American Journal of Pharmacological Sciences, 2025, Vol. 13, No. 1, 6-18
Available online at http://pubs.sciepub.com/ajps/13/1/2
Published by Science and Education Publishing
DOI:10.12691/ajps-13-1-2

Designing and Evaluation of Novel Thiazole Derivatives As COX Inhibitor by *Iv*lcb: *In-vitro* Like Computational Bioassay & Docking Analysis

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Received March 14, 2025; Revised April 16, 2025; Accepted April 23, 2025

Abstract COX (Cyclooxygenase) is also known as prostaglandin-endoperoxide synthase (PTGS) which is responsible for inflammation and related issues. In the present study eleven thiazole derivatives were designed and computationlly evaluated for their inhibitory activity against COX enzyme. All eleven novel designed molecules were evaluated by *Iv*LCB: *In-vitro* like computational bioassay and SwissDock. These molecules were also evaluated for their ADME descriptors and bioactivity prediction using Molinspiration for bioacitivity scores for the drug targets like GPCR ligands, kinase inhibitors, ion channel modulators, nuclear receptors etc. As per the analysis done it was found that designed molecule 2A8 shows High activity pattern, good % inhibition and strong binding ability to PDB ID: 4M11 with 14 hydrogen bonds and binding affinity of -10 kcal/mol.

Keywords: *COX inhibitors, thiazole derivatives, computational study, docking, in-silico analysis, in-vitro like computational bioassay*

Cite This Article: Utsav Kumar, Nitin Sharma, Harsh Tyagi, Ajeet, Babita Kumar, Shabnam Ain, and Qurratul Ain, "Designing and Evaluation of Novel Thiazole Derivatives As COX Inhibitor by *Iv*lcb: *In-vitro* Like Computational Bioassay & Docking Analysis." *American Journal of Pharmacological Sciences*, vol. 13, no. 1 (2025): 6-18. doi: 10.12691/ajps-13-1-2.

1. Introduction

Inflammation is a natural process that involves many disorders and diseases such as arthritis, psoriasis, cancer, infections, asthma, and more. Since COX plays a major role in inflammation, traditional treatments include the use of non-steroidal anti-inflammatory drugs (NSAIDs), which are selective or non-selective COX inhibitors [1,2,3]. Bacteria and viruses cause tissue inflammation, which is the immune system, and secrete the cytokines nitric oxide (NO), prostaglandins (PG), interleukin 6 (IL-6), and tumor necrosis factor (TNF). However, the loss of NO and PG is evident in inflammation [4,5]. The development of pain should be prevented [6].

Diseased areas can react to free radicals such as hydroxyl (-OH), superoxide (O2 -) and hydrogen peroxide (-OOH, -OOR) and produce more disease. Cyclooxygenase-2 (COX-2) is an enzyme that stimulates inflammation, so inhibiting the activity of this enzyme will be the target in the treatment of inflammation [7]. The body is exposed to bacteria and viruses, allergens, irritants, poisons, etc. (exogenous or endogenous) [8]

Associated risks Due to the inflammatory process, it is difficult for doctors to find better anti-inflammatory drugs. Most of the existing anti-inflammatory drugs, especially those that have been shown to be effective, such as aspirin, indomethacin, flufenamic acid, ibuprofen, etc., are acidic. Non-steroidal anti-inflammatory drugs (NSAIDs) cause tissue damage by inhibiting the cyclooxygenase (COX) enzyme involved in prostaglandin synthesis [9,10] and are an important part of the drugs used in the treatment of pain. [11,12,13,14,15]

It is well known that NSAIDs block prostaglandin production by inhibiting cyclooxygenase (COX). There are at least two known isoforms of COX: COX-1 and COX-2. COX-1 is generally considered a housekeeping enzyme. It is widely distributed in most tissues and often plays a physiological role, such as protecting the intestinal mucosa, controlling and maintaining renal function, or controlling platelet aggregation by stimulating thromboxane A2 (TXA2). In contrast, COX-2 is thought to be responsible for the initiation and maintenance of the inflammatory process, with minor effects such as stimulating the production of prostacyclin (PGI2) and thus preventing platelet aggregation [16,17,18].

It has been confirmed that gastrointestinal side effects are mainly related to the inhibition of cyclooxygenase-1 (COX-1), while cardiovascular side effects are directly related to the inhibition of cyclooxygenase-1 (COX-1). Inhibition of COX-2 (probably by blocking PGI2 biosynthesis without blocking TXA2 production [17] Most COX-2 specific inhibitors have been removed from the market, such as coxib (valdecoxib, rofecoxib), the initial goal of creating COX-2 inhibitors with the goal of

reducing intestinal inflammation is not good because they have a high risk of heart disease [19] a. It seems that the CV risk increases as the specificity of COX-2 inhibition increases. This observation is supported by the fact that celecoxib, the only coxib currently approved by the US Food and Drug Administration (FDA), is the most specific for COX-2 among all coxibs and shows a higher percentage of COX-1 inhibitor. More effect than other coxibs [20] On the other hand, COX-1 inhibitors such as acetylsalicylic acid are known to cause gastric ulcers, since this particular COX isoenzyme is responsible for the formation of gastroprotective prostaglandins. In addition, this group of drugs can increase blood diathesis due to the inhibition of COX-1-catalyzed thromboxane A2 (TXA2) production. The seriousness of side effects from COX-1 or combined COX-1/COX-2 inhibitors (e.g. ibuprofen) has led to interest in the development of COX-2 inhibitors, and this has been inspired by evidence supporting the specific isoenzyme in inflammatory conditions. However, promises that new-generation drugs will be more effective and have fewer side effects than their predecessors are challenged by their association with the risk of myocardial infarction and increased cardiovascular events. These serious side effects are mainly caused by the inhibition of COX-2-catalyzed production of prostacyclin (PGI2), a prostaglandin with vasodilator and anti-aggregative properties [21,22,23,24]. It is well known that compounds containing sulfur atoms play an important role in living organisms [25,26]. In particular, thiazole is a well-known heterocyclic aromatic compound having sulfur atoms and nitrogen atoms at positions 1 and 3 of its five rings, respectively [27].

