RESEARCH PAPER

Design Of Etoricoxib-Based Selective Cox-2 Inhibitors: An *In-Silico* Approach

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Received: 14th Sep, 2025; Revised: 15th Oct 2025; Accepted: 18th Dec, 2025; Available Online: 1st Mar, 2025

Abstract

Combinatorial library development, analog docking, and in silico screening are currently established practices in drug design. We tried to develop optimized etoricoxib molecules that are selective for COX-2 using computer-aided drug design (CADD) based on information from a comprehensive source of literature and databases about COX inhibitors. We created a compound library of 60 compounds based on the structure of etoricoxib and other published COX inhibitors. Fifty-seven (57) of the above compounds satisfied Lipinski's rule of five. The above-screened compounds underwent further docking to determine their differential COX 2 binding affinities. Of these 57 compounds, only seven (11, 18, 24, 26, 30, 32, and 35) exhibited differential binding affinity comparable to or greater than etoricoxib. Compounds 30, 11, and 26 displayed the highest differential binding affinities, with values of -2.1, -1.4, and -1, respectively. These compounds had synthetic accessibility scores between 2.62 and 3.10, comparable to etoricoxib. These compounds could be successfully synthesized to assess their potential activity. So, *in silico* methods are a handy tool for quick and inexpensive search for possible drug candidates.

Keywords: Computer-aided drug design, Lipinski's rule, differential binding affinities, cyclooxygenase inhibitors, drug design.

How to cite this article: Patnaik S, Bagherian N, Pattanayak P, Trivarna VL, Tripathy S. Design of etoricoxib-based selective cox-2 inhibitors: an in-silico approach. Int J Drug Deliv Technol. 2026;16(3s): 874-878; DOI: 10.25258/ijddt.16.3s.106

1. INTRODUCTION

Structural modification of currently used drugs could be employed as a strategy in the design of newer drugs with better safety profiles and receptor selectivity [1]. Design and synthesis of novel drugs is a time-consuming process that entails searching for promising hits, developing those hits into leads, and then validating those leads into therapeutic candidates in clinical trials. However, despite enormous efforts, the drug research and development process has low efficiency and a high failure rate, which limits their production. Computer-aided drug design (CADD) is one of the most compelling contemporary methods for facilitating this process and accelerating it by reducing costs, time, and resources [2, 3].

The selective COX-2 inhibitors are as effective as other non-steroidal anti-inflammatory drugs in suppressing inflammation without producing adverse effects like peptic ulceration and upper gastrointestinal bleeding, renal damage, and platelet dysfunction [4]. Etoricoxib (Fig. 1) is a bipyridine-based selective COX-2 inhibitor used to treat joint pain and muscle swelling.

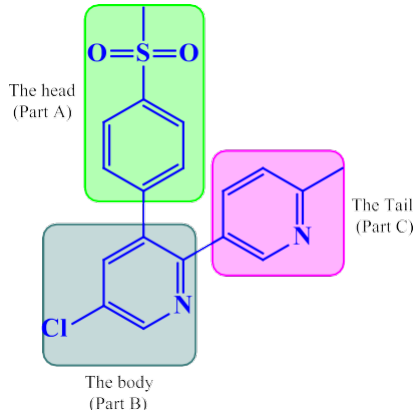

Fig. 1. Structure of Etoricoxib with different parts

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COX-2 Selectivity, commonly expressed as COX-1/COX-2 IC_{50} ratio, is a measure of the quantity of drug required to inhibit each PG-synthase isozyme activity by 50%. This concept is being applied during *in vitro* screening of drugs for their COX-2 selectivity [5,6]. Etoricoxib has an IC_{50} COX-1/COX-2 ratio of 344±48 in human whole blood tests [7,8]. According to the information, etoricoxib may be an excellent alternative to traditional NSAIDs for treating pain and arthritis, with the potential advantages of simple once-daily dosage and more excellent gastrointestinal tolerability. Combinatorial methods, which are used in computer-aided drug design, may produce a wide range of structurally varied compounds by methodically connecting several building blocks [9]. Once ready, the wide range of chemical substances may be examined concurrently for possible interactions with significant biological targets. By extensive literature survey and reviewing various databases about COX, we tried to generate selective COX-2 inhibitors by optimizing etoricoxib molecules using various CADD tools. The newly designed molecules are further subjected to docking analysis to find their binding affinities with the cyclooxygenase receptor, followed by their drug-likeness and synthetic accessibility study.

