Supporting Information for "Streamlined Synthesis of a Bicyclic Amine Moiety using an Enzymatic Amidation and Identification of a Novel Solid Form"

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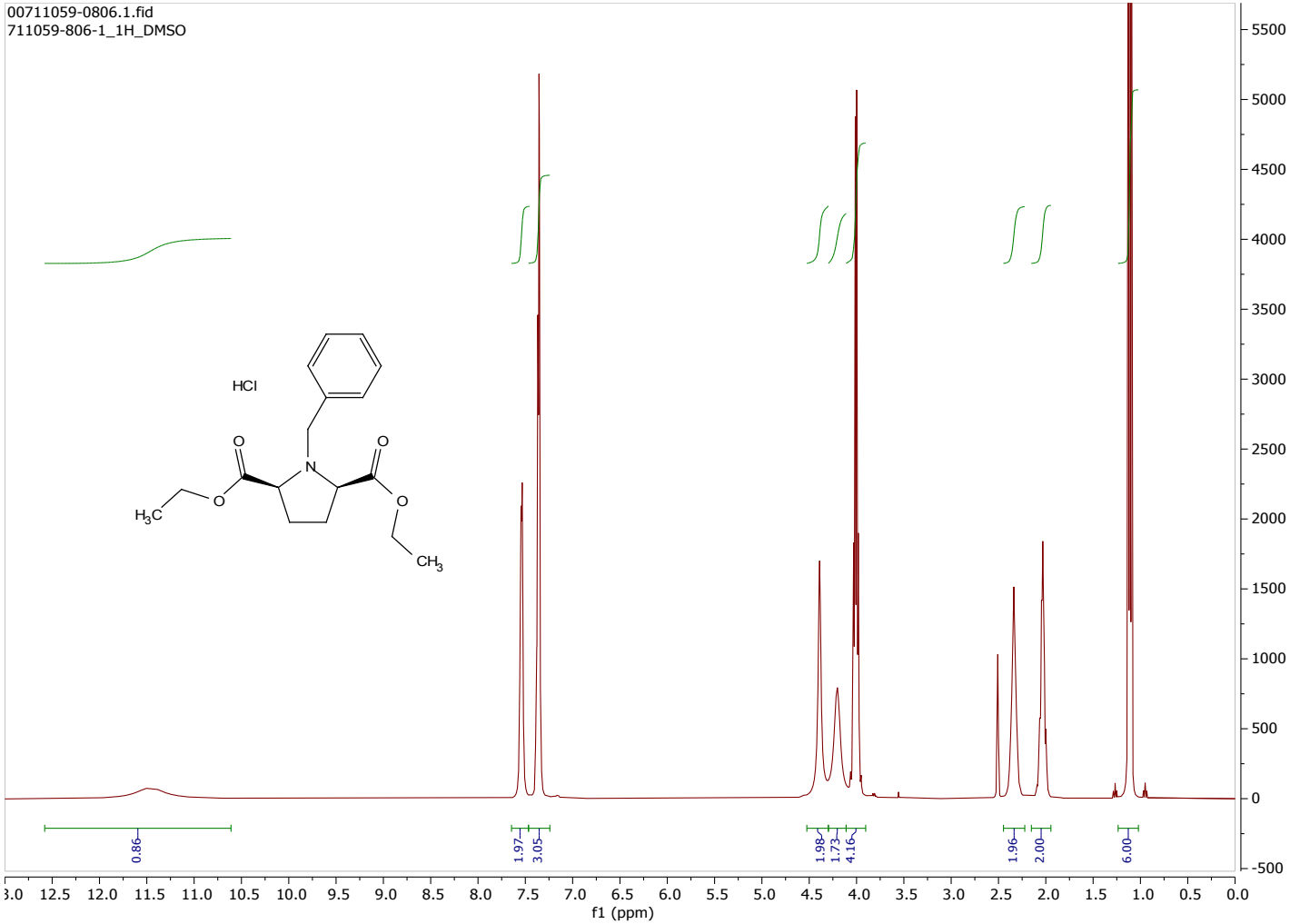
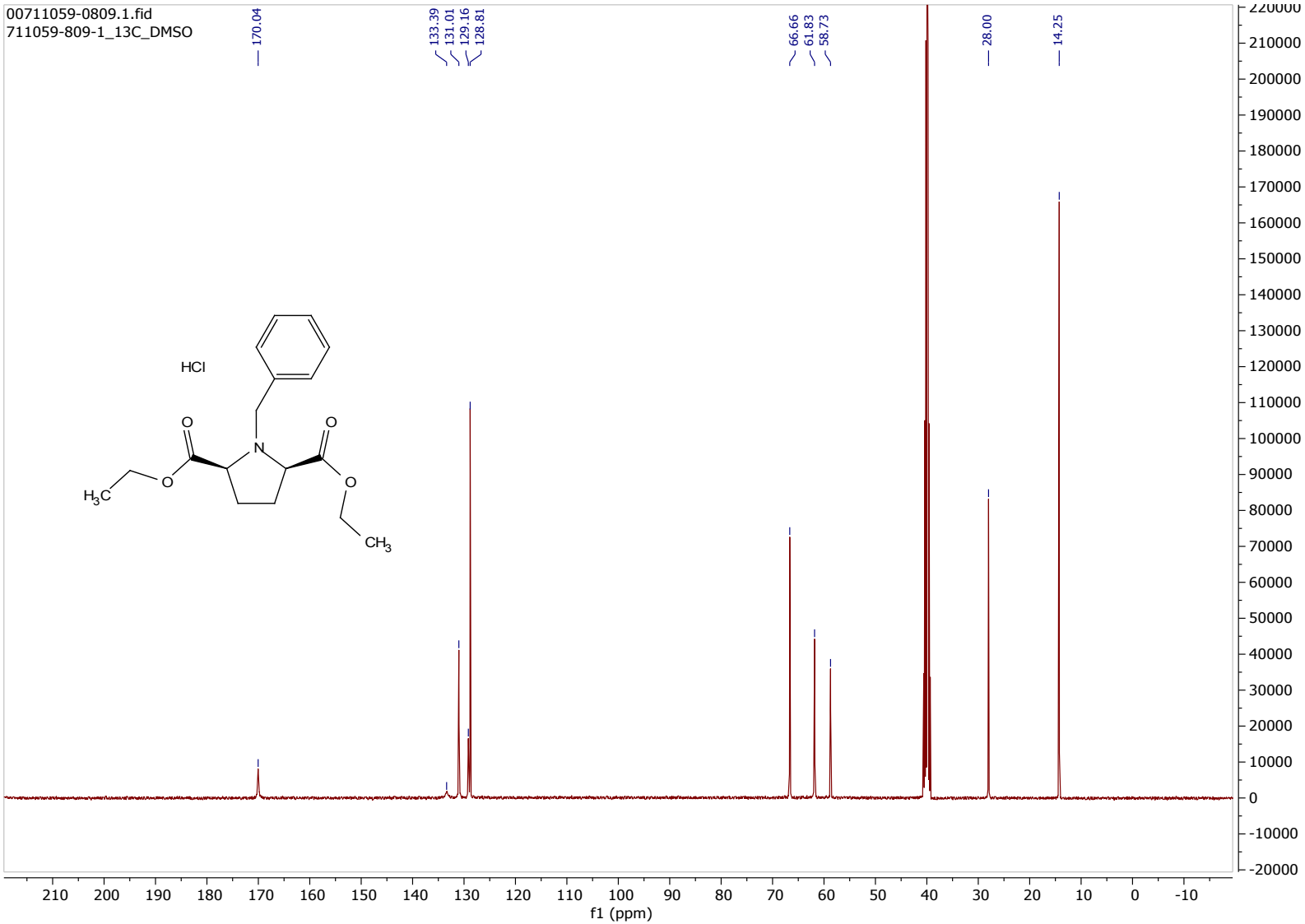
NMR Spectra of Compounds

