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3D-QSAR and Molecular Docking studies of COX-1 (PDB: 3KK6) and COX-2 (PDB: 3LN1) Enzyme Inhibitors with Simulation Dynamic on Series of Benzimidazole Derivatives

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Abstract: The aim of this study was to investigate cyclooxygenase-1 (COX-1) (PDB: 3KK6) and cyclooxygenase-2 (COX-2) (PDB: 3LN1) enzyme inhibitory, and inflammatory activities of a new series of 1H-benzimidazole derivatives, for their possible use as multi-action therapeutic agents. Molecular Design Suite was used to conduct Combi Lab investigations and 3D-QSAR. Schrodinger Maestro was used for the molecular docking investigation. Five Derivative's i.e. Derivative's 6; Derivative's 5; Derivative's 11; Derivative's 13 and Derivative's 15 in a library of 15 compounds created using a combinatorial approach demonstrated superior projected biological activity as inflammatory than the dataset's most active molecule. These chemicals exhibited proximal contact with amino acid residues on COX-2 (PDB: 3LN1) such as Phe381, Leu-384, Tyr-385, Trp-387, Phe-518, Gly-526, Met-522, Tyr348, Val-349, Leu-352. This study determined the structural elements affecting by carefully changing the substituents, ring modifications, and linker groups. The logical creation and optimization of more powerful and selective molecules is made possible by these discoveries. In contrast to the reference ligand, the current study produced more powerful benzimidazoles as inhibiting compounds for COX-1 (PDB: 3KK6) and COX-2 (PDB: 3LN1) with excellent interaction. The study's findings could aid in the creation of new COX-1 (PDB: 3KK6) and COX-2 (PDB: 3LN1) inhibitors to treat inflammatory conditions.

Keywords: Inflammation, ADMET, Benzimidazole, Molecular docking, COX-1 (PDB: 3KK6), COX-2 (PDB: 3LN1)

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Introduction

The exploration and subsequent synthesis of innovative hybrid molecules, characterized by a multifaceted array of pharmacological activities achievable through the modulation of a diverse spectrum of biochemical pathways, holds considerable promise in the therapeutic intervention of a wide range of pathological conditions, as it is well acknowledged that multi-factorial disorders can have multiple origins (El Ayadi *et al.*, 2020). Because the hazards of drug-drug interactions are reduced, this approach has distinct advantages over drug combinations or multicomponent medications, notwithstanding the enormous difficulty in designing and optimizing such molecules. Atypical antipsychotics, such as olanzapine, risperidone, and aripiprazole, predominantly function as antagonists at dopamine and serotonin receptors, exhibiting a comparatively diminished affinity for histaminergic, cholinergic muscarinic, and α-adrenergic receptor subtypes (Tottoli *et al*., 2020). The synchronized combining of various advantageous moieties on similar substance, particularly for treatment of particular illness, is one of the promising developments in drug discovery (Gillitzer and Goebeler, 2001). The exordium for engendering avant-garde compounds exhibiting pleiotropic pharmacological effects resides optimally within the domain of pharmaceutical advantages that mitigate the exigency for polypharmacy, encompassing therapeutic modalities that concurrently attenuate iatrogenic sequelae, abrogate symptomatic manifestations, or potentiate salutary outcomes via adjuvant therapeutic mechanisms (Andriana *et al*., 2019). Even if they have a lot of potential for therapeutic use, this is important to assess possibility of adverse consequences. High atomic weight is a common characteristic of dual inhibitors, which may lessen the likelihood of their therapeutic effects. Consequently, while designing dual inhibitors, the safety profiles and pharmacokinetic characteristics must be carefully taken into account (Syed *et al*., 2020). The combination of imidazole with benzene results in the heterocyclic aromatic organic molecule known as benzimidazole. Because of their many effects, i.e., analgesic, anti-tumor, antiviral, and psychoactive properties, they have played a significant role in medicinal chemistry (Li *et al*., 2020). The intricate biological reaction of bodily tissues to infections is defensive action towards immune cells (Oke-Altuntas *et al*., 2017). Cyclooxygenase (COX), which comes in the forms COX-1 (PDB: 3KK6) and COX-2 (PDB: 3LN1), is essential protein needed to convert arachidonic acid to prostaglandins. Prostaglandins are supplied by COX-1 (PDB: 3KK6) while COX-2 (PDB: 3LN1) is produced subsequent to inflammatory stimuli (Shi *et al*., 2019). In human cancers, COX-2 (PDB: 3LN1) contributes to angiogenesis as well as cell division and death. One technique for figuring out how a protein and ligand interact is called molecular docking, and it explains the molecule's orientation, binding interactions, and binding energy (George *et al*., 1971). Predicting the shared molecular characteristics those in molecular interactions with biological target and initiate response requires the use of pharmacophore methods (Lin *et al*., 2005). The purpose of this investigation was to determine the molecular interactions in benzimidazoles analogues and COX, as well as to screen the synthetic compounds' physicochemical and ADMET characteristics (Chew *et al*., 2023). Additionally, pharmacophore modelling studies were used to examine distinctive traits. Since benzimidazole derivatives reported to have anti-inflammatory features, it is necessary to demonstrate how they work (Alborghetti and Nicoletti, 2019). To ascertain these compounds *in silico* inhibitory effect, were docked with COX-1 (PDB: 3KK6) and COX-2 (PDB: 3LN1). As a result, *in silico* research helps identify how benzimidazoles work to block COX enzymes, which is what gives them their anti-inflammatory properties. Inflammation is a vital defensive mechanism against all forms of physical, chemical, and viral assault (Baweja *et al*., 2024). When this mechanism is dysregulated, the body develops pathological conditions, such as organ rejection,