2 EXPERIMENTAL

2.1. Compound library generation

By using combinatorial libraries, we can generate a large number of chemical structures that can be screened or optimized for desired activities. For this purpose, we have used SmiLib software to generate the combinatorial library [10, 11]. Etoricoxib could be divided into three parts, as shown in Figure 1. Here, the body of etoricoxib serves as a connection between parts A and C and is made up of three sections: the head (part A), the tail (part C), and the body (part B). We created three fragment databases for sections A, B, and C with fragment numbers 5, 4, and 3, respectively, as shown below (Fig. 2), using the structures of previously reported COX inhibitors as a guide.

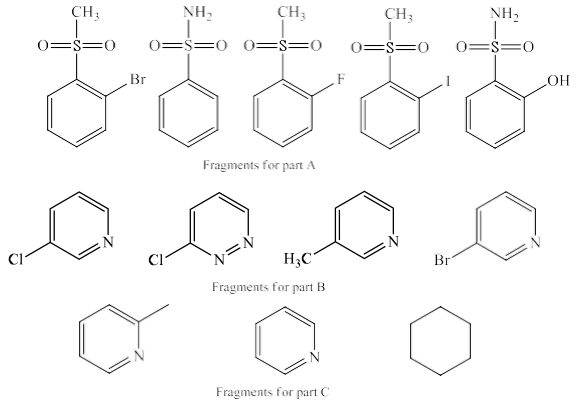

Fig. 2. Fragment databases for Etoricoxib

By permutation and combination, these three fragment groups could react with each other to generate 60 compounds (Fig. 3). The generated compound library of 60 compounds (ligands) was further screened for their drug-likeness and then docked with cyclooxygenase receptors to obtain therapeutically effective leads.

