 MHz, DMSO-d_6, 373 K) δ 9.75 (br s, 1 H, NH), 8.83 (dd, *J* = 4.2, 1.7 Hz, 1 H, HC_{Ar}), 8.45 (dd, *J* = 7.7, 1.4 Hz, 1 H, HC_{Ar}), 8.31 (dd, *J* = 8.3, 1.7 Hz, 1 H, HC_{Ar}), 7.61–7.52 (m, 2 H, HC_{Ar}), 7.48 (t, *J* = 7.9 Hz, 1 H, HC_{Ar}), 7.39–7.31 (m, 2 H, HC_{Ar}), 7.27–7.20 (m, 2 H, HC_{Ar}), 4.42 (ddd, *J* = 15.0, 3.5, 1.8 Hz, 1 H, NC*H*HCHCO), 4.25 (dddd, *J* = 13.2, 4.6, 2.4, 2.4 Hz, 1 H, NC*H*HCH$_2$), 3.37–3.27 (m, 2 H, NCH*H*CHCO, CHCO), 3.17 (ddd, *J* = 12.3, 4.1, 4.1 Hz, 1 H, CHAr), 3.03–2.91 (m, 1 H, NCH*H*CH$_2$), 2.69 (dddd, *J* = 12.3, 12.3, 12.3, 4.6, 1 H, NCH$_2$C*H*H), 1.76–1.69 (m, 1 H, NCH$_2$CH*H*), 1.25 (s, 9 H, C(CH$_3$)$_3$); ^{13}C NMR (101 MHz, DMSO-d_6, 373 K) δ 169.9 (C=O amide), 153.4 (C=O carbamate), 147.9 (C_{Ar}), 141.6 (C_{Ar} quat), 137.6 (C_{Ar} quat), 135.7 (C_{Ar}), 133.9 (C_{Ar} quat), 130.4 (C_{Ar} quat), 128.7 (2 × C_{Ar}), 127.4 (2 × C_{Ar}), 127.2 (C_{Ar} quat), 126.1 (C_{Ar}), 121.2 (C_{Ar}), 120.8 (C_{Ar}), 115.7 (C_{Ar}), 77.9 (*C*(CH$_3$)$_3$), 46.2 (NCH$_2$CHCO), 45.7 (*C*HCO), 43.0 (NCH$_2$CH$_2$), 41.6 (*C*HAr), 27.4 (C(*C*H$_3$)$_3$), 25.1 (NCH$_2$*C*H$_2$); HRMS (ESI$^+$) ***m/z*** Calculated for $C_{26}H_{29}N_3O_3Cl^+$ [M+H]$^+$ 466.1897; Found 466.1891.

Minor (**16e**): R_f 0.47 (3% MeCN/CH_2Cl_2); mp = 59–65 °C (from Et_2O/pentane); ν_{max} (film)/cm^{-1} 3348 (NH), 2930, 1678 (C=O), 1525, 1486, 1424, 1366, 1325, 1234, 1156, 1125, 1092, 825, 790, 759; ^{1}H NMR (400 MHz, DMSO-d_6, 373 K) δ 9.73 (br s, 1 H, NH), 8.85 (dd, *J* = 4.2, 1.7 Hz, 1 H, HC_{Ar}), 8.39 (dd, *J* = 7.7, 1.4 Hz, 1 H, HC_{Ar}), 8.31 (dd, *J* = 8.3, 1.7 Hz, 1 H, HC_{Ar}), 7.61–7.54 (m, 2 H, HC_{Ar}), 7.47 (t, *J* = 8.0 Hz, 1 H, HC_{Ar}), 7.40–7.34 (m, 2 H, HC_{Ar}), 7.24–7.19 (m, 2 H, HC_{Ar}), 4.36 (ddd, *J* = 12.6, 3.4, 1.7, 1 H, NC*H*HCHCO), 4.13 (ddt, *J* = 13.3, 4.5, 2.2 Hz, 1 H, NC*H*HCH$_2$), 3.16–3.00 (m, 3 H, NCH*H*CHCO, CHCO, CHAr), 2.99–2.89 (m, 1 H, NCH*H*CH$_2$), 1.81 (dq, *J* = 13.2, 2.9 Hz, 1 H, NCH$_2$C*H*H), 1.74–1.60 (m, 1 H, NCH$_2$CH*H*), 1.49 (s, 9 H, C(CH$_3$)$_3$); ^{13}C NMR (101 MHz, DMSO-d_6, 373 K) δ 169.8 (C=O amide), 153.4 (C=O carbamate), 148.0 (C_{Ar}), 141.9 (C_{Ar} quat), 137.7 (C_{Ar} quat), 135.7 (C_{Ar}), 133.5 (C_{Ar} quat), 130.6 (C_{Ar} quat), 128.7 (2 × C_{Ar}), 127.7 (2 × C_{Ar}), 127.2 (C_{Ar} quat), 126.1 (C_{Ar}), 121.4 (C_{Ar}), 121.3 (C_{Ar}), 116.3 (C_{Ar}), 78.6 (*C*(CH$_3$)$_3$), 49.3 (*C*HCO), 46.2 (NCH$_2$CHCO), 43.8 (*C*HAr), 43.3 (NCH$_2$CH$_2$), 32.0 (NCH$_2$*C*H$_2$), 27.7 (C(*C*H$_3$)$_3$); HRMS (ESI$^+$) ***m/z*** Calculated for $C_{26}H_{29}N_3O_3Cl^+$ [M+H]$^+$ 466.1897; Found 466.1893.

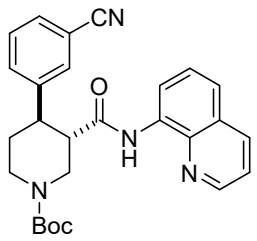
Benzyl _cis_-(±)-4-(3-(ethoxycarbonyl)phenyl)-3-(quinolin-8-ylcarbamoyl)piperidine-1-carboxylate (17i):

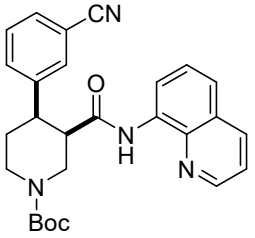


Prepared according to **General Procedure A** using amide **14** (195 mg) and ethyl 3-iodobenzoate (414 mg). Purification by flash column chromatography (40% EtOAc/hexane) afforded the *cis*-configured arylated product **17i** as a white solid (67.8 mg, 25%). R_f 0.27 (40% EtOAc/hexane); mp = 49–55 °C (from Et_2O/pentane); ν_{max} (film)/cm^{-1} 3345 (NH), 2924, 2855, 1682 (C=O), 1521, 1485, 1425, 1366, 1323, 1278, 1234, 1190, 1105, 1010, 826, 791, 753, 695; ^{1}H NMR (400 MHz, DMSO-d_6, 373 K) δ 9.72 (br s, 1 H, NH), 8.74 (dd, *J* = 4.2, 1.7 Hz, 1 H, HC_{Ar}), 8.41 (dd, *J* = 7.7, 1.4 Hz, 1 H, HC_{Ar}), 8.29 (dd, *J* = 8.3, 1.7 Hz, 1 H, HC_{Ar}), 7.98-7.92 (m, 1 H, HC_{Ar}), 7.67 (dt, *J* = 7.7, 1.4 Hz, 1 H, HC_{Ar}), 7.63–7.49 (m, 3 H, HC_{Ar}), 7.46 (t, *J* = 7.9 Hz, 1 H, HC_{Ar}), 7.33 (t, *J* = 7.7 Hz, 1 H, HC_{Ar}), 7.27–7.10 (m, 5 H, HC_{Ar}), 5.10-4.96 (m, 2 H, OCH$_2$Ph), 4.51 (ddd, *J* = 13.8, 2.2, 1.8 Hz, 1 H, NC*H*HCHCO), 4.36 (dddd, *J* = 13.1, 4.4, 2.7, 1.8 Hz, 1 H, NC*H*HCH$_2$), 4.23 (q, *J* = 7.1 Hz, 2 H, OC*H*$_2$CH$_3$), 3.42 (dd, *J* = 13.8, 3.7 Hz, 1 H, NCH*H*CHCO), 3.40–3.27 (m, 2 H, CHAr, CHCO), 3.10 (ddd, *J* = 12.7, 12.7, 3.2, 1 H, NCH*H*CH$_2$),

2.75 (dddd, *J* = 12.2, 12.2, 12.2, 4.6, 1 H, NCH_2CHH), 1.79 (dddd, *J* = 12.3, 3.2, 3.2, 3.2, 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 169.9 (C=O amide), 165.2 (C=O ester), 154.3 (C=O carbamate), 147.8 (C_{Ar}), 143.0 (C_{Ar} quat), 137.6 (C_{Ar} quat), 136.5 (C_{Ar} quat), 135.7 (C_{Ar}), 133.7 (C_{Ar} quat), 131.6 (C_{Ar}), 129.7 (C_{Ar} quat), 127.8 (C_{Ar}), 127.6 (C_{Ar}), 127.4 (2 × C_{Ar}), 127.2 (C_{Ar} quat), 126.8 (C_{Ar}), 126.6 (2 × C_{Ar}), 126.5 (C_{Ar}), 126.1 (C_{Ar}), 121.2 (C_{Ar}), 120.9 (C_{Ar}), 115.9 (C_{Ar}), 65.7 (OCH_2Ph), 59.8 (OCH_2CH_3), 46.0 (NCH_2CHCO), 45.5 ($CHCO$), 43.3 (NCH_2CH_2), 42.1 ($CHAr$), 25.1 (NCH_2CH_2), 13.4 (OCH_2CH_3); HRMS (ESI$^+$) *m/z* Calculated for $C_{32}H_{32}N_3O_5^+$ $[M+H]^+$ 538.2342; Found 538.2357.

tert-Butyl _cis_-(±)-3-(quinolin-8-ylcarbamoyl)-4-(_p_-tolyl)piperidine-1-carboxylate (15y) and **_tert_-butyl _trans_-(±)-4-(3-cyanophenyl)-3-(quinolin-8-ylcarbamoyl)piperidine-1-carboxylate (16y):**



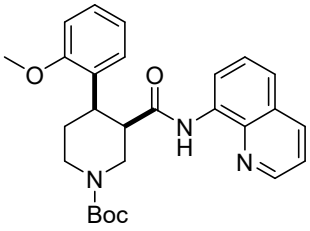


Prepared according to **General Procedure A** using amide **13** (178 mg) and 3-iodobenzonitrile (344 mg). Purification by flash column chromatography (20% acetone/pentane) afforded the minor product *tert*-butyl *trans*-(±)-4-(3-cyanophenyl)-3-(quinolin-8-ylcarbamoyl) piperidine-1-carboxylate **16y** as a white solid (29.0 mg, 13%) followed by the major product *tert*-butyl *cis*-(±)-3-(quinolin-8-ylcarbamoyl)-4-(*p*-tolyl)piperidine-1-carboxylate **15y** as a pale yellow solid (56.4 mg, 25%).

Major (**15y**): R_f 0.12 (20% acetone/pentane); mp = 77–85 °C (from Et_2O/pentane); ν_{max} (film)/cm^{-1} 3346 (NH), 2972, 2228 (CN), 1683 (C=O), 1522, 1484, 1424, 1380, 1365, 1323, 1244, 1161, 1122, 1013, 826, 792, 758, 690; ^{1}H NMR (400 MHz, DMSO-d_6, 373 K) δ 9.71 (br s, 1 H, NH), 8.83 (dd, *J* = 4.2, 1.7 Hz, 1 H, HC_{Ar}), 8.41 (dd, *J* = 7.6, 1.4 Hz, 1 H, HC_{Ar}), 8.30 (dd, *J* = 8.3, 1.7 Hz, 1 H, HC_{Ar}), 7.73 (t, *J* = 1.7 Hz, 1 H, HC_{Ar}), 7.67 (dddd, *J* = 7.9, 1.9, 1.3, 0.7 Hz, 1 H, HC_{Ar}), 7.60–7.52 (m, 2 H, HC_{Ar}), 7.51–7.44 (m, 2 H, HC_{Ar}), 7.40 (t, *J* = 7.9 Hz, 1 H, HC_{Ar}), 4.45 (ddd, *J* = 14.6, 3.7, 1.8 Hz, 1 H, $NCHHCHCO$), 4.27 (dddd, *J* = 13.2, 4.7, 2.6, 2.6 Hz, 1 H, $NCHHCH_2$), 3.40–3.32 (m, 2 H, $NCHCHCO$, CHCO), 3.28 (dt, *J* = 12.2, 4.2 Hz, 1 H, CHAr), 3.01 (ddd, *J* = 13.1, 11.9, 3.3 Hz, 1 H, $NCHCH_2$), 2.71 (dddd, *J* = 12.3, 12.3, 12.3, 4.6, 1 H, NCH_2CHH), 1.79 (dq, *J* = 12.7, 3.2 Hz, 1 H, NCH_2CHH), 1.28 (s, 9 H, $C(CH_3)_3$); ^{13}C NMR (101 MHz, DMSO-d_6, 373 K) δ 169.5 (C=O amide), 153.3 (C=O carbamate), 147.7 (C_{Ar}), 144.1 (C_{Ar} quat), 137.6 (C_{Ar} quat), 135.5 (C_{Ar}), 133.7 (C_{Ar} quat), 131.6 (C_{Ar}), 130.5 (C_{Ar}), 129.1 (C_{Ar}), 128.4 (C_{Ar}), 127.1 (C_{Ar} quat), 125.9 (2 × C_{Ar}), 121.0 (C_{Ar}), 120.8 (C_{Ar}), 117.9 (CN), 115.8 (C_{Ar}), 110.8 ($C_{Ar}CN$ quat), 77.9 ($C(CH_3)_3$), 46.0 (NCH_2CHCO), 45.4 ($CHCO$), 42.8 (NCH_2CH_2), 41.6 ($CHAr$), 27.3 ($C(CH_3)_3$), 24.7 (NCH_2CH_2); HRMS (ESI$^+$) *m/z* Calculated for $C_{27}H_{29}N_4O_3^+$ $[M+H]^+$ 457.2240; Found 457.2248.

Minor (**16y**): R_f 0.17 (20% acetone/pentane); mp = 182–185 °C (from Et_2O/pentane); ν_{max} (film)/cm^{-1} 3327 (NH), 2928, 2228 (CN), 1683 (C=O), 1531, 1487, 1423, 1363, 1238, 1161, 1127, 822, 785, 762, 694; ^{1}H NMR (500 MHz, DMSO-d_6, 373 K) δ 9.77 (br s, 1 H, NH), 8.86 (dd, *J* = 4.2, 1.7 Hz, 1 H, HC_{Ar}), 8.36 (dd, *J* = 7.7, 1.3 Hz, 1 H, HC_{Ar}), 8.31 (dd, *J* = 8.3, 1.7 Hz, 1 H, HC_{Ar}), 7.85 (t, *J* = 1.8 Hz, 1 H, HC_{Ar}), 7.66 (dt, *J* = 7.9, 1.5 Hz, 1 H, HC_{Ar}), 7.61–7.55 (m, 2 H, HC_{Ar}), 7.49–7.44 (m, 2 H, HC_{Ar}), 7.37 (t, *J* = 7.8 Hz, 1 H, HC_{Ar}), 4.37 (ddd, *J* = 13.1, 4.2, 1.7 Hz, 1 H, $NCHHCHCO$), 4.15 (dddd, *J* = 11.7, 4.5, 2.5, 1.7 Hz, 1 H, $NCHHCH_2$), 3.27 (td, *J* = 11.0, 4.1 Hz, 1 H, CHCO), 3.18 (td, *J* = 11.6, 3.8 Hz, 1 H, CHAr), 3.05 (dd, *J* = 13.1, 10.9 Hz, 1 H, $NCHCHCO$), 3.01–2.91 (m, 1 H, $NCHCH_2$), 1.83 (dq, *J* = 13.3, 3.1 Hz, 1 H, NCH_2CHH), 1.70 (qd, *J* = 12.6, 4.5, 1 H, NCH_2CHH), 1.49 (s, 9 H, $C(CH_3)_3$); ^{13}C NMR (126 MHz, DMSO-d_6, 373 K) δ 169.7 (C=O amide), 153.3 (C=O carbamate), 148.1 (C_{Ar}), 144.6 (C_{Ar} quat), 137.8 (C_{Ar} quat), 135.7 (C_{Ar}), 133.4 (C_{Ar} quat), 132.0 (C_{Ar}), 130.4 (C_{Ar}), 129.6 (C_{Ar}), 128.8 (C_{Ar}), 127.2 (C_{Ar} quat), 126.1 (C_{Ar}), 121.5 (C_{Ar}), 121.3 (C_{Ar}), 118.1 (CN), 116.5 (C_{Ar}), 111.2 ($C_{Ar}CN$ quat), 78.6 ($C(CH_3)_3$), 48.8 ($CHCO$), 46.1 (NCH_2CHCO), 44.2 ($CHAr$), 43.2 (NCH_2CH_2), 31.8 (NCH_2CH_2), 27.7 ($C(CH_3)_3$), 19.8 (CH_3); HRMS (ESI$^+$) *m/z* Calculated for $C_{27}H_{29}N_4O_3^+$ $[M+H]^+$ 457.2240; Found 457.2242.

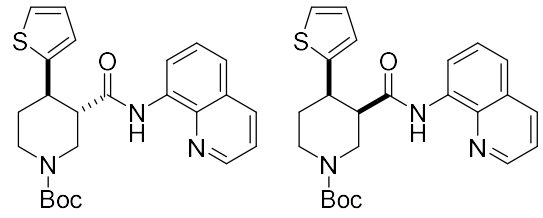
***tert*-Butyl *cis*-(±)-4-(2-methoxyphenyl)-3-(quinolin-8-ylcarbamoyl)piperidine-1-carboxylate (15z)**



Prepared according to **General Procedure A** using amide **13** (178 mg) and 2-iodoanisole (351 mg). The crude material was purified by flash column chromatography (10% acetone/pentane), the product containing fractions were combined and the solvent was removed under reduced pressure. CH_2Cl_2 (5 mL) and pentane (5 mL) were added and the solvent was removed under reduced pressure to afford the the *cis*-configured arylated product **15z** as a white solid (102 mg, 44%).

R_f 0.18 (10% acetone/pentane); mp = 80–86 °C (from CH_2Cl_2/pentane); ν_{max} (film)/cm^{-1} 3350 (NH), 2928, 1685 (C=O), 1521, 1487, 1460, 1423, 1364, 1323, 1236, 1160, 1120, 1028, 1005, 826, 791, 751; ^{1}H NMR (400 MHz, DMSO-d_6, 373 K) δ 9.64 (br s, 1 H, NH), 8.81 (dd, *J* = 4.2, 1.7 Hz, 1 H, HC_{Ar}), 8.44 (dd, *J* = 7.6, 1.4 Hz, 1 H, HC_{Ar}), 8.29 (dd, *J* = 8.3, 16 Hz, 1 H, HC_{Ar}), 7.57–7.52 (m, 2 H, HC_{Ar}), 7.46 (t, *J* = 7.9 Hz, 1 H, HC_{Ar}), 7.19 (dd, *J* = 7.6, 1.7 Hz, 1 H, HC_{Ar}), 7.04 (ddd, *J* = 8.1, 7.3, 1.7 Hz, 1 H, HC_{Ar}), 6.92 (dd, *J* = 8.2, 1.2 Hz, 1 H, HC_{Ar}), 6.72 (td, *J* = 7.5, 1.2 Hz, 1 H, HC_{Ar}), 4.44–4.37 (m, 1 H, NC*H*HCHCO), 4.26 (dddd, *J* = 13.0, 4.2, 2.4, 1.8 Hz, 1 H, NC*H*HCH$_2$), 3.88 (s, 3 H, OCH_3), 3.47 (dt, *J* = 12.5, 4.0 Hz, 1 H, CHAr), 3.34–3.25 (m, 2 H, NCH*H*CHCO, CHCO), 3.04–2.95 (m, 1 H, NCH*H*CH$_2$), 2.74 (qd, *J* = 12.6, 4.6, 1 H, NCH$_2$C*H*H), 1.59 (dq, *J* = 12.9, 3.2 Hz, 1 H, NCH$_2$CH*H*), 1.29 (s, 9 H, C(CH$_3$)$_3$); ^{13}C NMR (101 MHz, DMSO-d_6, 373 K) δ 170.1 (C=O amide), 156.4 (OC_{Ar} quat), 153.5 (C=O carbamate), 147.9 (C_{Ar}), 137.5 (C_{Ar} quat), 135.7 (C_{Ar}), 134.0 (C_{Ar} quat), 130.1 (C_{Ar} quat), 127.13 (C_{Ar} quat), 127.08 (C_{Ar}), 126.7 (C_{Ar}), 126.2 (C_{Ar}), 121.2 (C_{Ar}), 120.6 (C_{Ar}), 119.6 (C_{Ar}), 115.3 (C_{Ar}), 110.5 (C_{Ar}), 77.9 (*C*(CH$_3$)$_3$), 55.1 (OCH_3), 46.0 (N*C*H$_2$CHCO), 44.0 (*C*HCO), 43.3 (N*C*H$_2$CH$_2$), 36.1 (*C*HAr), 27.5 (C(*C*H$_3$)$_3$), 24.8 (NCH$_2$*C*H$_2$); HRMS (ESI$^+$) *m/z* Calculated for $C_{27}H_{32}N_3O_4^+$ [M+H]$^+$ 462.2393; Found 462.2399.

***tert*-Butyl *cis*-(±)-3-(quinolin-8-ylcarbamoyl)-4-(thiophen-2-yl)piperidine-1-carboxylate (15u)** and ***tert*-butyl *trans*-(±)-3-(quinolin-8-ylcarbamoyl)-4-(thiophen-2-yl)piperidine-1-carboxylate (16u):**



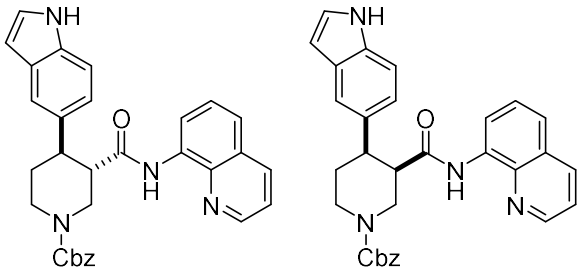
Prepared according to **General Procedure A** using amide **13** (178 mg) and 2-iodothiophene (315 mg). Purification by flash column chromatography (3% MeCN/CH_2Cl_2) afforded the minor product *tert*-butyl *trans*-(±)-3-(quinolin-8-ylcarbamoyl)-4-(thiophen-2-yl) piperidine-1-carboxylate **16u** as a pale yellow solid solid (52.8 mg, 24%) followed by the major product *tert*-butyl *cis*-(±)-3-(quinolin-8-ylcarbamoyl)-4-(thiophen-2-yl)piperidine-1-carboxylate **15u** as a pale pink solid (89.4 mg, 41%).

Major (**15u**): R_f 0.44 (3% MeCN/CH_2Cl_2); mp = 107–112 °C (from Et_2O/pentane); ν_{max} (film)/cm^{-1} 3344 (NH), 2976, 1685 (C=O), 1522, 1484, 1423, 1365, 1324, 1245, 1160, 1120, 1000, 825, 791, 760, 695; ^{1}H NMR (400 MHz, DMSO-d_6, 373 K) δ 9.88 (br s, 1 H, NH), 8.82 (dd, *J* = 4.2, 1.7 Hz, 1 H, HC_{Ar}), 8.44 (dd, *J* = 7.6, 1.4 Hz, 1 H, HC_{Ar}), 8.28 (dd, *J* = 8.3, 1.7 Hz, 1 H, HC_{Ar}), 7.57–7.50 (m, 2 H, HC_{Ar}), 7.45 (t, *J* = 7.9 Hz, 1 H, HC_{Ar}), 7.15 (dd, *J* = 5.1, 1.2 Hz, 1 H, SCH), 6.92 (m, 1 H, SCHCHC*H*), 6.81 (dd, *J* = 5.1, 3.5 Hz, 1 H, SCHC*H*), 4.21 (ddd, *J* = 13.8, 3.8, 1.6 Hz, 1 H, NC*H*HCHCO), 4.03 (dtd, *J* = 13.7, 10.9, 4.5, 1 H, NC*H*HCH$_2$), 3.49 (dt, *J* = 10.2, 4.5, 1 H, CHAr), 3.38 (dd, *J* = 13.3, 4.3, 1.5 Hz, 1 H, NCH*H*CHCO), 3.28 (q, *J* = 4.1, 1 H, CHCO), 3.06 (ddd, *J* = 13.7, 10.9, 4.5, 1 H, NCH*H*CH$_2$), 2.57 (dtd, *J* = 13.7, 10.9, 4.5, 1 H, NCH$_2$C*H*H), 1.83 (dq, *J* = 12.6, 4.0, 1 H,NCH$_2$CH*H*), 1.25 (s, 9 H, C(CH$_3$)$_3$); ^{13}C NMR (101 MHz, DMSO-d_6, 373 K) δ 169.8 (C=O amide), 153.4 (C=O carbamate), 148.0 (C_{Ar}), 145.9 (C_{Ar} quat), 137.7 (C_{Ar} quat), 135.8 (C_{Ar}), 134.1 (C_{Ar} quat), 127.2 (C_{Ar} quat), 126.2 (C_{Ar}), 125.8 (SCH*C*H$_{Ar}$), 123.5 (SCHCH*C*H$_{Ar}$), 122.9 (S*C*H$_{Ar}$), 121.3 (C_{Ar}), 120.8 (C_{Ar}), 115.9 (C_{Ar}), 78.0 (*C*(CH$_3$)$_3$), 46.0 (*C*HCO), 45.4 (N*C*H$_2$CHCO), 42.4 (N*C*H$_2$CH$_2$), 38.0 (*C*HAr), 27.8 (NCH$_2$*C*H$_2$), 27.4 (C(*C*H$_3$)$_3$); HRMS (ESI$^+$) *m/z* Calculated for $C_{24}H_{28}N_3O_3S^+$ [M+H]$^+$ 438.1851; Found 438.1854.

Minor (**16u**): R_f 0.56 (3% MeCN/CH_2Cl_2); mp = 56–60 °C (from Et_2O/pentane); ν_{max} (film)/cm^{-1} 3335 (NH), 2974, 1682 (C=O), 1525, 1486, 1424, 1366, 1324, 1243, 1158, 950, 826, 791, 759, 695; ^{1}H NMR (400 MHz, DMSO-d_6, 373 K) δ 9.88 (br s, 1 H, NH), 8.87 (dd, *J* = 4.2, 1.7 Hz, 1 H, HC_{Ar}), 8.49

(dd, *J* = 7.7, 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, 1.3 Hz, 1 H, HC_{Ar}), 7.58 (dd, *J* = 8.3, 4.2 Hz, 1 H, HC_{Ar}), 7.51 (t, *J* = 8.0 Hz, 1 H, HC_{Ar}), 7.18 (dd, *J* = 5.1, 1.2 Hz, 1 H, SCH), 6.99 (ddd, *J* = 3.5, 1.2, 0.7 Hz, 1 H, SCHCHC*H*), 6.82 (dd, *J* = 5.1, 3.5 Hz, 1 H, SCHC*H*), 4.36–4.27 (m, 1 H, NC*H*HCHCO), 4.10 (ddt, *J* = 13.4, 4.5, 2.5 Hz, 1 H, NC*H*HCH$_2$), 3.52–3.40 (m, 1 H, CHAr), 3.11–2.92 (m, 3 H, CHCO, NCH*H*CH$_2$, NCH*H*CHCO), 2.01 (ddt, *J* = 13.3, 3.9, 2.8 Hz, 1 H, NCH$_2$C*H*H), 1.76–1.64 (m, 1 H, NCH$_2$CH*H*), 1.47 (s, 9 H, C(CH$_3$)$_3$); ^{13}C NMR (101 MHz, DMSO-*d*$_6$, 373 K) δ 169.8 (C=O amide), 153.4 (C=O carbamate), 148.1 (C_{Ar}), 146.1 (C_{Ar} quat), 137.8 (C_{Ar} quat), 135.8 (C_{Ar}), 133.6 (C_{Ar} quat), 127.2 (C_{Ar} quat), 126.1 (C_{Ar}), 126.0 (SCH*C*H$_{Ar}$), 123.3 (SCHCH*C*H$_{Ar}$), 122.8 (S*C*H$_{Ar}$), 121.4 (C_{Ar}), 121.3 (C_{Ar}), 116.3 (C_{Ar}), 78.6 (*C*(CH$_3$)$_3$), 51.1 (*C*HCO), 46.2 (N*C*H$_2$CHCO), 43.2 (N*C*H$_2$CH$_2$), 38.9 (*C*HAr), 33.0 (NCH$_2$*C*H$_2$), 27.6 (C(*C*H$_3$)$_3$); HRMS (ESI$^+$) *m/z* Calculated for $C_{24}H_{28}N_3O_3S^+$ $[M+H]^+$ 438.1851; Found 438.1834.

Benzyl *cis*-(±)-4-(1H-indol-5-yl)-3-(quinolin-8-ylcarbamoyl)piperidine-1-carboxylate (17x) and **benzyl *trans*-(±)-4-(1H-indol-5-yl)-3-(quinolin-8-ylcarbamoyl)piperidine-1-carboxylate (18x):**



Prepared according to **General Procedure A** using amide **14** (195 mg) and 5-iodo-1H-indole (365 mg). The crude material was purified by flash column chromatography (40% EtOAc/hexane), the product containing fractions were combined and the solvent was removed under reduced pressure. CH_2Cl_2 (5 mL) and pentane (5 mL) were added and the solvent was removed under reduced pressure to afford the minor product benzyl *trans*-(±)-4-(1H-indol-5-yl)-3-(quinolin-8-ylcarbamoyl)piperidine-1-carboxylate **18x** as a white solid solid (49.2 mg, 19%) followed by the major product benzyl *cis*-(±)-4-(1H-indol-5-yl)-3-(quinolin-8-ylcarbamoyl)piperidine-1-carboxylate **17x** as a white solid (118 mg, 47%).

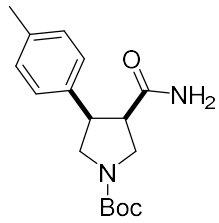
Major (**17x**): R_f 0.21 (40% EtOAc/hexane); mp = 94–98 °C (from CH_2Cl_2/pentane); ν_{max} (film)/cm^{-1} 3305 (NH), 1677 (C=O), 1523, 1485, 1420, 1357, 1324, 1114, 824, 790, 762, 729, 696; ^{1}H NMR (400 MHz, DMSO-*d*$_6$, 373 K) δ 10.54 (br s, 1 H, HN_{Indole}), 9.64 (s, 1 H, CONH), 8.62 (dd, *J* = 4.2, 1.7 Hz, 1 H, HC_{Ar}), 8.44 (dd, *J* = 7.6, 1.4 Hz, 1 H, HC_{Ar}), 8.25 (dd, *J* = 8.3, 1.7 Hz, 1 H, HC_{Ar}), 7.53 (dd, *J* = 8.3, 1.4 Hz, 1 H, HC_{Ar}), 7.51–7.42 (m, 3 H, HC_{Ar}), 7.28–7.19 (m, 3 H, HC_{Ar}), 7.19–7.12 (m, 4 H, HC_{Ar}), 7.09 (dd, *J* = 8.4, 1.8 Hz, 1 H, HC_{Indole}), 6.27 (ddd, *J* = 3.0, 1.9, 0.9 Hz, 1 H, NHCHC*H*$_{Indole}$), 5.09–4.99 (m, 2 H, OCH$_2$Ph), 4.50 (ddd, *J* = 13.7, 2.3, 1.7 Hz, 1 H, NC*H*HCHCO), 4.36 (dddd, *J* = 13.1, 4.6, 2.8, 1.7 Hz, 1 H, NC*H*HCH$_2$), 3.43 (dd, *J* = 13.6, 3.5 Hz, 1 H, NCH*H*CHCO), 3.24–3.26 (m, 2 H, CHCO, CHAr), 3.12 (ddd, *J* = 13.1, 12.0, 3.3, 1 H, NCH*H*CH$_2$), 2.83–2.70 (m, 1 H, NCH$_2$C*H*H), 1.87–1.79 (m, 1 H, NCH$_2$CH*H*); ^{13}C NMR (101 MHz, DMSO-*d*$_6$, 373K) δ 170.3 (C=O amide), 154.3 (C=O carbamate), 147.7 (C_{Ar}), 137.5 (C_{Ar} quat), 136.6 (C_{Ar} quat), 135.6 (C_{Ar}), 134.4 (C_{Indole} quat), 133.9 (C_{Ar} quat), 132.6 (C_{Indole} quat), 127.5 (2 × C_{Ar}), 127.3 (C_{Ar} quat), 127.1 (C_{Indole} quat), 126.8 (C_{Ar}), 126.6 (2 × C_{Ar}), 126.1 (C_{Ar}), 124.4 (NH*C*H$_{Indole}$), 121.1 (C_{Ar}), 120.6 (C_{Ar}), 120.3 (CH$_{Indole}$), 117.9 (CH$_{Indole}$), 115.6 (C_{Ar}), 110.4 (CH$_{Indole}$), 100.4 (NHCH*C*H$_{Indole}$), 65.6 (O*C*H$_2$Ph), 46.6 (*C*HCO), 46.1 (N*C*H$_2$CHCO), 43.6 (N*C*H$_2$CH$_2$), 42.6 (*C*HAr), 25.9 (NCH$_2$*C*H$_2$); HRMS (ESI$^+$) *m/z* Calculated for $C_{31}H_{29}N_4O_3^+$ $[M+H]^+$ 505.2240; Found 505.2240.

Minor (**18x**): R_f 0.26 (40% EtOAc/hexane); mp = 92–98 °C (from CH_2Cl_2/pentane); ν_{max} (film)/cm^{-1} 3323 (NH), 1676 (C=O), 1524, 1485, 1424, 1324, 1282, 1229, 1117, 825, 791, 762, 728, 697; ^{1}H NMR (400 MHz, DMSO-*d*$_6$, 373 K) δ 10.53 (br s, 1 H, HN_{Indole}), 9.66 (s, 1 H, CONH), 8.69 (dd, *J* = 4.2, 1.7 Hz, 1 H, HC_{Ar}), 8.39 (dd, *J* = 7.7, 1.4 Hz, 1 H, HC_{Ar}), 8.25 (dd, *J* = 8.3, 1.7 Hz, 1 H, HC_{Ar}), 7.56–7.47 (m, 3 H, HC_{Ar}), 7.45–7.36 (m, 5 H, HC_{Ar}), 7.36–7.30 (m, 1 H, HC_{Ar}), 7.21 (d, *J* = 8.4 Hz, 1 H, HC_{Indole}), 7.14 (t, *J* = 2.7 Hz, 1 H, NHC*H*$_{Indole}$), 7.06 (dd, *J* = 8.4, 1.7 Hz, 1 H, HC_{Indole}), 6.31–6.27 (m, 1 H, NHCHC*H*$_{Indole}$), 5.19 (s, 2 H, OCH$_2$Ph), 4.48–4.39 (m, 1 H, NC*H*HCHCO), 4.21 (ddt, *J* = 13.2, 4.3, 2.1 Hz, 1 H, NC*H*HCH$_2$), 3.24–3.13 (m, 3 H, NCH*H*CHCO, CHCO, CHAr), 3.07 (td, *J* = 12.8, 3.2 Hz, 1 H, NC*H*HCH$_2$), 1.91–1.84 (m, 1 H, NCH$_2$C*H*H), 1.84–1.72 (m, 1 H, NCH$_2$CH*H*); ^{13}C NMR (101 MHz, DMSO-*d*$_6$, 373 K) δ 170.1 (C=O amide), 154.1 (C=O carbamate), 147.8 (C_{Ar}), 137.5 (C_{Ar} quat), 136.6 (C_{Ar} quat), 135.6 (C_{Ar}), 134.5 (C_{Indole} quat), 133.5 (C_{Ar} quat), 133.1 (C_{Indole} quat), 127.8 (2 × C_{Ar}), 127.5 (C_{Ar} quat), 127.2 (C_{Ar}), 127.1 (C_{Indole} quat), 127.0 (2 × C_{Ar}), 126.0 (C_{Ar}), 124.5 (NH*C*H$_{Indole}$), 121.2 (C_{Ar}), 121.1 (C_{Ar}), 120.2 (CH$_{Indole}$), 117.8 (CH$_{Indole}$), 115.9 (C_{Ar}), 110.7 (CH$_{Indole}$),

100.4 ($NHCH\mathit{C}H_{Indole}$), 65.9 ($O\mathit{C}H_2Ph$), 50.1 (*C*HCO), 46.5 ($N\mathit{C}H_2CHCO$), 44.5 (*C*HAr), 43.8 ($N\mathit{C}H_2CH_2$), 33.1 ($NCH_2\mathit{C}H_2$); HRMS (ESI^+) *m/z* Calculated for $C_{31}H_{29}N_4O_3^+$ $[M+H]^+$ 505.2240; Found 505.2238.

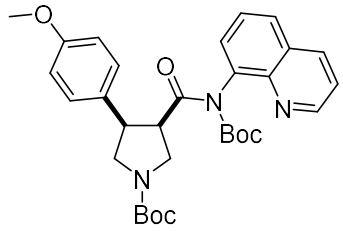
Removal of AQ Directing Group **(19–28)**

tert-Butyl *cis*-(±)-3-carbamoyl-4-(*p*-tolyl)pyrrolidine-1-carboxylate (19)



Using conditions reported by Maulide,[4] arylated amide **2c** (86.3 mg, 0.20 mmol) was dissolved in dry CH_2Cl_2 (13.0 mL) in a flame-dried round-bottom flask, cooled to –78 °C and a stream of ozone was passed through until the characteristic blue colour appeared after 10 min minutes. A stream of oxygen was passed through until decolorization and the mixture was quenched with DMS (50.0 μL). After stirring at room temperature for 2 h, the mixture was concentrated under reduced pressure. The residue was redissolved in NH_4OH (28%)/THF (2.60 mL, 1:1) and stirred for 20 h at 25 °C. The mixture was diluted with CH_2Cl_2 (10 mL) and H_2O (5 mL). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (4 × 15 mL). The combined organic layers were dried over Na_2SO_4 and the solvent was removed under reduced pressure. The crude material was purified by flash column chromatography (0% to 5% MeOH/CH_2Cl_2), the product containing fractions were combined and the solvent was removed under reduced pressure. Et_2O (5 mL) and pentane (5 mL) were added and the solvent was removed under reduced pressure to afford the free amide **19** as a white solid (33 mg, 49%). R_f 0.35 (5% MeOH/CH_2Cl_2); mp = 63–67 °C (from Et_2O/pentane); ν_{max} (film)/cm^{-1} 3331 (NH_2 br), 2976, 1663 (C=O), 1400, 1365, 1163, 1116, 876, 821, 771; ^{1}H NMR (500 MHz, DMSO-d_6, 373 K) δ 7.12–7.09 (m, 2 H, HC_{Ar}), 7.09–7.05 (m, 2 H, HC_{Ar}), 6.57 (br s, 2H, NH_2), 3.69–3.62 (m, 2 H, NCH_2CHAr), 3.62–3.56 (m, 2 H, CHAr, NC*H*HCHCO), 3.48 (dd, *J* = 11.0, 7.5 Hz, 1 H, NCH*H*CHCO), 3.27–3.23 (m, 1 H, CHCO), 2.27 (s, 3 H, CH_3), 1.45 (s, 9 H, C(CH_3)$_3$); ^{13}C NMR (126 MHz, DMSO-d_6, 373 K) δ 172.0 (C=O amide), 153.2 (C=O carbamate), 135.8 (C_{Ar} quat), 134.9 (C_{Ar} quat), 128.0 (2 × C_{Ar}), 127.1 (2 × C_{Ar}), 77.8 (*C*(CH_3)$_3$), 50.2 (N*C*H_2CHAr), 47.5 (N*C*H_2CHCO), 47.0 (*C*HCO), 44.5 (*C*HAr), 27.8 (C(*C*H_3)$_3$), 19.9 (CH_3); HRMS (ESI$^+$) m/z Calculated for $C_{17}H_{24}N_2O_3Na^+$ [M+Na]$^+$ 327.1685; Found 327.1692.

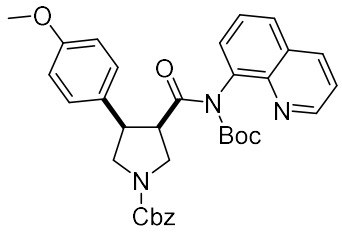
tert-Butyl *cis*-(±)-3-((*tert*-butoxycarbonyl)(quinolin-8-yl)carbamoyl)-4-(4-methoxyphenyl)-pyrrolidine-1-carboxylate (20)



A flame-dried reaction tube was charged with amide **2a** (224 mg, 0.5 mmol), followed by di-*tert*-butyl dicarbonate (Boc_2O, 546 mg, 2.5 mmol) and 4-(dimethylamino)pyridine (DMAP, 122 mg, 1.0 mmol). The reaction vessel was sealed and purged with argon, then dry MeCN (1.0 mL, 0.5 M) was added by syringe. The reaction tube was then placed in a preheated oil bath and stirred at 55 ºC for 1 h. The reaction mixture was then allowed to cool to rt and sat. aq. NH_4Cl (2 mL) and CH_2Cl_2 (2 mL) were added. The phases were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were dried over Na_2SO_4 and filtered. The solvent was removed under reduced pressure. The crude material was purified by flash column chromatography (20% acetone/pentane), the product containing fractions were combined and the solvent was removed under reduced pressure. Et_2O (5 mL) and pentane (5 mL) were added and the solvent was removed under reduced pressure to afford product **20** as a white solid (241 mg, 88%). R_f 0.37 (20% acetone/pentane); mp = 73–78 °C (from Et_2O/pentane); ν_{max} (film)/cm^{-1} 2974, 1735 (C=O), 1692 (C=O), 1515, 1392, 1367, 1293, 1250, 1155, 1122, 1031, 853, 830, 791, 767; ^{1}H NMR (400 MHz, DMSO-d_6, 373 K) δ 8.86 (dd, *J* = 4.2, 1.7 Hz, 1 H, HC_{Ar}), 8.34 (dd, *J* = 8.3, 1.7 Hz, 1 H, HC_{Ar}), 7.89 (dd, *J* = 8.3, 1.4 Hz, 1 H, HC_{Ar}), 7.52 (dd, *J* = 8.3, 4.2 Hz, 1 H, HC_{Ar}), 7.45 (dd, *J* = 8.3, 7.4 Hz, 1 H, HC_{Ar}), 7.22–7.17 (m, 2 H, HC_{Ar}), 6.96–6.90 (m, 2 H, HC_{Ar}), 6.74 (dd, *J* = 7.4, 1.3 Hz, 1 H, HC_{Ar}), 4.67 (td, *J* = 7.4, 5.4 Hz, 1 H, CHCO), 3.91 (q, *J* = 7.2 Hz, 1 H, CHAr), 3.82 (dd, *J* = 11.3, 5.4 Hz, 1 H, NC*H*HCHCO), 3.79 (s, 3 H, OCH_3), 3.74 (dd, *J* = 10.5, 7.3 Hz, 1 H, NC*H*HCHAr), 3.69–3.61 (m, 2 H, NCH*H*CHAr, NCH*H*CHCO), 1.45 (s, 9 H, C(CH_3)$_3$), 1.17 (s, 9 H, C(CH_3)$_3$); ^{13}C NMR (101 MHz, DMSO-d_6, 373 K) δ 173.2 (C=O amide), 158.0 (OC_{Ar} quat), 153.1 (C=O carbamate), 151.6 (C=O carbamate), 149.7 (C_{Ar}), 143.2 (C_{Ar} quat), 135.9 (C_{Ar} quat), 135.4 (C_{Ar}), 130.7 (C_{Ar} quat), 128.3 (2 × C_{Ar}), 127.8 (C_{Ar}, C_{Ar} quat), 127.3 (C_{Ar}), 125.2 (C_{Ar}), 121.0 (C_{Ar}), 113.5 (2 × C_{Ar}), 81.8 (*C*(CH_3)$_3$), 78.0 (*C*(CH_3)$_3$), 54.8 (OCH_3), 50.3 (N*C*H_2CHAr), 47.9 (*C*HCO), 47.8 (N*C*H_2CHCO), 44.4 (*C*HAr), 27.7

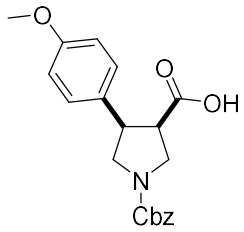
($C(CH_3)_3$), 26.7 ($C(CH_3)_3$); HRMS (ESI^+) m/z Calculated for $C_{31}H_{38}N_3O_6^+$ $[M+H]^+$ 548.2761; Found 548.2740.

Benzyl *cis*-(±)-3-((*tert*-butoxycarbonyl)(quinolin-8-yl)carbamoyl)-4-(4-methoxyphenyl)-pyrrolidine-1-carboxylate (21)



A flame-dried reaction tube was charged with amide **9a** (100 mg, 0.21 mmol), followed by di-*tert*-butyl dicarbonate (Boc_2O, 227 mg, 1.0 mmol) and 4-(dimethylamino)pyridine (DMAP, 50.6 mg, 0.41 mmol). The reaction vessel was sealed and purged with argon, then dry MeCN (450 μL, 0.5 M) was added by syringe. The reaction tube was then placed in a preheated oil bath and stirred at 55 ºC for 1 h. The reaction mixture was then allowed to cool to rt and sat. sol. NH_4Cl (1 mL) and CH_2Cl_2 (1 mL) were added. The phases were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic extracts were dried over Na_2SO_4 and filtered. The solvent was removed under reduced pressure. The crude material was purified by flash column chromatography (20% acetone/pentane), the product containing fractions were combined and the solvent was removed under reduced pressure. Et_2O (5 mL) and pentane (5 mL) were added and the solvent was removed under reduced pressure to afford product **21** as a white solid (105 mg, 86%). R_f 0.19 (20% acetone/pentane); mp = 153–156 °C (from Et_2O/pentane); ν_{max} (film)/cm^{-1} 2976, 1735 (C=O), 1698 (C=O), 1514, 1416, 1367, 1292, 1249, 1153, 1122, 1030, 829, 791, 765, 697; ^1H NMR (400 MHz, DMSO-d_6, 373 K) δ 8.84 (dd, *J* = 4.2, 1.7 Hz, 1 H, HC_{Ar}), 8.34 (dd, *J* = 8.3, 1.7 Hz, 1 H, HC_{Ar}), 7.89 (dd, *J* = 8.3, 1.4 Hz, 1 H, HC_{Ar}), 7.51 (dd, *J* = 8.3, 4.2 Hz, 1 H, HC_{Ar}), 7.45 (dd, *J* = 8.2, 7.4 Hz, 1 H, HC_{Ar}), 7.40–7.28 (m, 5 H, HC_{Ar}), 7.23–7.18 (m, 2 H, HC_{Ar}), 6.95–6.90 (m, 2 H, HC_{Ar}), 6.75 (dd, *J* = 7.2, 1.3 Hz, 1 H, HC_{Ar}), 5.13 (s, 2 H, OCH_2Ph), 4.72 (td, *J* = 7.4, 5.5 Hz, 1 H, CHCO), 4.01–3.87 (m, 2 H, CHAr, NC*H*HCHCO), 3.84 (dd, *J* = 10.4, 7.4 Hz, 1 H, NC*H*HCHAr), 3.79 (s, 3 H, OCH_3), 3.78–3.71 (m, 2 H, NCH*H*CHAr, NCH*H*CHCO), 1.17 (s, 9 H, $C(CH_3)_3$); ^{13}C NMR (101 MHz, DMSO-d_6, 373 K) δ 173.2 (C=O amide), 158.0 (OC_{Ar} quat), 153.5 (C=O Cbz), 151.6 (C=O Boc), 149.7 (C_{Ar}), 143.2 (C_{Ar} quat), 136.7 (C_{Ar} quat), 135.8 (C_{Ar} quat), 135.4 (C_{Ar}), 130.5 (C_{Ar} quat), 128.3 (2 × C_{Ar}), 127.8 (C_{Ar}, C_{Ar} quat), 127.7 (2 × C_{Ar}), 127.3 (C_{Ar}), 127.1 (C_{Ar}), 126.8 (2 × C_{Ar}), 125.2 (C_{Ar}), 121.0 (C_{Ar}), 113.5 (2 × C_{Ar}), 81.8 ($C(CH_3)_3$), 65.4 (OCH_2Ph), 54.8 (OCH_3), 50.4 (NCH_2CHAr), 48.0 (NCH_2CHCO), 47.8 (*C*HCO), 44.4 (*C*HAr), 26.7 ($C(CH_3)_3$); HRMS (ESI^+) m/z Calculated for $C_{34}H_{36}N_3O_6^+$ $[M+H]^+$ 582.2604; Found 582.2614.

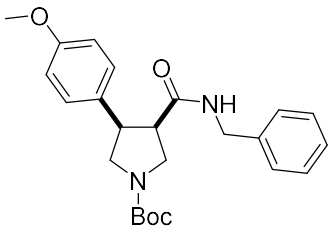
***cis*-(±)-1-((Benzyloxy)carbonyl)-4-(4-methoxyphenyl)pyrrolidine-3-carboxylic acid (22)**



A solution of H_2O_2 (30.6 μL, 0.30 mmol, 30 wt.% in H_2O) in THF (300 μL) was added to a solution of $LiOH{\cdot}H_2O$ (8.4 mg, 0.20 mmol) in H_2O (300 μL) at 0 °C under argon. The resulting mixture was added dropwise to a solution of Boc-protected amide **21** (58.2 mg, 0.10 mmol) in THF (400 μL) at 0 °C under argon. The reaction was then stirred at 20 °C for 1 h. Sat. aq. $Na_2S_2O_3$ (1 mL), EtOAc (1 mL) were then added and the reaction mixture acified to pH ~ 2 with 1N HCl. The phases were separated and the aqueous layer was extracted with EtOAc (3 × 5 mL). The combined organic extracts were dried over Na_2SO_4 and filtered. The solvent was removed under reduced pressure. The crude material was purified by flash column chromatography (5% MeOH/CH_2Cl_2), the product containing fractions were combined and the solvent was removed under reduced pressure. Et_2O (5 mL) and pentane (5 mL) were added and the solvent was removed under reduced pressure to afford acid **22** as a white solid (30.7 mg, 92%, single diastereoisomer). R_f 0.20 (5% MeOH/CH_2Cl_2); mp = 109–111 °C (from Et_2O/pentane); ν_{max} (film)/cm^{-1} 2953 (OH br), 1726, 1701 (C=O), 1660 (C=O), 1612, 1514, 1416, 1360, 1247, 1204, 1180, 1112, 1028, 830, 747, 696; ^1H NMR (400 MHz, $CDCl_3$, 298 K, observed as mixture of rotamers) δ 8.51 (br s, 1 H, OH), 7.48–7.29 (m, 5 H, HC_{Ar}), 7.09 (d, *J* = 8.2 Hz, 2 H, HC_{Ar}), 6.79 (d, *J* = 8.2 Hz, 2 H, HC_{Ar}), 5.27–5.08 (m, 2 H, OCH_2Ph), 3.88–3.77 (m, 3 H, NCH_2CHAr, NC*H*HCHCO), 3.75 (s, 3 H, OCH_3), 3.73–3.62 (m, 2 H, NCH*H*CHCO, CHAr), 3.36 (m, 1 H, CHCO); ^{13}C NMR (101 MHz, $CDCl_3$, 298 K, observed as mixture of rotamers) δ 176.2 and 175.9 (COOH), 158.7 (OC_{Ar} quat), 154.84 and 154.76 (C=O carbamate), 136.5 (C_{Ar} quat), 129.7 and 129.5 (C_{Ar} quat), 128.54 (2 × C_{Ar}),

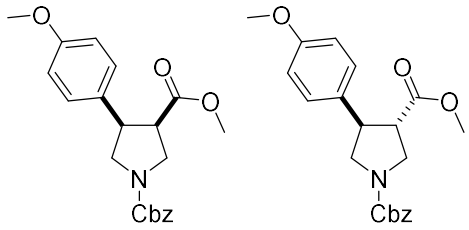
128.46 (2 × C_{Ar}), 128.0 (C_{Ar}), 127.87 and 127.85 (2 × C_{Ar}), 113.9 (2 × C_{Ar}), 67.1 (O*C*H_2Ph), 55.1 (OCH_3), 51.0 and 50.3 (N*C*H_2CHAr), 48.6 and 47.7 (*C*HCO), 47.4 and 46.6 (N*C*H_2CHCO), 45.4 and 44.4 (*C*HAr); HRMS (ESI$^+$) m/z Calculated for $C_{20}H_{22}NO_5^+$ [M+H]$^+$ 356.1498; Found 356.1515.

tert-Butyl _cis_-(±)-3-(benzylcarbamoyl)-4-(4–methoxyphenyl)pyrrolidine-1–carboxylate (23)



A flame-dried reaction tube was charged with Boc-protected amide **20** (54.7 mg, 0.10 mmol) and dry toluene (200 μL, 0.5 M). The reaction vessel was cooled down to 0 °C and benzylamine (16.0 μL, 0.15 mmol) was added. The microwave vial was sealed, purged with argon and stirred at 60 ºC for 24 h. The reaction mixture was then allowed to cool down to rt and sat. aq. NH_4Cl (1 mL) and CH_2Cl_2 (1 mL) were added. The phases were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic extracts were dried over Na_2SO_4 and filtered. The solvent was removed under reduced pressure. The reaction mixture was purified by flash column chromatography (20% acetone/pentane). The product containing fractions were combined and the solvent was removed under reduced pressure. Et_2O (5 mL) and pentane (5 mL) were added and the solvent was removed under reduced pressure to afford amide **23** as a white solid (28.5 mg, 69%, single diasteeoisomer). R_f 0.20 (20% acetone/pentane); mp = 55–60 °C (from Et_2O/pentane); ν_{max} (film)/cm^{-1} 3297 (NH br), 2973, 1690 (C=O), 1647 (C=O), 1515, 1401, 1364, 1247, 1165, 1113, 1031, 877, 831, 730, 698; ^{1}H NMR (400 MHz, DMSO-d_6, 373 K) δ 7.83 (br t, *J* = 5.1 Hz, 1 H, NH), 7.25–7.14 (m, 3 H, HC_{Ar}), 7.16–7.07 (m, 2 H, HC_{Ar}), 6.94 (dd, *J* = 7.2, 2.2 Hz, 2 H, HC_{Ar}), 6.85–6.76 (m, 2 H, HC_{Ar}), 4.14 (dd, *J* = 15.1, 6.2 Hz, 1 H, NHC*H*H), 4.03 (dd, *J* = 15.1, 5.5 Hz, 1 H, NHCH*H*), 3.75 (s, 3 H, OCH_3), 3.73–3.66 (m, 1 H, NC*H*HCHAr), 3.66–3.58 (m, 3 H, NCH*H*CHAr, CHAr, NC*H*HCHCO), 3.52 (dd, *J* = 11.0, 7.3 Hz, 1 H, NCH*H*CHCO), 3.29 (dt, *J* = 7.0, 4.4 Hz, 1 H, CHCO), 1.46 (s, 9 H, C(CH_3)$_3$); ^{13}C NMR (101 MHz, DMSO-d_6, 373 K) δ 170.3 (C=O amide), 157.7 (OC_{Ar} quat), 153.2 (C=O carbamate), 138.5 (C_{Ar} quat), 130.3 (C_{Ar} quat), 128.3 (2 × C_{Ar}), 127.3 (2 × C_{Ar}), 126.7 (2 × C_{Ar}), 125.9 (C_{Ar}), 113.2 (2 × C_{Ar}), 77.8 (*C*(CH_3)$_3$), 54.6 (OCH_3), 49.9 (N*C*H_2CHAr), 47.8 (N*C*H_2CHCO), 47.4 (*C*HCO), 44.5 (*C*HAr), 41.6 (NH*C*H_2), 27.8 (C(*C*H_3)$_3$); HRMS (ESI$^+$) m/z Calculated for $C_{24}H_{31}N_2O_4^+$ [M+H]$^+$ 411.2284; Found 411.2296.

1-Benzyl 3-methyl _cis_-(±)-4-(4-methoxyphenyl)pyrrolidine-1,3-dicarboxylate (_cis_-24) and **1-benzyl 3-methyl _trans_-(±)-4-(4-methoxyphenyl)pyrrolidine-1,3-dicarboxylate (_trans_-24):**



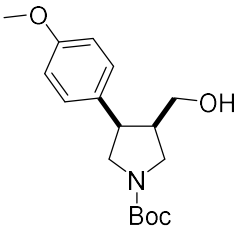
According to Chen's procedure,[5] a reaction tube was charged with K_2CO_3 (27.6 mg, 0.2 mmol), flame-dried, and allowed to cool under argon. Boc-protected amide **21** (58.2 mg, 0.1 mmol) was added and the reaction vessel sealed, purged with argon and cooled at 0 °C. Then dry MeOH (2.0 mL, 0.05 M) was added by syringe. The reaction was then stirred at 25 °C for 22 h. The reaction mixture was diluted with EtOAc (2 mL). The resulting mixture was filtered through a pad of Celite, eluting with further EtOAc (2 × 5 mL). The solvent was removed under reduced pressure. The reaction mixture was purified by flash column chromatography (10% to 20% acetone/pentane). The product containing fractions were combined and the solvent was removed under reduced pressure. Et_2O (2 mL) and pentane (2 mL) were added and the solvent was removed under reduced pressure to afford the major product 1-benzyl 3-methyl *cis*-(±)-4-(4-methoxyphenyl)pyrrolidine-1,3-dicarboxylate *cis*-**24** as a white solid (21.1 mg, 54%), followed by the minor product 1-benzyl 3-methyl *trans*-(±)-4-(4-methoxyphenyl)pyrrolidine-1,3-dicarboxylate *trans*-**24** as a colourless oil (11.0 mg, 29%).

Major (*cis*-**24**): R_f 0.34 (20% acetone/pentane); mp = 69–71 °C (from Et_2O/pentane); ν_{max} (film)/cm^{-1} 2960, 2880, 1732 (C=O ester), 1703 (C=O carbamate), 1515, 1414, 1353, 1327, 1305, 1251, 1194, 1135, 1028, 1001, 832, 816, 766, 733, 695; ^{1}H NMR (500 MHz, DMSO-d_6, 373 K) δ 7.42–7.35 (m, 4 H, HC_{Ar}), 7.34–7.28 (m, 1 H, HC_{Ar}), 7.25–7.19 (m, 2 H, HC_{Ar}), 6.92–6.86 (m, 2 H, HC_{Ar}), 5.11 (s, 2 H, OCH_2Ph), 3.88–3.80 (m, 2 H, NC*H*HCHAr, NC*H*HCHCO), 3.76 (s, 3 H, PhOCH_3), 3.62–3.54 (m, 5 H, CHAr, NCH*H*CHCO, COOCH_3), 3.36 (t, *J* = 9.8 Hz, 1 H, NCH*H*CHAr), 3.29 (q, *J* = 9.0 Hz, 1 H, CHCO); ^{13}C NMR (126 MHz, DMSO-d_6, 373 K) δ 171.6 (C=O ester), 158.0 (OC_{Ar} quat), 153.2

(C=O carbamate), 136.5 (C_{Ar} quat), 130.9 (C_{Ar} quat), 127.74 (2 × C_{Ar}), 127.67 (2 × C_{Ar}), 127.1 (C_{Ar}), 126.8 (2 × C_{Ar}), 113.7 (2 × C_{Ar}), 65.5 (O*C*H_2Ph), 54.7 (PhO*C*H_3), 51.9 (N*C*H_2CHAr), 51.0 (COO*C*H_3), 48.6 (*C*HCO), 48.0 (N*C*H_2CHCO), 45.7 (*C*HAr); HRMS (ESI$^+$) m/z Calculated for $C_{21}H_{24}NO_5^+$ $[M+H]^+$ 370.1654; Found 370.1655.

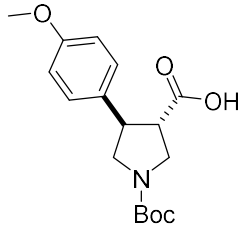
Minor (*trans*-**24**): R_f 0.29 (20% acetone/pentane); ν_{max} (film)/cm^{-1} 2958, 1717 (C=O ester), 1695 (C=O carbamate), 1517, 1419, 1356, 1329, 1252, 1208, 1179, 1132, 1026, 831, 767, 734, 697; ^{1}H NMR (500 MHz, DMSO-d_6, 373 K) δ 7.40–7.36 (m, 4 H, HC_{Ar}), 7.34–7.30 (m, 1 H, HC_{Ar}), 7.09–7.05 (m, 2 H, HC_{Ar}), 6.87–6.84 (m, 2 H, HC_{Ar}), 5.15 (s, 2 H, OCH_2Ph), 3.79 (qd, *J* = 9.4, 6.6 Hz, 1 H, NC*H*HCHAr), 3.75 (s, 3 H, PhOCH_3), 3.73–3.63 (m, 4 H, NCH_2CHCO, CHAr, NCH*H*CHAr), 3.49 (td, *J* = 7.1, 5.7 Hz, 1 H, CHCO), 3.38 (s, 3 H, COOCH_3); ^{13}C NMR (126 MHz, DMSO-d_6, 373 K) δ 170.9 (C=O ester), 157.9 (OC_{Ar} quat), 153.5 (C=O carbamate), 136.7 (C_{Ar} quat), 130.0 (C_{Ar} quat), 127.8 (2 × C_{Ar}), 127.7 (2 × C_{Ar}), 127.1 (C_{Ar}), 126.8 (2 × C_{Ar}), 113.4 (2 × C_{Ar}), 65.5 (O*C*H_2Ph), 54.6 (PhO*C*H_3), 50.4 (COO*C*H_3), 49.8 (N*C*H_2CHAr), 47.2 (*C*HCO), 46.9 (N*C*H_2CHCO), 44.0 (*C*HAr); HRMS (ESI$^+$) m/z Calculated for $C_{21}H_{24}NO_5^+$ $[M+H]^+$ 370.1654; Found 370.1653.

tert-Butyl *cis*-(±)-3-(hydroxymethyl)-4-(4-methoxyphenyl)pyrrolidine-1-carboxylate (25)



A solution of Boc-protected amide **20** (54.8 mg, 0.1 mmol) in dry THF (400 μL) was added dropwise to a suspension of $LiAlH_4$ (15.1 mg, 0.4 mmol) in dry THF (100 μL) at 0 °C under argon atmosphere. The mixture was then stirred at 20 °C for 30 min. The reaction mixture was then quenched by slow addition of sat. aq. NH_4Cl (2 mL) at 0 °C and stirred at rt for 30 min. The resulting suspension was filtered through a pad of Celite, eluting with EtOAc (3 × 5 mL). The phases were separated and the aqueous layer was extracted with EtOAc (3 × 5 mL). The combined organic extracts were dried over Na_2SO_4 and filtered. The solvent was removed under reduced pressure. Purification by flash column chromatography (20% acetone/pentane) afforded primary alcohol **25** as a colourless paste (23.5 mg, 76%, single diastereoisomer). R_f 0.28 (20% acetone/pentane); ν_{max} (film)/cm^{-1} 3407 (OH br), 2935, 1683 (C=O), 1513, 1401, 1365, 1246, 1162, 1124, 1027, 876, 826, 772; ^{1}H NMR (400 MHz, DMSO-d_6, 373 K) δ 7.10–7.05 (m, 2 H, HC_{Ar}), 6.90–6.85 (m, 2 H, HC_{Ar}), 4.08 (t, *J* = 4.9 Hz, 1 H, OH), 3.75 (s, 3 H, OCH_3), 3.62 (dd, *J* = 10.7, 7.2 Hz, 1 H, NC*H*HCHAr), 3.51 (dd, *J* = 10.7, 5.8 Hz, 1 H, NCH*H*CHAr), 3.49–3.40 (m, 2 H, NC*H*HCHCH_2OH, CHAr), 3.25 (dd, *J* = 10.8, 6.6 Hz, 1 H, NCH*H*CHCH_2OH), 3.14 (dt, *J* = 10.2, 5.1 Hz, 1 H, C*H*HOH), 3.03–2.95 (m, 1 H, CH*H*OH), 2.57–2.47 (m, 1 H, C*H*CH_2OH), 1.46 (s, 9 H, C(CH_3)$_3$); ^{13}C NMR (101 MHz, DMSO-d_6, 373 K) δ 157.6 (OC_{Ar} quat), 153.3 (C=O carbamate), 131.2 (C_{Ar} quat), 128.1 (2 × C_{Ar}), 113.4 (2 × C_{Ar}), 77.8 (*C*(CH_3)$_3$), 59.6 (*C*H_2OH), 54.7 (OCH_3), 50.2 (N*C*H_2CHAr), 47.6 (N*C*H_2CHCH_2OH), 44.1 (*C*HCH_2OH), 43.2 (*C*HAr), 27.8 (C(*C*H_3)$_3$); HRMS (ESI$^+$) m/z Calculated for $C_{17}H_{26}NO_4^+$ $[M+H]^+$ 308.1862; Found 308.1857.

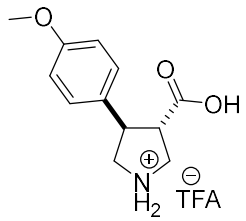
***trans*-(±)-1-(*tert*-Butoxycarbonyl)-4-(4-methoxyphenyl)pyrrolidine-3-carboxylic acid (26)**



A reaction tube was charged with amide **2a** (89.5 mg, 0.20 mmol), followed by NaOH (80.0 mg, 2.0 mmol). The reaction vessel was sealed and EtOH (1.0 mL, 0.2 M) was added by syringe. The reaction tube was then placed in a preheated oil bath and stirred at 100 ºC for 30 min. The reaction mixture was then allowed to cool down to rt and diluted with EtOAc (1 mL) and 1N NaOH (1 mL). The aqueous alkaline layer was collected, and the organic layer extracted with 1N NaOH (3 × 5 mL). All of the aqueous alkaline layers were combined, washed with EtOAc (10 mL), and acidified to pH 2–3 with conc. HCl. The acidic layer was extracted with EtOAc (5 × 20 mL). The combined organic extracts were dried over Na_2SO_4 and filtered. Solvent was removed under reduced pressure. Et_2O (5 mL) and pentane (5 mL) were added and the solvent was removed under reduced pressure to afford the pure *trans*–acid **26** as a pale orange solid (58.1 mg, 86%, single diastereoisomer). R_f 0.19 (80:20:0.5 acetone/pentane/TFA); mp = 144–148 °C (from Et_2O/pentane); ν_{max} (film)/cm^{-1} 3101 (OH br), 2979, 1727 (C=O), 1662 (C=O), 1517, 1435, 1408, 1369, 1253, 1165, 1136, 1030, 883, 817, 765, 666; ^{1}H NMR (400 MHz, $CDCl_3$, 298 K, observed as mixture of rotamers) δ 7.17 (d, *J* = 8.6 Hz, 2 H, HC_{Ar}), 6.86 (d, *J* = 8.5 Hz, 2 H, HC_{Ar}), 3.94–3.74 (m, 5 H, NC*H*HCHAr, NC*H*HCHCO, OCH_3), 3.66–3.53 (m, 2 H, NCH*H*CHCO, CHAr), 3.44–3.28 (m,

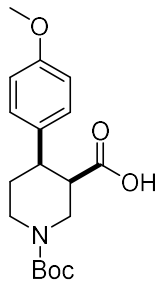
1 H, NCH*H*CHAr), 3.22–3.09 (m, 1 H, CHCO), 1.48 and 1.46 (2 × s, 9 H, C(CH_3)$_3$); ^{13}C NMR (101 MHz, $CDCl_3$, 298 K, observed as mixture of rotamers) δ 177.2 (COOH), 158.8 (OC_{Ar} quat), 154.1 (C=O carbamate), 130.8 and 130.7 (C_{Ar} quat), 128.3 (2 × C_{Ar}), 114.2 (2 × C_{Ar}), 80.0 (*C*(CH_3)$_3$), 55.2 (OCH_3), 52.9 and 52.2 (N*C*H_2CHAr), 50.4 and 49.4 (*C*HCO), 48.7 and 48.5 (N*C*H_2CHCO), 47.0 and 46.2 (*C*HAr), 28.4 (C(*C*H_3)$_3$); HRMS (ESI$^+$) m/z Calculated for $C_{17}H_{24}NO_5^+$ $[M+H]^+$ 322.1654; Found 322.1642.

***trans*-(±)-4-(4-Methoxyphenyl)pyrrolidine-3-carboxylic acid trifluoroacetic acid salt (27)**



Freshly-distilled trifluoroacetic acid (74 μL, 1.0 mmol) was added to a solution of Boc-protected *trans*-acid **26** (33.5 mg, 0.1 mmol) in CH_2Cl_2 (1.0 mL, 0.1 M) at 0 °C. The reaction was allowed to warm up and stirred at 25 °C for 22 h. The solvent was removed under reduced pressure, affording *trans*-aminoacid **27** as the correspondent trifluoroacetate salt (brown paste, 32.9 mg, 98%, containing <7% of inseparable 2,3-disubstituted isomer). ν_{max} (film)/cm^{-1} 2920 (OH br), 1664 (C=O), 1516, 1427, 1250, 1177, 1130, 1031, 829, 796, 721; ^{1}H NMR (400 MHz, CD_3OD, 298 K) δ 7.29 (d, *J* = 8.7 Hz, 2 H, HC_{Ar}), 6.92 (d, *J* = 8.7 Hz, 2 H, HC_{Ar}), 3.78 (s, 3 H, OCH_3), 3.77–3.59 (m, 4 H, NC*H*HCHAr, NCH_2CHCO, CHAr), 3.37–3.28 (m, 2 H, NCH*H*CHAr, CHCO); ^{13}C NMR (101 MHz, CD_3OD, 298 K) δ 174.1 (COOH), 160.9 (OC_{Ar} quat), 130.5 (C_{Ar} quat), 129.6 (2 × C_{Ar}), 115.4 (2 × C_{Ar}), 55.7 (OCH_3), 52.8 (N*C*H_2CHAr), 50.8 (*C*HCO), 49.1 (N*C*H_2CHCO), 48.5 (*C*HAr); ^{19}F NMR (377 MHz, CD_3OD, 298 K) δ –76.9 (s, CF_3); HRMS (ESI$^+$) m/z Calculated for $C_{12}H_{16}NO_3^+$ $[M+H]^+$ 222.1130; Found 222.1132.

***cis*-(±)-1-(*tert*-Butoxycarbonyl)-4-(4-methoxyphenyl)piperidine-3-carboxylic acid (28):**

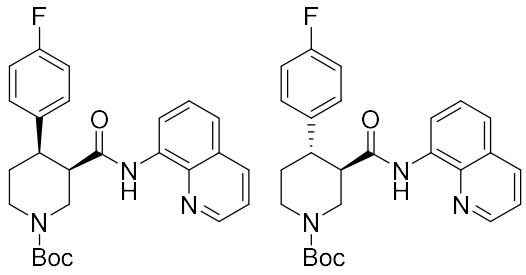


A flame-dried reaction tube was charged with amide **15a** (138 mg, 0.30 mmol), followed by di-*tert*-butyl dicarbonate (Boc_2O, 327 mg, 1.50 mmol) and 4-(dimethylamino)pyridine (DMAP, 7.3 mg, 0.06 mmol). The reaction vessel was sealed and purged with argon, then MeCN (500 μL, 0.6 M) was added by syringe. The reaction tube was then placed in an oil bath and gradually warm up to 70 ºC. The reaction mixture was then stirred at 70 °C for 48 h. The reaction mixture was then allowed to cool to rt and sat. aq. NH_4Cl (1 mL) and CH_2Cl_2 (1 mL) were added. The phases were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic extracts were dried over Na_2SO_4 and filtered. The solvent was removed under reduced pressure to afford the crude *N*-Boc protected piperidine derivative.

A solution of H_2O_2 (306 μL, 3.0 mmol, 30 wt.% in H_2O) in THF (700 μL) was added to a solution of LiOH·H_2O (101 mg, 2.4 mmol) in H_2O (400 μL) at 0 °C under argon. The resulting mixture was added dropwise to a solution of crude *N*-Boc protected piperidine in THF (600 μL) at 0 °C under argon. The reaction was then stirred at 45 °C for 24 h. The reaction mixture was then allowed to cool down to rt and sat. aq. $Na_2S_2O_3$ (2 mL), EtOAc (2 mL) and 1N NaOH (2 mL) were added. The aqueous alkaline layer was collected, and the organic layer extracted with 1N NaOH (3 × 5 mL). All of the aqueous alkaline layers were combined, washed with EtOAc (15 mL), and acidified to pH 2–3 with conc. HCl. The acidic layer was extracted with EtOAc (5 × 25 mL). The combined organic extracts were washed with brine (30 mL), dried over Na_2SO_4 and filtered. Solvent was removed under reduced pressure. Et_2O (5 mL) and pentane (5 mL) were added and the solvent was removed under reduced pressure to afford the pure *cis*–acid **28** as a pale yellow solid (59.1 mg, 61% over 2 steps, single diastereoisomer). R_f 0.17 (3% MeOH/CH_2Cl_2); mp = 186–191 °C (from Et_2O/pentane); ν_{max} (film)/cm^{-1} 2933 (OH br), 1706 (C=O), 1681 (C=O), 1514, 1465, 1418, 1366, 1244, 1178, 1118, 1040, 1006, 830, 769; ^{1}H NMR (400 MHz, $CDCl_3$, 298 K) δ 7.20–7.11 (m, 2 H, HC_{Ar}), 6.85–6.80 (m, 2 H, HC_{Ar}), 4.44 (br d, *J* = 13.6, 1 H, NC*H*HCHCO), 4.27 (br d, *J* = 12.5, 1 H, NC*H*HCH_2), 3.78 (s, 3 H, OCH_3), 3.18 (dd, *J* = 13.9, 3.8 Hz, 1 H, NCH*H*CHCO), 2.99–2.81 (m, 3 H, CHCO, CHAr, NCH*H*CH_2), 2.54 (qd, *J* = 12.3, 4.5 Hz, 1 H, NCH_2C*H*H), 1.67 (dq, *J* = 13.0, 3.3 Hz, 1 H, NCH_2CH*H*), 1.39 (s, 9 H, C(CH_3)$_3$); ^{13}C NMR (101 MHz, DMSO-d_6, 373 K) δ 176.6 (COOH), 158.3 (OC_{Ar} quat), 154.6 (C=O carbamate), 134.2 (C_{Ar} quat), 128.4 (2 × C_{Ar}), 113.8 (2 × C_{Ar}), 79.8 (*C*(CH_3)$_3$), 55.2 (OCH_3), 46.1 (N*C*H_2CHCO), 45.4 (*C*HCO), 43.9 (N*C*H_2CH_2), 42.3 (*C*HAr), 28.3 (C(*C*H_3)$_3$), 25.9 (NCH_2*C*H_2); HRMS (ESI$^+$) *m/z* Calculated for $C_{18}H_{26}NO_5^+$ $[M+H]^+$ 336.1811; Found 336.1819.

Formal Stereocontrolled Synthesis of (–)-Paroxetine:

***tert*-Butyl (+)-(*3R,4R*)-4-(4-fluorophenyl)-3-(quinolin-8-ylcarbamoyl)piperidine-1-carboxylate ((+)-15d)** and ***tert*-butyl (–)-(*3R,4S*)-4-(4-fluorophenyl)-3-(quinolin-8-ylcarbamoyl)piperidine-1-carboxylate ((–)-16d)**:



A large microwave vial (10–20 mL recommended volume) was charged with K_2CO_3 (553 mg, 4.0 mmol), flame-dried, and allowed to cool under argon. *tert*-Butyl (*R*)-3-(quinolin-8-ylcarbamoyl)piperidine-1-carboxylate **(*R*)-13** (1.42 g, 4.0 mmol), 4-fluoroiodobenzene (2.66 g, 12.0 mmol), $Pd(OAc)_2$ (45.1 mg, 0.2 mmol) and PivOH (409 mg, 4.0 mmol) were added sequentially. The reaction vessel was sealed and purged with argon, then $PhCF_3$ (2.0 mL, 2.00 M) was added by syringe. The reaction tube was then placed in a preheated oil bath and stirred at 110 ºC for 18 h. The reaction mixture was then allowed to cool to rt and EtOAc (20 mL) was added. The resulting mixture was filtered through a pad of Celite, eluting with further EtOAc (2 × 50 mL). The solvent was removed under reduced pressure. The reaction mixture was purified by two consecutive flash column chromatographies: one (5% to 10% acetone/pentane) to isolate the major product *tert*-butyl (+)-(*3R,4R*)-4-(4-fluorophenyl)-3-(quinolin-8-ylcarbamoyl)piperidine-1-carboxylate **(+)-15d** followed by a second (50:40:10 hexane/Et_2O/CH_2Cl_2) to isolate the minor product *tert*-butyl (–)-(*3R,4S*)-4-(4-fluorophenyl)-3-(quinolin-8-ylcarbamoyl)piperidine-1-carboxylate **(–)-16d**. The product containing fractions were combined and the solvent was removed under reduced pressure. Et_2O (20 mL) and pentane (20 mL) were added and the solvent was removed under reduced pressure to afford the major product **(+)-15d** as a white solid (775 mg, 43%, 99.3% *ee*) and the minor product **(–)-16d** (216 mg, 12%, 99.2% *ee*).

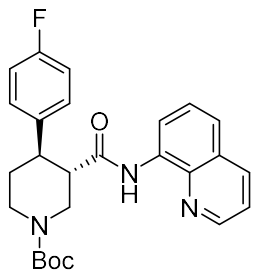
Major (**(+)-15d**): $[\alpha]_D^{21}$ +33.0 (*c* 1.21, $CHCl_3$). Characterisation data identical to that reported for racemic piperidine **15d** (see S60).

HPLC Conditions: Chiralpak IA 3-column, 85:15 *n*-hexane:*i*-PrOH, flow rate: 1 mL·min^{-1}, 35 ºC, UV detection wavelength: 210.4 nm. Retention times: 11.1 min (3*S,*4*S* enantiomer), 17.6 min (3*R,*4*R* enantiomer).

Minor (**(–)-16d**): $[\alpha]_D^{21}$ –22.2 (*c* 1.35, $CHCl_3$). Characterisation data identical to that reported for racemic piperidine **16d** (see S60).

HPLC Conditions: Chiralpak IA 3-column, 85:15 *n*-hexane:*i*-PrOH, flow rate: 1 mL·min^{-1}, 35 ºC, UV detection wavelength: 210.4 nm. Retention times: 8.4 min (3*R,*4*S* enantiomer), 10.2 min (3*S,*4*R* enantiomer).

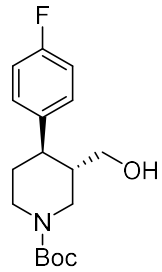
***tert*-Butyl (+)-(*3S,4R*)-4-(4-fluorophenyl)-3-(quinolin-8-ylcarbamoyl)piperidine-1-carboxylate ((+)-16d)**



A flame-dried reaction tube was charged with *cis*-3,4-disubstituted piperidine **(+)-15d** (266 mg, 0.59 mmol) and 1,8-diazabicyclo(5.4.0)undec-7-ene (DBU, 268 μL, 1.77 mmol). The reaction vessel was sealed and purged with argon, then dry toluene (590 μL, 1.0 M) was added by syringe. The reaction tube was then placed in a preheated oil bath and stirred at 110 ºC for 18 h. The reaction mixture was then allowed to cool to rt and EtOAc (5 mL) and sat. aq. NH_4Cl (5 mL) were added. The phases were separted and the aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic extracts were dried over Na_2SO_4 and filtered. The solvent was removed under reduced pressure. The reaction mixture was purified by flash column chromatography (10% acetone/pentane). The product containing fractions were combined and the solvent was removed under reduced pressure. Et_2O (10 mL) and pentane (10 mL) were added and the solvent was removed under reduced pressure to afford amide *tert*-butyl (+)-(*3S,4R*)-4-(4-fluorophenyl)-3-(quinolin-8-ylcarbamoyl) piperidine-1-carboxylate **(+)-16d** as a white solid (252 mg, 95%, 99.4% *ee*). $[\alpha]_D^{21}$ +29.4 (*c* 2.0, $CHCl_3$). Characterisation data identical to that reported for racemic piperidine **16d** (see S60).

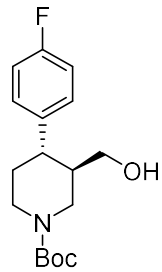
HPLC Conditions: Chiralpak IA 3-column, 85:15 *n*-hexane:*i*-PrOH, flow rate: 1 mL·min^{-1}, 35 ºC, UV detection wavelength: 210.4 nm. Retention times: 8.4 min (3*R*,4*S* enantiomer), 10.2 min (3*S*,4*R* enantiomer).

