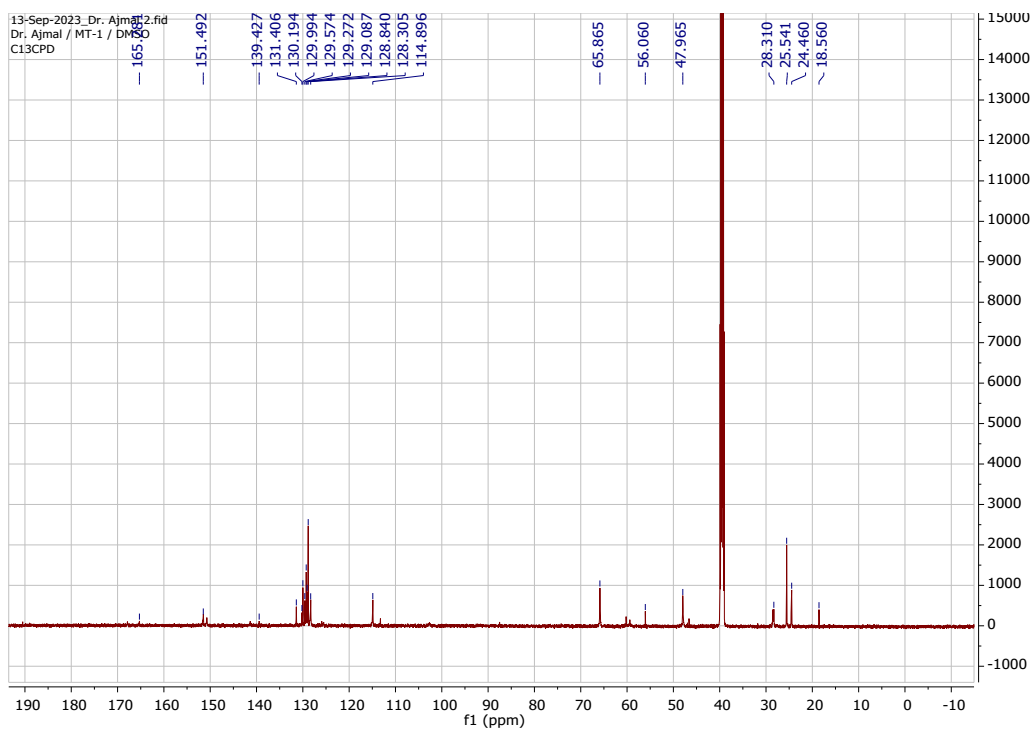
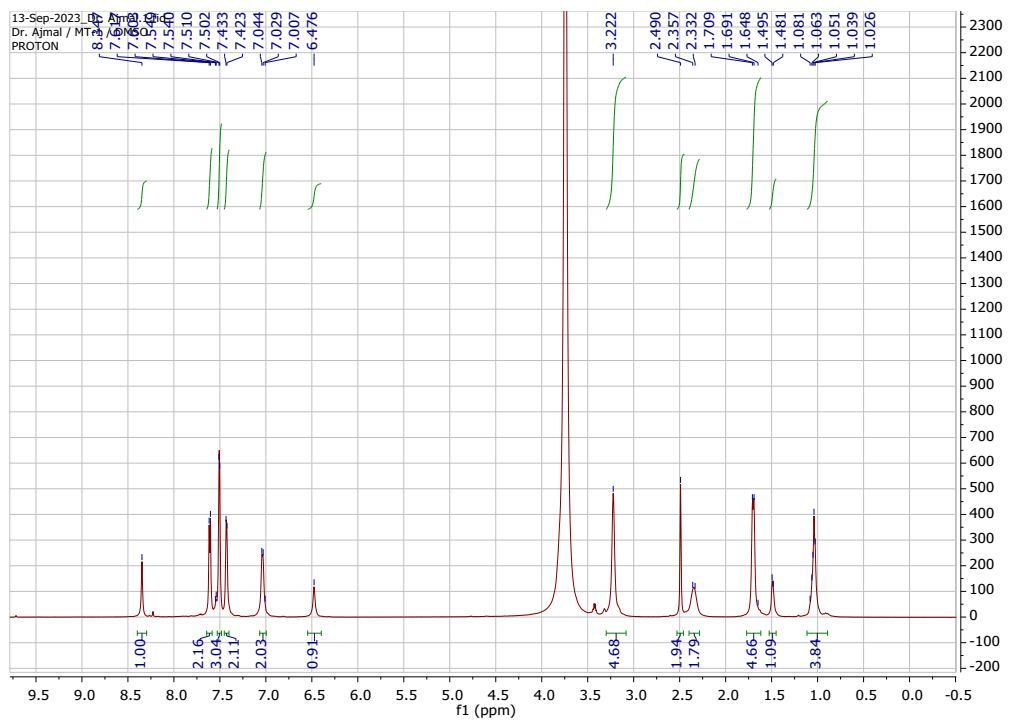
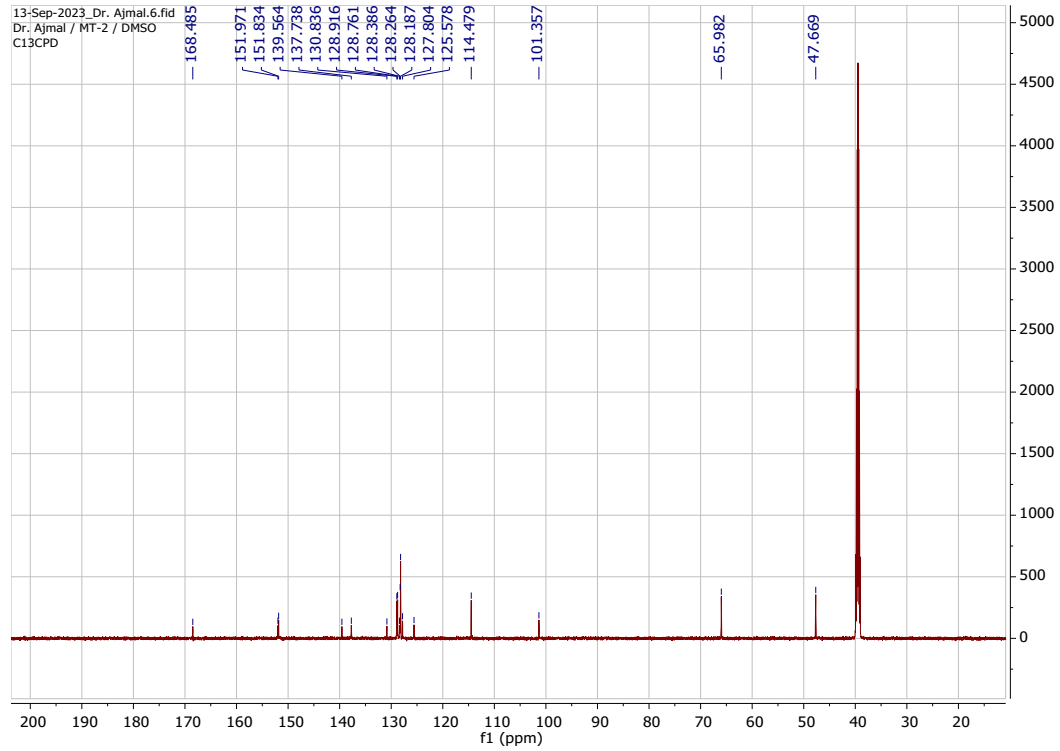
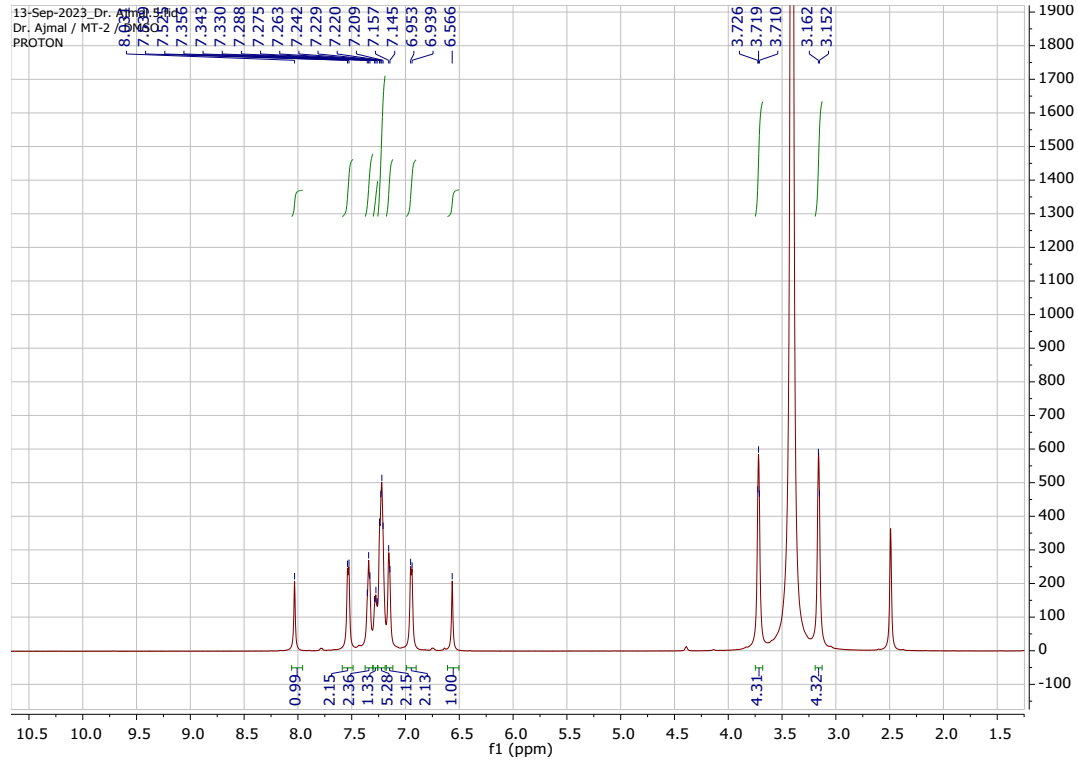


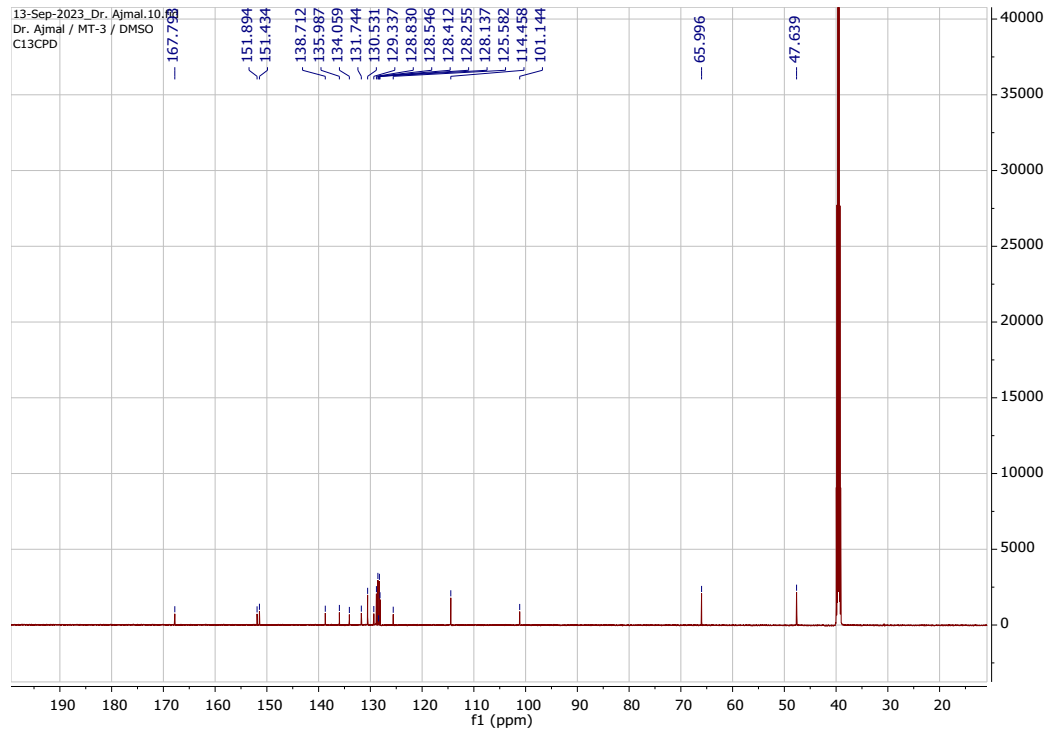
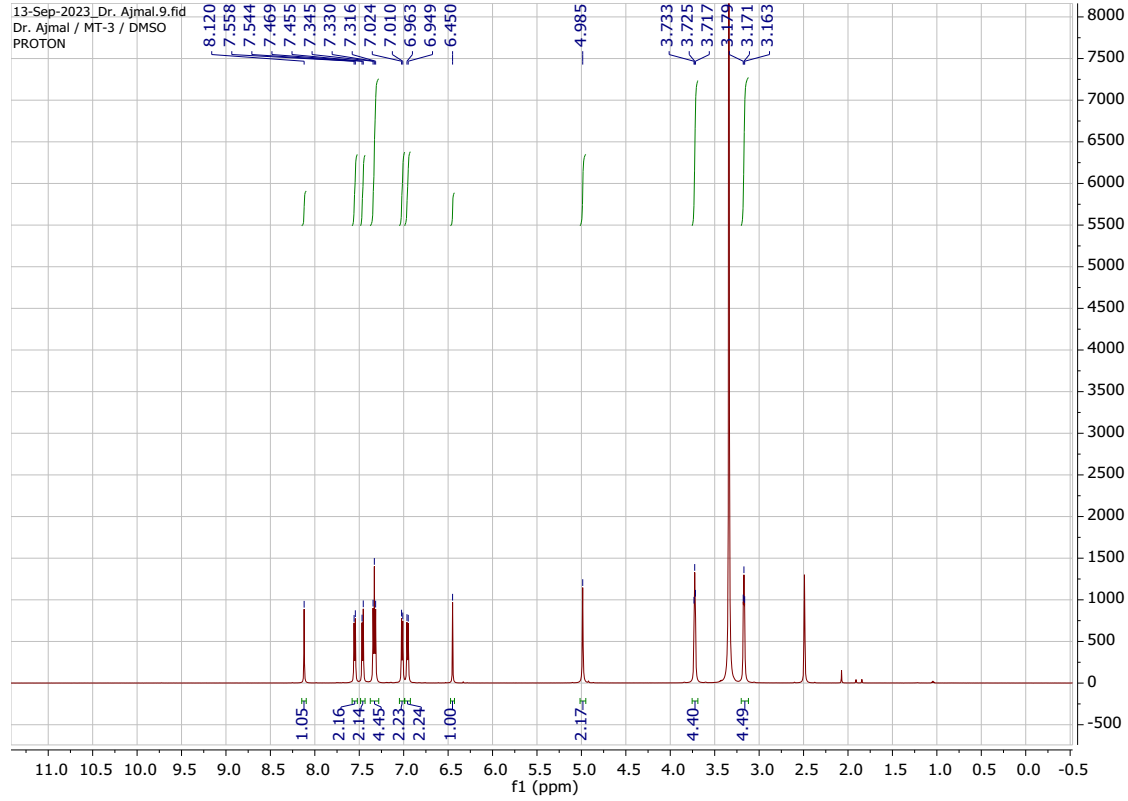
¹H NMR and ¹³C NMR of 3:



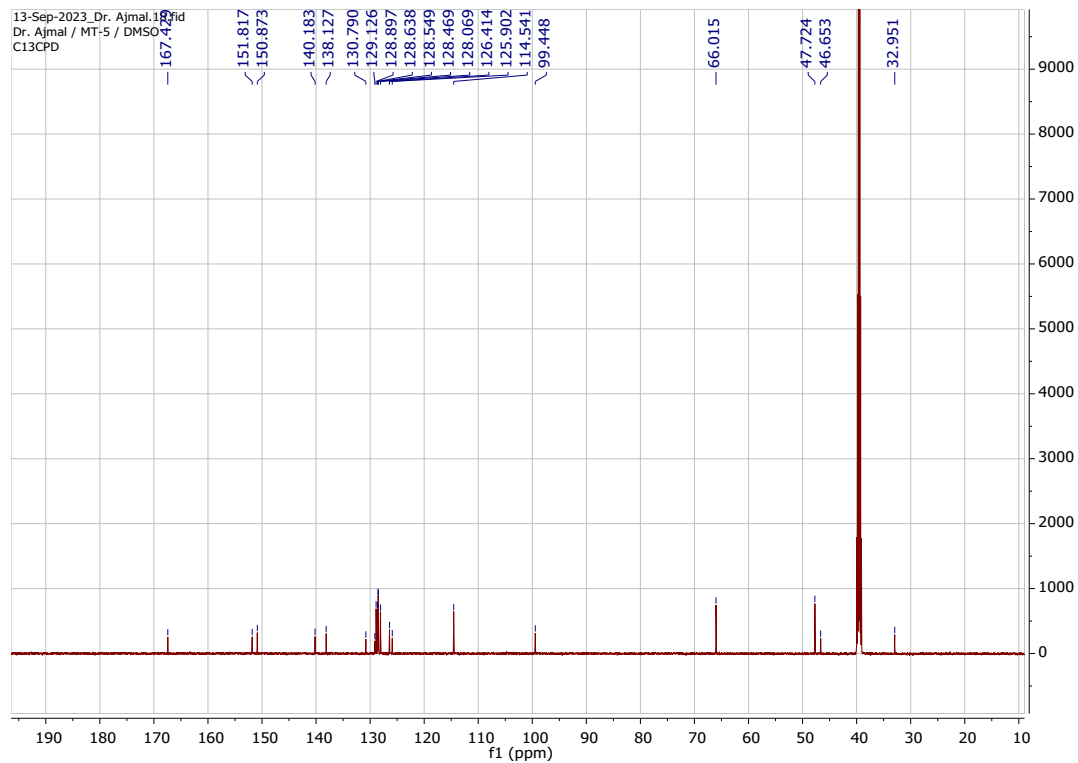
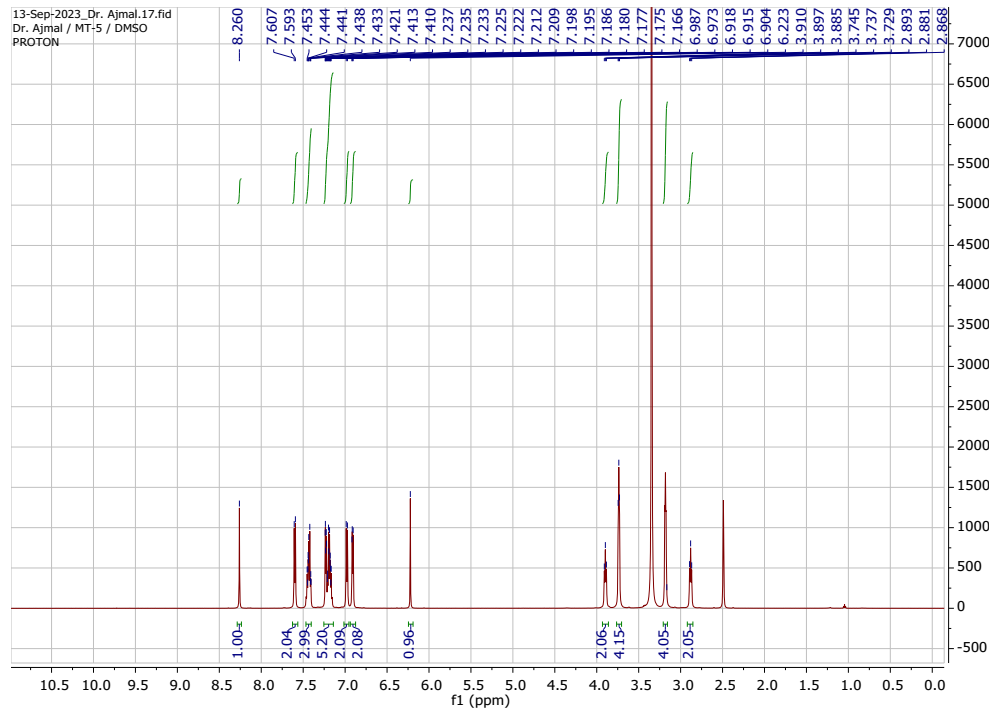
HNMR and ¹³CNMR of 4:



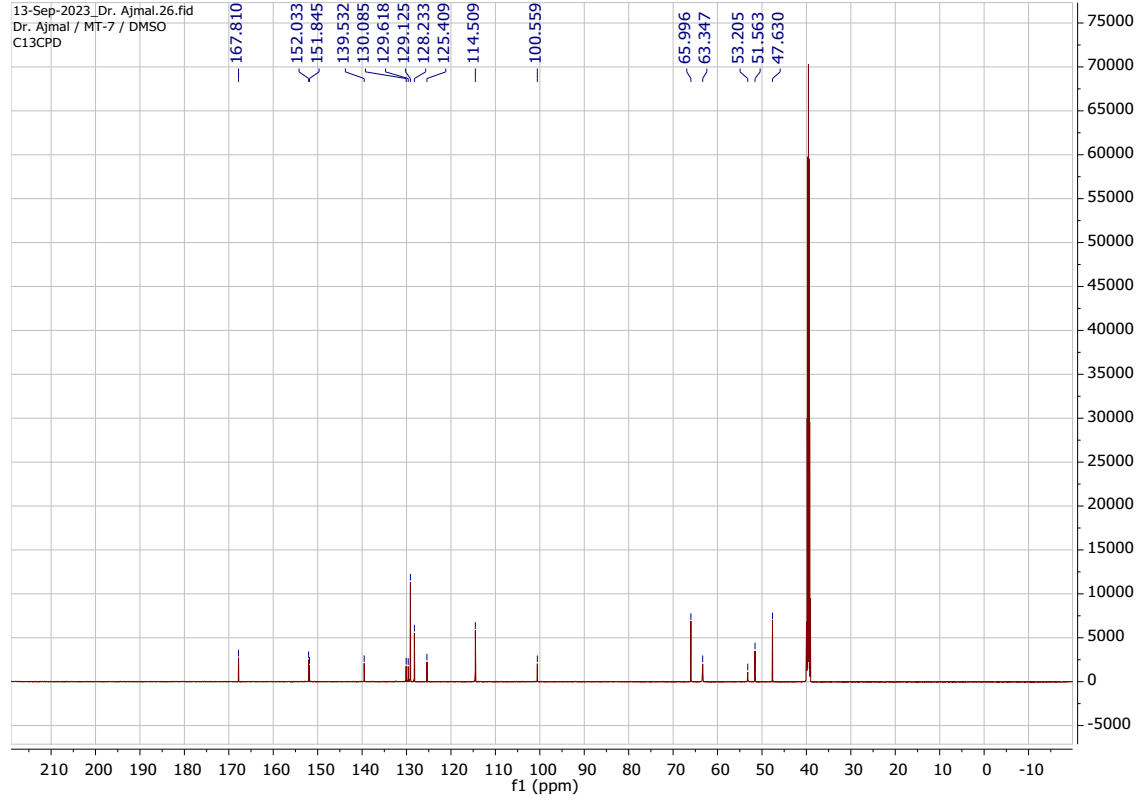
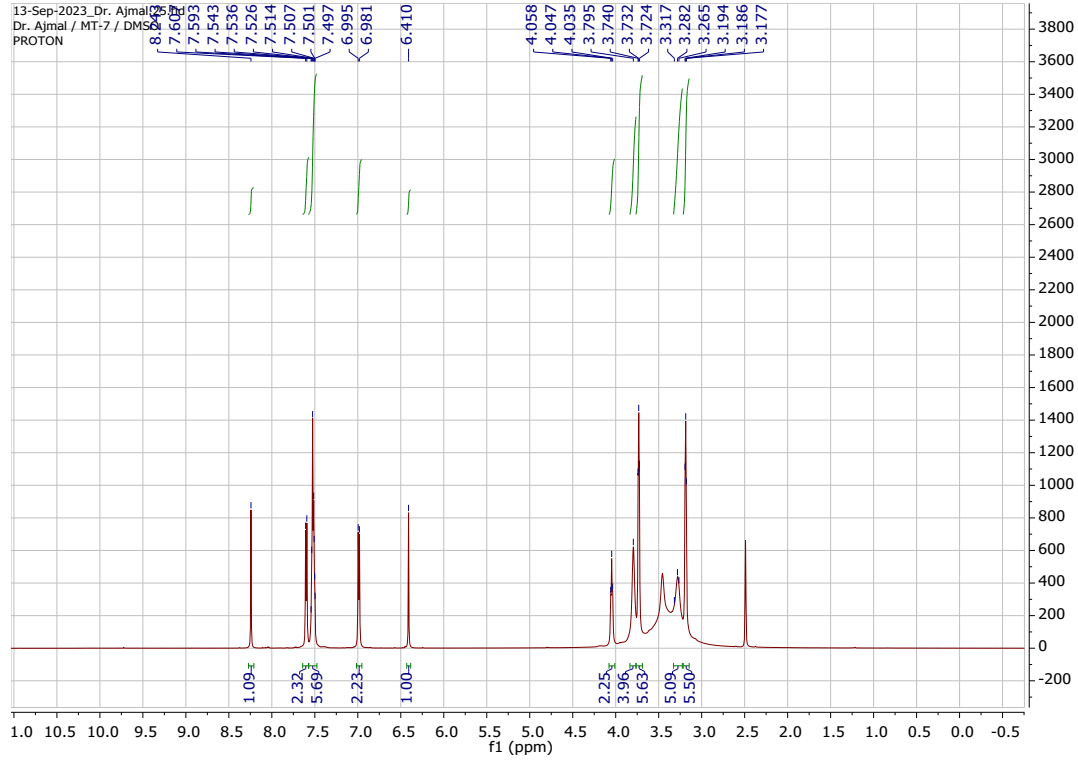
¹H NMR and ¹³C NMR of 5:



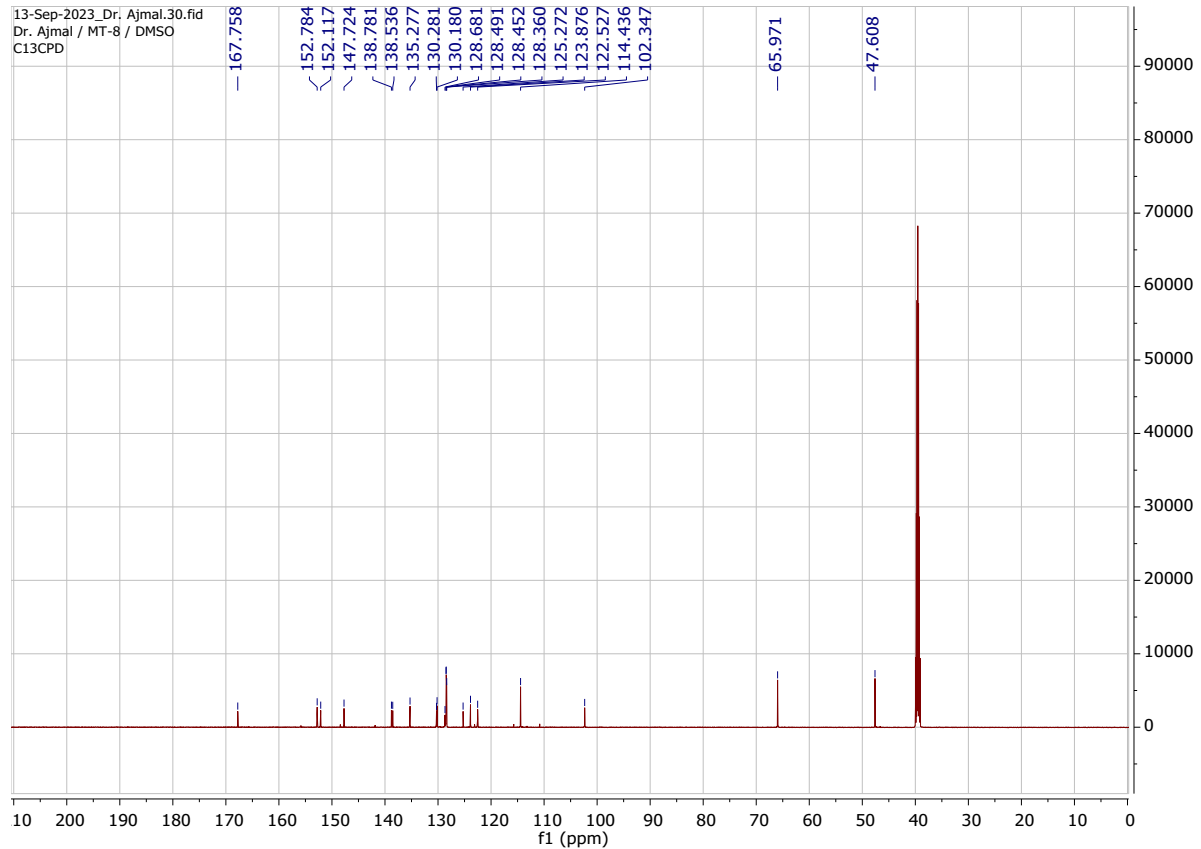
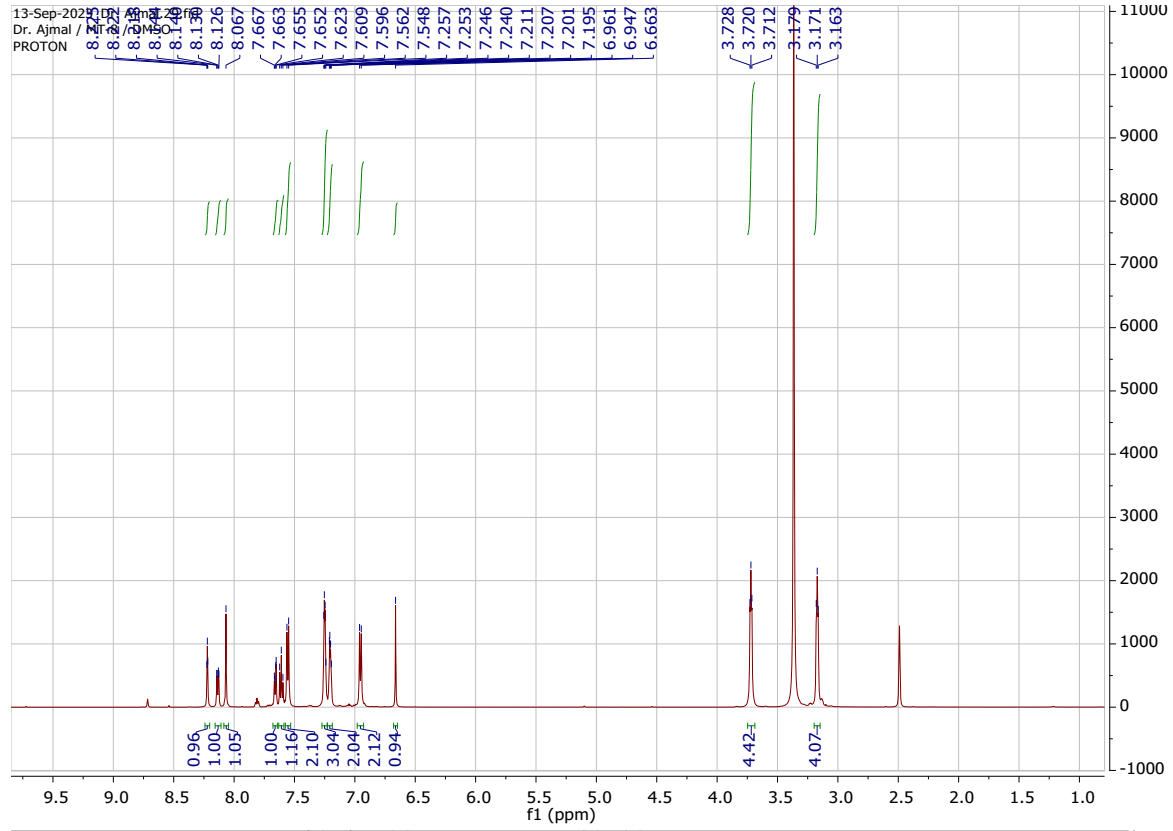
¹H NMR and ¹³C NMR of 6:



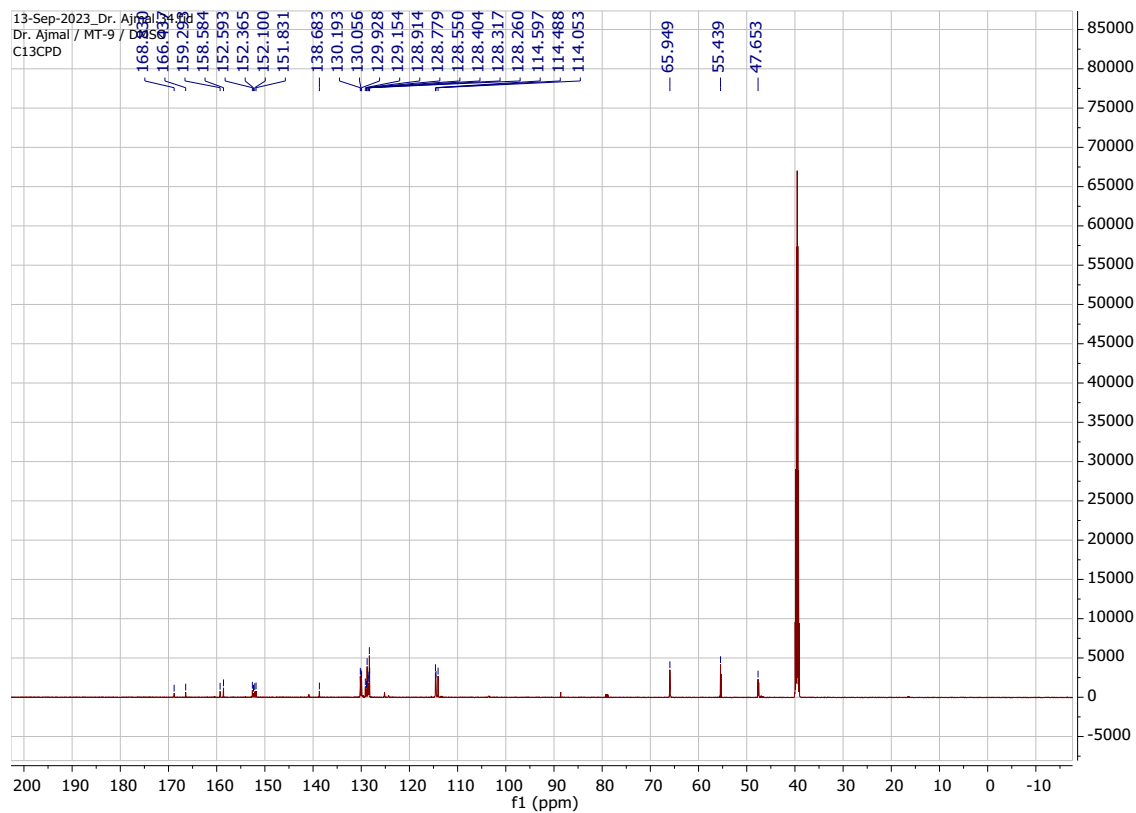
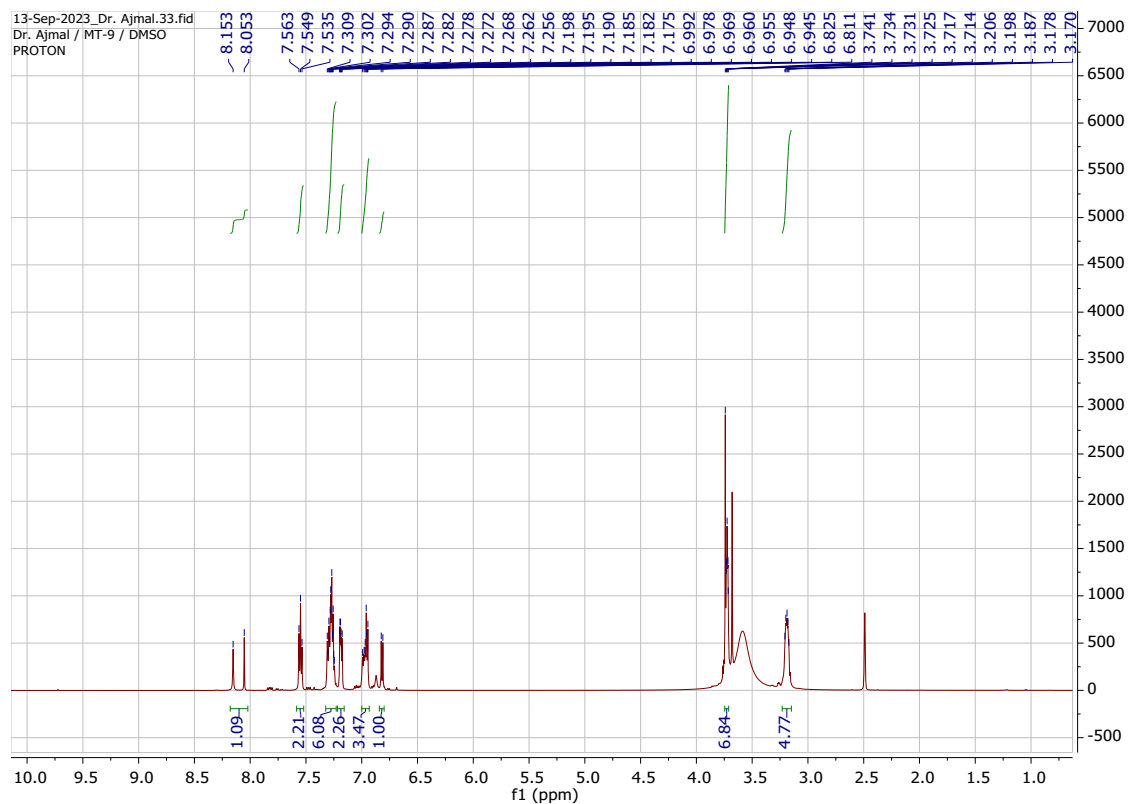
¹H NMR and ¹³C NMR of 7:



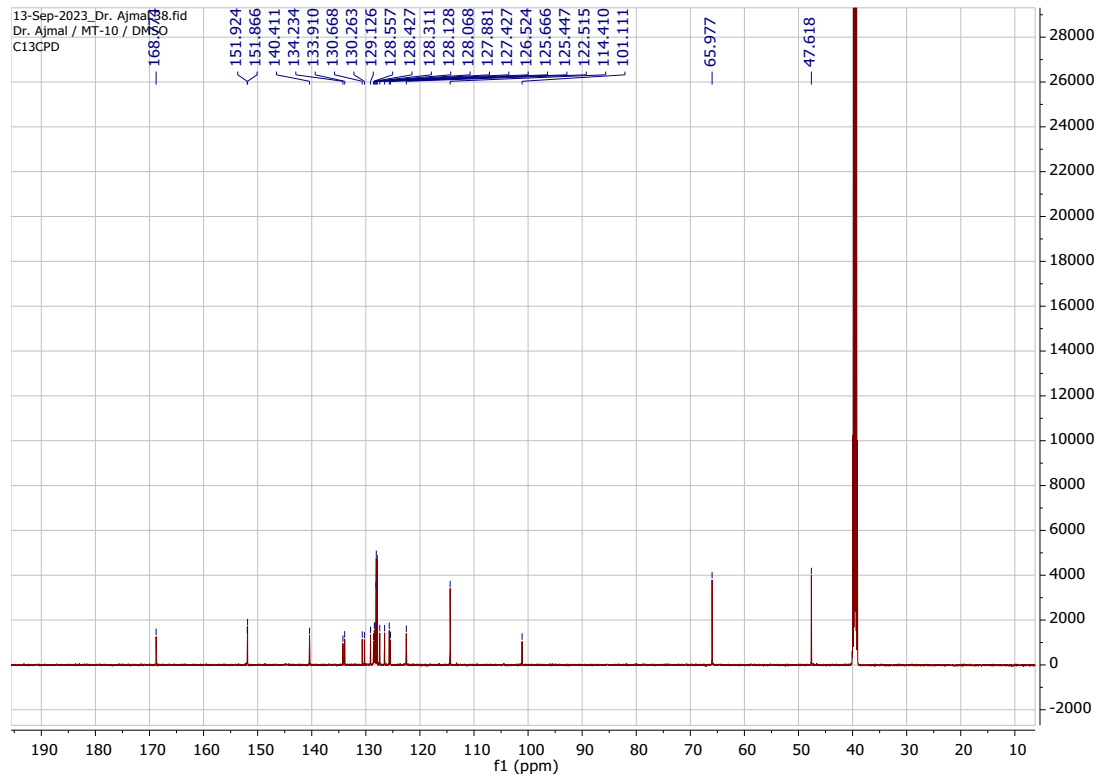
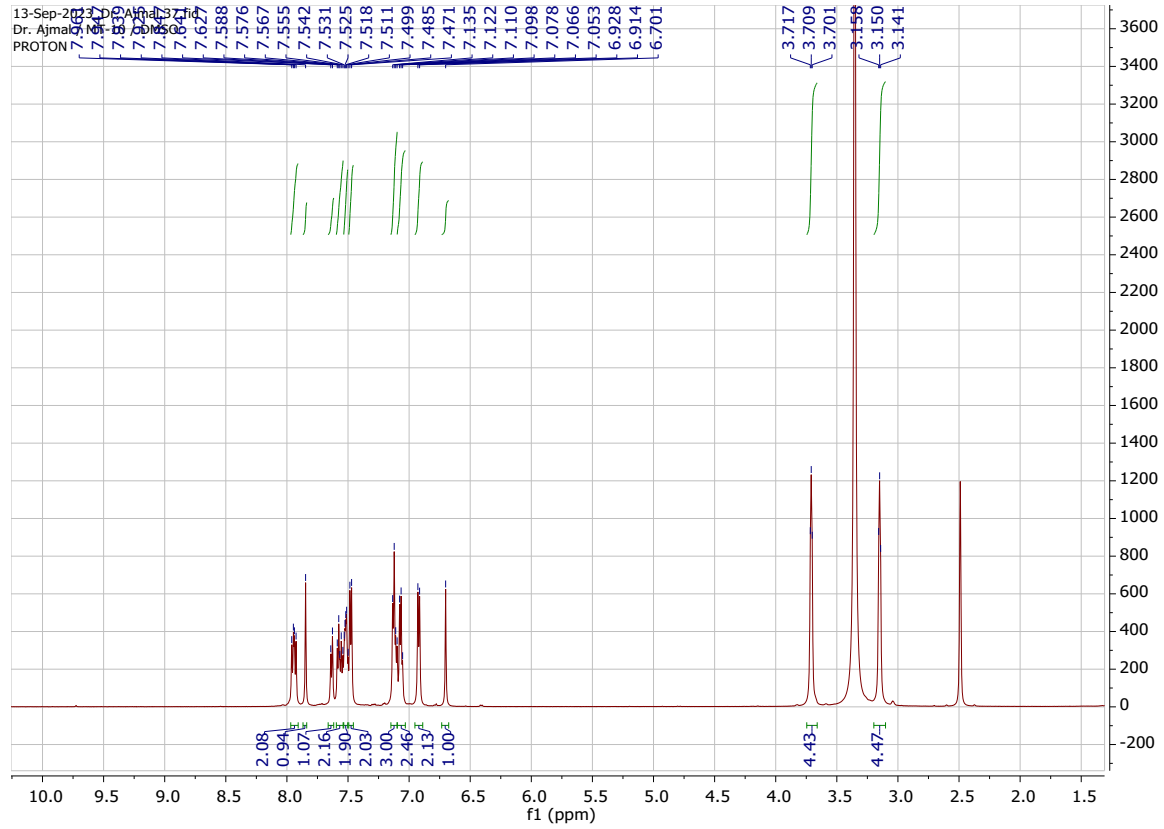
¹H NMR and ¹³C NMR of 8:



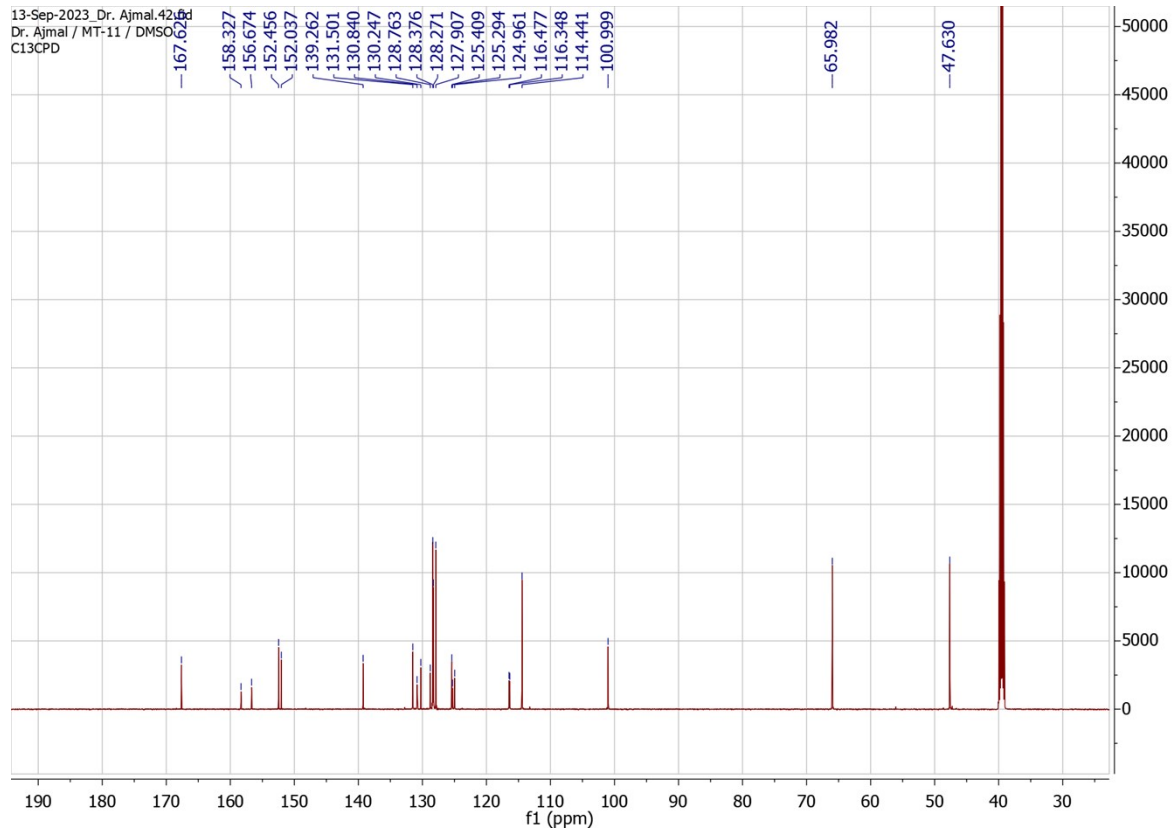
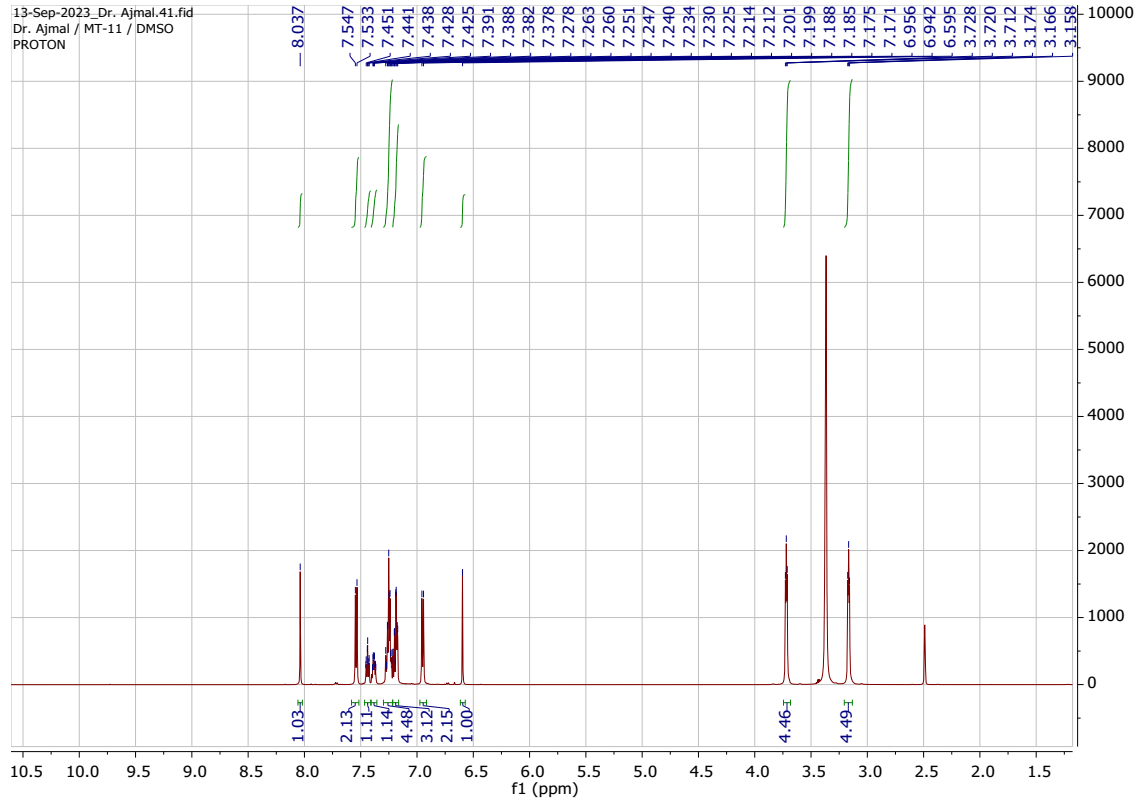
¹HNMR and ¹³CNMR of 9: (MT-9)



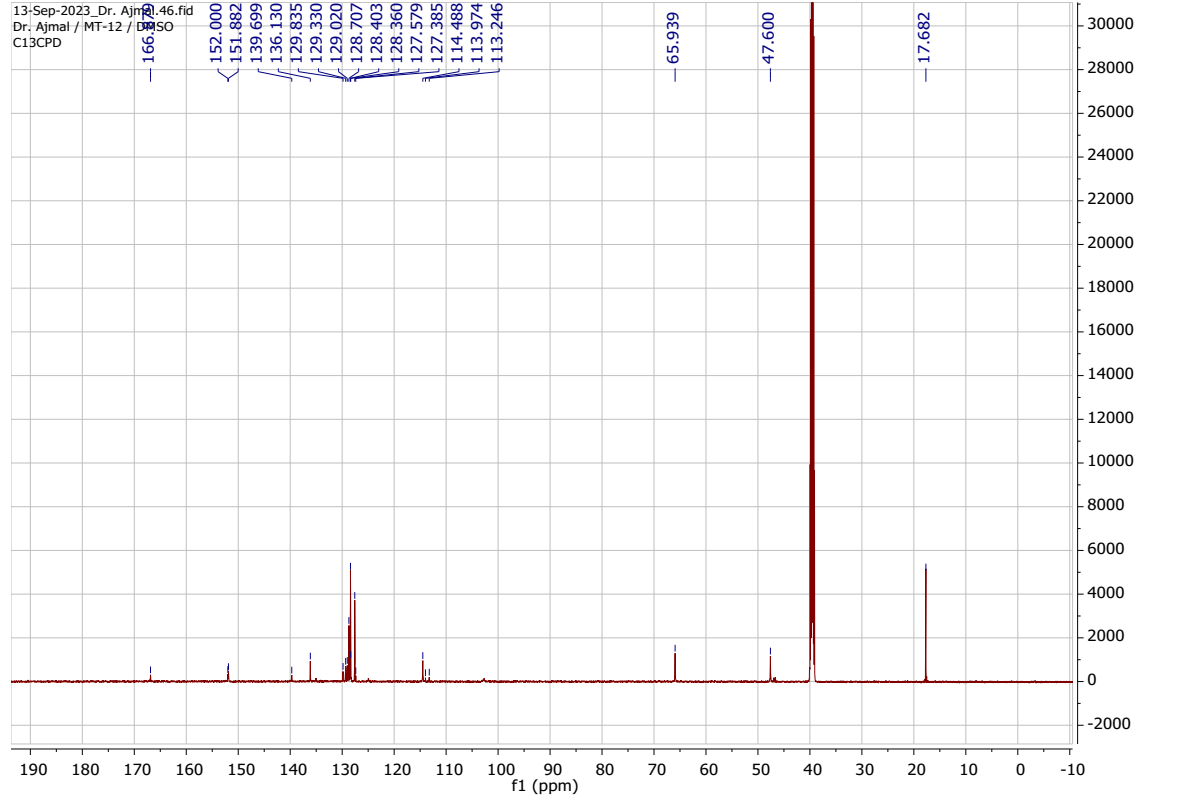
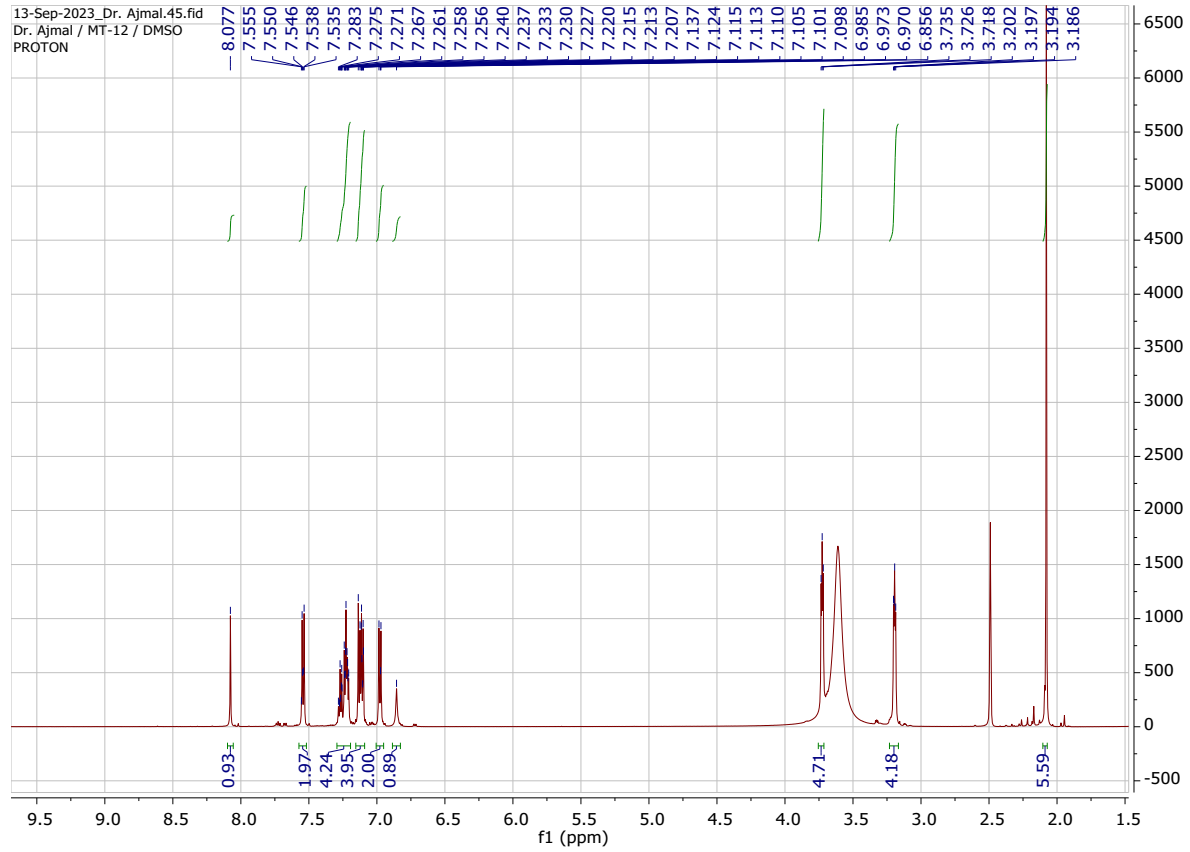
¹HNMR and ¹³CNMR of 10:



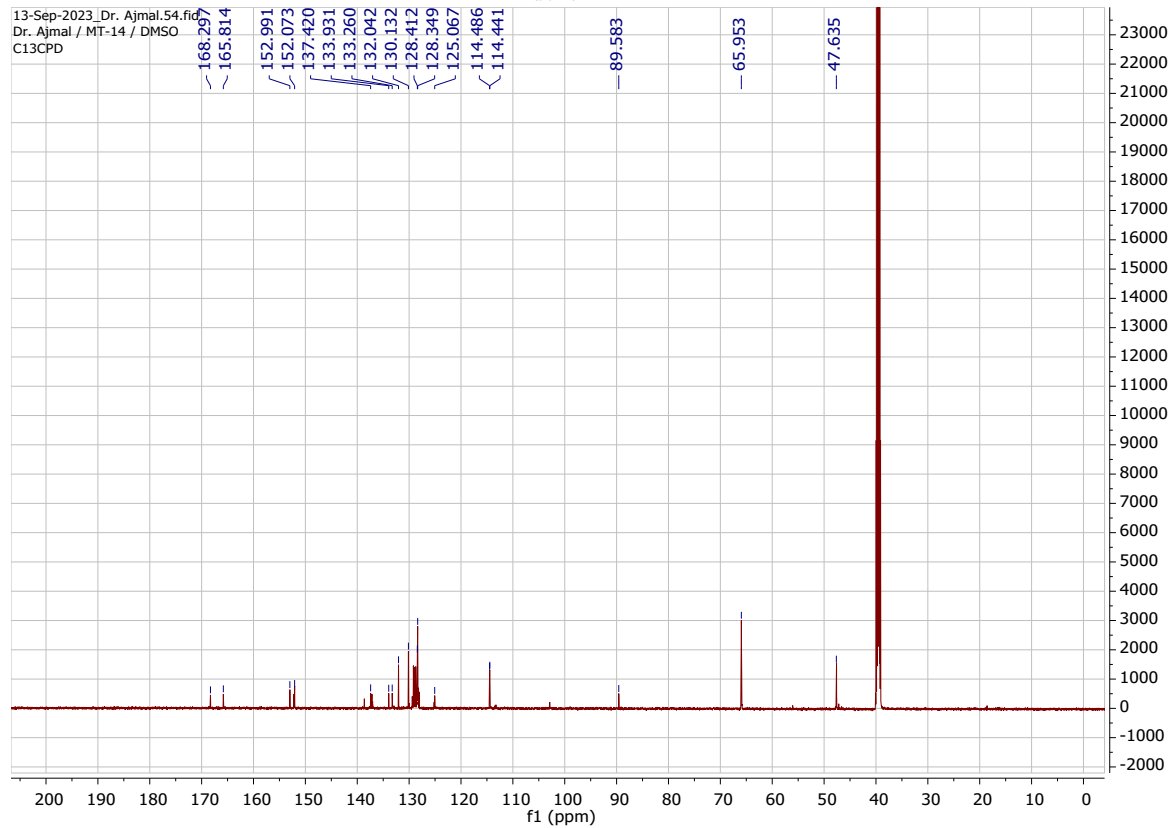
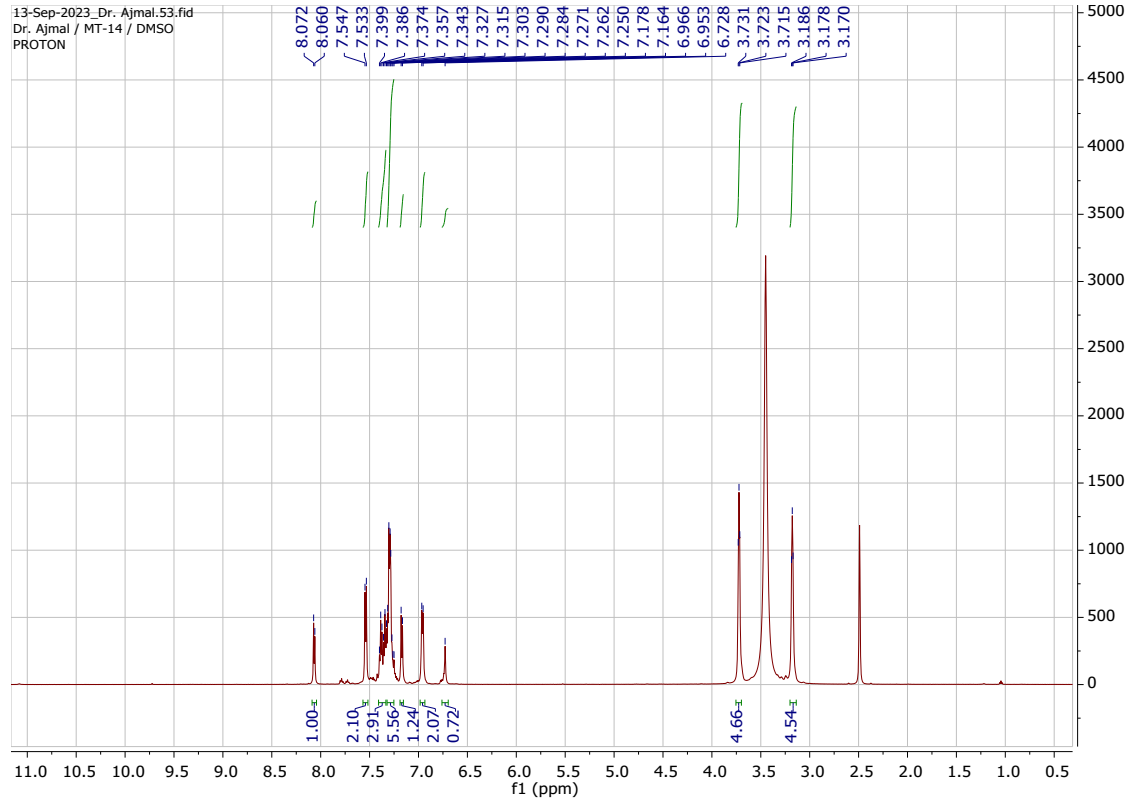
HNMR and ¹³CNMR of 11:



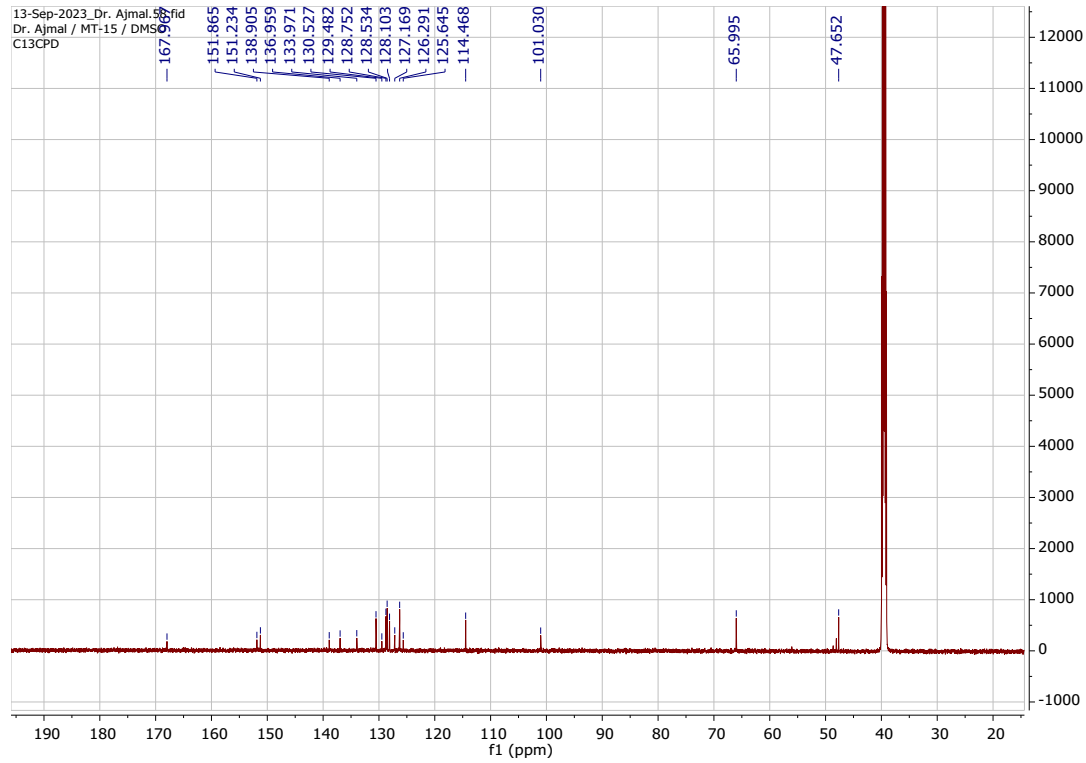
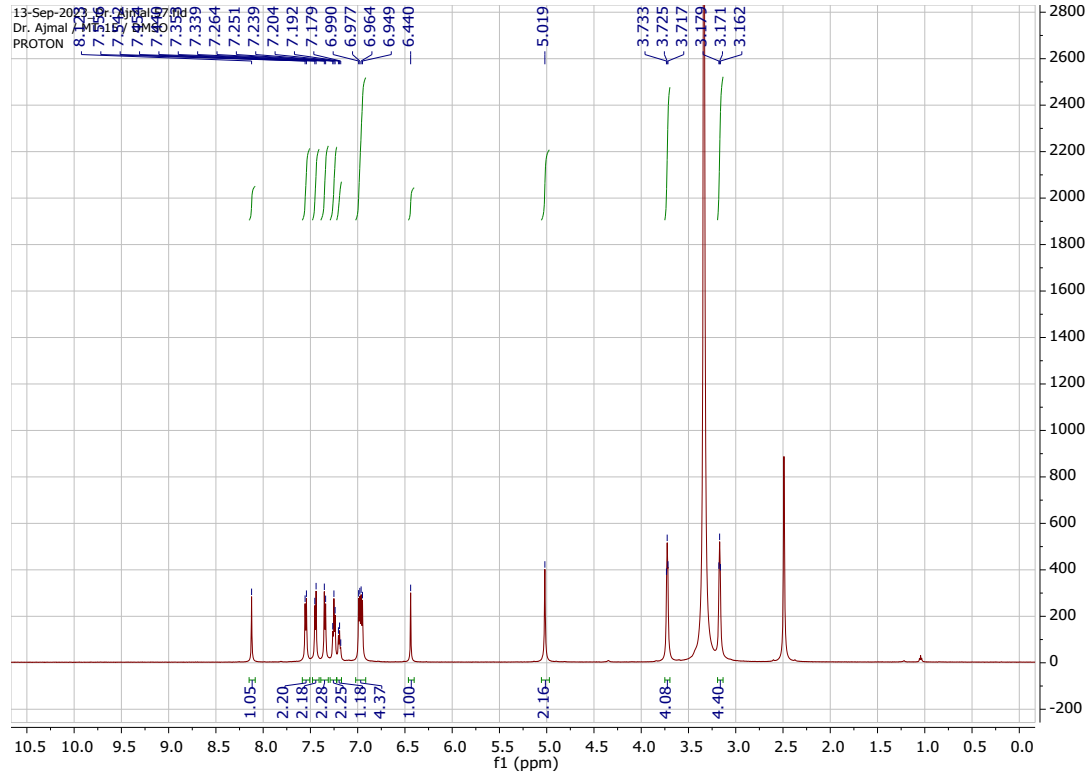
¹H NMR and ¹³C NMR of 12:



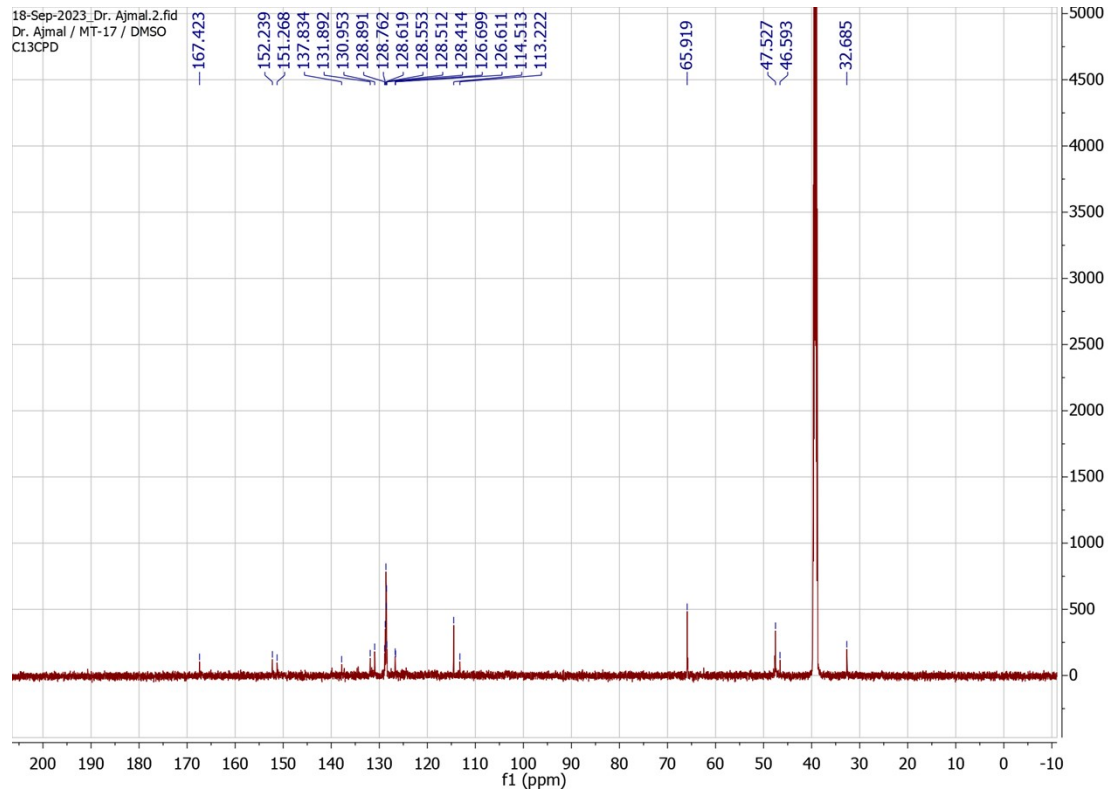
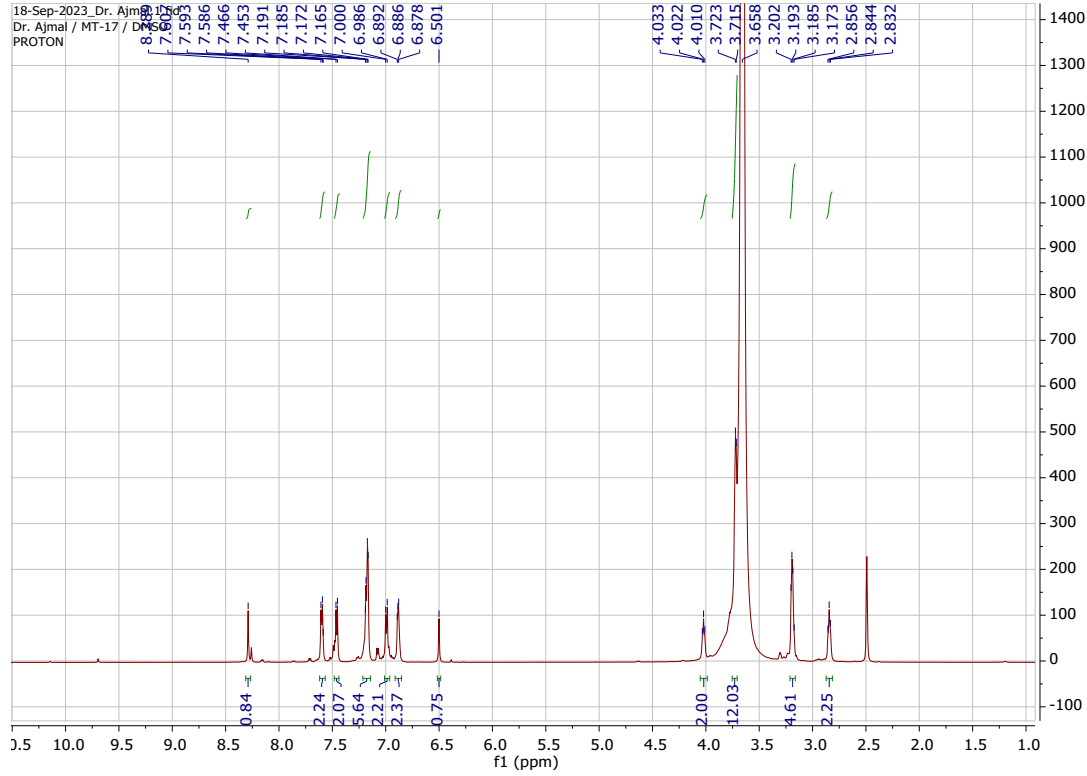
¹H NMR and ¹³C NMR of 13:



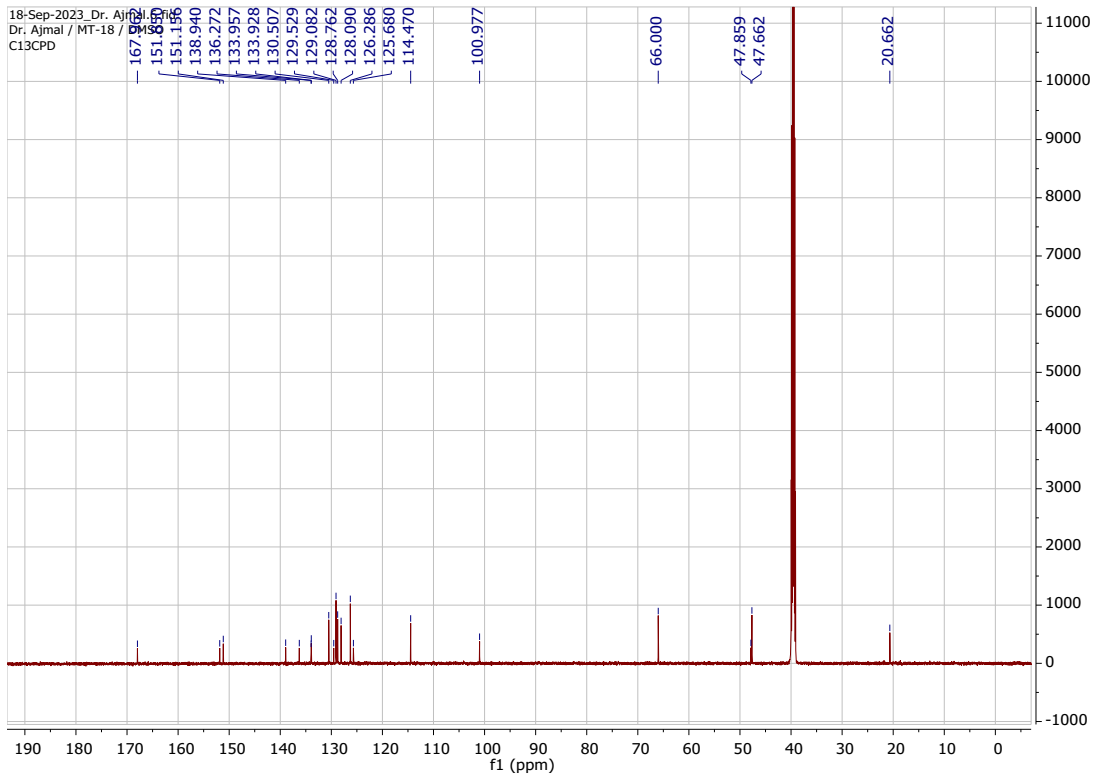
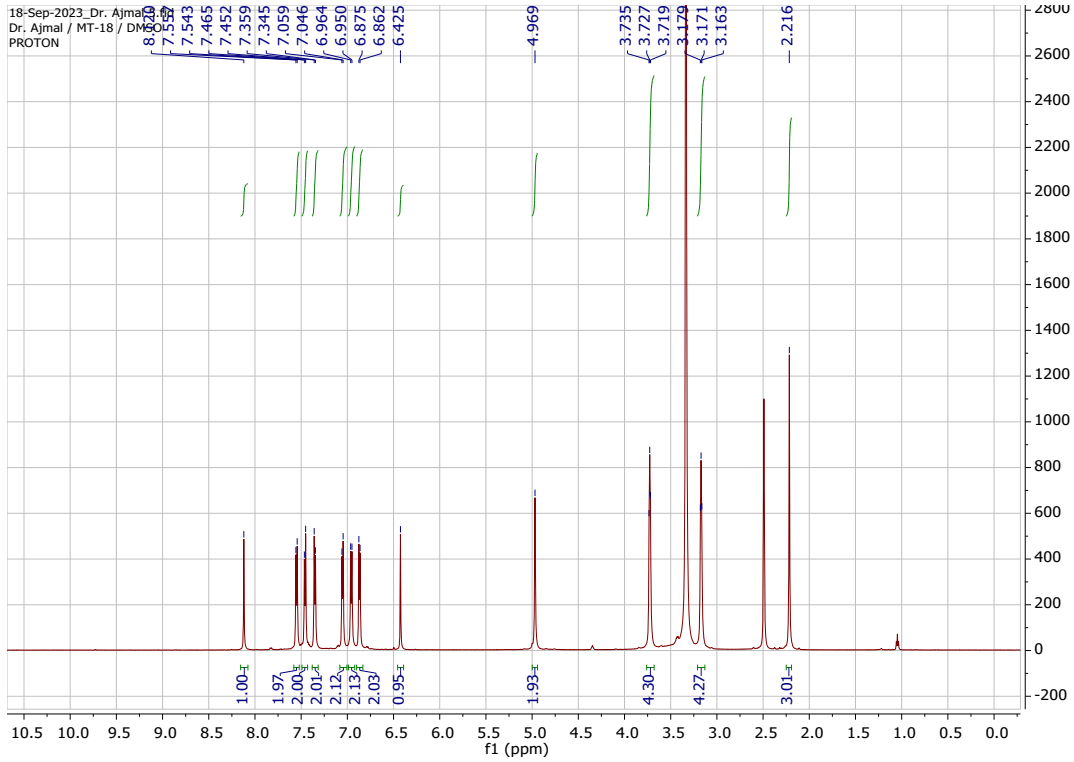
¹H NMR and ¹³C NMR of 14:



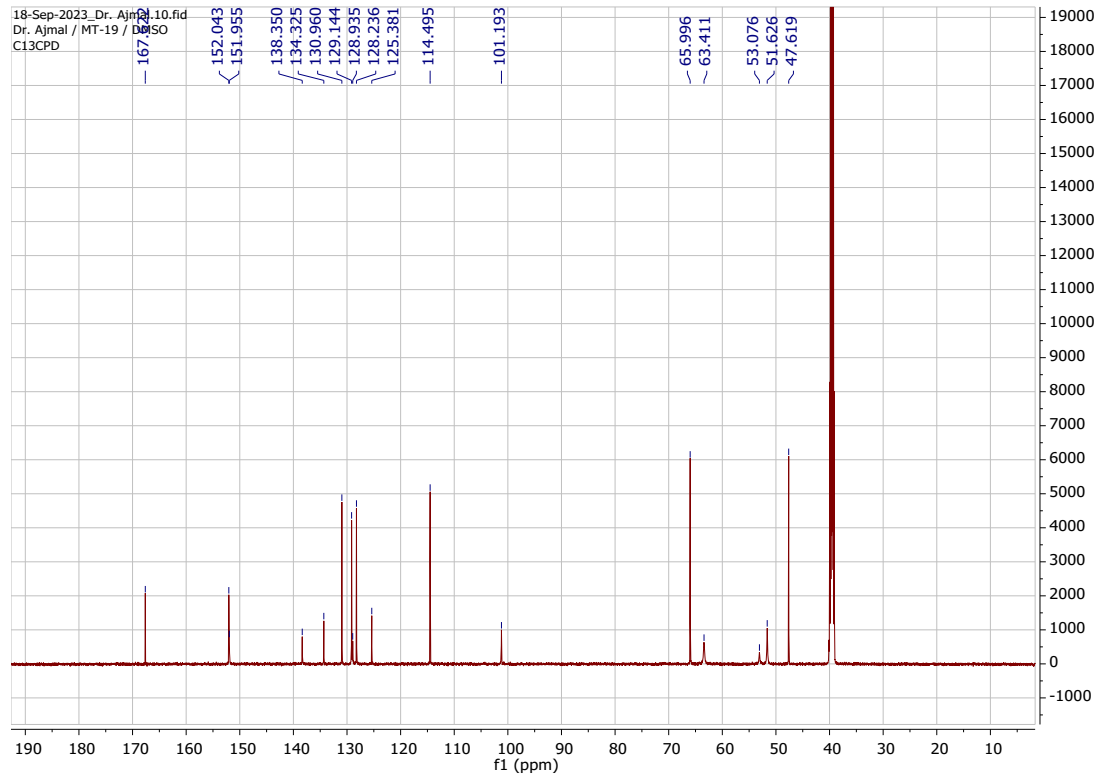
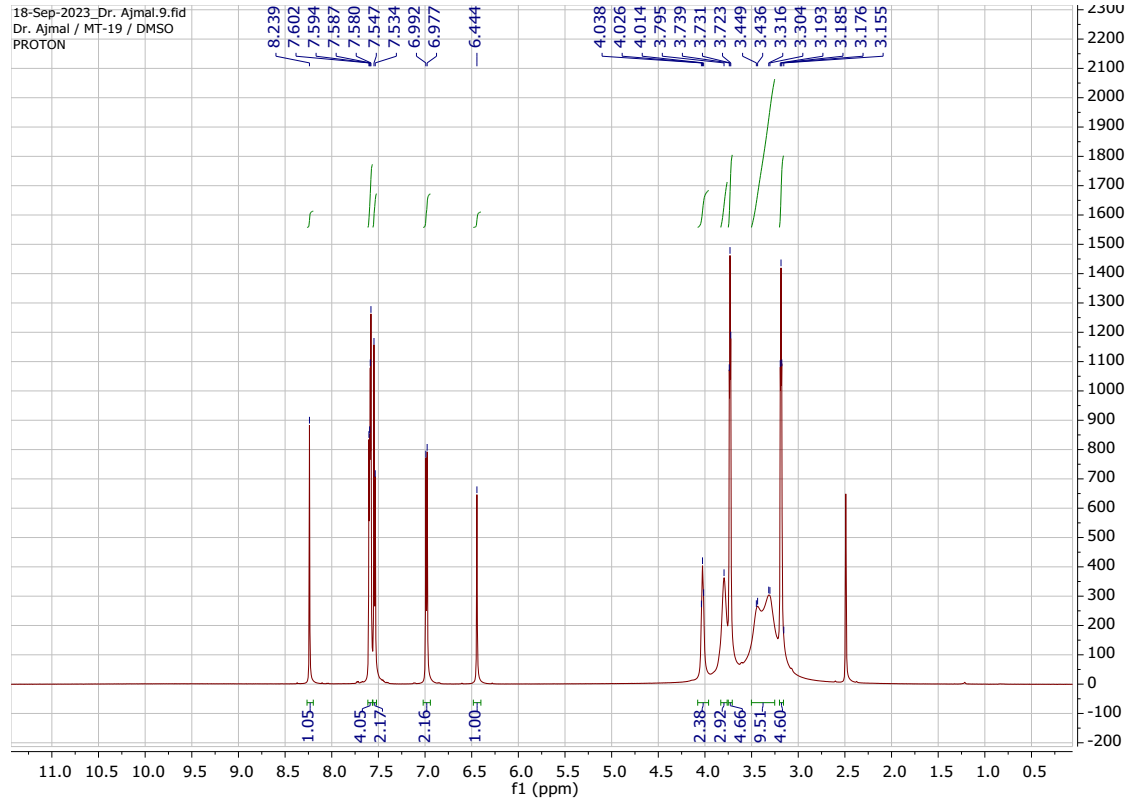
¹H NMR and ¹³C NMR of 15:



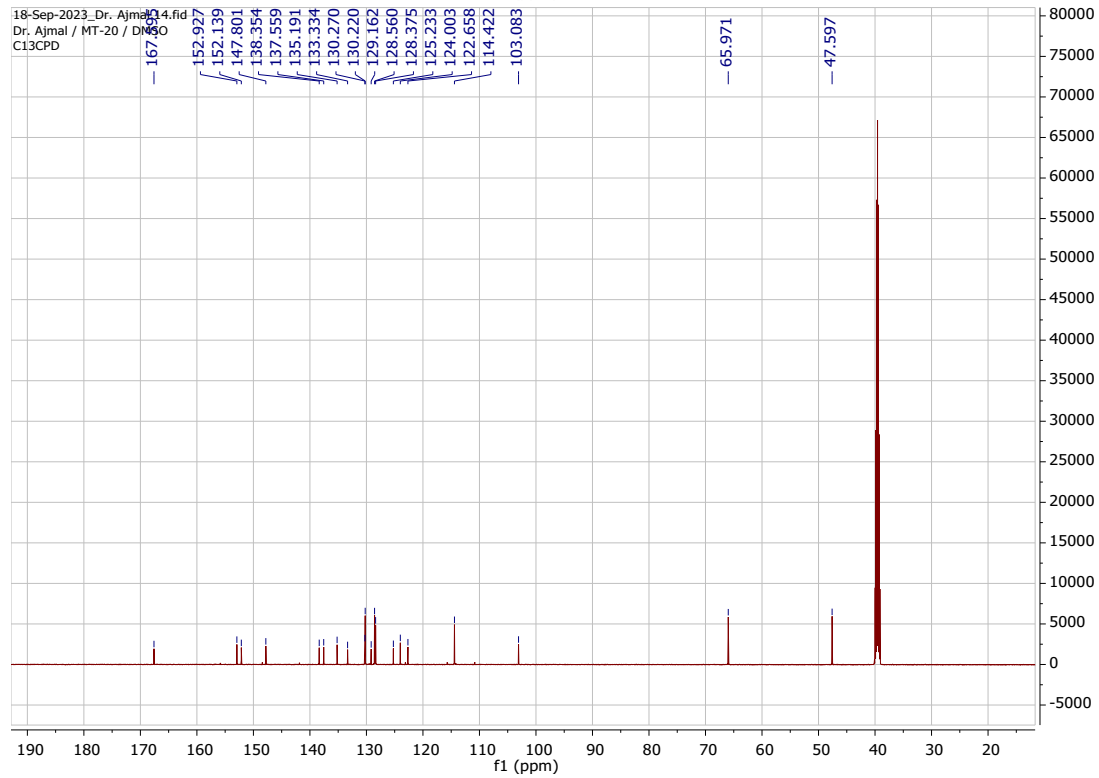
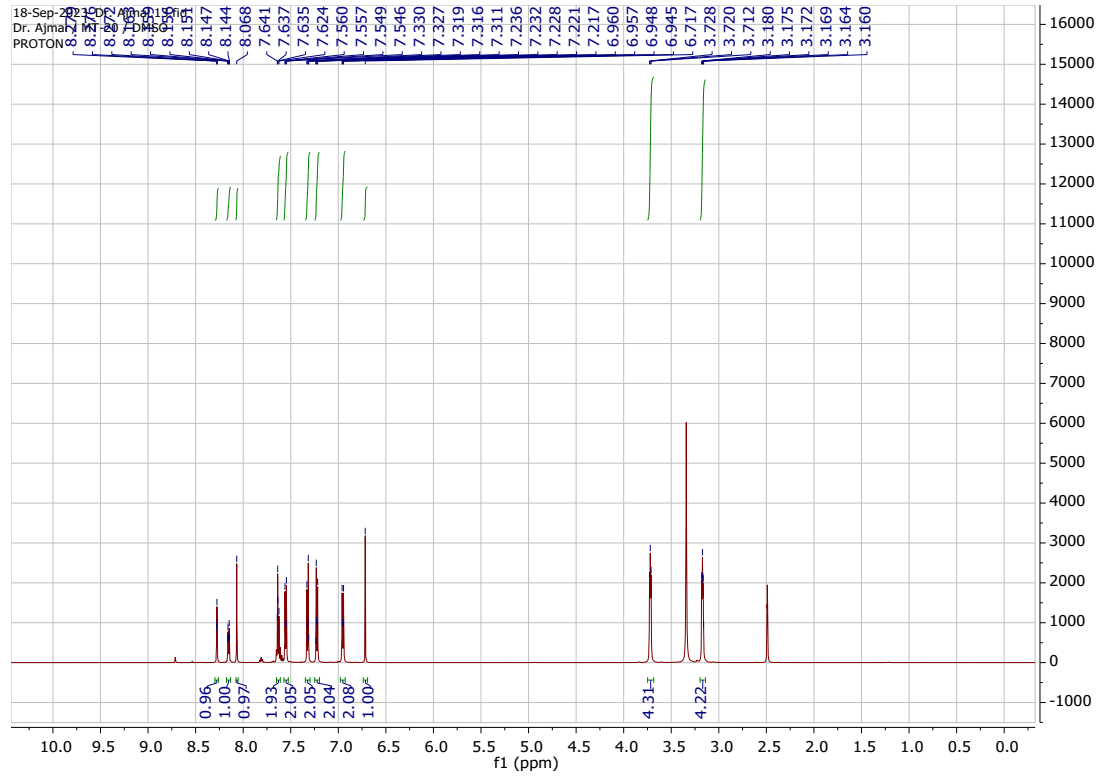
¹H NMR and ¹³C NMR of 16:



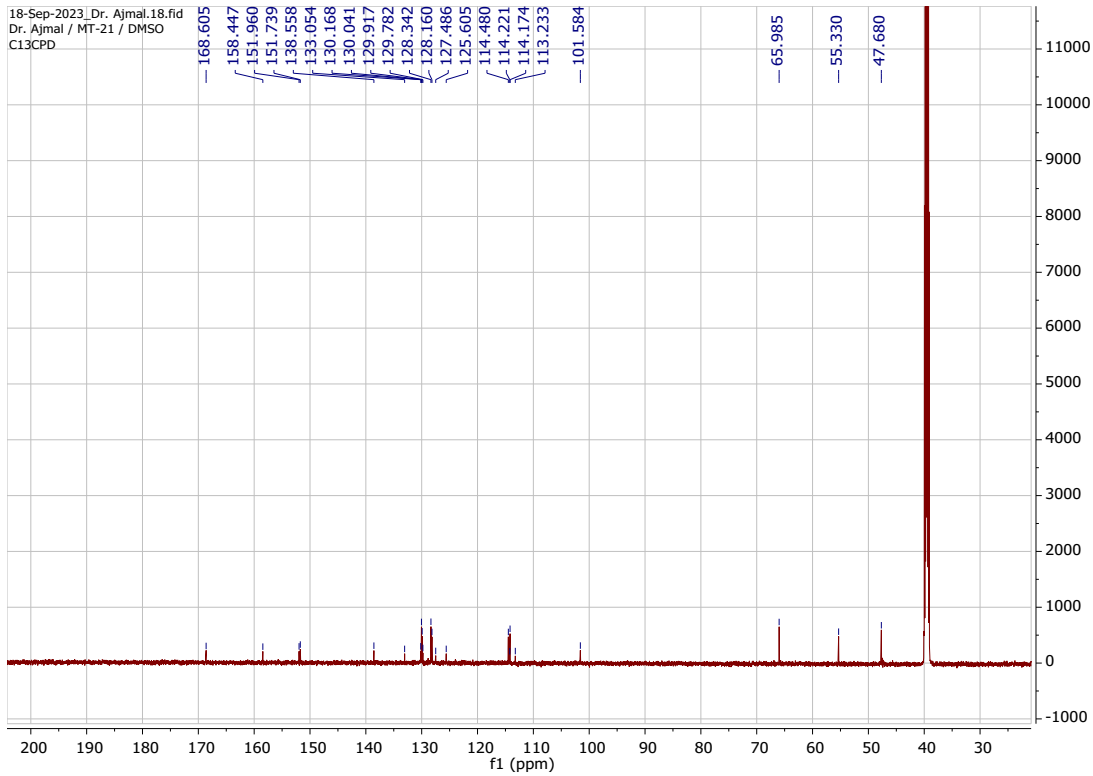
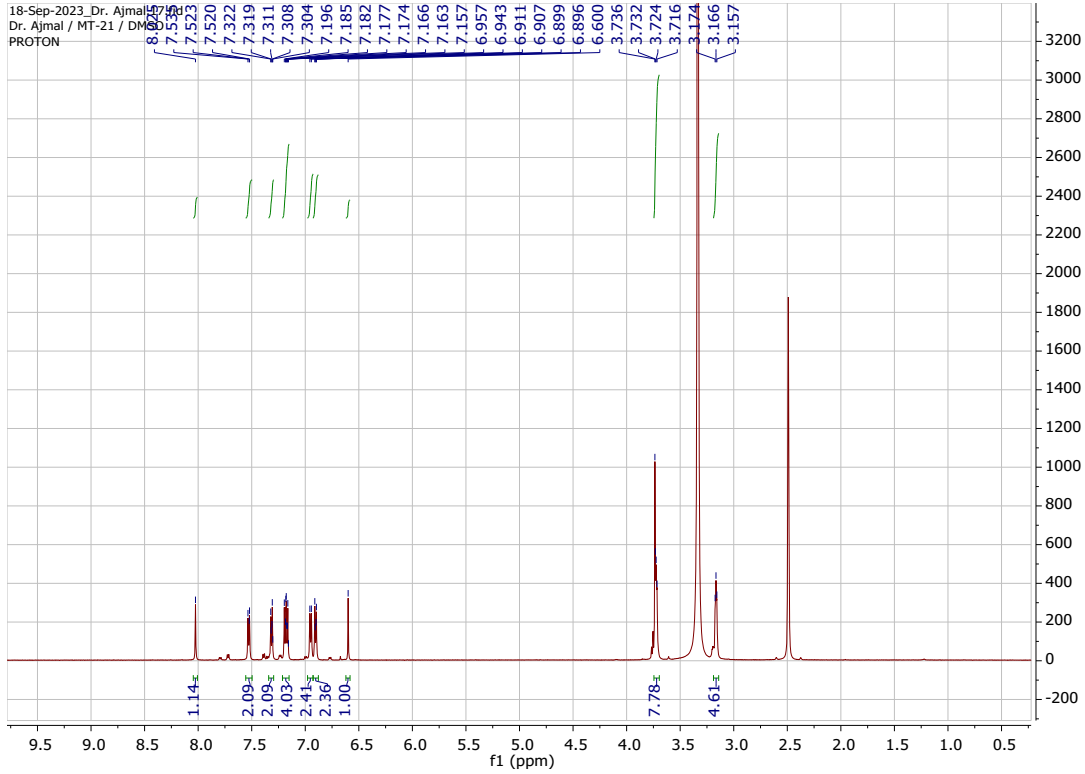
¹H NMR and ¹³C NMR of 17:



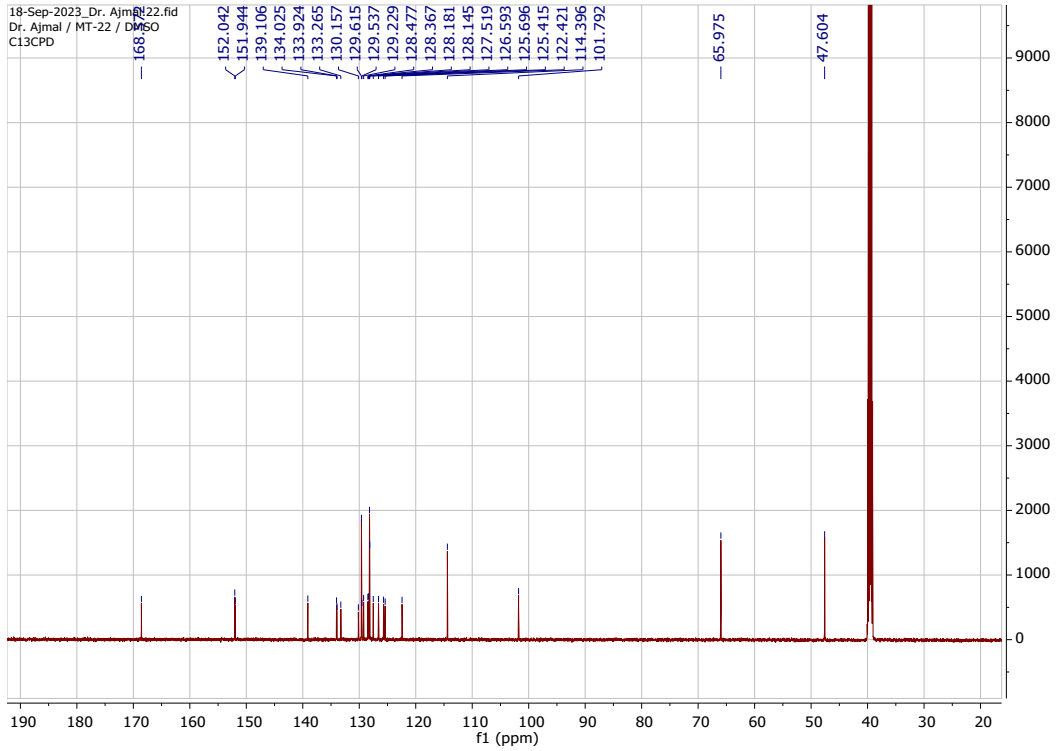
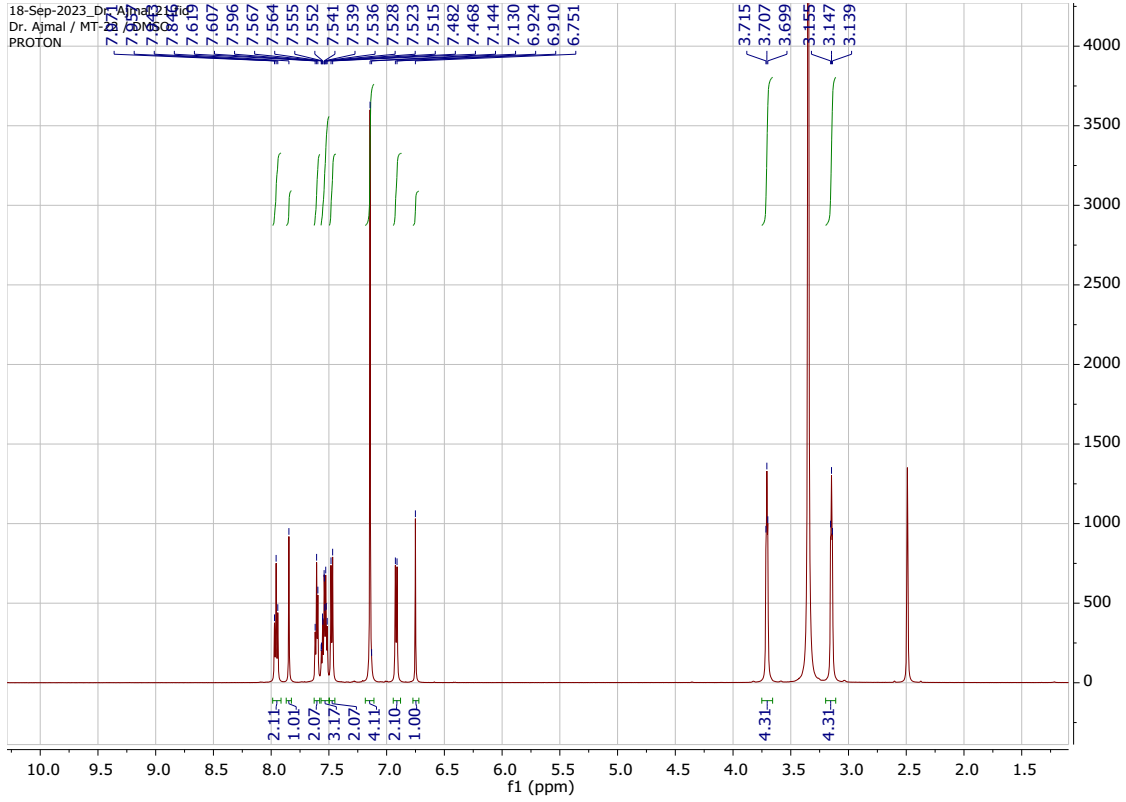
¹H NMR and ¹³C NMR of 18:



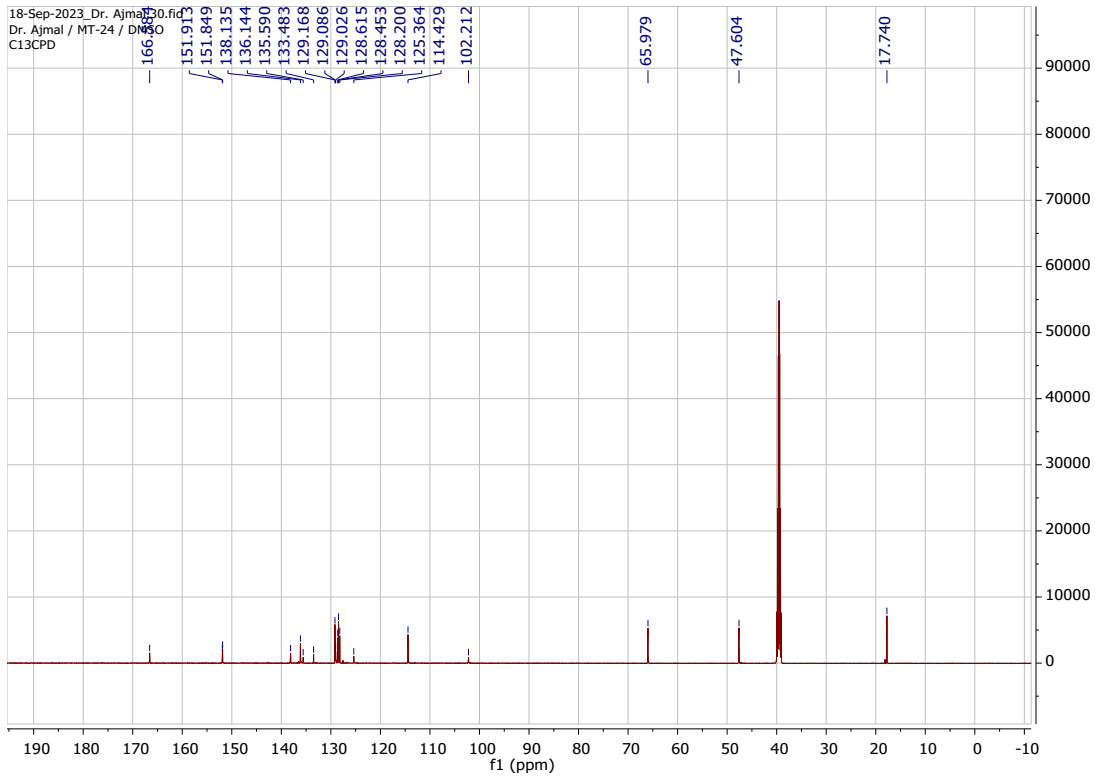
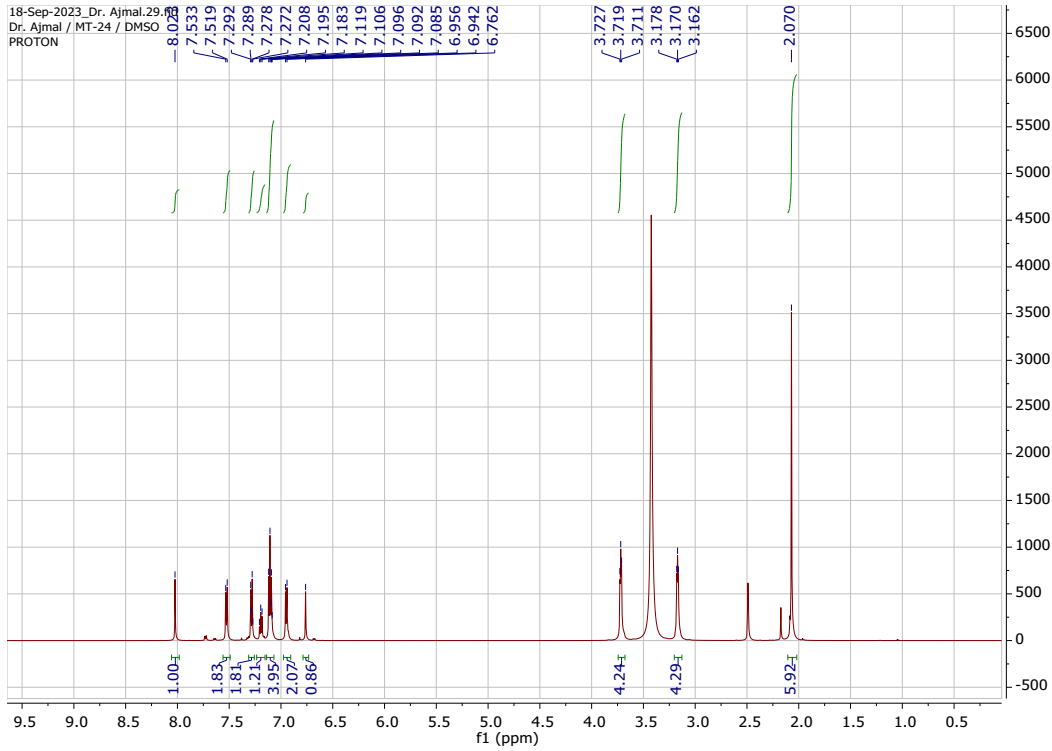
¹H NMR and ¹³C NMR of 19:



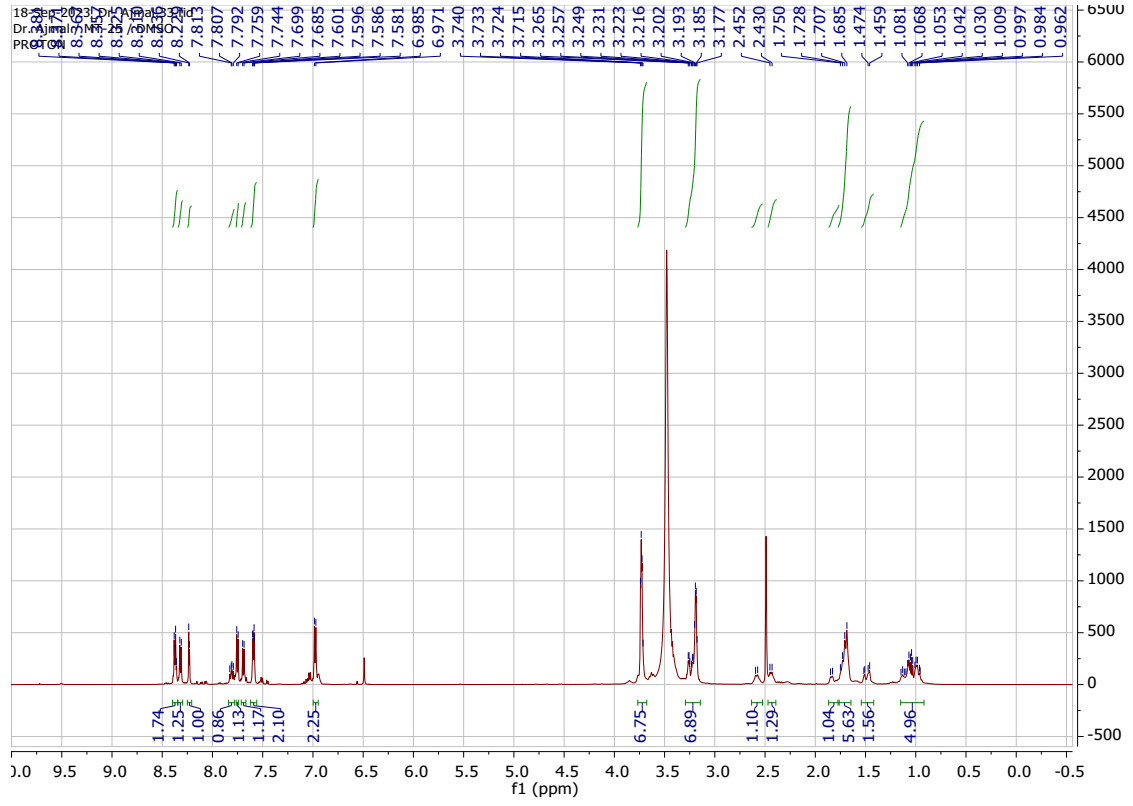
¹H NMR and ¹³C NMR of 20:



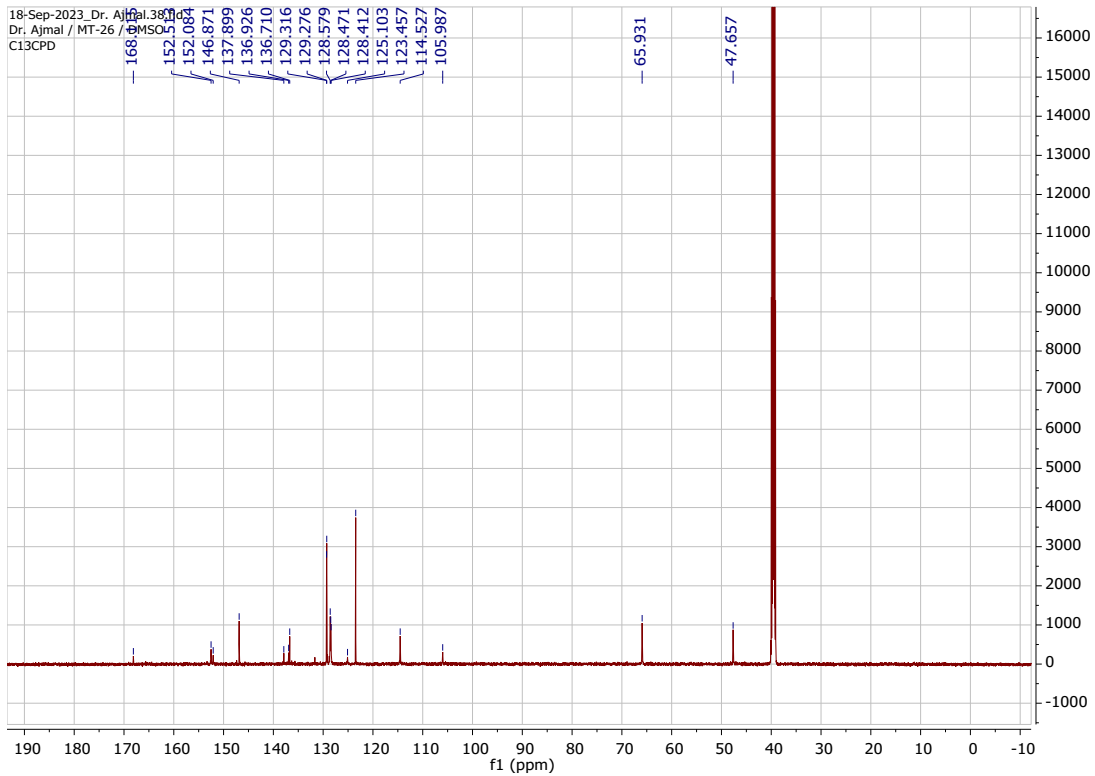
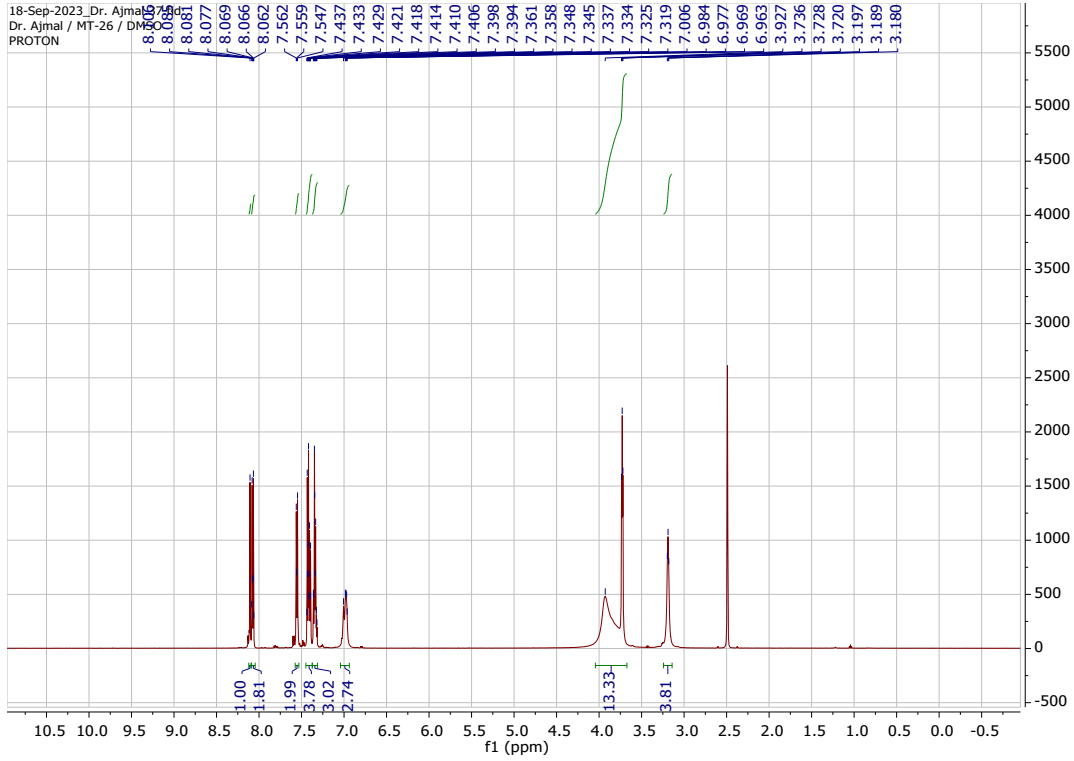
¹H NMR and ¹³C NMR of 21:



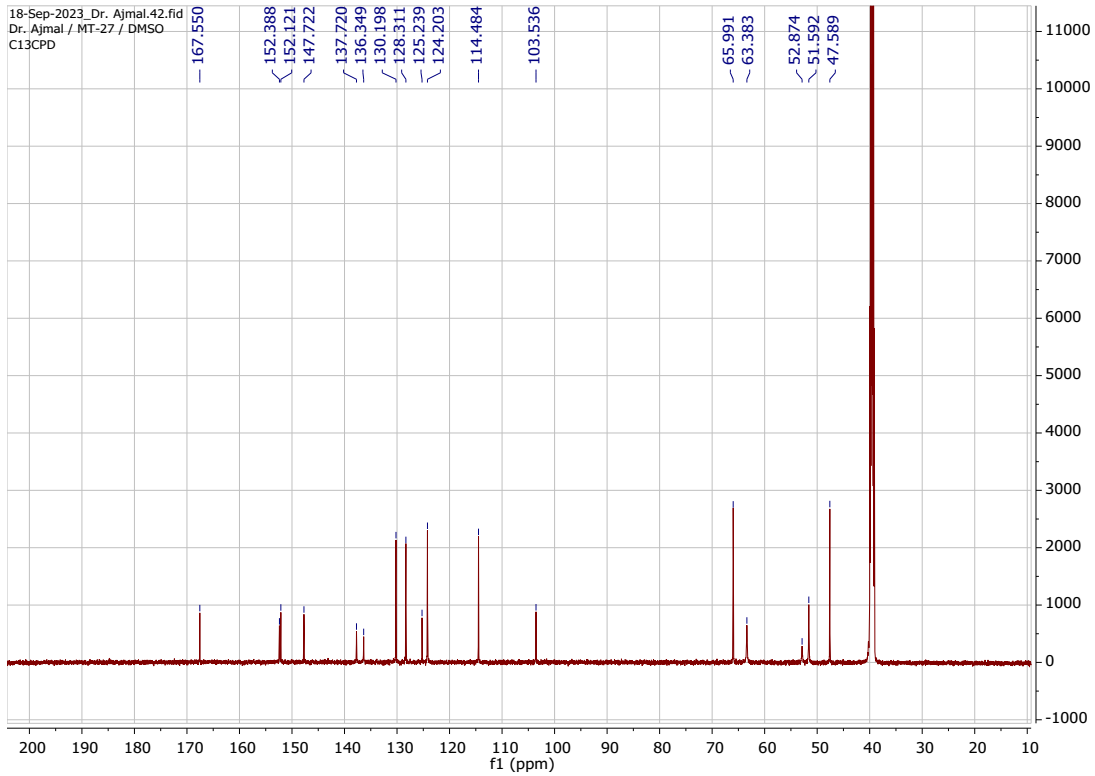
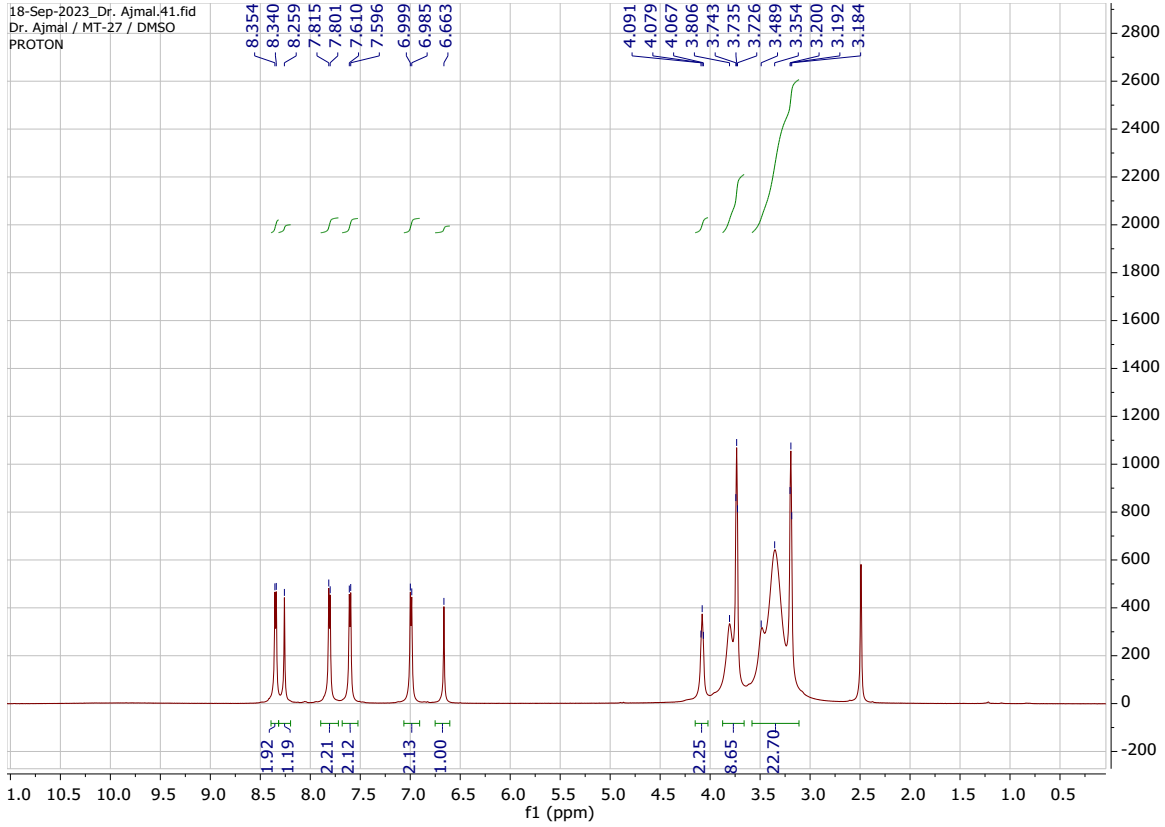
¹H NMR and ¹³C NMR of 22



¹H NMR and ¹³C NMR of 23:

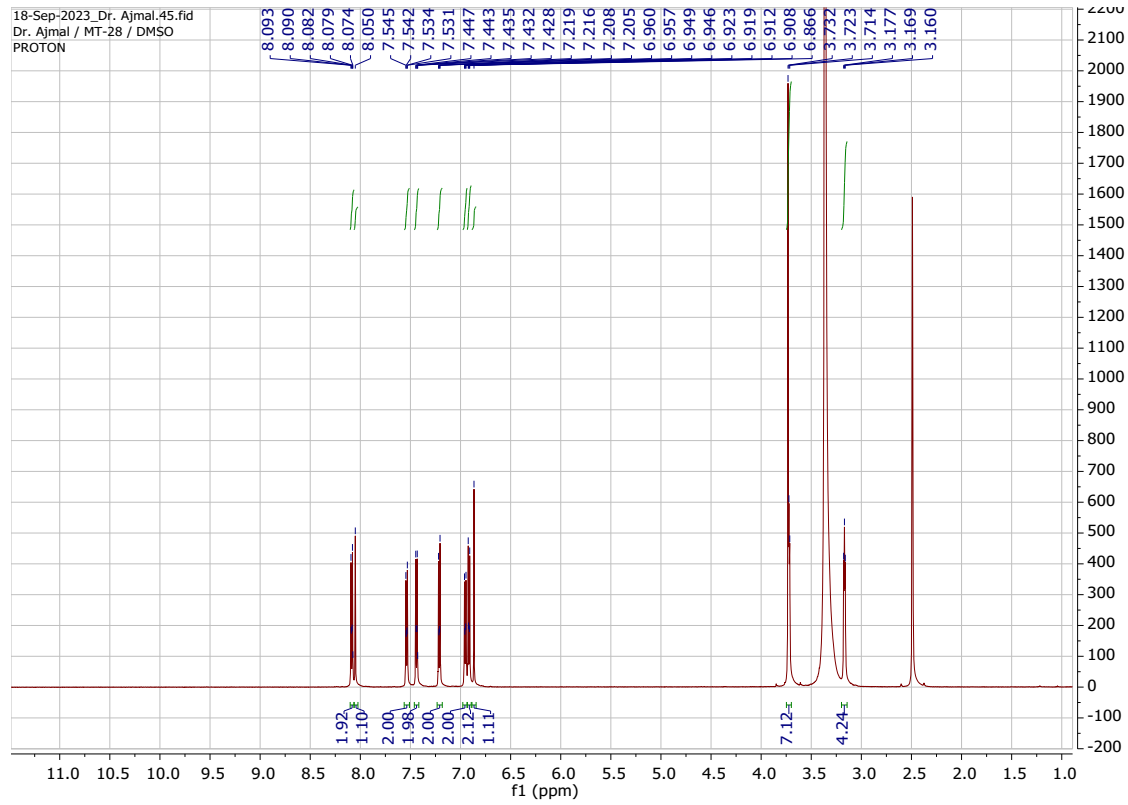


¹H NMR and ¹³C NMR of 24:

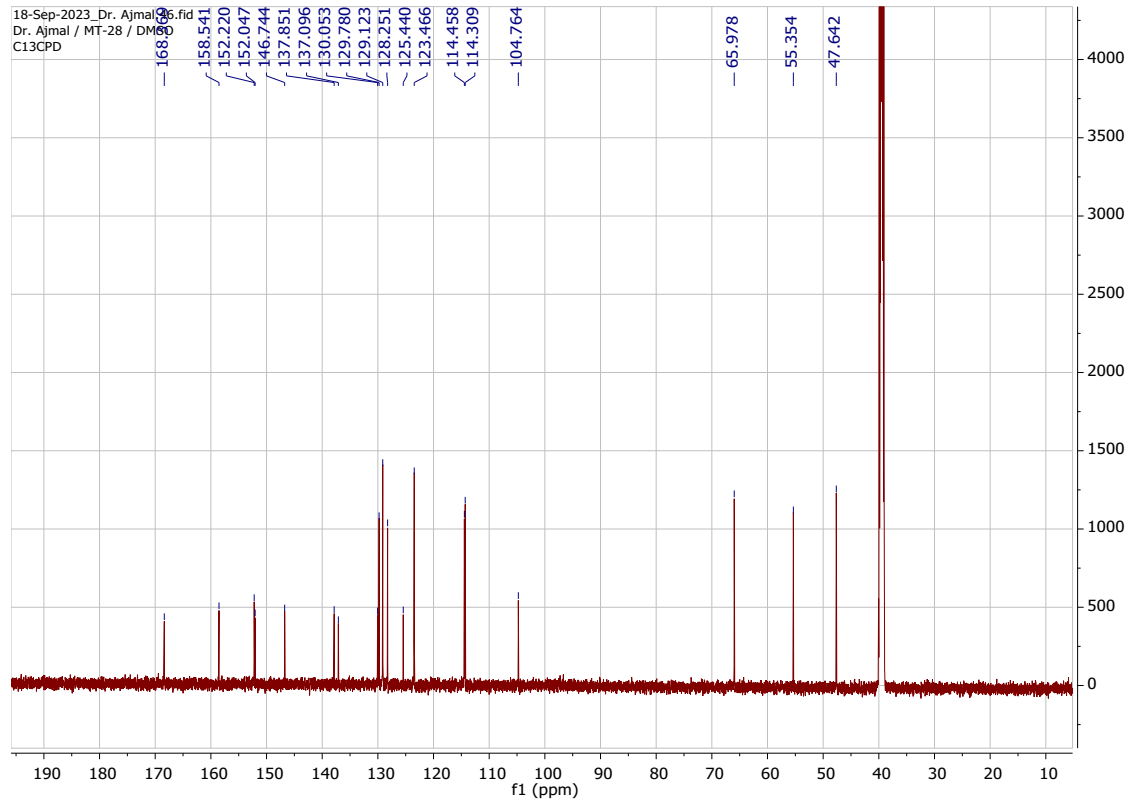


¹H NMR and ¹³C NMR of 25:

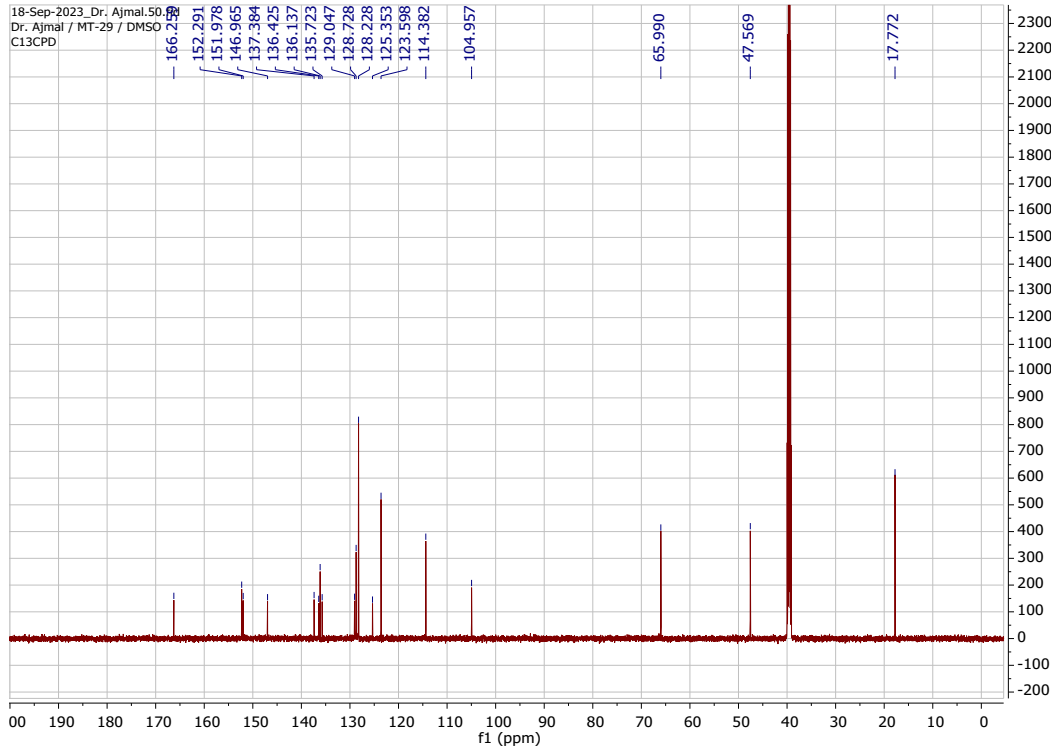
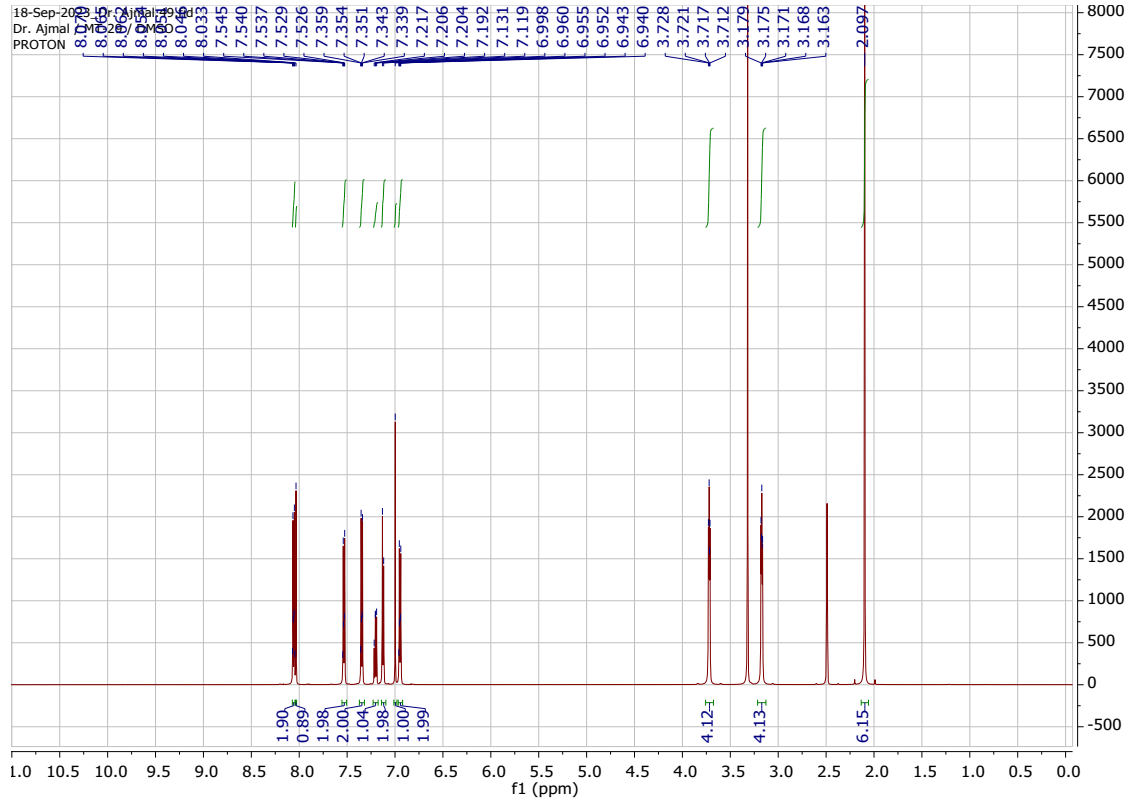
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Dr. Ajmal / MT-28 / DMSO
PROTON



