Supporting Information

An Efficient, Safe, and Scalable Method for the Preparation of D- and L-Penicillamines

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I. Experimental section:

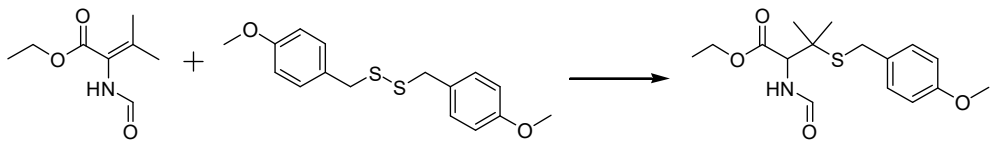
Preparation of 1-methoxy-4-({[(4-methoxyphenyl)methyl]disulfanyl}methyl)benzene (21):[1,2]

A mixture consisting of finely powdered $Na_2S_2O_3.5H_2O$ (0.20 mol, 50.0 g) and 4-Methoxybenzyl chloride (0.21 mol, 33.12 g) in wet DMSO (200 mL DMSO + 20 mL H_2O) was stirred at a temperature of 60-70 °C. The progress of the reaction was monitored by litmus paper. After stirring for 8h, the color of litmus paper changed from yellow to red. Then the reaction was worked up by adding H_2O (500 mL) and extracted with 1:1 n-hexane/EtOAc (3× 500 mL). The product was purified by recrystallization from n-hexane to afford **21** in 19.5 g, 60% yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.17 (d, J = 8.6 Hz, 4H), 6.86 (d, J = 8.6 Hz, 4H), 3.80 (s, 6H), 3.59 (s, 4H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.1, 130.6, 129.5, 113.9, 55.4, 42.8.

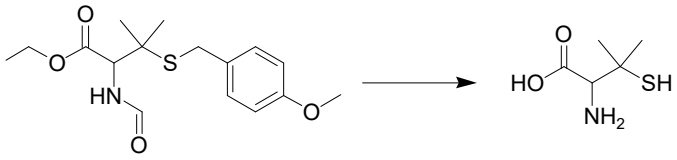
<u>Scale up experiments:</u>

Synthesis of ethyl 2-formamido-3-{[(4-methoxyphenyl)methyl]sulfanyl}-3-methylbutanoate (22):



A mixture of of Ethyl 2-(formylamino)-3-methyl-2-butenoate **18** (100 g, 0.58 mol), 4-methoxybenzyl disulfide **21** (89 g, 0.29 mol), Roganlite (360 g, 2.34 mol), and Cs_2CO_3 (285 g, 0.87 mol) in DMF (1.0 L) was stirred at 65 °C for 4 hours followed by room temperature for 12 hours. Then the reaction was worked up by adding H_2O (3.0 L) and extracted with EtOAc (5.0 L). The organic phase was dried over anhydrous sodium sulfate, filtered and the solvent was evaporated under vacuum. The product was purified by recrystallization from n-hexane to afford desired product **22** as a white solid (180 g, 94% yield).

Synthesis of D,L-penicillamine (D,L-1):



22 **D,L-1**

10N HCl (895 mL) was added to ethyl 2-formamido-3-{[(4-methoxyphenyl)methyl]sulfanyl}-3-methylbutanoate **22** (179 g, 0.549 mol) and the reaction mixture was allowed to stir for 48 hours at 85 °C. Upon completion (TLC control, 20% Methanol in DCM), the reaction mass was concentrated under reduced pressure to get a brown syrup. The residue obtained was dissolved in isopropyl alcohol (358 mL) and again concentrated until no distillate observed. The residue was dissolved in methanol (537 mL), cooled the solution to 0 °C and adjusted to pH=6.9 using triethylamine (161 mL). The resulting reaction mixture was allowed to stir for 3 hours at 0 °C and the solid precipitate was collected by filtration and dried to afford **D,L-1** as an off-white solid (65 g, 79% yield).

Synthesis of D-penicillamine (D-1):

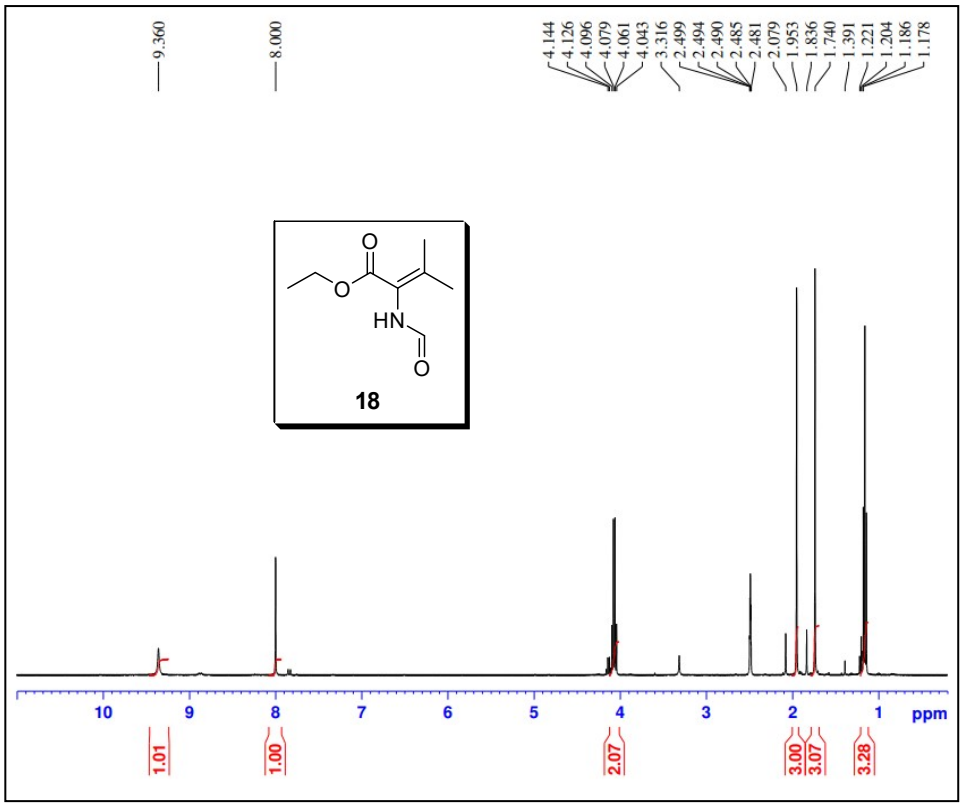
D,L-penicillamine **D,L-1** (32 g, 0.214 mol) was suspended in a mixture of acetic acid (96 mL) and methanol (192 mL), followed by slow addition of D-tartaric acid (48.3 g, 0.322 mol) under nitrogen. The reaction mixture was stirred for 3 hours at 40 °C. The reaction mass was cooled to room temperature and the precipitated salt was filtered. The crude salt was washed with methanol (32 mL) and dried. The salt was dissolved in methanol (205 mL) under nitrogen and adjusted to pH=6.9 using triethylamine (128 mL) and the reaction mass was stirred for 1 hour at room temperature. The resultant solid precipitate was filtered, washed with methanol and dried to afford **D-1** as a white solid (13.0 g, 81% yield).

Synthesis of L-penicillamine (L-1):

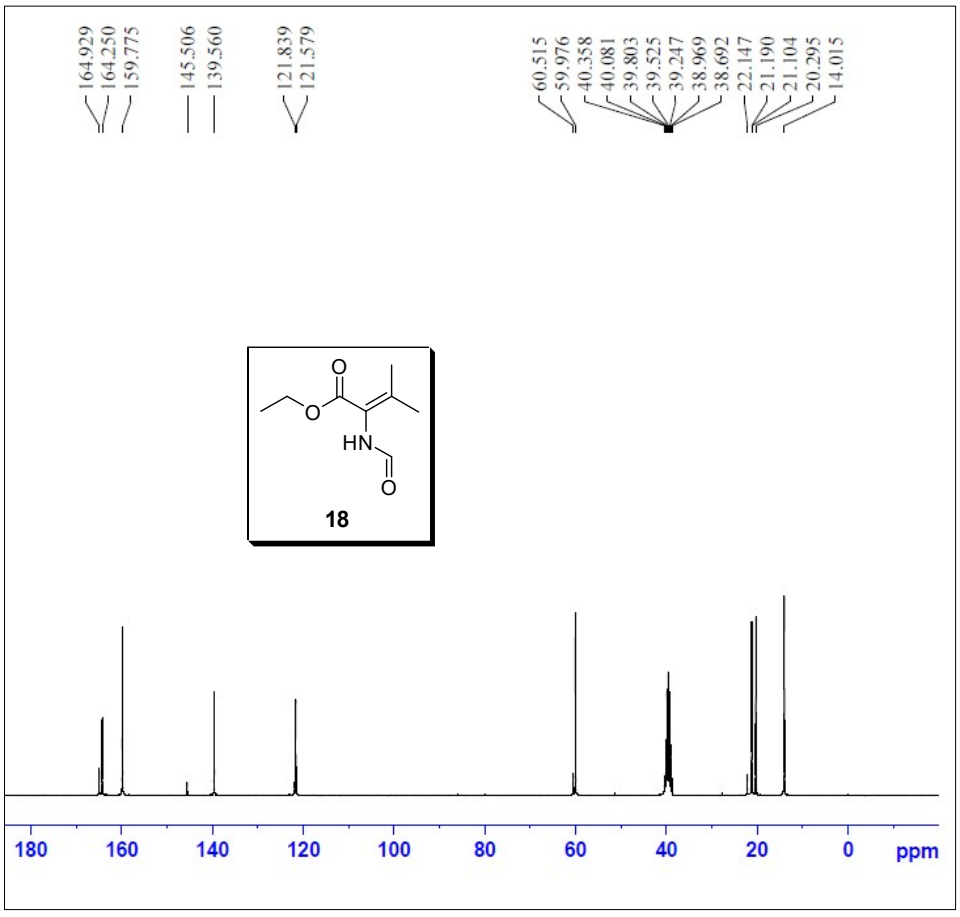
D,L-penicillamine **D,L-1** (32 g, 0.214 mol) was suspended in a mixture of acetic acid (96 mL) and methanol (192 mL), followed by slow addition of L-tartaric acid (48.3 g, 0.322 mol) under nitrogen. The reaction mixture was stirred for 3 hours at 40 °C. The reaction mass was cooled to room temperature and the precipitated salt was filtered. The crude salt was washed with methanol (32 mL) and dried. The salt was dissolved in methanol (205 mL) under nitrogen and adjusted to pH=6.9 using triethylamine (128 mL) and the reaction mass was stirred for 1 hour at room temperature. The resultant solid precipitate was filtered, washed with methanol and dried to afford **L-1** as a white solid (12.5 g, 78% yield).

