Isoniazid-Rhodanine Molecular Hybrids: Design, Synthesis, Antimycobacterial Activity and Computational Validation

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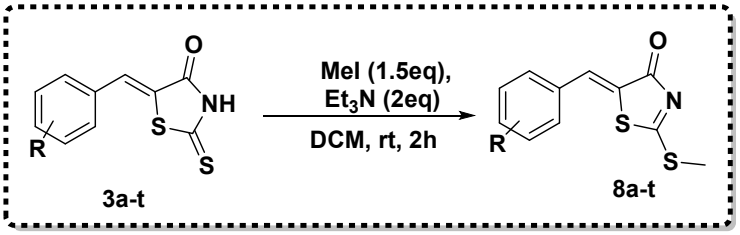
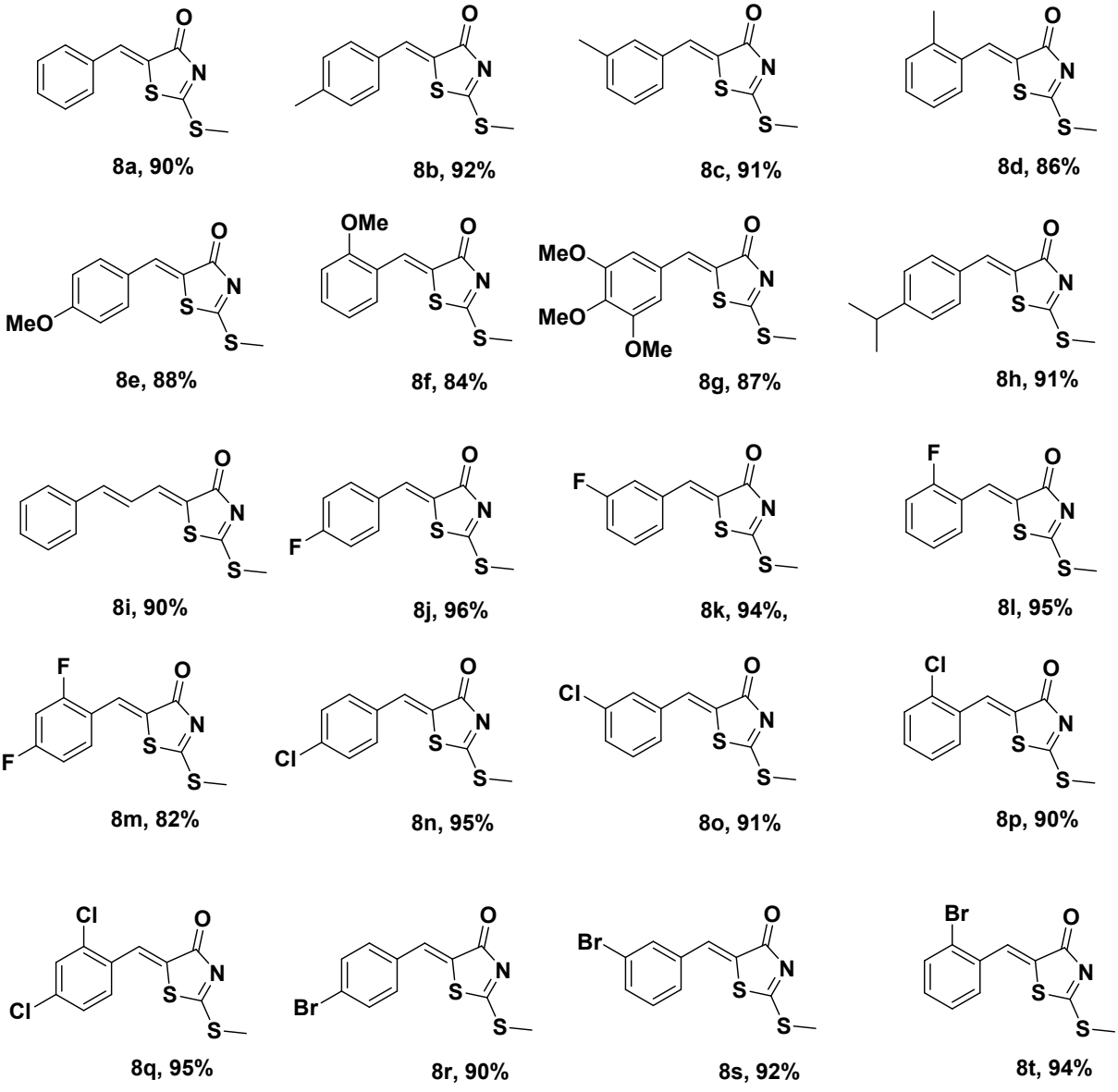
Supporting Information

Contents

1. Materials and Methods

1.1. Synthesis of 8a-t.

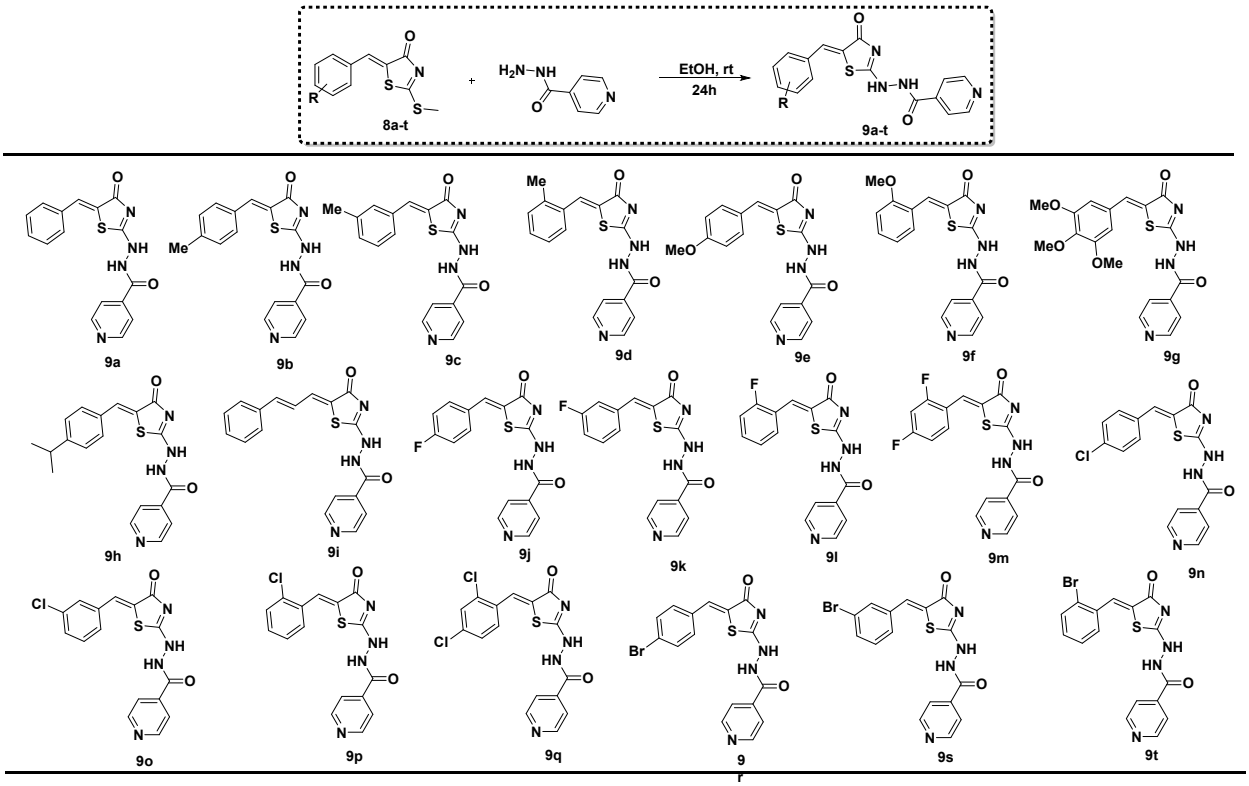




Scheme S1. The synthesis of intermediate **8a-t**.

1.2. General procedures for the synthesis of molecular hybrids 9a-t

In a round-bottom flask of 50ml, intermediate **8a-t** (1.0eq.) and INH (1.0eq.) were stirred at room temperature for 24 hours (**Scheme S2**). The reaction was analyzed by TLC. After the completion of the reaction, 10 mL of ethanol was added to the reaction mixture. The solid formed was filtered using the Buchner funnel and purified further by recrystallization using ethanol.



Scheme S2. The synthesis of INH-Rh molecular hybrids.

2. Computational studies

2.1. Molecular docking

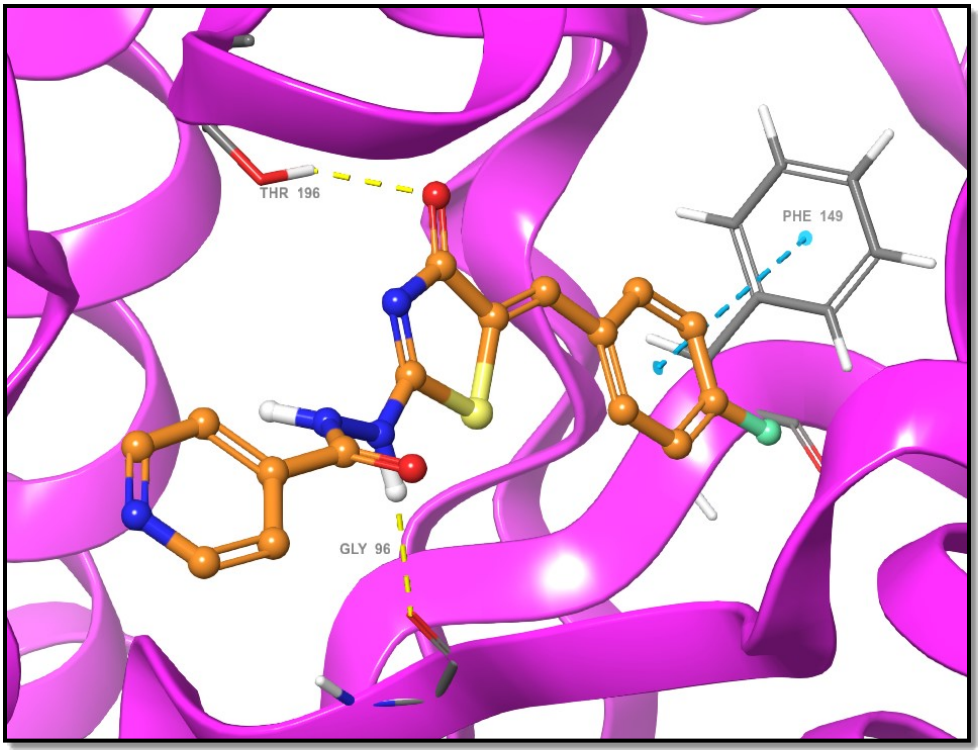


Figure S1. The 3D representation of the ligand-receptor complex of compound **9j**.

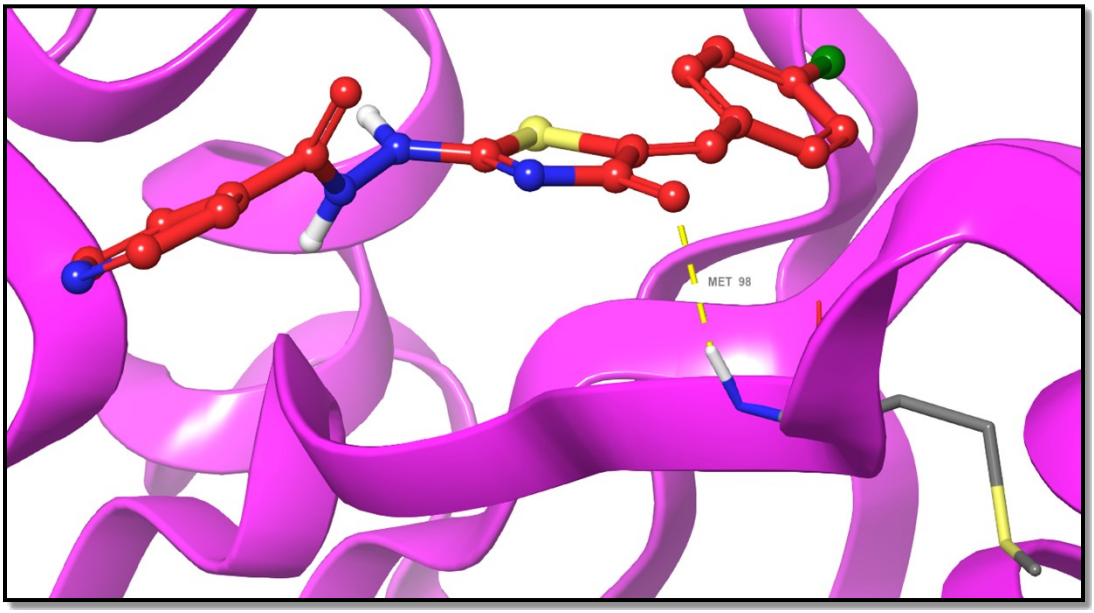


Figure S2. The 3D representation of the ligand-receptor complex of compound **9n**.

Table S1. The ADME studies of compound **9d**, **9j** and **9n**.					
S. No.	**Parameter**	**9d**	**9j**	**9n**	**Standard range**
1	Mw	338	342	358	<500[1]
2	No. of rot. bond	5	5	5	2-10[1]
3	HBD	2	2	2	0-6.0[2]
4	HBA	4	5	4	2-20[2]
5	QPlogPo/w	1.666	1.64	1.88	-2.0 to 6.5[1]
6	QPlogS	-44.09	-4.06	-4.41	-6.5 to -0.5[1]
7	TPSA	108.75	108.75	108.75	0-140[2]
8	RO_3	0	0	0	<3[2]
9	RO_5	0	0	0	<4[2]

2.2. ADME

Table S2. *In silico* rules for bioavailability and bioavailability score for compounds **9d**, **9j** and **9n**.							
Code	**Druglikeness properties**					**Bioavailbility score**	**Synthetic accessibility**
	Lipinski	**Muegge**	**Ghose**	**Veber**	**Egan**		
9d	yes	yes	yes	yes	yes	0.55	3.66
9j	yes	yes	yes	yes	yes	0.55	3.51
9n	yes	yes	yes	yes	yes	0.55	3.52

Table S3. ADMET prediction using pkCSM for compounds **9d, 9j, and 9n**.

Name	Absorption		Distribution			Metabolism							Excretion		Toxicity
	Water solubility	Intestinal absorption	BBB	VDss	CNS	CyP							Total clearance	AMES toxicity	Skin Sense
	Log mol/L	Numeric (% absorbed)	(logBB)	Numeric (log L/Kg)	Numeric (logPS)	2D6 substrate	3A4 substrate	1A2 inhibitor	2C19	2C9	2D6	3A4			
						Categorical (yes/no)							Numeric (log ml/min/kg)	(Yes/No)	
9d	-4.01	94.19	-1.45	-0.66	-2.32	no	yes	no	no	yes	no	no	-0.45	no	no
9j	-3.84	93.28	-1.34	-0.60	-2.16	no	yes	no	no	no	no	no	-0.50	no	no
9n	-4.218	92.33	-1.31	-0.28	-2.24	no	yes	no	no	no	no	no	-0.48	no	no

2.3. DFT

Study of global reactivity and chemical properties

The global reactivity parameter of the compounds were calculated to determine their drug properties and interactions with the biological target, and results are shown in **Table S4**.[3-5] It is widely recognized that frontier molecular orbitals (FMOs), such as the Highest Occupied Molecular Orbital (HOMO) and Lowest Unoccupied Molecular Orbital (LUMO), are crucial to a variety of scientific field, including electronics, optics, photochemical reaction and pharmaceutical research.[6-8]

Ionization energy indicates a molecule's electron-donating propensity and reactivity, with lower values correlating with higher donating ability and heightened reactivity.[9] Accordingly, all the compounds were predicted to be good electron donor ability.

Table S4. The Global reactivity properties of the compounds **9d**, **9j**, and **9n**.

S.No	Properties	9d	9j	9n
1	I (eV)	5.13	4.94	4.96
2	A (eV)	2.21	2.31	2.23
3	η (eV)	1.45	1.31	1.31
4	χ (eV)	2.60	2.51	2.52
5	S (eV^{-1})	0.19	0.20	0.20
6	μ (eV)	-2.60	-2.51	-2.52
7	ω (eV)	2.33	2.40	2.42

I = Ionization energy; A = Electron affinity; η = Chemical hardness; χ = Electronegativity; S = Chemical softness; μ = Chemical potential; ω = Global electrophilicity index.

Meanwhile, electron affinity denotes the energy released by a gaseous atom upon acquisition of an electron, and is linked to enhancing electron-accepting capabilities. The calculated data revealed that the compound **9d**, **9j** and **9n** have a strong electron acceptor capability.

Electronegativity is a key factor for successful binding, indicating the ability of the ligand to bond with protein.[10] **Table S4** demonstrated that the compound **9d** has a higher value for electronegativity, which may show a better catalytic ability as well as greater binding affinity with protein.[11, 12]

A molecule's chemical hardness (η) measures its resistance to charge transfer, while its chemical softness (S), the inverse of chemical hardness, measures its susceptibility to charge transfer.[13] A molecule with a low chemical hardness and a high chemical softness will interact more effectively with nearby biomolecules and transfer more charge.[14, 15] In the case of **9d, 9j** and **9n**, were found to be a lower hardness and higher softness values

The chemical potential indicated with a lower value has more potential for electrophilicity. Compound **9d** was found to have lower electrochemical potential, as depicted in **Table S4**. The electrophilicity index (ω) refers to the reactivity of the molecule, the more considerable electrophilicity value indicates the high reactivity of the molecules, hence more significant biological potential.[16] All compounds have been found with higher electrophilicity index in the range 2.33-2.42.

2.4. Molecular electrostatic potential (MEP) surface analysis

The molecular electrostatic potential surfaces are important to predict the reactive sites as well as to determine the interactions with target proteins.[17, 18] The positive region in blue indicates the best site for the nucleophilic attack, while the negative region in red and yellow indicates the best site for electrophilic attack.[19] **Figure S3** indicated that the carbonyl group of rhodanine ring and N-atoms of INH moiety were electron-rich center can show interactions with a nearby biomolecule further demonstrating the significance of this moiety in their activity.

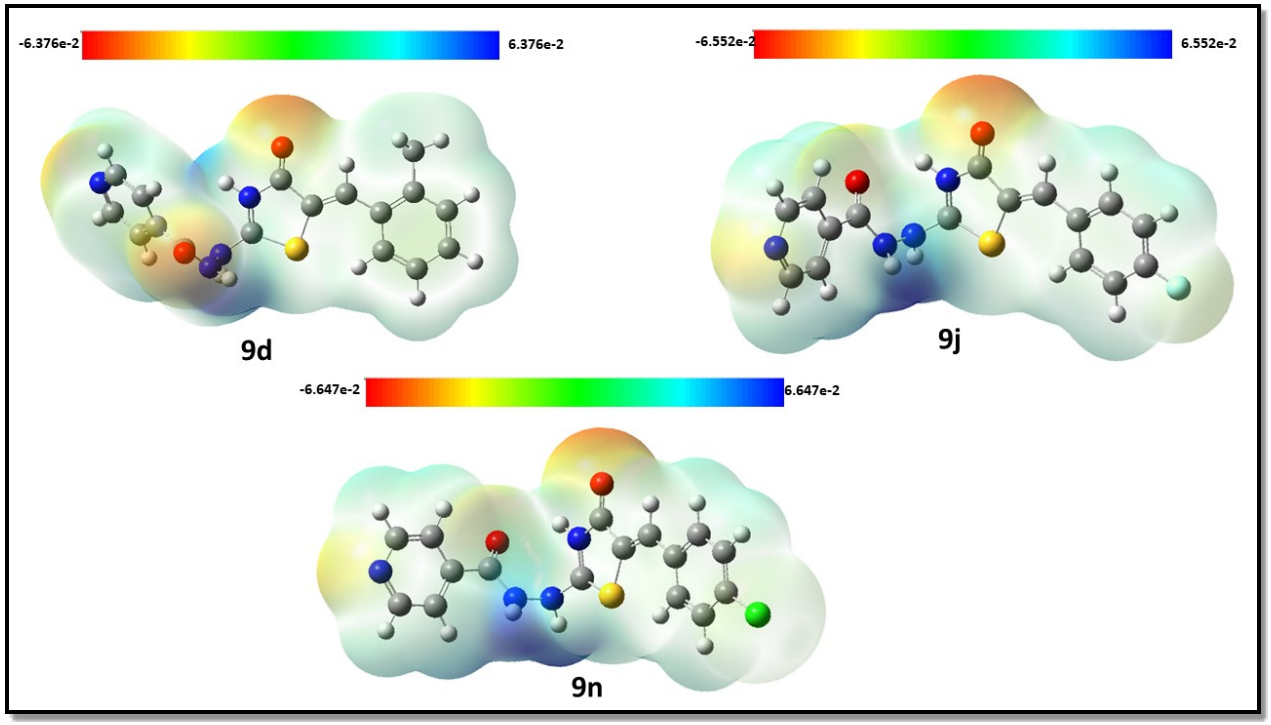
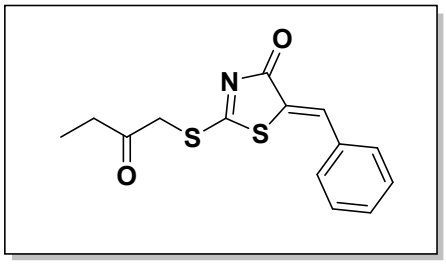


Figure S3. Illustrate the MEP map of compound **9d**, **9j**, and **9n** at the B3LYP/6-311++G (d, p) level of theory.

3. Analytical data

3.1. The analytical data of compound 8’

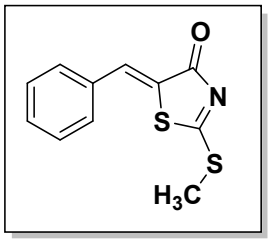


^{1}H-NMR (600 MHz, DMSO-d6): 1.20 (t, *J* = 7.06 Hz, 3H, CH_3), 4.15 (q, *J* = 7.06 Hz, 2H, CH_2), 4.30 (s, 2H, CH_2), 7.50-7.56 (m, 3H, ArH), 7.65 (d, *J* = 7.45 Hz, 2H, ArH), 7.88 (s, 1H, olefinic-H).

^{13}C-NMR (150 MHz, DMSO-d6): 14.43, 35.39, 62.20, 126.40, 129.92, 130.94, 131.56, 133.55, 136.29, 167.50, 178.98, 191.75.

3.2. The analytics data of compounds 8a-t

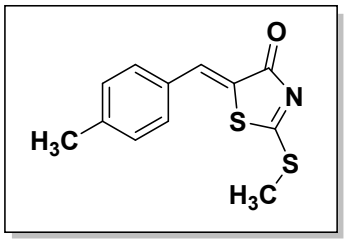
8a.



^{1}H-NMR (600 MHz, DMSO-d6): 2.82 (s, 3H, SCH_3), 7.49-7.56 (m, 3H, ArH), 7.65 (d, *J* = 7.42 Hz, 2H, ArH), 7.84 (s, 1H, olefinic-H).

^{13}C-NMR (150 MHz, DMSO-d6): 15.96, 126.69, 129.88, 130.87, 131.39, 133.67, 135.54, 179.46, 193.80.

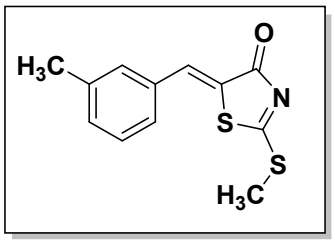
8b.



^{1}H-NMR (600 MHz, DMSO-d6): 2.36 (s, 3H, CH_3), 2.82 (s, 3H, SCH_3), 7.34 (d, *J* = 7.88 Hz, 2H, ArH), 7.53 (d, *J* = 7.96 Hz, 2H, ArH), 7.80 (s, 1H, olefinic-H).

^{13}C-NMR (150 MHz, DMSO-d6): 15.92, 21.60, 125.45, 130.52, 130.89, 130.99, 135.66, 141.86, 179.56, 193.41.

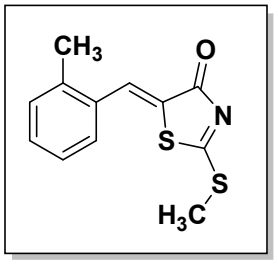
8c.



^{1}H-NMR (600 MHz, DMSO-d6): 2.42 (s, 3H, SCH_3), 2.88 (s, 3H, SCH_3), 7.37 (d, *J* = 6.91 Hz, 1H, ArH), 7.47-7.50 (m, 3H, ArH), 7.84 (s, 1H, olefinic-H).

^{13}C-NMR (150 MHz, $CDCl_3$): 16.02, 21.42, 126.08, 127.67, 129.13, 131.13, 131.66, 133.50, 136.22, 139.03, 179.96, 193.05.

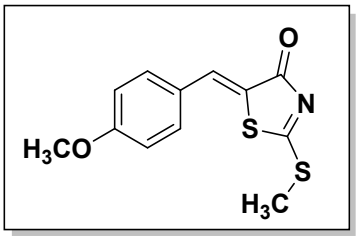
8d.



^{1}H-NMR (600 MHz, $CDCl_3$): 2.46 (s, 3H, CH_3), 2.82 (s, 3H, SCH_3), 7.25-7.28 (m, 3H, ArH), 7.45 (d, *J* = 7.93 Hz, 1H, ArH), 8.09 (s, 1H, olefinic-H).

^{13}C-NMR (150 MHz, $CDCl_3$): 15.99, 20.00, 126.59, 127.90, 130.61, 131.05, 132.97, 133.73, 139.50, 179.49, 193.69 (one carbon coalesced).

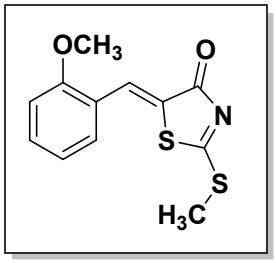
8e.



^{1}H-NMR (600 MHz, DMSO-d6): 2.81 (s, 3H, SCH_3), 3.83 (s, 3H, OCH_3), 7.08 (d, *J* = 7.86 Hz, 2H, ArH), 7.60 (d, *J* = 8.71 Hz, 2H, ArH), 7.78 (s, 1H, olefinic-H).

^{13}C-NMR (150 MHz, DMSO-d6): 15.86, 56.04, 115.52, 123.60, 126.12, 133.10, 135.72, 161.98, 179.68, 192.84.

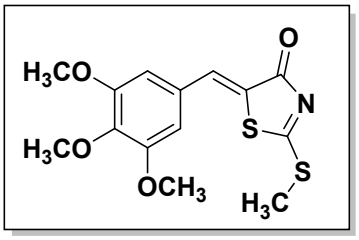
8f.



^{1}H-NMR (600 MHz, $CDCl_3$): 2.81 (s. 3H, SCH_3), 3.89 (s, 3H, OCH_3), 6.93 (d, *J* = 8.26 Hz, 1H, ArH), 7.01 (t, *J* = 7.43 Hz, 1H, ArH), 7.39-7.44 (m, 2H, ArH) 8.28 (s, 1H, olefinic-H).

^{13}C-NMR (150 MHz, DMSO-d6): 15.95, 56.30, 112.34, 121.51, 122.00, 126.37, 129.57, 130.00, 133.46, 158.80, 179.49, 193.64.

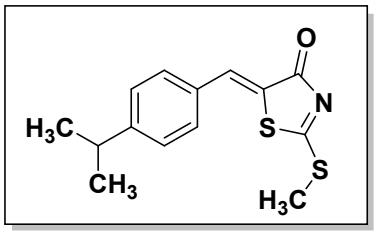
8g.



^{1}H-NMR (600 MHz, DMSO-d6): 2.82 (s, 3H, SCH_3), 3.37 (s, 3H, OCH_3), 3.84 (s, 6H, $2OCH_3$), 6.96 (s, 2H, ArH), 7.77 (s, 1H, olefinic-H).

^{13}C-NMR (150 MHz, DMSO-d6): 16.06, 56.52, 60.70, 108.43, 125.62, 129.15, 135.89, 140.39, 153.71, 179.40, 193.14.

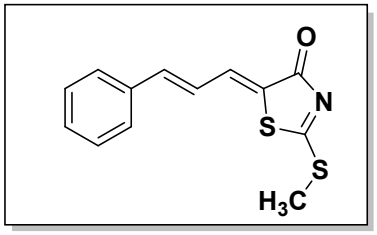
8h.



^{1}H-NMR (600 MHz, DMSO-d6): 1.20 (d, *J* = 6.89 Hz, 6H, $2CH_3$), 2.81 (s, 3H, SCH_3), 2.89 (sept, 1H, CH), 7.40 (d, *J* = 8.08 Hz, 2H, ArH), 7.56 (d, *J* = 8.14 Hz, 2H, ArH), 7.80 (s, 1H, olefinic-H).

^{13}C-NMR (150 MHz, DMSO-d6): 15.95, 23.93, 33.92, 125.59, 127.90, 131.13, 131.32, 135.64, 152.41, 179.54, 193.43.

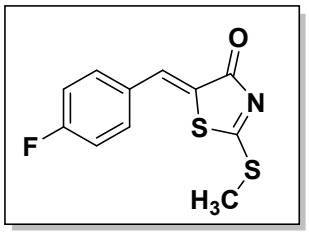
8i.



^{1}H-NMR (600 MHz, DMSO-d6): 2.78 (s, 3H, SCH_3), 7.05 (dd, *J* = 11.47 Hz, *J* = 15.25 Hz, 1H, C=CH), 7.37-7.43 (m, 5H, ArH), 7.53 (dd, *J* = 15.62 Hz, *J* = 11.40 Hz, 1H, C=CH), 7.67 (d, *J* = 7.18 Hz, 1H, olefinic-H).

^{13}C-NMR (150 MHz, $CDCl_3$): 16.01, 124.78, 127.73, 128.99, 129.09, 130.07, 135.20, 135.46, 144.23, 179.28, 191.01.

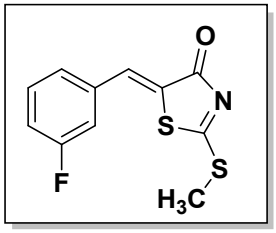
8j.



^{1}H-NMR (600 MHz, $CDCl_3$): 2.83 (s, 3H, SCH_3), 7.38 (t, *J* = 8.74 Hz, 2H, ArH), 7.73 (dd, *J* = 5.59 Hz, *J* = 8.56 Hz, 2H, ArH), 7.86 (s, 1H, olefinic-H).

^{13}C-NMR (150 MHz, DMSO-d6): 15.98, 117.02,117.16, 126.45, 130.37, 130.39, 133.37, 133.43, 134.45, 164.51, 179.44, 193.71. (multiple carbon peaks observed due to fluorine-carbon coupling)

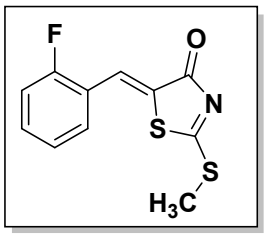
8k.



^{1}H-NMR (600 MHz, DMSO-d6): 2.83 (s, 3H, SCH_3), 7.34 (t, *J* = 7.76 Hz, 1H, ArH), 7.48 (t, *J* = 7.51 Hz, 2H, ArH), 7.57 (dd, *J* = 7.75 Hz, *J* = 14.04 Hz, 1H, ArH), 7.84 (s, 1H, olefinic-H).

^{13}C-NMR (150 MHz, DMSO-d6): 16.06, 117.36 117.50, 118.04, 118.19, 126.48, 126.50, 128.24, 131.90, 131.95, 133.97, 133.99, 136.06, 136.11, 163.61, 179.31, 194.00. (multiple carbon peaks observed due to fluorine-carbon coupling)

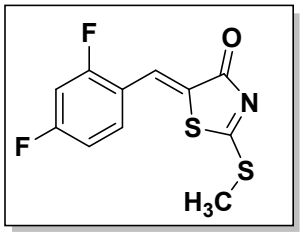
8l.



^{1}H-NMR (600 MHz, $CDCl_3$): 2.83 (s, 3H, SCH_3), 7.13 (t, *J* = 9.01 Hz, 1H, ArH), 7.24 (t, *J* = 7.56 Hz, 1H, ArH), 7.41 (dd, *J* = 7.51 Hz, *J* = 6.87 Hz, 1H, ArH), 7.48 (t, *J* = 7.27 Hz, 1H, ArH), 8.09 (s, 1H, olefinic-H).

^{13}C-NMR (150 MHz, $CDCl_3$): 16.06, 116.19, 116.34, 122.02, 122.09, 124.72, 124.74, 127.46, 127.51, 128.37, 129.18, 132.47, 132.53, 160.80, 162.50, 179.43, 193.03. (multiple carbon peaks observed due to fluorine-carbon coupling)

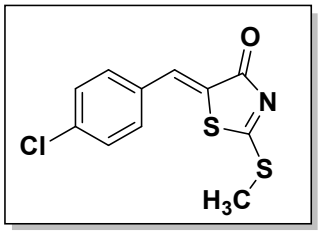
8m.



^{1}H-NMR (600 MHz, DMSO-d6): 2.83 (s, 3H, SCH_3), 7.28 (ddd, *J* = 2.05 Hz, *J* = 8.57 Hz, *J* = 10.36 Hz, 1H, ArH), 7.47 (dd, *J* = 2.32 Hz, *J* = 11.37 Hz, 1H, ArH), 7.62 (dd, *J* = 8.65 Hz, *J* = 15.06 Hz, 1H, ArH), 7.74 (s, 1H, olefinic-H).

^{13}C-NMR (150 MHz, DMSO-d6): 16.11, 105.41, 105.59, 105.76, 113.46, 113.48, 113.61, 113.63 118.49, 118.52, 118.57, 118.60, 125.28, 125.31, 128.93, 131.35, 131.37, 131.42, 131.44, 160.82, 163.32, 179.09, 194.06. (multiple carbon peaks observed due to fluorine-carbon coupling)

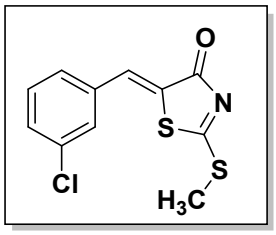
8n.



^{1}H-NMR (600 MHz, DMSO-d6): 2.82 (s, 3H, SCH_3), 7.58 (d, *J* = 8.48 Hz, 2H, Ar-H), 7.65 (d, *J* = 8.40 Hz, 2H, Ar-H), 7.82 (s, 1H, olefinic-H).

^{13}C-NMR (150 MHz, DMSO-d6): 16.04, 127.32, 129.93, 132.04, 132.47, 134.10, 136.00, 179.37, 193.67.

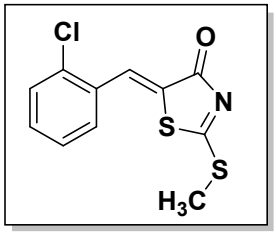
8o.



[1]H-NMR (600 MHz, DMSO-d6): 2.84 (s, 3H, SCH_3), 7.57-7.60 (m, 3H, Ar-H), 7.73 (s, 1H, Ar-H), 7.83 (s, 1H, olefinic-H).

[13]C-NMR (150 MHz, DMSO-d6): 16.08, 128.36, 128.74, 130.59, 130.91, 131.67, 133.77, 134.52, 135.90, 179.25, 193.96.

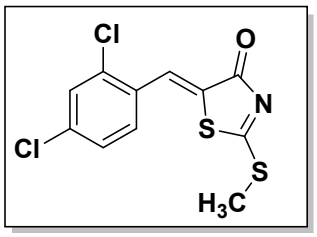
8p.



[1]H-NMR (600 MHz, $CDCl_3$): 2.83 (s, 3H, SCH_3), 7.34 (dd, *J* = 6.36 Hz, *J* = 3.67 Hz, 2H, Ar-H), 7.47 (dd, *J* = 7.70 Hz, *J* = 3.20 Hz, 1H, Ar-H), 7.52 (t = 5.35 Hz, 1H, Ar-H), 8.23 (s, 1H, olefinic-H).

[13]C-NMR (150 MHz, $CDCl_3$): 16.13, 127.32, 129.18, 129.42, 130.46, 131.45, 131.64, 132.24, 136.32, 179.16, 193.33.

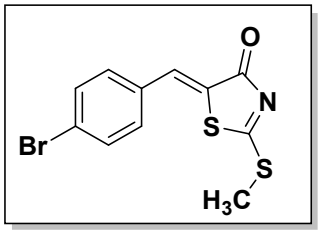
8q.



[1]H-NMR (600 MHz, $CDCl_3$): 2.83 (s, 3H, SCH_3), 7.33 (dd, *J* = 1.89 Hz, *J* = 8.42 Hz, 1H, Ar-H), 7.44 (d, *J* = 8.45 Hz, 1H, Ar-H), 7.49 (d, *J* = 1.99 Hz, 1H, Ar-H), 8.13 (s, 1H, olefinic-H).

^{13}C-NMR (150MHz, $CDCl_3$): 16.21, 127.60, 127.74, 129.84, 130.31, 130.38, 130.88, 136.83, 136.96, 179.04, 193.05.

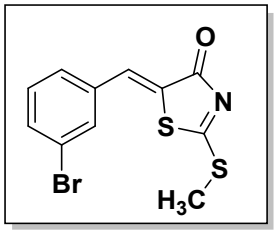
8r.



^{1}H-NMR (600 MHz, $CDCl_3$): 2.08 (s, 3H, SCH_3), 6.38 (t, *J* = 6.87 Hz, 1H, Ar-H), 6.49 (t, *J* = 7.76 Hz, 1H, Ar-H), 6.66 (q, *J* = 6.69 Hz, 1H, Ar-H), 6.72 (t, *J* = 8.78 Hz, 1H, Ar-H), 7.32 (s, 1H, olefinic-H).

^{13}C-NMR (150 MHz, $CDCl_3$): 16.07, 116.30, 121.91, 121.99, 124.74, 127.38, 129.14, 132.52, 132.58, 179.43, 193.09.

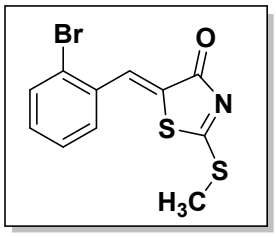
8s.



^{1}H-NMR (600 MHz, DMSO-d6): 2.84 (s, 3H, SCH_3), 7.49 (t, *J* = 7.89 Hz,1H, Ar-H), 7.64 (d, *J* = 7.82 Hz, 1H, Ar-H), 7.69 (d, *J* = 7.72 Hz, 1H, Ar-H), 7.83 (s, 1H, Ar-H), 7.87 (s, 1H, olefinic-H).

^{13}C-NMR (150 MHz, DMSO-d6): 16.08, 123.02, 128.35, 129.08, 131.89, 133.49, 133.73, 133.81, 136.17, 179.24, 193.96.

8t.

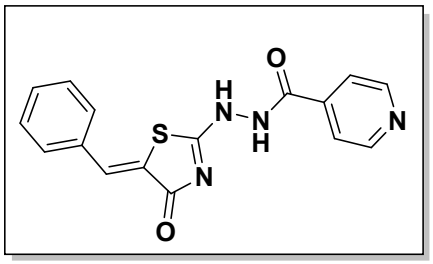


^{1}H-NMR (600 MHz, $CDCl_3$): 2.83 (s, 3H, SCH_3), 7.25 (t, *J* = 7.53 Hz, 1H, Ar-H), 7.39 (t, *J* = 7.66 Hz, 1H, Ar-H), 7.51 (d, *J* = 7.71 Hz, 1H, Ar-H), 7.66 (d, = 8.06 Hz, 1H, Ar-H), 8.16 (s, 1H, olefinic-H).

^{13}C-NMR (150 MHz, $CDCl_3$): 16.11, 126.64, 127.91, 129.31, 129.74, 131.52, 133.76, 134.17, 134.30, 179.01, 193.38.

3.3. Analytical data of final compounds 9a-9t

(Z)-N'-(5-benzylidene-4-oxo-4,5-dihydrothiazol-2-yl)isonicotinohydrazide (9a).



R*f* value: 0.40 (10%, MeOH/DCM, 1/9)

Yield: 95%, (130.97 mg)

Appearance: white solid

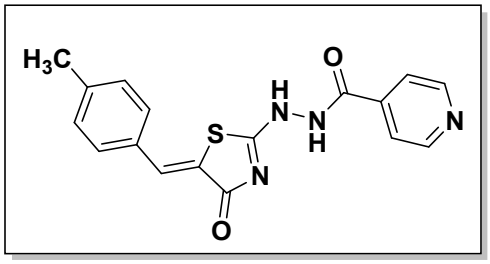
FTIR: (ATR): 3180.79, 2960.45, 2768.3, 1709.80, 1650.64, 1614.01 cm^{-1}

^{1}H-NMR (600 MHz, DMSO-d6): 7.44 (dd, *J* = 7.30 Hz, *J* = 14.61 Hz, 1H, Ar-H), 7.51 (t, *J* = 7.51 Hz, 2H, Ar-H), 7.60 (d, *J* = 7.49 Hz, 2H, Ar-H), 7.67 (s, 1H, olefinic-H), 7.80 (d, *J* = 4.99 Hz, 2H, ArPy-H), 8.78 (d, *J* = 4.96 Hz, 2H, ArPy-H), 11.44 (s, 1H, NH) 12.66 (s, 1H, NH).

^{13}C-NMR (150 MHz, DMSO-d6): 121.91, 122.00, 129.77, 130.13, 130.32, 130.49, 133.70, 140.43, 150.68, 150.83, 162.67 (one carbon coalesced).

HRMS: (ESI^--MS, m/z) $[M-H]^-$ calcd for [C_{16} H_{11} N_4 O_2 S]: 323.0603; found: 323.0604.

(Z)-N'-(5-(4-methylbenzylidene)-4-oxo-4,5-dihydrothiazol-2-yl)isonicotinohydrazide (9b).



R*f* value: 0.42 (10%, MeOH/DCM, 1/9)

Yield: 92%, (124.88 mg)

Appearance: white solid

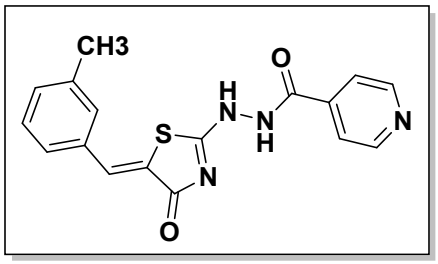
FTIR: (ATR): 3186.44, 2977.40, 1712.62, 1650.64, 1622.46 cm^{-1}

^{1}H-NMR (600 MHz, DMSO-d6): 2.33 (s, 3H, CH_3), 7.32 (d, *J* = 7.67 Hz, 2H, Ar-H), 7.48 (d, *J* = 7.55 Hz, 2H, Ar-H), 7.63 (s, 1H, olefinic-H), 7.80 (d, *J* = 4.50 Hz, 2H, ArPy-H), 8.77 (d, *J* = 4.44 Hz, 2H, ArPy-H), 11.42 (s, 1H, NH) 12.60 (s, 1H, NH).

^{13}C-NMR (150 MHz, DMSO-d6): 21.50, 121.55, 121.92, 122.05, 130.19, 130.32, 130.92, 140.50, 140.63, 150.60, 150.77, 162.66, 167.99.

HRMS: (ESI$^-$-MS, m/z) $[M-H]^-$ calcd for [C_{17} H_{13} N_4 O_2 S]: 337.0759; found: 337.0760.

(Z)-N'-(5-(3-methylbenzylidene)-4-oxo-4,5-dihydrothiazol-2-yl)isonicotinohydrazide (9c).



R*f* value: 0.48 (10%, MeOH/DCM, 1/9)

Yield: 90%, (122.16 mg)

Appearance: light yellow solid

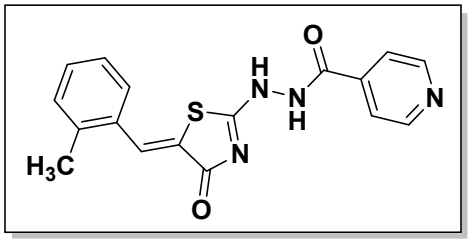
FTIR: (ATR): 3192.09, 2977.40, 2768.36, 1718.26, 1650.64, 1622.46 cm^{-1}

^{1}H-NMR (600 MHz, DMSO-d6): 2.34 (s, 3H, CH_3), 7.26 (d, *J* = 7.14 Hz, 1H, Ar-H), 7.38-7.41 (m, 3H, Ar-H), 7.62 (s, 1H, olefinic-H), 7.80 (d, *J* = 5.36 Hz, 2H, ArPy-H), 8.77 (d, *J* = 5.18 Hz, 2H, ArPy-H), 11.40 (s, 1H, NH) 12.62 (s, 1H, NH).

^{13}C-NMR (150 MHz, DMSO-d6): 21.40, 121.93, 122.65, 127.07, 129.66, 130.24, 131.09, 131.24, 133.70, 139.08, 140.51, 150.65, 150.81, 162.71, 167.89.

HRMS: (ESI$^-$-MS, m/z) $[M-H]^-$ calcd for $[C_{17}\ H_{13}\ N_4\ O_2\ S]$: 337.0759; found: 337.0765.

(Z)-N'-(5-(2-methylbenzylidene)-4-oxo-4,5-dihydrothiazol-2-yl)isonicotinohydrazide (9d).



R*f* value: 0.41 (10%, MeOH/DCM, 1/9)

Yield: 96%, (130.31 mg)

Appearance: yellow solid

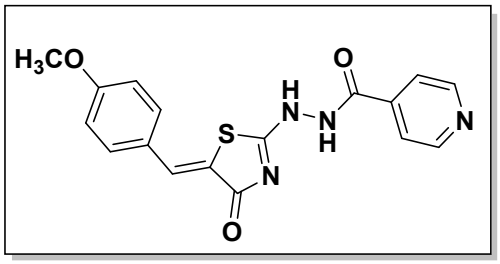
FTIR: (ATR): 3163.84, 2971.75, 2779.66, 1712.62, 1692.90, 1630.92 cm^{-1}

^{1}H-NMR (600 MHz, $CDCl_3$): 2.38 (s, 3H, CH_3), 7.32-7.33 (m, 2H, Ar-H), 7.34-7.38 (m, 2H, Ar-H), 7.42 (s, 1H, olefinic-H), 7.76 (d, *J* = 5.41 Hz, 2H, ArPy-H), 8.75 (d, *J* = 5.40 Hz, 2H, ArPy-H), 11.40 (s, 1H, NH), 12.66 (s, 1H, NH).

^{13}C-NMR (150 MHz, DMSO-d6): 19.85, 121.87, 121.98, 127.07, 127.54, 127.92, 130.21, 130.36, 131.37, 132.88, 138.75, 140.46, 150.66, 150.80. (one carbon is coalesced).

HRMS: (ESI$^-$-MS, m/z) $[M-H]^-$ calcd for $[C_{17}\ H_{13}\ N_4\ O_2\ S]$: 337.0759; found: 337.0750.

(Z)-N'-(5-(4-methoxybenzylidene)-4-oxo-4,5-dihydrothiazol-2-yl)isonicotinohydrazide (9e).



R*f* value: 0.44 (10%, MeOH/DCM, 1/9)

Yield: 94%, (125. 56 mg)

Appearance: light yellow solid

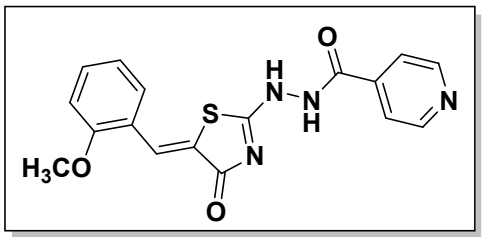
FTIR: (ATR): 3186.44, 2977.40, 2774.01, 1709.80, 1647.82, 1622.46 cm^{-1}

^{1}H-NMR (600 MHz, DMSO-d6): 3.80 (s, 3H, OCH_3), 7.08 (d, *J* = 8.78 Hz, 2H, Ar-H), 7.56 (d, *J* = 8.69 Hz, 2H, Ar-H), 7.63 (s, 1H, olefinic-H), 7.80 (d, *J* = 5.70 Hz, 2H, ArPy-H), 8.78 (d, *J* = 5.61 Hz, 2H, ArPy-H), 11.40 (s, 1H, NH), 12.54 (s, 1H, NH).

^{13}C-NMR (150 MHz, DMSO-d6): 55.88, 115.32, 119.56, 121.90, 122.02, 126.16, 130.16, 132.11, 132.32, 140.48, 150.65, 150.82, 161.08.

HRMS: (ESI^--MS, m/z) $[M-H]^-$ calcd for [C_{17} H_{13} N_4 O_3 S]: 353.0708; found: 353.0698.

(Z)-N'-(5-(2-methoxybenzylidene)-4-oxo-4,5-dihydrothiazol-2-yl)isonicotinohydrazide (9f).



R*f* value: 0.41 (10%, MeOH/DCM, 1/9)

Yield: 88%, (117.55 mg)

Appearance: yellow solid

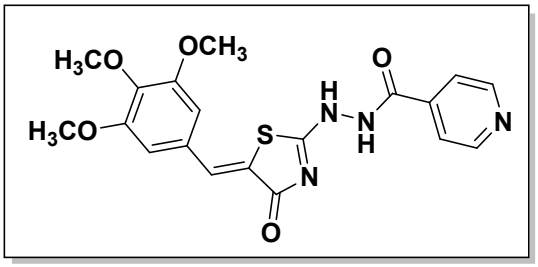
FTIR: (ATR): 319209, 2954.80, 2774.01 1715.44, 1645.00, 1622.46 cm^{-1}

^{1}H-NMR (600 MHz, $CDCl_3$): 3.88 (s, 3H, OCH_3), 7.07 (dd, *J* = 7.46 Hz, *J* = 15.41 Hz, 1H, Ar-H), 7.11 (dd, *J* = 7.39 Hz, *J* = 15.60 Hz, 1H, Ar-H), 7.43 (d, *J* = 7.62 Hz, 2H, Ar-H), 7.79 (d, *J* = 4.94 Hz, 2H, ArPy-H), 7.87 (s, 1H, olefinic-H), 8.77 (d, *J* = 4.50 Hz, 2H, ArPy-H), 11.40 (s, 1H, NH), 12.62 (s, 1H, NH).

^{13}C-NMR (150 MHz, $CDCl_3$): 56.25, 112.28, 121.40, 121.89, 122.18, 122.67, 124.61, 128.81, 132.41, 140.49, 150.80, 158.32, 162.62.

HRMS: (ESI^--MS, m/z) $[M-H]^-$ calcd for $[C_{17}\ H_{13}\ N_4\ O_3\ S]$: 353.0708; found: 337.0700.

(Z)-N'-(5-(3,4,5-trimethoxybenzylidene)-4-oxo-4,5-dihydrothiazol-2-yl)isonicotinohydrazide (9g).



R*f* value: 0.44 (10%, MeOH/DCM, 1/9)

Yield: 90%, (114.64 mg)

Appearance: dark yellow solid

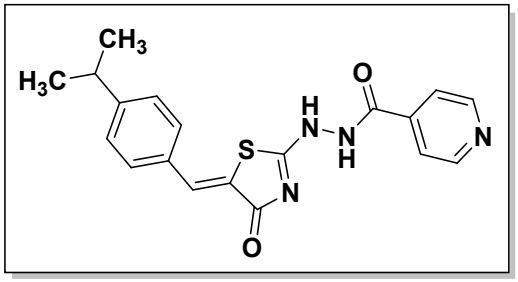
FTIR: (ATR): 3175.14, 2937.85, 2757.06, 1706.99, 1650.64, 1625.28 cm^{-1}

^{1}H-NMR (600 MHz, DMSO-d6): 3.80 (s, 3H, OCH_3), 3.85 (s, 6H, $2OCH_3$), 6.91 (s, 2H, Ar-H), 7.62 (s, 1H, olefinic-H), 7.76 (d, *J* = 4.77 Hz, 2H, ArPy-H), 8.76 (d, *J* = 3.97 Hz, 2H, ArPy-H), 11.40 (s, 1H, NH), 12.60 (s, 1H, NH).

^{13}C-NMR (150 MHz, DMSO-d6): 56.55, 60.72, 108.63, 121.89, 121.99, 128.92, 129.18, 129.36, 133.61, 135.91, 139.65, 150.81, 153.65, 167.43.

HRMS: (ESI^--MS, m/z) $[M-H]^-$ calcd for $[C_{19}\ H_{17}\ N_4\ O_5\ S]$: 413.0920; found: 413.0923.

(Z)-N'-(5-(4-isopropylbenzylidene)-4-oxo-4,5-dihydrothiazol-2-yl)isonicotinohydrazide (9h).



R*f* value: 0.50 (10%, MeOH/DCM, 1/9)

Yield: 94%, (140.49 mg)

Appearance: yellow solid

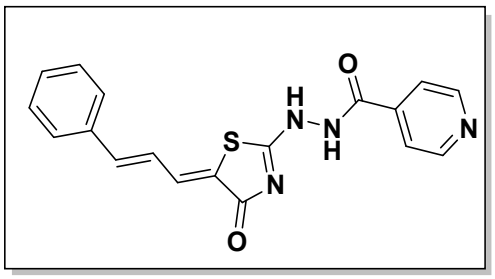
FTIR: (ATR): 3045.19, 2954.80, 2762.71, 1709.80, 1650.64, 1614.01 cm^{-1}

^{1}H-NMR (600 MHz, DMSO-d6): 1.19 (d, *J* = 6.84 Hz, 6H, $2CH_3$), 2.89 (sept, 1H, CH), 7.39 (d, *J* = 7.88 Hz, 2H, Ar-H), 7.52 (d, *J* = 7.82 Hz, 2H, Ar-H), 7.64 (s, 1H, olefinic-H), 7.80 (d, *J* = 5.03 Hz, 2H, ArPy-H), 8.78 (d, *J* = 4.88 Hz, 2H, ArPy-H), 11.43 (s, 1H, NH), 12.63 (s, 1H, NH).

^{13}C-NMR (150 MHz, DMSO-d6): 24.00, 33.84, 121.90, 122.00, 127.76, 127.79, 130.19, 130.32, 130.48, 131.37, 150.67, 150.83, 151.31. (one carbon is coalesced)

HRMS: (ESI^--MS, m/z) $[M-H]^-$ calcd for [C_{19} H_{17} N_4 O_2 S]: 365.1072; found: 365.1075.

N'-((Z)-4-oxo-5-((E)-3-phenylallylidene)-4,5-dihydrothiazol-2-yl)isonicotinohydrazide (9i).



R*f* value: 0.43 (10%, MeOH/DCM, 1/9)

Yield: 86%, (120.59 mg)

Appearance: yellow solid

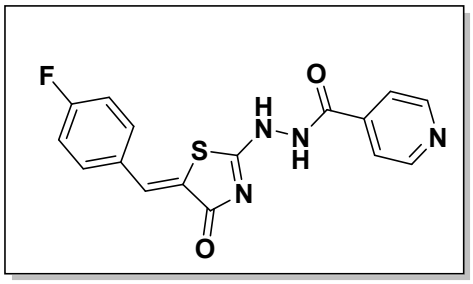
FTIR: (ATR): 3197.74, 2994.35, 2774.01, 1712.62, 1650.64, 1625.28, 1602.74 cm^{-1}

^{1}H-NMR (600 MHz, DMSO-d6): 6.98 (dd, *J* = 11.49 Hz, *J* = 15.13 Hz, 1H, olefinic-H), 7.02 (d, *J* = 15.19 Hz, 1H, olefinic-H), 7.33-7.38 (m, 4H, Ar-H), 7.41 (d, *J* = 7.46 Hz, 1H, Ar-H), 7.64 (d, *J* = 7.43 Hz, 1H, olefinic-H), 7.80 (d, *J* = 4.83 Hz, 2H, ArPy-H), 8.78 (d, *J* = 4.66 Hz, 2H, ArPy-H), 11.40 (s, 1H, NH), 12.46 (s, 1H, NH).

^{13}C-NMR (150 MHz, DMSO-d6): 121.79, 123.98, 125.65, 128.15, 128.48, 129.31, 129.91, 130.47, 135.69, 136.23, 142.78, 145.29, 150.84, 178.97.

HRMS: (ESI^{-}-MS, m/z) $[M-H]^{-}$ calcd for $[C_{19}\ H_{13}\ N_4\ O_2\ S]$: 349.0759; found: 349.0762.

(Z)-N'-(5-(4-fluorobenzylidene)-4-oxo-4,5-dihydrothiazol-2-yl)isonicotinohydrazide (9j).



R*f* value: 0.32 (10%, MeOH/DCM, 1/9)

Yield: 87%, (120.35 mg)

Appearance: yellow solid

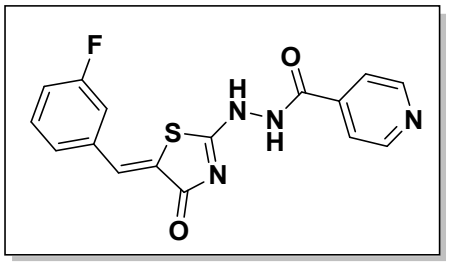
FTIR: (ATR): 3180.79, 2960.45, 1712.62, 1659.09, 1616.83 cm^{-1}

^{1}H-NMR (600 MHz, DMSO-d6): 7.36 (t, *J* = 8.28 Hz, 2H, Ar-H), 7.67 (d, *J* = 7.01 Hz, 2H, Ar-H), 7.69 (s, 1H, olefinic-H), 7.82 (d, *J* = 4.55 Hz, 2H, ArPy-H), 8.79 (d, *J* = 4.46 Hz, 2H, ArPy-H), 11.46 (s, 1H, NH), 12.54 (s, 1H, NH).

