Exploration of Novel Triazolo-thiadiazine Hybrids of Deferasirox as Multi-Target Directed Anti-Neuroinflammatory Agents with Structure-Activity Relationship (SAR): A New Treatment Opportunity for Alzheimer's Disease

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Table S1. Physical characteristics of compounds (**10-13**)

Compounds	**M.P (◦C)**	**Color**	**Yield**	**R_f value *n*-hexane:ethylacetate**
10	oil	Dark yellow	65	0.3
11	167-168	White	86	0.5
12	199-201	Light brown	78	0.4
13	245-256	Off-white	88	0.5

Table S2. Physical characteristics of compounds

Compounds	M.P (°C)
14a	Obs.: 91-93, Lit.:93-95
14b	Obs.: 92-94, Lit.: 94-96
14c	Obs.: 90-92, Lit.: 92-94
14d	Obs.: 51-52, Lit.:51-52
14e	Obs.: 67-69, Lit.:70-71
14f	Obs.: 40-42, Lit.: 44-46
14g	Obs.: 50-52, Lit.:50-52
14h	Obs.: 172-174
14i	Obs.: 123-125
14j	Obs.: 127-128, Lit.:123-126
14k	Obs.: 22-24, Lit.:24

Table S3. Physical characteristics of compounds (15-25)

Compounds	**M.P. (◦C)**	**Yield**	**R_f values***
15	141-143	81	0.5[a]
16	166-167	85	0.4[b]
17	177-176	68	0.5[b]

18	171-172	73	0.6[b]
19	182-184	67	0.5[c]
20	178-179	63	0.5[a]
21	171-172	77	0.5[a]
22	177-179	88	0.4[a]
23	199-201	65	0.4[a]
24	156-158	88	0.5[a]
25	199-202	78	0.5[a]

[*]*n*-hexane:Ethylacetate, a: 2:, b: 3:2, c: 4:1

Table S4: Data of ligand interaction with different targeted enzymes AChE and BChE

Sr #	Binding energy kJ/mol	Hydrogen bond interactions	Hydrophobic interactions	Binding energy kJ/mol	Hydrogen bond interactions	Hydrophobic interactions
	AChE			**BChE**		
09	-7.1015	Gly118, Gly119, Phe331 (Conventional hydrogen bond)	Tyr334, Phe330, Trp279 (pi-pi)	-7.8481	His438, Gly117, Gly115, Tyr128 (Conventional hydrogen bond)	Trp231, Phe329, Gly116, Trp82 (pi-pi)
10	-7.1871	Tyr121, Asp72, (Conventional hydrogen bond)	Tyr70, Phe330 (pi-pi)	-7.9663	Glu197, Gly117 (Conventional hydrogen bond)	Gly116, Trp231, Phe329, Trp82, Gly115(pi-pi)
11	-7.7815	Glu199, Phe331 (Conventional hydrogen bond), Trp84 (pi-sulfur)	Tyr334, Phe330, His440 (pi-pi)	-7.2876	Trp82, Glu197, Gly117, Gly116,(Conventional hydrogen bond), Trp430, Tyr332 (pi-sulfur)	Phe329, His438, Gly115(pi-pi) Trp231,(pi-lone pair)
13	-7.5908	Glu199, Tyr130, Ser81 (Conventional hydrogen bond),	Trp84, Tyr121, Phe330 (pi-pi)	-7.2007	Trp82,Trp430,Gly117,Ser287 (Conventional hydrogen bond), Trp440 (pi-sulfur)	Gly115, Tyr332, Trp231, (pi-pi)
15				-8.7031	Gln119, Gly117, Pro285 (Conventional hydrogen bond) Trp82 (pi-sulfur)	Trp430, Gly116 (pi-pi)
16					Thr284, Gly116, Gly117, Glu197(Conventional	Tyr332 (pi-pi)

				-8.4920	hydrogen bond), Trp85 (pi-sulfur)	
17				-7.6317	Lle69, Asn83, Gly115,Tyr128, Trp82, Trp430(Conventional hydrogen bond), Tyr440 (pi-sulfur)	Asp70, (pi-anion) Tyr332(pi-pi)
18				-8.8203	Gly116, Gly117,Glu197 (Conventional hydrogen bond), Trp82 (pi-sulfur)	Tyr332,Trp430(pi-pi)
19				-8.7788	Leu286, Asp70,Asn83 (Conventional hydrogen bond)	Phe329, Trp231, Trp82 (pi-pi)
20				-8.8328	Glu197,Gly117,Gly116 (Conventional hydrogen bond), Trp82, His438 (pi-sulfur)	Tyr332, (pi-pi) Ala328 (pi-sigma)
21				-8.8256	Leu286, Asp70, Asn83 (Conventional hydrogen bond), Phe398 (pi-sulfur)	----
22				-9.1950	Asn83, Gly116,Gly117 (Conventional hydrogen bond), Tyr82 (pi-sulfur)	Lle69, Tyr332, (pi-pi)
23				-9.6624	Gly117, Ser79(Conventional hydrogen bond), Trp430 (pi-sulfur)	Phe329, (pi-pi)
24				-8.2383	Thr120,Tyr332,Trp82,Gly78 (Conventional hydrogen bond), Tyr440 (pi-sulfur)	His438 (pi-pi)
25				-8.9153		Asp70 (pi-anion)

Table S5: Data of ligand interaction with different targeted enzymes MAO-A and MAO-B

Codes	Binding energy kJ/mol	Hydrogen bond interactions	Hydrophobic interactions	Binding energy Kj/mol	Hydrogen bond interactions	Hydrophobic interactions
	MAO-A			**MAO-B**		
09	-8.7685	Tyr69,Met45 (Conventional hydrogen bond)	Tyr407,Tyr444, Gly66,Trp397, (pi-pi)	-7.9061	Tyr60, Trp388, (Conventional hydrogen bond),Met438, Cys397 (pi-sulfur)	Tyr435, Gly57, Tyr398 (pi-pi)
10	-9.2840	Ala68,Tyr444, Ala68(Conventional hydrogen bond), Cys406(pi-sulfur)	Tyr407 (pi-pi)	-8.2758	Tyr60,(Conventional hydrogen bond), Cys172 (pi-sulfur)	Tyr398, Tyr435 (pi-pi)

12	-9.4415	Arg51,Thr435, (Conventional hydrogen bond), Met445(pi-sulfur)	Gly66,Trp397, Tyr407,Tyr444 (pi-pi)	-8.6640	Ser59, (Conventional hydrogen bond),Cys172, Phe168,(pi-sulfur)	Tyr435, Tyr60, Gly57, Trp388, Trp398, Tyr326 (pi-pi)
13	-10.3061	Gly49,Thr52,Tyr69, Met445 (Conventional hydrogen bond)	Tyr444,Gly66, Trp397,Tyr407 (pi-pi)	-8.6638	Ser59,Leu171, (Conventional hydrogen bond),Phe168,Cys178, (pi-sulfur)	Tyr60, Tyr435, Trp388, Tyr398, Phe343, Tyr326 (pi-pi)
15	-10.9165	Thr435,LLe23, Ser24,Ars51, Cys406(Conventional hydrogen bond), Glu43 (halogen-interaction)	Gly66,Tyr444, Tyr407 (pi-pi)	-2.0772	Thr201, Tyr435, (Conventional hydrogen bond), Cys172, Tyr188, (pi-sulfur)	Tyr398, Phe343, Tyr326, Phe168 (pi-pi)
16	-6.8256	Ars45,Ars51, Ser24(Conventional hydrogen bond), Cys406,Met445 (pi-sulfur)	Tyr407, Tyr444, Trp397 (pi-pi)	-4.7753	Ile199, Met436, Gln65, Ser59 (Conventional hydrogen bond), Cys172 (pi-sulfur)	Phe343, Tyr398 (pi-pi)
17	-0.1233	Thr435 (Conventional hydrogen bond)	Tyr444 (pi-pi), Gly22 (pi-sigma)	1.1810	Gly434, Phe168 (Conventional hydrogen bond), Met436, Cys172 (pi-sulfur)	Phe343, Tyr398 (pi-pi)
18	-9.6374	Lle207,Tyr69, Asn181,(Conventional hydrogen bond) Cys406,Trp397 (pi-sulfur)	Tyr40, Rhe352, (pi-pi), Gln215, (pi-lone pair)	-4.0571	Lys296 (Conventional hydrogen bond), Cys172, Tyr398 (pi-sulfur)	Tyr435, Tyr326, Phe343 (pi-pi)
19	-3.8283	Gly443,Lle207, Asn181(Conventional hydrogen bond), Cys406, Trp397(pi-sulfur)	Tyr444, Tyr407, Phe352 (pi-pi)	2.1811	Cys172, Gln65, Tyr60, Ser59 (Conventional hydrogen bond)	Tyr398, Tyr435 (pi-pi)
20	-6.5063	Ala68,Tyr69, Ala272,Lle23, Ser24,Ars51 (Conventional hydrogen bond), Cys406,Met445 (pi-sulfur)	Tyr407, Gly66 (pi-pi)	-6.2628	Tyr326, Ile199, Tyr188 (Conventional hydrogen bond), Cys172 (pi-sulfur)	Phe343, Tyr398 (pi-pi)
21	-3.7661	Lle207,Asn181, Tyr69,(Conventional hydrogen bond), Cys406,Trp397,(pi-sulfur)	Phe352, Tyr407, Tyr444, (pi-pi)	-0.5073	Gln206, Thr201, Tyr188, Cys172, (Conventional hydrogen bond), Tyr60, Lys296, Phe343 (pi-sulfur)	Tyr398 (pi-pi)
22	-47365	Ars45,Ser403, Lle23,Thr52, (Conventional hydrogen bond), Thr435,(pi-sulfur)	Gln43, (pi-lone pair)	1.1065	Pro102, Phe168, (Conventional hydrogen bond), Cys172, Phe343, Tyr60 (pi-sulfur)	----
23	-11.0394	Cys406,Tyr69, Gly67,Ars51, Ser403,Ars45 (Conventional	Tyr407, Gln66, Trp397, Tyr444,		Tyr60, Cys296, Gly205, Gln206 (Conventional hydrogen bond), Cys397 (pi-sulfir)	Gly57, Tyr398, Tyr435, Phe343 (pi-pi)

		hydrogen bond)	Tyr402, (pi-pi)	-3.7149		
24	-4.5861	Ars45,Ser403, Ars51,Gly49, (Conventional hydrogen bond), Tyr407(pi-sulfur)	Trp397, Gly66, (pi-pi)	-4.8501	Cys397, Tyr398, Cys172 (Conventional hydrogen bond)	Trp388 (pi-pi)
25	-10.3947	Tyr69, Ars51, Thr52, Gly49, Ser24(Conventional hydrogen bond), Cys407,Met445, Lle23(pi-sulfur)	Tyr444, Tyr407, Trp397 (pi-pi)	-3.2324	Tyr60, Ser59 (Conventional hydrogen bond), Cys172 (pi-sulfur)	Tyr398, Tyr326 (pi-pi)

Table S6 ~~7~~: Data of ligand interaction with different targeted enzymes LOX-5 and COX-2

Codes	Binding energy kJ/mol	Hydrogen bond interactions	Hydrophilic interactions	Binding energy Kj/mol	Hydrogen bond interactions	Hydrophilic interactions
	COX-2			LOX-5		
09	-7.6938	Ile517, Ser353, His90, Tyr355 (Conventional hydrogen bond)	Gly526, Phe518 (pi-pi)	-5.8788	Arg596, is600,Lys296, Gln303 (Conventional hydrogen bond)	His432, Trp599, (pi-pi)
10	-7.6582	Arg120, Ser530, Tyr355, (Conventional hydrogen bond), Met522, (pi-sulfur)	Trp387, Gly526, (pi-pi), Ser353 (pi-sigma)	-6.2530	Pro569, Arg596, (Conventional hydrogen bond)	Trp599, His435 (pi-pi)
12	-6.0783	Val523, Gln192, Tyr355, (Conventional hydrogen bond)	Gly526 (pi-pi), Leu531 (pi-sigma)	-7.1918	Thr364, Asn407 (Conventional hydrogen bond)	His432, Trp599, Phe359, His372 (pi-pi),
13	-4.6521	Gln192, Leu352, Arg513, Tyr355 (Conventional hydrogen bond), His90 (pi-sulfur)	Glu526, Phe518, (pi-pi), Ser303 (pi-sigma)	-6.6865	Ile673, Asn407, Arg596 (Conventional hydrogen bond), Phe359, His600, Trp599 (pi-sulfur)	Ala410 (pi-pi)
15	-23.2472	Gln192, Tyr355 (Conventional hydrogen bond)	Asp515, Gly526 (pi-pi)	-7.7092	Arg596, Lys296, (Conventional hydrogen bond), His432 (pi-sulfur)	Ala410, Phe359, Trpo599 (pi-pi)

16	13.4101	Tyr385, Thr94, Gly354, Tyr355, Arg120 (Conventional hydrogen bond), His90, Phe381, Ser530 (pi-sulfur)	------	-8.3160	Arg596, Gln303, His360 (Conventional hydrogen bond), Phe359 (pi-sulfur)	Ala410, Leu414 (pi-sigma)