*NMR Spectra of **31***

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

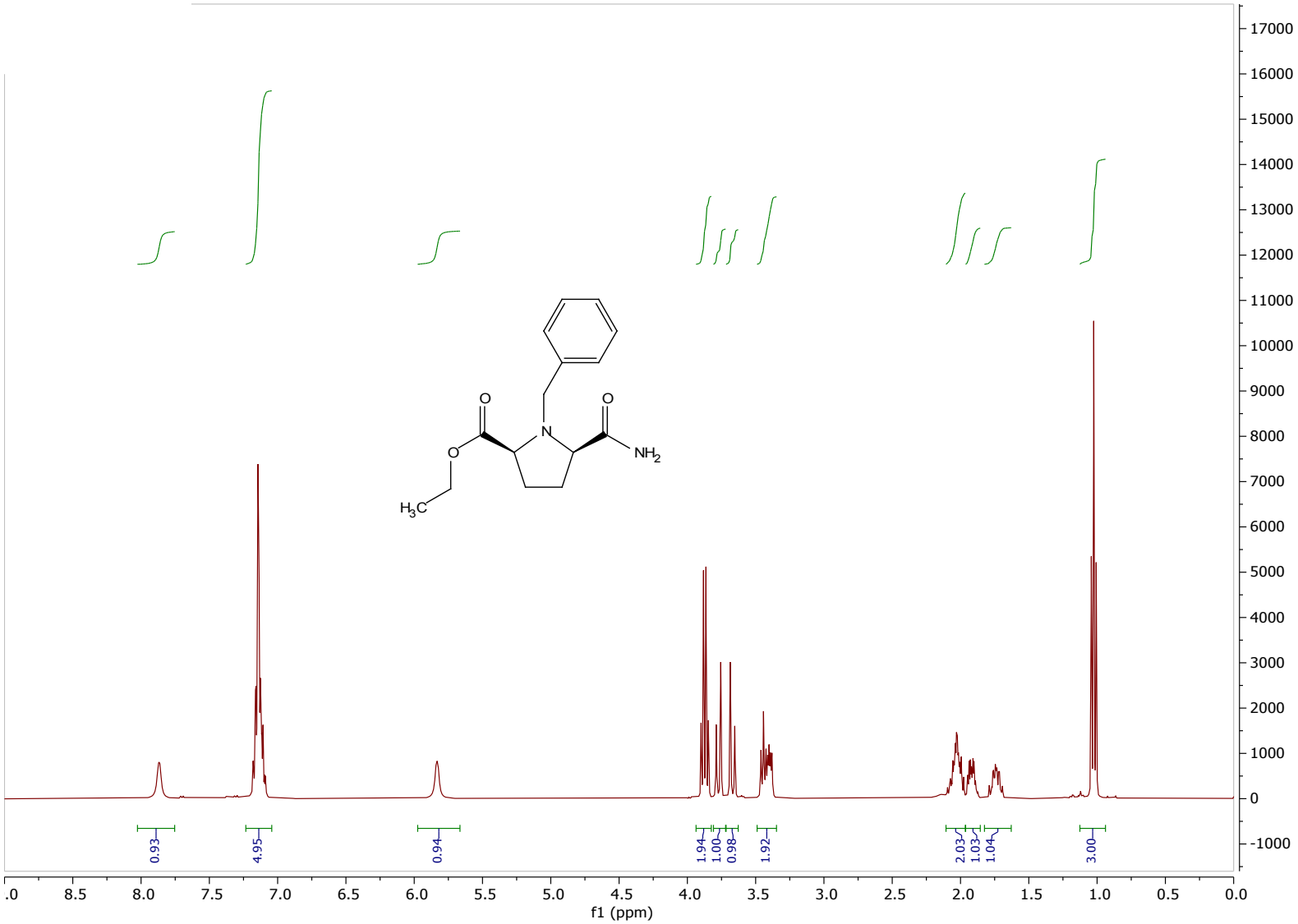


^{13}C-NMR, 100MHz, DMSO-d_6

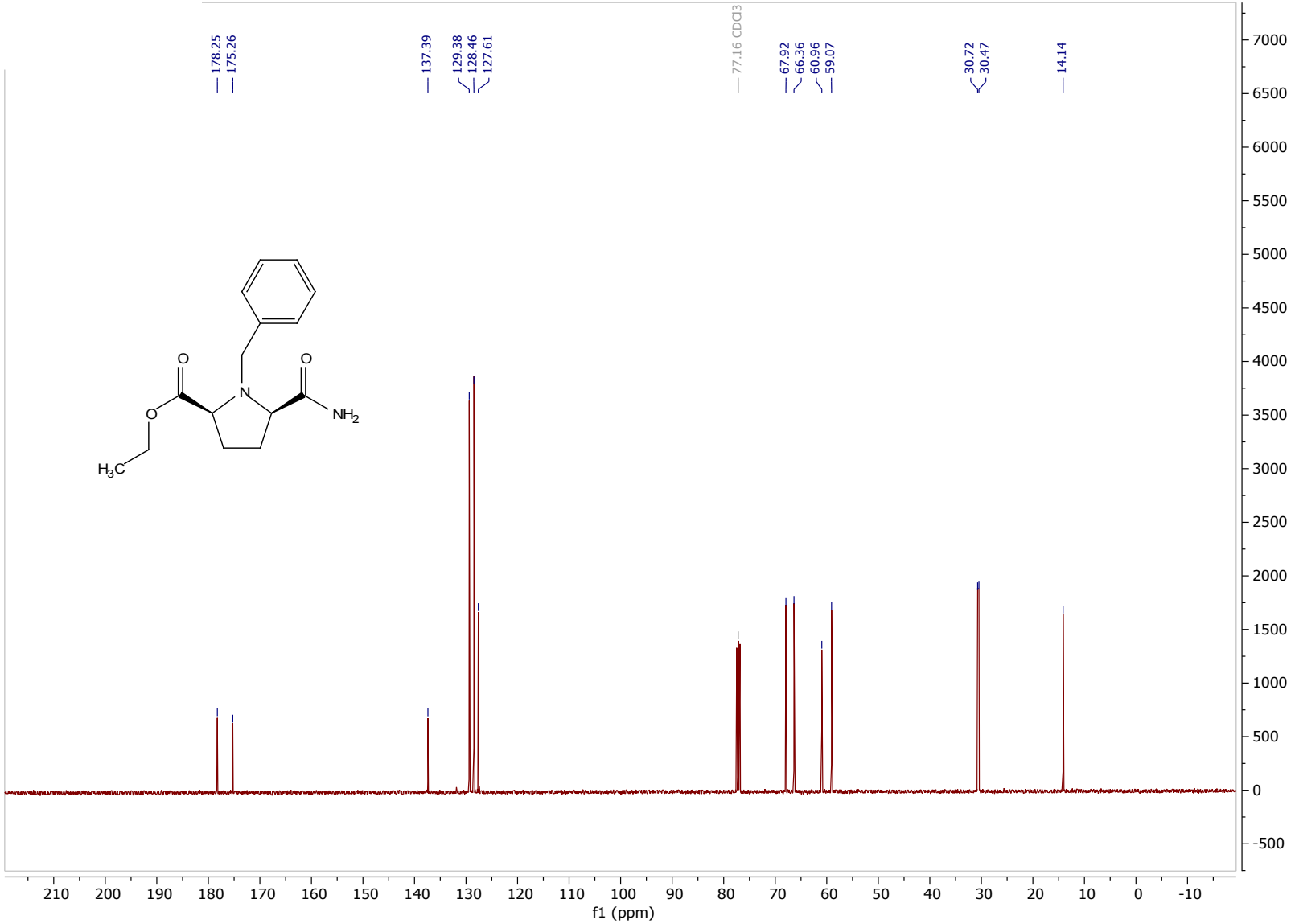


*NMR Spectra of **10***

^{1}H-NMR, 400 MHz, $CDCl_3$

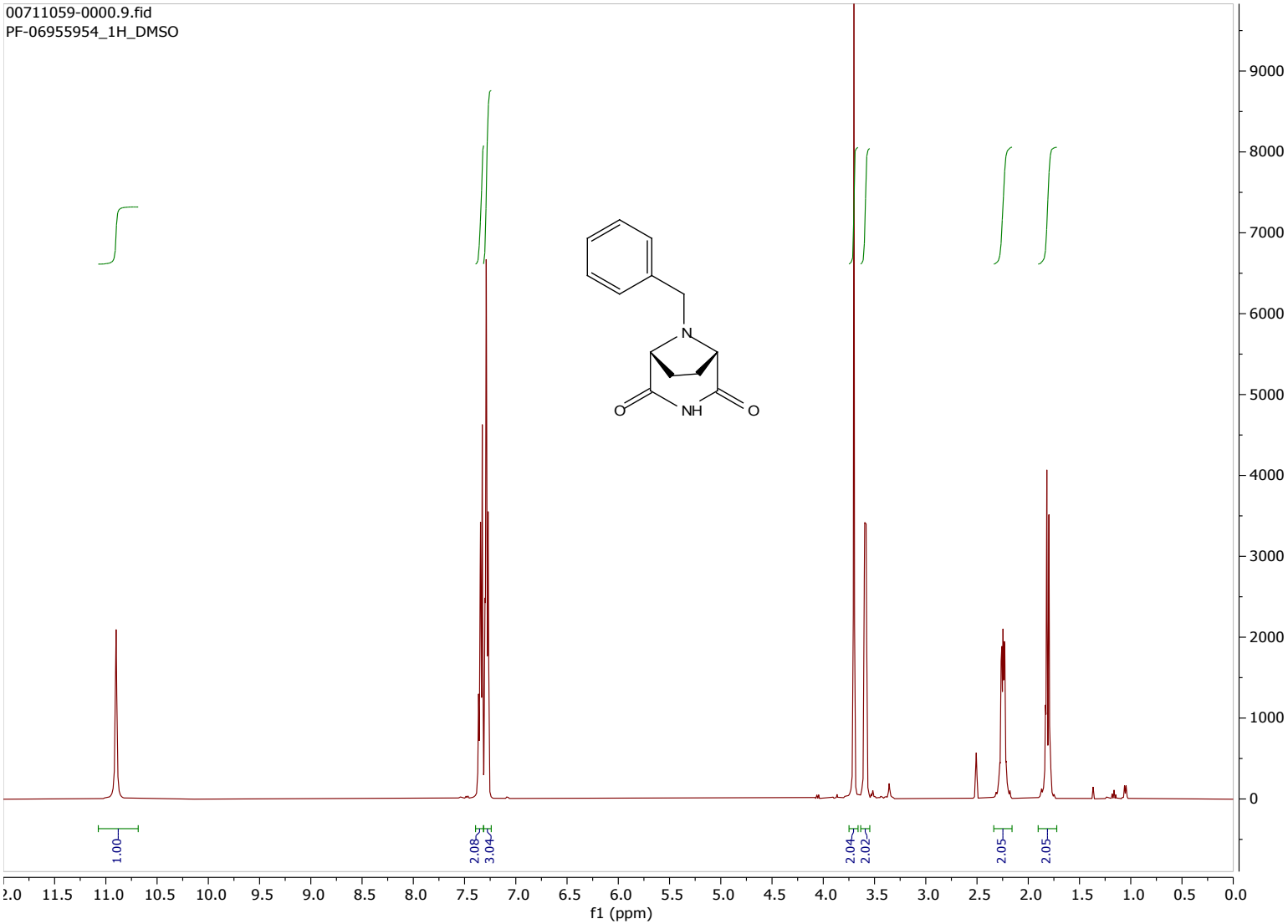


^{13}C-NMR, 100 MHz, $CDCl_3$

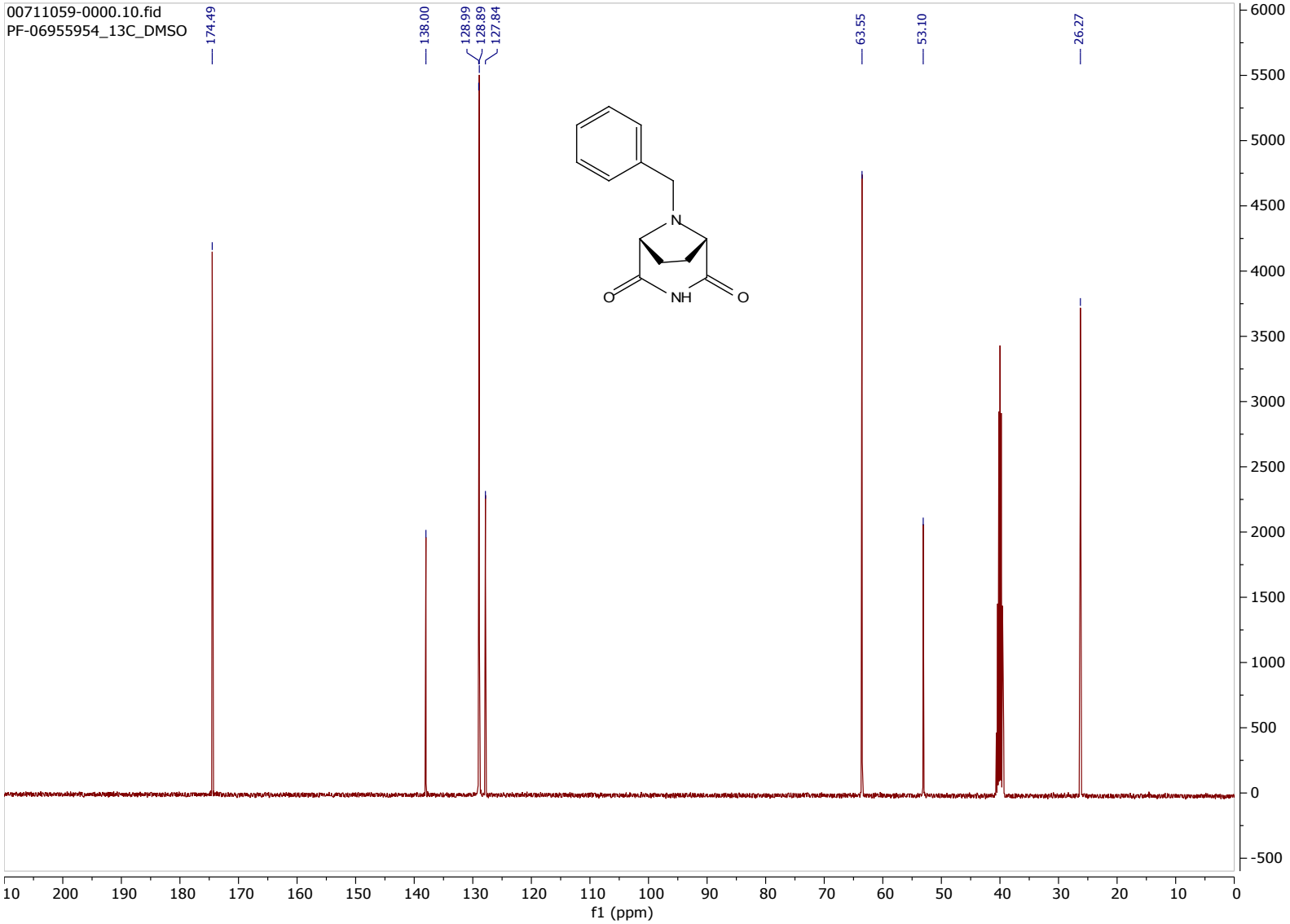


NMR Spectra of 7

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

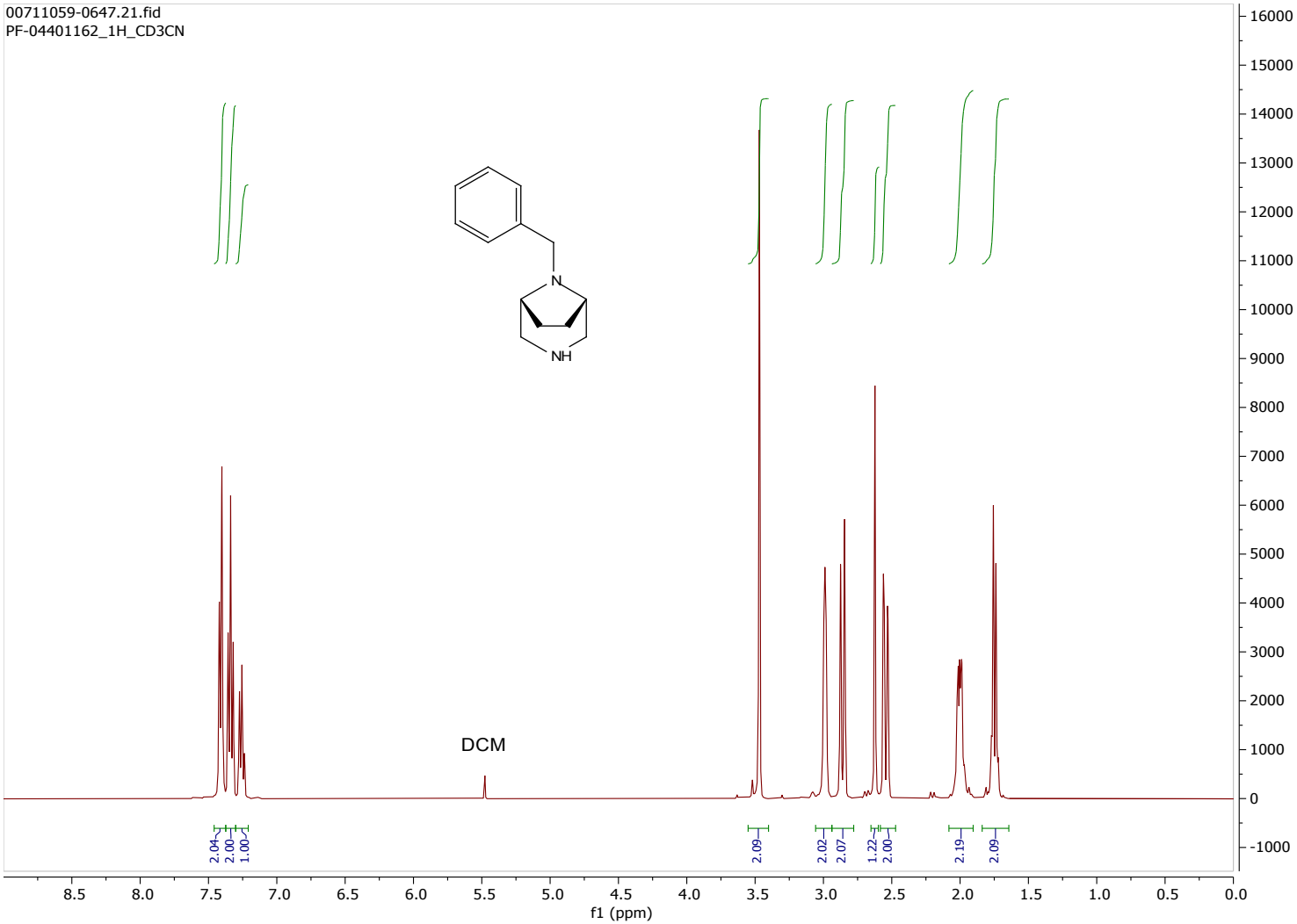


^{13}C-NMR, 100 MHz, DMSO-d_6

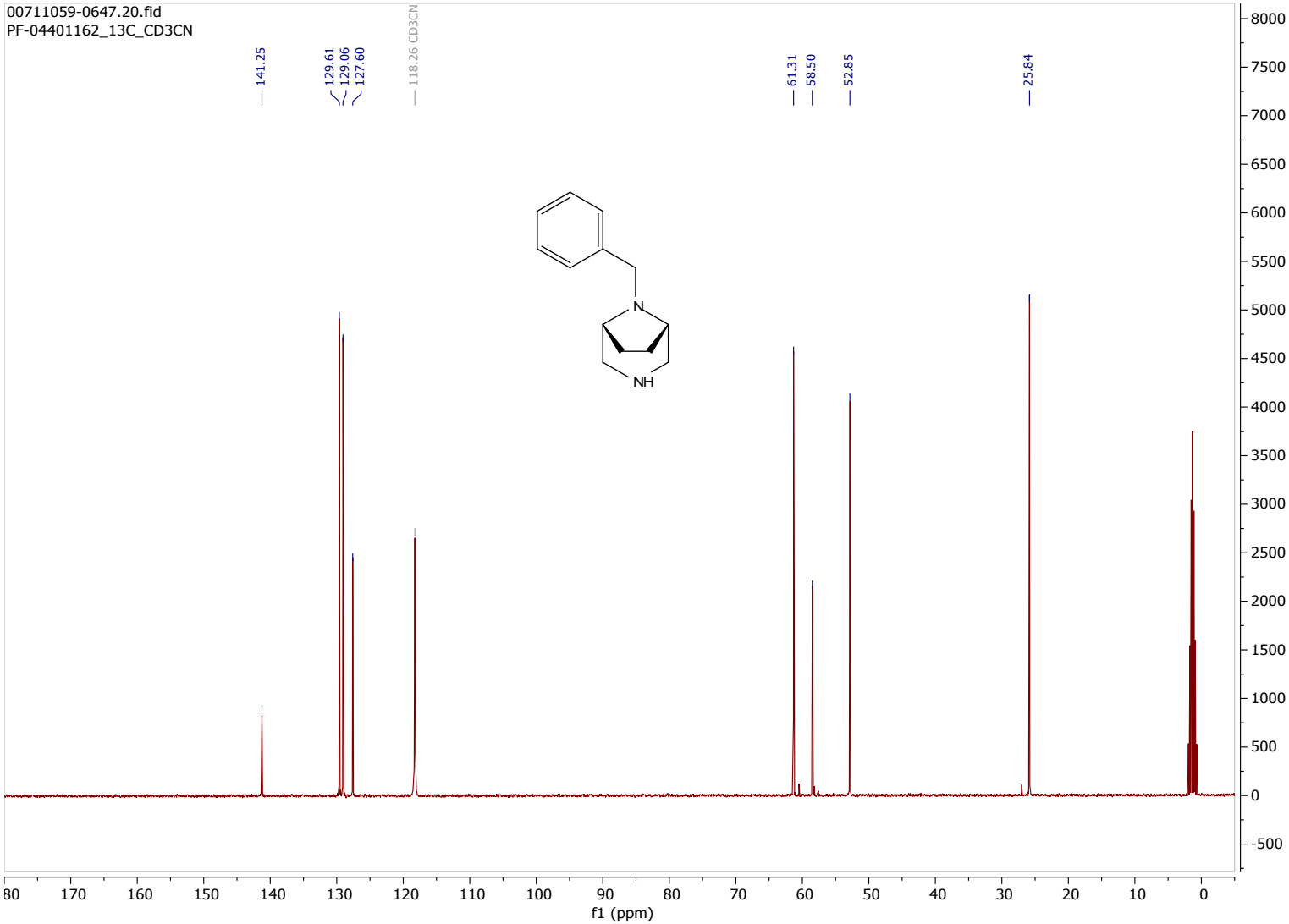


*NMR Spectra of **11***

^{1}H-NMR, 400 MHz, CD_3CN

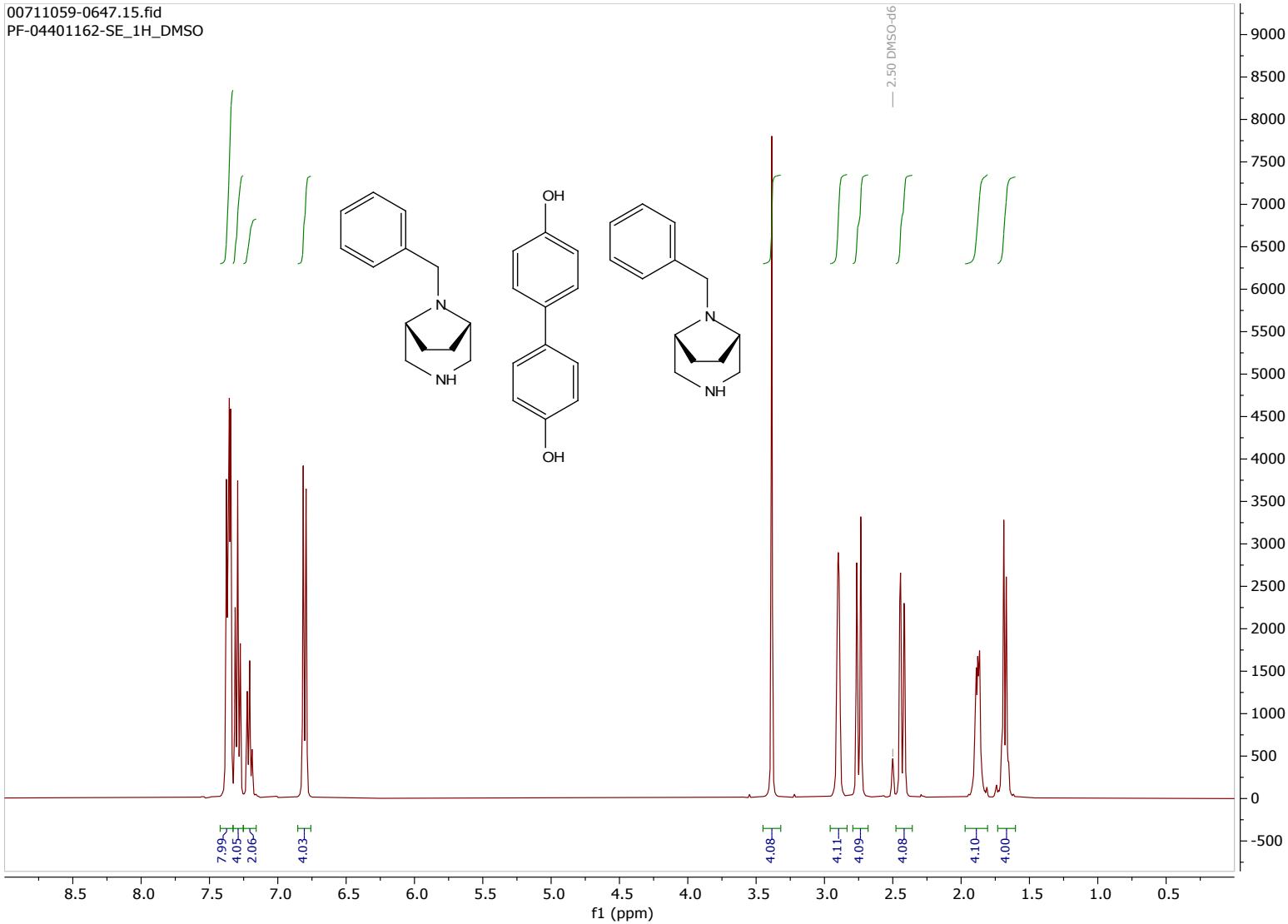


^{13}C-NMR, 100 MHz, CD_3CN

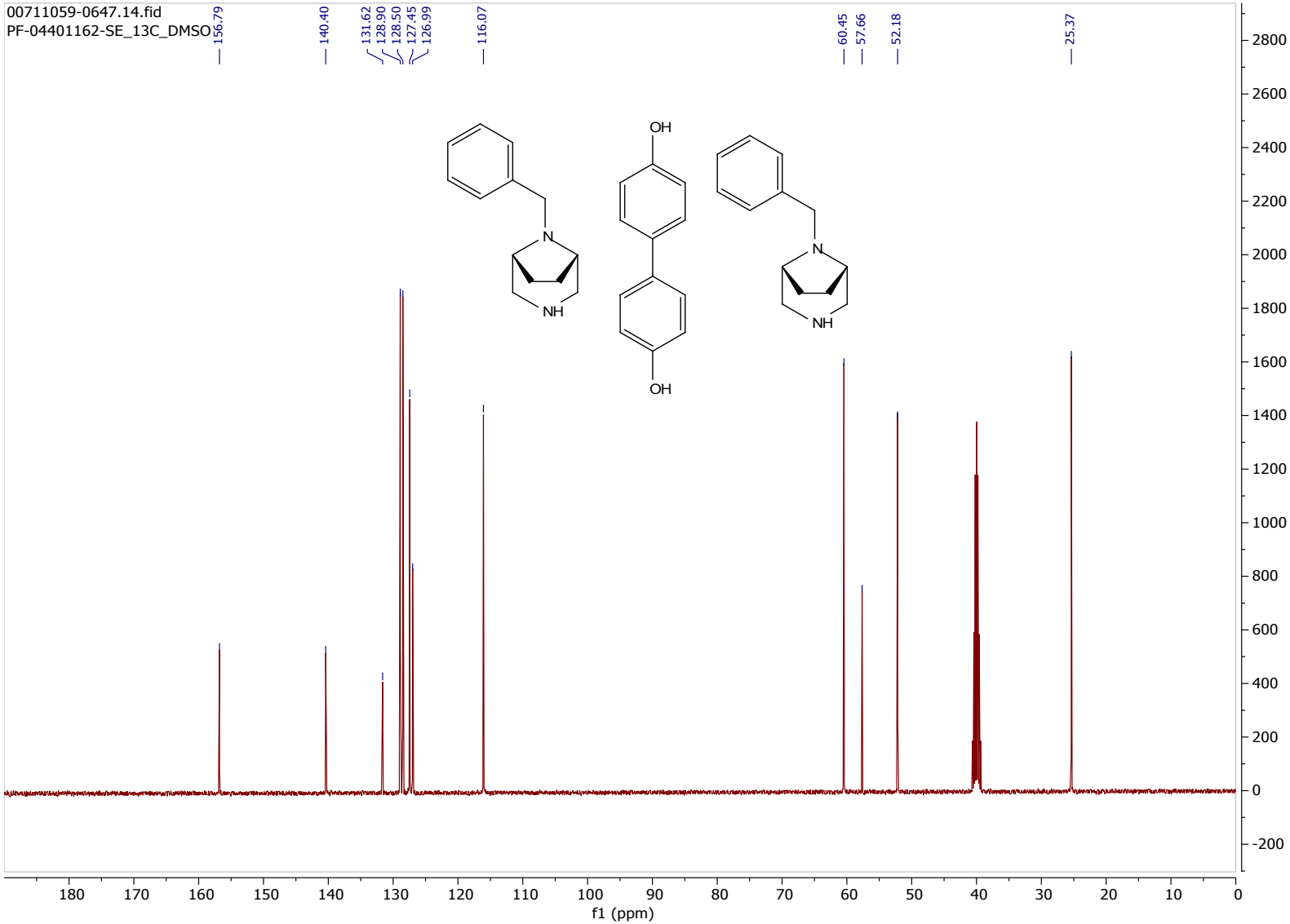


*NMR Spectra of **21***

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

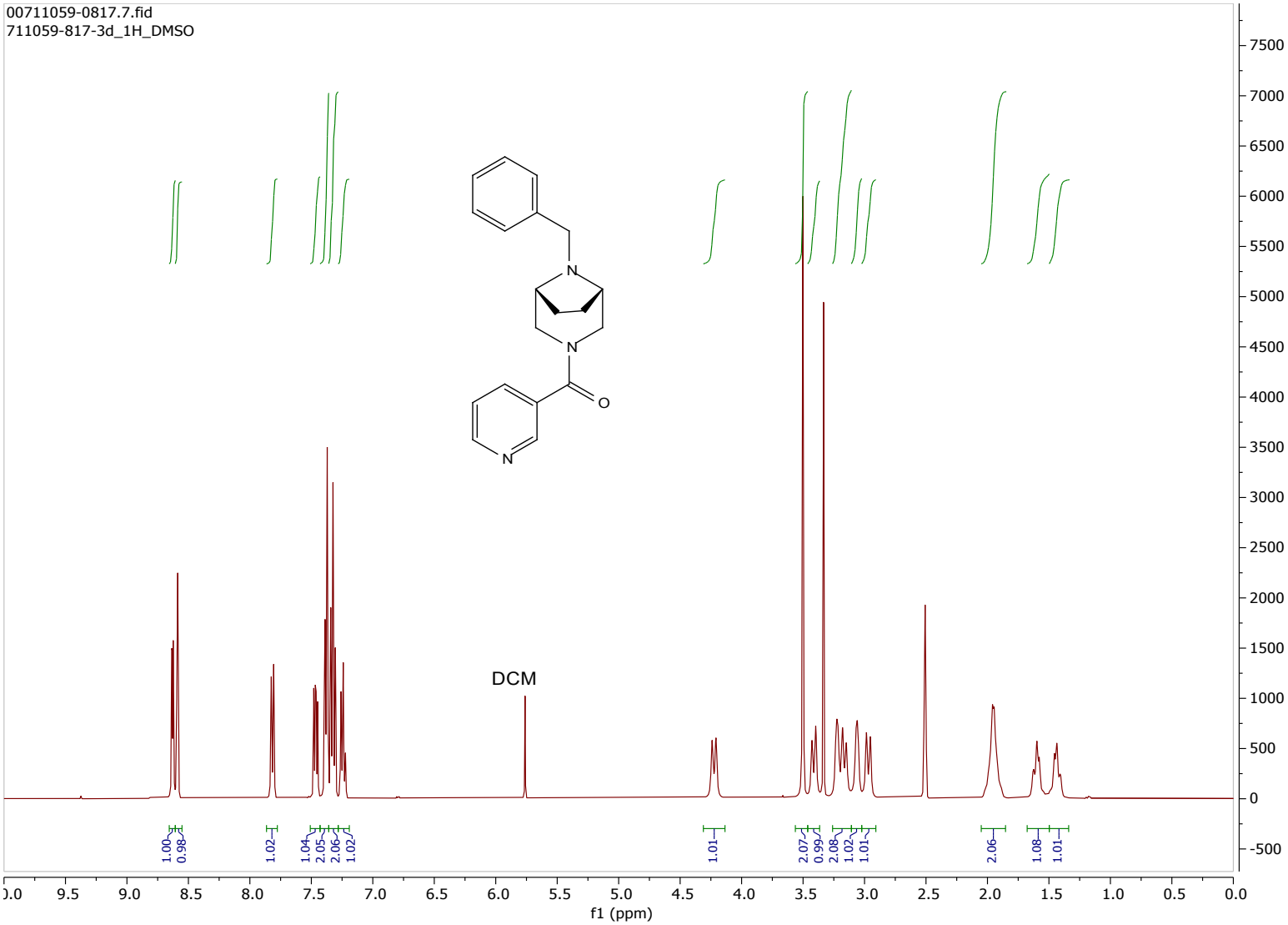


^{13}C-NMR, 100 MHz, DMSO-d_6

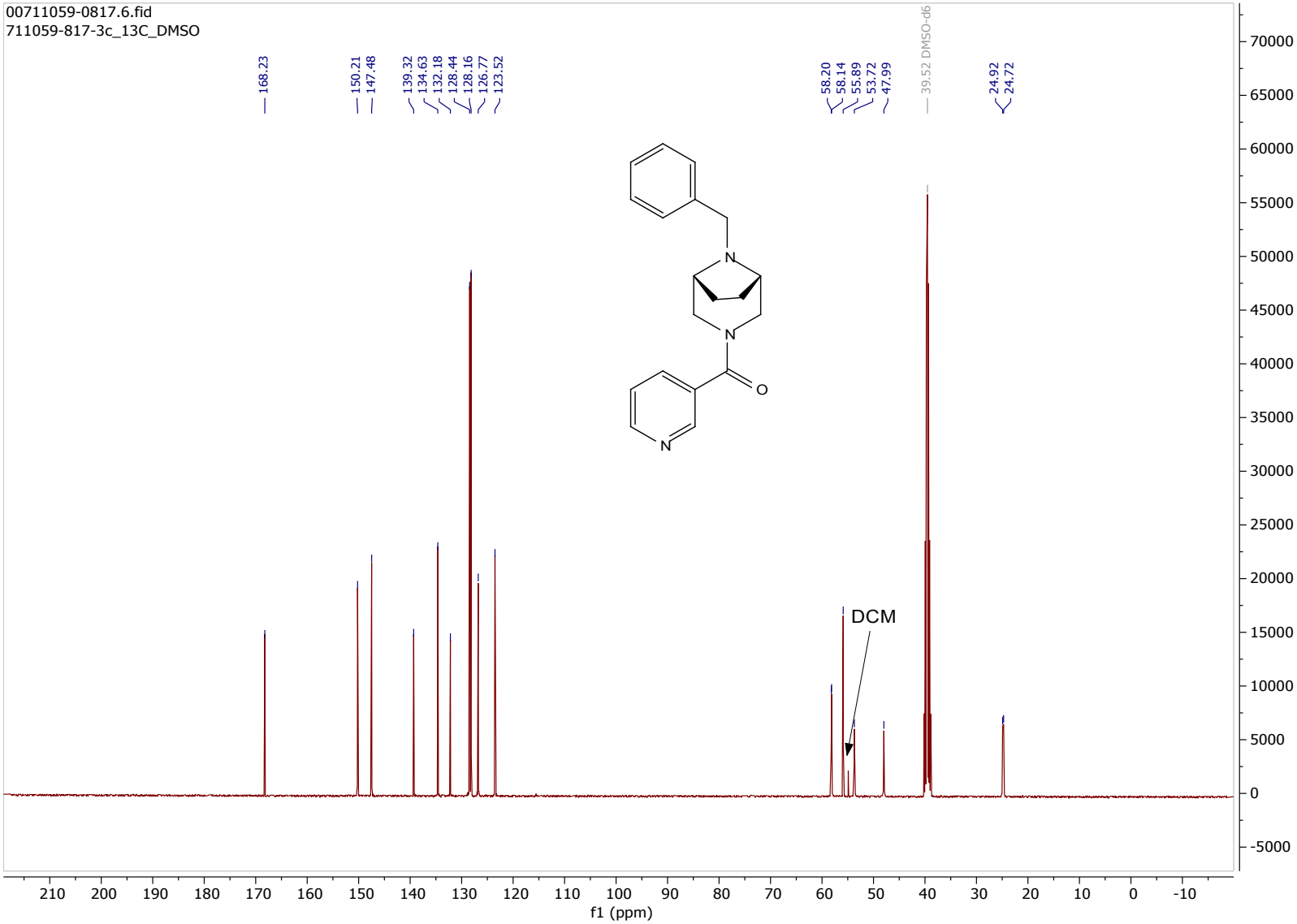


NMR Spectra of ***28***

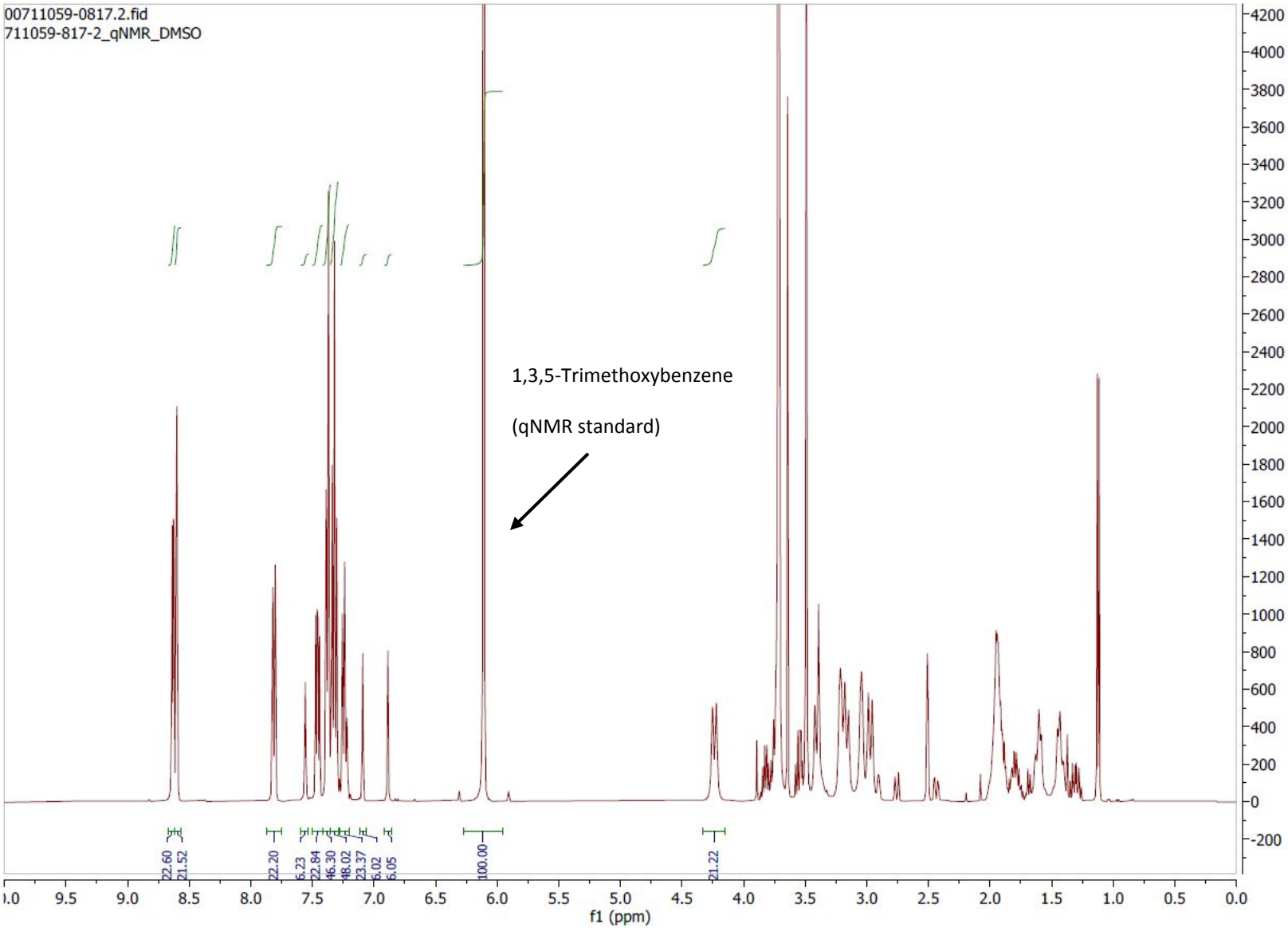
^{1}H-NMR, 400 MHz, DMSO-d_6



^{13}C-NMR, 100 MHz, DMSO-d_6

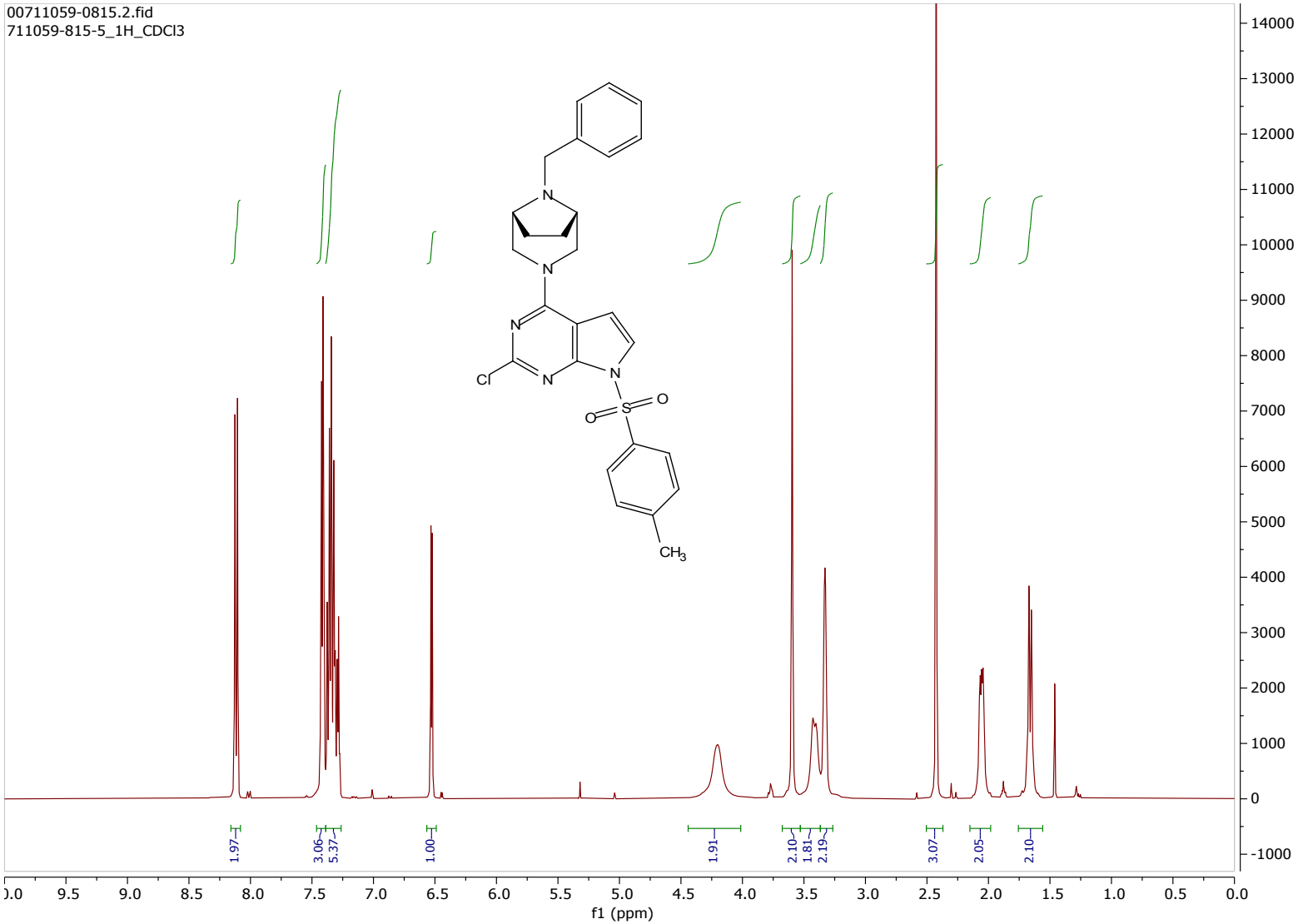


NMR assay (qNMR), 400 MHz, DMSO-d_6 (39.0 mg 1,3,5-TMB; 58.0 mg product)

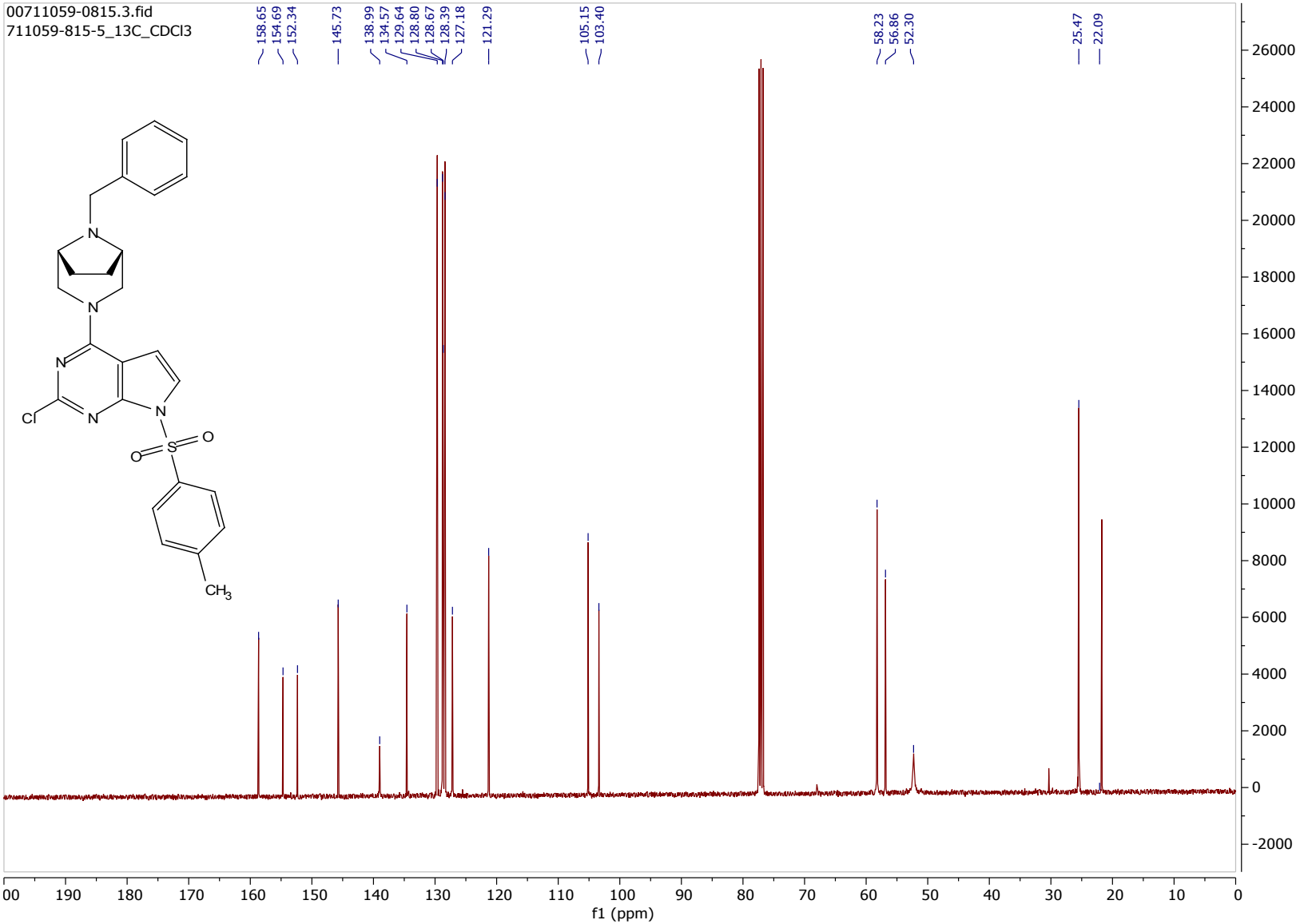


*NMR Spectra of **30***

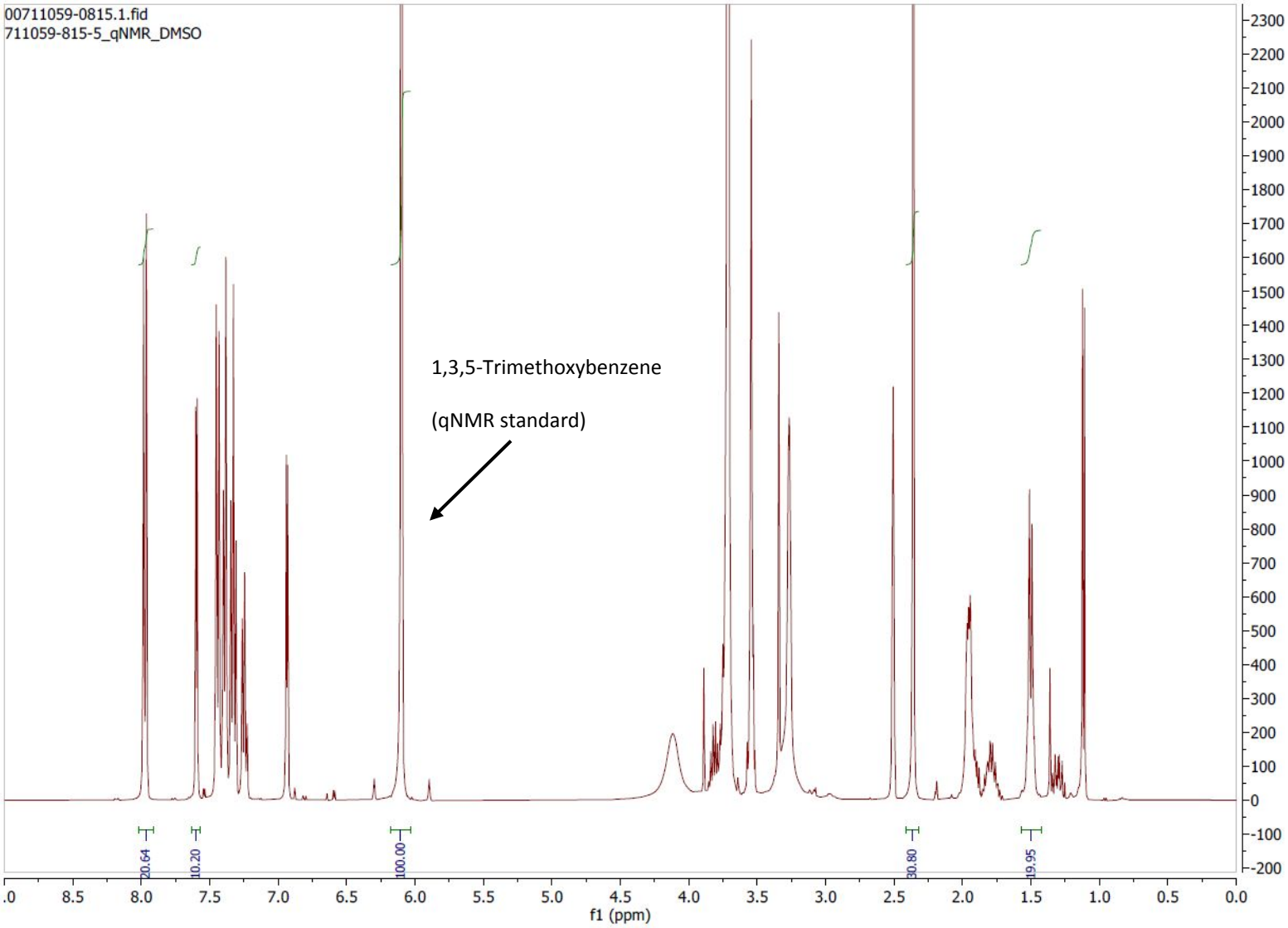
^{1}H-NMR, 400 MHz, $CDCl_3$



^{13}C-NMR, 100 MHz, $CDCl_3$



NMR assay (qNMR), 400 MHz, DMSO-d_6 (29.2 mg 1,3,5-TMB; 29.5 mg product)

