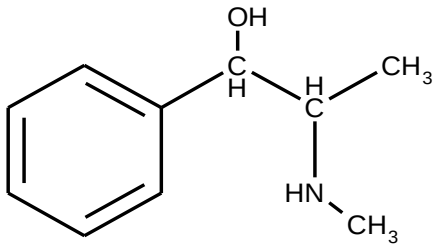
PSEUDOEPHEDRINE

Latest Revision: June 22, 2005



1. SYNONYMS

CFR: Pseudoephedrine

NIST #: Base: 245957
Hydrochloride: 116820

Other Names: (αS)-α-[(1S)-1-(Methylamino)ethyl]benzenemethanol

(1S,2S)-2-Methylamino-1-phenylpropan-1-ol
d-ε-Ephedrine
d-Isoephedrine

2. CHEMICAL AND PHYSICAL DATA

2.1. CHEMICAL DATA

Form	Chemical Formula	Molecular Weight	Melting Range (°C)
Base	$C_{10}H_{15}NO$	165.23	118-118.7
Hydrochloride	$C_{10}H_{15}NO \cdot HCl$	201.70	182.5-183.5

2.2. SOLUBILITY

Form	A	C	E	H	M	W
Base	***	FS	FS	***	FS	PS
Hydrochloride	***	PS	VSS	***	FS	FS

A=acetone, C=chloroform, E=ether, H=hexane, M=methanol, W=water, VS=very soluble, FS=freely soluble, S= soluble, PS=sparingly soluble, SS=slightly soluble, VSS=very slightly soluble, I=insoluble

3. SCREENING TECHNIQUES

3.1. COLOR TESTS

REAGENT	COLOR PRODUCED	PREPARATION
Chen's	Purple	Reagents: 1) 1% acetic acid solution 2) 1% copper sulfate solution 3) 2.0 N NaOH

3.2. CRYSTAL TESTS

REAGENT	TEST	DESCRIPTION OF CRYSTALS
Gold chloride in diluted H_3PO_4	Direct Hanging drop, volatility	High birefringence, thin branching sticks, blades, spearheads High birefringence, thin branching sticks, combs
Bismuth iodide in diluted H_2SO_4	Hanging drop, volatility	Orange-red rhomboids, sticks, forms readily

3.3. THIN-LAYER CHROMATOGRAPHY

Visualization

Acidified potassium permanganate solution

COMPOUND	System TLC5
adrenaline	0.0
ephedrine	0.8
methamphetamine	0.9
pseudoephedrine	1.0
amphetamine	1.2
cathine	1.2
phenylpropanolamine	1.3
caffeine	1.5

3.4. GAS CHROMATOGRAPHY/MASS SPECTROMETRY (GC/MS)

Method PSE-GCMS1

Instrument:	Gas chromatograph operated in split mode/mass selective detector
Column:	5% phenyl/95% methylsiloxane, 30 m x 0.25 mm i.d. x 0.25 µm film thickness
Carrier gas:	Nitrogen at 1.1 mL/min
Temperatures:	Injector: 280°C Detector: 280°C Oven Program: 1) initial temperature 60°C (hold 2 min) 2) ramp at 20°C/min to 280°C 3) hold final temperature for 6 min
Injection Parameters:	Split Ratio = 80:1, 1 µL injected

Samples are dissolved in an appropriate solvent (i.e. methanol, chloroform/base extract) and filtered prior to injection.

COMPOUND	RRT	COMPOUND	RRT
dimethylsulfone	0.49	guaifenesin	1.22
amphetamine	0.59	acetaminophen	1.26
P2P	0.76	pheniramine	1.36
methamphetamine	0.81	caffeine	1.37
ephedrine	0.99	ketamine	1.38
pseudoephedrine)	**1.00 (7.66 min)**	lidocaine	1.40
nicotinamide	1.02	chlorpheniramine	1.48
MDA	1.09	procaine	1.50
MD-P2P	1.09	naproxen	1.53
MDMA	1.13	cocaine	1.61
MDEA	1.16	triprolidine	1.64

3.5. GAS CHROMATOGRAPHY/VAPOR PHASE INFRARED SPECTROSCOPY (GC-IRD)

Method PSE-IRDS1

Instrument:	Gas chromatograph operated in splitless mode/infrared detector
Column:	100% methylpolysiloxane, 15 m x 0.32mm i.d. x 0.25µm film thickness
Carrier gas:	Helium at 1.0 mL/min
Temperatures:	Injector: 275°C Oven Program: 1) initial temperature 70°C (hold 1 min) 2) ramp at 15°C/min to 280°C 3) hold final temperature for 3 min
Injection Parameters:	Splitless, 1 µL injected

Samples are dissolved in an appropriate solvent (i.e. methanol, chloroform) and filtered prior to injection.

Note: Reference the RRT from GC section 3.4 as listed above as this parameter is column dependent.

4. SEPARATION TECHNIQUES

Pseudoephedrine hydrochloride can be isolated from several adulterants and diluents as well as several controlled substances by the use of solvent extractions. For example, pseudoephedrine hydrochloride can be separated from common tablet excipients by performing a chloroform extraction of the mixture. Pseudoephedrine will dissolve in the chloroform extract, leaving behind the tableting material.

Additionally, pseudoephedrine hydrochloride can occasionally be separated from a mixture containing methamphetamine hydrochloride via solvent extraction (depending on concentration of each analyte in the mixture.) Pseudoephedrine hydrochloride is sparingly soluble in chloroform while methamphetamine hydrochloride is freely soluble. To isolate pseudoephedrine hydrochloride, a small amount of the mixture is placed into a cotton-plugged pipette or other appropriate filtering device and a small volume of chloroform is rapidly washed through the mixture. The methamphetamine hydrochloride will dissolve in the chloroform extract, leaving behind the pseudoephedrine hydrochloride in the cotton-plugged pipette. If the methamphetamine hydrochloride was removed completely by the chloroform extraction and the mixture was comprised of only these two components, the remaining powder will be pseudoephedrine hydrochloride, which can be subsequently analyzed. If additional components are present in the mixture, use of a different solvent may be required to isolate the pseudoephedrine hydrochloride. Since pseudoephedrine hydrochloride is very slightly soluble in ether, it may be possible to subsequently isolate the pseudoephedrine hydrochloride from the remaining solid mixture (if the remaining mixture contains only diluents) by washing with ether; however, this step is concentration dependent.

5. QUANTITATIVE PROCEDURES

5.1. GAS CHROMATOGRAPHY

Method PSE-GCQ1

Internal Standard Stock Solution:
4.0 mg/mL tridecane in chloroform.

Standard Solution Preparation:
In a volumetric flask, accurately weigh and prepare a standard solution of pseudoephedrine hydrochloride at a target concentration of 1.6 mg/mL in 1 part methanol, 1 part internal standard stock solution, and 3 parts chloroform. In order to preserve the standard stock solution, a 1-2 mL aliquot of the solution may be transferred to a 13mm x 100mm test tube and base extracted with 5 N NaOH, ensuring a pH ~14. Remove the bottom layer and filter through a cotton-plugged pipette or other appropriate filtering device. Additionally, the entire standard solution may be extracted by adding 5 N NaOH directly into the flask, ensuring a pH ~14. Remove the bottom layer and filter through a cotton-plugged pipette or other appropriate filtering device.

Sample Preparation:
In a volumetric flask, accurately weigh and prepare a sample solution of pseudoephedrine hydrochloride at a target concentration of 1.6 mg/mL in 1 part methanol, 1 part internal standard stock solution, and 3 parts chloroform. Add an appropriate amount of 5 N NaOH directly into the flask and shake vigorously to ensure that all pseudoephedrine hydrochloride is dissolved. Check pH to ensure a pH ~14. Vortex and centrifuge if necessary. Remove the bottom layer and filter through a cotton-plugged pipette or other appropriate filtering device into an autosampler vial.

Instrument:	Gas chromatograph operated in split mode with FID
Column:	100% methylpolysiloxane, 15 m x 0.32 mm i.d. x 0.25 µm film thickness
Carrier gas:	Helium at 2.2 mL/min
Temperatures:	Injector: 275°C Detector: 280°C Oven Program: 130°C isothermal for 7.0 min
Injection Parameters:	Split Ratio = 35:1, 1 µL injected
Typical Retention Time:	Pseudoephedrine: 2.07 Tridecane: 1.74
Linear Range:	0.2-4.0 mg/mL
Repeatability:	RSD < 1.0%
Correlation Coefficient:	0.9999

Note 1: Although pseudoephedrine readily dissolves in methanol, its solubility in chloroform is limited; and in many instances, matrix effects can be problematic. Therefore, the entire sample solution must be base extracted with 5 N NaOH.
Note 2: The pKa of pseudoephedrine hydrochloride is 9.22. Use of a concentrated sodium hydroxide solution (pH ~14) is necessary to ensure complete conversion of the pseudoephedrine hydrochloride into the base, with subsequent extraction into the organic chloroform layer. Running pseudoephedrine (and other

phenethylamines) as the base strongly recommended. Failure to do so will result in poor chromatographic peak shape due to the interaction of the amine salts with the stationary phase of the column. DO NOT USE sodium carbonate or sodium bicarbonate solutions to extract the pseudoephedrine as the pH of these solutions is not sufficiently high to fully convert the hydrochloride to the base form and extract the base into the chloroform layer. In cases of strongly acidic liquids, a higher normality of NaOH may be required to obtain a pH of 14. Note 3: Triprolidine and chlorpheniramine are common adulterants in tablets. These compounds will not elute under the isothermal conditions before the 7 minute time elapses. If these compounds are present in a sample, the temperature should be ramped after 7 minutes and held until these compounds elute.

