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Molecular docking study of hydroxyquinolone derivatives as COX enzyme inhibitors

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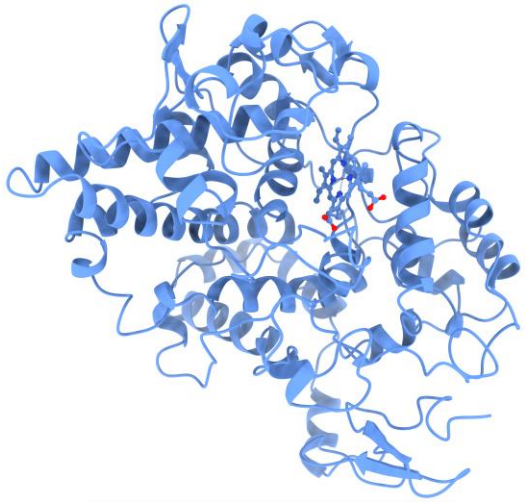
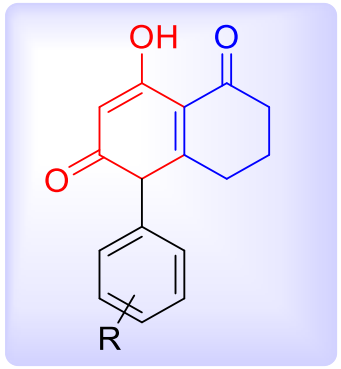
Graphical Abstract

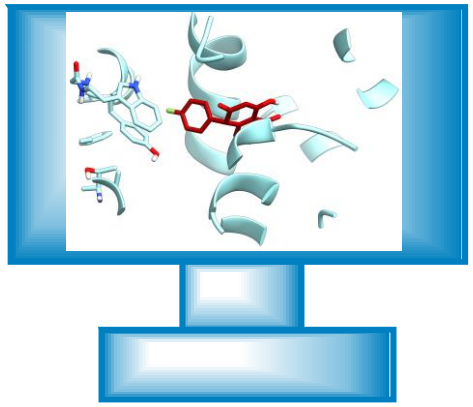


COX-2 enzyme



R: Ph, F, H

Hydroxyquinolone compounds



Molecular docking

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Abstract:

Cyclooxygenases (COXs) are essential enzymes involved in the biosynthesis of prostanoids, which play key roles in inflammation and various physiological processes. COX-1 maintains normal cellular functions, while COX-2 is inducible and becomes active during inflammation and disease states. Nonsteroidal anti-inflammatory drugs (NSAIDs) inhibit COX enzymes to reduce inflammation, but their non-selective inhibition often causes side effects, leading to the development of selective COX-2 inhibitors.
This study investigated hydroxyquinolin-2-one derivatives heterocyclic compounds known for their broad pharmacological activities, including antibacterial, anticancer, and anti-inflammatory properties as potential COX inhibitors. Using molecular docking techniques, the binding affinities of investigated derivatives were evaluated against the COX-2 enzyme. All compounds displayed favorable docking scores, suggesting strong potential for COX-2 inhibition. The most active derivatives interacted effectively with key amino acid residues within the COX-2 active site through hydrogen bonding and other stabilizing interactions. The carbonyl and hydroxyl groups present in the molecules were particularly important for enhancing binding affinity and stability within the enzyme pocket. Overall, these findings indicate that hydroxyquinolin-2-one derivatives could serve as promising scaffolds for the development of novel anti-inflammatory agents with improved selectivity and reduced adverse effects.

Keywords: *Cyclooxygenases ; hydroxyquinolin-2-ones ; molecular docking ; anti-inflammatory.*