***tert*-Butyl (–)-(*3S,4R*)-4-(4-fluorophenyl)-3-(hydroxymethyl)piperidine-1-carboxylate ((–)-29)**



A flame-dried reaction tube was charged with amide **(+)-16d** (66.0 mg, 0.15 mmol), followed by di-*tert*-butyl dicarbonate (Boc_2O, 128 mg, 0.59 mmol) and 4-(dimethylamino)pyridine (DMAP, 4.1 mg, 0.03 mmol). The reaction vessel was sealed and purged with argon, then MeCN (300 μL, 0.5 M) was added by syringe. The reaction tube was then placed in a preheated oil bath and stirred at 35 ºC for 24 h. The reaction mixture was then allowed to cool to rt and sat. aq. NH_4Cl (1 mL) and CH_2Cl_2 (1 mL) were added. The phases were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic extracts were dried over Na_2SO_4 and filtered. The solvent was removed under reduced pressure to afford the crude *N*-Boc protected piperidine derivative. This was solubilised in dry THF (600 μL) and the resulting solution was added dropwise to a suspension of $LiAlH_4$ (22.8 mg, 0.60 mmol) in dry THF (100 μL) at 0 °C under argon atmosphere. The mixture was then stirred at 25 °C for 30 min. The reaction mixture was then quenched by slow addition of sat. aq. NH_4Cl (2 mL) at 0 °C and stirred at rt for 30 min. The resulting suspension was filtered through a pad of Celite, eluting with EtOAc (3 × 5 mL). The phases were separated and the aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic extracts were dried over Na_2SO_4 and filtered. The solvent was removed under reduced pressure. Purification by flash column chromatography (10% acetone/pentane) afforded primary alcohol **(–)-29** as a colourless paste (36.5 mg, 79% over 2 steps, 99.1% *ee*). $[\alpha]_D^{22}$ –5.1 (*c* 1.56, MeOH). R_f 0.18 (10% acetone/pentane); ν_{max} (film)/cm^{-1} 3407 (OH), 2920, 1664 (C=O), 1509, 1425, 1365, 1280, 1223, 1158, 1128, 1059, 1015, 830, 769; ^{1}H NMR (400 MHz, $CDCl_3$, 298 K) δ 7.19–7.12 (m, 2 H, HC_{Ar}), 7.03–6.97 (m, 2 H, HC_{Ar}), 4.37 (br d, *J* = 13.4 Hz, 1 H, NC*H*HCHCH$_2$OH), 4.20 (br s, 1 H, NC*H*HCH$_2$), 3.44 (dd, *J* = 11.0, 3.2 Hz, 1 H, C*H*HOH), 3.26 (dd, *J* = 11.0, 6.4 Hz, 1 H, CH*H*OH), 2.86–2.65 (m, 2 H, NCH*H*CHCO, NCH*H*CH$_2$), 2.54 (td, *J* = 11.9, 3.9 Hz, 1 H, CHAr), 1.86–1.73 (m, 2 H, C*H*CH$_2$OH, NCH$_2$C*H*H), 1.73–1.60 (m, 2 H, NCH$_2$CH*H*, OH), 1.49 (s, 9 H, C(CH$_3$)$_3$); ^{13}C NMR (101 MHz, DMSO-*d*$_6$, 373 K) δ 161.6 (d, J_{CF} = 244.6 Hz, FC_{Ar} quat), 154.9 (C=O), 139.5 (d, J_{CF} = 2.7 Hz, F-*p*-C_{Ar} quat), 128.7 (d, J_{CF} = 7.8 Hz, 2 × F-*m*-C_{Ar}), 115.5 (d, J_{CF} = 21.1 Hz, 2 × F-*o*-C_{Ar}), 79.6 (*C*(CH$_3$)$_3$), 63.1 (*C*H$_2$OH), 46.9 (N*C*H$_2$CHCH$_2$OH), 44.4 (N*C*H$_2$CH$_2$), 44.1 (*C*HAr), 43.9 (*C*HCH$_2$OH), 34.1 (NCH$_2$*C*H$_2$), 28.5 (C(*C*H$_3$)$_3$); ^{19}F NMR (376 MHz, DMSO-*d*$_6$, 373 K) δ –116.4 (br s).
HPLC Conditions: Chiralpak IA 3-column, 90:10 *n*-hexane:*i*-PrOH, flow rate: 1 mL·min^{-1}, 35 ºC, UV detection wavelength: 210.4 nm. Retention times: 7.3 min (3*R*,4*S* enantiomer), 8.7 min (3*S*,4*R* enantiomer).
The observed characterisation data (IR, ^{1}H NMR, ^{13}C NMR) and the specific rotation ($[\alpha]_D^{22}$) were consistent with those previously reported in the literature.[1]

***tert*-Butyl (+)-(*3R,4S*)-4-(4-fluorophenyl)-3-(hydroxymethyl)piperidine-1-carboxylate ((+)-29)**



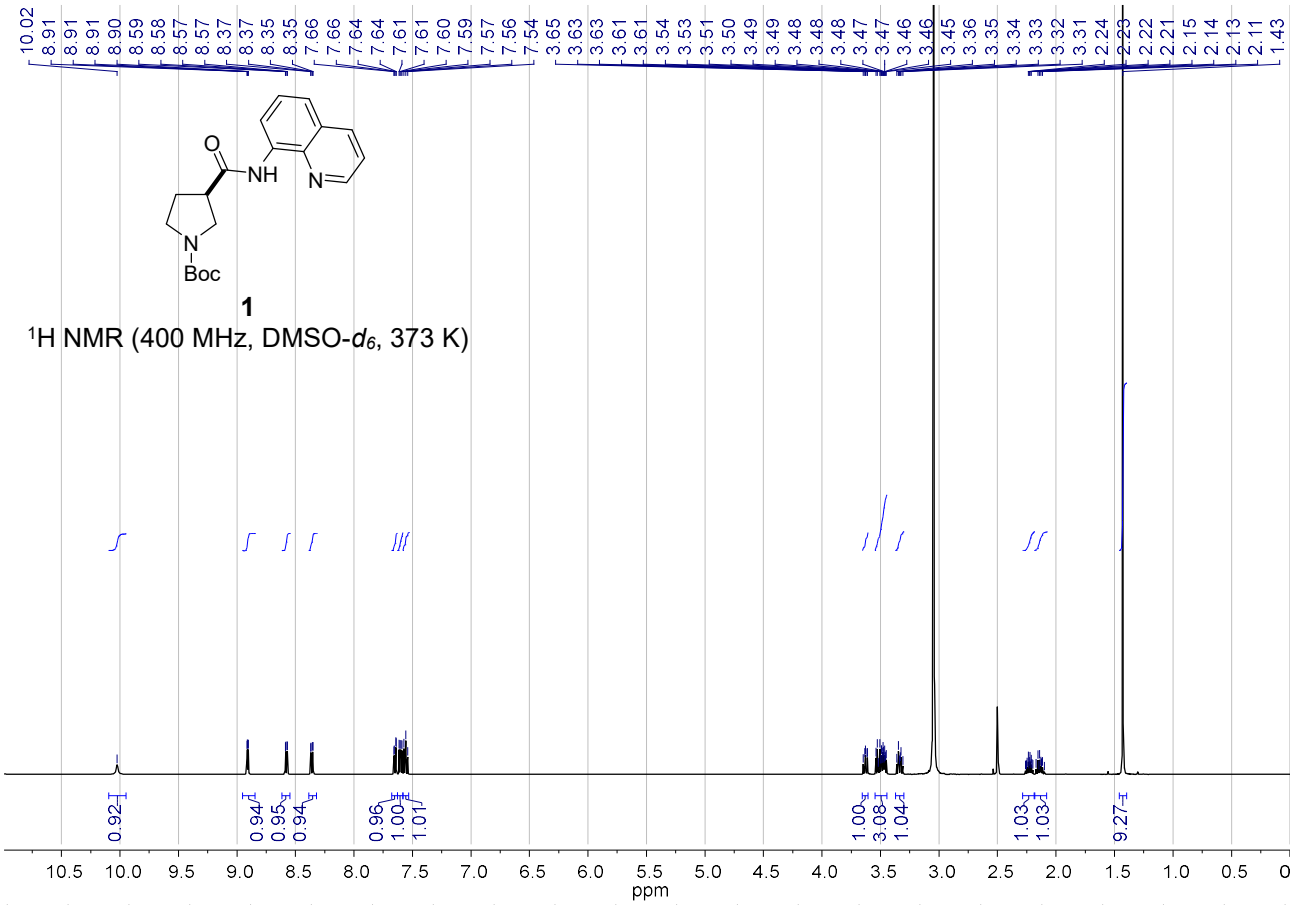
A flame-dried reaction tube was charged with amide **(–)-16d** (71.0 mg, 0.16 mmol), followed by di-*tert*-butyl dicarbonate (Boc_2O, 138 mg, 0.63 mmol) and 4-(dimethylamino)pyridine (DMAP, 3.9 mg, 0.03 mmol). The reaction vessel was sealed and purged with argon, then MeCN (300 μL, 0.5 M) was added by syringe. The reaction tube was then placed in a preheated oil bath and stirred at 35 ºC for 24 h. The reaction mixture was then allowed to cool to rt and sat. aq. NH_4Cl (1 mL) and CH_2Cl_2 (1 mL) were added. The phases were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic extracts were dried over Na_2SO_4 and filtered. The solvent was removed under reduced pressure to afford the crude *N*-Boc protected piperidine derivative. This was solubilised in dry THF (700 μL) and the resulting solution was added dropwise to a suspension of $LiAlH_4$ (24.2 mg, 0.64 mmol) in dry THF (200 μL) at 0 °C under argon atmosphere. The mixture was then stirred at 25 °C for 30 min. The reaction mixture was then quenched by slow addition of sat. aq. NH_4Cl (2 mL) at 0 °C and stirred at rt for 30 min. The resulting suspension was filtered through a pad of Celite, eluting with EtOAc (3 × 5 mL). The phases

were separated and the aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic extracts were dried over Na_2SO_4 and filtered. The solvent was removed under reduced pressure. Purification by flash column chromatography (10% acetone/pentane) afforded primary alcohol **(+)-29** as a colourless paste (38.6 mg, 78% over 2 steps, 98.6% *ee*). $[\alpha]_D^{22}$ +5.8 (*c* 0.92, MeOH).
HPLC Conditions: Chiralpak IA 3-column, 90:10 *n*-hexane:*i*-PrOH, flow rate: 1 mL·min^{-1}, 35 ºC, UV detection wavelength: 210.4 nm. Retention times: 7.3 min (3*R*,4*S* enantiomer), 8.7 min (3*S*,4*R* enantiomer).
Characterisation data identical to that reported for alcohol **(–)-29**. The specific rotation ($[\alpha]_D^{22}$) was consistent with that previously reported in the literature.[1]

References

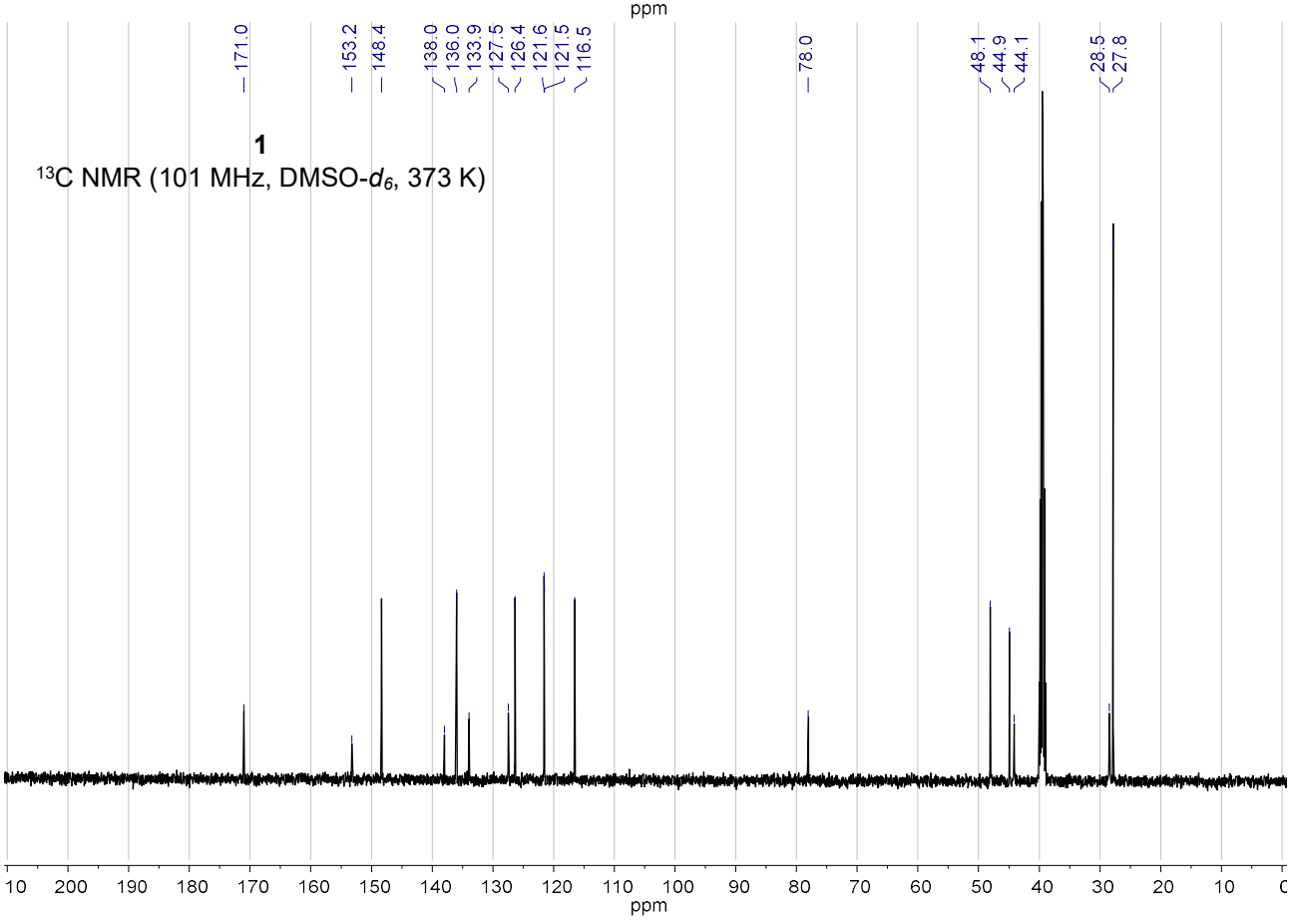
(1) Amat, M.; Bosch, J.; Hidalgo, J.; Cantó, M.; Pérez, M.; Llor, N.; Molins, E.; Miravitlles, C.; Orozco, M.; Luque, J. *J. Org. Chem.* **2000**, *65*, 3074.
(2) (a) For a comparison see the chemical shift for the C(2) proton of *N*-Boc 2-aryl pyrrolidine 3-carboxylic acid derivatives (δ 4.97–5.23): Buchholz, M.; Reißig, H.-U. *Eur. J. Org. Chem.* **2003**, 3524. (b) For stereochemical assignement, see: Chung, J. Y. L.; Wasicak, J. T.; Arnold, W. A.; May, C. S.; Nadzan, A. M.; Holladay, M. W. *J. Org. Chem.* **1990**, *55*, 270.
(3) Bull, J. A.; Mousseau, J. J.; Charette, A. B. *Org. Lett.* **2008**, *10*, 5485.
(4) Berger, M.; Chauhan, R.; Rodrigues, C. A. B.; Maulide, N. *Chem. Eur. J.* **2016**, *22*, 16805.
(5) Feng, Y.; Wang, Y.; Landgraf, B.; Liu, S.; Chen, G. *Org. Lett.* **2010**, *12*, 3414.

^{1}H, ^{13}C and ^{19}F NMR Spectra for Selected Compounds



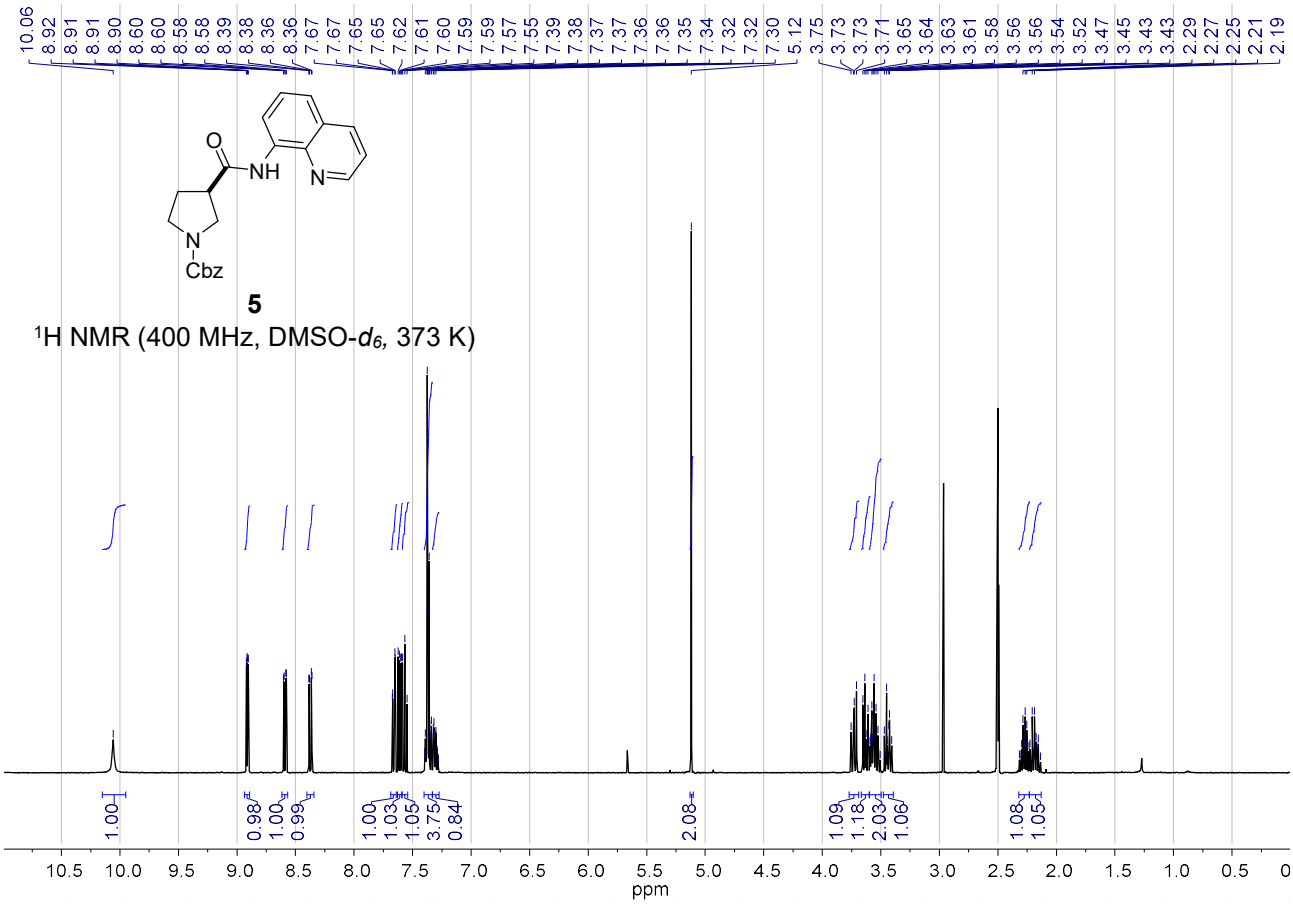
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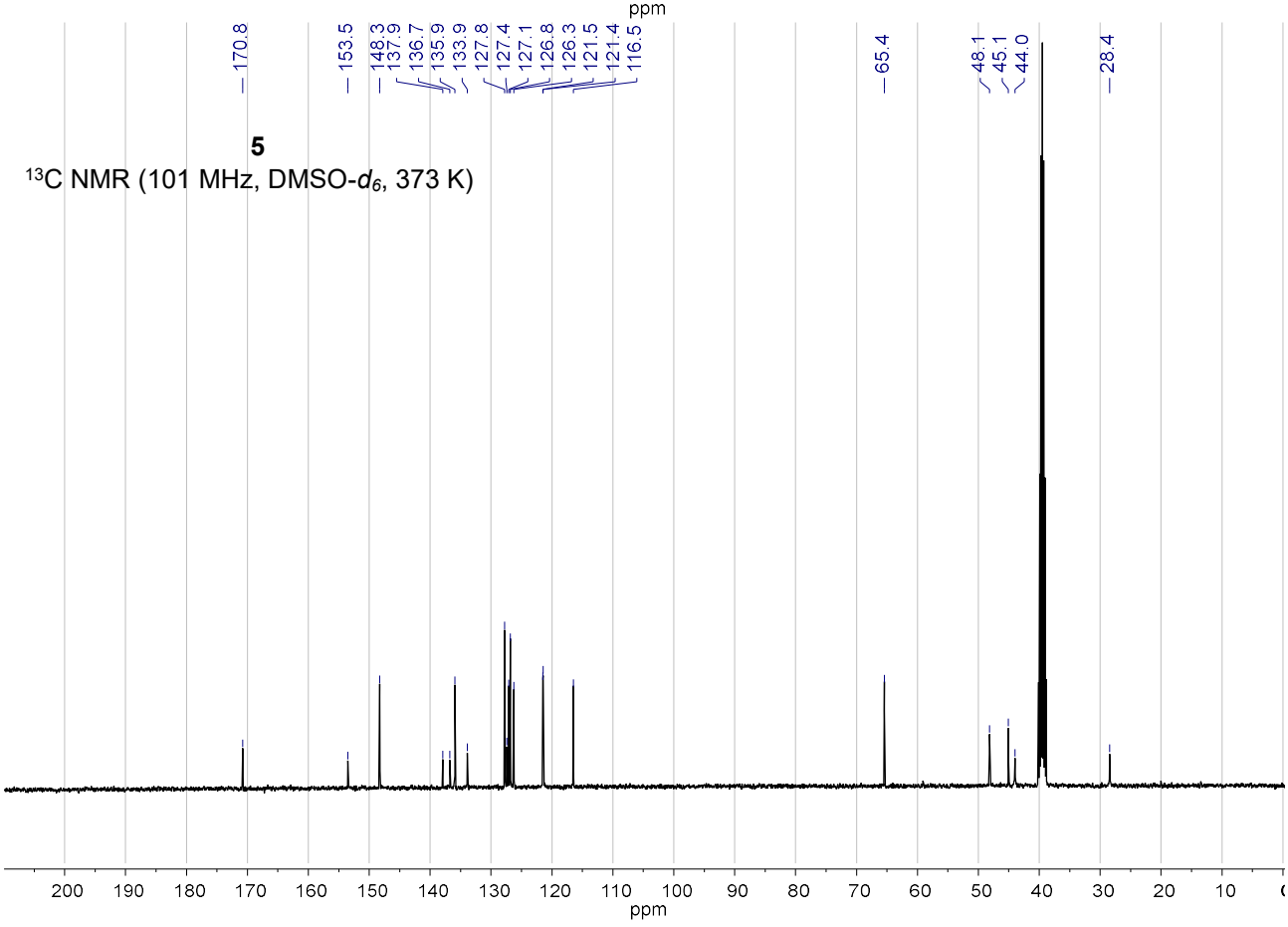
^{1}H NMR (400 MHz, DMSO-d_6, 373 K)

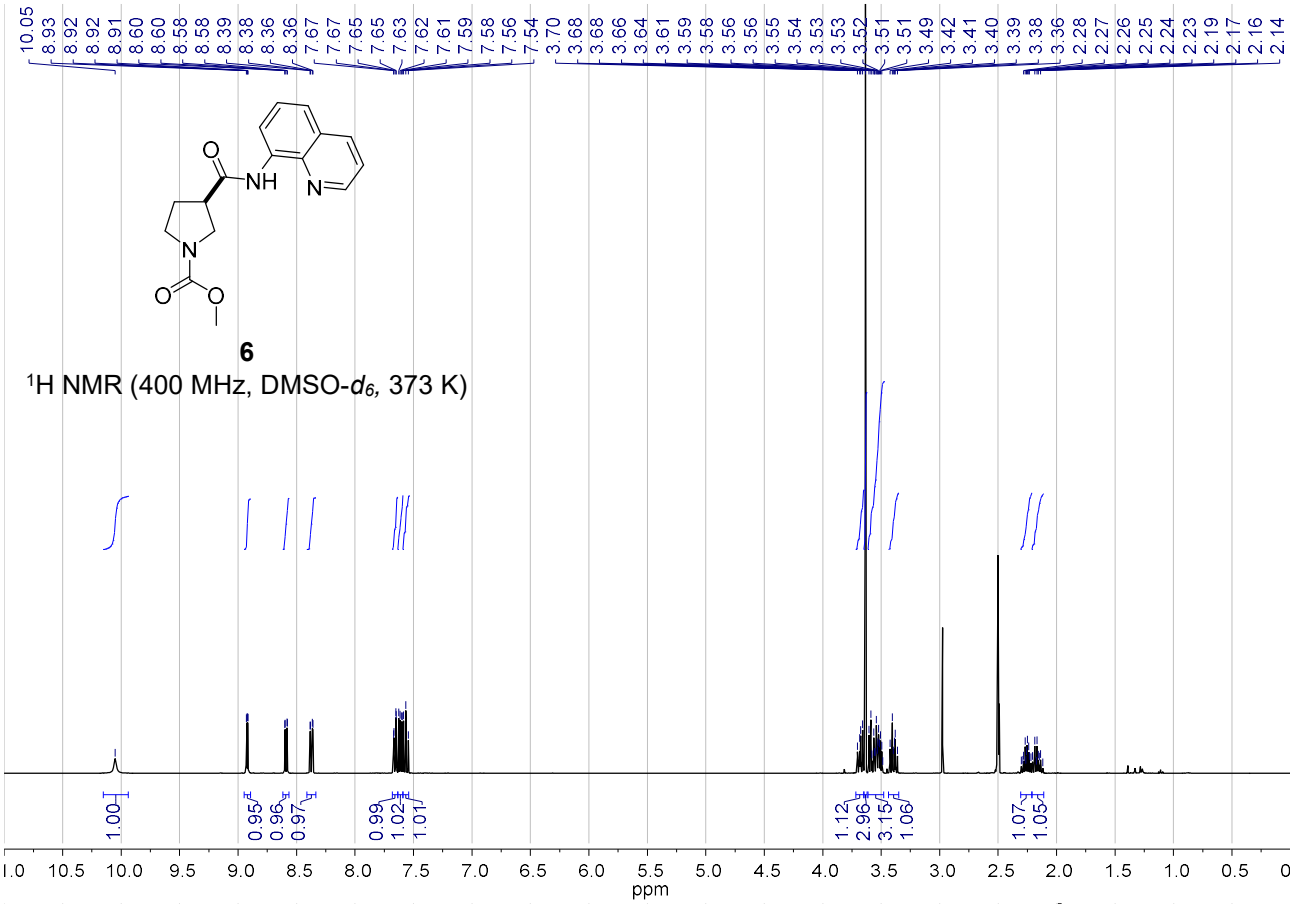


1

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

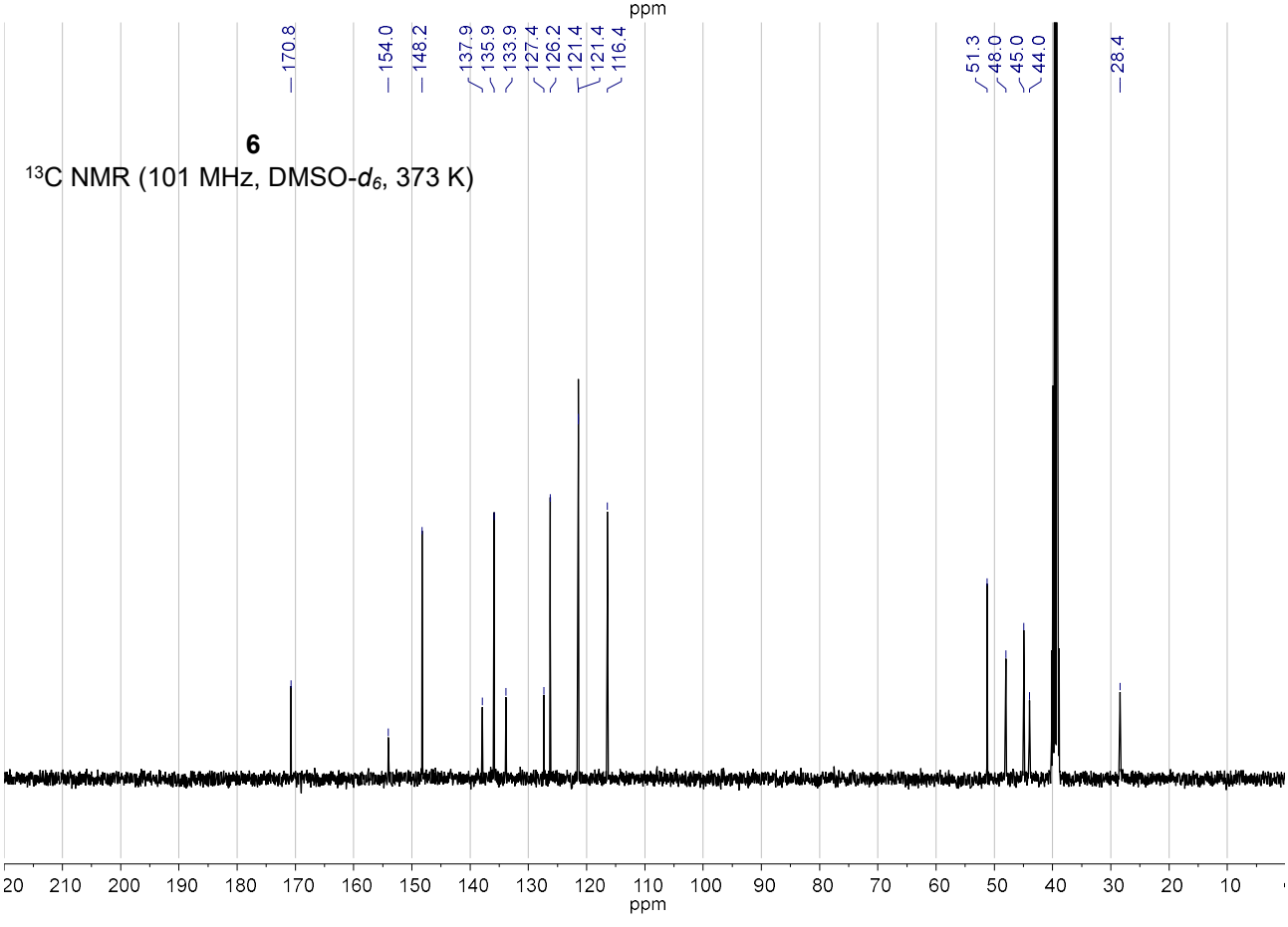

10.06 8.92 8.91 8.91 8.90 8.60 8.60 8.58 8.58 8.39 8.38 8.36 8.36 7.67 7.67 7.65 7.65 7.62 7.61 7.60 7.59 7.59 7.57 7.55 7.39 7.38 7.37 7.37 7.36 7.36 7.35 7.34 7.32 7.32 7.30 5.12 3.75 3.73 3.73 3.71 3.65 3.64 3.63 3.61 3.58 3.56 3.54 3.52 3.47 3.45 3.43 3.43 2.29 2.27 2.25 2.21 2.19
O
NH
N
N
Cbz
5
1H NMR (400 MHz, DMSO-d6, 373 K)
1.00 0.98 1.00 0.99 1.00 1.03 1.05 3.75 0.84 2.08 1.09 1.18 2.03 1.06 1.08 1.05
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0
ppm


170.8 153.5 148.3 137.9 136.7 135.9 133.9 127.8 127.4 127.1 126.8 126.3 121.5 121.4 116.5 65.4 48.1 45.1 44.0 28.4
5
13C NMR (101 MHz, DMSO-d6, 373 K)
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
ppm



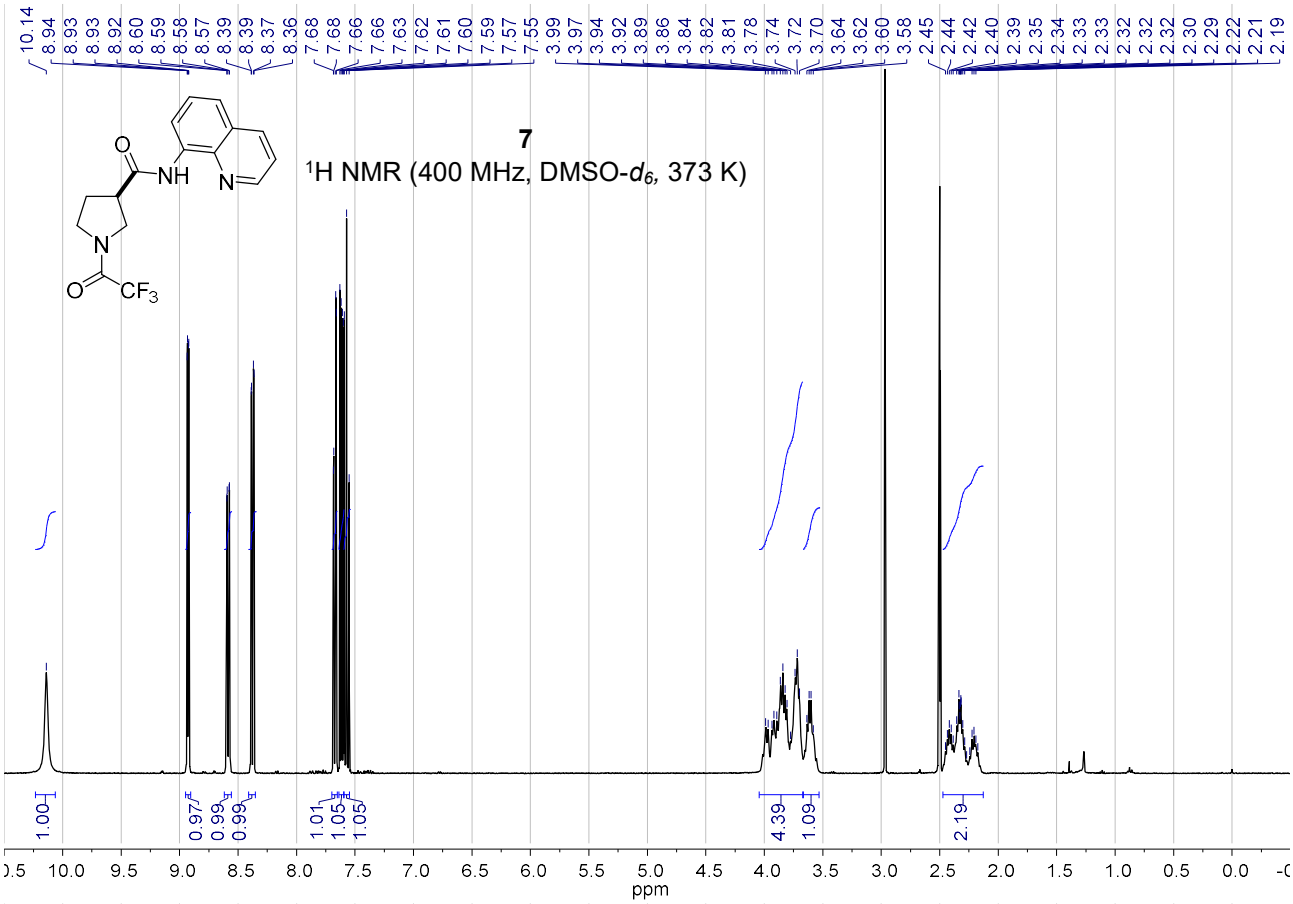
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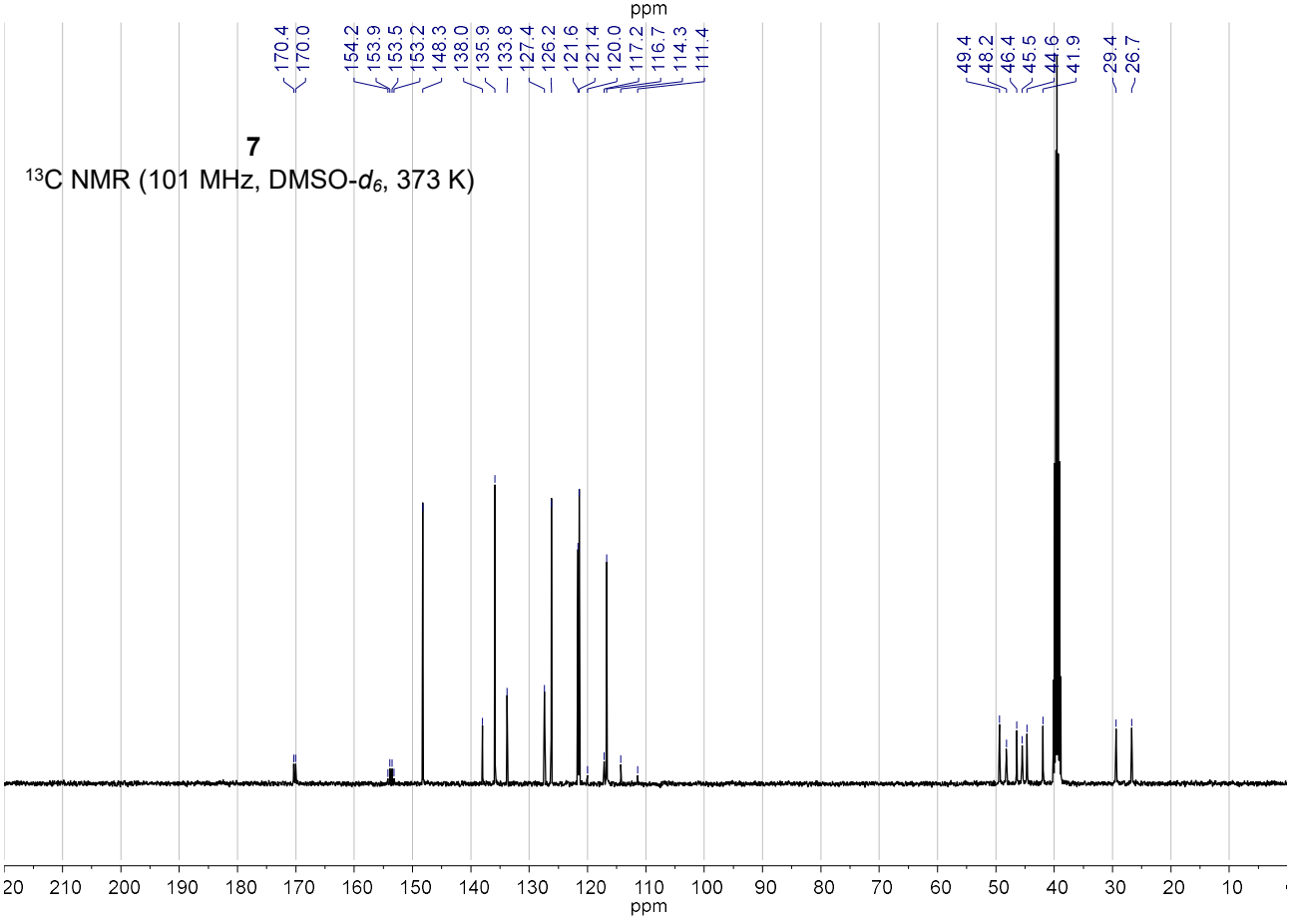
^{1}H NMR (400 MHz, DMSO-d_6, 373 K)



6

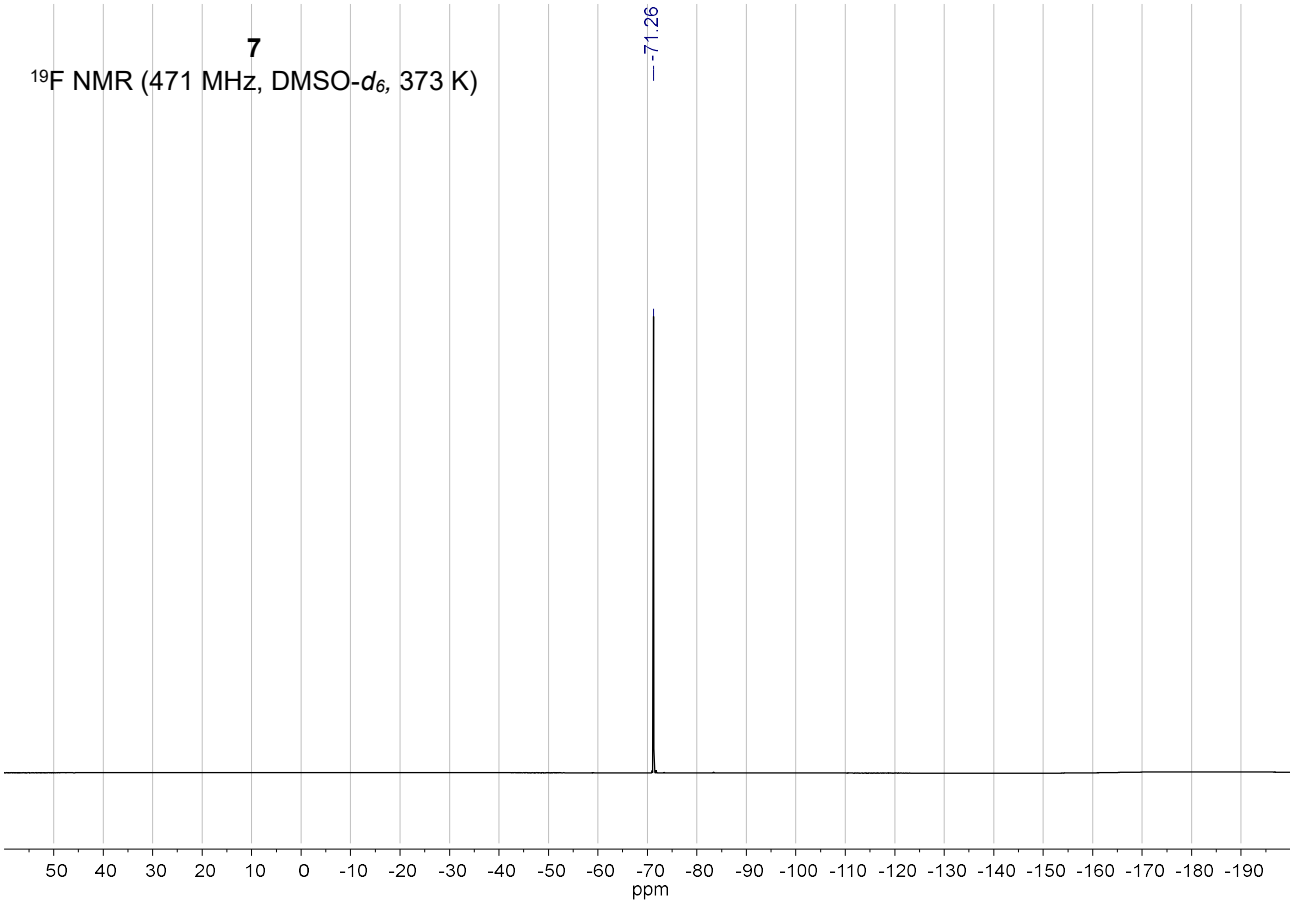
^{13}C NMR (101 MHz, DMSO-d_6, 373 K)

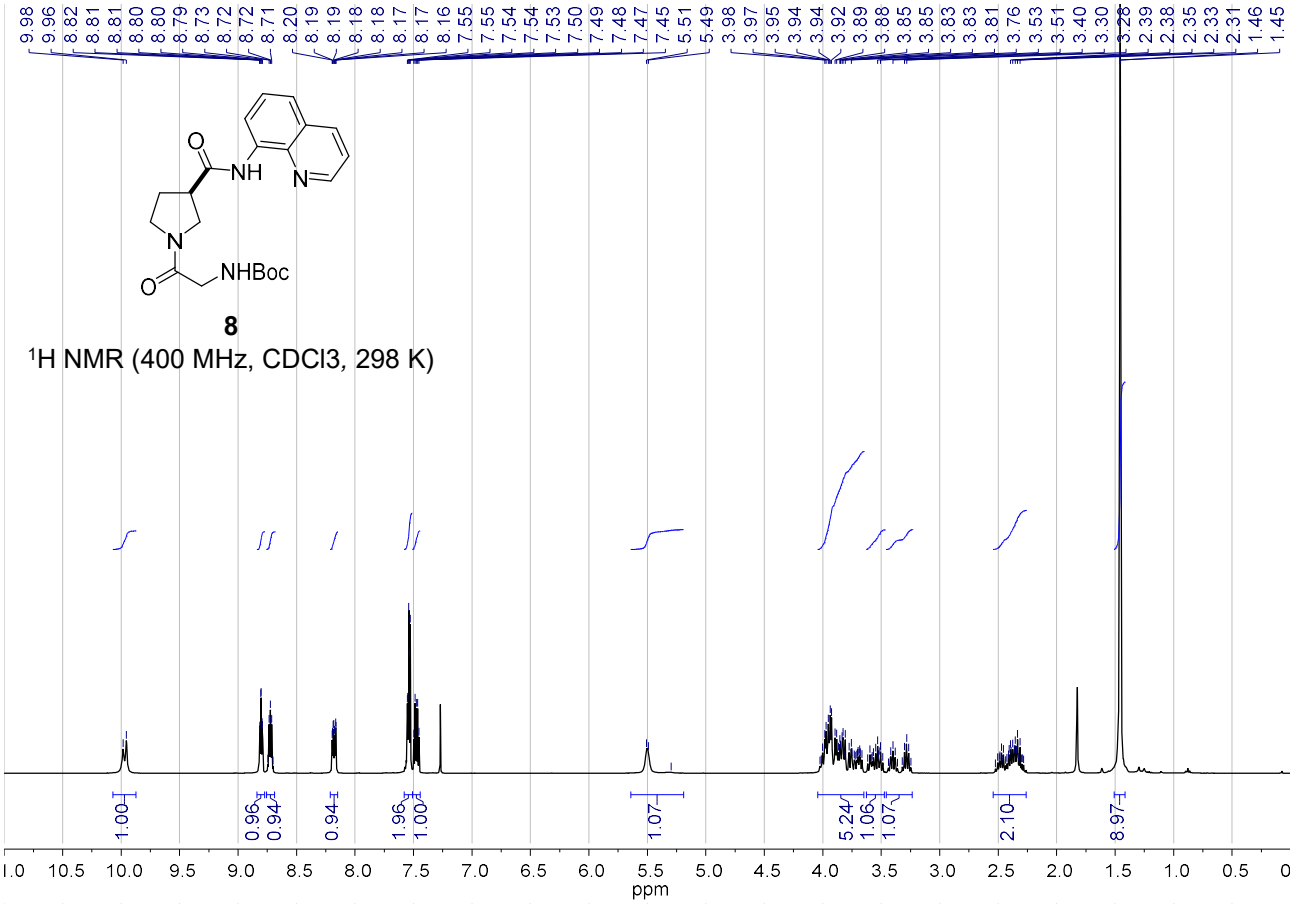

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2.34
2.33
2.33
2.32
2.32
2.32
2.30
2.29
2.22
2.21
2.19
7
^{1}H NMR (400 MHz, DMSO-d_6, 373 K)
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NH
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N
O
CF_3
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0.97
0.99
0.99
1.01
1.05
1.05
4.39
1.09
2.19
ppm


170.4
170.0
154.2
153.9
153.5
153.2
148.3
138.0
135.9
133.8
127.4
126.2
121.6
121.4
120.0
117.2
116.7
114.3
111.4
49.4
48.2
46.4
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44.6
41.9
29.4
26.7
7
^{13}C NMR (101 MHz, DMSO-d_6, 373 K)
ppm

7

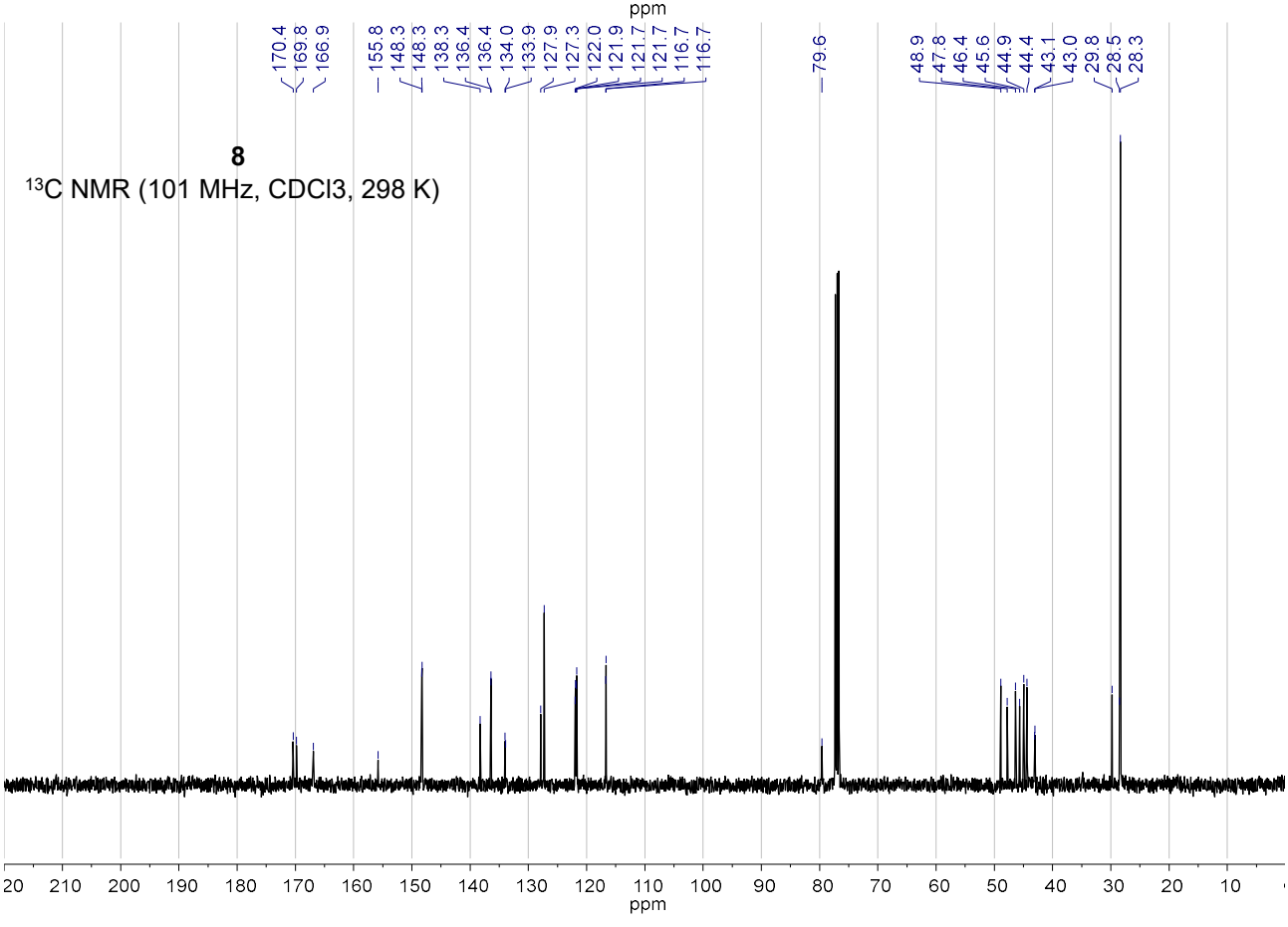
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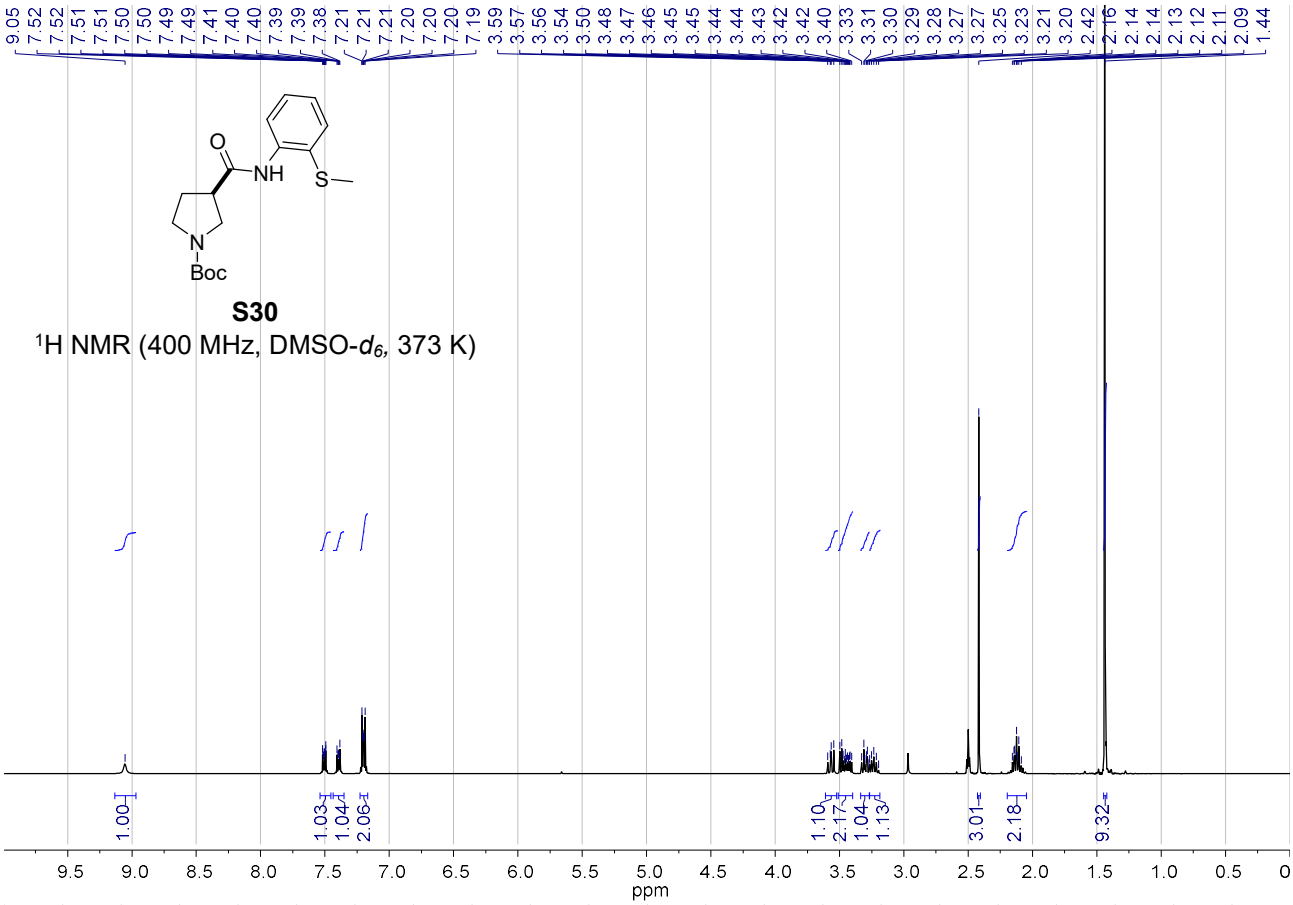
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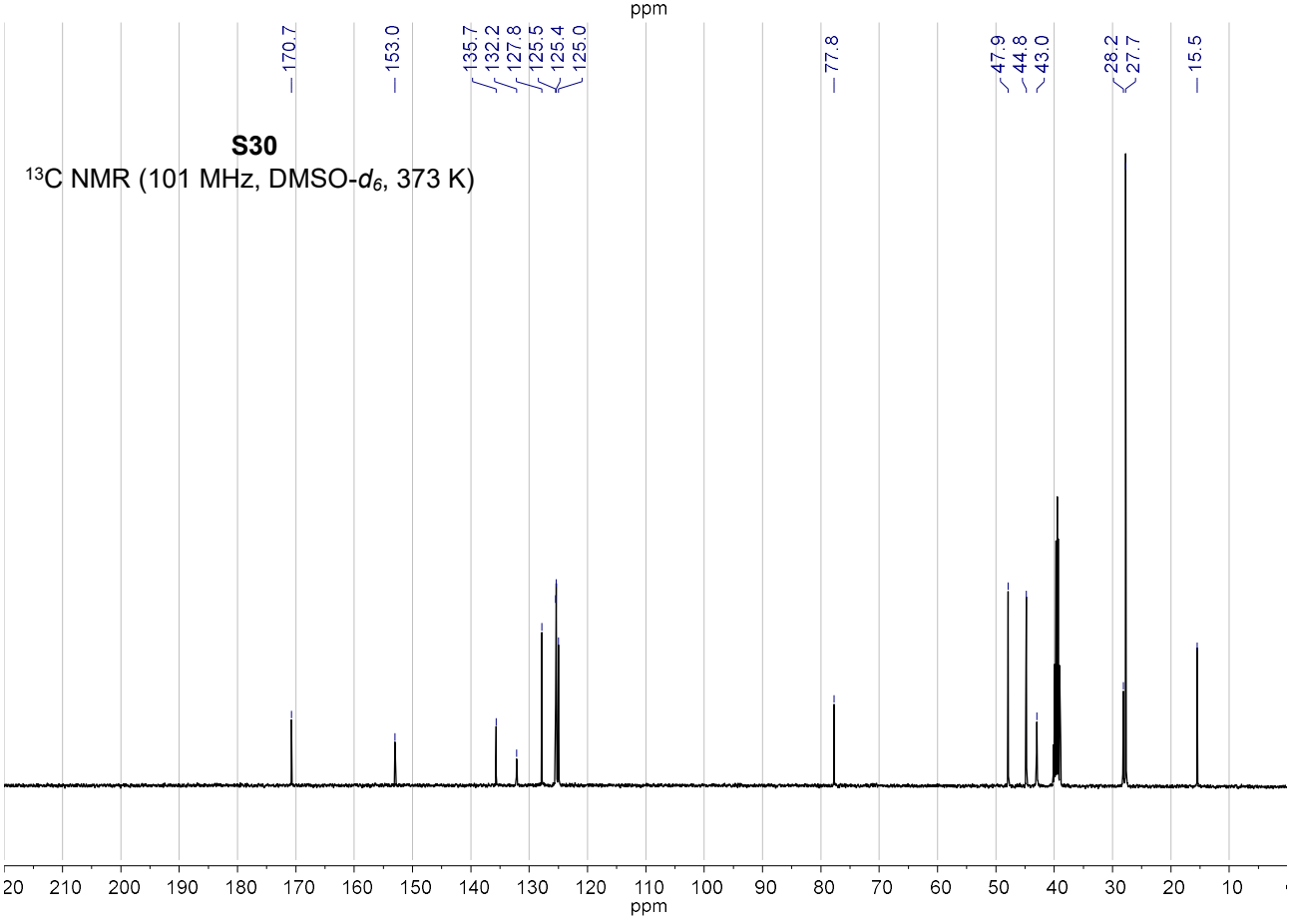
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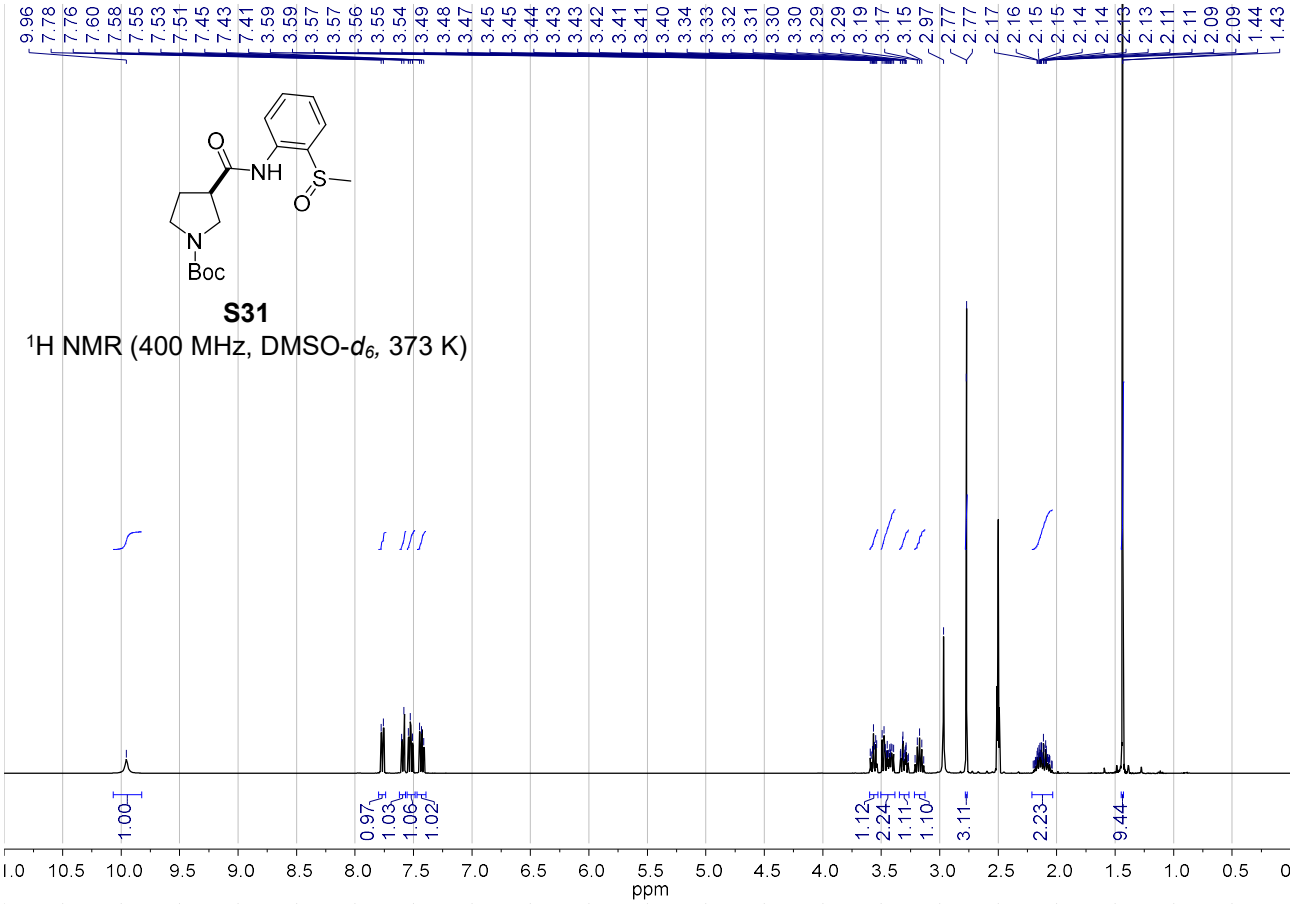
S30

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



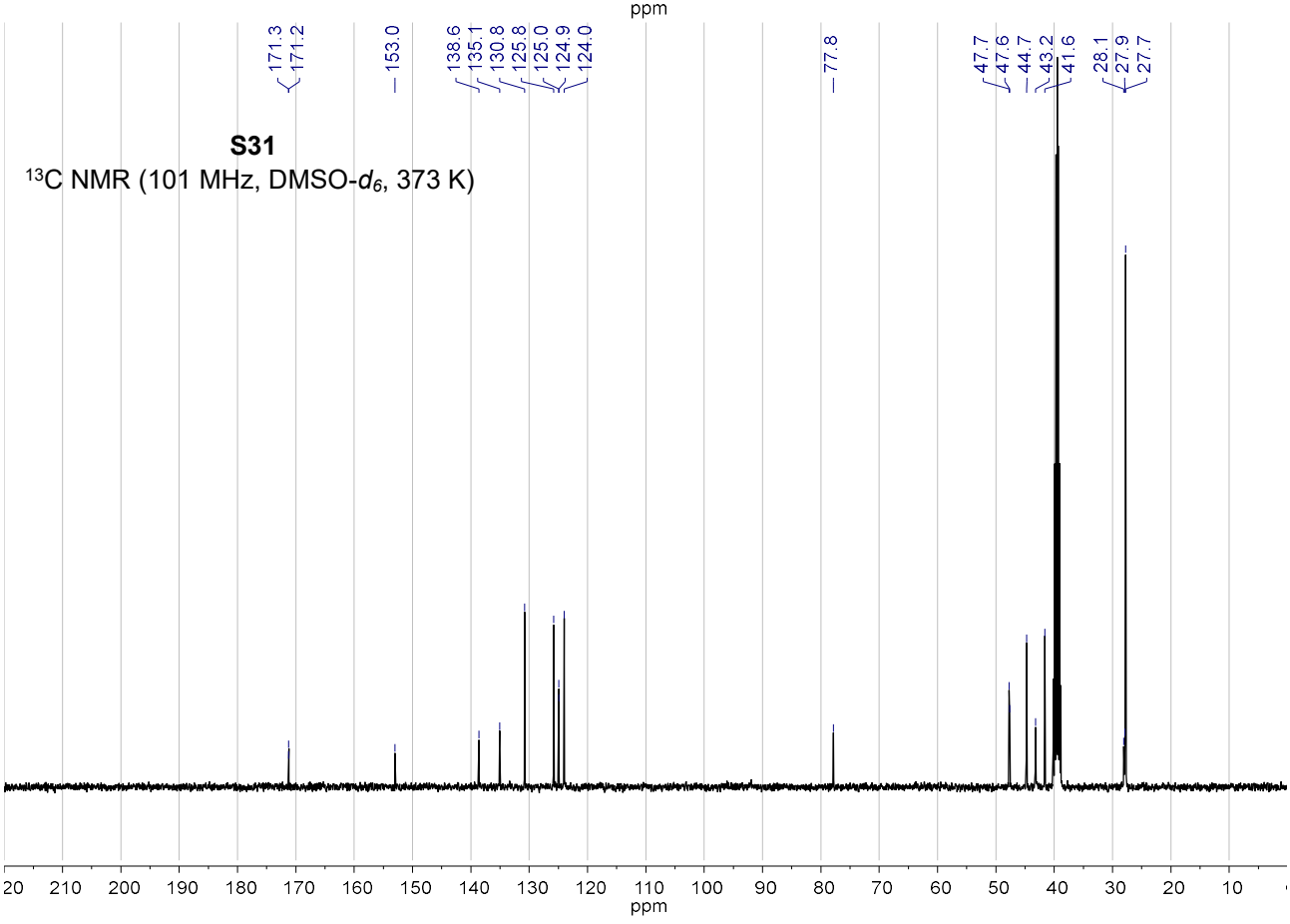
S30

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



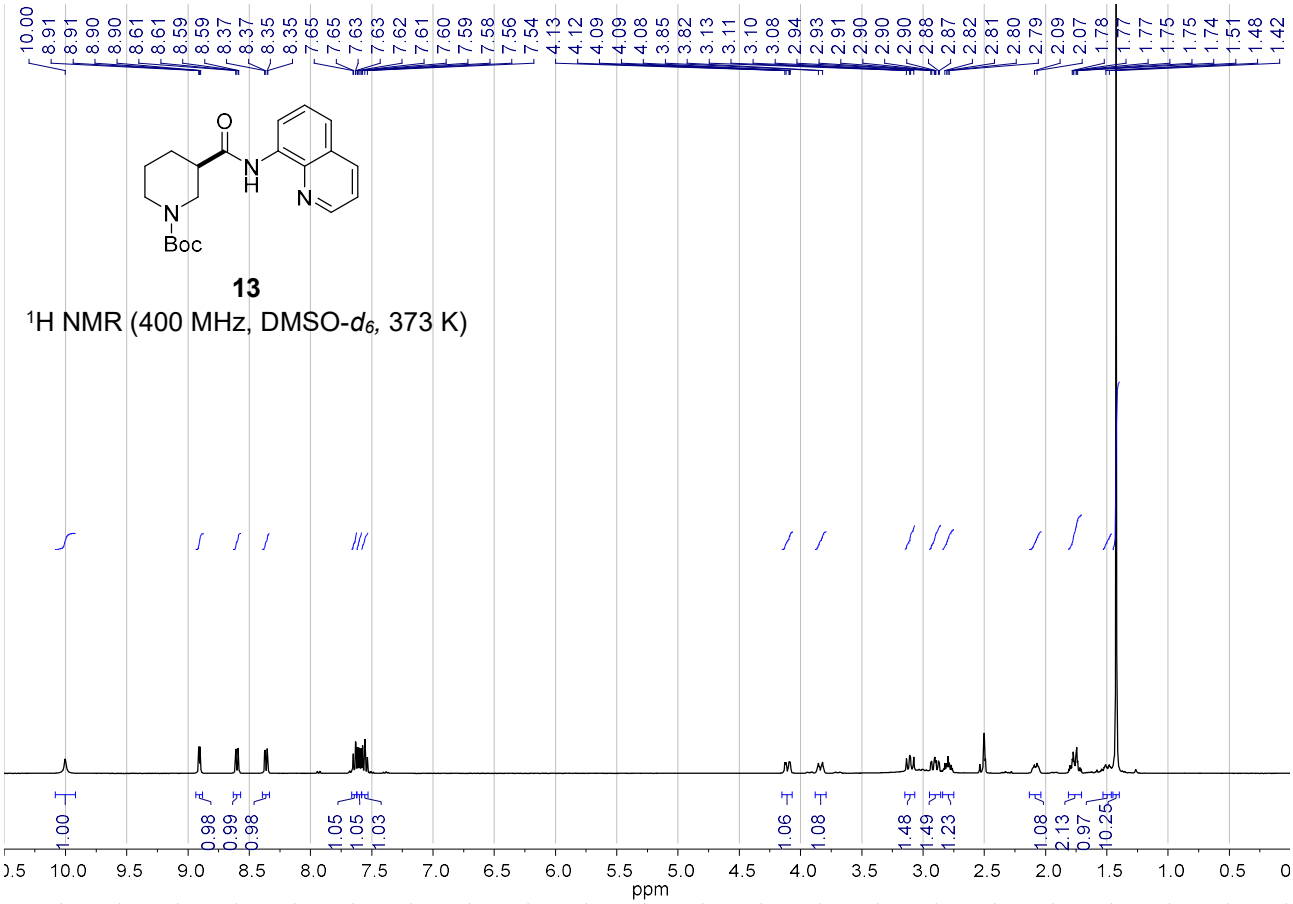
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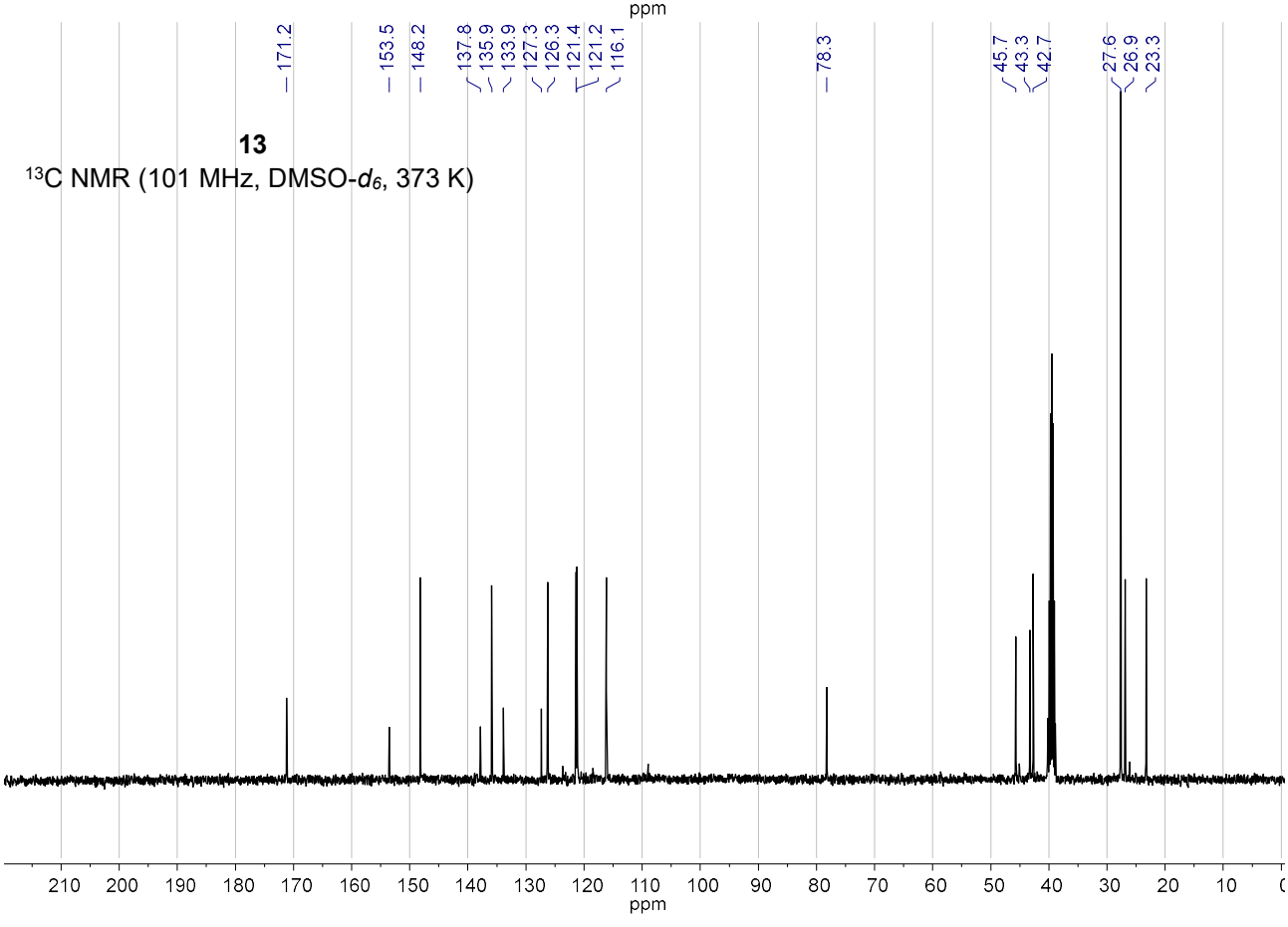
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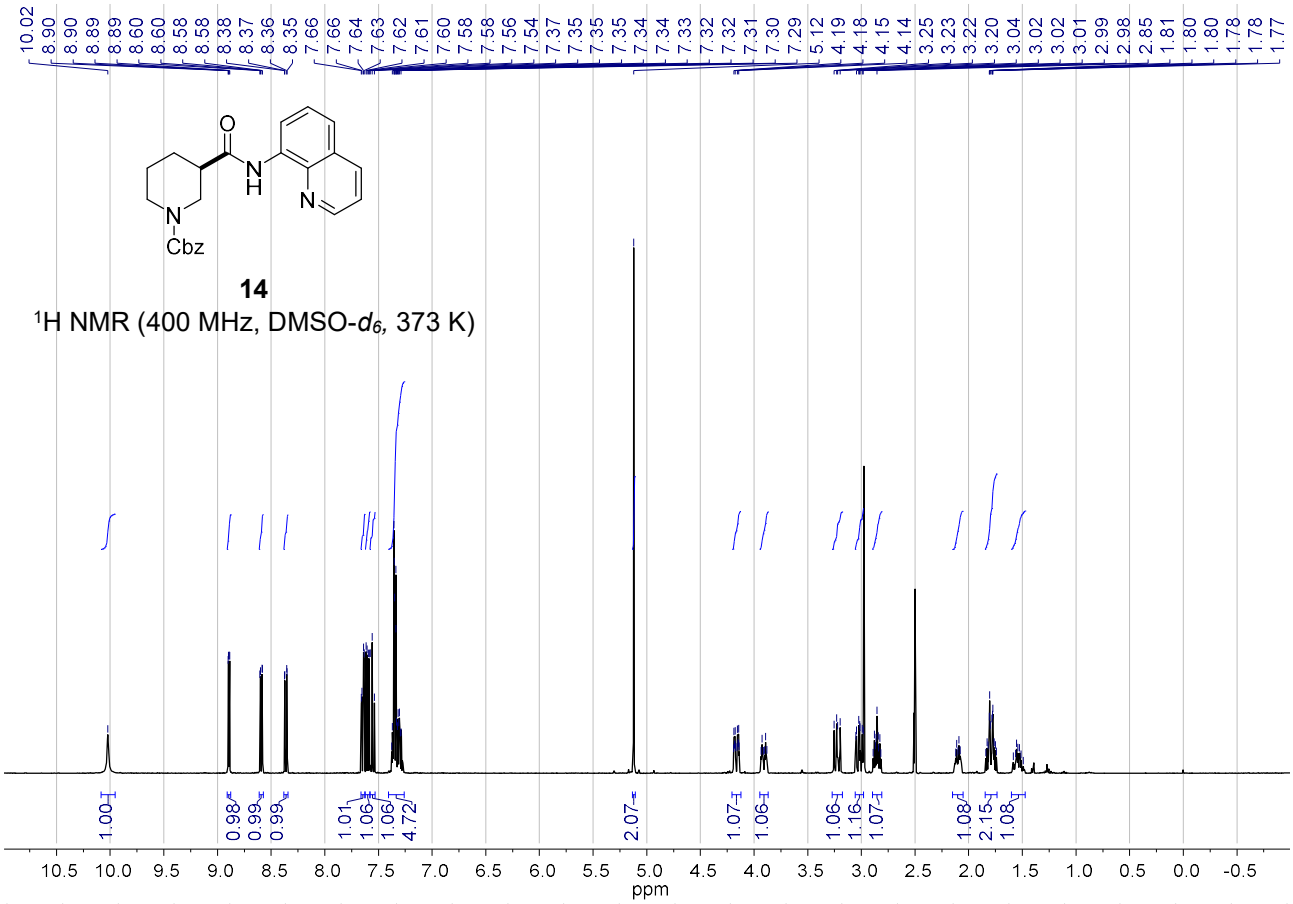
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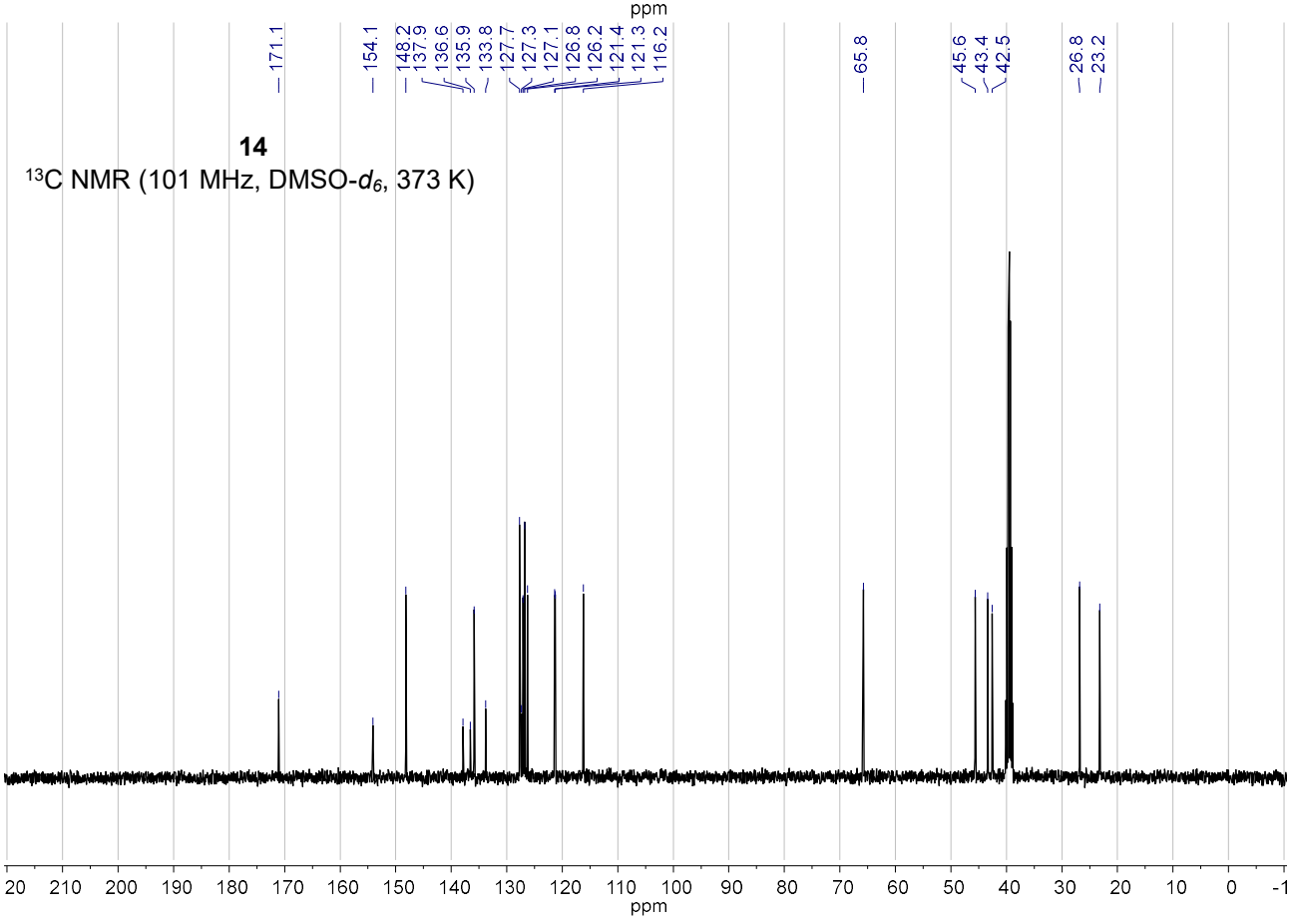
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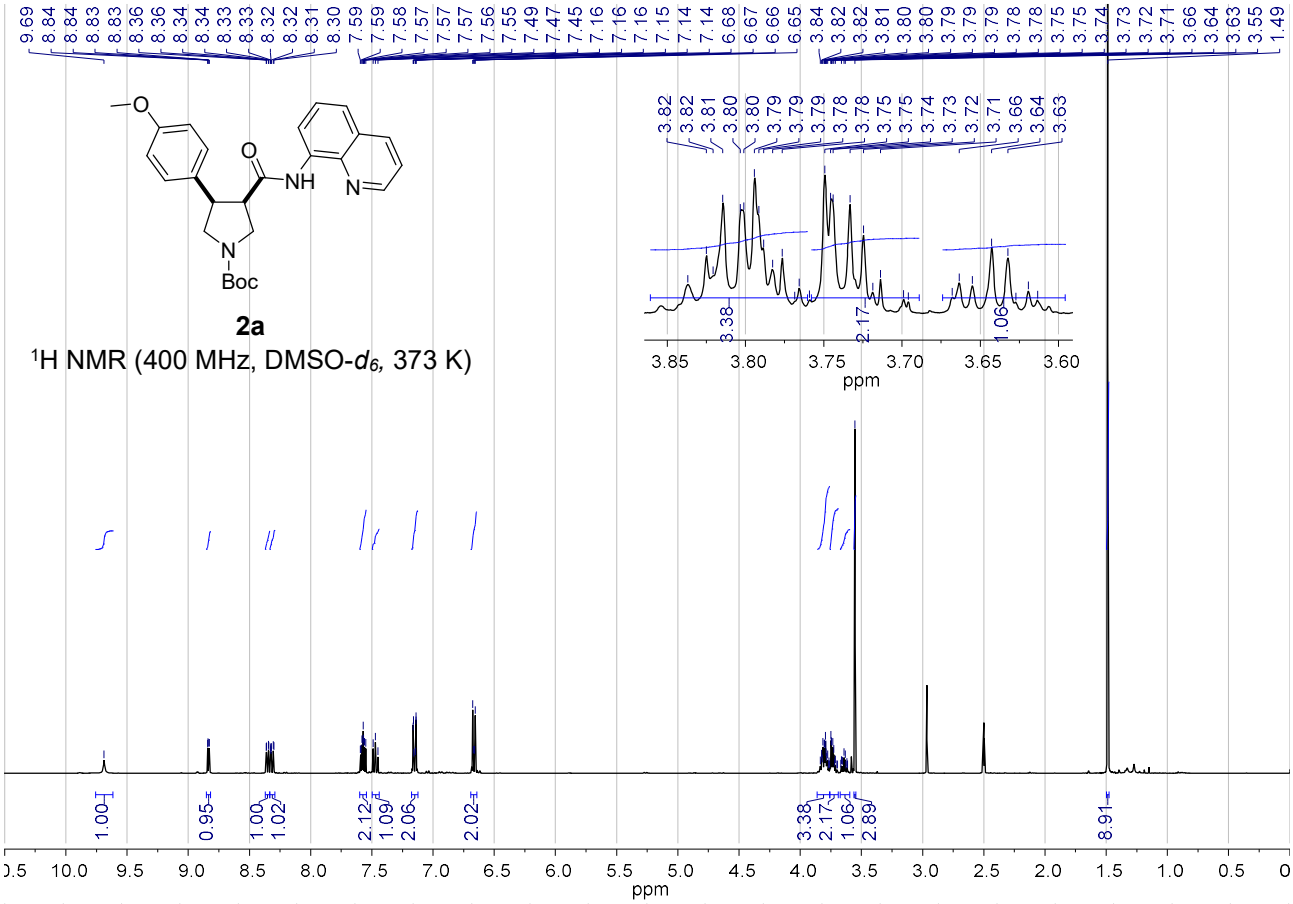
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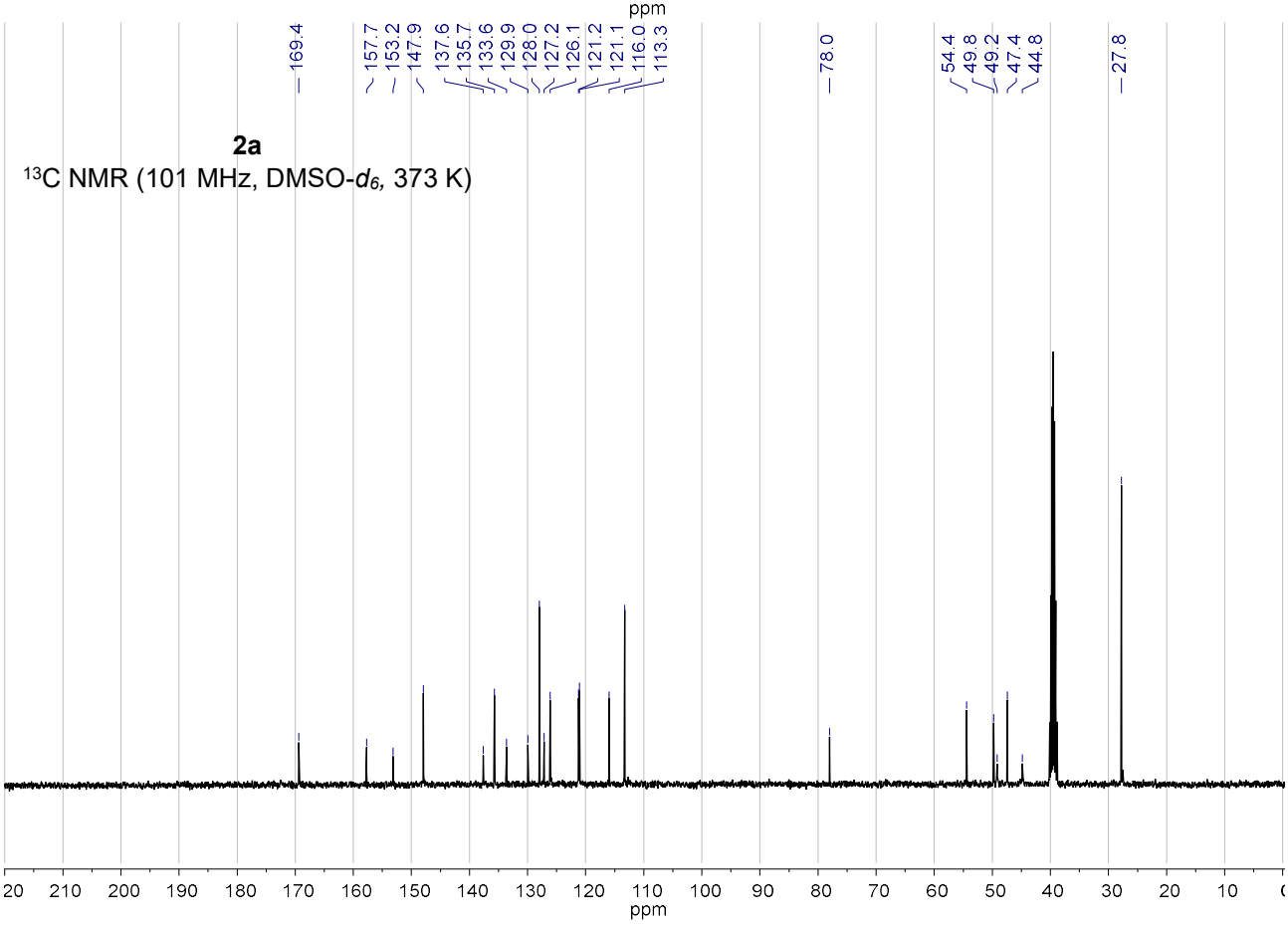
^{1}H NMR (400 MHz, DMSO-d_6, 373 K)

