

The following supplementary data has been given:

1. Molecular modeling data
2. Chemical data
3. Biological data

1. Molecular modeling data

Table S1. Experimental and predictive activities of external set compounds (S1-S152).

Compound	Experimental pK_i	Predicted pK_i	Residual
S1	9.124	8.701	0.423
S2	9.387	9.537	-0.150
S3	9.795	8.974	0.821
S4	9.229	9.306	-0.077
S5	8.853	8.458	0.395
S6	9.251	8.312	0.939
S7	9.602	8.824	0.778
S8	9.585	9.146	0.439
S9	9.920	9.616	0.304
S10	8.795	9.276	-0.481
S11	9.259	8.796	0.463
S12	8.769	9.256	-0.487
S13	8.346	9.102	-0.756
S14	6.651	7.255	-0.604
S15	7.494	8.091	-0.597
S16	6.931	7.679	-0.748
S17	6.809	7.371	-0.562
S18	6.903	7.715	-0.812
S19	7.619	7.283	0.336
S20	6.850	7.010	-0.160
S21	7.221	7.748	-0.527
S22	6.679	7.257	-0.578
S23	6.818	7.469	-0.651
S24	7.124	6.601	0.523
S25	7.275	7.726	-0.451
S26	5.623	5.992	-0.369
S27	6.183	6.173	0.010
S28	6.293	6.819	-0.526
S29	6.958	7.738	-0.780
S30	7.229	6.461	0.768
S31	7.744	7.594	0.150
S32	6.191	5.783	0.408

Supplementary material

S33	8.301	7.454	0.847
S34	7.602	7.271	0.331
S35	7.408	7.357	0.051
S36	6.692	6.854	-0.162
S37	7.481	6.641	0.840
S38	7.347	6.58	0.767
S39	6.337	6.581	-0.244
S40	6.625	7.125	-0.500
S41	6.501	7.125	-0.624
S42	6.522	6.447	0.075
S43	6.777	6.873	-0.096
S44	7.301	8.134	-0.833
S45	6.978	6.797	0.181
S46	6.623	6.818	-0.195
S47	8.327	7.856	0.471
S48	8.045	8.919	-0.874
S49	8.045	8.945	-0.900
S50	8.119	8.925	-0.806
S51	8.102	7.810	0.292
S52	8.421	8.933	-0.512
S53	8.283	8.628	-0.345
S54	7.522	7.003	0.519
S55	7.853	7.061	0.792
S56	7.522	7.651	-0.129
S57	8.000	7.714	0.286
S58	7.913	6.979	0.934
S59	7.309	7.549	-0.240
S60	7.921	7.283	0.638
S61	8.522	8.471	0.051
S62	7.886	7.664	0.222
S63	7.698	7.630	0.068
S64	7.886	7.749	0.137
S65	7.494	7.766	-0.272
S66	7.481	7.752	-0.271
S67	7.853	7.752	0.101
S68	7.619	7.765	-0.146
S69	7.221	7.167	0.054
S70	8.229	7.571	0.658
S71	8.657	8.912	-0.255
S72	8.744	7.684	1.060
S73	8.091	7.451	0.640
S74	8.508	7.691	0.817
S75	6.536	7.315	-0.779

Supplementary material

S76	8.236	7.453	0.783
S77	8.229	7.854	0.375
S78	6.954	7.532	-0.578
S79	6.987	7.195	-0.208
S80	8.921	7.974	0.947
S81	8.638	8.057	0.581
S82	9.638	8.816	0.822
S83	8.522	8.023	0.499
S84	8.585	8.127	0.458
S85	8.921	8.216	0.705
S86	8.602	8.295	0.307
S87	6.986	7.041	-0.055
S88	7.009	7.079	-0.070
S89	5.680	6.569	-0.889
S90	5.659	6.714	-1.055
S91	5.421	6.461	-1.040
S92	5.658	6.318	-0.660
S93	5.851	6.481	-0.630
S94	5.750	6.298	-0.548
S95	6.059	6.766	-0.707
S96	6.000	6.656	-0.656
S97	6.229	6.563	-0.334
S98	7.105	6.412	0.693
S99	7.373	7.560	-0.187
S100	6.982	7.518	-0.536
S101	7.203	7.127	0.076
S102	8.136	7.387	0.749
S103	7.326	7.613	-0.287
S104	7.366	7.492	-0.126
S105	6.211	6.631	-0.420
S106	7.411	7.133	0.278
S107	7.869	7.613	0.256
S108	7.823	7.141	0.682
S109	6.101	6.399	-0.298
S110	7.809	7.477	0.332
S111	7.185	6.482	0.703
S112	6.782	6.898	-0.116
S113	7.065	7.715	-0.650
S114	6.735	6.887	-0.152
S115	6.728	6.333	0.395
S116	7.407	6.718	0.689
S117	7.108	6.528	0.580
S118	7.183	6.687	0.496

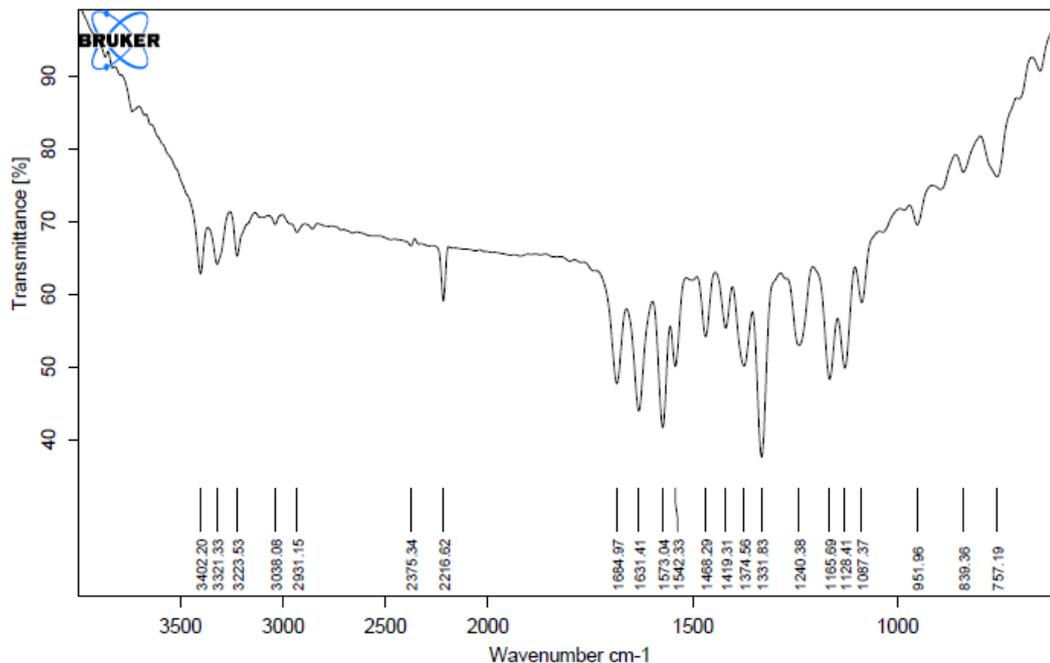
Supplementary material

S119	7.651	6.757	0.894
S120	7.926	7.626	0.300
S121	6.872	6.674	0.198
S122	6.903	6.674	0.229
S123	7.756	7.658	0.098
S124	8.148	7.936	0.212
S125	8.207	8.407	-0.200
S126	7.958	7.974	-0.016
S127	7.593	7.701	-0.108
S128	6.657	7.534	-0.877
S129	6.570	7.534	-0.964
S130	7.619	7.497	0.122
S131	8.823	8.051	0.772
S132	7.853	8.033	-0.180
S133	7.600	8.056	-0.456
S134	8.440	7.923	0.517
S135	8.590	8.120	0.470
S136	8.470	8.059	0.411
S137	7.710	8.101	-0.391
S138	8.714	8.120	0.594
S139	8.396	8.122	0.274
S140	8.812	8.059	0.753
S141	8.573	8.124	0.449
S142	8.694	7.930	0.764
S143	7.924	8.125	-0.201
S144	7.538	7.571	-0.033
S145	8.215	7.798	0.417
S146	5.415	6.128	-0.713
S147	9.268	9.068	0.200
S148	9.000	8.996	0.004
S149	8.119	8.127	-0.008
S150	7.013	7.330	-0.317
S151	8.022	8.140	-0.118
S152	8.301	8.498	-0.197

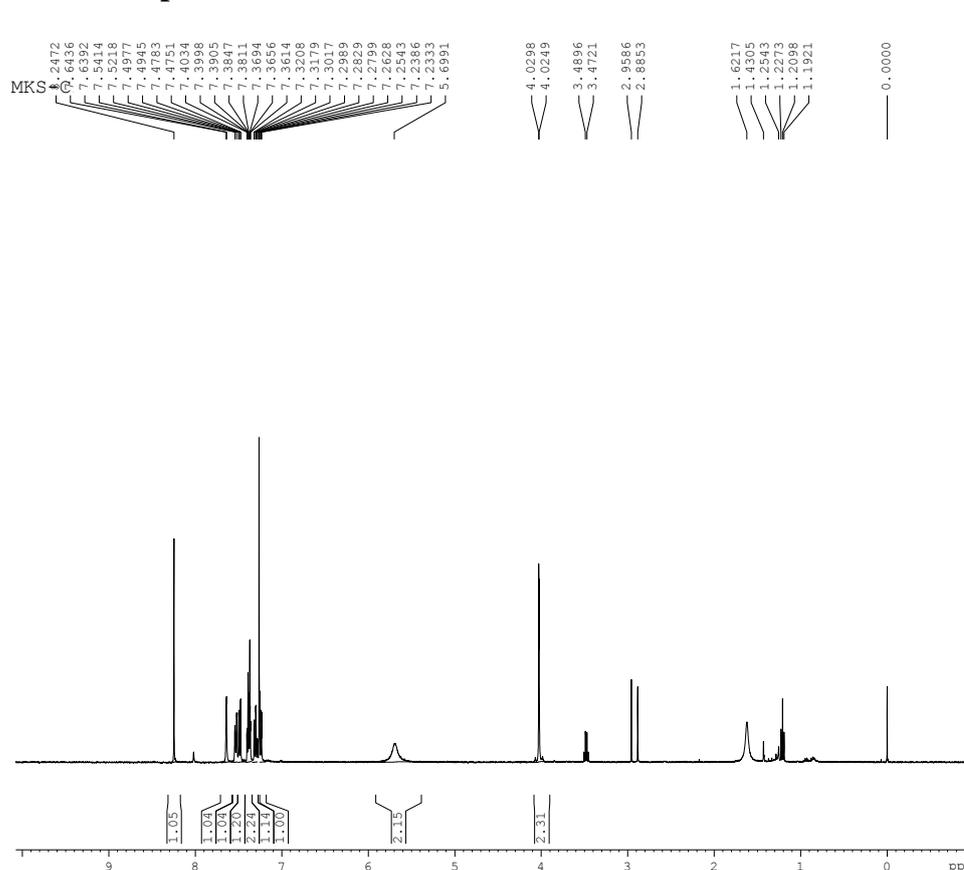
2. Chemical data (Result & Discussion; Chemistry)

4-Amino-2-(2-(2-trifluoromethyl-10H-phenothiazin-10-yl)-2-oxoethylthio)-pyrimidine-5-carbonitrile (1)

IR Spectrum



¹H-NMR Spectrum



BRUKER
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Spectrometer
SAIF
Panjab University
Chandigarh