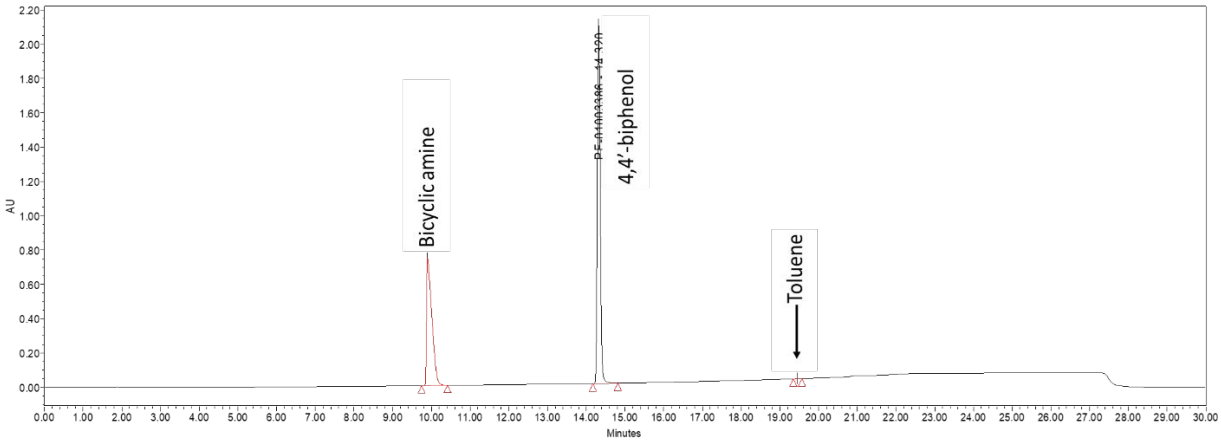


Representative Purity Analysis of Compound 21

HPLC Conditions

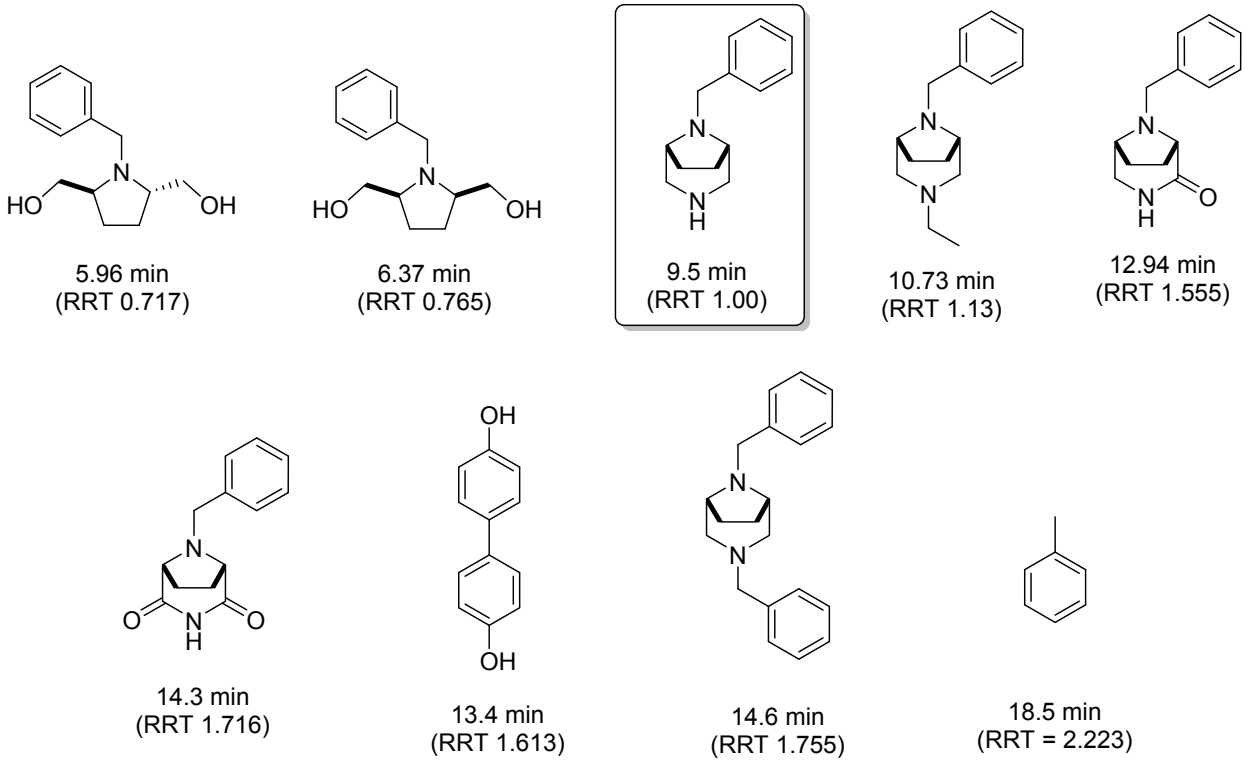
Solutions							
Mobile Phase A (v/v)	5mM Monobasic Potassium Phosphate (KH_2PO_4) in Water pH with 1M Potassium Hydroxide (KOH) to pH 6.5 ±0.05						
Mobile Phase B (v/v)	Methanol						
Diluent (v/v)	50/50 Methanol/Water						
Seal Wash (v/v)	90/10 water/acetonitrile						
Instrument Parameters							
Column	*Waters Xterra MS C18, 4.6 x 150mm, 3.5µm, Part No. 186000440*						
Column Temperature (°C)	*40˚C*						
Injection Volume (µL)	5 to 10µL						
Detector Wavelength (nm)	*210nm*						
Flow Rate (mL/minute)	1.0 mL/min						
Gradient Program	Time (minutes)	Initial	2.0	20.0	25.0	25.1	30.0
	% A (v/v)	98	98	15	15	98	98
	% B (v/v)	2	2	85	85	2	2
Run Time	*30 minutes*						
Column Storage After Use	*Wash column with 90/10 water/methanol (v/v) for at least 20 minutes, followed by flushing with 10/90 water/methanol (v/v) for at least another 20 minutes.*						

Sample Chromatogram



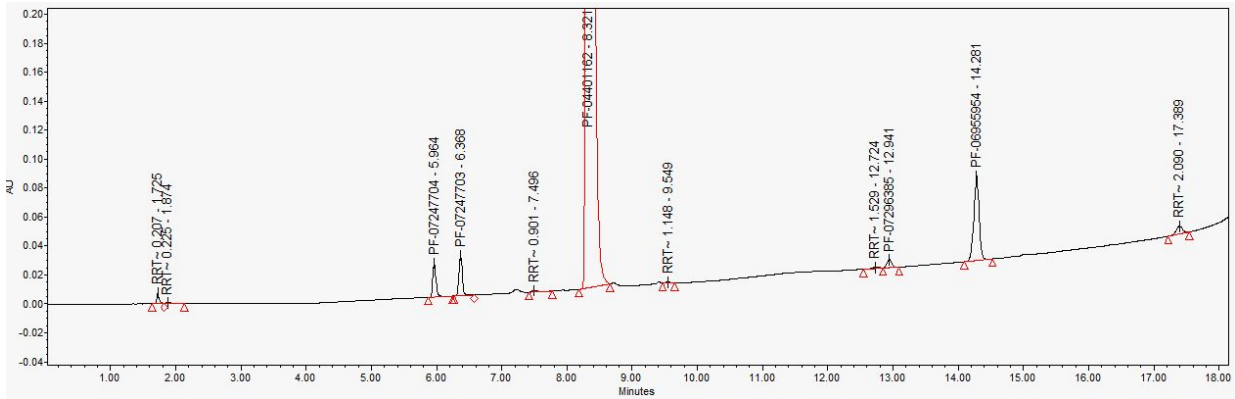
*For purity analysis, the 4,4'-biphenol and toluene peaks are not integrated, but are shown as reference

Retention Times of Relevant Species



*Testing Impurity Purge in Formation of Co-crystal **21***

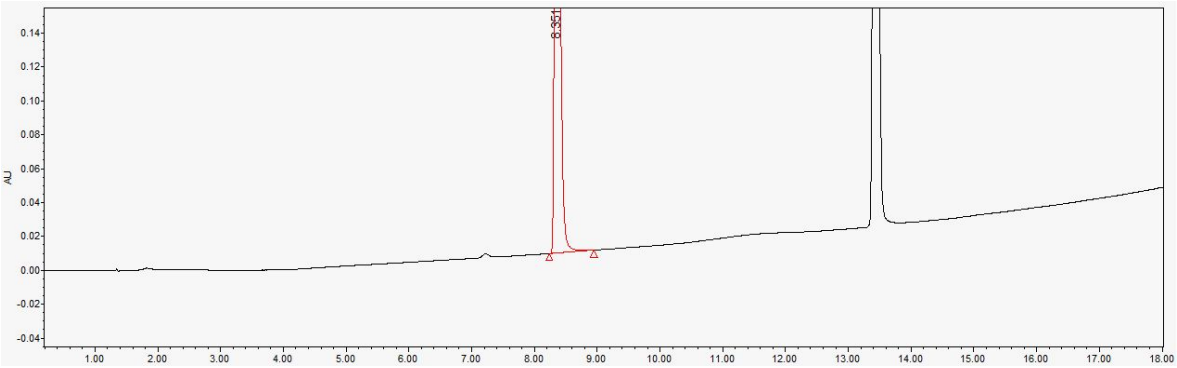
HPLC analysis of reaction mixture containing amine **11** prior to addition of 4,4'-biphenol:



Compound	RT (RRT)	Area %
RRT ~0.207	1.725 (0.207)	0.29
Diol **23**	5.964 (0.717)	1.27
Diol **22**	6.368 (0.765)	1.53
RRT ~0.901	7.496 (0.901)	0.11
Amine **11**	8.321 (1.000)	90.29
RRT ~1.048	8.720 (1.048)	0.06
RRT ~1.130	9.403 (1.130)	0.06
RRT ~1.148	9.549 (1.148)	0.08

Compound	RT (RRT)	Area %
RRT ~1.529	12.724 (1.529)	0.11
Amide **25**	12.941 (1.555)	0.44
4,4'-biphenol	13.420 (1.613)	
Imide **7** + bis-benzyl **24**	14.281 (1.716)	5.15
RRT ~1.804	15.009 (1.804)	0.07
RRT ~2.090	17.389 (2.090)	0.56
Toluene	18.500 (2.223)	

HPLC analysis of co-crystal **21** isolated from above mixture:



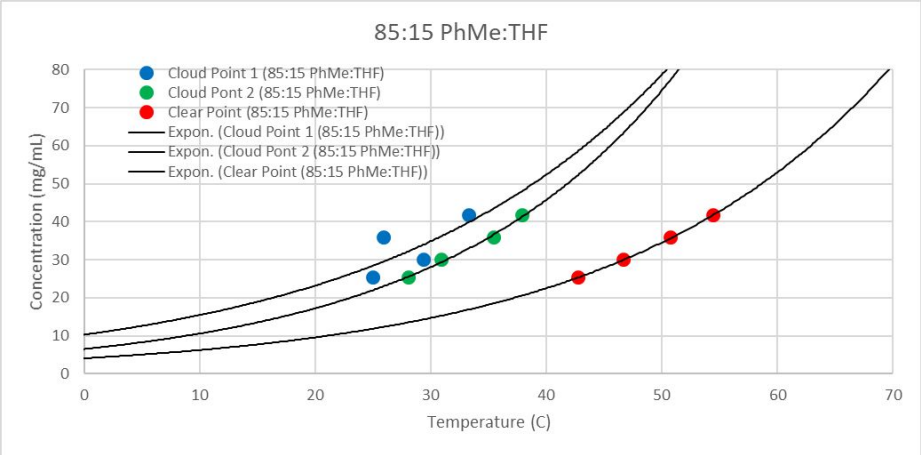
Compound	RT (RRT)	Area %
Diol **23**	5.964 (0.717)	ND
Diol **22**	6.368 (0.765)	ND
Amine **11**	8.321 (1.000)	100
Amide **25**	12.941 (1.555)	ND
4,4’-biphenol	13.420 (1.613)	-
Imide **7** + bis-benzyl **24**	14.281 (1.716)	ND
Toluene	18.500 (2.223)	-

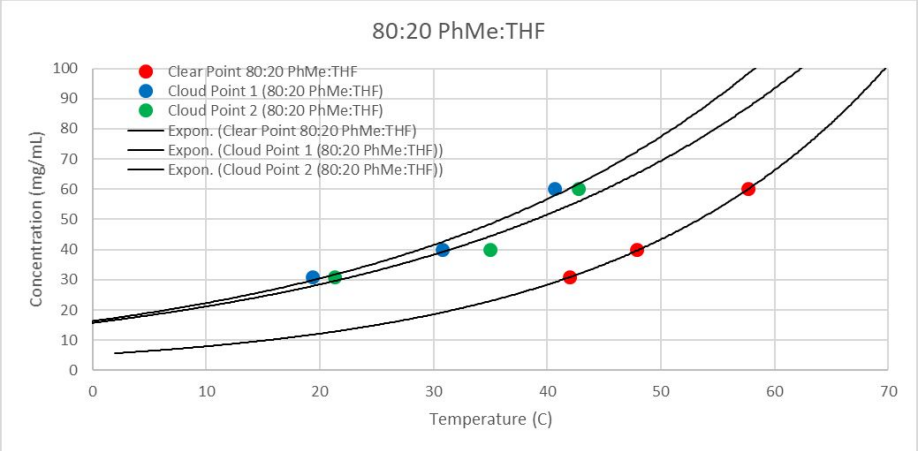
Additional Solubility Data for Compounds

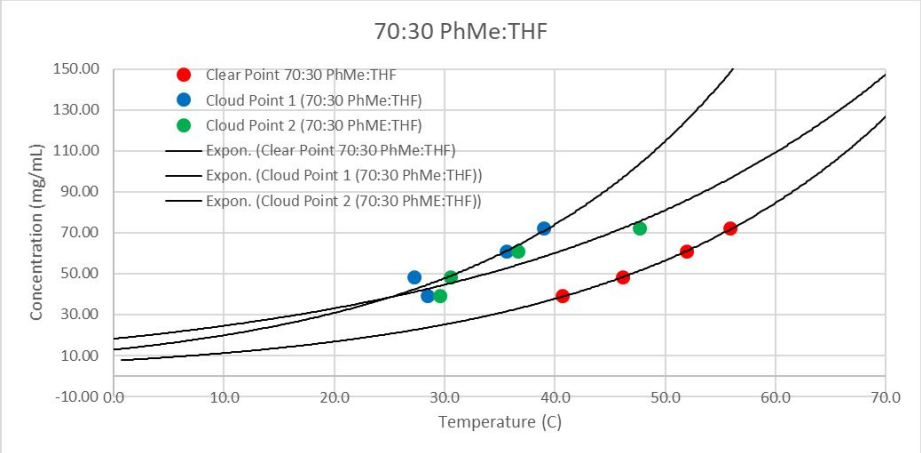
Room Temperature Solubility Data

Solubility data		co-crystal **(21)**	4,4'-biphenol **(20)**	imide **(7)**	bis-ester HCl salt **(31)**
#	**Solvent (v/v)**	**mg/mL solution**	**mg/mL solution**	**mg/mL solution**	**mg/mL solution**
1	methanol	64	64	61	>90
2	ethanol	36	63	32	>90
3	1-propanol	30	36	29	>90
4	2-propanol	17	41	22	>90
5	1-butanol	23	28	22	>90
6	acetone	30	48	>95	84
7	MEK	22	88	>95	13
8	MIBK	12	34	38	<1
9	ethyl acetate	11	24	74	<1
10	propyl acetate	10	18	54	<1
11	isopropyl acetate	8	15	43	<1
12	butyl acetate	9	14	42	<1
13	isobutyl acetate	7	10	36	<1
14	THF	74	>95	>95	7
15	2-MeTHF	32	>95	>95	3
16	t-AmOH	7	31	48	20
17	MTBE	6	13	27	<1
18	cyclopentylmethyl ether	13	16	43	<1
19	t-amyl methyl ether	5	7	17	<1
20	DCM	13	0	>95	>90
21	toluene	0	0	21	<1
22	a,a,a-trifluorotoluene	0	0	6	<1
23	anisole	5	0	>95	<1
24	acetonitrile	5	12	>95	60
25	DMAc	>95	>95	>95	>90
26	DMF	>95	>95	>95	>90
27	DMSO	>95	>95	>95	>90
28	heptane	0	0	0	<1
29	methylcyclohexane	0	0	0	<1
30	water	0	0	1	>48
31	Propylene Carbonate	7	27	87	>90
32	20:80 toluene:THF	56	>95		
33	40:60 toluene:THF	39	92		
34	60:40 toluene:THF	26	40		
35	80:20 toluene:THF	15	10		
36	20:80 toluene:2-propanol	32	51		
37	40:60 toluene:2-propanol	44	46		
38	60:40 toluene:2-propanol	46	31		
39	80:20 toluene:2-propanol	34	13		
40	95:5 toluene:EtOH				43
41	90:10 toluene:EtOH				75

*Temperature Dependent Solubility of Co-crystal **21***



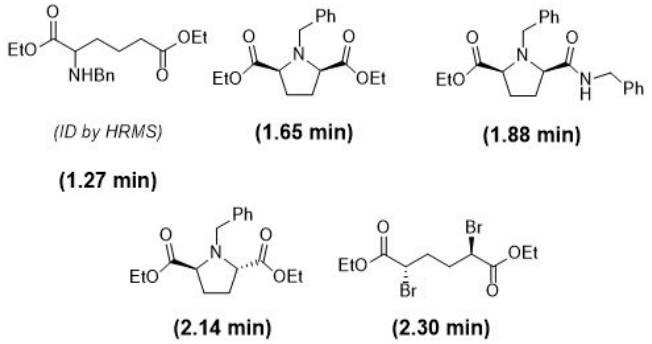




Analytical Methods for Cyclization using Dibromide 1

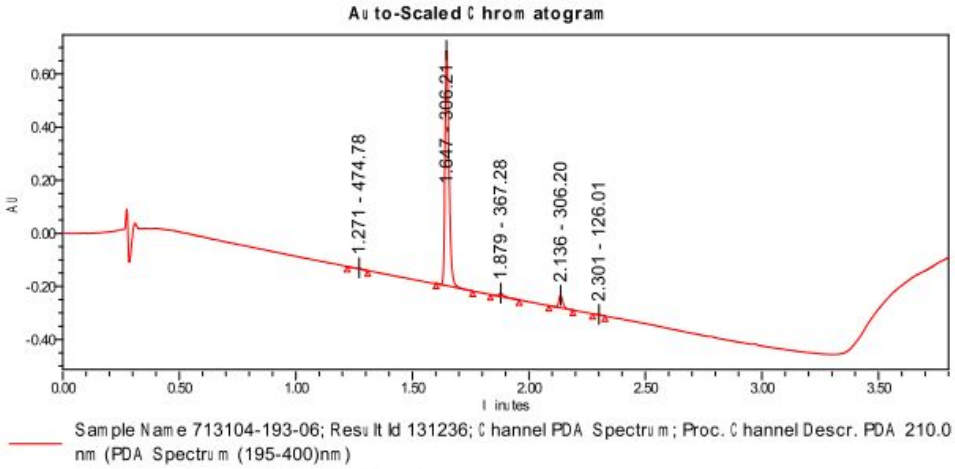
UPLC method:
Column: Acquity HSS T3 2.1x50mm 1.8um
Column temperature: 45 °C
Mobile Phase: 0.1% TFA (A)/Acetonitrile (B)
Flow Rate: 0.65 mL/min
Run time: 3.8 min
Detection: Measured at 210nm

time (min)	% A	% B
0	95	5
3.0	5	95
3.2	5	95
3.3	95	5
3.8	95	5



- The relative UV response (210 nm) for the dibromide starting material (**1**) is significantly weaker than the other species containing a benzyl group; however, it is still sufficient for quantitation.

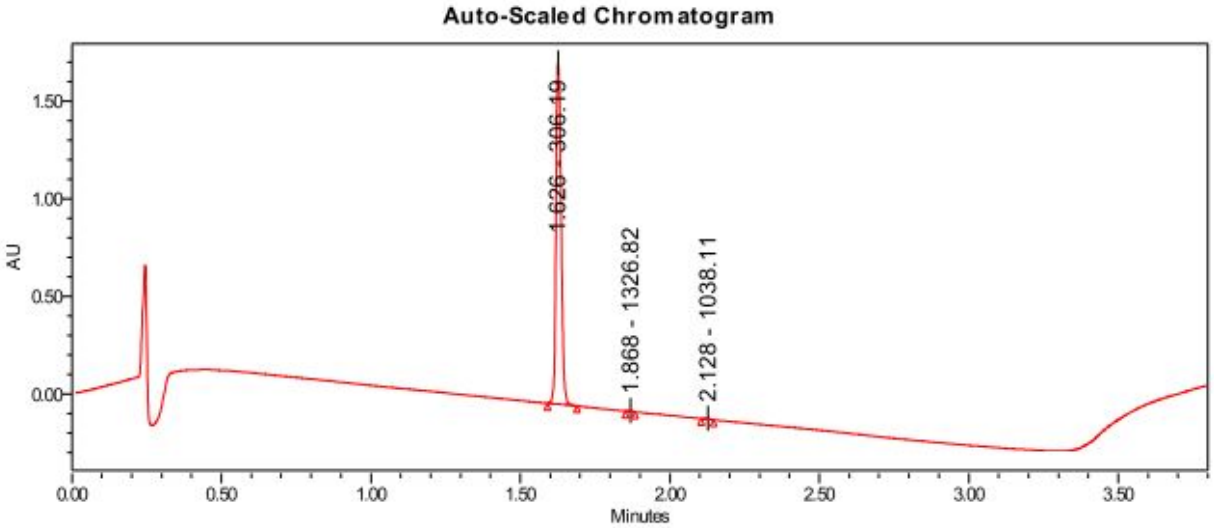
Sample UPLC trace of **crude product**:



Peak Results
Proc Ch Descr.: PDA 210.0 nm (PDA Spectrum (195-400)nm)

	Sample Name	Proc Ch Descr.	Peak RT	% Area	Area	% Height	Height	Base Peak (m/z)
1	713104-193-06	PDA 210.0 nm (PDA Spectrum (195-400)nm)	1.271	0.44	4933	0.41	3925	474.8
2	713104-193-06	PDA 210.0 nm (PDA Spectrum (195-400)nm)	1.647	93.12	1052406	93.07	887298	306.2
3	713104-193-06	PDA 210.0 nm (PDA Spectrum (195-400)nm)	1.879	1.50	16953	1.36	12968	367.3
4	713104-193-06	PDA 210.0 nm (PDA Spectrum (195-400)nm)	2.136	4.78	53977	4.98	47495	306.2
5	713104-193-06	PDA 210.0 nm (PDA Spectrum (195-400)nm)	2.301	0.17	1892	0.18	1720	126.0

Sample UPLC trace of **purified** salt **31**:



Sample Name 711059-589-2_M1; Result Id 116166; Channel PDA Spectrum; Proc. Channel Descr. PDA Spectrum PDA 210.0 nm (PDA Spectrum (195-400)nm)

Peak Results

Proc Ch Descr.: PDA Spectrum PDA 210.0 nm (PDA Spectrum (195-400)nm)

	Sample Name	Proc Ch Descr.	Peak RT	% Area	Area	% Height	Height	Base Peak (m/z)
1	711059-589-2_M1	PDA Spectrum PDA 210.0 nm (PDA Spectrum (195-400)nm)	1.626	99.60	2107999	99.45	1746589	306.2
2	711059-589-2_M1	PDA Spectrum PDA 210.0 nm (PDA Spectrum (195-400)nm)	1.868	0.24	5039	0.34	5899	1326.8
3	711059-589-2_M1	PDA Spectrum PDA 210.0 nm (PDA Spectrum (195-400)nm)	2.128	0.16	3441	0.21	3770	1038.1

GC-FID Method:

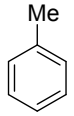
Alternatively, a GC-FID method can be utilized which gives better quantitation of meso-dibromide **1** to determine conversion; however, the method does not separate syn vs. anti diatereomers of the product:

Column:	Zebron ZB-1ms 30 m, 0.32 mm id, 1 µl film thickness (Cat 7HM-G011-22)
Injector temp:	250 °C
Inlet pressure:	14.2 psi (initial)
Split:	56:1
Flow:	3.27 ml/min, constant flow Helium gas
Detector temp:	300 °C
Oven temp:	Initial 50 °C, hold 2 minutes Ramp 1 20 °C/min to 220 °C Ramp 2 30 °C/min to 270 °C Hold 270 °C for 7.83 minutes.

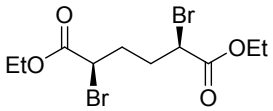
Species	Retention Time
meso-dibromide **1**	11.9 min
syn-diester product (**9**)	13.0 min
anti-diester (**12**)	13.0 min
Toluene	4.4 min
Benzylamine	6.8 min

*HPLC Method for Monitoring meso Purity of **1***

Column:	Chiral Technologies Chiralpak IG-3, 250 x 4.6 mm, 3.0 µm (Part No. 87525)
Column temperature:	40°C
Flow rate:	1.0mL/min
Run time:	32min
Injection volumn:	10uL
Mobile Phase:	A: 0.1% H_3PO_4 in water B: Acetonitrile
Detection:	210nm
Gradient table:	Time (min) / B (%) 0.0 / 50 5.0 / 50 25.0 / 90 27.0 / 90 27.1 / 50 32.0 / 50
Column storage:	Wash column with 90 water: 10 ACN (v:v) for at least 20 min, followed by flushing with 10 water: 90 ACN (v:v) for at least 20 min

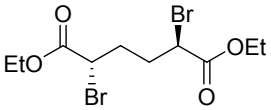


7.5 min
(not integrated)



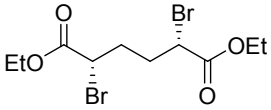
(or enantiomer)

14.19 min
(RRT = 0.94)



PF-07262763 (meso)

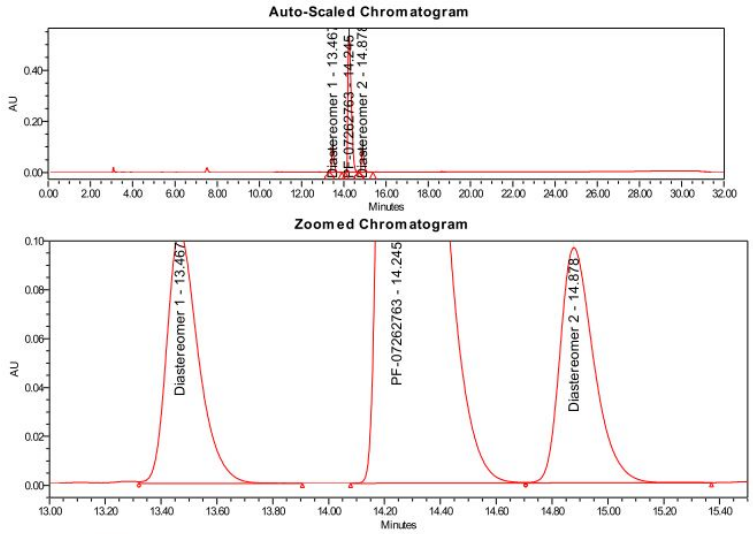
15.04 min
(RRT = 1.00)



(or enantiomer)

15.83 min
(RRT = 1.05)

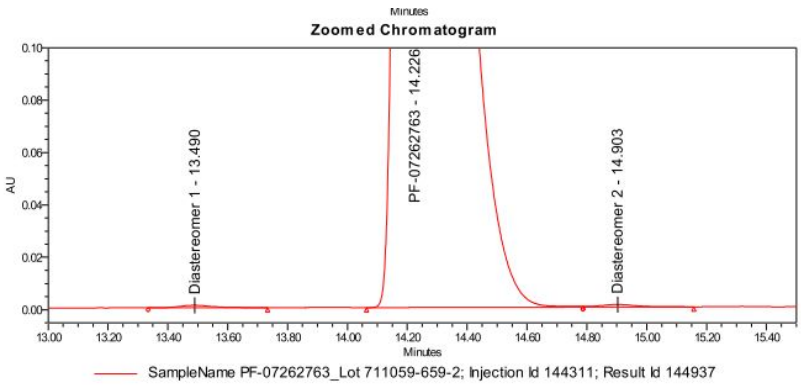
Sample chromatogram of low purity dibromide (dr = 10.6 : 78.7 : 10.6):



Peak Results

	Name	RT	RRT_Alpha	Area	% Area
1	Toluene	7.500			
2	Diastereomer 1	13.467	0.945	802615.90	10.63
3	PF-07262763	14.245	1.000	5940141.26	78.69
4	Diastereomer 2	14.878	1.044	805686.19	10.67

Sample chromatogram of high purity dibromide (99.8% *meso*):



Peak Results

	Name	RT	RRT_Alpha	Area	% Area
1	Toluene	7.500			
2	Diastereomer 1	13.490	0.948	7932.35	0.11
3	PF-07262763	14.226	1.000	7415647.47	99.78
4	Diastereomer 2	14.903	1.048	8779.27	0.12

Screening Data for Cyclization of *meso*-dibromide 1

Organic Base Screens

- Screen of organic bases in different solvents to evaluate syn/anti ratio:

Base	Solvent	Duration (hours)	Temp.	Pyrrolidine % syn
1,5-Diazabicyclo[4.3.0]non-5-ene (DBN)	MeCN	18	50	91.57
1,5-Diazabicyclo[4.3.0]non-5-ene (DBN)	MeCN	18	75	89.46
NMM	Cyclohexane	24	75	88.99
2,2,6,6-Tetramethylpiperidine	2-MeTHF	18	75	88.95
NEt3	Cyclohexane	24	75	88.02
Quinoline	2-MeTHF	18	50	86.31
2,6-Lutidine (2,6-Dimethylpyridine)	2-MeTHF	18	50	86.11
2,2,6,6-Tetramethylpiperidine	PhMe	18	75	86.07
NEt3	TAME	24	75	85.96
2,2,6,6-Tetramethylpiperidine	2-MeTHF	18	50	85.69
N-methylpyrrolidine	MTBE	24	55	83.95
Pyridine	Cyclohexane	24	75	83.34
NMM	MTBE	24	55	83.30
Quinoline	PhMe	18	50	82.97
NEt3	CPME	24	75	82.25
Triethylamine	2-MeTHF	18	50	82.13
BnNH2	TAME	24	75	81.78
2,2,6,6-Tetramethylpiperidine	IPA	18	50	81.43
NEt3	MTBE	24	55	81.38
N-methylpyrrolidine	Cyclohexane	24	75	80.88
BnNH2	Cyclohexane	24	75	80.87
BnNH2	CPME	24	75	80.06
Quinoline	2-MeTHF	18	75	80.00
Quinuclidine	IPA	18	50	79.91
N-methylpyrrolidine	CPME	24	75	79.79
BnNH2	MTBE	24	55	79.61

