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Original Article

3D-QSAR and Molecular Docking Studies on Benzimidazole Derivatives: Validation of Experimental Inhibitory Potencies Towards COX-1 (PDB: 2OYE) and COX-2 (PDB: 4COX)

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ABSTRACT

Background: The computational study of benzimidazole derivatives is the main topic of this article. All compounds' cytotoxicity against inflammation was assessed, and the outcomes showed that several of them had strong inhibitions. This study investigates the many pharmacological characteristics of benzimidazole derivatives, including their anticancer, antibacterial, antioxidant, anti-inflammatory, and anticonvulsant effects. The proposed approach summarizes each activity *in silico* research. The structure-activity correlations and pharmacological effects of compounds containing benzimidazole are examined in this study. Using a variety of computational techniques, *in silico* studies allow for forecasting structural changes and how they would impact the pharmacological properties as well as the efficiency of these modifications. **Materials and Methods:** Molecular Design Suite was used to conduct Combi Lab investigations and 3D-QSAR. Schrodinger Maestro was used for the molecular docking investigation. **Results:** Seven compounds (PVK1 and PVK15) in a library of 15 compounds created using a combinatorial approach demonstrated superior projected biological activity than the dataset's most active molecule. These chemicals exhibited proximal contact with amino acid residues on COX-2 such as TYR355 and/or ARG120. **Conclusion:** 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-2 with excellent interaction. The study's findings could aid in the creation of new COX-2 inhibitors to treat inflammatory conditions.

Keywords: ADMET, Benzimidazole, COX 1, COX 2, Inflammation, Molecular Docking.

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INTRODUCTION

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 (Abdelgawad *et al.*, 2017). The intricate biological reaction of bodily tissues to infections, which is defensive action towards immune cells (Achar *et al.*, 2010). Cyclooxygenase (COX), which comes in the forms COX-1 & 2, is essential protein needed for convert arachidonic acid to prostaglandins. Prostaglandins are supplied by COX-1, while COX-2 is produced subsequent to inflammatory stimuli (Al-Hakimi *et al.*, 2020). In human cancers, COX-2 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 (Conrad *et al.*, 2000). Predicting the shared molecular characteristics those in molecular interactions with biological target and initiate response requires the use of pharmacophore methods (Deshmukh *et al.*, 2006). 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 (Goudgaon *et al.*, 2004). Additionally, pharmacophore modelling studies were used

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to examine distinctive traits. Since the benzimidazole derivatives have been shown to have anti-inflammatory properties, it is necessary to demonstrate how they work (Grimmett, 1997). To ascertain these compounds *in silico* inhibitory effect, were docked with COX-1 (PDB: 2OYE) and COX-2 (PDB: 4COX). As a result, in-silico research helps identify how benzimidazoles work to block COX enzymes (Jayachandran *et al.*, 2003), which is what gives them their anti-inflammatory properties. Inflammation is a vital defensive mechanism against all forms of physical, chemical, and viral assault (Abdelatty *et al.*, 2023b). When this mechanism is dysregulated, the body develops pathological conditions, such as organ rejection, autoimmune diseases, and allergies (Abdelazeemm *et al.*, 2024). 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 (Agrwal *et al.*, 2022) and Thromboxane (TXs). Needleman and Isakson originally described two cyclooxygenase isoenzymes in 1997 (Allayeh *et al.*, 2024). The "House Keeping" enzyme, COX1, 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 (Banerjee *et al.*, 2018). It is currently unclear what the exact roles of a COX-3 isoform that is solely expressed in particular brain and spinal cord areas are. The second COX type (COX-2) produced in pathogenic and pro-inflammatory stimuli, including cytokines, lipopolysaccharides, and phorbol esters. COX2 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 (Batool *et al.*, 2024). As a result, also used in cancer treatment. In order to mitigate these serious side effects, selective COX-2 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 (Figure 2). 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 (Cambra *et al.*, 2018). 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/COX-2 activity of inhibition synthesized derivatives were evaluated. Lastly, the synthesized compounds docked into COX-2 site to clarify their possible method of action.

MATERIALS AND METHODS

The Protein Data Bank supplied the Ribbon Structure structures for COX-1 (PDB: 2OYE) and COX-2 (PDB: 4COX). Auto dock version was 1.5.6. Chain A was chosen. Polar hydrogens and Gasteiger charges were then introduced after the 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 showed the superimposition of the crystallized form of the Ribbon Structure Protein structure and Figure 2 showed Ramachandran Plot.

