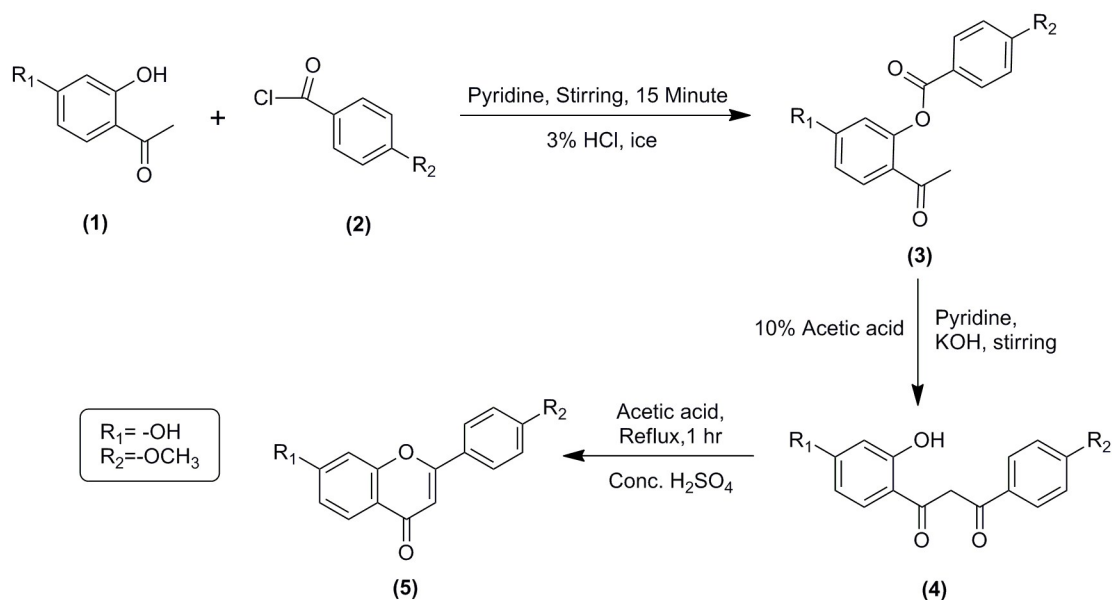


Supporting information

Design, Synthesis and Biological Evaluation of Novel 2-phenyl-1-benzopyran-4-one Derivatives as potential poly-functional anti-Alzheimer's agents



Scheme S1: The synthetic methodology employed to develop intermediate **5**.

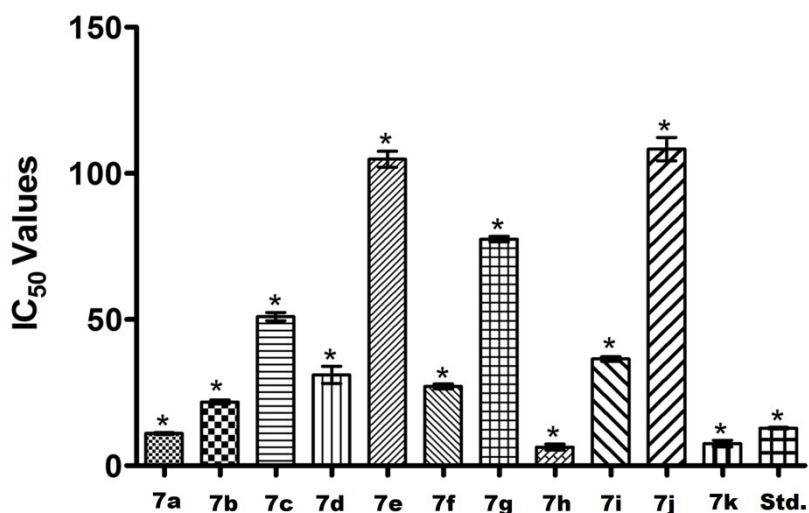


Figure S1: Graphical representation of IC₅₀ values of 2-phenyl-1-benzopyran-4-one derivatives for AChE inhibitory activity with the standard drug Donepezil. The mean±SD values from three independent experiments were shown. Data were statistically analyzed by one way ANOVA; *P<0.05 vs Std

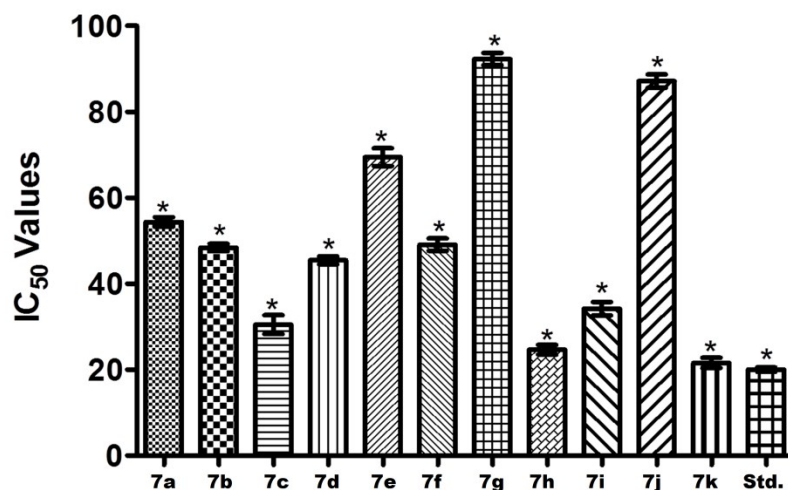


Figure S2: Graphical representation of IC₅₀ values of 2-phenyl-1-benzopyran-4-one derivatives for free radical scavenging activity with the standard drug Ascorbic acid. The mean±SD values from three independent experiments were shown. Data were statistically analyzed by one way ANOVA; *P<0.05 vs Std

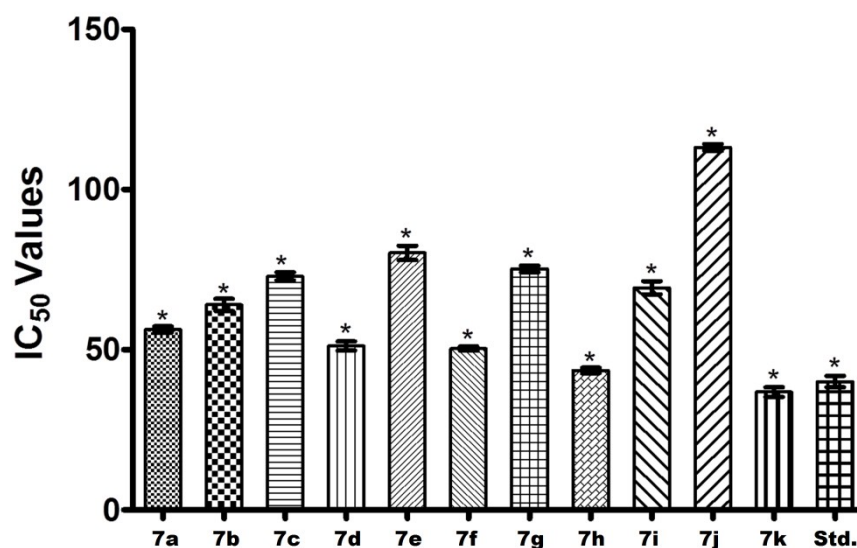


Figure S3: Graphical representation of IC₅₀ values of 2-phenyl-1-benzopyran-4-one derivatives for Advanced glycation end products (AGEs) formation inhibitory with the standard drug aminoguanidine. The mean±SD values from three independent experiments were shown. Data were statistically analyzed by one way ANOVA; *P<0.05 vs Std

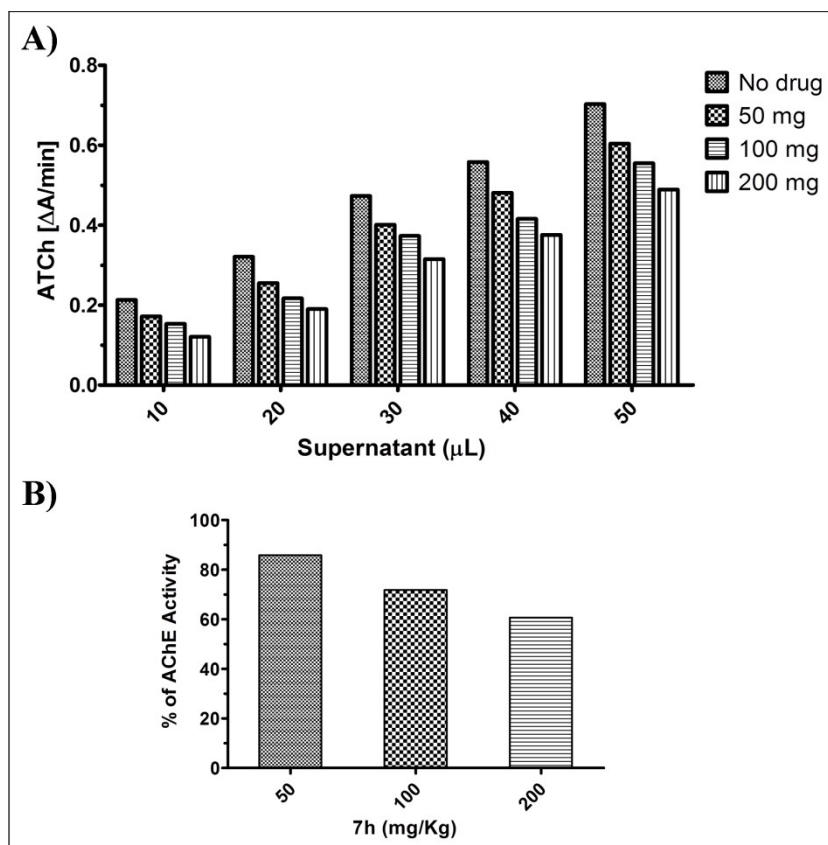


Figure S4: Determination of brain AChE activity to evaluate BBB penetration of 7h. (A) Rate of hydrolysis of acetylthiocholine (ATCh) by AChE in brain homogenates from mice injected with 7h; (B) AChE activity of brain homogenates from mice injected with 7h, expressed as a percentage of the AChE activity of corresponding preparations from control mice.

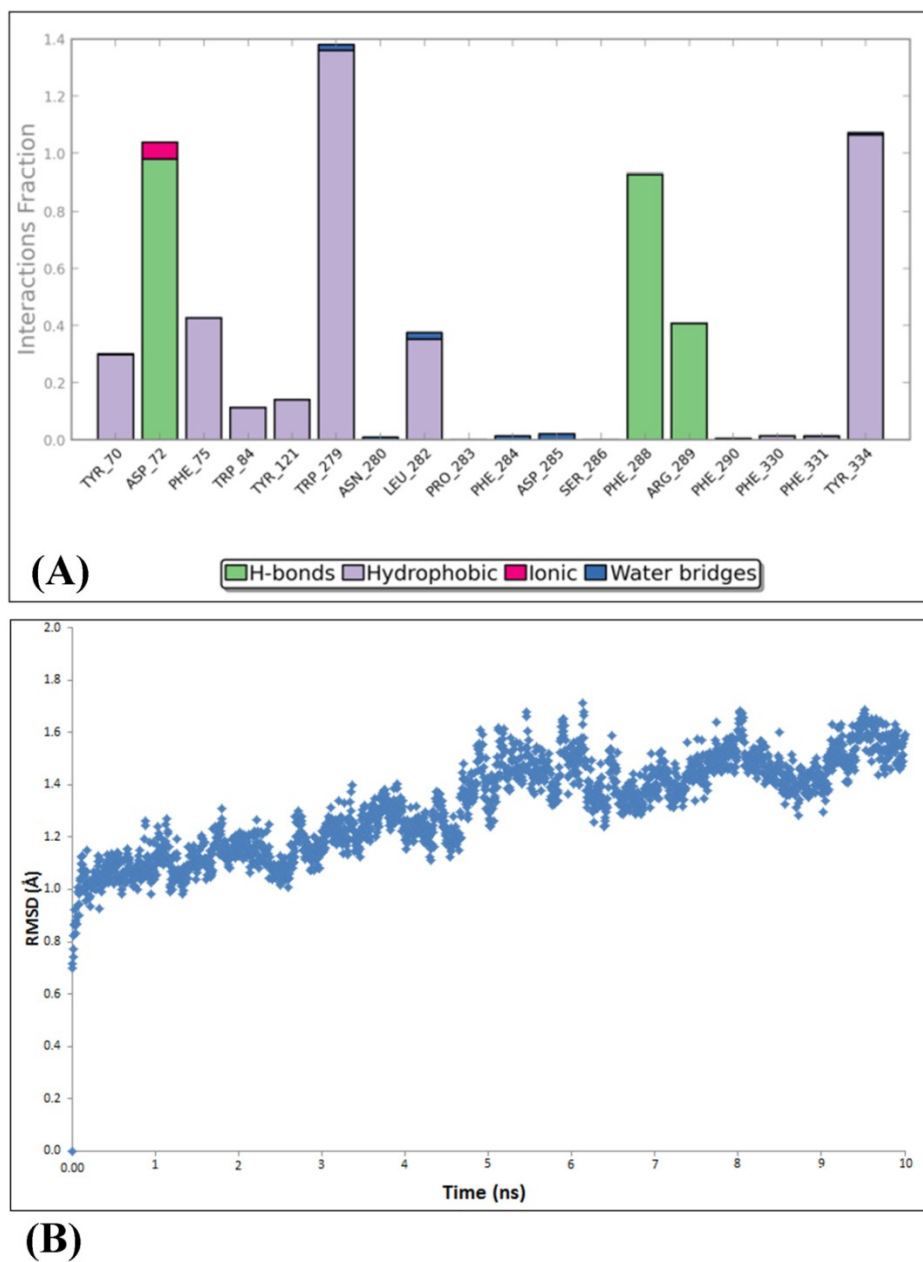


Figure S5: (A) Protein interactions fractions with the ligand (**7h**) plot throughout the simulation. (B) RMSD trajectory plot for compound **7h**.

