ECMC-P 2025 Conference

The 1st International Electronic Conference on Medicinal Chemistry and Pharmaceutics

01–30 November 2025 | Online

MDPI

In Silico Evaluation of Novel Oxaprozin-Based Anti-Inflammatory Agents Targeting Cyclooxygenases

Anđela Gogić[1], Miloš Nikolić[2], Nikola Nedeljković[2], Ana Živanović[2], Vladimir Dobričić[3], Marina Vesović[2]

[1]Department of Medical Statistics and Informatics, Faculty of Medical Sciences, University of Kragujevac, 34000 Kragujevac, Serbia
[2]Department of Pharmacy, Faculty of Medical Sciences, University of Kragujevac, 34000 Kragujevac, Serbia
[3]Department of Pharmaceutical Chemistry, Faculty of Pharmacy, University of Belgrade, 11221 Belgrade, Serbia

INTRODUCTION & AIM

Non-steroidal anti-inflammatory drugs (NSAIDs) alleviate inflammation by inhibiting cyclooxygenase-mediated prostaglandin synthesis, but their gastrointestinal toxicity underscores the need for safer and more selective anti-inflammatory agents.

Oxaprozin (Ox) is a propionic acid-based NSAID that exerts anti-inflammatory and analgesic effects primarily through cyclooxygenase inhibition and suppression of prostaglandin synthesis (Figure 1). Beyond COX inhibition, oxaprozin also exhibits PPARγ-mediated and NF-κB-dependent activity, as well as inhibition of anandamide catabolism.

The aim of the study was to evaluate the binding affinities of five novel oxaprozin derivatives and the reference drug against the COX-1 and COX-2 isoenzymes.

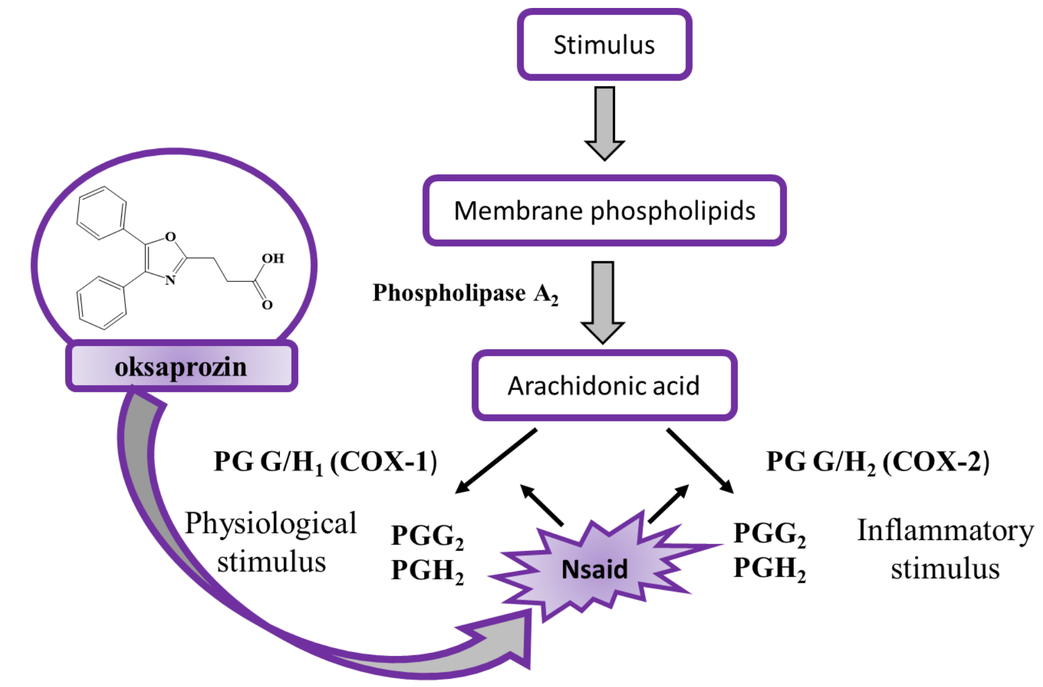
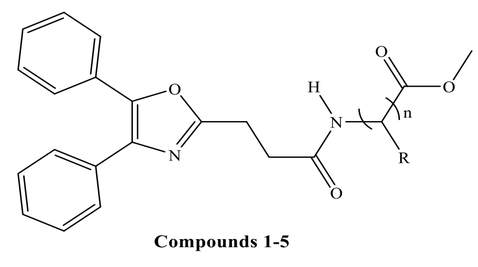