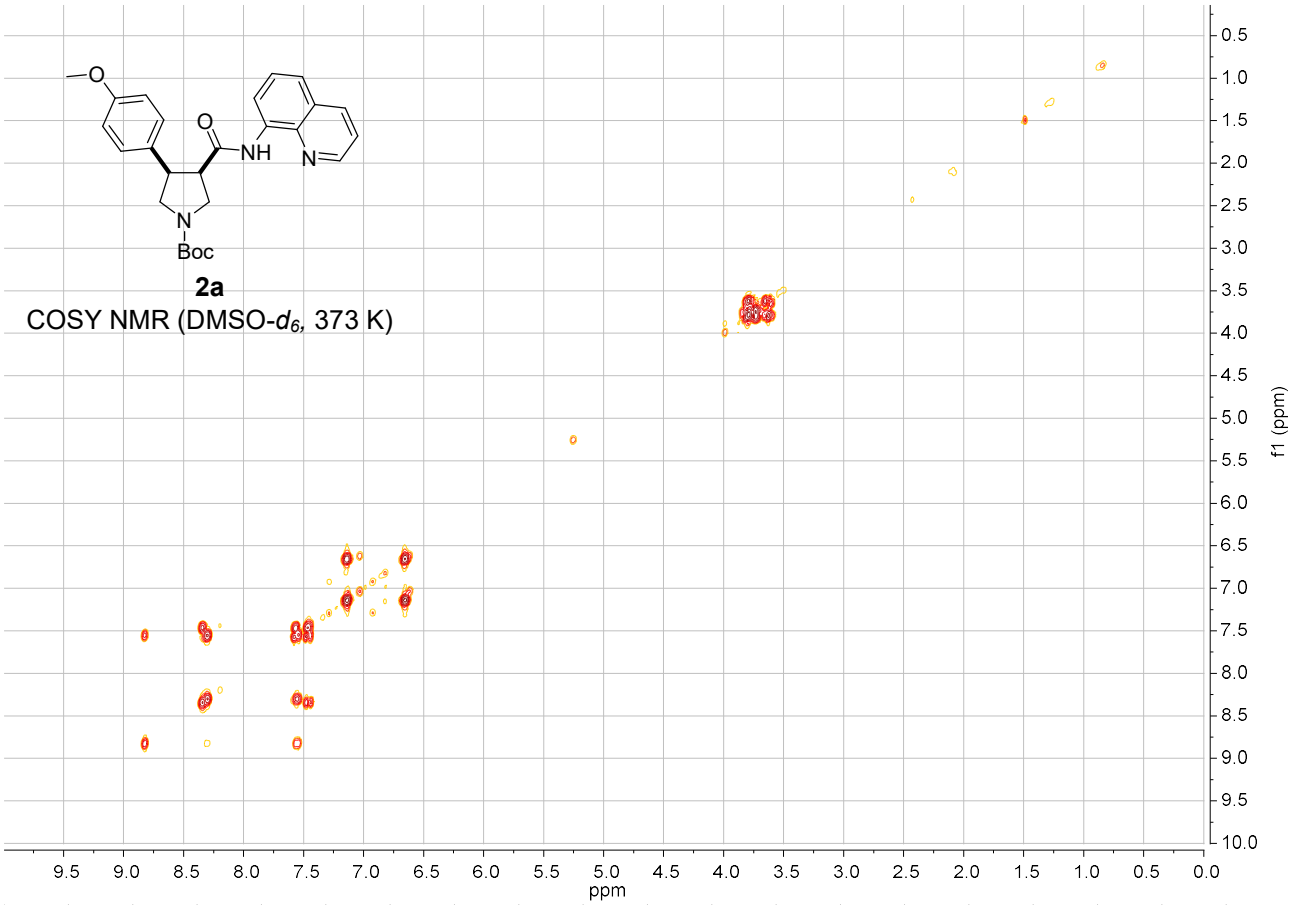


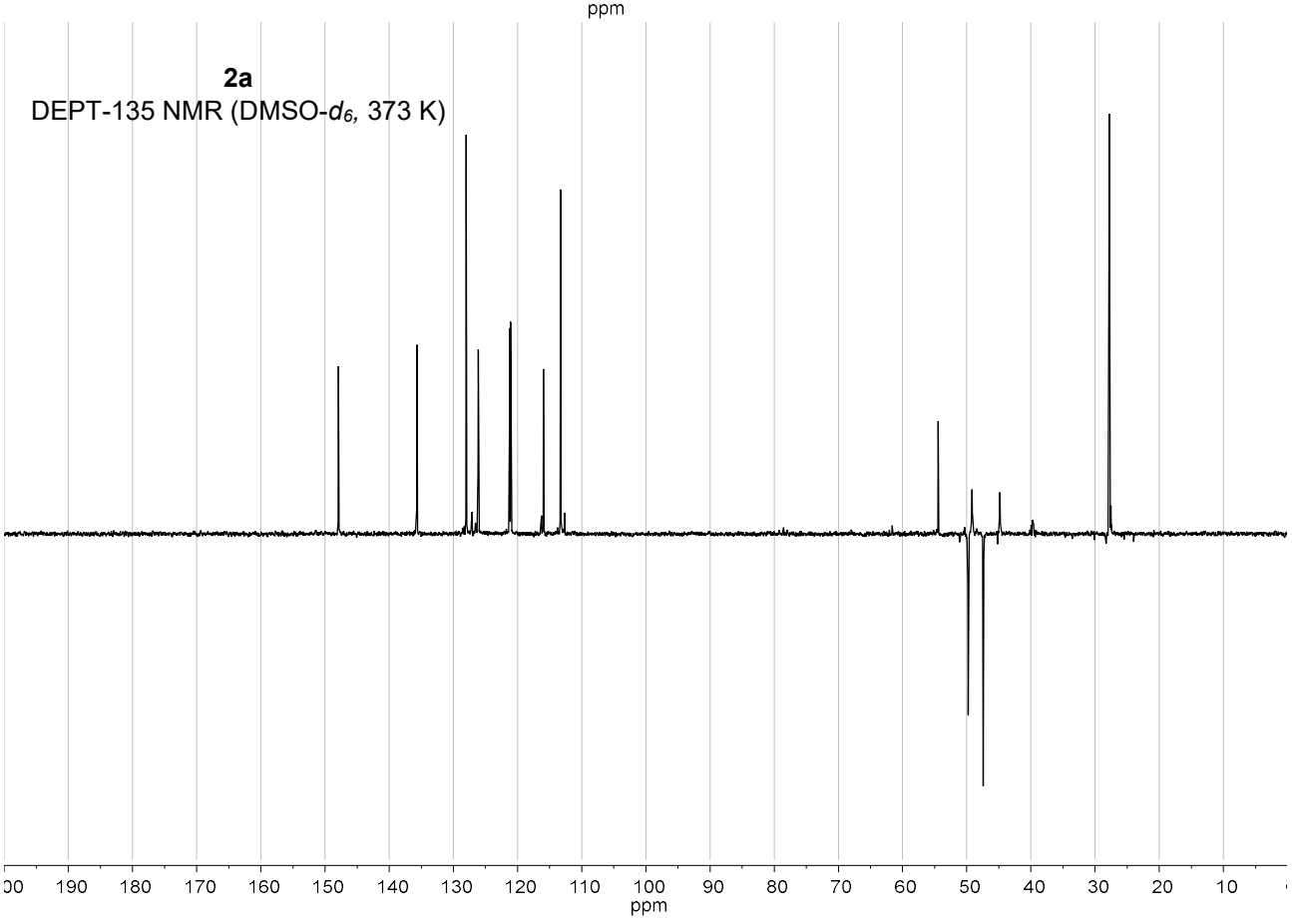
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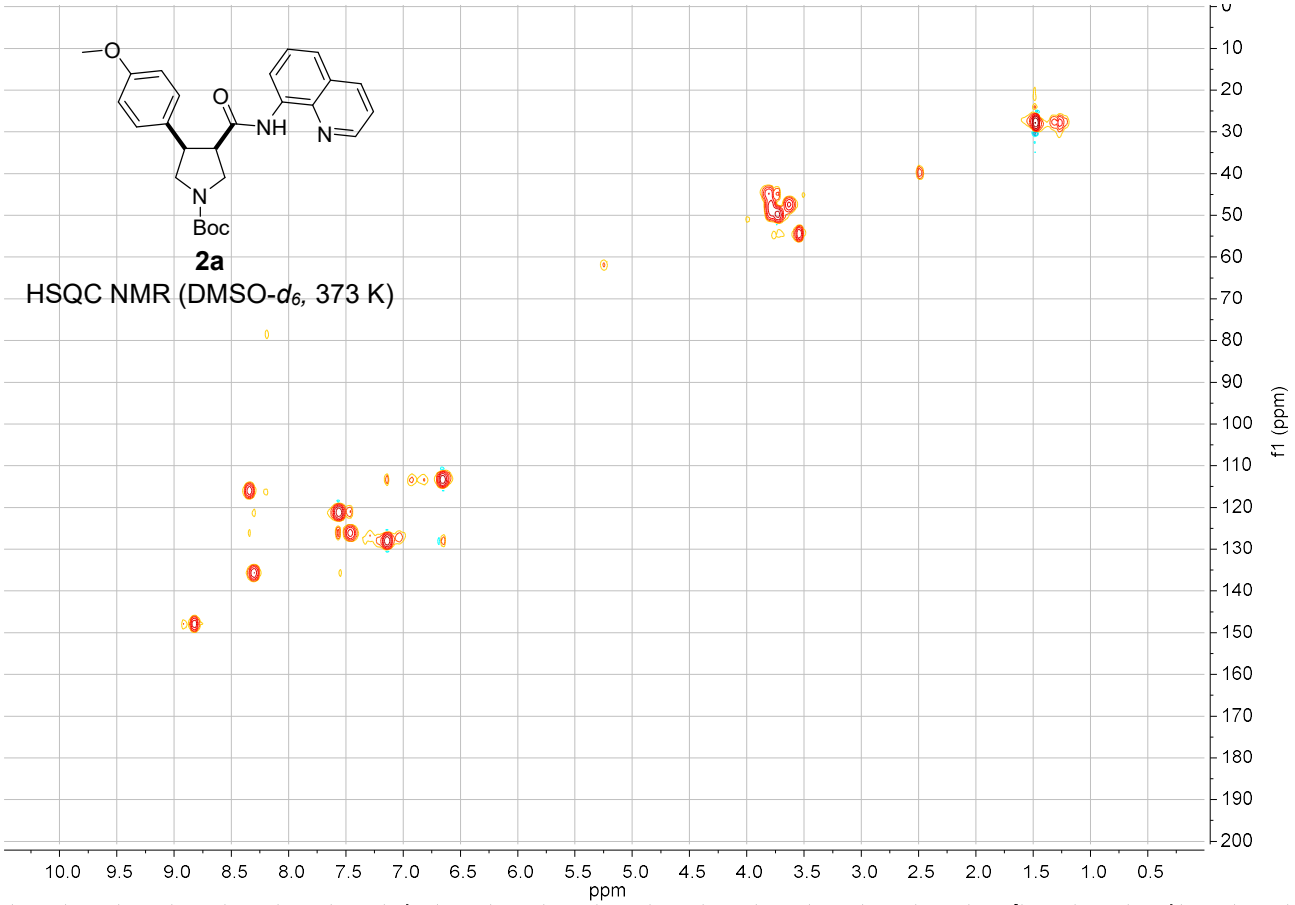
^{13}C NMR (101 MHz, DMSO-d_6, 373 K)

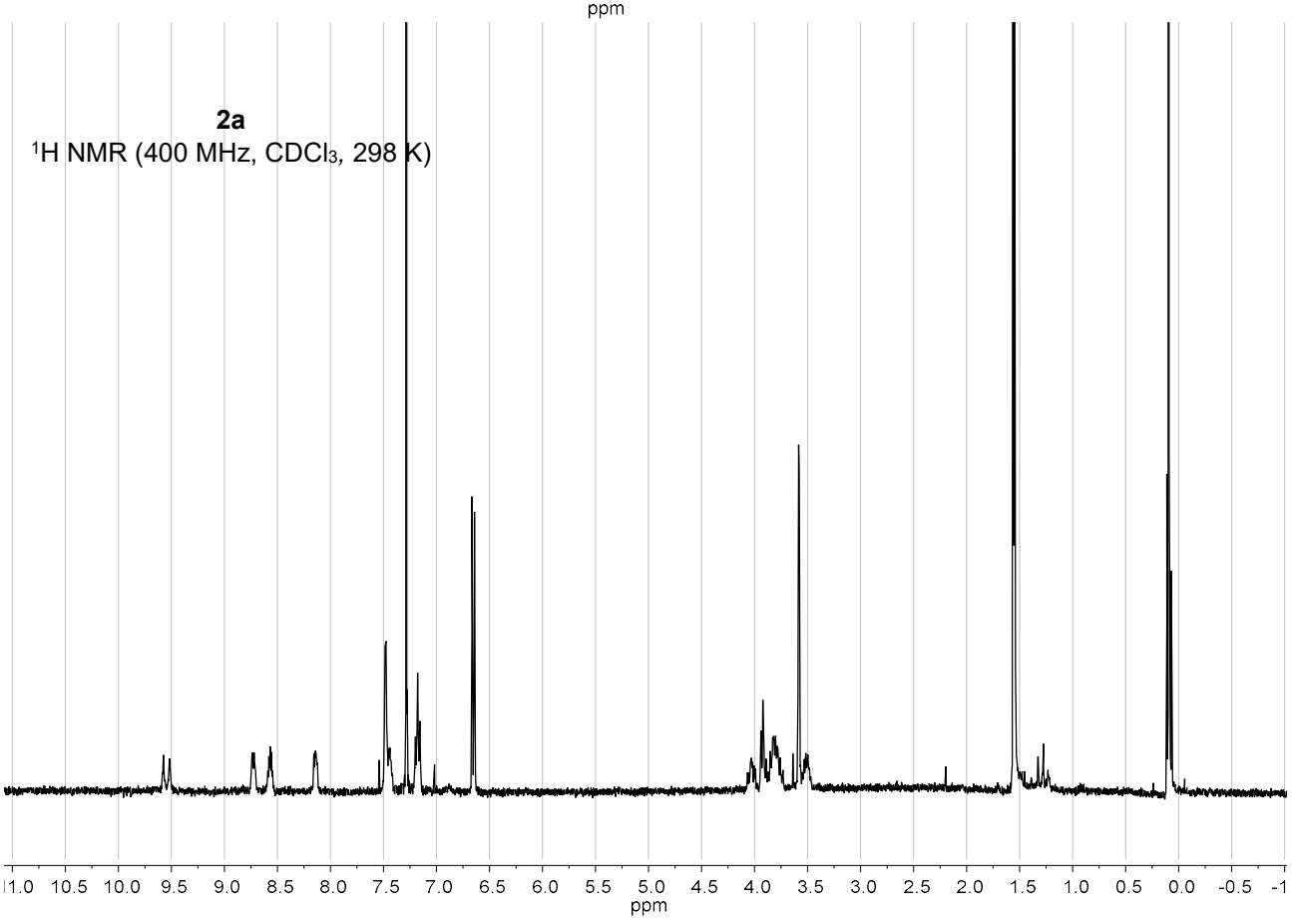

O
O
NH
N
N
Boc
2a
1H NMR (400 MHz, DMSO-d6, 373 K)
ppm

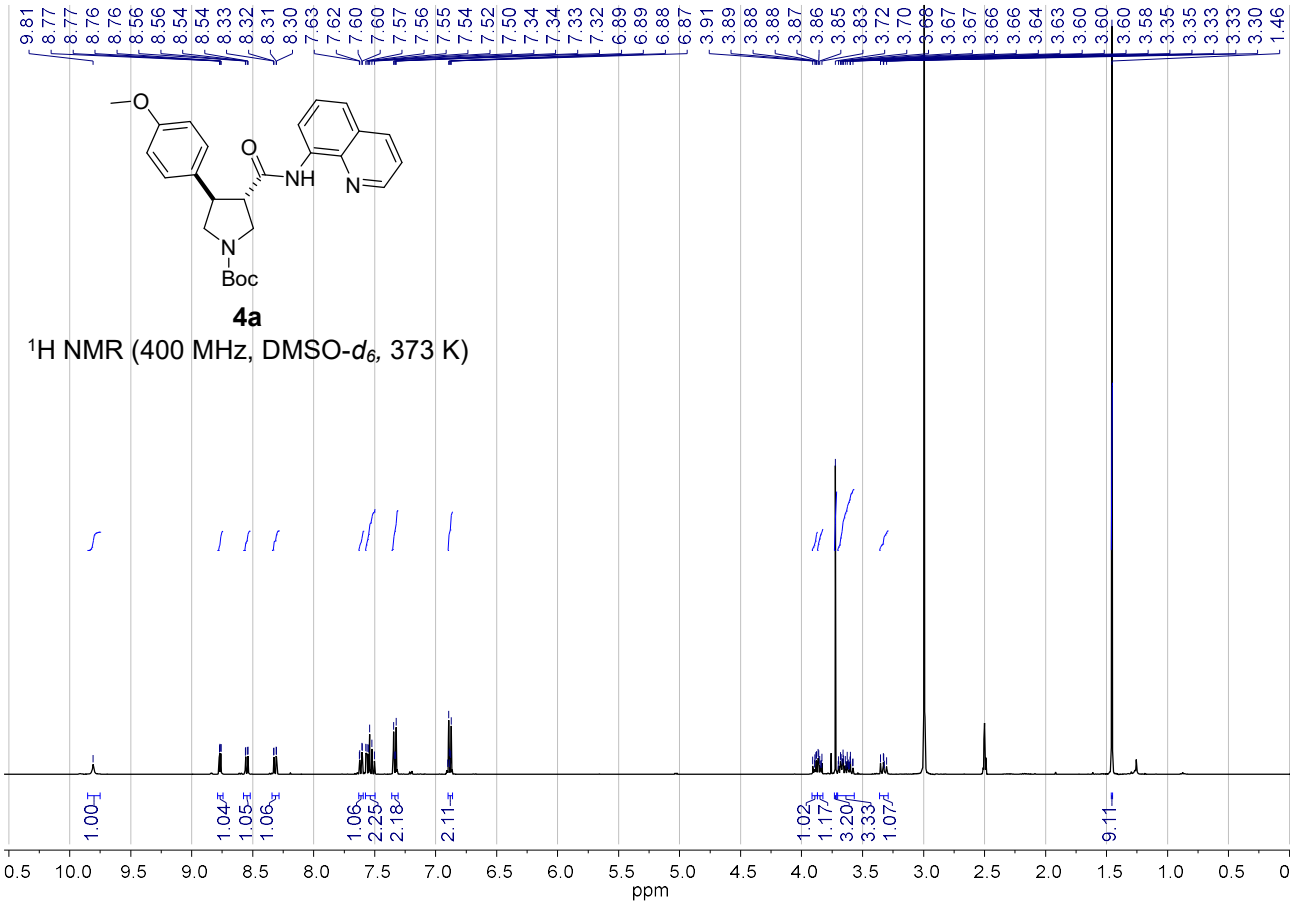

2a
13C NMR (101 MHz, DMSO-d6, 373 K)
ppm

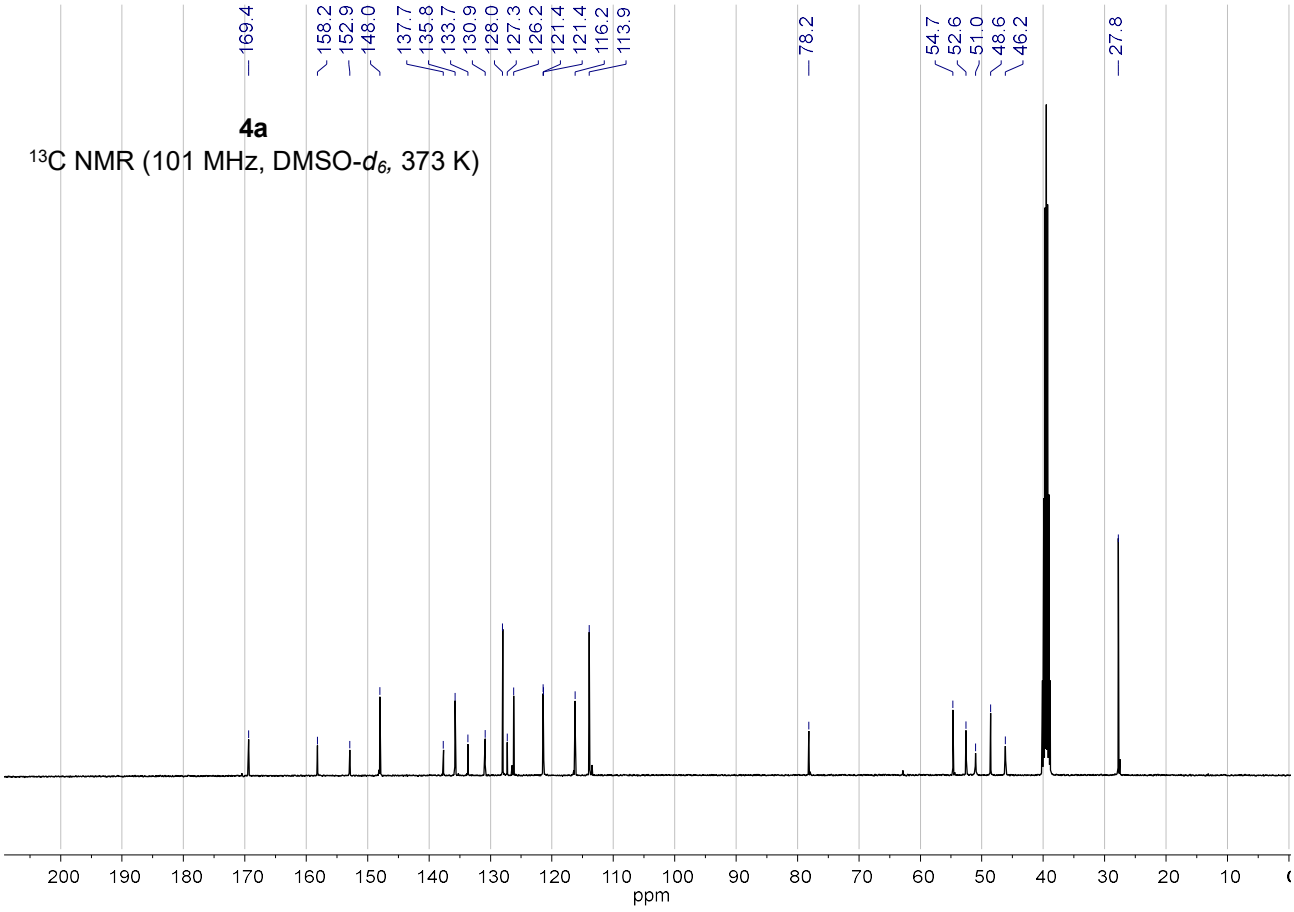

O
O
NH
N
N
Boc
2a
COSY NMR (DMSO-d6, 373 K)
f1 (ppm)
ppm

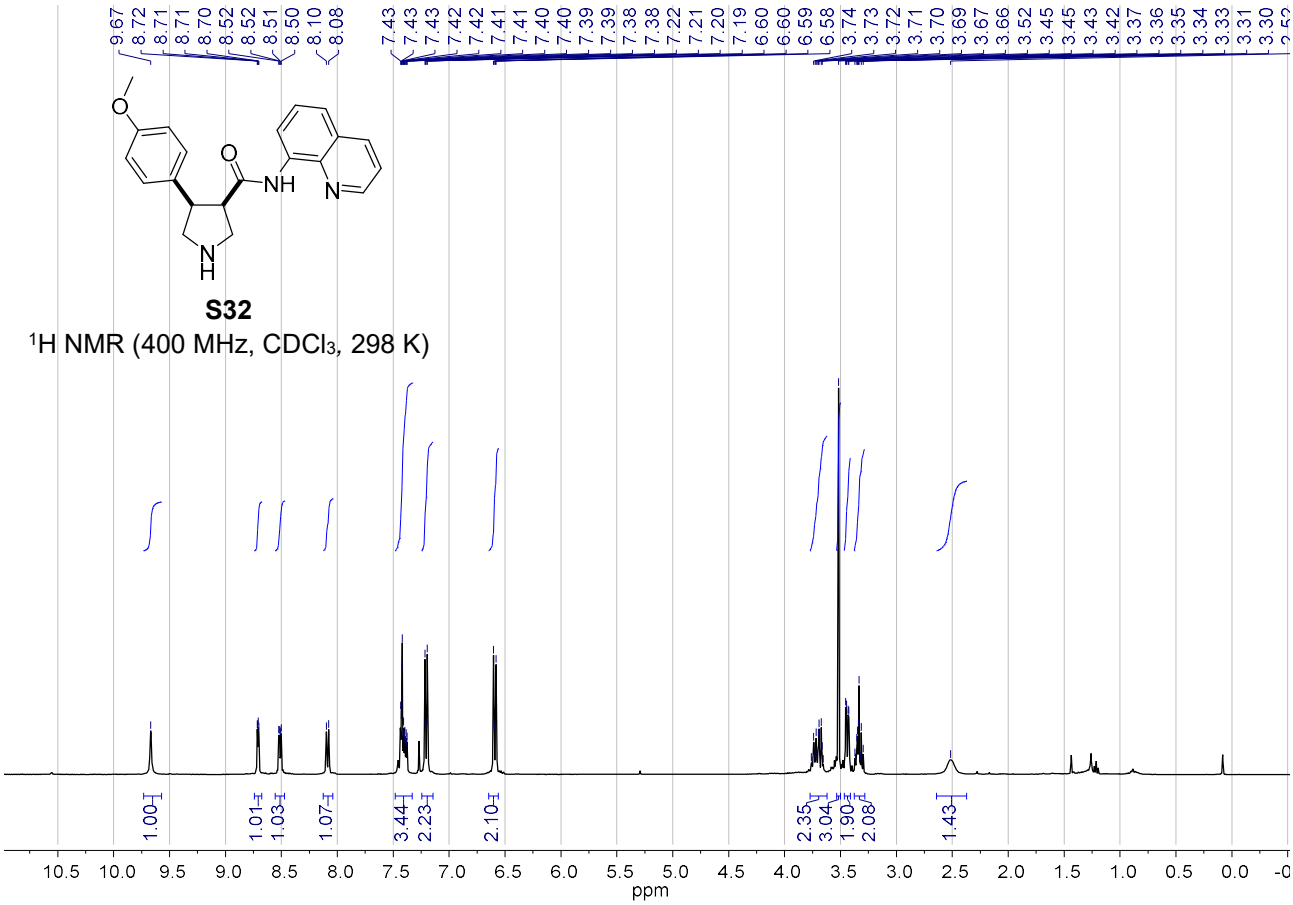

2a
DEPT-135 NMR (DMSO-d6, 373 K)
ppm

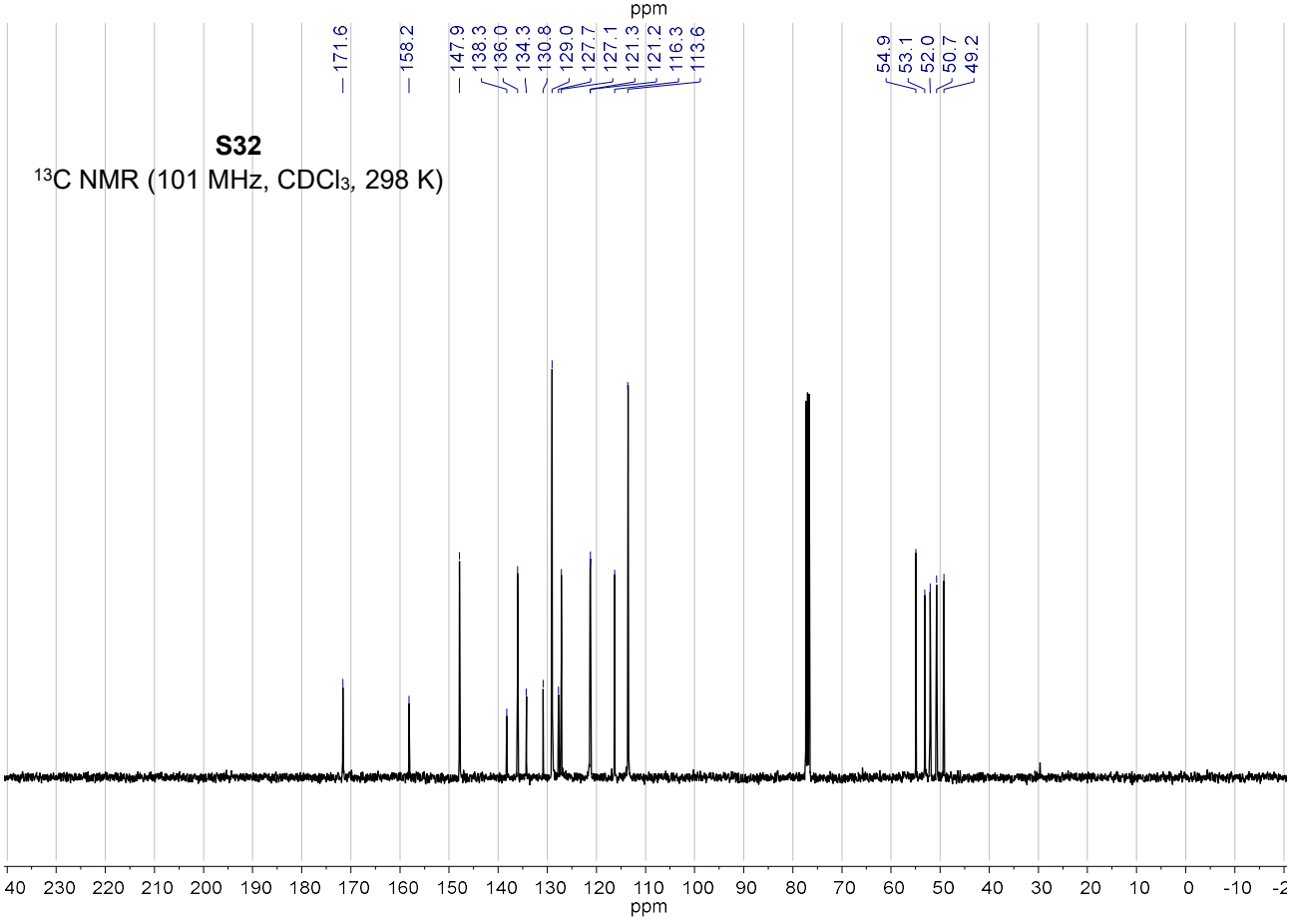

O
O
NH
N
N
Boc
2a
HSQC NMR (DMSO-d_6, 373 K)
f1 (ppm)
ppm

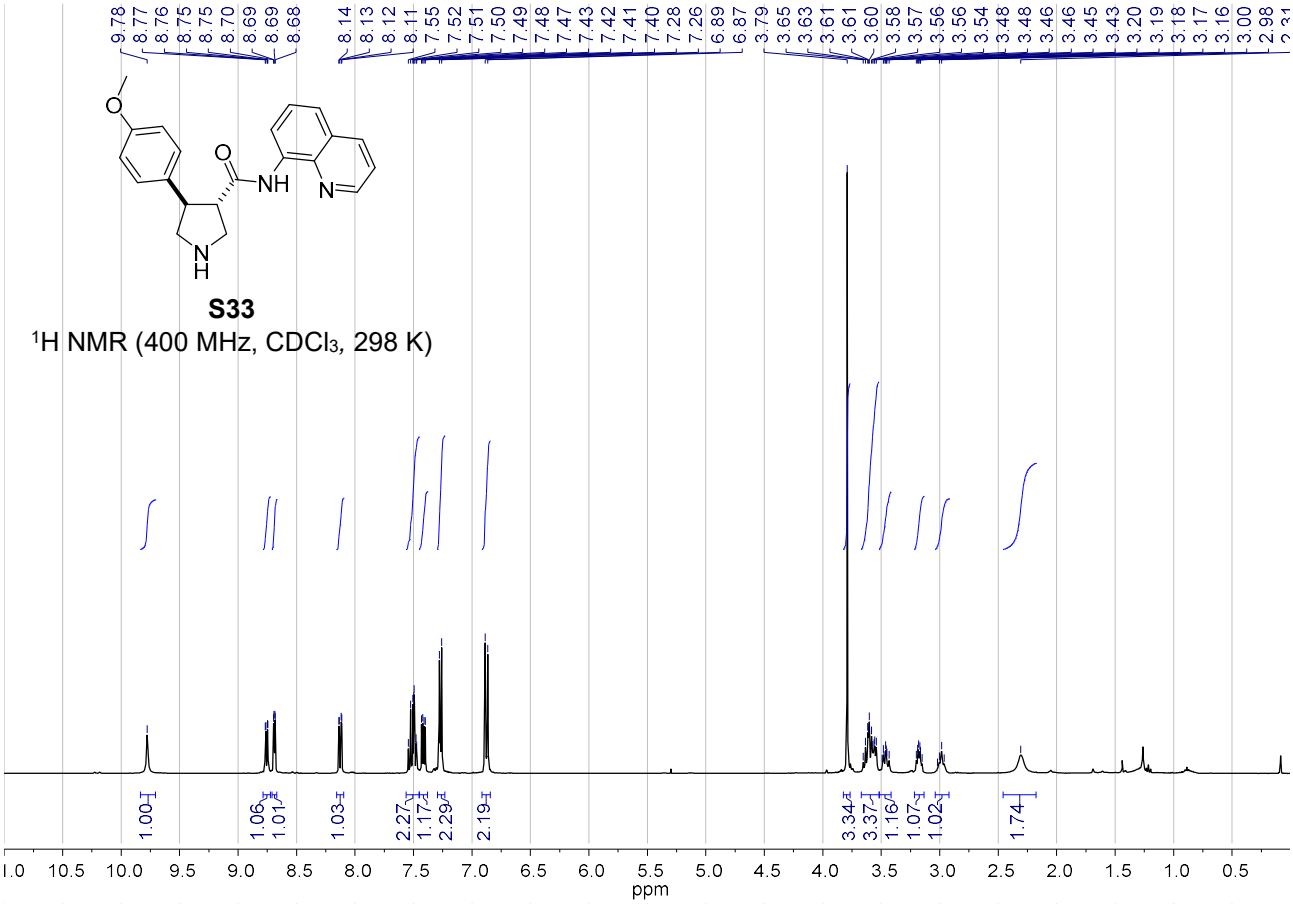

2a
^{1}H NMR (400 MHz, $CDCl_3$, 298 K)
ppm


9.81 8.77 8.77 8.76 8.76 8.56 8.56 8.54 8.54 8.33 8.32 8.31 8.30 7.63 7.62 7.60 7.60 7.57 7.56 7.55 7.54 7.52 7.50 7.34 7.34 7.33 7.32 6.89 6.88 6.87 3.91 3.89 3.88 3.87 3.86 3.85 3.83 3.72 3.70 3.66 3.67 3.67 3.66 3.66 3.64 3.63 3.60 3.60 3.60 3.58 3.35 3.35 3.33 3.33 3.30 1.46
O
O
NH
N
N
Boc
4a
1H NMR (400 MHz, DMSO-d6, 373 K)
1.00 1.04 1.05 1.06 1.06 2.25 2.18 2.11 1.02 1.17 3.20 3.33 1.07 9.11
0.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0
ppm


169.4
158.2 152.9 148.0 137.7 135.8 133.7 130.9 128.0 127.3 126.2 121.4 121.4 116.2 113.9
78.2
54.7 52.6 51.0 48.6 46.2
27.8
4a
13C NMR (101 MHz, DMSO-d6, 373 K)
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
ppm

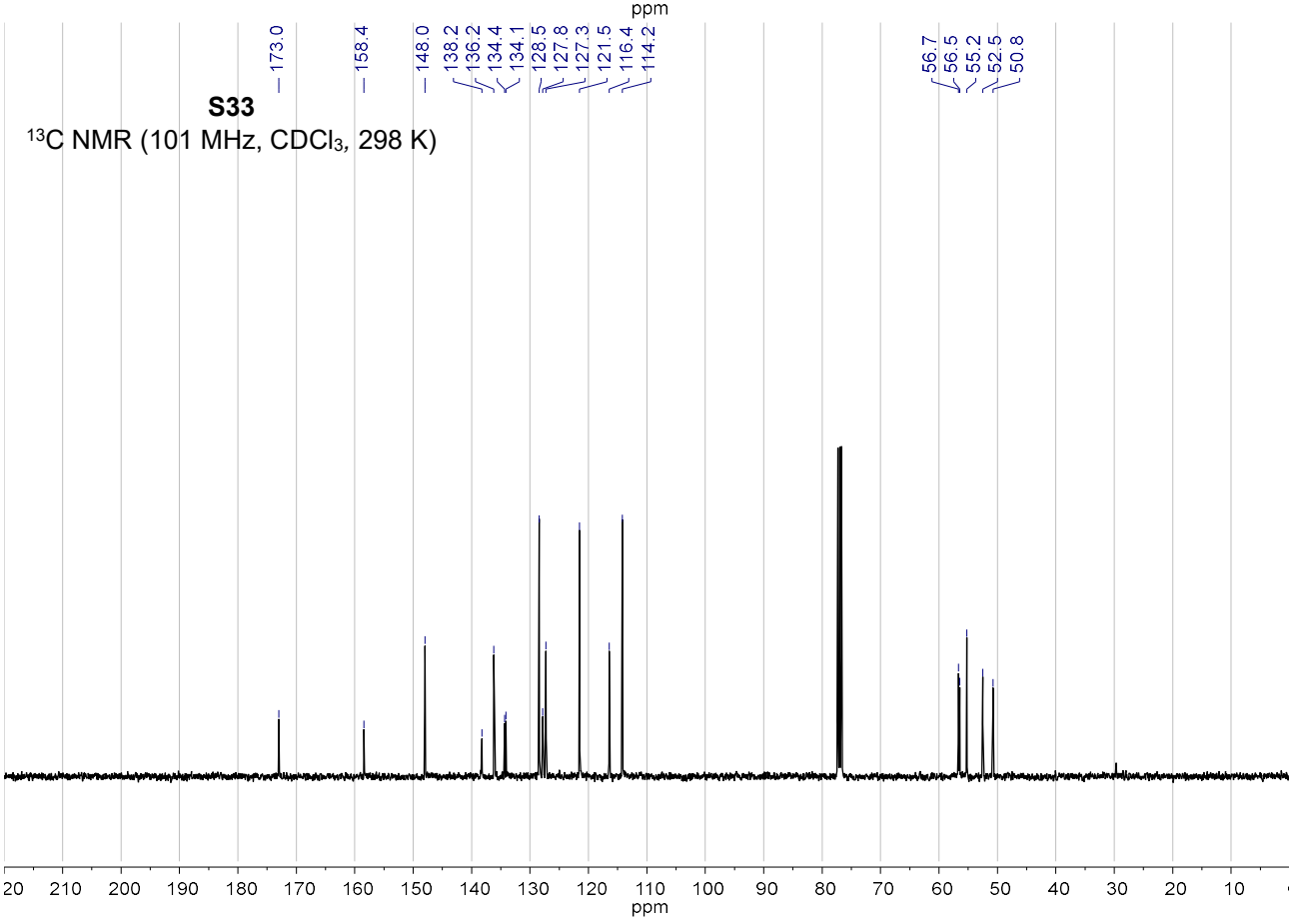

9.67
8.72
8.71
8.71
8.70
8.52
8.52
8.51
8.50
8.10
8.08
7.43
7.43
7.43
7.42
7.42
7.41
7.41
7.40
7.40
7.39
7.39
7.38
7.38
7.22
7.21
7.20
7.19
6.60
6.59
6.58
3.74
3.73
3.72
3.71
3.70
3.69
3.67
3.66
3.52
3.45
3.45
3.43
3.42
3.37
3.36
3.35
3.34
3.33
3.31
3.30
O
O
NH
N
N
H
S32
1H NMR (400 MHz, CDCl3, 298 K)
1.00
1.01
1.03
1.07
3.44
2.23
2.10
2.35
3.04
1.90
2.08
1.43
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
ppm


171.6
158.2
147.9
138.3
136.0
134.3
130.8
129.0
127.7
127.1
121.3
121.2
116.3
113.6
54.9
53.1
52.0
50.7
49.2
S32
13C NMR (101 MHz, CDCl3, 298 K)
40 230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
ppm



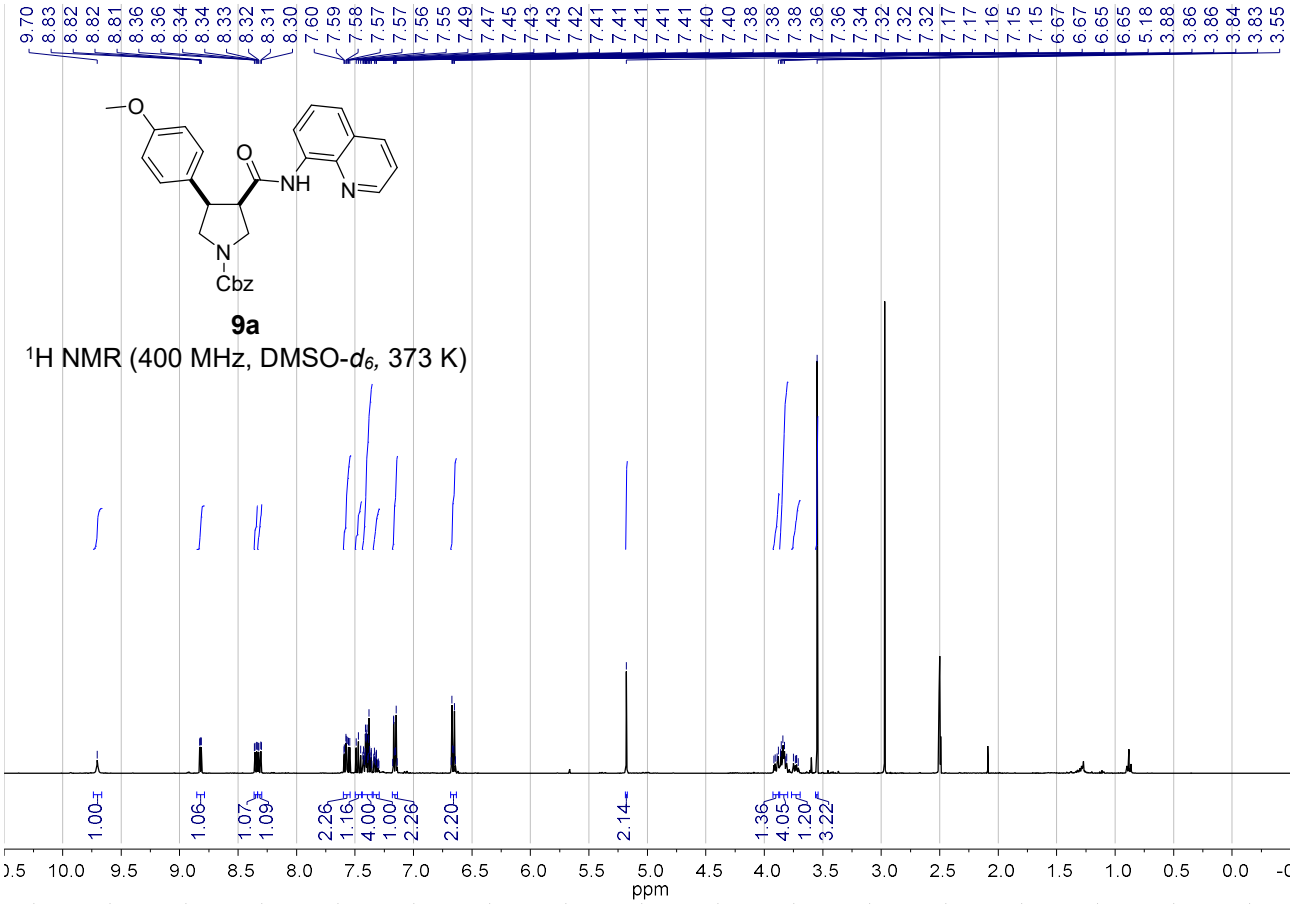
S33

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



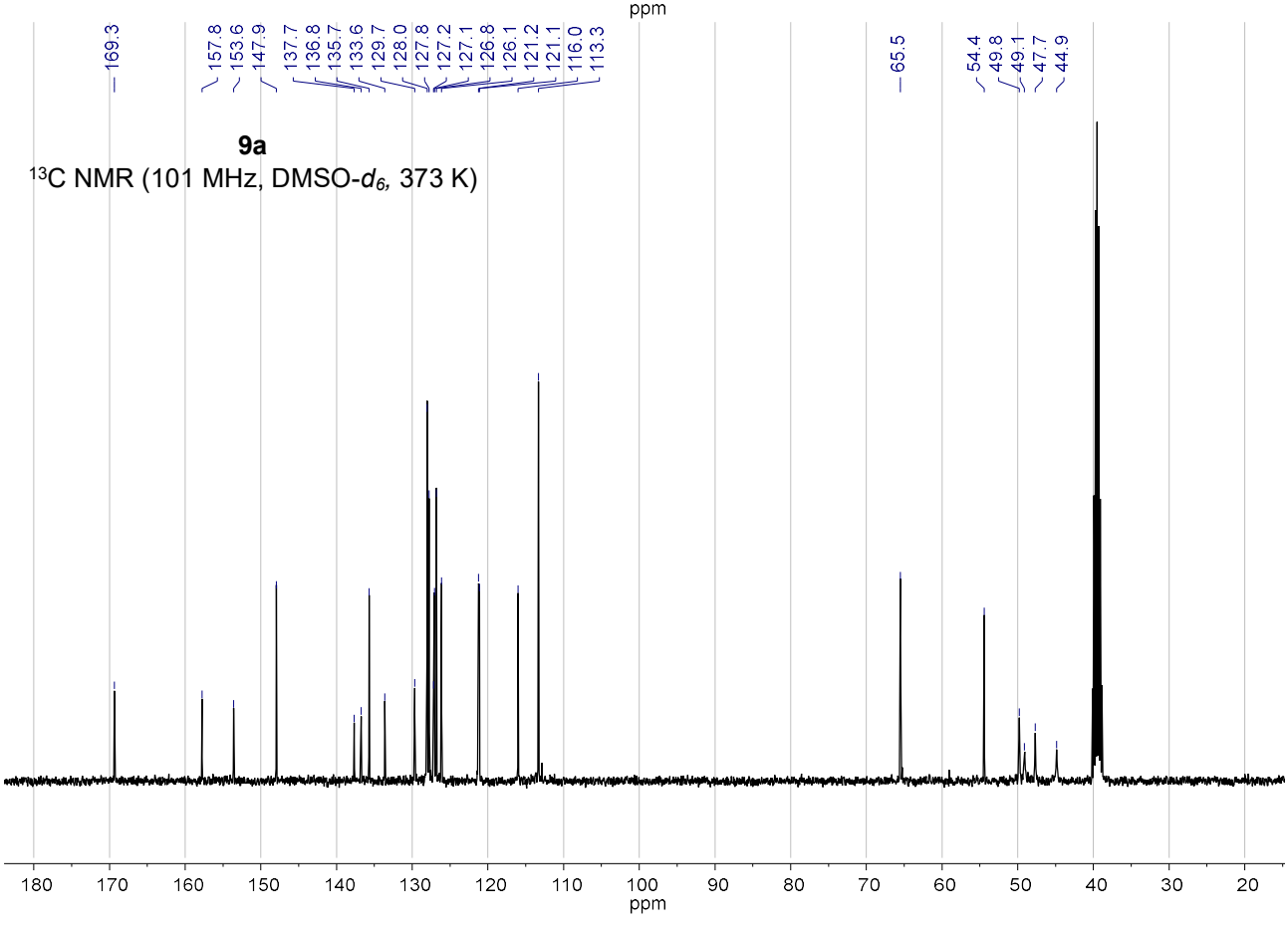
S33

^{13}C NMR (101 MHz, $CDCl_3$, 298 K)



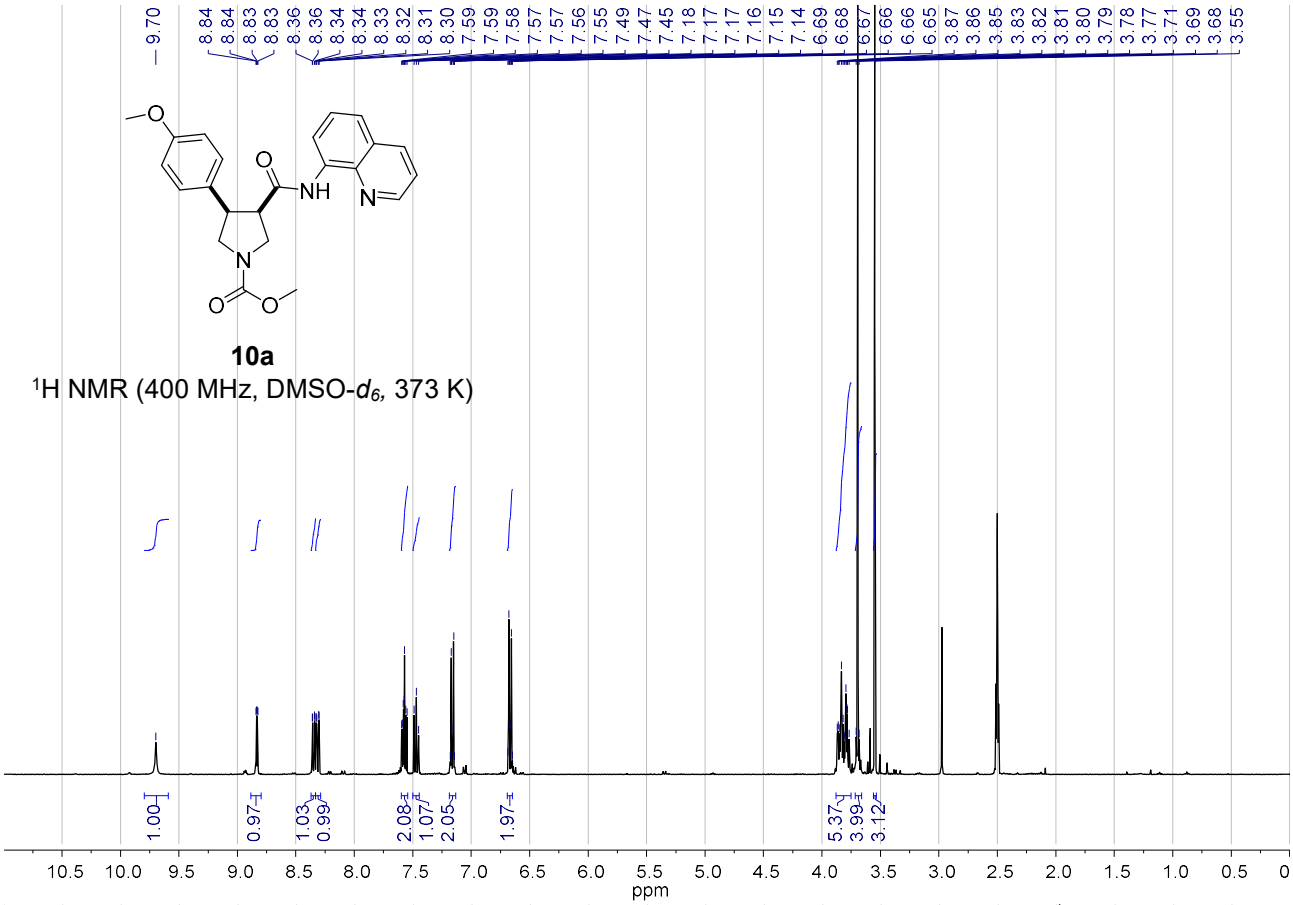
9a

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



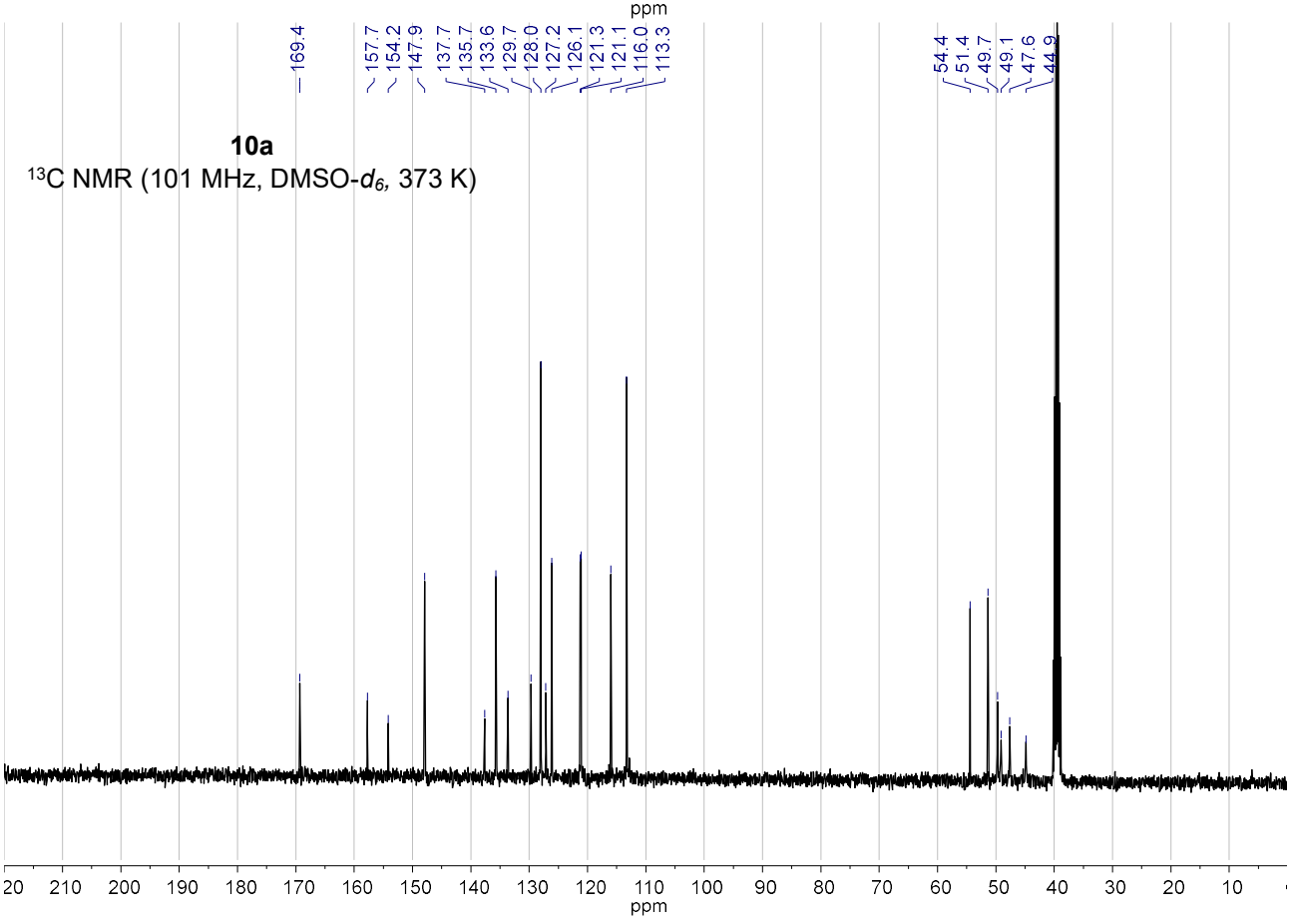
9a

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



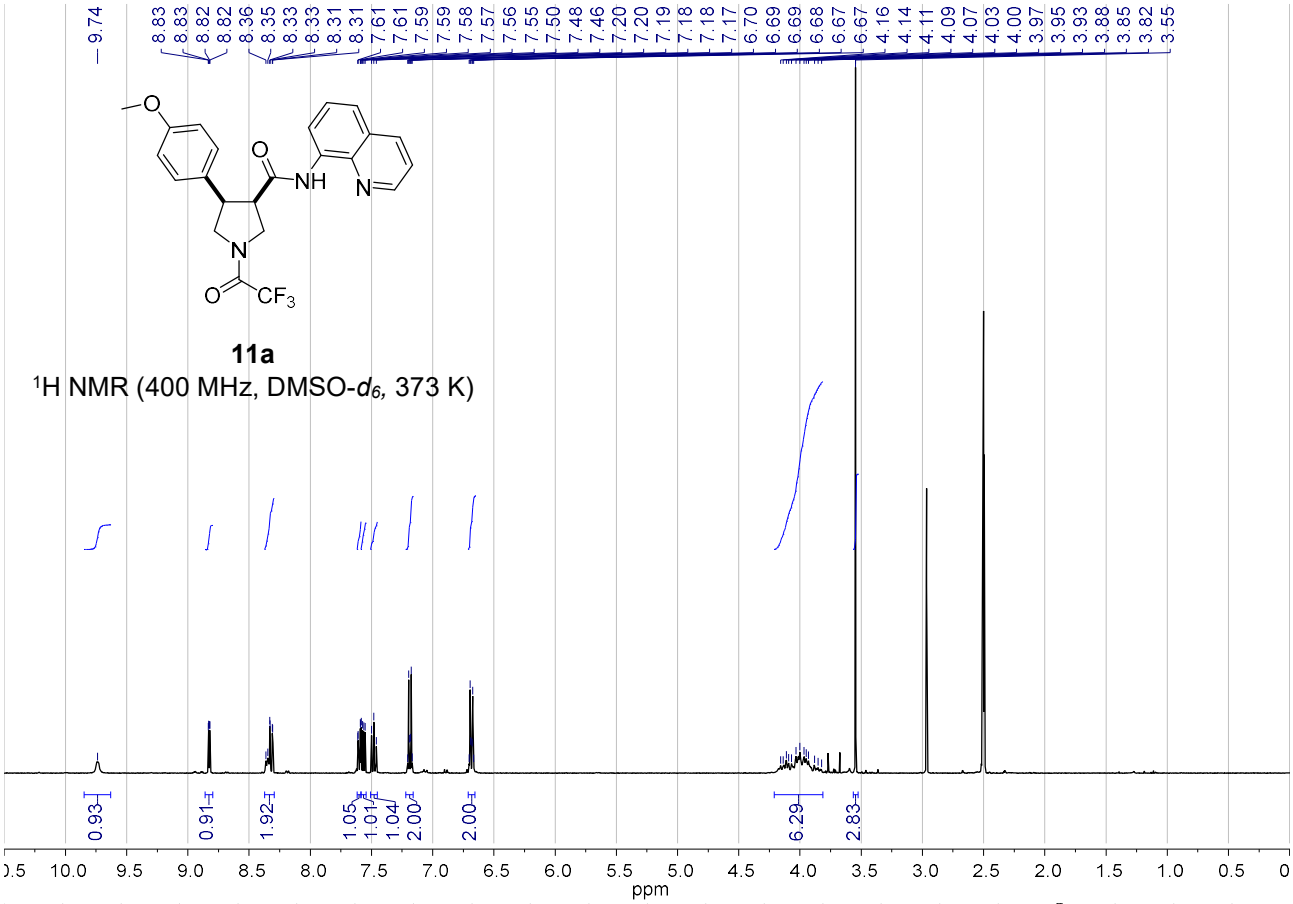
10a

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



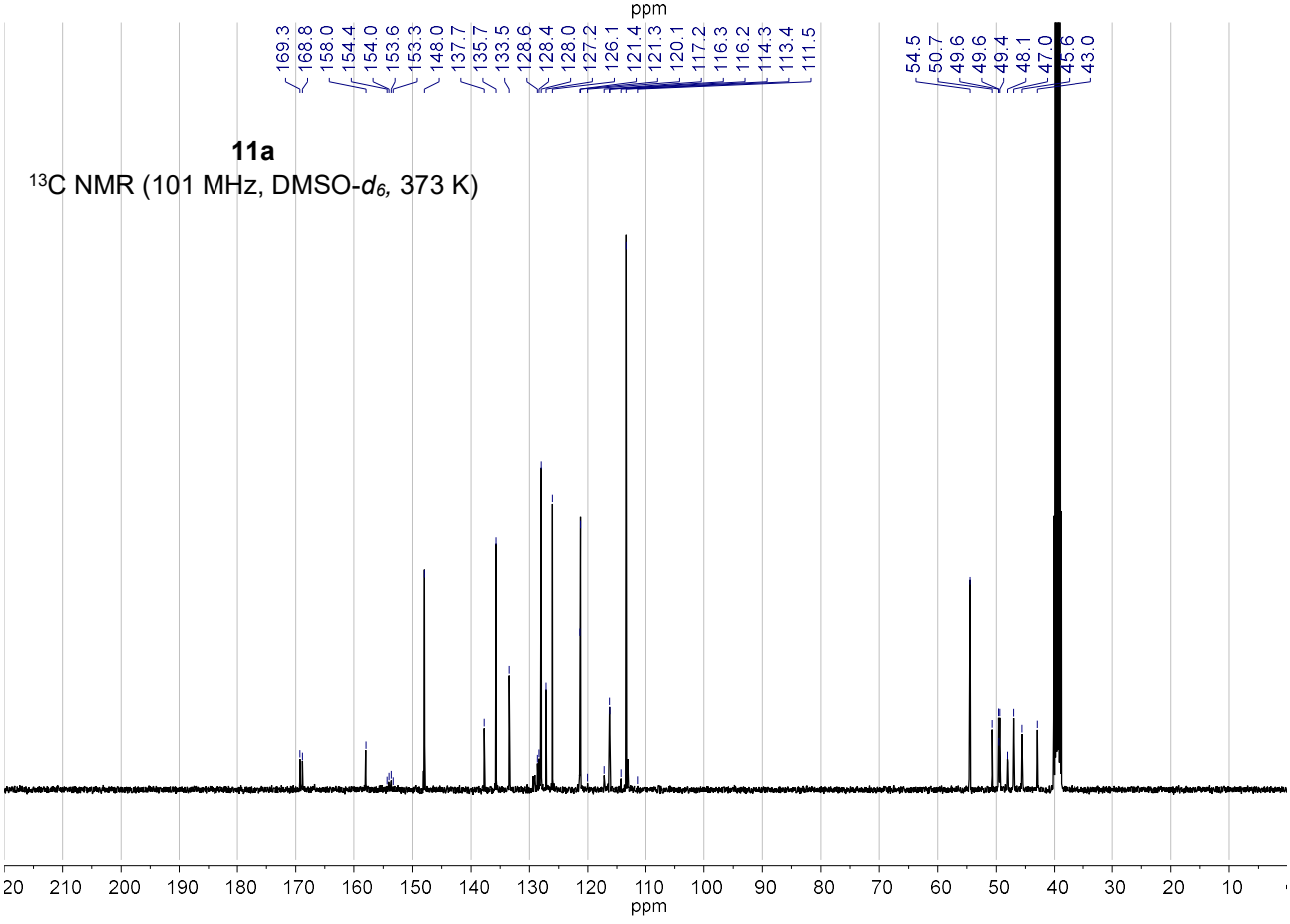
10a

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



11a

^{1}H NMR (400 MHz, DMSO-*d*$_6$, 373 K)

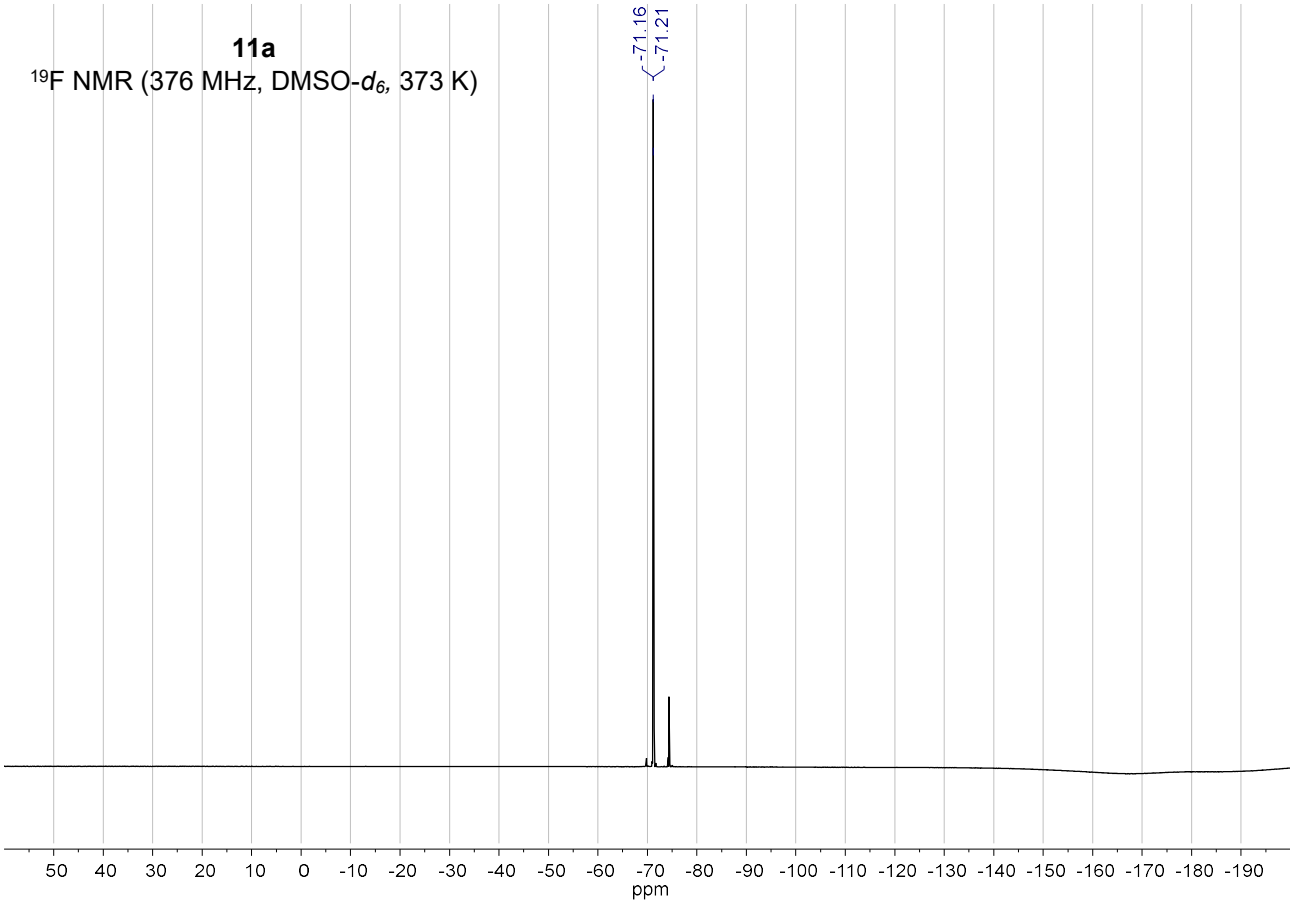


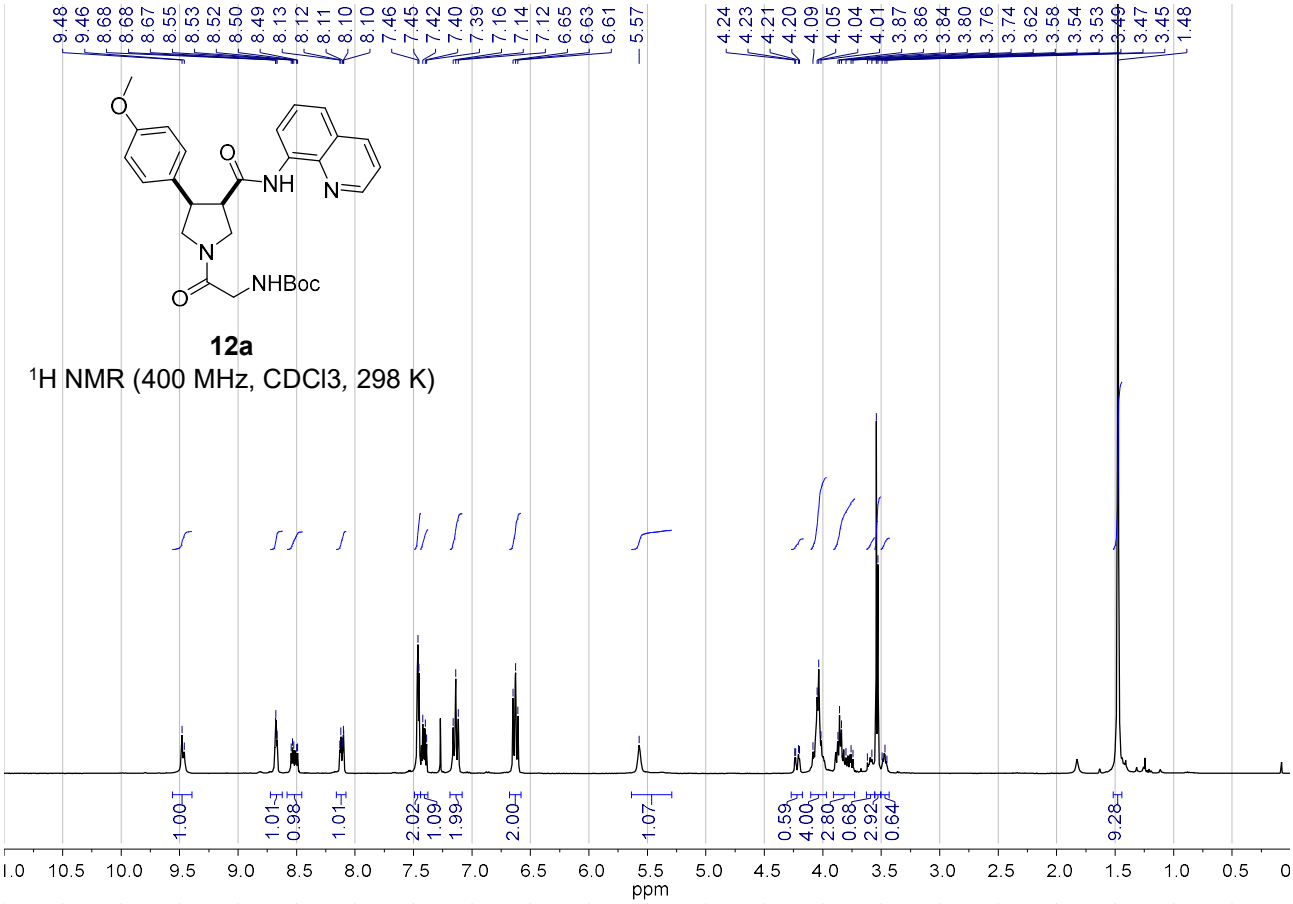
11a

^{13}C NMR (101 MHz, DMSO-*d*$_6$, 373 K)

11a

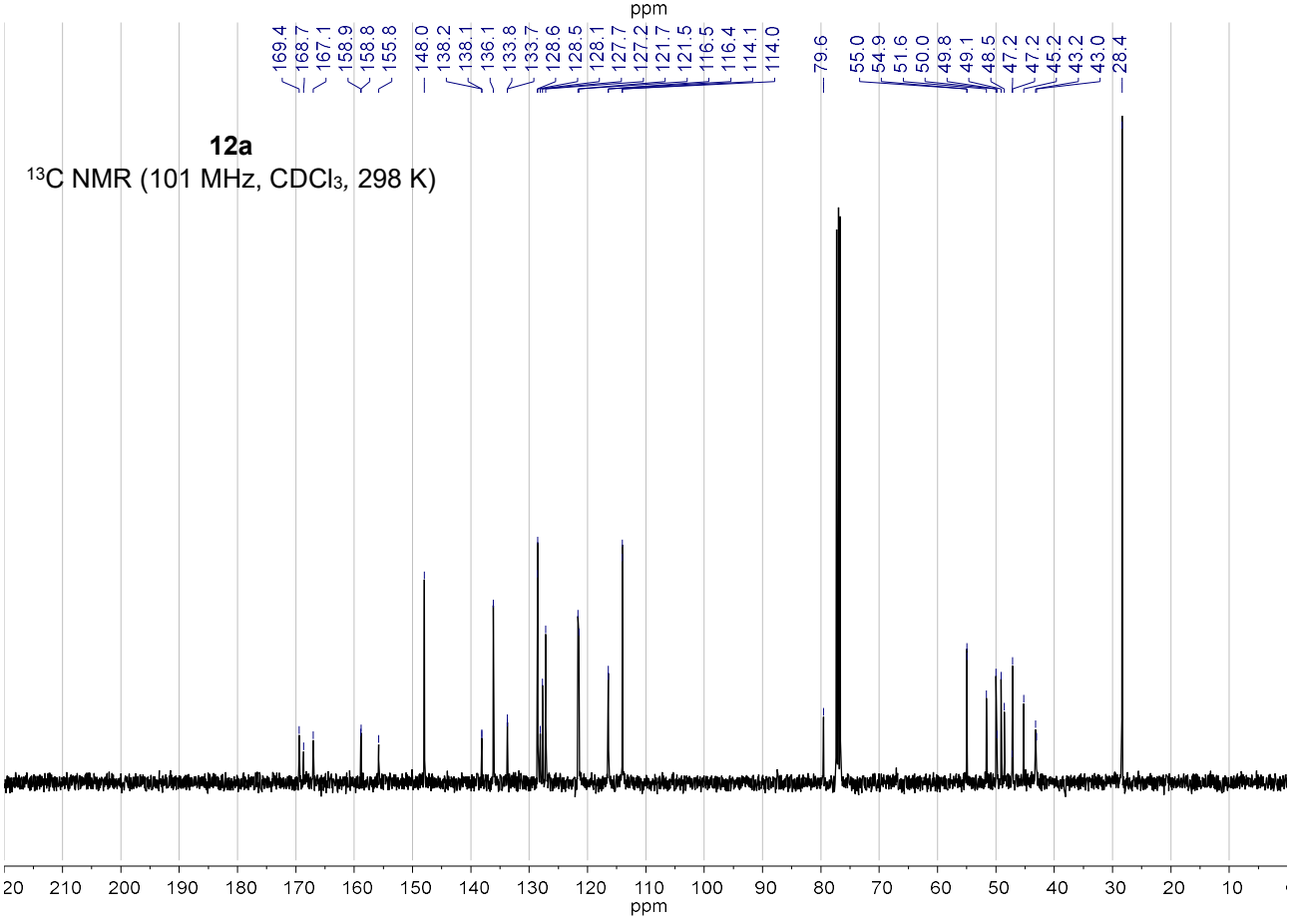
^{19}F NMR (376 MHz, DMSO-d_6, 373 K)





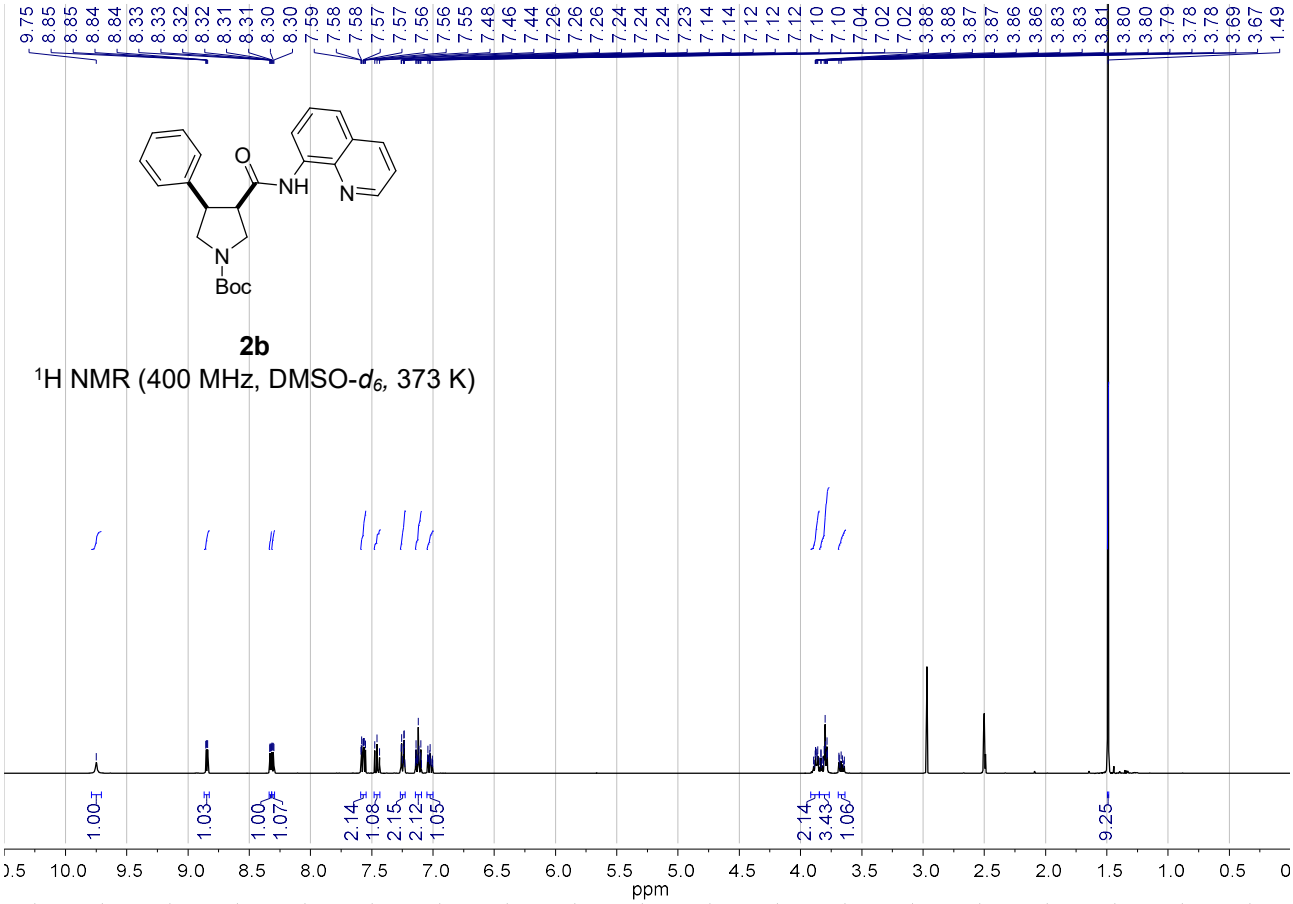
12a

^{1}H NMR (400 MHz, CDCl3, 298 K)



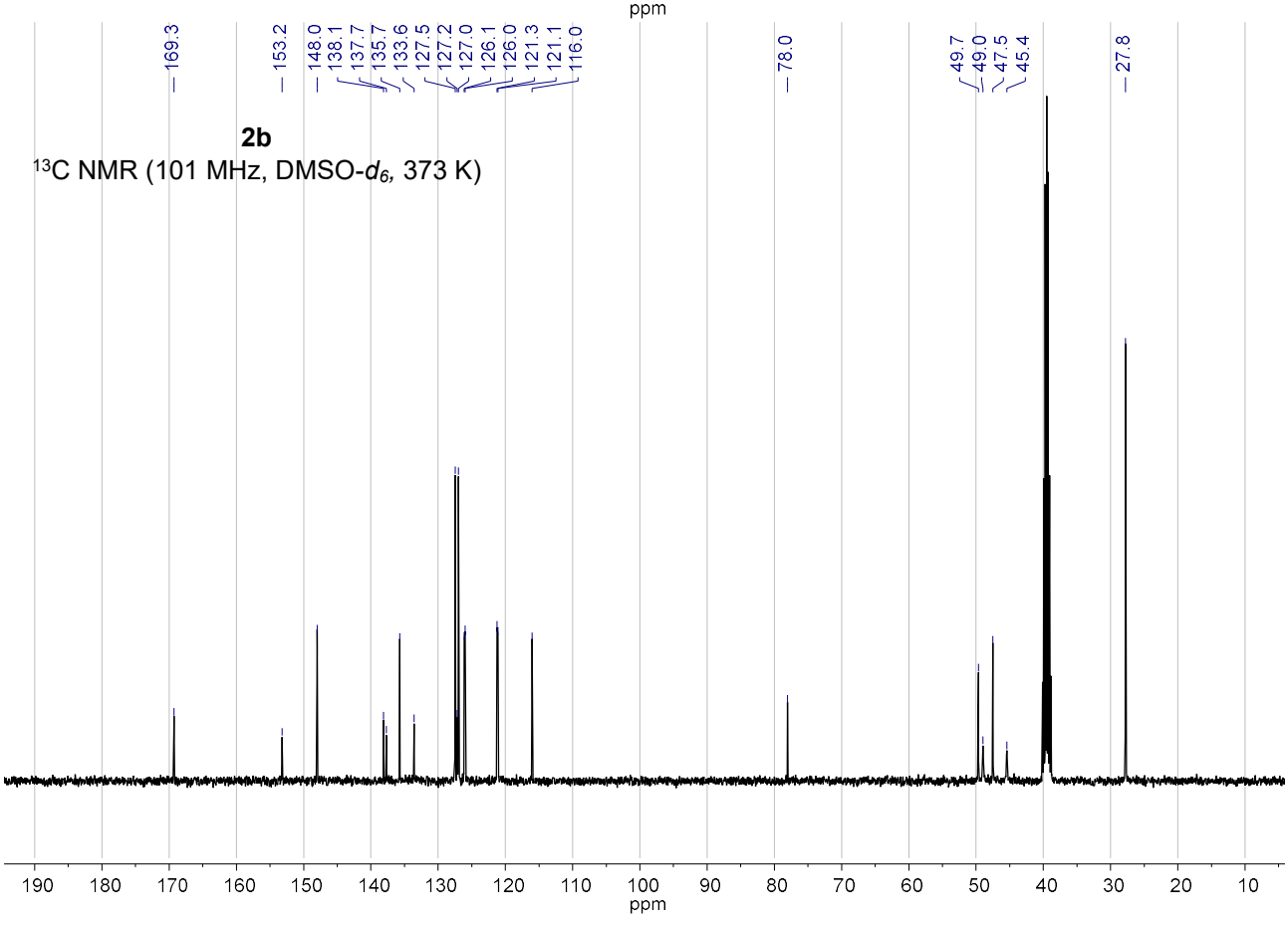
12a

^{13}C NMR (101 MHz, $CDCl_3$, 298 K)



