Supporting Information

Sustainable synthesis of a potent and selective 5-HT$_7$ receptor antagonist using a mechanochemical approach

Vittorio Canale,[a,*] Valeria Frisi,[a] Xavier Bantreil,[b,*] Frédéric Lamaty,[b] Paweł Zajdel[a]

[a]Jagiellonian University Medical College, Faculty of Pharmacy, Department of Medicinal Chemistry, 9 Medyczna Str., 30-688 Kraków, Poland

[b]IBMM, Univ Montpellier, CNRS, ENSCM, Montpellier, France

*Corresponding authors:
vittorio.canale@uj.edu.pl
xavier.bantreil@umontpellier.fr

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I. Calculation of green metrics

Different parameters can be used to evaluate the environmental impact of the different synthetic pathways. This part details the calculation of the E Factor (EF) [1] and Ecoscale score [2].

A. Synthetic methods

Following methods were used for the calculation of the E Factor, and the Ecoscale score. Procedures in solution are described according to our previously reported publication [3].

Alkylation of 2-phenylphenol in solution

2-Phenylphenol (1 g, 5.87 mmol, 1 eq) and previously grinded K_2CO_3 (2.03 g 14.68 mmol, 2.5 eq), KOH (0.16 g, 2.94 mmol, 0.5 eq) were suspended in 20 ml of acetone, Next, epichlorohydrin (0.57 mL, 11.74 mmol, 2 eq) was slowly dropped to the mixture which was stirred at 60°C for 24 hours. Then, the inorganic residues were filtered off and the mixture concentrated under vacuum followed by re-solubilization in CH_2Cl_2 (20 ml) and washed with 2N NaOH aqueous solution (3 x 7 mL) and saturated NaCl solution (1 x 7 mL). The organic phase was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The obtained crude product was purified on silica gel with ethyl acetate/hexane (1/9 *v*/*v*) as eluting system yielding intermediate **1a** as white powder (820 mg, yield 62%).

Alkylation of 2-phenylphenol in ball-mill

2-Phenylphenol (80.7 mg, 0.474 mmol, 1 eq) and previously grinded K_2CO_3 (196.6 mg, 1.42 mmol, 3 eq) were introduced in a 35 mL PTFE jar with one stainless steel ball ($\varnothing_{ball}$ = 1.5 cm) followed by addition of epichlorohydrin (44.6 µL, 0.569 mmol, 1.2 eq) and 2-propanol (50 µL, η = 0.15 µL·mg^{-1}). The reaction was carried out for 140 minutes at rt. The mixture was then solubilized in CH_2Cl_2 (15 mL) and the organic phase was washed with 2N NaOH aqueous solution (3 x 5 mL), saturated NaCl solution (1 x 5 mL), dried over Na_2SO_4 and finally filtered and concentrated under reduced pressure yielding intermediate **1a** as white powder (91 mg, yield 85%).

Alkylation of 4-Boc-N-aminopiperidine in solution

4-Boc-*N*-aminopiperidine (0.85 g, 4.24 mmol, 1.2 eq) was dissolved in EtOH (15 mL), followed by addition of intermediate **1a** (0.8 g, 3.54 mmol, 1 eq) and the mixture was stirred under reflux for 4 hours. Inorganic residues were filtered off and organic mixture was concentrated under reduced pressure. The obtained crude product was purified using silica gel column chromatography with CH_2Cl_2/MeOH (9/1 *v*/*v*) as an eluting system yielding intermediate **3a** as white powder (1.17 g, yield 78%).

Alkylation of 4-Boc-N-aminopiperidine in ball-mill

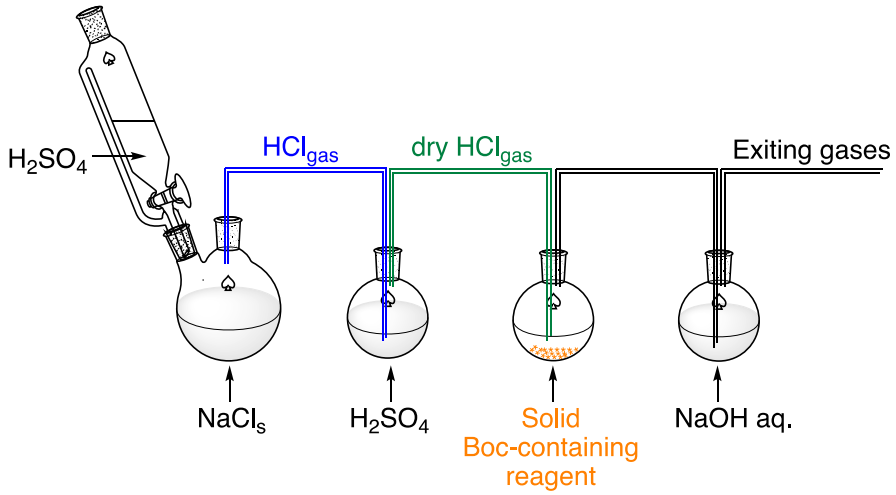
Intermediate **1a** (175.1 mg, 0.774 mmol, 1 eq) and 4-Boc-amino-piperidine (154.9 mg, 0.774 mmol, 1 eq) were introduced in a 35 mL PTFE jar with one stainless steel ball ($\varnothing_{ball}$ = 1.5 cm) followed by addition of EtOH (33 µL, η = 0.1 µL mg^{-1}) as liquid assistant. The reaction was carried out for 70 minutes at rt. Then, the product was solubilized in ethyl acetate (20 mL) and the organic phase was washed with $KHSO_4$ aqueous solution at pH = 3.5 (3 x 7 mL), saturated NaCl solution (1 x 7 mL), dried over Na_2SO_4 and finally filtered and concentrated under reduced pressure yielding intermediate **3a** as white powder (297 mg, yield 90%).

General procedure for deprotection of Boc function in solution

To a solution of the intermediate **3a** (1 g, 2.35 mmol) in EtOH (35 mL), 12 mL of HCl 2N in EtOH were added. The mixture was left stirring for 6 hours at rt. The obtained white powder **4** was filtrated under vacuum and left drying overnight (832 mg, yield 98%).

General procedure for deprotection of Boc function in solid state

Intermediate **3a** (0.5 g, 1.16 mmol) was submitted to HCl_{gas} for 2 h at r.t., according to Scheme S1, to afford the primary amine **4** as a white hydrochloride salt (0.4 g, yield 98%).



Scheme S1. Experimental set-up for HCl_{gas} production and use in solid-state reaction

Sulfonylation of primary amine in solution

A mixture of the obtained primary amine **4** (300 mg, 0.92 mmol, 1 eq) in CH_2Cl_2 (4 mL), and TEA (0.39 mL, 2.75 mmol, 3 eq) was cooled down (ice bath), and 3-chlorobenzenesulfonyl chloride (154 µl, 1.1 mmol, 1.2 eq) was added in one portion. The reaction mixture was stirred for 2 hours under cooling. Then, the solvent was evaporated, and the crude mixture was purified using silica gel column chromatography with CH_2Cl_2/MeOH (9/0.5 *v*/*v*) as an eluting system yielding final compound **5a** as white powder (330 mg, yield 72%).

Sulfonylation of primary amine in ball-mill

Intermediate **4** (168.2 mg, 0.463 mmol, 1 eq), 3-chlorobenzenesulfonyl chloride (65.24 µL, 0.463 mmol, 1 eq), and previously grinded K_2CO_3 (64.0 mg, 0.463, 1 eq) were introduced in a 35 mL PTFE jar with one stainless steel ball ($\varnothing_{ball}$ = 1.5 cm). The reaction was carried out for 1 min at rt. Then, the crude mixture was solubilized in ethyl acetate (20 mL) and the organic phase was washed with $KHSO_4$ aqueous solution at pH = 3.5 (3 x 7 mL), saturated NaCl solution (1 x 7 mL), dried over Na_2SO_4 and finally filtered and concentrated under vacuum yielding final compound **5a** (**PZ-1361**) as white powder (200.1 mg, yield 86%).

B. Calculation of E Factor

The E Factor is the ratio of the weight of generated waste to the total weight of the end product. It is a useful tool for rapid evaluation of processes based on generated waste.

$$\mathrm{EF} = \frac{\sum \mathrm{m(Raw\ materials)} + \sum \mathrm{m(solvent)} + \sum \mathrm{m(water)} - \mathrm{m(products)}}{\mathrm{m(products)}}$$

E factor values are reported in the following tables for the synthesis of **PZ-1361** (final compound **5a**) in the ball-mill and magnetic stirrer conditions. A summary is given in Table S1.

Table S1. Summary of E factor for the synthesis of **PZ-1361**

	E factor			
	Step 1 Alkylation of 2-Phenylphenol	**Step 2** Alkylation of 4-Boc-N-aminopiperidine	**Step 3** Boc deprotection	**Step 4** Sulfonylation
Solution	509	554	46	804
Solid-state	548	**181**	**2**	**230**

The E factor values were also calculated for the whole synthesis of PZ-1361, starting from 1 g of 2-Phenylphenol. All the quantities were then calculated according to the equivalents and yield obtained in each step. The following values were calculated:

	E factor
Solution	1932
Solid-state	**715**

Alkylation of 2-phenylphenol in solution

Reagents	CAS	Molecular Formula	M(g/mol)	m(g)	V (mL)	n (mmoles)	d	eq
2-phenylphenol	90-43-7	C12H10O	170.21	0.999		5.87		1
acetone	67-64-1	C3H6O	58.08	15.820	20.000		0.791	
potassium carbonate	584-08-7	K2CO3	138.21	2.03		14.68		2.5
potassium hydroxide	1310-58-3	KOH	56.11	0.165		2.935		0.5
epichlorhydrin	106-89-8	C3H5ClO	92.52	1.086	0.918	11.74	1.183	2
Extraction								
dichloromethane	75-09-2	CH2Cl2	84.93	26.500	20.000		1.325	
sodium hydroxide	1310-73-2	NaOH	40	1.680		42		
sodium chloride	7647-14-5	NaCl	58.44	1.82				
water	7732-18-5	H2O	18	26.18		1454.44		
Purification								
ethyl acetate	141-78-6	C4H8O2	88.11	45.10	50	511.86	0.902	
hexane	110-54-3	C6H14	86.18	296.55	450	3441.05	0.659	

product	m (g)	M (g/mol)	yield
alkylated 2-phenylphenol **1a**	0.82	226.28	0.62

E-factor

		m (g)
Product	alkylated 2-phenylphenol **1a**	0.820
Reagents	2-phenylphenol	0.999
	acetone	15.820
	potassium carbonate	2.028
	potassium hydroxide	0.165
	epichlorhydrin	1.086
	dichloromethane	26.500
	sodium hydroxide	1.680
	sodium chloride	1.820
	water	26.180
	ethyl acetate	45.100
	hexane	296.55

E-factor =	417.11	/	0.820	=	**509**

Alkylation of 2-phenylphenol in ball-mill

Reagents	CAS	Molecular Formula	M(g/mol)	m(g)	V (mL)	n (mmoles)	d	eq
2-phenylphenol	90-43-7	C12H10O	170.21	0.081		0.474		1
potassium carbonate	584-08-7	K2CO3	138.21	0.20		1.42		3
epichlorhydrin	106-89-8	C3H5ClO	92.52	0.053	0.044	0.5688	1.183	1.2
iso propanol	67-63-0	C3H8O	60.1	0.039	0.050		0.785	
Extraction								
dichloromethane	75-09-2	CH2Cl2	84.93	19.875	15.000		1.325	
sodium hydroxide	1310-73-2	NaOH	40	1.680		42		
sodium chloride	7647-14-5	NaCl	58.44	1.82				
water	7732-18-5	H2O	18	26.18		1454.444		

product	m (g)	M (g/mol)	yield
alkylated 2-phenylphenol	0.091	226.28	0.85

E-factor

		m (g)
Product	alkylated 2-phenylphenol **1a**	0.091
Reagents	2-phenylphenol	0.081
	potassium carbonate	0.197
	epichlorhydrin	0.053
	iso propanol	0.039
	dichloromethane	19.875
	sodium hydroxide	1.680
	sodium chloride	1.820
	water	26.180

E-factor =	49.83	/	0.091	=	**548**

Alkylation of 4-Boc-N-aminopiperidine in solution

Reagents	CAS	Molecular Formula	M(g/mol)	m(g)	V (mL)	n (mmoles)	d	eq
alkylated 2-phenylphenol **1a**			226.28	0.801		3.54		1
ethanol	64-17-5	C2H6O	46.07	11.835	15.0		0.789	
4-boc-N-aminopiperidine	73874-95-0	C10H20N2O2	200.28	0.85		4.25		1.2
Purification								
dichloromethane	75-09-2	CH2Cl2	84.93	596.250	450.0	7020.5	1.325	
methanol	67-56-1	CH4O	32.04	39.550	50.0	1234.4	0.791	

product	m (g)	M (g/mol)	yield
amination product **3a**	1.17	426.56	0.77

E-factor

		m (g)
Product	amination product **3a**	1.170
Reagents	alkylated 2-phenylphenol **1a**	0.801
	ethanol	11.835
	4-boc-N-aminopiperidine	0.851
	dichloromethane	596.250
	methanol	39.550

E-factor =	648.12	/	1.170	=	**554**

Alkylation of 4-Boc-N-aminopiperidine in ball-mill

Reagents	CAS	Molecular Formula	M(g/mol)	m(g)	V (mL)	n (mmoles)	d	eq
alkylated 2-phenylphenol **1a**			226.28	0.175		0.774		1
ethanol	64-17-5	C2H6O	46.07	0.026	0.033		0.789	
4-boc-N-aminopiperidine	73874-95-0	C10H20N2O2	200.28	0.155		0.774		1
Extraction								
ethyl acetate	141-78-6	C4H8O2	88.11	18.04	20	204.74	0.902	
potassium bisulfate	7646-93-7	KHSO4	136.17	0.0002860		0.00210		
sodium chloride	7647-14-5	NaCl	58.44	1.82				
water	7732-18-5	H2O	18	26.18		1454.444		

product	m (g)	M (g/mol)	yield
amination product **3a**	0.297	426.56	0.90

E-factor

		m (g)
Product	amination product **3a**	0.297
Reagents	alkylated 2-phenylphenol **1a**	0.053
	ethanol	7.902
	4-boc-N-aminopiperidine	0.047
	ethyl acetate	18.040
	potassium bisulfate	0.000286
	sodium chloride	1.820
	water	26.180

E-factor =	53.74	/	0.297	=	**181**

Deprotection of Boc function in solution

Reagents	CAS	Molecular Formula	M(g/mol)	m(g)	V (mL)	n (mmoles)	d	eq
Intermediate **3a**			426.56	1.002		2.35		1
ethanol	64-17-5	C2H6O	46.07	37.083	47.0		0.789	
Hydrochloric acid 2N in EtOH	7647-01-0	HCl	36.46	0.88		24.00		10.2

product	m (g)	M (g/mol)	yield
Intermediate **4**	0.832	362.9	0.98

E-factor

		m (g)
Product	Amine **4**	0.832
Reagents	Intermediate **3a**	1.002
	ethanol	37.083
	Hydrochloric acid 2N in EtOH	0.875

E-factor =	38.13	/	0.832	=	**46**

Deprotection of Boc function in solid state

Reagents	CAS	Molecular Formula	M(g/mol)	m(g)	V (mL)	n (mmoles)	d	eq
Intermediate **3a**			426.56	0.495		1.16		1
Hydrochloric acid gas	7647-01-0	HCl	36.46	0.43		11.83		10.2

product	m (g)	M (g/mol)	yield
Intermediate **4**	0.412	362.9	0.98

E-factor

		m (g)			
Product	Amine **4**	0.412			
Reagents	Intermediate **3a**	1.002			
	HCl	0.430			
E-factor =	1.02	/	0.412	=	**2**

Sulfonylation of primary amine in solution

Reagents	CAS	Molecular Formula	M(g/mol)	m(g)	V (mL)	n (mmoles)	d	eq
amine **4**			362.9	0.334		0.92		1
dichloromethane	75-09-2	CH2Cl2	84.93	5.300	4.000		1.325	
triethylamine	121-44-8	(C2H5)3N	101.19	0.28	0.385	2.76	0.726	3
3-chlorobenzenesulfonyl chloride	#2888-06-4	C6H4SO2Cl2	211.07	0.233	0.155	1.104	1.499	1.2
Purification								
CH2Cl2	75-09-2	CH2Cl2	84.93	251.750	190.000		1.325	
MeOH	67-56-1	CH4O	32.04	7.920	10		0.792	

product	m (g)	M (g/mol)	yield
final compound **5a (PZ-1361)**	0.33	501.04	0.72

E-factor

		m (g)			
Product	final compound **5a**	0.330			
Reagents	amine **4**	0.300			
	dichloromethane	5.300			
	triethylamine	0.279			
	3-chlorobenzenesulfonyl chloride	0.233			
	CH2Cl2	251.750			
	MeOH	7.920			
E-factor =	265.45	/	0.330	=	**804**

Sulfonylation of primary amine in ball-mill

Reagents	CAS	Molecular Formula	M(g/mol)	m(g)	V (mL)	n (mmoles)	d	eq
amine **4**			362.9	0.168		0.463		1
potassium carbonate	584-08-7	K2CO3	138.21	0.064		0.46		1
3-chlorobenzenesulfonyl chloride	#2888-06-4	C6H4SO2Cl2	211.07	0.098	0.065	0.463	1.499	1
Extraction								
ethyl acetate	141-78-6	C4H8O2	88.11	18.04	20	204.74	0.902	
potassium bisulfate	7646-93-7	KHSO4	136.17	0.0002860		0.00210		
sodium chloride	7647-14-5	NaCl	58.44	1.82				
water	7732-18-5	H2O	18	26.18		1454.444		

product	m (g)	M (g/mol)	yield
final compound **5a (PZ-1361)**	0.2001	501.04	0.86

E-factor

		m (g)			
Product	final compound **5a**	0.200			
Reagents	amine **4**	0.046			
	potassium carbonate	0.019			
	3-chlorobenzenesulfonyl chlo	0.030			
	ethyl acetate	18.040			
	potassium bisulfate	0.000286			
	sodium chloride	1.820			
	water	26.180			
E-factor =	45.93	/	0.200	=	**230**

*Total synthesis of PZ-1361(**5a**) in solution*

Total synthesis of PZ-1361

Step 1
Alkylation

Reagents	CAS	Molecular Formula	M(g/mol)	m(g)	V (mL)	n (mmoles)	d	eq
2-phenylphenol	90-43-7	C12H10O	170.21	0.999		5.87		1
acetone	67-64-1	C3H6O	58.08	15.819	19.999	272.37	0.791	46.4
potassium carbonate	584-08-7	K2CO3	138.21	2.03		14.68		2.5
potassium hydroxide	1310-58-3	KOH	56.11	0.165		2.935		0.5
epichlorhydrin	106-89-8	C3H5ClO	92.52	1.086	0.918	11.74	1.183	2
Extraction								
dichloromethane	75-09-2	CH2Cl2	84.93	26.522	20.000	312.28	1.325	53.2
sodium hydroxide	1310-73-2	NaOH	40	1.691		42.26		7.2
sodium chloride	7647-14-5	NaCl	58.44	1.82		31.11		5.3
water	7732-18-5	H2O	18	26.18		1454.59		247.8
Purification								
ethyl acetate	141-78-6	C4H8O2	88.11	45.10	50	511.86	0.902	87.2
hexane	110-54-3	C6H14	86.18	296.54	450	3440.99	0.659	586.2

product	m (g)	M (g/mol)	yield
alkylated 2-phenylphenol **1a**	0.82	226.28	0.62

Step 2
Amination

Reagents	CAS	Molecular Formula	M(g/mol)	m(g)	V (mL)	n (mmoles)	d	eq
alkylated 2-phenylphenol **1a**			226.28	0.824		3.64		1
ethanol	64-17-5	C2H6O	46.07	12.168	15.0	264.11	0.789	72.57
4-boc-N-aminopiperidine	73874-95-0	C10H20N2O2	200.28	0.87		4.37		1.2
Purification								
dichloromethane	75-09-2	CH2Cl2	84.93	612.996	450.0	7217.7	1.325	1983.2
methanol	67-56-1	CH4O	32.04	40.661	50.0	1269.1	0.791	348.7

product	m (g)	M (g/mol)	yield
amination product **3a**	1.21	426.56	0.78

Step 3
Boc removal

Reagents	CAS	Molecular Formula	M(g/mol)	m(g)	V (mL)	n (mmoles)	d	eq
Intermediate **3a**			426.56	1.211		2.84		1
ethanol	64-17-5	C2H6O	46.07	44.795	47.0	972.32	0.789	342.52
Hydrochloric acid 2N in EtOH	7647-01-0	HCl	36.46	1.06		28.96		10.2

product	m (g)	M (g/mol)	yield
Intermediate **4**	1.01	362.9	0.98

Step 4
Sulfonylation

Reagents	CAS	Molecular Formula	M(g/mol)	m(g)	V (mL)	n (mmoles)	d	eq
amine **4**			362.9	1.010		2.78		1
dichloromethane	75-09-2	CH2Cl2	84.93	16.019	4.000	188.617	1.325	67.8
triethylamine	121-44-8	(C2H5)3N	101.19	0.84	1.163	8.35	0.726	3
3-chlorobenzenesulfonyl chloride	#2888-06-4	C6H4SO2Cl2	211.07	0.705	0.470	3.33834883	1.499	1.2
Purification								
CH2Cl2	75-09-2	CH2Cl2	84.93	761.267	190.000	8963.467	1.325	3222.0
MeOH	67-56-1	CH4O	32.04	23.950	10	747.512	0.792	268.7

product	m (g)	M (g/mol)	yield
final compound **5a (PZ-1361)**	1.00	501.04	0.72

product	m (g)	M (g/mol)	yield
final compound **5a (PZ-1361)**	1.000	501.04	0.34

E-factor

		m (g)
Product	final compound **5a (PZ-1361)**	1.000
Reagents	2-phenylphenol	0.999
	acetone	15.819
	potassium carbonate	2.028
	potassium hydroxide	0.165
	epichlorhydrin	1.086
	dichloromethane	26.522
	sodium hydroxide	1.691
	sodium chloride	1.818
	water	26.183
	ethyl acetate	45.100
	hexane	296.54
	ethanol	12.168
	4-boc-N-aminopiperidine	0.875
	dichloromethane	612.996
	methanol	40.661
	ethanol	44.795
	Hydrochloric acid 2N in EtOH	1.056
	dichloromethane	16.019
	triethylamine	0.845
	3-chlorobenzenesulfonyl chlo	0.705
	CH2Cl2	761.267
	MeOH	23.950