Figure 1. Mechanism of action of NSAIDs.

METHOD

To evaluate the binding affinities of compounds **1-5** (Figure 2) and the reference drug oxaprozin towards COX-1 and COX-2 isozymes, the crystal structures of the ligand-enzyme complexes were obtained from the Protein Data Bank (PDB): PDB ID 5WBE (COX-1 in complex with mofezolac), and PDB ID 1CX2 (COX-2 in complex with SC-558). The target proteins were prepared using the *MAKE Receptor* software (version 3.2.0.2). Ligand conformer data were generated using *OMEGA* (version 2.5.1.4), and molecular docking was performed using the *OEDocking* software (version 3.2.0.2), employing the *FRED* algorithm for fast exhaustive rigid docking [1-3].



Compounds 1-5

Compound 1 R = -CH_3, n = 1
Compound 2 R = -H, n = 2
Compound 3 R = -H, n = 3
Compound 4 R = -CH_2-(1*H*-indol-3-yl), n = 1
Compound 5 R = -H, n = 7

Figure 2. Structures of oxaprozin derivatives.

FUTURE WORK / REFERENCES

These results highlight compound **2** as a promising candidate for further development as a novel anti-inflammatory agent, warranting future *in vitro* and *in vivo* studies to validate its therapeutic potential.

[1]. FRED 3.2.0.2: OpenEye Scientific Software, Santa Fe, NM, USA; http://www.eyesopen.com.
[2]. McGann M (2011). J Chem Inf Model 51: 578-596.
[3]. McGann M (2012). J Comput Aid Mol Des 26: 897-906.

RESULTS & DISCUSSION

Docking analysis of the COX-1 isoform revealed that compounds **2** and **4** exhibited the strongest binding affinities, comparable to oxaprozin. Compound **2** formed stable hydrogen and hydrophobic interactions with Arg120, Leu352, and Trp387 (Figure 3), while compound **3** showed three key hydrogen bonds with Arg120, Tyr355, and Ala527. In contrast, derivatives **1** and **5** displayed weaker binding, dominated by hydrophobic contacts, with compound **5** additionally showing an unfavorable steric clash with Val116. The reduced binding efficiency of compound **4** was also attributed to steric hindrance within the active site.

