

Supplementary Material

Synthetic strategies and structure-activity relationships of 2-chloro-tetrahydrocarbazolones: privileged organic scaffolds targeting polyketide synthase 13 for antitubercular activity

Priyanka Sanjay Waghmare^a, Anuruddha Rajaram Chabukswar^{*a}, Samidha Sameer Bag^a, Pratik Sanjay Manka^a, and Swati Changdeo Jagdale^a

^a Department of Pharmaceutical Sciences, School of Health Sciences and Technology, Dr. Vishwanath Karad MIT-World Peace University, Kothrud, Pune, Maharashtra, India- 411038
Email: anuruddha.chabukswar@mitwpu.edu.in

Table of Contents

Spectral Data.....	S2
¹ H NMR Spectra (Figures S1–S8)	
IR Spectra (Figures S9–S12)	
¹ H NMR Spectra (Figures S13–S16)	
¹³ C NMR spectra (Figures S17-S20)	
HRMS Spectra (Figures S21–S24)	
Molecular docking (Figure S25 and Table S1).....	S14
Antitubercular activity (Figure S26 and Table S3).....	S14
PreADMET study (Table S3)	S16

A 1

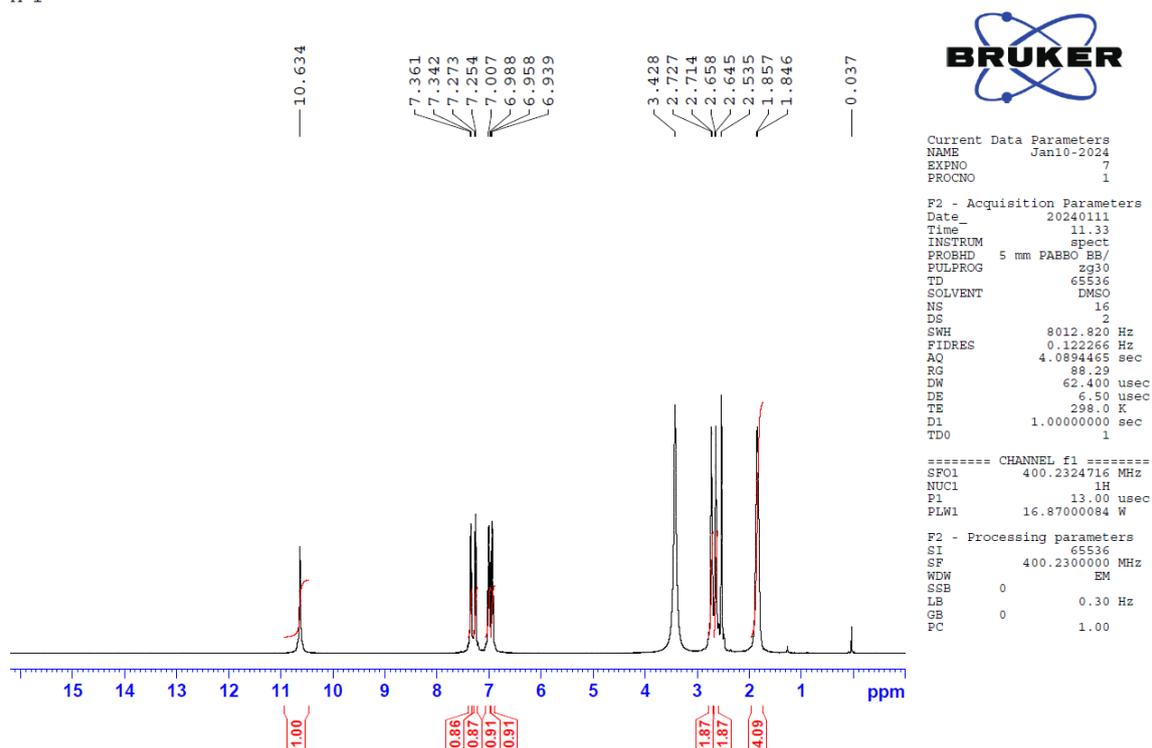


Figure S1. ¹H NMR of 1.

B 1

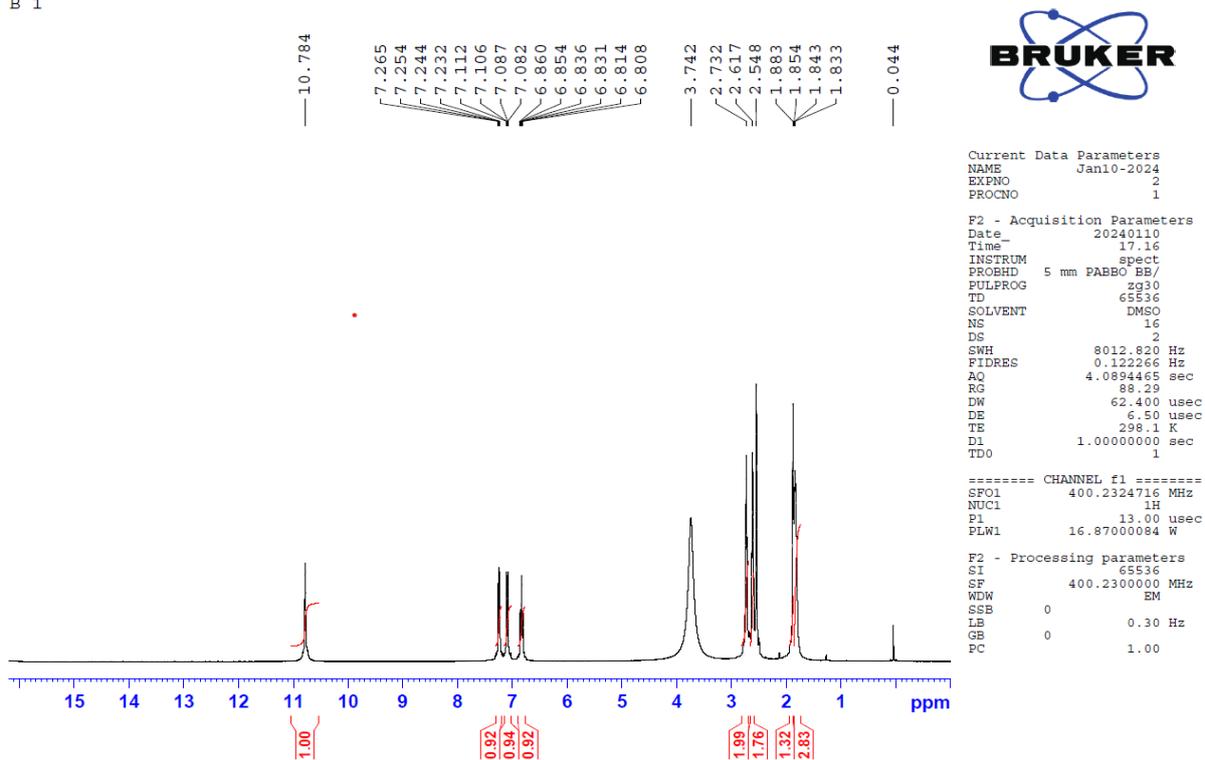
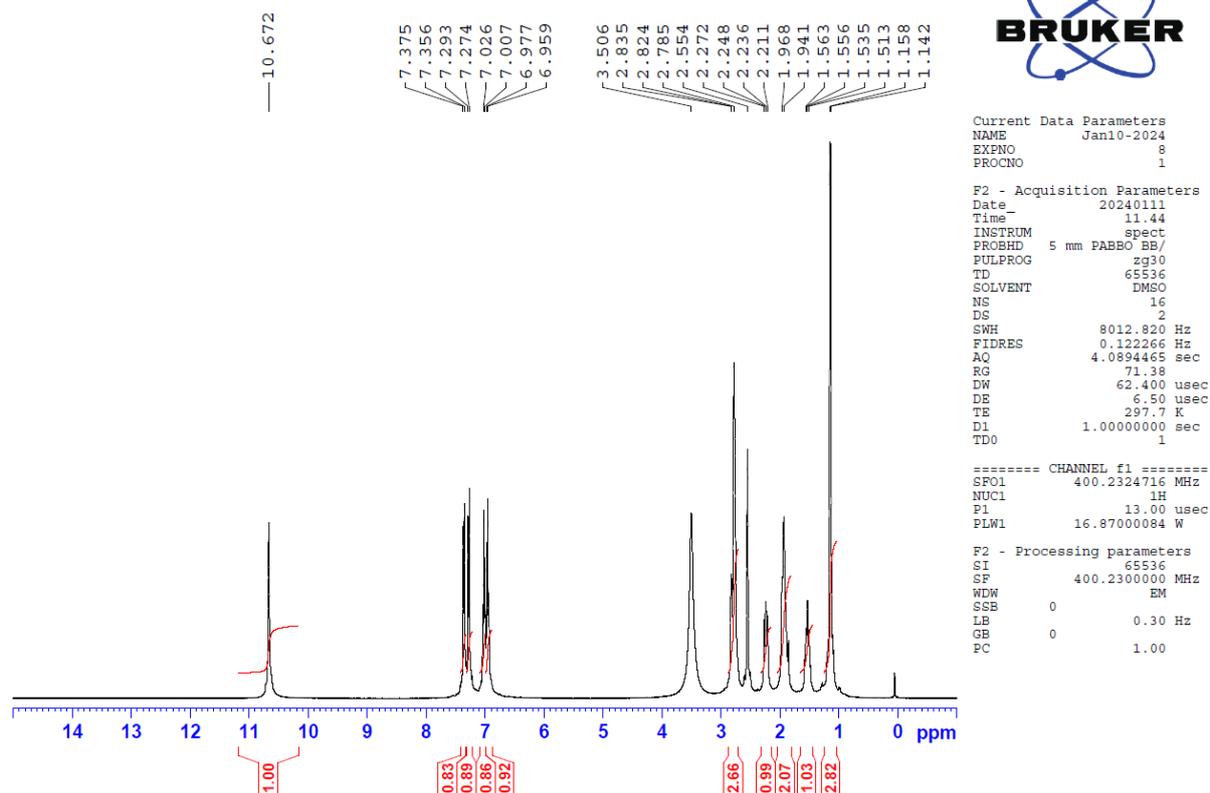
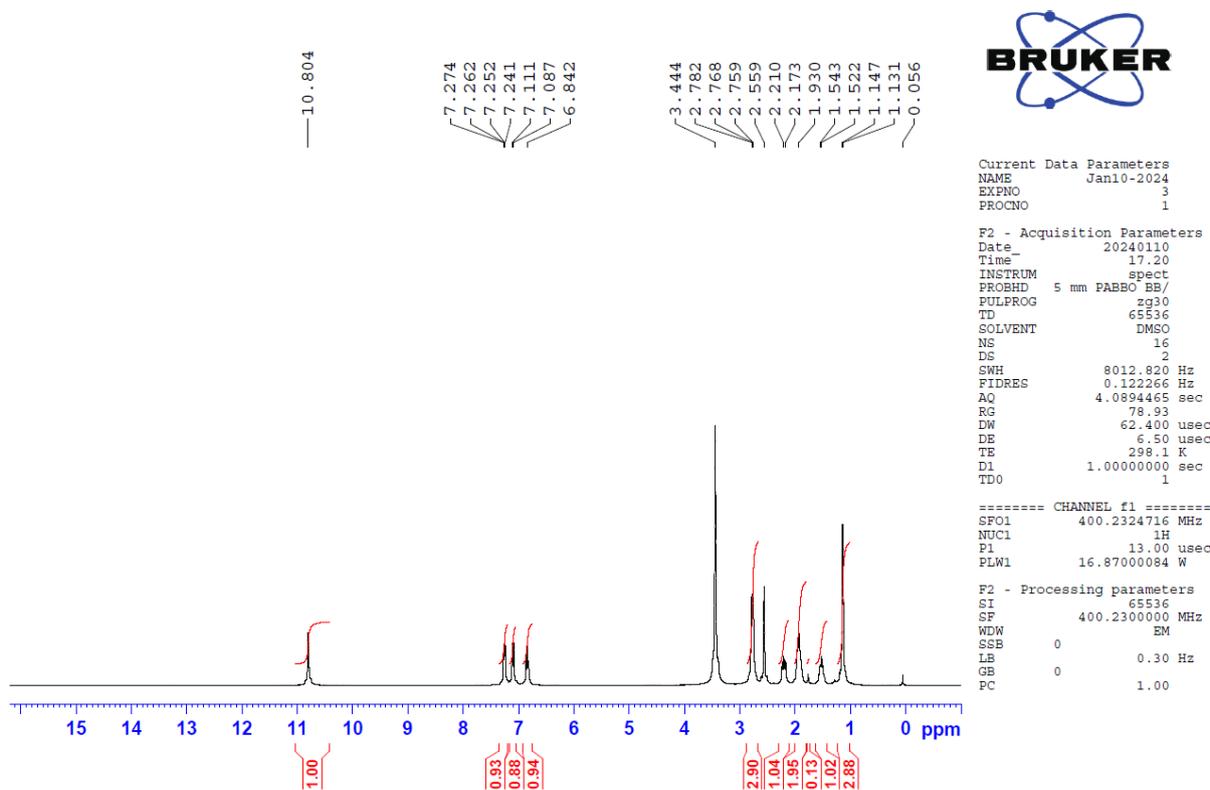


