Electronic Supporting Information

for

Synthesis, Structural Characterization, Anticancer Evaluation, and Computational Studies of Novel Quinoline-1,2,3-Triazole Glycohybrids

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Corresponding author email. divyakush.mmvbhu@ac.in

1. NMR and HRMS spectra of Compounds

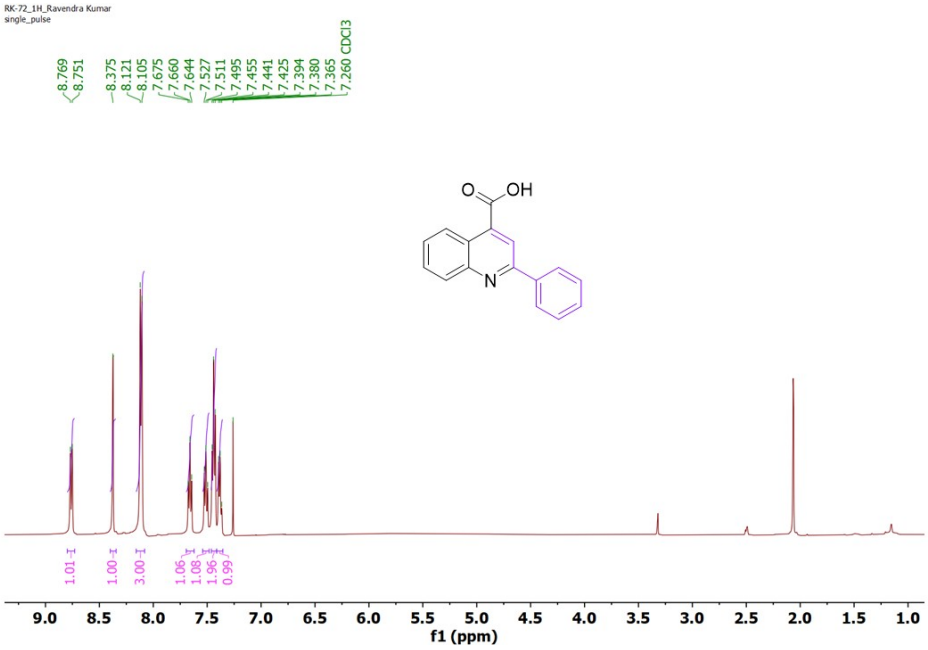


Fig. S1: ^{1}H NMR spectrum of **3a**

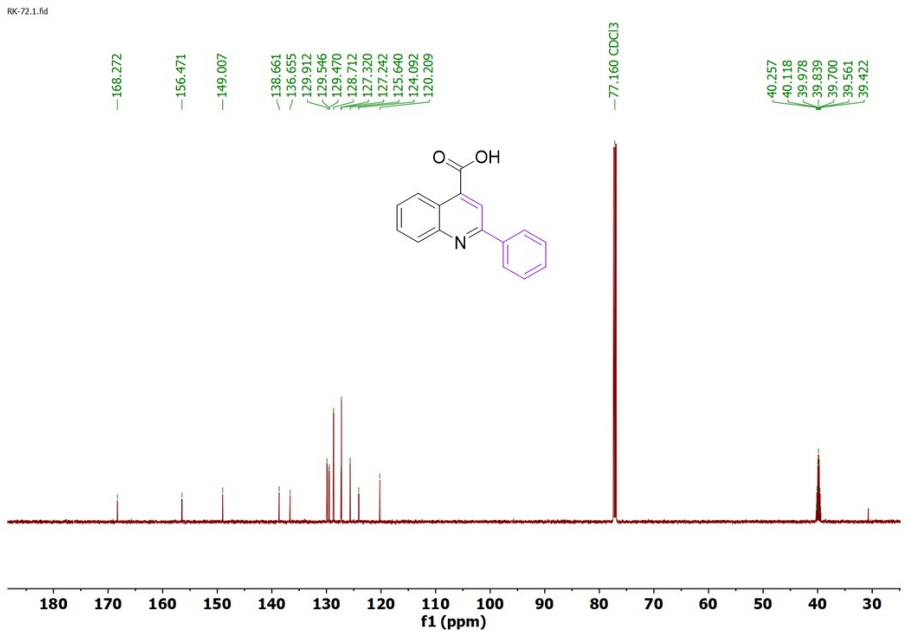


Fig. S2: ^{13}C NMR spectrum of **3a**

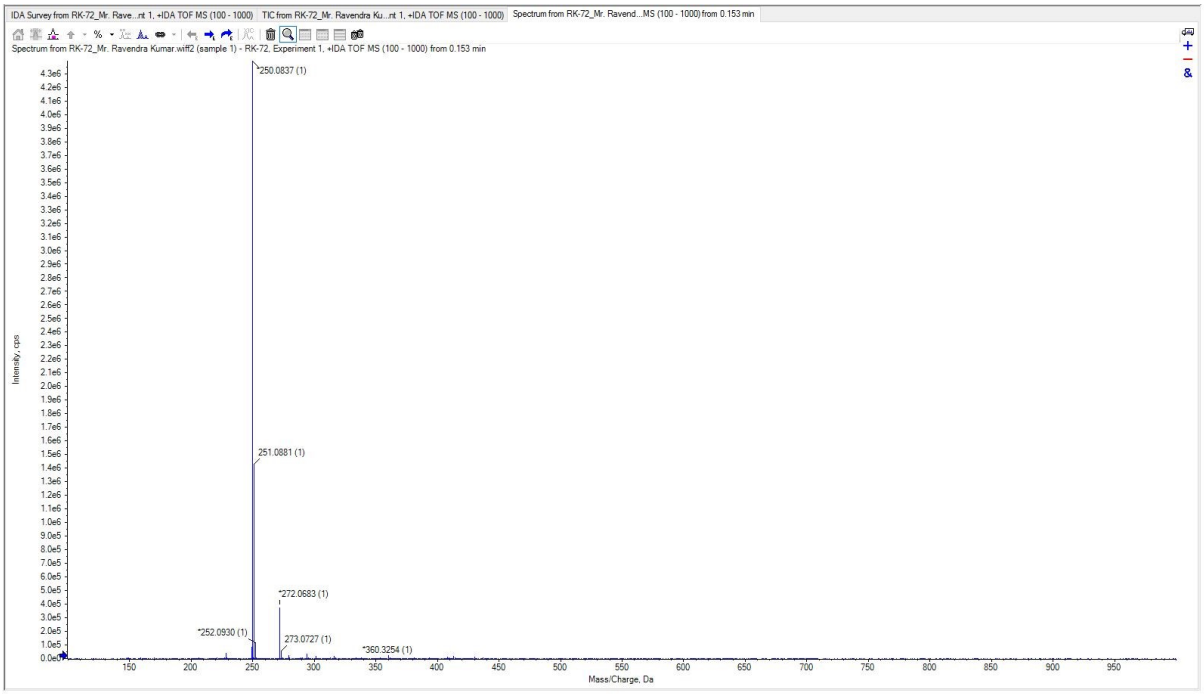


Fig. S3: HRMS spectrum of **3a**

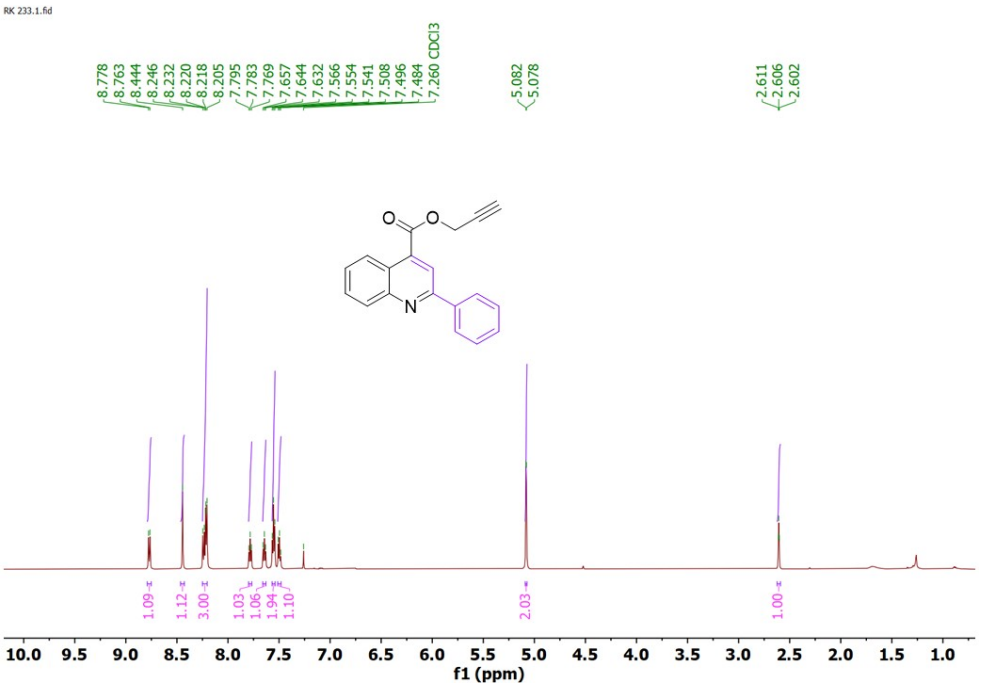


Fig. S4: ^{1}H NMR spectrum of **4a**

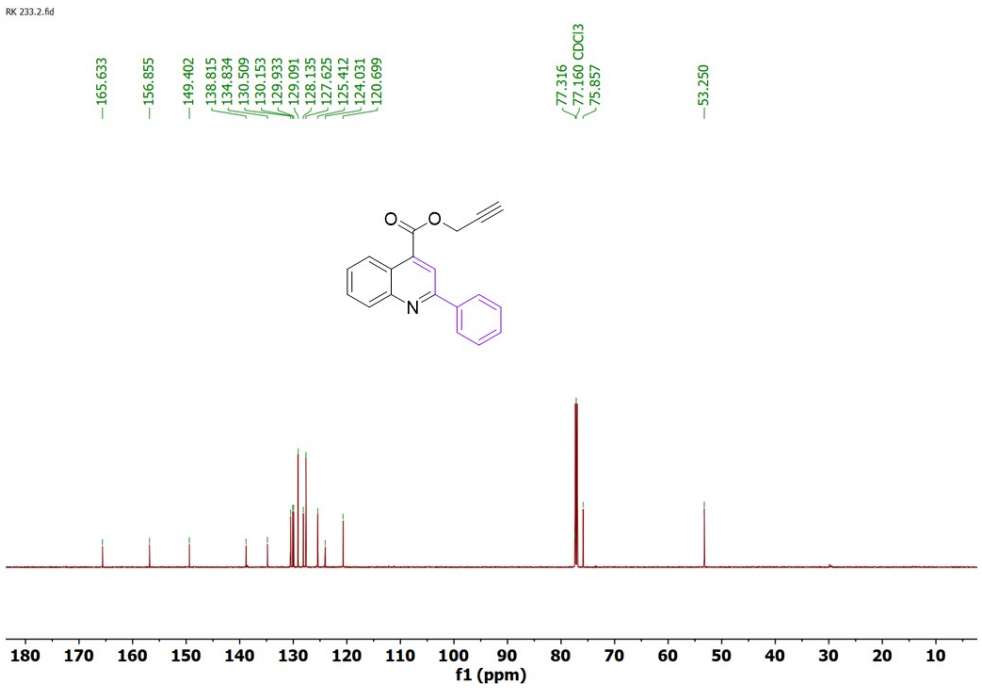


Fig. S5: ^{13}C NMR spectrum of **4a**

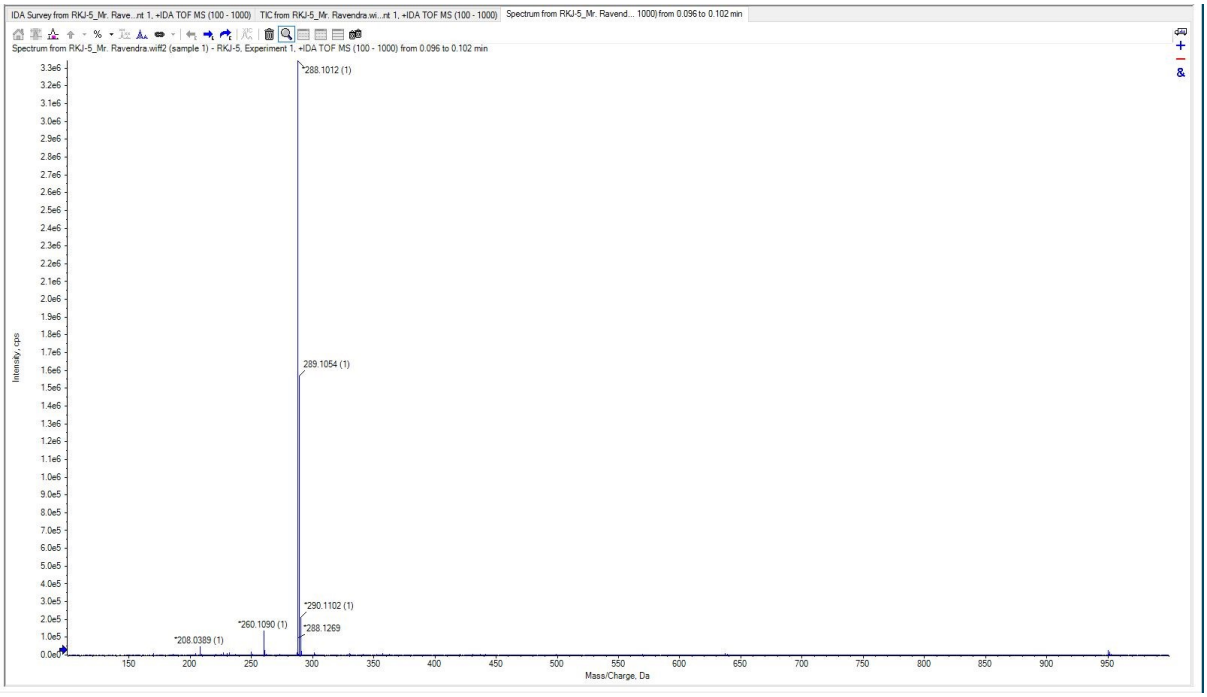


Fig. S6: HRMS spectrum of **4a**

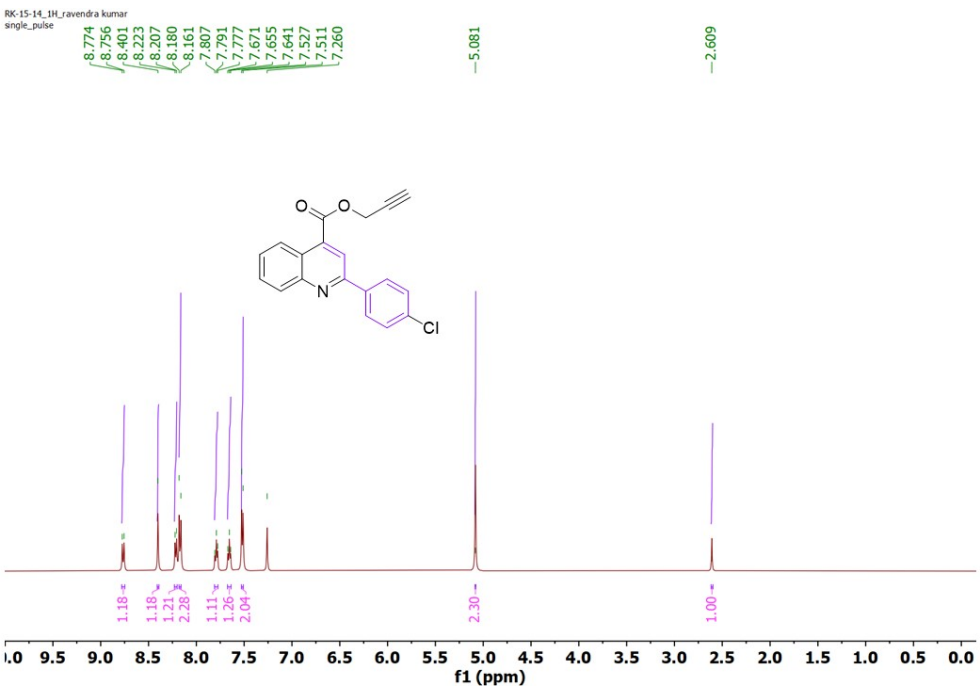


Fig. S7: ^{1}H NMR spectrum of **4b**

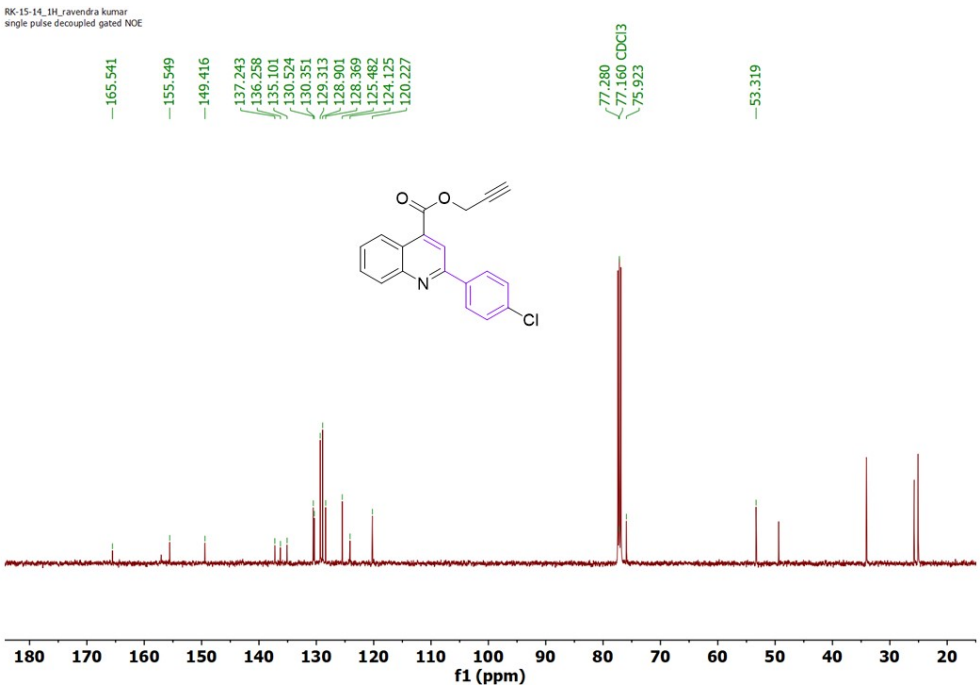


Fig. S8: ^{13}C NMR spectrum of **4b**

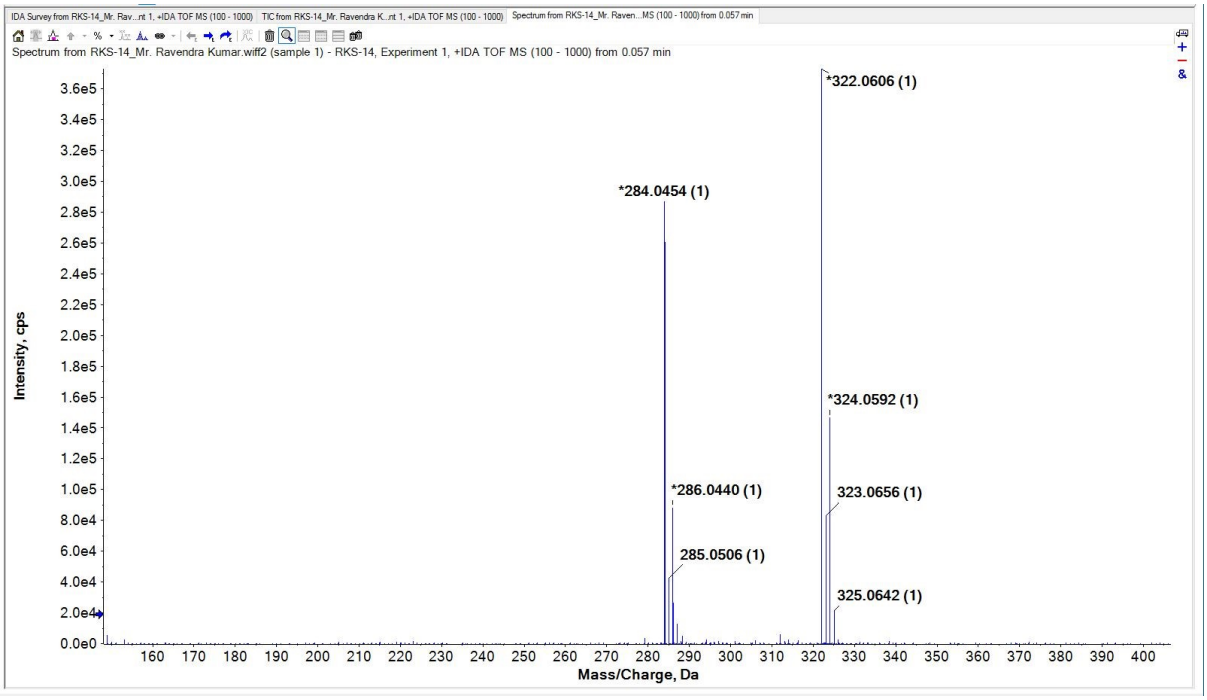


Fig. S9: HRMS spectrum of **4b**

