

# Computational Design and Evaluation of Modified AEW-1 Chalcone Derivatives as Potential Anti-Inflammatory Agents

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## ABSTRACT

Long-term therapy of inflammation is limited by gastrointestinal, cardiovascular, and renal side effects, motivating the search for safer, multi-target anti-inflammatory agents. The chalcone derivative AEW-1, which exhibits in vivo anti-inflammatory activity comparable to ibuprofen, was selected for rational optimization. Three new AEW-1 derivatives were designed by introducing trihydroxy substitutions on the A ring and evaluated in silico using target prediction, molecular docking, and pharmacokinetic/drug-likeness prediction. Target prediction indicated iNOS as the most probable target for AEW-1 and all its derivatives, supporting iNOS as an additional anti-inflammatory target alongside COX-2. For docking to COX-2, compound 1 exhibited the best binding profile and showed a binding affinity comparable to that of the native ligand, with key interactions involving Ser530. For docking to iNOS, compound 1 also demonstrated the most favorable profile among the derivatives and formed a hydrogen bond with Glu377, a key residue. However, its binding affinity was lower than that of the native ligand. All AEW-1 derivatives satisfied drug-likeness criteria and exhibited improved pharmacokinetic profiles compared to AEW-1. Overall, compound 1, consistent with the 2,4,6-trihydroxy substitution pattern, emerged as the most promising candidate as a dual COX-2/iNOS inhibitor, warranting further validation through molecular dynamics simulations and in vitro enzyme inhibition assays.

**Keywords:** Chalcone derivatives, AEW-1, in silico, anti-inflammation

## INTRODUCTION

Inflammation is the body's biological response to injury or infection; however, when it occurs chronically, it can trigger various degenerative diseases (Hirano, 2021). Nonsteroidal anti-inflammatory drugs (NSAIDs) have long been used to treat these conditions through multiple pathways, including the inhibition of Cyclooxygenase-1 (COX-1), Cyclooxygenase-2 (COX-2), Lipoxygenase (LOX), and nitric oxide (NO) (Yadav et al., 2024). Despite being the primary treatment option for chronic inflammatory diseases, the long-term use of conventional NSAIDs is often associated with serious adverse effects on the gastrointestinal, cardiovascular, and renal systems. For instance, COX-1 inhibitors (NSAIDs) frequently cause adverse reactions ranging from dyspepsia to gastric ulcers (Mahboubi-Rabbani et al., 2023; Scarpignato et al., 2015). Conversely, drugs such as celecoxib were developed as selective COX-2 inhibitors to minimize gastrointestinal risks (Scarpignato et al., 2015). However, the use of non-aspirin COX inhibitors may increase the risk of cardiovascular events, including myocardial infarction and stroke, particularly in patients with a history of heart disease (DuBois et al., 1998). Furthermore, both selective and non-selective NSAIDs carry a risk of renal impairment (approximately 1–5%) due to reduced prostaglandin production, which induces vasoconstriction of the renal afferent arteriole (Curtis et al., 2019). The mortality risk associated with these complications ranges from 21 per million for NSAIDs to 24.8 per million for low-dose aspirin (Scarpignato et al., 2015).

Inflammation is a complex physiological process involving mediators such as prostaglandin E2 (PGE2), nitric oxide, and phospholipase A2 (PLA2); targeting these mediators is crucial for the design of safer anti-inflammatory agents. In this context, the exploration of chalcone derivatives has attracted considerable attention in medicinal chemistry. The chalcone framework, or (E)-1,3-

diphenyl-2-propene-1-one (Figure 1), offers advantages such as a simple chemical structure, ease of synthesis, and broad pharmacological activity through modulation of various molecular targets. Numerous chalcone derivatives, both natural and synthetic, have demonstrated promising anti-inflammatory activity due to their inhibitory potential against multiple therapeutic targets, including cyclooxygenase (COX), lipoxygenase (LOX), interleukins (IL), prostaglandins (PG), nitric oxide synthase (NOS), leukotriene D4 (LTD4), nuclear factor- $\kappa$ B (NF- $\kappa$ B), intracellular cell adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1), monocyte chemoattractant protein-1 (MCP-1), and toll-like receptor 4/myeloid differentiation protein-2 (TLR4/MD-2), among others (Mahapatra et al., 2017).