E-factor =	1932.29	/	1.000	=	**1932**

*Total synthesis of PZ-1361(**5a**) in solid state*

Total synthesis of PZ-1361

Step 1
Alkylation

Reagents	CAS	Molecular Formula	M(g/mol)	m(g)	V (mL)	n (mmoles)	d	eq
2-phenylphenol	90-43-7	C12H10O	170.21	0.081		0.474		1
potassium carbonate	584-08-7	K2CO3	138.21	0.20		1.4220		3
epichlorhydrin	106-89-8	C3H5ClO	92.52	0.053	0.044	0.5688	1.183	1.2
iso propanol	67-63-0	C3H8O	60.1	0.039	0.050		0.785	
Extraction								
dichloromethane	75-09-2	CH2Cl2	84.93	19.875	15.000	234.0138	1.325	493.7
sodium hydroxide	1310-73-2	NaOH	40	1.680		41.9964		88.6
sodium chloride	7647-14-5	NaCl	58.44	1.82		31.1418		65.7
water	7732-18-5	H2O	18	26.18		1454.4690		3068.5

product	m (g)	M (g/mol)	yield
alkylated 2-phenylphenol **1a**	0.091	226.28	0.85

Step 2
Amination

Reagents	CAS	Molecular Formula	M(g/mol)	m(g)	V (mL)	n (mmoles)	d	eq
alkylated 2-phenylphenol **1a**			226.28	0.091		0.402		1
ethanol	64-17-5	C2H6O	46.07	0.014		0.294	0.789	0.73
4-boc-N-aminopiperidine	73874-95-0	C10H20N2O2	200.28	0.081		0.402		1
Extraction								
ethyl acetate	141-78-6	C4H8O2	88.11	9.37	10.391	106.37	0.902	264.5
potassium bisulfate	7646-93-7	KHSO4	136.17	0.0001486		0.0011		0.002713
sodium chloride	7647-14-5	NaCl	58.44	0.945		16.17		40.2
water	7732-18-5	H2O	18	13.602		755.69		1879.1

product	m (g)	M (g/mol)	yield
amination product **3a**	0.154	426.56	0.90

Step 3
Boc removal

Reagents	CAS	Molecular Formula	M(g/mol)	m(g)	V (mL)	n (mmoles)	d	eq
Intermediate **3a**			426.56	0.154		0.362		1
Hydrochloric acid gas	7647-01-0	HCl	36.46	0.135		3.69		10.2

product	m (g)	M (g/mol)	yield
Intermediate **4a**	0.129	362.9	0.98

Step 4
Sulfonylation

Reagents	CAS	Molecular Formula	M(g/mol)	m(g)	V (mL)	n (mmoles)	d	eq
amine **4**			362.9	0.129		0.355		1
potassium carbonate	584-08-7	K2CO3	138.21	0.049		0.355		1
3-chlorobenzenesulfonyl chloride	#2888-06-4	C6H4SO2Cl2	211.07	0.075	0.050	0.355	1.499	1
Extraction								
ethyl acetate	141-78-6	C4H8O2	88.11	13.82	15.3	156.85	0.902	442.2
potassium bisulfate	7646-93-7	KHSO4	136.17	0.0002191		0.00161		0.004536
sodium chloride	7647-14-5	NaCl	58.44	1.40		23.871		67.3
water	7732-18-5	H2O	18	20.057		1114.261		3141.4

product	m (g)	M (g/mol)	yield
final compound **5a (PZ-1361)**	0.153	501.04	0.86

product	m (g)	M (g/mol)	Overall yield
final compound **5a (PZ-1361)**	0.153	501.04	0.64

E-factor

		m (g)
Product	alkylated 2-phenylphenol **1a**	0.153
Reagents	2-phenylphenol	0.081
	potassium carbonate	0.197
	epichlorhydrin	0.053
	iso propanol	0.039
	dichloromethane	19.875
	sodium hydroxide	1.680
	sodium chloride	1.820
	water	26.180
	ethanol	0.014
	4-boc-N-aminopiperidine	0.081
	ethyl acetate	9.372
	potassium bisulfate	0.000149
	sodium chloride	0.945
	water	13.602
	HCl	0.135
	potassium carbonate	0.049
	3-chlorobenzenesulfonyl chlo	0.075
	ethyl acetate	13.820
	potassium bisulfate	0.000219
	sodium chloride	1.395
	water	20.057

E-factor =	109.32	/	0.153	=	**715**

C. Calculation of Ecoscale score

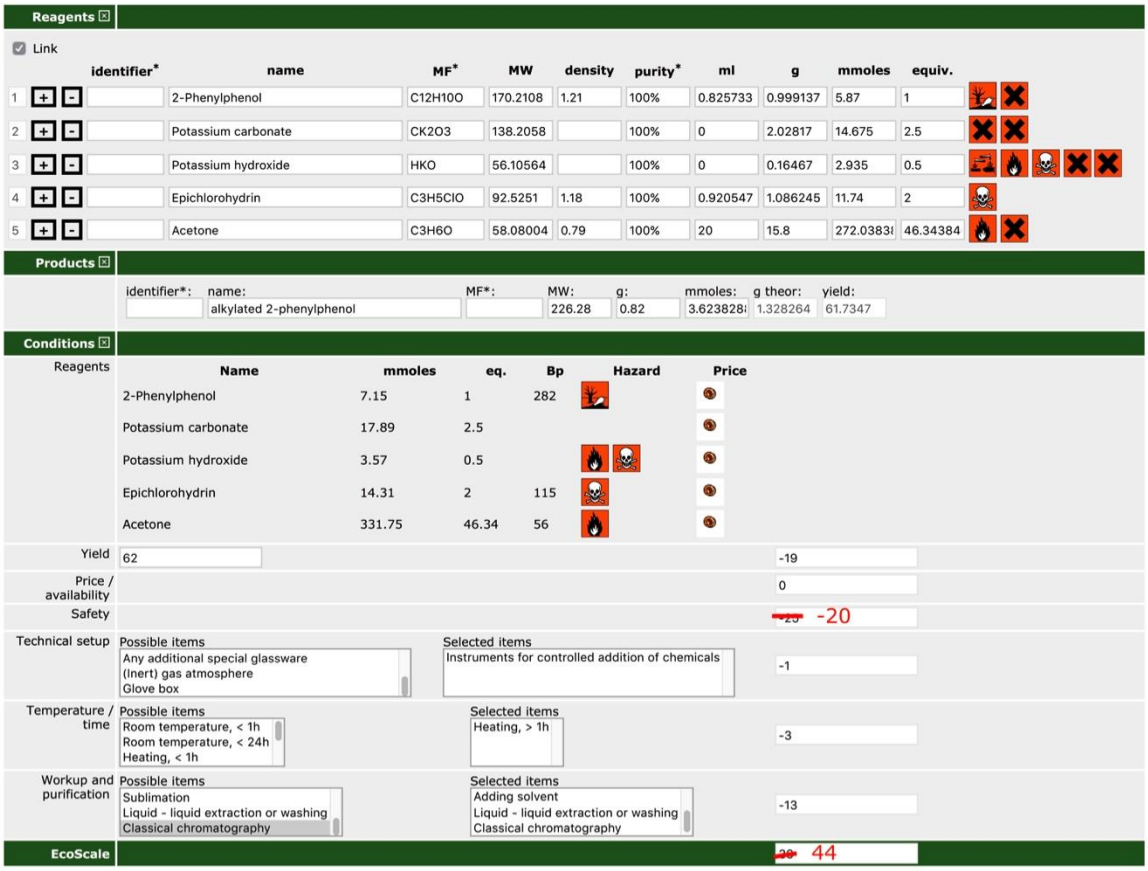
According to Van Aken *et al.*: "*The Ecoscale tool uses a scale from 0 to 100 with 0 representing a totally failed reaction (0% yield) and 100 representing the ideal reaction which is defined as follows: Compound **A** (substrate) undergoes a reaction with (or in the presence of) inexpensive compound(s) **B** to give the desired compound **C** in 100% yield at room temperature with a minimal risk for the operator and a minimal impact on the environment. Six general parameters which influence the quality of reaction conditions are analyzed. Within each of these parameters, individual penalty points of various relative weights are assigned that take into account all possible situations when setting up an organic chemistry experiment. The penalty points are cumulative for all components of the preparation. In order to simplify the EcoScale design, the usual differentiation between solvents, reagents, auxiliary or co-reagents and catalysts is not made.*
Ecoscale can be summarized by this simple equation: EcoScale = 100 - sum of individual penalties."[4]
Ranking of reaction conditions is defined as follow: On a scale from 0 to 100 using the following scores: > 75 is excellent; > 50 is acceptable and < 50 is inadequate.

Below, Ecoscale score tables using magnetic stirrer or ball-mill are displayed, using the web version http://ecoscale.cheminfo.org/calculator of this green metric. Quantities used were obtained from the protocols reported above. As suggested on the web-calculator, penalties due to hazard should be limited to a maximum score of 20. Thus, even if this penalty number was found higher on the calculator, we corrected it to 20 (corrections in red in the following pictures).

Table S2. Summary of Ecoscale score calculations for the synthesis of **PZ-1361**

	ECOSCALE SCORE			
	Step 1	**Step 2**	**Step 3**	**Step 4**
	Alkylation of 2-Phenylphenol	Alkylation of 4-Boc-N-aminopiperidine	Boc deprotection	Sulfonylation
Solution	44	58	70	49
Solid-state	71	71	**81**	**78**

Alkylation of 2-phenylphenol in solution



Reagents

Link

	identifier*	name	MF*	MW	density	purity*	ml	g	mmoles	equiv.
1		2-Phenylphenol	C12H10O	170.2108	1.21	100%	0.825733	0.999137	5.87	1
2		Potassium carbonate	CK2O3	138.2058		100%	0	2.02817	14.675	2.5
3		Potassium hydroxide	HKO	56.10564		100%	0	0.16467	2.935	0.5
4		Epichlorohydrin	C3H5ClO	92.5251	1.18	100%	0.920547	1.086245	11.74	2
5		Acetone	C3H6O	58.08004	0.79	100%	20	15.8	272.0383	46.34384

Products

identifier*:	name:	MF*:	MW:	g:	mmoles:	g theor:	yield:
	alkylated 2-phenylphenol		226.28	0.82	3.623828	1.328264	61.7347

Conditions

Reagents

Name	mmoles	eq.	Bp	Hazard	Price
2-Phenylphenol	7.15	1	282		
Potassium carbonate	17.89	2.5			
Potassium hydroxide	3.57	0.5			
Epichlorohydrin	14.31	2	115		
Acetone	331.75	46.34	56		

Yield	62	-19
Price / availability		0
Safety		-20
Technical setup	Possible items: Any additional special glassware; (Inert) gas atmosphere; Glove box — Selected items: Instruments for controlled addition of chemicals	-1
Temperature / time	Possible items: Room temperature, < 1h; Room temperature, < 24h; Heating, < 1h — Selected items: Heating, > 1h	-3
Workup and purification	Possible items: Sublimation; Liquid - liquid extraction or washing; Classical chromatography — Selected items: Adding solvent; Liquid - liquid extraction or washing; Classical chromatography	-13
EcoScale		44

Alkylation of 2-phenylphenol in ball-mill

Reagents

Link

	identifier*	name	MF*	MW	density	purity*	ml	g	mmoles	equiv.
1		2-Phenylphenol	C12H10O	170.2108	1.21	100%	0.066678	0.08068	0.474	1
2		Potassium carbonate	CK2O3	138.2058		100%	0	0.196529	1.422	3
3		Epichlorohydrin	C3H5ClO	92.5251	1.18	100%	0.0446	0.052628	0.5688	1.2
4		Isopropanol	C3H8O	60.09592	0.785	100%	0.05	0.03925	0.6531225	1.3778956

Products

identifier*:	name:	MF*:	MW:	g:	mmoles:	g theor:	yield:
	alkylated 2-phenylphenol		226.28	0.091	0.402156	0.107257	84.8429

Conditions

Reagents

Name	mmoles	eq.	Bp	Hazard	Price
2-Phenylphenol	5.2	1	282		
Potassium carbonate	15.62	3			
Epichlorohydrin	6.25	1.2	115		
Isopropanol	7.17	1.37	81		

Yield	85		-8
Price / availability			0
Safety			-15
Technical setup	Possible items: Unconventional activation technique; Pressure equipment, > 1 atm	Selected items: Unconventional activation technique	-2
Temperature / time	Possible items: Room temperature, < 1h; Room temperature, < 24h; Heating, < 1h	Selected items: Room temperature, < 24h	-1
Workup and purification	Possible items: Cooling to room temperature; Adding solvent; Simple filtration	Selected items: Liquid - liquid extraction or washing; Adding solvent	-3

EcoScale 71

Alkylation of 4-Boc-N-aminopiperidine in solution

Reagents

Link

	identifier*	name	MF*	MW	density	purity*	ml	g	mmoles	equiv.
1	Name, MF or	alkylated 2-phenylphenol		226.28		100%	0	0.801031	3.540000	1
2		4-N-Boc-Aminopiperidine	C10H20N2O	200.281		100%	0	0.850794	4.248	1.2
3		Ethanol	C2H6O	46.06904	0.79	100%	15	11.85	257.22263	72.661762

Products

identifier*:	name:	MF*:	MW:	g:	mmoles:	g theor:	yield:
	amination product 3		426.56	1.17	2.7428732	1.510022	77.48230(

Conditions

Reagents

Name	mmoles	eq.	Bp	Hazard	Price
alkylated 2-phenylphenol	3.02	1			
4-N-Boc-Aminopiperidine	3.63	1.2			
Ethanol	219.84	72.66			

Yield	77		-11
Price / availability			-8
Safety			-10
Technical setup	Possible items: Any additional special glassware; (Inert) gas atmosphere; Glove box	Selected items: Common set-up	0
Temperature / time	Possible items: Heating, > 1h; Cooling to 0°C; Cooling, < 0°C	Selected items: Heating, > 1h	-3
Workup and purification	Possible items: Sublimation; Liquid - liquid extraction or washing; Classical chromatography	Selected items: Classical chromatography; Simple filtration; Cooling to room temperature	-10
EcoScale			58

Alkylation of 4-Boc-N-aminopiperidine in ball-mill

Reagents

Link

	identifier*	name	MF*	MW	density	purity*	ml	g	mmoles	equiv.
1	Name, MF or	alkylated 2-phenylphenol 1a		226.28		100%	0	0.175141	0.774	1
2		4-N-Boc-Aminopiperidine	C10H20N2O	200.281		100%	0	0.155017	0.774	1
3		Ethanol	C2H6O	46.06904	0.79	100%	0.033	0.02607	0.565889	0.7311237

Products

identifier*:	name:	MF*:	MW:	g:	mmoles:	g theor:	yield:
	amination product 3a		426.56	0.297	0.696267	0.330157	89.9572

Conditions

Reagents

Name	mmoles	eq.	Bp	Hazard	Price
alkylated 2-phenylphenol 1a	2.6	1			
4-N-Boc-Aminopiperidine	2.6	1			
Ethanol	1.9	0.73			

Yield	90		-5
Price / availability			-8
Safety			-10
Technical setup	Possible items: Common set-up; Instruments for controlled addition of chemicals; Unconventional activation technique	Selected items: Unconventional activation technique	-2
Temperature / time	Possible items: Room temperature, < 1h; Room temperature, < 24h; Heating, < 1h	Selected items: Room temperature, < 24h	-1
Workup and purification	Possible items: Sublimation; Liquid - liquid extraction or washing; Classical chromatography	Selected items: Liquid - liquid extraction or washing	-3
EcoScale			71

General procedure for deprotection of Boc function in solution

Reagents

Link

	identifier*	name	MF*	MW	density	purity*	ml	g	mmoles	equiv.
1	Name, MF or	Intermediate 3a		426.56		100%	0	1.002416	2.35	1
2		Hydrochloric acid	HCl	36.46094		100%	0	0.873969	23.97	10.2
3		Ethanol	C2H6O	46.06904	0.79	100%	47	37.13	805.9642	342.96351

Products

identifier*:	name:	MF*:	MW:	g:	mmoles:	g theor:	yield:
	Intermediate 4		362.9	0.832	2.292642	0.852815	97.559300

Conditions

Reagents

Name	mmoles	eq.	Bp	Hazard	Price
Intermediate 3a	2.82	1			
Hydrochloric acid	28.81	10.19	57		
Ethanol	968.7	342.96			

Yield	98		-1
Price / availability			-8
Safety			-20
Technical setup	Possible items: Common set-up; Instruments for controlled addition of chemicals; Unconventional activation technique	Selected items: Common set-up	0
Temperature / time	Possible items: Room temperature, < 1h; Room temperature, < 24h; Heating, < 1h	Selected items: Room temperature, < 24h	-1
Workup and purification	Possible items: Adding solvent; Simple filtration; Removal of solvent with bp < 150°C; Crystallization and filtration	Selected items: Simple filtration	0
EcoScale			70

General procedure for deprotection of Boc function in solid state

Reagents

Link

	identifier*	name	MF*	MW	density	purity*	ml	g	mmoles	equiv.
1	Name, MF or	Intermediate 3a		426.56		100%	0	0.49481	1.16	1
2		Hydrochloric acid	HCl	36.46094		100%	0	0.431406	11.831999	10.2

Products

identifier*:	name:	MF*:	MW:	g:	mmoles:	g theor:	yield:
	Intermediate 4		362.9	0.412	1.1352989	0.420964	97.8706

Conditions

Reagents

Name	mmoles	eq.	Bp	Hazard	Price
Intermediate 3a	2.81	1			
Hydrochloric acid	28.71	10.19	57		

Yield	98		-1
Price / availability			-5
Safety			-10
Technical setup	Possible items: Common set-up; Instruments for controlled addition of chemicals; Unconventional activation technique	Selected items: Unconventional activation technique	-2
Temperature / time	Possible items: Room temperature, < 1h; Room temperature, < 24h; Heating, < 1h	Selected items: Room temperature, < 24h	-1
Workup and purification	Possible items: None; Cooling to room temperature; Adding solvent	Selected items: None	0
EcoScale			81

Sulfonylation of primary amine in solution

Reagents

Link

	identifier*	name	MF*	MW	density	purity*	ml	g	mmoles	equiv.
1	Name, MF or	Amine 4		362.9		100%	0	0.333868	0.92	1
2		3-Chlorobenzenesulfonyl chloride	C6H4Cl2O2S	211.06256		100%	0	0.233013	1.104	1.2
3		Triethylamine	C6H15N	101.1918	0.728	100%	0.383639	0.279289	2.760000(	3
4		Dichloromethane	CH2Cl2	84.93288	1.325	100%	4	5.3	62.402216	67.828496

Products

identifier*:	name:	MF*:	MW:	g:	mmoles:	g theor:	yield:
	Final compound PZ-1361		501.04	0.33	0.658630(	0.460957	71.590200

Conditions

Reagents

Name	mmoles	eq.	Bp	Hazard	Price
Amine 4	2.78	1			
3-Chlorobenzenesulfonyl chloride	3.34	1.2	102		
Triethylamine	8.36	3	90		
Dichloromethane	189.09	67.82	39		

Yield	72		-14
Price / availability			-13
Safety			-10
Technical setup	Possible items: Common set-up; Instruments for controlled addition of chemicals; Unconventional activation technique	Selected items: Common set-up	0
Temperature / time	Possible items: Heating, > 1h; Cooling to 0°C; Cooling, < 0°C	Selected items: Cooling to 0°C	-4
Workup and purification	Possible items: Sublimation; Liquid - liquid extraction or washing; Classical chromatography	Selected items: Removal of solvent with bp < 150°C; Classical chromatography	-10
EcoScale			49

Sulfonylation of primary amine in ball-mill

Reagents

Link

	identifier*	name	MF*	MW	density	purity*	ml	g	mmoles	equiv.
1	Name, MF or	Amine 4		362.9		100%	0	0.168023	0.463	1
2		3-Chlorobenzenesulfonyl chloride	C6H4Cl2O2S	211.06256		100%	0	0.097722	0.463	1
3		Potassium carbonate	CK2O3	138.2058		100%	0	0.063989	0.463	1

Products

identifier*:	name:	MF*:	MW:	g:	mmoles:	g theor:	yield:
	Final compound PZ-1361		501.04	0.2001	0.399369	0.231982	86.2567

Conditions

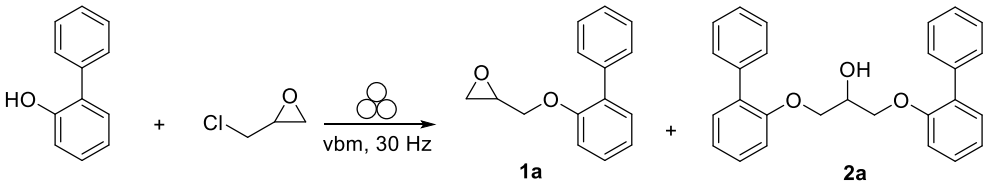
Reagents

Name	mmoles	eq.	Bp	Hazard	Price
Amine 4	2.31	1			
3-Chlorobenzenesulfonyl chloride	2.31	1	102		
Potassium carbonate	2.31	1			

Yield	86		-7
Price / availability			-10
Safety			0
Technical setup	Possible items: Common set-up; Instruments for controlled addition of chemicals; Unconventional activation technique	Selected items: Unconventional activation technique	-2
Temperature / time	Possible items: Room temperature, < 1h; Room temperature, < 24h; Heating, < 1h	Selected items: Room temperature, < 1h	0
Workup and purification	Possible items: Sublimation; Liquid - liquid extraction or washing; Classical chromatography	Selected items: Liquid - liquid extraction or washing	-3
EcoScale			78

II. Additional experimental data for alkylation of 2-phenylphenol in ball-mill

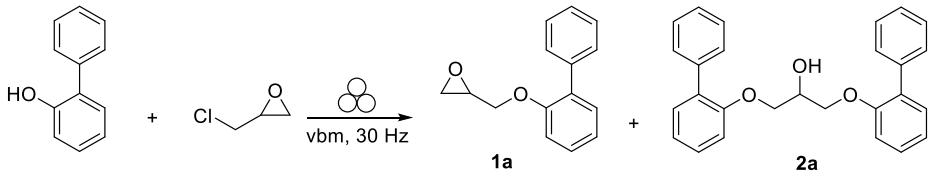
Table S3. Optimization of the kind of base for the alkylation of 2-phenylphenol[a]



Entry	Base (eq)	Conv. %[b]	
		1a	2a
1	$NaHCO_3$ (3)	2	0
2	Na_2CO_3 (3)	1	0
3	K_2CO_3 (3)	35	0
4	K_2CO_3/KOH (3/0.5)	26	0
5	K_2CO_3/KOH (2/1.5)	35	3
6	Cs_2CO_3 (3)	29	10
7	NaOH (3)	16	0
8	KOH (3)	36	10
9	NaO*t*But (3)	32	3
10	DIEA (3)	2	0
11	TEA (3)	5	0

[a] Reaction conditions: 2-phenylphenol (1 eq), epichlorohydrin (1 eq), vbm 30 Hz, 10 mL PTFE jar, ⌀ = 1 cm, 80 min, total mass of reagents: 100 mg; [b] Conversions were determined by UPLC/MS analysis.