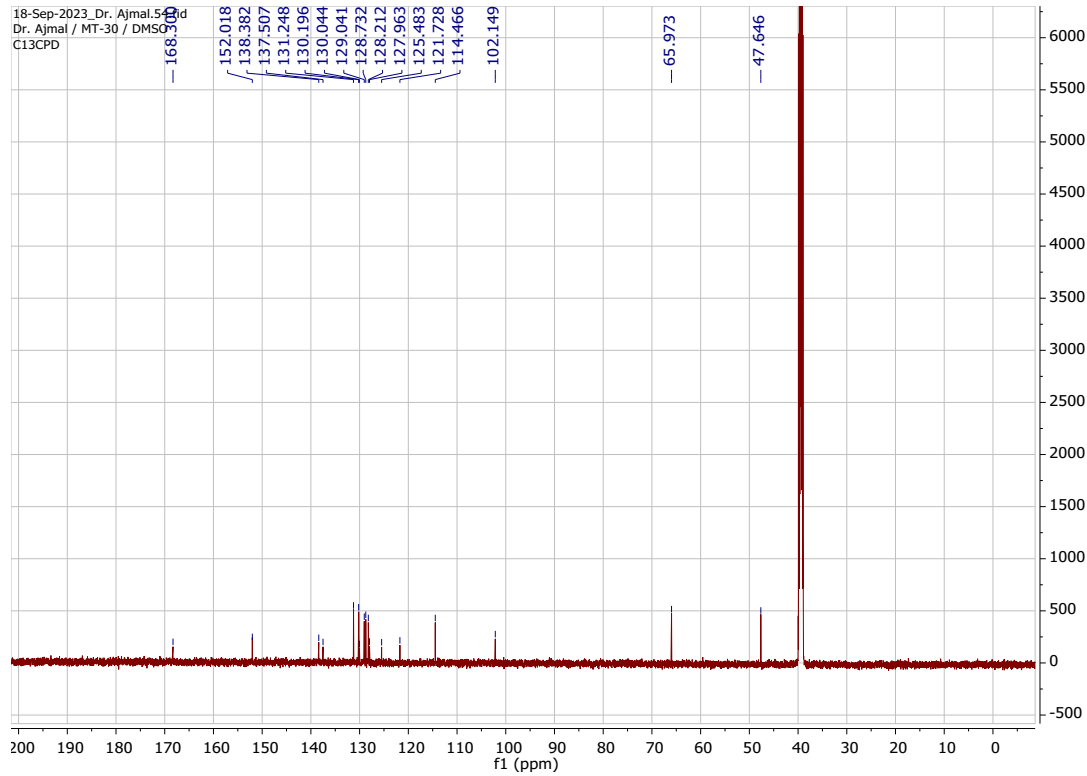
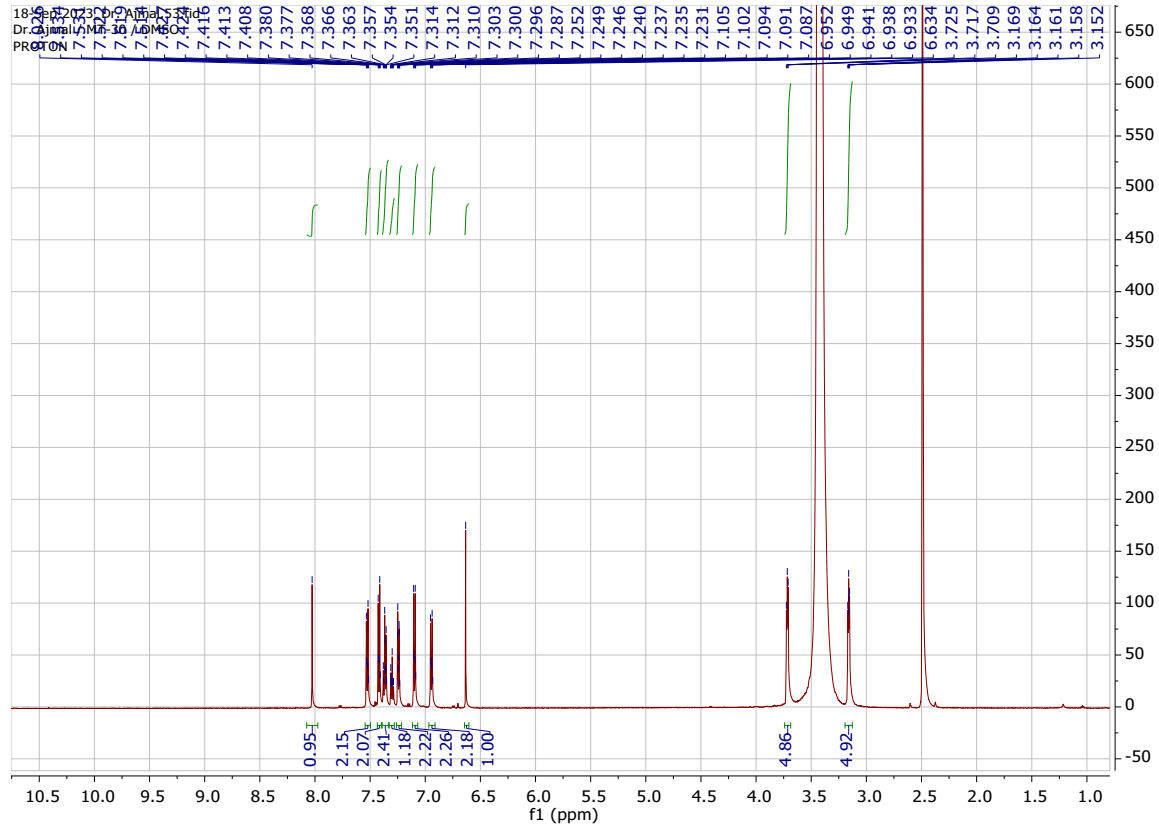
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Dr. Ajmal / MT-28 / DMSO
C13CPD



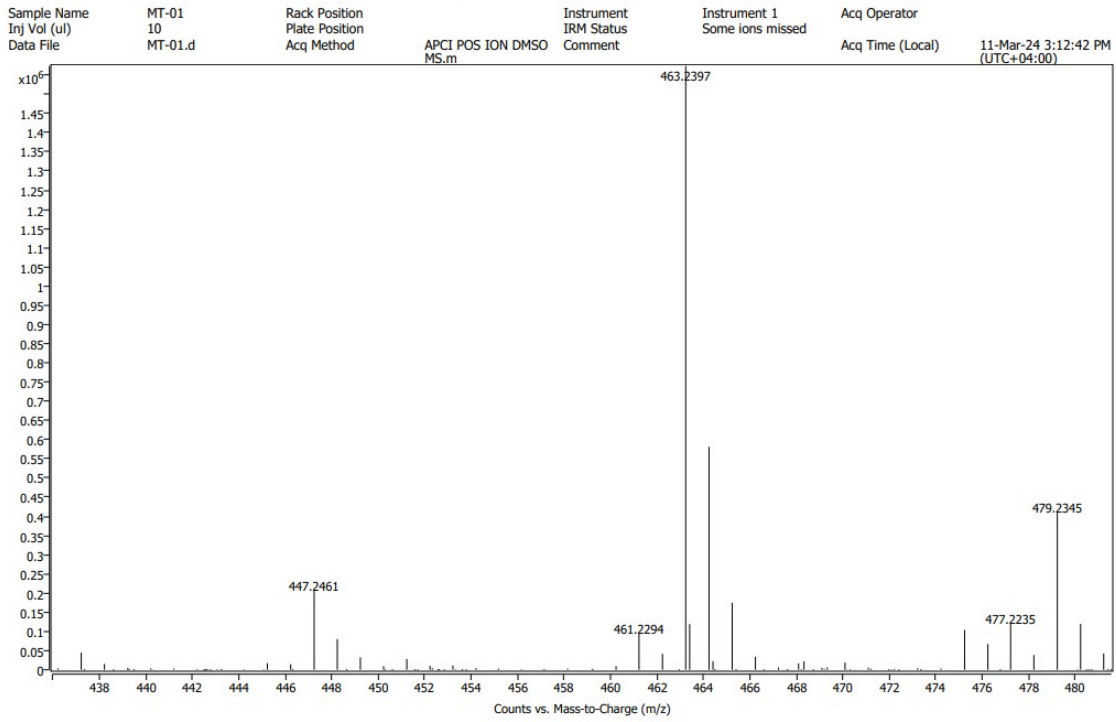
¹H NMR and ¹³C NMR of 26:



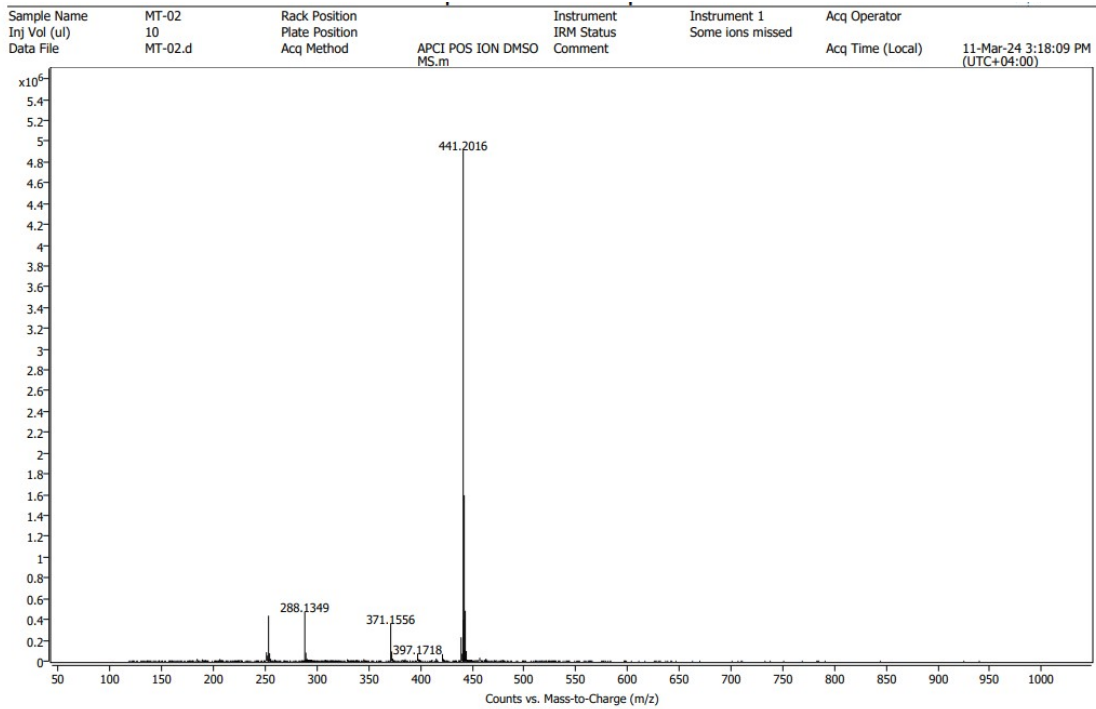
¹H NMR and ¹³C NMR of 27:



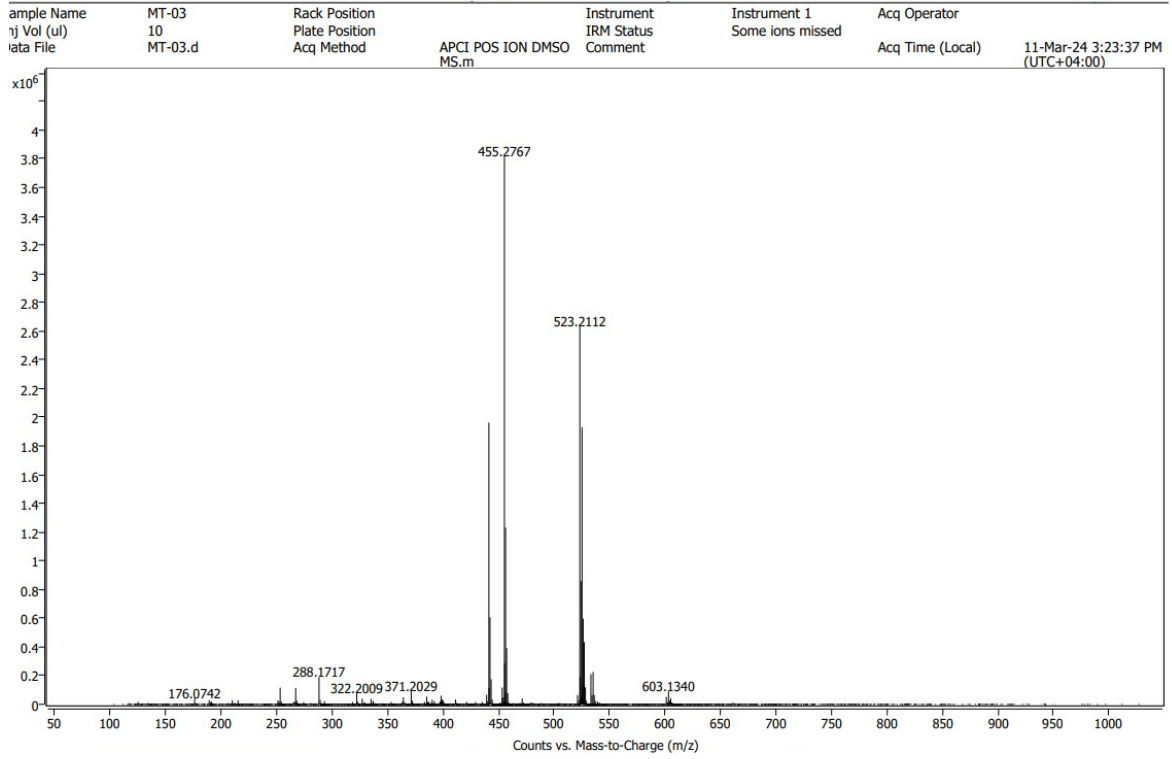
QTOF-MS Spectrum of 3



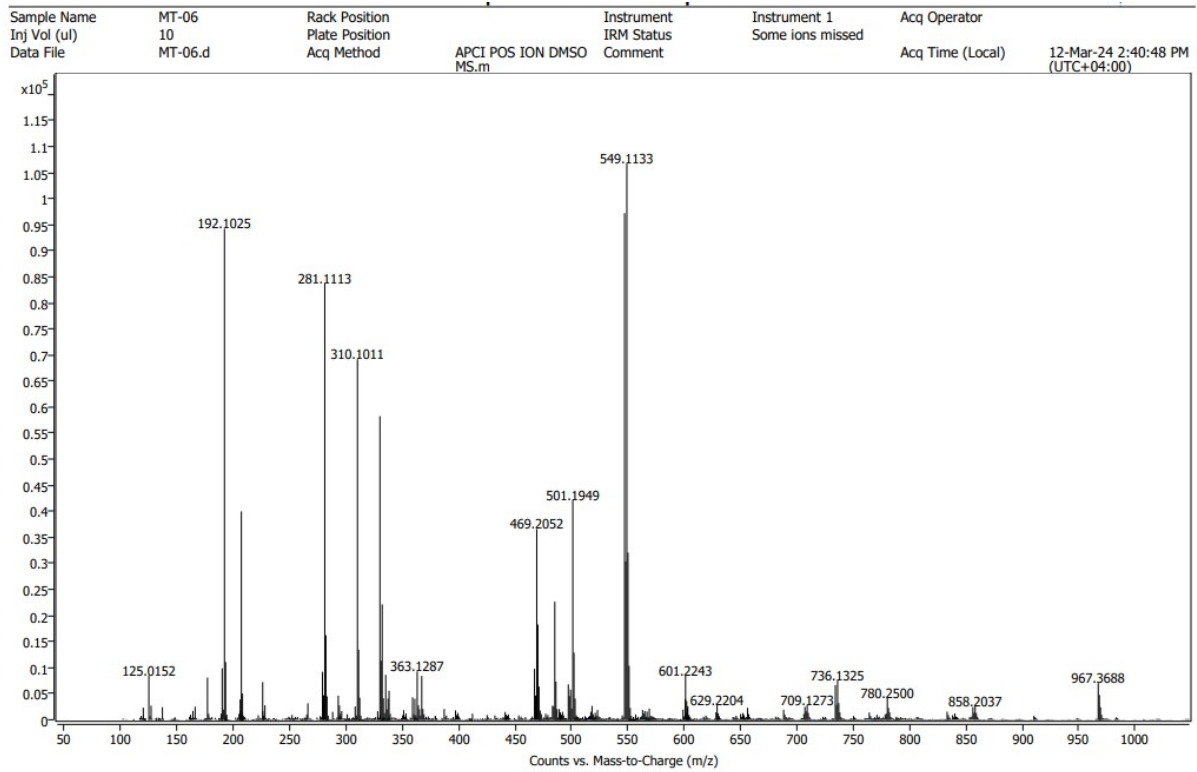
QTOF-MS Spectrum of 4



QTOF-MS Spectrum of 5

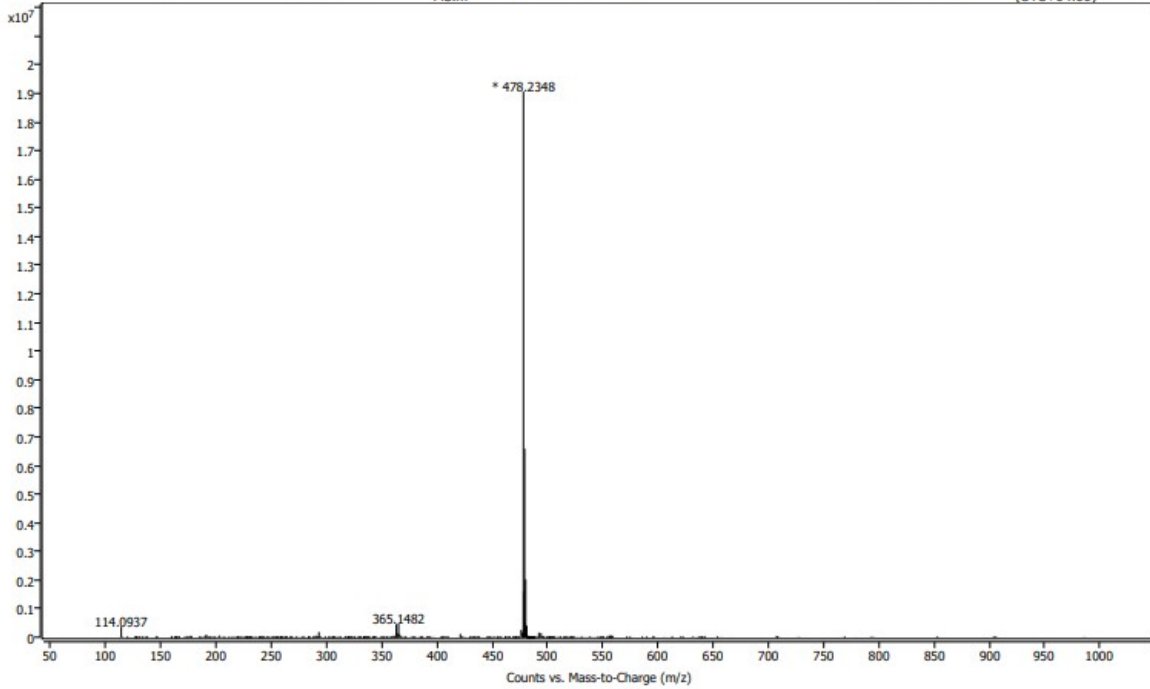


QTOF-MS Spectrum of 6



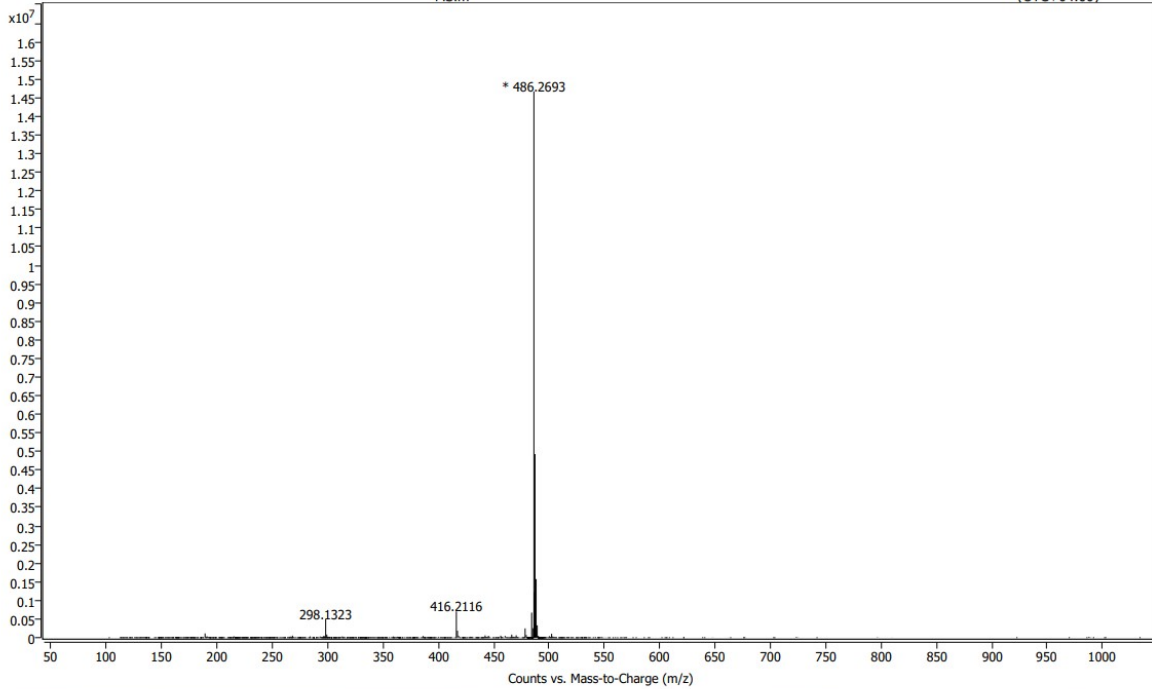
QTOF-MS Spectrum of 7

Sample Name	MT-07	Rack Position		Instrument	Instrument 1	Acq Operator
Inj Vol (ul)	10	Plate Position		IRM Status	Some ions missed	
Data File	MT-07.d	Acq Method	APCI POS ION DMSO MS.m	Comment		Acq Time (Local)
						12-Mar-24 2:46:42 PM (UTC+04:00)

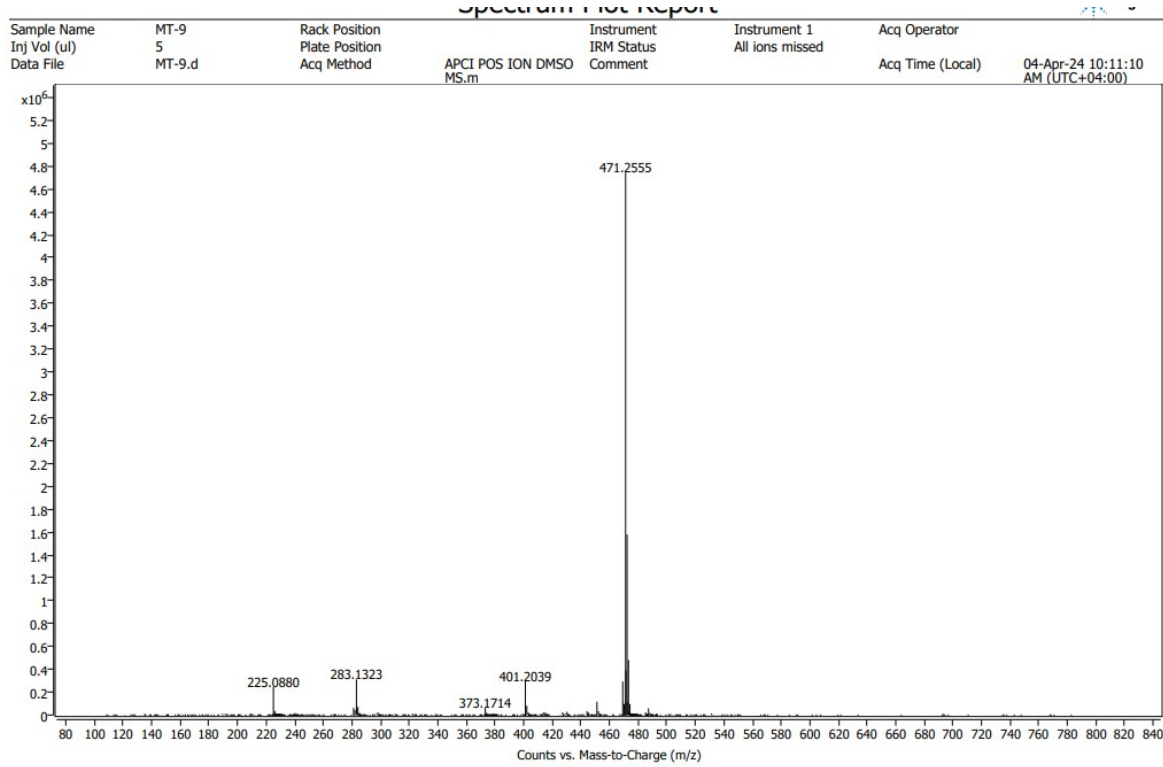


QTOF-MS Spectrum of 8

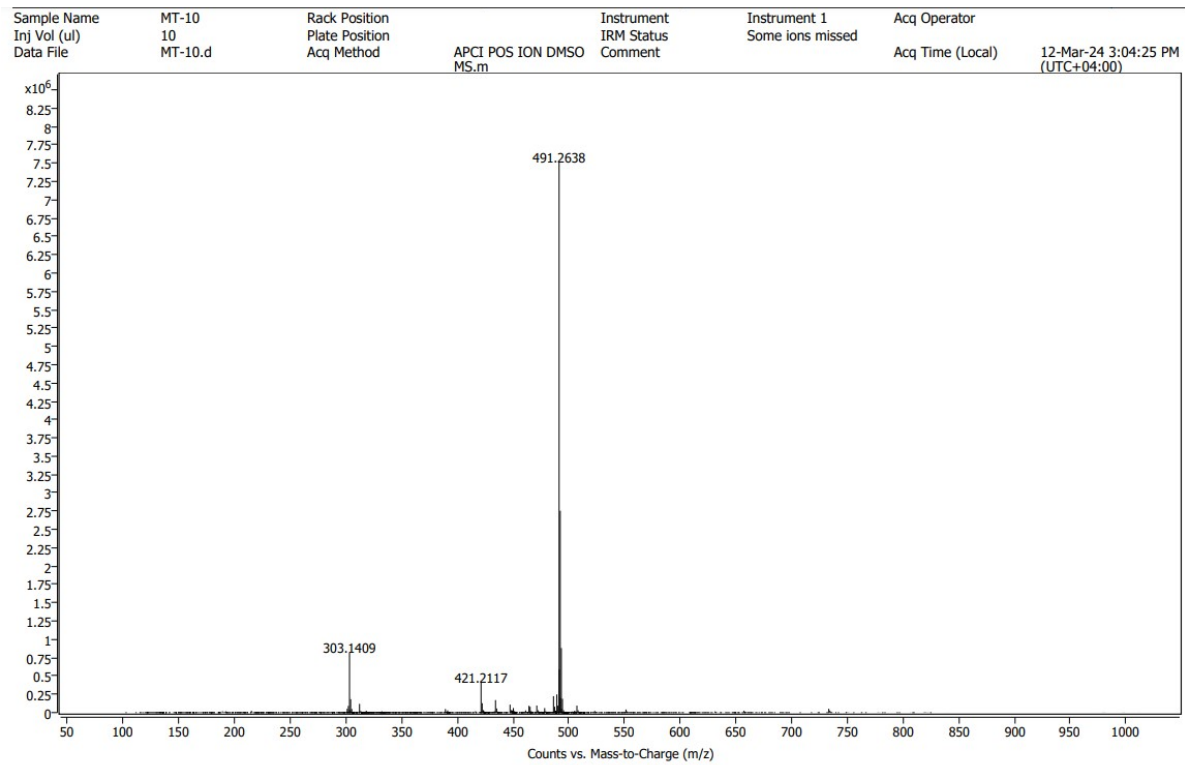
Sample Name	M1-08	Rack Position		Instrument	Instrument 1	Acq Operator
Inj Vol (ul)	10	Plate Position		IRM Status	Some ions missed	
Data File	MT-08.d	Acq Method	APCI POS ION DMSO MS.m	Comment		Acq Time (Local)
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QTOF-MS Spectrum of 9