COMPOUND	RRT	COMPOUND	RRT
tridecane	1.00 (1.74)	MDP2P	1.68
dimethylsulfone	0.40	MDA	1.76
P2P	0.57	MD-P2P-ol	1.78
amphetamine	0.59	BZP	1.87
methamphetamine	0.68	MDMA	2.24
safrole	0.91	pentadecane	2.26
phenylpropanolamine (note co-elution with tridecane)	1.00	MDEA	2.79
piperonal (note co-elution with tridecane)	1.00	MDP2P oxime	3.84
isosafrole #1	1.06	caffeine	4.50
ephedrine	1.19	N-acetyl MDA	4.63
pseudoephedrine	**1.20 (2.07 min)**	ketamine	4.65
isosafrole #2	1.22	PCP	4.81
PMA	1.22	N-acetyl N-acetoxy MDA	5.08
PMMA	1.53		

5.2. HIGH PERFORMANCE LIQUID CHROMATOGRAPHY

Method PSE-LCQ1

Standard Solution Preparation:
In a volumetric flask, accurately weigh and prepare a standard solution of pseudoephedrine hydrochloride at a target concentration of 0.3 mg/mL in 0.1 N HCl.
Sample Preparation:
In a volumetric flask, accurately weigh and prepare a sample solution of pseudoephedrine hydrochloride at a target concentration of 0.3 mg/mL in 0.1 N HCl. Sonicate 20-30 minutes or until all pseudoephedrine hydrochloride dissolves. Completely invert the flask and shake to obtain a uniform concentration of analyte in solution. Filter solution through a 0.45µm filter.

Instrument:	High performance liquid chromatograph equipped with a UV-diode array
Column:	Phenomenex LUNA C18(2), 150 mm x 3.0 mm i.d. x 5 µm particle size *Guard column:* Phenomenex security guard column, 4 mm x 2.0 mm i.d., C18 cartridge
Detector:	UV-DAD, 200 nm and/or 210 nm
Flow:	1.5 mL/min
Injection Volume:	2.5 µL
Buffer:	4000 mL HPLC grade water, 10.0 g NaOH, 30 mL phosphoric acid, 8.0 mL hexylamine, 10 mg sodium azide; pH = 2.0 (measured)
Mobile Phase:	Buffer: acetonitrile (98:2)

Note 1: Although pseudoephedrine readily dissolves in the 0.1 N HCl solution, sugars, inorganic salts, and some of the more common tablet excipients are insoluble. This may require additional sonication time in order to release all of the pseudoephedrine from the excipient matrix.
Note 2: Resolution between pseudoephedrine and ephedrine is less than the 1.5 critical value necessary for accurate quantitation if both compounds are present. Do NOT use this method for quantitation if both ephedrine and pseudoephedrine are present.
Note 3: Triprolidine does not elute under these conditions. A gradient ramp to buffer:ACN (50:50) must be added to the end of the method in order to elute triprolidine.

COMPOUND	RRT	COMPOUND	RRT

phenylpropanolamine	0.67	amphetamine	1.26
ephedrine	0.92	methamphetamine	1.61
pseudoephedrine	**1.00 (1.84 min)**	chlorpheniramine	2.19

6. QUALITATIVE DATA

See spectra on the following pages for FT-IR, Raman, ATR, Mass Spectrometry, Nuclear Magnetic Resonance, Vapor Phase IR, GC/MS-TPC, and CD-ORD results.

7. REFERENCES

Budavari, S., *The Merck Index, 13th Edition*, Merck and Co., Inc., 2001, pgs. 1416-1417.

Fulton C. C., *Modern Microcrystal Tests for Drugs*, Wiley-Interscience, New York, 1969, pgs. 204-205.

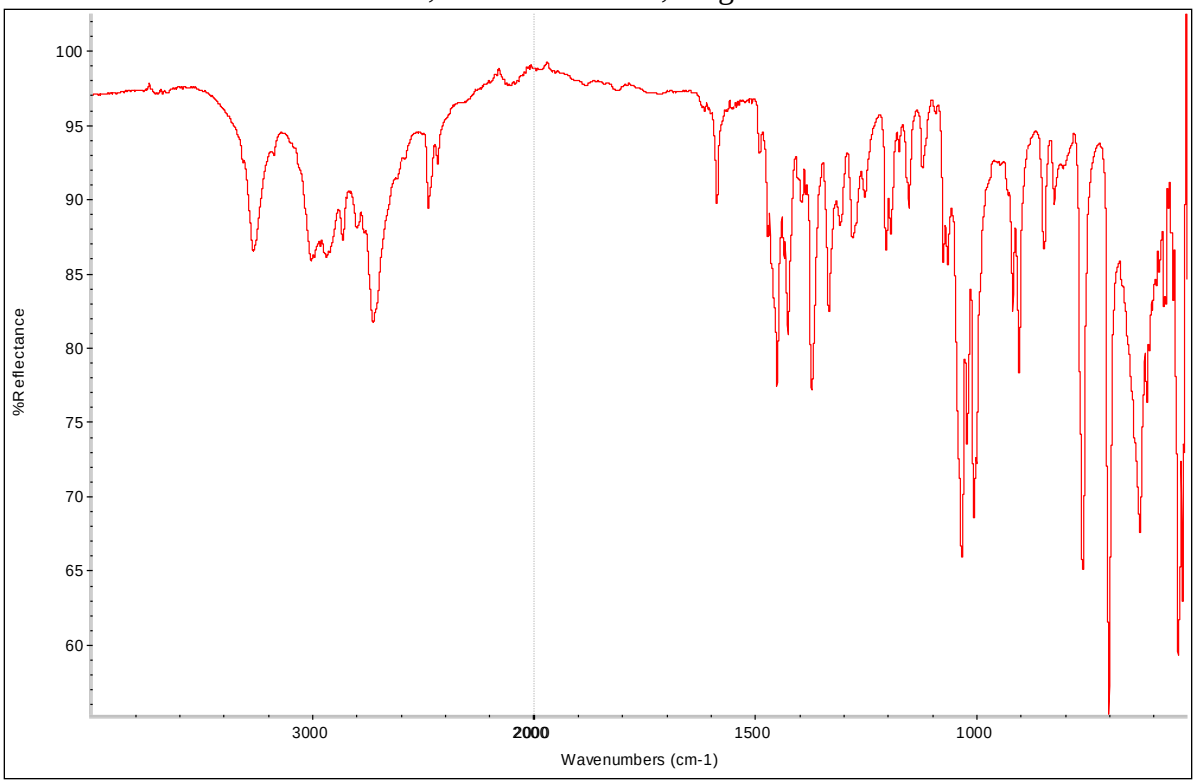
Moffat A. C., Sr. Ed., *Clarke's Isolation and Identification of Drugs*, The Pharmaceutical Press, London, Second Edition, 1996, pgs. 944-945.

