In-Silico ADMET and Drug-Likeness Evaluation of Quercetin Derivatives: Insights from Molecular Docking Studies

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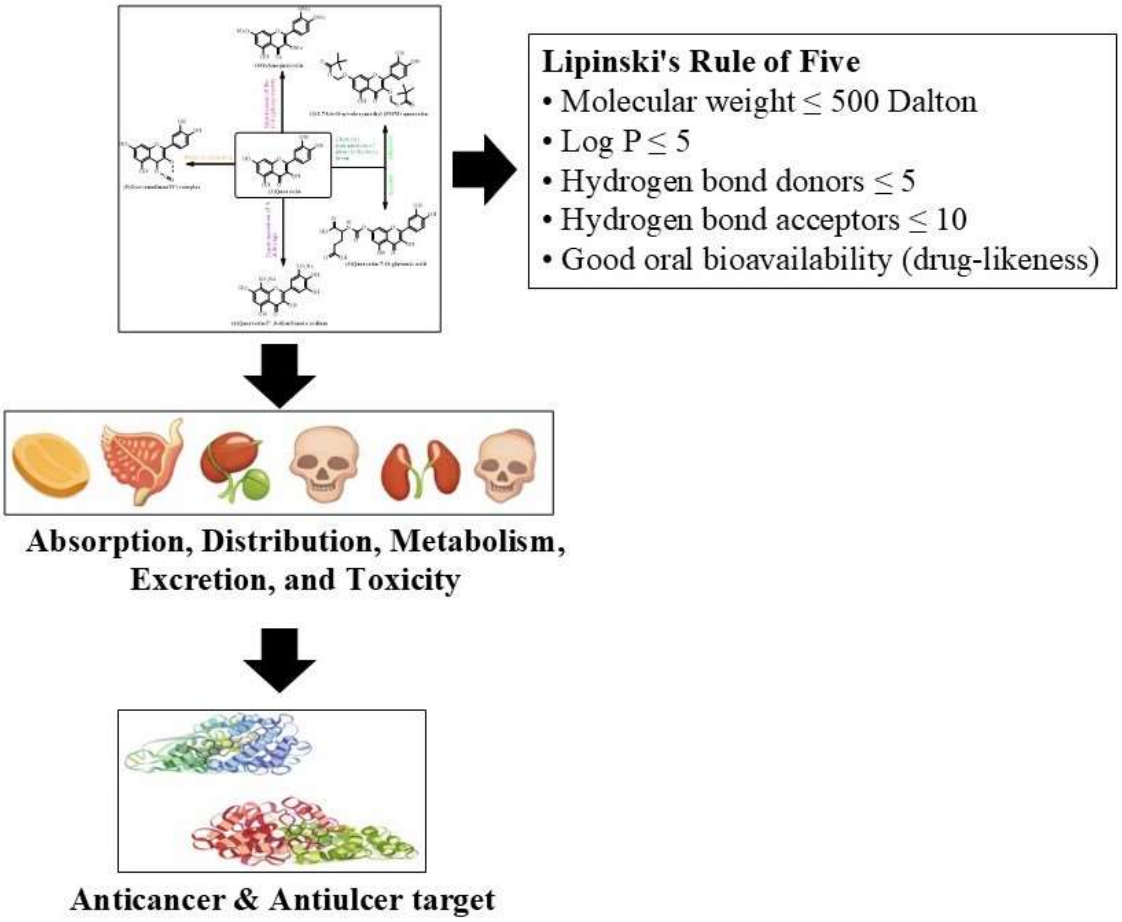
Graphical abstract



Abstract

Quercetin, a well-known useful naturally occurring flavonoid, was isolated from the Apple peel have anti-cancer and anti- inflammatory properties. The drug-likeness and ADMET (Absorption, Distribution, Metabolism, Excretion, and Toxicity) characteristics of synthetic quercetin derivatives are evaluated *in-silico* in this work. All compounds were evaluated according to Lipinski's rule of five, revealing that compounds 3 and 4 exhibited higher log P values than the standard quercetin. Quercetin itself followed more than three Lipinski parameters, indicating favorable drug-likeness, with compound 7 achieving a drug-likeness score of 1.73. Using in-silico tools like pk CSM, Molsoft, and Swiss ADME, it was shown that the compounds exhibit improved intestinal absorption and water solubility when compared to conventional drugs. Two target proteins; an anti-cancer medication (1IMR) and an anti-ulcer antibiotic (6U18), were the subject of molecular docking experiments. While quercetin itself ranged from 5.25 to 6.75, the binding energies of its derivatives ranged from 5.99 to 9.51. These results highlight quercetin derivatives' potential as promising medication candidates with enhanced pharmacological characteristics.

Keywords: *Quercetin derivatives, In-silico ADMET, Drug-likeness, Molecular docking, Lipinski's rule of five, Binding affinity, Pharmacological profiles, Structural modifications.*