The thiazole moiety is present in many bioactive compounds of natural origin (for example, many pharmacological activities such as thiamine [26,27], mycothiazole (28), cyctothiazole C (29), and anti-bacterial (30-35), anti-viral (36-37), anti-tuberculosis (30,38) anti-inflammatory [39,40,41], anxiolytic [42], anaesthetic [43], anticonvulsant [44,45,46,47].

Many drug depots are called thiazoles, such as anthelmintic thiabendazole, antibiotic sulfathiazole, anticonvulsant riluzole, antiulcer arizatidine, anti-parkinson's talipexole, the anti-schistosomal niridazole, anti-viral ritonabir and anti-inflammatory meloxicam.

1.1. Cyclooxygenase Isoform, Structure and Function

The first purified preparation of the COX enzyme was reported in 1976 [48]. More than a decade later, COX was cloned in 1988 [49,50,51]. In 1990, an inducible isoform, now known as COX-2 [52,53,54], was discovered. Originally known as prostaglandin-H synthase (PGHS), COX is primarily responsible for the oxidation of AA to PGG2 and PGH2. The molecule O2 is converted to PGG2, and in the peroxidase reaction, PGG2 is reduced to PGH2 by two-electron reduction. COX isoforms are heme-containing enzymes that exhibit expression spectra and roles in a variety of physiological processes. The core structure of COX-1 consists of 602 amino acids, while that of COX-2 consists of 604 amino acids. COX-1 and COX-2 isoforms show identity in animals and approximately 90% sequence divergence between species [55]. Sheep COX-1 and NSAIDs were released in 1994. The first crystal structure of the flurbiprofen complex [56]. COX-1 isoforms are consistently expressed at high levels in cells and tissues throughout the body, such as the endothelium, monocytes, platelets, renal collecting ducts, and blood vessels, suggesting that it is a developmental regulator [57]. The COX-2 enzyme is produced and induced by inflammatory mediators (such as lipopolysaccharide (LPS), interleukin-1 (IL1), tumor necrosis factor (TNF) in many cells and tissues (such as vascular endothelium, osteoclasts, etc.), rheumatoid synovial endothelial cells, monocytes, and macrophages. Recent studies have shown that expressed COX-2 functions particularly in reproduction, renal physiology, bone resorption, and neurotransmission [58,59,60,61].

1.2. *In-silico* Studies

In-silico studies refer to the use of computer simulations, models, and algorithms to conduct experiments, analyze data, or make predictions in biological, chemical, and pharmaceutical research. The term "*in-silico*" is derived from the Latin word silicon, referring to the computer chips that power such virtual research methods, analogous to terms like *in-vitro* (experiments in glass) or *in-vivo* (experiments in living organisms). *In-silico* studies are commonly employed in drug discovery, genomics, molecular biology, and systems biology, where they can simulate complex biological processes and predict the behavior of molecules or systems in silico, or "on silicon."

1.2.1. Types of *In-Silico* Studies

In-silico studies encompass a variety of research methodologies. The main types include:

Molecular Docking: This method predicts the preferred orientation of one molecule (typically a drug) to another (typically a protein), helping to understand binding affinity and interaction mechanisms. It is particularly used in drug design.

Molecular Dynamics (MD) Simulations: These simulations study the physical movements of atoms and molecules over time, allowing researchers to explore molecular interactions, conformational changes, and other dynamic behaviors in biological systems.

Quantitative Structure-Activity Relationship (QSAR): QSAR modeling involves correlating the chemical structure of compounds with their biological activity. It is useful for predicting the biological effects of chemical compounds based on their molecular structure.

Homology Modeling: In cases where a high-resolution structure of a protein is not available, homology modeling can be used to create a model based on a known structure of a similar protein. This is especially useful in drug discovery for target identification.

Systems Biology Modeling: This involves simulating biological networks and cellular pathways to understand complex biological behaviors, such as metabolic networks, signal transduction pathways, and gene regulatory networks.

Pharmacophore Modeling: A pharmacophore model represents the essential chemical features required for a molecule to bind to a specific biological target. It is used in drug design to identify lead compounds.

Virtual Screening: This method involves using computational techniques to screen large libraries of molecules for potential drug candidates, identifying molecules that may interact favorably with a given target protein.

Population Pharmacokinetics and Pharmacodynamics: In silico studies can simulate how a drug is absorbed, distributed, metabolized, and excreted in different populations, helping to predict responses across different patient groups.

2. Materials and Methods

2.1. Descriptors

Descriptors refer to the measurable or quantifiable properties or characteristics that describe the behavior or attributes of a drug. These descriptors help researchers understand how a drug interacts with the body (pharmacokinetics) and how it exerts its effects (pharmacodynamics) These descriptors are essential for designing and optimizing new drugs, as they help predict how a drug will behave in the body, how effective it will be, and how safe it is.

In-silico **studies** (computer-based simulations or computational studies), descriptors play a critical role in predicting and analyzing the behavior of drugs, proteins, or other biomolecules. These **descriptors** are used to quantify molecular properties, interactions, and behaviors, which can inform drug design, optimize lead compounds, and reduce the need for expensive and time-consuming wet lab experiments. Descriptors are also crucial for predicting the **ADMET** (Absorption, Distribution, Metabolism, Excretion, and Toxicity) properties of drug candidates. Computational models can predict these properties by correlating molecular descriptors with experimental data:

Absorption: Descriptors related to solubility, polarity, and membrane permeability (e.g., LogP, molecular weight, and hydrogen bond donors/acceptors)

Metabolism: Descriptors related to metabolic stability (e.g., CYP450 enzyme binding affinities).

