

Supporting Information

A Simple and Expedient Procedure for the Preparation of Gabapentin Lactam (2-aza-spiro[4,5]decan-3-one)

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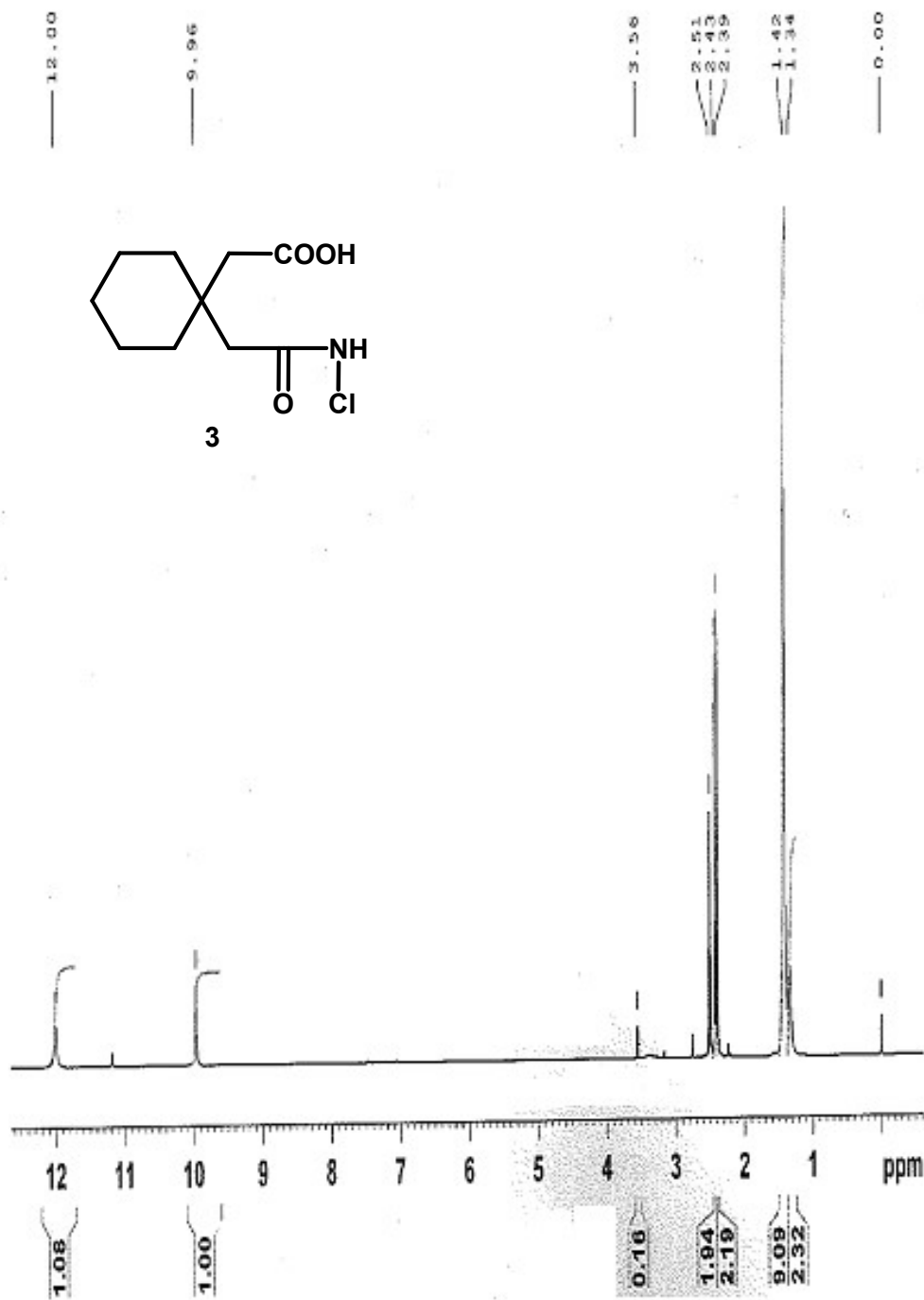
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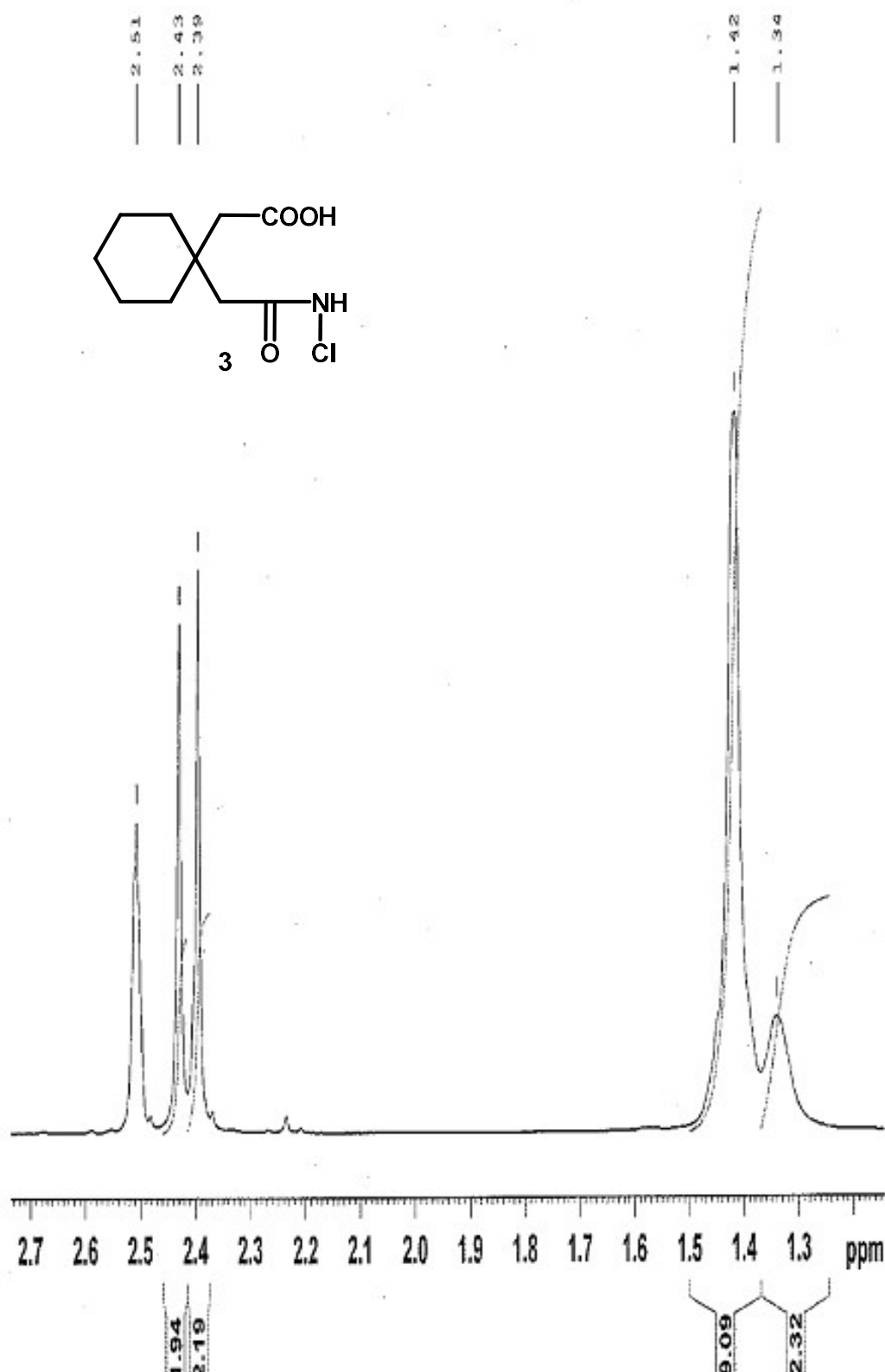
Contents:	Page Number
NMR Spectra	2
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N-chloroamide (3):

