SUPPORTING INFORMATION

Inhibiting SARS-CoV-2 Viral Entry by Targeting Spike:ACE2 Interaction with *O*-Modified Quercetin Derivatives

Reuben James Z. Rosal,[a] Monissa C. Paderes*[a]

[a]Institute of Chemistry, College of Science, University of the Philippines Diliman, Quezon City 1101 Philippines

This contains the NMR spectra and *in vitro* data of all the synthesized compounds.

I. NMR Spectra

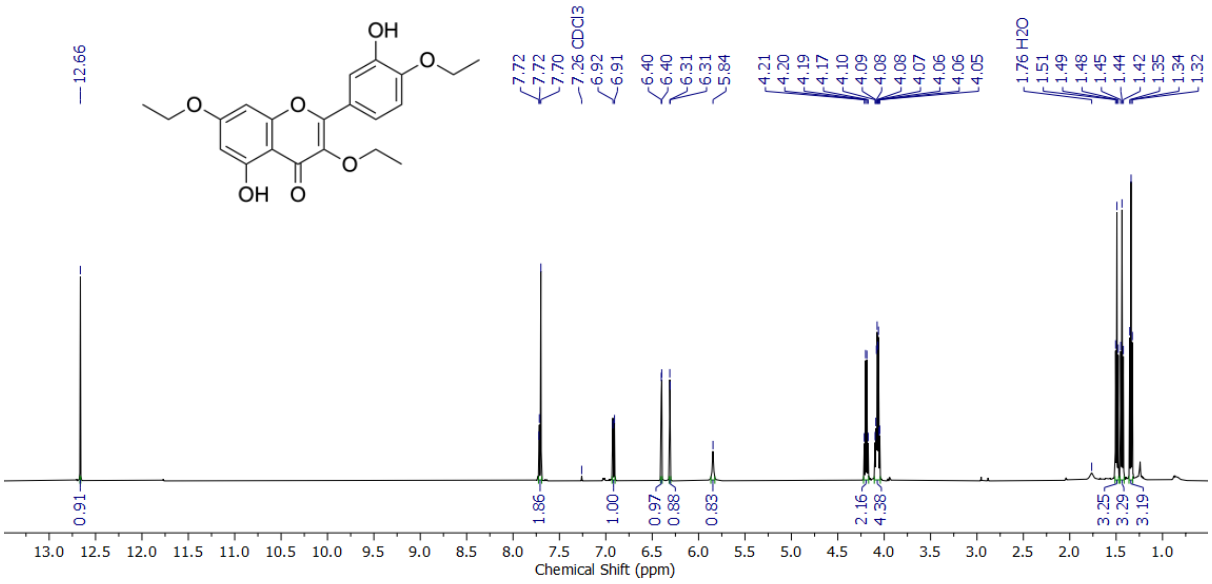

Figure S1. ^{1}H-NMR spectrum of compound **2a**

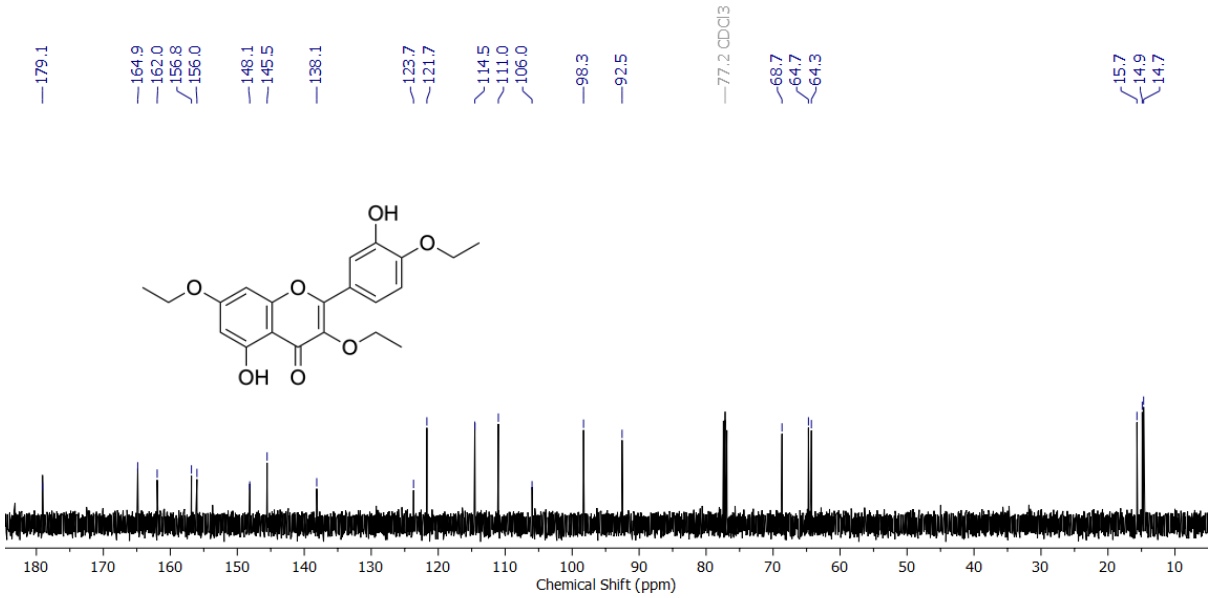

Figure S2. ^{13}C-NMR spectrum of compound **2a**

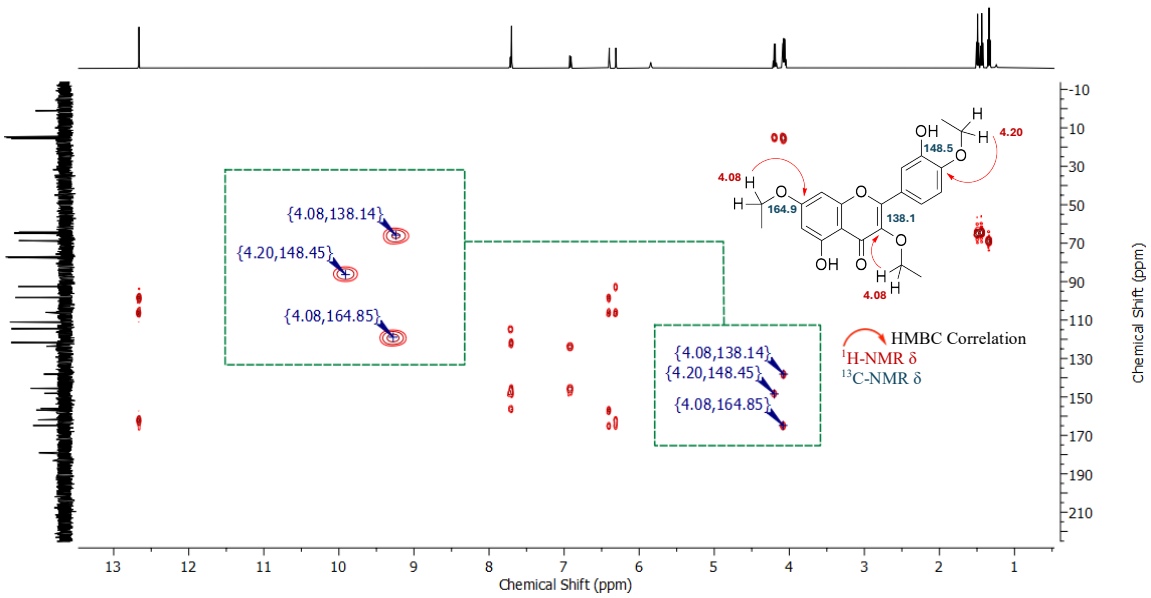

Figure S3. HMBC spectrum of compound **2a**

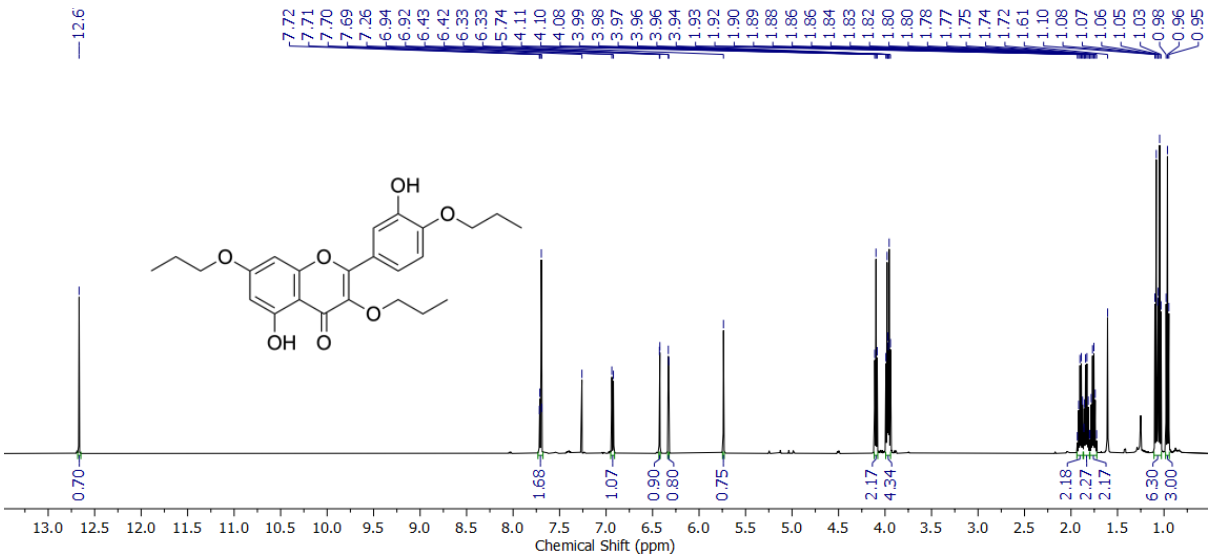

Figure S4. [1]H-NMR spectrum of compound **2b**

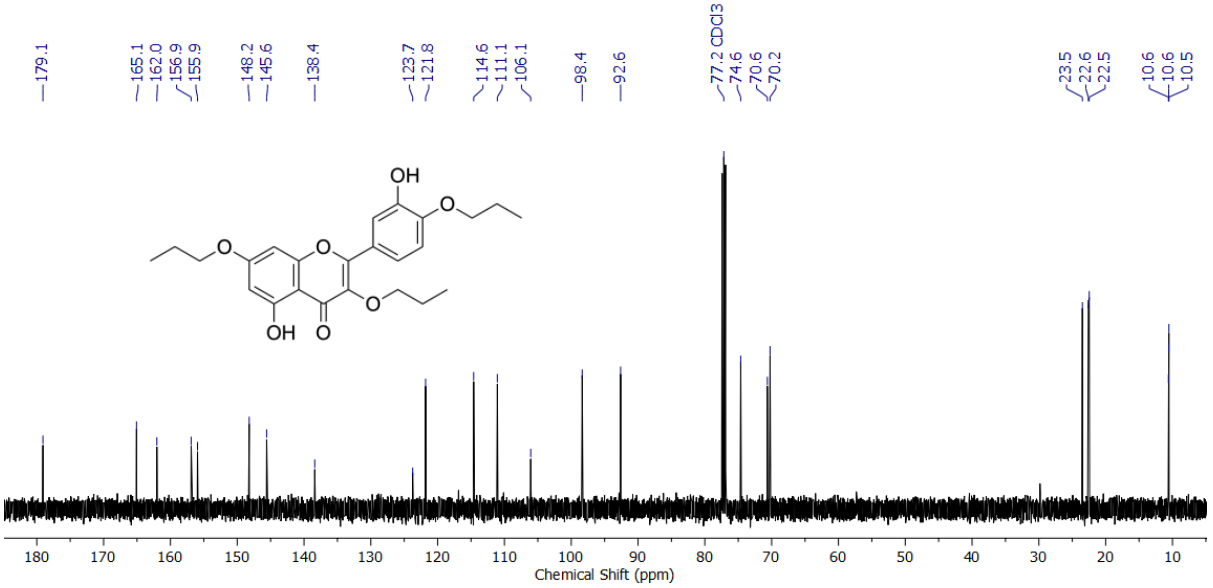

Figure S5. [13]C-NMR spectrum of compound **2b**

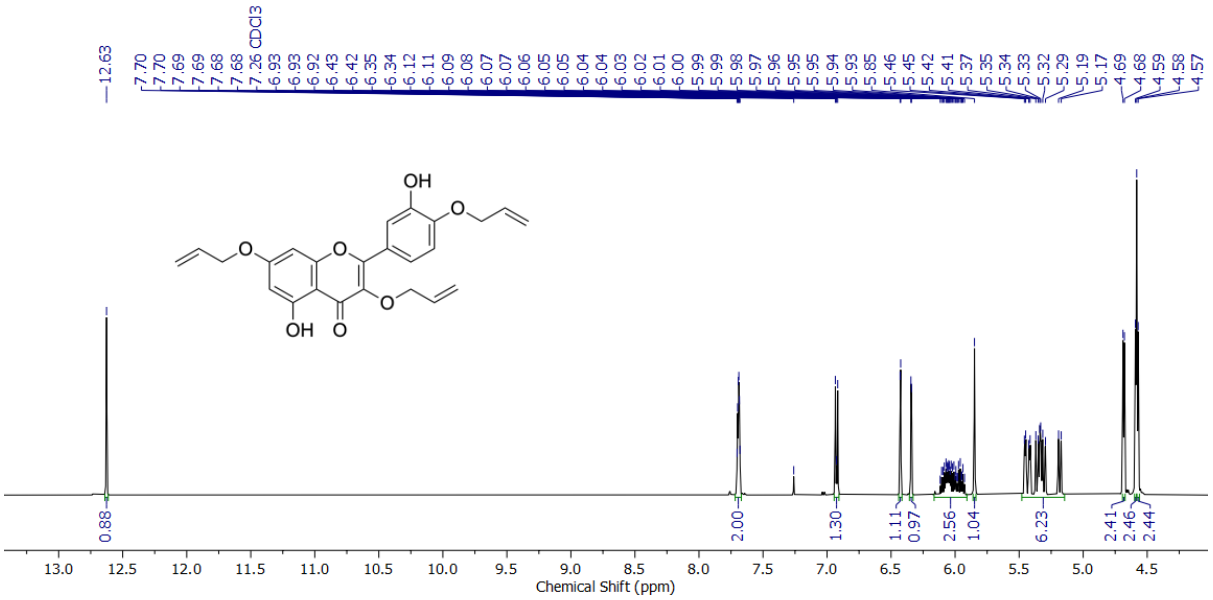

Figure S6. ^{1}H-NMR spectrum of compound **2c**

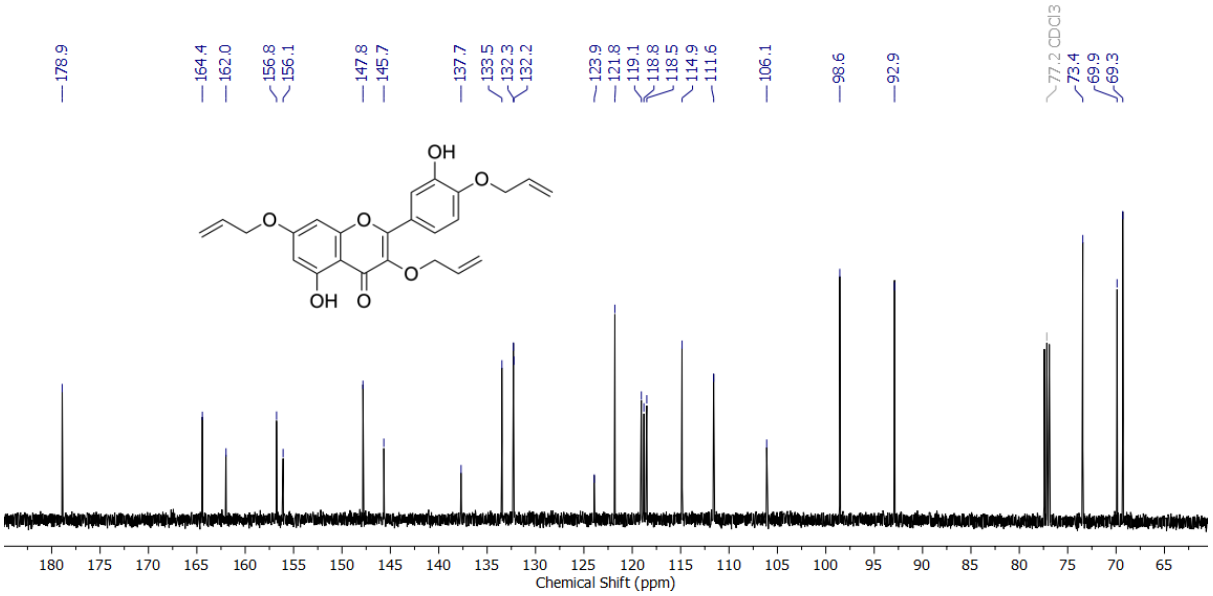

Figure S7. ^{13}C-NMR spectrum of compound **2c**

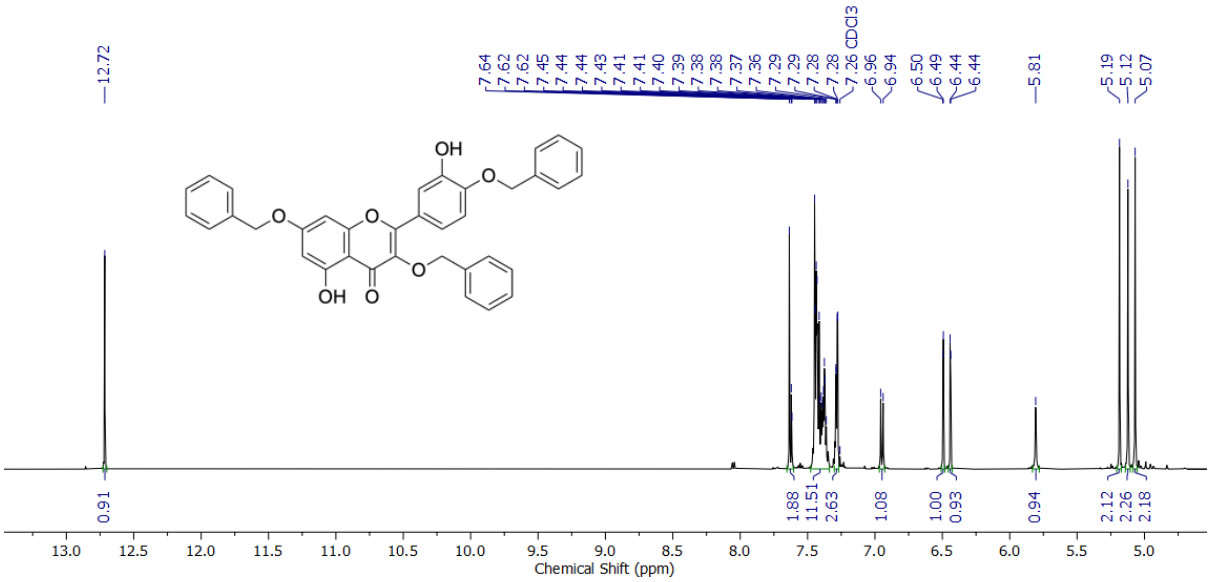

Figure S8. [1]H-NMR spectrum of compound **2d**