Molecular Docking and Ligand preparation

Preceding molecular docking, test compounds PVK1-PVK15 structures and scheme of benzimidazole were given in Figure 3 and Table 1. We optimized by using the semi-empirical approach and the Argus Lab 4.0.1 software program. Getting proteins ready we used a variety of different COX-1 (PDB: OYE) and COX-2 (PDB: 4COX) enzyme crystal structures via the RCSB for docking studies.

Modelling Platform

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 i7-7700 CPU at 3.60 GHz x8 with 8GB RAM and 1000 GB HDD. Drug likeness, physicochemical characteristics, and ADMET of compounds were studied.

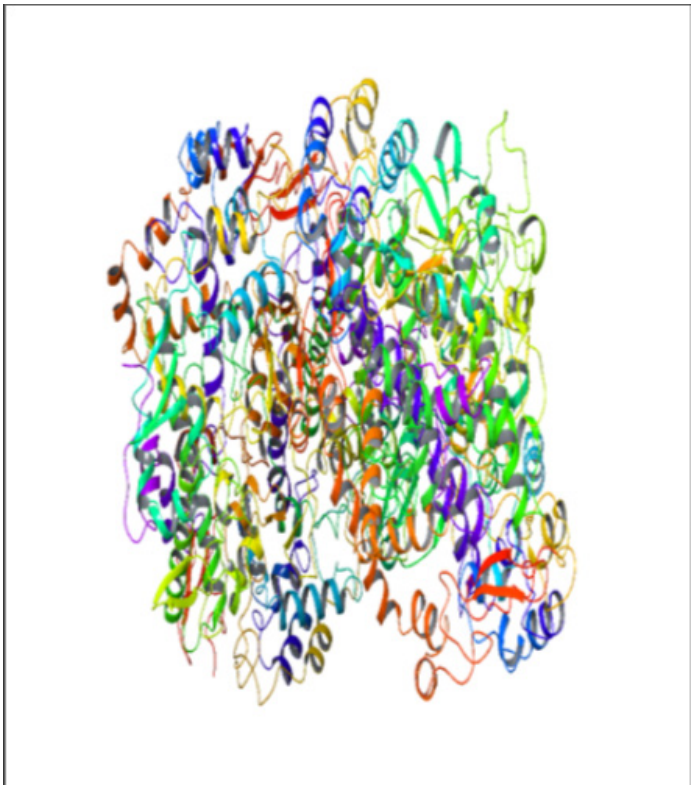
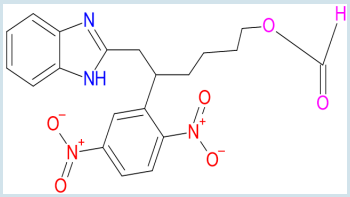
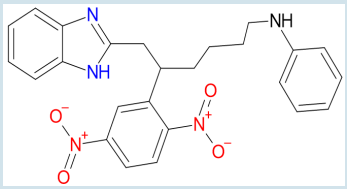
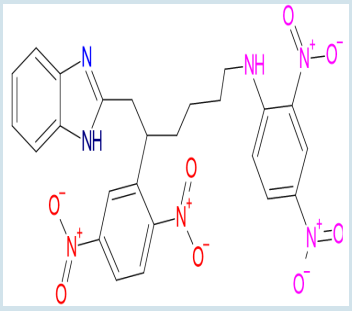
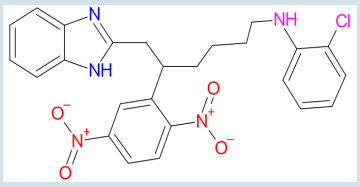
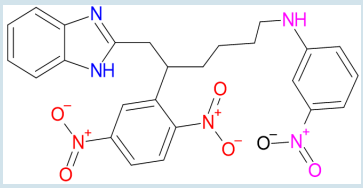
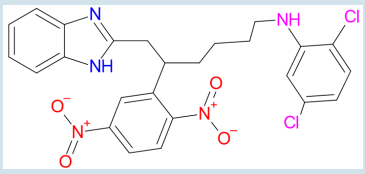
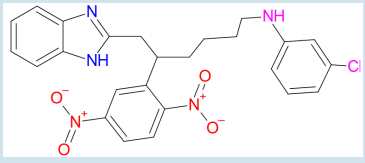
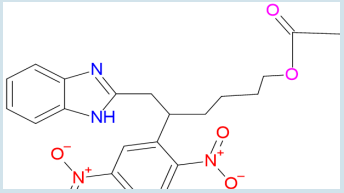
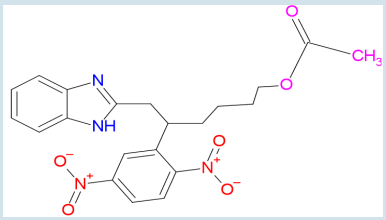
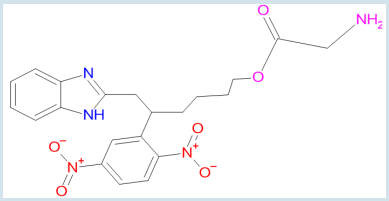
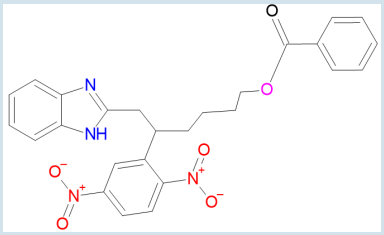
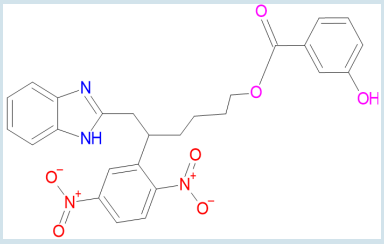
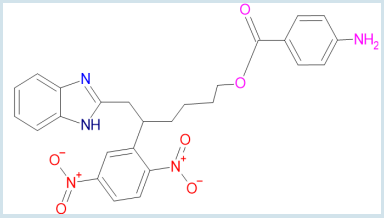
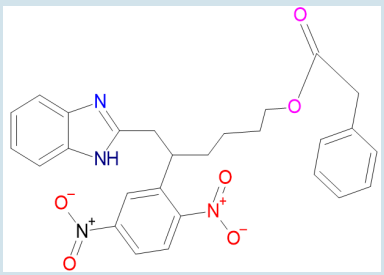
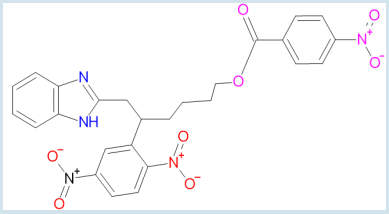