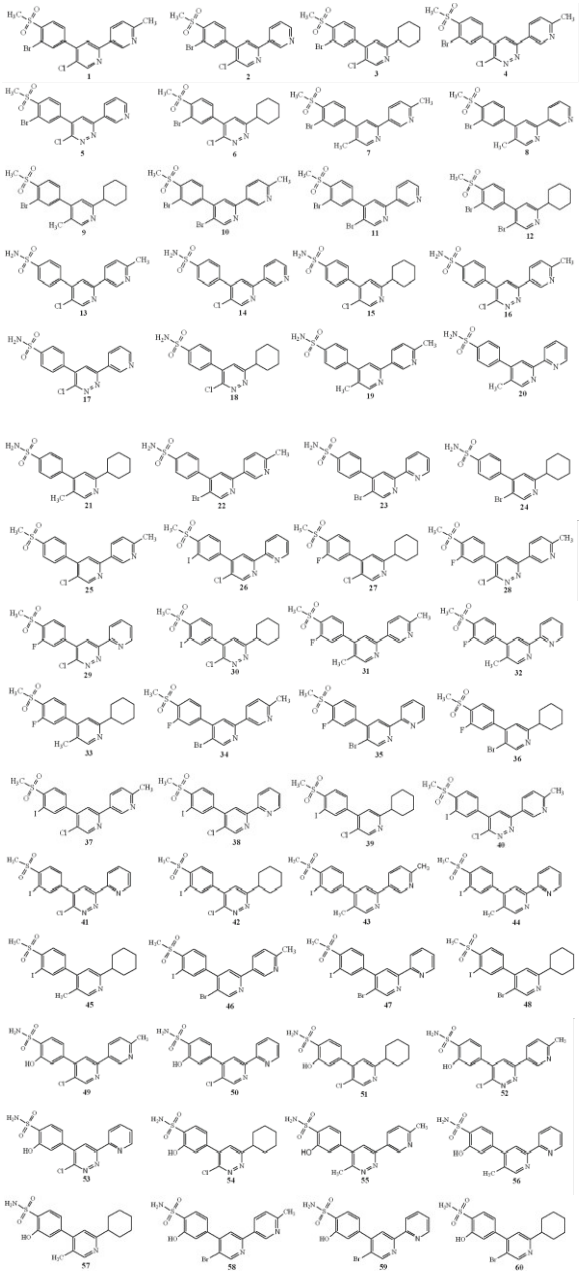

Fig. 3. The optimized compound library of etoricoxib

2.2. Virtual screening

DruLiTo (Drug Likeness Tools) is an open-source, Java-based tool to filter compounds based on various popular drug-like filters. Using Marvin Sketch, the above-generated libraries are combined into a single file, converted into an SDF (structural data file) format, and saved. DruLiTo screened the combined SDF file to filter the compounds based on Lipinski's rule of five [12]. Among the 60 combinations in the library, except for three compounds (42, 46, and 47), all remaining compounds accepted Lipinski's rule of five (Fig. 4). These filtered compounds or molecules were further used for docking studies.

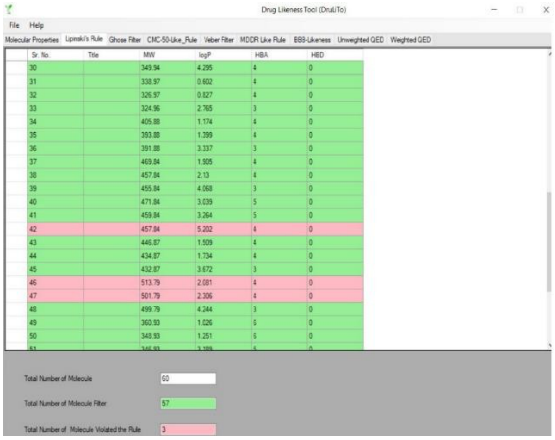

Fig. 4. Screening of compound libraries with DruLiTo

2.3 Molecular docking

The docking simulations of the 57 screened ligands towards COX-1 and COX-2 proteins were carried out using AutoDock Vina to measure their binding affinity towards the receptors. The protein structures used, COX-1 (PDB ID: 5U6X) [13] and COX-2 (PDB ID: 3RR3) [14], for docking simulations, were extracted from the Protein Data Bank. The pre-docking preparation of the protein(s) was carried out by adding polar hydrogen atoms with Gasteiger-Huckel charges, and the water molecules were removed. Then, receptors were checked for missing residues using PyMol software, followed by maintaining the ionization state of the amino acids present in the receptor using the H++ server. The structures of the synthesized molecules were drawn using ChemDraw Ultra 12 software. Then, all the three-dimensional coordinates were added to the system using Open Babel software. The total energy of the ligands was minimized using the Swiss PDB viewer with the 20 steepest decent processes. AutodockVina and AutoDock Tools (ADT) of the MGL software package were employed for docking analysis and conversion of PDB format into PDBQT format [15].

3. RESULTS AND DISCUSSION

Compound library creation, virtual screening, and docking are the methodologies most often utilized in this study. Referring to the structures of published COX inhibitors, a compound library was generated from the structure of etoricoxib.

The 60 compounds generated were screened for their drug-likeness based on Lipinski's rule of five, and the results were studied. Three (compounds 42, 46, and 47) out of the 60 ligands violated Lipinski's rule of five, and the remaining 57 ligands were further used for docking studies using AutoDock Vina. The docking experiments showed that some compounds had much higher docking potential against the COX-2 enzyme than COX-1. The docking process successfully generated root mean square deviation (RMSD) values less than 2 Å for all compounds and reference compounds. Table 1 displays the differential COX-2 binding affinities of all the ligands.

Table 1. The differential binding affinity of the screened compounds (ligands)