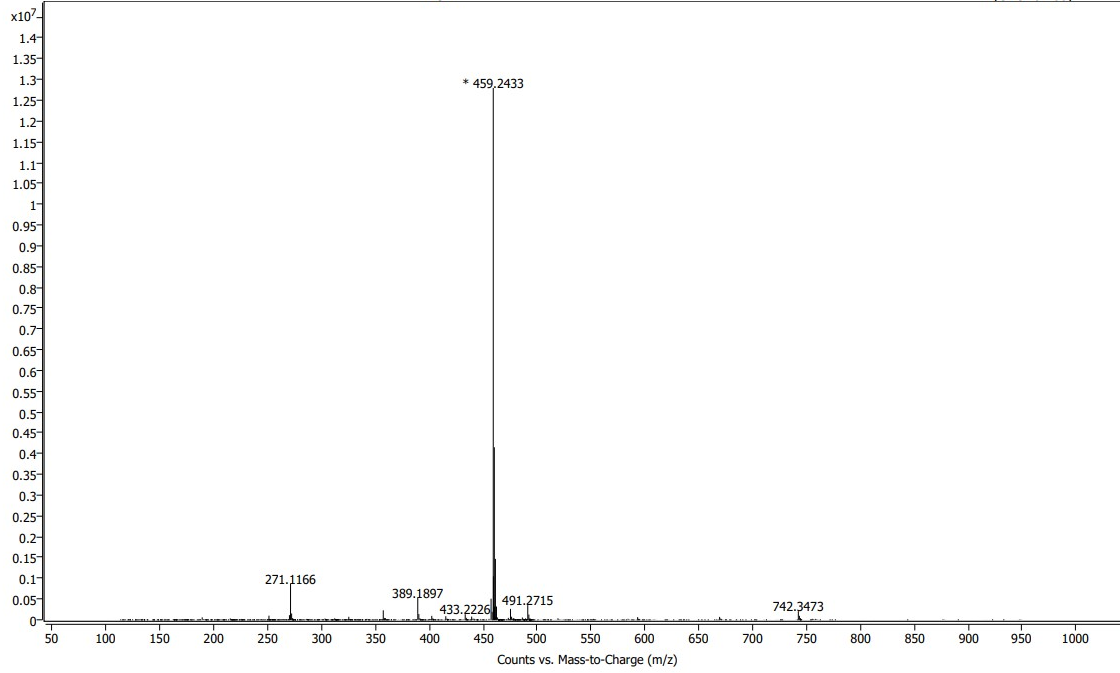


QTOF-MS Spectrum of 10



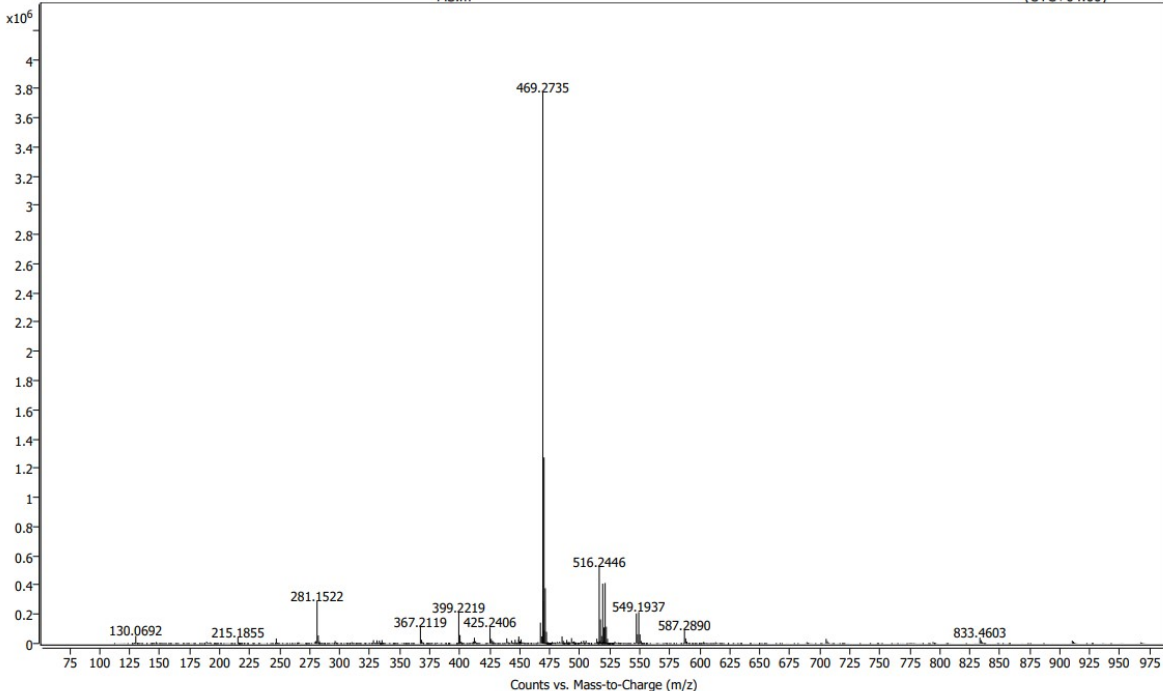
QTOF-MS Spectrum of 11

Sample Name	MT-11	Rack Position		Instrument	Instrument 1	Acq Operator
Inj Vol (ul)	10	Plate Position		IRM Status	Some ions missed	
Data File	MT-11.d	Acq Method	APCI POS ION DMSO MS.m	Comment		Acq Time (Local) 12-Mar-24 3:10:22 PM (UTC+04:00)



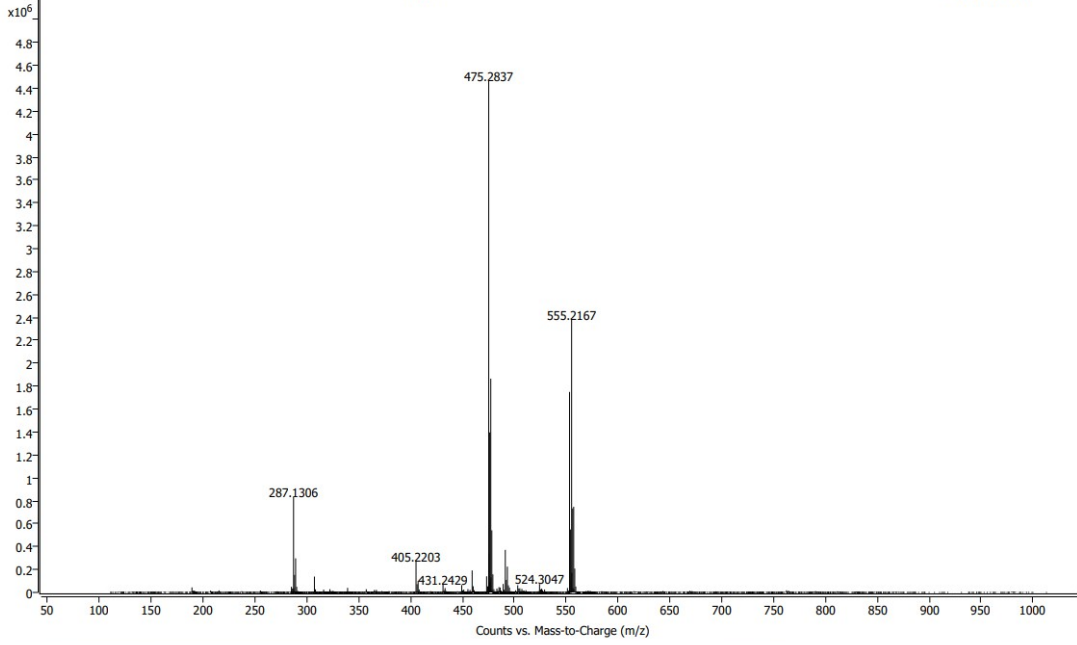
QTOF-MS Spectrum of 12

Sample Name	MT-31	Rack Position		Instrument	Instrument 1	Acq Operator
Inj Vol (ul)	10	Plate Position		IRM Status	Some ions missed	
Data File	MT-31.d	Acq Method	APCI POS ION DMSO MS.m	Comment		Acq Time (Local) 13-Mar-24 1:17:23 PM (UTC+04:00)



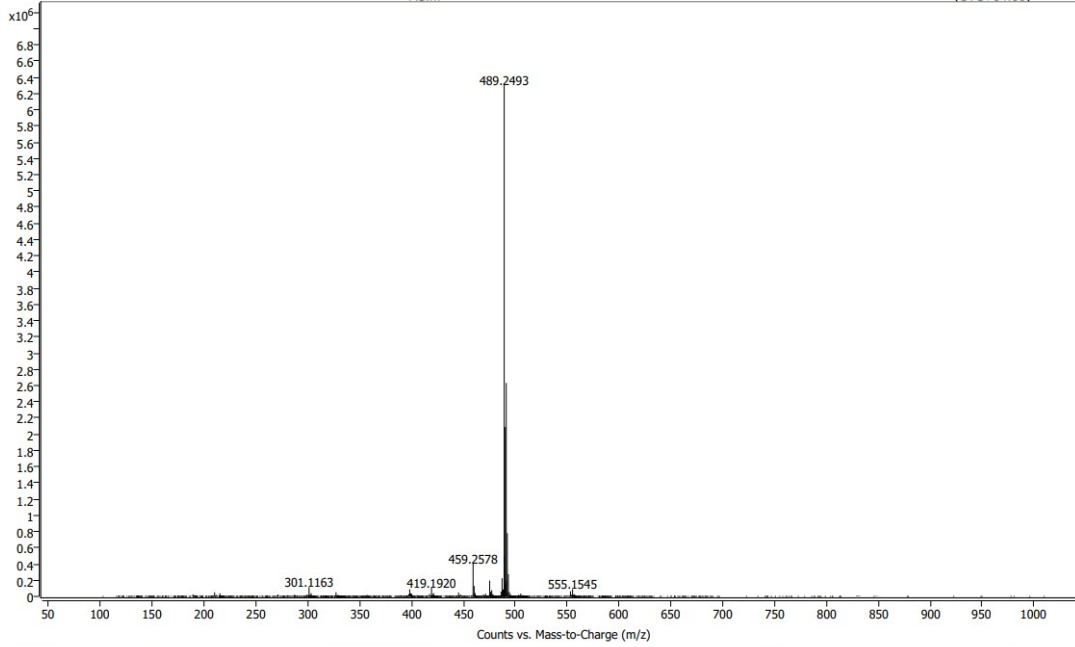
QTOF-MS Spectrum of 13

Sample Name	MT-14	Rack Position	Instrument	Instrument 1	Acq Operator
Inj Vol (ul)	10	Plate Position	IRM Status	Some ions missed	
Data File	MT-14.d	Acq Method	Comment		Acq Time (Local)
		APCI POS ION DMSO			12-Mar-24 3:28:06 PM (UTC+04:00)
		MS.m			

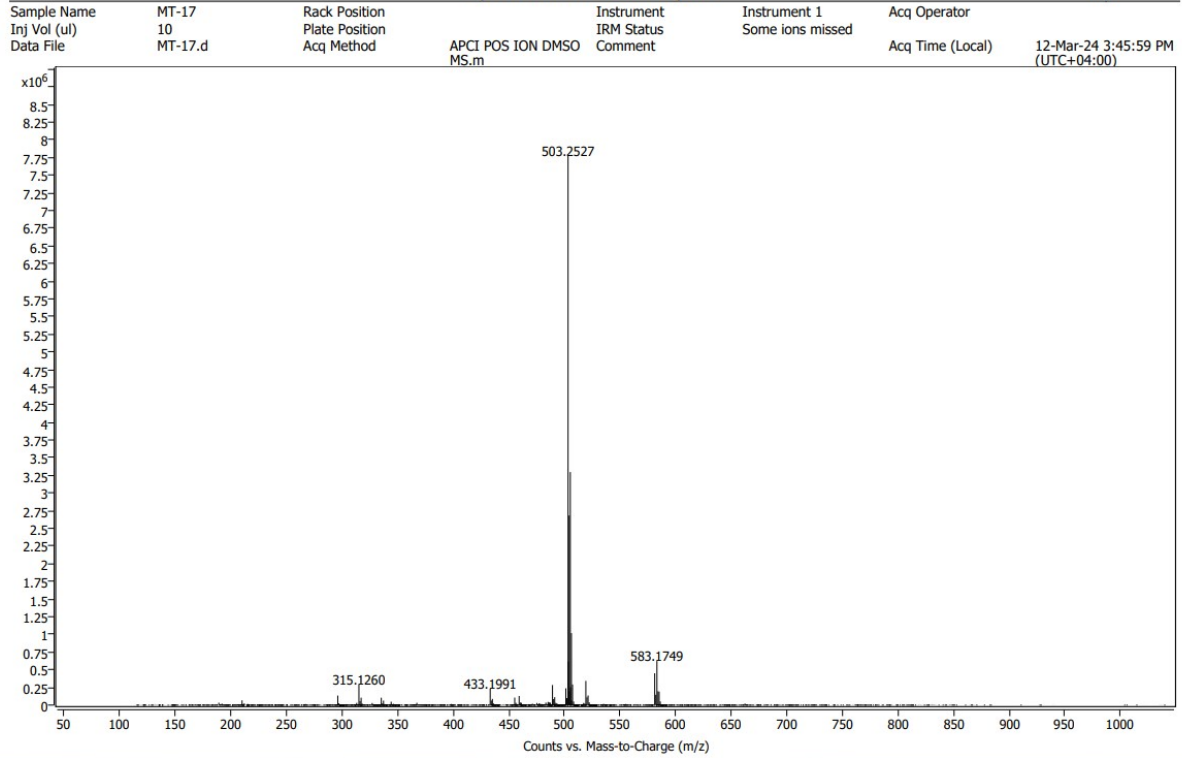


QTOF-MS Spectrum of 14

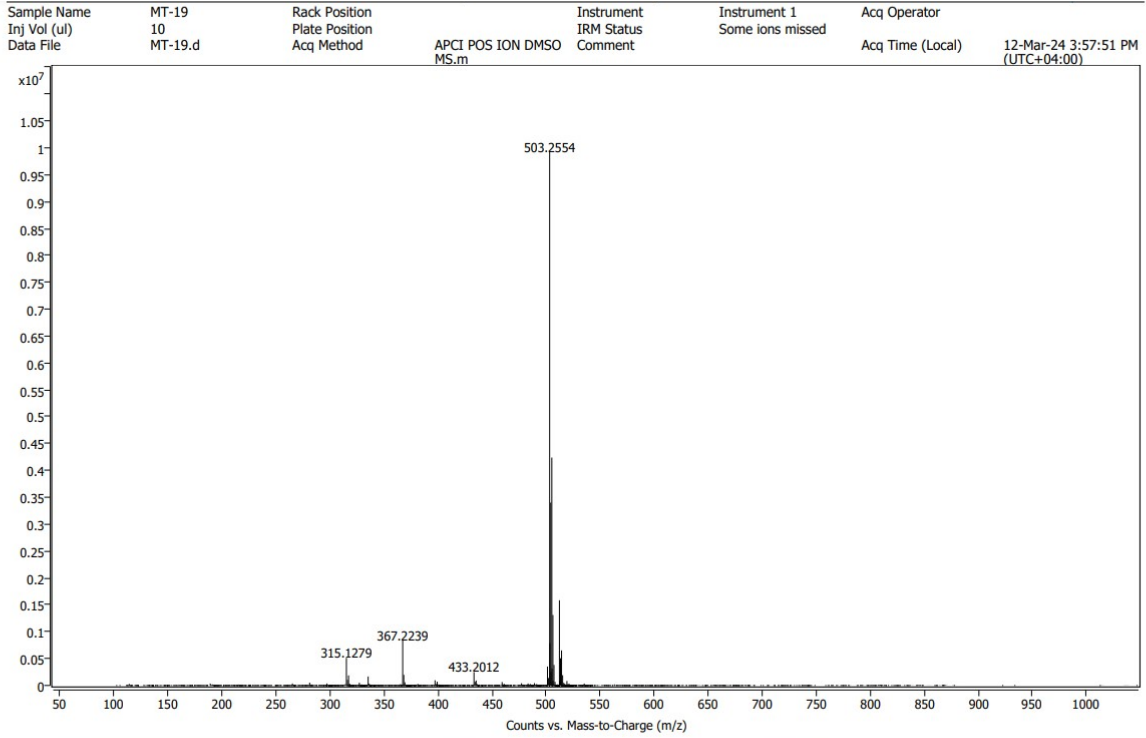
Sample Name	MT-15	Rack Position	Instrument	Instrument 1	Acq Operator
Inj Vol (ul)	10	Plate Position	IRM Status	Some ions missed	
Data File	MT-15.d	Acq Method	Comment		Acq Time (Local)
		APCI POS ION DMSO			12-Mar-24 3:34:03 PM (UTC+04:00)
		MS.m			