Figure 1: Ribbon Structure Protein structure.

Table 1: Derivatives of designed compound of Benzimidazole.

Comp. code	structure
PVK1	
PVK2	
PVK3	
PVK4	
PVK5	
PVK6	
PVK7	
PVK8	

Comp. code	structure
PVK9	
PVK10	
PVK11	
PVK12	
PVK13	
PVK14	
PVK15	

RESULTS

Molecular docking

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 utilized in investigation. The protein preparation wizard utilized for protein preparation. The PDB data bank provided the X-ray crystal structures of COX-1 (PDB:2OYE) and COX-2 (PDB:4COX). The grid generated using Receptor Grid Generation Wizard. Receptor Grid Generation Wizard were 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 2.56-4.35. The substances being studied have donors of hydrogen bonds.

Two COX enzymes were docked with the drugs, and the molecular interactions between them were examined. Table 3 summarize interactions between chemicals with residues of dynamic amino acids, whereas Table 4 display the 2D - 3D conformations for molecular bindings. 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. QSAR is one such technique that was covered in the previous chapter. This 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 agents with predictable oral therapeutic effectiveness. Drug development process follows Lipinski's "rule of five" which is computational and experimental method for estimating solubility, permeability. 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 maintaining their drug-like physicochemical characteristics.

In silico Admet

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. Molecular modelling utilizes quantum techniques to evaluate possibility of interaction, including cytochrome P450s, which has role in ADME processes. QSAR techniques is commonly used for data modelling. These look for relationships between a collection of chemical and structural molecules in question and certain property using statistical methods. Choosing appropriate mathematical method, appropriate chemical