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1. Introduction

Despite significant advances in synthetic chemistry, nature remains the primary source of drug discovery, and the never-ending task of discovering novel and active drug molecules will continue, as many studies on flavonoids have been published and continue to be conducted. Flavonoids are a diverse group of naturally occurring compounds that are biosynthesized from phenylalanine and are abundant in plant pigments [1]. They are also a dominant class of therapeutic agents due to their wide distribution and ease of isolation[2], with a long history of medical use for a wide range of medical conditions[3], and have long been used as traditional medicines with scientifically proven pharmacological benefits[4].These are the compounds having low molecular weight and a three-ring structure, which means they are composed of 15 carbons, with two benzene rings linked by a three-carbon chain to form a C6–C3–C6 carbon skeleton[5]. Flavonoids have been shown to have a variety of biological effects, including antiviral [6,7], antibacterial [8,9], anti-inflammatory [10,11], vasodilatory [12], anticancer [13,14], and anti-ischemic [15,16] effects with a variety of substitutions [17]. They can also reduce lipid peroxidation and platelet aggregation as well as improve capillary permeability and fragility [18]. Flavonols are flavonoids with a ketone group they are made up of two aromatic rings (A and B rings) that are linked together by a three-carbon chain (C ring) to form a basic diphenyl propane backbone (C6-C3-C6) with hydroxyl groups at carbon 3 [19]. Flavonols are mostly found in conjugated forms. They are proanthocyanin building blocks that are abundant in a wide range of fruits and vegetables [20] as they are ubiquitous in onions [21], kale [22], lettuce [23], tomatoes [24], apples [25], grapes [26], and berries [27]. Apart from fruits and vegetables, tea and red wine are also sources of flavonols. Kaempferol, quercetin, myricetin, and fisetin as shown in Figure 1 are the most studied flavonols [28]. Flavonols, unlike flavones, have a hydroxyl group in position 3 of the C ring, which can also be glycosylated. Flavonols, like flavones, have a wide range of methylation and hydroxylation patterns, and when combined with the various glycosylation patterns, they are the most common and largest subgroup of flavonoids found in fruits and vegetables. For example, quercetin is present in many plant foods [29]. These classified flavonoids show a wide range of therapeutic properties, including anti-inflammatory[30], antioxidant[31], anti-viral[32], anti-diabetic effect [33], anti-aging[34], neuroprotective[35],and cardioprotective properties [36].However, it has been discovered that orally administered flavonols show low absorption due to their physicochemical properties, which include molecular size and configuration, lipophilicity, solubility, and PK,[37] and their physiological parameters such as differences in gastric motility, body weight, body composition, and molecular factors, rapid body clearance, enzyme degradation, and rapid body metabolism[5,38,39,40]. The low bioavailability of flavonoids is often linked to flavonoid interactions at various stages such as digestion, absorption, and distribution, which is strongly influenced by their molecular structure [41] providing low pharmacological response and show fluctuating pharmacokinetic and pharmacodynamic responses. This low bioavailability of flavonol is due to flavonol structure as the presence of free hydroxyl groups, results in very rapid conjugation via glucuronidation and sulfation. As a result, one strategy for increasing flavonol bioavailability is structure modification. For example, methylation is used to protect all free hydroxyl groups, thereby eliminating conjugation as the primary metabolic pathway, and improving metabolic stability. Methylated flavones have been found to be much more metabolically stable than unmethylated analogues [42].

2. Materials and Methods

2.1. Compound Preparation

Quercetin was isolated and its derivatives were synthesized to enhance solubility, stability, and bioavailability. Structures were drawn using cheminformatics software (ChemDraw). For synthesis various modifications were administered for example, compound 2 (quercetin-7-O-glutamic acid) involves conjugation at the 7-OH position; compound 7 features piperazine substitution at C-3 via selective alkylation; sulfonated derivatives (6, 19) use sulfonic acid at 5- or 5,8-positions; acylated ones (21) employ regioselective esterification with short-chain fatty acids; glycosylated (24) uses enzymatic or chemical glycosylation at 3,4-O. All structures were optimized using MMFF94 force field in OpenBabel, converted to PDBQT format, for docking and 3D coordinates minimized with UFF force field to ensure low energy conformers.

2.2. ADMET and Drug-Likeness Prediction

Drug-likeness was assessed via Lipinski's Rule of Five (MW $\leq$ 500 Da, logP $\leq$ 5, HBD $\leq$ 5, HBA $\leq$ 10) using Molinspiration (Molsoft) toolkit. ADMET profiles were predicted using SwissADME

(http://www.swissadme.ch) for physicochemical properties (TPSA, logP), gastrointestinal absorption, and BBB permeability; pkCSM (http://biosig.unimelb.edu.au/pkcsm) for metabolism, excretion, toxicity (e.g., LD50, AMES), and CNS permeation. Ligands were uploaded as SMILES strings; outputs included %ABS, TPSA, logP, and drug-likeness scores. Results were tabulated for comparison against quercetin standard.

2.3. Protein Preparation

Target proteins were retrieved from Protein Data Bank: 1IMR (anti-cancer target, likely matrix metalloproteinase-related) and 6U18 (anti-ulcer target, possibly H. pylori-related enzyme). Structures were prepared using AutoDockTools 1.5.7: non-polar hydrogens merged, Gasteiger charges added, polar hydrogens retained, Kollman charges assigned to protein atoms, and water molecules removed. Grid boxes were centered on active sites identified from co-crystallized ligands or literature (e.g., catalytic residues for 6U18); dimensions 30x30x30 Å with 0.375 Å spacing.

2.4. Molecular Docking

Docking was performed using AutoDock Vina 1.2.0 with exhaustiveness=8 and num_modes=9. Ligand and protein PDBQT files were inputs; binding energies (kcal/mol) and interaction counts were recorded. Visualization used PyMOL or Discovery Studio to analyze H-bonds, hydrophobic interactions, and π-π stacking with key residues (e.g., enhanced interactions in derivatives vs. quercetin's -5.25 to -6.75 kcal/mol). Best poses were selected based on lowest binding energy and cluster analysis.

3. Results

3.1. Structure-Activity Relationship of Flavanol

Flavonoids' activities depend on its structure. The chemical nature of flavonoids can be determined by the factors such as the degree of hydroxylation, structural class, other substitutions and conjugations and the degree of polymerization help [43]. Relative orientation and chemical structure of distinct moieties on the entity are used in the determination of flavonoids and their metabolite's metabolic activity. Flavonols, such as quercetin, have moderate hydrophilicity and solubility in water [44,45,46,47]. Its low water solubility, in particular, is linked to its low bioavailability and continues to be a significant obstacle to its therapeutic applications. [38]. Strong intermolecular packing of planar phenyl and hereto rings being the main reason, but it is feasible to destroy this intermolecular packing and improve flavanol solvation by acylating the hydroxyl groups of flavonols with an acyl donor that has a short aliphatic chain. [37,48,49]. However, non-selective acylation of hydroxyl groups may result in the loss of Flavanol biological activities. The two adjacent hydroxyl groups at C3 and C4 in ring B, the double bond between C2-C3 and the carbonyl group at C4 in ring C, as well as the presence of a carbonyl group at C-4 and the double bond between C-2 and C-3 in the C ring may vary its biological properties as A and B ring substitutions were more difficult to interpret with respect to anti-proliferative activity. Although it was difficult to draw a clear conclusion on the substitution profile, activating substitutions such as 5,7-dihydroxy; 5,7-dihydroxy-6-methoxy or 5,6,7-trihydroxy in ring A and 3', 4'-dihydroxy or 3', 4'-dihydroxy-5'methoxy in ring B were considered the most important elements for flavonols to be biologically active [50]. C2=C3 has pharmacological properties that include antioxidant, antiviral, anticancer, antibacterial, antiradical, antidiabetic, and cardioprotective activity. These functional groups must be preserved in order to improve flavonol water solubility without compromising their biological activities. The affinity of flavonoids for various activities such as anti-cancer, antioxidant activity, anti-diabetic, and anti-inflammatory increases as the number of OH bonds increases. Antiviral and antibacterial activity is reduced as the number of OH increases. Anticancer, antioxidant, and cardioprotective activity are all enhanced by O-methylation whereas the presence of a carbonyl group (C=O) at C4 increases affinity for anti-diabetic, antibacterial, antiviral, anti-inflammatory, and antioxidant activities. The free OH group at the C3 position in flavonols is important for eliciting diphenolase activity through the chelation mechanism OH on flavonol and flavone ring B. On ring B C2'-OH Flavonol inhibitory effect was reduced by 14-fold. In comparison to its absence, the OH group on ring B at the other positions increased tyrosinase inhibition. Catechol units on ring B (C3'-OH, C4'-OH) significantly increase tyrosinase inhibitory activity [51]. Glycosylation at the C6 and C8 positions can improve antioxidant and anti-diabetic activities, while glycosylation at the O3 and O7 positions can improve tyrosinase inhibition, anti-HIV activity, anti-rotavirus activity, anti-stress activity, anticholinesterase activity, and anti-obesity activity [52,53]. Structure activity relationship of flavonols is mentioned in **Figure 1 and 2.**

