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**Research Article**

# In-Silico Design, Molecular Docking and ADME Evaluation of Quercetin-7-O-Sodium Sulfonate Derivatives as Potential Anti-Inflammatory Agents: A Research

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## ABSTRACT

Quercetin is a naturally occurring flavonoid with reported anti-inflammatory potential, although its physicochemical characteristics may limit its pharmaceutical performance. The present computational study investigated structural modification of quercetin through the design of Quercetin-7-O-Sodium Sulfonate and related derivatives, followed by evaluation against cyclooxygenase-2 (COX-2). A library of ten quercetin-based ligands was examined using molecular docking against three COX-2 structures, PDB IDs 5F19, 5IKR and 3LN1, using the CB-Dock2 platform. Comparative screening identified Quercetin-7-O-Sodium Sulfonate, 3′,4′-O-Dimethyl-Quercetin-7-O-Sodium Sulfonate and 4′-O-Ethyl-Quercetin-7-O-Sodium Sulfonate for detailed evaluation. Among these, the 3′,4′-O-dimethyl derivative produced the most favourable docking score of −10.7 kcal/mol against 3LN1, whereas the parent sulfonated compound and the 4′-O-ethyl derivative showed scores of −10.3 and −10.4 kcal/mol, respectively, with the same receptor structure. Analysis of the docked complexes indicated multiple hydrogen-bonding, hydrophobic and other non-covalent interactions within the predicted binding regions. SwissADME assessment further demonstrated differences in lipophilicity, polarity and predicted pharmacokinetic behaviour among the selected compounds. The results suggest that B-ring substitution of the sulfonated quercetin scaffold can influence its predicted interaction with COX-2, with the 3′,4′-O-dimethyl derivative emerging as the most promising computational candidate. Experimental synthesis and biological evaluation are required to confirm these predictions.

## INTRODUCTION

Inflammation is a coordinated biological response to tissue injury, infection or abnormal immune stimulation. Although it is normally protective, persistent inflammatory signalling can contribute to chronic disease[1,2]. Cyclooxygenase-2 (COX-2), an inducible enzyme involved in prostaglandin

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formation, plays an important role in inflammatory processes and is therefore a widely investigated target for anti-inflammatory drug discovery [3-4].

Quercetin is a naturally occurring flavonol with reported antioxidant and anti-inflammatory properties[5,6]. Its polyphenolic structure contains several hydroxyl groups that can participate in molecular interactions and also provide suitable positions for chemical modification. However, unmodified quercetin has physicochemical and biopharmaceutical limitations that may restrict its pharmaceutical usefulness. Structural modification of the quercetin scaffold has therefore been investigated as a strategy to alter polarity, lipophilicity, solubility and molecular interaction behaviour [7,8].

Modification of hydroxyl groups through sulfation, methylation and ethylation can change the balance between hydrophilic and hydrophobic regions of the molecule. Previous studies have shown that such modifications may influence the pharmacokinetic properties and biological behaviour of quercetin derivatives [7-11]. Computational methods such as molecular docking and ADME prediction provide a useful approach for comparing these derivatives before experimental evaluation [21-23]. Molecular modelling, docking and quantitative structure–activity approaches have also been applied in medicinal-chemistry investigations for the design and comparative evaluation of bioactive compounds [21–23].

In the present study, Quercetin-7-O-Sodium Sulfonate was selected as the principal modified scaffold, while additional methyl and ethyl substitutions were introduced at selected B-ring hydroxyl positions. This design allowed the effect of substitution pattern on predicted COX-2 interaction and ADME behaviour to be compared within a closely related ligand series.

Although quercetin and several of its derivatives have previously been investigated against COX-2 [12-15], comparative evaluation of Quercetin-7-O-Sodium Sulfonate and its methyl- and ethyl-substituted derivatives across multiple COX-2 receptor structures remains limited. Therefore, a ten-member quercetin-based ligand library was evaluated against three COX-2 structures, 5F19, 5IKR and 3LN1, using CB-Dock2 with AutoDock Vina. Selected compounds were further examined for protein–ligand interactions and SwissADME-derived physicochemical and pharmacokinetic properties. The study aimed to identify promising quercetin-based candidates for future experimental investigation.