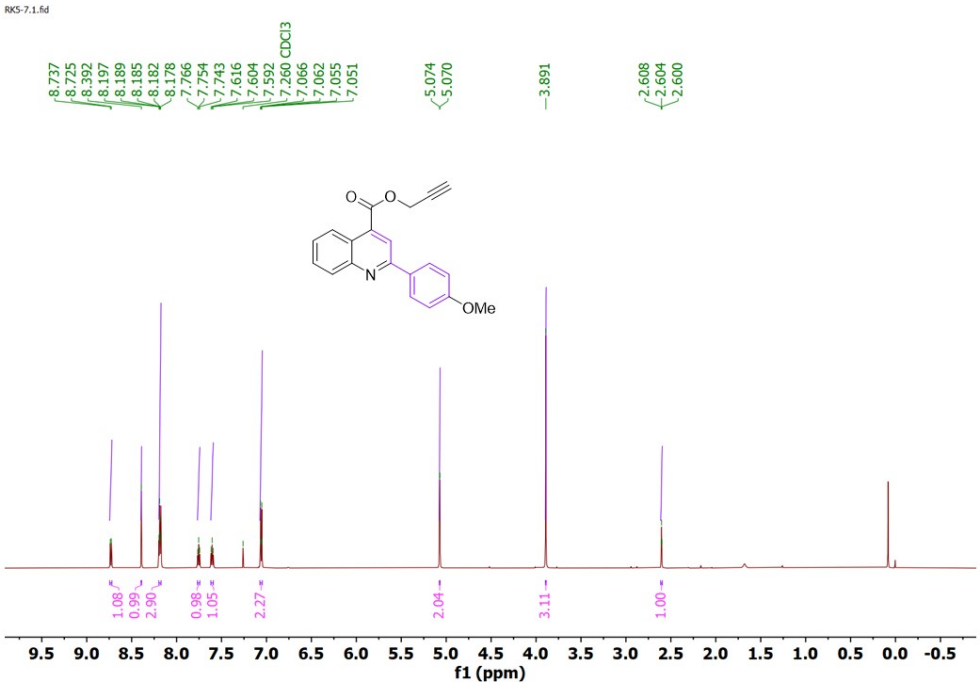


Fig. S10: ^{1}H NMR spectrum of **4c**

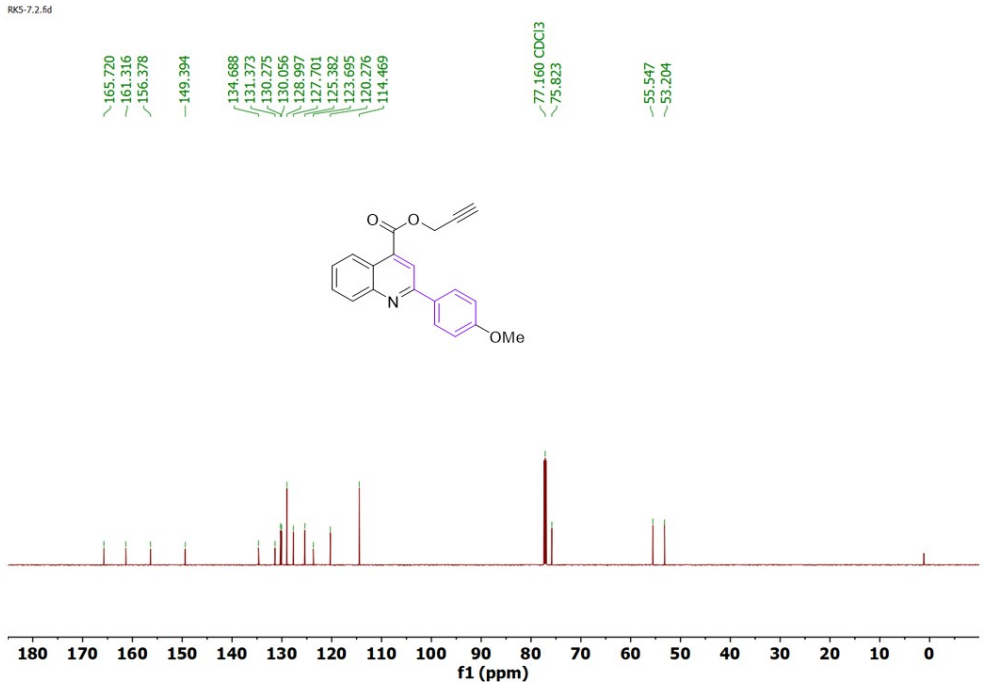


Fig. S11: ^{13}C NMR spectrum of **4c**

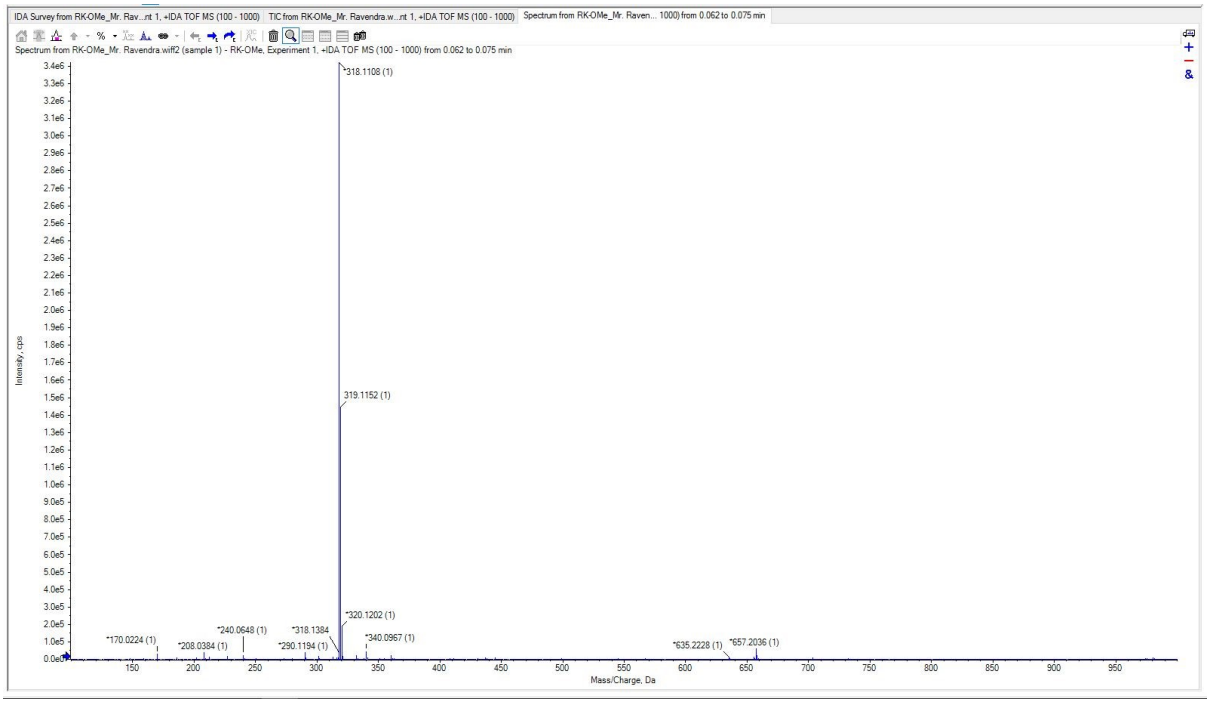


Fig. S12: HRMS spectrum of **4c**

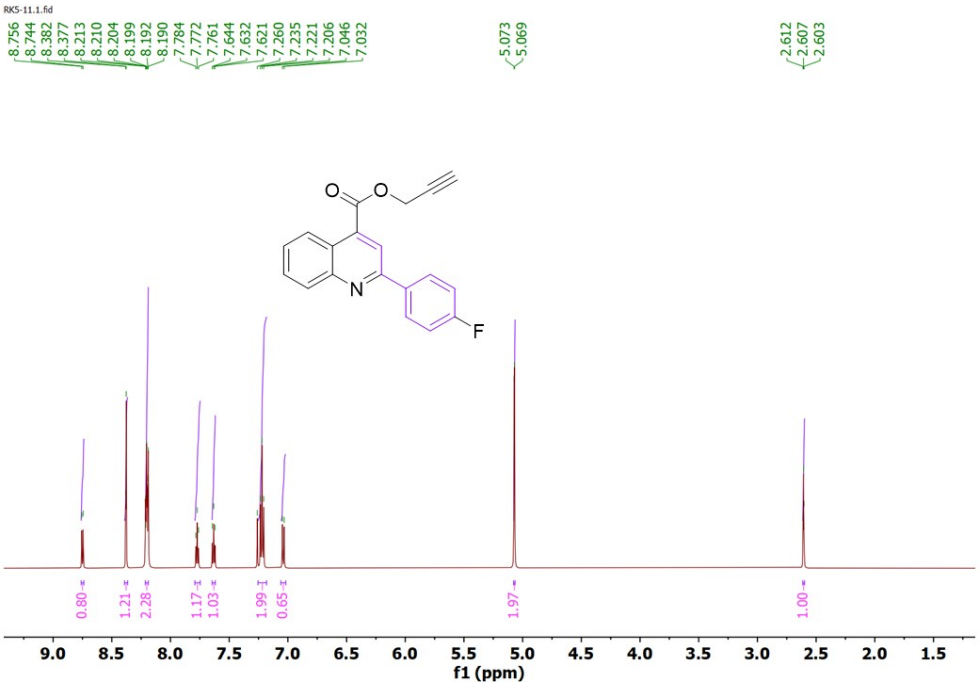


Fig. S13: ^{1}H NMR spectrum of **4d**

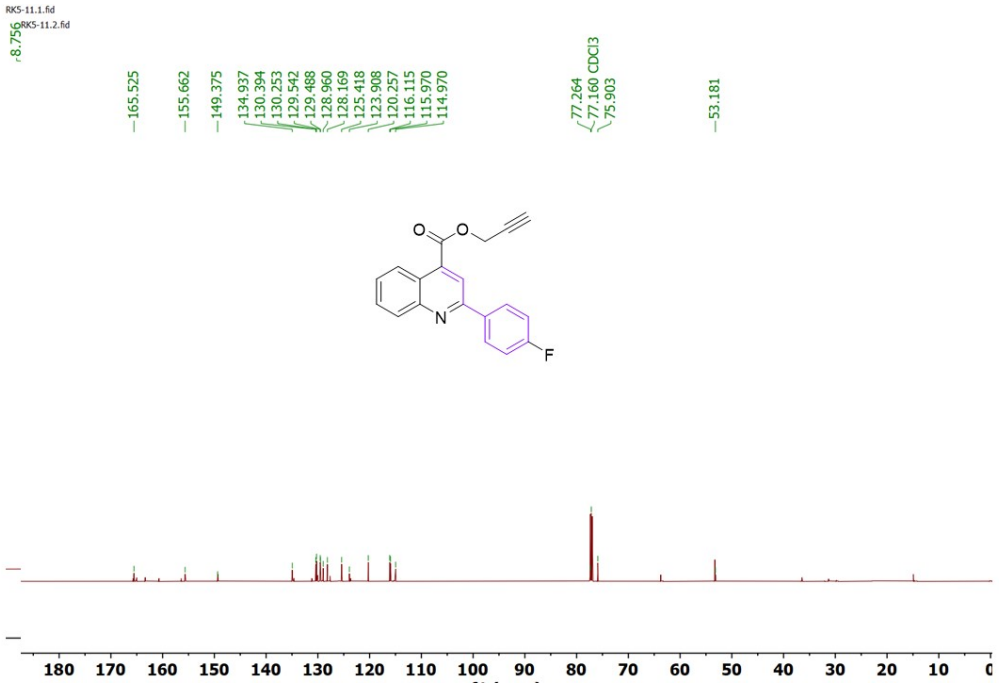


Fig. S14: ^{13}C NMR spectrum of **4d**

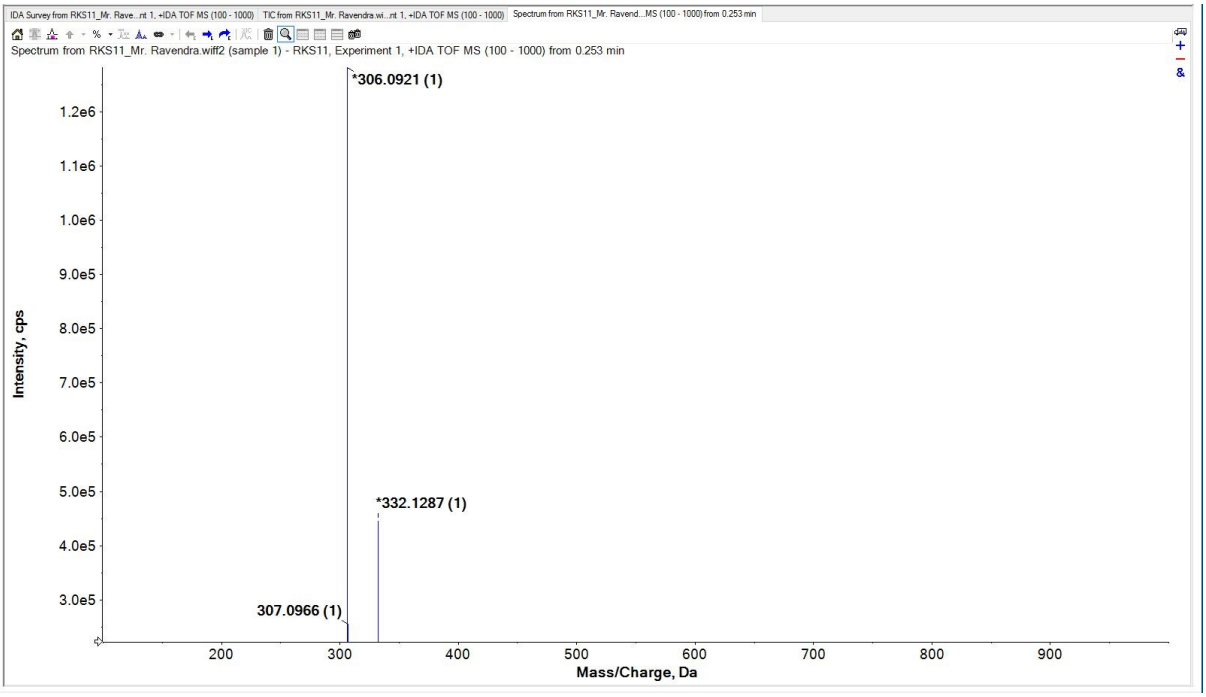


Fig. S15: HRMS spectrum of **4d**

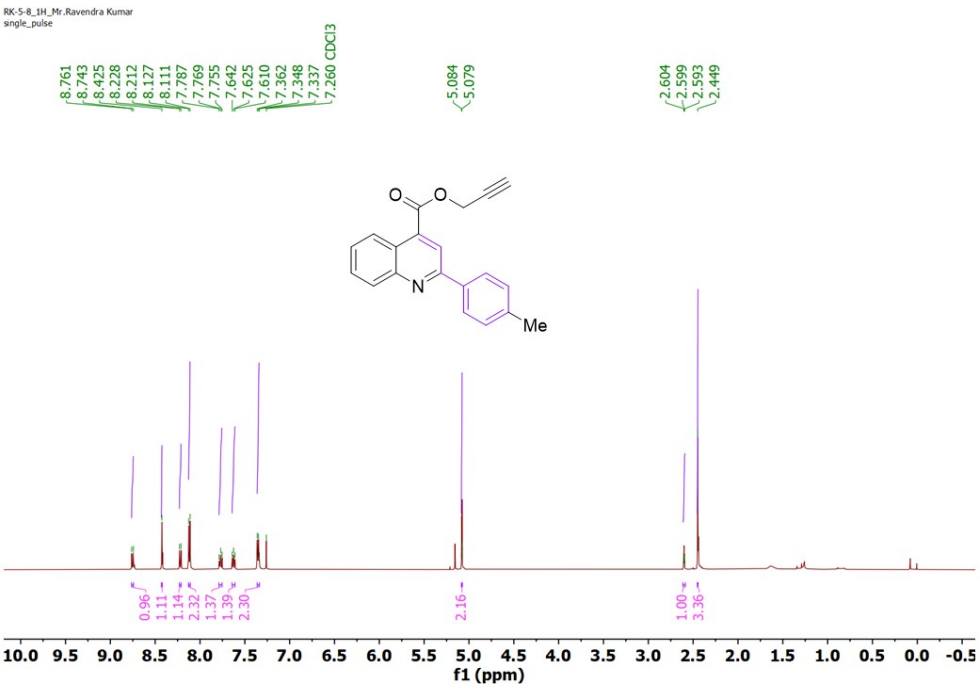


Fig. S16: ^{1}H NMR spectrum of **4e**

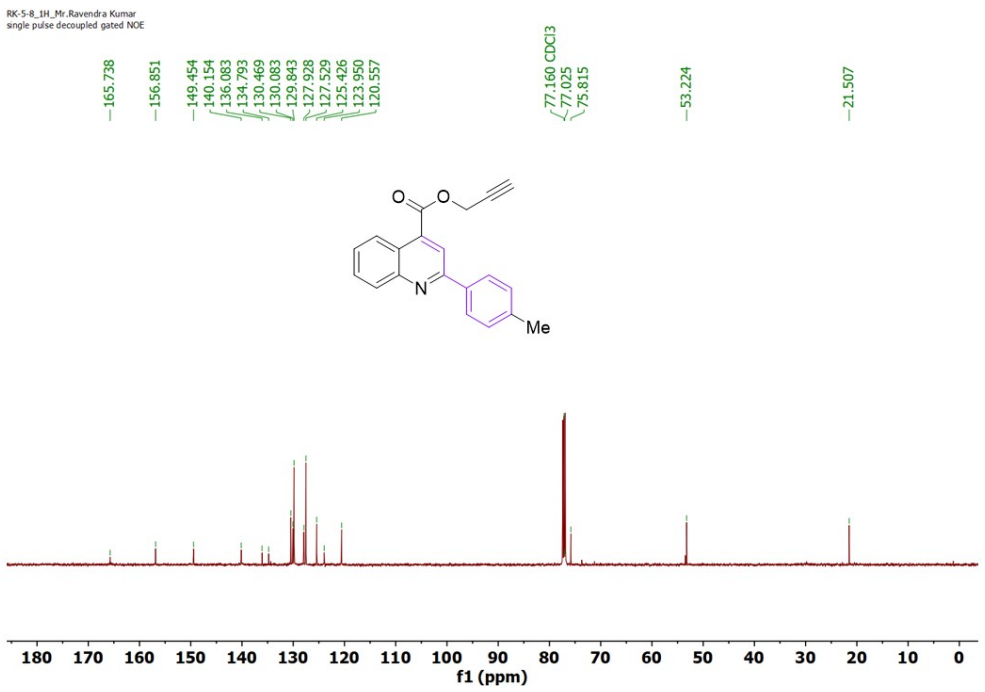


Fig. S17: ^{13}C NMR spectrum of **4e**

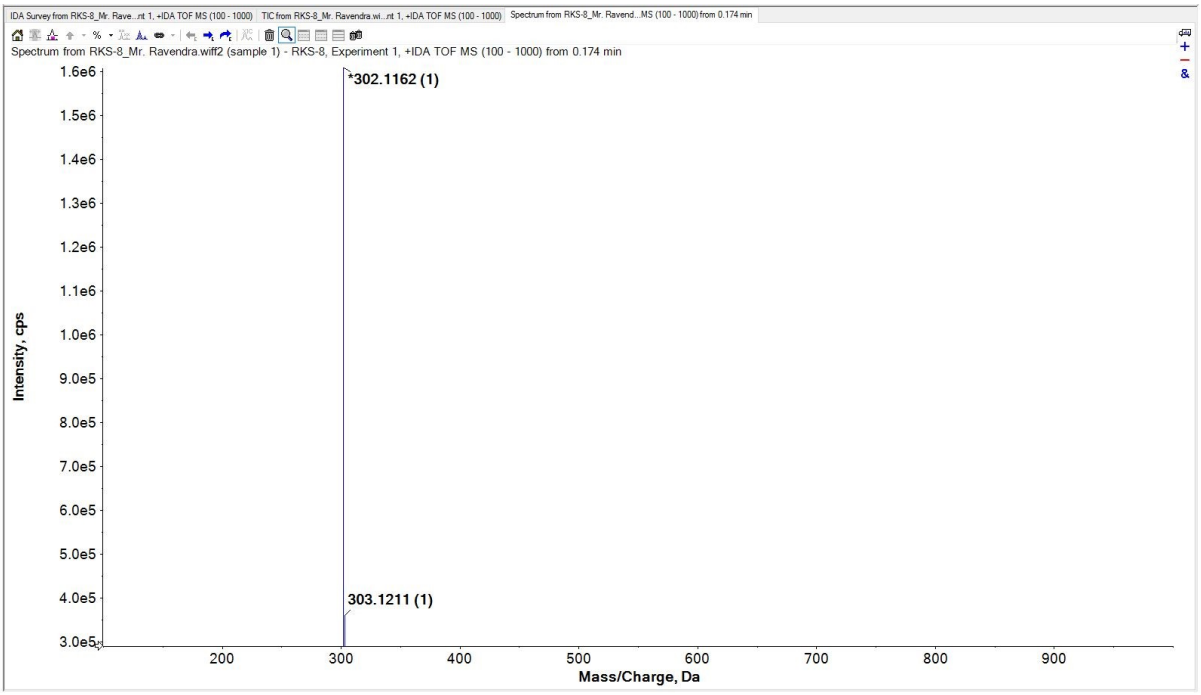


Fig. S18: HRMS spectrum of **4e**

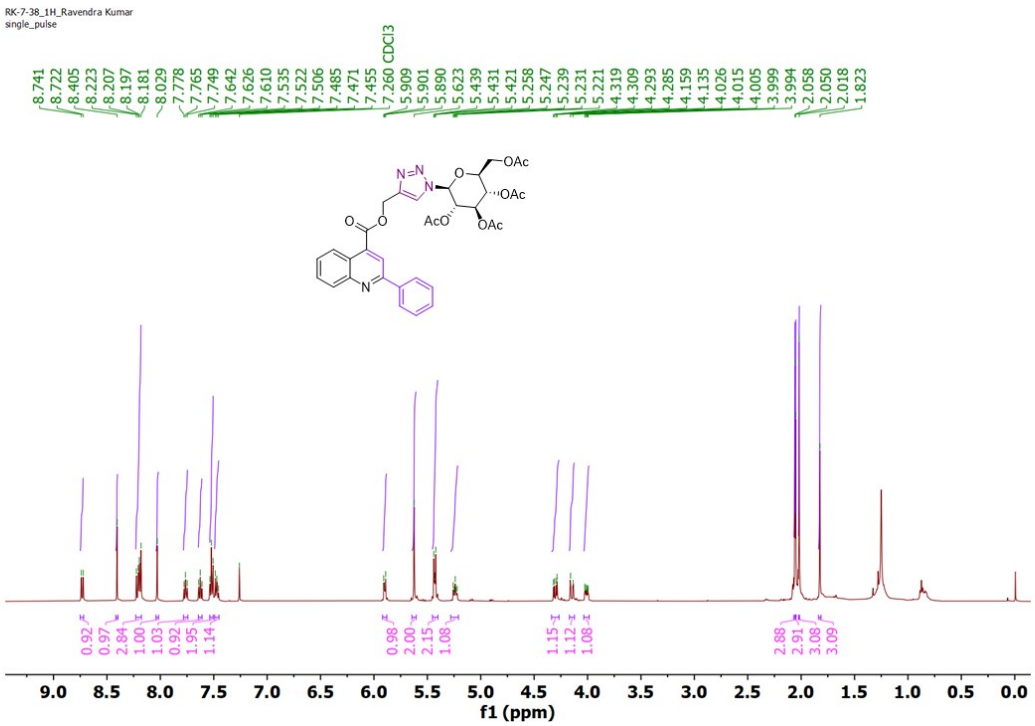


Fig. S19: ^{1}H NMR spectrum of **6a**

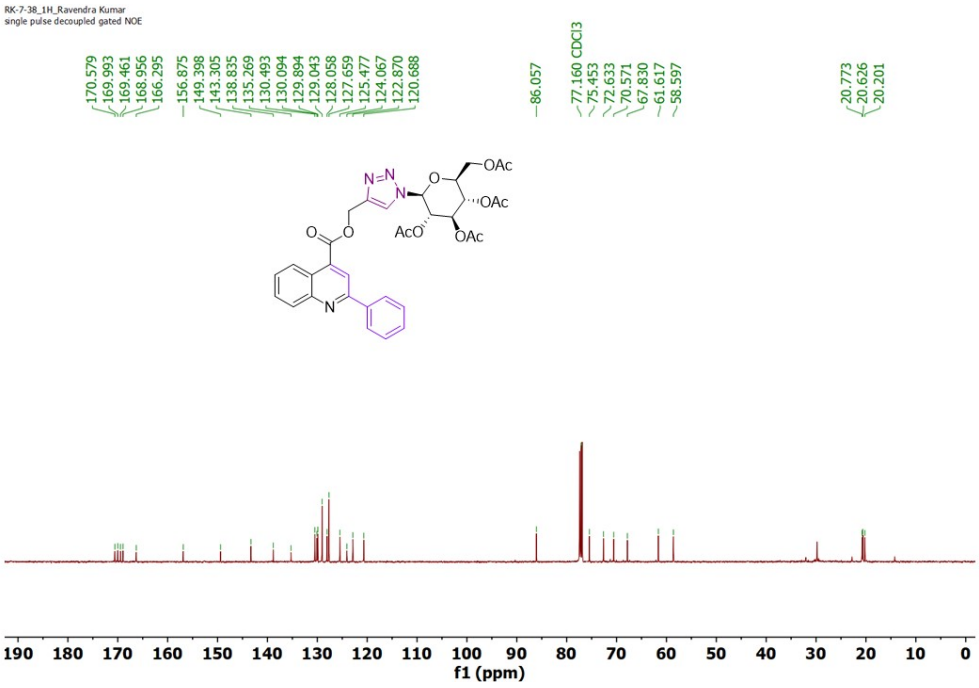


Fig. S20: ^{13}C NMR spectrum of **6a**

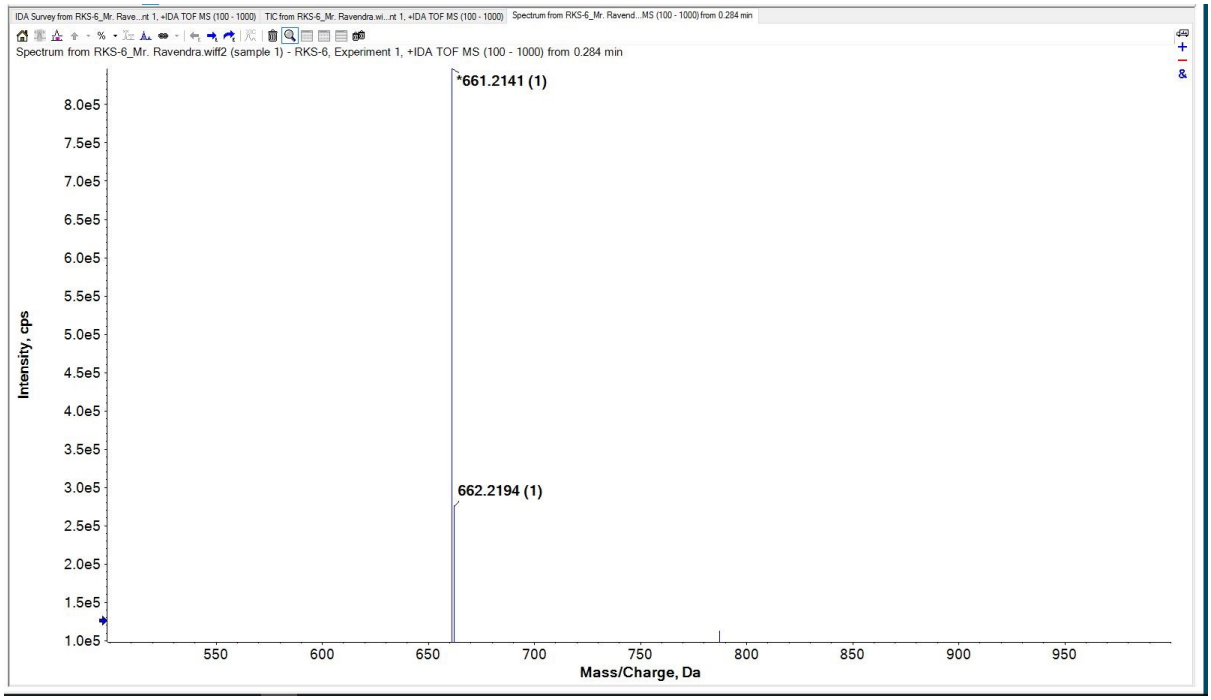


Fig. S21: HRMS spectrum of **6a**

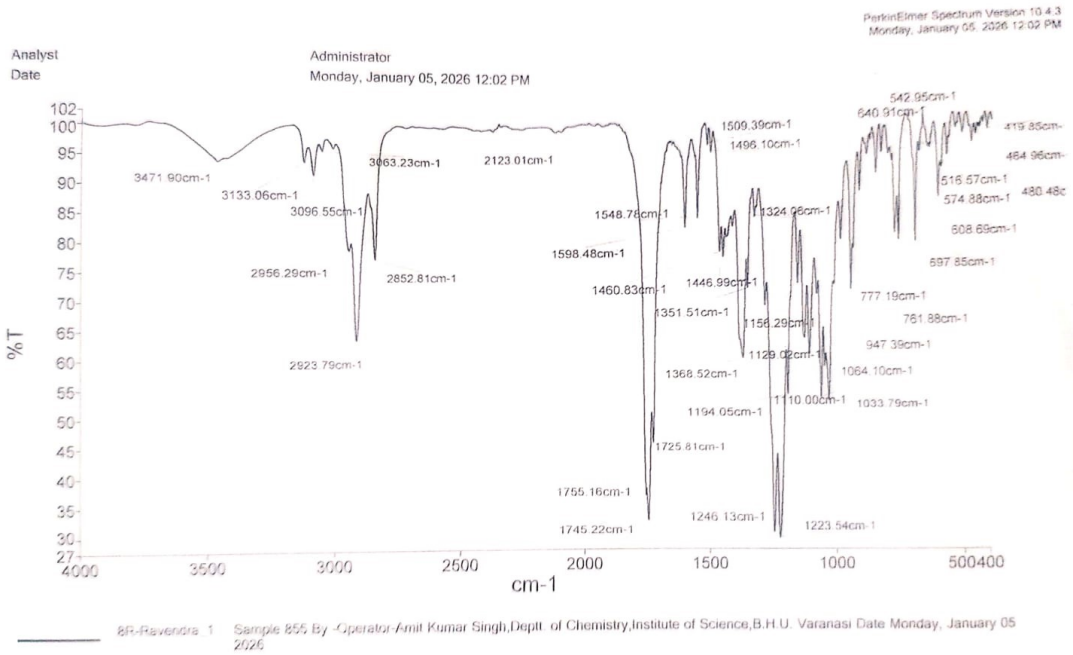


Fig. S22: FT-IR spectrum of **6a**