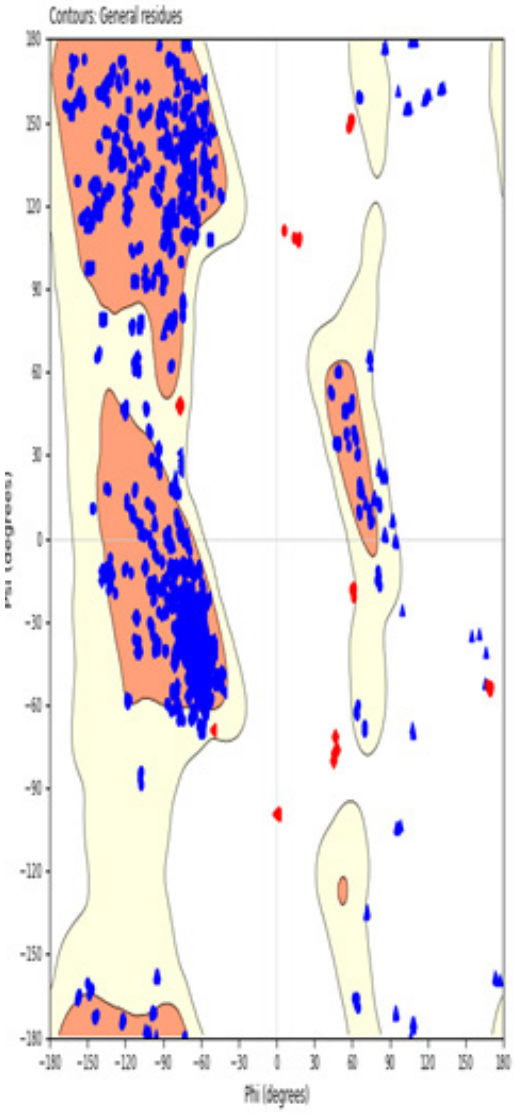


Figure 2: Ramachandran Plot.

Table 2: *In Silico* ADMET of Benzimidazole derivatives.

COMP. CODE	ESOL Class	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
PVK1	Moderately soluble	Low	No	Yes	No	Yes	Yes	No	Yes	0.55	0	3	3	4.36
PVK2	Poorly soluble	Low	No	Yes	No	Yes	Yes	No	Yes	0.55	0	2	3	4.77
PVK3	Poorly soluble	Low	No	Yes	No	Yes	Yes	No	Yes	0.17	0	2	3	5.07
PVK4	Poorly soluble	Low	No	Yes	No	No	Yes	No	Yes	0.55	0	2	3	4.77
PVK5	Poorly soluble	Low	No	Yes	No	Yes	Yes	No	Yes	0.17	0	2	3	4.9
PVK6	Poorly soluble	Low	No	Yes	No	No	Yes	No	Yes	0.17	0	2	3	4.78
PVK7	Poorly soluble	Low	No	Yes	No	No	Yes	No	Yes	0.55	0	2	3	4.75
PVK8	Poorly soluble	Low	No	Yes	No	Yes	Yes	No	Yes	0.17	0	2	3	4.94
PVK9	Moderately soluble	Low	No	No	No	Yes	Yes	No	Yes	0.55	0	3	3	4.39
PVK10	Moderately soluble	Low	No	Yes	No	Yes	Yes	No	Yes	0.55	0	2	3	4.47
PVK11	Moderately soluble	Low	No	Yes	No	Yes	No	No	Yes	0.55	0	2	3	4.55
PVK12	Poorly soluble	Low	No	Yes	No	Yes	Yes	No	Yes	0.55	0	2	3	4.7
PVK13	Poorly soluble	Low	No	Yes	No	Yes	Yes	No	No	0.17	0	2	3	4.73
PVK14	Poorly soluble	Low	No	Yes	No	Yes	Yes	No	Yes	0.17	0	3	3	4.79
PVK15	Poorly soluble	Low	No	Yes	No	Yes	Yes	No	Yes	0.55	0	2	3	4.88

descriptors for ADMET endpoint, sizable enough collection of data pertaining with same endpoint for model validation are all essential components of effective prediction models for ADMET parameters. Recent developments in the prediction of ADME-related physicochemical qualities (like lipophilicity), ADME properties (like absorption), and toxicity problems (like drug-drug interactions) are discussed in this article see Table 2. During the next ten years or so, automated medium and HTS *in vitro* tests will be employed.

DISCUSSION

All of the "compounds had molecular weights less than 500," according to data warrior results, suggesting that they will bind action site. 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 6.0 and 6.8 kcal/mol, suggesting their binding energies lower to benzimidazole, which has "binding energy" of 6.0 kcal/mol. Analogues with best interactions and far from zero auto dock score determined as best conformation. Both complexes' Ramachandran Plot RMSD plot analysis revealed that the PVK7-protein complex had a stable trajectory for more research after achieving excellent stability at 100 ns. Analysis of the synthetic benzimidazole derivatives. Interactions towards COX-1 and COX-2 revealed that they have anti-inflammatory properties. 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 (2OYE). PVK5 and PVK11 demonstrated Pi-Pi stacking to Tyr385 and Trp387 via the benzimidazole and H-bond with Ser-530 via nitrogen of the benzimidazole ring. PVK12 demonstrated Pi-Pi stacking with Tyr385 via the benzimidazole ring and hydrogen bonding with Ser530. PVK14 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), PVK14 and PVK15 had a satisfactory docking score of -7.572 kcal/mol. Phe381, Leu384, Tyr385, Trp387, were active amino acids in the enzyme COX-2 (4COX). BI5 demonstrated H-Bond with Ser-530 nitrogen of