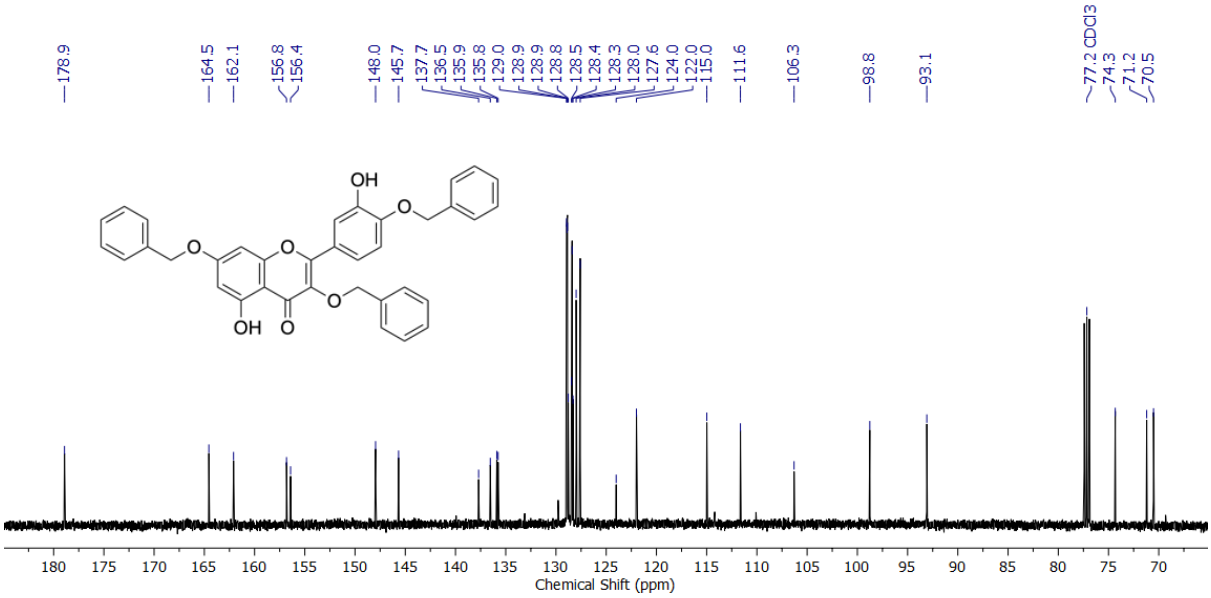

Figure S9. [13]C-NMR spectrum of compound **2d**

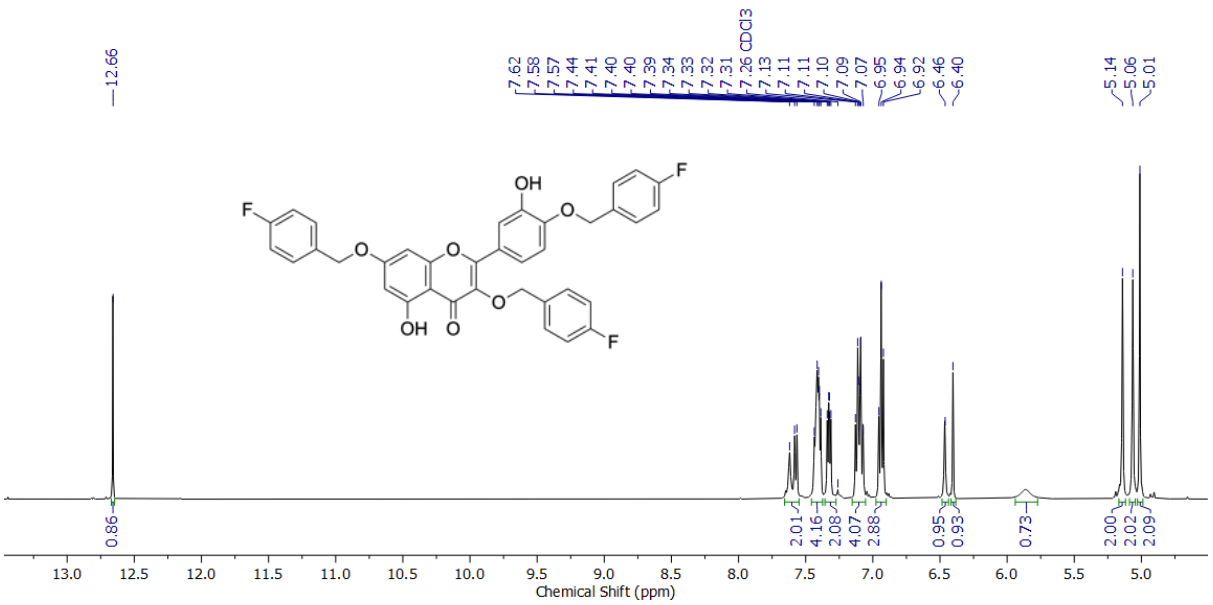

Figure S10. [1]H-NMR spectrum of compound **2e**

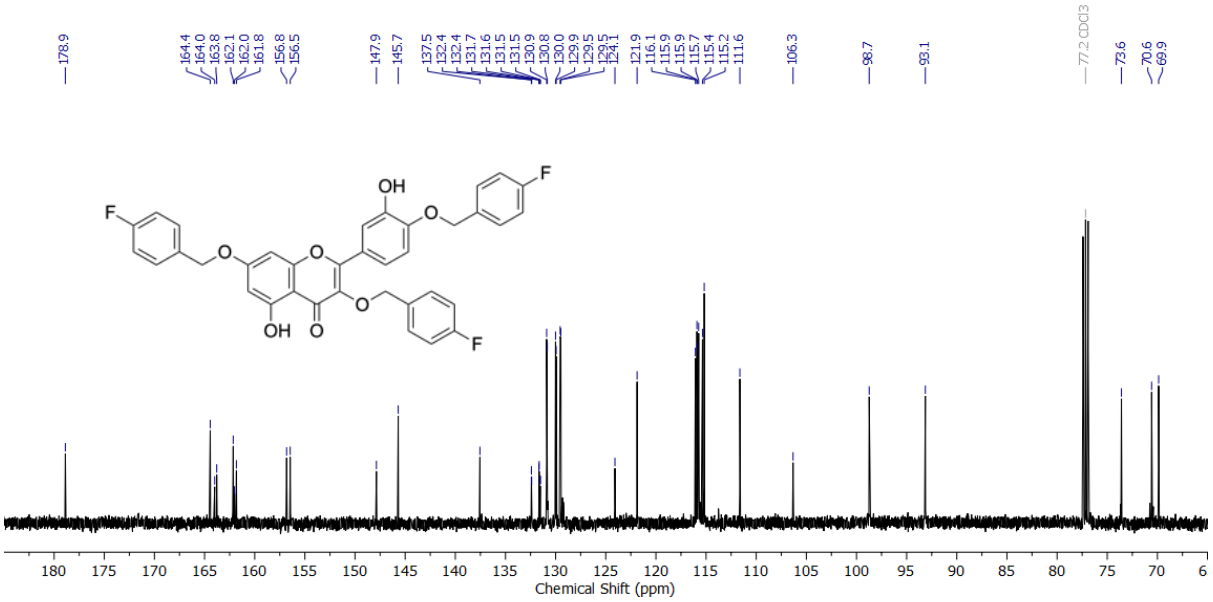

Figure S11. [13]C-NMR spectrum of compound **2e**

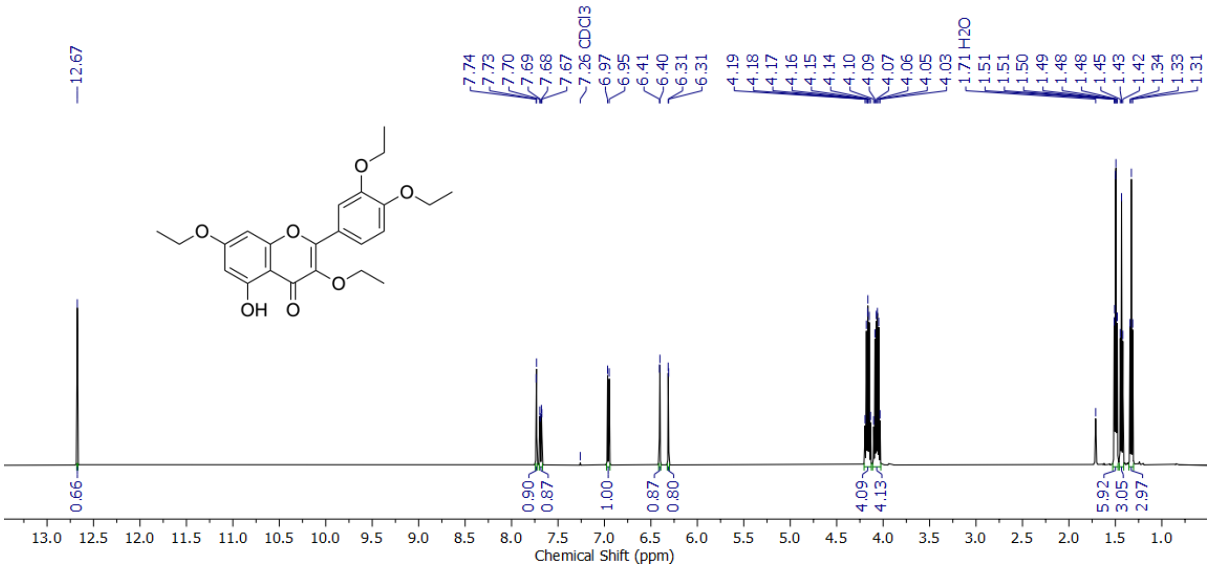

Figure S12. [1]H-NMR spectrum of compound **3a**

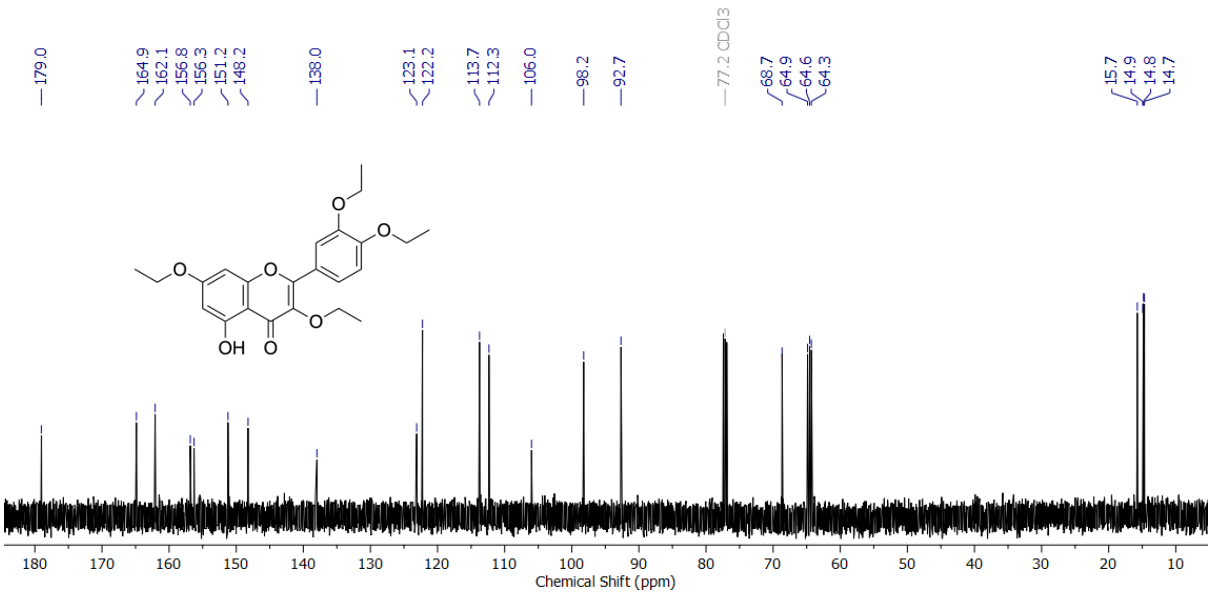

Figure S13. [13]C-NMR spectrum of compound **3a**

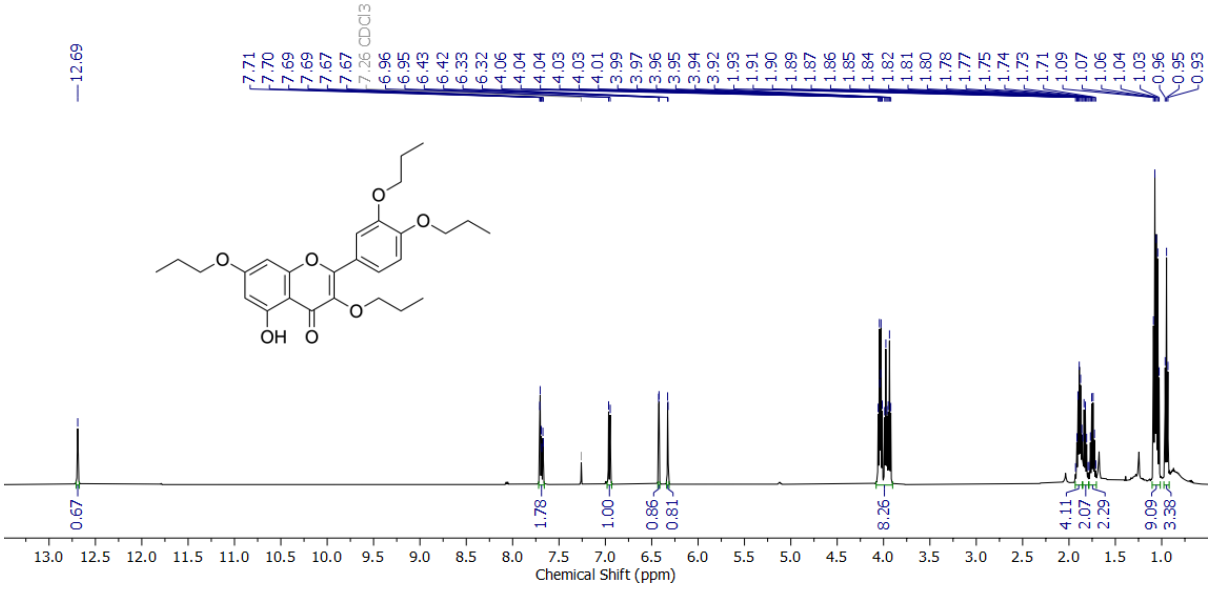

Figure S14. [1]H-NMR spectrum of compound **3b**

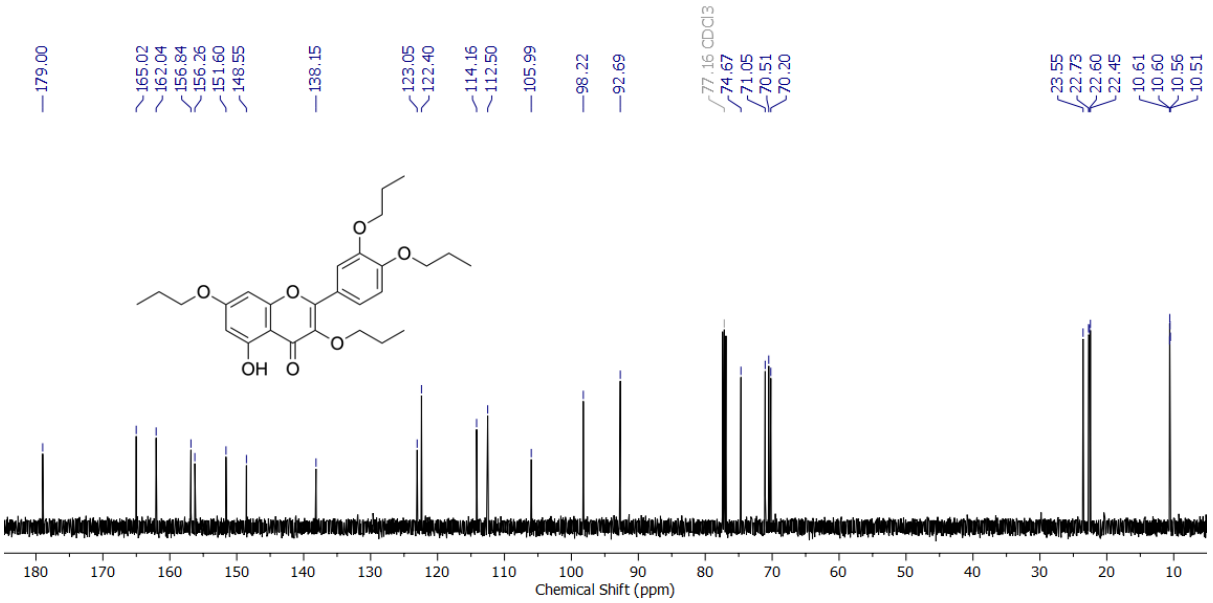

Figure S15. [13]C-NMR spectrum of compound **3b**

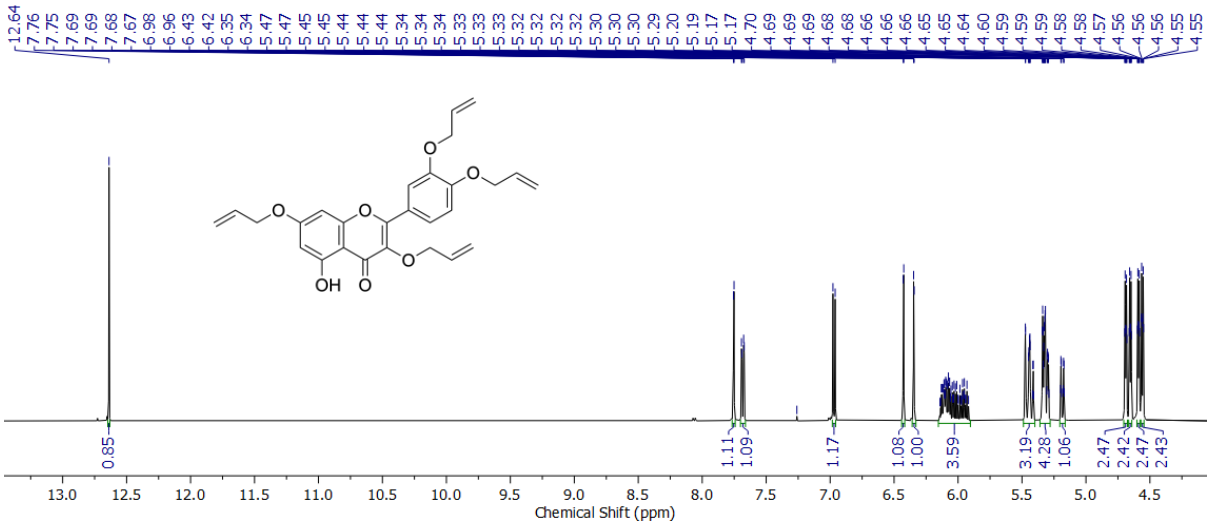

Figure S16. [1]H-NMR spectrum of compound **3c**

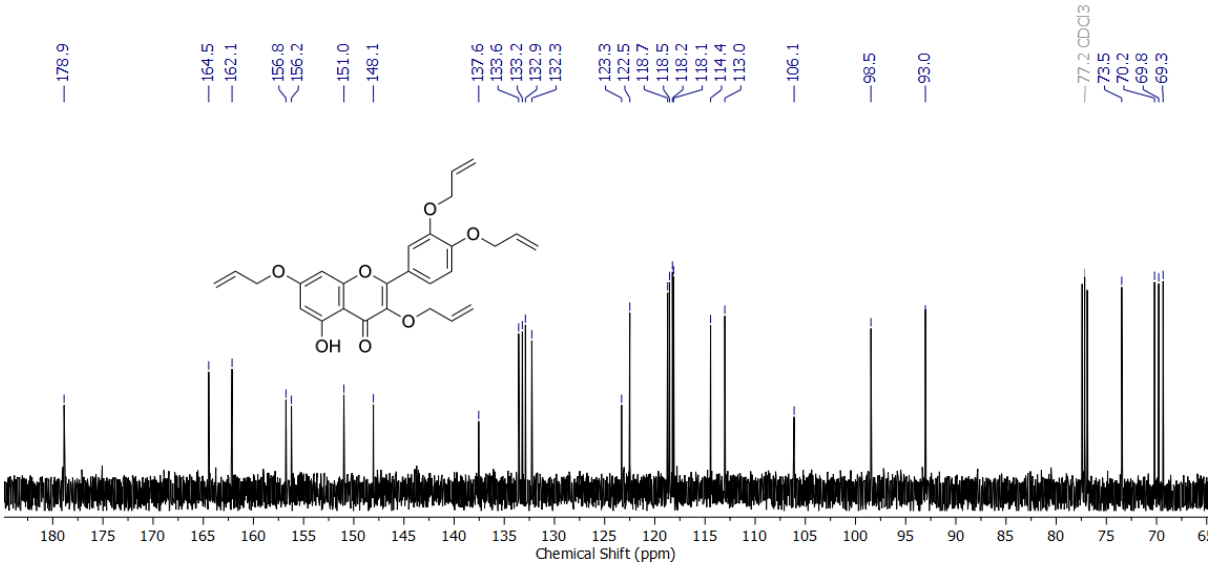

Figure S17. [13]C-NMR spectrum of compound **3c**

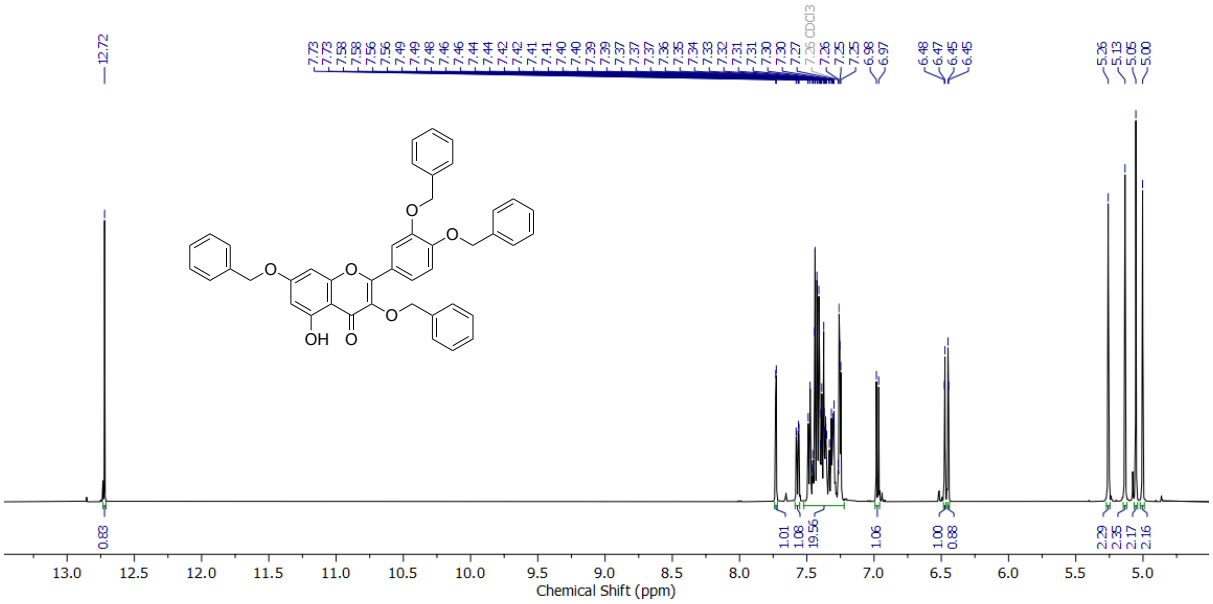

Figure S18. ^{1}H-NMR spectrum of compound **3d**

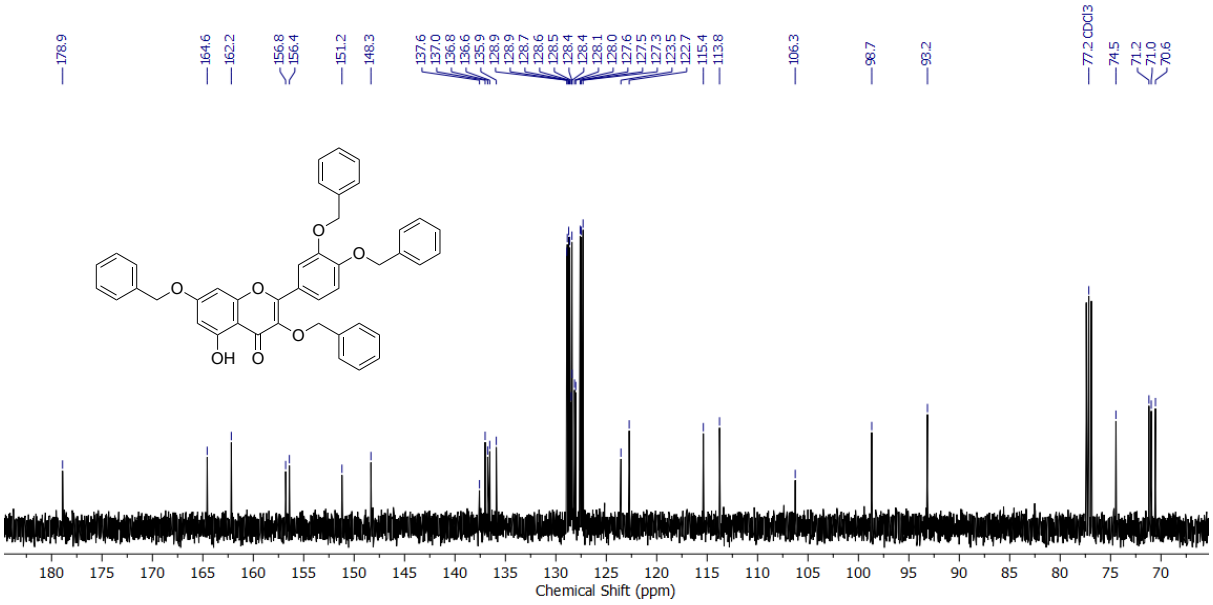

Figure S19. ^{13}C-NMR spectrum of compound **3d**

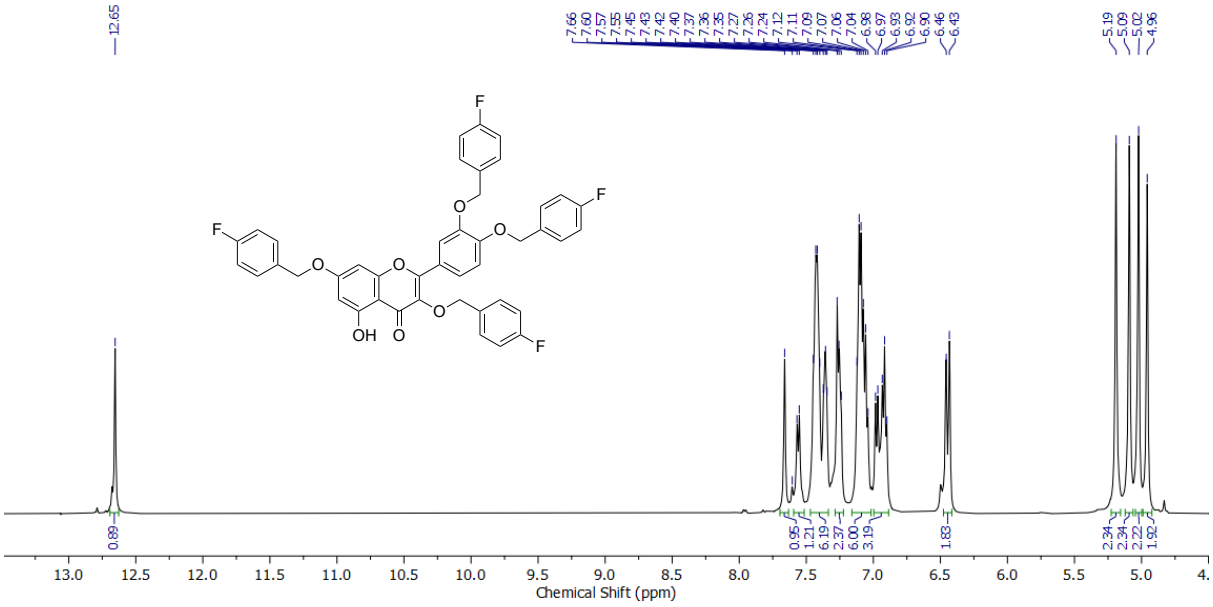

Figure S20. ^{1}H-NMR spectrum of compound **3e**

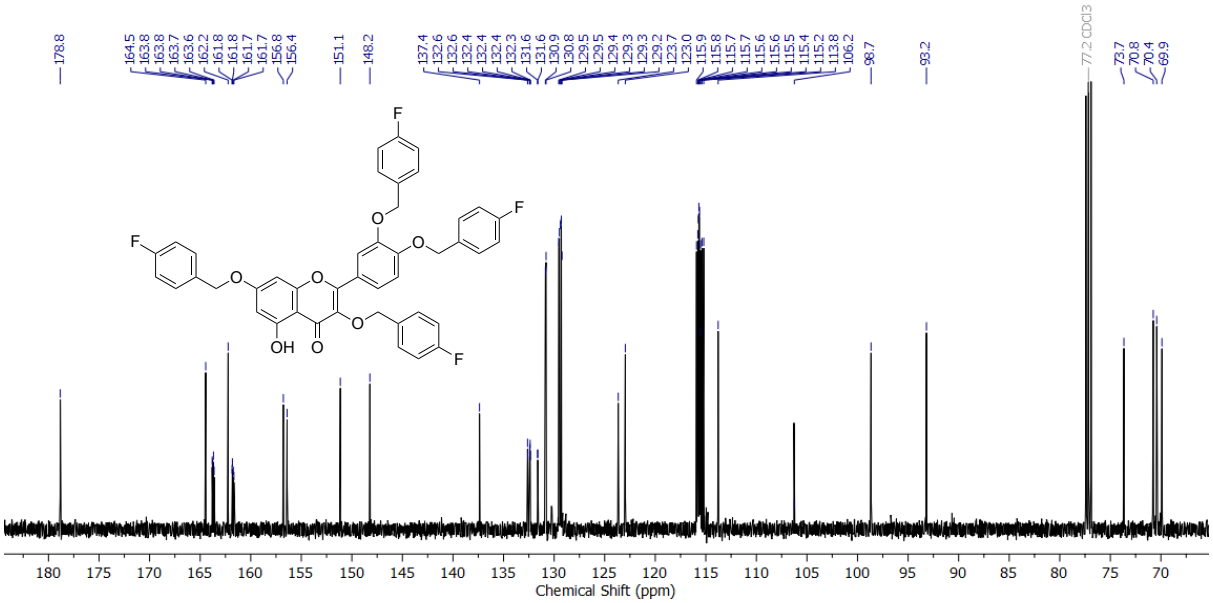