II. 1H NMR, 13C NMR, LC-MS and FT-IR Spectra:

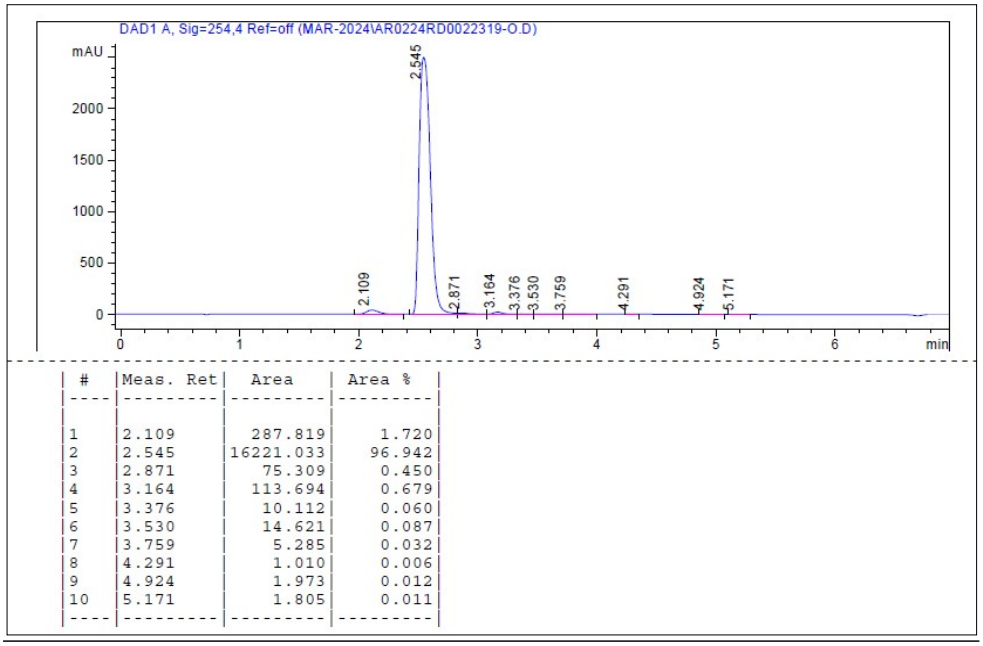
^{1}H-NMR of 18 (DMSO-d_6):



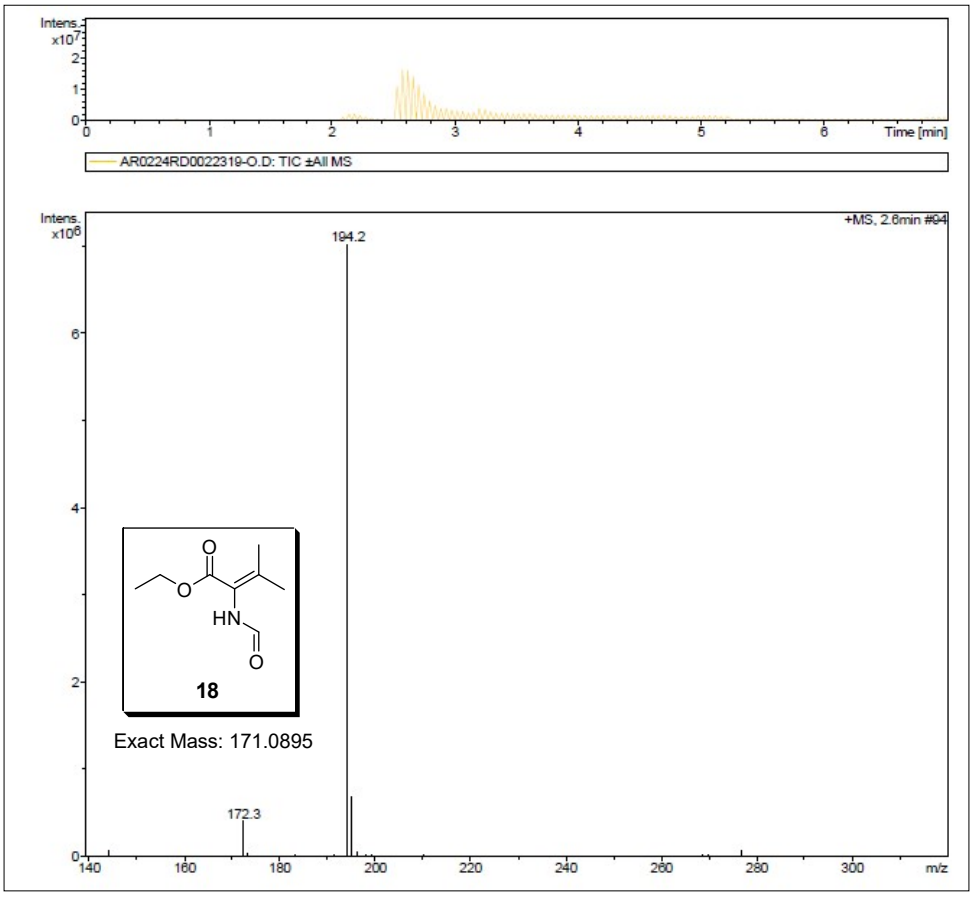
^{13}C-NMR of 18 (DMSO-d_6):



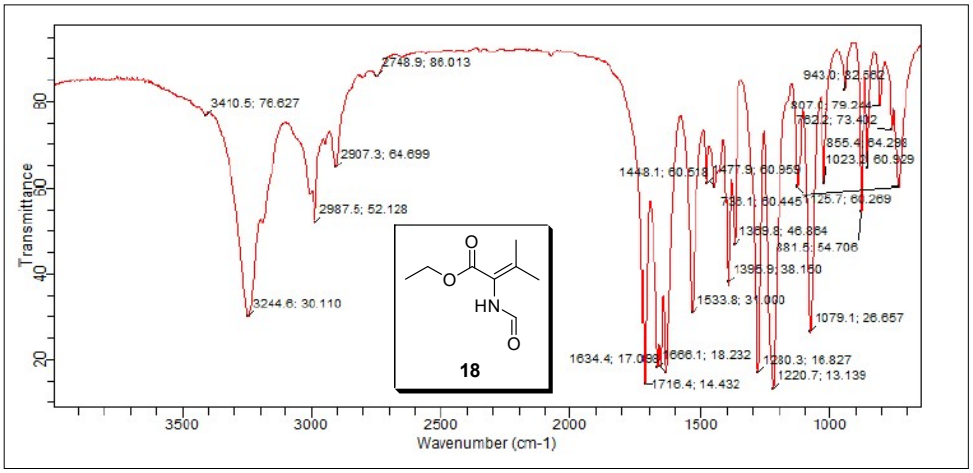
LC-MS of 18:



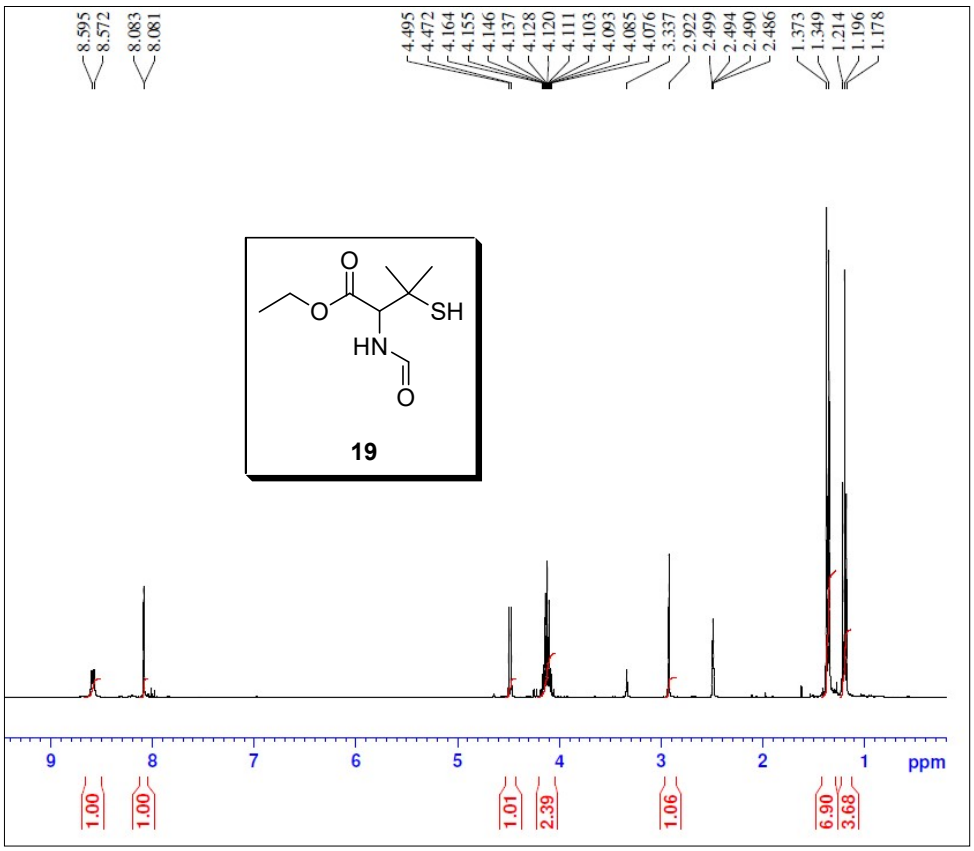
#	Meas. Ret	Area	Area %
1	2.109	287.819	1.720
2	2.545	16221.033	96.942
3	2.871	75.309	0.450
4	3.164	113.694	0.679
5	3.376	10.112	0.060
6	3.530	14.621	0.087
7	3.759	5.285	0.032
8	4.291	1.010	0.006
9	4.924	1.973	0.012
10	5.171	1.805	0.011



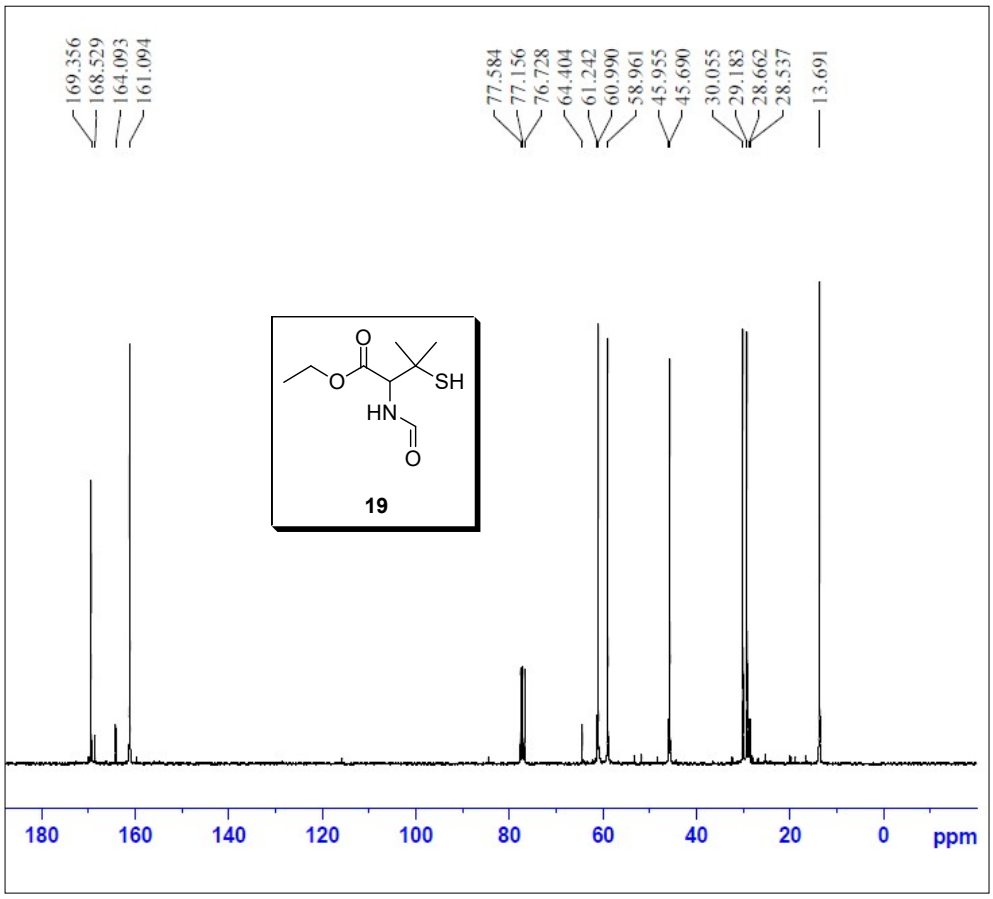
FT-IR of 18:



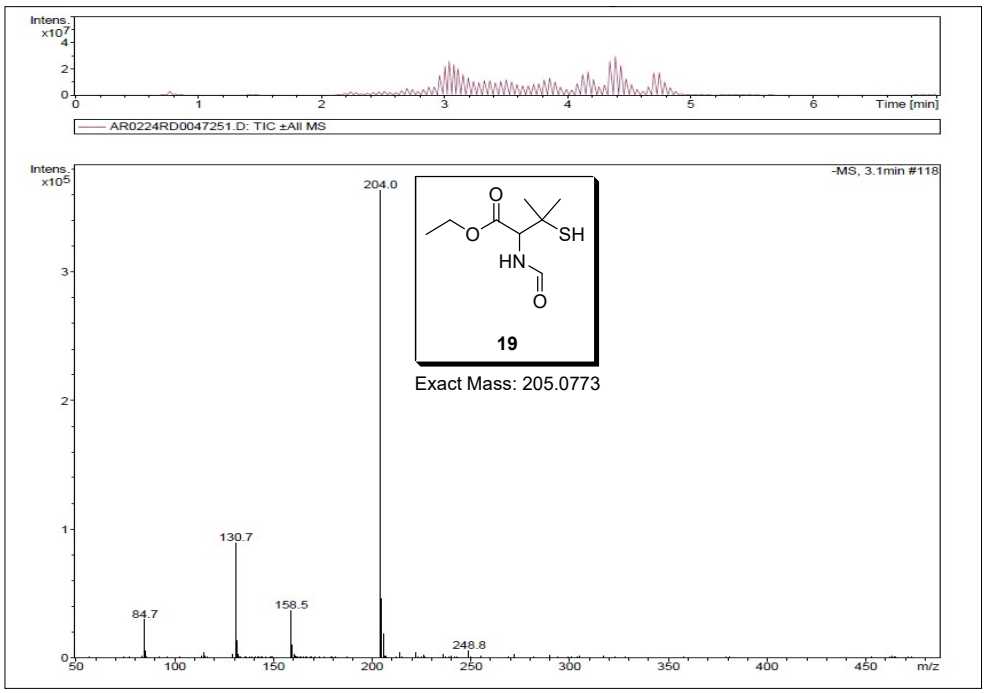
^{1}H-NMR of 19 (DMSO-d_6):



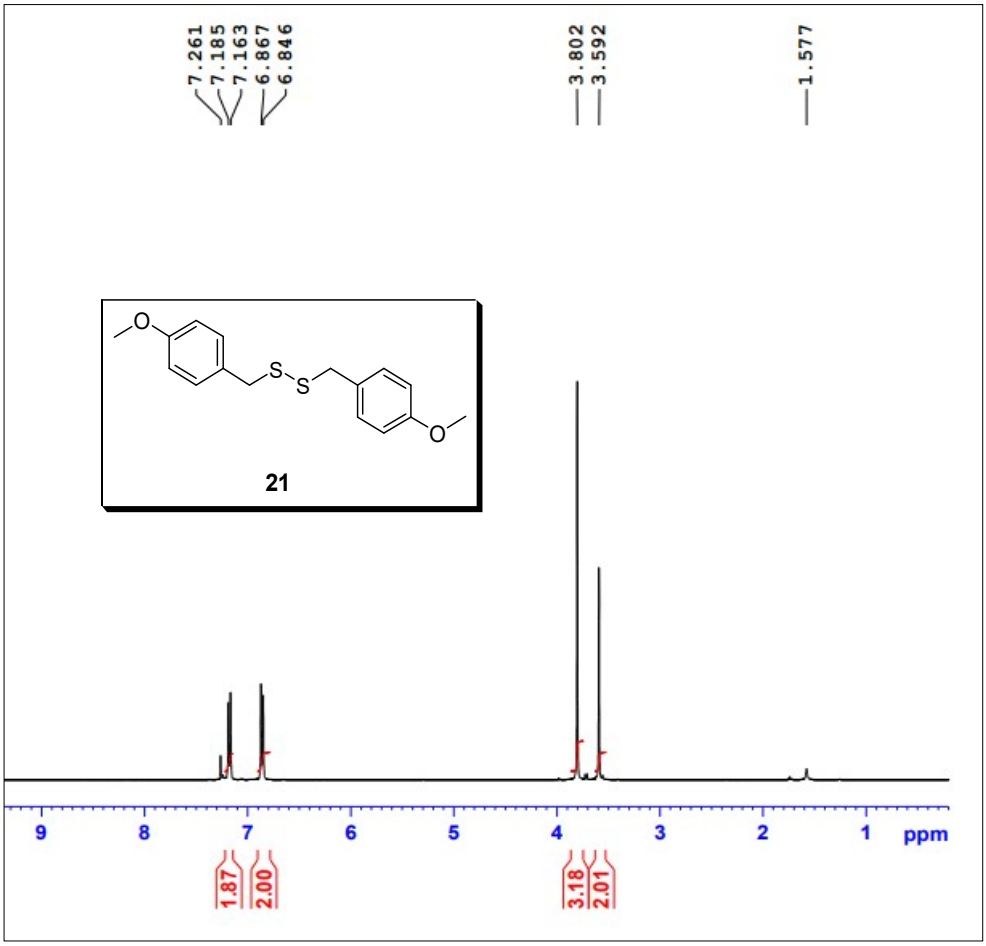
^{13}C-NMR of 19 ($CDCl_3$):



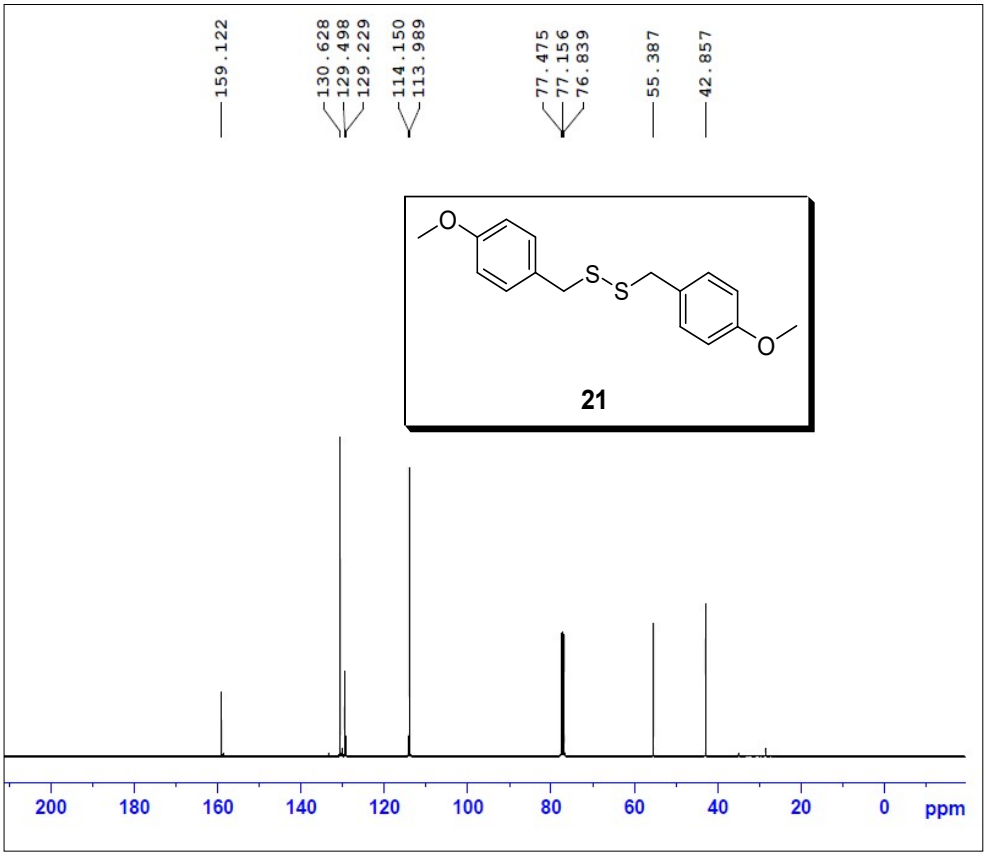
MS of 19:



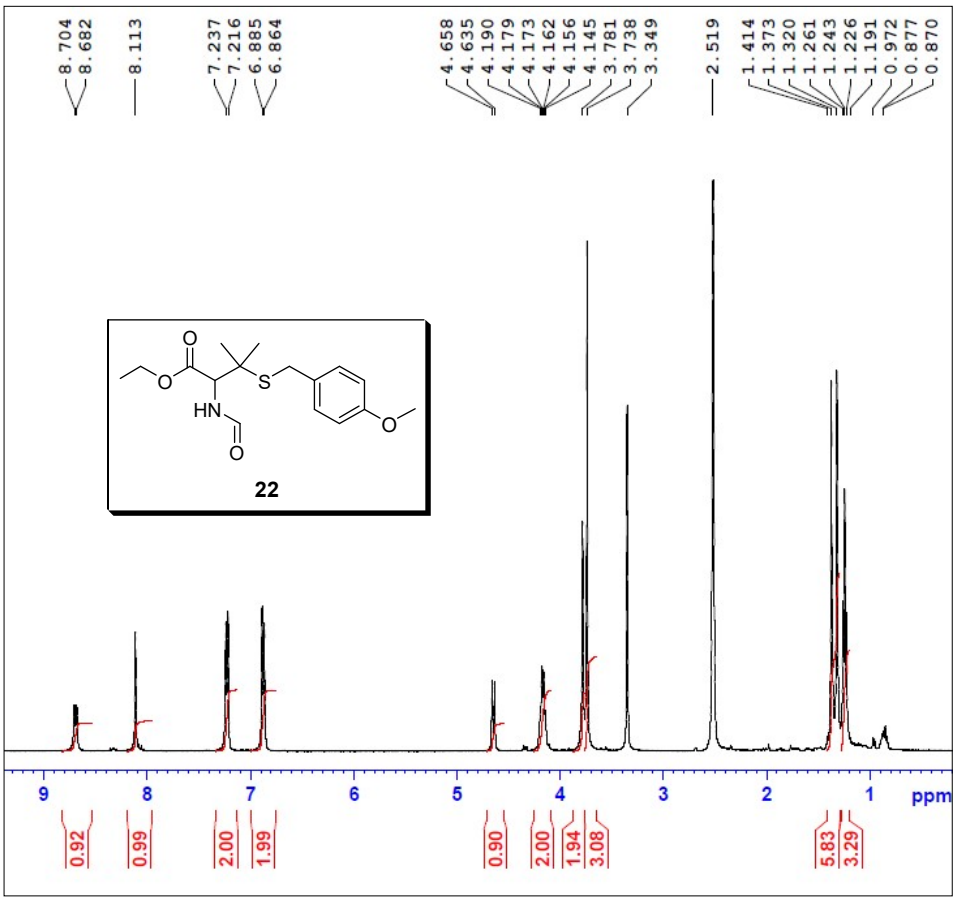
^{1}H-NMR of 21 ($CDCl_3$):