One chalcone derivative that has been reported to exhibit anti-inflammatory activity in vivo is 1-(2,5-dihydroxyphenyl)-3-(pyridine-2-yl)-prop-2-en-1-one (AEW-1) (Figure 2). Previous studies have shown that this compound exhibits anti-inflammatory activity of  $50.05 \pm 16.244\%$ , which is not significantly different from ibuprofen ( $57.22 \pm 20.134\%$ ) in carrageenan-induced male Wistar rats (*Rattus norvegicus* L.) (Wibowo et al., 2021). The anti-inflammatory activity of AEW-1 can be further enhanced through structural modification. Mahapatra et al. (2017) reported that chalcone derivatives modified with hydroxyl, methoxyl, carboxyl, and prenyl groups, as well as heterocyclic moieties such as thiophene, furan, or indole, exhibit promising anti-inflammatory activity. Therefore, this study aims to design new AEW-1 derivatives through structural modification and to evaluate their in silico potential using target prediction, molecular docking, and pharmacokinetic property analysis.

## METHODS

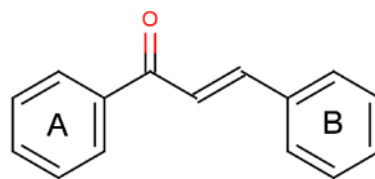
### Materials

The materials used in this study included the SMILES codes for the parent compound AEW-1, three structurally modified derivatives, and reference compounds such as aspirin, celecoxib, and mefenamic acid. The target protein structures were obtained from the Protein Data Bank (PDB) database via the official website of the Research Collaboratory for Structural Bioinformatics (RCSB) (<https://www.rcsb.org/>). The software used in this study included SwissTargetPrediction (<https://www.swisstargetprediction.ch/>) for biological target prediction, Molecular Operating Environment (MOE) version 2022.02, officially licensed by the Faculty of Pharmacy, Universitas Gadjah Mada for molecular docking simulations, Discovery Studio Visualizer (DSV) for visualization of docking results, and SwissADME (<https://www.swissadme.ch/>) for drug-likeness and pharmacokinetic prediction.

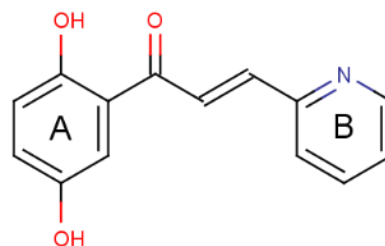
### Procedure

Structural modifications were performed on the parent compound AEW-1, resulting in three new derivative compounds through functional group substitutions on the A ring based on a rational design approach to enhance biological activity. The potential targets of these derivatives, along with AEW-1, were predicted by inputting their SMILES codes into SwissTargetPrediction with *Homo sapiens* selected as the target species. In addition to COX-2, selected as the primary anti-inflammatory target, another inflammation-related target with a high probability according to SwissTargetPrediction results was selected for docking simulations.

The ligand structures were generated by inputting the SMILES codes into MOE and subsequently optimized using the semi-empirical Parameterized Model 3 (PM3) method. The protein



**Figure 1. Structure of chalcone scaffold.**



**Figure 2. Structure of the AEW-1 compound.**

structures of COX-2 (PDB ID: 5IKR) and inducible nitric oxide synthase (iNOS) (PDB ID: 3E7G) were used in the molecular docking study. The protein–ligand complex structures were prepared using MOE, followed by redocking simulations to validate the docking protocol. The redocking parameters evaluated included RMSD values, binding free energy, and interactions with specific amino acid residues.

The docking procedure was performed using the Triangle Matcher placement method, Induced Fit refinement, and the generalized born volume integral/weighted surface area (GBVI/WSA) dG scoring function. The docking results were analyzed based on binding free energy and interactions with key amino acid residues. Both redocking and docking results were visualized in two-dimensional (2D) and three-dimensional (3D) representations. Furthermore, the drug-likeness and pharmacokinetic properties of AEW-1 and its derivatives were predicted using SwissADME by inputting their SMILES codes.