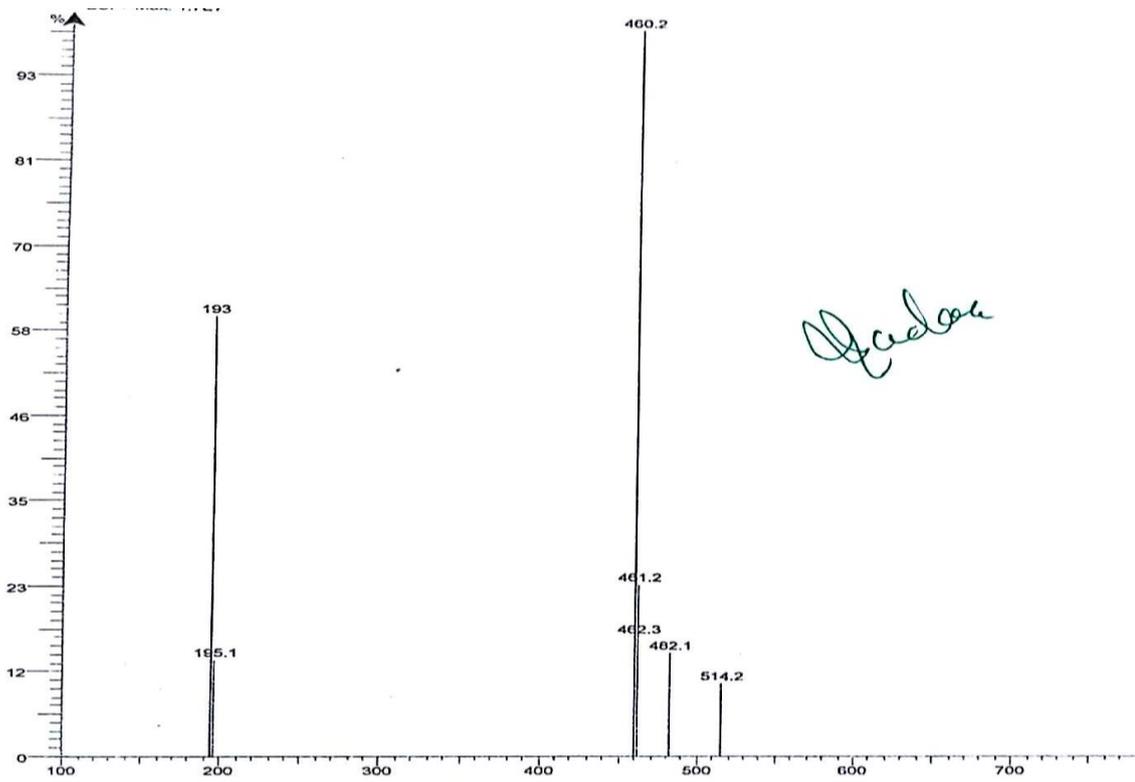
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SOLVENT   CDCl3
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DS         2
SWH        12019.230 Hz
FIDRES     0.183399 Hz
AQ         2.7263477 sec
RG         912
DW         41.600 usec
DE         6.00 usec
TE         295.2 K
D1         1.00000000 sec
TD0        1

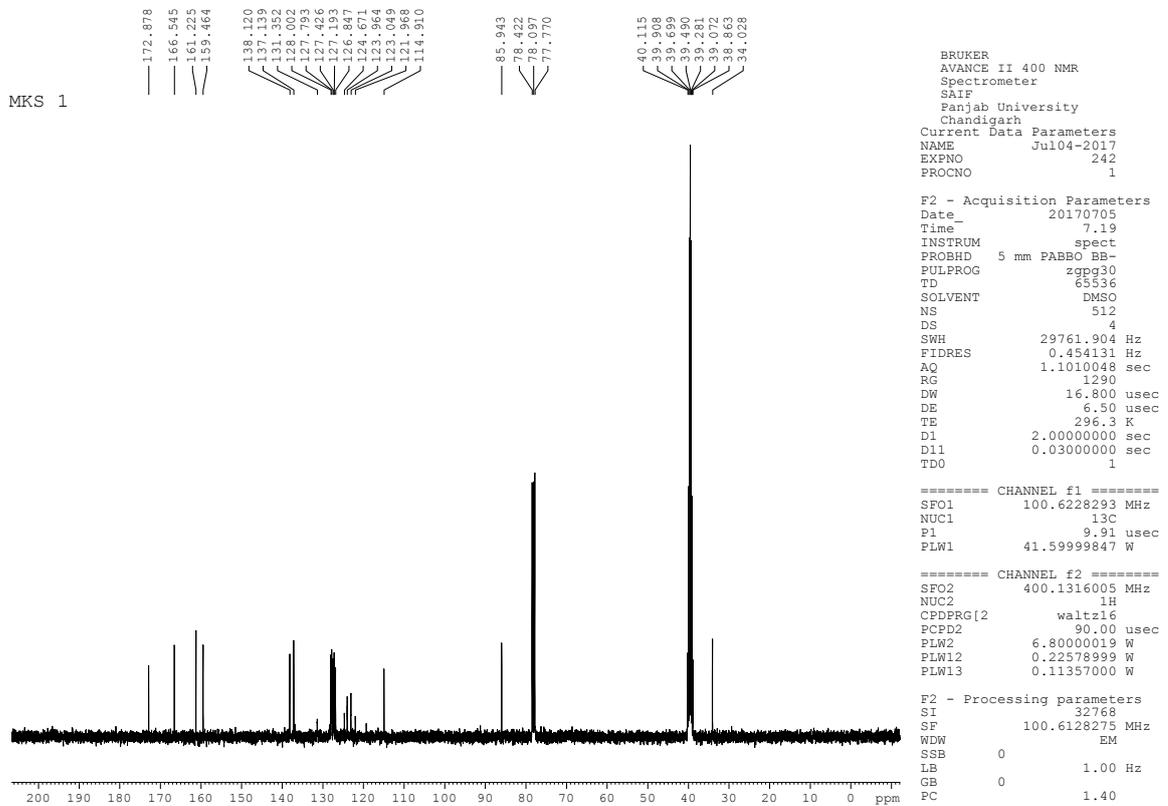
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P1        10.90 usec
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PC        1.00
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MASS Spectrum

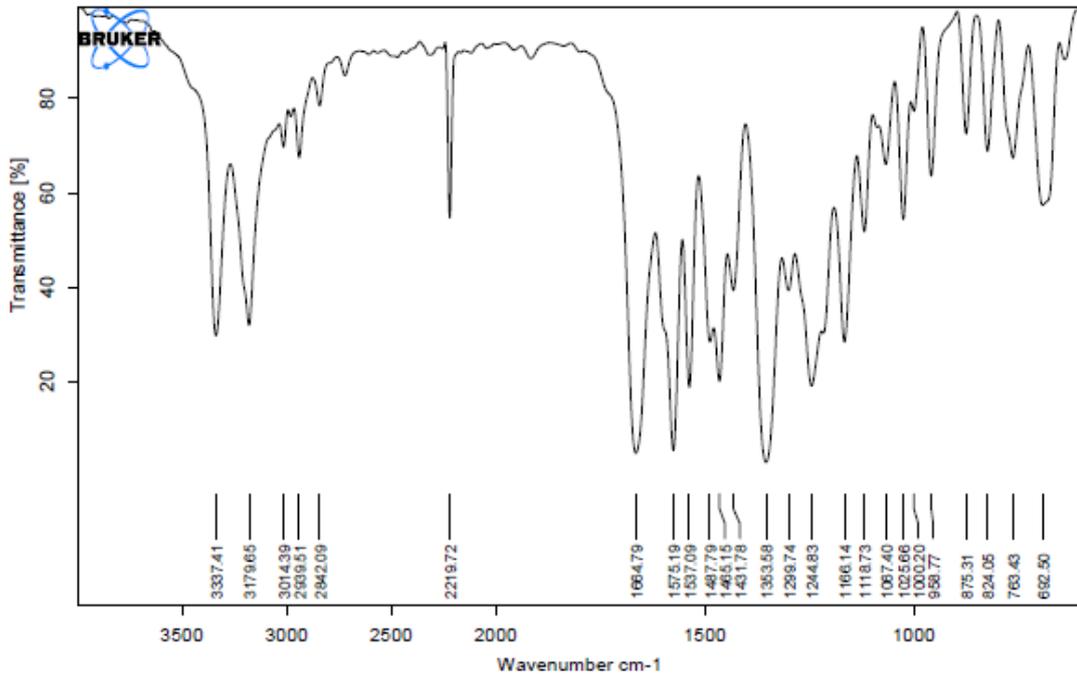


¹³C-NMR Spectrum



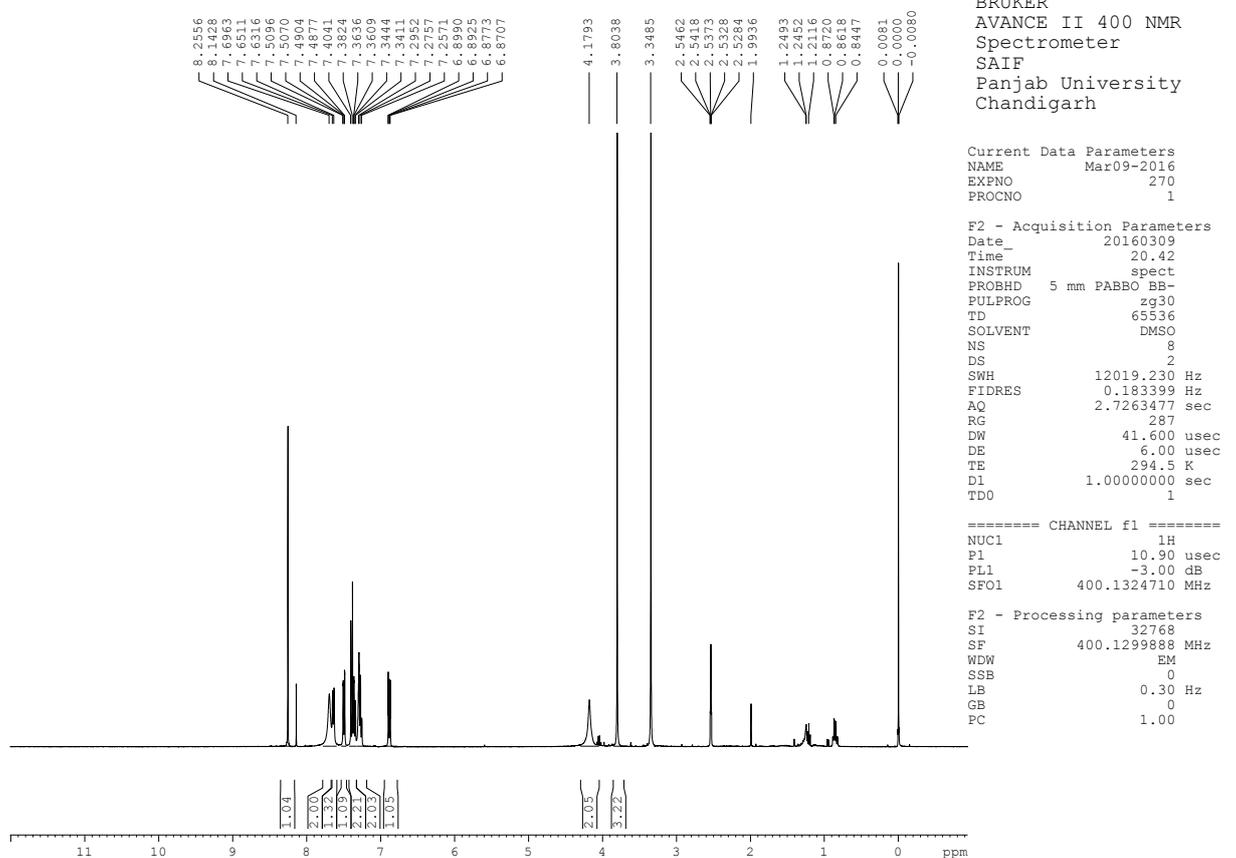
4-Amino-2-(2-(2-methoxy-10H-phenothiazin-10-yl)-2-oxoethylthio)pyrimidine-5-carbonitrile (19)

