SUPPLEMENTARY MATERIALS

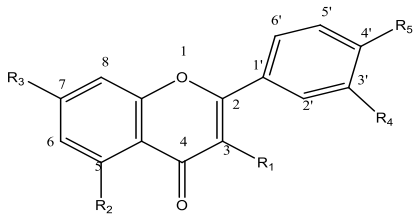


Figure S1: Quercetin nucleus

Table S1: Binding affinity of quercetin and its synthesized derivatives (kcal/mol)

Ligands							Binding affinity (kcal/mol)			
S/N	**R1**	**R2**	**R3**	**R4**	**R5**	**Others**				
							2GHU	**3QVI**	**4YA8**	**6GJG**
1	OH	OH	OH	OH	OH		-8.0	-7.9	-7.3	-8.2
2	OAc	OAc	OAc	OAc	OAc	C=C at C3	-9.0	7.4	7.4	8.0
3	OH	OH	OH	OH	OH	C=C at C1 & C3. No =O at C4	-8.1	8.1	7.9	8.2
4	OH	OH	OH	------	------	C=O at C2 &Ar at C3	-7.8	-8.4	-7.9	-7.9
5	OH	OH	H	OH	OH		-9.2	-8.8	-7.1	-8.2
6	OH	OH	OH	OH	H		-7.9	-7.6	-6.8	-8.3
7	OH	OH	OH	H	OH		-8.3	-8.2	-7.3	-8.0
8	OH	OH	OH	OH	OH	-OH in place of =O at C4	-8.3	-7.7	-7.3	-9.0
9	OH	OH	OH	OCH_3	OH		-8.6	-8.1	-7.2	-8.2
10	OH	OCH_3	OH	OH	OH		-9.0	-8.2	-7.2	
11	OH	OCH_3	OCH_3	OH	OH		-7.8	-8.1	-6.7	-7.5
12	OH	OH	OH	OH	OCH_3		-8.4	-8.3	-7.0	-7.8
13	OH	OH	OH	OCH_3	OH		-8.8	-8.2	-7.5	
14	OH	OCH_3	OCH_3	OCH_3	OCH_3		-8.0	-7.4	-6.6	-6.5
15	OCH_3	OCH_3	OCH_3	OCH_3	OCH_3		-7.8	7.5	-6.5	

16	OCH_3	OH	OH	OH	OH		-8.0	-8.0	-7.2	
17	OH	OH	OH	OH	OH	OH at 5''	-8.9	-8.1	-7.8	
18	OH	OH	OH	OH	OH	No = between C2 and C3	-8.8	-8.6	-7.8	-8.8
19	$OCOCH_3$	OH	OH	OH	OH	No double bond between C2 and C3	-8.9	-8.1	-8.1	-9.5
20	$OCOCH_3$	OH	OH	OH	OH		-7.5	-7.8	-7.0	-7.6
21	$OCOCH_3$	OH	OH	OH	OH	No C=O at C4	-7.9	-7.9	-7.6	-9.3
22	OH	OH	OH	OH	OH	No C=O at C4	-8.1	-8.0	-7.6	-8.6
23	H	OH	OH	OH	OH	No C=O at C4	-8.2	-7.7	-7.6	-8.0
24	H	OH	OH	OH	OH	No C=O at C4, No = between C2 & C4	-8.6	-8.1	-7.6	-9.5
25	$OCOCH_2CH_3$	OH	OH	OH	OH		-7.9	-7.7	-7.2	-9.1
26	$OCOCH_2CH_2CH_3$	OH	OH	OH	OH		-9.2	-8.2	-8.4	-9.6
27	$OCOCH(CH_3)_2$	H	OH	OH	OH		-8.6	-8.4	-8.4	-9.4
28	OCOCH(CH3)3	H	OH	OH	OH	No double bond between C2 & C3	-8.6	-8.6	-8.9	-9.7
29	$OCOC(CH_3)_3$	OH	OH	OH	OH	No double bond between C2 & C3	-8.7	-8.4	-8.4	-8.9
30	$OCOC(CH_3)_3$	OH	OH	OH	OH	No double bond between C2 & C3	-8.5	-8.5	-8.3	-9.5
31	$OCOCH_2CH_3$	OH	OH	OH	OH		-8.6	-8.0	-7.4	-9.6
32	$OCOCH_2CH_3$	OH	OH	OH	OH	OH at C4	-8.0	-7.7	-7.1	-8.5
33	$OCOC(CH_3)_3$	OH	OH	OH	OH	No C=O at C4	-8.6	-8.3	-8.5	-9.6
34	H	H	H	H	H		-7.8	-7.8	-7.1	-8.2
35	OH	H	OH	OH	OH		-9.2	-8.4	-6.8	-7.9
36	Ar	OH	OH	…….	…..	OCOCH3 at C2	-8.5	-8.1	-7.4	-9.9
37	Ar	OH	OH	OH	……	OCOCH2CH3 at C2	-7.9	-7.5	-7.1	-8.6