## RESULT AND DISCUSSION

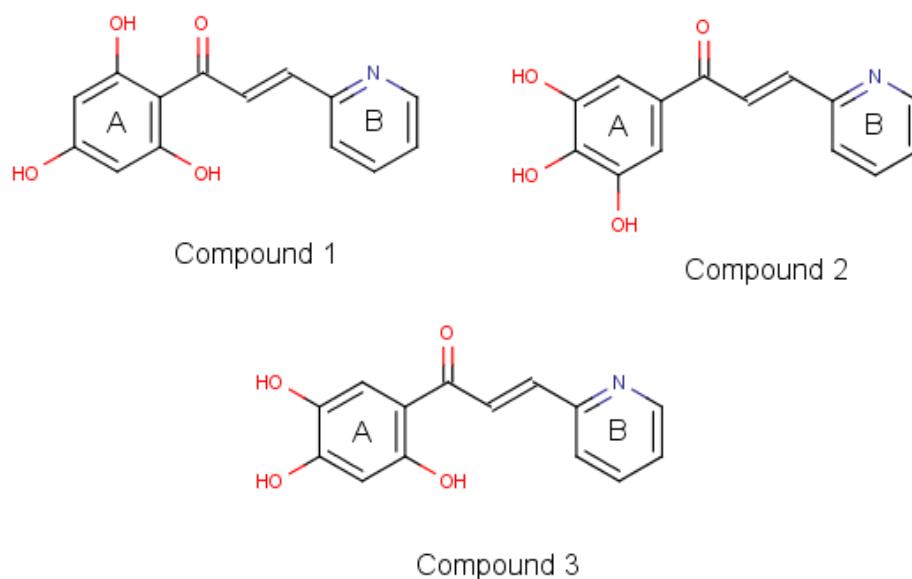
The structure of AEW-1 is characterized by a dihydroxy substituent on ring A and a pyridyl substituent on ring B. The hydroxyl groups have the potential to increase affinity for the binding site by forming a hydrogen bond network (Cramer et al., 2019). The structure of AEW-1 was modified by introducing trihydroxy substituents on ring A at three different positions. The addition of these hydroxyl groups is expected to enhance binding to target proteins, thereby improving their potential as COX-2 inhibitors and as inhibitors of other targets involved in inflammatory pathways. The proposed structures are presented in Figure 3.

These three compounds, along with AEW-1, were subjected to target prediction to evaluate their potential anti-inflammatory activity through mechanisms beyond COX-2 inhibition. The prediction results (Table 1) indicate that all four compounds show the highest probability of targeting the iNOS protein compared to other proteins. The iNOS enzyme, originally identified in macrophages as part of a cytotoxic mechanism and known to be expressed and activated during inflammation, is now considered a promising target for anti-inflammatory therapies (Wang et al., 2014). Therefore, the potential inhibition of iNOS by AEW-1 chalcone derivatives warrants further investigation.

AEW-1, its three derivatives, and reference compounds (aspirin, celecoxib, and mefenamic acid) were docked to the target proteins COX-2 and iNOS. Before molecular docking, redocking was performed on both standard protein–ligand complexes. The COX-2 complex from the PDB contains mefenamic acid as the native ligand, whereas the iNOS complex contains AR-C95791. The redocking results yielded RMSD values of 0.325 and 1.546 Å, respectively. The reliability of a docking method is generally indicated by an RMSD value of less than 2 Å (Cole et al., 2005), confirming that the docking protocol used in this study is valid. The binding free energy and interaction profiles from both redocking and docking are presented in Table II.

The native ligand (mefenamic acid) exhibited a binding free energy of  $-7.171$  kcal/mol, with specific hydrogen bond interactions involving Ser530 and Tyr385 in COX-2. This finding is consistent with Orlando & Malkowski (2016), who reported that the carboxyl group of mefenamic acid forms hydrogen bonds with the phenolic oxygen of Tyr385 and the hydroxyl oxygen of Ser530. These residues are recognized as key amino acids within the ligand-binding pocket. Hydrogen bonding plays a crucial role in determining ligand orientation within the binding site and significantly contributes to binding affinity by stabilizing protein–ligand interactions (Yunta, 2017). Compounds 1, 2, 3, AEW-1, and aspirin also formed hydrogen bonds with Ser530, indicating binding at the active site. Compounds 1, 2, and 3 showed lower binding free energy values than AEW-1 and aspirin and were comparable to mefenamic acid, although still higher than celecoxib. These results suggest that compounds 1, 2, and 3 possess binding affinities toward COX-2 like that of mefenamic acid.