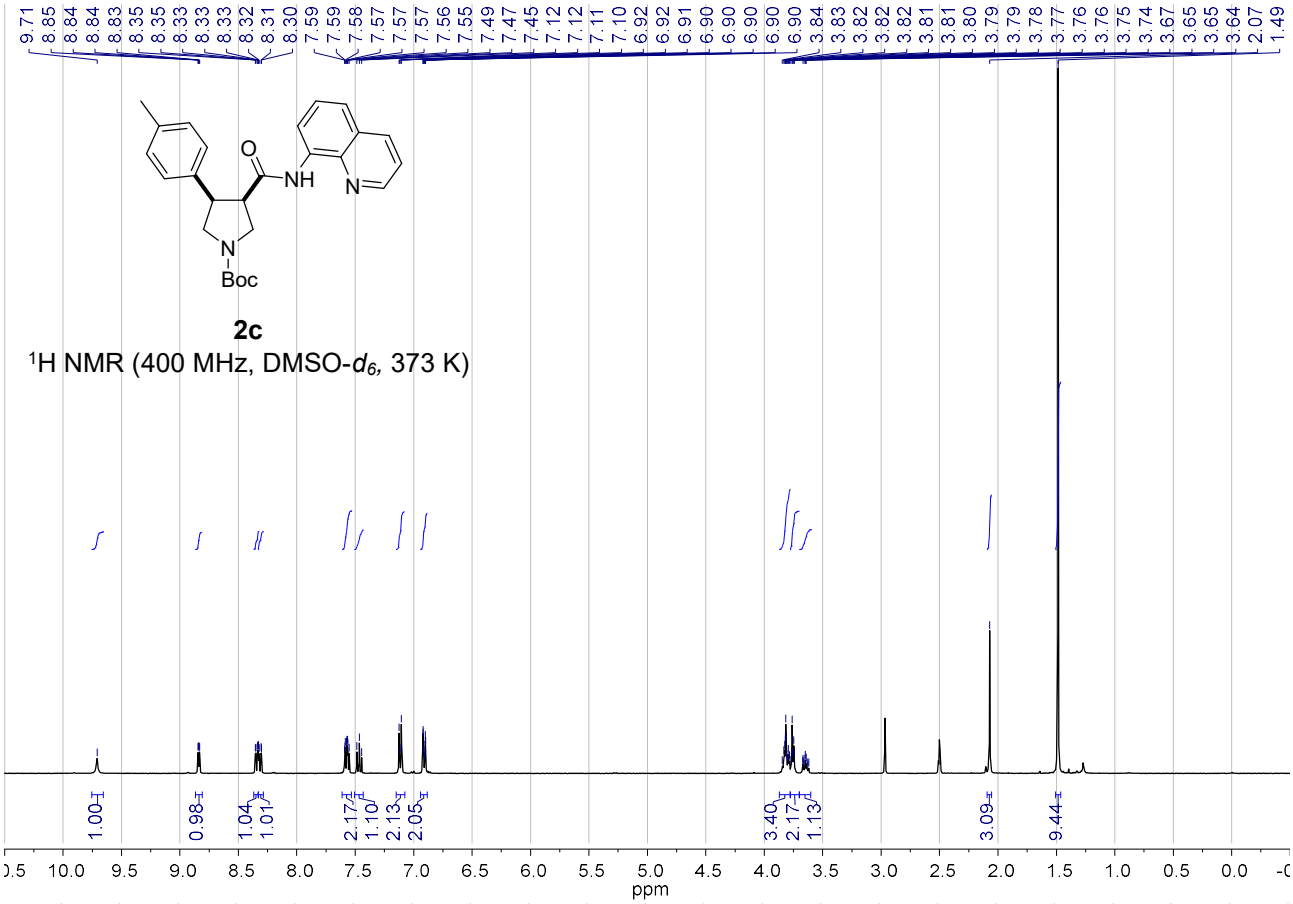
2b

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



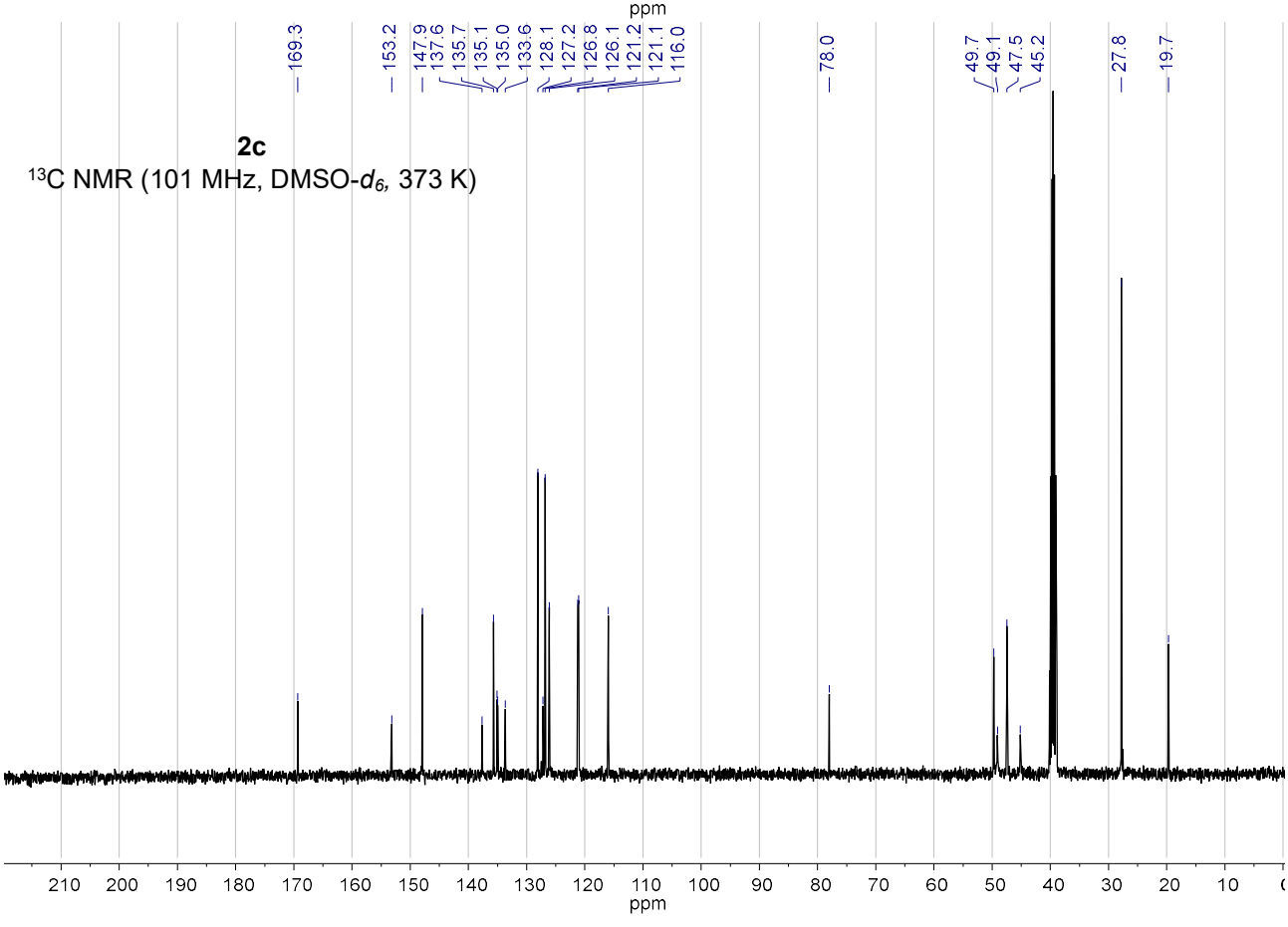
2b

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



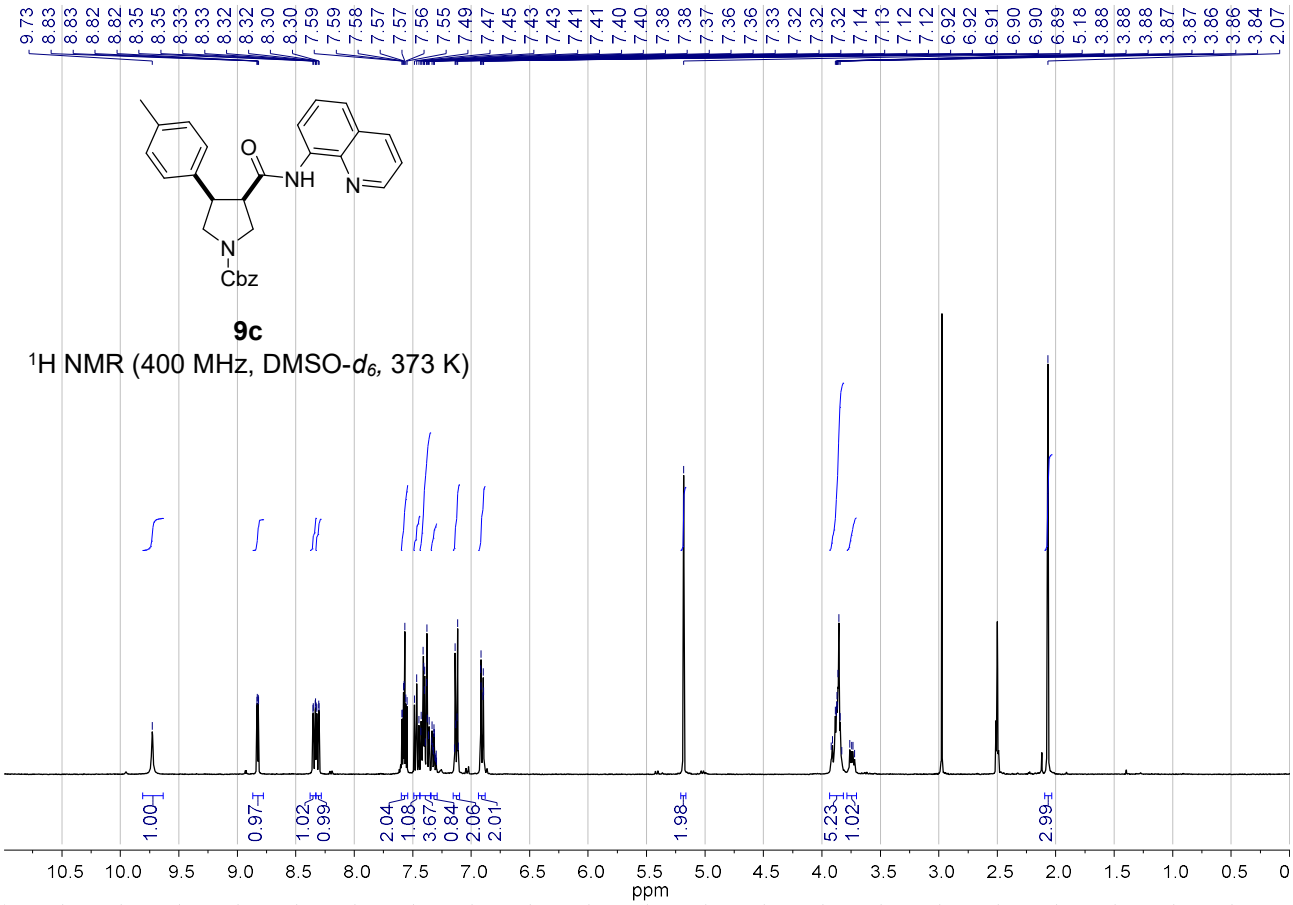
2c

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



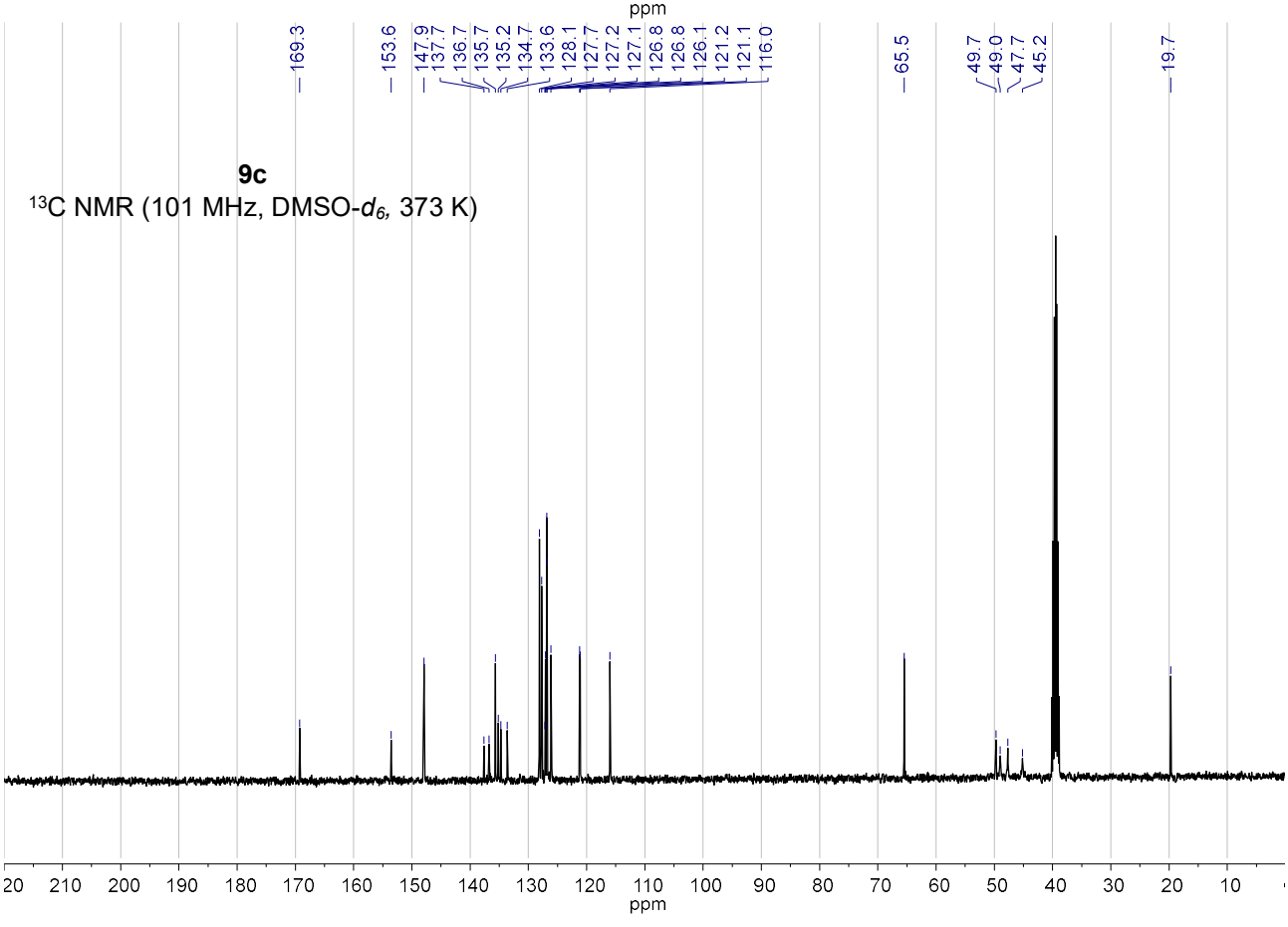
2c

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



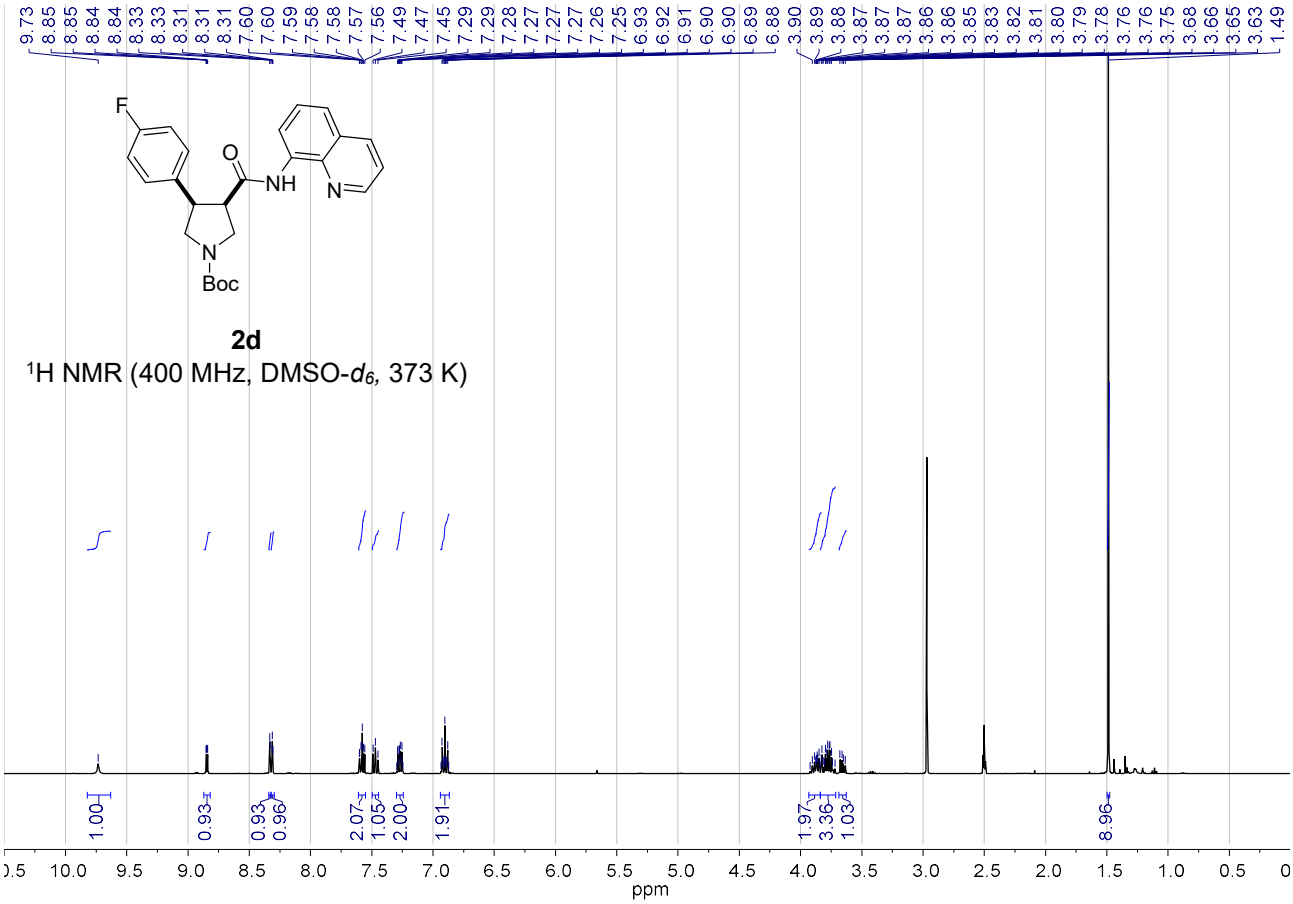
9c

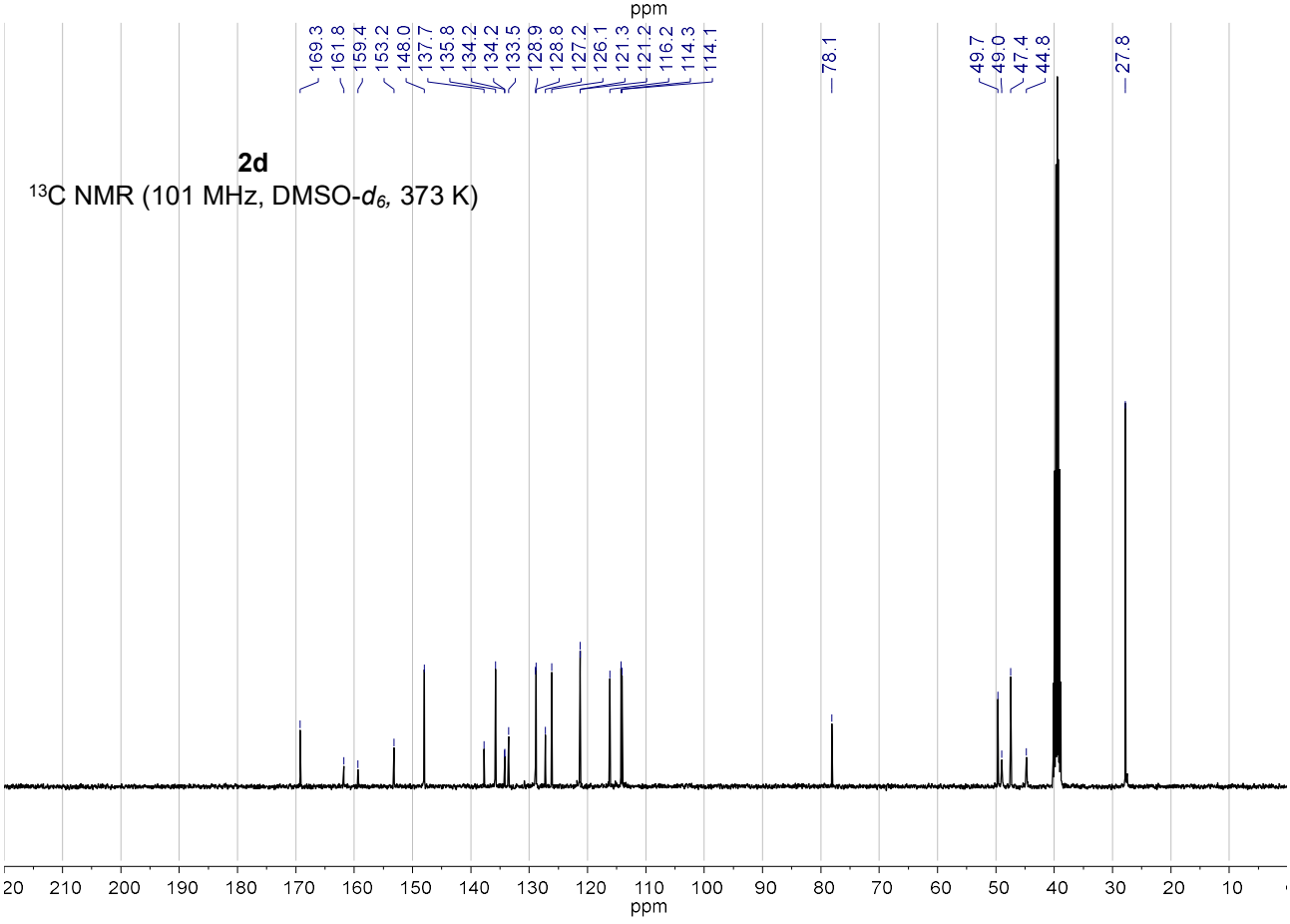
^{1}H NMR (400 MHz, DMSO-d_6, 373 K)



9c

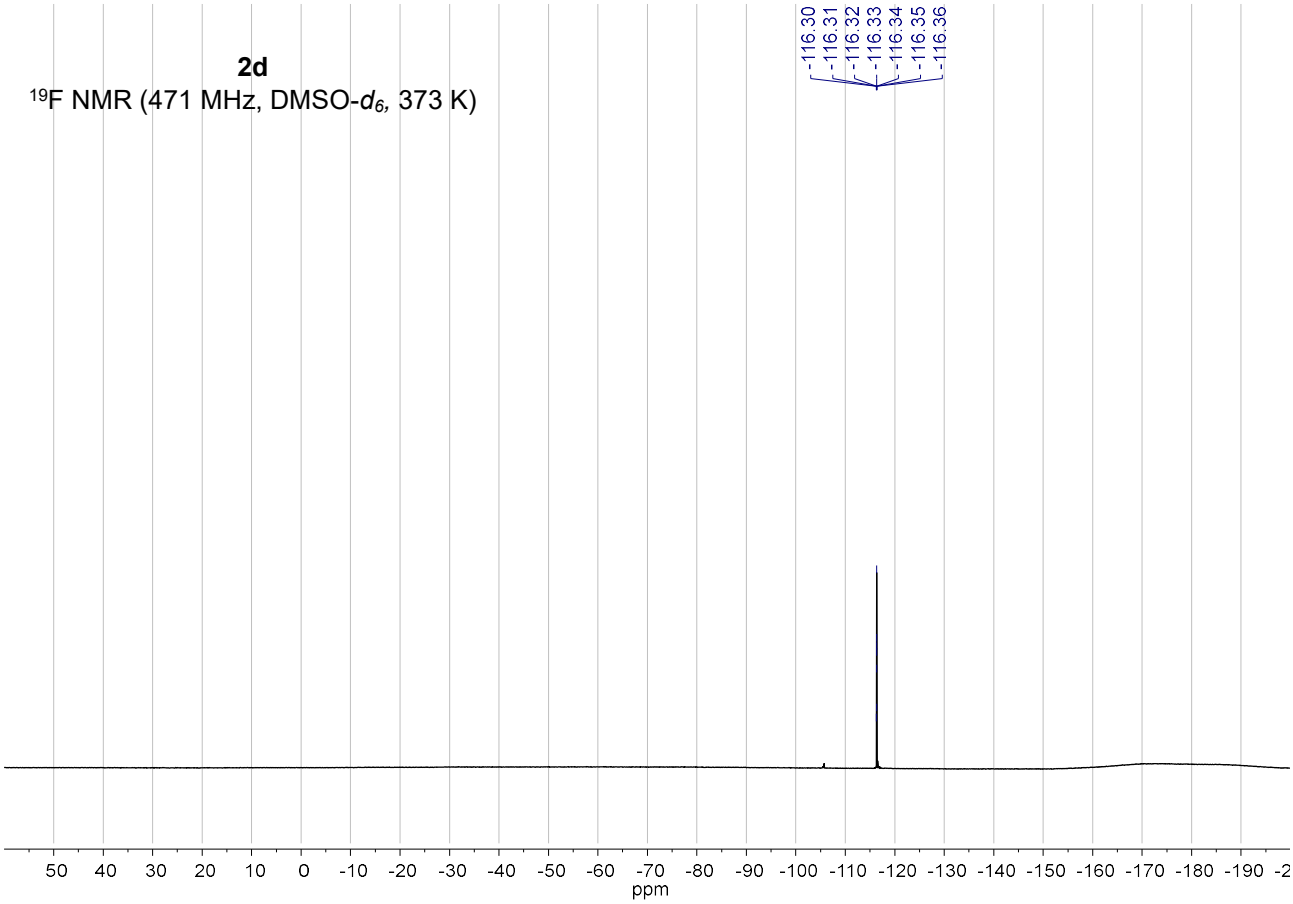
^{13}C NMR (101 MHz, DMSO-d_6, 373 K)

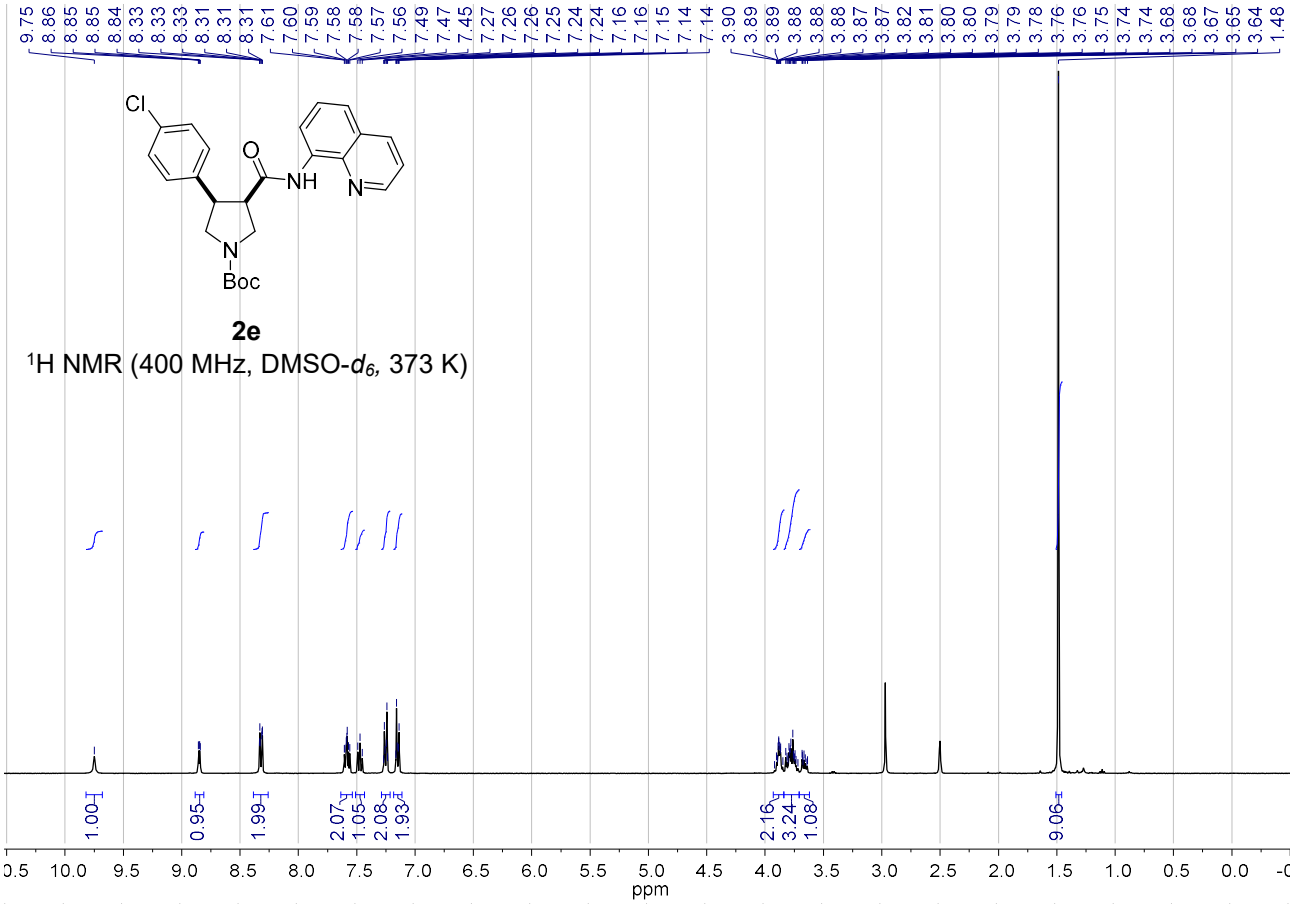

F
O
NH
N
N
Boc
2d
1H NMR (400 MHz, DMSO-d6, 373 K)
ppm


2d
13C NMR (101 MHz, DMSO-d6, 373 K)
ppm

2d

^{19}F NMR (471 MHz, DMSO-d_6, 373 K)



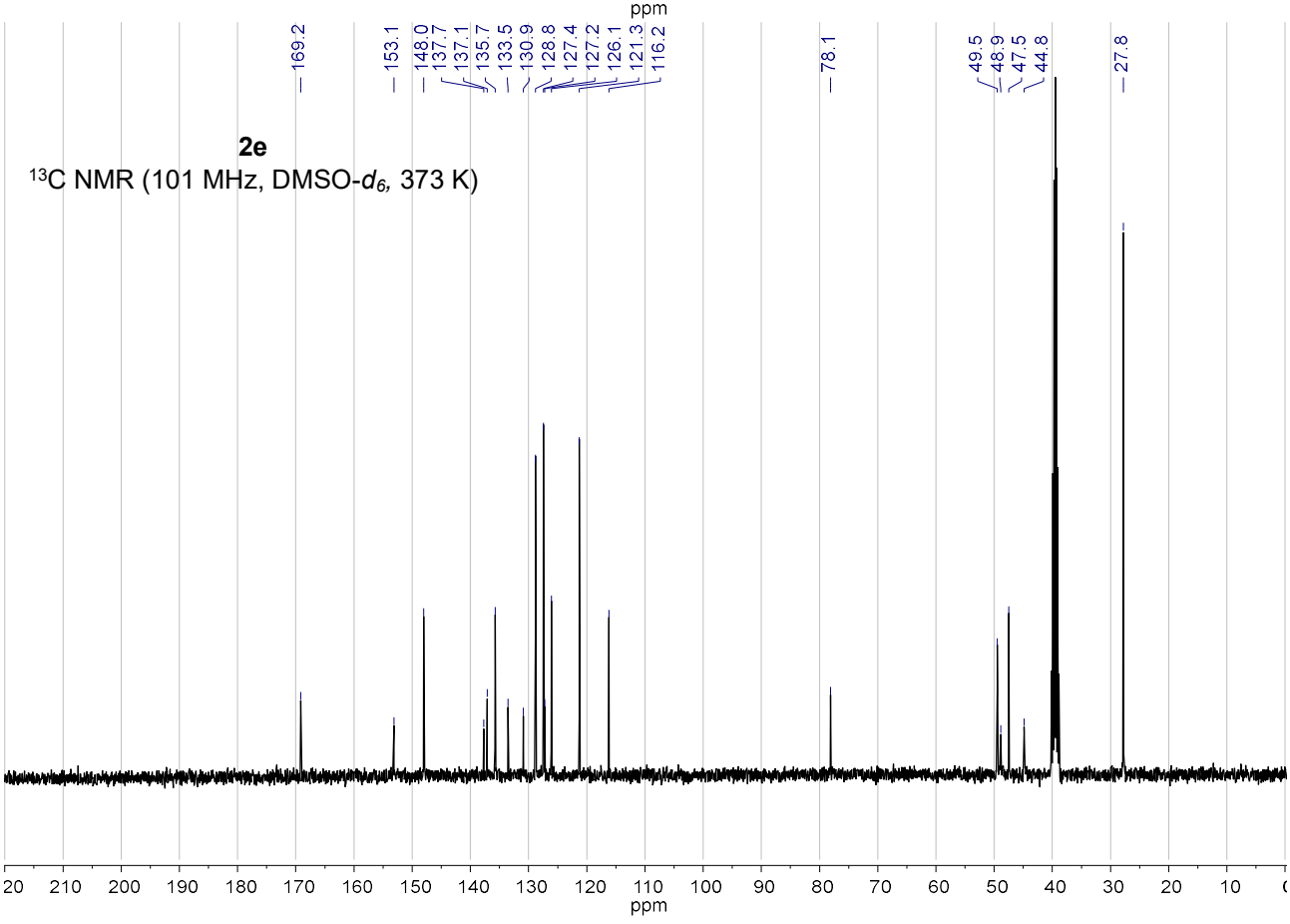


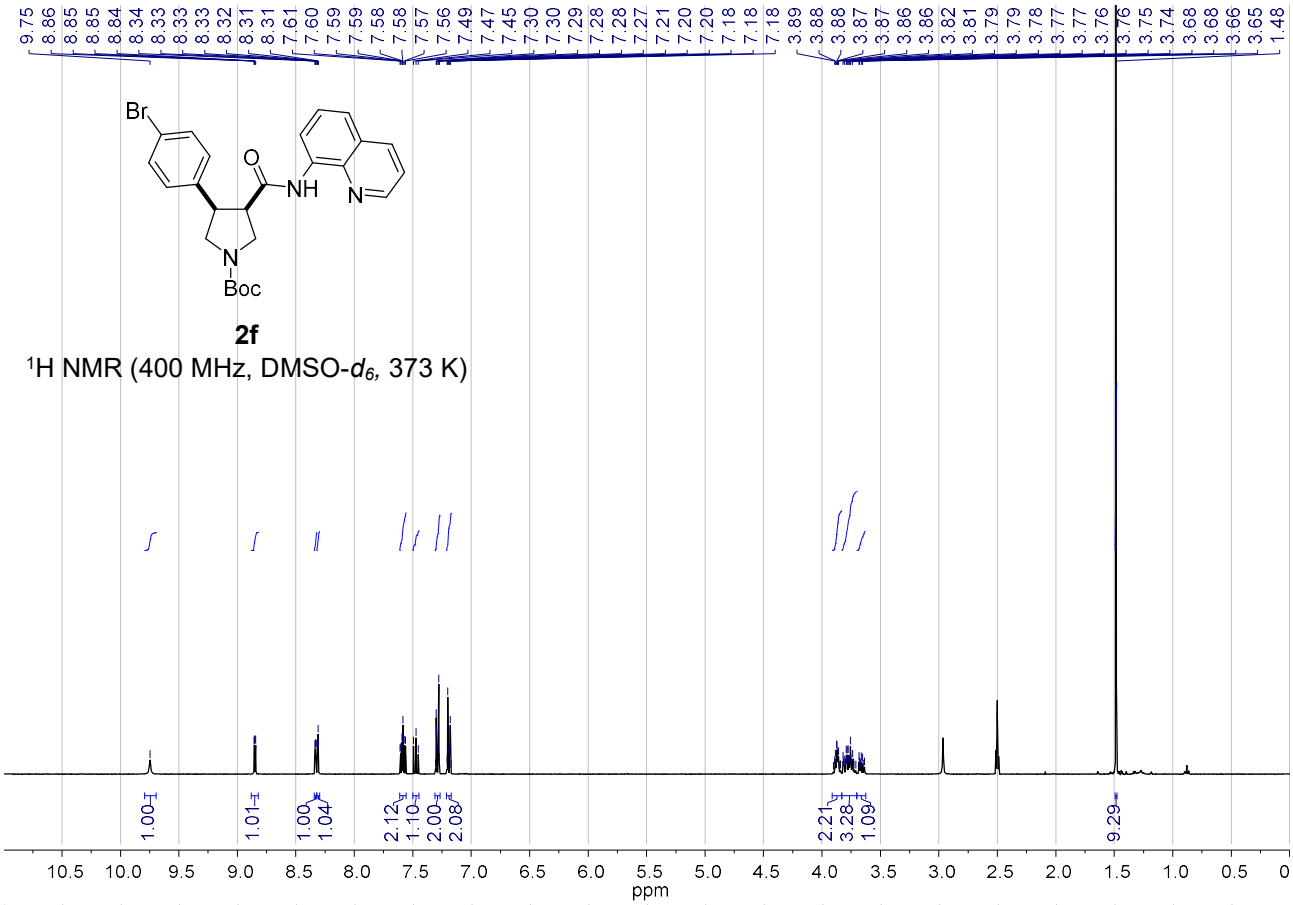
2e

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

2e

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



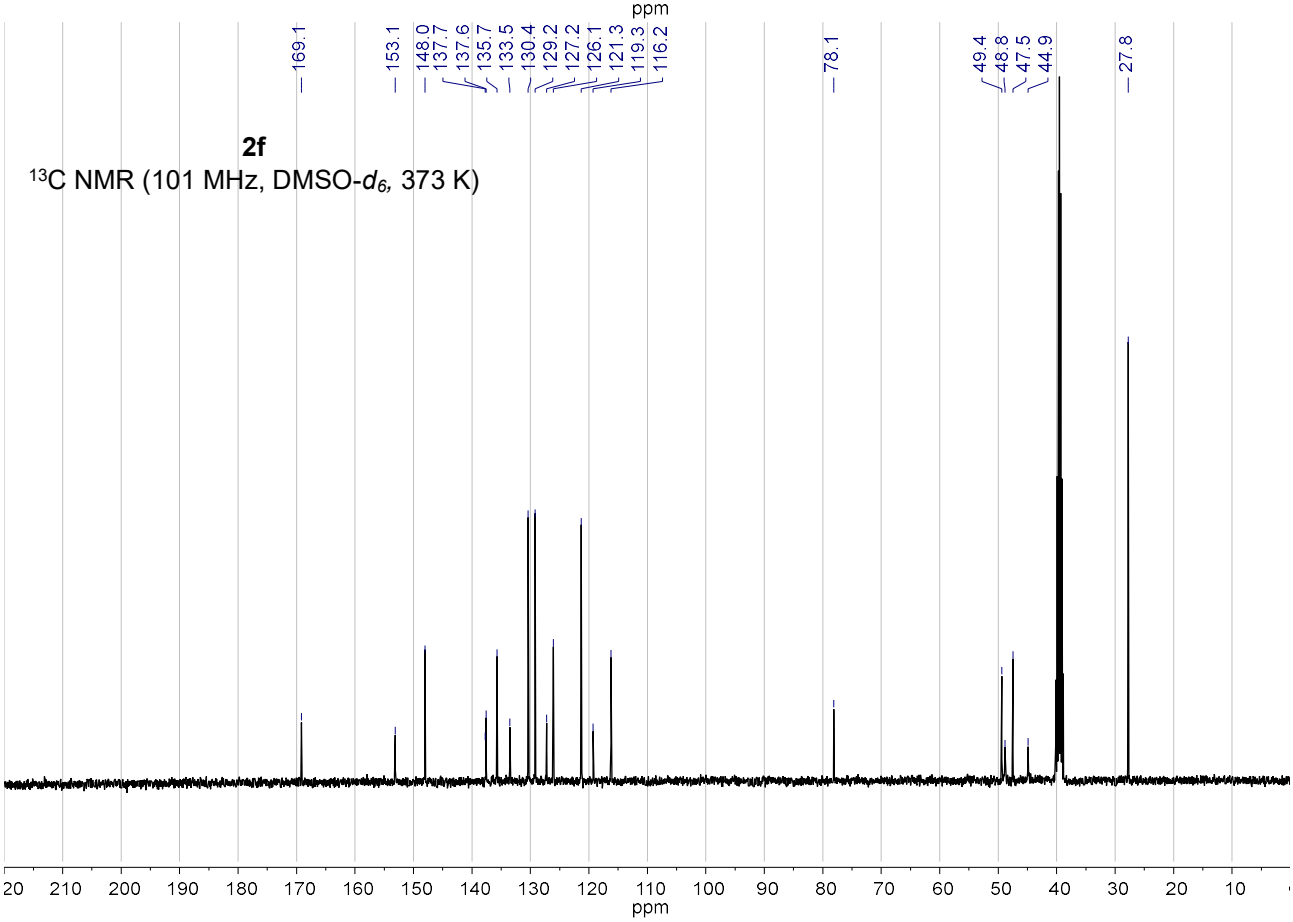


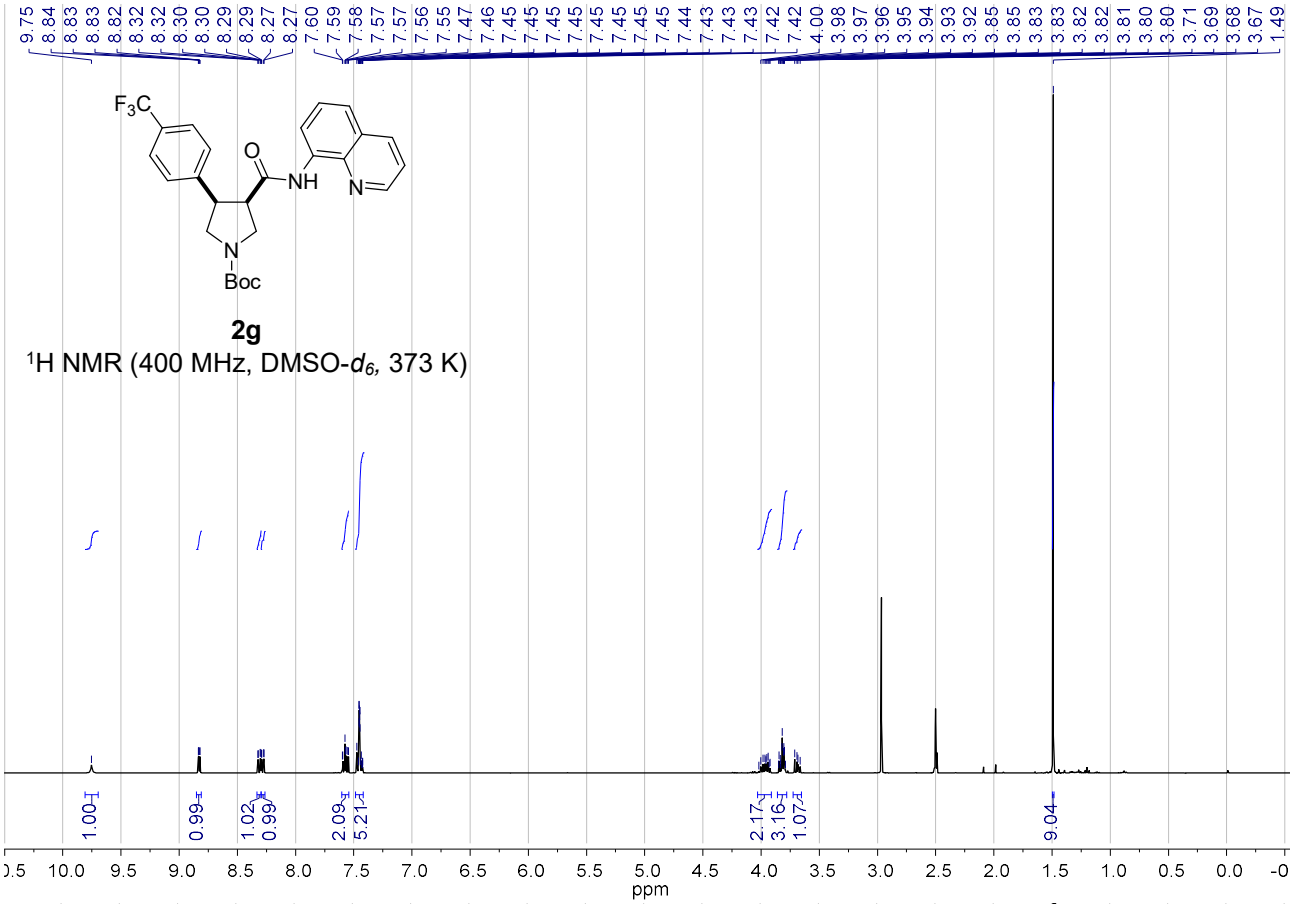
2f

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

2f

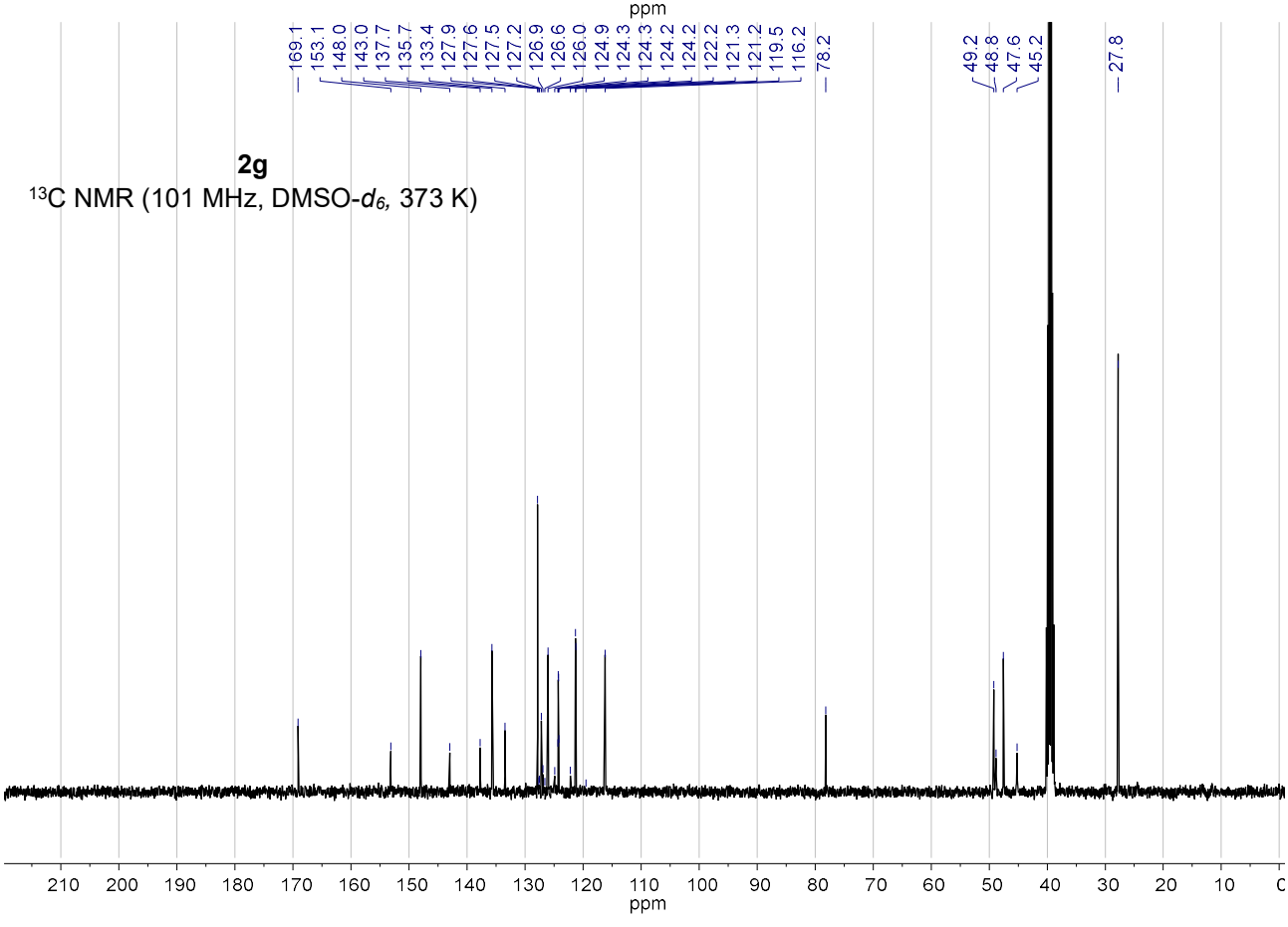
^{13}C NMR (101 MHz, DMSO-d_6, 373 K)





2g

^{1}H NMR (400 MHz, DMSO-*d*$_6$, 373 K)

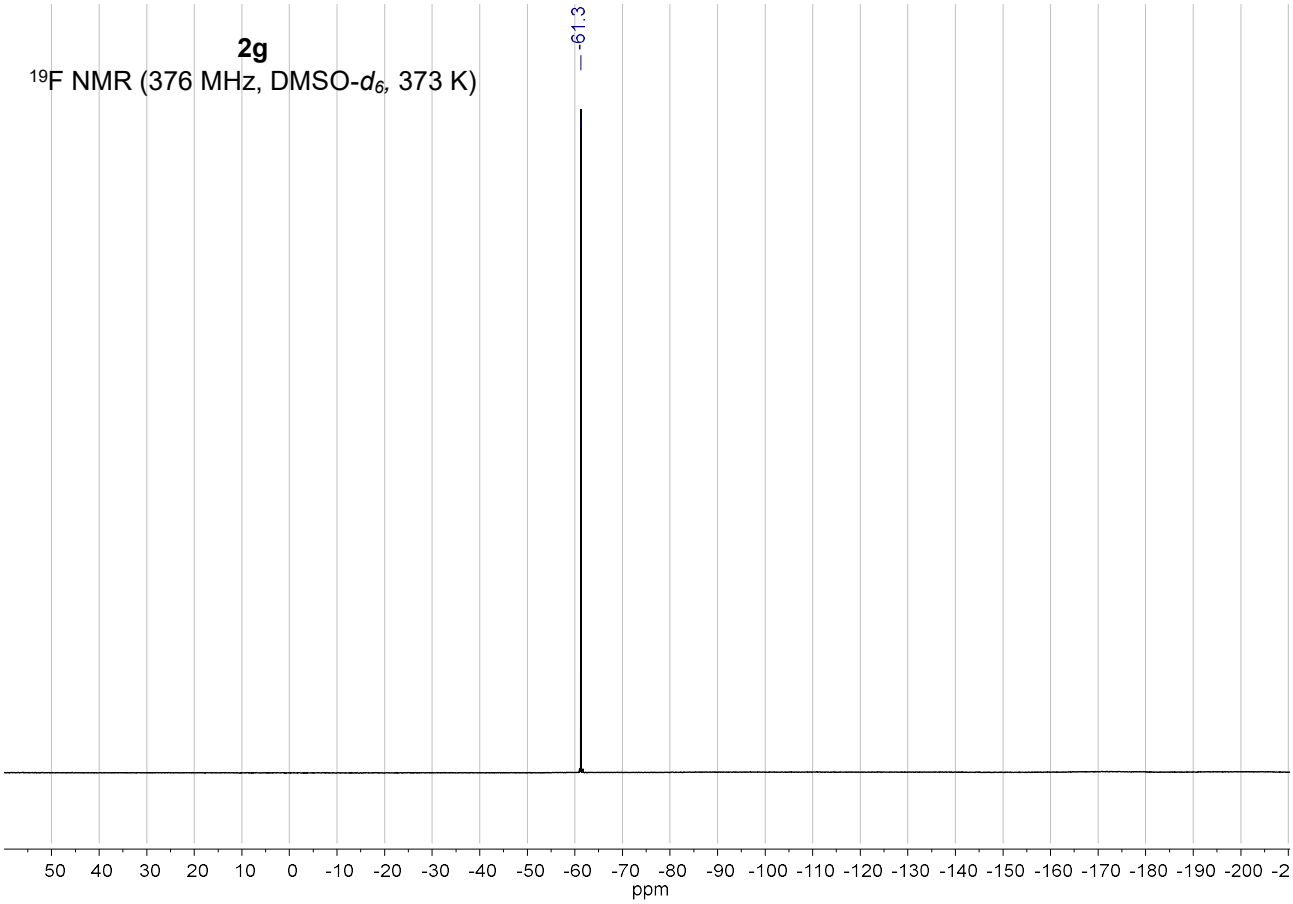


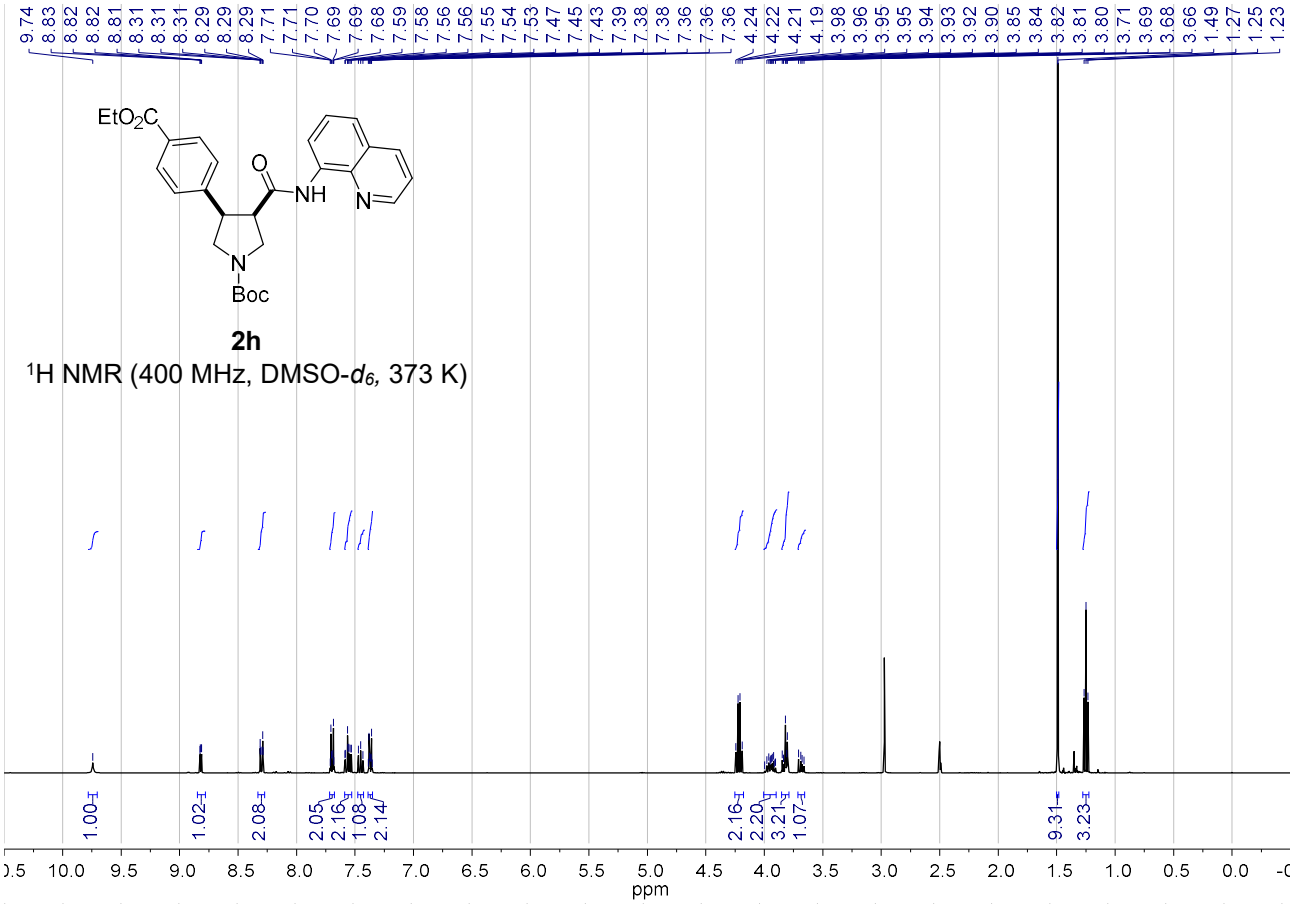
2g

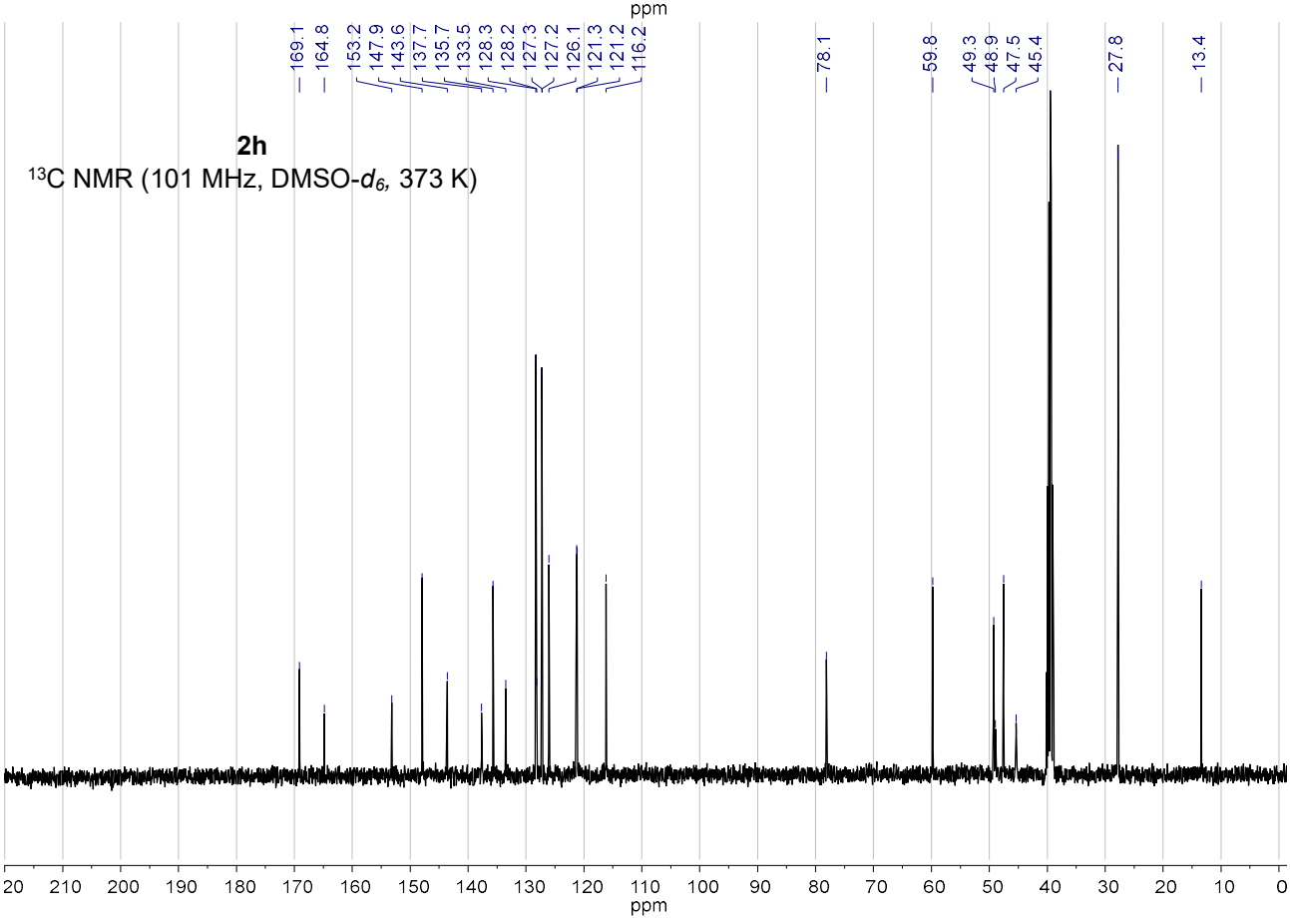
^{13}C NMR (101 MHz, DMSO-*d*$_6$, 373 K)

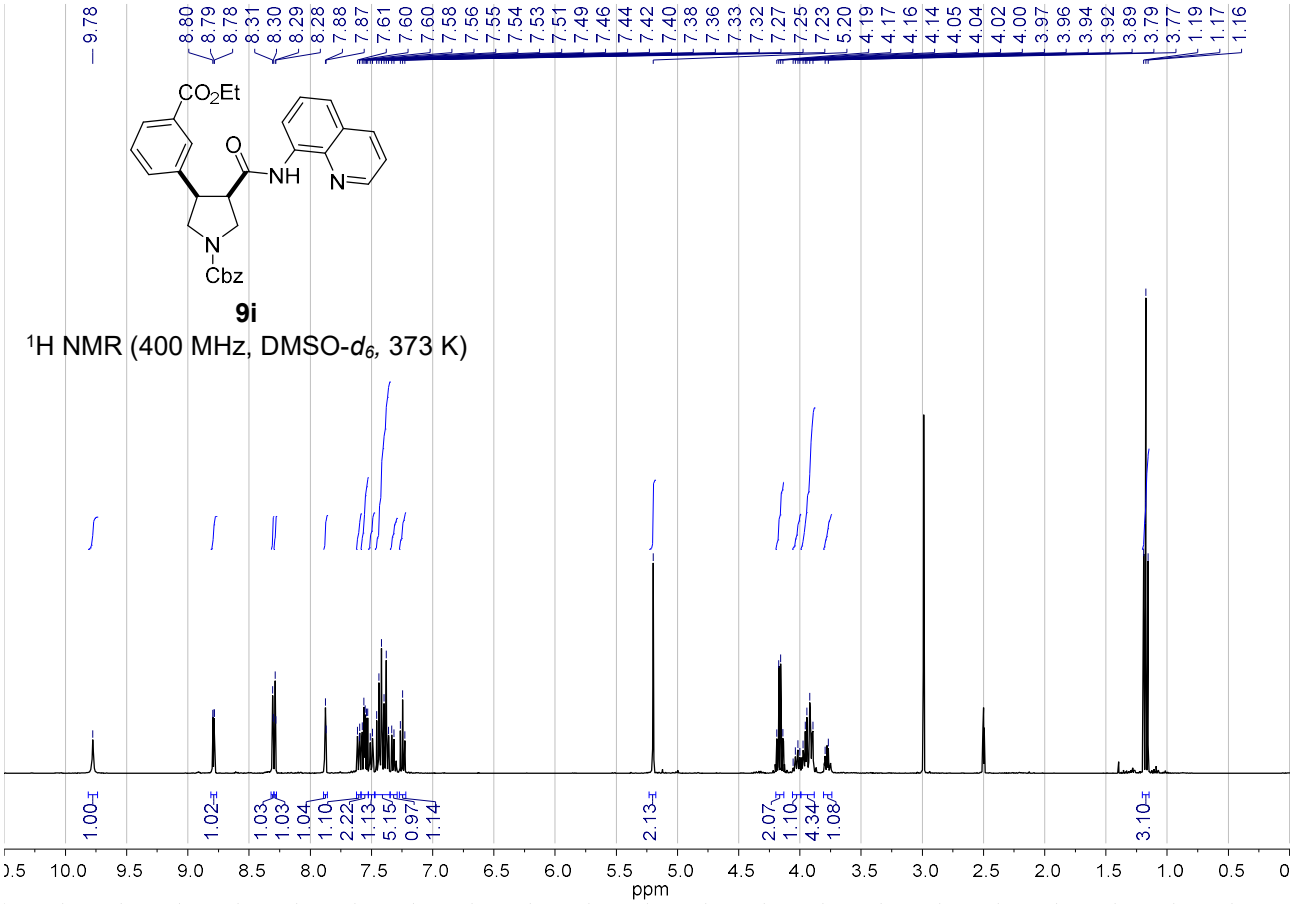
2g

^{19}F NMR (376 MHz, DMSO-d_6, 373 K)



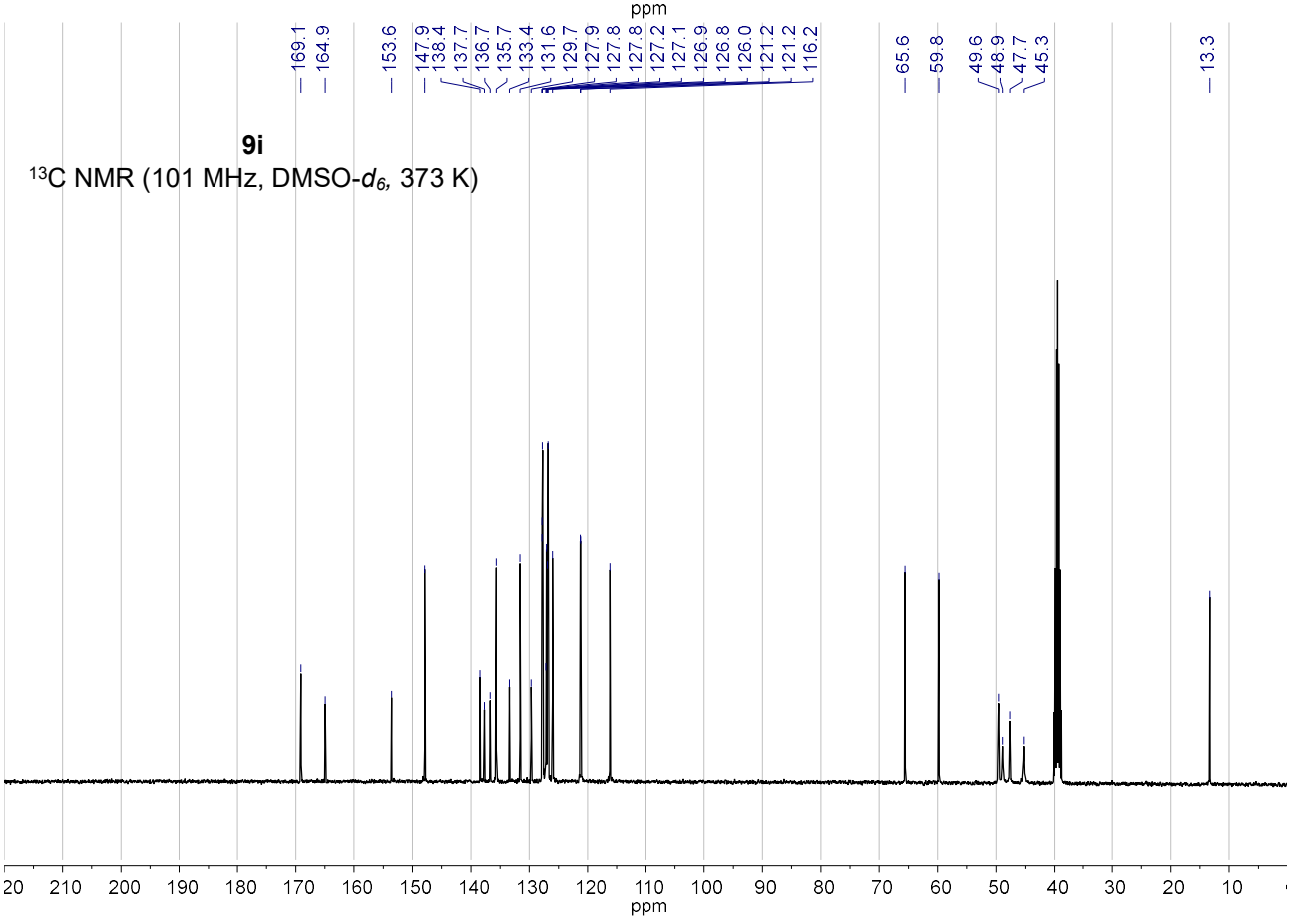

EtO2C
O
NH
N
N
Boc
2h
1H NMR (400 MHz, DMSO-d6, 373 K)
ppm


2h
13C NMR (101 MHz, DMSO-d6, 373 K)
ppm



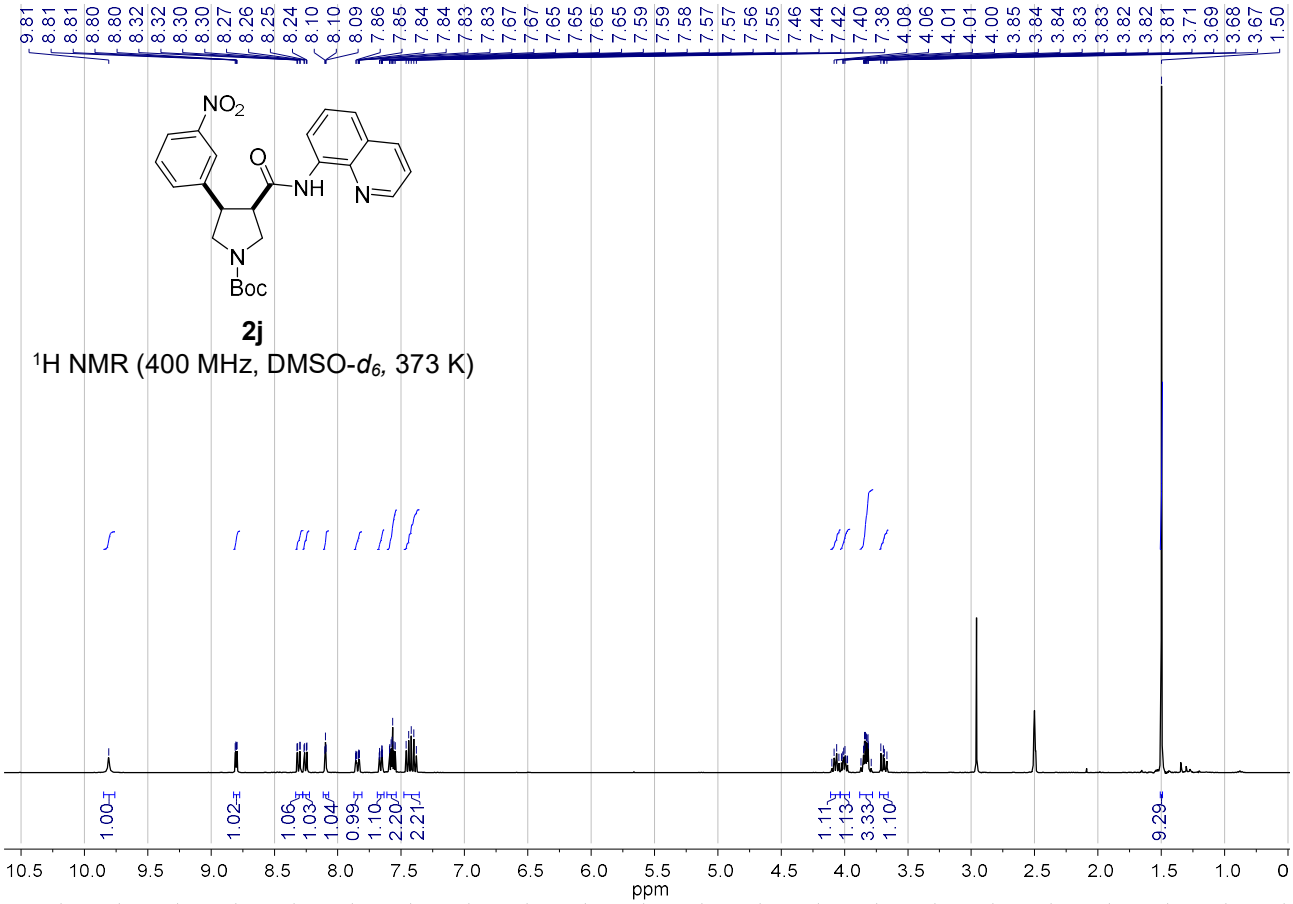
9i

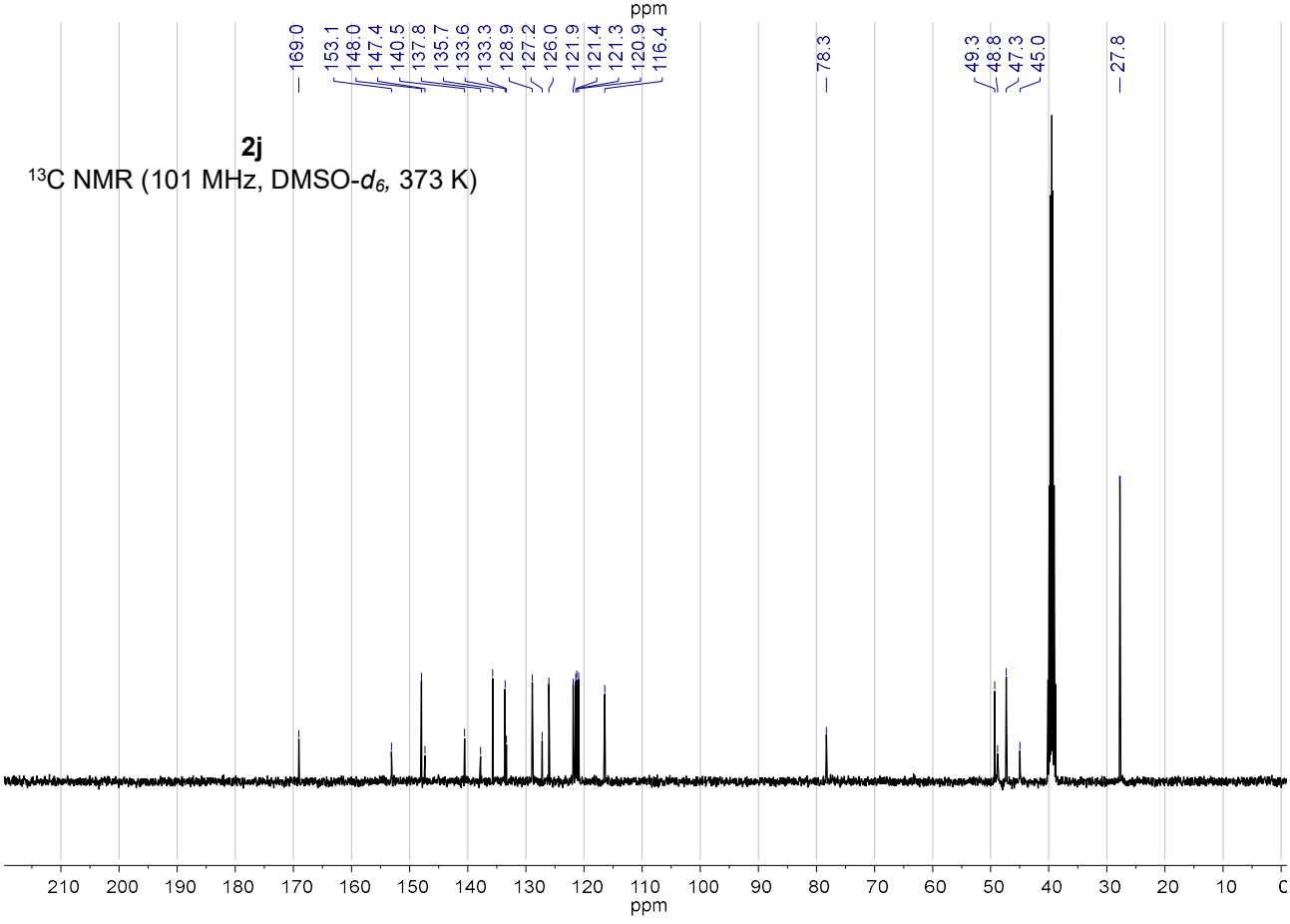
^{1}H NMR (400 MHz, DMSO-d_6, 373 K)

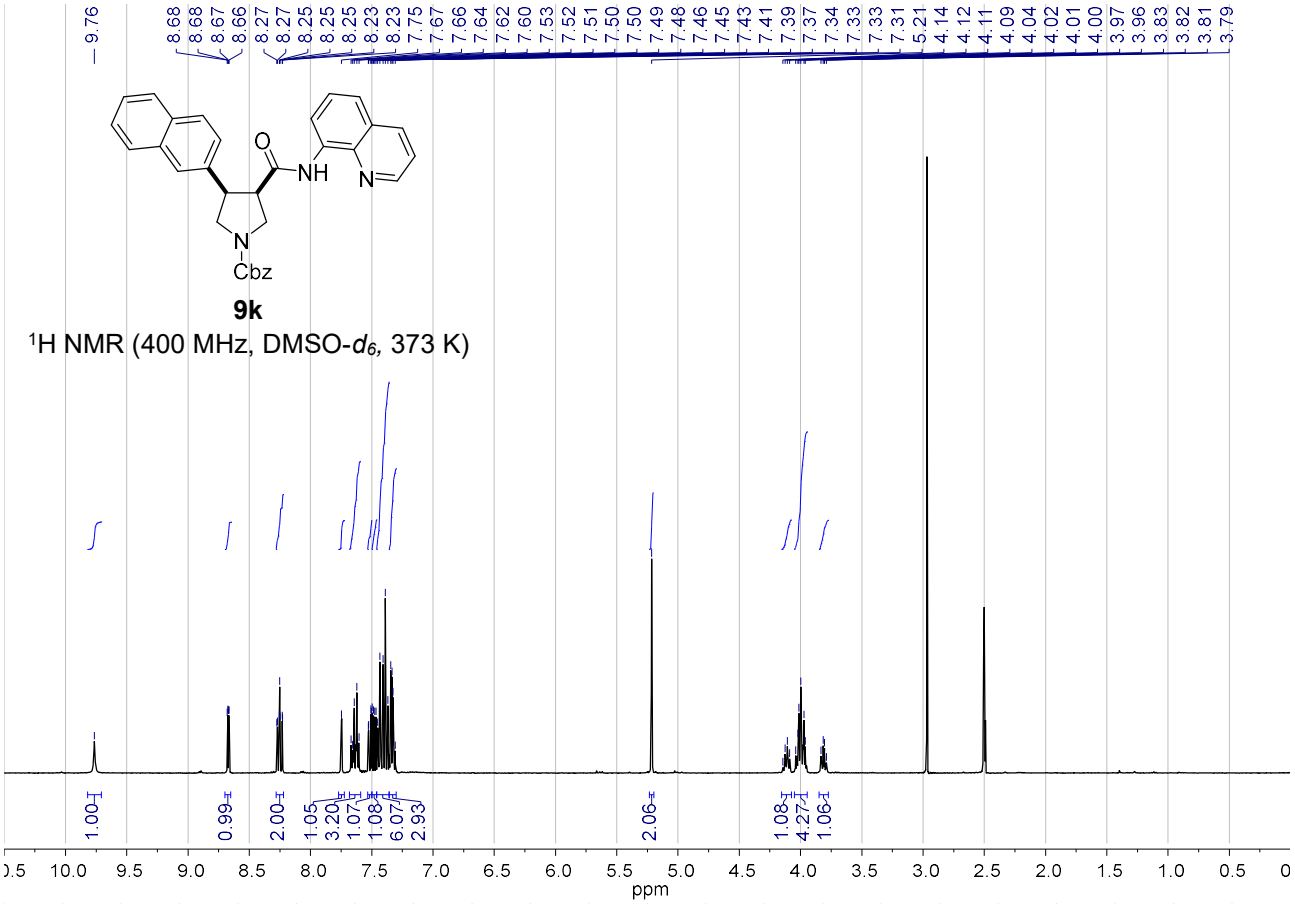


9i

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

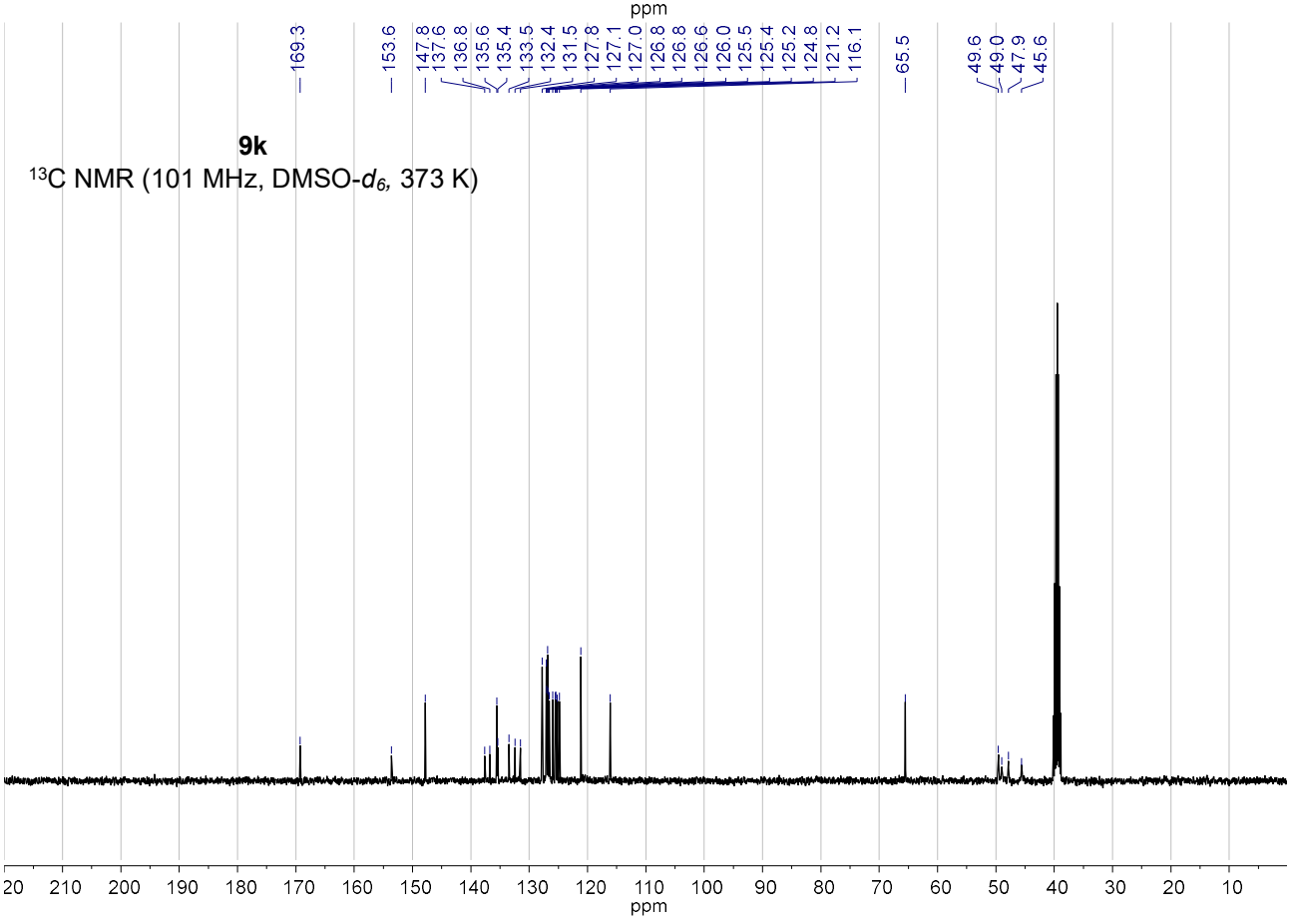

NO2
O
NH
N
N
Boc
2j
1H NMR (400 MHz, DMSO-d6, 373 K)
ppm


2j
13C NMR (101 MHz, DMSO-d6, 373 K)
ppm



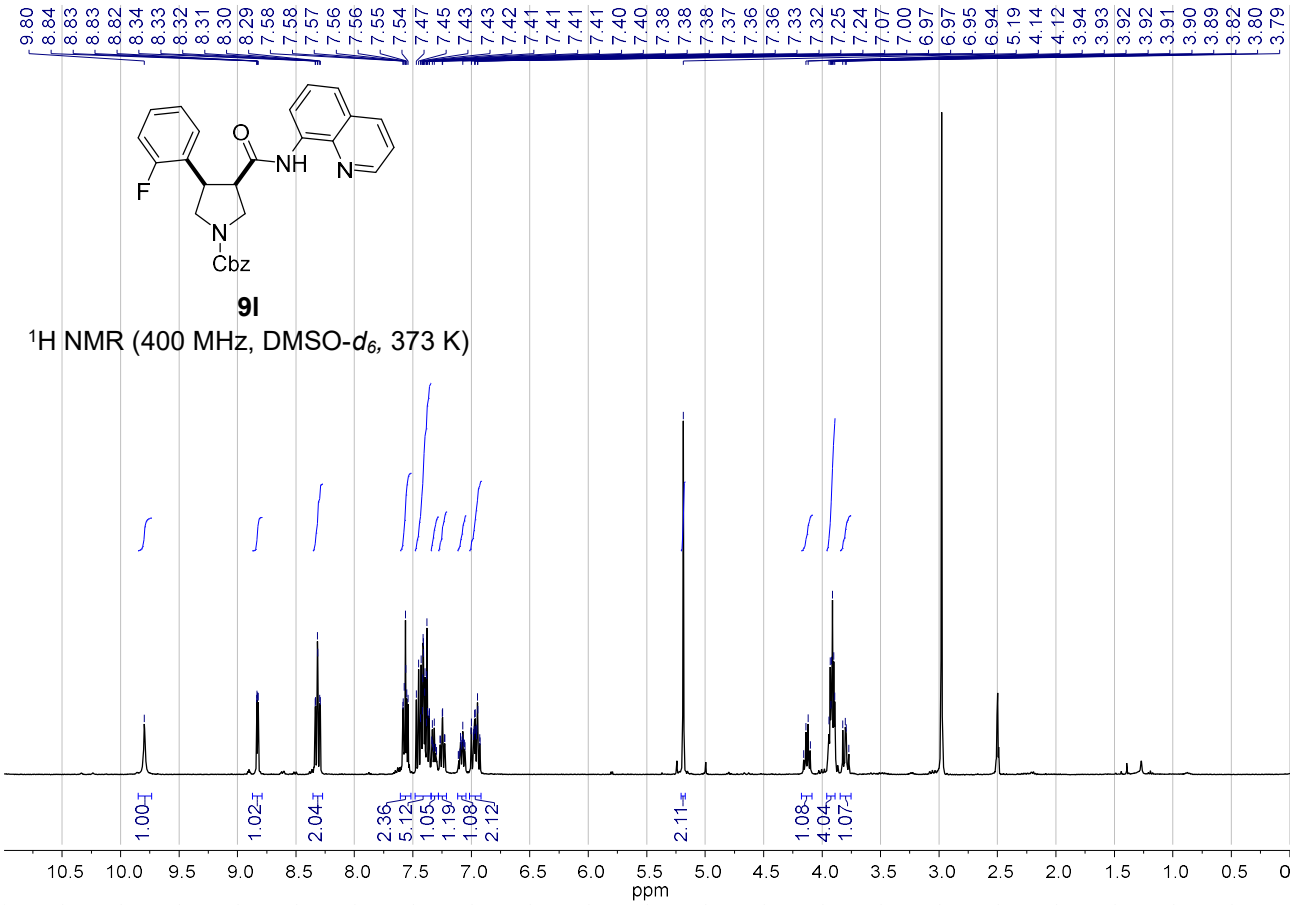
9k

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



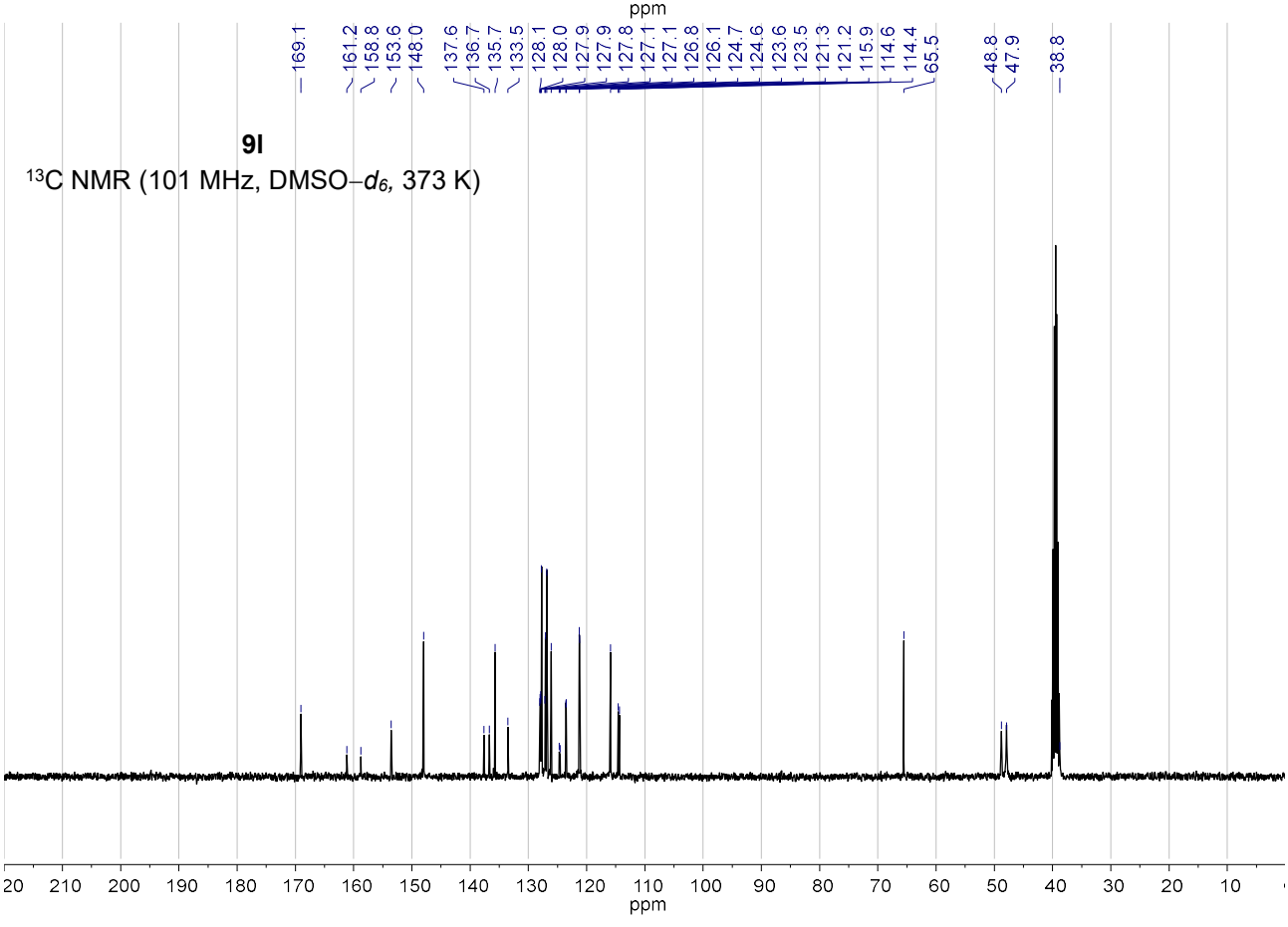
9k

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



9l

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

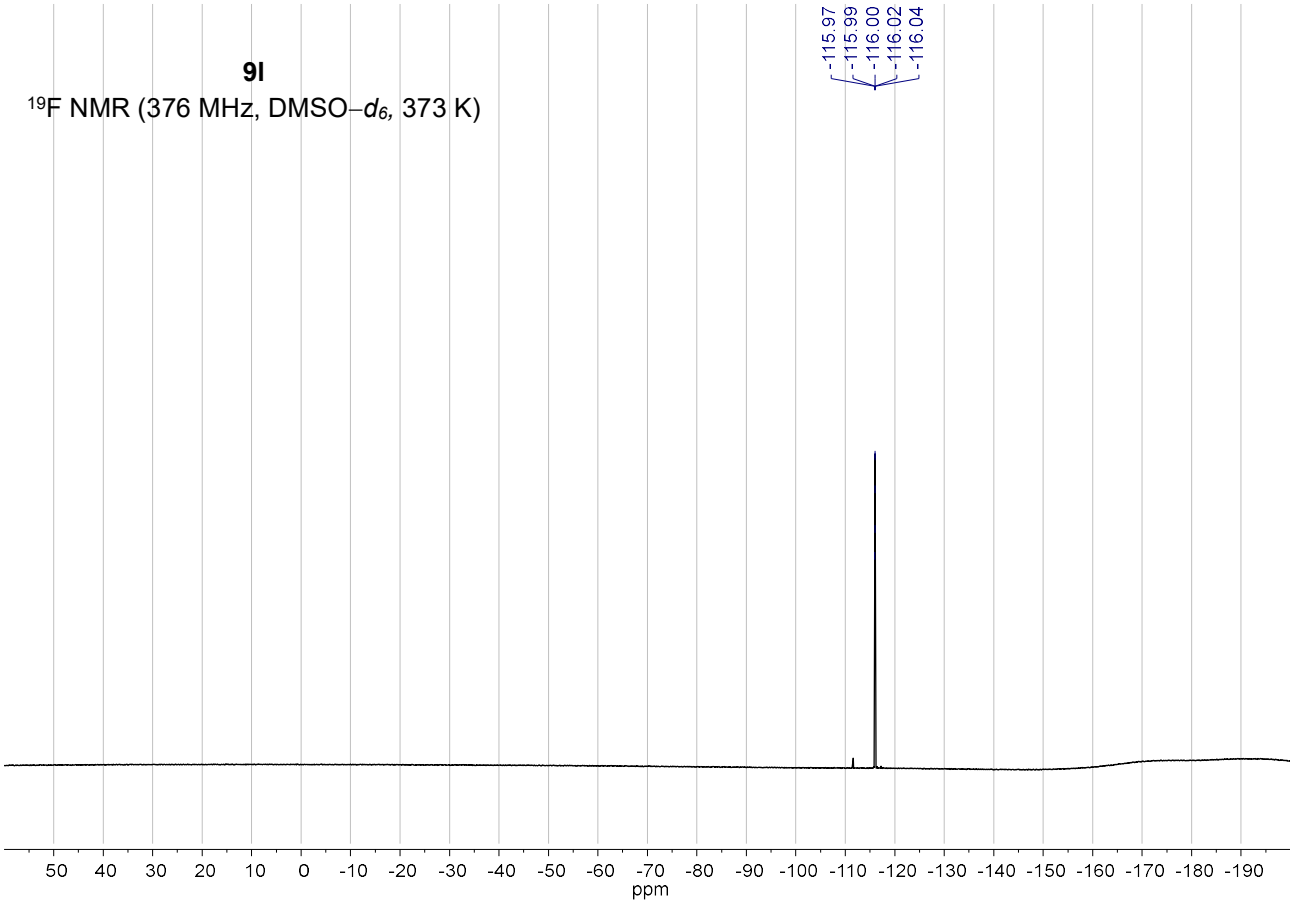


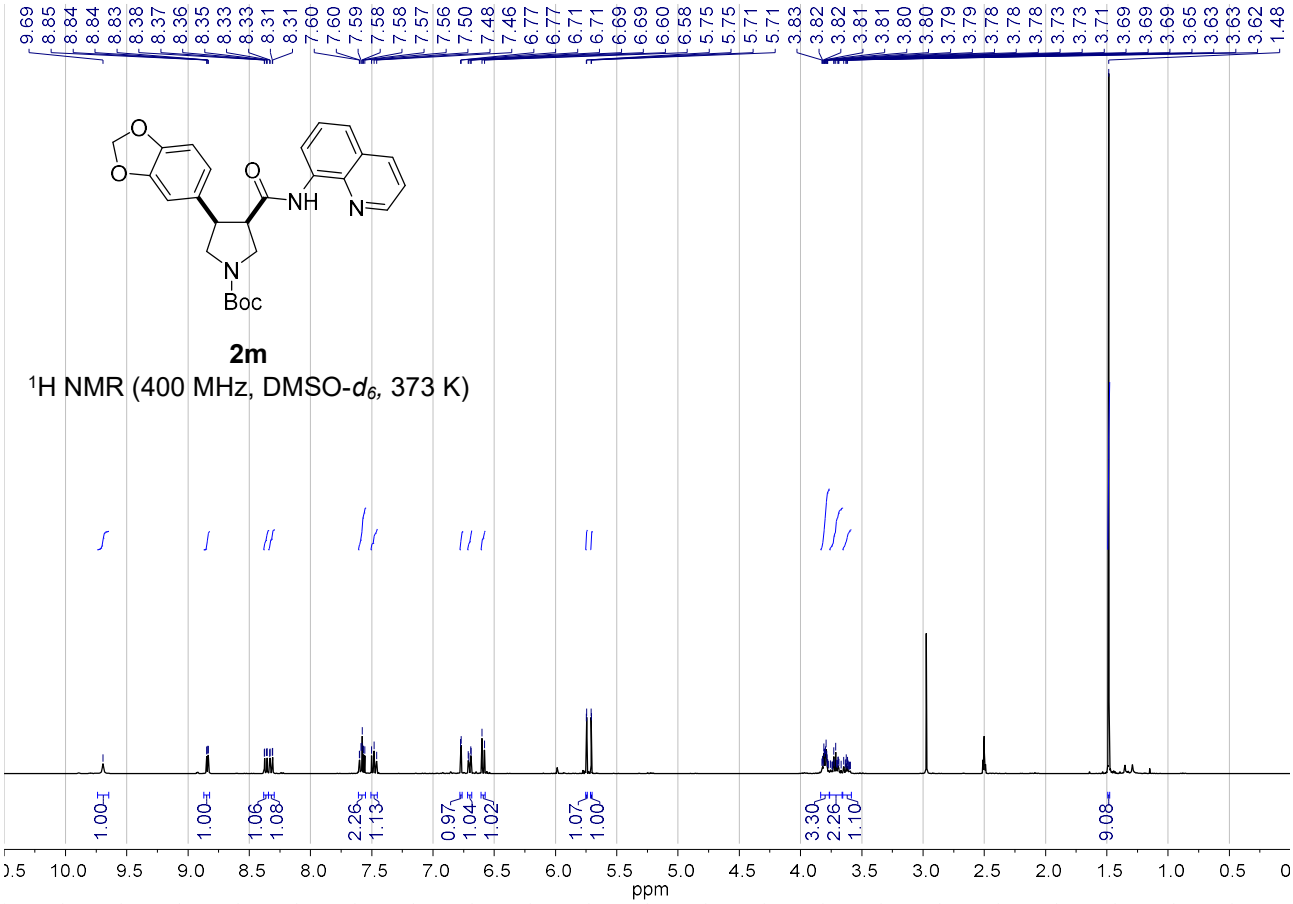
9l

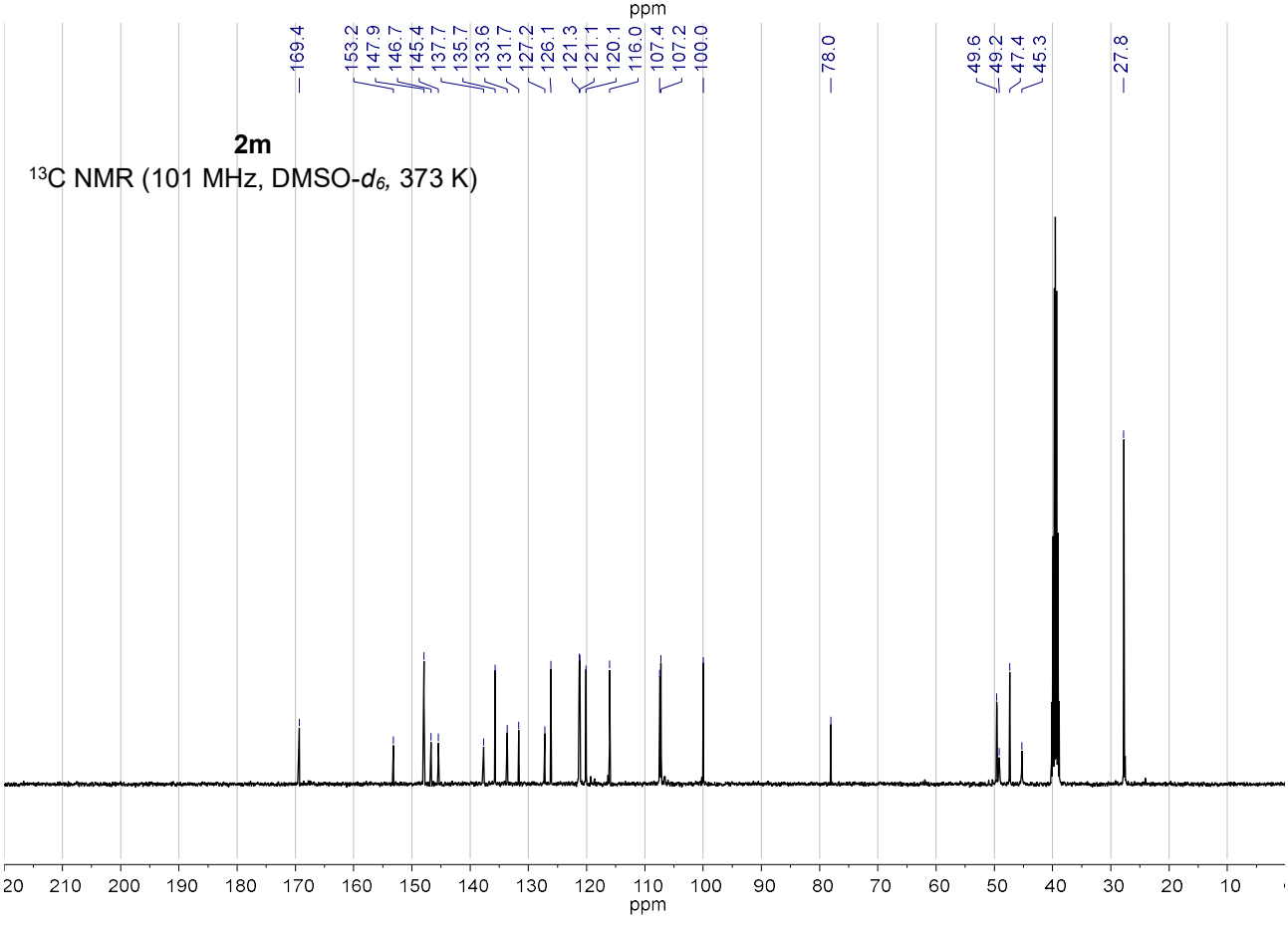
^{13}C NMR (101 MHz, DMSO–d_6, 373 K)