Figure S21. ^{13}C-NMR spectrum of compound **3e**

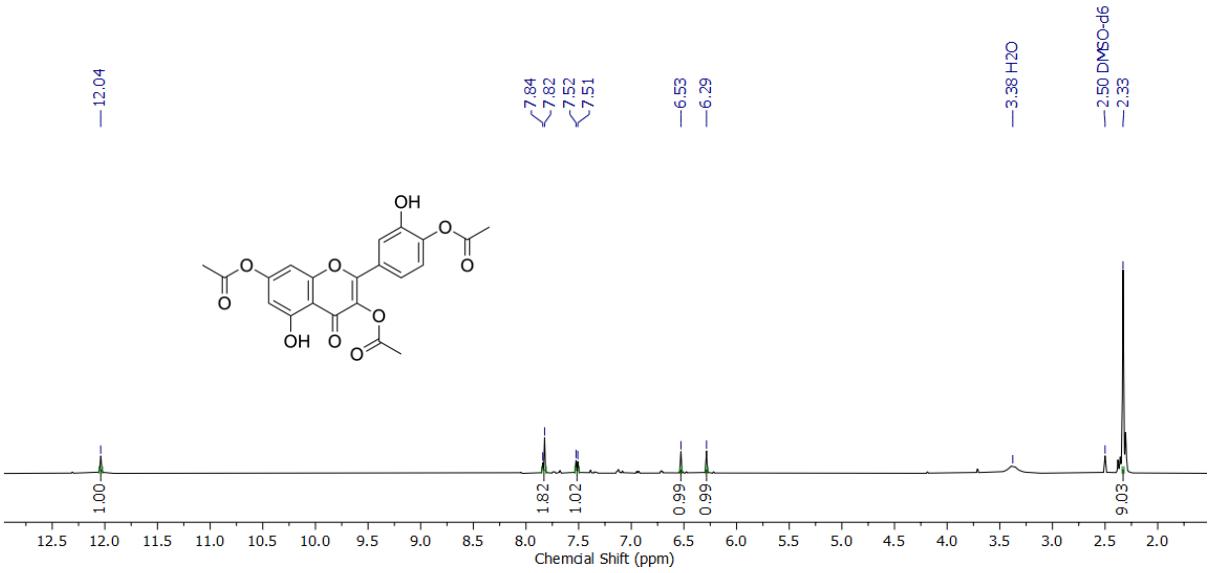

Figure S22. ^{1}H-NMR spectrum of compound **4a**

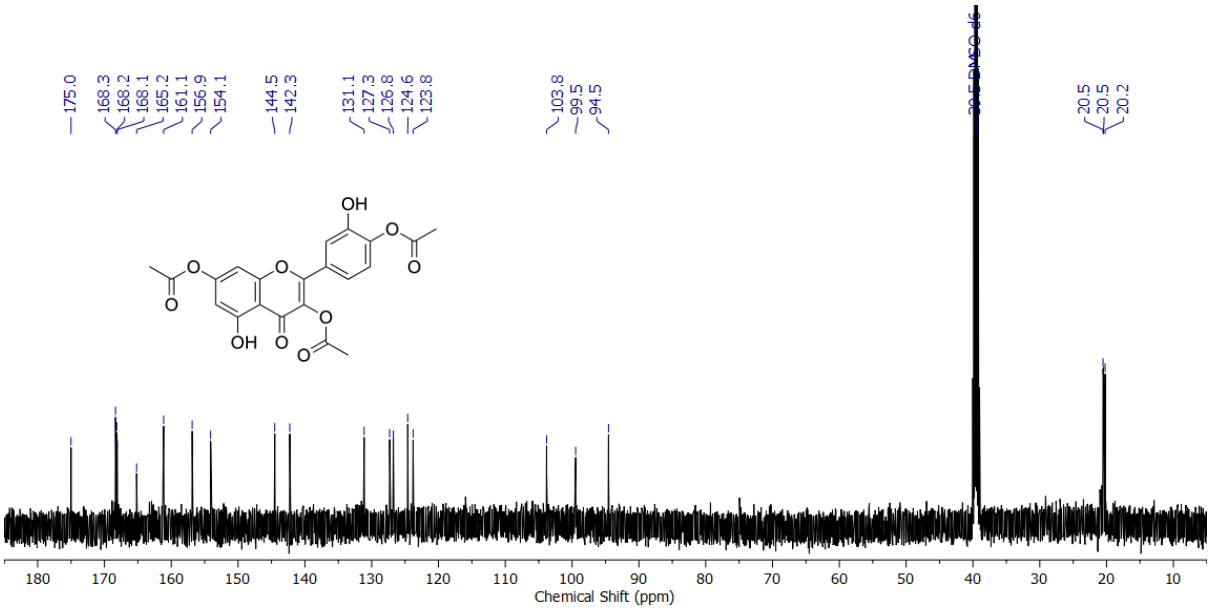

Figure S23. ^{13}C-NMR spectrum of compound **4a**

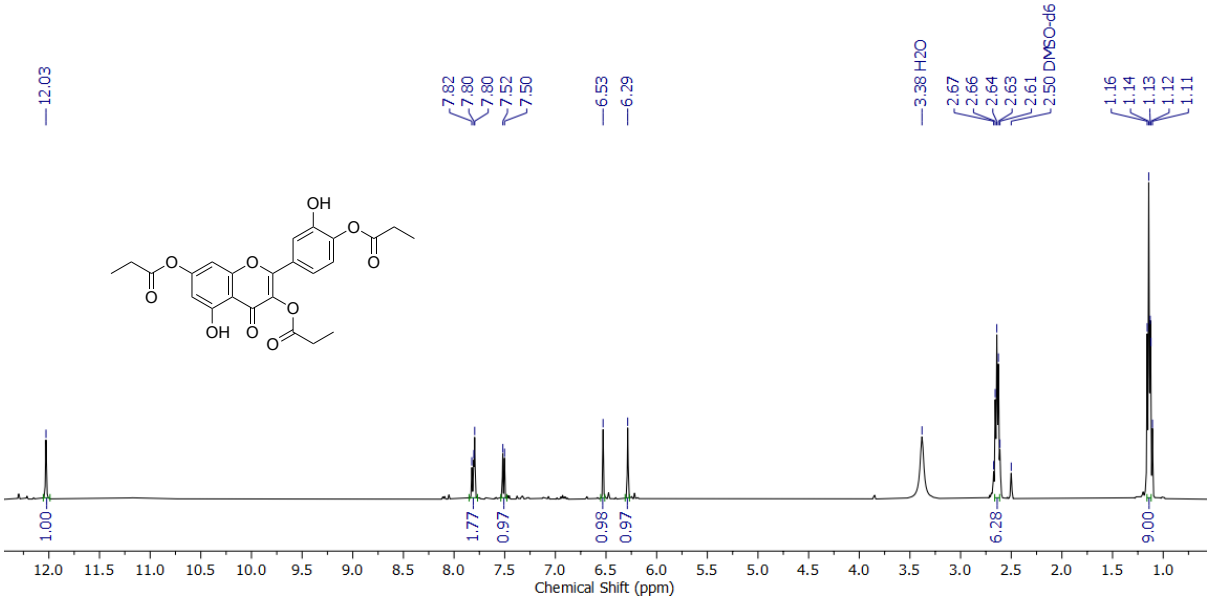

Figure S24. [1]H-NMR spectrum of compound **4b**

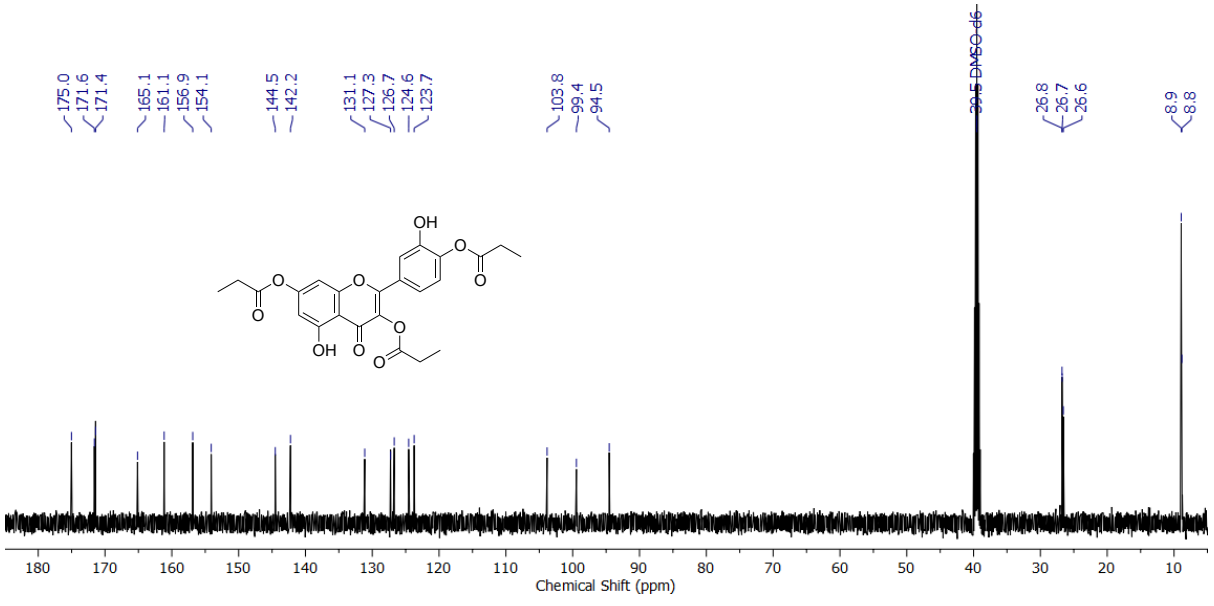

Figure S25. [13]C-NMR spectrum of compound **4b**

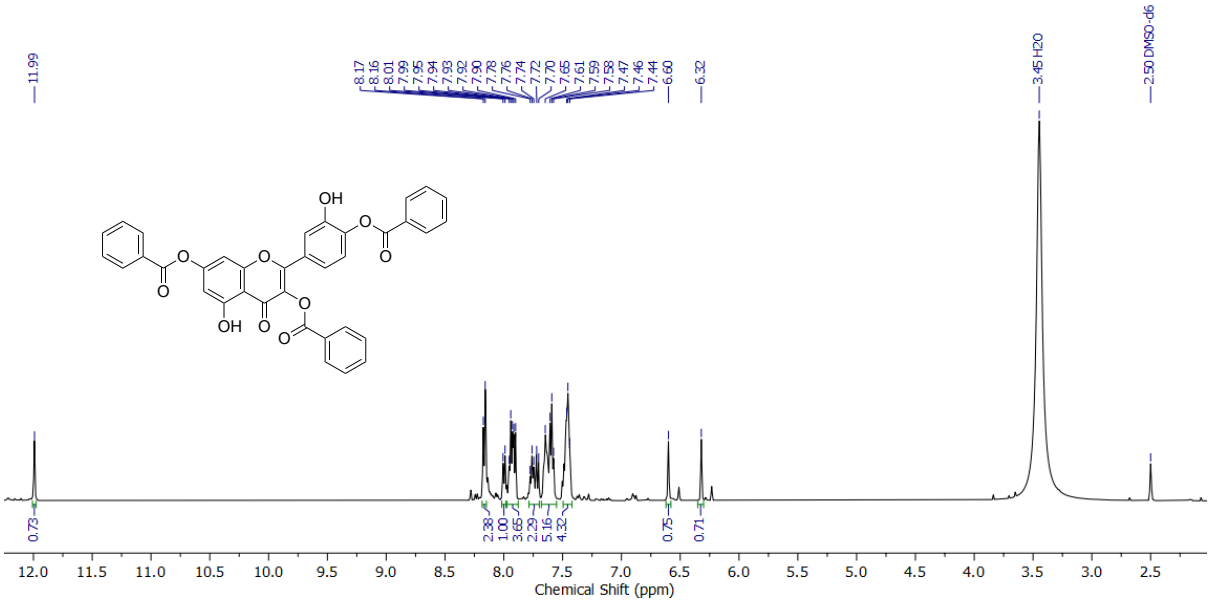

Figure S26. ^{1}H-NMR spectrum of compound **4c**

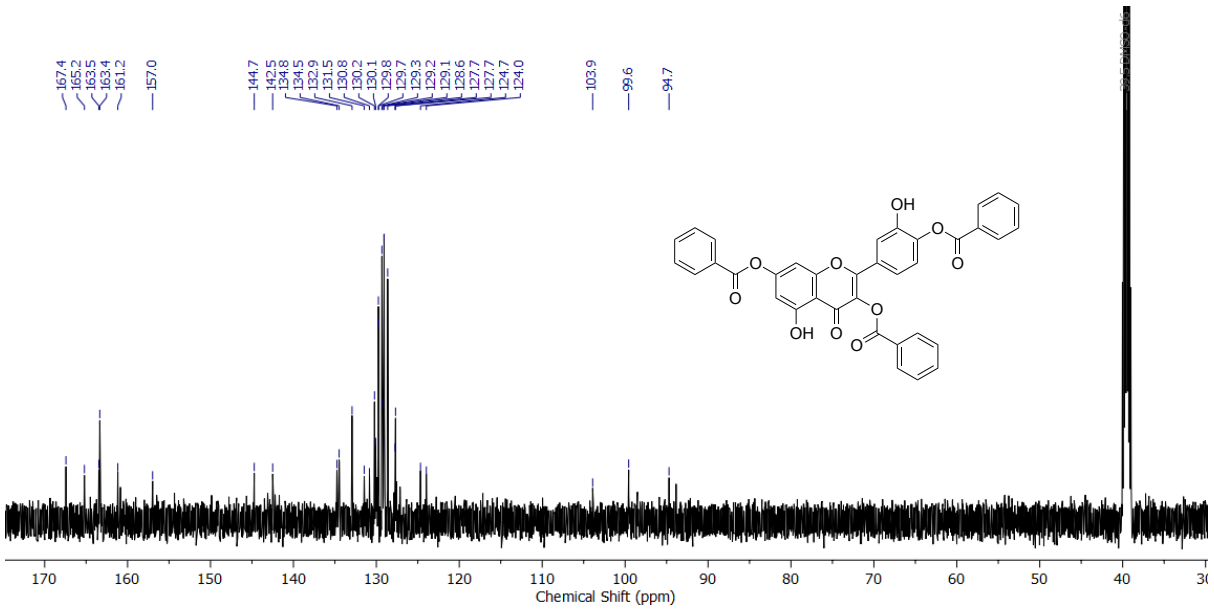

Figure S27. ^{13}C-NMR spectrum of compound **4c**

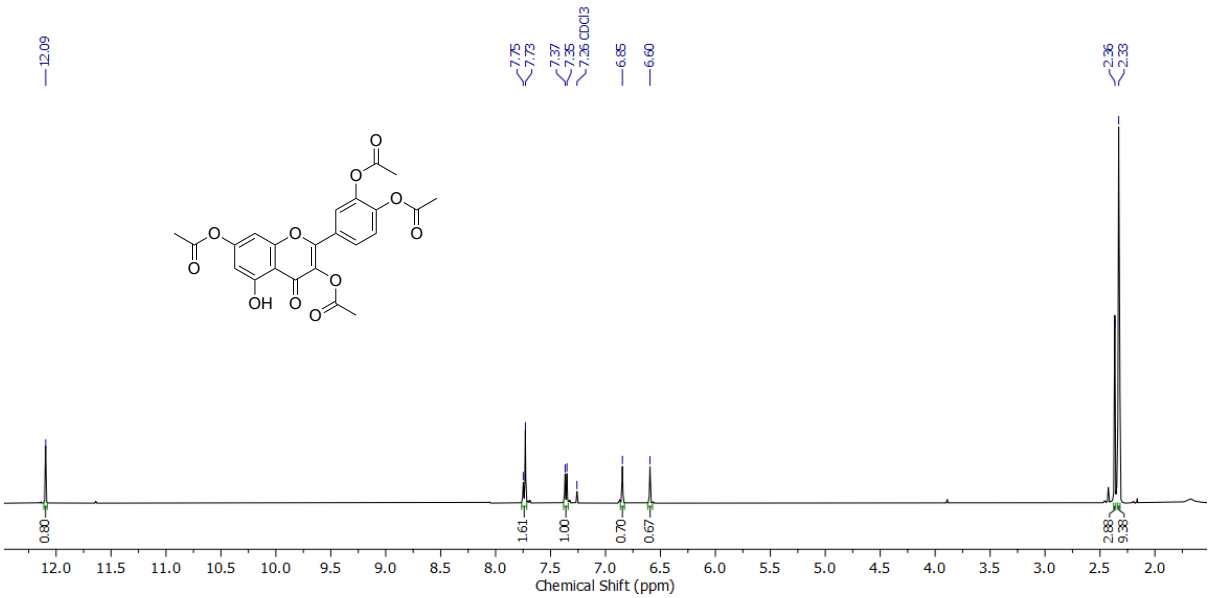

Figure S28. ^{1}H-NMR spectrum of compound **5a**

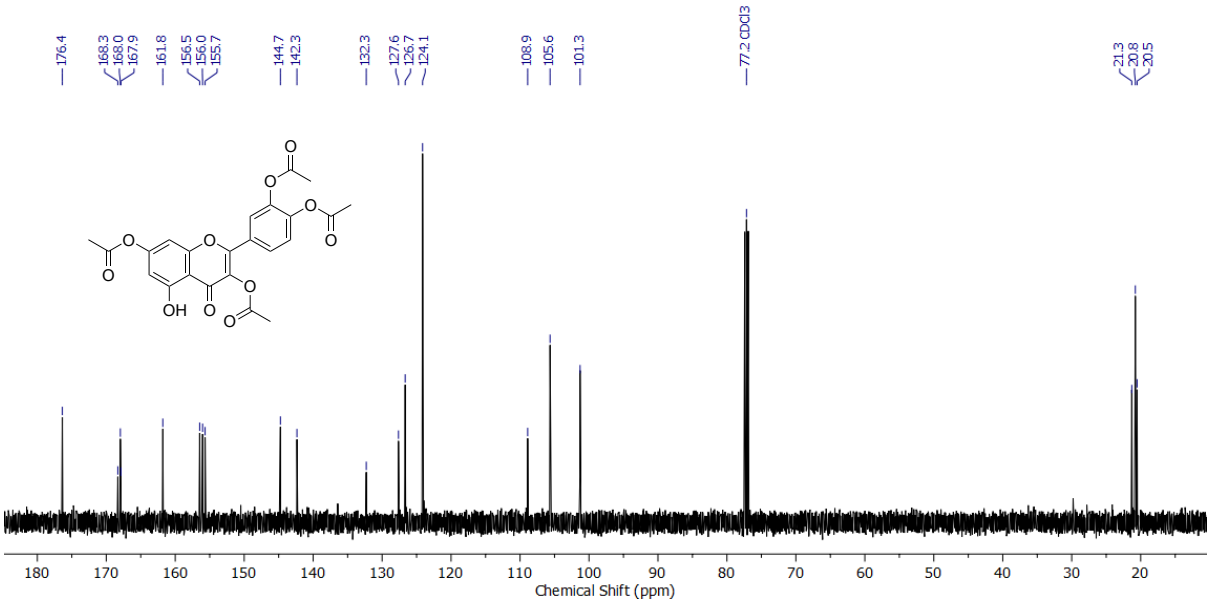

Figure S29. ^{13}C-NMR spectrum of compound **5a**

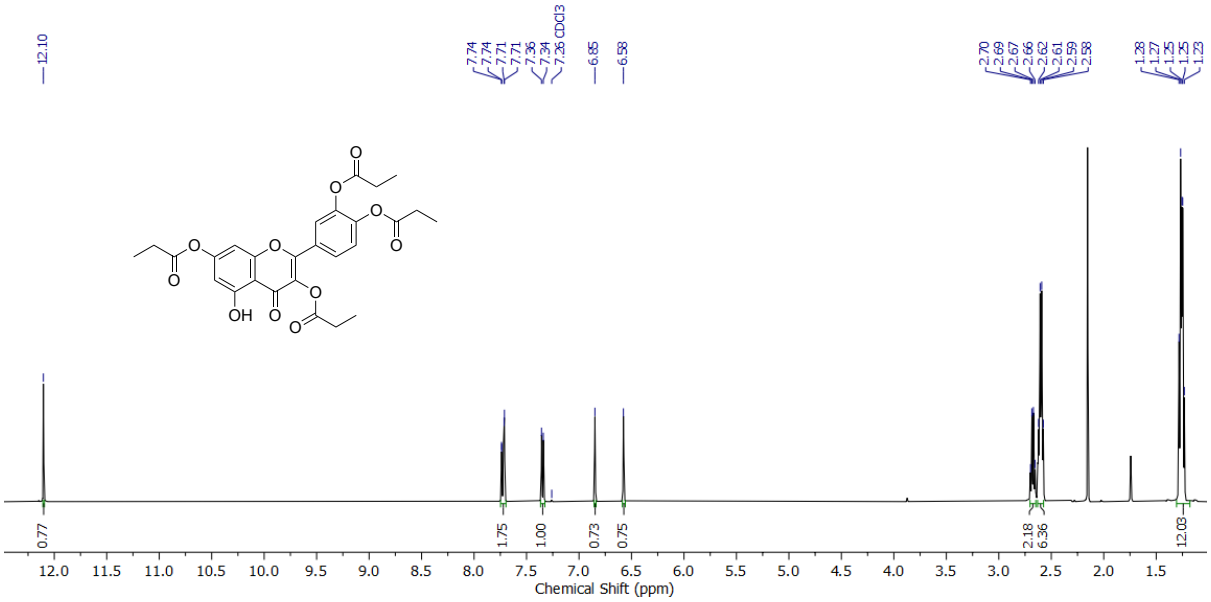

Figure S30. ^{1}H-NMR spectrum of compound **5b**

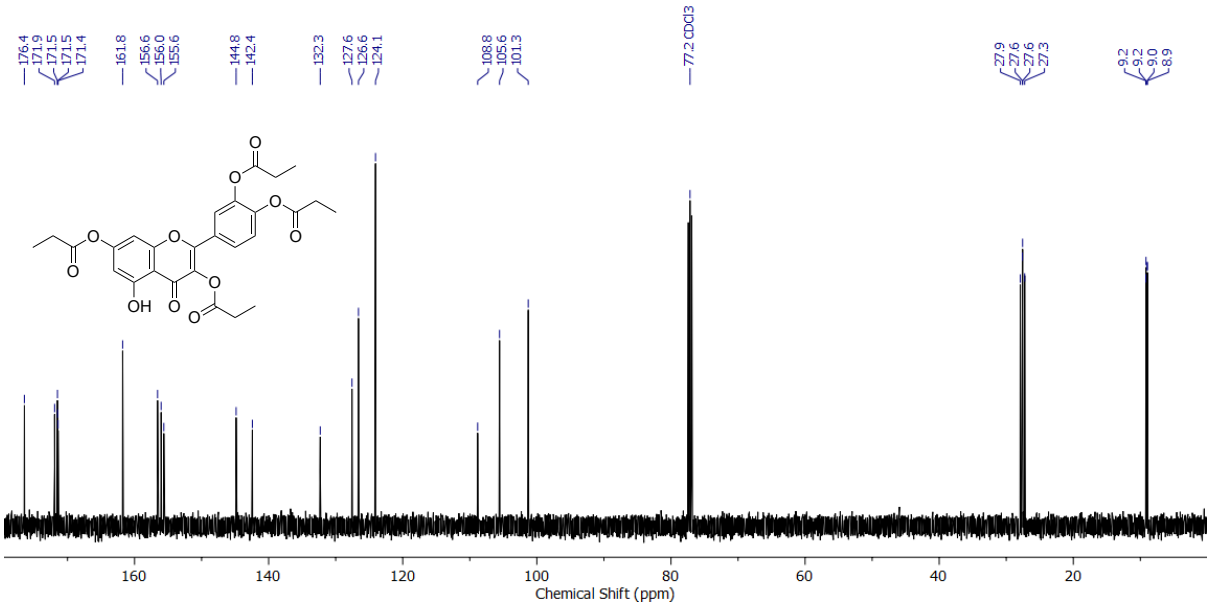

Figure S31. ^{13}C-NMR spectrum of compound **5b**

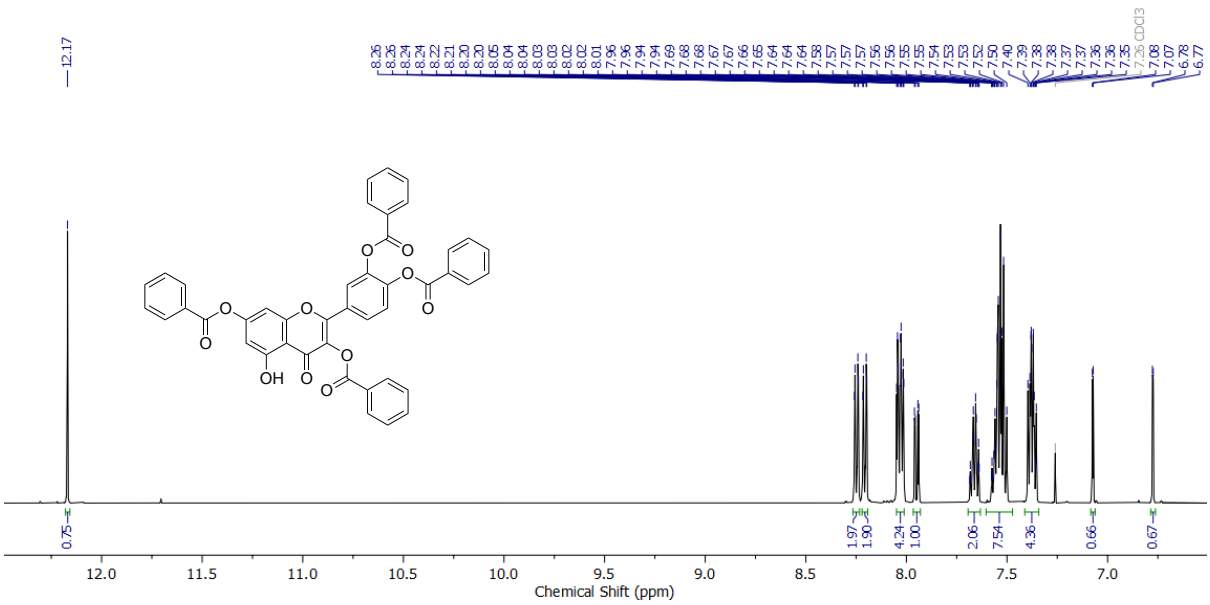

Figure S32. [1]H-NMR spectrum of compound **5c**

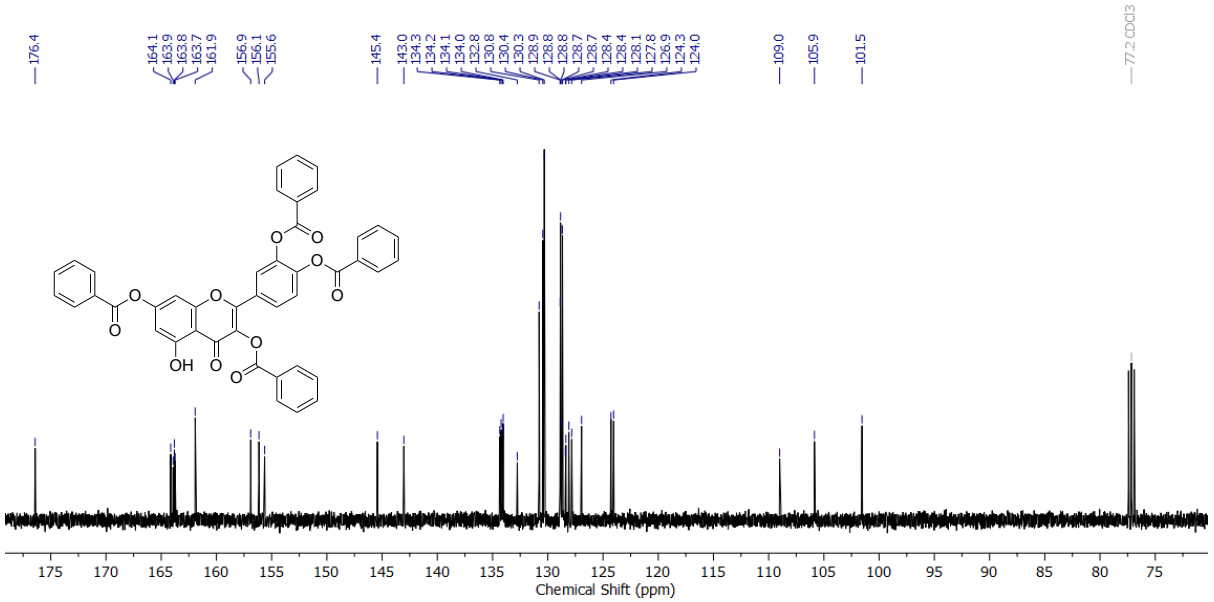

Figure S33. [13]C-NMR spectrum of compound **5c**