Toxicity: Toxicological risk is assessed by using descriptors that predict mutagenicity, carcinogenicity, or organ toxicity (e.g., structural alerts or molecular properties linked to toxic outcomes).

Excretion: Descriptors that indicate renal or biliary excretion efficiency.

Descriptors allow researchers to predict the biological activity of a compound before it is synthesized or tested experimentally. By correlating these descriptors with observed outcomes like binding affinity, efficacy, or toxicity

EMOS is research group are engaged in understanding the fundamental processes of degradation and analysis of organic pollutants. Emos runs (https://armakovic.com/) with the organization **AIDASCO** (Association for the International Development of Acedmic and Scientific Collaboration) (https://aidasco.org/) which runs **ADME Calculator** (https://armakovic.com/online-tools/adme-calculator/) to calculate the molecular properties, interactions, and behaviors and reduce the need for expensive and time-consuming wet lab experiments, thus we used ADME calculator for the computational studies

2.2. *In-silico* / Computational Bioassay

Computational Bioassay was performed by the Computational Bioassays for Biochemical Experiments (CBBE) accessed via https:// assay. smallmoles. com/cbbeapps/, In-vitro like computational bioassay (IvLCB); a research product of CBBE (Computational Biology for Biochemical Experiments; www.smallmoles.com) which is a web based software that is designed as a tool for evaluating the newly designed derivatives.

2.3. Bioactivity Score: For Different-bioactivities

A bioactivity score is a quantitative value that reflects the biological activity of a compound or molecule in a specific biological context. In drug discovery and other bioscience applications, bioactivity scores are used to assess the potency or effectiveness of a compound (such as a drug candidate) in interacting with a biological target, such as a receptor, enzyme, or gene. The score provides a measure of how well a compound performs in relation to a desired biological effect, and it is often derived from experimental data or computational prediction The main purpose of a bioactivity score is to provide an objective, quantifiable measure of the biological effect of a compound, which can help guide decisions in drug discovery, toxicology, and other areas of bioscience research.

Molinspiration (https://www.molinspiration.com) supports internet chemistry community by offering for calculation of important molecular properties.

We have used web based software **Molinspiration** https://www.molinspiration.com/cgi/properties) to calculate the log P, polar surface area, number of hydrogen bond donors and acceptors and others, as well as prediction of bioactivity score for the most important drug targets (GPCR ligands, kinase inhibitors, ion channel modulators, nuclear receptors) of newly designed Thiazole molecules.

2.4. Docking Studies

Docking tool: Docking was performed with SwissDock (AutoDockVina) which is web based docking software that predicts the molecular interactions likely to occur between a target protein and a small molecule docking software. It is virtual screening software for computational drug discovery that can be used to screen libraries of compounds against potential drug targets. It enables medicinal chemists to run virtual screening form any platform and helps users in every steps of this process from data preparation to job submission and analysis of the results [62,63].

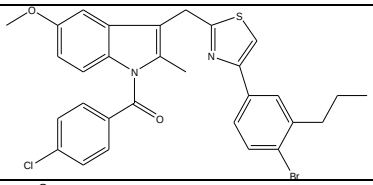
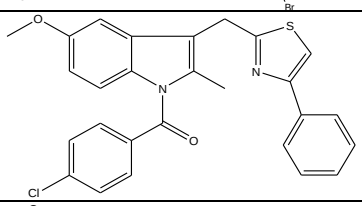
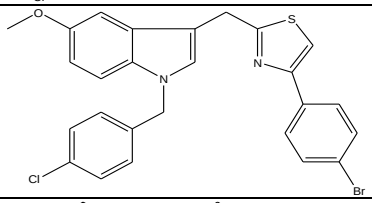
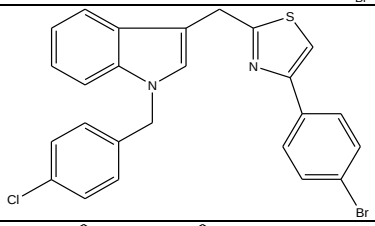
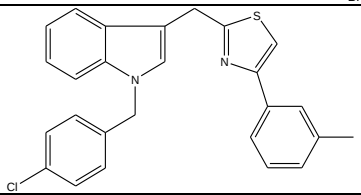
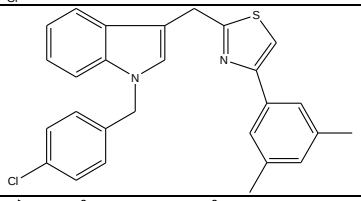
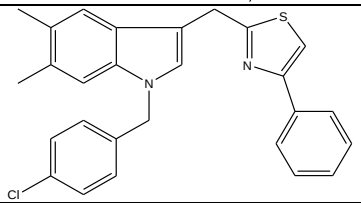
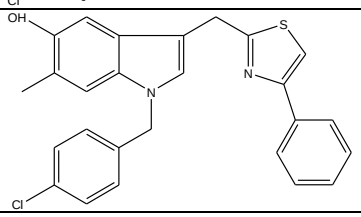
Receptor: Cyclooxygenase-2 Complex with Meloxicam

3. Results and Discussion

3.1. Designed Molecules

A list of designed molecules has been shown in Table.1. These molecules were designed by keeping in mind the pharmacophoric concept of drug.

