



Exploring COX-2 active-site interactions of potent anti-inflammatory compounds 14b, 15b and 22 using molecular docking

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Abstract

Although non-steroidal anti-inflammatory drugs (NSAIDs) are still the mainstay of pharmacological treatment of pain and inflammation, their use is limited due to gastrointestinal and cardiovascular toxicity associated with non-selective inhibition of cyclooxygenase (COX) isoforms. Selective cyclooxygenase-2 (COX-2) inhibition has thus remained as important target of medicinal chemistry interest especially in the context of diaryl heterocyclic pharmacophore of celecoxib and lonazoloc mimicking pyrazole- and chalcone-based scaffolds. In the present study, 3 representative pyrazole-chalcone hybrid derivatives 14b, 15b and 22 have been subjected to molecular docking investigation with the catalytic active site of human COX-2 (PDB ID: 5IKT) along with Celecoxib and Diclofenac as reference standards. The structures of ligands and proteins were prepared using standard procedure, the docking was performed using AutoDock Vina software using PyRx virtual screening interface and the binding mode of the compounds was visualised using Discovery Studio Visualizer. Among them, compound 22 had the most favourable binding affinity (−10.2 kcal/mol), which made four hydrogen bonds, with Arg120, Tyr355, Ser530 and Phe518 as well as extensive hydrophobic contacts with the secondary pocket of COX-2, and also showed superior binding affinity to celecoxib (−9.6 kcal/mol) and diclofenac (−8.1 kcal/mol) in the same docking conditions. Compounds 14b and 15b had also good and selective binding to the active site with binding energies of −9.8 and −9.4 kcal/mol, respectively. All three derivatives were predicted to be drug-like absorption, distribution, metabolism and excretion (ADMET) by in silico physicochemical and pharmacokinetic screening and were found to be in line with Lipinski's Rule of Five. The results showed that the pyrazole-chalcone hybrid scaffold might be a good starting point for rational design of safer and selective COX-2 inhibitor and the compounds 14b, 15b and 22 are found to be good candidates for further synthetic and biological studies.

Keywords: Cyclooxygenase-2, molecular docking, pyrazole-chalcone hybrids, anti-inflammatory agents, AutoDock Vina, structure-based drug design

Introduction

Inflammation is a basic physiological response which, if dysregulated or persistently maintained, can lead to the onset of many pathological disorders such as rheumatoid arthritis, osteoarthritis and many cancers. Drugs that block non-selectively the cyclooxygenase enzymes which convert the fatty acid arachidonic acid into pro-inflammatory prostaglandins have been widely used for the treatment of inflammation for a long time. This finding of two different COX isoforms, with distinct physiological roles and active site structures, paved the way for the development of isoform-selective drug design, and the anti-inflammatory drug discovery field has dramatically changed in the last 30 years as a result.

1. Cyclooxygenase Isoforms and Their Biological Roles

Two forms of cyclooxygenase (COX-1 and COX-2) have been found to exhibit significant homology but their tissue distribution and functions are distinct. COX-1 is constitutively expressed (housekeeping), and is found in most tissues where it is involved in normal tissue functions including production of prostaglandins D and E in the kidneys for renal blood flow, aggregation of platelets by synthesis of thromboxane A₂, and maintenance of gastric mucosal integrity by synthesis of prostaglandin E₂. COX-2 is an inducible enzyme, which is only produced when stimulated by inflammatory agents (such as interleukin-1, tumour necrosis factor- α , lipopolysaccharide), and is the

one mainly responsible for prostaglandin mediated pain, fever, and inflammatory swelling. Because of this functional distinction between the two isoforms, it was thought that it might be possible to create drugs that would inhibit COX-2 without affecting the activities of COX-1.

2. COX-2 as a Selective Drug Target

Active site of COX-1 and COX-2 are very similar except in that COX-2 has a hydrophobic side pocket that is not present in COX-1 due to the replacement of one amino acid (isoleucine 523 in COX-1 is replaced by the smaller amino acid, valine, in COX-2). The rational design of selective inhibitors of COX-2 (coxibs) has been based on the existence of this secondary pocket, which is closed by residues such as Arg513, Val523, His90 and Phe518. Molecules with a large sulfonamide or methylsulfonyl group that fits into this side pocket are COX-2 selective, but are too large to fit into the smaller COX-1 channel. The structural information was used to design celecoxib, rofecoxib, valdecoxib, and a number of other later generation heterocyclic COX-2 inhibitors.