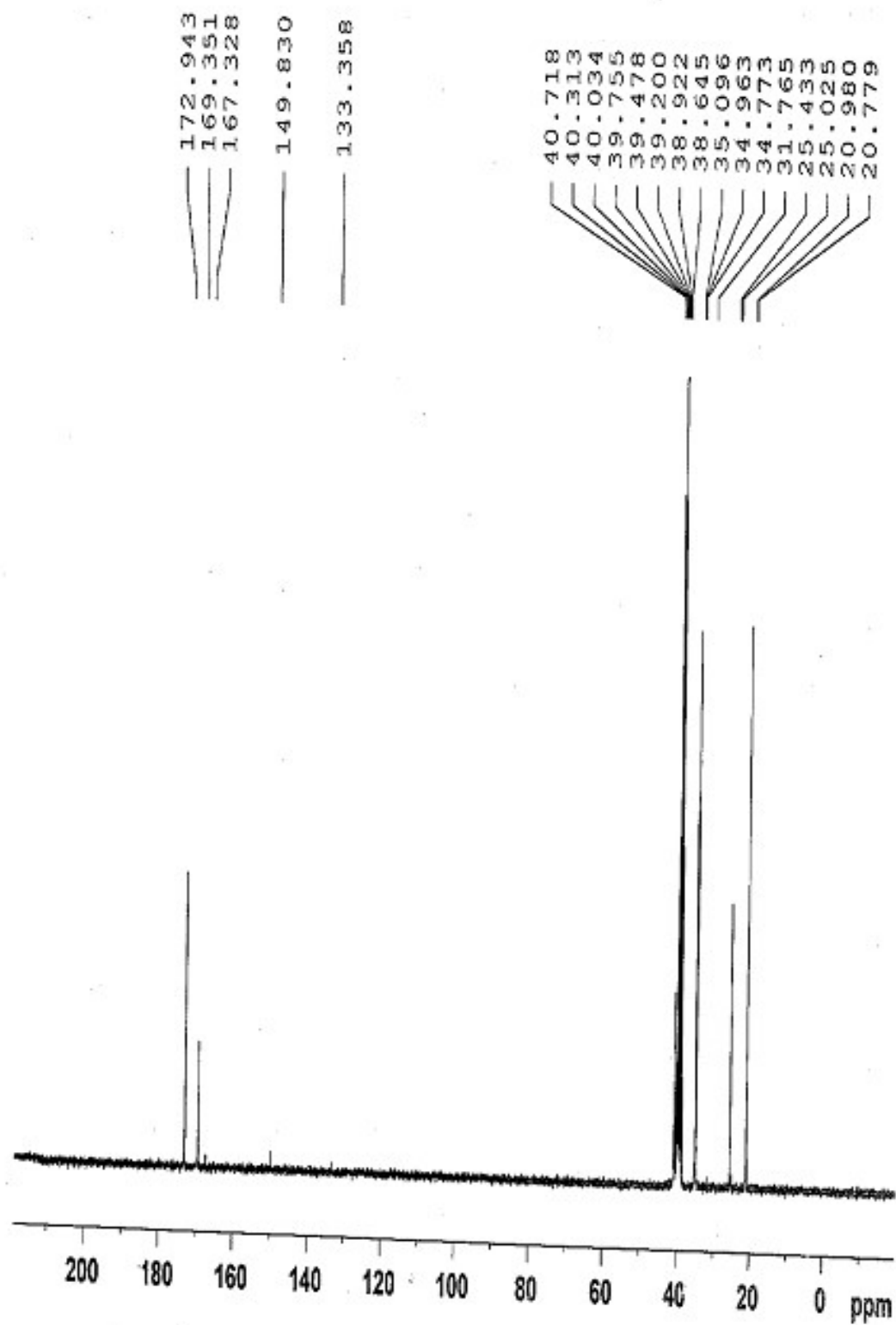
¹H-NMR of 3 (Main page):



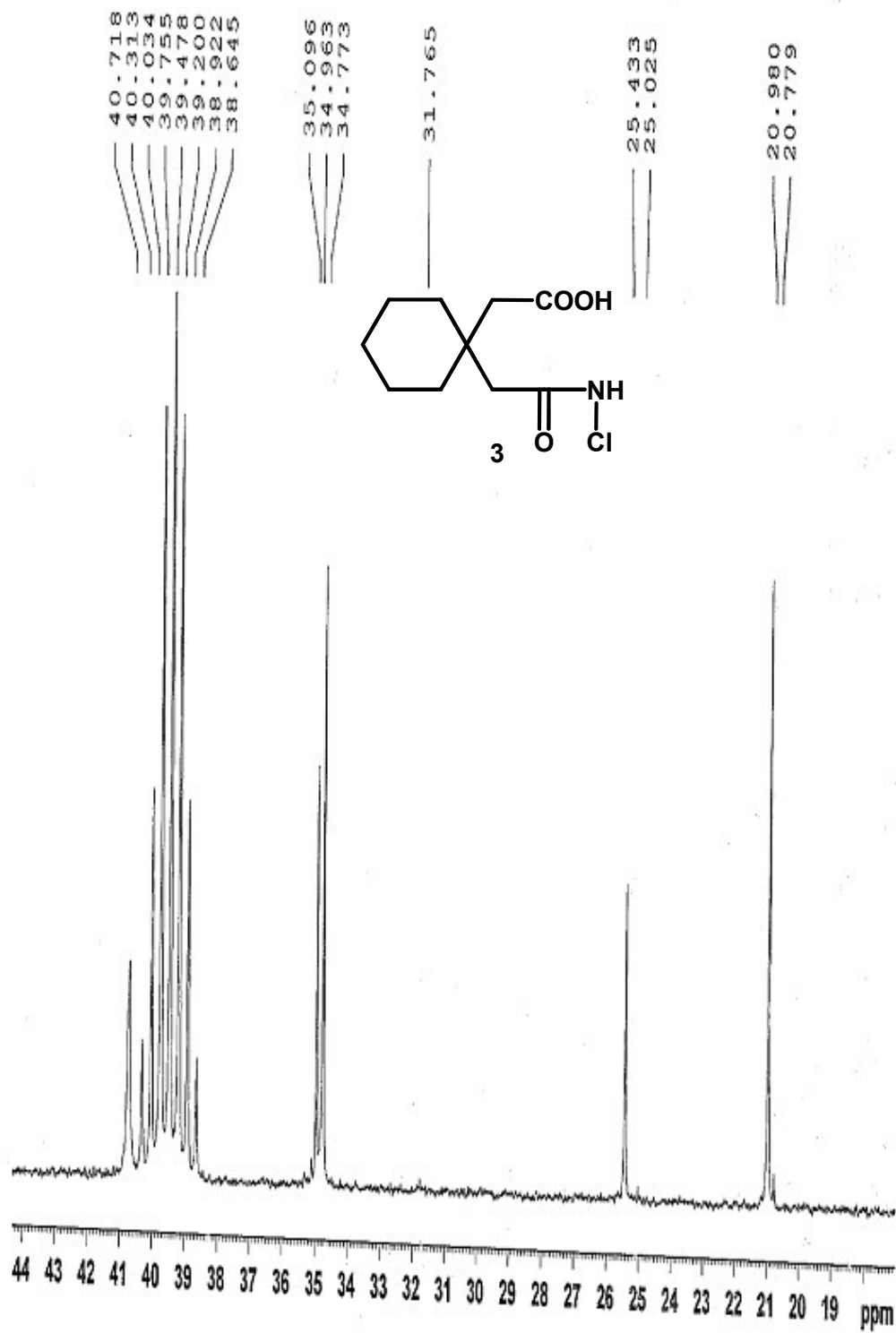
¹H-NMR of 3 (Expanded page):