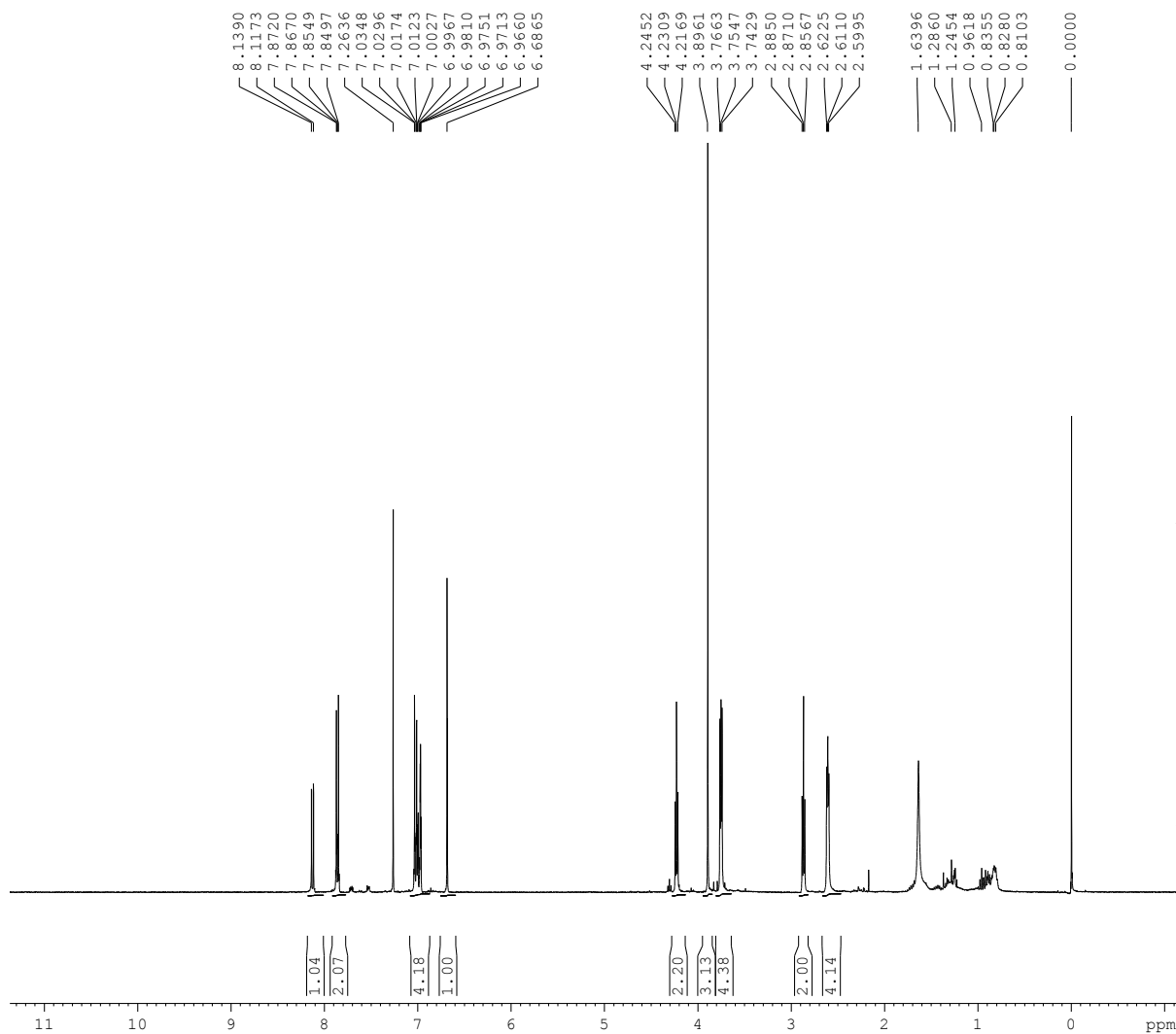
Table S1. Predicted ADMET properties of the target compounds

Comp.	Mol_MW ^a (130-725)	HB donors ^a (0-6)	HB acceptors ^a (2-20)	QPlogPo/w ^a (-2 to 6.5)	PSA ^a (7-200)	SASA ^a (300-1000)	Rule of Five	CNS ^a	QPPMDCK (<25 poor, >500 great)	QPPCaco ^a (<25 poor, >500 great)	QPlogBB ^a (-3 to 1.2)	QPlogKhsa ^a (-1.5 to 1.5)	QPlogS ^a (-6.5 to 0.5)	% Human Oral Absorption ^a (>80% high, <25% poor)	Calculated MMGBS ADG Binding Energy (kcal/mol) AChE
7a	381.427	0	7.7	2.862	66.188	689.895	0	1	368.305	693.186	0.049	-0.136	-3.225	94.552	-69.57
7b	379.455	0	6	3.939	54.614	715.507	0	1	383.00	718.737	0.053	0.451	-4.601	100	-84.48
7c	380.443	1	7.5	2.853	72.556	755.555	0	1	45.347	90.92	0.031	0.355	-3.946	78.709	-75.91
7d	394.469	0	8	3.05	62.541	787.465	0	1	80.702	154.978	0.304	0.159	-3.698	84.003	-60.02
7e	365.428	0	6	3.601	54.916	683.705	0	1	362.69	683.404	0.051	0.306	-3.998	100	-84.11
7f	367.444	0	6	3.813	53.362	687.177	0	1	392.266	734.81	-0.026	0.289	-3.739	100	-77.92
7g	339.39	0	6	3.172	55.146	654.307	0	1	351.544	663.951	0.041	0.099	-3.441	96.03	-69.10
7h	393.482	0	6	4.311	54.618	737.46	0	1	383.301	719.259	0.047	0.594	-5.017	100	-87.40
7h	415.488	0	6	4.311	54.618	774.46	0	1	397.923	744.606	-0.076	0.698	-5.343	100	-80.31
7j	362.384	0	6	3.844	67.709	675.859	0	0	725.395	1424.905	-0.683	0.178	-5.069	100	-71.55
7k	424.496	1	9.7	2.287	69.586	784.686	0	1	122.234	147.022	-0.469	0.038	-3.101	70.265	-48.85
Donepezil	379.498	0	5.5	4.467	44.612	723.535	0	1	501.72	922.694	0.118	0.621	-4.852	100	-78.70

^aMW: molecular weight, HBA: hydrogen-bond acceptor atoms, HBD: hydrogen-bond donor atoms, PSA: polar surface area, SASA: total solvent accessible surface area, QPlogPo/w: Predicted octanol/water partition coefficient, QPlogS: Predicted aqueous solubility, CNS: Predicted central nervous system activity on a -2 (inactive) to +2 (active) scale, QPPCaco: Caco-2 cell permeability in nm/sec, QPPMDCK: Predicted apparent MDCK cell permeability in nm/sec, QPlogBB: brain/blood partition coefficient, QPlogKhsa: binding to human serum albumin, Percent Human-Oral Absorption: human oral absorption on 0 to 100% scale.

7a

MORPHO-FLV



BRUKER
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Spectrometer
SAIF
Panjab University
Chandigarh

Current Data Parameters
NAME May20-2015
EXPNO 440
PROCNO 1

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PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 8
DS 2
SWH 12019.230 Hz
FIDRES 0.183399 Hz
AQ 2.7263477 sec
RG 512
DW 41.600 usec
DE 6.00 usec
TE 295.6 K
D1 1.00000000 sec
TD0 1

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PL1 -3.00 dB
SFO1 400.1324710 MHz

F2 - Processing parameters
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SF 400.1300082 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00

avtar saifpu@yahoo.co.in

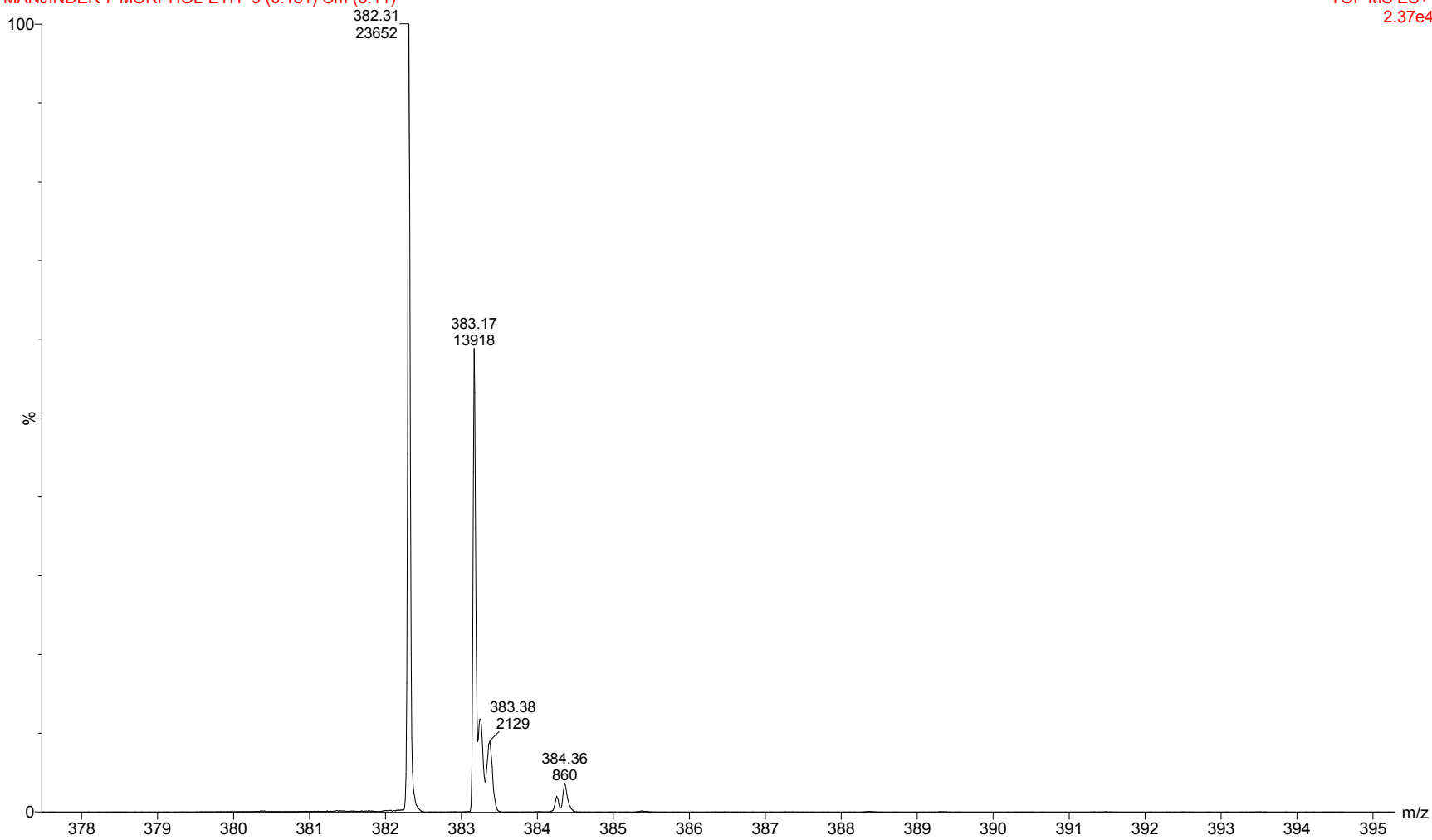
WATERS, Q-TOF MICROMASS (ESI-MS)

MANJINDER 7-MORPHOL-ETH- 9 (0.181) Cm (6:11)

SAIF/CIL,PANJAB UNIVERSITY,CHANDIGARH

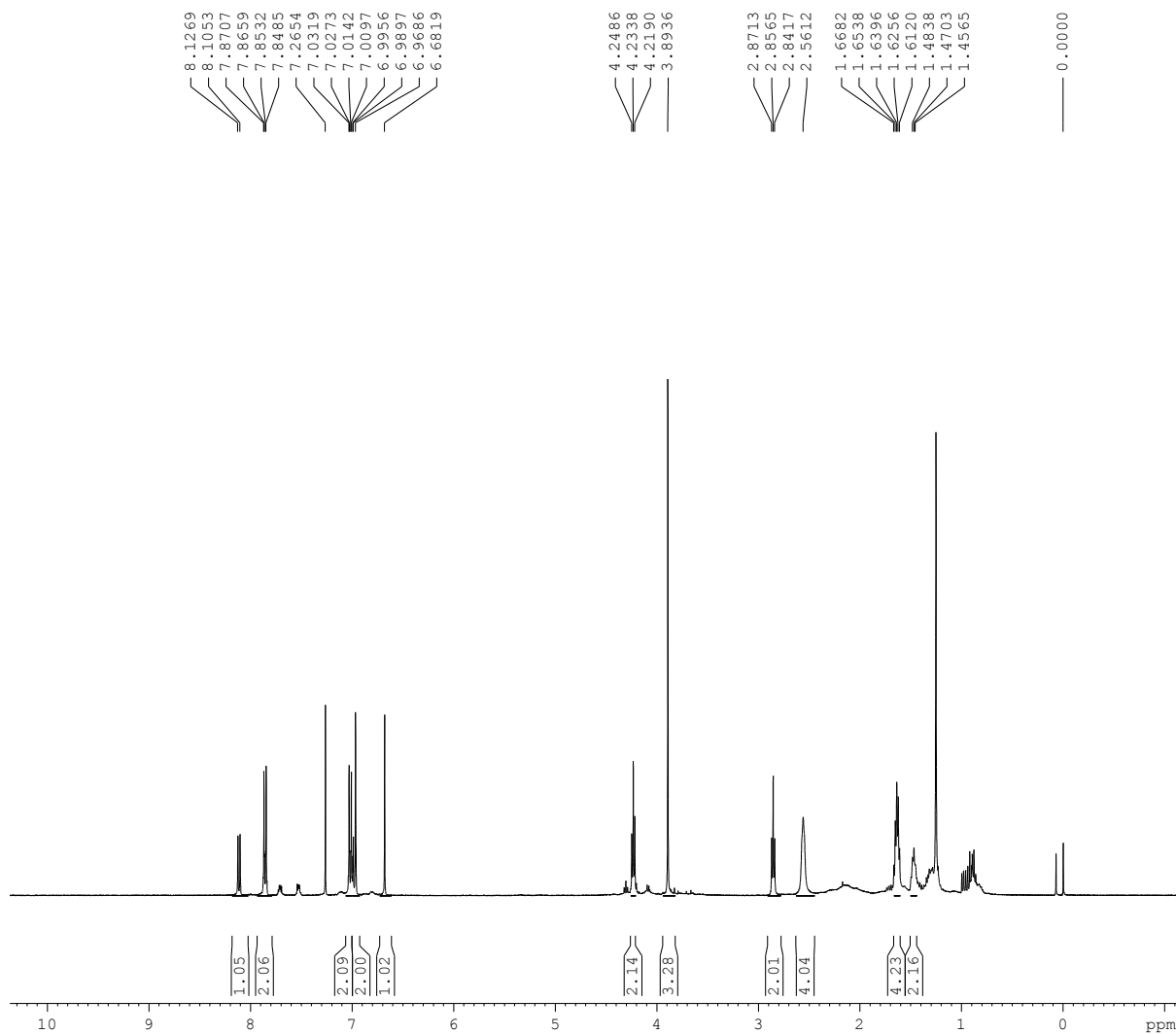
TOF MS ES+

2.37e4



7b:

7-PIPERD



BRUKER
AVANCE II 400 NMR
Spectrometer
SAIF
Panjab University
Chandigarh

Current Data Parameters
NAME Oct21-2015
EXPNO 20
PROCNO 1

F2 - Acquisition Parameters
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SOLVENT CDCl3
NS 8
DS 2
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TD0 1