7-Methyl-1,5,7-triazabicyclo[4.4.0]dec-5-ene (MTBD)	IPA	18	75	79.53
tert-Butylimino-tri(pyrrolidino)phosphorane (BTPP)	MeCN	18	75	79.42
2,2,6,6-Tetramethylpiperidine	PhMe	18	50	79.11
2,6-Lutidine (2,6-Dimethylpyridine)	2-MeTHF	18	75	79.02
1,5-Diazabicyclo[4.3.0]non-5-ene (DBN)	IPA	18	75	78.63
Pyridine	IPA	18	50	77.83
Quinoline	PhMe	18	75	77.60
Quinoline	IPA	18	50	77.42
N-methylpyrrolidine	TAME	24	75	77.39
2,6-Lutidine (2,6-Dimethylpyridine)	IPA	18	50	77.15
NaOEt	Cyclohexane	24	75	77.07
2,6-Lutidine (2,6-Dimethylpyridine)	PhMe	18	50	76.40
N-Methylpiperidine	TAME	24	75	75.86
N-Methylpiperidine	CPME	24	75	75.78
Quinuclidine	IPA	18	75	75.70
N,N-Dicyclohexylmethylamine	2-MeTHF	18	50	75.56
NMM	CPME	24	75	75.00
1-Methylmorpholine	2-MeTHF	18	50	74.98
NMM	TAME	24	75	74.80
Pyridine	IPA	18	75	74.68
N-Methylpiperidine	Cyclohexane	24	75	74.59
2,2,6,6-TMP	CPME	24	75	74.03
Quinoline	IPA	18	75	73.98
Triethylamine	PhMe	18	75	73.75
2,6-Lutidine (2,6-Dimethylpyridine)	PhMe	18	75	73.64
1-Methylimidazole	IPA	18	50	73.24
1,5-Diazabicyclo[4.3.0]non-5-ene (DBN)	IPA	18	50	72.87
2,2,6,6-TMP	TAME	24	75	72.63
7-Methyl-1,5,7-triazabicyclo[4.4.0]dec-5-ene (MTBD)	MeCN	18	50	72.58
1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU)	2-MeTHF	18	75	72.40
2,6-Lutidine (2,6-Dimethylpyridine)	IPA	18	75	72.23
N-Methylpiperidine	MTBE	24	55	72.13
Diisopropylethylamine (Hunig's)	2-MeTHF	18	50	72.08
7-Methyl-1,5,7-triazabicyclo[4.4.0]dec-5-ene (MTBD)	MeCN	18	75	72.00
1-Methylmorpholine	IPA	18	50	71.98
Triethylamine	2-MeTHF	18	75	71.96
7-Methyl-1,5,7-triazabicyclo[4.4.0]dec-5-ene (MTBD)	IPA	18	50	71.57
1-Methylmorpholine	2-MeTHF	18	75	71.46
1,4-Diazabicyclo[2.2.2]octane (DABCO)	MeCN	18	50	71.17
2,6-Lutidine	Cyclohexane	24	75	71.07
1-Methylmorpholine	PhMe	18	50	71.00
Triethylamine	PhMe	18	50	70.72
Quinuclidine	MeCN	18	50	70.57
2,2,6,6-TMP	Cyclohexane	24	75	70.40
1-Methylimidazole	IPA	18	75	70.26
1-Methylmorpholine	PhMe	18	75	70.05
1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU)	MeCN	18	50	70.02
1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU)	PhMe	18	50	70.00
1,4-Diazabicyclo[2.2.2]octane (DABCO)	MeCN	18	75	69.92
1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU)	MeCN	18	75	69.88
Tributylamine (HAT)	2-MeTHF	18	50	69.47
2,2,6,6-Tetramethylpiperidine	IPA	18	75	69.40
1,4-Diazabicyclo[2.2.2]octane (DABCO)	IPA	18	75	69.37
Diisopropylethylamine (Hunig's)	PhMe	18	50	69.31
1,4-Diazabicyclo[2.2.2]octane (DABCO)	IPA	18	50	69.27
1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU)	2-MeTHF	18	50	69.04
4-(N,N-Dimethylamino)pyridine (DMAP)	IPA	18	75	68.93
N,N-Dicyclohexylmethylamine	PhMe	18	50	68.67
1-Methylimidazole	MeCN	18	75	68.57
2,2,6,6-TMP	MTBE	24	55	68.32

Quinuclidine	MeCN	18	75	68.30
Tributylamine (HAT)	IPA	18	50	68.30
Quinoline	MeCN	18	50	68.15
Pyridine	MeCN	18	50	68.12
Diisopropylethylamine (Hunig's)	PhMe	18	75	68.07
4-(N,N-Dimethylamino)pyridine (DMAP)	MeCN	18	75	67.82
2-tert-Butyl-1,1,3,3-tetramethylguanidine (BTMG)	MeCN	18	75	67.27
1-Methylimidazole	MeCN	18	50	67.24
Diisopropylethylamine (Hunig's)	IPA	18	50	66.93
Quinuclidine	2-MeTHF	18	50	66.85
2,6-Lutidine (2,6-Dimethylpyridine)	MeCN	18	50	66.81
1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU)	PhMe	18	75	66.67
Triethylamine	IPA	18	50	66.62
Pyridine	MeCN	18	75	66.58
N,N-Dicyclohexylmethylamine	IPA	18	50	66.48
2,6-Lutidine	TAME	24	75	66.25
1-Methylmorpholine	IPA	18	75	66.16
Pyridine	2-MeTHF	18	50	66.10
Quinuclidine	2-MeTHF	18	75	65.60
2-tert-Butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine (BEMP)	MeCN	18	75	65.48
Tributylamine (HAT)	PhMe	18	50	65.36
N-Methylpiperidine	2-MeTHF	18	75	65.16
N,N,N',N'-Tetramethylethylenediamine	IPA	18	50	65.10
Quinoline	MeCN	18	75	65.02
tert-Butylimino-tri(pyrrolidino)phosphorane (BTPP)	MeCN	18	50	64.93
N-methylpyrrolidine	IPA	18	50	64.60
N-Methylpiperidine	IPA	18	50	64.56
1-Methylimidazole	PhMe	18	50	64.49
DABCO	TAME	24	75	64.20
2,6-Lutidine	MTBE	24	55	64.17
Tributylamine (HAT)	2-MeTHF	18	75	64.09
2,2,6,6-Tetramethylpiperidine	MeCN	18	50	64.02
1,1,3,3-Tetramethylguanidine (TMG)	MeCN	18	75	63.74
1,4-Diazabicyclo[2.2.2]octane (DABCO)	IPA	18	75	63.60
DBN	Cyclohexane	24	75	63.11
DIPEA	MTBE	24	55	62.88
4-(N,N-Dimethylamino)pyridine (DMAP)	2-MeTHF	18	75	62.86
Pyridine	2-MeTHF	18	75	62.80
N-methylpyrrolidine	IPA	18	75	62.64
Tributylamine (HAT)	PhMe	18	75	62.61
Diisopropylethylamine (Hunig's)	2-MeTHF	18	75	62.40
1-Methylimidazole	PhMe	18	75	62.14
1,1,3,3-Tetramethylguanidine (TMG)	MeCN	18	50	62.05
Pyridine	PhMe	18	50	62.01
N-Methylpiperidine	2-MeTHF	18	50	61.98
1-Methylimidazole	2-MeTHF	18	50	61.93
N,N,N',N'-Tetramethylethylenediamine	IPA	18	75	61.91
Tributylamine (HAT)	IPA	18	75	61.87
DMAP	MTBE	24	55	61.66
N-Methylpiperidine	IPA	18	75	61.66
NMI	MTBE	24	55	61.29
1-Methylimidazole	2-MeTHF	18	75	61.28
DBU	CPME	24	75	61.22
1,4-Diazabicyclo[2.2.2]octane (DABCO)	2-MeTHF	18	75	61.05
Triethylamine	IPA	18	75	60.97
2,6-Lutidine (2,6-Dimethylpyridine)	MeCN	18	75	60.85
DBU	TAME	24	75	60.82
DABCO	CPME	24	75	60.68
NMI	TAME	24	75	60.60

Diisopropylethylamine (Hunig's)	IPA	18	75	60.32
N,N-Dicyclohexylmethylamine	2-MeTHF	18	75	60.29
N,N-Dicyclohexylmethylamine	IPA	18	75	60.23
1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU)	IPA	18	75	60.13
DABCO	MTBE	24	55	59.94
Quinuclidine	IPA	18	75	59.52
2,2,6,6-Tetramethylpiperidine	MeCN	18	75	59.37
DBU	Cyclohexane	24	75	59.33
N,N-Dicyclohexylmethylamine	PhMe	18	75	59.21
4-(N,N-Dimethylamino)pyridine (DMAP)	PhMe	18	75	59.13
NMI	Cyclohexane	24	75	58.84
DIPEA	CPME	24	75	58.51
1-Methylmorpholine	MeCN	18	50	58.47
N,N,N',N'-Tetramethylethylenediamine	MeCN	18	75	58.33
BTMG	MTBE	24	55	58.31
N,N,N',N'-Tetramethylethylenediamine	PhMe	18	50	58.22
DMAP	TAME	24	75	58.22
Pyridine	PhMe	18	75	58.16
NMI	CPME	24	75	58.13
2-tert-Butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine (BEMP)	MeCN	18	50	58.07
1,4-Diazabicyclo[2.2.2]octane (DABCO)	2-MeTHF	18	50	57.96
N,N,N',N'-Tetramethylethylenediamine	PhMe	18	75	57.91
DIPEA	TAME	24	75	57.80
N,N,N',N'-Tetramethylethylenediamine	2-MeTHF	18	75	57.73
N-Methylpiperidine	PhMe	18	50	57.72
DABCO	Cyclohexane	24	75	57.56
Pyridine	TAME	24	75	57.21
N-Methylpiperidine	PhMe	18	75	57.18
N-methylpyrrolidine	MeCN	18	75	57.18
DMAP	CPME	24	75	57.14
N,N,N',N'-Tetramethylethylenediamine	2-MeTHF	18	50	57.13
2,6-Lutidine	CPME	24	75	57.04
Quinuclidine	IPA	18	50	56.96
N,N,N',N'-Tetramethylethylenediamine	MeCN	18	50	56.93
1,4-Diazabicyclo[2.2.2]octane (DABCO)	IPA	18	50	56.63
N-methylpyrrolidine	MeCN	18	50	56.56
Pyridine	MTBE	24	55	56.55
1-Methylmorpholine	MeCN	18	75	56.54
2-tert-Butyl-1,1,3,3-tetramethylguanidine (BTMG)	MeCN	18	50	56.52
DCHM	Cyclohexane	24	75	56.47
N-Methylpiperidine	MeCN	18	75	56.39
DIPEA	Cyclohexane	24	75	56.39
DCHM	MTBE	24	55	56.26
N-methylpyrrolidine	2-MeTHF	18	50	55.57
Triethylamine	MeCN	18	75	55.51
Triethylamine	MeCN	18	50	55.39
N-Methylpiperidine	MeCN	18	50	55.38
Tributylamine (HAT)	MeCN	18	75	55.29
N,N-Dicyclohexylmethylamine	MeCN	18	50	55.04
Tributylamine (HAT)	MeCN	18	50	54.96
N,N-Dicyclohexylmethylamine	MeCN	18	75	54.89
DBU	MTBE	24	55	54.43
Diisopropylethylamine (Hunig's)	MeCN	18	50	54.22
Diisopropylethylamine (Hunig's)	MeCN	18	75	54.15
BTMG	Cyclohexane	24	75	53.94
1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU)	IPA	18	50	53.92
DCHM	CPME	24	75	53.89
7-Methyl-1,5,7-triazabicyclo[4.4.0]dec-5-ene (MTBD)	2-MeTHF	18	75	53.65
N-methylpyrrolidine	2-MeTHF	18	75	53.60

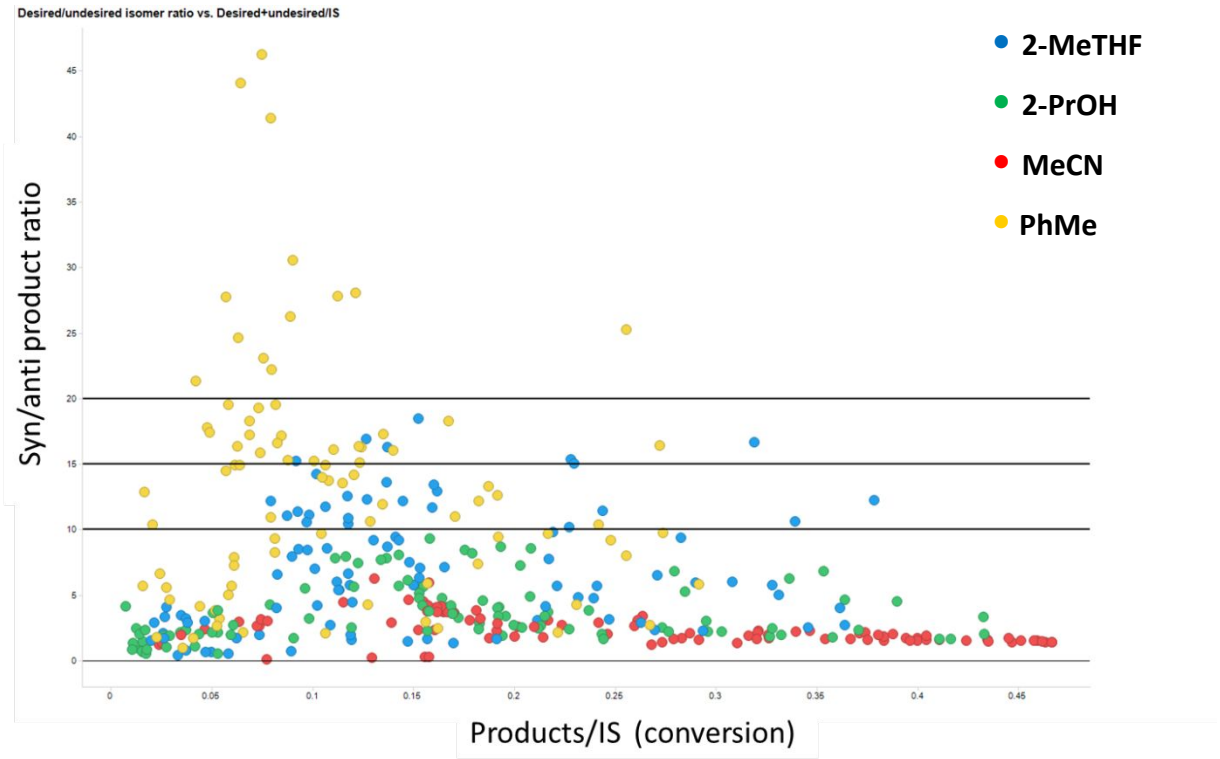
DCHM	TAME	24	75	53.53
Pyridine	CPME	24	75	53.35
NaOEt	TAME	24	75	52.94
DMAP	Cyclohexane	24	75	52.61
N-methylpyrrolidine	PhMe	18	50	52.58
2-tert-Butyl-1,1,3,3-tetramethylguanidine (BTMG)	IPA	18	75	52.32
1,1,3,3-Tetramethylguanidine (TMG)	IPA	18	75	52.22
7-Methyl-1,5,7-triazabicyclo[4.4.0]dec-5-ene (MTBD)	2-MeTHF	18	50	51.72
Quinuclidine	MTBE	24	55	50.85
N-methylpyrrolidine	PhMe	18	75	50.84
1,1,3,3-Tetramethylguanidine (TMG)	IPA	18	50	50.84
BTMG	TAME	24	75	50.64
TMEDA	Cyclohexane	24	75	50.47
7-Methyl-1,5,7-triazabicyclo[4.4.0]dec-5-ene (MTBD)	PhMe	18	75	50.21
1,1,3,3-Tetramethylguanidine (TMG)	2-MeTHF	18	75	49.55
TMEDA	TAME	24	75	49.51
TMEDA	MTBE	24	55	49.41
Quinuclidine	Cyclohexane	24	75	49.21
TMEDA	CPME	24	75	49.19
BTMG	CPME	24	75	48.94
Quinuclidine	TAME	24	75	48.87
2-tert-Butyl-1,1,3,3-tetramethylguanidine (BTMG)	IPA	18	50	48.37
1,1,3,3-Tetramethylguanidine (TMG)	2-MeTHF	18	50	47.74
1,1,3,3-Tetramethylguanidine (TMG)	PhMe	18	75	46.98
Quinuclidine	CPME	24	75	46.69
4-(N,N-Dimethylamino)pyridine (DMAP)	IPA	18	50	46.33
7-Methyl-1,5,7-triazabicyclo[4.4.0]dec-5-ene (MTBD)	PhMe	18	50	46.32
1,1,3,3-Tetramethylguanidine (TMG)	PhMe	18	50	45.92
tert-Butylimino-tri(pyrrolidino)phosphorane (BTPP)	2-MeTHF	18	75	45.29
tert-Butylimino-tri(pyrrolidino)phosphorane (BTPP)	PhMe	18	75	44.85
MTBD	CPME	24	75	44.71
2-tert-Butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine (BEMP)	2-MeTHF	18	75	44.02
MTBD	TAME	24	75	43.94
TMG	CPME	24	75	43.90
2-tert-Butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine (BEMP)	PhMe	18	75	43.61
TMG	TAME	24	75	43.25
TMG	Cyclohexane	24	75	43.23
TMG	MTBE	24	55	43.18
2-tert-Butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine (BEMP)	2-MeTHF	18	50	42.85
tert-Butylimino-tri(pyrrolidino)phosphorane (BTPP)	2-MeTHF	18	50	42.63
tert-Butylimino-tri(pyrrolidino)phosphorane (BTPP)	PhMe	18	50	42.53
2-tert-Butyl-1,1,3,3-tetramethylguanidine (BTMG)	PhMe	18	75	42.48
2-tert-Butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine (BEMP)	PhMe	18	50	42.43
MTBD	Cyclohexane	24	75	42.35
2-tert-Butyl-1,1,3,3-tetramethylguanidine (BTMG)	2-MeTHF	18	75	42.11
MTBD	MTBE	24	55	42.09
2-tert-Butyl-1,1,3,3-tetramethylguanidine (BTMG)	2-MeTHF	18	50	40.23
4-(N,N-Dimethylamino)pyridine (DMAP)	MeCN	18	50	34.68
4-(N,N-Dimethylamino)pyridine (DMAP)	PhMe	18	50	30.25
4-(N,N-Dimethylamino)pyridine (DMAP)	2-MeTHF	18	50	23.93
2-tert-Butyl-1,1,3,3-tetramethylguanidine (BTMG)	PhMe	18	50	13.14
TBD	MTBE	24	55	0.00
KOtBu	MTBE	24	55	0.00
NaOtBu	MTBE	24	55	0.00
DBN	MTBE	24	55	0.00
NaOEt	MTBE	24	55	0.00

TBD	CPME	24	75	0.00
KOtBu	CPME	24	75	0.00
NaOtBu	CPME	24	75	0.00
DBN	CPME	24	75	0.00
NaOEt	CPME	24	75	0.00
TBD	TAME	24	75	0.00
KOtBu	TAME	24	75	0.00
NaOtBu	TAME	24	75	0.00
DBN	TAME	24	75	0.00
TBD	Cyclohexane	24	75	0.00
KOtBu	Cyclohexane	24	75	0.00
NaOtBu	Cyclohexane	24	75	0.00
1,5,7-Triazabicyclo[4.4.0]dec-5-ene (TBD)	MeCN	18	50	0.00
1,5,7-Triazabicyclo[4.4.0]dec-5-ene (TBD)	2-MeTHF	18	50	0.00
1,5-Diazabicyclo[4.3.0]non-5-ene (DBN)	2-MeTHF	18	50	0.00
1,5,7-Triazabicyclo[4.4.0]dec-5-ene (TBD)	IPA	18	50	0.00
tert-Butylimino-tri(pyrrolidino)phosphorane (BTPP)	IPA	18	50	0.00
2-tert-Butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine (BEMP)	IPA	18	50	0.00
1,5,7-Triazabicyclo[4.4.0]dec-5-ene (TBD)	PhMe	18	50	0.00
1,5-Diazabicyclo[4.3.0]non-5-ene (DBN)	PhMe	18	50	0.00
1,5,7-Triazabicyclo[4.4.0]dec-5-ene (TBD)	MeCN	18	75	0.00
1,5,7-Triazabicyclo[4.4.0]dec-5-ene (TBD)	2-MeTHF	18	75	0.00
1,5-Diazabicyclo[4.3.0]non-5-ene (DBN)	2-MeTHF	18	75	0.00
1,5,7-Triazabicyclo[4.4.0]dec-5-ene (TBD)	IPA	18	75	0.00
tert-Butylimino-tri(pyrrolidino)phosphorane (BTPP)	IPA	18	75	0.00
2-tert-Butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine (BEMP)	IPA	18	75	0.00
1,5,7-Triazabicyclo[4.4.0]dec-5-ene (TBD)	PhMe	18	75	0.00
1,5-Diazabicyclo[4.3.0]non-5-ene (DBN)	PhMe	18	75	0.00

Inorganic Base Screens

- Screen of 24 inorganic bases under "anhydrous" conditions to evaluate solvent effects on syn/anti ratio & conversion:

LiOH	NaOH	KOH	NaHCO3	KHCO3	Li2CO3	Na2CO3	K2CO3	Cs2CO3	NaH2PO4	Na2HPO4	Na3PO4
KH2PO4	K2HPO4	K3PO4	LiOAc	NaOAc	KOAc	NaOPiv	KOPiv	NaOSiMe3	KOSiM3	KF	CsF



- Follow-up screen focusing on non-polar solvents to evaluate impact of different bases and reaction mode (anhydrous base vs. aqueous base) on the syn/anti ratio:

Base	Solvent	T ©	Time (hr)	Anhydrous/Aqueous	Pyrrolidine (% syn)
K2CO3	Cyclohexane	75	25	Anhydrous	97.98
KOAc	CPME	75	25	Aqueous	97.48
Cs2CO3	MTBE	55	25	Aqueous	97.34
LiOAc	CPME	75	25	Aqueous	97.33
K2CO3	CPME	75	25	Aqueous	97.00
KOAc	MTBE	55	25	Anhydrous	96.84
NaOAc	CPME	75	25	Aqueous	96.76
KOAc	TAME	75	25	Aqueous	96.46
LiOAc	TAME	75	25	Aqueous	96.03
Li2CO3	CPME	75	25	Aqueous	95.98
Na2CO3	CPME	75	25	Aqueous	95.92
Na3PO4	TAME	75	25	Aqueous	95.83
LiOAc	Cyclohexane	75	25	Aqueous	95.80
Li2CO3	TAME	75	25	Aqueous	95.79
KOAc	MTBE	55	25	Aqueous	95.79
KOAc	Cyclohexane	75	25	Aqueous	95.79
NaOAc	TAME	75	25	Aqueous	95.71
KOAc	CPME	75	25	Anhydrous	95.66
K2CO3	TAME	75	25	Anhydrous	95.66
LiOAc	MTBE	55	25	Anhydrous	95.61

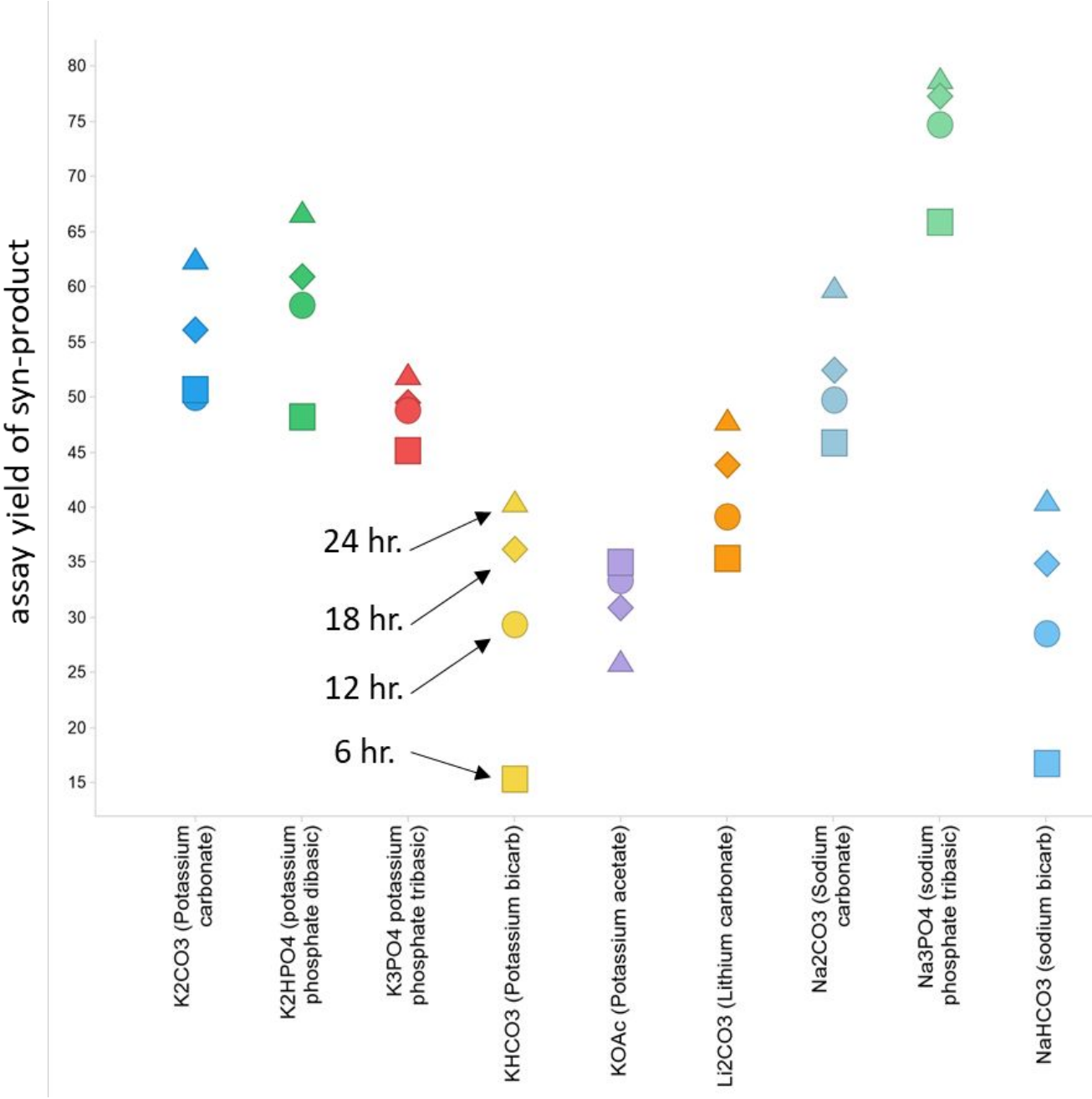
NaOAc	Cyclohexane	75	25	Aqueous	95.34
Li2CO3	Cyclohexane	75	25	Aqueous	95.26
KOAc	Cyclohexane	75	25	Anhydrous	95.24
LiOAc	MTBE	55	25	Aqueous	95.07
K2CO3	TAME	75	25	Aqueous	95.07
KOAc	TAME	75	25	Anhydrous	94.78
Na2CO3	TAME	75	25	Aqueous	94.77
K2CO3	MTBE	55	25	Aqueous	94.73
Na3PO4	CPME	75	25	Aqueous	94.66
NaOAc	MTBE	55	25	Aqueous	94.55
Na2CO3	Cyclohexane	75	25	Aqueous	94.43
KHCO3	TAME	75	25	Aqueous	94.38
KHCO3	CPME	75	25	Aqueous	94.28
KOPiv	MTBE	55	25	Aqueous	94.09
Na2HPO4	CPME	75	25	Aqueous	94.04
NaHCO3	TAME	75	25	Aqueous	93.90
K2CO3	Cyclohexane	75	25	Aqueous	93.70
Na2HPO4	TAME	75	25	Aqueous	93.40
Cs2CO3	CPME	75	25	Aqueous	93.27
NaHCO3	CPME	75	25	Aqueous	93.26
CsF	Cyclohexane	75	25	Aqueous	93.22
Na3PO4	Cyclohexane	75	25	Aqueous	93.15
NaOAc	MTBE	55	25	Anhydrous	93.08
Cs2CO3	TAME	75	25	Aqueous	93.07
NaHCO3	Cyclohexane	75	25	Aqueous	92.77
KF	Cyclohexane	75	25	Aqueous	92.48
KHCO3	Cyclohexane	75	25	Aqueous	92.39
Na2HPO4	Cyclohexane	75	25	Aqueous	92.17
CsF	CPME	75	25	Aqueous	91.85
Cs2CO3	Cyclohexane	75	25	Aqueous	91.54
CsF	TAME	75	25	Aqueous	91.14
Na3PO4	TAME	75	25	Anhydrous	91.13
K2HPO4	Cyclohexane	75	25	Aqueous	90.61
LiOAc	Cyclohexane	75	25	Anhydrous	90.57
KHCO3	TAME	75	25	Anhydrous	90.11
KF	CPME	75	25	Aqueous	90.10
Li2CO3	MTBE	55	25	Aqueous	89.92
KOPiv	MTBE	55	25	Anhydrous	89.42
KF	TAME	75	25	Aqueous	89.33
K2HPO4	TAME	75	25	Aqueous	89.04
Na3PO4	Cyclohexane	75	25	Anhydrous	89.01
K2HPO4	CPME	75	25	Aqueous	88.28
NaOPiv	MTBE	55	25	Aqueous	87.96
K3PO4	MTBE	55	25	Aqueous	87.34
LiOH	Cyclohexane	75	25	Aqueous	86.99
Na2CO3	MTBE	55	25	Aqueous	86.97
KHCO3	Cyclohexane	75	25	Anhydrous	86.95
K2CO3	CPME	75	25	Anhydrous	86.37
KHCO3	MTBE	55	25	Aqueous	86.29
Na2HPO4	MTBE	55	25	Aqueous	85.93
Na3PO4	MTBE	55	25	Aqueous	85.66
Na3PO4	CPME	75	25	Anhydrous	85.49
KH2PO4	Cyclohexane	75	25	Anhydrous	83.49
NaOH	CPME	75	25	Aqueous	83.36
Na2HPO4	Cyclohexane	75	25	Anhydrous	83.14
LiOAc	TAME	75	25	Anhydrous	83.04
Na2CO3	Cyclohexane	75	25	Anhydrous	82.96
K2HPO4	CPME	75	25	Anhydrous	82.76
LiOH	TAME	75	25	Aqueous	82.59
CsF	TAME	75	25	Anhydrous	81.23