^{13}C-NMR (150 MHz, DMSO-d6): 116.81, 116.91, 121.90, 122.01, 122.50, 129.05, 130.38, 132.47, 132.53, 132.68, 132.74, 140.40, 150.66, 150.82, 162.21, 163.86. (multiple carbon peaks observed due to fluorine-carbon coupling)

HRMS: (ESI$^-$-MS, m/z) [M-H]$^-$ calcd for [$C_{16}H_{10}N_4O_2SF$]: 341.0508; found: 341.0511.

(Z)-N'-(5-(3-fluorobenzylidene)-4-oxo-4,5-dihydrothiazol-2-yl)isonicotinohydrazide (9k).



R*f* value: 0.09 (10%, MeOH/DCM, 1/9)

Yield: 95%, (128.41)

Appearance: light yellow solid

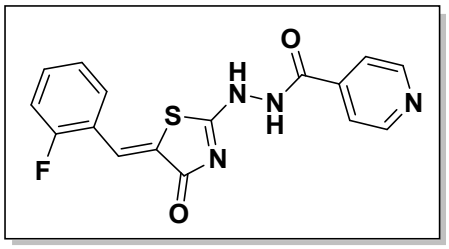
FTIR: (ATR): 3141.24, 2966.10, 1701.35, 1659.09, 1636.55 cm^{-1}

^{1}H-NMR (600 MHz, DMSO-d6): 7.29 (t, *J* = 8.20 Hz, 1H, Ar-H), 7.43 (dd, *J* = 7.90 Hz, *J* = 14.84 Hz, 2H, Ar-H), 7.55 (dd, *J* = 7.58 Hz, *J* = 14.38 Hz, 1H, Ar-H), 7.67 (s, 1H, olefinic-H), 7.79 (d, *J* = 5.53 Hz, 2H, ArPy-H), 8.77 (d, *J* = 4.48 Hz, 2H, ArPy-H), 11.45 (s, 1H, NH), 12.69 (s, 1H, NH).

^{13}C-NMR (150 MHz, DMSO-d6): 116.94, 117.09, 117.15, 117.29, 121.92, 121.99, 124.57, 125.82, 128.71, 131.80, 131.85, 136.11, 136.17, 140.43, 150.67, 150.81, 161.94, 163.56. (multiple carbon peaks observed due to fluorine-carbon coupling)

HRMS: (ESI$^-$-MS, m/z) [M-H]$^-$ calcd for [$C_{16}H_{10}N_4O_2SF$]: 341.0508; found: 341.0511.

(Z)-N'-(5-(2-fluorobenzylidene)-4-oxo-4,5-dihydrothiazol-2-yl)isonicotinohydrazide (9l).



R*f* value: 0.41 (10%, MeOH/DCM, 1/9)

Yield: 96%, (129.77 mg)

Appearance: yellow solid

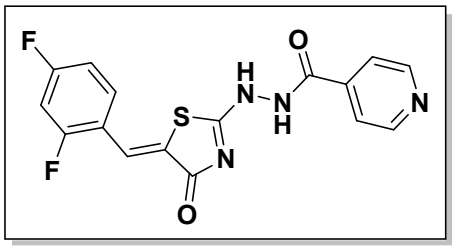
FTIR: (ATR): 3152.54, 3050.84, 2774.01, 1687.26, 1628.10, 1597.11 cm^{-1}

^{1}H-NMR (600 MHz, DMSO-d6): 7.36 (d, *J* = 8.20 Hz, 2H, Ar-H), 7.49 (dd, *J* = 6.27 Hz, *J* = 12.57 Hz, 1H, Ar-H), 7.55 (t, *J* = 7.34 Hz, 1H, Ar-H), 7.67 (s, 1H, olefinic-H), 7.80 (d, *J* = 4.59 Hz, 2H, ArPy-H), 8.77 (d, *J* = 4.32 Hz, 2H, ArPy-H), 11.47 (s, 1H, NH), 12.62 (s, 1H, NH).

^{13}C-NMR (150 MHz, DMSO-d6): 116.53, 116.67, 120.99, 121.57, 121.64, 121.91, 122.03, 125.56, 125.81, 125.83, 129.25, 132.68, 132.73, 140.38, 150.65, 150.80, 160.00, 161.66. (multiple carbon peaks observed due to fluorine-carbon coupling)

HRMS: (ESI^--MS, m/z) $[M-H]^-$ calcd for [$C_{16}H_{10}N_4O_2SF$]: 341.0508; found: 341.0497.

(Z)-N'-(5-(2,4-difluorobenzylidene)-4-oxo-4,5-dihydrothiazol-2-yl)isonicotinohydrazide (9m).



R*f* value: 0.51 (10%, MeOH/DCM, 1/9)

Yield: 97%, (128.85 mg)

Appearance: white solid

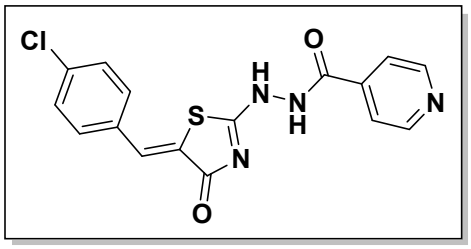
FTIR: (ATR): 3169.49, 2994.35, 2779.66, 1721.07, 1650.64, 1625.28 cm^{-1}

^{1}H-NMR (600 MHz, DMSO-d6): 7.26 (t, *J* = 7.71 Hz, 1H, Ar-H), 7.46 (t, *J* = 8.95 Hz, 1H, Ar-H), 7.61 (s, 1H, olefinic-H), 7.55 (d, *J* = 8.95 Hz, 1H, Ar-H), 7.79 (d, *J* = 5.06 Hz, 2H, ArPy-H), 8.77 (d, *J* = 4.72 Hz, 2H, ArPy-H), 11.47 (s, 1H, NH), 12.77 (s, 1H, NH).

^{13}C-NMR (150 MHz, DMSO-d6): 105.30, 105.47, 105.64, 113.26, 113.41, 118.47, 120.19, 121.88, 121.98, 125.42, 130.80, 130.83, 130.88, 130.91, 140.32, 150.69, 150.84, 160.42, 162.03, 162.58. (multiple carbon peaks observed due to fluorine-carbon coupling)

HRMS: (ESI^--MS, m/z) $[M-H]^-$ calcd for $[C_{16}H_8N_4O_2SF_2]$: 359.0403; found: 359.0402.

(Z)-N'-(5-(4-chlorobenzylidene)-4-oxo-4,5-dihydrothiazol-2-yl)isonicotinohydrazide (9n).



R*f* value: 0.38 (10%, MeOH/DCM, 1/9)

Yield: 90%, (120.22 mg)

Appearance: yellow solid

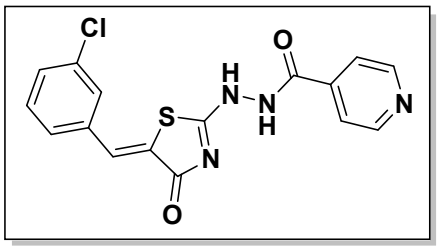
FTIR: (ATR): 3158.17, 2965.14, 1700.86, 1682.16, 1628.75, 1602.04 cm^{-1}

^{1}H-NMR (600 MHz, DMSO-d6): 7.57 (d, *J* = 8.38 Hz, 2H, Ar-H), 7.62 (d, *J* = 8.25 Hz, 2H, Ar-H), 7.67 (s, 1H, olefinic-H), 7.80 (d, *J* = 4.08 Hz, 2H, ArPy-H), 8.78 (d, *J* = 5.20 Hz, 2H, ArPy-H), 11.46 (s, 1H, NH), 12.69 (s, 1H, NH).

^{13}C-NMR (150 MHz, DMSO-d6): 121.90, 121.98, 128.79, 129.82, 129.90, 131.72, 131.95, 132.64, 134.99, 140.39, 150.69, 150.83.

HRMS: (ESI^--MS, m/z) $[M-H]^-$ calcd for $[C_{16}H_{10}N_4O_2SCl]$: 357.0213; found: 357.0214.

(Z)-N'-(5-(3-chlorobenzylidene)-4-oxo-4,5-dihydrothiazol-2-yl)isonicotinohydrazide (9o).



R*f* value: 0.38 (10%, MeOH/DCM, 1/9)

Yield: 89%, (118.88 mg)

Appearance: white solid

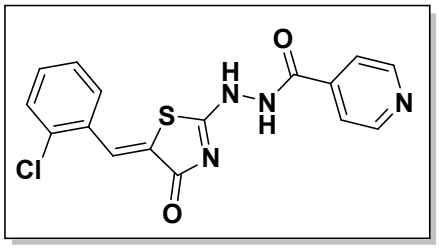
FTIR: (ATR): 3206.43, 2997.31, 2793.56, 1724.90, 1655.45, 1626.07 cm^{-1}

^{1}H-NMR (600 MHz, DMSO-d6): 7.51-7.59 (m, 3H, Ar-H), 7.67 (s, 1H, olefinic-H), 7.68 (d, *J* = 6.84 Hz, 1H, Ar-H), 7.80 (d, *J* = 5.10 Hz, 2H, ArPy-H), 8.77 (d, *J* = 4.46 Hz, 2H, ArPy-H), 11.45 (s, 1H, NH), 12.71 (s, 1H, NH).

^{13}C-NMR (150 MHz, DMSO-d6): 121.93, 121.99, 127.88, 128.03, 128.49, 130.07, 130.24, 131.59, 134.35, 135.94, 140.40, 150.68, 150.82, 162.72.

HRMS: (ESI^{-}-MS, m/z) $[M-H]^{-}$ calcd for $[C_{16}H_{10}N_4O_2SCl]$: 357.0213; found: 357.0200.

(Z)-N'-(5-(2-chlorobenzylidene)-4-oxo-4,5-dihydrothiazol-2-yl)isonicotinohydrazide (9p).



R*f* value: 0.37 (10%, MeOH/DCM, 1/9)

Yield: 91%, 121.55 mg)

Appearance: yellow solid

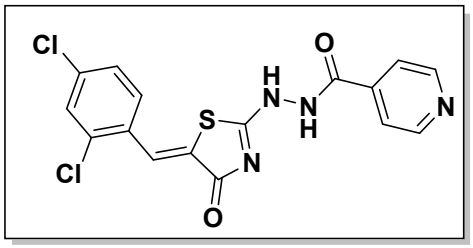
FTIR: (ATR): 3124.29, 3000.00, 2790.96, 1684.45, 1636.55, 1597.11 cm^{-1}

^{1}H-NMR (600 MHz, DMSO-d6): 7.43-7.49 (m, 2H, Ar-H), 7.57 (t,s, *J* = 8.49 Hz, 3H, Ar-H & olefinic-H merge) , 7.78 (d, *J* = 5.30 Hz, 2H, ArPy-H), 8.76 (d, *J* = 5.00 Hz, 2H, ArPy-H), 11.46 (s, 1H, NH), 12.76 (s, 1H, NH).

^{13}C-NMR (600 MHz, DMSO-d6): 121.89, 122.01, 125.15, 126.52, 128.49, 129.30, 130.73, 131.71, 131.85, 134.67, 140.37, 150.65, 150.77, 167.51.

HRMS: (ESI^{-}-MS, m/z) $[M-H]^{-}$ calcd for $[C_{16}H_{10}N_4O_2SCl]$: 357.0213; found: 357.0206.

(Z)-N'-(5-(2,4-dichlorobenzylidene)-4-oxo-4,5-dihydrothiazol-2-yl)isonicotinohydrazide (9q).



R*f* value: 0.34 (10%, MeOH/DCM, 1/9)

Yield: 87%, (112.83 mg)

Appearance: red solid

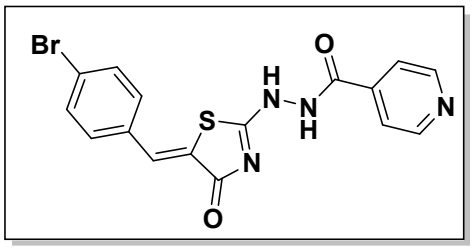
FTIR: (ATR): 3067.79, 2915.25, 1701.35, 1670.36, 1636.55 cm^{-1}

^{1}H-NMR (600 MHz, DMSO-d6): 7.58-7.62 (m, 2H, Ar-H), 7.73 (s, 1H, Ar-H), 7.78 (d, *J* = 4.72 Hz, 2H, ArPy-H), 7.81 (s, 1H, olefinic-H), 8.76 (d, *J* = 4.35 Hz, 2H, ArPy-H), 11.48 (s, 1H, NH), 12.79 (s, 1H, NH).

^{13}C-NMR (150 MHz, DMSO-d6): 121.88, 123.93, 127.26, 128.78, 130.31, 130.45, 130.76, 135.44, 135.55, 140.31, 150.68, 150.81, 162.61, 167.47.

HRMS: (ESI^{-}-MS, m/z) $[M-H]^{-}$ calcd for $[C_{16}H_9N_4O_2SCl_2]$: 390.9823; found: 390.9812.

(Z)-N'-(5-(4-bromobenzylidene)-4-oxo-4,5-dihydrothiazol-2-yl)isonicotinohydrazide (9r).



R*f* value: 0.33 (10%, MeOH/DCM, 1/9)

Yield: 92%, (118.83 mg)

Appearance: yellow solid

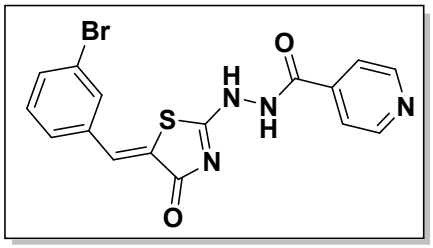
FTIR: (ATR): 3180.79, 3000.00, 1704.17, 1676.09, 1619.65 cm^{-1}

^{1}H-NMR (600 MHz, DMSO-d6): 7.53 (d, *J* = 8.42 Hz, 2H, Ar-H), 7.64 (s, 1H, olefinic-H) 7.70 (d, *J* = 7.82 Hz, 2H, Ar-H), 7.80 (d, *J* = 5.11 Hz, 2H, ArPy-H), 8.77 (d, *J* = 3.98 Hz, 2H, ArPy-H), 11.47 (s, 1H, NH), 12.77 (s, 1H, NH).

^{13}C-NMR (150 MHz, DMSO-d6): 121.90, 122.00, 123.86, 128.87, 132.11, 132.54, 132.73, 140.38, 150.66, 150.82, 162.62, 167.41.

HRMS: (ESI^{-}-MS, m/z) $[M-H]^{-}$ calcd for $[C_{16}H_{10}N_4O_2SBr]$: 400.9708; found: 400.9694.

(Z)-N'-(5-(3-bromobenzylidene)-4-oxo-4,5-dihydrothiazol-2-yl)isonicotinohydrazide (9s).



R*f* value: 0.37 (10%, MeOH/DCM, 1/9)

Yield: 90%, (116.25 mg)

Appearance: white solid

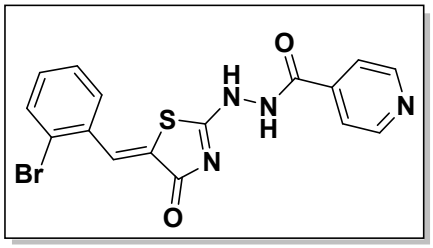
FTIR: (ATR): 3045.57, 2975.87, 2793.56, 1716.88, 1652.78, 1623.40 cm^{-1}

^{1}H-NMR (600 MHz, DMSO-d6): 7.47 (t, *J* = 7.89 Hz, 1H, Ar-H), 7.58 (d, *J* = 7.79 Hz, 1H, Ar-H), 7.64 (d, *J* = 9.66 Hz, 2H, Ar-H) 7.79 (d, *J* = 5.27 Hz, 2H, ArPy-H), 7.83 (s, 1H, olefinic-H), 8.77 (d, *J* = 5.20 Hz, 2H, ArPy-H), 11.45 (s, 1H, NH), 12.72 (s, 1H, NH).

^{13}C-NMR (150 MHz, DMSO-d6): 121.94, 122.01, 122.90, 122.93, 128.35, 128.44, 131.80, 132.95, 133.13, 136.18, 140.41, 150.68, 150.82. (one carbon is coalesced).

HRMS: (ESI^{-}-MS, m/z) $[M-H]^{-}$ calcd for $[C_{16}H_{10}N_4O_2SBr]$: 400.9708; found: 400.9691.

(Z)-N'-(5-(3-bromobenzylidene)-4-oxo-4,5-dihydrothiazol-2-yl)isonicotinohydrazide (9t).



R*f* value: 0.41 (10%, MeOH/DCM, 1/9)

Yield: 91%, (117.54 mg)

Appearance: yellow solid

FTIR: (ATR): 2943.69, 2788.20, 1687.50, 1631.42, 1599.37 cm^{-1}

^{1}H-NMR (600 MHz, DMSO-d6): 7.35 (t, *J* = 7.50 Hz, 1H, Ar-H), 7.51 (t, *J* = 7.76 Hz, 1H, Ar-H), 7.56 (t, *J* = 7.77 Hz, 1H, Ar-H), 7.69 (d, *J* = 6.25 Hz, 2H, ArPy-H), 7.78 (s, 1H, olefinic-H), 7.80 (dd, *J* = 3.92 Hz, 1H, Ar-H), 8.76 (d, *J* = 5.46 Hz, 2H, ArPy-H), 11.46 (s, 1H, NH), 12.80 (s, 1H, NH).

^{13}C-NMR (150 MHz, DMSO-d6): 121.90, 122.03, 125.54, 126.53, 127.93, 129.06, 129.43, 132.06, 133.42, 134.01, 140.35, 150.66, 150.79, 162.70.

HRMS: (ESI^{-}-MS, m/z) $[M-H]^{-}$ calcd for $[C_{16}H_{10}N_4O_2SBr]$: 400.9708; found: 400.9703.

4. Spectral data

4.1. Spectral data of compounds 8’

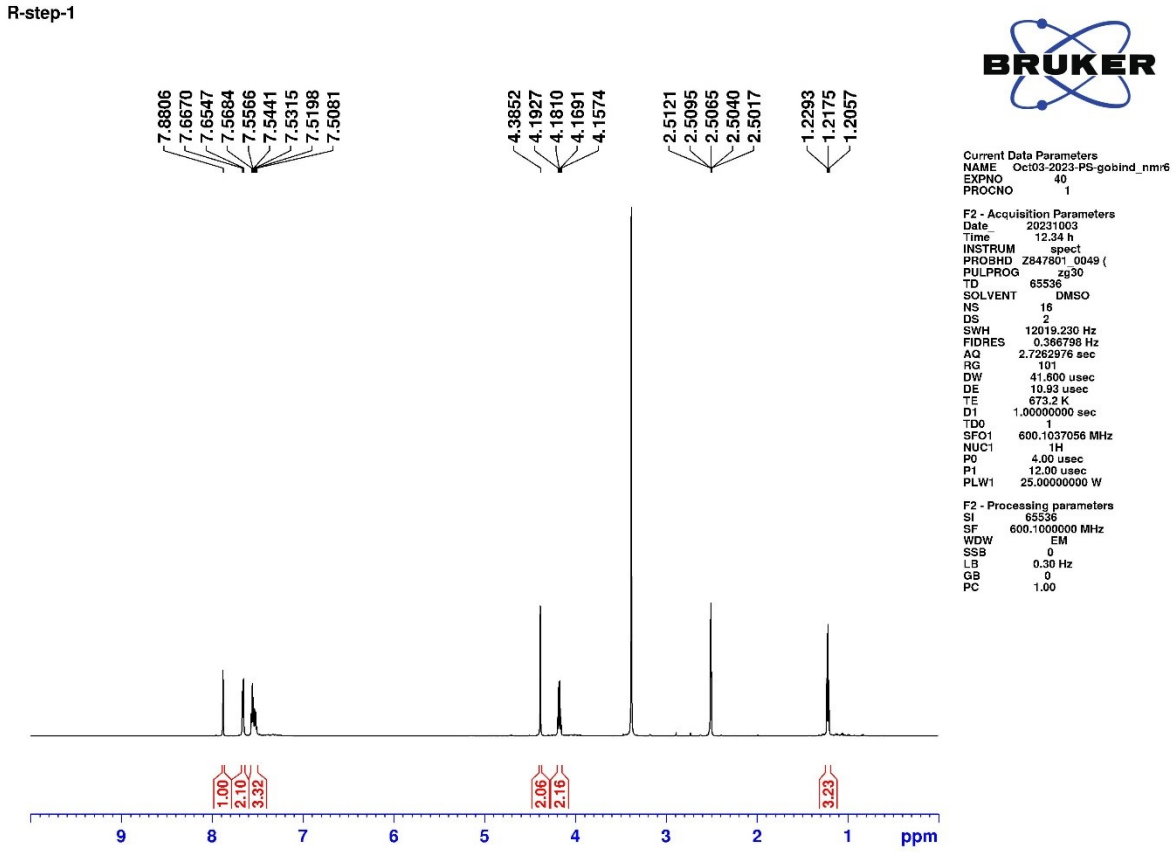


Figure S4. ^{1}H-NMR of compound **8’**.

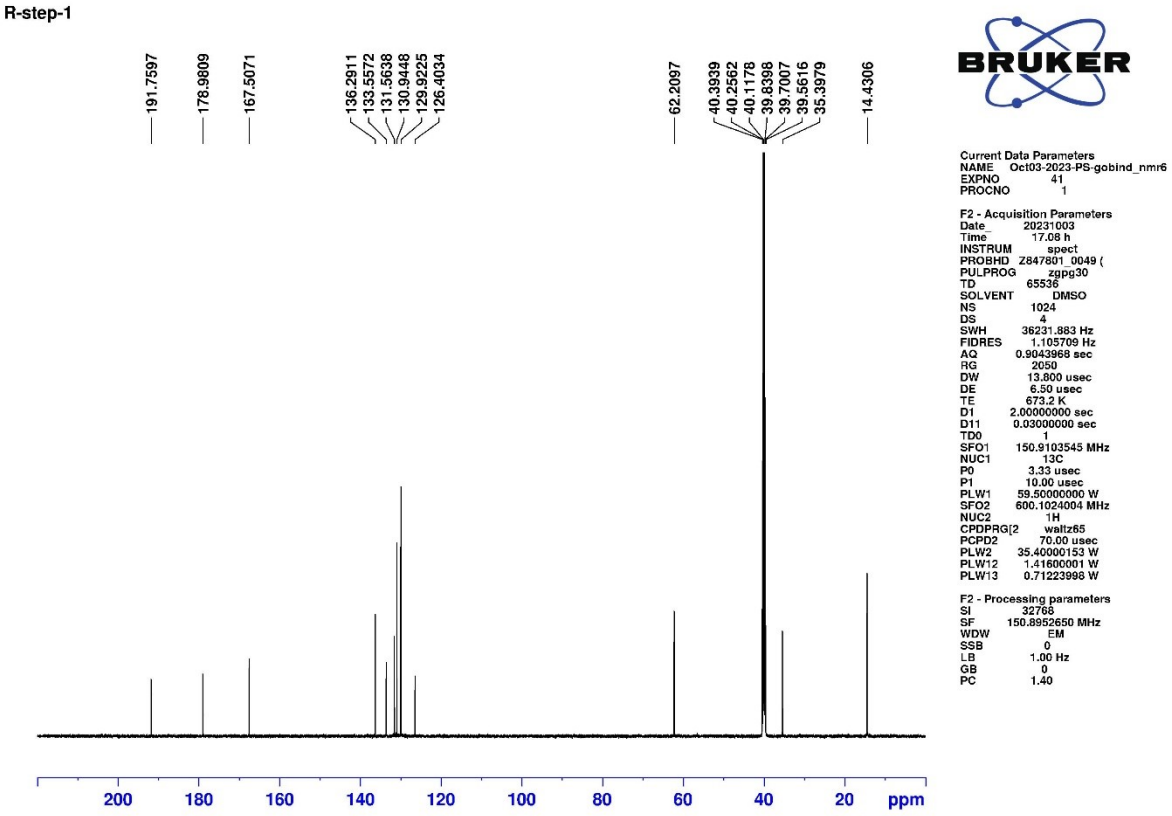


Figure S5. ^{13}C-NMR of compound **8'**.

4.2. Spectral data of compounds 8a-t

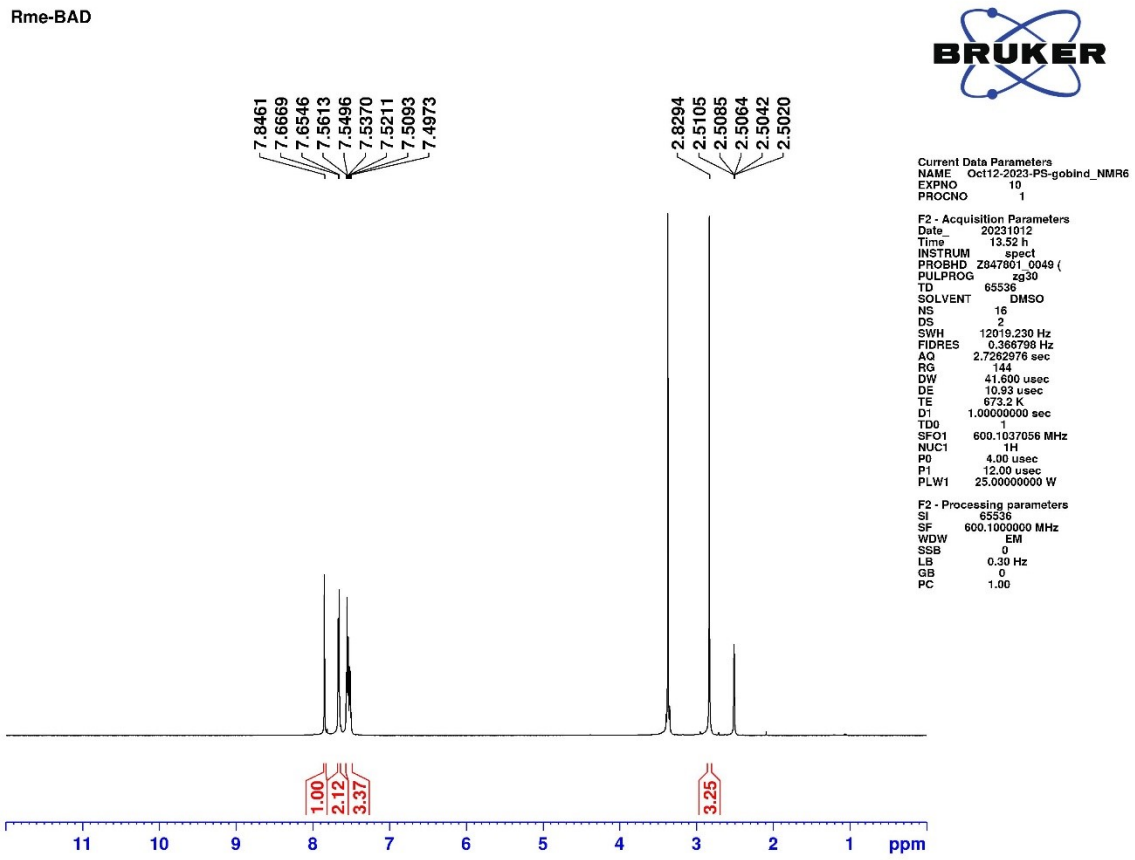


Figure S6. ^{1}H-NMR of compound **8a**.

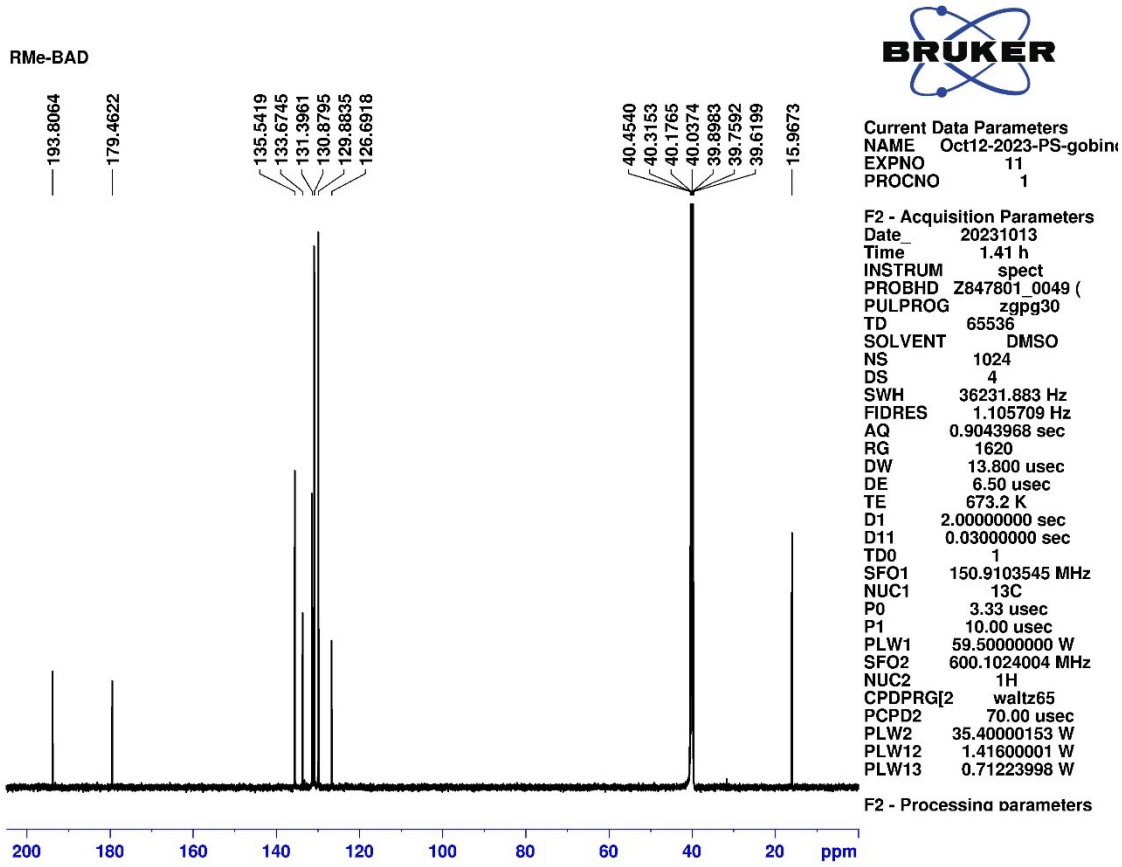


Figure S7. ^{13}C-NMR of compound 8**a**.

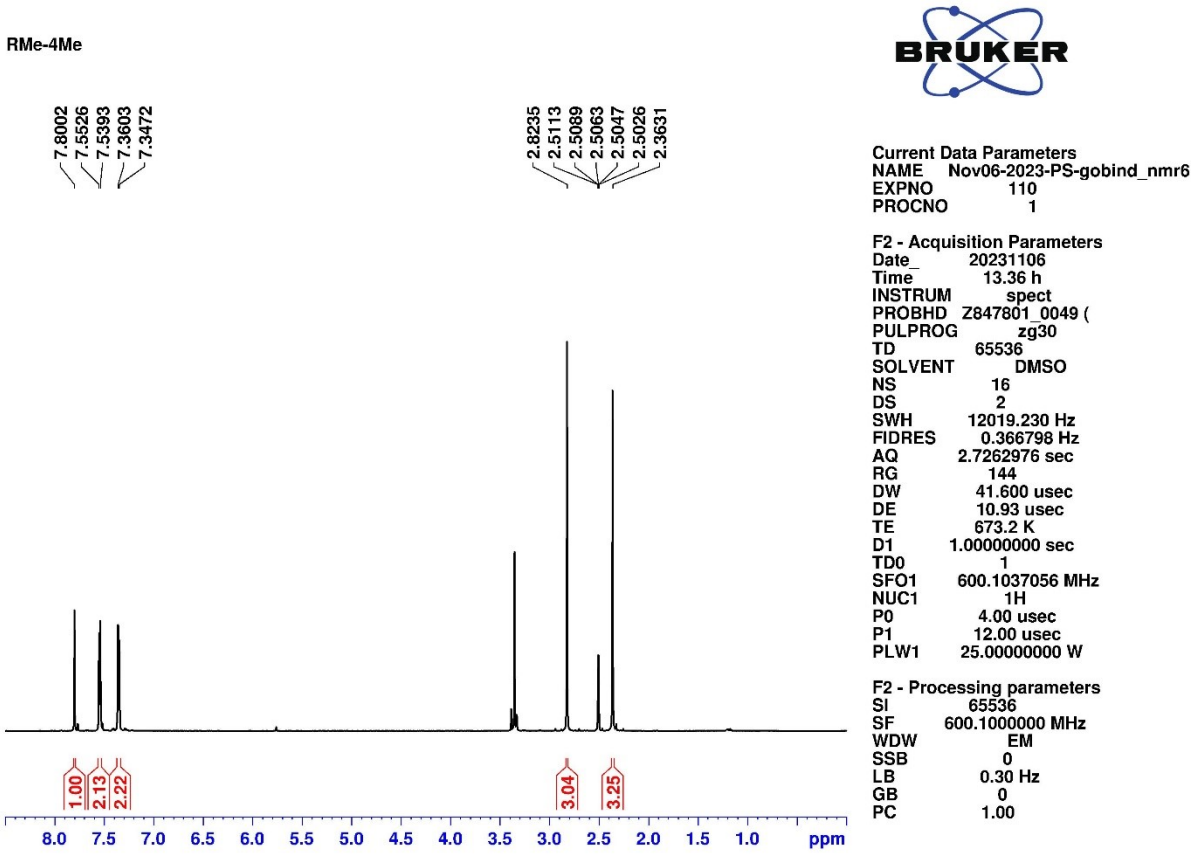


Figure S8. ^{1}H-NMR of compound **8b**.

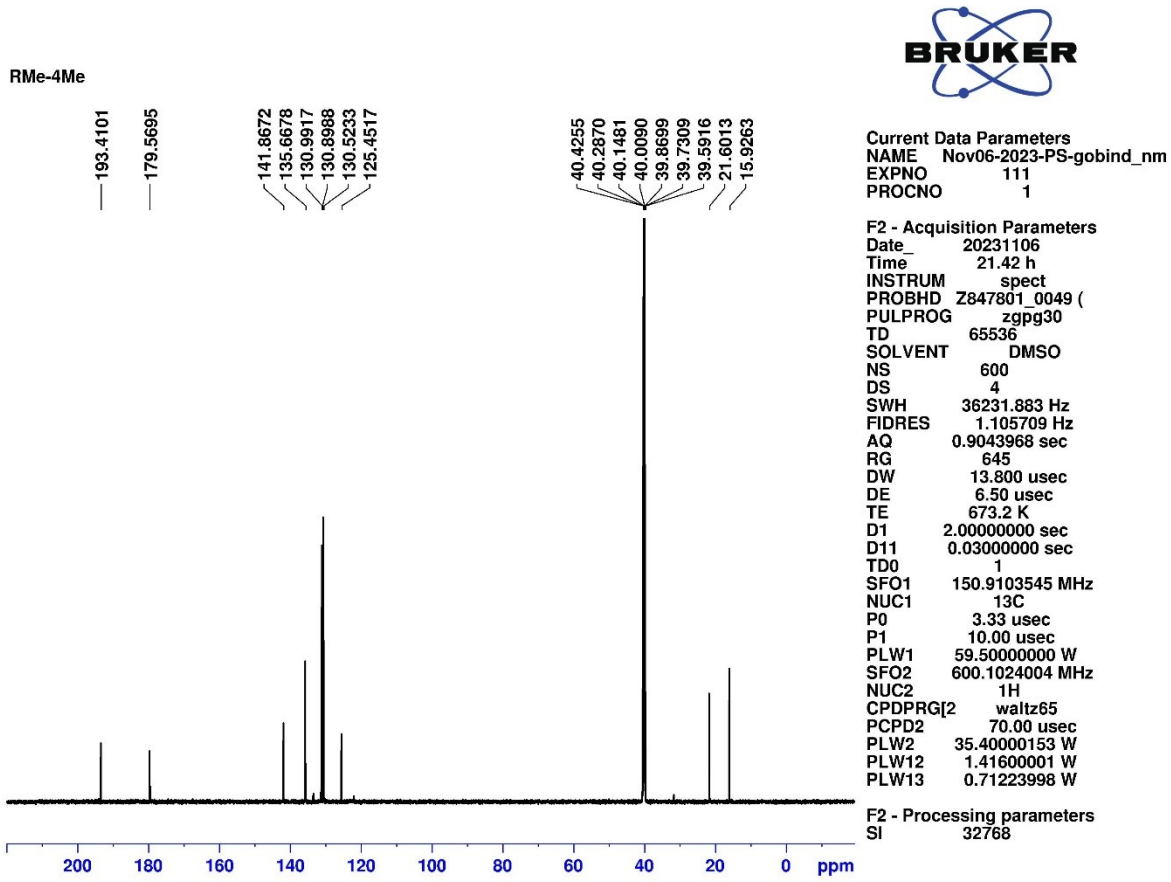


Figure S9. ^{13}C-NMR of compound **8b**.

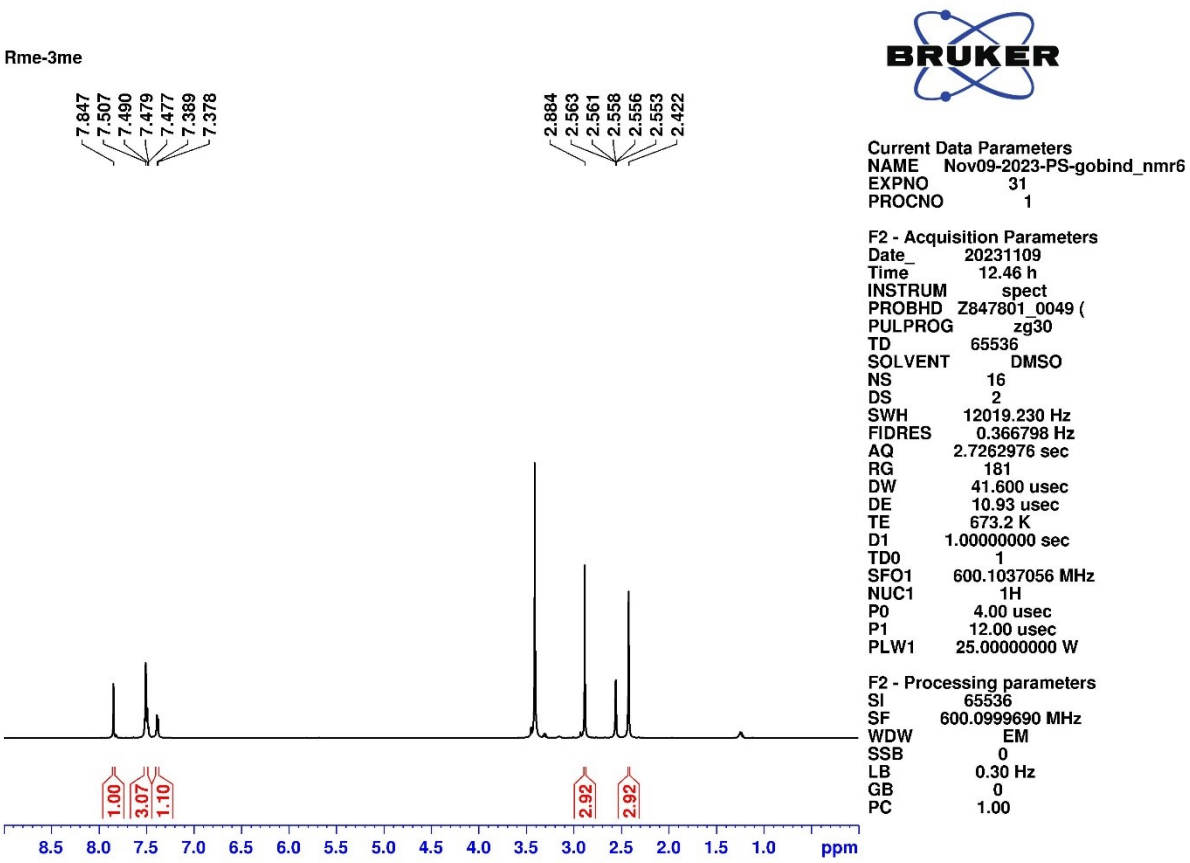


Figure S10. ^{1}H-NMR of compound **8c**.

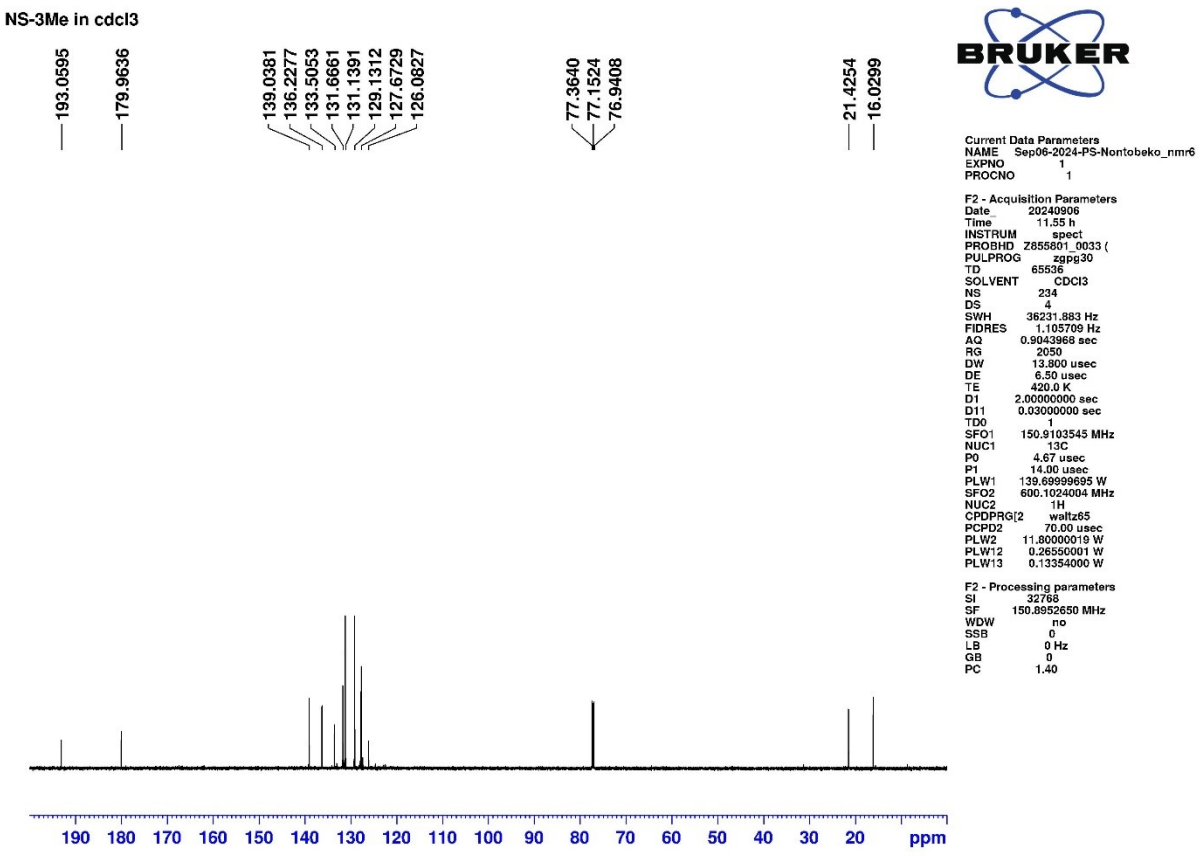


Figure S11. ^{13}C-NMR of compound **8c**.

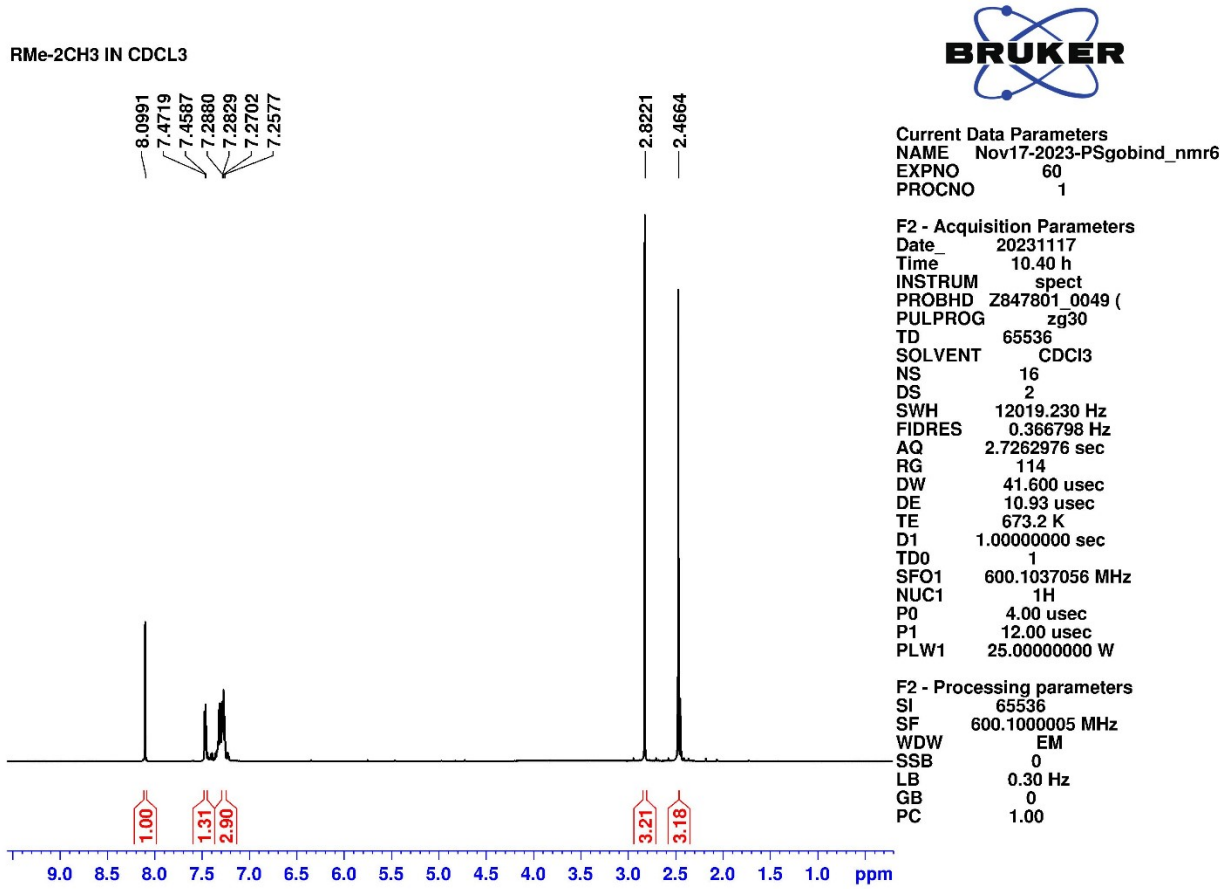


Figure S12. ^{1}H-NMR of compound **8d**.

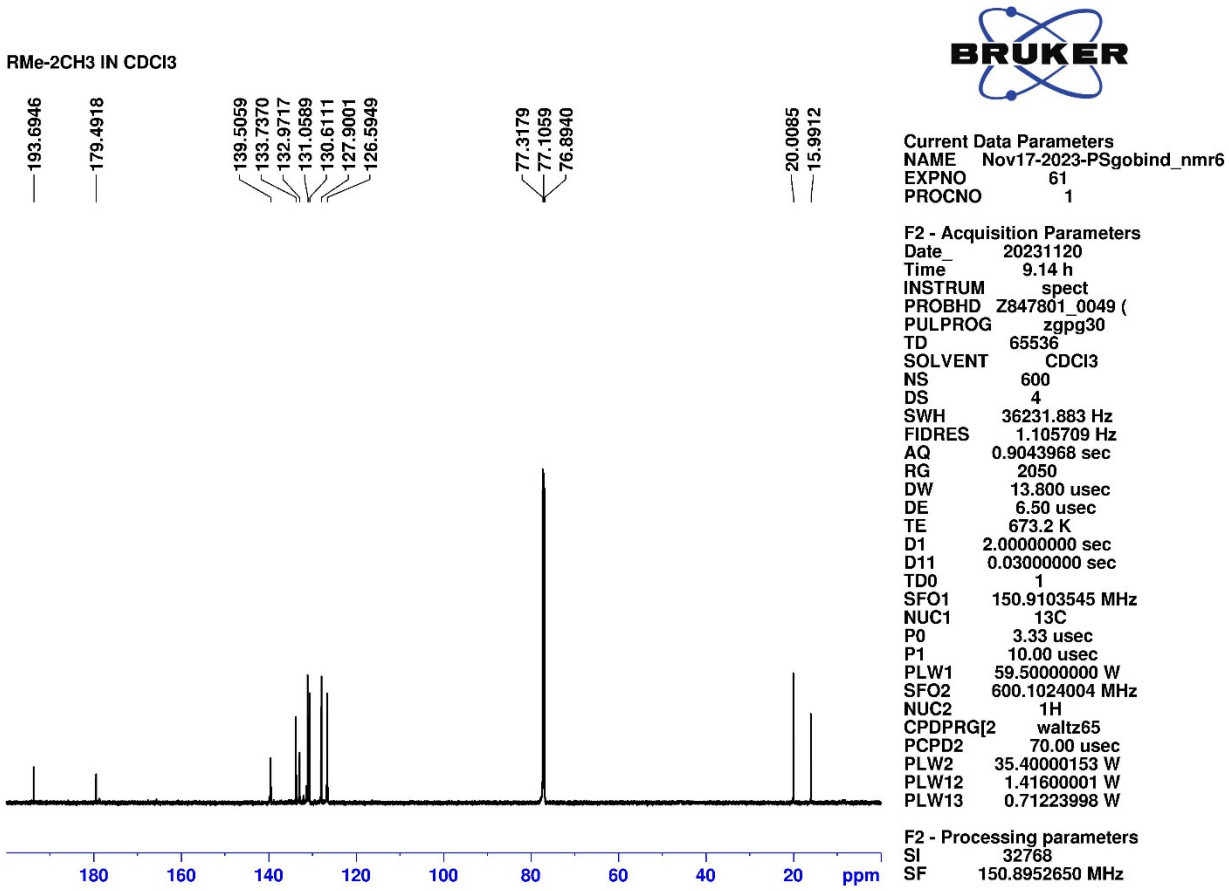


Figure S13. ^{13}C-NMR of compound **8d**.

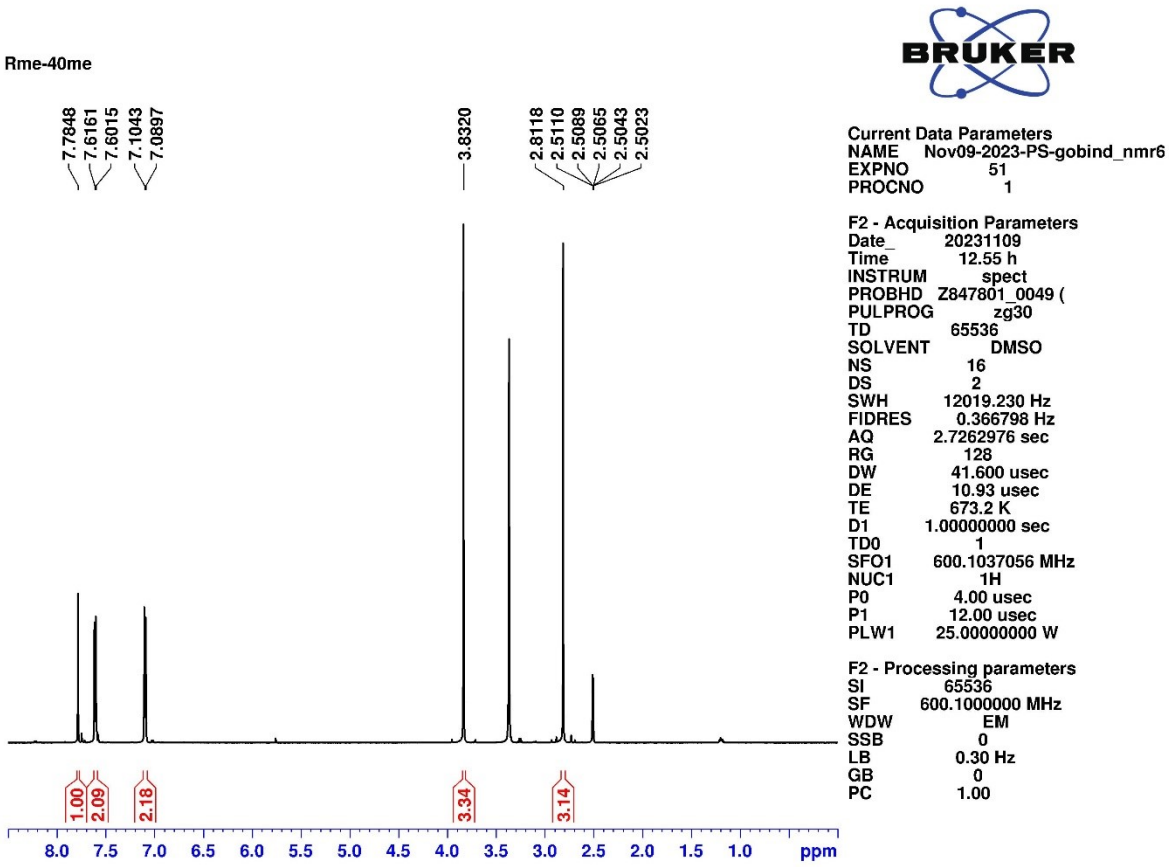


Figure S14. ^{1}H-NMR of compound **8e**.

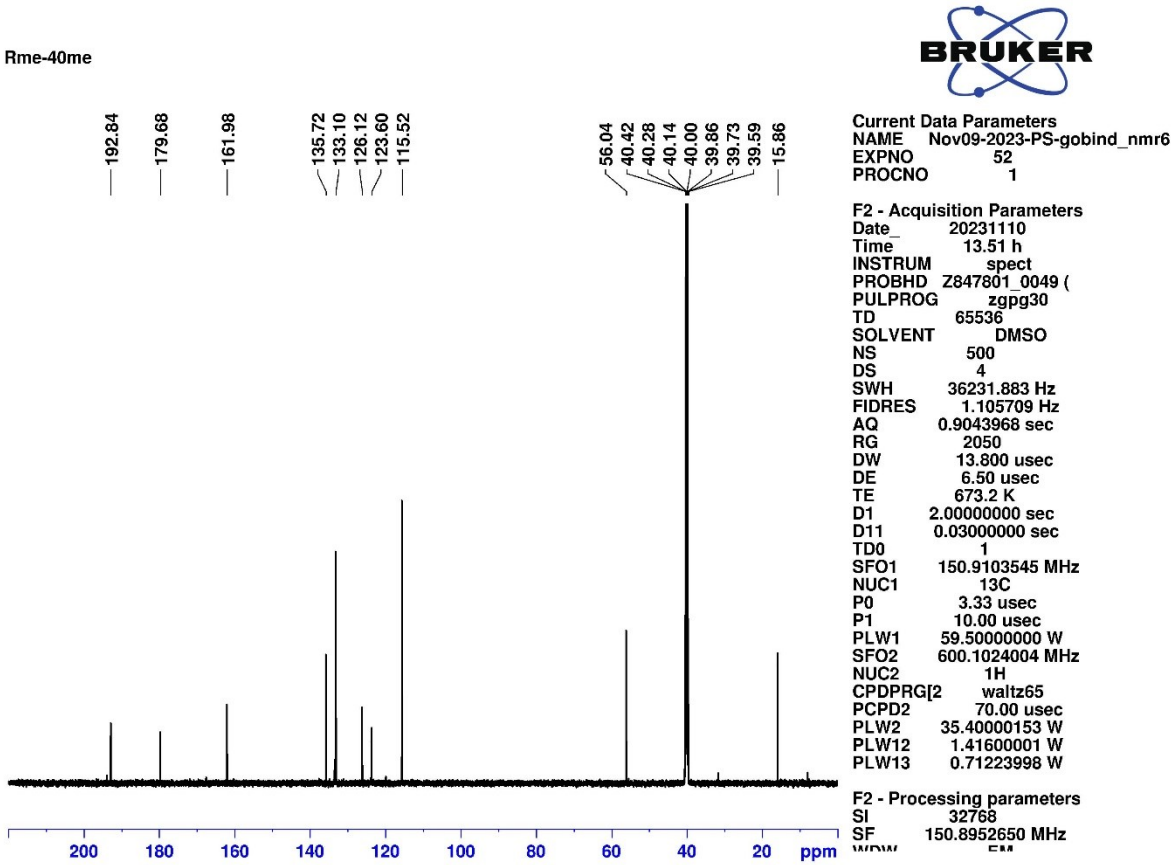


Figure S15. ^{13}C-NMR of compound **8e**.