IR Spectrum

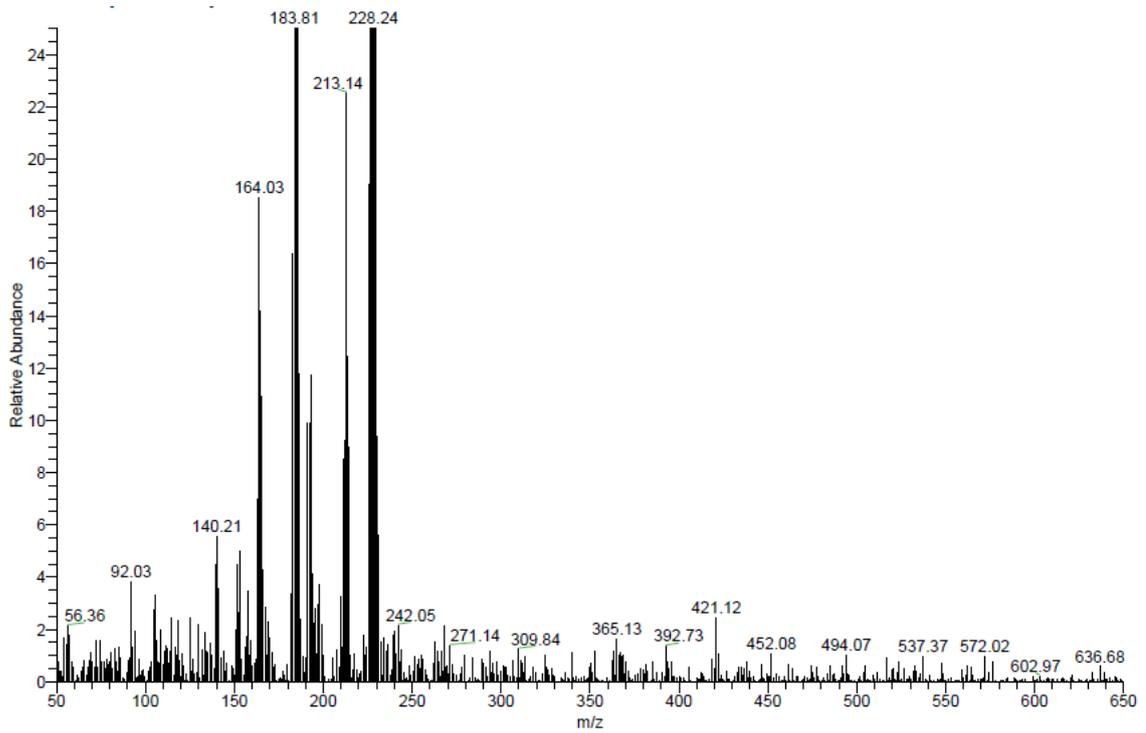


¹H-NMR Spectrum

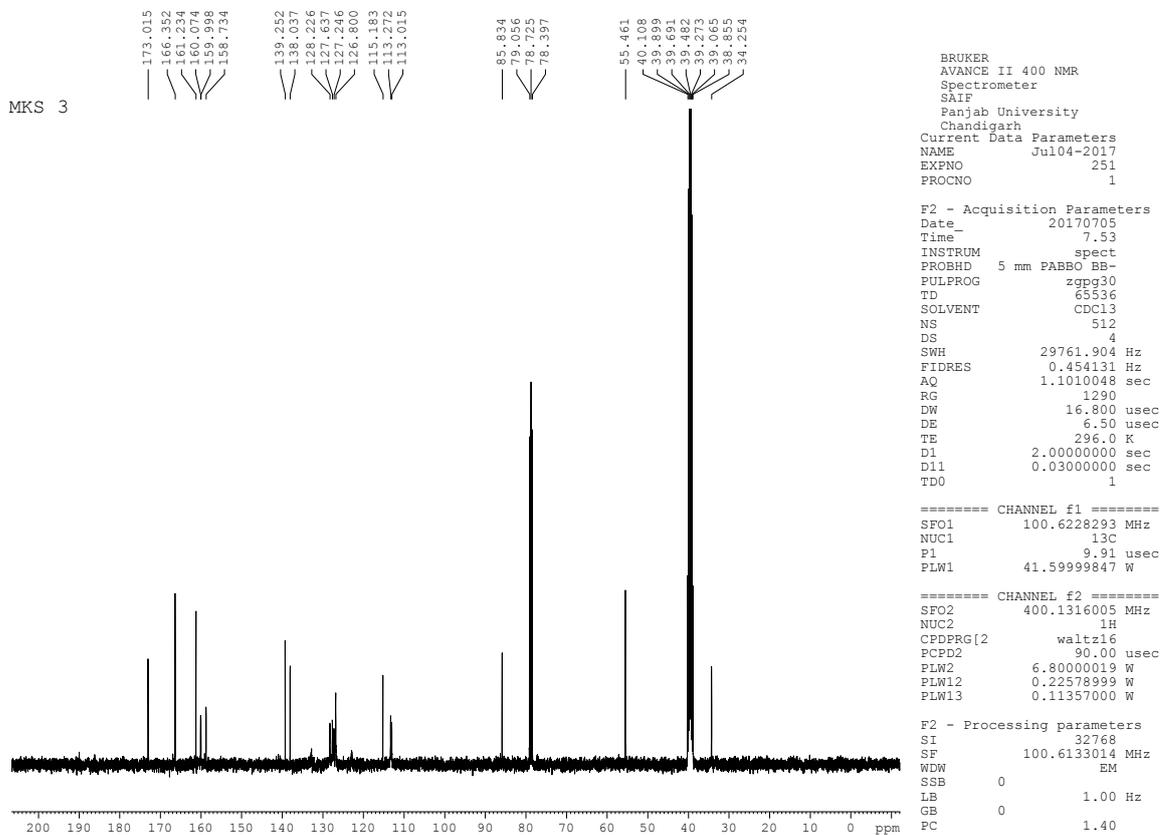
MKS3



MASS Spectrum

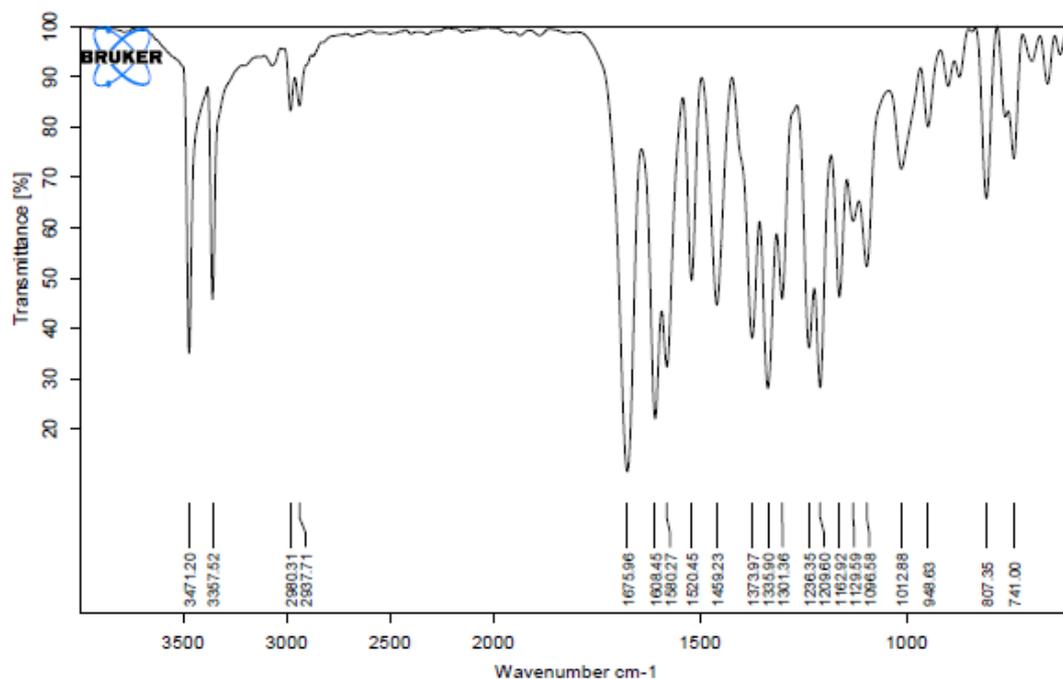


¹³C-NMR Spectrum



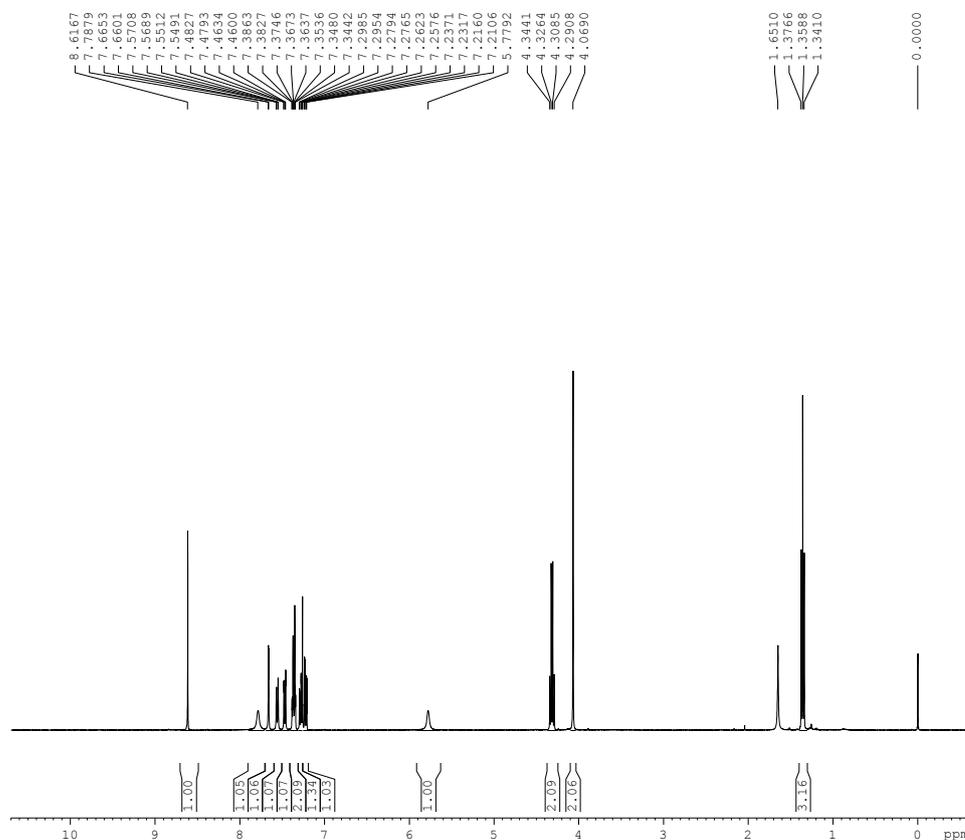
Ethyl 4-amino-2-(2-(2-chloro-10H-phenothiazin-10-yl)-2-oxoethylthio)pyrimidine-5-carboxylate (22)

IR Spectrum



¹H-NMR Spectrum

MKS 11



BRUKER
 AVANCE II 400 NMR
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 Panjab University
 Chandigarh

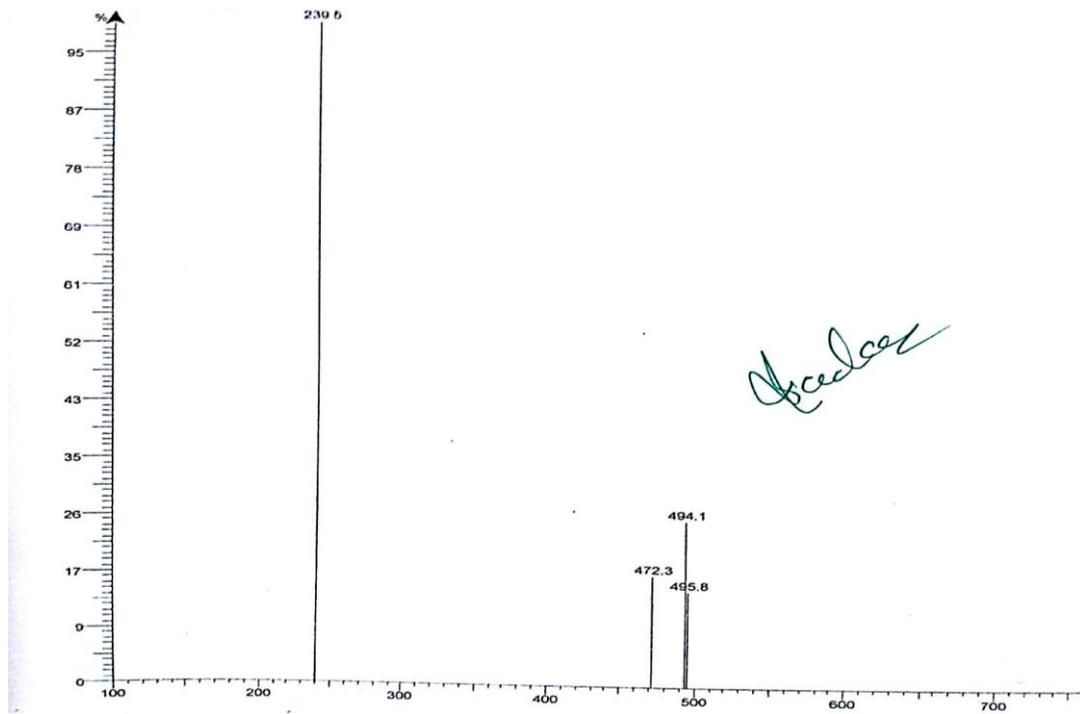
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 PULPROG zg30
 TD 65536
 SOLVENT CDCl3
 NS 8
 DS 2
 SWH 12019.230 Hz
 FIDRES 0.183399 Hz
 AQ 2.7263477 sec
 RG 812
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 DE 6.00 usec
 TE 298.8 K
 D1 1.00000000 sec
 TDO 1