II. Percent Inhibition of Quercetin and its Derivative Against the SARS-CoV-2 S_1:ACE2 Interaction

Table S1. Summary of the percent inhibition of quercetin and its derivative against the SARS-CoV-2 S_1:ACE2 interaction

Concentration (µM)	**Compound 1**			**Concentration (µM)**	**Compound 2a**		
	Trial 1	**Trial 2**	**Trial 3**		**Trial 1**	**Trial 2**	**Trial 3**
100	46.34	-1.61	45.38	100	109.46	71.68	108.93
20	41.09	25.23	61.11	20	115.04	96.91	108.30
4	5.44	-13.15	24.79	4	112.77	100.85	105.39
0.8	-13.55	-40.18	-0.41	0.8	104.08	102.82	102.86
IC_{50}	**n.d.**	**n.d.**	**n.d.**	**IC_{50}**	**n.d.**	**n.d.**	**n.d.**
Concentration (µM)	**Compound 2b**			**Concentration (µM)**	**Compound 2c**		
	Trial 1	**Trial 2**	**Trial 3**		**Trial 1**	**Trial 2**	**Trial 3**
100	102.40	25.06	103.59	100	115.36	57.90	95.00
20	113.09	60.67	105.92	20	113.74	88.32	103.84
4	103.31	59.33	97.43	4	107.58	112.75	108.30
0.8	87.82	71.14	94.12	0.8	105.96	97.72	97.86
IC_{50}	**n.d.**	**n.d.**	**n.d.**	**IC_{50}**	**n.d.**	**n.d.**	**n.d.**
Concentration (µM)	**Compound 2d**			**Concentration (µM)**	**Compound 2e**		