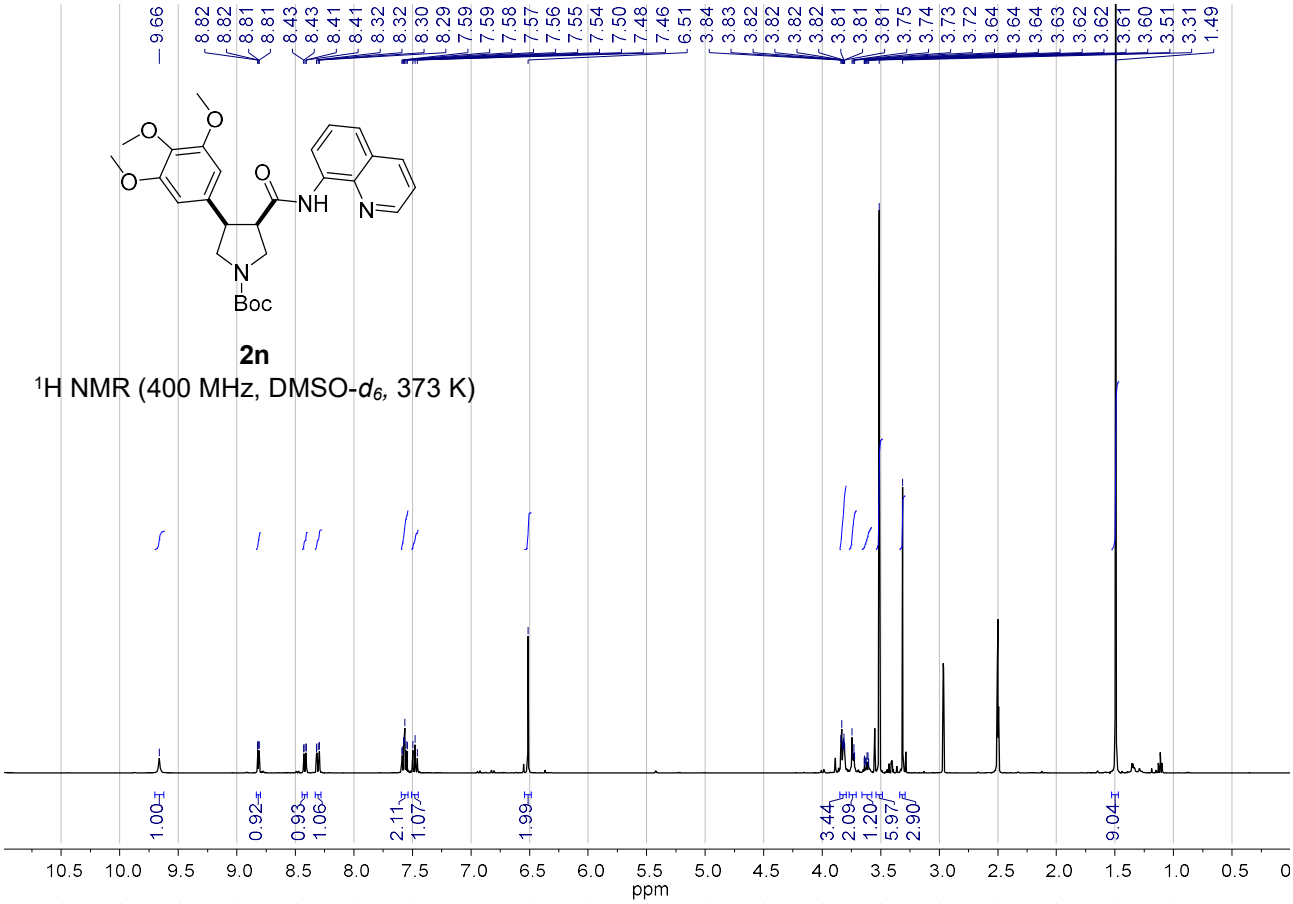
9l

^{19}F NMR (376 MHz, DMSO–d_6, 373 K)



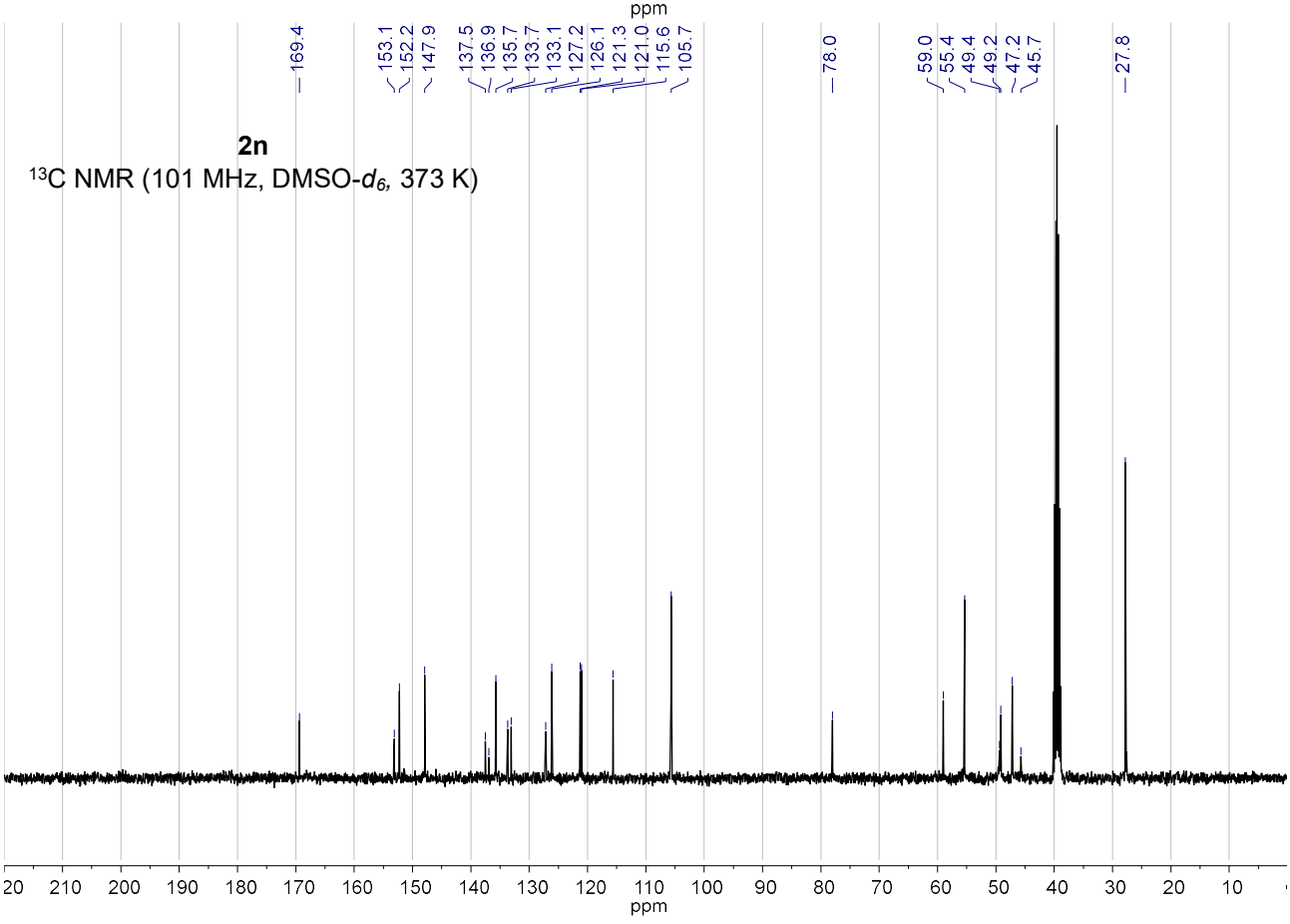

9.69 8.85 8.84 8.84 8.83 8.38 8.37 8.36 8.35 8.33 8.31 8.31 7.60 7.59 7.58 7.58 7.57 7.56 7.50 7.48 7.46 6.77 6.77 6.71 6.71 6.69 6.69 6.60 6.58 5.75 5.75 5.71 5.71 3.83 3.82 3.82 3.81 3.81 3.80 3.80 3.79 3.79 3.78 3.78 3.78 3.73 3.73 3.71 3.69 3.69 3.69 3.65 3.63 3.63 3.62 1.48
O
O
O
NH
N
N
Boc
2m
1H NMR (400 MHz, DMSO-d6, 373 K)
1.00 1.00 1.06 1.08 2.26 1.13 0.97 1.04 1.02 1.07 1.00 3.30 2.26 1.10 9.08
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0
ppm


169.4 153.2 147.9 146.7 145.4 137.7 135.7 133.6 131.7 127.2 126.1 121.3 121.1 120.1 116.0 107.4 107.2 100.0 78.0 49.6 49.2 47.4 45.3 27.8
2m
13C NMR (101 MHz, DMSO-d6, 373 K)
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
ppm



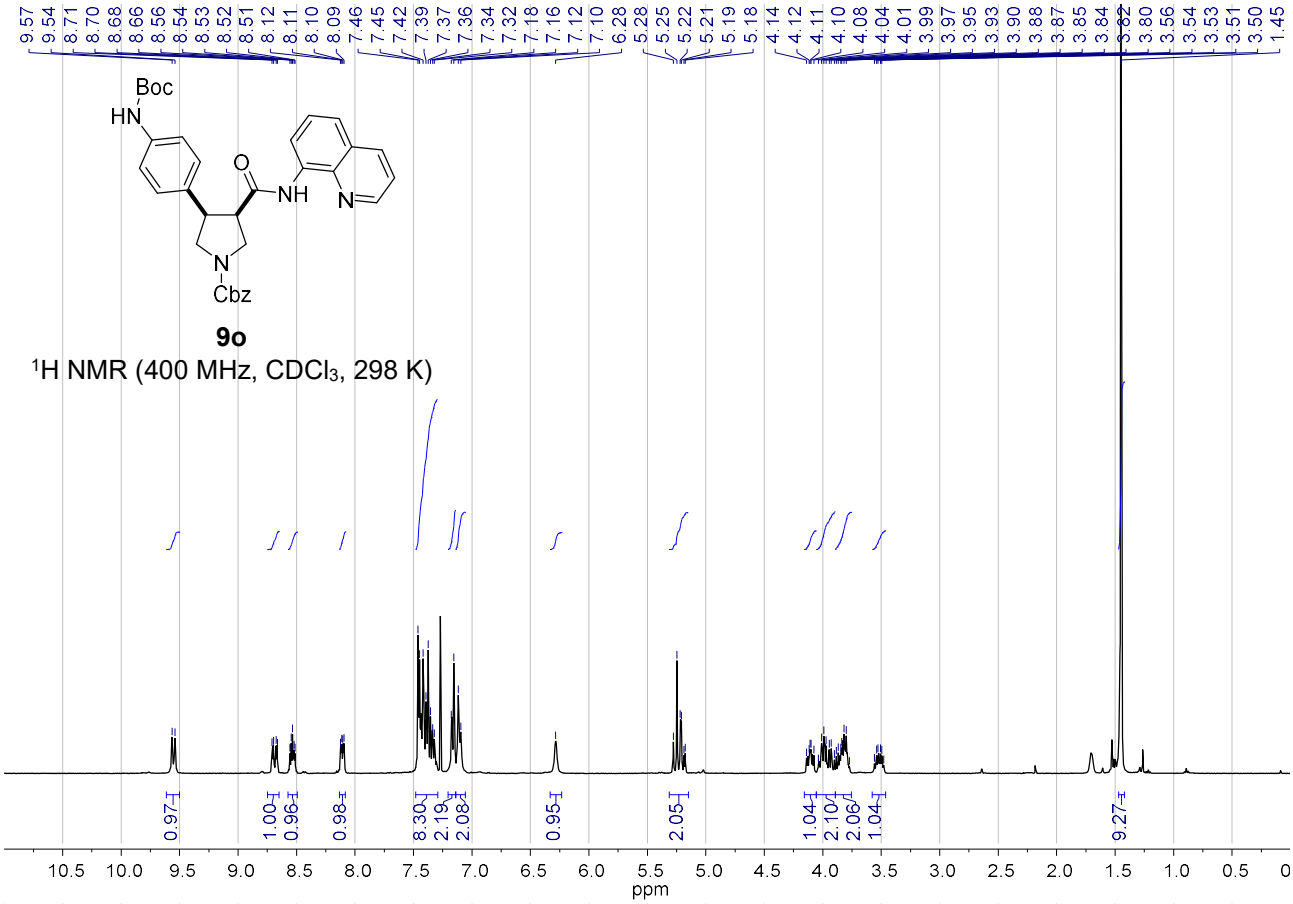
2n

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



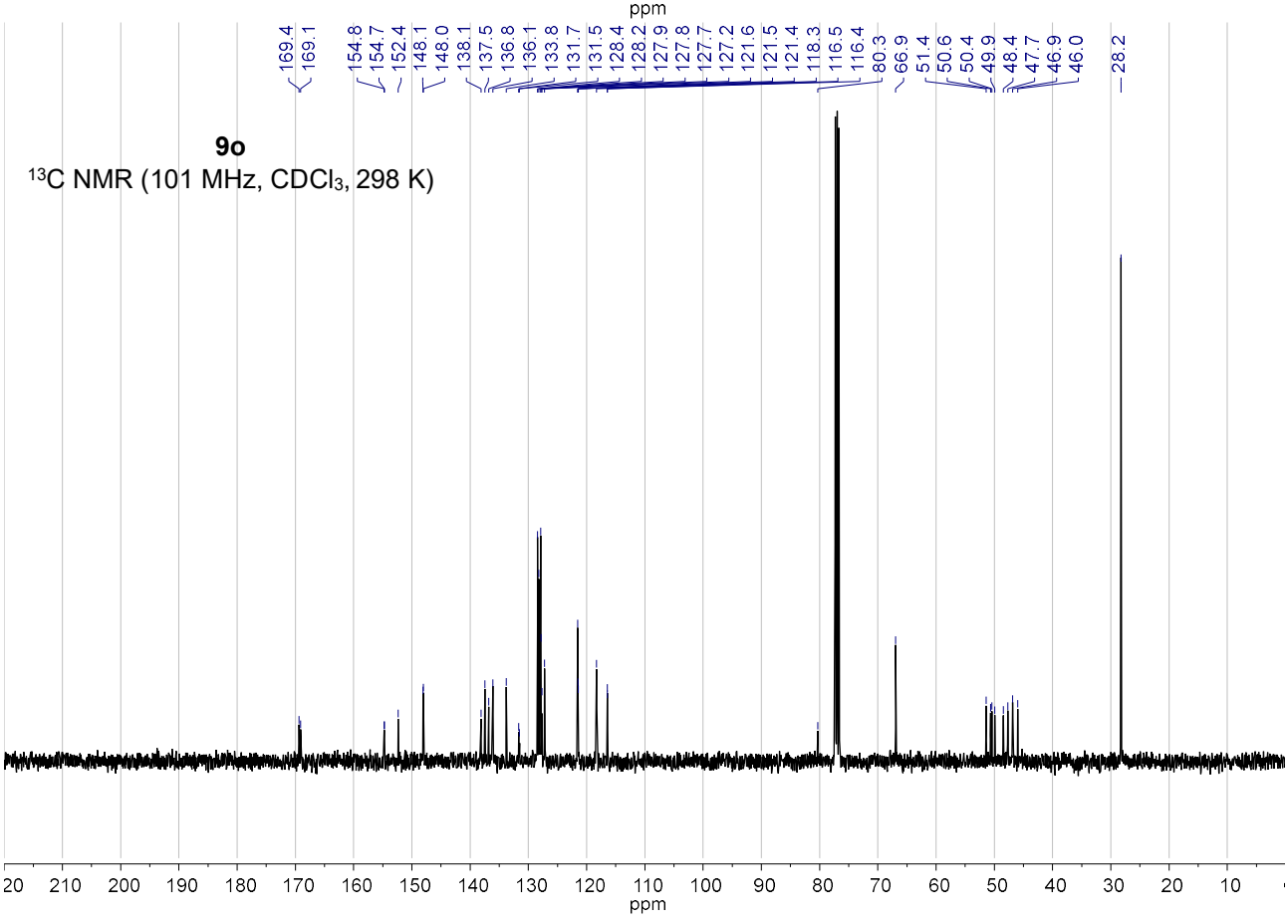
2n

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



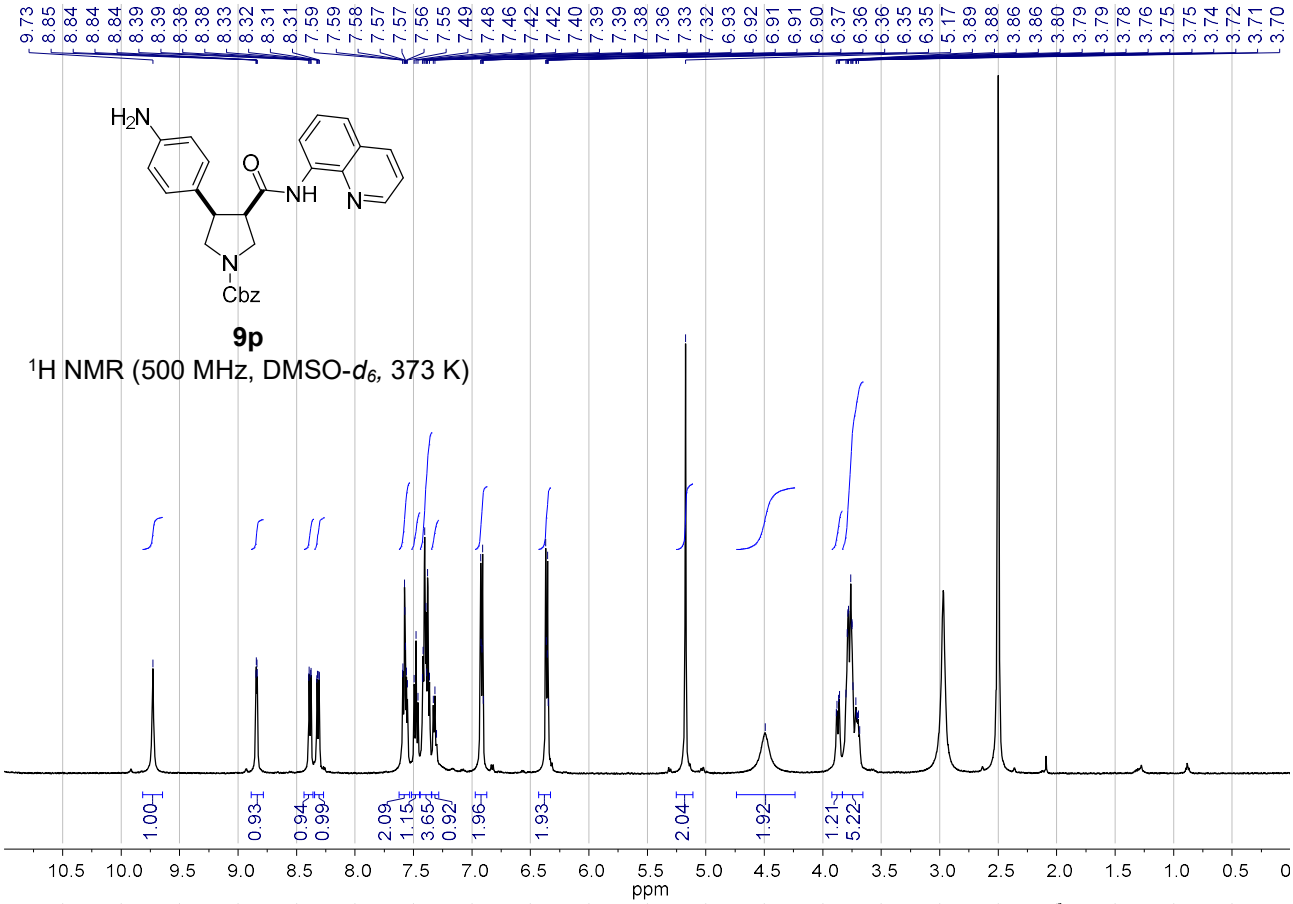
9o

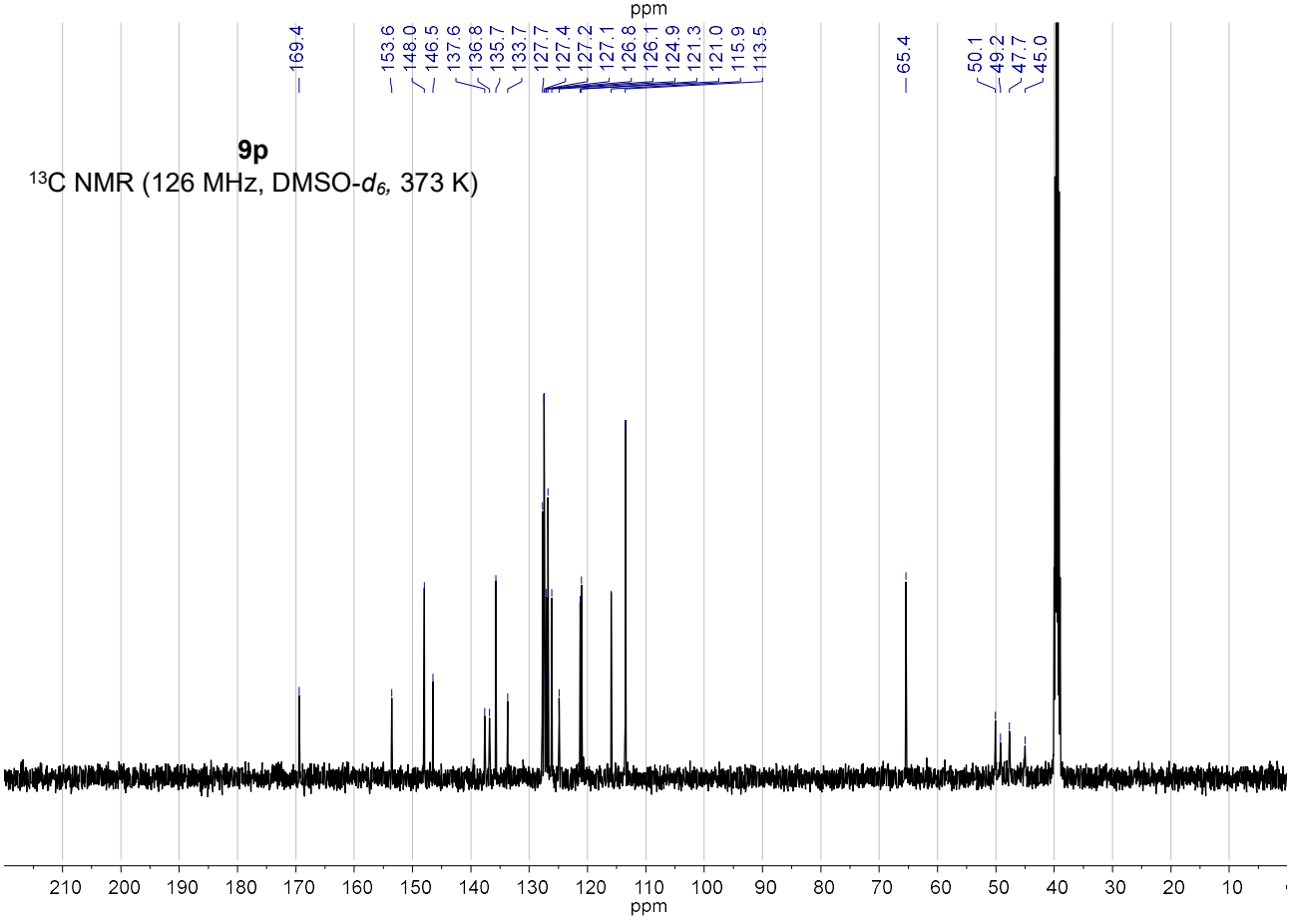
^{1}H NMR (400 MHz, $CDCl_3$, 298 K)

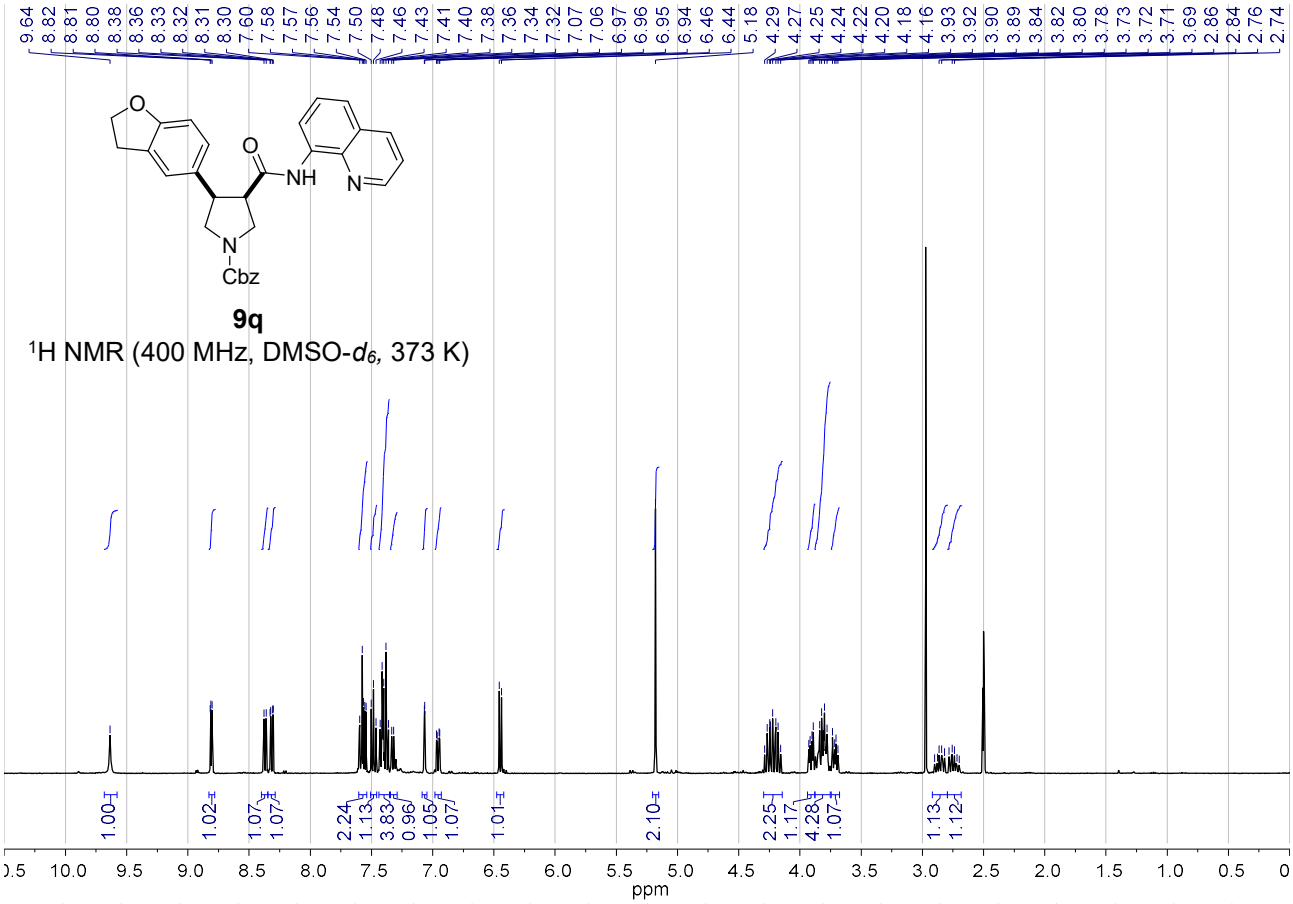


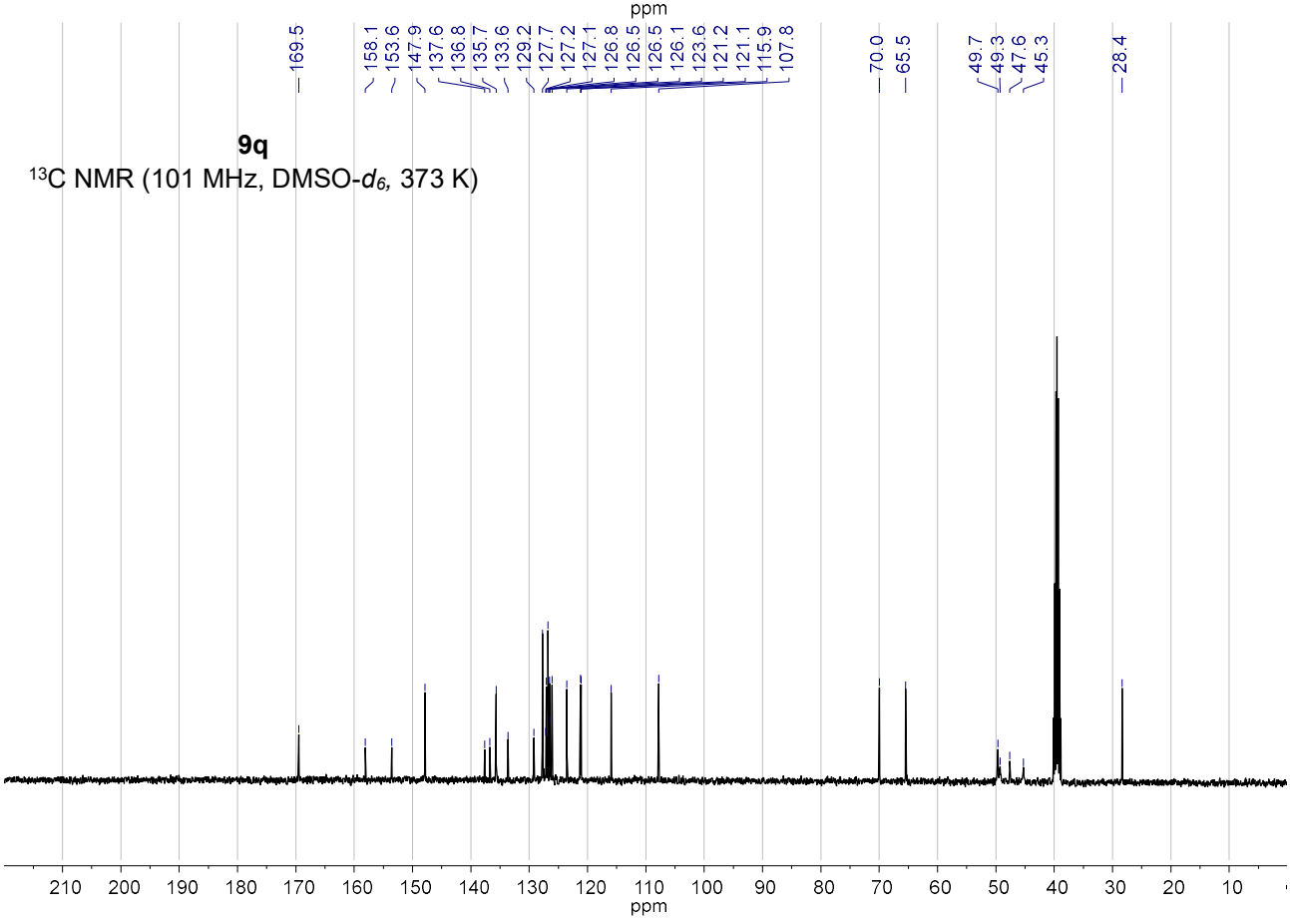
9o

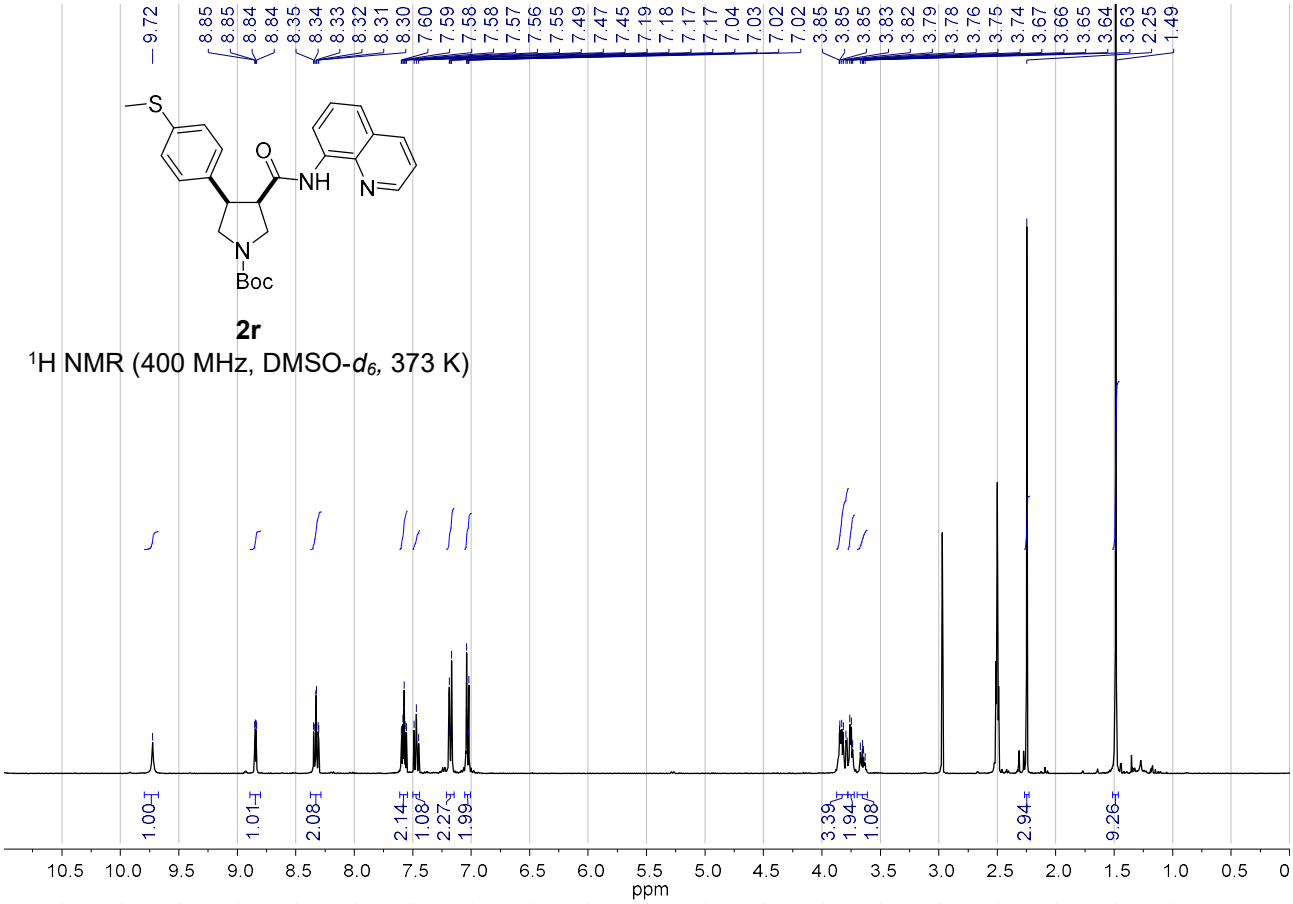
^{13}C NMR (101 MHz, $CDCl_3$, 298 K)


9.73 8.85 8.84 8.84 8.84 8.39 8.39 8.38 8.38 8.33 8.32 8.31 8.31 7.59 7.59 7.58 7.57 7.57 7.56 7.55 7.49 7.48 7.46 7.42 7.42 7.40 7.39 7.39 7.38 7.36 7.33 7.32 6.93 6.92 6.91 6.91 6.90 6.37 6.36 6.36 6.35 6.35 5.17 3.89 3.88 3.86 3.86 3.80 3.79 3.79 3.78 3.76 3.75 3.75 3.74 3.72 3.71 3.70
H2N
O
NH
N
N
Cbz
9p
1H NMR (500 MHz, DMSO-d6, 373 K)
1.00 0.93 0.94 0.99 2.09 1.15 3.65 0.92 1.96 1.93 2.04 1.92 1.21 5.22
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0
ppm


169.4
153.6 148.0 146.5 137.6 136.8 135.7 133.7 127.7 127.4 127.2 127.1 126.8 126.1 124.9 121.3 121.0 115.9 113.5
65.4
50.1 49.2 47.7 45.0
9p
13C NMR (126 MHz, DMSO-d6, 373 K)
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
ppm

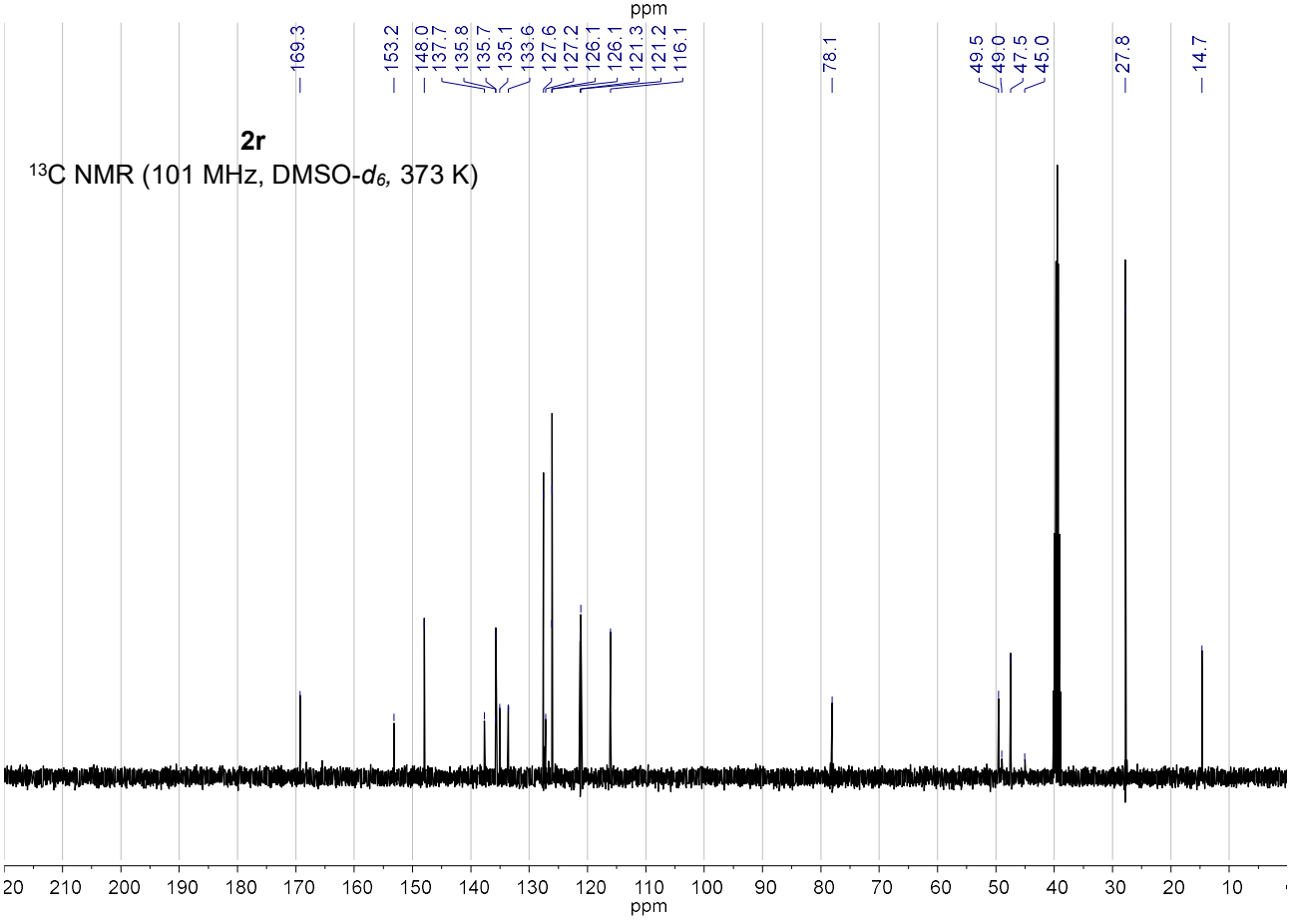

9.64 8.82 8.81 8.80 8.38 8.36 8.33 8.32 8.31 8.30 7.60 7.58 7.57 7.56 7.54 7.50 7.48 7.46 7.43 7.41 7.40 7.38 7.36 7.34 7.32 7.07 7.06 6.97 6.96 6.95 6.94 6.46 6.44 5.18 4.29 4.27 4.25 4.24 4.22 4.20 4.18 4.16 3.93 3.92 3.90 3.89 3.84 3.82 3.80 3.78 3.73 3.72 3.71 3.69 2.86 2.84 2.76 2.74
O
O
NH
N
N
Cbz
9q
1H NMR (400 MHz, DMSO-d6, 373 K)
1.00 1.02 1.07 1.07 2.24 1.13 3.83 0.96 1.05 1.07 1.01 2.10 2.25 1.17 4.28 1.07 1.13 1.12
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0
ppm


169.5
158.1 153.6 147.9 137.6 136.8 135.7 133.6 129.2 127.7 127.2 127.1 126.8 126.5 126.5 126.1 123.6 121.2 121.1 115.9 107.8
70.0 65.5
49.7 49.3 47.6 45.3
28.4
9q
13C NMR (101 MHz, DMSO-d6, 373 K)
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
ppm



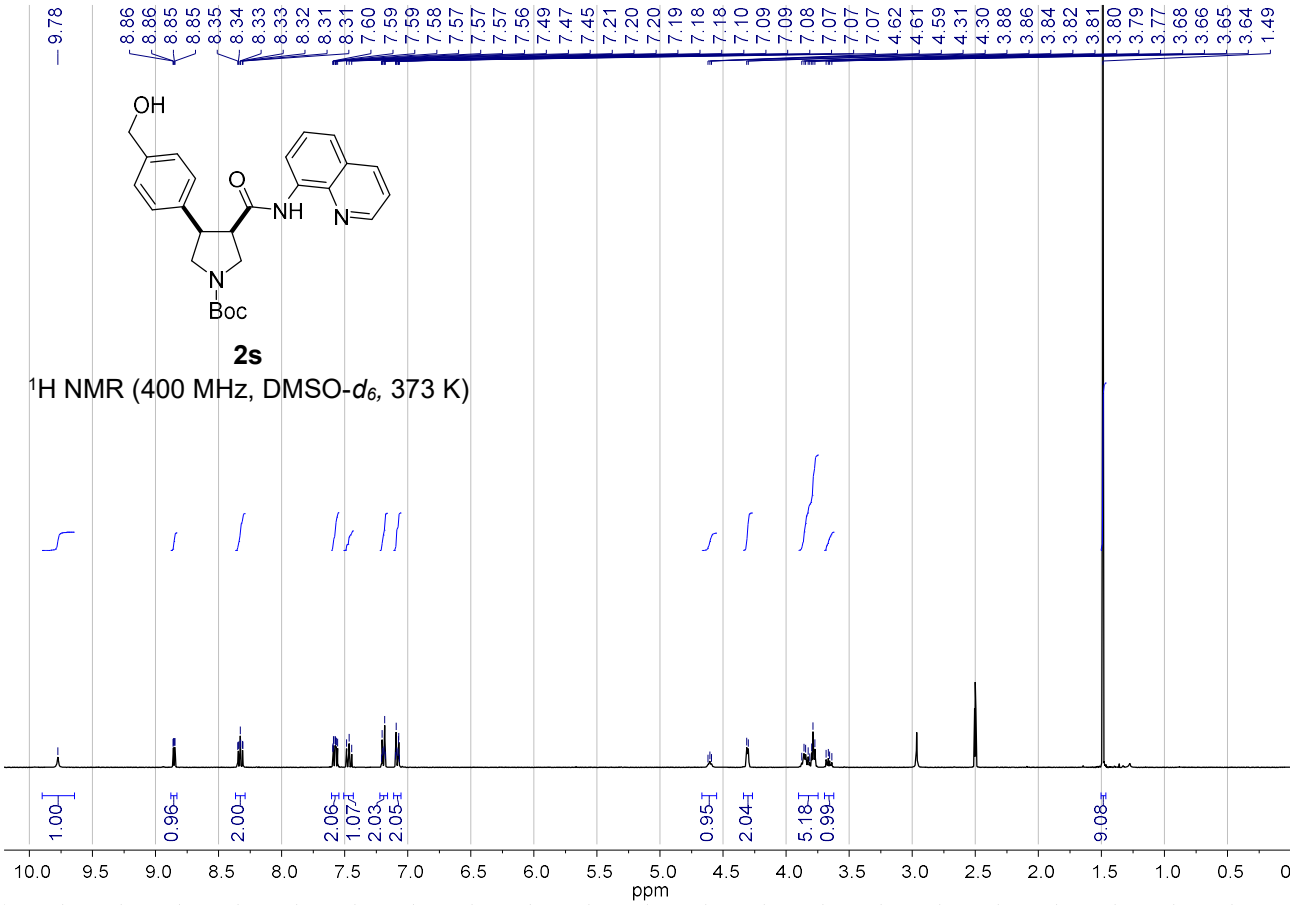
2r

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



2r

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

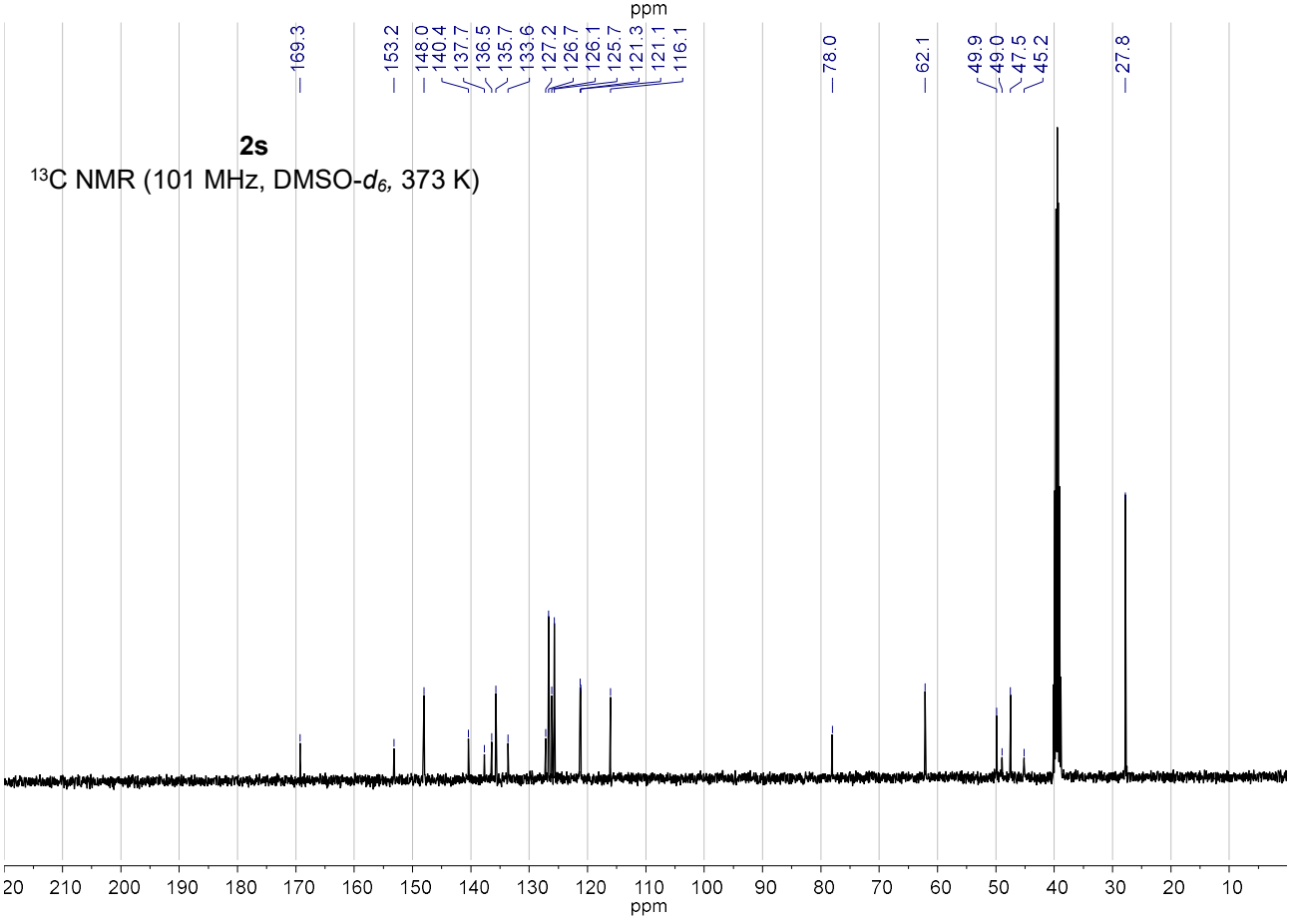


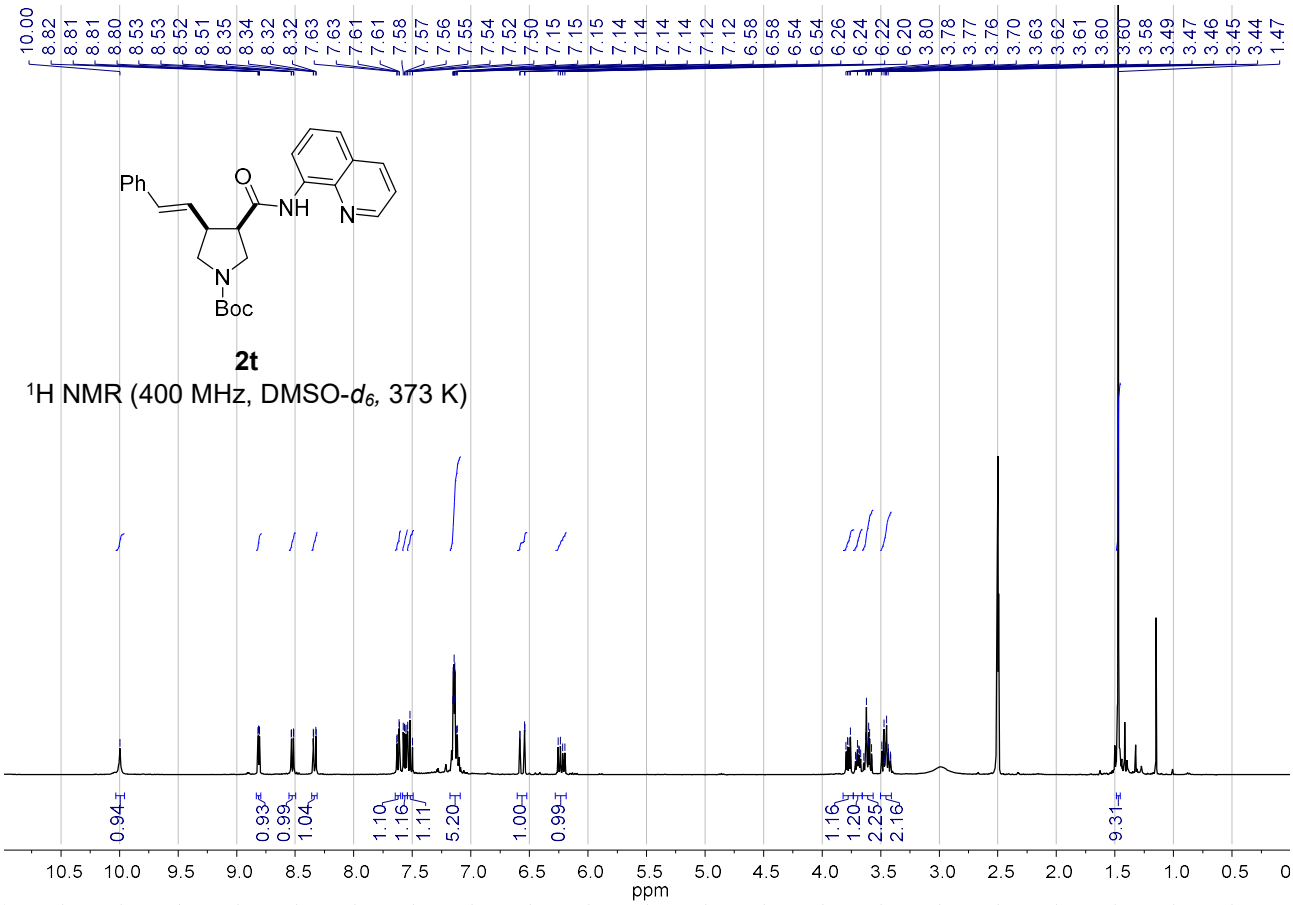
2s

^{1}H NMR (400 MHz, DMSO-*d*$_6$, 373 K)

2s

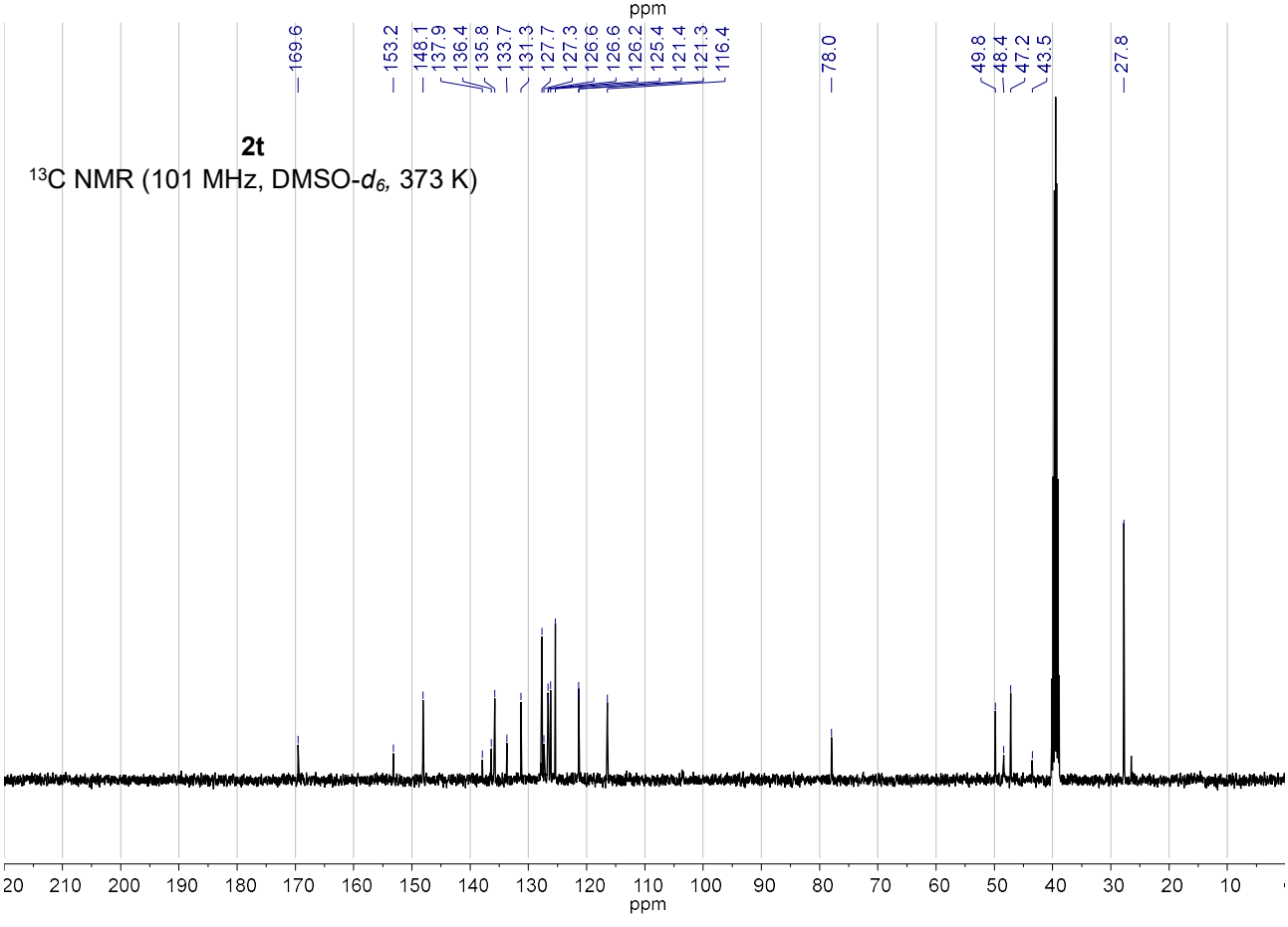
^{13}C NMR (101 MHz, DMSO-*d*$_6$, 373 K)





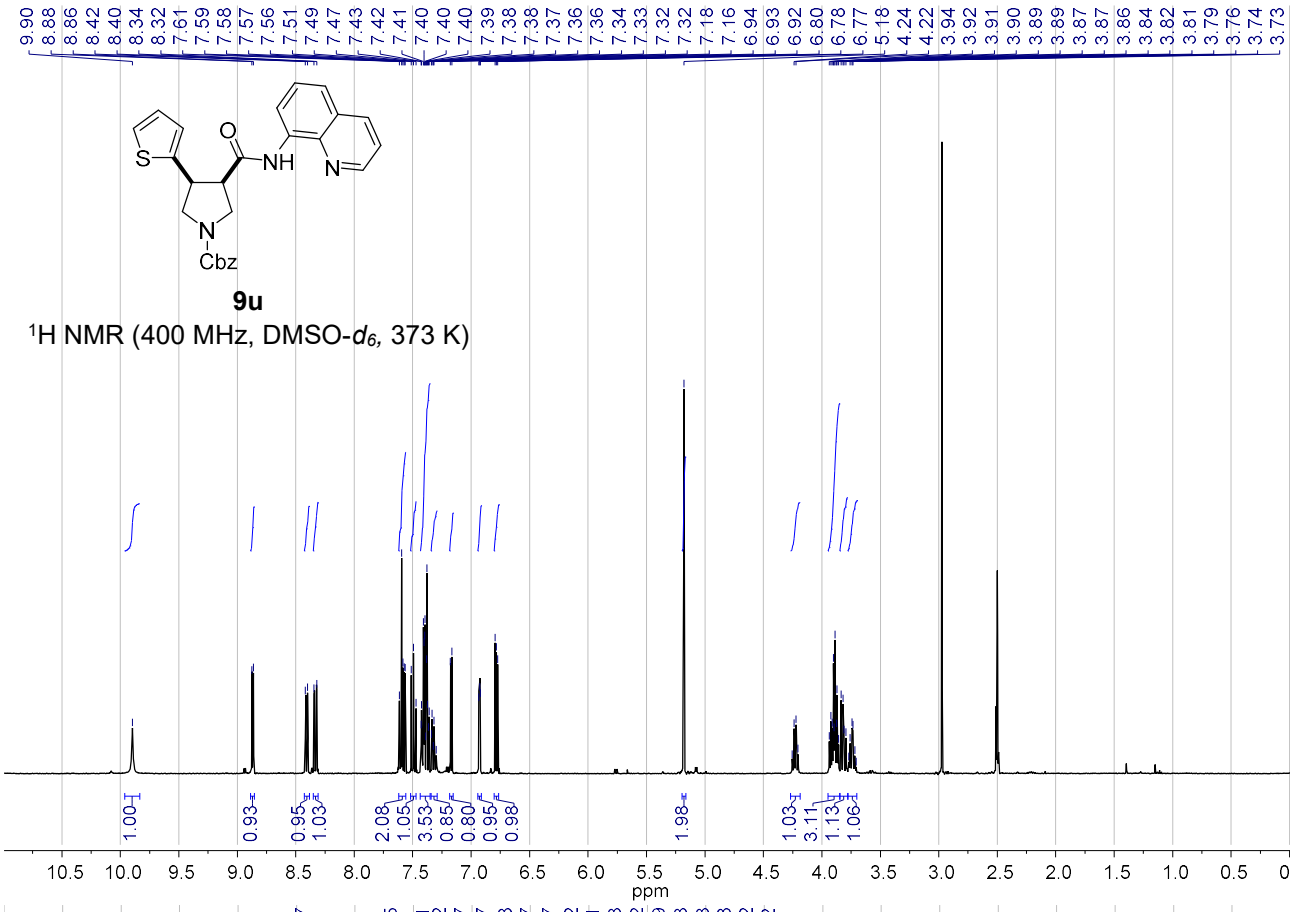
2t

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



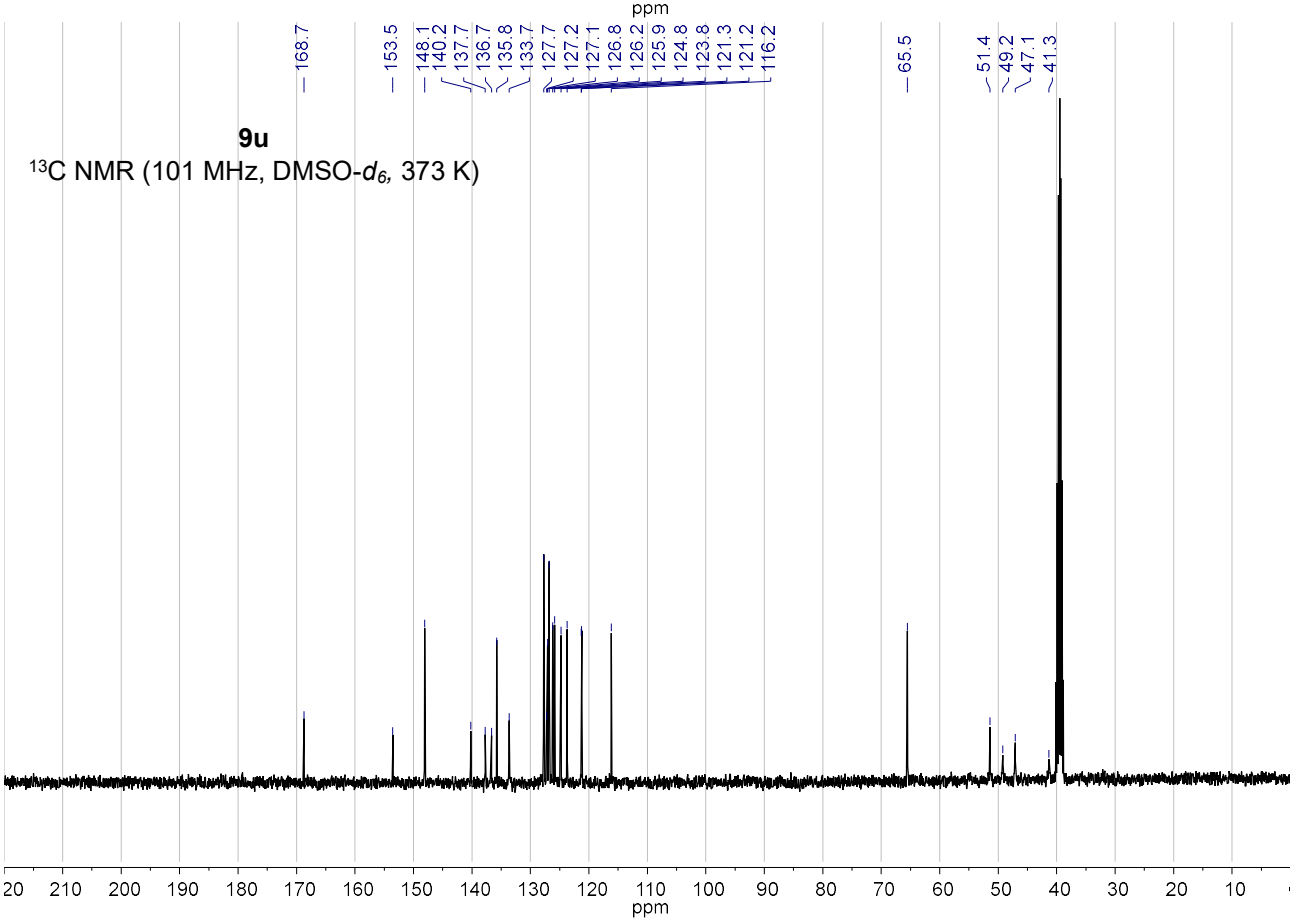
2t

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



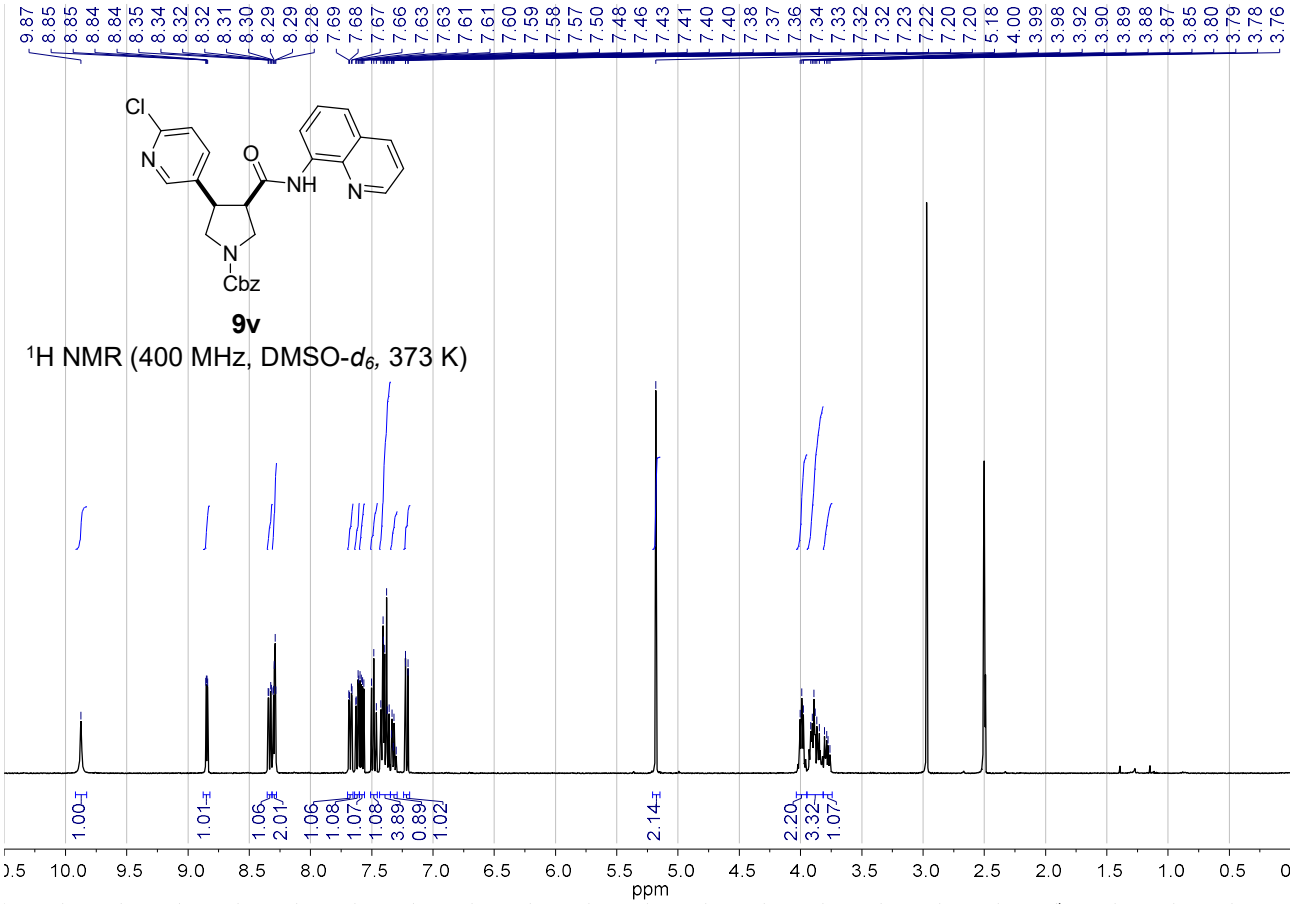
9u

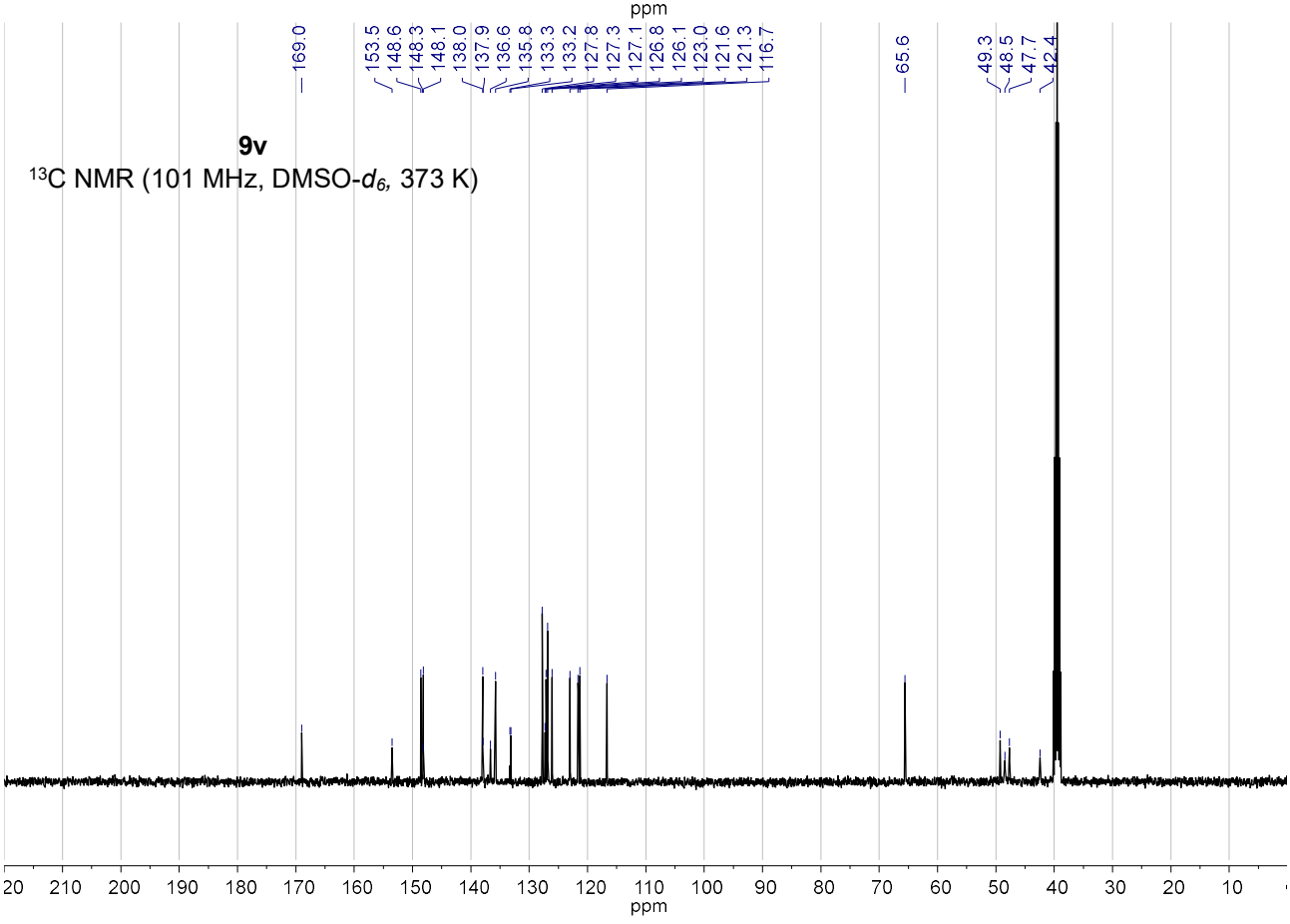
^{1}H NMR (400 MHz, DMSO-d_6, 373 K)