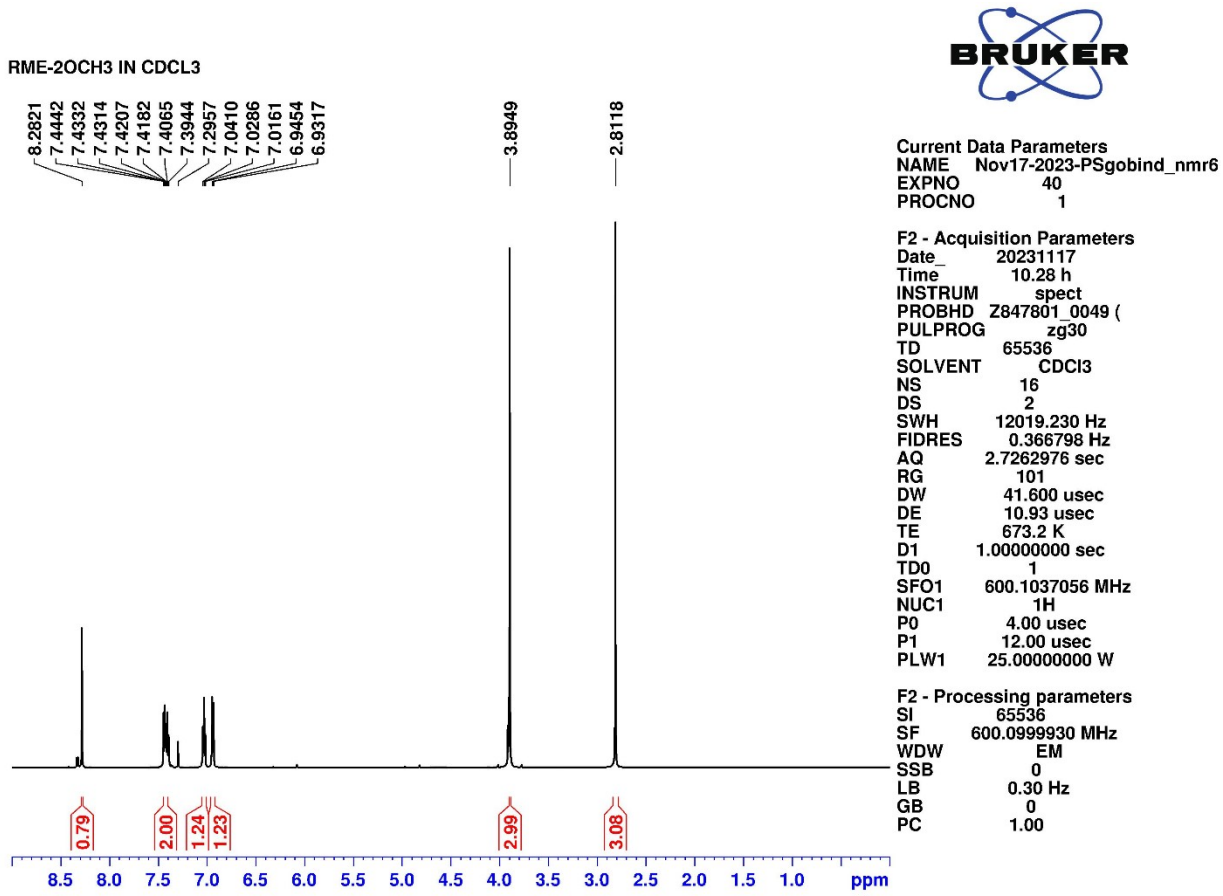


Figure S16. ^{1}H-NMR of compound **8f**.

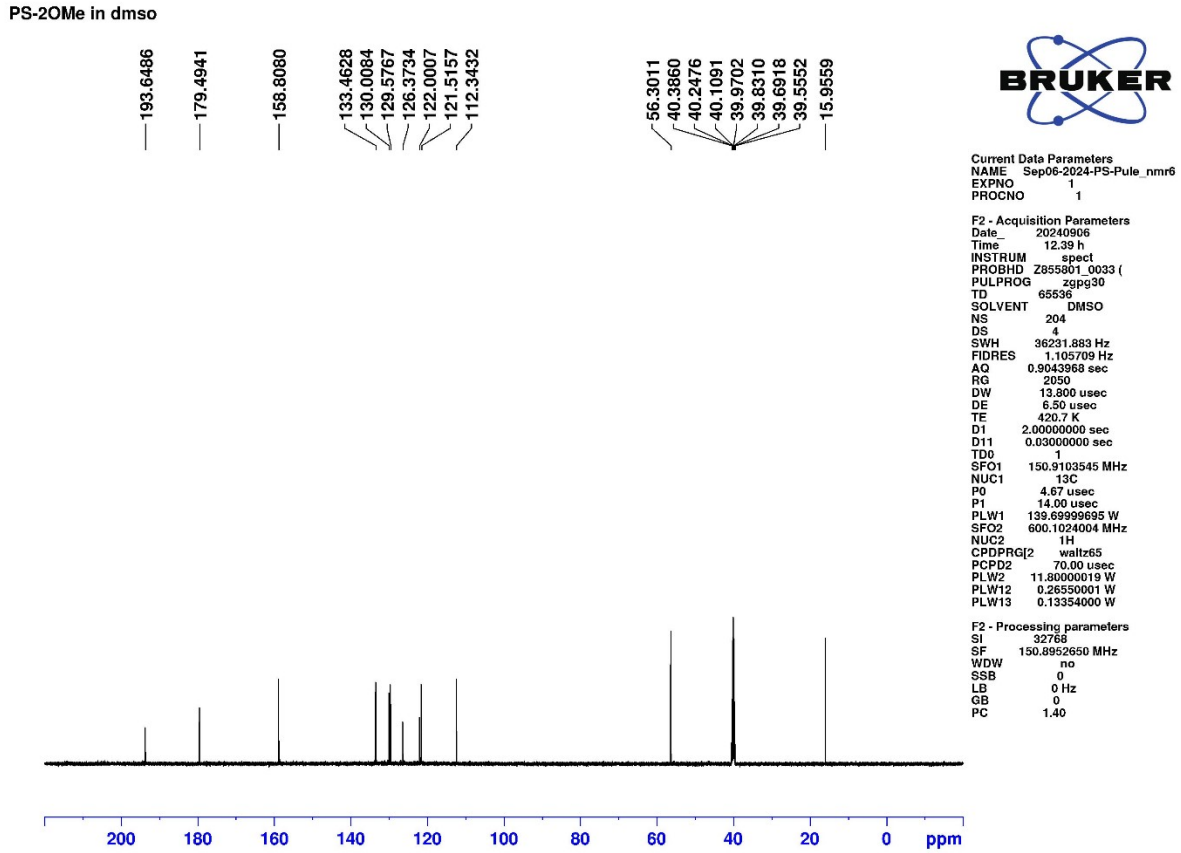


Figure S17. ^{13}C-NMR of compound **8f**.

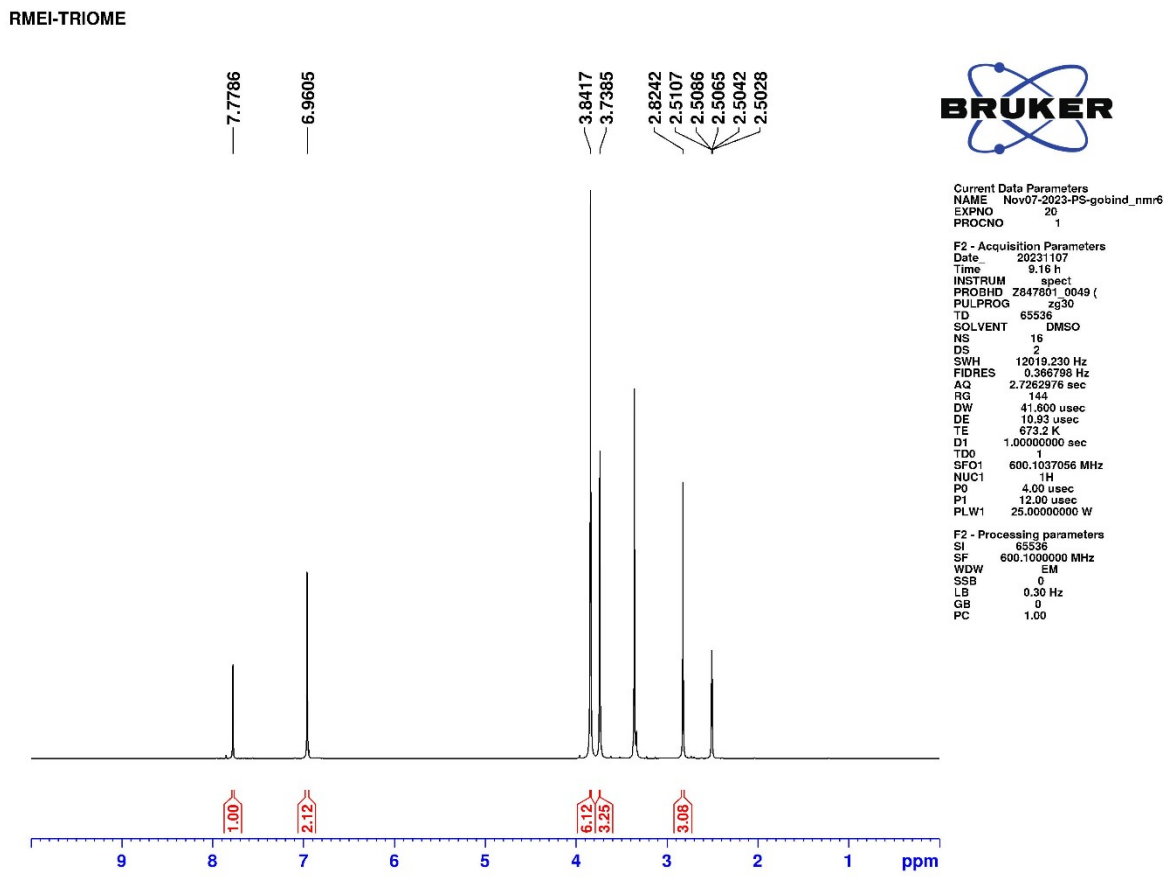


Figure S18. ^{1}H-NMR of compound **8g**.

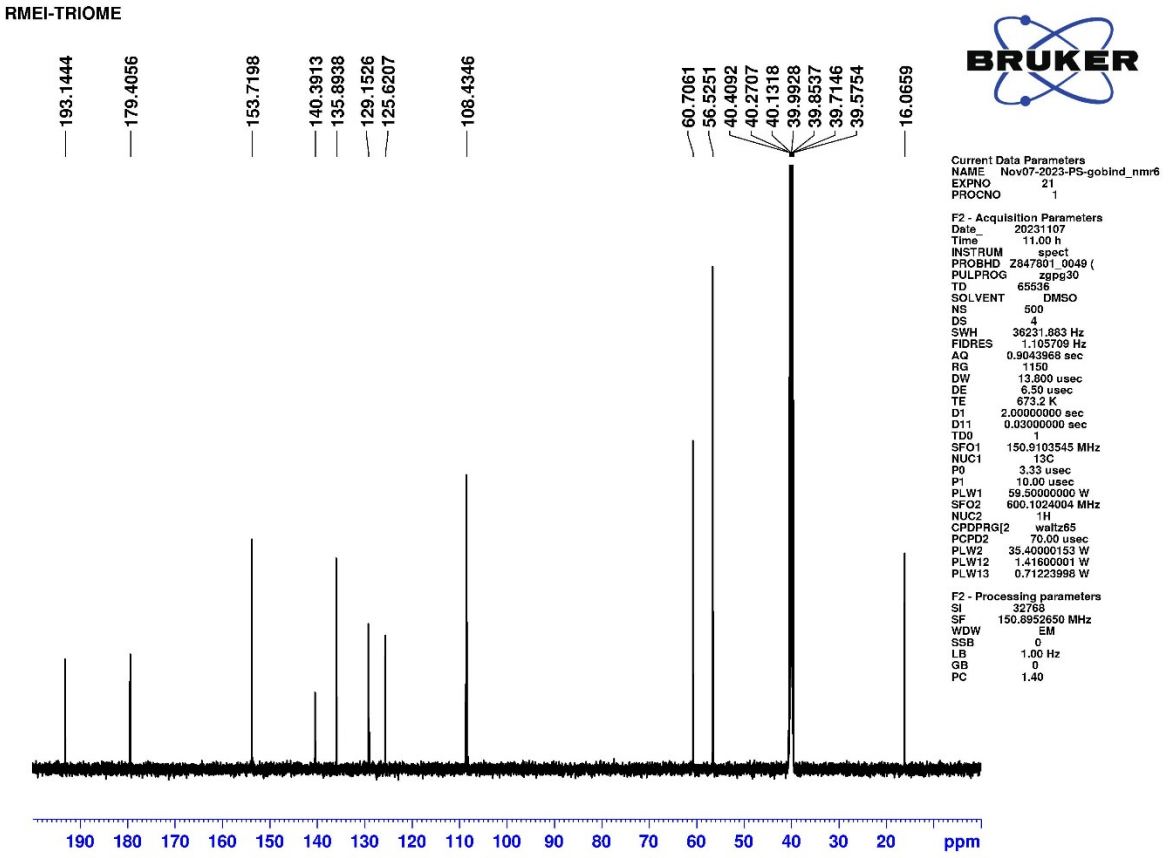


Figure S19. ^{13}C-NMR of compound **8g**.

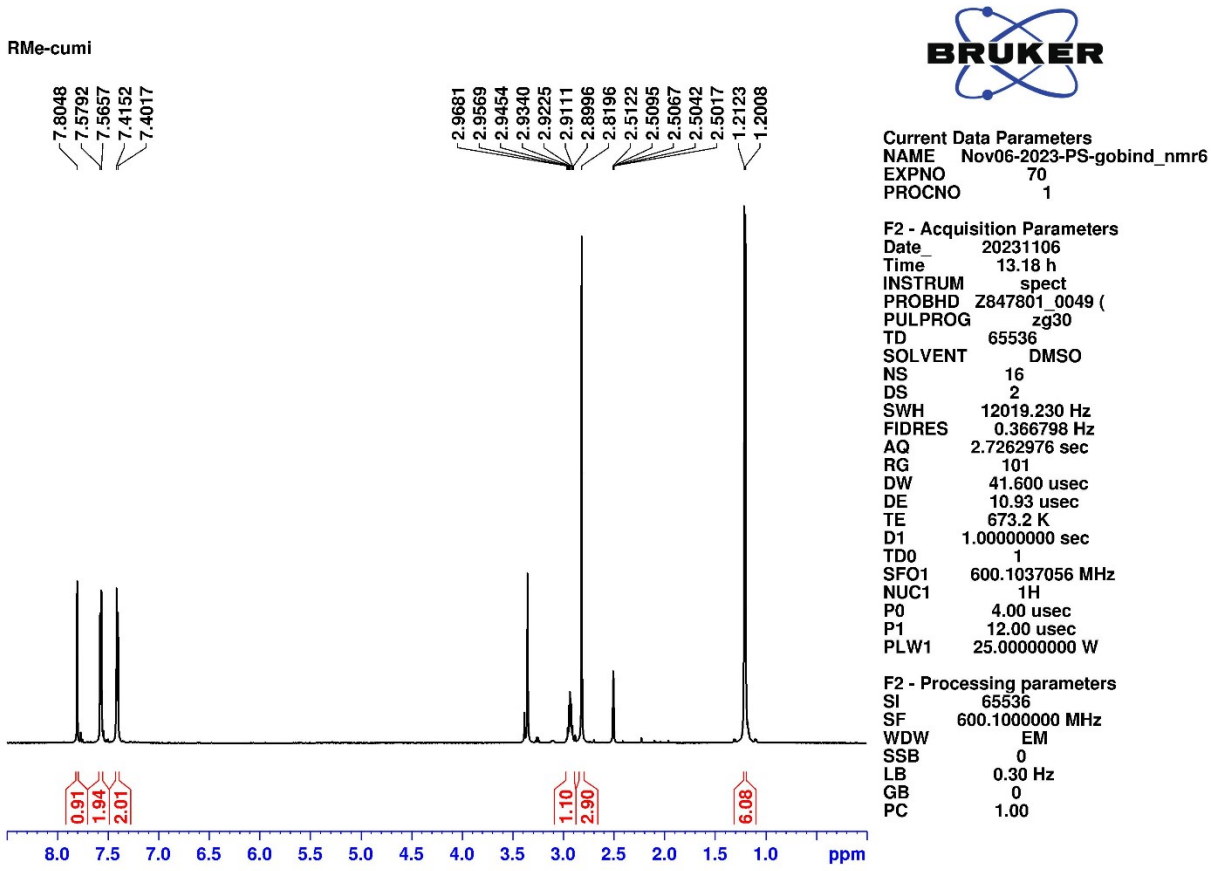


Figure S20. ^{1}H-NMR of compound **8h**.

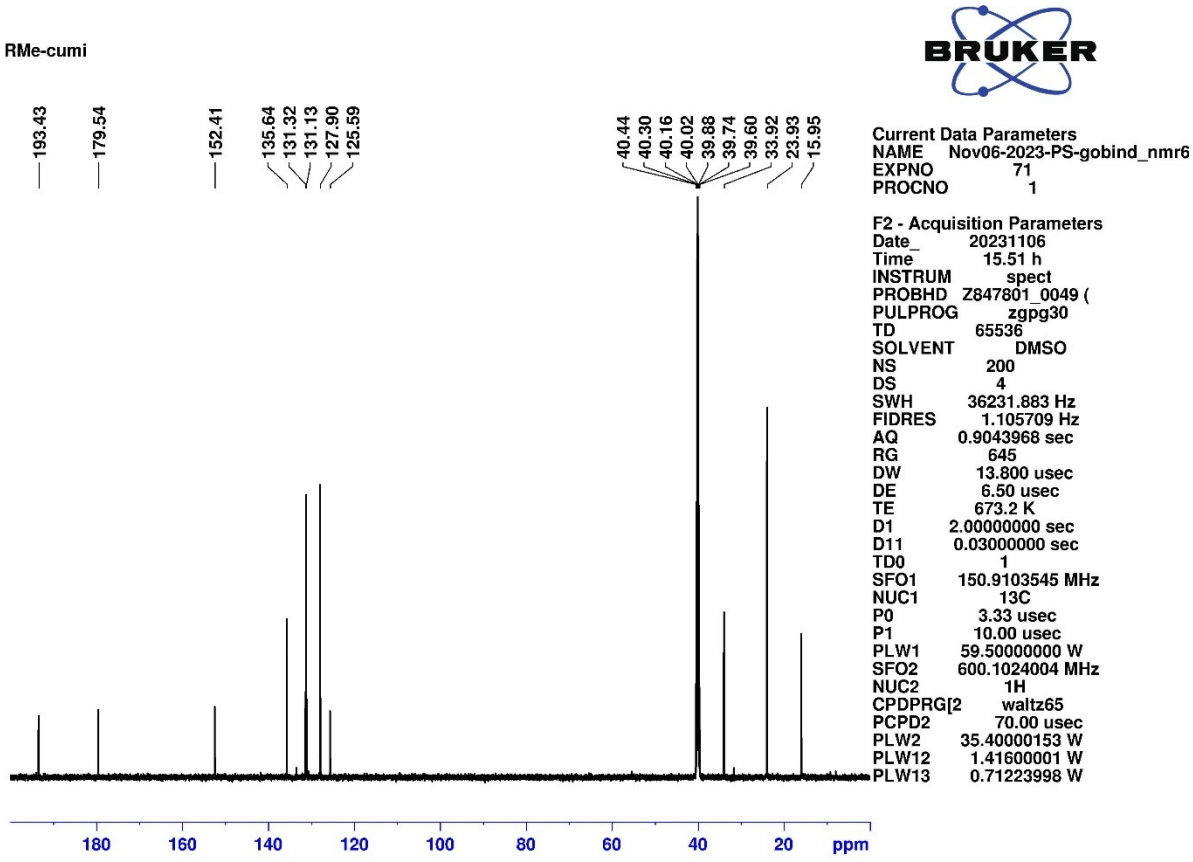


Figure S21. ^{13}C-NMR of compound **8h**.

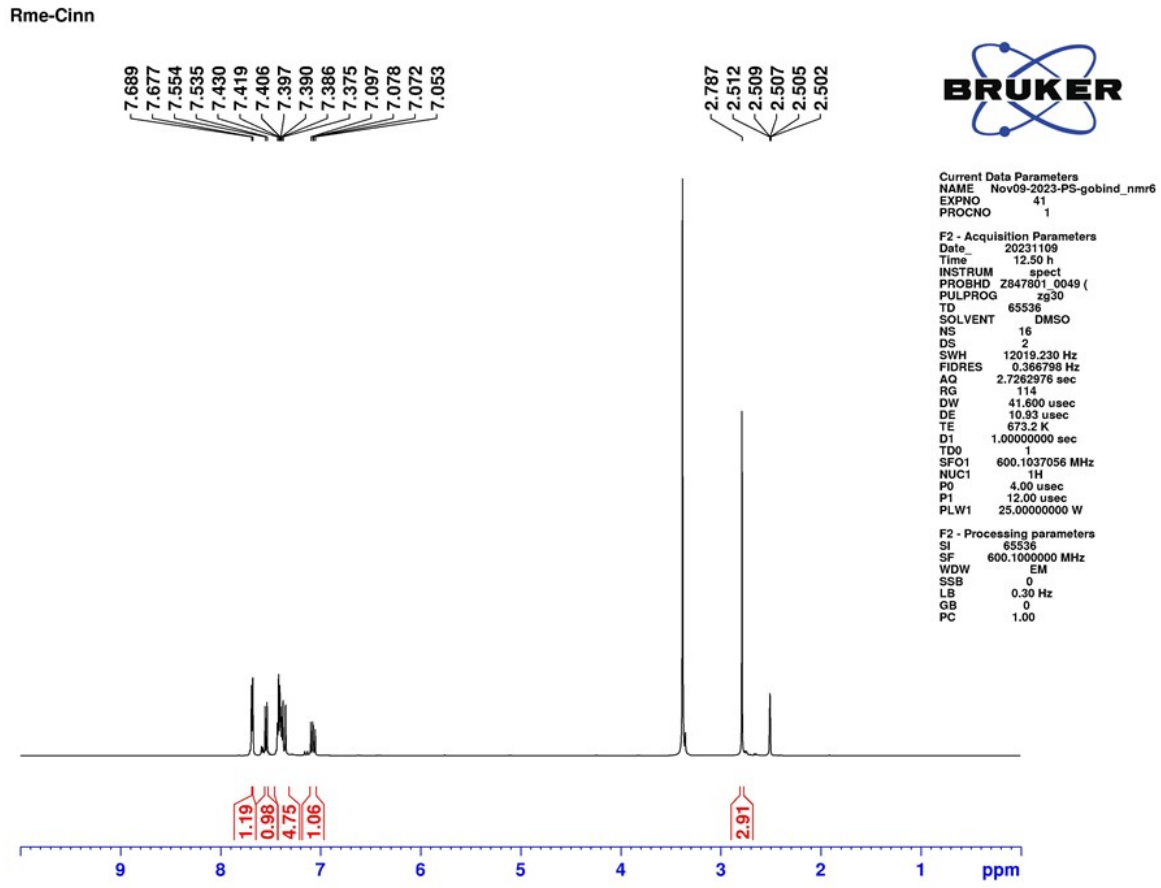


Figure S22. ^{1}H-NMR of compound **8i**.

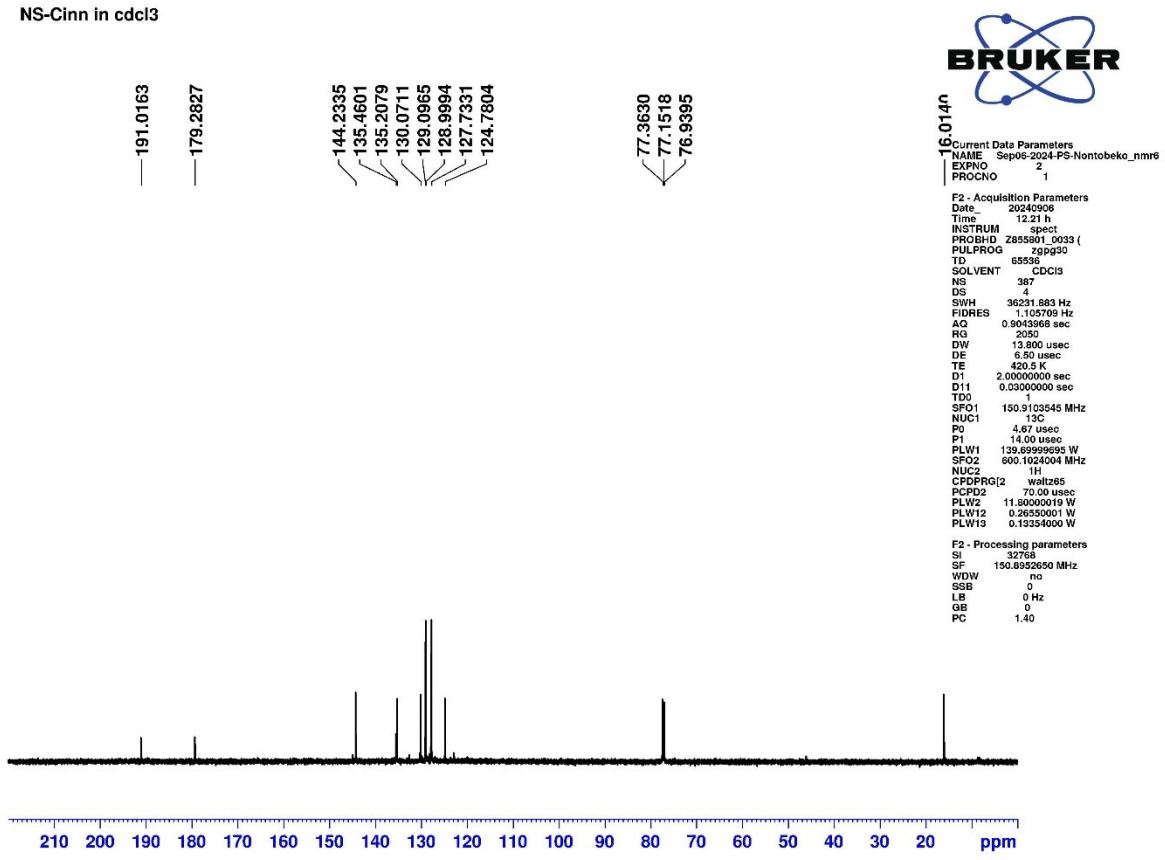


Figure S23. ^{13}C-NMR of compound **8i**.

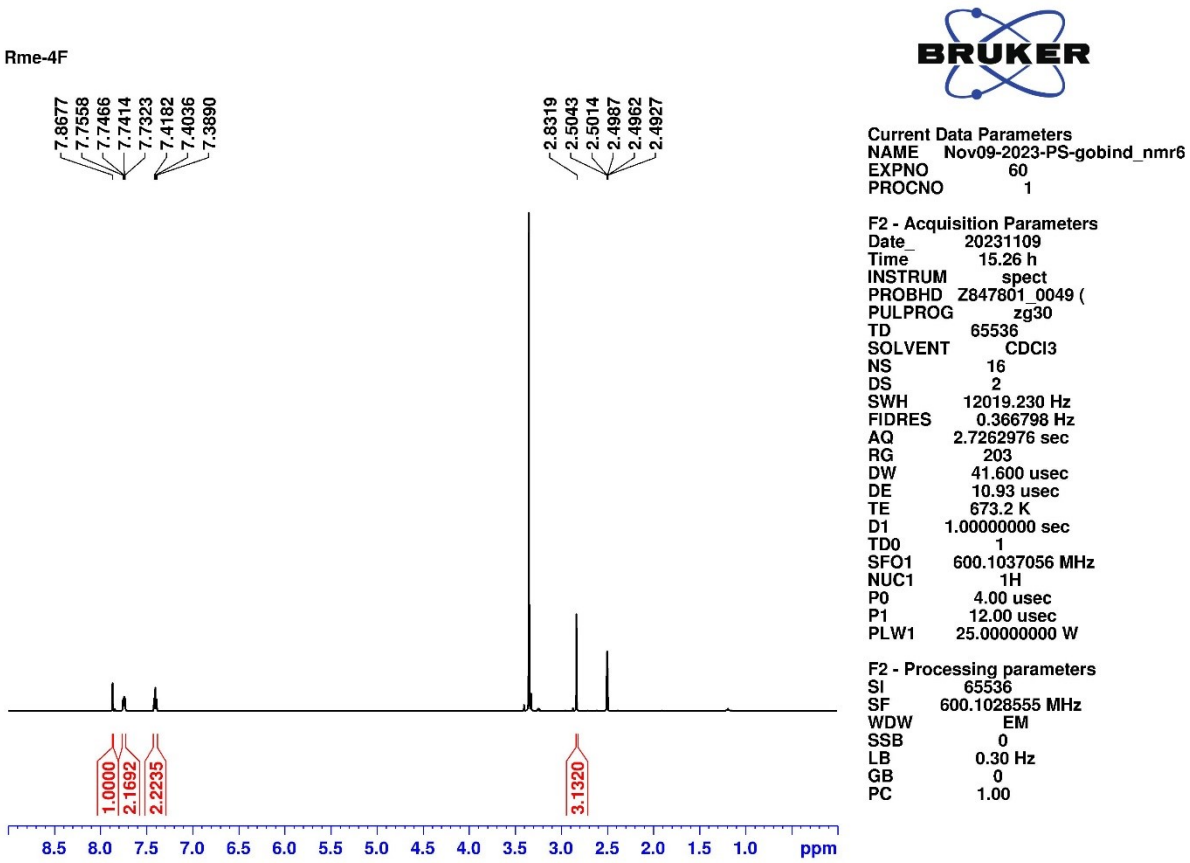


Figure S24. [1]H-NMR of compound **8j**.

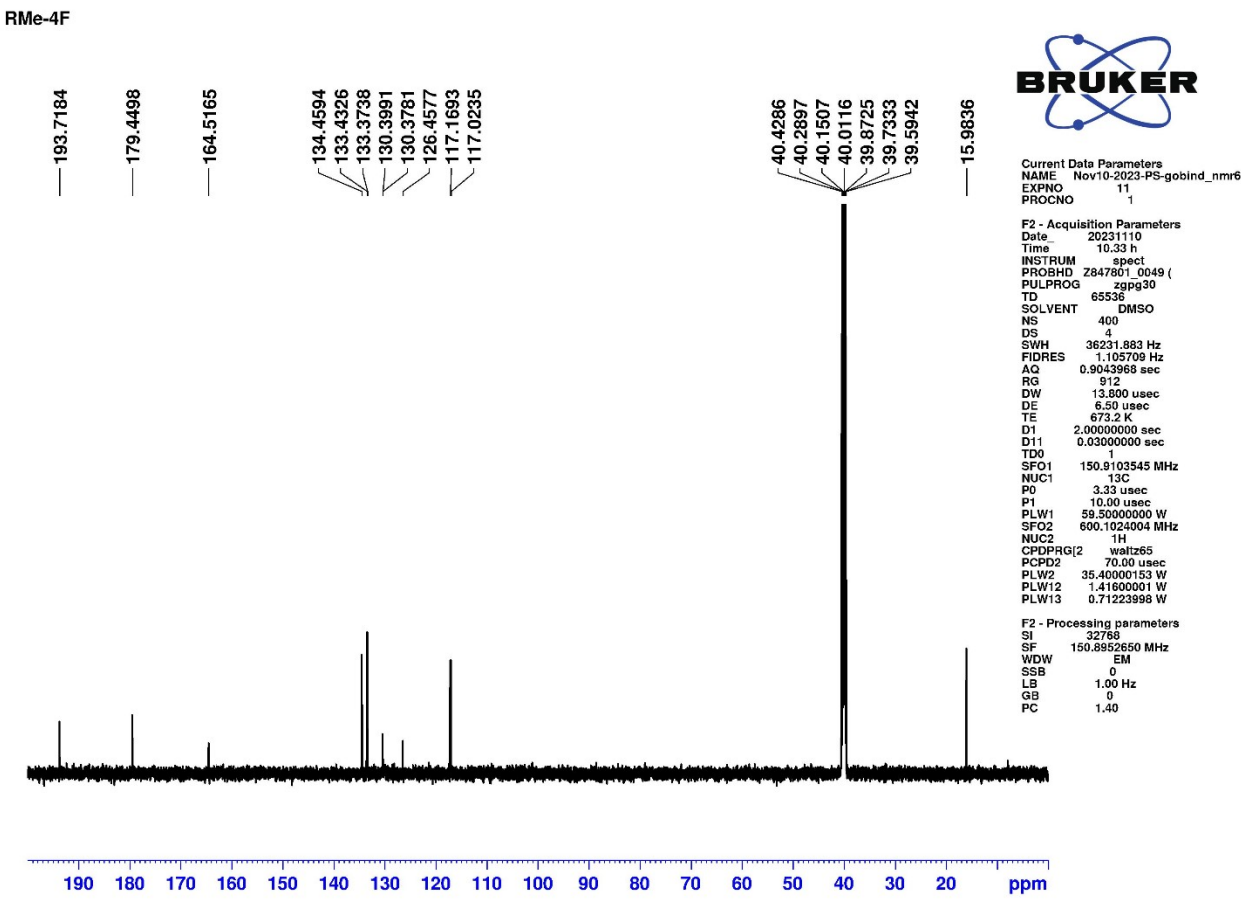


Figure S25. ^{13}C-NMR of compound **8j**.

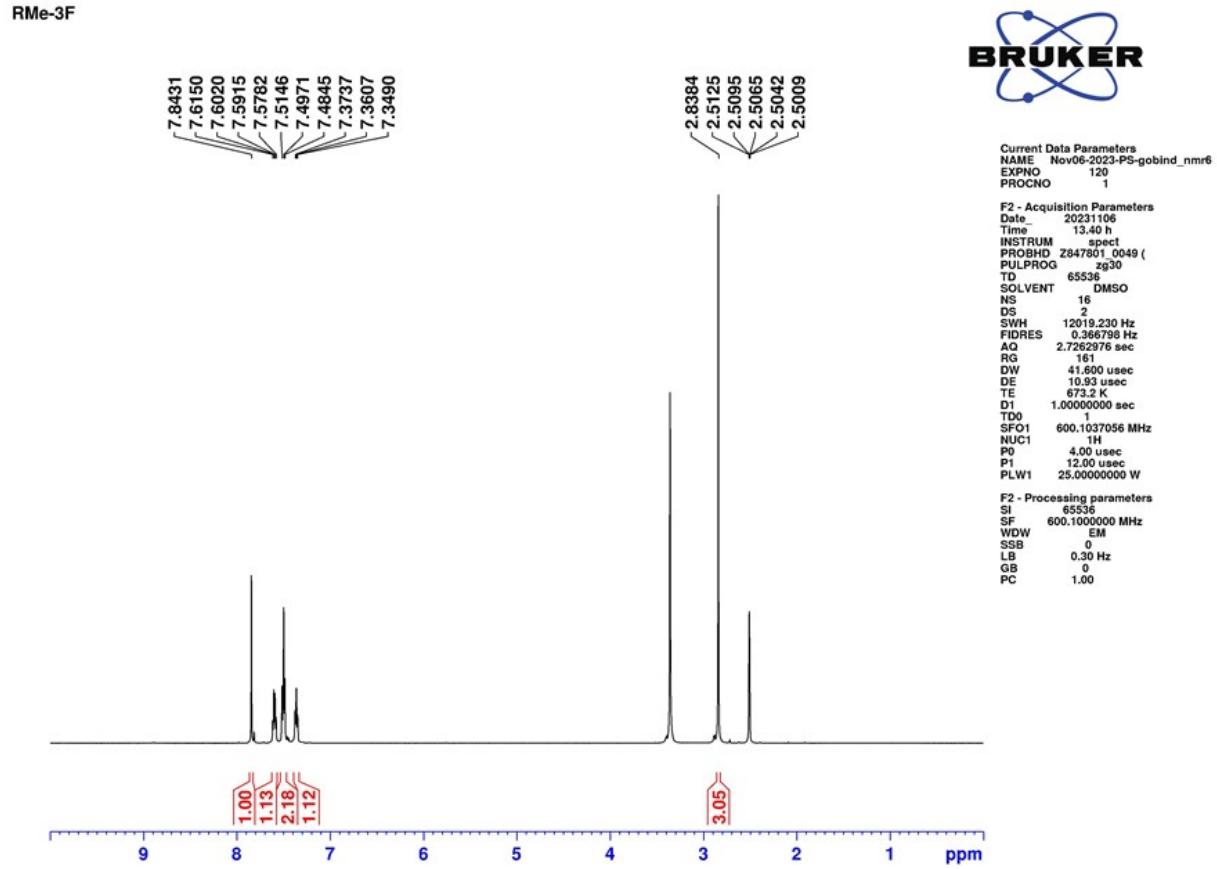


Figure S26. ^{1}H-NMR of compound **8k**.

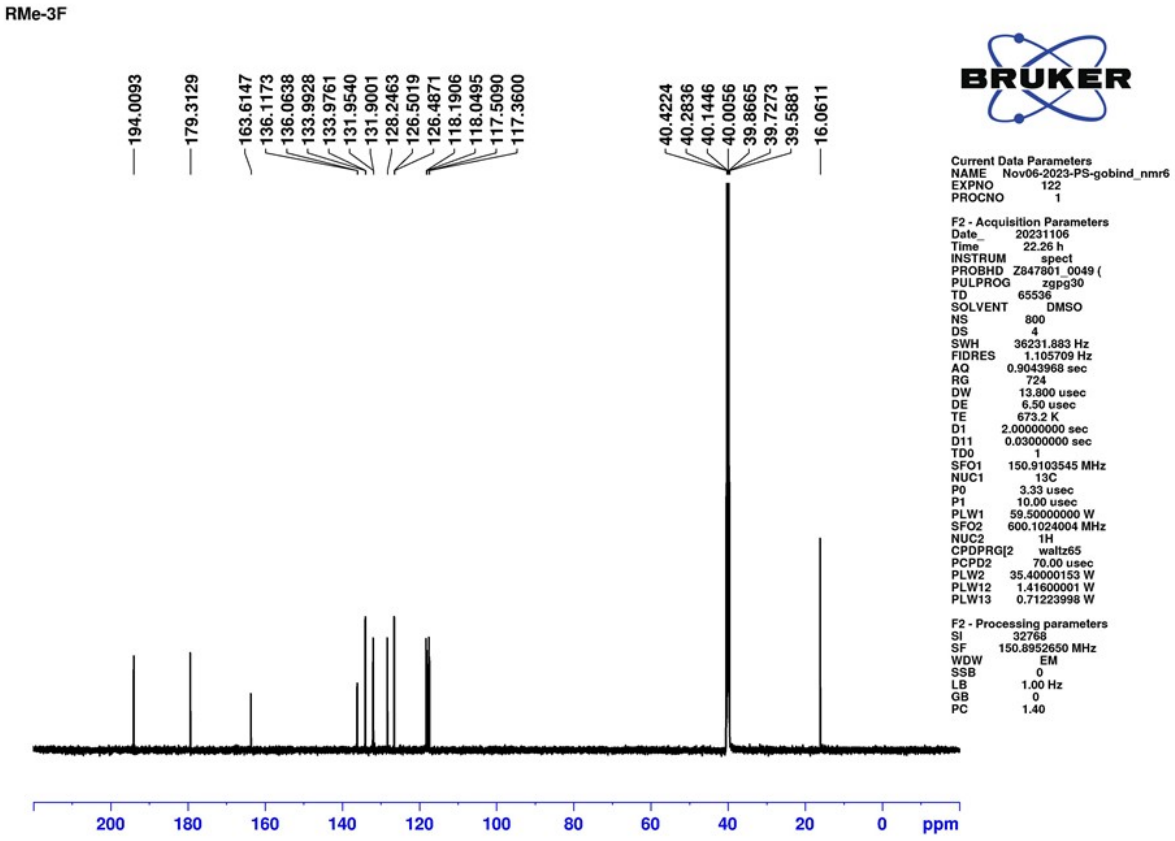


Figure S27. ^{13}C-NMR of compound **8k**.

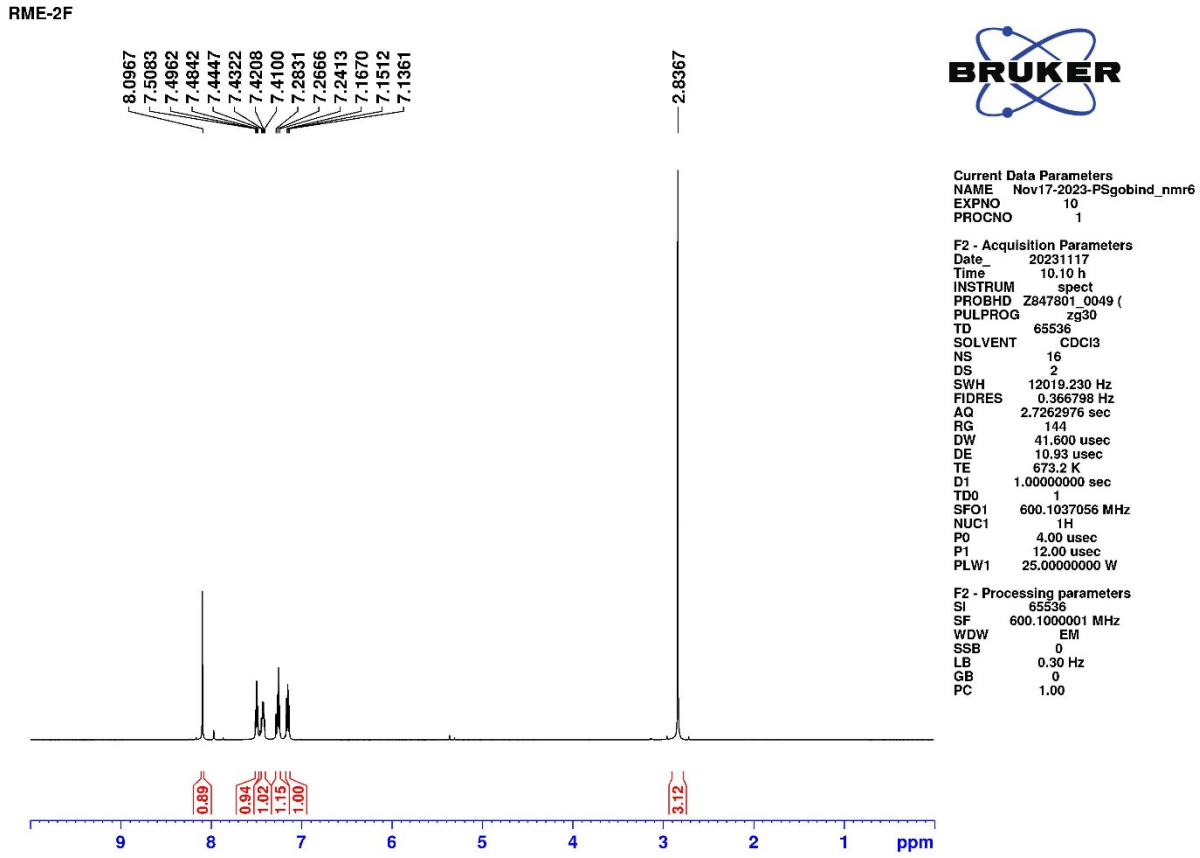


Figure S28. ^{1}H-NMR of compound **8l**.

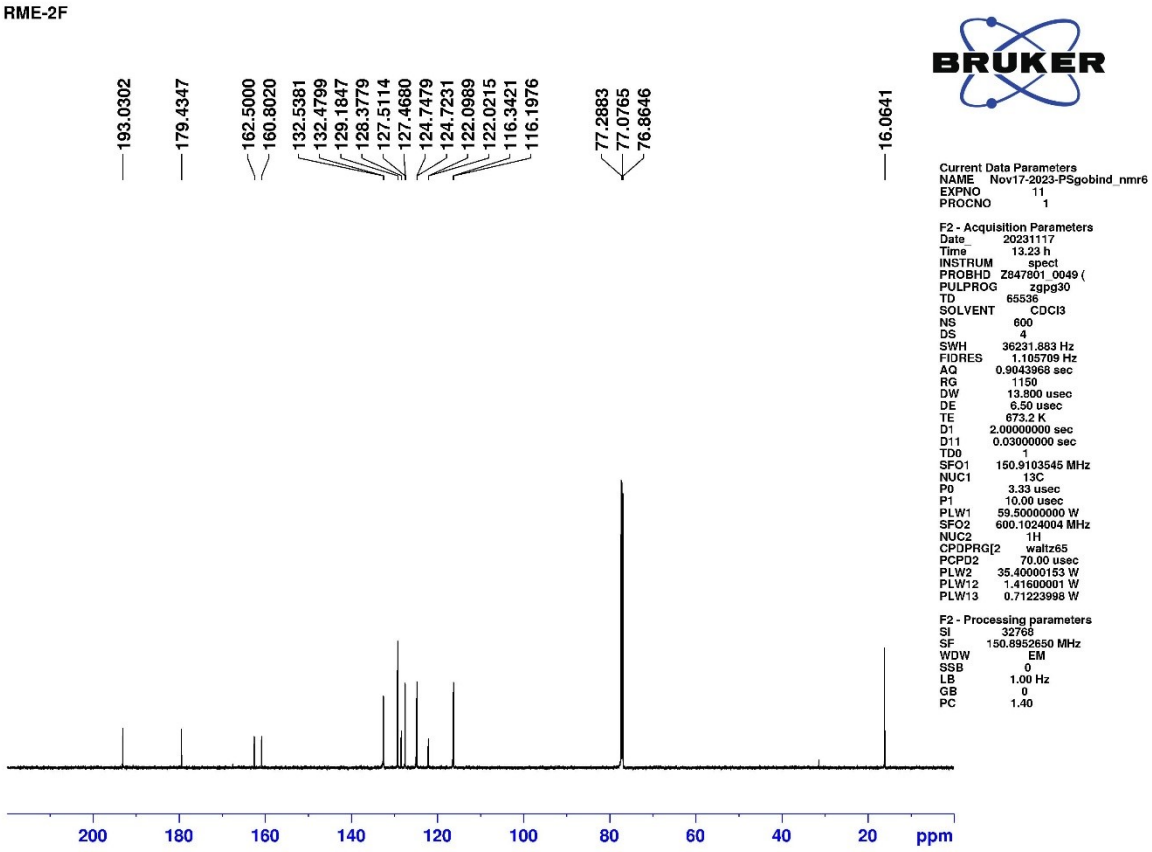


Figure S29. ^{13}C-NMR of compound **8l**.

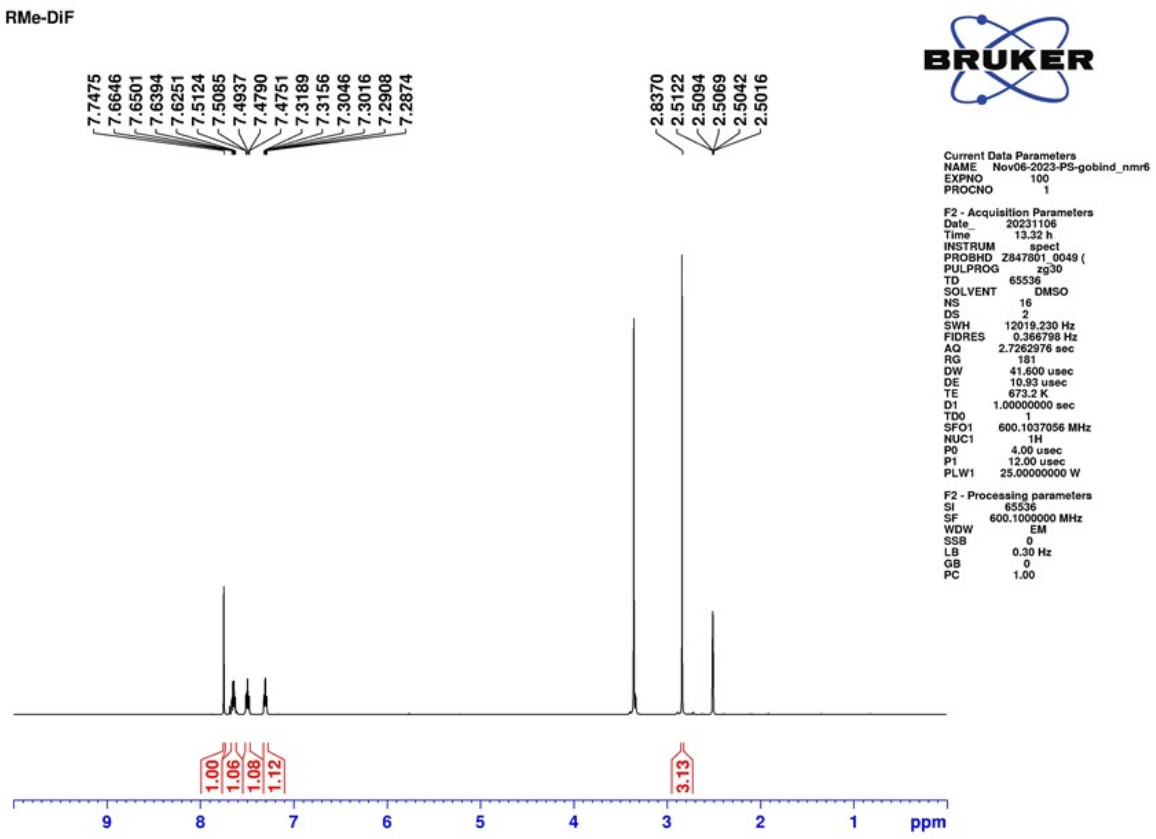


Figure S30. ^{1}H-NMR of compound **8m**.

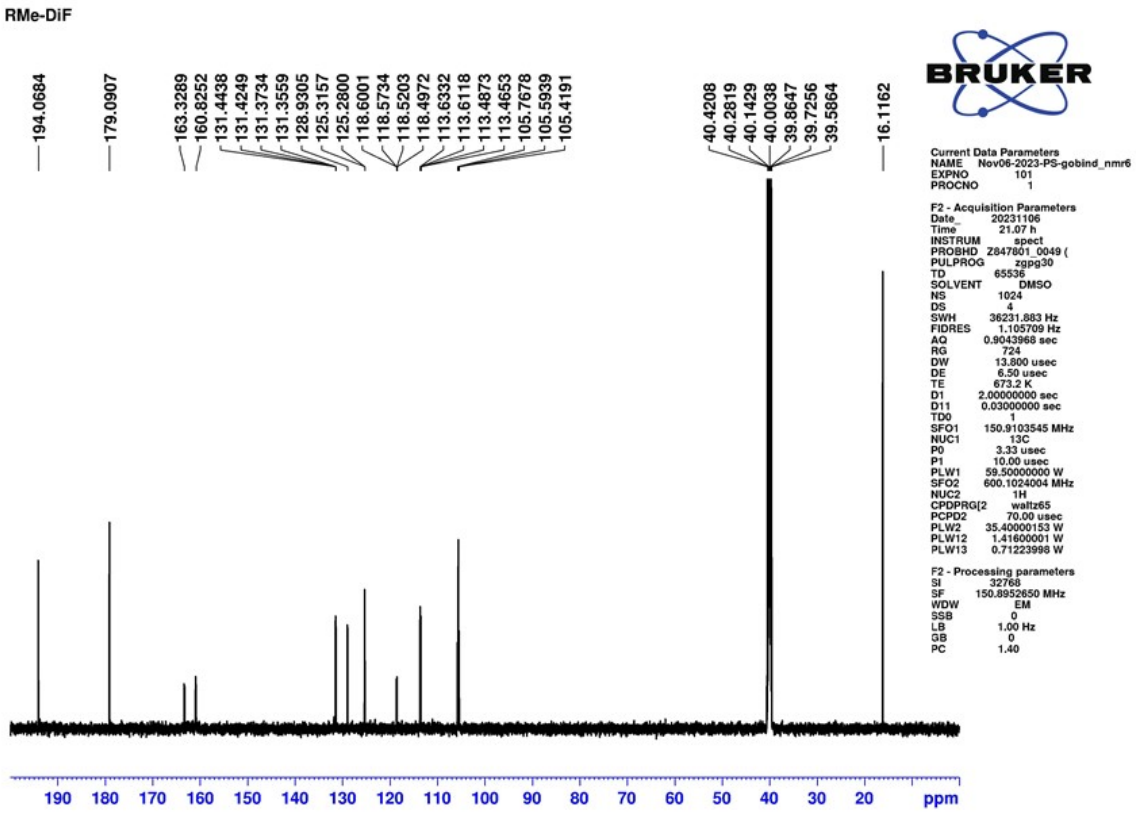


Figure S31. ^{13}C-NMR of compound **8m**.

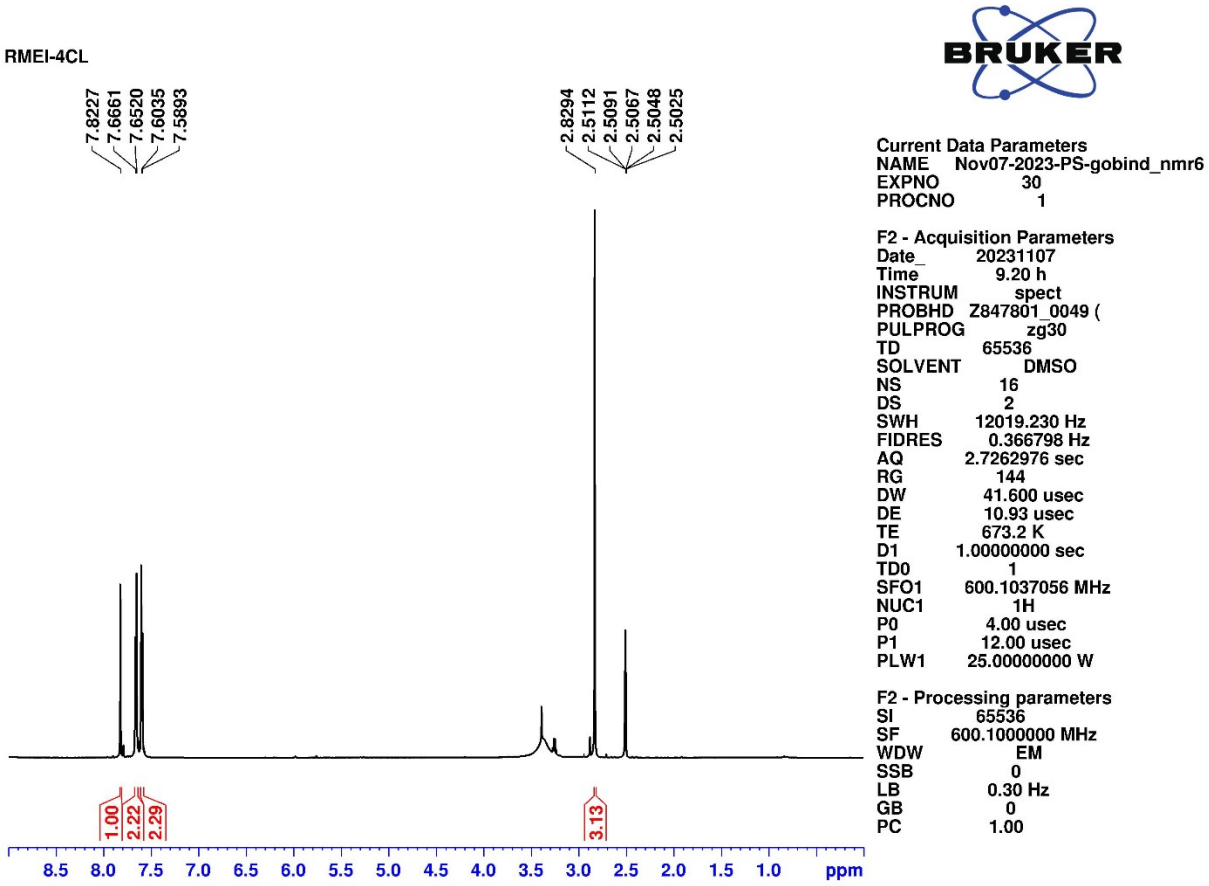


Figure S32. ^{1}H-NMR of compound **8n**.