	Trial 1	**Trial 2**	**Trial 3**		**Trial 1**	**Trial 2**	**Trial 3**
100	106.93	62.46	74.41	100	54.05	73.02	47.27
20	110.50	100.22	98.88	20	43.81	57.00	44.60
4	111.41	96.38	97.96	4	29.94	54.68	4.39
0.8	102.46	92.17	79.85	0.8	-14.71	21.83	-7.94
IC_{50}	**n.d.**	**n.d.**	**n.d.**	**IC_{50}**	**6.99**	**1.53**	**14.03**
				Average IC_{50}	**7.52 ± 6.27**		

Concentration (µM)	Compound 3a			Concentration (µM)	Compound 3b		
	Trial 1	Trial 2	Trial 3		Trial 1	Trial 2	Trial 3
100	68.63	97.45	97.82	100	50.68	70.96	83.64
20	69.41	95.66	86.89	20	38.50	48.77	65.96
4	16.46	58.34	59.50	4	-17.30	13.96	25.90
0.8	-21.52	36.69	33.58	0.8	-70.64	-2.15	8.72
IC_{50}	**11.07**	**1.95**	**1.99**	**IC_{50}**	**51.30**	**16.75**	**9.04**
Average IC_{50}	**5.00 ± 5.25**			**Average IC_{50}**	**25.70 ± 22.50**		
Concentration (µM)	**Compound 3c**			**Concentration (µM)**	**Compound 3d**		
	Trial 1	**Trial 2**	**Trial 3**		**Trial 1**	**Trial 2**	**Trial 3**
100	79.52	91.63	86.79	100	23.83	35.16	41.62
20	71.22	92.53	78.49	20	-1.52	15.37	10.08
4	54.12	77.40	49.07	4	4.85	24.15	23.48
0.8	-8.49	44.65	37.56	0.8	21.54	17.24	24.03
IC_{50}	**4.19**	**0.88**	**1.60**	**IC_{50}**	**n.d.**	**n.d.**	**n.d.**