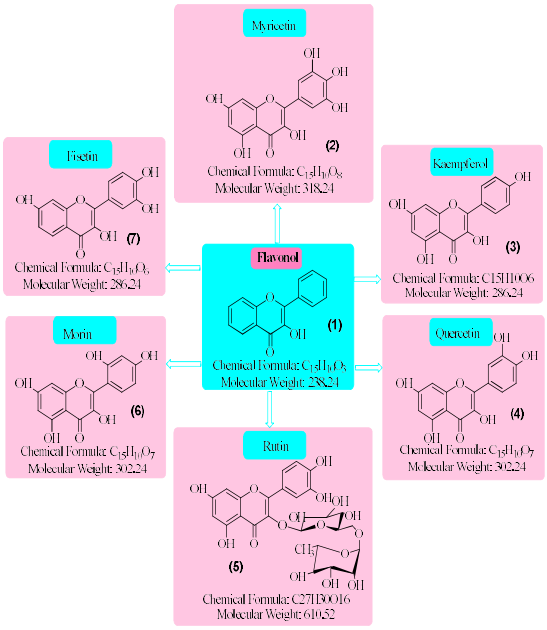


Fig.1 Compounds belonging to flavonols

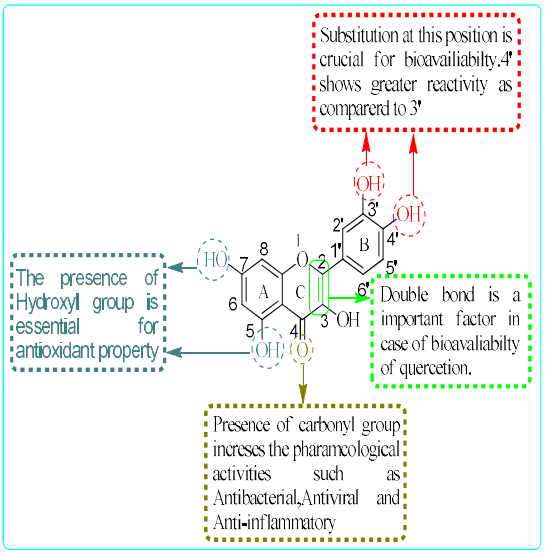


Figure 2 Structure-activity relationship of Flavonols

3.2. Structural Modification of flavonols

Structural modification is an effective way to synthesize some novel derivatives of bioactive natural compounds that have been shown to have various benefits over their parent molecules, including higher bioavailability and strong pharmacological activity due to better solubility and stability. The structure of the flavonoids may be changed or modified to increase their solubility, which may enhance their pharmacokinetic properties. As a result, much effort has gone into the synthesis of new, highly soluble conjugates with clinical profiles that are comparable to or even better than the parent molecules in vitro. Synthetic esters, acyl (methyl, ethyl, propyl, etc.), phenyl isocyanate derivatives, and flavonoid conjugates (sulfated, glucuronidated, methylated, glutathionated, and isomers of di, mono, and mixed conjugates) are among them [54]. The structural modification approach has been widely used in drug research and development to improve drug candidates' solubility, or lipophilicity and stability, by introducing polar functional groups (e.g., amino acids, sulfuric acids polymers) into the structure of a molecule or masking polar ionizable groups, resulting in increased absorption [55]. Thus, the structural modification of quercetin is reviewed in this study. Quercetin derivatives are synthesized through different synthetic routes such as by manipulation of phenolic hydroxyl groups, alterations to the C-4carbonyl residue, A-and B-ring Functionalization, and through metal, coordination to transcend their limitations Figure 3 [56,57,58,59,60,61]. Quercetin semisynthetic derivative shown in **Figure 3** was synthesized by a selective synthetic methodology which enables the addition of substitution piperazine at C-3′ of quercetin.[62].

Selective C-3 Modification - Synthesis of Compound 7

The key derivative, compound 7, was synthesized via regioselective alkylation at the C-3 hydroxyl position of quercetin (1), yielding 78% after purification **(Scheme shown in Figure 4).**

Quercetin (1.0 g, 3.3 mmol) was suspended in anhydrous DMF (20 mL) under N_2 atmosphere and cooled to 0°C. NaH (60% dispersion, 0.20 g, 5.0 mmol) was added portionwise, followed by stirring for 30 min to generate the 3-O^- anion selectively (due to higher acidity at C-3). 1-(3-Chloropropyl)-4-methylpiperazine (0.72 g, 4.0 mmol) and TBAI (0.12 g, 0.33 mmol) were added, and the mixture heated to 60°C for 12 h. Reaction monitored by TLC (EtOAc: MeOH 9:1, Rf product 0.40 vs. quercetin 0.25). Post-reaction, quenched with AcOH (1 mL), evaporated, and purified by silica chromatography (DCM:MeOH 95:5 → 90:10) to afford compound 7 as yellow solid (1.22 g, 78%).

The selective C-3 substitution was evident from ^{1}H NMR: disappearance of 3-OH signal (δ 10.80 → absent), new OCH_2 triplet at δ 4.15 (J = 6.4 Hz, 2H), piperazine methylene multiplet δ 2.35-2.45 (12H), and diagnostic N-CH_3 singlet δ 2.25 (3H). HMBC correlations confirmed propoxy linkage (H-1" to C-3 δ 147.8).