## 2. MATERIALS AND METHODS

### 2.1 Ligand Selection and Preparation

A ten-member quercetin-based ligand library was prepared for computational screening. The set included quercetin, quercetin 3-sulfate, isoquercetin, Quercetin-7-O-Sodium Sulfonate and its methyl- and ethyl-substituted derivatives. Quercetin-7-O-Sodium Sulfonate was used as the principal designed scaffold, while additional substitutions were introduced at the 3′- and/or 4′-positions of the B-ring to compare the influence of methyl and ethyl modification.

Two-dimensional structures were prepared in ChemDraw and checked for correct connectivity and substitution pattern. Three-dimensional models were then generated and geometry-optimised in Avogadro [16] before molecular docking.

### 2.2 Protein Retrieval and Preparation

Three experimentally determined COX-2 structures, PDB IDs 5F19, 5IKR and 3LN1, were obtained from the Protein Data Bank [17].

Multiple receptor structures were used to reduce dependence on a single protein conformation and to provide a broader comparison of ligand docking behaviour. Each receptor was inspected, unnecessary components were removed, and the prepared structures were submitted separately for cavity detection and docking.

### 2.3 Molecular Docking and Ligand Selection

Molecular docking was performed using CB-Dock2 [18], which uses AutoDock Vina [19] for docking and scoring. All ten ligands were docked independently against 5F19, 5IKR and 3LN1. CB-Dock2 automatically identified potential binding cavities and generated ligand poses within the predicted pockets. Vina docking scores were recorded in kcal/mol, with more negative values interpreted as comparatively more favourable predictions under the applied conditions.

Docking results were compared across all three receptor models rather than on the basis of a single score. Based on the overall docking pattern and the structural-comparison strategy, Quercetin-7-O-Sodium Sulfonate, 3′,4′-O-Dimethyl-Quercetin-7-O-Sodium Sulfonate and 4′-O-Ethyl-Quercetin-7-O-Sodium Sulfonate were selected for detailed evaluation.

The selected complexes were examined using BIOVIAN Discovery Studio Visualizer to assess ligand orientation and predicted hydrogen-bonding, hydrophobic, electrostatic and π-associated interactions.

### 2.4 In-Silico ADME Evaluation

The three selected ligands were evaluated using SwissADME [20]. Predicted physicochemical properties, lipophilicity, aqueous solubility, gastrointestinal absorption, blood–brain barrier permeation, P-glycoprotein substrate behaviour and drug-likeness were compared. Relevant descriptors included molecular mass, hydrogen-bonding capacity, molecular flexibility, molar refractivity and topological polar surface area.

Drug-likeness was interpreted using the available SwissADME filters, including Lipinski classification and predicted rule violations. The docking and ADME findings were then considered together to compare the computational profiles of the selected compounds.

## 3. RESULTS AND DISCUSSION

### 3.1 Molecular Docking Screening of the Ligand Library

The ten quercetin-based ligands were docked against three COX-2 receptor structures, namely 5F19, 5IKR and 3LN1. Differences in Vina scores were observed across both ligands and receptor models, indicating that predicted binding behaviour was influenced by ligand substitution as well as receptor conformation. Quercetin produced docking scores of −9.7, −10.4 and −9.1 kcal/mol against 5F19, 3LN1 and 5IKR, respectively, whereas isoquercetin showed favourable scores of −9.7, −10.9 and −10.2 kcal/mol. The principal designed compound, Quercetin-7-O-Sodium Sulfonate, showed corresponding values of −9.4, −10.3 and −9.8 kcal/mol.

Among the modified sulfonated derivatives, 3′,4′-O-Dimethyl-Quercetin-7-O-Sodium Sulfonate produced scores of −9.3, −10.7 and −10.2 kcal/mol, while the 4′-O-ethyl derivative gave −9.4, −10.4 and −10.0 kcal/mol against 5F19, 3LN1 and 5IKR, respectively. The screening results therefore indicated that substitution of the B-ring influenced docking performance, although the magnitude of this effect varied between the receptor structures.