¹³C-NMR of 3 (Main page):

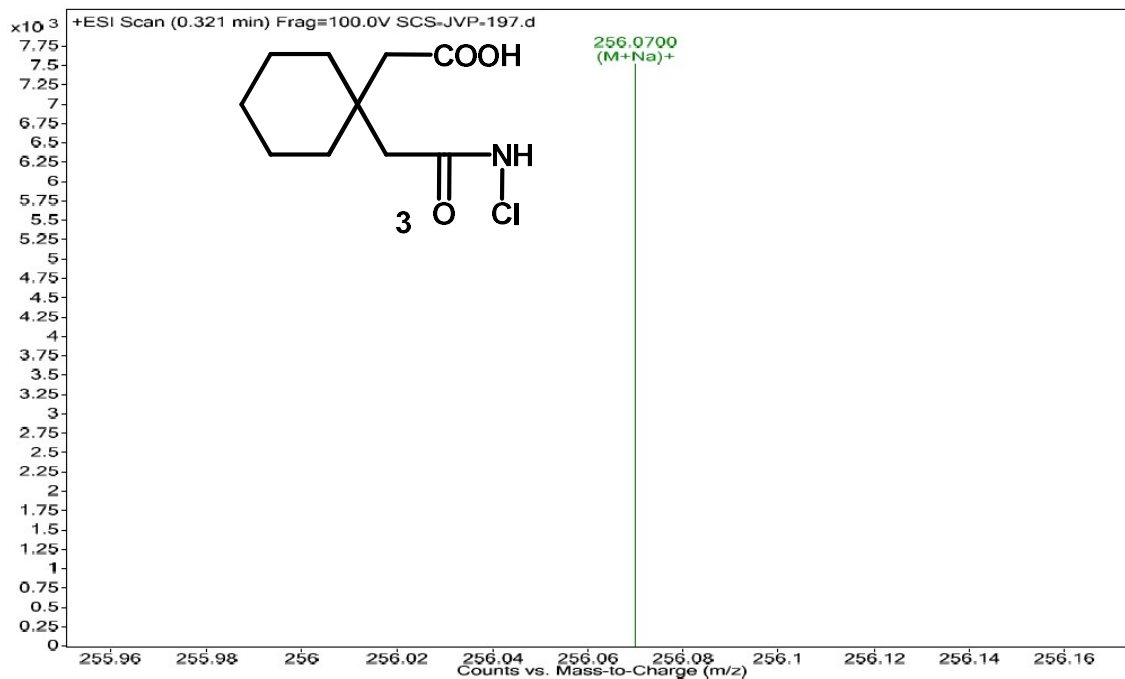


¹³C-NMR of 3 (Expanded page):



High Resolution Mass Spectrum of 3:

Sample Name SCS-JVP-197 **Position** Vial 1 **Instrument Name** Instrument 1 **User Name**
Inj Vol 1 **InjPosition** **SampleType** Sample **IRM Calibration Status** Success
Data Filename SCS-JVP-197.d **ACQ Method** **Comment** **Acquired Time** 8/25/2016 4:20:37 F

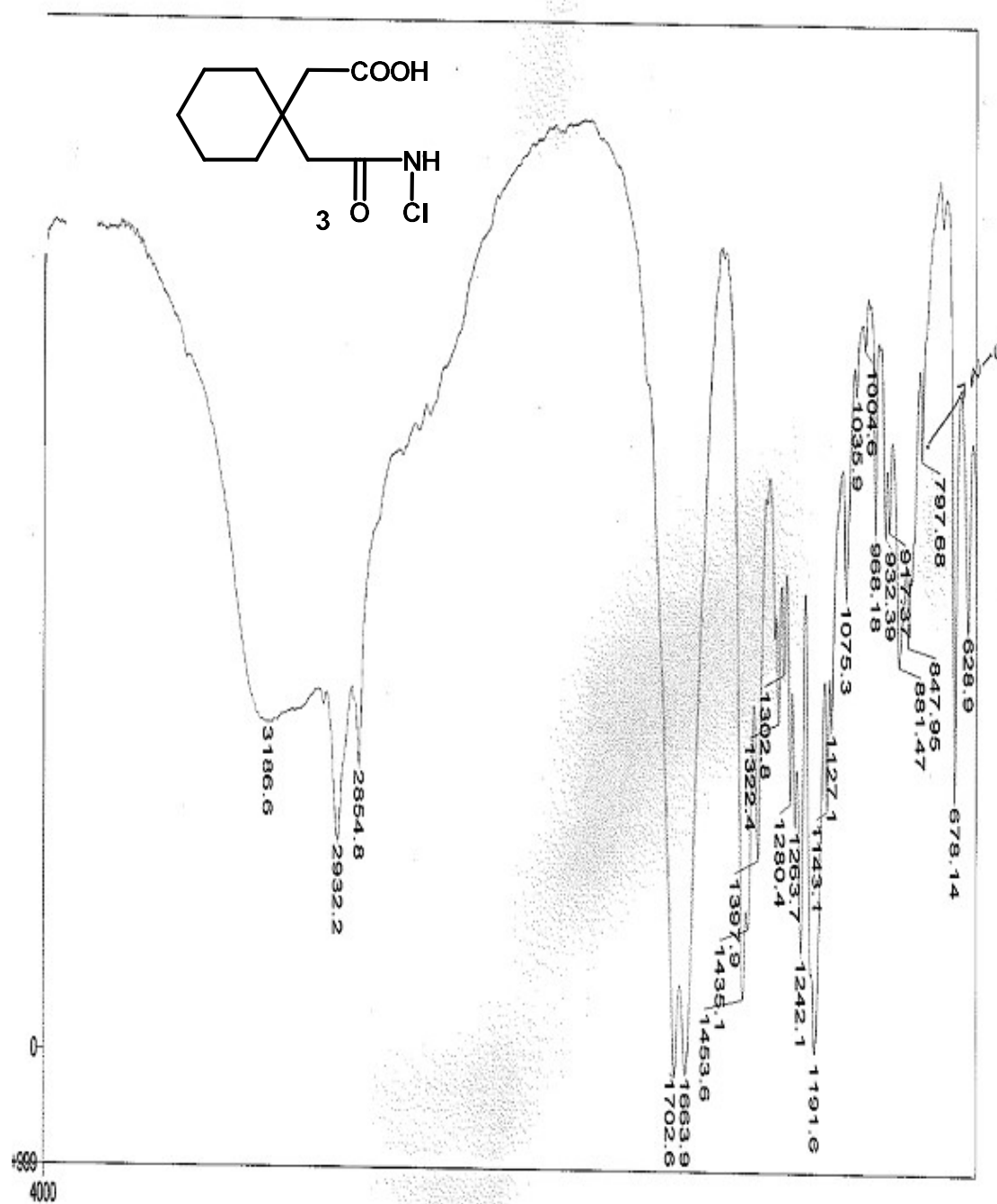


MS Formula Results: + Scan (0.321 min) - SCS-JVP-197.d (SCS-JVP-197.d)