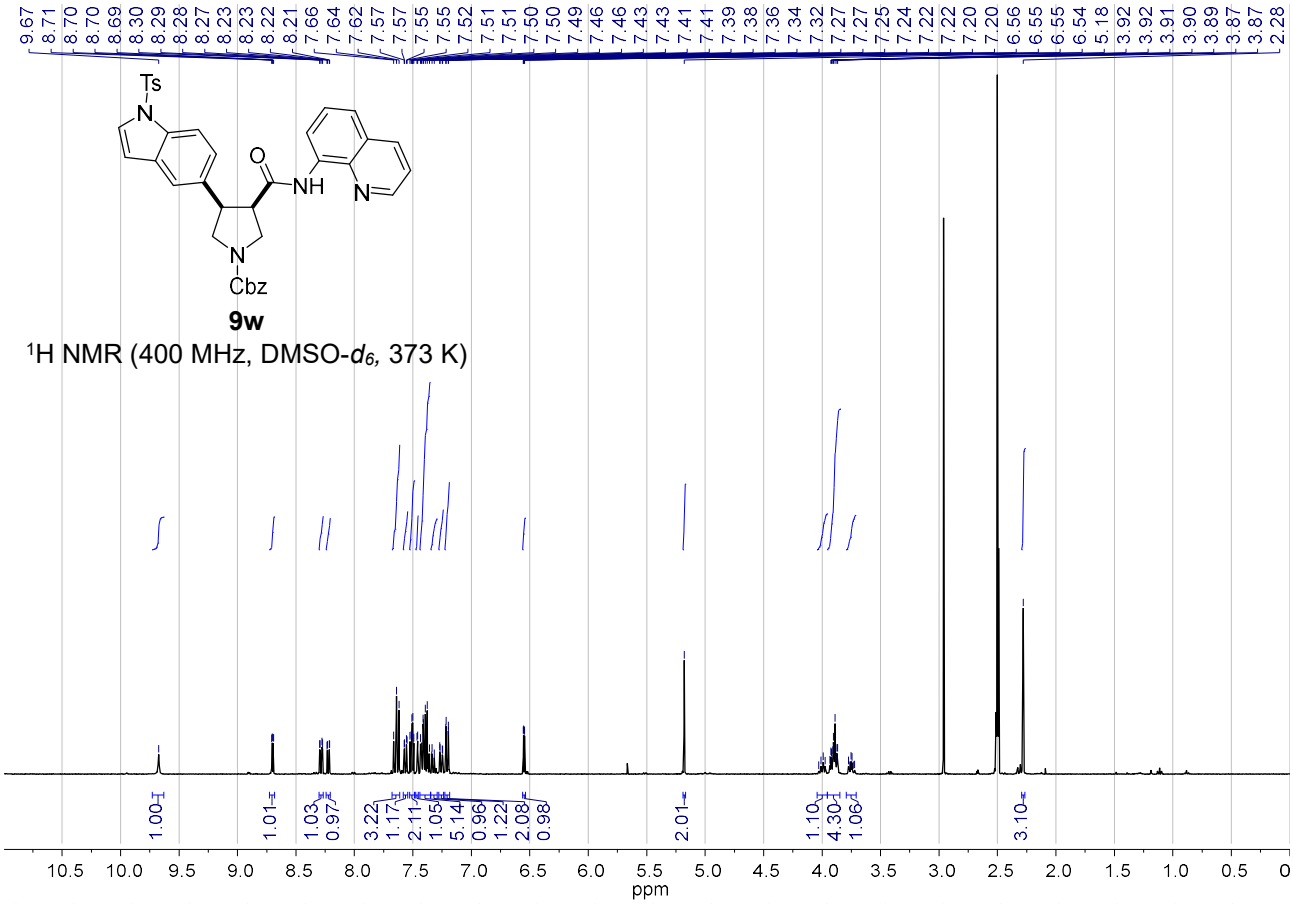


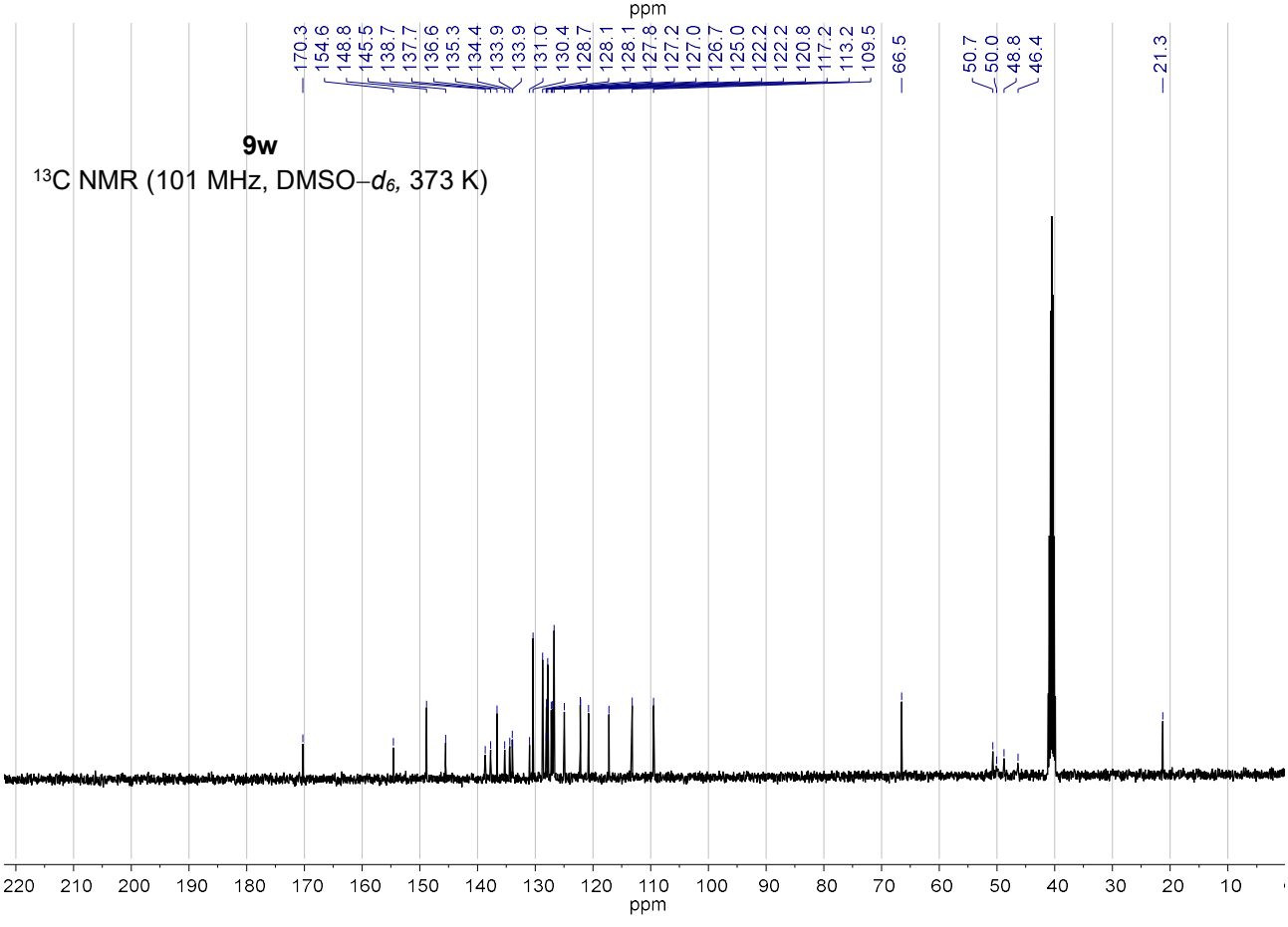
9u

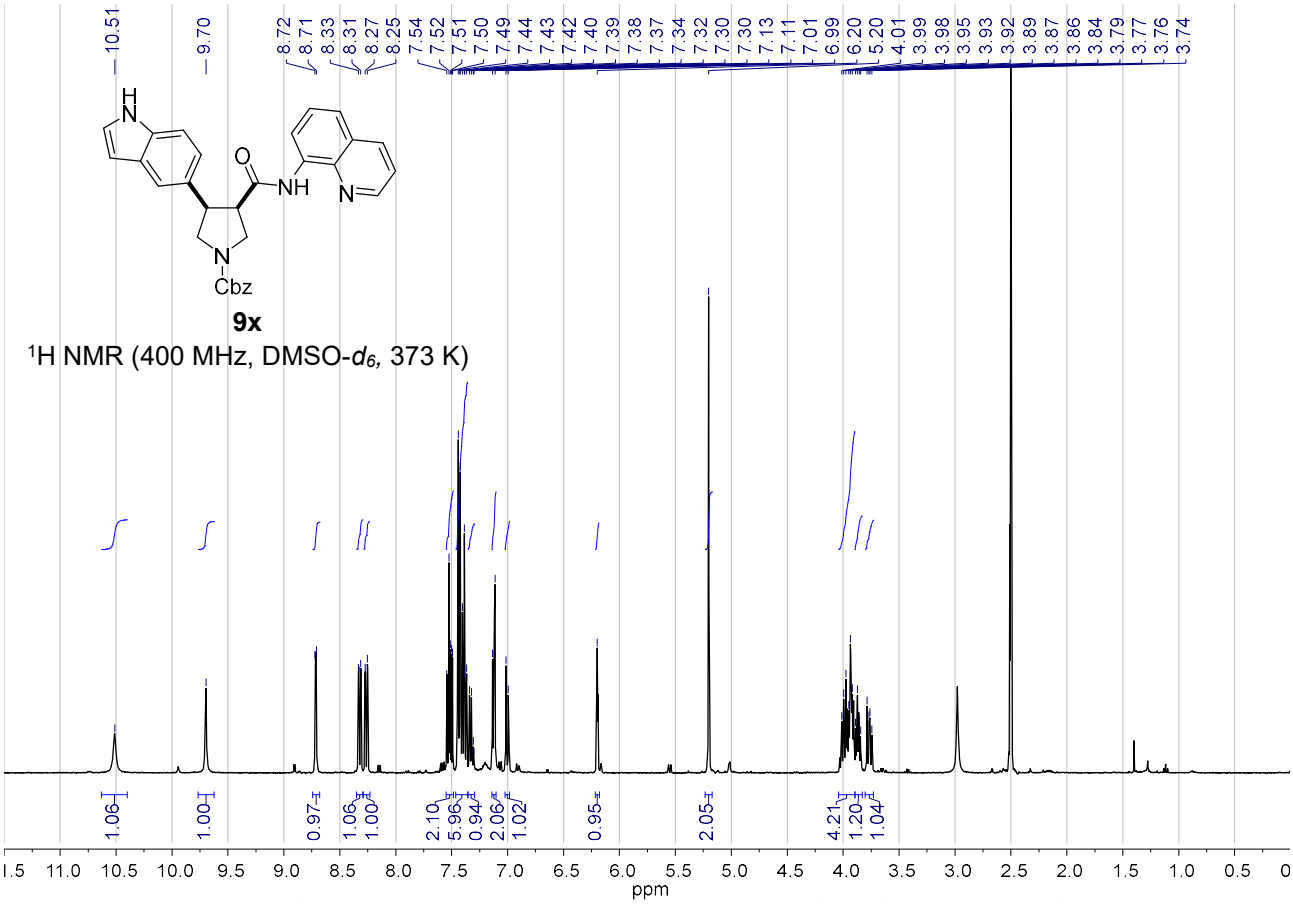
^{13}C NMR (101 MHz, DMSO-d_6, 373 K)


9.87 8.85 8.85 8.84 8.84 8.35 8.34 8.32 8.32 8.31 8.30 8.29 8.29 8.28 7.69 7.68 7.67 7.66 7.63 7.61 7.61 7.60 7.59 7.58 7.57 7.50 7.48 7.46 7.43 7.41 7.40 7.40 7.38 7.37 7.36 7.34 7.33 7.32 7.32 7.23 7.22 7.20 7.20 5.18 4.00 3.99 3.98 3.92 3.90 3.89 3.88 3.87 3.85 3.80 3.79 3.78 3.76
Cl
N
O
NH
N
N
Cbz
9v
1H NMR (400 MHz, DMSO-d6, 373 K)
1.00 1.01 1.06 2.01 1.06 1.08 1.07 1.08 3.89 0.89 1.02 2.14 2.20 3.32 1.07
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0
ppm


169.0
153.5 148.6 148.3 148.1 138.0 137.9 136.6 135.8 133.3 133.2 127.8 127.3 127.1 126.8 126.1 123.0 121.6 121.3 116.7
65.6
49.3 48.5 47.7 42.4
9v
13C NMR (101 MHz, DMSO-d6, 373 K)
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
ppm

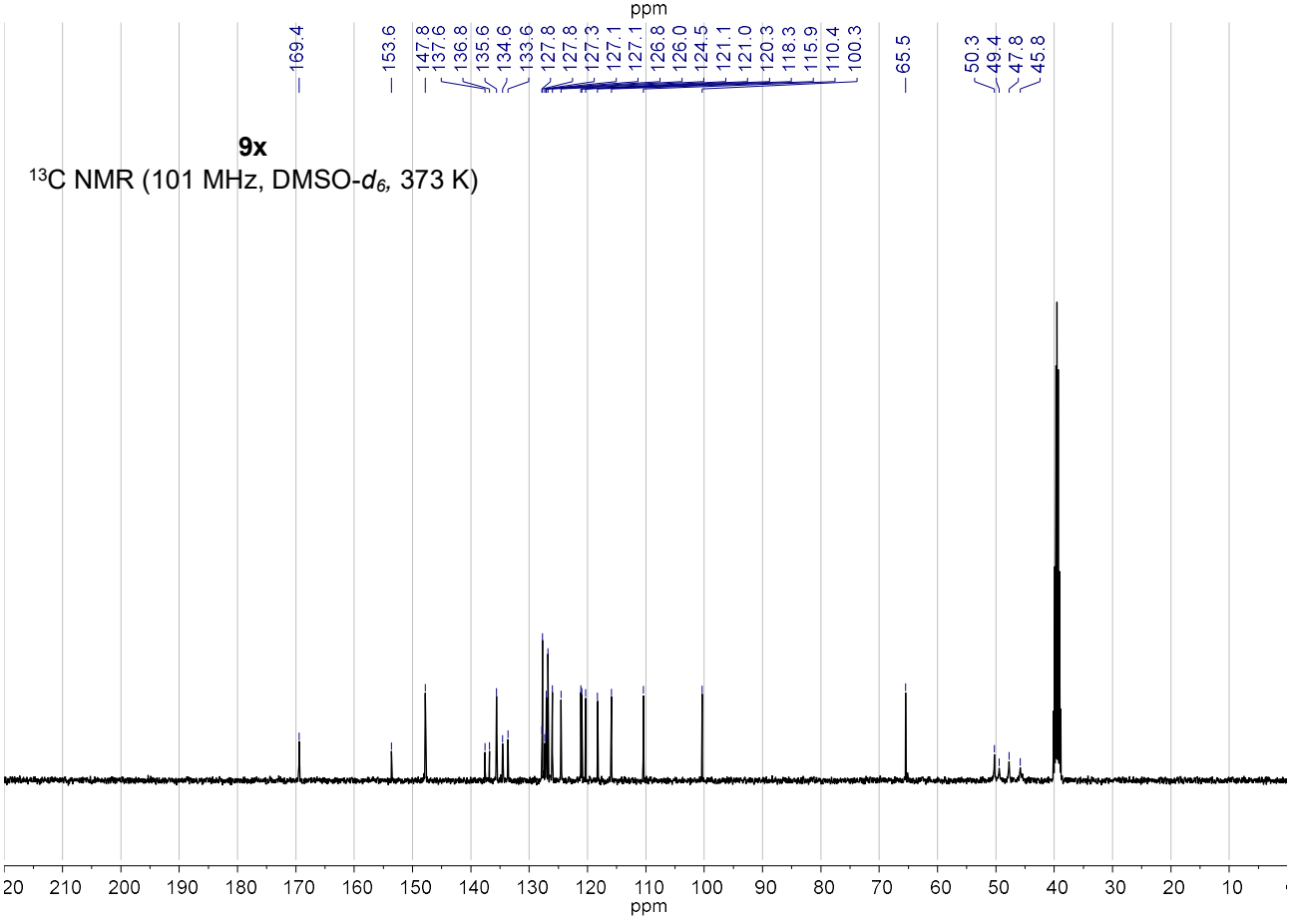

Ts
N
O
NH
N
N
Cbz
9w
^{1}H NMR (400 MHz, DMSO-d_6, 373 K)
ppm


9w
^{13}C NMR (101 MHz, DMSO–d_6, 373 K)
ppm



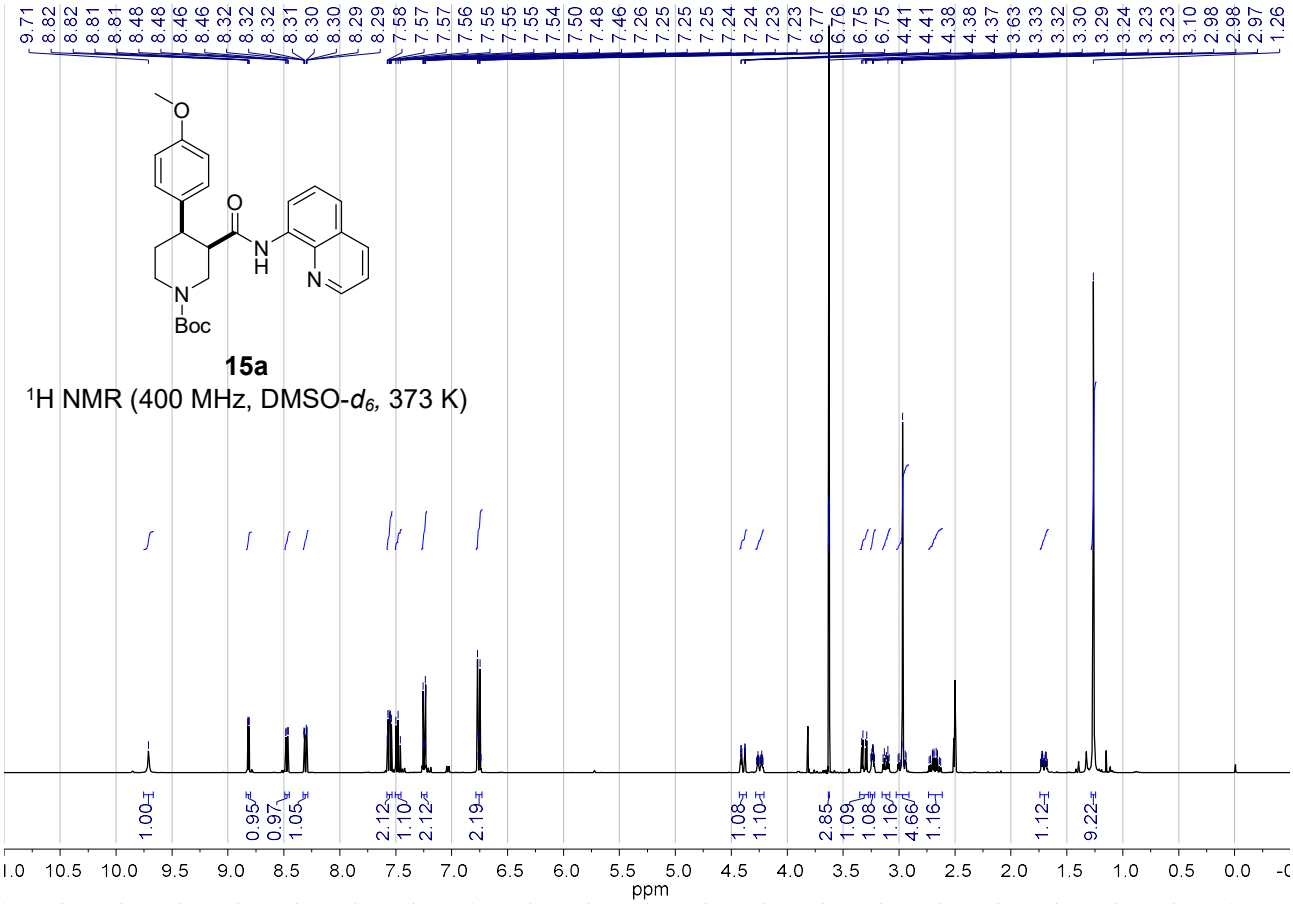
9x

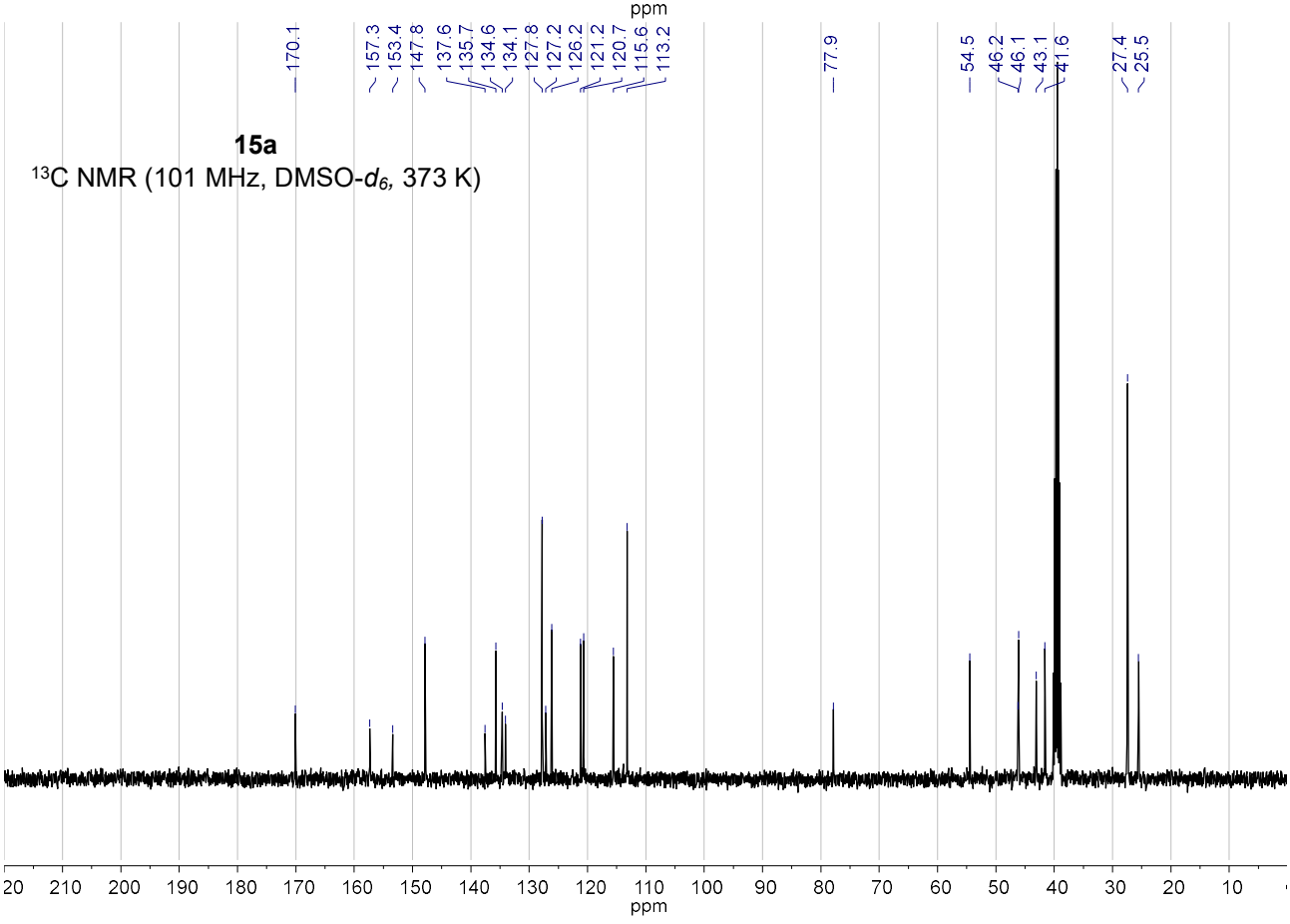
^{1}H NMR (400 MHz, DMSO-d_6, 373 K)

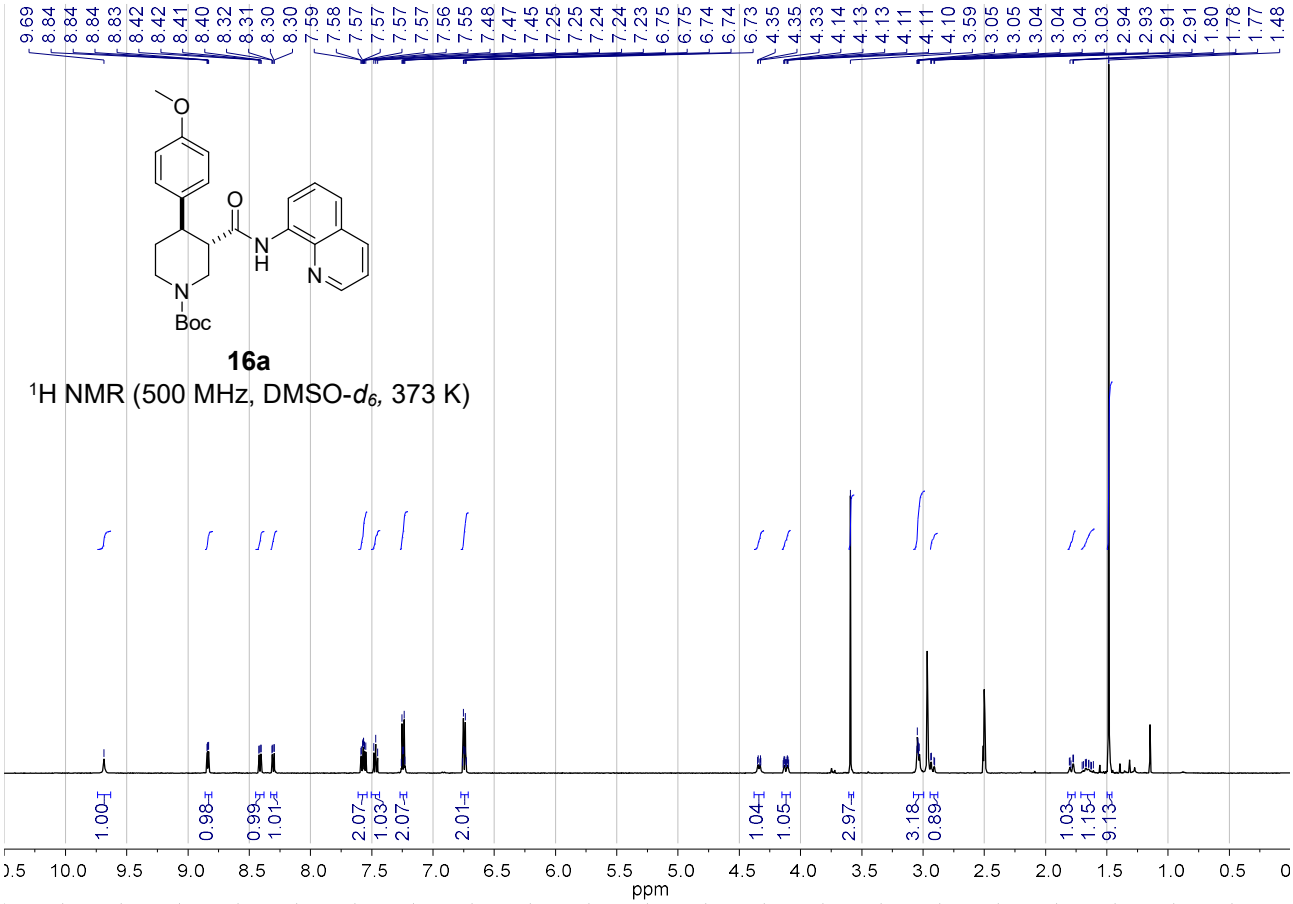


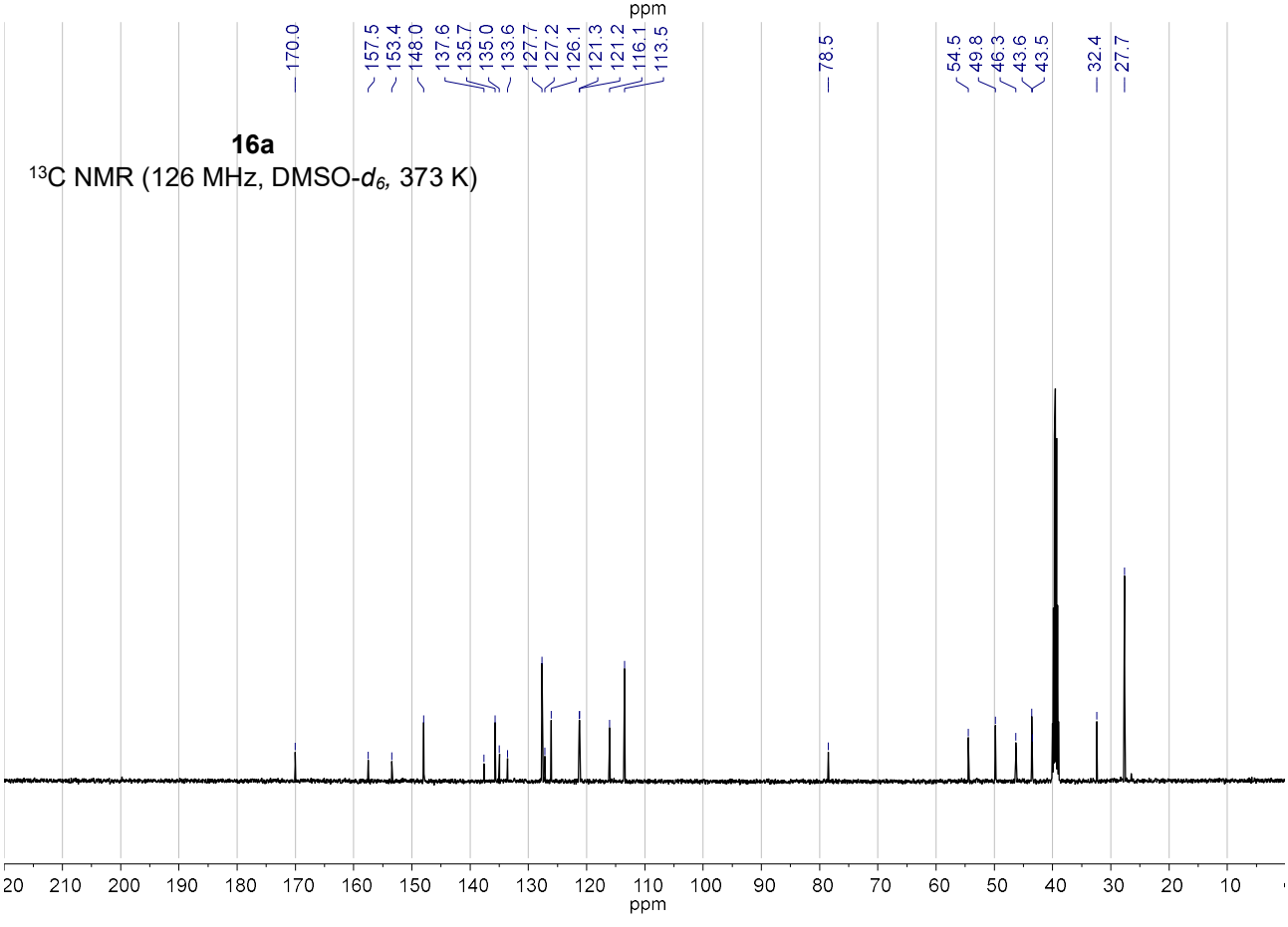
9x

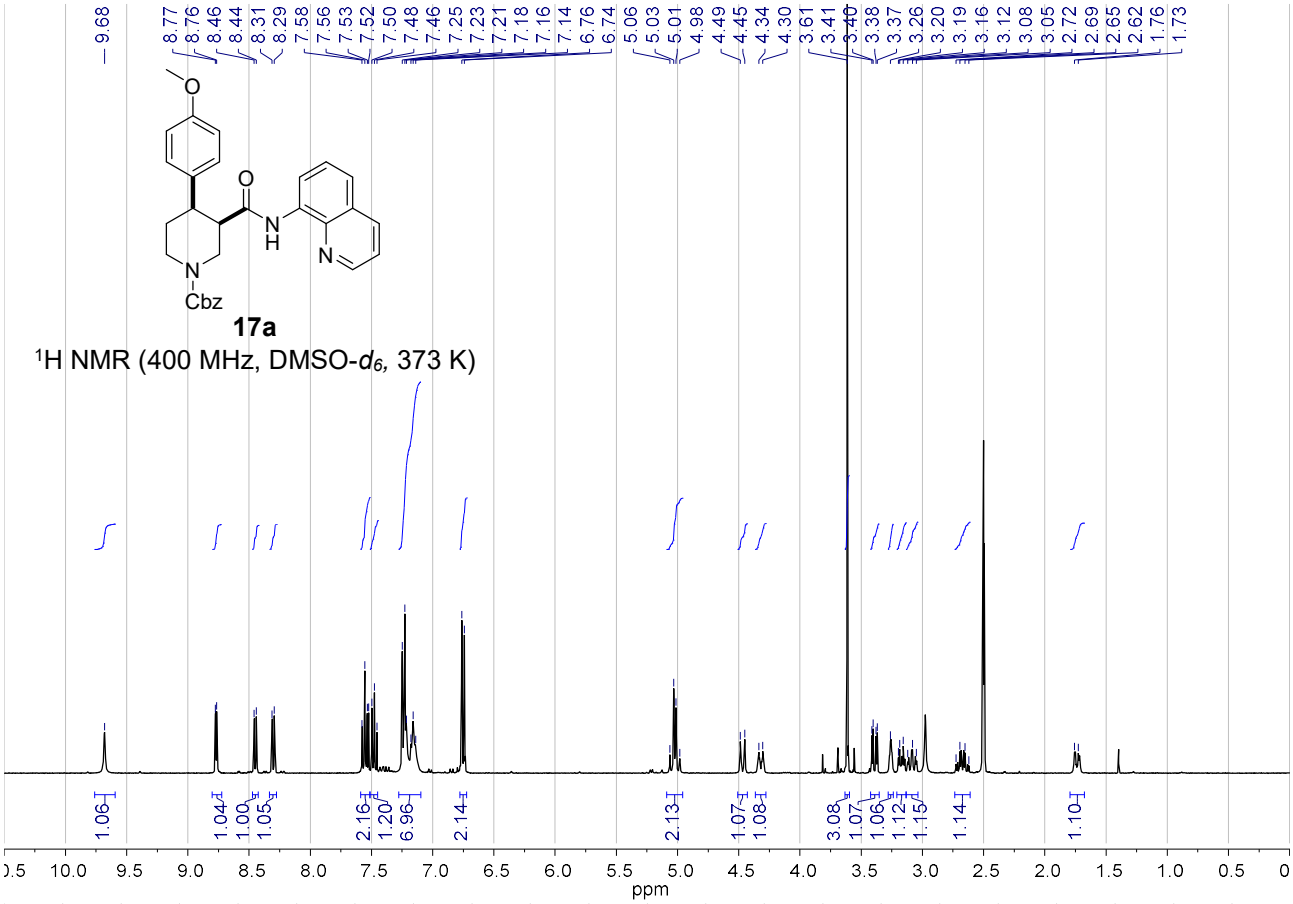
^{13}C NMR (101 MHz, DMSO-d_6, 373 K)


9.71 8.82 8.82 8.81 8.81 8.48 8.48 8.46 8.46 8.32 8.32 8.31 8.30 8.29 8.29 7.58 7.57 7.57 7.56 7.55 7.55 7.55 7.54 7.50 7.48 7.46 7.26 7.25 7.25 7.25 7.24 7.24 7.23 7.23 6.77 6.76 6.75 6.75 4.41 4.41 4.38 4.38 4.37 3.63 3.33 3.32 3.30 3.29 3.24 3.23 3.23 3.10 2.98 2.98 2.97 1.26
O
O
N
H
N
N
Boc
15a
1H NMR (400 MHz, DMSO-d6, 373 K)
1.00 0.95 0.97 1.05 2.12 1.10 2.12 2.19 1.08 1.10 2.85 1.09 1.08 1.16 4.66 1.16 1.12 9.22
ppm


170.1
157.3 153.4 147.8 137.6 135.7 134.6 134.1 127.8 127.2 126.2 121.2 120.7 115.6 113.2
77.9
54.5 46.2 46.1 43.1 41.6
27.4 25.5
15a
13C NMR (101 MHz, DMSO-d6, 373 K)
ppm

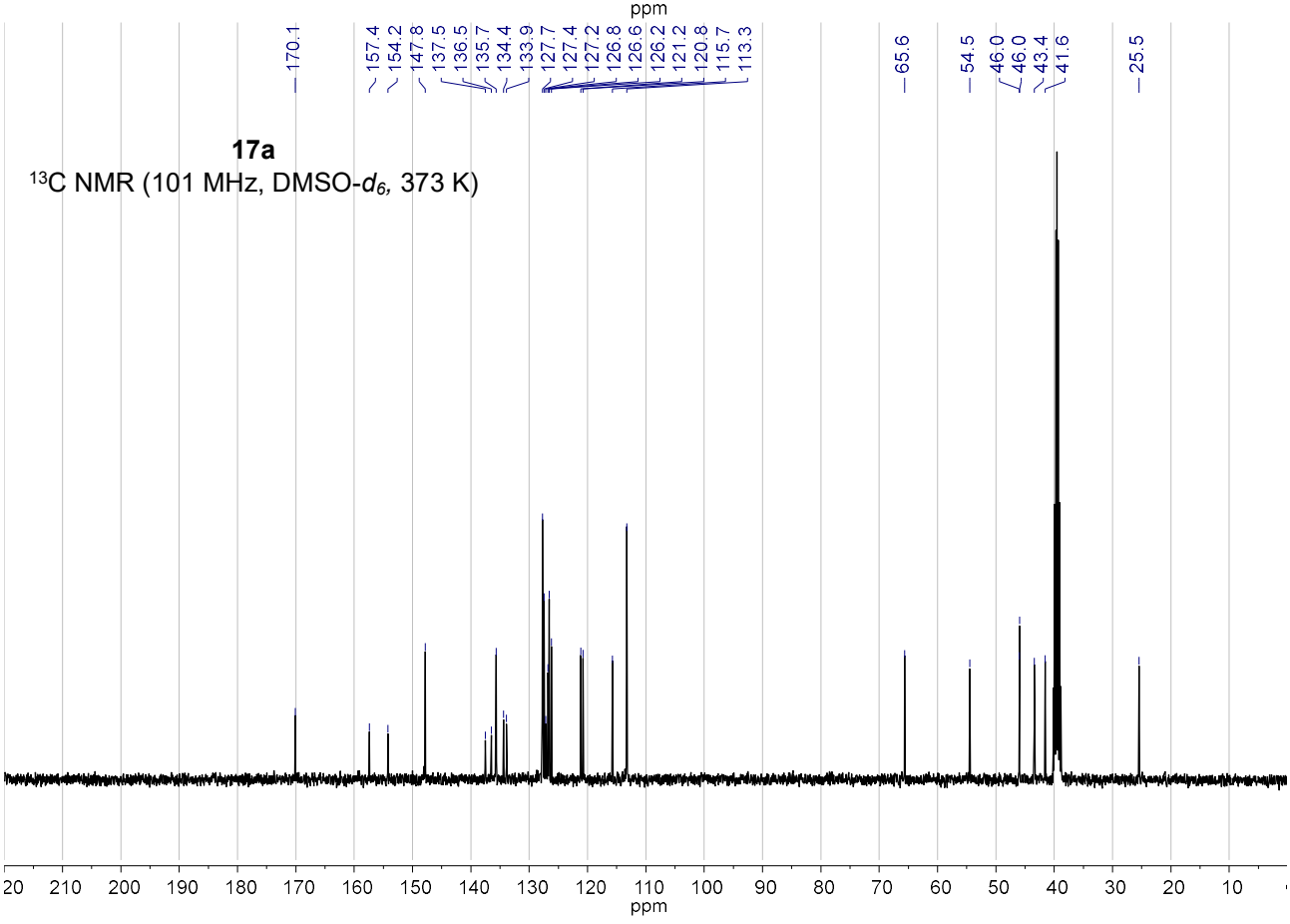

9.69 8.84 8.84 8.84 8.83 8.42 8.42 8.41 8.40 8.32 8.31 8.30 8.30 7.59 7.58 7.57 7.57 7.57 7.57 7.56 7.55 7.48 7.47 7.45 7.25 7.25 7.24 7.24 7.23 6.75 6.75 6.74 6.74 6.73 4.35 4.35 4.33 4.14 4.13 4.11 4.11 4.10 3.59 3.05 3.05 3.04 3.04 3.04 3.03 2.94 2.93 2.91 2.91 1.80 1.78 1.77 1.48
O
O
N
H
N
N
Boc
16a
1H NMR (500 MHz, DMSO-d6, 373 K)
1.00 0.98 0.99 1.01 2.07 1.03 2.07 2.01 1.04 1.05 2.97 3.18 0.89 1.03 1.15 9.13
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0
ppm


170.0
157.5 153.4 148.0 137.6 135.7 135.0 133.6 127.7 127.2 126.1 121.3 121.2 116.1 113.5
78.5
54.5 49.8 46.3 43.6 43.5
32.4 27.7
16a
13C NMR (126 MHz, DMSO-d6, 373 K)
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
ppm



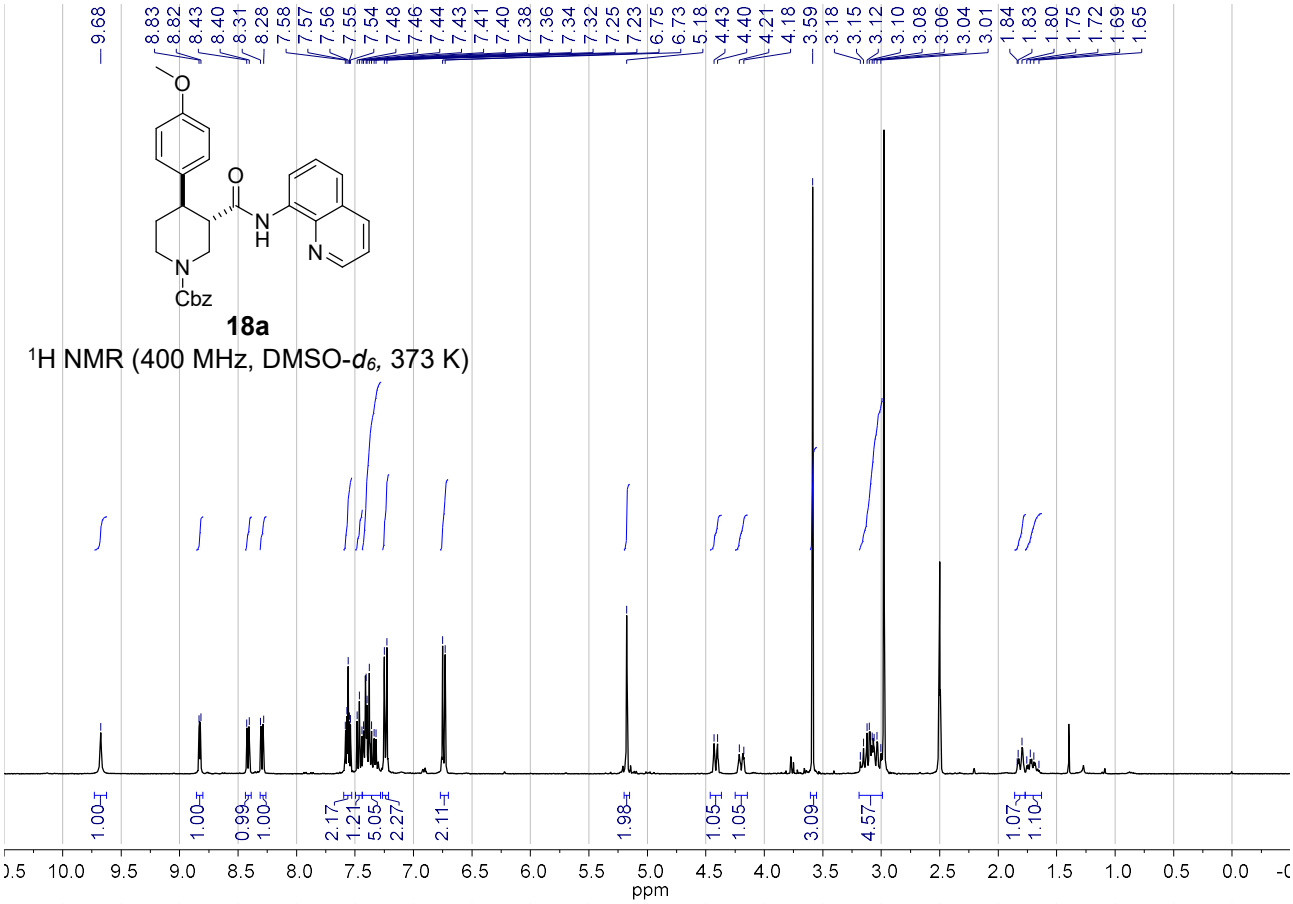
17a

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



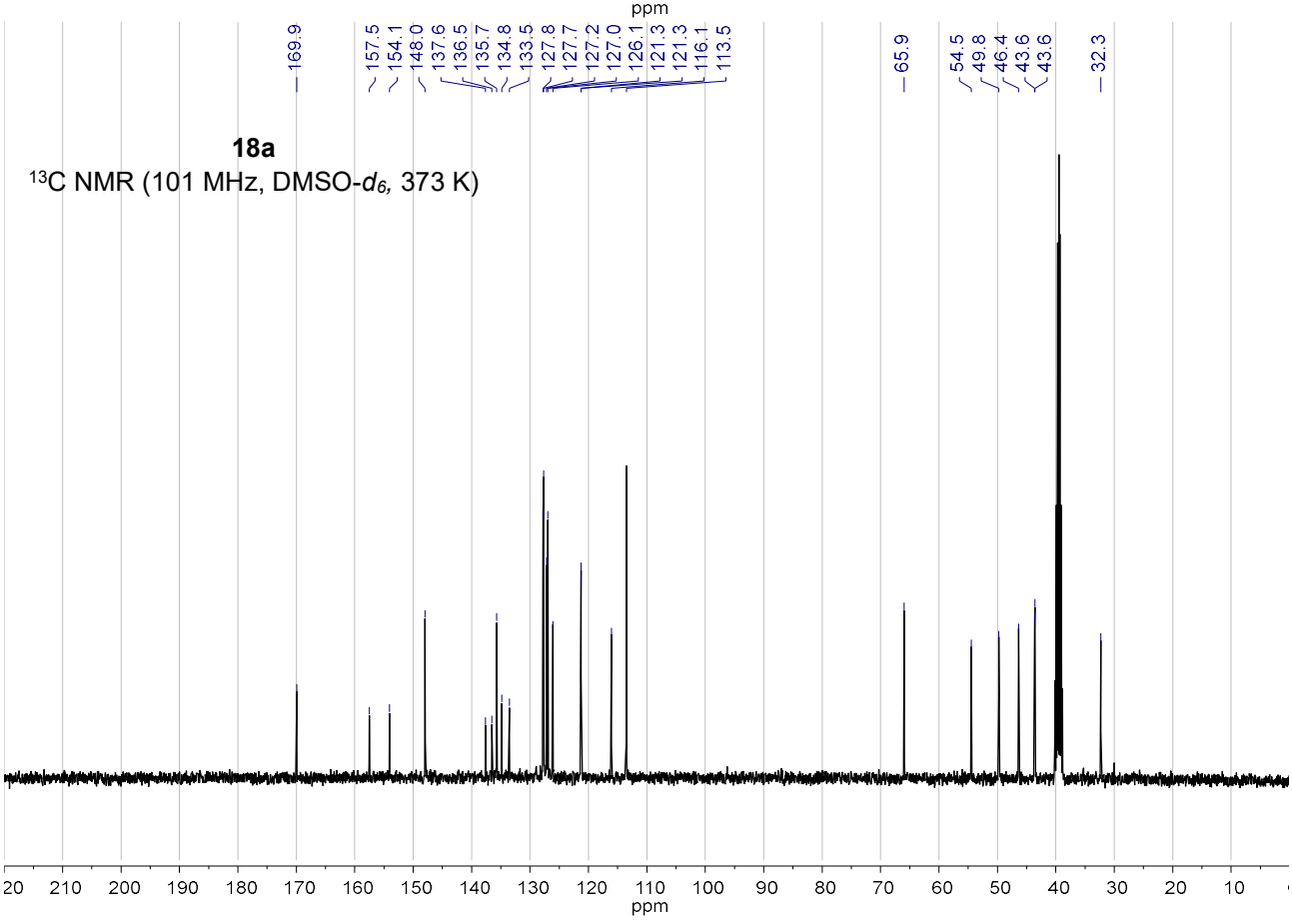
17a

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



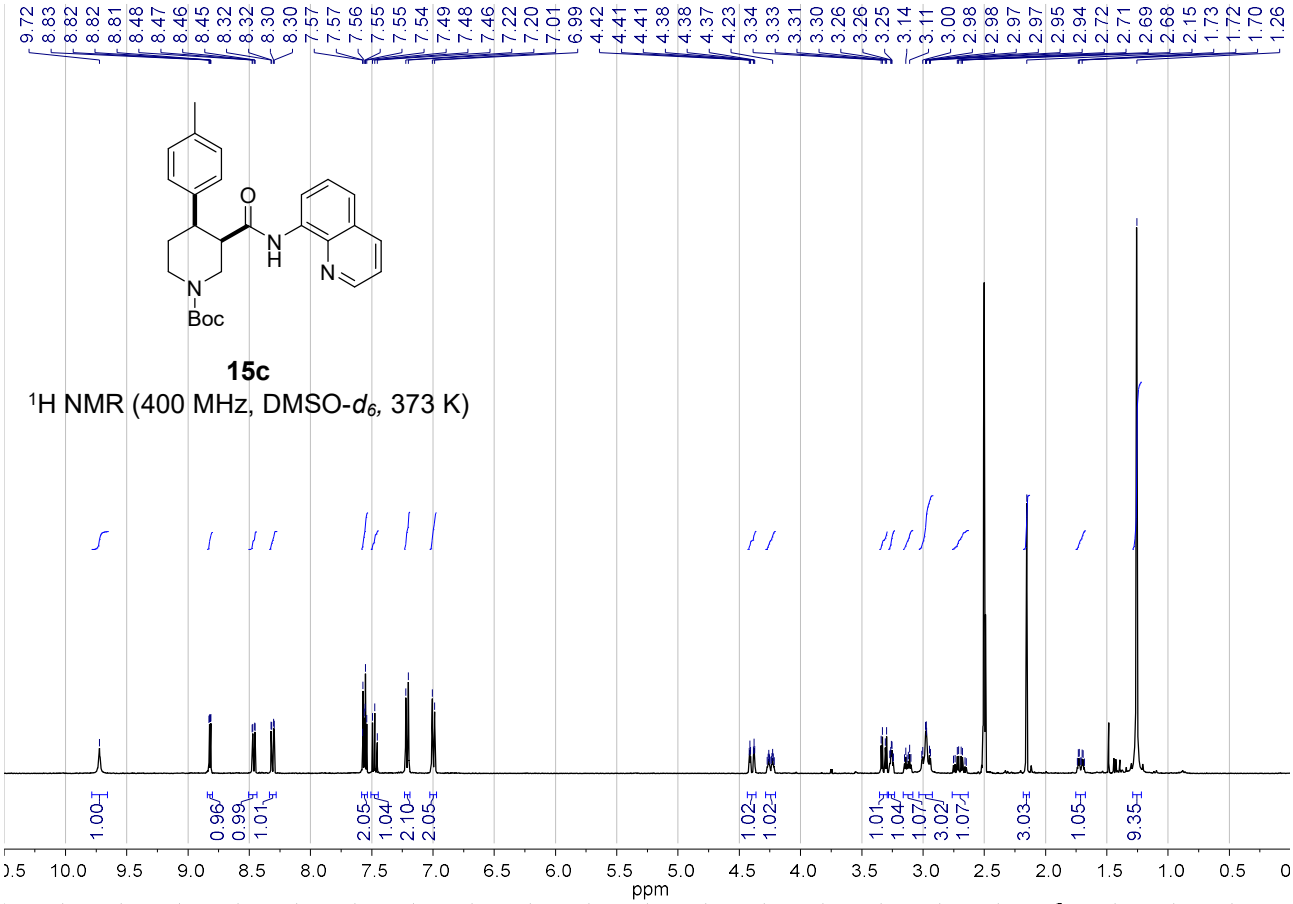
18a

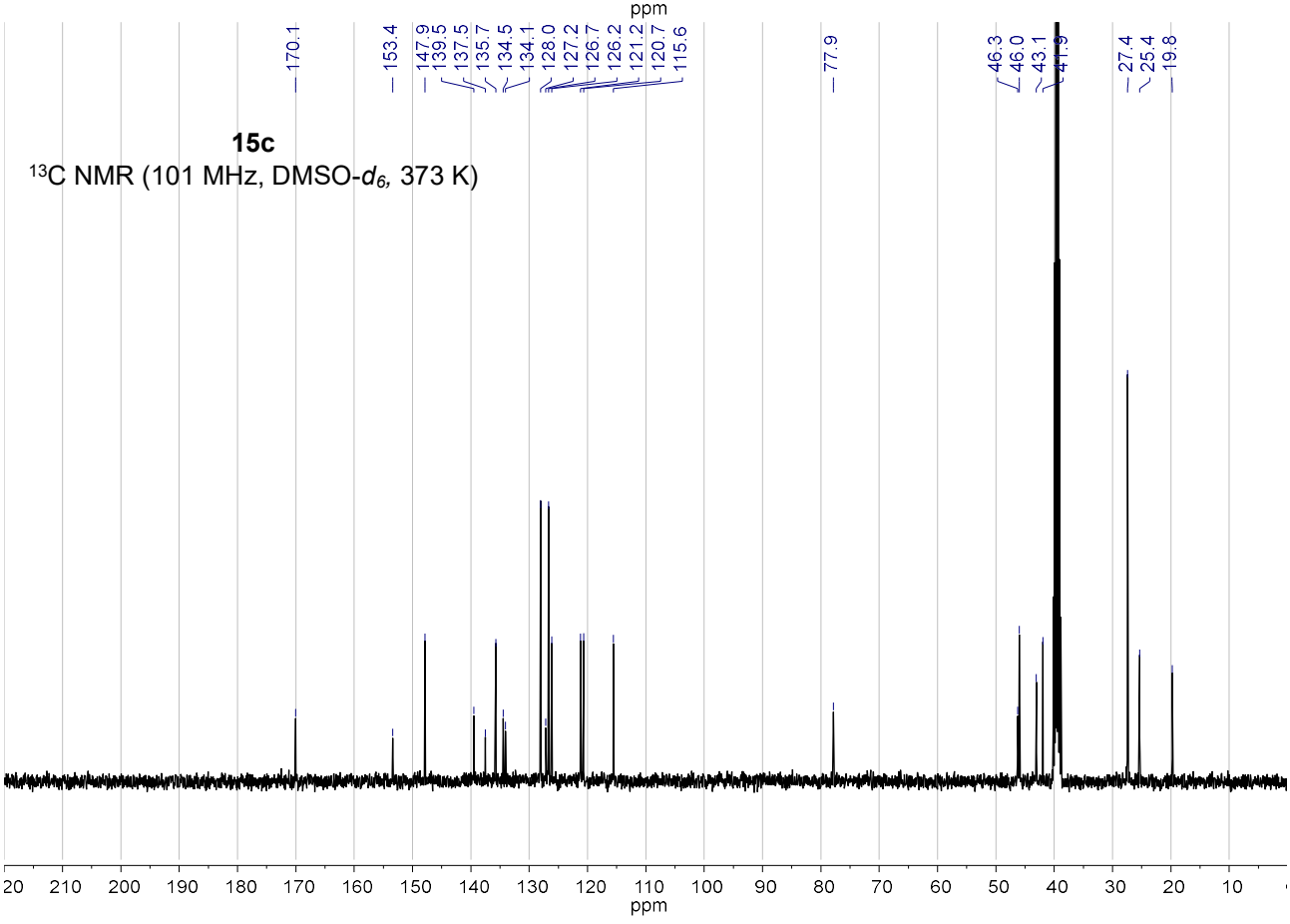
^{1}H NMR (400 MHz, DMSO-*d*$_6$, 373 K)

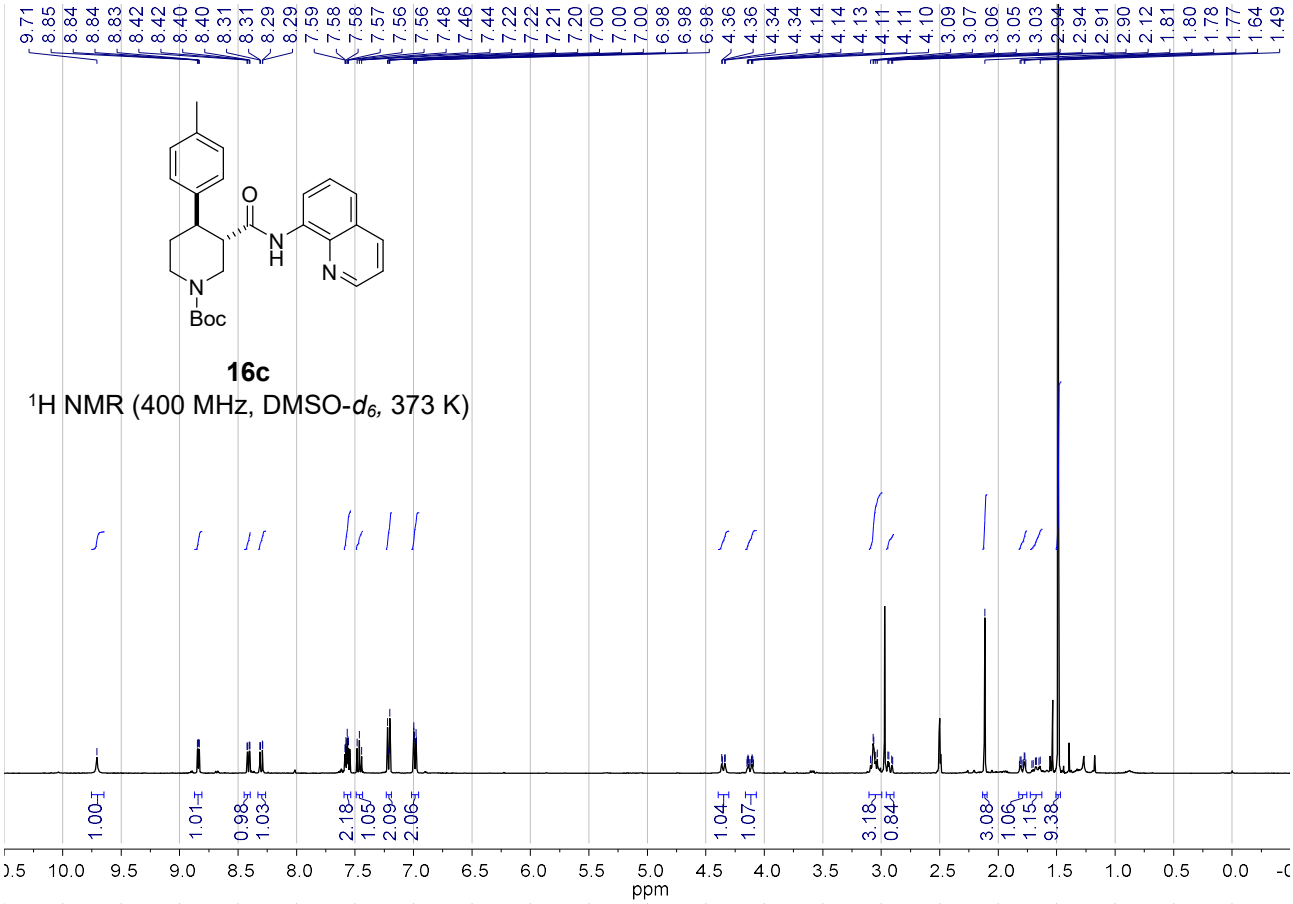


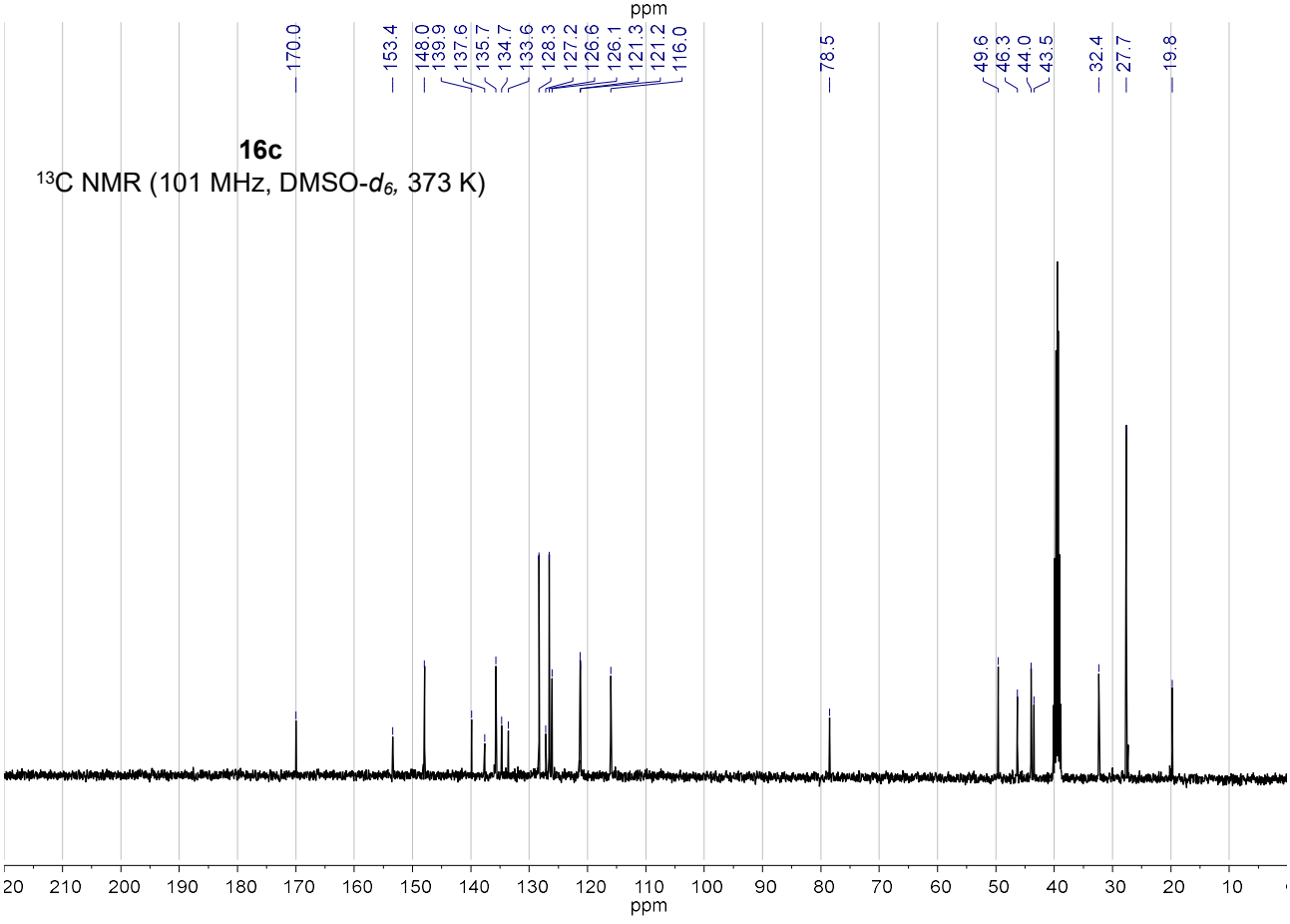
18a

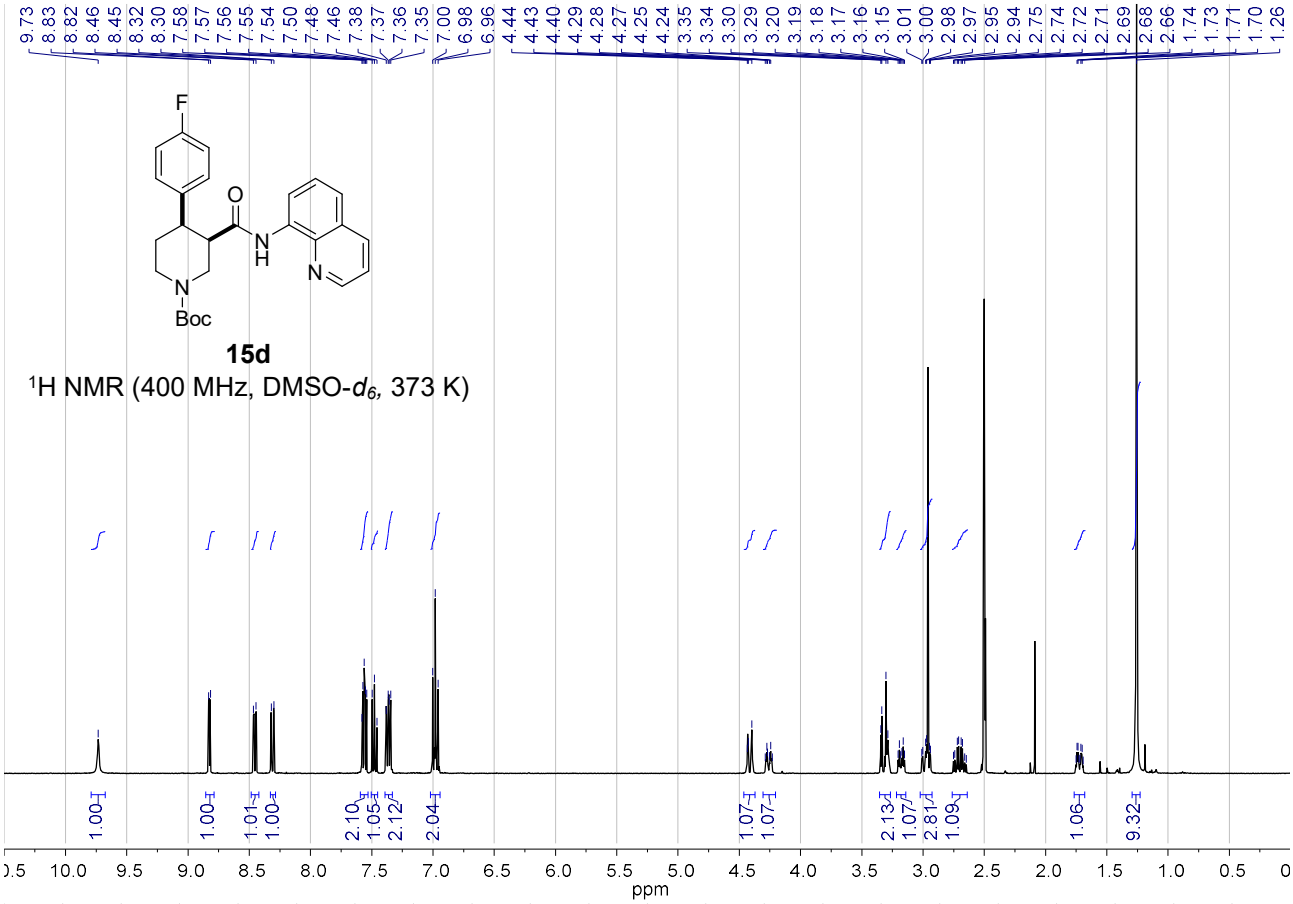
^{13}C NMR (101 MHz, DMSO-*d*$_6$, 373 K)


9.72 8.83 8.82 8.82 8.81 8.48 8.47 8.46 8.45 8.32 8.30 8.30 7.57 7.56 7.55 7.55 7.54 7.49 7.48 7.46 7.22 7.20 7.01 6.99 4.42 4.41 4.41 4.38 4.38 4.37 4.23 3.34 3.33 3.31 3.30 3.26 3.26 3.25 3.14 3.11 3.00 2.98 2.98 2.97 2.97 2.95 2.94 2.72 2.71 2.69 2.68 2.15 1.73 1.72 1.70 1.26
O
N
H
N
N
Boc
15c
1H NMR (400 MHz, DMSO-d6, 373 K)
1.00 0.96 0.99 1.01 2.05 1.04 2.10 2.05 1.02 1.02 1.01 1.04 1.07 3.02 1.07 3.03 1.05 9.35
ppm


170.1 153.4 147.9 139.5 137.5 135.7 134.5 134.1 128.0 127.2 126.7 126.2 121.2 120.7 115.6 77.9 46.3 46.0 43.1 41.9 27.4 25.4 19.8
15c
13C NMR (101 MHz, DMSO-d6, 373 K)
ppm

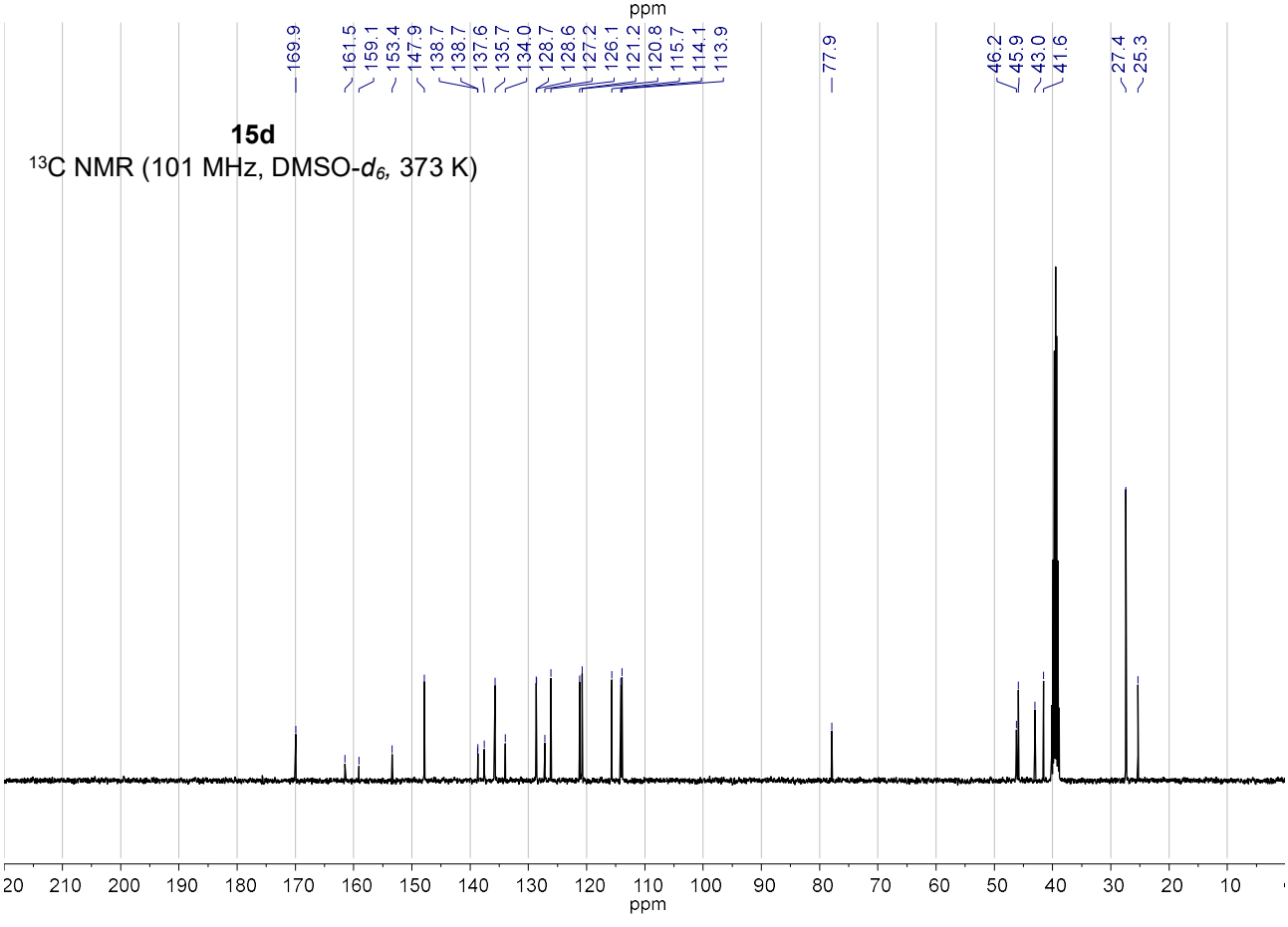

9.71 8.85 8.84 8.84 8.83 8.42 8.42 8.40 8.40 8.31 8.31 8.29 8.29 7.59 7.58 7.58 7.57 7.56 7.56 7.48 7.46 7.44 7.22 7.22 7.21 7.20 7.00 7.00 7.00 6.98 6.98 6.98 4.36 4.36 4.34 4.34 4.14 4.13 4.11 4.11 4.10 3.09 3.07 3.06 3.05 3.03 2.94 2.94 2.91 2.90 2.12 1.81 1.80 1.78 1.77 1.64 1.49
O
N
H
N
N
Boc
16c
1H NMR (400 MHz, DMSO-d6, 373 K)
1.00 1.01 0.98 1.03 2.18 1.05 2.09 2.06 1.04 1.07 3.18 0.84 3.08 1.06 1.15 9.38
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
ppm


170.0 153.4 148.0 139.9 137.6 135.7 134.7 133.6 128.3 127.2 126.6 126.1 121.3 121.2 116.0 78.5 49.6 46.3 44.0 43.5 32.4 27.7 19.8
16c
13C NMR (101 MHz, DMSO-d6, 373 K)
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
ppm



15d

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

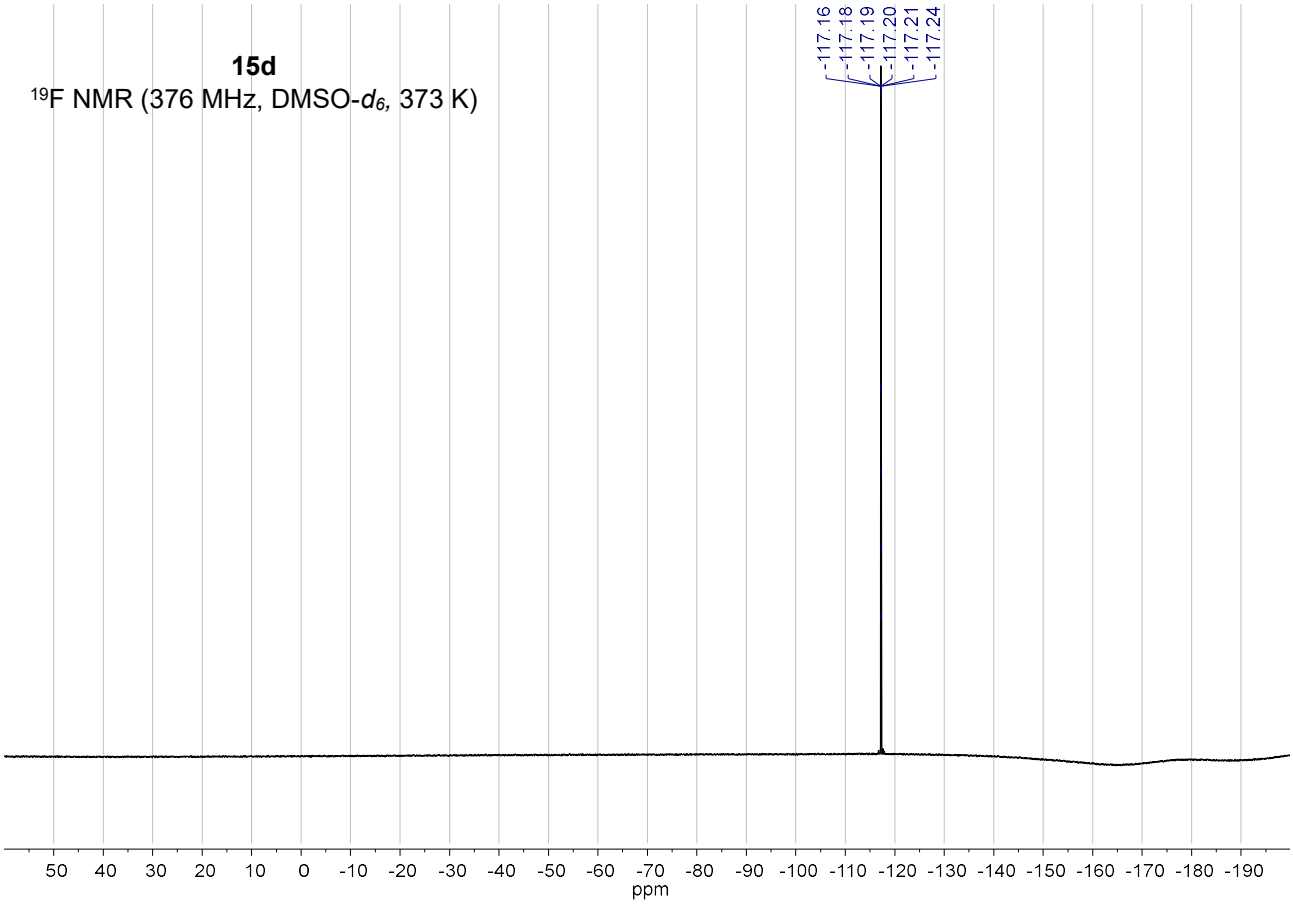


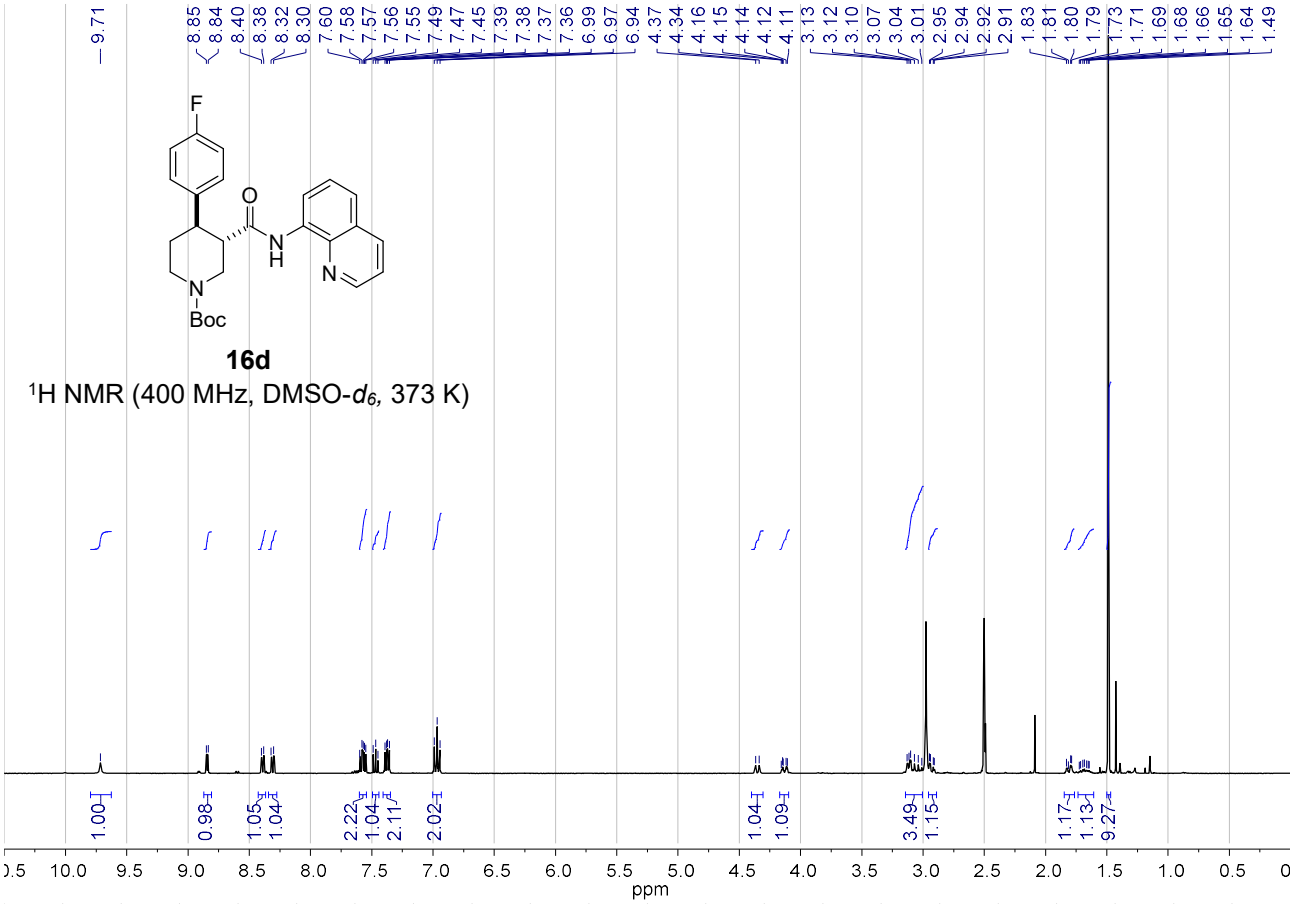
15d

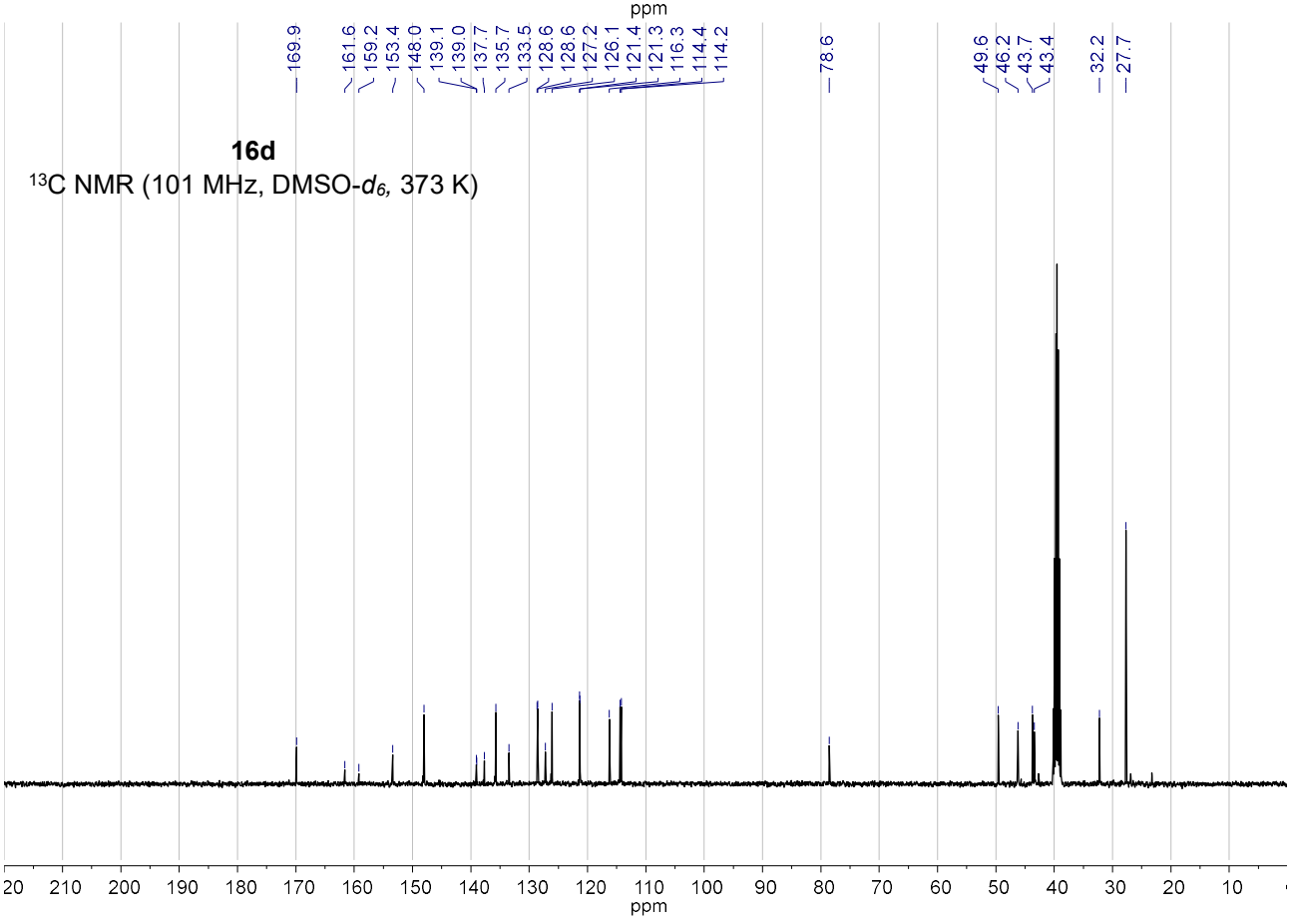
^{13}C NMR (101 MHz, DMSO-d_6, 373 K)

15d

^{19}F NMR (376 MHz, DMSO-d_6, 373 K)