Figure S2. ¹H NMR of 2.

C 1

Figure S3. ¹H NMR of 3.

D 1

Figure S4. ¹H NMR of 4.

A 2

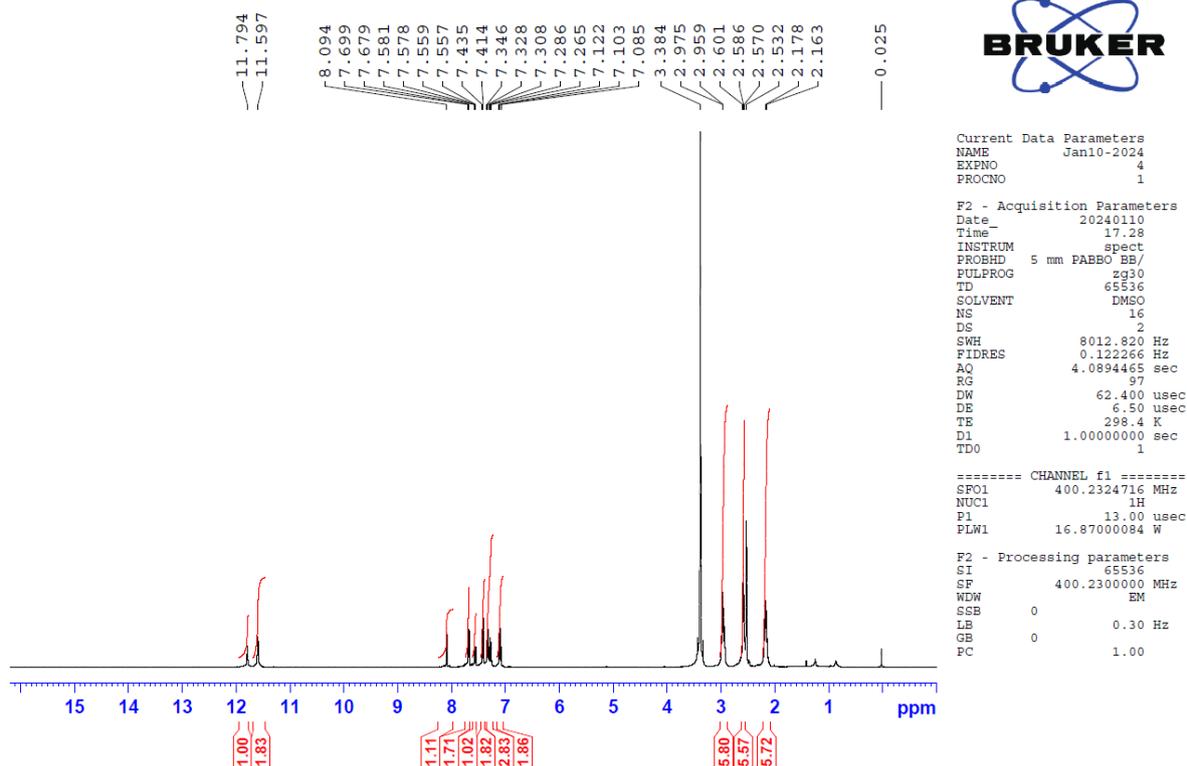


Figure S5. ¹H NMR of 5.

B 2

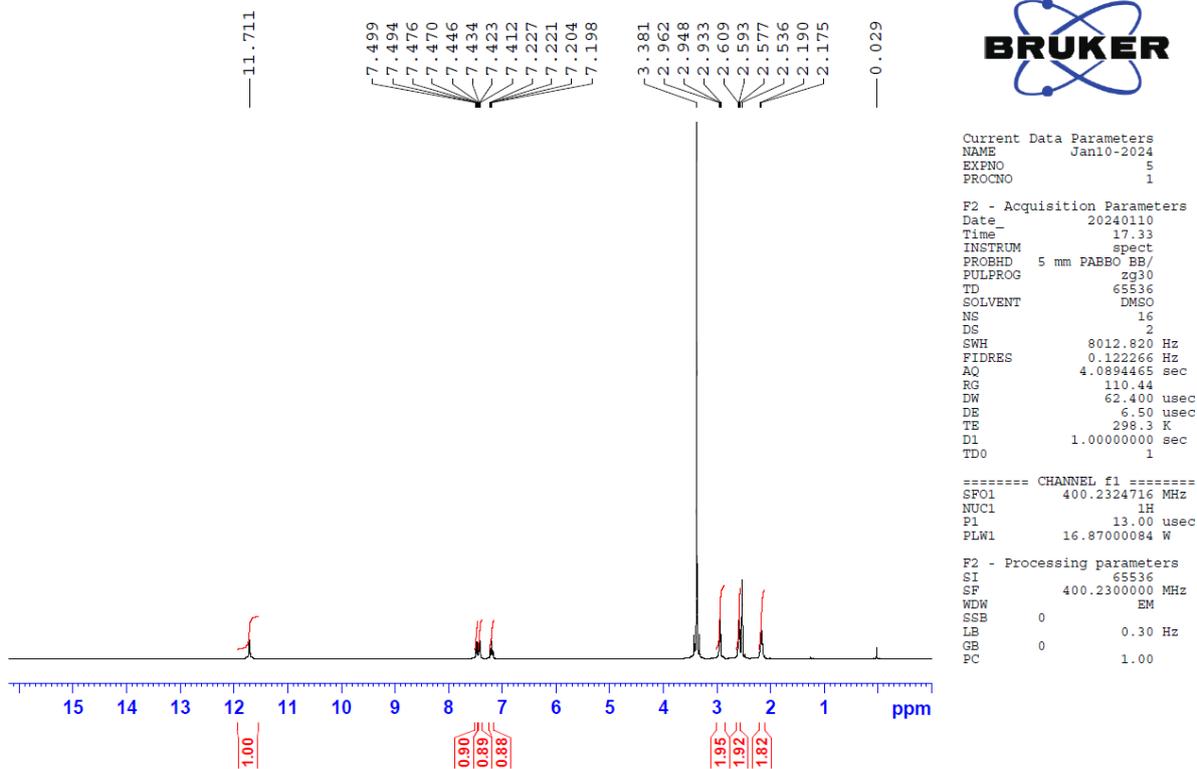


Figure S6. ¹H NMR of 6.

C 2

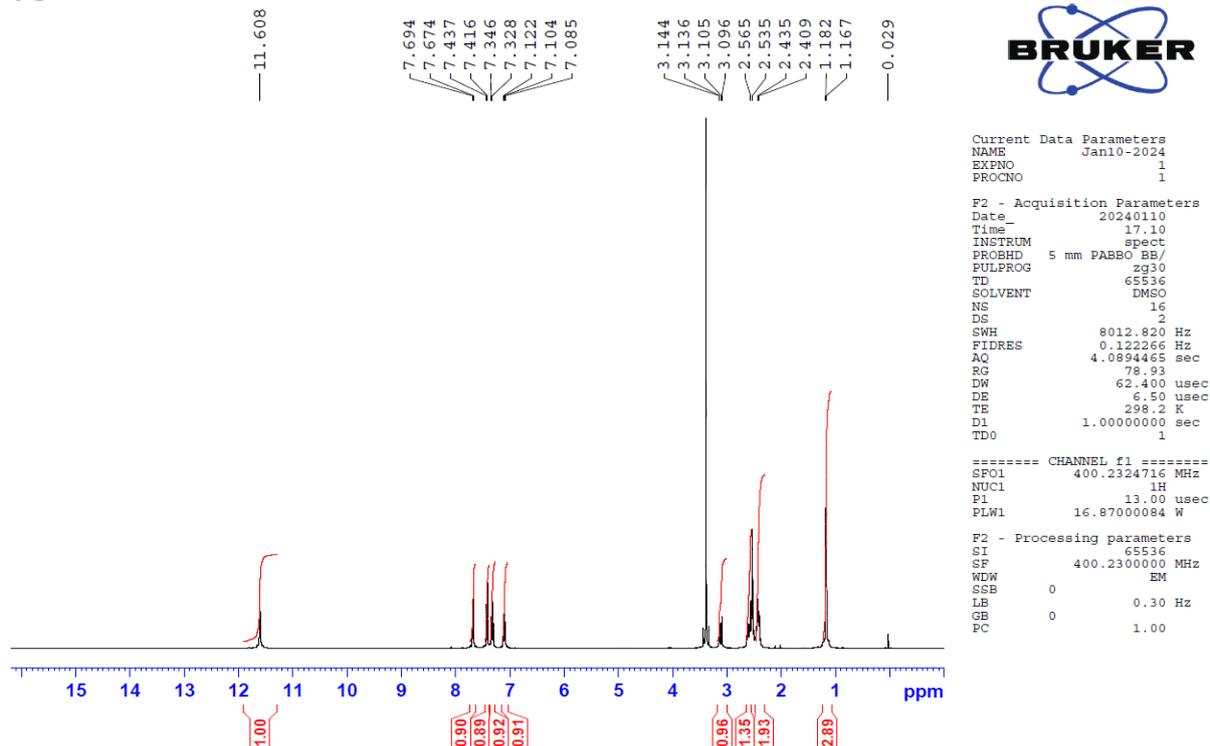


Figure S7. ¹H NMR of 7.