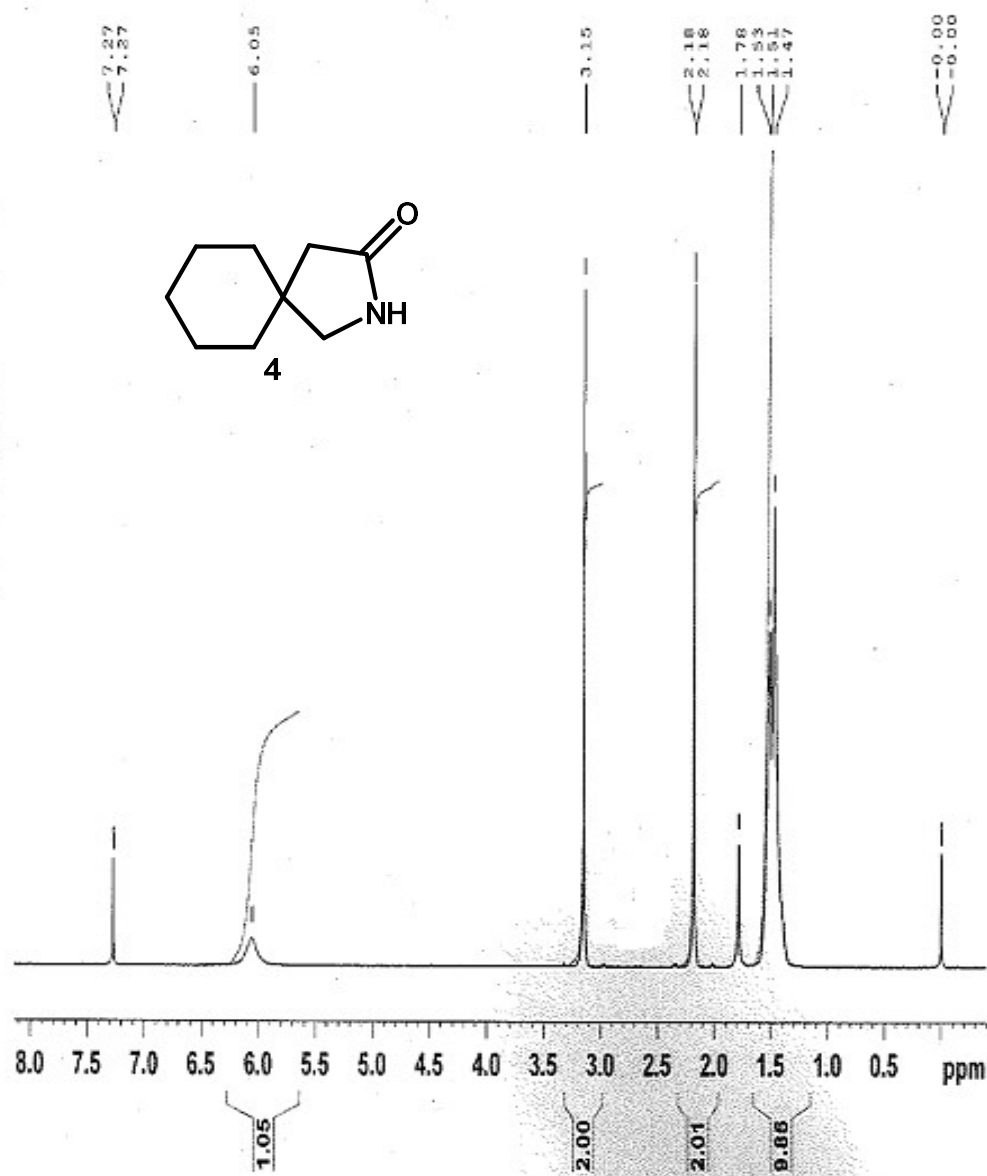
m/z	Ion	Formula	Abundance
256.07	(M+Na)+	C10H15ClNNaO3	7507

Best	Formula (M)	Ion Formula	Calc m/z	Score	Cross Score	Mass	Calc Mass	Diff (ppm)	Abs Diff (ppm)	Abund Match	Spacing Match	Mass Match	m/z	DBE
<input checked="" type="checkbox"/>	C10H16ClN O3	C10H16ClN Na O3	256.0711	42.84		233.0808	233.0819	4.79	4.79	0	0	89.97	256.07	3

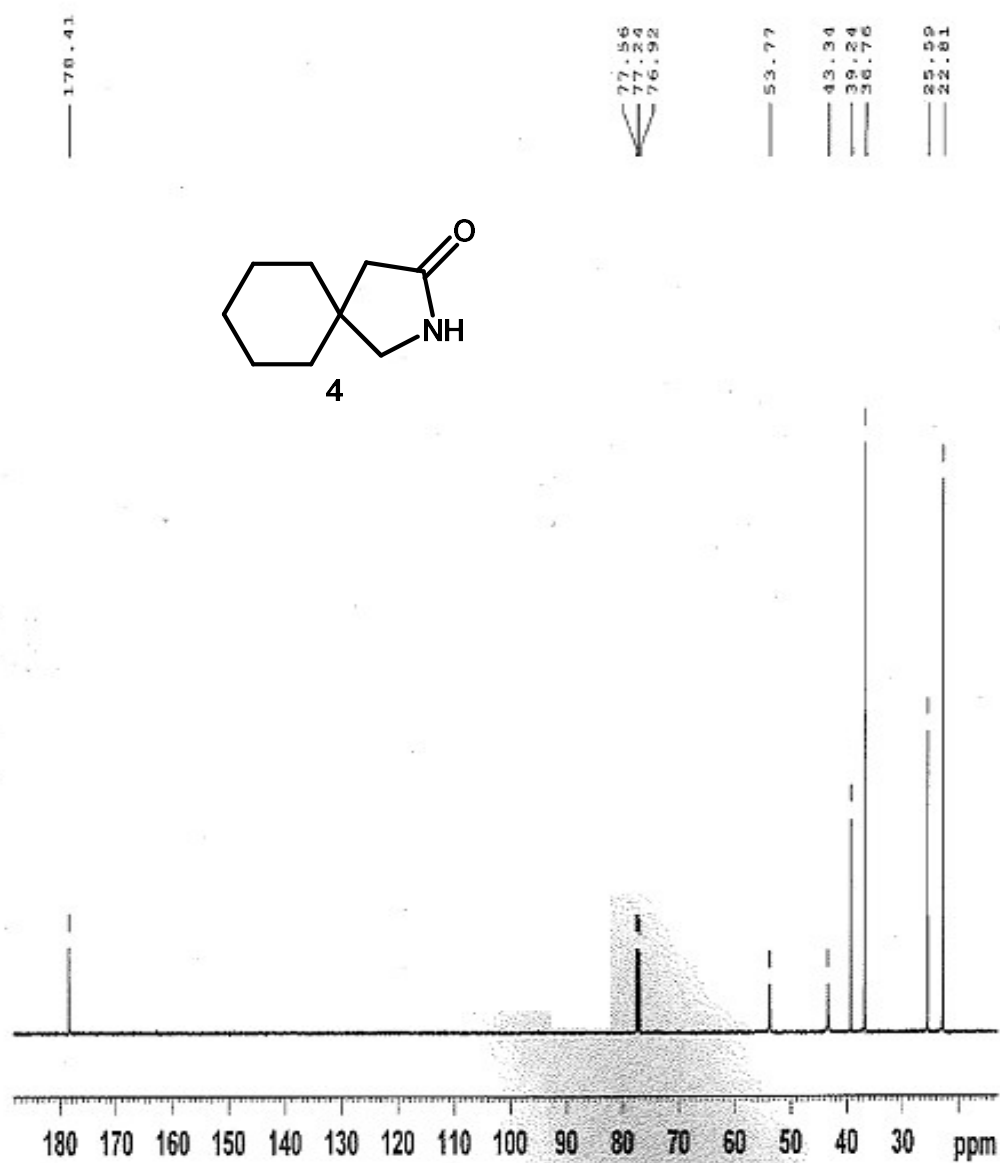
IR spectrum of 3:



¹H-NMR of 4:



¹³C-NMR of 4:

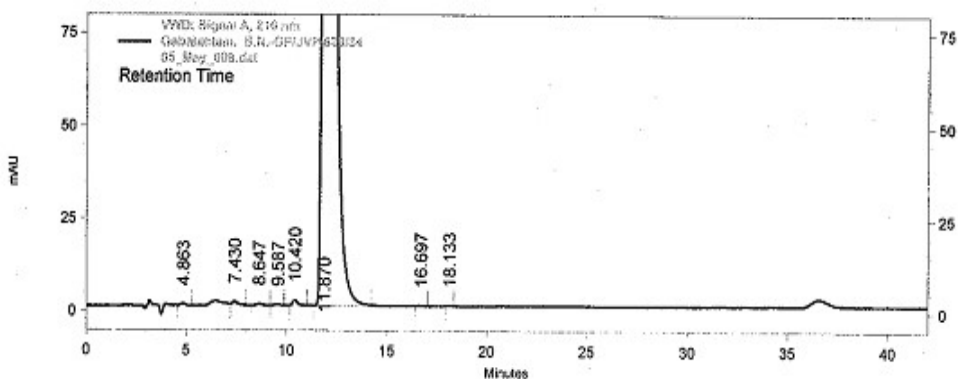


HPLC purity of gabapentin lactam (4) obtained from example 1:

Sample ID : Gabalactam, B.N.-GP/JVP/639/34
 eUser : Roopa
 File Name : D:\System 90\LC_12\Data\2012\May-2012\05052012\Gaba lcms\05_May_009.dat
 Method : D:\System 90\LC_12\Method\Gabapentin LCMS 1.met
 Acquired : 5/5/2012 6:07:11 PM
 Printed : 5/5/2012 7:07:18 PM

Chromatographic Conditions :

Column : Atlantis T-3 150mm x 4.6mm x 3u
 Mobile phase : 50:50/0.05% Formic acid in Water:Methanol
 Detector : 210 nm , Flow :0.6 ml/min, Inj Vol :20µl Col temp:40° C



VWD: Signal
 A, 210 nm
 Results

Pk #	Retention Time	Height	Area	Area Percent	Relative RT
1	4.863	7517	108894	0.0271	0.409
2	7.430	13670	218155	0.0542	0.626
3	8.647	7275	150359	0.0374	0.728✓
4	9.587	3328	80635	0.0200	0.807✓
5	10.420	22119	364212	0.0905	0.878✓
6	11.870	15234118	401463044	99.7537	1.000
7	16.697	2475	43574	0.0108	1.407
8	18.133	1751	25613	0.0064	1.528

Totals		15292253	402454486	100.0000	
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9/5/11

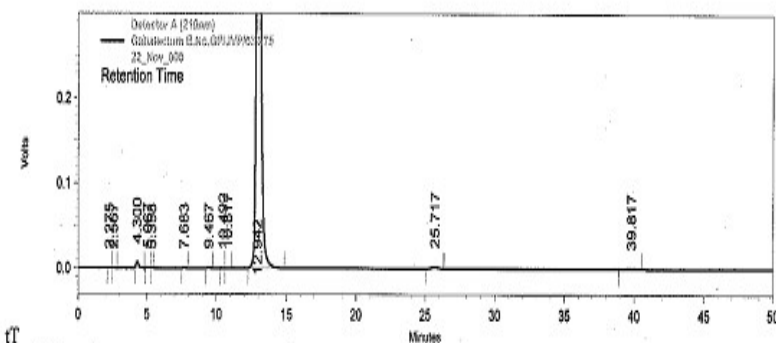
HPLC purity of gabapentin lactam (4) obtained from example 2:

Sample Details

Sample ID : Gabalactum B.No.GP/JVP/639/75
 User Name : Raj
 Filename : E:\System No 44\Le_03\Data\2012\Nov-2012\22112012\Gabalactum\22_Nov_008
 Method Name : E:\System No 44\Le_03\Method\Gabalactum LCMS.met
 Sequence Name : {Sequence Name}
 Run Time : 11/22/2012 6:12:32 PM
 Print Time : 11/22/2012 8:28:18 PM

Chromatographic Conditions

Column : Atlantis T-13 150X4.6X3u
 Mobile Phase : 50:50/0.05%Formic acid in water :Methanol Col temp: 40° C
 Wavelength : 210nm, Flow Rate :0.6ml/min Injection volume : 20ul,



tT

Area % Report

Detector A
(210nm)

Pk #	Retention Time	Area	Height	Area Percent	Relative RT
1	2.275	4565	477	0.0321	0.18
2	2.567	4739	503	0.0334	0.20
3	4.300	91041	7020	0.6407	0.33
4	5.067	8341	785	0.0587	0.39
5	5.358	446	58	0.0031	0.41
6	7.683	6313	509	0.0444	0.59
7	9.467	7304	562	0.0514	0.73
8	10.492	1803	162	0.0127	0.81
9	10.817	2386	128	0.0168	0.84
10	12.942	13980516	633130	98.3942	1.00
11	25.717	73649	2378	0.5183	1.99
12	39.817	27577	532	0.1941	3.08

Totals		14208680	646244	100.0000	
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Sakya
12/11/12

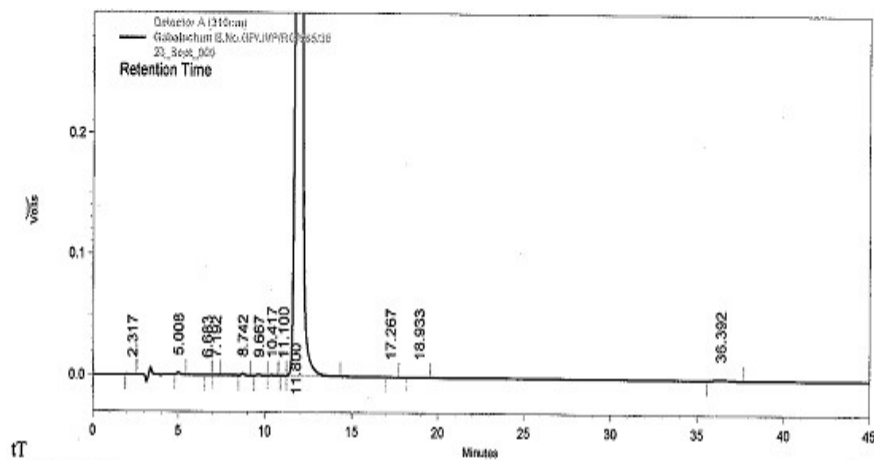
HPLC purity of gabapentin lactam (4) obtained from example 3:

Sample Details

Sample ID : Gabalactum B.No.GP/JVP/RG/665/35
 User Name : Uday
 Filename : E:\System No 44\Le_03\Data\2012\September2012\23092012\GabaLACTUM\23_Sept_006
 Method Name : E:\System No 44\Le_03\Method\Gabalactum LCMS.met
 Sequence Name : {Sequence Name}
 Run Time : 9/23/2012 2:21:15 PM
 Print Time : 9/22/2012 3:29:24 PM