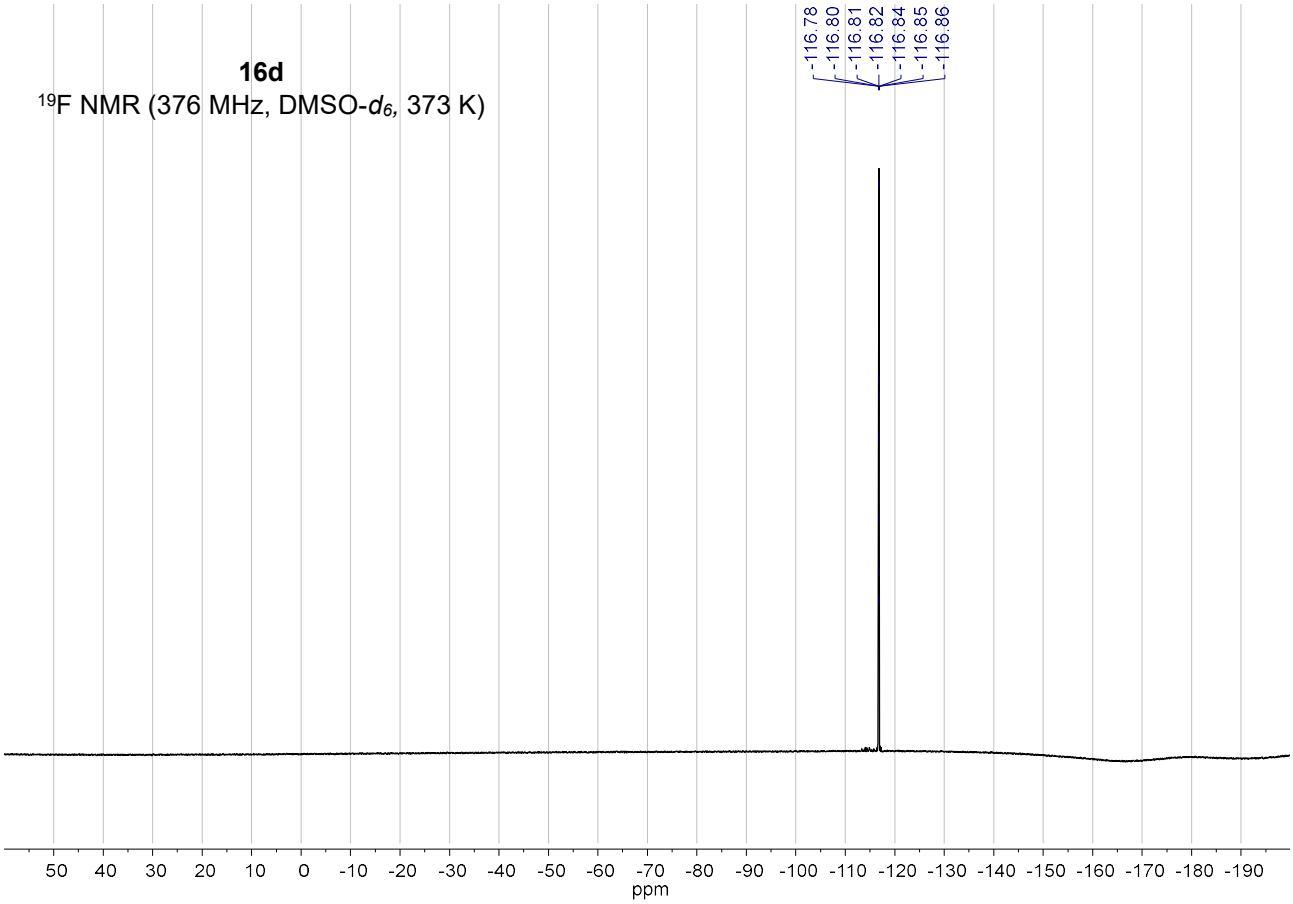


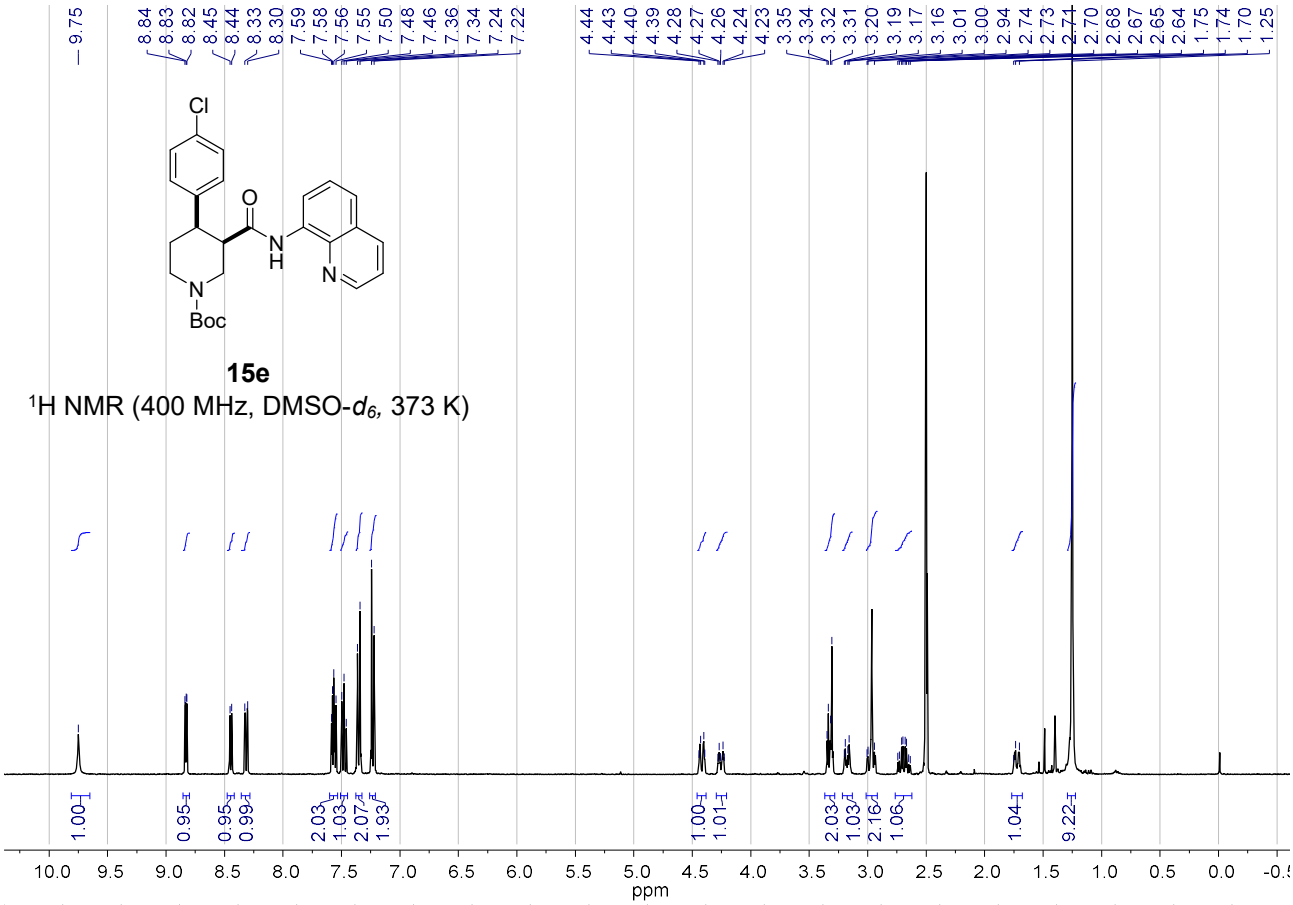

F
O
N
H
N
N
Boc
16d
^{1}H NMR (400 MHz, DMSO-d_6, 373 K)
ppm

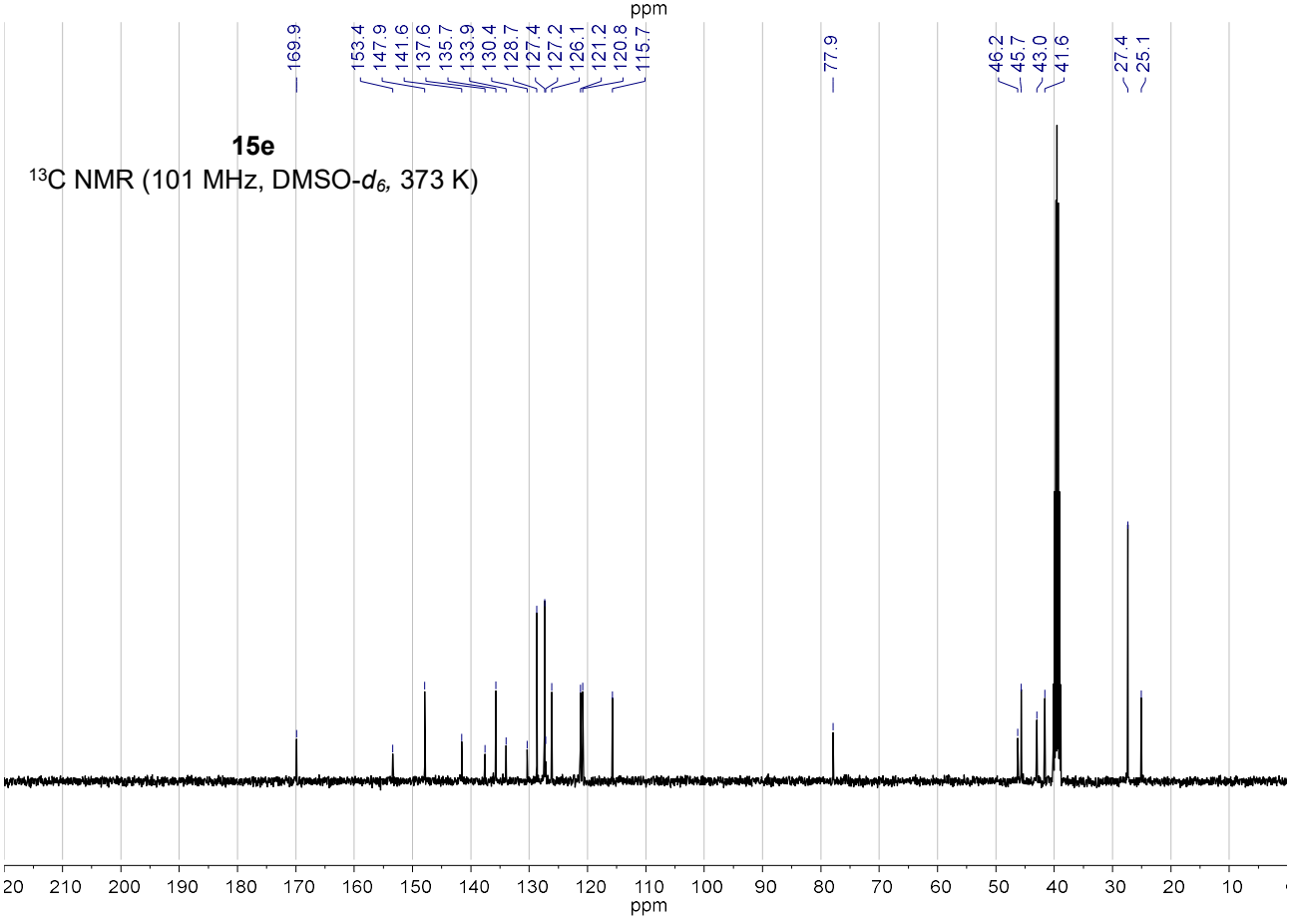

16d
^{13}C NMR (101 MHz, DMSO-d_6, 373 K)
ppm

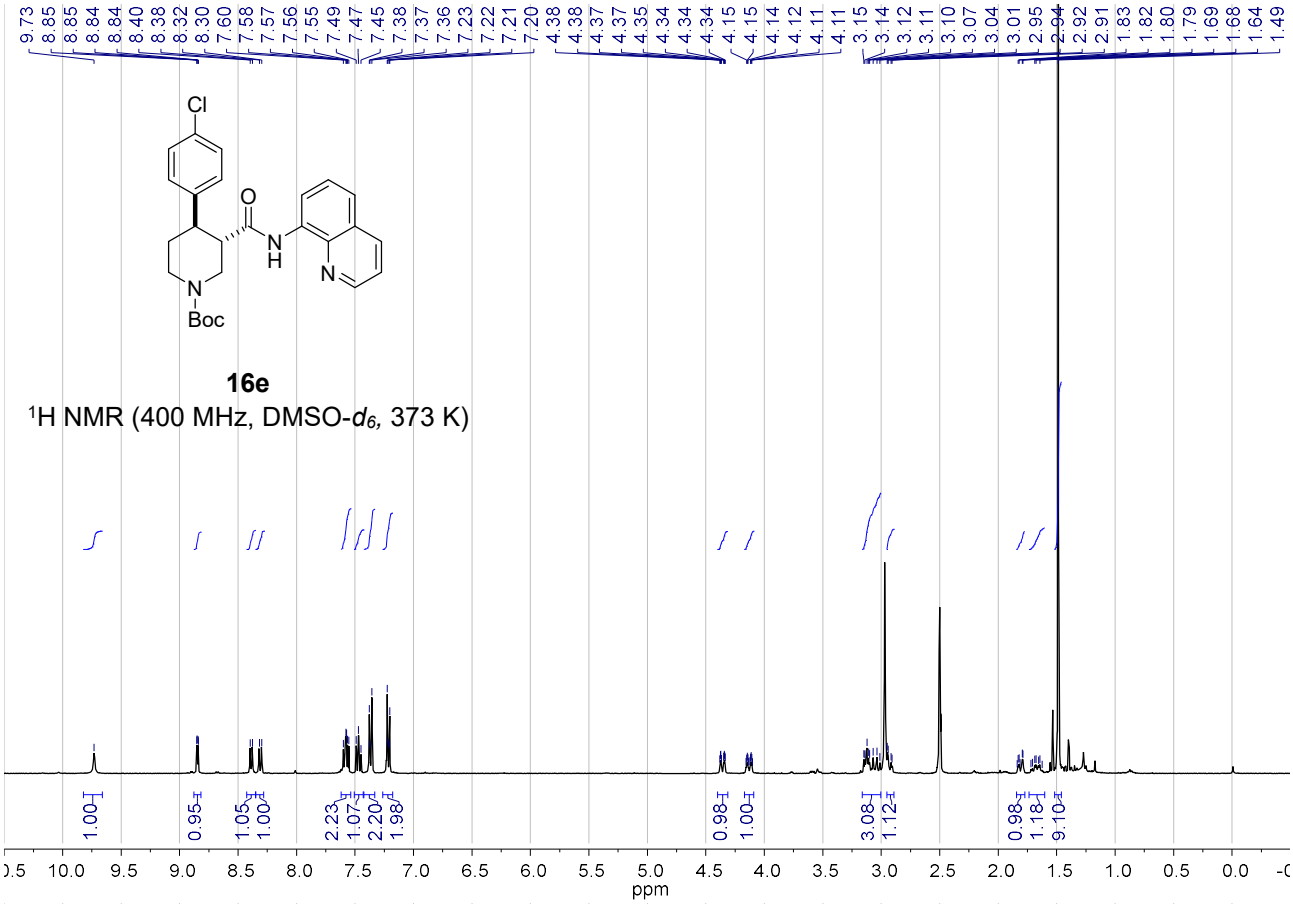
16d

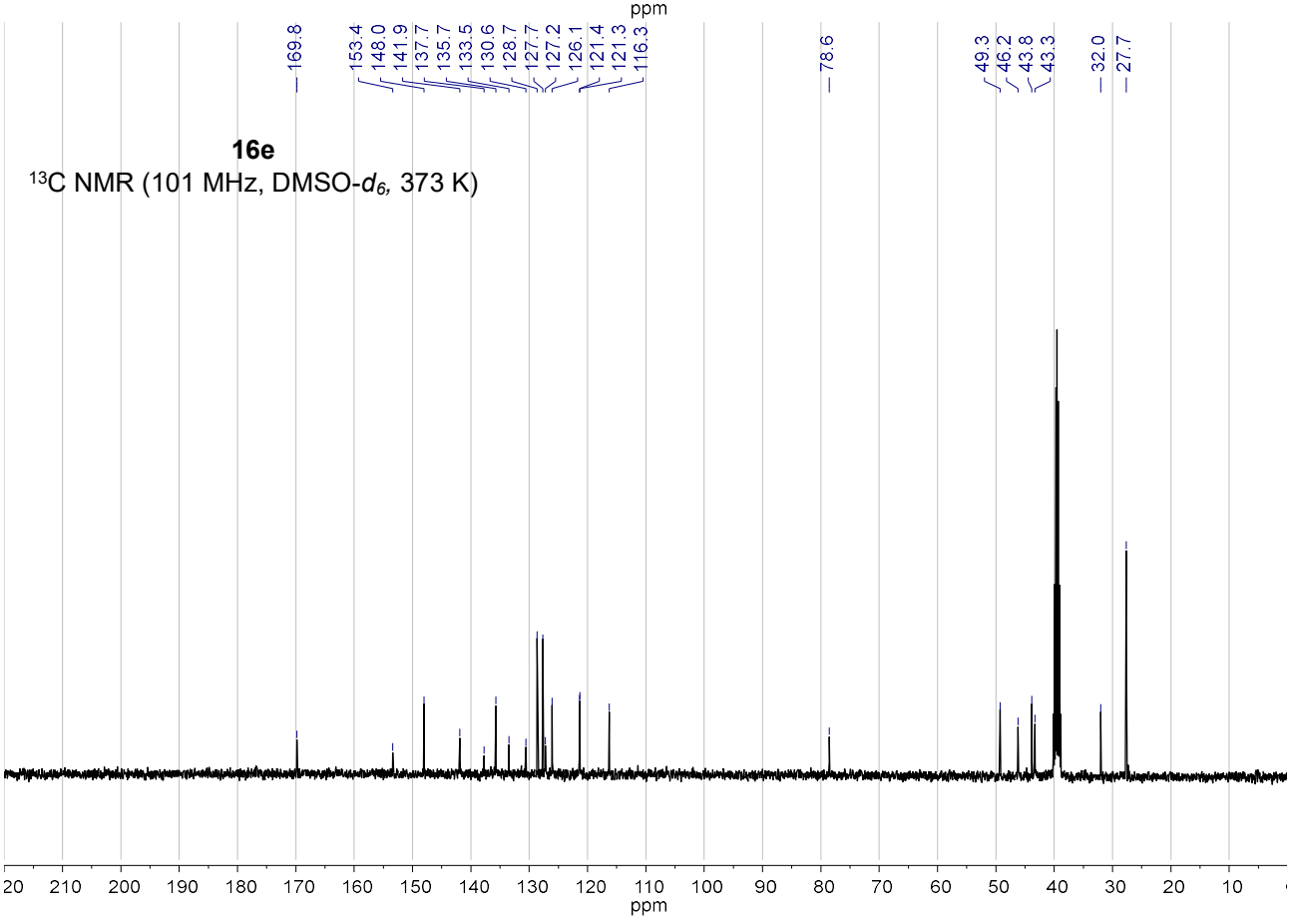
^{19}F NMR (376 MHz, DMSO-d_6, 373 K)

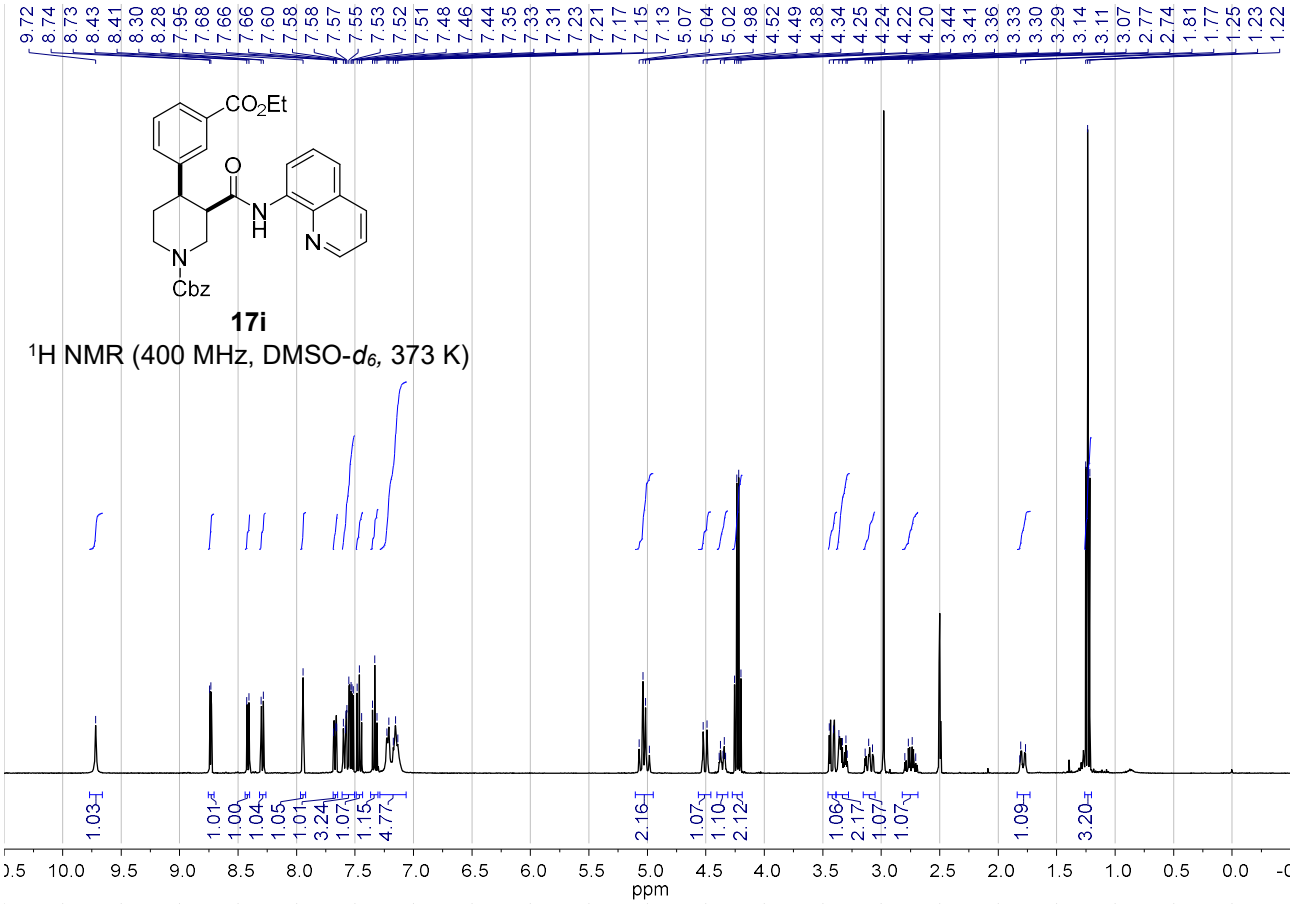



Cl
O
N
H
N
N
Boc
15e
1H NMR (400 MHz, DMSO-d6, 373 K)
ppm


15e
13C NMR (101 MHz, DMSO-d6, 373 K)
ppm

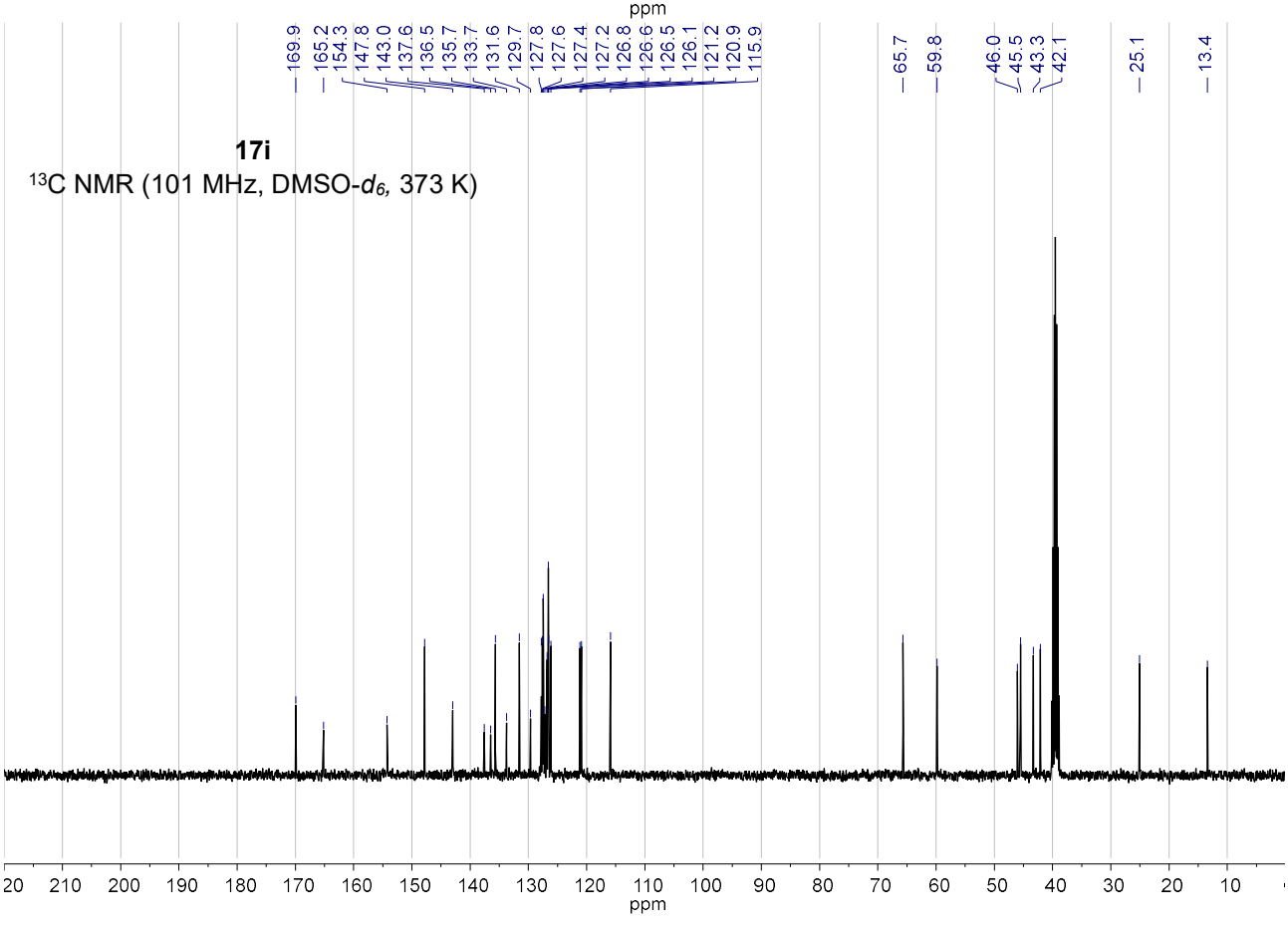

Cl
O
N
H
N
N
Boc
16e
1H NMR (400 MHz, DMSO-d6, 373 K)
ppm


16e
13C NMR (101 MHz, DMSO-d6, 373 K)
ppm



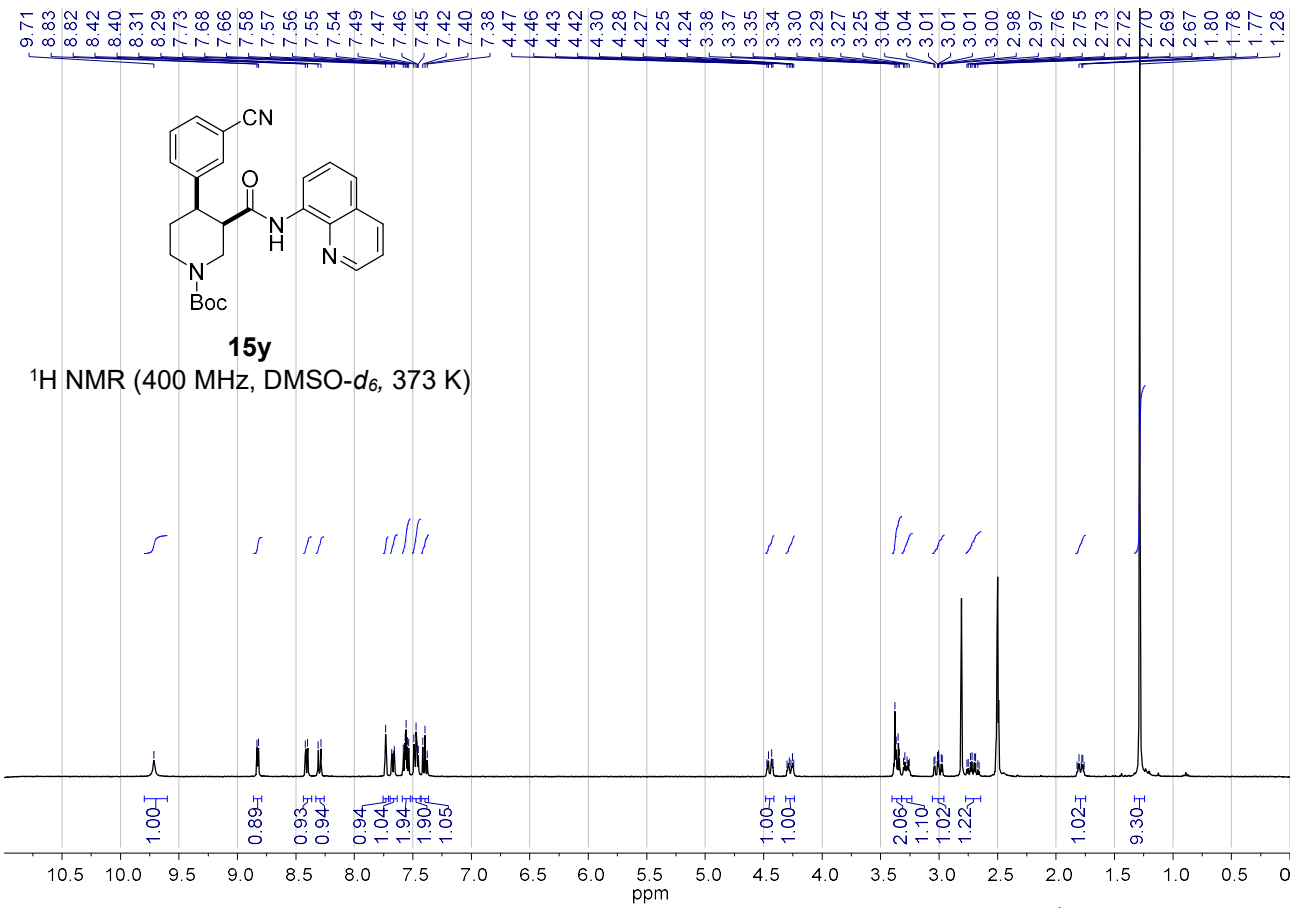
17i

^{1}H NMR (400 MHz, DMSO-*d*$_6$, 373 K)



17i

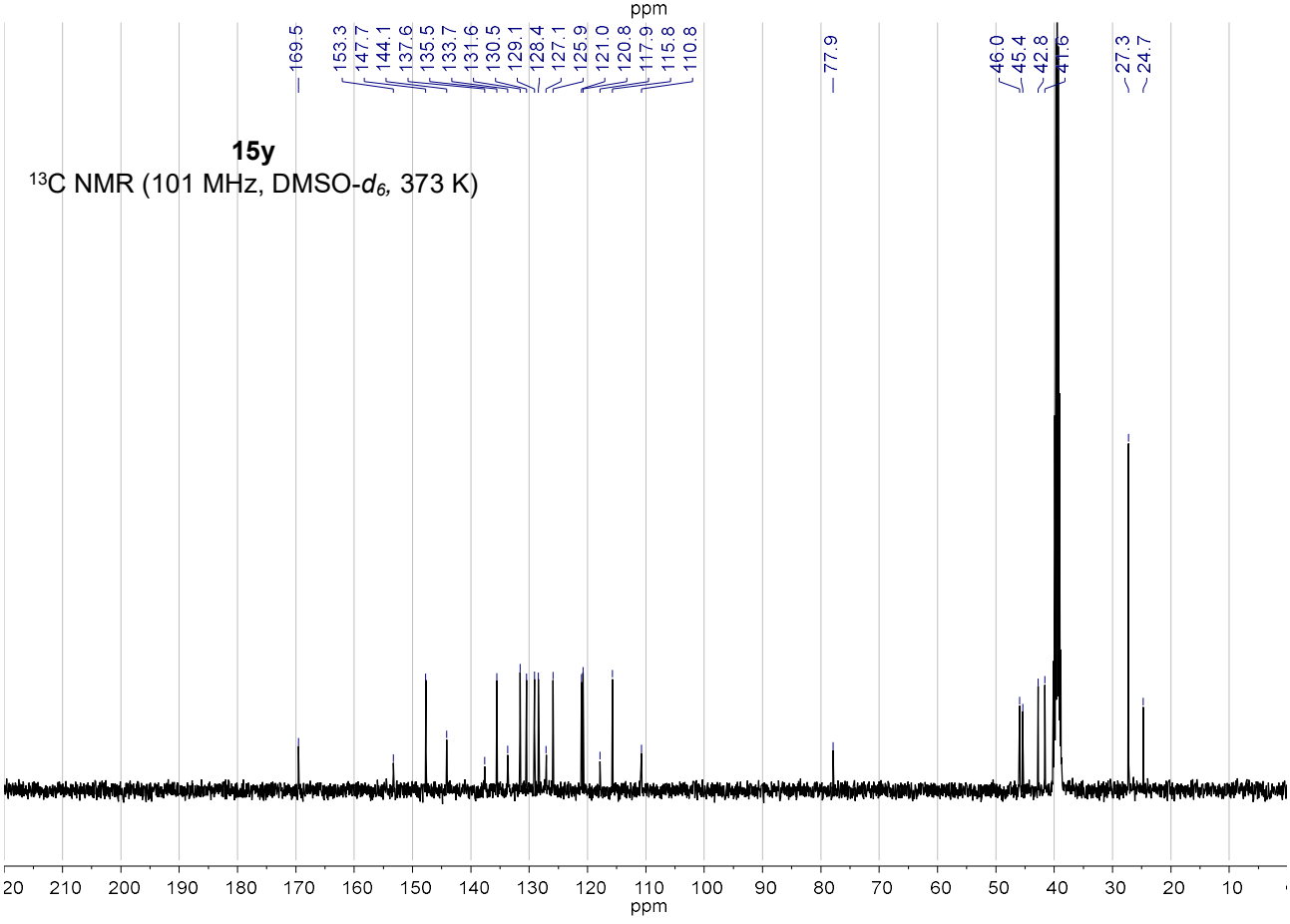
^{13}C NMR (101 MHz, DMSO-*d*$_6$, 373 K)

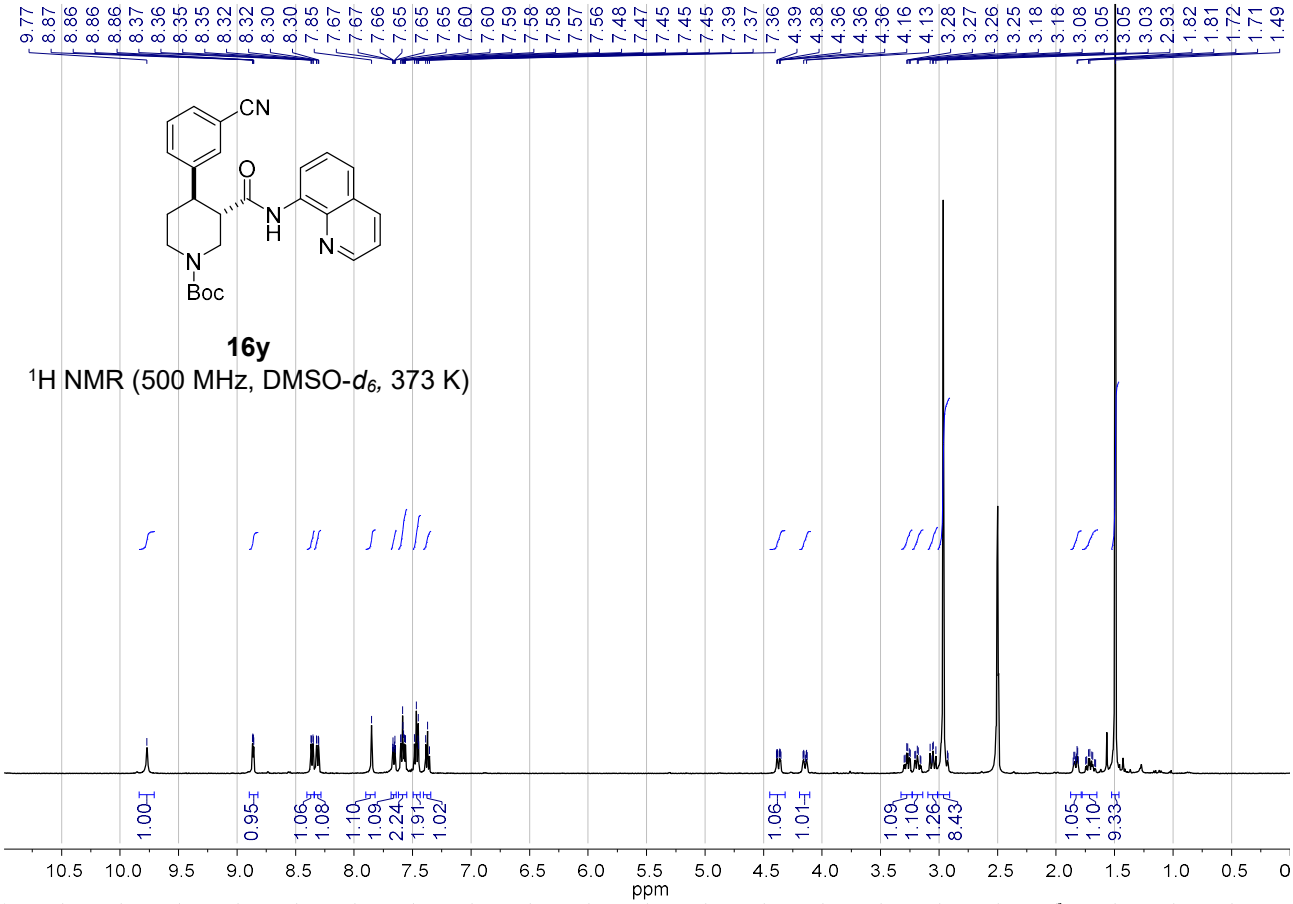


15y

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

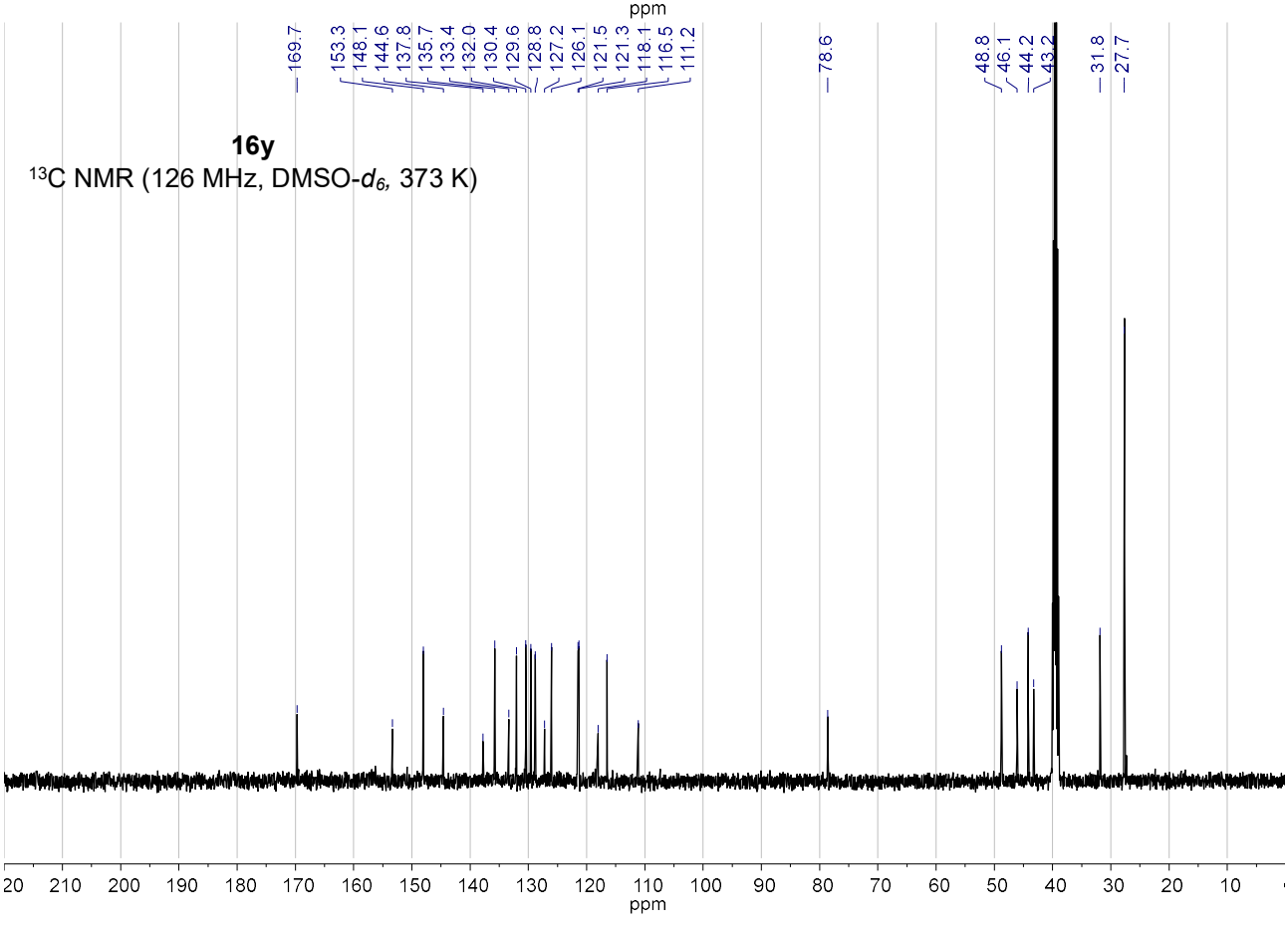
^{13}C NMR (101 MHz, DMSO-d_6, 373 K)