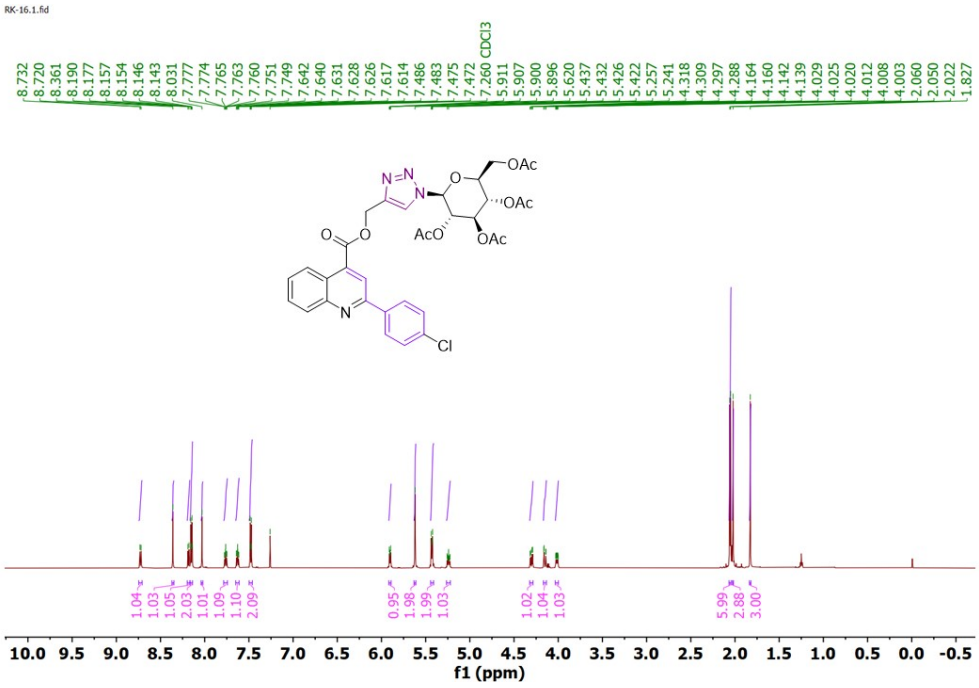


Fig. S23: ^{1}H NMR spectrum of **6b**

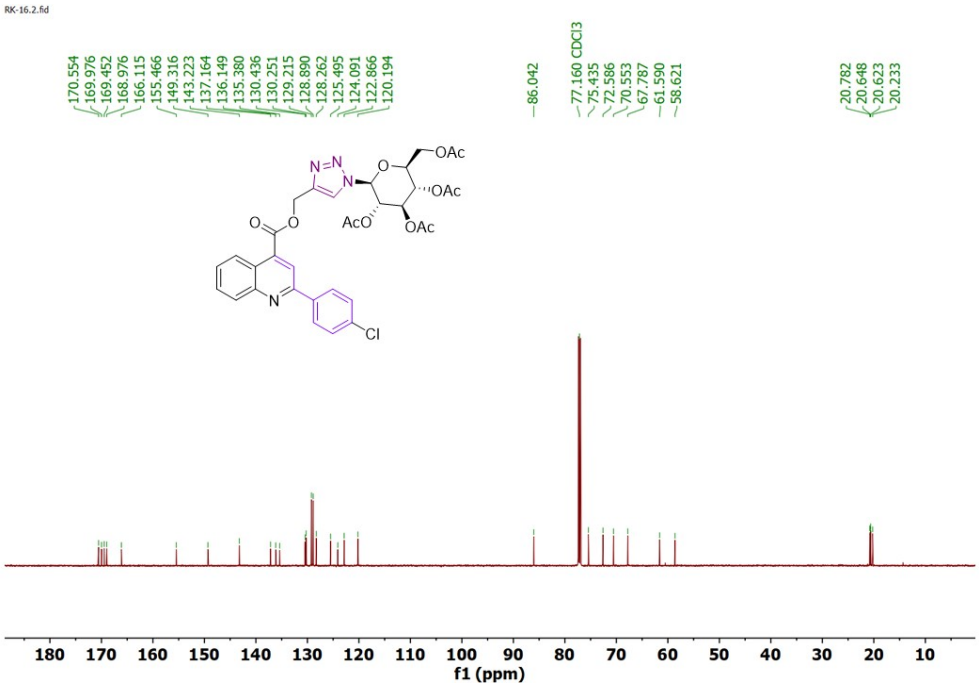


Fig. S24: ^{13}C NMR spectrum of **6b**

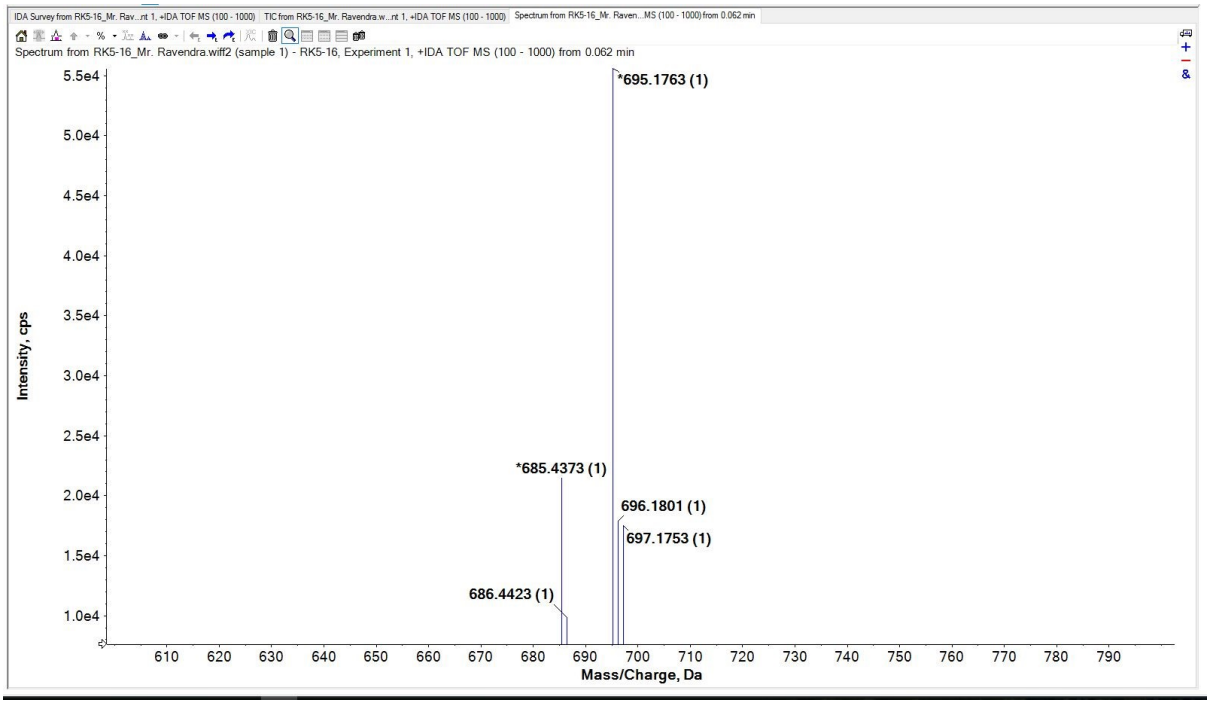


Fig. S25: HRMS spectrum of **6b**

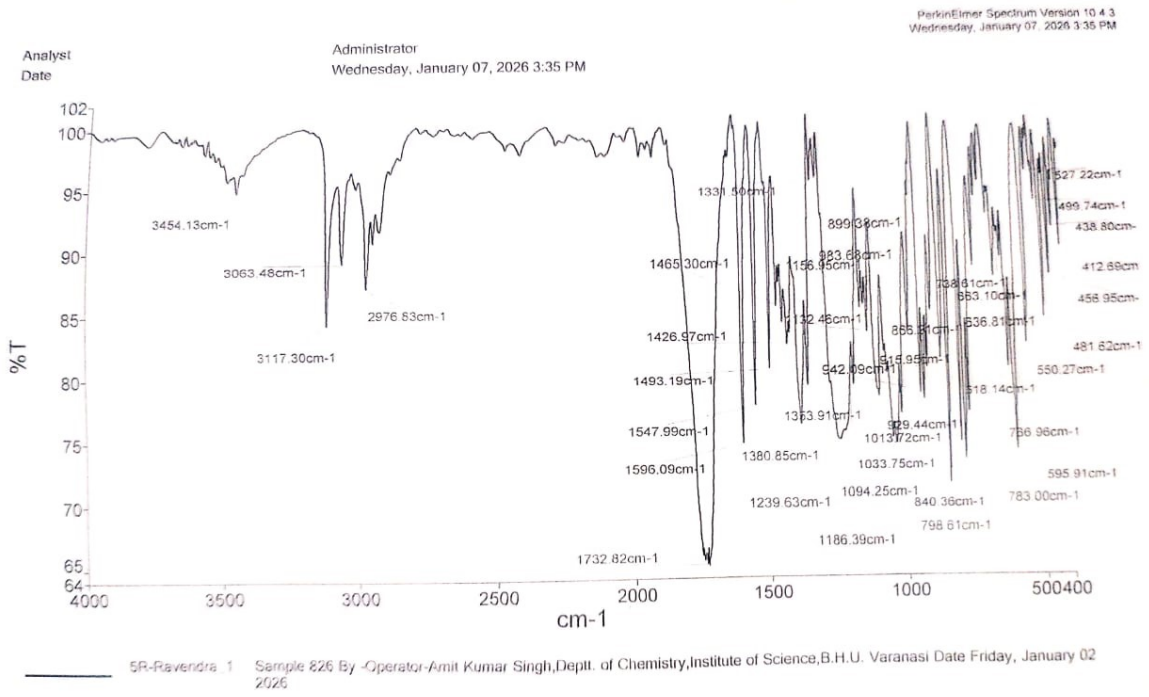


Fig. S26: FT-IR spectrum of **6b**

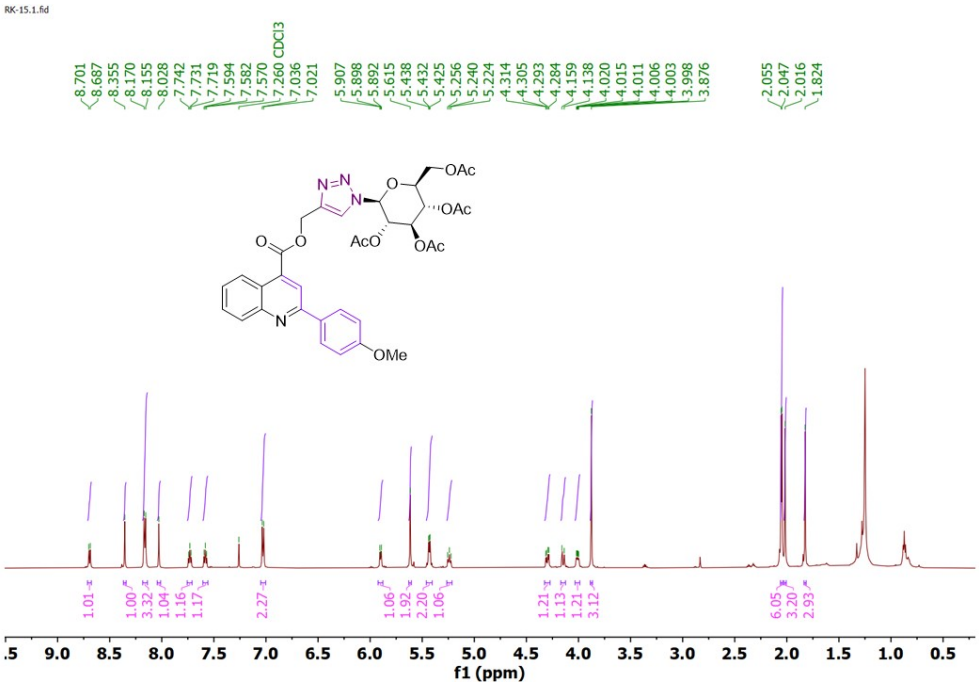


Fig. S27: ^{1}H NMR spectrum of **6c**

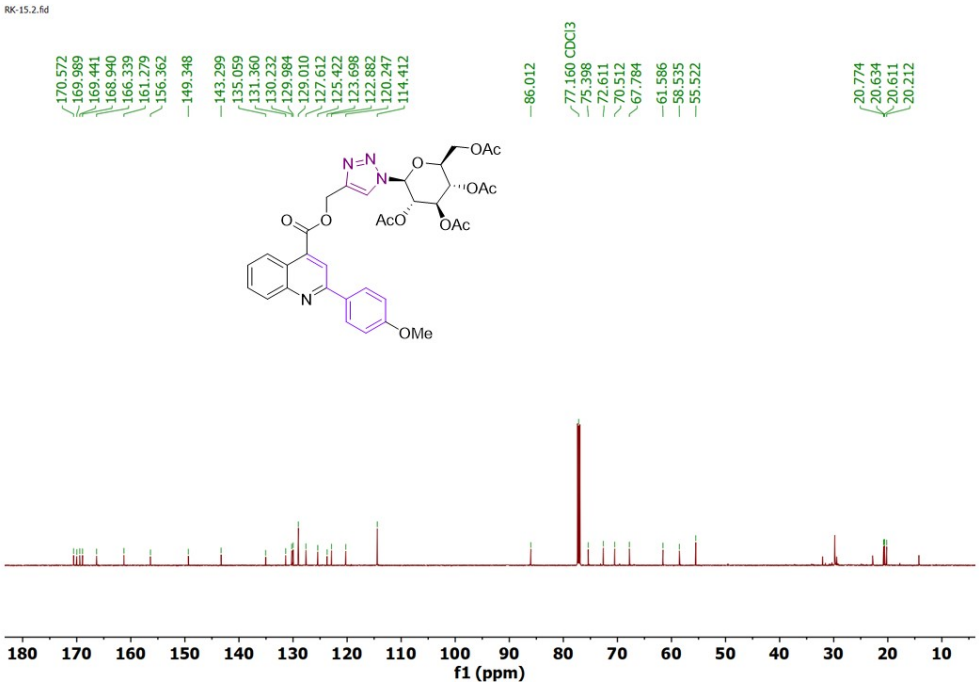


Fig. S28: ^{13}C NMR spectrum of **6c**

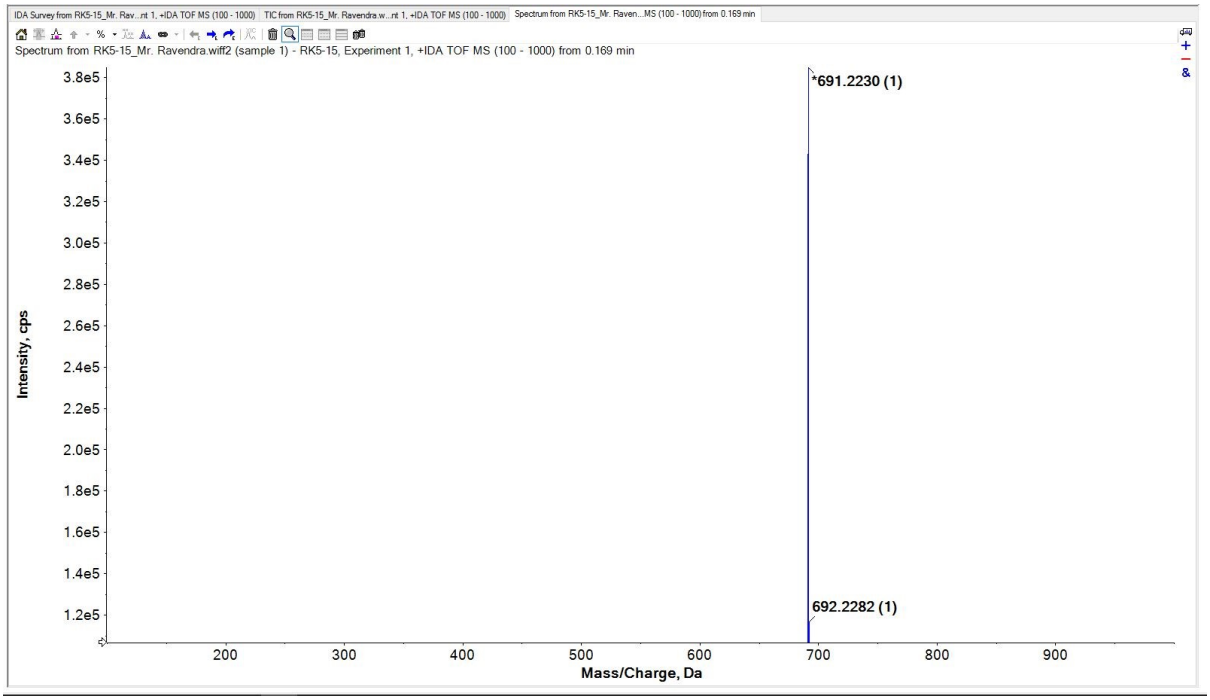


Fig. S29: HRMS spectrum of **6c**

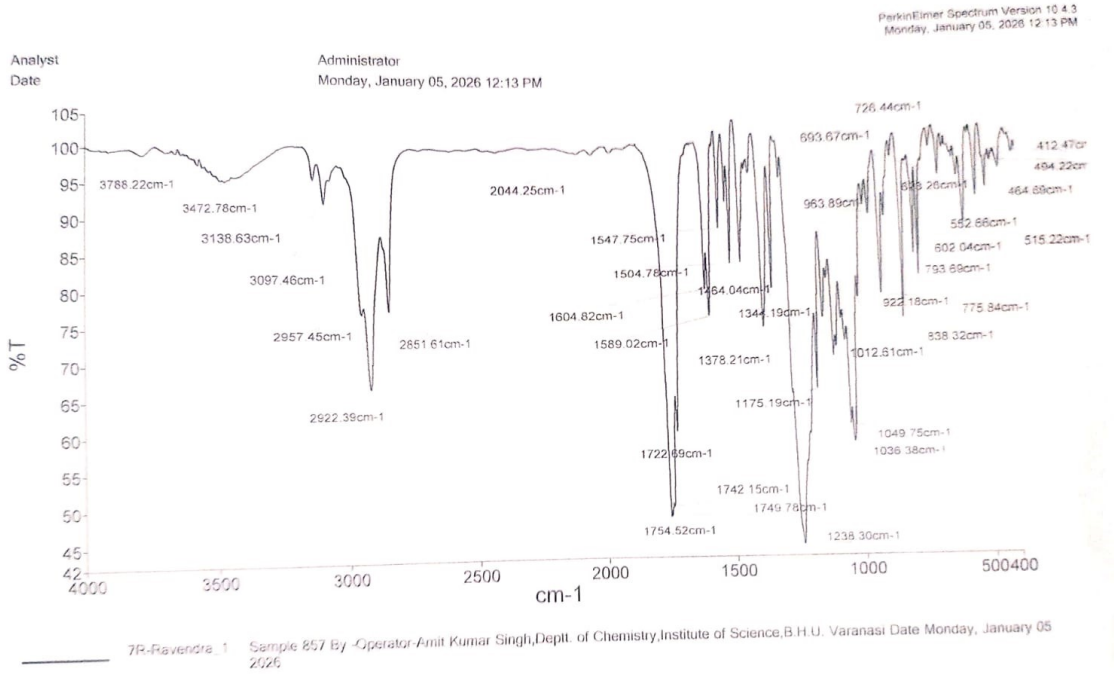


Fig. S30: FT-IR spectrum of **6c**

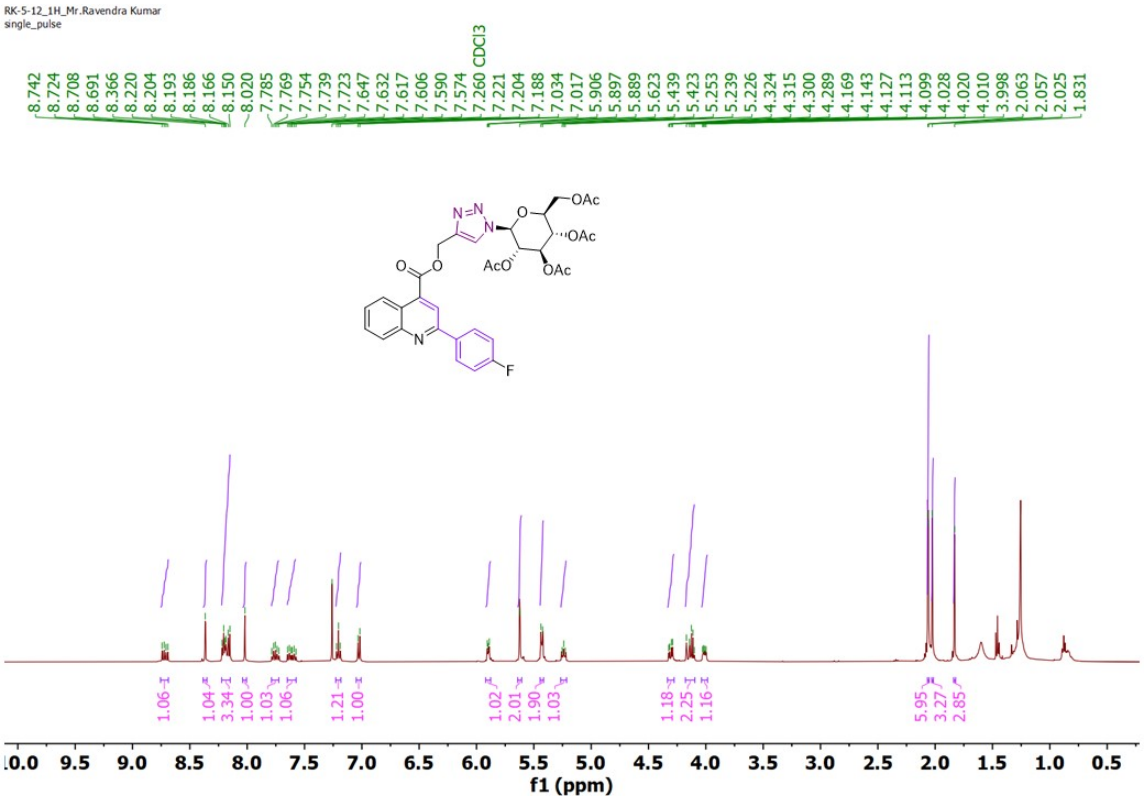


Fig. S31: ^{1}H NMR spectrum of **6d**

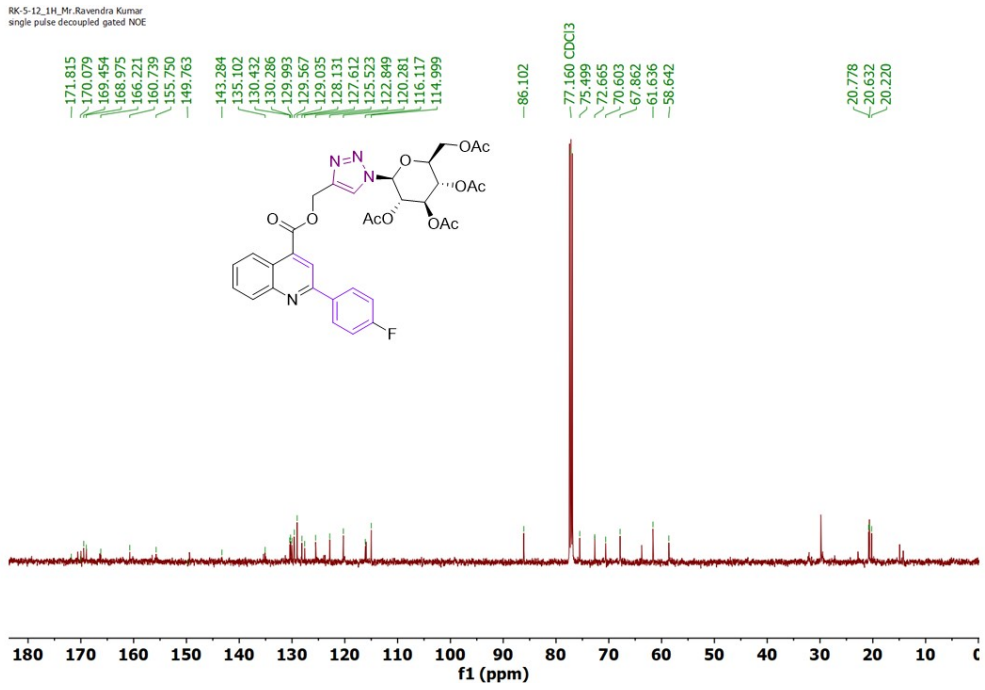


Fig. S32: ^{13}C NMR spectrum of **6d**

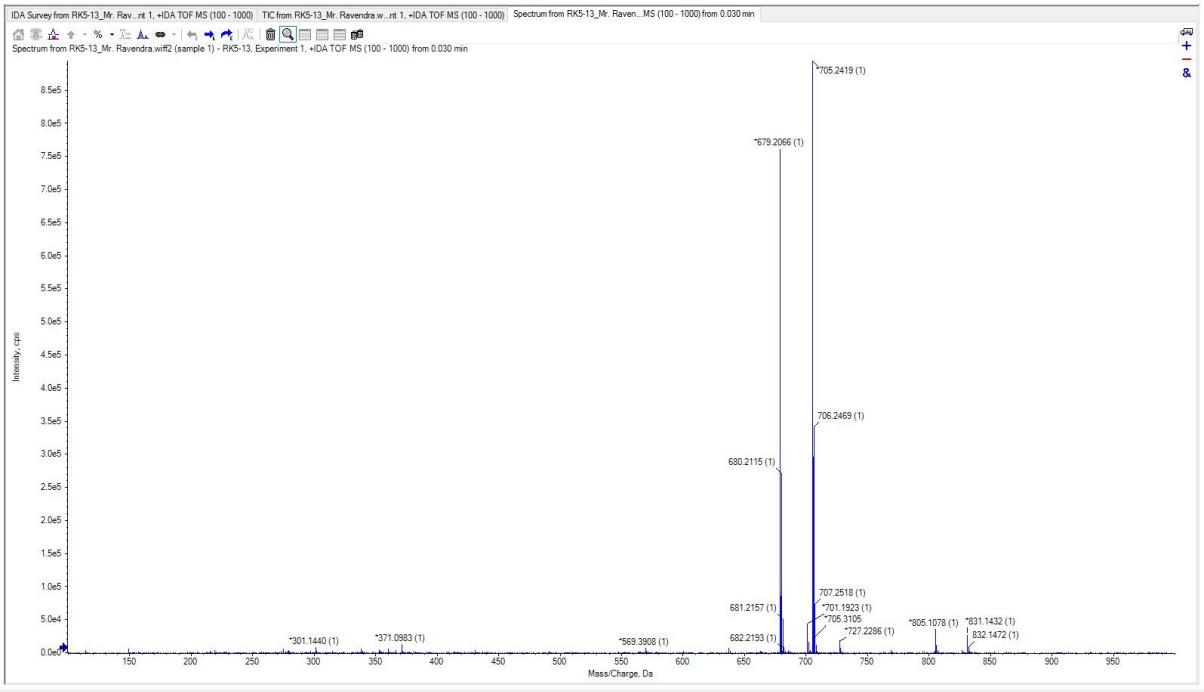


Fig. S33: HRMS spectrum of **6d**

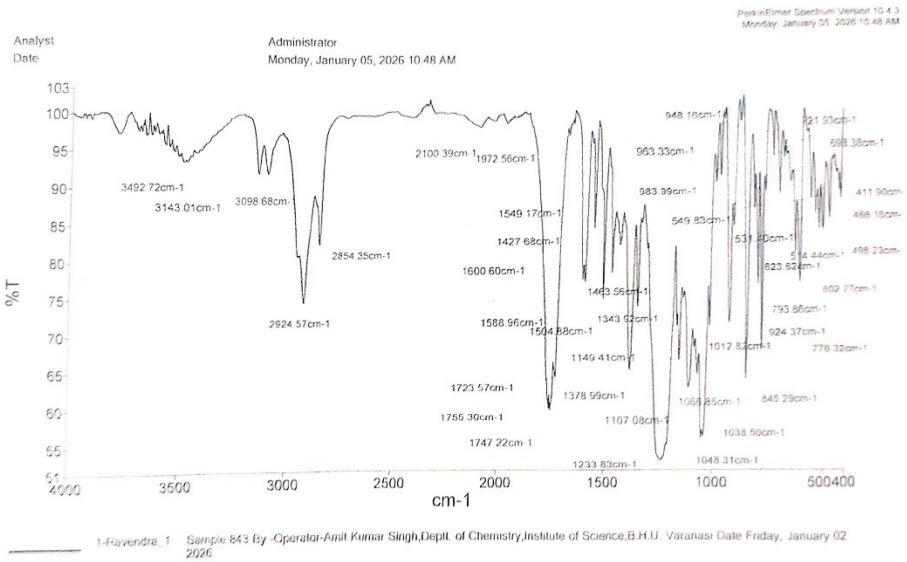


Fig. S34: FT-IR spectrum of **6d**

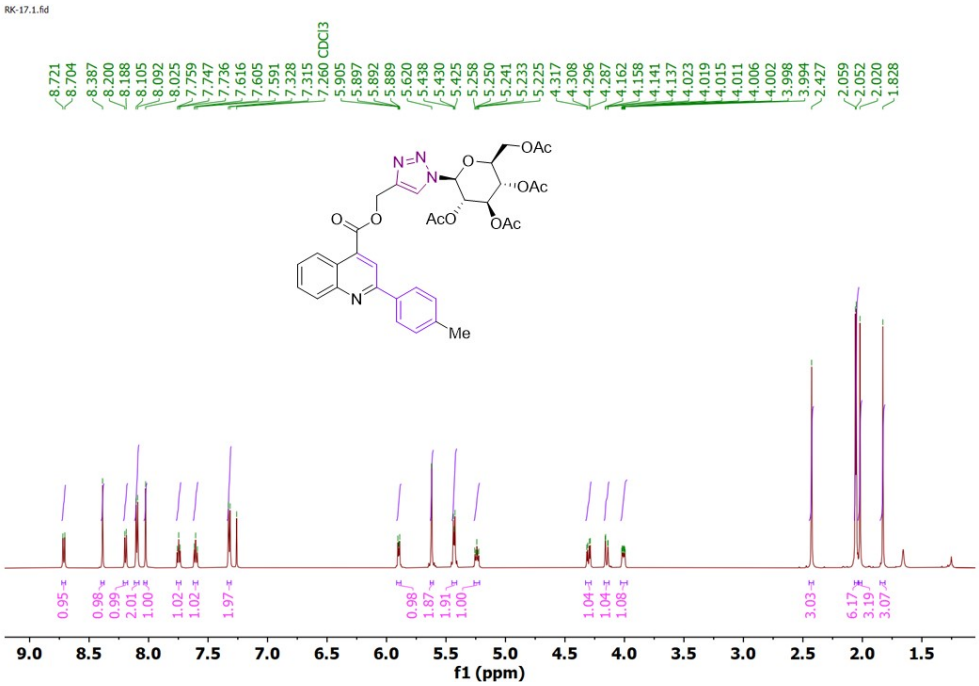


Fig. S35: ^{1}H NMR spectrum of **6e**

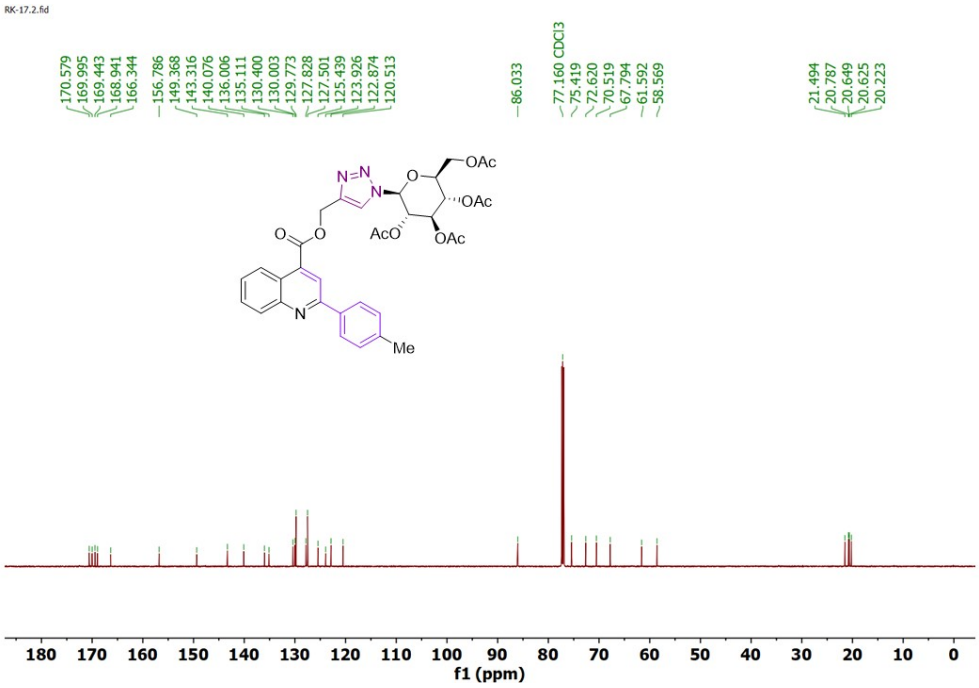