Table S4. Optimization of milling time for the alkylation of 2-phenylphenol[a]

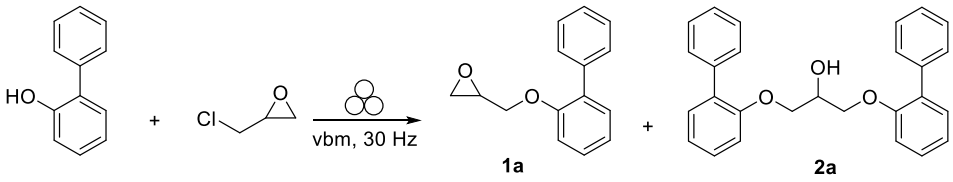


1a 2a

Entry	Base (eq)	Time (min)	Conv.%[b]	
			1a	2a
1	K_2CO_3 (3)	40	15	0
2		80	35	0
3		120	40	0.5
4		140	43	2
5		160	45	3.5
6		180	47.5	5
7		200	48.5	7.5
8		210	50	8.5
9		220	52	10

[a] Reaction conditions: 2-phenylphenol (1 eq), epichlorohydrin (1 eq), vbm 30 Hz, 10 mL PTFE jar, ⌀ = 1 cm, total mass of reagents: 100 mg; [b] Conversions were determined by UPLC/MS analysis.

Table S5. Optimization of the milling conditions for the alkylation of 2-phenylphenol[a]



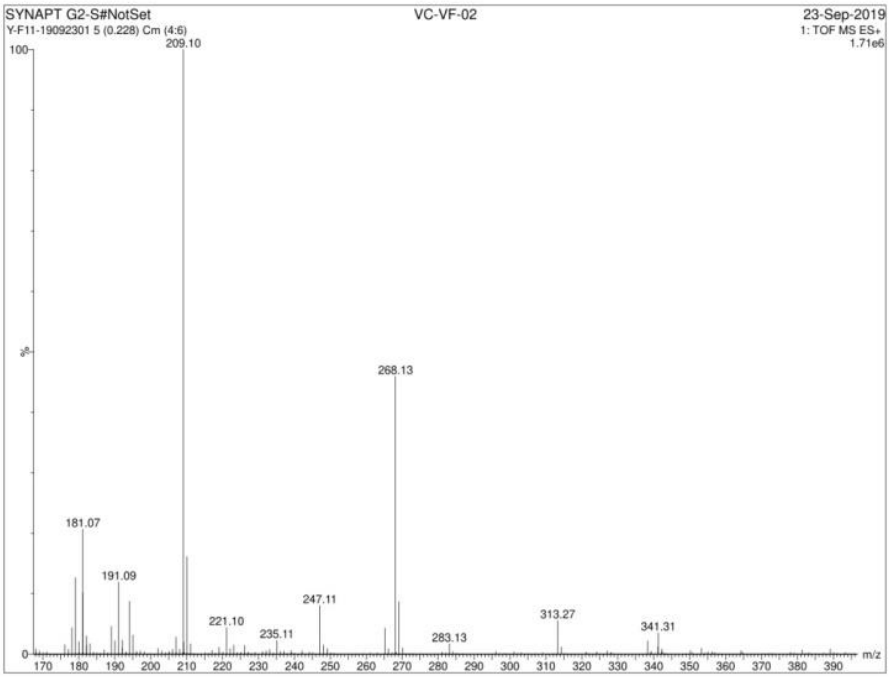
Entry	Base (eq)	Epich.	⌀	Time (min)	Conv. %[b]	
					1a	2a
1		1 eq	1 cm	140	42.5	2.5
2	K_2CO_3	1 eq	1.5 cm		61	2.5
3	(3)	1.2 eq	1.5 cm		90	2
4		1.5 eq	1.5 cm		86	1

[a] Reaction conditions: 2-phenylphenol (1 eq), vbm 30 Hz, total mass of reagents: 100 mg; 10 mL PTFE jar; [b] Conversions were determined by UPLC/MS analysis.

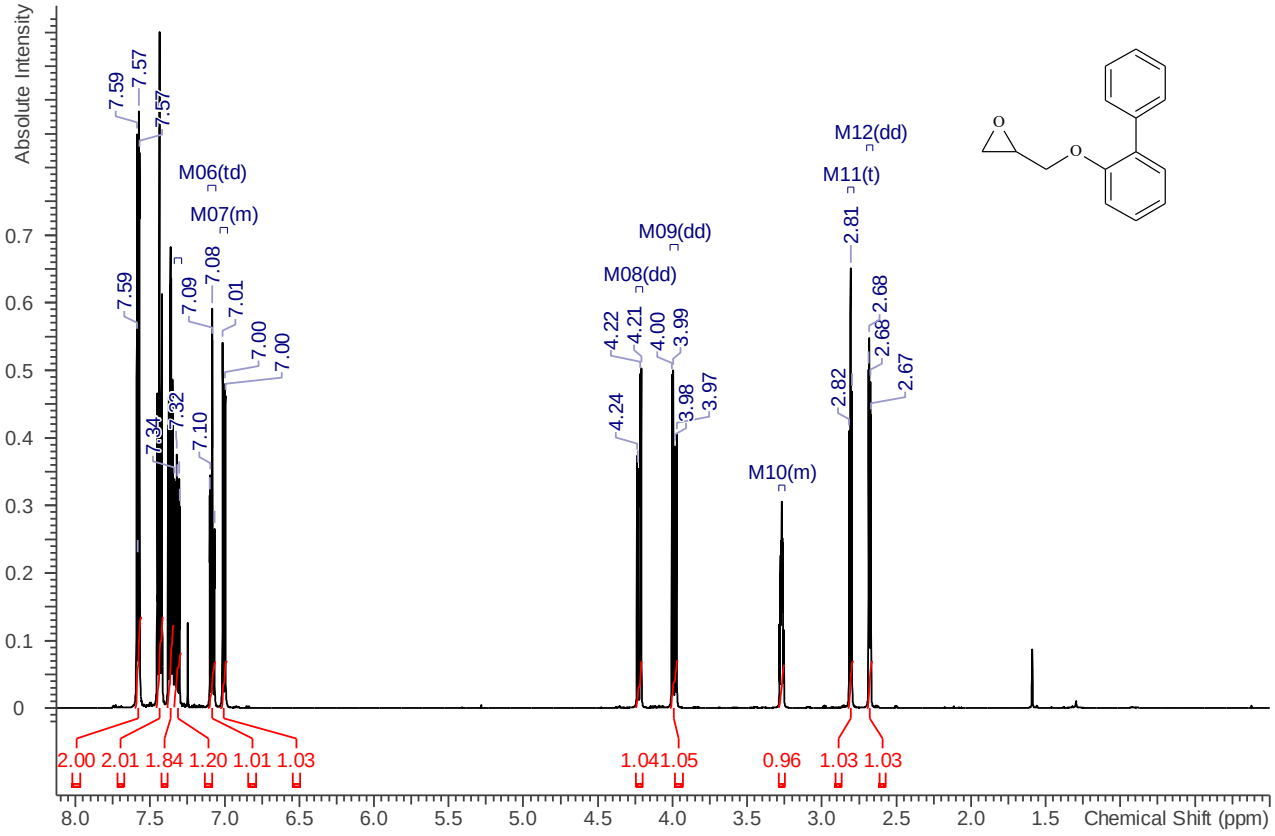
III. HRMS, ^{1}H- and ^{13}C-NMR spectra

2-(([1,1'-Biphenyl]-2-yloxy)methyl)oxirane (**1a**)

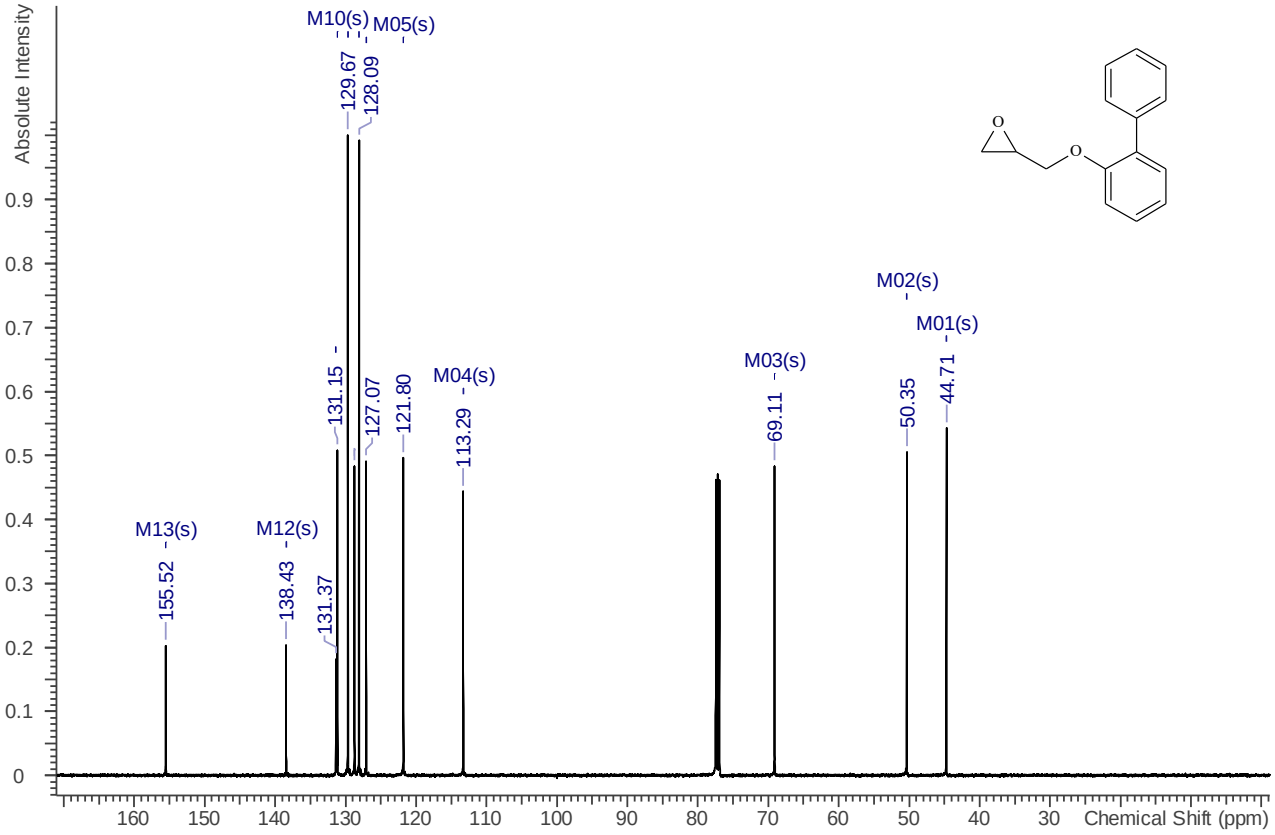
HRMS



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

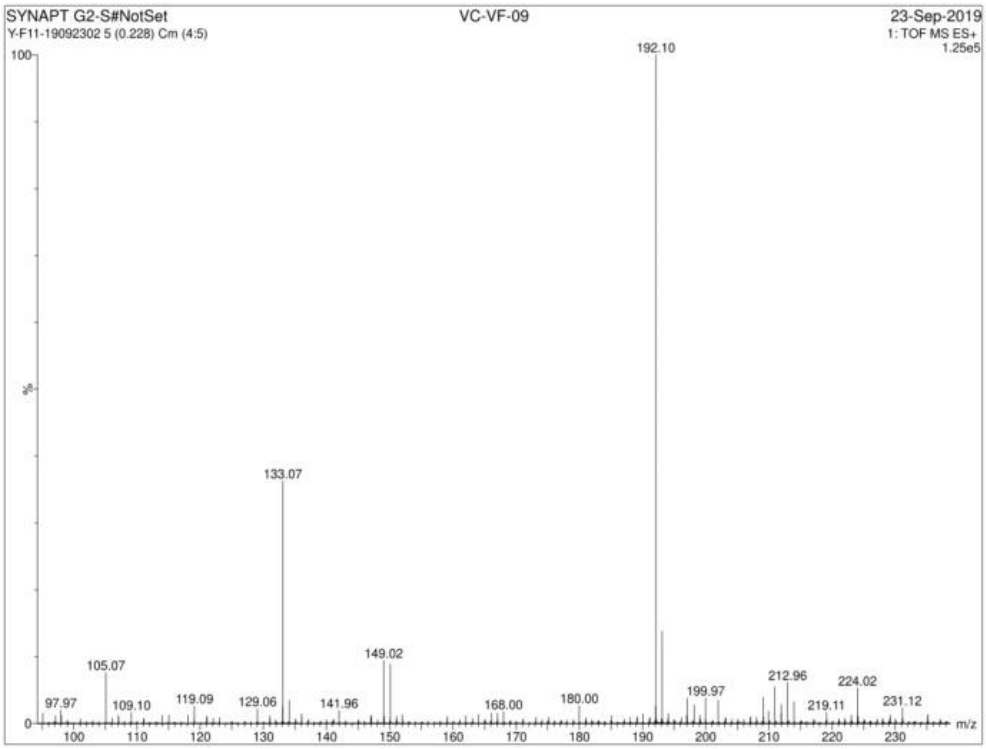


^{13}C-NMR ($CDCl_3$, 126 MHz)

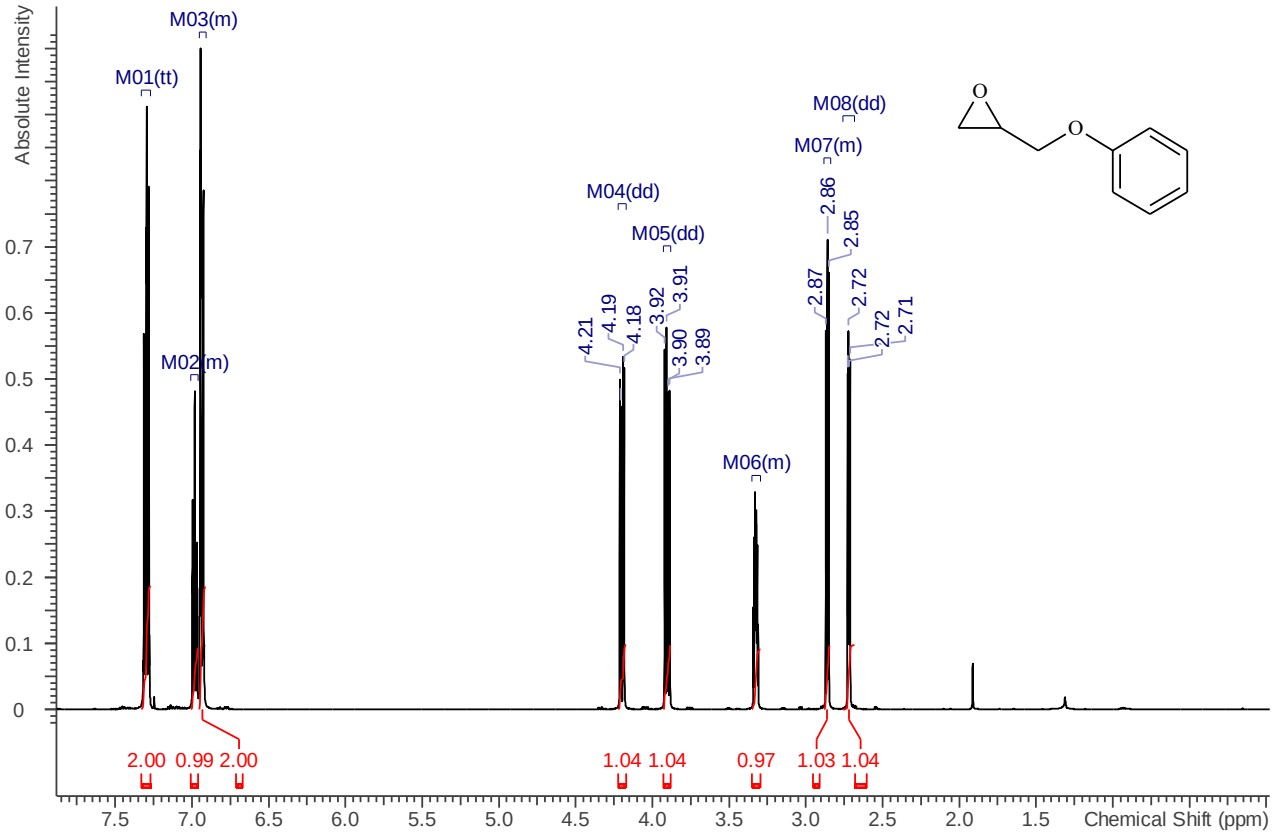


2-(Phenoxymethyl)oxirane (**1b**)