Average IC_{50}	**2.22 ± 1.74**						
Concentration (µM)	**Compound 3e**			**Concentration (µM)**	**Compound 4a**		
	Trial 1	**Trial 2**	**Trial 3**		**Trial 1**	**Trial 2**	**Trial 3**
100	11.48	23.36	63.44	100	95.07	70.51	92.77
20	9.13	66.25	32.70	20	94.94	93.51	100.83
4	19.10	66.36	48.42	4	95.46	87.34	79.07
0.8	10.26	4.93	-3.81	0.8	74.34	75.88	39.84
IC_{50}	**n.d.**	**n.d.**	**n.d.**	**IC_{50}**	**n.d.**	**n.d.**	**n.d.**
				Average IC_{50}	**3.28 ± 2.69**		

Concentration (µM)	Compound 4b			Concentration (µM)	Compound 4c		
	Trial 1	Trial 2	Trial 3		Trial 1	Trial 2	Trial 3
100	89.37	108.72	49.70	100	83.08	95.00	91.07
20	77.12	74.63	70.28	20	52.14	83.60	83.65
4	46.21	68.19	43.53	4	41.87	79.00	76.57
0.8	-11.28	46.62	3.91	0.8	36.92	50.35	36.73
IC_{50}	**6.27**	**1.05**	**2.51**	**IC_{50}**	**n.d.**	**n.d.**	**n.d.**
Average IC_{50}	**3.28 ± 2.69**						
Concentration (µM)	**Compound 5a**			**Concentration (µM)**	**Compound 5b**		
	Trial 1	**Trial 2**	**Trial 3**		**Trial 1**	**Trial 2**	**Trial 3**
100	38.86	59.62	54.34	100	68.77	66.25	63.14
20	49.72	79.22	64.42	20	46.79	71.60	95.84
4	56.10	73.25	58.74	4	61.12	106.23	94.26