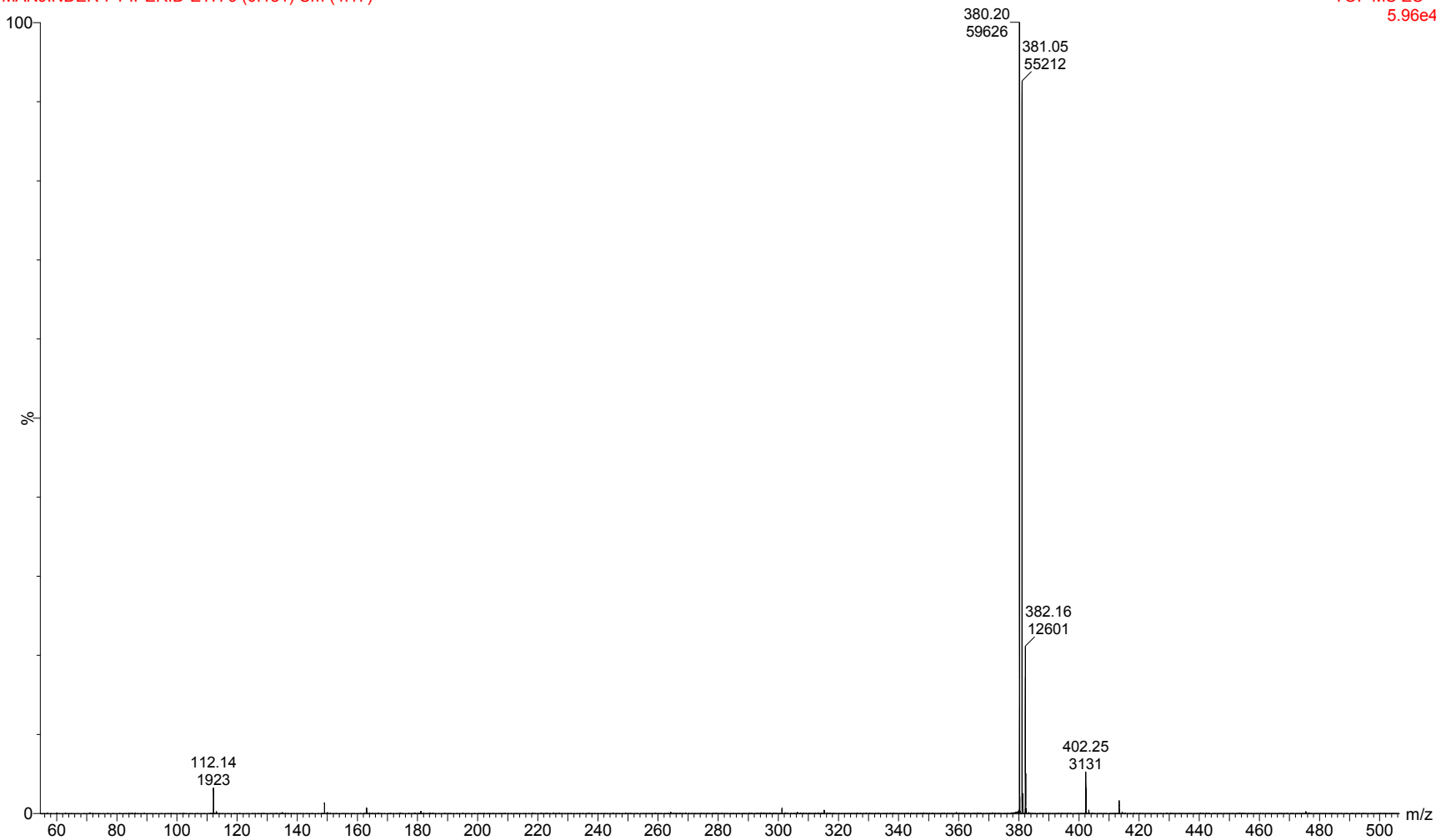
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F2 - Processing parameters
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SF 400.1300076 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00

manishkumarmanu1986@gmail.com

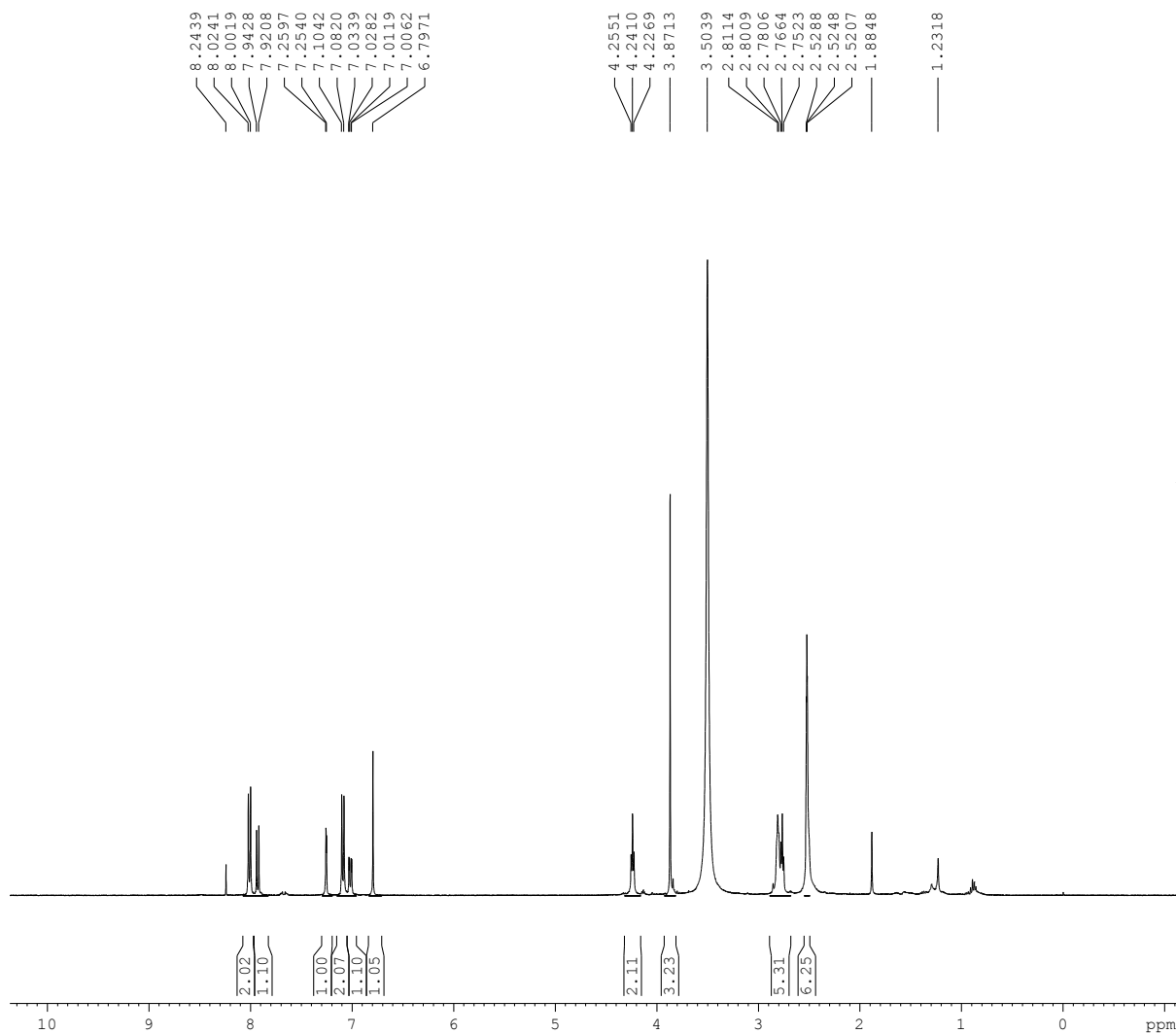
WATERS, Q-TOF MICROMASS (ESI-MS)
MANJINDER 7-PIPERID-ETH 9 (0.181) Cm (4:17)

SAIF/CIL,PANJAB UNIVERSITY,CHANDIGARH
TOF MS ES+
5.96e4



7c

7-PIPERZIN-FIV



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Spectrometer
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Current Data Parameters
NAME Oct21-2015
EXPNO 10
PROCNO 1

F2 - Acquisition Parameters
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Time_ 13.24
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PULPROG zg30
TD 65536
SOLVENT DMSO
NS 8
DS 2
SWH 12019.230 Hz
FIDRES 0.183399 Hz
AQ 2.7263477 sec
RG 228
DW 41.600 usec
DE 6.00 usec
TE 295.3 K
D1 1.00000000 sec
TD0 1

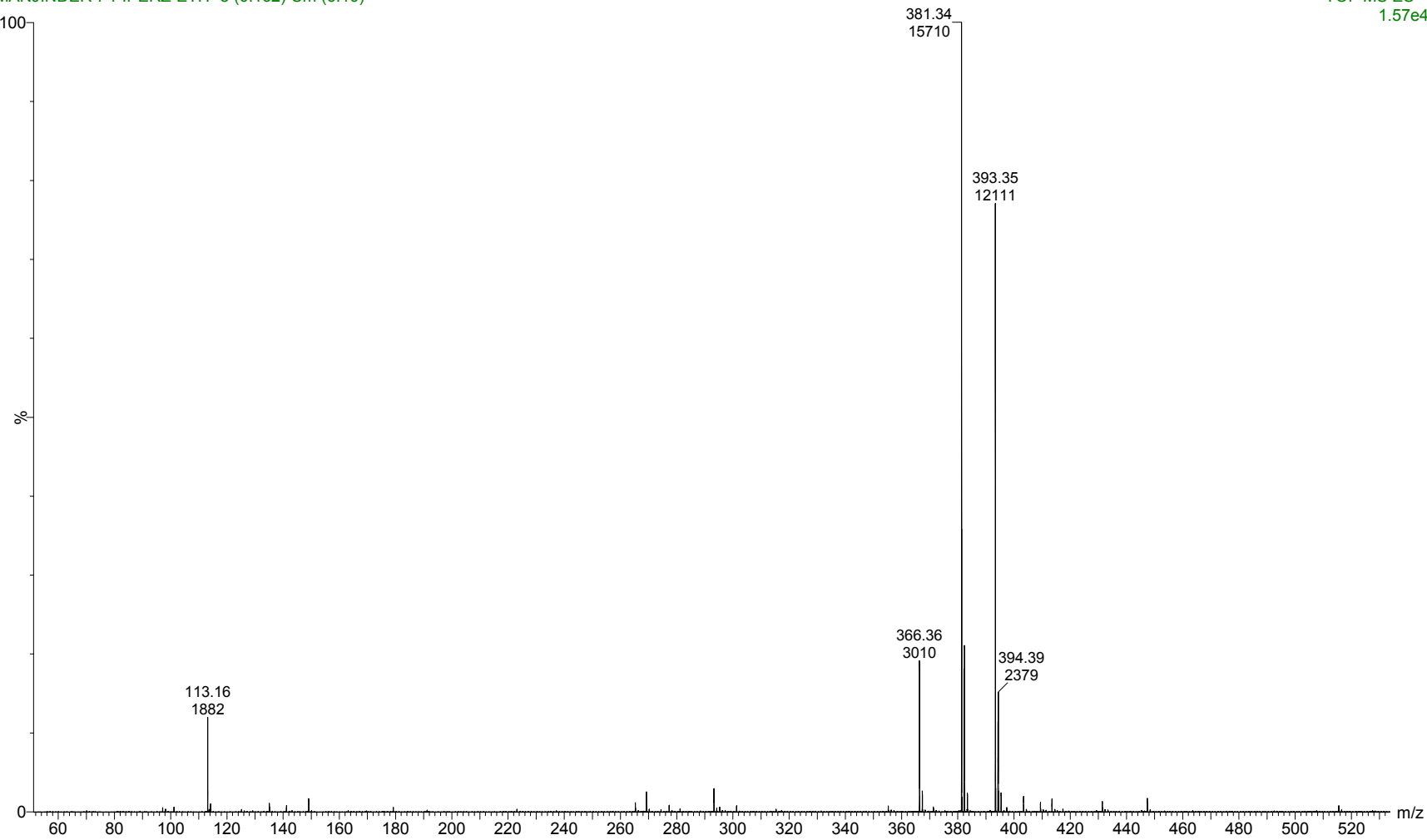
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WDW EM
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LB 0.30 Hz
GB 0
PC 1.00

manishkumarmanu1986@gmail.com

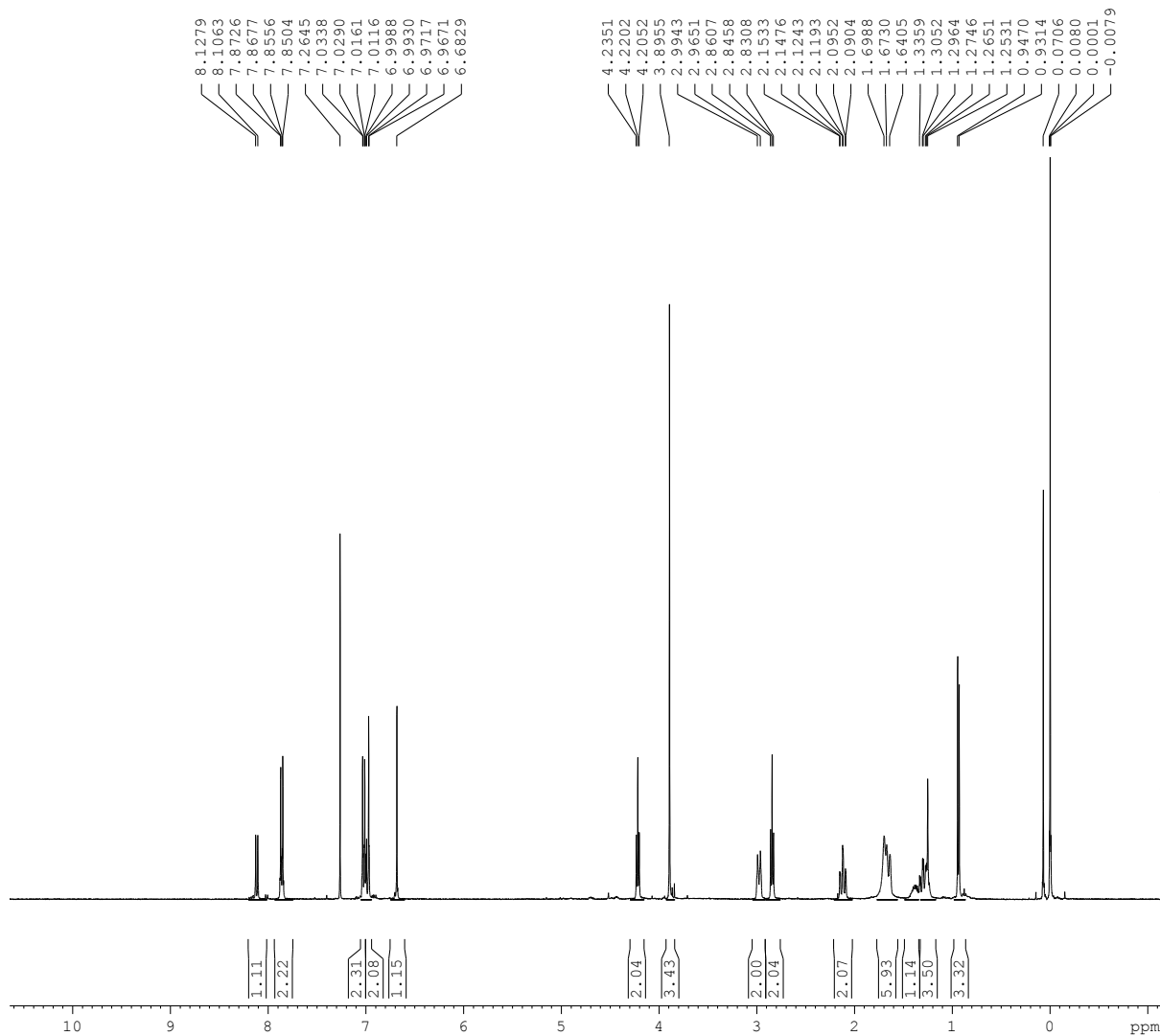
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MANJINDER 7-PIPERZ-ETH- 8 (0.162) Cm (6:10)