benzimidazole and Pi-Pi stacking with Tyr-385 via benzene. PVK10 demonstrated Pi-cation interaction to Arg-120 via benzimidazole and Pi-pi stacking with Tyr-385 and Trp-387 via benzene. PVK9 demonstrated H-bond with Ser-530 via benzimidazole and Pi-Pi stacking with Tyr-385. Comparing 15 benzimidazole derivatives to the standard Indomethacin (-10.099 kcal/mol), PVK14, PVK15, PVK2, and PVK9 showed elevated docking scores, from -7.25 to -7.51 kcal/mol (Table 4). Compound PVK5's binding affinity score with 2OYE is -56.79 kcal/mol, whereas compound PVK2's binding score with 4COX 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. 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 absorption, it suggested that used as 3D descriptor

Table 3: Chemical interactions between the chemicals and the residues of active amino acids.

Name	Distance	Category	Type	Docking score
PVK2				
				-7.279
C:GLN203:HE21 - Aniline:O24	2.10892	Hydrogen Bond	Conventional Hydrogen Bond	
Aniline:N23 - Aniline	4.53268	Electrostatic	Pi-Cation	
C:HIS207 - Aniline	4.43066	Hydrophobic	Pi-Pi Stacked	
Aniline - C:VAL447	4.26887	Hydrophobic	Alkyl	
Aniline - C:VAL447	4.3565	Hydrophobic	Alkyl	
Aniline - C:VAL295	4.44748	Hydrophobic	Pi-Alkyl	
Aniline - C:LEU391	4.64206	Hydrophobic	Pi-Alkyl	
Aniline - C:LEU391	5.34079	Hydrophobic	Pi-Alkyl	
Aniline - C:LEU408	5.39828	Hydrophobic	Pi-Alkyl	
Aniline - C:VAL444	4.91713	Hydrophobic	Pi-Alkyl	
Aniline - C:LEU294	5.20831	Hydrophobic	Pi-Alkyl	
C:HIS388 - Aniline	5.31072	Hydrophobic	Pi-Alkyl	
PVK7				
				-6.674
3-Chloroaniline:H55 - C:HIS207:NE2	2.61681	Hydrogen Bond	Conventional Hydrogen Bond	
C:GLN203:HE22 - 3-Chloroaniline:N7	2.66161	Hydrogen Bond	Conventional Hydrogen Bond	
C:GLN203:HE22 - 3-Chloroaniline:O25	2.87752	Hydrogen Bond	Conventional Hydrogen Bond	
3-Chloroaniline:H54 - 3-Chloroaniline:O24	2.69776	Hydrogen Bond	Carbon Hydrogen Bond	
3-Chloroaniline:N23 - 3-Chloroaniline	4.66402	Electrostatic	Pi-Cation	
3-Chloroaniline:H55 - C:HIS207	3.24992	Hydrogen Bond	Pi-Donor Hydrogen Bond	
3-Chloroaniline - 3-Chloroaniline	5.6637	Hydrophobic	Pi-Pi T-shaped	
C:HIS214 - 3-Chloroaniline	5.9637	Hydrophobic	Pi-Pi T-shaped	
C:HIS386 - 3-Chloroaniline	5.57709	Hydrophobic	Pi-Pi T-shaped	
3-Chloroaniline - C:VAL444	5.37652	Hydrophobic	Alkyl	
3-Chloroaniline - C:VAL447	4.45833	Hydrophobic	Alkyl	
3-Chloroaniline - C:VAL295	5.0621	Hydrophobic	Pi-Alkyl	
3-Chloroaniline - C:VAL295	4.17386	Hydrophobic	Pi-Alkyl	
3-Chloroaniline - C:LEU391	4.96357	Hydrophobic	Pi-Alkyl	
3-Chloroaniline - C:LEU391	4.7873	Hydrophobic	Pi-Alkyl	
3-Chloroaniline - C:LEU408	5.14361	Hydrophobic	Pi-Alkyl	
3-Chloroaniline - C:VAL444	5.18344	Hydrophobic	Pi-Alkyl	
3-Chloroaniline - C:LEU294	5.31648	Hydrophobic	Pi-Alkyl	
3-Chloroaniline - C:LEU408	5.29695	Hydrophobic	Pi-Alkyl	
C:HIS214 - 3-Chloroaniline:Cl35	5.21717	Hydrophobic	Pi-Alkyl	