0.8	62.54	33.20	45.74	0.8	46.75	56.43	82.68
IC_{50}	**n.d.**	**n.d.**	**n.d.**	**IC_{50}**	**n.d.**	**n.d.**	**n.d.**
Concentration (µM)	**Compound 5c**			**Concentration (µM)**	**Erythrosine B**		
	Trial 1	**Trial 2**	**Trial 3**		**Trial 1**	**Trial 2**	**Trial 3**
100	7.48	10.22	-1.10	100	105.37	106.16	102.84
20	15.93	26.07	12.49	20	95.97	97.97	82.98
4	8.61	7.35	5.76	4	47.26	52.91	51.82
0.8	8.74	-18.80	-1.37	0.8	10.11	-18.41	-7.67
IC_{50}	**n.d.**	**n.d.**	**n.d.**	**IC_{50}**	**5.49**	**6.63**	**6.33**
				Average IC_{50}	**6.16 ± 0.59**		

Not determined (n.d.): compounds that did not exhibit a dose-dependent inhibition at the working concentration range (0.8 – 100 µM)

III. Raw Data of the Toxicity Profiles of the O-Modified Quercetin Derivatives

Table S2. Criteria for the cytotoxicity summary

Cytotoxicity Conclusion	Criteria
Safe	Cytotoxicity is < 10% in 3 out of 3 trials, or Cytotoxicity is < 10% in 2 out of 3 trials, and the cytotoxicity mean ± SEM across all 3 trials is < 10%
Equivocal	Cytotoxicity is < 10% in 2 out of 3 trials, but the cytotoxicity mean ± SEM across all 3 trials is ≥ 10%