Compounds	COX-2	COX-1	Differential binding affinity (Kcal/mol)[a]	RMSD value
3	-7.2	-6.9	-0.3	035
6	-9.0	-8.9	-0.1	1.22
11	-8.9	-7.5	-1.4	1.7
13	-8.5	-8.3	-0.2	0.51
15	-8.5	-8.2	-0.3	0.92
16	-8.7	-8.5	-0.2	1.15
18	-8.7	-7.9	-0.8	1.07
20	-8.6	-8.2	-0.4	0.58
22	-8.6	-8.3	-0.3	0.90
24	-8.6	-8.0	-0.6	1.75
26	-8.9	-7.9	-1	1.14
27	-8.7	-8.4	-0.3	0.51
28	-7.3	-6.9	-0.4	0.92
30	-8.6	-6.5	-2.1	1.15
32	-8.9	-8.4	-0.5	1.17
35	-8.8	-8.2	-0.6	0.55
38	-8.7	-8.5	-0.2	0.96
40	-8.6	-8.2	-0.4	1.19
57	-7.0	-6.9	-0.1	1.11
60	-8.9	-8.6	-0.3	1.73
Etoricoxib	-8.7	-8.2	-0.5	0.54

[a]Compounds with differential binding affinity

The docking study predicted that the differential binding affinity of etoricoxib towards COX-2 was -0.5. Out of the 57 compounds, only 20 showed a differential binding affinity. Only 7 (compounds 11, 18, 24, 26, 30, 32, and 35) out of these 20 compounds showed differential binding affinity equal to or greater than etoricoxib. These compounds possess better binding affinity as compared to etoricoxib with the target proteins. Compounds 30, 11, and 26 showed the highest docking score towards the target protein 3RR3, having differential binding affinity of -2.1, -1.4, and -1, respectively (Fig. 5). The docking interaction of

compound 11 showed a favorable hydrogen bond interaction between the oxygen atom of the S=O group of the compound and the hydrogen of the side chain of GLY135. The halogen atoms interact hydrophobically with the residues TYR136 and TRP323. The 'N' atom of the pyridine ring interacts hydrophobically with MET48 and SER548 while the aromatic rings interact hydrophobically with ALA156, GLN327, and GLU46 (Fig. 6). These interactions stabilize the ligand-receptor interactions and play an essential role in COX-2 inhibitory activity. The compound 26 also forms a hydrogen bond with the side chain residue ASP157, similar to etoricoxib. Like etoricoxib, the halogen atoms and the aromatic rings interact hydrophobically with residues ALA156, VAL155, GLY135, CYS36, and TYR136. The same interaction pattern was observed for compound 30, which had the highest differential binding affinities.

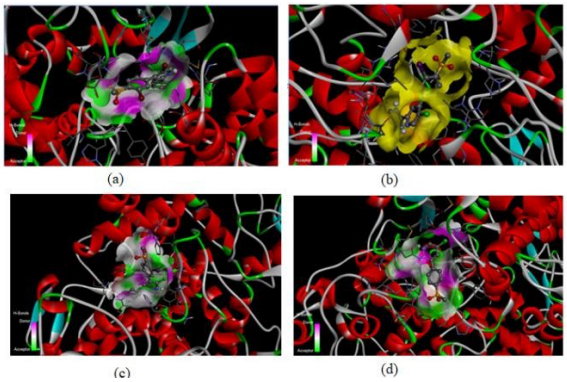

Fig. 5. Docking simulation of receptor interaction of compounds (a) 11, (b) 26, (c) 30, and (d) etoricoxib