D 2

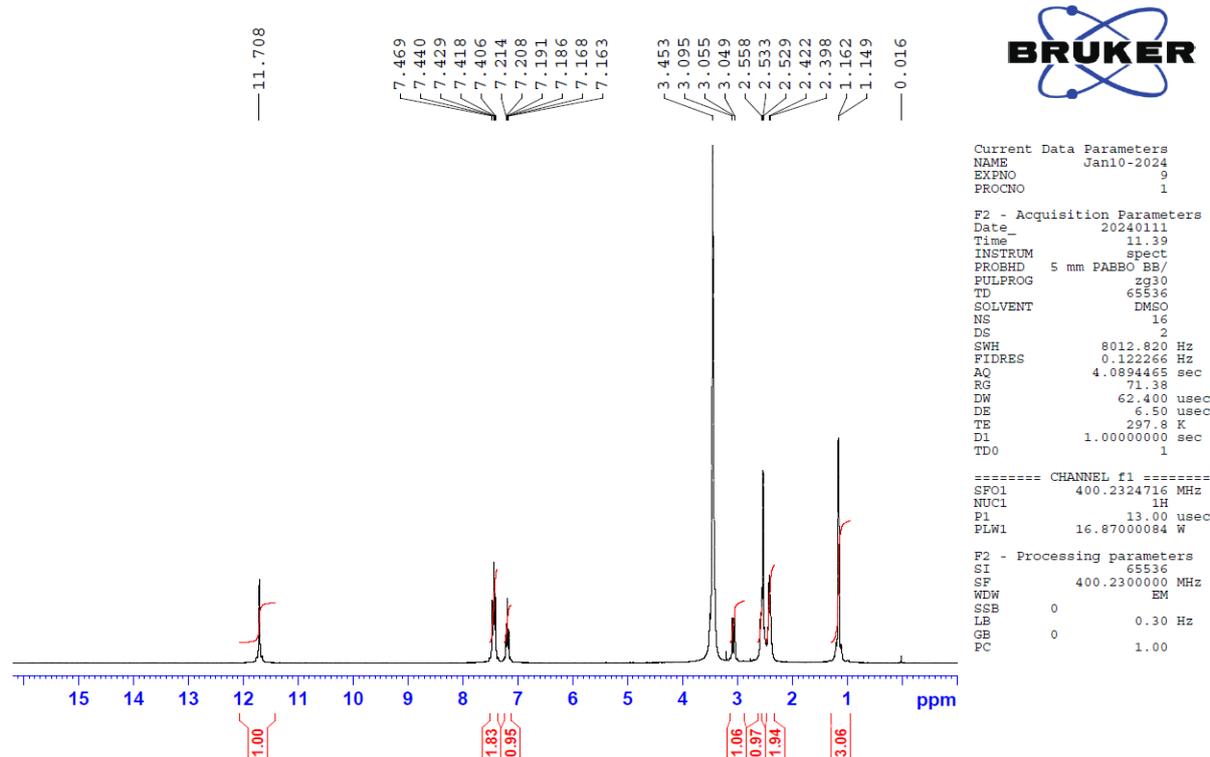


Figure S8. ¹H NMR of 8.

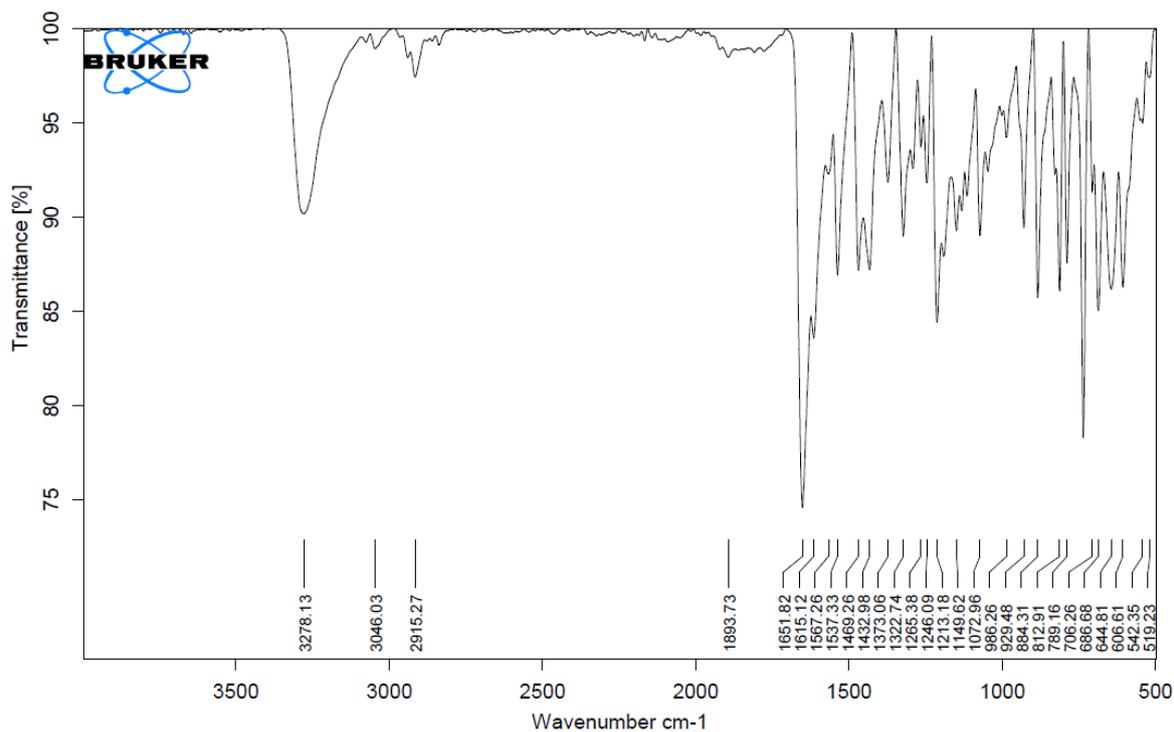


Figure S9. IR of 9.

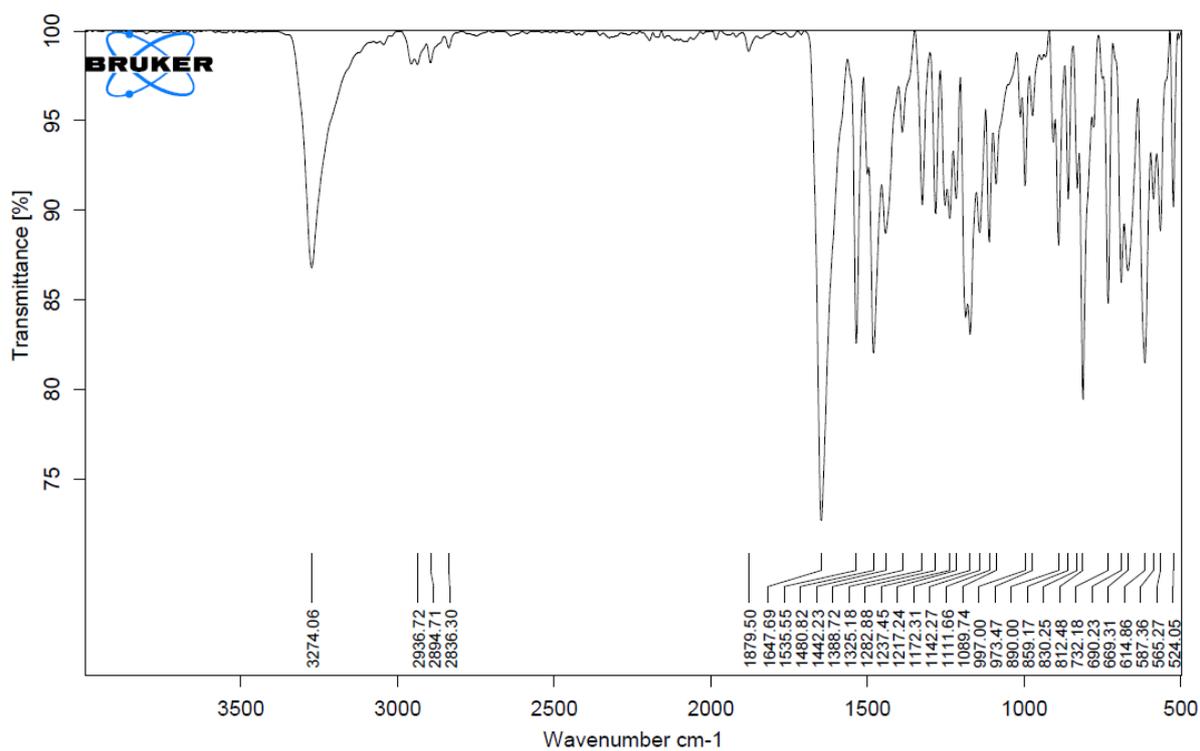


Figure S10. IR of 10.