Chromatographic Conditions

Column : Atlantis T-13 150X4.6X3u
 Mobile Phase : 50:50/0.05%Formic acid in water :Methanol Col temp: 40° C
 Wavelength : 210nm, Flow Rate :0.6ml/min Injection volume : 20ul,



IT

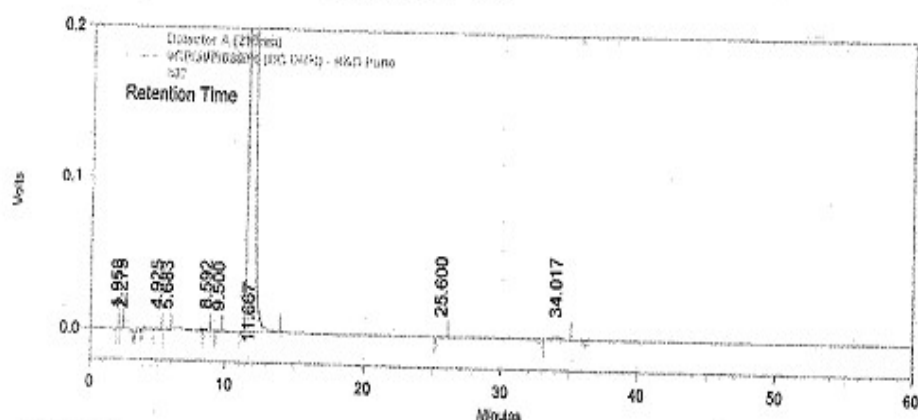
Area % Report
Detector A
(210nm)

Pk #	Retention Time	Area	Height	Area Percent	Relative RT
1	2.317	2839	197	0.013	0.20
2	5.008	20121	1682	0.092	0.42
3	6.683	1966	187	0.009	0.57
4	7.192	690	55	0.003	0.61
5	8.742	16263	1283	0.074	0.74
6	9.667	8591	572	0.039	0.82
7	10.417	4743	338	0.022	0.88
8	11.100	569	59	0.003	0.94
9	11.800	21830378	915848	99.503	1.00
10	17.267	1079	46	0.005	0.00
11	18.933	2430	87	0.011	0.00
12	36.392	49797	989	0.227	3.09

Totals		21939466	921343	100.000	
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HPLC purity of gabapentin lactam (4) obtained from example 4:

Sample name : #GP/JVP/639/96 (DC DMH) - R&D Pune
 Method name : D:\CLASS-VP\BNZ LACTAM\METHOD\BNZ FORMIC.met
 Data file : D:\CLASS-VP\BNZ LACTAM\DATA\JUL - 2014\BNZ FORMIC\26052015\007
 Sequence name : D:\CLASS-VP\BNZ LACTAM\SEQUENCE\BNZ FORMIC\May2015\25052015.seq
 Acquired time : 26/05/2015 15:47:29
 Print time : 26/05/2015 16:53:38
 Injection Vol : 20
 Vial : 10005
 Instrument ID : AQC 06 (Offline)
 Sample description : COLUMN ID : H-69 NEW

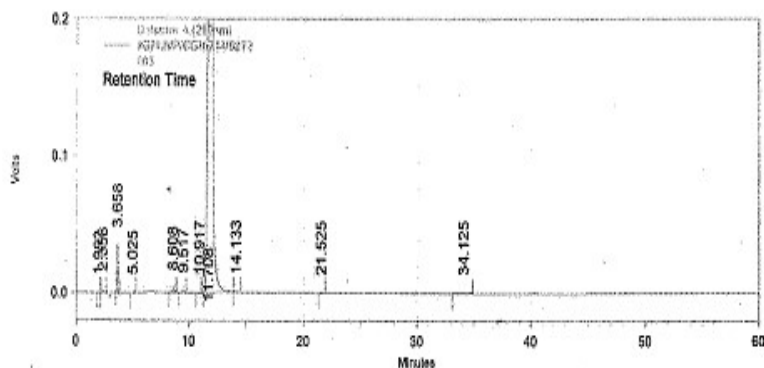


Detector A (210nm)						
	Pk #	Retention Time	Area	Area Percent	Relative RT	Name
1		1.958	2026	0.01	0.17	UNK
2		2.275	2819	0.02	0.19	UNK
3		4.925	6381	0.03	0.42	UNK
4		5.683	4398	0.02	0.49	UNK
5		8.592	14476	0.08	0.74	IMIDE
6		9.500	4975	0.03	0.81	UNK
7		11.667	18477242	99.43	1.00	BNZ
8		25.600	2815	0.02	2.20	UNK
9		34.017	67264	0.36	2.92	Solvent
Totals			18582396	100.00		

1
 26/5/15

HPLC purity of gabapentin lactam (4) obtained from example 5:

Sample name : #GP/JVP/CGH/714/82T2
 Method name : D:\CLASS-VP\BNZ LACTAM\METHOD\BNZ FORMIC.met
 Data file : D:\CLASS-VP\BNZ LACTAM\DATA\JUL - 2014\BNZ FORMIC\27052015\003
 Sequence name : D:\CLASS-VP\BNZ LACTAM\SEQUENCE\BNZ FORMIC\May2015\25052015.seq
 Acquired time : 27/05/2015 11:19:55
 Print time : 27/05/2015 13:50:50
 Injection Vol : 20
 Vial : 10003
 Instrument ID : AQC 06 (Offline)
 Sample description : COLUMN ID : ~~F-69~~ NEW



Pk #	Retention Time	Area	Area Percent	Relative RT	Name
1	1.992	1847	0.01	0.17	Unknown
2	2.358	17675	0.10	0.20	Unknown
3	3.658	285604	1.65	0.31	Unknown
4	5.025	4033	0.02	0.43	Unknown
5	8.608	38823	0.22	0.74	Unknown
6	9.517	22001	0.13	0.81	IMIDE
7	10.917	2807	0.02	0.93	Unknown
8	11.708	16867585	97.67	1.00	BNZ
9	14.133	6222	0.04	1.21	Unknown
10	21.525	1400	0.01	1.84	Unknown
11	34.125	22597	0.13	2.92	Solvent

known (starting material)
 (4)

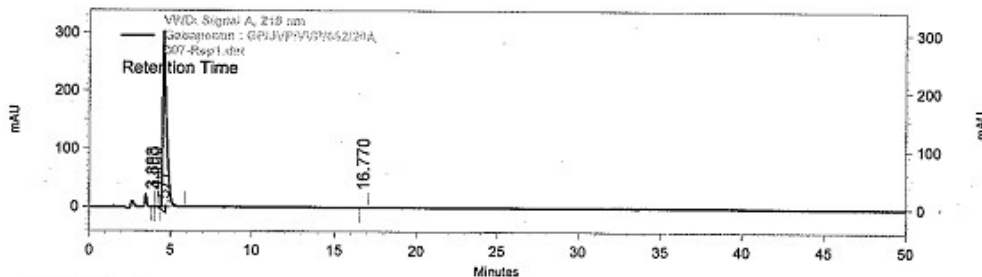
Totals		17270594	100.00		
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27/5/15

HPLC purity of gabapentin 1 obtained from gabalactam 4 via intermediate 3 (Gaba early method):¹

Gabapentin API (1) obtained from first lot of gabapentin hydrochloride (5):