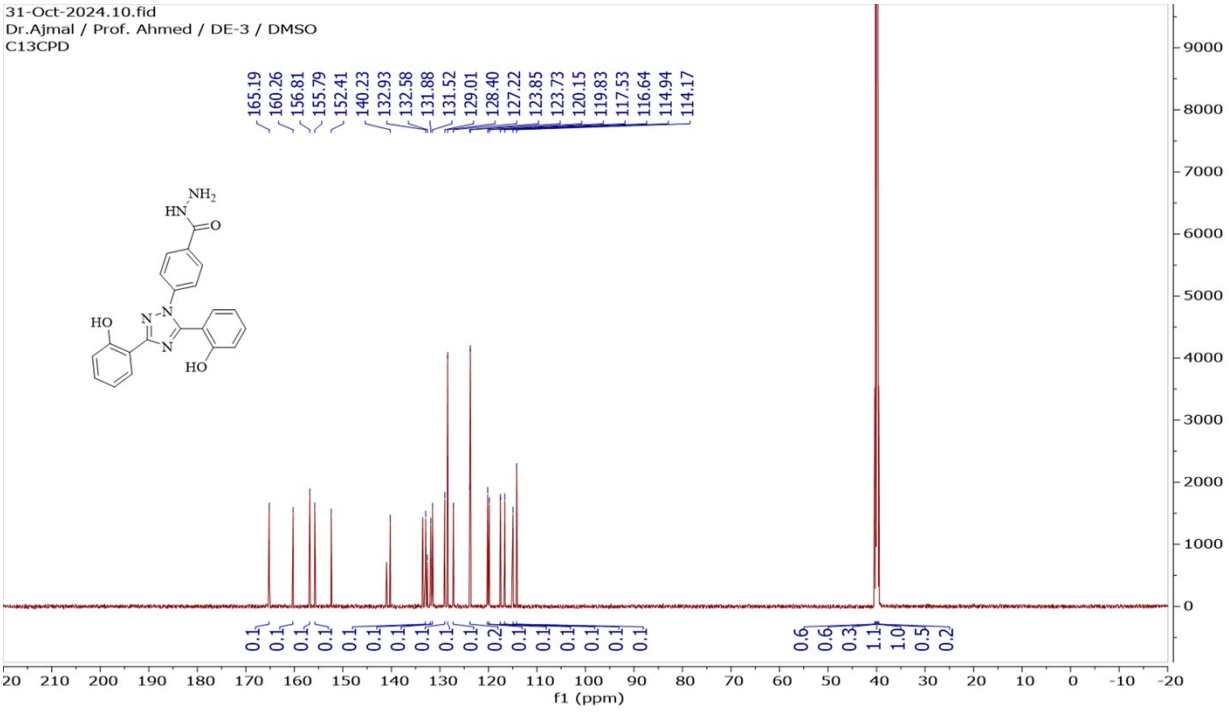

Figure S1. C^{13} NMR of compound **11**

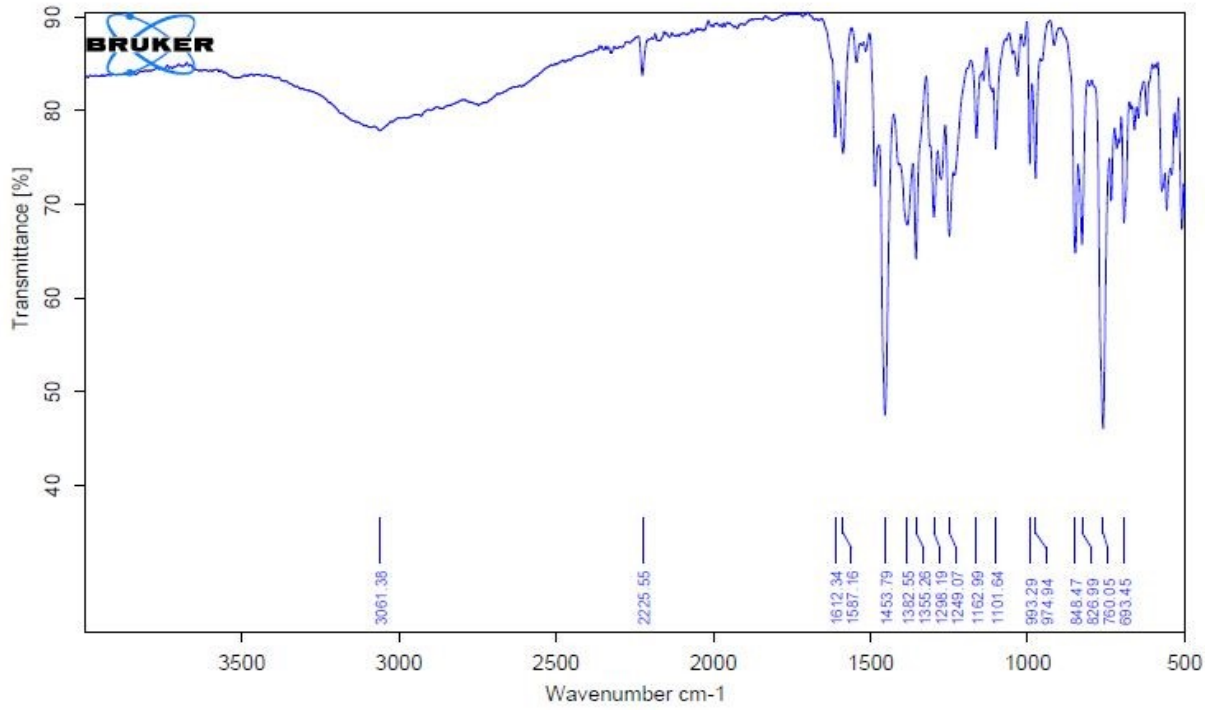

Figure S2: FTIR of compound 15

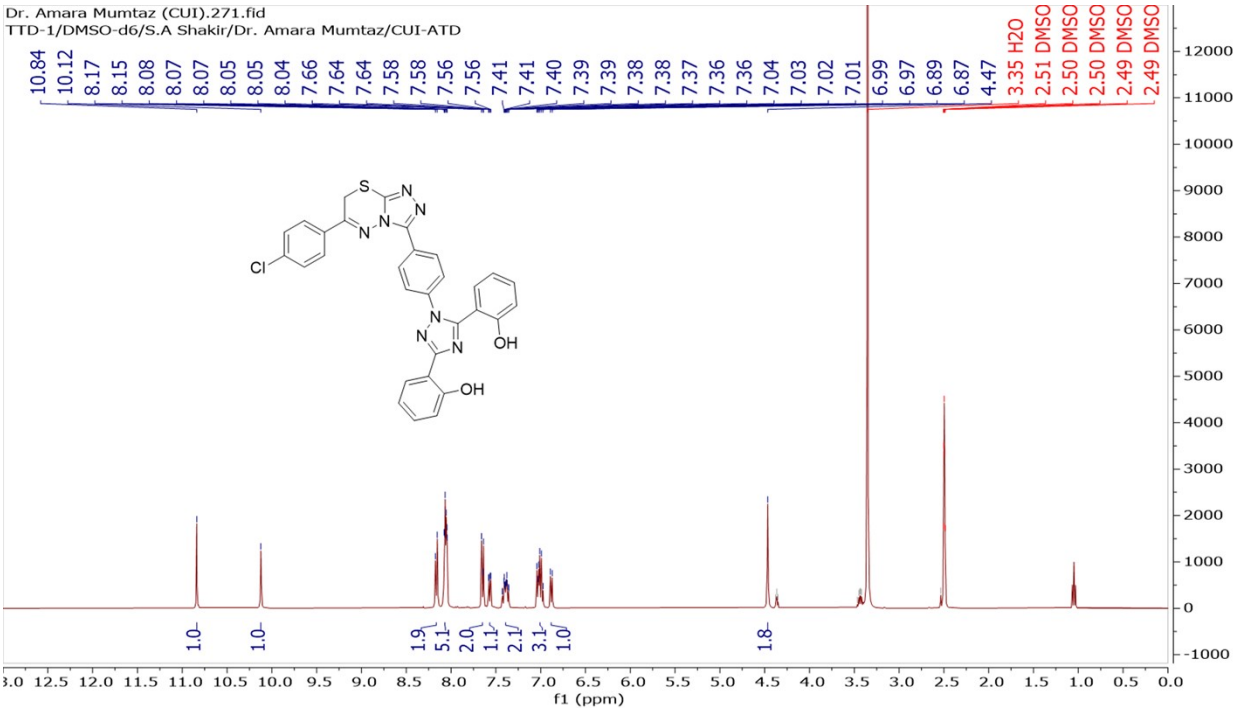

Figure S3: ^{1}H NMR of compound 15

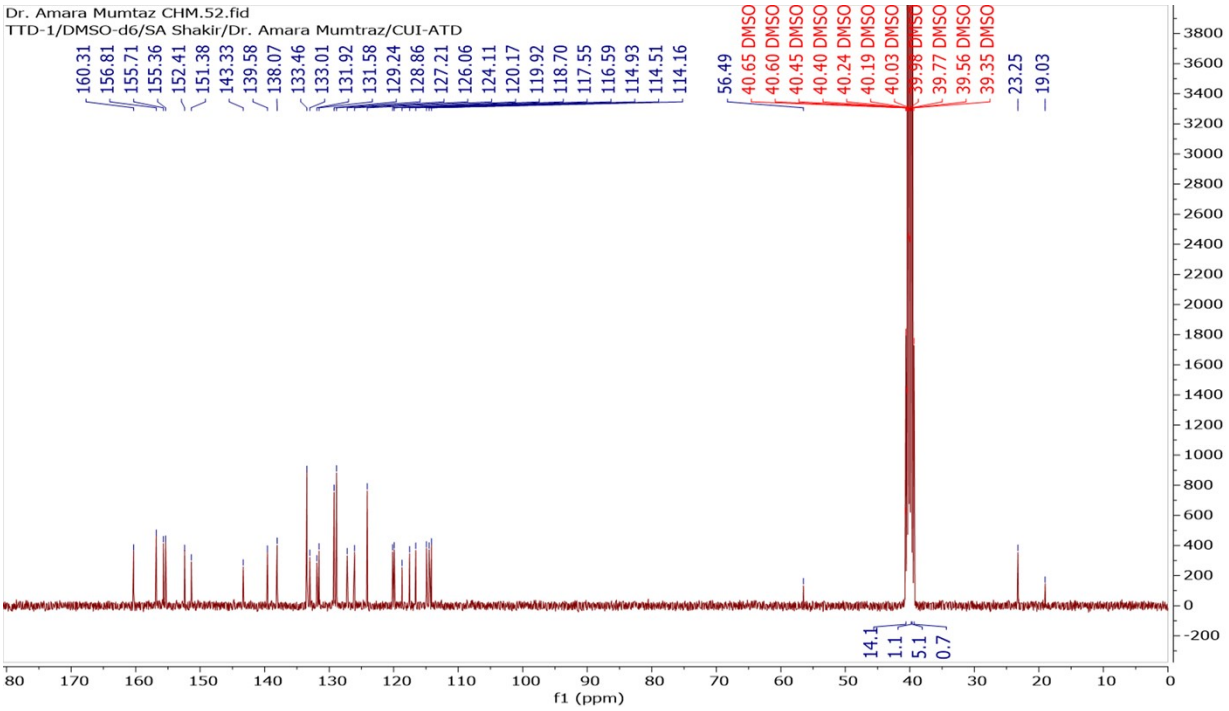

Figure S4: ^{13}C NMR of compound 15

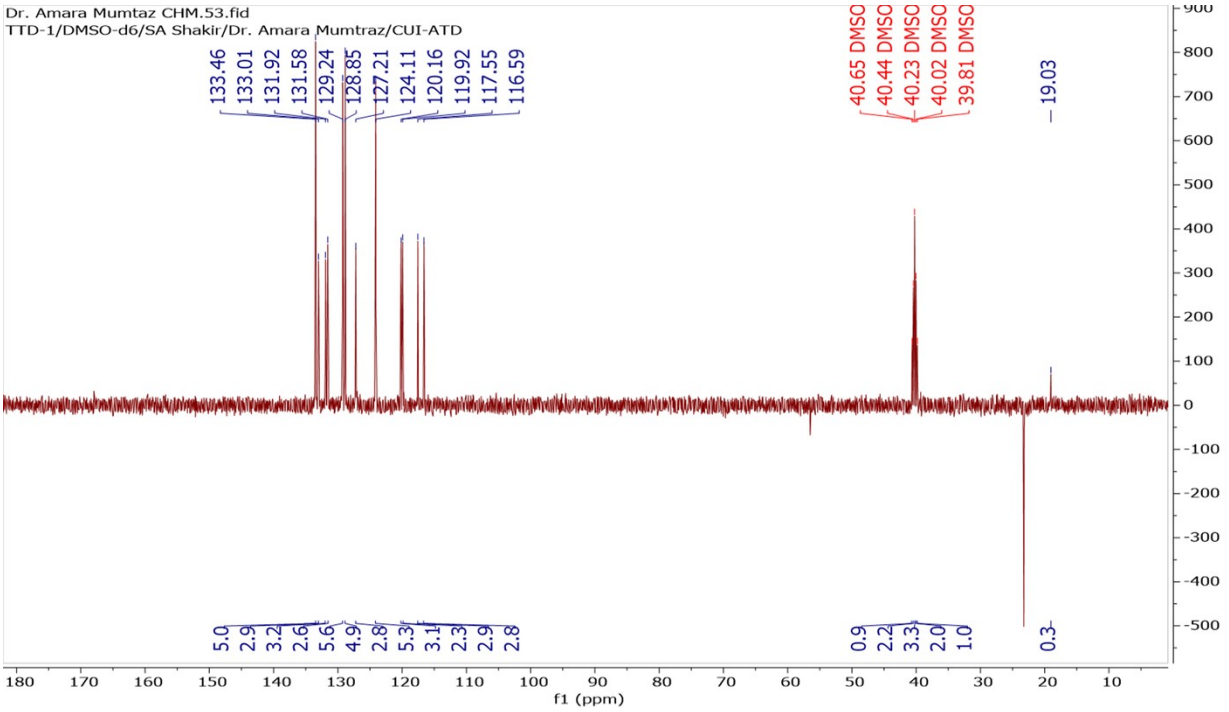

Figure S5: DEPT-135 NMR of compound 15

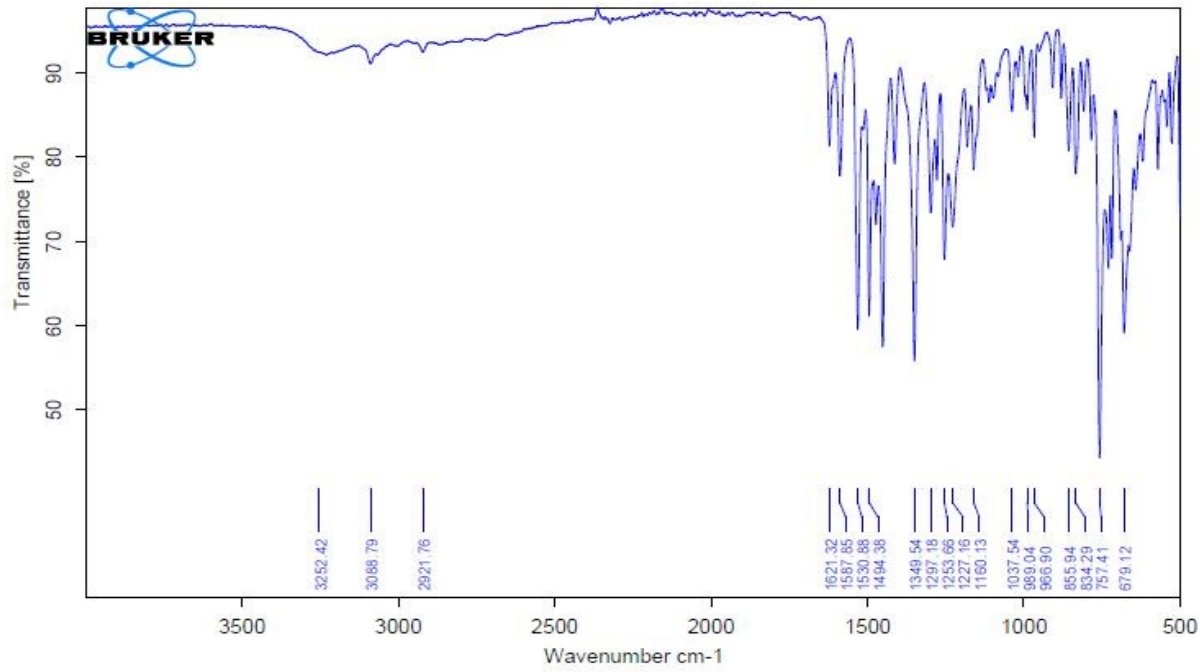

Figure S6: FTIR of compound 16

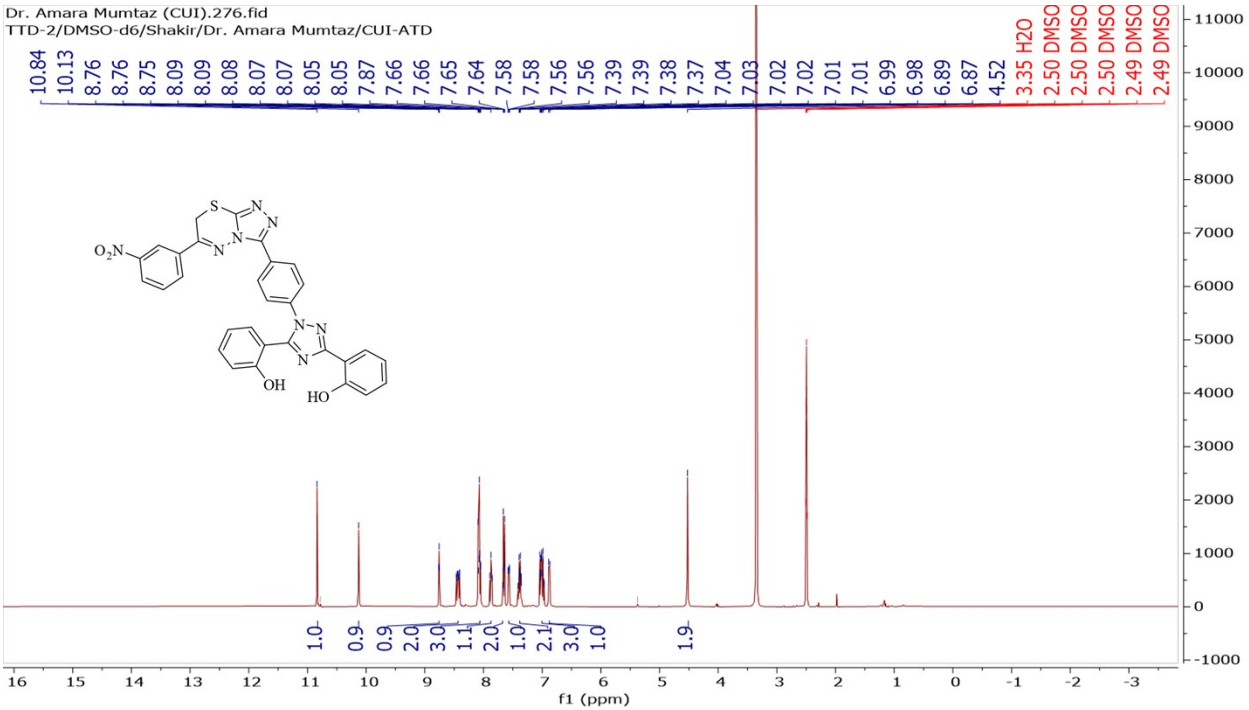

Figure S7: ^{1}H NMR of compound 16

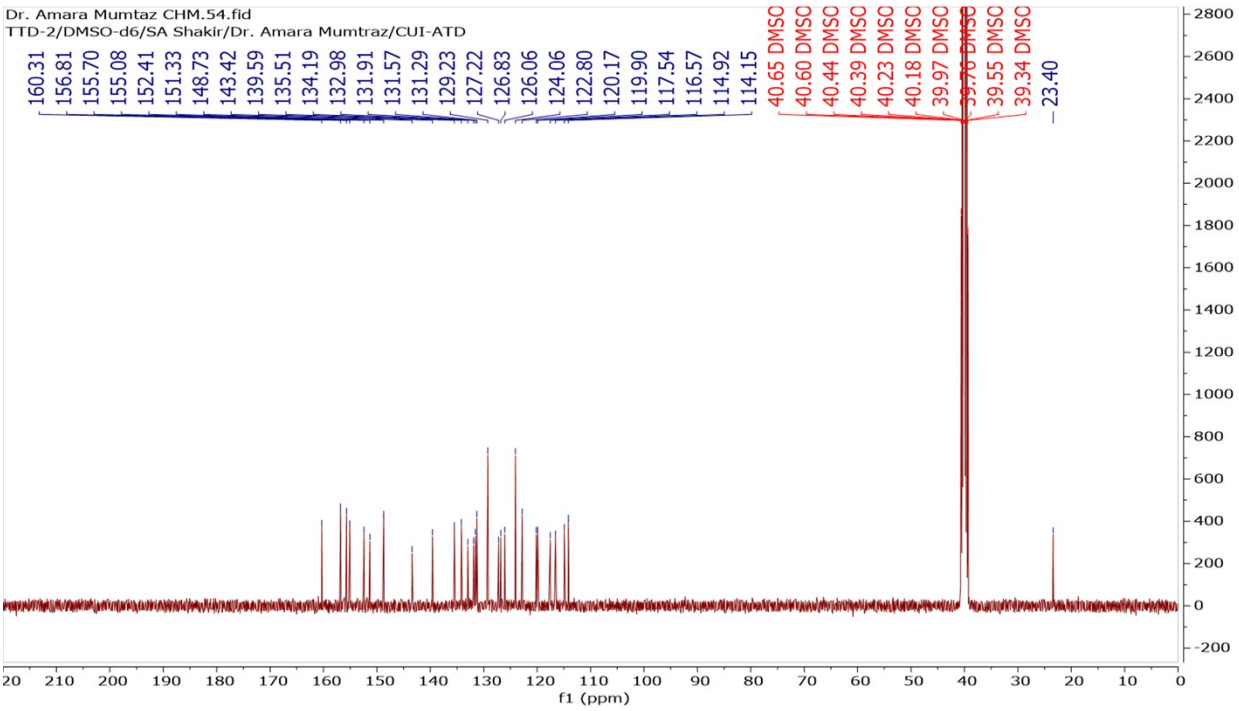

Figure S8: ^{13}C NMR of compound 16

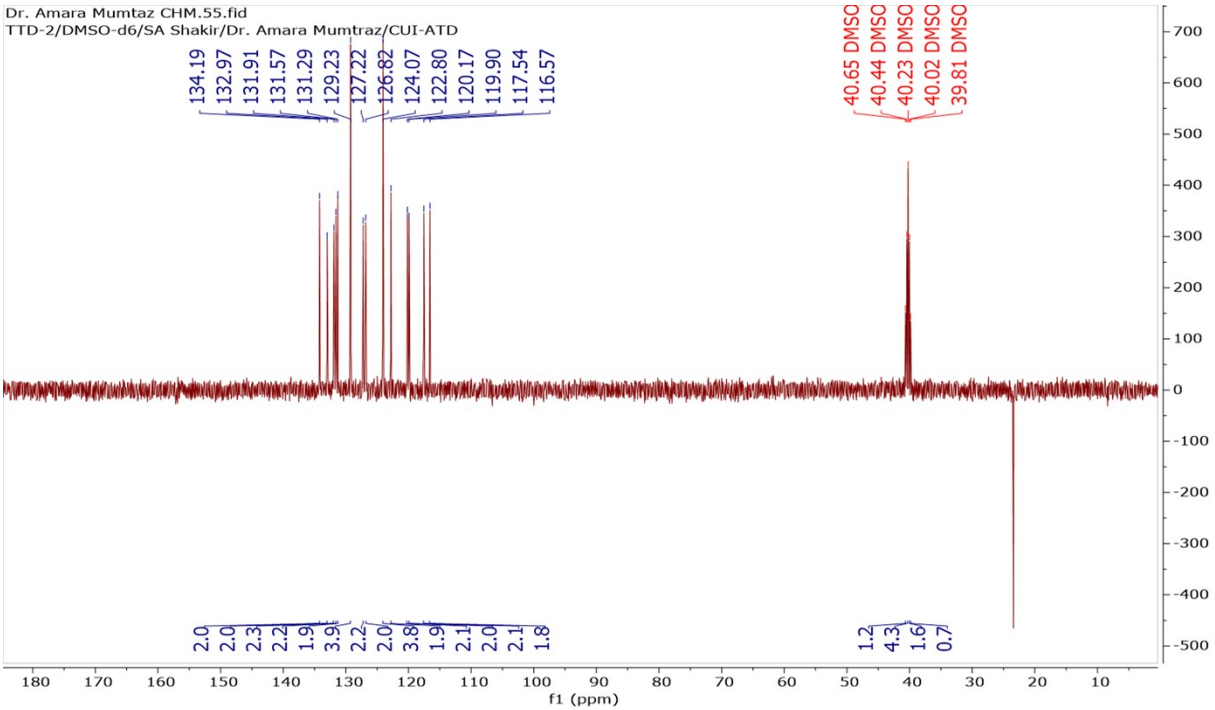

Figure S8: DEPT-135 NMR of compound 16

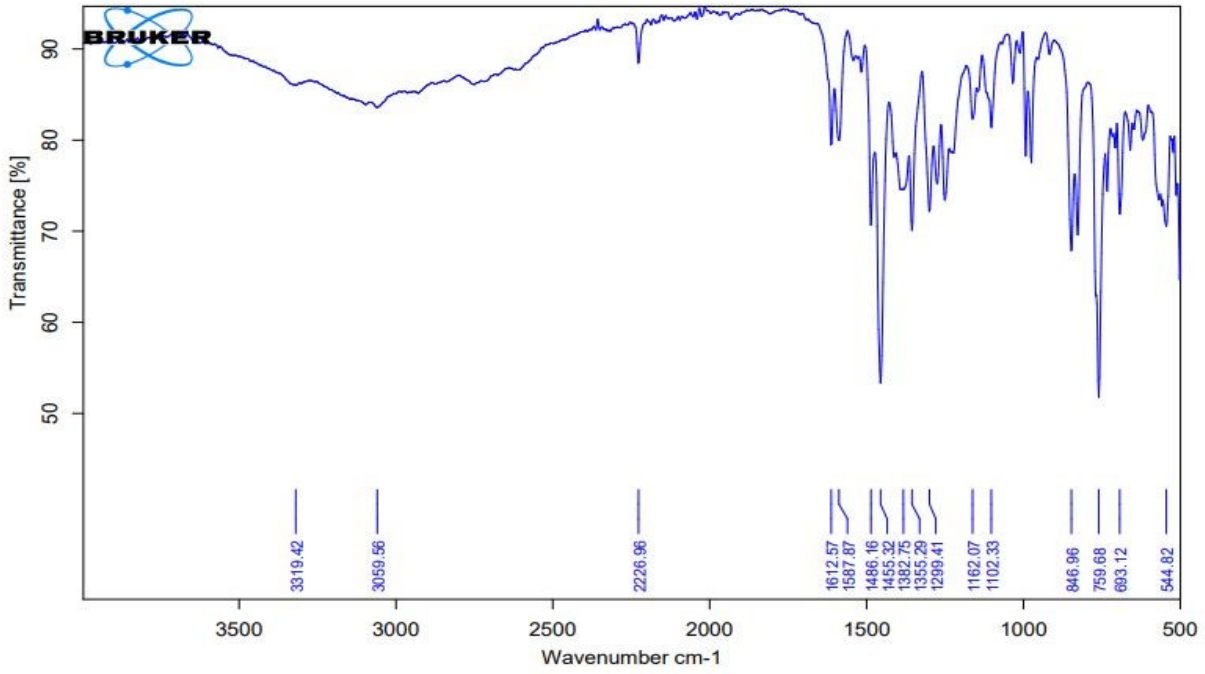

Figure S10: FTIR of compound 17

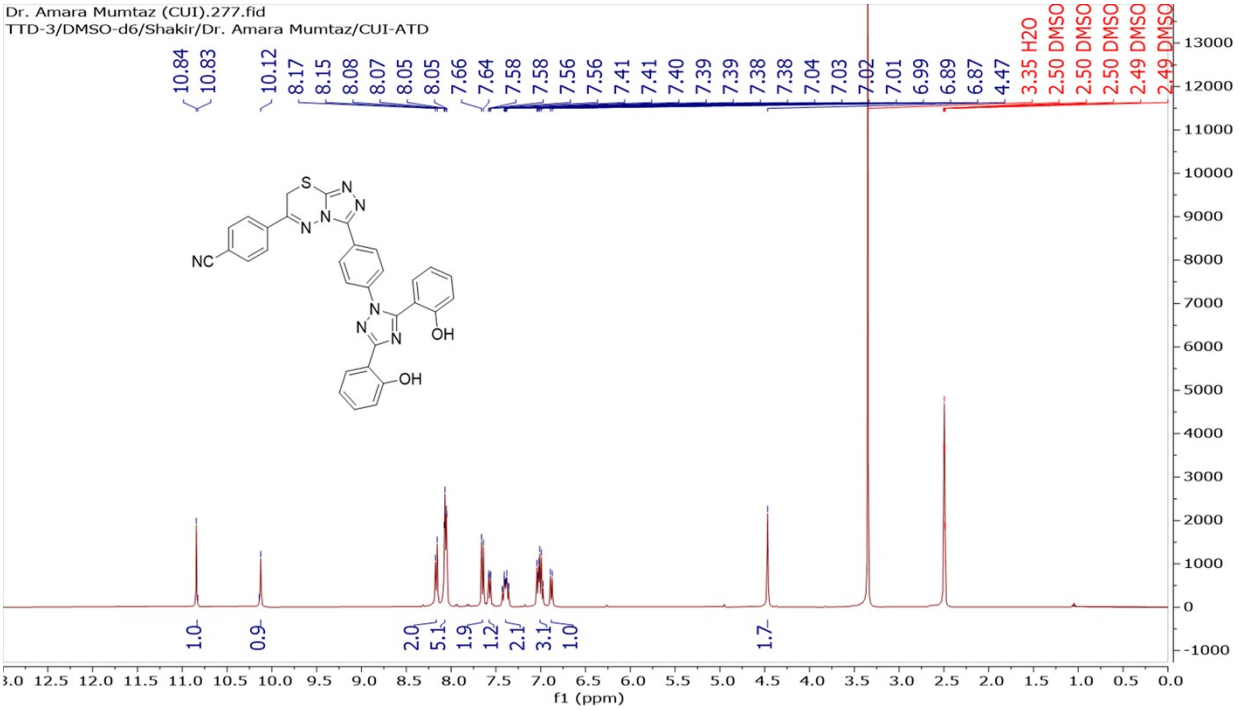

Figure S11: ^{1}H NMR of compound 17

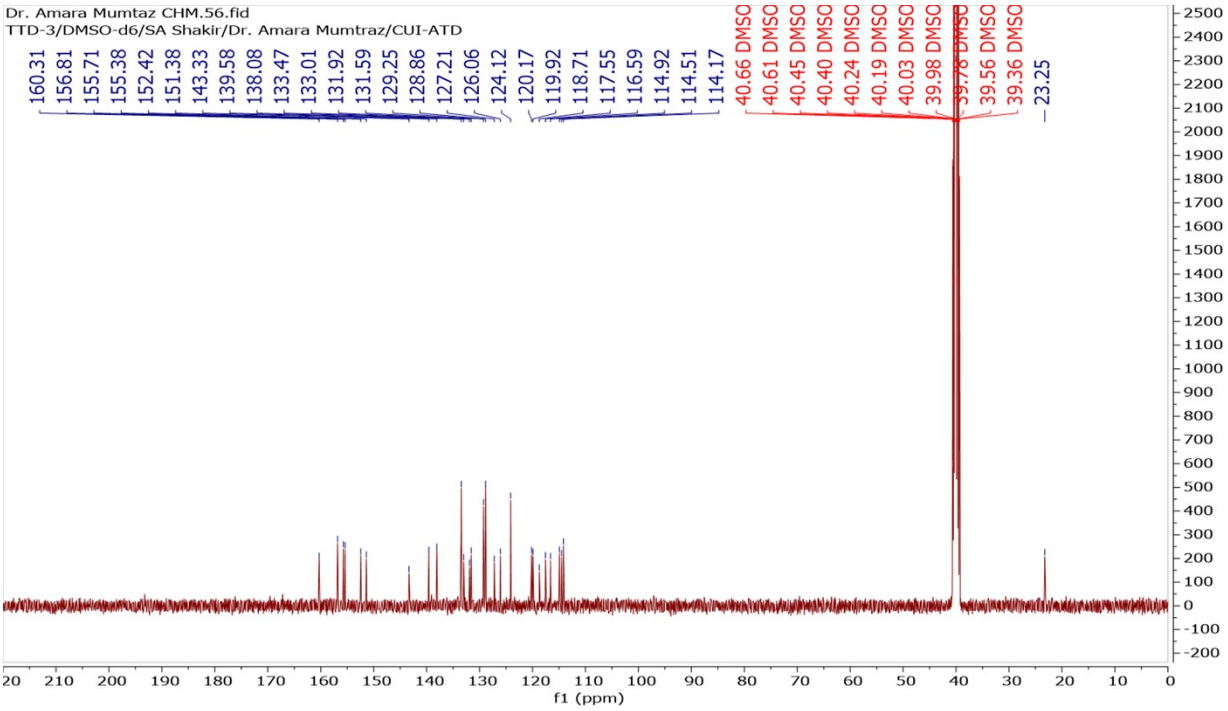

Figure S12: ^{13}C NMR of compound 17

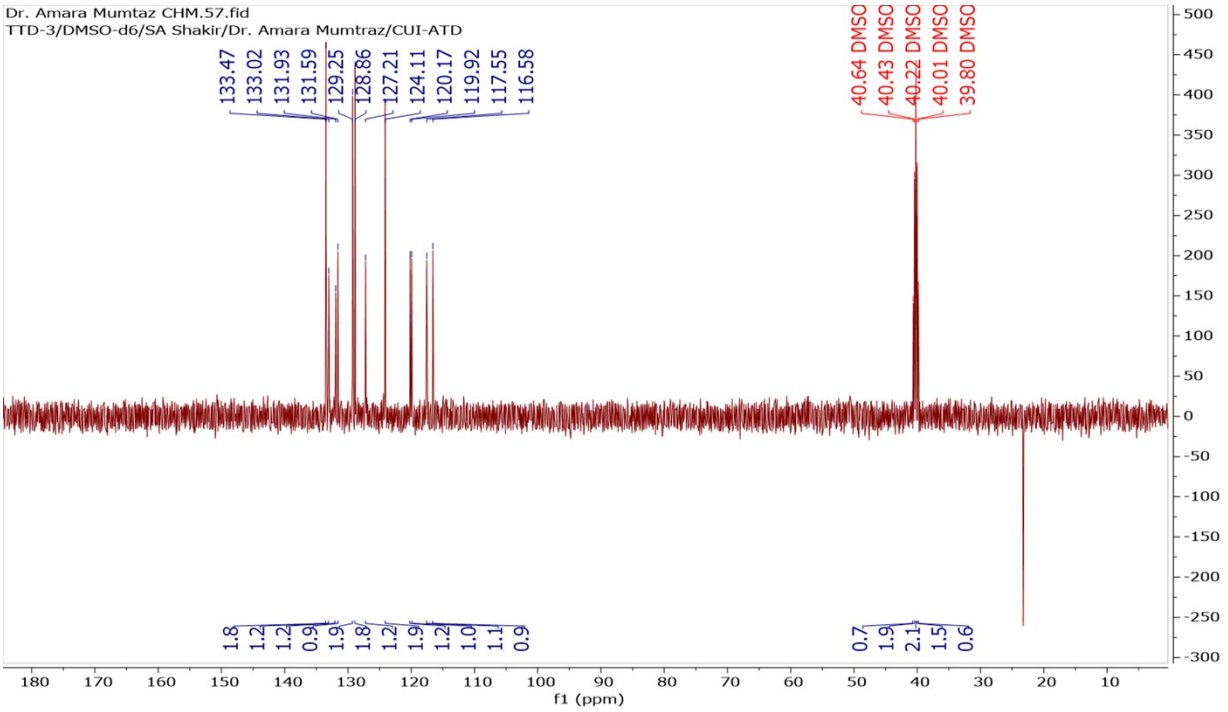

Figure S13: DEPT-135 NMR of compound 17