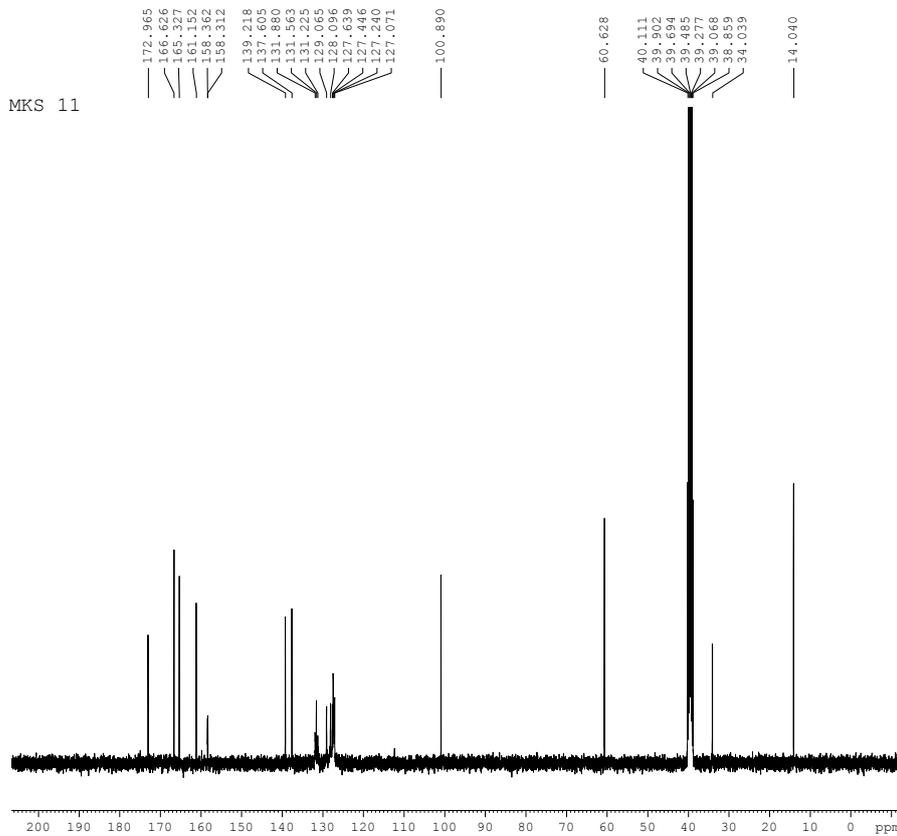
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 P1 10.90 usec
 PL1 -3.00 dB
 SFO1 400.1324710 MHz

F2 - Processing parameters
 SI 32768
 SF 400.1300087 MHz
 WDW EM
 SSB 0
 LB 0.30 Hz
 GB 0
 PC 1.00

MASS Spectrum



¹³C-NMR Spectrum



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BRUKER
AVANCE II 400 NMR
Spectrometer
SAIF
Panjab University
Chandigarh
Current Data Parameters
NAME      Jul04-2017
EXPNO     261
PROCNO    1

F2 - Acquisition Parameters
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PULPROG   zgpg30
TD         65536
SOLVENT   CDCl3
NS         512
DS         4
SWH       29761.904 Hz
FIDRES    0.454131 Hz
AQ         1.1010048 sec
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DE         6.50 usec
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D1         2.00000000 sec
D11        0.03000000 sec
TD0        1

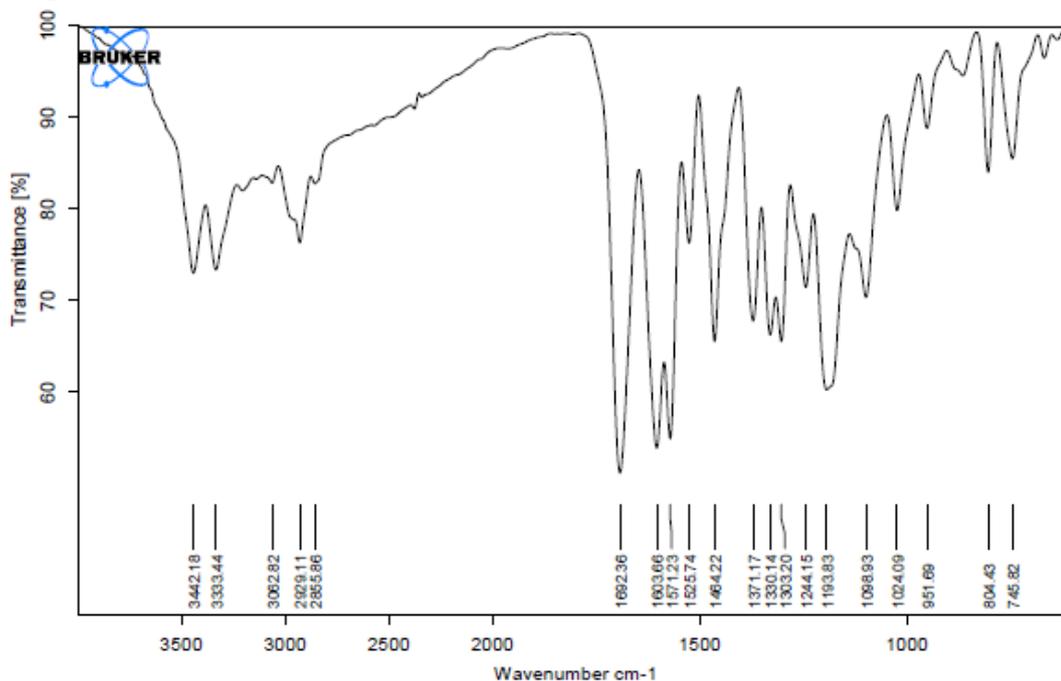
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NUC1      13C
P1         9.91 usec
PLW1      41.59999847 W

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NUC2      1H
CPDPRG2   waltz16
PCPD2     90.00 usec
PLW2      6.80000019 W
PLW12     0.22578999 W
PLW13     0.11357000 W

F2 - Processing parameters
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WDW        EM
SSB        0
LB         1.00 Hz
GB         0
PC         1.40
manishkumarmanu1986@gmail.com
    
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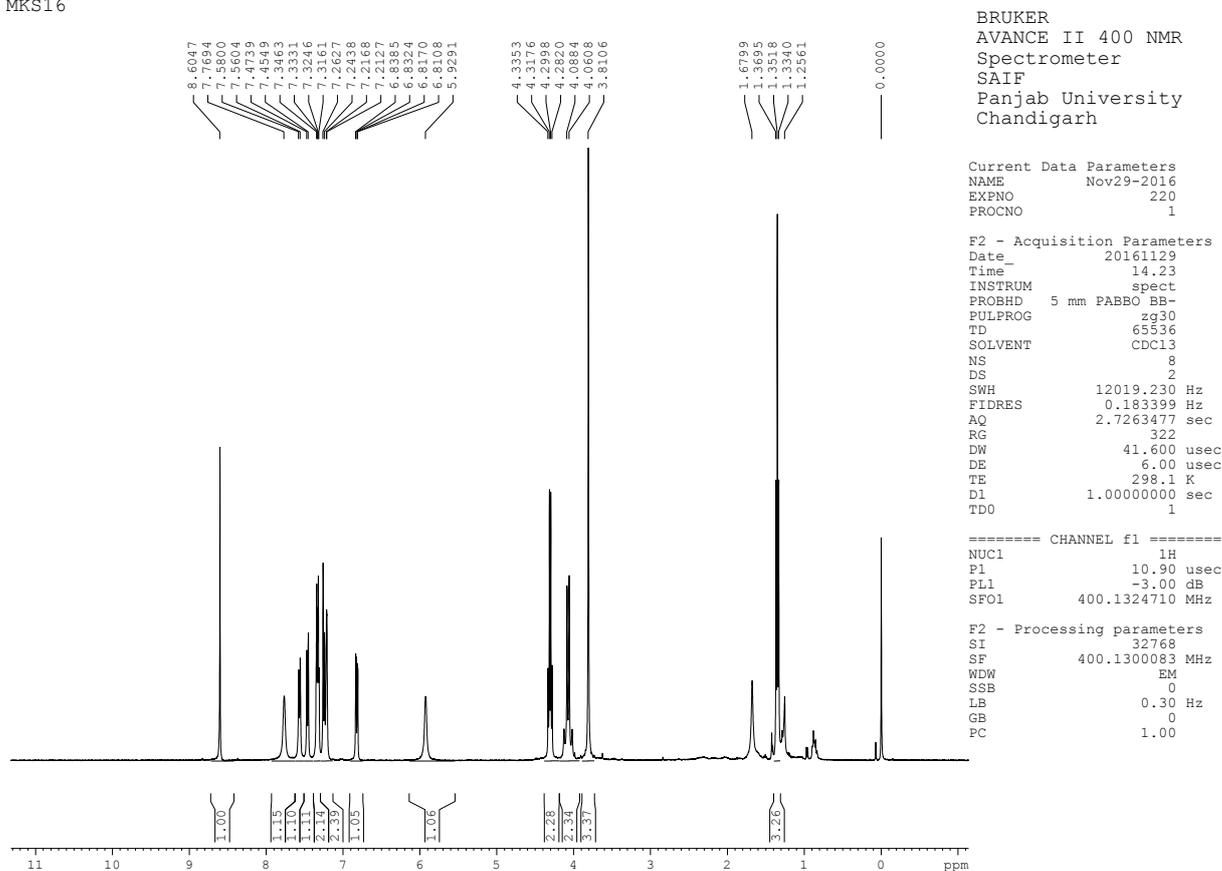
Ethyl 4-amino-2-(2-(2-methoxy-10*H*-phenothiazin-10-yl)-2-oxoethylthio)-pyrimidine-5-carboxylate (23)