autoimmune diseases, and allergies (Tripathi and Ayyannan, 2019). Since NSAID show lowering fever, inflammation, and pain, millions of patients use them all over the world. NSAIDs function pharmacologically by blocking the actions of COX, which stops enzymatic biotransformation of arachidonic acid into related pro-inflammatory prostaglandins and thromboxane (TXs). Needleman and Isakson (1997) originally described two cyclooxygenase isoenzymes. The "House Keeping" enzyme, COX-1 (PDB: 3KK6) and COX-2 (PDB: 3LN1), regulates a basic level of PGs for homeostasis preservation, including intestinal integrity. The "Inducible" enzyme, COX-2, causes inflammatory reactions and is triggered by a variety of events. It is currently unclear what are the exact roles of a COX-2 isoform that is solely expressed in particular brain and spinal cord areas. The second COX type (COX-2) (PDB: 3LN1) is produced in pathogenic and pro-inflammatory stimuli, including cytokines, lipopolysaccharides, and phorbol esters. COX2(PDB: 3LN1), is responsible for both PGs release and the inflammation. Numerous studies have linked COX-2 to a range of clinical illnesses, such as cancer, neurological disorders, and inflammation. In order to mitigate these serious side effects, selective COX-2 (PDB: 3LN1), inhibitor medications i.e., celecoxib, rofecoxib, and valdecoxib were created. These medications have analgesic property same as non-selective COX inhibitors, but they also have improved gastric safety profiles. Unfortunately, as they have adverse effects on COX pathway, which include an elevated risk of myocardial infarction and high blood pressure, valdecoxib and rofecoxib have both been removed from the market. The distinct chemical makeup of valdecoxib and rofecoxib was associated with their adverse effects. As a result, research for selective anti-inflammatory medications with superior safety profiles than the NSAIDs on the market is still ongoing. In COX-1 (PDB: 3KK6) and COX-2 (PDB: 3LN1), activity of inhibition synthesized derivatives were evaluated. Lastly, the synthesized compounds docked into COX2(PDB: 3LN1), site to clarify their possible method of action.

Materials and Methods

We used a variety of different COX-1 (PDB: 3KK6) and COX-2 (PDB: 3LN1), enzyme crystal structures via the RCSB for docking studies. Maestro 11.9 was used for all computational analysis. Software were installed on Dell Inc. 27-inch computer that was on Linux x86_64 as OS and has Intel Core i7-7600U CPU at 3.90 GHz x8 with 16 GB RAM and 1 TB SSD. Drug likeness, physicochemical characteristics, and ADMET of compounds were studied. The PDB supplied Ribbon composition for COX-1 (PDB: 3KK6) and COX-2 (PDB: 3LN1). Auto dock version was 1.5.6. Chain A was chosen. Hydrogen with polarity and Gasteiger charges introduced after water was removed. They decided on a grid map. The compounds' 2D formula was drawn using ChemDraw Ultra 12.0. Avogadro software was used to minimize energy use. Autodock Vina was used to realize the docking process, while Discovery Studio 3.5 was used to visualize the interactions. Celecoxib (CEL) crystal structures were compared to the anticipated conformations of docking data in order to optimize the docking method. Figure 1 shows the superimposition of the crystallized form of the Ribbon Structure Protein structure and Figure 2 shows Ramachandran Plot. Preceding molecular docking, test compounds of Derivative's 1– Derivative's 15 structures and scheme of benzimidazole is given in Figure 3 and Table 1. Figure 4 mentions about receptor grid generation Wizard optimized by using the semi-empirical approach.

Results

Molecular docking and Lipinski's rule of five:

QSAR is one such technique that covered drug discovery in the above session/chapter. In this above session/chapter will cover the newly developed idea of "drug-likeness" as well as the computer modelling of a number of biological and physicochemical characteristics that are crucial in turning a clinical lead into a commercially available medication. Pharmacologists and medicinal chemists have looked for beneficial drug-like chemical characteristics that produce

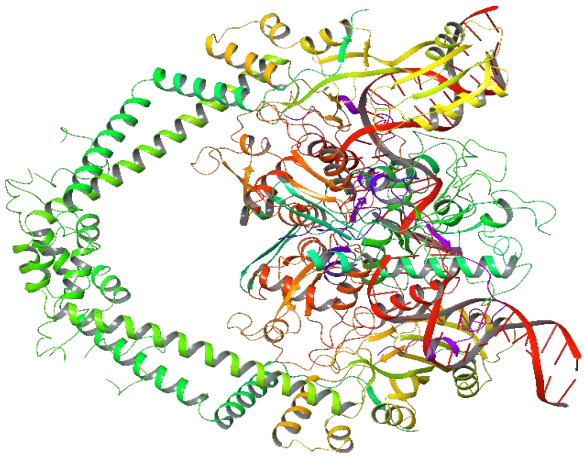


Fig. 1: Ribbon Structure Protein structure.

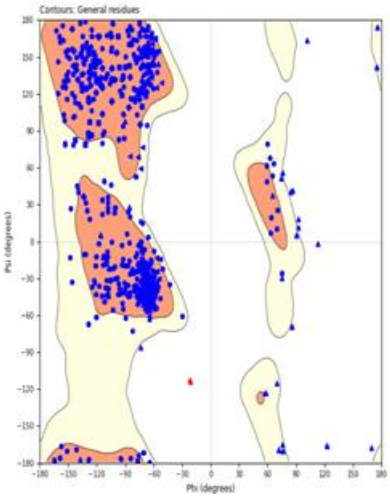


Fig. 2: Ramachandran Plot.