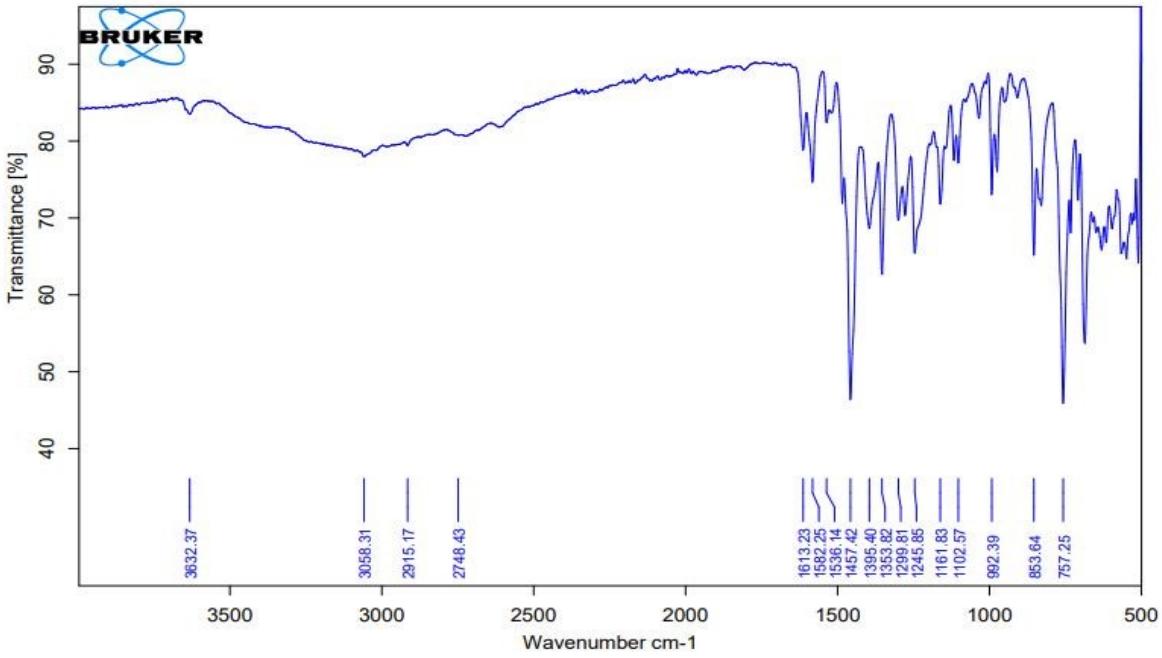

Figure S14: FTIR of compound 18

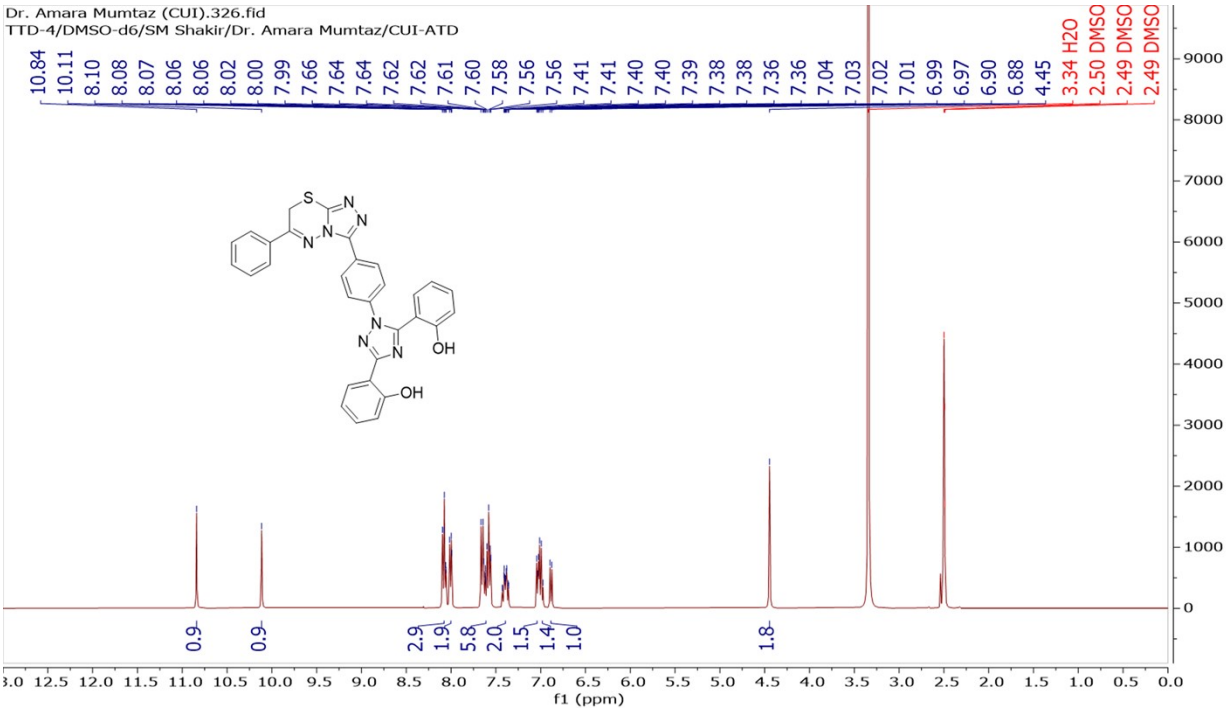

Figure S15: ^{1}H NMR of compound 18

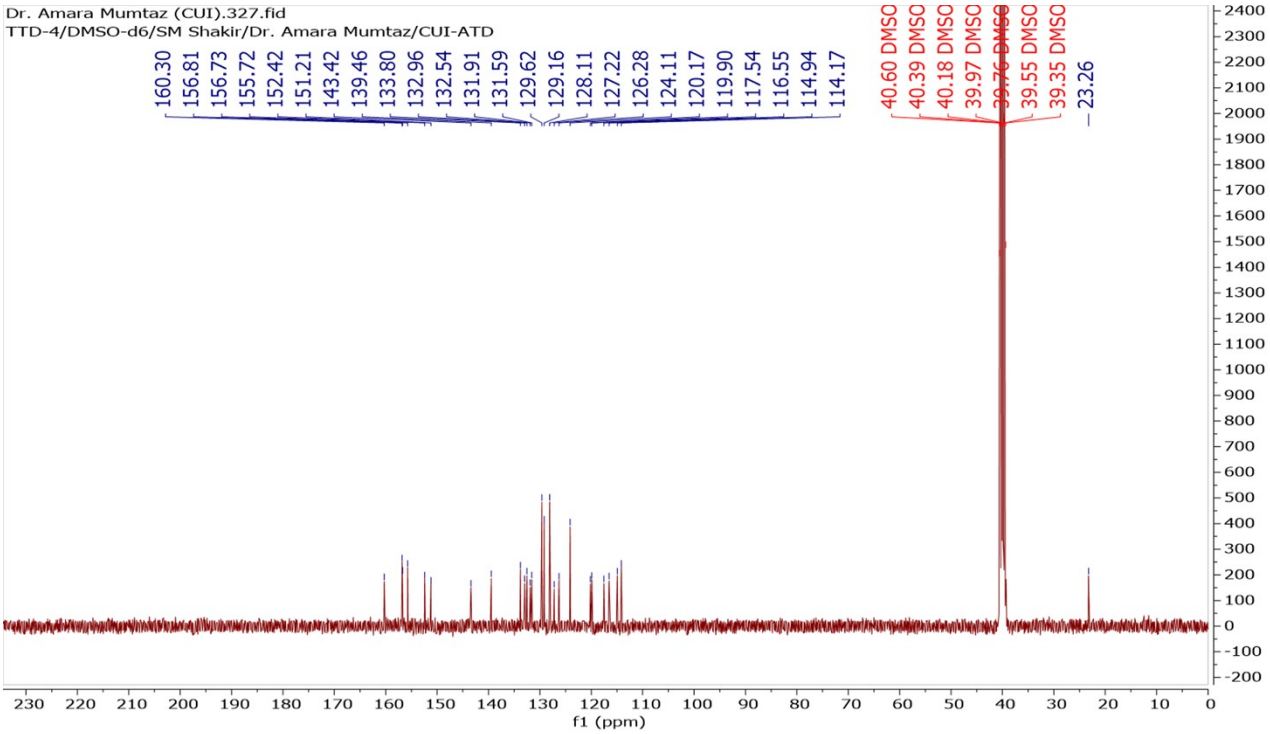

Figure S16: ^{13}C NMR of compound 18

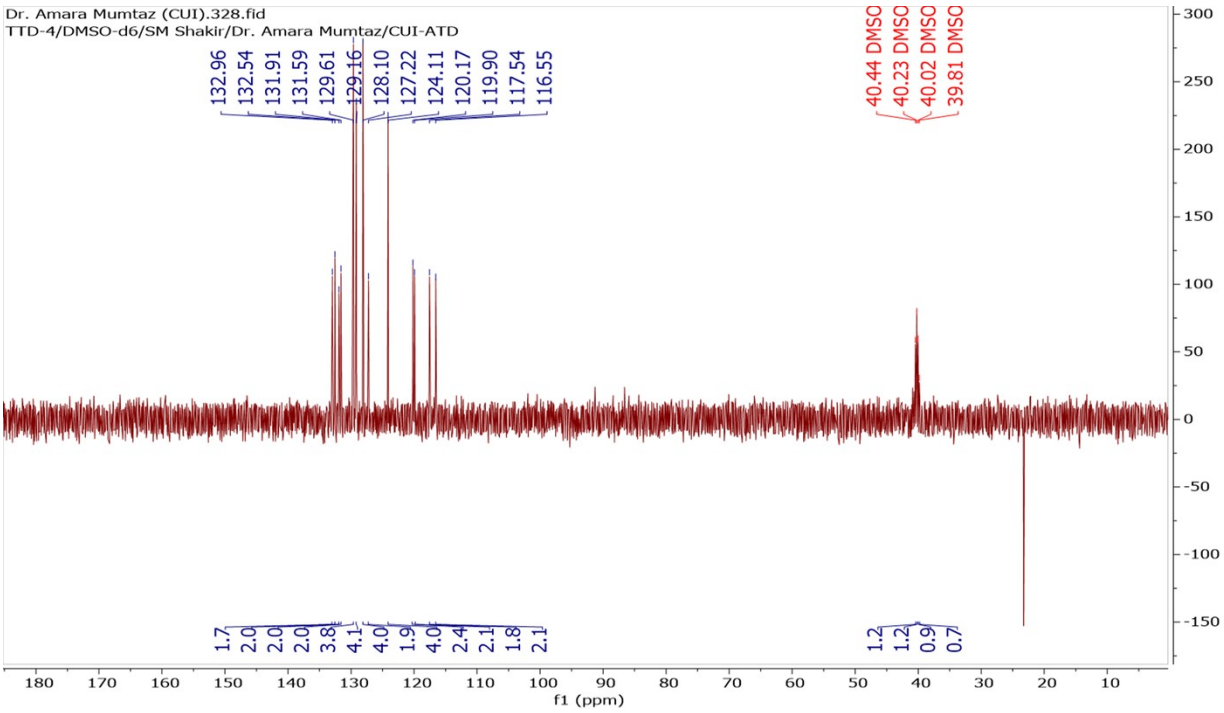

Figure S17: DEPT-135 NMR of compound 18

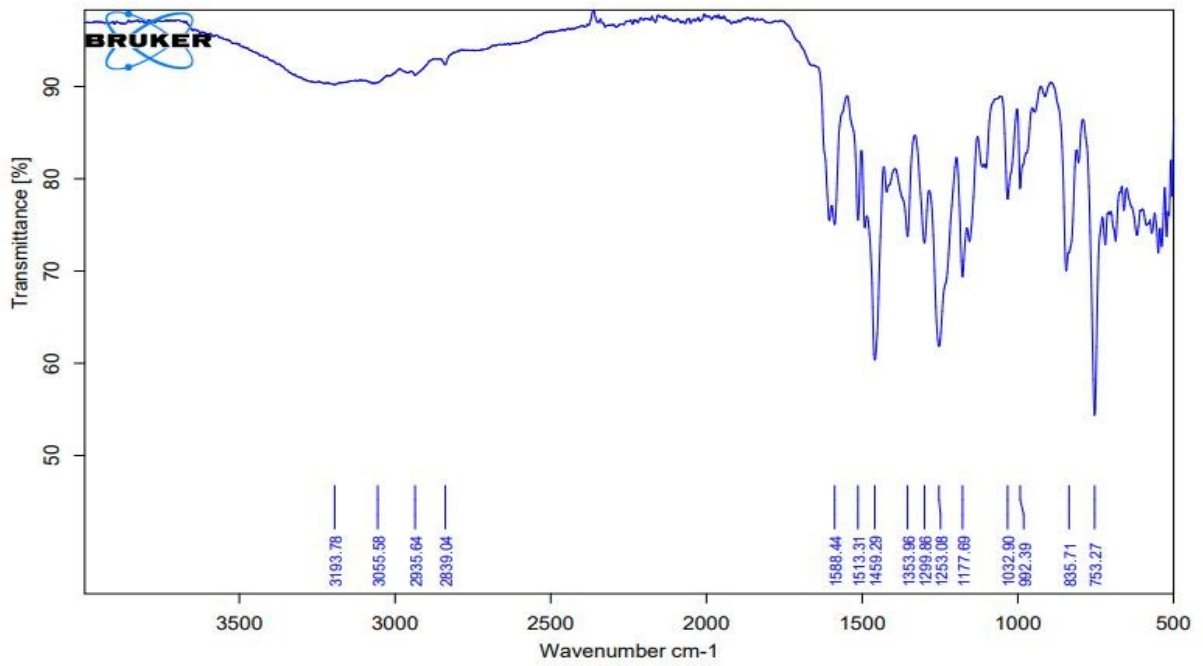

Figure S18: FTIR of compound 19

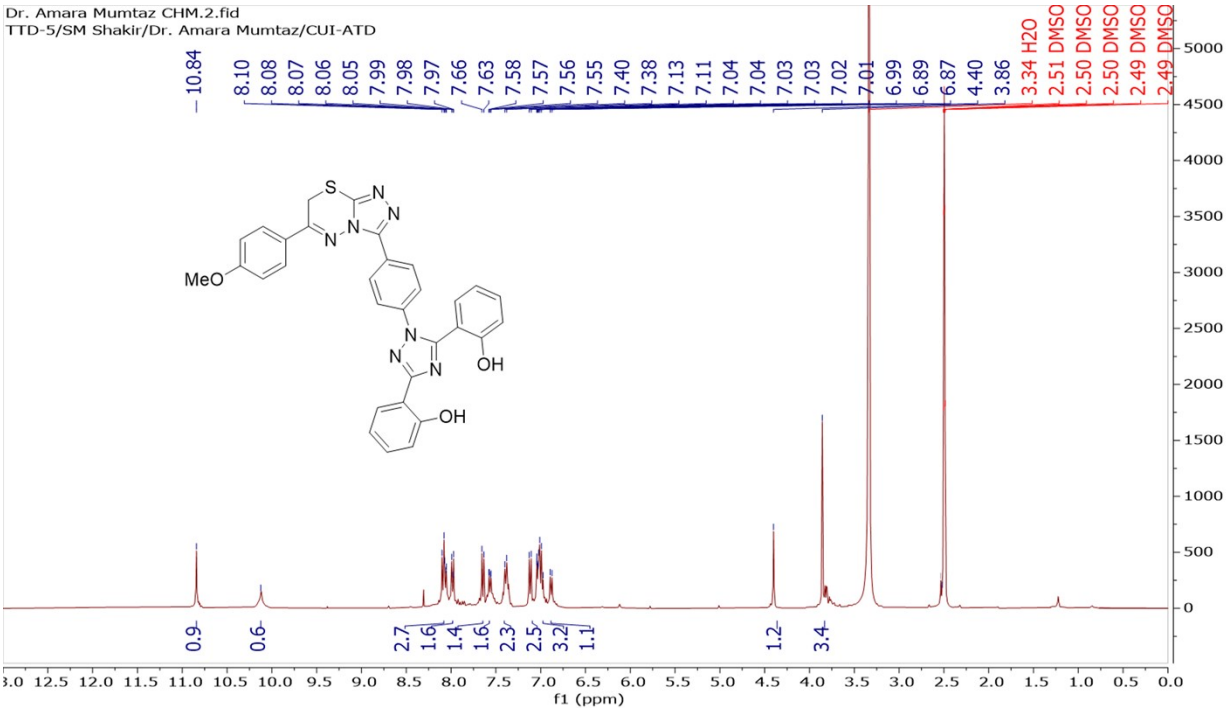

Figure S19: ^{1}H NMR of compound 19

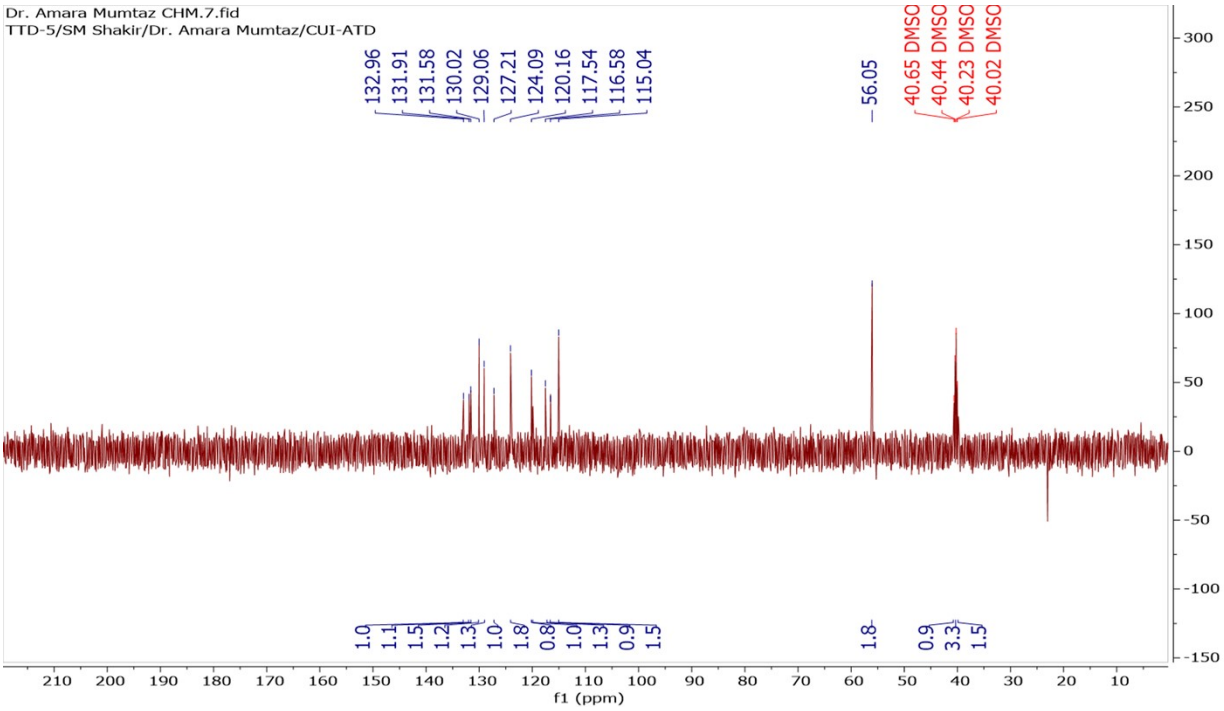

Figure S20: DEPT-135 NMR of compound 19

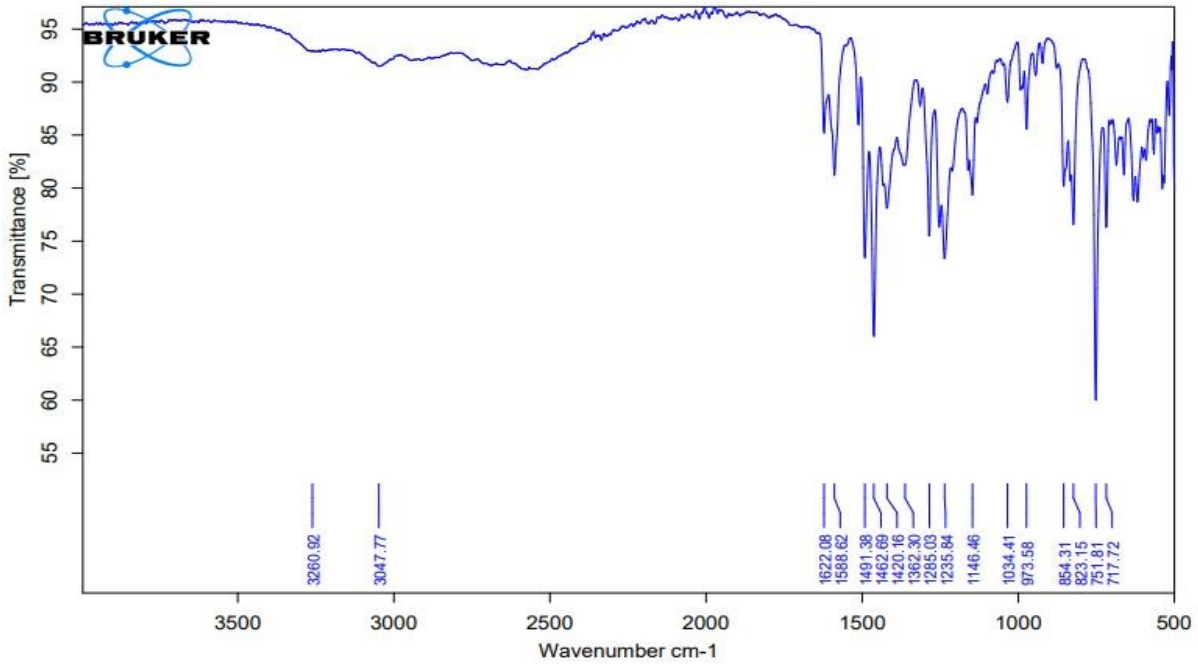

Figure S21: FTIR of compound 20

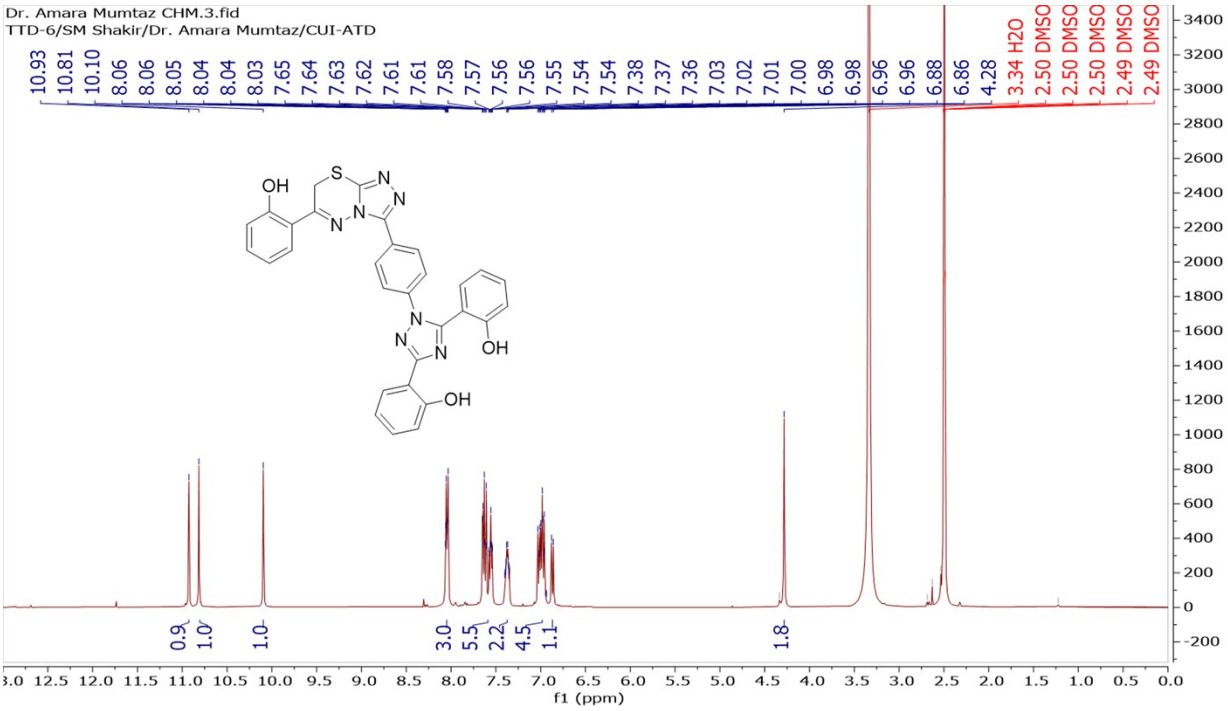

Figure S22: ^{1}H NMR of compound 20

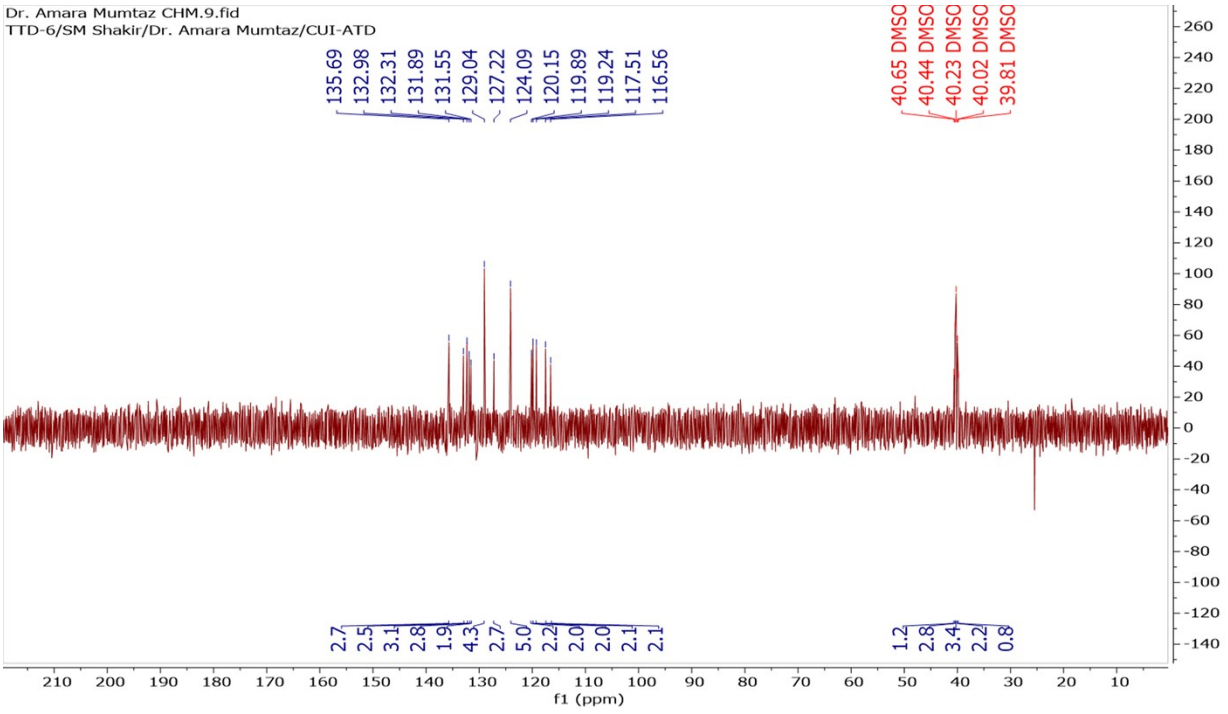

Figure S23: DEPT-135 NMR of compound 20

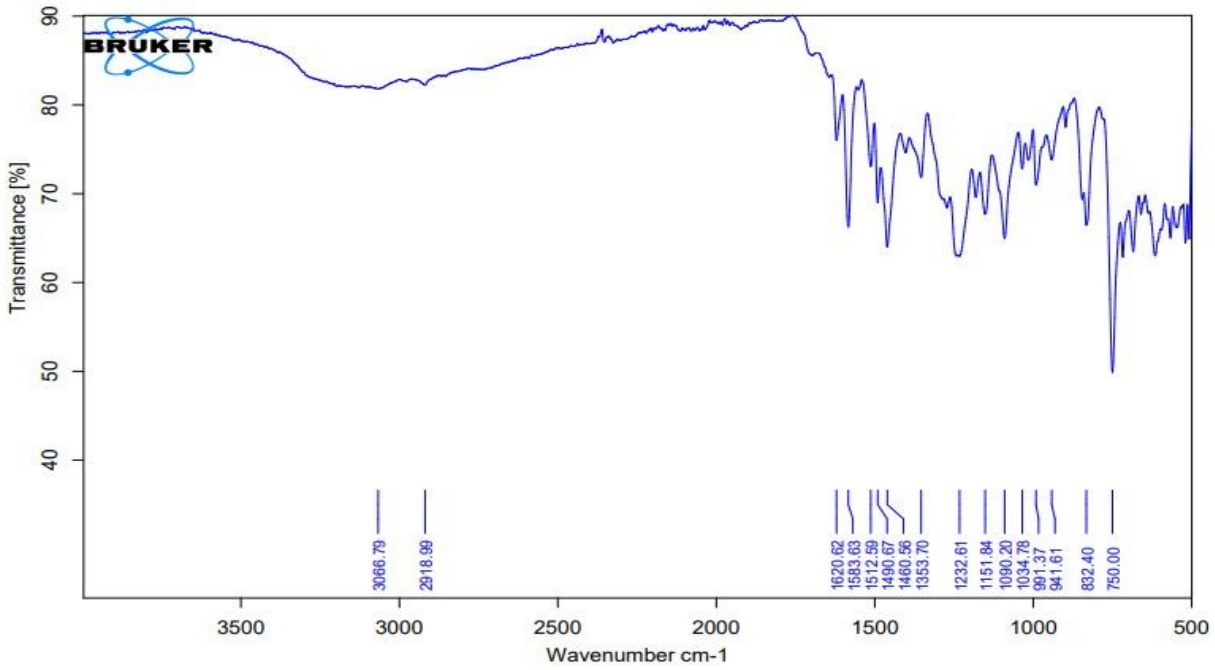

Figure S24: FTIR of compound 21

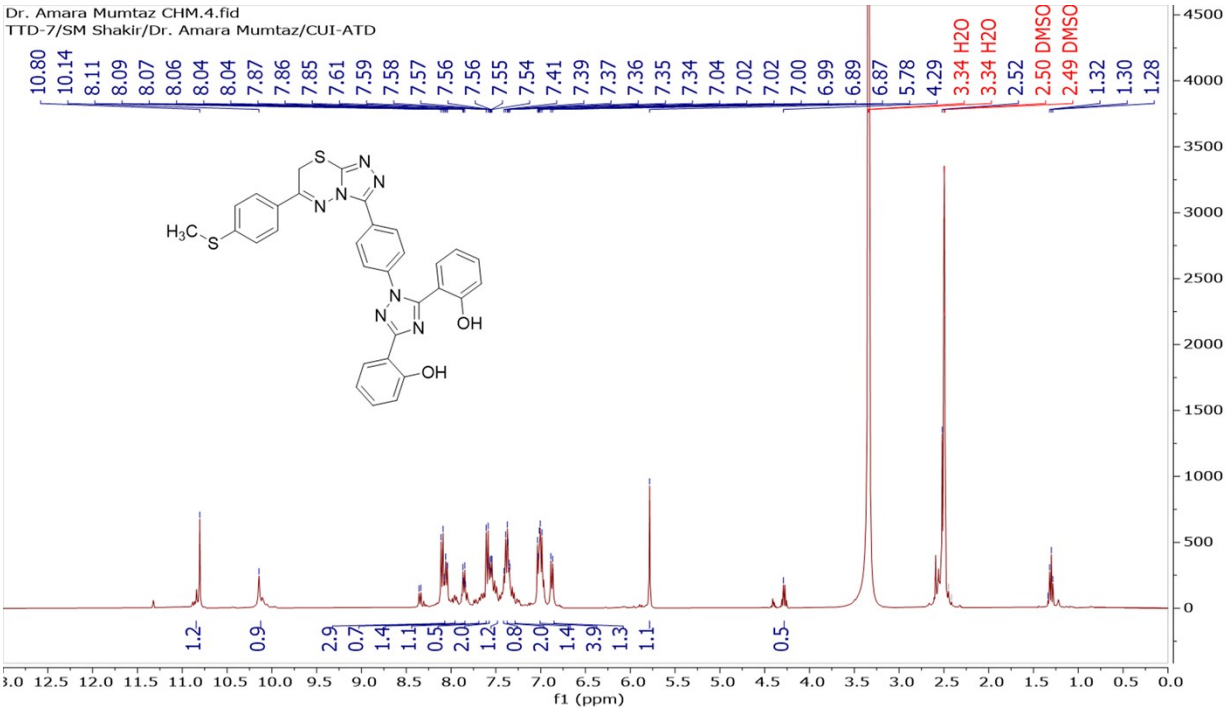

Figure S25: ^{1}H NMR of compound 21

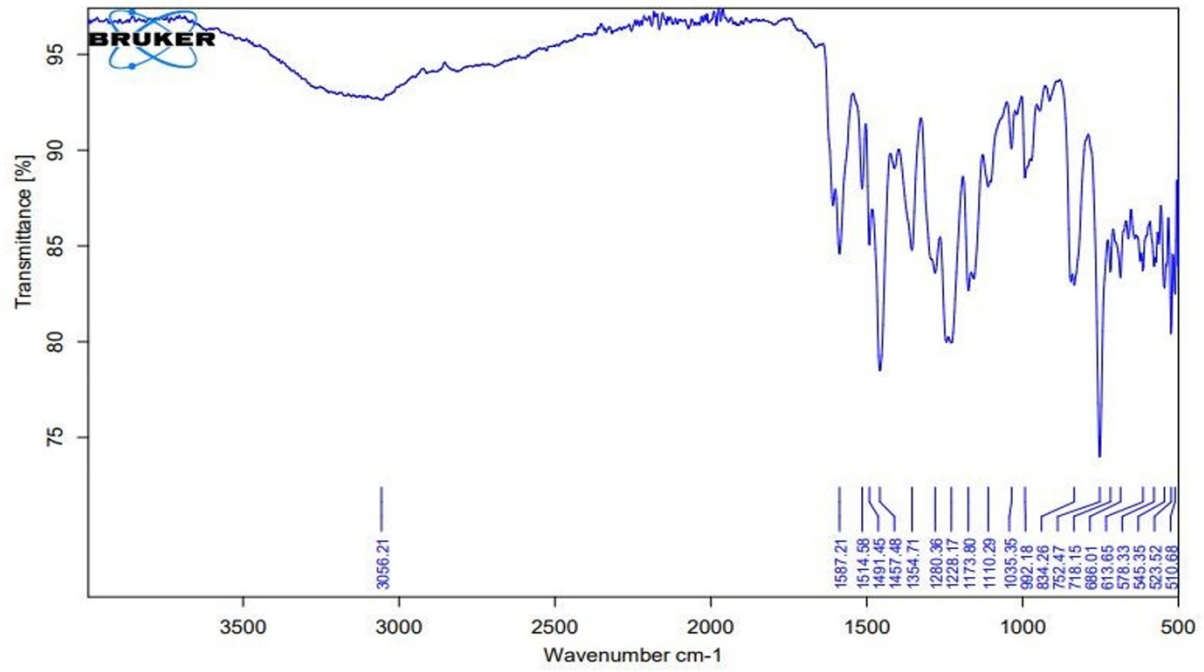

Figure S26: FTIR of compound 24