Na2CO3	TAME	75	25	Anhydrous	80.88
Na2CO3	CPME	75	25	Anhydrous	80.58
NaHCO3	MTBE	55	25	Aqueous	80.32
CsF	CPME	75	25	Anhydrous	79.62
NaHCO3	TAME	75	25	Anhydrous	79.35
CsF	Cyclohexane	75	25	Anhydrous	79.01
NaOAc	Cyclohexane	75	25	Anhydrous	78.66
KH2PO4	TAME	75	25	Anhydrous	78.56
Na2HPO4	TAME	75	25	Anhydrous	78.32
CsF	MTBE	55	25	Anhydrous	78.31
LiOH	CPME	75	25	Aqueous	78.23
NaH2PO4	MTBE	55	25	Aqueous	77.66
NaHCO3	CPME	75	25	Anhydrous	77.38
K2HPO4	MTBE	55	25	Aqueous	77.30
KH2PO4	CPME	75	25	Anhydrous	77.20
KF	Cyclohexane	75	25	Anhydrous	77.17
KOSiM3	Cyclohexane	75	25	Anhydrous	77.11
CsF	MTBE	55	25	Aqueous	77.06
K2HPO4	TAME	75	25	Anhydrous	76.29
KF	TAME	75	25	Anhydrous	76.17
KH2PO4	MTBE	55	25	Anhydrous	75.79
KH2PO4	MTBE	55	25	Aqueous	75.66
Na2HPO4	CPME	75	25	Anhydrous	75.63
NaHCO3	Cyclohexane	75	25	Anhydrous	75.55
Na2HPO4	MTBE	55	25	Anhydrous	75.54
NaH2PO4	MTBE	55	25	Anhydrous	75.11
LiOAc	CPME	75	25	Anhydrous	74.71
KF	MTBE	55	25	Aqueous	74.32
NaOH	Cyclohexane	75	25	Aqueous	74.20
NaH2PO4	Cyclohexane	75	25	Anhydrous	74.18
Cs2CO3	MTBE	55	25	Anhydrous	74.10
KF	CPME	75	25	Anhydrous	73.87
KHCO3	CPME	75	25	Anhydrous	73.86
Na3PO4	MTBE	55	25	Anhydrous	73.67
NaOH	TAME	75	25	Aqueous	73.53
K3PO4	TAME	75	25	Aqueous	73.49
KF	MTBE	55	25	Anhydrous	72.85
K3PO4	TAME	75	25	Anhydrous	71.89
K3PO4	Cyclohexane	75	25	Anhydrous	71.86
K3PO4	CPME	75	25	Aqueous	71.61
K3PO4	Cyclohexane	75	25	Aqueous	71.11
K2CO3	MTBE	55	25	Anhydrous	70.56
K2HPO4	Cyclohexane	75	25	Anhydrous	70.56
NaOSiMe3	CPME	75	25	Aqueous	70.00
K2HPO4	MTBE	55	25	Anhydrous	69.96
K3PO4	CPME	75	25	Anhydrous	69.50
NaOAc	TAME	75	25	Anhydrous	68.99
NaOSiMe3	Cyclohexane	75	25	Anhydrous	68.97
KH2PO4	CPME	75	25	Aqueous	68.35
NaOPiv	MTBE	55	25	Anhydrous	67.73
KH2PO4	TAME	75	25	Aqueous	67.66
NaOAc	CPME	75	25	Anhydrous	66.98
KH2PO4	Cyclohexane	75	25	Aqueous	66.67
NaOPiv	CPME	75	25	Aqueous	65.21
NaOPiv	TAME	75	25	Aqueous	63.92
NaH2PO4	TAME	75	25	Aqueous	63.64
NaH2PO4	TAME	75	25	Anhydrous	63.11
Li2CO3	MTBE	55	25	Anhydrous	62.83
K3PO4	MTBE	55	25	Anhydrous	62.64
KOPiv	CPME	75	25	Aqueous	62.16

KOSiM3	Cyclohexane	75	25	Aqueous	61.96
Cs2CO3	Cyclohexane	75	25	Anhydrous	61.16
Cs2CO3	CPME	75	25	Anhydrous	60.99
NaOH	MTBE	55	25	Anhydrous	60.92
Na2CO3	MTBE	55	25	Anhydrous	60.80
Cs2CO3	TAME	75	25	Anhydrous	60.75
NaH2PO4	CPME	75	25	Aqueous	60.21
NaOSiMe3	Cyclohexane	75	25	Aqueous	58.49
NaH2PO4	CPME	75	25	Anhydrous	58.43
KOPiv	TAME	75	25	Aqueous	58.35
NaOH	MTBE	55	25	Aqueous	58.11
KOSiM3	CPME	75	25	Aqueous	56.45
Li2CO3	CPME	75	25	Anhydrous	53.94
Li2CO3	Cyclohexane	75	25	Anhydrous	53.68
NaOPiv	Cyclohexane	75	25	Aqueous	53.28
Li2CO3	TAME	75	25	Anhydrous	52.72
NaH2PO4	Cyclohexane	75	25	Aqueous	52.51
KOH	TAME	75	25	Anhydrous	51.97
KOH	MTBE	55	25	Aqueous	50.84
KOH	CPME	75	25	Anhydrous	50.39
KOPiv	Cyclohexane	75	25	Aqueous	50.32
KOH	Cyclohexane	75	25	Aqueous	49.78
KOH	Cyclohexane	75	25	Anhydrous	49.66
KOH	TAME	75	25	Aqueous	49.62
NaHCO3	MTBE	55	25	Anhydrous	49.39
KOH	CPME	75	25	Aqueous	49.18
KOH	MTBE	55	25	Anhydrous	49.08
KHCO3	MTBE	55	25	Anhydrous	47.19
NaOH	CPME	75	25	Anhydrous	45.55
KOSiM3	TAME	75	25	Aqueous	45.45
NaOH	Cyclohexane	75	25	Anhydrous	44.80
NaOH	TAME	75	25	Anhydrous	44.16
LiOH	MTBE	55	25	Aqueous	44.04
NaOPiv	Cyclohexane	75	25	Anhydrous	43.27
KOSiM3	MTBE	55	25	Aqueous	40.86
KOSiM3	TAME	75	25	Anhydrous	38.34
NaOSiMe3	MTBE	55	25	Aqueous	29.85
NaOPiv	CPME	75	25	Anhydrous	25.84
LiOH	MTBE	55	25	Anhydrous	23.36
LiOH	TAME	75	25	Anhydrous	23.14
LiOH	Cyclohexane	75	25	Anhydrous	21.96
LiOH	CPME	75	25	Anhydrous	20.32
NaOPiv	TAME	75	25	Anhydrous	17.83
KOPiv	CPME	75	25	Anhydrous	9.28
KOPiv	TAME	75	25	Anhydrous	5.20
KOPiv	Cyclohexane	75	25	Anhydrous	4.85
KOSiM3	MTBE	55	25	Anhydrous	0.00

Screening for Rate Enhancements

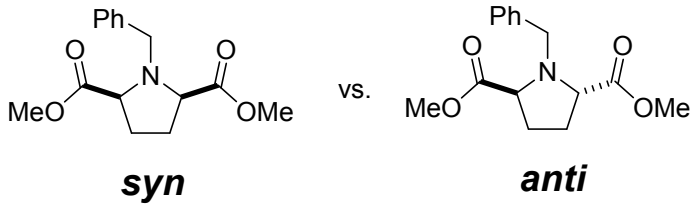
- Screen of inorganic bases using cyclohexane/water @ 75 °C to examine impact of different bases on rate of product formation.



Computing Relative Energies of *syn*- and *anti*-Diesters

Computations were performed using Spartan 18[1] and Gaussian 16[2]. Visualizations were created using CYLview.[3]

To simplify conformational sampling, the bis-methyl esters were used instead of the bis-ethyl esters described in the manuscript:



Initial conformer generation was performed using the automated conformer searching protocol in Spartan '18. This consists of the following steps:

1) Conformer search using MMFF[4] – kept up to 500 conformers (cutoff of ≤40 kJ/mol)
2) Geometry optimization using HF[5]/3-21G[6] – kept up to 200 conformers (cutoff of ≤40 kJ/mol)
3) Single point energy calculation using ωB97X-D[7]/6-31G*[8] – kept up to 100 conformers (cutoff of ≤15 kJ/mol)
4) Geometry optimization using ωB97X-D/6-31G* – kept up to 50 conformers (cutoff of ≤10 kJ/mol)

From this process, a total of 32 *syn*-conformers were obtained and 24 *anti*-conformers. These were subjected to further geometry optimization using Gaussian 16 with either ωB97X-D/6-31+G(d,p)[9] or M06-2X[10]/6-31+G(d,p) with a CPCM solvation model for either MeOH or toluene. In each case, the resulting optimized structures were inspected, and any duplicates removed from the analysis. The table below shows the calculated ratio of *syn*:*anti* for different functionals and solvation models. This is obtained from a Boltzmann analysis of all unique conformers. The lowest energy *syn* and *anti* conformer (with xyz coordinates) is also shown for each functional and solvent.

Functional/Basis set	CPCM Solvation model	*syn*:*anti* ratio (calculated)
wB97X-D/6-31+G(d,p)	MeOH	61 : 39
wB97X-D/6-31+G(d,p)	PhMe	35 : 65
M06-2X/6-31+G(d,p)	MeOH	43 : 57
M06-2X/6-31+G(d,p)	PhMe	32 : 68

Conformer ranking for M06-2X/6-31+G(d,p) using MeOH:

Filename	OK?	SCF	Im.Freq	T(K)	P(atm)	Hcorr	Gcorr	G(Gr)corr	H	G(Gr)*	Rel.G(Gr)*	Bolztmann Average (%)	
OPT_FREQ_SOLV_M062X_MeOH_N_benzyl_anti_conf9.out	Yes	-938.371	0	298.15	1	0.347692	0.278623	0.28215	-938.023	-938.086	0	13	
OPT_FREQ_SOLV_M062X_MeOH_N_benzyl_anti_conf3.out	Yes	-938.37	0	298.15	1	0.347886	0.276776	0.281354	-938.022	-938.086	0.2	10	
OPT_FREQ_SOLV_M062X_MeOH_N_benzyl_anti_conf7.out	Yes	-938.37	0	298.15	1	0.347774	0.278162	0.282117	-938.023	-938.085	0.3	7.2	
OPT_FREQ_SOLV_M062X_MeOH_N_benzyl_anti_conf18.out	Yes	-938.37	0	298.15	1	0.347762	0.278709	0.282263	-938.023	-938.085	0.4	6.7	
OPT_FREQ_SOLV_M062X_MeOH_N_benzyl_anti_conf10.out	Yes	-938.37	0	298.15	1	0.347811	0.277964	0.282135	-938.022	-938.085	0.7	4.1	
OPT_FREQ_SOLV_M062X_MeOH_N_benzyl_anti_conf6.out	Yes	-938.369	0	298.15	1	0.347871	0.277177	0.281553	-938.021	-938.084	0.9	3	
OPT_FREQ_SOLV_M062X_MeOH_N_benzyl_anti_conf17.out	Yes	-938.369	0	298.15	1	0.347913	0.27748	0.281866	-938.021	-938.084	0.9	2.8	
OPT_FREQ_SOLV_M062X_MeOH_N_benzyl_anti_conf14.out	Yes	-938.369	0	298.15	1	0.347991	0.277063	0.281689	-938.021	-938.084	1.1	2.1	
OPT_FREQ_SOLV_M062X_MeOH_N_benzyl_anti_conf22.out	Yes	-938.369	0	298.15	1	0.347867	0.27756	0.281703	-938.021	-938.084	1.2	1.6	
OPT_FREQ_SOLV_M062X_MeOH_N_benzyl_anti_conf12.out	Yes	-938.368	0	298.15	1	0.347861	0.276168	0.281146	-938.02	-938.084	1.3	1.5	
OPT_FREQ_SOLV_M062X_MeOH_N_benzyl_anti_conf8.out	Yes	-938.368	0	298.15	1	0.347861	0.276178	0.281151	-938.02	-938.084	1.3	1.4	
OPT_FREQ_SOLV_M062X_MeOH_N_benzyl_anti_conf19.out	Yes	-938.368	0	298.15	1	0.347882	0.276501	0.281356	-938.02	-938.084	1.4	1.3	
OPT_FREQ_SOLV_M062X_MeOH_N_benzyl_anti_conf20.out	Yes	-938.369	0	298.15	1	0.347928	0.278321	0.28213	-938.021	-938.083	1.4	1.1	
OPT_FREQ_SOLV_M062X_MeOH_N_benzyl_anti_conf21.out	Yes	-938.368	0	298.15	1	0.348039	0.278222	0.282161	-938.02	-938.083	2	0.5	**Total Anti**
OPT_FREQ_SOLV_M062X_MeOH_N_benzyl_anti_conf23.out	Yes	-938.368	0	298.15	1	0.34797	0.278985	0.28247	-938.02	-938.083	1.9	0.5	**56.8**

Filename	OK?	SCF	Im.Freq	T(K)	P(atm)	Hcorr	Gcorr	G(Gr)corr	H	G(Gr)*	Rel.G(Gr)*	Boltzmann Average (%)	
OPT_FREQ_SOLV_M062X_MeOH_N_benzyl_syn_conf19.out	Yes	-938.371	0	298.15	1	0.347726	0.278364	0.282015	-938.023	-938.086	0.2	9.8	
OPT_FREQ_SOLV_M062X_MeOH_N_benzyl_syn_conf3.out	Yes	-938.37	0	298.15	1	0.347759	0.278002	0.281933	-938.022	-938.085	0.3	7.5	
OPT_FREQ_SOLV_M062X_MeOH_N_benzyl_syn_conf23.out	Yes	-938.37	0	298.15	1	0.34765	0.277649	0.281659	-938.022	-938.085	0.4	6.7	
OPT_FREQ_SOLV_M062X_MeOH_N_benzyl_syn_conf22.out	Yes	-938.369	0	298.15	1	0.347652	0.277127	0.281569	-938.022	-938.085	0.6	5	
OPT_FREQ_SOLV_M062X_MeOH_N_benzyl_syn_conf25.out	Yes	-938.37	0	298.15	1	0.3477	0.27845	0.282159	-938.022	-938.085	0.8	3.6	
OPT_FREQ_SOLV_M062X_MeOH_N_benzyl_syn_conf4.out	Yes	-938.369	0	298.15	1	0.347735	0.277584	0.281864	-938.022	-938.084	0.8	3.2	
OPT_FREQ_SOLV_M062X_MeOH_N_benzyl_syn_conf30.out	Yes	-938.369	0	298.15	1	0.347937	0.277863	0.281974	-938.021	-938.084	1.2	1.8	
OPT_FREQ_SOLV_M062X_MeOH_N_benzyl_syn_conf8.out	Yes	-938.368	0	298.15	1	0.347743	0.277175	0.281704	-938.021	-938.084	1.3	1.4	
OPT_FREQ_SOLV_M062X_MeOH_N_benzyl_syn_conf2.out	Yes	-938.368	0	298.15	1	0.347933	0.279002	0.282579	-938.02	-938.083	1.9	0.6	
OPT_FREQ_SOLV_M062X_MeOH_N_benzyl_syn_conf26.out	Yes	-938.367	0	298.15	1	0.347703	0.27728	0.281552	-938.02	-938.083	2	0.5	
OPT_FREQ_SOLV_M062X_MeOH_N_benzyl_syn_conf28.out	Yes	-938.368	0	298.15	1	0.34778	0.278689	0.28224	-938.02	-938.083	2	0.5	
OPT_FREQ_SOLV_M062X_MeOH_N_benzyl_syn_conf32.out	Yes	-938.367	0	298.15	1	0.347668	0.276737	0.281222	-938.019	-938.083	2	0.5	
OPT_FREQ_SOLV_M062X_MeOH_N_benzyl_syn_conf9.out	Yes	-938.368	0	298.15	1	0.348001	0.279197	0.282687	-938.02	-938.083	1.9	0.5	
OPT_FREQ_SOLV_M062X_MeOH_N_benzyl_syn_conf13.out	Yes	-938.367	0	298.15	1	0.348008	0.277526	0.281841	-938.019	-938.082	2.1	0.4	
OPT_FREQ_SOLV_M062X_MeOH_N_benzyl_syn_conf10.out	Yes	-938.367	0	298.15	1	0.348011	0.276822	0.281478	-938.019	-938.082	2.3	0.3	
OPT_FREQ_SOLV_M062X_MeOH_N_benzyl_syn_conf11.out	Yes	-938.368	0	298.15	1	0.347851	0.278397	0.282135	-938.02	-938.082	2.1	0.3	
OPT_FREQ_SOLV_M062X_MeOH_N_benzyl_syn_conf18.out	Yes	-938.366	0	298.15	1	0.348013	0.27648	0.281387	-938.018	-938.082	2.3	0.3	
OPT_FREQ_SOLV_M062X_MeOH_N_benzyl_syn_conf14.out	Yes	-938.367	0	298.15	1	0.348015	0.276944	0.281546	-938.019	-938.082	2.4	0.2	
OPT_FREQ_SOLV_M062X_MeOH_N_benzyl_syn_conf17.out	Yes	-938.366	0	298.15	1	0.34802	0.276138	0.281229	-938.018	-938.082	2.6	0.2	
OPT_FREQ_SOLV_M062X_MeOH_N_benzyl_syn_conf21.out	Yes	-938.367	0	298.15	1	0.347801	0.27841	0.282307	-938.019	-938.081	2.8	0.1	**Total Syn**
OPT_FREQ_SOLV_M062X_MeOH_N_benzyl_syn_conf31.out	Yes	-938.366	0	298.15	1	0.347826	0.278545	0.282301	-938.018	-938.081	3	0.1	**43.5**

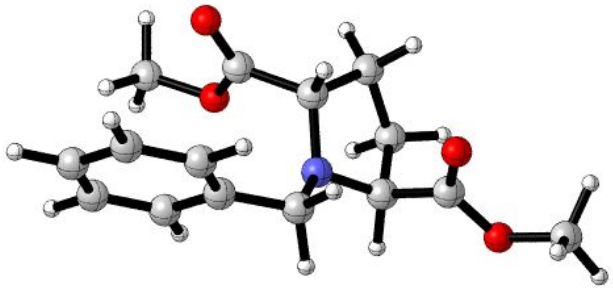
Lowest energy *anti*-conformer:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	7	0	0.017089	0.527014	-0.401762
2	6	0	0.225795	0.511263	1.045687
3	6	0	0.164567	1.999687	1.477995
4	6	0	-0.342562	2.735139	0.228734
5	6	0	0.214328	1.870297	-0.911746
6	6	0	0.638214	-0.564828	-1.139451
7	6	0	0.070766	-1.900470	-0.709602
8	6	0	-1.001141	-4.351135	0.134293
9	6	0	-1.307962	-2.133767	-0.778682
10	6	0	0.903567	-2.906222	-0.217055
11	6	0	0.372776	-4.128398	0.201881
12	6	0	-1.841773	-3.349964	-0.360149
13	6	0	1.679084	2.233144	-1.137888
14	8	0	1.817716	3.181278	-2.067862
15	6	0	3.155522	3.646567	-2.299414
16	8	0	2.609731	1.752926	-0.524471
17	6	0	-0.833123	-0.306266	1.772779
18	8	0	-2.074457	0.023534	1.412531
19	6	0	-3.126167	-0.699398	2.061754
20	8	0	-0.584629	-1.120399	2.639226
21	1	0	1.192050	0.064717	1.316449
22	1	0	1.170683	2.333989	1.738944
23	1	0	-0.480561	2.160557	2.344558
24	1	0	-0.011694	3.774933	0.180426
25	1	0	-1.433596	2.709323	0.176991
26	1	0	-0.327881	2.013606	-1.851374
27	1	0	0.431161	-0.398455	-2.203745
28	1	0	1.731938	-0.575206	-1.008217
29	1	0	-1.417412	-5.297802	0.464320
30	1	0	-1.959618	-1.345246	-1.145977
31	1	0	1.974289	-2.729202	-0.151488
32	1	0	1.031984	-4.900195	0.586990
33	1	0	-2.913124	-3.518833	-0.416751
34	1	0	3.568376	4.069401	-1.382020
35	1	0	3.783882	2.821885	-2.639436
36	1	0	-3.084968	-0.542007	3.141022
37	1	0	-3.032210	-1.765478	1.841282
38	1	0	3.072569	4.408910	-3.070415
39	1	0	-4.053109	-0.304600	1.651340

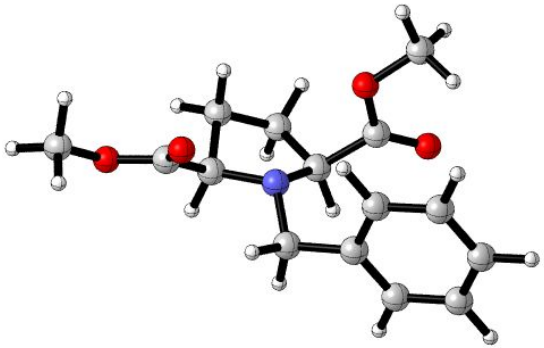
Lowest energy *syn*-conformer:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	7	0	-0.227063	-0.037613	0.710305
2	6	0	0.100100	-0.258926	2.105824
3	6	0	0.939435	0.974759	2.461277
4	6	0	0.174923	2.092392	1.744207
5	6	0	-0.463496	1.393565	0.513806
6	6	0	-1.281615	-0.893934	0.180145
7	6	0	-1.429586	-0.708830	-1.313579
8	6	0	-1.663178	-0.307166	-4.079244
9	6	0	-2.644979	-0.309430	-1.871182
10	6	0	-0.328405	-0.909226	-2.155324
11	6	0	-0.443152	-0.709525	-3.528770
12	6	0	-2.764794	-0.111458	-3.248588
13	6	0	0.137537	1.910272	-0.784712
14	8	0	1.394998	1.508187	-0.966669
15	6	0	2.027913	1.960633	-2.169085
16	8	0	-0.439319	2.665179	-1.541483
17	6	0	0.880286	-1.542485	2.317514
18	8	0	0.969485	-1.821596	3.621748
19	6	0	1.727542	-2.989979	3.965356
20	8	0	1.384812	-2.222656	1.452253
21	1	0	-0.793964	-0.300853	2.753877
22	1	0	1.944170	0.859697	2.042508
23	1	0	1.017782	1.130865	3.537947
24	1	0	0.819431	2.929142	1.466202
25	1	0	-0.619841	2.479222	2.385808
26	1	0	-1.536625	1.624446	0.454747
27	1	0	-2.247951	-0.689207	0.674315
28	1	0	-1.005732	-1.931101	0.399813
29	1	0	-1.751648	-0.148031	-5.149393
30	1	0	-3.501988	-0.142724	-1.223263
31	1	0	0.622992	-1.204563	-1.720680
32	1	0	0.418106	-0.865332	-4.171713
33	1	0	-3.715293	0.202757	-3.668497
34	1	0	1.477752	1.589792	-3.037307
35	1	0	2.062005	3.051229	-2.193280
36	1	0	2.757657	-2.882828	3.621664
37	1	0	1.278182	-3.874398	3.510858
38	1	0	3.033020	1.545151	-2.147707
39	1	0	1.690302	-3.055525	5.050202

Lowest energy *anti*-conformer (M06-2X/6-31+G(d,p) in MeOH):



Lowest energy *syn*-conformer (M06-2X/6-31+G(d,p) in MeOH):



Conformer ranking for M06-2X/6-31+G(d,p) using toluene:

Filename	OK?	SCF	Im.Freq	T(K)	P(atm)	Hcorr	Gcorr	G(Gr)corr	H	G(Gr)*	Rel.G(Gr)*	Boltzmann Average (%)	
OPT_FREQ_SOLV_M062X_PhMeN_benzyl_syn_conf6.out	Yes	-938.363	0	298.15	1	0.347702	0.277234	0.281485	-938.016	-938.079	0.4	6.5	
OPT_FREQ_SOLV_M062X_PhMeN_benzyl_syn_conf27.out	Yes	-938.363	0	298.15	1	0.347798	0.277482	0.281752	-938.015	-938.078	0.6	4.5	
OPT_FREQ_SOLV_M062X_PhMeN_benzyl_syn_conf22.out	Yes	-938.363	0	298.15	1	0.347735	0.277022	0.281536	-938.015	-938.078	0.8	3.4	
OPT_FREQ_SOLV_M062X_PhMeN_benzyl_syn_conf5.out	Yes	-938.363	0	298.15	1	0.347784	0.277718	0.2819	-938.015	-938.078	0.8	3.2	
OPT_FREQ_SOLV_M062X_PhMeN_benzyl_syn_conf23.out	Yes	-938.363	0	298.15	1	0.347834	0.277912	0.28192	-938.015	-938.078	1	2.2	
OPT_FREQ_SOLV_M062X_PhMeN_benzyl_syn_conf4.out	Yes	-938.363	0	298.15	1	0.347784	0.278415	0.282251	-938.015	-938.077	1.2	1.8	
OPT_FREQ_SOLV_M062X_PhMeN_benzyl_syn_conf2.out	Yes	-938.363	0	298.15	1	0.348181	0.279529	0.282965	-938.015	-938.077	1.2	1.7	
OPT_FREQ_SOLV_M062X_PhMeN_benzyl_syn_conf19.out	Yes	-938.362	0	298.15	1	0.348076	0.277681	0.281917	-938.014	-938.077	1.3	1.5	
OPT_FREQ_SOLV_M062X_PhMeN_benzyl_syn_conf28.out	Yes	-938.363	0	298.15	1	0.348047	0.279289	0.282665	-938.015	-938.077	1.3	1.4	
OPT_FREQ_SOLV_M062X_PhMeN_benzyl_syn_conf9.out	Yes	-938.363	0	298.15	1	0.348221	0.279425	0.282959	-938.015	-938.077	1.4	1.3	
OPT_FREQ_SOLV_M062X_PhMeN_benzyl_syn_conf8.out	Yes	-938.362	0	298.15	1	0.347877	0.277899	0.281995	-938.014	-938.077	1.6	0.8	
OPT_FREQ_SOLV_M062X_PhMeN_benzyl_syn_conf11.out	Yes	-938.362	0	298.15	1	0.348074	0.278993	0.282594	-938.014	-938.077	1.7	0.7	
OPT_FREQ_SOLV_M062X_PhMeN_benzyl_syn_conf32.out	Yes	-938.361	0	298.15	1	0.347892	0.277361	0.281681	-938.013	-938.077	1.8	0.6	
OPT_FREQ_SOLV_M062X_PhMeN_benzyl_syn_conf24.out	Yes	-938.361	0	298.15	1	0.348152	0.277099	0.281674	-938.013	-938.076	1.9	0.5	
OPT_FREQ_SOLV_M062X_PhMeN_benzyl_syn_conf26.out	Yes	-938.361	0	298.15	1	0.347922	0.277845	0.281972	-938.013	-938.076	2	0.5	
OPT_FREQ_SOLV_M062X_PhMeN_benzyl_syn_conf3.out	Yes	-938.36	0	298.15	1	0.347828	0.27608	0.281094	-938.013	-938.076	1.9	0.5	
OPT_FREQ_SOLV_M062X_PhMeN_benzyl_syn_conf13.out	Yes	-938.361	0	298.15	1	0.348141	0.277504	0.281877	-938.013	-938.076	2.1	0.4	
OPT_FREQ_SOLV_M062X_PhMeN_benzyl_syn_conf14.out	Yes	-938.36	0	298.15	1	0.348202	0.277035	0.28167	-938.012	-938.076	2.4	0.2	
OPT_FREQ_SOLV_M062X_PhMeN_benzyl_syn_conf17.out	Yes	-938.36	0	298.15	1	0.348273	0.276672	0.281606	-938.012	-938.075	2.6	0.2	
OPT_FREQ_SOLV_M062X_PhMeN_benzyl_syn_conf21.out	Yes	-938.361	0	298.15	1	0.347996	0.278498	0.282468	-938.013	-938.075	2.5	0.2	**Total Syn**
OPT_FREQ_SOLV_M062X_PhMeN_benzyl_syn_conf31.out	Yes	-938.361	0	298.15	1	0.34804	0.278924	0.282588	-938.013	-938.075	2.7	0.1	**32.2**

Filename	OK?	SCF	Im.Freq	T(K)	P(atm)	Hcorr	Gcorr	G(Gr)corr	H	G(Gr)*	Rel.G(Gr)*	Boltzmann Average (%)	
OPT_FREQ_SOLV_M062X_PhMe_N_benzyl_anti_conf3.out	Yes	-938.364	0	298.15	1	0.348062	0.277127	0.281635	-938.016	-938.079	0	13	
OPT_FREQ_SOLV_M062X_PhMe_N_benzyl_anti_conf9.out	Yes	-938.365	0	298.15	1	0.347887	0.278661	0.282295	-938.017	-938.079	0.1	11.4	
OPT_FREQ_SOLV_M062X_PhMe_N_benzyl_anti_conf5.out	Yes	-938.365	0	298.15	1	0.347992	0.27865	0.28246	-938.017	-938.079	0.1	11.2	
OPT_FREQ_SOLV_M062X_PhMe_N_benzyl_anti_conf4.out	Yes	-938.364	0	298.15	1	0.348161	0.277986	0.282265	-938.016	-938.079	0.4	6.9	
OPT_FREQ_SOLV_M062X_PhMe_N_benzyl_anti_conf6.out	Yes	-938.363	0	298.15	1	0.347978	0.275507	0.280794	-938.015	-938.079	0.4	6.4	
OPT_FREQ_SOLV_M062X_PhMe_N_benzyl_anti_conf18.out	Yes	-938.364	0	298.15	1	0.347923	0.278579	0.282315	-938.016	-938.078	0.6	4.7	
OPT_FREQ_SOLV_M062X_PhMe_N_benzyl_anti_conf10.out	Yes	-938.364	0	298.15	1	0.348018	0.278359	0.282414	-938.016	-938.078	0.7	3.8	
OPT_FREQ_SOLV_M062X_PhMe_N_benzyl_anti_conf2.out	Yes	-938.363	0	298.15	1	0.34823	0.277893	0.282255	-938.015	-938.078	0.9	3	
OPT_FREQ_SOLV_M062X_PhMe_N_benzyl_anti_conf22.out	Yes	-938.363	0	298.15	1	0.348091	0.278015	0.282061	-938.015	-938.078	1.1	1.9	
OPT_FREQ_SOLV_M062X_PhMe_N_benzyl_anti_conf19.out	Yes	-938.362	0	298.15	1	0.348074	0.276917	0.281703	-938.014	-938.077	1.3	1.4	
OPT_FREQ_SOLV_M062X_PhMe_N_benzyl_anti_conf12.out	Yes	-938.362	0	298.15	1	0.348091	0.27642	0.281441	-938.013	-938.077	1.4	1.2	
OPT_FREQ_SOLV_M062X_PhMe_N_benzyl_anti_conf16.out	Yes	-938.363	0	298.15	1	0.348133	0.278641	0.282365	-938.014	-938.077	1.4	1.2	
OPT_FREQ_SOLV_M062X_PhMe_N_benzyl_anti_conf21.out	Yes	-938.362	0	298.15	1	0.348277	0.278365	0.282334	-938.014	-938.077	1.7	0.8	
OPT_FREQ_SOLV_M062X_PhMe_N_benzyl_anti_conf13.out	Yes	-938.362	0	298.15	1	0.348176	0.2793	0.28276	-938.014	-938.076	2.1	0.4	
OPT_FREQ_SOLV_M062X_PhMe_N_benzyl_anti_conf24.out	Yes	-938.362	0	298.15	1	0.348361	0.2795	0.283021	-938.013	-938.076	2.2	0.3	**Total Anti**
OPT_FREQ_SOLV_M062X_PhMe_N_benzyl_anti_conf15.out	Yes	-938.361	0	298.15	1	0.348244	0.279104	0.282809	-938.013	-938.075	2.6	0.2	**67.8**