Table 1. Designed moleculesS.NO

	COMPOUND	STRUCTURE
1	2AN	
2	2A1	
3	2A2	
4	2A3	
5	2A4	
6	2A5	
7	2A6	
8	2A7	

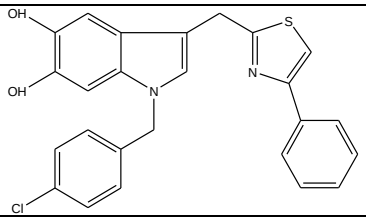
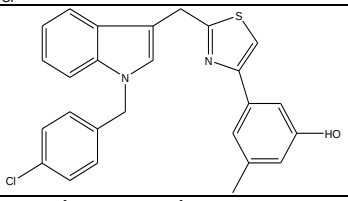
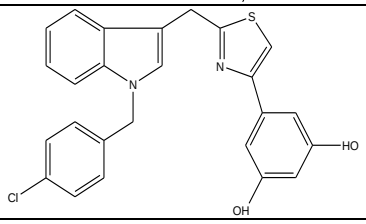
9	2A8	
10	2A9	
11	2A10	

Table 2. ***Descriptors*** **(Lipinski Rule Of Five)**

S.NO	COMP	MOL.WT	LOG.P	n.HBD	n.HBA	MR	TPSA
1	2A N	593.974	8.73	0	5	156.458	44.12
2	2A 1	472.997	7.015	0	5	134.763	44.12
3	2A 2	523.883	7.828	0	4	137.1	27.05
4	2A 3	493.857	7.82	0	3	130.548	17.82
5	2A 4	428.988	7.366	0	3	127.585	17.82
6	2A 5	443.015	7.674	0	3	132.322	17.82
7	2A 6	443.015	7.674	0	3	132.322	17.82
8	2A 7	444.987	7.071	1	4	129.25	38.05
9	2A 8	446.959	6.459	2	5	126.178	58.28
10	2A 9	444.987	7.071	1	4	129.25	38.05
11	2A 10	446.959	6.459	2	5	126.178	25.28

3.2. Descriptors (Lipinski rule of five)

An initial descriptor calculation has also performed in order to observe designed compounds with its drug ability property (Lipinski Rule of Five) (Table 2).

Lipinski rule of five helps in distinguishing between drug like and non-drug like molecules. It predicts high probability of success or failure due to drug likeness for molecules. It was observed that all the designed molecules pass the Lipinski rule of five.

3.3. Docking

To perform docking, the receptor was downloaded from NCBI website with PDB ID 4M11, all the designed ligands have been docked with protein (receptor) with SwissDock (AutoDockVina) web based software having its default settings. Docking study of different proteins were performed with the designed inhibitors is given in Figure.1 and Table 3; number of hydrogen bonds & binding pattern such as element, type of bond, atom number and residue at binding site were evaluated.

On docking analysis, designed compound 2AN has been found to be strongly docked with 4M11 with 4 hydrogen bonds and binding affinity of: -9.8 Kcal/mol. On residue study were found to be significant. Asn375 and Arg376 On the account of ligand oxygen atom is significant in binding with donor bonds, whereas significant element in receptor is oxygen.

On docking analysis, designed compound 2A1 has been found to be strongly docked with 4m11 with 4 hydrogen bonds and binding affinity of: -10.2Kcal/mol. On residue study Asn375 and Arg376 were found to be significant. On the account of ligand oxygen atom is significant in binding with donor bonds, whereas significant element in receptor is oxygen.

On docking analysis, designed compound 2A2 has been found to be strongly docked with 4m11 with 4 hydrogen bonds and binding affinity of: -9.6 Kcal/mol. On residue study Asn375, Arg376 and Gly 372 were found to be significant. On the account of ligand oxygen atom is significant in binding with donor bonds, whereas significant element in receptor is oxygen.

On docking analysis, designed compound 2A3 has been found to be strongly docked with 4m11 with 1 hydrogen bonds and binding affinity of: -9.4 Kcal/mol. On residue study Arg 376 were found to be significant. On the account of ligand oxygen atom is significant in binding with donor bonds, whereas significant element in receptor is nitrogen.

On docking analysis, designed compound 2A4 has been found to be strongly docked with 4m11 with 4 hydrogen bonds and binding affinity of: -9.6 Kcal/mol. On residue study N/A were found to be significant.

On docking analysis, designed compound 2A5 has been found to be strongly docked with 4m11 with 4 hydrogen bonds and binding affinity of: -9.6 Kcal/mol. On residue study N/A were found to be significant.

On docking analysis, designed compound 2A6 has been found to be strongly docked with 4m11 with 4 hydrogen bonds and binding affinity of: -9.6 Kcal/mol. On residue study N/A were found to be significant.

On docking analysis, designed compound 2A7 has been found to be strongly docked with 4m11 with 1 hydrogen bonds and binding affinity of: -10.3Kcal/mol.

On residue study Asn375 were found to be significant. On the account of ligand oxygen atom is significant in binding with donor bonds, whereas significant element in receptor is nitrogen.

On docking analysis, designed compound 2A8 has been found to be strongly docked with 4m11 with 14 hydrogen bonds and binding affinity of: -10.0 Kcal/mol. On residue study Asn375, Arg376, Lue224, Ser143 and Gln374 were found to be significant. On the account of ligand oxygen atom is significant in binding with donor bonds, whereas significant element in receptor is oxygen.

On docking analysis, designed compound 2A9 has been found to be strongly docked with 4m11 with 8 hydrogen bonds and binding affinity of: -10.5Kcal/mol. On residue study Gln536, Tyr373, Pro538, Gly536 and Gly225 were found to be significant. On the account of ligand oxygen atom is significant in binding with donor bonds, whereas significant element in receptor is oxygen.

On docking analysis, designed compound 2A10 has been found to be strongly docked with 4m11 with 20 hydrogen bonds and binding affinity of: -10.5Kcal/mol. On residue study Gly225, His226, Gly536, Pro538, and Tyr373 were found to be significant. On the account of ligand oxygen atom is significant in binding with donor bonds, whereas significant element in receptor is oxygen.