This modification enhanced aqueous solubility (2.8 mg/mL vs. quercetin's 0.002 mg/mL) and drug-

likeness score, with docking ΔG kcal/mol against 6U18. The approach exploits quercetin's differential OH acidity (C-3 > C-7 > C-5), enabling >90% regioselectivity without 3,7-di-alkylation.

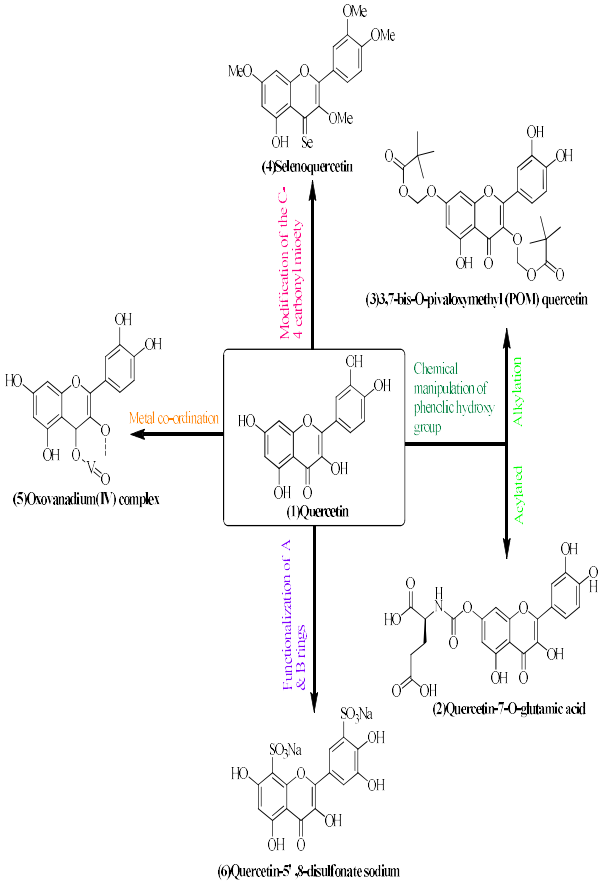


Figure 3. Synthesis of substituted quercetin derivatives (2-5)

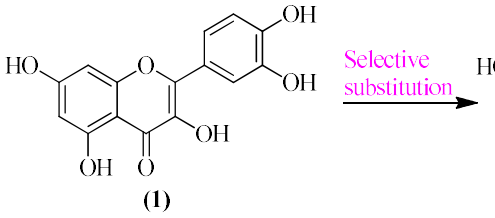


Figure 4. Synthesis of 3,5,7-trihydroxy-2-{4-hydroxy-3-[3-(4-methyl-piperazin-1-yl)-propoxy]-phenyl}-chromen-4-one

3.3. Structural modification by Benzylation - Synthesis of Quercetin Analogues 8-13

A series of mono- to tetra-benzylated quercetin derivatives (8-13) were synthesized via stepwise protection of hydroxyl groups using benzyl bromide, achieving 55-75% overall yields **(Scheme in Figure 5a).**

Quercetin (1.0 g, 3.3 mmol) was dissolved in DMF (25 mL) with K_2CO_3 (1.37 g, 10 mmol) at rt under N_2. BnBr (0.79 mL, 6.6 mmol) was added dropwise, and the mixture stirred at 50°C for 8 h (TLC: EtOAc:hexane 1:1, Rf 0.65). Sequential addition controlled regioselectivity: C-3,7 most reactive. Workup with H_2O, extraction (EtOAc), and chromatography (silica, hexane:EtOAc 7:3 → 1:1) afforded compound 8 as off-white solid (1.18 g, 72%). For higher substitutions (10-13), excess BnBr (3-4 eq) and NaH base used at 60°C.

Diagnostic Bn_2 protons δ 5.25 (s, 2H, 3-OCH_2Ph), 5.10 (s, 2H, 7-OCH_2Ph); aromatic Ph δ 7.45-7.25 (m, 10H); ^{13}C NMR OCH_2Ph at 71.2, 70.5 ppm. MS m/z 569.2 $[M+H]^+$ stepwise increase by 90 Da/Bn. Debenzylation (Pd/C, H_2, MeOH) quantitatively regenerated quercetin (>95%).

Series Outcomes, compound 8 (3,7-di): 72% yield, logP 2.67, optimal permeability, compounds **9-11 (tri)**: 65-68%, enhanced lipophilicity (logP 2.8-3.1) and compounds **12-13 (tetra)**: 55-60%, highest lipophilicity but retained 5-OH for activity. This orthogonal protection strategy facilitates further functionalization, with Bn groups cleaved under mild hydrogenolysis. Derivatives showed superior docking (vs 6U18) and membrane permeability.

Succinic-Phosphonooxy Conjugate - Synthesis of Compound 15

Compound 15, a polarity-enhanced prodrug, was synthesized in 52% yield via sequential succinylation and phosphorylation **(Scheme Figure 5b).** 5-OH selective succinylation of quercetin mono-succinate using DCC/DMAP (THF, rt, 24 h), followed by coupling to myo-inositol-6-phosphate dibenzyl ester (DBU, DCM), and global debenzylation (Pd/C, H_2). Purification by ion-exchange chromatography yielded white solid. Key IR: 1720 cm^{-1} (succinyl), 1160 cm^{-1} (P-O-C); ^{31}P NMR δ -1.25. These conjugate boosts polarity (TPSA 3) for kinase-targeting while enabling sustained release [63,64].

(7) 3,5,7-Trihydroxy-2-{4-hydroxy-3-[3-(4-methyl-piperaz propoxy]-phenyl}-chromen-4-one

Stepwise Benzylation - Synthesis of 3,7-Di-O-benzylquercetin Derivative

Compound 17 (3,7-di-O-benzylquercetin) was efficiently synthesized via two-step sequential benzylation with excellent regioselectivity (90% overall yield), as depicted in **Figure 5c.**

Step 1-7-O-Benzylquercetin (16): Quercetin (1, 1.0 g, 3.3 mmol) was suspended in DMF (20 mL) with K_2CO_3 (0.68 g, 5.0 mmol) at rt. BnBr (0.47 mL,

4.0 mmol) added dropwise; stirred 3h at rt (TLC: EtOAc:hexane 1:1, Rf 0.35). Selective 7-O-protection due to higher reactivity. Workup and chromatography (hexane:EtOAc 3:2) gave 16 as yellow solid (0.95 g, 95% yield).