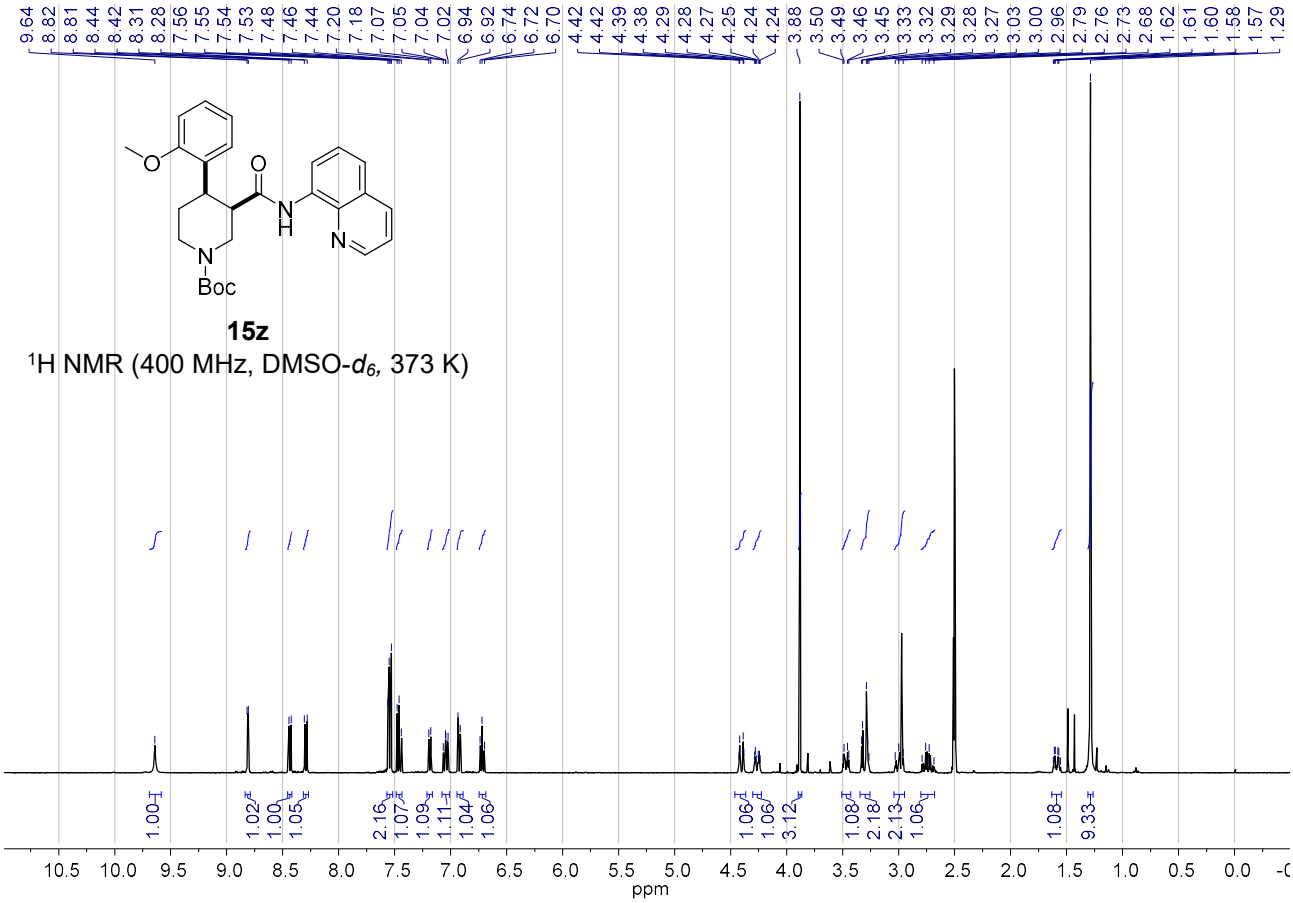
16y

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



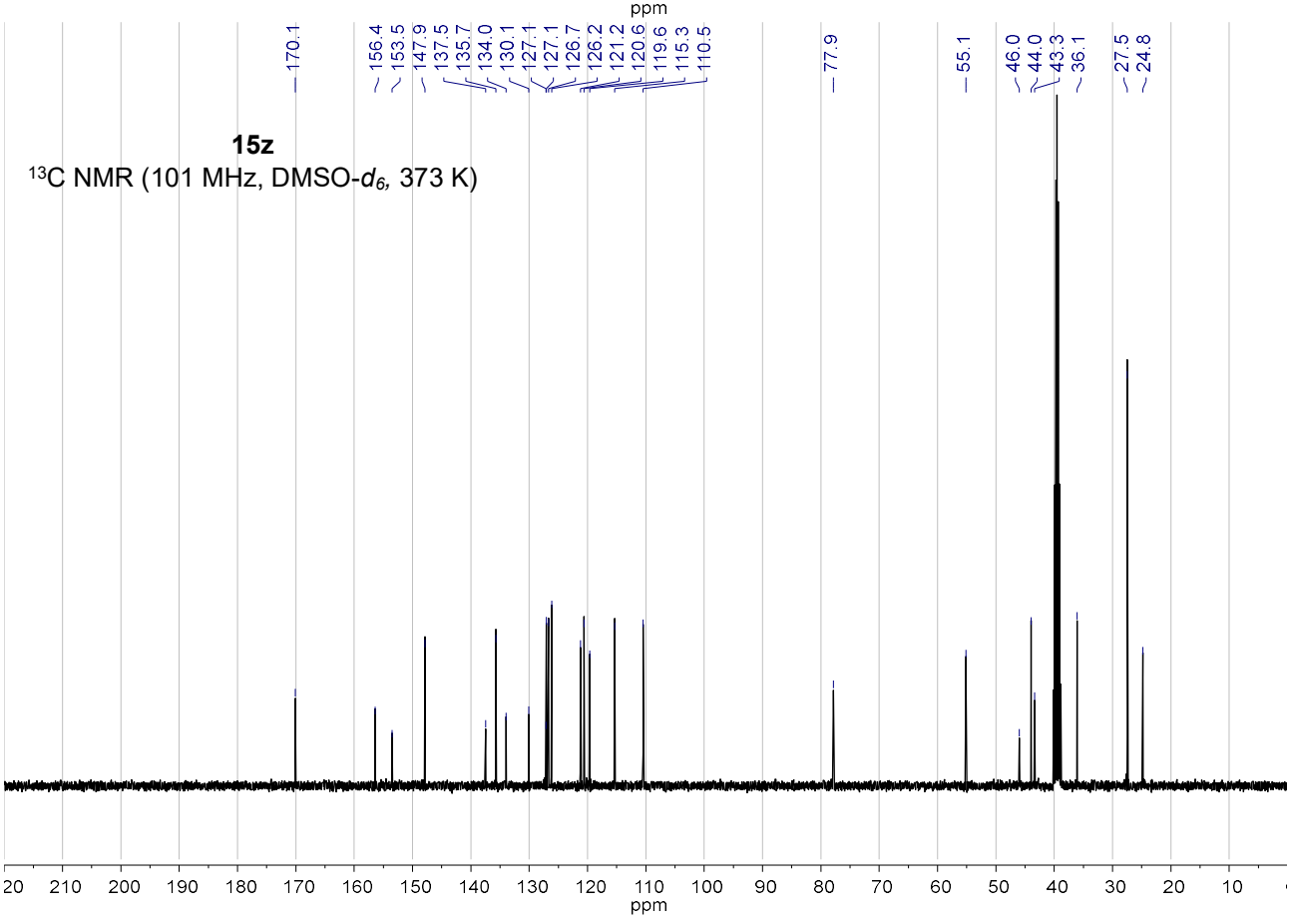
16y

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



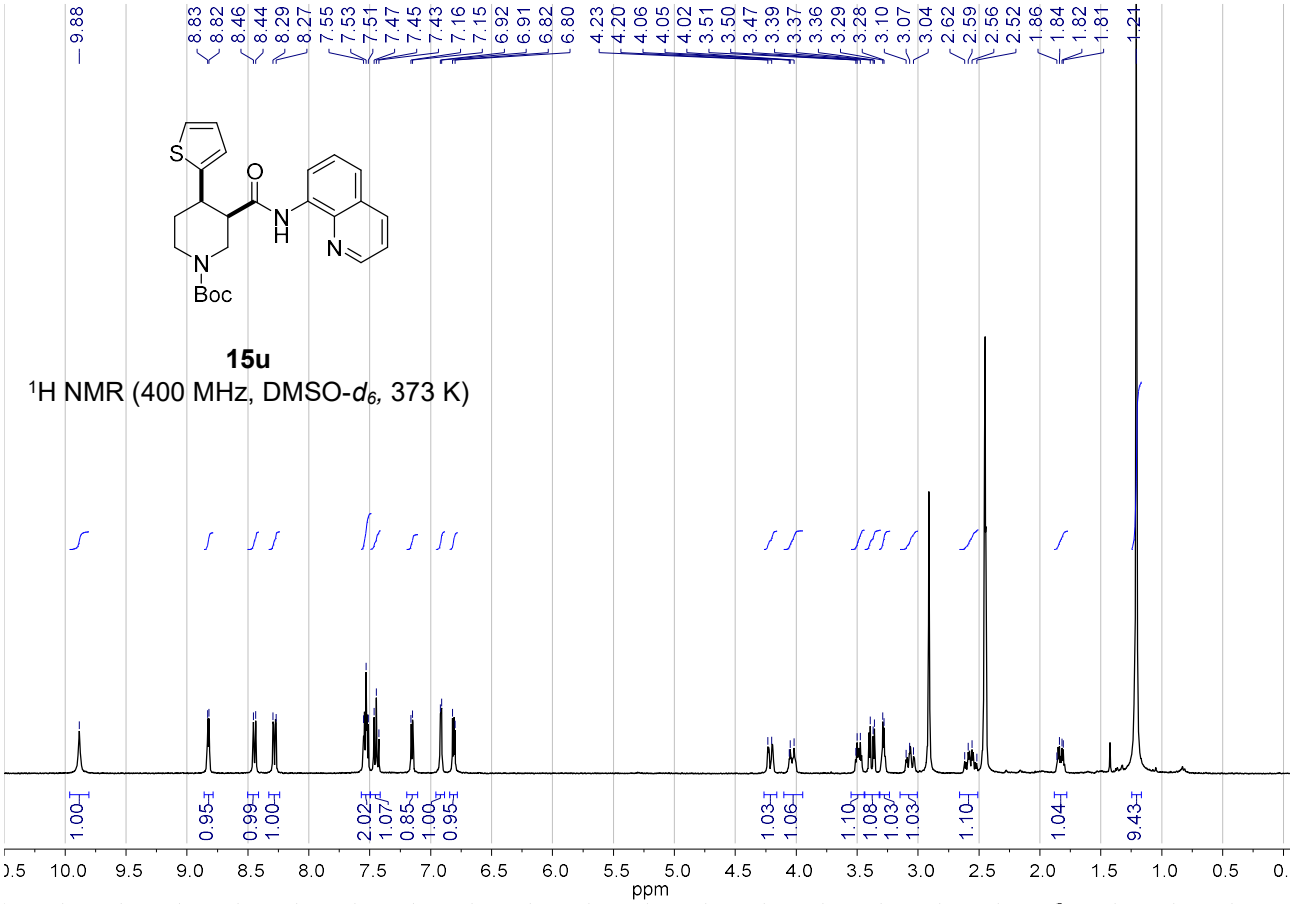
15z

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



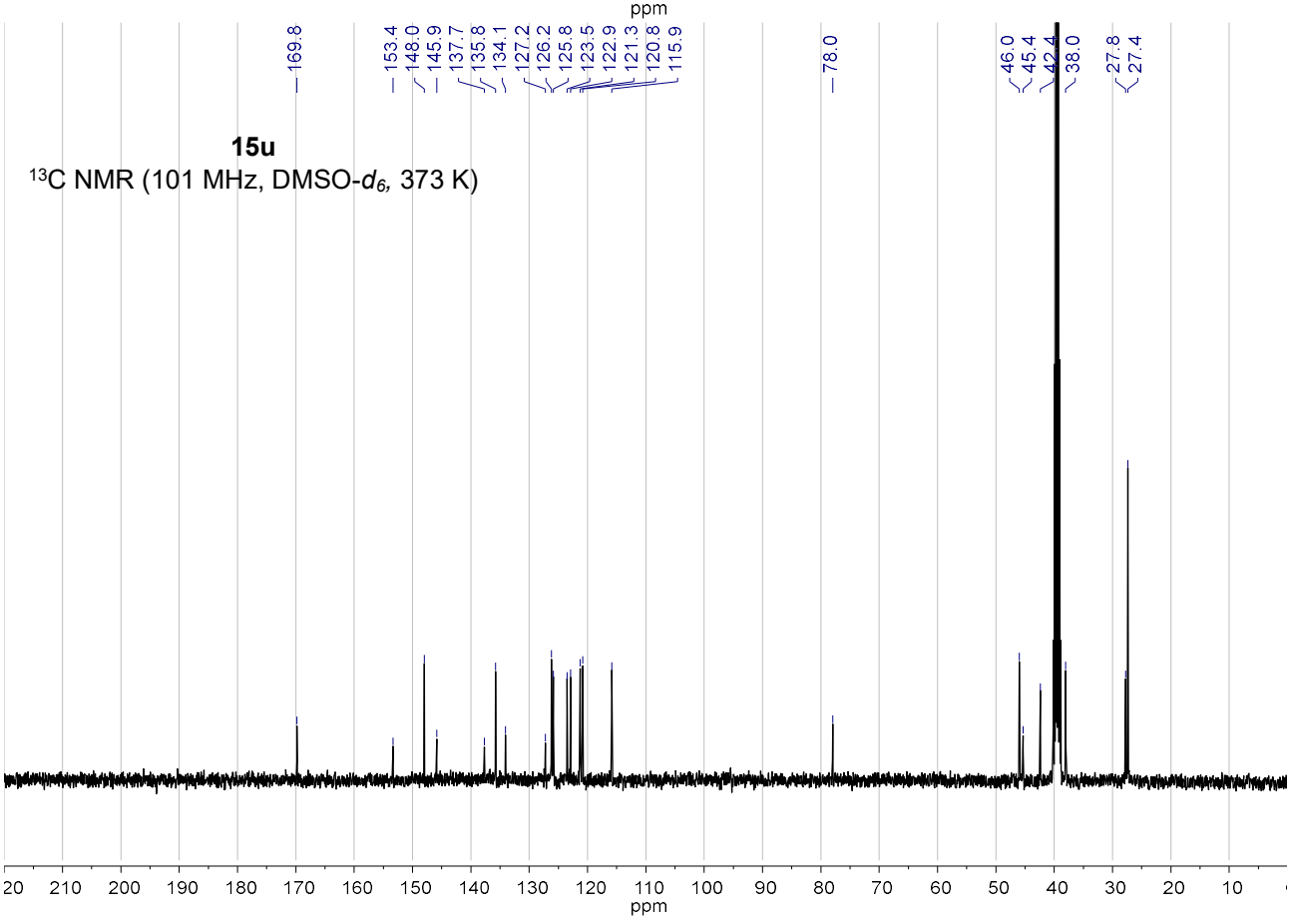
15z

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



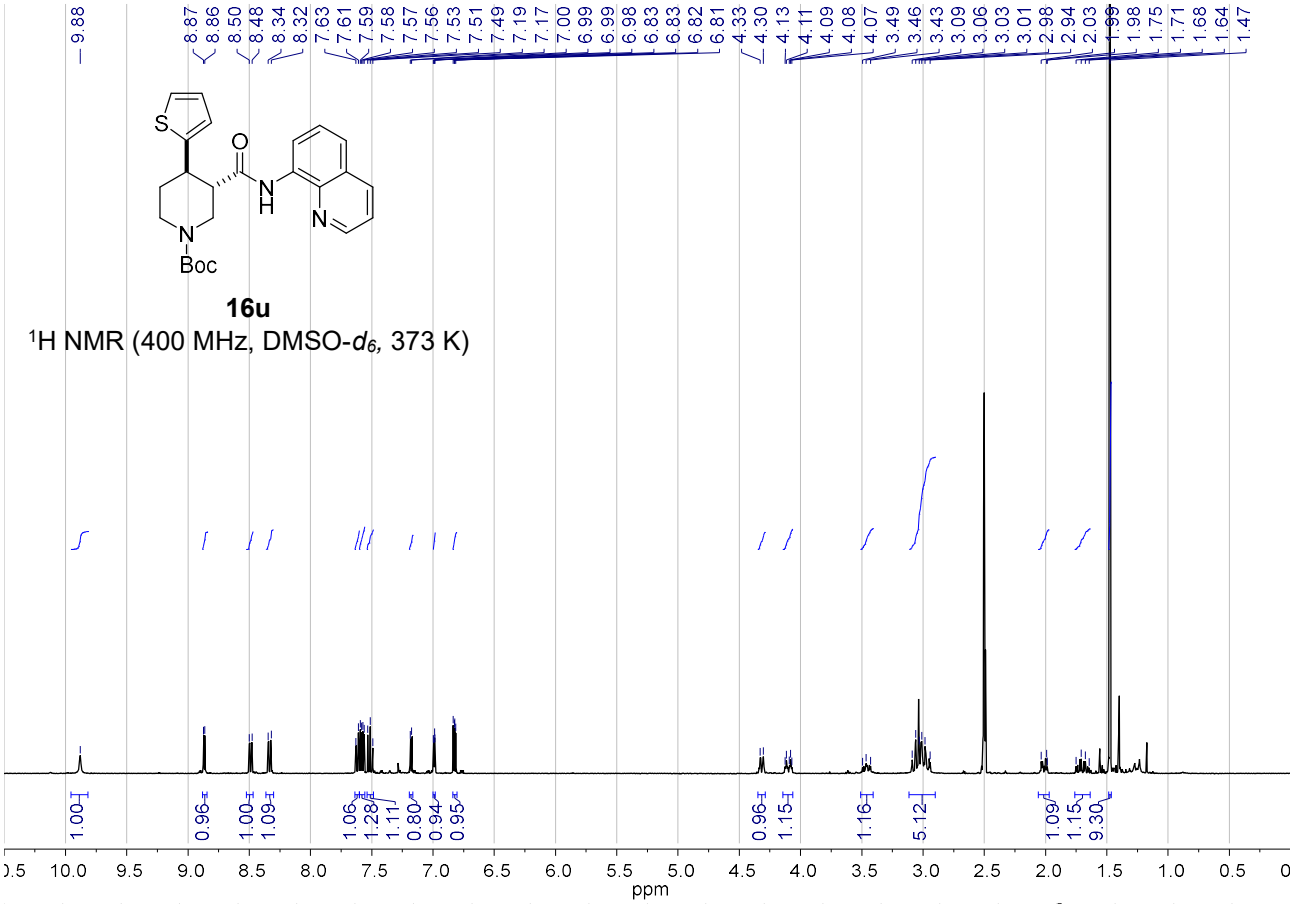
15u

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



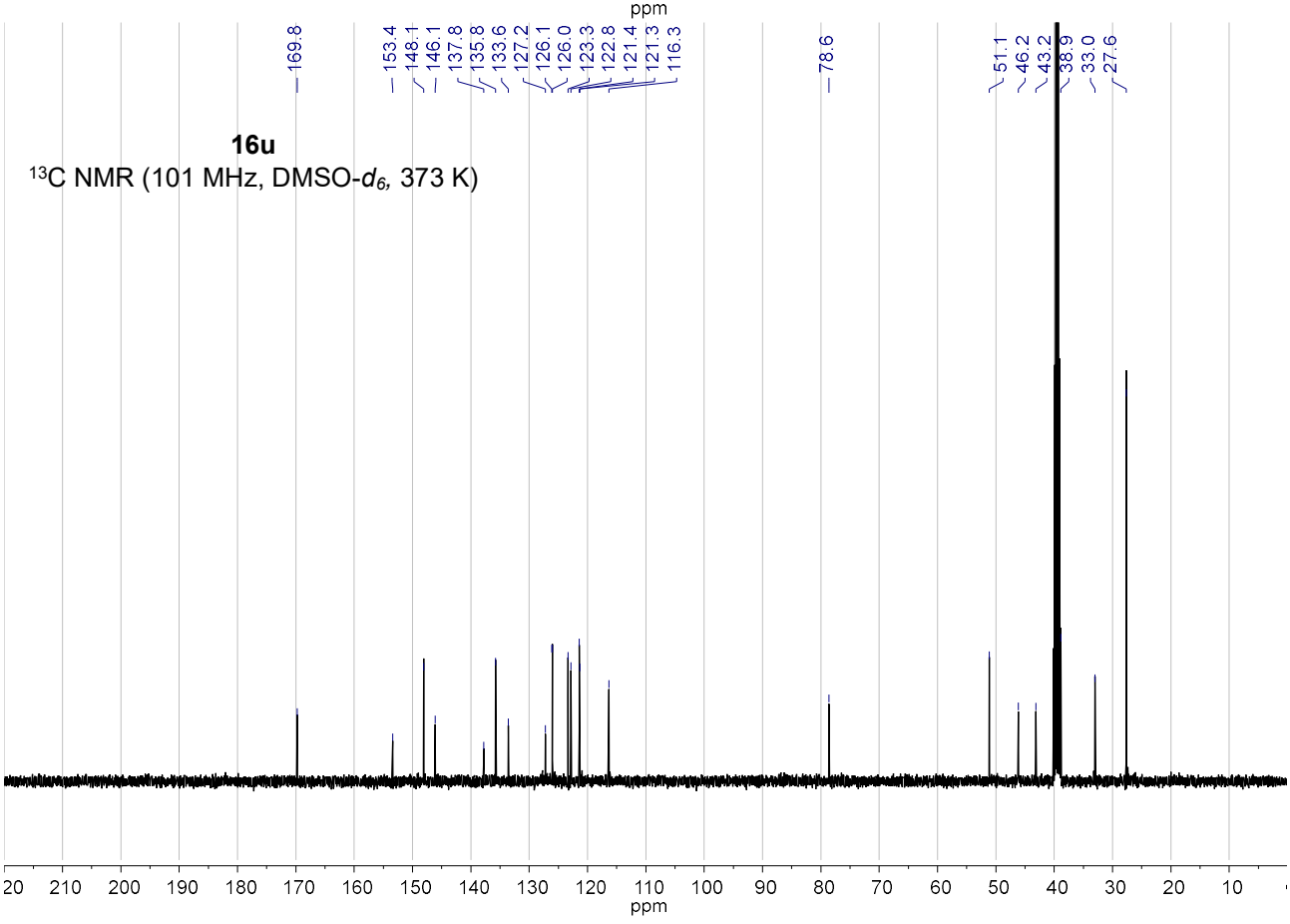
15u

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



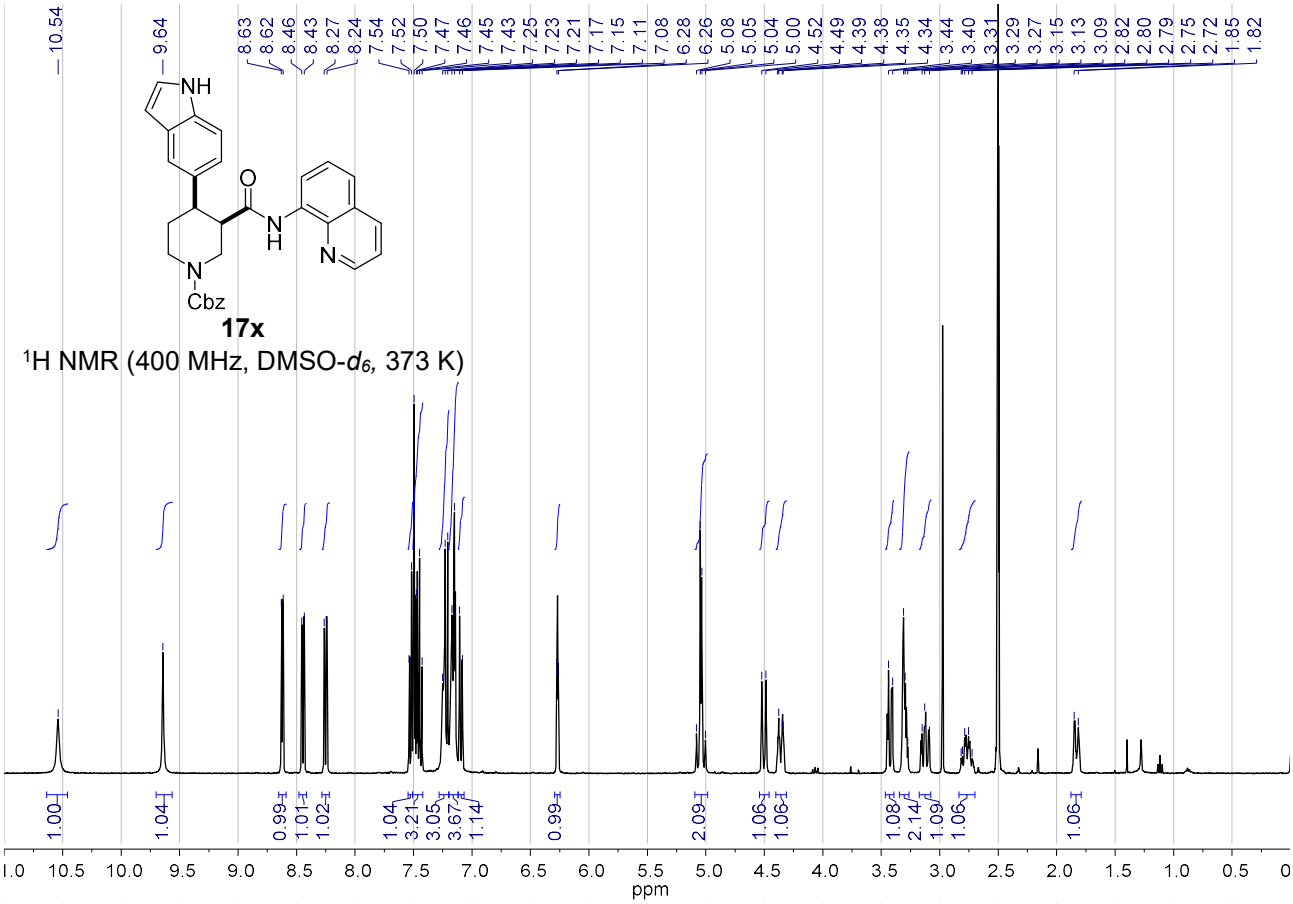
16u

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



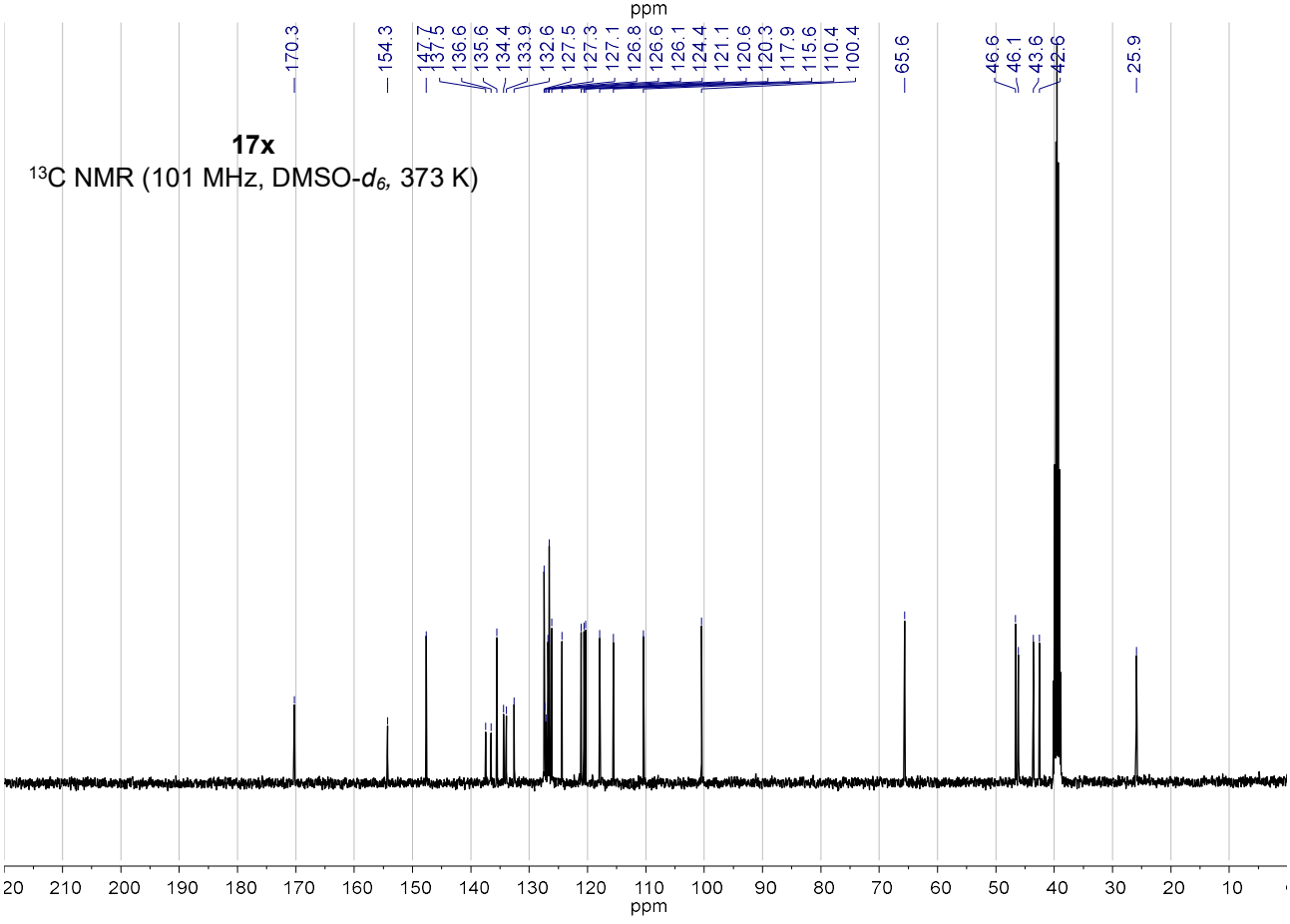
16u

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



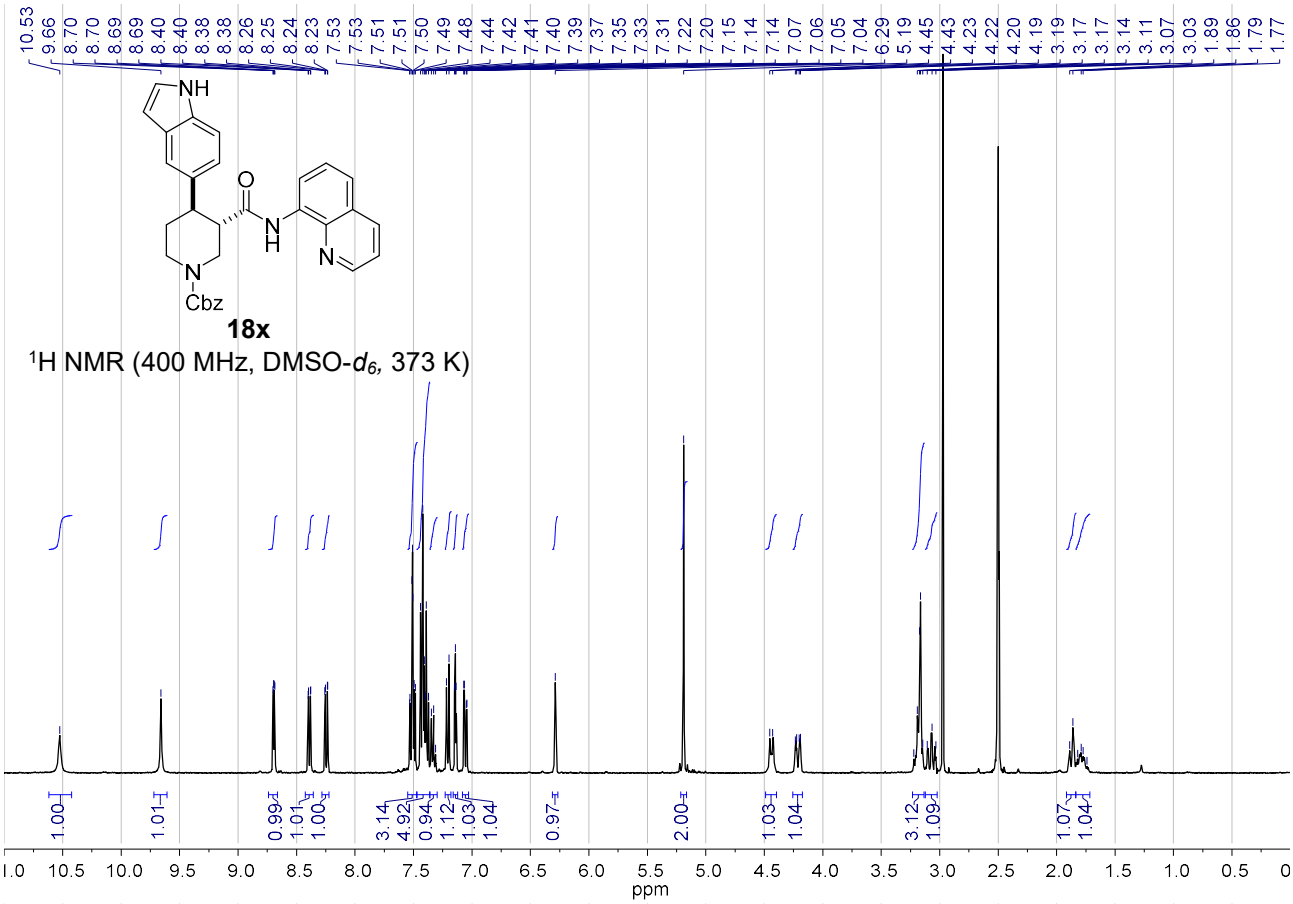
17x

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



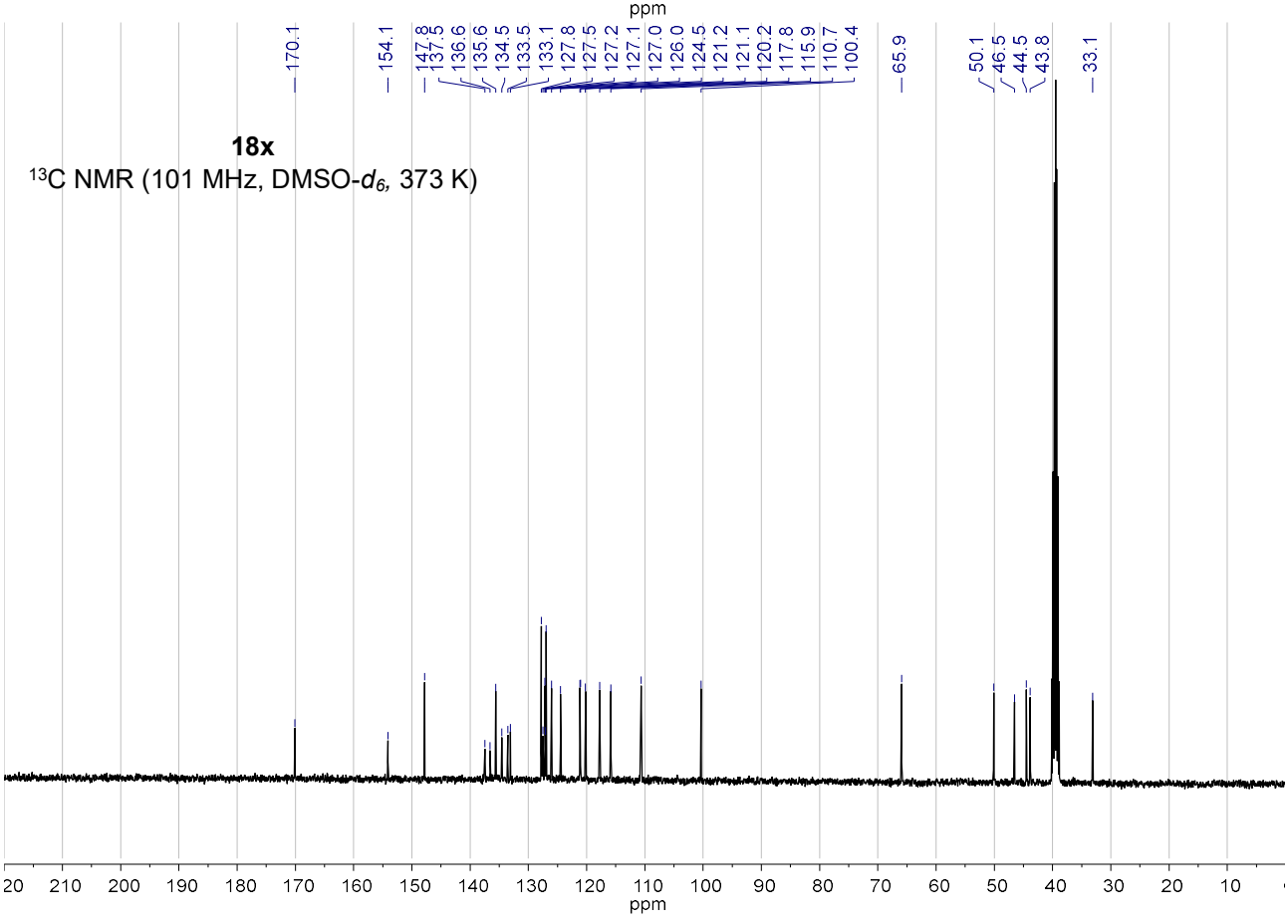
17x

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



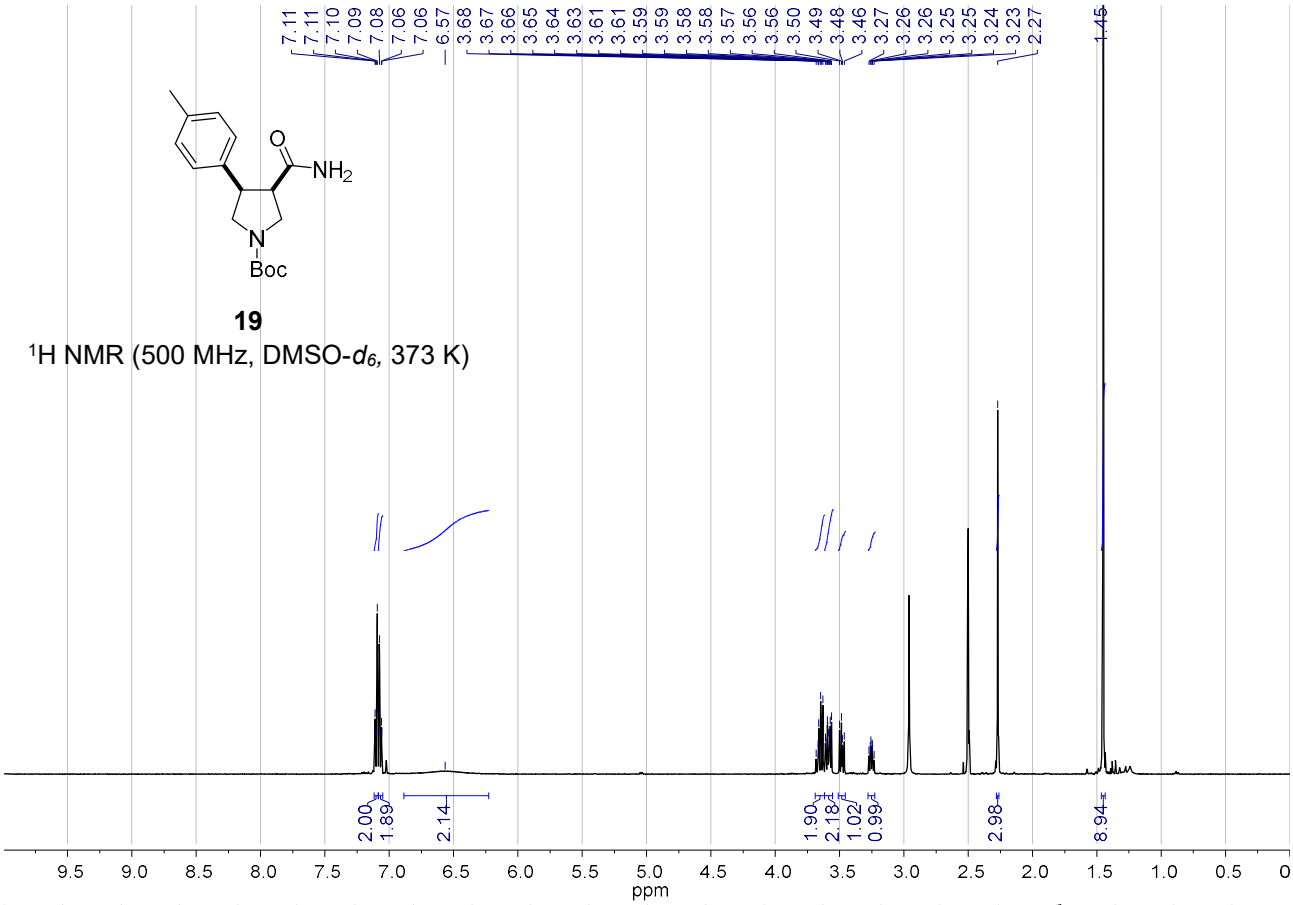
18x

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



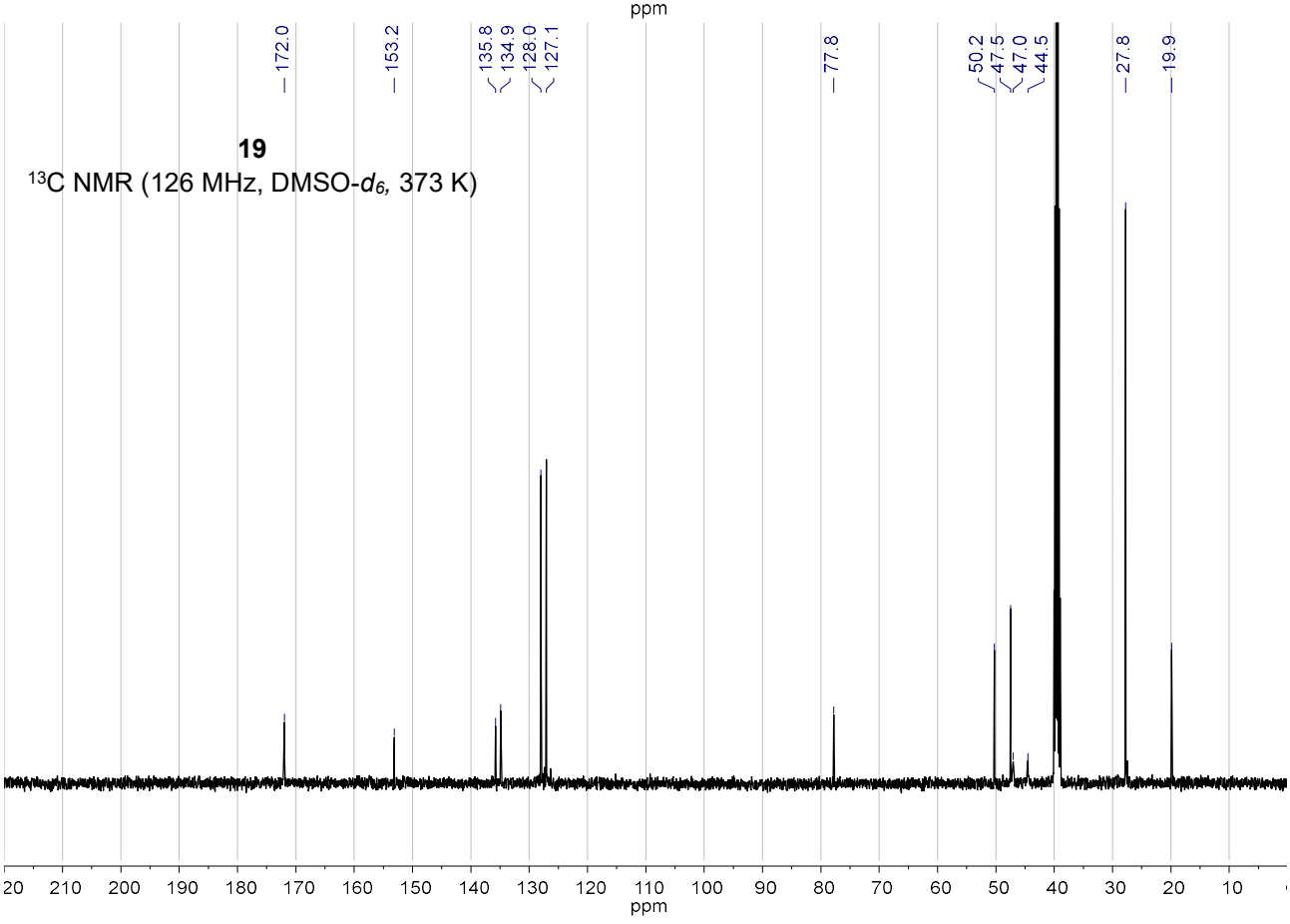
18x

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



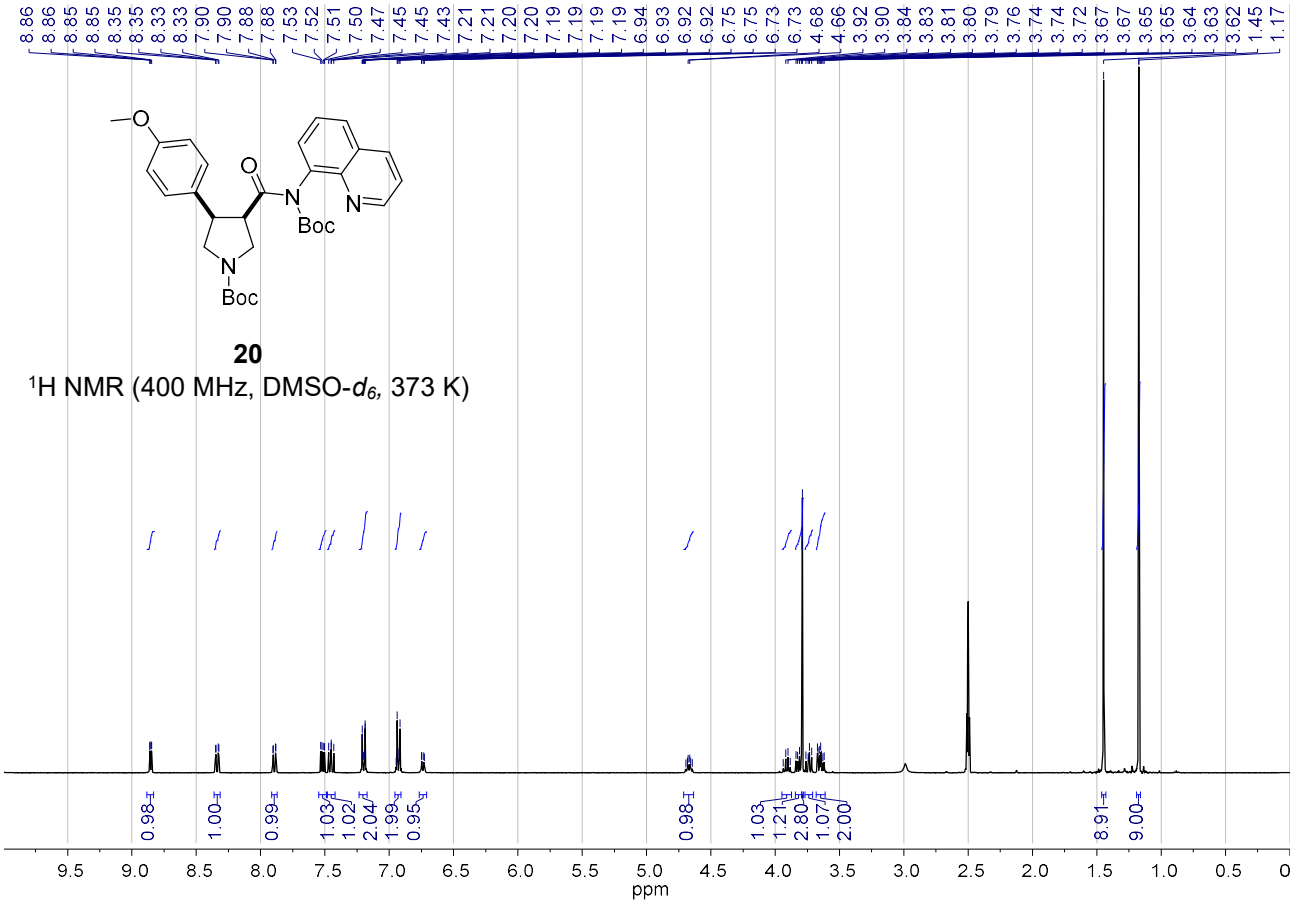
19

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



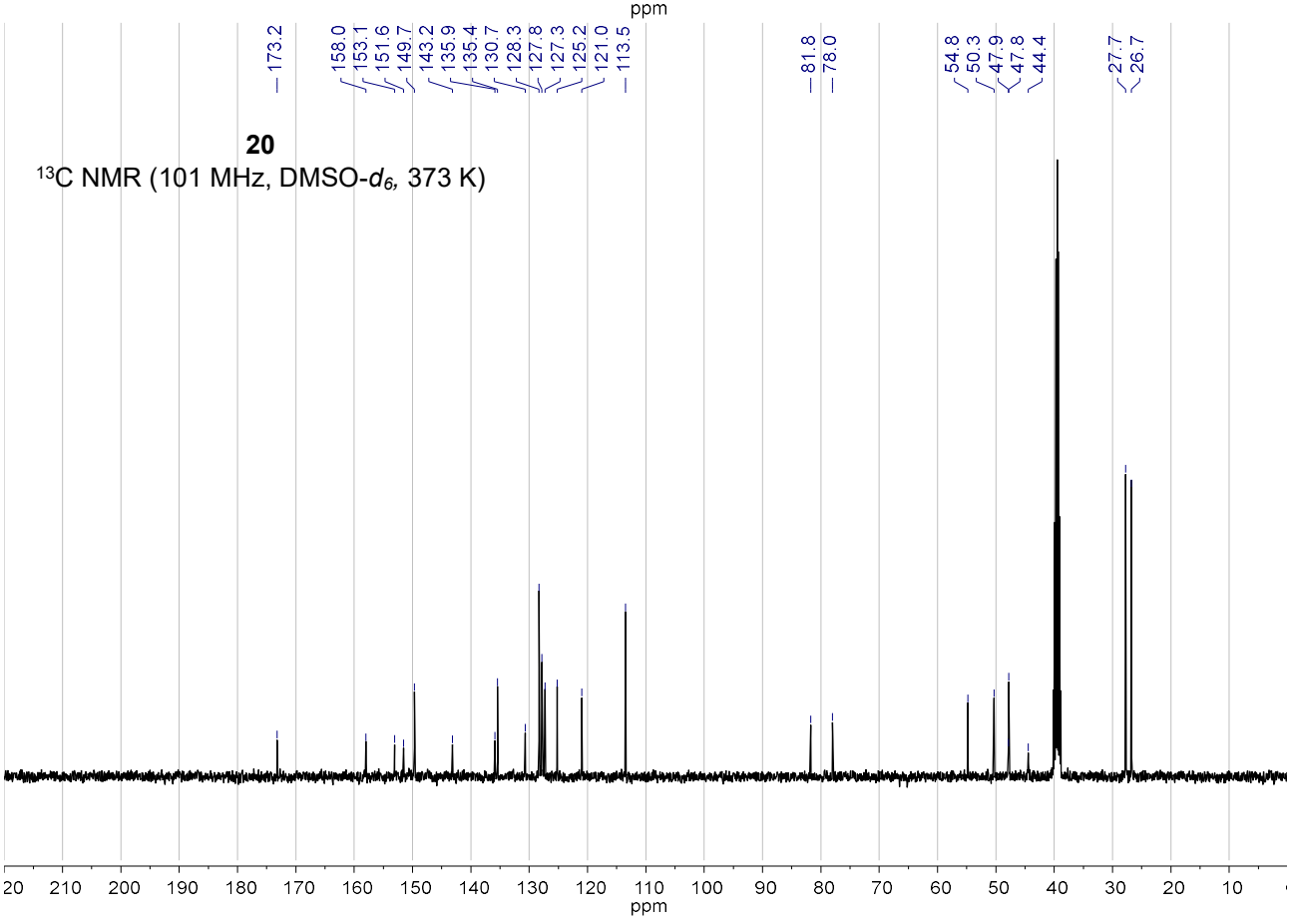
19

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



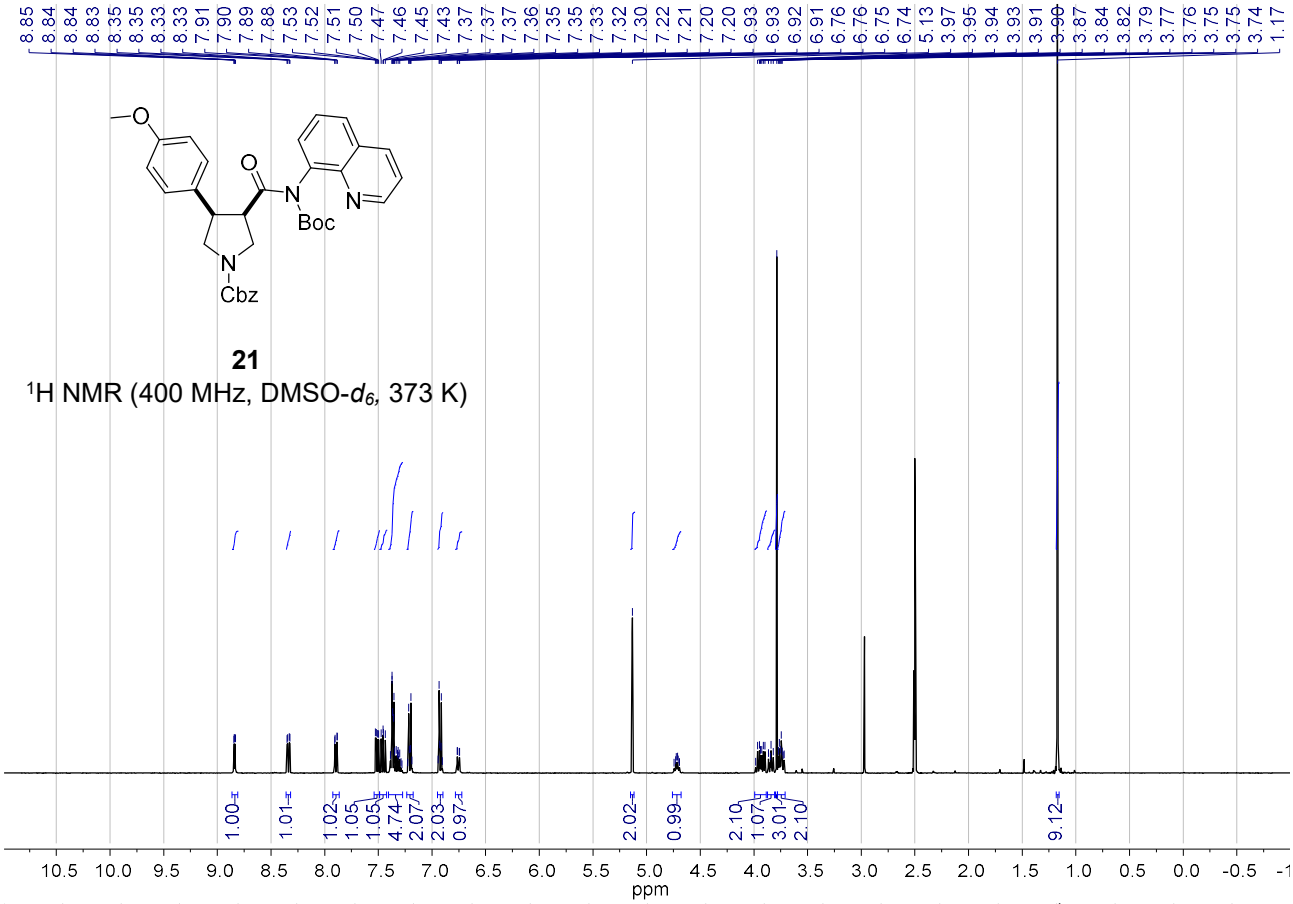
20

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



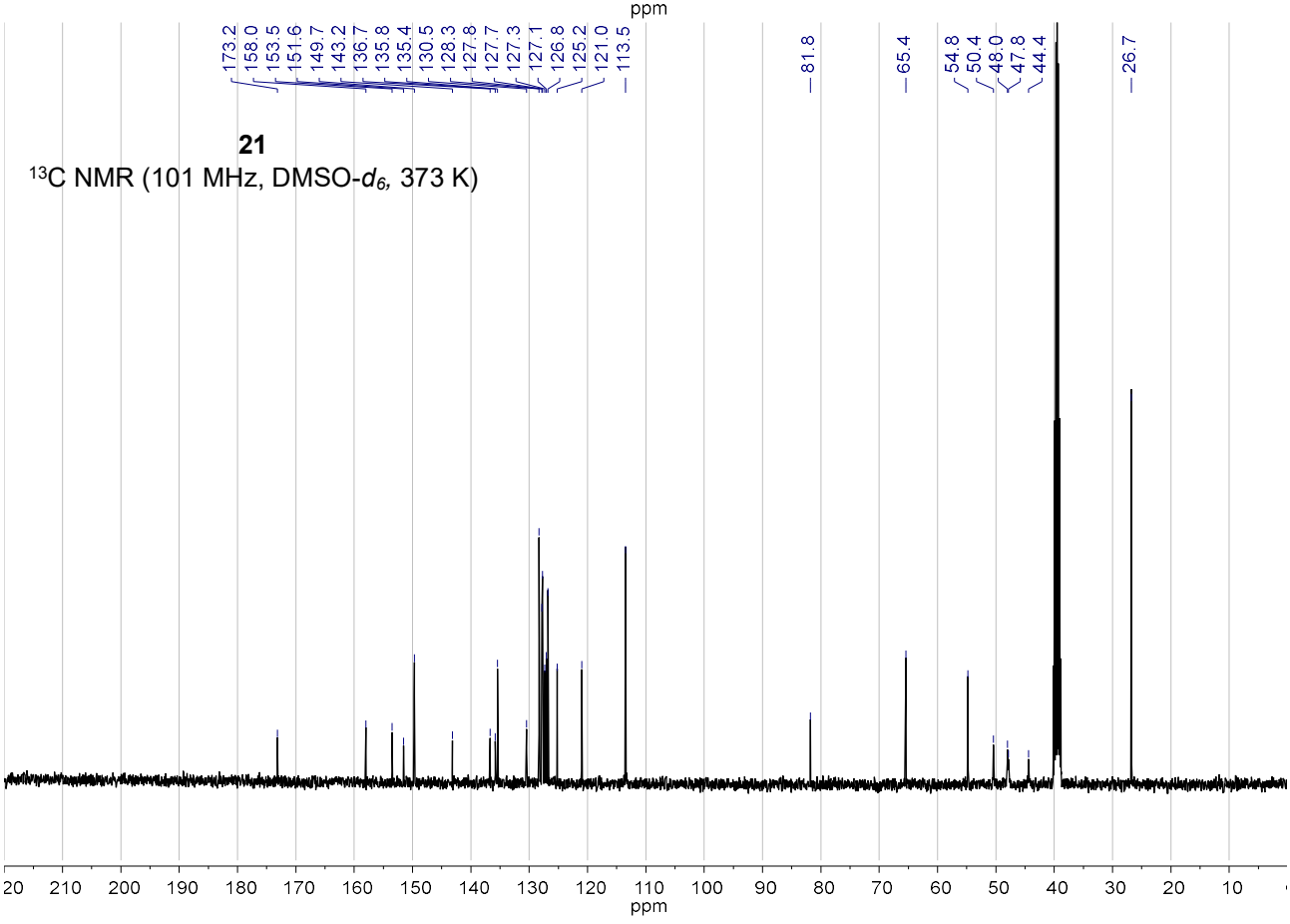
20

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



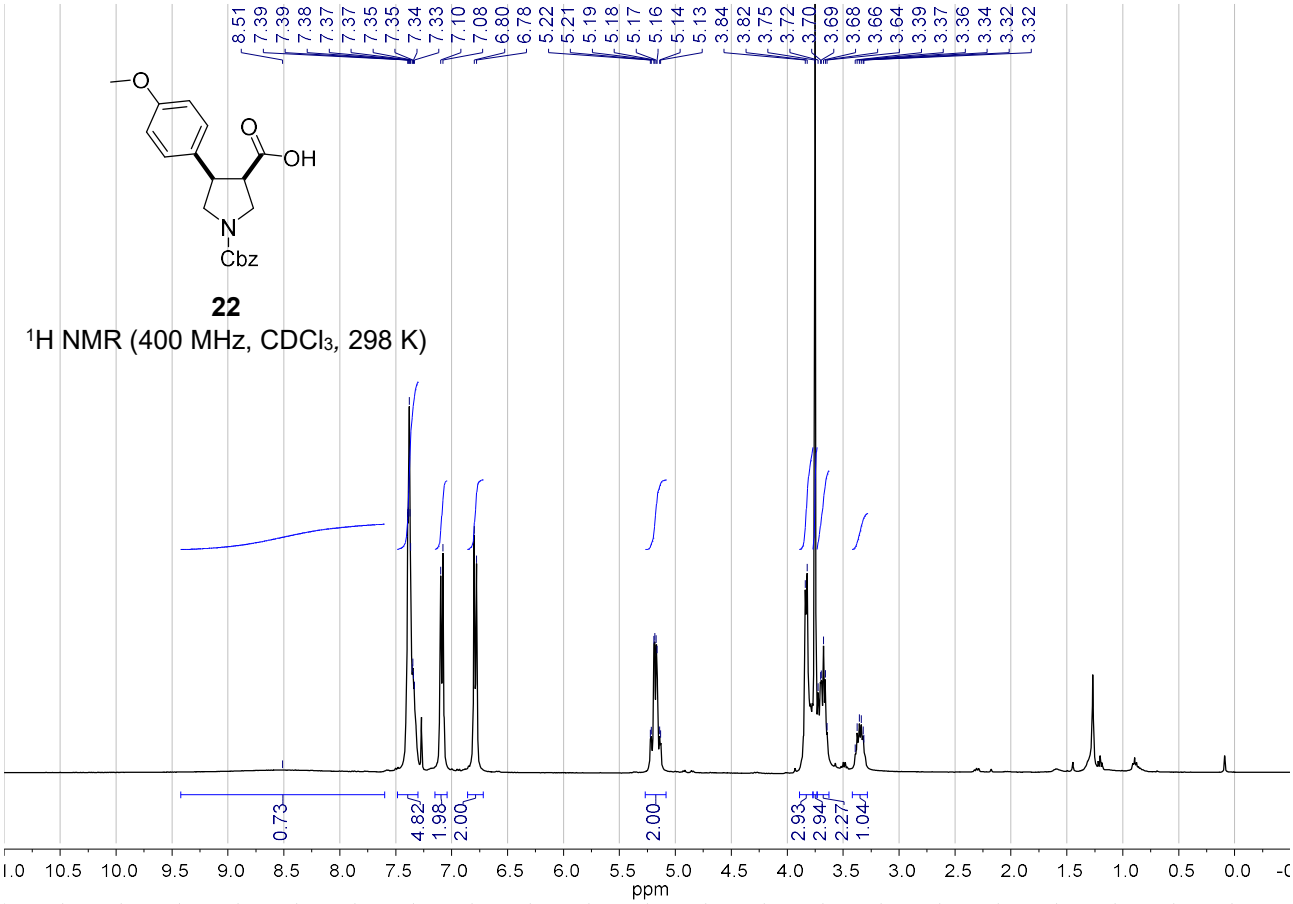
21

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



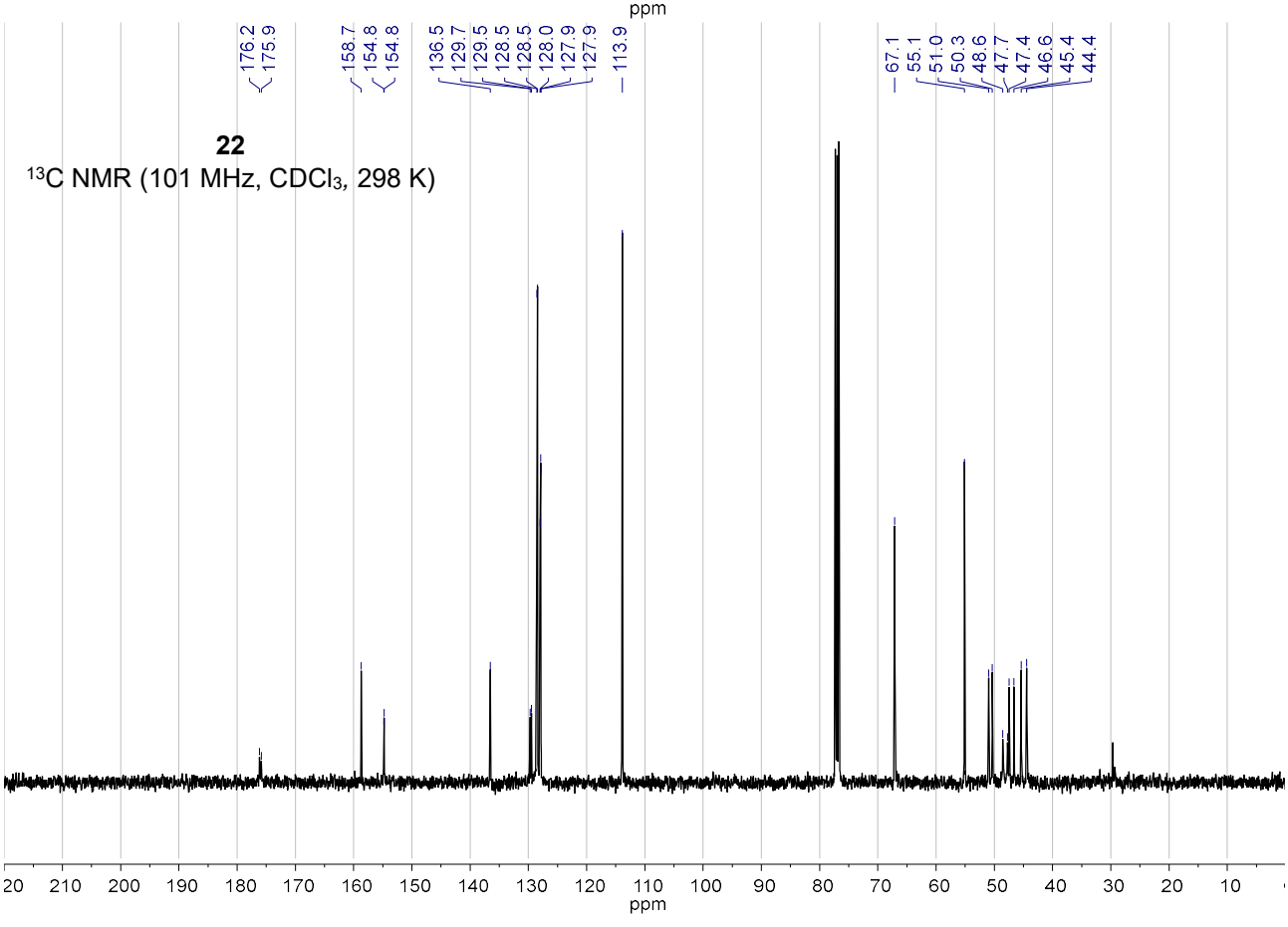
21

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



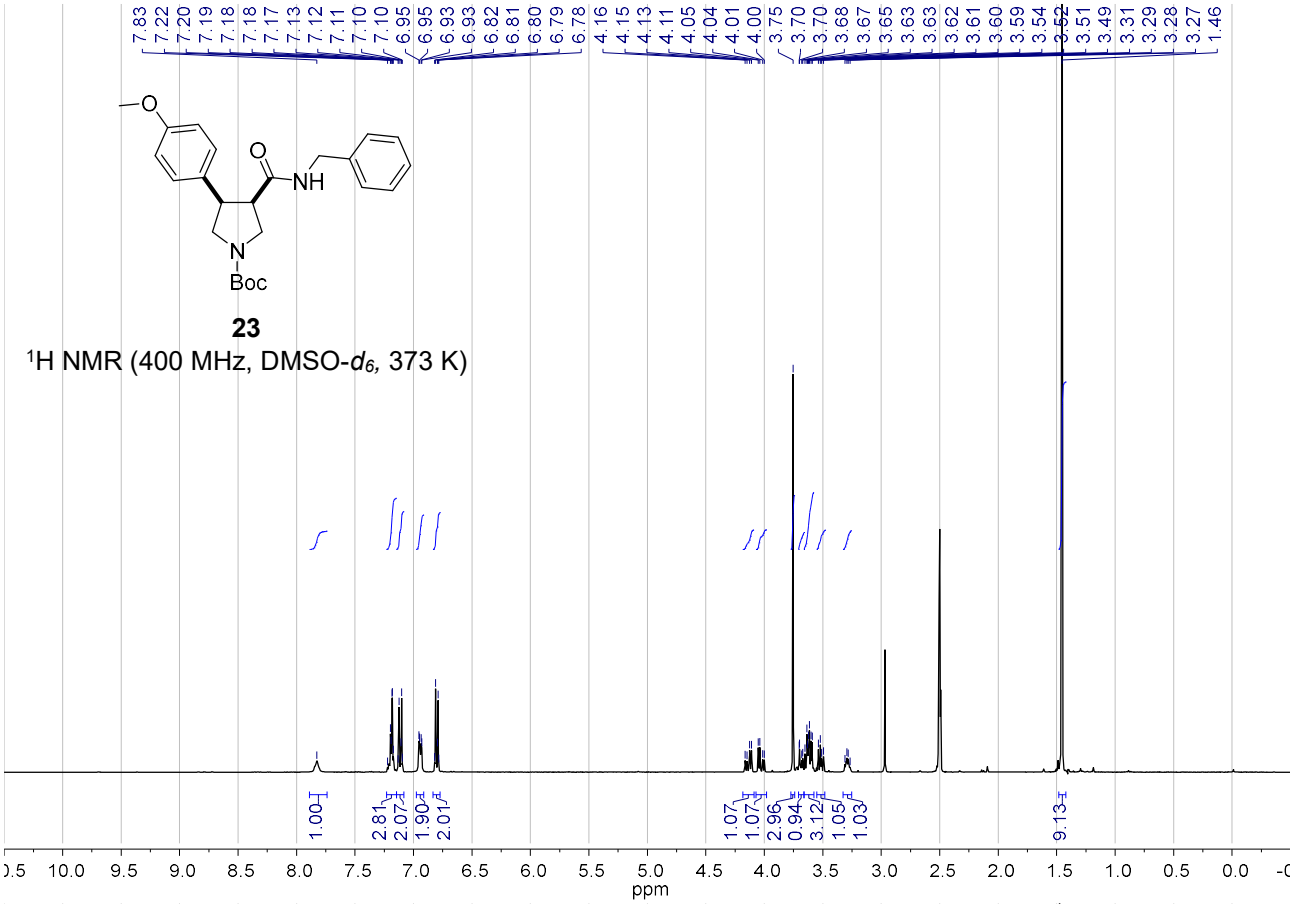
22

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



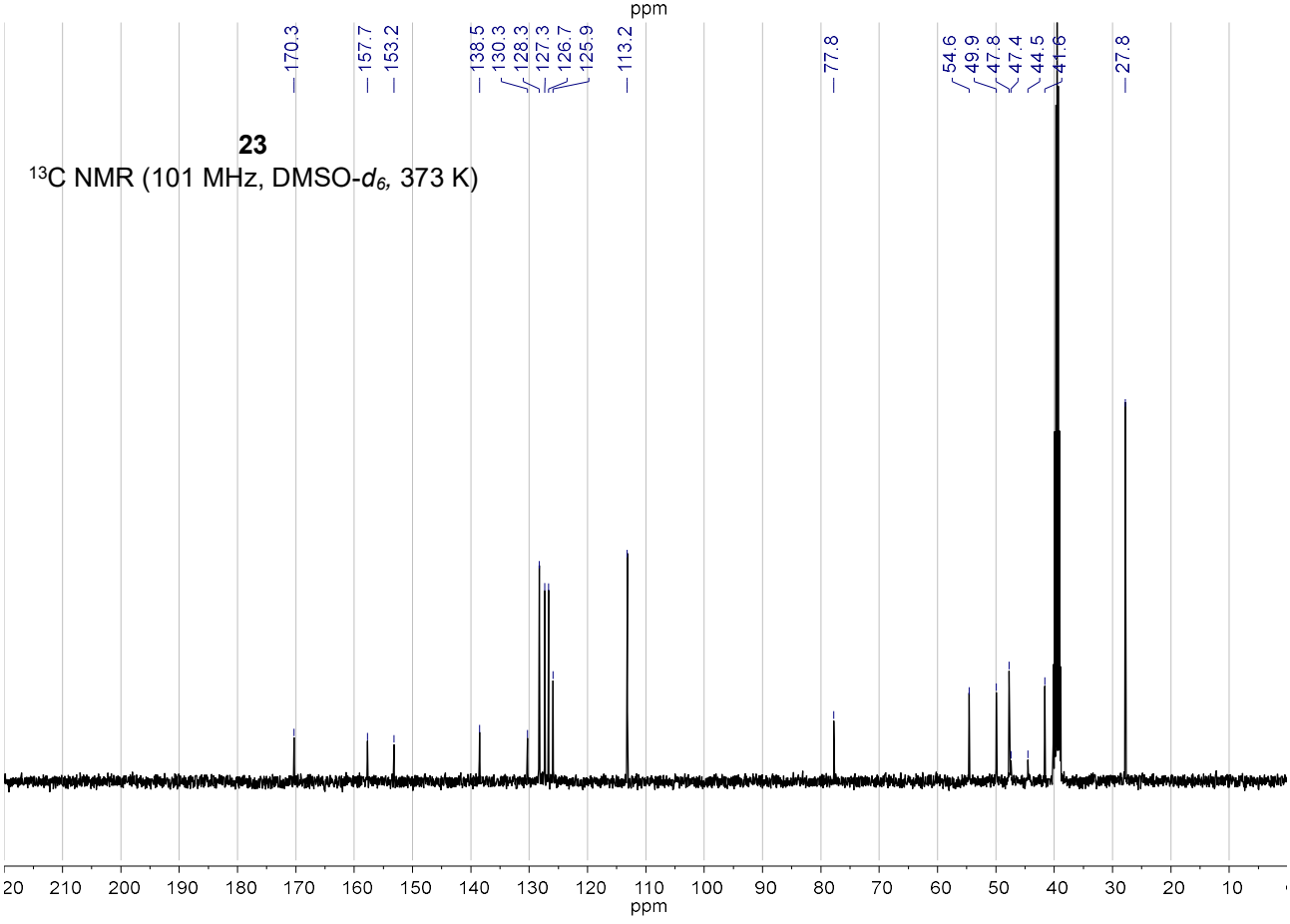
22

^{13}C NMR (101 MHz, $CDCl_3$, 298 K)



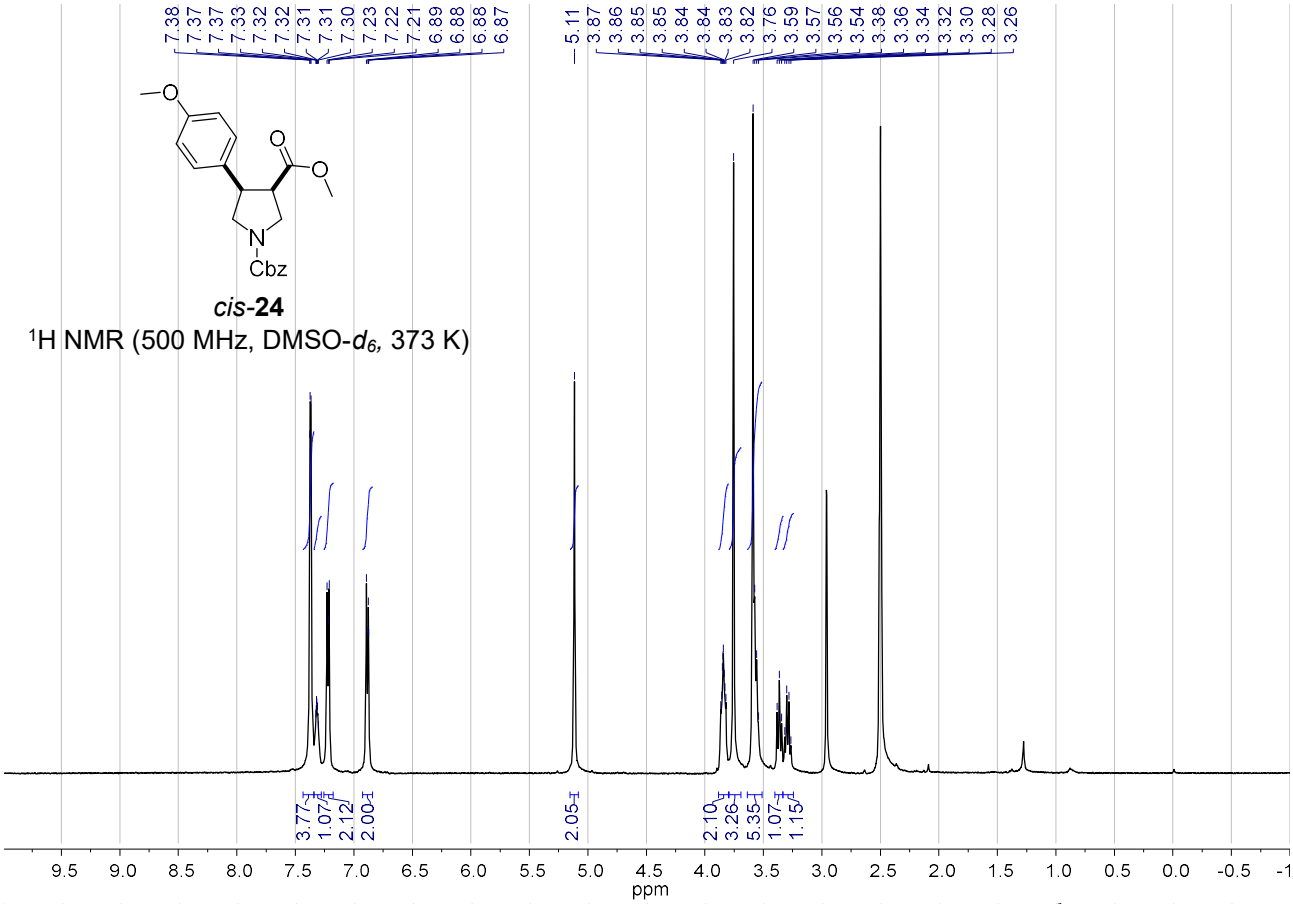
23

^{1}H NMR (400 MHz, DMSO-*d*$_6$, 373 K)



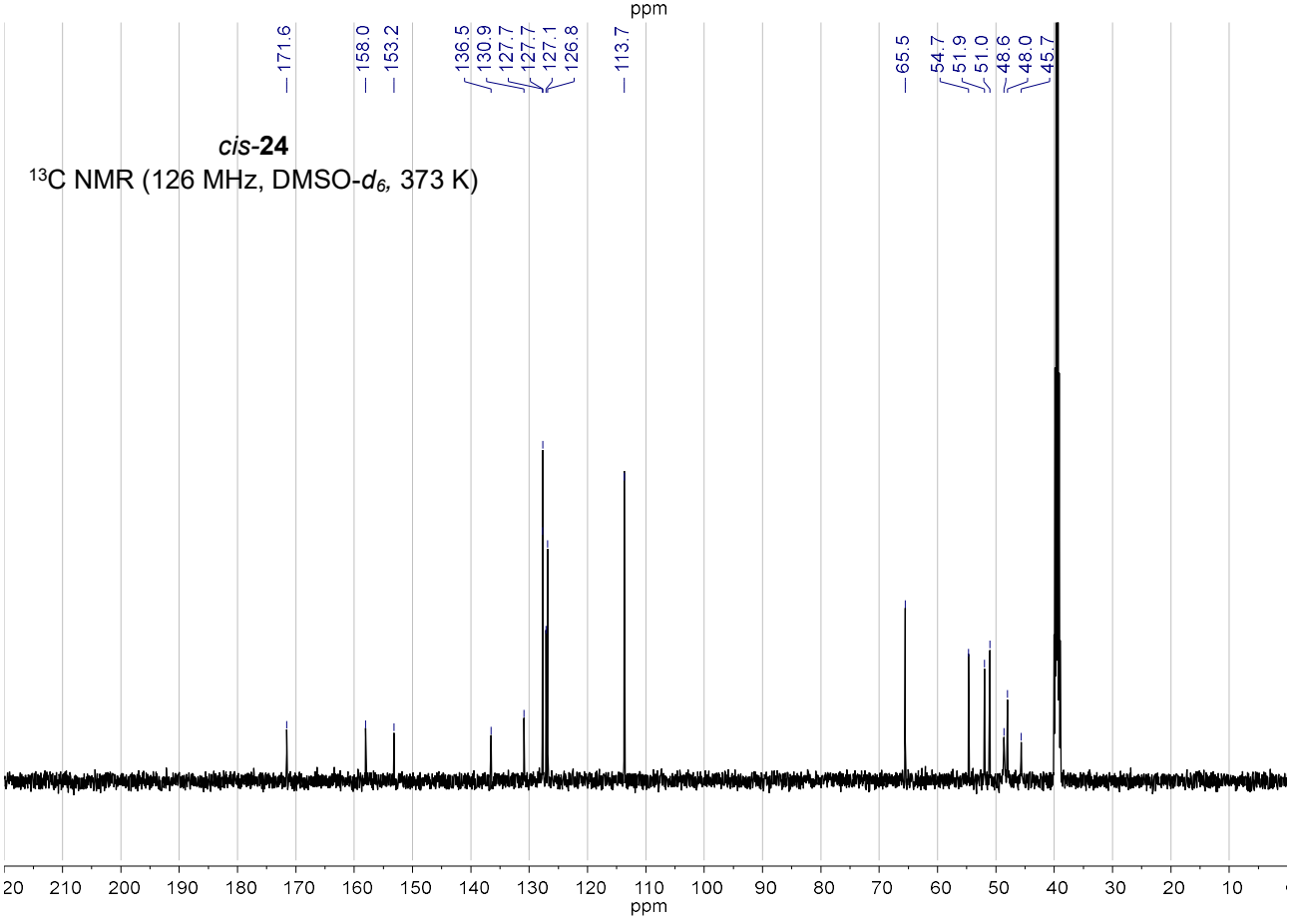
23

^{13}C NMR (101 MHz, DMSO-*d*$_6$, 373 K)



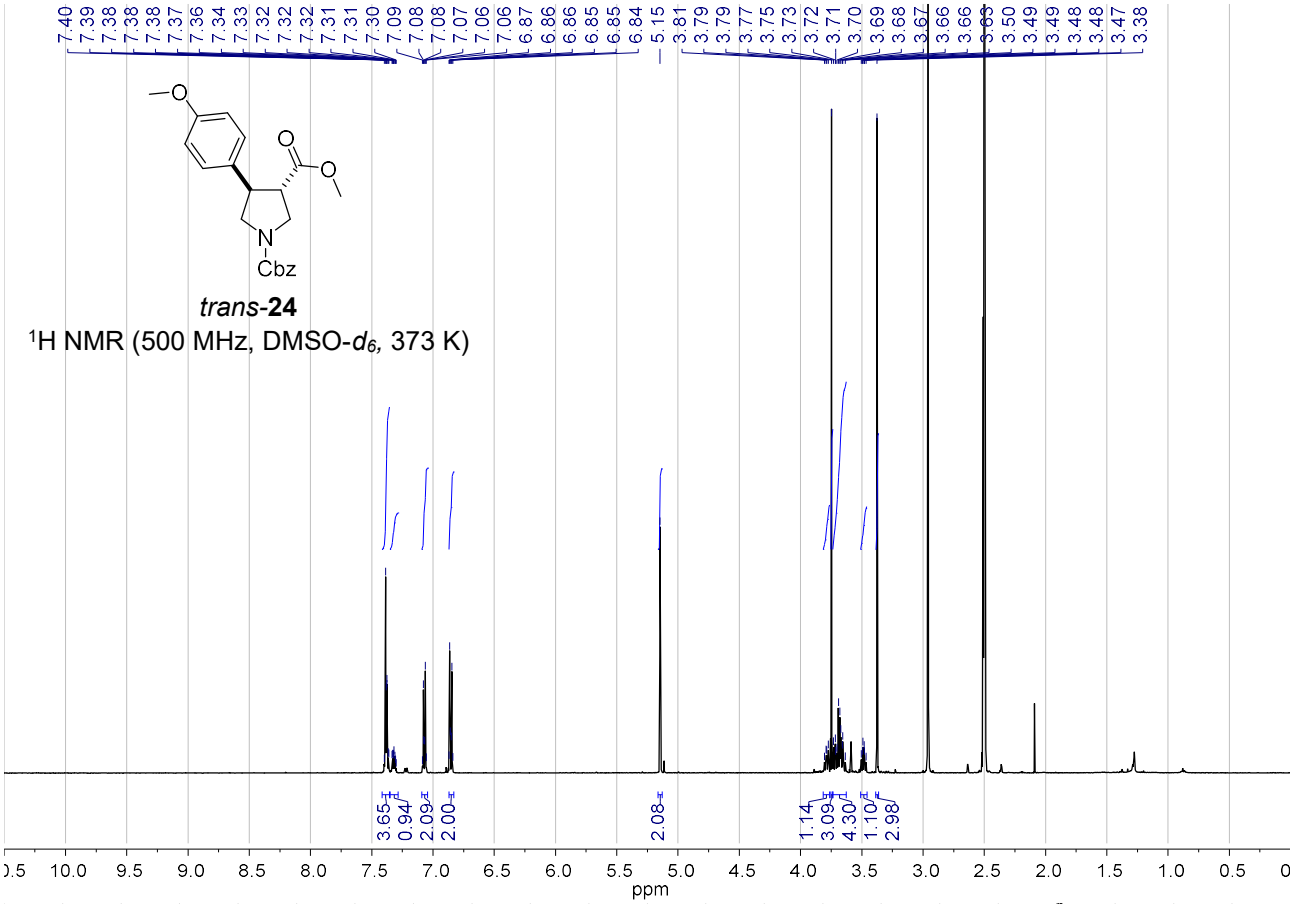
cis-**24**

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



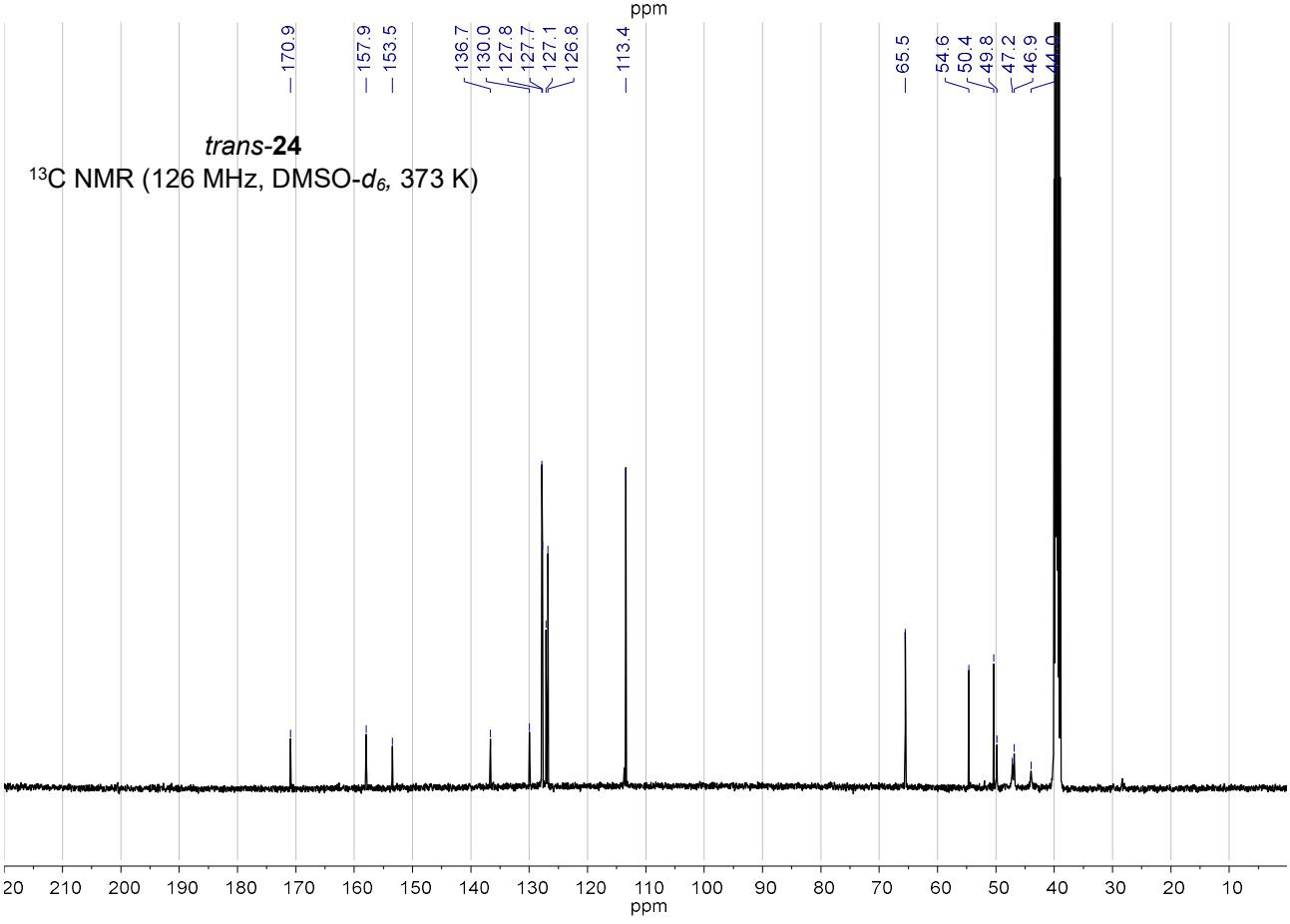
cis-**24**

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



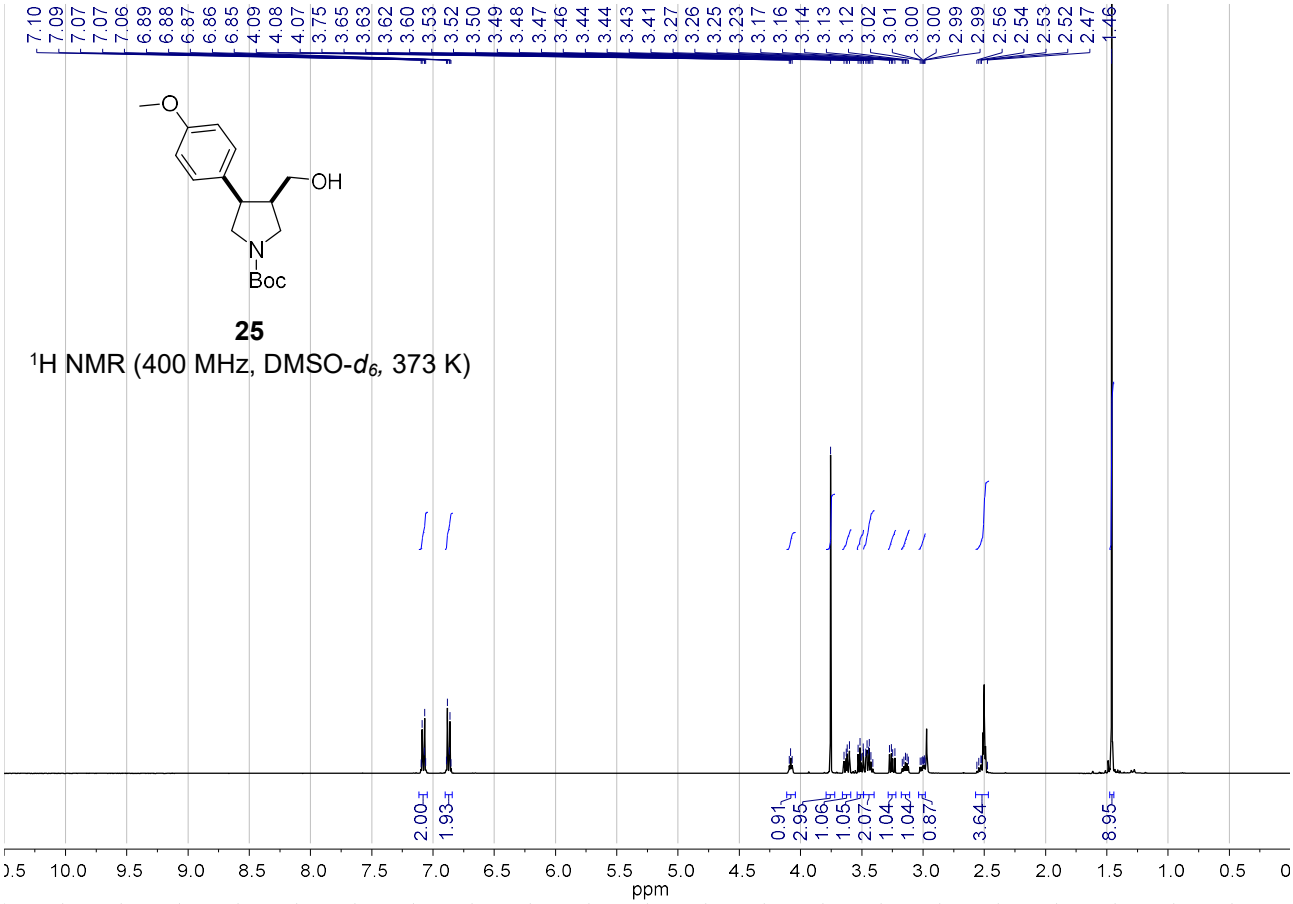
trans-**24**

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



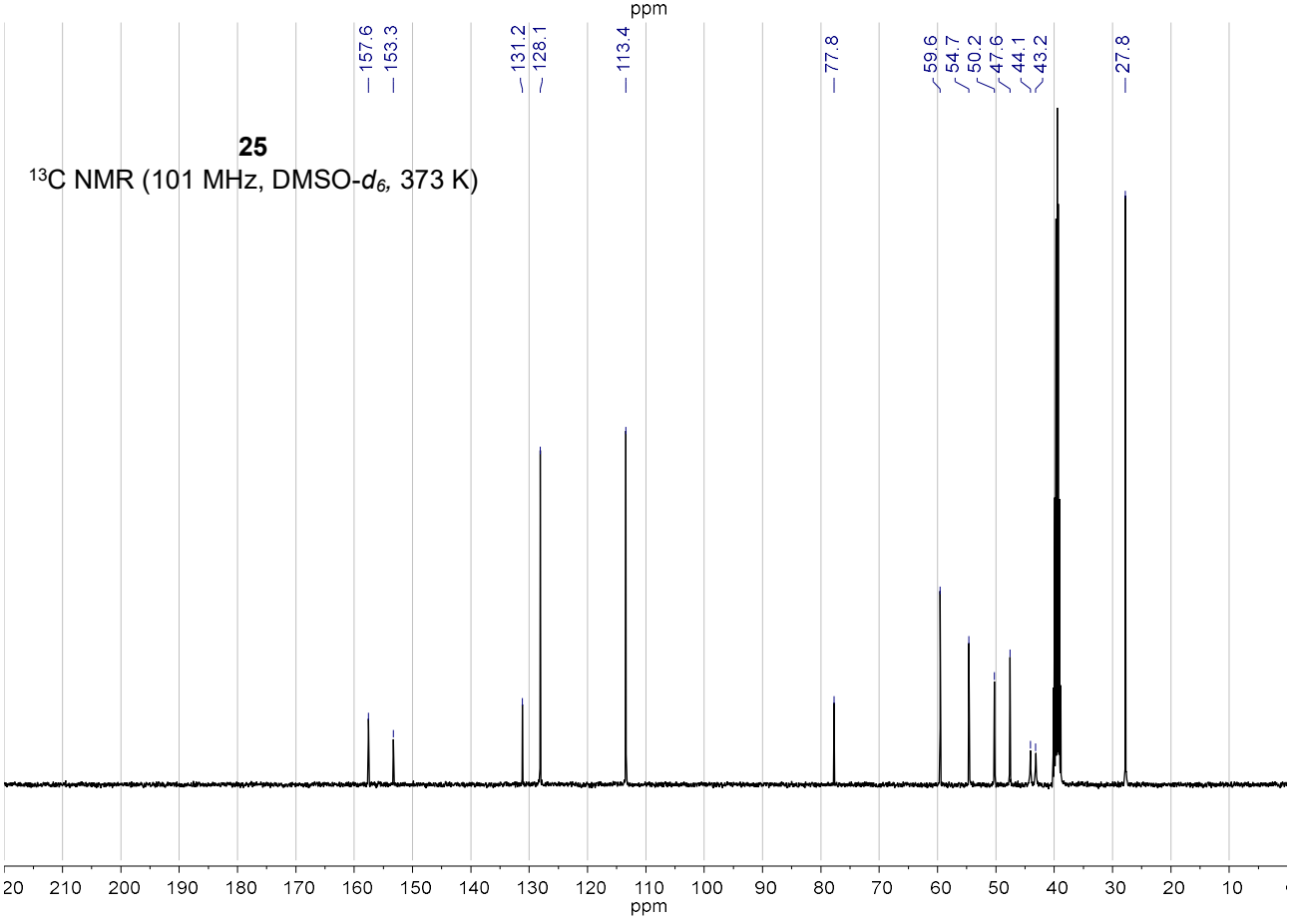
trans-**24**

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



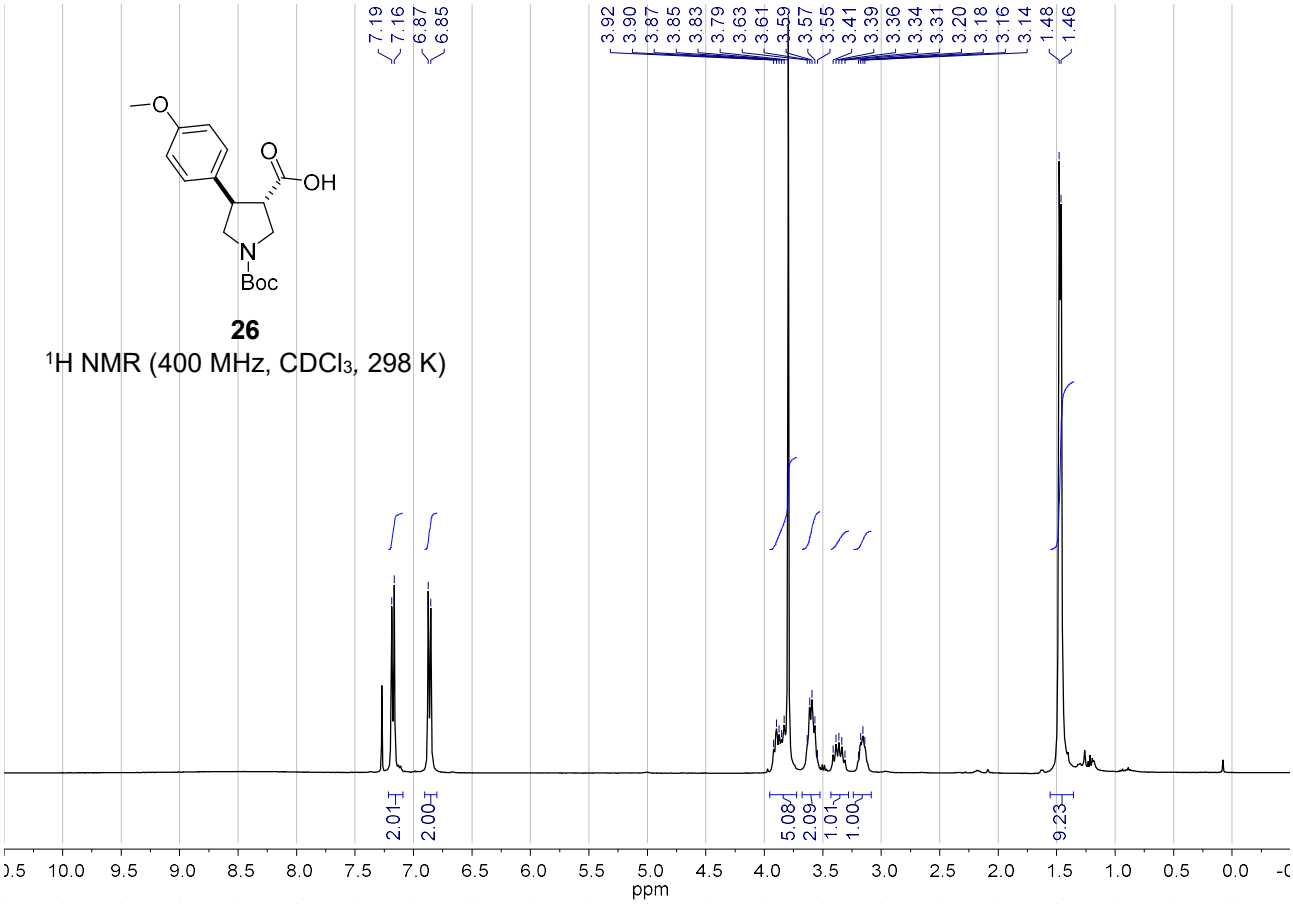
25

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



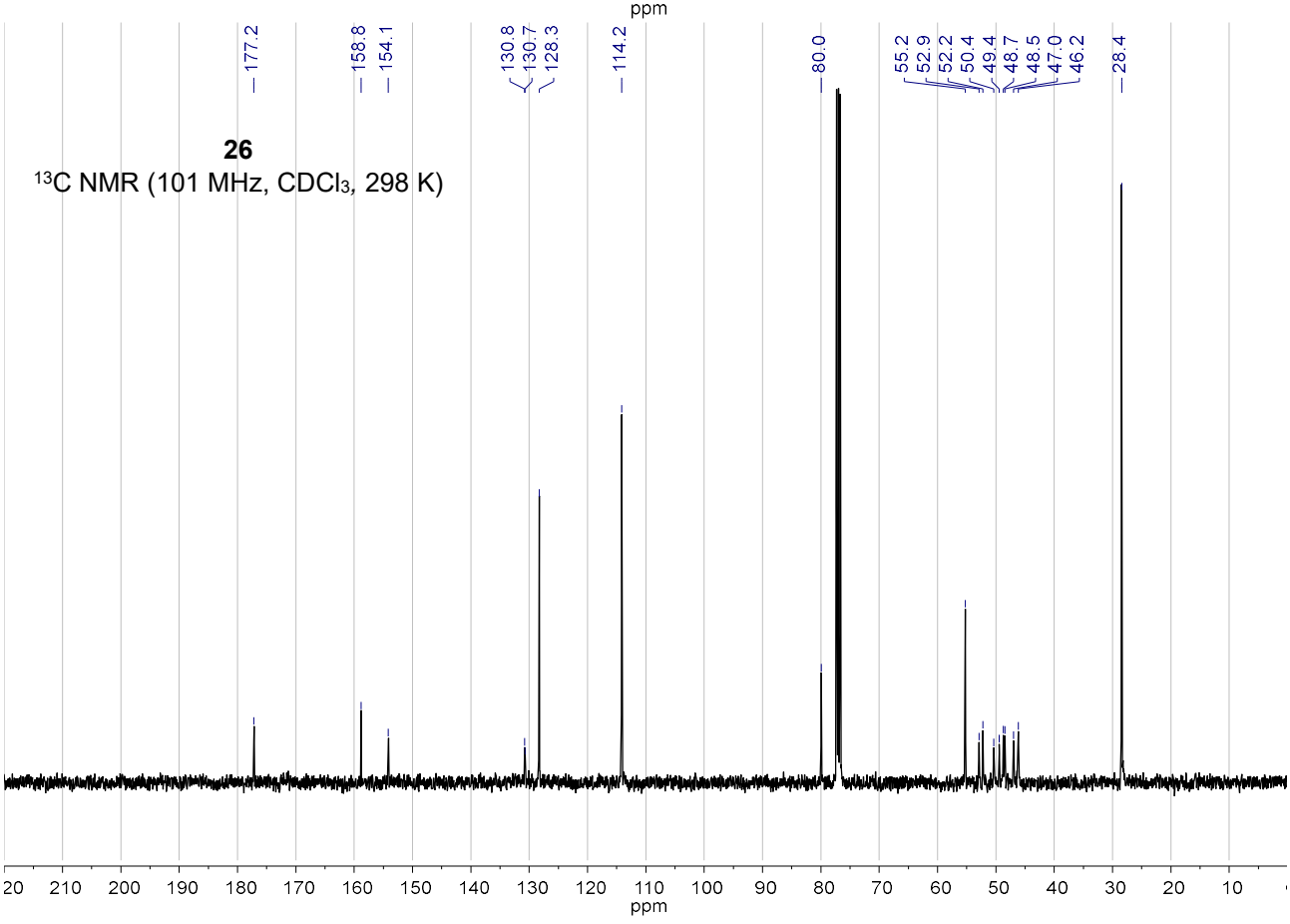
25

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



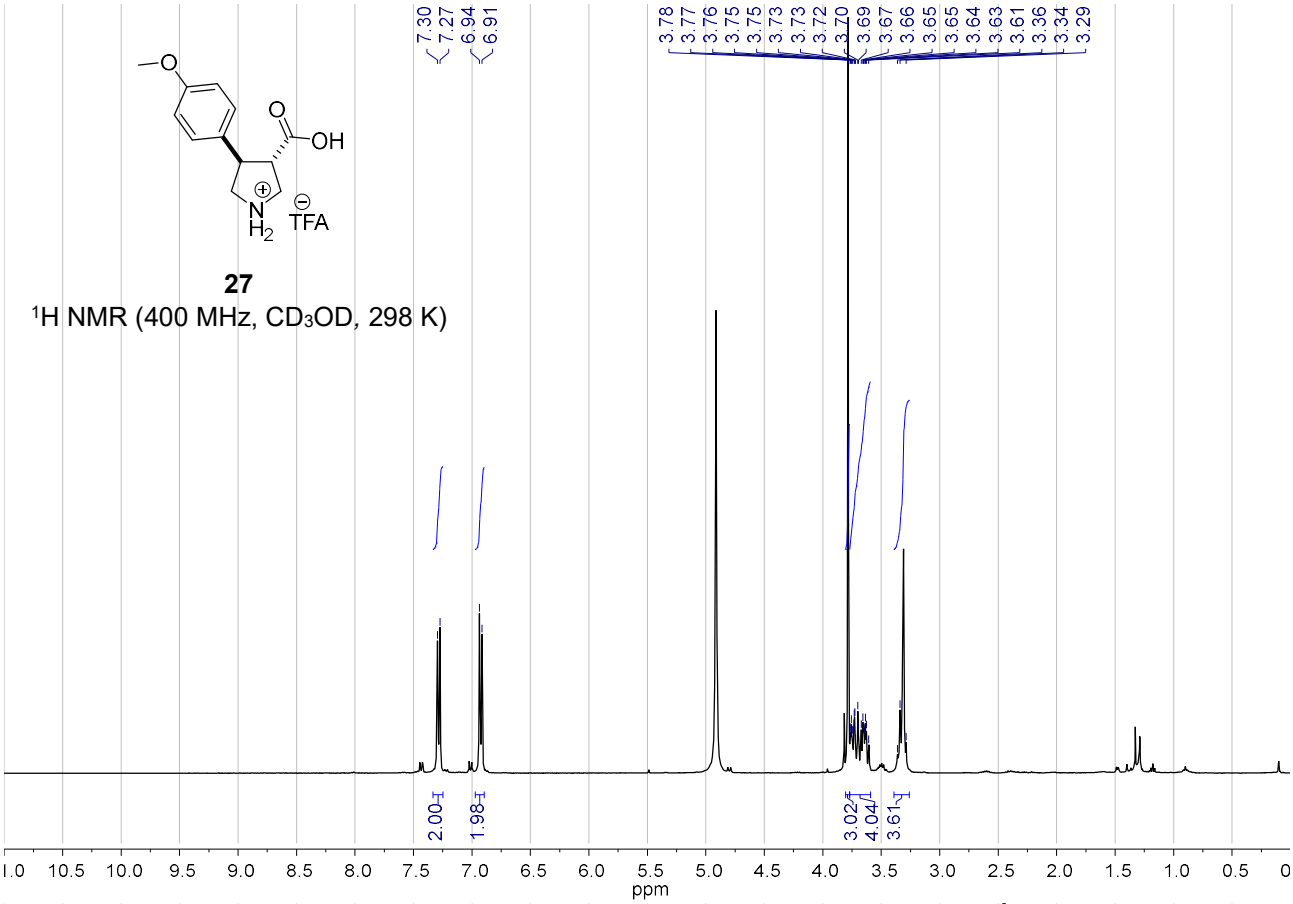
26

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



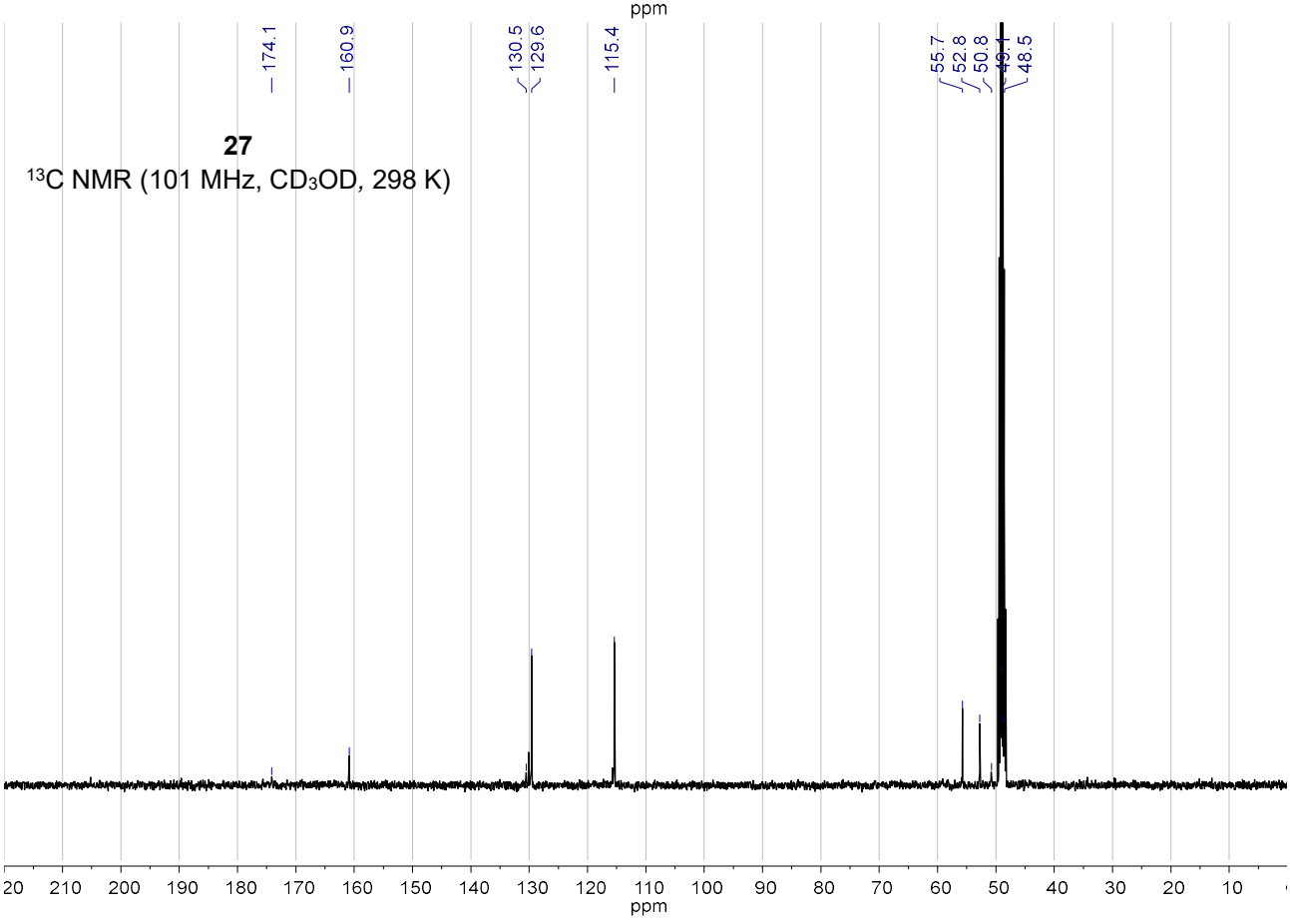
26

^{13}C NMR (101 MHz, $CDCl_3$, 298 K)



27

^{1}H NMR (400 MHz, CD_3OD, 298 K)

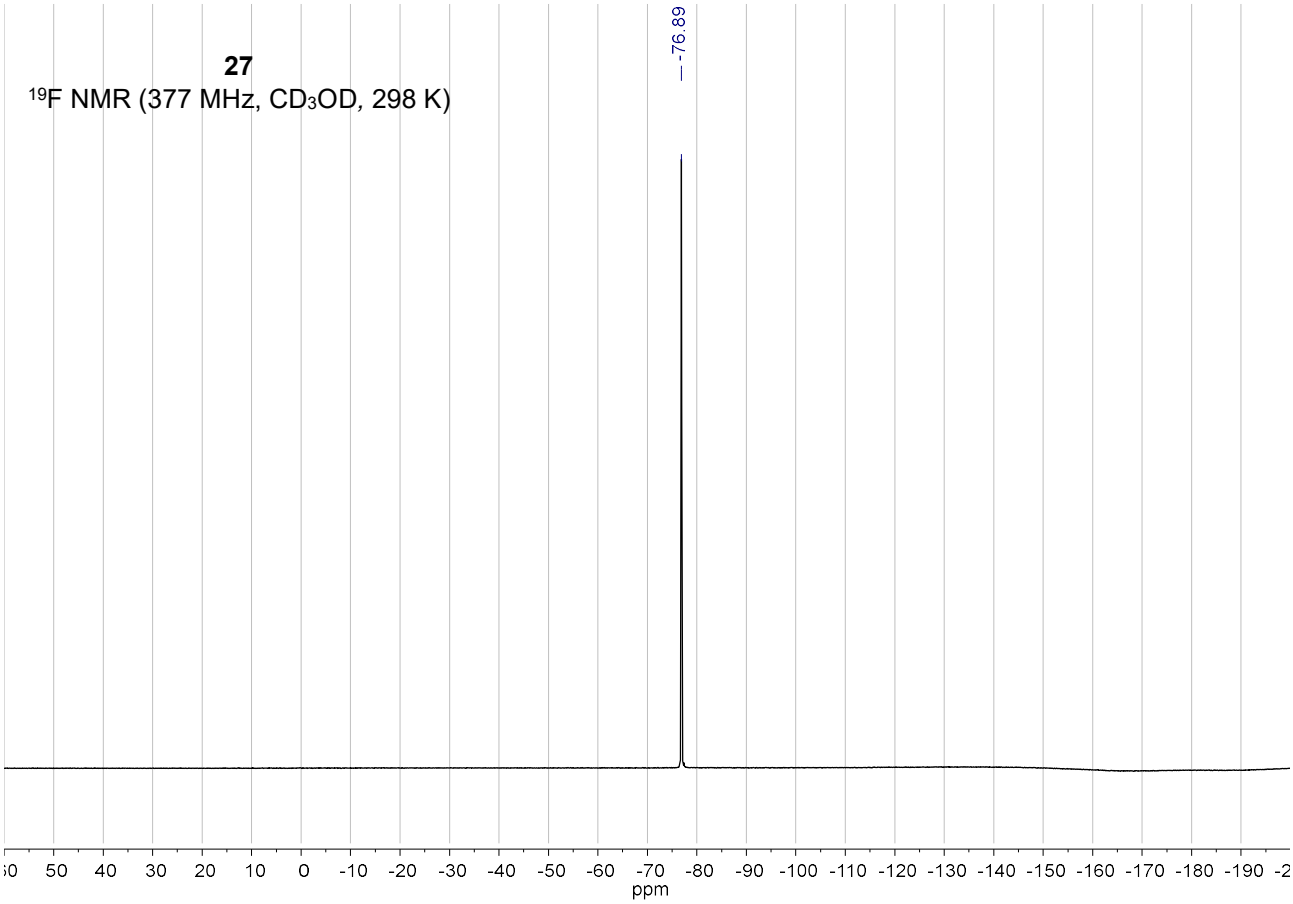


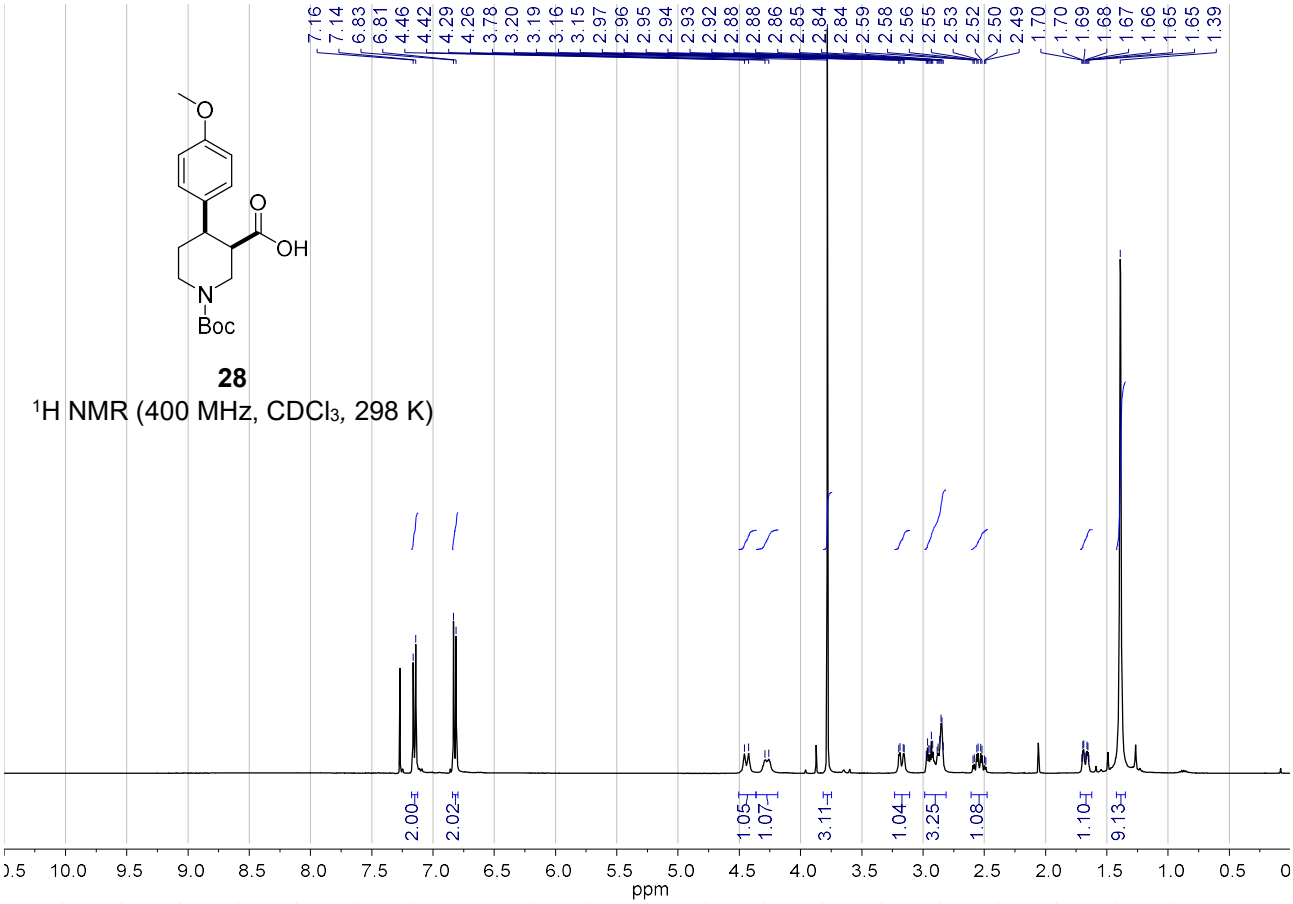
27

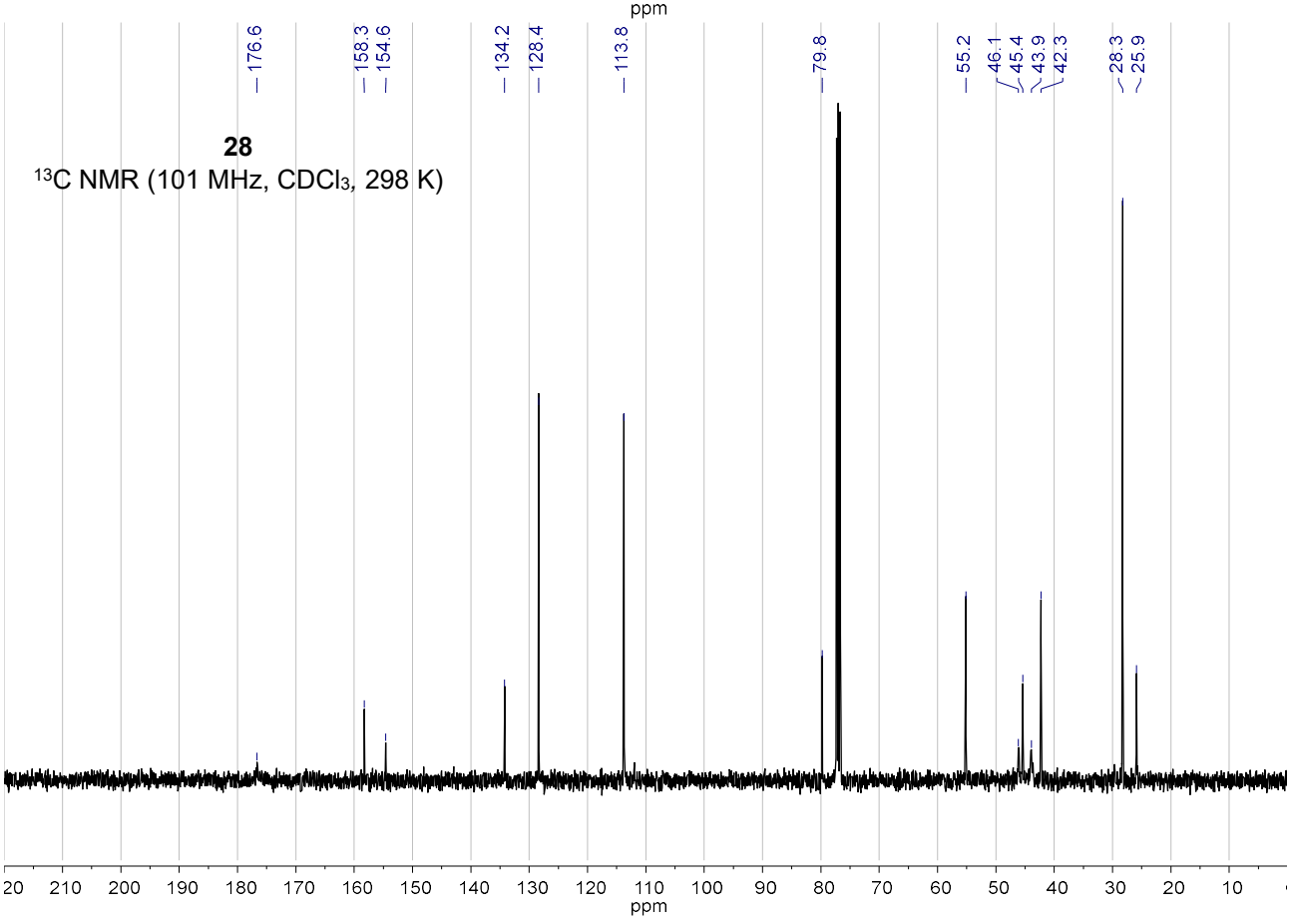
^{13}C NMR (101 MHz, CD_3OD, 298 K)

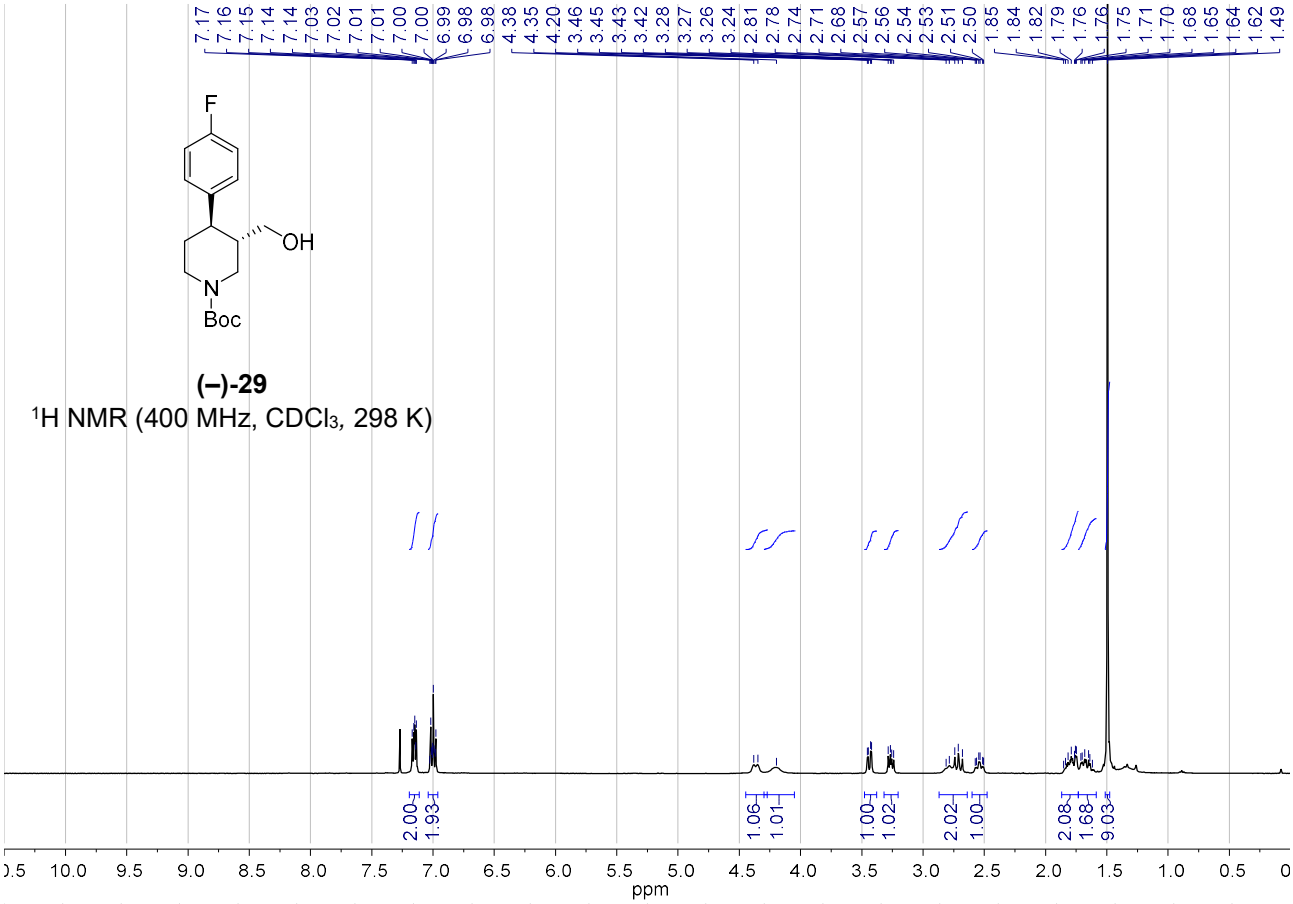
27

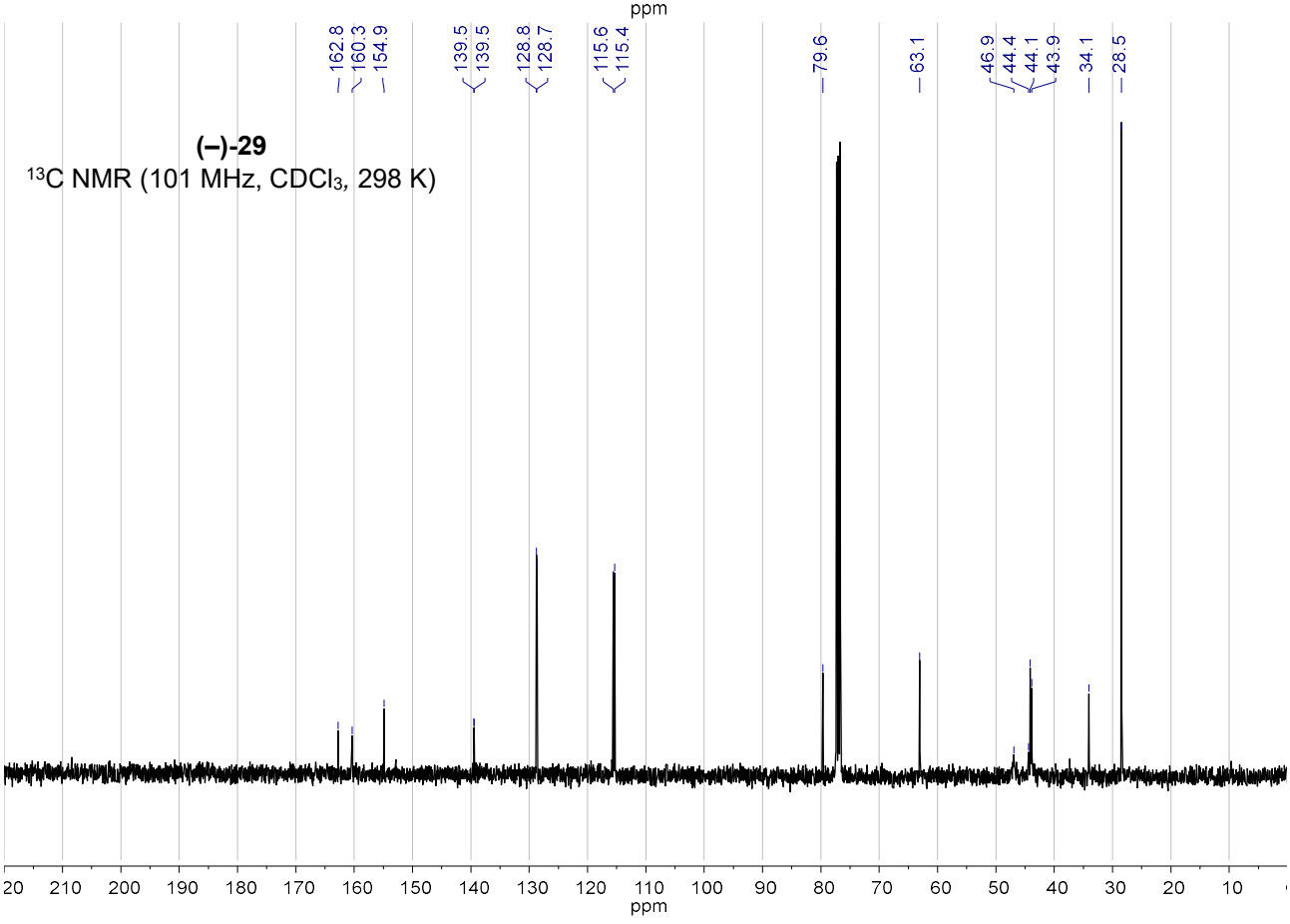
^{19}F NMR (377 MHz, CD_3OD, 298 K)




7.16
7.14
6.83
6.81
4.46
4.42
4.29
4.26
3.78
3.20
3.19
3.16
3.15
2.97
2.96
2.95
2.94
2.93
2.92
2.88
2.88
2.86
2.85
2.84
2.84
2.59
2.58
2.56
2.55
2.53
2.52
2.50
2.49
1.70
1.70
1.69
1.68
1.67
1.66
1.65
1.65
1.39
O
O
OH
N
Boc
28
1H NMR (400 MHz, CDCl3, 298 K)
2.00
2.02
1.05
1.07
3.11
1.04
3.25
1.08
1.10
9.13
ppm


176.6
158.3
154.6
134.2
128.4
113.8
79.8
55.2
46.1
45.4
43.9
42.3
28.3
25.9
28
13C NMR (101 MHz, CDCl3, 298 K)
ppm


F
OH
N
Boc
(–)-29
1H NMR (400 MHz, CDCl3, 298 K)
ppm


(–)-29
13C NMR (101 MHz, CDCl3, 298 K)
ppm

(–)-29

^{19}F NMR (377 MHz, $CDCl_3$, 298 K)