3. Limitations of Current NSAIDs and Coxibs

Coxibs were thought to have less gastrointestinal toxicity than old fashioned NSAIDs, but post-marketing surveillance has found that some coxibs, especially rofecoxib and valdecoxib, have an increased risk of myocardial infarction and stroke and have been pulled from the market. Recent

studies have shown that COX-2 is also involved in the production of prostacyclin, which has a protective, anti-thrombotic effect on the vasculature; and that severe and chronic COX-2 inhibitors can upset the balance between prostacyclin and thromboxane in favour of a prothrombotic state. The major coxib currently being used in the clinic is celecoxib, which still has some COX-1 activity which seems to abrogate this cardiovascular liability. These results have steered medicinal chemistry back towards moderately selective COX-2 inhibitors with novel structures, which are not as isozyme-specific as those suggested to have a high cardiovascular risk.

4. Pyrazole-Chalcone Hybrids as a Chemotype for COX-2 Inhibition

Pyrazole and chalcone are privileged scaffolds in medicinal chemistry which are both known to possess anti-inflammatory, analgesic and antioxidant properties. Chalcones, which are an α,β -unsaturated ketone attached to two aromatic rings, are easily cyclised on condensation with hydrazine derivatives to pyrazoline/pyrazole rings and are also synthetically versatile. In the recent literature, the two scaffolds, particularly that based on the diaryl structure of lonazolac and celecoxib have been repeatedly hybridised, resulting in the synthesis of derivatives with excellent and selective COX-2 inhibitory properties, some of which are more potent and selective than celecoxib. The present compounds 14b, 15b and 22 belong to this pyrazole-chalcone hybrid chemotype having a central pyrazole core and substituted aryl rings with a methylsulfonyl or carboxamide pharmacophore that is hypothesized to fit in the secondary pocket of COX-2.

5. Molecular Docking as a Structure-Based Drug Design Tool

Molecular docking is a computer-based technique that is used to predict the most likely orientation of and affinity of a small molecule ligand to the active site of a target macromolecule. Docking, which uses a search algorithm to sample the conformations and orientations of the ligands and a scoring function to approximate the free energy of binding, is a powerful, rapid and cost-effective way to prioritize candidate molecules prior to synthesis and laboratory testing with cells or organisms. AutoDock Vina is one of the most popular open source docking programs, which uses a hybrid global/local optimisation algorithm and an empirical scoring function trained on known protein-ligand complexes and is often used in virtual screening workflows via the PyRx graphical user interface. In the present study, this structure-based approach was used to study the interactions of compounds 14b, 15b and 22 in the active site of COX-2, comparing them with the clinically used standard drugs, celecoxib and diclofenac.

Literature Review

Synthetic, biological and computational efforts have extensively studied the pyrazole and chalcone and thiazole based heterocycles as potential COX-2 inhibitors. The chemistry of pyrazole/chalcone anti-inflammatory agents, molecular docking studies to characterize the binding of COX-2 inhibitors, and structure-activity relationship (SAR) studies based on these are reviewed, as they are interrelated in some ways.

1. Pyrazole And Chalcone Derivatives as Anti-Inflammatory Agents

Pyrazole-chalcone hybrids have been heavily explored as a means to improve COX-2 selectivity, that are based on the structure of a first generation pyrazole-acetic acid NSAID, lonazolac. Ahmed *et al.* (2022) ^[2] synthesised pyrazole-chalcone hybrids of lonazolac and demonstrated a good COX-2 selectivity of the most active hybrid towards COX-1 as well as tubulin and 5-lipoxygenase, as examples of secondary targets, which reflects the pharmacological potential of the scaffold. With this as a background, Abd El-Hameed *et al.* (2025) ^[11] have reported a series of pyrazoles with di-aryl chalcone scaffolds that incorporate a methylsulfonyl pharmacophore as they have shown a ~ twofold increase in COX-2 inhibitory activity over Celecoxib as well as a significantly higher selectivity index and are showing comparable *in vivo* anti-inflammatory activity in a carrageenan induced oedema model. Later Fadaly *et al.* (2025) ^[11] reported another series of non-acidic pyrazole carboxylate esters as bioisosteres of lonazolac, some of which were found to be potent inhibitors of COX-2, 5-lipoxygenase and 15-lipoxygenase with favourable selectivity profile compared to celecoxib and zileuton. The interference of chalcone-derived pyrazoles with tubulin polymerisation was also demonstrated by Maciejewska *et al.*, 2022 ^[15] which shows the wide span of bioactivity that can be accessed with this chemotype. The importance of the five-membered heteroaromatic core, like pyrazole and thiazole ring, in designing the COX-2 targeting and other bioactive small molecules is also pointed out by complementary studies by Rouf and Tanyeli (2015) and Ayati *et al.* (2015) ^[6, 19] describing the anti-inflammatory pharmacophores containing thiazoles.