SAIF/CIL,PANJAB UNIVERSITY,CHANDIGARH
TOF MS ES+
1.57e4



7d

7-N-METH-PIPER2-ETH



BRUKER
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Current Data Parameters
 NAME Dec07-2015
 EXPNO 500
 PROCNO 1

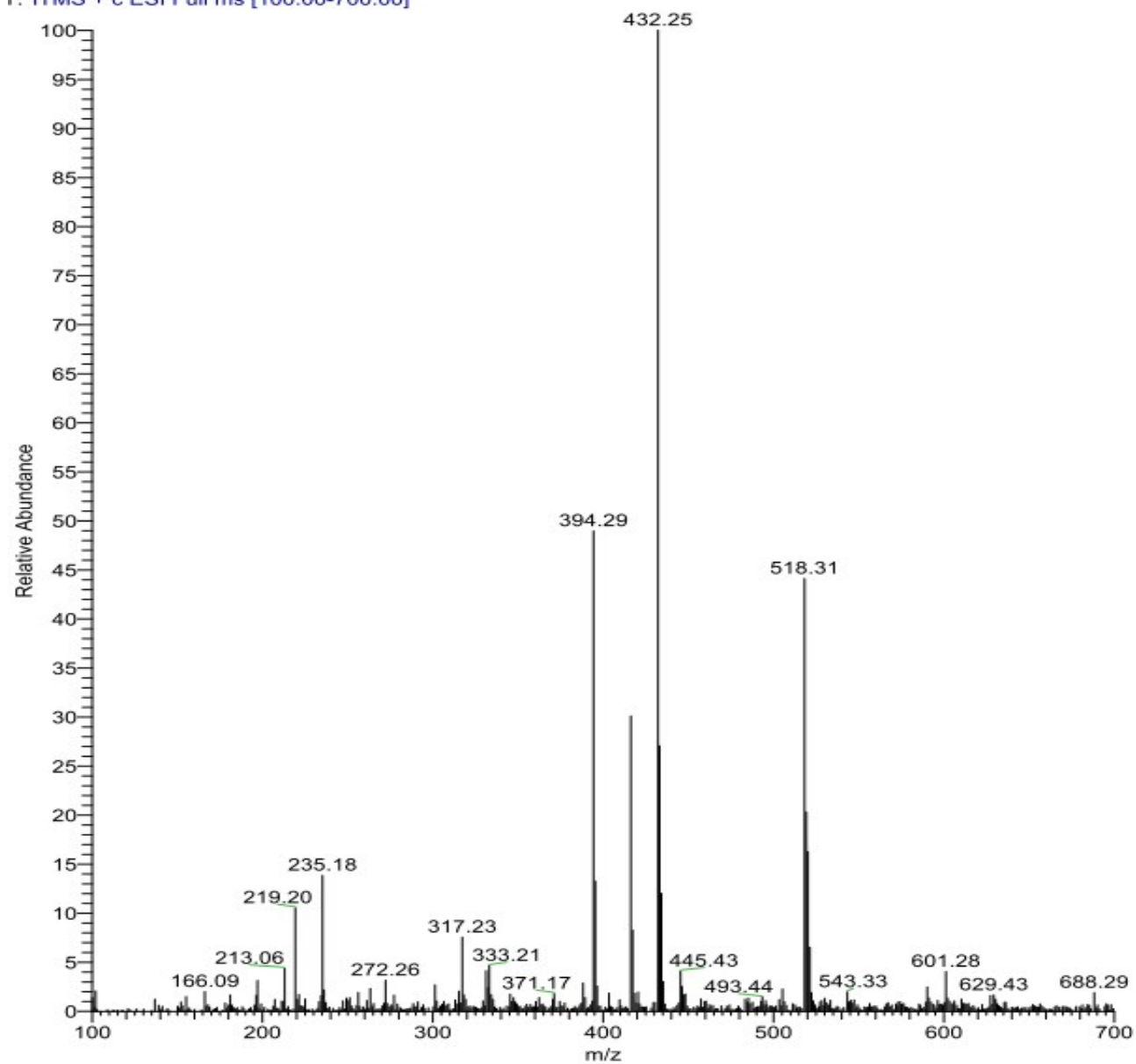
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 NS 8
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 SWH 12019.230 Hz
 FIDRES 0.183399 Hz
 AQ 2.7263477 sec
 RG 456
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 DE 6.00 usec
 TE 294.7 K
 D1 1.00000000 sec
 TD0 1

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 PL1 -3.00 dB
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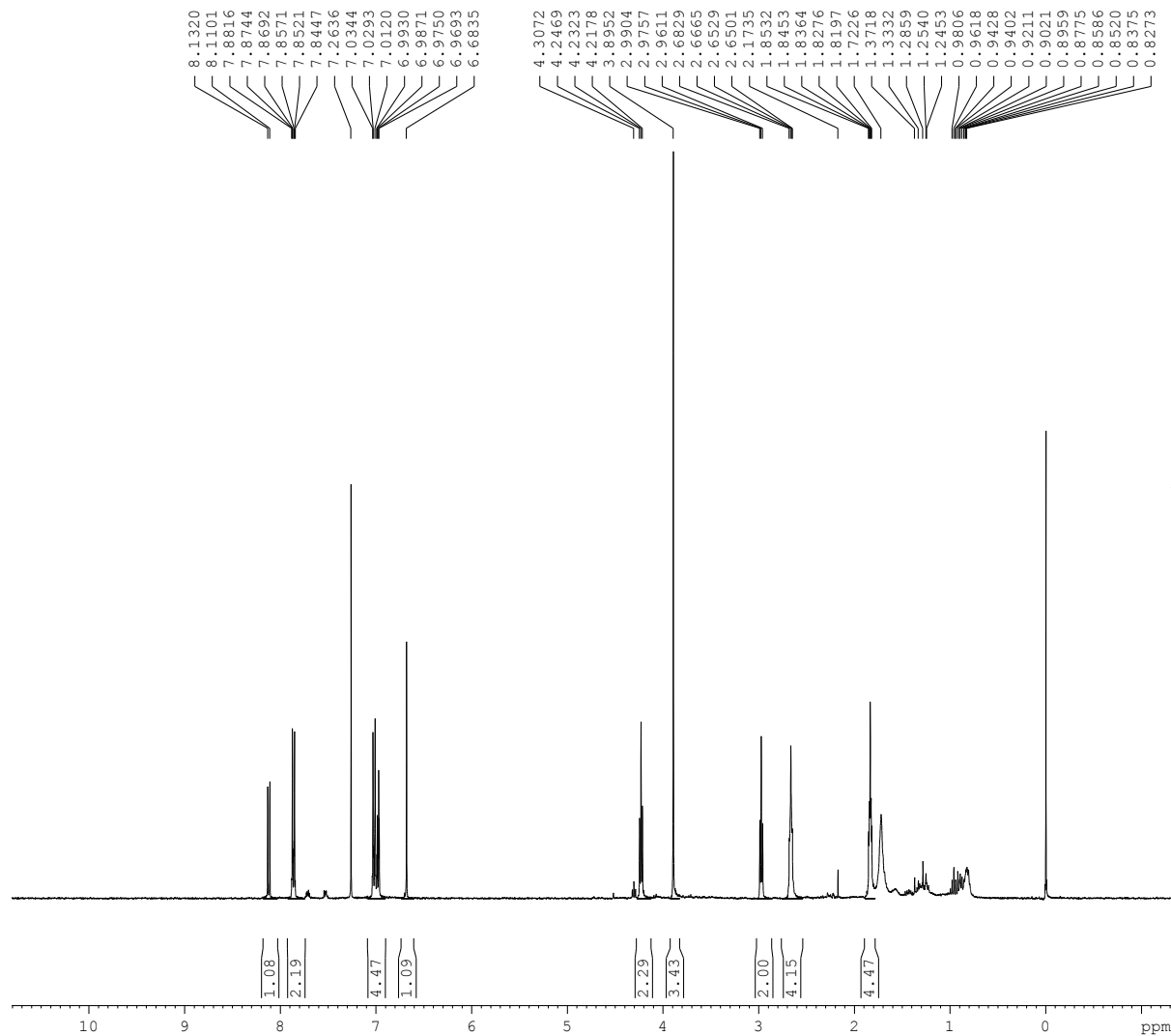
manishkumarmanu1986@gmail.com

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Γ: ITMS + c ESI Full ms [100.00-700.00]



7e

PYR-FLV



BRUKER
 AVANCE II 400 NMR
 Spectrometer
 SAIF
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 Chandigarh

Current Data Parameters
 NAME May20-2015
 EXPNO 430
 PROCNO 1

F2 - Acquisition Parameters
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 DS 2
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 FIDRES 0.183399 Hz
 AQ 2.7263477 sec
 RG 912
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 DE 6.00 usec
 TE 295.6 K
 D1 1.00000000 sec
 TD0 1

===== CHANNEL f1 =====
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 P1 10.90 usec
 PL1 -3.00 dB
 SFO1 400.1324710 MHz

F2 - Processing parameters
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 SF 400.1300083 MHz
 WDW EM
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 GB 0
 PC 1.00

manishkumarmanu1986@gmail.com

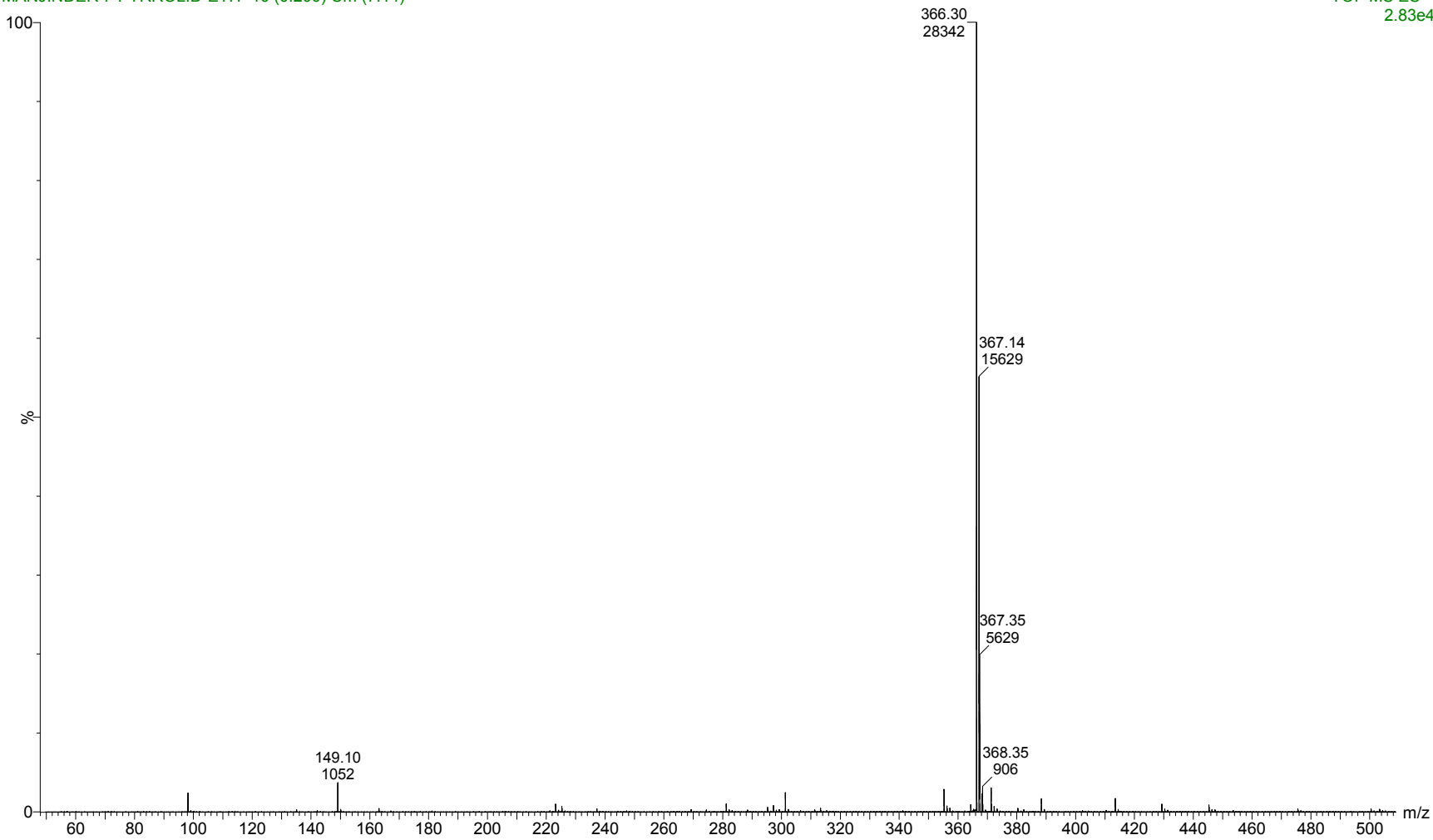
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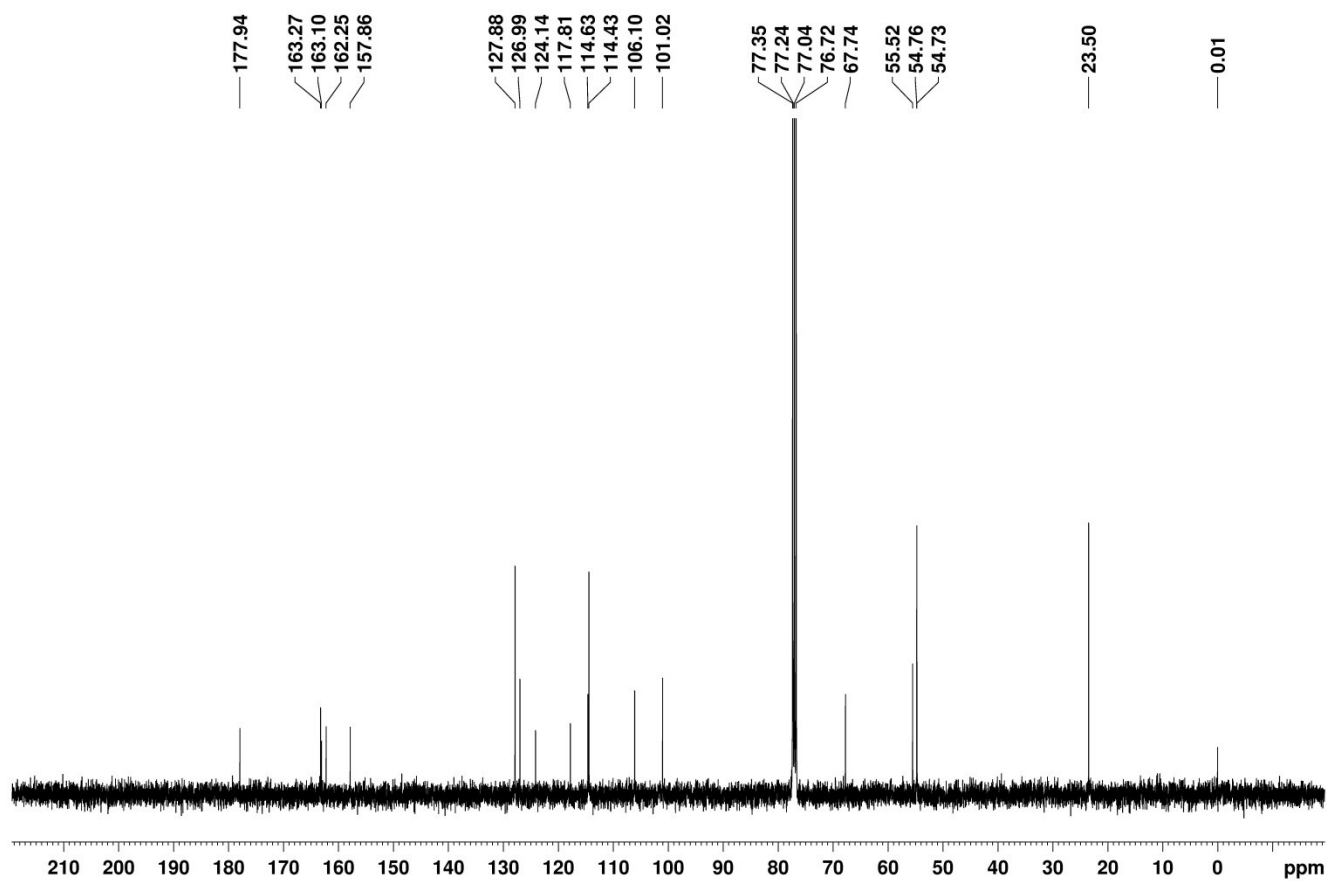
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SAIF/CIL,PANJAB UNIVERSITY,CHANDIGARH