8. ADDITIONAL RESOURCES

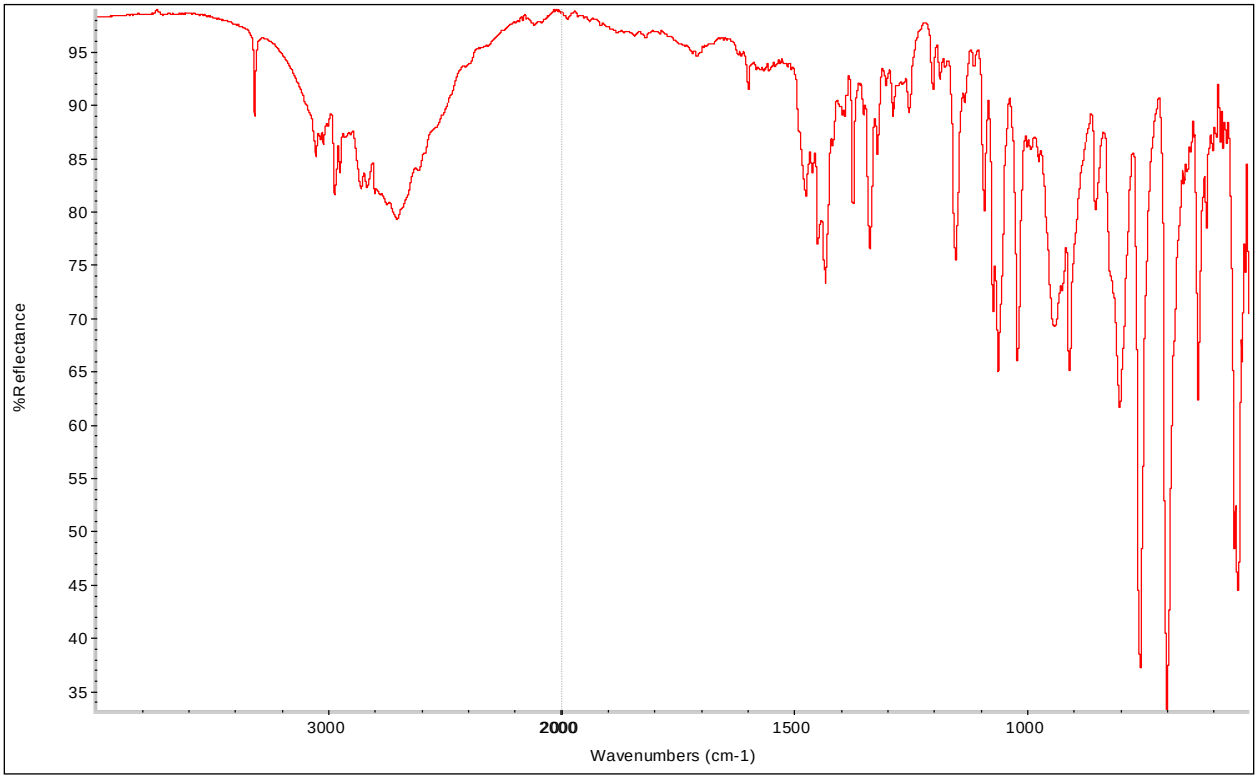
Forendex

Wikipedia

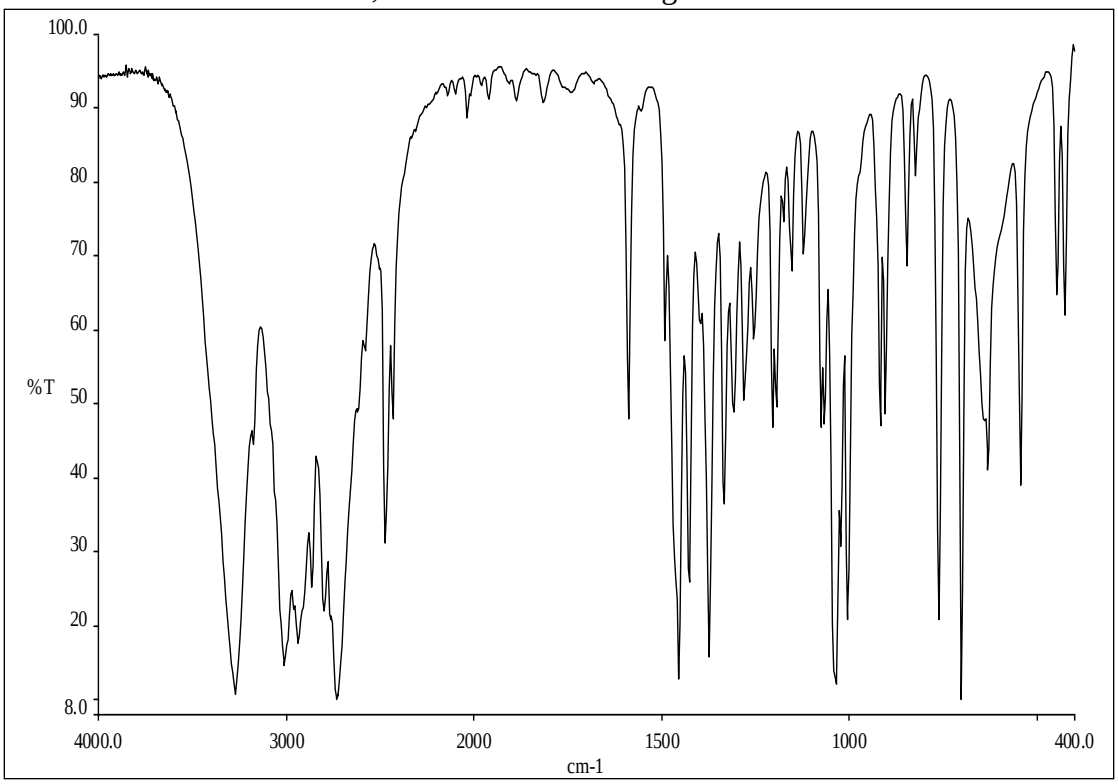
FTIR (ATR): Pseudoephedrine hydrochloride
16 scans, 2 cm^{-1} resolution, range 4000-600



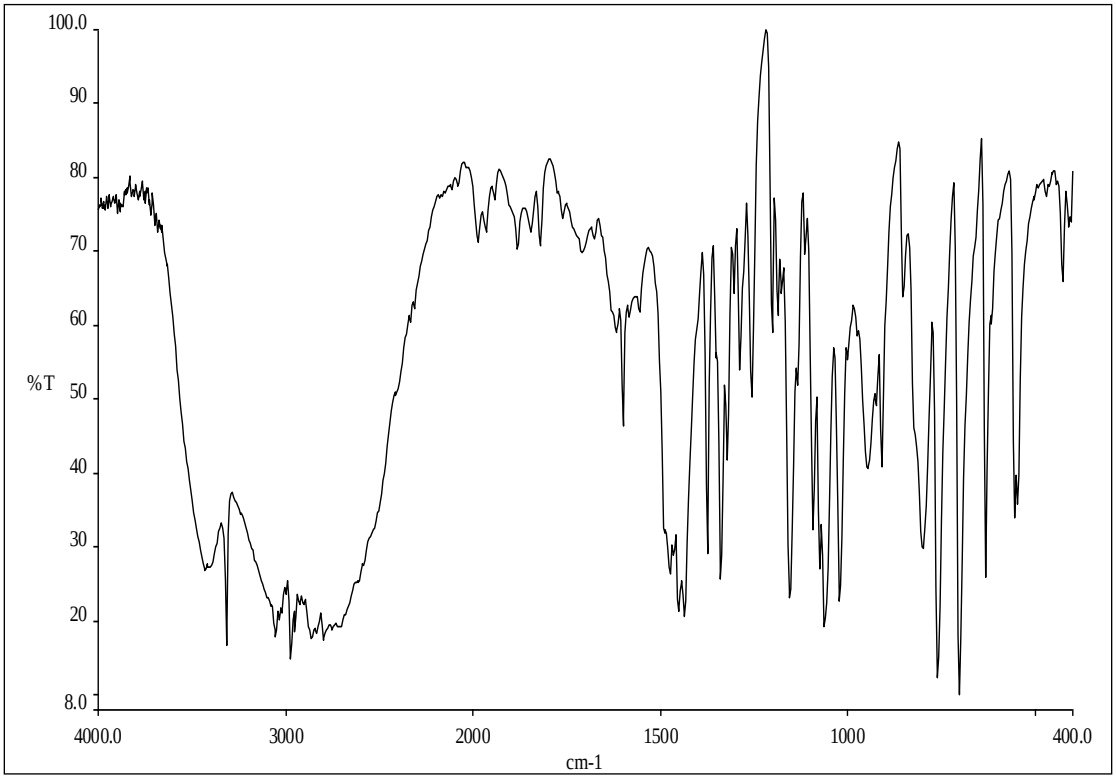
FTIR (ATR): Pseudoephedrine base
16 scans, 2 cm^{-1} resolution, range 4000-600



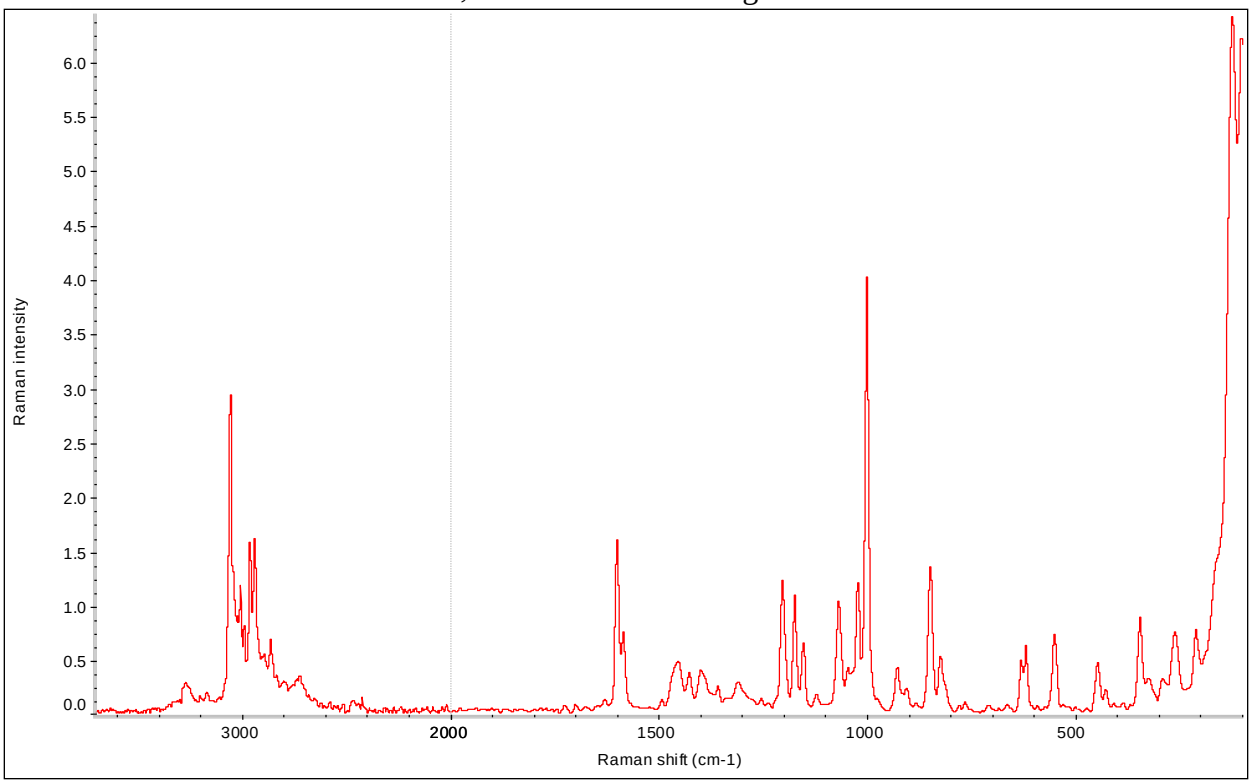
FTIR: Pseudoephedrine Hydrochloride, direct in KBr
2 scans, 4 cm^{-1} resolution Range: 4000-400