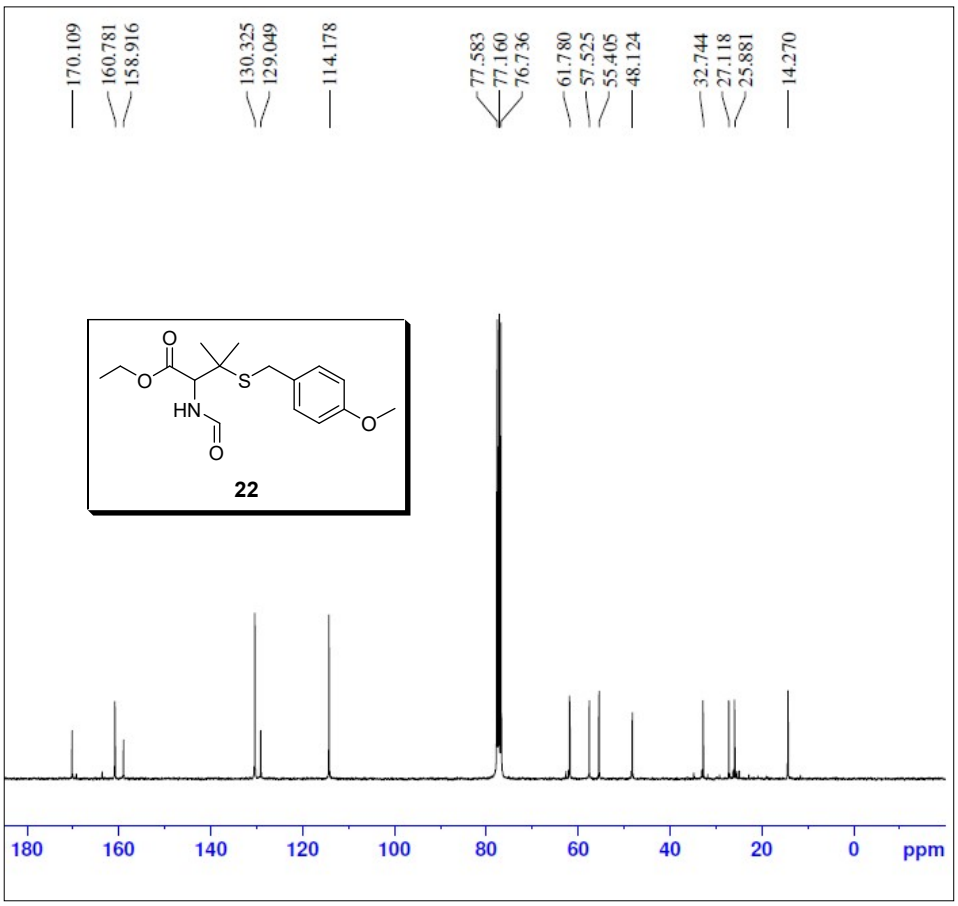
^{13}C-NMR of 21 ($CDCl_3$):



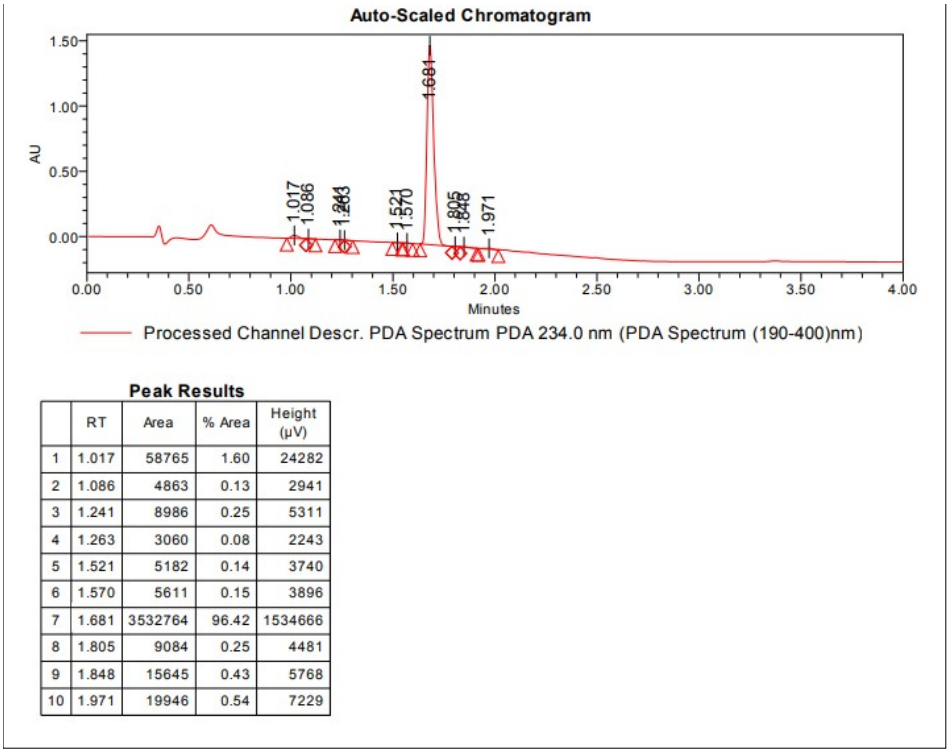
^{1}H-NMR of 22 (DMSO-d_6):



^{13}C-NMR of 22 ($CDCl_3$):

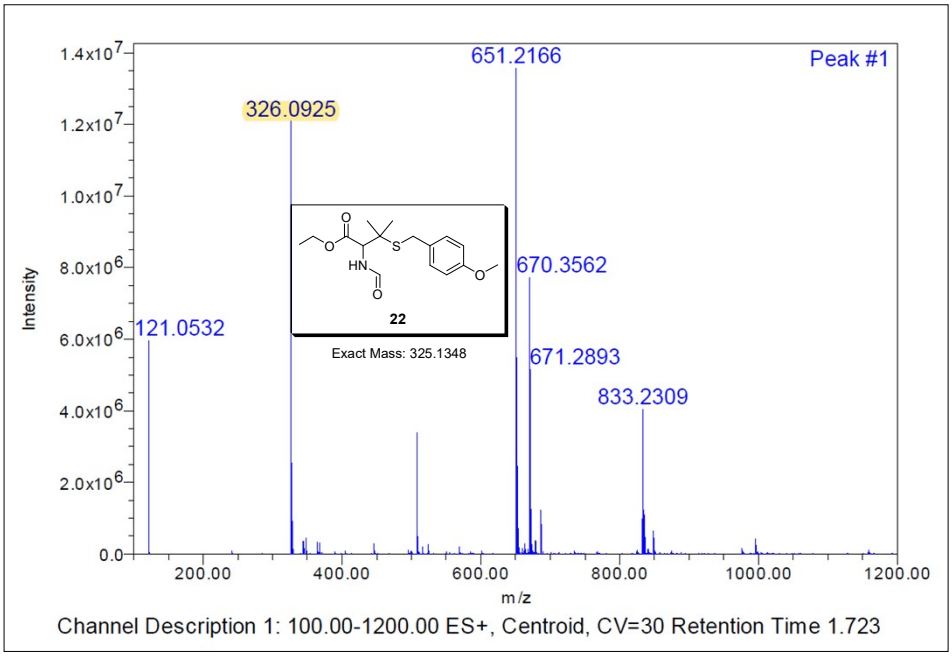


LC-MS of 22:

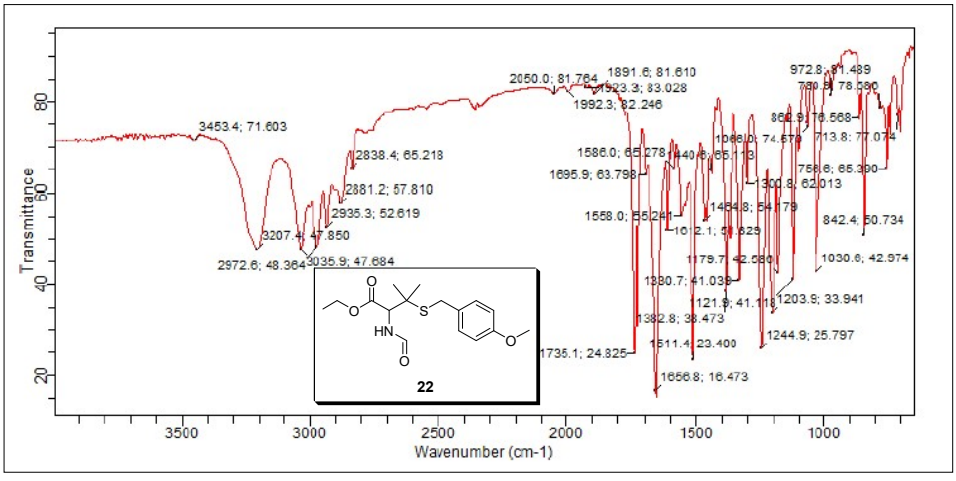


Peak Results

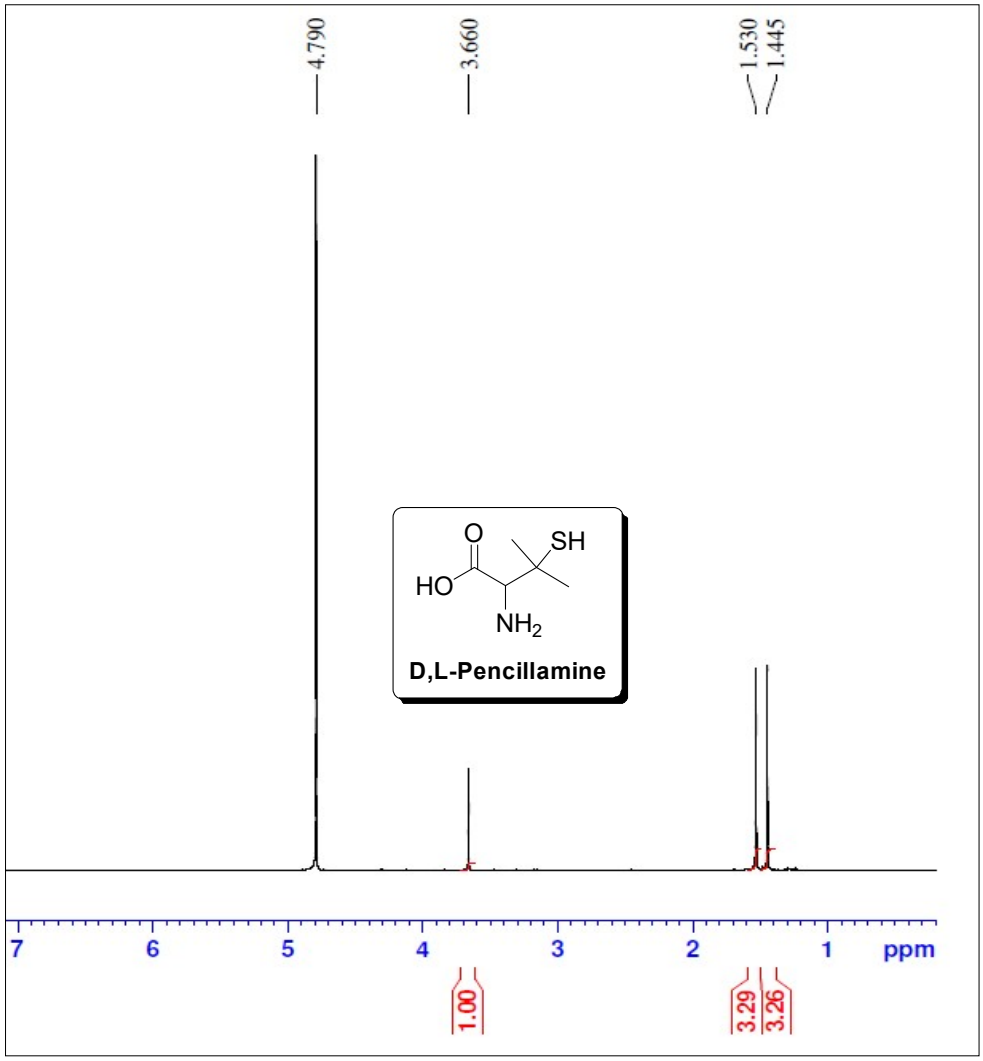
	RT	Area	% Area	Height (µV)
1	1.017	58765	1.60	24282
2	1.086	4863	0.13	2941
3	1.241	8986	0.25	5311
4	1.263	3060	0.08	2243
5	1.521	5182	0.14	3740
6	1.570	5611	0.15	3896
7	1.681	3532764	96.42	1534666
8	1.805	9084	0.25	4481
9	1.848	15645	0.43	5768
10	1.971	19946	0.54	7229