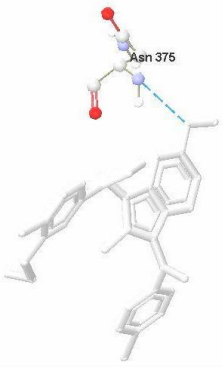
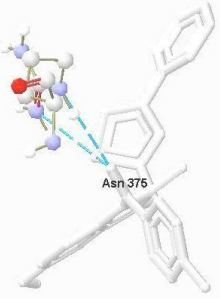
3.4. Computational Bioassay by *Iv*LCB (*In-vitro* Like Computational Bioassay)

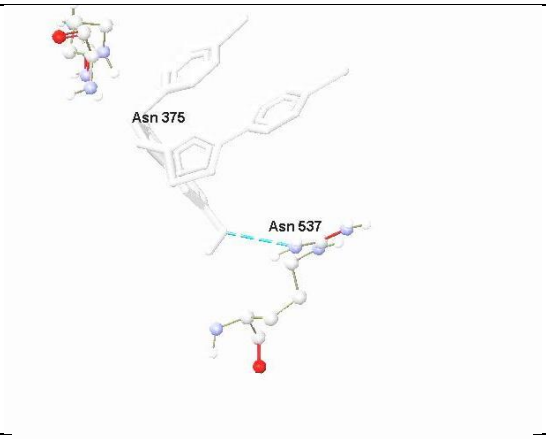
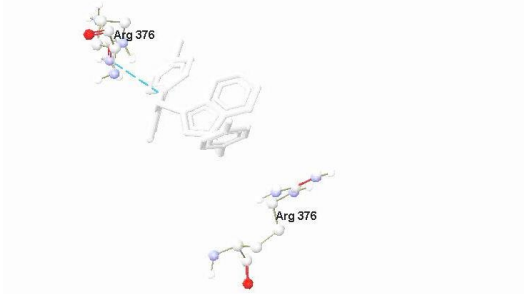
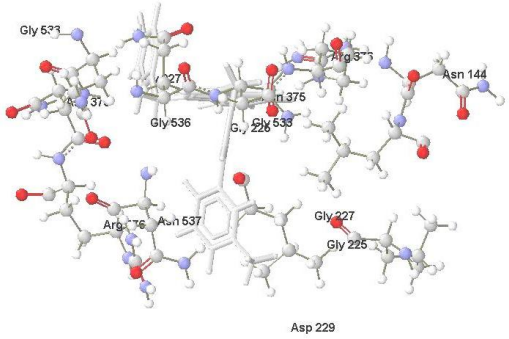
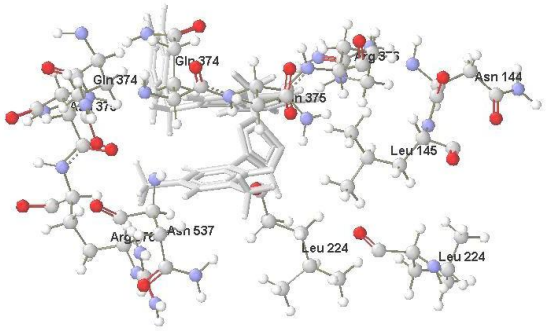
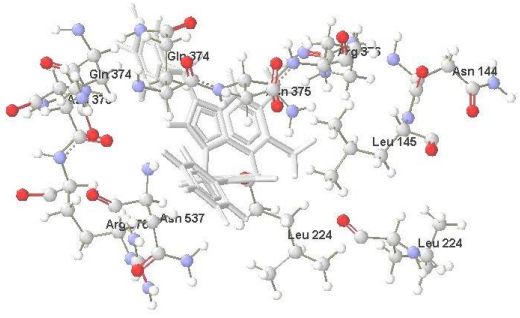
A computational evaluation has been performed by licensed subscription of *Iv*LCB (*In-vitro* like computational bioassay) which estimates the comparison of possible **% inhibition** of novel designed molecule at predefined concentration gradient as we do in *in-vitro* experiments (Table 4). It also shows relation between % inhibition variations on the ground of normalized concentration gradient in the form of Graph which is shown in Figure 2 for designed molecule 2A10.

It also predicts activity representative of designed molecules in terms of Q-**Score** & C-Score independently for Query and Control compound along with **Activity Pattern.** Among all designed molecules, molecule 2A8 is found with highest Q-score of 16.541 which closest to control drug. As far as its activity pattern is concern *Iv*LCB shows High activity pattern which supports the molecule for its activity.

It gives an **idea about how our current query compound is close to predefined standard drugs** in the form of regression plot (Figure 2). Our designed molecules keep floating in graph very close to Aspirin which again supports the designed molecules for its better and positive activity as anti-inflammatory molecule.

It can **compare our designed molecule's activity among themselves**, i.e. which one is better among all designed molecules. On comparing all the parameters of *Iv*LCB, designed molecule 2A8 is found to be most active molecule among all.