IR Spectrum

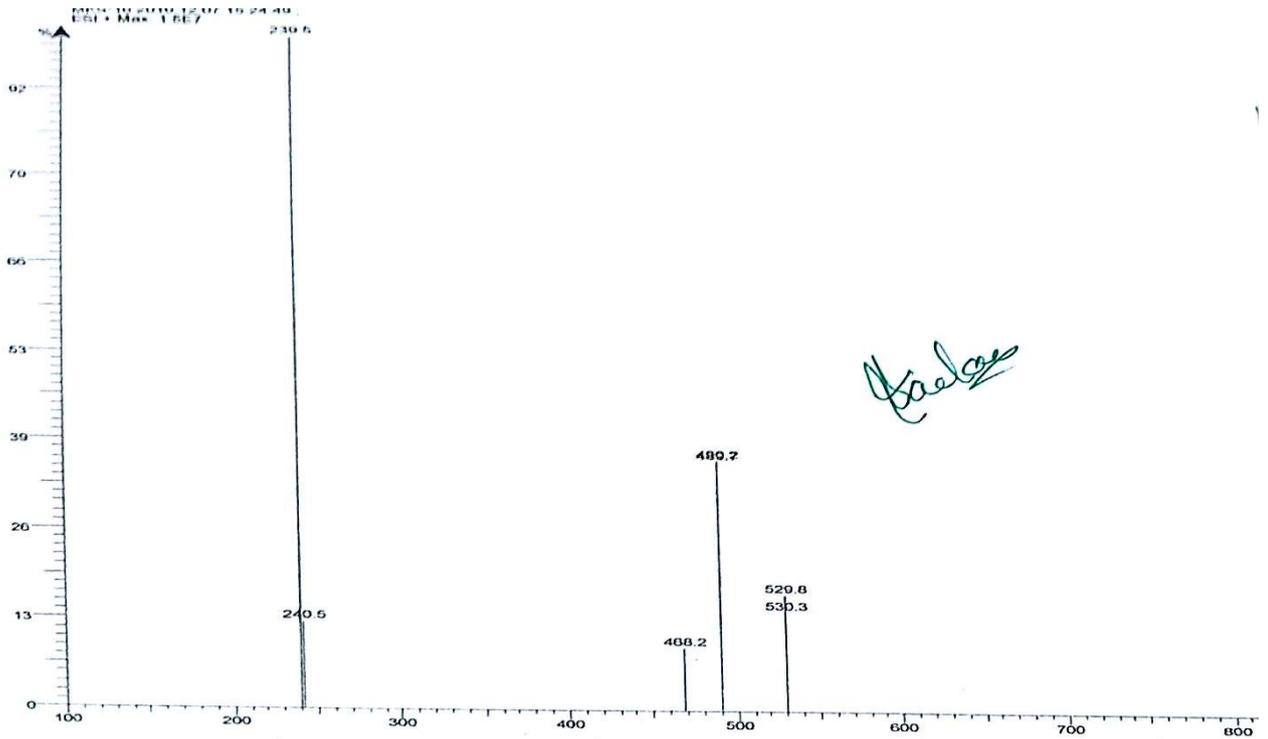


¹H-NMR Spectrum

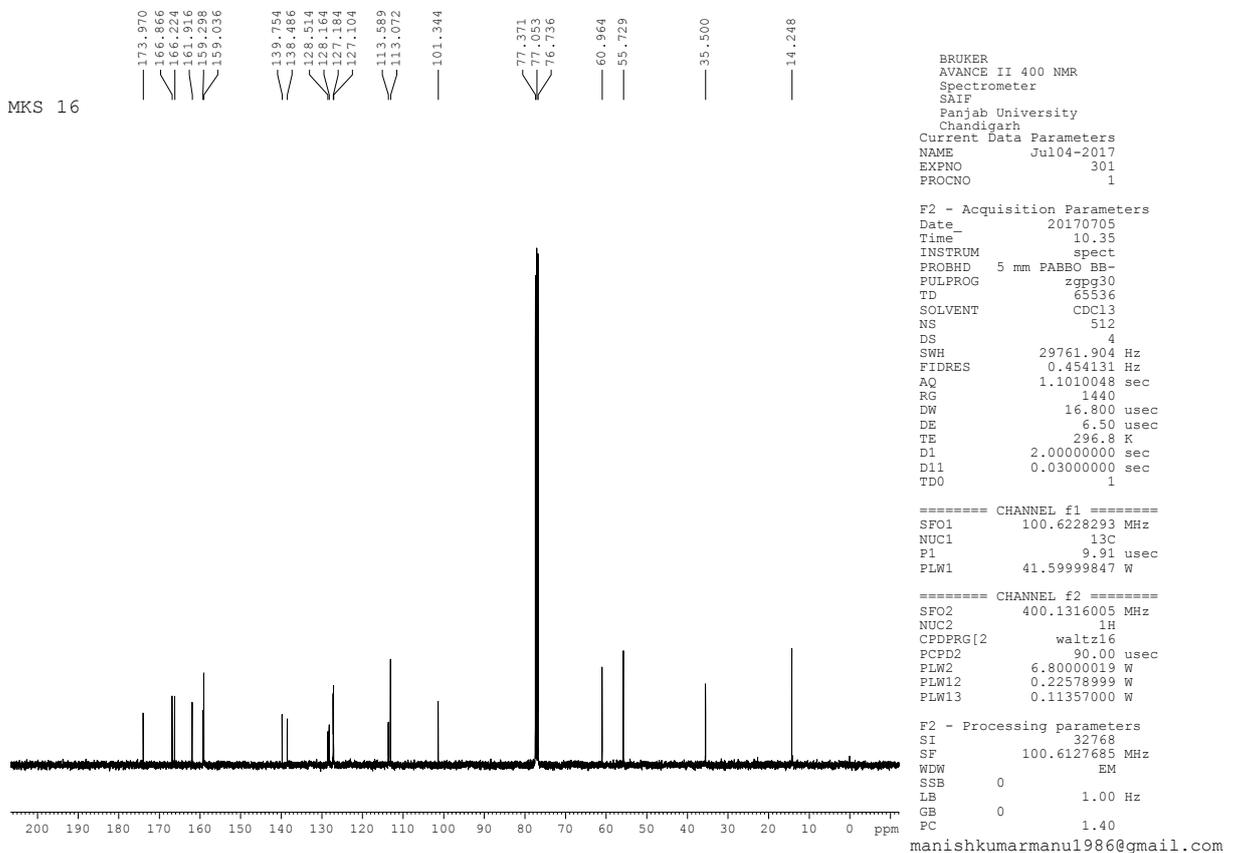
MKS16



MASS Spectrum

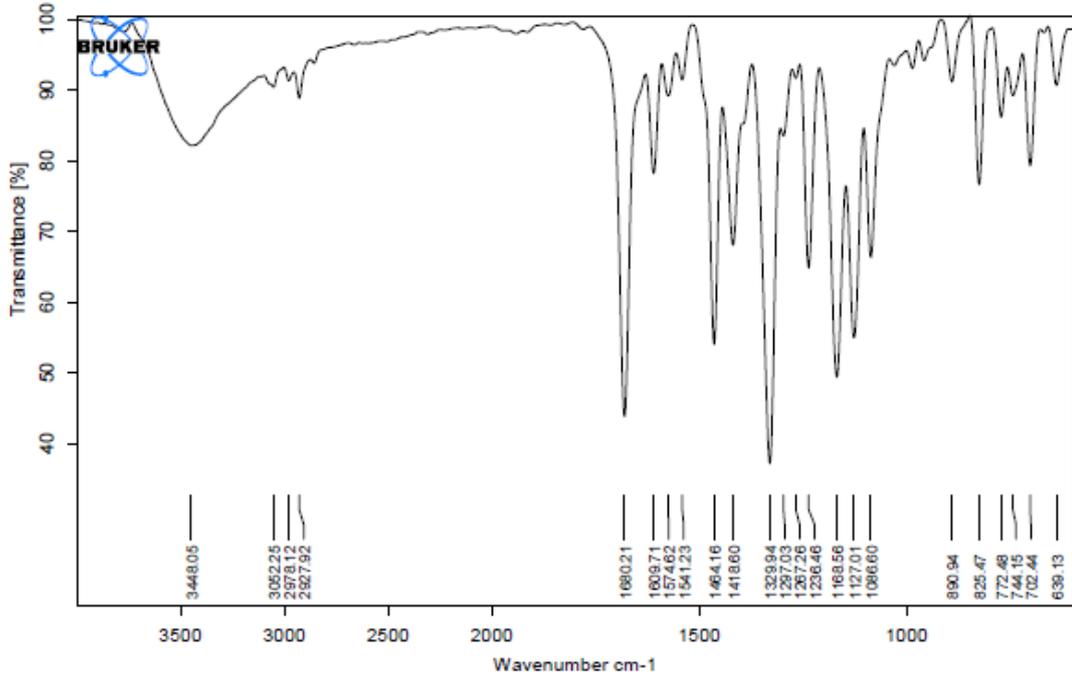


¹³C-NMR Spectrum



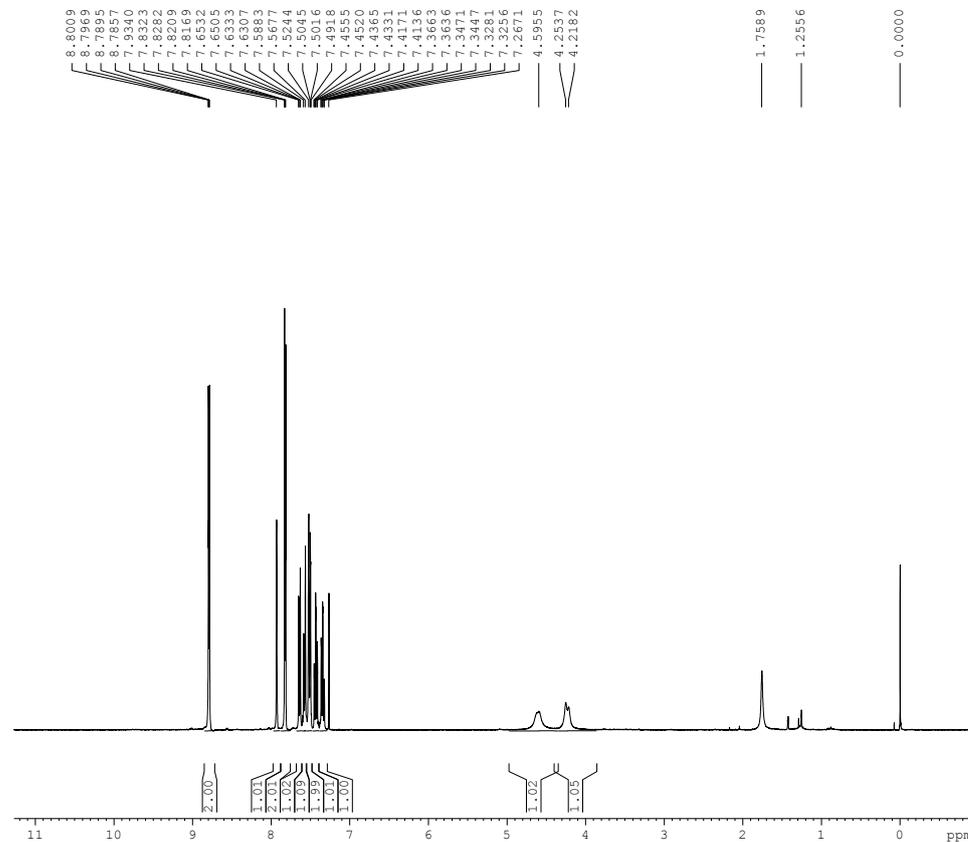
2-(5-(4-Pyridyl)-1,3,4-oxadiazol-2-ylthio)-1-(2-trifluoromethyl-10H-phenothiazin-10-yl)ethanone (25)

IR Spectrum



¹H-NMR Spectrum

MKS 20



BRUKER
 AVANCE II 400 NMR
 Spectrometer
 SAIF
 Panjab University
 Chandigarh

Current Data Parameters
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 EXPNO 300
 PROCNO 1

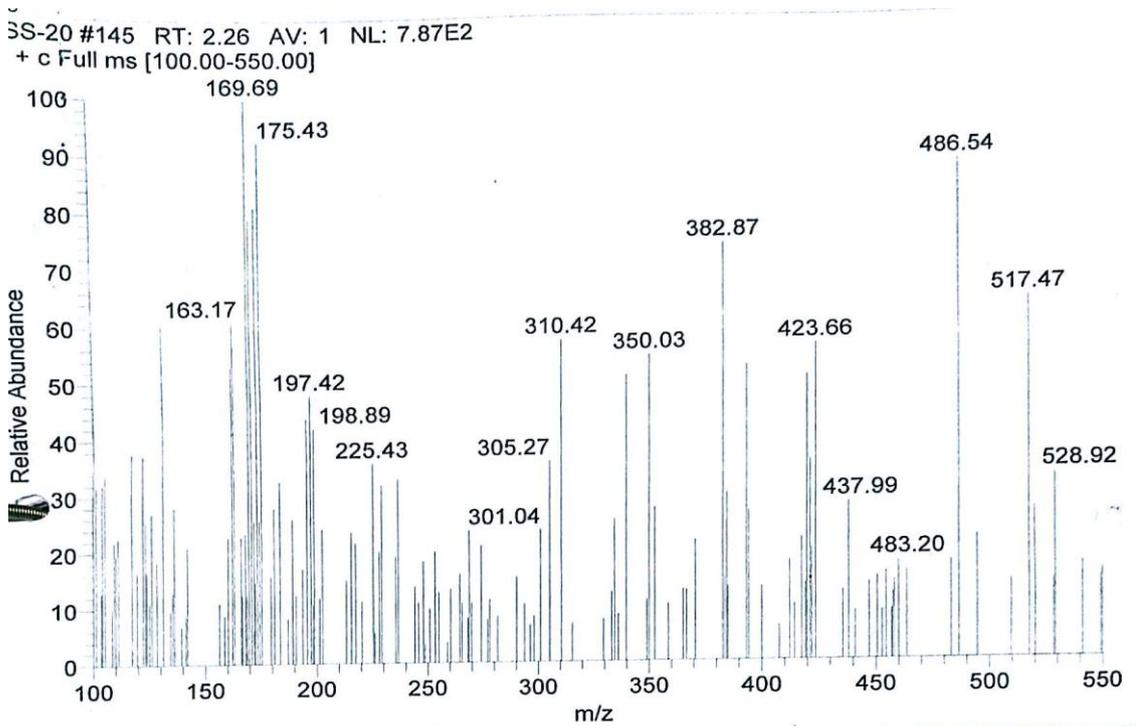
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 TD 65536
 SOLVENT CDCl3
 NS 8
 DS 2
 SWH 12019.230 Hz
 FIDRES 0.183399 Hz
 AQ 2.7263477 sec
 RG 645
 DW 41.600 usec
 DE 6.00 usec
 TE 297.2 K
 D1 1.0000000 sec
 TD0 1

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 PL1 -3.00 dB
 SFO1 400.1324710 MHz

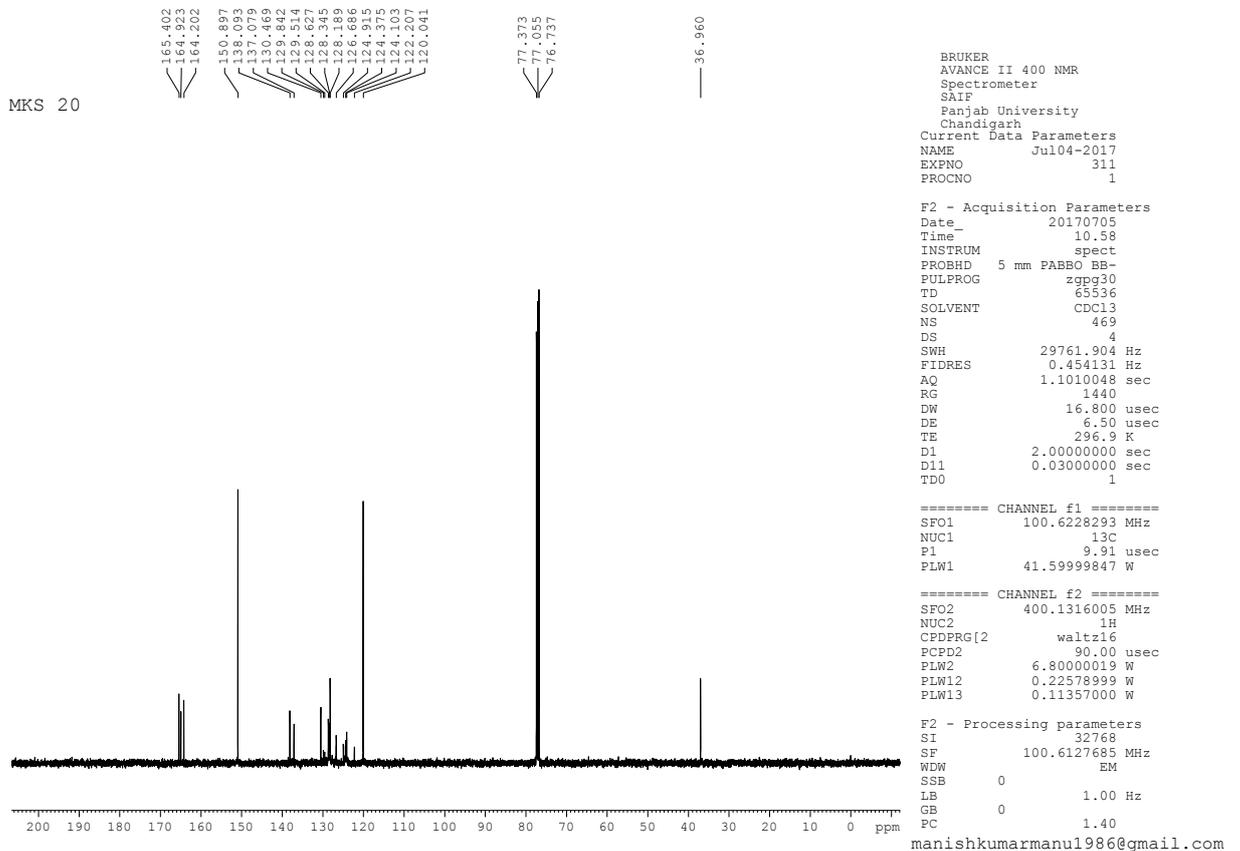
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 LB 0.30 Hz
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manishkumarmanu1986@gmail.com