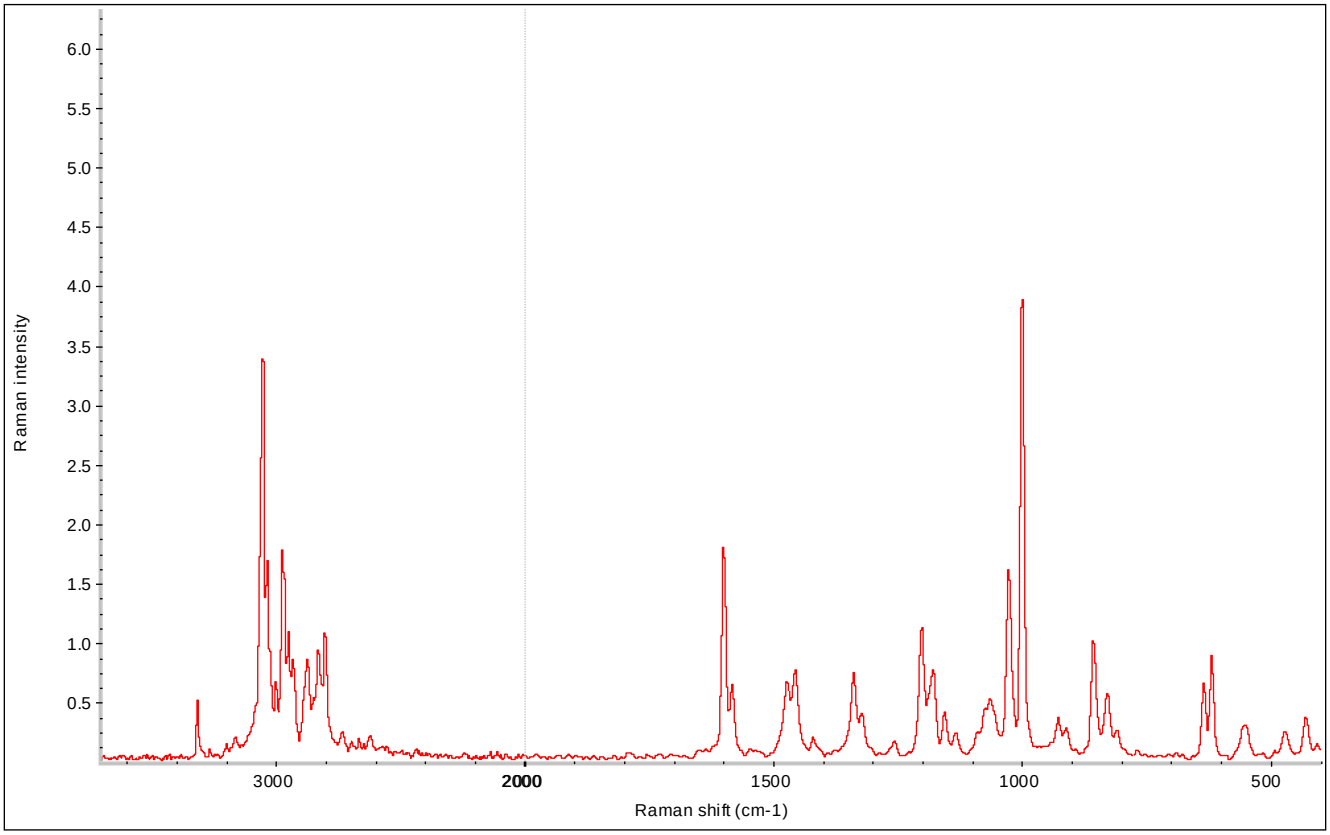
FTIR: Pseudoephedrine Base, direct in KBr
2 scans, 4 cm^{-1} resolution, range: 4000-400 cm^{-1}



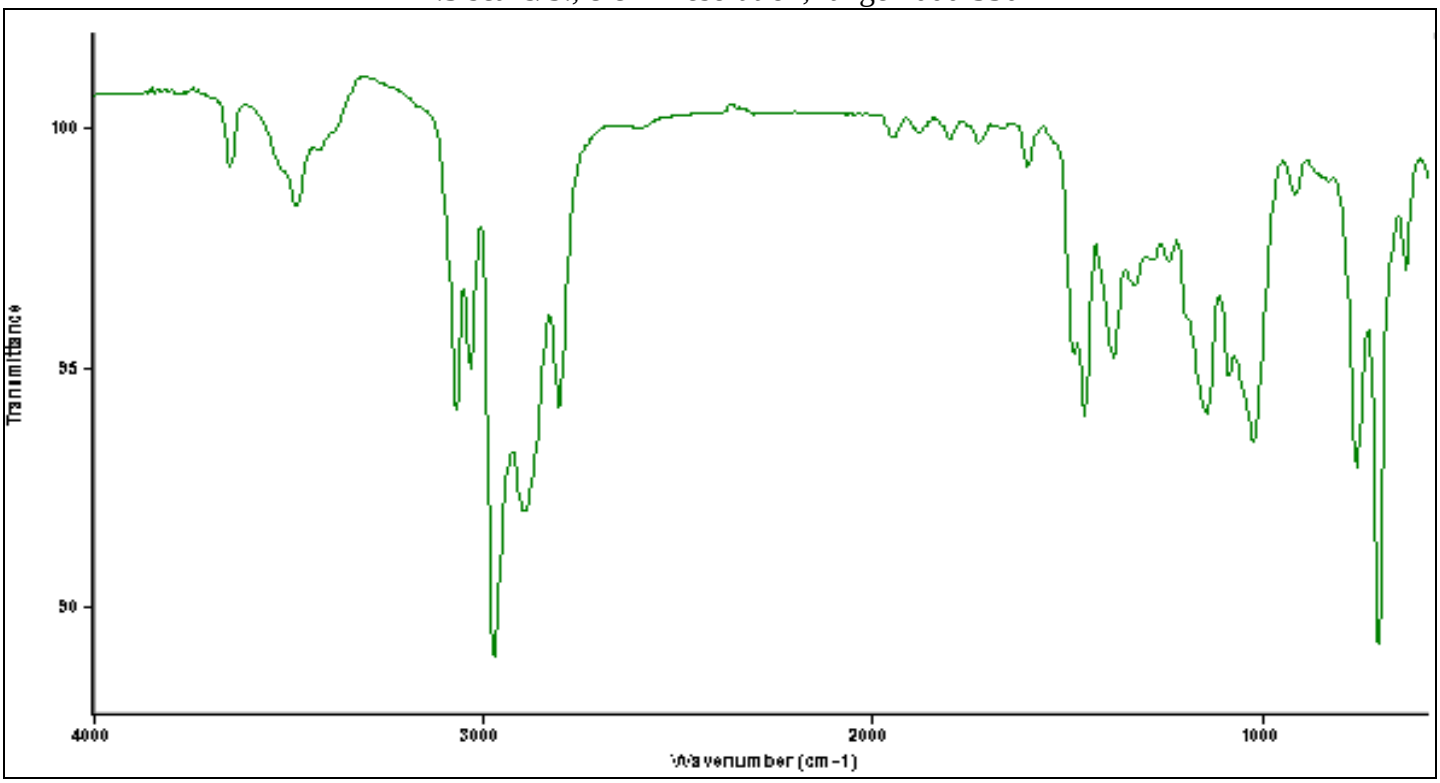
FT RAMAN: Pseudoephedrine hydrochloride
64 scans, 8 cm^{-1} resolution range 3700-410