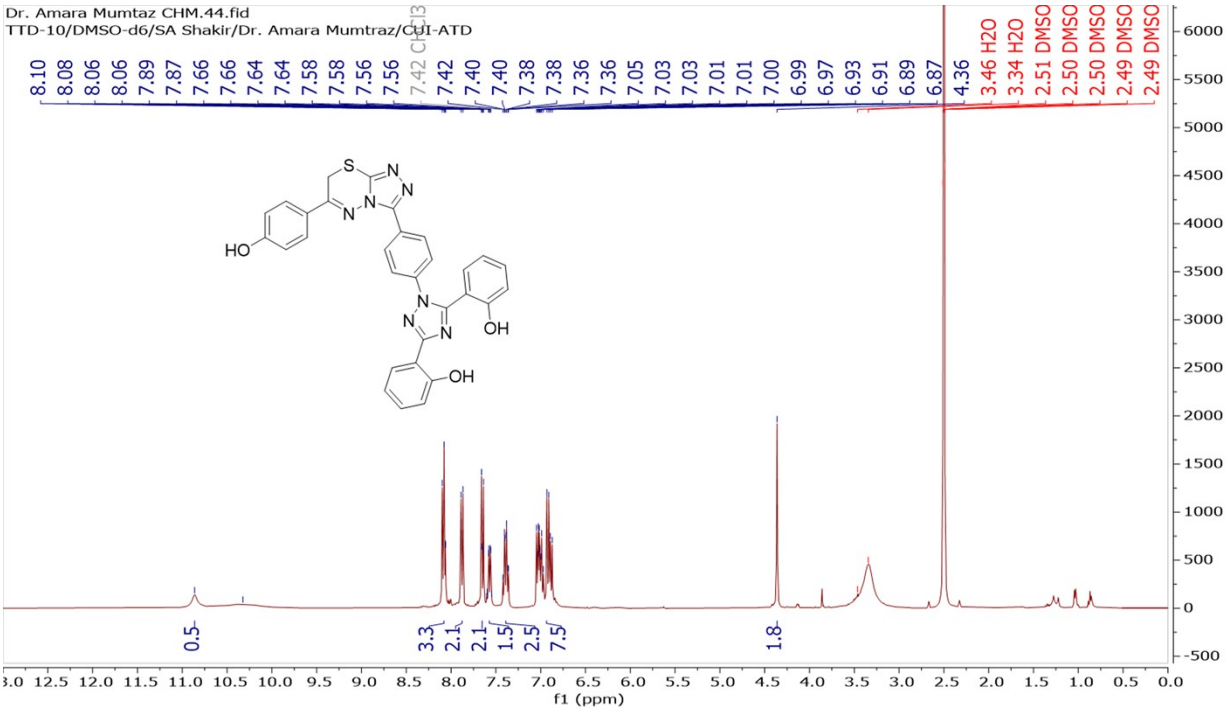

Figure S27: ^{1}H NMR of compound 24

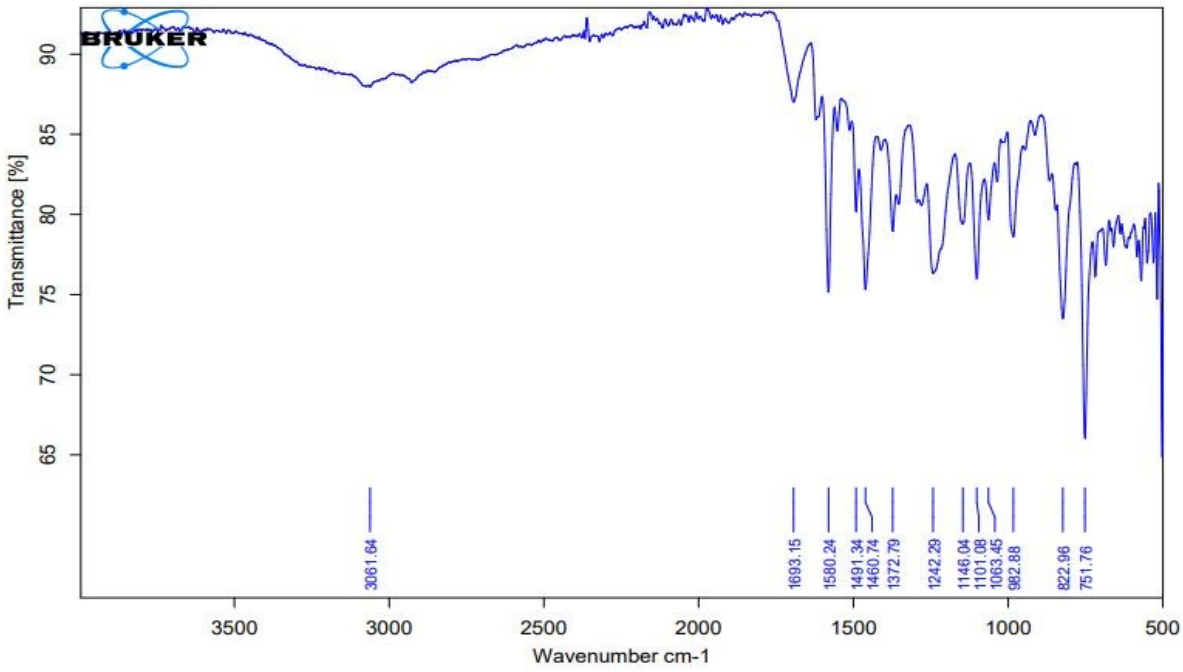

Figure S28: FTIR of compound 25

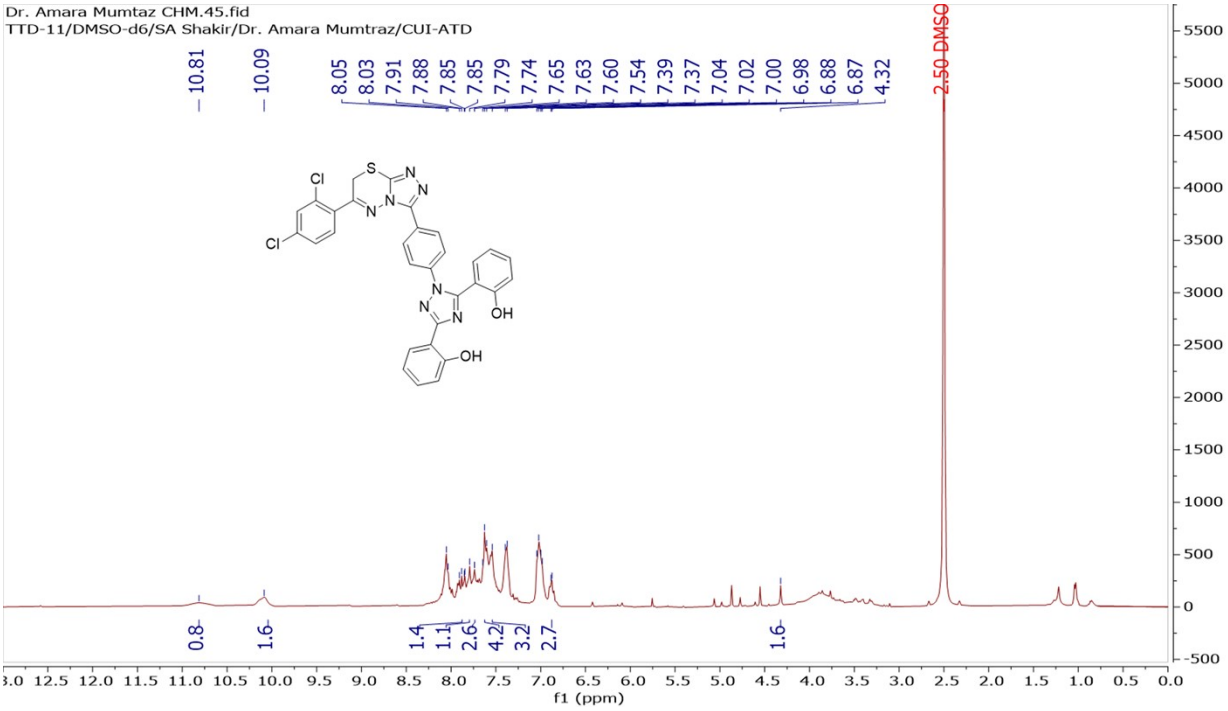

Figure S29 : ^{1}H NMR of compound 25

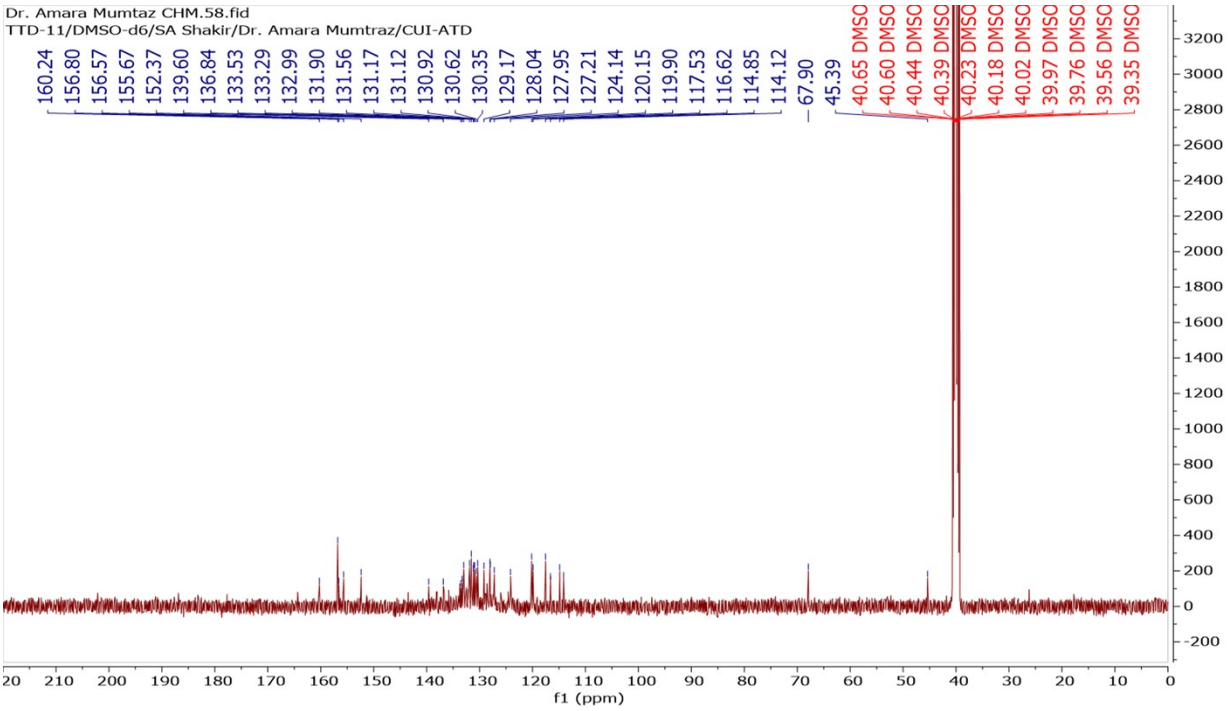

Figure S30: ^{13}C NMR of compound 25

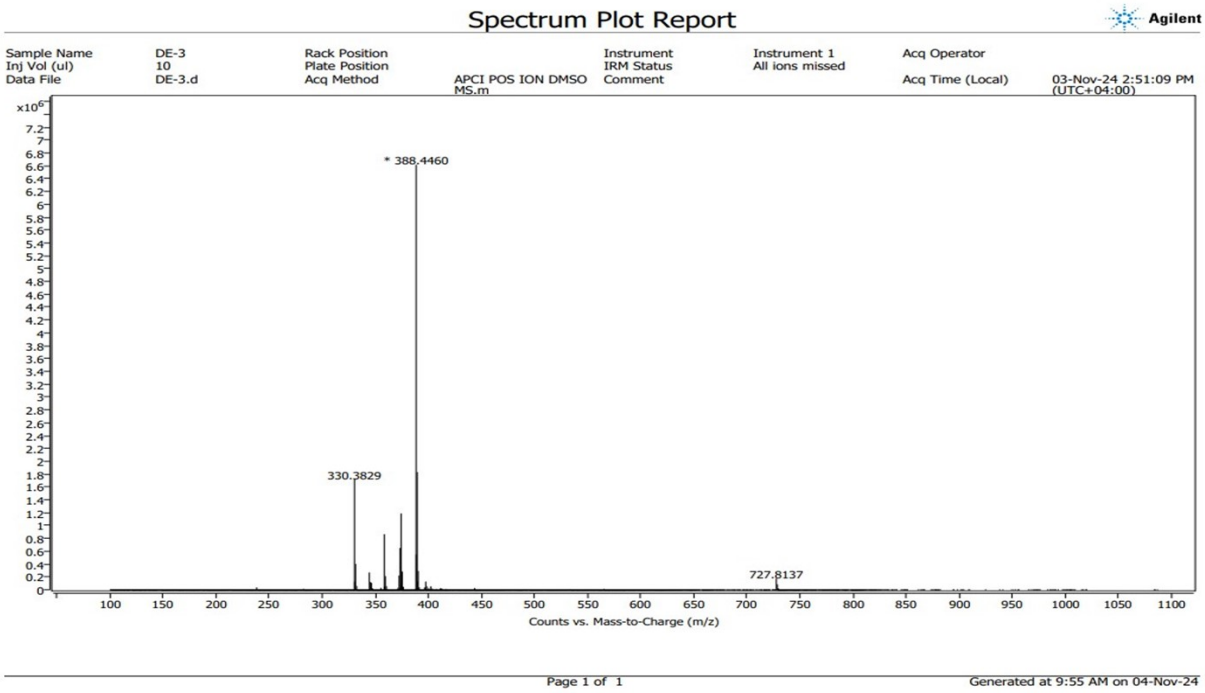

Figure S31. HRMS Spectrum of **11**

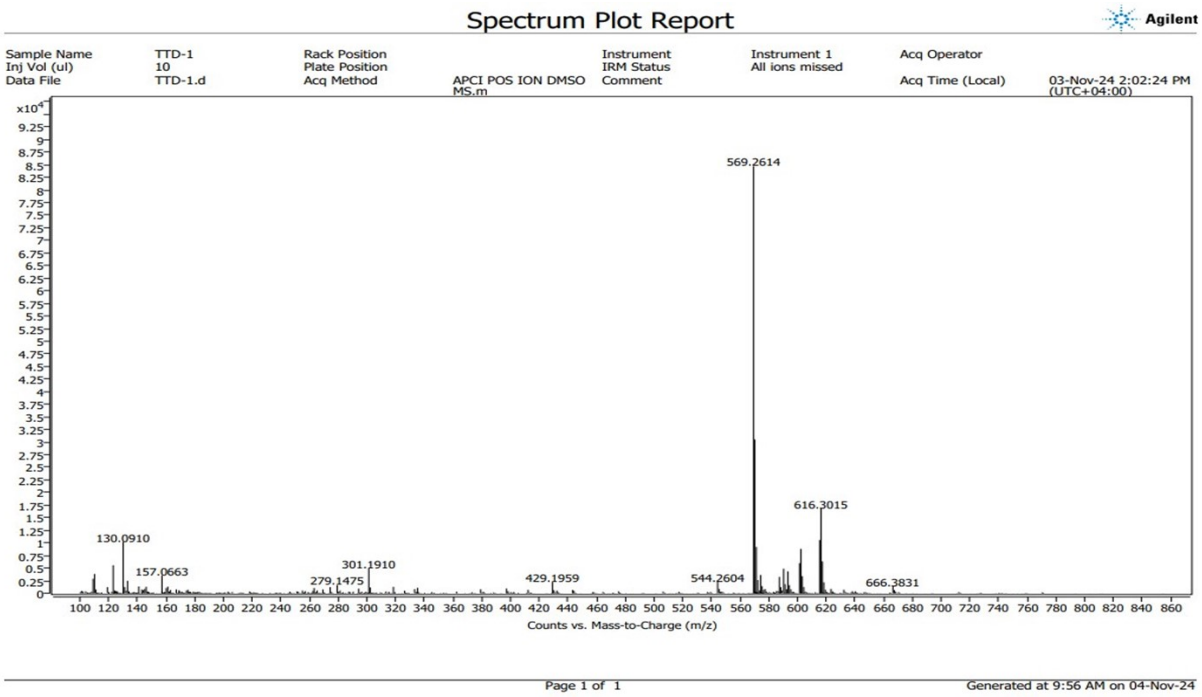

Figure S32. HRMS Spectrum of **15**

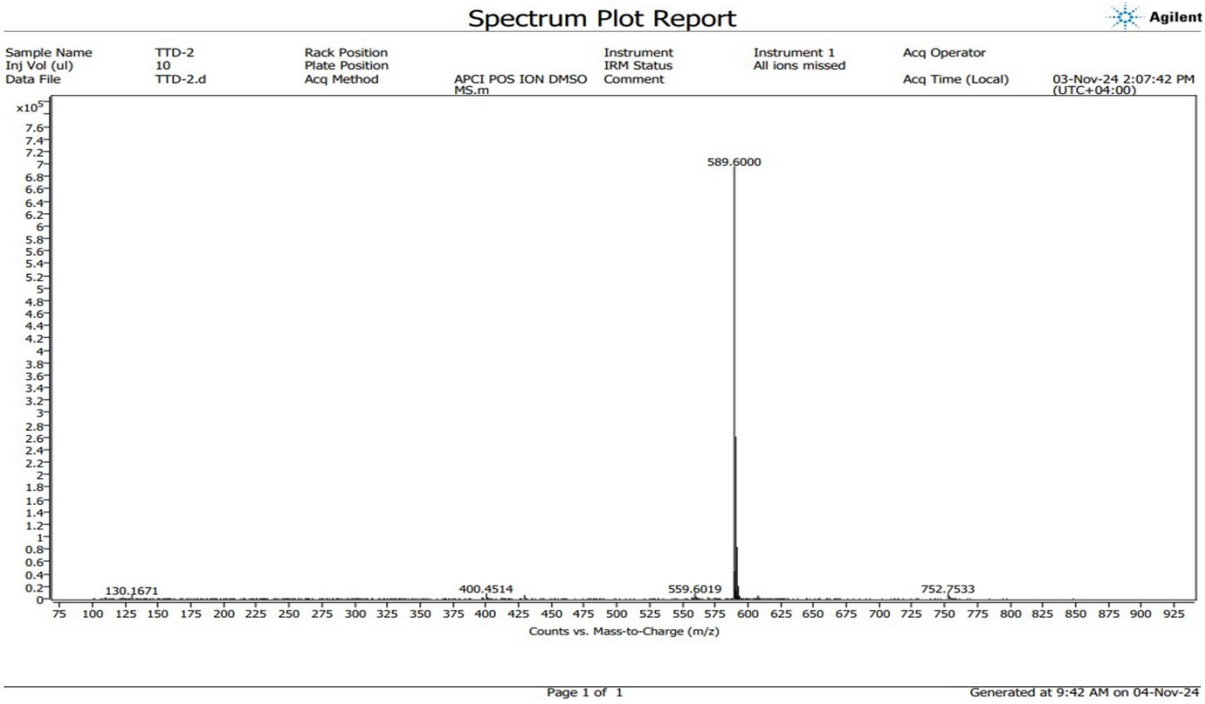

Figure S33. HRMS Spectrum of **16**

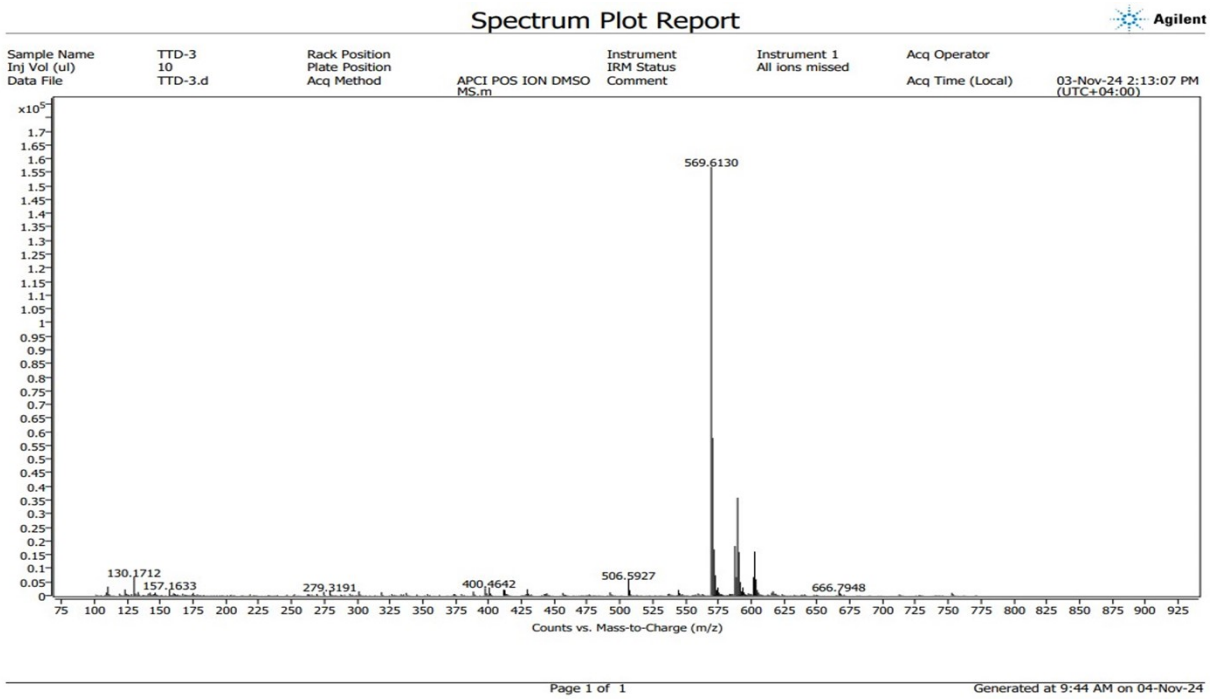

Figure S34. HRMS Spectrum of **17**

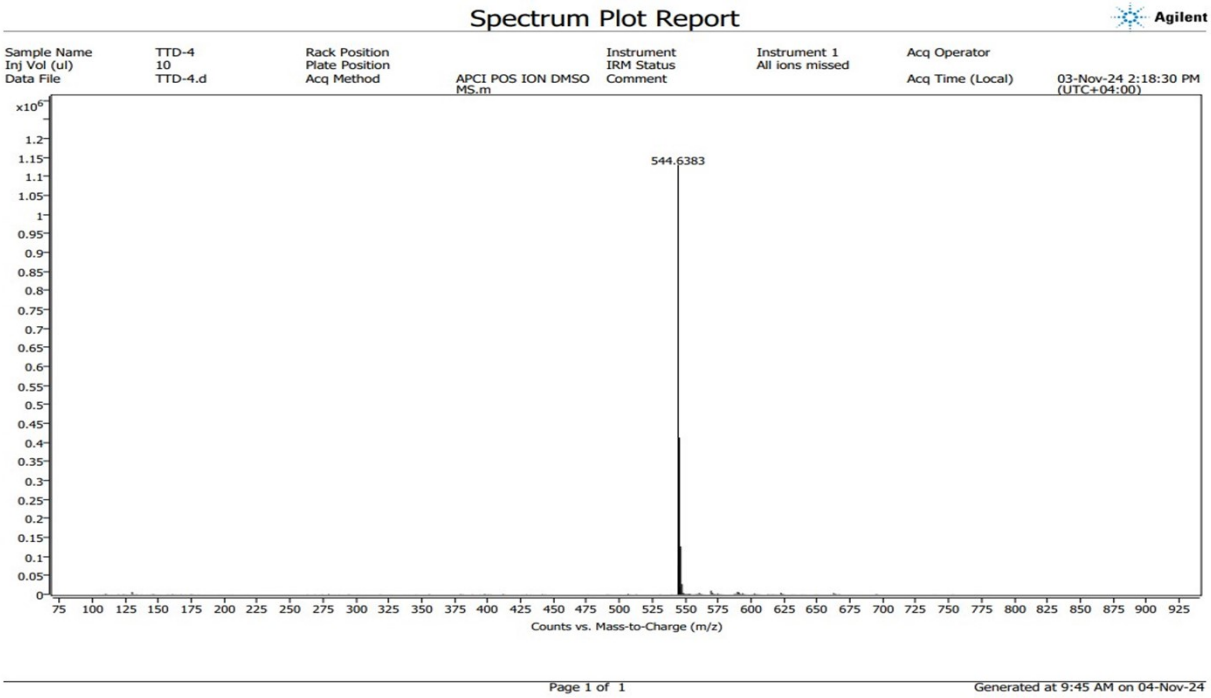

Figure S35. HRMS Spectrum of **18**

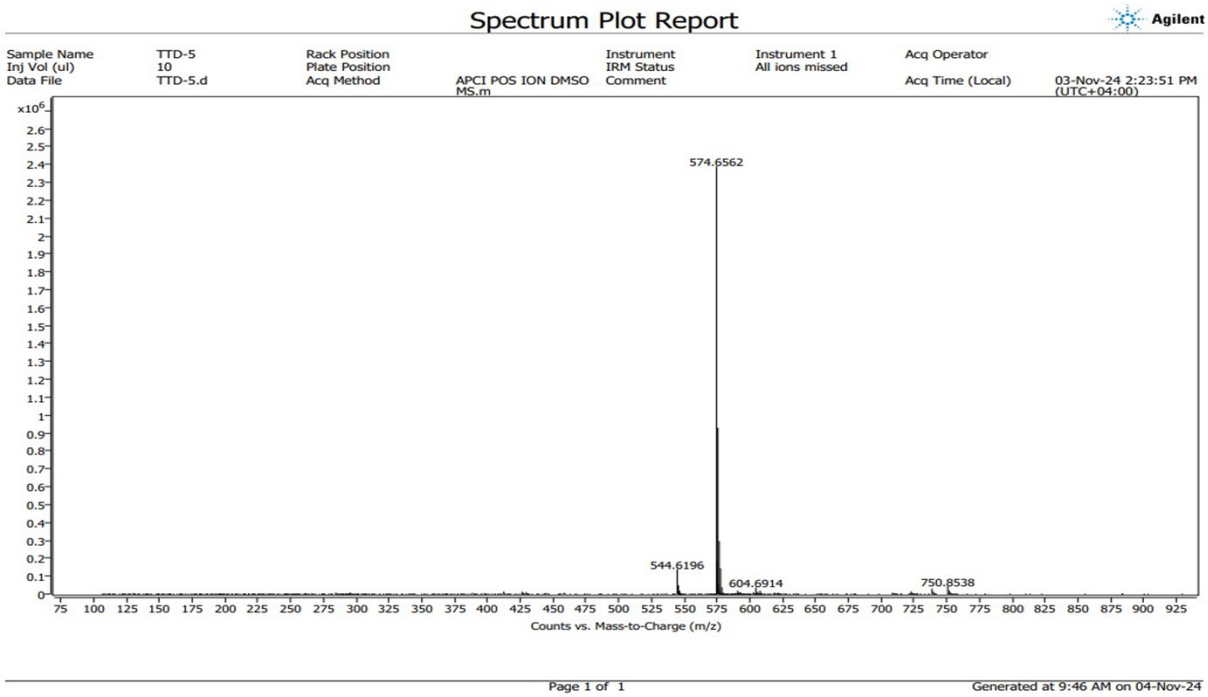

Figure S36. HRMS Spectrum of **19**

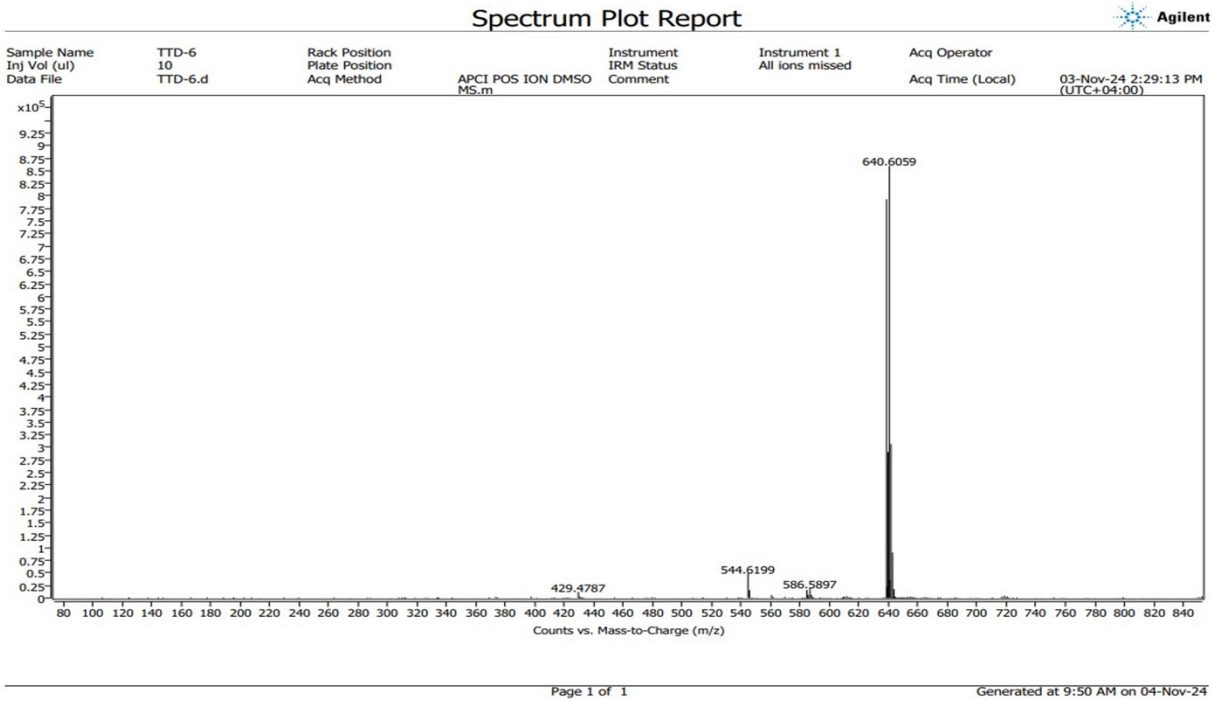

Figure S37. HRMS Spectrum of **20**

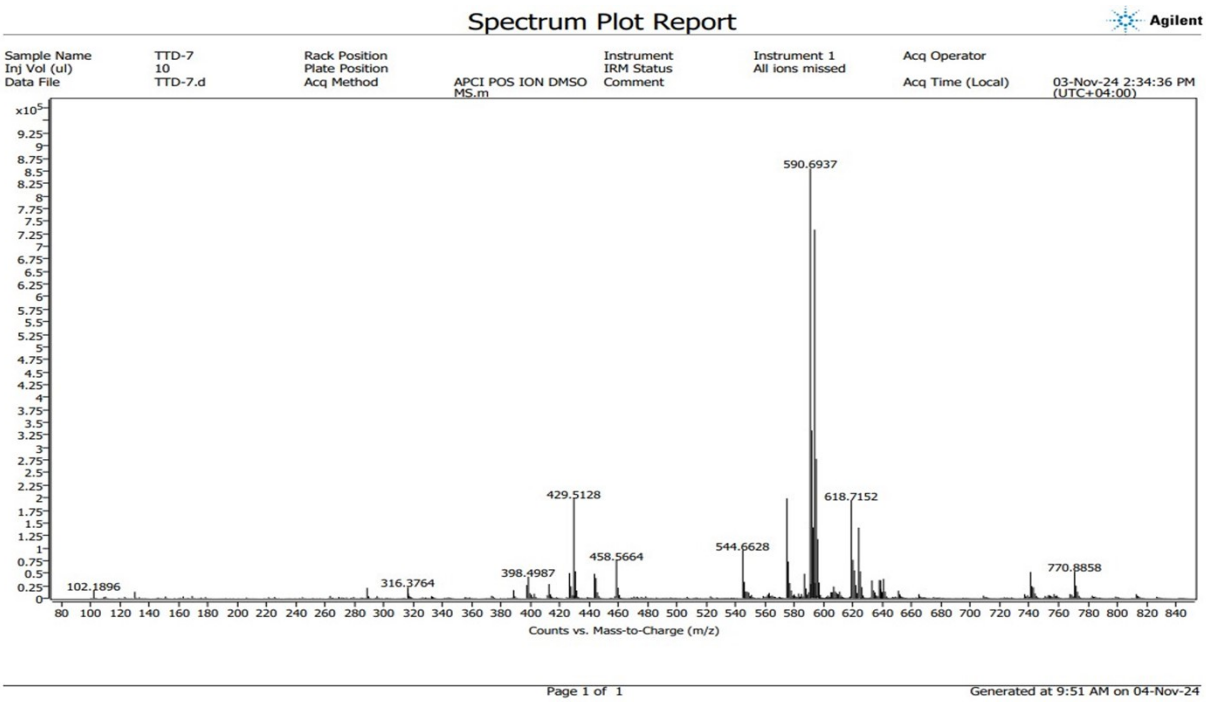

Figure S38. HRMS Spectrum of **21**

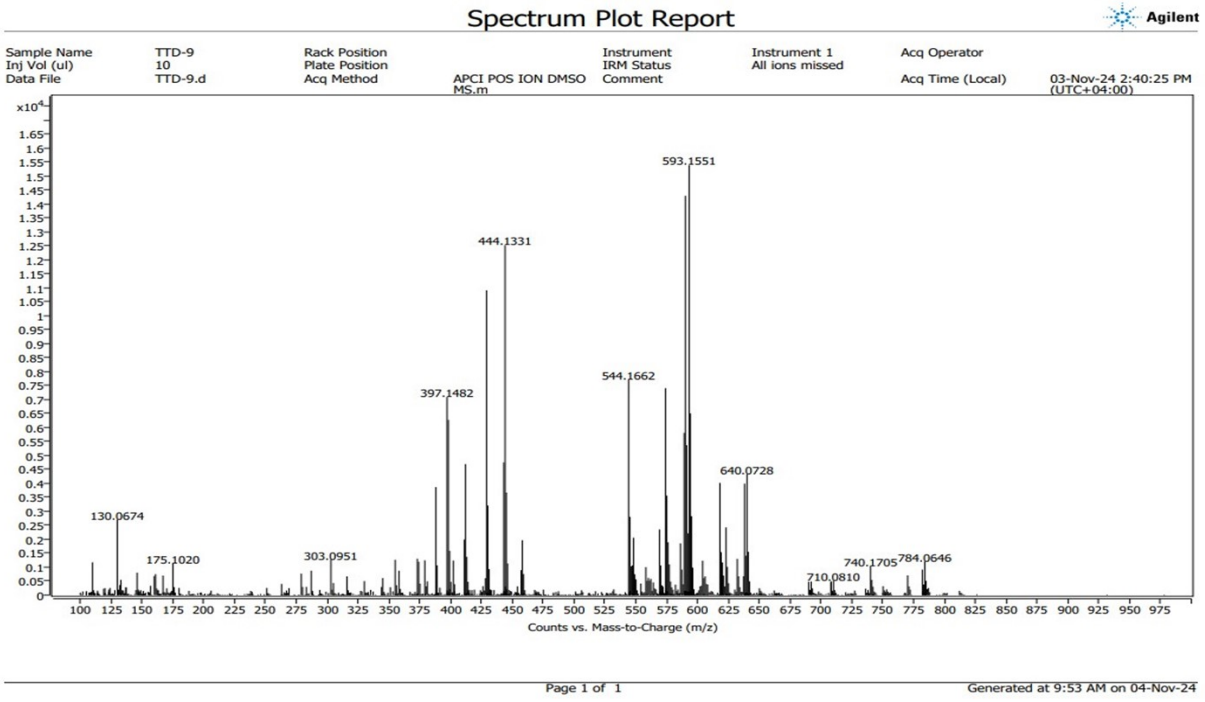

Figure S39. HRMS Spectrum of **23**