On the other hand, for the iNOS protein, the native ligand exhibited a binding free energy of  $-6.164$  kcal/mol, with hydrogen bond interactions involving Glu377, Trp372, and Asp382. Among these residues, Glu377 is recognised as a key active-site residue in iNOS (Garcin et al., 2008). Compounds 1, 2, 3, and AEW-1 interact with this residue through different interaction types, namely hydrogen bonding, van der Waals,  $\pi$ -anion, and van der Waals interactions, respectively. This finding indicates that compound 1 exhibits stronger interactions with key amino acid residues. Celecoxib



**Figure 3. The proposed structures of AEW-1 derivatives.**

**Table I. Target prediction results of AEW-1 and its chalcone derivatives**

| Compound   | Target                                                  | Common Name | Target Class              | Probability* |
|------------|---------------------------------------------------------|-------------|---------------------------|--------------|
| AEW-1      | Nitric oxide synthase, inducible                        | NOS2        | Enzyme                    | 0.0717       |
|            | Aldose reductase                                        | AKR1B1      | Enzyme                    | 0.0535       |
|            | Neuronal acetylcholine receptor protein alpha-7 subunit | CHRNA7      | Ligand-gated ion channel  | 0.0535       |
| Compound 1 | Nitric oxide synthase, inducible                        | NOS2        | Enzyme                    | 0.2063       |
|            | Calcium-activated potassium channel subunit alpha-1     | KCNMA1      | Voltage-gated ion channel | 0.1120       |
|            | 6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase 3  | PFKFB3      | Enzyme                    | 0.1120       |
| Compound 2 | Nitric oxide synthase, inducible                        | NOS2        | Enzyme                    | 0.1277       |
|            | 6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase 3  | PFKFB3      | Enzyme                    | 0.1120       |
|            | Alpha-synuclein                                         | SNCA        | Unclassified protein      | 0.1120       |
| Compound 3 | Nitric oxide synthase, inducible                        | NOS2        | Enzyme                    | 0.1670       |
|            | Neuronal acetylcholine receptor protein alpha-7 subunit | CHRNA7      | Ligand-gated ion channel  | 0.1120       |
|            | Aldose reductase                                        | AKR1B1      | Enzyme                    | 0.1120       |

\*Probability for the query molecule - assumed as bioactive - to have this protein as a target.

**Table II. Binding free energy and interaction profiles of compounds docked with COX-2 (PDB ID: 5IKR)**

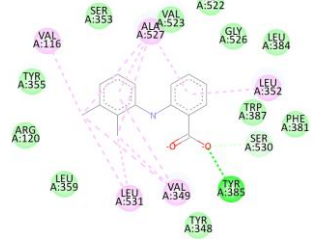
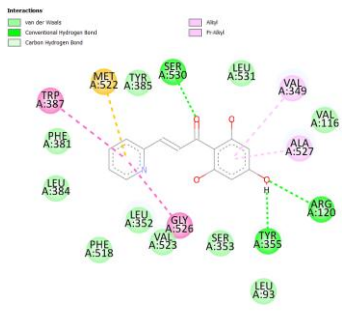
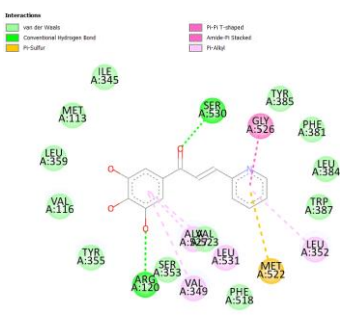
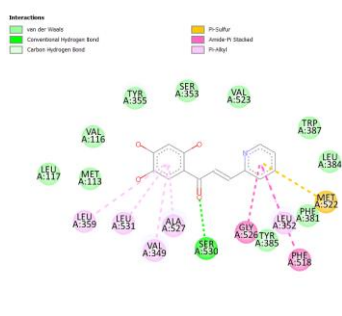
| Compound                          | Binding Free Energy (kcal/mol) | Interaction                                                                          | H-bond Interaction           |
|-----------------------------------|--------------------------------|--------------------------------------------------------------------------------------|------------------------------|
| Mefenamic Acid<br>(Native ligand) | -7.171                         |    | Tyr385,<br>Ser530            |
| Compound 1                        | -7.095                         |   | Ser530,<br>Tyr355,<br>Arg120 |
| Compound 2                        | -7.000                         |  | Ser530,<br>Arg120            |
| Compound 3                        | -6.956                         |  | Ser530                       |

Table II. (Continued)