MASS Spectrum

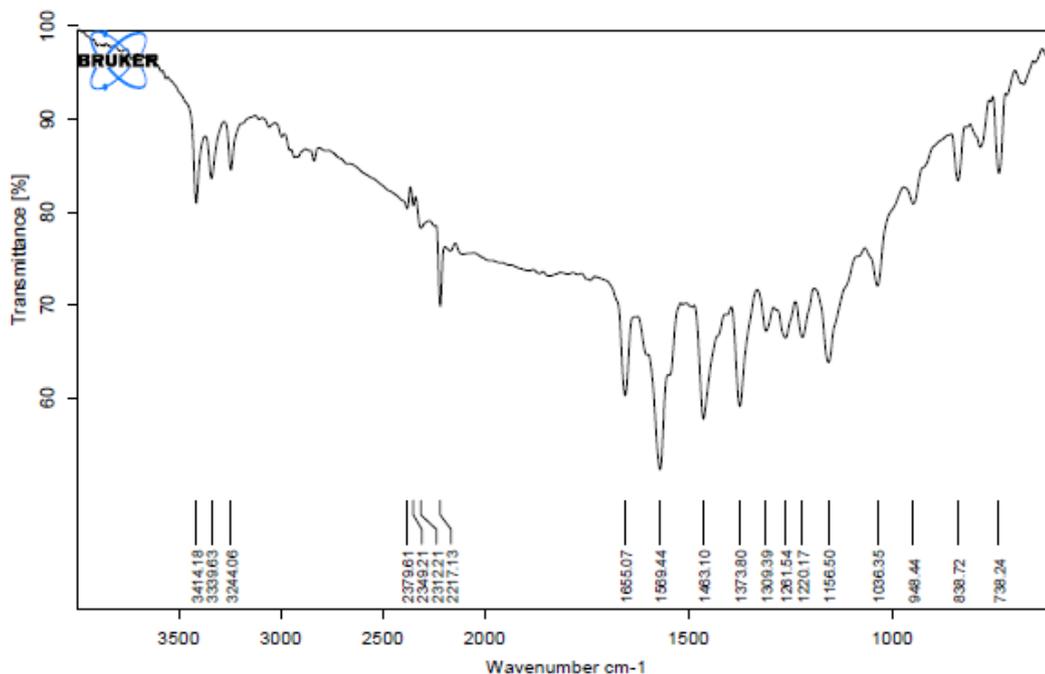


¹³C-NMR Spectrum



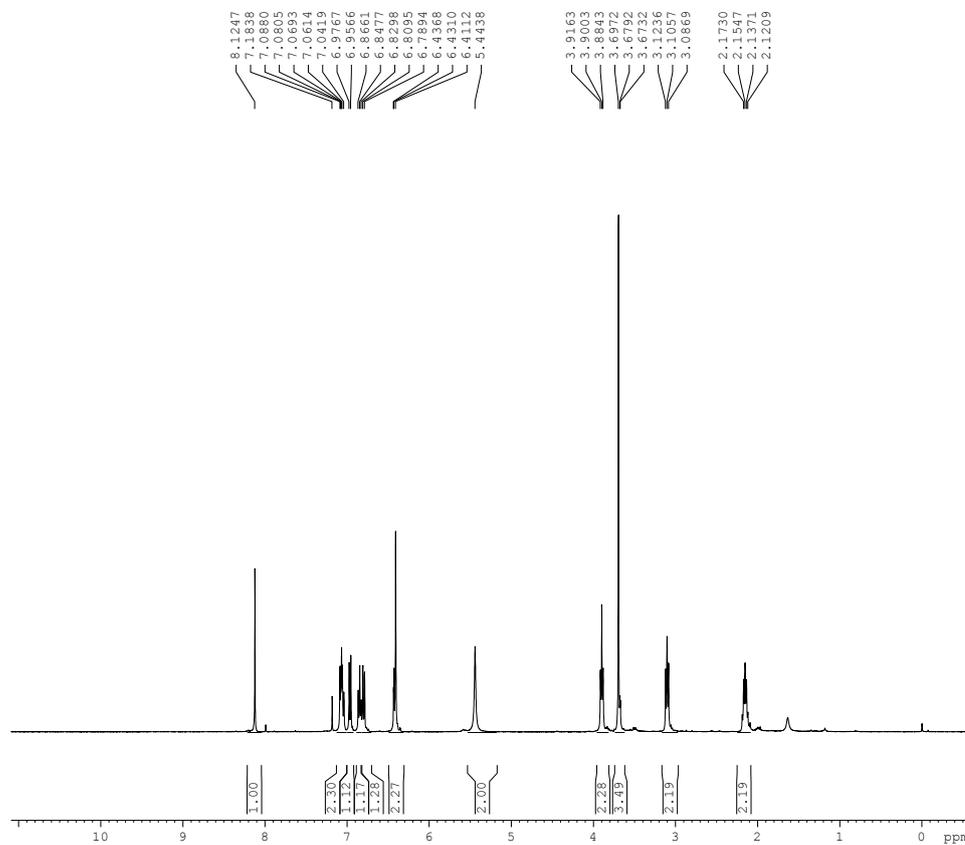
4-Amino-2-(3-(2-methoxy-10H-phenothiazin-10-yl)propylthio)pyrimidine-5-carbonitrile (40)

IR Spectrum



¹H-NMR Spectrum

MKS-30



BRUKER
AVANCE II 400 NMR
Spectrometer
SAIF
Panjab University
Chandigarh

Current Data Parameters
NAME Dec08-2016
EXPNO 80
PROCNO 1

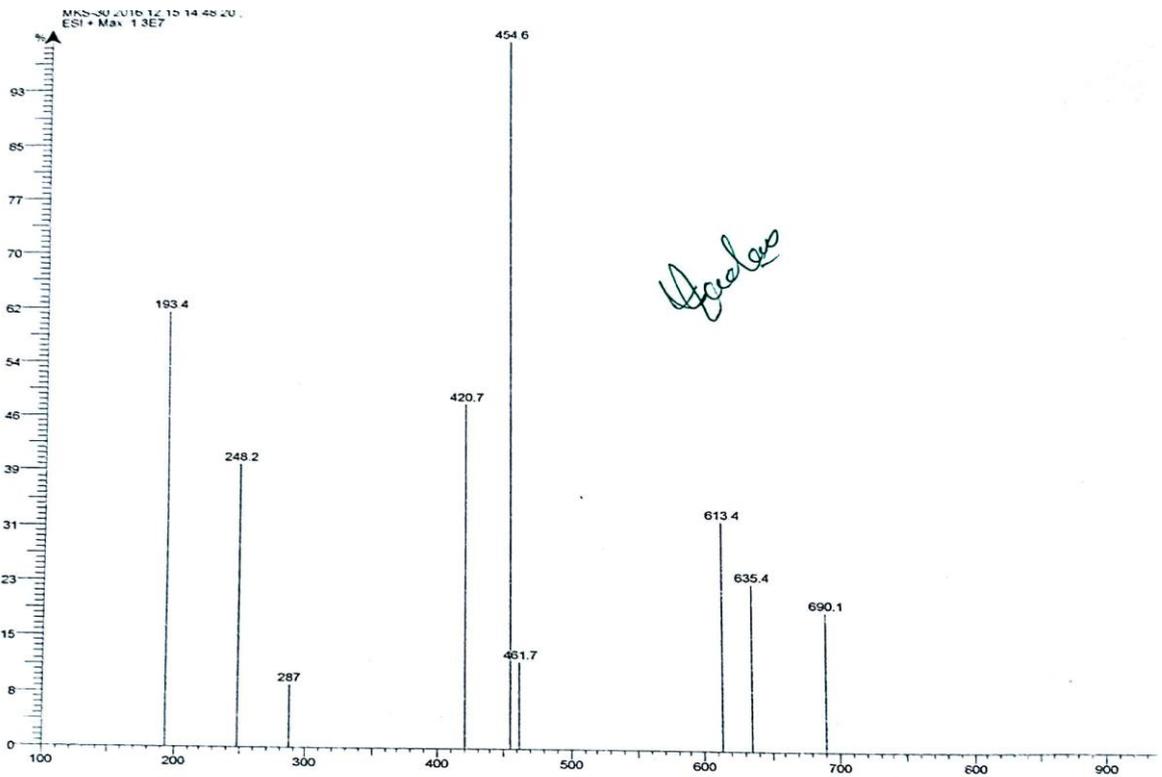
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NS 8
DS 2
SWH 12019.230 Hz
FIDRES 0.183399 Hz
AQ 2.7263477 sec
RG 406
DW 41.600 usec
DE 6.00 usec
TE 296.7 K
D1 1.00000000 sec
TDO 1

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

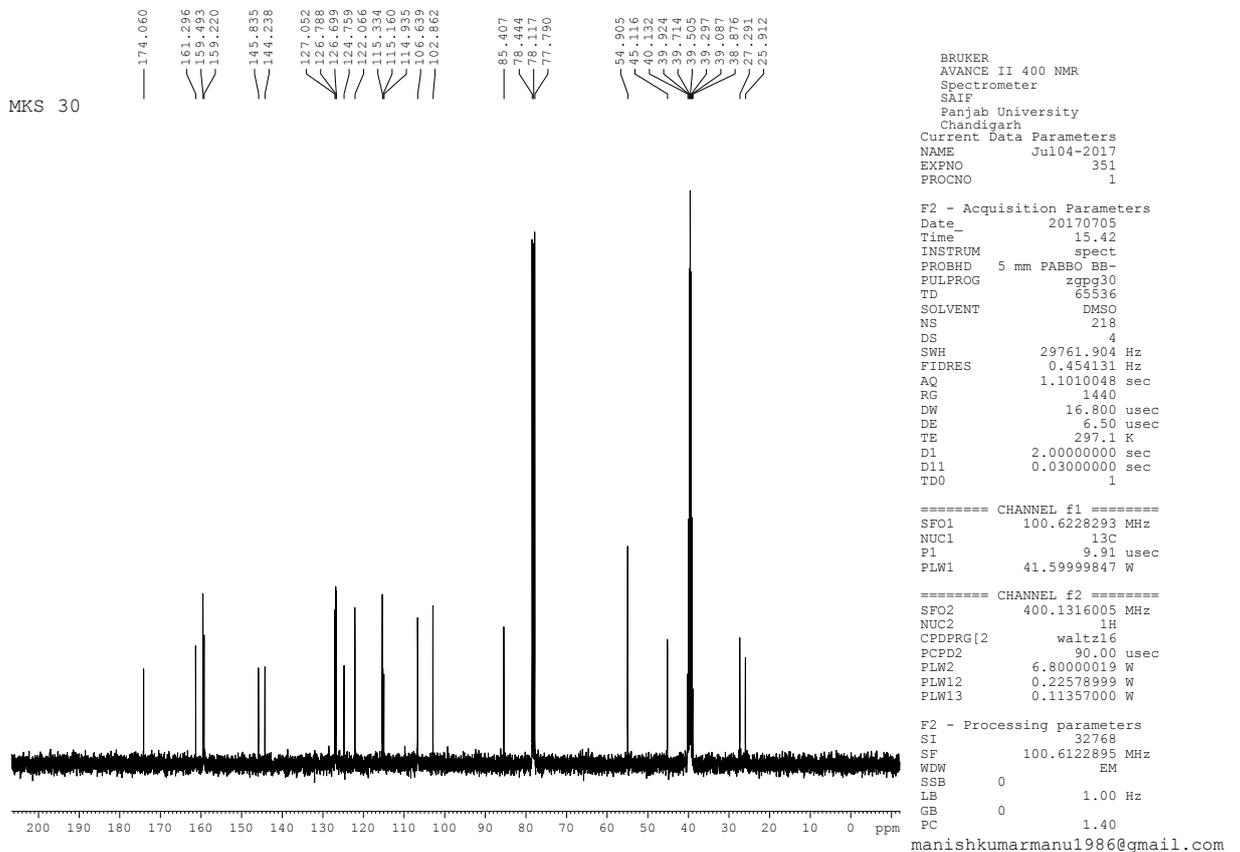
F2 - Processing parameters
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LB 0.30 Hz
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PC 1.00