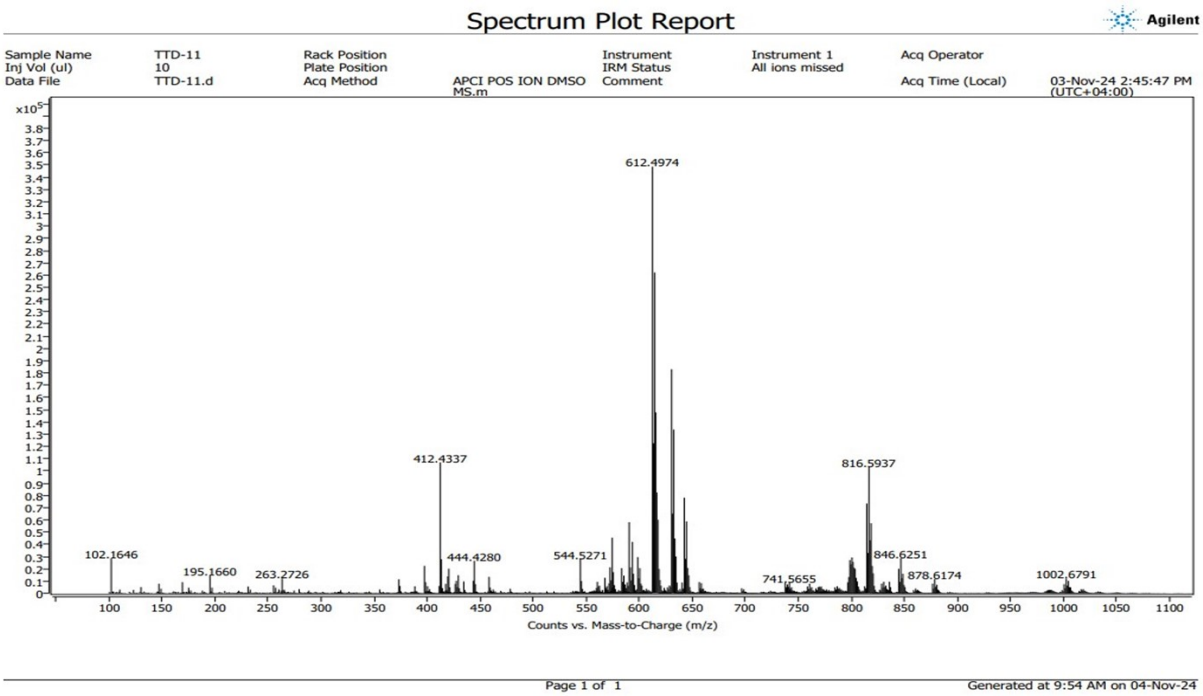

Figure S40. HRMS Spectrum of **25**

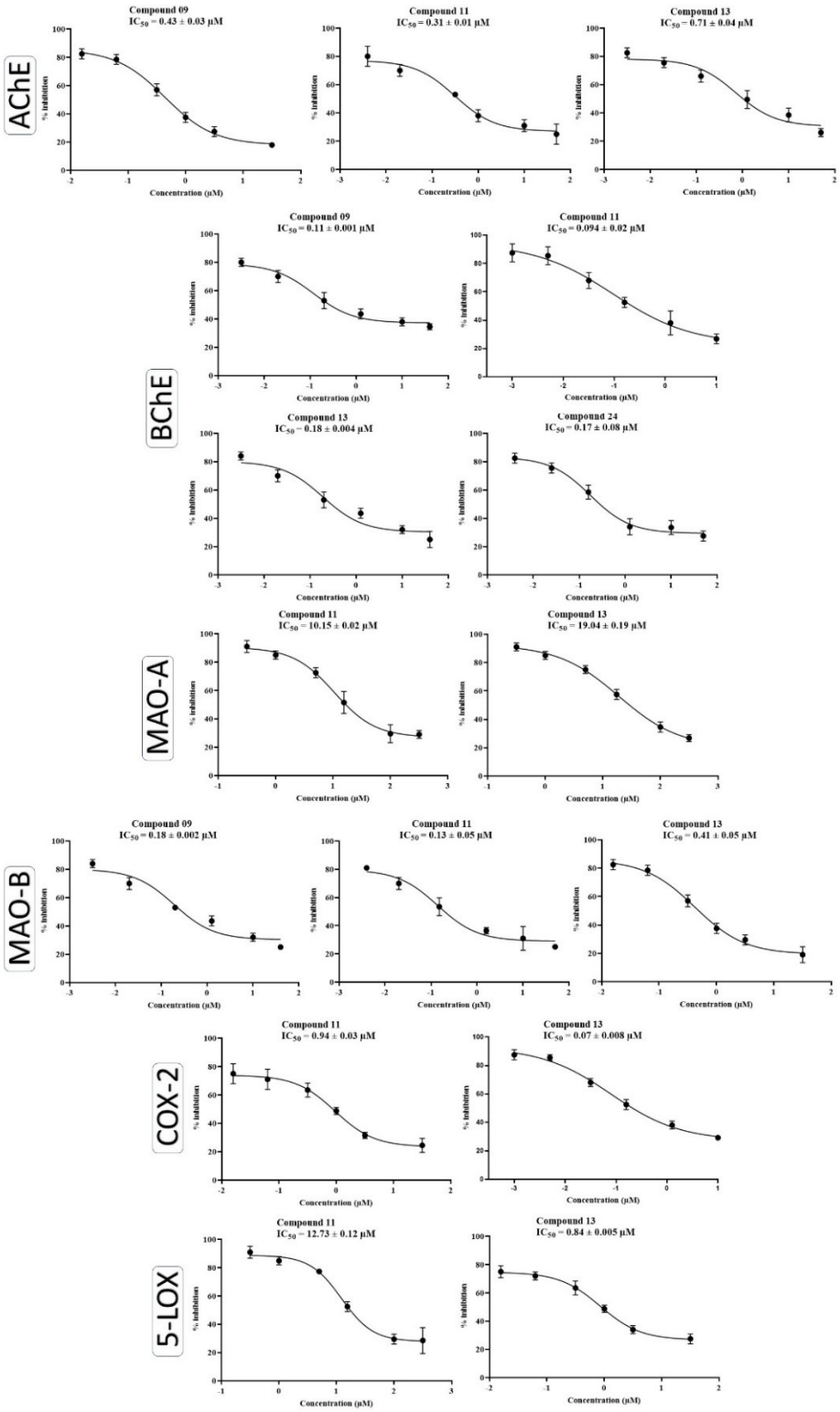

Figure S41: IC_{50} Graphs of most potent compounds

Results and Discussion

2.6. ADMET analysis

All compounds demonstrated significant gastrointestinal (GI) absorption, indicating their potential as promising candidates for therapeutic effects. Regarding the dynamics of drug action, many of the compounds exhibited the ability to inhibit crucial enzymes, specifically CYP2C19, CYP2C9, and CYP3A4. The comprehensive physicochemical and kinetic characteristics of these derivatives are outlined in Table S7.

Table S7. ADMET characteristics of synthesized hybrid compounds **9-11, 13, 15, 16-25.**

Molecule	9	10	11	13	15	16	17	18	19	20	21	22	23	24	25
MW	373.36	387.39	387.39	443.48	578.04	590.61	570.62	545.61	575.64	561.61	591.71	665.72	694.56	561.61	614.5
Number of Heavy atoms	28	29	29	32	41	43	42	40	42	41	42	49	46	41	42
Number of Aromatic heavy atoms	23	23	23	28	34	29	29	29	29	29	29	29	23	29	29