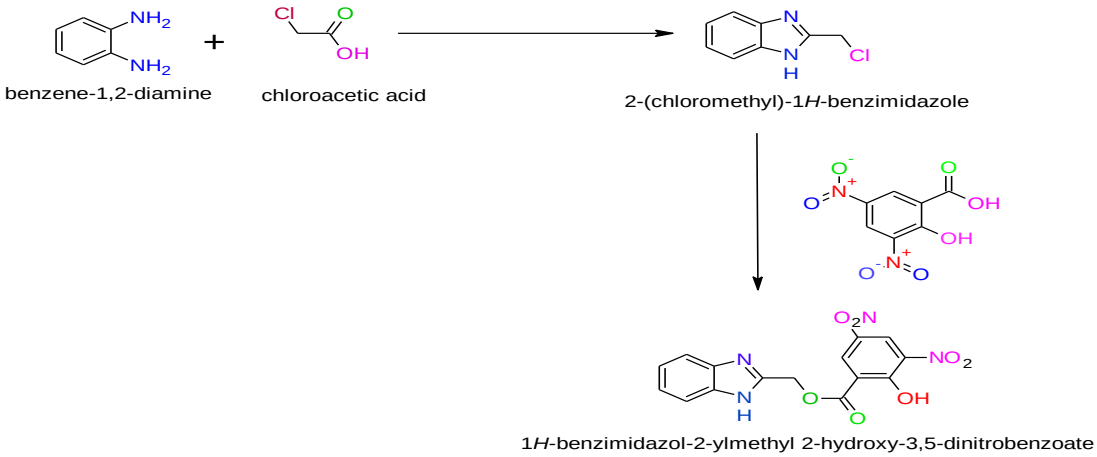
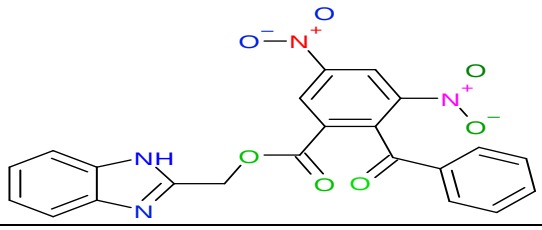
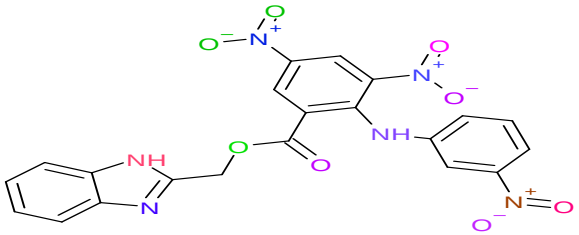
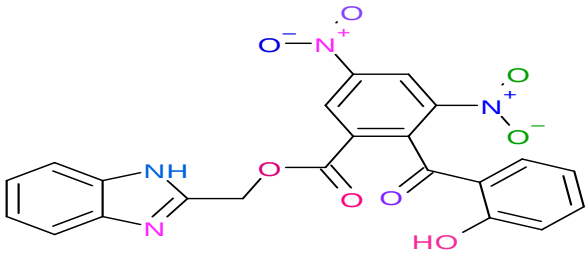
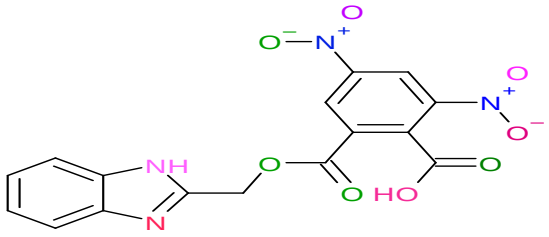
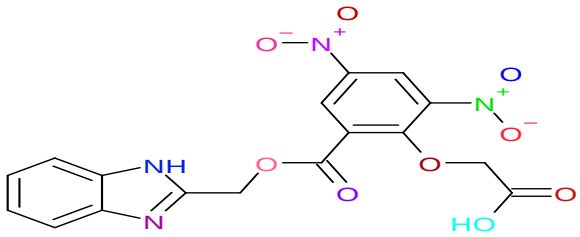
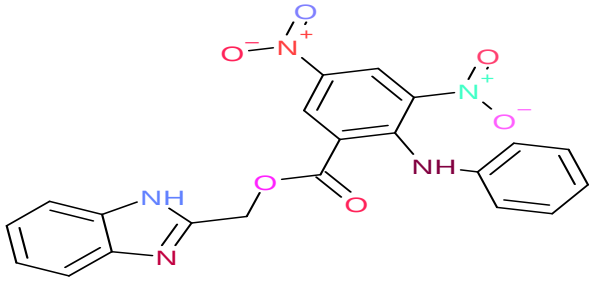
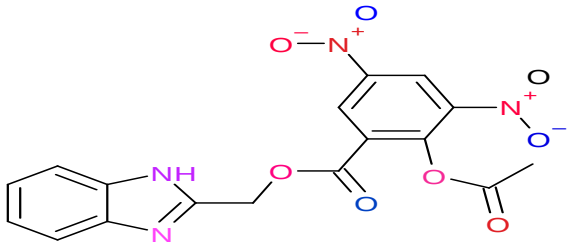
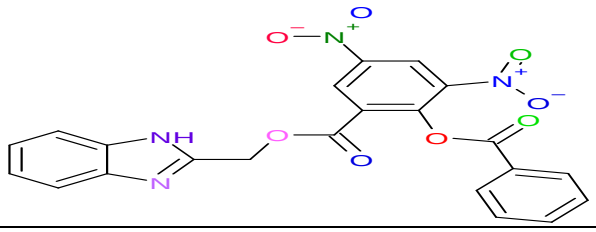
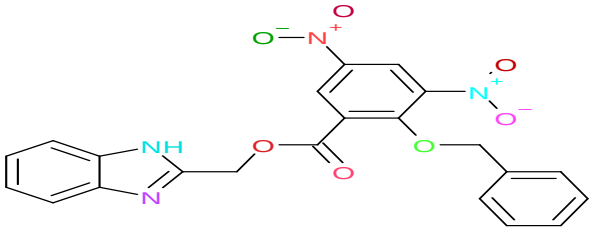
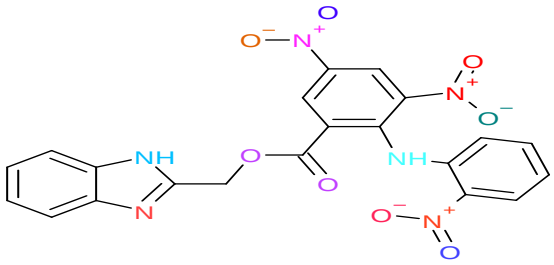
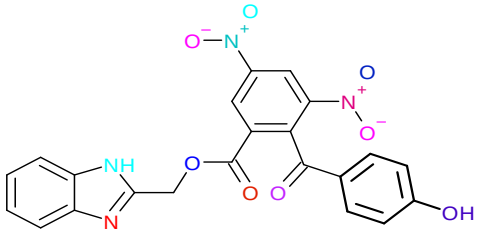
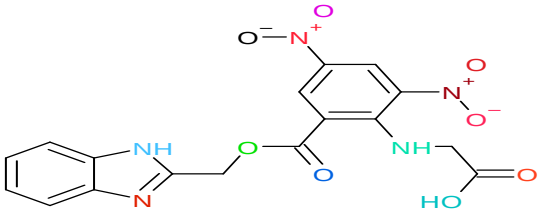
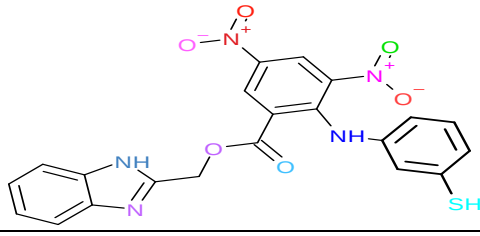
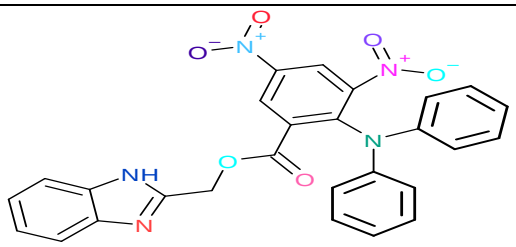
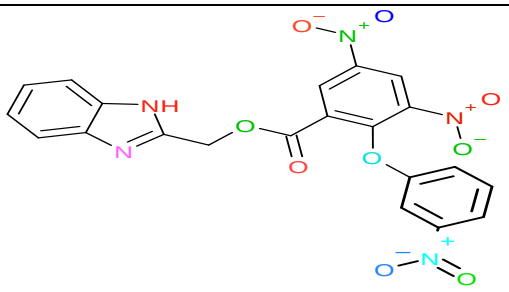