**Table 1. Molecular docking scores of the ten-ligand library against COX-2**

| Ligand | 5F19 | 3LN1 | 5IKR |
|---|---|---|---|
| Quercetin | −9.7 | −10.4 | −9.1 |
| Quercetin 3-sulfate | −8.9 | −9.6 | −9.8 |
| Isoquercetin | −9.7 | −10.9 | −10.2 |
| Quercetin-7-O-Sodium Sulfonate | −9.4 | −10.3 | −9.8 |
| 3′-O-Methyl derivative | −8.8 | −9.6 | −9.8 |
| 4′-O-Methyl derivative | −9.8 | −9.9 | −10.3 |
| 3′-O-Ethyl derivative | −9.0 | −9.6 | −9.7 |
| 4′-O-Ethyl derivative | −9.4 | −10.4 | −10.0 |
| 3′,4′-O-Dimethyl derivative | −9.3 | −10.7 | −10.2 |
| 3′,4′-O-Diethyl derivative | −8.9 | −10.1 | −9.5 |

Docking scores are expressed in kcal/mol.

Although isoquercetin produced the most negative value in the complete screening library (−10.9 kcal/mol against 3LN1), selection for detailed evaluation was not based solely on the single best numerical score. Quercetin-7-O-Sodium Sulfonate was retained as the central designed scaffold, while the 3′,4′-O-dimethyl and 4′-O-ethyl analogues were selected to permit direct comparison of B-ring methyl and ethyl substitution within the same sulfonated scaffold.

### 3.2 Comparative Docking and Molecular Interaction Analysis

Among the three prioritised compounds, Quercetin-7-O-Sodium Sulfonate produced docking scores of −9.4, −9.8 and −10.3 kcal/mol against 5F19, 5IKR and 3LN1, respectively. The 3′,4′-O-dimethyl derivative gave values of −9.3, −10.2 and −10.7 kcal/mol, while the 4′-O-ethyl derivative showed scores of −9.4, −10.0 and −10.4 kcal/mol. Thus, the 3′,4′-O-dimethyl derivative showed the strongest individual docking result among the three selected compounds, with a Vina score of −10.7 kcal/mol against 3LN1.

Differences between the ligands were relatively small against 5F19, whereas clearer improvement was observed for the substituted derivatives against 5IKR and 3LN1. Against 5IKR, the dimethyl derivative showed the most favourable score (−10.2 kcal/mol), followed by the ethyl derivative (−10.0 kcal/mol) and the parent sulfonated scaffold (−9.8 kcal/mol). A similar order was observed against 3LN1, where the corresponding values were −10.7, −10.4 and −10.3 kcal/mol.

Residue-level analysis demonstrated that docking was supported by combinations of polar and non-polar contacts. For the Quercetin-7-O-Sodium Sulfonate–5IKR complex, conventional hydrogen bonds involved HIS A:39, GLN A:461, TYR A:130 and ARG A:44, while LYS A:137 contributed an attractive charge interaction. Hydrophobic and π-associated contacts were also observed within the predicted cavity.

The 3′,4′-O-dimethyl derivative docked with 3LN1 formed hydrogen-bond contacts with ASN B:24, ALA B:142, ASN B:19, GLN A:313, TRP A:309 and SER B:34. Hydrophobic interactions with residues including PRO B:139, CYS B:21, CYS B:32 and LEU B:138 further contributed to the predicted interaction environment. The 4′-O-ethyl derivative also maintained both polar and hydrophobic interactions within 3LN1, including hydrogen bonds involving GLY A:121, CYS A:32, GLU A:451 and ALA A:142.

These findings suggest that methyl and ethyl substitution altered the balance of hydrogen-bonding, hydrophobic and π-associated interactions without preventing accommodation of the common sulfonated quercetin scaffold within the predicted COX-2 cavities.

Previous computational studies have likewise reported favourable COX-2 interactions for quercetin and other flavonoid derivatives,

although docking performance varies according to ligand structure and receptor model [12–15].

### 3.3 In-Silico ADME Evaluation

SwissADME analysis demonstrated measurable physicochemical differences among the three selected compounds. The hydrogen-bond donor count decreased from four for Quercetin-7-O-Sodium Sulfonate to two for the dimethyl derivative and three for the ethyl derivative. TPSA similarly decreased from 176.70 Å² for the principal scaffold to 154.71 Å² and 165.71 Å² for the dimethyl and ethyl derivatives, respectively. Both modified derivatives also contained more rotatable bonds than the parent sulfonated compound.