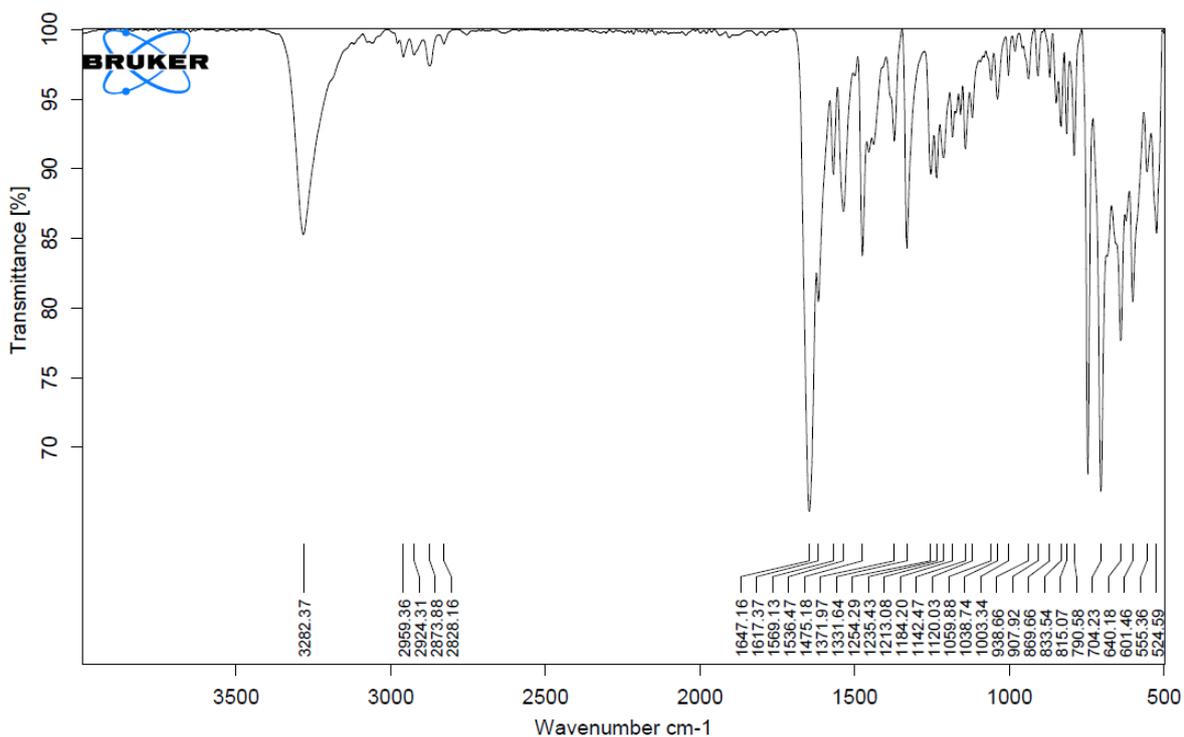


Figure S11. IR of 11.

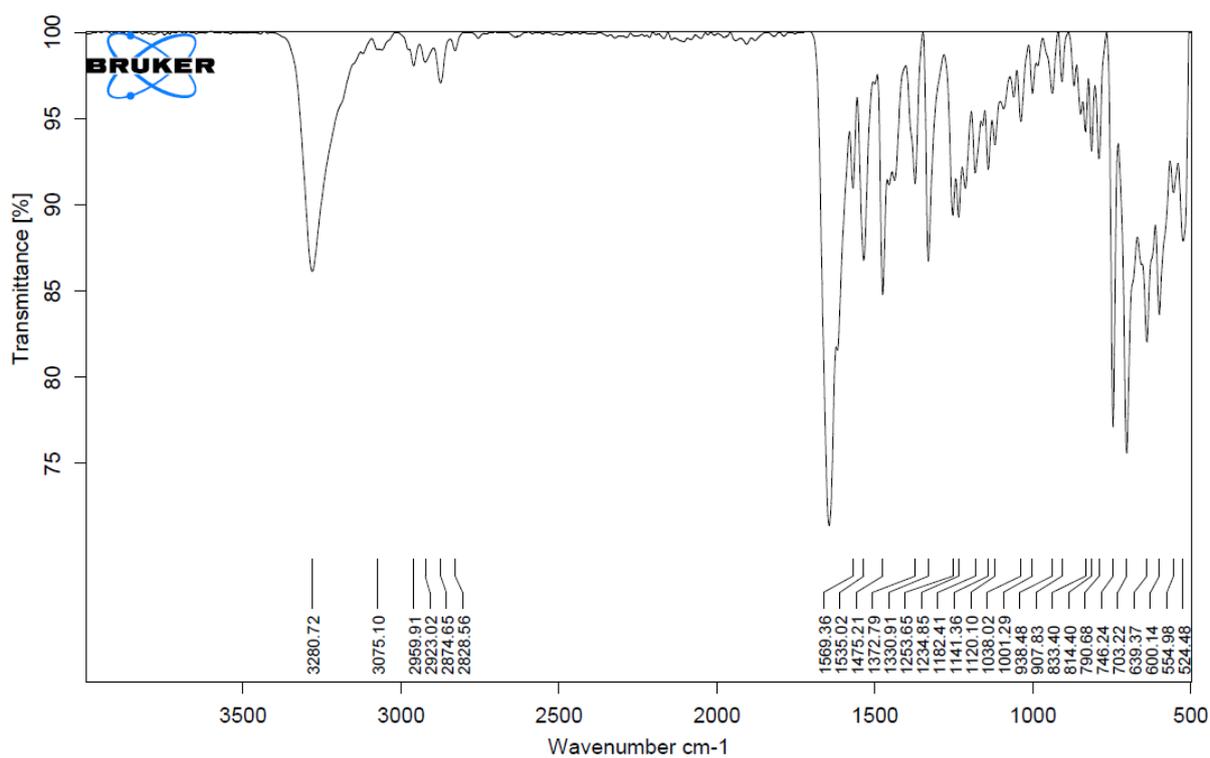


Figure S12. IR of 12.

A 3

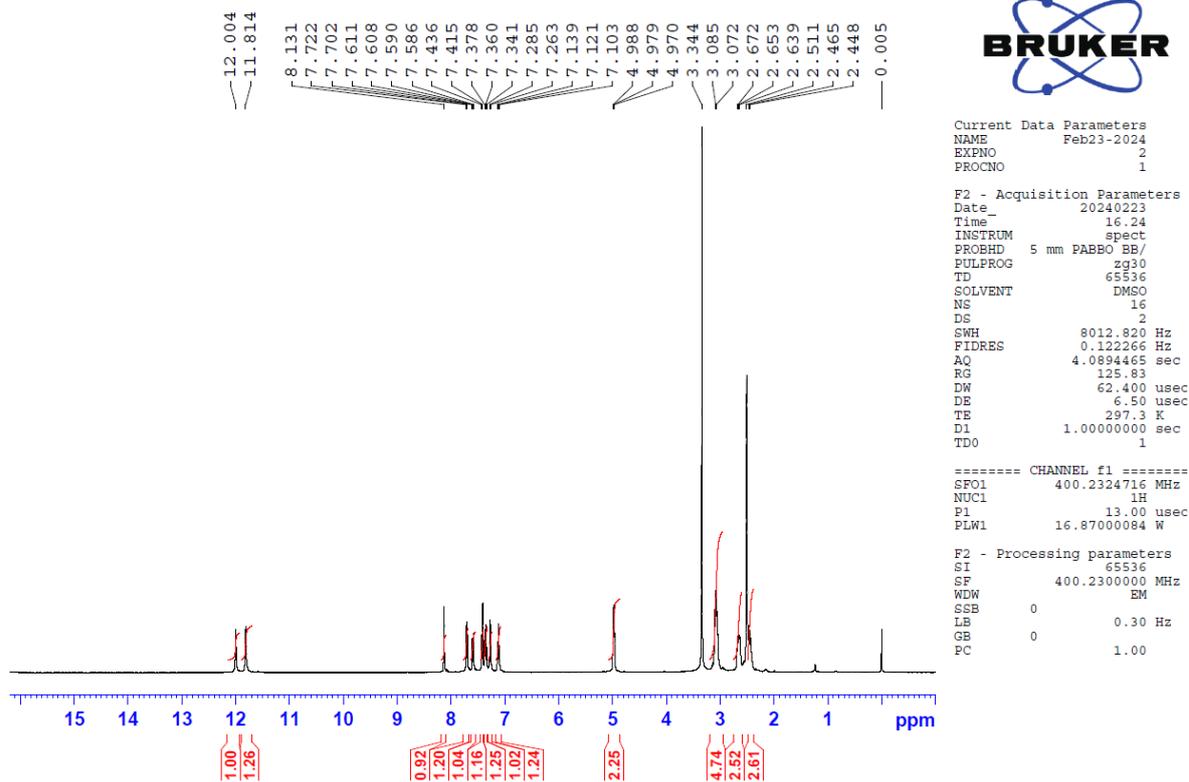


Figure S13. ¹H NMR of 9.

B 3

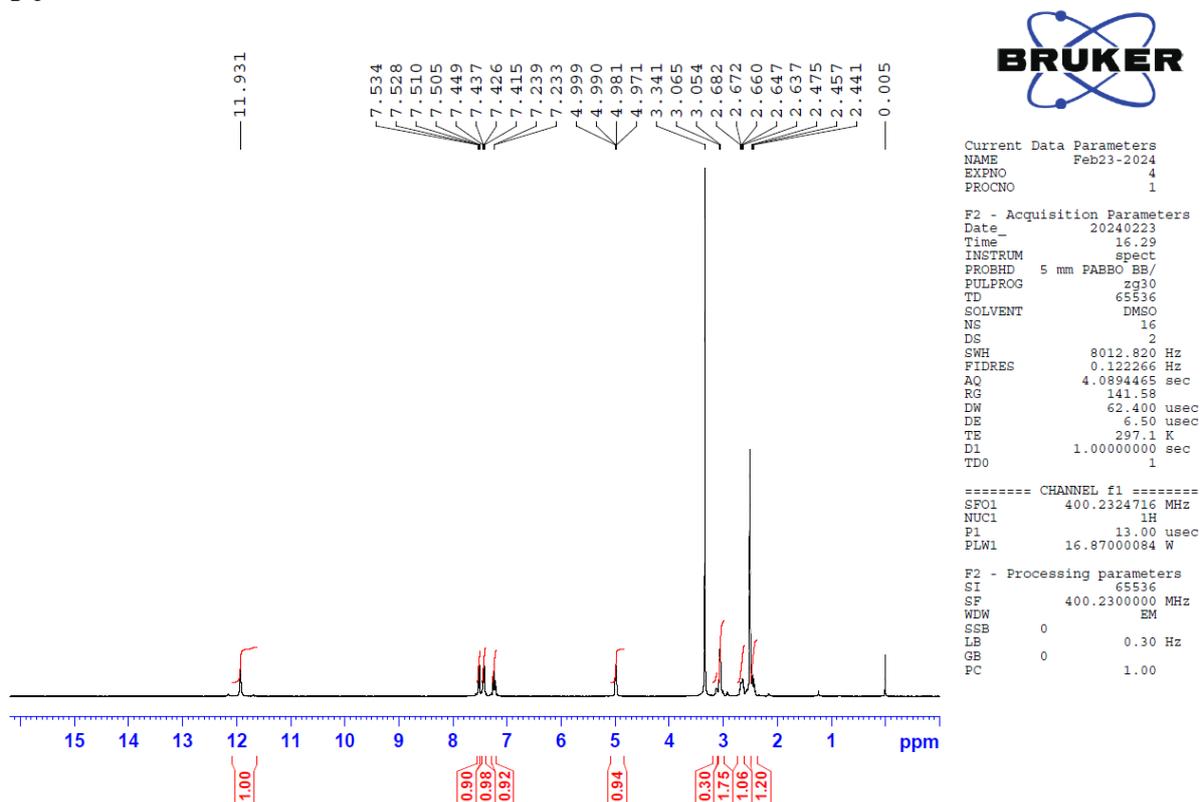


Figure S14. ¹H NMR of 10.