Fig. 3: Scheme of Benzimidazole.

Table 1: Derivatives of designed compound of Benzimidazole

Derivative's Code	Structure
1	
2	
3	
4	
5	
6	

7	
8	
9	
10	
11	
12	
13	

14	
15	

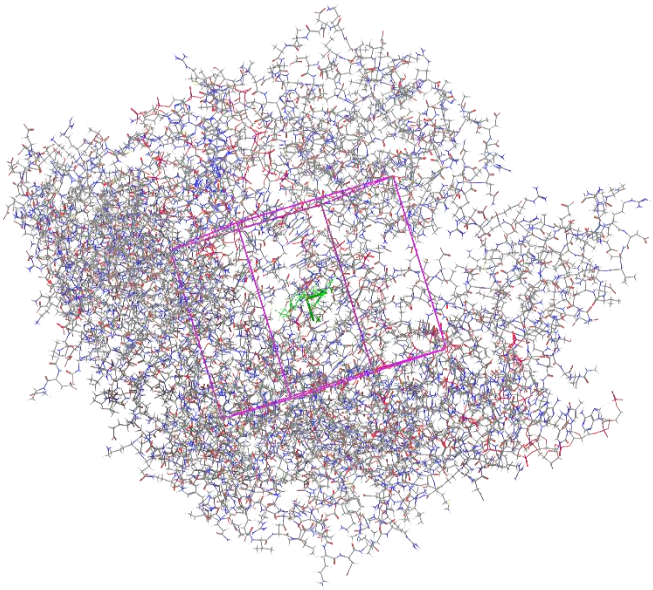


Fig. 4: Receptor Grid Generation Wizard.

agents with predictable oral therapeutic effectiveness. Drug development process follows Lipinski's "rule of five" which is computational and experimental method for estimating solubility, and permeability. COX-1 (PDB: 3KK6) and COX-2 (PDB: 3LN1) enzymes were docked with the drugs, and the molecular interactions between them were examined. Table 2 summarizes interactions between chemicals with residues of dynamic amino acids, whereas Figures 5 and 6 display the 2D - 3D conformations for molecular bindings of Derivative's 1–Derivative's 15. Computer-aided molecular design (CAMD) has traditionally concentrated on lead optimization and identification, and several creative techniques have been created to help increase the binding affinities of drug candidates to certain receptors. Those are general guideline which assesses drug-likeness and establishes whether molecule has pharmacological activity. The rule was founded on the finding that the majority of medications that work well when taken orally are tiny, somewhat lipophilic molecules. It is employed in the process of developing new drugs when pharmacologically active lead structures are gradually improved to boost their activity and selectivity while

Table 2: Chemical interactions between the chemicals and the residues of active amino acids