Fig. S36: ^{13}C NMR spectrum of **6e**

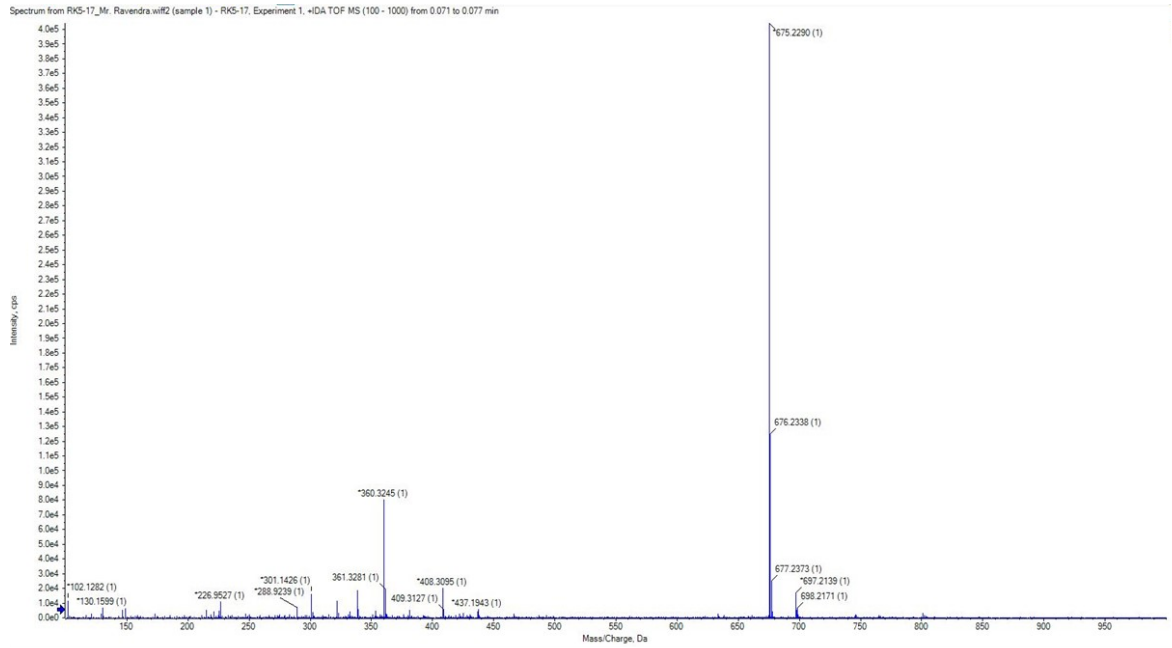


Fig. S37: HRMS spectrum of **6e**

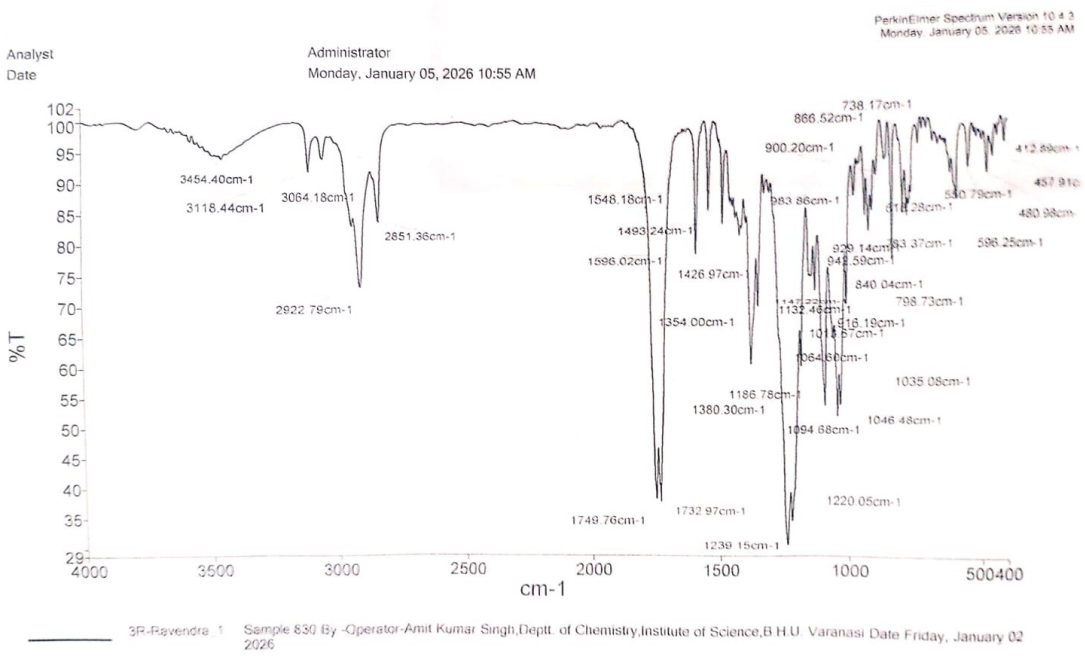


Fig. S38: FT-IR spectrum of **6e**

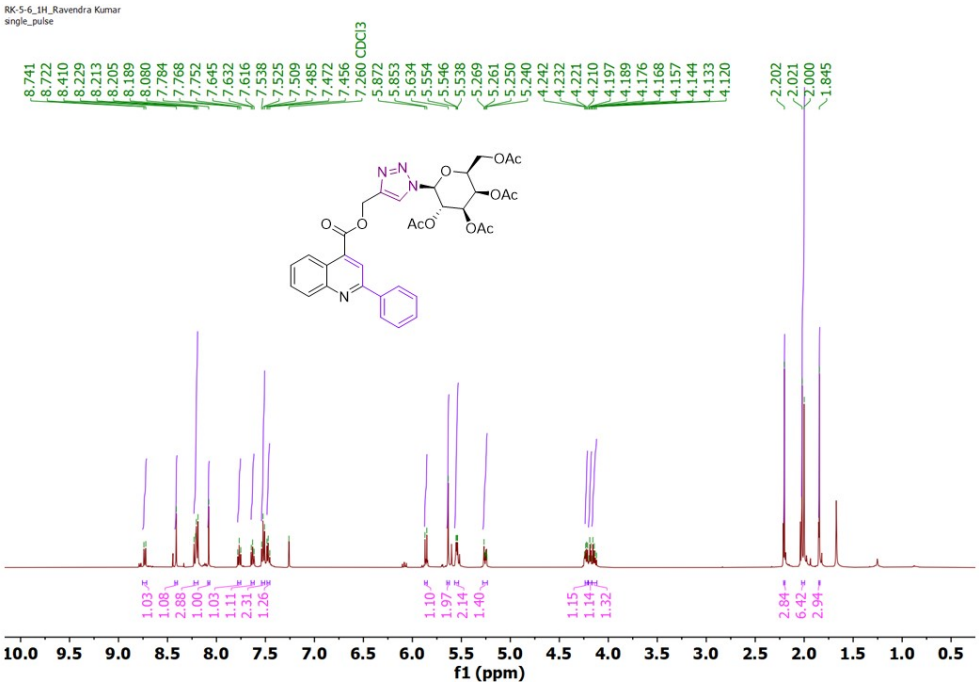


Fig. S39: ^{1}H NMR spectrum of **6f**

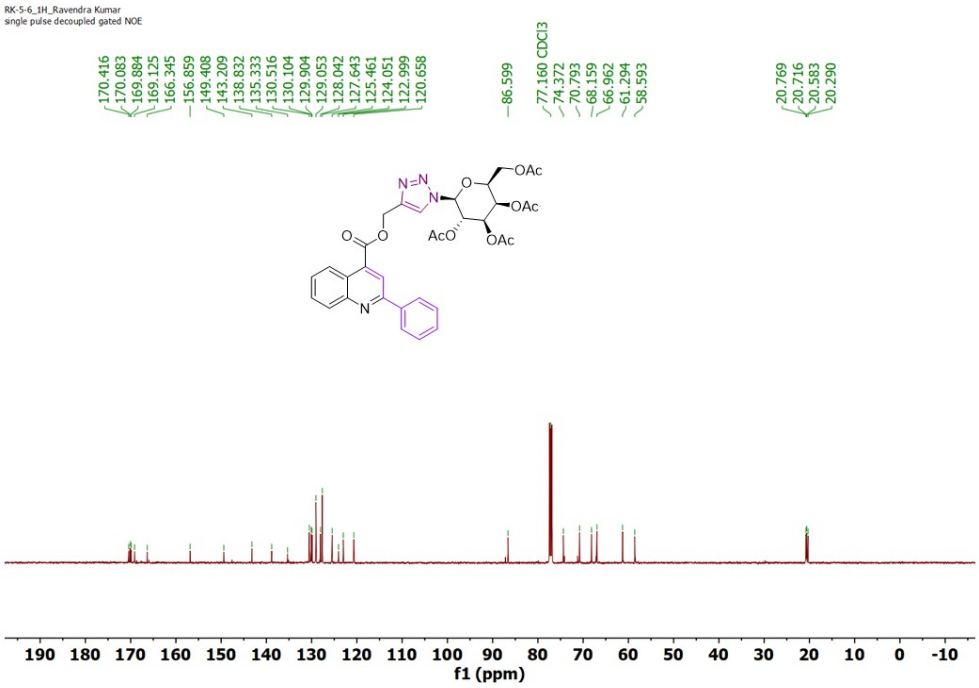


Fig. S40: ^{13}C NMR spectrum of **6f**

Fig. S41: HRMS spectrum of **6f**

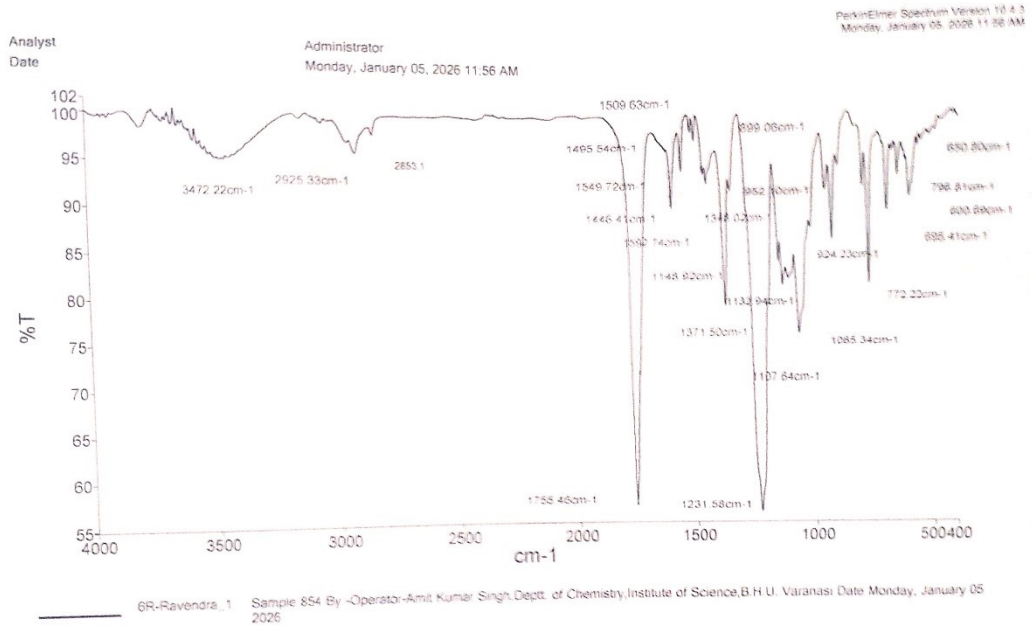


Fig. S42: FT-IR spectrum of **6f**

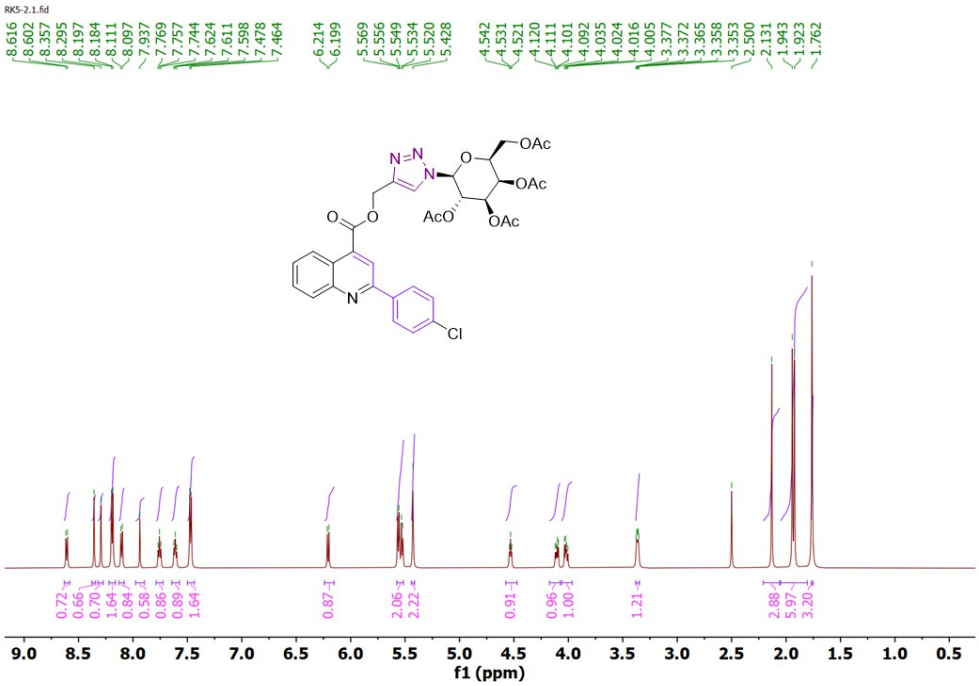


Fig. S43: ^{1}H NMR spectrum of **6g**

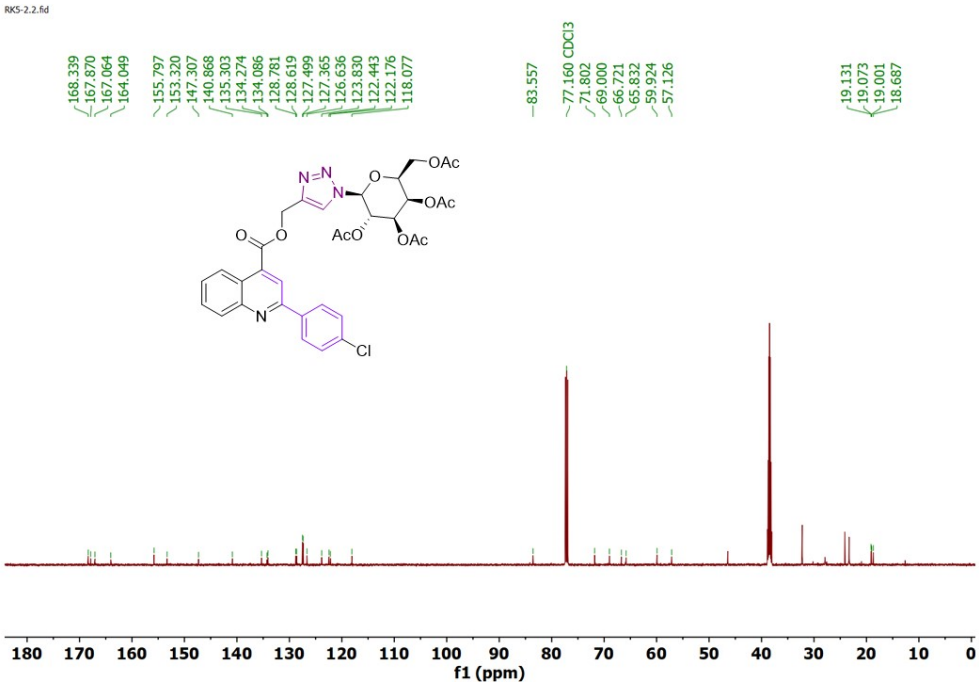


Fig. S44: ^{13}C NMR spectrum of **6g**

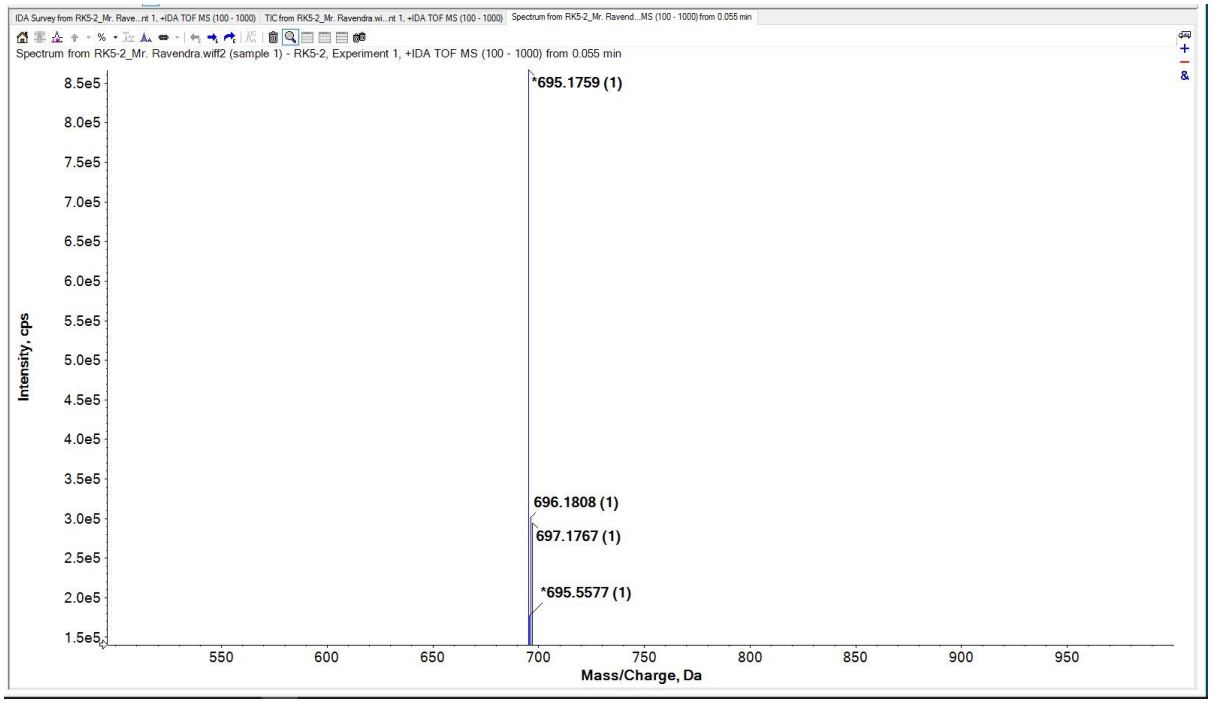


Fig. S45: HRMS spectrum of **6g**

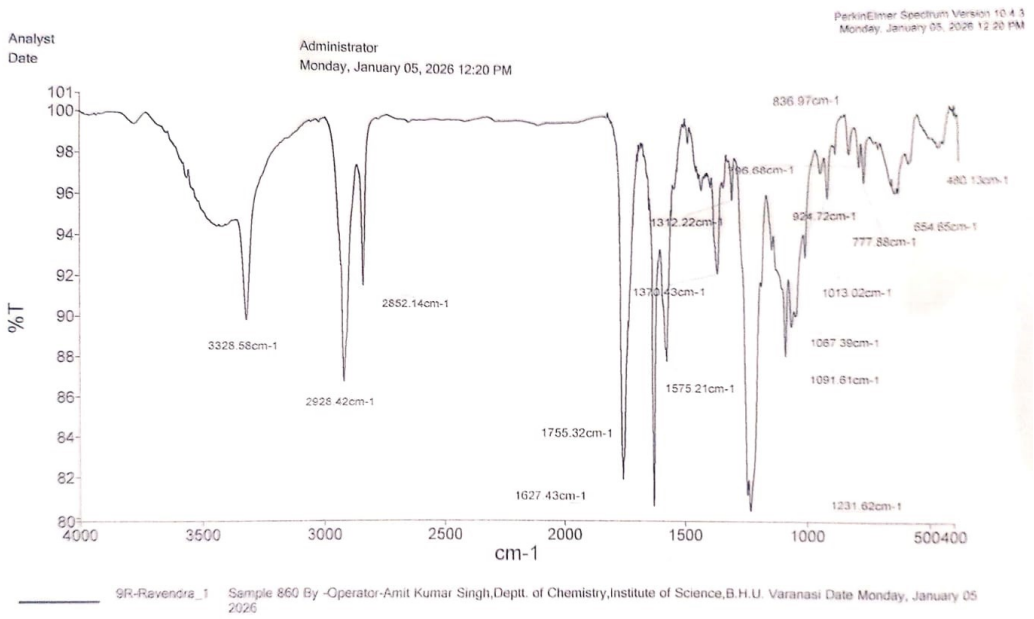


Fig. S46: FT-IR spectrum of **6g**

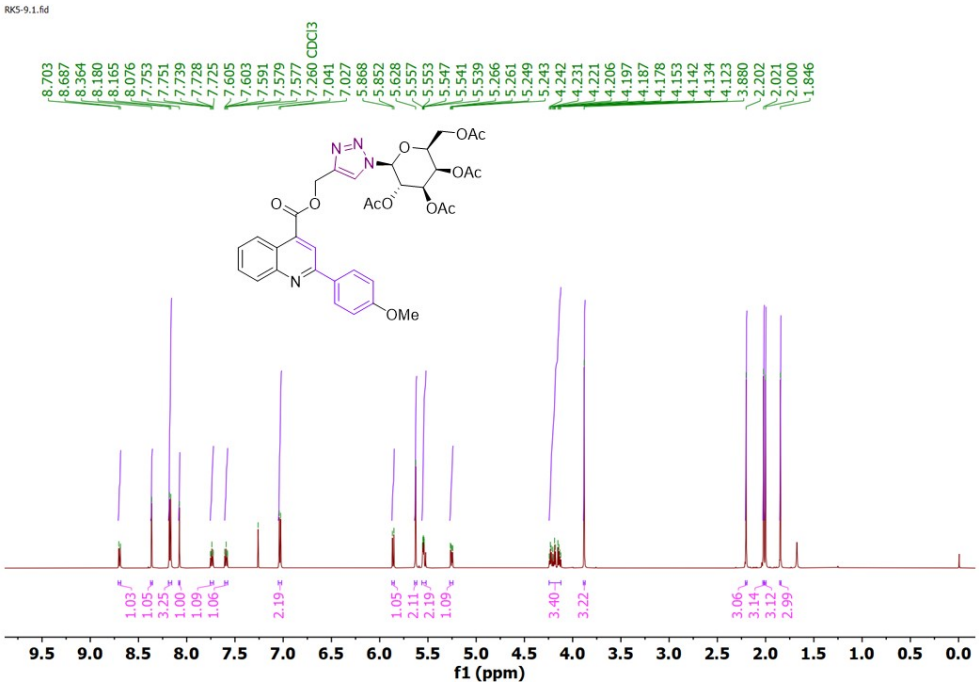


Fig. S47: ^{1}H NMR spectrum of **6h**

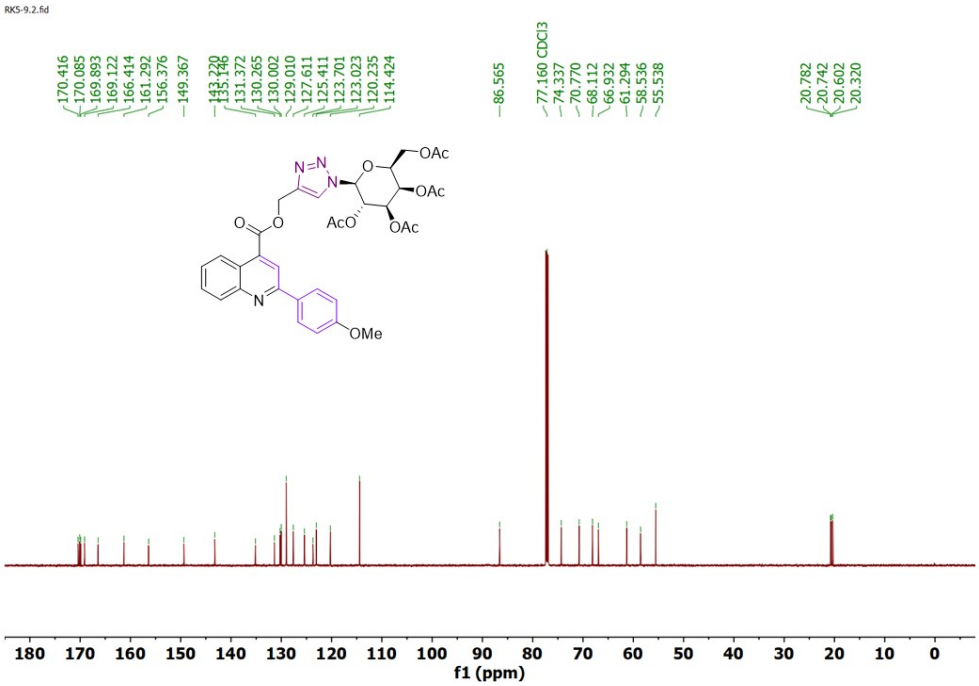


Fig. S48: ^{13}C NMR spectrum of **6h**

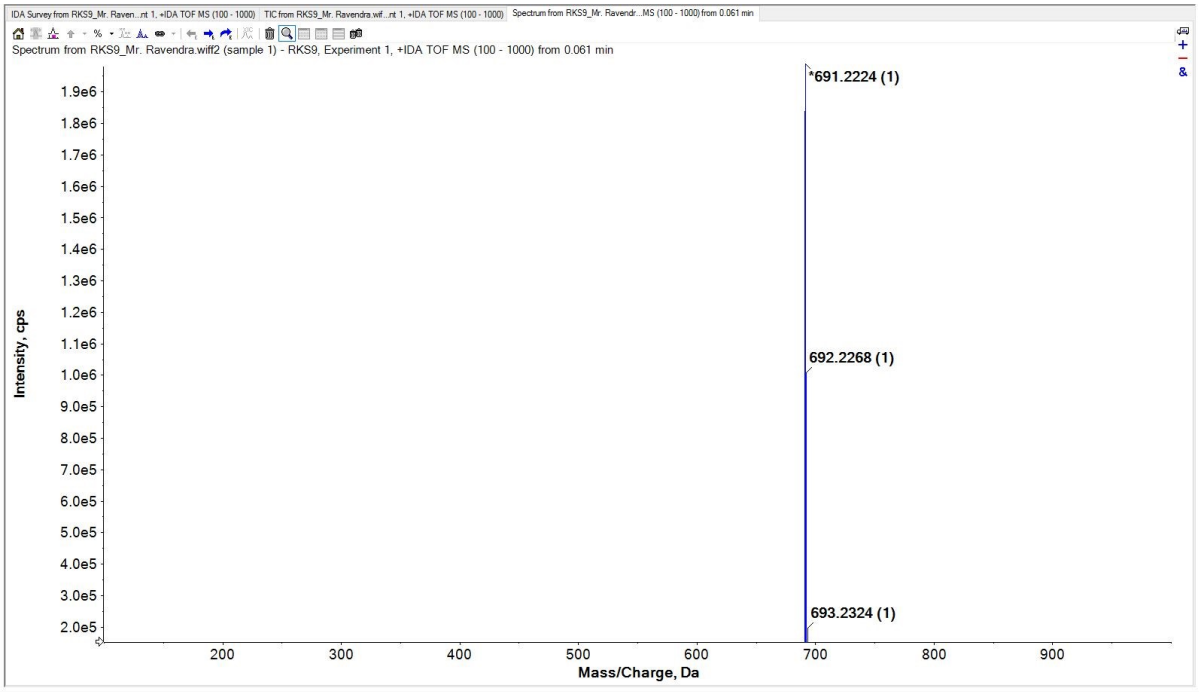


Fig. S49: HRMS spectrum of **6h**