Flagged	Cytotoxicity is ≥ 10% in at least 2 out of 3 trials

Table S3. Hepatotoxicity of sample compounds at their respective bioactive concentrations in HepG2 cells

Sample	Concentration (ppm)	Cytotoxicity (%)			Cytotoxicity
		Trial 1	Trial 2	Trial 3	
Quercetin (1)	30.22	< 0	1.23	3.99	Safe
2e	4.71	< 0	1.21	< 0	Safe
3a	2.07	0.81	1.53	2.06	Safe
3b	12.09	1.17	< 0	< 0	Safe
3c	1.03	< 0	< 0	< 0	Safe
4b	1.54	< 0	0.63	< 0	Safe

Table S4. Nephrotoxicity of sample compounds at their respective bioactive concentrations in HK-2 cells

Sample	Concentration (ppm)	Cytotoxicity (%)			Cytotoxicity
		Trial 1	Trial 2	Trial 3	
Quercetin (1)	30.22	4.18	< 0	0.50	Safe
2e	4.71	1.72	< 0	2.15	Safe
3a	2.07	9.06	3.13	4.32	Safe
3b	12.09	0.73	2.43	1.97	Safe
3c	1.03	< 0	0.12	< 0	Safe
4b	1.54	0.54	< 0	0.24	Safe

Table S5. Cardiotoxicity of sample compounds at their respective bioactive concentrations in H9c2 cells

Sample	Concentration (ppm)	Cytotoxicity (%)			Cytotoxicity
		Trial 1	Trial 2	Trial 3	
Quercetin (1)	30.22	0.47	32.23	6.57	Equivocal
2e	4.71	2.03	< 0	1.61	Safe
3a	2.07	0.33	< 0	< 0	Safe
3b	12.09	0.15	< 0	2.99	Safe
3c	1.03	0.47	< 0	5.02	Safe
4b	1.54	< 0	< 0	5.85	Safe