Number of H-bond acceptors	6	6	6	5	7	8	7	6	7	7	6	8	8	7	6
No of H-bond donors	3	2	4	4	2	3	3	3	3	4	3	3	3	4	3
MR	103.24	107.56	107.17	122.83	162.67	179.89	175.78	171.06	177.56	173.09	182.78	201.82	193.34	173.09	181.08
TPSA	108.47	97.47	126.29	162.89	139.54	182.28	160.25	136.46	145.69	156.69	161.76	162.76	162.76	156.69	136.46
iLOGP	2.58	3.44	2.38	2.92	4.45	2.93	3.4	3.93	4.02	3.54	3.96	4.13	3.71	3.63	4.15
XLOGP3	3.8	4.13	2.81	3.24	6.56	6.19	6.08	6.36	6.33	6	6.87	6.44	6.47	6	7.61
WLOGP	3.71	3.8	2.62	3.66	5.9	3.4	3.36	3.49	3.5	3.2	4.21	2.19	3.76	3.2	4.8
MLOGP	2.81	3.03	2.43	2.77	5.33	4.05	4.2	4.84	4.53	4.34	5.3	5.15	4.9	4.34	5.76
GI absorption	High	High	High	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low
BBB permeant	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No
Pgp substrate	No	No	No	No	No	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	No
CYP1A2 inhibitor	No	No	Yes	No	No	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
CYP2C19 inhibitor	No	No	No	No	No	Yes	Yes	Yes	Yes	Yes	Yes	No	No	Yes	Yes