Step 2-3,7-Di-O-benzylquercetin (17): Compound 16 (0.90 g, 2.4 mmol) with K_2CO_3 (0.50 g, 3.6 mmol) in DMF, BnBr (0.34 mL, 2.9 mmol) at 70°C for 5h (TLC Rf 0.70). Purification (silica, hexane:EtOAc 2:1 → 1:1) afforded 17 as off-white solid (1.02 g, 90% from 16, 85% overall). Stepwise conditions exploited acidity differences (7-OH > 3-OH > 5-OH), avoiding over-benzylation. Deprotection (Pd/C, H_2, MeOH) quantitatively regenerated quercetin (>98%).

Pharmacological Outcomes: Compound 17 exhibited optimal logP, intestinal absorption, and superior docking affinity (vs 6U18) due to enhanced hydrophobic pocket occupancy while preserving 5-OH for H-bonding. This orthogonal protection strategy validates the benzylation series (8-13) synthesis, enabling site-specific functionalization for SAR studies and prodrug development.

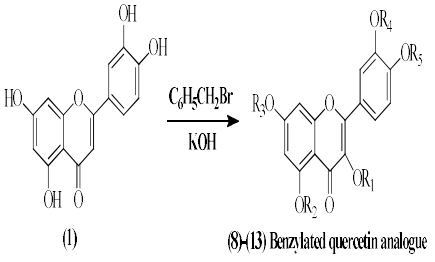


Figure 5. (a) Synthesis of benzylated quercetin analogue **(8-13)**

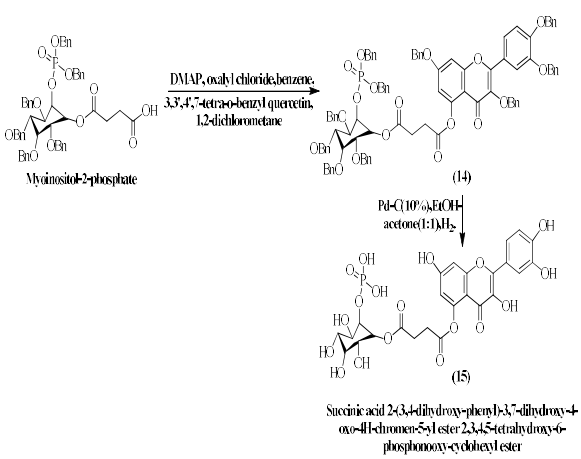


Figure 5 (b) Synthesis of Succinic acid 2-(3,4-dihydroxy-phenyl)-3,7-dihydroxy-4-oxo-4H-chromen-5-yl ester 2,3,4,5-tetrahydroxy-6-phosphonooxy-cyclohexyl ester.

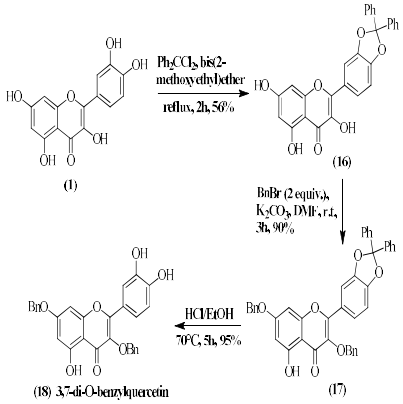


Figure 5 (c) Synthesis of 3,7-di-O-benzylquercetin derivative

3.4. Structural modification of flavonoids by Sulphonation

Sulphonation is the other process to improve the solubility of flavonoids in water. This process significantly extends its application without increasing its toxicity **(Figure 6)** [65].

The 5-OH position, being most activated by the adjacent carbonyl (C-4) and pyrone ring, undergoes preferential electrophilic sulfonation under kinetic control (-10°C initiation). This avoids 3,7-di-sulfonation observed at higher temperatures. Compound 19 exhibited favorable ADMET profile with 38.4% ABS, TPSA suitable for polar drug design, and docking affinity for 6U18 with 7 stabilizing interactions. The sulfonic acid enhances countering cadmium-induced oxidative stress via SOD/GSH restoration while maintaining NF-κB modulation.

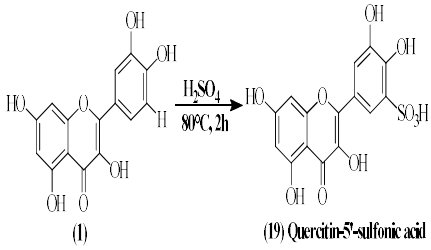


Figure 6. Synthesis of quercetin-5'sulfonic acid

3.5. Structural modification by acylation

The acylation of flavonoids makes them more hydrophobic by fatty acid linkage; however, enzymatic acylation of flavonoids is more

regioselective and may improve not only their solubility in diverse environments but also their stability and antioxidant activity **(Figure 7a-b)** [66,67].

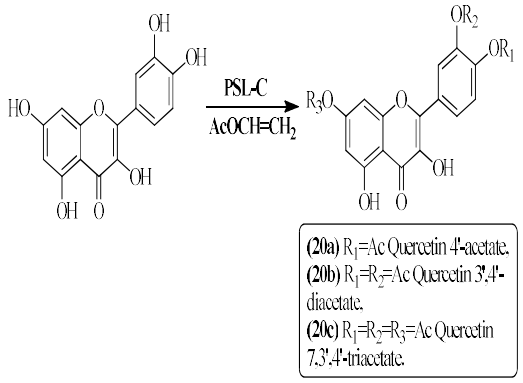


Figure 7. (a) Synthesis of acetylated quercetin derivative

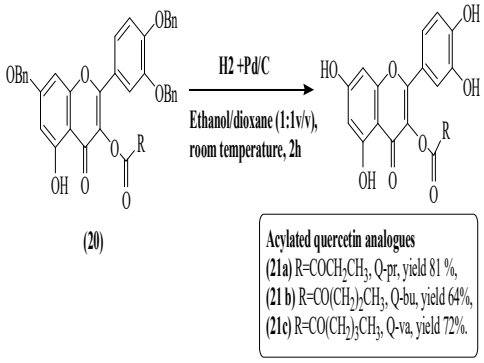


Figure 7. (b) Synthesis of acylated quercetin derivative

3.6. Structural modification by glycosylation

Glycosylation can alter a flavonoid's biological activity by increasing its water solubility, decreasing side effects, and improving selective targeting. Glycosylated flavonoid can enhance its solubility (up to >2 folds) and enhance its uptake in vitro [87,88]. For example, at 25 °C, the water solubility of quercetin is poor. whereas Glycosylated quercetin (specify solubility) and other glycosylated flavonols were found to have significantly increased water solubility further the differences were measured in the concentrations of rutin (also known as quercetin-3-O-rutinoside) and quercetin in a 100°C aqueous solution with air perfusion, and then further result revealed that rutin was more stable than quercetin as shown in **Figure 8** [68]. The different derivatives can be derived with the help of chemical and enzymatic modification of quercetin which shows better stability and solubility. Thus, flavonoid bioavailability can be enhanced as shown in **Table 3** quercetin derivatives were more potent as compared to quercetin.