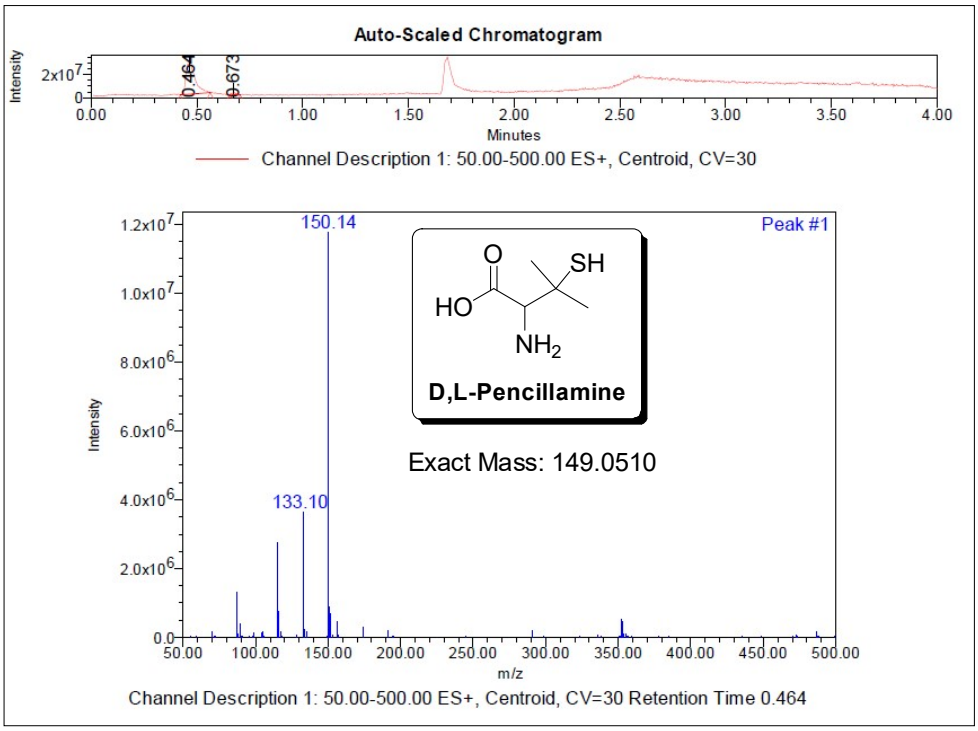
FT-IR of 22:



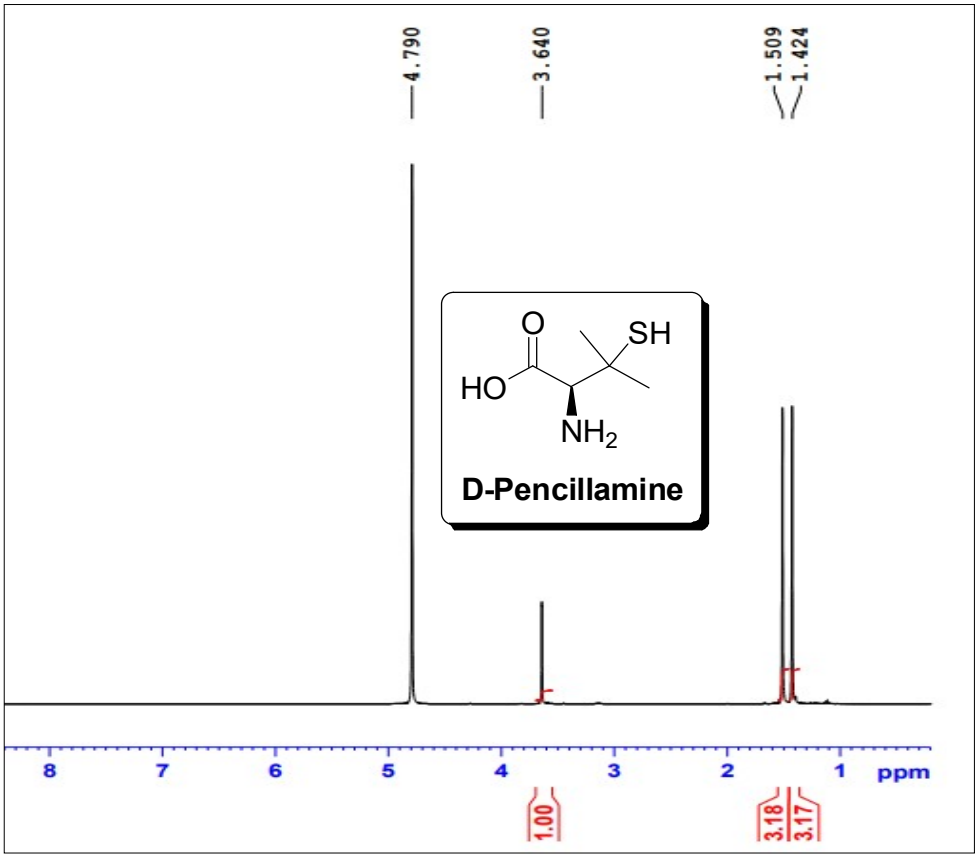
^{1}H-NMR of D,L-1 (D_2O):



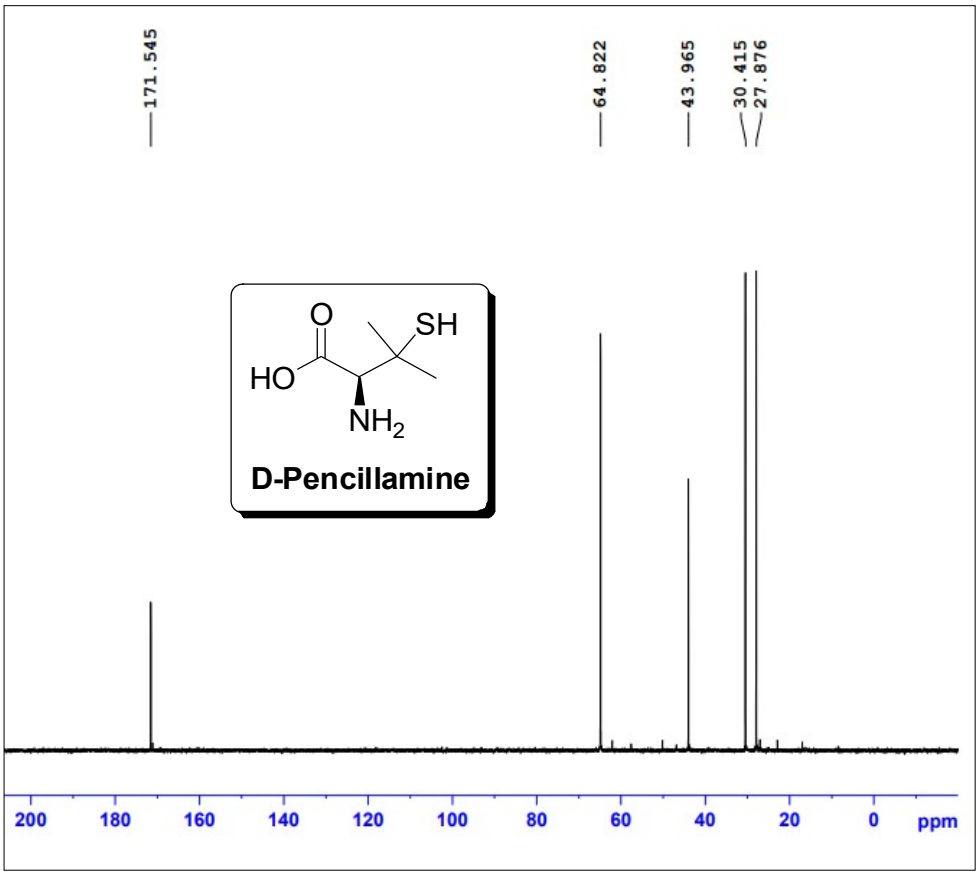
MS of D,L-1:



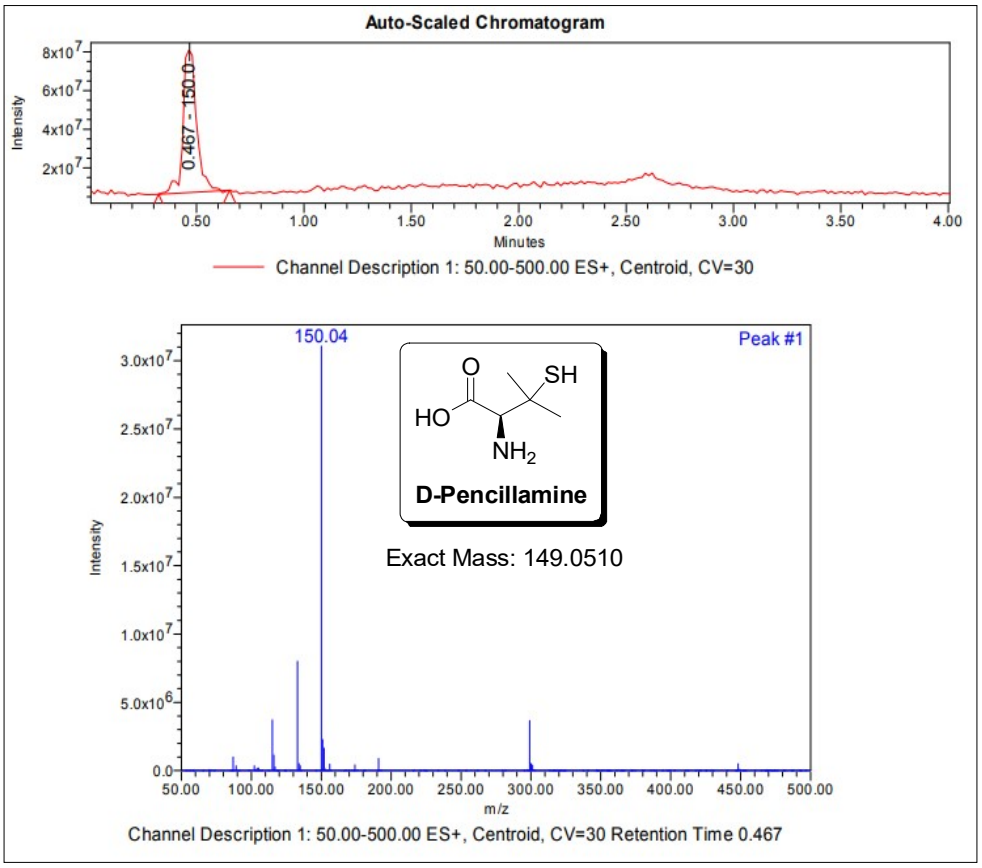
^{1}H-NMR of D-1 (D_2O):



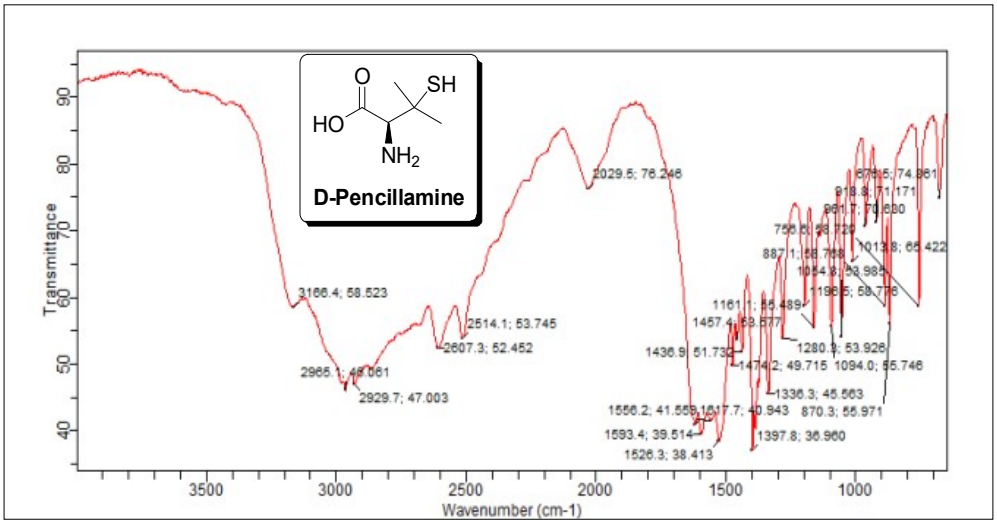
^{13}C-NMR of D-1 (D_2O):