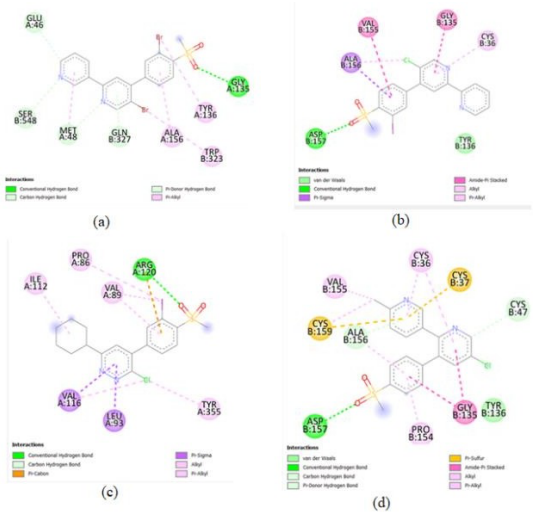

Fig. 6. 2D interaction with receptors (a) 11, (b) 26, (c) 30, and (d) etoricoxib

Studying drug-likeness properties helps in the drug development process before their synthesis [16]. Fifty-seven out of sixty compounds have accepted Lipinski's rule of five. For oral bioavailability of drugs, Lipinski suggested not more than one violation of the criteria, i.e., molecular weight ≤ 500 dalton, number of hydrogen bond acceptors ≤ 10, number of hydrogen bond donors ≤ 5, and lipophilicity ≤ 5. To further study the oral bioavailability, other drug-likeness descriptors such as molar refractivity, number of rotatable bonds, and total polar surface area were also analyzed for the seven compounds. TPSA and molecular weight both have a significant impact on the permeability of a drug through biological barriers. High TPSA and molecular weight represent lower drug permeability through biological barriers [17]. Lipophilicity (expressed as Log P) is another critical parameter that determines the absorption of drugs in the body. Drugs with higher Log P values have a lower absorption rate in the body [18]. Any single non-ring bond linked to a non-terminal, non-hydrogen atom is referred to as rotatable, except C-N bonds, due to their high barrier to rotation. The number of rotatable bonds particularly impacts bioavailability and binding potency. The conformational flexibility is constrained as the number of rotatable bonds decreases, and the molecule becomes stiff. Additionally, it could freeze the molecule in a bioactive conformation, giving the molecule the drug status. So, the number of rotatable bonds (the acceptable range is less than 10) also influences the drug-likeness properties of a drug. Table 2 lists the molecular descriptors of drug-likeness of the seven tested compounds (11, 18, 24, 26, 30, 32, and 35) that had COX-2 binding affinities that were equal to or greater than etoricoxib. All seven of the selected compounds adhered to Lipinski's drug-likeness rules. The drug-likeness properties of each of them yielded positive findings, and as a result, they were all identified as prospective drug candidates. Predicting the synthetic accessibility of drug-like molecules is crucial in the de novo drug development process. Lead molecules, which have difficult synthetic accessibility, require more time and resources. The development and validation of the *in silico* method can characterize the synthetic accessibility of molecules on a scale between 1 (easy to make) and 10 (very difficult to make) (Table 2) [19]. The synthetic accessibility score of these screened compounds was similar to that of etoricoxib, ranging between 2.62 and 3.10, suggesting their ease of synthesis.

Table 2. The drug-likeness studies and synthetic accessibility score of the screened compounds

Drug Likeness Properties	**11**	**18**	**24**	**26**	**30**	**32**	**35**	**Etoricoxib**
Molecular weight	468.16	351.85	395.31	470.71	476.76	342.39	407.26	358.84
Consensus log $P_{o/w}$	3.94	3.05	3.47	3.97	4.50	3.43	3.67	3.65
Number of HBA[a]	4	5	4	4	4	5	5	4

Number of HBD[b]	0	1	1	0	0	0	0	0
Molar refractivity	101.40		95.25	103.72	105.18	90.92	93.66	95.97
Number of rotatable bonds	3	3	3	3	3	3	3	3
TPSA(Å^2)[c]	68.30	94.32	81.43	68.30	68.30	68.30	68.30	68.30
Bioavailability score	0.55	0.55	0.55	0.55	0.55	0.55	0.55	0.55
Synthetic accessibility score	3.00	2.95	2.78	2.76	3.10	2.62	2.75	2.75

[a]Number of hydrogen bond acceptors; [b]number of hydrogen bond donors; [t]otal polar surface area.

4. CONCLUSION

The ligands that showed differential binding affinity in favor of COX-2 were reported. In this study, we conclude that out of 60 ligands generated in the compound library, seven compounds showed differential binding affinity towards COX-2, which can be tested for further optimization to reach the next stage of drug design and development. To conclude, in silico approaches are indeed a handy tool in the search for potential drug candidates with reduced cost and time.

COMPETING INTERESTS

The authors report that there are no competing interests to declare.

AUTHORS CONTRIBUTIONS

All authors contributed to the conception and design of the study. Nafiseh Bagherian, Swastik Patnaik, Priyabrata Pattanayak and V. Lee Trivarna performed material preparation, data collection, and analysis. Nafiseh Bagherian, Swastik Patnaik, Shyamalendu Tripathy and Priyabrata Pattanayak have written and reviewed the paper. All authors read and approved the final manuscript.

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