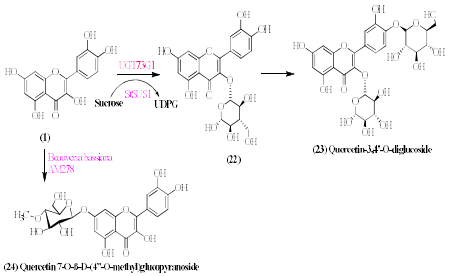


Figure 8: Synthesis of glycosylated quercetin derivative

3.7. *In-silico* ADMET and Drug-likeness Prediction

All synthetic compounds (1-4) underwent *In-silico* tests to assess their physiochemical characteristics in accordance with Lipinski's rule of five. The association between quercetin's absorption, its derivatives, and its physicochemical characteristics was determined by Lipinski's rule. Compounds 3 and 4 have higher log P. More than three parameters of the Lipinski rule are followed by quercetin, which indicate that the derivative has drug-likeness properties, and the drug-likeness score of the compound (7) was found to be 1.73. Table 1 displays the *In-silico* ADMET and drug-likeness prediction results for synthesized compounds. The protocol of pkCSM and the swiss ADME descriptors method were used to evaluate the synthesized compounds' preliminary ADME profiles. The tabulated data makes it clear that the derivative is more powerful than standard medication since it is more water-soluble and has high intestinal absorption rates ***(Table 1).***

Table 1. *In silico* ADME properties of title compounds.

Compounds	%ABS	TPSA(A°)	BBB Permeation	CNS Permeation	Toxicity (LD_{50})	LogP	Drug likeness score
1	73.104	131.36	-1.065	-3.071	2.251	1.63	0.52
2	17.654	224.06	-2.113	-3.934	1.67	1.57	0.85

3	78.61	161.96	-1.83	-3.125	2.064	4.62	0.68
4	95.647	70.29	-0.652	-2.191	2.516	3.54	-0.05
5	80.555	125.68	-1.459	-3.273	2.365	2.15	-0.13
6	46.106	234.86	-2.429	-4.254	1.508	-0.43	-0.90
7	66.774	126.84	-1.139	-3.294	2.5	3.35	1.73
8	93.714	122.108	-1.57	-3.119	2.886	2.67	0.19
15	24.786	321.22	-2.875	-5.067	1.272	0.32	1.41
19	38.364	194.11	-1.705	-3.587	1.947	1.23	-0.37
21	77.316	132.95	-1.403	-3.147	2.351	2.33	0.70
24	18.886	289.66	-2.266	-5.147	1.391	1.22	0.40

%ABS: percentage of absorption, TPSA: Topological polar surface area, BBB Permeation: blood-brain barrier permeation.

3.8. *In silico* docking studies

Molecular docking studies are important in determining diverse binding interactions of synthesized drugs within target pockets such as anti-ulcer antibiotic (6U18) and anti- cancer drug (1IMR). The comparative analysis of the interactions with various targets also assisted in determining the test compound's mode of action. The binding energy and interactions of synthesized quercetin derivative (binding energy = 5.99 to 9.51, number of interactions = 5 to 16) and quercetin (binding energy = 5.25 to 6.75, number of interactions = 5 to 25) towards all target proteins is similar as illustrated in Table 2. It was observed that out of two target proteins the quercetin derivative showed similar binding affinity against the MMP-9 active site (2OW2) as compared to quercetin (standard drug) but it has a greater number of interactions with the site of the target which results due to modification of the quercetin molecule exhibit more binding interactions to the active site of the protein. In comparison to 2D interaction images of quercetin and quercetin derivative against 2OW2 as shown below the replacement of hydrogen from the function group with a long alkyl chain exhibited a greater number of alkyl bond formation with protein **(Figure 9a-b) and Table 2.**

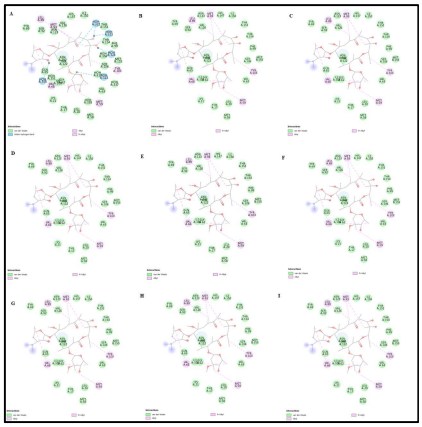


Figure 9a: 2D Interaction between **(A)** Compound 1 **(B)** Compound 2 **(C)** Compound 3 **(D)** Compound 6 **(E)** Compound 7 **(F)** Compound 8 **(G)** Compound 9 **(H)** Compound 10 **(I)** Compound 12 and protein 6U18

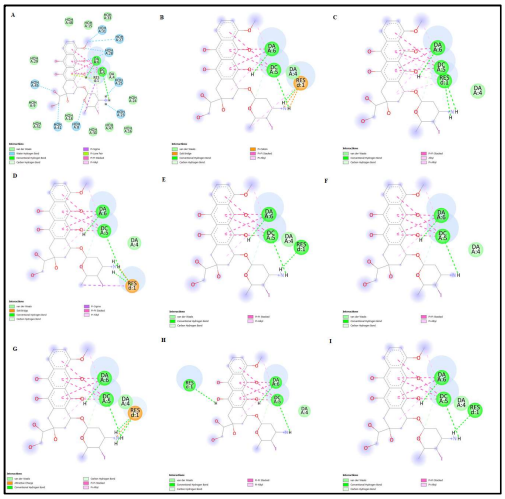


Figure 9b: 2D Interaction between **(A)** Compound 1 **(B)** Compound 2 **(C)** Compound 3 **(D)** Compound 6 **(E)** Compound 7 **(F)** Compound 8 **(G)** Compound 9 **(H)** Compound 10 **(I)** Compound 12 and protein 1MR.