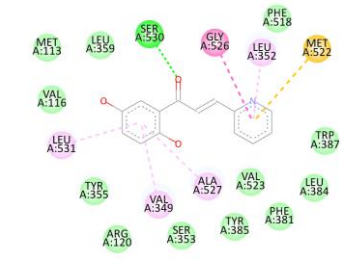
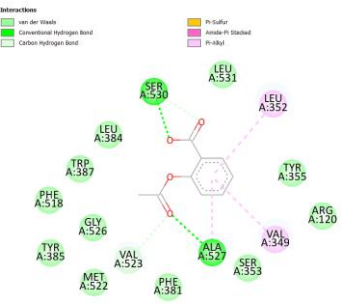
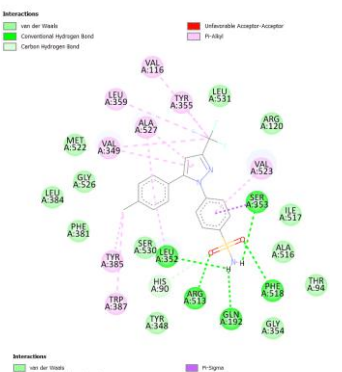
| Compound  | Binding Free Energy (kcal/mol) | Interaction                                                                                                                                                                                                                                     | H-bond Interaction                                           |
|-----------|--------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------|
| AEW-1     | -6.760                         |                                                                                                                                                               | Ser530                                                       |
| Aspirin   | -5.807                         |  <p>Interactions:<br/>van der Waals<br/>Conventional Hydrogen Bond<br/>Carbon Hydrogen Bond<br/>pi-Sigma<br/>Kinked Pi Stacked<br/>pi-alkyl</p>              | Ser530,<br>Ala527,<br>Val523                                 |
| Celecoxib | -8.784                         |  <p>Interactions:<br/>van der Waals<br/>Conventional Hydrogen Bond<br/>Carbon Hydrogen Bond<br/>Unfavorable Acceptor-Acceptor<br/>pi-Sigma<br/>pi-alkyl</p> | Ser353,<br>Phe518,<br>Gln192,<br>Arg513,<br>Leu352,<br>His90 |

Table III. Binding free energy and interaction profiles of compounds docked with iNOS (PDB ID: 3E7G)

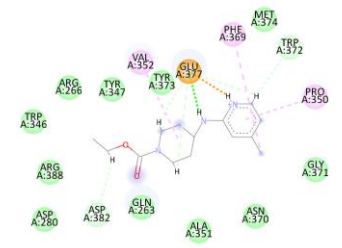
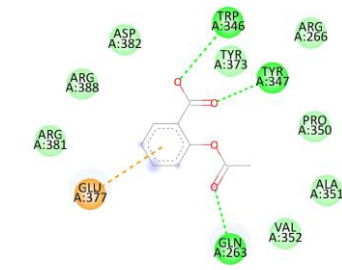
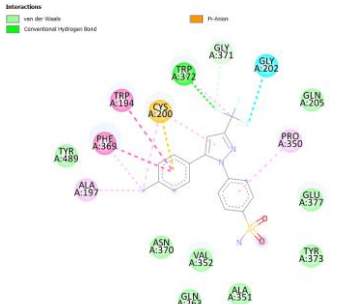
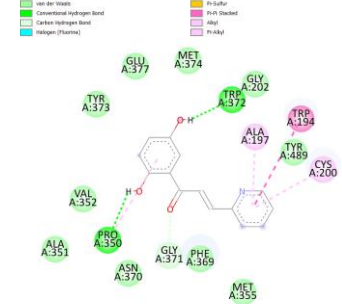
| Compound                     | Binding Free Energy (kcal/mol) | Interaction                                                                                                                                                                                                                   | H-bond Interaction           |
|------------------------------|--------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------|
| AR-C95791<br>(Native ligand) | -6.164                         |  <p>Interactions:<br/>van der Waals<br/>Salt Bridge<br/>Conventional Hydrogen Bond<br/>Carbon Hydrogen Bond<br/>pi-Sigma<br/>pi-alkyl</p> | Glu377,<br>Trp372,<br>Asp382 |

Table III. (Continued)

| Compound   | Binding Free Energy (kcal/mol) | Interaction | H-bond Interaction           |
|------------|--------------------------------|-------------|------------------------------|
| Compound 1 | -5.896                         |             | Gly371,<br>Glu377            |
| Compound 2 | -5.215                         |             | Tyr373,<br>Asp382            |
| Compound 3 | -5.415                         |             | Tyr373,<br>Trp372            |
| AEW-1      | -5.661                         |             | Trp372,<br>Pro350,<br>Gly371 |