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MASS Spectrum

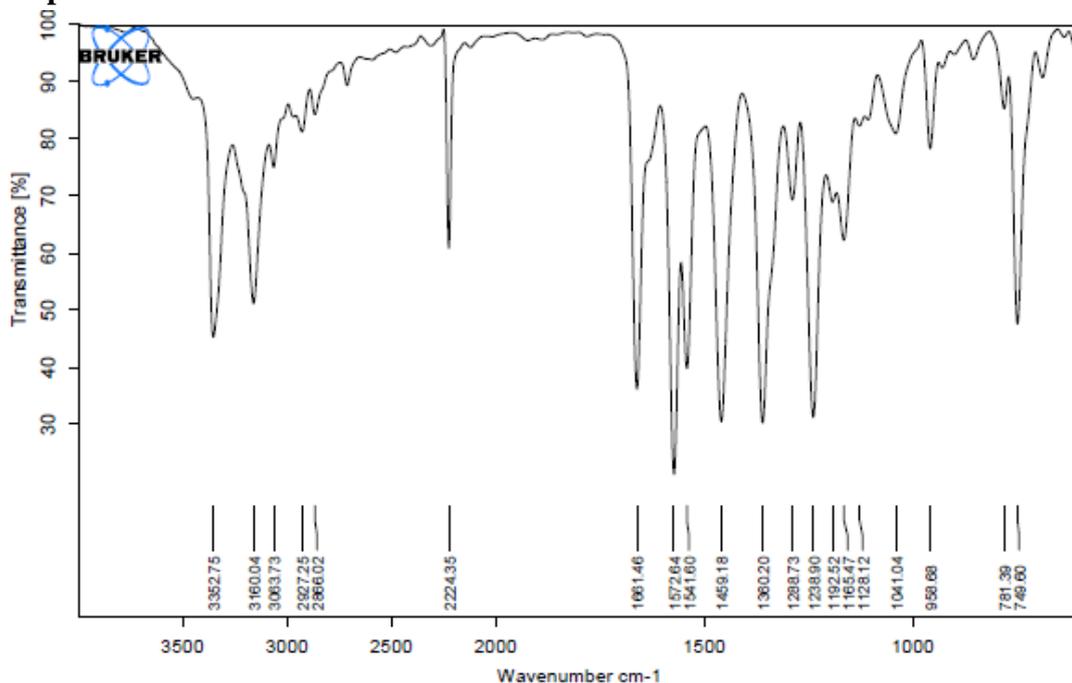


¹³C-NMR Spectrum



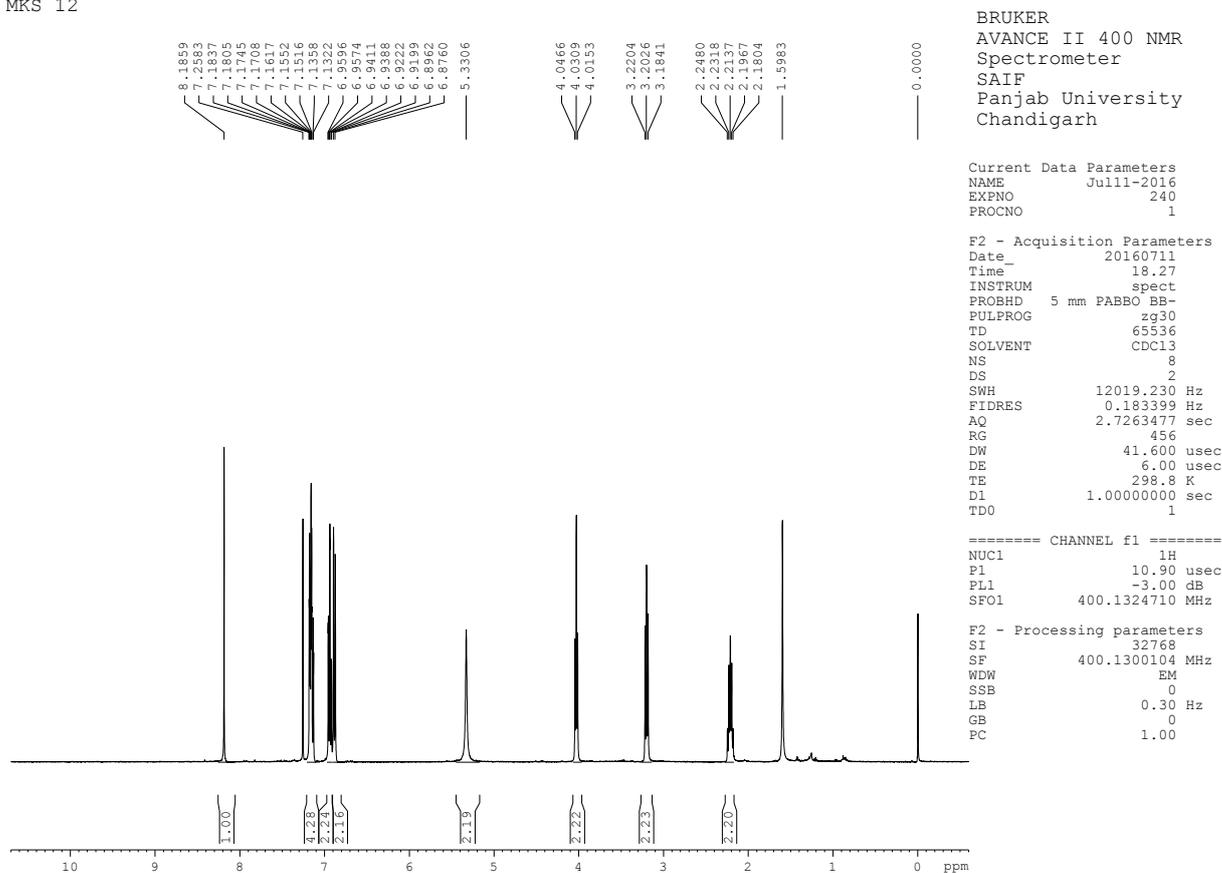
4-Amino-2-(3-(10H-phenothiazin-10-yl)propylthio)pyrimidine-5-carbonitrile (41)