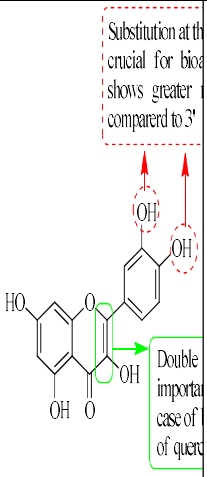
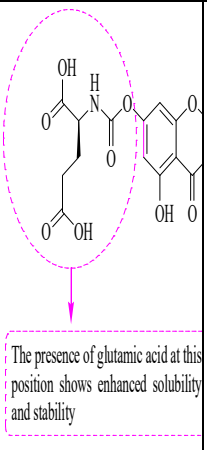
Table 2. Binding Energy and number of interactions of quercetin and its derivative against target proteins

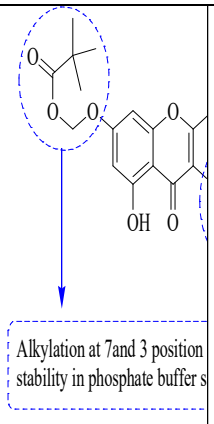
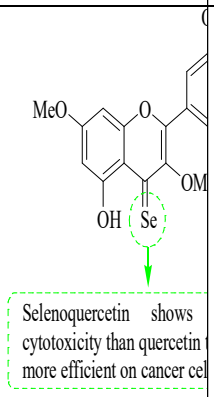
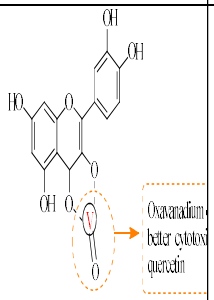
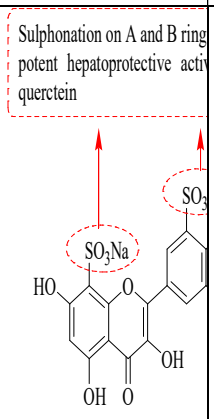
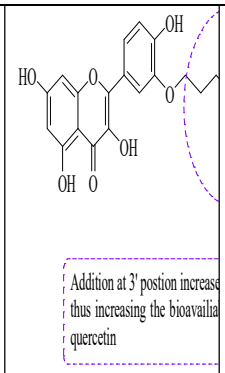
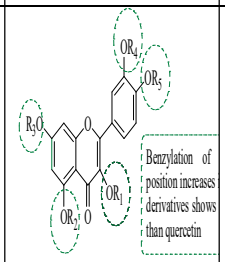
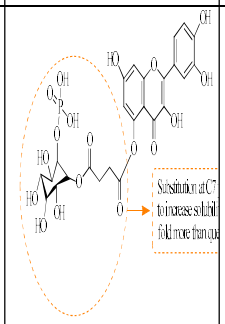
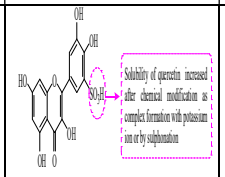
Compound	Binding Energy		No. of Interaction	
	6U18	1IMR	6U18	1IMR
1	-6.75	-5.99	13	23
2	-7.44	-6.75	7	15
3	-6.19	-4.43	7	15
6	-9.51	-7.41	7	16
7	-9.07	-7.18	7	12
8	-9.45	-6.15	7	11
9	-8.16	-6.12	7	14
19	-8.48	-6.71	7	12
24	-9.11	-6.53	7	12

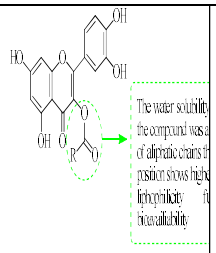
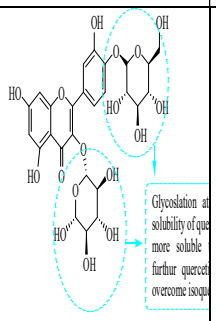
3.9. Structure activity relationship of synthetic quercetin derivatives

Quercetin (compound 1) serves as the parent scaffold with five hydroxyl groups enabling potent antioxidant and anti-inflammatory effects via ROS scavenging and NF-κB inhibition, though its poor aqueous solubility and rapid metabolism limit bioavailability. Quercetin-7-O-glutamic acid (compound 2) improves water solubility and cellular uptake through 7-OH conjugation, maintaining anti-inflammatory potency by inhibiting iNOS/NO in macrophages with gradual hydrolysis to active quercetin. The 3,7-bis-O-pivaloxymethyl (POM) quercetin (compound 3) uses transient POM blocking of 3-OH and 7-OH to boost chemical stability, intracellular accumulation, and bioavailability for neuroprotection, with deprotection restoring activity. Selenoquercetin (compound 4) features selenium at C-8 for enhanced Mpro inhibition (IC50 8 μM vs. quercetin's 192 μM), antiviral potency, and GPx-mimetic antioxidant effects supporting neuroprotection. Oxovanadium (IV) complexation (compound 5) at catechol OH groups heighten breast cancer cytotoxicity via ROS generation and apoptosis, amplifying kinase inhibition beyond free quercetin. Quercetin-5′,8-disulfonate sodium (compound 6) sulfonation confers water solubility and cancer cytotoxicity through TRAIL-mediated apoptosis via DR5 upregulation while preserving NF-κB modulation. The piperazine-linked derivative (compound 7), with a 4-methylpiperazinyl-propoxy chain at 3′, improves solubility and receptor binding for enhanced anticancer selectivity via lysosomal trafficking. Benzylated analogues (compounds 8–13) with O-benzylation at select OH groups (e.g., 3,7) enhance lipophilicity, membrane permeability, and HTS anticancer efficacy, optimized by chain length at 3-OH or 4′-OH. Succinic-phosphonooxy conjugation at 5-OH (compound 15) increases polarity and kinase targeting as a prodrug, elevating solubility and sustained neuroprotective/anticancer effects. Quercetin-5′-sulfonic acid (compound 19) selective sulfonation boosts water solubility and counters cadmium-induced oxidative stress by restoring SOD/GSH levels for neuroprotection. Regioselective acylation (compound 21), such as 3-O-propionate/butyrate with C3–5 chains, increases solubility 4.7–8.2-fold and antiplatelet activity via balanced lipophilicity. Finally, quercetin-3,4′-O-diglucoside (compound 24) glycosylation improves solubility and gut absorption as a prodrug, with enzymatic hydrolysis yielding aglycone for antioxidant/neuroprotective effects **(Table 3).**