C 3

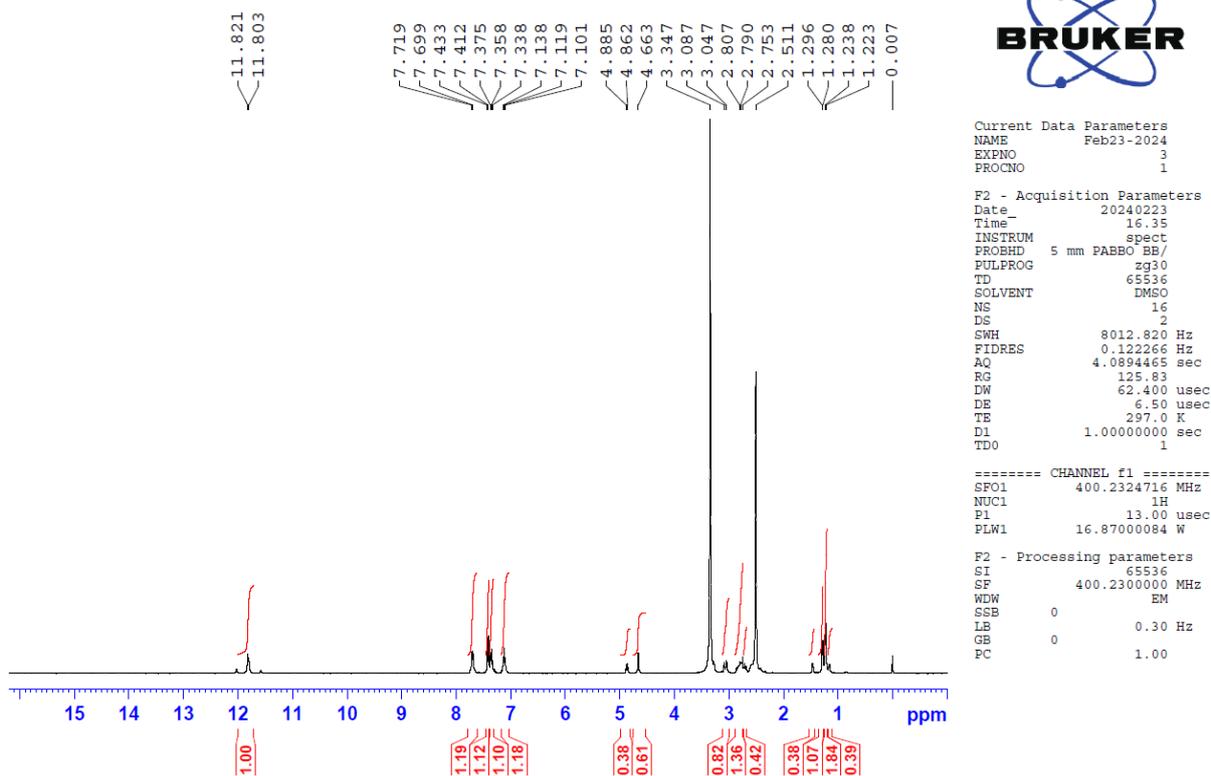


Figure S15. ¹H NMR of 11.

D 3

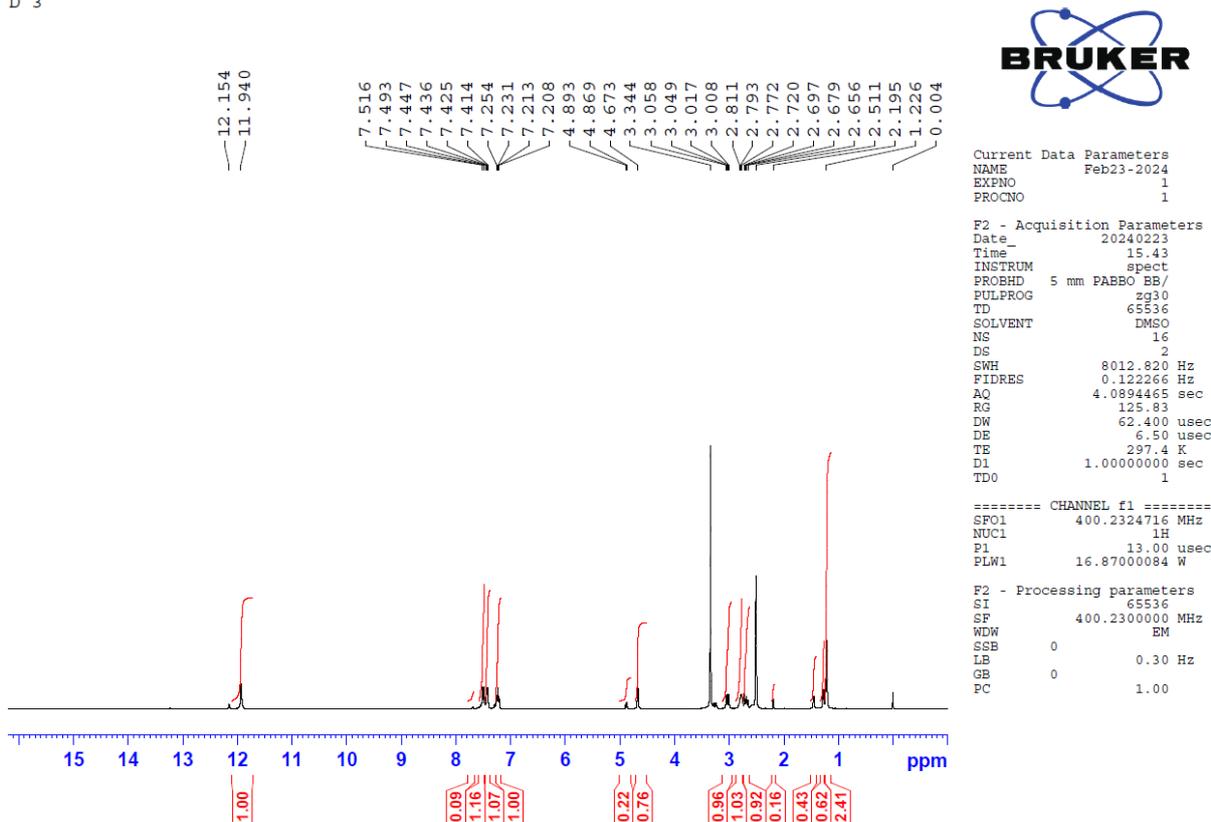
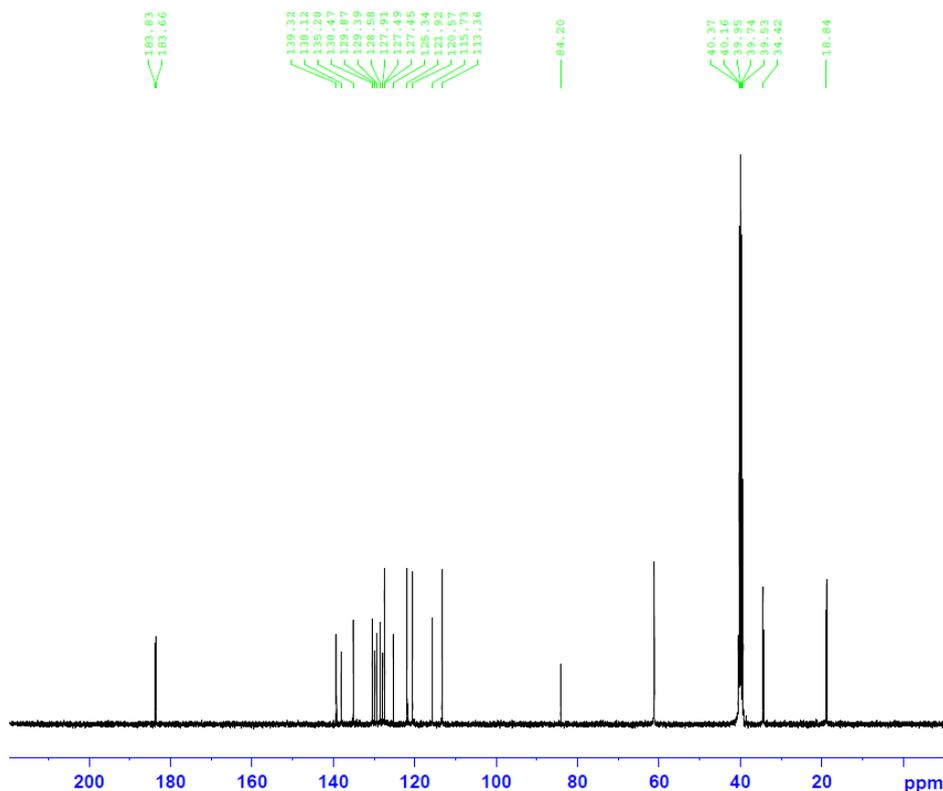


Figure S16. ¹H NMR of 12.