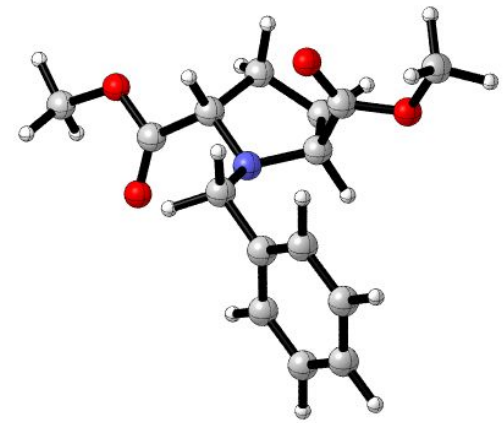
Lowest energy *anti*-conformer:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	7	0	-0.050423	0.545638	-0.282294
2	6	0	0.572756	0.228453	0.989125
3	6	0	0.841660	1.624316	1.571201
4	6	0	-0.413253	2.414517	1.169610
5	6	0	-0.906721	1.710044	-0.122411
6	6	0	-0.648701	-0.548176	-1.041158
7	6	0	0.322937	-1.693034	-1.196319
8	6	0	2.177726	-3.780574	-1.428173
9	6	0	0.107416	-2.907163	-0.542594
10	6	0	1.479617	-1.530122	-1.966867
11	6	0	2.401114	-2.566915	-2.083967
12	6	0	1.029837	-3.949655	-0.657660
13	6	0	-0.839640	2.608827	-1.348321
14	8	0	-1.688449	3.640076	-1.215353
15	6	0	-1.723003	4.561743	-2.310121
16	8	0	-0.145512	2.443624	-2.323587
17	6	0	-0.330436	-0.556995	1.933348
18	8	0	0.374420	-1.303093	2.791212
19	6	0	-0.391823	-2.052123	3.741591
20	8	0	-1.542104	-0.500329	1.935172
21	1	0	1.492689	-0.344411	0.842160
22	1	0	1.731139	2.028638	1.081985
23	1	0	1.013087	1.610631	2.650038
24	1	0	-0.206973	3.474969	1.012822
25	1	0	-1.184316	2.333782	1.938319
26	1	0	-1.964992	1.429285	-0.001492
27	1	0	-1.575021	-0.907967	-0.564404
28	1	0	-0.910407	-0.147105	-2.026868
29	1	0	2.896582	-4.588837	-1.519799
30	1	0	-0.788861	-3.036745	0.060713
31	1	0	1.650562	-0.580134	-2.467468
32	1	0	3.293867	-2.432042	-2.686930
33	1	0	0.850629	-4.889644	-0.144879
34	1	0	-0.737809	5.007741	-2.458948
35	1	0	-2.029569	4.049144	-3.223854
36	1	0	-1.047252	-2.754233	3.222364
37	1	0	-0.994150	-1.379422	4.354905
38	1	0	-2.450821	5.321598	-2.033349
39	1	0	0.334296	-2.584405	4.352052

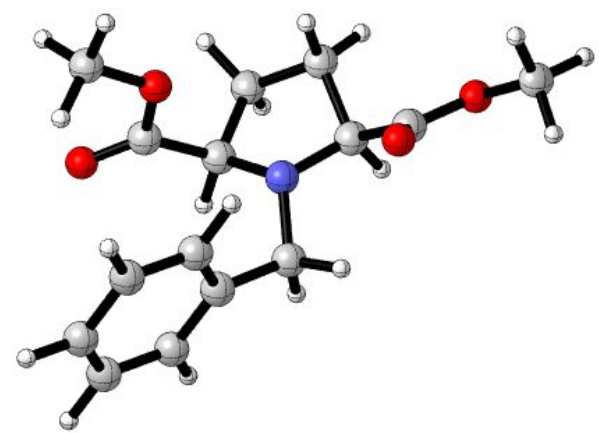
Lowest energy *syn*-conformer:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	7	0	-0.552958	0.606615	0.086944
2	6	0	-0.403836	0.411598	1.526776
3	6	0	-0.061453	1.813287	2.093207
4	6	0	0.267964	2.649045	0.852549
5	6	0	-0.651955	2.020093	-0.202102
6	6	0	-1.531653	-0.260748	-0.548370
7	6	0	-1.102937	-1.707034	-0.436715
8	6	0	-0.230445	-4.356528	-0.187154
9	6	0	-1.914408	-2.662737	0.172993
10	6	0	0.153755	-2.086551	-0.923647
11	6	0	0.587050	-3.403464	-0.800772
12	6	0	-1.482394	-3.985025	0.296550
13	6	0	-0.192519	2.342155	-1.612492
14	8	0	-0.417525	3.634259	-1.890725
15	6	0	0.003609	4.072106	-3.187948
16	8	0	0.319767	1.571982	-2.389849
17	6	0	0.679583	-0.604716	1.862886
18	8	0	1.824170	-0.362615	1.217297
19	6	0	2.882511	-1.289287	1.475354
20	8	0	0.544046	-1.495979	2.672495
21	1	0	-1.323358	0.019599	1.984671
22	1	0	0.756920	1.787937	2.816203
23	1	0	-0.942616	2.218563	2.597312
24	1	0	1.310191	2.499812	0.553411
25	1	0	0.082374	3.715638	0.986962
26	1	0	-1.677495	2.418894	-0.088460
27	1	0	-1.590828	0.024396	-1.604079
28	1	0	-2.536013	-0.133739	-0.104308
29	1	0	0.110532	-5.382124	-0.085675
30	1	0	-2.885576	-2.370454	0.565020
31	1	0	0.787377	-1.330072	-1.380041
32	1	0	1.563456	-3.689459	-1.180987
33	1	0	-2.119853	-4.718920	0.779675
34	1	0	1.079918	3.930619	-3.301589
35	1	0	-0.519934	3.509006	-3.962666
36	1	0	2.571903	-2.295152	1.182069
37	1	0	3.143457	-1.284355	2.535537
38	1	0	-0.253155	5.127945	-3.240055
39	1	0	3.722425	-0.954491	0.869822

Lowest energy *anti*-conformer (M06-2X/6-31+G(d,p) in PhMe):



Lowest energy *syn*-conformer (M06-2X/6-31+G(d,p) in PhMe):



Conformer ranking for ωB97X-D/6-31+G(d,p) using MeOH:

Filename	OK?	SCF	Im.Freq	T(K)	P(atm)	Hcorr	Gcorr	G(Gr)corr	H	G(Gr)*	Rel.G(Gr)*	Boltzmann Average (%)	
OPT_FREQ_SOLV_wB97XD_MeOH_N_benzyl_anti_conf18.out	Yes	-938.477	0	298.15	1	0.347992	0.277648	0.281875	-938.129	-938.192	0.4	6.8	
OPT_FREQ_SOLV_wB97XD_MeOH_N_benzyl_anti_conf3.out	Yes	-938.477	0	298.15	1	0.34823	0.277156	0.281725	-938.128	-938.192	0.4	6.7	
OPT_FREQ_SOLV_wB97XD_MeOH_N_benzyl_anti_conf6.out	Yes	-938.476	0	298.15	1	0.348148	0.276424	0.281272	-938.128	-938.192	0.5	5.5	
OPT_FREQ_SOLV_wB97XD_MeOH_N_benzyl_anti_conf7.out	Yes	-938.477	0	298.15	1	0.348216	0.278206	0.282309	-938.128	-938.191	0.7	4.2	
OPT_FREQ_SOLV_wB97XD_MeOH_N_benzyl_anti_conf2.out	Yes	-938.476	0	298.15	1	0.348224	0.276646	0.281533	-938.128	-938.191	0.8	3.6	
OPT_FREQ_SOLV_wB97XD_MeOH_N_benzyl_anti_conf8.out	Yes	-938.475	0	298.15	1	0.348136	0.276459	0.28131	-938.127	-938.191	1	2.4	
OPT_FREQ_SOLV_wB97XD_MeOH_N_benzyl_anti_conf10.out	Yes	-938.476	0	298.15	1	0.348306	0.278325	0.282527	-938.128	-938.191	1	2.4	
OPT_FREQ_SOLV_wB97XD_MeOH_N_benzyl_anti_conf12.out	Yes	-938.475	0	298.15	1	0.348146	0.276528	0.281353	-938.127	-938.191	1	2.3	
OPT_FREQ_SOLV_wB97XD_MeOH_N_benzyl_anti_conf22.out	Yes	-938.475	0	298.15	1	0.348263	0.276729	0.281475	-938.127	-938.19	1.3	1.3	
OPT_FREQ_SOLV_wB97XD_MeOH_N_benzyl_anti_conf4.out	Yes	-938.476	0	298.15	1	0.348425	0.278096	0.282419	-938.127	-938.19	1.5	1.1	
OPT_FREQ_SOLV_wB97XD_MeOH_N_benzyl_anti_conf19.out	Yes	-938.475	0	298.15	1	0.348249	0.277186	0.281842	-938.127	-938.19	1.6	0.9	
OPT_FREQ_SOLV_wB97XD_MeOH_N_benzyl_anti_conf24.out	Yes	-938.476	0	298.15	1	0.348553	0.279291	0.283007	-938.127	-938.19	1.8	0.6	
OPT_FREQ_SOLV_wB97XD_MeOH_N_benzyl_anti_conf21.out	Yes	-938.475	0	298.15	1	0.3484	0.278698	0.282489	-938.127	-938.189	1.9	0.5	**Total Anti**
OPT_FREQ_SOLV_wB97XD_MeOH_N_benzyl_anti_conf13.out	Yes	-938.475	0	298.15	1	0.348396	0.278919	0.282629	-938.126	-938.189	2.1	0.4	**38.7**

Filename	OK?	SCF	Im.Freq	T(K)	P(atm)	Hcorr	Gcorr	G(Gr)corr	H	G(Gr)*	Rel.G(Gr)*	Boltzman Average (%)	
OPT_FREQ_SOLV_wB97XD_MeOH_N_benzyl_syn_conf1.out	Yes	-938.477	0	298.15	1	0.348043	0.277578	0.281794	-938.129	-938.192	0	12.9	
OPT_FREQ_SOLV_wB97XD_MeOH_N_benzyl_syn_conf22.out	Yes	-938.477	0	298.15	1	0.347992	0.276779	0.281496	-938.129	-938.192	0.2	9.7	
OPT_FREQ_SOLV_wB97XD_MeOH_N_benzyl_syn_conf27.out	Yes	-938.477	0	298.15	1	0.348029	0.277866	0.281981	-938.129	-938.192	0.2	9.3	
OPT_FREQ_SOLV_wB97XD_MeOH_N_benzyl_syn_conf23.out	Yes	-938.477	0	298.15	1	0.348048	0.277404	0.281817	-938.129	-938.192	0.3	8.1	
OPT_FREQ_SOLV_wB97XD_MeOH_N_benzyl_syn_conf25.out	Yes	-938.476	0	298.15	1	0.34805	0.277847	0.28202	-938.128	-938.191	0.6	4.4	
OPT_FREQ_SOLV_wB97XD_MeOH_N_benzyl_syn_conf4.out	Yes	-938.476	0	298.15	1	0.348064	0.277626	0.281972	-938.128	-938.191	0.7	4	
OPT_FREQ_SOLV_wB97XD_MeOH_N_benzyl_syn_conf19.out	Yes	-938.476	0	298.15	1	0.347985	0.277241	0.281628	-938.128	-938.191	0.8	3.6	
OPT_FREQ_SOLV_wB97XD_MeOH_N_benzyl_syn_conf30.out	Yes	-938.476	0	298.15	1	0.348064	0.277014	0.281612	-938.128	-938.191	0.8	3.4	
OPT_FREQ_SOLV_wB97XD_MeOH_N_benzyl_syn_conf8.out	Yes	-938.475	0	298.15	1	0.348204	0.277065	0.281806	-938.127	-938.191	1.1	2	
OPT_FREQ_SOLV_wB97XD_MeOH_N_benzyl_syn_conf24.out	Yes	-938.475	0	298.15	1	0.348465	0.27773	0.282169	-938.127	-938.19	1.6	0.8	
OPT_FREQ_SOLV_wB97XD_MeOH_N_benzyl_syn_conf7.out	Yes	-938.475	0	298.15	1	0.348434	0.277909	0.282244	-938.127	-938.19	1.7	0.8	
OPT_FREQ_SOLV_wB97XD_MeOH_N_benzyl_syn_conf14.out	Yes	-938.474	0	298.15	1	0.348461	0.277196	0.281896	-938.126	-938.189	1.9	0.6	
OPT_FREQ_SOLV_wB97XD_MeOH_N_benzyl_syn_conf17.out	Yes	-938.474	0	298.15	1	0.34845	0.276064	0.281388	-938.125	-938.189	1.9	0.5	
OPT_FREQ_SOLV_wB97XD_MeOH_N_benzyl_syn_conf20.out	Yes	-938.474	0	298.15	1	0.3482	0.277483	0.281883	-938.125	-938.189	2.3	0.3	
OPT_FREQ_SOLV_wB97XD_MeOH_N_benzyl_syn_conf16.out	Yes	-938.473	0	298.15	1	0.347972	0.277334	0.281552	-938.125	-938.189	2.4	0.2	
OPT_FREQ_SOLV_wB97XD_MeOH_N_benzyl_syn_conf32.out	Yes	-938.473	0	298.15	1	0.34804	0.277424	0.281754	-938.125	-938.188	2.6	0.2	
OPT_FREQ_SOLV_wB97XD_MeOH_N_benzyl_syn_conf28.out	Yes	-938.473	0	298.15	1	0.348093	0.278092	0.282146	-938.125	-938.188	2.6	0.2	
OPT_FREQ_SOLV_wB97XD_MeOH_N_benzyl_syn_conf9.out	Yes	-938.473	0	298.15	1	0.348205	0.278283	0.282253	-938.125	-938.188	2.6	0.1	
OPT_FREQ_SOLV_wB97XD_MeOH_N_benzyl_syn_conf11.out	Yes	-938.473	0	298.15	1	0.348102	0.277853	0.281907	-938.125	-938.188	2.9	0.1	**Total Syn**
OPT_FREQ_SOLV_wB97XD_MeOH_N_benzyl_syn_conf31.out	Yes	-938.472	0	298.15	1	0.348082	0.277581	0.281854	-938.124	-938.188	3	0.1	**61.3**

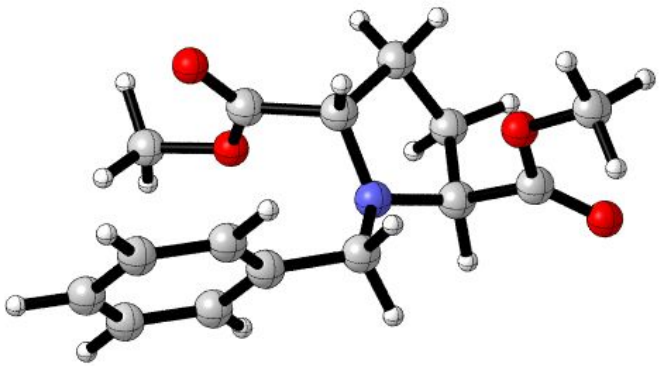
Lowest energy *anti*-conformer:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	7	0	0.598048	-0.246603	0.584102
2	6	0	1.292731	-0.475963	1.835501
3	6	0	1.239152	0.907628	2.500150
4	6	0	-0.154638	1.423793	2.118171
5	6	0	-0.450499	0.753532	0.751457
6	6	0	0.266990	-1.408219	-0.226281
7	6	0	-0.051658	-1.025004	-1.655527
8	6	0	-0.649948	-0.267795	-4.288898
9	6	0	0.900840	-0.364768	-2.439173
10	6	0	-1.301770	-1.305420	-2.207919
11	6	0	-1.601760	-0.931794	-3.518876
12	6	0	0.605300	0.013906	-3.745110
13	6	0	-0.465576	1.786893	-0.368622
14	8	0	0.740079	2.288477	-0.625976
15	6	0	0.817478	3.262456	-1.672569
16	8	0	-1.481157	2.163407	-0.923986
17	6	0	0.689615	-1.534266	2.762720
18	8	0	-0.642854	-1.560978	2.720193
19	6	0	-1.300039	-2.497234	3.586338
20	8	0	1.353776	-2.253486	3.484024
21	1	0	2.320738	-0.800441	1.648245
22	1	0	2.019430	1.530881	2.057055
23	1	0	1.398459	0.871928	3.580056
24	1	0	-0.191468	2.514269	2.071534
25	1	0	-0.900689	1.094216	2.843435
26	1	0	-1.451090	0.301672	0.752207
27	1	0	1.137690	-2.073948	-0.211312
28	1	0	-0.583496	-1.969155	0.194489
29	1	0	-0.882049	0.029828	-5.306780
30	1	0	1.871135	-0.131906	-2.010595
31	1	0	-2.052131	-1.810833	-1.605392
32	1	0	-2.580563	-1.153111	-3.933125
33	1	0	1.352251	0.530432	-4.340356
34	1	0	0.494716	2.819145	-2.617535
35	1	0	0.195417	4.128311	-1.437795
36	1	0	-1.063626	-2.276314	4.628726
37	1	0	-0.990384	-3.515443	3.344416
38	1	0	1.865691	3.549709	-1.727641
39	1	0	-2.364141	-2.368003	3.400749

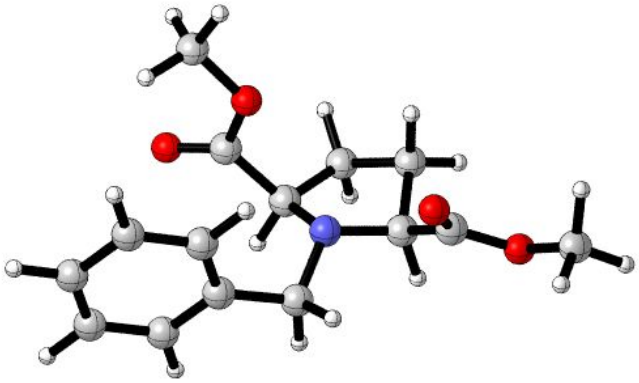
Lowest energy *syn*-conformer:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	7	0	-0.292560	0.692179	0.000827
2	6	0	-0.789231	0.321725	1.324381
3	6	0	-0.469777	1.530482	2.242322
4	6	0	0.455954	2.411014	1.399683
5	6	0	-0.035416	2.118260	-0.024374
6	6	0	-1.086057	0.184449	-1.110788
7	6	0	-1.128314	-1.327686	-1.119693
8	6	0	-1.184530	-4.131599	-1.069431
9	6	0	-2.339233	-2.011291	-1.005019
10	6	0	0.057634	-2.064503	-1.215517
11	6	0	0.031734	-3.455538	-1.187872
12	6	0	-2.370477	-3.406497	-0.982495
13	6	0	1.005777	2.507740	-1.059829
14	8	0	0.942130	3.818248	-1.308512
15	6	0	1.915862	4.347457	-2.219667
16	8	0	1.813027	1.765131	-1.577800
17	6	0	-0.165110	-0.961385	1.857131
18	8	0	1.151855	-1.014648	1.680004
19	6	0	1.810621	-2.199524	2.141949
20	8	0	-0.799950	-1.821225	2.439924
21	1	0	-1.871074	0.132852	1.313403
22	1	0	-0.017954	1.235694	3.191848
23	1	0	-1.397883	2.061537	2.466183
24	1	0	1.497156	2.090516	1.501695
25	1	0	0.386261	3.469584	1.653941
26	1	0	-0.944263	2.710455	-0.229741
27	1	0	-0.625172	0.541451	-2.037784
28	1	0	-2.116365	0.581130	-1.080703
29	1	0	-1.204891	-5.216718	-1.045079
30	1	0	-3.266165	-1.449705	-0.922017
31	1	0	1.004550	-1.539026	-1.292766
32	1	0	0.960097	-4.014456	-1.257242
33	1	0	-3.320393	-3.923732	-0.889054
34	1	0	2.923710	4.180168	-1.835350
35	1	0	1.811234	3.876944	-3.198942
36	1	0	1.425525	-3.070891	1.607085
37	1	0	1.661310	-2.328160	3.215646
38	1	0	1.704929	5.412781	-2.284619
39	1	0	2.865449	-2.053216	1.918174

Lowest energy *anti*-conformer (ωB97X-D/6-31+G(d,p) in MeOH):



Lowest energy *syn*-conformer (ωB97X-D/6-31+G(d,p) in MeOH):



Conformer ranking for ωB97X-D/6-31+G(d,p) using toluene:

Filename	OK?	SCF	Im.Freq	T(K)	P(atm)	Hcorr	Gcorr	G(Gr)corr	H	G(Gr)*	Rel.G(Gr)*	Boltzmann Average (%)	
OPT_FREQ_SOLV_PhMe_wB97XD_N_benzyl_anti_conf10.out	Yes	-938.47	0	298.15	1	0.348353	0.278111	0.282418	-938.122	-938.185	1	2.9	
OPT_FREQ_SOLV_PhMe_wB97XD_N_benzyl_anti_conf11.out	Yes	-938.468	0	298.15	1	0.348291	0.275632	0.28105	-938.12	-938.184	1	2.6	
OPT_FREQ_SOLV_PhMe_wB97XD_N_benzyl_anti_conf12.out	Yes	-938.468	0	298.15	1	0.348199	0.27529	0.280795	-938.12	-938.185	0.9	3.4	
OPT_FREQ_SOLV_PhMe_wB97XD_N_benzyl_anti_conf14.out	Yes	-938.469	0	298.15	1	0.348434	0.276773	0.281703	-938.121	-938.185	0.8	3.8	
OPT_FREQ_SOLV_PhMe_wB97XD_N_benzyl_anti_conf15.out	Yes	-938.468	0	298.15	1	0.348483	0.278402	0.282398	-938.12	-938.183	2.1	0.4	
OPT_FREQ_SOLV_PhMe_wB97XD_N_benzyl_anti_conf16.out	Yes	-938.469	0	298.15	1	0.348544	0.278627	0.282506	-938.121	-938.184	1.5	1.2	
OPT_FREQ_SOLV_PhMe_wB97XD_N_benzyl_anti_conf18.out	Yes	-938.47	0	298.15	1	0.34825	0.277861	0.282153	-938.122	-938.185	0.9	3.5	
OPT_FREQ_SOLV_PhMe_wB97XD_N_benzyl_anti_conf19.out	Yes	-938.469	0	298.15	1	0.348352	0.276842	0.281721	-938.12	-938.184	1.4	1.3	
OPT_FREQ_SOLV_PhMe_wB97XD_N_benzyl_anti_conf20.out	Yes	-938.469	0	298.15	1	0.34855	0.278703	0.282551	-938.121	-938.184	1.5	1.2	
OPT_FREQ_SOLV_PhMe_wB97XD_N_benzyl_anti_conf21.out	Yes	-938.469	0	298.15	1	0.34863	0.278999	0.28279	-938.12	-938.183	1.9	0.7	
OPT_FREQ_SOLV_PhMe_wB97XD_N_benzyl_anti_conf22.out	Yes	-938.469	0	298.15	1	0.348439	0.276594	0.281459	-938.12	-938.184	1.2	2.1	
OPT_FREQ_SOLV_PhMe_wB97XD_N_benzyl_anti_conf3.out	Yes	-938.47	0	298.15	1	0.348299	0.276444	0.28136	-938.122	-938.186	0	15.1	
OPT_FREQ_SOLV_PhMe_wB97XD_N_benzyl_anti_conf4.out	Yes	-938.47	0	298.15	1	0.348368	0.277354	0.28197	-938.122	-938.185	0.6	5.6	
OPT_FREQ_SOLV_PhMe_wB97XD_N_benzyl_anti_conf5.out	Yes	-938.471	0	298.15	1	0.348225	0.277443	0.281939	-938.123	-938.186	0.1	11.8	
OPT_FREQ_SOLV_PhMe_wB97XD_N_benzyl_anti_conf6.out	Yes	-938.469	0	298.15	1	0.348333	0.27669	0.281549	-938.121	-938.185	1	3	**Total Anti**
OPT_FREQ_SOLV_PhMe_wB97XD_N_benzyl_anti_conf9.out	Yes	-938.471	0	298.15	1	0.348224	0.278235	0.282249	-938.122	-938.185	0.5	6.2	**64.8**

Filename	OK?	SCF	Im.Freq	T(K)	P(atm)	Hcorr	Gcorr	G(Gr)corr	H	G(Gr)*	Rel.G(Gr)*	Boltzmann Average (%)	
OPT_FREQ_SOLV_PhMe_wB97XD_N_benzyl_syn_conf1.out	Yes	-938.47	0	298.15	1	0.348046	0.27708	0.281568	-938.122	-938.185	0.6	5.6	
OPT_FREQ_SOLV_PhMe_wB97XD_N_benzyl_syn_conf11.out	Yes	-938.467	0	298.15	1	0.348391	0.278907	0.282552	-938.119	-938.181	2.9	0.1	
OPT_FREQ_SOLV_PhMe_wB97XD_N_benzyl_syn_conf14.out	Yes	-938.468	0	298.15	1	0.348575	0.277226	0.281924	-938.119	-938.183	2.1	0.5	
OPT_FREQ_SOLV_PhMe_wB97XD_N_benzyl_syn_conf15.out	Yes	-938.47	0	298.15	1	0.348142	0.276501	0.28146	-938.121	-938.185	0.6	5.2	
OPT_FREQ_SOLV_PhMe_wB97XD_N_benzyl_syn_conf16.out	Yes	-938.468	0	298.15	1	0.34826	0.27805	0.282118	-938.12	-938.183	2.1	0.4	
OPT_FREQ_SOLV_PhMe_wB97XD_N_benzyl_syn_conf17.out	Yes	-938.467	0	298.15	1	0.348645	0.277504	0.28219	-938.119	-938.182	2.4	0.3	
OPT_FREQ_SOLV_PhMe_wB97XD_N_benzyl_syn_conf18.out	Yes	-938.468	0	298.15	1	0.34854	0.277295	0.282033	-938.12	-938.183	1.9	0.6	
OPT_FREQ_SOLV_PhMe_wB97XD_N_benzyl_syn_conf2.out	Yes	-938.468	0	298.15	1	0.348283	0.27769	0.281995	-938.12	-938.183	1.7	0.9	
OPT_FREQ_SOLV_PhMe_wB97XD_N_benzyl_syn_conf22.out	Yes	-938.47	0	298.15	1	0.348116	0.277191	0.281764	-938.122	-938.185	0.8	4.2	
OPT_FREQ_SOLV_PhMe_wB97XD_N_benzyl_syn_conf23.out	Yes	-938.469	0	298.15	1	0.348064	0.277321	0.281742	-938.121	-938.185	0.9	3.4	
OPT_FREQ_SOLV_PhMe_wB97XD_N_benzyl_syn_conf25.out	Yes	-938.47	0	298.15	1	0.3482	0.277083	0.28177	-938.121	-938.185	0.9	3.6	
OPT_FREQ_SOLV_PhMe_wB97XD_N_benzyl_syn_conf26.out	Yes	-938.467	0	298.15	1	0.348197	0.27766	0.281988	-938.119	-938.182	2.5	0.2	
OPT_FREQ_SOLV_PhMe_wB97XD_N_benzyl_syn_conf27.out	Yes	-938.47	0	298.15	1	0.348083	0.277358	0.281787	-938.122	-938.185	0.8	4.3	
OPT_FREQ_SOLV_PhMe_wB97XD_N_benzyl_syn_conf28.out	Yes	-938.468	0	298.15	1	0.348258	0.278016	0.282101	-938.12	-938.183	2.1	0.4	
OPT_FREQ_SOLV_PhMe_wB97XD_N_benzyl_syn_conf30.out	Yes	-938.468	0	298.15	1	0.348052	0.277617	0.281857	-938.12	-938.183	1.8	0.7	
OPT_FREQ_SOLV_PhMe_wB97XD_N_benzyl_syn_conf31.out	Yes	-938.466	0	298.15	1	0.348302	0.278325	0.282303	-938.118	-938.181	3.2	0.1	
OPT_FREQ_SOLV_PhMe_wB97XD_N_benzyl_syn_conf32.out	Yes	-938.467	0	298.15	1	0.348171	0.277593	0.28187	-938.119	-938.182	2.4	0.3	
OPT_FREQ_SOLV_PhMe_wB97XD_N_benzyl_syn_conf4.out	Yes	-938.469	0	298.15	1	0.348158	0.277527	0.281983	-938.121	-938.184	1.1	2.3	
OPT_FREQ_SOLV_PhMe_wB97XD_N_benzyl_syn_conf7.out	Yes	-938.468	0	298.15	1	0.348568	0.277858	0.282278	-938.12	-938.183	1.9	0.6	
OPT_FREQ_SOLV_PhMe_wB97XD_N_benzyl_syn_conf8.out	Yes	-938.469	0	298.15	1	0.348284	0.277513	0.282085	-938.12	-938.183	1.6	1	**Total Syn**
OPT_FREQ_SOLV_PhMe_wB97XD_N_benzyl_syn_conf9.out	Yes	-938.468	0	298.15	1	0.348526	0.278912	0.282788	-938.119	-938.182	2.4	0.3	**35**

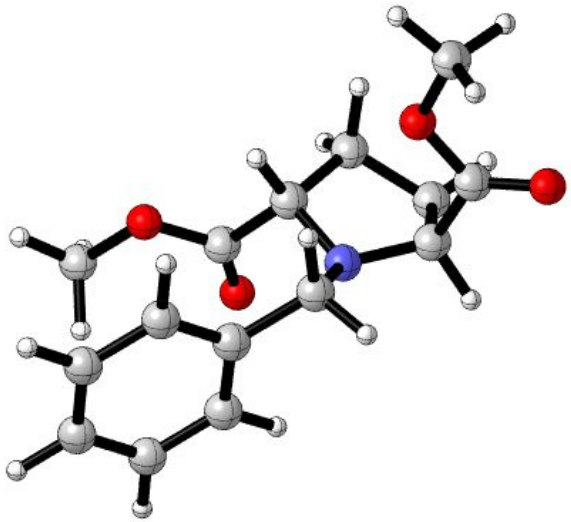
Lowest energy *anti*-conformer:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	7	0	0.366047	-0.784269	0.587332
2	6	0	0.679490	-1.547172	1.779243
3	6	0	1.851153	-0.756809	2.378532
4	6	0	1.463534	0.702023	2.101382
5	6	0	0.637034	0.637133	0.795606
6	6	0	-0.853237	-1.120075	-0.126887
7	6	0	-0.828281	-0.647860	-1.565640
8	6	0	-0.775536	0.221944	-4.230414
9	6	0	0.237485	-0.990635	-2.403221
10	6	0	-1.863369	0.134620	-2.077064
11	6	0	-1.841205	0.567245	-3.403158
12	6	0	0.265709	-0.558777	-3.725688
13	6	0	1.430705	1.203002	-0.379760
14	8	0	0.792595	2.222303	-0.962938
15	6	0	1.427942	2.787975	-2.114572
16	8	0	2.520734	0.805467	-0.731255
17	6	0	-0.446695	-1.695682	2.805425
18	8	0	-1.223777	-0.608699	2.885014
19	6	0	-2.285712	-0.654796	3.845856
20	8	0	-0.605269	-2.681596	3.494416
21	1	0	0.969273	-2.568617	1.514779
22	1	0	2.758586	-1.023615	1.831855
23	1	0	2.009839	-0.964794	3.439162
24	1	0	2.338760	1.348251	2.011287
25	1	0	0.833301	1.092580	2.902890
26	1	0	-0.292638	1.213168	0.890346
27	1	0	-0.949241	-2.212426	-0.109024
28	1	0	-1.745013	-0.706884	0.373512
29	1	0	-0.752568	0.560995	-5.261566
30	1	0	1.057422	-1.578639	-2.001732
31	1	0	-2.690368	0.417871	-1.430885
32	1	0	-2.652795	1.178667	-3.785636
33	1	0	1.102447	-0.828076	-4.363087
34	1	0	2.410340	3.186440	-1.852875
35	1	0	1.532942	2.025941	-2.889907
36	1	0	-1.881606	-0.785986	4.851543
37	1	0	-2.966978	-1.476661	3.617190
38	1	0	0.767258	3.584859	-2.451061
39	1	0	-2.798208	0.301583	3.760901