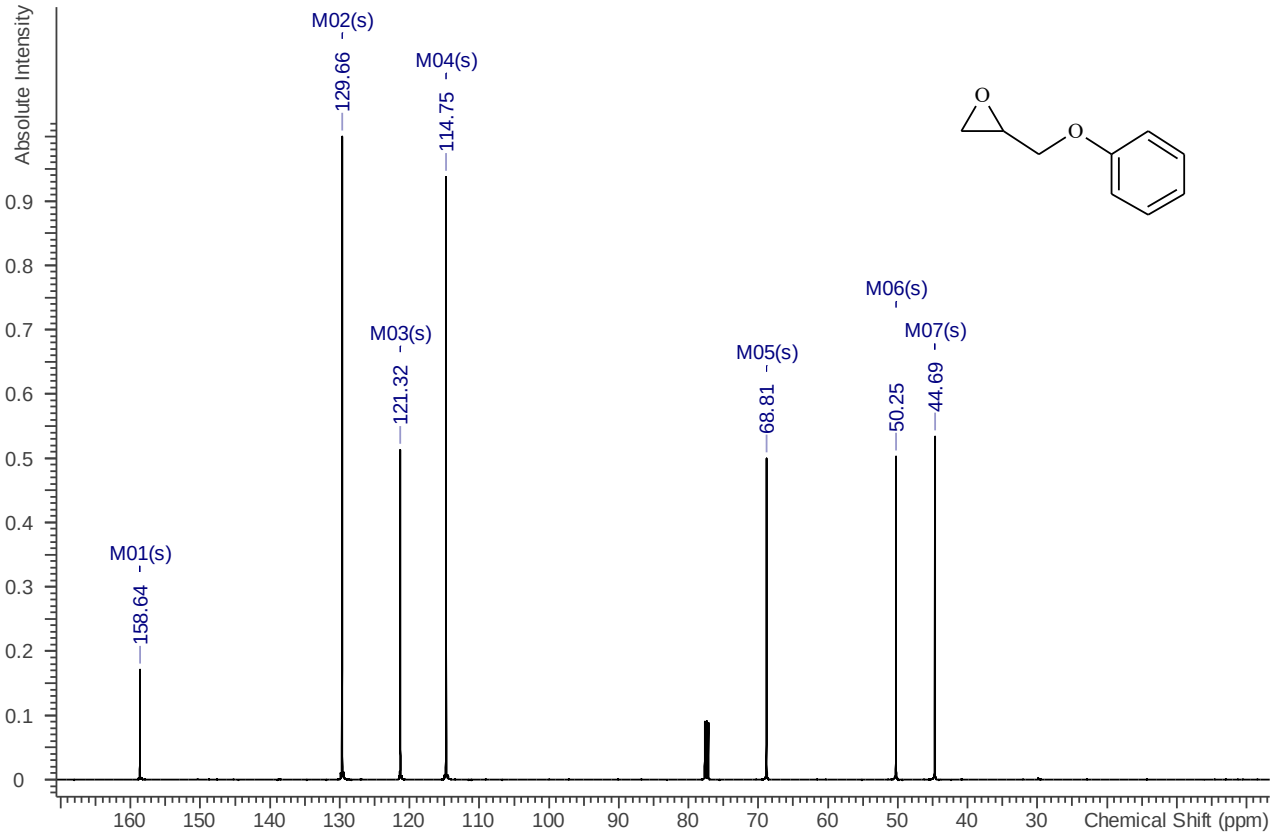
HRMS



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

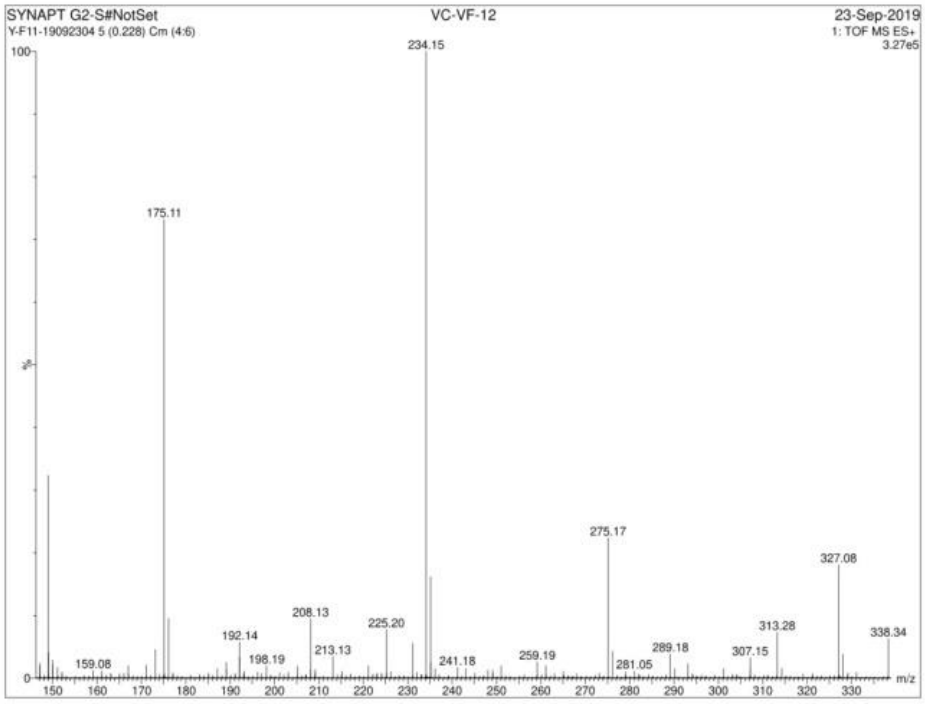


^{13}C-NMR ($CDCl_3$, 126 MHz)

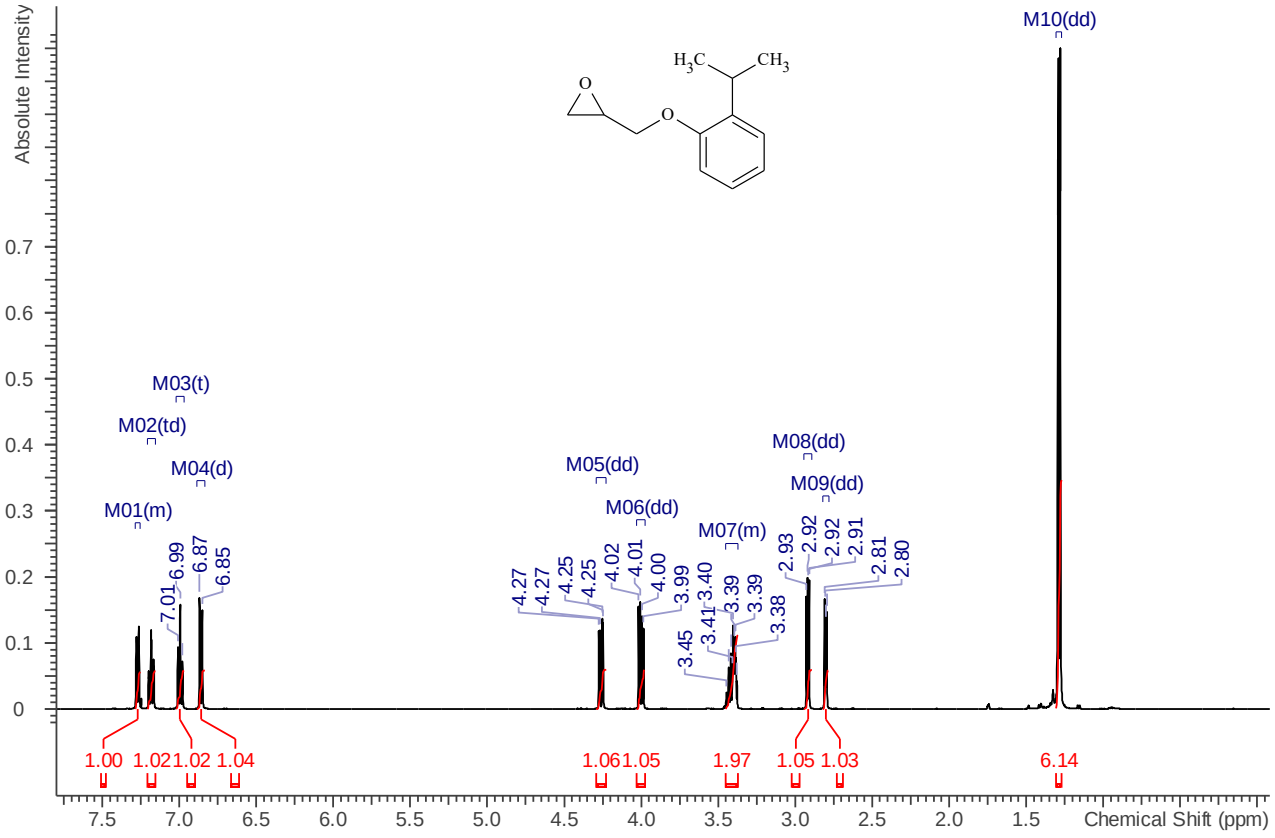


2-((2-Isopropylphenoxy)methyl)oxirane (**1c**)

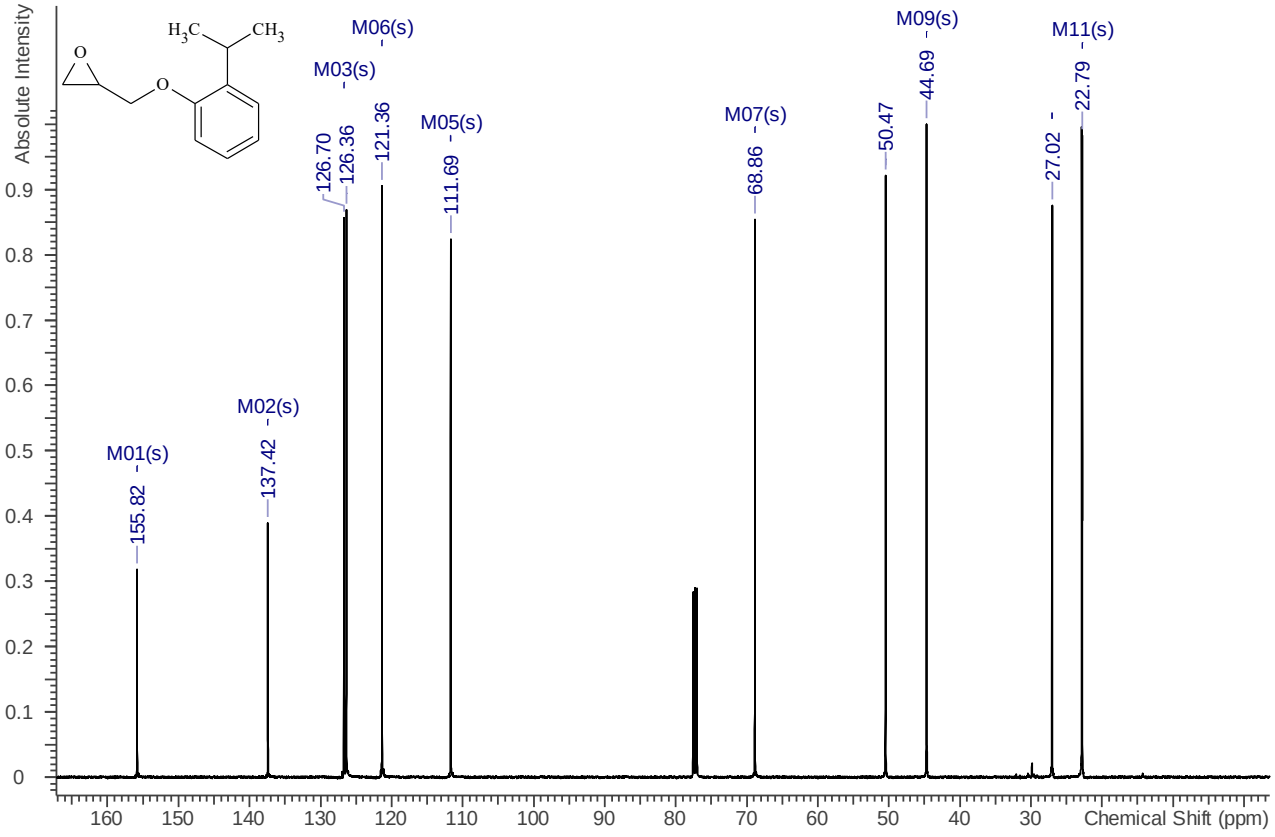
HRMS



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

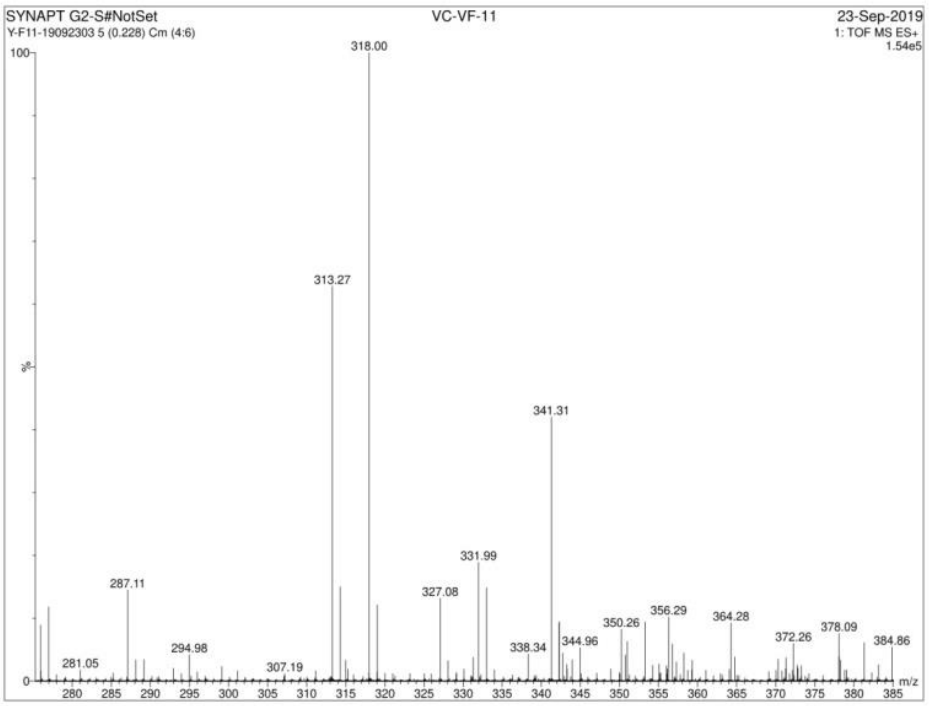


^{13}C-NMR ($CDCl_3$, 126 MHz)

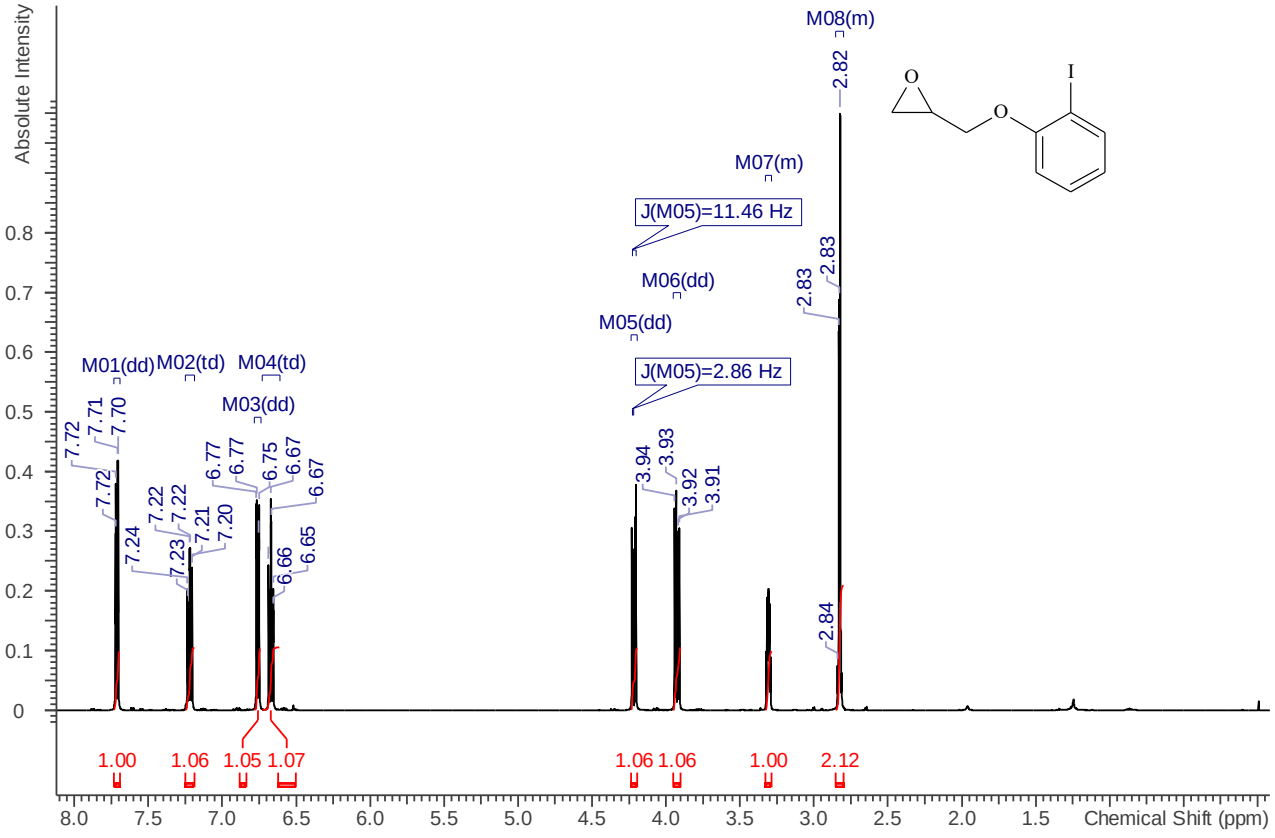


2-((2-Iodophenoxy)methyl)oxirane (**1d**)

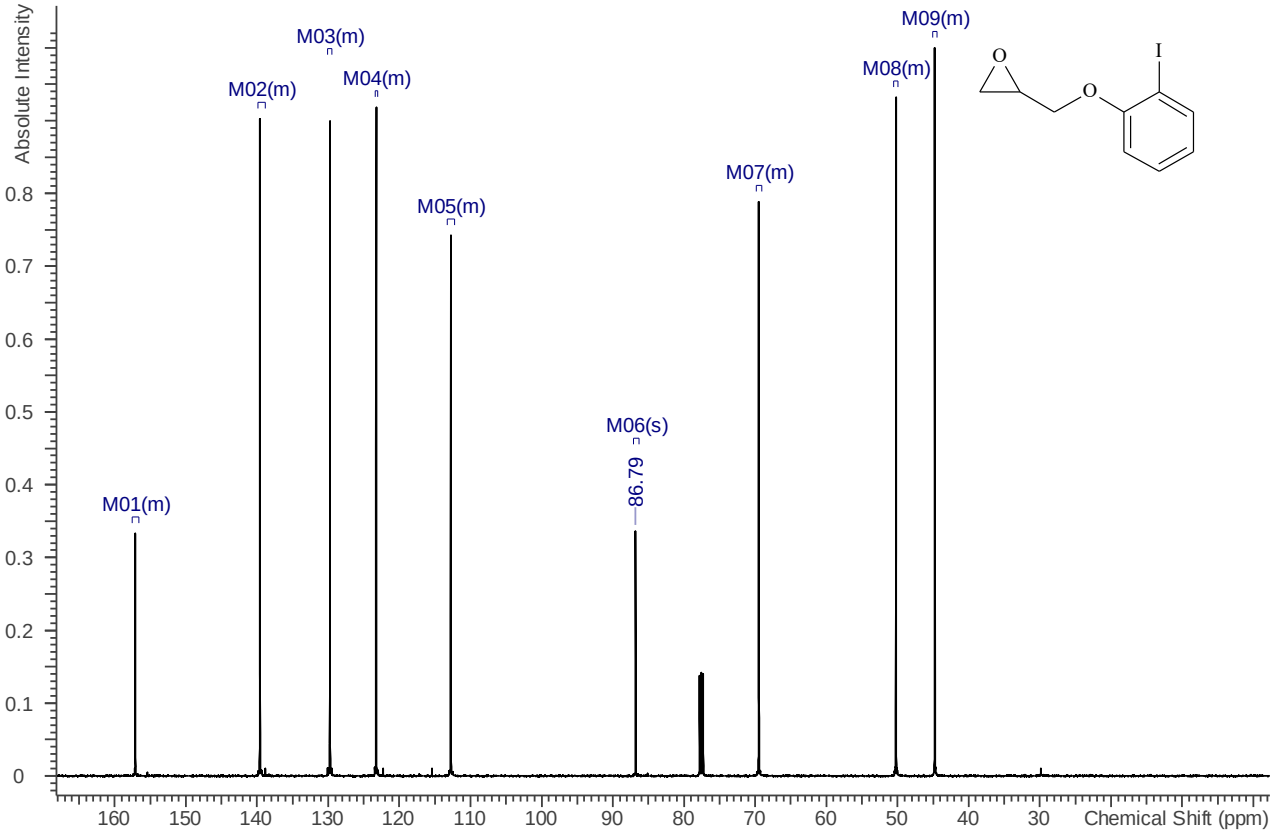
HRMS



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

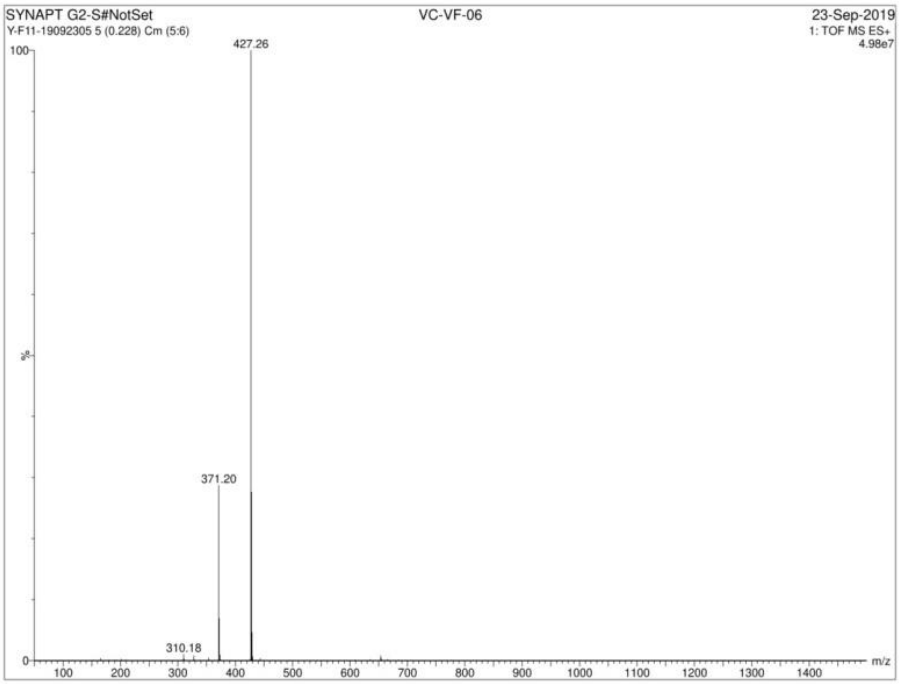


^{13}C-NMR ($CDCl_3$, 126 MHz)