Sample ID : Gabapentin : GP/JVP/VVP/652/20A
 User : Guru
 File Name : D:\System No 83\LC_13\Data\2012\May 2012\14052012\Gaba early\007-Rep1.dat
 Method : D:\System No 83\LC_13\Methods\Gaba early.met
 Acquired : 5/14/2012 5:12:22 PM
 Printed : 5/15/2012 8:48:01 AM
Chromatographic Conditions :
 Column : Phenomenex luna C-18 250 x 4.6 x 5µ Column no:178
 Mobile Phase : Buffer:ACN / 76:24
 Buffer : 1.83g sodium perchlorate + 0.58g amm.dihydrogen phosphate in 1 ltr water pH 1.8 with perchloric acid
 Diluent : 2.32g amm. dihydrogen phosphate in 1ltr water pH 2.0 with OPA
 Flow rate : 1.0ml/min, Volume: 20 µl , Oven Temp: 40 °C Detector : 215nm



VWD: Signal
 A, 215 nm
 Results

Pk #	Retention Time	Height	Area	Area Percent	Relative RT
1	3.89	1601	8973	0.0118	0.850
2	4.10	1697	9828	0.0129	0.896
3	4.58	5050419	76262262	99.9460	1.000
4	16.77	1350	22429	0.0294	3.670
Totals		5055067	76303492	100.0000	

Continued to page number 16

Sheet2

Gabapentin B.NO: Gp/JVP/652/20A

GP Area	Imp- E
78377001	153037
78316065	158484
78123148	152623

SAMPLE AREA				Unknown	Unknown
GABA	IMP-E	IMP-A	IMP-B	Imp@1.4rrt	imp RRT 3.7
76262262	0	0	0	0	24795
76461137					
76361700	0	0	0	0	24795

Average	76346533
SD	43088.26
RSD	0.056

154714.67
3270.90
2.11

Imp-E Std	2.21
Std Prepr	351.98 mg of Gaba WS---->25 ML Add 2.5ml of Imp-E Soln
(GP WS + Imp E)	
Sample	141.58 mg of gaba ws to 10ml 14.158 mg/ml

Moisture Content----->0

GP	IMP-E
14.079mg/ml	0.009mg/ml

					Result %	LIMIT
Imp E	0	0.009	1	100	0.0000	0.10%
	154714.67	14.158	1			
Imp A	0	0.009	1	100	0.0000	0.10%
	154714.67	14.158	5.3			
Imp B	0	0.009	1	100	0.0000	0.05%
	154714.67	14.158	0.35			
Unknown Impurity 1.4RRT	0	0.009	1	100	0.000	0.05%
	154714.67	14.158	0.41			

ASSAY	76361700	14.079	100	100	99.46	98.7 to 101%
as such	76346533	14.158	100.00			

Unknown Impurity 3.7 RRT	24795	0.009	1	100	0.0244	0.05%
	154714.67	14.158	0.41			

Unknown Impurity 0.85 RRT	9559	0.009	1	100	0.0094	0.05%
	154714.67	14.16	0.41			

Unknown Impurity 0.89 RRT	10827	0.01	1	100	0.0107	0.05%
	154714.67	14.16	0.41			

BP
14/05/11

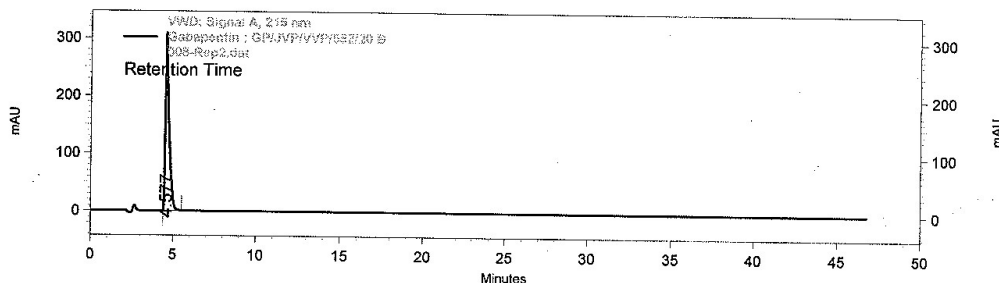
Gabapentin API (1) obtained from second lot of gabapentin hydrochloride (5) (Gaba early method):

Page 1 of 1

Sample ID : Gabapentin : GP/JVP/VVP/652/20 B
 User : Guru
 File Name : D:\System No 83\LC_13\Data\2012\May 2012\14052012\Gaba early\008-Rep2.dat
 Method : D:\System No 83\LC_13\Methods\Gaba early-1.met
 Acquired : 5/14/2012 7:34:47 PM
 Printed : 5/14/2012 8:23:36 PM

Chromatographic Conditions :

Column : Phenomenex luna C-18 250 x 4.6 x 5 μ Column no: 178 21 L
 Mobile Phase : Buffer: ACN / 76:24
 Buffer : 1.83g sodium perchlorate + 0.58g amm.dihydrogen phosphate in 1 ltr water pH 1.8 with perchloric acid
 Diluent : 2.32g amm. dihydrogen phosphate in 1ltr water pH 2.0 with OPA
 Flow rate : 1.0ml/min, Volume: 20 μ l , Oven Temp: 40 $^{\circ}$ C Detector : 215nm



VWD: Signal
 A, 215 nm
 Results

Pk #	Retention Time	Height	Area	Area Percent	Relative RT
1	4.58	5170253	77636851	100.0000	1.000
Totals		5170253	77636851	100.0000	

Continued to page number 18

Sheet2

Gabapentin B.NO: Gp/JVP/652/20B

GP Area	Imp- E
76377001	153037
76316065	158484
76123148	152623

SAMPLE AREA	IMP-E	IMP-A	IMP-B	Unknown Imp@1.4rrt	Unknown imp RRT 3.6
GABA					
77897610	0	0	0	0	36394
77636851					
77767231	0	0	0	0	36394

Average	76346533	154714.67
SD	43088.26	3270.90
RSD	0.056	2.11

Imp-E Std	2.21
Std Prepr (GP WS + Imp E)	351.98 mg of Gaba WS---->25 ML Add 2.5ml of Imp-E Soln
Sample	144.54 mg of gaba ws to 10ml 14.454 mg/ml

Moisture Content----->0

GP	IMP-E
14.079mg/ml	0.009mg/ml

Imp E	0	0.009	1	100	Result %	LIMIT
	154714.67	14.454	1		0.0000	0.10%

Imp A	0	0.009	1	100	Result %	LIMIT
	154714.67	14.454	5.3		0.0000	0.10%

Imp B	0	0.009	1	100	Result %	LIMIT
	154714.67	14.454	0.35		0.0000	0.06%

Unknown Impurity 1.4RRT	0	0.009	1	100	Result %	LIMIT
	154714.67	14.454	0.41		0.000	0.05%

Unknown Impurity 0.76 RRT	25328	0.009	1	100	Result %	LIMIT
	154714.67	14.45	0.41		0.0244	0.05%

ASSAY as such	77767231	14.079	100	100	Result %	LIMIT
	76346533	14.454	100.00		99.22	98.7 to 101%

Unknown Impurity 3.7 RRT	36394	0.009	1	100	Result %	LIMIT
	154714.67	14.454	0.41		0.0351	0.05%