Name	Distance	Category	Type	Docking Score
Derivative's 5				**-8.263**
TYR355:HH :	2.04716	Hydrogen Bond	Conventional Hydrogen Bond	
SER530:HG	1.97445	Hydrogen Bond	Conventional Hydrogen Bond	
SER530:HB1	2.9116	Hydrogen Bond	Carbon Hydrogen Bond	
A:TYR355	5.86833	Other	Pi-Sulfur	
PHE381	5.70974	Hydrophobic	Pi-Pi Stacked	
TYR385	4.68387	Hydrophobic	Pi-Pi T-shaped	
TRP387	4.89914	Hydrophobic	Pi-Pi T-shaped	
TRP387	5.20476	Hydrophobic	Pi-Pi T-shaped	
TRP387 -	5.45224	Hydrophobic	Pi-Pi T-shaped	
ALA527:N	4.47114	Hydrophobic	Amide-Pi Stacked	
ALA527:N	4.43481	Hydrophobic	Amide-Pi Stacked	
LEU384	5.42753	Hydrophobic	Pi-Alkyl	
MET522	5.04609	Hydrophobic	Pi-Alkyl	
VAL349	3.959	Hydrophobic	Pi-Alkyl	
ALA527	3.49315	Hydrophobic	Pi-Alkyl	
LEU531	5.15618	Hydrophobic	Pi-Alkyl	
Derivative's 6				**-8.387**
ARG120:HH12	2.28016	Hydrogen Bond	Conventional Hydrogen Bond	
ARG120:NH1	4.58916	Electrostatic	Pi-Cation	
LEU93	5.21572	Hydrophobic	Pi-Alkyl	
VAL116	4.33303	Hydrophobic	Pi-Alkyl	
VAL116	3.40784	Hydrophobic	Pi-Alkyl	
VAL349	4.39845	Hydrophobic	Pi-Alkyl	
ALA527	3.86229	Hydrophobic	Pi-Alkyl	
LEU352	4.80044	Hydrophobic	Pi-Alkyl	
Derivative's11				**-8.922**
ARG120:HH11 -	2.6146	Hydrogen Bond	Conventional Hydrogen Bond	
ARG120:HH12 - :	2.70138	Hydrogen Bond	Conventional Hydrogen Bond	
A:TYR355:HH -	2.07332	Hydrogen Bond	Conventional Hydrogen Bond	
ARG120:NH1 -	3.04352	Electrostatic	Pi-Cation	
ARG120:NH1 -	4.01185	Electrostatic	Pi-Cation	
ARG120:NH2 -	3.7088	Electrostatic	Pi-Cation	
A:VAL89	4.82507	Hydrophobic	Pi-Alkyl	
A:VAL116	4.83282	Hydrophobic	Pi-Alkyl	
VAL349	5.05315	Hydrophobic	Pi-Alkyl	
ALA527	3.52281	Hydrophobic	Pi-Alkyl	
VAL349	5.17522	Hydrophobic	Pi-Alkyl	

LEU352	5.48619	Hydrophobic	Pi-Alkyl	
ALA527	4.71168	Hydrophobic	Pi-Alkyl	
Derivative's 13				
TYR355:HH	1.99025	Hydrogen Bond	Conventional Hydrogen Bond	
SER530:HG	2.02067	Hydrogen Bond	Conventional Hydrogen Bond	
SER530:HB1	3.02406	Hydrogen Bond	Carbon Hydrogen Bond	
PHE381	5.69178	Hydrophobic	Pi-Pi Stacked	
TYR385	4.67032	Hydrophobic	Pi-Pi T-shaped	
TRP387	5.11958	Hydrophobic	Pi-Pi T-shaped	
TRP387	4.89984	Hydrophobic	Pi-Pi T-shaped	**-8.471**
TRP387 -	5.44236	Hydrophobic	Pi-Pi T-shaped	
VAL116	4.26357	Hydrophobic	Alkyl	
LEU359	5.01817	Hydrophobic	Alkyl	
LEU531	4.97275	Hydrophobic	Alkyl	
LEU384	5.39901	Hydrophobic	Pi-Alkyl	
MET522	5.03786	Hydrophobic	Pi-Alkyl	
VAL349	3.94823	Hydrophobic	Pi-Alkyl	
ALA527	3.49084	Hydrophobic	Pi-Alkyl	
LEU531	5.19681	Hydrophobic	Pi-Alkyl	
Derivative's 15				
ARG120:HH11	2.12873	Hydrogen Bond	Conventional Hydrogen Bond	
TYR355:HH -	1.92239	Hydrogen Bond	Conventional Hydrogen Bond	
ARG120:NH1 -	3.56621	Electrostatic	Pi-Cation	
TYR115	5.18484	Hydrophobic	Pi-Pi T-shaped	
VAL349	5.13415	Hydrophobic	Pi-Alkyl	
VAL349	4.82907	Hydrophobic	Pi-Alkyl	**-8.157**
LEU352	5.0732	Hydrophobic	Pi-Alkyl	
VAL523	5.36067	Hydrophobic	Pi-Alkyl	
VAL523	4.9863	Hydrophobic	Pi-Alkyl	
ALA527	3.95758	Hydrophobic	Pi-Alkyl	
ALA527	4.39767	Hydrophobic	Pi-Alkyl	
VAL116	4.98707	Hydrophobic	Pi-Alkyl	
VAL89	4.7953	Hydrophobic	Pi-Alkyl	
LEU93	5.32878	Hydrophobic	Pi-Alkyl	

maintaining their drug-like physicochemical characteristics. Bonds rotation; H-bond acceptors; H-bond donors; Lipinski; Ghose; Veber; Egan and Muegge violations are given in Table 3. ADMET (which stands for absorption, distribution, excretion, and toxicity) characteristics for substances are necessary to create effective oral medications. The toxicity of a ligand is thought to be required to ligand as function to effective discovery tool, and Qik-Prop produces physically relevant descriptions. The Ligprep module used for ligand preparation was utilized in investigation. The protein preparation wizard was utilized for protein preparation. The PDB data bank provided the X-ray crystal structures of COX-1 (PDB: 3KK6) and COX-2 (PDB: 3LN1). The grid