S.NO.	COMPOUND NAME	DOCKED IMAGES
1.	2A N	
2.	2A 1	

3.	2A 2	
4.	2A 3	
5.	2A 4	
6.	2A 5	
7.	2A 6	

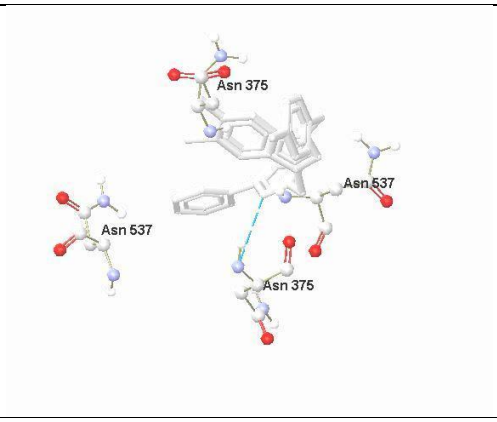
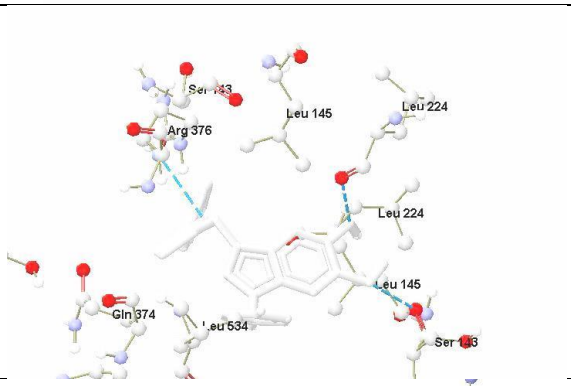
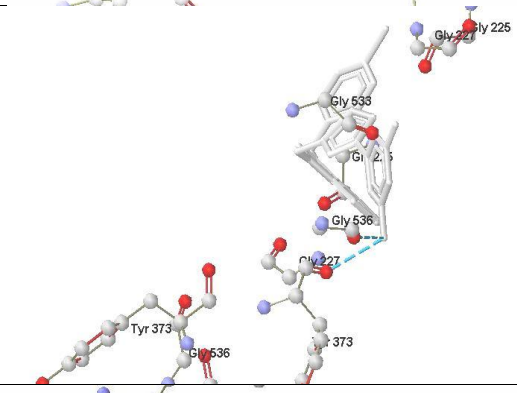
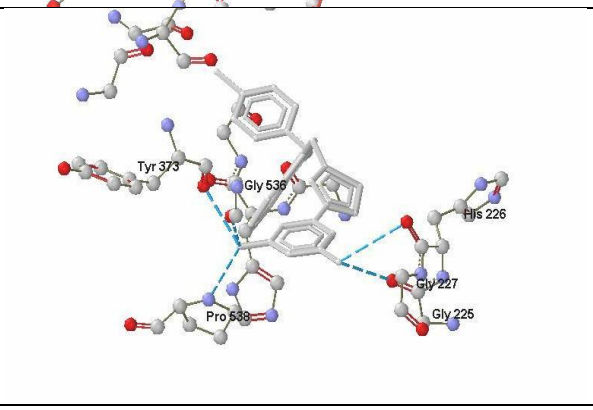
8.	2A 7	
9.	2A 8	
10.	2A 9	
11.	2A 10	

Figure 1. Docked images of designed molecules with PDB ID: 4M11 (Shown with binding Amino acids / Residues)

Table 3. Docking results of all the compounds with receptor 4M11 (Showing binding affinity, Number of hydrogen bonds along with details of binding elements and binding residues)

LIGAND	AFFINITY Kcal/mol	H-bond	H-Binding Ligand			H- Binding Receptor			
			Element	At.ID	Type	Residue	Element	At.ID	Type
2A N	-9.8	4	O	16	ACCEPTOR	Asn 375	N	2808	DONOR
			O	18	ACCEPTOR	Asn 375	N	2808	DONOR
			O	16	ACCEPTOR	Asn 375	N	2808	DONOR
			O	19	ACCEPTOR	Asn 375	N	2808	DONOR
			O	19	ACCEPTOR	Arg 376	N	2825	DONOR
2A 1	-10.2	4	O	31	ACCEPTOR	Asn 375	N	2808	DONOR

LIGAND	AFFINITY Kcal/mol	H-bond	H-Binding Ligand			H- Binding Receptor			
			Element	At.ID	Type	Residue	Element	At.ID	Type
			O	23	ACCEPTOR	Arg 376	N	2823	DONOR
			O	23	ACCEPTOR	Arg 376	N	2826	DONOR
			O	31	ACCEPTOR	Asn 375	N	2808	DONOR
			O	31	ACCEPTOR	Asn 375	N	2808	DONOR
2A 2	-9.6	4	O	30	ACCEPTOR	Asn 375	N	2808	DONOR
			O	30	ACCEPTOR	Arg 376	N	2825	DONOR
			O	30	ACCEPTOR	Asn 375	N	2808	DONOR
			O	30	ACCEPTOR	Gly 372	N	2786	DONOR
2A 3	-9.4	1	N	11	ACCEPTOR	Arg 376	N	2326	DONOR
2A 4	-10.1	0	-	-	-	-	-	-	-
2A 5	-10.1	0	-	-	-	-	-	-	-
2A 6	-10.3	0	-	-	-	-	-	-	-
2A 7	-10.3	1	N	21	ACCEPTOR	Asn 375	N	2808	DONOR
2A 8	-10.0	14	O	31	BOTH	Asn 375	O	2811	ACCEPTOR
			O	31	BOTH	Arg 376	N	2823	DONOR
			O	31	BOTH	Arg 376	N	2826	DONOR
			O	29	BOTH	Gln 374	O	2806	ACCEPTOR
			O	31	BOTH	Gln 374	O	2806	ACCEPTOR
			O	29	DONOR	Asn 375	O	2811	ACCEPTOR
			O	29	BOTH	Gln 374	O	2806	ACCEPTOR
			O	31	BOTH	Arg 376	N	2823	DONOR
			O	31	BOTH	Asn 375	O	2811	ACCEPTOR
			N	19	ACCEPTOR	Arg 376	N	2826	DONOR
			O	29	BOTH	Lue 224	O	1555	ACCEPTOR
			O	31	BOTH	Ser 143	O	904	ACCEPTOR
			O	29	BOTH	Asn 375	O	2811	ACCEPTOR
			O	29	BOTH	Arg 376	N	2823	DONOR
			O	31	BOTH	Asn 375	O	2811	ACCEPTOR
2A 9	-10.5	8	O	13	BOTH	Gln 536	O	4113	ACCEPTOR
			O	13	BOTH	Tyr 373	O	2790	ACCEPTOR
			O	13	BOTH	Tyr 373	O	2790	ACCEPTOR
			O	13	BOTH	Gly 536	O	4113	ACCEPTOR
			O	13	BOTH	Pro 538	N	4122	ACCEPTOR
			O	13	BOTH	Gly 225	O	1563	ACCEPTOR
			O	13	BOTH	Gly 536	O	4113	ACCEPTOR
			O	13	BOTH	Tyr 373	O	2790	ACCEPTOR
2A 10	-10.5	20	O	14	BOTH	Gly 225	O	1563	ACCEPTOR
			O	14	BOTH	His 226	O	1567	ACCEPTOR
			O	12	BOTH	Gly 536	O	4113	ACCEPTOR
			O	12	BOTH	Tyr 373	O	2790	ACCEPTOR
			O	12	BOTH	Gly 225	O	1563	ACCEPTOR
			O	12	BOTH	His 226	O	1567	ACCEPTOR
			O	14	BOTH	Gly 536	O	4113	ACCEPTOR
			O	14	BOTH	Tyr 373	O	2790	ACCEPTOR
			O	14	BOTH	Tyr 373	O	2790	ACCEPTOR
			O	14	BOTH	Gly 536	O	4113	ACCEPTOR
			O	14	BOTH	Pro 538	N	4122	ACCEPTOR
			O	12	BOTH	His 226	O	1567	ACCEPTOR
			O	12	BOTH	Pro 538	N	4122	ACCEPTOR
			O	12	BOTH	Tyr 373	O	2790	ACCEPTOR
			O	12	BOTH	Gly 536	O	4113	ACCEPTOR
			O	12	BOTH	Gly 225	O	1563	ACCEPTOR
			O	12	BOTH	His 226	O	1567	ACCEPTOR
			O	14	BOTH	Pro 538	N	4122	ACCEPTOR
			O	14	BOTH	Tyr 373	O	2790	ACCEPTOR
			O	14	BOTH	Gly 536	O	4113	ACCEPTOR