38	Ar	OH	OH	OH		OCO(CH2)2CH3 at C2	-8.2	-7.4	-7.8	-9.1
39	Ar	OH	OH	OH	…….	OCOCH(CH3)2 at C2	-8.7	-8.0	-7.9	-10.4
40	Ar	OH	OH	OH		OCO(CH3)2 at C2, No C=C between C2 & C3	-8.7		-7.9	-9.8
41	Ar	OH	OH	OH	……	OCO(CH3)2 at C2 and No C=O at C4	-8.6	-8.0	-7.8	-10.6
CQ							-7.0	-8.0	-6.4	-7.9
DHA							-8.3	-7.1	-7.2	-8.5

2GHU = Falcipain-2, 3QVI = Histo-aspartic protease, 4YA8 = plasmepsin II, 6GJG = dihydroorotate dehyrogenase

NB: S/N 1, 2, and 3 are quercetin; 3, 5, 7, 3', 4' -penta-acetoxyflav-3-ene (Flav-3); and 3,3',4',5,7-pentahydroxyflavylium (Flav); respectively

Table S2: Amino acid residue and bonding involved in *Plasmodium falciparum* (2ghu) and the selected ligands

Ligand	**Binding Affinity**	**H-bonding**	**Akyl/ pi- akyl**	**Others**
Quercetin	-8.0	Ala:C:110, Gln: A208	Val:A:30, Cys: C: 144	Phe: A:215, Arg: A25
Flav-3	-9.0	Asn: D: 16	Trp: A:206	Gly: A:40, Gln: A23
Flav	-8.1	Asn: D:16	Trp: A:210	Gly: A:40,Cys: A:42
CQ	-7.0	Ala:A:157	Trp: D 206	Glu: D:222, Asp: D: 18
DHA	-8.3	Asn: A:38	Gln: A: 36	Glu: D:14, Asn: A:173

Table S3: Molecular properties of ligands with the best activity

Ligand	**log P**	**No of atoms**	**MW**	**nON(acceptors)**	**nOHNH(donors)**	**n Violators**
Quercetin	1.68	22	302.24	7	5	0
Flav-3	2.22	23	316.61	7	4	0
Flav	3.68	24	326.30	6	2	0
CQ	3.77	25	342.35	6	2	0
DHA	1.78	26	360.32	8	4	0

Figure S2: 2D visualization of the binding interaction between quercetin with *Plasmodium falciparum* (2ghu)

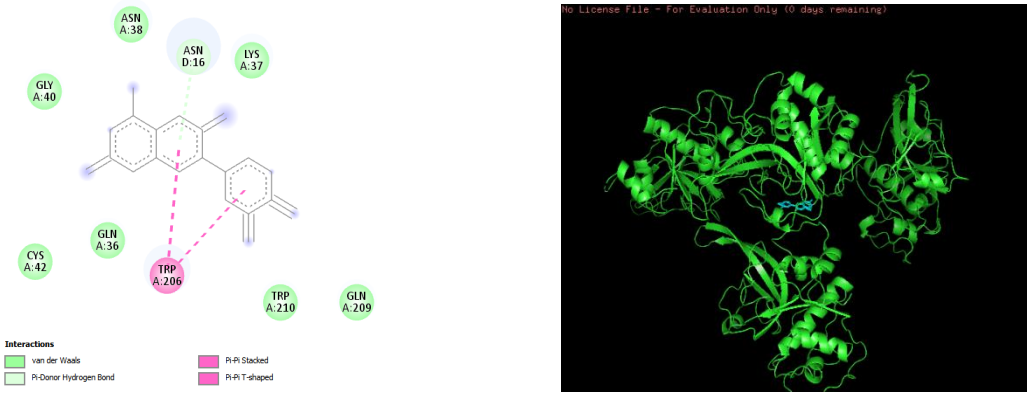


Figure S3: 2D visualization of the binding interaction between 3, 3′, 4′, 4, 7′ - pentahydroxyflavylium with *Plasmodium falciparum* (2ghu).