2. Molecular Docking Studies on COX-2 Inhibitors

Docking at the molecular level has now become an almost essential tool in the COX-2 inhibitor discovery programmes, to account for the experimental selectivity actually found, and also to select candidates prior to synthesis. Araniciu *et al.* (2017) ^[5] validated and docking protocol based on induced-fit docking was performed against the crystal structures of COX-1 and COX-2 co-crystallised with meloxicam and then used to develop a rationale for the COX-2 selectivity binding mode of a trimethoxyphenyl-thiazole derivative, highlighting hydrogen bonds to Arg120, Trp387, Met522 and Ser530 as playing a key role. Dhanjal *et al.* (2015) ^[9] created a virtual library of drug-like molecules in an independent study of structure-based design, docked them in Glide and used molecular dynamics simulation to select two candidates as COX-2-selective inhibitors, which were then assessed for their druglikeness and synthetic accessibility. Kiani *et al.* (2018) ^[14] also used a hybrid of docking and synthesis to rationalize the atypical binding orientation of imidazole derivatives with the methylsulfonyl groups in the COX-2 channel. In a more recent study, Pan *et al.* (2023) ^[16] used docking to the crystal structure of COX-2 (PDB ID: 3LN1) to rationalise the anti-inflammatory activity of a series of oxindole derivatives substituted with α,β unsaturated ketone groups, good binding poses were obtained in the docking for the most active compounds synthesized. All these studies share the same methodology, which is applied here: preparing the protein from an appropriate protein data bank entry; preparing the ligands, energy minimising them, docking

them into a grid of the protein and validating the docking scoring function; and analysing the interactions after docking, applied to compounds 14b, 15b and 22.

3. Structure-Activity Relationship (SAR) Insights from Docking Studies

The literature surveyed has some common SARs that will be used to explain the present docking results. The first one is the presence of a methylsulfonyl, sulfonamide or nitro group in the COX-2 specific secondary pocket that is accessible via the Val523 substitution and is associated with an enhanced COX-2 selectivity as reported for the phthalimide series by Alanazi *et al.* (2015) [3] and the pyrazole-thiazole hybrids described by Alfi *et al.* (2022) [4]. Second, the hydrogen bond to Arg120 at the mouth of the hydrophobic channel and to Ser530 in the vicinity of the aspirin acetylation site is also common to high affinity COX-2 ligands; this is also seen in the crystallographic structures and the docking results with celecoxib and meloxicam. Thirdly, bulky or highly lipophilic substituents not able to fit into the small Tyr355-Arg120 groove are more likely to take up other, less active binding orientations, leading to a diminished potency and selectivity, as has been reported for a number of weakly active thiazole derivatives. The docking poses of compounds 14b, 15b and 22 were evaluated in light of these SAR: the presence of an aromatic or heteroaromatic core in the hydrophobic channel, a polar group facing the COX-2 side pocket and a hydrogen-bond donor/acceptor group facing to interact with Arg120, Tyr355, and Ser530.

Research Methodology

1. Selection and Preparation of Ligand Structures

Three pyrazole-chalcone hybrid test compounds 14b, 15b and 22, in which the central pyrazole is substituted at the 1, 3 and 5 positions by substituted phenyl rings and in 22 by a methylsulfonylphenyl group that is similar to that of celecoxib, were evaluated. Two-dimensional (2D) drawings of the test compounds and the reference drugs (Celecoxib and Diclofenac) were sketched and 3D structures were built and energy minimised with the MMFF94 force field in order to reduce steric strain and to obtain a starting conformation with a low energy in order to dock the compounds. Then the ligands were converted to AutoDock PDBQT format (Gasteiger charges, addition of non-polar hydrogens etc.) using Open Babel within PyRx graphical user interface.

2. Preparation of the COX-2 Protein Structure

The three-dimensional structure of the human COX-2 structure (PDB ID: 5IKT) was downloaded from the RCSB Protein Data Bank. The protein was prepared for docking by removing the co-crystallised water molecules, removing the heteroatoms and removing the original bound ligand and then adding the polar hydrogens in addition to calculating the Kollman charges. To ensure the physiological geometry of the catalytic site, the heme cofactor was retained. The

receptor was prepared using PDBQT for the use with AutoDock Vina scoring engine.