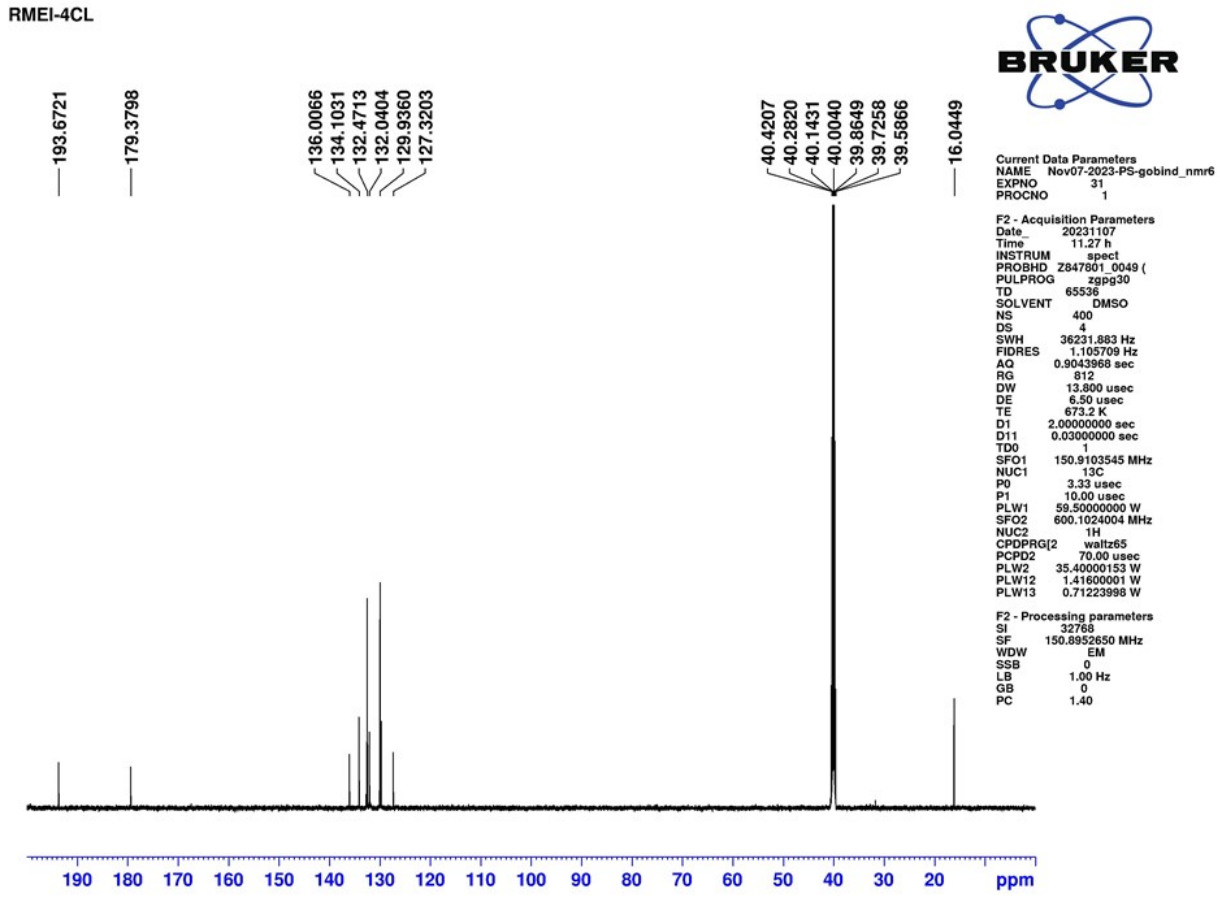


Figure S33. ^{13}C-NMR of compound **8n**.

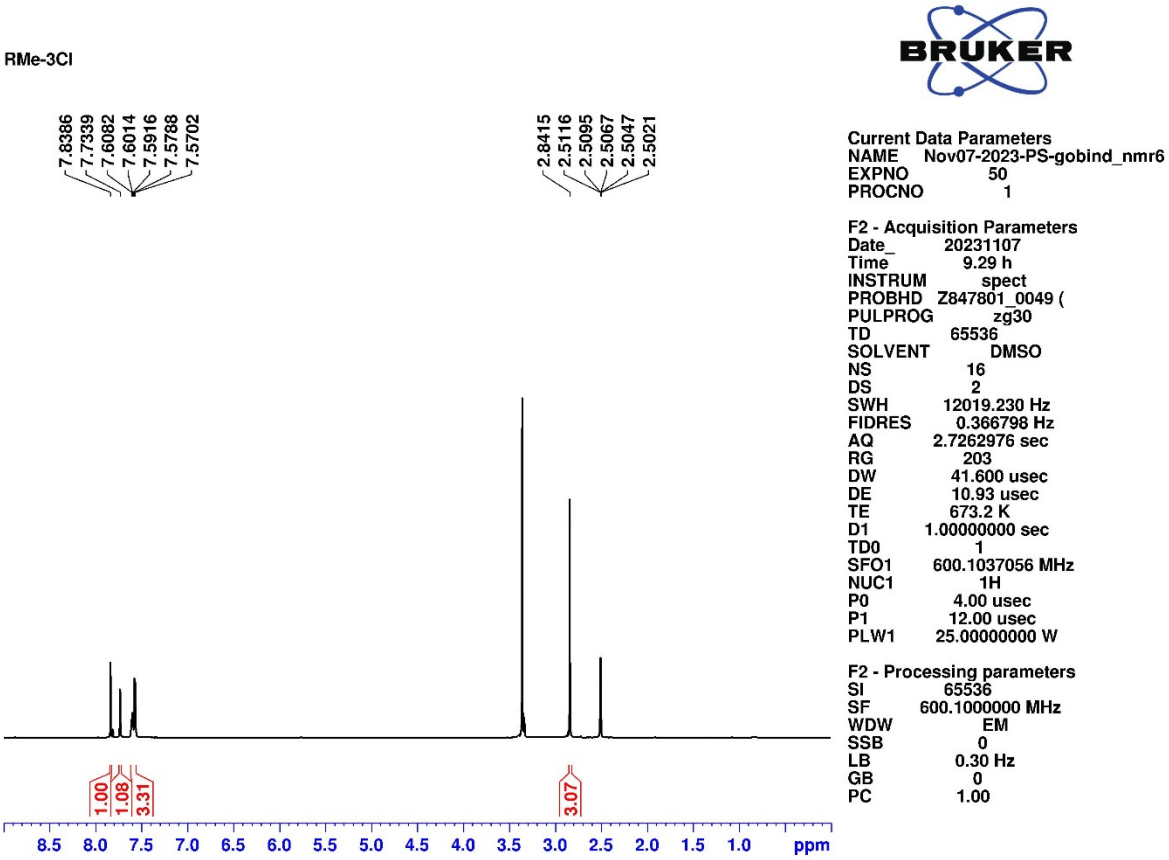


Figure S34. ^{1}H-NMR of compound **8o**.

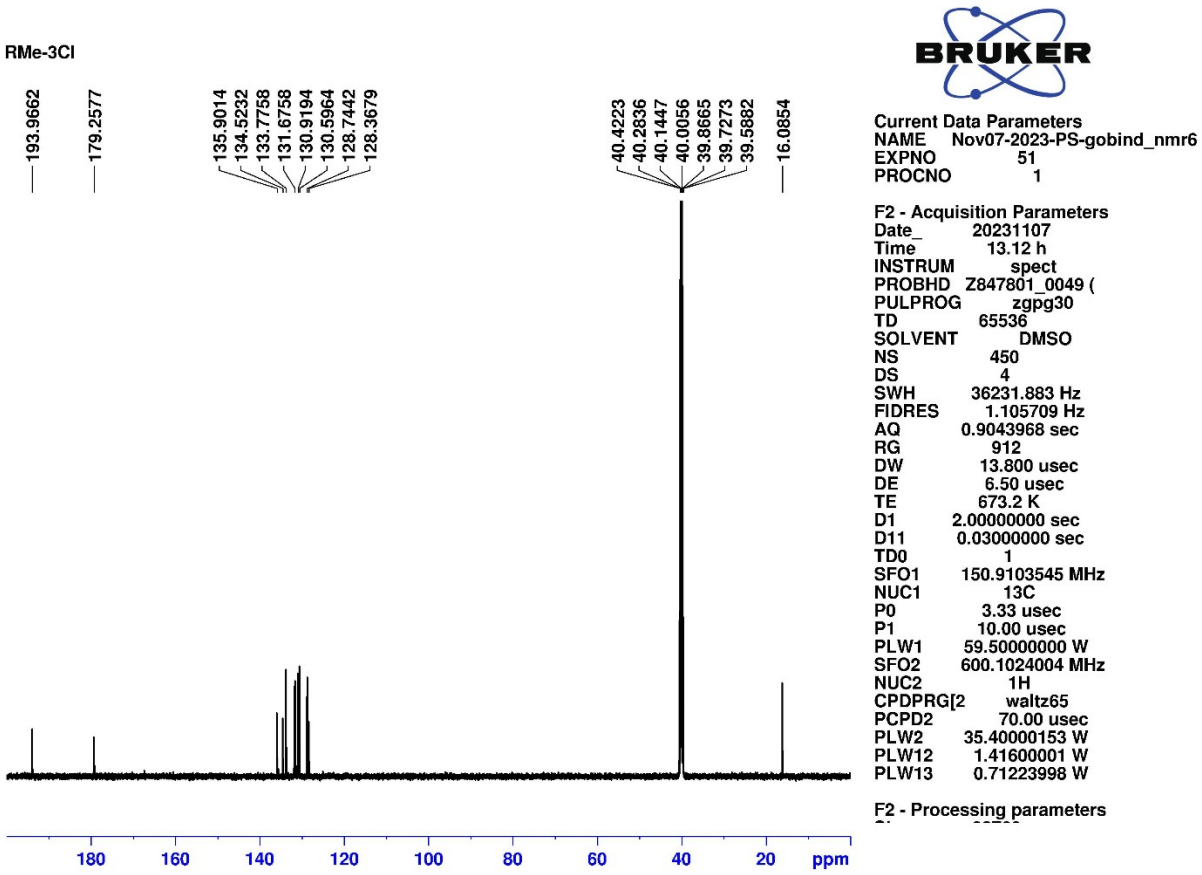


Figure S35. ^{13}C-NMR of compound **8o**.

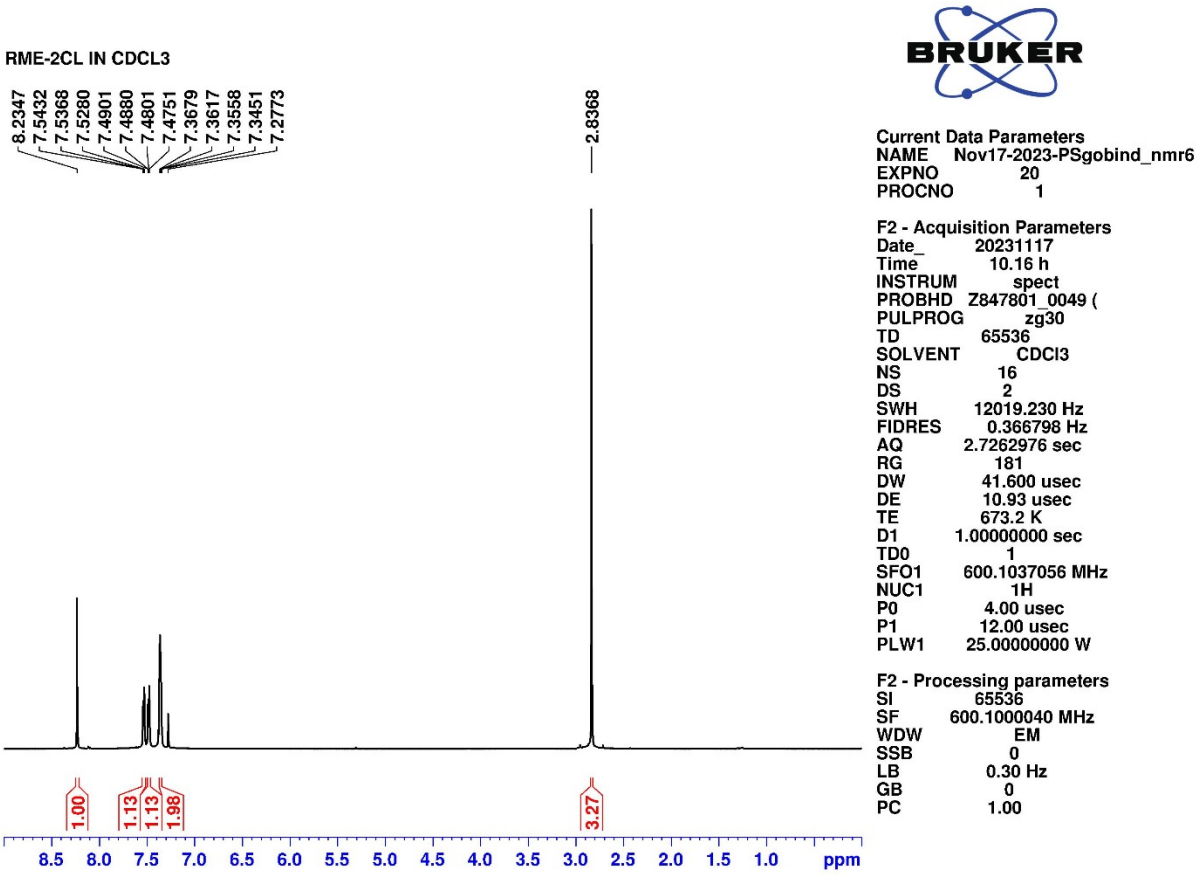


Figure S36. ^{1}H-NMR of compound **8p**.

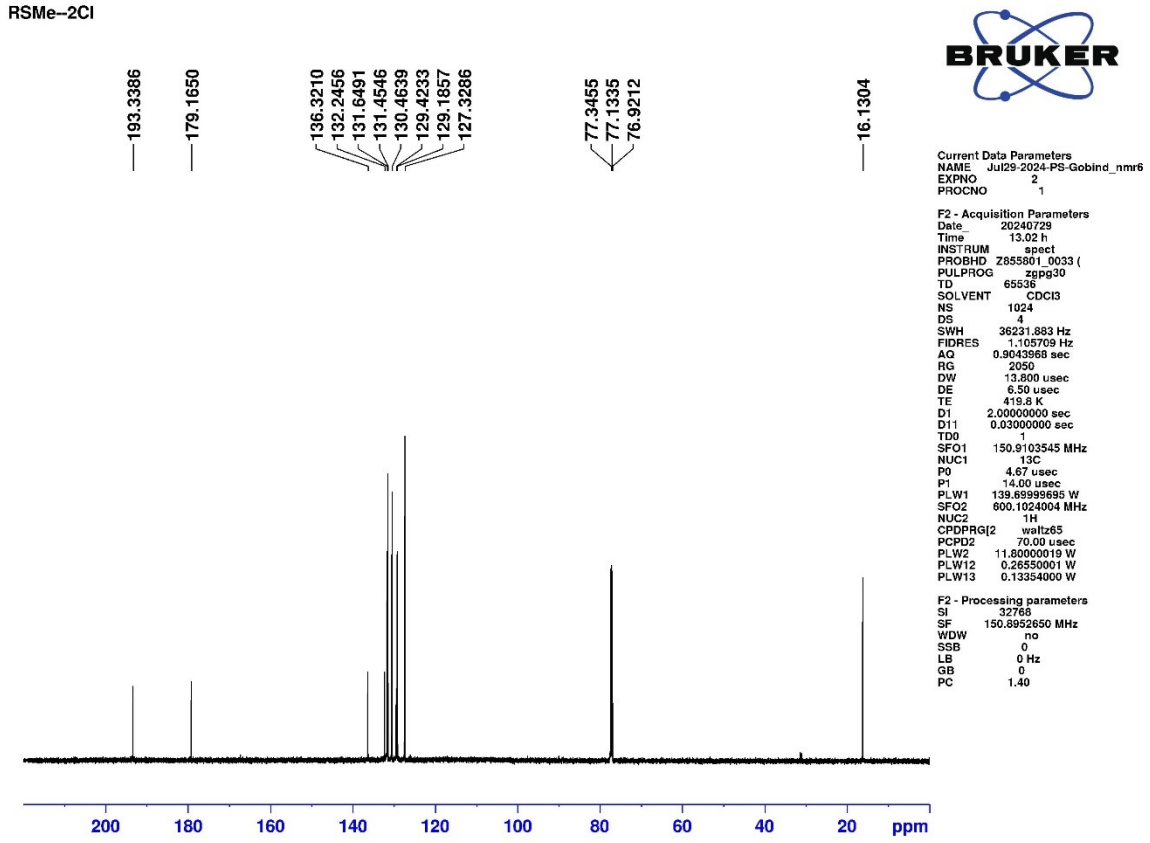


Figure S37. ^{13}C-NMR of compound **8p**.

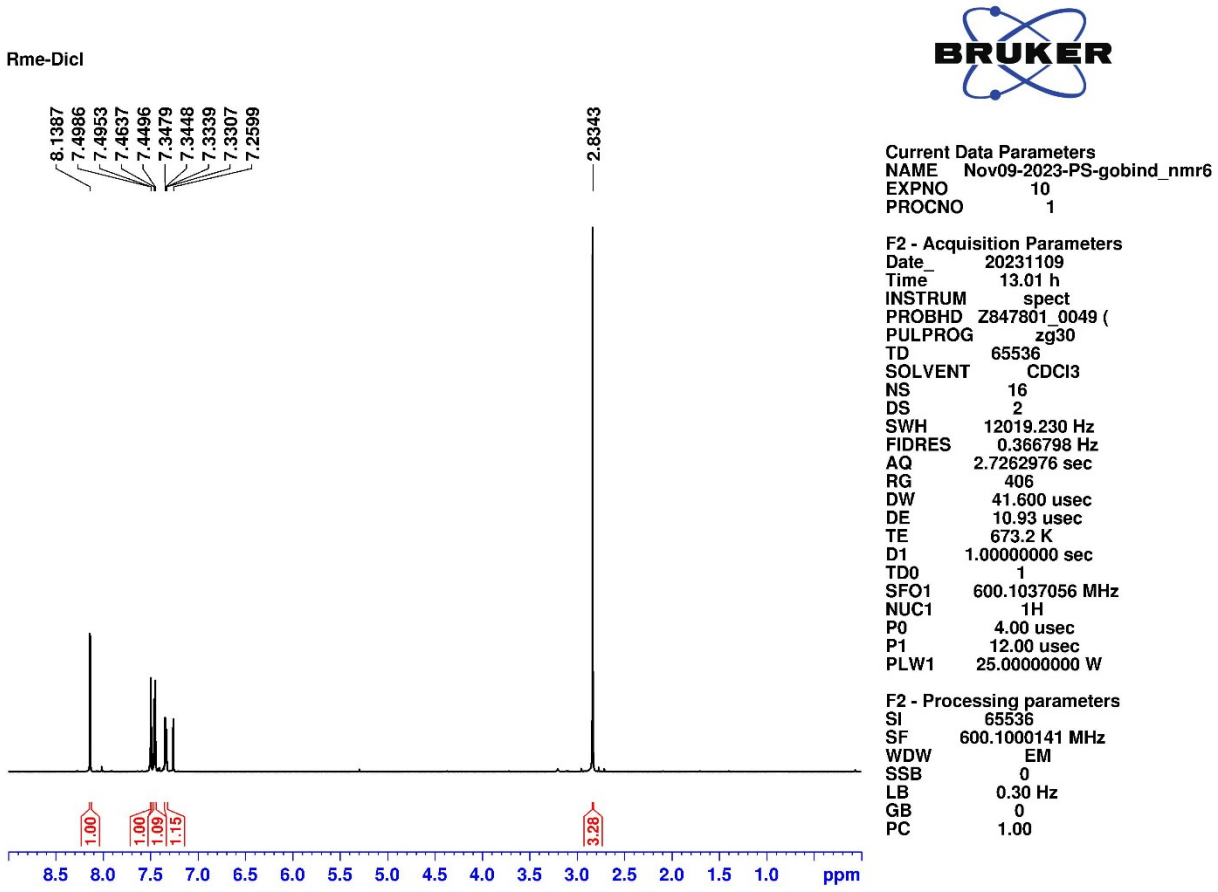


Figure S38. ^{1}H-NMR of compound **8q**.

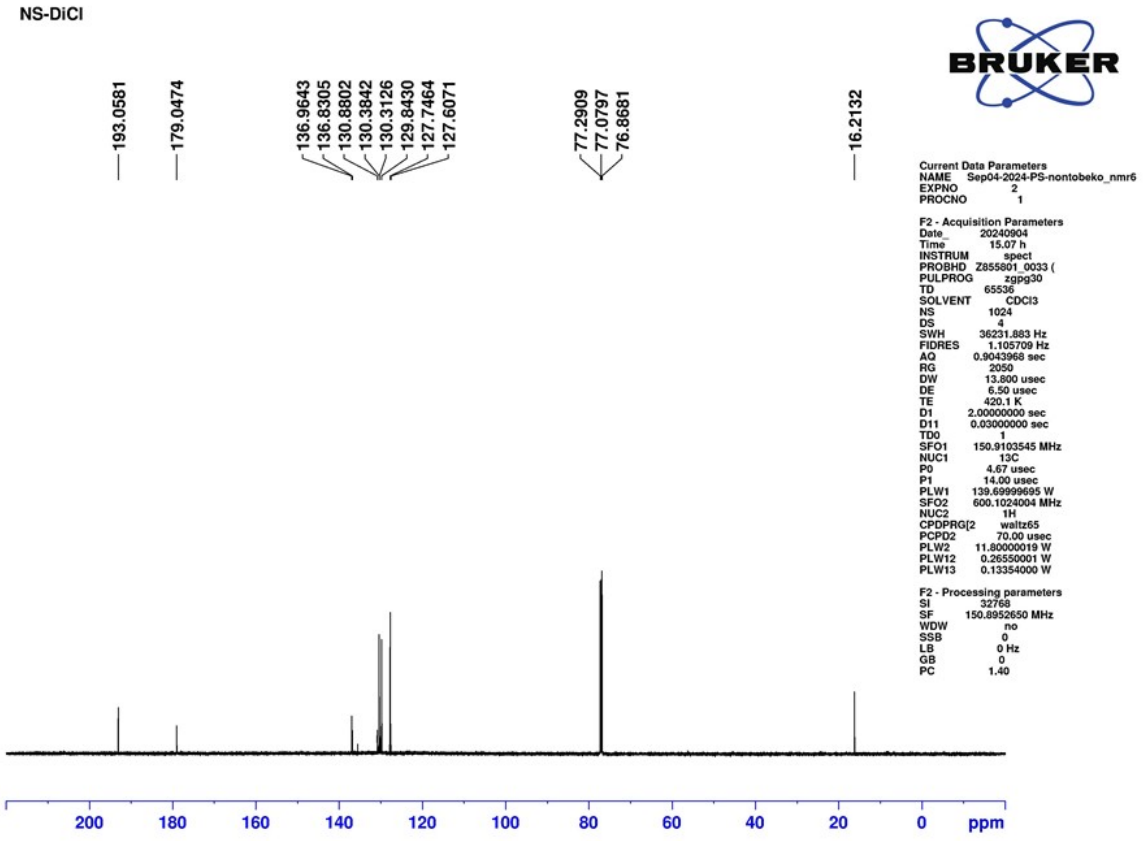


Figure S39. ^{13}C-NMR of compound **8q**.

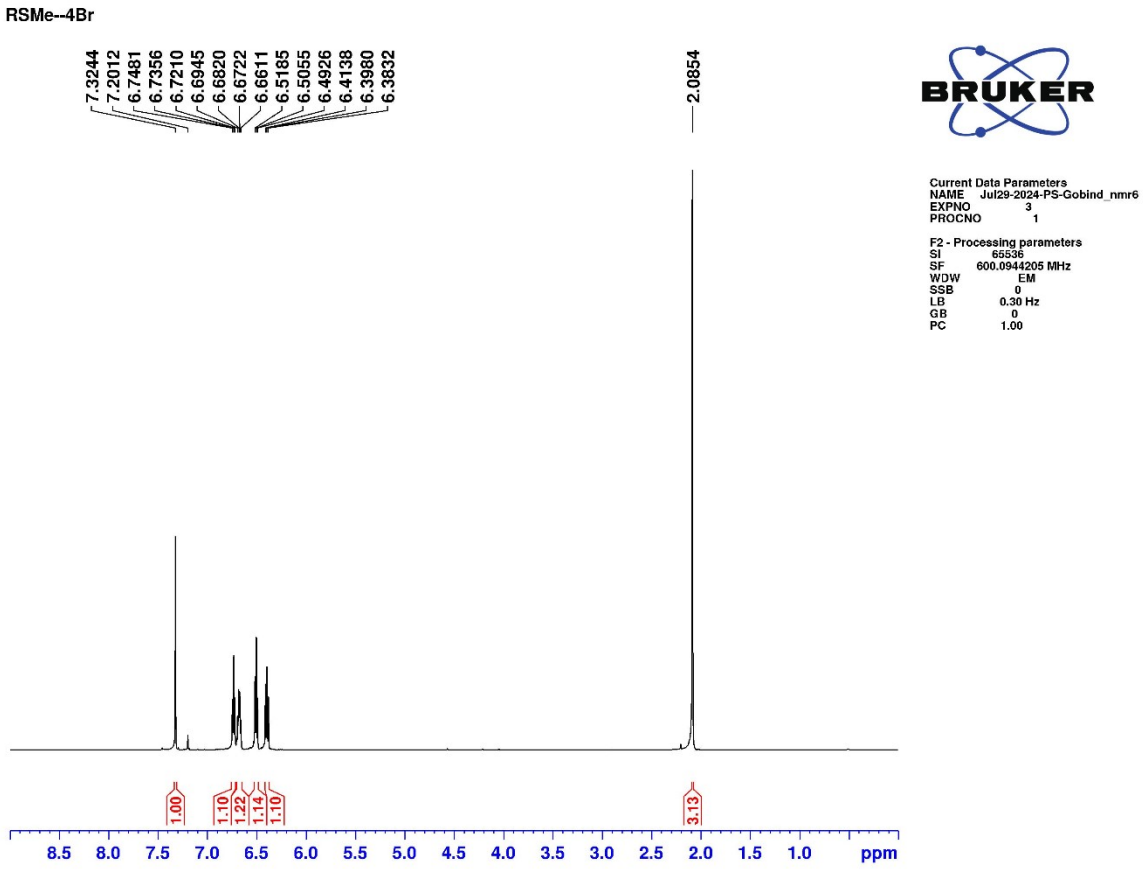


Figure S40. ^{1}H-NMR of compound **8r**.

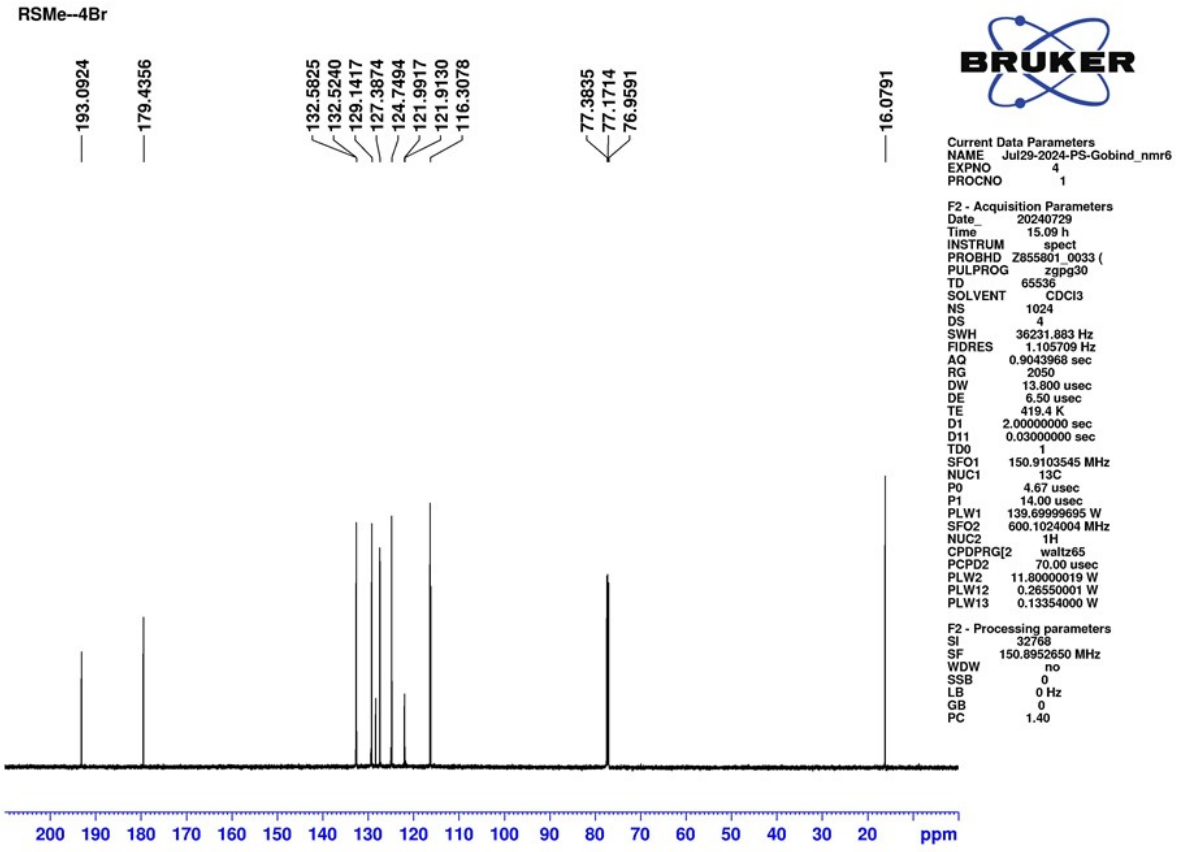


Figure S41. ^{13}C-NMR of compound **8r**.

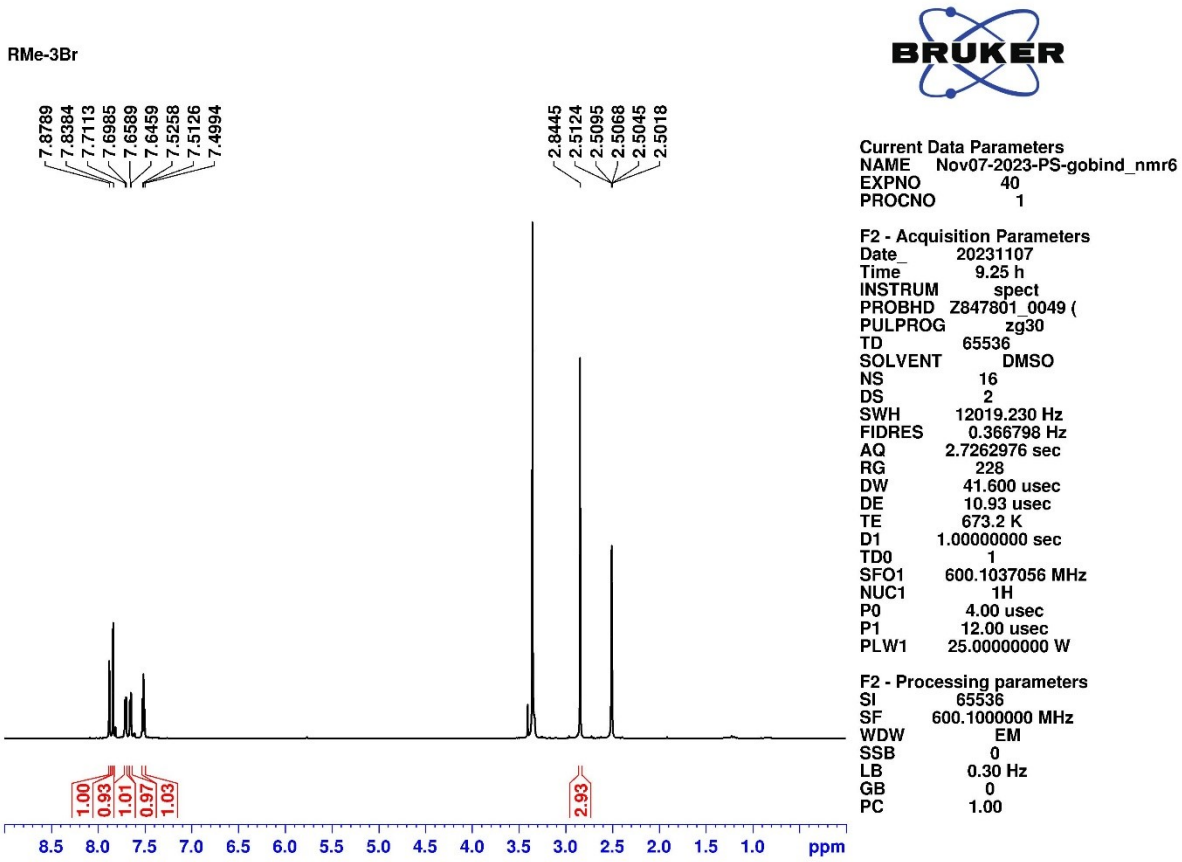


Figure S42. [1]H-NMR of compound **8s**.

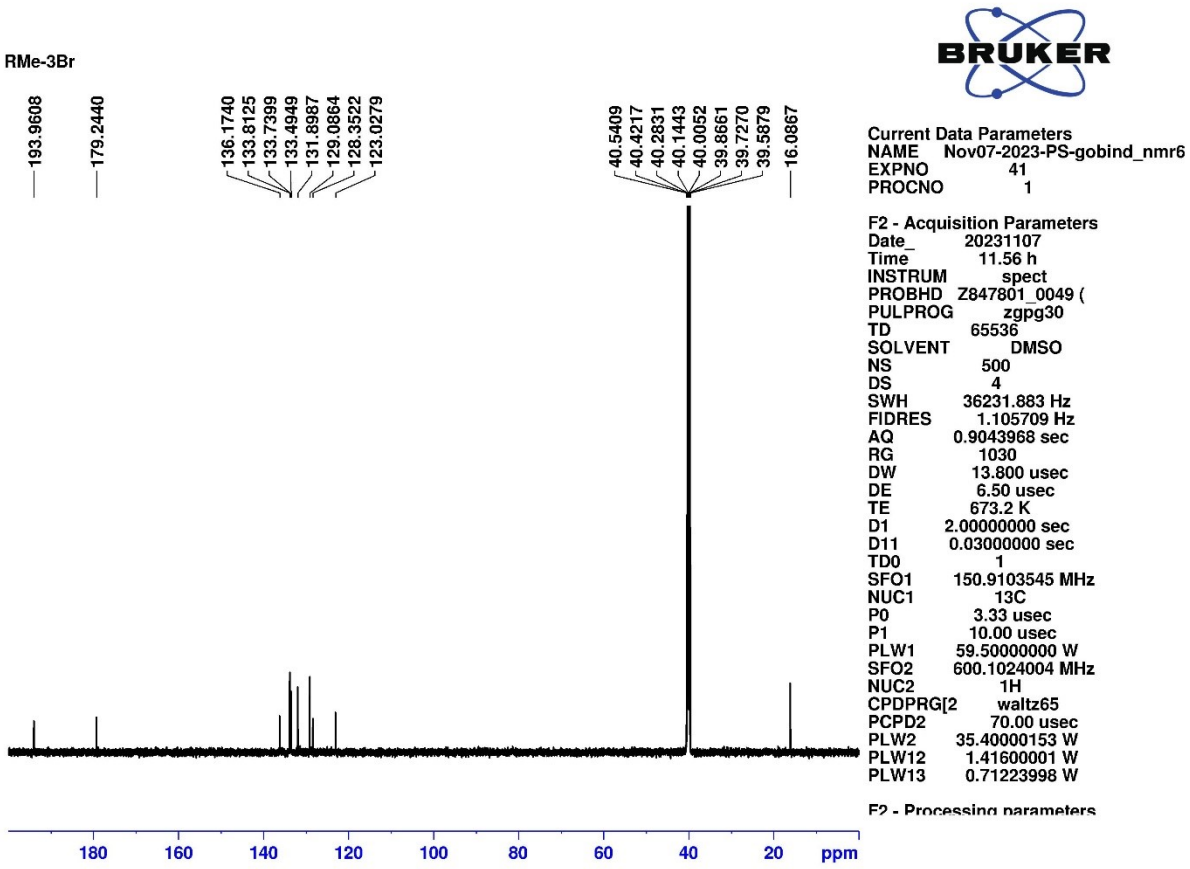


Figure S42. ^{13}C-NMR of compound **8s**.

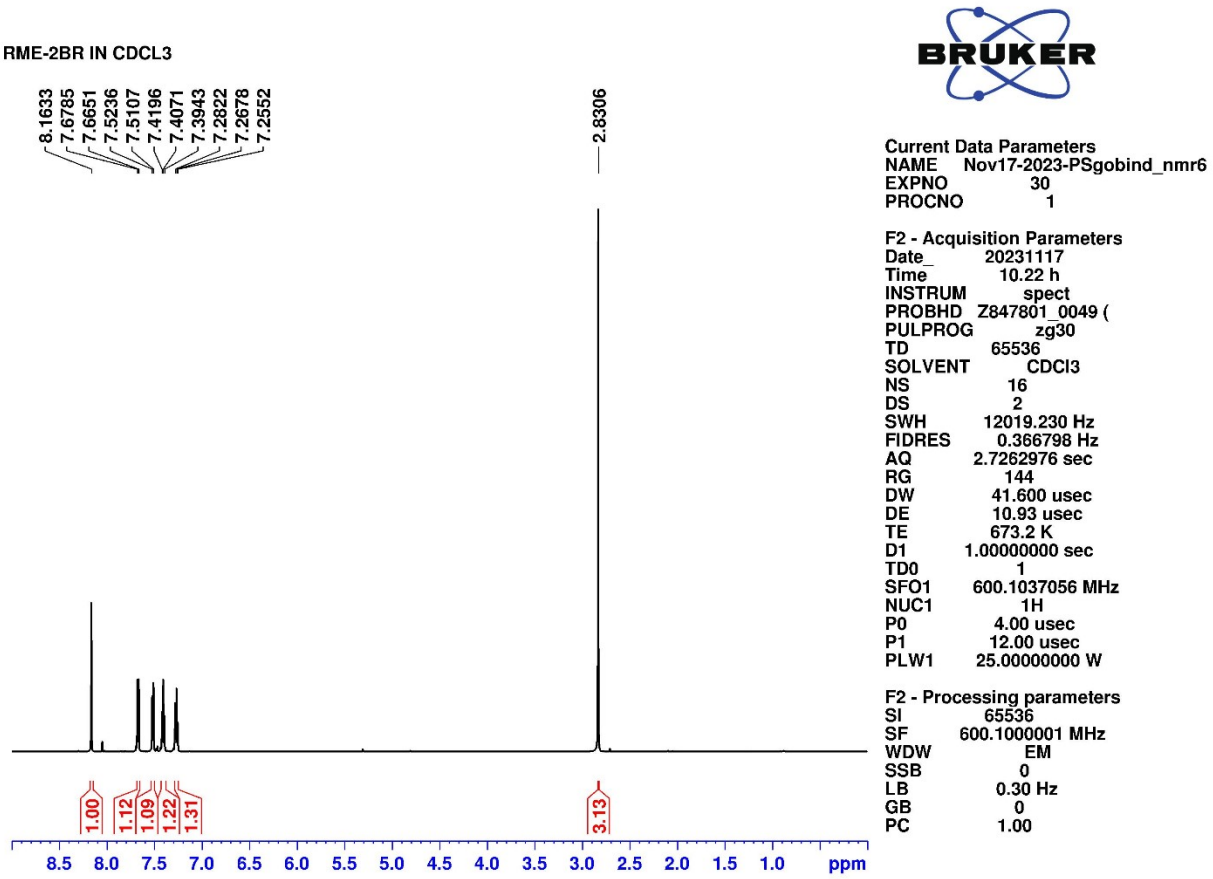


Figure S43. ^{1}H-NMR of compound **8t**.

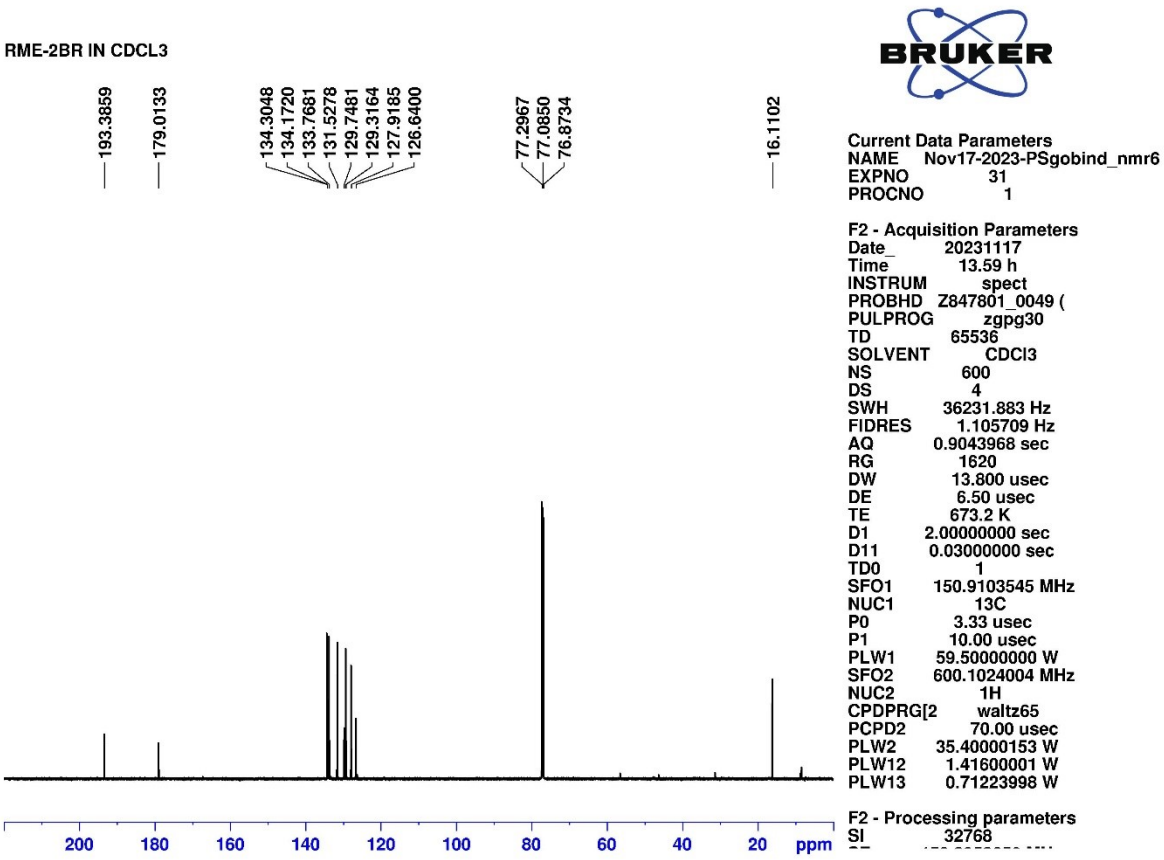


Figure S44. ^{13}C-NMR of compound **8t**.

4.3. Spectral data of final compounds 9a-t

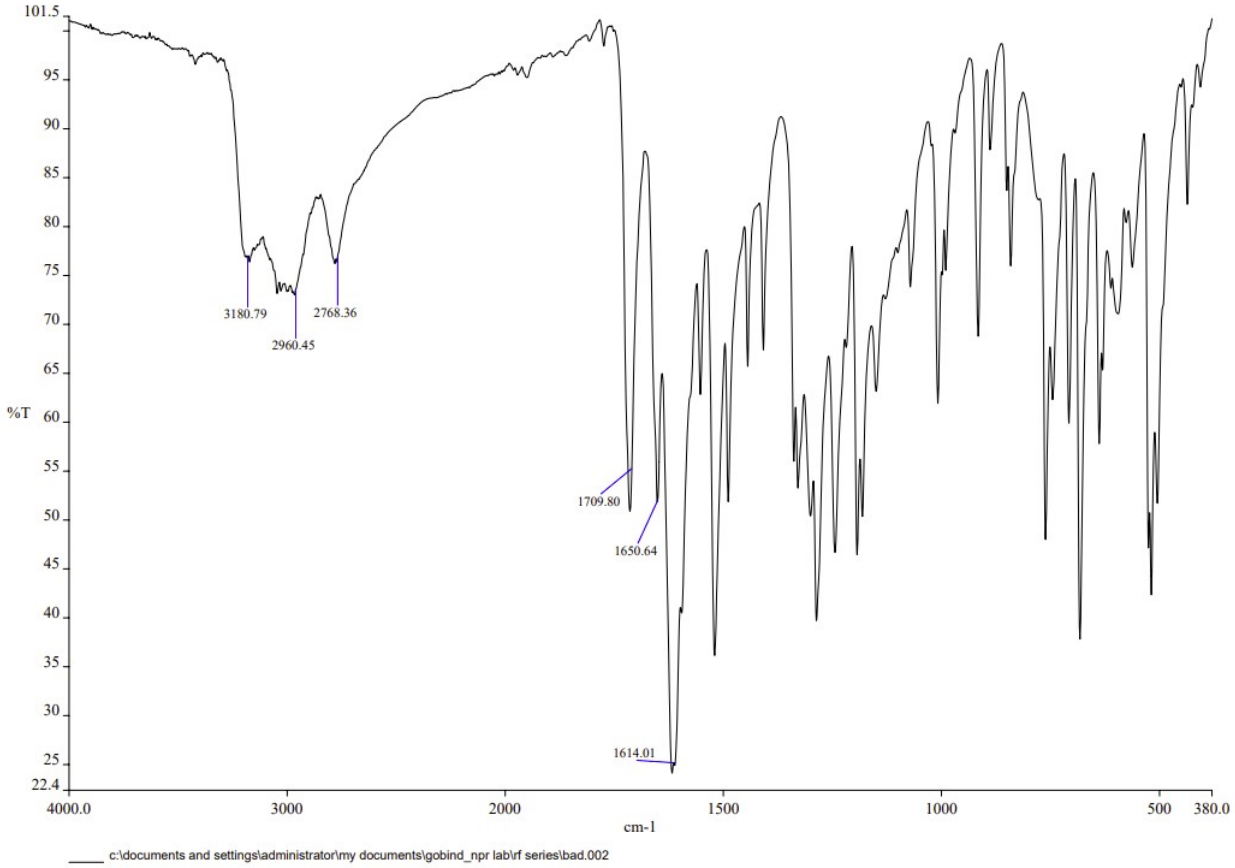


Figure S45. IR spectra of compound **9a**.

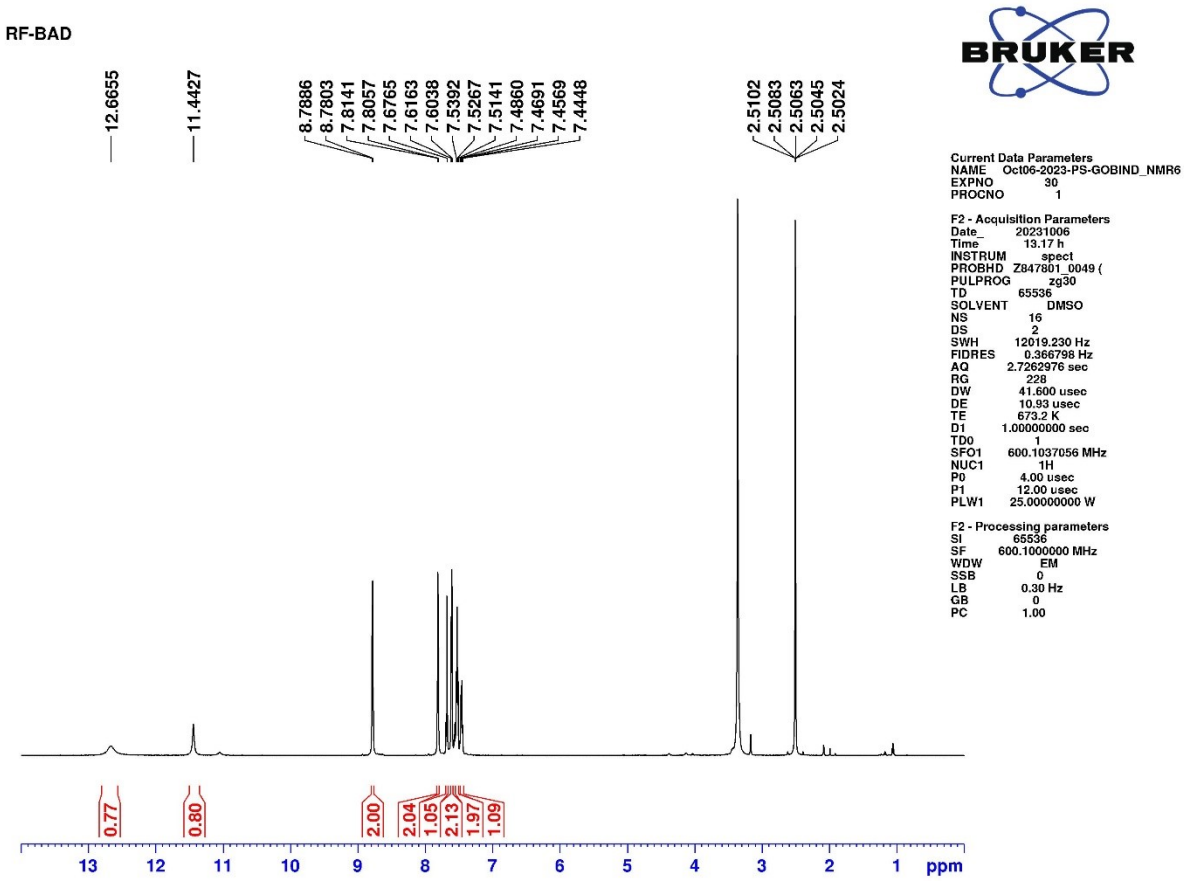


Figure S46. ^{1}H-NMR of compound **9a**.

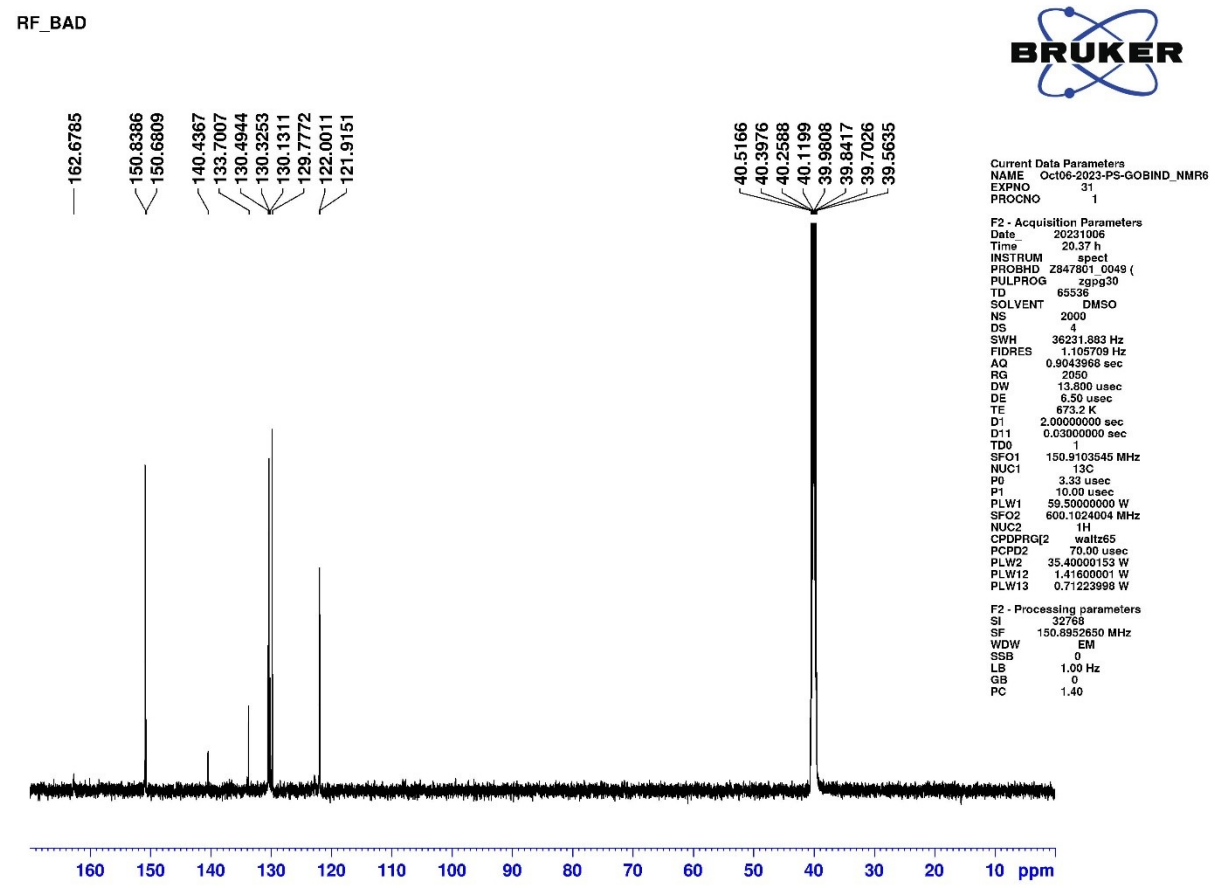


Figure S47. ^{13}C-NMR of compound **9a**.

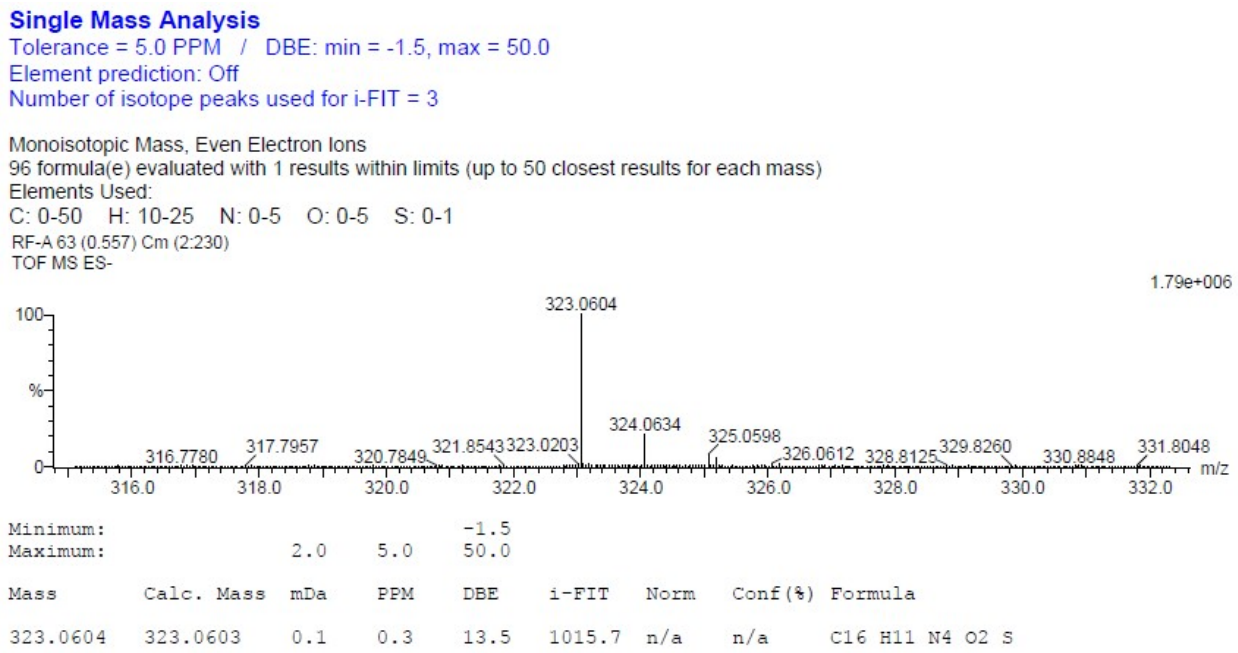


Figure S48. HRMS of compound **9a**.

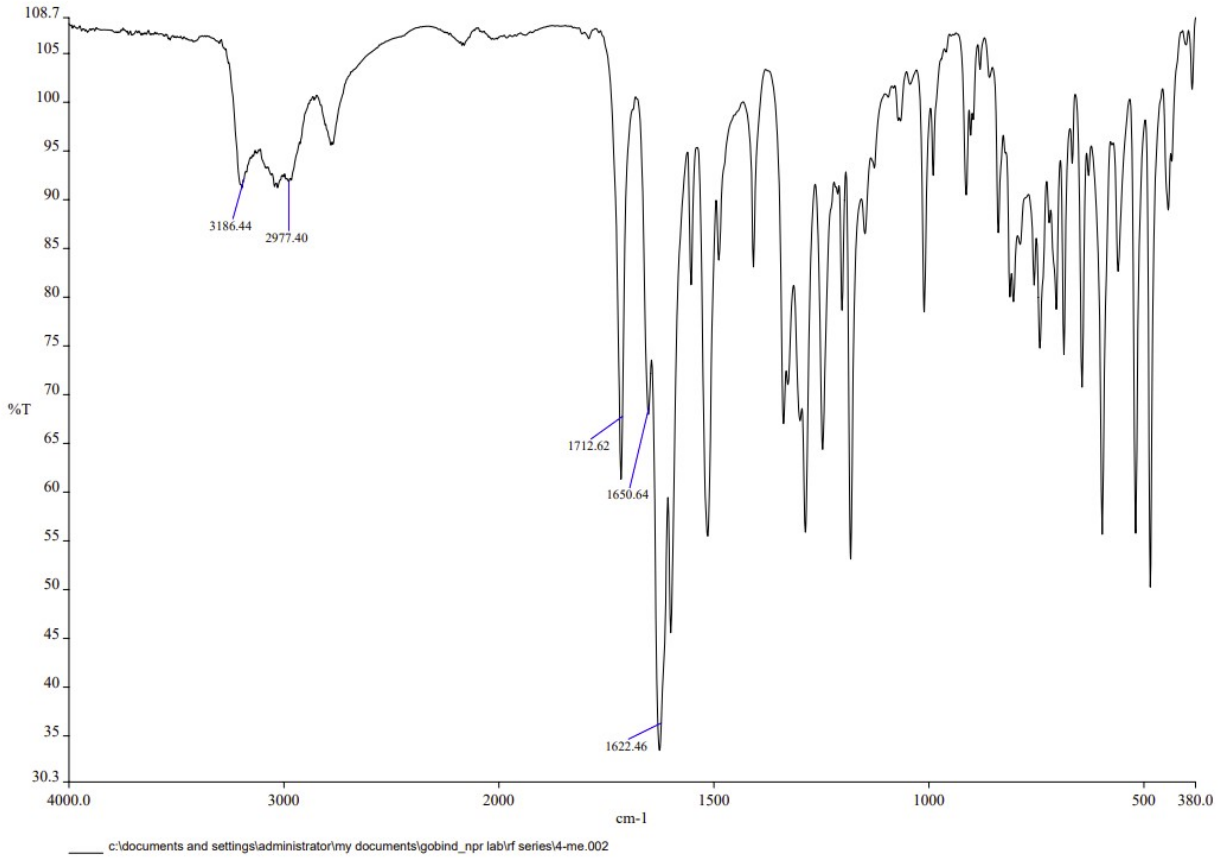


Figure S49. IR spectra of compound **9b**.