Introduction

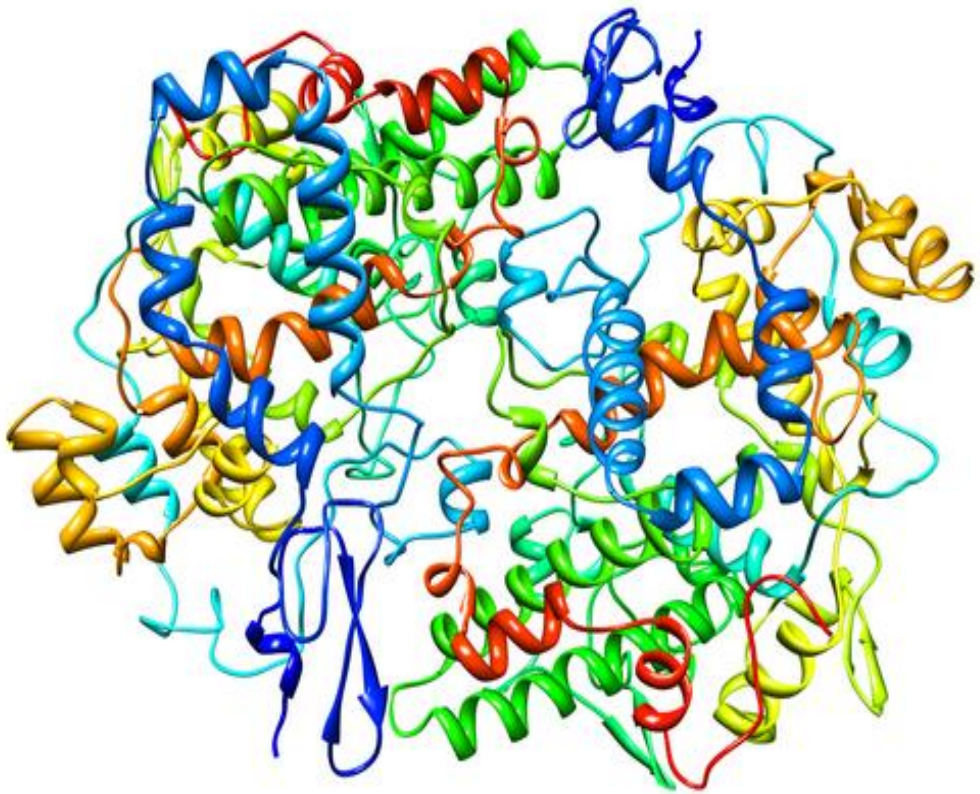
Cyclooxygenase (COX) enzymes, also known as prostaglandin-endoperoxide synthases (PTGS), are key enzymes in the biosynthesis of prostaglandins, prostacyclins, and thromboxanes. All of which are lipid mediators derived from arachidonic acid.

Reaction catalyzed: COX catalyzes two main steps in the conversion of arachidonic acid (AA) to prostaglandin H_2 (PGH_2), a common precursor of all prostanoids.

Cyclooxygenase reaction: arachidonic acid to prostaglandin G_2 (PGG_2).

Peroxidase reaction: PGG_2 to prostaglandin H_2 (PGH_2).

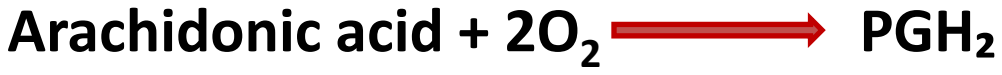
3D structure of COX



Rouzer, C. A., & Marnett, L. J. (**2009**). Cyclooxygenases: structural and functional insights. *J. lipid res*, 50, S29-S34.

Introduction

General reaction



Mitchell, J. A., & Warner, T. D. (**2006**). COX isoforms in the cardiovascular system: understanding the activities of non-steroidal anti-inflammatory drugs. *Nat. Rev. Drug Discov*, 5(1), 75-86.

COX Isoforms

There are two main isoenzymes

Enzyme	Gene	Expression	Function
COX-1	PTGS1	Constitutive (always expressed) in most tissues	Produces prostaglandins for physiological functions (gastric protection, platelet aggregation, renal blood flow)
COX-2	PTGS1	Inducible (expressed during inflammation, injury, or infection)	Produces prostaglandins involved in pain, fever, inflammation

Introduction

Expression and regulation

- ✓ Inflammatory stimuli (e.g., IL-1, TNF-α)
- ✓ Growth factors
- ✓ OncogenesEndotoxins (LPS)

Gene and structure

- ✓ Gene: PTGS2 (located on chromosome 1 in humans)
- ✓ Protein: ~604 amino acids, ~70 kDa
- ✓ Structure: Homodimeric membrane-bound enzyme located in the endoplasmic reticulum and nuclear envelope.

Biological roles of COX-2

- ✓ Pain sensitization (PGE_2 acts on pain receptors)
- ✓ Fever induction (PGE_2 in hypothalamus)
- ✓ Inflammation (vasodilation, vascular permeability)
- ✓ Angiogenesis and tumor growth (via PGE_2 and PGI_2)
- ✓ Osteogenesis and reproduction (local prostaglandin signaling)

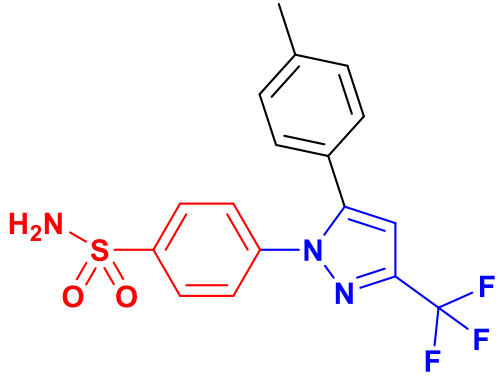
Simon, L. S. (**1999**). Role and regulation of cyclooxygenase-2 during inflammation. *Am J Med*, 106(5), 37S-42S.