TOF MS ES+

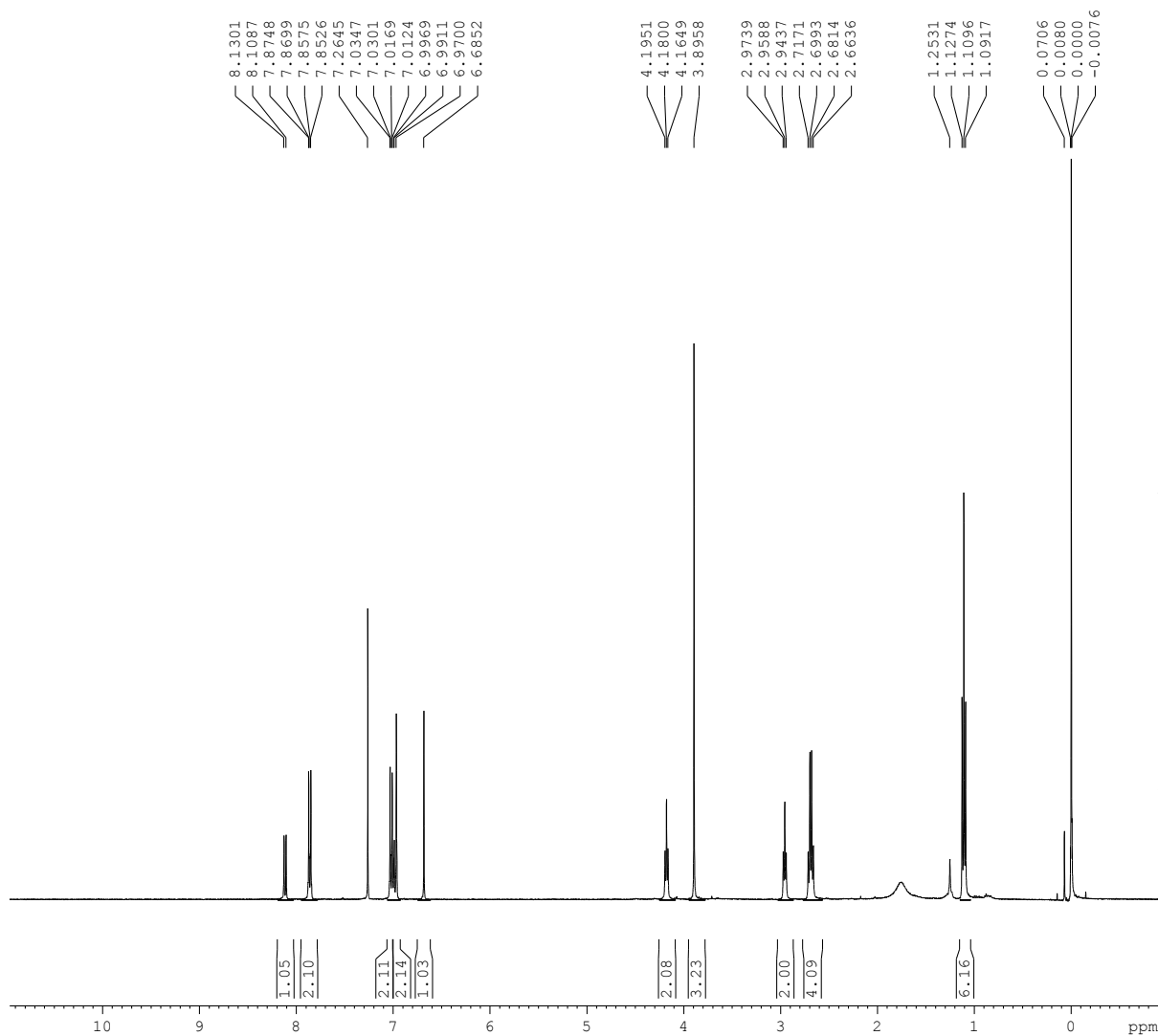
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7f

DIETHAIN-ETH-1



BRUKER
AVANCE II 400 NMR
Spectrometer
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Panjab University
Chandigarh

Current Data Parameters
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EXPNO 510
PROCNO 1

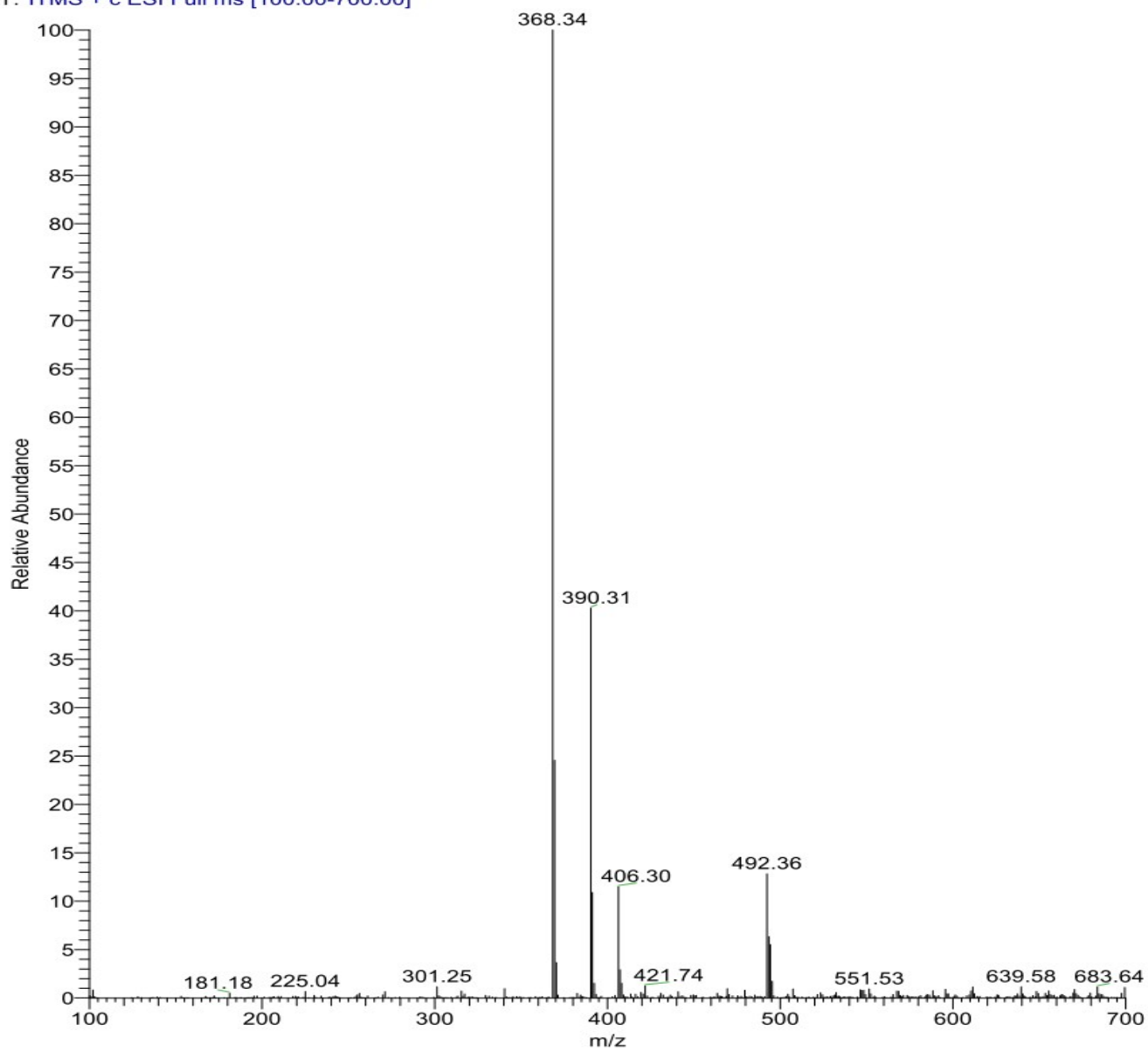
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NS 8
DS 2
SWH 12019.230 Hz
FIDRES 0.183399 Hz
AQ 2.7263477 sec
RG 456
DW 41.600 usec
DE 6.00 usec
TE 294.6 K
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===== CHANNEL f1 =====
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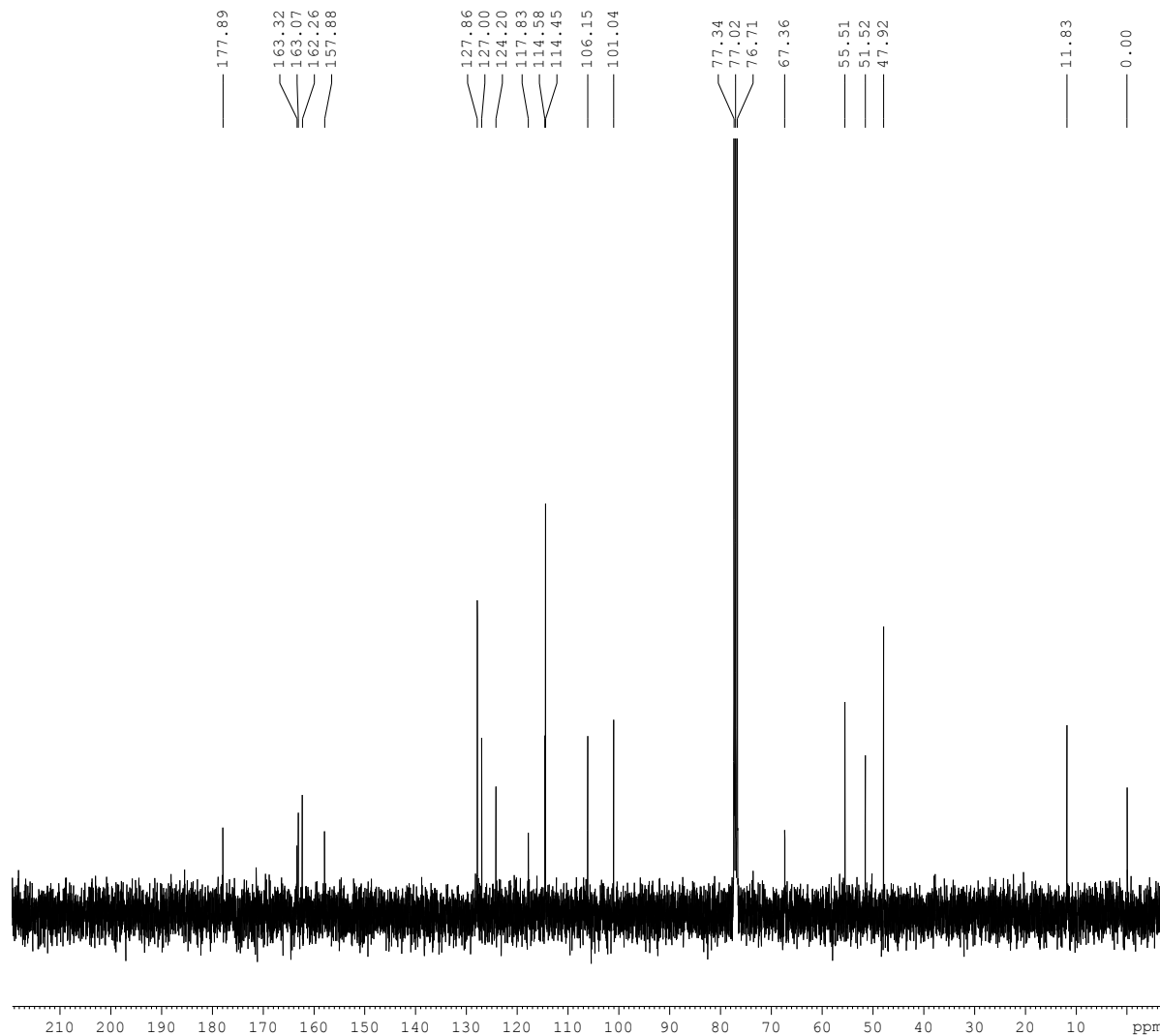
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SSB 0
LB 0.30 Hz
GB 0
PC 1.00

manishkumarmanu1986@gmail.com

S-02 29-04-2016_160429110202 #149 RT: 0.30 AV: 1 NL: 4.59E5
T: ITMS + c ESI Full ms [100.00-700.00]



7F



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AVANCE II 400 NMR
Spectrometer
SAIF
Panjab University
Chandigarh