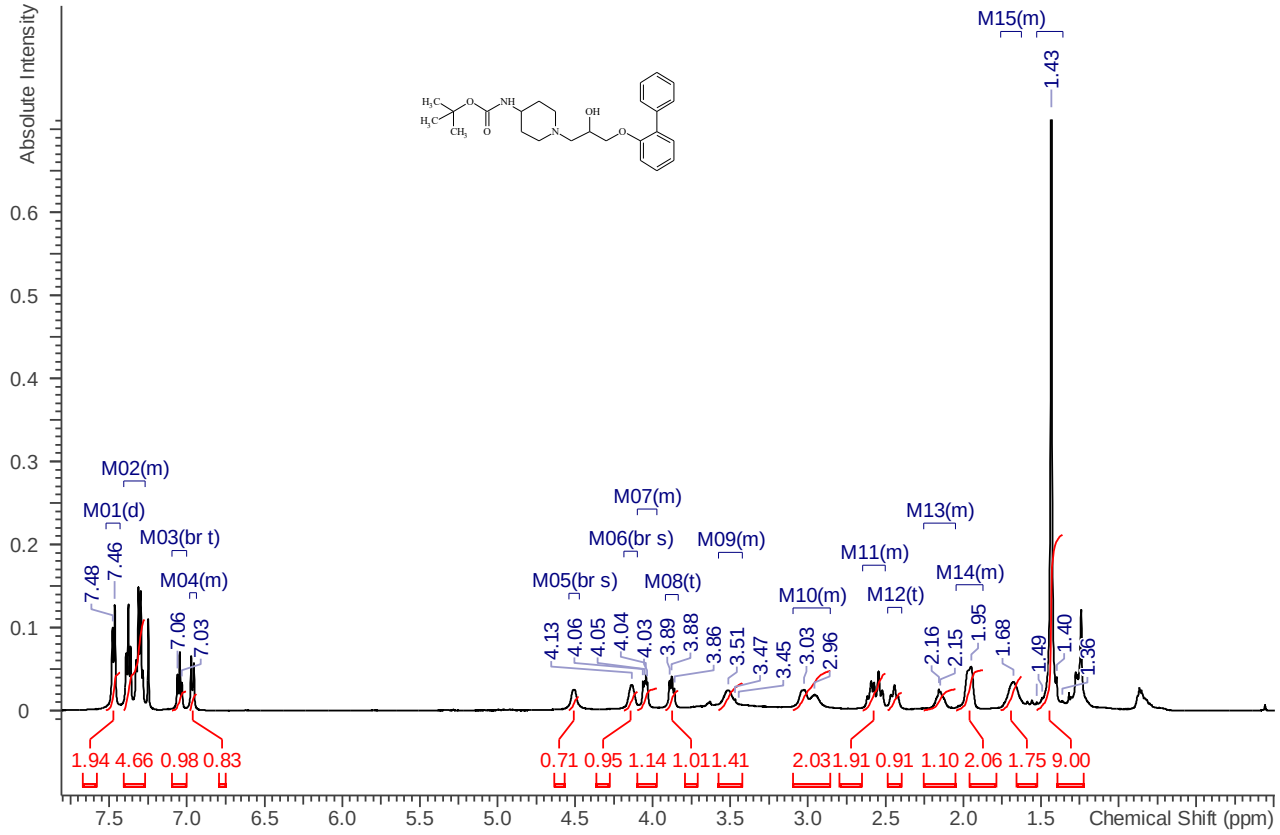


Tert-butyl (1-(3-([1,1'-biphenyl]-2-yloxy)-2-hydroxypropyl)piperidin-4-yl)carbamate (**3a**)

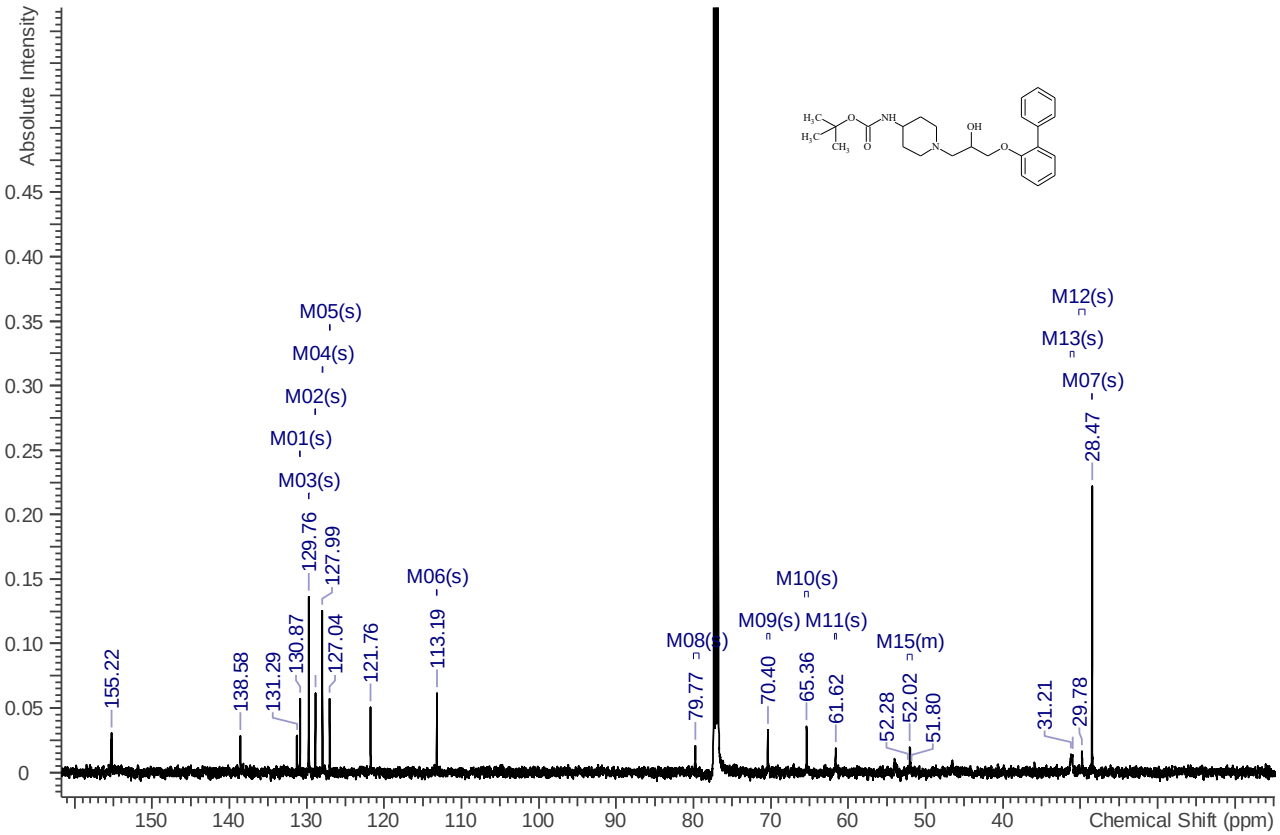
HRMS



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

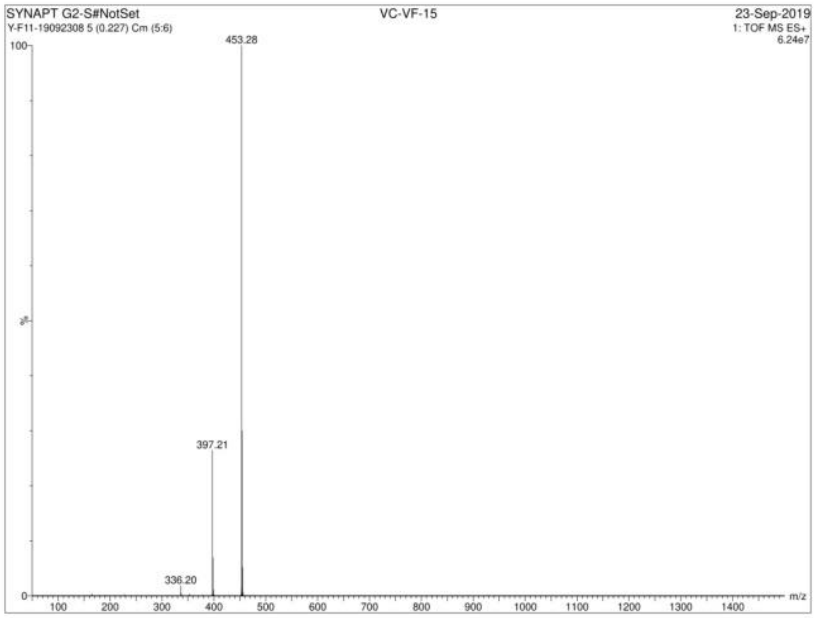


^{13}C-NMR ($CDCl_3$, 126 MHz)

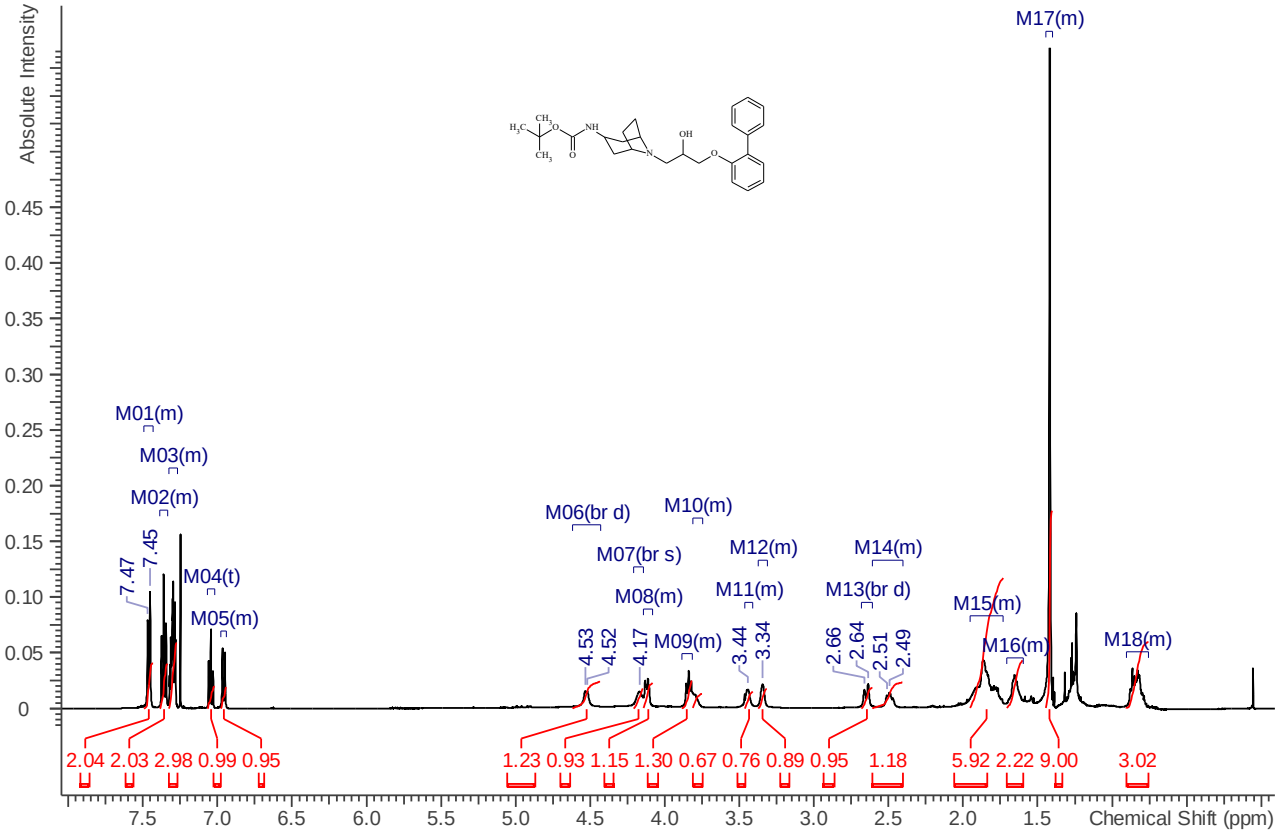


Tert-butyl ((1R,5S)-8-(3-([1,1'-biphenyl]-2-yloxy)-2-hydroxypropyl)-8-azabicyclo[3.2.1]octan-3-yl)carbamate (**3b**)

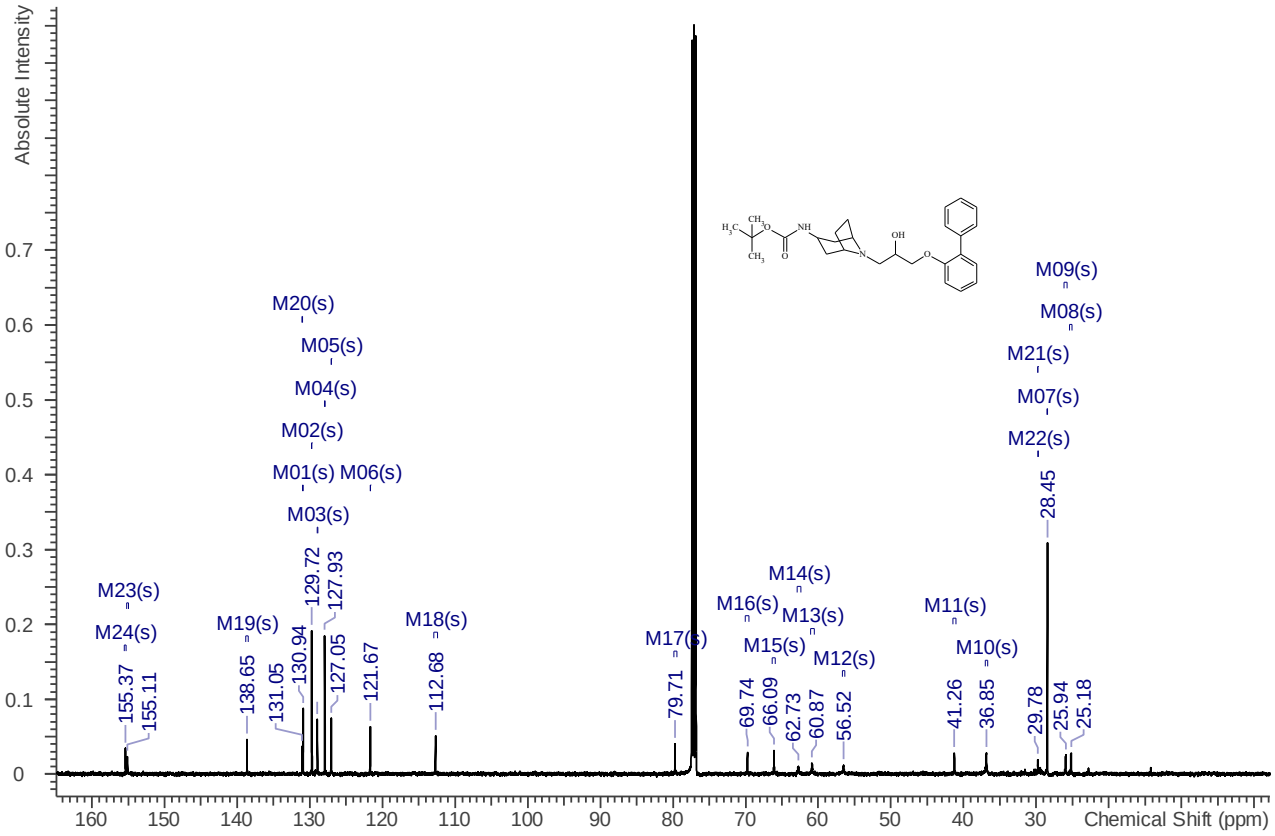
HRMS



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

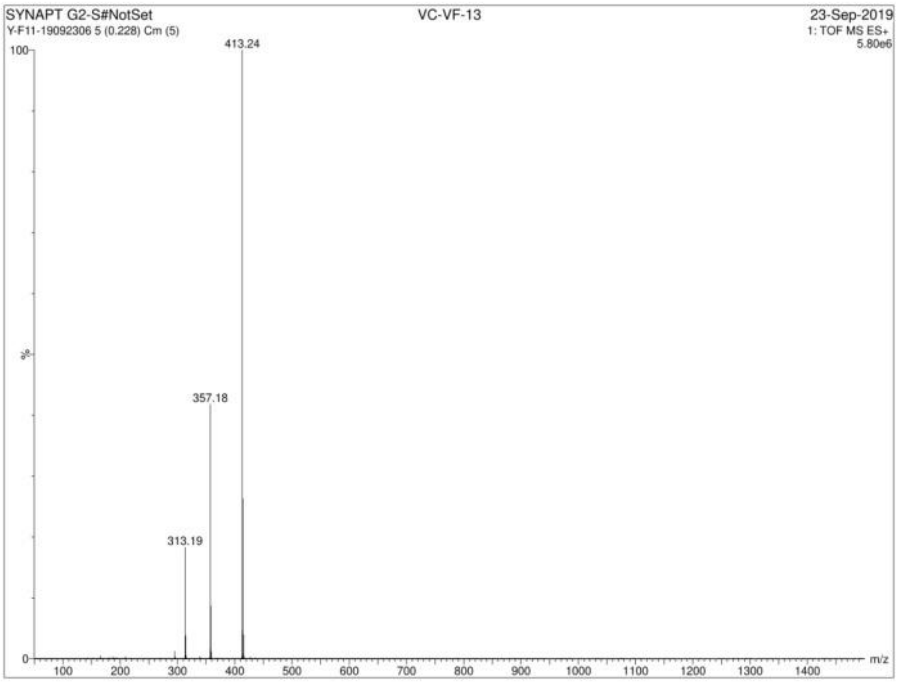


^{13}C-NMR ($CDCl_3$, 126 MHz)

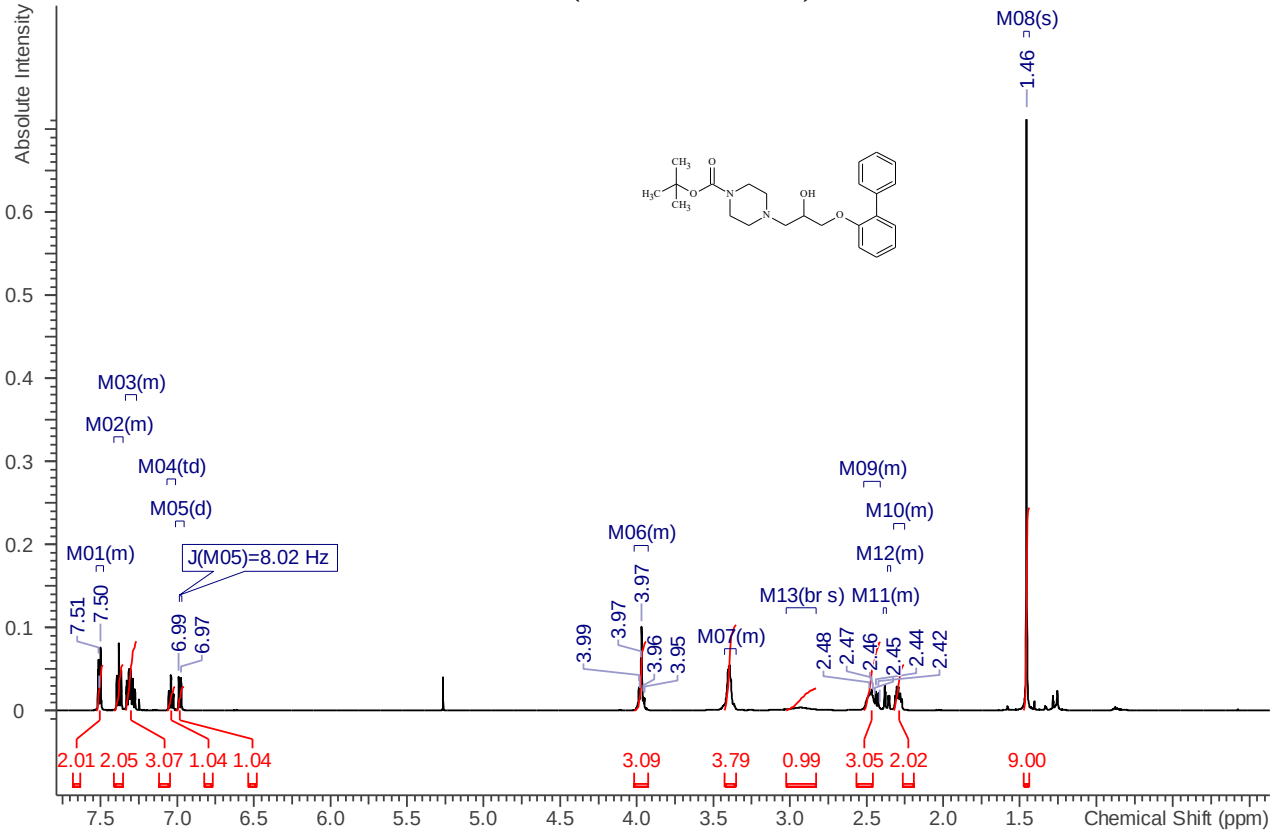


Tert-butyl 4-(3-([1,1'-biphenyl]-2-yloxy)-2-hydroxypropyl)piperazine-1-carboxylate (**3c**)