CYP2C9 inhibitor	No	Yes	No	No	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
CYP2D6 inhibitor	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No
CYP3A4 inhibitor	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No
Bioavailability Score	0.56	0.55	0.55	0.55	0.17	0.17	0.17	0.17	0.17	0.17	0.17	0.17	0.17	0.17	0.17
Synthetic Accessibility	2.95	3.06	3.04	3.42	4.5	5.1	5.05	5	5.11	5.05	5.12	6.3	6.1	5.03	5.02

Figure S42 presents a radar chart illustrating the ADMET properties of synthesized hybrid compounds **9-11, 13, 15, and 16-25**. Each parameter is represented on an individual axis, with data points interconnected to create a polygon, thereby offering a visual summary of the comprehensive pharmacokinetic profile. The Swiss-Target Prediction tool was utilized to identify potential protein targets, with rankings determined by probability scores, as shown in Figure 12.

A higher score signifies an increased probability of the molecule interacting with the designated protein target. The results were cross-validated with experimental data to establish a conclusive understanding. Experimental data indicate that nearly all synthesized hybrid derivatives may function as potential inhibitors of specific isozymes.

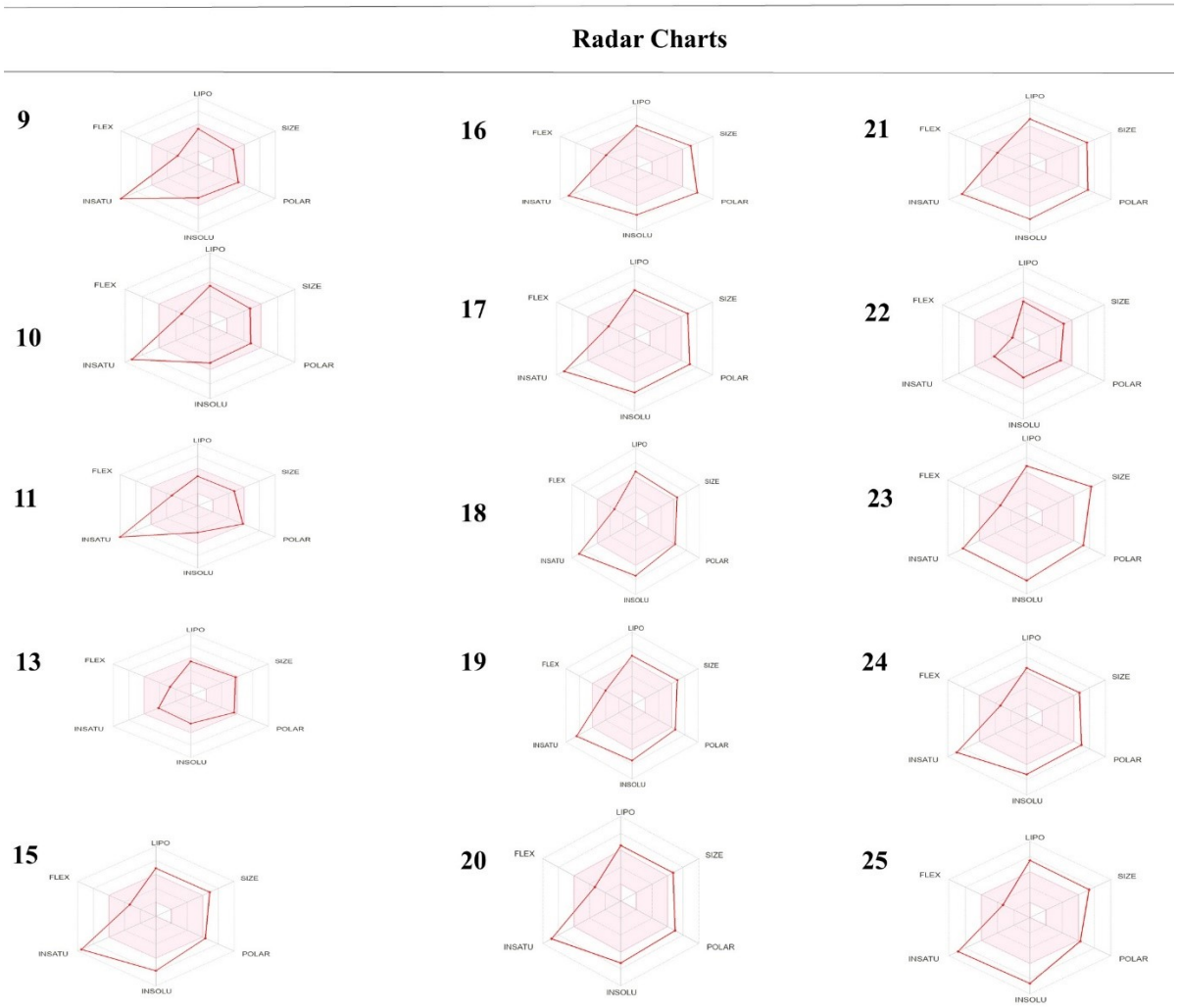

Figure S43. Radar charts describing physicochemical and pharmacokinetic properties of synthesized hybrid compounds along with predicted protein targets of compounds **9-11, 13, 15, 16-25**

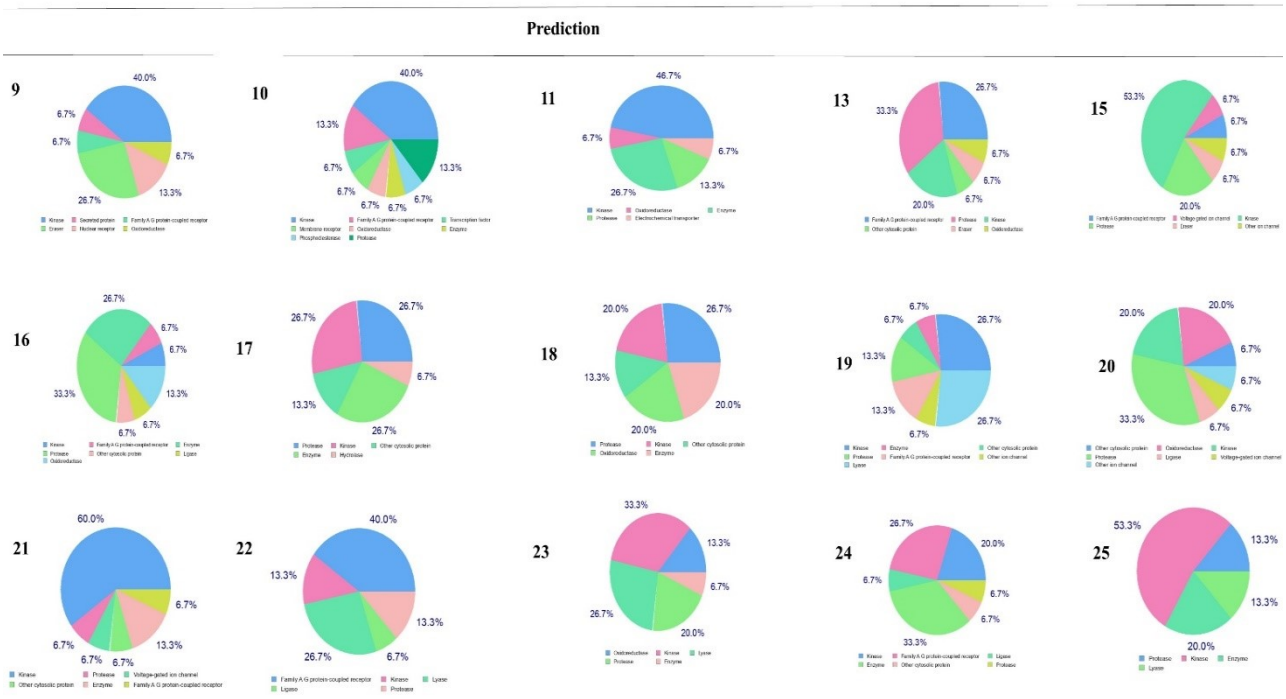

Figure S44. Predictions describing physicochemical and pharmacokinetic properties of synthesized hybrid compounds alongwith predicted protein targets of compounds **9-11, 13, 15, 16-25**

The boiled egg diagram (Figure S33) provides a visual representation that may be used to visualize drug-likeness qualities, especially when it comes to blood-brain barrier (BBB) permeability. None of the substances under investigation could pass across the blood-brain barrier.

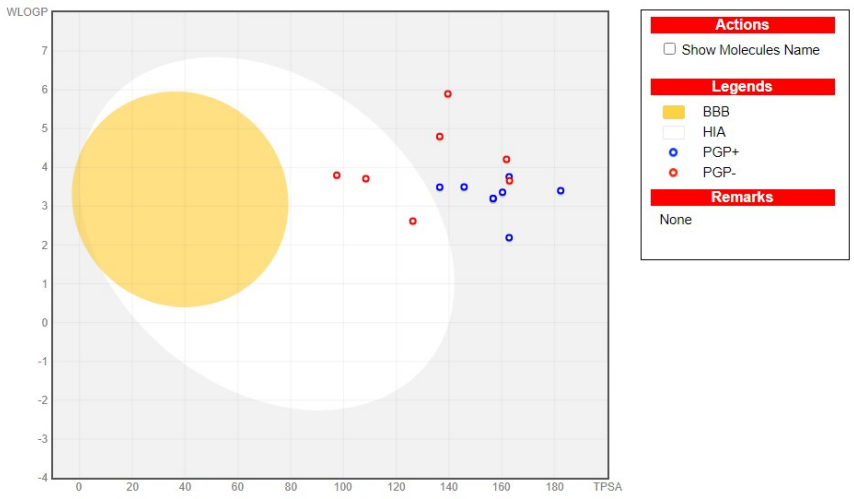

Figure S45. Boiled egg diagram for derivatives compounds **9-11, 13, 15, 16-25**