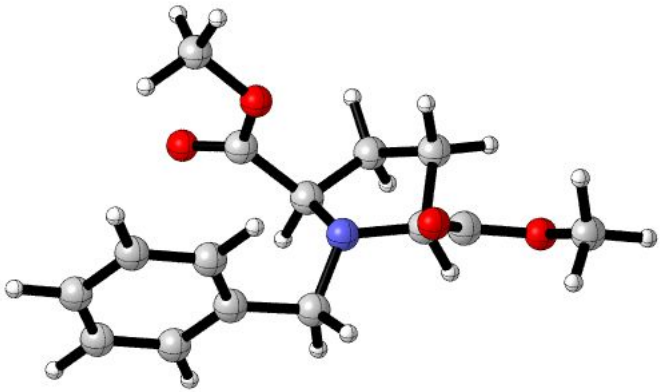
Lowest energy *syn*-conformer:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	7	0	-0.417145	0.716368	0.032024
2	6	0	-0.853568	0.356287	1.375876
3	6	0	-0.501290	1.578240	2.260493
4	6	0	0.450110	2.405038	1.393113
5	6	0	-0.080439	2.120906	-0.018961
6	6	0	-1.240393	0.201606	-1.048296
7	6	0	-1.191999	-1.309738	-1.100081
8	6	0	-1.053372	-4.107305	-1.142313
9	6	0	-2.349386	-2.077156	-0.978750
10	6	0	0.040508	-1.955876	-1.245443
11	6	0	0.110150	-3.344819	-1.265611
12	6	0	-2.283419	-3.471033	-1.001797
13	6	0	0.960555	2.428579	-1.082877
14	8	0	1.075842	3.753580	-1.244336
15	6	0	2.057760	4.193358	-2.190093
16	8	0	1.617428	1.620041	-1.698997
17	6	0	-0.196962	-0.918316	1.894046
18	8	0	1.117897	-0.948154	1.676769
19	6	0	1.798624	-2.131400	2.103068
20	8	0	-0.799653	-1.786454	2.492367
21	1	0	-1.933001	0.155675	1.413501
22	1	0	-0.062812	1.296343	3.220285
23	1	0	-1.414065	2.144114	2.465344
24	1	0	1.474767	2.031352	1.480392
25	1	0	0.438909	3.468787	1.635223
26	1	0	-0.954108	2.767565	-0.220523
27	1	0	-0.848457	0.606620	-1.986717
28	1	0	-2.289593	0.537262	-0.954927
29	1	0	-0.998268	-5.191493	-1.153392
30	1	0	-3.310004	-1.584004	-0.853082
31	1	0	0.941601	-1.354771	-1.322689
32	1	0	1.072380	-3.835975	-1.376458
33	1	0	-3.191785	-4.056637	-0.899518
34	1	0	3.051608	3.853932	-1.891423
35	1	0	1.825472	3.807949	-3.184872
36	1	0	1.399385	-3.000400	1.574387
37	1	0	1.685783	-2.274619	3.179802
38	1	0	2.006347	5.280494	-2.180074
39	1	0	2.844592	-1.975948	1.844438

Lowest energy *anti*-conformer (ωB97X-D/6-31+G(d,p) in PhMe):



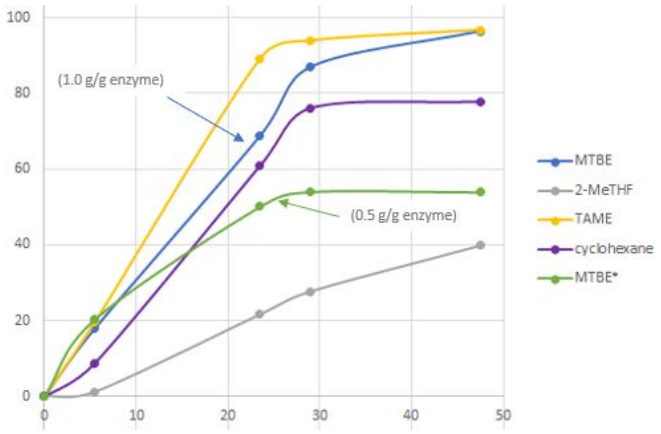
Lowest energy *syn*-conformer (ωB97X-D/6-31+G(d,p) in PhMe):



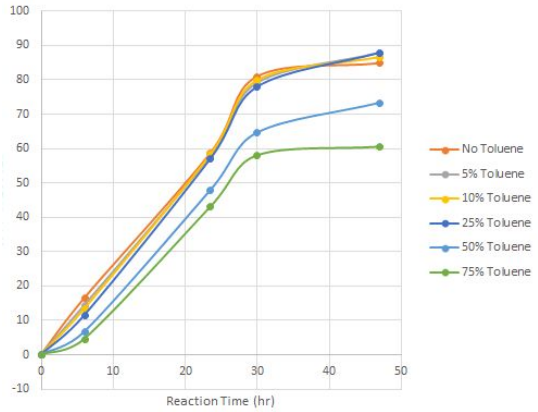
Spiking Studies for Enzymatic Amidation

Spiking studies were run before the benefit of added water was known. Reactions were run in vials using syn-diester **9 (50mg), CalB ImmoPlus (50mg), solvent (1mL MTBE, or 1mL total volume if other solvents spiked), HMDS (3 x 0.5 equivs, added at approx. 0, 6, & 23 hours) 40-50°C, vials placed in a shaker @ 240rpm*

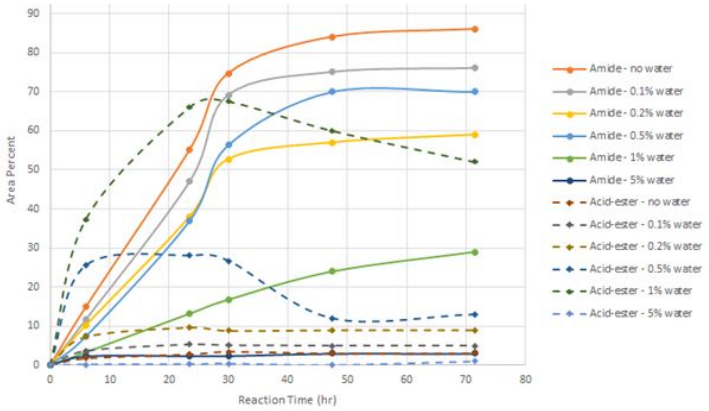
Solvent screen:



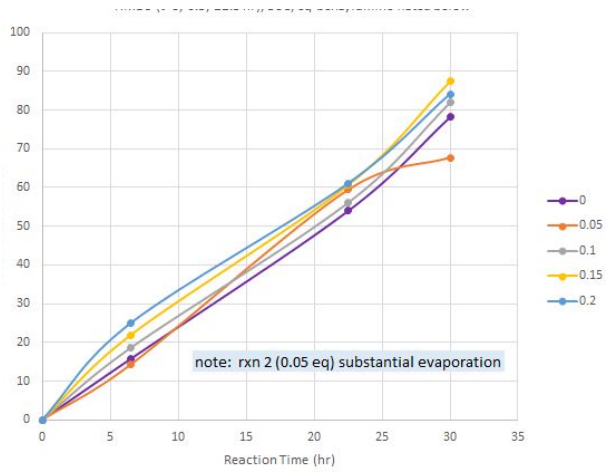
Toluene spiking study:



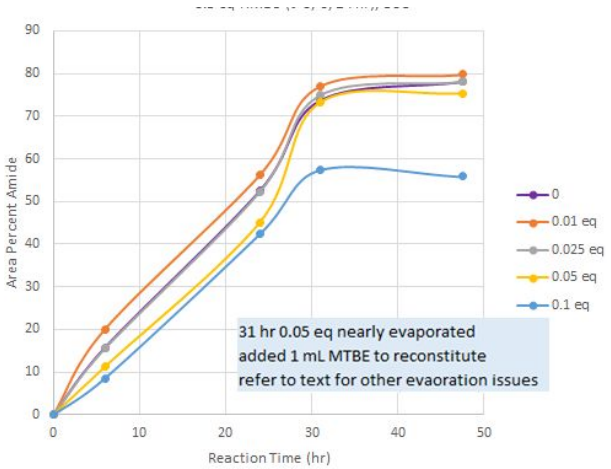
Water spiking study:



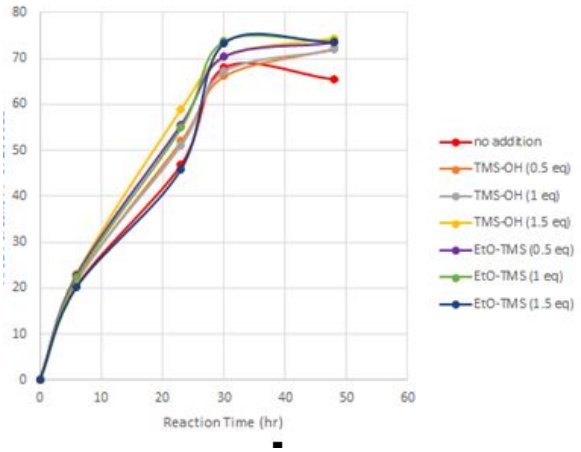
Benzylamine spiking study:



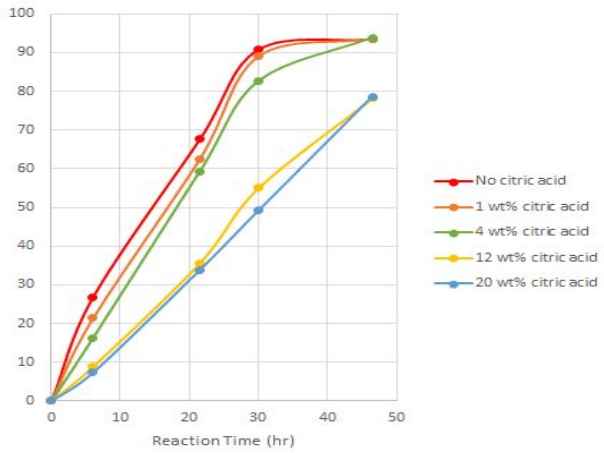
meso-dibromide spiking study:



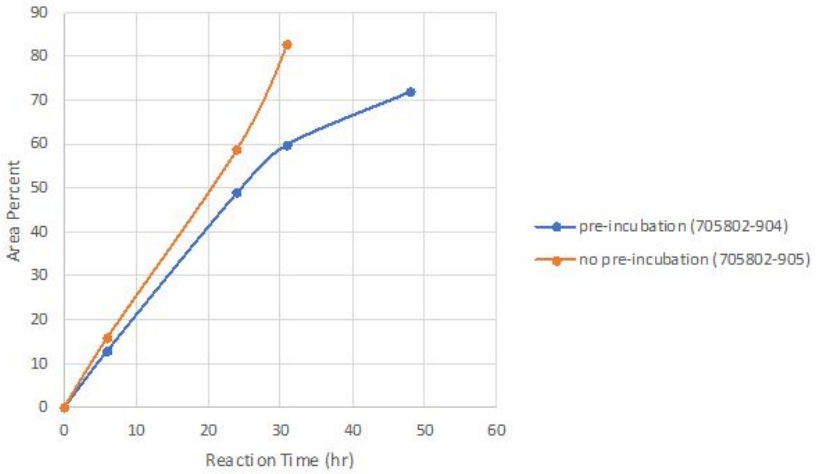
EtOTMS and TMSOH spiking study:



Citric acid spiking study:



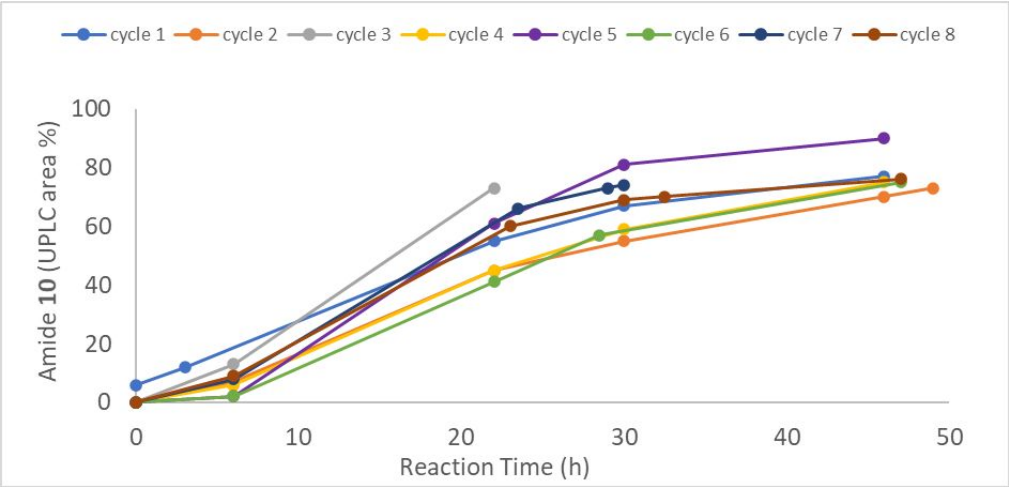
Enzyme incubated with 0.5 equivs of HMDS in MTBE before reaction:



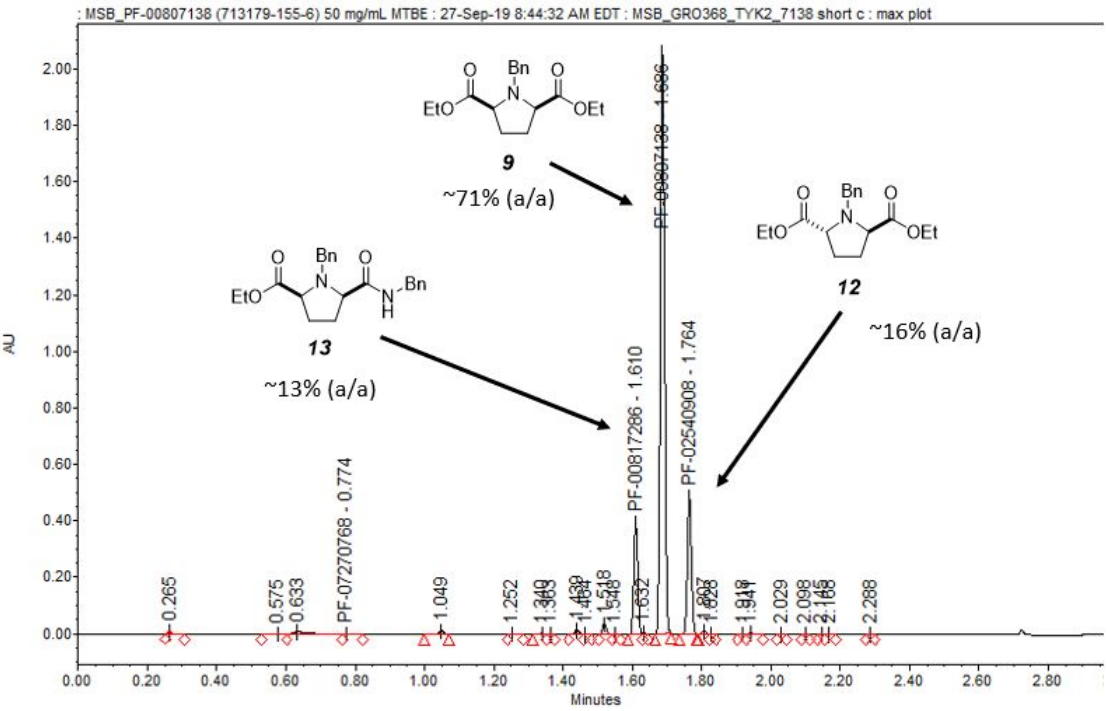
Details of Enzyme Washing for Recycling Studies

All reactions were run using 2.0g of ingoing ester **9** and 2.0g of enzyme. Reactions were run using 40mL MTBE, 1.5 equivs of HMDS added gradually over 6 hrs, and run at 40 °C. Reactions were sampled periodically to determine progress. The ingoing starting material contained ~71% (UPLC area %) of ester **9** and therefore were deemed to be complete once the desired amide product **10** was present at ~70-75% by UPLC area %. In runs where the amount of product was higher than this (Run #5), it was found to correspond to a decrease in the amount of *trans*-diester **12** suggesting that the reaction had been run for longer than necessary resulting in conversion of the undesired diastereomer.

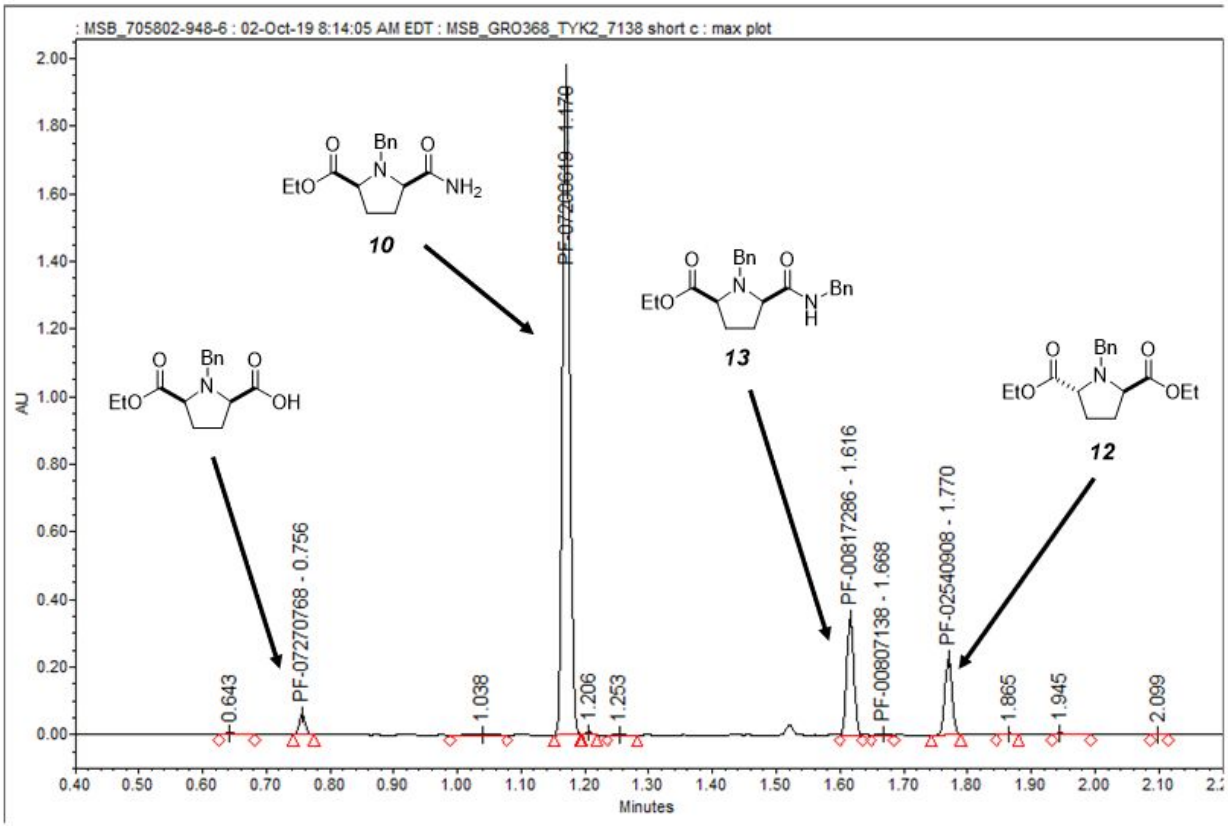
Cycle	Post Reaction Enzyme Treatment	Approx. Cycle Completion Time (hr.)
1	a) MTBE wash (5 vol, room temp, short swirl); b) 5.5% ethanol in MTBE (5 vol, room temp, short swirl); c) MTBE soak (5 vol, room temp, short swirl)	**46**
2	a) MTBE wash (5 vol, room temp, 30 min); b) 5.5% ethanol in MTBE soak (5 vol, refrigerate, 4 hr); c) MTBE soak (2.5 vol, refrigerate 10 days)	**49**
3	a) MTBE wash (5 vol, room temp, 30 min); b) 5.5% ethanol in MTBE soak (5 vol,refrigerate, 4.5 hr); c) MTBE soak (2.5 vol, refrigerate overnight)	**22**
4	a) MTBE wash (5 vol, room temp, 30 min); b) 5.5% ethanol in MTBE soak (5 vol, refrigerate, 4 hr); c) MTBE soak (0.5 vol, refrigerate 3 days)	**46**
5	a) MTBE wash (5 vol, room temp, 30 min); b) 5.5% ethanol in MTBE soak (5 vol, refrigerate, 4 hr); c) MTBE wash (0.5 vol) solvent removed, refrigerate overnight	**30-46**
6	a) MTBE wash (5 vol, room temp, 30 min); b) 5.5% ethanol in MTBE soak (5 vol, refrigerate, 4 hr); c) MTBE soak (0.5 vol, refrigerate 3 days)	**72**
7	a) MTBE wash (2.5 vol, room temp, 30 min); b) 5.5% ethanol in MTBE soak (5 vol, refrigerate, 1 hr); c) MTBE soak (0.5 vol, refrigerate 4 days)	**30**
8	a) MTBE wash (2.5 vol, room temp, 30 min); b) 5.5% ethanol in MTBE soak (5 vol, refrigerate, 4 hr); c) MTBE soak (0.5 vol, refrigerate 2 days)	**32**



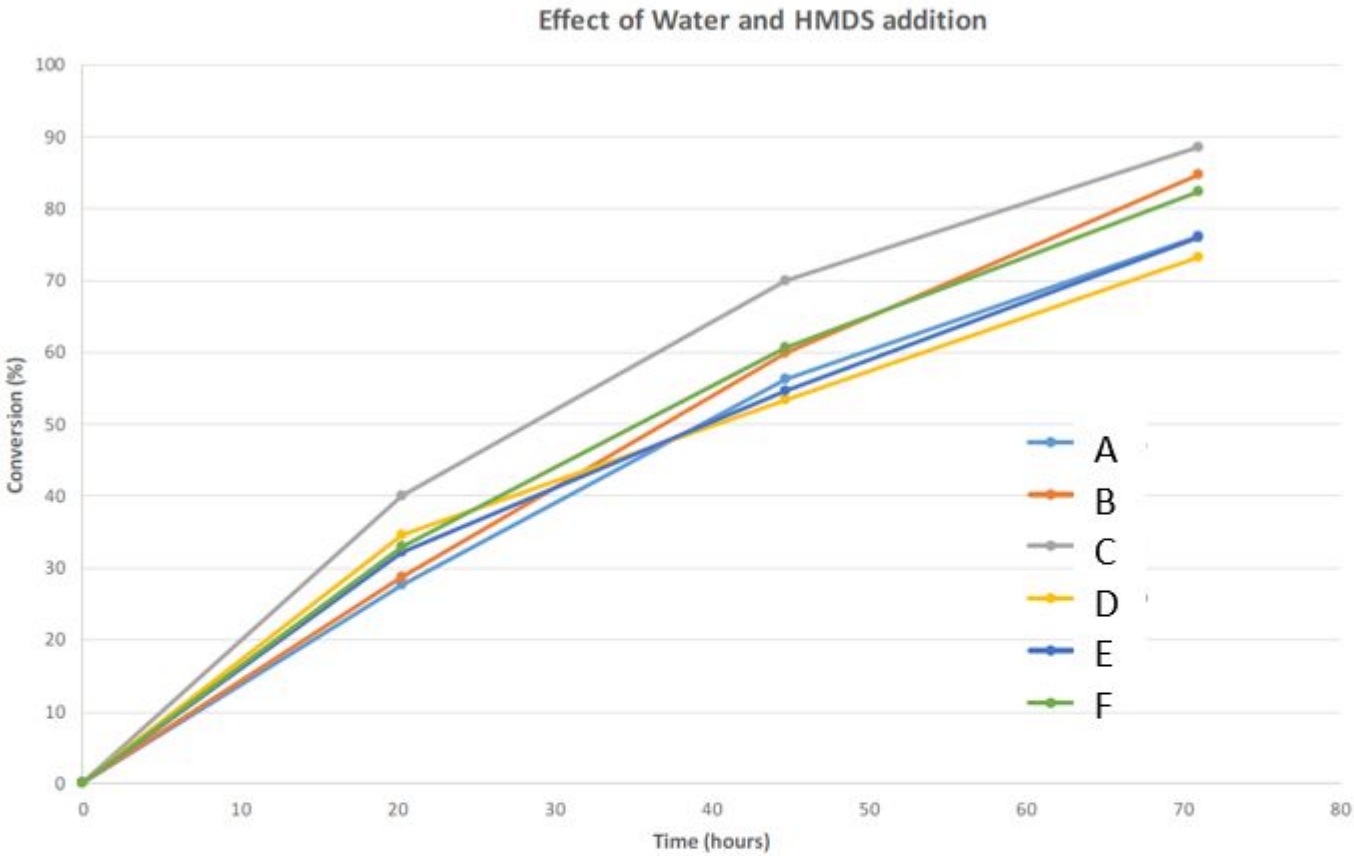
Typical starting material for enzyme recycling studies:



Typical product analysis for enzyme recycling studies:



Examining Stoichiometry of Water and HMDS on Enzymatic Transformation

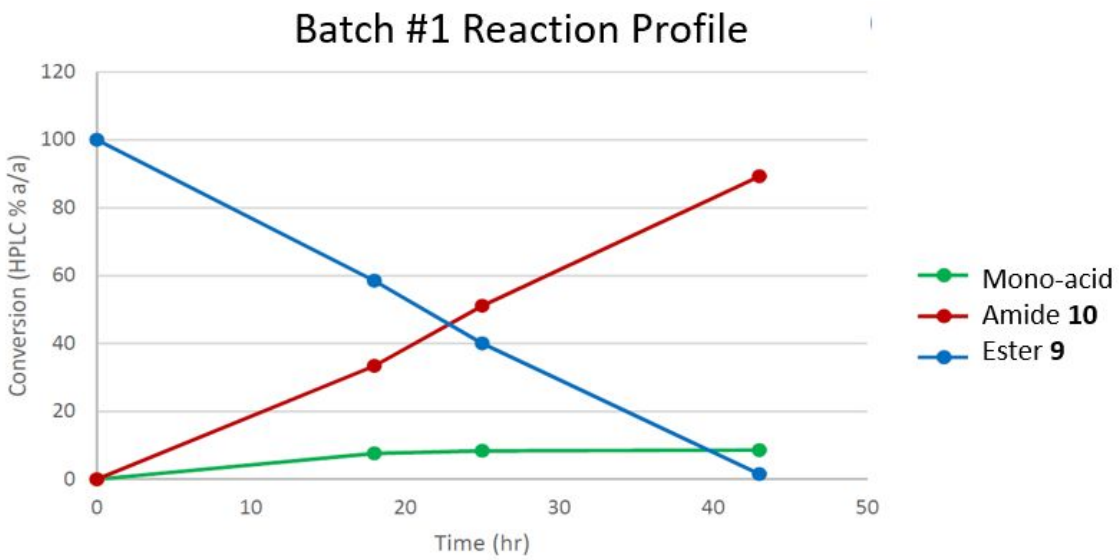


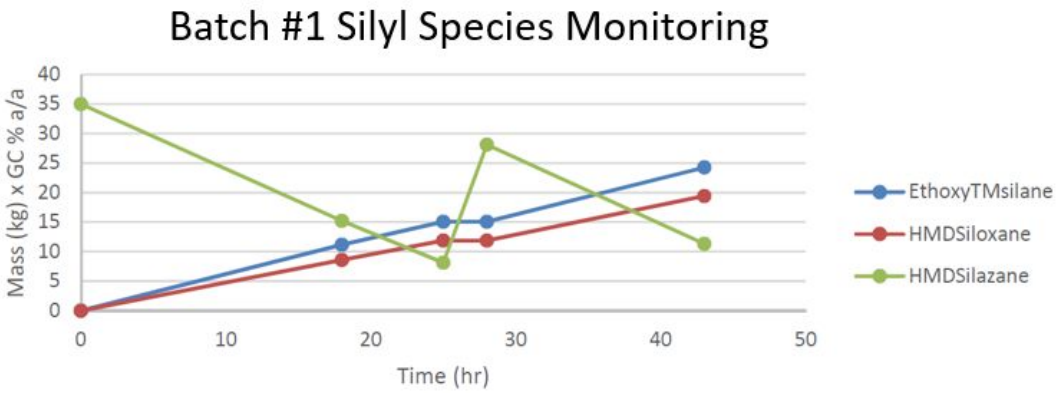
Screen examining influence of HMDS and Water addition						
		Enzyme (mg)	Substrate (mg)	MTBE (ml)	Water (eq)	HMDS (eq)
A	CalB Immoplus	75	450	5	0.68	1.25
B	CalB Immoplus	75	450	5	0.68	1.34
C	CalB Immoplus	75	450	5	0.68	1.45
D	CalB Immoplus	75	450	5	0.80	1.25
E	CalB Immoplus	75	450	5	0.80	1.34
F	CalB Immoplus	75	450	5	0.80	1.45
Temperature 35 C						
HMDS and water added in 2 portions - at start and after 21 hours						

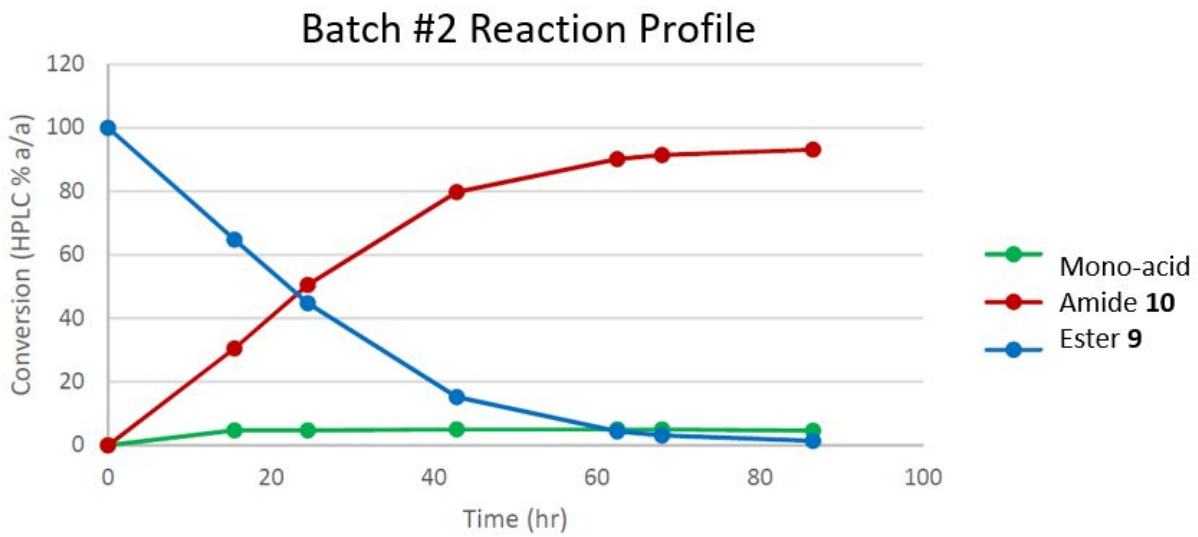
Comparison of Enzymatic Reaction Performance on Scale

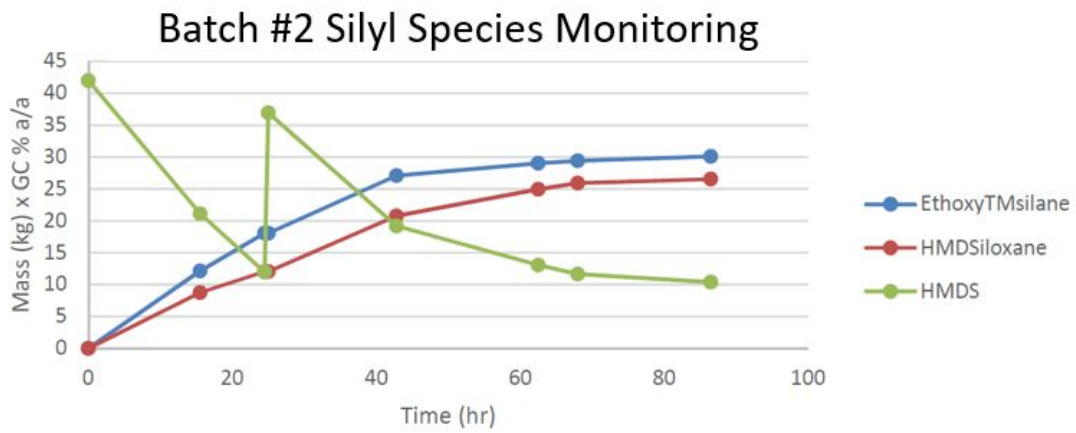
Comparison of HMDS and water charges and IPC results:

Batch 1 (0.15 g/g enzyme)			Batch 2 (0.125 g/g enzyme)		
Time (h)	Equivs added		Time (h)	Equivs added	
	HMDS	Water		HMDS	Water
0	0.85	0.41	**0**	0.8	0.26
28	0.49		**24.5**		0.17
30		0.09	**25**	0.48	
			43.5		0.08
			64		0.03
Total	1.34	0.5	**Total**	1.28	0.54
Final IPC Results					
Amide **10**	89.30%		Amide **10**	93.10%	
Ester **9**	1.50%		Ester **9**	1.40%	
Mono-acid	8.60%		Mono-acid	4.60%	









GC-FID method for measuring silylated species during enzymatic reaction:

Column:	Zebron ZB-1ms 30 m, 0.32 mm id, 1 µl film thickness (Cat 7HM-G011-22)
Injector temp:	250 °C
Inlet pressure:	14.2 psi (initial)
Split:	56:1
Flow:	3.27 ml/min, constant flow Helium gas
Detector temp:	300 °C
Oven temp:	Initial 50 °C, hold 2 minutes Ramp 1 20 °C/min to 220 °C Ramp 2 30 °C/min to 270 °C Hold 270 °C for 7.83 minutes.