Table 4. Results found by *Iv*LCB (*In-vitro* like computational bioassay) such as Query score, % inhibition and Query activity

S.NO.	COMP.	Q.SCORE	C.SCORE	INHIBITION %	Q. ACTIVITY	ASSAY
1	2AN	3.085	19.554	0,0.04,0.08,0.12,0.16,0.1 9,0.23,0.27,0.31,0.35,0.3 8	Low activity 0.149	COX1
2	2A1	14.411	14.411	0,0.23,0.46,0.68,0.91,1.1 2,1.34,1.55,1.75,1.96,2.1 6	High activity 0.149	COX1
3	2A2	14.327	19.997	0,3.50,6.67,9.56,12.20,14 .63,16.87,18.94,20.86,22. 64,24.30	High activity 0.152	COX1
4	2A3	14.688	19.411	0,4.10,7.77,11.09,14.10,1 6.84,19.35,21.65,23.77,2 5.73,27.55	High activity 0.153	COX1
5	2A4	14.717	18.862	0,4.48,8.47,12.05,15.28,1 8.21,20.88,23.31,25.55,2 7.62,29.53	High activity 0.153	COX1
6	2A5	15.037	18.738	0,4.86,9.16,12.99,16.44,1 9.55,22.37,24.93,27.29,2 9.45,31.44	High activity 0.153	COX1
7	2A6	14.959	17.817	0,5.53,10.37,14.66,18.47, 21.88,24.96,27.74,30.27, 32.59,34.71	High activity 0.153	COX1
8	2A7	15.207	17.359	0,6.24,11.66,16.39,20.58, 24.29,27.62,30.61,33.32, 35.79,38.04	High activity 0.153	COX1
9	2A8	16.541	17.383	0,7.90,14.59,20.33,25.30, 29.65,33.50,36.91,39.97, 42.73,45.22	High activity 0.153	COX1
10	2A9	14.931	17.794	0,5.52,10.36,14.63,18.44, 21.85,24.92,27.70,30.23, 32.55,34.67	High activity 0.153	COX1
11	2A10	16.144	17.88	0,6.81,12.66,17.74,22.20, 26.15,29.66,32.81,35.64, 38.21,40.55	High activity 0.153	COX1

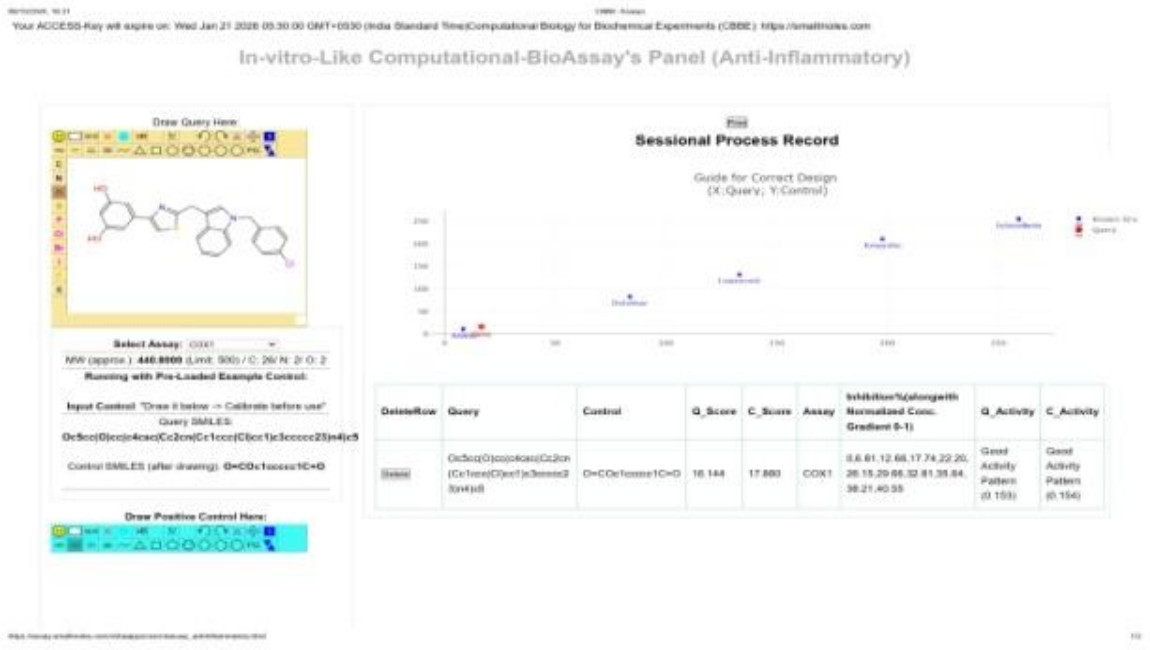


Figure 2. Results found on *Iv*LCB (In-vitro like computational bioassay) web tool for designed molecule 2A10