Current Data Parameters
NAME May31-2016
EXPNO 140
PROCNO 1

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Time_ 16.58
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PROBHD 5 mm PABBO BB-
PULPROG zgpg30
TD 65536
SOLVENT CDC13
NS 512
DS 4
SWH 29761.904 Hz
FIDRES 0.454131 Hz
AQ 1.1010548 sec
RG 2050
DW 16.800 usec
DE 6.00 usec
TE 298.1 K
D1 2.00000000 sec
d11 0.03000000 sec
DELTA 1.89999998 sec
TD0 1

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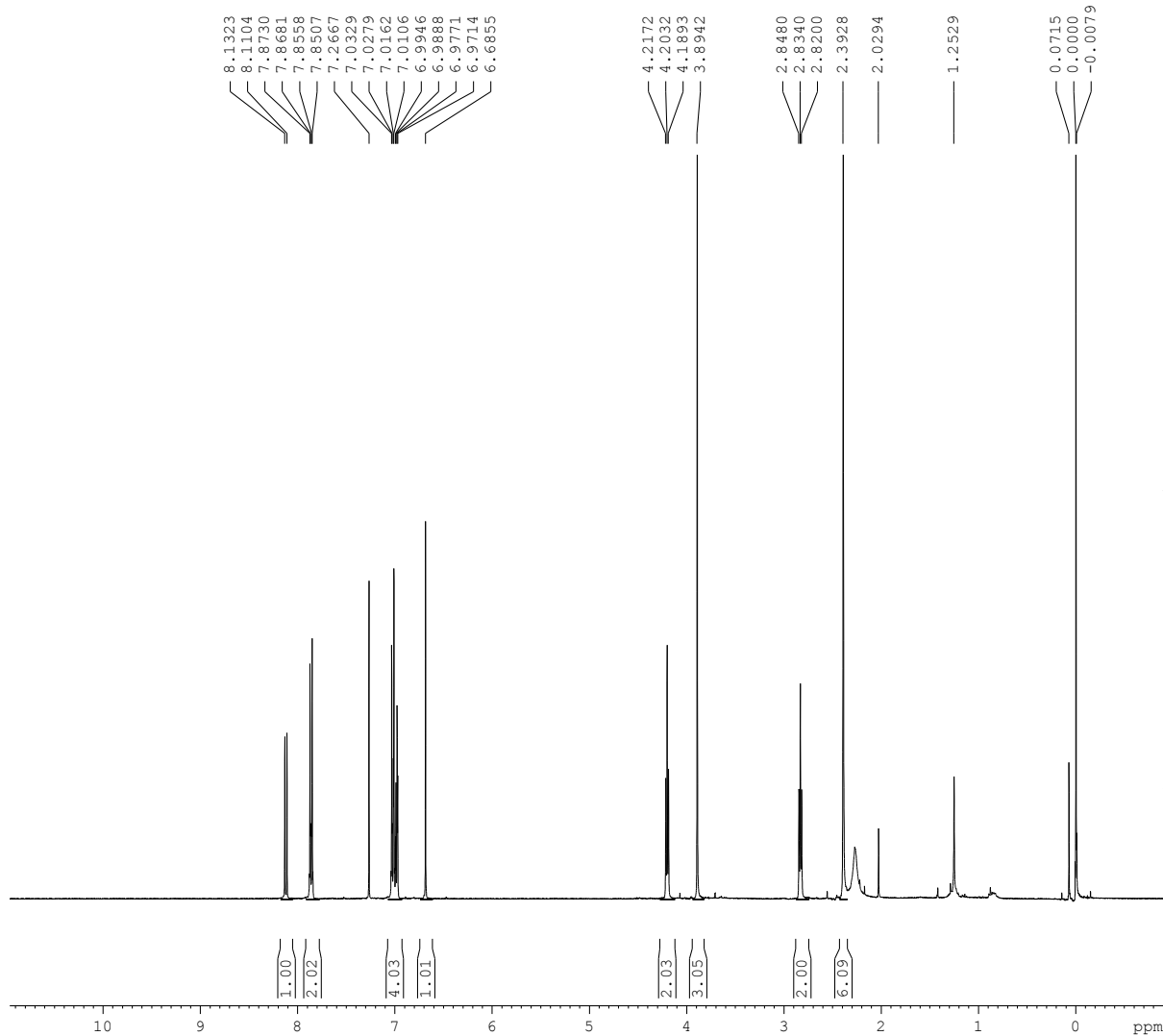
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PL2 -3.00 dB
PL12 14.31 dB
PL13 18.00 dB
SFO2 400.1316005 MHz

F2 - Processing parameters
SI 32768
SF 100.6127684 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40

manishkumarmanu1986@gmail.com

7g

7-DIMETHAMIN-ETH



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Chandigarh

Current Data Parameters
NAME Dec07-2015
EXPNO 590
PROCNO 1

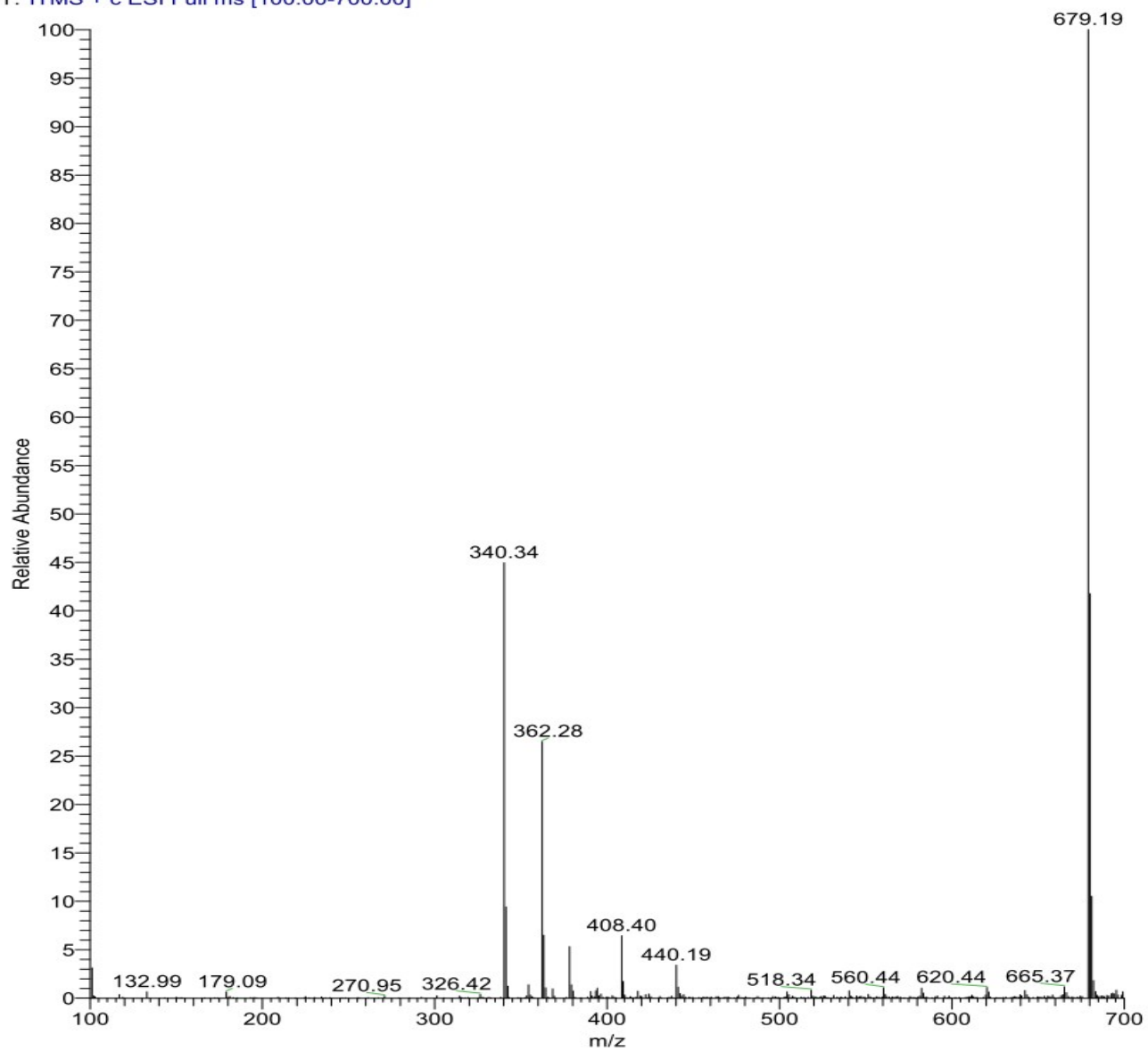
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PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 8
DS 2
SWH 12019.230 Hz
FIDRES 0.183399 Hz
AQ 2.7263477 sec
RG 406
DW 41.600 usec
DE 6.00 usec
TE 294.5 K
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TD0 1

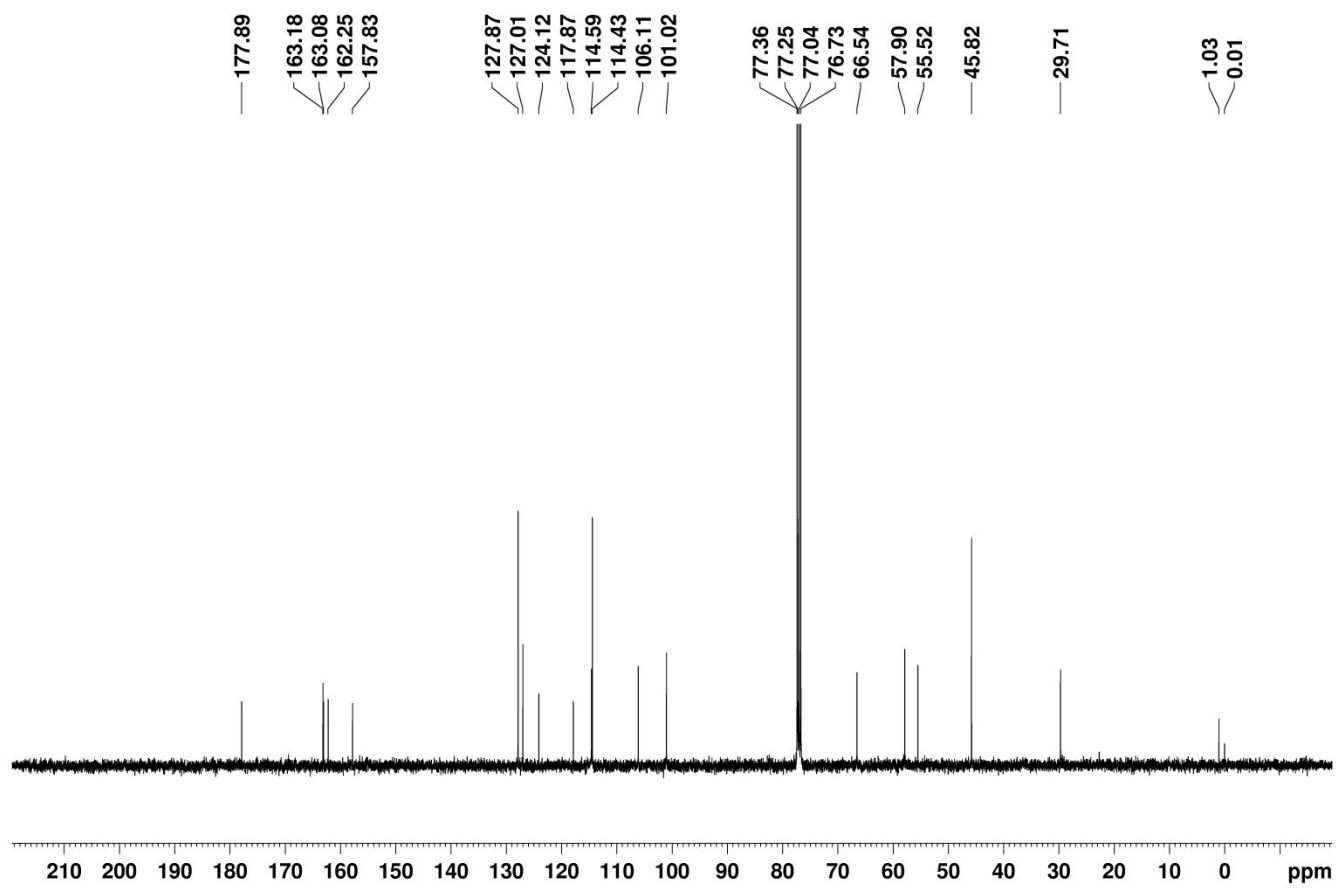
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F2 - Processing parameters
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SF 400.1300071 MHz
WDW EM
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GB 0
PC 1.00

manishkumarmanu1986@gmail.com

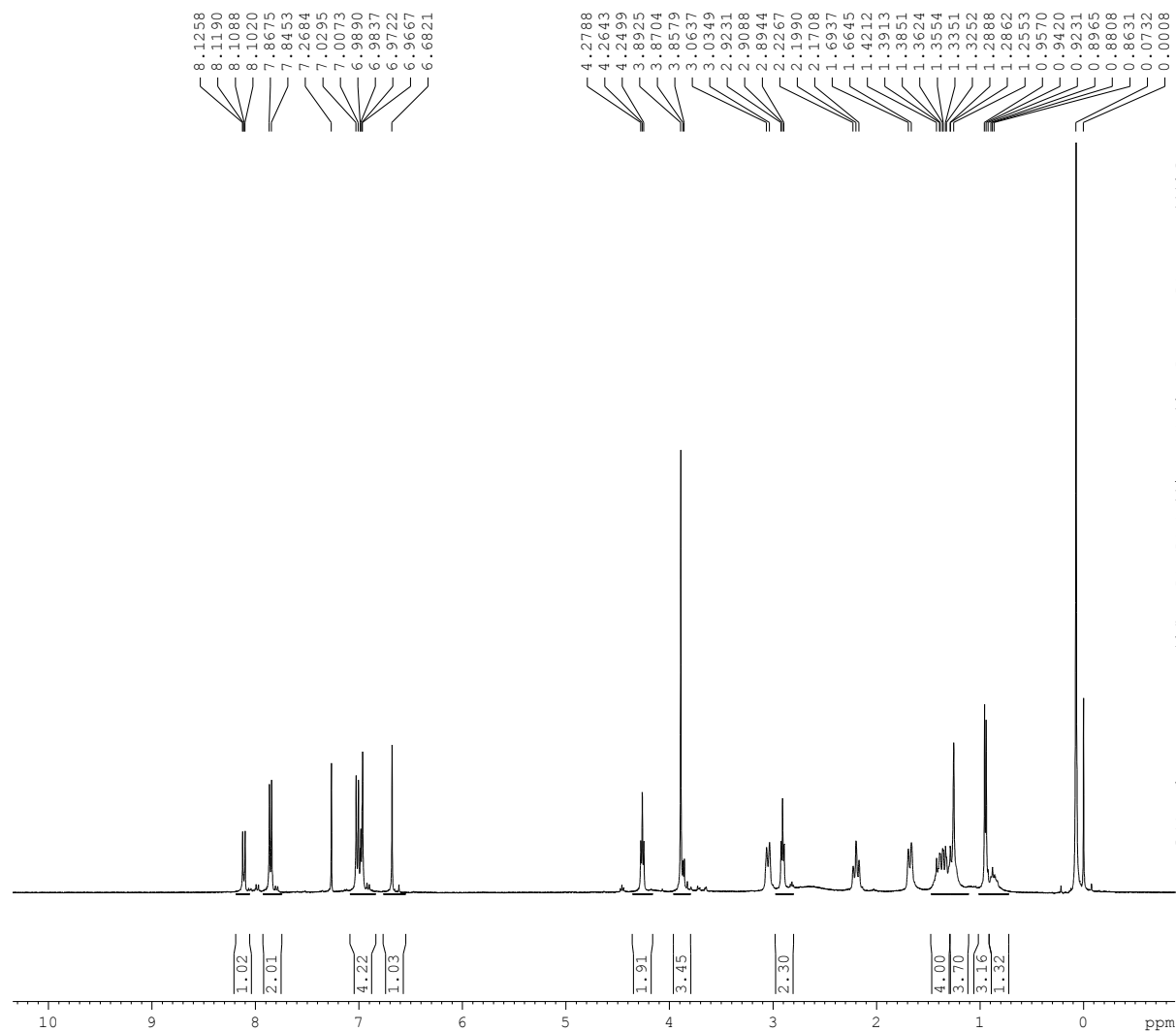
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7h