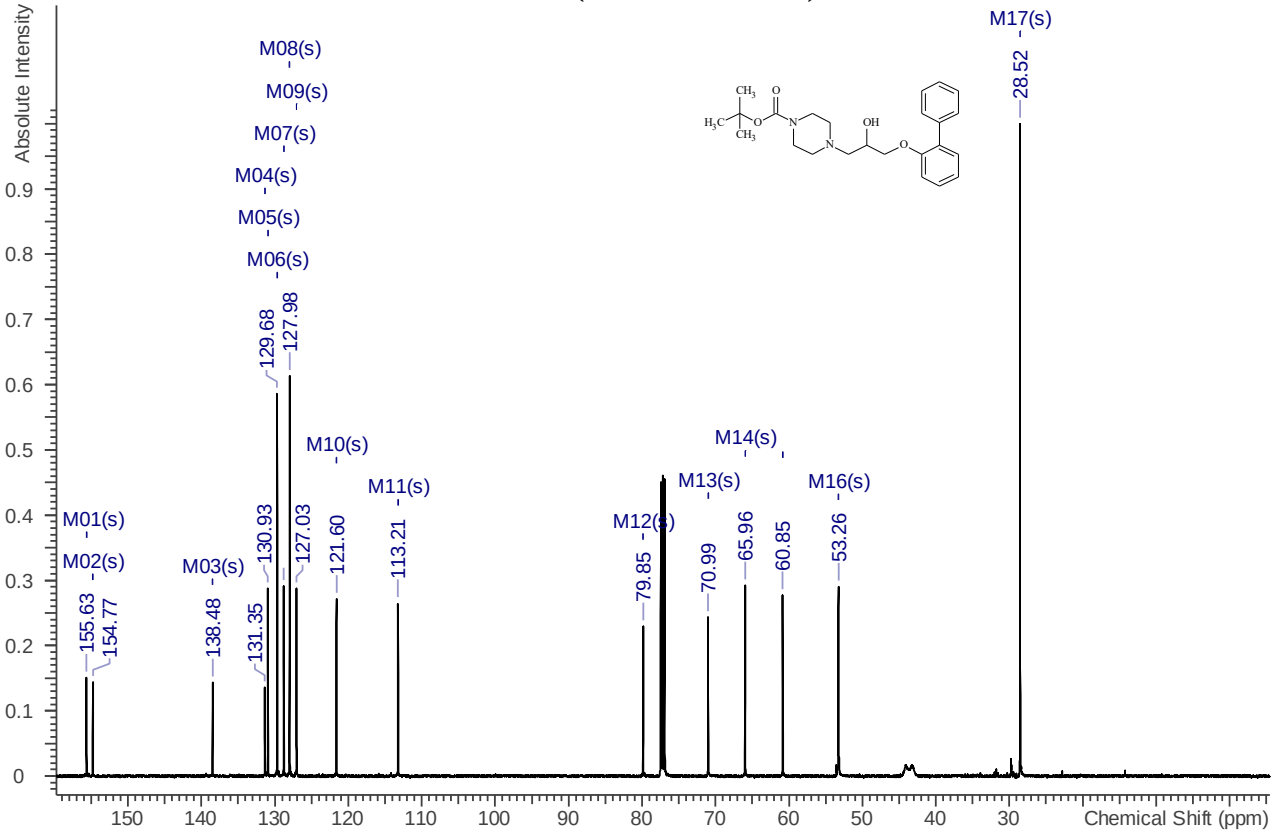
HRMS



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

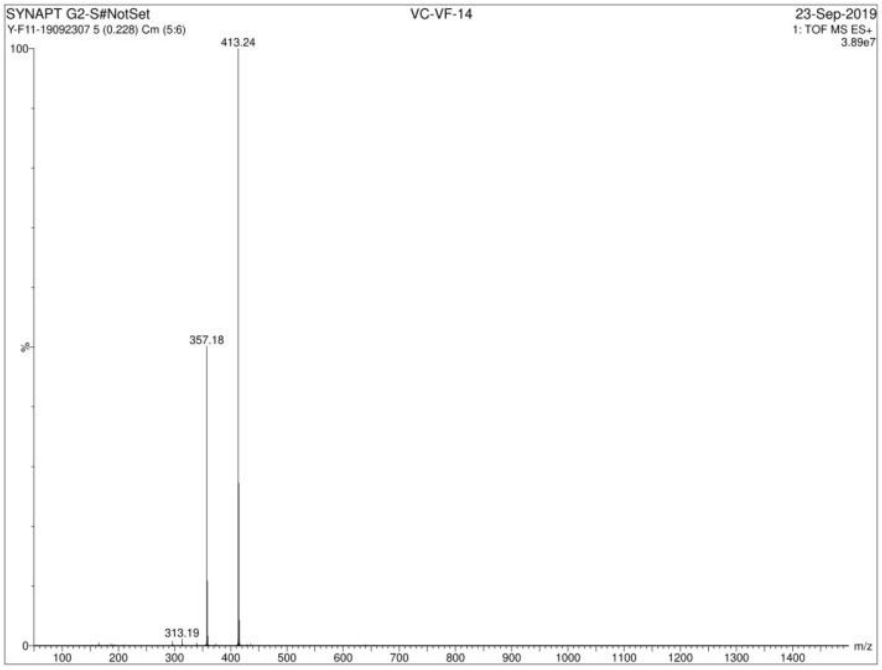


^{13}C-NMR ($CDCl_3$, 126 MHz)

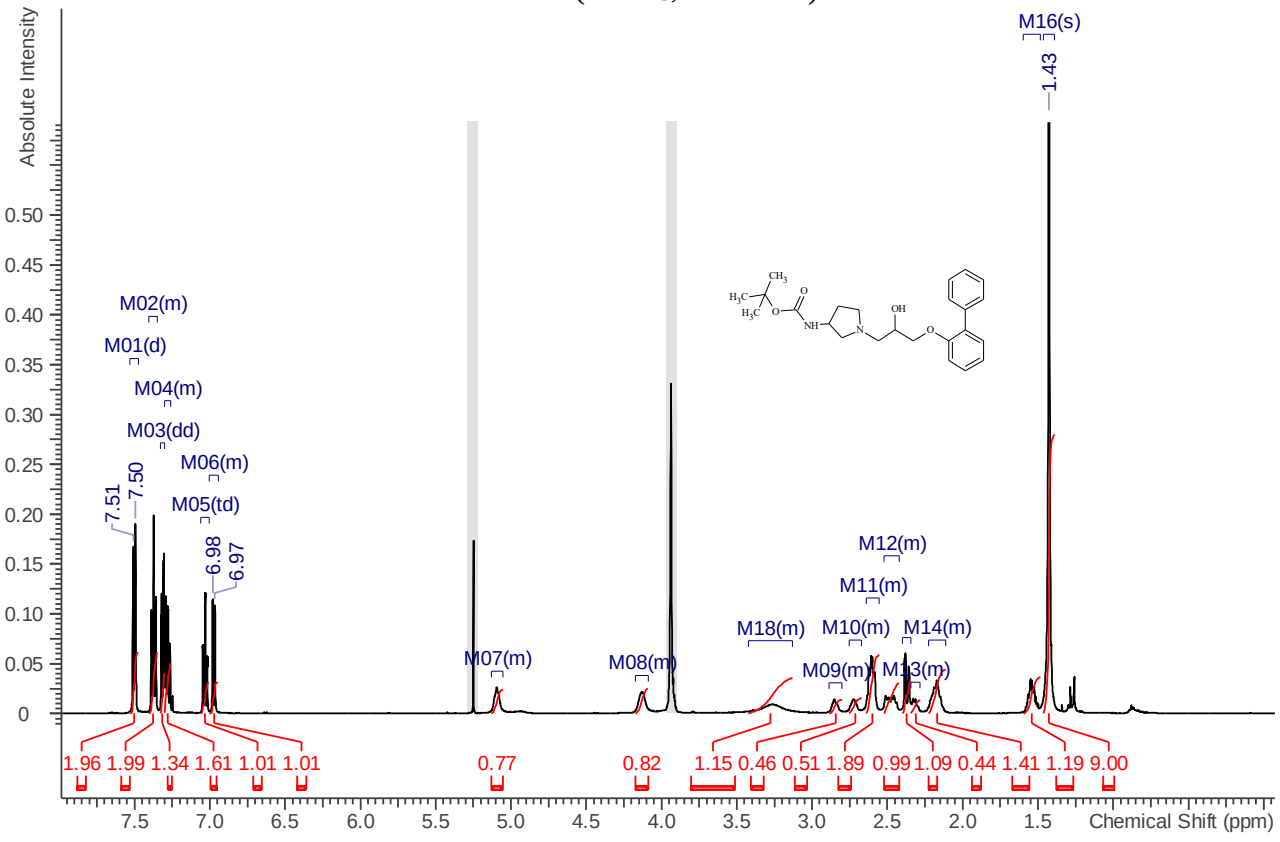


Tert-butyl (1-(3-([1,1'-biphenyl]-2-yloxy)-2-hydroxypropyl)pyrrolidin-3-yl)carbamate (**3d**)

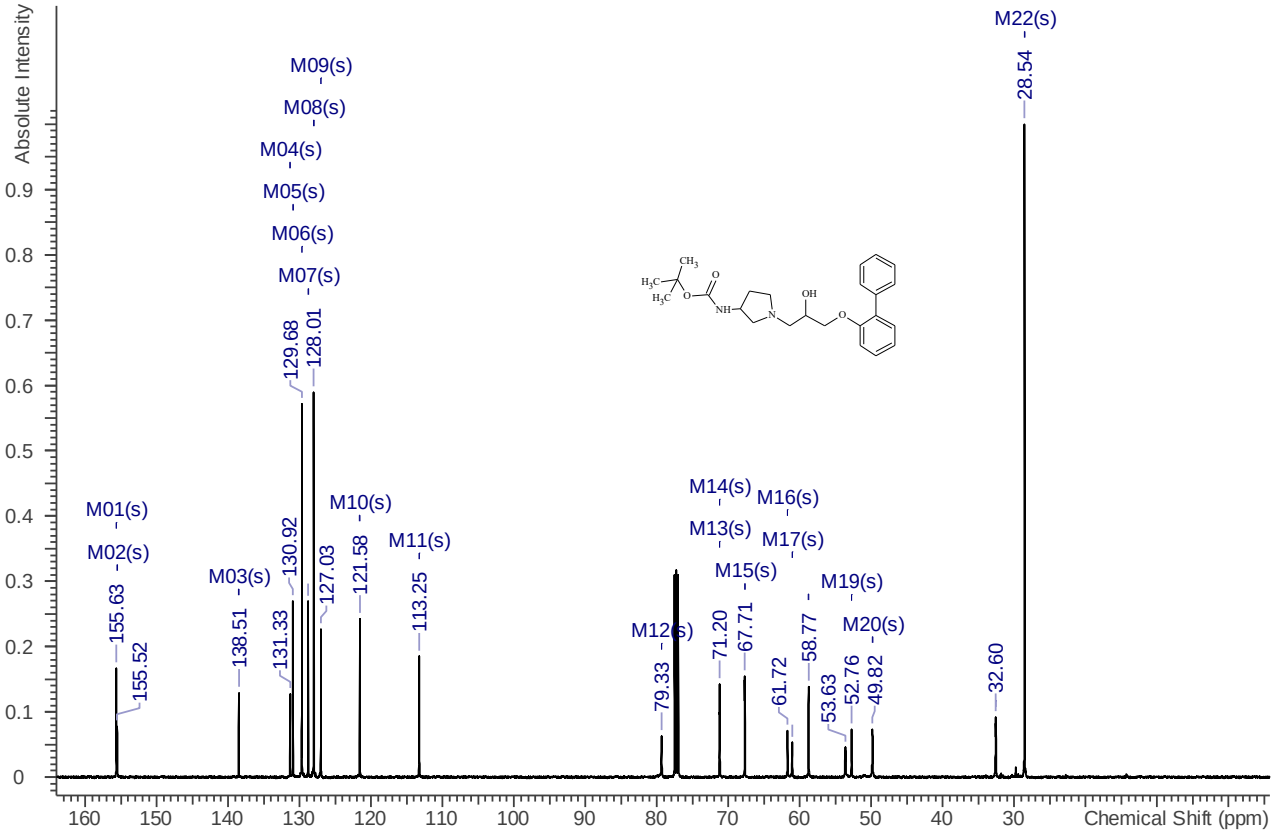
HRMS



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

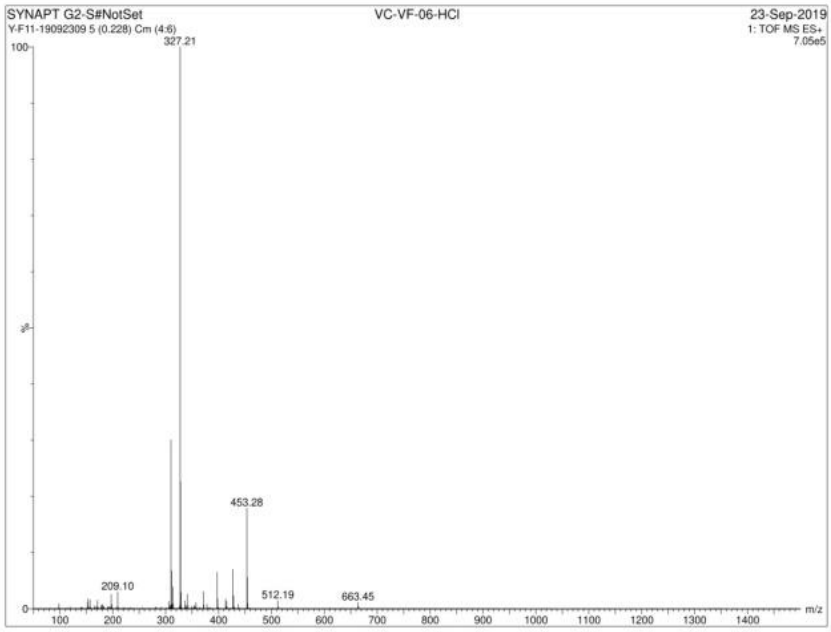


^{13}C-NMR ($CDCl_3$, 126 MHz)



1-([1,1'-Biphenyl]-2-yloxy)-3-(4-aminopiperidin-1-yl)propan-2-ol (**4**)

HRMS



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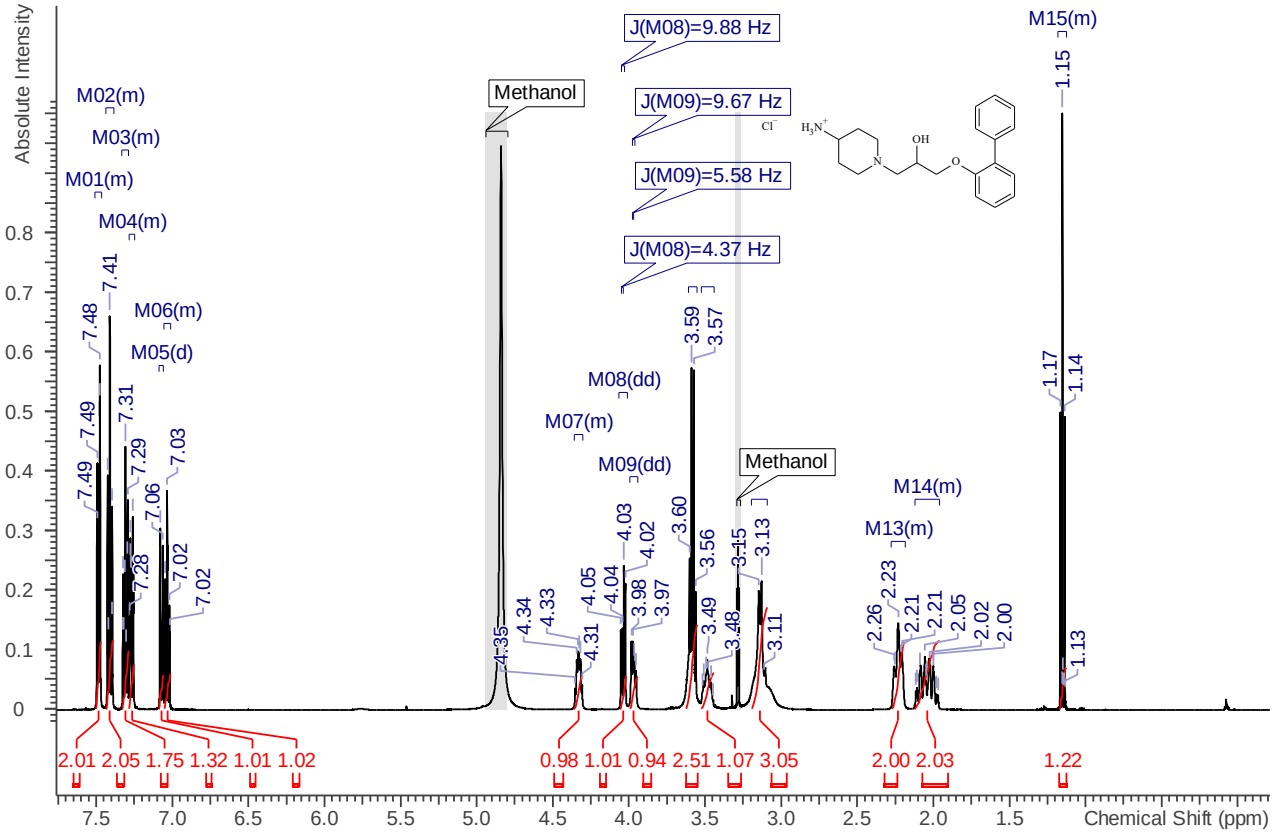
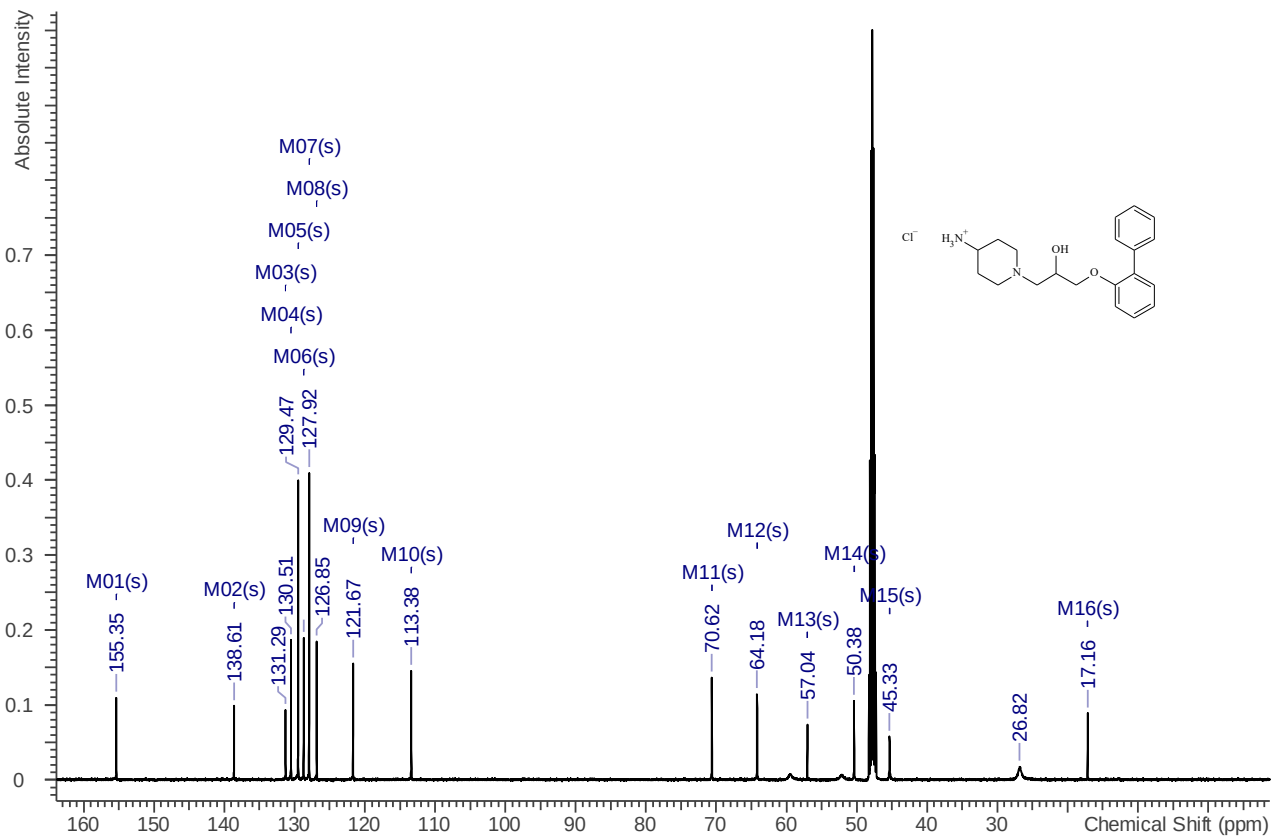
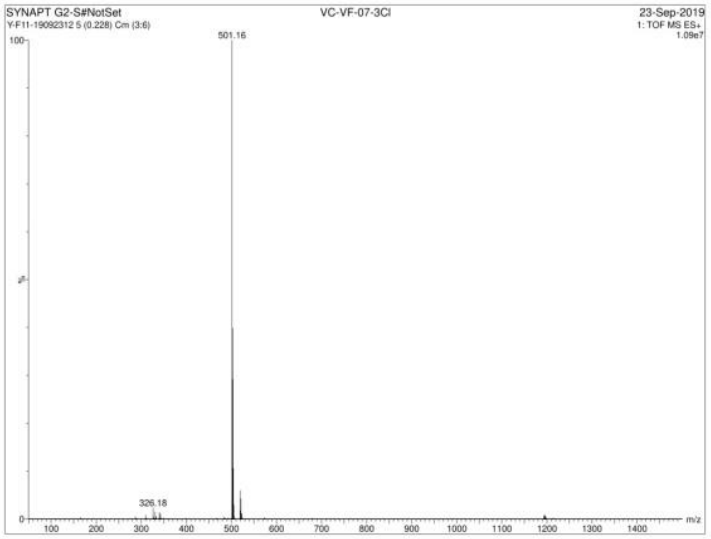