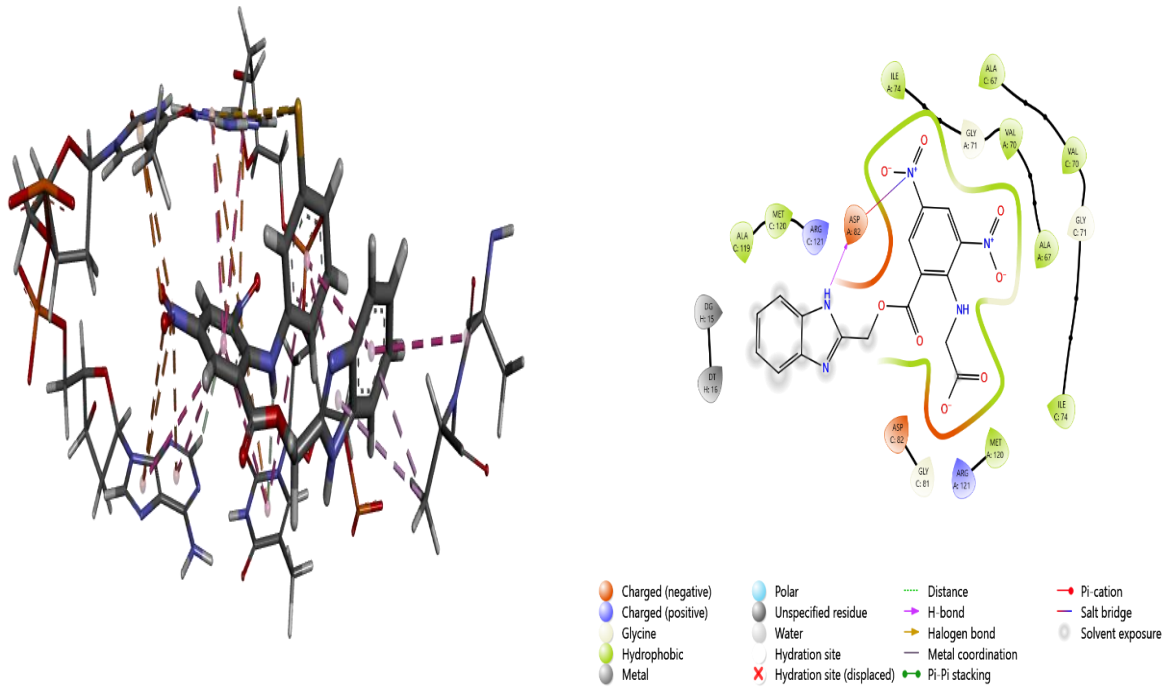


Fig. 5: 2D and 3D conformations of the molecular bindings with Computer-aided molecular design (CAMD) of Derivative's 13.

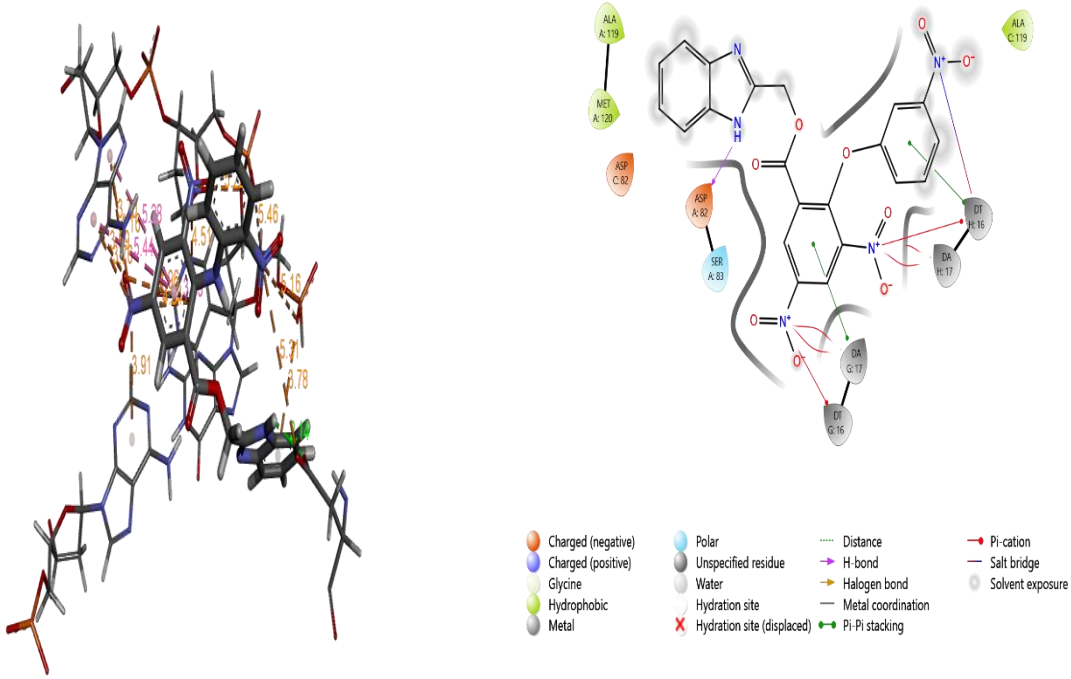


Fig. 6: 2D and 3D conformations of the molecular bindings with Computer-aided molecular design (CAMD) of Derivative's 15.

Table 3: Rotatable bonds; H-bond acceptors; H-bond donors; Lipinski violations; Ghose violations; Veber violations; Egan violations and Muegge violations of Benzimidazole Derivatives

Derivative's code	Rotatable bonds	#H-bond acceptors	#H-bond donors	Lipinski #violations	Ghose #violations	Veber #violations	Egan #violations	Muegge #violations
1	8	8	1	1	0	1	1	1
2	9	9	2	1	0	1	1	2
3	8	9	2	1	0	1	1	1
4	7	9	2	1	0	1	1	1
5	9	10	2	1	0	1	1	1
6	8	7	2	1	0	1	1	2
7	8	9	1	1	0	1	1	1
8	9	9	1	1	0	1	1	1
9	9	8	1	1	0	1	1	1
10	9	9	2	1	0	1	1	2
11	8	9	2	1	0	1	1	1
12	9	9	3	1	0	1	1	1
13	8	7	2	1	0	1	1	2
14	9	7	1	2	3	1	2	1
15	9	10	1	1	0	1	1	1

generated by using Receptor Grid Generation Wizard. Receptor Grid Generation Wizard is given in Figure 4. Glide XP coupled the ligand with the protein, and the interactions were seen. Based on the optimal ligand-protein interaction, the scoring function assigns points. The extra-precision mode was used to assess the docking positions. The program detects steric conflicts, metal-ligation interactions, hydrophobic interactions, and hydrogen bonding. Every substance has a molecular weight between 400 and 500, which is less than 500. The compounds' computed log P values fall between 3.56-5.35. The substances being studied have donors of hydrogen bonds.