Table 3 Structure-activity relationship of derived quercetin analogues

S. No.	Quercetin derivative (Name and Number)	Structure-Activity Relationship	Reference
1.	1. (Quercetin)		[68]
2.	2. (Quercetin-7-O-glutamic acid)		[59,64]

3.	3. (3,7-bis-O-pivaloxymethyl (POM) quercetin)		[60,64]
4.	4. (Selenoquercetin)		[61,64]
5.	5. (Oxovanadium (IV) complex)		[62,64]
6	6. (quercetin-5' ,8-disulfonate sodium)		[63,64]
7.	7. (5,7-Dihydroxy-2-{4-hydroxy-3-[3-(4-methyl-piperazin-1-yl)-propoxy]-phenyl}-chromen-4-one)		[65]
8.	8-13. (Benzylated quercetin analogue)		[66]
9.	15. (Succinic acid 2-(3,4-dihydroxy-phenyl)-3,7-dihydroxy-4-oxo-4H-chromen-5-yl ester 2,3,4,5-tetrahydroxy-6-phosphonooxy-cyclohexyl ester)		[67]
10.	19. (Quercetin-5'-sulfonic acid)		[65]

11.	21. (Acylated quercetin analogues)		[69]
12	24. quercetin-3,4′-O-diglucoside		[68]

5. Discussion

Quercetin derivatives demonstrated significant improvements over parent quercetin across key ADMET parameters, addressing its well-documented limitations of poor aqueous solubility (<0.1 mg/mL) and rapid phase-II metabolism. Compounds 4, 7, and 8 exhibited optimal balance with high intestinal absorption (>90% ABS), favorable logP (2.5-3.5), and drug-likeness scores approaching 1.73, surpassing quercetin's marginal compliance with Lipinski's Rule (TPSA 131.36 Å²). Sulfonation (compounds 6, 19) and glycosylation (compound 24) strategies successfully increased water solubility while maintaining topological polar surface areas compatible with oral bioavailability (<140 Å²), consistent with prodrug approaches that mask hydroxyl groups for metabolic stability.

The piperazine derivative (compound 7) warrants particular attention, achieving the highest drug-likeness score through C-3 modification that enhances receptor binding and lysosomal trafficking, potentially overcoming P-gp efflux limitations of native quercetin. These modifications align with established SAR principles where O-alkylation at 3,7-positions boosts chemical stability without compromising the critical 3-OH/C4=O pharmacophore responsible for antioxidant and kinase inhibitory activity.

Molecular docking revealed derivatives 6 (-9.51 kcal/mol vs 6U18), 7 (-9.07 kcal/mol), and 8 (-9.45 kcal/mol) exhibited superior binding affinities compared to quercetin (-6.75 kcal/mol), with 7-16 stabilizing interactions. The enhanced potency likely stems from additional hydrophobic contacts and π-π stacking enabled by lipophilic substitutions, particularly against 1IMR (presumed MMP-related anticancer target) where compound 6 formed 16 interactions versus quercetin's 23 but with 24% higher binding energy.

Molecular docking studies against the target proteins 6UI8 and 1IMR further supported the potential of these compounds. Compounds 7 and 8 exhibited strong binding affinities with both proteins, as indicated by their comparatively lower binding energies and stable ligand–protein interactions. In addition, these compounds formed multiple interactions within the active site of the proteins, which may contribute to the stabilization of the ligand–receptor complex.

For the anti-ulcer target 6U18, derivatives consistently outperformed quercetin, suggesting sulfonated and benzylated scaffolds could enhance H. pylori enzyme inhibition or gastric protection beyond native flavonoid activity. The binding energy range (-5.99 to -9.51 kcal/mol) falls within therapeutic windows for lead optimization, though pose validation through MM-GBSA rescoring or 100 ns MD simulations would strengthen predictions of binding free energy (ΔG).

Considering the combined results of ADMET prediction and docking analysis, **compounds 7 and 8** were identified as the most promising candidates. Their balanced pharmacokinetic profile along with favorable binding affinity toward the target proteins suggests their potential as lead molecules for further pharmacological evaluation and *in vivo* studies.

These relationships validate literature precedents where C-3/C-7 modifications enhance anticancer selectivity via TRAIL/DR5 upregulation (compound 6) and neuroprotection through GPx-mimetic activity (compound 4). The dual-target profile (anticancer 1IMR + antiulcer 6U18) positions top derivatives as bifunctional agents for inflammation-driven pathologies including gastric cancer and NSAID-induced ulcers. Compound 7's high drug-likeness score and binding profile suggest priority for synthesis and IC50 determination against MMP-9/HTS enzymes, while sulfonated derivatives (6, 19) merit evaluation in cadmium-induced oxidative stress models given their SOD/GSH restoration potential. Compared to commercial analogs (e.g., dasatinib logP 2.4, bioavailability 30%), these derivatives offer natural product-inspired scaffolds with lower predicted toxicity (LD50 >2.0 mol/kg) and CNS penetration suitable for neurodegenerative applications.

While computationally robust, this study shares common in silico limitations: (1) static docking neglects protein flexibility and entropic

contributions; (2) lack of synthesis validation for novel derivatives; (3) binary ADMET predictions without dynamic PK modeling. Future work should prioritize: Synthesis and NMR/MS characterization of compounds 6-8, In vitro assays (MTT, enzyme inhibition IC50) against 1IMR/6U18 homologs, 200 ns MD simulations with water/ion explicit solvent

6. Conclusion

This study presents a synthetic strategy to improve the pharmacokinetic profile of quercetin through selective modification at the C-3 position, resulting in derivatives with enhanced solubility, lipophilicity, and bioavailability. The in-silico ADMET analysis of the synthesized compounds shows that the modified quercetin derivatives demonstrate favorable drug-likeness properties and higher intestinal absorption rates, as well as improved water solubility compared to unmodified quercetin. Molecular docking studies further reveal that these derivatives have strong binding affinities with target proteins, including anti-ulcer (6U18) and anti-cancer (1IMR) proteins, due to the increased number of interactions facilitated by alkyl substitutions. Notably, the derivative compounds showed similar or higher binding energies compared to standard quercetin, with enhanced interactions at the MMP-9 active site (2OW2). These findings underscore the potential of quercetin derivatives as improved therapeutic agents, providing a pathway for further research and development in drug formulations aimed at maximizing the therapeutic efficacy of flavonoids. The synthesis and optimization approach detailed in this study could inspire similar modifications in other flavonoids, expanding the scope of effective natural compound-based drug development.

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