Name	Distance	Category	Type	Docking score
PVK9				
Chloroacetic Acid:H36 - Chloroacetic Acid:O25	2.11088	Hydrogen Bond	Conventional Hydrogen Bond	-7.234
C:GLN203:HE21 - Chloroacetic Acid:O28	2.3911	Hydrogen Bond	Conventional Hydrogen Bond	
C:ASN382:HD22 - Chloroacetic Acid:O31	2.0848	Hydrogen Bond	Conventional Hydrogen Bond	
C:HIS207:HD2 - Chloroacetic Acid:O28	2.88377	Hydrogen Bond	Carbon Hydrogen Bond	
C:HIS388:HE1 - Chloroacetic Acid:O22	2.93758	Hydrogen Bond	Carbon Hydrogen Bond	
C:LEU391:HD11 - Chloroacetic Acid	2.84854	Hydrophobic	Pi-Sigma	
Chloroacetic Acid - Chloroacetic Acid	4.25957	Hydrophobic	Pi-Pi T-shaped	
Chloroacetic Acid - Chloroacetic Acid	5.51634	Hydrophobic	Pi-Pi T-shaped	
Chloroacetic Acid - C:VAL447	4.16739	Hydrophobic	Alkyl	
Chloroacetic Acid - C:VAL295	5.22315	Hydrophobic	Pi-Alkyl	
Chloroacetic Acid - C:VAL295	4.27938	Hydrophobic	Pi-Alkyl	
Chloroacetic Acid - C:LEU391	4.6771	Hydrophobic	Pi-Alkyl	
Chloroacetic Acid - C:LEU408	5.21899	Hydrophobic	Pi-Alkyl	
Chloroacetic Acid - C:VAL444	5.08013	Hydrophobic	Pi-Alkyl	
Chloroacetic Acid - C:LEU294	5.49533	Hydrophobic	Pi-Alkyl	
C:HIS388 - Chloroacetic Acid	4.72011	Hydrophobic	Pi-Alkyl	
PVK12				
C:HIS388:HE2 - :Benzoic Acid:O1	2.52023	Hydrogen Bond	Conventional Hydrogen Bond	-6.831
C:HIS388 - :Benzoic Acid	4.66368	Hydrophobic	Pi-Pi T-shaped	
C:ALA202:C,O;GLN203:N - :Benzoic Acid	5.01118	Hydrophobic	Amide-Pi Stacked	
:Benzoic Acid - C:LEU408	5.33122	Hydrophobic	Alkyl	
:Benzoic Acid - C:VAL444	5.0705	Hydrophobic	Alkyl	
:Benzoic Acid - C:VAL291	4.21068	Hydrophobic	Pi-Alkyl	
:Benzoic Acid - C:LEU294	5.11734	Hydrophobic	Pi-Alkyl	
:Benzoic Acid - C:ALA446	5.18402	Hydrophobic	Pi-Alkyl	
:Benzoic Acid - C:VAL447	5.48161	Hydrophobic	Pi-Alkyl	
C:HIS388 - :Benzoic Acid	4.69503	Hydrophobic	Pi-Alkyl	
PVK14				
:p-aminobenzoic acid:H25 - C:TYR385:O	2.04806	Hydrogen Bond	Conventional Hydrogen Bond	-7.51
C:GLN203:HE22 - :p-aminobenzoic acid:N1	2.7527	Hydrogen Bond	Conventional Hydrogen Bond	
C:GLN203:HE22 - :p-aminobenzoic acid:O2	2.8351	Hydrogen Bond	Conventional Hydrogen Bond	
:p-aminobenzoic acid:N3 - :p-aminobenzoic acid	4.74308	Electrostatic	Pi-Cation	
:p-aminobenzoic acid - :p-aminobenzoic acid	5.76998	Hydrophobic	Pi-Pi T-shaped	
:p-aminobenzoic acid - C:VAL444	5.26143	Hydrophobic	Alkyl	
:p-aminobenzoic acid - C:VAL447	4.36797	Hydrophobic	Alkyl	
:p-aminobenzoic acid - C:VAL447	4.45025	Hydrophobic	Alkyl	
:p-aminobenzoic acid - C:VAL295	5.09936	Hydrophobic	Pi-Alkyl	
:p-aminobenzoic acid - C:VAL295	4.19352	Hydrophobic	Pi-Alkyl	
:p-aminobenzoic acid - C:LEU391	4.95439	Hydrophobic	Pi-Alkyl	
:p-aminobenzoic acid - C:LEU391	4.7797	Hydrophobic	Pi-Alkyl	
:p-aminobenzoic acid - C:LEU408	5.13721	Hydrophobic	Pi-Alkyl	
:p-aminobenzoic acid - C:VAL444	5.14409	Hydrophobic	Pi-Alkyl	
:p-aminobenzoic acid - C:LEU294	5.33547	Hydrophobic	Pi-Alkyl	
:p-aminobenzoic acid - C:LEU408	5.47391	Hydrophobic	Pi-Alkyl	
C:HIS388 - :p-aminobenzoic acid	4.83812	Hydrophobic	Pi-Alkyl	