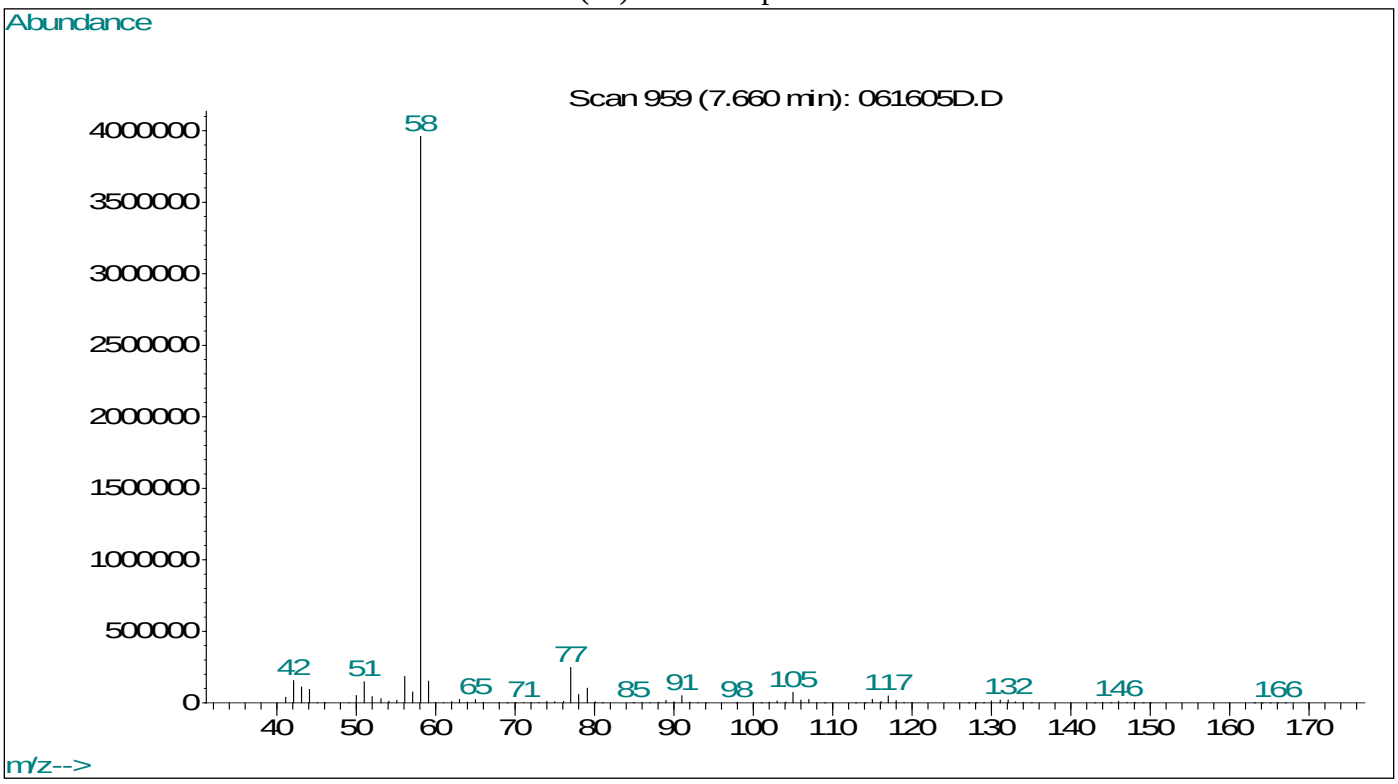
FT-RAMAN: Pseudoephedrine base
64 scans, 8 cm^{-1} resolution Range 3700-410



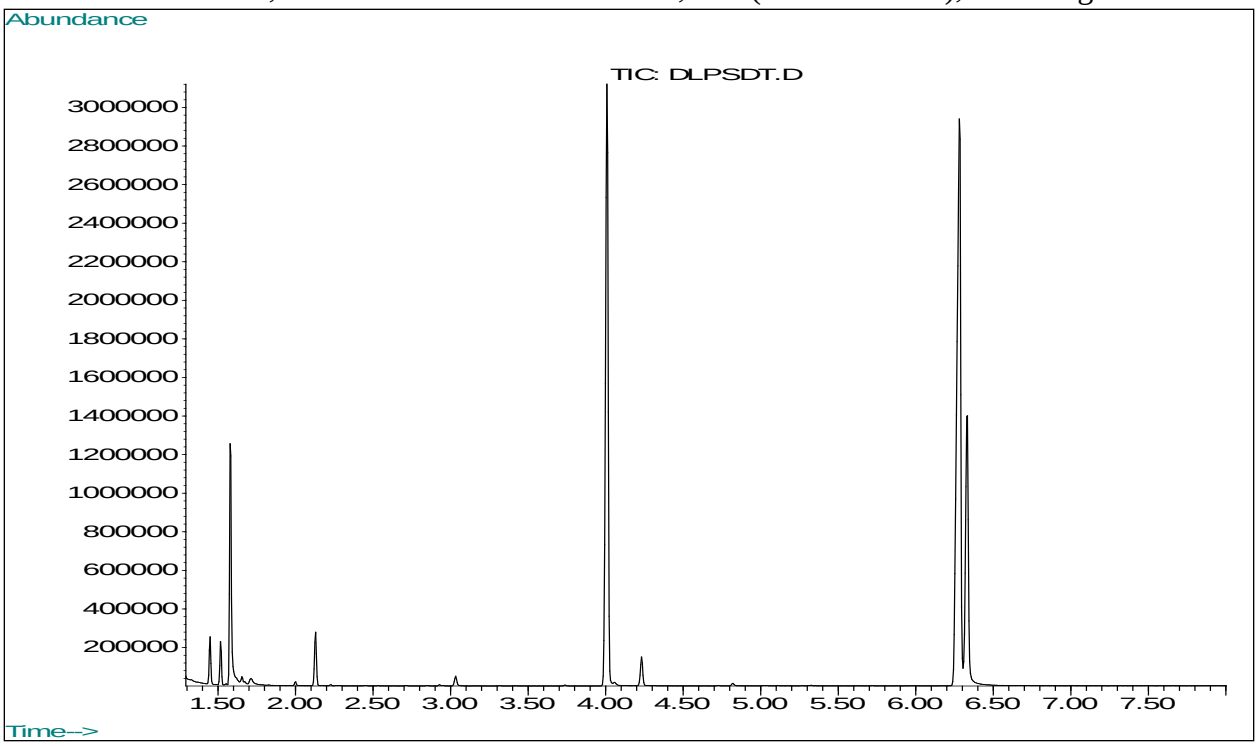
IR (Vapor Phase): Pseudoephedrine base, 1 mg/mL
1.5 scans/S., 8 cm^{-1} resolution, range 4000-550