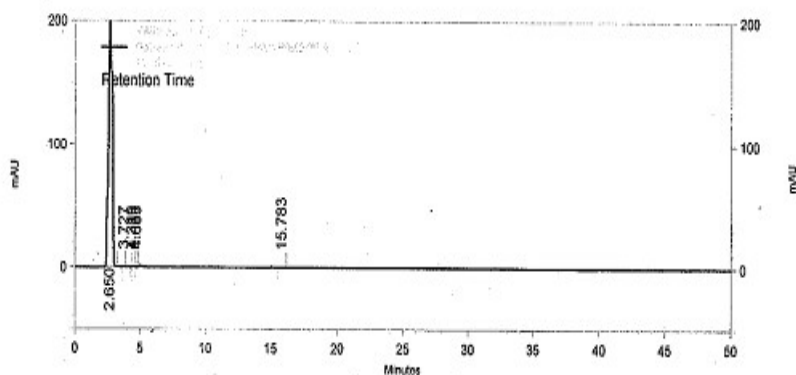
Unknown Impurity 0.85 RRT	13875	0.009	1	100	Result %	LIMIT
	154714.67	14.45	0.41		0.0134	0.05%

Unknown Impurity 0.90 RRT	31046	0.01	1	100	Result %	LIMIT
	154714.67	14.45	0.41		0.0299	0.05%

HPLC purity of gabapentin API (1) obtained from gabalactam 4 via intermediate 3 (Gaba later method):

Gabapentin API (1) obtained from first lot of gabapentin hydrochloride (5) (Gaba later method):

Sample ID : Gabapentin pure: GP/JVP/VVP/652/20 A
 User : Guru
 File Name : D:\System 90\LC_12\Data\2012\May-2012\11052012\Gaba later\11_May_012.dat
 Method : D:\System 90\LC_12\Method\Gaba Later.met
 Acquired : 5/11/2012 2:08:31 PM
 Printed : 5/11/2012 3:41:57 PM
Chromatographic Conditions :
 Column : Phenomenex C-18 250mm x 4.6mm x 5 μ [Col No:HBR-LC-178]
 Mobile Phase : 35:35:30 / Buffer:ACN: MeOH
 Buffer : 0.58g Amm.phosphate +1.83g sodium perchlorate in 1L Water,adjust pH 1.8 with HClO4.
 Flow rate : 1.0ml/min, Volume: 20 μ l, Detector : 215nm, Column Temp:40°C



VWD: Signal A,
 215 nm Results

Pk #	Retention Time	Height	Area	Area Percent	Relative RT
1	2.65	3647611	70594769	99.9132	0.167
2	3.73	1648	13711	0.0194	0.236
3	4.31	1533	8142	0.0115	0.273
4	4.48	1290	9474	0.0134	0.284
5	4.68	2086	13363	0.0189	0.296
6	15.78	902	16622	0.0235	1.000
Totals		3655070	70656081	100.0000	

Continued to page number 20

Gabapentin-USP (Late eluting impurity)

standard imp-D		
1	535072	
2	531392	
3	535322	
Average	533929	
Std	2200.37	
RSD	0.41	

Gabapentin

B.No:GPI/JVP/VVP/652/20 A

imp-D Std	2.83 mg---->10 ml-->1ml-->100ml	0.00283 mg/ml
Sample conc	142.02 mg---->10ml	14.202 mg/ml

Any impurity=	Area of imp Area of imp-D	wt of imp-D 10	1 100	25 wt of spl	1 factor	100
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impurity-D	16622	0.00283	1	100	0.001	%
	533929	14.202	1.0			

unknown impurity (RRT 0.23)	13711	0.00294	1	100	0.021	%
	533929	14.202	0.025			

unknown impurity (RRT 0.84)	0	0.00283	1	100	0.000000	%
	533929	14.202	66.000			

unknown impurity (RRT 0.27)	8142	0.00283	1	100	0.012	%
	533929	14.202	0.025			

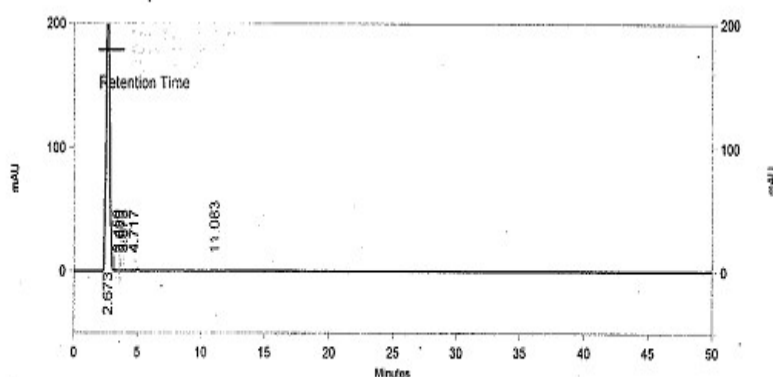
unknown impurity (RRT 0.28)	9474	0.00283	1	100	0.014	%
	533929	14.202	0.025			

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DM
11/05/12

Gabapentin API (1) obtained from second lot of gabapentin hydrochloride (5) (Gaba later method):

Sample ID : Gabapentin pure: GP/JVP/VVP/652/20 B
 User : Guru
 File Name : D:\System 90\LC_12\Data\2012\May-2012\11052012\Gaba later\11_May_013.dat
 Method : D:\System 90\LC_12\Method\Gaba Later.met
 Acquired : 5/11/2012 3:03:50 PM
 Printed : 5/11/2012 4:09:35 PM
Chromatographic Conditions :
 Column : Phenomenex C-18 250mm x 4.6mm x 5 μ [Col No:HBR-LC-178]
 Mobile Phase : 35:35:30 / Buffer: ACN: MeOH
 Buffer : 0.58g Amm.phosphate +1.83g sodium perchlorate in 1L Water, adjust pH 1.8 with HClO₄.
 Flow rate : 1.0ml/min, Volume: 20 μ l, Detector : 215nm, Column Temp: 40°C



VWD: Signal A, 215
 nm Results

Pk #	Retention Time	Height	Area	Area Percent
1	2.67	3810775	71613095	99.8647
2	3.45	3444	19051	0.0266
3	3.63	815	3149	0.0044
4	3.87	2822	20864	0.0291
5	4.72	4899	31365	0.0437
6	11.08	1149	22605	0.0315
Totals		3823904	71710129	100.0000

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Gabapentin-USP (Late eluting impurity)

standard imp-D	
1	535072
2	531392
3	535322
Average	
533929	
Std	2200.37
RSD	0.41

Gabapentin

B.No:GP/JVP/VVP/652/20 B

imp-D Std	2.83 mg---->10 ml-->1ml-->100ml	0.00283 mg/ml
Sample conc	141.16 mg---->10ml	14.116 mg/ml

Any impurity=	Area of imp Area of imp-D	wt of imp-D 10	1 100	25 wt of spl	1 factor	100	
impurity-D	0	0.00283	1	100	0.000	%	
	533929	14.116	1.0				
unknown impurity (RRT 0.22)	19051	0.00294	1	100	0.030	%	
	533929	14.116	0.025				
unknown impurity (RRT 0.84)	0	0.00283	1	100	0.000000	%	
	533929	14.116	66.000				
unknown impurity (RRT 0.23)	3149	0.00283	1	100	0.005	%	
	533929	14.116	0.025				
unknown impurity (RRT 0.24)	20864	0.00283	1	100	0.031	%	
	533929	14.116	0.025				
unknown impurity (RRT 0.70)	22605	0.00283	1	100	0.034	%	
	533929	14.116	0.025				

PM
11/05/12

Note:

1. Gabapentin hydrochloride was obtained from gabalactam in two lots (first lot & second lot) and these two lots are separately processed to final gabapentin API (1) by following the patents reported by us (Reference 25 in the main manuscript). HPLC analyses were done by following the US Pharmacopeia method (Gaba early & Gaba later methods).