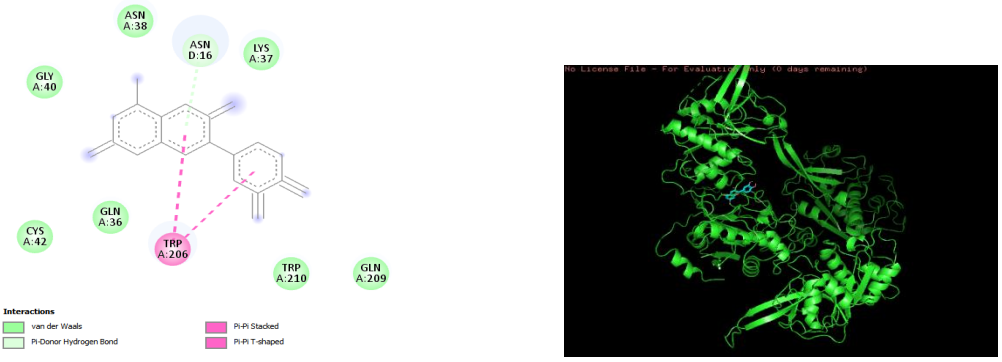


Figure S4: 2D visualization of the binding interaction between 3, 3′, 4′, 5, 7, -pentahydroxyflav-3-ene with *Plasmodium falciparum* (2ghu)

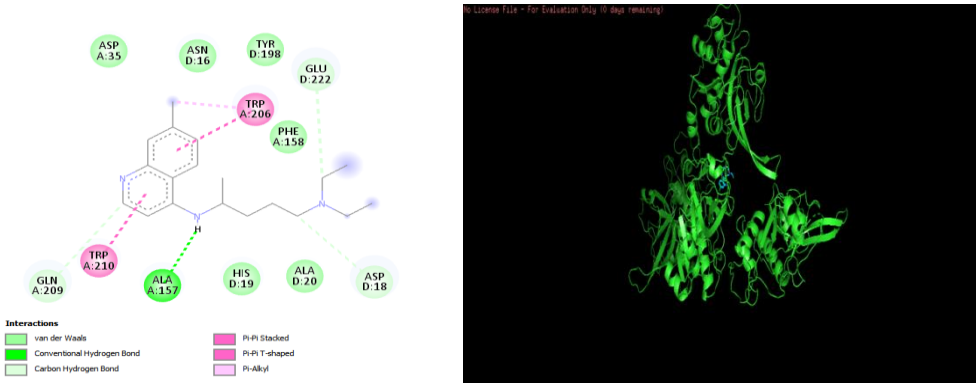


Figure S5: 2D visualization of the binding interaction between chloroquine with *Plasmodium falciparum* (2ghu)

Figure S6: 2D visualization of the binding interaction between dihydroartimisinin (DHA) *with Plasmodium falciparum* (2ghu)

Table S4: Pharmacokinetic properties of quercetin and its synthesized derivatives with the best binding affinity

Ligand	Intestinal absorptn (human) in %	Fraction unbound (human) (Fu)	CYP3A4 inhibition	Total Clearance (log ml/min/kg)	AMES toxicity	Max. tolerated dose (human) (log mg/kg/day	LD_{50} (mol/kg	Oral Rat Chronic Toxicity (log mg/kgbw/day)	Hepatotoxicity	Water solubility (log mol/L
Quercetin	74.634	0.132	No	0.547	Yes	0.951	2.562	1.735	No	-3.18
Flav-3-ene	93.541	0.15	No	0.238	Yes	0.606	2.041	1.766	Yes	-3.448
Flavylium	84.575	0.144	No	0.104	No	1.001	2.374	1.917	No	-3.04
CQ	75.251	0.109	Yes	0.242	Yes	0.543	2.259	1.786	Yes	-4.487
DHA	79.737	0.155	Yes	0.307	Yes	0.875	2.454	1.349	No	-3.187