A 3 - 9



```

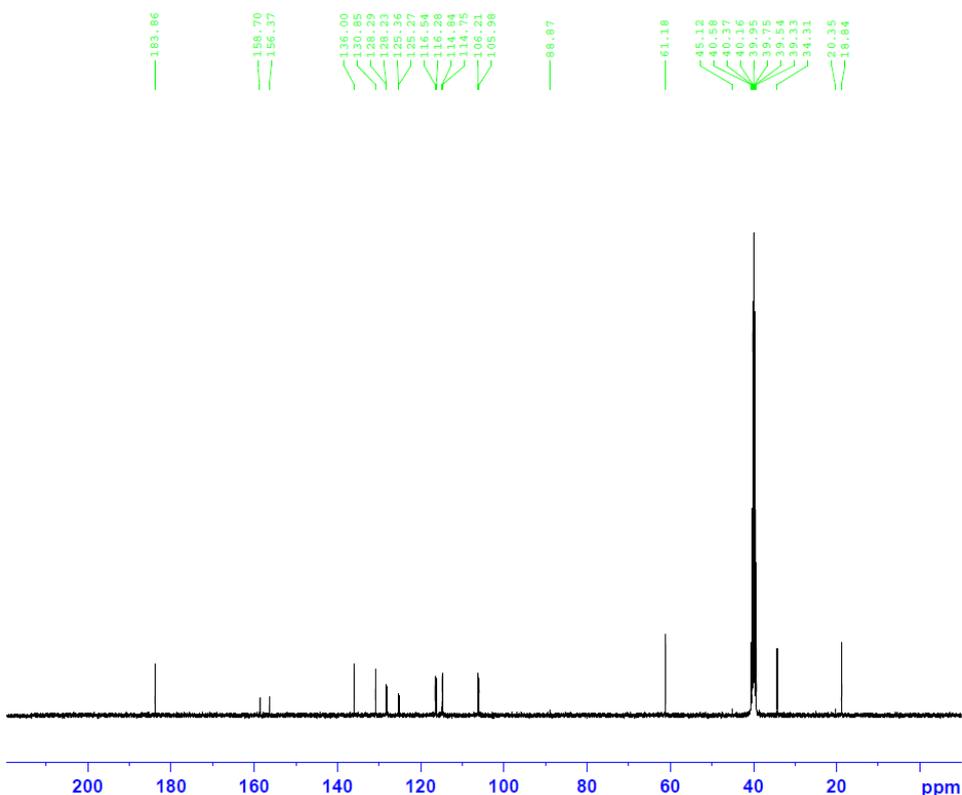
Current Data Parameters
NAME Jun09-2025
EXPNO 1
PROCNO 1

F2 - Acquisition Parameters
Date 20250609
Time 12.00 h
INSTRUM spect
PROBHD Z108618_0837 (
PULPROG zgpg30
TD 65536
SOLVENT DMSO
NS 514
DS 4
SWH 24038.461 Hz
FIDRES 0.733596 Hz
AQ 1.3631488 sec
RG 199.8
DW 20.800 usec
DE 6.50 usec
TE 295.9 K
D1 2.00000000 sec
D11 0.03000000 sec
TDO 1
SFO1 100.6479773 MHz
NUC1 13C
PQ 3.27 usec
P1 9.80 usec
PLW1 70.75000000 W
SFO2 400.2316009 MHz
NUC2 1H
CPDPRG2 waltz65
PCPD2 90.00 usec
PLW2 16.87000084 W
PLW12 0.35198000 W
PLW13 0.17704000 W

F2 - Processing parameters
SI 32768
SF 100.6379135 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40
    
```

Figure S17. ¹³C NMR of 9.

B 3 - 10



```

Current Data Parameters
NAME Jun09-2025
EXPNO 3
PROCNO 1

F2 - Acquisition Parameters
Date 20250609
Time 12.47 h
INSTRUM spect
PROBHD Z108618_0837 (
PULPROG zgpg30
TD 65536
SOLVENT DMSO
NS 557
DS 4
SWH 24038.461 Hz
FIDRES 0.733596 Hz
AQ 1.3631488 sec
RG 199.8
DW 20.800 usec
DE 6.50 usec
TE 297.0 K
D1 2.00000000 sec
D11 0.03000000 sec
TDO 1
SFO1 100.6479773 MHz
NUC1 13C
PQ 3.27 usec
P1 9.80 usec
PLW1 70.75000000 W
SFO2 400.2316009 MHz
NUC2 1H
CPDPRG2 waltz65
PCPD2 90.00 usec
PLW2 16.87000084 W
PLW12 0.35198000 W
PLW13 0.17704000 W

F2 - Processing parameters
SI 32768
SF 100.6379135 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40
    
```

Figure S18. ¹³C NMR of 10.

C 3 - 11

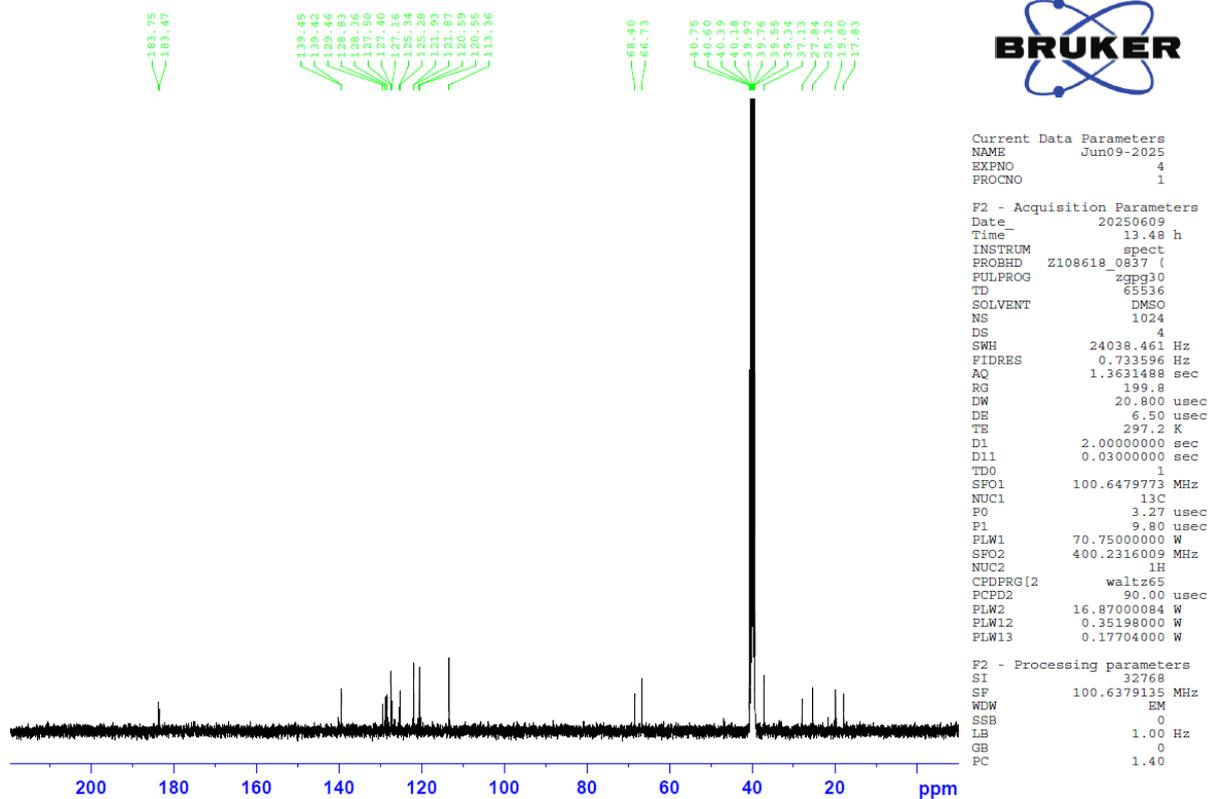


Figure S19. ¹³C NMR of 11.

D 3 - 12

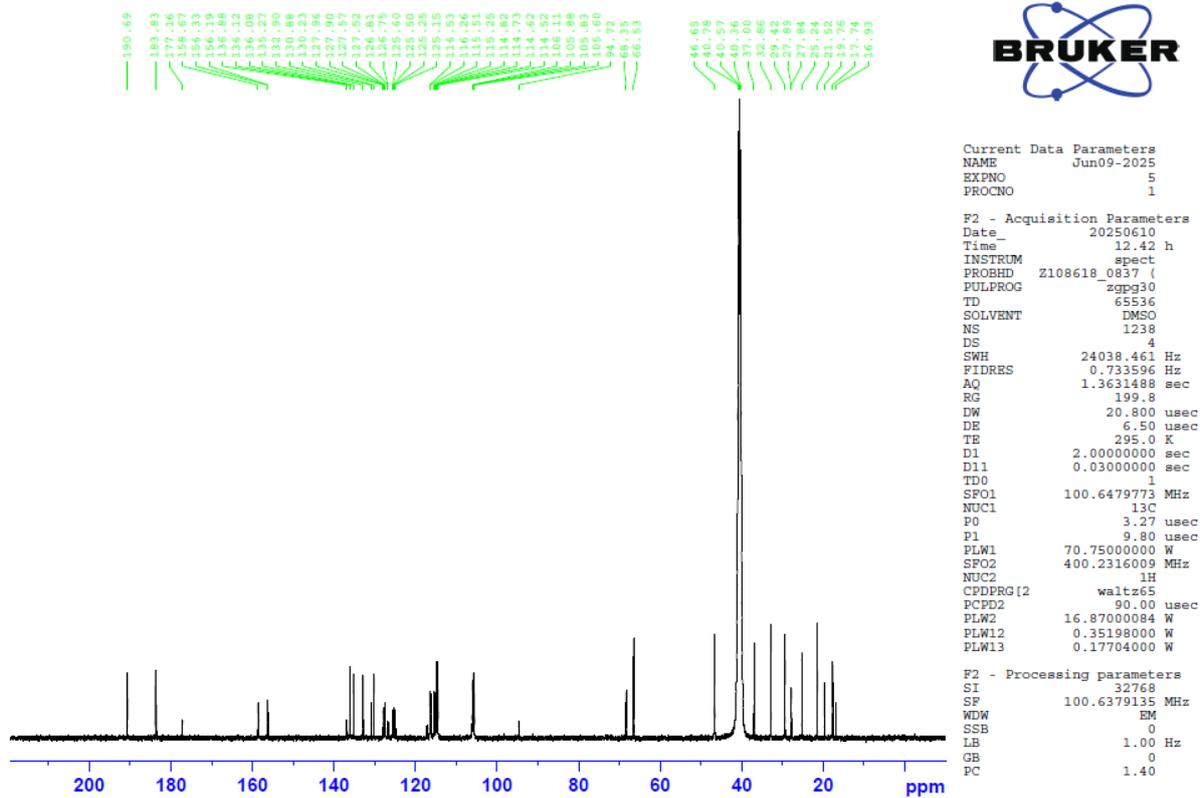


Figure S20. ¹³C NMR of 12.