4-METHPIPERD-ETH



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Panjab University
Chandigarh

Current Data Parameters
NAME Feb29-2016
EXPNO 160
PROCNO 1

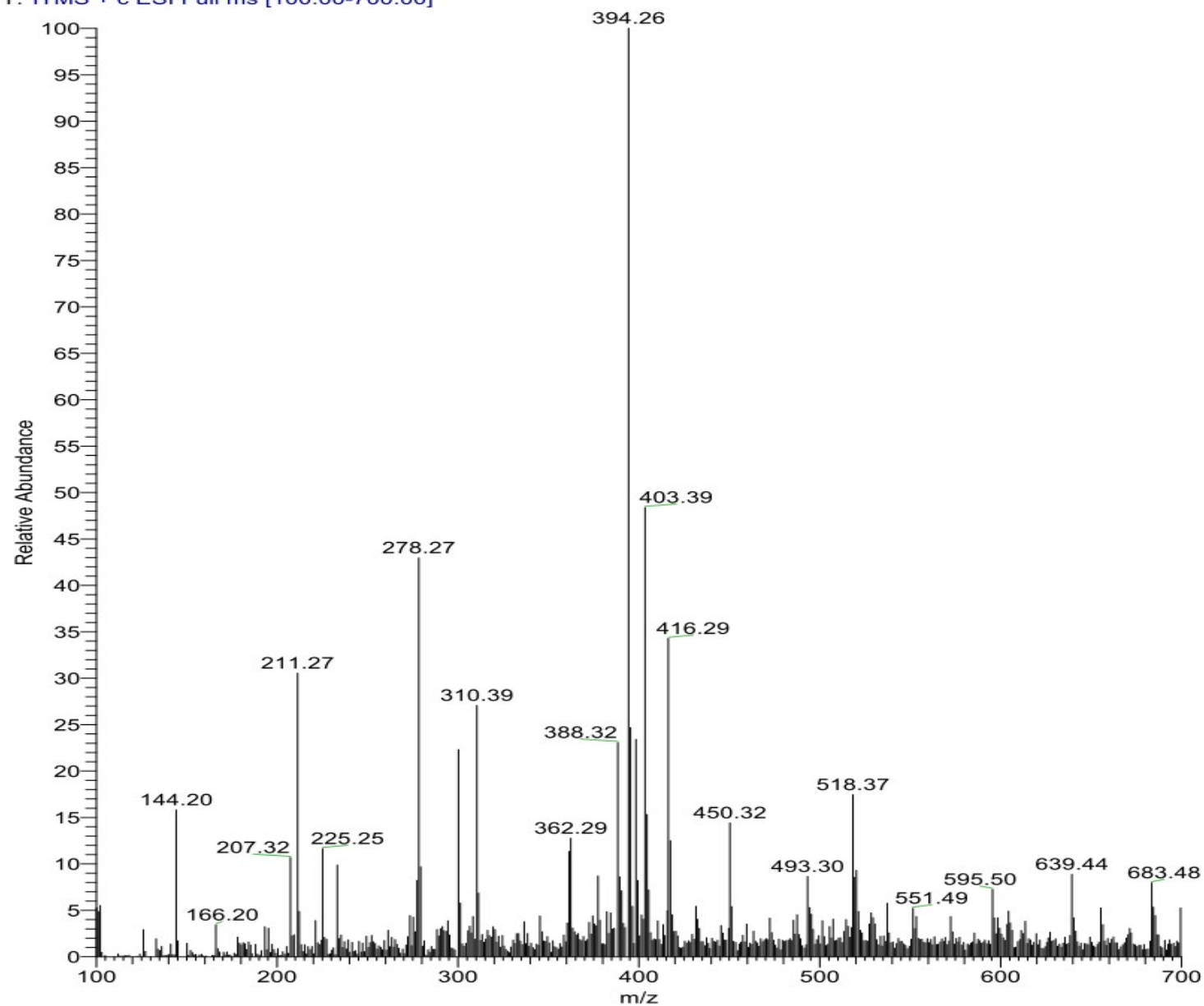
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Time_ 19.11
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PULPROG zg30
TD 65536
SOLVENT CDC13
NS 16
DS 2
SWH 12019.230 Hz
FIDRES 0.183399 Hz
AQ 2.7263477 sec
RG 512
DW 41.600 usec
DE 6.00 usec
TE 295.2 K
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TD0 1

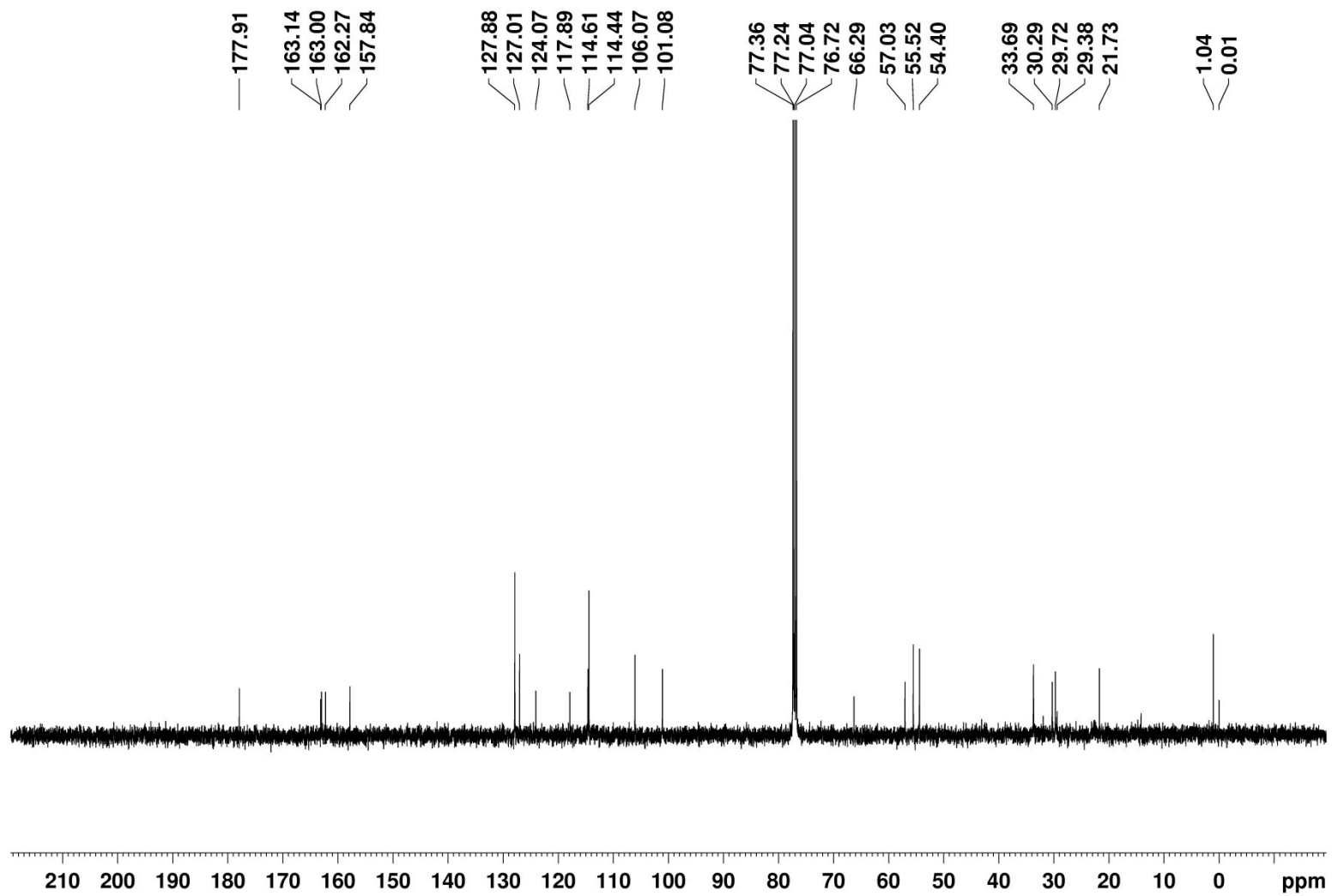
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F2 - Processing parameters
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PC 1.00

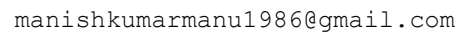
manishkumarmanu1986@gmail.com

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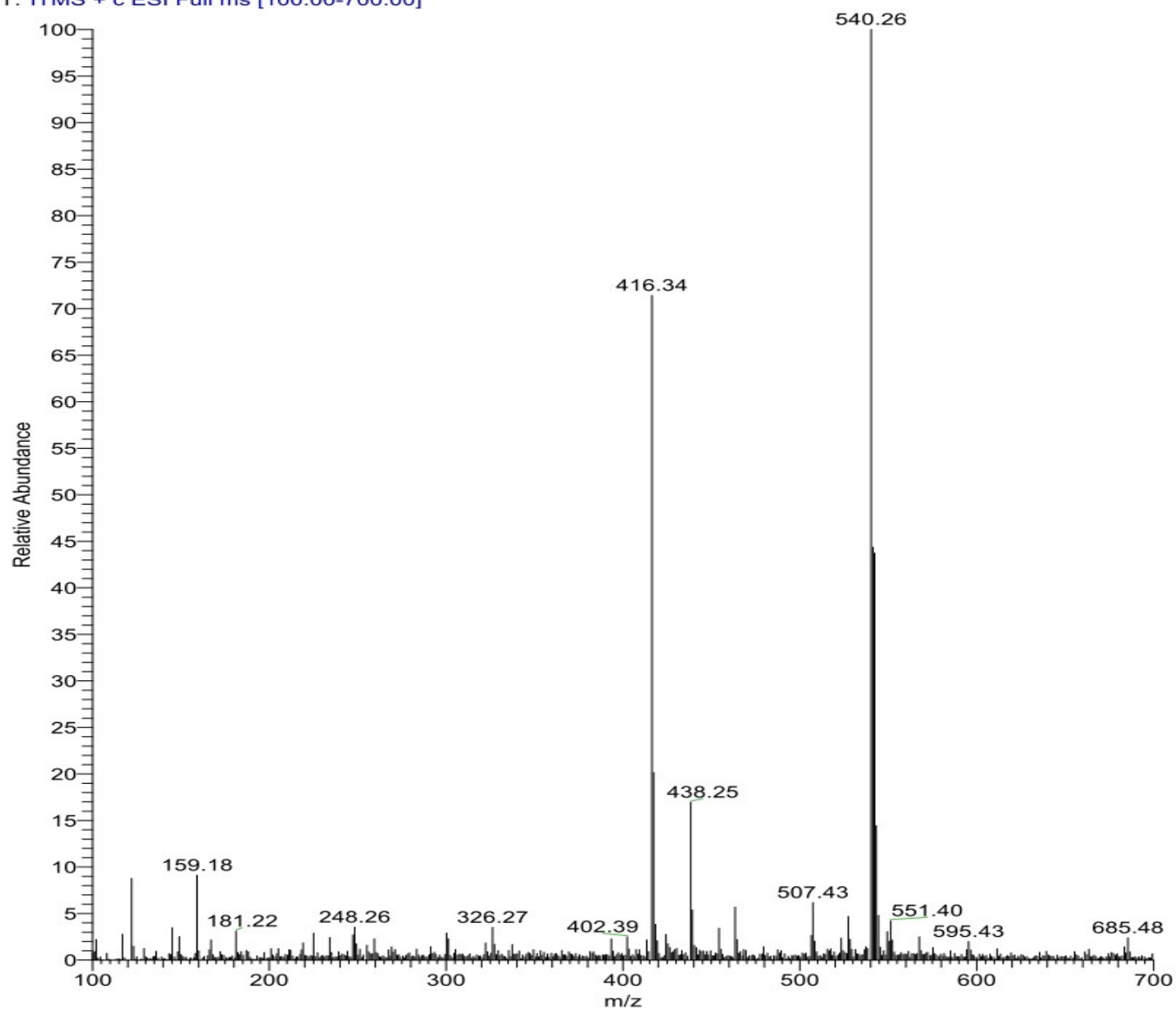