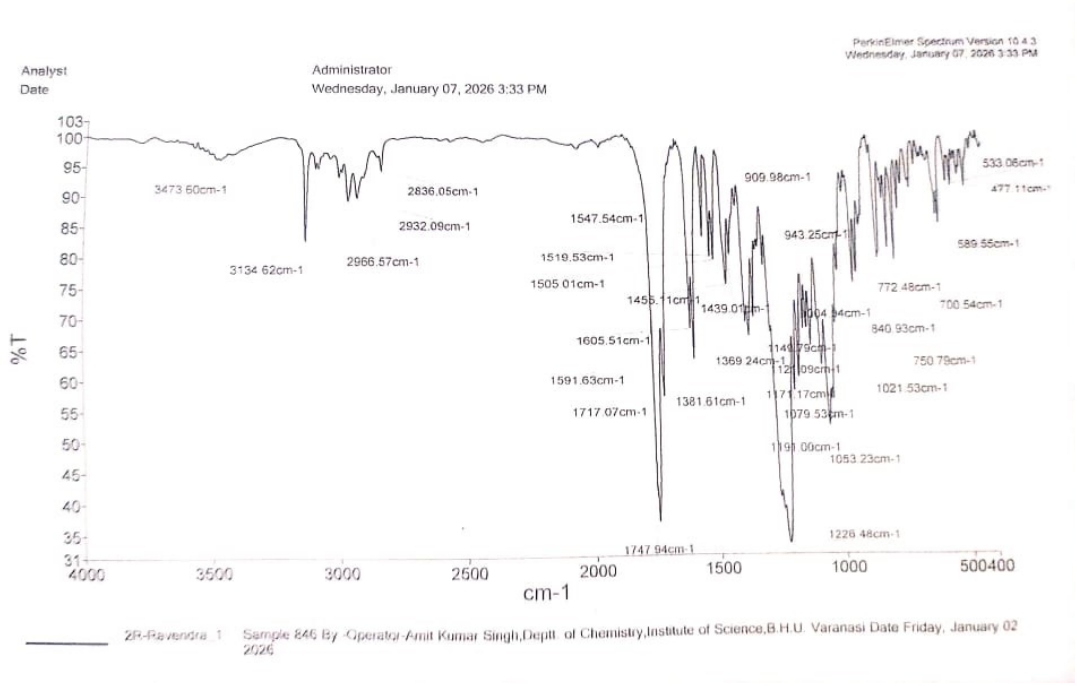


Fig. S50: FT-IR spectrum of **6h**

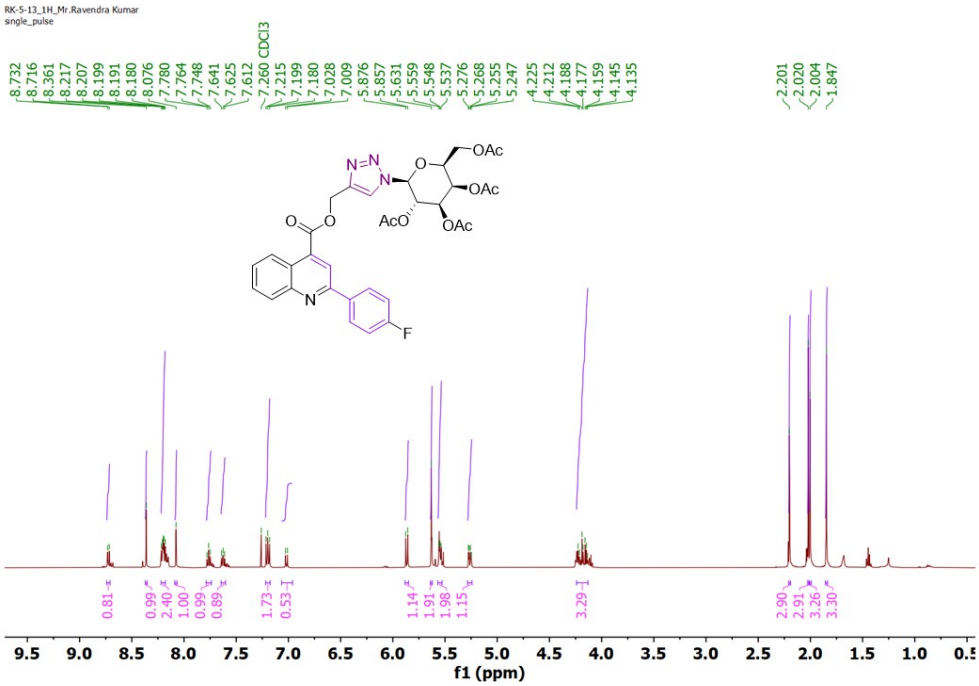


Fig. S51: ^{1}H NMR spectrum of **6i**

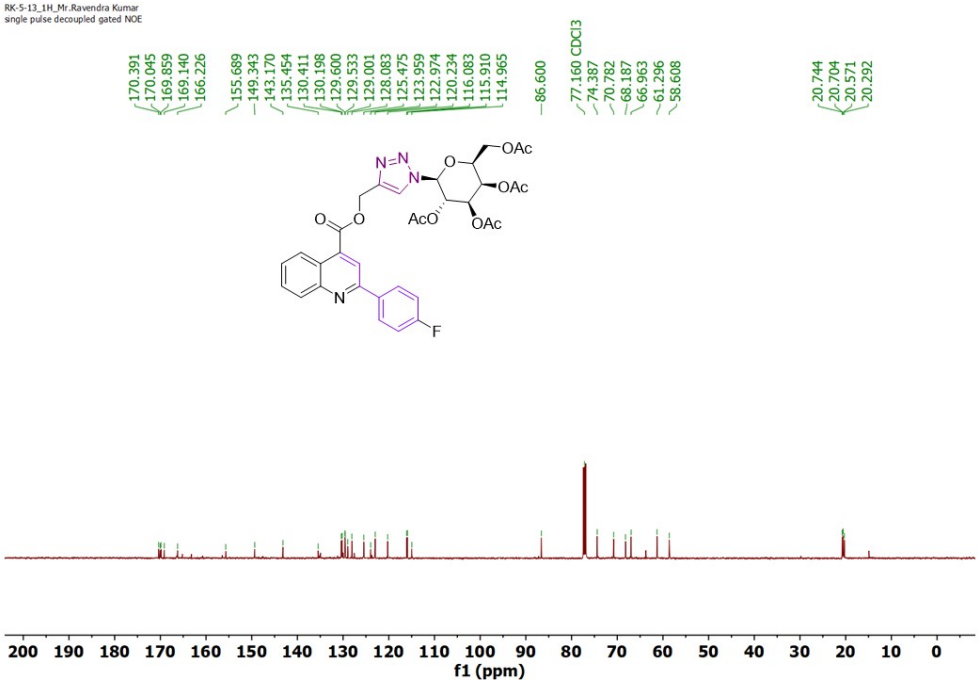


Fig. S52: ^{13}C NMR spectrum of **6i**

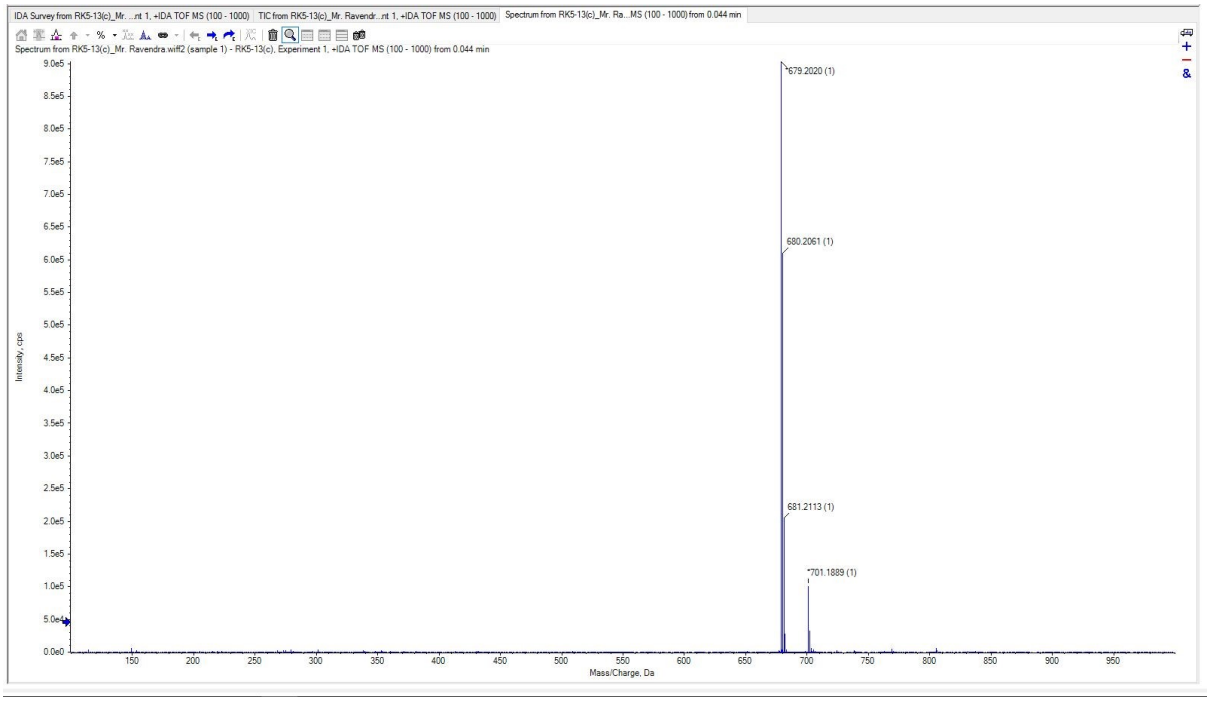


Fig. S53: HRMS spectrum of **6i**

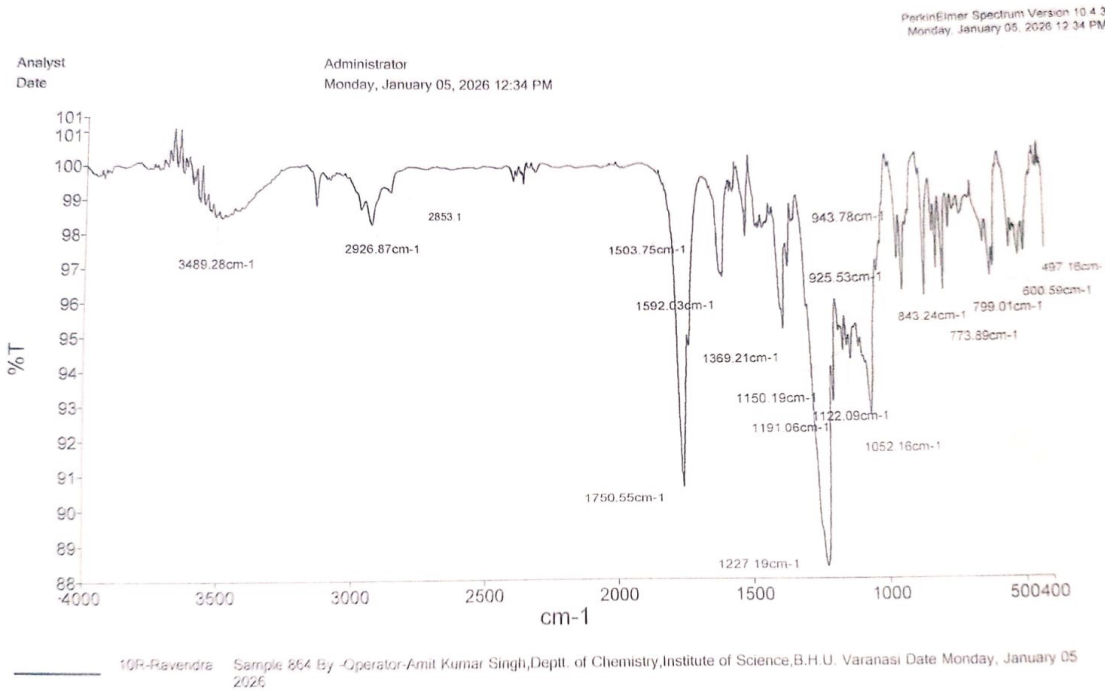


Fig. S54: FT-IR spectrum of **6i**

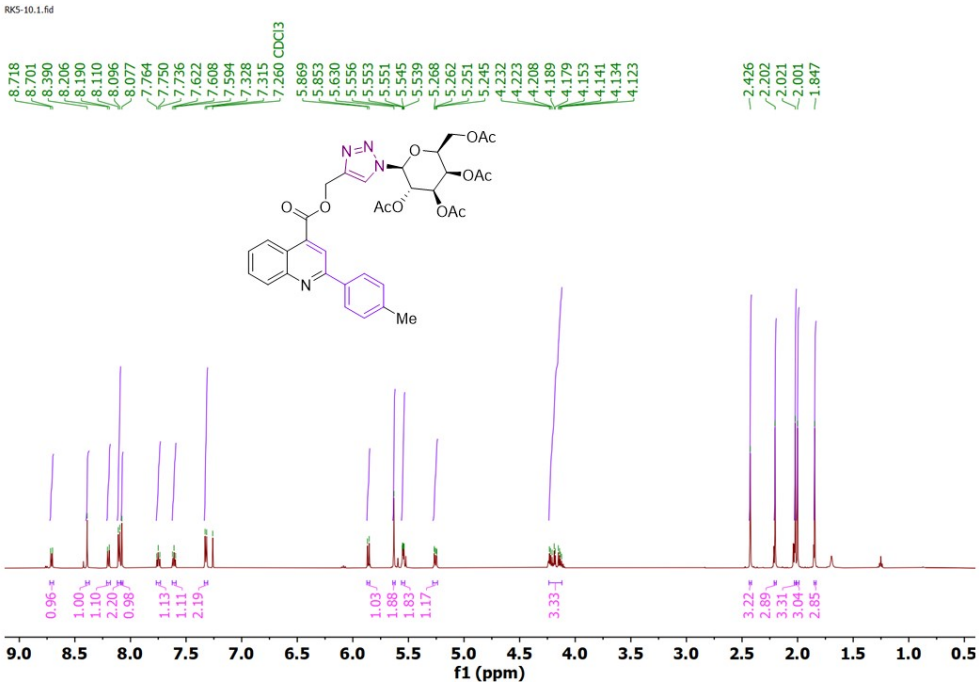


Fig. S55: ^{1}H NMR spectrum of **6j**

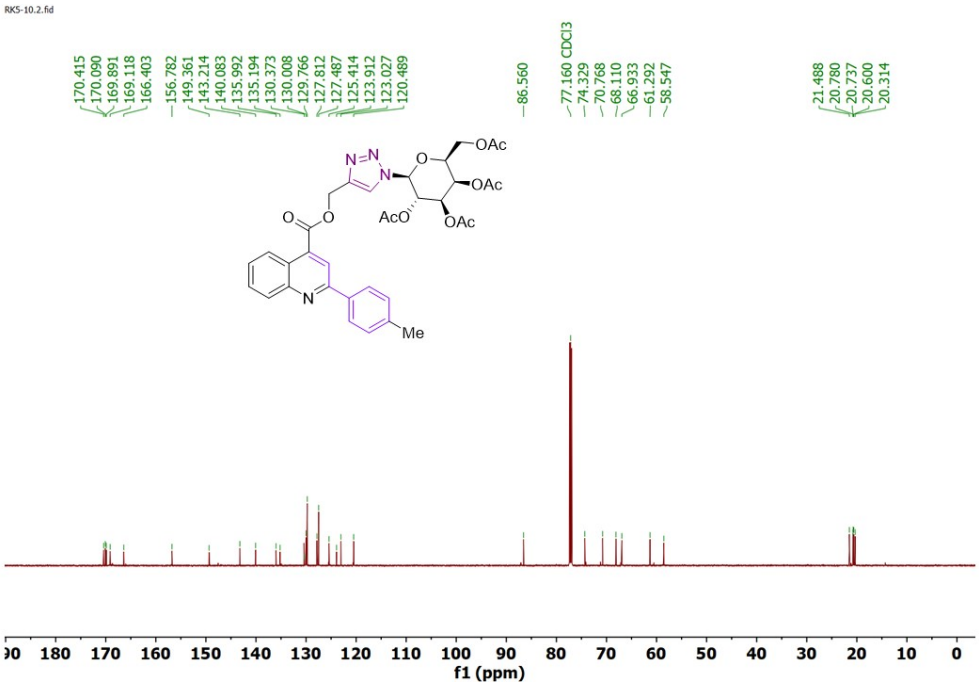


Fig. S56: ^{13}C NMR spectrum of **6j**

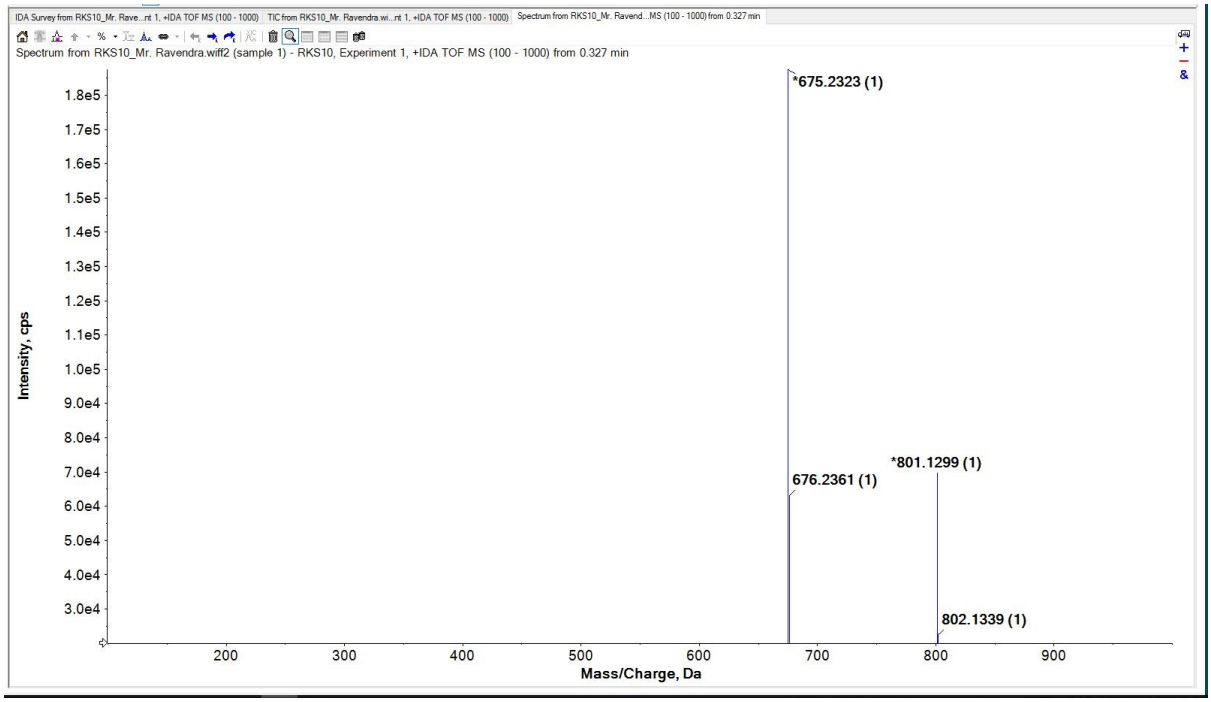


Fig. S57: HRMS spectrum of **6j**

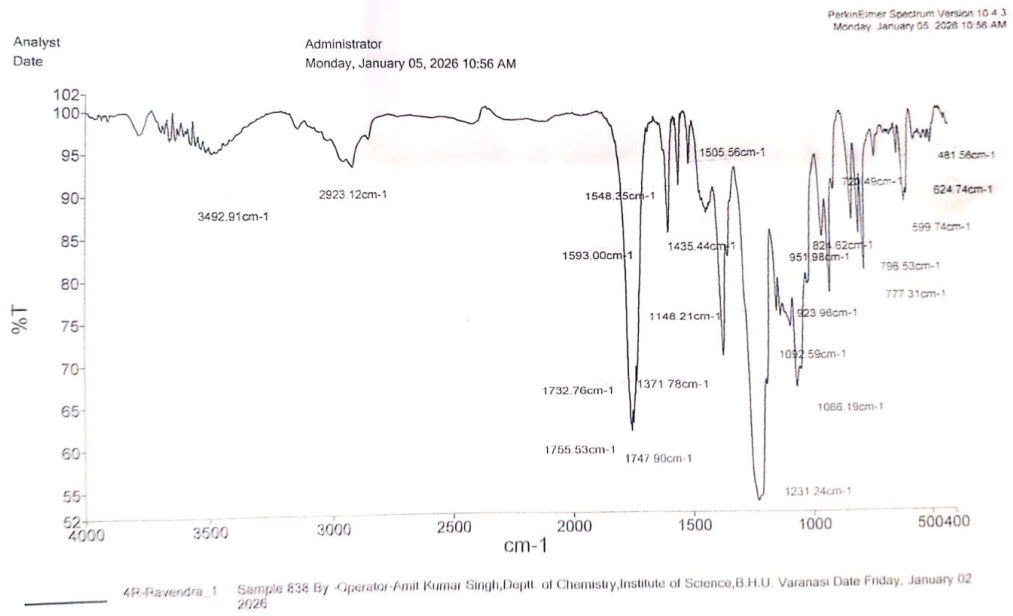


Fig. S58: FT-IR spectrum of **6j**

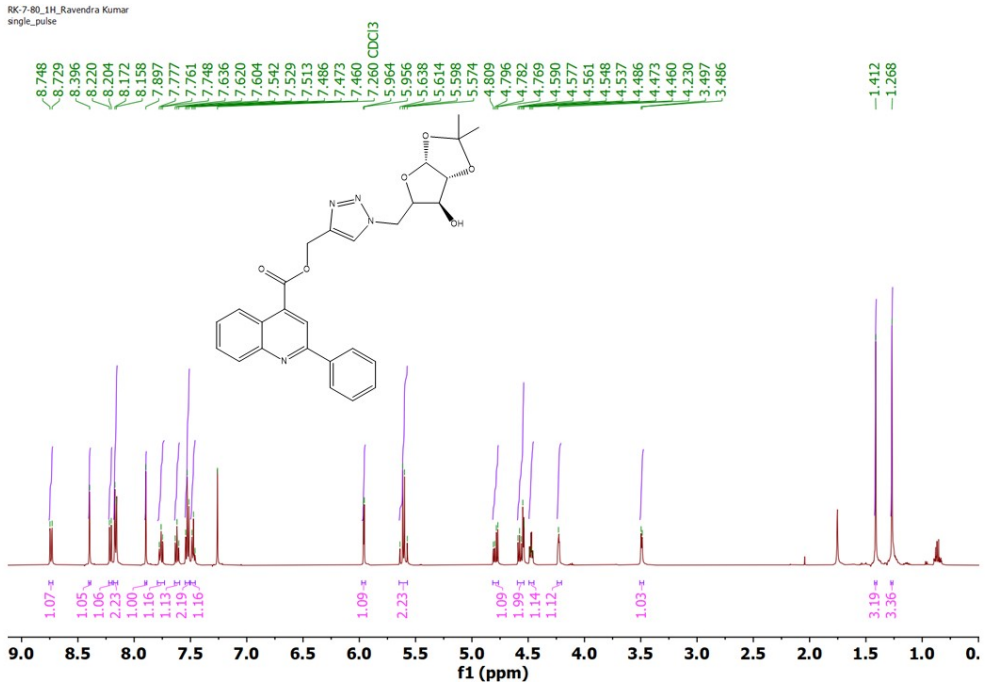


Fig. S59: ^{1}H NMR spectrum of **6K**

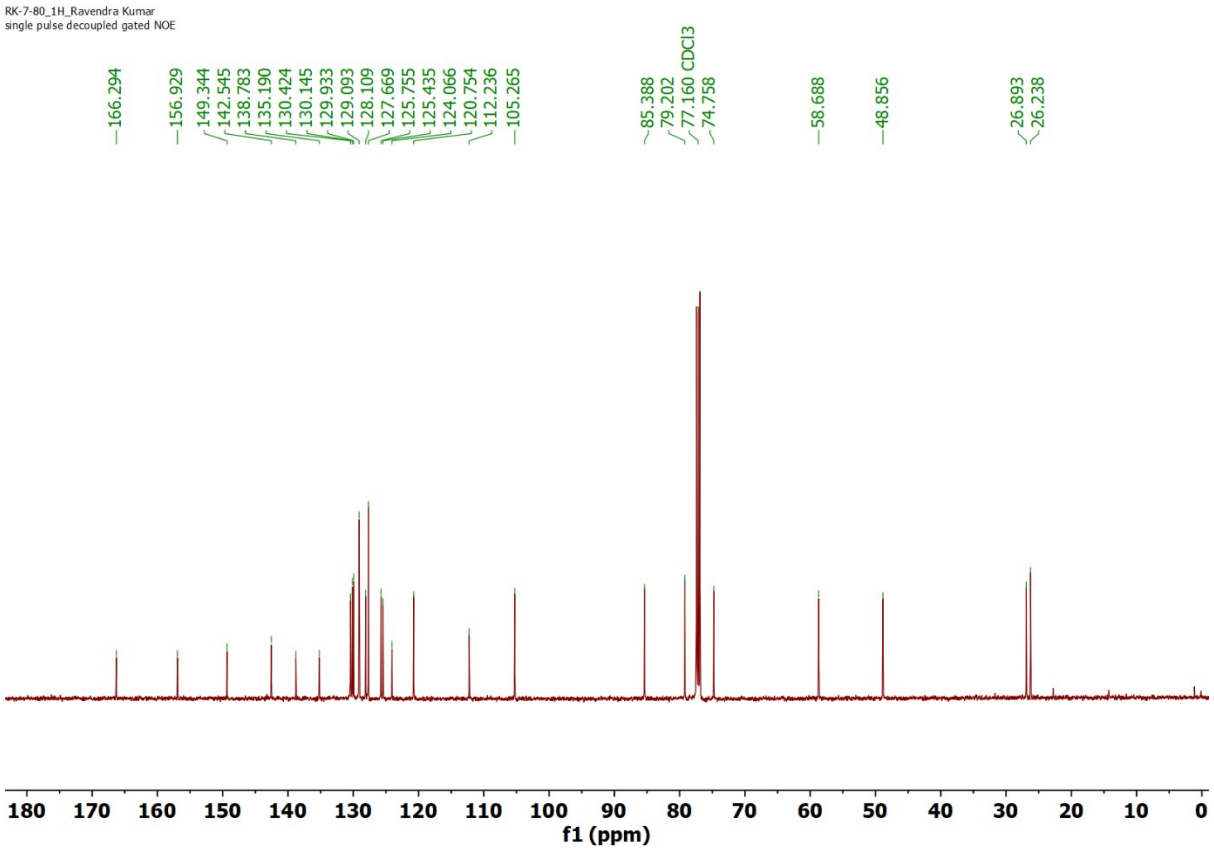


Fig. S60: ^{13}C NMR spectrum of **6K**

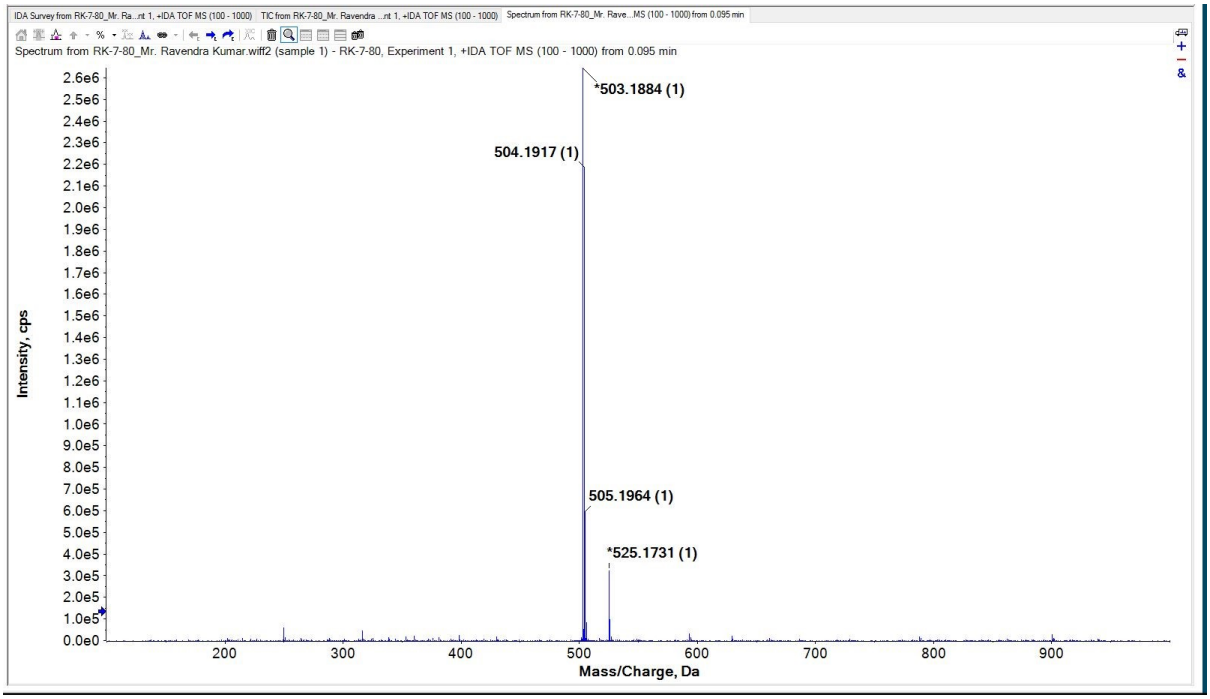


Fig. S61: HRMS spectrum of **6K**

2.0 Crystal structure Intraction