IR Spectrum



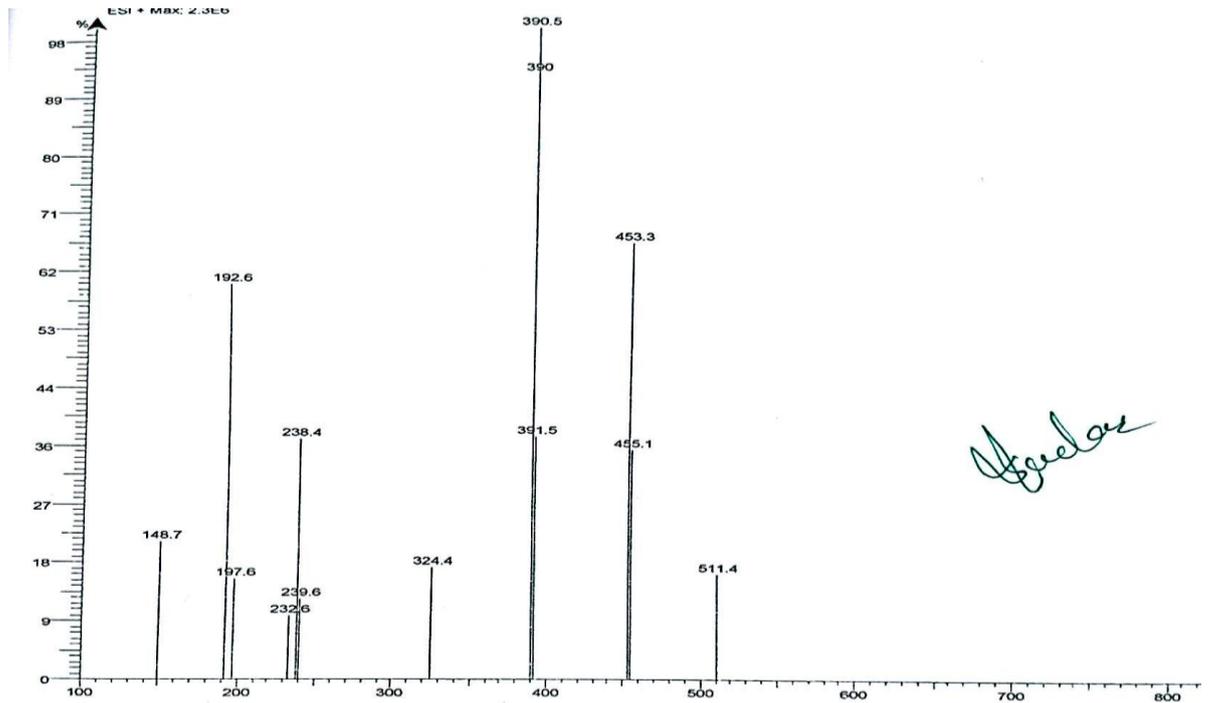
¹H-NMR Spectrum

MKS 12

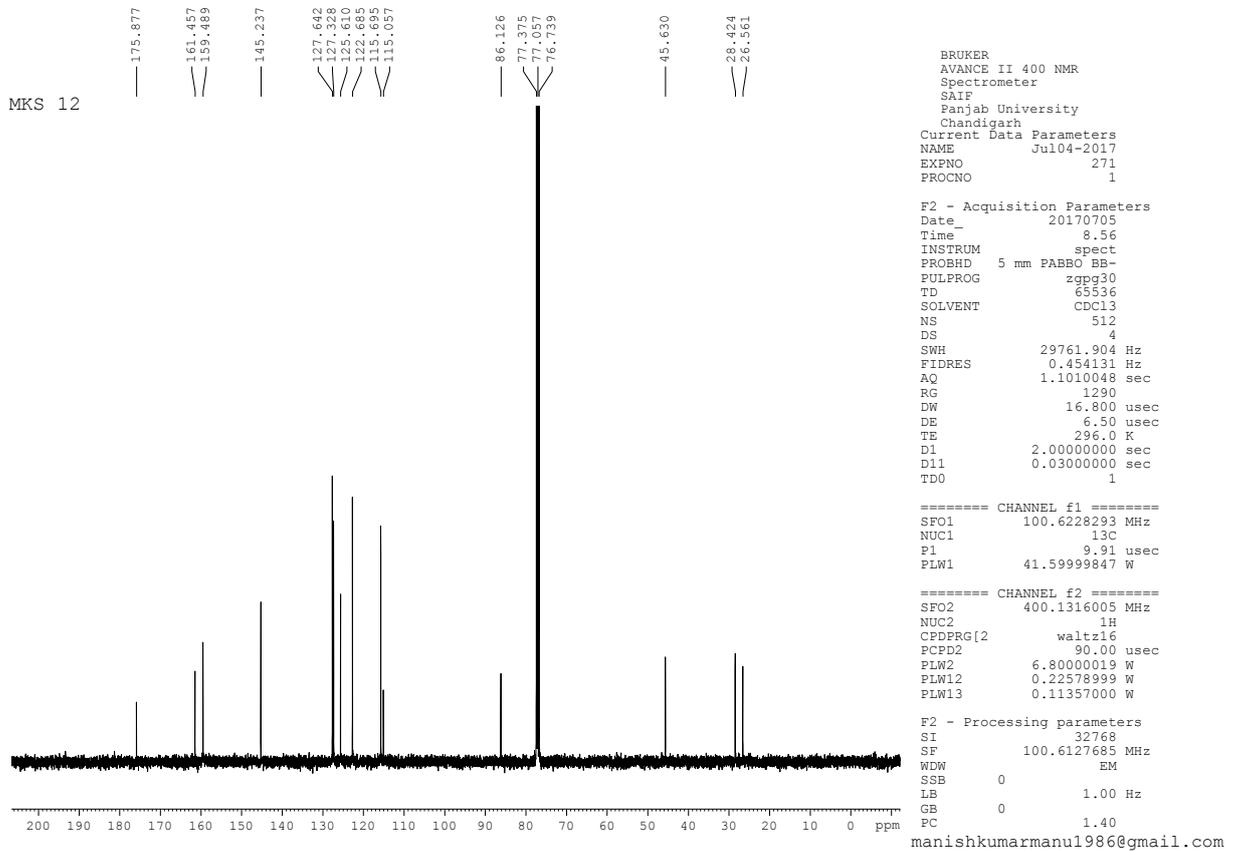


manishkumaranu1986@gmail.com

MASS Spectrum

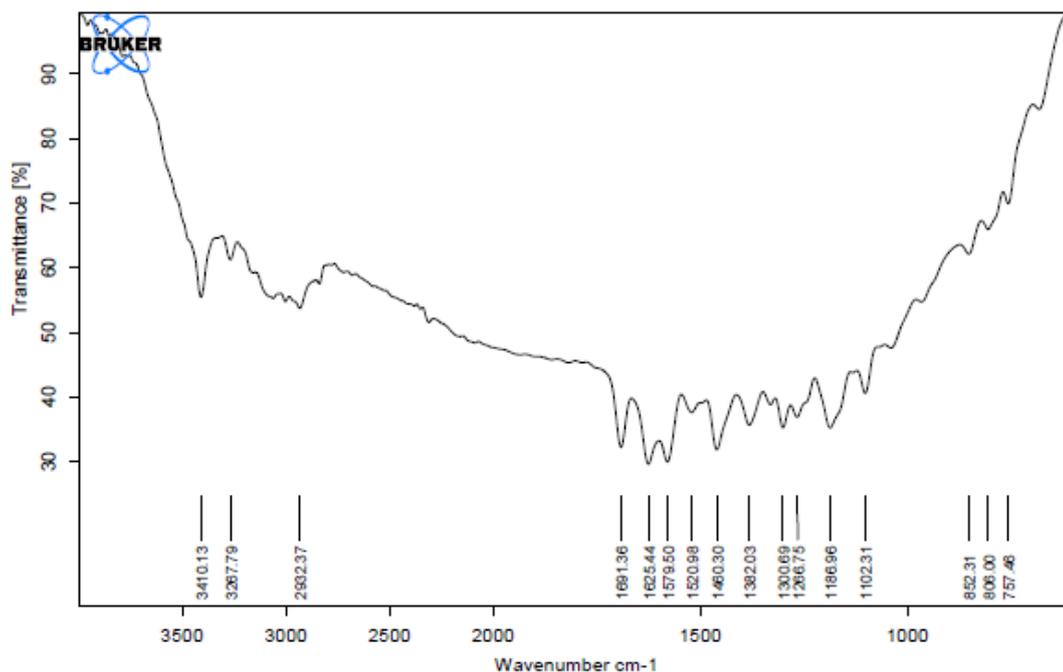


¹³C-NMR Spectrum



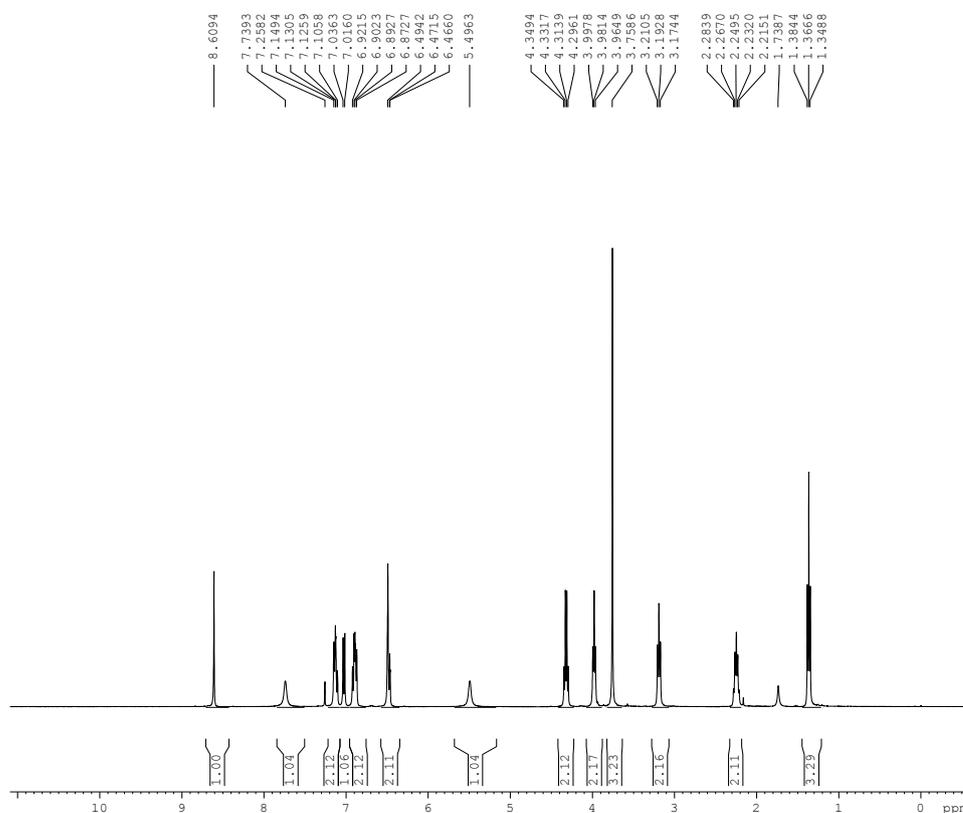
Ethyl 4-amino-2-(3-(2-methoxy-10H-phenothiazin-10-yl)propylthio)pyrimidine-5-carboxylate (44)

IR Spectrum



¹H-NMR Spectrum

MKS-29



BRUKER
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Spectrometer
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Current Data Parameters
NAME Dec08-2016
EXPNO 70
PROCNO 1

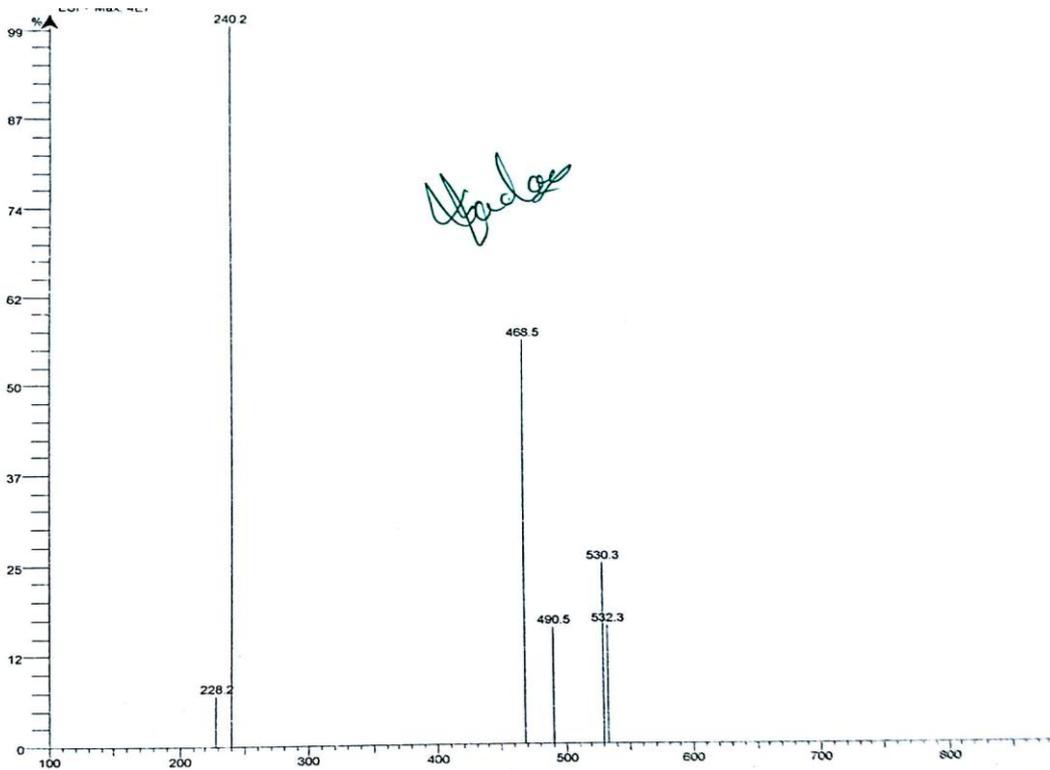
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PULPROG zg30
TD 6536
SOLVENT CDCl3
NS 8
DS 2
SWH 12019.230 Hz
FIDRES 0.183399 Hz
AQ 2.7263477 sec
RG 203
DW 41.600 usec
DE 6.00 usec
TE 296.7 K
D1 1.00000000 sec
TDO 1

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

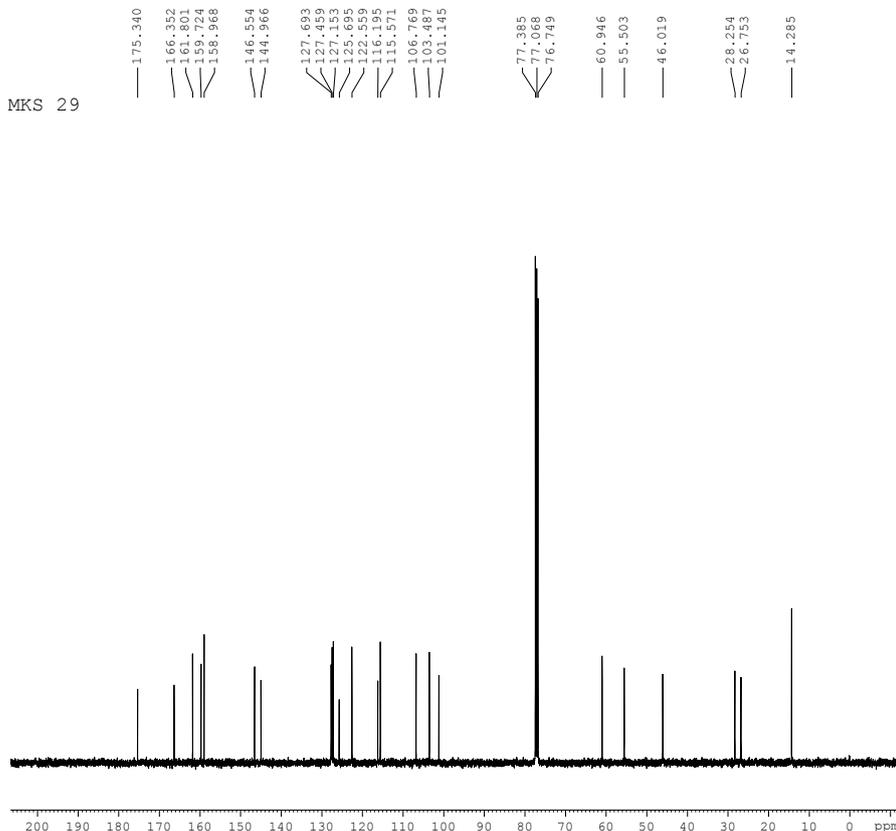
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SI 32768
SF 400.1300100 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00

manishkumarmanu1986@gmail.com

MASS Spectrum



¹³C-NMR Spectrum



BRUKER
 AVANCE II 400 NMR
 Spectrometer
 SAIF
 Panjab University
 Chandigarh
 Current Data Parameters
 NAME Jul04-2017
 EXPNO 341
 PROCNO 1

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 Date_ 20170705
 Time 15.24
 INSTRUM spect
 PROBHD 5 mm PABBO BB-
 PULPROG zgpg30
 TD 65536
 SOLVENT CDC13
 NS 512
 DS 4
 SWH 29761.904 Hz
 FIDRES 0.454131 Hz
 AQ 1.1010048 sec
 RG 1440
 DW 16.800 usec
 DE 6.50 usec
 TE 296.8 K
 D1 2.0000000 sec
 D11 0.0300000 sec
 TD0 1

==== CHANNEL f1 =====
 SFO1 100.6228293 MHz
 NUC1 13C
 P1 9.91 usec
 PLW1 41.59999847 W

==== CHANNEL f2 =====
 SFO2 400.1316005 MHz
 NUC2 1H
 CPDPRG2 waltz16
 PCPD2 90.00 usec
 PLW2 6.8000019 W
 PLW12 0.22578999 W
 PLW13 0.11357000 W

F2 - Processing parameters
 SI 32768
 SF 100.6127685 MHz
 WDW EM
 SSB 0
 LB 1.00 Hz
 GB 0
 PC 1.40

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3. Biological data

Table S2. Permeability (P_e 10^{-6} cm s $^{-1}$) of nine commercial quality standards in the PAMPA-BBB assay.

Commercial drugs	Reported value ^a	Experimental value ^b
Diazepam	16	21.2±1.8
Verapamil	13	15.1±1.2
Progesterone	9.3	12.2±1.1
Clonidine	6.2	9.4±0.4
Corticosterone	5.1	8.2±0.5
Lomefloxacin	1.1	2.3±0.2
Ofoxacin	0.8	1.5±0.3
Atenolol	0.8	3.2±0.4
Dopamine	0.2	1.8±0.2

^aTaken from reference (Di et al. 2003). ^bDetermined using PAMPA-BBB assay. Data are expressed as mean ± SEM of three independent experiments.

Table S3. Ranges of permeability (P_e , 10^{-6} cm s $^{-1}$) in the PAMPA-BBB assay.

	PBS/ethanol (70:30)
Compounds of high BBB permeation (CNS+)	$P_e > 6.2$
Compounds of uncertain BBB permeation (CNS+/-)	$6.2 > P_e > 3.8$
Compounds of low BBB permeation (CNS-)	$P_e < 3.8$