Name	Distance	Category	Type	Docking score
PVK15				
C:ARG222:NH2 - :Phenylacetic acid:O2	5.15742	Electrostatic	Attractive Charge	-7.184
C:GLN203:HE22 - :Phenylacetic acid:O6	2.72987	Hydrogen Bond	Conventional Hydrogen Bond	
C:THR212:H - :Phenylacetic acid:O3	2.08821	Hydrogen Bond	Conventional Hydrogen Bond	
C:HIS214:HE2 - :Phenylacetic acid:N1	2.40208	Hydrogen Bond	Conventional Hydrogen Bond	
C:ASN382:HD21 - :Phenylacetic acid:O5	2.93383	Hydrogen Bond	Conventional Hydrogen Bond	
C:GLN454:HE22 - :Phenylacetic acid:N1	2.35594	Hydrogen Bond	Conventional Hydrogen Bond	
C:THR212:HB - :Phenylacetic acid:O3	2.84374	Hydrogen Bond	Carbon Hydrogen Bond	
C:HIS386:HA - :Phenylacetic acid:O4	2.59363	Hydrogen Bond	Carbon Hydrogen Bond	
C:HIS388:HE1 - :Phenylacetic acid:O4	2.48053	Hydrogen Bond	Carbon Hydrogen Bond	
:Phenylacetic acid:N4 - C:HIS386	3.89995	Electrostatic	Pi-Cation	
:Phenylacetic acid:O4 - C:HIS386	3.71022	Electrostatic	Pi-Anion	
C:ASN382:HD22 - :Phenylacetic acid	3.08968	Hydrogen Bond	Pi-Donor Hydrogen Bond	
C:HIS207 - :Phenylacetic acid	4.52379	Hydrophobic	Pi-Pi Stacked	
:Phenylacetic acid - C:VAL447	5.00265	Hydrophobic	Alkyl	
:Phenylacetic acid - C:VAL447	5.23147	Hydrophobic	Pi-Alkyl	
:Phenylacetic acid - C:ALA450	3.70725	Hydrophobic	Pi-Alkyl	
:Phenylacetic acid - C:ALA450	4.32366	Hydrophobic	Pi-Alkyl	
:Phenylacetic acid - C:VAL295	4.27984	Hydrophobic	Pi-Alkyl	
:Phenylacetic acid - C:LEU391	4.67153	Hydrophobic	Pi-Alkyl	
:Phenylacetic acid - C:LEU408	5.30262	Hydrophobic	Pi-Alkyl	
C:HIS386 - :Phenylacetic acid	5.39567	Hydrophobic	Pi-Alkyl	
C:HIS388 - :Phenylacetic acid	5.43511	Hydrophobic	Pi-Alkyl	