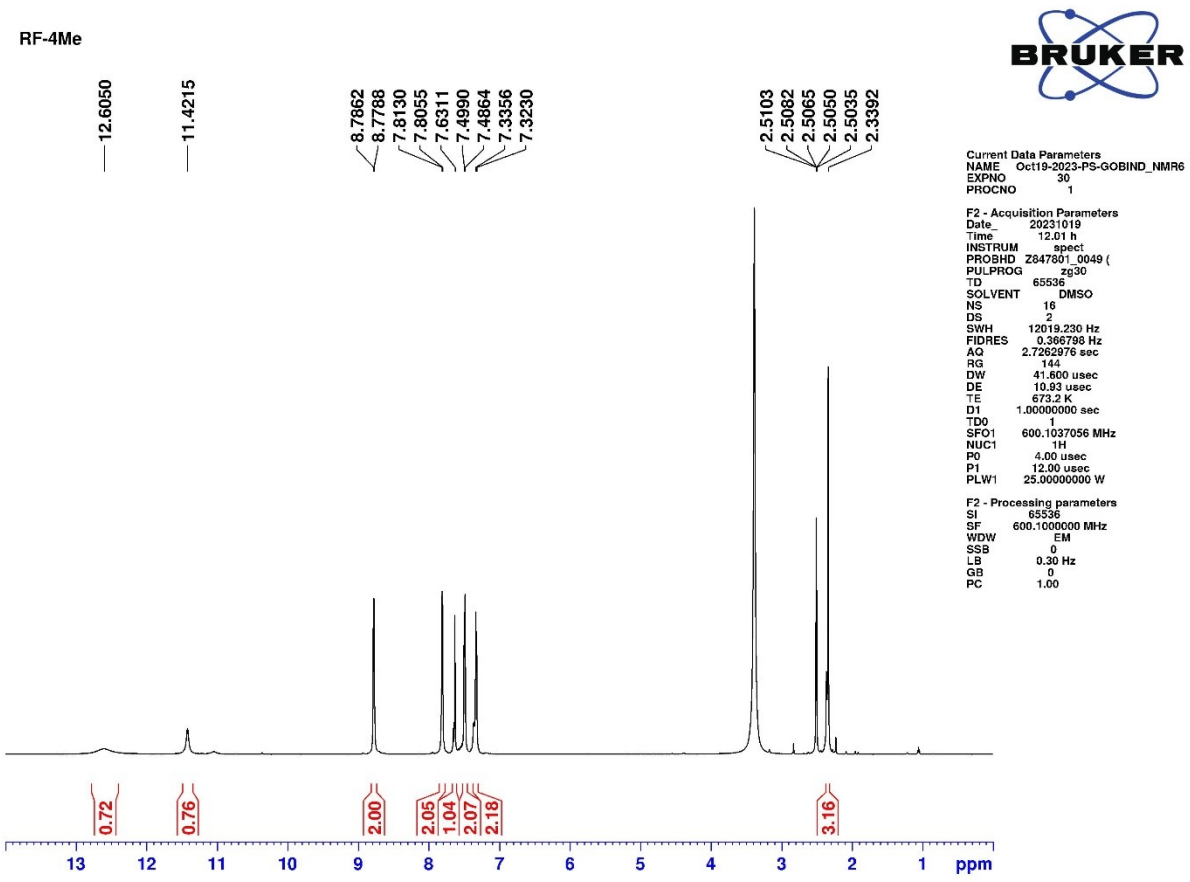


Figure S50. ^{1}H-NMR of compound **9b**.

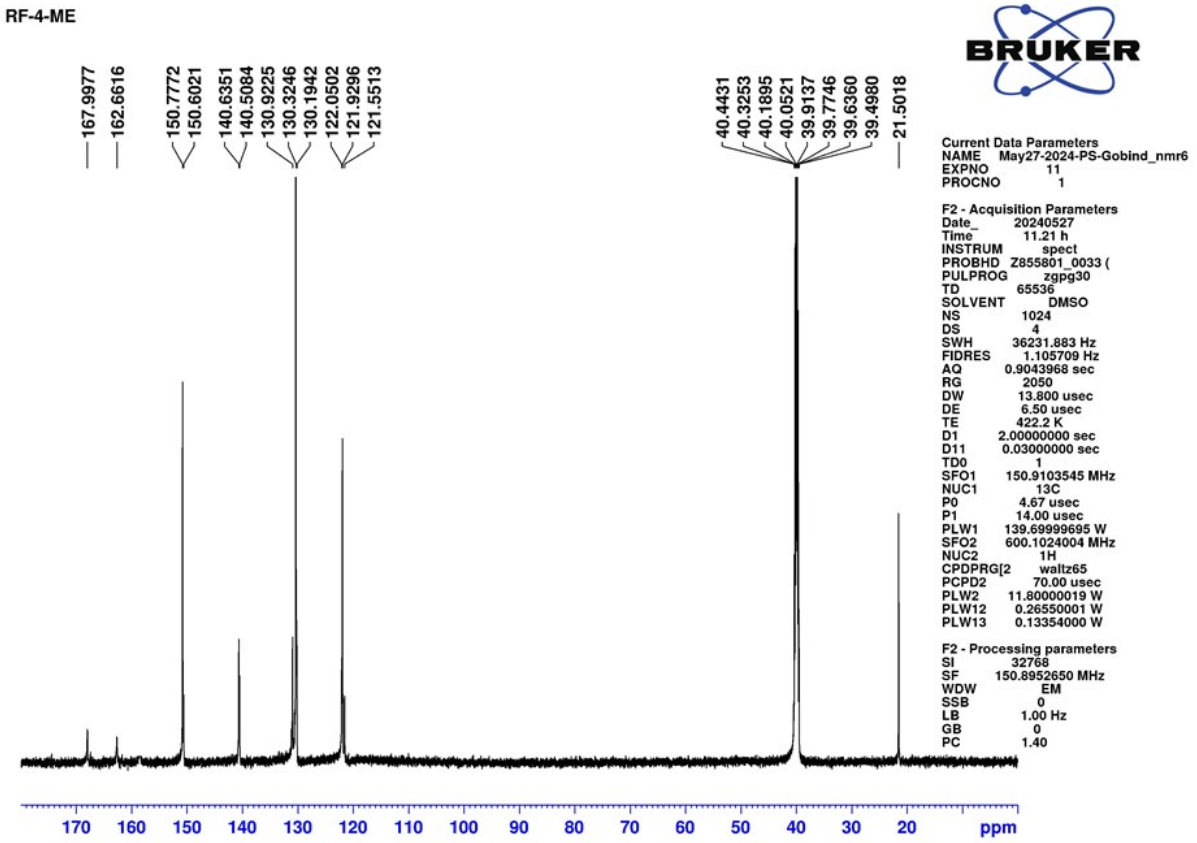
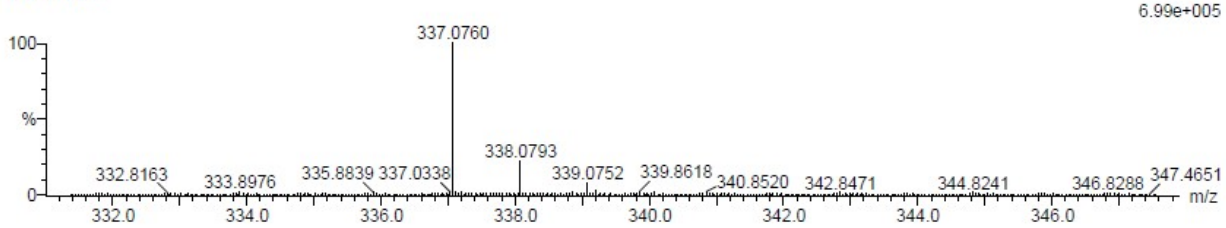


Figure S51. ^{13}C-NMR of compound **9b**.

Single Mass Analysis
Tolerance = 5.0 PPM / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
96 formula(e) evaluated with 1 results within limits (up to 50 closest results for each mass)
Elements Used:
C: 0-50 H: 10-25 N: 0-5 O: 0-5 S: 0-1
RF-B 142 (1.234) Cm (2:230)
TOF MS ES-



Minimum:				-1.5				
Maximum:		2.0	5.0	50.0				
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Norm	Conf(%)	Formula
337.0760	337.0759	0.1	0.3	13.5	903.4	n/a	n/a	C17 H13 N4 O2 S

HRMS of compound **9b**.

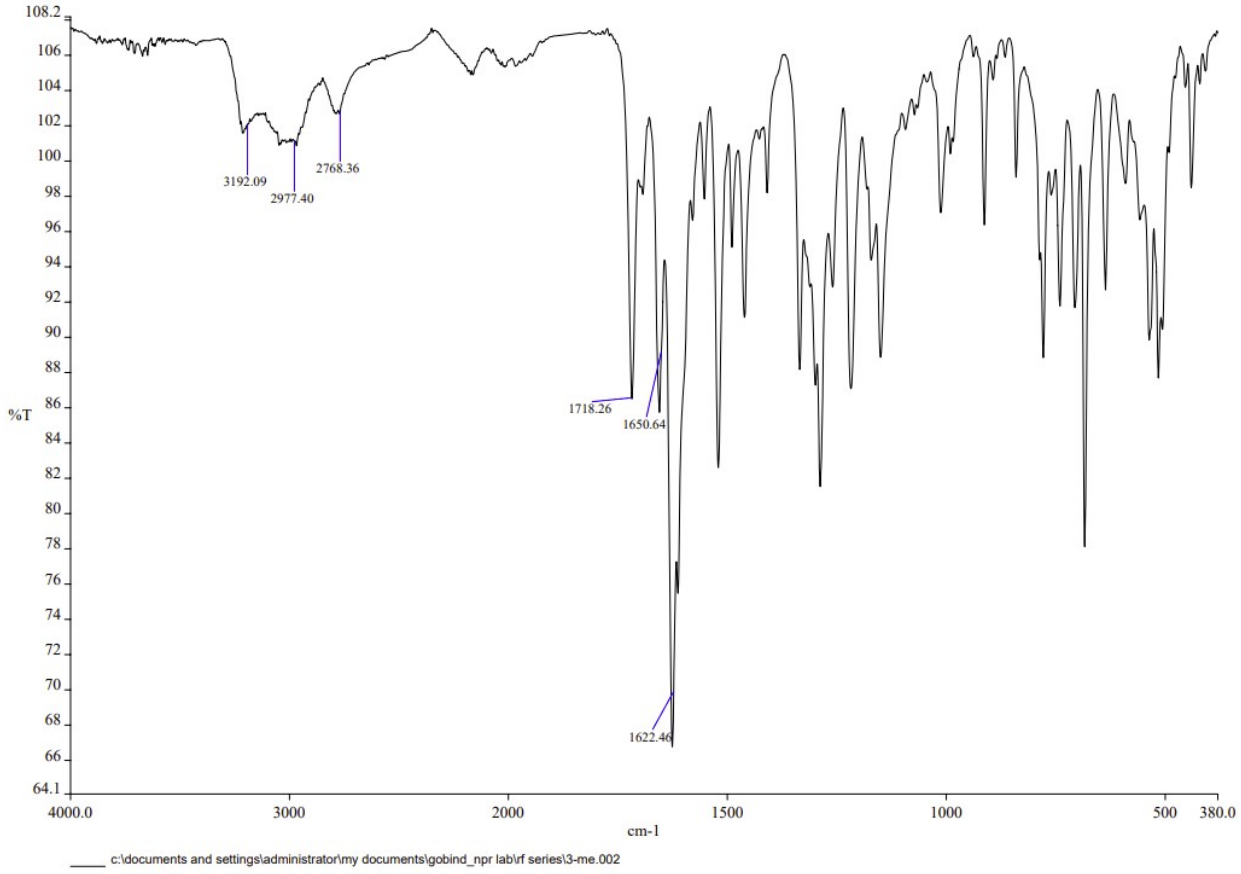


Figure S52. IR spectra of compound **9c**.

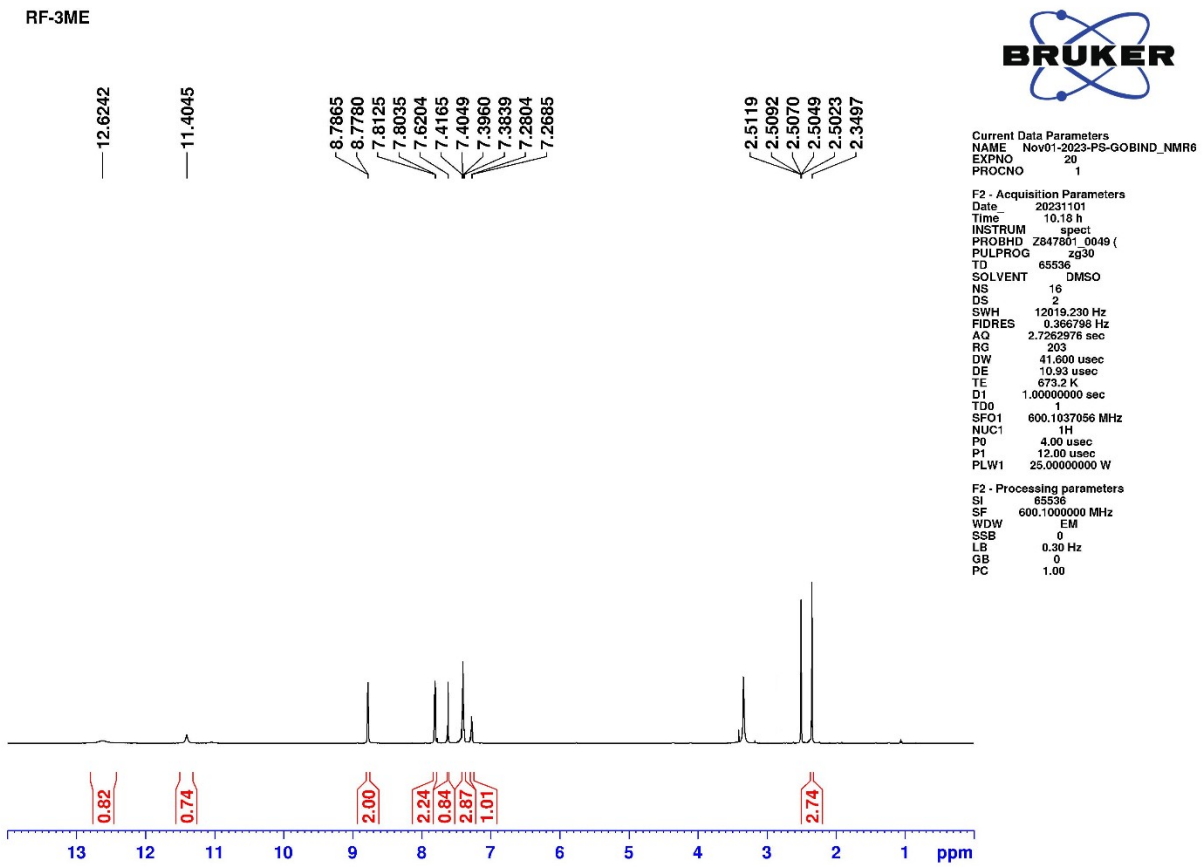


Figure S53. ^{1}H-NMR of compound **9c**.

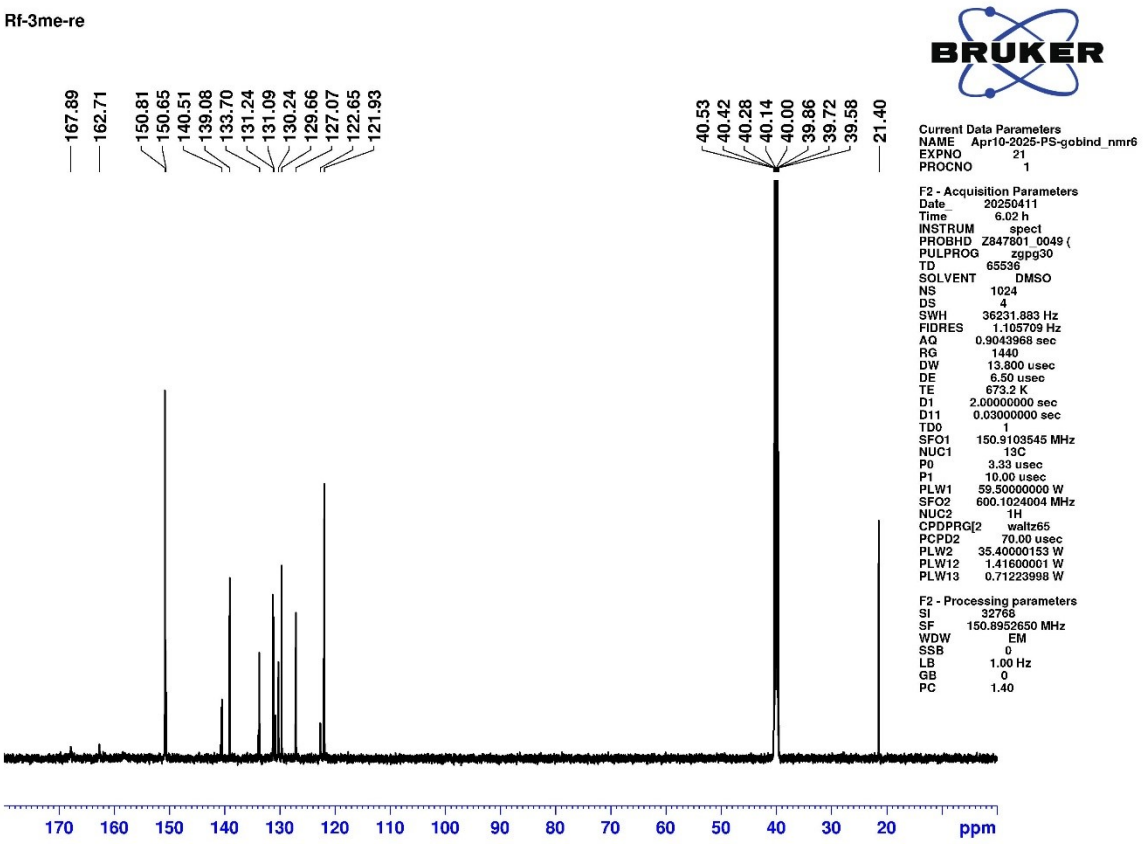
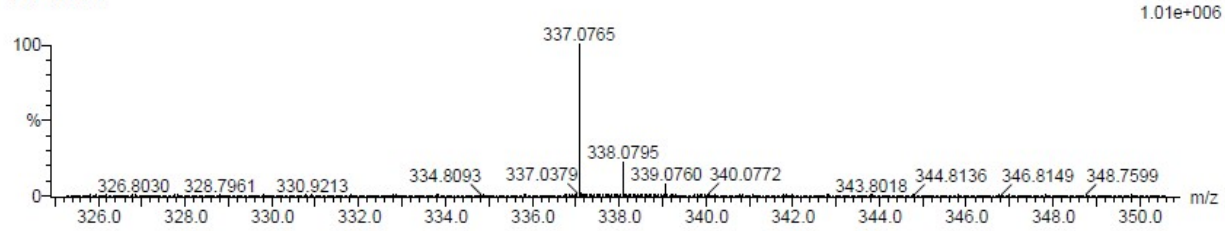


Figure S54. ^{13}C-NMR of compound **9c**.

Single Mass Analysis
Tolerance = 5.0 PPM / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
40 formula(e) evaluated with 1 results within limits (up to 50 closest results for each mass)
Elements Used:
C: 0-50 H: 5-20 N: 1-5 O: 0-5 S: 1-1
RF-M 21 (0.197) Cm (2:230)
TOF MS ES-



Minimum:				-1.5				
Maximum:		2.0	5.0	50.0				
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Norm	Conf(%)	Formula
337.0765	337.0759	0.6	1.8	13.5	970.3	n/a	n/a	C17 H13 N4 O2 S

Figure S55. HRMS of compound **9c**.

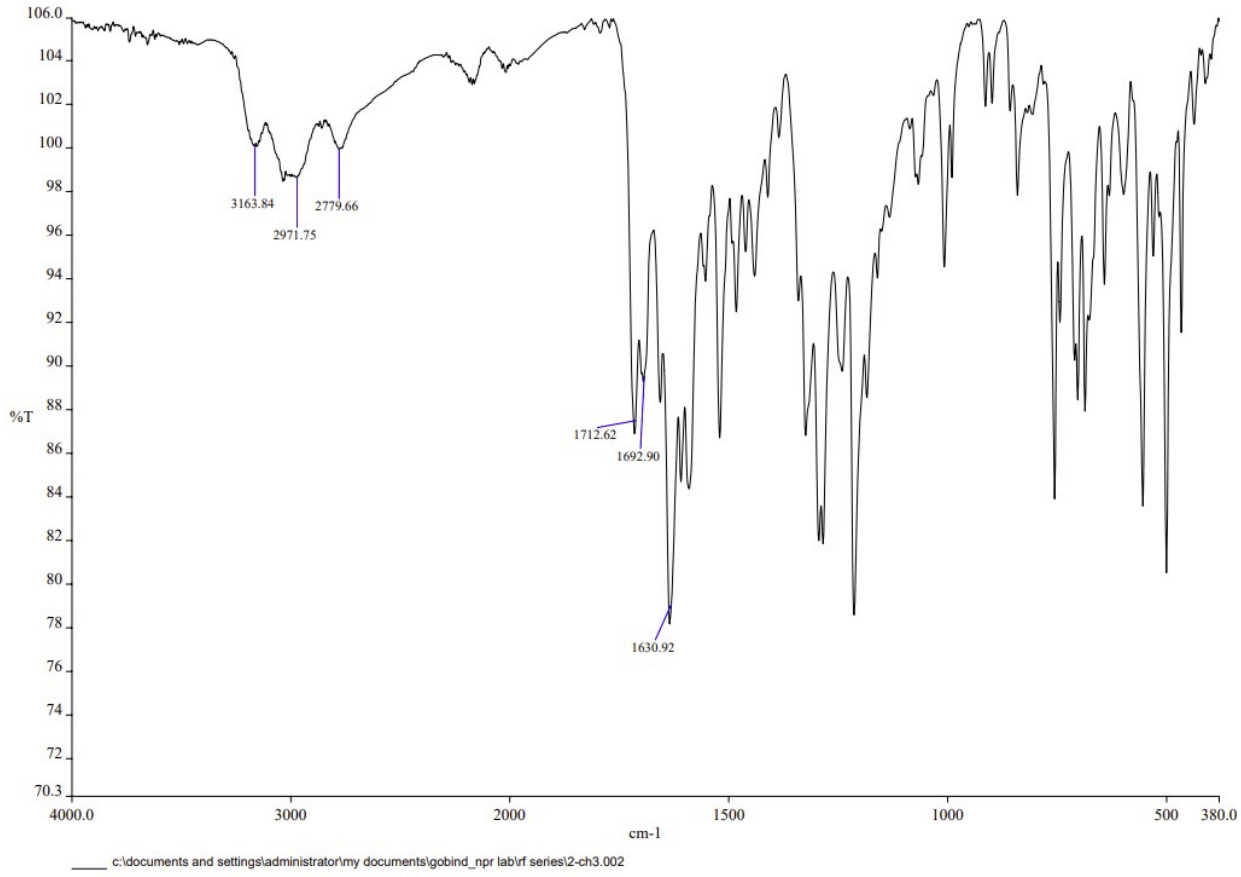


Figure S56. IR spectra of compound **9d**.

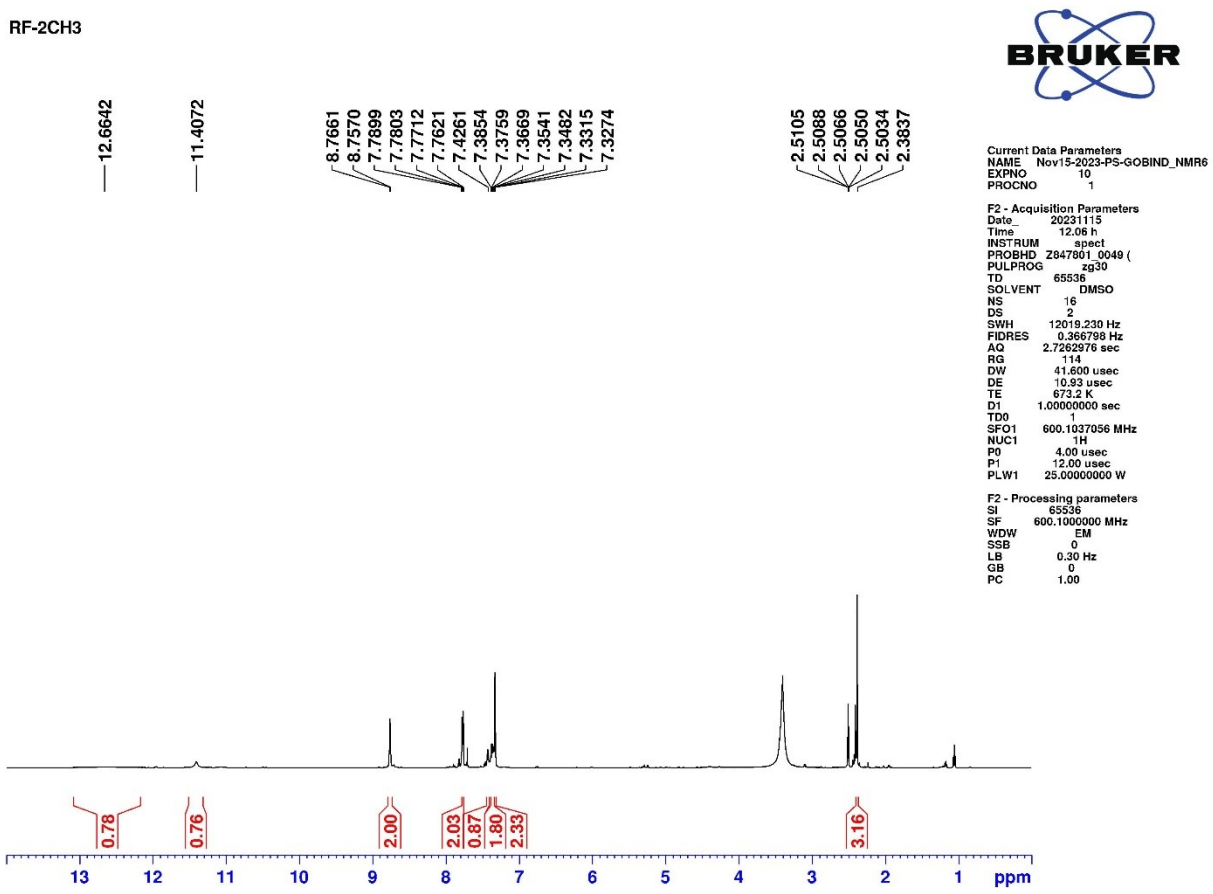


Figure S57. ^{1}H-NMR of compound **9d**.

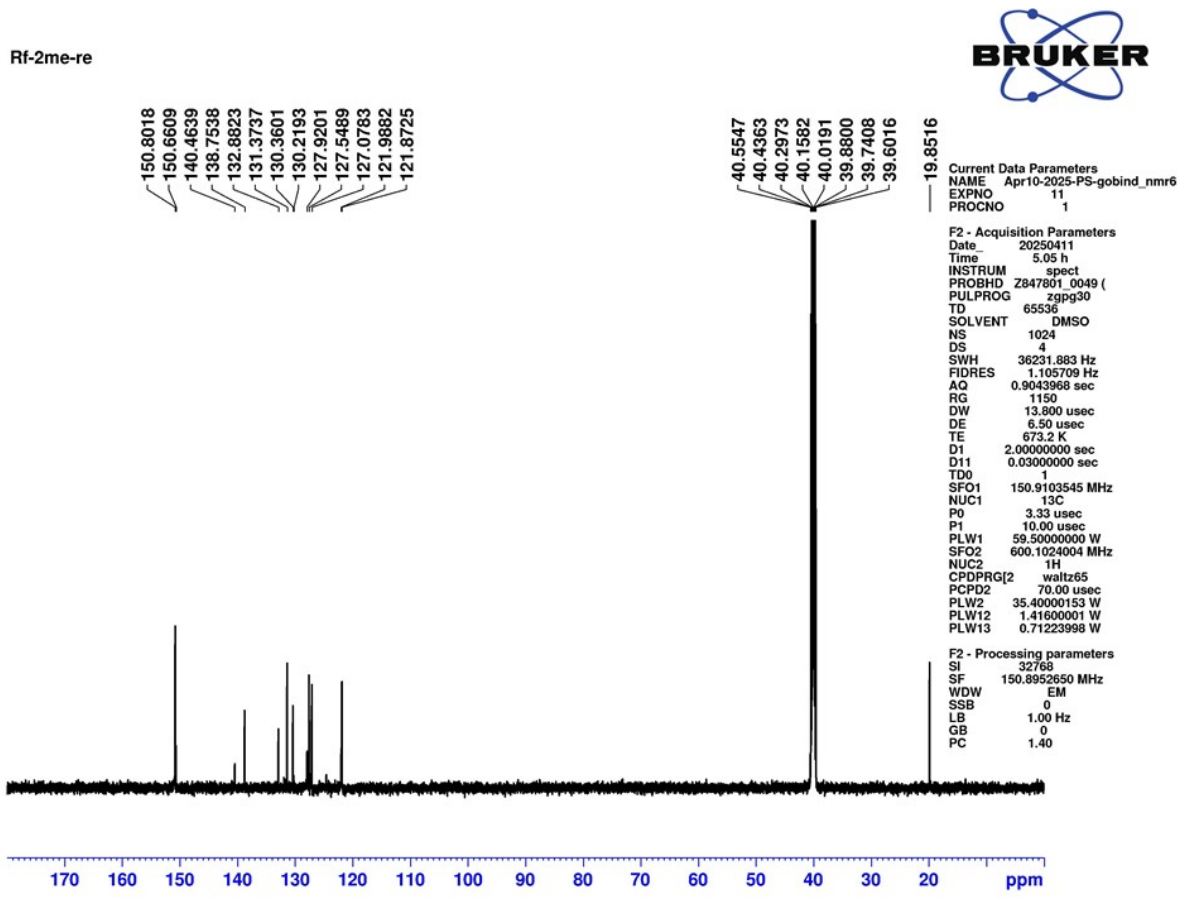
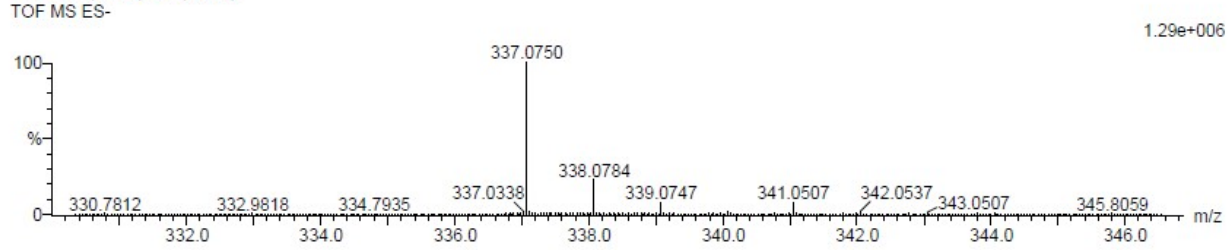


Figure S58. ^{13}C-NMR of compound **9d**.

Single Mass Analysis
Tolerance = 5.0 PPM / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
40 formula(e) evaluated with 1 results within limits (up to 50 closest results for each mass)
Elements Used:
C: 0-50 H: 5-20 N: 1-5 O: 0-5 S: 1-1
RF-T 223 (1.927) Cm (2:230)
TOF MS ES-



Minimum:				-1.5				
Maximum:		2.0	5.0	50.0				
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Norm	Conf(%)	Formula
337.0750	337.0759	-0.9	-2.7	13.5	959.5	n/a	n/a	C17 H13 N4 O2 S

Figure S59. HRMS of compound **9d**.

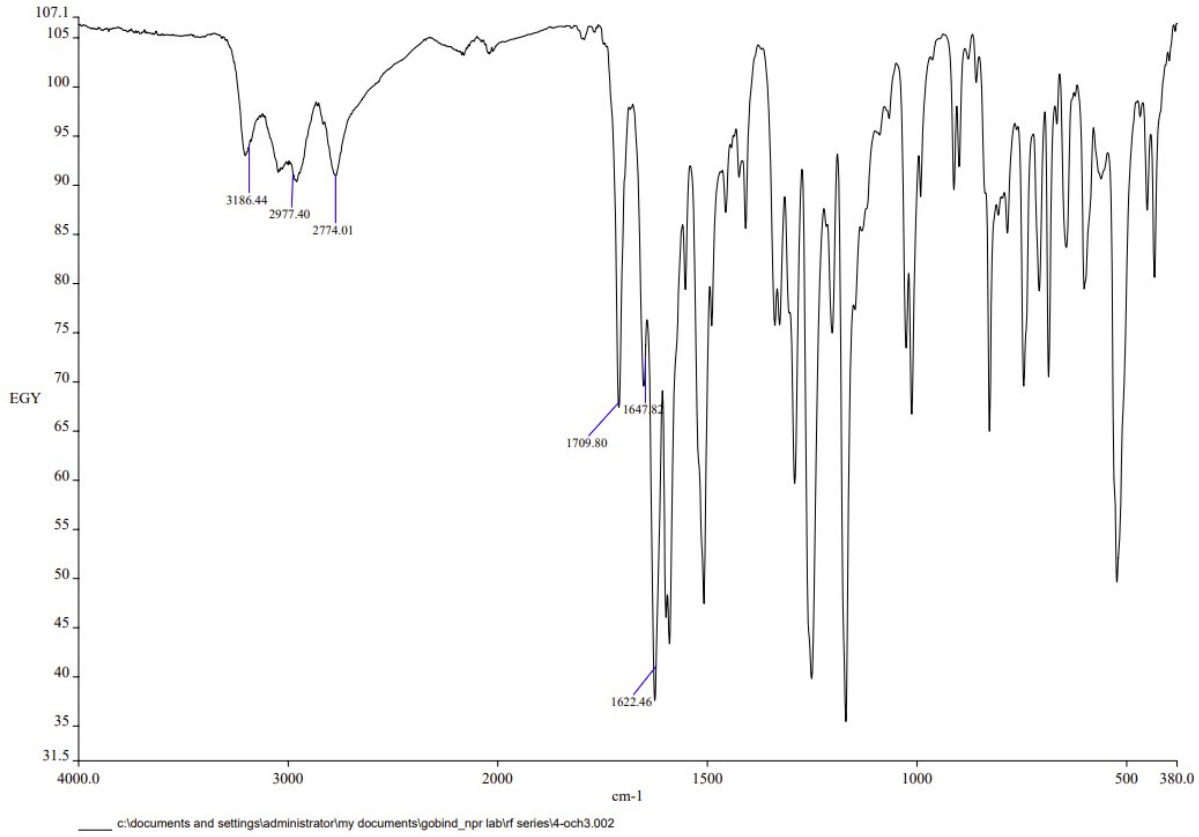


Figure S60. IR spectra of compound **9e**.

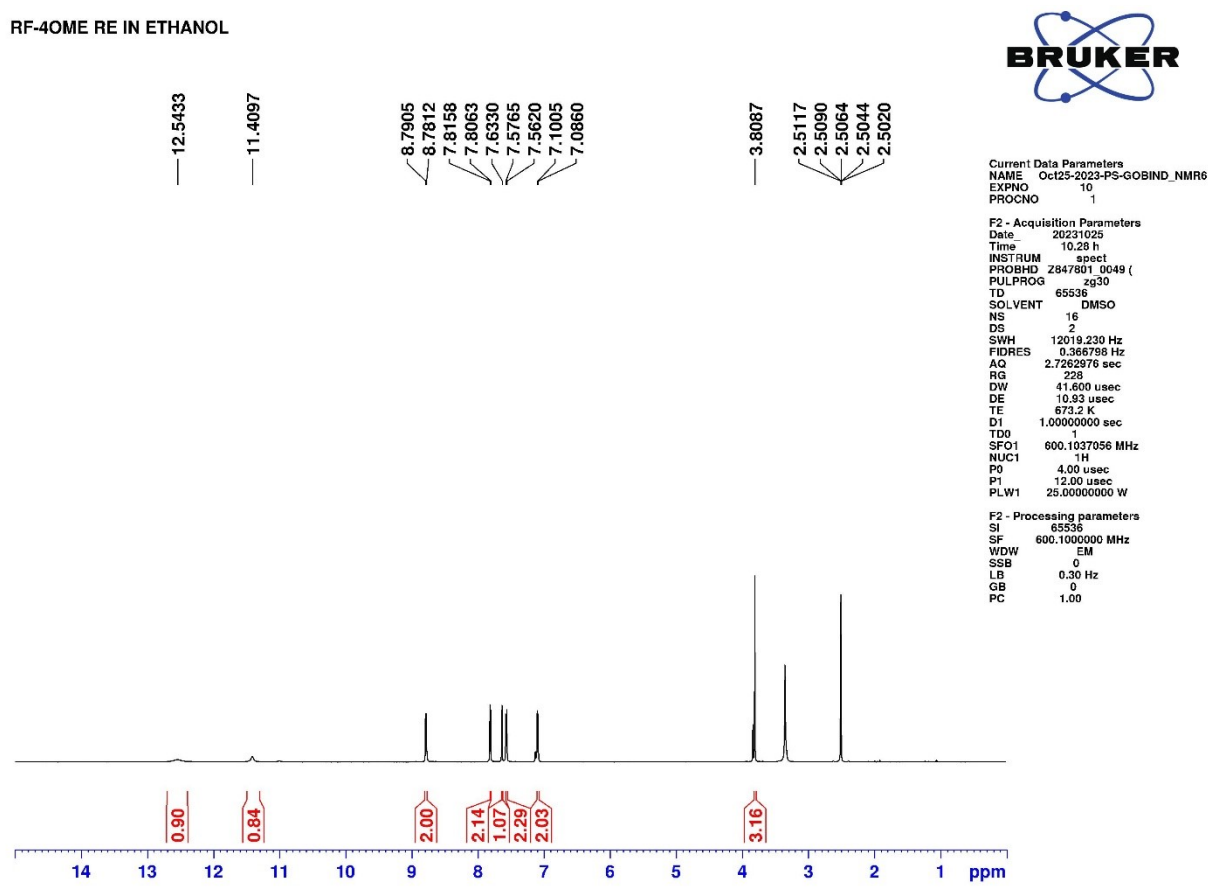


Figure S61. ^{1}H-NMR of compound **9e**.

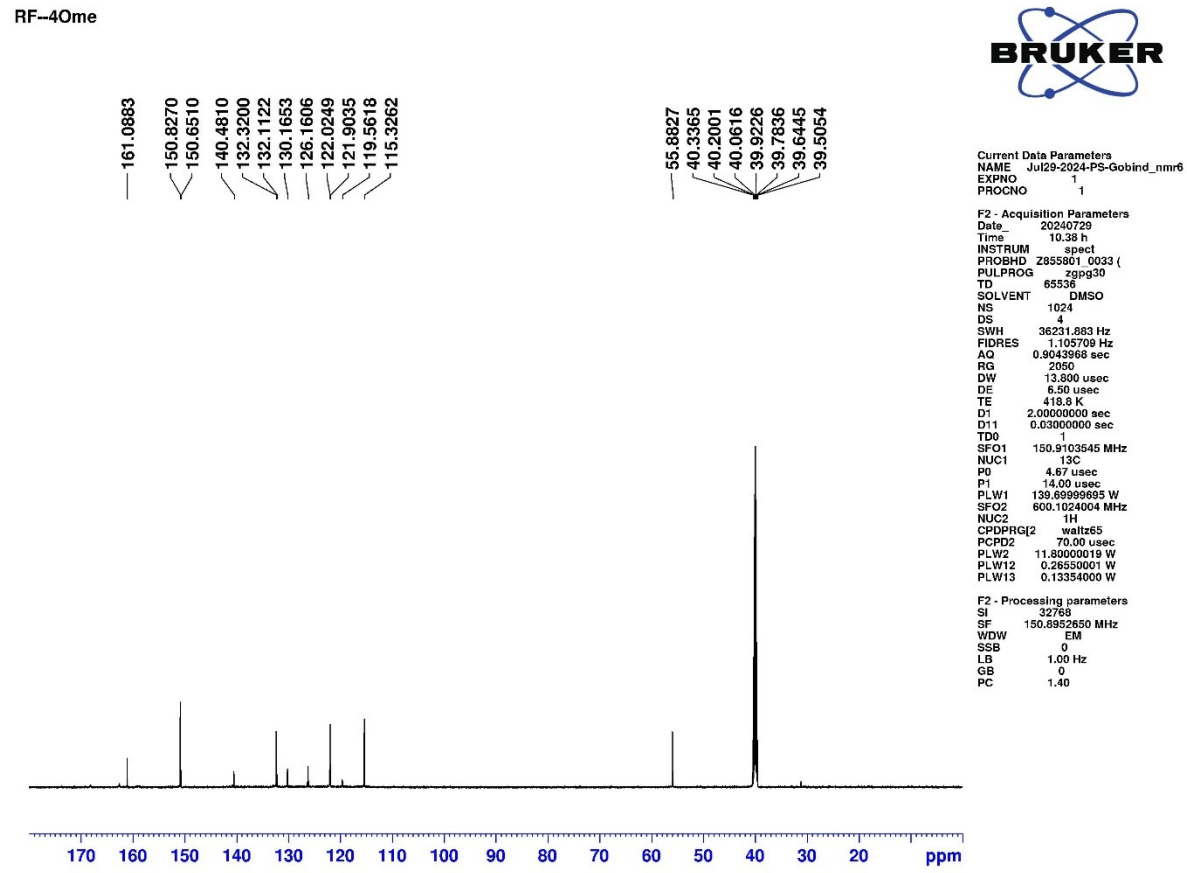


Figure S62. ^{13}C-NMR of compound **9e**

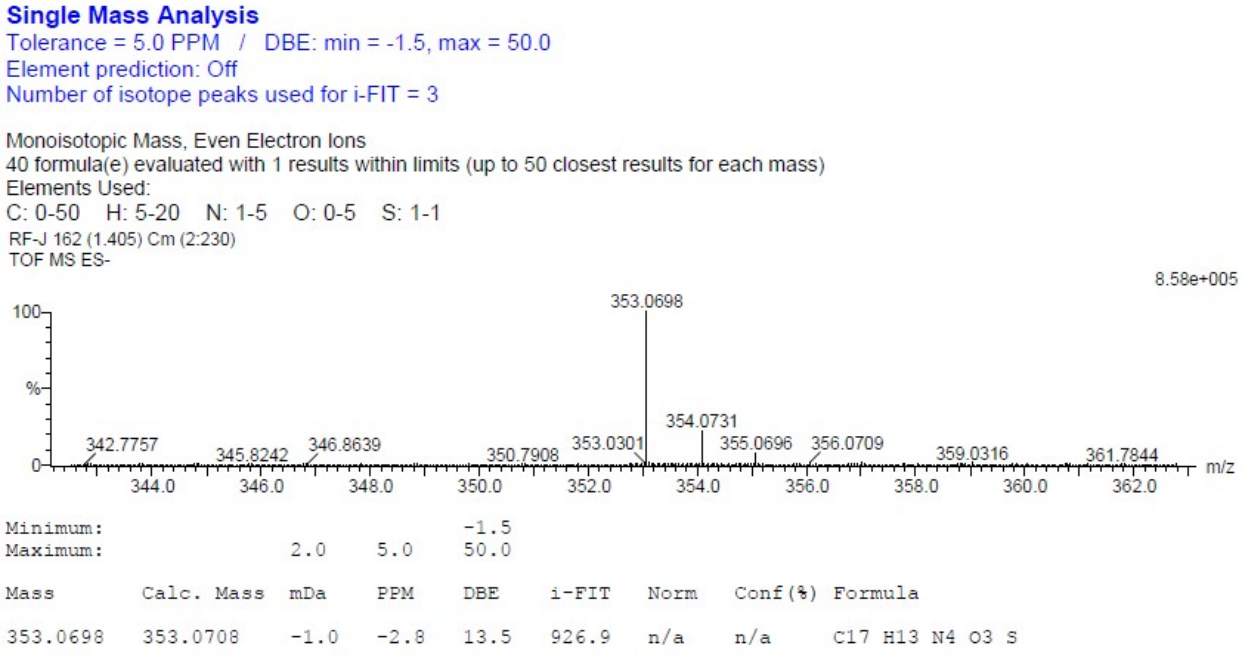


Figure S63. HRMS of compound **9e**.

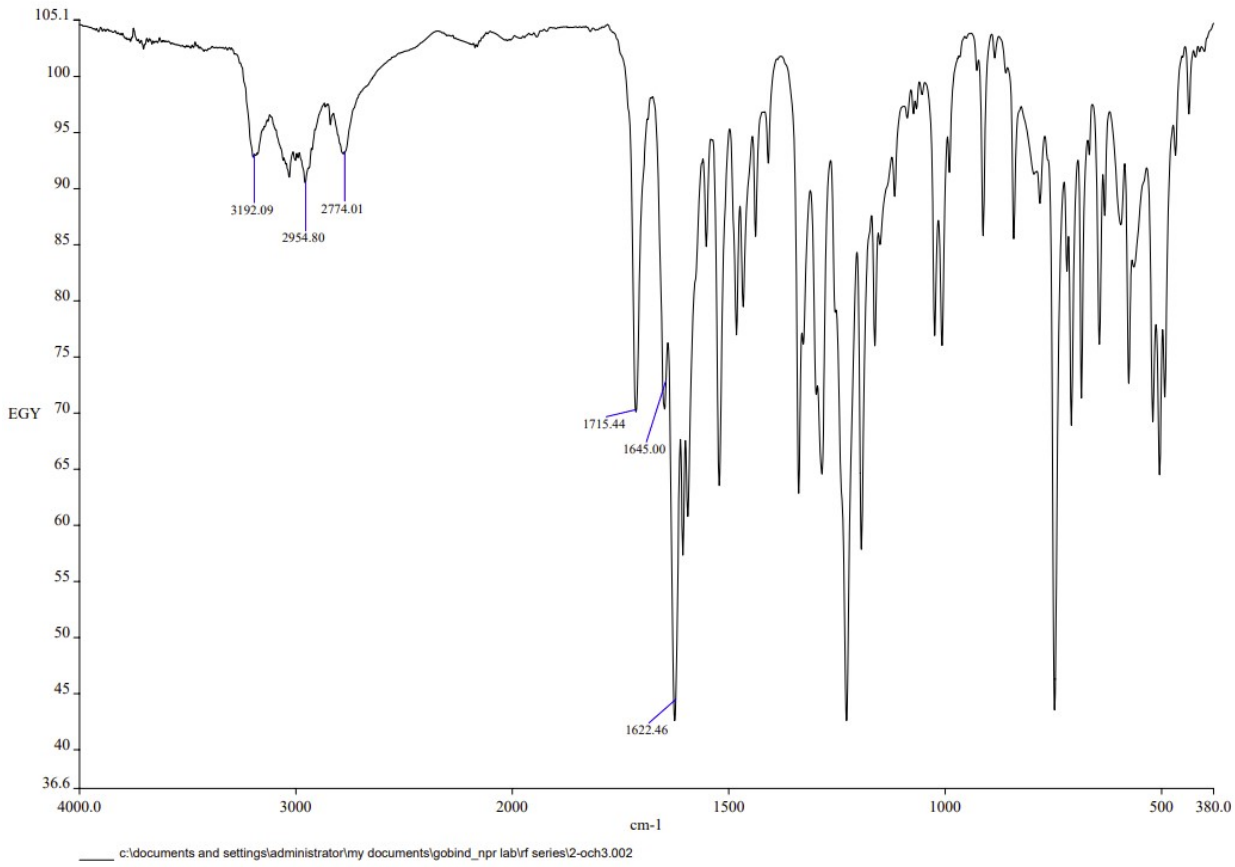


Figure S64. IR spectra of compound **9f**.

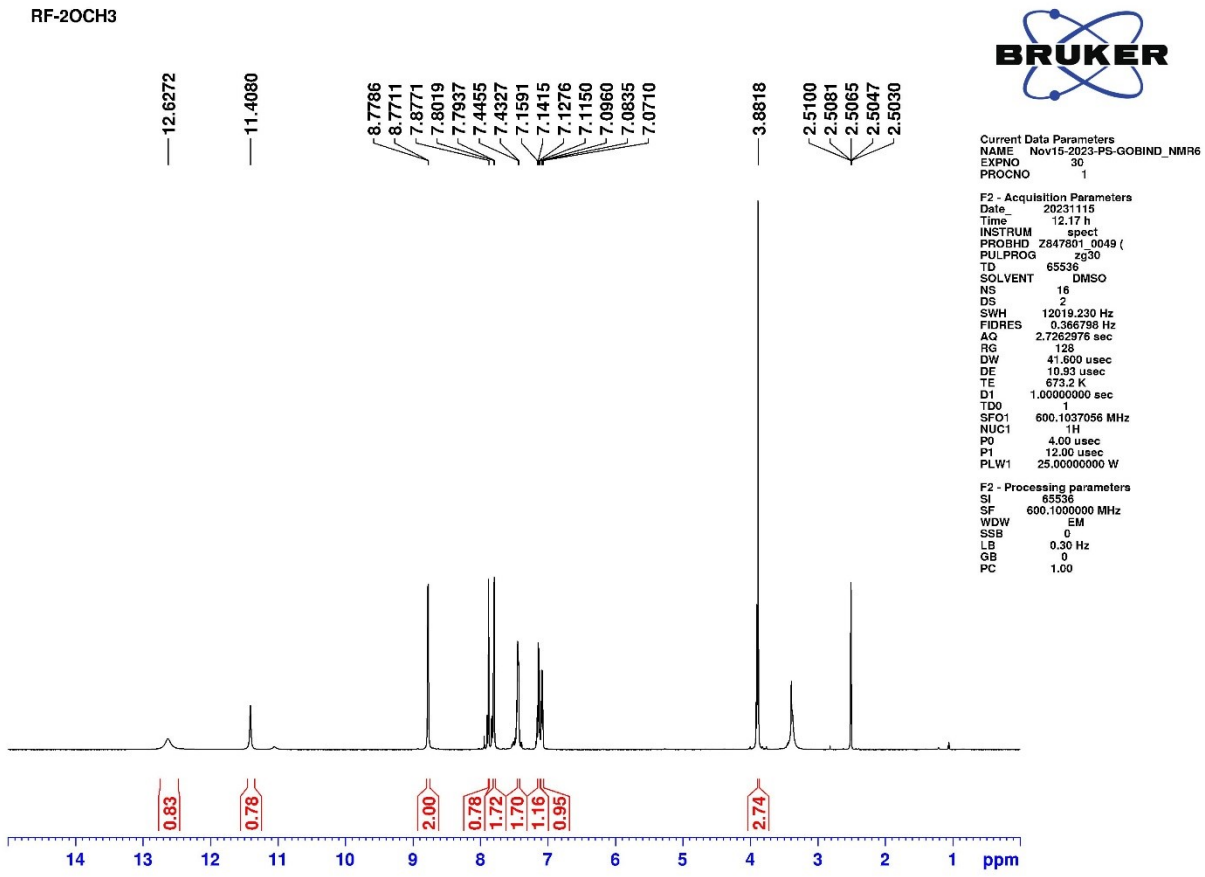


Figure S65. [1]H-NMR of compound **9f**.

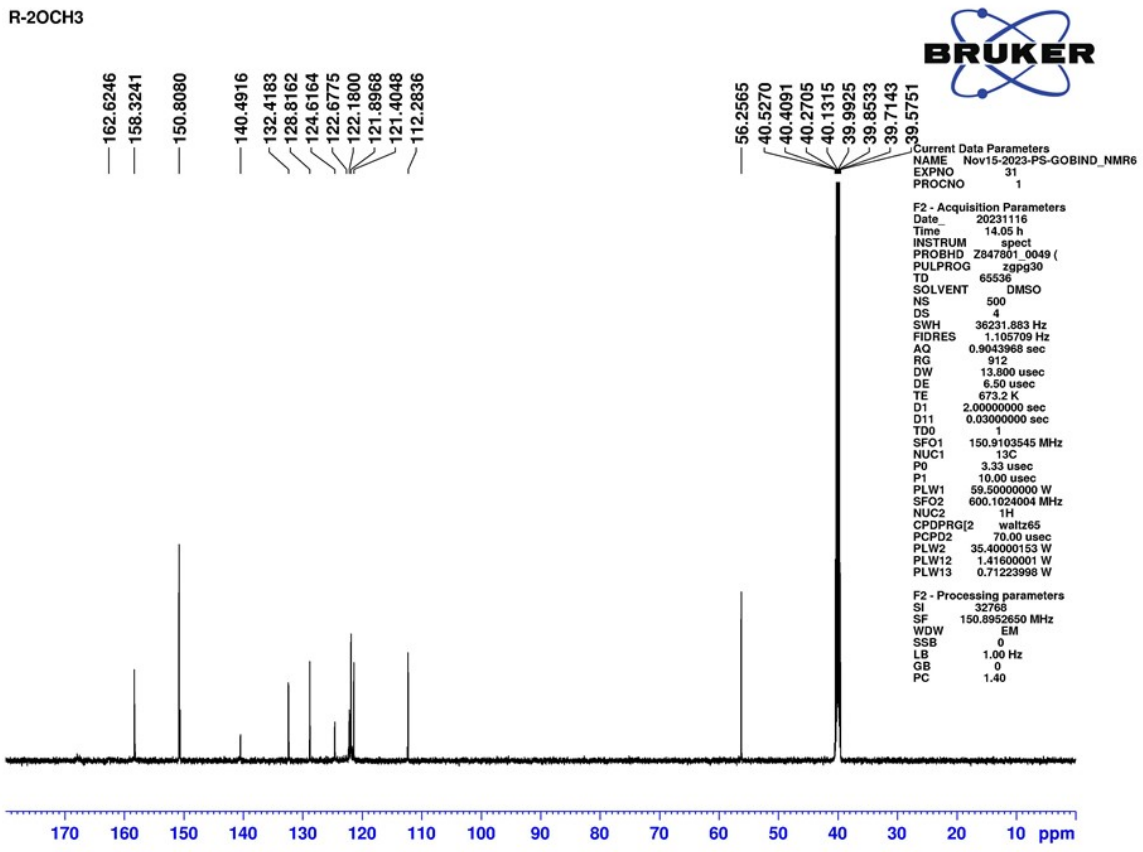


Figure S66. ^{13}C-NMR of compound **9f**.

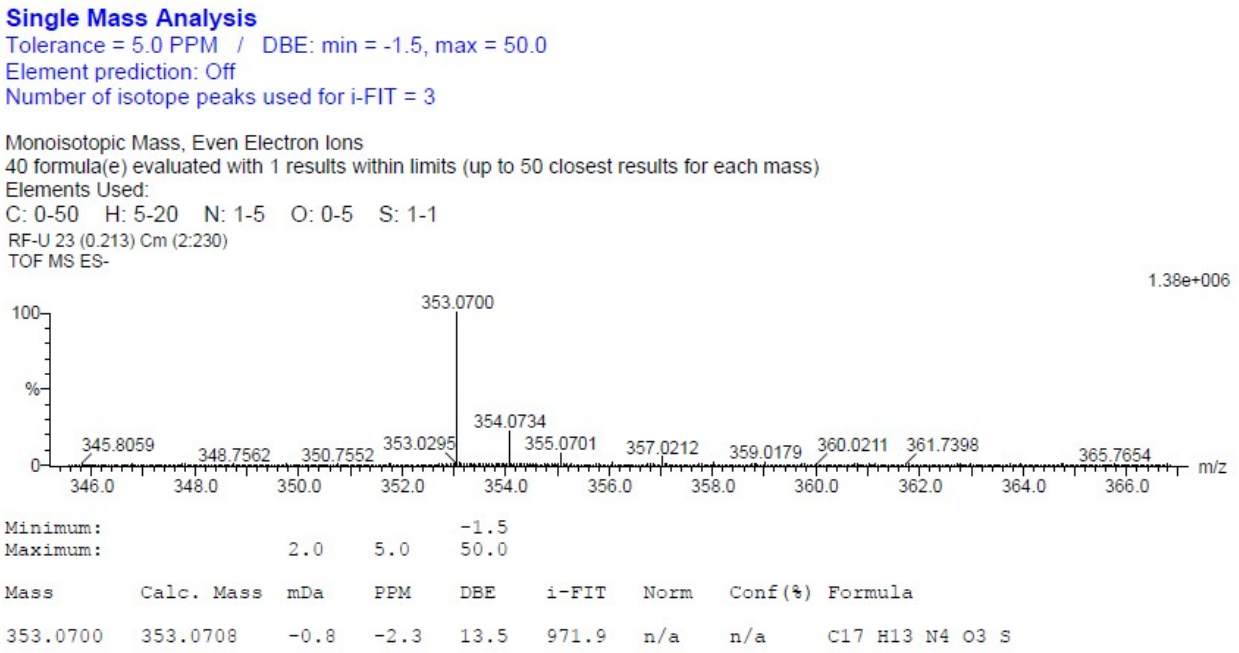


Figure S67. HRMS of compound **9f**.