^{13}C-NMR ($CDCl_3$, 126 MHz)

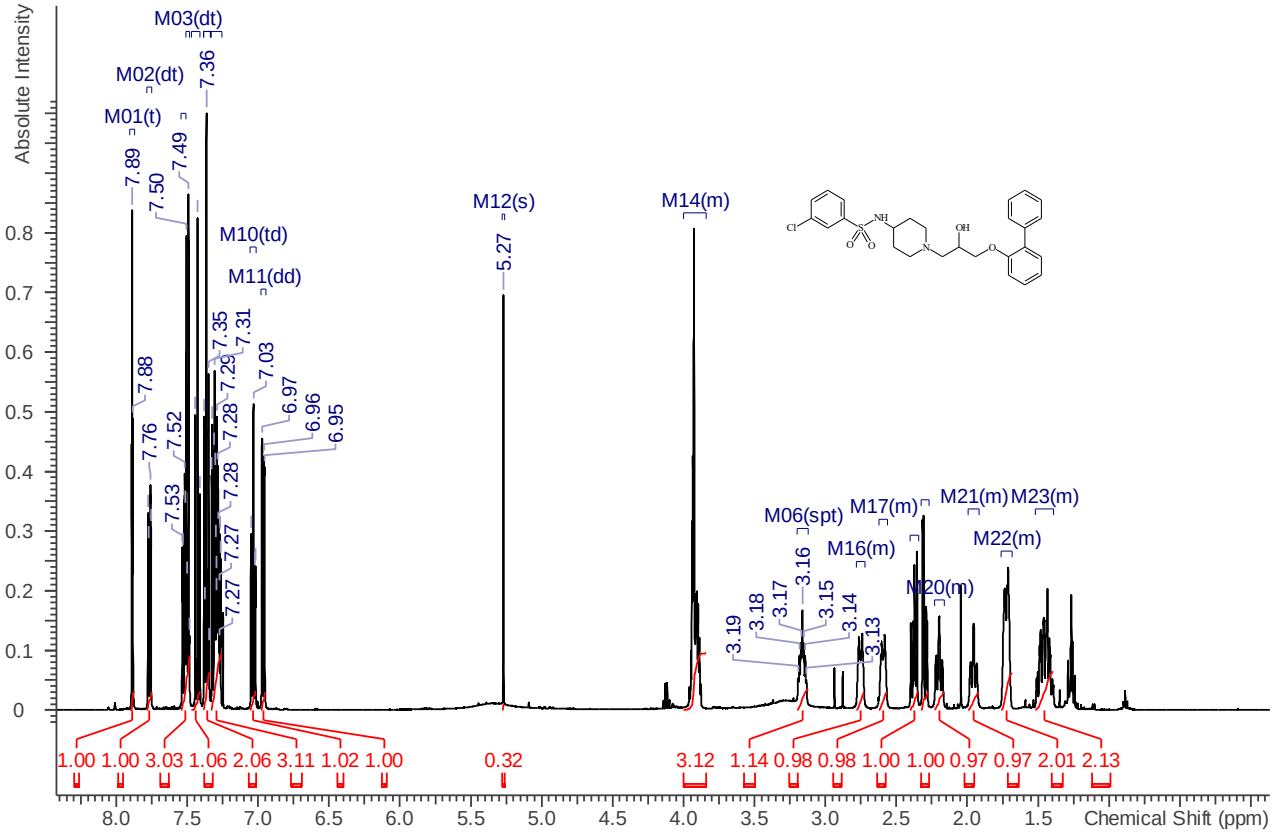


3-Chloro-N-(1-(3-([1,1'-biphenyl]-2-yloxy)-2-hydroxypropyl)piperidin-4-yl)-benzene sulfonamide (**5a**)

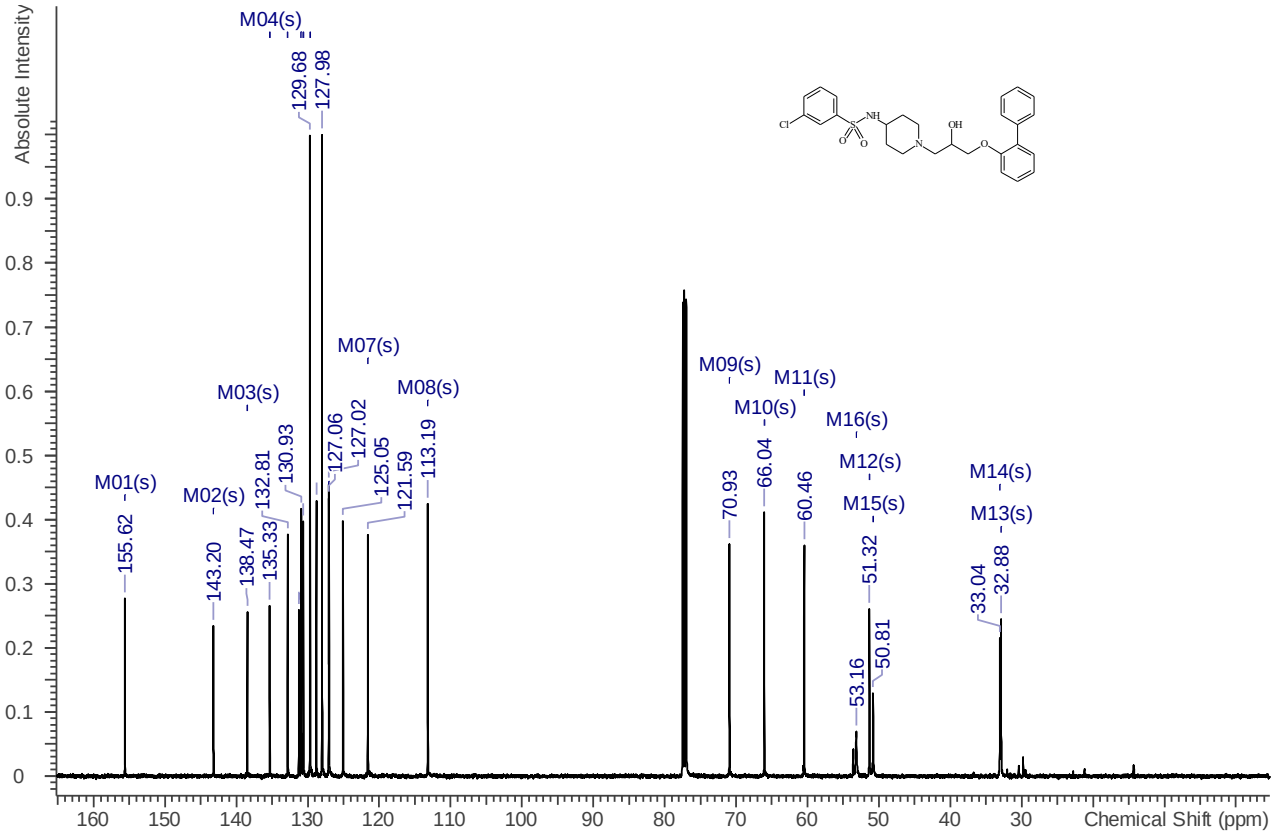
HRMS



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

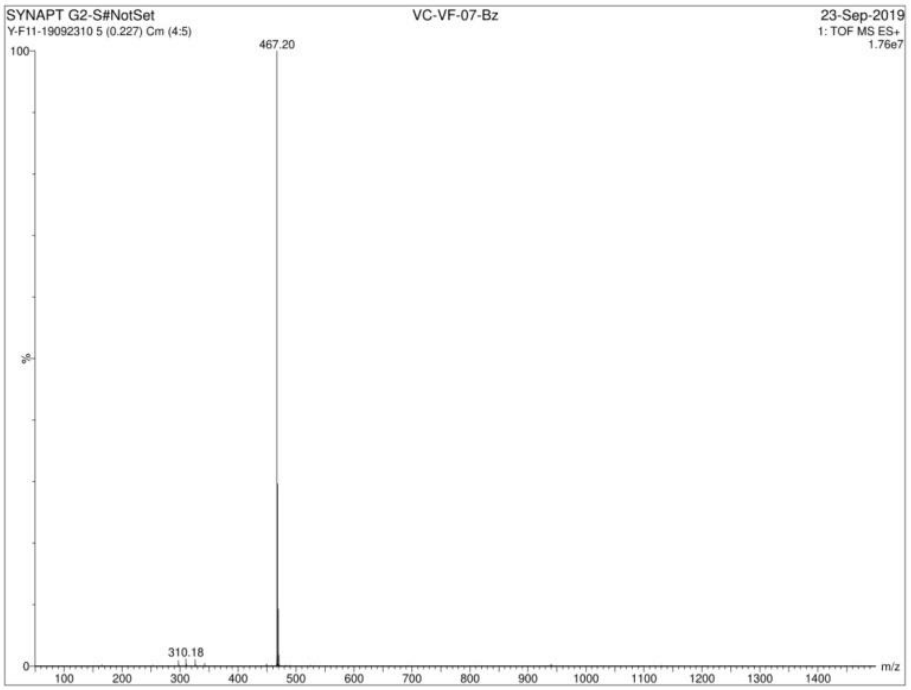


^{13}C-NMR ($CDCl_3$, 126 MHz)

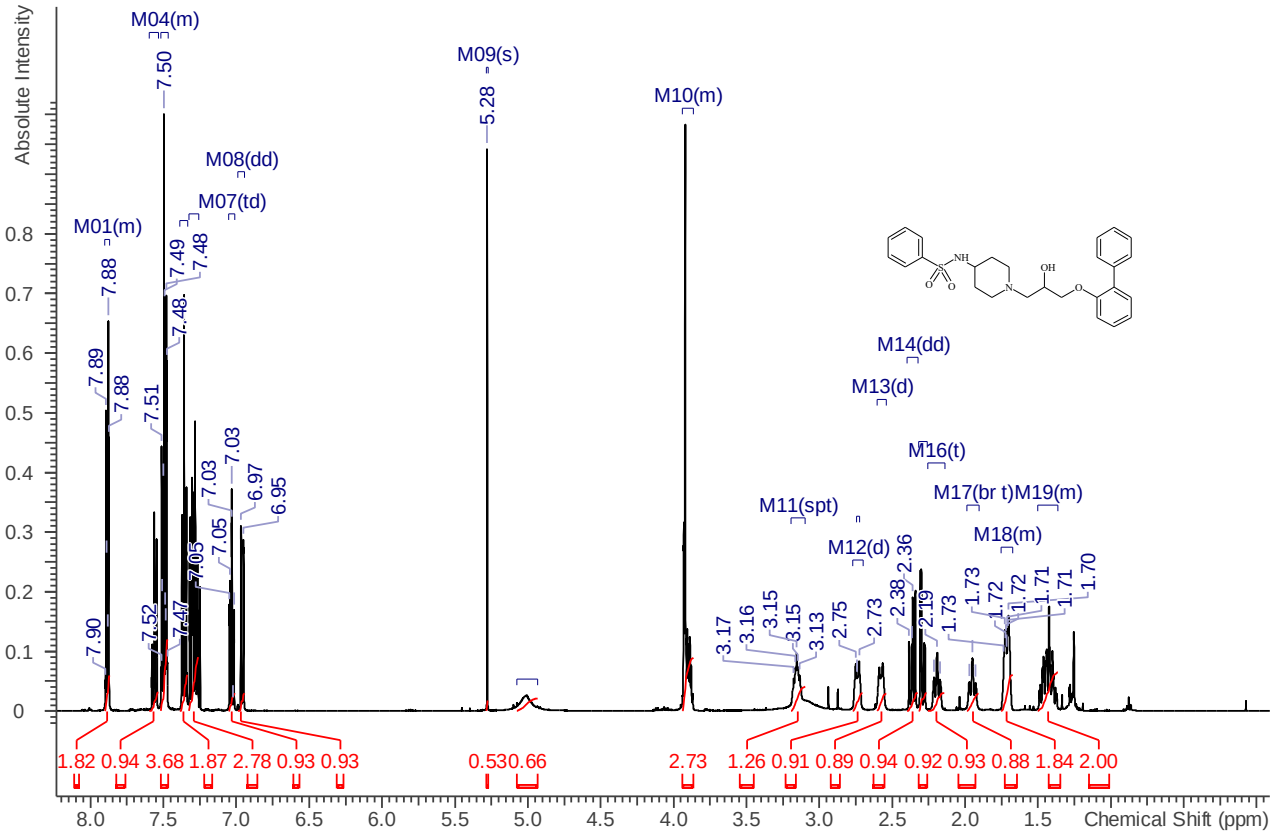


N-(1-(3-([1,1'-Biphenyl]-2-yloxy)-2-hydroxypropyl)piperidin-4-yl)benzenesulfonamide (**5b**)

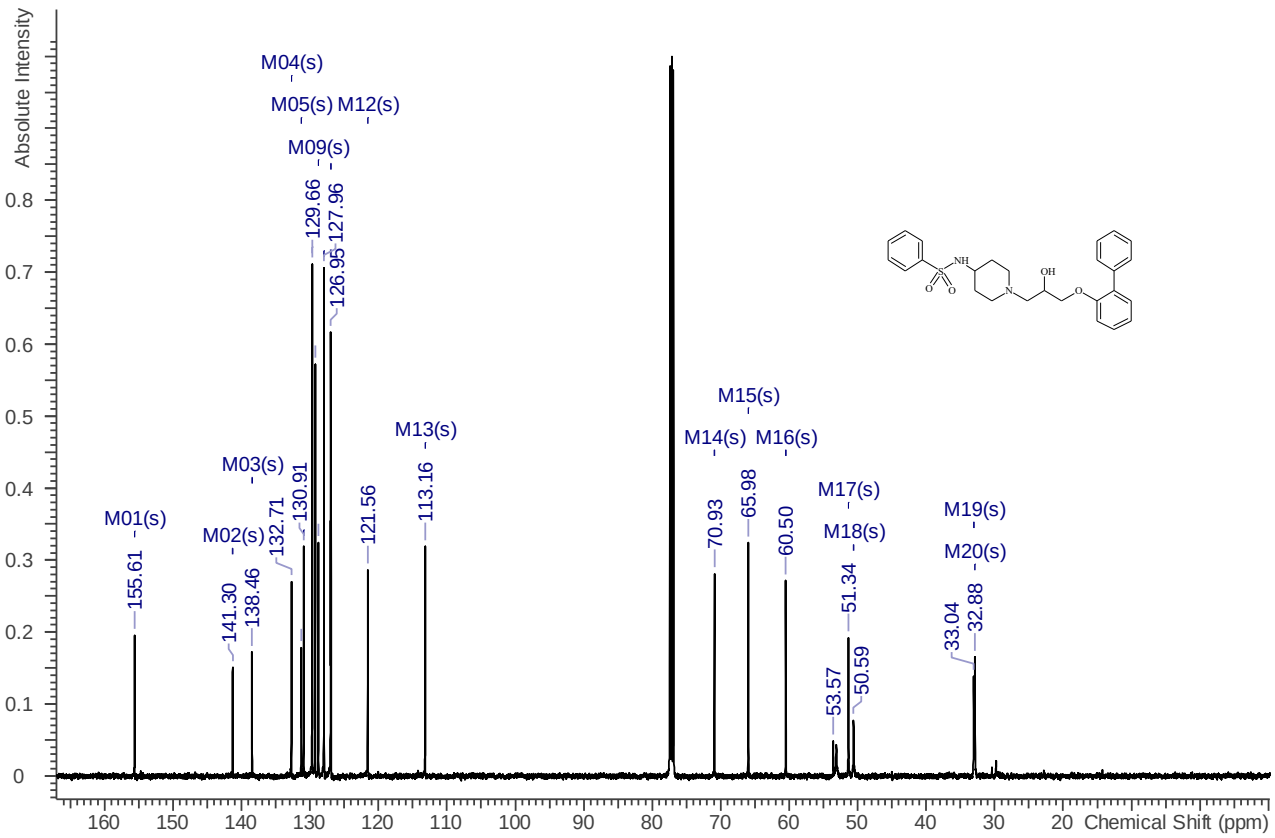
HRMS



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

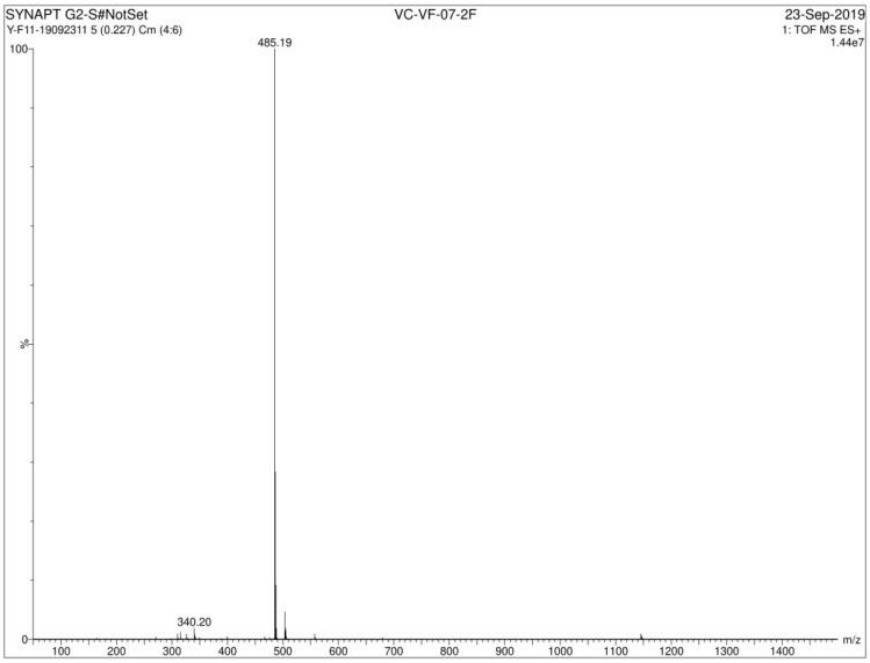


^{13}C-NMR ($CDCl_3$, 126 MHz)

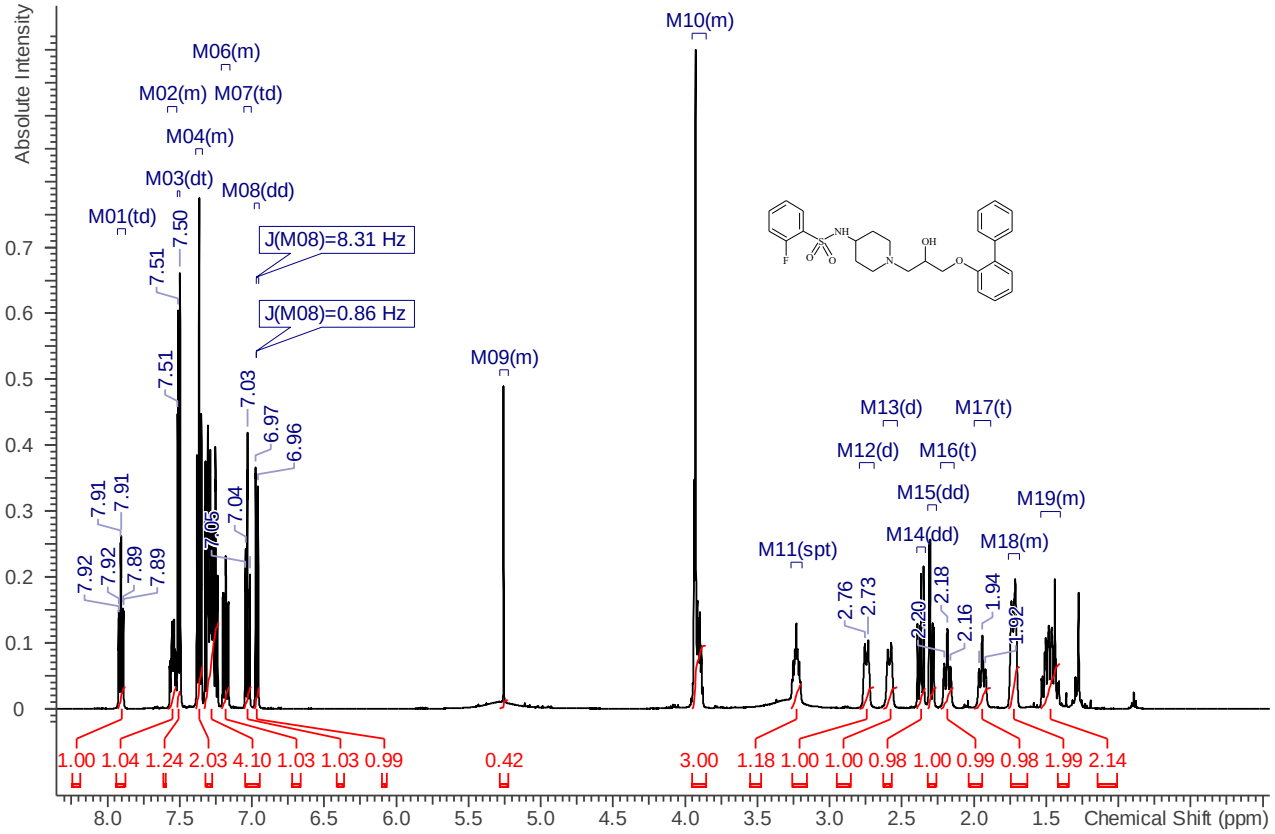


2-Fluoro-N-(1-(3-([1,1'-biphenyl]-2-yloxy)-2-hydroxypropyl)piperidin-4-yl)-benzene sulfonamide (**5c**)