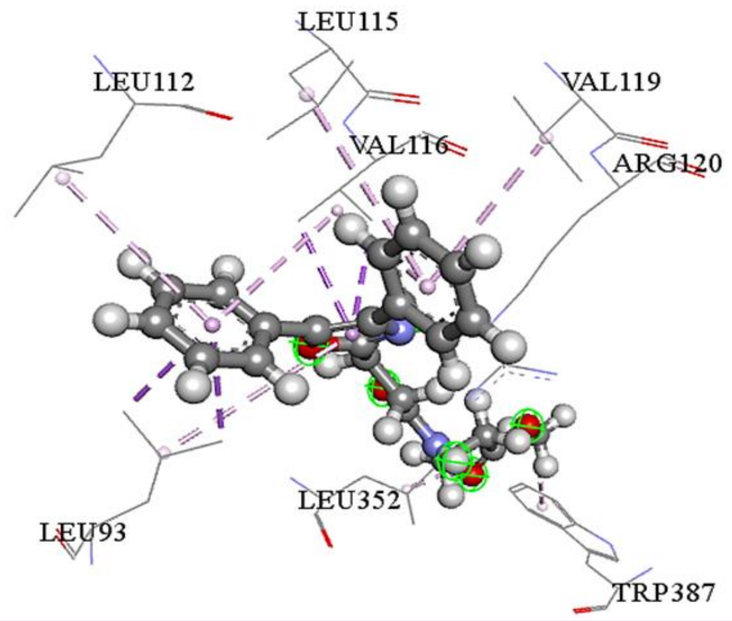


Figure 3. Molecular docked model of compound **2** with COX-1 (PDB ID: 5WBE). Conventional hydrogen bonds are shown as green dotted lines, and hydrophobic interactions are shown as magenta dashed lines.

Docking analysis showed that compounds **1** and **2** exhibited similar binding behavior within the COX-2 active site, forming key hydrogen and hydrophobic interactions, with compound **2** showing stronger stabilization through additional bonds with His90 and Arg513, resulting in a better docking score than oxaprozin (Figure 4). Compound **1** showed steric clashes with His90, while compound **3** displayed a comparable binding profile but lacked a crucial interaction with Arg513. Compounds **4** and **5** showed weak and unstable binding within the COX-2 pocket due to steric constraints, consistent with their low docking score.

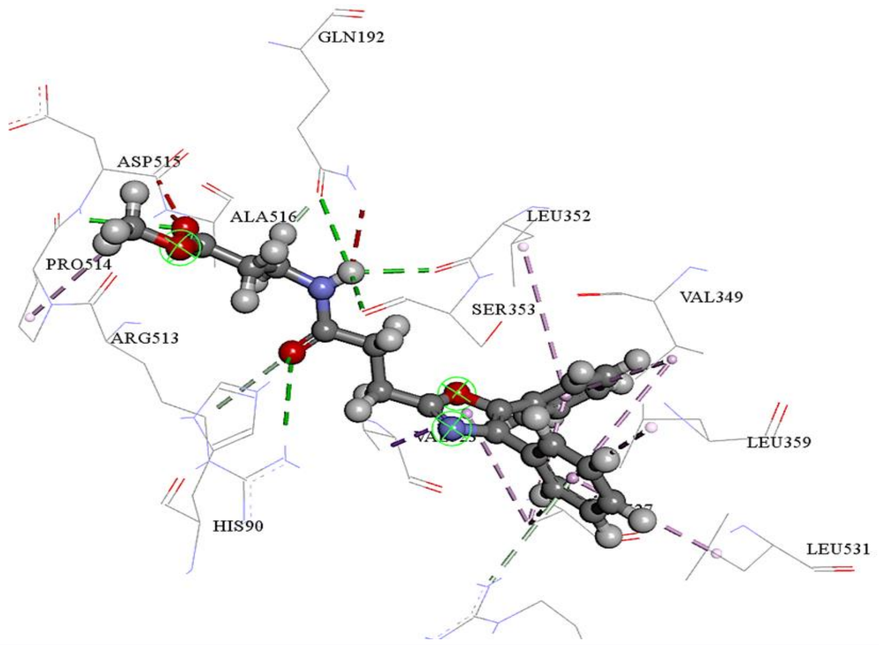


Figure 4. Molecular docked model of compound **2** with COX-2 (PDB ID: 1CX2). Conventional hydrogen bonds are shown as green dotted lines, hydrophobic interactions as magenta dashed lines, and electrostatic interactions as orange dotted lines.

CONCLUSION

Molecular docking analysis of the oxaprozin derivatives against COX-1 and COX-2 revealed that compound **2** consistently exhibited the most favorable binding interactions, forming stable hydrogen bonds and hydrophobic contacts within the active sites of both isoforms. Its superior docking scores compared to other derivatives and oxaprozin suggest a strong affinity and potential dual inhibition of cyclooxygenase enzymes.