Introduction

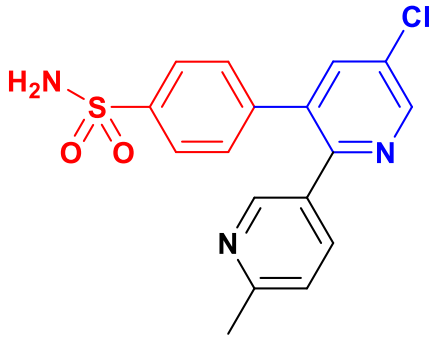
Inhibition and pharmacology

COX-2 inhibitors were designed to reduce inflammation and pain without damaging the gastric mucosa, a problem caused by COX-1 inhibition.

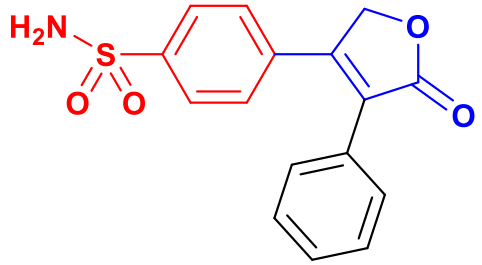
Examples



Celecoxib



Etoricoxib



Rofecoxib

Results and discussion

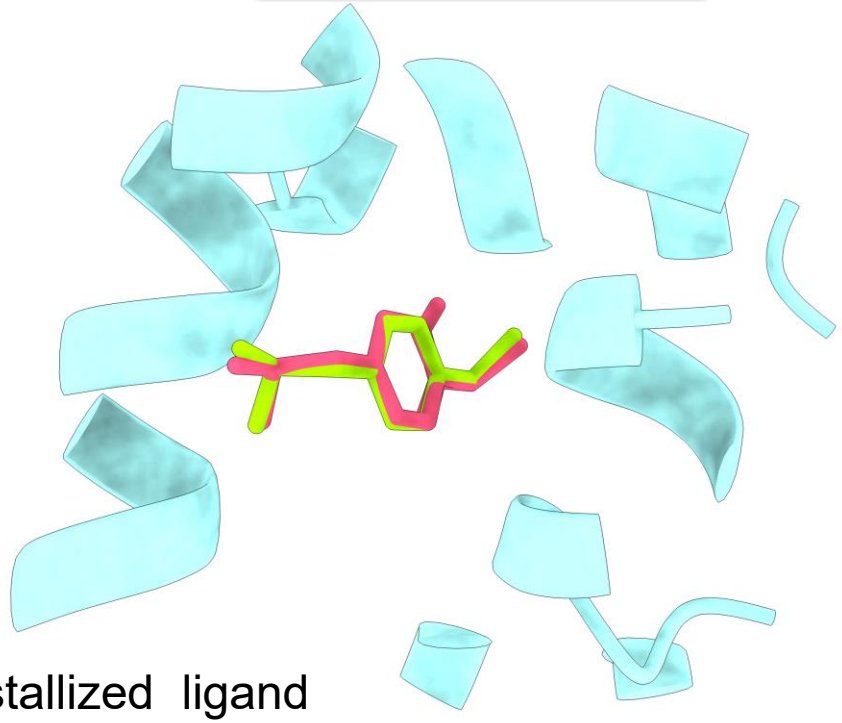
Molecular docking results

The molecular docking protocol was validated by re-docking of the ibuprofen into the active site of the enzyme COX-2, where the docked ibuprofen nearly overlapped with the crystallized form (***RMSD = 0.32 Å***).

Docking simulations were performed with ***Glide*** (extra-precision, SP) in the Schrödinger Suite 2023-1, and the docked complexes were analyzed using ***ChimeraX***.

Orlando, B. J., Lucido, M. J., & Malkowski, M. G. (**2015**). The structure of ibuprofen bound to cyclooxygenase-2. *J. Struct. Biol*, 189(1), 62-66.