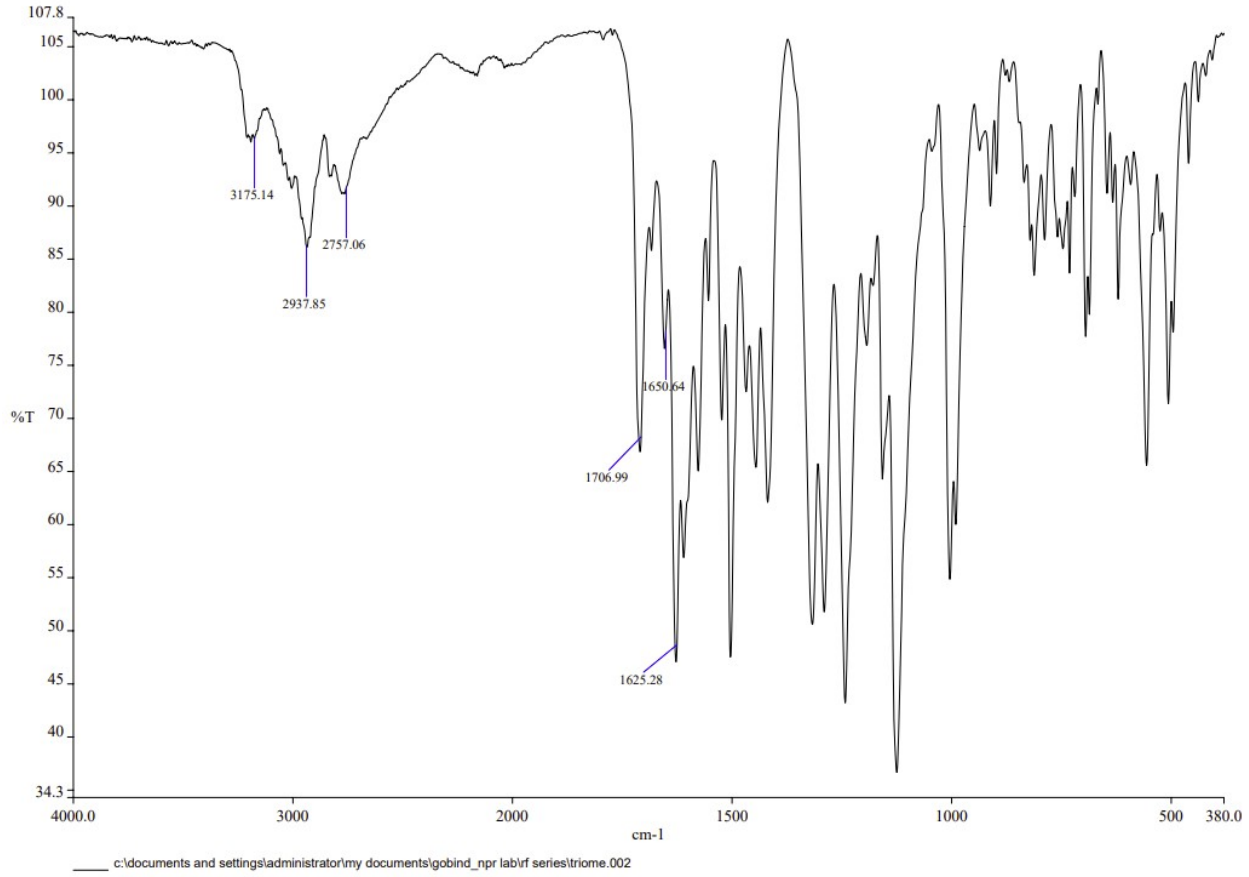


Figure S68. IR spectra of compound **9g**.

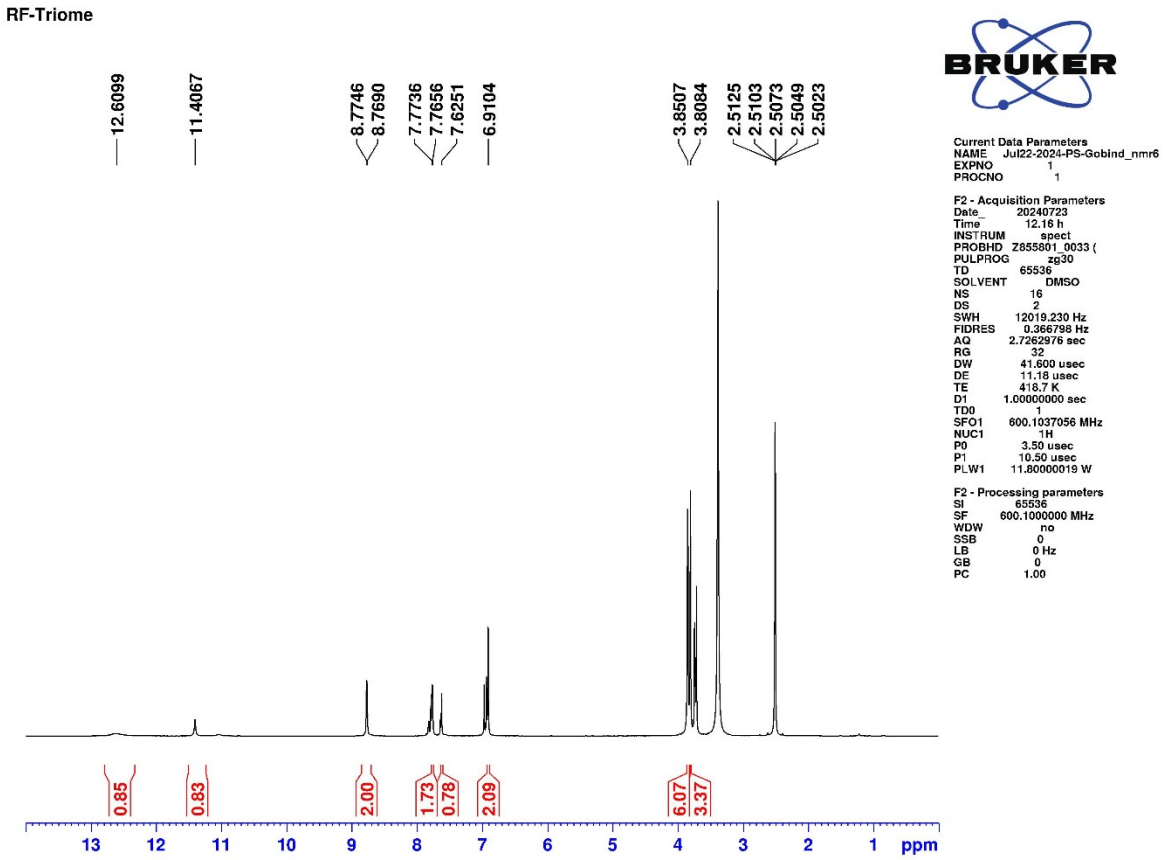


Figure S69. ^{1}H-NMR of compound **9g**.

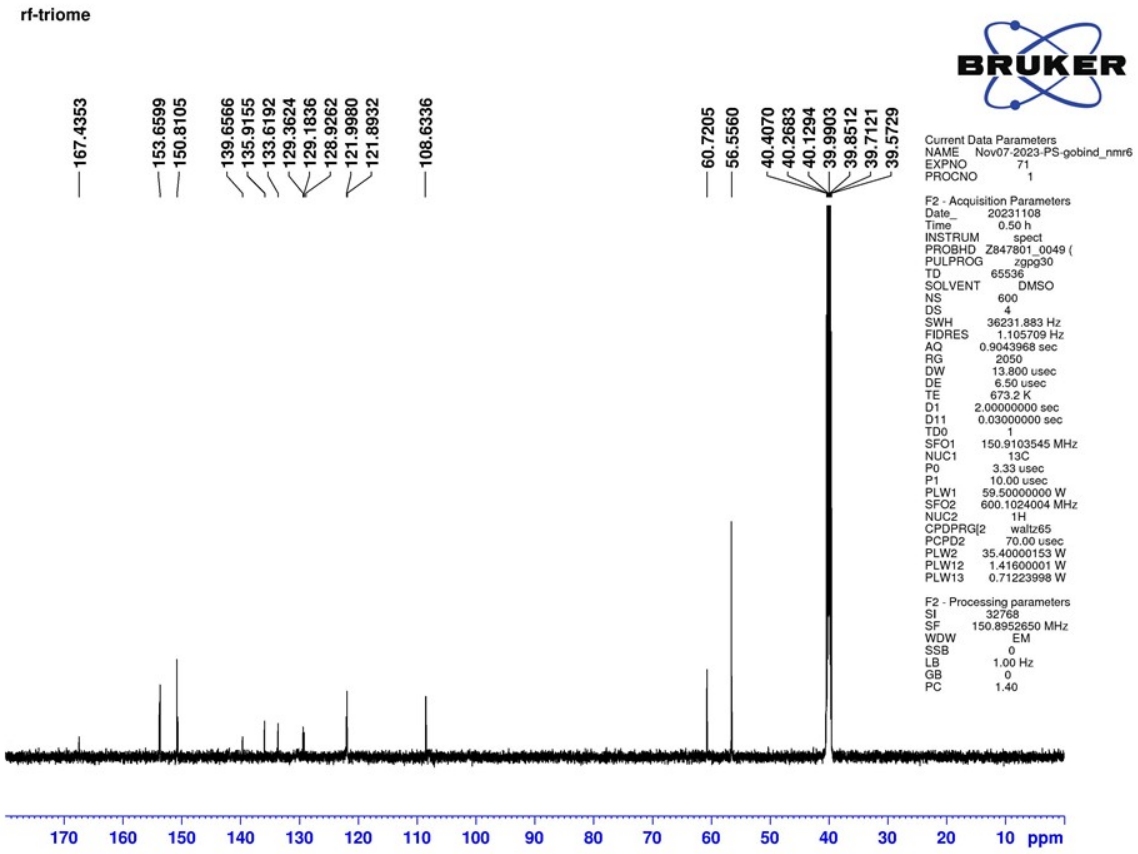
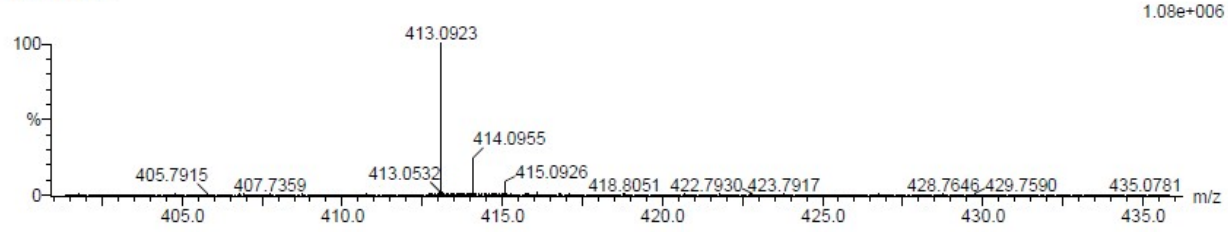


Figure S70. ^{13}C-NMR of compound **9g**.

Single Mass Analysis
Tolerance = 5.0 PPM / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
40 formula(e) evaluated with 1 results within limits (up to 50 closest results for each mass)
Elements Used:
C: 0-50 H: 5-20 N: 1-5 O: 0-5 S: 1-1
RF-O 102 (0.891) Cm (2:230)
TOF MS ES-



Minimum:				-1.5				
Maximum:		2.0	5.0	50.0				
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Norm	Conf(%)	Formula
413.0923	413.0920	0.3	0.7	13.5	957.7	n/a	n/a	C19 H17 N4 O5 S

Figure S71. HRMS of compound **9g**.

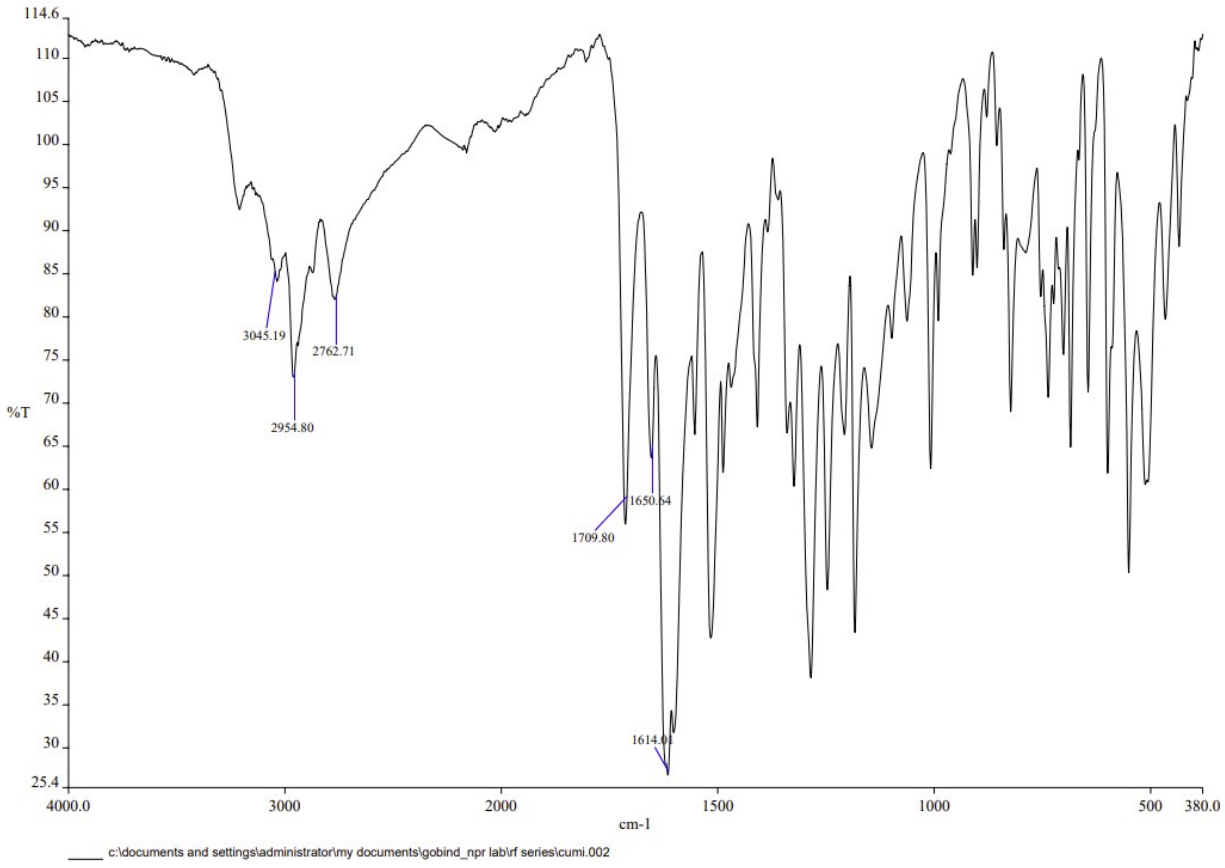


Figure S72. IR spectra of compound **9h**.

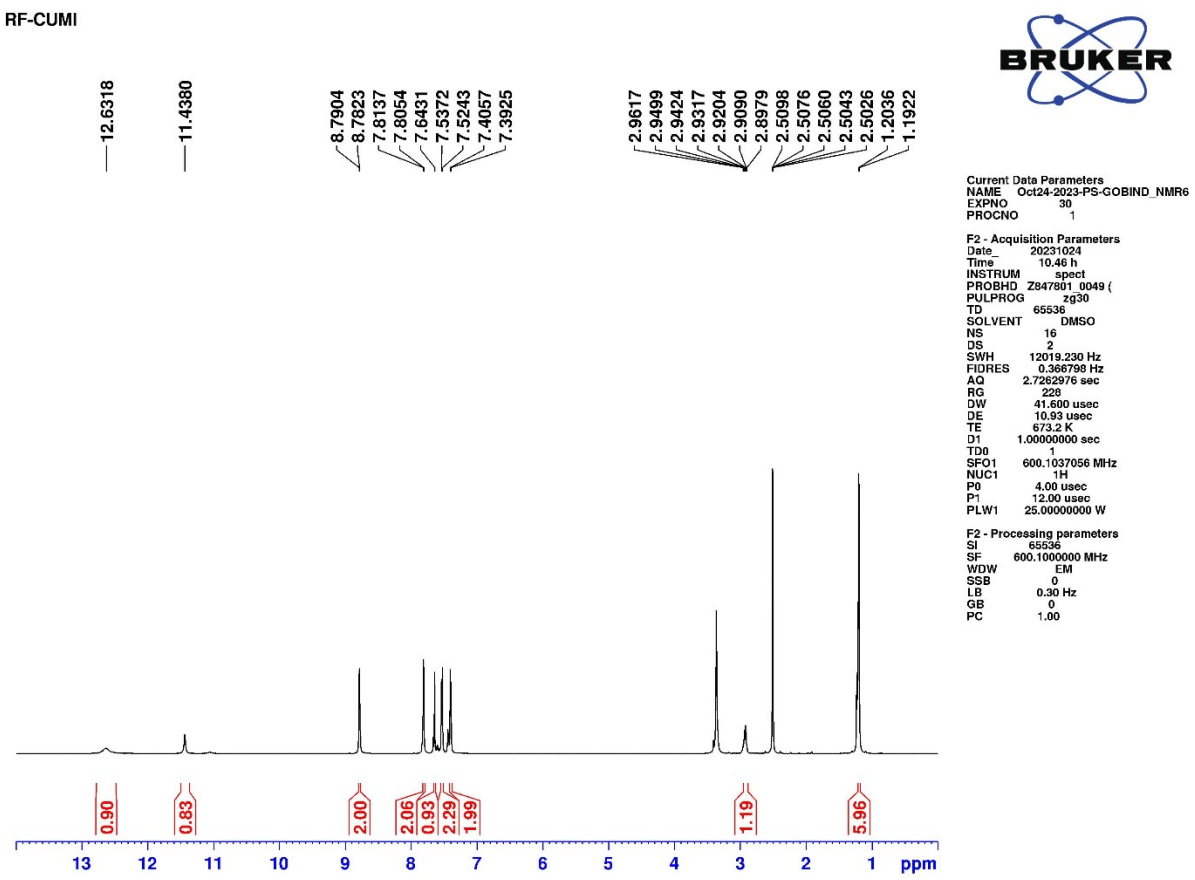


Figure S73. ^{1}H-NMR of compound **9h**.

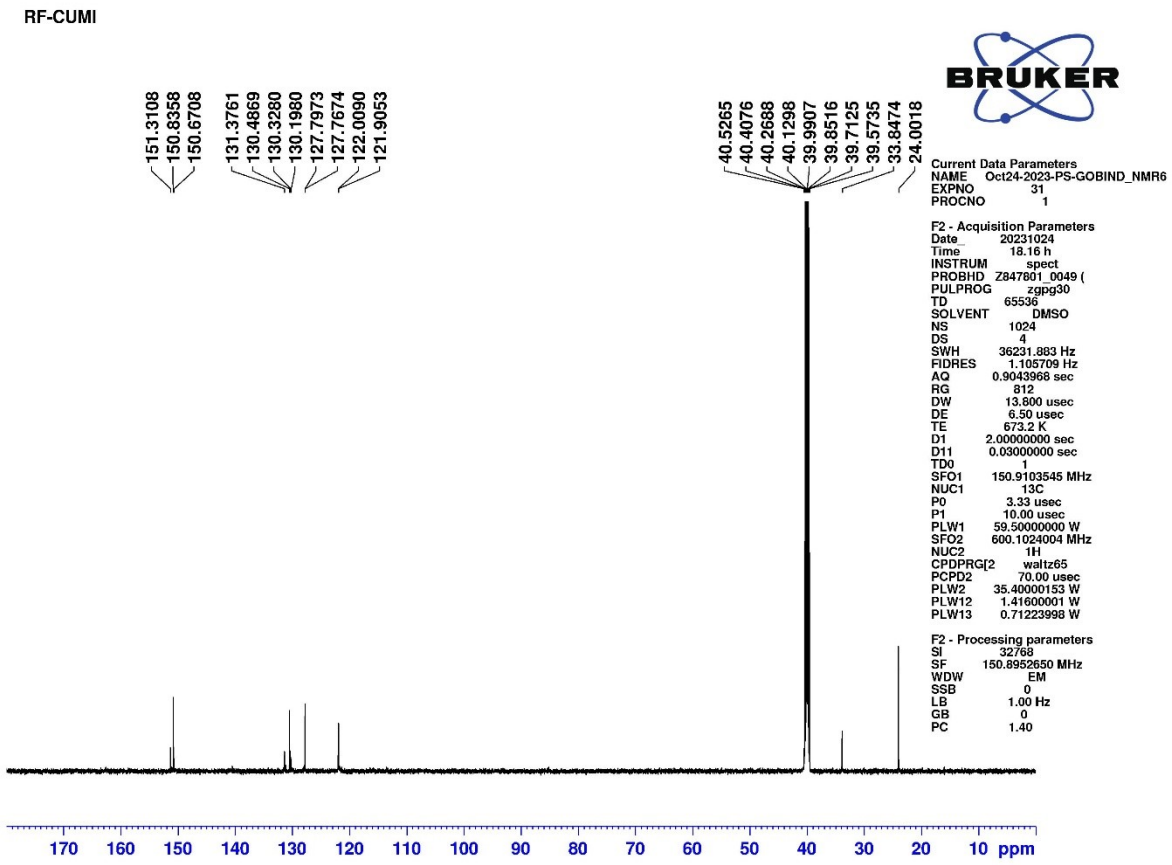


Figure S74. ^{13}C-NMR of compound **9h**.

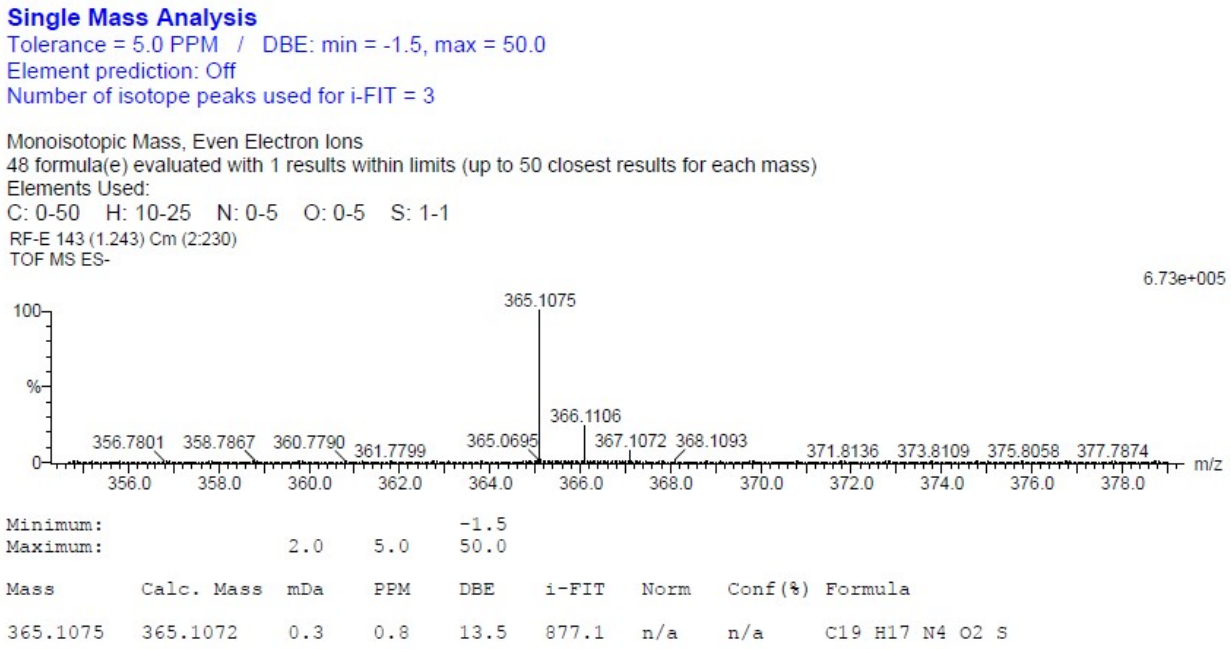


Figure S75. HRMS of compound **9h**.

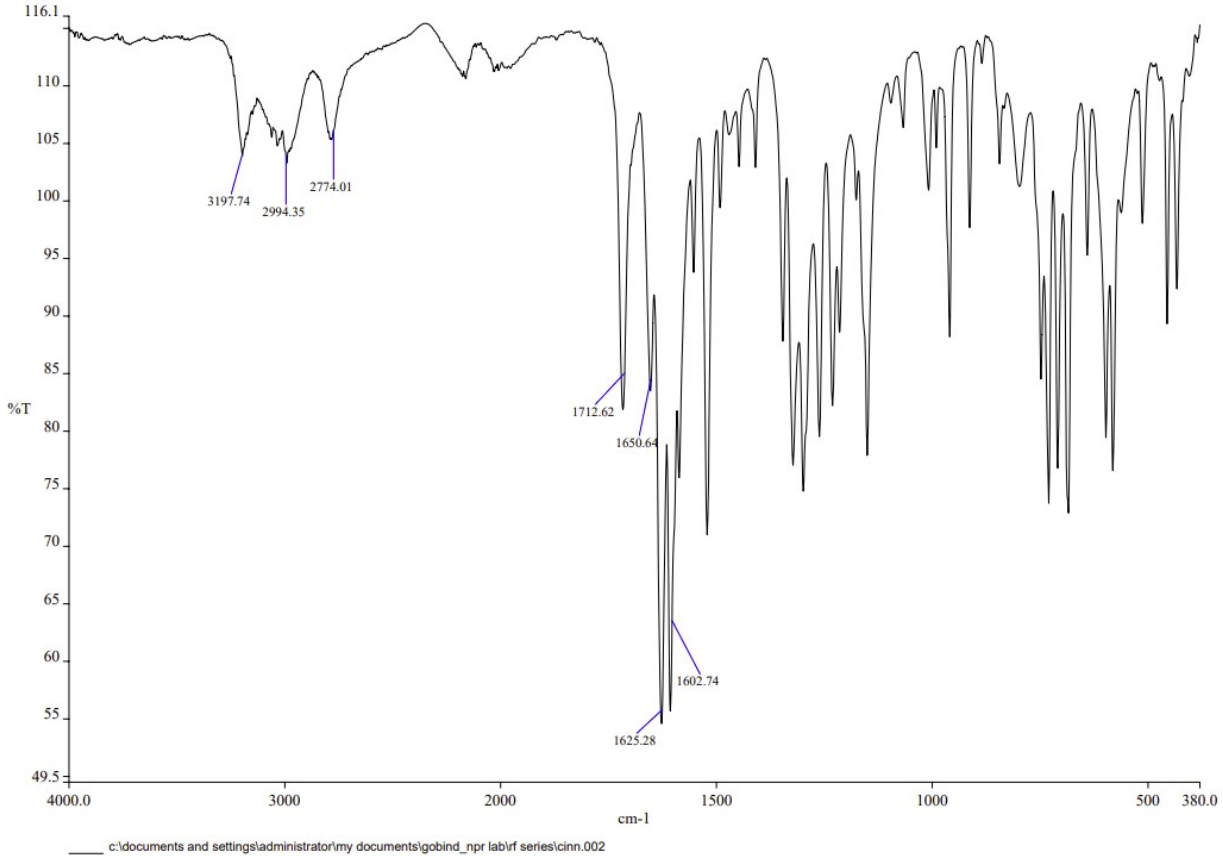


Figure S76. IR spectra of compound **9i**.

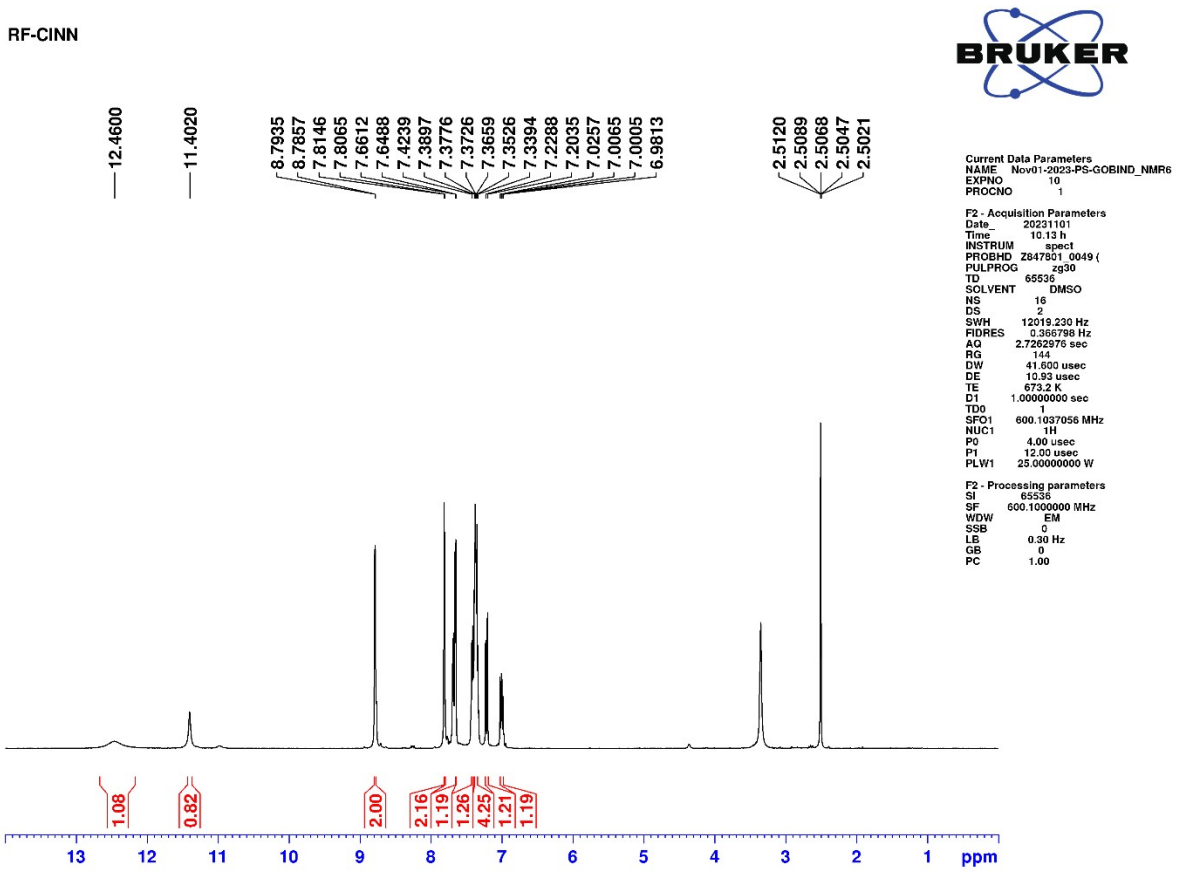


Figure S77. ^{1}H-NMR of compound **9i**.

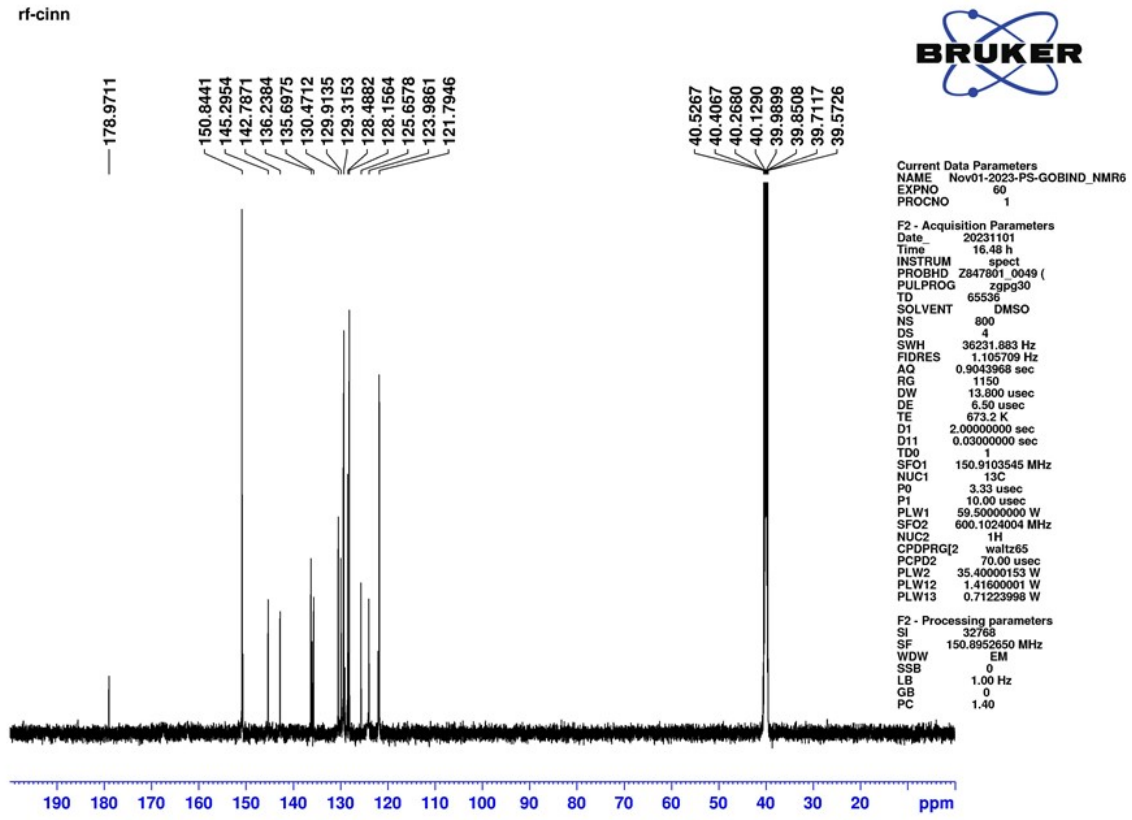


Figure S78. ^{13}C-NMR of compound **9i**.

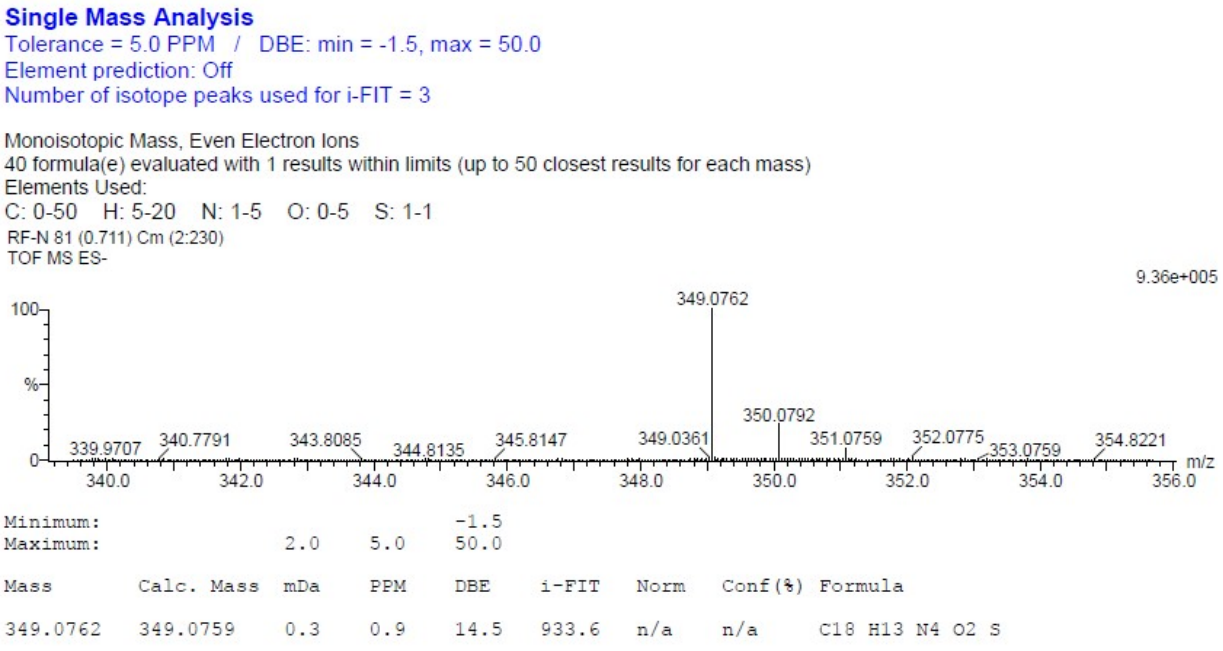


Figure S79. HRMS of compound **9i**.

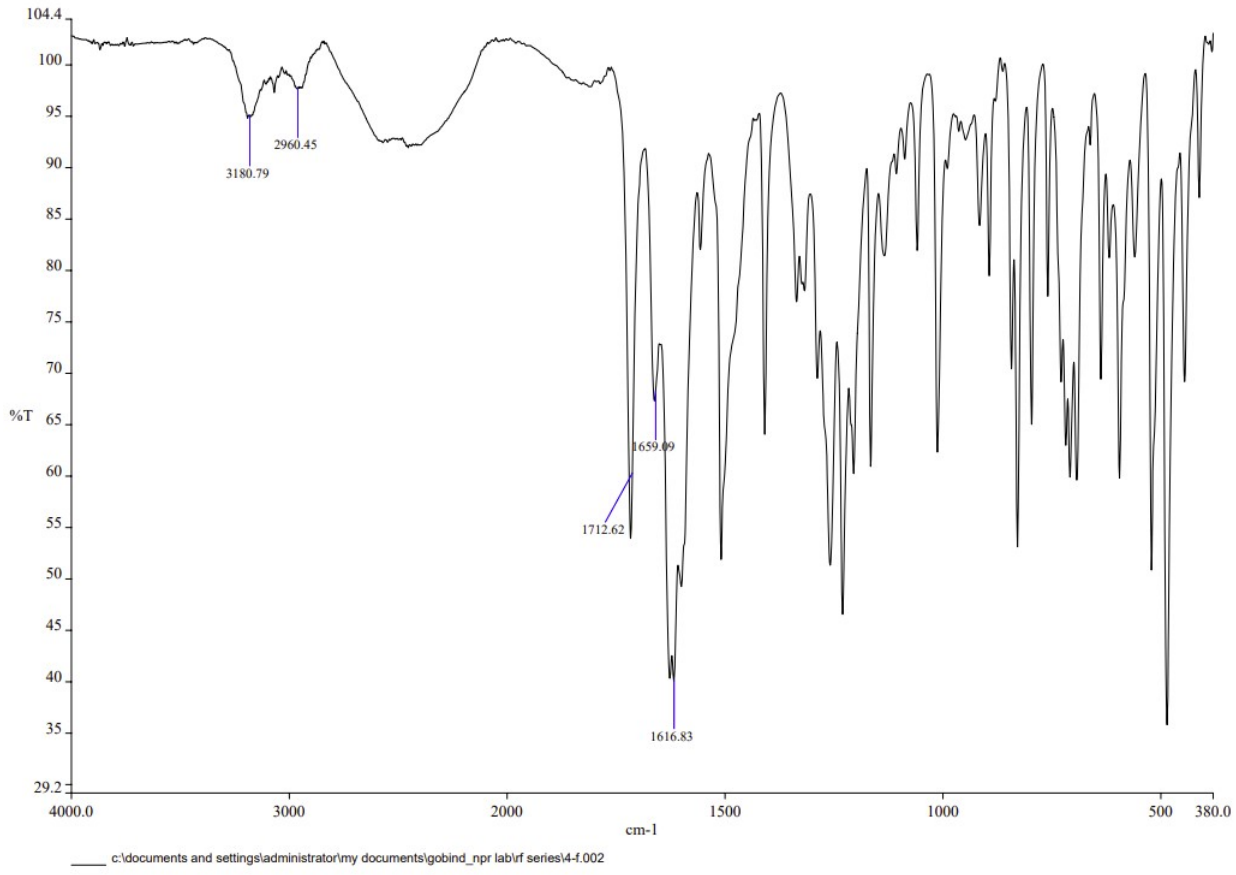


Figure S80. IR spectra of compound **9j**.

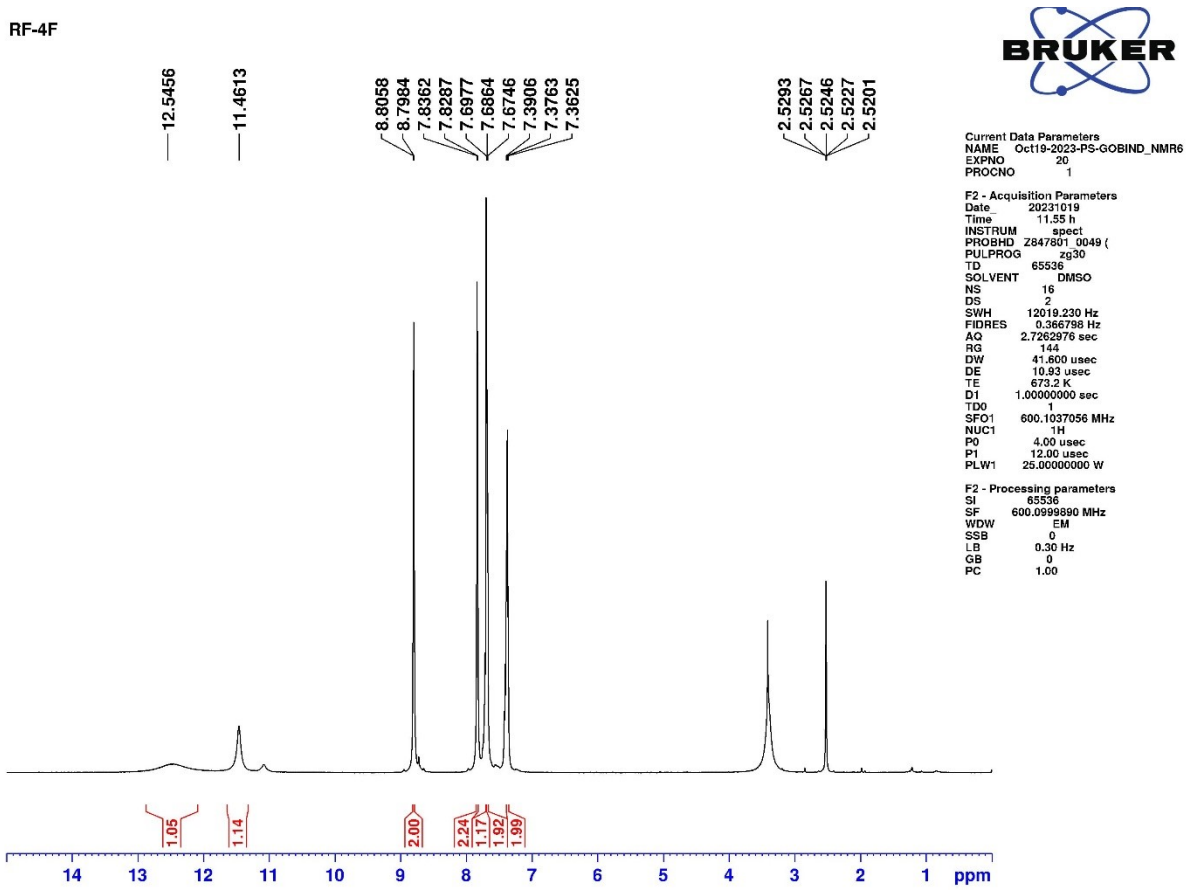


Figure S81. ^{1}H-NMR of compound **9j**.

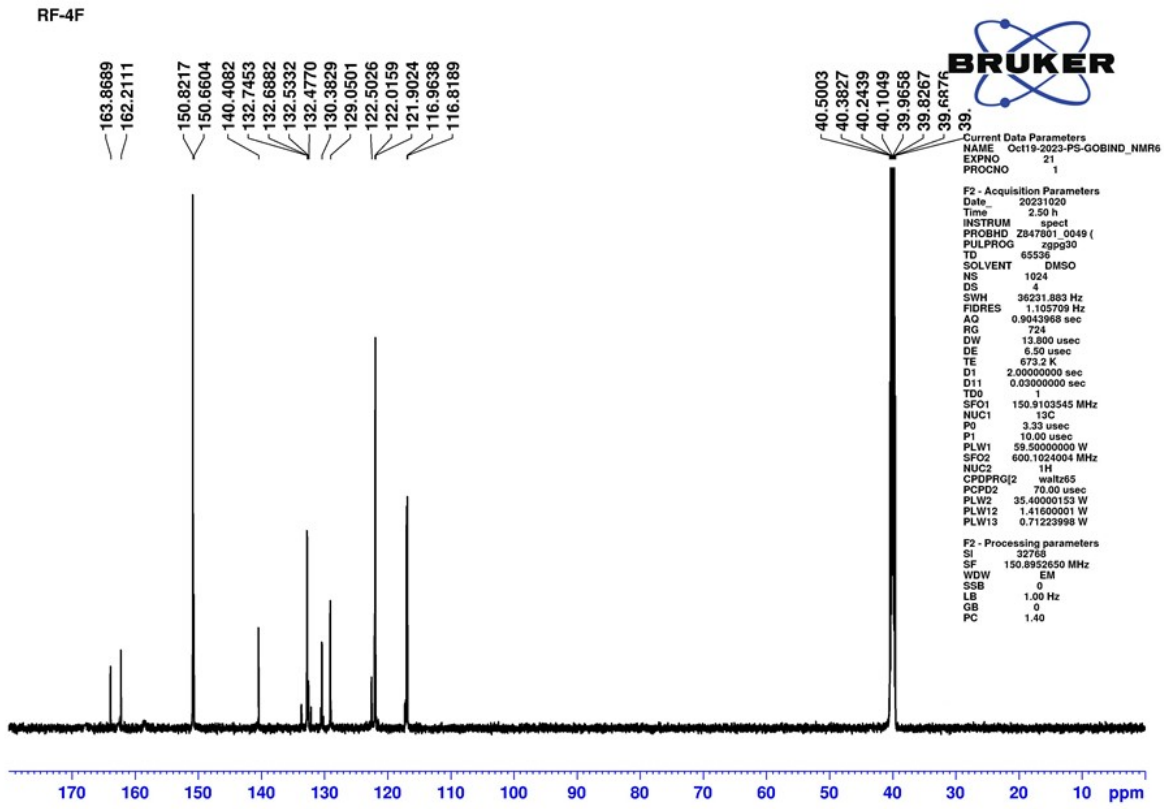
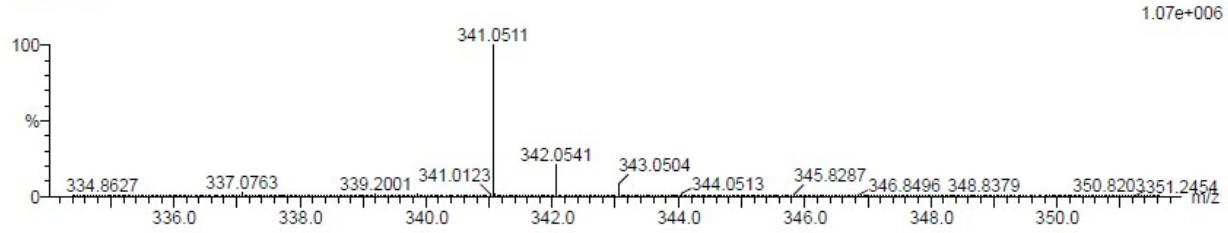


Figure S82. ^{13}C-NMR of compound **9j**.

Single Mass Analysis
Tolerance = 5.0 PPM / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
192 formula(e) evaluated with 1 results within limits (up to 50 closest results for each mass)
Elements Used:
C: 0-50 H: 10-25 N: 0-5 O: 0-5 S: 0-1 F: 0-1

RF-C 223 (1.928) Cm (2:230)
TOF MS ES-



Minimum:				-1.5				
Maximum:		2.0	5.0	50.0				
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Norm	Conf(%)	Formula
341.0511	341.0508	0.3	0.9	13.5	993.3	n/a	n/a	C16 H10 N4 O2 S F

Figure S83. HRMS of compound **9j**.

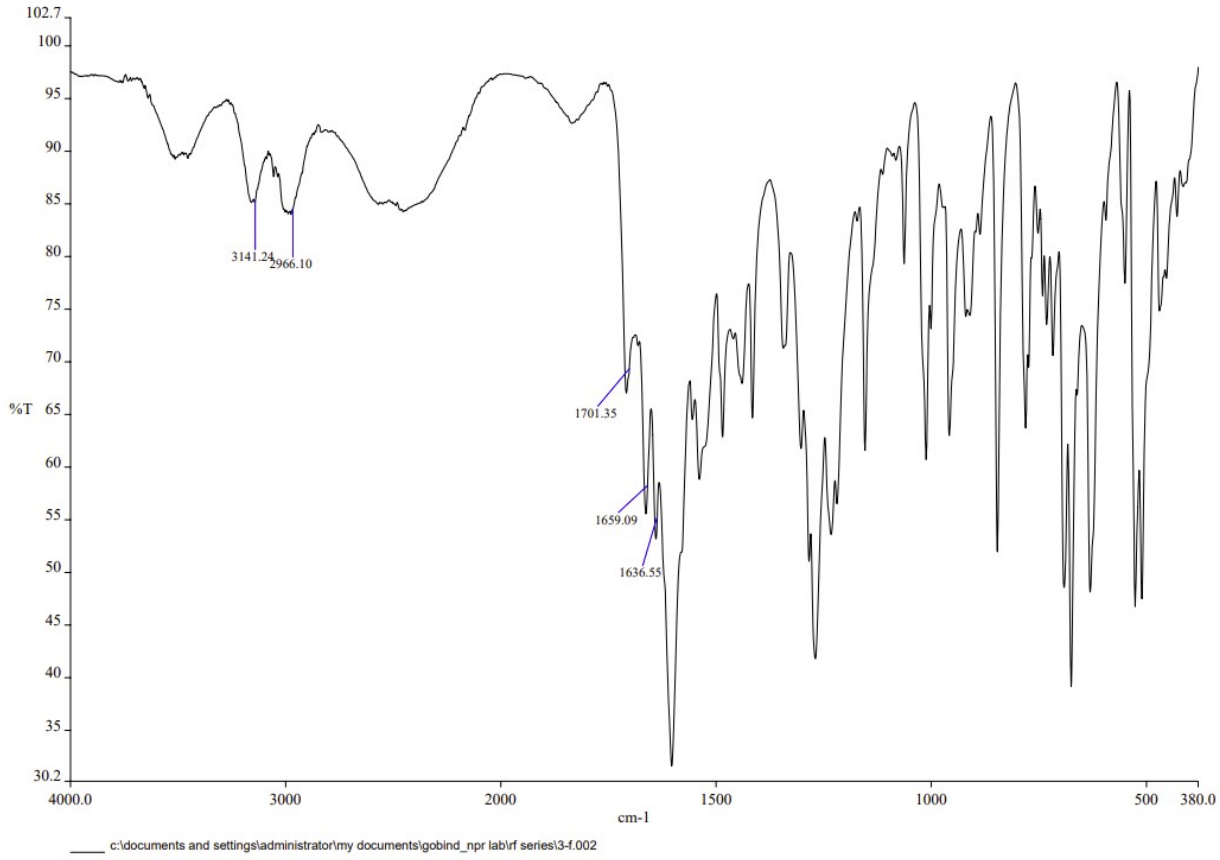


Figure S84. IR spectra of compound **9k**.

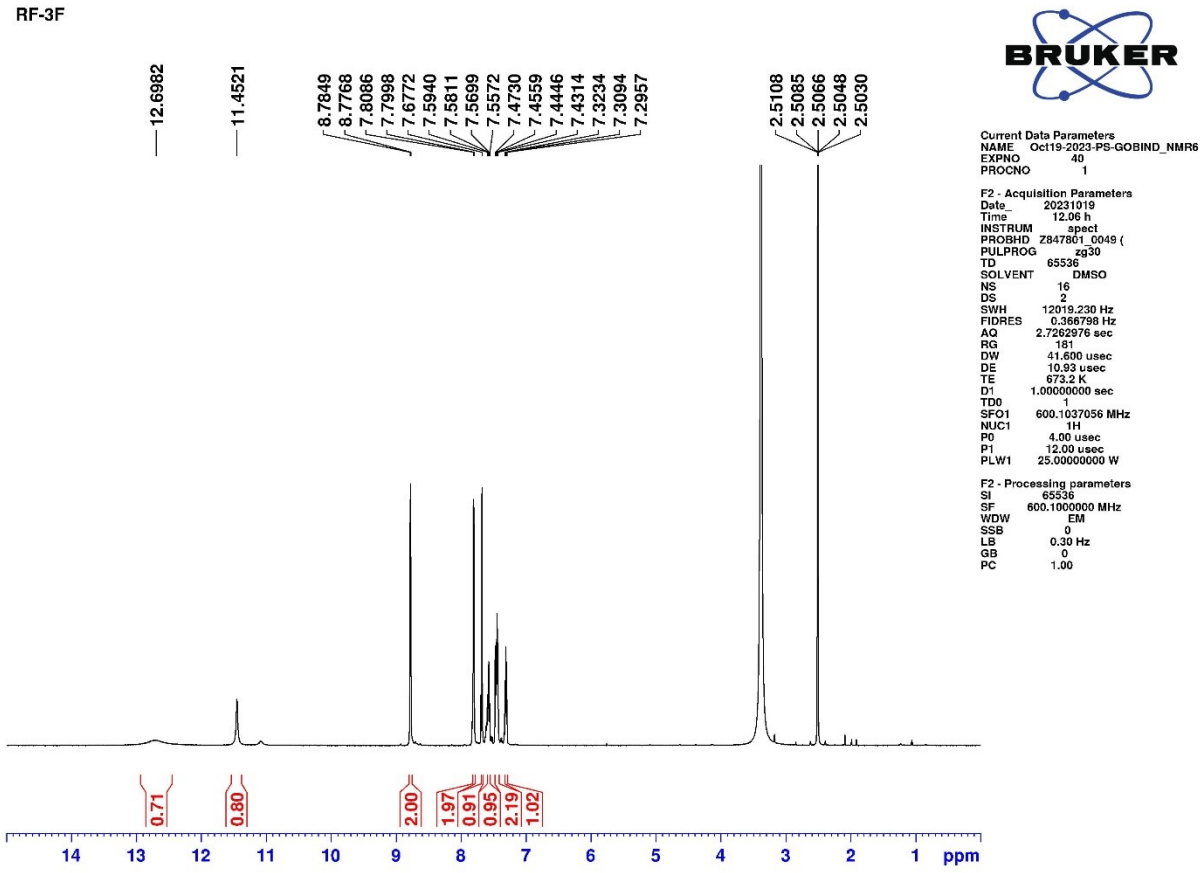


Figure S85. ^{1}H-NMR of compound **9k**.