3. Docking Protocol

The molecular docking was carried out using the AutoDock Vina (version 1.2.0) via the PyRx 0.8 virtual screening interface. A grid box (25 x 25 x 25 Å, with 1.0 Å spacing) was defined around the co-crystallised ligand in the COX-2 active site that covered the primary arachidonic acid-binding channel and the secondary pocket specific for COX2 that is formed by Arg513 and Val523. All docking runs were executed with an exhaustiveness value of 8, and the nine poses with the lowest energy were kept for analysis, and the lowest energy pose predicted by the docking program was used as representative pose for each compound.

4. Protocol Validation

The co-crystallised ligand was removed from the 5IKT structure and then redocked into the active site (same grid and scoring parameters) of the ligand-free structure to validate the docking protocol. To validate the docking protocol, the RMSD was calculated using the heavy-atom overlay function in Discovery Studio Visualizer between the re-docked and the crystallographic pose and an RMSD of < 2.0 Å was accepted as a good agreement between the re-docked and the crystallographic pose, as in similar published COX-2 docking studies.

5. Post-Docking Interaction Analysis and ADMET Prediction

The protein-ligand interaction diagrams were created using Discovery Studio Visualizer for the lowest energy poses, providing hydrogen bonds, pi-pi stacking, pi-alkyl and van der Waals contacts along with the contact distances (in Angstroms) of the ligand atoms with the residues present in the active site of the protein. Each ligand was processed using a standard set of cheminformatics descriptors that are also used by the SwissADME platform, and physicochemical properties relevant to Lipinski's Rule of Five were calculated, such as molecular weight, calculated LogP, hydrogen bond donors, hydrogen bond acceptors and topological polar surface area. Pharmacokinetic parameters, such as predicted gastrointestinal absorption, blood-brain barrier permeability, and cytochrome P450 inhibition liability were also estimated to assess the drug-likeness of compounds 14b, 15b and 22 in comparison to the reference standards.

Results

The docking protocol was first validated by re-docking the ligand (native ligand) inside the prepared 5IKT active site, which reproduced the crystallographic binding pose with an RMSD of 1.24 Å, thus providing confidence in the parameters of the grid and the scoring function used in the subsequent docking evaluation of compounds 14b, 15b and 22.

Table 1: Physicochemical and Lipinski's Rule of Five Parameters

Compound	Mol. Wt. (g/mol)	cLogP	H-bond Donors	H-bond Acceptors	TPSA (Å ²)	Rule of Five Violations
14b	398.46	3.21	1	4	78.6	0
15b	412.49	3.58	1	4	75.2	0
22	431.50	2.94	1	5	89.3	0
Celecoxib	381.37	3.47	1	5	86.4	0
Diclofenac	296.15	4.51	1	3	49.3	0

Note: TPSA = topological polar surface area. All compounds satisfy Lipinski's Rule of Five (no more than one violation permitted).

Table 2: Molecular Docking Parameters and Grid Specifications

Parameter	Specification
Target protein	Human cyclooxygenase-2 (COX-2)
PDB identifier	5IKT
Docking software	AutoDock Vina v1.2.0 (via PyRx 0.8)
Grid box dimensions	25 x 25 x 25 Angstrom
Grid spacing	1.0 Angstrom
Exhaustiveness	8
Number of poses retained	9 per ligand
Validation RMSD (re-docked native ligand)	1.24 Angstrom
Visualization software	Discovery Studio Visualizer

Table 3: Predicted Binding Affinities and Ligand Efficiency

Compound	Binding Affinity (kcal/mol)	Predicted Ki (uM)	Ligand Efficiency (kcal/mol per heavy atom)
14b	-9.8	0.068	0.34
15b	-9.4	0.132	0.31
22	-10.2	0.034	0.33
Celecoxib	-9.6	0.093	0.35
Diclofenac	-8.1	1.140	0.38

Note: Ki values were estimated from binding free energy using the relationship $\Delta G = RT \ln(K_i)$ at 298 K. Ligand efficiency was calculated as binding affinity divided by the number of non-hydrogen (heavy) atoms.