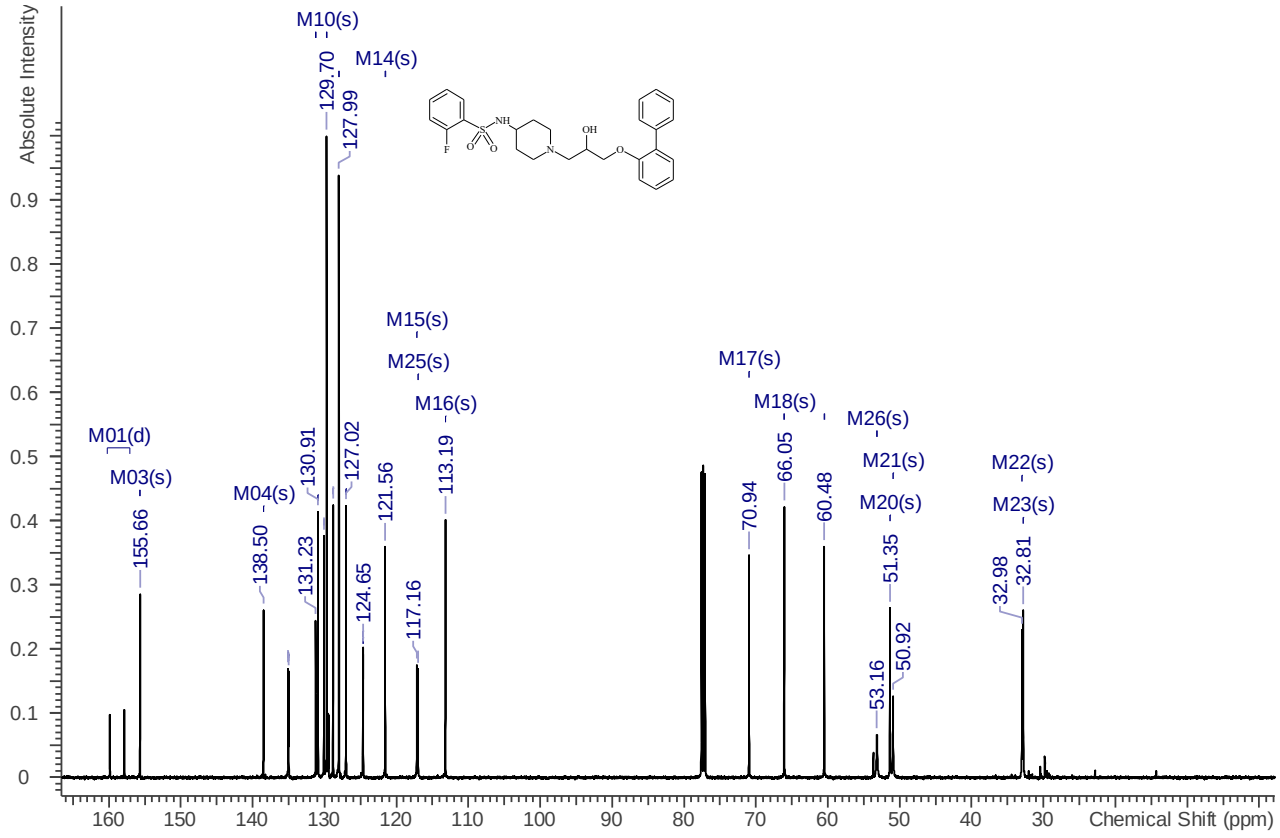
HRMS



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

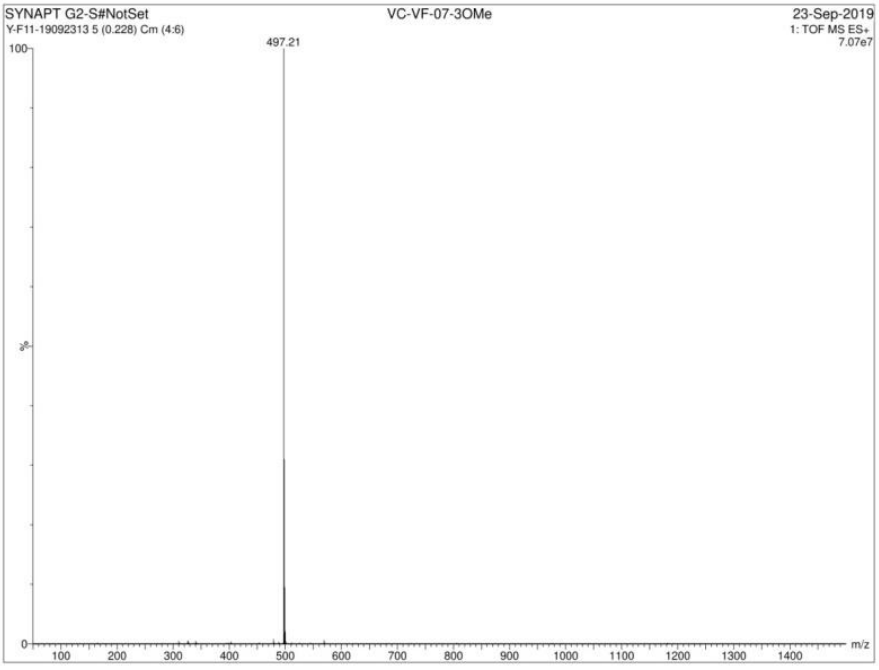


^{13}C-NMR ($CDCl_3$, 126 MHz)

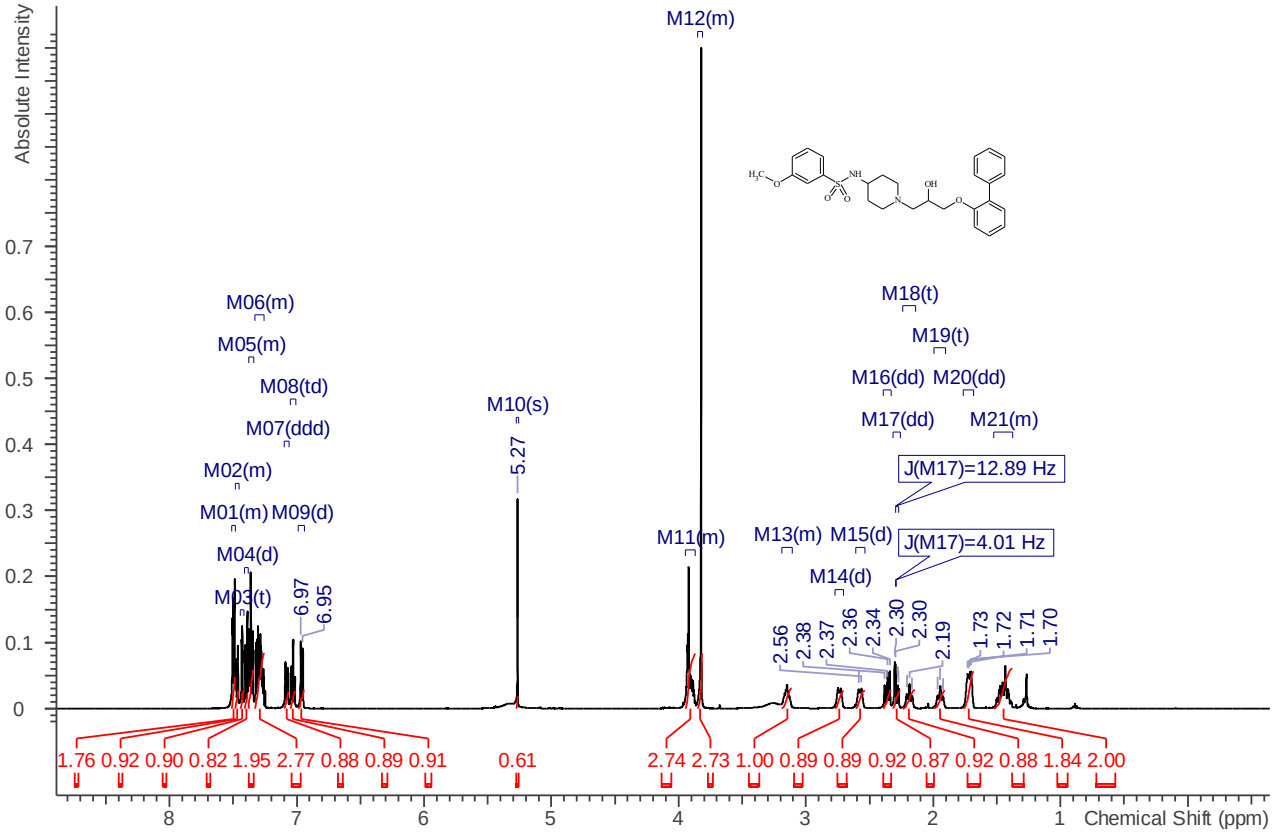


3-Methoxy-N-(1-(3-([1,1'-biphenyl]-2-yloxy)-2-hydroxypropyl)piperidin-4-yl)-benzene sulfonamide (**5d**)

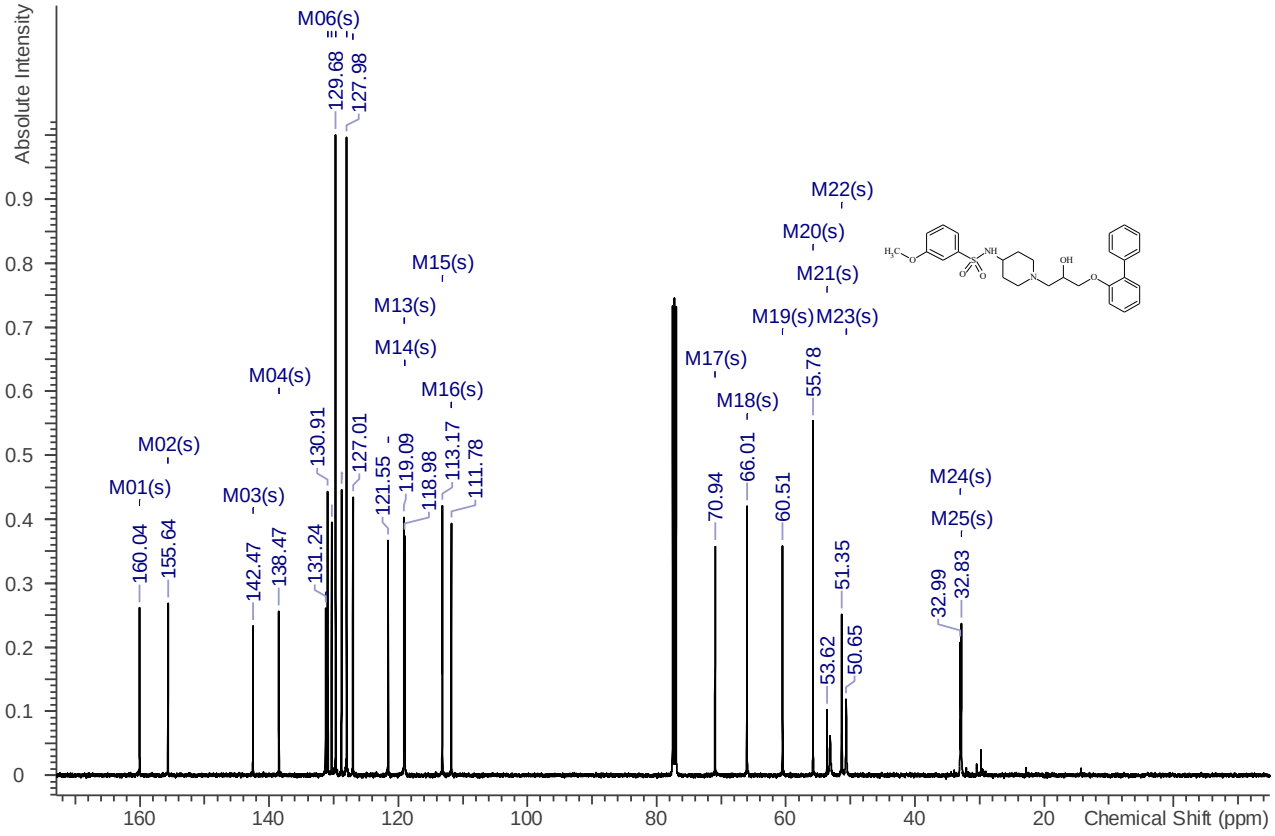
HRMS



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

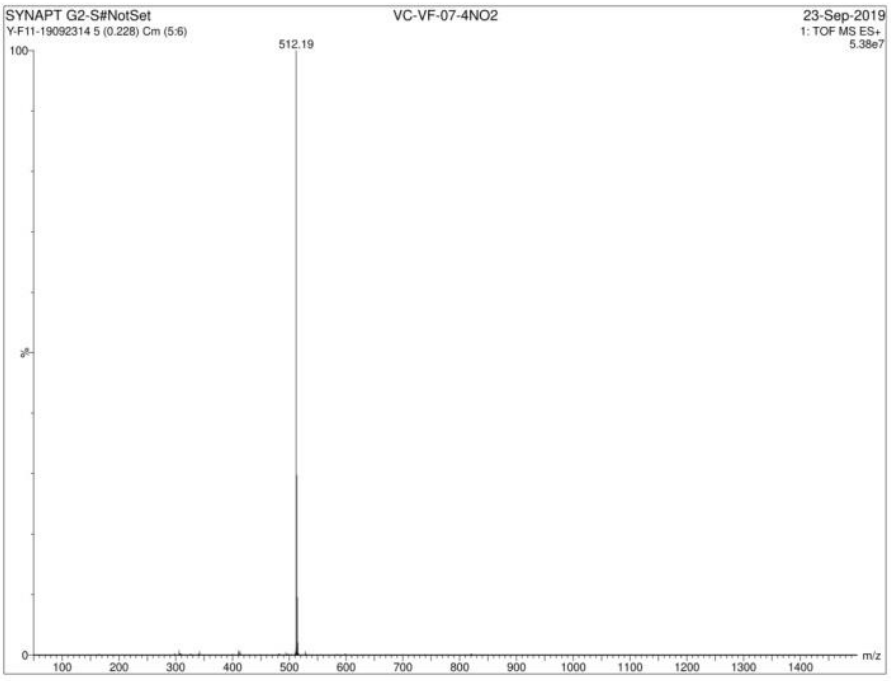


^{13}C-NMR ($CDCl_3$, 126 MHz)

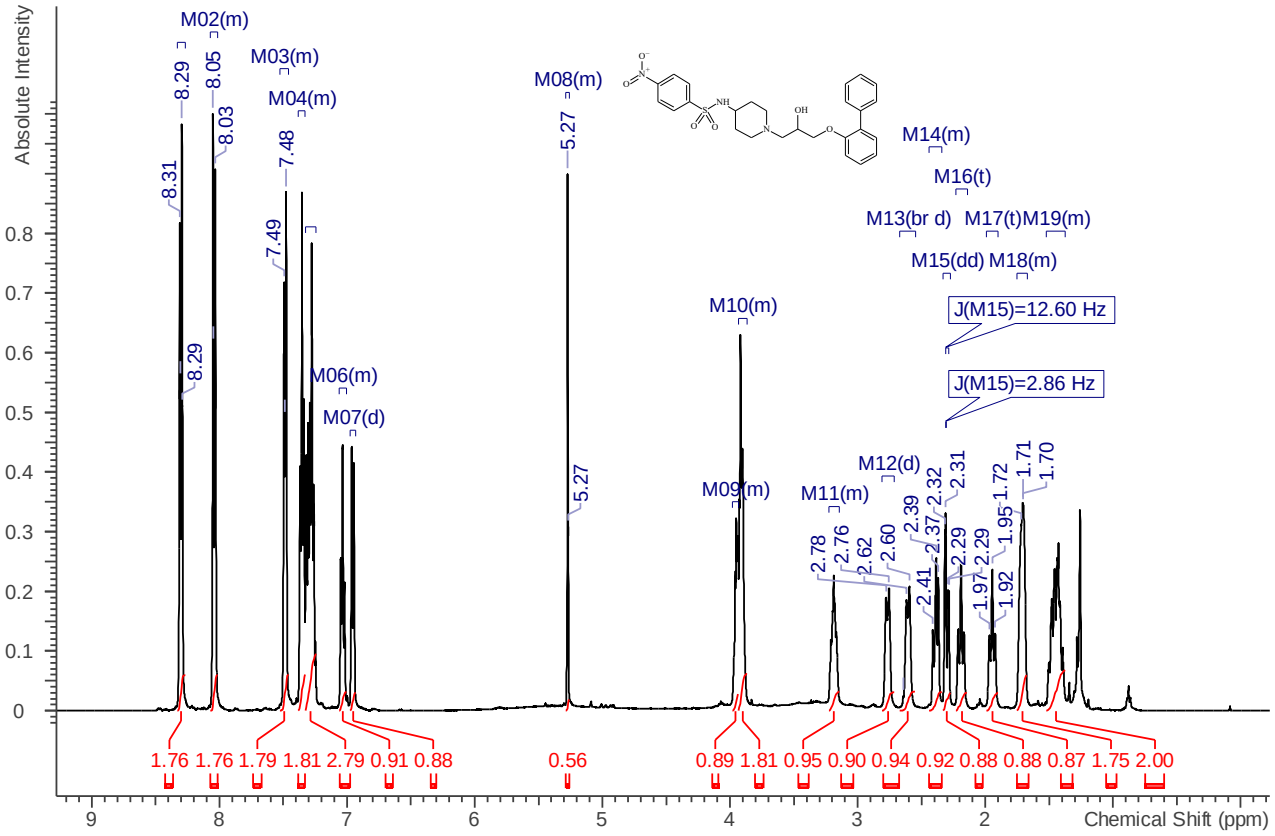


4-Nitro-N-(1-(3-([1,1'-biphenyl]-2-yloxy)-2-hydroxypropyl)piperidin-4-yl)-benzene sulfonamide (**5e**)

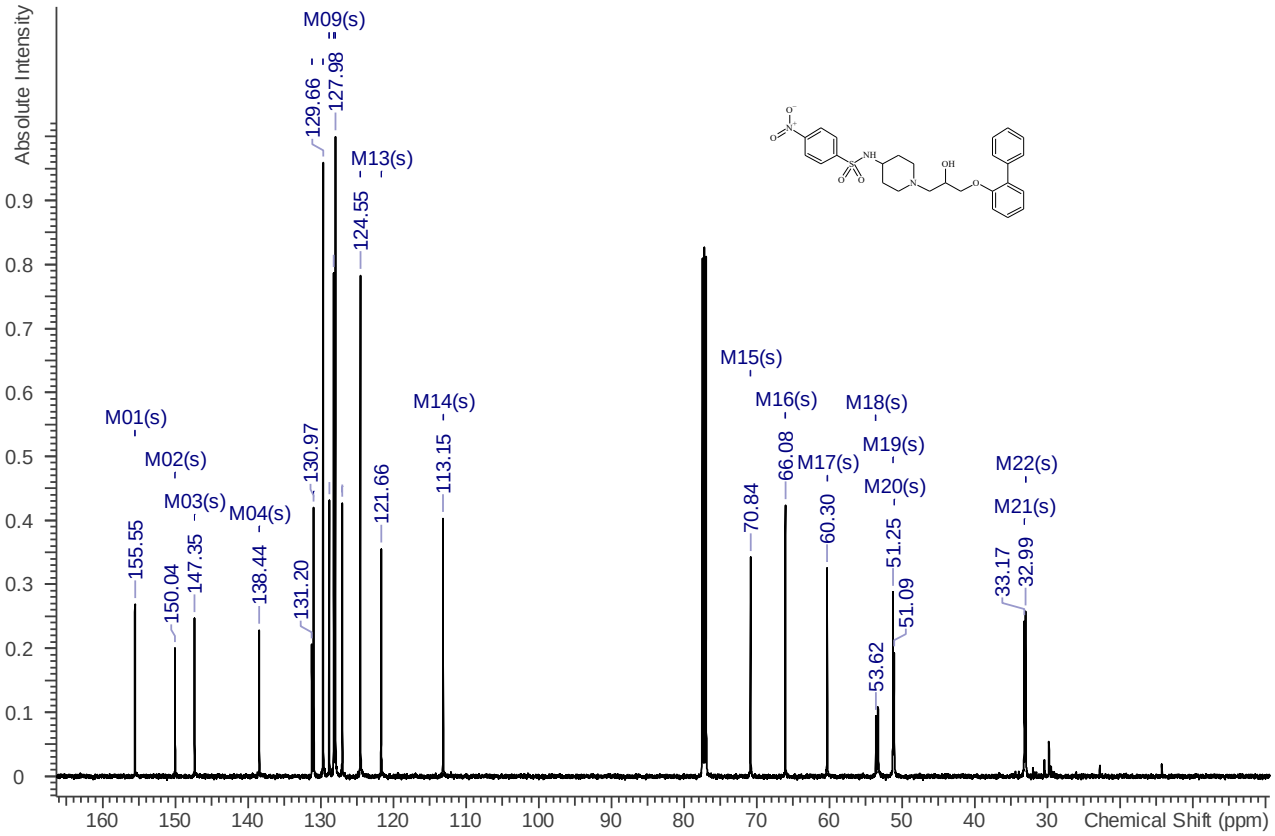
HRMS



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



^{13}C-NMR ($CDCl_3$, 126 MHz)



IV. References

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