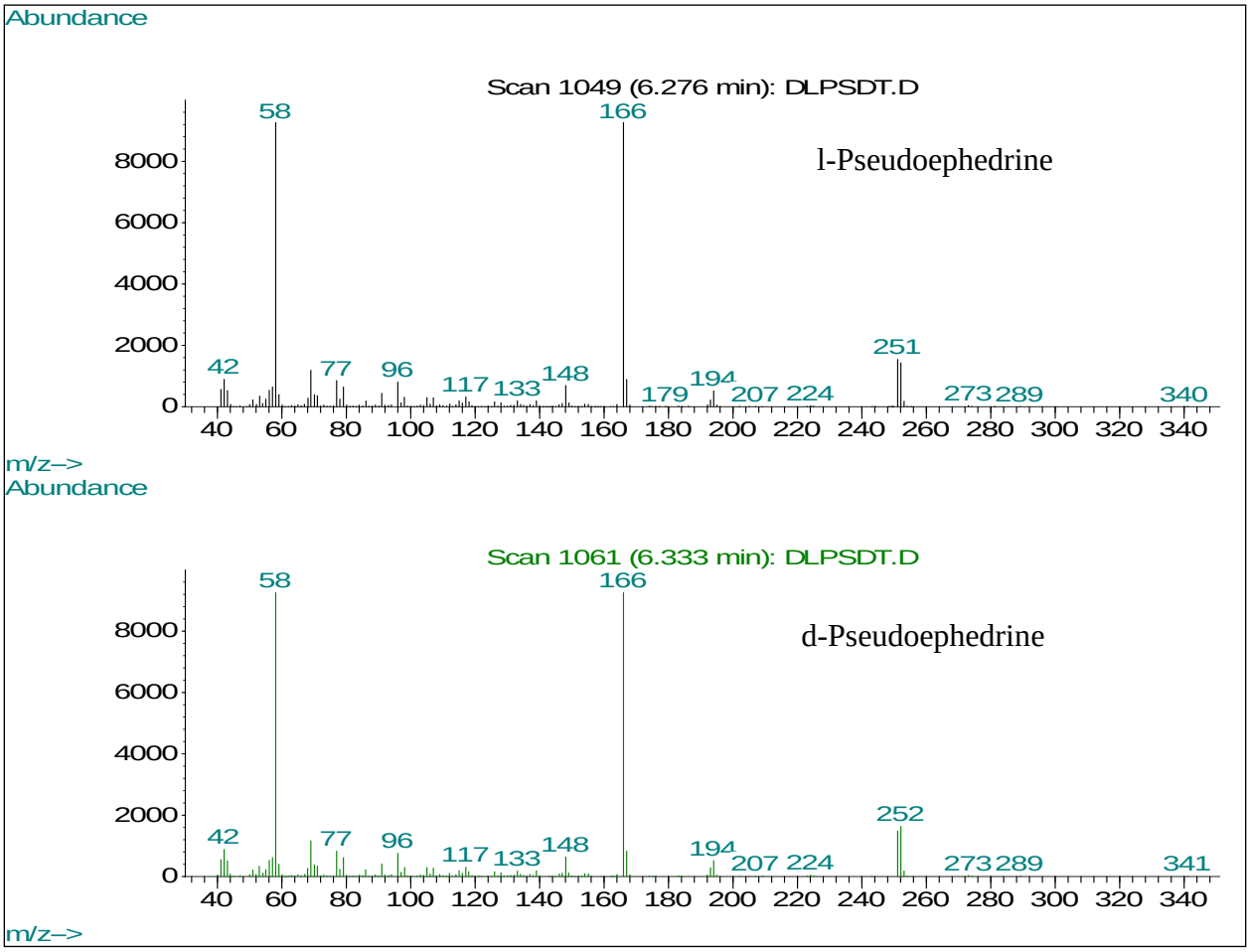


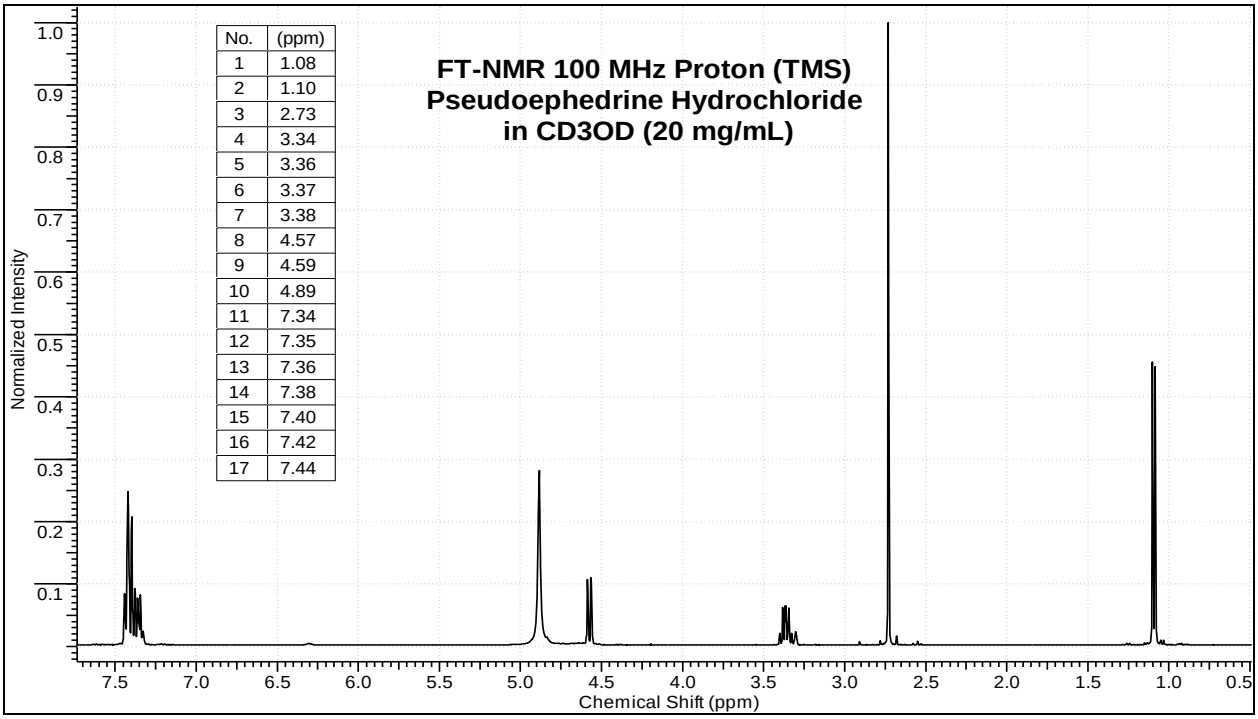
MS (EI): Pseudoephedrine



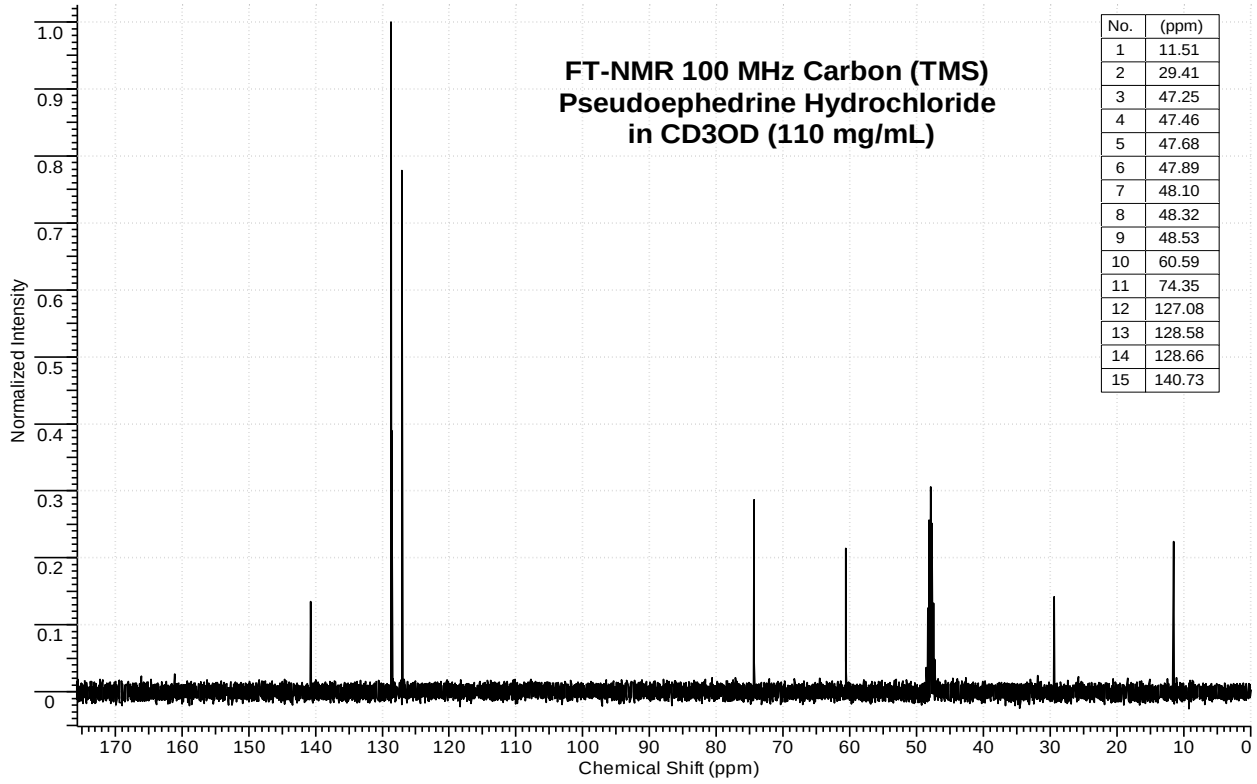
GC/MS-TPC: d,l-Pseudoephedrine
chloroform, base extracted with 5 N NaOH, C-4 (time reference), TPC reagent