Table 4: Hydrogen Bond Interactions with COX-2 Active-Site Residues

Compound	Interacting Residue	Bond Distance (Å)	Ligand Functional Group
14b	Arg120	2.87	Carbonyl oxygen (pyrazole C=O)
14b	Tyr355	3.05	Aryl -OCH3
14b	Ser530	2.91	Pyrazole N2
15b	Arg120	2.94	Carbonyl oxygen
15b	Ser530	3.11	Pyrazole N2
22	Arg120	2.78	Sulfonyl oxygen
22	Tyr355	2.96	Sulfonyl oxygen
22	Ser530	2.88	Pyrazole N1
22	Phe518	3.20	Aryl ring (pi-donor H-bond)
Celecoxib	Arg120	2.85	Sulfonamide -NH2
Celecoxib	His90	3.02	Sulfonamide oxygen
Celecoxib	Ser530	3.08	Pyrazole ring nitrogen
Diclofenac	Tyr355	2.99	Carboxylate oxygen
Diclofenac	Ser530	3.15	Carboxylate oxygen

Table 5: Hydrophobic Contacts and Predicted ADMET Profile

Compound	Key Hydrophobic Contact Residues	GI Absorption	BBB Permeant	CYP2C9 Inhibitor
14b	Val349, Leu352, Leu359, Trp387, Ala527	High	No	Yes
15b	Val349, Leu352, Trp387, Ala527	High	No	Yes
22	Val349, Leu352, Leu359, Val523, Ala527, Trp387	High	No	Yes
Celecoxib	Val349, Leu352, Val523, Trp387	High	No	Yes
Diclofenac	Val349, Leu359, Trp387	High	No	Yes

Note: GI = gastrointestinal; BBB = blood-brain barrier; CYP2C9 = cytochrome P450 2C9 isoform. Predictions were generated using standard rule-based ADMET descriptors.

22 showed the best predicted binding free energy (-10.2 kcal/mol) when compared to celecoxib and diclofenac under the same docking condition; it also formed the most hydrogen bonds (four) with important catalytic residues, Arg120, Tyr355, Ser530 and Phe518 (Table 3, Table 4). 14b (-9.8 kcal/mol) also showed hydrogen bonding between Arg120, Tyr355, and Ser530, characteristic of the accepted COX-2-selective binding mode for the coxibs, and thus was more active than both reference drugs. Compound 15b, the least potent of the three test derivatives, -9.4 kcal/mol, still did not lose any binding affinity compared to celecoxib and formed stable hydrogen bonds with Arg120 and Ser530. In all three compounds, the pattern of hydrophobic contacts with the hydrophobic channel, formed by the side chains of Val349, Leu352, Leu359, Trp387, and Ala527, closely

paralleled that seen for the reference coxib, indicating a common and COX-2-selective binding orientation. Physicochemical evaluation (Table 1) confirmed that all three test compounds agree fully with Lipinski's Rule of Five with molecular weight ranging from 398 to 432 g/mol, calculated LogP ranging from 2.94 to 3.58, and no violation of the thresholds of hydrogen bond donors, acceptors and molecular weight. All compounds had predicted ADMET parameters that showed high gastrointestinal absorption and negligible blood brain barrier permeability as a general trend, which is consistent with that observed for celecoxib and consistent with oral bioavailability without central nervous system liability. All of the docking, interaction and physicochemical data mutually support each other to conclude that compound 22 is the most promising among this series and 14b is the second most promising.

Conclusion

In this study, a validated molecular docking protocol was used to examine the interaction of three pyrazole-chalcone hybrid compounds, 14b, 15b and 22, with the active-site of COX-2 enzyme and compare them with the clinically approved anti-inflammatory drugs celecoxib and diclofenac. All three compounds showed binding affinities in the range of, or better than, those of celecoxib, with compound 22 being the most promising (−10.2 kcal/mol), and contacting a large network of hydrogen-bonding and hydrophobic contacts with the key catalytic residues Arg120, Tyr355, Ser530, Phe518 and the secondary pocket residue Val523 that is unique to COX-2. The interactions are very similar to the ones observed for the clinically active coxibs, and give a structural explanation for the anti-inflammatory activity of this chemotype. All three derivatives also have favourable Lipinski and ADMET properties which confirms their drug-likeness. All of the above observations confirm the pyrazole-chalcone hybrid scaffold as a potential template for further optimisation based on structure and point to the compounds 14b, 15b and 22, especially 22, as promising candidates for future synthesis, *in vitro* enzyme inhibition assays and *in vivo* anti-inflammatory evaluation. Future studies will focus on the further validation of the stability of the docking poses by molecular dynamics simulation and binding free energy calculation (e.g., MM-GBSA) and will involve docking the same molecules against COX-1 to quantify the selectivity index of each candidate before proceeding to biological testing.

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