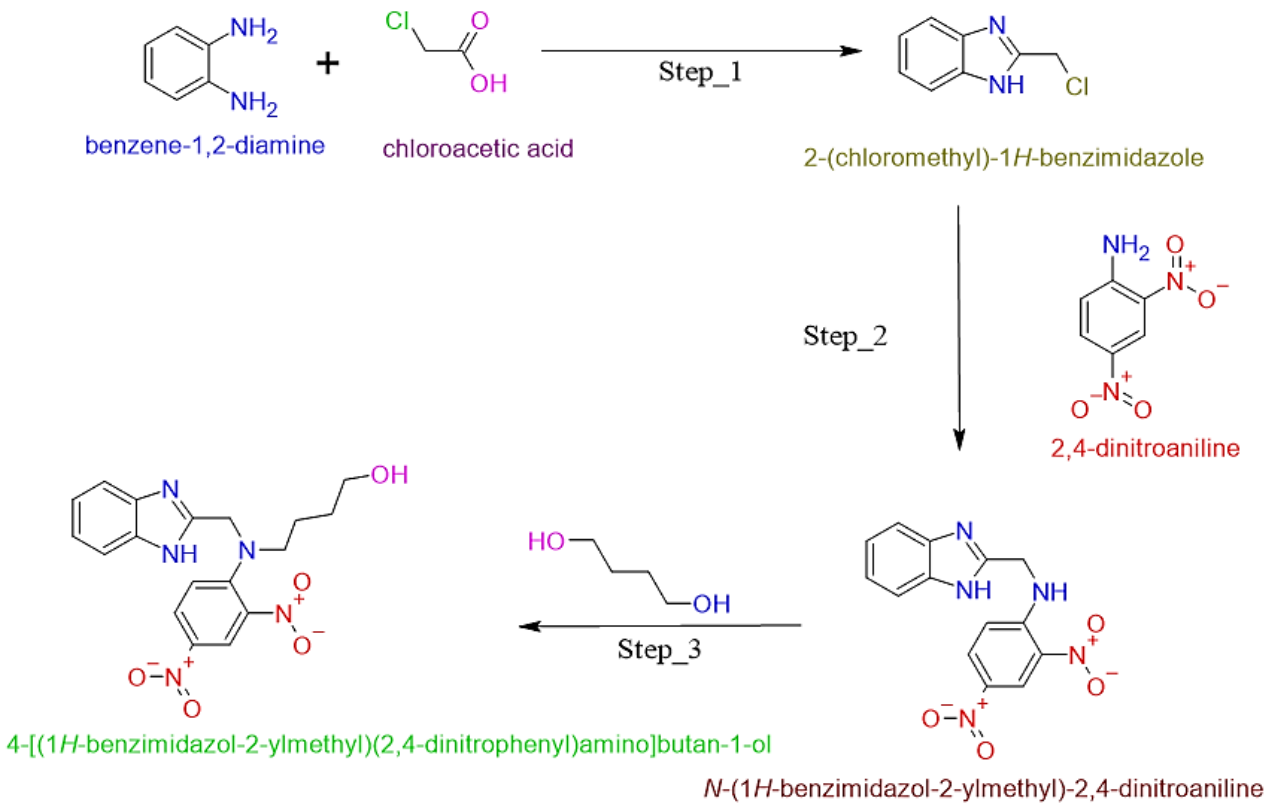


Figure 3: Scheme of Benzimidazole.

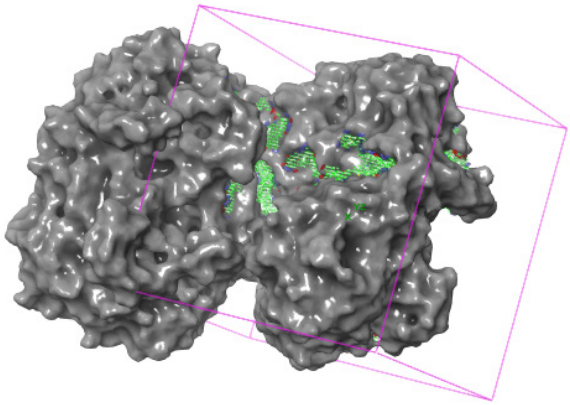
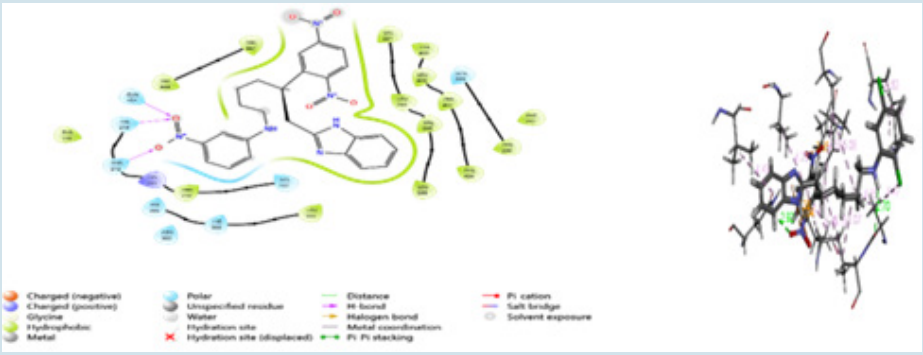


Figure 4: Receptor Grid Generation Wizard.

Table 4: 2D and 3D conformations of Active molecule with molecular bindings. Computer-Aided Molecular Design (CAMD).

Comp. Code	2D Images	3D Images
PVK4		
PVK5		

in number of hydrogen bonding groups. 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.

CONCLUSION

To ascertain their anti-inflammatory properties, benzimidazole analogues were docked with COX-1 (2OYE) and COX-2 (4COX). 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. The ligands PVK14 and PVK15 had high docking scores with COX-2 (-7.122 kcal/mol) and COX-1 (-7.572 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 & benzimidazoles, responsible for anti-inflammatory properties.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

mg/kg: Milligram/ kilograms; **sec:** Seconds; **kcal:** Kilocalorie; **Mol. Wt:** Molecular Weight; **g:** Gram; **LEU:** Leucine; **THR:** Threonine; **ALA:** Alanine; **MET:** Methionine; **PHE:** Phenylalanine; **COX:** Cyclooxygenase Enzyme; **WHO:** World health association; **Log P:** Partition coefficient.

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