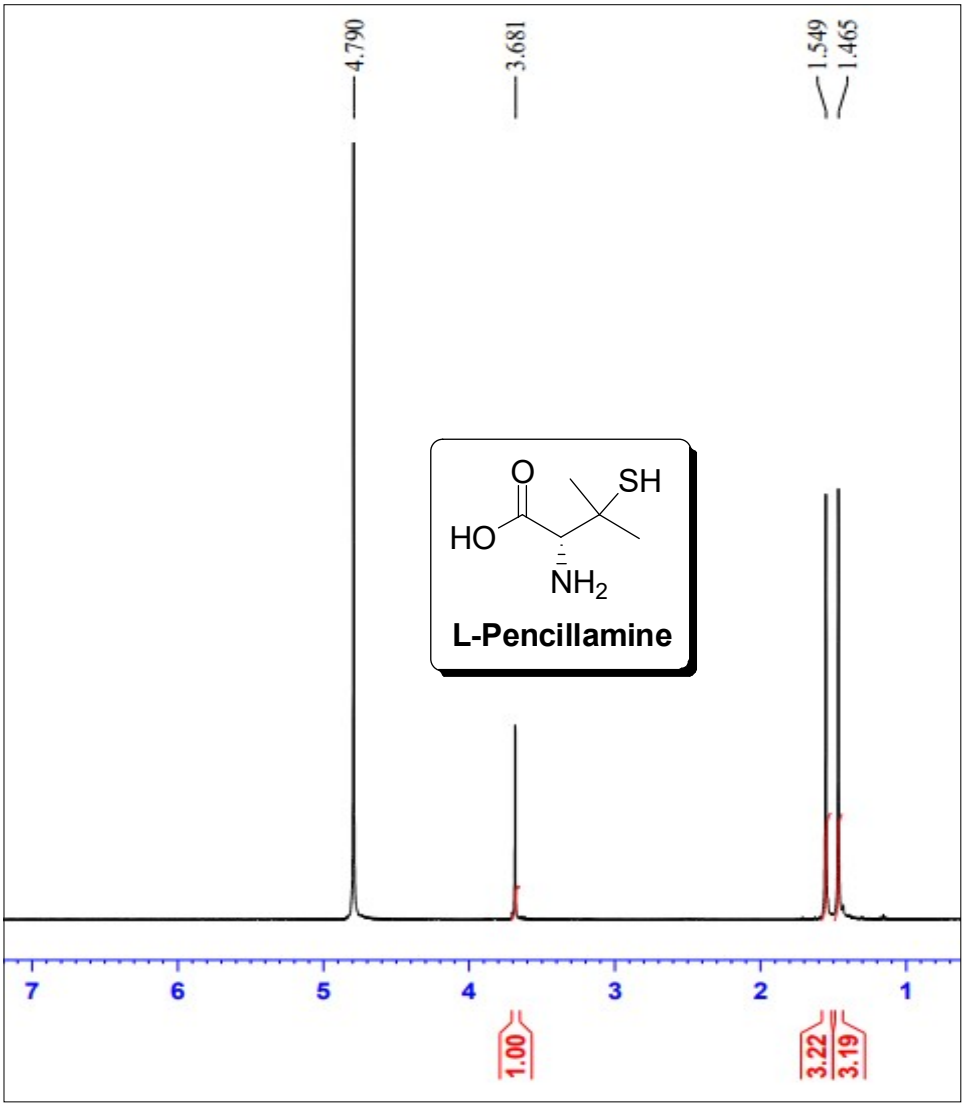
MS of D-1:



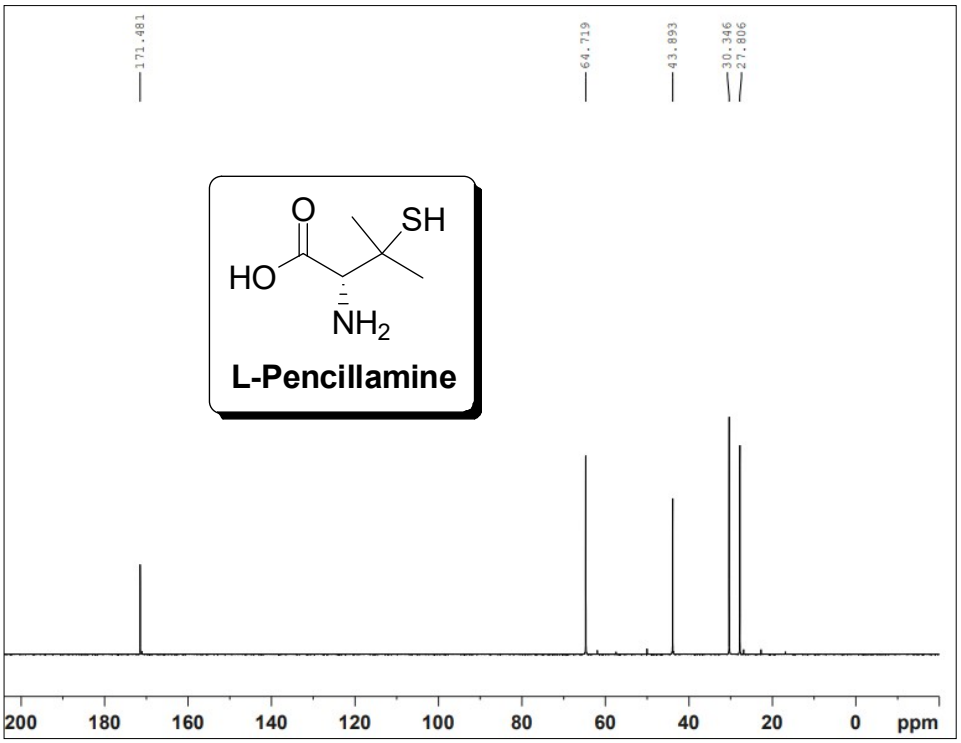
FT-IR of D-1:



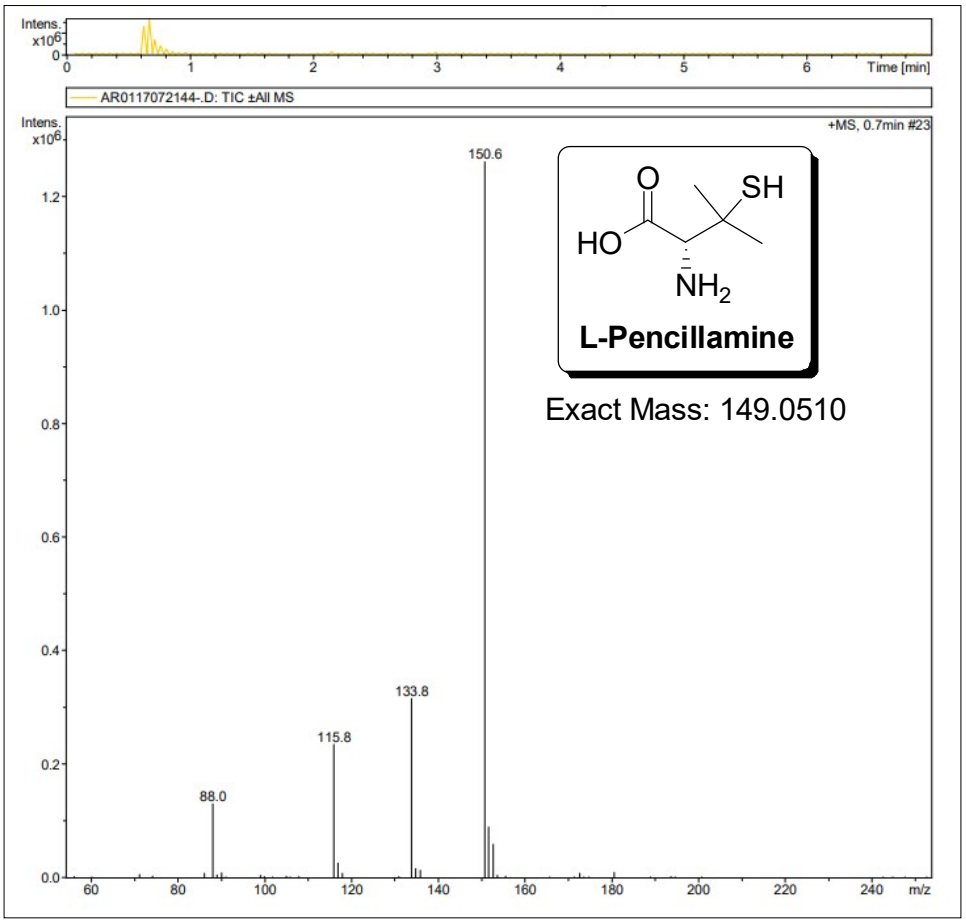
[1]H-NMR of L-1 (D_2O):



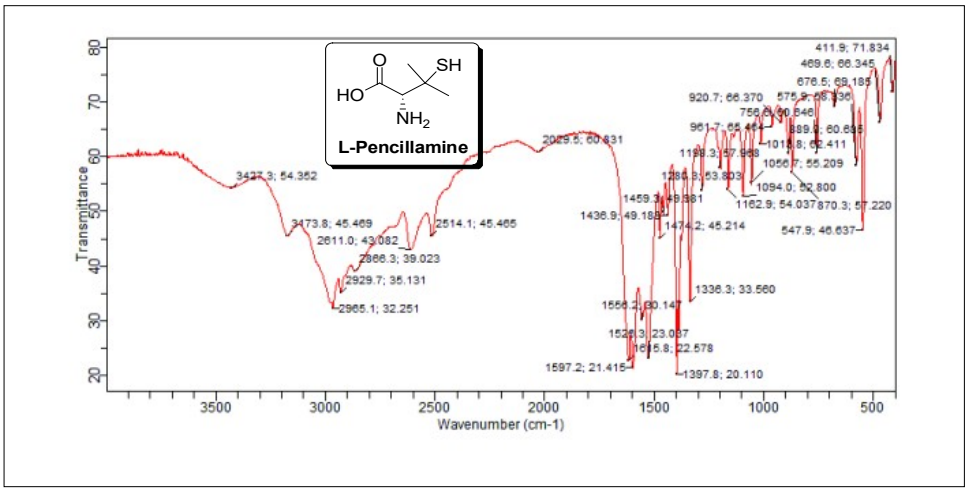
[13]C-NMR of L-1 (D_2O):



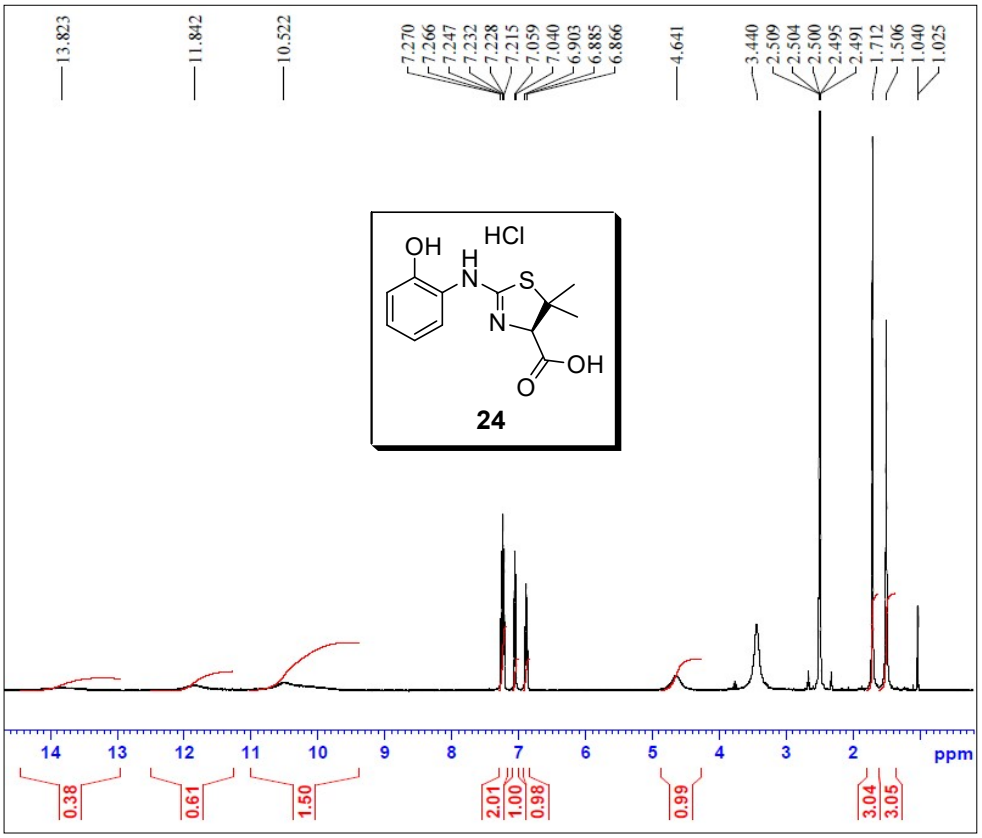
MS of L-1:



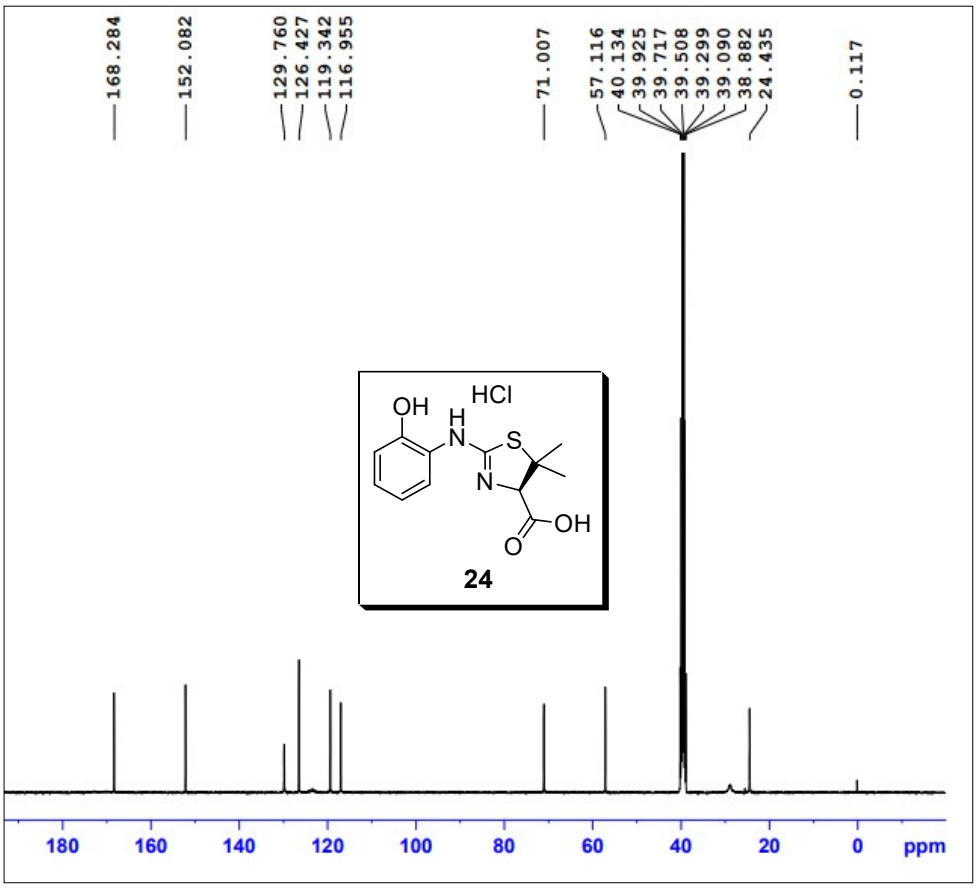
FT-IR of L-1:



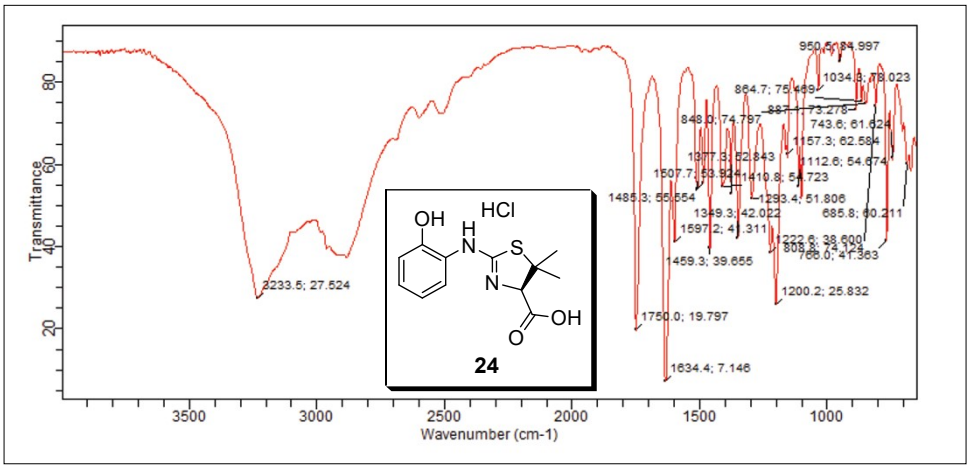
[1]H-NMR of 24 (DMSO-d_6):



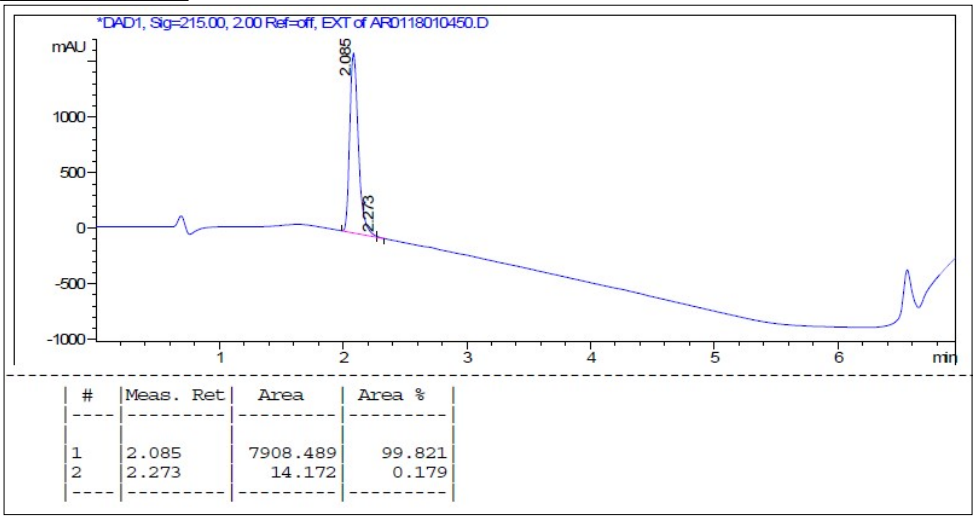
[13]C-NMR of 24 (DMSO-d_6):



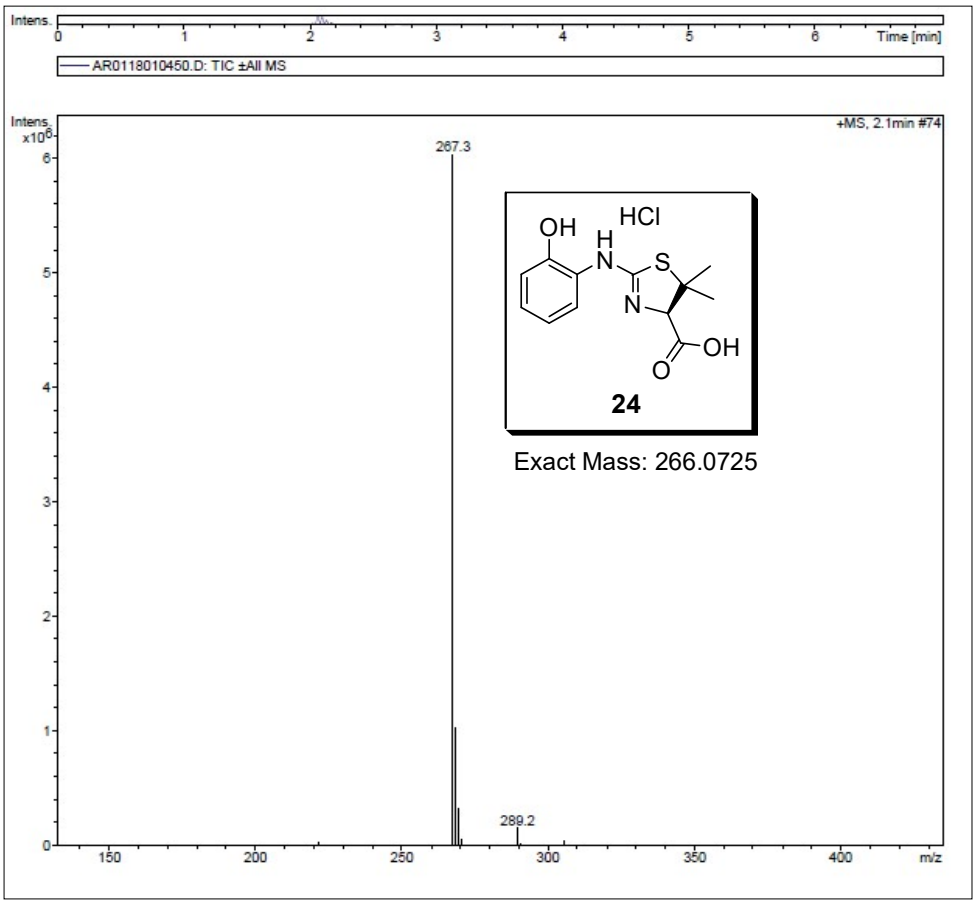
FT-IR of 24:



LC-MS of 24:

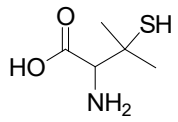


#	Meas. Ret	Area	Area %
1	2.085	7908.489	99.821
2	2.273	14.172	0.179



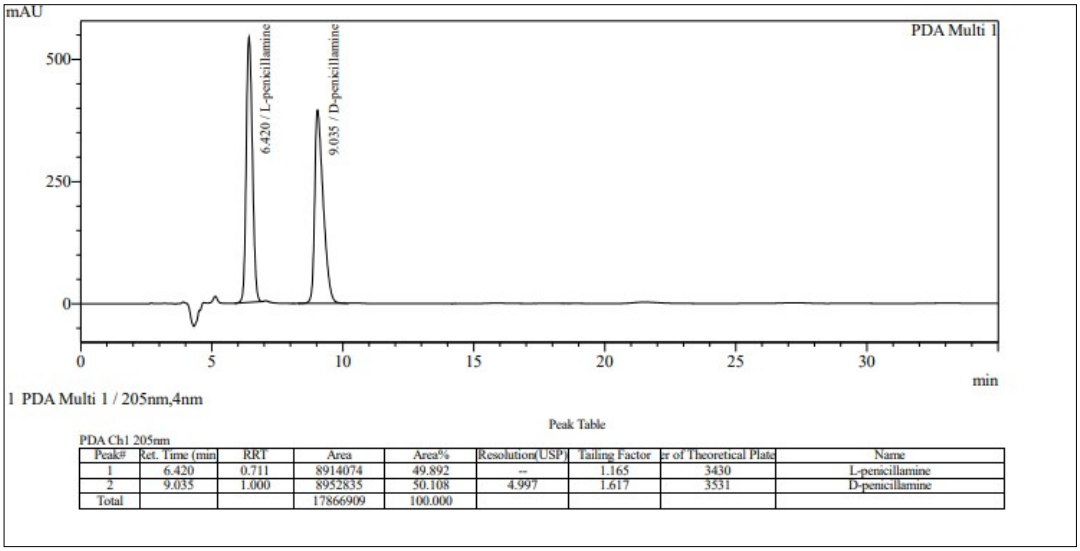
Exact Mass: 266.0725

III. HPLC traces:



D,L-Pencillamine

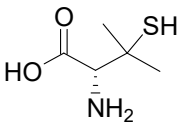
(HPLC conditions: Astec CHIROBIOTIC®TAG 150*4.6mm.5µm column, 10 mM Ammonium dihydrogen phosphate in water / Methanol:ACN::80:20 (v/v), Diluent = Water, Injection volume = 10.0 µL, flow rate = 0.5 mL/min, DAD / VWD detector, Run time- 35 min, column temperature = 40 °C, wavelength = 205 nm, t_R = 6.42 min for L-Pen, t_R = 9.03 min for D-Pen).