Table 5. Bioactivity values of all designed molecules

S.NO.	COMP.	GPCR LIGD.	ION CH. MOD.	KINASE INH.	NUCLEAR RECP. LIGD.	PROTEASE INH.	ENZYME INH.
1	2A N	0.09	-0.4	-0.09	0.02	-0.25	0.15
2	2A 1	0.11	-0.3	0	0.03	-0.19	0.19
3	2A 2	0.11	-0.22	0.13	-0.17	-0.26	0.08
4	2A 3	0.15	-0.16	0.15	-0.18	-0.21	0.12
5	2A 4	0.22	-0.15	0.18	-0.08	-0.15	0.15
6	2A 5	0.21	-0.15	0.16	-0.08	-0.14	0.14
7	2A 6	0.2	-0.15	0.17	-0.09	-0.15	0.14
8	2A 7	0.2	-0.14	0.22	0.03	-0.15	0.18
9	2A 8	0.27	-0.06	0.27	0.02	-0.12	0.24
10	2A 9	0.23	-0.12	0.21	0.03	-0.15	0.19
11	2A 10	0.26	-0.07	0.24	0.03	-0.12	0.23

Table 6. Molecular descriptors of all designed moleculesS.NO

	COMP.	miLogP	TPSA	natoms	MW	nON	nOHNH	nviolations	nrotb	volume
1	2a n	8.64	44.13	37	593.97	4	0	2	7	473.66
2	2a 1	6.86	44.13	33	473	4	0	1	5	405.61
3	2a 2	7.57	27.06	32	523.88	3	0	2	6	404.75
4	2a 3	7.53	17.83	30	493.86	2	0	1	5	379.21
5	2a 4	7.15	17.15	30	428.99	2	0	1	5	377.88
6	2a 5	7.55	17.83	31	443.01	2	0	1	5	394.44
7	2a 6	7.53	17.83	31	443.01	2	0	1	5	394.44
8	2a 7	7.07	38.05	31	444.99	3	1	1	5	385.9
9	2a 8	5.73	58.28	31	446.96	4	2	1	5	377.36
10	2a 9	6.62	38.05	31	444.99	3	1	1	5	385.9
11	2a 10	5.69	58.28	31	446.96	4	2	1	5	377.36

3.5. Bioactivity Score: For Different-bioactivities

All the designed molecules were passed from bioactivity score predictor for the most important drug targets like GPCR ligands, kinase inhibitors, ion channel modulators, nuclear receptors etc. All predicted scores are given in Table 5.

After analysis it was observed that 7 designed molecules (2A3, 2A4, 2A5, 2A6, 2A8, 2A9 & 2A10) were found to be with highest score for G-protein coupled receptor. 2 molecules (2A2 & 2A7) were found to be with higher score as kinase inhibitor. 2 molecules (2AN & 2A1) were found to be with higher score as general enzyme inhibitor.

3.6. Descriptor Calculation

Some drug design descriptors were also calculated for general idea of designed molecules which are given in Table 6. All the novel designed compounds were found within the prescribed range.

3.7. Comparison with Previous Studies

Researchers El-Sayed *et al*. investigated thiazole-pyrazole hybrids for their dual inhibitory activity against COX and lipoxygenase (LOX) enzymes. Docking studies using the Glide module of Schrödinger Suite demonstrated that these hybrids occupied the COX-2 active site efficiently, forming key interactions with Arg120, Tyr355, and Ser530. [64] A computational study by scientist Ali et al. employed molecular docking and molecular dynamics simulations to evaluate thiazole derivatives as dual COX-1/COX-2 inhibitors. The docking results indicated that thiazole derivatives with a carboxylate group exhibited strong binding to both COX isoforms, with higher affinity for COX-2. The study also identified key residues, such as His90 and Arg513, as critical for stabilizing the inhibitor-enzyme complex. [65] A recent study by Gupta *et al*. focused on thiazole-Schiff bases and their potential as COX inhibitors. Docking analysis using the MOE software revealed that these compounds formed stable complexes with COX-2, primarily through π-π stacking and hydrogen bonding interactions. The study suggested that the incorporation of electron-withdrawing groups on the thiazole ring enhanced binding affinity and selectivity.

4. Conclusion

COX (Cyclooxygenase) is also known as prostaglandin-endoperoxide synthase (PTGS) which is responsible for inflammation and related issues. Eleven thiazole derivatives were designed and computationlly evaluated for their inhibitory activity against COX enzyme. All novel designed molecules were evaluated by *Iv*LCB: *In-vitro* like computational bioassay and SwissDock. These molecules were also evaluated for their ADME descriptors and bioactivity prediction using Molinspiration for bioacitivity scores for the drug targets like GPCR ligands, kinase inhibitors, ion channel modulators, nuclear receptors etc. As per the analysis done it was found that designed molecule 2A8 shows High activity pattern, good % inhibition and strong binding ability to PDB ID:

4M11 with 14 hydrogen bonds & binding affinity of -10 kcal/mol. All the above studies supported the molecules for good and potent anti-inflammatory activity but then also a biochemical experimental study is required to confirm the findings.

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