In silico ADMET

Molecular modelling utilizes quantum techniques to evaluate possibility of interaction, including cytochrome P450s, which has role in ADME processes. ADME properties (like absorption), and toxicity problems (like drug–drug interactions) are discussed (Table 4). QSAR techniques is commonly used for data modelling of Derivative's 1–Derivative's 15. These look for relationships between a collection of chemical and structural molecules likes GI absorption; BBB permeant; Pgp substrate; CYP1A2 inhibitor; CYP2C19 inhibitor; CYP2C9 inhibitor; CYP2D6 inhibitor; and CYP3A4 inhibitor in question and certain property using statistical methods. Choosing appropriate mathematical method, appropriate chemical descriptors for ADMET endpoint, and sizable enough collection of data pertaining with same endpoint for model validation are all essential components of effective prediction models for ADMET parameters. Good ADMET property prediction techniques are becoming more and more necessary to achieve two main goals. In order to lower the risk, novel compounds libraries should be designed first. Secondly, screening and testing should be optimized by focusing on the most promising compounds. Predicting characteristics like oral absorption, bioavailability, BBB penetration, clearance, and Vd (for frequency) which give information about dosage quantity and frequency is our goal. Molecular modelling and data modelling are the two categories of computational techniques that are employed. Recent developments is the prediction of ADME-related physicochemical qualities (like lipophilicity).

Discussion

Analogues with best interactions and far from zero

Table 4: *In Silico* ADMET of Benzimidazole derivatives

Derivative's code	GI absorption	BBB permeant	Pgp substrate	CYP1A2 inhibitor	CYP2C19 inhibitor	CYP2C9 inhibitor	CYP2D6 inhibitor	CYP3A4 inhibitor	Bioavailability Score	PAINS #alerts	Brenk #alerts	Leadlikeness #violations	Synthetic Accessibility
1	Low	No	Yes	No	Yes	No	No	No	0.55	0	2	3	4.3
2	Low	No	Yes	No	Yes	Yes	No	No	0.55	0	2	3	4.42
3	Low	No	Yes	No	Yes	Yes	No	No	0.55	0	2	3	4.33
4	Low	No	Yes	No	Yes	No	No	No	0.55	0	2	1	3.95
5	Low	No	Yes	No	Yes	No	No	No	0.55	0	2	2	4
6	Low	No	Yes	No	Yes	Yes	No	No	0.55	0	2	3	4.32
7	Low	No	Yes	No	Yes	No	No	No	0.55	0	3	2	3.99
8	Low	No	Yes	No	Yes	No	No	No	0.55	0	3	3	4.27
9	Low	No	Yes	No	Yes	Yes	No	No	0.55	0	2	3	4.25
10	Low	No	Yes	No	Yes	Yes	No	No	0.55	0	2	3	4.42
11	Low	No	Yes	No	Yes	No	No	No	0.55	0	2	3	4.28
12	Low	No	Yes	No	Yes	No	No	No	0.55	0	2	3	4.12
13	Low	No	Yes	No	Yes	No	No	No	0.55	0	3	3	4.36
14	Low	No	Yes	No	Yes	Yes	No	No	0.17	0	2	3	4.69
15	Low	No	Yes	No	Yes	Yes	No	No	0.55	0	2	3	4.36

auto dock score was determined as best conformation. Both complexes' Ramachandran Plot RMSD plot analysis revealed that the Derivative's 9-protein complex had a stable trajectory for more research after achieving excellent stability at 100 ns. All of the "compounds had molecular weights less than 500", according to data warrior results, suggesting that they will bind action site. To have a good *in vivo* response, pharmacodynamic and pharmacokinetic characteristics must be balanced. Further details on medication dose and regimen are also provided by ADMET. According to "Lipinski's rule of five", an oral medication is selected if its molecular weight is < 500, hydrogen bond donors is less than five, hydrogen bond acceptors is less than ten, and log P value less than five. Oral bioavailability depends on molecular flexibility, which is shown by the number of rotatable bonds. Additionally, as TPSA is indirectly related to percentage absorp-tion, it suggested that used as 3D descriptor in number of hydrogen bonding groups. All drugs had LogP below 5, which indicates excellent penetration and absorption across cell membranes. Furthermore, the dock score values of all the produced compounds ranged from 7.5 and 8.8 kcal/mol, suggesting their binding energies lower to benzimidazole, which has "binding energy" of 8.0 kcal/mol. Interactions towards COX-1 (PDB: 3KK6) and COX-2 (PDB: 3LN1) revealed that they have anti-inflammatory properties.ADME properties (like absorption), and toxicity problems (like drug–drug interactions) are discussed in Tables 3 and 4: Chemical interactions between the chemicals and the residues of active amino acids. Phe381, Leu-384, Tyr-385, Trp-387, Phe-518, Gly-526, Met-522, Tyr348, Val-349, Leu-352 were active amino acids in COX-1 (PDB: 3KK6) and COX-2 (PDB: 3LN1). Derivative's 5 and Derivative's 6 demonstrated Pi-Pi stacking to TYR355: HH; SER530:HG; SER530:HB1; TYR355; PHE381; TYR385; TRP387; TRP387; TRP387; ALA527:N; LEU384; MET522; VAL349; ALA527; and LEU531 via the benzimidazole and H-bond with Ser-530 via nitrogen of the benzimidazole ring. Derivative's 15 demonstrated Pi-Pi stacking with Tyr385 via the benzimidazole ring and hydrogen bonding with Ser530. Derivative's 11 demonstrated Pi-Pi stacking with ARG120:HH11; ARG120:HH12; TYR355:HH; ARG120:NH1; ARG120:NH2; VAL89; VAL116; VAL349; ALA527; VAL349 and LEU352; ALA527 via benzene ring and H-bond with Met-522 via nitrogen. Comparing the 16 benzimidazole derivatives to the standard Indomethacin (- 10.705 kcal/mol), Derivative's 15 and Derivative's 11 had a satisfactory docking score of -8.572 kcal/mol. ARG120:HH11; ARG120:HH12; TYR355: HH; ARG120:NH1; ARG120:NH2; VAL89; VAL116; VAL349; ALA527; VAL349 and LEU352; ALA527, were active amino acids in the enzyme COX-1 (PDB: 3KK6) and COX-2 (PDB: 3LN1) enzymes. Derivative's 5 demonstrated H-Bond with TYR355: HH; SER530:HG; SER530:HB1; TYR355; PHE381; TYR385; TRP387; TRP387; TRP387; ALA527:N; LEU384; MET522; VAL349; ALA527; and LEU531 nitrogen of benzimidazole and Pi-Pi stacking with Tyr-385 via benzene. Derivative's 13 demonstrated Pi-cation interaction to TYR355:HH; SER530:HG; SER530:HB1; PHE381; TYR385; TRP387; TRP387; TRP387; VAL116; LEU359; LEU531; LEU384; MET522; VAL349; ALA;527 and LEU531 via benzimidazole and Pi-pi stacking with Tyr-385 and Trp-387 via benzene. Derivative's 9 demonstrated H-bond with ARG120:HH12; ARG120:NH1; LEU93; VAL116; VAL116; VAL349; ALA527; LEU352 and Ser-530 via benzimidazole and Pi-Pi stacking with Tyr-385. Comparing 16 benzimidazole derivatives to the standard Indomethacin (-10.099 kcal/mol), Derivative's 5, Derivative's 6, Derivative's 11, Derivative's 13 and Derivative's 15 showed elevated docking scores, from -8.25 to -8.51 kcal/mol (Table 5). Compound Derivative's 5's binding affinity score with COX-1 (PDB: 3KK6) is -56.79 kcal/mol, whereas compound Derivative's6 binding score with COX-2 (PDB: 3LN1) is -60.27 kcal/mol. Late-stage drug attrition may now be decreased and the most promising compounds can be found using *in silico* ADME screens. They should thus have high oral absorption; nevertheless, this quality cannot be used to explain variances in bioactivity.