Peak Table

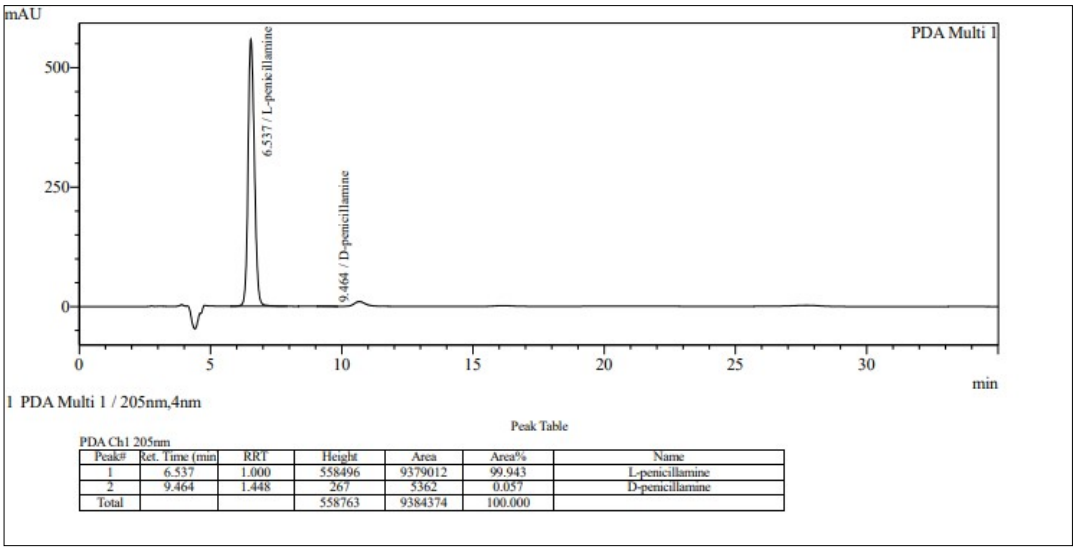
PDA Ch1 205nm

Peak#	Ret. Time (min	RRT	Area	Area%	Resolution(USP)	Tailing Factor	er of Theoretical Plate	Name
1	6.420	0.711	8914074	49.892	--	1.165	3430	L-penicillamine
2	9.035	1.000	8952835	50.108	4.997	1.617	3531	D-penicillamine
Total			17866909	100.000				



L-Pencillamine

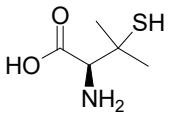
99.94% (HPLC conditions: Astec CHIROBIOTIC®TAG 150*4.6mm.5µm column, 10 mM Ammonium dihydrogen phosphate in water / Methanol:ACN::80:20 (v/v), Diluent = Water, Injection volume = 10.0 µL, flow rate = 0.5 mL/min, DAD / VWD detector, Run time- 35 min, column temperature = 40 °C, wavelength = 205 nm, tR = 6.53 min for L-Pen).



Peak Table

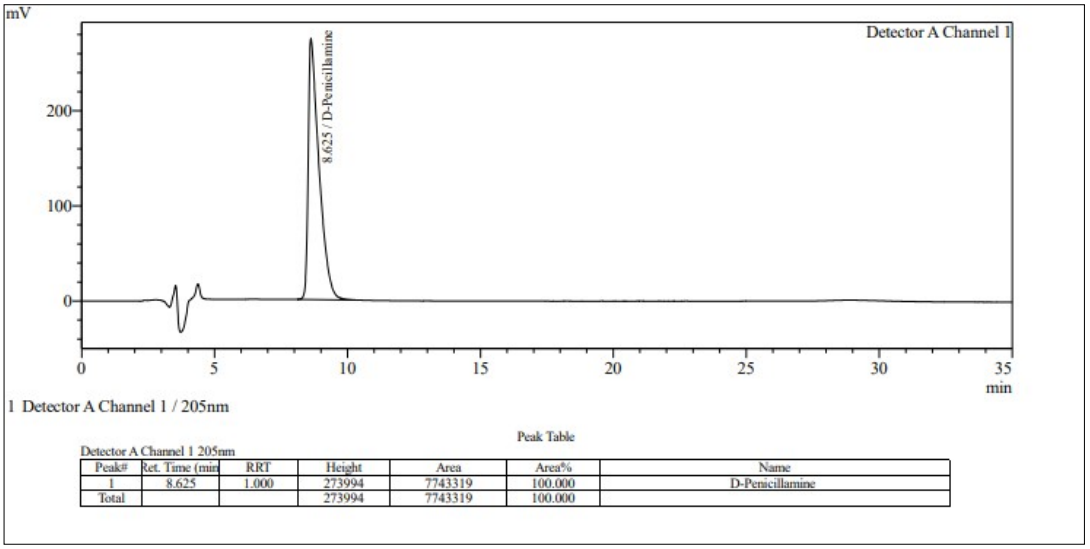
PDA Ch1 205nm

Peak#	Ret. Time (min	RRT	Height	Area	Area%	Name
1	6.537	1.000	558496	9379012	99.943	L-penicillamine
2	9.464	1.448	267	5362	0.057	D-penicillamine
Total			558763	9384374	100.000	



D-Pencillamine

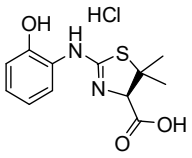
100% (HPLC conditions: Astec CHIROBIOTIC®TAG 150*4.6mm.5µm column, 10 mM Ammonium dihydrogen phosphate in water / Methanol:ACN::80:20 (v/v), Diluent = Water, Injection volume = 10.0 µL, flow rate = 0.5 mL/min, DAD / VWD detector, Run time- 35 min, column temperature = 40 °C, wavelength = 205 nm, tR = 8.62 min for D-Pen).



Peak Table

Detector A Channel 1 205nm

Peak#	Ret. Time (min	RRT	Height	Area	Area%	Name
1	8.625	1.000	273994	7743319	100.000	D-Penicillamine
Total			273994	7743319	100.000	



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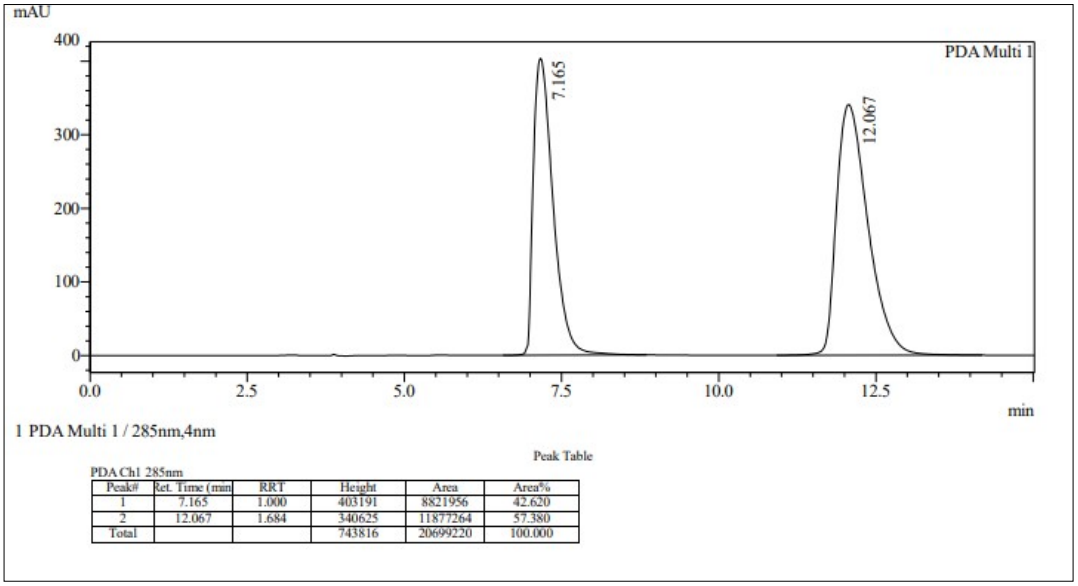
100% (HPLC conditions: Chiralcel OX-3 (250mm, 4.6mm, 3µ) column, 0.3 % TFA in n-Hexane/ 0.1% DEA in (EtOH:IPA::80:20), Diluent = Ethanol:Methanol (1:1), Injection volume = 10.0 µL, flow rate = 1.0 mL/min, DAD / VWD detector, Run time- 15 min, column temperature = 25 °C, wavelength = 285 nm, tR = 7.19 min for **24.**

Racemic:

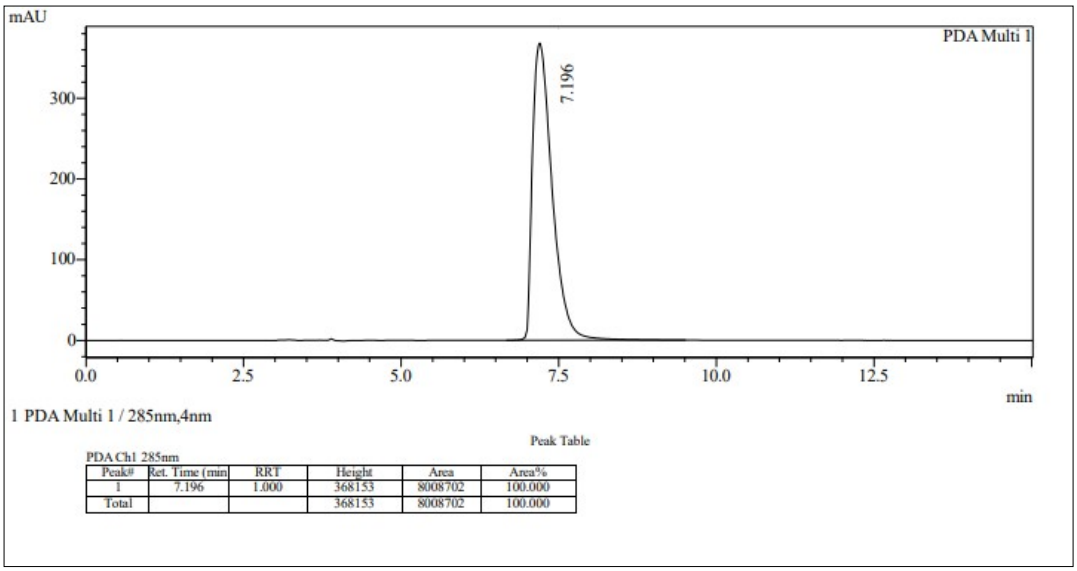


Peak Table

PDA Ch1 285nm

Peak#	Ret. Time (min	RRT	Height	Area	Area%
1	7.165	1.000	403191	8821956	42.620
2	12.067	1.684	340625	11877264	57.380
Total			743816	20699220	100.000

Chiral:



Peak Table

PDA Ch1 285nm

Peak#	Ret. Time (min	RRT	Height	Area	Area%
1	7.196	1.000	368153	8008702	100.000
Total			368153	8008702	100.000

IV. References:

[1] M. Abbasi, M. R. Mohammadizadeh and N. Saeedi, *New J. Chem*., 2016, **40**, 89-92.

[2] Y. Feng, J. Nie, S. Xie, Z. He, H. Hong,J. Li and Y. Li, *Chem. Commun.,*2024, **60**, 1140-1143.