Lipophilicity increased after B-ring substitution. Consensus Log P increased from 0.32 for Quercetin-7-O-Sodium Sulfonate to 1.03 for the dimethyl derivative and 1.02 for the ethyl derivative. However, this increase was accompanied by reduced predicted aqueous solubility. While all compounds were classified as soluble by the ESOL model, the Ali and SILICOS-IT models classified the two modified derivatives as moderately soluble compared with the principal scaffold.

**Table 2. Key predicted ADME characteristics of the selected ligands**

| Parameter | Q-7-O-Sodium Sulfonate | 3′,4′-O-Dimethyl | 4′-O-Ethyl |
|---|---|---|---|
| H-bond donors | 4 | 2 | 3 |
| H-bond acceptors | 9 | 9 | 9 |
| TPSA (Å²) | 176.70 | 154.71 | 165.71 |
| Consensus Log P | 0.32 | 1.03 | 1.02 |
| ESOL Log S | −3.01 | −3.42 | −3.45 |
| GI absorption | Low | Low | Low |
| BBB permeant | No | No | No |
| P-gp substrate | No | No | No |
| Lipinski violations | 0 | 0 | 0 |
| Bioavailability score | 0.55 | 0.55 | 0.55 |
| PAINS alerts | 1 | 0 | 0 |

All three ligands showed low predicted gastrointestinal absorption, no predicted BBB permeation and no P-glycoprotein substrate behaviour. Each compound satisfied the Lipinski criteria with zero violations and had a predicted bioavailability score of 0.55. A notable difference was observed in the structural-alert profile: the principal sulfonated scaffold generated one catechol-associated PAINS alert, whereas both modified derivatives showed no PAINS alerts.

The observed changes in polarity and lipophilicity following B-ring modification are consistent with previous studies demonstrating that chemical modification of quercetin can alter its predicted physicochemical and pharmacokinetic behaviour [7–11].

### 3.4 Overall Interpretation

Taken together, the docking and ADME results indicate that B-ring modification influenced both predicted COX-2 interaction and physicochemical behaviour. The 3′,4′-O-dimethyl derivative provided the strongest docking result among the prioritised compounds (−10.7 kcal/mol against 3LN1) and showed reduced polar surface area and increased predicted lipophilicity relative to Quercetin-7-O-Sodium Sulfonate. The 4′-O-ethyl derivative also maintained favourable docking, with a best score of −10.4 kcal/mol against 3LN1. However, the increased lipophilicity of both derivatives was accompanied by some reduction in predicted aqueous solubility, and low gastrointestinal absorption remained common to all three compounds.

Therefore, the 3′,4′-O-dimethyl derivative emerged as the most promising computational candidate within the three prioritised sulfonated compounds, although the results should be regarded as predictive and require experimental synthesis and biological validation.

## 4. CONCLUSION

The present in-silico study evaluated a ten-member quercetin-based ligand library against three COX-2 receptor structures and further compared the docking and ADME profiles of three prioritised sulfonated compounds. Among the selected ligands, 3′,4′-O-Dimethyl-Quercetin-7-O-Sodium Sulfonate showed the most favourable individual docking score of −10.7 kcal/mol against 3LN1, followed by the 4′-O-ethyl derivative and Quercetin-7-O-Sodium Sulfonate with scores of −10.4 and −10.3 kcal/mol, respectively.

Structural modification of the B-ring influenced the predicted interaction pattern, polarity and lipophilicity of the common sulfonated scaffold. The two modified derivatives showed lower polar surface area and greater predicted lipophilicity, together with fewer structural alerts; however, low gastrointestinal absorption remained a common predicted limitation.

Overall, the 3′,4′-O-dimethyl derivative emerged as the most promising computational candidate among the three prioritised compounds. Nevertheless, the present findings represent computational predictions and do not establish actual COX-2 inhibition or anti-inflammatory efficacy. Experimental synthesis, structural characterisation and biological evaluation are required to validate the observed results

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