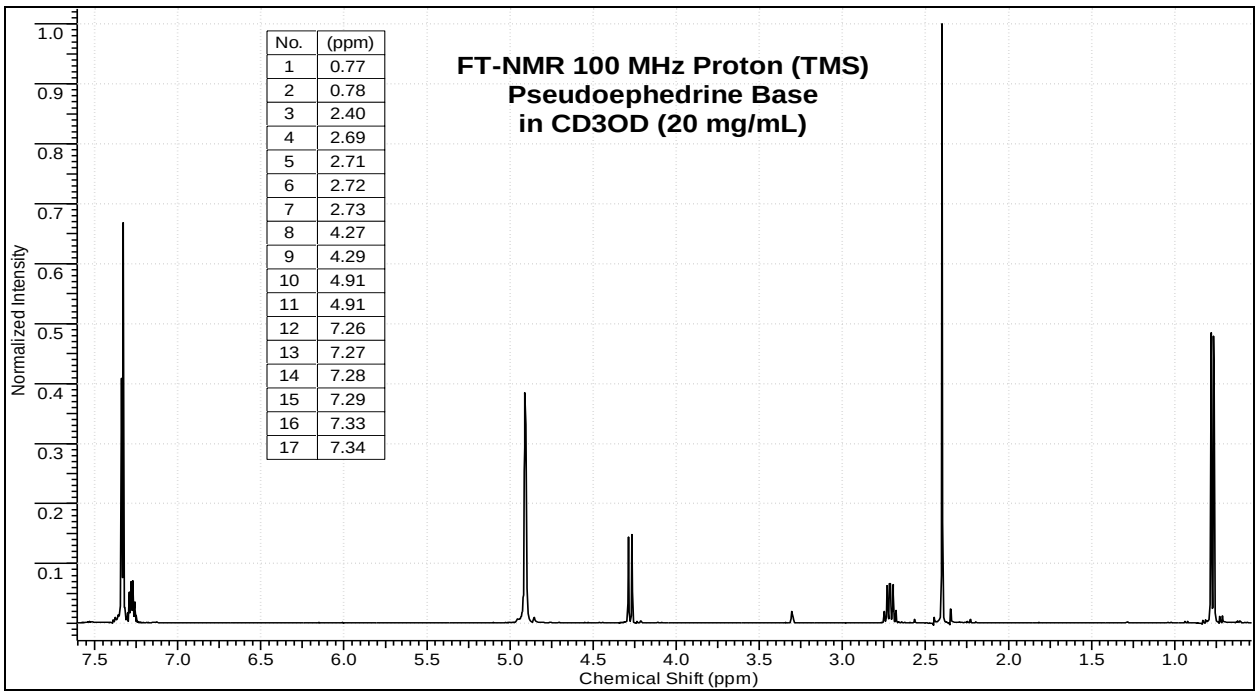




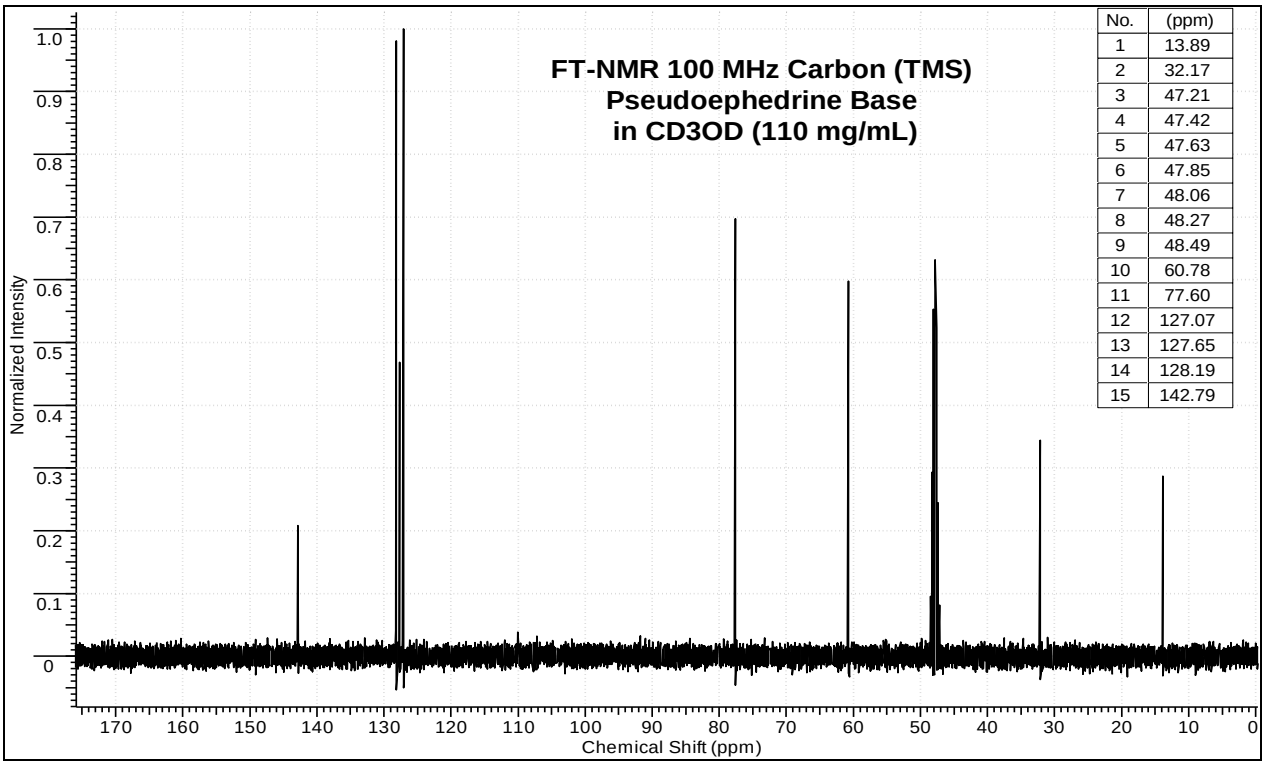
No.	(ppm)
1	1.08
2	1.10
3	2.73
4	3.34
5	3.36
6	3.37
7	3.38
8	4.57
9	4.59
10	4.89
11	7.34
12	7.35
13	7.36
14	7.38
15	7.40
16	7.42
17	7.44



No.	(ppm)
1	11.51
2	29.41
3	47.25
4	47.46
5	47.68
6	47.89
7	48.10
8	48.32
9	48.53
10	60.59
11	74.35
12	127.08
13	128.58
14	128.66
15	140.73

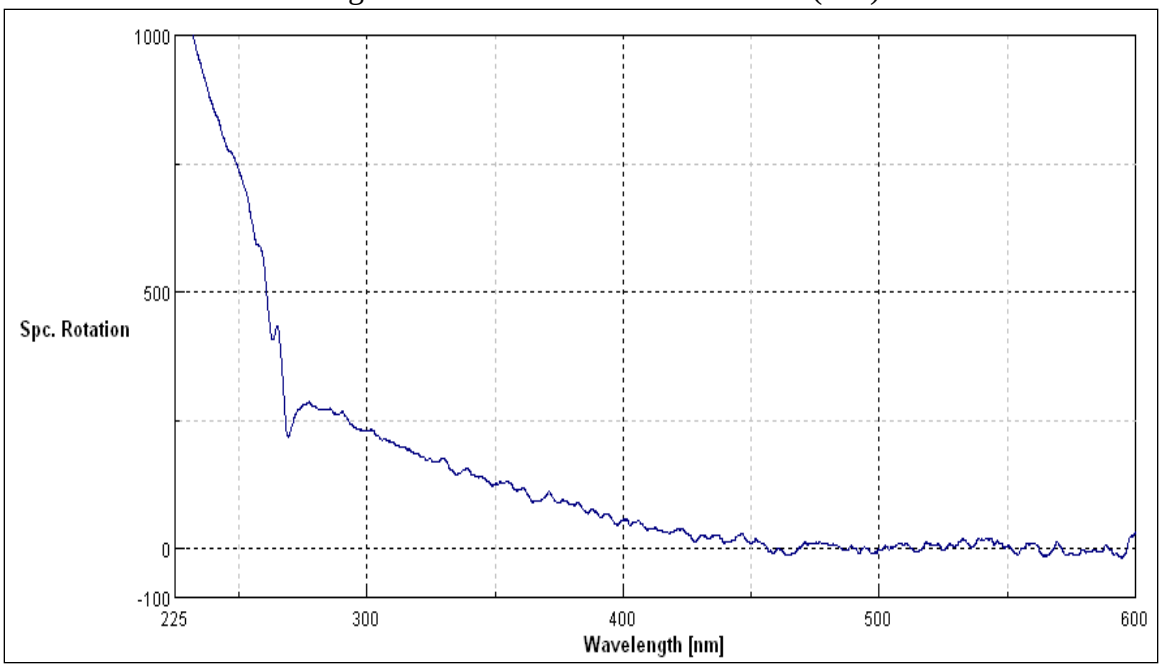


No.	(ppm)
1	0.77
2	0.78
3	2.40
4	2.69
5	2.71
6	2.72
7	2.73
8	4.27
9	4.29
10	4.91
11	4.91
12	7.26
13	7.27
14	7.28
15	7.29
16	7.33
17	7.34

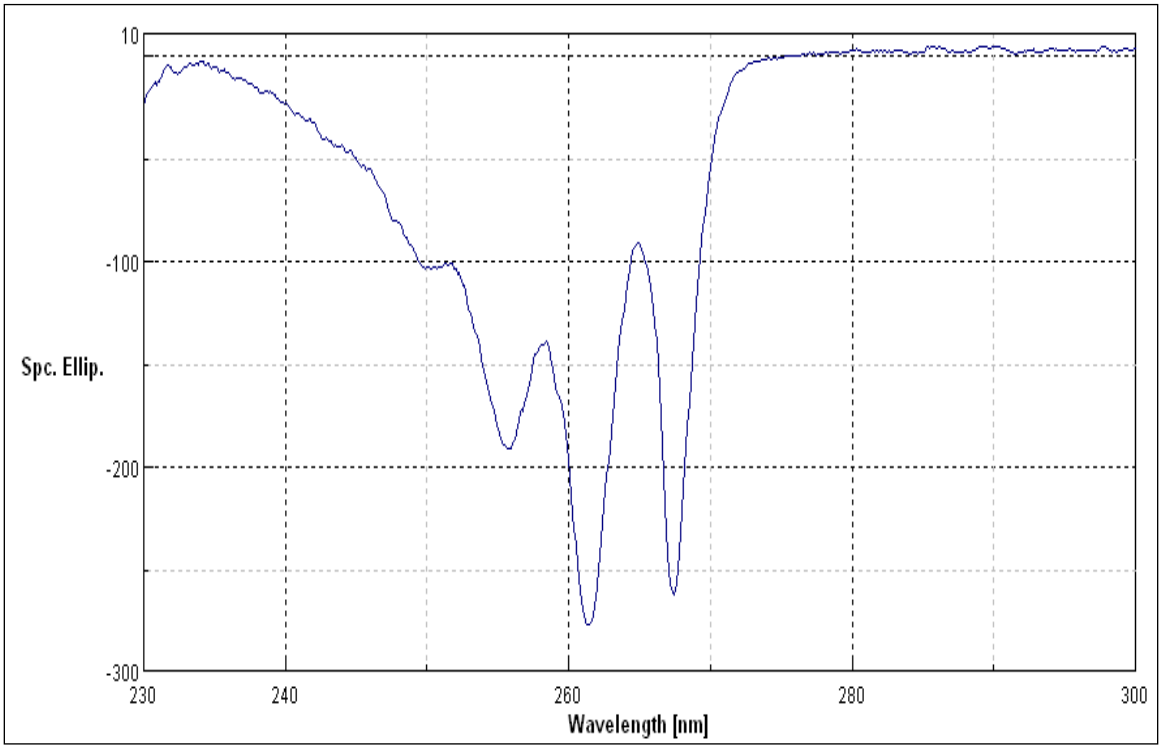


No.	(ppm)
1	13.89
2	32.17
3	47.21
4	47.42
5	47.63
6	47.85
7	48.06
8	48.27
9	48.49
10	60.78
11	77.60
12	127.07
13	127.65
14	128.19
15	142.79