Table III. (Continued)

| Compound       | Binding Free Energy (kcal/mol) | Interaction                                                                          | H-bond Interaction           |
|----------------|--------------------------------|--------------------------------------------------------------------------------------|------------------------------|
| Aspirin        | -4.950                         |    | Trp346,<br>Tyr347,<br>Gln263 |
| Celecoxib      | -6.220                         |   | Gly371,<br>Trp372            |
| Mefenamic Acid | -5.727                         |  | Trp372,<br>Pro350,<br>Gly371 |

shows a lower binding free energy compared to the native iNOS ligand, indicating a higher binding affinity. In contrast, compounds 1, 2, 3, AEW-1, aspirin, and mefenamic acid exhibit lower binding affinities than the native ligand. Nevertheless, compound 1 appears superior among the chalcone derivatives, as it demonstrates the best binding affinity and forms hydrogen bond interactions with key amino acid residues.

Based on the predicted drug-likeness (Table IV) and pharmacokinetic properties (Table V), all chalcone derivatives, including AEW-1, satisfy the Lipinski, Ghose, Veber, Egan, and Muegge criteria. Furthermore, all compounds exhibit high gastrointestinal (GI) absorption and are not predicted to inhibit cytochrome P450 (CYP450) enzymes. CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A4 are the CYP450 isoforms involved in drug metabolism (Wilkinson, 2005). These results suggest that the compounds are likely to be well absorbed in the intestine and have a low potential to interfere with the metabolism of other drugs mediated by CYP450 enzymes. Compounds 1, 2, and 3 are predicted to be non-permeable to the blood-brain barrier (BBB), whereas AEW-1 is predicted to be BBB-permeable. Compounds capable of crossing the BBB may enter the central nervous system and potentially cause adverse effects. Therefore, the AEW-1 derivatives are predicted to exhibit improved pharmacokinetic profiles compared to the parent compound.

**Table IV. Drug-likeness of AEW-1 and its chalcone derivatives**

| Compound   | Drug-likeness |       |       |      |        |
|------------|---------------|-------|-------|------|--------|
|            | Lipinski      | Ghose | Veber | Egan | Muegge |
| AEW-1      | Yes           | Yes   | Yes   | Yes  | Yes    |
| Compound 1 | Yes           | Yes   | Yes   | Yes  | Yes    |
| Compound 2 | Yes           | Yes   | Yes   | Yes  | Yes    |
| Compound 3 | Yes           | Yes   | Yes   | Yes  | Yes    |

**Table V. Pharmacokinetic profiles of AEW-1 and its chalcone derivatives**

| Compound   | GI         | BBB      | CYP1A2    | CYP2C19   | CYP2C9    | CYP2D6    | CYP3A4    |
|------------|------------|----------|-----------|-----------|-----------|-----------|-----------|
|            | Absorption | permeant | Inhibitor | Inhibitor | Inhibitor | Inhibitor | Inhibitor |
| AEW-1      | High       | Yes      | No        | No        | No        | No        | No        |
| Compound 1 | High       | No       | No        | No        | No        | No        | No        |
| Compound 2 | High       | No       | No        | No        | No        | No        | No        |
| Compound 3 | High       | No       | No        | No        | No        | No        | No        |

Based on docking results and pharmacokinetic predictions, compound 1 shows higher binding affinity for both COX-2 and iNOS than compounds 2 and 3. This suggests that the presence of three hydroxyl groups on the A ring of the chalcone, particularly at positions 2,4,6 (two ortho and one para), enhances binding interactions within the active sites of COX-2 and iNOS. However, the three AEW-1 derivatives do not exhibit significant differences in binding affinity and share similar pharmacokinetic properties.

## CONCLUSION

The iNOS enzyme was identified as an additional target for the development of anti-inflammatory agents based on AEW-1 chalcone derivatives, alongside COX-2. Structural modification of AEW-1 successfully generated new derivatives with promising anti-inflammatory potential, as indicated by target prediction, molecular docking, and pharmacokinetic profiling. Among the designed compounds, compound 1 exhibited the most favorable profile as a potential dual inhibitor of COX-2 and iNOS, making it a promising candidate for further investigation. Future studies are required to validate the stability of protein–ligand interactions via molecular dynamics simulations and to evaluate inhibitory activity against COX-2 and iNOS enzymes using *in vitro* assays.

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