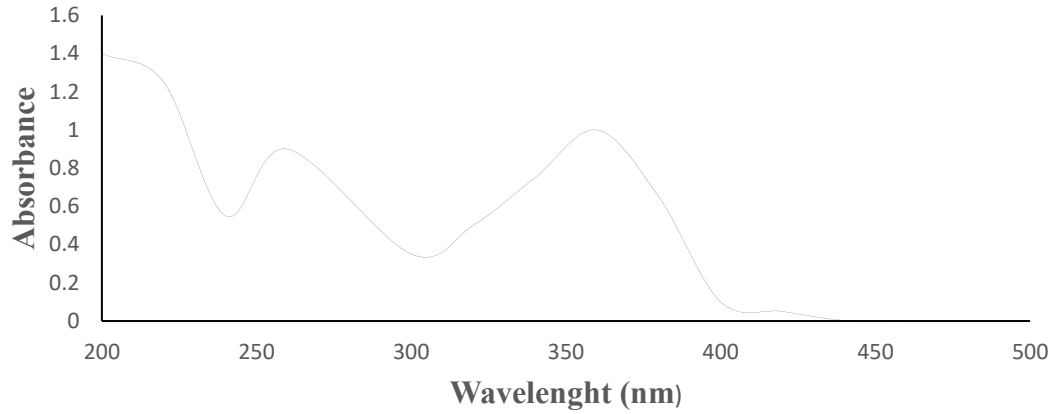


Figure S7: UV Spectrum of Quercetin

Source: UV-Visible UH4100 Chromatogram (2023).

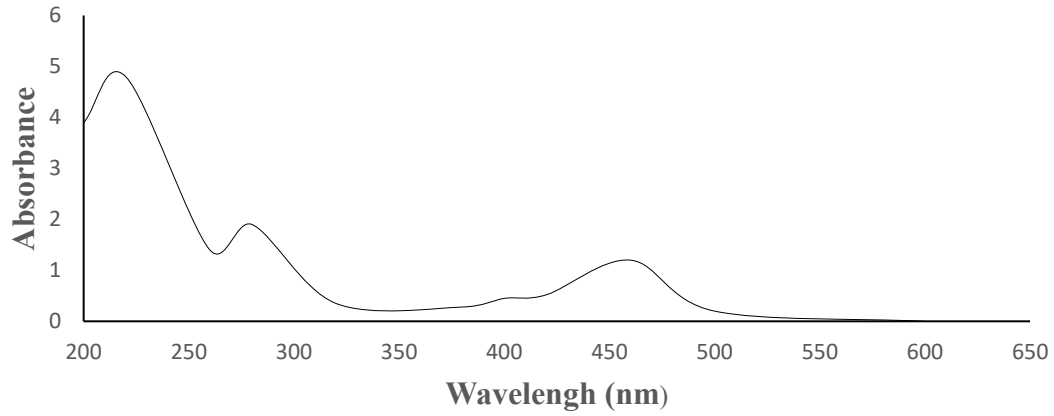


Figure S8: UV Spectrum of flav-3-ene

Source: UV-Visible UH4100 Chromatogram (2023)