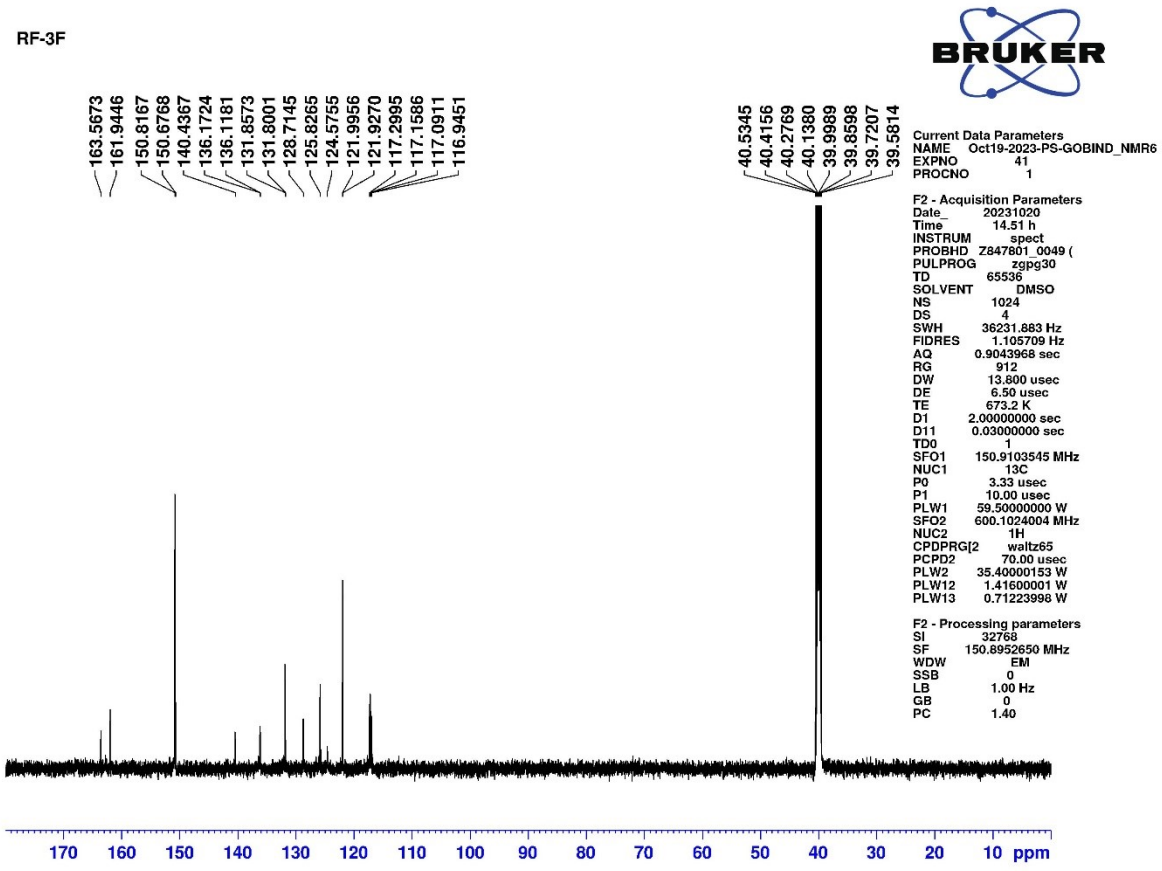


Figure S86. ^{13}C-NMR of compound **9k**.

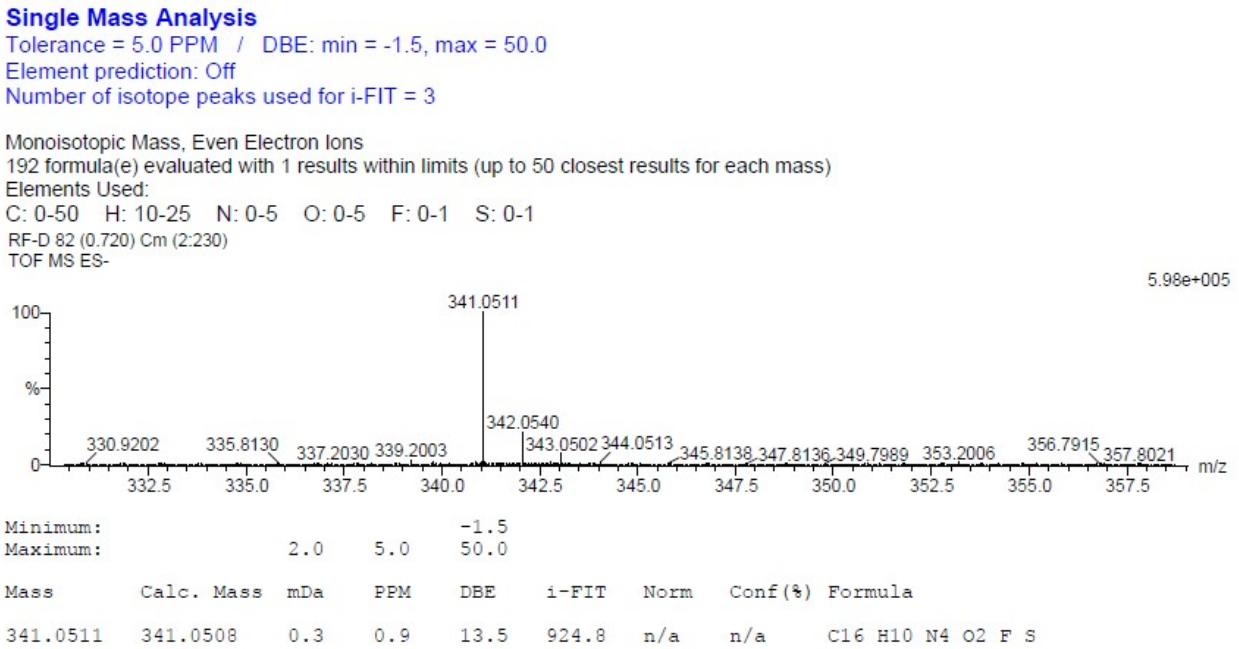


Figure S87. HRMS of compound **9k**.

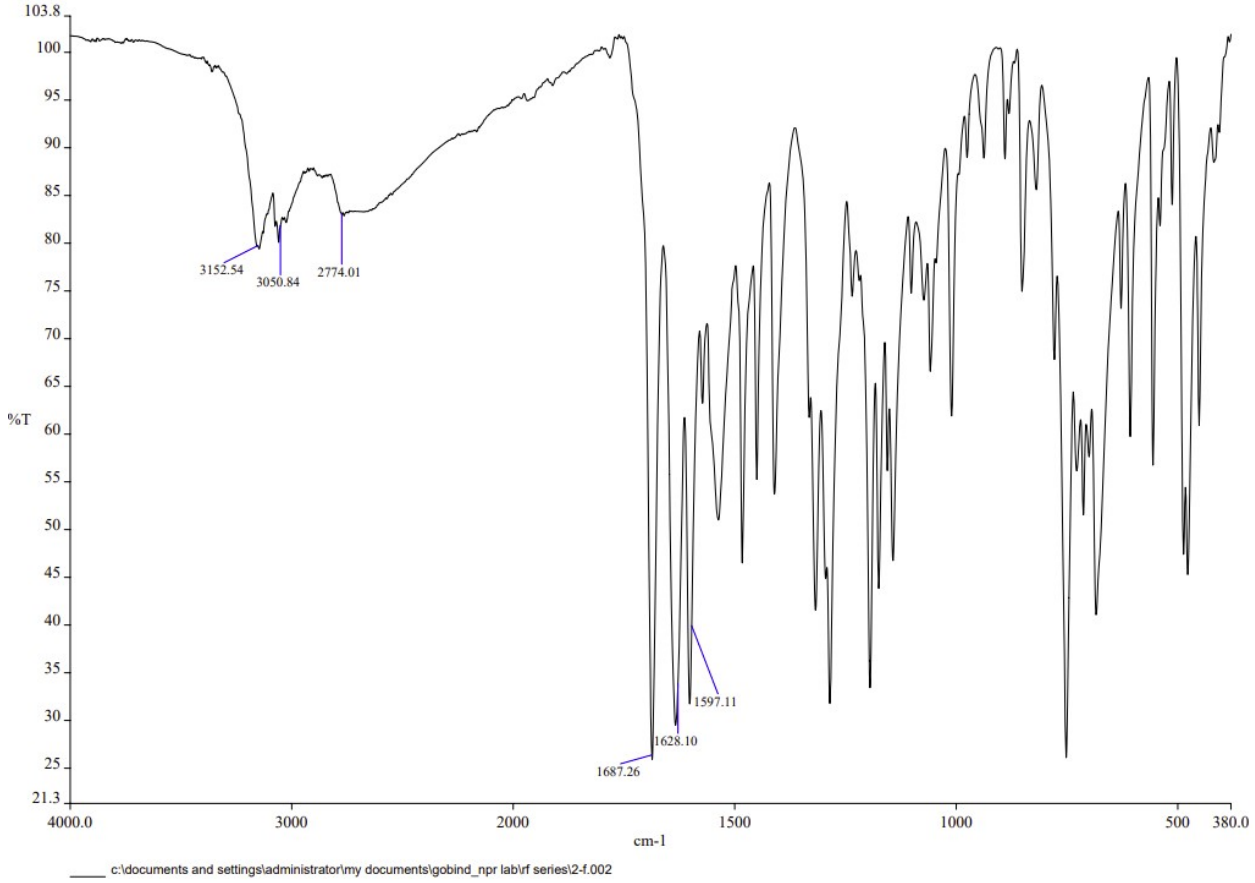


Figure S88. IR spectra of compound **9l**.

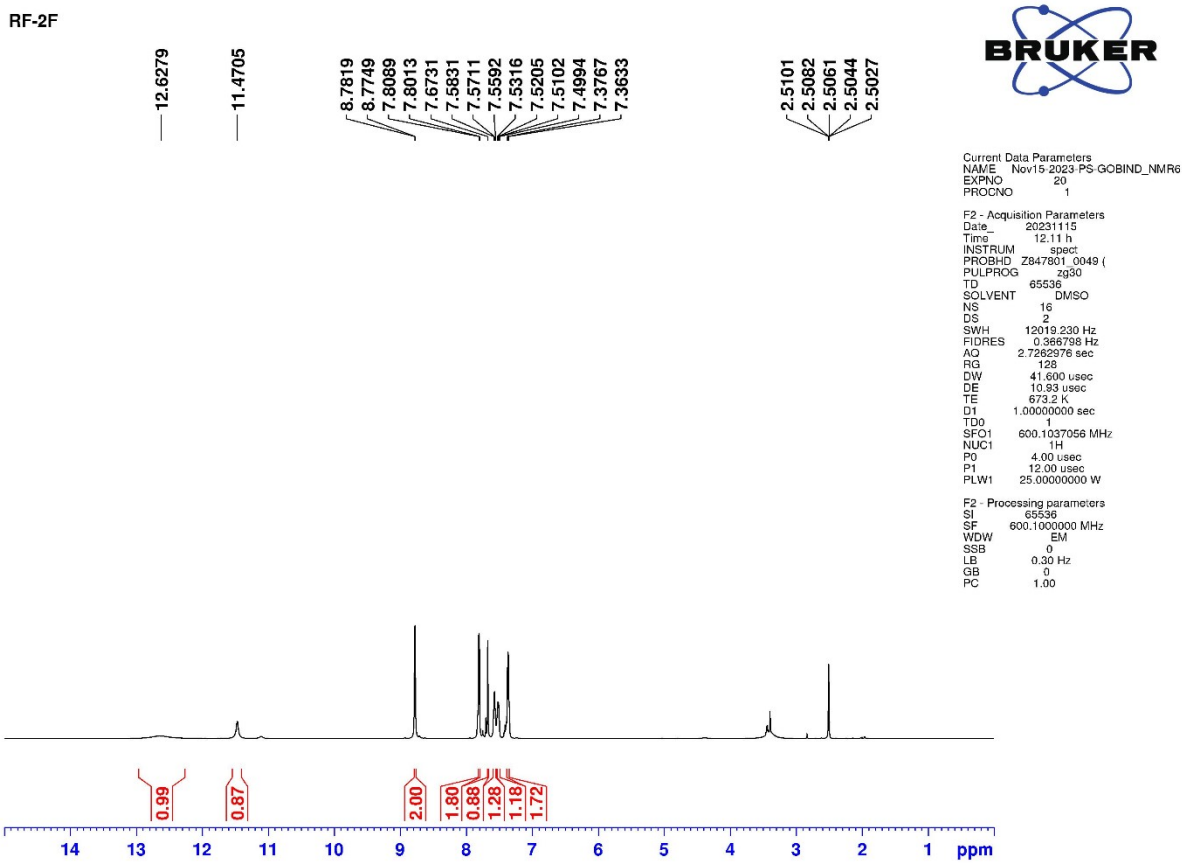


Figure S89. ^{1}H-NMR of compound **9l**.

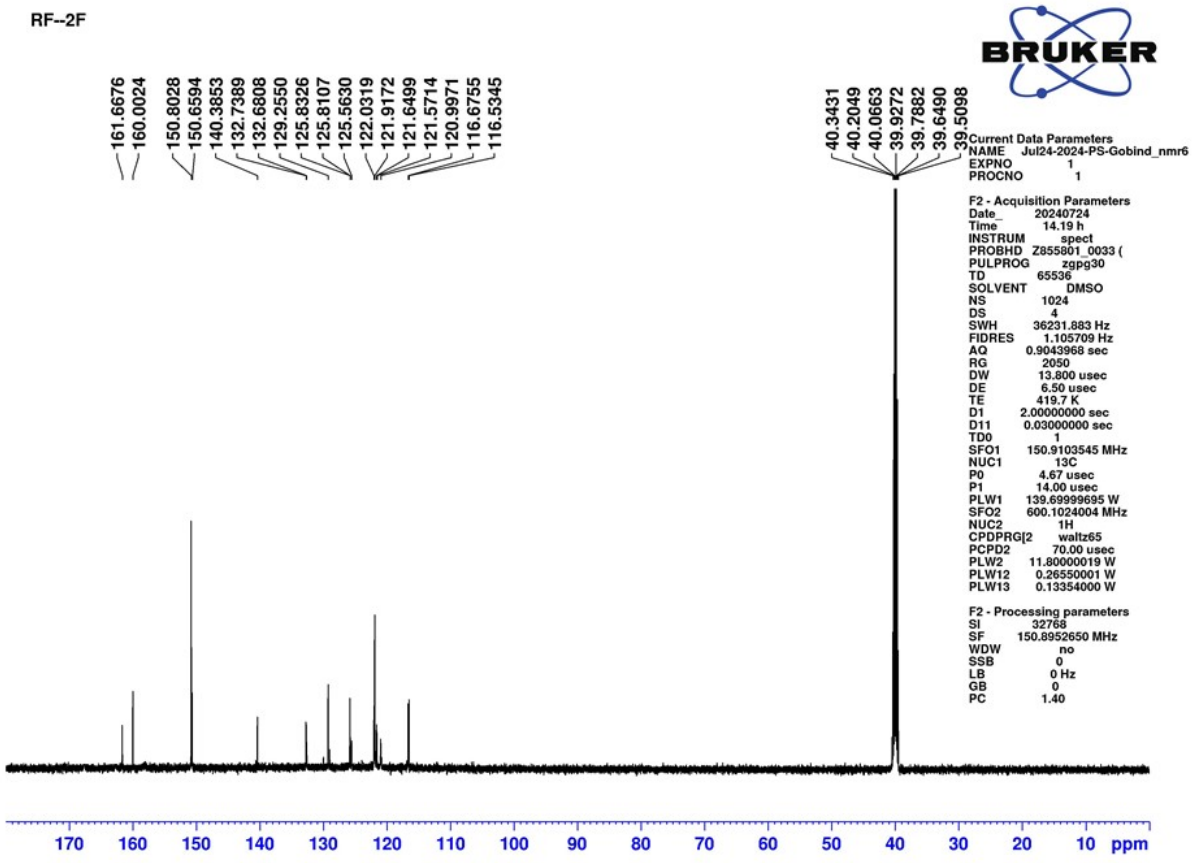


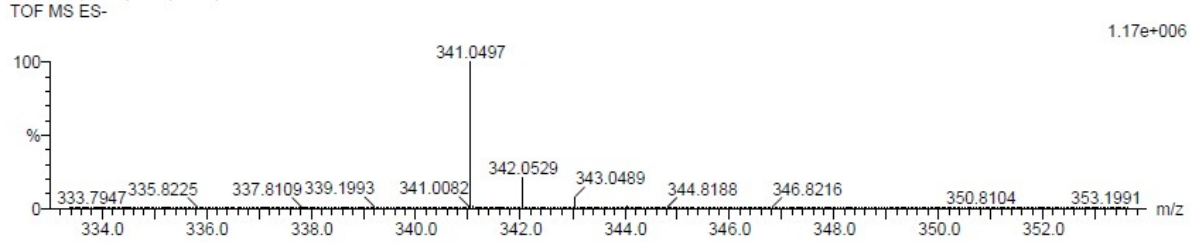
Figure S90. ^{13}C-NMR of compound **9l**.

Elemental Composition Report **Page 1**

Single Mass Analysis
Tolerance = 5.0 PPM / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
40 formula(e) evaluated with 1 results within limits (up to 50 closest results for each mass)
Elements Used:
C: 0-50 H: 5-20 N: 1-5 O: 0-5 S: 1-1 F: 1-1

RF-S 25 (0.231) Cm (2:230)
TOF MS ES-



Minimum:				-1.5				
Maximum:		2.0	5.0	50.0				
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Norm	Conf(%)	Formula
341.0497	341.0508	-1.1	-3.2	13.5	960.8	n/a	n/a	C16 H10 N4 O2 S F

Figure S91. HRMS of compound **9l**.

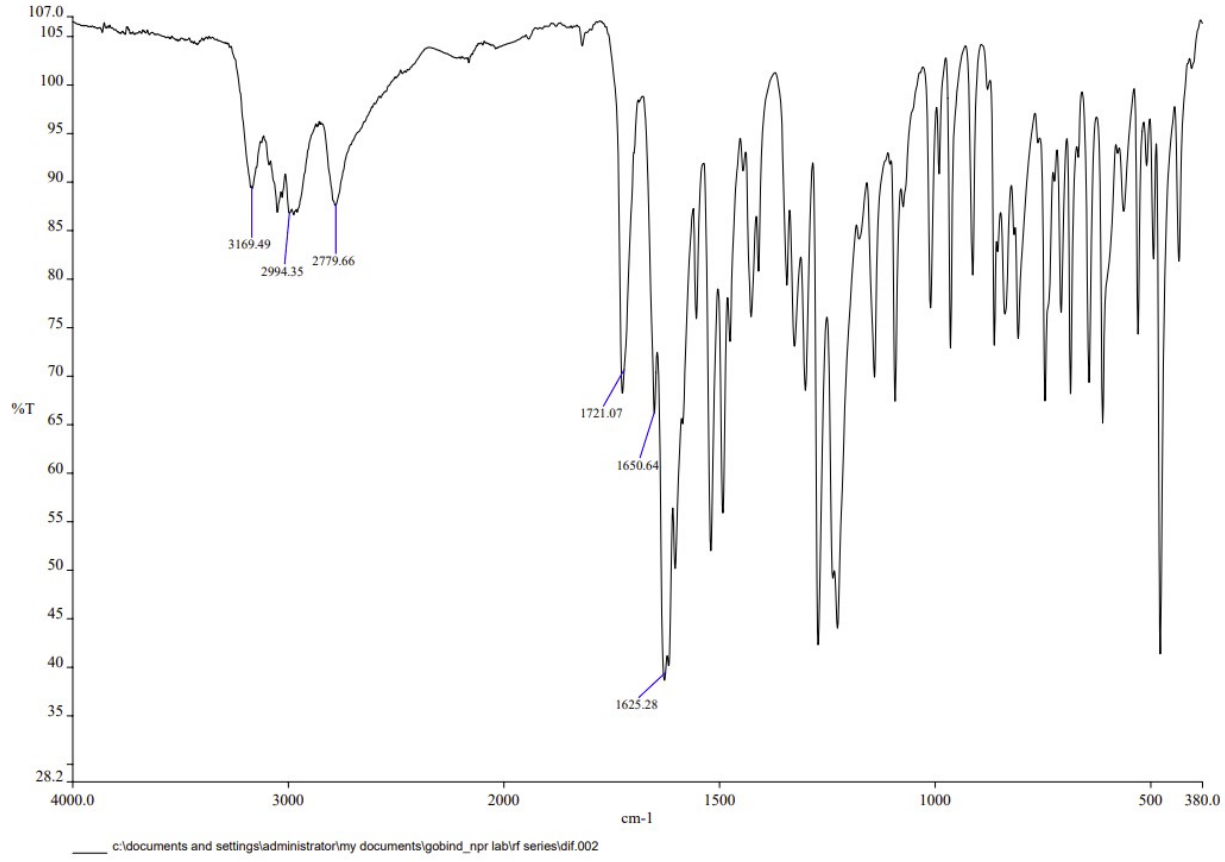


Figure S92. IR spectra of compound **9m**.

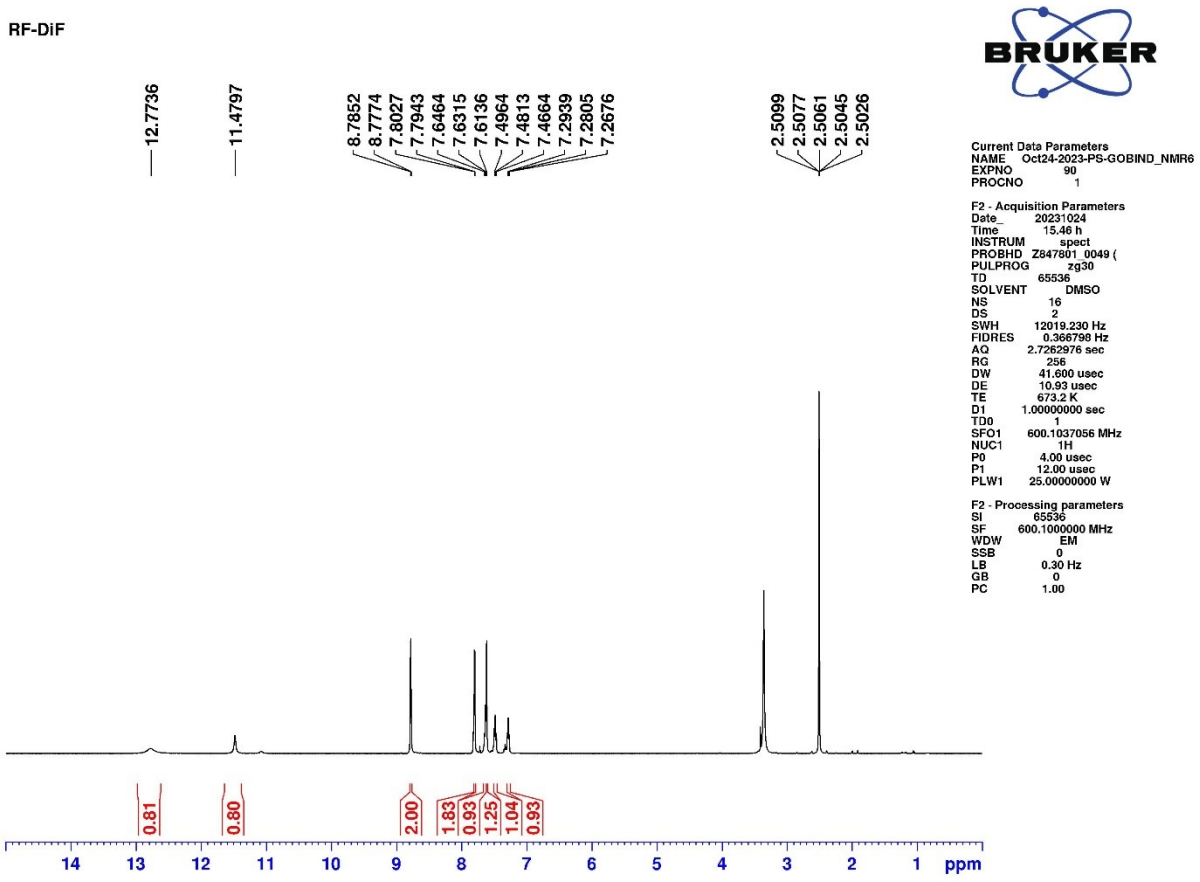


Figure S93. [1]H-NMR of compound **9m**.

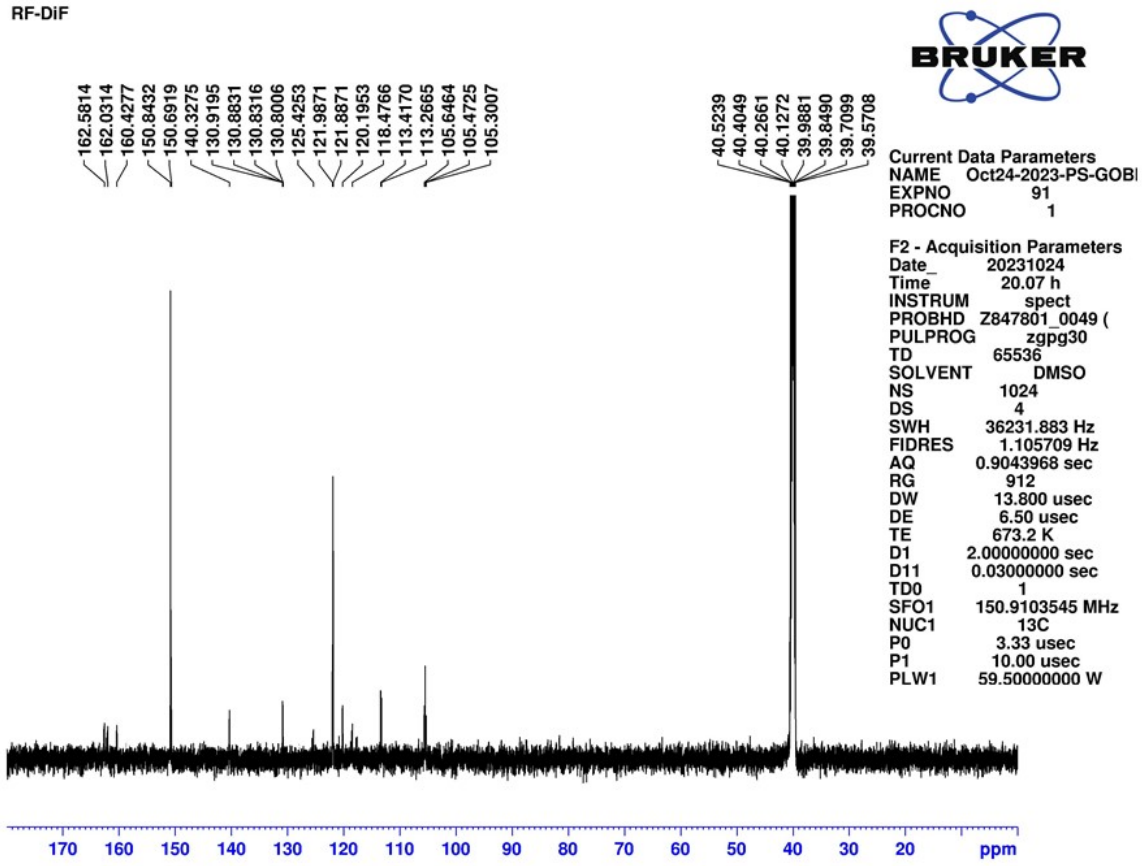


Figure S94. ^{13}C-NMR of compound **9m**.

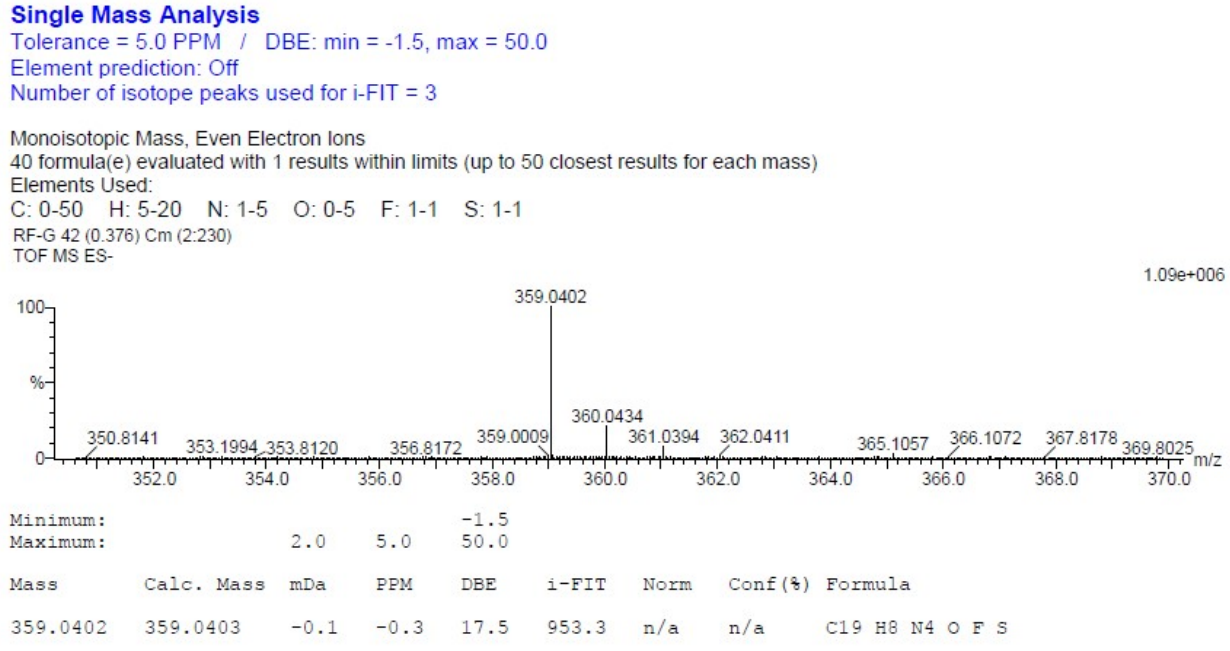


Figure S95. HRMS of compound **9m**.

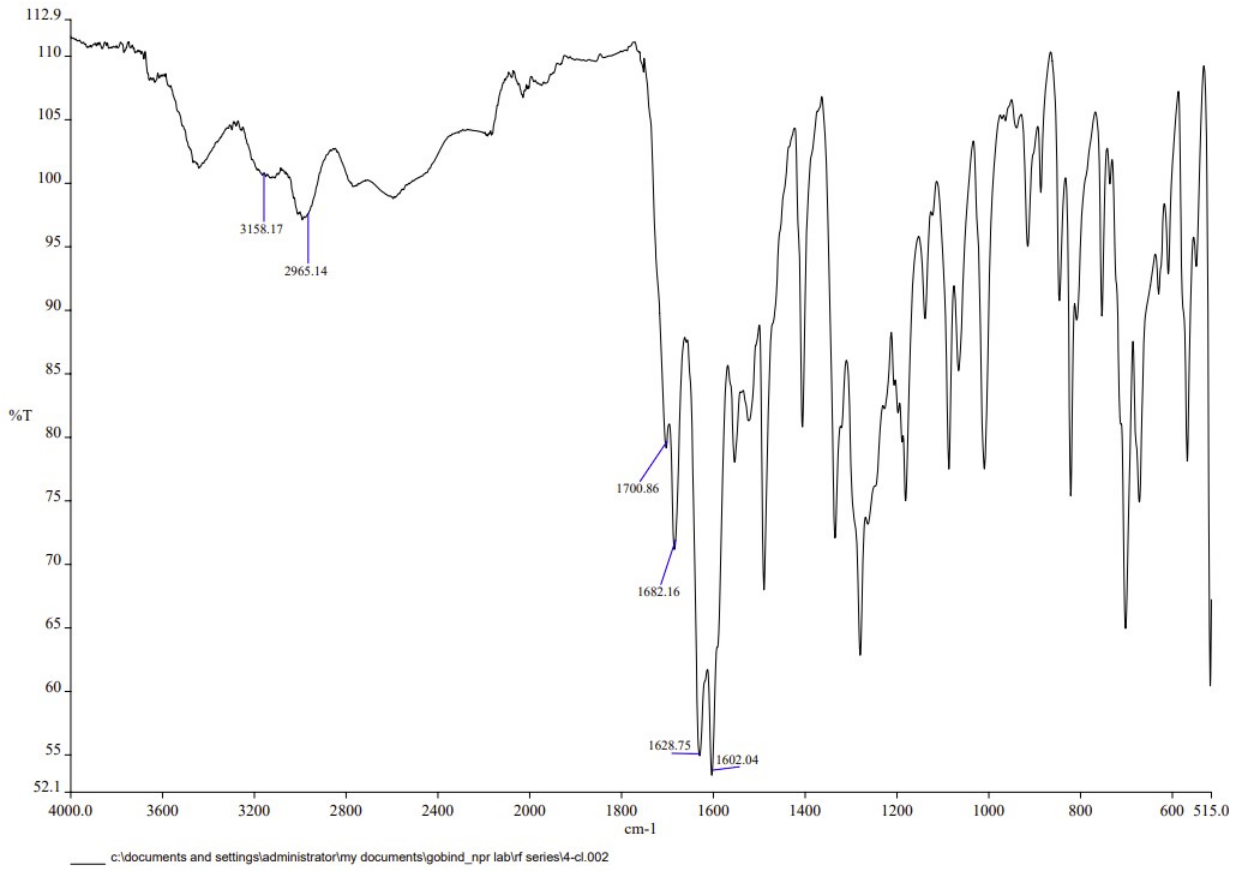


Figure S96. IR spectra of compound **9n**.

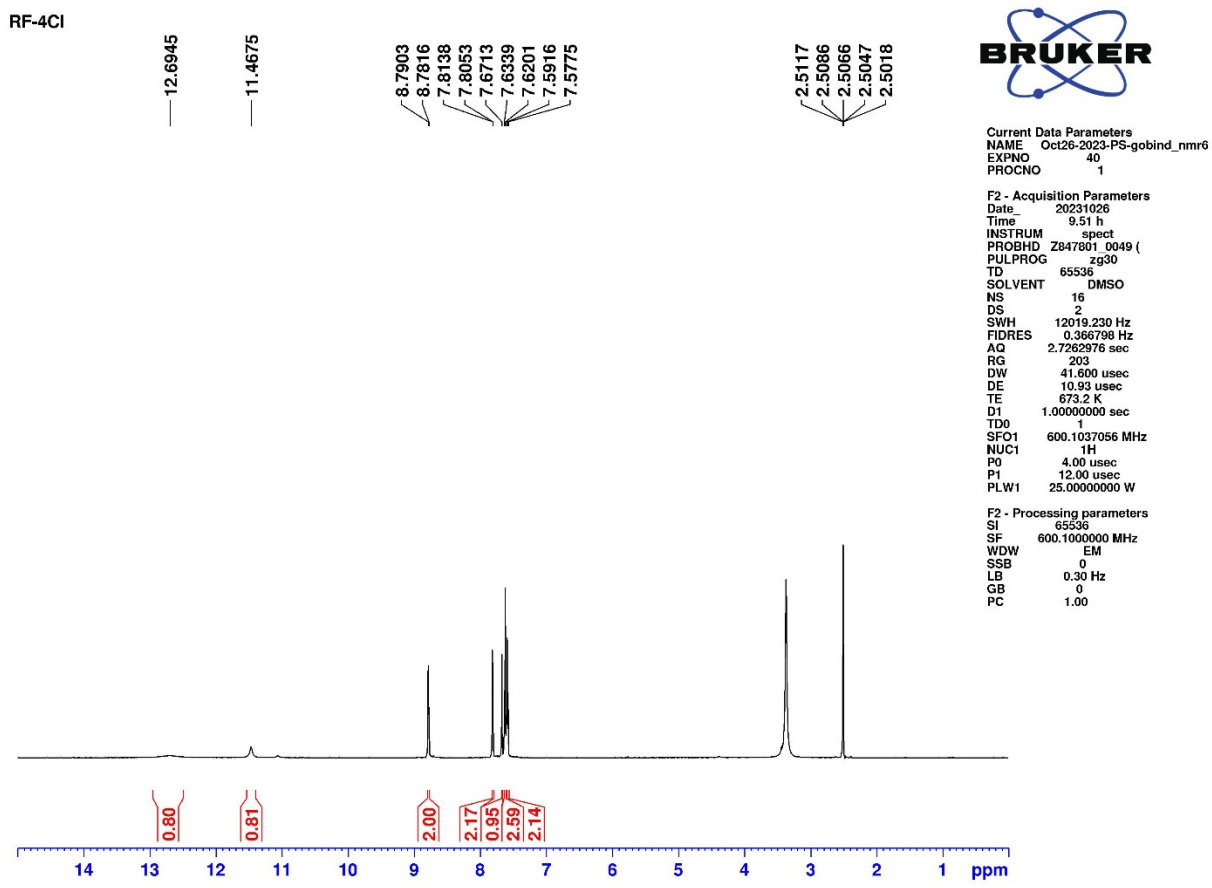


Figure S97. ^{1}H-NMR of compound **9n**.

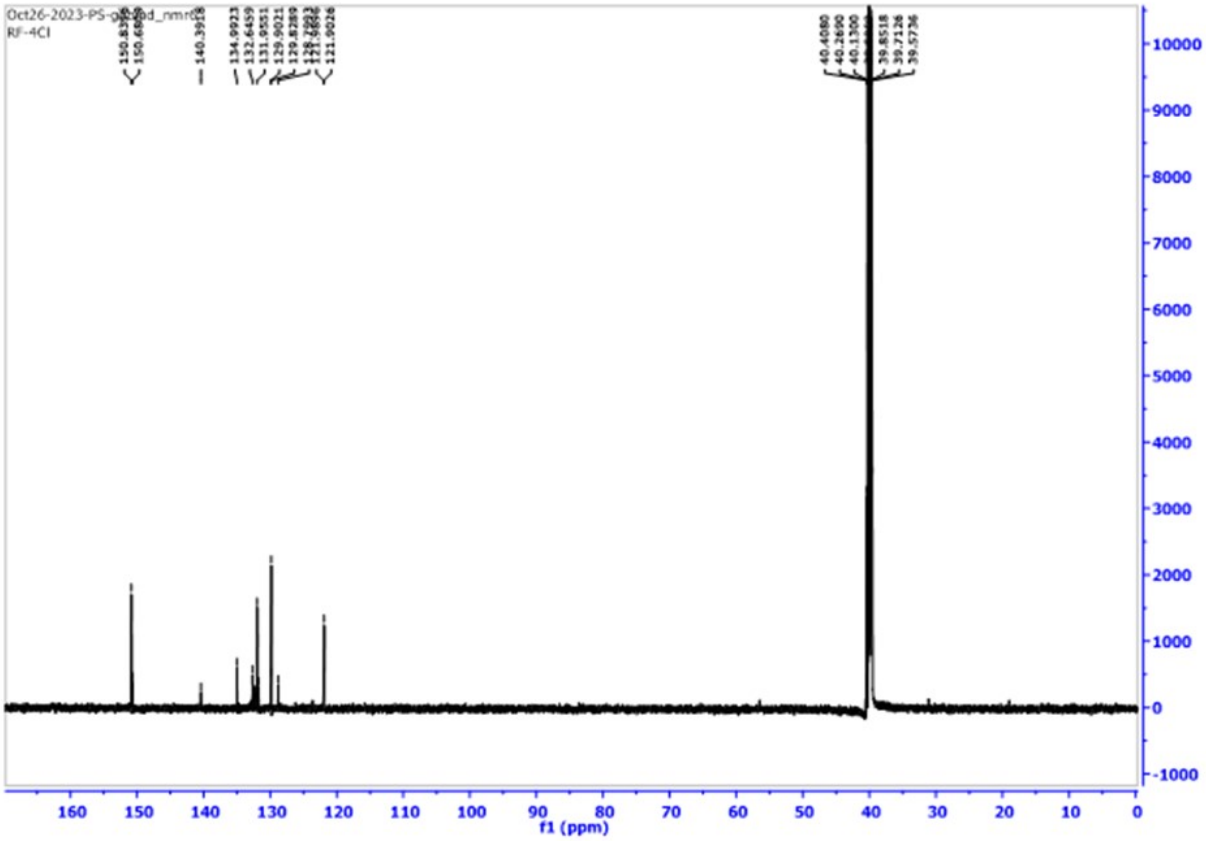


Figure S98. ^{13}C-NMR of compound **9n**.

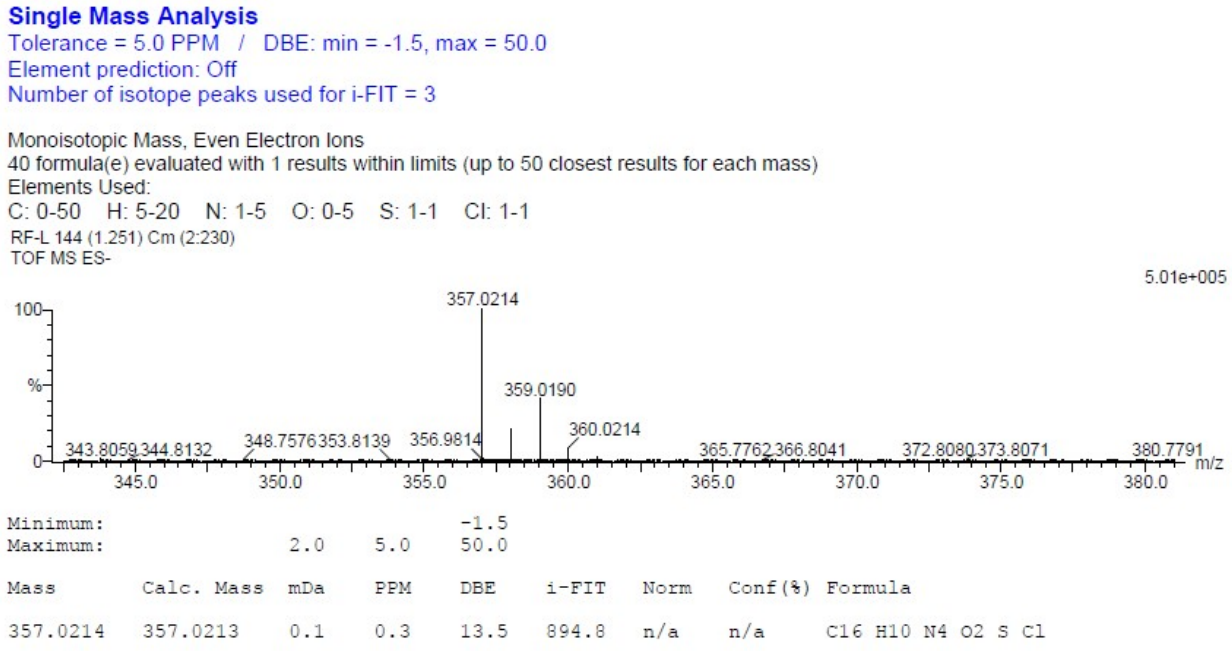


Figure S99. HRMS of compound **9n**.

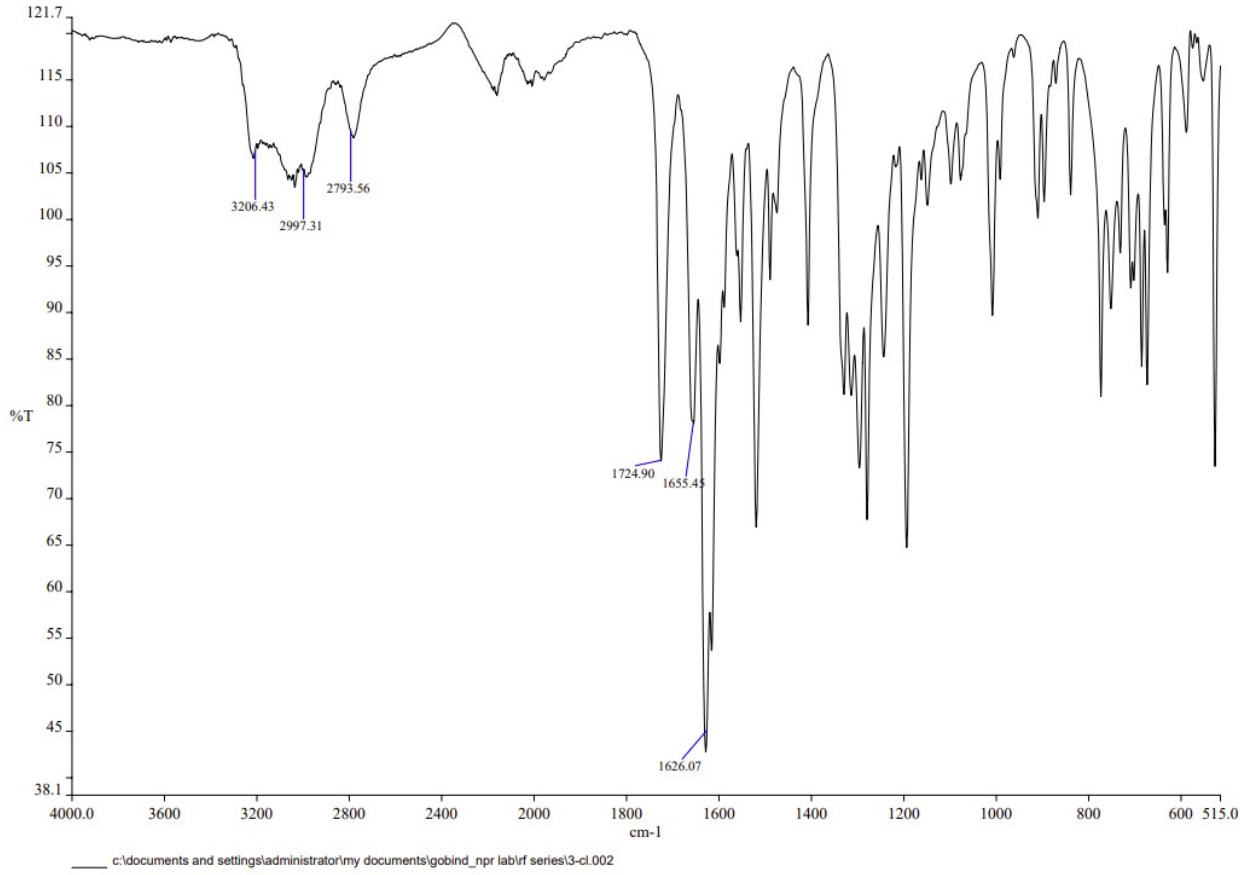


Figure S100. IR spectra of compound **9o**.

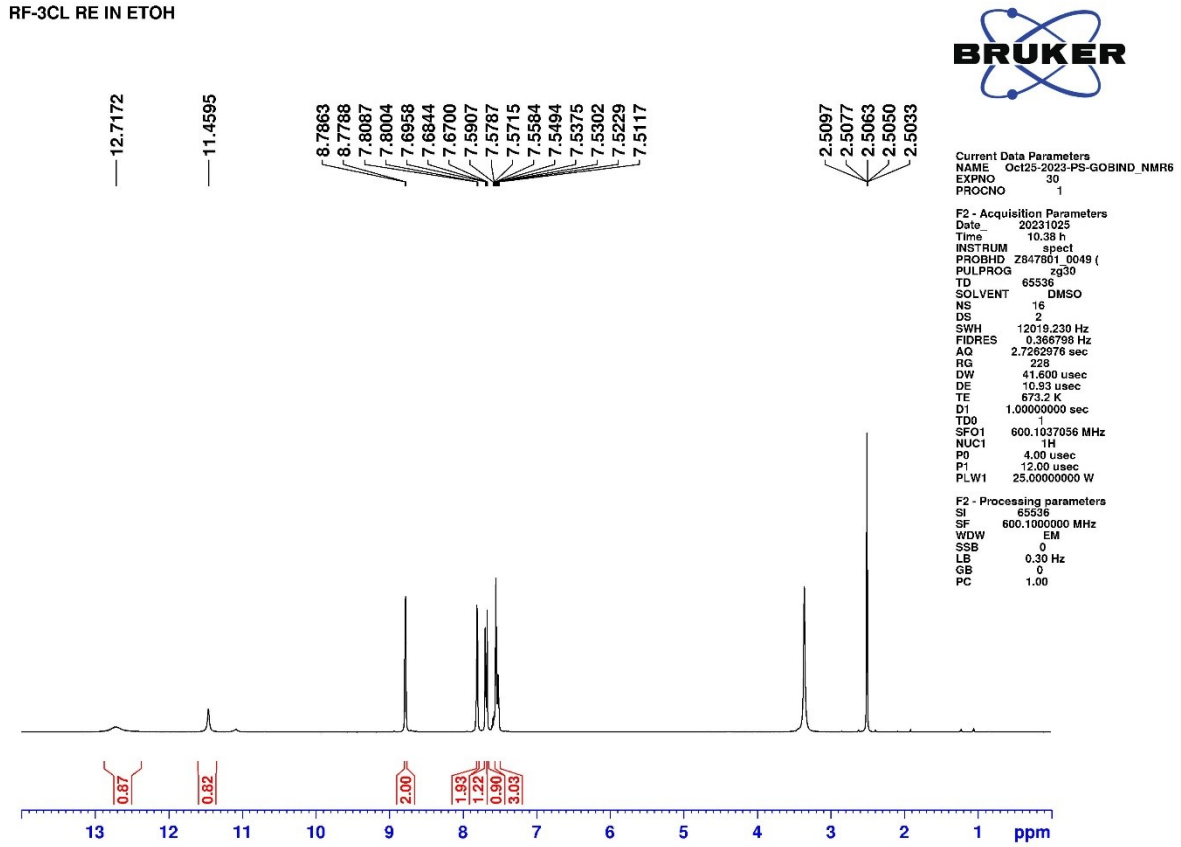


Figure S101. ^{1}H-NMR of compound **9o**.

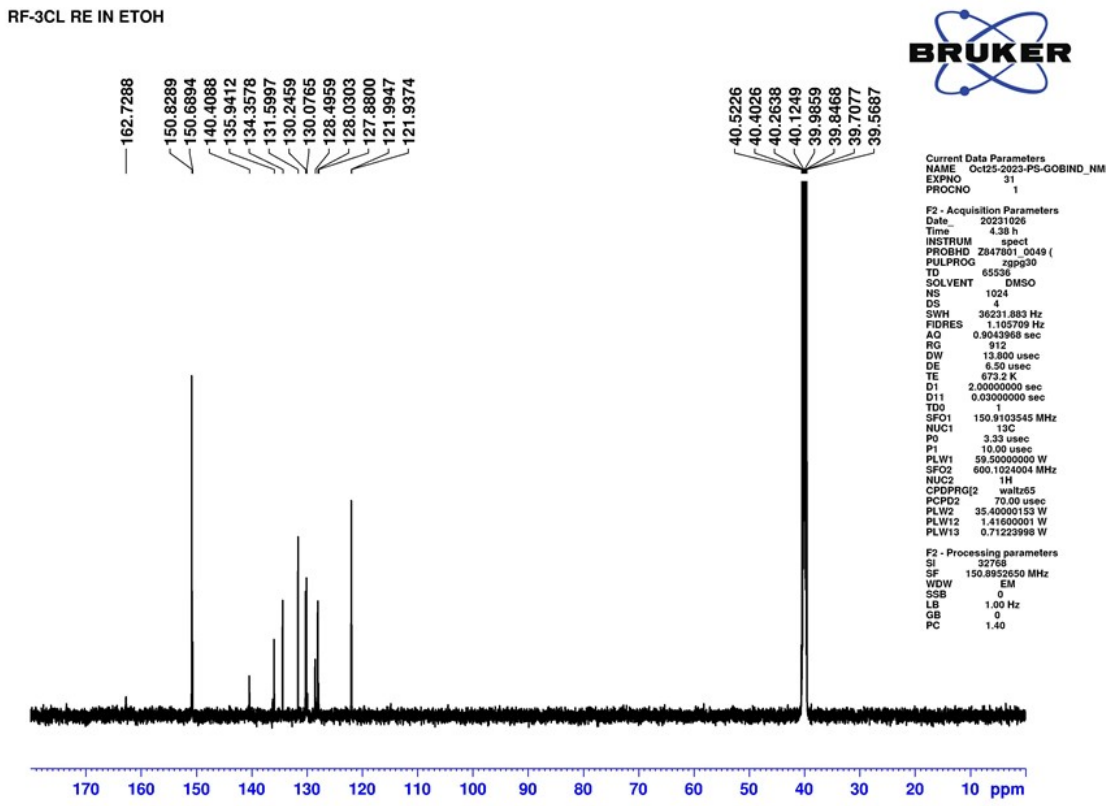
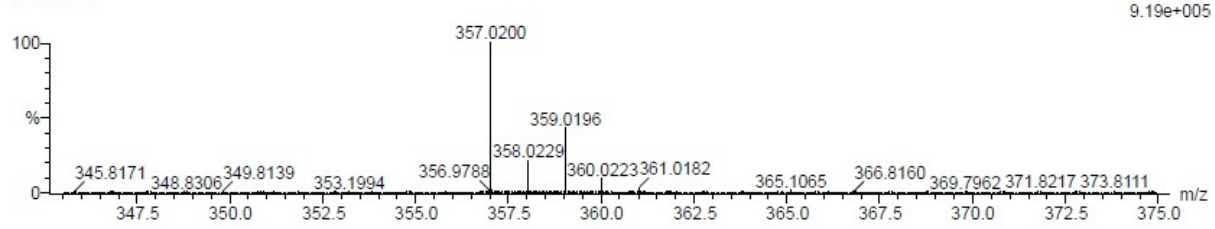


Figure S102. ^{13}C-NMR of compound **9o**.

Single Mass Analysis
Tolerance = 5.0 PPM / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
40 formula(e) evaluated with 1 results within limits (up to 50 closest results for each mass)
Elements Used:
C: 0-50 H: 5-20 N: 1-5 O: 0-5 S: 1-1 Cl: 1-1
RF-H 123 (1.070) Cm (2:230)
TOF MS ES-



Minimum:				-1.5				
Maximum:		2.0	5.0	50.0				
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Norm	Conf(%)	Formula
357.0200	357.0213	-1.3	-3.6	13.5	1000.7	n/a	n/a	C16 H10 N4 O2 S Cl

Figure S103. HRMS of compound **9o**.

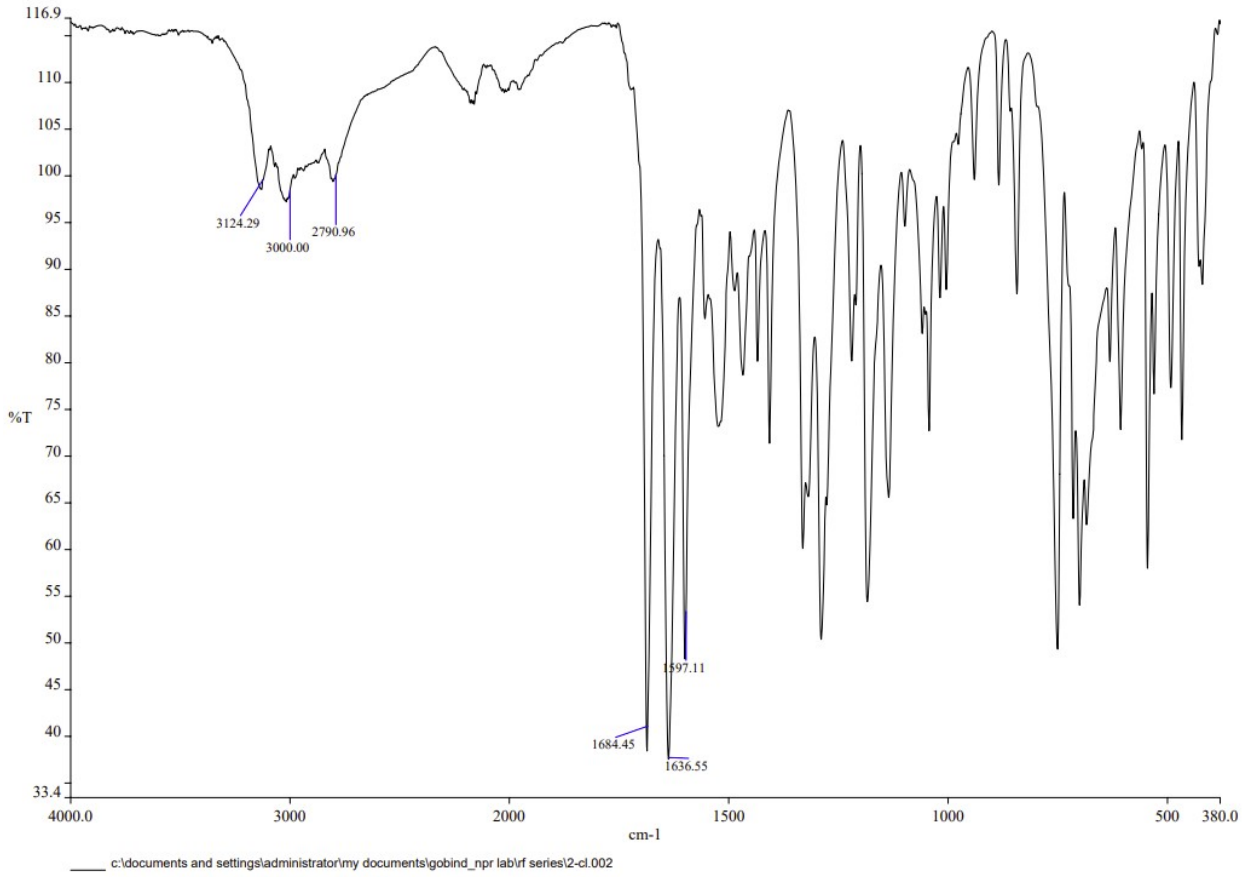


Figure S104. IR spectra of compound **9p**.