Species	Retention Time
EtOTMS	2.8 min
$SiMe_3OSiMe_3$	3.5 min
$SiMe_3NHSiMe_3$	4.8 min
Amide **10**	14.0 min

Co-Crystal Data

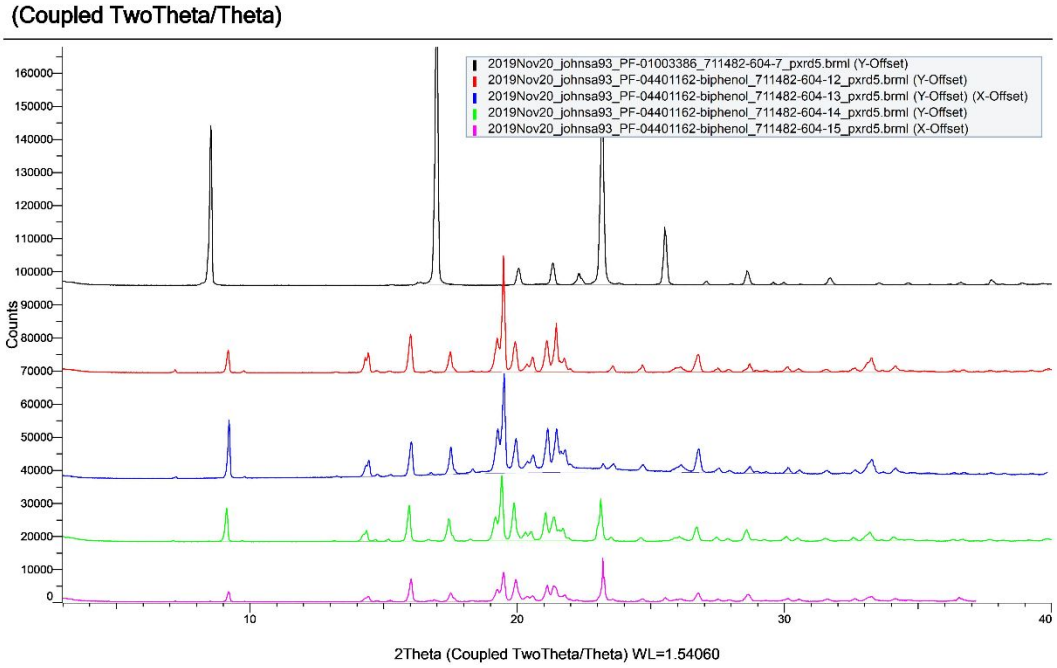
Computational Ranking of Possible Co-Formers using COSMOquick

Nr	Coformer	G_mix[kcal/mol]	f_fit	coformer_ranking	H_ex[kcal/mol]
43	phenol	-1.38931943	-2.11034	1	-3.64094
41	**4,4-biphenol**	**-1.56573943**	**-1.777305**	**2**	**-4.328305**
32	saccharin	-0.59003943	0.058445	3	-1.472155
54	p-hydroxybenzamide	-0.53676443	0.794415	4	-1.756585
15	butylacetate	-1.10633943	0.87051	5	-2.70089
3	fucose,l	-0.75850443	0.943145	6	-2.118055
33	thiabendazole	-0.42991943	1.045745	7	-0.484855
13	.alpha.-d-ribopyranose	-0.59745943	1.178155	8	-1.883045
16	imidazole	-0.18157443	1.20649	9	-0.32411
40	2-aminopyrimidine	-0.31354443	1.319305	10	-0.211295
50	2-pyrrolidinone	-0.29460943	1.40092	11	-0.12968
31	pyridoxine	-0.77650443	1.410565	12	-2.160835
42	1,4-diazabicyclo[2.2.2]octane	-0.45238443	1.41362	13	-0.11698
39	2-pyridone	-0.14024443	1.431225	14	-0.099375
49	2-piperidinone	-0.32942943	1.44986	15	-0.08074
48	phenylurea	-0.42896943	1.5183	16	-1.0327
51	2,3,5,6-tetramethylpyrazine	-0.40949943	1.532785	17	0.002185
44	2,5-piperazinedione	0.22197557	1.547875	18	0.017275
45	hexamethylbenzene	-0.36013443	1.62972	19	0.09912
5	menthol	-0.45040443	1.675695	20	-0.365105
46	benzamide	-0.28632443	1.707795	21	-0.333005
38	pyrazine	-0.29694443	1.72414	22	0.19354
55	pinacol	-0.54137443	1.73335	23	-0.81765
8	l-threonine	-0.52059943	1.73568	24	-1.83572
17	isonicotinamide	-0.14047443	1.84077	25	-0.20003
35	urea	0.33289057	1.88435	26	-0.15645
53	picolinamide	-0.27362943	1.91004	27	-0.13076
24	l-proline	-0.28379943	1.953295	28	-0.087505
52	pyrazinamide	-0.19492943	1.9662	29	-0.0746
14	guanidine	0.25138057	1.991755	30	-0.049045
7	l-serine	-0.32935443	2.015305	31	-1.556095
26	l-tyrosine	-0.60849443	2.191985	32	-1.889615
47	1,3,5-triazine-2,4,6-triamine	-0.12381443	2.205885	33	-0.345115
29	n-(2-hydroxyethyl)morpholine	-0.40935943	2.526375	34	-0.024625
4	dl-alanine	-0.11734443	2.604265	35	0.053265
30	inositol	-0.13742943	2.898455	36	-1.183145
9	l-valine	-0.26610443	2.964915	37	-0.096285
25	dl-tryptophan	-0.36276443	2.98174	38	-0.58966
23	l-phenylalanine	-0.27603943	3.461665	39	-0.109735
10	arabinose	-0.52803443	3.46727	40	-1.63473
20	l-histidine	0.15244057	3.544755	41	-0.026645
19	l-glutamine	-0.03654443	3.745715	42	-0.846085
22	dl-methionine	-0.22112443	3.967965	43	-0.113635
36	xylitol	-0.05141443	4.30046	44	-1.31174
2	d-sorbose	-0.16863443	4.754645	45	-1.367755
28	1-monobutyrin	-0.41834443	4.787695	46	-0.314305
6	panthenol	-0.58872943	5.030455	47	-1.091945
12	mannitol	-0.15045443	5.10952	48	-1.52308
21	dl-lysine	-0.23447943	5.12408	49	0.02208
34	triacetin	-0.39224943	5.159405	50	0.057405
18	l-arginine	0.03820557	5.33515	51	-0.27705
11	lactose	-0.24440943	5.70675	52	-1.43605
27	n-methyl-d-glucamine	-0.39147943	5.8646	53	-0.768

*Screening for Novel Co-crystals of Amine **11**.*

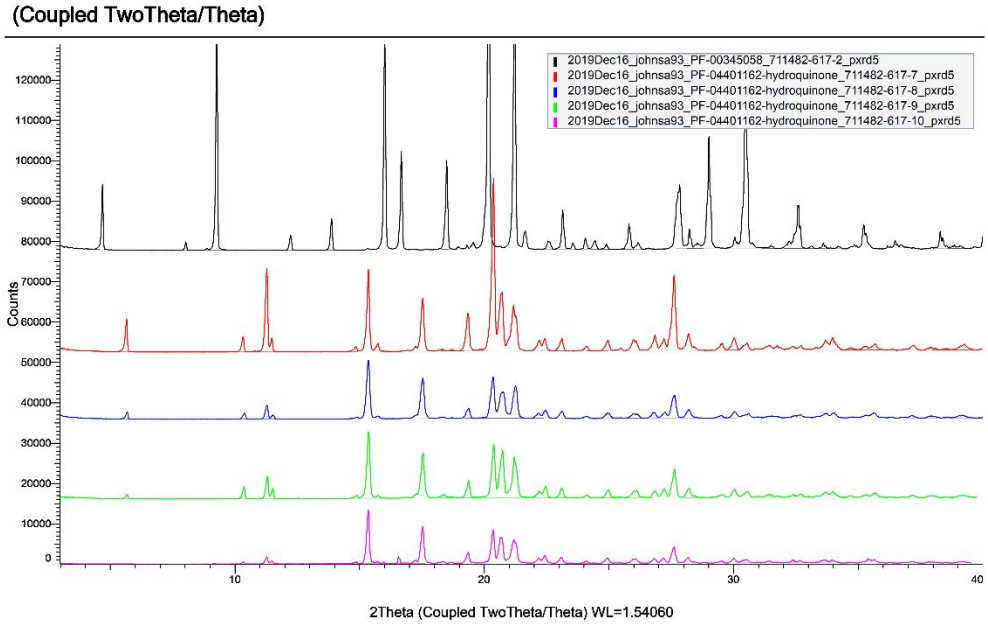
Initial screening was performed by preparing vials containing amine **11** (~10 mg), the desired coformer (1.1 equiv), and a small amount (10 µL) of solvent (either THF & MeOH). Each vial was capped and centrifuged @ 4200 rpm for at least 6 hours. Any vial that contained solids was filtered, and the solids analyzed by PXRD. Samples were compared against a PXRD of the authentic co-formers to see whether a new crystalline form was present.

Several co-formers that appeared to show new crystalline forms were further scaled-up for validation. For these larger scale runs, amine **11** (100 mg) and the desired co-formers (1.1 equiv) were placed in a vial, along with various solvents (500 µL – either THF, MeOH, MeCN, or PhMe) and a magnetic stirbar. The vials were heated (with stirring) to either 60 °C (THF, MeOH) or 80 °C (MeCN, PhMe), held for 1 hour, then cooled to 20 °C @ 0.2 °C/min. Vials that remained solutions were further cooled to 0 °C @ 0.2 °C/min. Any vials that contained slurries were filtered, and the results analyzed by PXRD. The results for several promising leads are shown below:



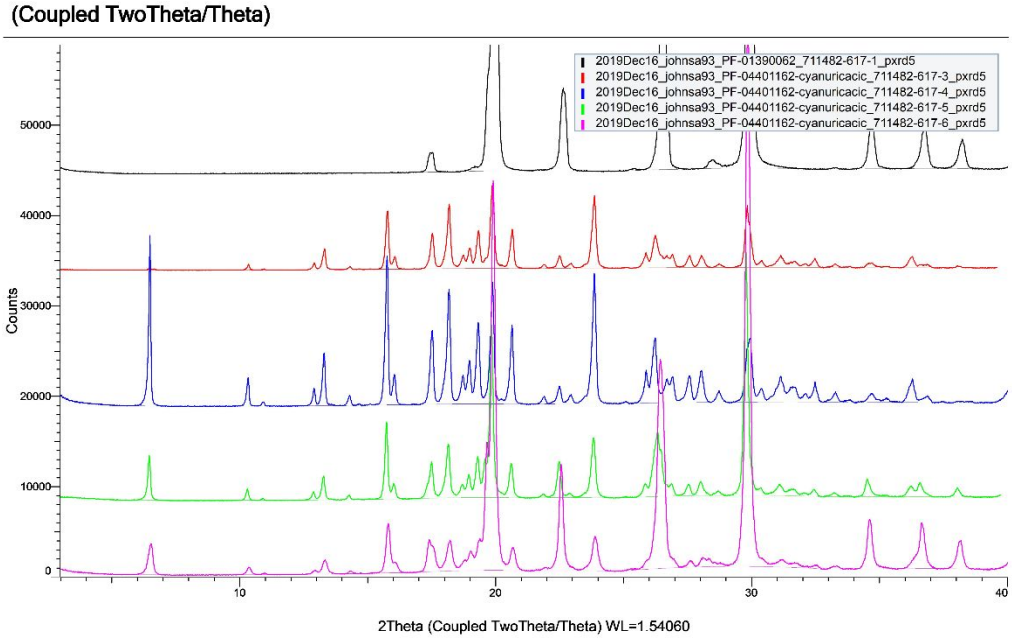
*1H-NMR analysis showed that the co-crystal consisted of a 2:1 ratio of amine: 4,4'-biphenol. Identical pattern was obtained from different solvents that do NOT match the original co-former.

Figure 1. PXRD analysis of solids recovered from co-former screen between amine 11 and 4,4'-biphenol. From top: 4,4-biphenol (black), solids isolated from THF (red), MeOH (blue), MeCN (green), and PhMe (magenta)



*1H-NMR analysis showed that the co-crystal consisted of a 1:1 ratio of amine:hydroquinone. Identical pattern was obtained from different solvents that do NOT match the original co-former.

Figure 2. PXRD analysis of solids recovered from co-former screen between amine 11 and hydroquinone. From top: hydroquinone (black), solids isolated from THF (red), MeOH (blue), MeCN (green), and PhMe (magenta)



*1H-NMR analysis showed that the co-crystal consisted of a 1:1 ratio of amine:cyanuric acid. Identical pattern was obtained from different solvents that do NOT match the original co-former.

Figure 3. PXRD analysis of solids recovered from co-former screen between amine 11 and cyanuric acid. From top: cyanuric acid (black), solids isolated from THF (red), MeOH (blue), MeCN (green), and PhMe (magenta)

*Single Crystal Data for Co-Crystal **21***

Data collection was performed on a Bruker D8 Quest diffractometer at room temperature. Data collection consisted of omega and phi scans. The structure was solved by intrinsic phasing using SHELX software suite in the Triclinic class space group P-1. The structure was subsequently refined by the full-matrix least squares method. All non-hydrogen atoms were found and refined using anisotropic displacement parameters. The hydrogen atoms located on nitrogen and oxygen were found from the Fourier difference map and refined with distances restrained. The remaining hydrogen atoms were placed in calculated positions and were allowed to ride on their carrier atoms. The final refinement included isotropic displacement parameters for all hydrogen atoms.

Crystal structure confirmed 2:1 ratio of Amine / 4,4'-biphenol co-crystal properties. Half of 4,4'-biphenol molecule was sitting on center of symmetry and generated the second half of the molecule into the adjacent Asymmetric unit. Crystal structure has not generated any Alert Levels "A" / "B" by CIF_Check module for quality assessment.

The final R-index was 5.4%. A final difference Fourier revealed no missing or misplaced electron density.

Crystallization	Tetrahydrofuran	
Empirical formula	C19 H23 N2 O	
Formula weight	295.39	
Temperature	296(2) K	
Wavelength	1.54178 Å	
Crystal system	Triclinic	
Space group	P-1	
Unit cell dimensions	a = 6.2556(3) Å	α= 72.476(3)°.
	b = 10.5692(5) Å	β= 88.682(2)°.
	c = 13.1146(5) Å	γ = 75.472(3)°.
Volume	799.12(6) $Å^3$	
Z	2	
Density (calculated)	1.228 Mg/m^3	
Absorption coefficient	0.594 mm^{-1}	
F(000)	318	
Crystal size	0.440 x 0.140 x 0.060 mm^3	
Theta range for data collection	3.540 to 80.822°.	
Index ranges	-7<=h<=8, -13<=k<=13, -16<=l<=16	
Reflections collected	14059	
Independent reflections	3351 [R(int) = 0.0387]	
Completeness to theta = 67.679°	97.9 %	
Absorption correction	Empirical	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3351 / 2 / 206	
Goodness-of-fit on F^2	1.078	
Final R indices [I>2sigma(I)]	R1 = 0.0540, wR2 = 0.1415	
R indices (all data)	R1 = 0.0563, wR2 = 0.1449	
Extinction coefficient	0.115(10)	
Largest diff. peak and hole	0.252 and -0.204 e.$Å^{-3}$	

Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for **21**. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
N(1)	5819(2)	4798(1)	8367(1)	48(1)
N(2)	5795(2)	6006(1)	6083(1)	43(1)
O(1)	2783(2)	4053(1)	9742(1)	58(1)
C(1)	103(2)	2804(1)	10270(1)	46(1)
C(2)	-693(2)	1672(1)	10349(1)	44(1)
C(3)	408(2)	622(1)	9940(1)	41(1)
C(4)	2316(2)	806(1)	9417(1)	56(1)
C(5)	3139(2)	1935(1)	9334(1)	56(1)
C(6)	2045(2)	2941(1)	9770(1)	44(1)
C(7)	7498(2)	4742(1)	6626(1)	49(1)
C(8)	6484(2)	3990(1)	7620(1)	53(1)
C(9)	4744(2)	6245(1)	7806(1)	47(1)
C(10)	5896(2)	6837(1)	6799(1)	44(1)
C(11)	8376(2)	6633(2)	7046(1)	56(1)
C(12)	9465(2)	5224(2)	6919(1)	58(1)
C(13)	6284(2)	6634(2)	4977(1)	54(1)
C(14)	4417(2)	7813(1)	4354(1)	49(1)
C(15)	4810(3)	8680(2)	3375(1)	62(1)
C(16)	3100(3)	9713(2)	2754(1)	76(1)
C(17)	1000(3)	9916(2)	3107(1)	74(1)
C(18)	579(3)	9075(2)	4081(1)	65(1)
C(19)	2286(2)	8026(2)	4697(1)	56(1)

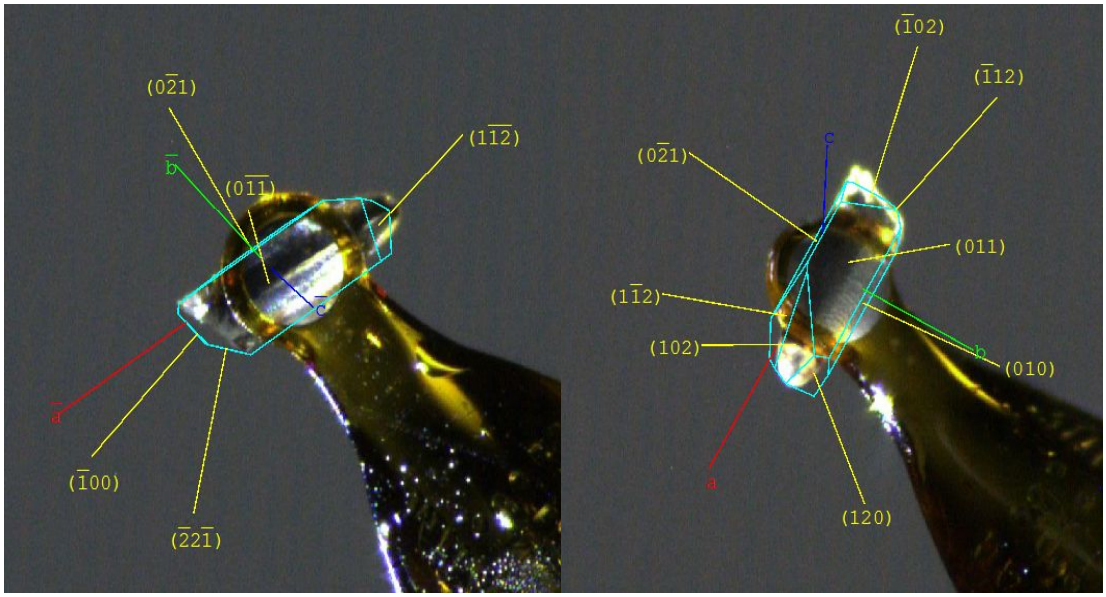


Figure 4. Single Crystal Face Indexation – Miller Indices

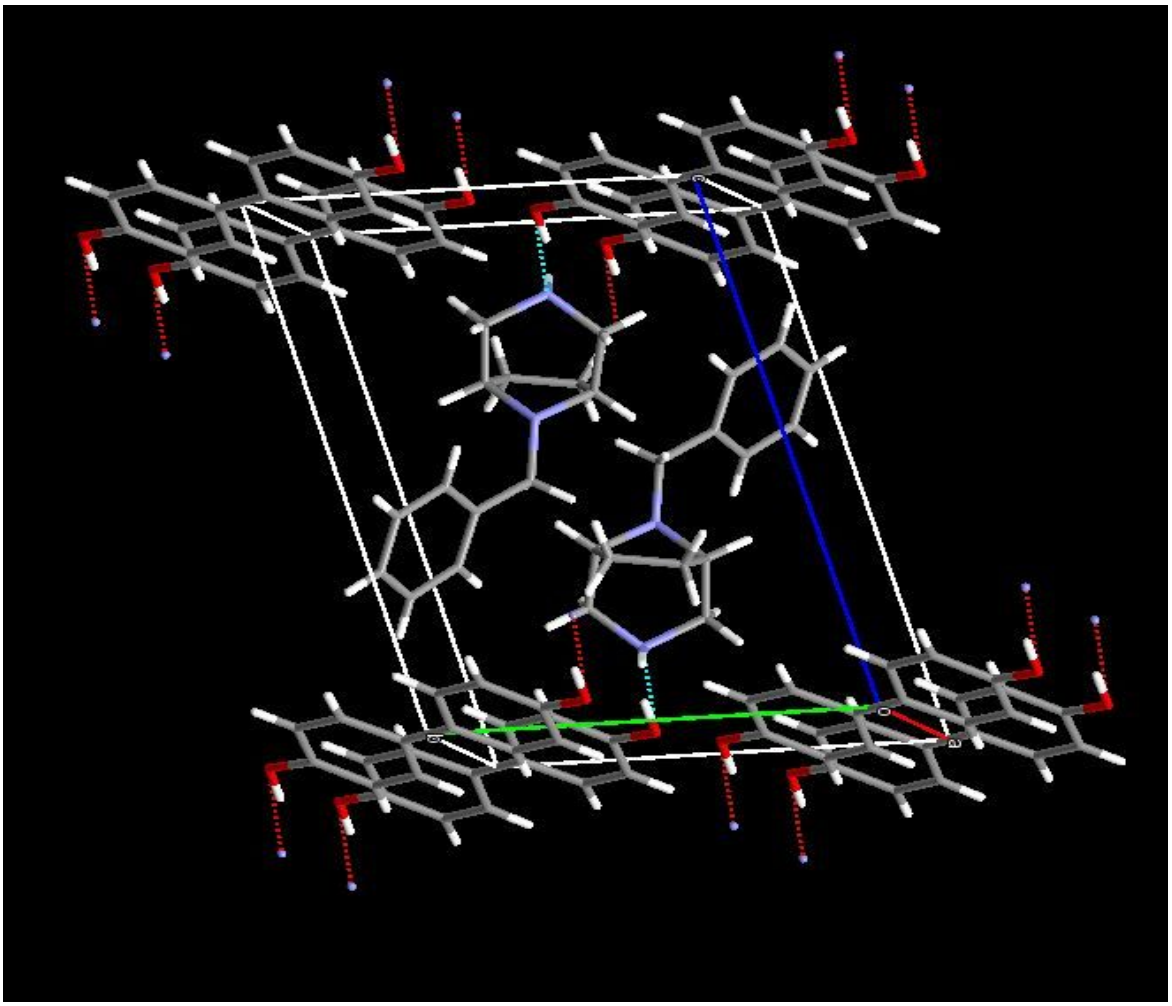


Figure 5. Unit Cell Packing diagram showing 2:1 ratio of Amine:4,4'-biphenol co-crystal entity by Mercury program

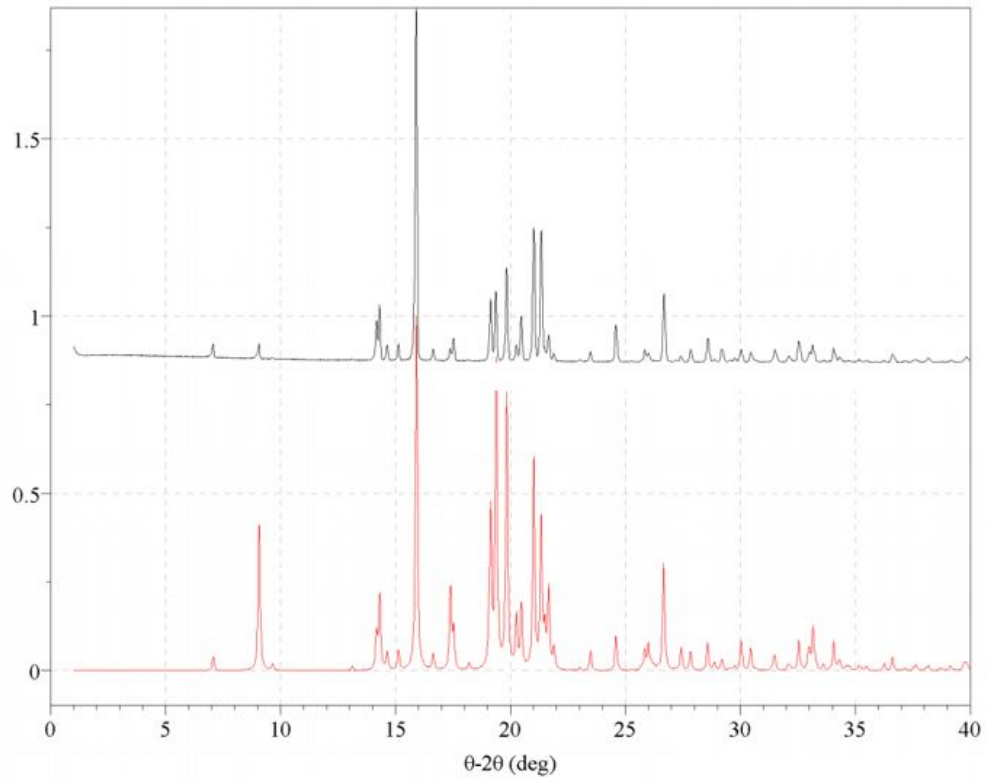
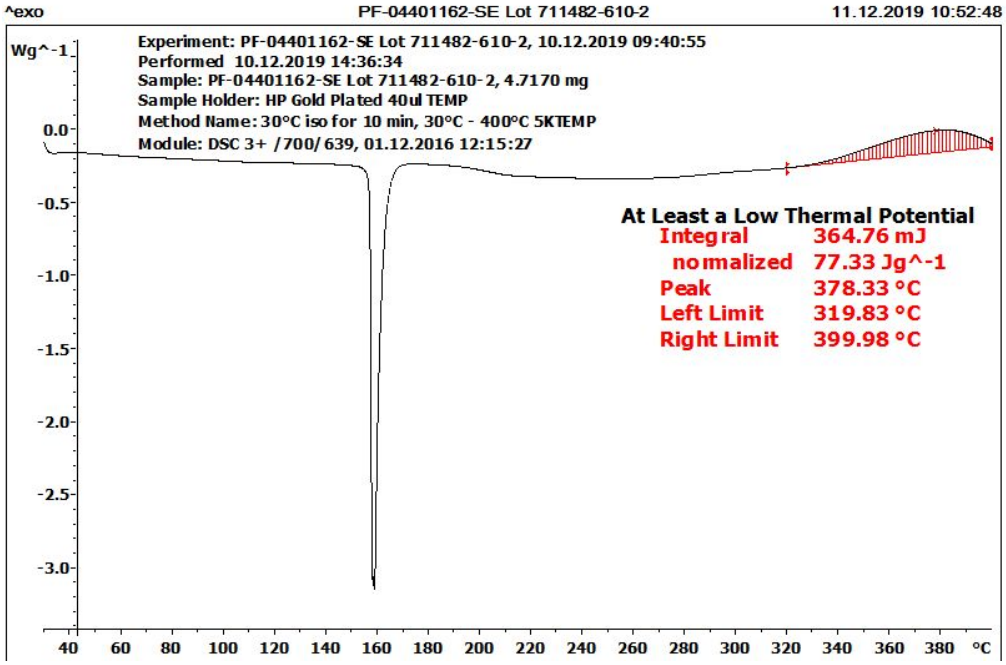


Figure 6. Experimental PXRD (top, black) vs. calculated pattern (bottom, red) based on single crystal data

*DSC data for Co-Crystal **21***



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