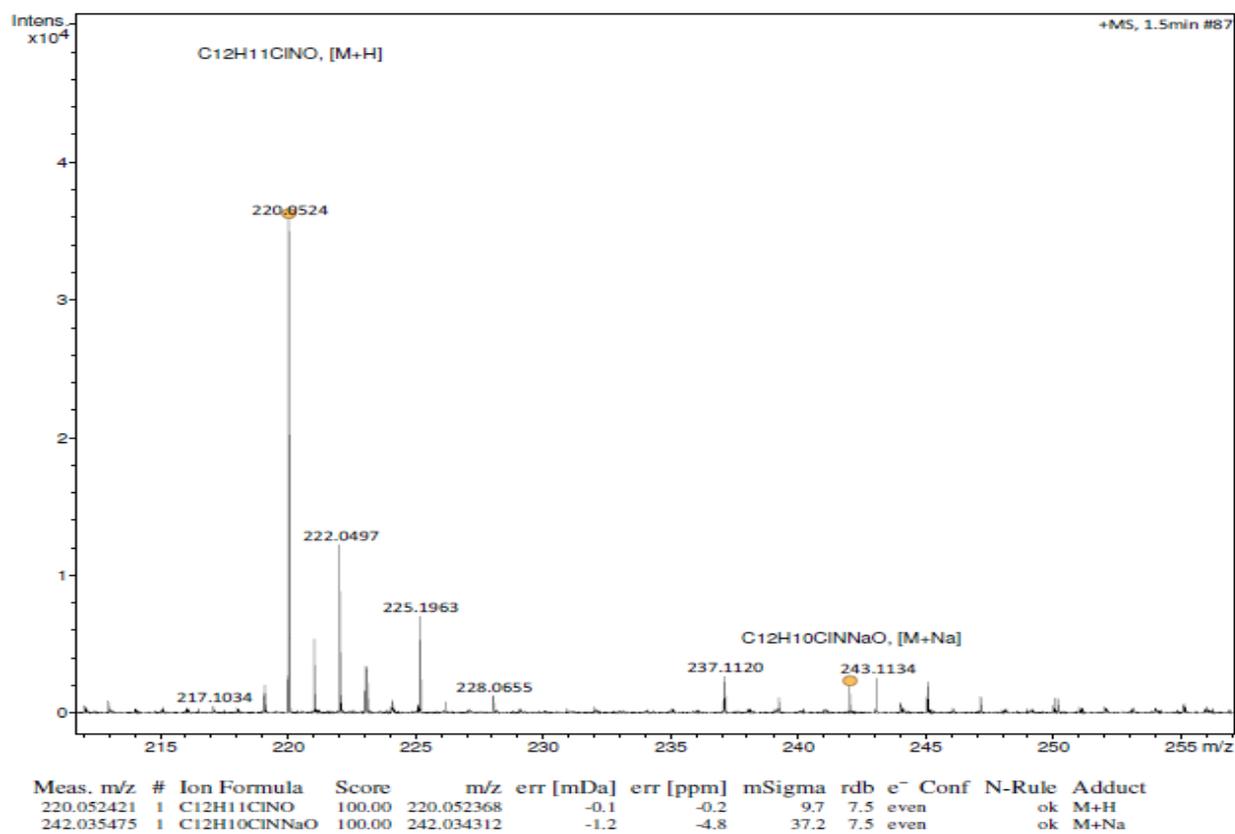


Figure S21. HRMS of 9.

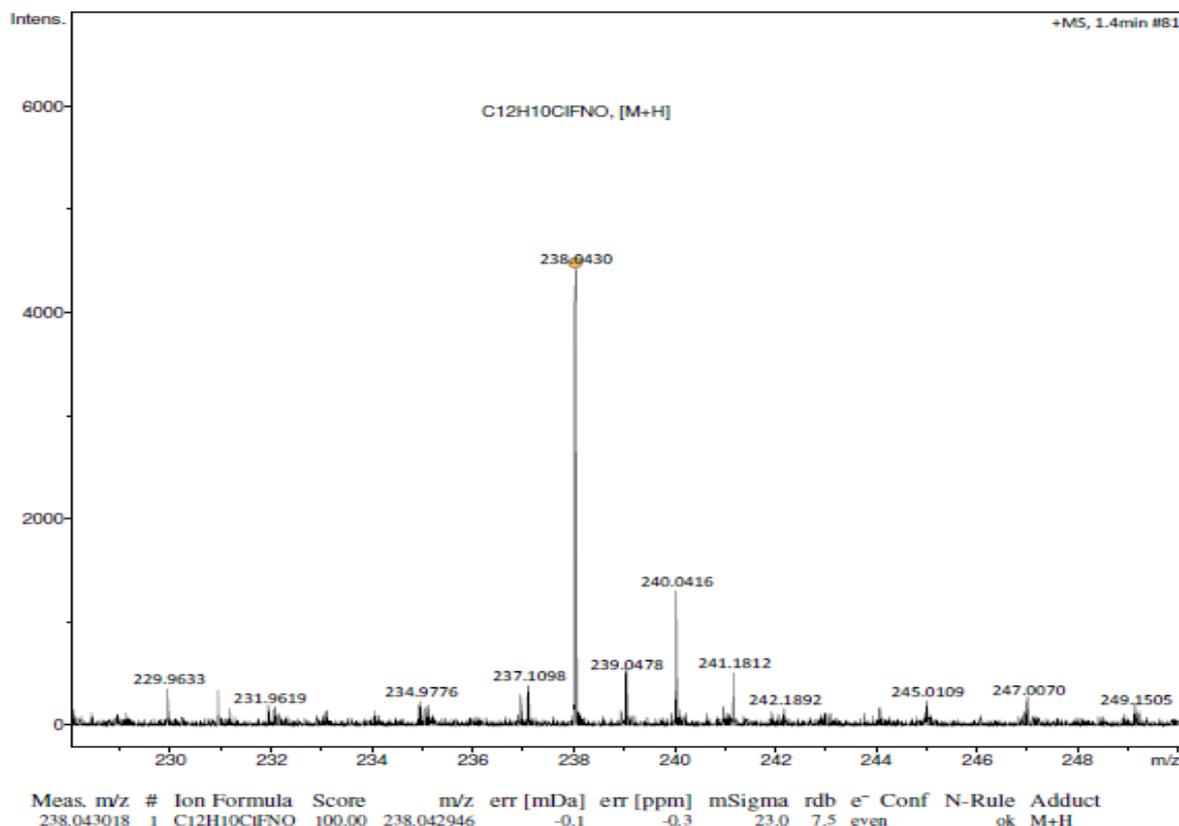


Figure S22. HRMS of 10.

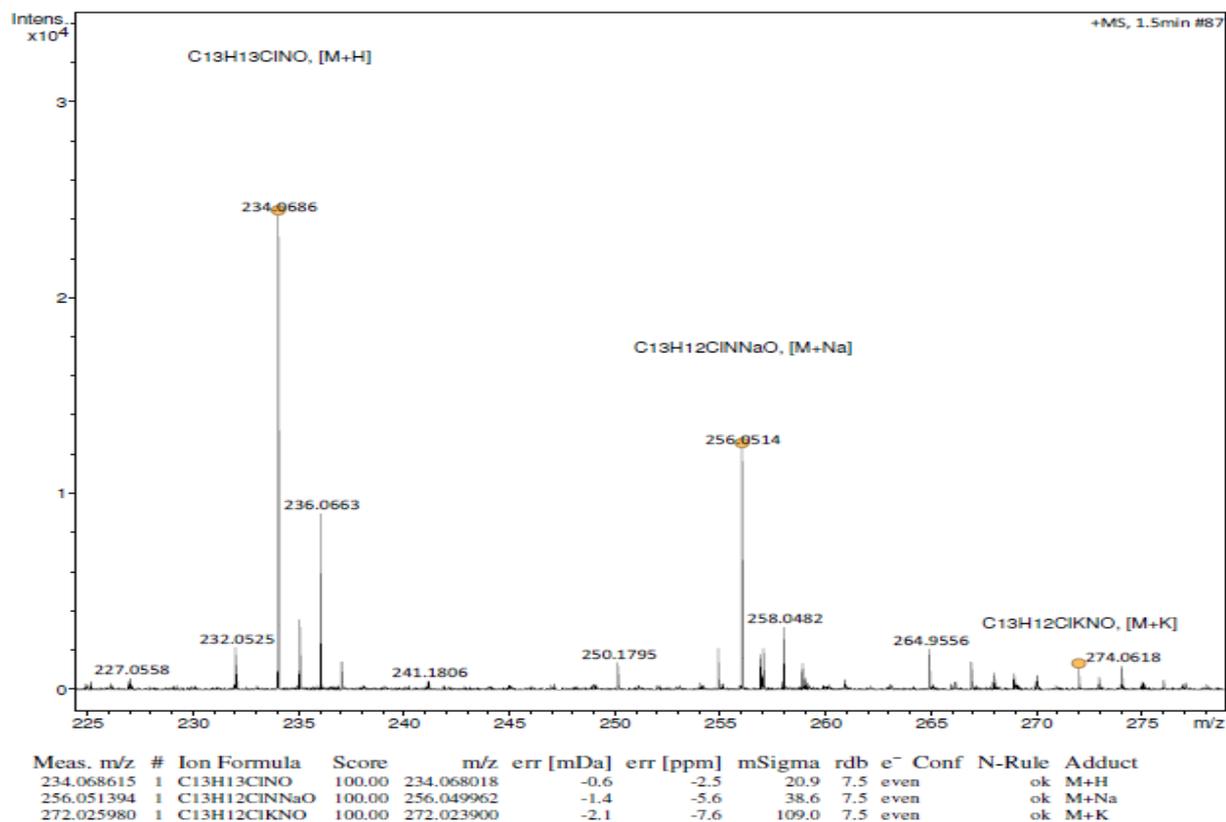


Figure S23. HRMS of 11.