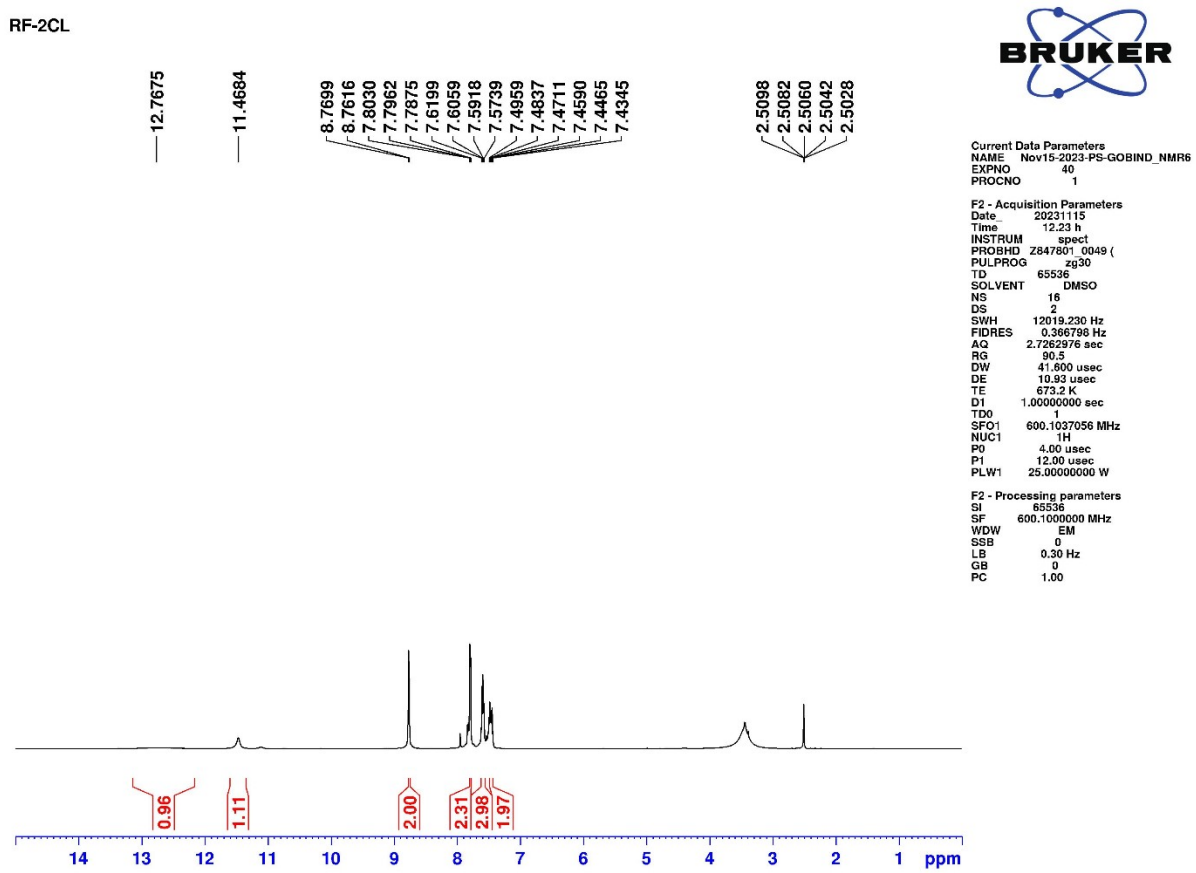


Figure S105. ^{1}H-NMR of compound **9p**.

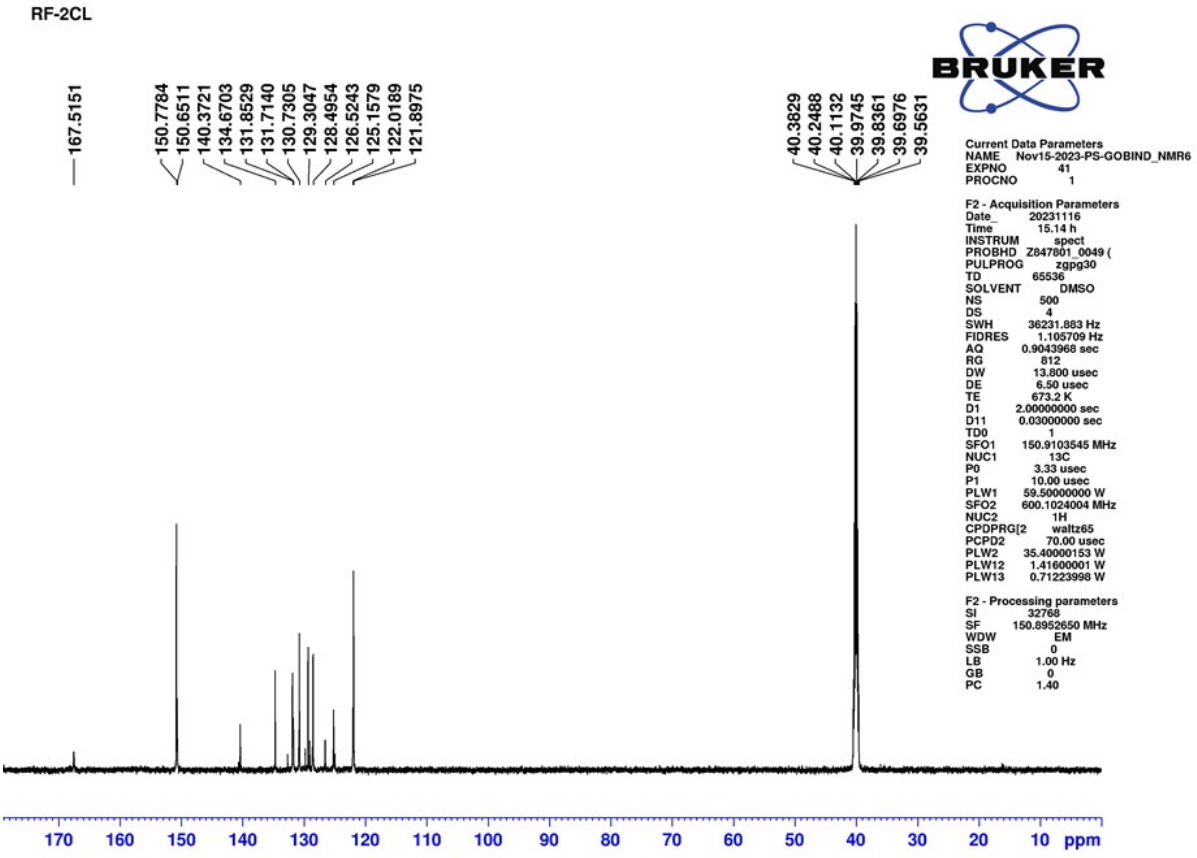


Figure S106. ^{13}C-NMR of compound **9p**.

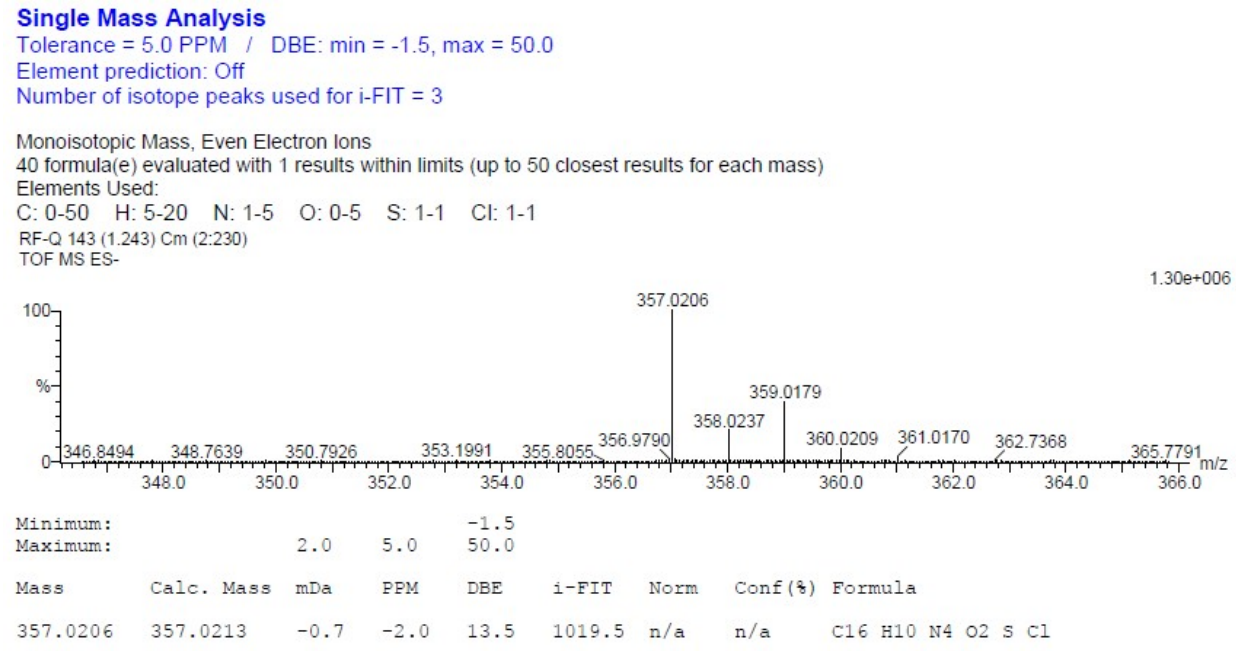


Figure S107. HRMS of compound **9p**.

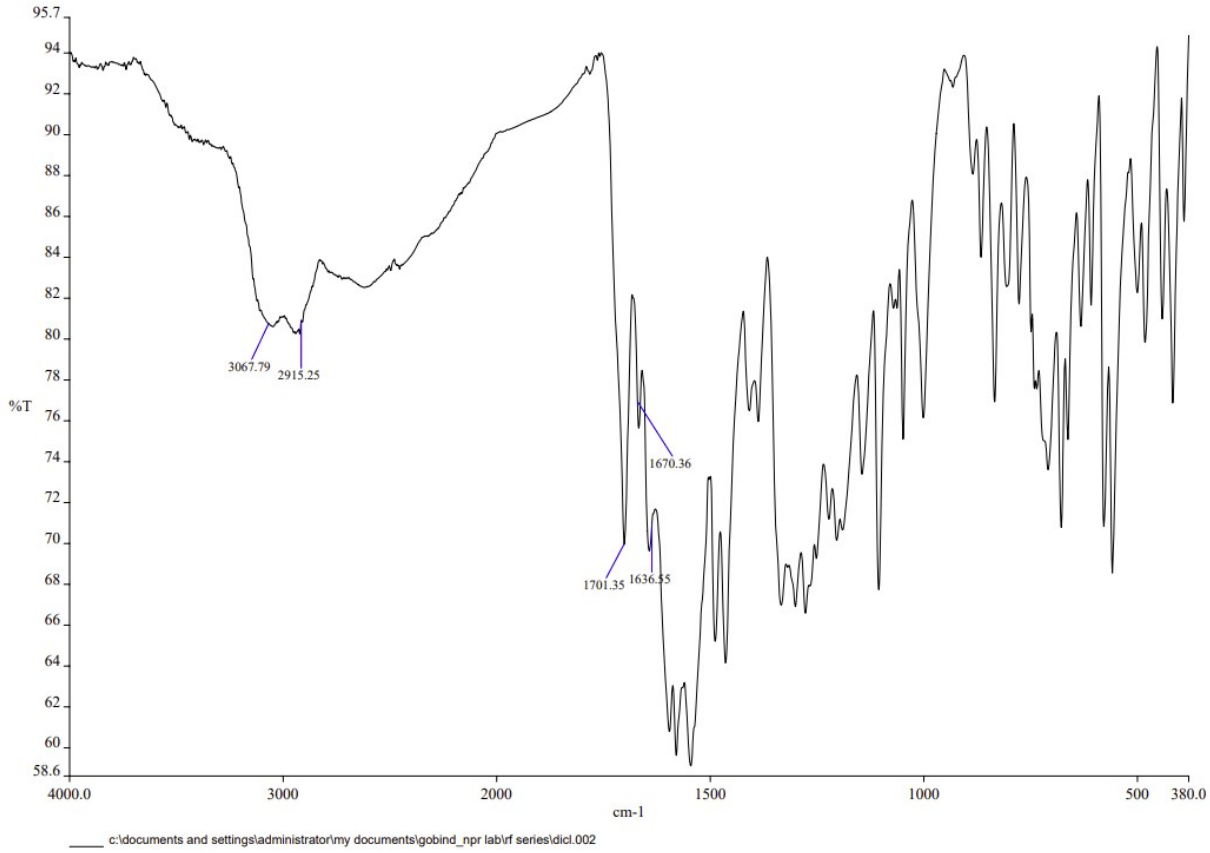


Figure S108. IR spectra of compound **9q**.

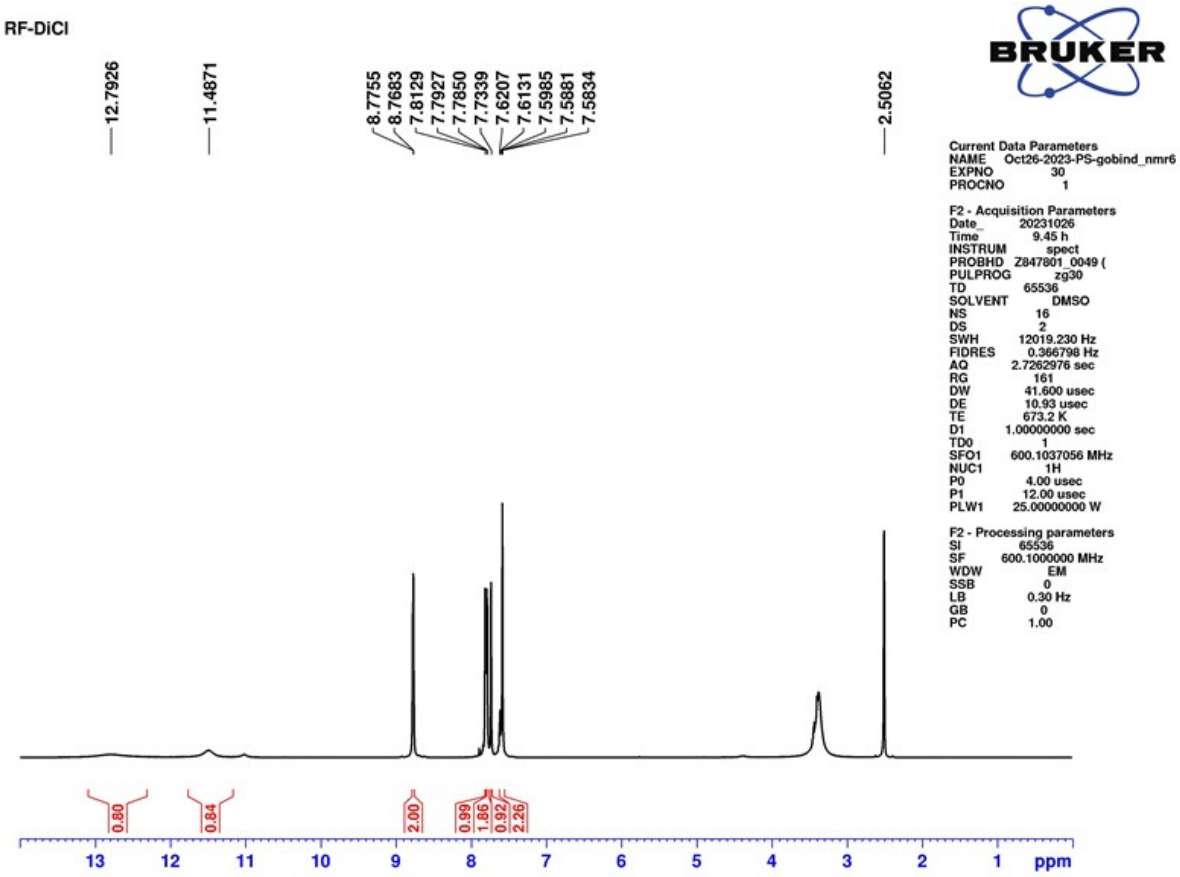


Figure S109. ^{1}H-NMR of compound **9q**.

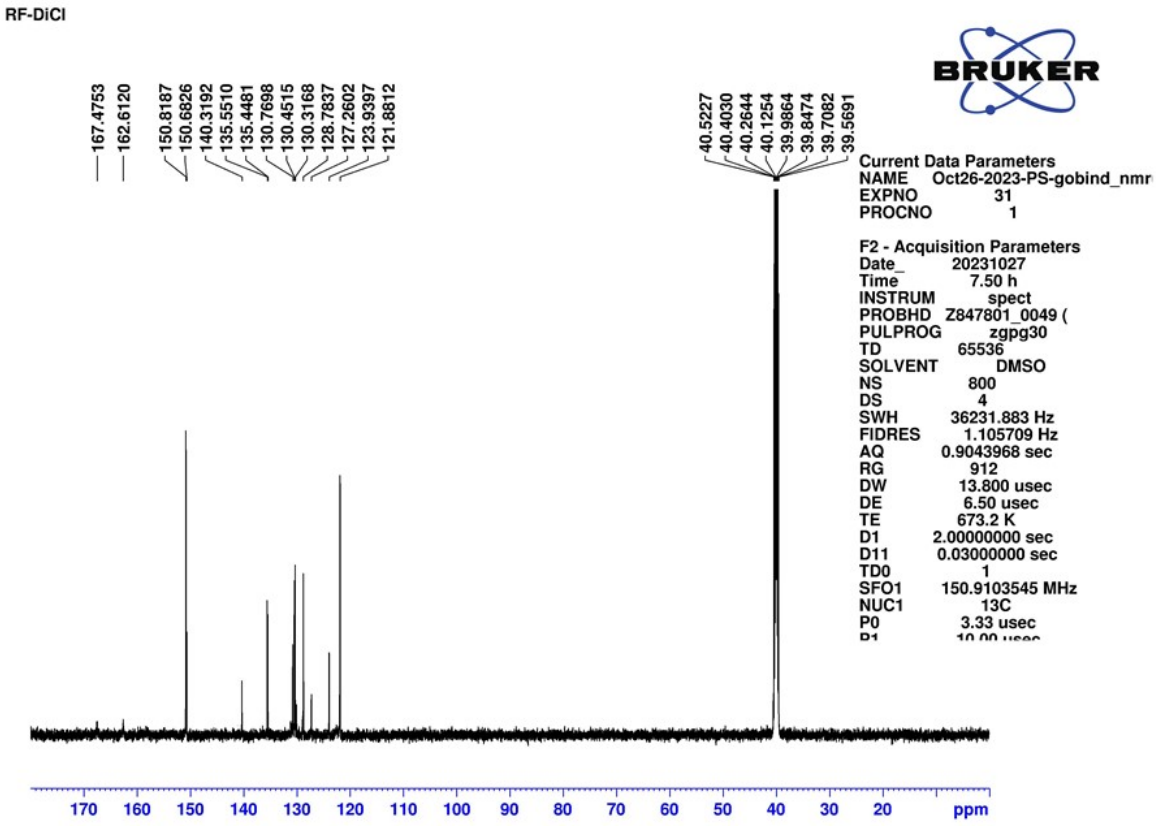


Figure S110. ^{13}C-NMR of compound **9q**.

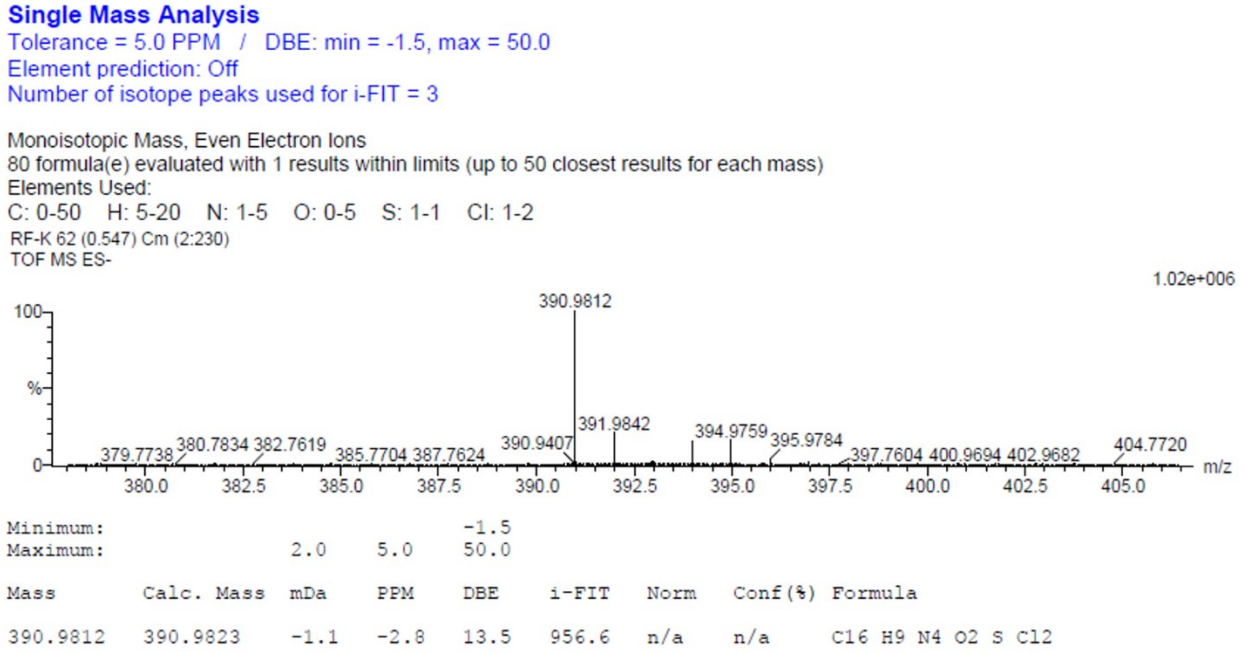


Figure S111. HRMS of compound **9q**.

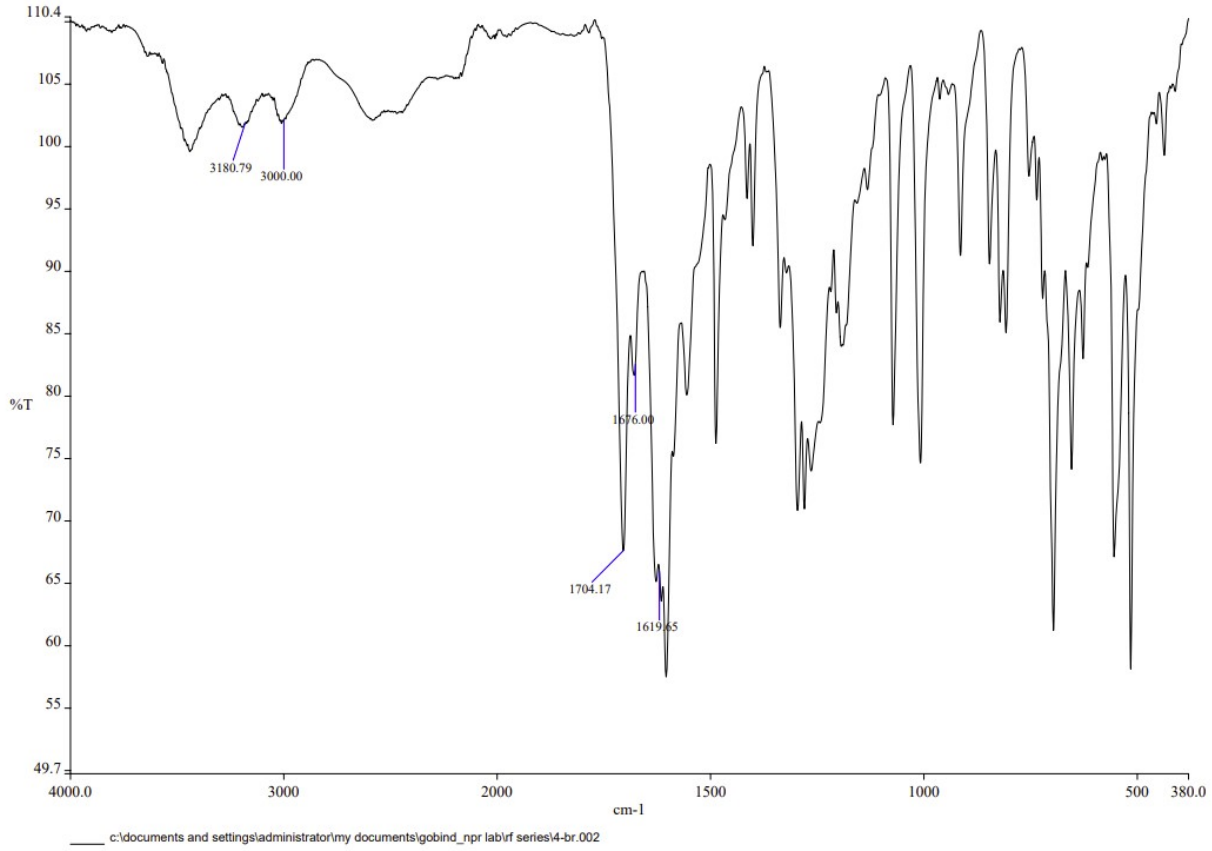


Figure S112. IR spectra of compound **9r**.

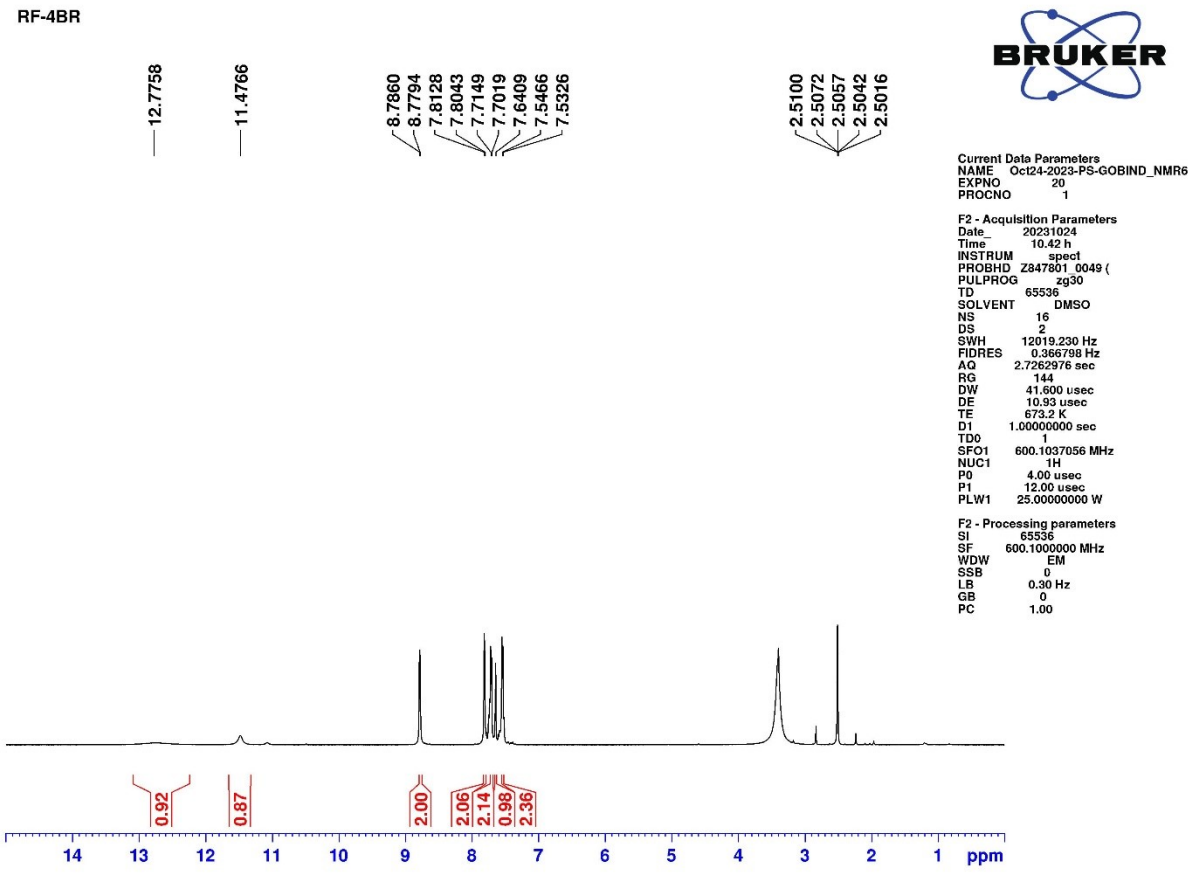


Figure S113. ^{1}H-NMR of compound **9r**.

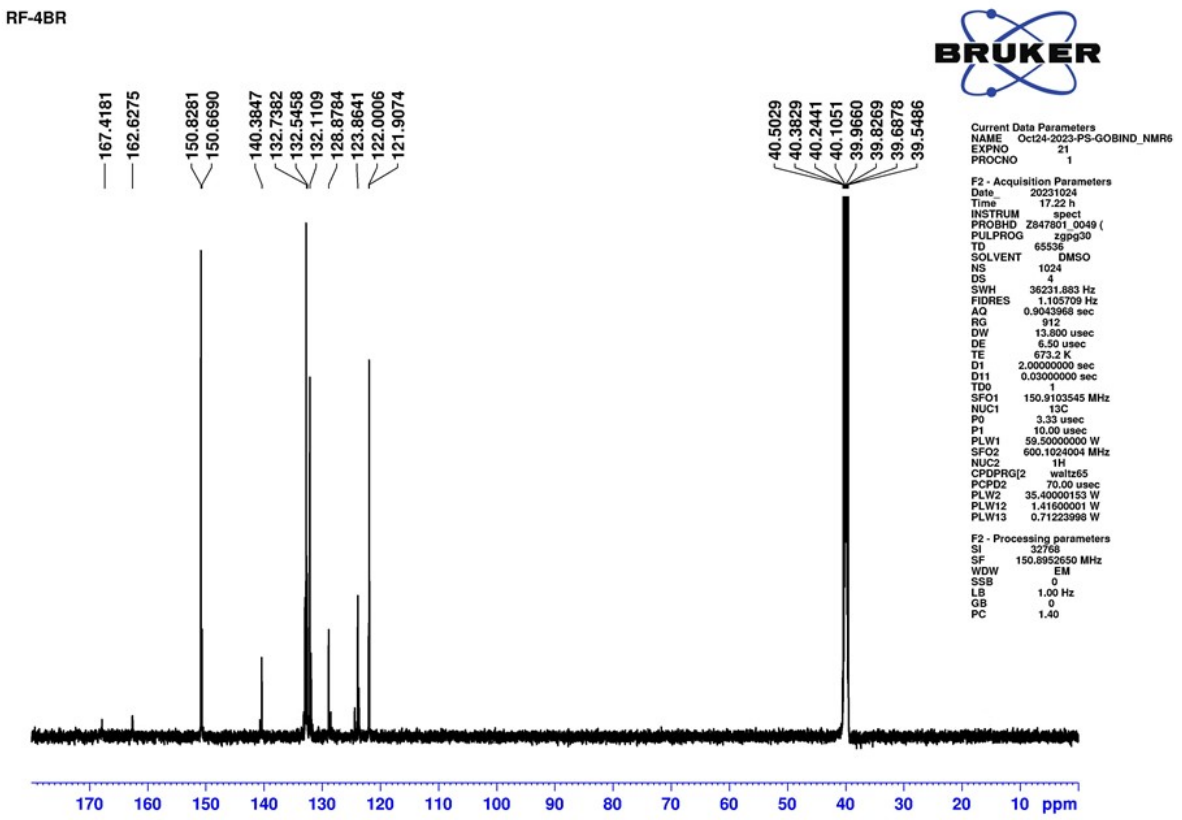


Figure S114. ^{13}C-NMR of compound **9r**.

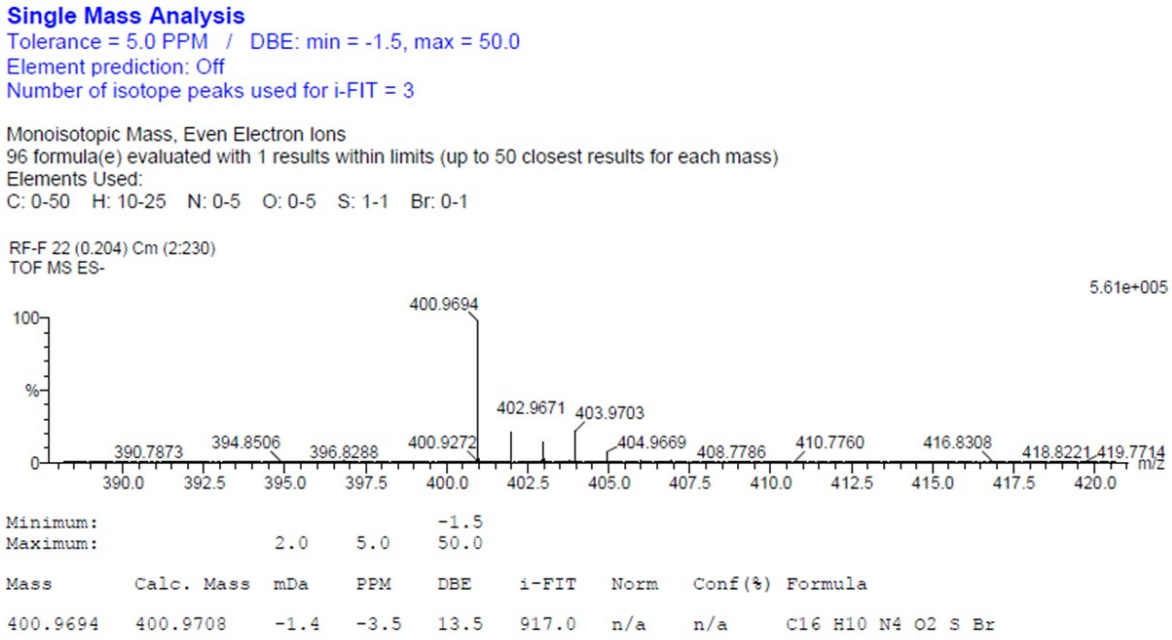


Figure S115. HRMS of compound **9r**.

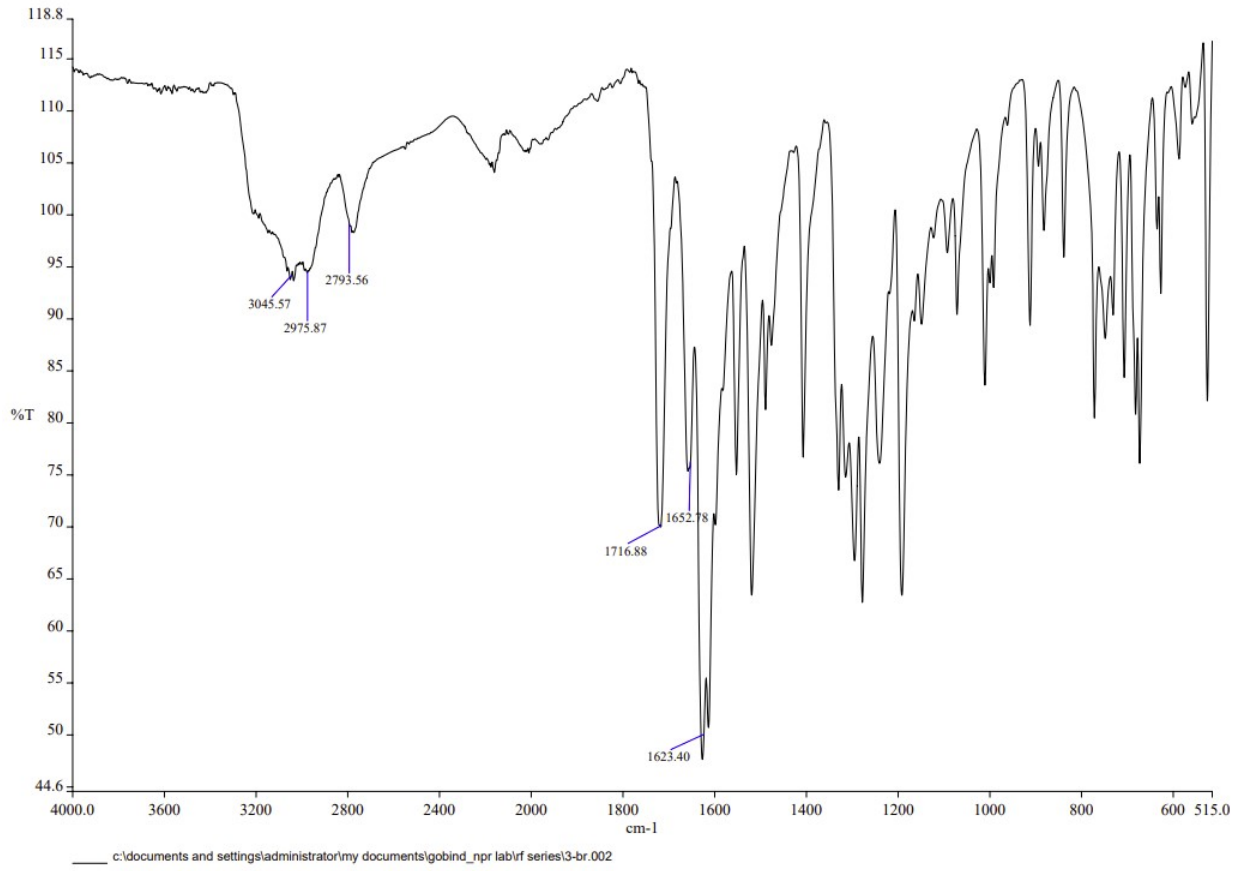


Figure S116. IR spectra of compound **9s**.

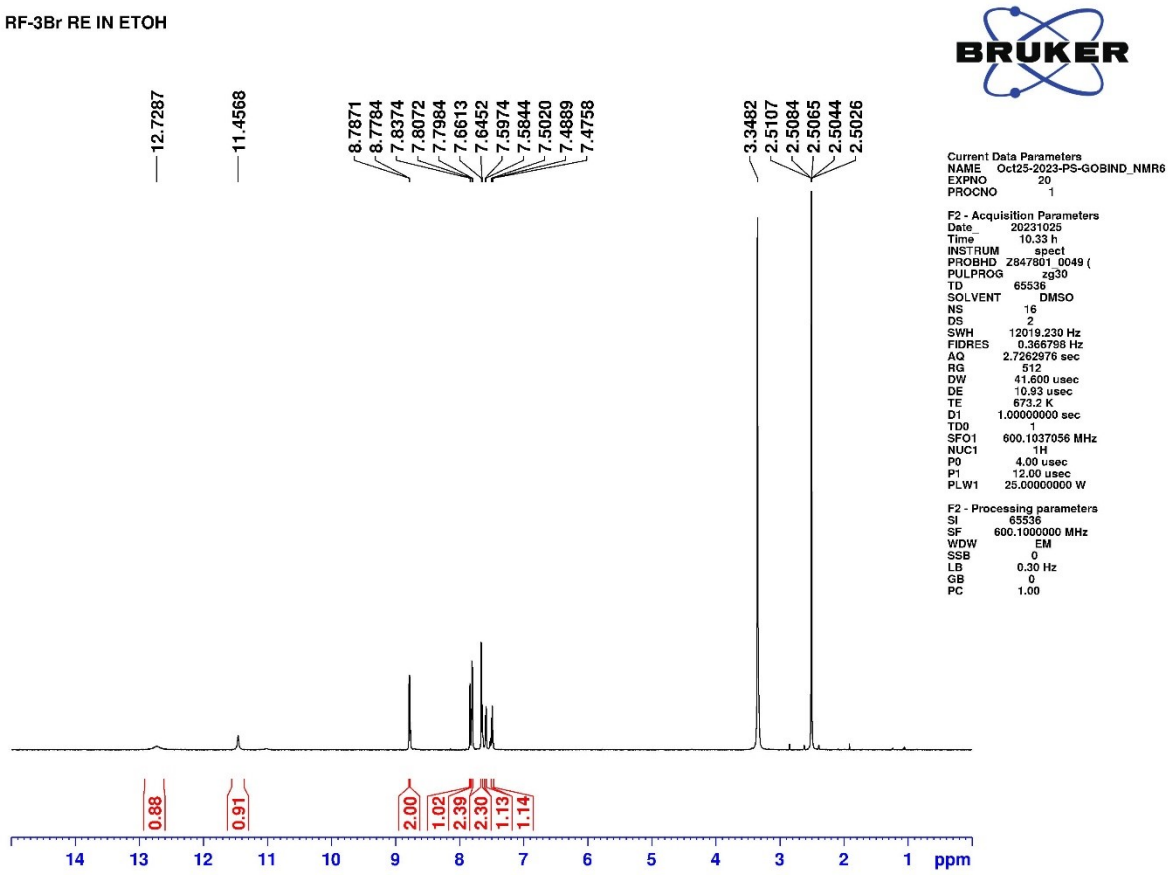


Figure S117. ^{1}H-NMR of compound **9s**.

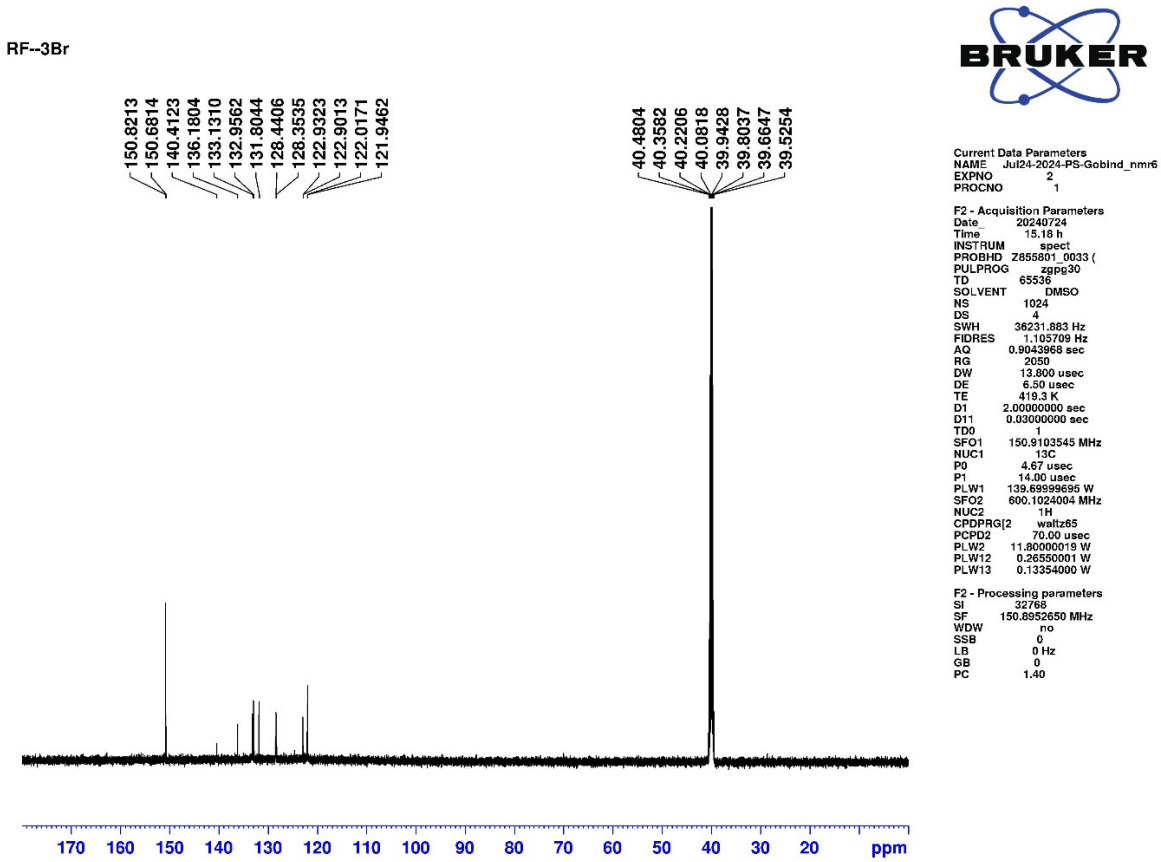


Figure S118. ^{13}C-NMR of compound **9s**.

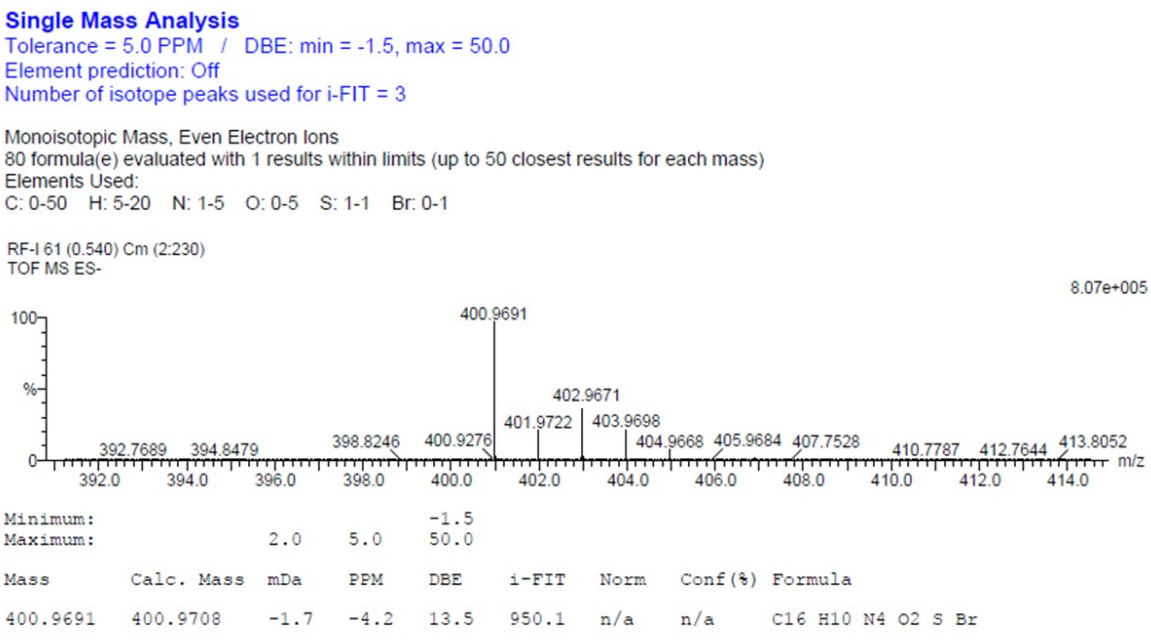


Figure S119. HRMS of compound **9s**.

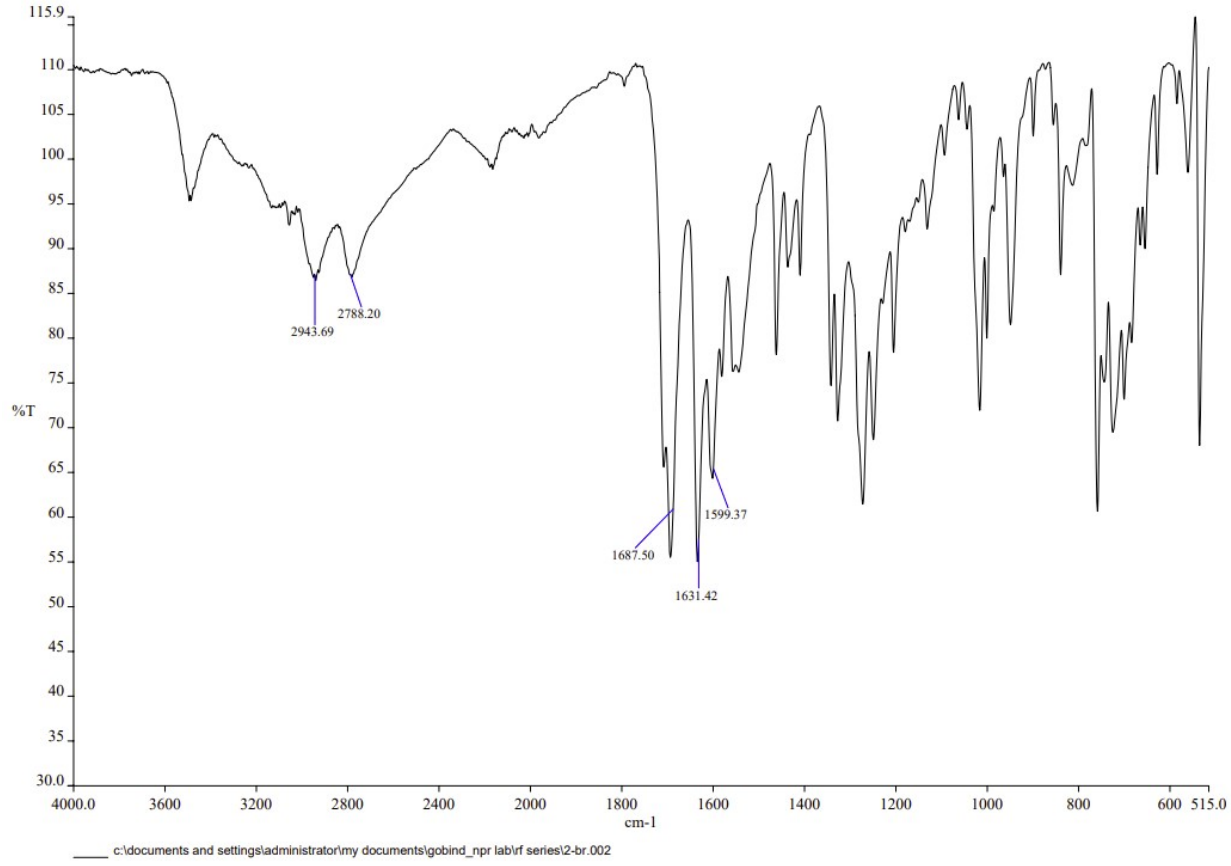


Figure S120. IR spectra of compound **9t**.

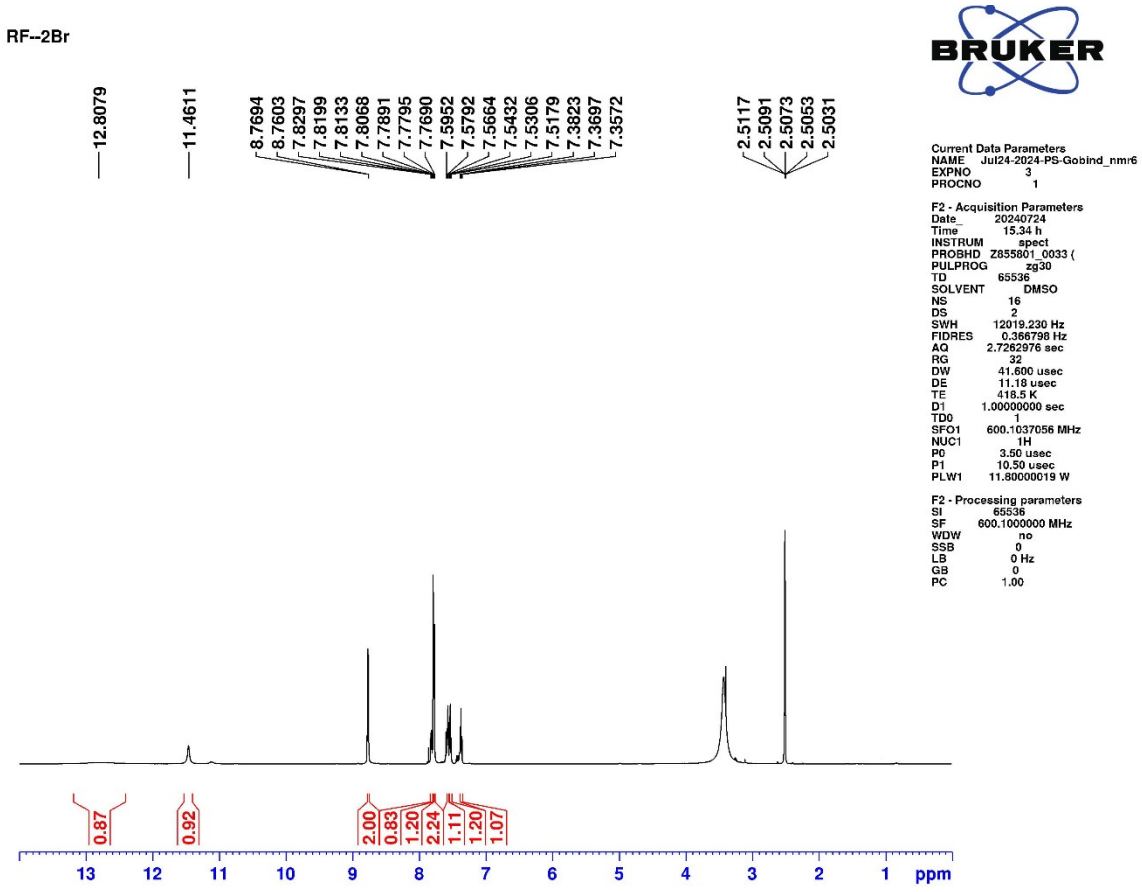


Figure S121. ^{1}H-NMR of compound **9t**.

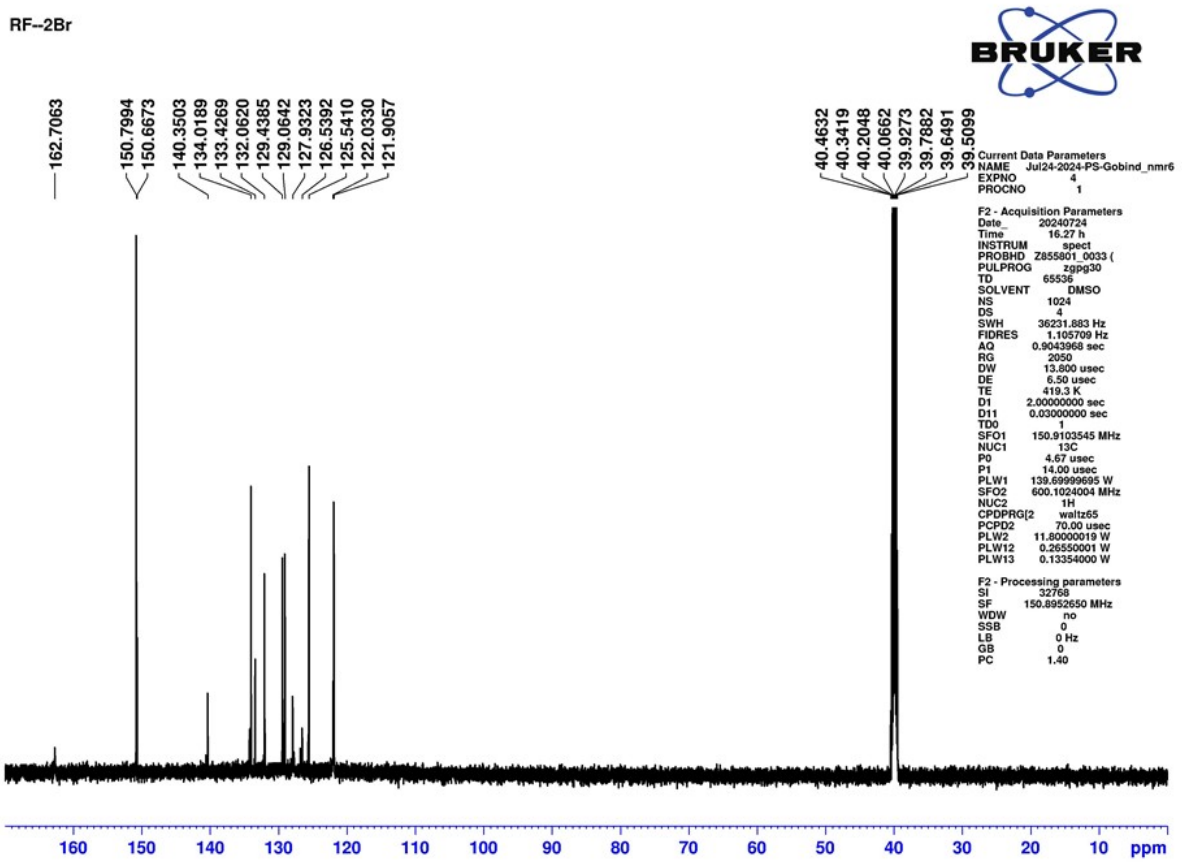
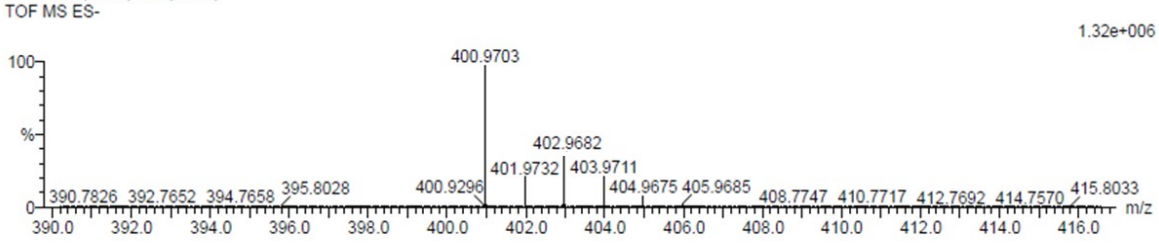


Figure S122. ^{13}C-NMR of compound **9t**.

Single Mass Analysis
Tolerance = 5.0 PPM / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
80 formula(e) evaluated with 1 results within limits (up to 50 closest results for each mass)
Elements Used:
C: 0-50 H: 5-20 N: 1-5 O: 0-5 S: 1-1 Br: 0-1

RF-R 221 (1.911) Cm (2:230)
TOF MS ES-



Minimum:				-1.5				
Maximum:		2.0	5.0	50.0				
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Norm	Conf(%)	Formula
400.9703	400.9708	-0.5	-1.2	13.5	1018.6	n/a	n/a	C16 H10 N4 O2 S Br

Figure S123. HRMS of compound **9t**.

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