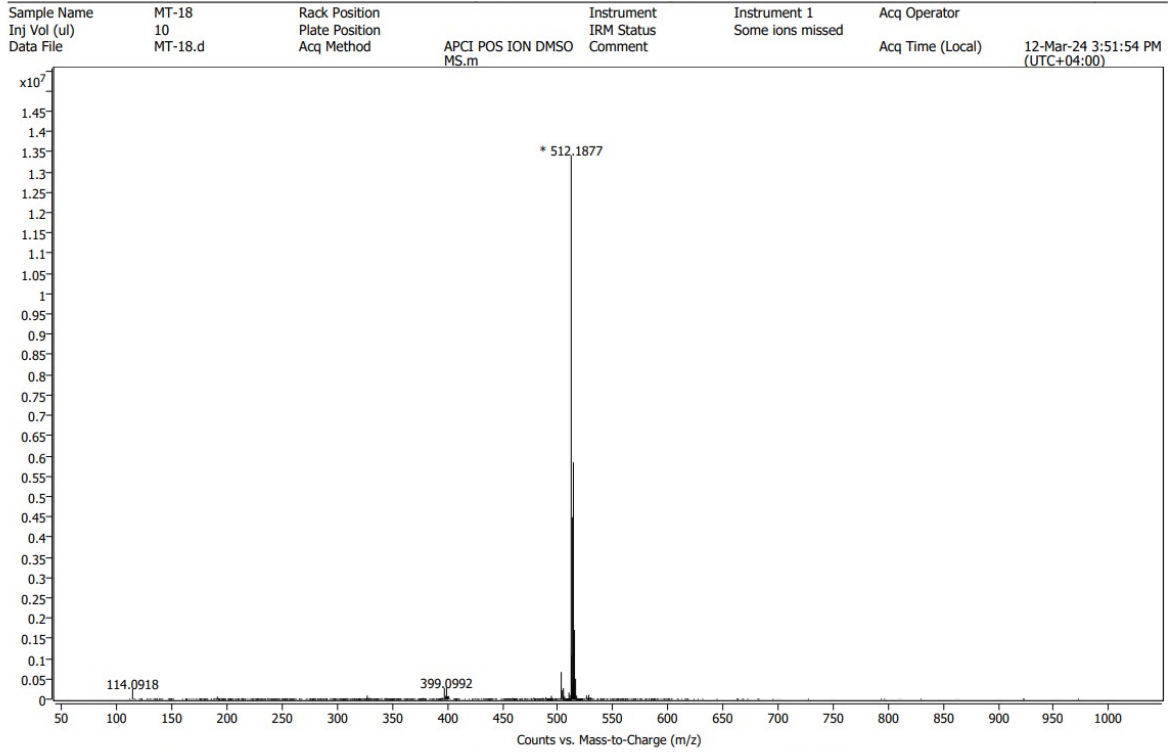
QTOF-MS Spectrum of 15



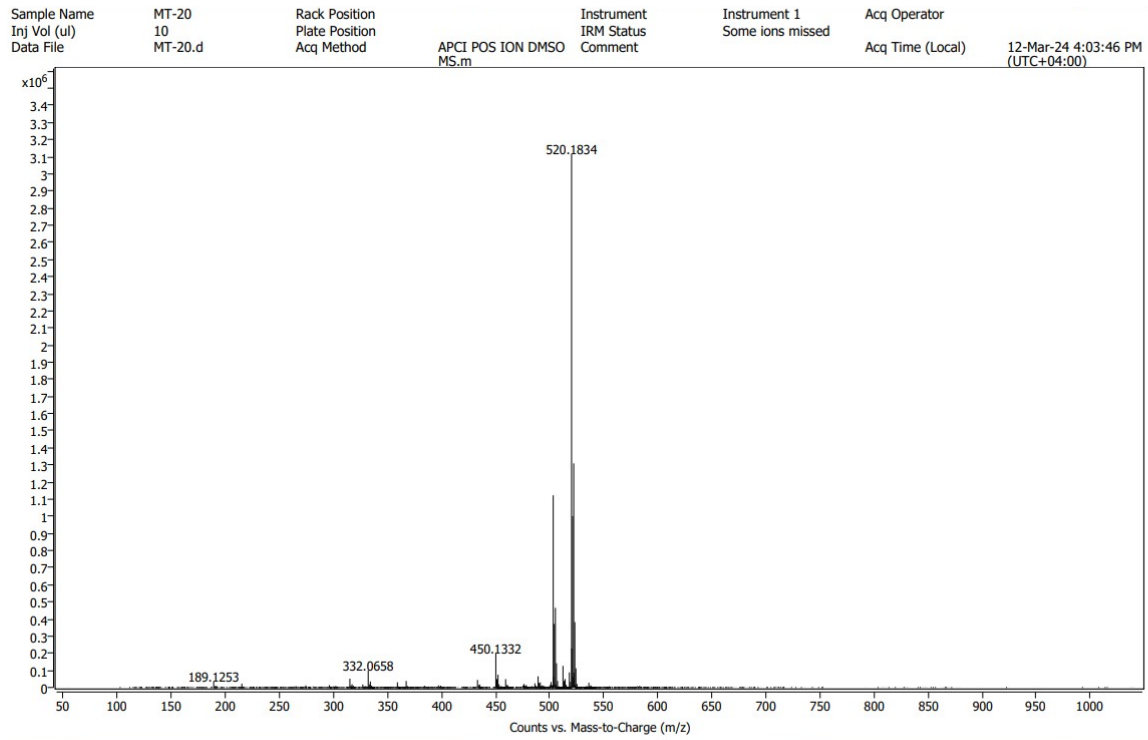
QTOF-MS Spectrum of 16



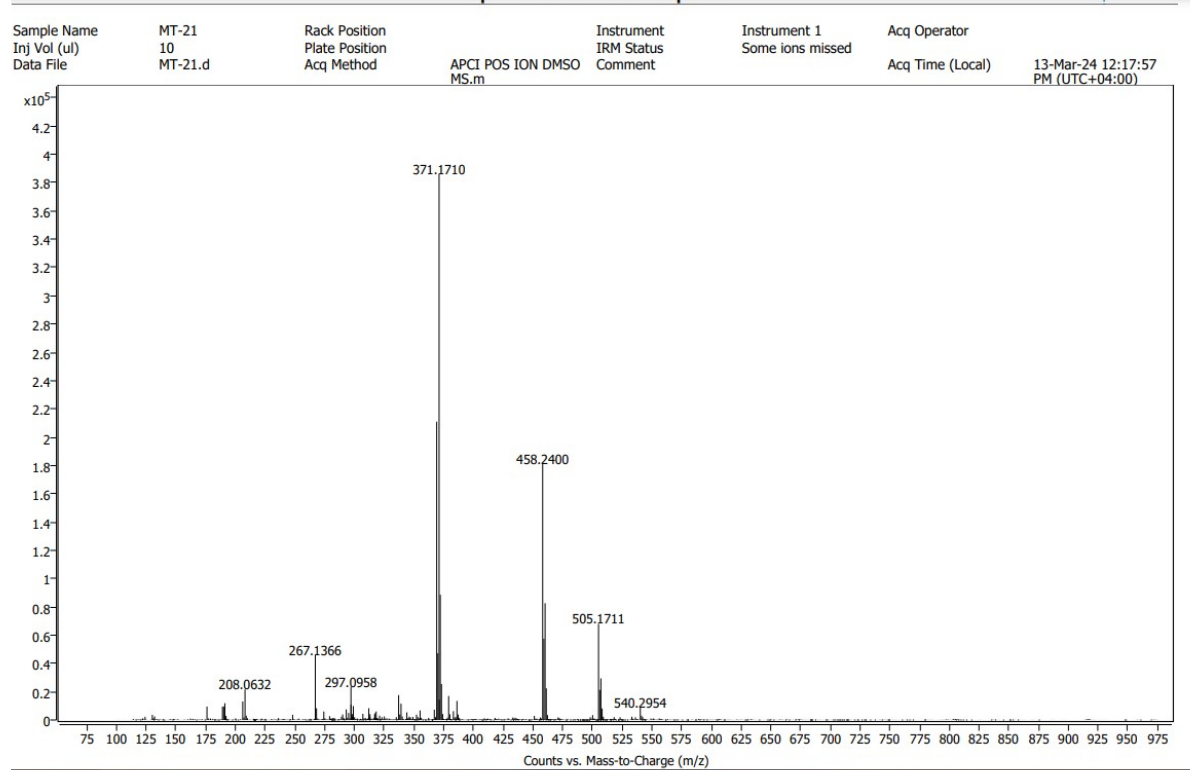
QTOF-MS Spectrum of 17



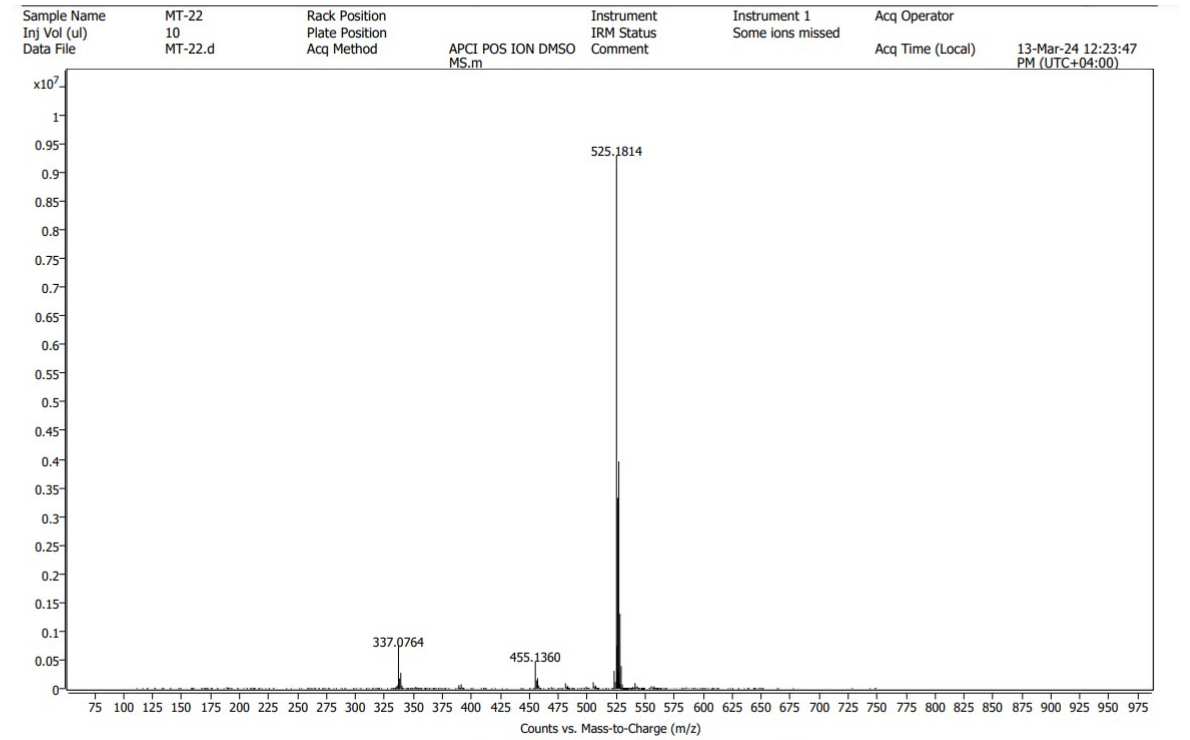
QTOF-MS Spectrum of 18



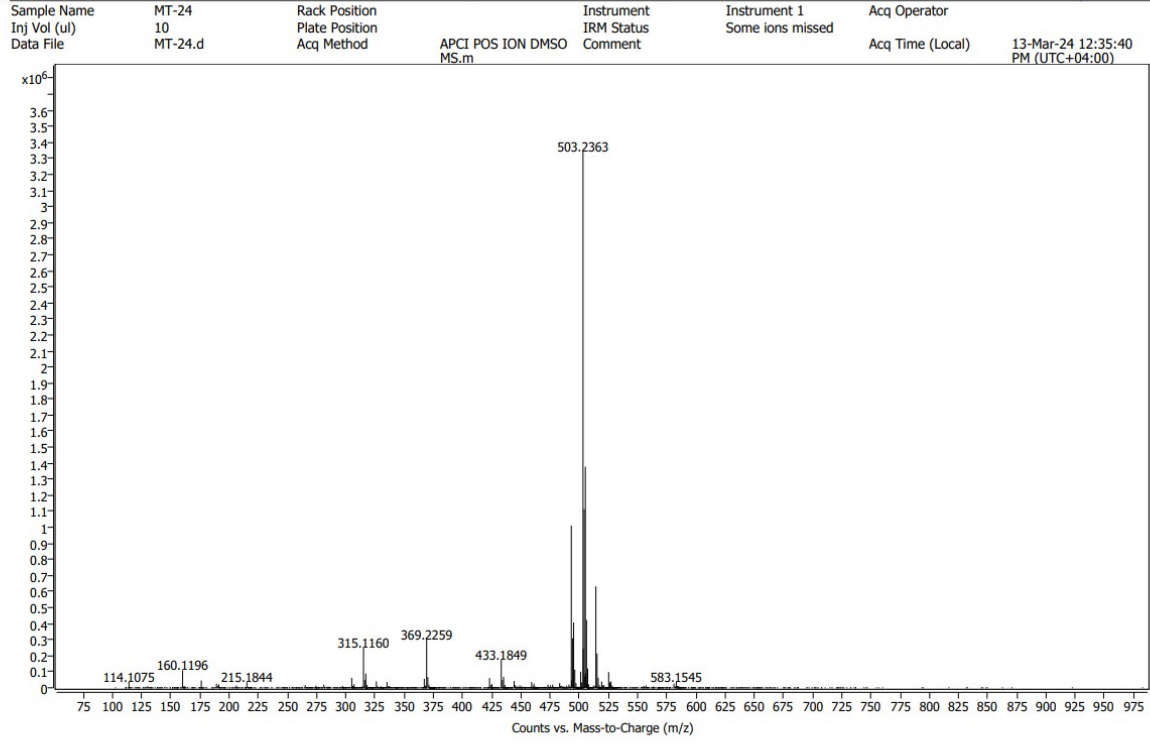
QTOF-MS Spectrum of 19



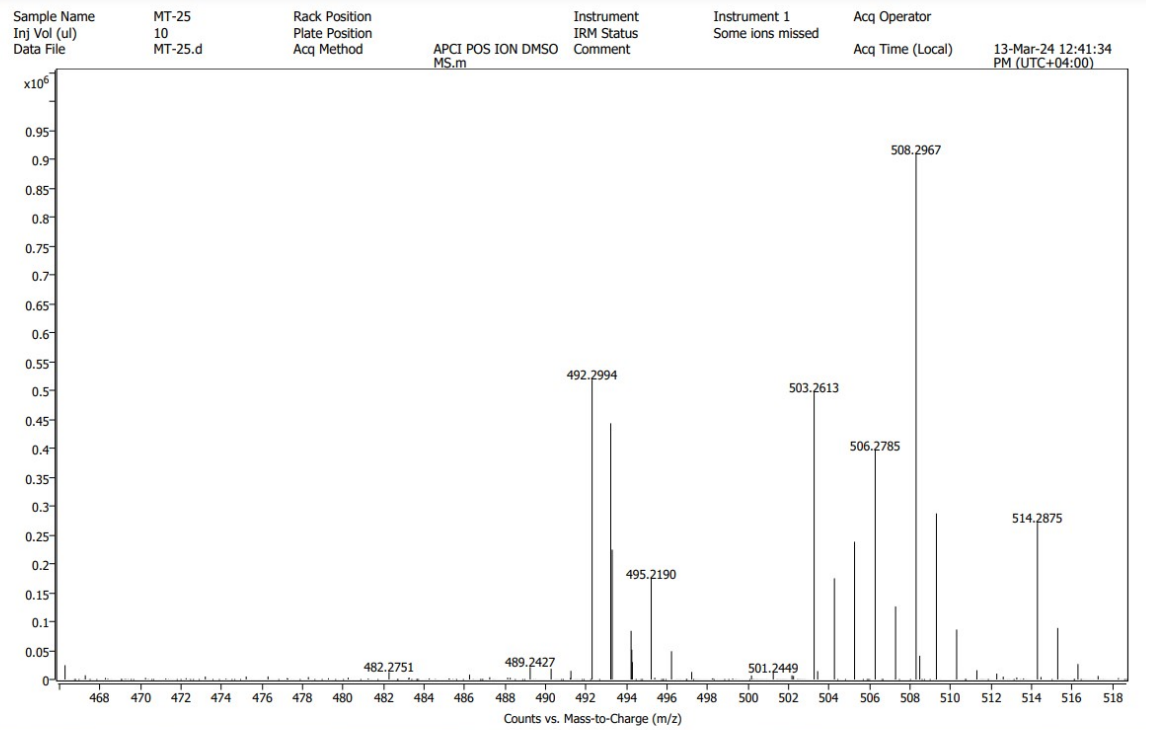
QTOF-MS Spectrum of 20



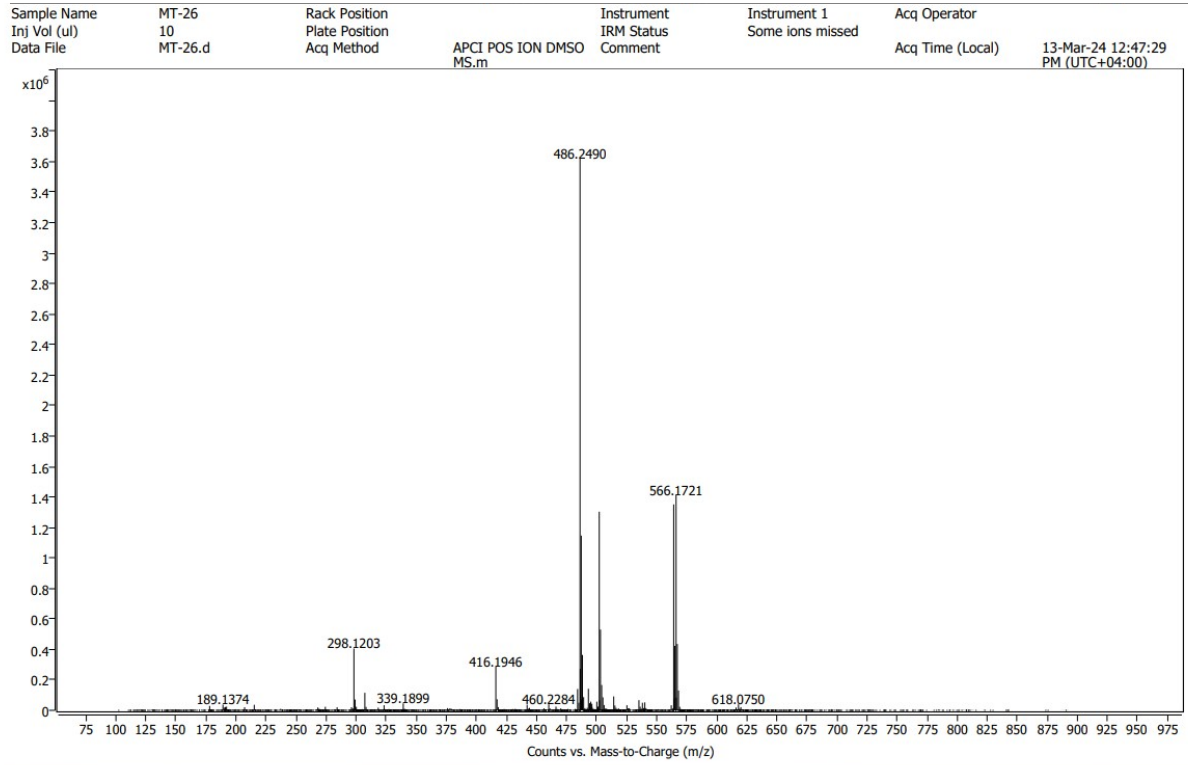
QTOF-MS Spectrum of 21



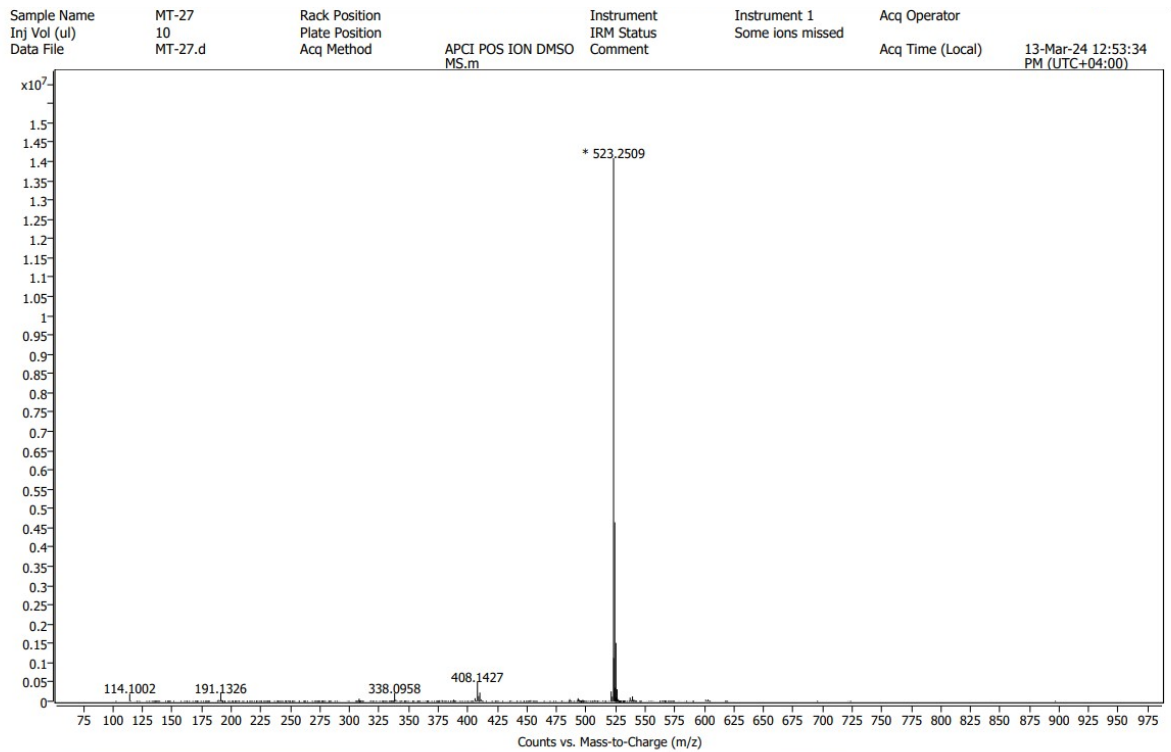
QTOF-MS Spectrum of 22



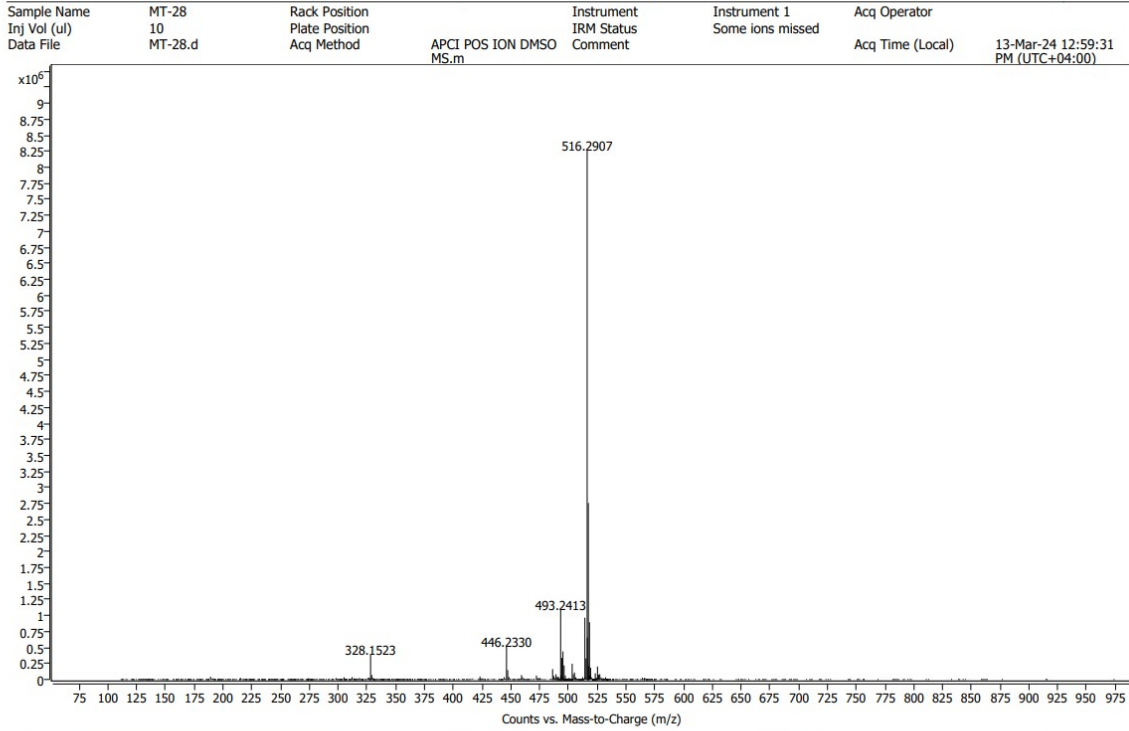
QTOF-MS Spectrum of 23



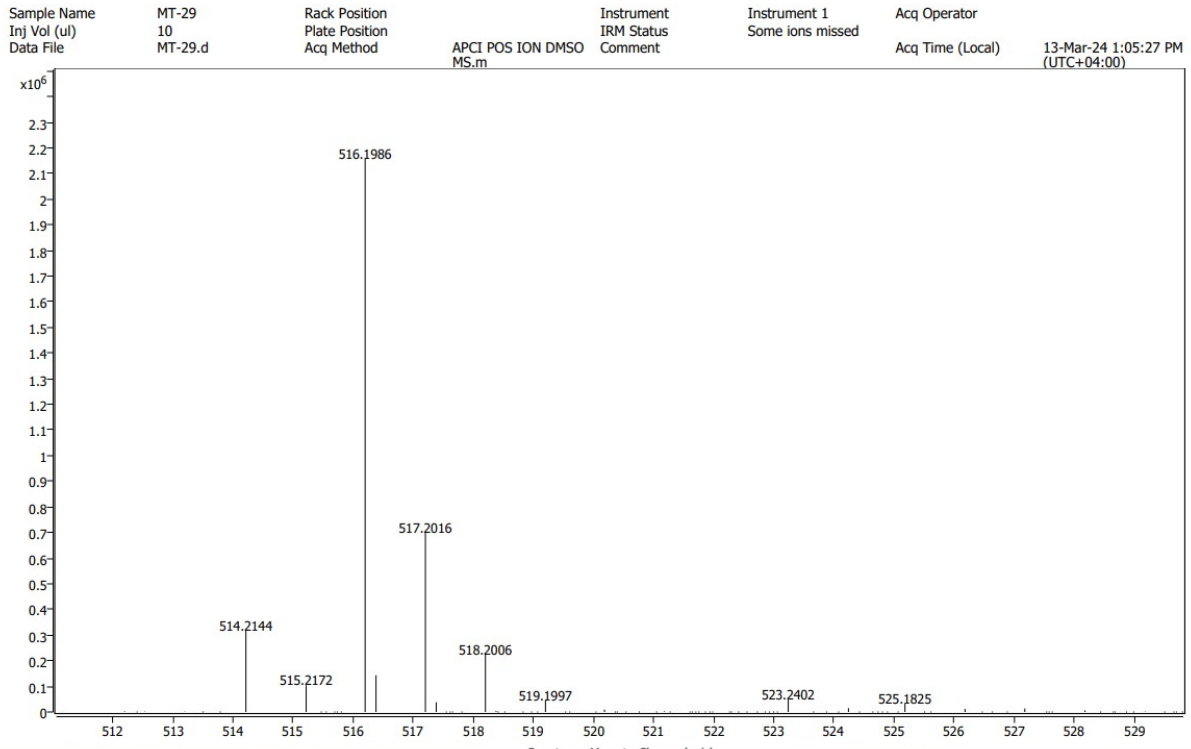
QTOF-MS Spectrum of 24



QTOF-MS Spectrum of 25



QTOF-MS Spectrum of 26



QTOF-MS Spectrum of 27

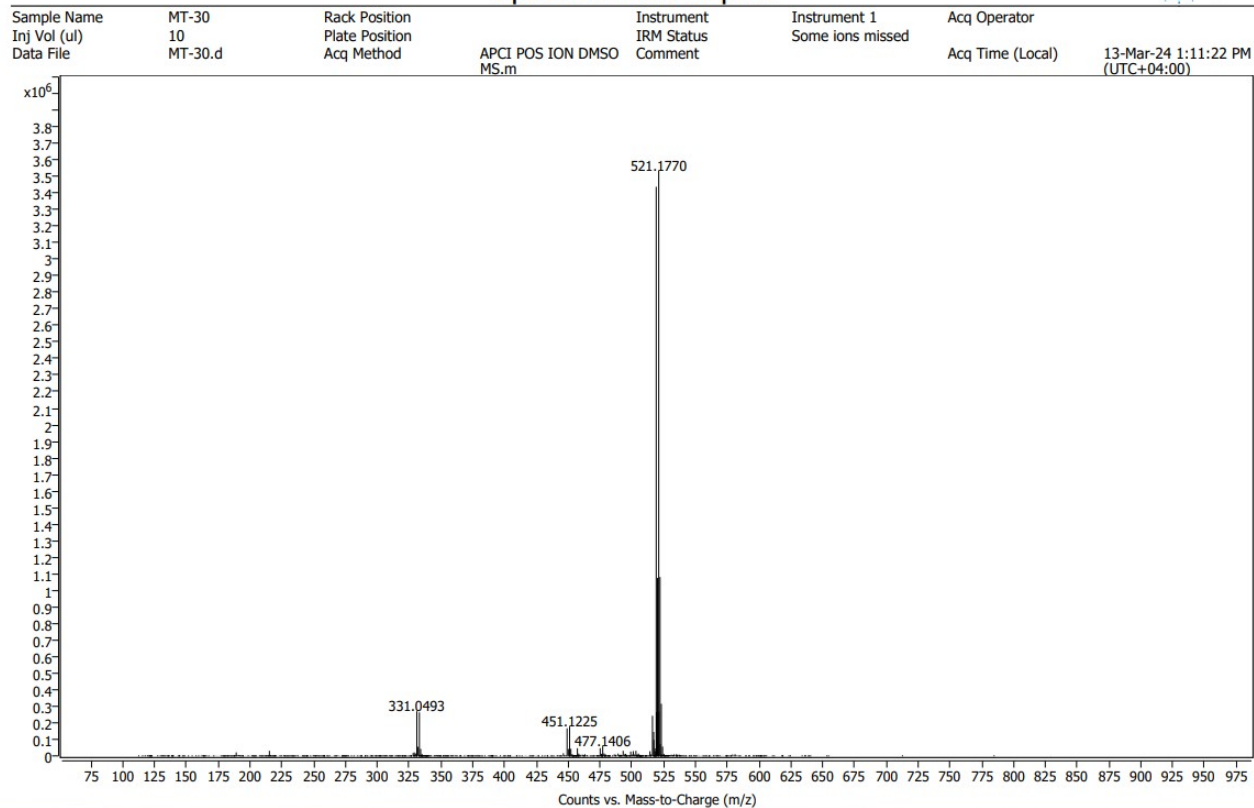


Table S1. Dataset splitting for the QSAR modelling

ID	Comp. Name	Status	$Y_{\text{cal. Exp. endpoint}}$	$Y_{\text{Pred. by model eq.}}$	Error
1	3	Prediction	4.51	4.0323	-0.4777
2	4	Training	4.61	4.639	0.029
3	5	Training	4.57	4.5481	-0.0219
4	6	Training	4.46	4.4517	-0.0083
5	7	Training	4.42	4.4326	0.0126
6	8	Training	4.56	4.4507	-0.1093
7	9	Training	4.47	4.4984	0.0284
8	10	Training	4.4	4.4975	0.0975
9	11	Prediction	4.35	4.56	0.21
10	12	Prediction	4.33	4.2367	-0.0933
11	13	Training	4.5	4.4835	-0.0165
12	14	Training	4.45	4.3885	-0.0615
13	15	Training	4.3	4.2933	-0.0067
14	16	Training	4.24	4.2696	0.0296
15	17	Training	4.29	4.2882	-0.0018

16	18	Training	4.22	4.2972	0.0772
17	19	Training	4.31	4.3509	0.0409
18	20	Training	4.44	4.3882	-0.0518
19	21	Prediction	4.41	4.0794	-0.3306
20	22	Prediction	4.7	4.3578	-0.3422
21	23	Training	4.78	4.8211	0.0411
22	24	Training	4.83	4.8231	-0.0069
23	25	Training	4.78	4.7482	-0.0318
24	26	Training	4.46	4.4201	-0.0399
25	27	Prediction	4.62	4.3779	-0.2421

Stepwise procedure for generation of GA-MLR based QSAR Modeling

Structure drawing, optimization and calculations of molecular descriptors

All structures of substituted 25 molecules were drawn using ChemBioDraw V.12.1. Furthermore, these 2D- structures were then converted to 3D- forms using the Chem3Dpro tool. Then, the MMFF94 force field was used for the optimization of all structures using TINKER. Open3DAlign was incorporated for alignments of the dataset molecules. Finally, PaDEL and ChemDes (a free web-based platform) were used for the calculations of molecular descriptors.

Pruning of molecular descriptors

It is important to note that pruning of molecular descriptors is a key step while developing QSAR models as PaDEL and ChemDes would provide more than >20,000 molecular descriptors including 1D- to 3D- for each molecule. Thus, the objective feature selection module from QSARINS ver. 2.2.2 was employed to exclude descriptors with high co-linearity ($|r| > 0.90$) and nearly constant ($> 95\%$) values. This avoided the inclusion of multi-collinear and spurious variables in GA-MLR models (the genetic algorithm–multi-linear regression models). At the end of the descriptor pruning step, we retained a dataset with **1394** molecular descriptors covering mono-dimensional (1D-), bi-dimensional (2D-) and three-dimensional (3D-) descriptor spaces (including but not limited to fingerprint, atom-pair and other molecular descriptors). Moreover, to avoid difficulty in QSAR model interpretations, we have removed various esoteric descriptors (the descriptors for which an exact explanation is not available) in the very next step.

QSAR model building

For the developments of statistically robust GA-MLR-based QSAR models, we utilized a popular QSARINS software. All derived models were then subjected to thorough external as well as internal statistical validations, Y-randomization and applicability domain analysis. These validations were carried out as per the OECD principles. The OECD principles followed for the developments of good statistical models are mentioned below:

(1) For the QSAR model developments, we first divided our dataset randomly using the random splitting option of QSARINS into training and test sets, i.e., prediction set. The splitting of datasets into a training and test set were carried out using well-established approaches of 70%, training set :30%, prediction set. Then, these training sets were used for the building of QSAR models, while prediction sets were employed for the external validation's parameters. We had also carried out the multiple splitting of dataset molecules in such a way that, every molecule would become part of training or test set during QSAR model developments. This technique ensured that maximum number and information was gained through molecular descriptors impacting or affecting biological potential/ activity.

1. While developing the GA-MLR-based QSAR models, we have kept all default settings available in QSARINS with Q^2_{LOO} as a selected fitness function. Furthermore, we noted that the value of Q^2_{LOO} was increased up to 4 variables, however after four variables, Q^2_{LOO} had only minor increments in it. Thus, models having 1-4 variables with best-selected fitness functions were further selected and analysed to avoid over-fitting issues. The values for the descriptors mentioned in our best QSAR models are available in the supporting information.

QSAR model validation

All our developed models were thoroughly validated using OECD principles of internal and external validations, Y-randomization and AD analysis. The statistical robustness and strength of QSAR model is based on (1) using external validation; (2) Y-randomization (or Y-scrambling); (3) internal validation based on leave-one-out (LOO) and leave-many-out (LMO) procedure (i.e., cross-validation (CV)); and (4) fulfilling of respective threshold values for the statistical parameters as follows:

$r^2_{\text{ex}} \geq 0.6$, $\text{RMSE}_{\text{tr}} < \text{RMSE}_{\text{cv}}$, $\Delta K \geq 0.05$, $Q^2\text{-F}^n \geq 0.60$, $r^2_{\text{tr}} \geq 0.6$, $Q^2_{\text{loo}} \geq 0.5$, $Q^2_{\text{LMO}} \geq 0.6$, $r^2 > Q^2$, $r^2_{\text{m}} \geq 0.6$, $\text{CCC} \geq 0.80$, $(1-r^2/r_o^2) < 0.1$, $0.9 \leq k \leq 1.1$ or $(1-r^2/r_o^2) < 0.1$, $0.9 \leq k' \leq 1.1$, $|r_o^2 - r_o'^2| < 0.3$, RMSE and MAE closer to zero. It is thus, noted that any of models unable to satisfy these criteria should be omitted.