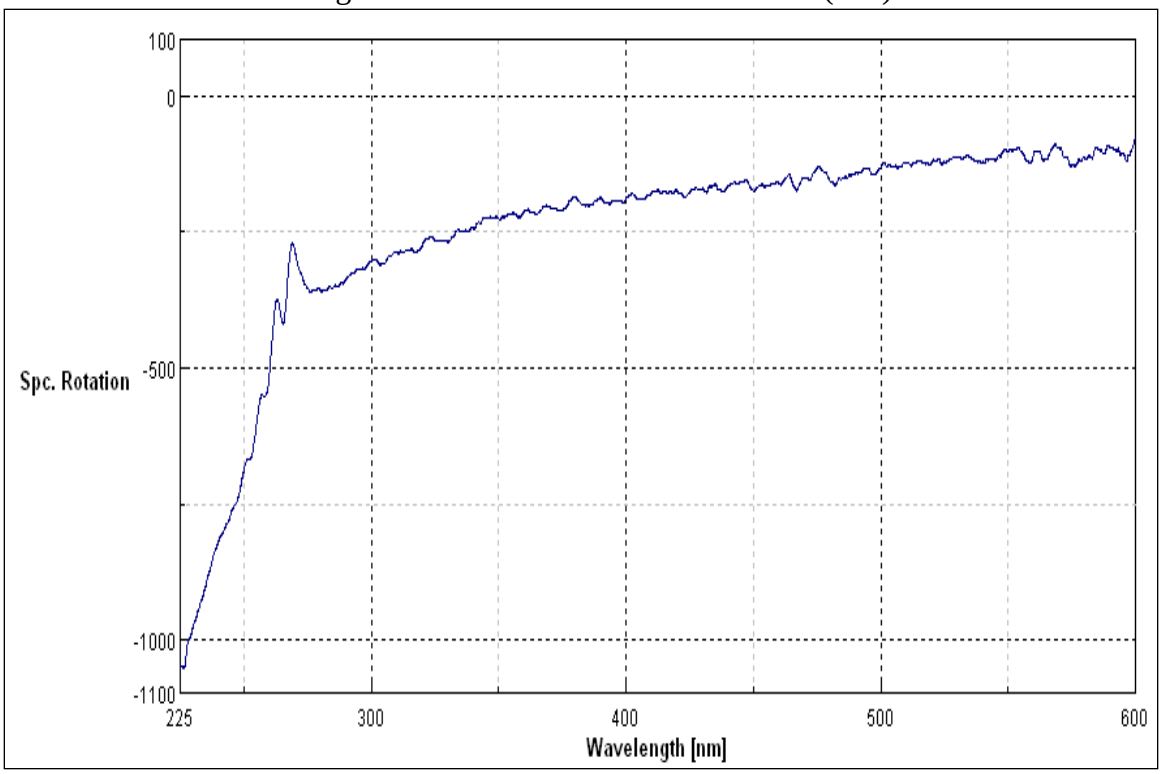
ORD: d-Pseudoephedrine base (methanol)
cell length: 1 cm concentration: 0.100304 (w/v)%



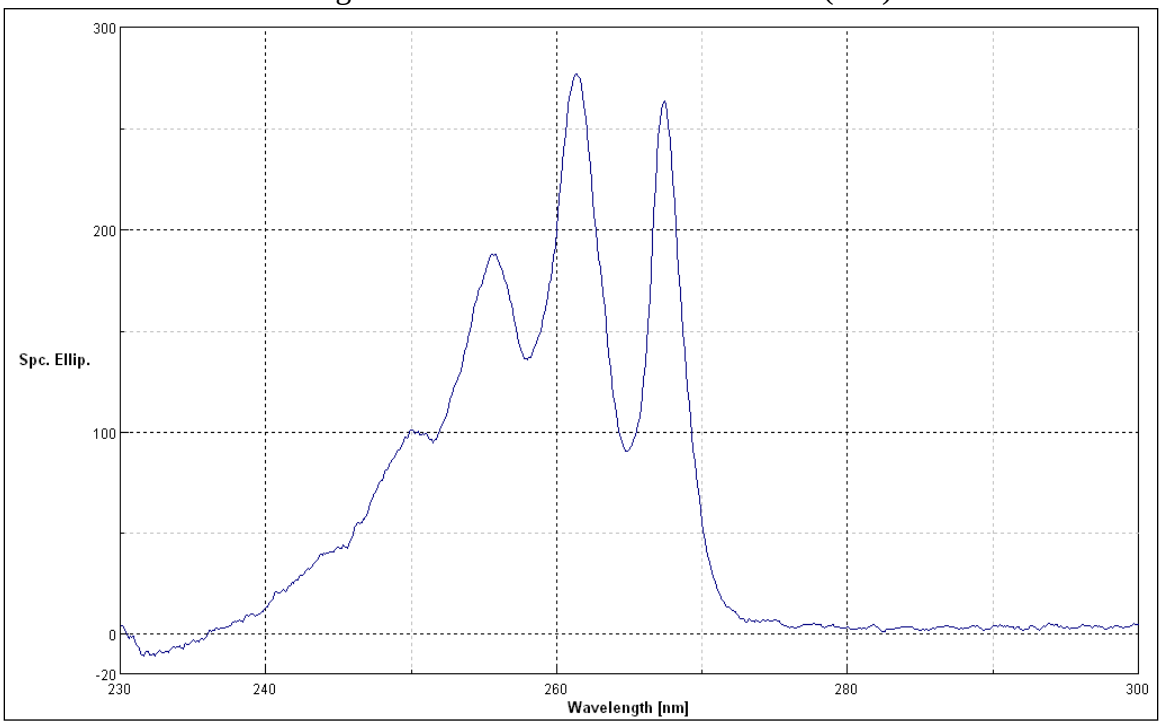
CD: d-Pseudoephedrine base (methanol)
cell length: 1 cm concentration: 0.100304 (w/v)%



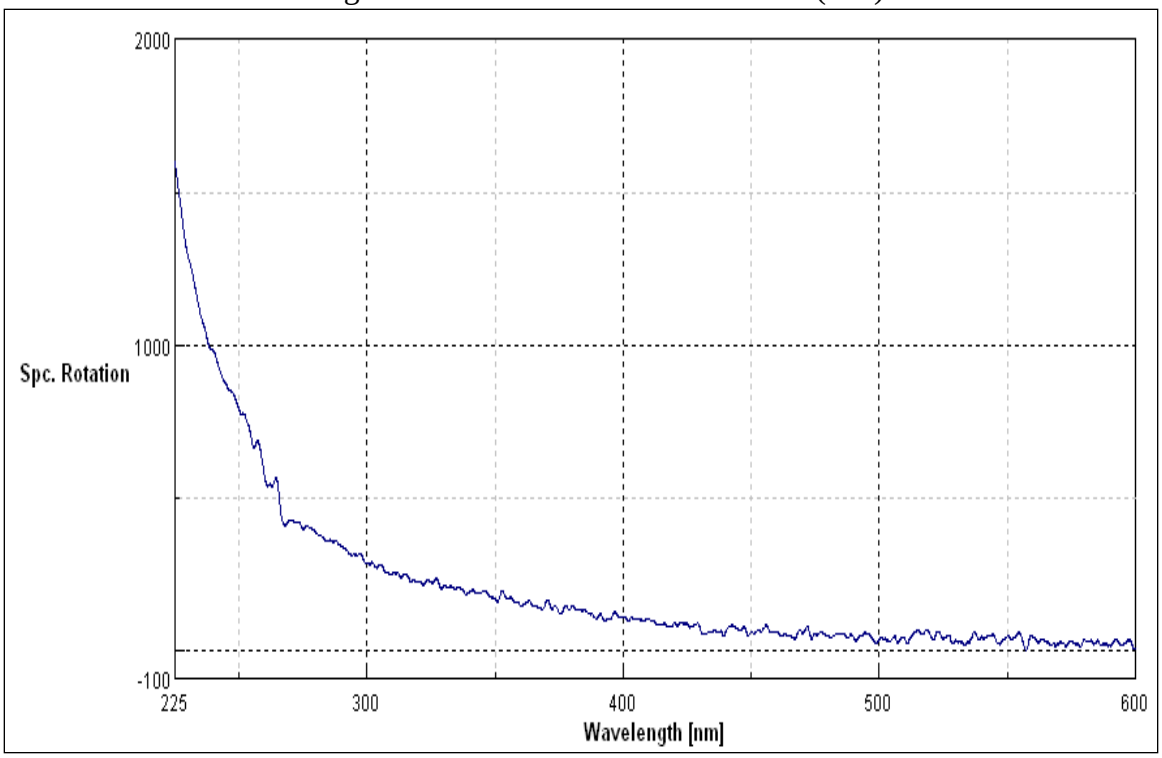
ORD: l-Pseudoephedrine base (methanol)
cell length: 0.5 cm concentration: 0.100504 (w/v)%



CD: l-Pseudoephedrine base (methanol)
cell length: 0.5 cm concentration: 0.100504 (w/v)%



ORD: d-Pseudoephedrine hydrochloride (water)
cell length: 0.5 cm concentration: 0.10189 (w/v)%



CD: d-Pseudoephedrine hydrochloride (water)
cell length: 0.5 cm concentration: 0.10189 (w/v)%