Table S1: Intermolecular C–H, N–H---N, C–H---N, and C–H---O interactions in compound **6a** and **6b** and **6e.**

6a		**6b**		**6e**	
Interaction	**Distance(Å)**	**Interaction**	**Distance(Å)**	**Interaction**	**Distance(Å)**
sp^2C–N…H($C\ sp^3$ sugar)	2.816	sp^2C–H…O(Csp^2)	2.708	sp^2C–H…O(Csp^2)	2.709
sp^2C–N…H(Csp^3 sugar)	2.807	sp^2C–N…H(Csp^3)	2.800	sp^2C–N…H(Csp^2)	2.778
sp^2C–N…H(Csp^2)	2.705	sp^2C–N…H(Csp^3)	2.840	sp^2C–N…H(Csp^3)	2.806
sp^3C–H…O($C\ sp^3$)	2.674	sp^2C–N…H(Csp^3)	2.786	sp^3C–H…O(Csp^3 sugar)	2.425
sp^3C–H…O($C\ sp^3$)	2.462	sp^3C–H…O(Csp^3 sugar)	2.901	sp^3C–H…O(Csp^3 sugar)	2.528
sp^3C–H…O($C\ sp^2$)	2.561	Sp^3C–H…O($C\ sp^2$)	2.947	sp^3C–H…O(Csp^3 sugar)	2.468
sp^3C–H…O($C\ sp^2$)	2.466	Sp^3C–H…O($C\ sp^2$)	2.494	sp^3C–H…O(Csp^3 sugar)	2.408
sp^3C–H…O($C\ sp^2$)	2.953	Sp^3C–H…O($C\ sp^2$)	2.590	-	-
-	-	Sp^3C–H…O($C\ sp^2$)	2.484	-	-

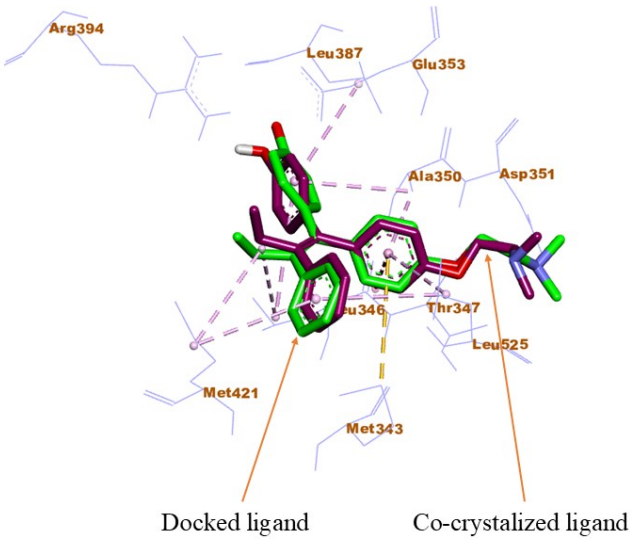
3.0 Molecular Docking

Table S2. Docking scores (free binding energies in kcal/mol) of compounds **6c, 6b, 6j,** and co-crystalized ligand 4-Hydroxy tamoxifen into the ERα active site (PDB: 3ERT).