N-BENZ-METH

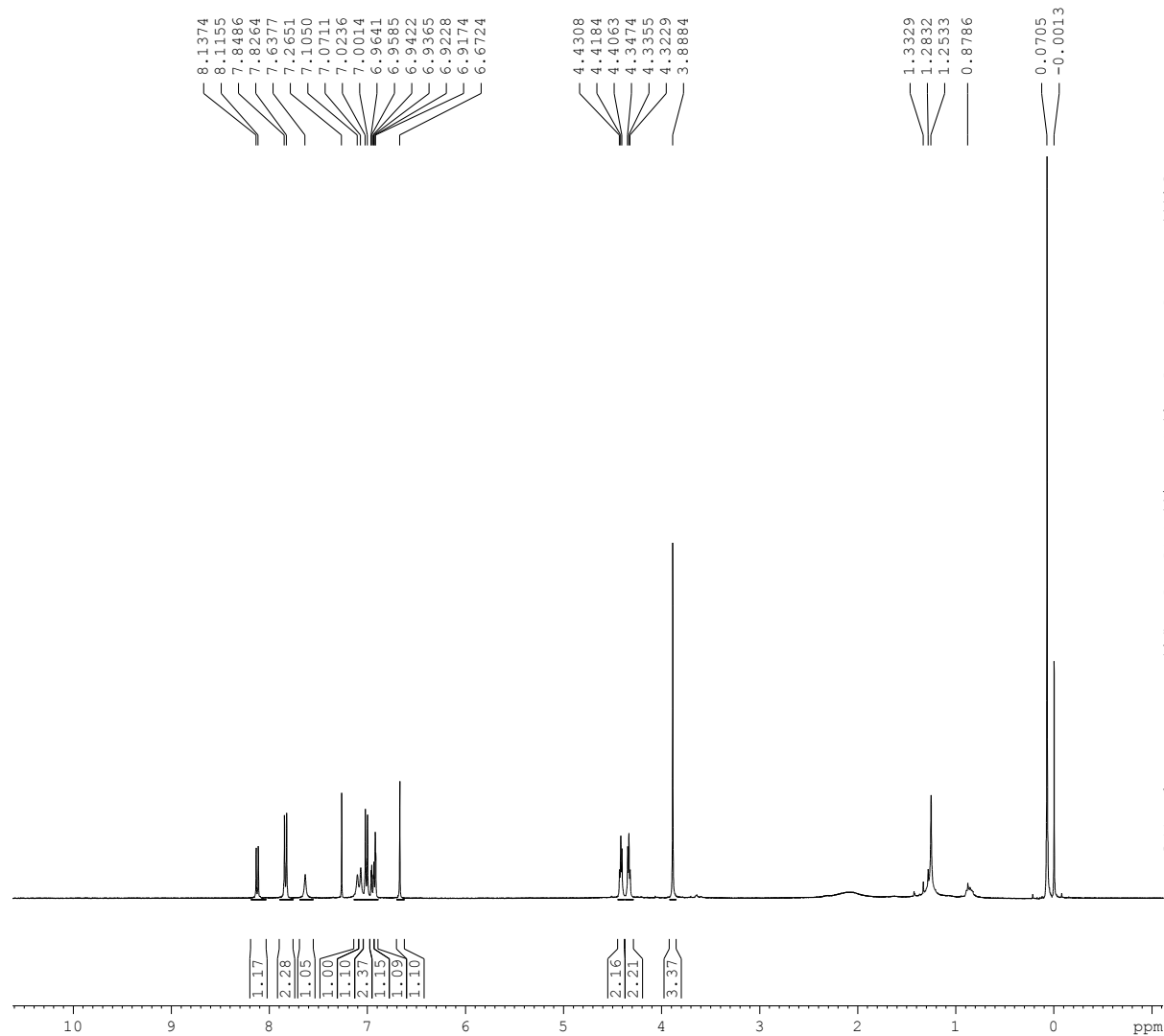


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7j

7J



BRUKER
 AVANCE II 400 NMR
 Spectrometer
 SAIF
 Panjab University
 Chandigarh

Current Data Parameters
 NAME May31-2016
 EXPNO 80
 PROCNO 1

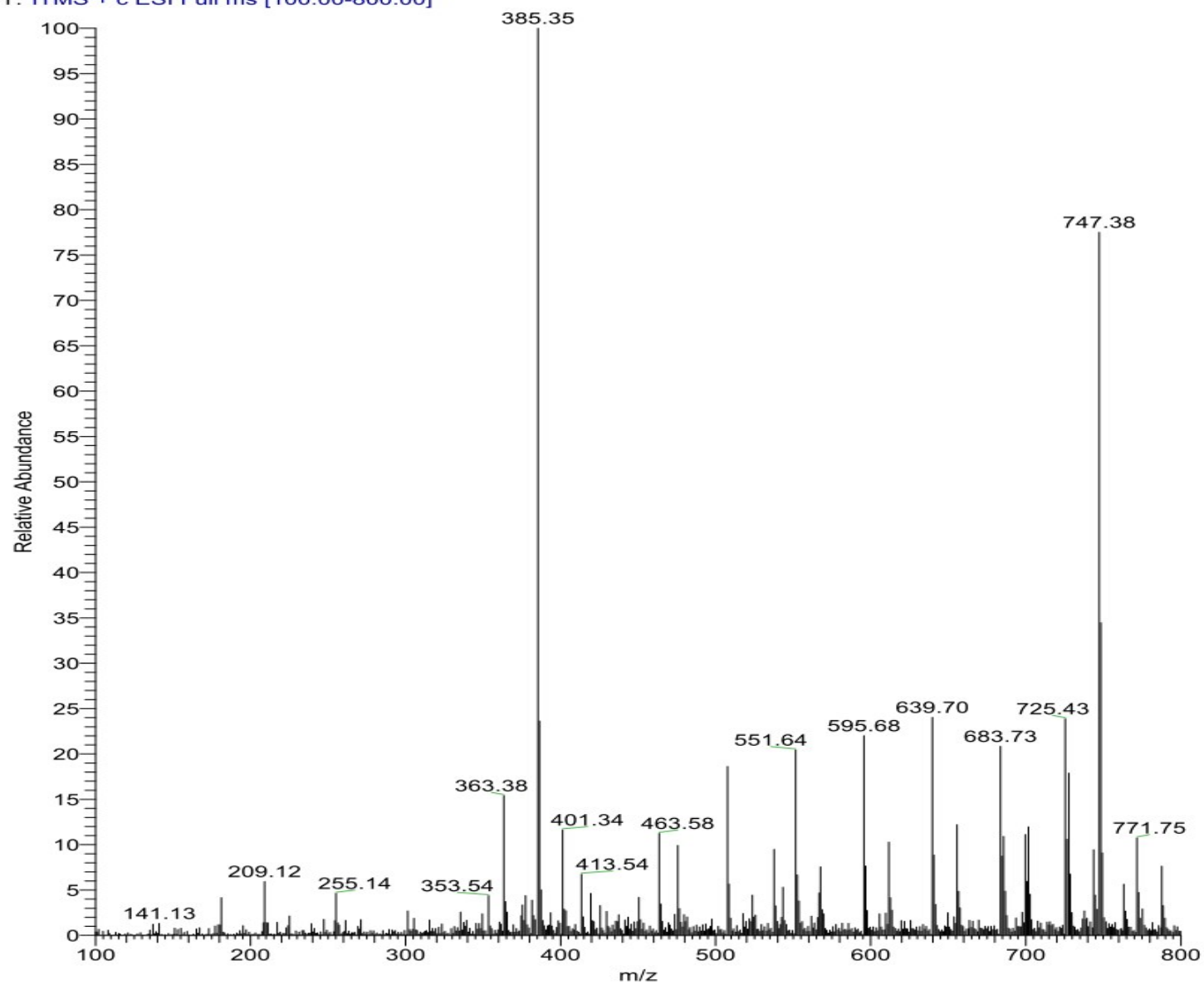
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 TD 65536
 SOLVENT CDCl3
 NS 8
 DS 2
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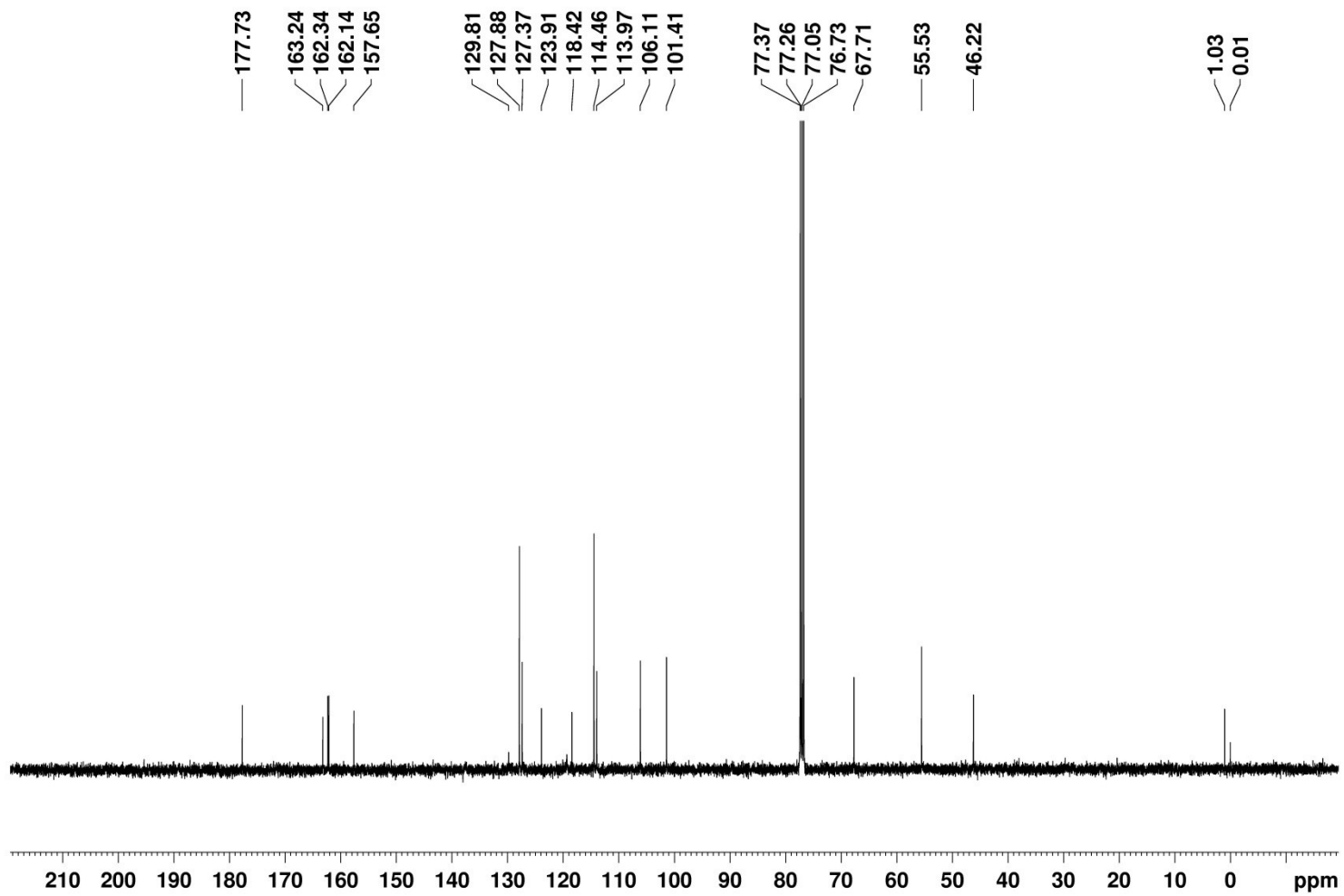
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F2 - Processing parameters
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 GB 0
 PC 1.00

manishkumarmanu1986@gmail.com

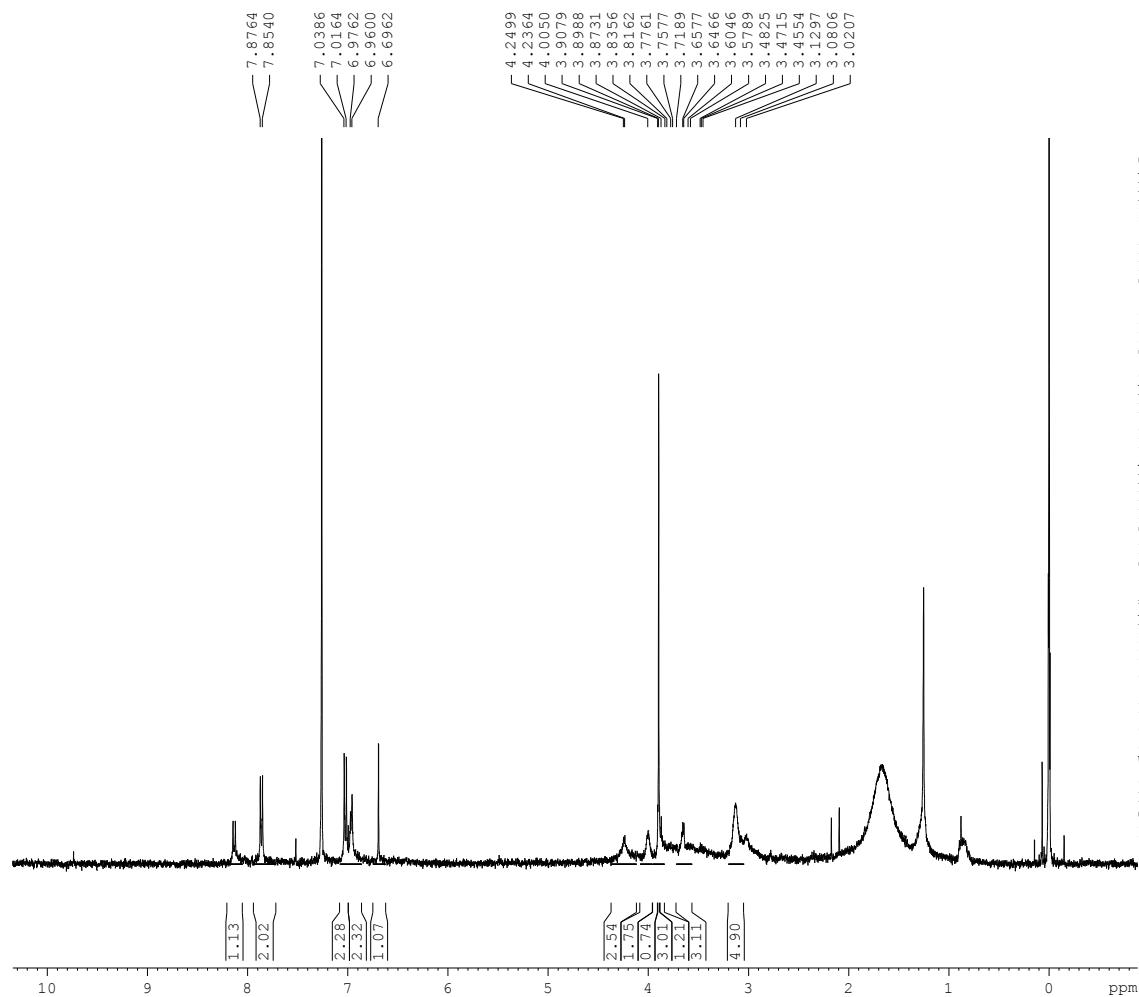
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7k

4-OH-ETH-PIPERZ



BRUKER
AVANCE II 400 NMR
Spectrometer
SAIF
Panjab University
Chandigarh

Current Data Parameters
NAME Feb29-2016
EXPNO 170
PROCNO 1

F2 - Acquisition Parameters
Date_ 20160229
Time 19.17
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DS 2
SWH 12019.230 Hz
FIDRES 0.183399 Hz
AQ 2.7263477 sec
RG 1150
DW 41.600 usec
DE 6.00 usec
TE 295.2 K
D1 1.00000000 sec
TD0 1

===== CHANNEL f1 =====
NUC1 1H
P1 10.90 usec
PL1 -3.00 dB
SFO1 400.1324710 MHz

F2 - Processing parameters
SI 32768
SF 400.1300086 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00

manishkumarmanu1986@gmail.com

MG-12 11-05-2016_160506171243 #108-198 RT: 0.23-0.41 AV: 91 NL: 2.06E5
T: ITMS + c ESI Full ms [100.00-800.00]