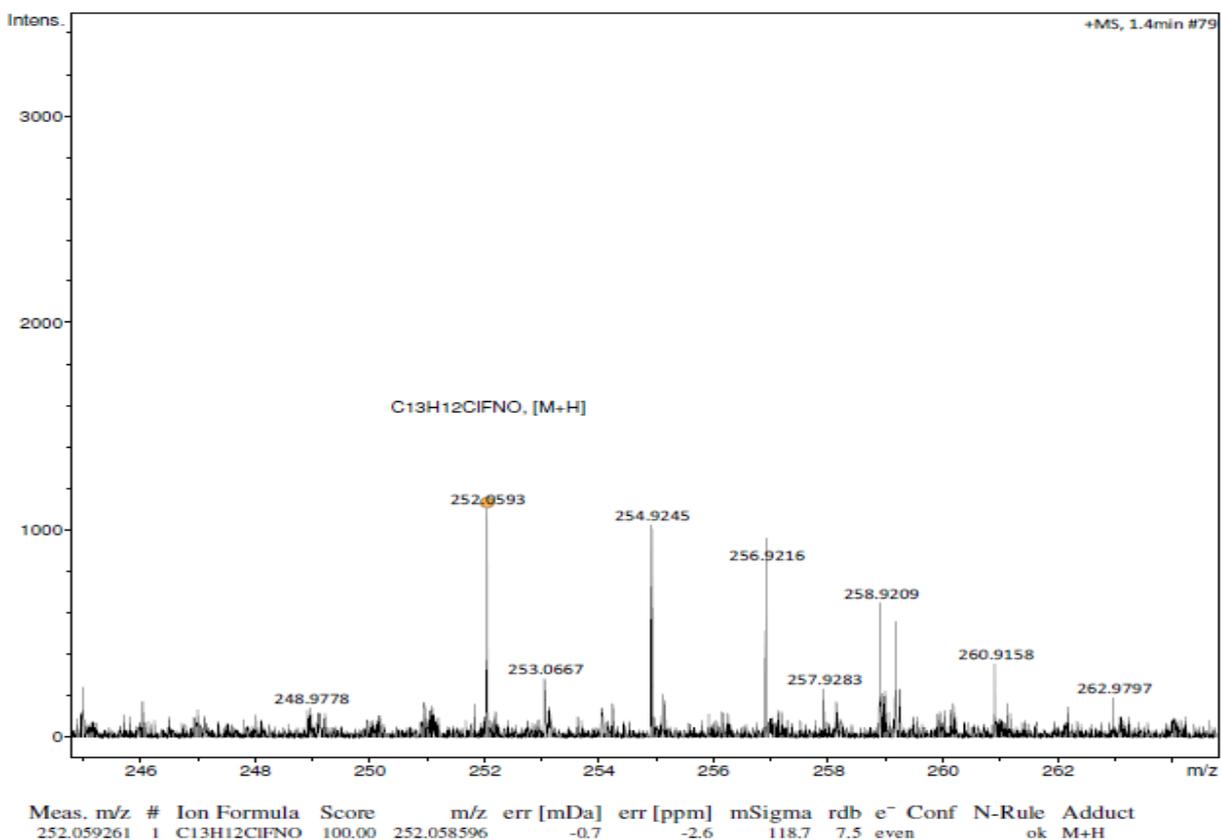


Figure S24. HRMS of 12.

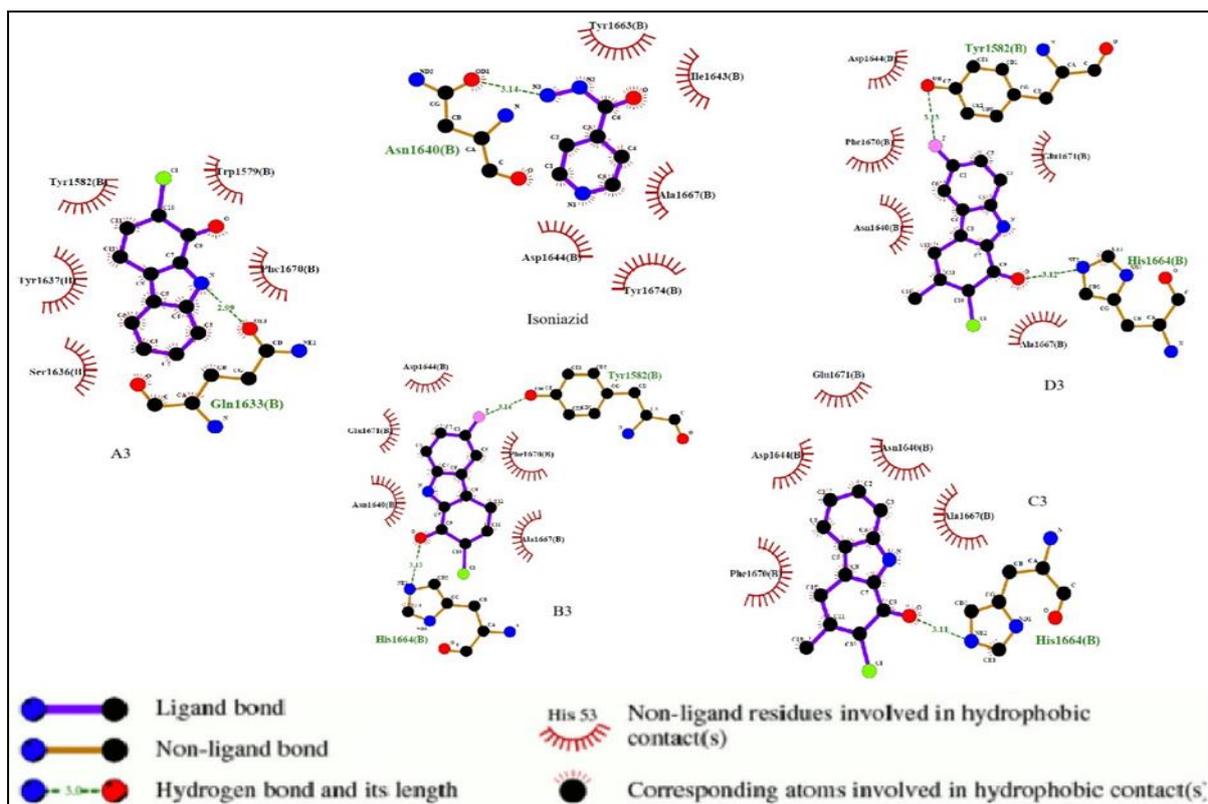


Figure S25. 2D interaction image of Isoniazid, 9(A3), 10(B3), 11(C3) and 12(D3).

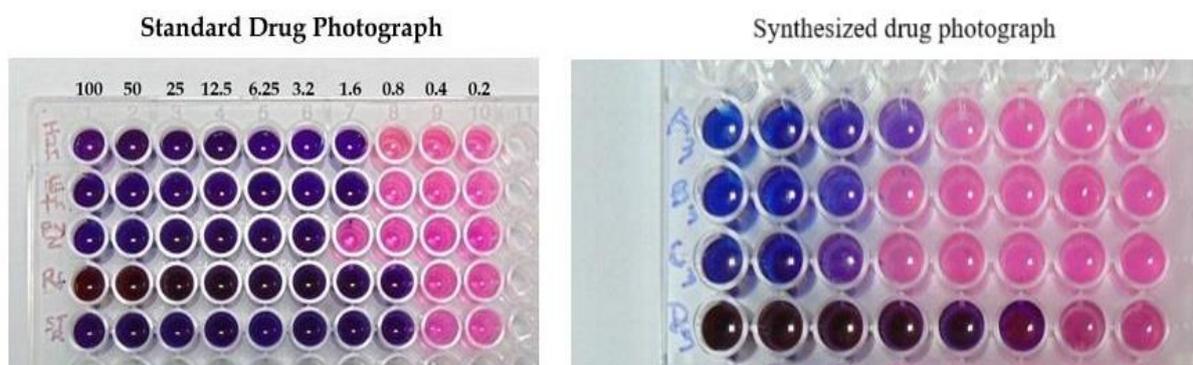


Figure S26. Image for MABA assay of antitubercular standard drug and synthesized drugs (9-12).

Table S1. Molecular Docking of derivatives on Pks 13 (PDB ID: 5V3Y)

Sr. No.	Compound code	Docking score (Kcal/mol)	H-bond interaction with distance	Other interaction
1	INH	-5.9	ASN1640 (3.14Å)	TYR1663, ALA1667, TYR1674, ASP1644, ILE1643
2	9	-8.0	GLN1633 (2.99Å)	TYR1637, SER1636, PHE1670, TYR1582, TRP1579
3	10	-8.3	HIS1664 (3.13Å), TYR1582 (3.14Å)	ASN1640, ALA1667, PHE1670, ASP1644, GLU1671
4	11	-8.4	HIS1664 (3.11Å)	ALA1667, ASN1640, GLU1671, ASP1644, PHE1670
5	12	-8.8	HIS1664 (3.12Å), TYR1582 (3.18Å)	ALA1667, ASN1640, PHE1670, ASP1644, GLU1671

Table S2. PreADMET Study of predicted analogues

Sr. No.	Parameters	9	10	12	13
1	CRV	0	0	0	0
2	MDDRV	1	1	1	1
3	RFV	0	0	0	0
4	MW	219.67	237.66	233.69	251.68
5	GI absorption	High	High	High	High
6	ClogP	2.75	3.06	2.98	3.3
7	BBB	Yes	Yes	Yes	Yes
8	CaCO ₂	7.68436	33.8423	35.3545	36.6872
9	HIA%	93.144571	93.147361	93.28796	93.293013
10	PPB%	100	96.60791	100	100
11	H-bond acceptor	1	2	1	2
12	H-bond donor	1	1	1	1
13	Rotatable bonds	0	0	0	0
14	Hepatotoxicity	Inactive	Inactive	Inactive	Inactive
15	Carcinogenicity	Inactive	Inactive	Inactive	Inactive
16	Immunotoxicity	Inactive	Inactive	Inactive	Active
17	Mutagenicity	Inactive	Inactive	Inactive	Inactive
18	Cytotoxicity	Inactive	Inactive	Inactive	Inactive

Where: CRV: CMC rule violations, MDDRV: MDDR violations, RFV: Rule of Five violations, GI: Gastrointestinal, BBB: Blood Brain-Barrier, PPB: Protein Plasma Binding, HIA: Human Intestinal Absorption.

Table S3. Antitubercular activity results by MABA Method (MIC)

Sr. No.	Sample	MIC*							
		100 µg/ml	50 µg/ml	25 µg/ml	12.5 µg/ml	6.2 µg/ml	3.12 µg/ml	1.6 µg/ml	0.8 µg/ml
1	9	S	S	S	S	R	R	R	R
2	10	S	S	S	R	R	R	R	R
3	11	S	S	S	R	R	R	R	R
4	12	S	S	S	S	S	S	R	R
5	INH	S	S	S	S	S	R	R	R
6	Ethambutol	S	S	S	S	S	R	R	R
7	Pyrazinamide	S	S	S	S	R	R	R	R
8	Rifampicin	S	S	S	S	S	R	R	R
9	Streptomycin	S	S	S	S	S	S	R	R

*MIC- Minimum Inhibitory Concentration