Compounds	Binding energy (kcal/mol)	C-H bond/Hydrogen bond	π- alkyl, π- anion, π- sigma, π- sulphur Amide- π-stacked	Vander waals interaction
6c	–9.1	Leu536	Leu525,Ala350, Leu346,Asp351 Cys530	Leu384,Met343,Thr347,Tyr526, Trp383,Met522,Leu354,Met528 , Pro535,Glu380,Leu539,Val534
6f	–8.9	Leu536,Trp383	Lys529,Leu525, Ala350,Asp351	Leu346,Leu384,Met522,Tyr526, Thr347,Leu353,Met528,Cys530, Glu380,Tyr537,Pro535,Val533, Val534
6d	–9.5	Arg394	Met421,Leu346, Leu391,Met343, Leu525	Leu384, Met388, Leu349, Met522, Phe404, Tyr526, Leu354, Leu536, Asp351, Pro535, Val533, Val534, Met528, Thr347, His524, Gly420, Ile424, Ala350, Trp383
4-Hydroxy Tamoxifen (Control)	–9.7	Arg394,Glu353, Asp351,	Met421,Leu525, Ala350,Leu346, Leu387,Met343	Phe404,Ile424,Leu428,Met388, Leu391Gly521,His524,Leu384, Thr347,Gly420,Glu419,Trp383, Leu349

*Control: Co-crystallized ligand (original pose)

3.1. Molecular Docking Analysis



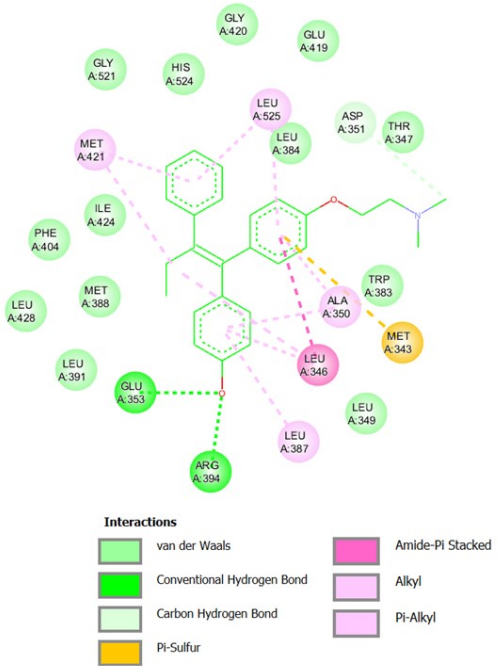


Fig. S48. Validation pose and redocking 3d and 2d pose with the 4-hydrxoy tamoxifen (control) (RMSD-1.541 Å)