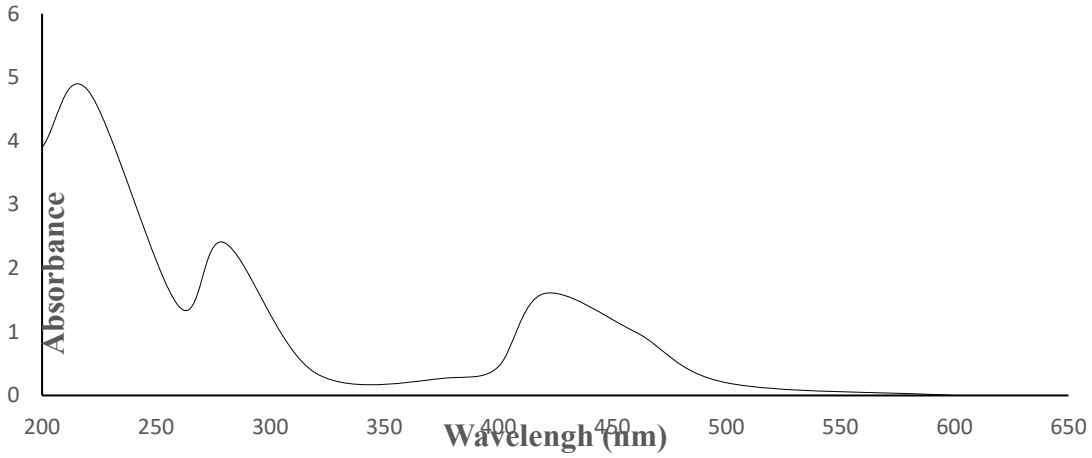


Figure S9: UV Spectrum of flavylium

Source: UV-Visible UH4100 Chromatogram (2023)

Table S5: Comparison Of Drug Exposure And Parasitaemia Clearance

Parameter	**F (%)**	**Parasitaemia (%)**
DHA only	55.44	72
DHA+ Q	53.20	60
DHA+ D_1	49.54	65
DHA+ D_2	58.63	83