Additionally, the compounds' oral absorption percentage ranged from 70.69 to 73.87%, indicating high ADME. Their TPSA values were 101.3 and 104.80 A2 (140 A2), respectively, and rotatable bonds ranged in 7 to 8 (<10). It is generally accepted that a molecule that is soluble in water and satisfies Lipinski's and Veber's criteria is said to possess both lipophilicity and hydrophilicity. Interactions towards COX-1 (PDB: 3KK6) and COX-2 (PDB: 3LN1) enzymes revealed that they have anti-inflammatory properties. TYR355: HH; SER530:HG; SER530:HB1; TYR355; PHE381; TYR385; TRP387; TRP387; TRP387; ALA527:N; LEU384; MET522; VAL349; ALA527; and LEU531 were active amino acids in COX-1 (PDB: 3KK6) and COX-2 (PDB: 3LN1) enzymes. Derivative's 13 and Derivative's 15 demonstrated Pi-Pi stacking to Tyr385 and Trp387 via the benzimidazole and H-bond with Ser-530 via nitrogen of the benzimidazole ring. Derivative's 12 demonstrated Pi-Pi stacking with TYR355: HH; SER530:HG; SER530:HB1; TYR355; PHE381; TYR385; TRP387; TRP387; TRP387; ALA527:N; VAL349; ALA527; and LEU531 via the benzimidazole ring and hydrogen bonding with Ser530. Derivative's 14 demonstrated Pi-Pi stacking with Tyr-385 via benzene ring and H-bond with Met-522 via nitrogen. Comparing the 15 benzimidazole derivatives to the standard Indomethacin (- 10.705 kcal/mol), Derivative's 14 and Derivative's 15 had a satisfactory docking score of -8.572 kcal/mol. Phe381, Leu384, Tyr385, Trp387, were active amino acids in the enzyme COX-1 (PDB: 3KK6) and COX-2 (PDB: 3LN1) enzymes. Derivative's I5 demonstrated H-Bond with Ser-530 nitrogen of benzimidazole and Pi-Pi stacking with Tyr-385 via benzene. Derivative's10 demonstrated Pi-cation interaction to TYR355: HH; SER530:HG; SER530:HB1; TYR355; PHE381; TYR385; TRP387; TRP387; TRP387; ALA527:N; LEU384; MET522; VAL349; ALA527; and LEU531 via benzimidazole and Pi-pi stacking with Tyr-385 and Trp-387 via benzene. Derivative's 1 demonstrated H-bond with TYR355: HH; SER530:HG; SER530:HB1; TYR355; PHE381; TYR385; TRP387; TRP387; TRP387; ALA527:N; LEU384; MET522; VAL349; ALA527; and LEU531 via benzimidazole and Pi-Pi stacking with Tyr-385. Comparing 15 benzimidazole derivatives to the standard Indomethacin (-10.099 kcal/mol), Late-stage drug attrition may now be decreased and the most promising compounds can be found using *in silico* ADME screens. To have a good *in vivo* response, pharmacodynamic and pharmacokinetic characteristics must be balanced. Further details on medication dose and regimen are also provided by ADMET.

Conclusion

The ligands Derivative's 15 and Derivative's 13 had high docking scores with COX-1 (PDB: 3KK6) enzymes (-9.492 kcal/mol) and COX-2 (PDB: 3LN1) (-8.572 kcal/mol), respectively, out of the 15 benzimidazole derivatives. Furthermore, the pharmacophoric characteristics that underlie their biological action were also disclosed. As a result, these *in silico* methods have helped identify binding and affinity between COX enzyme and benzimidazoles, responsible for anti-inflammatory properties To ascertain their anti-inflammatory properties, benzimidazole analogues were docked with COX-1 (PDB: 3KK6) and COX-2 (PDB: 3LN1) enzymes. All of the compounds' values were discovered to be within the typical range, and Lipinski's rule of five was not broken. Therefore, it is anticipated that the compounds will have a high oral bioavailability.

Ethical Statement

No animal or microbes have been used or sacrificed for this study, hence Ethical Approval not required.

Author Contributions

Each author has contributed equally to the study's planning, analysis, writing, and editing. All authors have read and agreed to the published version of the manuscript.

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Conflict of Interest

The authors declare no conflicts of interest.

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