4.0 HirshField surface (HS) Analysis

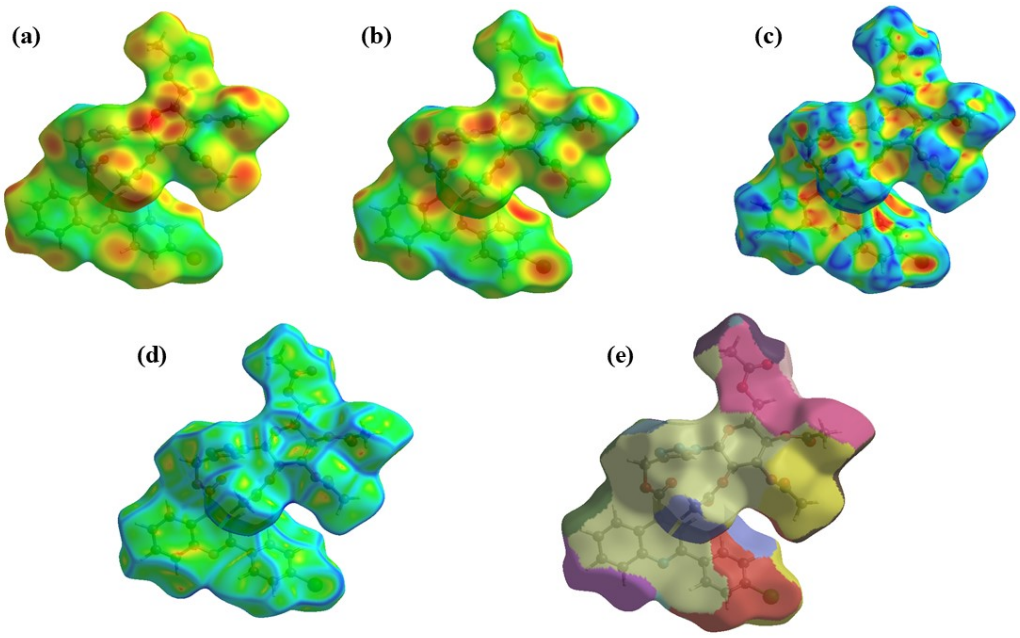


Fig. S49. Hirshfeld surface graph for compound **6b**

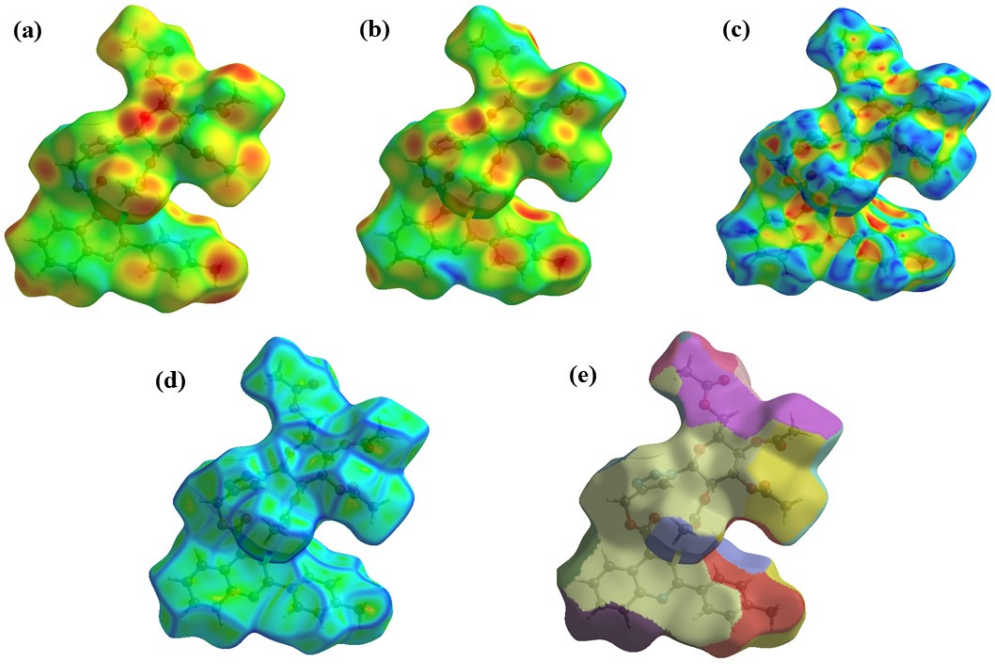


Fig. S50. Hirshfeld Surface graph for compound **6e**

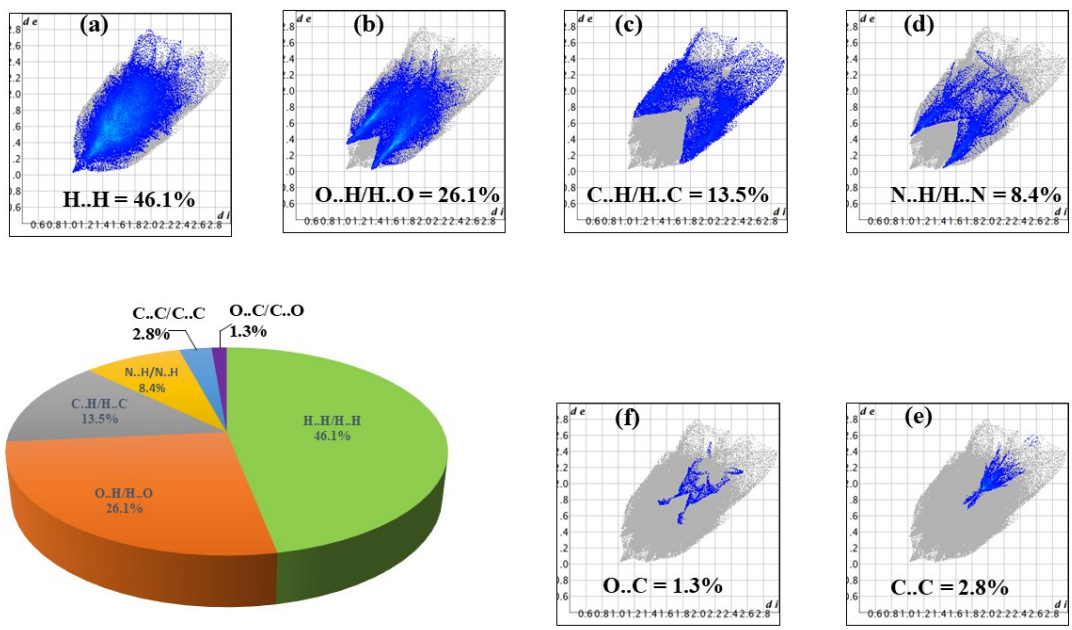


Fig. S51. 2D finger plot % contribution graph for compound **6a**

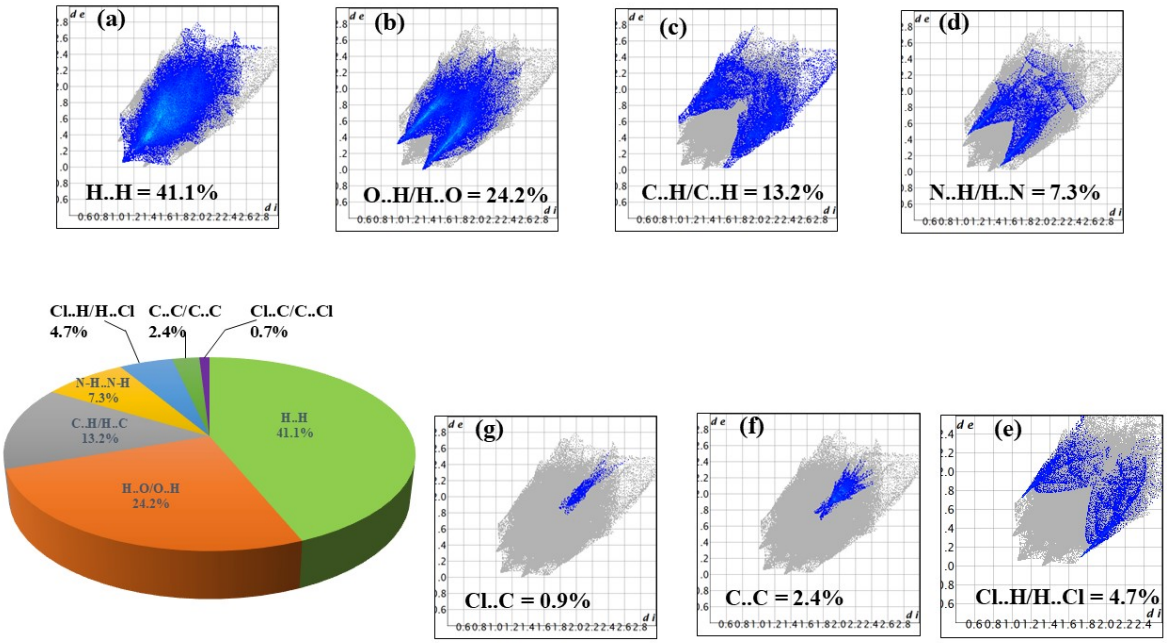


Fig. S52. 2D finger plot % contribution graph for compound **6b**

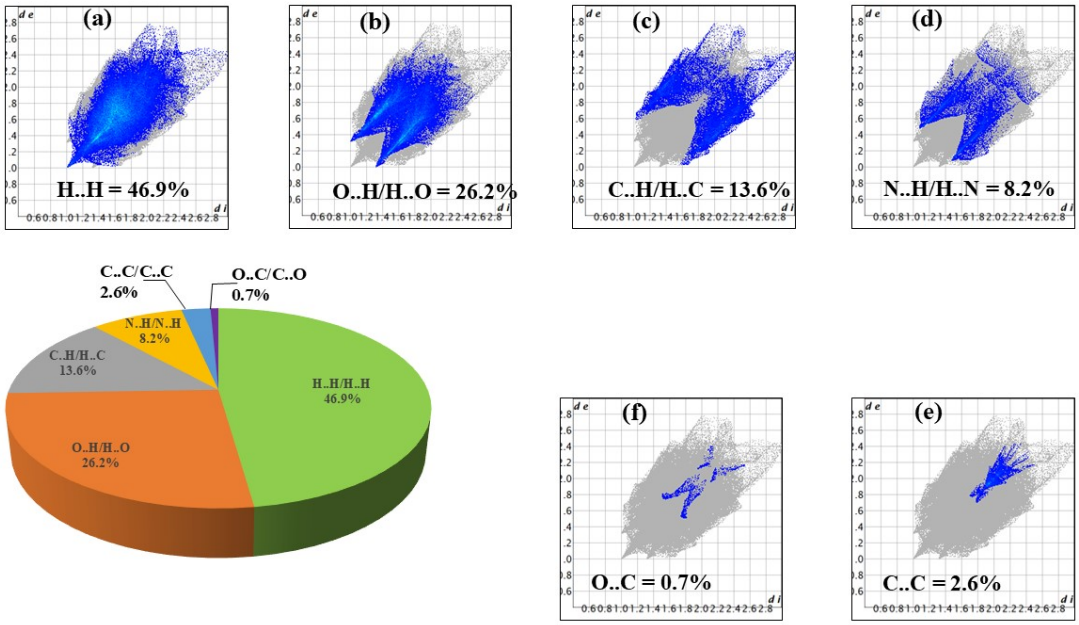


Fig. S53. 2D finger plot % contribution graph for compound **6e**

5.0 DFT Study

5.1 Thermochemical parameter

Table S3. Calculated thermochemical and energetics parameters for the ground state optimized geometrical (in gas phase) of highest binding affinity compounds **6a**, **6b** and **6e** at B3LYP/6-31G (d, p) level of theory.

S/No.	Property/ Parameter	Compounds		
		6a	6b	6e
1	Molecular mass(a.m.u)	660.2068	694.1678	674.2224
2	ZPVE[a](kcal/mol)	391.4593	385.2141	408.5889
3	Zero point correction[b](Hartree/particle)	0.6238	0.6139	0.6511
4	Thermal correction to energy[c](Hartree/particle)	0.6684	0.6597	0.6976
5	Thermal correction to Enthalpy[d](Hartree/particle)	0.6693	0.6607	0.6986
6	Thermal correction to Gibbs free energy[e](Hartree/particle)	0.5387	0.5246	0.5628
7	Sum of electronic and zero-point energies[f] (a.u)	-2322.71	-2782.30	-2362.01
8	Sum of electronic and thermal energies[g](a.u)	-2322.67	-2782.26	-2361.96
9	Sum of electronic and thermal enthalpies[h](a.u)	-2322.67	-2782.26	-2361.96
10	Sum of electronic and thermal free energies[i](a.u)	-2322.80	-2782.39	-2362.10
11	E_{tot}[j] (kcal/mol)	419.429	413.975	437.756
12	S_{tot} [k](cal/mol-kelvin)	275.04	286.332	285.821
13	CV_{tot}[l](cal/mol-kelvin)	180.604	168.598	164.523

5.2 NBO analysis

Table S4. Second order perturbation theory analysis of Fock matrix in NBO basis of compound **6a**, $E^{(2)}$ means energy of hyper conjugative interactions (stabilization energy in kcal/mol). E(j) – E(i) is energy difference between donor and acceptor i and j NBO orbitals. F(i,j) is the Fock matrix element between i and j NBO orbitals.

S. No.	Donor Orbital	Acceptor Orbital	$E^{(2)}$ (kcal/mol)	E(j)-E(i) (a.u.)	F(i,j) (a.u.)
1	C1–C6(π)	C2–C3(π*)	17.33	0.29	0.064
2	C1–C6(π)	C4–C5(π*)	16.78	0.28	0.064
3	C2–C3(π)	C1–C6(π*)	17.39	0.29	0.064
4	C2–C3(π)	C4–C5(π*)	17.38	0.28	0.065
5	C4–C5(π)	C1–C6(π*)	16.36	0.28	0.065
6	C4–C5(π)	C2–C3(π*)	14.71	0.28	0.062
7	C4–C5(π)	N7–C8(π*)	14.9	0.26	0.058
8	C4–C5(π)	C9–C10(π*)	17.48	0.27	0.065
9	N7–C8(π)	C4–C5(π*)	20.8	0.33	0.078

10	C9–C10(π)	N7–C8(π*)	21.13	0.29	0.07
11	C11–C12(π)	C13–C14(π*)	19.95	0.28	0.067
12	C11–C12(π)	C15–C16(π*)	19.56	0.28	0.067
13	C13–C14(π)	C11–C12(π*)	20.53	0.28	0.069
14	C15–C16(π)	C11–C12(π*)	19.44	0.28	0.067
15	C15–C16(π)	C13–C14(π*)	20.99	0.28	0.068
16	C21–C25(π)	N22–N23(π*)	27.51	0.24	0.077
17	N22–N23(π)	C21–C25(π*)	16.49	0.37	0.073
	Total energy π ⟶ π*		**297.74**	**4.86**	**1.143**
18	O18 LP	C10–C17(σ*)	17.81	0.68	0.101
19	O18 LP	C17–O19(σ*)	31.93	0.64	0.129
25	O34 LP	O33–C35(σ*)	35.43	0.62	0.133
26	O34 LP	C35–C36 (σ*)	18.67	0.64	0.101
29	O38 LP(2)	O37–C39(σ*)	36.81	0.6	0.135
30	O38 LP	C39–C40(σ*)	18.1	0.65	0.1
33	O42 LP	O41–C43(σ*)	35.08	0.62	0.133
34	O42 LP	C43–C44(σ*)	18.71	0.64	0.101
37	O46 LP	O45–C47(σ*)	34.3	0.62	0.132
38	O46 LP	C47–C48(σ*)	17.7	0.65	0.098
	Total energy LP⟶ σ*		**264.54**	**6.36**	**1.163**
20	O19 LP	C17–O18 (π*)	49.69	0.33	0.115
21	N24 LP(1)	C21–C25 (π*)	35.85	0.3	0.096
22	N24 LP(1)	N22–N23(π*)	43.86	0.24	0.093
23	O33 LP	O34–C35(π*)	46.12	0.33	0.111
27	O37 LP	O38–C39(π*)	42.66	0.34	0.108
28	O38 LP	RY*(1) C39	17.3	1.43	0.141
31	O41 LP	O42–C43(π*)	47.29	0.33	0.112
32	O42 LP	RY*(1) C43	16.76	1.42	0.138
35	O45 LP	O46–C47(π*)	48.21	0.33	0.113
	Total energy		**347.74**	**5.05**	**1.027**

	LP⟶ π*				
39	C4–C5 π*	C1–C6(π*)	179.23	0.01	0.078
40	C4–C5 π*	C2–C3(π*)	170.87	0.02	0.078
41	N7–C8 π*	C9–C10(π*)	227.65	0.01	0.083
42	N7–C8 π*	C11–C12(π*)	65.98	0.03	0.062
43	C17–O18 π*	C9–C10(π*)	45.09	0.03	0.067
44	N22–N23 π*	C21–C25(π*)	41.39	0.06	0.068
	Total energy π*⟶ π*		**730.21**	**0.16**	**0.436**

Table S5. Second order perturbation theory analysis of Fock matrix in NBO basis of compound **6b**, $E^{(2)}$ means energy of hyper conjugative interactions (stabilization energy in kcal/mol). E(j) – E(i) is energy difference between donor and acceptor i and j NBO orbitals. F(i,j) is the Fock matrix element between i and j NBO orbitals.

S. No.	Donor Orbital	Acceptor Orbital	$E^{(2)}$ (kcal/mol)	E(j)-E(i) (a.u.)	F(i,j) (a.u.)
1	C1–C6 (π)	C2–C3(π*)	17.25	0.29	0.064
2	C1–C6(π)	C4–C5(π*)	16.99	0.28	0.064
3	C2–C3(π)	C1–C6(π*)	17.37	0.3	0.064
4	C2–C3(π)	C4–C5(π*)	17.55	0.28	0.065
5	C4–C5(π)	C1–C6(π*)	16.13	0.28	0.065
6	C4–C5(π)	C2–C3(π*)	14.51	0.29	0.061
7	C4–C5 (π)	N7–C8(π*)	15.46	0.26	0.059
8	C4–C5 (π)	C9–C10(π*)	17.5	0.27	0.065
9	N7–C8 (π)	C4–C5(π*)	20.57	0.33	0.077
10	C9–C10 (π)	N7–C8 (π*)	21.19	0.29	0.07
11	C9–C10 (π)	C12–O13(π*)	22.51	0.26	0.069
12	C11–C21 (π)	N7–C8 (π*)	17.25	0.26	0.06
13	C11–C21(π)	C17–C18(π*)	19.64	0.28	0.068
14	C11–C21(π)	C19–C20 (π*)	21.79	0.26	0.068
15	C16–C22(π)	N24–N25(π*)	28.32	0.24	0.078
16	C17–C18(π)	C11–C21(π*)	18.91	0.28	0.066

17	C17–C18(π)	C19–C20(π*)	21.48	0.27	0.068
18	C19–C20(π)	C11–C21 (π*)	18.88	0.3	0.068
19	C19–C20 (π)	C17–C18(π*)	17.94	0.3	0.066
	Total energy π ⟶ π*		**361.24**	**5.32**	**1.805**
20	LP(2) O13	C10–C12(σ*)	17.81	0.68	0.1
21	LP(2) O13	C12–O14 (σ*)	31.34	0.64	0.128
30	LP(2) O40	O37–C38 (σ*)	36.02	0.61	0.134
31	LP(2) O40	C38–C39 (σ*)	18.61	0.64	0.1
33	LP(2) O43	O35–C41 (σ*)	35.4	0.62	0.133
34	LP(2) O43	C41–C42 (σ*)	18.6	0.65	0.1
36	LP(2) O46	O36–C44 (σ*)	34.13	0.62	0.132
37	LP(2) O46	C44–C45(σ*)	18.59	0.65	0.101
38	LP(2) O48	O34–C47(σ*)	38.58	0.58	0.135
39	LP(2) O48	C47–C49(σ*)	18.74	0.62	0.099
	Total energy LP⟶ σ*		**267.82**	**6.31**	**1.162**
22	LP(2) O14	C12–O13 (π*)	51.58	0.32	0.116
23	LP(1) N23	C16–C22 (π*)	35.95	0.3	0.097
24	LP(1) N23	N24–N25 (π*)	41.52	0.25	0.091
25	LP(2) O34	C47–O48 (π*)	37.82	0.35	0.103
26	LP(2) O35	C41–O43 (π*)	46.64	0.33	0.112
27	LP(2) O36	C44–O46 (π*)	47.74	0.33	0.113
28	LP(2) O37	C38–O40 (π*)	45.39	0.34	0.111
	Total energy LP⟶ π*		**306.64**	**2.22**	**0.743**
40	C4–C5(π*)	C1–C6 (π*)	150.84	0.02	0.078
41	C4–C5(π*)	C2–C3 (π*)	148.92	0.02	0.078
42	N7–C8(π*)	C9–C10 (π*)	255.21	0.01	0.084
43	N7–C8(π*)	C11–C21 (π*)	101.72	0.02	0.065
44	C12–O13(π*)	C9–C10 (π*)	52.3	0.03	0.072
45	C19–C20(π*)	C11–C21 (π*)	201.26	0.02	0.084

46	C19–C20 (π*)	C17–C18 (π*)	134.15	0.02	0.079
47	N24–N25(π*)	C16–C22 (π*)	42.89	0.06	0.069
	Total energy π ⟶ π*		**1087.29**	**0.2**	**0.609**

Table S6. Second order perturbation theory analysis of Fock matrix in NBO basis of compound **6e**, $E^{(2)}$ means energy of hyper conjugative interactions (stabilization energy in kcal/mol). E(j) – E(i) is energy difference between donor and acceptor i and j NBO orbitals. F(i,j) is the Fock matrix element between i and j NBO orbitals.

S. No.	Donor Orbital	Acceptor Orbital	$E^{(2)}$ (kcal/mol)	E(j)-E(i) (a.u.)	F(i,j) (a.u.)
1	C1–C6(π)	C2–C3(π*)	17.37	0.29	0.064
2	C1–C6(π)	C4–C5(π*)	16.73	0.28	0.064
3	C4–C5(π)	C1–C6(π*)	16.44	0.28	0.065
4	C4–C5(π)	C2–C3(π*)	14.71	0.28	0.062
5	C4–C5(π)	N7–C8(π*)	14.85	0.26	0.058
6	C4–C5(π)	C9–C10(π*)	17.47	0.27	0.065
7	N7–C8(π)	C4–C5(π*)	20.91	0.33	0.078
8	N7–C8(π)	C9–C10(π*)	12.32	0.33	0.057
9	C9–C10(π)	C4–C5(π*)	14.42	0.29	0.061
10	C9–C10(π)	N7–C8(π*)	20.99	0.29	0.07
11	C9–C10(π)	C17–O18(π*)	19.45	0.27	0.065
12	C11–C12(π)	N7–C8(π*)	17.08	0.26	0.059
13	C11–C12(π)	C13–C14(π*)	18.98	0.28	0.066
14	C11–C12(π)	C15–C16(π*)	19.91	0.28	0.068
15	C13–C14(π)	C11–C12(π*)	22.07	0.28	0.071
16	C13–C14(π)	C15–C16(π*)	17.88	0.28	0.065
17	C15–C16(π)	C11–C12(π*)	18.51	0.28	0.065
18	C15–C16(π)	C13–C14(π*)	21.55	0.28	0.07
19	C21–C25(π)	N22–N23(π*)	27.54	0.24	0.077
20	N22–N23(π)	C21–C25(π*)	16.47	0.37	0.073
	Total energy π ⟶ π*		**365.65**	**5.72**	**1.323**

21	LP(2) O18	C10–C17(σ*)	17.77	0.69	0.101
22	LP(2) O18	C17–O19(σ*)	31.9	0.64	0.129
28	LP(2) O34	O33–C35(σ*)	36.79	0.6	0.135
29	LP(2) O34	C35–C36(σ*)	18.09	0.65	0.1
32	LP(2) O38	O37–C39(σ*)	35.07	0.62	0.133
33	LP(2) O38	C39–C40(σ*)	18.71	0.64	0.101
36	LP(2) O42	O41–C43(σ*)	34.32	0.62	0.132
37	LP(2) O42	C43–C44(σ*)	17.73	0.65	0.098
40	LP(2) O47	O46–C48(σ*)	35.41	0.62	0.133
41	LP(2) O47	C48–C49(σ*)	18.68	0.64	0.101
	Total energy LP⟶ σ*		**264.47**	**6.37**	**1.163**
23	LP(2) O19	C17–O18(π*)	49.64	0.33	0.115
24	LP(1) N24	C21–C25(π*)	35.85	0.3	0.096
25	LP(1) N24	N22–N23(π*)	43.88	0.24	0.093
26	LP(2) O33	O34–C35(π*)	42.67	0.34	0.108
30	LP(2) O37	O38–C39(π*)	47.32	0.33	0.112
34	LP(2) O41	O42–C43(π*)	48.14	0.33	0.113
38	LP(2) O46	O47–C48(π*)	46.15	0.33	0.111
	Total energy LP⟶ π*		**313.65**	**2.2**	**0.748**
42	C4–C5(π*)	C1–C6(π*)	181.83	0.01	0.078
43	C4–C5(π*)	C2–C3(π*)	173.54	0.02	0.078
44	N7–C8(π*)	C9–C10(π*)	235.88	0.01	0.083
45	N7–C8(π*)	C11–C12(π*)	66.54	0.03	0.063
46	C17–O18(π*)	C9–C10(π*)	44.86	0.03	0.067
47	N22–N23(π*)	C21–C25(π*)	41.3	0.06	0.068
	Total energy π ⟶ π*		**743.95**	**0.13**	**0.437**