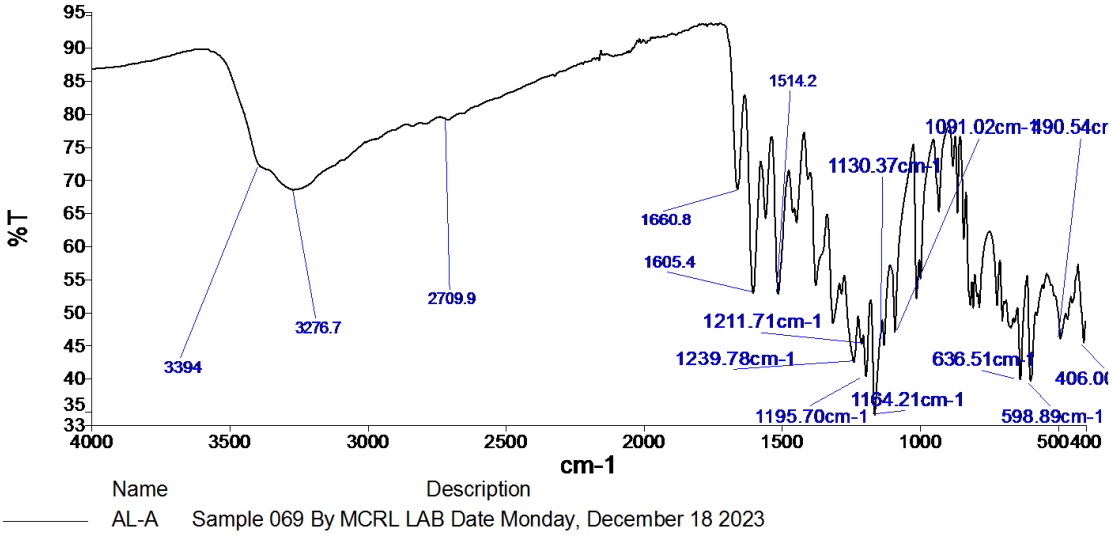


Figure S10: FT-IR of Quercetin

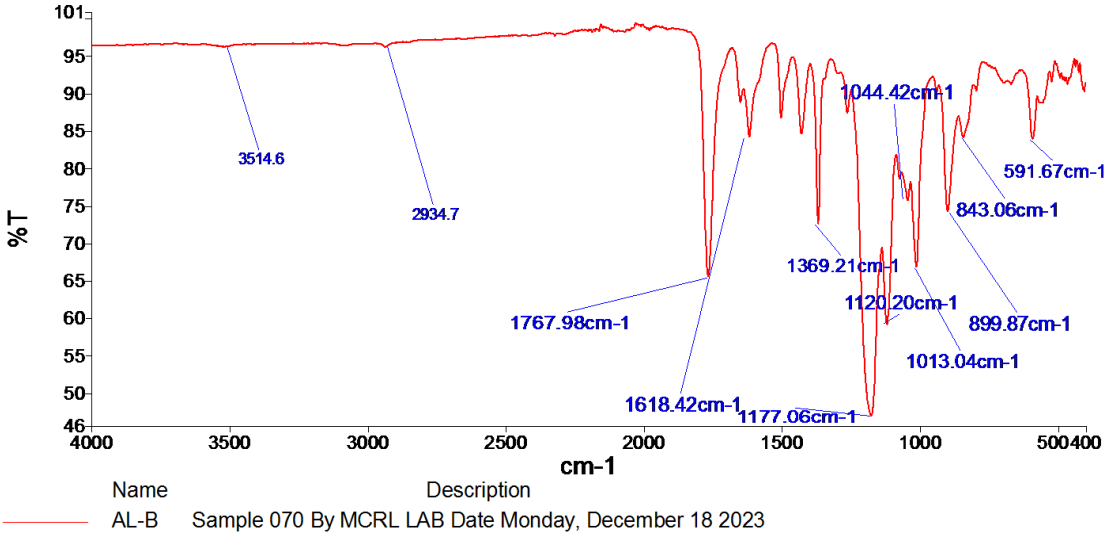


Figure S11: FT-IR of 3, 5, 7, 3', 4' -penta-acetoxyflav-3-ene

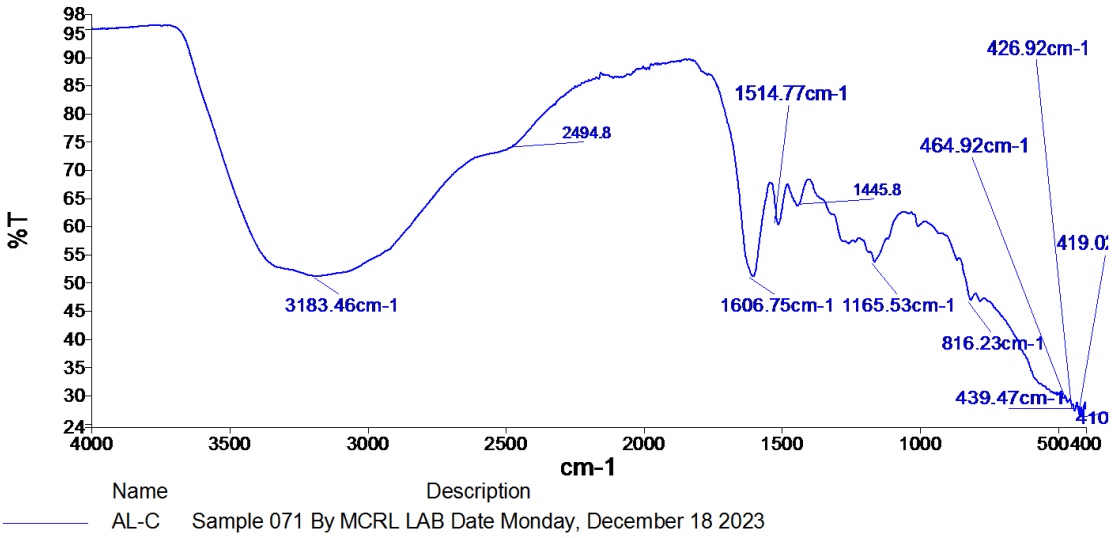


Figure S12: FT-IR of 3,3’,4', 5,7-pentahydroxyflavylium

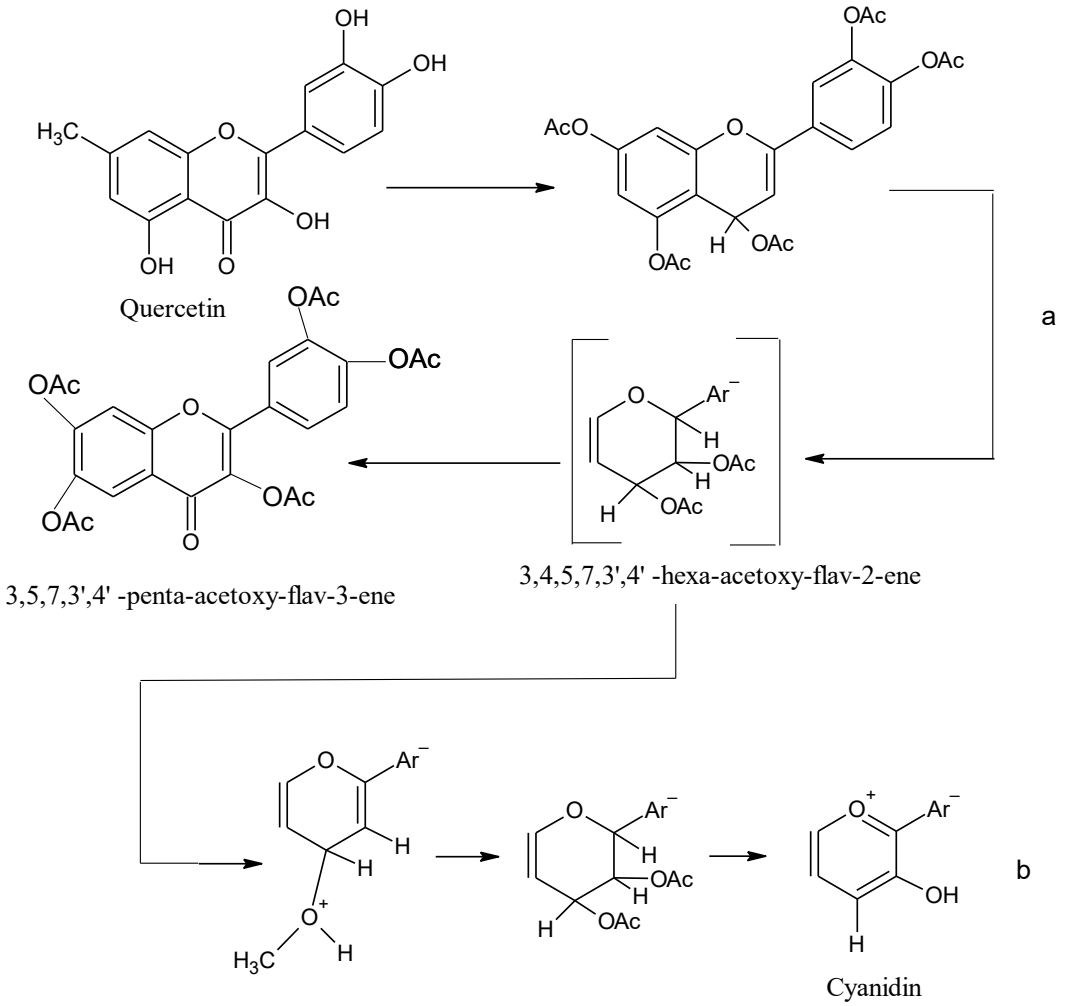
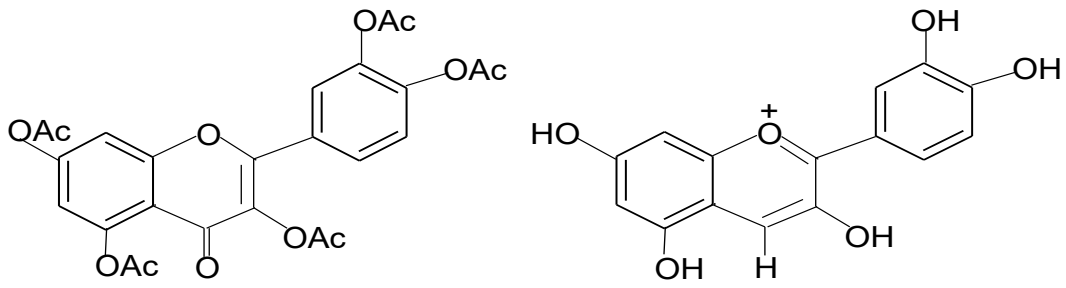


Figure S13: Scheme for the synthesis of the derivatives



3, 3′, 4′ 5, 7-penta-acetoxyflav-3-ene

3, 3′, 4′, 5, 7- pentahydroxyflavylium

Figure S14: Structures of the synthesized derivatives

Preparation of Simulated Intestinal Fluid (SIF) Test Solution

The simulated intestinal fluid (SIF) was prepared without pancreatin. Exactly 13.61g and 1.80g of KP_2PO4 and NaOH, respectively were dissolved separately in distilled water in 500 mL beakers and later decanted into 2.0 L volumetric flask. The beakers were rinsed severally into the volumetric flask and swirled for complete homogenization. The pH was adjusted to 6.80 ± 0.01 with HCI and NaOH solutions, and the volume was finally made up to 2.0 L mark with distilled water. This was used in the dissolution of the formulated drugs (DHA and AQ) for calibration curve as well as reconstitution of the extracted drug from the serum for UV-spectrophotometric drug concentration determination.