PDB: 4PH9



Results and discussion

Molecular docking results

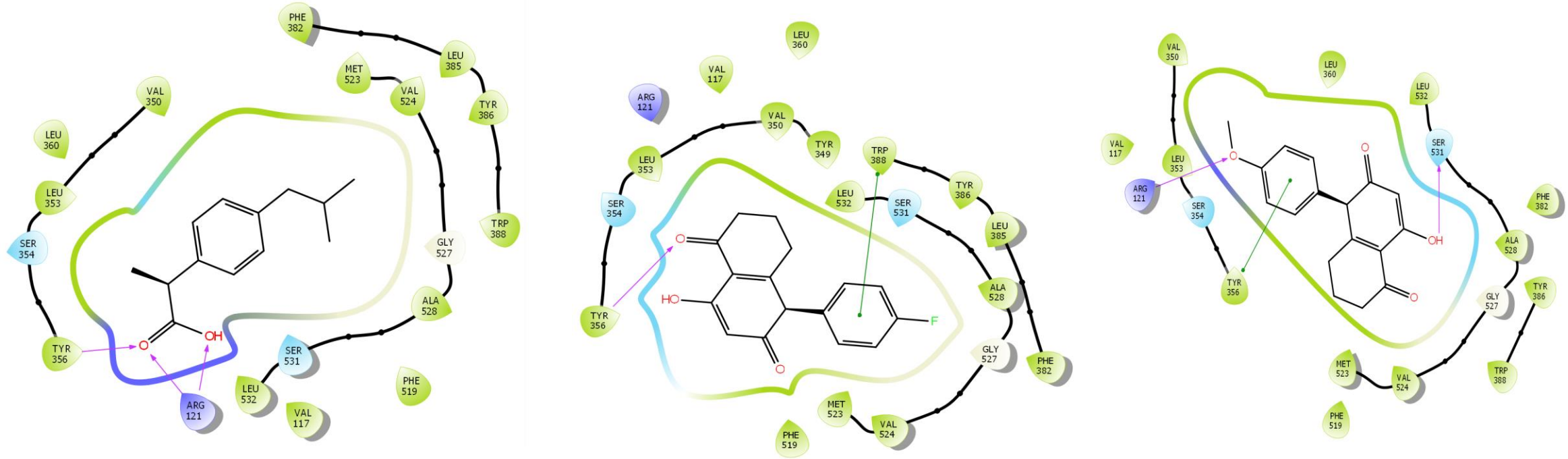
The reference ligand (**Ibuprofen**) exhibited a good docking score of **-7.53** kcal/mol and maintained nearly the same binding orientation as the co-crystallized ligand. Among the three docked hydroxyquinolone derivatives, **S2** showed the highest docking score **-8.75**, which can be attributed to the presence of a fluorine substituent that enhances binding interactions within the COX-2 active site. The **S3** derivative, bearing a methoxy group, also displayed a strong docking score of -8.60 kcal/mol. In contrast, the **S1** derivative, which lacks any substituent (bearing only a hydrogen atom), exhibited a lower docking score compared to the substituted analogues, suggesting that the presence of electron-withdrawing or electron-donating groups can significantly influence binding affinity.

Obtained docking score

Compound	Docking score (kcal/mol)
S2	-8.75
S3	-8.60
S1	-7.27
Refrence ligand	-7.53

Results and discussion

Binding mode analysis



Ibuprofen	Pi-cation	Hydrphobic	S2	S3
	Pi-Pi stacking	H-bond		

2D binding disposition of ibuprofen and **hydroxyquinolone ligands (S2, S3)** in the active site of COX-2.

Results and discussion

Binding mode analysis

The reference ligand (Ibuprofen) formed three key hydrogen bonds with critical residues Tyr356 and Arg121 of the COX-2 enzyme through its hydroxyl and carbonyl groups of the carboxylic acid moiety. Additionally, it engaged in hydrophobic interactions, which further enhanced the stability of the ligand–enzyme complex. Among the three hydroxyquinolone derivatives studied, two ligands (**S2**, **S3**) exhibited higher docking scores than the Ibuprofen demonstrated significant interactions with key residues within the COX-2 active site. These derivatives formed hydrogen bonds, hydrophobic contacts, and π–π stacking interactions with essential residues such as Ser531, Tyr356, Arg121, and Trp388, which are known to play crucial roles in COX-2 enzymatic activity. The interactions were primarily mediated by the carbonyl and hydroxyl functional groups present in the ligand structures, underscoring their importance in enhancing binding affinity, molecular stability, and overall interaction strength within the active site of the enzyme.

Conclusions

In this study, molecular docking analysis was successfully employed to investigate the interaction of hydroxyquinolin-2-one derivatives with the COX-2 enzyme. The docking protocol was validated using ibuprofen, which showed good alignment with the co-crystallized ligand (RMSD = 0.32 Å) and a docking score of -7.53 kcal/mol. Among the tested compounds, derivatives **S2** and **S3** exhibited the highest binding affinities (-8.75 and -8.60 kcal/mol, respectively), outperforming the reference ligand. These results highlight the crucial role of substituents such as fluorine and methoxy groups in enhancing ligand-enzyme interactions. Detailed binding mode analysis revealed that the most active derivatives formed multiple hydrogen bonds, hydrophobic interactions, and π–π stacking with key active site residues including Tyr356, Arg121, Ser531, and Trp388, which are essential for COX-2 activity. The presence of carbonyl and hydroxyl groups also contributed significantly to binding stability and affinity

Acknowledgments

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